Non-steroidal Cyclooxygenase (COX) Inhibitors

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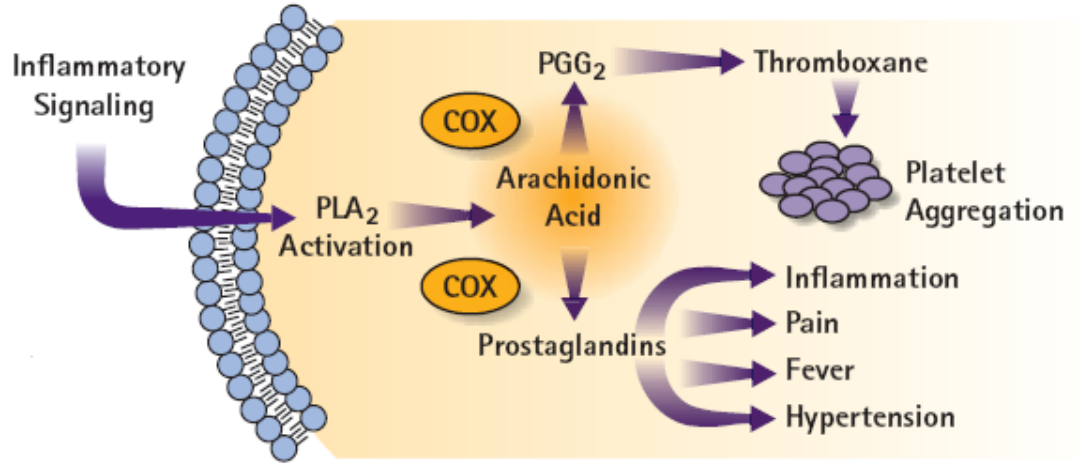
Cyclooxygenases (COXs), also known as prostaglandin H synthases, are fatty acid oxygenases that contain about 600 amino acid residues and act on arachidonic acid to generate prostaglandins (PG). All vertebrates contain two COX genes: one encoding the constitutive COX-1 and another inducible COX-2. COX-1 and COX-2 share approximately 60-65% amino acid identity. These COX isoforms are bifunctional hemoproteins that catalyze both the bioxygenation of arachidonic acid to form PGG_2 and the peroxidative reduction of PGG_2 to form PGH_2. Hence, the catalytic domain of COX is considered to contain both cyclooxygenase and peroxidase active sites. The peroxidase site is required for the activation of heme groups that participate in the cyclooxygenase reaction. The active site is reported to be about 8 Å wide and 25 Å long that opens in the membrane-binding domain and accepts the arachidonic acid released from the membrane by phospholipases. The amino terminus of COX contains a single epidermal growth factor (EGF) module with conserved disulfide bonds, which functions as a dimerization domain. Following this domain are four amphipathic helices that anchor COX to the cell membrane. The active site of COX-2 is slightly larger and can accommodate bigger structures than those that are able to reach the active site of COX-1.

COX-1 is an ubiquitously and constitutively expressed enzyme that is associated with the endoplasmic reticulum (ER). It is responsible for maintaining normal physiologic functions and is considered as a "housekeeping" enzyme. It is normally expressed in the gastrointestinal tract, kidneys, and platelets and appears to be responsible for mediating the production of thromboxane A_2 and prostaglandins. COX-2 is an inducible enzyme and is generally present at very low levels. It is mainly associated with the nuclear envelope and is primarily associated with inflammation. Cytokines and growth factors increase the expression of COX-2, mainly at inflammatory sites, producing prostaglandins, which mediate inflammation, pain, and fever. The lumen of the ER is important for both the structure and function of COXs: its oxidative potential allows formation of the disulfide bonds of the enzymes and the N-linked glycosylation, which occurs in the ER, appears to be necessary for proper folding of the enzyme. The newly synthesized COX is activated at Tyr^{384} (in human COX-1) or at Tyr^{371} (in human COX-2) to produce a tyrosyl radical, which converts arachidonic acid to an arachidonyl radical, which in-turn then reacts with two molecules of oxygen to yield PGG_2. PGG_2 diffuses to the peroxidase site where it is reduced to form PGH_2. COXs have a short catalytic half-life because of the fact that the enzyme is auto-inactivated.



Most non-steroidal anti-inflammatory drugs (NSAIDs) exert anti-inflammatory and analgesic effects through the inhibition of prostaglandin synthesis by blocking COX activity. Traditional NSAIDs inhibit prostaglandin formation through the inhibition of both COX-1 and COX-2. Inhibition of COX-1 is not necessary for anti-inflammatory and analgesic effects, but is thought to account for much of the toxicity of traditional NSAIDs. Based on structural differences in the active sites of these two isozymes, several new drugs have been developed that specifically inhibit only the COX-2 activity. COX-2 inhibitors have the potential to provide the traditional benefits of NSAID with significantly reduced incidence of endoscopic ulcers. Hence, they offer greater therapeutic promise in the treatment of inflammation and cancer. The selective COX-2 inhibitors have great clinical significance because they can allow the preservation of COX-1 activity, which is essential in maintaining prostaglandins that are important for normal platelet function and protection of the gastrointestinal mucosa, and still inhibit COX-2 to reduce inflammation and other pathologic processes. Increased expression of COX-2 has been associated with increased incidence of colon and breast cancers. It is over-expressed in about 50% of adenomas and 85% of adenocarcinomas of the colon. Hence, COX-2 inhibitors offer greater therapeutic promise not only in the treatment of inflammation, but also some forms of cancer. COX-2 inhibitors are also shown to augment photosensitization by increasing apoptosis and improve the responsiveness of photodynamic therapy.

More recently, there has been an upsurge of interest in COX-2 inhibitors as possible candidates for the treatment of Alzheimer's disease. This is due to the fact that researchers have begun to think about "inflammation as a factor" in the development and/or progression of Alzheimer's disease. Studies have shown that aggregated synthetic $A\beta_{1\text{-}40}$ peptide induces COX-2 expression in SH-SY5Y neuroblastoma cells and also stimulates oxygenase and peroxidase activities of COX-2 in a cell free system. Since neuronal excitation and oxidative stress have been linked to the pathogenesis of several neurodegenerative disorders, inhibiting excessive COX-2 activity may reduce the oxidative stress-induced neuronal damage and trauma. Several epidemiological studies have indeed shown that groups of people on NSAIDs, for unrelated conditions, such conditions as rheumatoid arthritis, have reduced incidence of Alzheimer's disease. NSAIDs are believed to inhibit human Aβ aggregation *in vitro* and reverse the β-sheet conformation of preformed fibrils.

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Antibodies for Cyclooxygenases

Product	Cat. No.	Comments	Size	Price
Anti-COX2, C-Terminal Rabbit pAb	236002	Immunoaffinity purified. Immunogen used was a synthetic peptide corresponding to a 17-amino acid sequence near the C-terminus of human COX2. Reacts with bovine, human, mouse, rat, sheep. Does not cross-react with COX1. Suitable for ELISA and immunoblotting.	50 µg	
Anti-COX2 Mouse mAb (5E10/D10)	236004	Immunoaffinity purified. Immunogen used was purified COX2 from HL-60 cells. Recognizes COX2. in human and mouse. Does not cross-react with COX1. Suitable for ELISA and immunoblotting.	100 µg	