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Design, synthesis and bioactivities of Celecoxib analogues or derivatives

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ABSTRACT

A series of Celecoxib analogues or derivatives were designed and synthesized, and their biological activities were studied. The results of inhibitory activity *in vitro* proved that compounds **1a, 1h, 1i, 1l** and **1p** had better inhibitory effect on COX-2, and the selectivity was higher. Among them, the inhibitory activity of compound **1h** to COX-2 was IC_{50} = 0.049 μmol/L and SI >1000. Moreover, the experimental results of anti-inflammatory activity *in vivo* showed that they had good anti-inflammatory activity and could inhibit the release of PGE-2. Therefore, these compounds have better druggability.

1. Introduction

Cycloxygenase (COX) is found in the endoplasmic reticulum of mammalian cells and has high biological activity. In 1990s, studies have shown that there are two subtypes of cyclooxygenase, namely COX-1 and COX-2. COX-1 is a constituent enzyme that is present in most tissues, generally, COX-1 levels are relatively stable.[1–3] In addition, maintaining a certain level of COX-1 can promote the synthesis of prostaglandins (PG) in the gastrointestinal tract to regulate the physiological activities of normal tissue cells, protect the gastrointestinal mucosa, regulate renal blood flow as well as promote platelet aggregation and other important role. COX-2 is an inducible enzyme that is very low in the body under normal physiological conditions and is expressed mainly in inflammatory cells. When COX-2 is stimulated by inflammatory substances, such as mitogen (LPS and SPA), inflammatory cytokines (TNF, IL-1, and PAF), endotoxin and other inflammatory substances, it can be induced and expressed at high levels. For example, the levels of PGE-1, PGE-2 and PGI-2 are increased, which promote the inflammation and tissue damage, resulting in swelling, edema, pain, fever and other symptoms.[4–6]

COX-1 and COX-2 are 71 kDa membrane-bound proteins, both of which are basically the same length and contain about 600 amino acid molecules.[7–9] X-ray diffraction crystal structure analysis showed that COX-1 (Fig. 1) and COX-2 (Fig. 2) are in the form of homodimers. The crystal structures of their is very similar in shape. As a hairpin, there is a long hydrophobic channel in the entire molecular space structure, this allows the arachidonic acid to enter directly from the membrane, which is converted to synthesize prostaglandin. The amino acids on the other side of hydrophobic channel are different. The 434 and 523 bits of COX-1 are isoleucine residues, and the two sites of COX-2 are valine residues. Because the molecular weight of valine residue is less than that of isoleucine residue, the structure is small, the larger binding space can be left, and the drug molecule can be covalently bonded.[10–12] In addition, COX-1 is a histidine residue at position 513, and COX-2 is an arginine residue, which makes the end of COX-2 be more flexible than COX-1, allowing it to interact with larger drug molecules. The differences in spatial structure provide the possibility for the design of selective inhibitors to COX-2.

The present study suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in the treatment of inflammation by inhibiting COX-2, COX-1, and other adverse effects.[13–15] Therefore, selective inhibition of COX-2 can be achieve to effectively treat inflammation while avoiding or reducing the adverse effects caused by inhibition of COX-1. Since 1990s, a number of selective COX-2 inhibitors have been used in clinical settings, such as Celecoxib, Rofecoxib, Valdecoxib, and Percoxib (Fig. 3). The present selective COX-2 inhibitors have the selectivity for up to hundreds of times, and inhibit the synthesis of physiological prostaglandins. At present, COX-2 inhibitors have been used as the nonsteroidal anti-inflammatory drugs for the first, and are clinically used in arthritis and other diseases. In recent years, clinical studies have shown that COX-2 inhibitors have effects on the antitumor and brain protection.[15,16]

Celecoxib is a highly selective COX-2 inhibitor, which is rapidly absorbed by oral administration and the bioavailability is about

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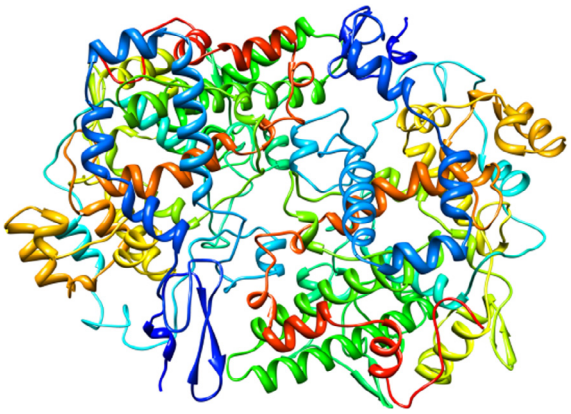

Fig. 1. Crystallographic structure of COX-1.

Fig. 2. Crystallographic structure of COX-2.

99%. After absorption, it is widely distributed in all tissues of the body, and is oxidized and metabolized in the liver. The methyl group in the benzene ring is hydroxylated and carboxylated, which is finally combined with glucuronic acid and excreted in urine.[17,18] The anti-inflammatory activity of drug is good, which has less adverse reactions to the stomach. In 1999, Celecoxib was approved by the FDA for the treatment of rheumatoid arthritis and osteoarthritis-induced pain. The inhibitory effect of Celecoxib on COX-2 was 400 times that of COX-1, and the selectivity was good.[19,20] Celecoxib was used as a lead compound, the structures of six-membered rings, five-membered heterocycles, and substituents on five-membered heterocycles were transformed by using the principle of bioisosterism (Fig. 4 and Scheme 1).

2. Results and discussion

2.1. Design and synthesis of Celecoxib analogues or derivatives

The design of novel selective COX-2 inhibitor was based on Celecoxib as the lead compound, and its structure was modified by the bioisosterism principle (Fig. 4). In terms of drug structure, these compounds had the same spatial structure as Celecoxib, so the possibility of drug formation was relatively large. In the modification, the basic frame structure of Celecoxib was retained, and the selective inhibition of COX-2 essential pharmacophore (sulphamoyl group) was also retained. In addition, the five-membered heterocycle was an important binding site of COX-2. It was necessary to modify the five-membered heterocycle to make it more stable. In the design process, N, O, S and other bioisosteres were selected to replace the C-4 on the original-five membered ring, and the C-2 on the five-membered ring was replaced by N atom. Because these atoms were easily linked to COX-2 in the form of covalent bonds, theoretically, the inhibitory activity should be better. Moreover, $-CH_3$ and $-CCl_3$ were introduced as the substituent groups on five-membered ring, because these substituents had a certain spatial structure, and the two subtypes of COX had a hollow

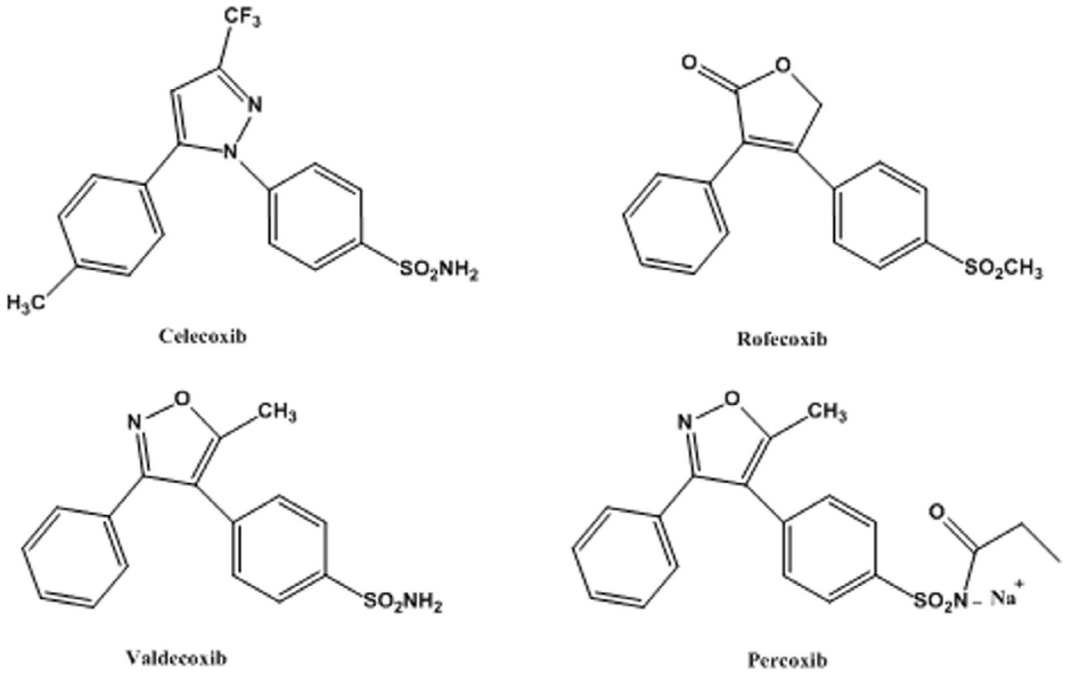

Fig. 3. The structures of selective COX-2 inhibitors.