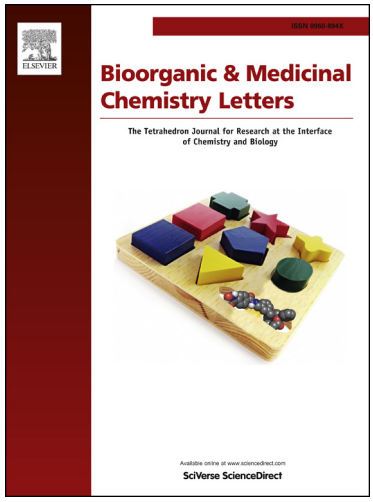

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Octahydropyrrolo[3,4-*c*]pyrrole negative allosteric modulators of $mGlu_1$

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Abstract—Development of SAR in an octahydropyrrolo[3,4-*c*]pyrrole series of negative allosteric modulators of $mGlu_1$ using a functional cell-based assay is described in this Letter. The octahydropyrrolo[3,4-*c*]pyrrole scaffold was chosen as an isosteric replacement for the piperazine ring found in the initial hit compound. Characterization of selected compounds in protein binding assays was used to identify the most promising analogs, which were then profiled in P450 inhibition assays in order to further assess the potential for drug-likeness within this series of compounds.

L-glutamic acid (glutamate) is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Activation of both ionotropic and metabotropic glutamate receptors occurs following binding to glutamate. The metabotropic glutamate receptors (mGlus) are members of family C within the broader G protein-coupled receptor (GPCR) family. The eight known mGlus have been further classified according to their structure, preferred signal transduction mechanisms, and pharmacology (Group I: $mGlu_1$ and $mGlu_5$; Group II: $mGlu_{2-3}$; Group III: $mGlu_{4-8}$).[1] The majority of these receptors have attracted the attention of researchers as potential therapeutic targets due to their association with a variety of CNS related disorders. Initially, work toward the design of drug-like orthosteric ligands that selectively bind a specific mGlu proved challenging. Perhaps this is not surprising, given that the orthosteric binding site across the mGlu family is highly conserved. A more recent approach that yielded more selective compounds has been the design and development of small molecules that modulate the activity of the receptor, either positively or negatively, through binding to an allosteric site.[2]

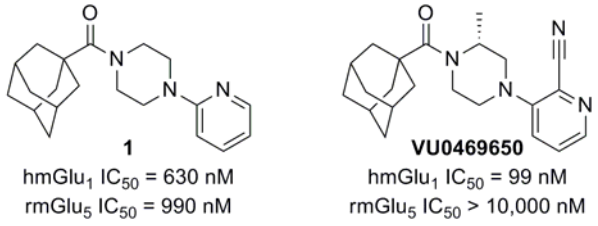

Figure 1. $mGlu_1$ NAM initial hit **1** and tool compound VU0469650

The design of selective small molecule negative allosteric modulators (NAMs) of $mGlu_1$ has been a fruitful area of research within the mGlu allosteric modulator field.[3] Multiple tool compounds have been discovered during recent years, and their evaluation in behavioral models has further established a potential for therapeutic benefit in a number of CNS-related disorders. Examples include addiction,[4] anxiety,[5] epilepsy,[6] pain,[5a,7] and psychotic disorders.[5a,8] Recent publications have also noted a potential role for $mGlu_1$ inhibition in the treatment of melanoma[9] and certain types of breast cancer.[10] We recently reported our own initial efforts directed toward the discovery and optimization of structurally novel $mGlu_1$ NAMs.[11] In