Introduction-

COX-2 inhibitors are implicated to possess a broad therapeutic spectrum besides anti-inflammatory, analgesic and to lesser extent antipyretic activities. For example inhibition of COX-2 can prevent growth of certain types of cancer, especially colon cancer. The expression of COX-2 in brain, kidney and bone marrow has made it an attractive therapeutic target for designing selective drugs for Alzheimer's disease, cancer etc. The efficacy of these drugs is proven to be better than that of traditional NSAIDs, with no or little side effects associated with traditional NSAIDs\(^1\).

Cyclooxygenase-2 and Cancer\(^2\): Cox-2 have been detected in gastric and breast tumors.

- **Cyclooxygenase-2: As a target for cancer chemoprevention\(^3\):** COX-2 inhibitors are considered as attractive candidates for the chemoprevention.

- **The role of cyclooxygenase-2 (COX-2) in breast cancer\(^4\):** COX-2 enzymes are also expressed in the breast cancer; that is they are involved in the pathogenesis of breast cancer.

- **Cyclooxygenase-2 Selective Inhibitors For Prostate Cancer Chemoprevention\(^5\):** COX-2 inhibitors are considered as attractive candidates for the chemoprevention.

- **COX-2 represents potential targets for the prevention/treatment of colorectal cancer\(^6\):** COX-2 inhibitors also play a promising role in the prevention of colorectal cancer.

- **Cyclooxygenase and colon cancer\(^7\):** It is also reported that COX-2 expression in intestinal epithelial cells increases resistance to apoptosis, promotes tumor angiogenesis, and enhances invasion and metastasis.

- **Cyclooxygenase 2: A pharmacological target for the prevention of cancer\(^8\):** Cyclooxygenase 2 (COX-2) an inducible form of the enzyme, is a potential pharmacological target to prevent cancer.
**Cox-2 inhibitors (Coxibs) and Cardiovascular Actions**\(^9\)\(^{-11}\): COX-2 inhibitors lack anti-platelet activity, coxibs are suited for the provision of cardiovascular prophylaxis and in patients at risk of myocardial infarction.

**Cyclooxygenase inhibition and thrombogenicity**\(^12\): COX-2 inhibitor-treated patients with diseases that predispose to thrombosis should be monitored carefully for such type of complications.

All computational studies were performed using V-Life sciences MDS Version 2.0. The compounds were constructed from the fragments in the V-life molecular Builder database with standard bond lengths and bond angles and geometry optimization was carried out using the standard Merck Molecular Force Field (MMFF)\(^ {48}\) with distance dependent-dielectric function and energy gradient of 0.001 kcal/mol Å. The initial conformations were selected and minimized using the Powell method till root-mean-square Deviation of 0.001 kcal/mol Å was obtained. Partial atomic charges were calculated using the Gasteiger method. Further geometry optimization was carried out for each compound with the MOPAC 6 package using the semi-empirical AM1 Hamiltonian\(^ {49}\)

- **2D-QSAR studies**: The 2D-QSAR will be performed using Partial least squares (PLS), Principle component regression (PCR) and Multiple Linear Regression (MLR) with simulated annealing (SA) as variable selection methods. Various 2D QSAR models will be generated using, SA-PLS, SA-PCR and SA-MLR combinations.

- **3D-QSAR kNN MFA**: 3 D QSAR studies will be performed using different kNN MFA analysis.
Design of new chemical entities using Lead grow tool  The information obtained from 2D and 3D QSAR studies will be used to optimize the 1,5-diaryl pyrazole nucleus for selective inhibition of the COX-2 enzyme. Following filters will used while generating CombiLib, to ensure drug like pharmacokinetic profile of the designed NCEs.

\[ A = \text{Number of hydrogen Bond Acceptor} \quad \text{(Not more than 8)} \]

\[ D = \text{Number of Hydrogen Bond Donor} \quad \text{(Not more than 5)} \]

\[ R = \text{Number of Rotatable Bond are in range} \quad \text{(Not more than 10)} \]

\[ X = X \log P \quad \text{Ideal range < 5} \]

\[ W = \text{Molecular Weight} \quad \text{Ideal range < 500 Dalton} \]

\[ S = \text{Polar surface area} \quad \text{(Not more than 60 Å)} \]

Docking studies

Molecular docking studies were performed using Glide Schrodinger software. Selected most active molecules will be docked on crystallographic structure of COX-2 enzyme available in the RCSB PDB Database (Code: 1CX2) with co-crystallized ligand SC-558. Molecular docking studies usually help us to determine possible interaction of NCEs with the enzyme on PDB (1CX2).

Design of New Chemical Entities (NCEs) Containing 1,5-Diaryl Pyrazole pharmacophore for selective inhibition of Cyclooxygenase-2 enzyme
The findings of 2D, 3-D QSAR studies and molecular docking studies will be used to decide the substitution pattern (electrostatic, steric and hydrophobic pattern) required around the 1,5-diaryl pyrazole pharmacophore. In order to optimize the pharmacophore structure for selective inhibitory activity against the enzyme Cyclooxygenase-2.