COX-2-Inhibitor — A New Class of Analgesic and Anti-inflammatory Drugs

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After more than a century of use, pharmacologists felt that they had discovered the mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs) when their inhibitory action on the production of prostaglandins was described. This action was located at the inhibition of the enzyme responsible for the conversion of arachidonic acid to prostaglandins, namely cyclooxygenase. Recently, it has been recognized that more than one isoform of the enzyme exists. The two forms of cyclooxygenase described are widely different in their location, activity, and role, especially because the COX-1 isoenzyme seems to be mainly a constitutive enzyme, whereas the COX-2 isoenzyme is inducible. This separation of activity appears to be correlated with the separation of function of the various prostaglandins, whereas the constitutive form is associated with "physiologic" functions and the inducible form with inflammatory responses. Recent advances have included the development of drugs with a high specificity towards the inducible enzyme (COX-2) to focus on the anti-inflammatory actions, because many of the unwanted side effects of NSAIDs have been associated with inhibition of the constitutive isoenzyme (COX-1). The present review discusses the development of COX-2 inhibitors and their introduction in the market as useful drugs.

Introduction

Prostaglandins (PGs) play a major role in the inflammation process, and the inhibition of PG production has been a common target of anti-inflammatory drug discovery. Nonsteroidal anti-inflammatory drugs (NSAIDs) that are active in reducing the pain and swelling associated with inflammation, also affect other PG regulated processes, not associated with inflammation. Thus, ingestion of high doses of most common NSAIDs can produce side effects, including life-threatening ulcers that may limit their therapeutic potential. NSAIDs have been found to prevent the production of prostaglandins by inhibiting conversion of arachidonic acid to PGs by the constitutive cyclooxygenase enzyme (COX-1). In the 90s, a previously unknown enzyme in the human arachidonic acid/prostaglandin pathway was discovered and designated "cyclooxygenase II (COX-2) or prostaglandin G/H synthase II".

COX-1 is the constitutive isoenzyme and is mainly responsible for the synthesis of cytoprotective prostaglandins in the gastrointestinal tract (GI) and of proaggregatory thromboxane in blood platelets. COX-2 is inducible and short lived; its expression is stimulated in response to endotoxin cytokines and mitogens. COX-2 plays a major role in prostaglandin biosynthesis in inflammatory cells (monocytes/macrophages) and in central nervous system. These observations suggest that COX-1 and COX-2 serve different physiological and pathological functions. Classical nonsteroidal anti-inflammatory drugs, (NSAIDs) inhibit, both COX-1 and COX-2 to varying extent.

The differential tissue distribution of COX-1 and COX-2 provides a rationale for the development of selective COX-2 inhibitors as anti-inflammatory and analgesic agent that lack the GI and hematologic liabilities exhibited by currently marketed NSAIDs. This hypothesis has been validated in animal models and has led to the marketing of two diaryl heterocycles celecoxib (1) and rofecoxib (2) as COX-2 inhibitors.

Literature Review

A literature survey revealed many selective COX-2 inhibitors. Two distinct classes of aryl containing compounds have been independently reported by Gans et al. DuP 697 (3) and Futaki et al. NS-398 (4) that demonstrate anti-inflammatory activity in the rat established adjuvant induced arthritis and without concomitant gastric lesions. In vitro and with human recombinant COX-1 and COX-2 enzyme have since confirmed that both DuP-697 (3) and NS-398 (4) are selective COX-2

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inhibitors. Seibert et al. reported that pyrazole SC-58125 (5) (COX-1 IC₅₀ > 100μM, COX-2 IC₅₀ = 0.09μM) is a selective inhibitor of the inducible form of human recombinant cyclooxygenase and is orally active in rat adjuvant induced arthritis.

Prasit et al. have reported that L-745,337 (6) is a selective COX-2 inhibitor with a potent anti-inflammatory activity in the rat adjuvant induced arthritis model.

Reitz et al. have reported novel 1,2-diaryl cyclooctene methyl sulphones as COX-2 inhibitors. Compound SC-57666 (7) and SC-58231 (8) were found to be very potent COX-2 inhibitors and devoid of COX-1 activity.

Li et al. have identified an extensive series of 1,2-diaryl cyclooctenes that act as potent and selective COX-2 inhibitors. Replacement of methyl sulphone moiety with a sulphonamide group on the second phenyl group was found to provide a substantial enhancement of in vivo potency, especially in the rat adjuvant-induced arthritis model, albeit with some decrease in COX-2 selectivity. It is also reported that in vitro COX-1/COX-2 selectivity in sulphonamide series can be increased in many cases by simply incorporating a halogen atom at the 3-position of one of the phenyl ring. The selective COX-2 inhibitor sulphonamide (9) has been shown to be a remarkably orally active anti-inflammatory agent with no indication of GI toxicity.

Huang et al. have reported a novel series of 5,6-diaryl spiro (2,4) hept-5-enes as highly potent and selective COX-2 inhibitors. Methyl sulphone (10) and sulphonamide (11) were shown to have superior in vivo pharmacological profiles, low GI toxicity and good oral bioavailability, and duration of action. They have also reported some diaryl indenes (12,13) and benzofurans (14,15) as potent and selective cyclooxygenase-2 inhibitors.

Li et al. have reported novel terphenyl compounds that are selective COX-2 inhibitors and orally active anti-inflammatory agents. SAR studies have indicated that central ring substituent play an important role in COX-2 potency and only 1,2-diaryl 4,5-disubstituted benzene were found to be potent COX-2 inhibitors (16). Incorporation of two fluorine atoms in the central ring provide 1,2-diaryl 4,5-difluorobenzene sulphonamide which were very potent and highly selective COX-2 inhibitors.

A series of 1,2-diaryl pyrroles have been synthesized and found to contain potent and selective inhibitors of the human cyclooxygenase-2 (COX-2) enzyme. Diarylpyrrole (17) is a potent and selective inhibitor, whereas the isomeric (18) is completely inactive against COX-2. But the isomeric sulphonamide derivative (19) is an excellent inhibitor of COX-2.

Khanna et al. have reported a series of 1,2-diaryl imidazoles as highly potent and selective inhibitors of the human COX-2 enzyme. Different portions of diarylimidazole (20) were modified to establish SAR. Systematic variations of the substituents in the aryl ring B have yielded very potent and selective inhibitors of the COX-2 enzyme.

A series of sulphonamide containing 1,5-diarylpyrazole derivatives were prepared and evaluated for their ability to block cyclooxygenase-2 (COX-2) in vitro and in vivo. Extensive structure activity relationship was carried out within this series and many potent and selective inhibitors of COX-2 were identified. Since an early structural lead SC-236 (21) exhibited an unacceptably long plasma half-life, several pyrazole analogs containing potential metabolic sites were evaluated further in vivo in an effort to identify compounds with acceptable pharmacokinetic profiles. This work led to identification of SC-58635, celecoxib (1) which is currently in use as a drug.

Aspirin is the only NSAID that covalently modifies both COX-1 and COX-2 by acetylation at an active site serine residue (Ser-530 in COX-1 and Ser-516 in COX-2). Aspirin is significantly more potent against COX-1 than COX-2. Kalugutkar et al. elected to structurally modify aspirin to a selective COX-2 inactivator. They synthesized and identified 2-acetoxy phenyl methyl sulphide (22) as a lead compound that demonstrated moderate inhibitory potency and selectivity for COX-2. Systematic structural modification led to the development of 2-acetoxy phenyl heptyl sulphide (23) which was found to have optimum COX-2 inhibitory potency. Introduction of a triple bond in the 2-position gave 2-acetoxy phenyl hept-2-yl sulphide (24) which was the most potent and selective COX-2 inhibitor of the series. The compound was 60 - times more reactive against COX-2 than aspirin and 100 - times more selective for its inhibition.

Song et al. have reported thiazolone and oxazolone derivatives of 2,6-di-tert-butyl phenol as selective COX-2 inhibitors. Initial mass screening and subsequent structure-activity relationship studies have
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(11)

R = CH₃

(12)

R = NH₂

(13)

(14) R = CH₃

(15) R = NH₂

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identified (25) as the most potent and selective COX-2 inhibitors within the thiazolone and oxazolone series. They further reported\(^1\) 1,3,4- and 1,2,4-thiadiazole derivatives of 2,6-di-tert-butylphenol as selective COX-2 inhibitors. Substituted 2,6-di-tert-butylphenols with structure (26-30) were identified as potent and selective COX-2 inhibitors. In 1,3,4-thiadiazole series when R=SH (26), the compound was active but not very selective, slightly favouring COX-2. When R was changed from SH to SME (27) more than 30-fold increase in activity against both enzymes was observed. When R was changed from SME to SME (28) the potency against COX-2 was unchanged but the activity against COX-1 was reduced more than 200-fold. Compound 28 was the most potent and selective COX-2 inhibitor of the series. In the 1,2,4-thiadiazole series, an acidic proton on the side chain seems to be important for potency and selectivity. It was noted that thiadiazole (29) and oxadiazole (30) showed similar enzyme potency.

Cyclopentenones containing a 4-(methyl sulphonyl) phenyl group in the 3-position and a phenyl ring in the 2-position are selective inhibitors of cyclooxygenase-2 (COX-2). Black et al.\(^4\) have reported that the selectivity for COX-2 over COX-1 is dramatically improved by substituting the 2-phenyl group with halogens in the meta-position or by replacing phenyl ring with 3-pyridyl ring. Thus the 3,5-difluoro phenyl derivative (31) and 3-pyridyl derivative (32) are particularly interesting as potential anti-inflammatory agents with reduced side effects profile. Both exhibit good oral bioavailability and are potent in standard models of pain, fever, and inflammation, yet have a much reduced effects on the GI integrity of rats compared to standard non-steroidal anti-inflammatory drugs.

Puig et al.\(^42\) have prepared a series of 3,4-diaryloxazolones and evaluated for their ability to inhibit cyclooxygenase-2. Extensive structure activity relationship identified several potent and selective COX-2 inhibitors. The replacement of methyl sulphone group on the 4-phenyl ring by a sulphonamide moiety resulted in compounds with superior in vivo anti-inflammatory properties. In the sulphonamide series the introduction of the methyl group at 5-position of oxazoline ring gave rise to a very selective COX-2 compound (33) but with decreased in vivo activity. A selected group of 3,4-diaryloxazolones exhibited excellent oral activity when tested in acute and chronic assays of inflammation, fever, and pain. Furthermore, these compounds were devoid of gastrointestinal toxicity at high doses. The overall pharmacological activity of the 3,4-diaryloxazolones suggests that these novel compounds constitute a promising series of oral anti-inflammatory agents with the potential for an improved side effects profile. Compounds (34-36) on the basis of their in vivo activity profiles and lack of gastrointestinal toxicity have been selected for further preclinical and clinical profiling.

Although diaryl heterocycles and other compounds have been extensively studied as selective COX-2 inhibitors, there are a few reports on the utilisation of well established NSAID template in the design of selective COX-2 inhibitors\(^37,38,41-45\). Of all NSAIDs, indomethacin (37), zomeprac (38), aspirin (24), and flurbiprofen (39) are the only examples of compounds that have been successfully elaborated into selective COX-2 inhibitors.

Replacement of 4-chlorobenzoyl group of indomethacin with a 4-bromobenzoyl moiety (37) generates a COX-2 selective inhibitors\(^41\). In contrast, exchanging the carboxylate moiety in aspirin with alkylsulphide functionalities, affords specific COX-2 inhibitors\(^37,38\).

Kalgutkar et al.\(^46\) have recently reported a biochemically based strategy for the facile conversion of carboxylic acid containing NSAIDs. Derivatisation of these compounds to esters and amides produces molecule, capable of binding tightly to COX-2 but not COX-1. Thus, conversion of carboxylic acid of indomethacin\(^47\) into esters (40) and amide (41) derivatives generates compounds that are potent and highly selective COX-2 inhibitors. Primary and secondary analogues of indomethacin were more potent COX-2 inhibitors than the corresponding tert amides.

Among the most potent and selective COX-2 inhibitors that have been identified is the 4-(5-methyl-3-phenyl isoxazol-4-yl) benzene sulphonamide, valdecoxib\(^48\) (42). Valdecoxib, potentially and selectively, inhibited a recombinant human COX-2 isoform with an IC\(_{50}\) value of 0.005 \(\mu M\) as compared to a value of 140 \(\mu M\) obtained for a recombinant human COX-1 isoform.

Talley et al.\(^49\) tried to develop an injectable COX-2 inhibitor commenced with the idea of identifying a water soluble prodrug of valdecoxib that would undergo biotransformation in vivo. To test whether an acylated sulphonamide would serve as a
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(26) R=SH
(27) R=SMe
(28) R=SEt

(29) X=S
(30) X=O

(31)

(32)

(33)
(34) R = H
(35) R = 2F
(36) R = 4F
(37)
(38)
(39)
(40)

R = Alkyl, Substituted Phenyl
The synthetic and anti-inflammatory properties of a series of diaryl isoxazoles. The lead compound (46) in this group exhibited excellent in vitro inhibitory potency against COX-2 with no inhibition of COX-1. Many compounds in this group also showed impressive activity in an in vivo model of inflammation. Incorporation of C-5 CF₃ substituent on the central isoxazole ring enhanced selectivity towards COX-2.

4,5-diphenyl-4-isoxazoline (47) possessing various substitutent (H, F, MeS, MeSO₂) at the p-position of one of the phenyl rings were synthesized and evaluated as analgesic and selective COX-2 inhibitory anti-inflammatory agents. In the series the compound 2,3-dimethyl-5-(4-methyl sulphonyl phenyl)-4-phenyl-4-isoxazoline exhibited excellent analgesic and anti-inflammatory activities and it was a potent and selective COX-2 inhibitor (48).

Conclusions
The two recently developed and clinically available selective COX-2 inhibitors, celecoxib and rofecoxib, are about 100-1000 times more selective on the COX-2 than on the COX-1 isozyme. In Europe, rofecoxib is presently indicated for the symptoms and signs of osteoarthritis, whereas celecoxib is indicated for both osteoarthritis and rheumatoid arthritis. The major clinical interest of these drugs is related to the lower incidence of gastrointestinal bleeding which, with the conventional COX-1/COX-2 agents has been a source of hospitalisation, disablement and death, especially in the elderly. Clinical trials have convincingly demonstrated that celecoxib and rofecoxib in clinical use induce very few gastrointestinal complications, compared to conventional and non-selective NSAIDs. However the well known contraindications for NSAIDs, such as late pregnancy, aspirin-induced asthma, congestive heart failure, and renal dysfunction, will so far apply also to the COX-2 inhibitors. Further research effort culminated in the discovery of another selective COX-2 inhibitor valdecoxib, which is useful in the treatment of osteoarthritis, rheumatoid arthritis, and pain. Agents, such as celecoxib and valdecoxib which are highly COX-2 specific and have shown excellent efficacy in relieving inflammation and associated pain, unfortunately exhibit only modest aqueous solubility. In order to overcome the solubility restriction of these drugs, produg approach was employed. The result has been the discovery of parecoxib sodium, a produg of valdecoxib, which can be given parenterally. Compared to the traditional and non-selective NSAIDs, COX-2 inhibitors may provide an insight into additional therapeutic areas, such as gastrointestinal cancer and dementia, where the potential relevance to COX-2 mechanisms are currently being explored and clinical trials being performed. With the rapid clinical acceptance of celecoxib, rofecoxib, valdecoxib, and parecoxib sodium, knowledge about their clinical usefulness in
R = R'-NH & R'N

R = Me; X = F; R1 = H, Me, CF3
R2 = H, Me, Et, CF3; R3 = H, Me, Ph, Cl, OM

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various inflammatory disease states and pain disorders is increasing. For the many patients suffering from such conditions, the selective COX-2 inhibitors are likely to become a significant addition to the therapeutic arsenal of analgesic and anti-inflammatory drugs.

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References


