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REVIEW ARTICLE

COX SELECTIVE ANTI-INFLAMMATORY DRUGS AND ITS DEVELOPMENT

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Abstract: Cyclooxygenases (COXs) catalyze the complex reaction of conversionof arachidonic acid to prostaglandins and thromboxanes, which play important role as chemical messengers in many physiological and pathophysiologicalresponses. It exists in two distinct isoform-first one is constitutiveform (COX-1) and another is inducible form (COX-2). COX-1 andCOX-2 share the same substrates, and catalyze the similar kind of reactions using identical catalyticmechanisms.In this review, inflammation and role of COX-1, and COX-2 firstdescribed in order to highlight the therapeutic interest of designing such compounds. Various types of structural families of selective COX-2, equally binding tendency to both COX-1 & COX-2 active site and dual inhibitorsare illustrated.

Key words: Cyclooxygenase, anti-inflammatory, pharmacophore, analgesic, gastrointestinal.

INTRODUCTION:

The word "Inflammation" has been defined in various ways. According to Ebert, inflammation is a process which begins following a sub-lethal injury to tissues and ends with complete healing, while Grawitz proposed that, it is the reaction of irritated and damaged tissues which still retain vitality. In short, inflammation is a defensive and normal response of the body to any noxious stimulus, varying from acute, transient and highly localized response to a minor mechanical injury (such as pin prick) to a complex sustained response involving the whole organism, which may lead to immunological rejection of transplanted tissues. It had been stressed that inflammation is a process and not a state.[1]

Inflammatory reactions consist of three phases in sequences:

i. Transudative Phase: Dialation of blood vessels and increased vascular permeability leading to erythema and edema at the site of noxious stimulus.
ii. Exudative Phase: Cellular infiltration and general "mopping up" reaction.
iii. Proliferative Phase: Tissue repair or healing phase.

The inflammatory response may be acute or chronic depending upon the duration and consequent nature of the reaction.

Prostaglandins

The term prostaglandin (PG) was first introduced by Von Euler,[2] to describe a smooth muscle stimulating lipid. PGs are ubiquitous fatty acid derivatives involved in many different physiological processes in addition to their well-recognized role in inflammation and immune response modulation. Various PGs contribute significantly to the genesis of signs and symptoms of the inflammatory processes[3] and also to the propagation, sustenance, limitation and termination of the inflammatory reactions.

The activity of PGs limited to the site of action by their short half life and also because they are synthesized on demand and not stored in tissues. The most important among the PGs are those belonging to the E-series which are intimately involved in the inflammatory responses.[4] The rank order of potency of vasodialating effects of different PGs has been reported to be PGE_2> PGA > PGE_1> PGD, PGE_2 being more potent than PGE_1.[5] The PGs of E-series also exert a number of anti-inflammatory effects as well and may serve a modulator function. In animal model of chronic inflammation, high doses of PGEs have been shown to exert anti-inflammatory action in vivo.[6, 7] In contrast to the PGs of the E series, the PGs of the F series have only anti-inflammatory properties collectively with thromboxanes, PGs form a group of oxygenated fatty acid derivative called prostanoids.

Prostanoid synthesis occurs in three stages (figure1):

a) Hydrolysis of arachidonic acid from phospholipids precursors catalyzed by a phospholypase A_2.
b) Oxygenation of arachidonic acid producing PGG_2 and later on, hydroperoxidation of PGG_2's 15-hydroperoxyl group into PGH_2. These two reactions (oxygenation and per oxidation) are catalyzed by the closely related isozymes, prostaglandin endoperoxide H synthase-1 and synthase-2 (COX-1 and COX-2).

Conversion of PGH_2 into biologically active end products:

PGD_2, PGE_2, PGI_2 (prostacyclin) and TXA_2 (thromboxane A_2), catalyzed by various specific syntheses (isomerases) or reductases.[8, 9]

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Various inflammatory diseases are currently treated with steroidal and non-steroidal anti-inflammatory drugs (NSAIDs).[10] NSAIDs are drug with analgesic, antipyretic and in higher doses anti-inflammatory effects-they reduce pain, fever and inflammation. They inhibit synthesis of inflammation mediators or their interactions.[11, 12] Most NSAIDs act as non-selective inhibitors of the enzyme cyclooxygenase (COX), by inhibiting the metabolism of arachidonic acid.[11]COX catalyses the formation of prostaglandins (PGs) and thromboxane from arachidonic acid itself derived from the cellular phospholipids bilayer by phospholipase A_2. PGs act as messenger molecules in the process of inflammation. Conventional NSAIDs that non-selectively inhibit major cyclooxygenase isoforms,[13-16] (COX-1 and COX-2), are widely used to treat the signs and symptoms of inflammation, particularly arthritic pain. COX-1, housekeeping enzyme, is the constitutive isoform and is mainly responsible for the synthesis of cytoprotective PGs in gastrointestinal (GI) tract whereas COX-2 is inducible and plays a major role in PG biosynthesis in inflammatory cells.[13, 17, 18] It is believed that it is the inhibition of COX-1 that causes unfavorable GI side effects.[19]

A high level of selective COX-2 inhibition represents, therefore, a therapeutic strategy to alleviate pain and inflammation, without the untoward gastrointestinal toxicity due to COX-1 inhibition. Therefore, the principal pharmacological effects of NSAIDs are derived from their ability to inhibit PG synthesis by blocking the cyclooxygenase activity of both COX-1 and COX-2. Traditional NSAIDs can be grouped into 3 classes based on their mode of inhibition of COX:

Class I: Simple, competitive, reversible inhibitors that compete with arachidonic acid for binding to the COX active site. This class includes ibuprofen, piroxicam, sulindac sulfide, flufenamate, mefenamic acid and naproxen.

Class II: Competitive, time dependent, reversible inhibitors that binds to the COX active site in a first phase, to form reversible enzyme inhibitor complexes, that if retained for a sufficient time causes a non-covalent conformational change in the protein, associated with tighter binding. Included in this class are indomethacine, flurbiprofen, meclofenamic acid and diclofenac.

Class III: Competitive, time dependent, irreversible inhibitors that form an enzyme inhibitor complex after a covalent conformational change in protein. This class possesses aspirin. The acetylation of COX-1 by aspirin is an irreversible process that inhibits COX activity but not the peroxidase activity. The antiplatelet effect of aspirin (which only have COX-1), lasts for the life time of the cell.[3,8,9, 20]

Pharmacokinetics

Most NSAIDs are weak acid with a pk_a value of 3-5. They are absorbed well from the stomach and intestinal mucosa. They are highly protein bound in plasma (typically > 95 %), usually to albumin, so that their volume of distribution typically approximates to plasma volume. Ibuprofen and diclofenac have short half lives (2-3 hours). Some NSAIDs (typically oxicams) have very long half lives (20-60 hours).

COX Active Site

It typically consists of a long narrow hydrophobic channel extending from the membrane binding domain (the lobby) to the heme cofactor.[21]Although, both isozymes are 60 % homologous there are small differences in the amino acid sequence lining the COX active sites. The COX-2 inhibitor binding site is about 20 % larger and has a slightly different form from that of COX-1. The change of two isoleucines (Ilc-434 and Ilc-523) in COX-1 by two valines in COX-2 appreciably increases the volume of the COX-2 active site. Another essential amino acid difference consists of Arg-513 inside this side pocket, in place of a histidine in COX-1. It generates a specific interaction site for inhibitors in COX-2.

The Fundamental Basis of COX-NSAID Relationship

The X-ray crystal structure established by Picot[22] and colleagues, suggested that COX-1 is a dimeric enzyme in monotopic arrangement with respect to the cell membrane where each monomer comprising three independent folding domains. The overall space arrangement defines a long hydrophobic channel which allows arachidonic acid to gain access directly from the membrane, and where several amino acids appear to play a critical role: arginine and glutamic acid forms a salt bridge together with tyrosine which makes a narrow constriction with arginine in the middle portion of the channel and tyrosine is thought to support oxygenase as peroxidase generated tyrosyl radical site generated mutagenesis studies[23] showed that arginine was important for biotransformation of arachidonic acid and required for inhibiting activity of NSAIDs containing a carboxylic acid whereas tyrosine was involved in stereospecificity of COX-1 towards *2-phenyl propionic acid* derivatives. NSAIDs such as DuP 697(figure 2),[24] which have shown a preferential inhibition of COX-2 over COX-1 inhibited wild type and arginine-mutated COX-1 in the same range, suggesting interaction

with amino acids other than arginine, whose spatial arrangement is not effected by mutation.

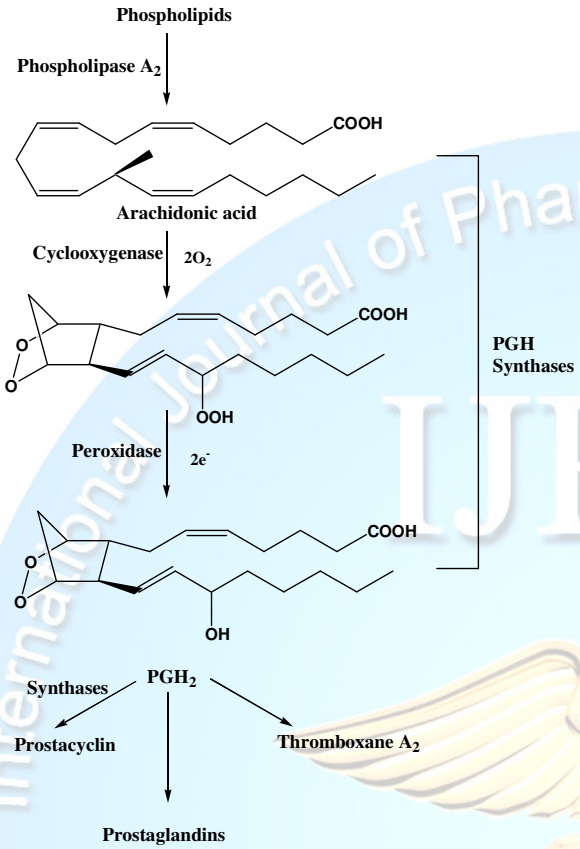


Figure 1.Prostanoid Biosynthetic Pathway

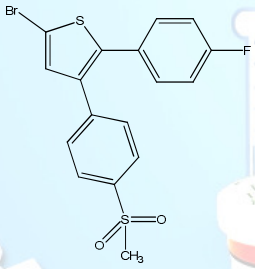


Figure2. NSAIDs such as DuP 697

Chemical Classification of classical NSAIDs

NSAIDs broadly can be divided as selective and non-selective COX inhibitors depending upon their mode of action.

a. Non selective COX inhibitors can be further classified into different groups:

i. Salicylic Acid Derivatives: These comprise two large classes, esters of salicylic acid (obtained by substitution of -COOH group) and salicylate esters of carboxylic acids which are retained and substitution is made in the hydroxyl group. Examples include aspirin, sodium salicylate, salicylic acid, choline magnesium trisalicylate, salsalate, difunisal, sulfasalazine, olsalazine (figure 3).

ii. Para Amino Phenol Derivatives: Acetaminophen.

iii. Indole and Indene Acetic Acids: Indomethacine (a methylated indole derivative), sulindac(figure 4). it is essentially a prodrug and most of its pharmacological activity resides in its sulfide moiety.

iv. Heteroaryl Acetic Acids: Tolmetin, diclofenac (it is a phenyl acetic acid derivative that was developed specifically as an anti inflammatory agent), ketorolac (figure 5).

v. Aryl Propionic Acids: They constitute a group of effective useful NSAIDs. Examples include ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin (figure 6).

vi. Fenamates: These are derivatives of N-phenylanthranilic acid. Examples include mefenamic acid, meclofenamic acid (figure 7).

vii. Oxicams: These are derivatives of enolic acids. Examples include piroxicam (it had an advantage of having long half-life which permits the administration of a single daily dose), meloxicam (figure 8).

viii. Alkanones: Nabumetone.

b. Selective COX-2 Inhibitors are classified as following groups(figure 9):

i. Diaryl Substituted Furanones: Rofecoxib (it possesses highly selective COX-2 inhibitory action along with analgesic and antipyretic activities).

ii. Diaryl Substituted Pyrazolones: Celecoxib (it is a fluorinated benzene sulfonamide derivative which possesses highly selective COX-2 inhibitory action along with analgesic and antipyretic actions, which are thought to be due to the inhibition of PG synthesis catalyzed by COX-2 (Marketed as Celebrex).

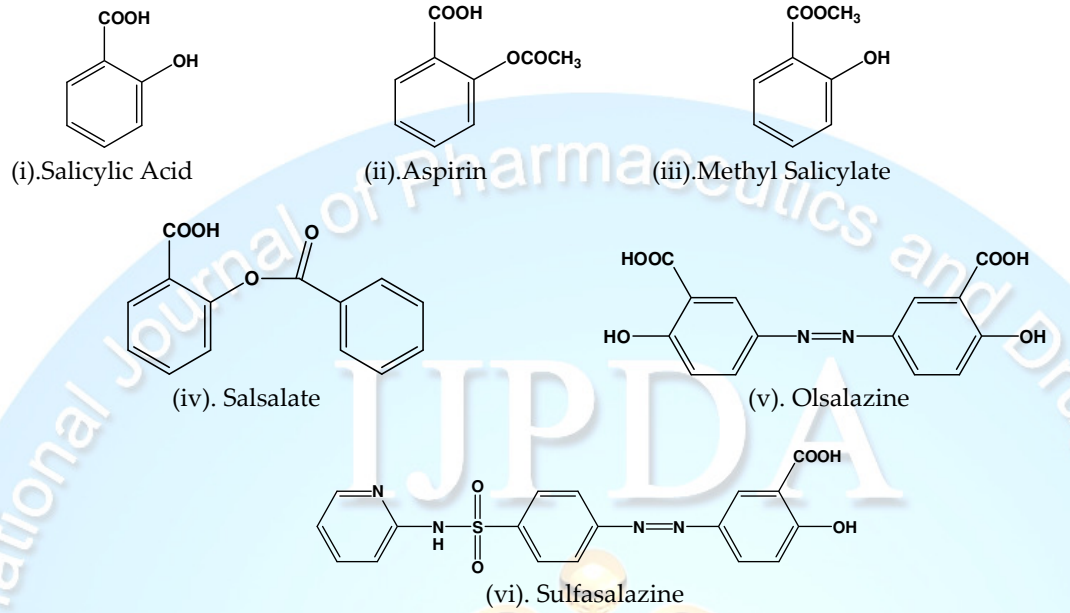
iii. Indole acetic acid derivative: Etodolac (it possess anti inflammatory activity towards COX-2).

iv. Sulfonanilides: Nimesulide (it has shown preferential action on COX-2 inhibition).

v. Adverse Effects Associated With NSAIDs

vi. Though selective COX-2 inhibitors (coxibs) with better safety profile have been marketed as a new generation of NSAIDs,[25, 26] but careful prospective examinations of coxibs have revealed unexpected adverse side effects. NSAIDs vary in their potency, duration of action and the way in which they are eliminated from the body. Another important difference is their ability to cause ulcers and promote bleeding. The more an NSAID blocks COX-1, the greater is its tendency to cause ulcer and promote bleeding. The two main adverse drug reactions (ADRs) associated with NSAIDs relate to gastrointestinal (GI) effects[27, 28] and renal effects (kidney failure) of the agents. Also, they have shown unexpected cardiovascular adverse ef-

fects.[29] Several other side effects are also associated with the use of NSAIDs which include nausea, rash, dizziness, headache, drowsiness, fluid retention leading to edema, etc. Therefore, development of novel compounds having anti-inflammatory activity with an improved safety profile is still a necessity.

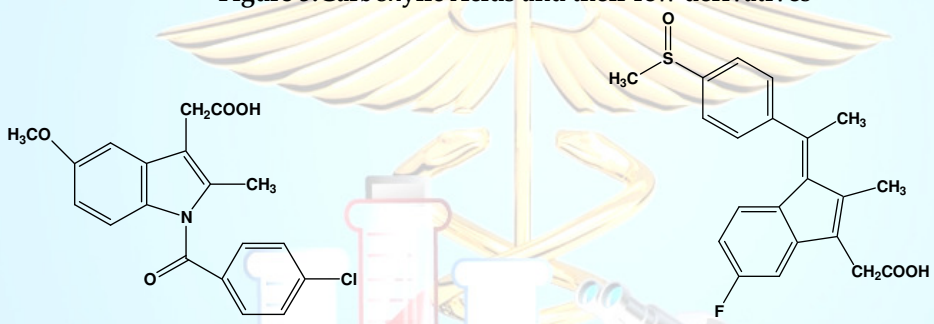


(i).Salicylic Acid (ii).Aspirin (iii).Methyl Salicylate

(iv). Salsalate (v). Olsalazine

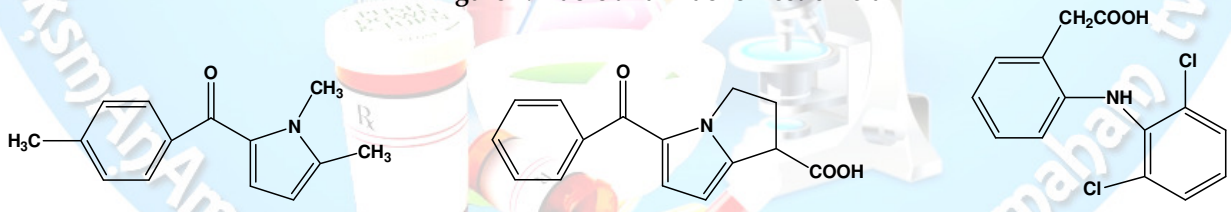
(vi). Sulfasalazine

Figure 3.Carboxylic Acids and their few derivatives



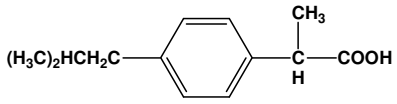
(i).Indomethacin (ii).Sulindac

Figure 4.Indole and Indene Acetic Acid

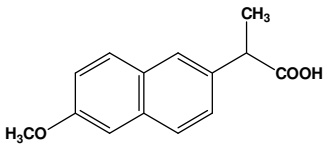


Tolmetin Ketorolac Diclofenac

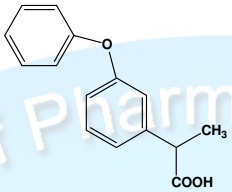
Figure 5.Heteroaryl Acetic Acid



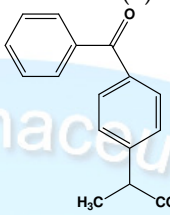
(i). Ibuprofen.



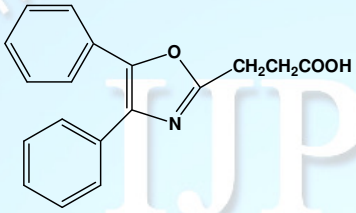
(ii). Naproxen.



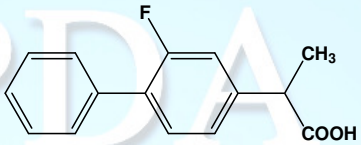
(iii). Fenoprofen



(iv).Ketoprofen

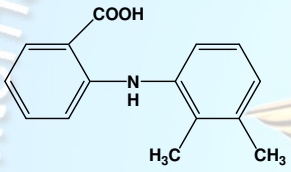


(v).Oxaprozin



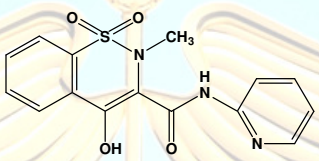
(vi).Flurbiprofen

Figure 6.Propionic Acid Derivatives

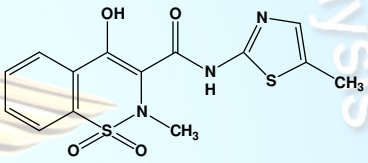


Mefenamic acid

Figure 7.Fenamate

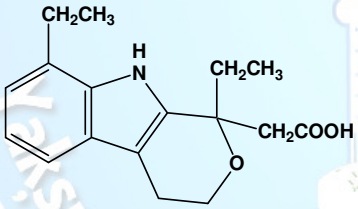


(i).Piroxicam

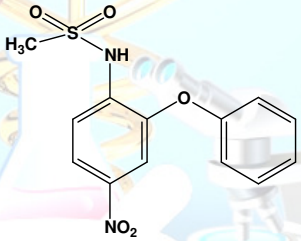


(ii).Meloxicam

Figure 8.Oxicams

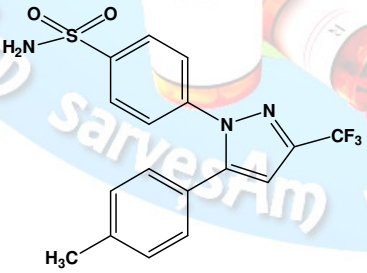


Etodolac

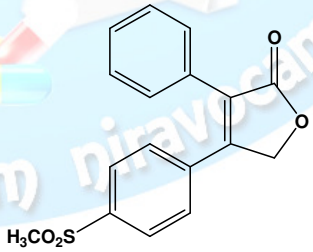


Nimesulide

Indole acetic acid derivative

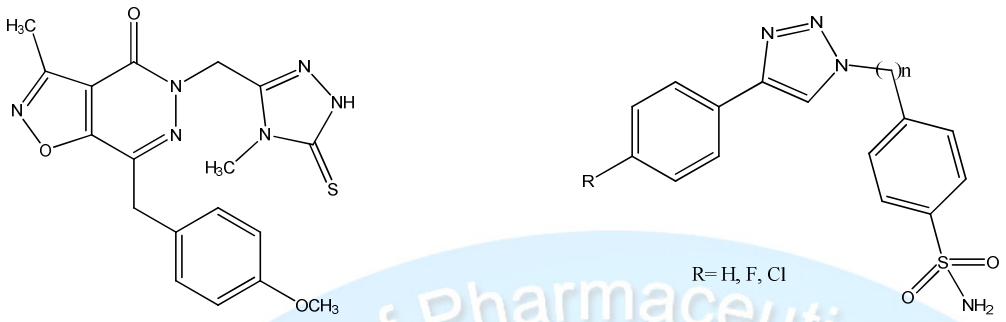


(i).Celecoxib



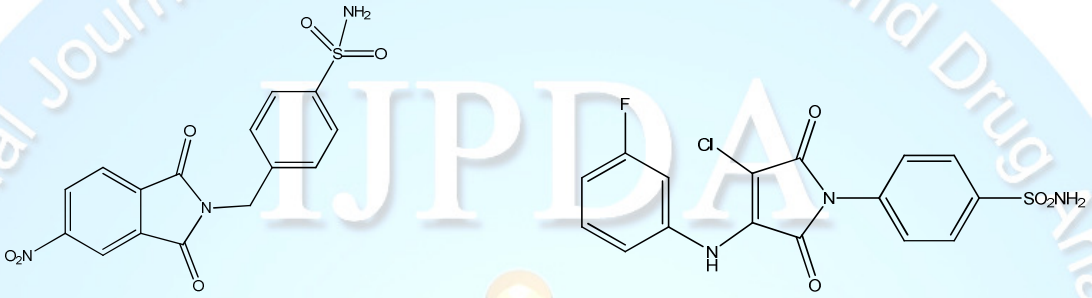
(ii).Rofecoxib

Figure 9.Coxibs



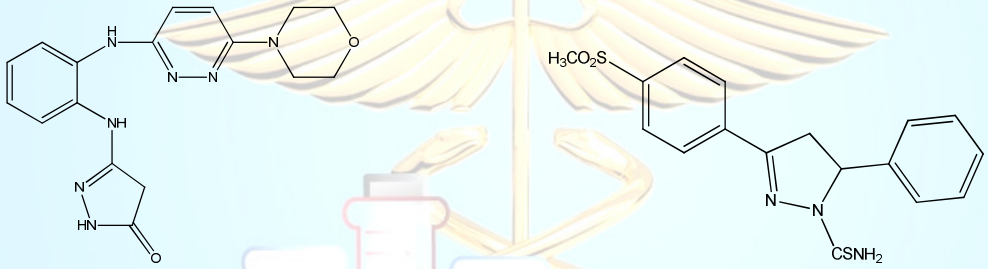
(a) (b)

Figure 12



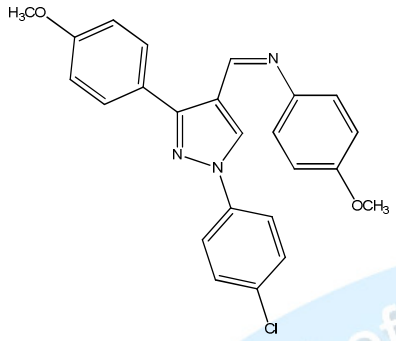
A B

Figure 13



A B

Figure 14



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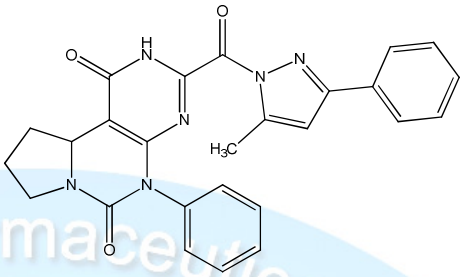
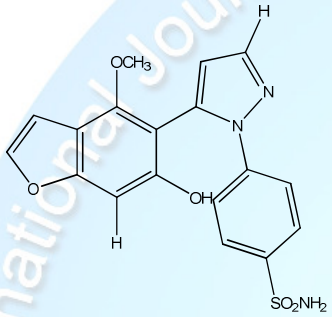


(b)



(c)

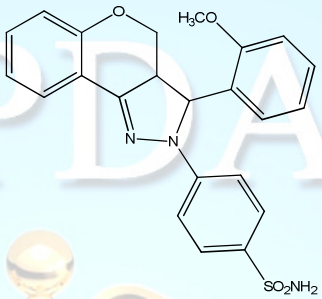


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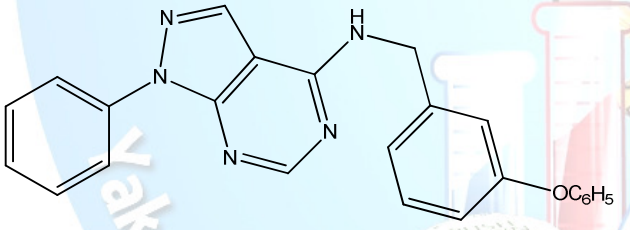
Figure 15



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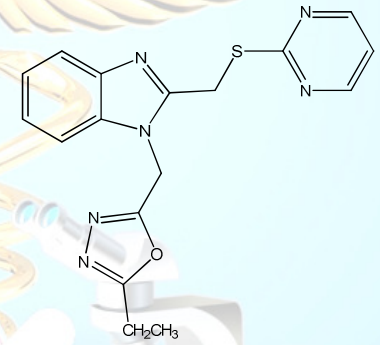
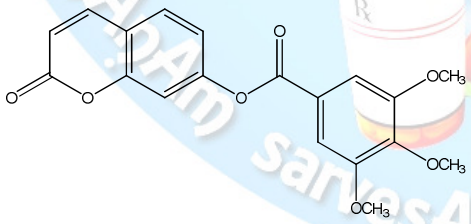


(b)

Figure 16



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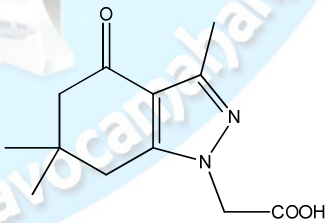

(b)

Figure 17

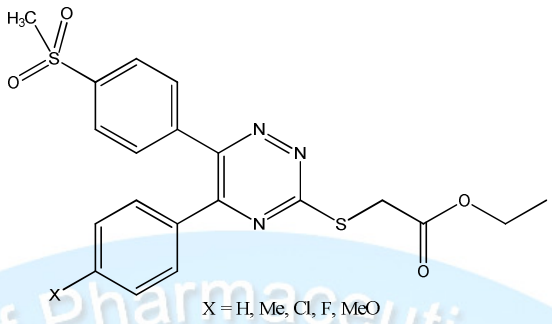

Figure 18

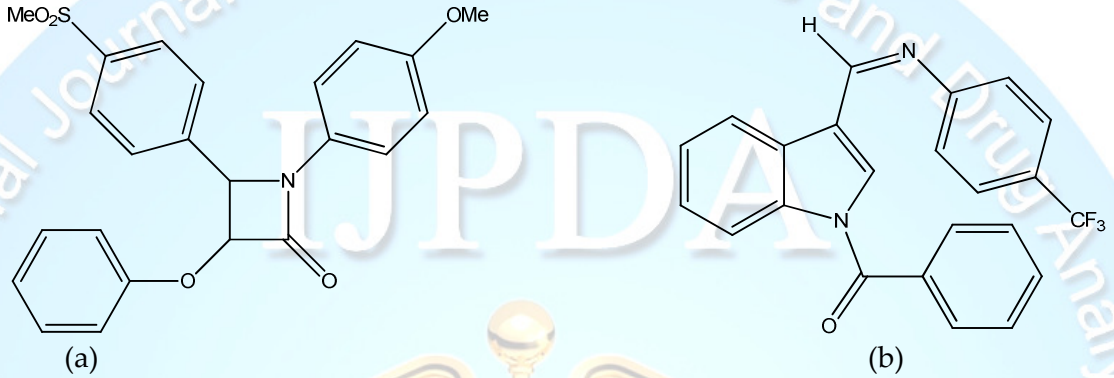

Figure 19

vii. Docking in Human COX-2 Models

viii. Though they are similar, the COX-2 active site is about 20 % larger than that of COX-1 which generates a specific interaction site for inhibitors in COX-2. The docking studies[21] for different binding modes of inhibitors were studied and reported with COX-2 active sites. The "coxib like" which is close to that adopted by SC-558 (figure 10) was co crystallized with COX-2.

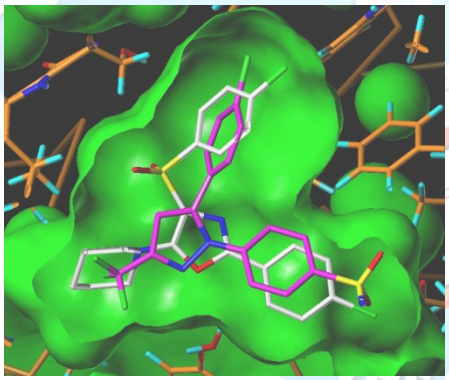

Figure 10.SC-558

The substituted aryl ring inserts into the side pocket and the other phenyl group occupies the upper part of channel. This was the most favorable interaction hypothesis proposed by GOLD.[21] They have shown three important interaction points (Tyr-355, Arg-120 and Phe-518) as well one hydrogen bond that involved tetrahydropyran oxygen with Tyr-115.

Binding of Drug with Receptors (Forces Used)

Several kinds of forces plays important role in binding of a particular drug to particular receptor among which aromatic interactions (weak non covalent interactions) play subtle role in drug receptor binding mechanisms. Since majority of biologically active components consists of aromatic and heteroaromatic units (made of amino acids), which provide a basis for weak interactions of C-H--π, and π--π types other than conventional H-bonds. These aromatic interactions are neither too strong nor too weak and therefore, they are a kind of perfect and balanced forces which are required to retain the drug-receptor complex for the time needed.

Pharmacophore based modification and development of various NSAIDs

Structural biology and X-ray crystallography had been provided much useful information for the development of COX-2 inhibitors. Generally, it has been established that for good COX-2 inhibitory activity and selectivity, compounds will require a key pharmacophore. Marriott et al. defined the pharmacophore as "an important and unifying concept in rational drug design that embodies the notion that molecules are active at a particular enzyme or receptor because they possess a number of chemical features i.e., functional groups that favorably interact with the target and which possess geometry complimentary to it." It is possible to derive pharmacophores by direct

analysis of the structure of a known ligand either in the most stable conformer or in the complexed form observed with the target protein. [17]

Modification of established non selective agent by changing or substituting with different functional groups can effectively increase the activity and selectivity of the drugs as for example, lengthening the carboxyl side chain of indomethacine have been strategies for the design of COX-2 selective inhibitors.[18, 30] Also, it is reported that to achieve good activity and selectivity, the diarylheterocycle COX-2 selective inhibitors require the presence of a 4-methylsulfonylphenyl group attached to an unsaturated ring to which an additional vicinal lypophilic moiety is present.[31](figure 11).

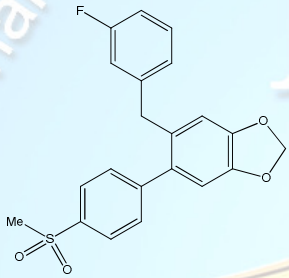

Figure 11

The methylsulphonyl group can only be replaced by a SO_2NH_2 group whereas the lipophilic pocket is usually occupied by an optionally substituted phenyl ring or a bulky alkoxy substituent. Therefore, it has been established that unlike the diverse chemical classes of non-selective NSAIDs, the COX-2 inhibitors have two major structural motifs: the acidic methanesulfonamide ($MeSO_2NH$) containing diphenylethers exemplified by nimesulide[32, 33] and sulfamoyl (SO_2Me) containing vicinal diarylheterocycles represented by celecoxib and etoricoxib, etc. The later class received more attention due to the known COX-2 enzyme ligand co crystal structure,[34] and various carbocycles[35, 36] and heterocycles[37-39] were discovered on this basis. Though, many coxibs have been launched so far, there still remains a need to develop more effective drugs as an alternative to the steroidal and narcotic drugs used in severe pains.

New series of substituted thiadiazole or a triazolewere synthesized and tested for anti-inflammatory activity in vitro (COX-1/COX-2, 5-LOX) and in vivo (rat paw edema assay). Among dual COX-2/5-LOX inhibitors, the most potent compound (28) exhibited the best anti-inflammatory inhibiting both COX-2 enzymes. It binds in both COX-2 and 5-LOX active sites. Furthermore, the dual acting COX-2/5-LOX compound in figure 12(a) exhibited a superior gastrointestinal safety compared to the reference drug ibuprofen. From this study it was found that compounds containing a vicinal diaryl substitution pattern display higher COX-2 inhibition potency compared to their counterparts.[40]Some compounds like in figure 12 (b) were identified as highly potent and exhibited appreciable COX-2 inhibitory potency and selectivity.[41, 42]

A group of cyclic imides[43]and maleimide[44] bearing benzene-sulfonamide were designed for evaluation as a selective COX-2 inhibitors and studied for their anti-inflammatory activity. These studied showed that the homo-sulfonamide fragment of compound in figure 13 inserted deep inside the 2-pocket of the COX-2 active site, where the SO_2NH_2 group makes H-bonding interaction with Gln192(2.95 Å), Phe518(2.82 Å) and Arg513(2.63 and 2.73 Å). Thus, these compounds can become potential leads for anti-inflammatory studies.

New *1-N-substituted-3,5-diphenyl-2-pyrazoline* derivatives (figure 14 a) and pyrazolone-pyridazine(figure 14 b) have been synthesized and inhibitory activities have been evaluated and found active against cyclooxygenase (COX-1 and COX-2).[45, 46] The synthesized compounds were also investigated the inhibition of the production of certain inflammatory cytokines such as TNF-a and IL-6 in serum.[46] Among the synthesized derivatives, few compounds like in figure 14 showed good analgesic and anti-inflammatory activities with lower ulcer index than the reference compound.

Some novel substituted pyrazoles were synthesized and screened for their anti-inflammatory and analgesic activities as well as their ulcerogenic liability.[47]These compounds showed anti-inflammatory and analgesic activities with better gastro-intestinal tract tolerance than the standard drug like phenylbutazone. Compound like in figure 15(a & b) among this series was found to be the most active as anti-inflammatory and analgesic agent. Some dihydropyrazolesulphonamide derivatives are also studied against human tumor cell and showed anti-proliferative activities (figure 15 c & d).Another *3-(pyridin-3-yl)pyrazole* derivatives with benzofuranin figure 15 exhibited the highest anti-inflammatory activity, and it is also equipotent to celecoxib.[47, 48] These are COX-1/COX-2 isozyme selective showed equal inhibition to both isoforms.

A novel set of pyrazolo-pyrimidine and its derivative were evaluated as potential anti-inflammatory agents. The results of in vivo study of few compounds like in figure 16(a) have significant anti-inflammatory and analgesic activities comparable to that of the control, ketorolac.[49] Dual inhibition with novel pyrazolopyrimidine derivatives of COXs and iNOS is a valid strategy for the development of anti-inflammatory/analgesic agents with the fewer side effects.

New molecules of benzimidazole endowed with oxadiazole were designed with the aim to acquire selective cyclooxygenase (COX-2) inhibitor activity. The synthesized compounds (figure 16 b) were screened by in vitro cyclooxygenase assays to determine COX-1 and COX-2 inhibitory potency and the results showed that they had good-to-remarkable activity and it was also found with docking study that it binds with COX binding site. In vitro anticancer activities of the hybrid compounds were also assessed by the National Cancer Institute (NCI), USA, against human cell lines, and the results showed a good activity. [50]

A series of *cycloalkyl/aryl-3,4,5-trimethylgallates*(as in figure 17 a) were evaluated for their anti-inflammatory activity as well as effect on gastric mucosa.[51] All the compounds of this series exhibited promising anti-inflammatory activity. The results of gastric mucosal studies suggested that these compounds are non-ulcerogenic and gastroprotective. It is found that Cycloalkyl/aryl-3,4,5-trimethylgallates (figure 17 a) are very potent and protective anti-inflammatory agents.

A novel series of *3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazole-1-acetic acid* derivatives like in figure 17 (b) was designed and *2-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazol-1-yl)acetic acid*emerged as a potent COX-2 inhibitor.[52] Based on these results, compound in figure 17 (b) can be considered as a lead compound for further development of new class of COX active compounds.

A new series of *ethyl 5,6-diaryl-1,2,4-triazine-3-ylthioacetate* derivatives like in figure 18 were designed and investigated the ability of compounds to inhibit COX-1/COX-2 enzymes and showed remarkable results.[53] Finally, in silico assessment revealed that the designed compounds are BBB permeable and as well as CNS active agents. The obtained results indicate that the prototype compounds in figure 18 can be reserved to develop potential agents in amyloid related diseases like AD.

A new series of b-lactams were designed for the evaluation as selective cyclooxygenase-2 (COX-2) inhibitors and among the synthesized series of compounds, *1-(4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-3-phenoxyazetidin-2-one* (figure 19 a) exhibited the highest COX-2 inhibitoryand potency even more potent than the reference celecoxibdrug.[54] Molecular docking studies indicated that the methylsulfonyland methoxy group at para position pharmacophore group inserted into the secondary pocket of COX-2 active site.

A group of N-1 and C-3 disubstituted-indole Schiff bases bearing an indolelike *1-Benzoyl-3-[(4-trifluoromethylphenylimino) methyl]indole* (figure 19 b) emerged as the most potent COX-2 inhibitor in this series of compound.[55] Molecular modeling studies of this compound showed that the phenyl CF_3 substituent is oriented towards the secondary pocket of the COX-2 active site, and the indole N-1 benzoyl make binding site near W387.

Conclusion

NSAIDs are widely used for as a anti-inflammatory drug as well as analgesic and also in treatment of many physical problems, such as arthritis. However, their chronic use has often been impaired by its adverse side effects they cause, especially in the gastro-intestinal tract and the kidney. Recently,it is found that overexpression of COX-2 is sufficient to cause tumorigenesis in animal models andsubsequently inhibition of the COX-2 pathway results in reductionin tumor incidence. Many selective COX-2 inhibitors have been developed and used in order to reduce NSAIDs-induced side effects that are associated with COX-1 inhibition. Selective cox-2 inhibitor theory is challenged by many drugs by showing as a key role in inflammation and pain perception for COX-1. Moreover, dual COX and 5-LOX inhibition have been observed by many leading compounds leads to an up-regulation of the 5- LOX pathway, yielding various adverse effects. As a result, a new strategy has been considered in drug designing, the dual inhibition of 5-LOX and COX enzymes. Various structural families of dual inhibitors have been designed and they are in preclinical or clinical development. Some new development with new SAR has been developed with other dual inhibition like anticancer property and also active against CNS problems. By preventing the biosynthesis ofprostanoids and LTs, and active binding with iNOSthey are potent anti-inflammatory agents and analgesic agents. Though none of these compounds synthesized and studied drugs have reached the market yet because of their almost complete lack of GI toxicity.

However, NSAIDs-associated gastrointestinal problemsdecrease when NSAIDs are administered with gastroprotectiveagents such as histamine H2-receptor antagonists, prostaglandinE2 analogues or proton-pump inhibitors. Finally, our recent studies output gives a new direction as COX-2 and 5-LOX are up-regulated in various cancers, development of drugs targeting both enzymes would be a useful in future in direction of development of new drugs for chemoprevention.

There is still uncertaintyas to which of these strategies is less toxic, more effective or cost-effective.Thus, despite remarkable progress within the last decade, the designof new safe, more effective and inexpensive therapy drug fortreating inflammatory conditions remains a challenge.

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