**PP13**

# The development of mGluR8 PAM agonists

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Glutamate is the main excitatory neurotransmitter in the central nervous system, which is essential for cognitive functions such as memory formation and learning.[1] Group III metabotropic glutamate receptors (mGluR4, mGluR6, mGluR7 and mGluR8) are considered promising drug targets for treatment of neurological disorders e.g. Parkinson's disease, schizophrenia, major depressive disorder and pain.[2]

We have synthesized and evaluated chemical scaffold (compounds **AH-48**, **MAH-14** and **MAH-15**) exhibiting mGluR8 Positive Allosteric Modulator activity along with a strong agonistic component. **AH-48** has the following characteristics:

- activates mGluR8 as an agonist ($EC_{50}$ = 2.6 uM),
- acts as a Positive Allosteric Modulator ($EC_{50}$ = 4.3 uM in the presence of 1 uM L-Glu),
- activity of AH-48 with or without presence of L-Glu is completely abolished by 10uM of **LY341495**,
- **AH-48** acts as mGluR8 full PAM-agonist in contrast to benchmark compound **AZ12216052** which activates the receptor only partially,
- **AH-48** activates mGluR4 and mGluR7,
- **MAH-14** acts as a mGluR8 PAM ($EC_{50}$ = 4.4uM),
- **MAH-15** acts as a mGluR8 PAM ($EC_{50}$ = 5.7uM).

We plan further tests (metabolic stability, genotoxicity, anti-target assays) which will help us establish lead structure in the study.

[1] McEntee W. J., Crook T. H. *Psychopharmacology*. 111 (1993) 391.

[2] Hovelsø N., Sotty F., Montezinho L. P. et al. *Curr. Neuropharmacol.* 10 (2012) 12.

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