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Enlarging the NSAIDs Family: Molecular Docking of Designed Pyrazole and Oxadiazole Derivatives as Novel Anti-Inflammatory Agents

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Introduction:

The development of the NSAID family represented in the treatment of inflammatory disorders, such as arthritis, and for the management of acute pains, concerning to the well-known traditional Non-Steroidal Anti-inflammatory Drugs (t-NSAIDs). Cyclooxygenase (COX) and lipoxygenase (LOX) pathways takes primary role in inflammation and has responsible for many human diseases, like cancer, arthritis, psoriasis, and neurological disorders.

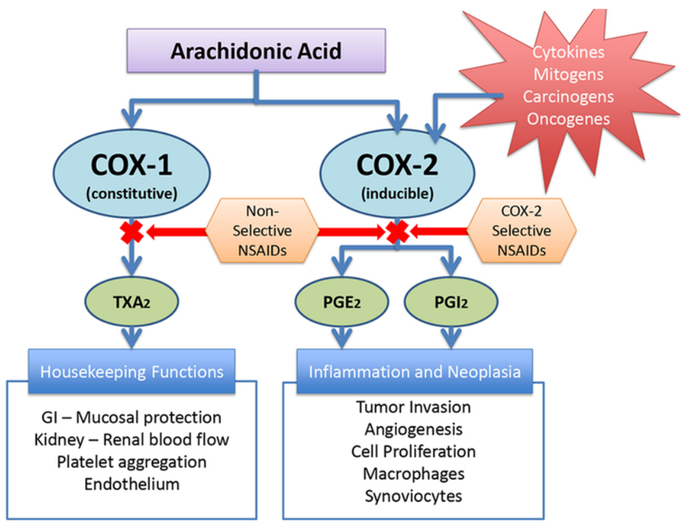


Fig 1. Biosynthesis and role of COX 1 & COX 2

Prompted by the pursuit for new cyclooxygenase-2 (COX-2) inhibitors, we have identified novel classes of pyrazole and oxadiazole derivatives as potentially powerful anti-inflammatory molecules through the molecular docking approach.

Goal of this Research:

In this present study, various derivatives of pyrazole and oxadiazole (ligands) were prepared and virtually docked against the protein biomolecule 1CX2 which is a potential anti-inflammatory receptor.

Experimental Methods:

Protein and ligand preparation:

Selection of protein : 3D Crystal structure of cyclooxygenase-II with PDB: 1CX2 having 3.00 Å resolution; ***RCSB Protein data bank.*** (https://www.rcsb.org/)

Processing of protein : ***PROCHECK*** tool to determine the quality of protein; binding pocket was predicted using ***CASTp3.0 server***

Preparation of ligand : Designed using ***ChemSketch*** and imported into ***BIOVIA Discovery Studio (DS) 2020*** to optimize. **Around 223 pyrazole and 30 oxadiazole derivatives were prepared.**

Molecular docking analysis : ***AutoDock Vina package of PyRx 0.8 software.***

Ligands were subjected to energy minimization and then converted to PDBQT format using the ***Open Babel plugin of PyRx.*** Docking interaction visualization and analysis of poseweres carried out using the ***BIOVIA DS 2020.***

Results and discussion:

Protein and ligand preparation:

Selection & processing of protein :

3D Crystal structure of cyclooxygenase-II with PDB: **1CX2** was selected for the analysis and processed to find out the binding pocket in the protein structure.

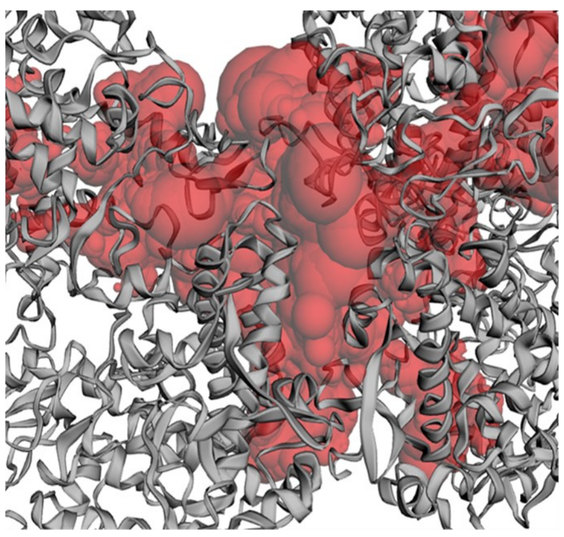


Fig 2.Binding pocket (red) present in 1CX2

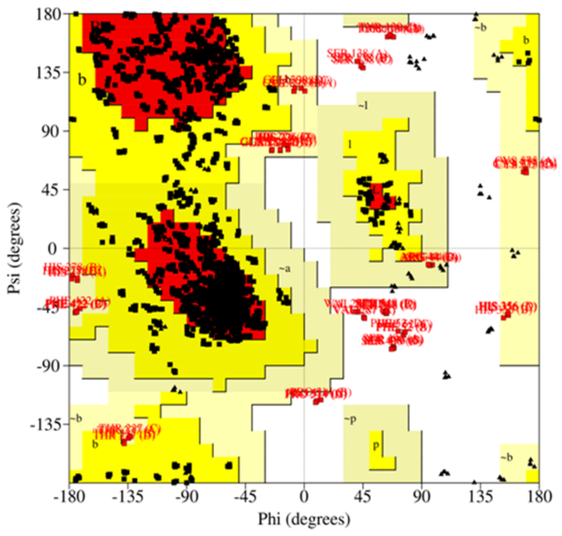
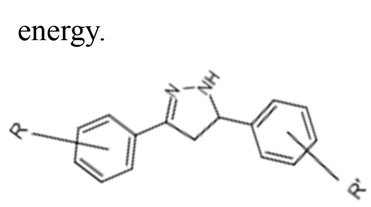


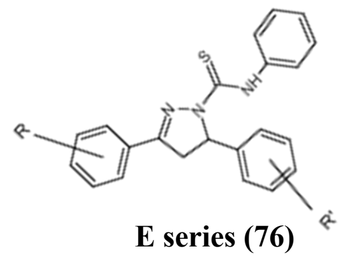
Fig 3. Ramachandran plot of the aromatase (1CX2) showing 76.3% residues in the favored region

Preparation of ligand :

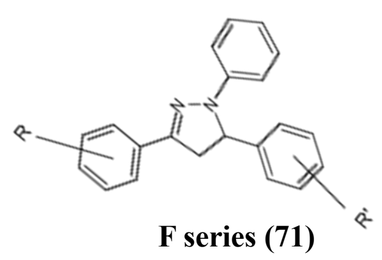
Around 223 pyrazole (D, E & F series) and 30 oxadiazole (VM1, VM2, VM3 series) derivatives were prepared virtually in 2D, converted to 3D and aligned to minimize the energy.



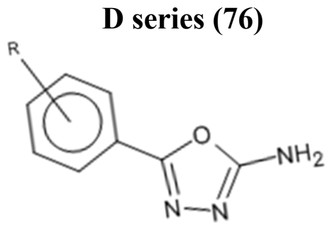
D series (76)



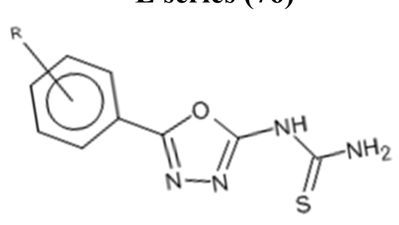
E series (76)



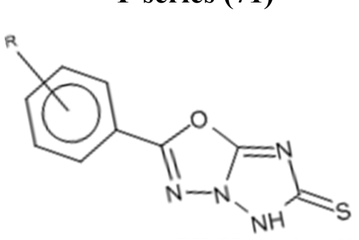
F series (71)



VM1 series (10)



VM2 series (10)



VM3 series (10)

Molecular docking analysis : ***AutoDock Vina package of PyRx 0.8 software.***

The binding affinity of synthesized compounds with targeted protein ranged from -6.7 to -10.7 kcal/mol. Among all ligands, **D305** and **D202** showed a higher binding affinity of -10.1 to -10.7 kcal/mol.

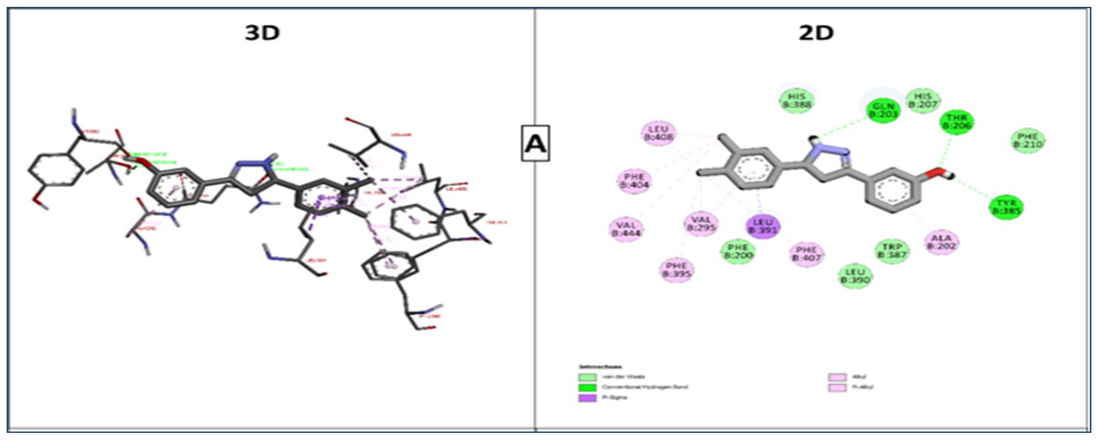


Fig 3. 2D and 3D interaction of comp. D305 with cyclooxygenase 2 (PDB: 1CX2)

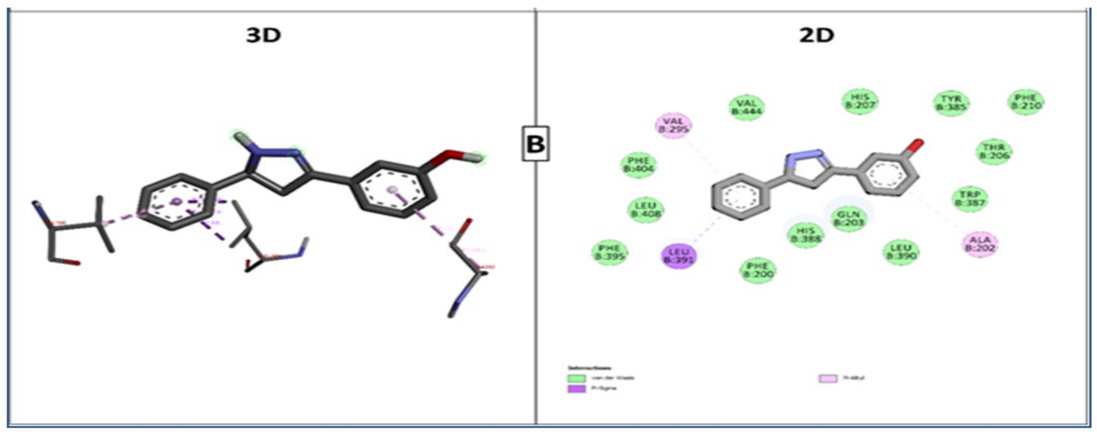


Fig 4. 2D and 3D interaction of comp. D202 with cyclooxygenase 2 (PDB: 1CX2)

Receptor protein and ligand binding interaction study:

The interaction of D305 and D202 with amino acid residues of 1CX2 such as **GLN203, THR206, TYR38, LEU391, LEU408, PHE404, VAL444, VAL295, PHE395, PHE407, ALA202, HIS388, HIS207, PHE210, TRP387, LEU390, and PHE200** and the **Conventional H bond, van der Waals, Π-Alkyl, and Π-Donor H bond** are the bonds formed between interacting residues and ligands.

Conclusion:

The molecular docking simulation was done by PyRx, which was immensely useful for predicting and confirming the binding behavior of ligands as an anti-inflammatory agent against cyclooxygenase-II protein (PDB: 1CX2). Designed compounds were virtually screened against protein biomolecule receptor cyclooxygenase-II (PDB: 1CX2). It was observed that all selected ligands have a good binding affinity with cyclooxygenase-II (PDB: 1CX2). Out of 253 derivatives, D305 and D202 were the two with highest binding affinity against targeted protein. This illustrates that, the ligands showing anti-inflammatory activity have the good binding affinity to the target protein and it binds to the residual binding as native ligands.

Acknowledgement:

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