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BOOK OF ABSTRACTS

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Docking studies of 3-hydroxy-3-arylpropionic acids as potentially selective COX-2 inhibitors

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Although non-steroidal anti-inflammatory agents (NSAID) are numerous, broad used and can be procured as OTC drugs, search for new non-steroidal NSAID is continuing. Main motive is to find compound which selectively inhibits inducible form of enzyme cyclooxygenase (COX-2), but would have at least 10 times less effect on constitutive form (COX-1). If this selectivity concept is achieved, adverse effect on gastric mucosa would be avoided [1]. According to current docking studies, a compound is considered selective if it can maintain interactions in hydrophilic side pocket, so called P3 region in the active site of COX-2 [2]. The aim of this study was to determine the impact of substitution of one or both phenyl rings in 3-hydroxy-3,3-diphenylpropanoic acid with some simple substituents on selectivity towards COX-2 inhibition. Molecular docking calculations were performed using Autodock v4.0.1 into the 3D structure of the catalytic site of COX-2 enzyme (pdb code: 1cx2). Structure of each compound was generated using the ChemOffice v7.0 Ultra software package and have been MM2 optimized. Each docking experiment consisted of 100 docking runs with 150 individuals and 500,000 energy evaluations. The structures were incorporated into 40x40x40 grid points receptor pocket, which was centered to the position of ibuprofen in crystallographic structure of the complex. Ibuprofen was used as a reference compound because of its structure similarity to tested compounds. All of the compounds have lower binding energies than ibuprofen (Fig. 1) and all of these compounds have the right structure which enables penetration into P3 region in the COX-2. Compound containing dimethylamino group penetrates deepest into this region indicating the best selectivity ratio of all tested compounds.

X	Y	E of R enatiomer (kcal/mol)	E of S enantiomer (kcal/mol)	3-hydroxy-3,3-diphenylpropanoic acid
NO_2	/	-7,67	-7,58	
CF_3	/	-7,27	-6,92	
Cl	/	-7,45	-7,30	
CH_3	/	-7,41	-7,29	
$NH(CH_3)_2$	$NH(CH_3)_2$	-8,86		
OCH_3	OCH_3	-7,33		
Cl	Cl	-7,68		

Ibuprofen	E of R enantiomer (kcal/mol)	E of S enantiomer (kcal/mol)
	-6,90	-7,44

Fig. 1. Binding energies of acid derivatives compared to binding energy of ibuprofen

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