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Synthesis, XRD analysis and molecular docking studies of novel di-(2-picolyl)amine appended sulfonamides towards cyclooxygenase-2 inhibitory activity

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Background: Non-Steroidal Anti-Infammatory Drugs (NSAIDs) are the most commonly prescribed group of drugs with the highest market share. These drugs are used for pain relief and to reduce inflammation. Long-term therapy has led to undesirable side effects including severe gastric mucosal damage as an impact of non-selective inhibition of both cyclooxygenase enzymes, COX-1 and COX-2, responsible for prostaglandin synthesis. Therefore, unlike traditional NSAIDs, the drugs that selectively inhibit COX-2 are clinically attractive. 1,4-benzodioxan and biphenyl scaffolds have been previously reported as potent COX-2 inhibitors towards inflammatory conditions.

Objective: To synthesize, characterize and perform docking studies of 1,4-benzodioxan and 4-methylbiphenyl based dipicolylamine ligands.

Method: In this study, two novel ligands $N(SO_2)$(bzd)dpa (L1) and $N(SO_2)$(4-Mebip)dpa (L2), were synthesized via N-sulfonylation of di-(2-picolyl)amine. Ligands were characterized by X-ray crystallography, spectroscopic methods such as ^{1}HNMR, UV-Vis, FTIR and fluorescence. Biological target predictions were carried out by using "SwissADME" and "SwissTargetPrediction" servers and "Pyrx 0.9.4" was used for molecular docking.

Results: Structural data obtained from single crystal X-ray diffraction for L1 and L2 confirm the formation of the ligand. Magnetically equivalent methylene protons of L1 and L2 were observed as singlet at 4.50 ppm and 4.57 ppm, respectively in ^{1}HNMR spectra in DMSO-d_6. None of them was found to be violating the Lipinski rule of five, which designates the drug-likeness of the ligands. Both ligands possess desirable pharmacokinetic properties; high lipophilicity and high gastrointestinal absorption. Furthermore, it was predicted that L1 and L2 show high binding affinity to COX-2 than COX-1, and molecular docking studies reveal the potential binding sites and the binding affinities -9.2 kcal/mol and -10.3 kcal/mol for COX-2 and -7.1 kcal/mol and -8.0 kcal/mol for COX-1, respectively.

Conclusion: We have synthesized and characterized two novel dipicolylamine based ligands. The target prediction and docking studies suggest that the synthesized ligands are promising as COX-2 drugs for the treatment of inflammatory diseases.

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