ACS Chemical Neuroscience

IN THIS ISSUE

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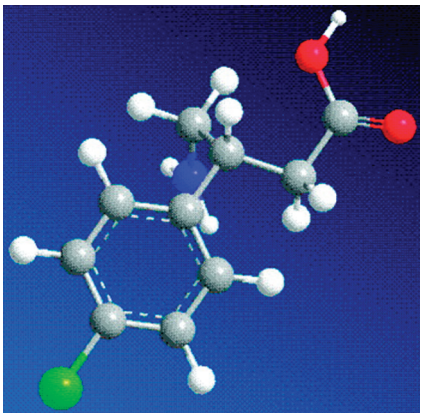
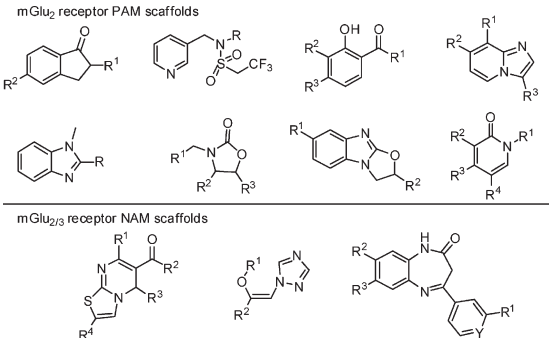
Approaches Toward Curing Fragile X Syndrome



Fragile X syndrome (FXS) is an inherited condition caused by the mutation of a single gene. FXS is characterized by autism and severe mental and cognitive impairment as well as a characteristic physical appearance. The underlying mutation occurs in the 5′-untranslated region (UTR) of the fragile X mental retardation 1 gene (*FMR1*). Typically, the UTR of this gene is characterized by 40−50 CGG repeats. However, confirmed cases of FXS can possess >200 of these trinucleotide repeats which decreases *FMR1* transcription. In the current issue, Healy et al. (DOI: 10.1021/cn200019z) review the latest approaches to treating this debilitating condition.

The authors provide a compilation of possible pharmaceutical targets for treating FXS. The targets include group I metabotropic receptor, mGluR5, γ-aminobutyric acid receptor, $GABA_B$, muscarinic-acetylcholine receptors, as well as enzymes such the GTPase, Rac1, and its associated p21-activated kinase implicated in actin polymerization. The authors also list modulatory compounds which affect these therapeutic targets. This review is an important read for researchers interested in the latest developments of potential approaches for treating FXS.

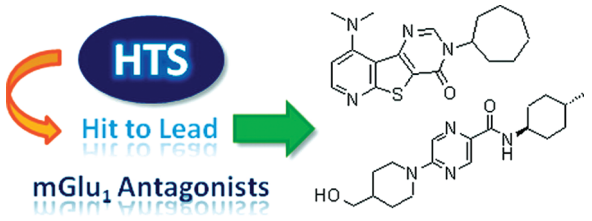
Modulating Glutamatergic Signaling the Group II mGlu Receptors Way



The Group II metabotropic glutamate (mGlu) receptors activate a G-protein that reduces the formation of cAMP by inhibiting adenylyl cyclase. This class of receptors present in the presynaptic region comprises two subtypes, metabotropic glutamate 2 ($mGlu_2$) and metabotropic glutamate 3 ($mGlu_3$). Importantly, mGlu receptors have been identified as possible therapeutic targets for treating neuropsychiatric and neurodegenerative diseases. In this issue, Sheffler et al. (DOI: 10.1021/cn200008d) offer a much-needed update on recently identified compounds that modulate mGlu receptors.

The authors focus their efforts on cataloging positive and negative allosteric regulatory compounds of mGlu receptors. In particular, several new positive allosteric modulators for $mGlu_2$ receptors and negative allosteric modulators for both $mGlu_2$ and $mGlu_3$ receptors have been identified through exhaustive structure−activity relationship studies. Importantly, the authors provide an overview of the behavioral effects of these compounds and, in doing so, help identify compounds offering the highest therapeutic promise.

Lessons Learned from Targeting a Key Glutamate Receptor



The metabotropic glutamate receptor 1 ($mGlu_1$) belongs to the Group I class of metabotropic glutamate receptors involved in phospholipase C activation and the resultant release of intracellular calcium. These mGlu1 receptors are localized in the postsynaptic region and bind excitatory neurotransmitter glutamate in the orthosteric site. Recent in vivo models suggest $mGlu_1$ receptors may be a possible target in pain therapy and may also play a role in several neurological disorders. In this issue, Dafydd Owen (DOI: 10.1021/cn2000124) focuses on the design and synthetic strategies for potential therapeutic compounds that modulate $mGlu_1$.

Recently, there has been decreased emphasis on the design of orthosteric (glutamate) binding site ligands and a greater focus on the creation of allosteric modulators of $mGlu_1$. While the author overviews some of the latest work involved in identifying effective orthosteric ligands, most of the content in the review covers the efforts of pharmaceutical companies such as Pfizer, Abbot, GlaxoSmithKline, Merck-Banyu, Schering-Plough, and Merz to design effective allosteric modulators with better drug properties. The author also provides a cautionary reminder surrounding the mechanistic safety of these compounds and concludes that further research is required before a real drug targeting $mGlu_1$ is identified.

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