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Azo Dyes as Potential Allosteric Modulators of the Metabotropic Glutamate Receptors mGluR4.

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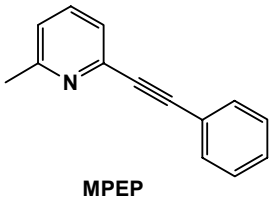
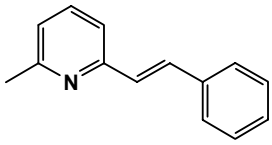
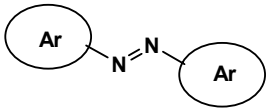
The glutamatergic system regulation by the metabotropic receptors (mGluR) appears as promising new therapy of central nervous system disorders. Until now, drug discovery programs have mainly focused on group I (mGluR1 and 5) and II (mGluR2 and 3). However, recent publications revealed high therapeutic potential of metabotropic glutamatergic receptor ligands of group III e.g. mGluR4, 7, and 8. Especially it seems that the non-competitive ligands (positive and negative allosteric modulators), which bind to the transmembrane heptahelical domain of mGlu receptors may have potential antidepressant properties. Moreover, the allosteric modulation of mGluR gives possibilities to more selective interactions with individual subtypes of mGluR family and increased tolerance in comparison to competitive agonists/antagonists.
The research progress of allosteric modulation of receptors group III is hampered mainly due to the very limited number of specific compounds.
The Department of Medicinal Chemistry is currently engaged in project (acronym “ModAll”) concerning among others discovery of mGluR4 selective modulators. On the basis of known non-competitive mGluR5 agonists – MPEP and SIB-1893, which are classified also as positive allosteric modulators of mGluR4 [1], a series of azo dyes – structural analogues of SIB-1893 – was designed and synthesized. The received compounds are currently evaluated in pharmacological tests.



MPEP



SIB-1893



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[1] Mathiesen J. M. et al.: *Br. J. Pharmacol. 138 (2003)*, 1026-1030.