POSITIVE ALLOSTERIC MODULATORS OF mGluR8 : DESIGN AND DEVELOPMENT

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It is widely acclaimed that targeting monoamine systems may not be the optimal strategy to treat complex CNS diseases such as schizophrenia. In recent years, group III metabotropic glutamate receptors (mGluR's) emerged as a potential therapeutic target for treatment of schizophrenia, Parkinson's disease, anxiety disorders, autism.[1] mGluR's are G_I/G_0 positively coupled class C GPCR's. The orthosteric binding site is located in venus flytrap domain while the allosteric site is located in seven transmembrane domain.

Our studies are focused on allosteric ligands which may exhibit properties superior to traditional orthosteric modulators, mainly due to only mild interference with endogenous glutamate. We have developed two distinctive series of mGluR8 agonist-positive allosteric modulators (ago-PAMs) using scaffold hopping and scaffold decoration approaches. These compounds were compared to the only commercially available mGluR8 ago-PAM, **AZ-12216052**.[2] Lead compound **AH-48** acts as a Positive Allosteric Modulator, EC_{50} = 3.1 μM in the presence of 1 μM L-Glu; **AH-48** activates mGluR8 as an agonist (EC_{50} = 2.6 μM); activity of **AH-48** with or without presence of L-Glu is completely abolished by 10 uM of **LY341495** (synthetic orthosteric antagonist), **AH-48** is not mGluR4 selective, **AH-48**, **MAH-14** and **MAH-15** act as mGluR8 full PAM-agonist (**MAH-14** EC_{50} = 4.4 μM, **MAH-15** EC_{50} = 5.7 μM), in contrast to benchmark compound **AZ12216052** which activates the receptor only partially. The series are still under lead optimization; better selectivity and compound solubility are sought. Patent application is in preparation.

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References

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