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Further optimization of the $mGlu_5$ PAM clinical candidate VU0409551/JNJ-46778212: Progress and challenges towards a back-up compound

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ABSTRACT

This Letter describes the progress and challenges in the continued optimization of the $mGlu_5$ positive allosteric modulator (PAM) clinical candidate VU0490551/JNJ-46778212. While many analogs addressed key areas for improvement, no one compound possessed the amalgamation of improvements needed within the (2(phenoxymethyl)-6,7-dihydrooxazolo[5,4-*c*]pyridine-5(4*H*)-yl(aryl)methanone scaffold to advance as a back-up clinical candidate. However, many analogs displayed excellent solubility and physiochemical properties, and were active in the amphetamine-induced hyperlocomotion (AHL) model. Moreover, the SAR was robust for this series of PAMs, and both polar and hydrogen-bond donors were found to be tolerated, leading to analogs with overall attractive profiles and good ligand efficiencies.

We recently disclosed the discovery and development of an orally bioavailable $mGlu_5$ PAM (**1**, VU0409551, JNJ-46778212)[1,2] for the treatment of schizophrenia (Fig. 1) via a fundamentally new molecular mechanism,[3–6] arising from a unique industrial-academic collaboration between Janssen Research and Development and the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD).[7–13] Immediately following its approval as a clinical candidate, we pursued a multidimensional optimization campaign (surveying modifications to the eastern and western aryl moieties as well as the central piperidine ring, Fig. 1) towards the discovery of a back-up compound within the (2(phenoxymethyl)-6,7-dihydrooxazolo[5,4-*c*]pyridine-5(4*H*)-yl(aryl)methanone series.[1,2] The optimization plan focused on blocking CYP-mediated aryl oxidation[2] and improving physiochemical properties of the scaffold, all in an effort to identify analogs with increased potency and increased efficacy in an amphetamine-induced hyperlocomotion (AHL) rodent model.

In order to access analogs of **1** and survey the SAR for the highlighted regions depicted in Figure 1, two synthetic routes were developed. In the first approach (Scheme 1), the 4-fluorophenyl benzamide of **1** was maintained while alternative aryl and heteroaryl phenolic moieties were introduced. Treatment of **1** with BBr_3 liberates the primary alcohol **3**, which readily participates in Mitsunobu reactions to deliver analogs **4** in good overall yields. To access analogs of **1** with greater structural variance, we begin with various, commercial piperidinones **5** (Scheme 2). Bromination provides **6** which, upon treatment with cinnamamide in the presence of silica gel and heat, affords styrenyloxadiazole **7** in 25% yield for the two steps. Then, a three step sequence of oxidation, cleavage and reduction provides alcohol **8** in 40% over the three steps. Mitsunobu reaction with various phenols and heteroaryl alcohols, followed by hydrolysis of the ethyl carbamate, gives secondary amine **9**. Standard acylation chemistry then provides analogs **10** in good to excellent yields.

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0960-894X/

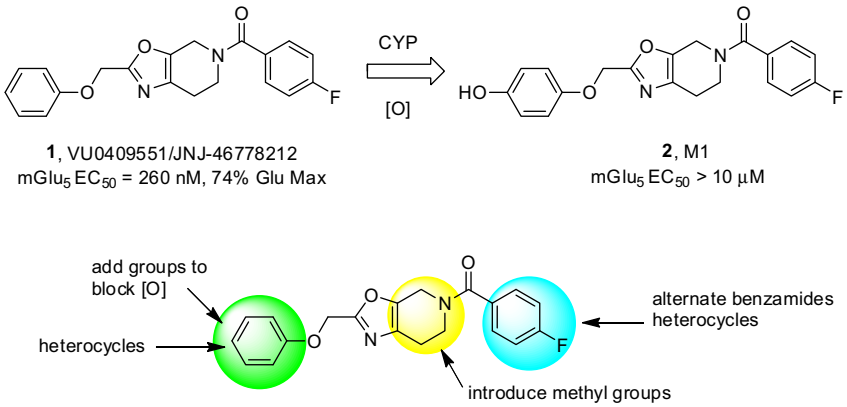
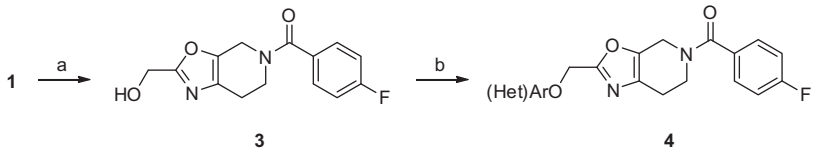
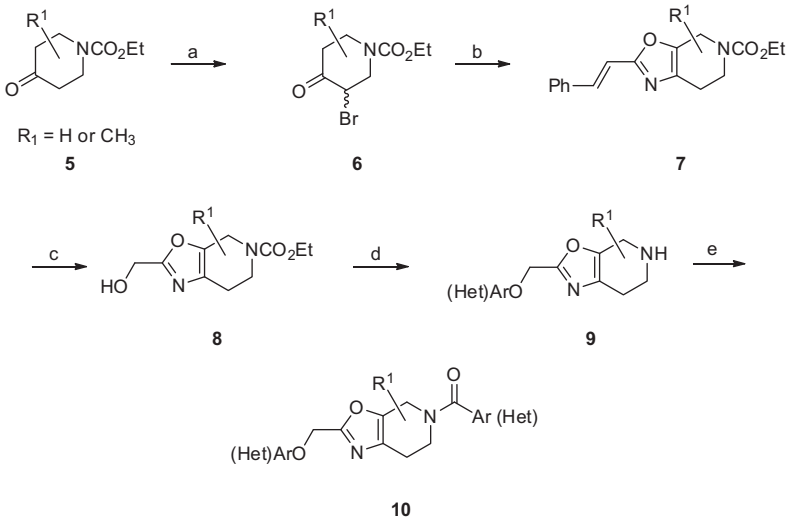


Figure 1. Structures and $mGlu_5$ PAM activities of the clinical candidate **1** (VU0409551/JNJ-46778212) and the inactive, primary metabolite **2** (M1). Inset, the multidimensional optimization back-up campaign for **1**.



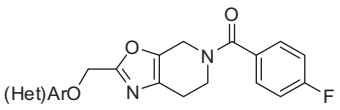
Scheme 1. Reagents and conditions: (a) BBr_3, DCE, 0 °C, 65%; (b) (Het)ArOH, DBAD, PPh_3, THF, 0 °C to rt, 20 min, 35–90%.



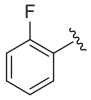
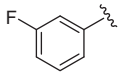
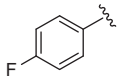
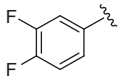
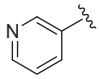
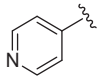
Scheme 2. Reagents and conditions: (a) Br_2, HBr (cat), THF, 0 °C to rt, 30 min; (b) cinnamamide, SiO_2, 125 °C, 16 h, 25% over two steps; (c) (i) OsO_4 (cat), NMO THF/acetone/H_2O, rt 16 h, (ii) $NaIO_4$, THF/MeOH/H_2O, rt, 2 h, (iii) $NaBH_4$, MeOH, 0 °C to rt, 30 min, 40% for three steps; (d) (i). (Het)ArOH, DBAD, PPh_3, THF, 0 °C to rt, 30 min, (ii) LiOH, dioxane/H_2O, 170 °C, 40 min, mw, 25–44% for two steps; (e) (Het)ArCOCl, DEIPA, DCM, 0 °C to rt or (Het)$ArCO_2H$, PyBrOP, DCE, rt, 56–95%.

With respect to analogs **4**, SAR was flat, with most substituted aryl moieties proving to be inactive, with the notable exception of fluoro congeners and certain pyridyl isomers (Table 1). Clear SAR was noted for the fluoro derivatives, with the 3-fluoro phenyl **4b** being a clear standout in terms of both $mGlu_5$ PAM potency (EC_{50} = 240 nM), efficacy (78% of the maximal response of glutamate) and leftward fold-shift of a full glutamate concentration-response curve (13×). The 4-fluoro analog **4c** lost potency, and when combined, the 3,4-difluoro congener **4d** lost significant efficacy. Similarly, pyridyl regioisomers displayed either no activity (e.g., **4e**, the 3-pyridyl) or a loss of potency as with **4f** and **4g**. Based on these data, we further evaluated **4b** in a battery of in vitro DMPK assays.[1,2] **4b** possessed a clean P450 inhibition profile (IC_{50} >30 μM against 3A4, 2D6, 2C9 and 1A2), displayed acceptable fraction unbound values in human (f_u, 0.018) and rat (f_u, 0.049) as well as an attractive cardiovascular safety pharmacology profile (hERG PX 26%@10 μM, IC_{50}s >10 μM at hERG, Ca and Na channels). Addition of the 3-fluoromoeity to **1** negatively impacted solubility (FaSSIF and SGF both 10 μg/mL), and quite unexpectedly, this single atom modification brought in $mGlu_3$ antagonist activity ($mGlu_3$ IC_{50} = 410 nM, 8% Glu min, >10 μM vs $mGlu_{1,2,4,6,7,8}$).[14,15] Still, based on excellent brain penetration (K_p = 2.7), we evaluated **4b** in our standard rodent (rat) pharmacodynamic model for the program, and **4b** (VU0413846) produced a dose- and concentration-dependent reversal of amphetamine induced hyperlocomotion upon oral administration (Fig. 2), displaying a maximum reversal

Table 1
Structures and activities of analogs **4**



4

Entry	R	pEC_{50}[a] (±SEM)	EC_{50}[a] (nM)	Glu max%[a] (±SEM)
4a		5.92 ± 0.06	1200	78 ± 3
4b		6.62 ± 0.02	240	78 ± 2
4c		6.18 ± 0.03	660	73 ± 4
4d		6.19 ± 0.09	640	40 ± 6
4e		5.61 ± 0.05	2460	75 ± 5
4f		<5[b]	>10,000	40
4g		5.76 ± 0.03	1700	71 ± 2

[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.

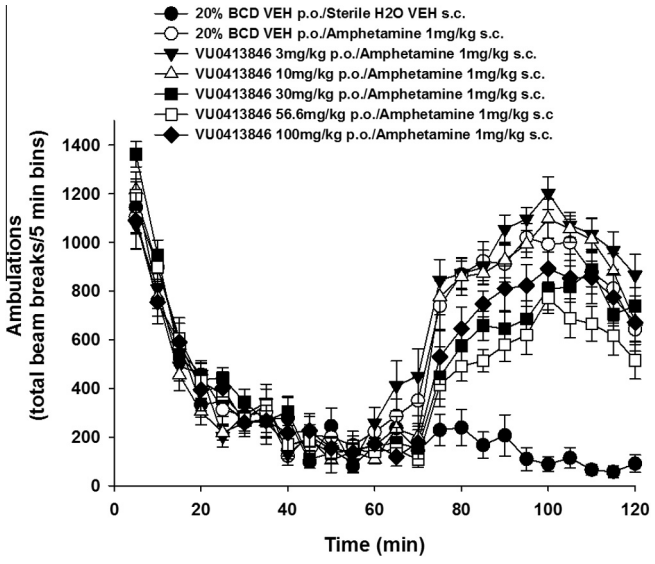


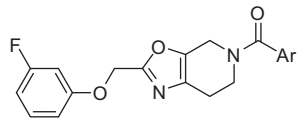
Figure 2. 4b (VU0413846) has antipsychotic-like activity in male, Sprague Dawley rats. **4b** dose-dependently (3–100 mg/kg, po) reverses AHL. Vehicle is 20% beta-cyclodextrin (homogeneous solutions).

of 37% at 56.6 mg/kg (terminal (1.5 h) plasma and brain concentrations in this study were linear by dose from 3 to 30 mg/kg, sublinear from 30 to 56.6 mg/kg, and flat from 56.6 to 100 mg/kg).

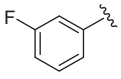
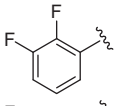
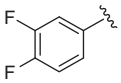
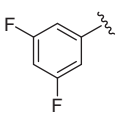
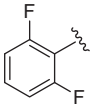
With a relatively high minimum effective dose (of (30 mpk), diminished solubility (3× lower than **1**),[1,2] lack of mGlu selectivity and modest in vivo efficacy precluded further advancement of **4b** as a potential back-up candidate. However, the 3-flurophenyl moiety was worthy of evaluation in the context of alternate benzamides, **10**. Here, robust SAR was observed (Table 2), but in all cases both solubility and efficacy in AHL were greatly diminished relative to **1**.[1,2] Therefore, we elected to focus the back-up effort on analogs of **1** wherein the western, unsubstituted phenoxy moiety was maintained, while surveying heterocyclic amides to enhance solubility, providing congeners **11** (Table 3). The vast majority of 5- and 6-membered heterocycles surveyed lost considerable $mGlu_5$ PAM potency, efficacy or both; however, certain indoles, indazoles and aza-indazoles, proved to be highly interesting compounds. While the 2-indoyl amide **11a** was inactive, the N–Me congener **11b** was active (EC_{50} = 510 nM); in contrast, 3-indoyl amides, both the N–H (**11c**) and N–Me (**11d**) derivatives, were comparably active (EC_{50}s of 230 nM and 290 nM, respectively). Moreover, the indazole analog **11e** was equipotent to the indole **11c**, yet both displayed poor solubility. Surveying azaindole analogs, **11f–h**, led to the discovery of **11h**, an $mGlu_5$ PAM with moderate potency (EC_{50} = 546 nM) and good efficacy (73% Glu Max), but with exceptional solubility (FaSSIF of 381 μg/mL) which warranted further characterization.

$mGlu_5$ PAM **11h** showed comparable activity at both human and rat receptors, along with fold-shifts of equal magnitude (7.3–9.3×) with modest ago-PAM activity. **11h** was a low molecular weight compound (375), possessed a favorable log *P* (2.4) and high ligand efficiency (0.31). Unlike **4b**, **11h** was inactive against all the mGlus (>30 μM versus $mGlu_{1-4,6-8}$) and displayed improved plasma protein binding (f_u (h,r): 0.04, 0.11). Other in vitro DMPK properties were also favorable, including clean P450 inhibition profile (IC_{50} ⩾30 μM against P4503A4, 2D6 and 1A2; 14.8 μM at 2C9), and a moderate predicted hepatic clearance (CL_{hep} (h,r);

Table 2
Structures and activities of analogs **10**

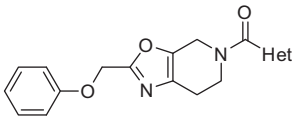


10

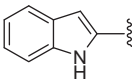
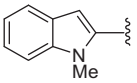
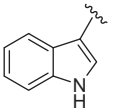
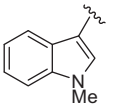
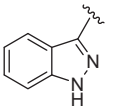
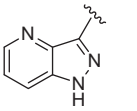
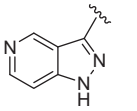
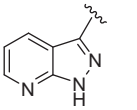
Entry	R	pEC_{50}[a] (±SEM)	EC_{50}[a] (nM)	Glu max%[a] (±SEM)
10a		6.53 ± 0.07	290	73 ± 5
10b		6.85 ± 0.05	139	75 ± 3
10c		6.21 ± 0.10	620	72 ± 4
10d		6.65 ± 0.06	220	71 ± 5
10e		6.82 ± 0.04	150	42 ± 3
10f		6.49 ± 0.06	370	82 ± 4

[a] Calcium mobilization assay using HEK293 expressing human $mGlu_5$; values are the average of three or more independent determinations.

Table 3
Structures and activities of analogs **11**



11

Entry	R	pEC_{50}[a] (±SEM)	EC_{50}[a] (nM)	Glu max%[a] (±SEM)
11a		<5[b]	>10,000	40
11b		6.29 ± 0.1	510	57 ± 4
11c		6.63 ± 0.06	230	71 ± 6
11d		6.53 ± 0.09	290	70 ± 3
11e		6.53 ± 0.06	290	68 ± 4
11f		<5[b]	>10,000	29
11g		5.85 ± 0.10	1400	53 ± 5
11h		6.26 ± 0.02	546	73 ± 2

[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.

9.1, 36 mL/min/kg). These attractive in vitro properties translated in vivo, with **11h** displaying low plasma clearance in rat (CL_p = 12.8 mL/min/kg), a moderate half-life (3.6 h), excellent oral bioavailability (%*F* = 85) and CNS penetration (K_p = 1.2). In our standard rodent AHL pharmacodynamic model (Fig. 3),[1,2] **11h** demonstrated efficacy with oral dosing, but the MED was 30 mg/kg p.o. (3-fold higher than for **1**, and the same as **4d**). The ED_{50} was 17.7 mg/kg, and the maximum reversal was 48.8% at a dose of 56.6 mg/kg (terminal (1.5 h) plasma and brain concentrations in this study were linear by dose from 3 to 30 mg/kg and sublinear from 30 to 56.6 mg/kg). Thus, like **4d**, **11h** proved to not possess the profile necessary to advance as a clinical back-up to **1**.

Before abandoning the (2(phenoxymethyl)-6,7-dihydrooxazolo[5,4-*c*]pyridine-5(4*H*)-yl(aryl)methanone series, we elected to evaluate the impact of the addition of methyl groups to the core piperidine nucleus as outlined in Figure 1, via the route depicted in Scheme 1. For this exercise, we employed **1** as our scaffold of reference (Fig. 4). Only one analog (**15**) proved more potent than **1** (EC_{50} = 170 nM, pEC_{50} = 6.76±0.01, 73±2%); however, this structural modification did not lead to improvements in

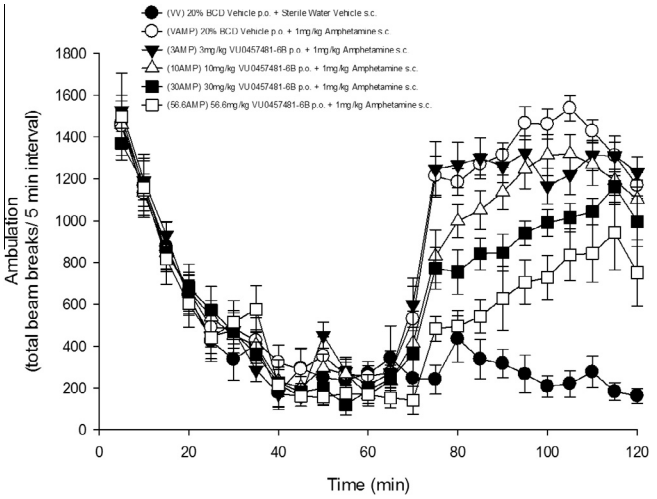


Figure 3. **11h** (VU0457481) has antipsychotic-like activity in male, Sprague Dawley rats. **11h** dose-dependently (3–56.6 mg/kg, po) reverses AHL. Vehicle is 20% beta-cyclodextrin (homogeneous solutions).

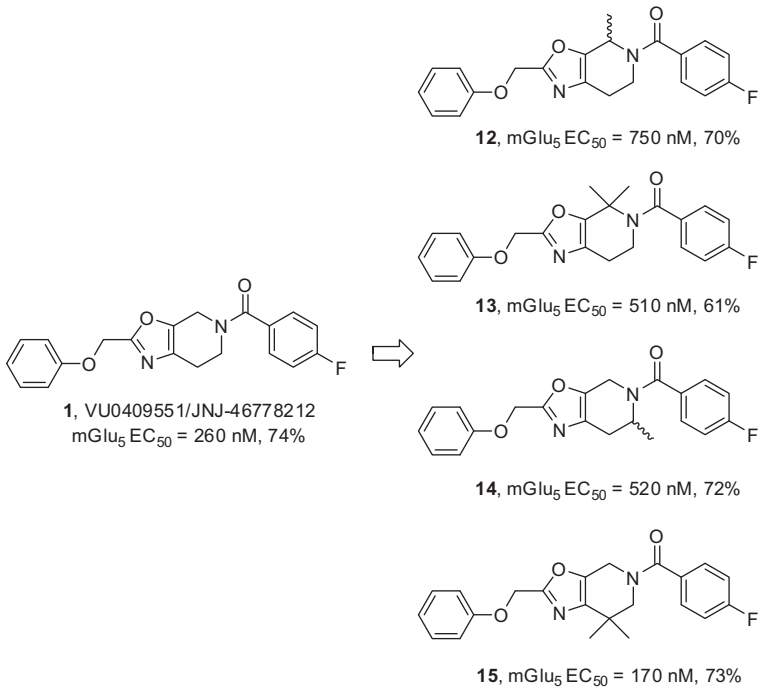


Figure 4. Impact of incorporation of either a racemic methyl or *gem*-dimethyl moiety into the piperidine core of **1**, providing analogs **12**–**15**.

physicochemical or DMPK properties, and thus, future efforts in this subseries were not pursued.

In summary, we have detailed our initial efforts towards a back-up compound for the $mGlu_5$ PAM clinical candidate (**1**, VU0409551/JNJ-46778212) while working within the (2(phenoxymethyl)-6,7-dihydrooxazolo[5,4-*c*]pyridine-5(4*H*)-yl(aryl)-methanone series. Robust SAR was observed within this series, which led to the discovery of two putative contenders, **4b** and **11h**, that individually addressed some of the areas targeted for improvement with **1**. Despite some notable advances, both **4b** and **11h** displayed diminished MEDs in our pivotal AHL model and were deemed not suitable for further advancement as back-up candidates. Efforts have shifted toward other chemical series and chemotypes from which to develop a back-up candidate, and these efforts will be reported in due course.

Acknowledgments

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References and notes

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