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## Ionotropic Glutamate Receptor Modulators: Design of New Scaffolds

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Ionotropic glutamate receptors attract a growing attention in the last decades as promising targets for development of drugs for the treatment of serious neurological and psychiatric disorders, such as schizophrenia, depression, age-related cognitive and memory disorders, Parkinson's disease, Alzheimer's disease, etc. AMPA receptor positive allosteric modulators were shown to reveal such neurophysiologic effects as induction of long-term potentiation of synaptic excitation, considered as a foundation for learning and memory, and significant increase of nerve growth factors expression, making them promising compounds for the development of nootropics and neuroprotectors.

Techniques for computer-aided design of AMPA receptor modulators based on new scaffolds as well as the approaches to their synthesis and the results of physiological activity studies are considered. The molecular dynamics simulations for a series of AMPA receptor PAMs bound on the interface between two glutamate-binding domains have demonstrated a good correlation of calculated binding energies with the experimental $pEC_{50}$ values. The Molecular Field Topology Analysis (MFTA) QSAR method was quite helpful in the modeling of ligand selectivity and multi-target activity in terms of local properties such as the atomic charges, group van der Waals radii, and local lipophilicity. In addition, the 3D QSAR and pharmacophore models of the AMPA receptor PAMs have been constructed. The *de novo* design of structures fitting the PAM binding site and based on new scaffolds allowed us to find novel highly potent positive allosteric modulators of AMPA receptors that have a unique combination of properties.

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