

## Design & synthesis of novel 4'-(4-(methylsulfonyl) phenyl) 3'- p-substituted phenyl -4'H-spiro [chroman-3, 5'-isoxazol]-4-one as selective COX-2 inhibitors

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**Background and Aims:** Nonsteroidal anti-inflammatory drugs (NSAIDs) that are widely used for the treatment of pain, fever, and inflammation, act as nonselective inhibitors of cyclooxygenase (COX) enzymes, which catalyze the formation of prostaglandins (PGs) from arachidonic acid. COX enzymes exist in at least two isoforms. COX-1 and COX-2 that inhibition of COX-1 causes the side effects of NSAIDs such as gastric ulceration, whereas inhibition of COX-2 accounts for their therapeutic effects. But recently rofecoxib (Vioxx<sub>®</sub>) and valdecoxib (Bextra<sub>®</sub>) withdrawn from the market for their side effects such as cardiovascular event. Accordingly there is still a need for novel, selective, and potent COX-2 inhibitors with a greater safe profile for the treatment of arthritis and cancer.

**Methods:** Molecular modeling studies were performed by Autodock Vina software. The synthesis of designed compounds was started from p-substituted-benzaldehydes that converted to p-substituted-benzaldoximes using hydroxylamine and then (E)-3-(4-(methylthio)benzylidene)chroman-4-one was obtained by reaction of chroman-4-one with 4-methylthio benzaldehyde under basic condition. Oxidation by oxone gave related methyl sulfone derivatives. The final reaction was 1, 3-Dipolar cycloaddition reaction of p-substituted-benzaldoximes with (E)-3-(4-(methylsulfonyl)benzylidene)chroman-4-one in biphasic medium of aqueous sodium hypochlorite and chloroform.

**Results:** A new series of 4'-(4-(methylsulfonyl) phenyl) 3'- p-substituted phenyl -4'H-spiro [chroman-3, 5'-isoxazol]-4-one compounds was designed and synthesized as selective cyclooxygenase-2 inhibitors. The purity of synthesized compounds was tested by chromatography. The overall yield of reactions was ranged from 60% to 92% in several stages of reaction. The structures of synthesized compounds were confirmed by <sup>1</sup>HNMR, IR and MS spectrometry.

**Conclusions:** Molecular modeling and docking study showed that the methyl sulfone pharmacophore group inserted in to the secondary pocket in the active site of COX-2 enzyme so we can expect COX-2 inhibitory activity for these compounds.

**Keywords:** Synthesis; Selective COX-2 Inhibitors; Spiroisoxazoles; Molecular modeling