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Short communication

Synthesis, evaluation and docking studies on 3-alkoxy-4-methanesulfonamido acetophenone derivatives as non ulcerogenic anti-inflammatory agents

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ABSTRACT

A series of 3-alkoxy-4-methanesulfonamido acetophenone derivatives were synthesized and evaluated for their anti-inflammatory activity in carrageenan-induced rat paw edema model. The synthesized compounds were also investigated for their gastric ulcerogenic potential. The compounds **4a**, **4c** and **4d** showed comparable anti-inflammatory activity to rofecoxib and indomethacin, the standard drugs taken in both studies and were also non ulcerogenic at the test doses. *In silico* (docking studies) were done to investigate the hypothetical binding mode of the target compounds to the cyclooxygenase isoenzyme (COX-2). A binding model has been proposed based on the docking studies. Selected physicochemical properties were calculated for theoretical ADME profiling of the compounds and excellent compliance was shown with Lipinski's rules.

1. Introduction

Inflammation is a protective response of our body that releases cells and mediators in order to combat foreign substances and to prevent infections [1]. Prostaglandins, produced by mast cells are the products of arachidonic acid metabolism which act as mediators and play an essential modulatory role in inflammation. Prostaglandins PGE_2, PGI_2 and PGD_2 are the powerful vasodilators in their own right and synergize with other inflammatory vasodilators, accounting for the characteristic vasodilation and erythema at the site of inflammation [2]. PGE_2 is reported to act synergistically with the primary mediators of inflammation, bradykinin and histamine producing inflammatory pain and it is considered as a principal prostaglandin for acute inflammation and chronic diseases such as rheumatoid arthritis and inflammatory bowel disease [3]. PGI_2 (prostacyclin) acts as a highly potent antithrombotic agent by inhibiting platelet aggregation (antithrombogenic effect). It is also involved in the maintenance of electrolyte balance for normal renal function in the kidneys and shows cytoprotective effect in the gastric mucosa [4–6]. Thromboxane TXA_2 found at the site of inflammation is known to have vasoconstrictive and platelet aggregative effects [4].

The term non-steroidal anti-inflammatory drugs or NSAIDs refers to a group of drugs with diverse structures of heterogeneous chemically unrelated agents, sharing common therapeutic actions and side effects. These drugs having analgesic, antipyretic (at low doses) and anti-inflammatory effects (at high doses), are usually indicated for the treatment of pain, fever and acute or chronic inflammatory diseases such as osteoarthritis, rheumatoid arthritis, dysmenorrhea and postoperative pain [7]. All NSAIDs are postulated to disrupt the biosynthesis of the prostaglandins and thromboxanes by inhibiting the enzyme cyclooxygenase [8,9]. However, inhibition of the gastrointestinal tract or renal prostaglandins results in their mechanism based toxicities manifested as gastric bleeding, life threatening gastrointestinal ulcers and on long term use it can lead to abnormal renal physiology with resultant suppression of the renal functions [10,11]. Indomethacin, ketoprofen and piroxicam appear to have highest prevalence of gastric adverse effects, while ibuprofen and diclofenac appear to have lower rates of gastric side effects [12]. Hence, the therapeutic usefulness of these potent and effective drugs gets considerably limited on account of their undesirable side effects and efforts are underway to design better anti-inflammatory drugs having lacking gastric and renal side effects.

COX-2 is the inducible form of cyclooxygenase enzyme and selective COX-2 inhibitors have been introduced in the recent years to improve upon the profile of traditional NSAIDs (t-NSAIDs).

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However, additional risks associated with several of these agents such as hepatotoxicity (nimesulide and more recently, lumiracoxib) and cardiotoxicity (rofecoxib, valdecoxib, parecoxib) has prompted their early withdrawal from the market in many countries [13]. This leaves plenty of scope for research to be carried out in this area. In this context, the present work describes the design, synthesis and the investigation of anti-inflammatory properties and ulcerogenic potential of new 3-alkoxy-4-methanesulfonamido acetophenone derivatives based on structural modification of selective COX-2 inhibitors nimesulide and flosulide. Further, a hypothetical binding model has been proposed for the compounds with respect to the target enzyme COX-2 based on *in silico* docking studies.

2. Results and discussion

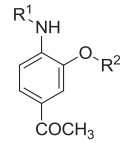
2.1. Design strategy and field alignment studies

Our design strategy involved modification of the structures of known selective COX-2 inhibitors nimesulide and flosulide in order to arrive at methanesulfonamido aryl ether class of compounds (Fig. 1). Chemical structures of the prepared compounds are shown in Table 1. Structure Activity Relationship (SAR) studies on the methanesulfonamido aryl ether series of compounds (nimesulide, flosulide, etc.) have emphasized the importance of an electron withdrawing moiety at *para* position with respect to methanesulfonamido moiety for their activity [14]. Amongst these *para* substituted methanesulfonamido aryl ethers, the compounds with nitro grouping are most active followed by cyano and acetyl groups in decreasing order. Nimesulide and NS-398 contains a nitro group and Flosulide contains an indanone carbonyl as electron withdrawing functionalities. An acetyl group of acetophenone system was included as the electron withdrawing moiety in our series. The results obtained for 3D similarity are shown in Table 2. The proposed compounds showed excellent 3D similarity to flosulide (73–82%) and good similarity to nimesulide. Fig. 2 displays the near perfect alignment of **4d** (maximum 3D similarity) with flosulide molecule along with very good superposition of field points. As expected, somewhat lower values were obtained with respect to the diaryl substituted heterocycles rofecoxib and celecoxib. In all the cases, similarity values for the compounds possessing methanesulphonamido system (**4a**–**4d**) were higher than the corresponding compounds having only amino functionality (**3a**–**3d**) in the same position.

2.2. Synthesis of compounds

Synthetic scheme for the preparation of target compounds **4a**–**4d** is summarized in Fig. 3. In the first step (protection step), 2-aminophenol was refluxed with urea in presence of concentrated hydrochloric acid at 150 °C to give the cyclized product 2-(*3H*)-benzoxazolinone through a previously reported procedure [15]. Acetylation of the 2-(*3H*)-benzoxazolinone in the presence of polyphosphoric acid and acetic acid gave 6-acetyl-2-(*3H*)-benzoxazolinone **1**, which on alkaline hydrolysis yielded 4-amino-3-hydroxy acetophenone **2** in very good yields. This was followed by reaction of **2** with selected alkyl bromides employing pyridine/potassium hydroxide system to give the corresponding 1-(4-amino-3-alkoxyphenyl)ethanone derivatives **3a**–**3d**. The ether derivatives **3a**–**3d** were, then subjected to reaction with methane sulfonyl chloride affording the target compounds **4a**–**4d** in good yields (65–80%). All the reactions were standardized with respect to various reaction conditions by monitoring their progress by thin layer chromatography. The structures of the final products were authenticated and their purity ascertained by various spectroscopic techniques including UV, IR, NMR and mass spectroscopic data.

Table 1
Chemical structures of the synthesized compounds.



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Compound No.	R^1	R^2
3a	H	n-C_4H_9
3b	H	n-C_5H_{11}
3c	H	n-C_6H_{13}
3d	H	cyclohexyl
4a	CH_3SO_2–	n-C_4H_9
4b	CH_3SO_2–	n-C_5H_{11}
4c	CH_3SO_2–	n-C_6H_{13}
4d	CH_3SO_2–	cyclohexyl

2.3. Pharmacological evaluation

2.3.1. In vivo anti-inflammatory studies

The prepared test compounds **3a**–**3d** and **4a**–**4d** were subjected to *in vivo* anti-inflammatory studies using carrageenan-induced rat paw edema model [16]. Rofecoxib and indomethacin were taken as standard drugs. Doses were selected by initial titration at different dose levels. Three dose levels were employed for the standard drugs as well as the test compounds, i.e., rofecoxib (15; 35; 45 mg/kg); indomethacin (5; 10; 15 mg/kg); test compounds (25; 50; 100 mg/kg). The standard drugs and the target compounds were suspended in the vehicle (0.5%w/v solution of carboxy methylcellulose CMC). Solution of carrageenan was prepared in 0.9% saline solution (900 mg in 100 ml of distilled water). Prior permission of the Institutional Animal Ethics Committee (IAEC), Panjab University, Chandigarh, India was obtained and all experiments were conducted according to the approved protocol. All the animals were allowed free access to food and water (*ad libidum),* in a constant light–dark cycle. The general behavior of the animals was normal during the course of the experiment. Statistical comparison of the

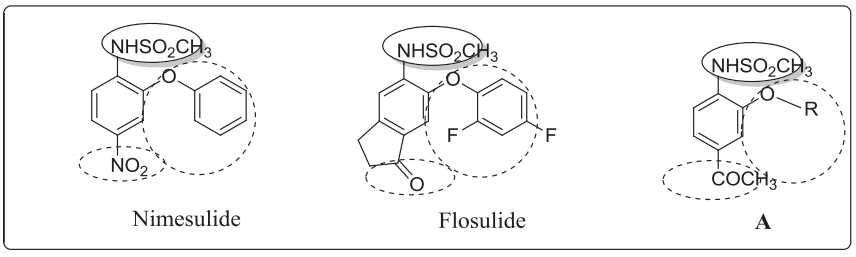

Fig. 1. Chemical structure correlation of the designed compound series (**A**) with the structures of the representative drugs.