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Synthesis, Molecular Modeling and Study of 2-Substituted-4-(Benzo[D][1,3]Dioxol-5-Yl)-6-Phenylpyridazin-3(2H)-One Derivatives as Potential Analgesic and Anti-Inflammatory Agents

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Abstract : Fighting pain and inflammation is a common problem faced by physicians while dealing with a wide variety of diseases. Since ancient time nonsteroidal anti-inflammatory agents (NSAIDs) and opioids have been the cornerstone of treatment therapy, however, the usefulness of both these classes is limited due to severe side effects. NSAIDs, which are mainly used to treat mild to moderate inflammatory pain, induce gastric irritation and nephrotoxicity whereas opioids show an array of adverse reactions such as respiratory depression, sedation, and constipation. Moreover, repeated administration of these drugs induces tolerance to the analgesic effects and physical dependence. Further discovery of selective COX-2 inhibitors (coxibs) suggested safety without any ulcerogenic side effects; however, long-term use of these drugs resulted in kidney and hepatic toxicity along with an increased risk of secondary cardiovascular effects. The basic approaches towards inflammation and pain treatment are constantly changing, and researchers are continuously trying to develop safer and effective anti-inflammatory drug candidates for the treatment of different inflammatory conditions such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, psoriasis and multiple sclerosis. Synthetic 3(2H)-pyridazinones constitute an important scaffold for drug discovery. Structure-activity relationship studies on pyridazinones have shown that attachment of a lactam at N-2 of the pyridazinone ring through a methylene spacer results in significantly increased anti-inflammatory and analgesic properties of the derivatives. Further introduction of the heterocyclic ring at lactam nitrogen results in improvement of biological activities. Keeping in mind these SAR studies, a new series of compounds were synthesized as shown in scheme 1 and investigated for anti-inflammatory, analgesic, anti-platelet activities and docking studies. The structures of newly synthesized compounds have been established by various spectroscopic techniques. All the synthesized pyridazinone derivatives exhibited potent anti-inflammatory and analgesic activity. Homoveratryl substituted derivative was found to possess highest anti-inflammatory and analgesic activity displaying 73.60 % inhibition of edema at 40 mg/kg with no ulcerogenic activity when compared to standard drugs indomethacin. Moreover, 2-substituted-4-benzo[d][1,3]dioxole-6-phenylpyridazin-3(2H)-ones derivatives did not produce significant changes in bleeding time and emerged as safe agents. Molecular docking studies also illustrated good binding interactions at the active site of the cyclooxygenase-2 (hCox-2) enzyme.

Keywords : anti-inflammatory, analgesic, pyridazin-3(2H)-one, selective COX-2 inhibitors
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