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Topic of Research: **Structure-Based Design, Synthesis and Biological Screening of new Scaffold Containing Anti-Inflammatory agents**

FINDINGS

Inflammation serves as a protective mechanism employed by the body to defend against various infections and harmful substances. The inflammatory response initiates a cascade of events, including the release of diverse inflammatory mediators and the migration of diverse cells toward the inflammatory site. If prolonged unnecessarily, this process can result in tissue damage. Macrophages play a key role in inflammation, producing pro-inflammatory mediators like TNF-α, IL-1β, IL-6, and activating COX-2 and iNOS upon activation. Non-steroidal anti-inflammatory drugs (NSAIDs) represent widely chosen therapeutic agents prescribed for the cure of inflammatory conditions. These medications work by inhibiting prostaglandin synthesis, an important mediator of inflammation. Despite their efficacy, NSAIDs have various side effects, including gastrointestinal perforation, ulceration, bleeding, and renal toxicity. The association of anti-inflammatory drugs with a range of mild to severe side effects poses a large challenge for researchers and pharmaceutical industries striving to develop novel chemical entities.

In response to these challenges and in pursuit of safe and effective lead molecules for anti-inflammatory drugs, the present research aims to synthesize and biologically evaluate molecules designed by combining the structural features of two or three pharmacophores bearing anti-inflammatory potential. Therefore, we effectively designed and synthesized three distinct series of potent compounds and assessed them for their efficacy in combating inflammatory diseases.

In the introduction **Chapter 1** of the thesis, we attempted to describe in detail about inflammation process, and available NSAIDs as anti-inflammatory drugs and also provided an up-to-date literature review about the development of various anti-inflammatory agents.

In **Chapter 2**, we report the synthesis of pyrimidine-based compounds (**P1-P8**). The synthesized derivatives were investigated for cytotoxicity on macrophage RAW 264.7 cell lines the compounds are nontoxic at low concentrations and all the compounds were screened for the production of nitric oxide (NO) in LPS-stimulated RAW264.7 cells, the compounds **P5** and **P6** shows decrease the nitric oxide production in LPS stimulated RAW cells. The compounds **P5** and **P6** were used to determine the mRNA expression level and found that both compounds downregulate the mRNA expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX 2). Finally, the anti-inflammatory properties of these lead compounds were confirmed by protein expression of COX 2 and iNOS by western blotting.

In **Chapter 3**, we report the synthesis of novel morphinyl pyrimidine compounds having different functionalities that were designed and synthesized by multicomponent petasis reaction. The lipopolysaccharide-induced NO release of compounds **V1-V8** was determined in RAW 264.7 cells by Griess assay. The two compounds **V4** and **V8** can decrease the nitric oxide production in LPS-stimulated RAW cells. The mRNA expression of iNOS, COX-2, and il-1β was evaluated using PCR the compound **V4** and **V8** shows a significant decrease in expression of mRNA.Western blot analysis was performed to evaluate the effect of selected compounds **V4** and **V8** on protein expression of inducible nitric oxide synthase (iNOS) and COX 2.

In **Chapter 4**, we report the synthesis of a new series of 7 hydroxy coumarin derivatives (**CU1** to **CU13**) as anti-inflammatory agents. These derivatives were screened against LPS-stimulated raw cells for NO determination by Griess assay. The compounds **CU11** and **CU13** were found to inhibit the NO generation. The effect of these lead molecules on the mRNA expression of iNOS and COX-2 was determined by PCR, the compound **CU11** decreased the expression of both iNOS and COX-2 mRNA, and the compound **CU11** and **CU13** also suppressed the expression of iNOS and COX-2 proteins. Molecular docking was performed to validate the in vitro results.

The present thesis focuses on the design, synthesis, and biological evaluation of novel compounds as potential anti-inflammatory agents.