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New Derivatives of Indole – Analogues of MMPIP – an Allosteric Modulator of the Metabotropic Glutamatergic Receptors mGluR7.

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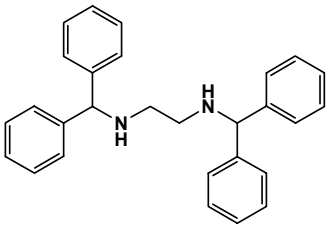
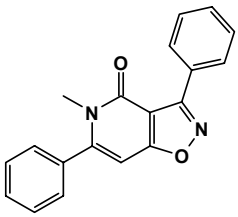
The mGluRs have recently become attractive therapeutic targets for drug development for the treatment of CNS diseases. So far, major drug discovery programs have largely focused on group I (mGlu1 and 5) and II (mGlu2 and 3) mGlu receptors, which have been implicated in neuropathological and various psychiatric disorders. The mGluR4, 7 and 8 belongs to III group of metabotropic glutamate receptors are especially promising, however, they were significantly less studied, mainly due to the limited number of specific agents. Recent advances in the identification of selective or specific compounds, and the generation of transgenic animals have, however, revealed important insights into the potential role of group III receptors in the pathophysiology of neurological and mood disorders.

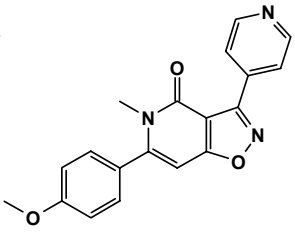
One of the main topic of the project ModAll, currently realized in the Institute of Pharmacology PAS, is the discovery of new selective allosteric modulators of mGluR7. Only a few selective mGlu7 receptor non-competitive agents are reported to date. The first selective mGluR7 allosteric agonist – AMN082 and antagonist – MDIP were identified by random high-throughput functional screening of chemical library, whereas MMPIP was obtained by subsequent chemical modification of MDIP [1,2]. In our approach, based on the MMPIP pattern, the new series of indole derivatives were designed and synthesized. The new compounds are currently under pharmacological evaluation.



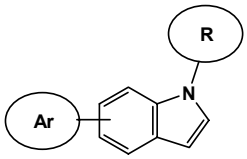
AMN082



MDIP



MMPIP



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[1] Mitsukawa K. et al.: *Proc. Natl. Acad. Sci. USA 102(51) (2005)*, 18712-7.
[2] Suzuki G. at al.: *J. Pharmacol. Exp. Ther. 323(1) (2007)*, 147-56.