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Design, synthesis and evaluation of some pyrazolo[3,4-*d*]pyrimidine derivatives bearing thiazolidinone moiety as anti-inflammatory agents

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ABSTRACT

Two new series of pyrazolo[3,4-*d*]pyrimidine bearing thiazolidinone moiety were designed and synthesized. The newly synthesized compounds were evaluated for their *in vitro* (COX-1 and COX-2) inhibitory assay. Compounds that showed promising COX-2 selectivity were further subjected to *in vivo* anti-inflammatory screening applying formalin induced paw edema (acute model) and cotton-pellet induced granuloma (chronic model) assays using celecoxib and diclofenac sodium as reference drugs. The histopathological and ulcerogenic potential were also determined. *In vivo* anti-inflammatory data showed that compounds **2**, **6**, **7d** displayed anti-inflammatory activity higher than both references in the formalin induced paw edema model. On the other hand, compounds **2**, **3d**, **3e**, **7b** and **7d** displayed anti-inflammatory activity greater than or nearly equivalent to diclofenac sodium in the cotton pellet-induced granuloma assay. Moreover, most of the tested compounds revealed good gastrointestinal safety profile. Collectively, compounds **2** and **7d** were considered as promising candidates in managing both acute and chronic inflammation with safe gastrointestinal margin.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the oldest, most successful and widely prescribed drugs known to modern medicine. They alleviate pain, fever and inflammation in diseases such as rheumatoid arthritis and osteoarthritis [1]. Regardless of the structural diversity, NSAIDs act through inhibition of cyclooxygenases (COX) pathway. Consequently, they reduce the biosynthesis of prostaglandins (PGs) which mediate a number of characteristic features of the body's response to tissue injury or inflammation [1]. In the COX pathway, the two known isoforms COX-1 and COX-2 catalyze the first committed step in the biosynthesis of PGs and thromboxanes whereas COX reaction converts arachidonic acid (AA) to PGs. However, the third isoform COX-3 is unlikely to possess prostaglandin producing activity in human tissues [2]. Indistinctive inhibition of both COX isoforms has been associated with deleterious side-effects on gastrointestinal (GI), cardiovascular (CV) and renal systems [3]. These side effects have been attributed to inhibition of beneficial COX-1 which plays an essential role in GI cytoprotection and platelet function [4,5]. Therefore, extensive work has been done to improve selectivity towards COX-2 to maintain the anti-inflammatory activity without altering the homeostatic functions of COX-1 [1]. These observations provide an acceptable rationale for the development of selective COX-2 inhibitors such as celecoxib (**I**, Fig. 1) that should retain the therapeutic potency of classical NSAIDs with less GI adverse effects [6]. However, recent concerns regarding these drugs and their association with significant CV side effects led to reconsideration of their appropriate use [7]. Therefore, development of novel compounds having anti-inflammatory activity with an improved safety profile is still a necessity.

Pyrazolo[3,4-*d*]pyrimidines constitute an important scaffold in several pharmacologically active compounds including anti-inflammatory agents [8–11]. Literature survey revealed that DPP; (N^4-benzyl-1-(*tert*-butyl)-N^6,N^6-dimethyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6-diamine) (**II**, Fig. 1) possessed anti-inflammatory, analgesic and anti-angiogenic activities. Besides, it showed 66 fold selectivity for COX-2 over COX-1 in human monocytes [12,13]. Moreover, some pyrazolo[3,4-*d*]pyrimidine derivatives were reported as dual inhibitors to COXs and inducible nitric oxide synthase (iNOS) enzymes with high anti-inflammatory and analgesic activities [14].

On the other hand, the thiazolidin-4-one ring system is one of the privileged structure fragments in modern medicinal chemistry, owing to its broad pharmacological activities and affinity for various biotargets. Among these biological activities, the anti-inflammatory and analgesic activities of thiazolidinones have been of particular interest

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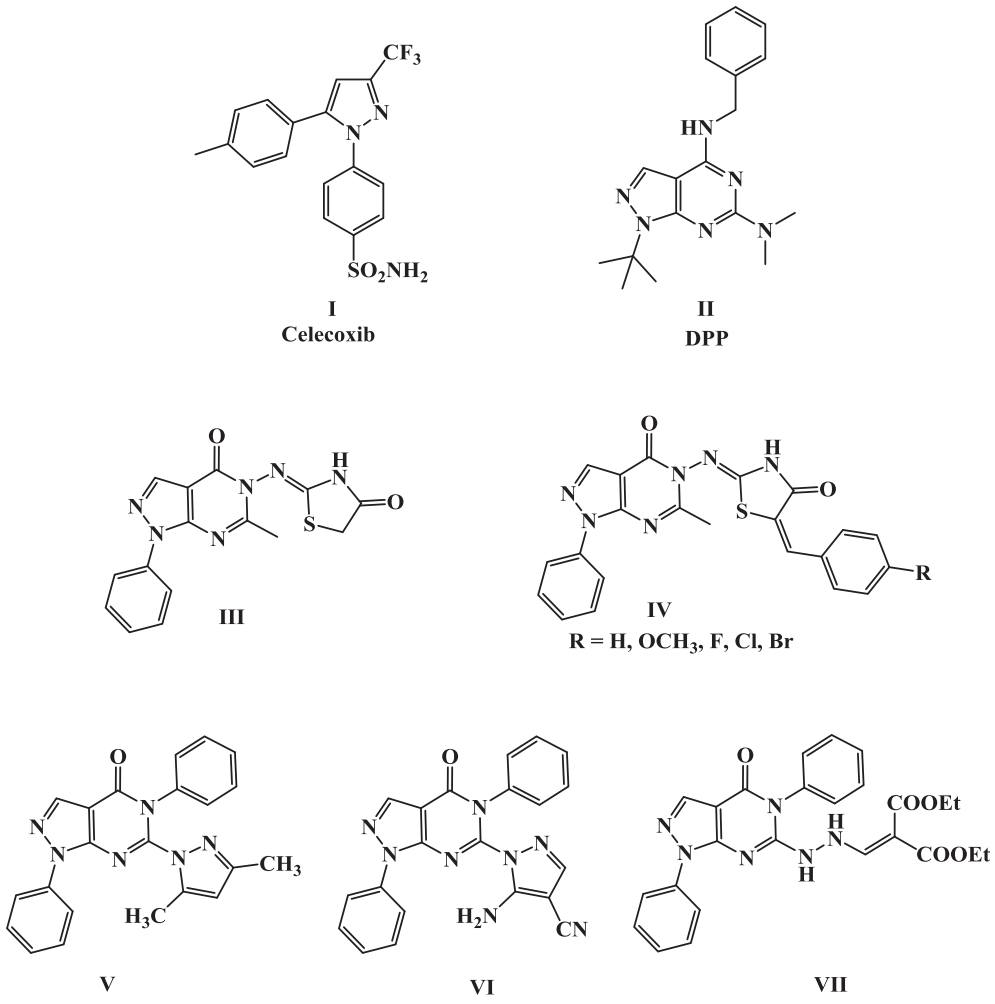

Fig. 1. Chemical structures of compounds I–VII.

recently [15–19]. Moreover, some thiazolidinones have been considered as effective lead anti-inflammatory COX-2 inhibitors [20–23]. Meanwhile, one of the most powerful and interesting strategies in modern medicinal chemistry to explore novel and highly active therapeutic molecules is the combination of two pharmacophores into a single hybrid molecule [22,24–26]. This approach was successfully applied, where several thiazolidinone linked to pyrazolo[3,4-*d*]pyrimidine through one atom spacer **(III**, **IV**, Fig. 1) were previously synthesized and were found to be potent and selective COX-2 inhibitor with high selectivity indices and safe GI profile [27]. Besides, other thiazolidinone derivatives either directly attached to pyrazolo[3,4-*d*] pyrimidine or separated by an imino linkage exhibited good anti-inflammatory in carrageenan-induced rat paw edema test [28].

Encouraged by the above mentioned facts and as a continuation of our research program devoted to the development of new pyrazolo[3,4-*d*]pyrimidines as anti-inflammatory agents devoid of the undesirable side effects associated with classical NSAIDs (**compounds V–VII**, Fig. 1) [29], it was attempted to synthesize some new structure hybrids comprising a thiazolidinone scaffold linked to the pyrazolo[3,4-*d*]pyrimidine skeleton through different atom spacers (**structures A** and **B;** Fig. 2). The incorporated thiazolidinone ring was further substituted with bulky benzylidene group as it was reported that this bulky substitution could maximize the interaction with the hydrophobic residues within COX-2 active site and enhance COX-2 selectivity [16,30]. Moreover, the existence of the active methylene in the thiazolidinone derivatives and the previous reports on the pharmacological significance of substitution at that particular position encouraged us to introduce various substituted aminomethyl moieties at that position in order to gain insight on the structure–activity relationship of this series of compounds [31].

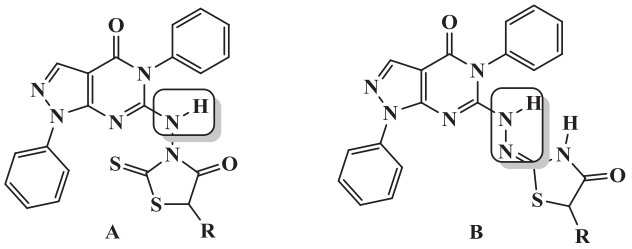

Fig. 2. Design of new 4-thiazolidinone-pyrazolo[3,4-*d*]pyrimidine hybrids.

2. Results and discussion

2.1. Chemistry

All the target compounds were prepared according to the synthetic pathways outlined in Scheme 1. The synthesis of the new thioxo-thiazolidinyl derivative **(2)** was proceeded by reacting the hydrazinyl derivative **(1)** [32] with bis(carboxymethyl)trithiocarbonate [33,34] in boiling ethanol. ^{1}H NMR spectrum of compound **(2)** revealed two doublets at 4.39 and 4.63 ppm due to thiazolidinone C_5-H_2 protons, in addition to a D_2O-exchangeable singlet at 9.78 ppm due to NH proton whereas, ^{13}C NMR spectrum showed a characteristic signal at