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Discovery of 6-(pyrimidin-5-ylmethyl)quinoline-8-carboxamide negative allosteric modulators of metabotropic glutamate receptor subtype 5

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ABSTRACT

Based on previous work that established fused heterocycles as viable alternatives for the picolinamide core of our lead series of $mGlu_5$ negative allosteric modulators (NAMs), we designed a novel series of 6-(pyrimidin-5-ylmethyl)quinoline-8-carboxamide $mGlu_5$ NAMs. These new quinoline derivatives also contained carbon linkers as replacements for the diaryl ether oxygen atom common to our previously published chemotypes. Compounds were evaluated in a cell-based functional $mGlu_5$ assay, and an exemplar analog **27** was >60-fold selective versus the other seven mGlu receptors. Selected compounds were also studied in metabolic stability assays in rat and human S9 hepatic fractions and exhibited a mixture of P450- and non-P450-mediated metabolism.

Glutamate is the major excitatory transmitter in the mammalian central nervous system and activates both ionotropic (iGlu) and metabotropic glutamate (mGlu) receptors. While the iGlu receptors are ligand-gated ion-channels, the mGlu receptors are a family of eight G protein-coupled receptors (GPCRs). Based on their structure, function, and effects on downstream signaling pathways, the mGlu receptors have been classified into three groups. Group I receptors ($mGlu_1$ and $mGlu_5$), which are found in postsynaptic locations, are coupled via G_q to the activation of phospholipase C. On the other hand, group II receptors ($mGlu_{2-3}$), which are found both pre and postsynaptically, and group III receptors ($mGlu_4$, $mGlu_{6-8}$), which are found primarily in presynaptic locations, are coupled via $G_{i/o}$ to the inhibition of adenylyl cyclase activity. The orthosteric glutamate binding site of the mGlu receptors is contained in the extracellular domain; however, the allosteric binding sites that have been discovered to date are found in the transmembrane domain.[1,2]

The design of drug-like orthosteric ligands that are highly selective for a single mGlu receptor versus the other seven mGlu family members can be quite challenging. One method for overcoming this hurdle that has proven successful for a variety of mGlu receptors has been the use of approaches focused on compounds that interact with an allosteric site.[3] Among these efforts, the design and optimization of negative allosteric modulators (NAMs) of $mGlu_5$ has been pursued extensively.[4] Likewise, preclinical and clinical studies have indicated many potentially interesting therapeutic applications for $mGlu_5$ NAMs.[1–4], In fact, phase II clinical trials have been conducted with small molecule $mGlu_5$ NAMs in fragile X syndrome (FXS),[5,6] major depressive disorder (MDD),[7] obsessive–compulsive disorder (OCD),[8] and Parkinson's disease levodopa-induced dyskinesia (PD-LID).[9,10] Regrettably, in most instances, the primary efficacy endpoints were not met;[5–9] however, some secondary efficacy endpoints have been noted in both MDD[7] and PD-LID.[10]

Small molecule $mGlu_5$ NAM research has been a major focus of our group and recently culminated in the identification of a highly

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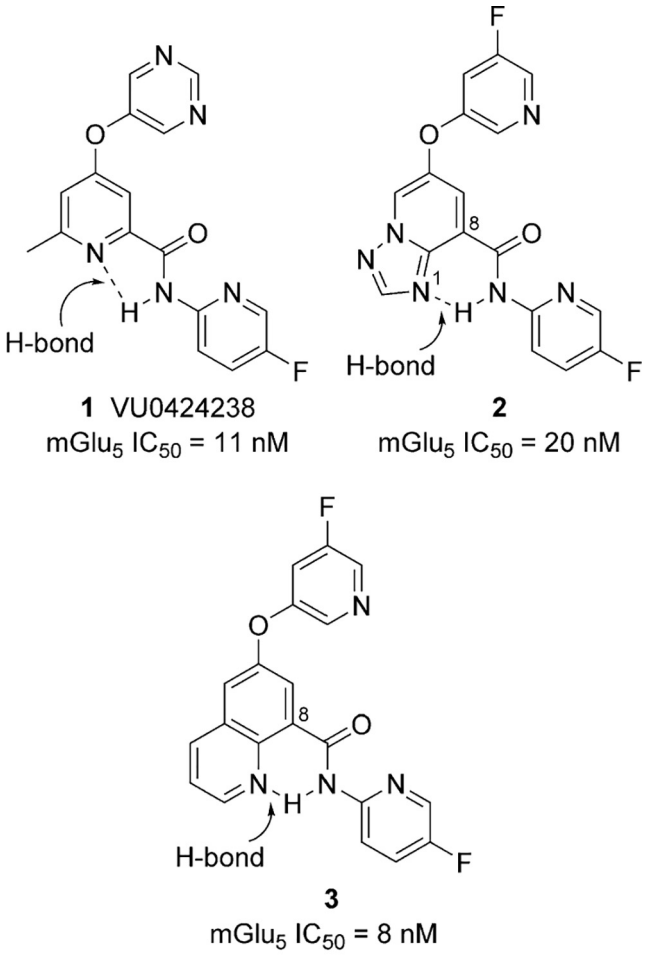
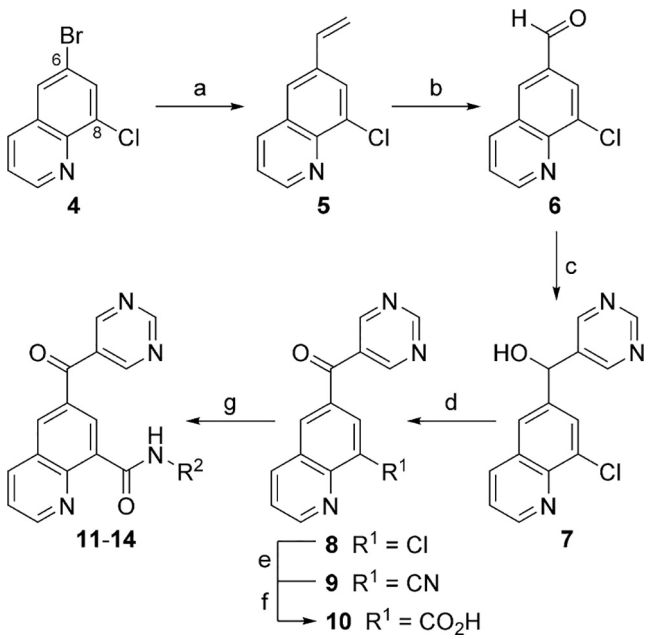


Fig. 1. Picolinamide $mGlu_5$ NAM candidate VU0424238 (1), [1,2,4]triazolo[1,5-*a*] pyridine-8-carboxamide $mGlu_5$ NAM 2, quinoline-8-carboxamide 3, and our plan for development of a new quinoline-8-carboxamide $mGlu_5$ NAM scaffold.

optimized $mGlu_5$ NAM candidate for clinical evaluation, VU0424238 (**1**) (Fig. 1),[11] a member of a series of picolinamide $mGlu_5$ NAMs. We also recently reported on the discovery of an additional backup series of heterocyclic $mGlu_5$ NAMs exemplified by [1,2,4]triazolo[1,5-*a*]pyridine-8-carboxamide **2**.[12] The discovery of **2** was based on a hypothesis that an internal hydrogen bond between the amide NH and the 1-nitrogen of the heteroaryl core of **2** would help orient the molecule similarly to the postulated conformation of VU0424238 (**1**), where an analogous hydrogen bond between the amide NH and the picolinamide nitrogen was assumed likely. The discovery of **2** and its analogs opened the door to investigate other heterocyclic cores such as quinoline-8-carboxamides. In fact, we synthesized compound **3,** a quinoline analog of **2**, and verified that it was similarly potent versus $mGlu_5$. Still, to further enhance the novelty of such new compounds and explore new SAR, we also sought to modify additional portions of the scaffold (Fig. 1). Specifically, we chose to replace the oxygen linker that had been constant across the chemotypes found in both **1** and **2** as well as other related series[13,14] by exchanging it with several carbon linkers. This Letter describes our efforts toward that end.

Synthetic work on the aforementioned ether analogs had employed nucleophilic aromatic substitution (S_NAr) as the means for joining the northern heteroaryl ring to the core of the scaffold.[11–14] Our plan to move to a carbon linker would thus necessitate a substantially different synthetic approach (Scheme 1).[15] Our first targets were a small set of ketone-linker containing analogs **11**–**14**. 6-Bromo-8-chloroquinoline **4** was converted to vinyl analog **5** via a Suzuki cross-coupling reaction with potassium vinyltrifluoroborate.[16] Ozonolysis of **5** followed by treatment with dimethyl sulfide afforded aldehyde **6**. Metal-halogen exchange of 5-bromopyrimidine was carried out at low temperature, and the resultant organolithium intermediate was treated with **6** *in situ* to yield secondary alcohol **7**. Oxidation of **7** was accomplished with manganese oxide to provide ketone **8**. A palladium-catalyzed reaction with zinc cyanide gave nitrile **9**, and subsequent acidic hydrolysis with heating gave the penultimate acid **10**. Formation of amide analogs **11**–**14** was accomplished with phosphorous oxychloride in pyridine, conditions that we have employed successfully in the past.[11–14]

Monofluoromethylene linker analogs **20**–**21** and difluoromethylene linker analogs **26**–**36** were prepared from intermediate **8** (Scheme 2). Suzuki cross-coupling reaction with potassium vinyltrifluoroborate as before afforded vinyl intermediate **15**. Reduction of the ketone was accomplished with sodium borohydride to provide alcohol **16**, which was treated with diethylaminosulfur trifluoride (DAST) to yield **17**. Ozonolysis of **17**



Scheme 1. Reagents and conditions: (a) $H_2C=CHBF_3K$, $PdCl_2(dppf)$, NEt_3, EtOH, 80 °C, 100%; (b) O_3, CH_2Cl_2, MeOH, −78 °C, then Me_2S, −78 °C to rt, 77%; (c) 5-bromopyrimidine, *n*-BuLi, THF, ether, −100 °C, then 6, −100 °C to rt, 81%; (d) MnO_2, CH_2Cl_2, 100%; (e) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, microwave, 140 °C, 20 min, 70%; (f) H_2SO_4, AcOH, sealed tube, 120 °C, 64%; (g) H_2NR^2, $POCl_3$, pyridine, −15 °C, 14% (10 → 11), 21% (10 → 12), 42% (10 → 13), 14% (10 → 14).