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Original article

Structure-based design of phthalimide derivatives as potential cyclooxygenase-2 (COX-2) inhibitors: Anti-inflammatory and analgesic activities

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ABSTRACT

A group of 30 cyclic imides (**1**–**10a-c**) was designed for evaluation as a selective COX-2 inhibitor and investigated *in vivo* for anti-inflammatory and analgesic activities. Compounds **6a**, **6b**, **7a** and **7b** exhibit optimal COX-2 inhibitory potency (IC_{50} = 0.18, 0.24, 0.28 and 0.36 μM; respectively) and selectivity index (SI) range of 363–668. *In vitro* COX-1/COX-2 inhibition structure–activity studies identified compound **6a** as a highly potent (IC_{50} = 0.18 μM), and an extremely selective [COX-2 (SI) = 668] comparable to celecoxib [COX-2 (SI) > 384], COX-2 inhibitor that showed superior anti-inflammatory activity (ED_{50} = 54.0 mg/kg) relative to diclofenac (ED_{50} = 114 mg/kg). Molecular Docking study of the synthesized compound **6a** into the active site of COX-2 revealed a similar binding mode to SC-558, a selective COX-2 inhibitor. Docking study showed that the methoxy moieties of **6a** inserted deep inside the 2°-pocket of the COX-2 active site, where the O-atoms of such groups underwent an H-bonding interaction with His^{90} (3.02 Å), Arg^{513} (1.94, 2.83 Å), and Gln^{192} (3.25 Å).

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1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most important class of widely used therapeutics for the treatment of inflammation and pain [1,2]. The clinical use of traditional NSAIDs for the treatment of inflammation and pain is often accompanied by adverse gastrointestinal effects [1–3]. The pharmacological effects of NSAIDs are due to inhibition of a membrane enzyme called cyclooxygenase (COX) which is involved in the prostaglandin biosynthesis [4–13]. There are two isoforms, COX-1 and COX-2 which share the same substrates, produce the same products and catalyze the same reaction using identical catalytic mechanisms, but differ in inhibitor selectivity [4–9]. The isoform, COX-1 has mainly a physiological role in kidneys and the stomach, and is responsible for maintaining homeostasis (gastric and renal integrity) [7–9]. Whereas COX-2 induces inflammatory conditions and is involved in the production of prostaglandins mediating pain [10,11]. Inhibition of COX-1 is responsible for the adverse gastrointestinal and renal effects of NSAIDs while the inhibition of COX-2 accounts for NSAIDs' therapeutic effects. All classical NSAIDs, such as aspirin and indomethacin are non selective inhibitors for both COX-1 and COX-2, but bind more tightly to COX-1. In order to prevent or decrease these side effects, a current strategy consists of designing selective COX-2 inhibitors with an improved gastric safety profile [14,15]. Several classes of compounds possessing selective COX-2 inhibitory activity have been reported in the literature such celecoxib (**A**) and SC-558 (**B**) (Fig. 1) [16,17].

On the other hand, cyclic imides such as phthalimides possessed structural features which conferred potential biological activity and pharmaceutical use [18–21]. The various classes of cyclic imides have received great attention due to their COX-1/2 inhibition, anti-inflammatory, antihyperlipidemic and antitumor activities [18–23]. Apart from biological activities; imide derivatives are

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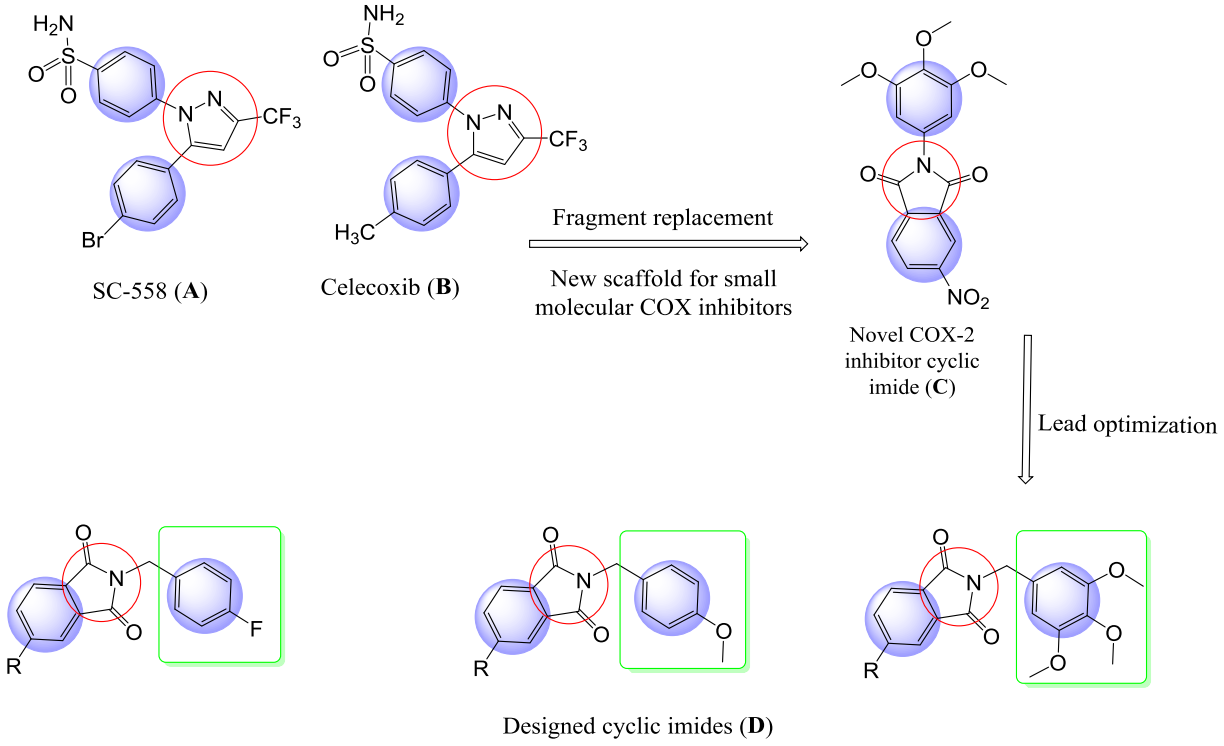

Fig. 1. Representative examples of selective COX-2 inhibitors (**A**, **B** and **C**) and the designed cyclic imides (**D**).

useful in the reactions involving condensation, alkylation, acylation, and cyclocondensation [24].

We have recently reported on the synthesis and COX-2-inhibiton of N-substituted cyclic imides [21,22] in which compound **C** (Fig. 1) was proved to be potent COX-2 inhibitors with IC_{50} value of 0.10 μM and an extremely selective [COX-2 (SI) = 400] [21]. Accordingly, we now describe the synthesis, COX-1/2 inhibition, anti-inflammatory and analgesic activities of a group of cyclic imides **1**–**10a-c** bearing 3,4,5-timethoxybenzyl, 4-methoxybenzyl, or 4-fluorobenzyl fragments, in conjunction with various substituents (H, Me, NO_2, Cl and *t*-butyl) at the cyclic imide core. The rationale for testing of these cyclic imides (Fig. 1, **D**) as COX-inhibitors was the following: (i) compare the efficacy of the 3,4,5-trimethoxybenzyl and 4-methoxybenzyl versus the 4-fluorobenzyl for the inhibitory power against various isoforms, such as COX-1 and COX-2, in compounds incorporating the same scaffold (i.e., succinimide; phthalimide, etc.); (ii) delineate the structure–activity relationship (SAR) for the inhibition of these COX isoforms with compounds incorporating cyclic imides with diversely substituted scaffolds. Thus, in addition to the monocyclic succinimide **(1a-c)**, derivatives of tetrahydrophthalimide (**2a-c**), phthalimide (**3a-c**) as well as phthalimide substituted with various moieties at the benzene core (such as methyl-, *tert*-butyl-, dichloro-, tetrachloro- and nitro-groups) of types **4-8a-c** were also included in the study. Furthermore, derivatives incorporating the heterocyclic pyrazine-2,3-dicarboximide **(9a-c)** or the bulkier naphthalene-1,10-dicarboximide (**10a-c**) moieties were also included in the study, in order to explore as much chemical space as possible.

2. Results and discussion

2.1. Chemistry

The preparation of target cyclic imides is shown in Scheme 1. Classical condensation of 3,4,5-trimethoxybenzyl amine or 4-substituted benzyl amine with an acid anhydride in refluxing acetic acid afforded the designed cyclic imides in satisfactory yields. The structures of the isolated products **1**–**10a-c** were established on the basis of their spectral analyses.

2.2. Biological activity

2.2.1. COX inhibition

According to the aforementioned rationale, the synthesized compounds are evaluated for their ability to inhibit COX-1 and COX-2 using an ovine COX-1/COX-2 assay kit (Catalog No. 560101, Cayman Chemicals Inc., Ann Arbor, MI, USA). IC_{50} (μM) is determined which is the means of two determinations acquired and the deviation from the mean is <10% of the mean value [21,22,25]. The selectivity index (SI values) was defined as IC_{50}(COX-1)/IC_{50}(COX-2). In the assay system, the IC_{50} values of celecoxib on COX-1 and COX-2 were determined to be > 100 and 0.26 μM respectively, indicating that celecoxib is a selective COX-2 inhibitor [COX-2 (SI) > 384.6]. The results showed that some of the tested compounds had potent inhibition against COX-2 ($IC_{50} \cong$ 0.18–8.5 μM) compared to the inhibition for COX-1 ($IC_{50} \cong$ 130.8 − >100 μM) as listed in Table 1. Nearly seven of the tested compounds (**6a**, **6b**, **7a**, **7b**, **8b**, **9a**, and **10a**) were found to be potent and selective against COX-2. Interestingly, methoxy substituents on the *N*-benzyl group play critical roles in the COX-inhibiting activity of the tested compounds compared with fluoro derivatives.

Compound **6a** was the most potent inhibitor in this series with the COX-2 inhibiting activity (IC_{50} = 0.18 μM, COX-2 (SI) = 668.3), 2-fold higher than celecoxib (IC_{50} = 0.26 μM, COX-2 (SI) > 384.6). The effects of substituents introduced into the phthaloyl moiety of compounds **3**–**8** were revealed to be directional, being dependent on the electronic nature of the substituents, that is introduction of a nitro group at the 5-position (compound **6a**) enhanced COX-2-inhibiting activity, resulting in a COX-2-selective inhibition (SI = 668.3). Moreover, introduction of two halogen atoms such as

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