IL-01

# Molecular Design of Bivalent or Dual Action Drugs

N. S. Zefirov, V. A.Palyulin, O. N. Zefirova

*Department of Chemistry, M. V. Lomonosov Moscow State University, Moscow 119991, Russia; E-mail: zefirov@org.chem.msu.ru;*
*Institute of Physiologically Active Compounds RAS, Chernogolovka, Moscow Region, 142432, Russia*

Design of new drugs is a sophisticated process involving the application of molecular modeling and QSAR techniques, virtual screening and molecular docking. The joint application of these approaches provides deeper understanding of both structure-activity relationships and ligand-receptor interactions as well as facilitates lead finding and optimization.

For the above discussed design the molecular models of all closed and open forms of metabotropic ($mGluR_{1-8}$) and ionotropic (NMDA and AMPA) glutamate receptors, adenosine, melatonin, $GABA_A$ and $GABA_C$ receptors and tubulin have been either built or refined. The docking of known agonists, antagonists, modulators, and channel blockers into the models was used to reveal binding modes of ligands and to explain known structure-activity relationships.

Dual action of a drug can be sub-classified into (1) its action on two different biotargets and (2) action on two different sites of the same biotarget. The first case will be exemplified by our design of new neuroprotective compounds. The second case will be clarified using (a) the bivalent positive modulator of AMPA receptor and (b) dual action conjugate of colchicine with a "simplified" taxol analogue interacting with tubulin.

This approach was successfully used in the design of new neuroprotectors with cognition enhancing properties (extraordinary high potency of some designed compounds starting from picomolar concentration had been revealed – absolute record among all currently known positive AMPA receptor modulators) as well as for synthesis of dual action compounds active against human lung carcinoma A549 cell line.

**References**

[1] N.S.Zefirov, V.A. Palyulin, Molecular Modeling of Central Nervous System Receptors, ***Mendeleev Commun.***, 2010, **20**, 243-248.

[2] (a) O.N.Zefirova, V.A. Palyulin, N.S.Zefirov et.al., ***VII All-Russian Conference: Chemistry and Medicine"***, Ufa, 6-8 apr. 2010. Thesis, p 191.
(b) O.N.Zefirova, S.A. Kuznetsov, N.S.Zefirov et.al., ***Bioorg. Med. Chem. Lett.***, 2008, **18**, 5091-5094.