Med Chem Res (2017) 26:662–671
DOI 10.1007/s00044-017-1786-0

MEDICINAL CHEMISTRY RESEARCH

CrossMark

ORIGINAL RESEARCH

Biological activity evaluation and molecular docking study of chromone derivatives as cyclooxygenase-2 inhibitors

Chirattikan Maicheen[1] · Narumol Phosrithong[2] · Jiraporn Ungwitayatorn[1]

Received: 8 July 2016 / Accepted: 10 January 2017 / Published online: 18 January 2017
© Springer Science+Business Media New York 2017

Abstract A series of chromone derivatives have been evaluated as potential cyclooxygenase-2 (COX-2) inhibitors. The four most potent compounds, **48**, **41**, **39**, and **35** displayed IC_{50} values of 3.30, 6.86, 7.36 and 7.46 µM, respectively. Compounds **35** and **38** showed higher selectivity for COX-2 (selectivity index, SI = 7.48 and 5.46, respectively) than celecoxib (SI = 4.17 in the same test) whereas compound **39** showed comparable selectivity (SI = 4.19) to celecoxib. The molecular volumes of compounds **35** (312.84 $Å^3$) and **38** (314.18 $Å^3$) were similar to celecoxib (299.28 $Å^3$) but larger than ibuprofen (211.83 $Å^3$). Docking results were in good agreement with the experimental biological data in terms of evaluation of binding energy and binding mode. Compounds **35**, **38**, and **39** had higher binding affinity against COX-2 (binding energy between −9.77 and −11.42 kcal/mole) than COX-1 (binding energy between −6.28 and −7.88 kcal/mole). These three chromone compounds also displayed active conformation in the same orientation as that of celecoxib. Thus, compounds in this series has the potential to be a new class of selective COX-2 inhibitor.

Keywords Chromone series · COX-2 inhibitory activity · Docking study

✉ Jiraporn Ungwitayatorn
jiraporn.ung@mahidol.ac.th

[1] Faculty of Pharmacy, Mahidol University, 447 Sri-Ayudhya Road, Bangkok 10400, Thailand

[2] Faculty of Pharmacy, Siam University, 38 Petkasem Road, Bangkok 10160, Thailand

Introduction

Cyclooxygenases (COXs), also known as prostaglandin H_2 (PGH_2) synthase, catalyzes the conversion of arachidonic acid to PGH_2. There are at least two isoforms of COXs, i.e., COX-1 and COX-2 (Fu et al. 1990; Xie et al. 1991). COX-1 is expressed in most tissues, particularly in the gastrointestinal tract and kidneys where it is mainly responsible for the synthesis of cytoprotective prostaglandins. COX-2 is selectively induced in response to a variety of pro-inflammatory stimuli such as tumor necrosis factor-α (TNF-α), interleukines, and growth factors and facilitates the release of prostaglandins involved in the inflammatory process (Crofford et al. 1994; Yucel et al. 1999; Simmons et al. 2004). The major difference between these two isoforms rather lies in physiological function rather than in structure. COX-1 and COX-2 are very similar in their structures with the molecular weights of 70–74 kDa (Flower 2003). They contain over 600 amino acids with an approximately 60% homology within the same species (Vane et al. 1998). The difference between COX-1 and COX-2 is that the Ile at positions 434 and 523 in COX-1 is replaced by Val in COX-2. The smaller Val side chain in COX-2 induces a conformational change at Tyr355, thereby forming an additional hydrophobic secondary internal pocket protruding off the primary binding site in COX-2 which is absent in COX-1 (Kurumbail et al. 1996). Consequently, the total volume of the COX-2 primary binding site including the secondary pocket (394 $Å^3$) is about 25% larger than that of the COX-1 binding site (316 $Å^3$) (Luong et al. 1996; Gierse et al. 1996; Guo et al. 1996). Another essential amino acid difference between COX-1 and COX-2, within the side pocket of COX-2, is Arg in place of His513 in COX-1 which can interact with polar moieties. These differences between the COX active sites have major