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DOCKING POTENTIAL OF SOME N-SUBSTITUTED-DIARYL-PYRAZOLINE ANALOGUES TOWARDS THE COX-2 ENZYME

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ABSTRACT

Some N-substituted-diaryl-pyrazoline analogues were investigated *insilico* for their docking potential towards the Cyclooxygenase (COX)-2 enzymes. The compounds were designed on the basis of rational selection & the PDB entry 1CX2 from RCSB Protein Data Bank was used for mimicking COX-2 binding sites. The Compound (E)-3-(4-(dimethylamino) phenyl)-1-(5-(4-(dimethylamino) phenyl)-3-(4-hydroxyphenyl)-4,5 dihydropyrazol-1-yl)prop-2-en-1-one (E5) was found to possess strong binding potential along with two H-bond. The H-bond with Tyr-355 residue suggests desired COX-2 inhibitory potential of compound E5.

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INTRODUCTION:

Cyclooxygenases enzyme catalyzes formation of inflammatory mediators *via* arachidonic acid path way. COX-1 and COX-2 are two major isoforms of cyclooxygenase[1]. COX-1 considered responsible for platelet aggregation & gastric safety while COX-2 is responsible for inflammatory response[2]. Therefore, various COX-2 inhibitors have been developed recently as anti-inflammatory compounds[3].

Molecular docking is a computational approach used to investigate interactions between the ligand and macromolecule thus helps to predict possible drug like effect of ligand. Various researchers investigated different compounds for their *insilico* binding affinity towards COX- 1 and COX-2. The computational chemistry also confirms selectivity of COX inhibitors since ARG513 residue of COX-2 responsible for drug-receptor binding replaced with HIS513 residue of COX-1; therefore selective inhibitor of COX-2 does not inhibit COX- 1[4-5].

EXPERIMENTAL:

Selection of docking parameters:

- *Torsion*: 0.2 A^0
- *Rigid-body orientation*: 5 A^0
- *Dihedral angles* : 5 A^0
- *Root Mean Square Deviation Tolerance*: 2.0 A^0

Preparation of Ligand Structures of diaryl pyrazoline analogues were designed using Chem Draw 3D software they were further energetically minimized by MOPAC, with minimum RMS gradient of 0.01 and saved as MDL Mol File. Other parameters such as; pH, partial charges and polar groups were optimized using molecular mechanics. Rotatable bonds and types of atom were also optimized and assigned.

Preparation of macromolecule (protein)

PDB entry 1CX2 was drawn from Protein Data Bank and after selecting protein chain, macromolecule was further optimized for presence of heteroatoms and water molecule. Protein binding sites were selected through co-crystallized ligand binding interaction.

Docking simulation Docking simulation involves docking of designed diaryl pyrazoline analogues with macromolecule (protein) after addition of hydrogen bonds and charge assignment. Auto-Dock online server was used for the same. The docking algorithm finds minimum energy function including interactions of the ligand with the receptor and optimization of best conformational poses. All analogues were compared according to the minimum free binding energy and formation of H-bond.

RESULT AND DISCUSSION:

Designed compounds (diaryl pyrazoline analogues) were investigated for their binding potential with COX-2 enzyme using docking techniques. The designed compounds (Figure 1) docked on the crystal structures of cyclooxygenase-2 available through RCSB Protein Data Bank (PDB entry 1CX2). The binding score of the compounds were calculated from minimized ligand protein complexes (Table 1). The score values showed good binding affinities and stable conformational complexes of ligand-receptor. The co-crystallized ligand Celecoxib reveals hydrogen bonds with Tyr355, His90 and Arg513 (Figure 2), while Diarylpyrazoline derivative E5 showed similar hydrogen bonds with Tyr355 and high binding affinity (Figure 3). Other compounds also exhibited good binding score without hydrogen bond might be due to the other bonding interactions.

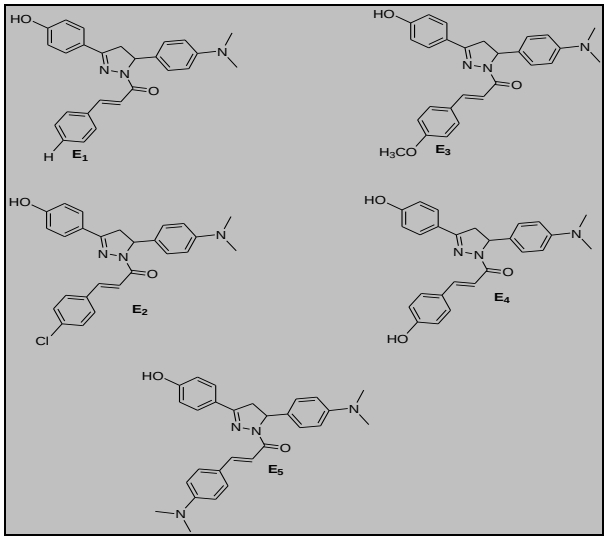

Figure 1: Structures of designed ligands

Table 1: Binding Score of Compounds

S. No.	Designed ligand Code	Designed ligand Name	No. of H-Bond	Binding energy of best pose
1	E1	(*E*)-1-(5-(4-(dimethylamino)phenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one	None	-4.64 kcal/ mol
2	E2	(*E*)-3-(4-chlorophenyl)-1-(5-(4-(dimethylamino)phenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazol-1-yl)prop-2-en-1-one	None	-4.36 kcal/ mol
3	E3	(*E*)-1-(5-(4-(dimethylamino)phenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazol-1-yl)-3-(4-methoxyphenyl)prop-2-en-1-one	None	-4.49 kcal/ mol
4	E4	(*E*)-1-(5-(4-(dimethylamino)phenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazol-1-yl)-3-(4-hydroxyphenyl)prop-2-en-1-one	None	-4.19 kcal/ mol
5	E5	(*E*)-3-(4-(dimethylamino)phenyl)-1-(5-(4-(dimethylamino)phenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazol-1-yl)prop-2-en-1-one	02	-4.19 kcal/ mol

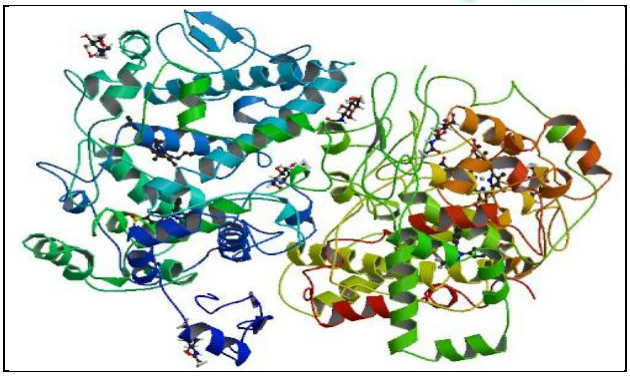

Figure 2: Binding pose of co-crystallized ligand Celecoxib

Figure 3: Binding pose of designed compound E5.

CONCLUSION:

N-substituted-diaryl-pyrazoline analogues were designed and investigated for their *insilico* docking potential towards the COX-2 enzyme. The literature based rational approach was utilized for designing ligand molecule. The designed compounds were docked on the crystal structures of COX-2 (PDB entry 1CX2) obtained from RCSB Protein Data Bank. The Compound (E)-3-(4-(dimethylamino) phenyl)-1-(5-(4-(dimethylamino) phenyl)-3-(4-hydroxyphenyl)-4,5 dihydropyrazol-1-yl)prop-2-en-1-one (E5) was found to form hydrogen bond with Tyr-355 residue. This interaction suggested that designed analogues may be used as potent COX-2 inhibitor after further investigations.

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