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MOLECULAR MODELLING AND DESIGN OF NOVEL SUBNANOMOLAR AMPA RECEPTOR MODULATORS

Vladimir A. Palyulin (1), Mstislav I. Lavrov (1), Dmitry S. Karlov (1), Eugene V. Radchenko (1), Elena B. Averina (1), Kseniya N. Sedenkova (1), Dmitry A. Vasilenko (1), Anna A. Nazarova (1), Nadezhda S. Temnyakova (1), Polina N. Veremeeva (1), Vladimir L. Zamoyski (2), Vladimir V. Grigoriev (1,2)

1) Department of Chemistry, Lomonosov Moscow State University, Moscow, 119991, Russia
2) Institute of Physiologically Active Compounds RAS, Severny Proezd 1, Chernogolovka, Moscow Region, 142432, Russia

A growing attention is attracted recently to AMPA receptors as a promising target for the development of drugs for the treatment of serious neurological and psychiatric disorders, such as schizophrenia, depression, multiple sclerosis, age-related cognitive and memory disorders, Parkinson's disease, Alzheimer's disease. The positive AMPA receptor allosteric modulators reveal such neurophysiological effects as induction of long-term potentiation of synaptic excitation, considered as a substrate for learning and memory, and significant increase of nerve growth factors expression. This makes them promising compounds for the development of nootropic agents and neuroprotectors. The negative modulators of AMPA receptors are also applicable as drugs and can be used as antiepileptics.

In this communication, a combined approach to the *de novo* design of AMPA receptor modulators is considered including molecular modelling and molecular dynamics simulation of modulator-agonist-receptor complexes. That allowed us to find both positive and negative highly potent allosteric modulators of AMPA receptors with new scaffolds. They include derivatives of 3,7-diazabicyclo[3.3.1]nonane, substituted bis(pyrimidines) and bis-amides with various linkers/spaces. Convenient synthetic approaches were elaborated for the designed compounds. Electrophysiological patch clamp experiments have demonstrated the pronounced influence of the studied compounds in sub-nanomolar concentrations on the kainate-induced currents recorded for Purkinje neurons from rat cerebellum. A series of other in vitro and in vivo studies has shown neuroprotective and cognition-enhancing properties for the positive modulators selected in the patch clamp studies. Several designed compounds have successfully passed preclinical studies.

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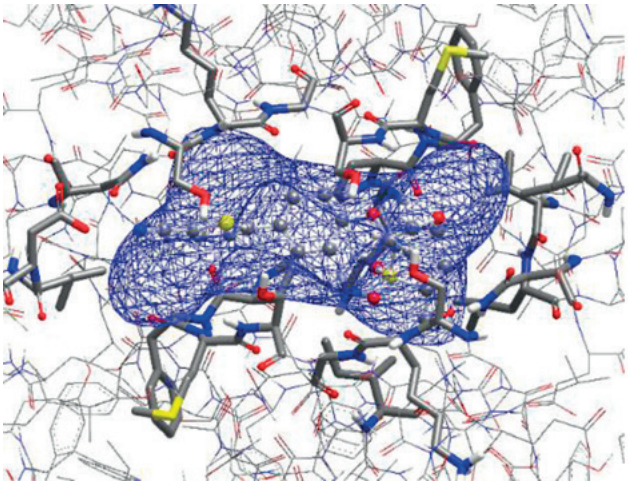

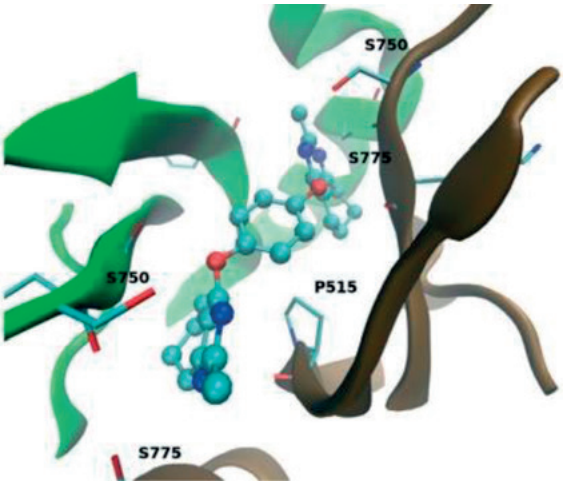

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