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# *N*-Acyl-*N*′-arylpiperazines as negative allosteric modulators of $mGlu_1$: Identification of VU0469650, a potent and selective tool compound with CNS exposure in rats

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ABSTRACT

Development of SAR in an *N*-acyl-*N*′-arylpiperazine series of negative allosteric modulators of $mGlu_1$ using a functional cell-based assay is described in this Letter. Characterization of selected compounds in protein binding assays was used to aid in selecting VU0469650 for further profiling in ancillary pharmacology assays and pharmacokinetic studies. VU0469650 demonstrated an excellent selectivity profile and good exposure in both plasma and brain samples following intraperitoneal dosing in rats.



L-Glutamic acid (glutamate) is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Glutamate produces its effects through binding to both ionotropic and metabotropic glutamate receptors. The metabotropic glutamate receptors (mGlus) belong to family C of the G protein-coupled receptors (GPCRs). Further classification of the mGlus discovered to date has been according to their structure, preferred signal transduction mechanisms, and pharmacology (Group I: $mGlu_1$ and $mGlu_5$; Group II: $mGlu_2$ and $mGlu_3$; Group III: $mGlu_4$, $mGlu_6$, $mGlu_7$, and $mGlu_8$).[1] Many of these receptors have attracted significant attention as promising targets for the treatment of a variety of CNS related disorders. The design of drug-like compounds that selectively target a specific mGlu has been complicated by the fact that the orthosteric binding site of the mGlus is highly conserved. An alternative strategy that has proven successful for overcoming such selectivity hurdles has been the optimization of compounds that modulate the function of the receptor through interaction with an allosteric binding site.[2]

An area within the mGlu allosteric modulator field that has garnered substantial interest has been the design and application of selective small molecule negative allosteric modulators (NAMs) of $mGlu_1$.[3] Several tool compounds have been discovered during recent years further establishing the link between $mGlu_1$ antagonism and the potential treatment of CNS related disorders such as addiction,[4] anxiety,[5] epilepsy,[6] pain,[5a,7] and psychotic disorders.[5a,8] Compounds **1**–**6** (Fig. 1) are representative of the $mGlu_1$ NAM chemotypes that have been discovered to date and examples of molecules with demonstrated efficacy in vivo. For example, JNJ16259685 (**1**) was efficacious in a rat model of anxiety[9] as well as rat[10] and squirrel monkey[11] models of addiction. A-841720 (**2**) was established as an analgesic in rat models of neuropathic pain[12] and post-operative pain.[13] Inhibition of nociceptive pain was observed with **3** in rats[14] and with YM298198 (**4**) in mice.[15] Antipsychotic activity as measured by acoustic prepulse inhibition models was noted with **5**[16] and **6**[17] in rats and with **1**[8] and **4**[8] in mice. Also of interest, recent research has identified a potential role for $mGlu_1$ inhibition in the treatment melanoma[18] and certain types of breast cancer.[19]

We have recently become interested in the discovery and development of structurally novel $mGlu_1$ NAMs with properties suitable

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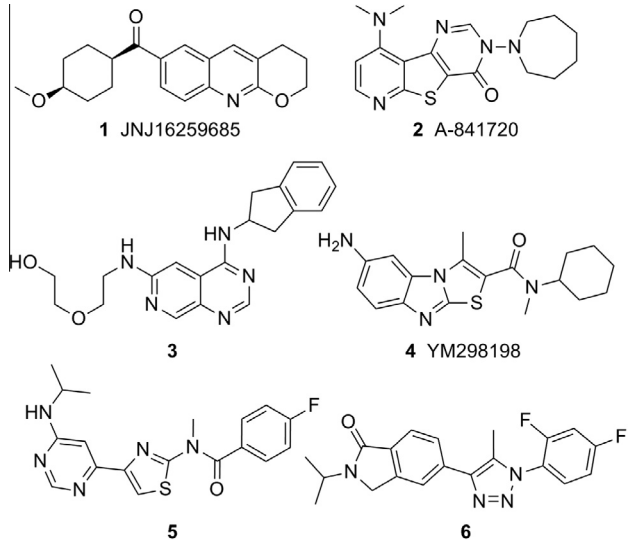
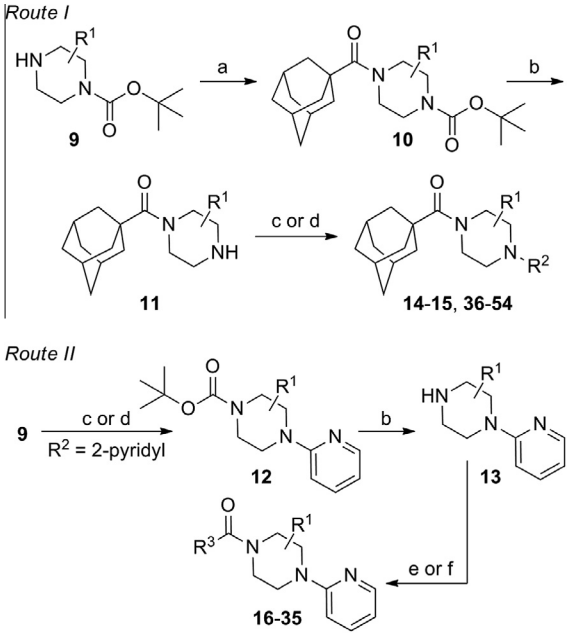



**Figure 1.** $mGlu_1$ NAM compounds with in vivo efficacy.

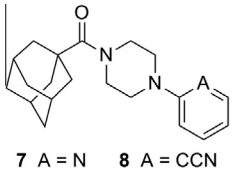



**Scheme 1.** Reagents and conditions: (a) 1-adamantoyl chloride, DIEA, $CH_2Cl_2$; (b) HCl, MeOH, dioxanes; (c) $R^2F$, NMP, $\mu$ wave, 250 °C, 10 min; (d) $R^2X$ (X = Cl, Br, or I), $Pd_2(dba)_3$ or $Pd(OAc)_2$, Xantphos, $NaO^tBu$ or $Cs_2CO_3$, dioxanes, $\mu$ wave, 120 °C, 10 min or 100 °C, 18 h; (e) $R^3COCl$, DIEA, $CH_2Cl_2$; (f) $R^3CO_2H$, HATU, DIEA, $CH_2Cl_2$.

for evaluation in rodent models of a variety of CNS disorders. A potential starting point for a hit to lead optimization program focused on $mGlu_1$ NAMs was identified through cross screening during the course of our recent work in the $mGlu_5$ NAM field (Fig. 2).[20] The adamantyl carboxamides **7** and **8** were $mGlu_5$ NAMs that were also found to behave as $mGlu_1$ NAMs in a functional cell based assay.[21] Our $mGlu_1$ assay measures the ability of the compound to block the mobilization of calcium by an $EC_{80}$ concentration of glutamate in cells expressing human $mGlu_1$.

One attractive feature of this scaffold was the fact that robust chemistry would allow to us to rapidly vary three distinct portions of the chemotype and evaluate considerable synthetic diversity (Scheme 1). For instance, commercially available and enantiopure piperazines **9** ($R^1 = CH_3$) were useful for evaluating substitution of the piperazine core. For the purpose of evaluating SAR about the aryl portion of the chemotype ($R^2$), substituted piperazines **9** were reacted with adamantoyl chloride to afford amide intermediates **10**. Removal of the carbamate protecting group under acidic conditions gave amine intermediates **11**. Target compounds were accessible from amines **11** through nucleophilic aromatic substitution reactions with aryl fluorides or Buchwald–Hartwig[22] amination reactions with suitable aryl halides.[23] For evaluation of SAR around the amide portion of the scaffold, a simple reorganization of the synthetic transformations was required. Reaction of amines **9** with either 2-fluoropyridine or 2-bromopyridine under appropriate conditions provided intermediate **12**. Following cleavage of the protecting group, amines **13** were readily converted to the target amide compounds using well established methods.[24]

Evaluation of methyl substituted piperazines was one of our first areas of investigation (Table 1). New compounds were prepared with the 2-pyridyl group found in hit **7** (**14**–**17**). Evaluation of these enantiopure analogs yielded some interesting results. A preference with regard to the $mGlu_1$ NAM activity was observed for one enantiomer versus the other in the case of both the 2-methyl and 3-methyl analogs. With the 2-methyl analogs a 15-fold preference was observed for the *R*-enantiomer (**15** vs **14**), while with the 3-methyl analogs a sixfold preference was observed for the *R*-enantiomer (**17** vs **16**). Furthermore, both **15** and **17** were approximately fourfold more potent than the unsubstituted comparator **7**. Moreover, an equally substantial discovery was noted upon testing of **15** and **17** in our functional $mGlu_5$ assay.[25] Both compounds were only weak antagonists in this assay ($IC_{50}$ >10 μM). In short order, we had moved from a hit compound with little to no group I mGlu selectivity to two compounds with more than 60-fold selectivity for $mGlu_1$ versus $mGlu_5$.




| | human $mGlu_1$ $IC_{50}$ | rat $mGlu_5$ $IC_{50}$ |
|---|---|---|
| **7** | 630 nM | 990 nM |
| **8** | 649 nM | 2350 nM |

**Figure 2.** $mGlu_1$ NAM starting points for hit to lead optimization.

We next chose to evaluate SAR around the amide portion of the chemotype in the context of both the (*R*)-2-methyl piperazine (series I) and the (*R*)-3-methyl piperazine (series II) cores (Table 2). A number of analogs (**18**–**35**) were prepared in an attempt to identify replacements for the 1-adamantyl group. This was not generally successful; however, there were some notable exceptions. In the context of the (*R*)-2-methyl piperazine but not the (*R*)-3-methyl piperazine, the cyclooctyl (**26**) and the *trans*-(*tert*-butyl)cyclohexyl (**30**) groups demonstrated weak to moderate NAM activity against $mGlu_1$. Additionally, the bicyclo[3.3.1]nonan-3-yl (**32**) group was essentially equipotent to **15**, though this was again not effective in the case of the (*R*)-3-methyl piperazine (**33** vs **17**). It has been reported that the cubyl group can function as an effective and less lipophilic isosteric replacement for the adamantyl group.[26] Unfortunately, such a modification was not effective in our chemotype (**34** and **35**).

Our attention next moved from the amide to the aryl portion of the template (Table 3). Using an approach similar to that previously described, we again observed only weak antagonists (**37**, **41**, **43**, **45**) and a compound (**39**) with no activity at the top concentration tested (30 μM) in the context of the (*R*)-3-methyl piperazine. Fortunately, the same was not observed with the (*R*)-2-methyl piperazine analogs. Though 4-pyridyl analog **38** demonstrated only weak $mGlu_1$ NAM activity, 3-pyridyl analog **36** exhibited good potency. Good to moderate potency was also noted with