

Discovery of VU0409551/JNJ-46778212: An mGlu₅ Positive Allosteric Modulator Clinical Candidate Targeting Schizophrenia

Susana Conde-Ceide,[†] Carlos M. Martínez-Vituro,[†] Jesús Alcázar,[‡] Pedro M. Garcia-Barrantes,[‡] Hilde Lavreysen,[§] Claire Mackie,^{||} Paige N. Vinson,^{‡,¶} Jerri M. Rook,^{‡,¶} Thomas M. Bridges,^{‡,¶} J. Scott Daniels,^{‡,¶} Anton Megens,[§] Xavier Langlois,[§] Wilhelmus H. Drinkenburg,[§] Abdellah Ahnaou,[§] Colleen M. Niswender,^{‡,¶} Carrie K. Jones,^{‡,¶} Gregor J. Macdonald,[§] Thomas Steckler,[§] P. Jeffrey Conn,^{‡,¶} Shaun R. Stauffer,^{‡,¶} José Manuel Bartolomé-Nebreda,^{*,†} and Craig W. Lindsley^{*,‡,¶}

[†]Neuroscience Medicinal Chemistry and [‡]Discovery Sciences Lead Discovery, Janssen Research and Development, Jarama 75A, 45007 Toledo, Spain

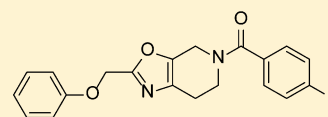
[§]Neuroscience and ^{||}Discovery Sciences ADME/Tox, Janssen Research and Development, Turnhoutseweg 30, B-2340 Beerse, Belgium

[‡]Department of Pharmacology and [¶]Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, Nashville, Tennessee 37232, United States

Supporting Information

ABSTRACT: Herein, we report the structure–activity relationship of a novel series of (2(phenoxy)methyl)-6,7-dihydrooxazolo[5,4-*c*]pyridine-5(4*H*)-yl(aryl)methanones as potent, selective, and orally bioavailable metabotropic glutamate receptor subtype 5 (mGlu₅) positive allosteric modulators (PAMs). On the basis of its robust *in vitro* potency and *in vivo* efficacy in multiple preclinical models of multiple domains of schizophrenia, coupled with a good DMPK profile and an acceptable therapeutic window, **17a** (VU0409551/JNJ-46778212) was selected as a candidate for further development.

KEYWORDS: Positive allosteric modulator (PAM), metabotropic glutamate receptor 5 (mGlu₅), 4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine, VU0409551, JNJ-46778212, schizophrenia



17a, VU0409551/JNJ-46778212

Schizophrenia is a complex and devastating psychiatric disorder that has been managed for decades with monoaminergic (dopamine and serotonin) targeted therapeutics, resulting in adverse effect liabilities and only limited treatment of the multiple symptom domains.¹ To effectively address this major unmet medical need, other neurotransmitter systems and circuits, such as those of the glutamatergic system, have emerged as high priority targets.^{2,3} Of these, the metabotropic glutamate receptor subtype 5 (mGlu₅), due to its localization in brain regions implicated in schizophrenia and its colocalization with *N*-methyl-D-aspartate (NMDA) receptors, is of great interest in the context of the NMDA receptor hypofunction hypothesis of schizophrenia.^{4–6} Positive allosteric modulation of mGlu₅, pioneered by our laboratories^{7,8} and now demonstrated by multiple chemotypes and laboratories (Figure 1), has provided key target validation data in a diverse array of preclinical antipsychotic and cognition models.⁶ However, issues remain with potential target-based neurotoxicity and seizure liability due to ago-PAM activity, high fold-shift and/or efficacy, or other unknown mechanisms that have somewhat diminished enthusiasm for this novel mechanism.^{9,10} Previous target validation attributed the efficacy of mGlu₅ PAMs, as well as adverse effect liability, to the potentiation of NMDA receptor currents. Emerging data on stimulus bias within allosteric GPCR signaling, however, may offer an approach to potentially mitigate these undesired effects that reduce the therapeutic

window and preclude development.^{11,12} In this Letter, we detail a unique industrial–academic collaboration between Janssen Research and Development and the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD)¹³ that led to the discovery of a potent, selective, and orally bioavailable mGlu₅ PAM clinical candidate **17a** that displays robust antipsychotic and cognition-enhancing efficacy in the absence (stimulus bias) of direct potentiation of NMDA receptor modulation. This is the first disclosure of the SAR and preclinical candidate profile of **17a**.

The Janssen–VCNDD collaboration¹³ initiated around the chemical series **12** and **13**, derived from independent SAR evaluation of HTS hits **10** and **11**, followed by subsequent hybridization of the series and lead optimization (Figure 2).^{14–21} While the VCNDD initially retained the phenyl acetylene moiety and explored Eastern SAR, Janssen in parallel was optimizing the Western linker region, improving metabolic stability, and identified the benzyloxy linker.^{14–20} We then evaluated a diverse array of heterobicyclic scaffolds utilizing optimal Eastern and Western moieties, providing novel mGlu₅ PAM chemotypes, minimally represented by **14–16**, which

Received: May 4, 2015

Accepted: May 20, 2015

Published: May 20, 2015

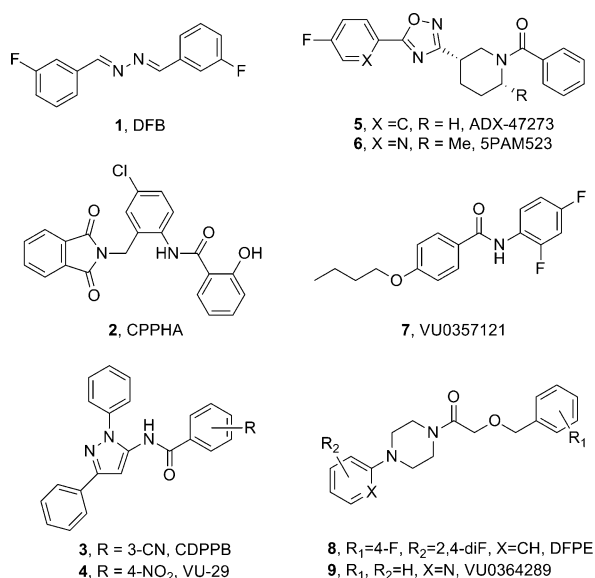


Figure 1. Representative, first generation MPEP-site and non-MPEP-site mGlu₅ PAMs 1–9.

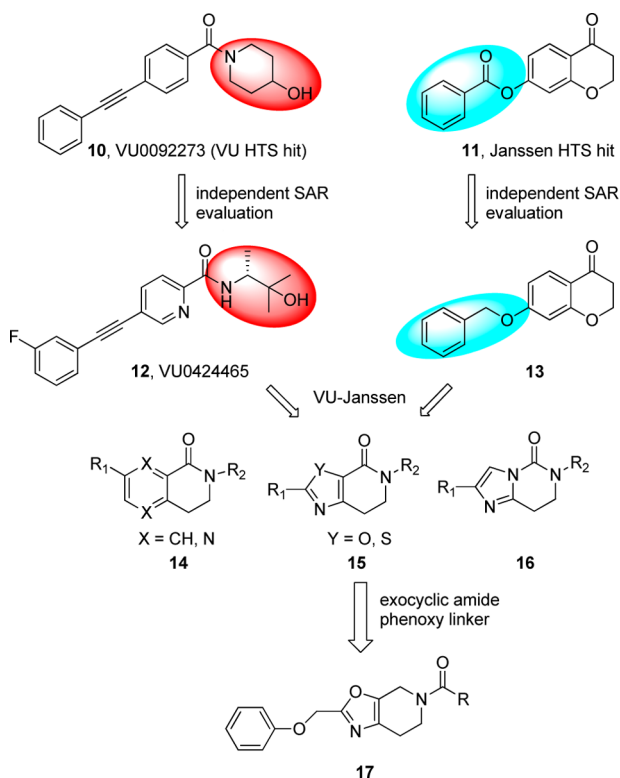
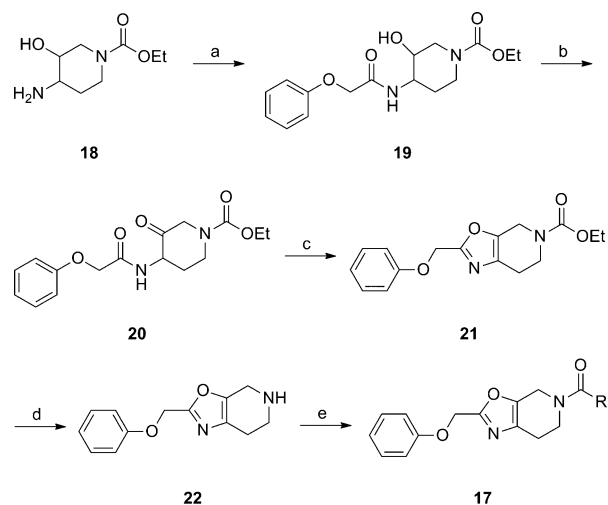


Figure 2. Chemical evolution of a series of (2(phenoxyethyl)-6,7-dihydrooxazolo[5,4-c]pyridine-5(4H)-yl(aryl)methanones 17 that provided the first mGlu₅ PAM clinical candidate.^{14–20}

afforded improved DMPK profiles.^{14–20} Further optimization efforts incorporated a phenoxy linker¹⁹ as well as exocyclic amide moieties in the 5,6-heterobiaryl scaffolds, which provided series 17.

As shown in Scheme 1, analogues 17 were prepared in five steps from commercial materials in good to excellent overall yields.²¹ Racemic amino alcohol 18 was acylated with 2-phenoxyacetyl chloride to provide 19 in 89% yield. Dess–Martin periodinane oxidation provided the corresponding

Scheme 1. Synthesis of Analogues 17^a



^aReagents and conditions: (a) 2-phenoxyacetyl chloride, Et₃N, DCM, 0 °C to rt, 1 h, 89%; (b) Dess–Martin periodinane, DCM, 1 h, rt, 86%; (c) POCl₃, dioxane, 100 °C, 1.5 h, 80%; (d) LiOH, dioxane/H₂O, 120 °C, 48 h, 65%; (e) RCOCl, Et₃N, DCM, 0 °C to rt, 1 h, 65–93%.

ketone 20 and the substrate for dehydration to yield the bicyclic oxazole core 21 in 77% overall yield for the two steps. Basic removal of the ethyl carbamate delivered secondary amine 22, which could be acylated under standard amide coupling conditions or by treatment with the desired acid chloride to afford the exocyclic amide congeners 17 in yields ranging from 65 to 93%.²¹

Representative SAR for this series is detailed in Table 1. Generally, aliphatic, cycloalkyl, and nonbasic aliphatic heterocyclic amides were inactive as mGlu₅ PAMs. While a number of functionalized aryl amide and 5-membered aromatic heterocyclic amide congeners were moderately active, they suffered from poor stability, solubility, and/or DMPK properties. Uniformly, fluorophenyl amides were found to be preferred, providing active mGlu₅ PAMs 17a,e-j with EC₅₀s ranging from 100 to 500 nM and with high efficacy (66–92% Glu Max). Interestingly, the 3- and 4-pyridyl amides (17l and 17m) were potent and efficacious mGlu₅ PAMs, but the 2-pyridyl analogue (17k) was inactive. Extensive in vitro and in vivo DMPK profiling quickly eliminated the majority of analogues from consideration as clinical candidates, as regioisomeric fluoroamides 17a,e-j displayed a dynamic range of metabolic stabilities, solubility, and PK, with most proving unfavorable in one or more parameters. From this effort, 17a emerged as an mGlu₅ PAM with the most balanced profile (*vide infra*) and worthy of further development, with no species differences (activity at rat mGlu₅ was comparable to human (rat EC₅₀ = 235 nM, pEC₅₀ = 6.63 ± 0.08, 74 ± 2% Glu Max).²²

The molecular pharmacology profile of 17a is highlighted in Figure 3. In the presence of an EC₂₀ concentration of glutamate, 17a potentiates the human mGlu₅ response in a concentration-dependent manner resulting in an EC₅₀ of 260 nM, with 84% Glu Max (Figure 3A). Analogue 17a (10 μM) also induces ~10-fold shift of the glutamate CRC on human mGlu₅ (Figure 3B). Moreover, 17a is an MPEP site PAM, fully displacing [³H]-mPEPy (Figure 3C), and is highly selective for mGlu₅ relative to mGlu_{1–4,6–8} at 10 μM (Figure 3D).²²

Table 1. SAR of Analogues of mGlu₅ PAM 17

17

Entry	R	pEC ₅₀ (±SEM) ^a	EC ₅₀ (nM) ^a	Glu Max % (±SEM) ^a
17a		6.58±0.04	260	84±4
17b		<5 ^b	>10,000	53
17c		<5 ^b	>10,000	22
17d		<5 ^b	>10,000	32
17e		6.30±0.05	495	66±7
17f		6.96±0.03	108	78±5
17g		6.31±0.09	480	92±6
17h		6.42±.11	380	75±2
17i		6.46±0.07	343	77±4
17j		6.65±.08	220	85±6
17k		<5 ^b	>10,000	51
17l		6.32±0.10	470	75±4
17m		6.31±0.08	480	76±3

^aCalcium mobilization assay using HEK293 expressing human mGlu₅; values are the average of three or more independent determinations.

^bData obtained from a single experiment not replicated.

Evaluation of the *in vitro* DMPK and physicochemical properties of 17a supported continued progression through the preclinical candidate flowchart. Metabolic stability assessment across species indicated 17a was stable to microsomal incubation (MetStab h, r, d: 15%, 35%, 26% remaining after 15 min), low plasma protein binding was noted (f_u h, r, m, d: 3.2%, 7%, 24.1%, 9.6%), and f_u brain was favorable (3.7%).²¹ Based on the pK_a (<2.0), no salts were possible; however, the free base demonstrated acceptable solubility (8–9 mg/mL in 30% BCD, 35 μ g/mL in FaSSiF). PAM 17a possessed an exceptional cytochrome P450 profile (1A2, 2C9, 2D6, 3A4, IC₅₀ >25 μ M), and no 3A4 TDI or induction. CYP phenotyping indicated 2D6 and 3A4 as major contributors, and the major metabolite, *p*-hydroxylation of the naked

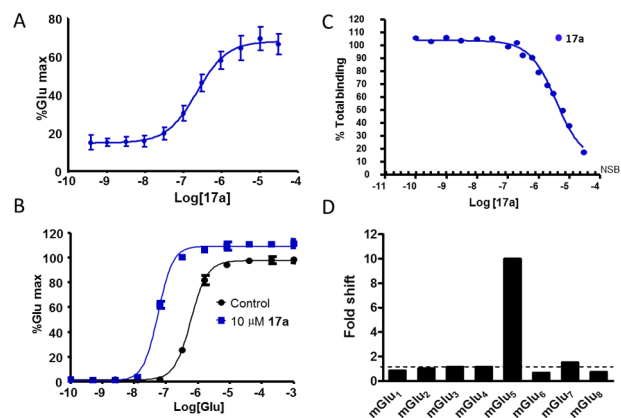


Figure 3. Molecular pharmacological profile of 17a. (A) Enhanced calcium release induced by suboptimal concentrations of glutamate (EC₂₀), the PAM CRC, with an EC₅₀ for potentiation of 260 nM. (B) Analogue 17a induces a 10-fold leftward shift of the glutamate CRC. (C) Binding study with [³H]-mPEPy, confirming an MPEP sight PAM (Human IC₅₀ = 4.37 μ M, 82%). (D) mGlu selectivity data (fold-shift at 10 μ M) showing that 17a is highly selective for mGlu₅. Each data point represents the mean \pm SD ($n = 3$).

Western phenyl ring, was inactive at mGlu₅.²¹ In terms of toxicity assessment, 17a was clean in AMES, a high content cytotoxicity assay (>30 μ M) and in GSH/CN trapping studies. *In vivo* pharmacokinetics for 17a were assessed across mouse, rat, and dog (Table 2), and moderate clearance across all three species was noted, with good half-lives and >40% oral bioavailability across species.²¹

Table 2. Pharmacokinetic Parameters for 17a

parameter	mouse ^a	rat ^a	dog ^a
dose (mg kg ⁻¹) iv/po	2.5/10	2.5/10	1/5
Cl (mL/min/kg) iv	39	24	12
Vd _{ss} (L/kg) iv	2.9	3.3	3.7
$t_{1/2}$ (h) iv	1.6	2.5	6.7
C _{max} (μ M) po	0.83	1.08	1.01
T _{max} (h) po	0.5	1.5	0.5
AUC _{0-inf} (ng·h/mL) po	1874	818	6460
F (%) po	44	96	51
brain/plasma (K_p)	1.0	2.3	

^aData reported as average of three animals.

In oral brain/plasma studies, 17a displayed excellent CNS penetration with K_p s of 1.0 and 2.3, for mouse and rat, respectively. Furthermore, 17a was also clean in a CV-relevant ion channel panel (hERG, Ca, Na channels, IC₅₀s >10 μ M) and was inactive in hERG patch clamp (22% inhibition @ 3 μ M). To confirm cardiovascular safety, 17a was also evaluated in an anesthetized guinea pig and standard CV dog models where no significant activities were noted, with a >80-fold window. Finally, ancillary pharmacology was assessed and found to be clean, with the exception of weak binding to MAO-B ($K_i = 6.4 \mu$ M).²²

In a preclinical assay predictive of antipsychotic-like activity, reversal of amphetamine-induced hyperlocomotion (AHL), 17a demonstrated robust dose-responsive efficacy (Figure 4) with a maximum reversal of ~78% at 100 mg/kg po and a minimum effective dose (MED) of 10 mg/kg po (ED₅₀ = 23 mg/kg). Moreover, only partial tolerance, but maintenance of efficacy, was noted after 7 days of subchronic dosing in this model.²¹

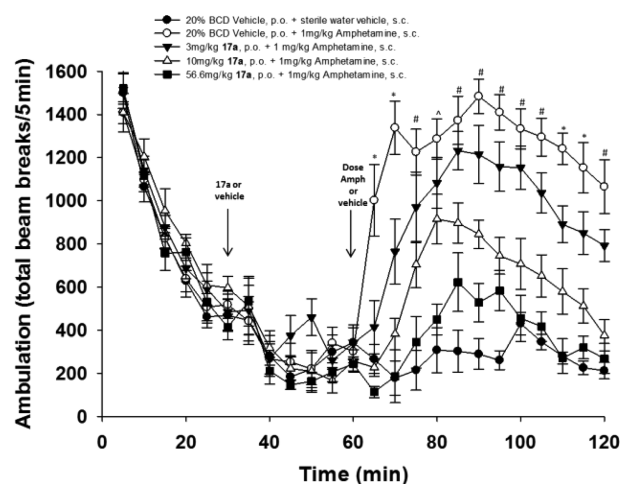


Figure 4. Analogue 17a has antipsychotic-like activity in rats and dose-dependently (3–56.6 mg/kg, po) reverses AHL. #, *, ^ $p < 0.05$ vs VAMP group, Dunnett's test.

Similar results were found when hyperlocomotion was induced by MK-801 and conditioned avoidance responding (CAR) with an ED_{50} of 65 mg/kg po.²² Consistent with current antipsychotics, 17a increased prefrontal dopamine levels (MED 10 mg/kg po) and absolutely no effect on prolactin levels in rats or catalepsy.²¹ In addition, 17a also induced septal cFos mRNA 153% (40 mg/kg po). The mGlu₅ PAM 17a was even more efficacious in several preclinical cognition models, showing a MED of 1 mg/kg po in contextual fear conditioning (CFC) and a MED of 3 mg/kg po in novel object recognition. These data strongly suggest that an mGlu₅ PAM may possess broader efficacy across multiple domains of schizophrenia, with fewer adverse events than existing antipsychotics.

mGlu₅ has a number of potential mechanism-mediated adverse events that must be considered and addressed before advancing into man.^{9–11} Previously, we reported that pure mGlu₅ PAMs do not possess seizure/epileptiform liabilities, as opposed to mGlu₅ agonists and ago-PAMs; thus, 17a, a pure mGlu₅ PAM in multiple cell lines and native systems, would avoid this key mechanism-based liability.^{11,23} Recent data with 6 suggests that mGlu₅ PAMs are neurotoxic and induce neuronal death in rodents, as assessed by increases in Fluoro-Jade C (FJC) staining, and that this may be related to large fold-shift and/or high efficacy.^{9–11} We assessed one of our historical ago-PAMs 12 in this paradigm and, similar to the Merck report, found FJC-positive neurons after acute, low dose (3 mg/kg i.p.) administration as well as seizure activity.²² In sharp contrast, we recently reported that 17a, a pure mGlu₅ PAM with high efficacy and large fold-shift, at a high dose of 120 mg/kg po for four consecutive days, did not induce FJC staining nor did it induce seizures in mice at doses >100-fold over the MED in AHL (CNS NOAEL of 108–147 $\mu\text{M}\cdot\text{h}$).²² Moreover, chronic dosing at 450 mg/kg po for 14 days also failed to elicit seizure activity in rats. The question at hand is what distinguished 17a from other mGlu₅ PAMs. As expected, 17a potentiates DHPG-induced long-term depression (LTD) and induces calcium mobilization and ERK phosphorylation; however, 17a does not potentiate mGlu₅ modulation of NMDA receptor currents nor NMDA receptor-dependent long-term potentiation (LTP), suggesting a unique signal bias for this mGlu₅ PAM that may contribute to the observed, favorable therapeutic window.²² From a conceptual point of view, it is

intriguing that selective mGlu₅ activation can provide antipsychotic and cognition-enhancing efficacy in the absence of potentiating NMDA receptor function.

Based on the favorable and unique profile of 17a, human PK predictions, based on trough plasma levels (400 ng/mL) from rat AHL and interspecies allometric scaling, led to predicted human clearance in the range of 1.5 to 3.6 mL/min/kg and with half-life of 10–24 h.²¹ Simulations of steady state dosing for 24 h coverage indicated 250–600 mg qd or 100–400 mg bid in man. If the 10-fold improved efficacy of CFC was employed (MED of 1 mg/kg), the dose required for plasma trough coverage drops considerably.²¹ However, in IND-enabling studies, chronic administration of 17a at a high dose of 360 mg/kg po for 30 days did induce FJC staining in a small number of rats. With limited occurrence only under high chronic dosing, these data raise the concern about potential human sensitivity to an mGlu₅ PAM; therefore, compound progression paused while other PAMs were profiled.

In summary, an industrial-academic collaboration between Janssen and the VCND developed an orally bioavailable mGlu₅ PAM for the treatment of schizophrenia via a fundamentally new molecular mechanism. Leveraging subject matter and drug discovery expertise across the two teams, coupled with a deep basic science component, enabled the joint project team to recognize and understand signal bias as a potential approach to afford an acceptable therapeutic window. Based on its *in vitro* and *in vivo* pharmacological and DMPK profiles, 17a (VU0409551/JNJ-46778212) was approved by Janssen as a preclinical candidate, and IND-enabling studies were initiated. Detailed findings will be reported in due course.

■ ASSOCIATED CONTENT

📄 Supporting Information

General methods for the synthesis and characterization of all compounds, and methods for the *in vitro* and *in vivo* DMPK protocols and supplemental figures. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.5b00181.

■ AUTHOR INFORMATION

Corresponding Authors

*Phone: 1 615-322-8700. Fax: 1 615-936-4381. E-mail: craig.lindsley@vanderbilt.edu.

*Phone: +34 925 245778. Fax: +34 925 245771. E-mail: jbartolo@its.jnj.com.

Author Contributions

C.W.L., J.M.B., P.J.C., S.R.S., C.M.N., and C.J.K. drafted/corrected the manuscript. C.M.V., J.A., P.M.G., and J.M.B. performed the chemical synthesis. C.W.L., J.M.B., P.J.C., S.R.S., C.M.N., J.M.K., C.J.K., T.S., G.M., C.M., and H.L. oversaw the target selection and interpreted the biological data. J.S.D., T.M.B., and C.M. performed the *in vitro* and *in vivo* DMPK studies. T.S., A.M., X.L., W.H.D., A.A., and C.K.J. performed the *in vivo* experiments. All authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): Both VCND and JNJ are actively developing mGlu₅ PAMs as therapeutic agents.

ACKNOWLEDGMENTS

The authors would also like to thank Dr. Brian Hrupka, Heidi Huysmans, Christ Nolten, Gerd Van Den Kieboom, and Sofie Versweyveld for their contribution with animal surgery and data collection.

ABBREVIATIONS

DCM, dichloromethane; AHL, amphetamine-induced hyperlocomotion; CFC, contextual fear conditioning; MED, minimum effective dose; LTD, long-term depression; metabotropic glutamate receptor, (mGlu); FJC, fluorjade; PAM, positive allosteric modulator

REFERENCES

- (1) Meltzer, H. Y. Treatment of schizophrenia and spectrum disorders: Pharmacotherapy, psychosocial treatments, and neurotransmitter interactions. *Biol. Psychiatry* **1999**, *46*, 1321–1327.
- (2) Goff, D. C.; Coyle, J. T. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am. J. Psychiatry* **2001**, *158*, 1367–1377.
- (3) Menniti, F. S.; Lindsley, C. W.; Conn, P. J.; Pandit, J.; Zagouras, P.; Volkman, R. A. Allosteric modulation for the treatment of schizophrenia: Targeting glutamatergic networks. *Curr. Top. Med. Chem.* **2013**, *13*, 26–54.
- (4) Conn, P. J.; Lindsley, C. W.; Jones, C. Allosteric modulation of metabotropic glutamate receptors as a novel approach for the treatment of schizophrenia. *Trends Pharmacol. Sci.* **2009**, *30*, 25–31.
- (5) Lecourtier, L.; Homayoun, H.; Tamagnan, G.; Moghaddam, B. Positive allosteric modulation of metabotropic glutamate 5 (mGlu₅) receptors reverses N-Methyl-D-aspartate antagonist-induced alteration of neuronal firing in prefrontal cortex. *Biol. Psychiatry* **2007**, *62*, 739–746.
- (6) Lindsley, C. W.; Stauffer, S. R. Metabotropic glutamate receptor 5 (mGlu₅) positive allosteric modulators for the treatment of schizophrenia: An historical perspective and a review of the patent literature. *Pharm. Patent Anal.* **2013**, *2*, 93–108.
- (7) O'Brien, J. A.; Lemaire, W.; Chen, T.-B.; Chang, R. S. L.; Jacobson, M. A.; Ha, S. N.; Lindsley, C. W.; Sur, C.; Pettibone, D. J.; Conn, J.; Williams, D. L. A family of highly selective allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGluR5). *Mol. Pharmacol.* **2003**, *64*, 731–741.
- (8) Lindsley, C. W.; Wisnoski, D. D.; Leister, W. H.; O'Brien, J. A.; Lemiere, W.; Williams, D. L., Jr.; Burno, M.; Sur, C.; Kinney, G. G.; Pettibone, D. J.; Iller, P. R.; Smith, S.; Duggan, M.E.; Hartman, G. D.; Conn, P. J.; Huff, J. R. Discovery of positive allosteric modulators for the metabotropic glutamate receptor subtype 5 from a series of N-(1,3-Diphenyl-1H-pyrazol-5-yl)benzamides that potentiate receptor function *in vivo*. *J. Med. Chem.* **2004**, *47*, S825–S828.
- (9) Parmentier-Batteur, S.; O'Brien, J. A.; Doran, S.; Nguyen, S. J.; Flick, R. B.; Uslaner, J. M.; Chen, H.; Finger, E. N.; Williams, T. N.; Jacobson, M. A.; Hutson, P. H. Differential effects of the mGluR5 positive allosteric modulator CDPPB in the cortex and striatum following repeated administration. *Neuropharmacology* **2012**, *62*, 1453–1460.
- (10) Parmentier-Batteur, S.; Hutson, P. H.; Menzel, K.; Uslaner, J. M.; Mattson, B. A.; O'Brien, J. A.; Magliaro, B. C.; Forest, T.; Stump, C. A.; Tynebor, R. M.; Anthony, N. J.; Tucker, T. J.; Zhang, X.-F.; Gomez, R.; Huszar, S. L.; Lambeng, N.; Faure, H.; Le Poul, E.; Poli, S.; Roshal, T. W.; Rocher, J.-M.; Hargreaves, R.; Williams, T. M. Mechanism based neurotoxicity of mGlu₅ positive allosteric modulators – Development challenges for a promising antipsychotic target. *Neuropharmacology* **2013**, *82*, 161–173.
- (11) Rook, J. M.; Noetzel, M. J.; Pouliot, W. A.; Bridges, T. M.; Vinson, P. N.; Cho, H. P.; Zhou, Y.; Gogliotti, R. D.; Manka, J. T.; Gregory, K. J.; Stauffer, S. R.; Dudek, F. E.; Xiang, Z.; Niswender, C. M.; Daniels, J. S.; Jones, J. K.; Lindsley, C. W.; Conn, P. J. Unique

signaling profiles of positive allosteric modulators of mGlu₅ determine differences in *in vivo* activity'. *Biol. Psychiatry* **2013**, *73*, 501–509.

- (12) Conn, P. J.; Lindsley, C. W.; Meiler, J.; Niswender, C. M. Opportunities and challenges in the discovery of allosteric modulators of GPCRs for the treatment of CNS disorders. *Nat. Rev. Drug Discovery* **2014**, *13*, 692–708.

- (13) MacDonald, G. J.; Lindsley, C. W. A unique industrial-academic collaboration towards the next generation of schizophrenia therapeutics'. *Curr. Top. Med. Chem.* **2014**, *14*, 304–312.

- (14) Zhou, Y.; Manka, J.; Rodriguez, A. L.; Weaver, C. D.; Jones, C. K.; Conn, P. J.; Lindsley, C. W.; Stauffer, S. R. N-Aryl piperazines as selective mGlu₅ potentiators with improved physiochemical properties and efficacy in a rodent model predictive of antipsychotic activity'. *ACS Med. Chem. Lett.* **2010**, *1*, 433–438.

- (15) Williams, R.; Manka, J. T.; Rodriguez, A. L.; Vinson, P. N.; Niswender, C. M.; Weaver, C. D.; Jones, C. K.; Conn, P. J.; Lindsley, C. W.; Stauffer, S. R. Synthesis and SAR of centrally active mGlu₅ positive allosteric modulators based on an aryl acetylenic bicyclic lactam scaffold. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1350–1353.

- (16) Manka, J.; Zhou, Y.; Williams, R.; Weaver, C. D.; Dawson, E. S.; Steckler, T.; Lavreysen, H.; Mackie, C.; Bartolome, J. M.; Macdonald, G. J.; Conn, P. J.; Lindsley, C. W.; Stauffer, S. R. Optimization of an ether series of mGlu₅ positive allosteric modulators: molecular determinants of MPEP-site interaction cross-over. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6481–6485.

- (17) Noetzel, M. J.; Gregory, K. J.; Vinson, J. T.; Manka, S. R.; Stauffer, S. R.; Daniels, S. J.; Lindsley, C. W.; Niswender, C. M.; Xiang, Z.; Conn, P. J. A novel metabotropic glutamate receptor 5 PAM acts at a unique site and confers stimulus bias to mGlu₅ signaling. *Mol. Pharmacol.* **2013**, *83*, 835–847.

- (18) Bartolome-Nebreda, J. M.; Conde-Ceide, S.; Delgado, F.; Pas tor, J.; Pena, M. A.; Trabanco, A. A.; Tresadern, G.; Wassvik, C. M.; Stauffer, S. R.; Jadhav, S.; Days, E.; Weaver, C. D.; Lindsley, C. W.; Niswender, C. M.; Jones, C. K.; Conn, P. J.; Rombouts, F.; Lavreysen, H.; Macdonald, G. J.; Mackie, C.; Steckler, T. Dihydrothiazolopyridone derivatives as a novel family of positive allosteric modulators of the mGlu₅ receptor. *J. Med. Chem.* **2013**, *56*, 7243–7259.

- (19) Turlington, M.; Malosh, C.; Jacobs, J.; Manka, J. T.; Vinson, P. N.; Gogi, K.; Jadhav, S.; Herman, E. J.; Lavreysen, H.; Mackie, C.; Bartolome, J. M.; Macdonald, G. J.; Steckler, T.; Daniels, J. S.; Weaver, C. D.; Niswender, C. M.; Jones, C. K.; Conn, P. J.; Lindsley, C. W.; Stauffer, S. R. Tetrahydronaphthyridine and dihydronaphthyridinone ethers as positive allosteric modulators of the metabotropic glutamate receptor 5 (mGlu₅). *J. Med. Chem.* **2014**, *57*, S620–S637.

- (20) Martin-Martin, M. L.; Bartolome-Nebreda, J. M.; Conde-Ceide, S.; Alonso, S. A.; Lopez, S.; Martinez-Vituro, C. M.; Tong, H. M.; Lavreysen, H.; Macdonald, G. J.; Steckler, T.; Mackie, C.; Daniels, S. J.; Niswender, C. M.; Jones, C. K.; Conn, P. J.; Lindsley, C. W.; Stauffer, S. R. Discovery and SAR of novel series of imidazopyrimidinones and dihydroimidazopyrimidinones as positive allosteric modulators of the metabotropic glutamate receptor 5 (mGlu₅). *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1310–1317.

- (21) See Supporting Information for full details.

- (22) Rook, J. M.; Xiang, Z.; Lv, X.; Ghosal, A.; Dickerson, J.; Bridges, T. M.; Johnson, K. A.; Bubser, M.; Gregory, K. J.; Vinson, P. N.; Byun, N.; Stauffer, S. R.; Daniels, J. S.; Niswender, C. M.; Lavreysen, H.; Mackie, C.; Conde-Ceide, S.; Alcazar, J.; Bartolome, J. M.; Macdonald, G. J.; Steckler, T.; Jones, C. K.; Lindsley, C. W.; Conn, P. J. Biased mGlu₅ positive allosteric modulators provide *in vivo* efficacy without potentiating mGlu₅ modulation of NMDAR currents. *Neuron* **2015**, *86*, 1029–1040.

- (23) Blobaum, A. L.; Bridges, T. M.; Byers, F. W.; Mattmann, M. E.; Morrison, R. D.; Mackie, C.; Lavreysen, H.; Bartolome, J. M.; Macdonald, G. J.; Steckler, T.; Jones, C. K.; Niswender, C. M.; Conn, P. J.; Lindsley, C. W.; Stauffer, S. R.; Daniels, J. S. Heterotropic activation of the midazolam hydroxylase activity of P450 3A by a positive allosteric modulator of metabotropic glutamate receptor 5: *In Vitro* to *In Vivo* translation and potential impact on clinically relevant drug-drug interactions. *Drug Metab. Dispos.* **2013**, *41*, 2066–2075.