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Evaluation *in silico* and *ex vivo*: Determining affinity, selectivity and presumable allosteric modulation of new compounds towards $\beta 1/\beta 2$ adrenoceptors

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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 $\beta 1/\beta 2$ adrenoceptors. We performed a global and local reactivity evaluation of the best ligands with $\beta 2$ 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 $\beta 2$ -adrenoceptors and with the orthosteric and allosteric site of $\beta 1$ 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 2.39×10^{-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 1×10^{-10} , $1 \times 10^{-9.5}$, 1×10^{-9} and $1 \times 10^{-8.5}$ M; all the above information allows us to propose that the designed drug works as a partial agonist of $\beta 2$ -adrenoceptor and according to Hill's equation we can associate a phenomenon of negative cooperativity.

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

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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 polyether - 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.

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