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Discovery of VU0409551/JNJ-46778212: An $mGlu_5$ Positive Allosteric Modulator Clinical Candidate Targeting Schizophrenia

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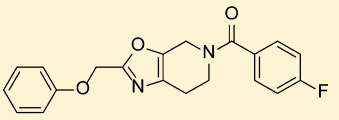
Supporting Information

ABSTRACT: Herein, we report the structure−activity relationship of a novel series of (2(phenoxymethyl)-6,7-dihydrooxazolo[5,4-*c*]pyridine-5(4*H*)-yl(aryl)methanones as potent, selective, and orally bioavailable metabotropic glutamate receptor subtype 5 ($mGlu_5$) 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.



17a, VU0409551/JNJ-46778212

KEYWORDS: *Positive allosteric modulator (PAM), metabotropic glutamate receptor 5 ($mGlu_5$), 4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine, VU0409551, JNJ-46778212, schizophrenia*

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 ($mGlu_5$), due to its localization in brain regions implicated in schizophrenia and its colocalization with *N*-methyl-D-asparatate (NMDA) receptors, is of great interest in the context of the NMDA receptor hypofunction hypothesis of schizophrenia.[4−6] Positive allosteric modulation of $mGlu_5$, 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 $mGlu_5$ 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 $mGlu_5$ 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 collaboration[13] 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 $mGlu_5$ PAM chemotypes, minimally represented by **14**−**16**, which

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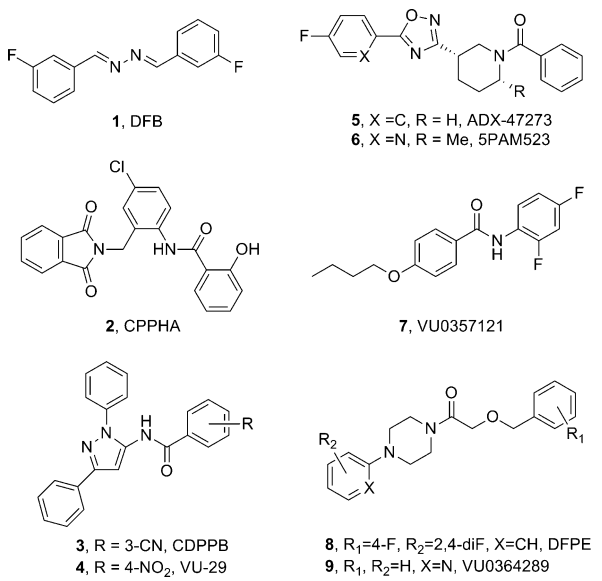


Figure 1. Representative, first generation MPEP-site and non-MPEP-site $mGlu_5$ PAMs **1**–**9**.

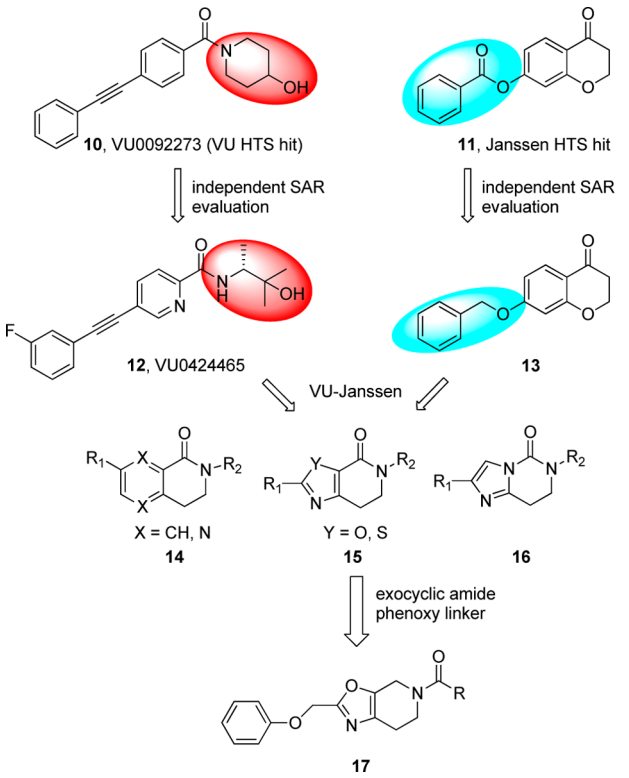
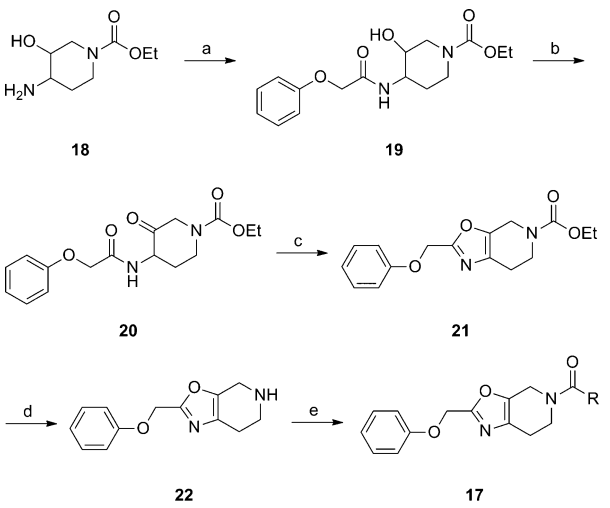


Figure 2. Chemical evolution of a series of (2(phenoxymethyl)-6,7-dihydrooxazolo[5,4-*c*]pyridine-5(4*H*)-yl(aryl)methanones **17** that provided the first $mGlu_5$ PAM clinical candidate.[14−20]

afforded improved DMPK profiles.[14−20] Further optimization efforts incorporated a phenoxy linker[19] 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]



[a]Reagents and conditions: (a) 2-phenoxyacetyl chloride, Et_3N, DCM, 0 °C to rt, 1 h, 89%; (b) Dess−Martin periodinane, DCM, 1 h, rt, 86%; (c) $POCl_3$, dioxane, 100 °C, 1.5 h, 80%; (d) LiOH, dioxane/H_2O, 120 °C, 48 h, 65%; (e) RCOCl, Et_3N, 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 $mGlu_5$ 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 $mGlu_5$ PAMs **17a,e-j** with EC_{50}s 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 $mGlu_5$ 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 $mGlu_5$ PAM with the most balanced profile (*vide infra*) and worthy of further development, with no species differences (activity at rat $mGlu_5$ was comparable to human (rat EC_{50} = 235 nM, pEC_{50} = 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 EC_{20} concentration of glutamate, **17a** potentiates the human $mGlu_5$ response in a concentration-dependent manner resulting in an EC_{50} of 260 nM, with 84% Glu Max (Figure 3A). Analogue **17a** (10 μM) also induces ∼10-fold shift of the glutamate CRC on human $mGlu_5$ (Figure 3B). Moreover, **17a** is an MPEP site PAM, fully displacing [^{3}H]-mPEPy (Figure 3C), and is highly selective for $mGlu_5$ relative to $mGlu_{1-4,6-8}$ at 10 μM (Figure 3D).[22]

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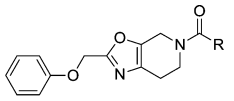
Table 1. SAR of Analogues of $mGlu_5$ PAM 17



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

[a]Calcium mobilization assay using HEK293 expressing human $mGlu_5$; values are the average of three or more independent determinations. [b]Data obtained from a single experiment not replicated.

Evaluation of the *in vitro* DMPK and physiochemical 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 μg/mL in FaSSIF). PAM **17a** possessed an exceptional cytochrome P450 profile (1A2, 2C9, 2D6, 3A4, IC_{50} >25 μM), and no 3A4 TDI or induction. CYP phenotyping indicated 2D6 and 3A4 as major contributors, and the major metabolite, *p*-hydroxylation of the naked

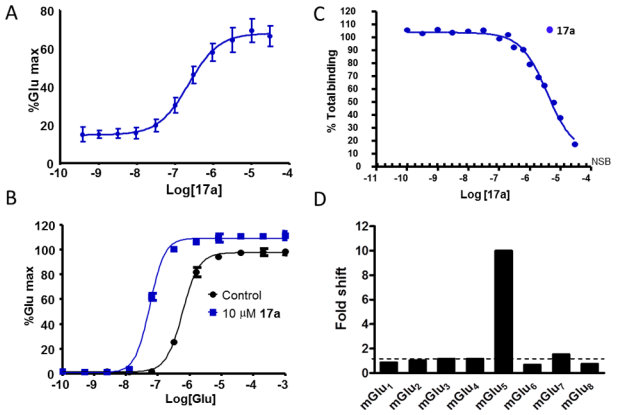


Figure 3. Molecular pharmacological profile of **17a**. (A) Enhanced calcium release induced by suboptimal concentrations of glutamate (EC_{20}), the PAM CRC, with an EC_{50} for potentiation of 260 nM. (B) Analogue **17a** induces a 10-fold leftward shift of the glutamate CRC. (C) Binding study with [^{3}H]-mPEPy, confirming an MPEP sight PAM (Human IC_{50} = 4.37 μM, 82%). (D) mGlu selectivity data (fold-shift at 10 μM) showing that **17a** is highly selective for $mGlu_5$. Each data point represents the mean ± SD (n = 3).

Western phenyl ring, was inactive at $mGlu_5$.[21] In terms of toxicity assessment, **17a** was clean in AMES, a high content cytotoxicity assay (>30 μM) 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} (μM) po	0.83	1.08	1.01
T_{max} (h) po	0.5	1.5	0.5
$AUC_{o\text{-}inf}$ (ng·h/mL) po	1874	818	6460
F (%) po	44	96	51
brain/plasma (K_p)	1.0	2.3	

[a]Data reported as average of three animals.

In oral brain/plasma studies, **17a** displayed excellent CNS penetration with K_ps 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, IC_{50}s >10 μM) and was inactive in hERG patch clamp (22% inhibition @ 3 μM). 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 μM).[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 (ED_{50} = 23 mg/kg). Moreover, only partial tolerance, but maintenance of efficacy, was noted after 7 days of subchronic dosing in this model.[21]

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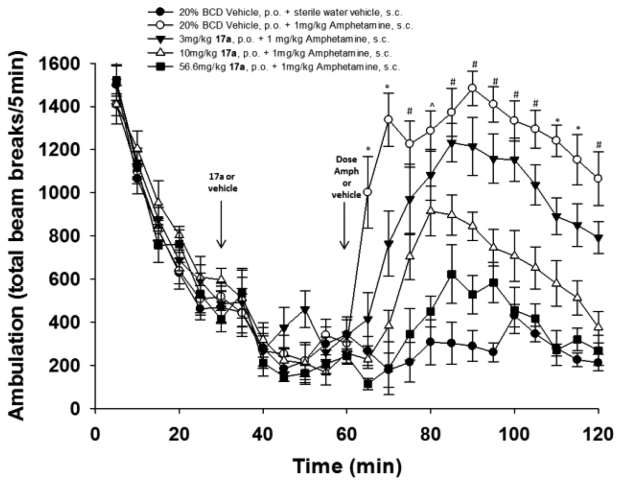

Figure 4. Analogue **17a** has antipsychotic-like activity in rats and dose-dependently (3−56.6 mg/kg, po) reverses AHL. $^{\#},^{*},^{\wedge}p < 0.05$ vs VAMP group, Dunnett's test.

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 catelpsy.[21] In addition, **17a** also induced septal cFos mRNA 153% (40 mg/kg po). The $mGlu_5$ PAM **17a** was even more efficacious in several preclinical cognition models, showing an MED of 1 mk/kg po in contextual fear conditioning (CFC) and an MED of 3 mg/kg po in novel object recognition. These data strongly suggest that an $mGlu_5$ PAM may possess broader efficacy across multiple domains of schizophrenia, with fewer adverse events than existing antipsychotics.

$mGlu_5$ 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 $mGlu_5$ PAMs do not possess seizure/epileptiform liabilities, as opposed to $mGlu_5$ agonists and ago-PAMs; thus, **17a**, a pure $mGlu_5$ PAM in multiple cell lines and native systems, would avoid this key mechanism-based liability.[11,23] Recent data with **6** suggests that $mGlu_5$ 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 $mGlu_5$ 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 μM·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 $mGlu_5$ PAMs. As expected, **17a** potentiates DHPG-induced long-term depression (LTD) and induces calcium mobilization and ERK phosphorylation; however, **17a** does not potentiate $mGlu_5$ modulation of NMDA receptor currents nor NMDA receptor-dependent long-term potentiation (LTP), suggesting a unique signal bias for this $mGlu_5$ PAM that may contribute to the observed, favorable therapeutic window.[22] From a conceptual point of view, it is intriguing that selective $mGlu_5$ 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 $mGlu_5$ PAM; therefore, compound progression paused while other PAMs were profiled.

In summary, an industrial-academic collaboration between Janssen and the VCNDD developed an orally bioavailable $mGlu_5$ 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.

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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 VCNDD and JNJ are actively developing $mGlu_5$ PAMs as therapeutic agents.

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■ 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.; Volkmann, 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 ($mGlu_5$) 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.; Wiliams, 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.; Lemiare, 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 recep tor subtype 5 from a series of *N*-(1,3-Diphenyl-1*H*-pyrazol-5- yl)benzamides that potentiate receptor function *in vivo*. *J. Med. Chem.* **2004**, *47*, 5825−5828.

(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 modualtor 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 $mGlu_5$ 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 $mGlu_5$ 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 $mGlu_5$ 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 $mGlu_5$ 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 $mGlu_5$ 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 dihydronapthyridinone ethers as positive allosteric modulators of the metabotropic glutamate receptor 5 ($mGlu_5$). *J. Med. Chem.* **2014**, *57*, 5620−5637.

(20) Martin-Martin, M. L.; Bartolome-Nebreda, J. M.; Conde-Ceide, S.; Alonso, S. A.; Lopez, S.; Martinez-Viturro, 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 ($mGlu_5$). *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 $mGlu_5$ positive allosteric modulators provide in vivo efficacy without potentiating $mGlu_5$ modulation of NMDAR currents. *Neuron* **2015**, *86*, 1029−1040.

(23) Blobaum, A. L.; Bridges, T. M.; Byers, F. W.; Mattmann, M. E.; Morrsion, 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.

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