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DEVELOPMENT OF NOVEL ANTI-INFLAMMATORY DRUGS TARGETING THE COX-2 ENZYME

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Abstract

Prostaglandin end peroxide synthase, also known as cyclooxygenase, is a crucial enzyme in the conversion of arachidonic acid to prostaglandins (COX). Both COX-1 and COX-2 are COX isoforms. In contrast to COX-1, which is often generated constitutively, COX-2 is easily induced (for example, in sites of inflammation and malignancy) (eg gastric mucosa). Traditional NSAIDs have an inhibitory effect on both enzymes, whereas selective COX-2 inhibitors (COXIB) like the ones being developed now exclusively target his COX-2 enzyme. This review explains why his COX-1 and COX-2 are so crucial to health and illness. Prostaglandins are produced by cyclooxygenase and play a crucial role in inflammation. The lipid atoms known as prostaglandins add to both intense and ongoing irritation. Anti-inflammatory medicine and different NSAIDs are the go-to for alleviating aggravation. There are a number of well-documented risks associated with using COX inhibitors, including erosive gastrointestinal tract, renal, and hepatic dysfunction. Inhibiting COX-1 is the primary cause of these severe negative consequences. Examination into decreasing the adverse consequences of NSAIDs prompted the making of particular COX-2 inhibitors like celecoxib and rofecoxib. There may be 2, 5 or more than 10 COX isoforms due to the different pharmacological effects, side effects and potencies of drugs in this category or their derivatives. .

Keywords: *Anti-Inflammatory Drugs, COX-2 Enzyme, Development, cyclooxygenase.*

INTRODUCTION

Aggravation is a significant piece of the resistant framework's protective component against the outside climate and is embroiled in numerous immunological problems. Synthetic substances, wounds, immunological reactions, and diseases may all set off aggravation, whether it's intense or constant. It has long been known that non-steroidal anti-inflammatory medications may mitigate inflammation (NSAIDs). Rheumatoid arthritis, acute fever, and other inflammatory disorders are cured in addition to the regular, daily pain that it alleviates. Aspirin was the first nonsteroidal anti-inflammatory drug used for treatment. It has been in operation for the better part of a century, having first seen action in 1898. Normal NSAIDs have been utilized in clinical treatment for quite a long time in the wake of being created and endorsed by the Food and Medication Organization (FDA). Inhibiting cyclooxygenase (COX) activity competitively is the mechanism by which nonsteroidal anti-inflammatory medicines (NSAIDs) reduce inflammation. Vane et al. 1971 identified NSAIDs as therapeutic targets when additional research revealed that inhibition of cyclooxygenase led directly to the cessation of production of prostaglandins (PGs), a major source of irritation. Was first shown to target cyclooxygenase as.

Due to their viability in decreasing the agony, fever, redness, and edema related with the arrival of inflammatory middle people, nonsteroidal anti-inflammatory meds (NSAIDs) are the medicines of decision in inflammatory sicknesses. And, cyclooxygenase (COX) inhibition is required for both the beneficial and detrimental effects of NSAIDs. COX-2 inhibition has been hypothesized to confer therapeutic benefits to NSAIDs, whereas COX-1 inhibition is associated with adverse effects in the gastrointestinal and renal systems. This audit looks into the anti-inflammatory impacts and results of particular COX-2 drugs and non-specific COX inhibitors. The COX isoenzymes, which are the basic components of NSAIDs' mechanisms of action, are being discussed for understanding.

The essential enzyme required to convert lachidonic acid to prostaglandins is known as prostaglandin peroxide synthase, also known as cyclooxygenase (COX). COX-1 and COX-2 refer to the chronological order in which these two COX isoforms were first identified. The public has had access to aspirin for more than a century. Centuries ago, however, instead of treating pain and fever, doctors used extracts from plants such as myrtle and willow bark that contained salicylic acid or its precursors. It was not until 1971 that the function of the COX enzyme in cancer and disease became better understood.

Explanations for the wide range of PG effects may be found in the variety of PG chemistries, the wide variety of receptors, and the ability to manipulate PG production. Late audits have investigated the underlying, cell, and atomic science of proteinoid receptors and COX. The effect of COX-1 and COX-2 on a few organ frameworks will be examined underneath. Many studies have been carried out over the last decade, revealing how each isoform contributes in different ways. One of the key aims of the pharmaceutical business is the development of a non-selective non-steroidal anti-inflammatory medication (NSAID), which is shown beneficial in treating pain and arthritis but may also have detrimental side effects. One of them was to create a medication with a wider therapeutic window for treating inflammation. Absolutely no adverse effects. Celecoxib (Celebrex) and rofecoxib (Vioxx) were two of the most popular COXIB medications, which led to their development.

- **COX isoenzymes**

It is well known that therapy with COX inhibitors is associated with a number of side effects including gastrointestinal

erosions, and renal and hepatic insufficiency. Such critical adverse reactions are mostly dependent on COX-1 inhibition. As a result of research focused on reduction of the adverse effects of NSAIDs, selective COX-2 inhibitors, such as celecoxib and rofecoxib have been developed. However, many data demonstrate that mechanisms of action of these drugs are multidirectional and complex. These drugs or their derivatives, which belong to the same group, have distinct pharmacological effects, side effects and potencies which implies that there may be more than two, five or even tens of COX isoforms

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These isoforms have been labeled as 'inducible' COX-2 and 'constitutive' COX-1, respectively. Brain, platelets, vascular endothelium, gastric mucosa, kidney, pancreas, islets of Langerhans, and seminal vesicles all manufacture prostaglandins (PGs) through COX-1. Phospholipase A2 is responsible for the first step in the synthesis of proteinoids, the liberation of arachidonic acid (AA) from membrane phospholipids. In a subsequent process, cyclooxygenase converts AA. Labile PGG2, initially produced by the COX reaction, is rapidly converted to PGH2 by the same enzyme in the peroxidase reaction. Prostacyclin, PG, and thromboxane are by-products of AA metabolism. COX-2 might have a capability in the beginning of obsessive cycles including irritation because of its enlistment by a wide assortment of development factors, proinflammatory specialists, endotoxins, mitogens, and anticancer drugs. Doing Prostaglandins (PGI2 and PGE2), which are produced by the COX-1 enzyme, boost fluid layer thickness, initiate bicarbonate generation, improve blood flow to the mucosa, and increase blood flow to the gastrointestinal (GIS) tract. Check for thoroughness. PGE2 stimulates mucus formation by gastric epithelial cells via increasing cAMP activity. Naturally produced glucocorticoids and hormones can repress COX-2 producing genes. More harm is finished to the stomach lining by drugs that restrain COX-1 instead of COX-2, like indomethacin, naproxen, and ibuprofen. Celecoxib and rofecoxib, two instances of particular COX-2 inhibitors, were made as a result of studies zeroing in on decreasing the adverse consequences of NSAIDs. Excited tissue produces COX-2, an instigating enzyme, while COX-1 is cytoprotective and constitutive.

LITRRETURE REVIWE

A. Inflammation and pro-inflammatory mediators:

Inflammation is a key step in the body's defense mechanisms that remove and repair damaged tissue and neutralize harmful chemicals. Inflammation, a Latin word meaning "to ignite," is the etymology of the word inflammation (Ferrero et al., 2006; Maslinska and Gajewski, The cascade involves the development of new tissue and blood vessels, circulating cells attaching to nearby capillaries). , Move (Geert, 2006). During inflammation, a wide range of pro-inflammatory mediators may be released or produced, including bradykinin, serotonin,

histamine, prostaglandins, and nitric oxide. Howard (2006) These The chemical causes hyperalgesia or allodynia and adds to the classic inflammatory symptoms including raised body temperature, redness, a painful odor, swelling, and impaired function.

Inflammation may be either chronic or acute:

Both short-term and long-term inflammation. The immune system's first reaction to infection or tissue injury is acute inflammation. Plasma and leukocyte trafficking to the site of infection is facilitated by eicosanoids and vasoactive amines, which drive this fast, self-limiting process (Charles et al., 2008). Redness, heat, discomfort, edema, and loss of function are symptoms of acute inflammation (Delas and Hortelano, 2009).

Short-term, high-intensity stimulation, which is generally seen as a net positive, aids the body in its battle against environmental toxins (Aggarwal et al., 2009; 2007). (Lin and Karin). Initiation of the inflammatory response is greatly aided by proinflammatory messengers like prostaglandins and leukotrienes (Samuelsson et al., 1987). Sexual mediators can lead to chronic inflammation (Serhan et al., 2009) .

Leukocytes, lymphocytes, and fibroblasts, all of which are resistant to demand are recruited after prolonged stimulation because of the many cytokines and developmental factors they generate. Long-term tissue damage may result from these cells' participation in inflammation (Aggarwal et al., 2009; 2007). (Lin and Karin). Foot fever, periodontal disease, rheumatoid arthritis, atheroma Atherosclerosis, cardiovascular problems, diabetes, obesity, respiratory disease, neurological infections, and diseases can also be met with constant stimulation

At this stage of carcinogenesis, inflammation is crucial. Cancer's multiple stages—from transformation to promotion to survival to proliferation to invasion to angiogenesis and metastasis—are all influenced by chronic inflammation (Mantovani, 2005; 2002, Coussens and Werb). Expanded articulation of inducible favorable to inflammatory qualities like COX-2 and iNOS brings about the production of inflammatory arbiters, which thusly cause inflammatory reactions and tissue harm. Pro-inflammatory prostaglandins and nitric oxide are produced in high quantities by inducible iNOS and cyclooxygenase-2, respectively, during the inflammatory phase (Vane et al., 1994; Jong and Co., 2006; Akira and Hajime, 2007). They assume a part in the development of inflammatory sicknesses and a few types of malignant growth in people. Constant creation of these mixtures during persistent aggravation has been connected to disease development (Israf et al., 2007).

B. Arachidonic acid's Function in Inflammation:

Arachidonic acid (AA), a polyunsaturated fatty acid with 20 carbons, is produced by membrane phospholipids and is a powerful inflammatory mediator. The primary polyunsaturated fatty acid in mammalian systems, arachidonic acid, serves as a precursor for the cyclooxygenase pathway, which in turn generates prostaglandins (PGs). Free AA levels inside of cells are low under normal circumstances. Most are retained in cell membranes as phospholipids (Brash, 2001).

Eicosanoid production depends on the availability of free AA. Several phospholipase compounds are therefore triggered by a multitude of impulses such as mechanical pressure, cytokines and developmental factors to unload this intermediary from the phospholipid layer (Stratton and Alberts, 2002).

Arachidonic acid is typically released by translocating cytoplasmic phospholipase A2 type IV to the endoplasmic reticulum and nuclear membrane. Eicosanoids are a large family of oxygenation products formed when arachidonic acid is rapidly

degraded by enzymatic and non-enzymatic pathways (Stables and Gilroy, 2011; Simmons and team, 2004).

The four major routes of arachidonic acid metabolism are:

Prostaglandins (PG), thromboxanes (Tx), and prostacyclins are delivered through the cyclooxygenase (COX) pathway. (ii) The lipoxygenase (LOX) pathway associated with the development of lipoxins and leukotrienes (LTs); iii) Howard (2006).

C. Cyclooxygenase pathway:

Prostaglandins and thromboxanes are produced from arachidonic corrosive by the enzyme cyclooxygenase, which catalyzes the development of intermediates with terminal peroxides. Two unique dynamic synergist locales on COX catalyze the transformation of arachidonic corrosive to prostaglandin G2 (PGG2) and prostaglandin H2 (PGH2), individually. Prostaglandin H2 (PGH2) is the precursor of a family of bioactive prostanoids that are synthesized by distinct tissue isomerases. This pathway produces five prostanoids:

PGE2, PGD2, PGF2, PGI2, and TxA2 (Figure 4). Specific synthases catalyze the formation of individual prostanoids, which have unique biological activities (Davies et al., 2002; Rocca, 2006).

CHEMISTRY AND PHARMACOLOGY OF NEW SYNTHETIC COX-2 INHIBITORS

A. Chemicals with a pyrazole ring

A – The abundance of sweet-smelling heterocycles called pyrazoles is recognized as a pharmacologically vast dynamic scaffold for binding substances, especially in the production of novel COX-2 inhibitors. Clinical drugs such as celecoxib, antipyrine, aminopyrine, and metamizole contain pyrazole fragments. Pyrazole compounds have been widely studied for their potential to inhibit cyclooxygenase-2 (COX-2) and hence decrease inflammation throughout the last decade. This is what Bansal and co. A 2014 invention. From a newly discovered chemical 1 with a pyrazole ring. In the carrageenan-actuated rodent paw edema model, compound 1 showed both specific restraint of COX-2 (IC50 = 0.31 mol/L, selectivity record (SI) > 222) and conceivable anti-inflammatory activity (ED50 = 74.3 mg/kg). Showed Compound 1's COX inhibitory movement was assessed utilizing a COX fluorescent inhibitor screening test unit, which included human COX-2 and sheep COX-1 recombinant enzymes, through an enzyme immunoassay (EIA). The two mixtures 3 and 4 (ED50 = 118 and 120 mg/kg, separately) and diclofenac (ED50 = 114 mg/kg) work on strong palliative endurance in an investigation of carrageenan-prompted rodent paw edema. Fundamentally, the cycloalkanone moiety might be changed out for others to change their activities definitely. Intensifies 2 and 3 tie to the COX-2 dynamic site in much the same way to the particular COX-2 inhibitor SC-558, as per atomic docking tests The Xu group found a novel family of chemicals by using a different approach to obtaining pyrazole N-arylsulfonates. This was modified by celecoxib's sulfonamide structure, which seems to be the selective COX-2 inhibitor's mechanism of action. Compounds 3, 6, 8, and 11 have shown strong COX-2 inhibitory action in in vitro EIA testing. The ligand and Arg interacted in docking simulations. Dependent quenching of COX-2 requires this. Abdellatif and coworkers in 2020 produced a series of halogenated triarylpyrazoles based on celecoxib.

able 1: Selectivity index and inhibition of COX-1 and COX-2 (IC50, mol/L) in vitro for compounds 3-11, relative to the standard agent.

Compd	COX-1[a]	COX-2[a]	COX-2 selectivity[b]
3	1.3	1.4562	566
6	87.62	2.1362	11,256
8	>200.00	2.365	>1236
7	>200.00	2.36	>215
11	>200.00	<1.26	-
Celecoxib	>200.00	1.23	563

[a]The employing a COX fluorescence inhibitor screening test kit, the average of three separate concentration-response curves was calculated (IC50, nmol/L) (Cayman Chemical, MI, USA).

[b]COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).

B. Imidazole and imidazoline-ringed compounds

The structural similarities between the imidazole and imidazoline groups make them attractive targets for NSAID development. Novel COX-2 inhibitors containing imidazole and imidazoline moieties were uncovered in various papers somewhere in the range of 2014 and 2021. They like Salumpitak. In 2014, we found and manufactured an effective imidazoline counterpart. The in vitro COX-2 inhibitory activity of compound 17 was equivalent to that of the clinically-used drug celecoxib (IC50 = 0.091 mol/L). The replacement of the methylsulfonyl group with a sulfonamide did not substantially lessen COX-2 inhibition, as shown by this research. Abdellatif et al. disclosed many of his tetrasubstituted imidazoline analogues four years later. Compounds 18–20 were more effective than celecoxib in inhibiting COX-2 activity. Ibuprofen and celecoxib, two similar medications, were shown to be less ulcerogenic than the fortifying agents17, 22, and 24. To add to this, Navidpour et al. In 2014, a bunch of 1, 5-diarylimidazole subordinates with a thioalkyl bunch in place 2 were accounted for without precedent for the logical writing. Although compound 25 demonstrated considerable inhibition (EIA) of COX-2 (IC50 = 14.2 minor), its selectivity (SI = 3.1) was lower than that of celecoxib (IC50 = 0.544 mol/L; SI = 19.4). The research found that 2-thiomethyl compounds outperformed 2-thioethyl derivatives in terms of activity.

Table 2: Evaluation of ulcerogenicity, selectivity index, and IC50 for COX-1/COX-2 inhibition in vitro for compounds 17-24; comparison to reference drugs.

Compd.	COX-1[a]	COX-2[a]	COX-2 selectivity[b]	Ulcer index
17	5.36	1.25	11.26	2.33
18	5.24	1.36	11.45	4.03
22	3.14	1.59	9.54	3.60
24	5.36	1.45	7.23	4.12
Celecoxib	9.58	1.46	4.23	6.02
Ibuprofen	-	-	-	3.025

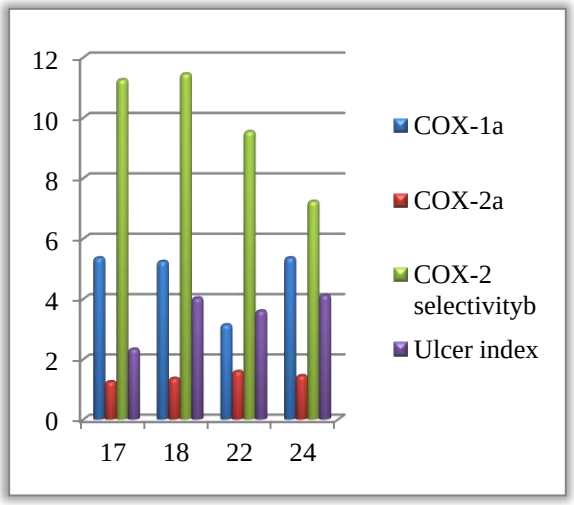

Figure 1: Assessment of ulcerogenicity, selectivity index, and IC50 for in vitro COX-1/COX-2 inhibition of compounds 17-24: a graphical depiction

[a]The Three separate tests were performed using a commercially available COX fluorescent inhibitor screening test kit to arrive at the average IC50 value given here .

[b]COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).

CONCLUSION

COX isoenzymes and eicosanoids are engaged with a wide assortment of physiological cycles. Headache medicine, indomethacin, and ibuprofen are nonsteroidal anti-inflammatory drugs (NSAIDs) that are broadly used to treat torment, rheumatoid joint pain, and cardiovascular sickness. Alzheimer's sickness and colon disease are likewise being investigated as possible focuses for these meds. As proof proposes that COX-2 specific medications are more successful than non-particular NSAIDs in treating torment, rheumatoid joint pain, and osteoarthritis, they have tracked down broad utilization in clinical practice. Many COX-2 inhibitors have been shown to deteriorate constant aggravation in creatures, recommending that prostaglandins might go about as key anti-inflammatory middle people in this unique situation. It isn't realized whether COX-2 inhibitors are valuable in treating IBD patients in view of the adverse consequences displayed in creature preliminaries.

Anti-inflammatory screens have identified substances that inhibit the COX-2 enzyme. It was also shown that these compounds do not exhibit suitable binding energies with different bond orientations. Nonetheless, current test results indicated that selectivity was introduced into the coupling of NAH compounds with isoxazole. A potent substance has been subjected to in vivo testing.

FUTURE SCOPE

The above issues are likely to receive even more attention in the coming years. He firmly believes that future studies of his COX-2 inhibitors using standard medicinal chemistry methods are inadequate to meet current therapeutic needs. Combining computer science, genetic engineering and enzyme engineering could solve future problems.

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