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NOVEL SUBNANOMOLAR AMPA RECEPTOR MODULATORS AS NEUROPROTECTORS AND COGNITIVE ENHANCERS

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The glutamatergic system is a promising target for the development of drugs which could restore the functionality of the central nervous system after brain accidents accompanied by neuronal inflammatory processes. The desired physiological effects include the restoration or enhancement of cognitive functions, neuroprotective activity, as well as suppression of neurotrophic pain. Among the substances acting on the glutamatergic system in this way, the most interesting are allosteric modulators of AMPA and KA receptors. The positive allosteric modulators of AMPA receptor reveal such neurophysiological effects as significant increase of nerve growth factors expression as well as induction of long-term potentiation of synaptic excitation, considered as a substrate for learning and memory. This makes them advantageous compounds for the development of nootropic agents and neuroprotectors. The negative modulators of AMPA receptors can be employed as antiepileptic drugs.

The manual de novo design of AMPA receptor modulators using previously refined receptor models was supplemented in our work with molecular dynamics simulation of the modulator-agonist-receptor complexes for various possible binding sites. That allowed us to find a series of new positive and negative highly potent allosteric modulators based on several new scaffolds. They include novel tricyclic derivatives of bispidine, substituted bis(pyrimidines) and bis-amides with various linkers/spacers. Convenient synthetic approaches were elaborated and scaled-up for the designed compounds. Electrophysiological patch clamp in vitro 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. Neuroprotective effects were revealed in an oxidative stress model in HT-22 cells, where compounds protect cells from damage also at sub-nanomolar concentrations. The in vivo studies based on behavioral models have shown cognition-enhancing properties for the designed positive modulators. The combinations of these properties with a very low toxicity allowed several compounds to successfully pass the preclinical studies.

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INDOLE-BASED DUAL COMPOUNDS TARGETING TSPO/CARBONIC ANHYDRASES AS A POTENTIAL TREATMENT OF NEURODEGENERATIVE DISEASES

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The translocator protein (TSPO) is an 18 kDa mitochondrial protein that is overexpressed in neuroglia in response to brain injury, making it a widely recognized marker of neuroinflammation, characteristic of neurodegenerative diseases. TSPO plays a crucial role in steroidogenesis, as it is involved in the internalization of cholesterol into the mitochondrion, the rate-limitingstep, thereby leading to the synthesis of anti-inflammatory steroid products, including neurosteroids. [1]

Carbonic Anhydrases (CAs) are enzymes that primarily catalyze the interconversion between carbon dioxide and bicarbonate through a metal hydroxide nucleophilic mechanism. Within the active site of α-CAs, a zinc (II) ion is coordinated with three histidine residues and a water molecule when the enzyme is inactive. Upon losing a proton, the enzyme becomes active. In the native state of the enzyme, the proton transfer occurs thanks to a proton shuttle, typically represented by the imidazole group of His64. Thus, a compound capable of acting as an additional proton shuttle can activate CAs. Activation of CAs has been identified as a potential therapeutic strategy for treating neurodegenerative diseases by promoting synaptic strength. [2]

In this respect, the objective of the present study is to develop dual derivatives capable of modulating both TSPO and CAs, aiming to obtain molecules with therapeutic potential for neurodegenerative diseases. Specifically, the basic structure of 2-phenylindol-3-ilglyoxylamide (PIGAs) derivatives [3], a class of highly selective and affine TSPO ligands, was modified by incorporating a protonatable chain to obtain compounds (Figure 1) capable of transferring a proton into the CA active site, while maintaining strong affinity for TSPO.

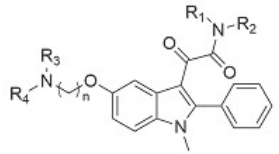

Figure 1.General structure of dual compounds

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