CHAPTER 1

Progress in the Medicinal Chemistry of Group III Metabotropic Glutamate Receptors

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Contents

1. INTRODUCTION

G-protein-coupled receptors (GPCRs), among the largest and most diverse protein families in mammalian genomes and accounting for 30% of all modern medicinal drugs, constitute a superfamily of proteins whose

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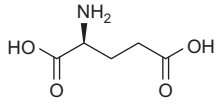
primary function is to transmit extracellular stimuli into intracellular signals. Sequence comparison of different GPCRs revealed the existence of at least six classes (A through F) [1]. Metabotropic glutamate (mGlu) receptors belong to the class C GPCR family and are activated by L-glutamate, a major excitatory neurotransmitter of the mammalian brain. To date, eight subtypes of mGlu receptors have been identified and divided into three groups based on sequence homology, signal transduction, and pharmacology. Group I includes mGlu1 and mGlu5; group II includes mGlu2 and mGlu3; and group III includes mGlu4, mGlu6, mGlu7, and mGlu8 receptors [2]. The widespread expression of mGlu receptors and their role in synaptic signaling throughout the central nervous system (CNS) have made them attractive therapeutic targets [3,4]. While significant progress has been made in identifying specific ligands for and in elucidating the function of group I and group II receptors, the evolution of group III mGlu receptors has been slow, in large part due to the lack of selective tool compounds. However, superior ligands for receptors in this group are emerging, for the mGlu4 receptor in particular. These chemical tools are beginning to unveil the important role of mGlu group III receptors, and their modulation has been shown to provide therapeutic potential for a number of indications such as Parkinson's disease (mGlu4) [5] and cognition impairment (mGlu7) [6]. This review focuses on the recent progress on identification of group III mGlu receptor ligands.

2. GROUP III ORTHOSTERIC LIGANDS

2.1. Group III agonists

The endogenous ligand L-glutamate (**1**) is a nonselective agonist, activating all mGlu receptors, as well as ligand-gated ionotropic (iGlu) receptors, and glutamate transporters. Depending on the specifics of the assay, the *in vitro* potency of L-glutamate is in the single or double-digit micromolar range at all mGlu receptors except mGlu7, at which its potency is in the millimolar range [7–9]. Other known mGlu group III-selective agonists (*e.g.*, **2–8**) also display much lower affinity at the mGlu7 receptor than at other mGlu receptors. This has caused speculation on the presence of a surrogate endogenous ligand for mGlu7, as well as suggested that this receptor may only be activated under specific conditions where elevation in the extracellular glutamate concentration is higher than during normal synaptic transmission.



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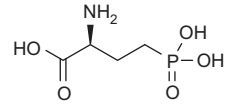
L-Glu



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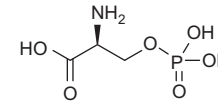
L-AP$_4$



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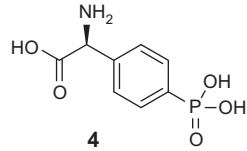
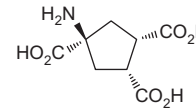
L-SOP



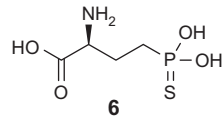
4
(*S*)-PPG



5
ACPT-1

To date, all of the known group III-selective agonists identified are amino acid derivatives bearing additional acidic groups to mimic L-glutamate and lack subtype selectivity. L-AP$_4$ (**2**), a γ-phosphonic acid, has been known as the most potent group III agonist for many years and is highly selective against group I and group II mGlu and iGlu receptors (EC_{50} =0.08, 2.08, 440, and 0.128 μM at mGlu4, mGlu6, mGlu7, and mGlu8, respectively) [10]. L-SOP, **3**, (*R*,*S*)-PPG, **4**, and ACPT-1, **5**, are some other early group III agonists [7–9,11]. Efforts by Acher and coworkers led to several new and potent group III agonists (**6–9**) in recent years. L-thio-AP$_4$, **6** was shown to be slightly more potent at all group III receptors (EC_{50} = 0.039, 0.73, 197, and 0.054 μM at mGlu4, mGlu6, mGlu7, and mGlu8, respectively) than L-AP$_4$ [10]. The enhanced potency of **6** was hypothesized to be derived from its stronger acidity of the thiophosphonate moiety (pK_a = 5.56) than that of the corresponding phosphonate of L-AP$_4$ (pK_a = 6.88), as determined by ^{31}P NMR.

In an effort to identify subtype-selective group III agonists, the strategy of conformationally constraining L-AP$_4$ was further explored [12]. Of the four possible stereoisomers of cyclopropane derivative **7**, the (1*S*,2*R*)-isomer was reported to be the most potent. Additional constrained analogs such as the cyclobutyl and cyclopentyl derivatives were significantly less potent [12,13]. Nonetheless, **7** displays very similar pharmacology to that of L-AP$_4$ and, therefore, is not subtype selective.

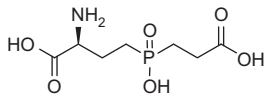


6
L-thio-AP$_4$

7
(1*S*,2*R*)-APCPr

In another attempt to identify subtype-selective agonists, longer-chain analogs of L-AP$_4$ were designed to test the hypothesis that these may

interact with less-conserved, remote regions in the glutamate binding pocket [14,15]. Based on this concept, a virtual high-throughput screen (vHTS) was carried out and agonist **8** was identified [16]. Structure–activity relationship (SAR) studies led to the identification of several compounds, such as **9**, with improved potency. Interestingly, **9** and some of its closely related analogs activate mGlu7 receptor more potently than known agonists. This is of particular interest, but for other reasons, as the mGlu7 receptor is difficult to activate [7–9]. Nevertheless, subtype-selective agonists were not identified from this approach. Another class of compounds with an aromatic moiety (*e.g.*, **10**) was also reported by the same group, which displays a similar subtype selectivity profile [15,17].



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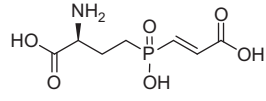
(*S*)-PCEP



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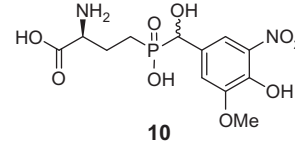
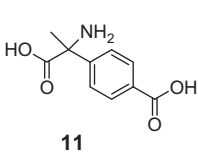


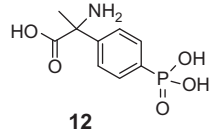
10
LSP1-2111

2.2. Group III antagonists

Following the report of the compound MCPG (**11**) as the first group III antagonist more than a decade ago [18], a number of antagonists have subsequently been identified. These include **12** [19], **13** [20], **14** [21], **15** [22,23], **16** [24], and **17** [25,26]. All these orthosteric antagonists are α-methyl or α-alkyl analogs of the group III agonists (*e.g.*, **15** *vs*. **2** and **16** *vs*. **3**). Although these compounds have been used as chemical tools to probe group III mGlu receptor function, their utility is limited by their low group III receptor affinity and paucity of selectivity over group I and group II receptors.



11
MCPG



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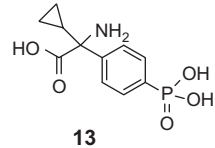
MPPG



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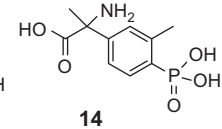
CPPG



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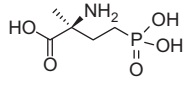

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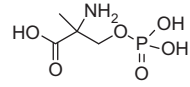
MAP4



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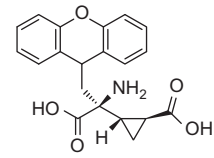
MSOP



17
LY341495

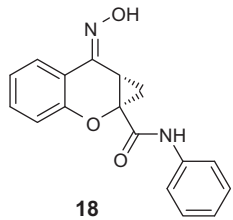
3. mGlu4 RECEPTOR ALLOSTERIC LIGANDS

3.1. mGlu4 receptor positive allosteric modulators

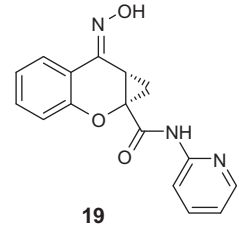
Due to the difficulty in identifying selective orthosteric ligands, as well as the opportunity to explore ligand/receptor interactions in regions of the receptor that may afford certain advantages from the target selectivity and CNS drug design perspectives [27], efforts were directed toward finding positive allosteric modulators (PAMs). Unlike the orthosteric ligands binding at the glutamate binding site, PAMs bind to a distinct region (the allosteric site) which in most cases is believed to be in the seven transmembrane region. This allosteric interaction enhances the activity of the receptor in the presence of an orthosteric agonist such as glutamate. Of the variety of research performed in the past few years, good progress has been recently made with the mGlu4 receptor in particular. Notably, the first subtype-selective mGlu4 PAM PHCCC (**18**) was independently discovered by two research groups [28,29]. Initially, racemic (±)-PHCCC was reported to be an mGlu1 receptor antagonist [30] and although the mGlu4-active enantiomer (−)-PHCCC still partially antagonizes the mGlu1b receptor ($IC_{50} = 3.4$ μM), it is inactive against other mGlu subtypes at 10 μM and is selective against a panel of 28 relevant CNS receptors [29]. (−)-PHCCC was shown to potentiate the responses of both human and rat mGlu4 receptors to L-glutamate or L-AP_4 with EC_{50} values in the range of 2.0–4.1 μM [28]. The study with mGlu4/1b chimeras clearly demonstrated that (−)-PHCCC binds to the seven transmembrane region (the allosteric binding motif) [29]. Being the first subtype-selective mGlu4 ligand, (−)-PHCCC has been used as a tool compound to probe mGlu4 functions in numerous *in vivo* studies [28,31–37]. Due to the suboptimal physicochemical properties and difficulties achieving central exposure levels upon peripheral administration of (−)-PHCCC, several of these studies were carried out through brain local injections, thus limiting its utility as a potential drug candidate.

Aimed at improving the potency and physicochemical properties of previous ligands, and to address the selectivity against mGlu1b of (−)-PHCCC, researchers at Vanderbilt University carried out SAR studies around the PHCCC scaffold [38,39]. In their efforts, the 2-pyridyl group was identified to be superior to the original phenyl ring, affording VU0359516 (**19**) with >fourfold improved potency ($EC_{50} = 380$ nM) over (−)-PHCCC and without mGlu1 activity. Replacement of the 2-pyridyl group with the classical pyridine mimetic 2-thiazole led to a dramatic reduction in potency (>5 μM) underscoring the ubiquitously narrow SAR reported for several structurally diverse series of mGlu4 PAMs (*vide infra*). The PAM activity of **19** was further characterized by a 22-fold leftward shift of the glutamate dose–response curve at 30 μM.

Unlike (−)-PHCCC, **19** did exhibit some mGlu4 agonist activity at high concentrations (>30 μM) showing this ligand to be a mixed allosteric modulator and orthosteric agonist in a calcium mobilization assay using Chinese hamster ovary (CHO) cells expressing human mGluR4 and a chimeric G-protein Gqi5.

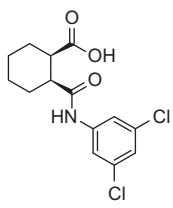


18
(–)-PHCCC



19
VU0359516

The same group of scientists at Vanderbilt University later described the identification of a class of cyclohexane-dicarboxylic monoamides as represented by **20** (hEC_{50} = 798 nM) [39]. Further investigation showed the *trans*-isomers of **20** to be inactive. The (+)-(1*R*,2*S*)- and (−)-(1*S*,2*R*)-*cis*-enantiomers were originally reported [39] to be of equal potency and efficacy, but it was recently discovered that the activity primarily resides on the (**1***R*,**2***S*) isomer [40]. Unlike (−)-PHCCC, which is a pure PAM, **20** also displayed some intrinsic agonist activity in a calcium mobilization assay, which could not be blocked by the known orthosteric antagonist LY341495 (**17**) indicating that **20** may not interact with the endogenous glutamate binding site. Compound **20** did not show activity at 10 μM in a panel of 67 GPCR, ion channel, and transporter selectivity assays. However, **20** was shown not to penetrate the brain upon peripheral administration, and its use as an *in vivo* CNS pharmacology tool is limited to intracerebral (icv) dosing [39]. Continuing efforts were focused on the SAR studies in all three ring systems of **20** and essentially all modifications resulted in inactive compounds or compounds with significantly reduced potency [41]. A notable exception discovered independently by researchers at Lundbeck is the primary amide Lu AF21934 (**21**), which has comparable potency to **20** and is brain penetrant (brain/plasma 0.8) [42]. Again, this work underscores the generally narrow SAR of mGlu4 PAMs and potential challenges in the lead optimization of these compounds.



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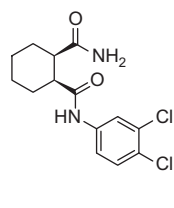
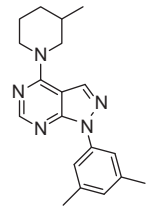
(±)-VU0155041



21
(+)-Lu AF21934



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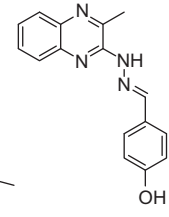

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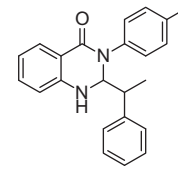
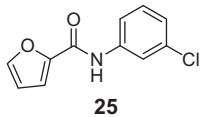


24
VU0092145

Among additional mGlu4 PAMs subsequently reported by the Vanderbilt group are **22–24** [43,44]. All of these new ligands were directly identified from their extensive high-throughput screen (HTS) campaign. The adenine derivative **22** potentiated glutamate with $EC_{50} = 5$ μM and caused a leftward shift of the glutamate response curve of 12- to 27-fold. However, **22** is also a full antagonist of mGlu1 receptor ($IC_{50} = 2.6$ μM) and has low stability in a liver microsomes preparation [43]. A general and efficient microwave-assisted synthesis was therefore developed to explore the SAR and to optimize this chemical series [45]. Disappointingly, all 126 analogs synthesized were uniformly inactive except a very small subset showing reduced potency compared to the original hit **22**. HTS hit **23** was found to be a relatively potent mGlu4 PAM ($EC_{50} = 650$ nM, Glu E_{max} 141%) and to induce a 36-fold shift of glutamate potency. This compound was also selective against other mGlu receptors in both activation (agonist/PAM) and inhibition (antagonist) assays. However, the unattractive and potentially labile hydrazone moiety prevented it from further advancement. All attempts to replace the hydrazone with other chemical moieties were reportedly unsuccessful. The identification of compound **24** represents another new chemotype which has a potency ($EC_{50} = 3.0$ μM) similar to that of **18** [44]. There are also some structural similarities between these two compounds, and two small libraries were synthesized in this series for SAR development and attempted optimization. Again the results were not fruitful as only two additional active compounds were identified, both with significantly weaker activity compared to the original hit **24**. Not to overstate it, but the now commonly occurring narrow SAR of mGlu4 PAMs (*vide infra*) represents a significant hurdle for medicinal chemists.

Adding to the list of new mGlu4 PAMs, the Vanderbilt group disclosed a class of heterobiarylamides as represented by ligands **25–27** [46]. The furan derivative **25** was one of the initial hits in its class with weak mGlu4 PAM activity ($EC_{50} > 5$ μM), and extensive optimization was then carried out for both the furyl and aniline regions. Compound **26** was among the most potent ($EC_{50} = 240$ nM) compounds identified with good brain penetration (brain/plasma 4.1) and reasonable drug free fraction (plasma free fraction 2.2%). However, **26** was characterized by high *in vivo* clearance in rat (894 mL/min/kg), consistent with its poor *in vitro* microsomal stability. The same group also disclosed a related diamide series as represented by **27** [47]. 2-Pyridyl again was shown to be the optimal group for mGlu4 potency. Compound **27** and some of its analogs are reportedly potent ($EC_{50} = 100$ nM), brain penetrant, and highly protein bound (plasma protein binding $> 99.5\%$).



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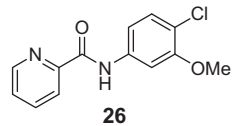

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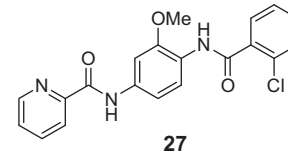
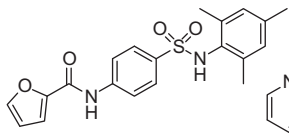


27
VU0415374

More recently, the Vanderbilt University group reported a class of biarylsulfonamides as potent mGlu4 PAMs [45]. Again, the lead compound (**28**, $EC_{50} = 6$ μM) was directly identified from their HTS campaign. Based on the SAR learned from the heterobiarylamide series (**25** and **26**), the 2-furyl was replaced by 2-pyridyl which resulted in 30-fold increase in potency. Further optimization led to identification of **29** ($EC_{50} = 20$ nM), which represents one of the most potent mGlu4 PAMs reported to date. Although being very potent, this class of compounds exhibited high protein binding and poor microsomal stability in both human and rat species, thus limiting its utility. Finally, another sulfonamide series represented by **30** was reported [48], and although this class of compounds is not highly potent (*e.g.*, **30** $EC_{50} = 3.5$ μM), it is characterized by relatively low protein binding (plasma free fraction > 3%), presumably related to improved aqueous solubility resulting from the nonplanar core and the presence of a basic nitrogen.



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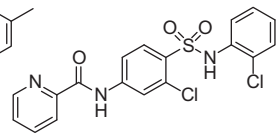
VU0130734



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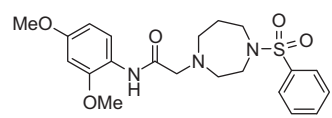
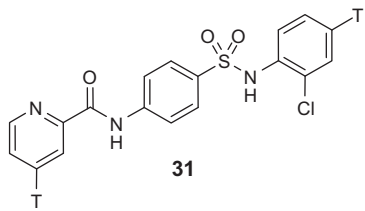


30

Recently, scientists at Merck reported the exact same biarylsulfonamide derivative class [49]. They also disclosed a series of phthalimides as mGlu4 PAMs [50]. Ultimately, two potent compounds were tritiated to provide radioligands **31** and **32** (34 and 160 nM, respectively) [51]. In a competition binding analysis, **31** and **32** reportedly displaced each other, indicating their allosteric binding sites are related. However, VU0155041 (**20**) enhances rather than displaces binding of **31** suggesting the existence of more than one allosteric binding site for various ligands.



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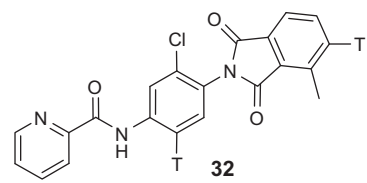
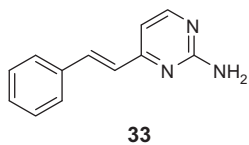


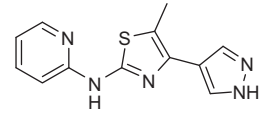
32

Compound **33**, structurally similar to mGlu5 NAMs SIB-1893 and MPEP (which also show weak mGlu4 PAM activity [52]), was recently reported by East *et al*. [53]. This compound was identified as an intermediate during resynthesis of a HTS hit and displayed an EC_{50} of 1 μM against both human and rat mGlu4 receptors. It is reportedly selective against mGlu5 (>10-fold) and has less than 50% activity at 10 μM for a panel of 68 targets. Though **33** is characterized by rapid *in vivo* clearance (75 mL/min/kg in rat), its high brain penetration (brain/plasma 2.9) and good oral bioavailability together with good CNS drug-like physicochemical properties have qualified it as a tool compound for acute *in vivo* proof of concept studies *via* peripheral administration.

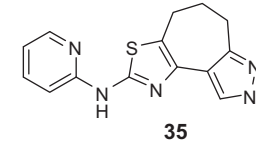
Most recently, scientists at Lundbeck reported a class of tricyclic thiazolopyrazoles (*e.g.*, **35**) as potent, selective, and orally bioavailable mGlu4 PAMs. These compounds were designed to improve upon previous derivatives and to expand the chemical diversity among ligands for mGlu4 [54]. The tricyclic derivatives have similar potency compared to their acyclic analogs (*e.g.*, EC_{50} = 13 nM for **34** and 9 nM for **35**), and compound **35** is a highly subtype-selective mGlu4 PAM (>1000-fold against mGlu1, 2, 3, 5, 6, 7 receptors) with a brain/plasma ratio of *ca.* 1.2 [55].



33



34



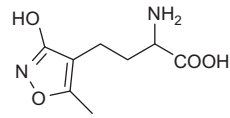
35

3.2. mGlu4 receptor negative allosteric modulators

While several groups, both in industry and in academia, have successfully identified numerous mGlu4 PAMs from HTS efforts, identification of mGlu4 NAMs has been shown to be challenging and none have been reported to date. Lacking any progress in this area, its significance remains another hard to interpret characteristic of allosteric mGlu4 modulators.

4. mGlu6 RECEPTOR LIGANDS

Unlike every other mGlu receptor, which is broadly expressed, the mGlu6 receptor is exclusively located in the retina [2]. The only selective mGlu6 ligand reported to date is **36** [56], an isoxazolyl bioisostere of 2-aminoadipic acid. Though compound **36** is a weakly potent orthosteric agonist (EC_{50} = 82 μM), it is selective against iGlu and other mGlu receptors. It was subsequently reported that all of the mGlu6 activity resides in the (*S*)-enantiomer [57].



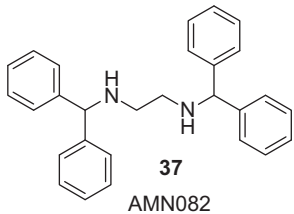
36
Homo-AMPA

5. mGlu7 RECEPTOR LIGANDS

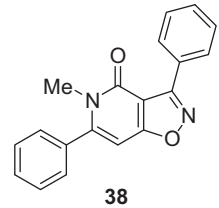
AMN082, **37**, is the only mGlu7 agonist reported to date [58]. This compound was shown to be a full agonist in both GTPγS binding (EC_{50} = 260 nM) and cAMP (EC_{50} = 64 nM) assays and to act *via* an allosteric site, as supported by results of chimeric receptor studies and competitive binding with known group III orthosteric agonists and antagonists. However, it has been shown that the mGlu7 activity of **37** is highly context dependent and could be demonstrated in some pathways and cell backgrounds but not in others, thus complicating any determination [58–61]. In addition, though **37** was initially reported to be selective over 30 targets [58], it has been found to interact with many other targets (26 of 71) in a broader screen [61]. Finally, a metabolite was identified *in vivo* in rodents with monoaminergic activity [62]. Since many *in vivo* studies have been done with **37** to probe mGlu7 receptor function prior to that elucidation, the results should be carefully interpreted.

More recently, a class of isoxazolopyridone derivatives represented by **38** and **39** were reported as potent and subtype-selective mGlu7 antagonists [63,64]. The lead compound MDIP (**38**) was identified from HTS and was subsequently optimized to generate **39** with comparable potency but with improved physicochemical and ADME properties. Compound **39** was shown to antagonize L-AP_4-induced responses in both Ca^{2+} mobilization (IC_{50} = 26 nM, rat mGlu7) and cAMP assays (EC_{50} values of 220 and 610 nM, in rat and human mGlu7 receptors, respectively) [63]. Compound **39** is reportedly selective against other mGlu receptors and a panel of 168 targets. In addition, **39** displayed a favorable rat pharmacokinetic profile characterized by good oral bioavailability (65%), low clearance (1.0 mL/min/kg), and good brain penetration (brain/plasma 1.0), making it a valuable tool compound to study mGlu7 receptor function. However, like **37**, the mGlu7 activity of **39** was also found to be context dependent [60]. For example, **39** did not block L-AP_4-induced inhibition of cAMP accumulation in HEK cells. Furthermore, **39** was unable to block agonist-mediated responses at the Schaffer collateral-CA1 synapse, a location at which neurotransmission has been shown to be modulated

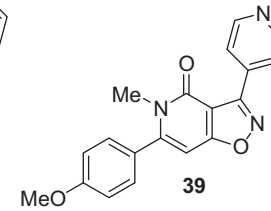
by mGlu7 receptor activity [60]. The context dependence of both agonist **37** and antagonist **39** further reveals the complexity of mGlu7 pharmacology.



37
AMN082



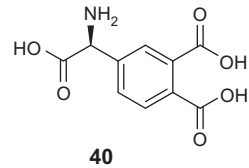
38
MDIP



39
MMPIP

6. mGlu8 RECEPTOR LIGANDS

(*S*)-3,4-DCPG (**40**), originally synthesized to search for potential selective ionotropic glutamate receptor (iGlu) antagonists [65], was found to be a subtype-selective mGlu8 agonist ($EC_{50} = 31$ nM, >100-fold selectivity over other mGlu receptors) [66] and has been widely used as a tool compound to selectively activate this receptor. Though effects on several regions of the brain were observed through systemic administrations (*e.g.*, ip dosing) [67], the majority of the *in vivo* studies with **40** were carried out *via* central administration due to the poor brain penetration of this polar amino acid with additional hydrophilic carboxylic acid groups [68–72]. To date there are no additional reports of mGlu8 ligands.



40
(*S*)-3,4-DCPG

7. CONCLUSIONS

While progress has been made over the past several years in identifying subtype-selective and systemically available ligands for some of the group III mGluRs, this field is still in its infancy. Most mGlu4 PAMs reported to date have undesired physicochemical and pharmacokinetic properties, limiting their utility as tool compounds and preventing them from drug candidate consideration. It is obvious from the various studies that the notoriously narrow SAR of mGlu4 PAMs, which leaves little room for lead optimization, is the greatest challenge. Concurrently,

scientific evidence continues to support the biological hypothesis that potentiation of the mGlu4 receptor may provide potential treatment for motor symptoms in Parkinson's disease as well as mood and neuroinflammation disorders. In addition, evidence is beginning to support the biological rationale for the use of mGlu7 modulation in cognition and mood disorders. With the limitations found for AMN082 and MMPIP, additional tool compounds need to be discovered to fully unravel the potential utility of this target. Likewise, the same is true for the mGlu8 receptor. Future progress and clinical validation will ultimately afford a clear perspective on the value of these receptors as potential drug targets.

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