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Simple aromatic compounds containing propenone moiety show considerable dual COX/5-LOX inhibitory activities

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Abstract—For the development of safer anti-inflammatory agents, simple aromatic compounds containing propenone moiety were prepared and evaluated for their dual COX/5-LOX inhibitory activities. Among the 17 prepared compounds, most of the compounds exhibited considerable COX/5-LOX inhibitory activities. Especially compound $\mathbf{C_{15}}$ showed the most significant dual COX/5-LOX inhibitory activity.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of inflammation, pain and fever by inhibiting cyclooxygenase (COX) enzymes thus resulted in the inhibition of the conversion of arachidonic acid to prostaglandins (PGs), which are important biological mediators of inflammation, pain and fever.[1] However, these classical NSAIDs have been associated with gastrointestinal (GI) tract haemorrhagia, ulceration and kidney disorders.[2] The two isozymes of COX were identified as COX-1 and COX-2. It has been reported that COX-1 is constitutively expressed in most tissues and is involved in the regulation of physiological functions in maintaining platelet aggregation and homeostasis of the GI tract and the kidney. However, COX-2 is rapidly induced in inflammatory cells in response to cytokines, growth factors and so on. The PGs produced by COX-2 play an important role in inflammatory symptoms.[3] In contrast, it has been reported that the PGs produced by COX-2 also play an important role in the regulation of renal function, ovulation, adaptive scytoprotection, vasodilation and anti-aggregation.[3d,4] In addition, PGs produced by COX-1 have also been shown to induce inflammatory responses and hyperalgesia.[5] Therefore the selective COX-2 inhibitors may not completely satisfy the safer anti-inflammatory agents. Recently, many medicinal chemists are interested in the dual COX/5-LOX (5-lipoxygenase) inhibitors that are expected to minimize the toxicity of NSAIDs.[6] 5-LOX has been reported to be involved in the biosynthesis of leucotrienes (LTs), which are the mediators of numerous inflammatory diseases and allergic disorders. In addition, LTs promote the development of GI damage, which is the most considerable side effect of NSAIDs.[7] Therefore dual COX/5-LOX inhibitors can be expected to improve the potency of anti-inflammatory effects as well as decrease the adverse side effects of NSAIDs.

In this study, we designed and prepared the 17 compounds having propenone moiety as COX/5-LOX inhibitors, and evaluated their COX/5-LOX inhibitory activities. The design was performed by simplification of clinically using selective COX-2 inhibitors such as celecoxib, refecoxib, valdecoxib and etrocoxib.[6a] The propenone moiety was utilized as a basic skeleton, and simple aromatic compounds such as phenyl, pyridyl, thienyl and furyl groups were attached to the propenone moiety (Fig. 1). Many of the prepared compounds exhibited considerable COX/5-LOX inhibitory activities.

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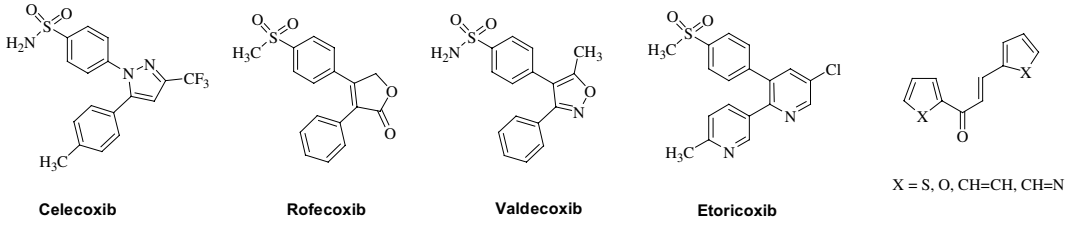
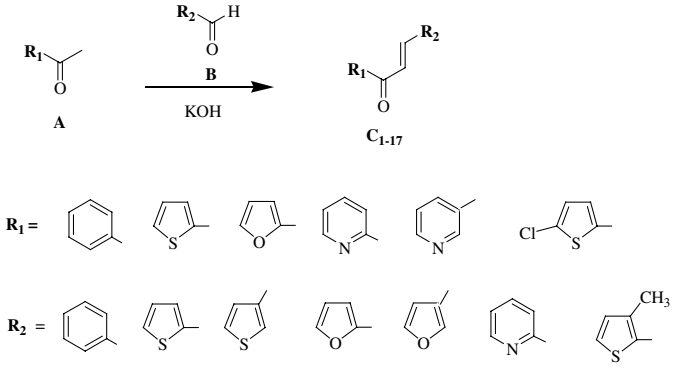


Figure 1.



Scheme 1.

2. Chemistry

Synthetic methods for the preparation of propenone derivatives (**C_1**–**C_{17}**) are summarized in Scheme 1. Acetyl derivatives **A** were treated with aldehyde derivatives **B** in the presence of KOH in methanol–water (5:1), to afford the products **C_{1-17}** in 75.8–97.1% yields. Figure 2 shows the prepared propenone derivatives (**C_1**–**C_{17}**).

3. Results and discussion

COX-1, COX-2 and 5-LOX inhibitory activities[8] for the 17 prepared propenone derivatives are shown in Table 1. Most of the prepared compounds exhibited considerable COX-1, COX-2 and 5-LOX inhibitory activities. Especially, compound **C_{15}**[9] showed a relatively strong 5-LOX inhibitory activity with moderate COX inhibitory activities. It has been reported that the dual COX/5-LOX inhibitors generally exhibit a IC_{50} value of 0.1–8 μM for 5-LOX inhibition, and a COX-1/COX-2 ratio of 2.5–500[6a] so far, even though some singly acting COX-2 or 5-LOX inhibitors show much stronger inhibitory activities. Compared to other reported dual COX/5-LOX inhibitors, our compounds are very simple and easy to prepare. In addition, it was discovered in our research group that **C_{15}** inhibited 90.0% of nitric oxide production at 50 μM, which is also related to the

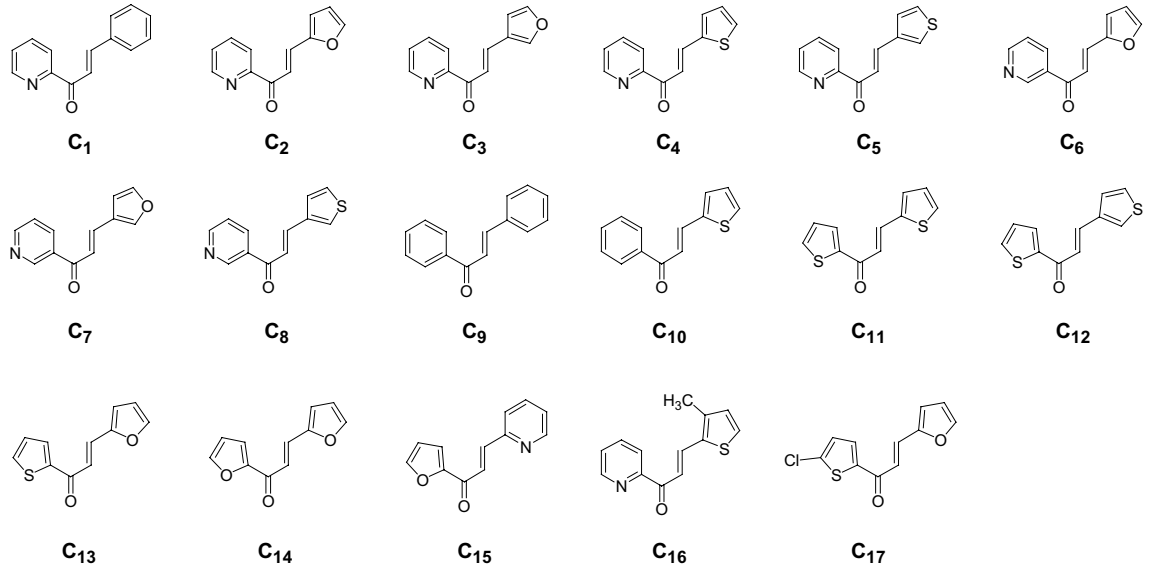


Figure 2.

Table 1. COX-1, COX-2 and 5-LOX inhibitory activities of prepared compounds

Compounds	IC_{50} (μM)		
	COX-1	COX-2	5-LOX
C_1	32.5	28.7	8.13
C_2	23.6	7.44	13.5
C_3	23.6	12.0	13.8
C_4	10.6	9.01	10.0
C_5	13.0	5.22	7.60
C_6	59.7	12.0	12.0
C_7	21.0	7.92	13.4
C_8	13.0	18.4	10.0
C_9	22.1	11.2	12.2
C_{10}	46.2	9.02	9.50
C_{11}	9.01	3.40	4.80
C_{12}	59.9	26.7	5.90
C_{13}	60.7	13.7	14.0
C_{14}	80.7	29.0	12.8
C_{15}	65.3	1.89	0.37
C_{16}	40.1	23.4	6.51
C_{17}	57.4	14.1	7.52
AA861[a]			0.032
NS398[b]	1.67	<0.002	

[a] Positive control for 5-LOX.[10]
[b] Positive control for COX-1 and COX-2.[11]

inflammatory process. This result will be published elsewhere. The structure–activity relationship study of the prepared compounds for COX-1, COX-2 and 5-LOX inhibitory activities showed that **C_{15}** containing 5-membered ring at C1 position and six-membered ring at C3 position showed 10–40 times more active for 5-LOX than other compounds.

In conclusion, we prepared the 17 aromatic compounds containing propenone moiety and evaluated their COX/5-LOX inhibitory activities. This was the first report of the dual COX/5-LOX inhibitory activities of simple propenone derivatives. The results of this study may provide valuable information to researchers who are working on the development of safer anti-inflammatory agents. Further studies are in progress to elaborate the structure–activity relationship.

Acknowledgements

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8. Bone marrow cells from male Balb/cJ mice were cultured for up to 10 weeks in 50% enriched medium (RPMI 1640 containing 2 mM L-glutamine, 0.1 mM nonessential amino acids, antibiotics and 10% foetal calf serum) and 50% WEHI-3 cell conditioned medium as a source of IL-3. After 3 weeks, >98% of the cells were found to be BMMC checked by the previously described procedure (13,15). For measuring inhibitory activity on COX-2 by prepared compounds, cells suspended at a cell density of 5×10^5 cells/mL in an enriched medium were preincubated with aspirin (10 μg/mL) for 2 h in order to irreversibly inactivate the preexisting COX-1. After washing, BMMC were activated with KL (100 ng/mL), IL-10 (100 μ/mL) and LPS (100 ng/mL) at 37 °C for 8 h in the presence or absence of the prepared compounds previously dissolved in dimethylsulfoxide (DMSO). For measuring COX-1 activity, cells without aspirin pretreatment were incubated at 37 °C for 2 h with activators. All reactions were stopped by centrifugation at 120*g* at 4 °C for 5 min. The supernatant and cell pellet were immediately frozen in liquid N_2 and stored at −80 °C for further analysis.
LTC_4 determination: BMMC suspended in an enriched medium at a cell density of 1×10^6 cells/mL were pretreated with prepared compounds for 30 min at 37 °C and stimulated with stem cell factor (SCF; 100 ng/mL). After 20 min of stimulation, the supernatants were isolated for further

analysis by EIA. The PGD_2 and the LTC_4 were determined using an enzyme immunoassay kit (Cayman Chemical, Ann Arbor, MI, USA) according to manufacturer's instruction. Under the conditions employed, COX-1, and COX-2-dependent phases of PGD_2 generation and LTC_4 reached 1.5 ng, 3.7 ng and 500 pg/10^6 cells, respectively. All data was the arithmetic mean of triplicate determinations.

9. The spectral data of $\mathbf{C_{15}}$: TLC (EtOAc–*n*-hexane = 1:2, v:v), $R_f = 0.17$ ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.70 (ddd, $J = 4.8$, 1.7, 0.9 Hz, 1H, pyridine H-6), 7.97 (d, $J = 15.4$ Hz, 1H, –C*H*=CH–CO), 7.84 (d, $J = 15.4$ Hz, 1H, –CH=C*H*–CO–), 7.75 (dt, $J = 7.7$, 1.8 Hz, 1H, pyridine H-4), 7.68 (dd, $J = 1.7$, 0.7 Hz, 1H, furan H-5), 7.48 (dt, $J = 7.8$, 1.2 Hz, 1H, pyridine H-3), 7.42 (dd, $J = 3.6$, 0.7 Hz, 1H, furan H-3), 7.31 (ddd, $J = 7.6$, 4.8, 1.1 Hz, 1H, pyridine H-5), 6.61 (dd, $J = 3.6$, 1.7 Hz, 1H, furan H-4). ESI LC/MS $[MH]^+$ 200.
   HPLC condition: column: C18 reverse phased, 1.5 × 150 mm, 5 μm, GL science, flow rate: 180 μL/min, injection volume: 5 μL of 100 μM solution, mobile phase: 0.1% formic acid in water (A), 0.1% formic acid in acetonitrile (B), 10% B in A to 90% B in A for 10 min and retaining for 10 min at 90% B in A, retention time: 15 min.
   MS ionization condition: sheath gas flow rate: 70 arb, Aux gas flow rate: 20 arb, I spray voltage: 4.5 kV, capillary temp.: 215 °C, capillary voltage: 21 V, TUBE LENS offset: 10 V.
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