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Design & synthesis of novel oxazolone & triazinone derivatives and their biological evaluation as COX-2 inhibitors

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ABSTRACT

A new series of oxazolones and triazinones were designed and synthesized and evaluated against both COX-1 and COX-2 enzymes. Full structure elucidation of the new derivatives was performed using micro-analyses, IR, 1H NMR, 13C NMR and mass spectra. Most of the derivatives showed good inhibitory activity against COX-2 enzyme specifically compounds IIIc, IIIe, IVd and IVg with IC50 values 0.024, 0.019, 0.011 and 0.014 μM compared to celecoxib as reference drug with IC50 value of 0.05 μM. Altogether, these results indicate that these derivatives can be effective anti-inflammatory agents.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) nonselective non-steroidal anti-inflammatory drugs (nsNSAIDs) and selective cyclooxygenase 2 NSAIDs (COXIBs) are some of the most widely prescribed drugs in the world, commonly used to treat fever, pain and inflammation.

But NSAIDs produce serious adverse effects, the most important being gastric injury up to gastric ulceration and renal damage [1]. After the discovery of two COX isoforms, it was recognized that selective inhibitors of the inducible form COX-2 expressed mainly in inflammatory cells could provide anti-inflammatory agents devoid of the undesirable effects associated with classical, nonselective NSAIDs [2].

Celecoxib (Celebrex)™ was the first selective COX-2 inhibitor (coxibs) that appeared on the world markets in 1999 as a safer replacement for NSAIDs (non-selective COX-1/COX-2 inhibitors) as it causes less gastrointestinal complications [3]. Many other compounds were used in the treatment of pain and inflammation, such as rofecoxib, valdecoxib and indomethacin [4] Fig. 1.

Oxazolones are important intermediates for the synthesis of several compounds such as amino alcohols, amides [5], amino acids [6,7], dyes [7,8]. Many oxazolones were found to have potent COX-2 inhibitory activity as the diaryl derivative **(1)** where the methyl sulfone group on the 4-phenyl ring was replaced by a sulfonamide moiety resulting in compounds with superior *in vivo* anti-inflammatory properties [9]. On the other hand, Oxaprozin **(2)** is an oxazole derivative that blocks prostaglandin synthesis by non-selective inhibition of both COX-1 & COX-2 [10]. Moreover, A series of 4,5-diphenyl-2-oxo-3H-1,3-oxazole derivatives (**3**) were prepared as selective cyclooxygenase-2 (COX-2) inhibitors [11] Fig. 2.

Triazine derivatives have been reported to possess a broad spectrum of biological activities including antifungal, anti-HIV, anticancer, anti-inflammatory, analgesic and anti-hypertensive [12]. New1,2,4-triazine derivatives bearing hydrazone compounds **(4)** were synthesized and exhibited good anti-inflammatory effect in carrageenan-induced rat paw edema [13]. Also, a series of 5-Aryl-6-(4-methylsulfonyl)-3-(metylthio)-1,2,4-triazine derivatives (**5**) which were evaluated for their COX-1/COX-2 inhibitory activity and showed strong inhibition of COX-2 over COX-1 [14]. Moreover, 5, 6–diphenyl–1,2,4–triazin–3(2H)–one derivatives bearing 5–substituted 1,3,4–oxadiazole **(6)** were found to possess potent COX-2 inhibitory activity [15].

From the above findings and for design purpose it was useful to build on well-established structural features of selective COX-2 inhibitors based on oxazolone and triazinone

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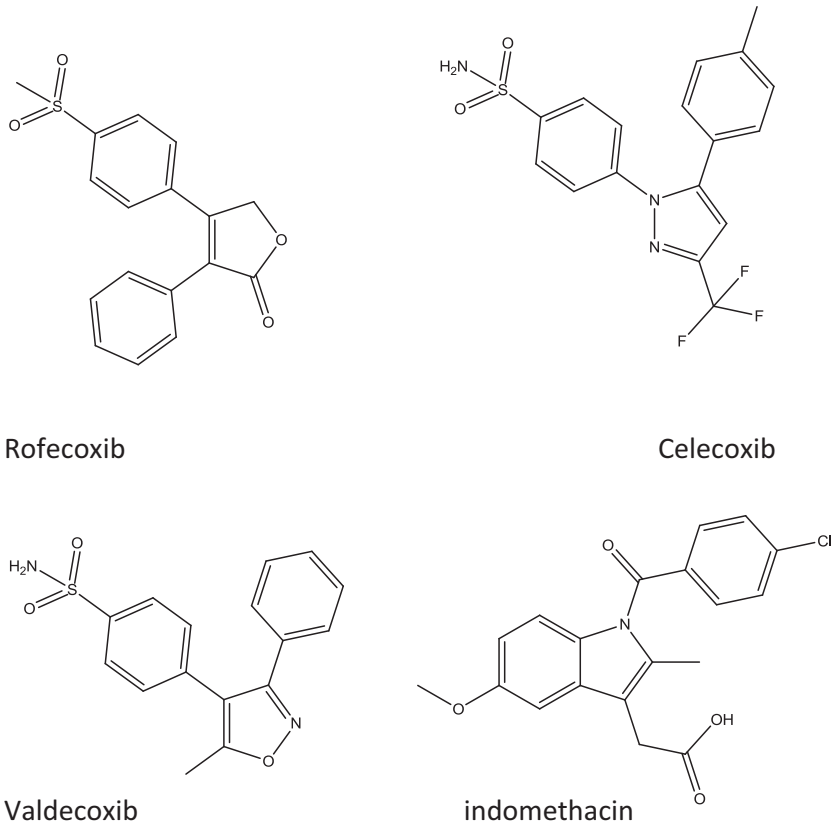

Fig. 1. Structure of some NSAIDs and COX inhibitors.

moiety and mimicking the structure of well-known COX-2 inhibitors.

2. Results and discussion

2.1. Chemistry

The target compounds **IIIa-g and IVa-g** were obtained as the reaction sequence outlined in Scheme 1 starting with nicotinic acid which was converted to nicotinoyl chloride using thionyl chloride by a previously reported procedure [16]. Nucleophilic substitution of chlorine atom in nicotinoyl chloride **I** with glycine in presence of triethylamine in chloroform provided 2-(nicotinamido) acetic acid (**II**) in quantitative yield. The second reaction was accompanied (as an one pot synthesis) by condensation with the appropriate aldehyde in presence of fused sodium acetate in acetic acid for 2 h producing **IIIa-g** in moderate to good yield, the structure was proven by IR spectral bands of CO at ranges from 1781 to 1681 cm^{-1}. In addition, the disappearance of OH band, moreover, 1HNMR spectra showed significant signal of =CH proton at range 7.5–7.8 ppm as a singlet signal. Finally, treatment of the oxazolone derivatives **IIIa-g** with phenyl hydrazine in the presence of fused sodium acetate in acetic acid resulted in the formation of the expected triazine derivatives **IVa-g** which showed the appearance of NH band in IR at 3400–3200 cm^{-1} and in 1HNMR at 3.4–6.16 ppm.

2.2. COX-1&2 inhibitory activities

Compounds **IIIa-g and IVa-g** were evaluated for their inhibitory activities towards COX-1 and COX-2 enzymes (Table 1).

Both series were substituted by an aldehyde bearing an aromatic moiety of different substitutions to examine their effect on activity in order to establish the structure activity relationship. The main difference in the structure of both COX-1 and COX-2 enzymes is larger active site of COX-2 [17] and hence the COX-2 selective drugs have bulky structure which makes the molecules too large to fit into the COX-1 active site but still able to fit the COX-2 active site [18]. Moreover, it was reported that optimal activity against COX-2 enzyme is achieved by tricyclic structure compounds bearing unsaturated heterocyclic ring with attached two aromatic rings [19]. In this paper, the two new synthesized series showed an improved inhibitory activity against COX-2 better than inhibiting COX-1owing to structural resemblance to reported COX-2 inhibitors Fig. 3, the trizine derivatives showed better inhibitory activity than the oxazolone derivatives on both COX-1 and COX-2 enzymes and this may be attributed to the larger size which make it fit better to COX-2 enzyme. Compound **IVd** was more active as COX-2 inhibitor than COX-1 owing to the bulky *p*-methoxy group with IC50 value of 0.011 μM followed by **IVg** a pyridine substituted triazine with IC50 value of 0.014 μM against COX-2 compared to 0.084 μM against COX-1. On the other hand, **IVf** an *o*-substituted hydroxyl triazine showed good inhibitory activity against COX-2 over COX-1 with IC50 values of 0.017 and 0.085 μM respectively. Compounds **IVc, IVe** and **IIIe** have similar inhibitory activity on COX-2 with IC50 value of 0.019 μM where they inhibited COX-1 with IC50 value of 0.096, 0.116 and 0,08 μM. **IIIc, IVb** and **IVa** showed moderate inhibitory activity towards COX-2 but still better than celecoxib with IC 50 values 0.024, 0.034 and 0.035 μM compared to 0.05 μM of celecoxib. Compounds **IIIa,b,d,g,f** though showed inhibitory activity against COX-2 better than COX-1 but their effect was less than celecoxib with IC 50 values 0.059, 0.075, 0.077, 0.085 and 0.106 u μM.