DETERMINATION OF THE MECHANISM OF CONCOMITANT ANTI-INFLAMMATORY ACTIVITY IN A NEW ANTICONVULSANT AGENT - A PYRAZOLOPYRIMIDINE DERIVATIVE

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Introduction. The pathogenic processes of seizure generation and recurrence are the subject of intensive preclinical and clinical investigations as their identification would enable development of novel treatments that prevent epileptic seizures and reduce seizure burden. As a crucial component of brain innate immunity, neuroinflammation initially contributes to neuronal tissue repair and maintenance. However, chronic inflammatory processes within the brain and associated blood–brain barrier impairment often cause neurotoxicity and hyperexcitability. Mounting evidence points to a mutual facilitation between inflammation and epilepsy, suggesting that blocking the undesired inflammatory signaling within the brain might provide novel strategies to treat seizures and epilepsy. Neuroinflammation is primarily characterized by the upregulation of proinflammatory mediators in epileptogenic foci, among which cyclooxygenase-2 (COX-2), interleukin-1b (IL-1b), transforming growth factor-b, toll-like receptor 4, high-mobility group box 1, and tumor necrosis factor-a have been extensively studied. Clearly, the presence of concomitant anti-inflammatory activity in a anticonvulsant substance is a desirable and effective combination.

Aim. The aim is to determine the molecular mechanisms of the anti-inflammatory action of 1-(4-methoxyphenyl)-5-(2-(4-(4-methoxyphenyl)piperazine-1-yl)-2-oxo-ethyl)pyrazol[3,4-d]pyrimidin-4-one.

Materials and methods. Virtual experiments were conducted using BioviaDraw2021, Biovia Discovery Studio2021, AutoDock Vina, AutoDock Tools, OpenBabel.The biomolecular target was acquired form Protein Data Bank: COX-2 (PDB ID 3LN1 and 4M11), CASP1(PDB ID 6PZP).

Results and discussion. The promising properties of 1-(4-methoxyphenyl)-5-[2-[2-[4-(4-methoxyphenyl)piperazine-1-yl]-2-oxo-ethyl]pyrazol[3,4-d]pyrimidin-4-one as a novel anticonvulsant agent have been proven by extensive *in vivo* studies, in line with international approaches to finding new AEDs. To predict the anti-inflammatory activity of a promising anticonvulsant drug, study its molecular mechanisms and determine the feasibility of an *in vivo* experiment, docking to cyclooxygenase-2 (COX-2) and IL-1β-converting enzyme inhibitor sites was performed. Validation of the docking methodology was performed by a re-docking procedure for the reference ligands – celecoxib, meloxicam and VX-765, respectively. The following level of affinity of the investigated ligand was predicted: -8.9 kcal/mol versus -12.2 kcal/mol for celecoxib in COX-2, -7.2 kcal/mol versus -10.5 kcal/mol for meloxicam in COX-2; -7.2 kcal/mol which corresponds to the value of VX-765 in IL-1β converting enzyme.

Conclusions. Detailed conformational placement of the ligand relative to the reference drugs showed a high probability of inhibiting cyclooxygenase 2 via the celecoxib site and a high degree of probability of anti-inflammatory activity, respectively.