LEAD OPTIMIZATION OF A NOVEL NEGATIVE ALLOSTERIC MODULATORS OF mGlu7 RECEPTOR

Katarzyna Kaczorowska[†], **Anna Stankiewicz**[†], **Maria Paluchowska**[†], **Aneta Kozioł**[†], **Piotr Brański**[‡], **Grzegorz Burnat**[‡], **Andrzej J. Bojarski**[†], **Andrzej Pilc**[‡]

Department of Medicinal Chemistry[†]*, Department of Neurobiology*[‡]
Institute of Pharmacology Polish Academy of Sciences, 12 Smętna Street, 31-343 Kraków

k.kaczor@if-pan.krakow.pl

The metabotropic glutamate receptors (mGluRs) represent the largest family of membrane receptors and have been important targets for drug development. Group III is the largest group of mGluRs and plays significant neuromodulatory roles throughout the brain [1]. The metabotropic glutamate receptor 7 (mGluR7) is localized presynaptically at the active zone and is a member of group III family that binds to protein G and inhibits the adenylate cyclase [2]. High mGluR7 expression is observed in several brain regions involved in reward, cognition and emotion, such as cortex, hippocampus and other forebrain regions [1-5]. The wide distribution in the central nervous system (CNS) suggest that mGluR7 is an important target for therapeutic intervention in a number of neurological and psychiatric disorders including anxiety, post-traumatic stress disorder, depression, autism, drug abuse, and schizophrenia [1-5]. The first nanomolar selective brain penetrant ligand ADX71743 (NAM mGluR7) discovered by Kalinichev et al., in 2013 seems to be crucial for understanding mGluR7 function [1,6].
Our drug development effort, resulted in production of number of active molecules, which showed variable selectivities for mGluR7 as well as mGluR4 and mGluR8. The present in-vitro and in-vivo results have shown that our novel derivatives are becoming promising mGluR7 negative allosteric modulators and may have potential as analgesic agents or antipsychotics.

References:
1. E. Palazzo et al., Current Neuropharmacology, 14 (2016), 504-513.
2. G. Suzuki et al., J.Pharmacol. Exp. Ther, 323 (2007), 147-156.
3. Xia Li et al., Neuropharmacology, 54 (2008), 542-551.
4. A.V. Golubeva et al., Current Drug Targets, 16 (2015), 1-80.
5. Masksymetz et al., Molecular Brain, 10 (2017), 1-19.
6. M. Kalinichev et al., J.Pharmacol. Exp. Ther., 344 (2013), 624-636.