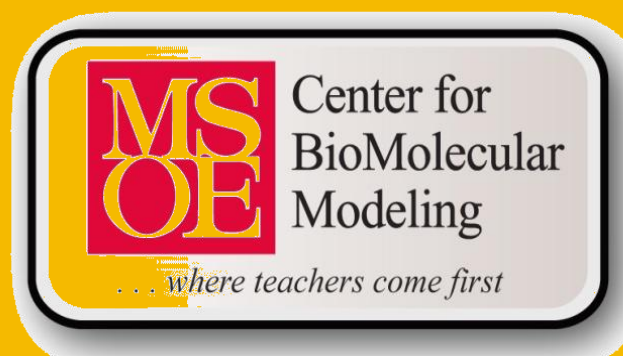


MODELING AND INHIBITION: CELECOXIB BINDS SELECTIVELY TO COX-2



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ABSTRACT

Pain management is often an important part of patient care as it is very real and relevant to a patient's mental state throughout their disease and recovery process. Typical over the counter (OTC) medications are not always sufficient to appropriately manage pain, nor does their OTC status render them safe for long term use. Many OTC medications are targeted to bind to proteins, like cyclooxygenase-isoform 2 (COX-2). Commonly used drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), bind to COX-2, blocking the inflammatory process. However, NSAIDs can also bind to cyclooxygenase-isoform 1 (COX-1), resulting in undesirable side effects in the stomach and intestines. The propensity of these NSAIDs to bind to both COX isoforms is why they are correctly referred to as non-selective NSAIDs. A selective NSAID, on the other hand, would be useful for patients who desire anti-inflammatory effects because selective NSAIDs bind more specifically to COX-2, avoiding the aforementioned side effects that result from the indiscriminate nature of non-selective NSAIDs. Our model shows how celecoxib (Celebrex), a selective NSAID, binds to COX-2, and the complementary relationship between them. While celecoxib offers pain management with fewer side effects than non-selective NSAIDs, drugs similar to celecoxib have caused serious cardiac problems. New research is being conducted to find drugs that are similar to celecoxib in regard to the lack of severe cardiovascular effect. Ideally, however, these new drugs would also be structurally different from celecoxib in a way that improves upon the selectivity for COX-2.

INTRODUCTION

In 1971, it was discovered that NSAIDs inhibit prostaglandin biosynthesis by inhibiting a cyclooxygenase (COX) enzyme involved in the arachidonic acid cascade.¹ Since then, selectivity has gotten greater and new drugs have been developed to try to increase the effectiveness of pain management while decreasing certain side effects of older NSAIDs.

While the selectivity of celecoxib on the COX-2 enzyme decreases a risk of bleeding, compared to that of traditional NSAIDs, there may be a link to an increased risk of clotting instead. The selective COX-2 inhibitor celecoxib is known to inhibit the production of vascular prostacyclin (PGI₂), an inhibitor of platelet aggregation and a vasodilator.² Unlike conventional NSAIDs, COX-2 inhibitors do not reduce the endogenous production of thromboxane A₂ (a potent platelet activator).² This may or may not increase the risk for CV events, such as heart attacks or strokes, because of the superior selectivity for the COX-2 enzyme.

Celecoxib is FDA approved for:

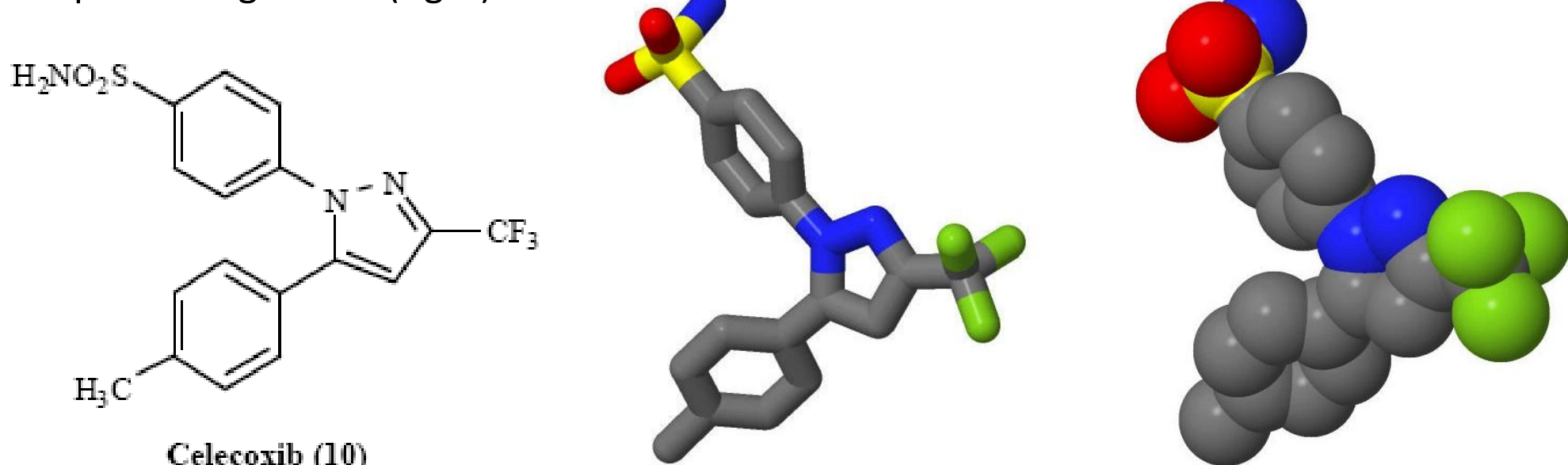
- Acute Pain
- Ankylosing spondylitis
- Juvenile rheumatoid arthritis
- Osteoarthritis
- Primary dysmenorrhea
- Rheumatoid arthritis

The COX-2:COX-1 ratio for celecoxib (based on concentrations of the drug to produce 50% inhibition) is approximately 0.003.²

Important clinical points for celecoxib:

- Can increase cardiovascular adverse events
- Poor metabolizers of CYP2C9 substrates; decreased metabolism, leading to high plasma levels; consider dosage adjustment or alternative therapy
- Concurrent use of NSAIDs should be met with extreme caution because of increased risk of bleeding

Fig 1: 2-D representation of celecoxib (left). 3-D representation of celecoxib (middle). Space filling model (right).



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MOLECULAR STORY

Hippocrates, the father of modern medicine, described the use of powder from the bark of a willow tree to treat pain, inflammation and fever. It was later discovered that this powder consisted of extracts containing salicylic acid, the chemical which led to the discovery of aspirin. Aspirin was the first NSAID to be introduced in 1897. While NSAIDs such as aspirin do have beneficial anti-inflammatory and analgesic effects, they also come with dangerous gastrointestinal side effects. Inhibition of COX by NSAIDs led to a reduction in all prostaglandin and thromboxane synthesis, resulting in both the beneficial and unfortunate adverse effects associated with these agents. For many years it was thought that COX was a single enzyme which existed in the same form in all cell types, but later a second enzyme, COX-2, was discovered. "It is now well documented that the inducible COX-2 is associated with inflammatory conditions, whereas the constitutively expressed COX-1 is responsible for the cytoprotective effects of prostaglandins."¹ This finding led researchers to the idea that a selective COX-2 inhibitor would exhibit all the beneficial anti-inflammatory and analgesic properties associated with NSAIDs, but would not produce unwanted gastric disturbances.

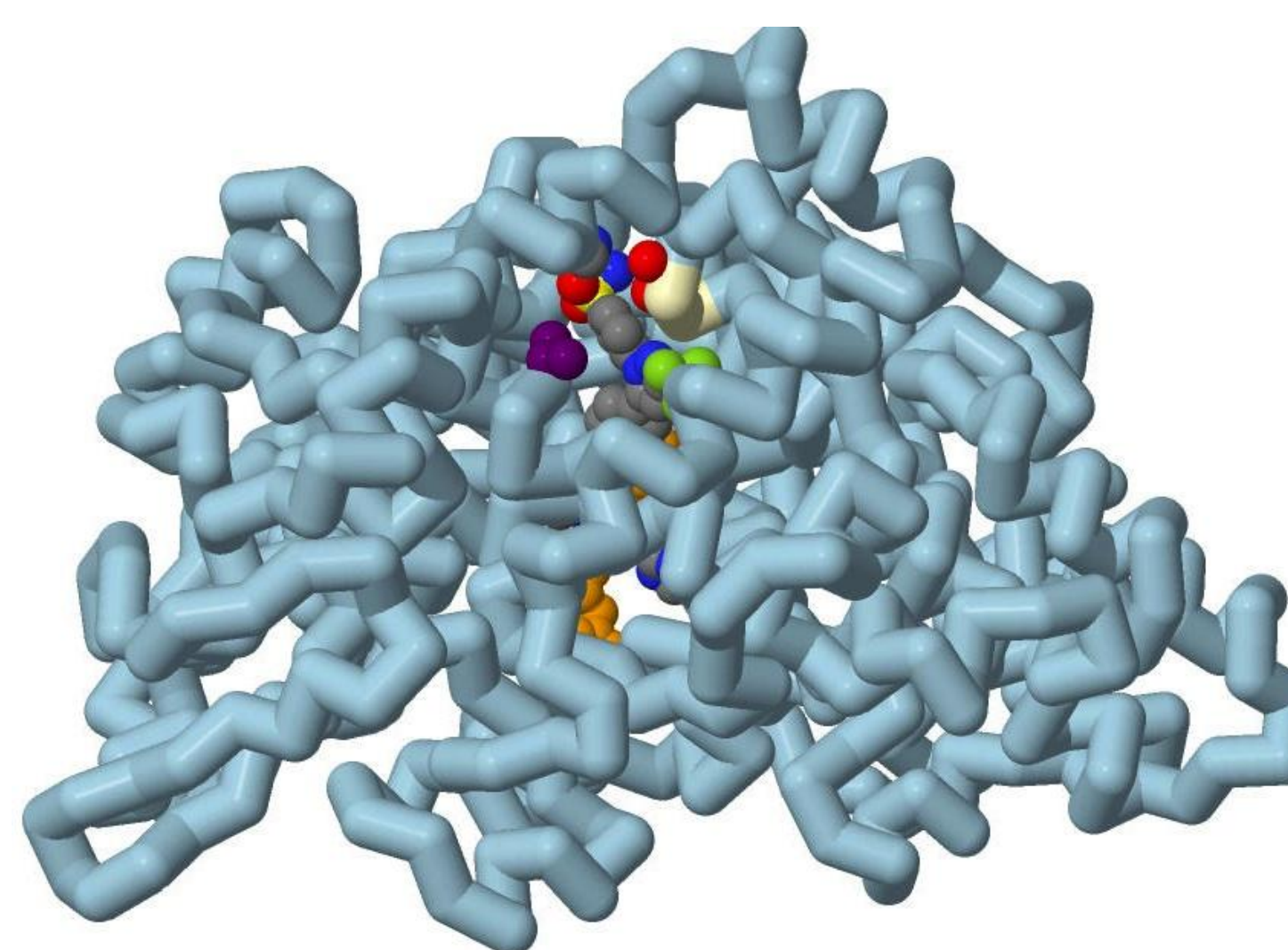


Fig 2: 3-D representation of celecoxib bound to COX-2. Valine, highlighted in violet, replaces an isoleucine found in COX-1 and gives celecoxib its selectivity.

Celecoxib derives its high specificity for COX-2 from interactions with two key amino acids on the COX-2 backbone: Leu338 and Ser339. In the COX-2 active site, celecoxib hydrogen bonds with these two amino acids, as well as with Gly178 and His75.^{3,4} The oxygens on leucine and serine form hydrogen bonds with the hydrogens on the nitrogen of celecoxib. Because of the strength of the hydrogen bonding interactions, celecoxib is maintained in its active site on COX-2. One significant difference between COX-1 and COX-2 is at position 509. COX-2 contains a valine, which interacts with celecoxib. COX-1 contains a bulkier isoleucine, which prevents tight celecoxib binding due to steric hindrance.⁵ Despite celecoxib's selectivity for COX-2, situations do arise where celecoxib is able to bind to COX-1. This has a great clinical impact because patients could experience adverse effects, such as bleeding. Pharmacists must be aware of this, especially when a patient is also on another medication that increases the risk of bleeding. For example, adding aspirin, a drug that inhibits COX-1, with celecoxib has additive effects on inhibiting COX-1, and therefore, an increased risk of bleeding.^{2,6}

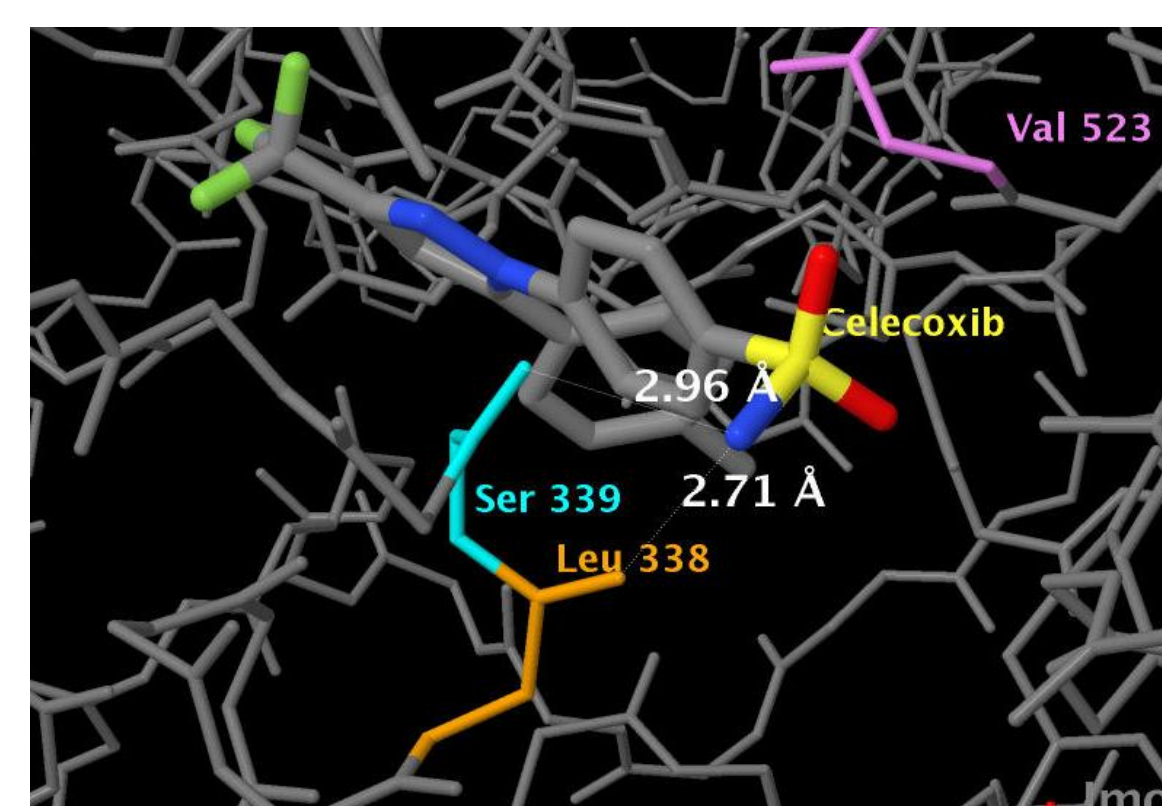


Fig 3: 3-D representation of celecoxib bound to COX-2. Shows hydrogen bonding of Ser 339 and Leu338 to celecoxib.

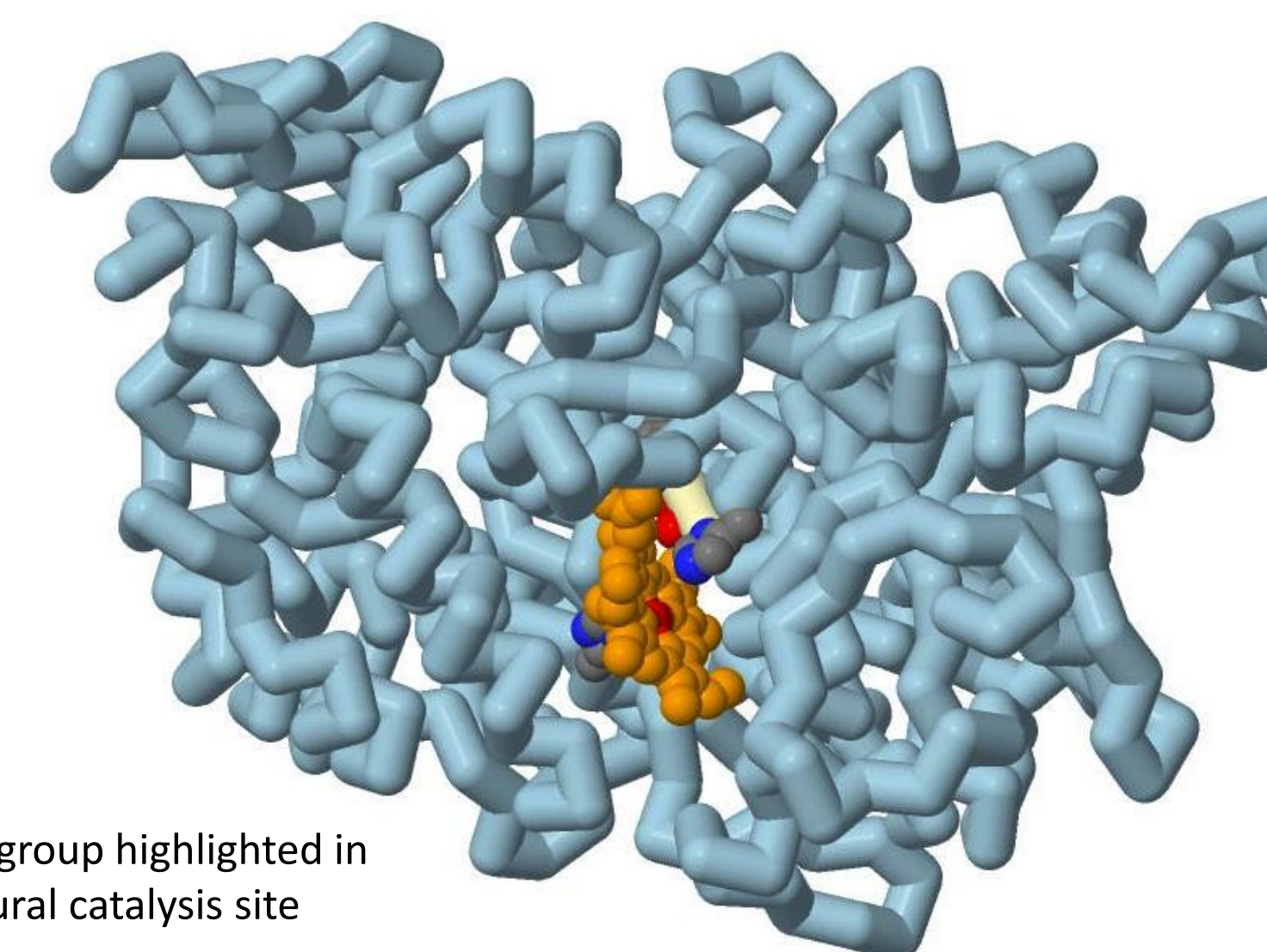


Fig 4: Heme group highlighted in orange, natural catalysis site

UNADDRESSED CLINICAL ISSUES

Referring to celecoxib as a selective COX-2 inhibitor is a bit misleading, because it is not fully selective. The shortcoming of celecoxib as an anti-inflammatory drug is that it *has* some mild affinity for the COX-1 enzyme. As a result of this mild affinity, celecoxib causes side effects after inhibiting COX-1, but to a lesser extent than do non-selective NSAIDs.

It is great to have a drug like celecoxib that can preferentially inhibit inflammation and provide a lower risk of bleeding relative to non-selective NSAIDs.⁷ However, there is still some risk of bleeding. This is where celecoxib could, and may be, improved upon in the future to create a new drug. Ideally, this new drug would have no affinity for COX-1 and full selectivity for COX-2.

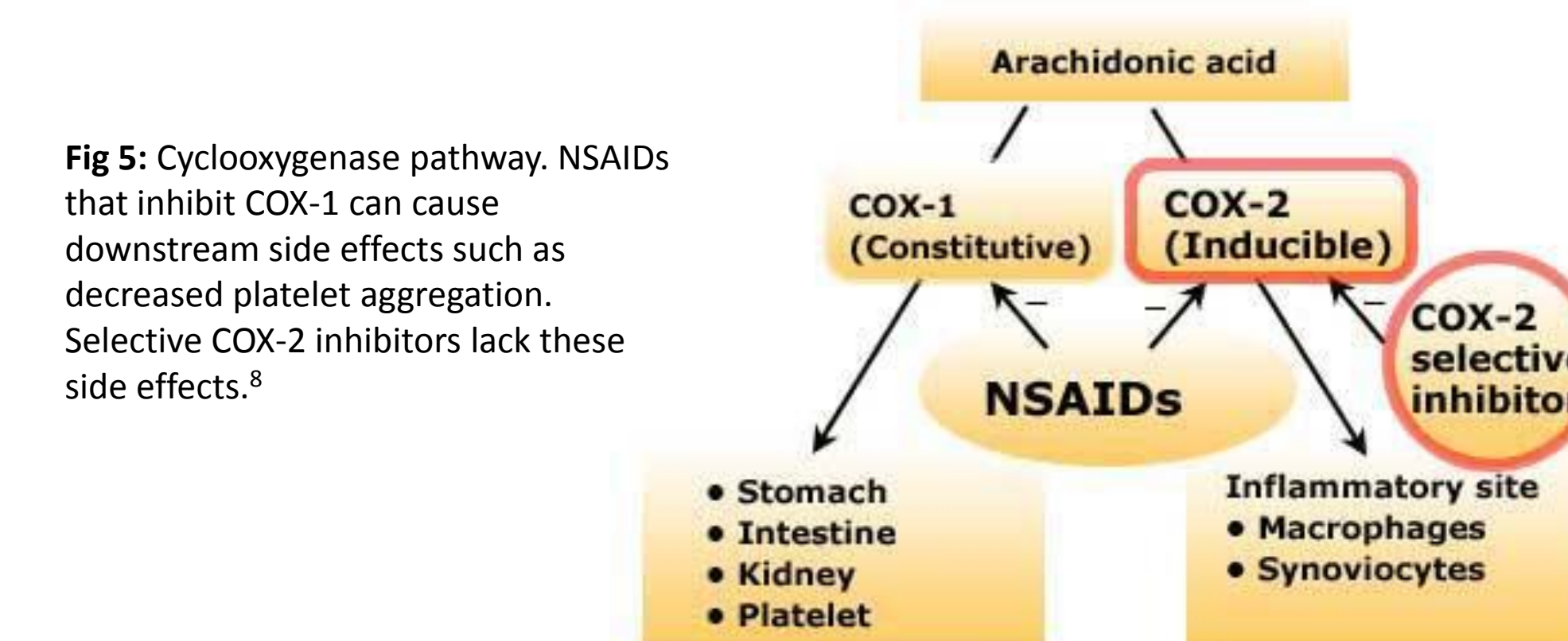


Fig 5: Cyclooxygenase pathway. NSAIDs that inhibit COX-1 can cause downstream side effects such as decreased platelet aggregation. Selective COX-2 inhibitors lack these side effects.⁸

Making a non-polar addition, for example, adding a methyl group, to the already non-polar portion of celecoxib may remove all binding affinity for COX-1. Loss of affinity for COX-1 could happen because there would be even more steric hindrance produced when Ile523 interacts with this, now bulkier, non-polar region. Making this methyl addition may also produce steric hindrance when celecoxib is in the COX-2 non-polar binding pocket, however, this could create a favorable situation in which there is still some affinity for COX-2, while celecoxib's affinity for COX-1 has been completely removed, rendering it a truly selective COX-2 inhibitor.

SUMMARY

Despite the advance in medicine that celecoxib represents, it is far from the final answer in anti-inflammatory therapy, but does have some unique properties which allows it to remain as the only COX-2 inhibitor left on the U.S. market.

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