

FINDING ALLOSTERIC MODULATORS OF METABOTROPIC GLUTAMATE RECEPTORS AS POTENTIAL CNS DRUGS

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CNS drug design remains an exclusively challenging area of medicinal chemistry. On one side, most CNS targets are G-Protein Coupled Receptors; finding selective and functional GPCR ligands is very work demanding. Another problem is narrow window of physicochemical properties which allows molecules to enter the brain and be orally bioavailable.

Glutamate is the main excitatory neurotransmitter in central nervous system (CNS). It is an essential molecule, eg. for cognitive functions such as memory formation and learning [1].

Metabotropic glutamate receptors belong to family C GPCR's - the orthosteric binding site is located in 'venus flytrap' domain. The allosteric binding site is located in the transmembrane part of the receptor. Group III metabotropic glutamate receptors (mGluR4, mGluR6, mGluR7 and mGluR8) are potential therapeutic targets for neurological disorders, e.g. Parkinson's disease, schizophrenia, major depressive disorder and pain [2]. Apart from the traditional concept of finding orthosteric ligands, mGluR allosteric modulation is considered a very promising approach [3]. Due to little differences in the aminoacid sequences of orthosteric binding sites of mGluR4, mGluR7 and mGluR8, finding selective ligands is notoriously difficult. The allosteric approach is beneficial as it does not interfere with natural regulatory processes. It is advantageous to either enhance or decrease the action of natural orthosteric agonist than to substitute for.

We have developed a series of mGluR4/mGluR8 positive allosteric modulators (PAM). Compound AH-48 is a first in class mGluR8 PAM/allosteric agonist (ago-PAM).

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ACKNOWLEDGEMENTS

The study was partially supported by the Polish-Norwegian Research Programme operated by the National Centre for Research and Development under the Norwegian Financial Mechanism 2009-2014 in the frame of Project PLATFORMex (Pol-Nor/198887/73/2013).

Databases in this study were created using ChemAxon JChem software