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(S)-EL-7 new selective competitive antagonists for AMPA and KA receptors

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Ionotropic glutamate receptors (iGluRs) constitute a family of ligand gated ion channels subdivided in three classes NMDA, AMPA (iGluA1-4) and KA (iGluA5-7 and KA1,2) according to the agonist that selectively activates them. They are critically important for normal brain function and are considered to be involved on neurological disorders and degenerative diseases such schizophrenia, Alzheimer's disease, brain damage following stroke and epilepsy. Extensive studies on GluA2 receptors were performed and many crystal structures as complexes of GluA2-LBD with agonists, partial agonists and antagonists were obtained. AMPA receptor antagonists are considered to have clinical potential as neuroprotective drug candidates. In order to identify the structural determinants for receptor selectivity between homomeric AMPA and KA receptors a serial of rigid and flexible biaromatic alanine derivatives carrying selected hydrogen bond acceptors and donors has been synthesized based on published X-ray structure of competitive antagonist (S)-ATPO co-crystallized with iGluR2(S1S2J) LBD. The compounds were tested in radioligand binding studies on recombinant iGluA1-7 receptors. Based on these results and on the results obtained from molecular modeling studies, important structure-activity relationships at AMPA and GluR5 were established. A group of compounds selective for either GluR5 or AMPA receptors were identified. Suitable crystals for X-ray crystallography were obtained from (S)-EL-7-iGluR2 (S1S2J) complex. This X-ray structure provides structural information on the water-mediated interactions between the ligand and Tyr702, a non-conserved amino acid residue within the ligand binding pocket among the four AMPA receptor subunits. It has been identified as important determinant for AMPA receptor agonist subunit selectivity. This position is not responsible for the observed subunit selectivity of (S)-EL7 as it was expected from the results acquired with molecular docking which suggested direct hydrogen bonding. The domain closure achieved by (S)-EL-7 ranges between 6.9˚-9.2˚ value in between what has been observed previously for antagonists (ATPO:2.5˚-5.1˚) and partial agonist (KA:13˚).

Biography

Zorica Naumovska is working currently as an Assistant Professor in Faculty of Pharmacy in Skopje, Macedonia in the Institute for Pharmaceutical Chemistry and is involved in teaching and research in Pharmaceutical Chemistry, Drug Discovery and Development, Pharmacogenetics, Drug Information and Clinical Pharmacy. She has finished her Master's degree working on the project in collaboration with Department of Drug Design and Pharmacology in Faculty of Health and Medical Sciences in University of Copenhagen. Her fields of interest are neurodegenerative and psychiatric diseases and she has defended PhD thesis considering influence of polymorphic variation of metabolic enzymes and transporter proteins in drug responses for these diseases. She has specialization in Drug Information and is Head of the National Drug Information Centre since 2014. She is active member in ISPOR-Macedonia, Pharmaceutical Association of the RM, Pharmaceutical Chamber of the RM, and European Association of Clinical Pharmacy.

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