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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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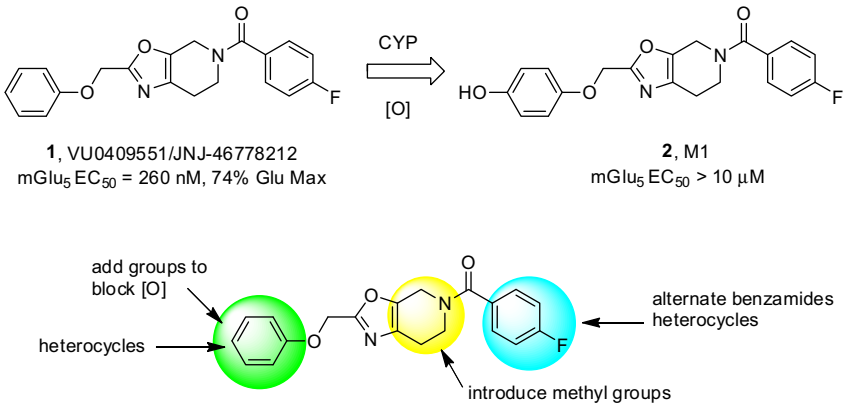
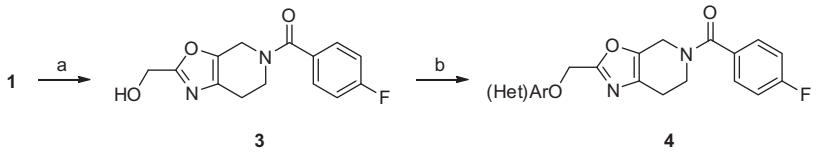
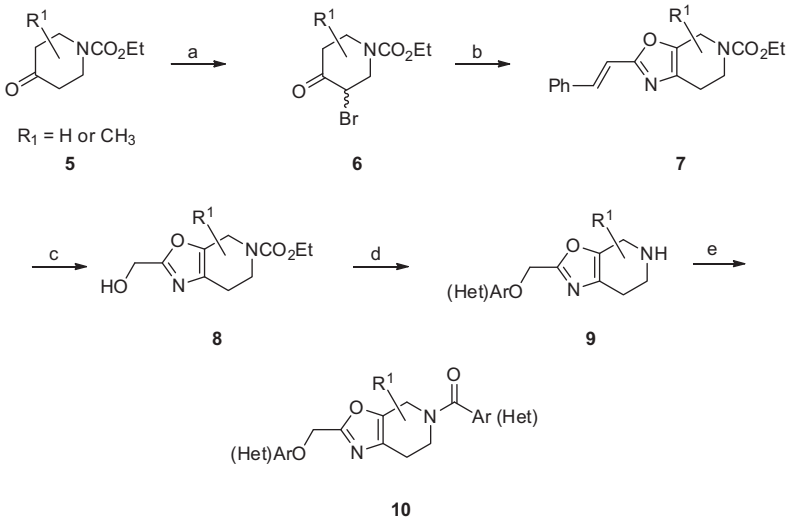


Figure 1. Structures and $mGlu_5$ PAM activities of the clinical candidate **1** (VU0409551/JNJ-46778212) and the inactive, primary metabolite **2** (M1). Inset, the multidimensional optimization back-up campaign for **1**.



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