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Design and Synthesis of New Methyl 1,2-Diaryl-4-Hydroxy-5-oxo -2,5-Dihydro-1H-Pyrrole-3-Carboxylate Derivatives as Selective COX-2 Inhibitors

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Abstract:
The use of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of inflammation and pain is often accompanied by adverse gastrointestinal and renal side effects. Their anti-inflammatory activity results from inflammation of cyclooxygenase (COX), which catalyzes bioconversion of arachidonic acid to prostaglandins. Nowadays, it is well established that there are at least two COX isozymes, COX-1 and COX-2. COX-1 is responsible for the physiological production of prostaglandins while COX-2 is responsible for the elevated production of prostaglandins during inflammation. Thus, selective inhibition of COX-2 over COX-1 is useful for the treatment of inflammation and inflammation associated disorders with reduced gastrointestinal toxicities compared to NSAIDs. The withdrawal of some diaryl heterocyclic selective COX-2 inhibitors due to the adverse cardiovascular side effects delineates the need to explore and evaluate a new structural ring template possessing COX inhibitory activity. Therefore, in this study, new methyl 1,2-diaryl-4-hydroxy-5-oxo -2,5-dihydro-1H-pyrrole-3-carboxylate 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, 4-(methylthio)benzaldehyde, arylamine derivatives, and dimethylacetylenedicarboxylate (DMAD) in the presence of para-toluene sulfonic acid (PTSA) were 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, a solution of Oxone and water was added to a well-stirred solution of the resulting product and diethylamine in acetonitrile. After the completion of the reaction, the resulting precipitates were filtered off and recrystallized with ethanol. In this study, new derivatives of new methyl 1,2-diaryl-4-hydroxy-5-oxo -2,5-dihydro-1H-pyrrole-3-carboxylate were designed, synthesized, and purified. The structure of the synthesized compounds was confirmed by FT- IR, 1HNMR, and MASS. We designed and synthesized some new methyl 1,2-diaryl-4-hydroxy-5-oxo -2,5-dihydro-1H-pyrrole-3-carboxylate derivatives as selective COX-2 inhibitors. The structure of synthesized compounds was confirmed by FT- IR, 1HNMR, and MASS. The COX-2 inhibitory activity of these compounds is under investigation.

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

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