Published in final edited form as:

Bioorg Med Chem Lett. 2014 August 1; 24(15): 3641–3646. doi:10.1016/j.bmcl.2014.04.087.

Discovery and SAR of a novel series of metabotropic glutamate receptor 5 positive allosteric modulators with high ligand efficiency

Mark Turlington^{a,b,c,d}, Meredith J. Noetzel^{a,b,c}, Thomas M. Bridges^{a,b,c}, Paige N. Vinson^{a,b,c}, Thomas Steckler^e, Hilde Lavreysen^e, Claire Mackie^f, José M. Bartolomé-Nebreda^g, Susana Conde-Ceide^g, Han Min Tong^g, Gregor J. Macdonald^e, J. Scott Daniels^{a,b,c}, Carrie K. Jones^{a,b,c}, Colleen M. Niswender^{a,b,c}, P. Jeffrey Conn^{a,b,c}, Craig W. Lindsley^{a,b,c,d}, and Shaun R. Stauffer^{a,b,c,d,*}

^aDepartment of Pharmacology, Vanderbilt University Medical Center, Nashville, TN 37232, USA

^bVanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, Nashville, TN 37232, USA

^cVanderbilt Specialized Chemistry Center for Probe Development (MLPCN), Nashville, TN 37232, USA

^dDepartment of Chemistry, Vanderbilt University, Nashville, TN 37232, USA

^eNeuroscience, Janssen Research and Development, Turnhoutseweg 30, B-2340, Beerse, Belgium

^fDiscovery Sciences ADME/Tox, Janssen Research and Development, Turnhoutseweg 30, B-2340, Beerse, Belgium

^gNeuroscience Medicinal Chemistry, Janssen Research and Development, Jarama 75, 45007-Toledo, Spain

Abstract

We report the optimization of a series of novel metabotropic glutamate receptor 5 (mGlu₅) positive allosteric modulators (PAMs) from a 5,6-bicyclic class of dihydropyrazolo[1,5-a]pyridin-4(5H)-ones containing a phenoxymethyl linker. Studies focused on a survey of nonamide containing hydrogen bond accepting (HBA) pharmacophore replacements. A highly potent and selective PAM, 2-(phenoxymethyl)-6,7-dihydropyrazolo[1,5-a]pyridin-4(5H)-one **11**, VU0462054, bearing a simple ketone moiety, was identified (LE = 0.52, LELP = 3.2). In addition, hydroxyl, difluoro, ether, and amino variations were examined. Despite promising lead properties and exploration of alternative core heterocycles, linkers, and ketone replacements, oxidative metabolism and *in vivo* clearance remained problematic for the series.

© 2014 Elsevier Ltd. All rights reserved.

*To whom correspondence should be addressed: shaun.stauffer@vanderbilt.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

metabotropic glutamate receptor 5; mGlu₅; positive allosteric modulator (PAM)

The pursuit of positive allosteric modulators (PAMs) of mGlu₅ as a novel and promising therapeutic approach to treat cognitive deficits in schizophrenia has been stimulated by evidence from several antipsychotic and cognitive animal models.^{1–6} During a decade in which industry and academic discovery groups began pursuing optimal molecules, over eight chemically diverse brain penetrant chemotypes with *in vivo* efficacy in preclinical models have been reported, beginning with CDPPB,⁷ ADX-47273 (**2**),^{8,9} acetylenes VU0360172 (**1**)¹⁰ and LSN2463359,^{11–13} piperazines VU0364289,¹⁴ DPFE (**4**),¹⁵ CPPZ;¹⁶ ether VU0404251 (**3**),¹⁷ and triazole LSN2814617 (Figure 1).¹² Recent findings from Merck-Addex and these laboratories have unveiled a target-mediated CNS adverse-effect (AE) liability, driven by excessive PAM cooperativity¹⁸ or allosteric agonism,^{19,20} respectively, suggesting that PAMs with lower cooperativity and devoid of allosteric agonism may be preferable for obtaining an improved therapeutic index. More recently, we disclosed phenoxy-based tool compounds derived from a dihydrothiazolopyridone²¹ and naphthyridinone²² series; these compounds include PAMs with low to moderate efficacy. Although CNS disposition was excellent, optimized modulators maintained relatively high clearance in rat and dog and were notably less potent relative to picolinamide-based acetylenic PAMs, which readily achieve sub-100 nM *in vitro* potency.

As part of an effort to examine the common amide motif present within chemotypes **1–4**, we were interested in determining if bicyclic acetylenic-based ketone **5** and alcohol **6** reported by Merz²³ as potent mGlu₅ PAMs (rat mGlu₅ EC₅₀ = 34 and 180 nM, respectively) would serve as an alternate hydrogen-bond acceptor (HBA) pharmacophore within one of our non-acetylene ether-based scaffolds. Incorporation of a chiral hydroxyl moiety was particularly attractive as a means to add sp³ character as well as an opportunity to carry a hydrogen bond donor to enhance aqueous solubility, a structural motif presently rare in mGlu₅ PAMs. Although encouraged at the outset, we were also cognizant of recent structure-activity relationships (SAR) in a picolinamide acetylene chemotype demonstrating that hydroxyl installation within an eastern amide either directly, or through bioactivation, uncovered an unexpected allosteric *agonist* activity at mGlu₅, a pharmacological profile associated with epileptiform activity and a target mediated AE liability.^{19,20,24} To test the viability of alternate HBA pharmacophores fragments like those found within the Merz tetralone scaffolds, we utilized a recently developed 5,6-bicyclic pyrazole lactam nucleus²⁵ as a template to test this hypothesis. To this end we focused on target **11**, which was envisioned to be synthesized via a Dieckmann condensation followed by Krapcho decarboxylation from key intermediate **9**. Synthesis of the initial proof-of-concept target ketone **11** began with prepreparation of known pyrazole ester **8** (Scheme 1). Subjection of phenoxyacetone to sodium ethoxide and addition of the resulting enolate to diethyl oxalate yielded β-diketone **7**. Condensation with hydrazine afforded the desired pyrazole ester **8**, which was carried forward without purification. Unfortunately, alkylation of **8** with ethyl 4-bromobutyrate and NaH in THF at 0 °C afforded exclusively undesired regioisomer **9'**. A screen of bases and solvents (LiOH, KOH, K₂CO₃, Cs₂CO₃, KO^tBu, LHMDS; MeCN, toluene, DMSO, DMF)

revealed that K_2CO_3 in DMF were optimal for alkylation of **8**, yielding in a 3:1 mixture of regioisomers **9** and **9'** (69% isolated yield **9**). With diester **9** in hand, Dieckmann condensation (KO^tBu , toluene, reflux) successfully afforded bicyclic β -ketoester **10** in 81% yield. LiCl mediated Krapcho decarboxylation provided access to ketone **11** in 77% yield, and was found to be more efficient than H_2SO_4 mediated decarboxylation (62% yield, 24 h).

With access to dihydropyrazolopyridin-one **11**, a number of analogs were synthesized to test the effect of hydrogen bond acceptors and donors in the northern region of the molecule and to probe the effect of steric bulk in the northern and eastern regions. To this end, a variety of keto-analogs with eastern substituents (**12**), alkyl ether analogs (**13**), alcohol analogs (**14**), and amine analogs (**15**) were prepared (Scheme 2). Eastern alkyl ketone analogs **12** were synthesized via enolate formation of **11** with NaH in THF followed by addition to alkyl halides (10–75% yield). Ketone analogs bearing eastern aryl groups were accessed *via* $Pd[P(t-Bu)_3]_2$ catalyzed α -arylation with aryl bromides in 43–85% yield.²⁶ However, α -arylation with substrate **11** under these and a variety of standard conditions exhibited a limited substrate scope and was incompatible with heteroaryl halides.

In parallel, the ketone moiety was replaced with alkyl ethers to test the impact of an ether hydrogen bond acceptor and the effect of steric bulk in the northern region of the molecule. Ether analogs **13** were prepared by carbonyl reduction of **11** with $NaBH_4$ (83% yield) followed by treatment with NaH in DMF and addition of alkyl halides. A limited number of analogs were also prepared from ketone analogs **12** bearing eastern substituents to test the effect of steric bulk at the eastern and northern regions of the scaffold.

Analogs containing northern hydrogen bond donors were pursued as shown in Scheme 2 through preparation of secondary and tertiary alcohols and secondary amines. Tertiary alcohols **14** were accessed by Grignard addition to ketone **11** in 50–83% yield or reaction with Ruppert's reagent (54% yield). Amine analogs **15** were synthesized *via* $TiCl_4$ mediated reductive amination (42–90% yield). In addition, selected analogs bearing tertiary amines were prepared.

The SAR are shown in Tables 1 – 3. Ketone **11** and analogs **12** are shown in Table 1, with the dihydropyrazolopyridin-one scaffold gratifyingly affording a number of highly potent analogs with moderate to high efficacy (52–96% Glu max). Parent ketone **11** exhibits excellent potency (129 nM); at a MW = 242, containing 18 non-hydrogen atoms, and a cLogP of 1.7, **11** displays excellent ligand efficiency metrics with an LE and LELP of 0.52 and 3.2, respectively.²⁷ In both human and rat mGlu selectivity panels, **11** was highly selective for mGlu₅ (mGlu_{1–3},^{6–8} > 10 μM). The presence of alkyl and aryl groups in the eastern region of the scaffold were well tolerated and often led to modest increases in potency. In particular, introduction of α -aryl groups (**12c**, **12d**), and spirocycle **12f** improved potency ~3-fold in relation to parent ketone **11**. These results suggest that the incorporation of some steric bulk in the eastern region of the molecule may be beneficial. However, the greatly reduced potency of dibenzyl analog **12g** and the diminished activity of disubstituted analogs **12h** and **12i** demonstrate limited steric bulk is required for optimal potency.

Encouraged by these results, we replaced the ketone hydrogen bond acceptor with alkyl ethers to ascertain the effect of this hydrogen bond acceptor and to determine whether steric bulk could be tolerated in the northern region of the scaffold (Table 2, **13**). This modification proved to be detrimental, as ether derivatives **13** displayed a greatly reduced potency in comparison to ketone **11**, with benzyl ether **13e** representing the only submicromolar modulator. Analogs bearing eastern substituents in addition to the northern alkyl ether were synthesized and methyl ester **13b**, bearing geminal α -methyl groups, displayed increased potency (796 nM) over des-methyl analog **13a**; however, the overall poor potency of alkyl ether analogs **13a–e** suggested a preference for the ketone moiety as a hydrogen bond acceptor at the allosteric binding site.

Evaluation of tertiary alcohols **14a–g** (Table 2), representing a desirable moiety to enhance physicochemical properties, revealed a similar loss of potency upon modification of the ketone as no analogs within the series achieved sub-micromolar potency. Direct comparison of ketone **11** to secondary alcohol **14a** revealed a drastic loss of potency (~15-fold). This was a surprising result given the minimal decrease in potency reported within the Merz tetralone acetylene series upon reduction of the ketone to the secondary alcohol (Figure 1, ~5-fold from **5** to **6**).²³ The introduction of steric bulk at R₂ slightly improved potency (**14c**, **14f–g**), while incorporation of the trifluoromethyl moiety (**14e**) further diminished activity. In contrast to picolinamide acetylenes containing a chiral hydroxyl moiety no agonist activity was observed for the more active quaternary carbinols (e.g. **14c** and **14g**); however, PAM potency is generally two orders of magnitude lower.²⁴

In parallel, analogs bearing northern amines were examined (Table 3, **15a–n**). While still possessing decreased potency relative to ketone analogs **11**, these analogs were found to afford better results than ether analogs **13** and alcohol analogs **14**. Primary amine **15a** was only weakly active, but incorporation of alkyl, aryl, and benzyl groups were beneficial for potency. Furthermore, both secondary and tertiary amines were found to be tolerated. Although undesirable, the potency displayed by aniline **15e** (269 nM) presented a promising starting point. A number of benzyl amine analogs were pursued as aniline replacements, with benzyl amine congener **15f** displaying a ~2-fold loss in potency relative to **15e**. Methylation to yield tertiary amine **15h** did not significantly alter potency, but introduction of geminal methyl groups β to the amine (**15g**) greatly reduced potency, demonstrating that increased steric bulk is not well tolerated within amines of type **15**. The 3-fluorobenzyl amine **15i** and 4-methoxybenzylamine **15l** were identified as equipotent analogs versus aniline **15e**.

We next evaluated the DMPK profiles of selected analogs. While ketone **11** and keto analogs **12** represented the most potent analogs, we were concerned that the carbonyl could be a metabolic liability. In a hepatic microsomal intrinsic clearance assay ketone **11** displayed moderate to high *in vitro* metabolism with predicted hepatic clearance (CL_{HEP}) = 46.1 mL min⁻¹ kg⁻¹ in rat and 15.2 mL min⁻¹ kg⁻¹ in human. Plasma protein binding experiments revealed that **11** was highly unbound (21% unbound in rat plasma, 23% unbound in human plasma,) and stable in plasma from both species (4 hr incubation; 37 °C). Analysis of the inhibition of the major cytochrome P450 (CYP) enzymes demonstrated that

11 has moderate inhibitory activity at 1A2 (6.2 μM), with no activity observed against the other major CYPs tested (2C9, 2D6, 3A4). Dimethyl analog **12e** displayed higher predicted clearance, near hepatic blood flow (64.4 $\text{mL min}^{-1} \text{kg}^{-1}$ in rat and 17.6 $\text{mL min}^{-1} \text{kg}^{-1}$ in human), with a reduced yet attractive fraction unbound (7% unbound in rat plasma, 10% unbound in human plasma). Like PAM **11**, **12e** displayed modest inhibitory activity at 1A2 (7.3 μM). α -Aryl congener **12c**, the most potent mGlu₅ PAM from this study as a racemic mixture (rat EC_{50} = 35 nM), was rapidly turned over *in vitro* (CL_{HEP} = 61.6 $\text{mL min}^{-1} \text{kg}^{-1}$ in rat and 16.0 $\text{mL min}^{-1} \text{kg}^{-1}$ in human) and was moderate to highly bound across species (3.2% unbound in rat plasma, 0.8% unbound in human plasma). The high *in vitro* metabolic turnover for the series was ultimately confirmed in a rat PK study (0.2 mg/kg, intravenous cassette paradigm, male Sprague-Dawley, n = 2) using PAM **12c**. As expected, **12c** proved to be a highly cleared compound *in vivo* with super hepatic clearance (rat CL_{p} = 120 $\text{mL min}^{-1} \text{kg}^{-1}$).

Given the poor DMPK profile of the keto analogs, benzylamine analog **15f** was next profiled in order to determine if replacement of the carbonyl with the secondary amine might afford improved metabolic stability. Although PAM **15f** maintained reasonable fraction unbound (f_{u} = 0.02 human plasma, f_{u} = 0.03 rat plasma), **15f** and other members in the amine series were highly metabolized *in vitro* (**15f**, CL_{HEP} = 68.1 $\text{mL min}^{-1} \text{kg}^{-1}$ rat, 18.8 $\text{mL min}^{-1} \text{kg}^{-1}$ human).

Based on metabolic soft-spot analysis from related ether series developed in our laboratories, oxidative metabolism of the electron rich western phenoxy moiety was believed to be a major contributor to the observed metabolic instability. In an effort to address this suspected instability, we prepared a series of *benzyloxy* analogs from 5-benzyloxy-2*H*-pyrazole-3-carboxylic acid ethyl ester in a fashion analogous to the phenoxy analogs shown in Scheme 1. The key benzyloxy comparators, activities, and *in vitro* metabolism data are summarized in Figure 2. Interestingly, the benzyloxy ketone **16**, which differs from **11** by virtue of the ether linker, was found to be inactive and maintained a poor metabolic profile. Benzyloxy ketone analogs bearing eastern substituents (**17**, **18**) and benzyl amine derivative **19** surprisingly regained activity, though potency was slightly diminished in comparison with their respective phenoxy congeners.

Once again, the metabolic profiles remained problematic (**16–18**, CL_{HEP} > 55 $\text{mL min}^{-1} \text{kg}^{-1}$ rat, >13 $\text{mL min}^{-1} \text{kg}^{-1}$ human) and metabolic soft-spot analysis in a related series suggested oxidative debenzoylation was likely a contributing factor. Based on our recently disclosed 1,3-azole containing tetrahydrobenzothiazole mGlu₅ PAM scaffold,²¹ the alternative 5,6-bicyclic thiazole ketone **20** was prepared to examine the effect on potency and metabolic stability relative to the pyrazole 5,6-bicyclic ring systems. Comparator thiazole **20** displayed only a ~3-fold reduction in potency versus **11**; however, compound **20** was highly metabolized *in vitro* based upon predicted hepatic clearance in human and rat (Figure 2). Lastly, unable to improve the DMPK profile with either western ether or core variations, we attempted a difluoro moiety as an alternate hydrogen bond acceptor to replace the ketone. From ketone **11** difluoro congener **21** was prepared in 43% yield via reaction with Deoxo-Fluor at 40 °C (Scheme 3). Interestingly the difluoro moiety within **21** was

tolerated, affording a PAM with moderate potency (625 nM) and efficacy (52% Glu max); however, metabolic instability remained an issue, ultimately proving to be a fatal flaw throughout each of the series investigated despite having promising ligand efficiency metrics.

In summary, we have developed a set of highly potent mGlu₅ PAMs with high ligand efficiency, achieving potency comparable to acetylene-based mGlu₅ PAMs (**12c**, rat EC₅₀ = 35 nM).^{6,10,25} Compounds were profiled in a rat mGlu₅ cell line with low receptor expression and in contrast to picolinamide-based acetylene mGlu₅ modulators,²⁵ agonism was not detected for compounds within series **13–15** and compounds **17–21**. DMPK profiling demonstrated generally moderate to high fraction unbound; however, metabolic instability proved to be an insurmountable issue for these novel mGlu₅ chemotypes. Studies within 5,6-pyrazole bicyclics that retain an amide structural element²⁵ are ongoing and will be communicated in due course.

Acknowledgments

Vanderbilt Center for Neuroscience Drug Discovery (VCNDD) research was supported by grants from Janssen, The Pharmaceutical Companies of Johnson & Johnson and in part by the NIH (NS031373, MH062646).

References and Notes

1. Conn PJ, Lindsley CW, Jones CK. Trends Pharmacol Sci. 2009; 30:25–31. [PubMed: 19058862]
2. Williams DL Jr, Lindsley CW. Curr Top Med Chem. 2005; 5:825–846. [PubMed: 16178729]
3. Lindsley CW, Wolkenberg SE, Shipe WD, Williams DL Jr. Curr. Opin. Drug. Disc. Dev. 2005; 8:449–457.
4. Chavez-Noriega LE, Marino MJ, Schaffhauser H, Campbell UC, Conn PJ. Curr. Neuropharmacol. 2005; 3:9–34.
5. Chavez-Noriega LE, Schaffhauser H, Campbell UC. Curr Drug Targets CNS Neurol Disord. 2002; 1:261–281. [PubMed: 12769619]
6. Stauffer SR. ACS Chem Neurosci. 2011; 2:450–470. [PubMed: 22860171]
7. Kinney GG, O'Brien JA, Lemaire W, Burno M, Bickel DJ, Clements MK, Chen TB, Wisnoski DD, Lindsley CW, Tiller PR, Smith S, Jacobson MA, Sur C, Duggan ME, Pettibone DJ, Conn PJ, Williams DL Jr. J Pharmacol Exp Ther. 2005; 313:199–206. [PubMed: 15608073]
8. Le Poul, E.; Bessis, AS.; Lutgens, R.; Bonnet, B.; Rocher, JP.; Epping-Jordan, MP.; Mutel, V. 5th International Metabotropic Glutamate Receptors Meeting; 2005; Taormina, Italy.
9. Liu F, Grauer S, Kelley C, Navarra R, Graf R, Zhang G, Atkinson PJ, Popielek M, Wantuch C, Khawaja X, Smith D, Olsen M, Kouranova E, Lai M, Pruthi F, Pulicicchio C, Day M, Gilbert A, Pausch MH, Brandon NJ, Beyer CE, Comery TA, Logue S, Rosenzweig-Lipson S, Marquis KL. J Pharmacol Exp Ther. 2008; 327:827–839. [PubMed: 18753411]
10. Rodriguez AL, Grier MD, Jones CK, Herman EJ, Kane AS, Smith RL, Williams R, Zhou Y, Marlo JE, Days EL, Blatt TN, Jadhav S, Menon UN, Vinson PN, Rook JM, Stauffer SR, Niswender CM, Lindsley CW, Weaver CD, Conn PJ. Mol Pharmacol. 2010; 78:1105–1123. [PubMed: 20923853]
11. Gastambide F, Cotel MC, Gilmour G, O'Neill MJ, Robbins TW, Tricklebank MD. Neuropsychopharmacology. 2012; 37:1057–1066. [PubMed: 22129780]
12. Gilmour G, Broad LM, Wafford KA, Britton T, Colvin EM, Fivush A, Gastambide F, Getman B, Heinz BA, McCarthy AP, Prieto L, Shanks E, Smith JW, Taboada L, Edgar DM, Tricklebank MD. Neuropharmacology. 2013; 64:224–239. [PubMed: 22884720]
13. Gastambide F, Gilmour G, Robbins TW, Tricklebank MD. Neuropharmacology. 2013; 64:240–247. [PubMed: 22884612]

14. Zhou Y, Manka JT, Rodriguez AL, Weaver CD, Days EL, Vinson PN, Jadhav S, Hermann EJ, Jones CK, Conn PJ, Lindsley CW, Stauffer SR. 2010; 1:433–438.
15. Gregory KJ, Herman EJ, Ramsey AJ, Hammond AS, Byun NE, Stauffer SR, Manka JT, Jadhav S, Bridges TM, Weaver CD, Niswender CM, Steckler T, Drinkenburg WH, Ahnaou A, Lavreysen H, Macdonald GJ, Bartolome JM, Mackie C, Hrupka BJ, Caron MG, Daigle TL, Lindsley CW, Conn PJ, Jones CK. *J Pharmacol Exp Ther.* 2013; 347:438–457. [PubMed: 23965381]
16. Spear N, Gadiant RA, Wilkins DE, Do M, Smith JS, Zeller KL, Schroeder P, Zhang M, Arora J, Chhajlani V. *Eur J Pharmacol.* 2011; 659:146–154. [PubMed: 21335002]
17. Manka JT, Vinson PN, Gregory KJ, Zhou Y, Williams R, Gogi K, Days E, Jadhav S, Herman EJ, Lavreysen H, Mackie C, Bartolome JM, Macdonald GJ, Steckler T, Daniels JS, Weaver CD, Niswender CM, Jones CK, Conn PJ, Lindsley CW, Stauffer SR. *Bioorg Med Chem Lett.* 2012; 22:6481–6485. [PubMed: 22981332]
18. Parmentier-Batteur S, Hutson PH, Menzel K, Uslaner JM, Mattson BA, O'Brien JA, Magliaro BC, Forest T, Stump CA, Tynebor RM, Anthony NJ, Tucker TJ, Zhang XF, Gomez R, Huszar SL, Lambeng N, Faure H, Le Poul E, Poli S, Rosahl TW, Rocher JP, Hargreaves R, Williams TM. *Neuropharmacology.* 2013
19. Rook JM, Noetzel MJ, Pouliot WA, Bridges TM, Vinson PN, Cho HP, Zhou Y, Gogliotti RD, Manka JT, Gregory KJ, Stauffer SR, Dudek FE, Xiang Z, Niswender CM, Daniels JS, Jones CK, Lindsley CW, Conn PJ. *Biol Psychiatry.* 2013; 73:501–509. [PubMed: 23140665]
20. Bridges TM, Rook JM, Noetzel MJ, Morrison RD, Zhou Y, Gogliotti RD, Vinson PN, Xiang Z, Jones CK, Niswender CM, Lindsley CW, Stauffer SR, Conn PJ, Daniels JS. *Drug Metab Dispos.* 2013; 41:1703–1714. [PubMed: 23821185]
21. Bartolome-Nebreda JM, Conde-Ceide S, Delgado F, Iturrino L, Pastor J, Pena MA, Trabanco AA, Tresadern G, Wassvik CM, Stauffer SR, Jadhav S, Gogi K, Vinson PN, Noetzel MJ, Days E, Weaver CD, Lindsley CW, Niswender CM, Jones CK, Conn PJ, Rombouts F, Lavreysen H, Macdonald GJ, Mackie C, Steckler T. *J Med Chem.* 2013; 56:7243–7259. [PubMed: 23947773]
22. Turlington M, Malosh C, Jacobs J, Manka JT, Noetzel MJ, Vinson PN, Jadhav S, Herman EJ, Lavreysen H, Mackie C, Bartolome-Nebreda JM, Conde-Ceide S, Martin-Martin ML, Tong HM, Lopez S, Macdonald GJ, Steckler T, Daniels JS, Weaver C, Niswender CM, Jones C, Conn JP, Lindsley CW, Stauffer SR. *J Med Chem.* 2014 submitted.
23. Vanejevs M, Jatzke C, Renner S, Muller S, Hechenberger M, Bauer T, Klochkova A, Pyatkin I, Kazyulkin D, Aksenova E, Shulepin S, Timonina O, Haasis A, Gutcaits A, Parsons CG, Kauss V, Weil T. *J Med Chem.* 2008; 51:634–647. [PubMed: 18173231]
24. Turlington M, Noetzel MJ, Chun A, Zhou Y, Gogliotti RD, Nguyen ED, Gregory KJ, Vinson PN, Rook JM, Gogi KK, Xiang Z, Bridges TM, Daniels JS, Jones C, Niswender CM, Meiler J, Conn PJ, Lindsley CW, Stauffer SR. *J Med Chem.* 2013; 56:7976–7996. [PubMed: 24050755]
25. Conn PJ, Lindsley CW, Stauffer SR, Bartolome- Nebreda JM, Conde-Ceide S, Macdonald GJ, Tong HM, Jones CK, Alcazar-Vaca MJ, Andres-Gil JI, Malosh C. 2012 WO 2012083224.
26. Kawatsura M, Hartwig JFJ. *Am. Chem. Soc.* 1999; 121:1473–1478.
27. Keseru GM, Makara GM. *Nat Rev Drug Discov.* 2009; 8:203. [PubMed: 19247303]

mGlu₅ PAMs possessing northern hydrogen bond acceptor:

Merz ketone and carbinol northern hydrogen bonding partners:

Figure 1.
Representative mGlu₅ PAMs with amide and non-amide hydrogen-bond acceptor (HBA) pharmacophores.

16

Inactive

 $CL_{\text{HEP}} = 56.8 \text{ mL min}^{-1} \text{ kg}^{-1}$ (rat) $17.2 \text{ mL min}^{-1} \text{ kg}^{-1}$ (human) **17**rat $EC_{50} = 228 \text{ nM}$, $56 \pm 4.1 \text{ GluMax}$
($pEC_{50} = 6.64 \pm 0.04$) $CL_{\text{HEP}} = 59.8 \text{ mL min}^{-1} \text{ kg}^{-1}$ (rat)
 $16.3 \text{ mL min}^{-1} \text{ kg}^{-1}$ (human) **18**rat $EC_{50} = 95 \text{ nM}$, $48 \pm 2.7 \text{ GluMax}$
($pEC_{50} = 7.02 \pm 0.15$) $CL_{\text{HEP}} = 61.2 \text{ mL min}^{-1} \text{ kg}^{-1}$ (rat)
 $13.8 \text{ mL min}^{-1} \text{ kg}^{-1}$ (human) **19**rat $EC_{50} = 618 \text{ nM}$, $48 \pm 2.1 \text{ GluMax}$
($pEC_{50} = 6.21 \pm 0.33$) CL_{HEP} not determined **20**rat $EC_{50} = 441 \text{ nM}$, $65 \pm 1.1 \text{ GluMax}$
($pEC_{50} = 6.36 \pm 0.05$) $CL_{\text{HEP}} = 61.4 \text{ mL min}^{-1} \text{ kg}^{-1}$ (rat)
 $19.1 \text{ mL min}^{-1} \text{ kg}^{-1}$ (human)

Figure 2.
Benzyloxy and thiazole ketone analogs.

Scheme 1.

Reagents and conditions: (a) Na, EtOH, 0 °C to rt, 2 h, 45%; (b) H₂NNH₂, EtOH, 80 °C, 1.5 h; (c) ethyl 4-bromobutyrate, K₂CO₃, DMF, rt, 18 h, (3:1 ratio **9**:**9'**), 69% **9** over 2 steps; (d) KO_tBu, toluene, rt to reflux, 1 h, 81%; (e) LiCl, H₂O, DMSO, 115 °C, 10 h, 77%.

Scheme 2.

Reagents and conditions: (a) NaH, THF, 0 °C; then RI or RBr, rt 3 h, 10–75% (b) ArBr, Pd(tBu₃P)₂, K₃PO₄, DMA, 80 °C, 18 h, 43–85% (c) NaBH₄, MeOH, 0 °C, 1 h, 65–80%; (d) NaH, DMF, 15 min; then RI or RBr 0 °C to rt, 16 h, 45–60%, (e) RMgBr, THF, –78 °C to rt, 50–83%; (f) TMSCF₃, TBAF (catalytic), THF, rt, 24 h, 54%; (g) TiCl₄, RNH₂, CH₂Cl₂, rt, 18 h; then NaCNBH₃, MeOH, rt, 30 min, 42–90%. All compounds were purified by silica-phase automated chromatography or preparative RP-HPLC.

Scheme 3.

Reagents and conditions a: Deoxo-Fluor/ CH_2Cl_2 (1:1), 40 °C, 60 h, 43%.

Table 1

Structures and activities of **11** and Ketone analogs **12**.^a

Cmpd	R ₁	R ₂	Rat pEC ₅₀ ^b (±SD)	EC ₅₀ (nM)	GluMax ^b (±SD)
11	H	H	6.89 (±0.05)	129	66 (±3.0)
12a	H	Me	6.55 (±0.17)	285	76 (±2.3)
12b	H		6.91 (±0.10)	124	73 (±3.4)
12c	H		7.45 (±0.07)	35	66 (±2.5)
12d	H		7.36 (±0.11)	43	68 (±3.9)
12e	Me	Me	7.06 (±0.02)	86	70 (±1.0)
12f			7.32 (±0.08)	48	60 (±2.5)
12g			>5.0	> 10,000	37 (±0.7)
12h	Me		6.64 (±0.06)	228	58 (±1.7)
12i	Me		6.18 (±0.01)	654	52 (±3.7)

^a HEK293 cells stably expressing ret mGlu5 receptor (ref. 24).

^b pEC₅₀ and Glu Max are average of three independent determinations performed in triplicate.

Table 2

Structures and activities of ether analogs **13** and tertiary alcohols **14**.^a

Cmpd	R ₁	R ₂	R ₃	Rat pEC ₅₀ ^b (±SD)	EC ₅₀ (mM)	GluMax ^b (±SD)
<i>Ether analogs 13</i>						
13a	Me	H	H	5.54 (±0.19)	2907	43 (±1.5)
13b	Me	H	Me	6.10 (±0.07)	796	75 (±3.4)
13c		H	H	5.60 (±0.02)	2518	43 (±4.9)
13d		H	H	6.00 (±0.09)	989	70 (±3.8)
13e		H	Me	5.63 (±0.07)	2325	64 (±6.9)
<i>Alcohol analogs 14</i>						
14a	H	H	H	5.70 (±0.07)	2009	47 (±8.0)
14b	H	H	Me	5.36 (±0.14)	4405	60 (±8.0)
14c	H	Me	H	5.78 (±0.09)	1678	39 (±2.7)
14e	H	CF ₃	H	5.42 (±0.07)	3781	54 (±5.6)
14f	H	Bu	H	5.74 (±0.01)	1822	44 (±0.7)
14g	H		H	5.92 (±0.01)	1199	49 (±5.1)

^a HEK293 cells stably expressing rat mGlu5 receptor (ref. 24).

^b pEC₅₀ and Glu Max are average of three independent determinations performed in triplicate.

Table 3

Structures and activities of amine analogs **15**.^a

Cmpd	NR ₁ R ₂	R ₃	Rat pEC ₅₀ ^b (±SD)	EC ₅₀ (nM)	GluMax ^b (±SD)
15a		H	>5.0	> 10,000	45 (±3.1)
15b		H	5.75 (±0.03)	1796	50 (±5.5)
15c		H	5.63 (±0.02)	2363	52 (±8.2)
15d		H	6.06 (±0.12)	870	71 (±10.4)
15e		H	6.57 (±0.06)	269	62 (±3.3)
15f		H	6.20 (±0.15)	632	74 (±0.2)
15g		Me	5.44 (±0.05)	3,618	65 (±2.3)
15h		H	6.16 (±0.05)	686	71 (±1.6)
15i		H	6.56 (±0.13)	275	75 (±3.7)
15j		H	6.50 (±0.06)	316	69 (±2.8)

Cmpd	NR ₁ R ₂	R ₃	Rat pEC ₅₀ ^b (±SD)	EC ₅₀ (nM)	GluMax ^b (±SD)
15k		H	6.20 (±0.14)	637	65 (±1.8)
15l		H	6.54 (±0.12)	290	60 (±0.8)
15m		H	5.55 (±0.06)	2840	59 (±5.0)
15n		H	5.59 (±0.04)	2573	68 (±1.7)

^a HEK293 cells stably expressing ret mGlu5 receptor (ref. 24).

^b pEC₅₀ and Glu Max are average of three independent determinations performed in triplicate.