NEW DERIVATIVES OF HETEROCYCLES AS A SOURCE OF POTENTIAL ALLOSTERIC MODULATORS OF GROUP III METABOTROPIC GLUTAMATE RECEPTORS

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Allosteric modulation of metabotropic glutamate receptors is new and attractive approach in research of GPCR targets. The third group of mGluRs (subtypes: 4, 7 and 8) are especially promising, however, they were significantly less studied due to insufficient amount of known modulators so far. Main advantages of allosteric mechanism, over traditional orthosteric agonists/antagonists, is that they exert their effects only in the presence of the endogenous ligand, and provides the possibility for more selective interaction with different subtypes of mGluR family. Moreover, the probability of receptor desensitization can be reduced, that gives hope for the development of new, safer treatments for central nervous system diseases [1].

The first step of the research was to create the compounds database with confirmed allosteric activity toward group III mGluR (more than 500 compounds) and grouping them into clusters of similar structure. A new derivatives of heterocyclic systems were designed based on the pattern of one group from the cluster. Indole, azaindole, indazole and other heterocyclic rings used as the central core were combined with appropriately substituted benzoyl and arylsulfonyl moieties. Pharmacophore models were developed from the known active ligands and mapping was performed for all proposed structures. The compounds of the best match were synthesized and then tested for the activity towards mGluR4.

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References

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