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Molecular characterization, biological activity, and *in silico* study of 2-(3,4-dimethoxyphenyl)-3-(4-fluorophenyl)-6-methoxy-4*H*-chromen-4-one as a novel selective COX-2 inhibitor

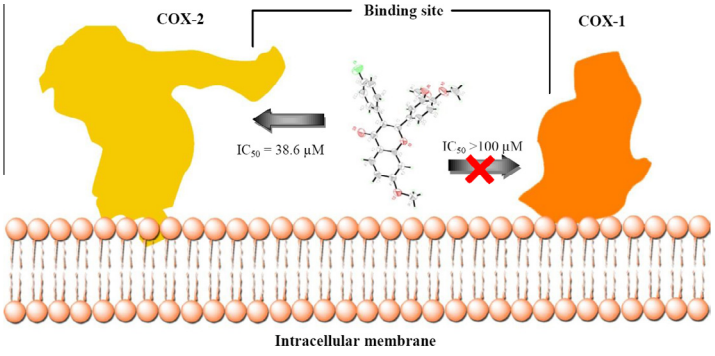
Kamal Rullah [a,e], Mohd Fadhlizil Fasihi Mohd Aluwi [a], Bohari M. Yamin [b], Mohd Syukri Baharuddin [c], Nor Hadiani Ismail [c,d], Hilwan Yuda Teruna [f], Syed Nasir Abbas Bukhari [a], Ibrahim Jantan [a], Juriyati Jalil [a], Khairana Husain [a], Lam Kok Wai [a,*]

[a] Drugs and Herbal Research Centre, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia
[b] School of Chemical Sciences and Food Technology, Universiti Kebangsaan Malaysia, 43600 Bangi, Selangor, Malaysia
[c] Atta-ur-Rahman Institute for Natural Product Discovery (RiND), Universiti Teknologi MARA, Kampus Puncak Alam, 42300 Bandar Puncak Alam, Shah Alam, Selangor, Malaysia
[d] Faculty of Science, Universiti Teknologi MARA, 50400 Shah Alam, Selangor, Malaysia
[e] Sekolah Tinggi Ilmu Farmasi Riau, Universitas Riau, Kampus Bina Widya Km 12.5, Simpang baru-Pekanbaru 28293, Indonesia
[f] Department of Chemistry, FMIPA-Universitas Riau, Kampus Bina Widya Km 12.5, Simpang baru-Pekanbaru 28293, Indonesia

HIGHLIGHTS

- We have successfully synthesized 2-(3,4-dimethoxyphenyl)-3-(4-fluorophenyl)-6-methoxy-4*H*-chromen-4-one, **22**.
- The structural characterization was performed by 1D and 2D NMR and single X-ray crystallographic analysis.
- The results presented provide understanding on the binding interactions between **22** and COX-2.

GRAPHICAL ABSTRACT



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ABSTRACT

The present study aimed to characterize and investigate 2-(3,4-dimethoxyphenyl)-3-(4-fluorophenyl)-6-methoxy-4*H*-chromen-4-one (**22**) as a novel selective COX-2 inhibitor. The data collected from the single X-ray crystallographic analysis and *in silico* study provide important insights on the molecular conformation and the binding interactions that are responsible for the COX-2 selectivity.

* Corresponding author. Tel.: +60 392 897 031.
E-mail address: david_lam_98@yahoo.com (L.K. Wai).

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are useful therapeutics for the treatment of pain and inflammation, particularly arthritis. The main drug target of NSAIDs is cyclooxygenase (COX), which bio-catalyzes the first committed step in arachidonic-acid metabolism [1]. Most NSAIDs not only selectively inhibit the production of prostaglandins (PGs) at the sites of inflammation but also other PGs which serve important functions in other parts of the body, a factor which accounts for some of the toxicity of these agents. The most frequent complication associated with NSAIDs usage can be found in the gastrointestinal tract (GIT). GI bleeding, ulceration, perforation, and obstruction are a significant cause of morbidity and mortality in patients who are treated with these agents [2,3]. To counter these limitations, novel scaffolds with selective COX-2 or mPGES-1 inhibition need to be designed and evaluated [4].

Since COX-2 enzyme, also known as PGH synthase was cloned in 1992 [5], DuPont company had developed a compound namely DuP-697 (**1**), that was potent in many anti-inflammatory assays and did not have the ulcerogenic effects like any conventional NSAIDs in rats at a single dose up to 400 mg/kg [6]. DuP-697 eventually became the major building-block for the synthesis of many other new COX-2 inhibitors. Celecoxib and rofecoxib, the first two COX-2 inhibitors that reached the market, were generally based on DuP-697. Celecoxib (**2**) (Celebrex®) is also the first and only COX-2 inhibitor available in the United States. However, rofecoxib (**4**) (Vioxx®) and valdecoxib (**6**) (Bextra®) were known to increase the risk of heart attacks and strokes with long term use, therefore, both drugs were withdrawn from the market in September 2004 and April 2005 [7–11]. This eventually led to the development of new selective COX-2 inhibitors that could act effectively without exerting major side effects associated with the traditional NSAIDs [12]. The solving of the 3D structures of an unliganded murine COX-2 and SC-558-protein complex (**3**) by Kurumbail et al. finally shed some light on the structural basis for the selective inhibition of COX-2 which also demonstrate some of the conformational changes associated with time-dependent inhibition [13]. The development of new generation of selective COX-2 inhibitors typically relied on the structural modifications of coxib drugs, for example DFU (**5**), etoricoxib (**7**), parecoxib (**8**), and MPO-0029 (**9**) [14–16] (Fig. 1).

Previous study had shown that 7-methanesulfonylamino-6-phenoxychromone (**10**), a synthetic chromone-based exhibited significant potency in the rat models of carrageenan-induced edema (CPE) and adjuvant-induced arthritis (AA) [17]. Further structural activity relationship study conducted on compound **10** led to the discovery of the lead structure, T-614 (**11**). T-614 not only demonstrated potent anti-arthritic activity in chronic inflammatory disease models but also low gastro-ulcerogenic liability in oral administration and appeared to be a good drug candidate [18,19]. T-614 was then introduced in clinical evaluation with 50 mg/day therapy and was found to be as effective as methotrexate (MTX) therapy in 24 weeks. This signifies a new option for the therapy of patients with active rheumatoid arthritis (RA) [20]. The presence of chromone scaffold in some natural and synthetic compounds without the presence of sulfonyl or sulfonamide moiety had also been reported for possessing good COX inhibition. For example, stellatin (**12**) and eugenin (**13**), isolated from *Dysophylla-stellata* were reported to be selective toward COX-2 inhibition [21,22]. On the other hand, a series of chrysin derivatives bearing dichloro group at positions 3′ and 4′ (e.g. compounds **14**–**16**) had been prepared and were found to exhibit good inhibitory activity on prostaglandin production by COX-2 (IC_{50} = 0.1–0.5 μM) [23]. In our previous study, we have also observed that the chromone scaffold significantly active in suppressing the PGE_2 production secreted by lipopolysaccharide-induced mouse macrophage cells (RAW 264.7) [24].

Conventionally, preserving the sulfonyl (R–SOO–R) or sulfonamide (R–SOO–NH_2) functional group is an important criterion in the design of inhibitors with potent COX-2 inhibition and high COX-1/COX-2 selectivity (e.g. compounds **1**–**11**). On the possible downside, long-term use of COX-2 traditional inhibitors bearing these moieties might be implicated with the increase in cardiovascular side effects such as heart attack and stroke incidents. Another distinctive characteristic of these inhibitors is the presence of a five-membered ring in the central core structure. Despite the fact that chromone structure has been well studied in recent years, the ligand–protein complex binding interactions between chromones and COX-2 have never been disclosed to date. To initiate this study, first the five-membered ring core was replaced with a chromone ring (Fig. 2) and then the synthesized compound was further evaluated for the COX-2 inhibitory activity and the COX-1/COX-2 selectivity. The compound structural conformation and

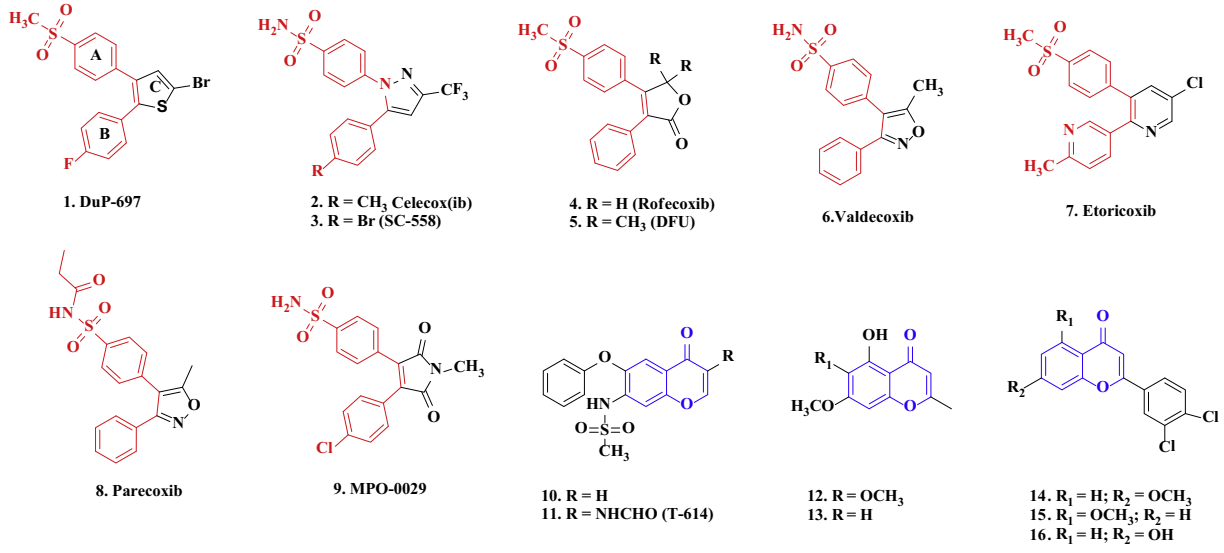

Fig. 1. Selected structures of COX-2 inhibitors.