Virtual Screening for Finding Novel COX-2 Inhibitors as Antitumor Agents

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Abstract: The cyclooxygenase-2 (COX-2) enzyme binds to arachidonic acid resulting in the release of metabolites that induce pain and inflammatory responses. Recent studies have shown that strong COX-2 expression is highly correlated with increased tumor risk. Therefore, the development of potent COX-2 inhibitors to relieve pain and treat cancers requires further investigation. We used virtual screening to find three COX-2 inhibitors (Phar-95239, T0511-4424 and Zu-4280011) from a huge zinc database containing 2000000 compounds. The effects of the compounds on COX-2 were compared to those on COX-1 using a colorimetric COX (ovine) screening assay kit. The selectivity index, the ratio of IC50 for COX-1 inhibition to that of COX-2, calculated were MTT assay was used to evaluate the cytotoxic activity of the compounds using different dilutions. The IC50 values were calculated. Based on the results of the MTT assay, the IC50 values for compounds Phar-95239, T0511-4424 and Zu-4280011 were 178.52, 143 and 97.61 μM, respectively, and the selectivity indices of the compounds were 11.36, 12.20 and 20.03, respectively. These results indicated a relationship between the selectivity index and anticancer activity. Zu-4280011 displayed the highest selectivity index and the best results in the MTT assay among selected compounds.

Keywords: Cyclooxygenase, MTT, Selectivity index, Virtual Screening, Zinc database.

INTRODUCTION

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of inflammation and pain is often accompanied by adverse gastrointestinal and renal side effects [1]. The anti-inflammatory activities of these drugs are mediated by the inhibition of cyclooxygenases (COXs), which catalyze the bioconversion of arachidonic acid to prostaglandins[2]. However, the inhibition of COXs may lead to undesirable side effects. Currently, it is well established that there are at least two COX isozymes, COX-1 and COX-2 [3]. The constitutively expressed COX-1 isozyme is produced in a variety of tissues and appears to be important for the maintenance of physiological functions such as gastroprotection and vascular homeostasis. On the other hand, the COX-2 isozyme is induced by mitogenic and proinflammatory stimuli, suggesting the involvement of this isozyme in inflammatory processes. Therefore, the selective inhibition of COX-2, but not COX-1 is useful for treating inflammation and inflammation-associated disorders. COX-2 inhibitors also have lower gastrointestinal toxicities than other NSAIDs [4]. Recent studies have shown that the progression of Alzheimer’s disease is reduced among some users of NSAIDs. Chronic treatment with selective COX-2 inhibitors may slow the progress of Alzheimer’s disease without causing gastrointestinal damage [5, 6]. Therefore, selective COX-2 inhibitors have been developed as a new generation of NSAIDs with diminished GI side effects. However, rofecoxib and valdecoxib, which are highly selective COX-2 inhibitors, have been withdrawn from the market due to an increased risk of cardiovascular complications. COX-2 mediates the biosynthesis of prostacyclin which is a vasodilator and an inhibitor of platelet aggregation. The indirect inhibition of prostacyclin production by selective COX-2 inhibitors might account for their adverse cardiovascular effects [7, 8].

In addition to the role of COX-2 in rheumatoid arthritis and osteoarthritis, COX-2 expression is triggered by inflammation and carcinogenesis. [4] COX-2 is overexpressed in many solid tumors such as colon [9], breast [10], prostate [11], liver [12] and lung [3] cancers. COX-2 inhibition in vitro using specific COX-2 inhibitors has demonstrated that COX-2 is a potential target for novel cancer therapies [13, 14]. Research attempts to discover selective COX-2 inhibitors have produced many classes of compounds such as