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Design and Synthesis of Novel Diaryl Oxo Pyrrole Derivative as Selective COX-2 Inhibitors

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Abstract:
Inflammation is the initial defense response of the body cells and tissues to various stimuli such as pathogens, infections, irritation, chemicals, mechanical or thermal injuries.These symptoms are due to the release of some inflammatory mediators including prostaglandins (PGs). Non-steroidal anti-inflammatory drugs (NSAIDs), widely used for the treatment of pain, pyrexia, inflammation, rheumatoid arthritis and osteoarthritis, block biosynthesis of prostaglandins by inhibiting the different isoforms of cyclooxygenase enzyme (COX-1,2) . The range of activities of NSAIDs against COX-1 compared with COX-2 explains the variations in the side effects of NSAIDs at their anti-inflammatory doses. Drugs which have a high potency against COX-2 and a low COX-2/COX-1 activity ratio will have potent anti-inflammatory activity with few side effects on the stomach and kidney. The recent market withdrawal of some coxibs such as rofecoxib and valdecoxib due to their adverse cardiovascular side effects clearly delineates the need to develop alternative structures with COX-2 inhibitory activity. For this reason novel scaffolds with high selectivity for COX-2 inhibition need to be found and evaluated for their anti-inflammatory effects. Therefore in this study, novel diaryl oxo pyrrole derivatives were designed and synthesized based on the structure-activity relationship of selective COX-2 inhibitors. Target compounds were synthesized in two steps: In the first step, a solution of 4-(Methylthio)benzaldehyde, arylamine derivatives and dimethylacetylenedicarboxylate (DMAD) in the presence of para-toluenesulfonic acid (PTSA) as a catalyst, was stirred in ethanol for 72 hours. After the completion of the reaction, the resulting product was filtered off and recrystallized with ethanol. In the second step, the resulting precipitates and diethylamine were stirred in acetonitrile. Then a solution of Oxone and water was added to the mixture. After the completion of the reaction, the resulting precipitates were filtered off and recrystallized with ethanol. A series of novel diaryl oxo pyrrole derivatives were synthesized in good yields and the structure of the compounds was confirmed by FT- IR, 1HNMR and MASS spectroscopy. In this study new derivatives of diaryl oxo pyrrole was synthesized in two steps. Molecular structures of the synthesized compounds were confirmed by FT- IR, 1HNMR and MASS spectroscopy.

Keywords: Design, Synthesis, Pyrrole, COX-2 Selective Inhibitor

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