Abstract:

Cyclooxygenase-2 (COX-2) is a critical enzyme that bridges chronic inflammation and carcinogenesis. Selective inhibition of COX-2 remains a premier strategy for developing safer anti-inflammatory drugs and potent chemopreventive agents. This study merges findings from three distinct series of novel heterocyclic derivatives: isoxazole-carboxamides, indole-acrylamides, and trifluoromethyl-pyrazole-carboxamides. Using molecular modeling as a framework, we rationalized binding orientations and chemical reactivity. Advanced structural characterization was achieved via Microcrystal Electron Diffraction (MicroED) to confirm 3D atomic connectivity. High-potency leads were identified across all scaffolds. The isoxazole analog MYM4 exhibited selective COX-2 inhibition (IC50 = 0.247 μM) and disrupted 3D HeLa/Hep3B tumor spheroid formation. The indole-acrylamide 6a demonstrated nanomolar potency (IC50 = 128 μM) with an exceptional selectivity index (SI) of 352. Trifluoromethyl- pyrazole derivatives (e.g., 3g) showed strong selectivity (SI = 1.68) and favorable ADMET profiles. Molecular docking confirmed that these leads optimally occupy the COX-2 secondary binding pocket, forming key interactions with Arg513 and His90. The synergy between computational modeling and structural validation (MicroED) allowed for the precise optimization of heterocyclic scaffolds. These leads represent promising candidates for clinical translation in the treatment of inflammation-driven malignancies.