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Design, synthesis of novel isoindoline hybrids as COX-2 inhibitors: Anti-inflammatory, analgesic activities and docking study

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ABSTRACT

A group of novel isoindoline hybrids incorporating oxime, hydrazone, pyrazole, chalcone or aminosulfonyl pharmacophores (**9–14**) was designed and characterized by spectral data and elemental analyses results. All newly synthesized compounds were evaluated as COX-2 inhibitors, anti-inflammatory and analgesic agents. Six hybrid derivatives (**10b, 10c**, **11a, 11d**, **13, 14**) were moderate COX-2 inhibitors (IC_{50} = 0.11–0.18 μM) close to standard celecoxib (IC_{50} = 0.09 μM). The most active compounds showed outstanding *in vivo* anti-inflammatory activity (% edema inhibition = 41.7–50, 1 h; 40.7–67.4, 3 h; 20–46.7, 6 h) better than reference drug diclofenac (% edema inhibition = 29.2, 1 h; 22.2, 3 h; 20, 6 h). Most compounds showed significant peripheral and/or central analgesic activity. The moderate selective COX-2 inhibitor; dimethoxychalcone **11d** (SI = 103) displayed excellent anti-inflammatory activity (% edema inhibition = 45.8–59.3) and increased thermal pain threshold (50–92.85%) comparable to piroxicam (75%). Molecular docking studies have been established.

1. Introduction

Non steroidal anti-inflammatory drugs (NSAIDs) are the most prescribed drugs for treatment of inflammation and pain associated with various pathological disorders. The mechanism of action of NSAIDs is attributed to inhibition of cyclooxygenase (COX) enzymes which catalyze prostaglandins (PGs) biosynthesis from arachidonic acid [1–3]. There are two known forms of COX enzymes. COX-1 is a constitutive enzyme responsible for production of cytoprotective PG in gastric and bowel mucosa, normal renal functions and haemostasis while COX-2 is an inducible enzyme induced for inflammatory response and other pathological conditions [4,5].

Traditional NSAIDs are non selective inhibitors of both the "housekeeping" COX-1 and the inflammatory response of COX-2 enzymes leading to various side effects such as gastric ulceration, bleeding and renal dysfunction [6]. Finding clinically useful NSAIDs *via* selective inhibition of COX-2 enzyme is a goal for medicinal chemists to alleviate inflammation without interrupting normal body functions [7]. Highly selective COX-2 inhibitors such as valdecoxib (Bextra)™ proved to cause cardiac toxicity and were withdrawn from market [8] while moderate selective COX-2 inhibitors as celecoxib (Celebrex)™ are considered as safe anti-inflammatory drugs [9].

Structure activity relationship studies identified the diverse chemical structures of reported COX-2 inhibitors. Generally, they possess two aryl ring substitution on a central scaffold. The central system is either carbo/heterocyclic ring system, or acyclic core system with 2 or 3 membered chain structure as iminic olefinic, azo, acetylenic or α,β-unsaturated ketone structures [10–12].

Isoindoline-1,3-dione derivatives (phthalimides) are nitrogen containing heterocycles that have been utilized extensively as building blocks in organic synthesis owing to their varied biological activities [13–18]. Also, *N*-functionalized isoindolines have received great

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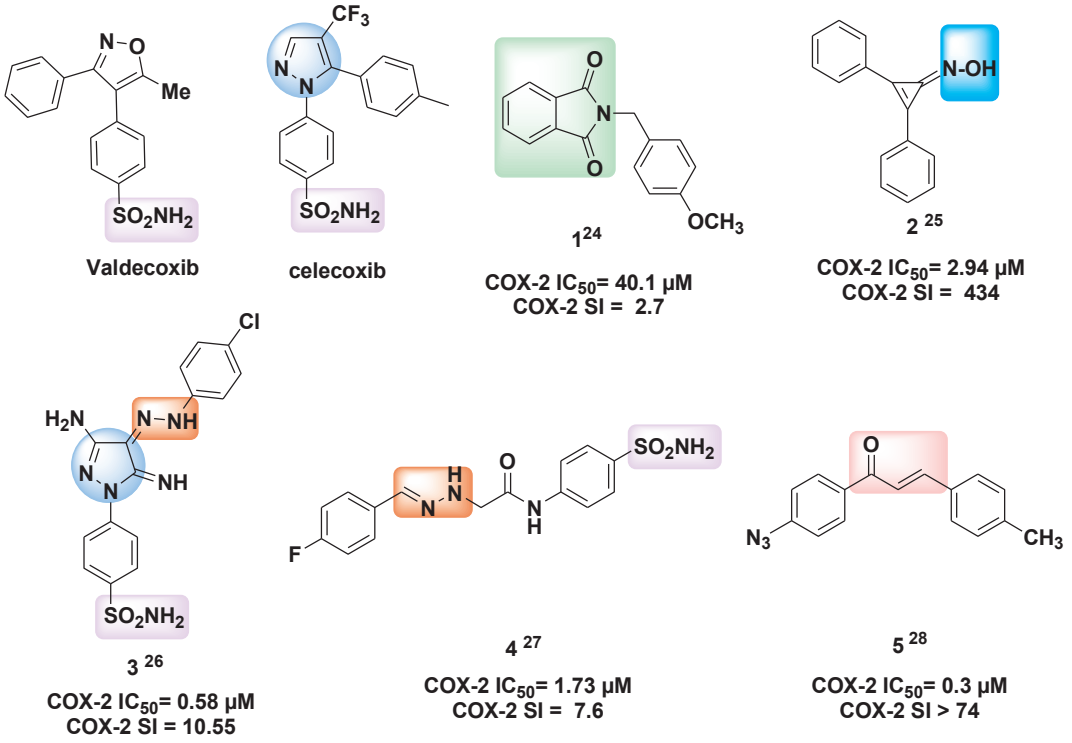

Fig. 1. Chemical structures of reported anti-inflammatory compounds as selective COX-2 inhibitors: valdecoxib, celecoxib, isoindoline (**1**), oxime (**2**), hydrazono-pyrazole (**3**), hydrazone (**4**) and chalcone (**5**) derivatives.

attention due to their COXs inhibitory activity, anti-inflammatory and analgesic properties [19–22]. This diversity of pharmacological activities may be due to the lipophilic nature of isoindoline moiety as it possesses a hydrophobic structural feature [O═C−N(R)−C═O] that facilitates crossing various biological membranes *in vivo* [23]. Further, a number of research articles reported the synthesis of compounds (**1–5**) endowed with the pharmacologically-interesting pharmacophores like phthalimide moiety [24], oxime group [25], hydrazono-bridge [26,27], chalcone moiety [28], pyrazole ring [26] and aminosulfonyl moiety [26,27] as selective COX-2 inhibitors with anti-inflammatory potential comparable with common drugs (Fig. 1). Also, it is worthy to note that the bulky bi-cyclic isoindoline ring system may enhance COX-2 selectivity as it maximizes the hydrophobic interactions within COX-2 active site [29].

Appreciation of these findings and in continuation with our previous work [26,30,31] to develop active anti-inflammatory agents, we report herein the synthesis of some novel *N*-functionalized isoindoline-1,3-diones using the concept of pharmacophore hybridization [32] to obtain multiple-ligands compounds combining two functionalities; isoindoline-1,3-dione with either oxime (**9**), hydrazono (**10a–d**), chalcone (**11a–d**), pyrazole (**12–14**) or aminosulfonyl (**10c** and **14**) moieties (Fig. 2A) in one compound in order to investigate the COX-1/COX-2 enzyme inhibition, *in vivo* anti-inflammatory and analgesic activities. Also, designed compounds (Fig. 2B) possessed either acyclic iminic (**10a–d**), acyclic α,β-unsaturated ketone (**11a–d**) or heterocyclic pyrazole ring (**12–14**) as central core structures substituted with two aryl rings in order to fulfill the common structural features of selective COX-2 inhibitors [10]. Finally, molecular docking study was applied to examine the probable binding modes of designed compounds inside COX-2 enzyme active site.

2. Results and Discussion

2.1. Chemistry

The synthetic steps adopted for the target compounds (**9, 10a–d, 11a–d, 12, 13, 14**) were outlined in (Schemes 1 and 2). 2-(3-Acetylphenyl)isoindoline-1,3-dione (**8**) was prepared according to

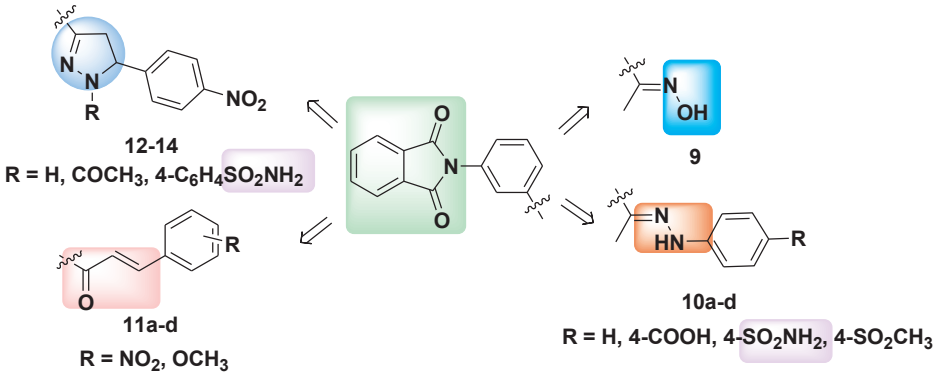

Fig. 2A. Design of the new compounds (**9, 10a–d, 11a–d** and **12–14**).