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Original article

Synthesis and biological evaluation of 4,5-diphenyloxazolone derivatives on route towards selective COX-2 inhibitors

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ABSTRACT

A series of 3-unsubstituted/substituted-4,5-diphenyl-2-oxo-3*H*-1,3-oxazole derivatives were prepared as selective cyclooxygenase-2 (COX-2) inhibitors. Among the synthesized compounds, 4-(4-phenyl-3-methyl-2-oxo-3*H*-1,3-oxazol-5-yl)benzensulfonamide (compound **6**) showed selective COX-2 inhibition with a selectivity index of >50 (IC_{50}COX-1 = >100 μm, IC_{50}COX-2 = 2 μm) in purified enzyme (PE) assay. Compound **6** also exhibited selective COX-2 inhibition in human whole blood assay. Molecular docking studies showed that **6** can be docked into the COX-2 binding site thus providing the molecular basis for its activity.

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1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAID) are among the most frequently prescribed medications being the drugs of the first choice for treatment of the inflammatory and rheumatic diseases. The common mechanism of NSAIDs involves the nonselective inhibition of cyclooxygenases (COXs) thereby preventing the biosynthesis of prostaglandins (PG) which are the important lipid mediators of inflammation as well as numerous homeostatic physiological functions [1]. As it is now well appreciated, COXs exist in two isoforms, namely COX-1 and COX-2 [2], while the existence of a third isoforom (COX-3) is still into debate. In general terms, COX-1 is the constitutive isoform providing normal production of PGs having roles in homeostasis and gastroprotection, whereas COX-2 is induced by proinflammatory stimuli at inflammatory sites [3]. The discovery of inducible COX-2 at sites of inflammation led to the development of selective COX-2 inhibitors with the hope of dimished gastrointestinal side effects associated with traditional NSAIDs [4,5]. However, recent studies have shown that COX-2 inhibitors are associated with increased thromboembolic phenomena in specific patient populations such as cardiovascular disease patients challenging the benefits of selective COX-2 inhibition [6–8]. Moreover, there is currently no clear evidence that COX-2 inhibitors represent an independent risk factor in patients at low demographic risk of cardiovascular diseases and therefore, clinical rationale for developing compounds with selective COX-2 inhibition still remains to be established [8,9]. Meantime, considerable interest in the further potential clinical utilities of COX-2 inhibitors has emerged [10–12]. Recent studies indicating the place of COX-2 inhibitors in cancer chemotherapy and neurological diseases such as Alzheimer's [13,14] and Parkinson [13,14] diseases still continues to attract investigations on development of COX-2 inhibitors.

The structural information on the tricyclic COX-2 selective inhibitors, for example vicinal diaryl substitution about a central heterocyclic ring, is described in detail in literature and having the characteristic sulfonyl group on one of the aryl rings are believed to play a crucial role on selectivity [15,16]. For this purpose, vicinal diaryl substituents on a central five- or six-membered ring template such as pyrazole, 2-(5*H*)-furanone, isoxazole, pyridine have been extensively investigated as selective COX-2 inhibitors [4] (Fig. 1). In addition, some studies for developing COX-2 inhibitors have concentrated on the preparation of the amide derivatives of currently used NSAIDs such as indomethacin [17,18] and

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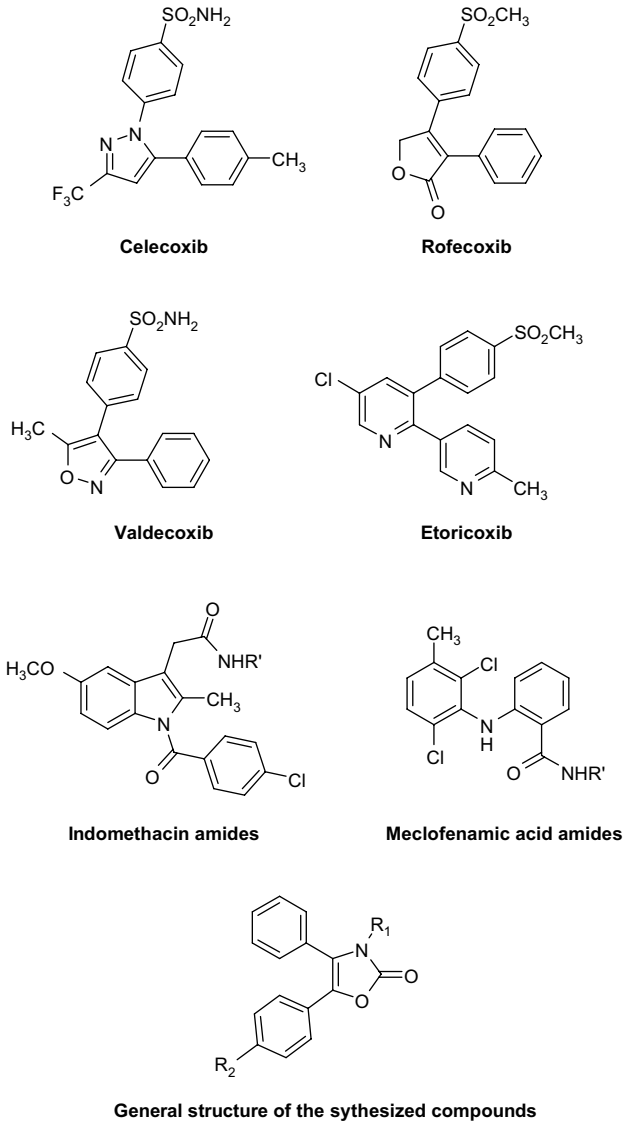

Fig. 1. Representative examples of selective COX-2 inhibitor compounds and the general structure of the synthesized 4,5-diphenyl-2-oxo-3*H*-1,3-oxazole derivatives.

meclofenamic acid [19] (Fig. 1) and found that neutralization of these NSAIDs by preparing the corresponding amide derivatives resulted into compounds that selectively inhibited COX-2 but not COX-1. As a part of our ongoing program to acquire structure–function relationship data for COX-2 inhibitors, we hereby describe the synthesis and the preliminary biological evaluation of a group of diphenyl substituted oxazolone derivatives possessing a sulfonyl group at the *para*-position of C-5 phenyl moiety in conjunction with a variety of substituents at the nitrogen atom of the central oxazolone ring (Fig. 1).

2. Chemistry

The synthetic routes for the synthesized compounds are outlined in Schemes 1–3. The starting compound, 4,5-diphenyl-2-oxo-3*H*-1,3-oxazole (**1**), was readily prepared by the reaction of benzoin and urethane under distillation conditions as shown in Scheme 1 [20]. Compound **1** was then reacted with dimethyl sulfate to obtain 4,5-diphenyl-3-methyl-2-oxo-3*H*-1,3-oxazole (**2**) [20–22]. Treatment of **1** and **2** with chlorosulfonic acid yielded the sulfonyl chloride derivatives (**3**, **4**) which were subsequently reacted with ammonium hydroxide to yield the sulfonamide derivatives (**5**, **6**) (Scheme 1). The methylsulfonyl derivative (**8**) was obtained by the methylation of the sodium salt of **4** with dimethyl sulfate as demonstrated in Scheme 1.

The preparation of the amide derivatives **15**–**21** are outlined in Scheme 2. Alkylation of **1** with ethyl bromoacetate generated ethyl 2-(4,5-diphenyl-2-oxo-3*H*-1,3-oxazol-3-yl)ethanoate (**9**) [23]. Subsequent hydrolysis of the ester linkage under basic conditions afforded 2-(4,5-diphenyl-2-oxo-3*H*-1,3-oxazol-3-yl)ethanoic acid (**10**) [24,25]. Amidation of **10** with appropriate secondary and tertiary amines in the presence of ethyl chloroformate in dichloromethane at room temperature, resulted in the synthesis of amide derivatives **15**–**21** with quantitative yields (51–66%).

The sulfonamide derivative having an acetic acid substitution on the nitrogen of oxazolone was prepared as shown in Scheme 3. Firstly, ester derivative **9** was reacted with chlorosulfonic acid to yield sulfonyl chloride derivative (**11**) under mild reaction conditions. After protection of sulfonyl chloride with dibenzylamine and subsequent treatment with concentrated sulfuric acid resulted in the target sulfonamide derivative (**13**), which was readily hydrolyzed under acid conditions to obtain the desired acid derivative **14**.

3. Results and discussion

The compounds reported herein were tested for their ability to inhibit COX-2 and/or COX-1 using the purified enzyme assay described by Futaki et al. [26] and Janusz et al. [27]. The in vitro activity results are reported as a percentage of inhibition of the purified enzymes at 10 μM (Table 1). For compounds which exhibited inhibition of more than 50% for COX-2, the inhibition of COX-1 at 10 μM and the IC_{50} values were also calculated from the concentration curves by means of the PRISM program. Furthermore, compound **6** was selected on the basis of its activity in the cell-free assay for evaluation of inhibition of human COX-2 and COX-1 using in vitro human whole blood assay described by Patrignani et al. [28].

In this preliminary study towards new potential COX-2 selective compounds as novel drug candidates for inflammatory and related diseases, we have introduced systematic modifications to the 4,5-diphenyloxazolone core structure. It is well established that 3,4-diaryloxazolones having a sulfone or sulfonamide on the 4-phenyl is a good template for selective COX-2 inhibition [29,30]. Thus, taking into account this structural feature, we planned a structure–activity relationship study using the 4,5-diphenyloxazolone core as a template. In particular, we envisaged a series of substitution on the N3-nitrogen atom of the heterocycle in order to introduce more flexibility to the template, while keeping the diphenyl portion unsubstituted or substituted with sulfone/sulfonamide which was required to maintain COX-2 selectivity. Results are shown in Table 1.

In general, none of the newly synthesized derivatives proved to be endowed with the desired activity profile at COX-2, as none but one of the compounds (compound **6**) inhibited at least 50% of the COX-2 isoform during preliminary screening.

Compound **6** is endowed with a *N*-methyl substitution and with a *p*-sulfonamide on the 5-phenyl ring. We found that *N*-methyl derivative with the unsubstituted 5-phenyl ring (**2**) had a diminished COX-2 activity (~5% inhibition) with respect to the sulfonamide (**6**, 70%) or methylsulfonyl (**8**, 49%) analogs. This preliminary results indicated that the presence of *p*-sulfone/sulfamoyl is important for COX-2 activity and sulfone on the 5-phenyl ring was less effective with regard to sulfamoyl at the same position which was in close agreement with literature results for related compounds [29,30]. Within the sulfonamide analogs, introduction of larger substituents on the N3 position, i.e., ester (**13**) or acid (**14**), caused a decrease in the observed COX-2 activity at 10 μM screning dose as compared to *N*-methyl analog (**6**).

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