International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 21-05-2022, Accepted: 06-06-2022, Published: 22-06-2022
Volume 7, Issue 2, 2022, Page No. 90-94

Overview: formulation and evaluation of cox2 inhibitor

Mayur Joshi*, Atul Kadam, Shubham Bhusari, Vyankatesh Shedge, Nikhil Chavan
Department of Pharmaceutics, Shree Santkrupa College of Pharmacy Ghogaon, Karad, Maharashtra, India

Abstract
Non-steroidal anti-inflammatory medicines are routinely given medications that have a variation of side-effects, including gastrointestinal ulcers as well as cardiovascular problems. We evaluated the direct cyclooxygenase (COX) inhibitory activity and studied the probable COX binding manner of certain previously described 2-(trimethoxyphenyl)-thiazoles in order to find safer NSAIDs. COX inhibition experiments were carried out *in-vitro* using ovine COX-1 & human recombinant COX-2. To understand the putative interactions between the inhibitors and the binding pockets of both COX isoforms, molecular docking experiments were conducted. Inflammation is a complex process that is required for human defence mechanisms but also has a role in the progression of various sicknesses. The finding of cyclooxygenase-2 (COX2) enhanced the pharmacology of non-steroidal anti-inflammatory medications (NSAIDs), offering a pure mechanism for prostaglandin control *in-vivo* and a novel target for COX-2-selective therapies with no GI side effects. Some literature papers must highlighted the effect of these anti-inflammatory agents in treatments, highlighting the importance of this pharmacological class. Until 2016, the most recent published literature on COX-2 inhibitors was considered in this paper. The most current advancements in this medicinal family are described using a broad chemical classification, emphasizing structure-activity correlations insights & mechanisms. There is also a summary of the most common side effects as well as an outline of the novel prospective healing indications for COX-2 inhibitors.

Keywords: COX-2 inhibitors, Irritation, NSAIDs, cyclooxygenase, COX-1/COX-2 inhibition, SAR

Introduction
It is commonly known that NSAIDs work by inhibiting cyclooxygenase, which prevents the formation of pro-inflammatory prostaglandins. COX-1 as well as COX-2 is two COX isoforms that have been recognized. COX-1 is mostly thought of as a "housekeeping enzyme." It is found in maximum tissues and serves mostly physiological meanings such as preserving the stomach mucosa, maintaining & protecting kidney function, and controlling platelet aggregation by activating thromboxane A2 (TXA2). COX-2, on the other-hand, is assumed to be predominantly liable for the start & maintenance of inflammation, with relatively minimal physiological functions such as increasing prostacyclin (PGI2) synthesis and thereby reducing platelet aggregation [2-3]. Inflammation is a complex process that is important in human defensive mechanisms but too has a role in the progression of various illnesses. Redness, heat, pain, and swelling are four cardinal indicators of the inflammatory process. Since the mechanism of action of non-steroidal anti-inflammatory medications is suppression of PG manufacture, PG remain the primary target of anti-inflammatory therapy among all mediators involved in the inflammation way [4]. Vane demonstrated in 1971 that aspirin's blocking of PG synthesis was due to the suppression of a Prostaglandin G/H Synthase (PGHS) enzyme, which he suggested to call Cyclooxygenase (COX). A second COX isoform were found twenty years later. The first COX isoform, discovered by Vane and purified by Hemler in 1976, was designated COX-1, while the second was not discovered until 1991. These two isoforms catalyse the same arachidonic acid biotransformation, although they differ in terms of expression, function, and structure. COX-1 is present in most tissues and has housekeeping roles in the stomach, such as maintaining homeostasis and cytoprotection. With the exception of the prostate, kidney, brain, and smooth muscle, COX-2 is inductible and usually undetectable in most tissues under physiological conditions. COX-2 is a pro-inflammatory isoform that is activated largely by pro-inflammatory stimuli. COX-2, on the other hand, has been linked to stomach mucosal defence, renal homeostasis, and vascular systems [6]. COX-1 & COX-2 have 60% sequence identity and a 3D structure that is very similar, but their active sites are very different. Nonsteroidal anti-inflammatory drugs, such as selective cyclooxygenase (COX)-2 inhibitors, have become widely used in the action of musculoskeletal problems [7]. COX-2 inhibitors like Etoricoxib have been shown to be active in treating osteoarthritis, rheumatoid arthritis, acute gouty arthritis, ankylosing spondylitis, low back pain, acute postoperative pain, and primary dysmenorrhea in clinical trials. The goal of this study was to create a new semisolid etoricoxib dosage form that would reduce the gastrointestinal side effects associated with oral administration [8]. Etoricoxib is a highly specific inhibitor of cyclooxygenase 2 (cox2). A fixed concentration of Etoricoxib cream (2%) was manufactured in the current study utilising a distinct combination of active component and excipients. Coxibs are nonsteroidal anti-inflammatory drugs that are highly selective for the COX2 enzyme [9]. Coxibs are analgesic and antiinflammatory because the COX2 enzyme mediates PG

formation, which causes inflammation and pain, but they don't have the negative effects associated with inhibiting the COX1 enzyme (e.g., bleeding and GI irritation). Coxibs are utilised in both OA and RA, similar to nonselective NSAIDs that affect both COX1 and COX2 enzymes. Celecoxib, rofecoxib, and valdecoxib are the three coxibs that are currently approved. Indomethacin, ibuprofen, and diclofenac are examples of non-selective NSAIDs. The reasons for why some patients respond to one NSAID or coxib but not to another are unknown. Before dismissing this type of therapy as ineffective, it is recommended that more than one of these medications be attempted. The use of various coxibs has been restricted due to their proclivity for causing blood pressure increases and their link to an increased risk of myocardial infarction. [10-12].

Pharmacosomes are a new type of medicine delivery method for vesicles. They're a colloidal dispersion of lipid-covalently bound drugs. They deliver an effective means of delivering drugs to the desired location. Both the medicine and the lipid influence the physicochemical qualities. Pharmacosomes can take the form of hexagonal aggregates, ultrafine vesicles, or micellar particles. Both synthetic and natural medications with problems such low solubility and permeability can be successfully formulated [13]. NSAIDs, proteins, cardiovascular and antineoplastic medicines have all had their pharmacosomes created. It has been discovered that developing pharmacosomes for medications improves absorption and reduces gastrointesinal toxicity [14-17]. Pharmacosomes are lipid-drug complexes that are amphiphilic. The amiphiphilic property aids in the reduction of interfacial tension, resulting in an increase in contact area and increased drug bioavailability. Inflammation is the body's natural defence system. It's the process through which the immune system recognises and eliminates harmful stimuli, allowing the body to heal. The two types of inflammation are acute and chronic inflammation. Acute inflammation is characterised by pain, redness, swelling, and heat. [18]. Fatigue, chest pain, abdominal pain, rash, fever, and joint pain are all symptoms of chronic inflammation. There are over a hundred different forms of arthritis and related diseases. Swelling, discomfort, stiffness, and finally restricted range of motion are all indications of arthritic joints. Non-steroidal anti-inflammatory medicines (NSAIDs), corticosteroids, disease-modifying anti-rheumatic drugs (DMARDS), and biological agents are the most popular treatments for rheumatoid arthritis or arthritis [19]. The oral route is the preferred method of medication delivery. Oral NSAID therapy has been linked to ulceration and gastrointestinal haemorrhage. Poor bioavailability is caused by its poor water solubility, which affects its dissolution in GI fluid. Patients with higher risk of peptic ulcer, perforation, or bleeding should take selective COX-2 inhibitors. If chosen, they should be given at the lowest dose for the shortest time possible [20]. It should also be avoided in patients with a history of ischemic heart disease, hypertension, heart failure, or cerebrovascular illness, among other things. To reduce toxicity, cardiovascular danger, and to improve therapeutic impact, the drug will be given through the skin. Pharmacosomes are a revolutionary drug delivery technology that solves numerous challenges and issues associated with traditional dosage forms, such as drug release at a specific place at a specified rate for regulated or targeted drug administration [21]. Because the medication is covalently bonded to the lipid and the entrapment efficiency is high, there is a risk of leakage upon handled. Both hydrophilic and lipophilic medicines can be delivered using pharmacosomes. Pharmacosomes lower therapy costs, side effects, and toxicity. They improve in the bioavailability of poorly soluble drugs [22].

Discuss some of the potential side effects of selective COX2 inhibitors on the cardiovascular system. [23-25]

Low-dose aspirin provides the same protective effects as NSAIDs and coxibs. Coxibs (selective COX2 inhibitors) reduce the formation of vascular prostacyclin (PGI2) and may alter the balance of prothrombotic and antithrombotic eicosanoids. However, the present research may only imply a possible increase in cardiovascular events when compared to standard NSAIDs. Maintaining low-dose daily aspirin in individuals receiving a coxib drug is recommended in patients who are at high risk of a cardiovascular event. Low-dose acetyl salicylic acid (ASA), on the other hand, may not always mitigate the possible cardiovascular risk with COX2 inhibitors.

As an example of an anti-inflammatory therapeutic approach in MD, COX-2 inhibition [26-30]

COX-2 inhibitors have an influence on the central nervous system's serotonergic system, either directly or through immunological mechanisms. The injection of rofecoxib to rats increased serotonin levels in the frontal and temporoparietal cortex. As a result, COX-2 inhibitors should have an antidepressant impact in clinical practise. In the bulbectomized rat depression animal model, chronic celecoxib treatment resulted in a decrease in hypothalamic cytokine levels and a change in behaviour. Acetylsalicylic acid, a combination COX-1/COX-2 inhibitor, had an additional antidepressant effect in another animal model of depression by speeding up the antidepressant effect of fluoxetine. The COX-2 inhibitor celecoxib was found to have a significant therapeutic benefit in MD in a randomised, double-blind pilot add-on study comparing reboxetine and celecoxib to reboxetine and placebo. The ratio of kynurenine to tryptophan, which measures the activity of the proinflammatory cytokine-driven enzyme IDO, was used to predict the antidepressant response to celecoxib therapy.

Celecoxib was more effective in people who had a lot of IDO activity or a lot of proinflammatory activity. Another randomised, double-blind study of 50 depressed MD patients indicated that the COX-2 inhibitor celecoxib combined with fluoxetine produced much better results than fluoxetine alone. This finding was replicated in 40 depressed patients using a sertraline and celecoxib combo. Interestingly, in both the sertraline (plus placebo) and celecoxib (plus sertraline) groups, blood levels of IL-6 predicted antidepressant response.

Evaluation Methods of Cox-2 Inhibitors:

Various approaches for evaluating pharmacological inhibitory activity against COX-1 and COX-2 have been developed. Both enzymes and cells are used in *in vitro* tests. Purified or recombinant enzymes, as well as cell line microsomal production, are the most commonly utilised enzymatic procedures. U937 Human whole blood, insect cells, mammalian cells, and platelets are among the cellular approaches used. However, the use of non-standardized methodologies for determining COX-1 and COX-2 IC50 makes it difficult to compare results between studies [29-30]. At least one enzymatic and one cellular experiment utilising known COX-2 inhibitors as a reference should be coupled to ensure a solid evaluation of COX-2 potency. Carrageenan-induced paw edoema assay is one of four main *in vivo* assays used. These assays enable to evaluate the anti-inflammatory, analgesic, chronic anti-inflammatory, and antipyretic characteristics of compound [31]. carrageenan induced analgesia models in rats 3adjuvantinduced arthritis model and endotoxin induced pyretic response in rats

COX-2 Selective Agents

Analogues of Classical NSAIDs Several analogues of classic NSAIDs have been created with the goal of preserving or improving potency and selectivity. Derivatives of Salicylates Many aspirin analogues have been produced; for example, replacing the acetate group with a sulfonamide moiety boosted COX-2 selectivity by 1000- to 10000-fold. Other compounds were complexed with metals and displayed strong and selective COX-2 inhibition [32]. Meclofenamic acid modified compounds with the carboxylate group replaced with amides were able to boost COX-2 selectivity by 900 to 1400-fold. A number of indomethacin analogues, notably aryl acetic acids, were found to have great potency and selectivity against COX-2. The synthesis of ortho-carbaborane derivatives was carried out by substituting a CF3 group for the Me (R1) of the parent medicine and big and complicated substituents for the acid carboxylic moiety (SI up to 333000 and IC50 = 0.3 nM for compounds 36r and 36s) [33]. SAR experiments on the diclofenac scaffold show that adding halogen atoms (Cl or F) improves selectivity. An alkyl group at meta-position on the phenyl containing the COOH moiety had the same effect. The strong COX-2 potency (IC50 = 7 nM) and selectivity (SI> 1428) of lumiracoxib (38c) can be explained by its methyl group, which allows for greater entry into the COX-2 active site. However, due to significant liver adverse effects, lumiracoxib was withdrawn from the market in various countries. When compared to his molecule parent (40a, SI = 142), etodolac-derived compounds had low COX2 selectivity (40b, SI>45). Indeed, substituting a methyl moiety for the oxygen atom in etodolac reduces COX-2 selectivity. The selectivity and inhibitory potency of arylpropionic COX-2 acids were improved in flurbiprofen derivatives that modified the phenyl ring connected to the arylpropionic acid. Several ketoprofen analogues (42b-c) demonstrated a significant increase in selectivity (COX-2 SI >1100) by swapping the R3 substituent (N3 >> SO2Me > NHCOMe). The insertion and stability of this 4-N3Ph group into the COX-2 side pocket explains this. With an IC50 of 0.06 M, Oxicams modified analogues increase COX-2 selectivity by >200-fold [34-35].

Cox Inhibitors: Future Cancer and Neuronal Disease Therapies Cox Inhibitors

Inhibitors were designed to treat inflammation, thus they can be used to treat a variety of inflammatory diseases. COX inhibitors, on the other hand, have been explored for more than two decades in the treatment of cancer and neurological diseases such as Alzheimer's and Parkinson's.

Cancer

COX-2's participation and overexpression in cancer has been documented. The ability of NSAIDS to prevent angiogenesis and restore apoptosis in APC-deficient cells appears to be the mechanism by which they reduce tumour growth. However, the anti-oncogenic mechanism is still unknown, and the participation of LOX and COX-independent pathways has been mentioned. NSAIDs may be used to help prevent and reduce tumour growth in a variety of malignancies. COX-2 overexpression is found in 80 percent of colorectal cancer patients. NSAIDs such as piroxicam, indomethacin, sulindac, ibuprofen, or ketoprofen reduce the incidence of colon cancer by 40-50 percent in animal models, according to several clinical investigations. Similarly, celecoxib or a combination of aspirin and sulindac suppresses the formation of adenomatous polyps and causes existing polyps to shrink in familial adenomatous polyposis (FAP). Several studies have examined the effectiveness of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) in the prevention of esophageal cancer. Coxibs, notably celecoxib, are used to prevent malignancies caused by tobacco smoking or to slow tumour growth. In prostate and breast cancer, celecoxib and its derivatives are effective antiproliferative drugs. Nimesulide is used to treat breast cancer patients with COX-2 overexpression of up to 40% [36-37].

Alzheimer’s disease (AD)

A relationship between long-term NSAID use and a decreased incidence of Alzheimer's disease has been discovered in several epidemiological research. The extent of protection, however, varies based on the NSAIDS used. Some nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen, have been found to lower the risk of Alzheimer's disease. However, rofecoxib had no preventive effect against the development of Alzheimer's disease in a 12- to 18-month clinical trial of people with mild cognitive impairment, and was even suspected of increasing the incidence of conversion to AD. In reality, numerous elements appear to be required for NSAIDS to protect against AD in the early stages of chronic NSAIDS exposure with COX-1 inhibition potency. Although the initial notion that COX-2 suppression was responsible for lower neuro inflammatory and

hence a protective effect has been disproved, the exact mechanisms of amyloid buildup reduction remain unknown [38-39].

Parkinson's disease (PD)

COX-2 is overexpressed in the brains of Parkinson's disease patients. COX-2 appears to be implicated in the development of Parkinson's disease, and it could be a promising target for delaying or stopping the disease's progression. Rofecoxib and Parecoxib, in particular, are thought to be neuroprotective agents [40-41].

Conclusion

Since its discovery in the 1990s, the COX-2 enzyme has sparked the development of a plethora of selective inhibitors with varying chemical variety, inhibitory potencies, and potential to minimise side effects and improve tolerability when compared to traditional Non-steroidal anti-inflammatory medicines. COX-2 selective medicines have recently received a lot of attention as potential treatments for a variety of malignancies and neurological illnesses. New research is currently focusing on nanotechnology, in which selected medications will be coupled with nanoparticles.

References

1. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature (London), New Biol,1971:231(25):232-235.
2. Chipman JG, Robertson DL, Erikson RL, Simmons DL. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc. Natl. Acad. Sci. U.S.A,1991:88(7):2692-2696.
3. Kulkarni SK, Jain NK. Pharmacological and pharmacokinetic studies on marketed gel formulations of nimesulide. Indian Drugs,2001:38:2:63-69.
4. Kujubu DA, Fletcher BS, Varnum BC, Lim RW, Herschman HR. TIS10, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homolog. J. Biol. Chem,1991:266(20):12866-12872.
5. Hemler M, Lands WEM, Smith WL. Purification of the cyclooxygenase that forms prostaglandins. Demonstration of two forms of iron in the holoenzyme. J. Biol. Chem,1976:251(18):5575-5579.
6. Xie W, Robertson DL, Simmons DL. Mitogen-inducible prostaglandin G/H synthase: a new target for nonsteroidal antiinflammatory drugs. Drug Dev. Res,1992:25(4):249-265.
7. Smith WL, DeWitt DL, Garavito RM. Cyclooxygenases: structural, cellular, and molecular biology. Annu. Rev. Biochem,2000:69:145-182.
8. Crofford LJ. COX-1 and COX-2 tissue expression: implications and predictions. (Progress toward a new class of therapeutics: selective COX-2 inhibition). J. Rheumatol. Suppl,1997:49:15-19.
9. Golden BD, Abramson SB. Selective cyclooxygenase-2 inhibitors. Rheum Dis Clin North Am,1999:25(2):359-378.
10. Penglis PS, James MJ, Cleland LG. Cyclooxygenase inhibitors: any reservations? Intern. Med. J,2001:31(1):37-41.
11. Claria J. Cyclooxygenase-2 biology. Curr. Pharm. Des,2003:9(27):2177-2190.
12. Griswold DE, Adams JL. Constitutive cyclooxygenase (COX-1) and inducible cyclooxygenase (COX-2): rationale for selective inhibition and progress to date. Med. Res. Rev,1996:16(2):181-206.
13. Al-Turki DA, Abou-Zeid LA, Shehata IA, Al-Omar MA. Therapeutic and toxic effects of new NSAIDs and related compounds: a review and prospective study. Int. J. Pharmacol,2010:6(6):813-825.
14. Cryer B, Dubois A. The advent of highly selective inhibitors of cyclooxygenase-a review. Prostaglandins Other Lipid Mediators,1998:56(5-6):341-361.
15. Luo C, He Ml, Bohlin L. Is COX-2 a perpetrator or a protector? Selective COX-2 inhibitors remain controversial. Acta Pharmacol. Sin,2005:26(8):926-933.
16. Kurumbail RG, Stevens AM, Gierse JK, McDonald JJ, Stegeman RA, Pak JY *et al*. Structural basis for selective inhibition of cyclooxygenase-2 by antiinflammatory agents. Nature (London),1996:384(6610):644-648.
17. Dannhardt, G.; Kiefer, W. Cyclooxygenase inhibitors – current status and future prospects. Eur. J. Med. Chem,2001:36(2):109126.
18. Flower RJ. The development of COX2 inhibitors. Nat. Rev. Drug Discov,2003:2(3):179-191.
19. Vane J. Towards a better aspirin. Nature,1994:367(6460):215216.
20. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full *in vitro* analysis. Proc. Natl. Acad. Sci. U.S.A,1999:96(13):7563-7568.
21. Barnett J, Chow J, Ives D, Chiou M, Mackenzie R, Osen E *et al*. Purification, characterization and selective inhibition of human prostaglandin G/H synthase 1 and 2 expressed in the baculovirus system. Biochim. Biophys. Acta, Protein Struct. Mol. Enzymol,1994:1209(1):130-139.
22. Engelhardt G, Boegel R, Schnitzer C, Utzmann R. Meloxicam: influence on arachidonic acid metabolism. Part. 1. *In vitro* findings. Biochem. Pharmacol,996:51(1):21-28.

23. Li CS, Black WC, Brideau C, Chan CC, Charleson S, Cromlish WA *et al*. A new structural variation on the methanesulfonylphenyl class of selective cyclooxygenase-2 inhibitors. Bioorg. Med. Chem. Lett,1999:9(22):3181-3186.
24. Panara MR, Greco A, Santini G, Sciulli MG, Rotondo MT, Padovano R. di Gamberardino, M.; Cipollone, F.; Cuccurullo, F.; Patrono, C; Patrignani, P. Effects of the novel anti-inflammatory compounds, N-[2-cyclohexyloxy)-4-nitrophenyl] methanesulfonamide (NS-398) and 5-methanesulfonylamido-6-(2,4difluorothiophenyl)-1-indanone (L-745,337), on the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases. Br. J. Pharmacol,1995:116(5):2429-2434.
25. Gierse JK, Hauser SD, Creely DP, Koboldt C, Rangwala SH, Isakson PC *et al*. Expression and selective inhibition of the constitutive and inducible forms of human cyclo-oxygenase. Biochem. J,1995:305(2):479-484.
26. Carabaza A, Cabre F, Rotllan E, Gomez M, Gutierrez M, Garcia ML *et al*. Stereoselective inhibition of inducible cyclooxygenase by chiral nonsteroidal antiinflammatory drugs. J. Clin. Pharmacol,1996:36(6):505-512.
27. Grossman CJ, Wiseman J, Lucas FS, Trevethick MA, Birch PJ. Inhibition of constitutive and inducible cyclooxygenase activity in human platelets and mononuclear cells by NSAIDs and Cox 2 inhibitors. Inflamm. Res,1995:44(6):253-257.
28. Richardson C, Emery P. The clinical implications of inhibition of the inducible form of cyclo-oxygenase. Drug Saf,1996:15(4):249-260.
29. Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG, Patrignani P. Pharmacodynamic of cyclooxygenase inhibitors in humans. Prostaglandins Other Lipid Mediat,2007:82(1-4):85-94.
30. Dannhardt G, Kiefer W. Cyclooxygenase inhibitors - current status and future prospects. Eur. J. Med. Chem,2001:36(2):109126.
31. Jouzeau JY, Terlain B, Abid A, Nedelec E, Netter P. Cyclooxygenase isoenzymes. How recent findings affect thinking about nonsteroidal anti-inflammatory drugs. Drugs,1997:53(4):563-582.
32. De Leval X, Delarge J, Somers F, De Tullio P, Henrotin Y, Pirotte B *et al*. Recent advances in inducible cyclooxygenase (COX-2) inhibition. Curr. Med. Chem,2000:7(10):10411062.
33. Winter CA, Risley EA, Nuss GW. Carrageenin-induced edema in hind paw of rat as an assay for antiinflammatory drugs. Proc. Soc. Exp. Biol. Med,1962:111:544-547.
34. Otterness IG, Moore PF. Carrageenan foot edema test. Methods Enzymol,1988:162:320-327.
35. Seibert K, Zhang Y, Leahy K, Hauser S, Masferrer J, Perkins W *et al*. Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proc. Natl. Acad. Sci. U.S.A,1994:91(25):12013-12017.
36. Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S *et al*. Synthesis and biological evaluation of the 1,5diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1h-pyrazol-1yl]benzenesulfonamide (SC-58635, celecoxib). J. Med. Chem,1997:40(9):1347-1365.
37. Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. Pain,1998:75(1):111-119.
38. Anderson GD, Hauser SD, McGarity KL, Bremer ME, Isakson PC, Gregory SA. Selective inhibition of cyclooxygenase (COX)-2 reverses inflammation and expression of COX-2 and cyclooxygenase (COX)-2 in rat adjuvant arthritis. J. Clin. Invest,1996:97(11):2672-2679.
39. Jaffee BD, Kerr JS, Jones EA, Giannaras JV, McGowan M, Ackerman NR. The effect of immunomodulating drugs on adjuvant-induced arthritis in Lewis rats. Agents Actions,1989:27(34):344-346.
40. Simon LS, Lanza FL, Lipsky PE, Hubbard RC, Talwalker S, Schwartz BD *et al*. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor, in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. Arthritis Rheum,1998:41(9):1591-1602.
41. Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. Proc. Natl. Acad. Sci. U.S.A,1993:90(24):11693-11697.