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S.M.A.R.T: Steroids-NMDA receptors modulators acting as CNS therapeutics

N-Methyl-D-aspartate receptors (NMDARs) play an important role in development, synaptic plasticity, learning and memory; however, abnormal activation of NMDA receptors has been shown to mediate neuronal degeneration/cell death. The NMDA receptor activity can be modulated by various ligands, including neurosteroids. To find novel potentially beneficial drugs to treat neurological damage/neurodegeneration is one of the most investigated areas in contemporary pharmacology and neuroscience. Therefore, we designed and synthesized SMART Steroids– Steroidal Molecules As Rapid-acting Therapeutics. SMART Steroids are neuroactive molecules, targeting primarily the NMDA receptors and show neuroprotective properties and minimal side effects in animal models. Our screening pipeline covers physicochemical and biological properties like: (i) Solubility (DLS); (ii) lipophilicity (logP, logD, ΔG_{solv}); (iii) patch-clamp recordings from HEK293 cells assessing NMDAR inhibition rates and IC_{50} values; (iv) Caco-2 assay, (v) treatment of glutamate and NMDA-induced neurotoxicity (survival rate, caspase-3, intracellular calcium levels, ROS); (vi) *in vitro* growth of postnatal neurons after neurosteroid administration, (vii) models of animal behavior (open field, elevated plus maze, forced swim test, etc.); (viii) PTZ-induced seizures; (ix) paclitaxel-induced peripheral neuropathy; and (x) pharmacokinetic properties. Our results indicate that these compounds may be beneficial in treatment of several neurological diseases like epilepsy, neuropathic pain, AD, PD and others.

Biography

Eva Kudova has completed her PhD in 2009 from Charles University in Prague. Then, she spent 2 years in the lab of Douglas F Covey, Washington University School of Medicine in St. Louis, Missouri, USA. She worked as the PI of the Targeted Research Group Neuroprotectives at the Institute of Organic Chemistry and Biochemistry, Academy of Sciences in Prague. Currently, she is the Targeted Research Group Leader Assistant of the group Steroidal Inhibitors at IOCB leading the project Neuroprotective Steroids.

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