Evaluation in silico and ex vivo: Determining affinity, selectivity and presumable allosteric modulation of new compounds towards β1/β2 adrenoceptors

José Raúl Bahena Herrera, Erik Andrade Jorge, Jesus García Gámez, Marvin Soriano Ursua and José G Trujillo Ferrara
Instituto Politécnico Nacional, México

Adrenergic receptors are important targets for pharmaceutical development and physiological studies. Although several drugs have been designed as agonist/antagonist for these receptors, the insights for rational design of highly selective molecules are still not widely described nor used. Therefore the aim for the present study was to determine the affinity and selectivity of a series of new rationally designed isoindoline derivatives with β1/β2 adrenoceptors. We performed a global and local reactivity evaluation of the best ligands with β2 adrenoceptor in order to understand the selectivity of the binding pocket. The results of the in silico experiments suggest that our molecules might be metabolized by CYP450 and they are in agreement with the Lipinski's rule of five; the docking studies show that the ligands interact with the orthosteric site of β2-adrenoceptors and with the orthosteric and allosteric site of β1 adrenoceptor with more selectivity for the first one. The ex vivo results in the isolated guinea pig trachea model indicates that EC50 for the molecule MD2p13-16 was 2.39 x 10^-8 M, with a ΔG of -10.8±1.2 Kcal/Mol. Finally Molecule MD2p13-16 have a higher potency in comparison to albuterol for concentrations 1 x10^-10, 1 x 10^-9.5, 1 x10^-9 and 1 x10^-8.5 M; all the above information allows us to propose that the designed drug works as a partial agonist of β2-adrenoceptor and according to Hill's equation we can associate a phenomenon of negative cooperativity.

Natural biopolymer-poly[3-(3,4-dihydroxyphenyl)glyceric acid] from comfrey and its synthetic analogues

M Merlani1, V Barbakadze1, T Nakano2, L Amiranashvili1, L Gogilashvili1 and B Chankvetadze3
1Tbilisi State Medical University, Georgia
2Hokkaido University, Japan
3Tbilisi State University, Georgia

From ancient times extracts, teas and pulps obtained from various comfrey species (Symphytum L., family Boraginaceae) and amongst them Caucasian ones (Symphytum asperum Lepech. and S. caucasicum Bieb. widespread in Georgia) are known in folk medicine as powerful wound healing and anti-inflammatory remedies. It was established that all aforementioned plants contain high molecular constituents namely a caffeic acid derived polymer - poly[3-(3,4-dihydroxyphenyl)glyceric acid] (PDPGA). Some of the plants medicinal effects, like its wound healing and anti-inflammatory properties, could be attributed to this polymer. Moreover, the polymer showed antioxidant, immunomodulatory and antitumor activity. Interestingly, this polymer is a first representative of a previously unknown class of natural occurring biopolymers: phenolic polyethers. Recently, racemic and pure enantiomeric forms of PDPGA monomer - 3-(3,4-dihydroxyphenyl)-glyceric acid were synthesized as well as a methylated analogue of PDPGA - poly(MCDMPO). Comparative investigation of antioxidant properties of natural polymer and its monomer revealed that the latter appeared 40 fold active than polymer in both DPPH and chemiluminescence assays.