# First and Second Generations of COX-2 Selective Inhibitors

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**Abstract:** The identification and characterization of the inducible form of cyclooxygenases (COX-2) stimulated the investigations to develop efficient, non-steroidal anti-inflammatory drugs (NSAIDs) with reduced side effects (essentially gastro-intestinal toxicity) compared to classical NSAIDs. This review focuses on the chemical and pharmacological properties (pre-clinical data) of marketed COX-2 inhibitors.

**Keywords:** COX-2 inhibitors, COX-2 selectivity, pre-clinical data.

## INTRODUCTION

Cyclooxygenases (COX) catalyse the transformation of arachidonic acid into endoperoxide $H_2$ as the first step in the biosynthesis of prostanoids, lipidic mediators involved both in physiological and pathological processes (inflammation and cancer). Since the early nineties[1,2], the existence of 2 COX isoforms (COX-1 and COX-2) is well established. Instead of COX-1 expression which is ubiquitous, COX-2 is mainly expressed during pathological processes. High levels of COX-1 are found in platelets [3], stomach [4] and kidneys [5]. Furthermore, prostanoids deriving from the COX-1 catalytic activity were demonstrated to be involved in the platelet aggregation, gastro-intestinal homeostasis and renal perfusion [6]. On the other hand, COX-2 expression is associated with the biosynthesis of large amounts of prostanoids observed during pathological conditions such as inflammation or cancer progression [7,8]. Nevertheless, COX-2 expression is also observed in some tissues such as vascular endothelium, kidney or brain under normal conditions, suggesting the involvement of COX-2 in the regulation of physiological processes.

Acting as non-selective COX inhibitors, classical NSAIDs have been widely used in the treatment of several ailments for a long time. Possessing anti-inflammatory, antipyretic and analgesic properties, this class of drugs is chiefly used to treat acute and chronic inflammation states. However, all these agents cause untoward side effects related to COX-1 inhibition of which gastro-intestinal irritation, sometimes leading to haemorrhage and ulceration is the most common. The recent discovery of two COX isozymes and the detection of their separate functions and regulations has renewed the interest of the pharmaceutical groups in the development of COX-2 selective inhibitors. Specifically, selective COX-2 inhibitor were developed in order to obtain potent anti-inflammatory, antipyretic and analgesic agents displaying reduced the side-effects in the gastro-intestinal tract commonly observed during or following NSAIDs treatment.

The concept of COX-2 selective inhibition is based on the differences of amino acids sequence existing between COX-1 and COX-2. The differences in the amino acid sequence between COX isoforms are responsible for differences in the enzyme structures and especially in the access to the COX catalytic site. Schematically, in comparison with the COX-1 isoform, the access to the COX-2 catalytic site is, due to the presence of a secondary pocket side, larger. This major structural difference permitted the synthesis of compounds interacting with the cyclooxygenase active site and possessing a "critical" size permitting a specific interaction with the COX-2 active site without inhibiting the COX-1 catalytic activity. During the last decade, this approach led to the development of a large number of compounds possessing an enhanced inhibitory selectivity against COX-2, which is mainly expressed as the ration between the $IC_{50}$ measured against COX-1 and COX-2. These compounds share the ability to possess a greater inhibitory potency against COX-2 compared to COX-1. Nevertheless, at high doses, these compounds are also able to inhibit the COX-1 activity. This lack of perfect selectivity led to the statement that although these drugs are commonly named COX-2 selective inhibitors, they are rather COX-2 preferential inhibitors.

In regard to the large amount of COX-2 "selective" inhibitors described, the present review will focus on the COX-2 inhibitors recently marketed or under clinical trials and especially on the chemical and pre-clinical data regarding these compounds. These recent and most well-documented COX-2 inhibitors are commonly classified as first or second generation COX-2 inhibitors [9].

## FIRST GENERATION OF COX-2 INHIBITORS

The three major compounds representing the first generation of COX-2 inhibitors are nimesulide (**1**), celecoxib (**2**) and rofecoxib (**3**) (Fig. (**1**)). Chemically, these compounds belong to two distinct classes of COX-2 inhibitors: the methanesulfonanilide class for nimesulide and the diary-substituted cycles class for celecoxib and rofecoxib

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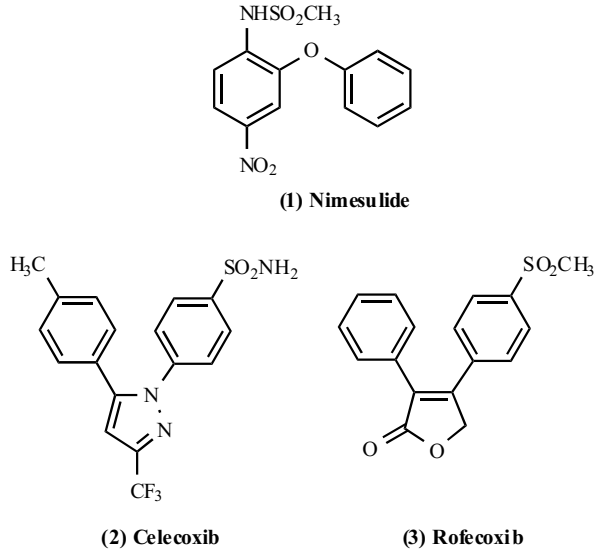


**Fig. (1).** Chemical structures of the first generation COX-2 inhibitors.

## 1.Nimesulide

Nimesulide (**1**), or 4-nitro-2-phenoxymethanesulfonanilide, was demonstrated to display a greater inhibitory potency against COX-2 compared to COX-1 in human whole blood assay (selectivity ration of 7.3) [10]. *In vivo*, this compound was also demonstrated to possess anti-inflammatory, analgesic and antipyretic properties in several animal models of inflammation [11-13]. For example, Carr *et al*. demonstrated the anti-inflammatory efficacy of nimesulide in the adjuvant arthritis test performed in rats at the dose of 0.2 mg/kg [14]. Furthermore, nimesulide was demonstrated to totally inhibit COX-2 *in vivo* in dogs while partially affecting the COX-1 catalytic activity at the dose of 5 mg/kg [15]. Nimesulide was also demonstrated to generate less GI side-effects compared to classical NSAIDs and this better tolerability was correlated to its preferential COX-2 inhibitory potency [16,17]. For example, Tanaka *et al*. demonstrated that the dosage in rats inducing ulceration in 50% of the animals ($UD_{50}$) was 106 mg/kg for nimesulide while the $UD_{50}$ for indomethacin was 2.9 mg/kg in the same test [18]. Furthermore, Borrelli *et al*. demonstrated that nimesulide decreased the gastric acid secretion in mice by a direct action on calcium channels [19].

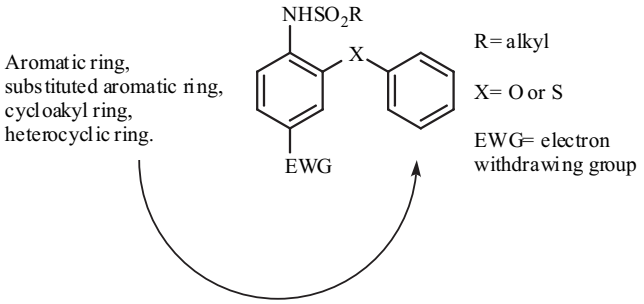


**Fig. (2).** General structure of sulfonanilide COX-2 inhibitors.

The interesting profile of nimesulide led to the synthesis of a large number of methanesulfonanilide-based potent COX-2 inhibitors among which NS-398 and flosulide are the most famous. Schematically, all these compounds share the common characteristics summarized in Fig. (**2**).

Finally, nimesulide was also demonstrated to display other pharmacological effects *in vivo* at therapeutic doses, or, *in vitro* at concentrations within the therapeutic range. Among these pharmacological effects are the reduction in release from neutrophils of cytokine, histamine, enzymes that degrade cartilage, superoxide anions and other toxic substances [17,20,21].

## 2. Celecoxib and Rofecoxib

Celecoxib and rofecoxib belong to the class of diaryl-substituted heterocycles as COX-2 inhibitors of which the origins are not well established. However, two diaryl-substituted heterocycles synthesized in the 1960s, indoxole (**4**) and oxaprozin (**5**), were identified as potent anti-inflammatory agents [22,23]. It was also suggested that oxaprozin could derive from phenylbutazone (**6**), leading to the suggestion that this well known NSAID was the first representative member of the diaryl-substituted heterocycles COX-2 inhibitors class (Fig. (**3**)). Of particular interest is the absence of well-characterized acidic function in indoxole. During the last decades, several groups of medicinal chemists became interested in this class of agents and a wide range of analogues were designed and evaluated for their COX-2 inhibitory potency. The major difference between compounds of this class is the nature of the central ring. Thiazole, oxazole, furan, pyrrole, pyrazole, imidazole, isoxazole, thiophene, cyclopentene structures and many others were proposed. The summary of the literature devoted to the biological evaluation of this class leads to the general statement that 4-methoxy- or 4-halo-substituted diaryl-substituted heterocycles possess enhanced anti-inflammatory potency compared to their unsubstituted analogues.

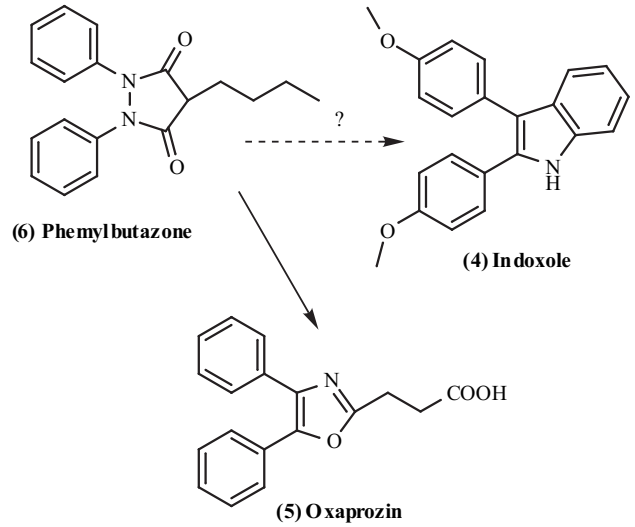


**Fig. (3).** Possible origin of the diary-substituted cycles as COX-2 inhibitors.

Celecoxib, compound (**2**) or SC-58635, appeared selective and potent against COX-2 *in vitro* (COX-1 $IC_{50}$ 13 μM; COX-2 $IC_{50}$ = 0,04 μM) and gave good results in the carrageenan-induced foot oedema and adjuvant-induced arthritis models in rats with $ED_{50}$ of 0.4 and 7 mg/kg, respectively [24]. *In vitro* using human whole blood assay,

SC-58635 displayed a selectivity ratio of 7.6, which is slightly better than the one measured with nimesulide [10]. Using human peripheral monocytes, Kato *et al*. found $IC_{50}$ for celecoxib against COX-1 and COX-2 of 82 and 6.8 μM, respectively. Subsequently, they estimated that the selectivity ratio of celecoxib was 12 [25]. In rats, celecoxib demonstrated a better intestinal tolerability compared to indomethacine and this improvement in GI safety seemed to be due to a combination of the absence of a topical toxicity and a selective inhibition of COX-2 [26].

Rofecoxib (MK-0966) (**3**), is a 3,4-diarylsubstituted furanone COX-2 inhibitor [27] which was demonstrated to inhibit COX-2 with an $IC_{50}$ of 0.77 μM without inhibiting the COX-1 activity at single doses up to 1000 mg in a human whole blood assay [28].On the other hand, Chan and co-workers evaluated the pre-clinical pharmacological profile of rofecoxib and, although they demonstrated the COX-2 inhibitory potency of this compound, they also observed a slight COX-1 inhibitory potency. In this study, rofecoxib was confirmed as a potent inhibitor of the COX-2-dependent production of $PGE_2$ in human osteosarcoma cells ($IC_{50}$ = 26 +/- 10 nM) and Chinese hamster ovary cells expressing human COX-2 ($IC_{50}$ = 18 +/- 7 nM) with a 1000-fold selectivity for the inhibition of COX-2 ($IC_{50}$ > 50 microM in U937 cells and $IC_{50}$ > 15 μM in Chinese hamster ovary cells expressing human COX-1). Rofecoxib also displayed a time-dependent inhibitory potency against purified human recombinant COX-2 ($IC_{50}$ = 0.34 μM) but caused inhibition of purified human COX-1 in a non-time-dependent manner that could only be observed at a very low substrate concentration with an $IC_{50}$ of 26 μM at 0.1 μM arachidonic acid concentration. In the *in vitro* human whole blood assay, rofecoxib selectively inhibited LPS-induced COX-2-derived $PGE_2$ synthesis with an $IC_{50}$ value of 0.53 +/- 0.02 μM but also inhibited the COX-1-derived thromboxane $B_2$ synthesis after blood coagulation with an $IC_{50}$ value of 18.8 +/- 0.9 μM. Using the ratio of the COX-1 $IC_{50}$ values over the COX-2 $IC_{50}$ values in the human whole blood assay, the authors found a selectivity ratio of 36 for rofecoxib while they found ratios of 6.6, 2, 3, and 0.4 for celecoxib, meloxicam, diclofenac, and indomethacine, respectively. These data suggest that rofecoxib is the most selective COX-2 inhibitor of the first generation COX-2 inhibitors family. In this study, rofecoxib was also evaluated as anti-inflammatory, analgesic and antipyretic agent in several *in vivo* rodent models. Rofecoxib showed a potent inhibitor of carrageenan-induced paw oedema ($ID_{50}$ = 1.5 mg/kg), carrageenan-induced paw hyperalgesia ($ID_{50}$ = 1.0 mg/kg), LPS-induced pyresis ($ID_{50}$ = 0.24 mg/kg), and adjuvant-induced arthritis with an $ID_{50}$ of 0.74 mg/kg/daily. Finally, rofecoxib also demonstrated a protective effect on adjuvant-induced destruction of cartilage and bone structures in rats. The ulcerogenic potency of rofecoxib was evaluated in a $^{51}Cr$ excretion assay for detection of gastrointestinal integrity in either rats or squirrel monkeys, where it had no effect at doses up to 200 mg/kg/day for 5 days [29].

## SECOND GENERATION OF COX-2 INHIBITORS

The three major compounds belonging to the second generation of COX-2 inhibitors are diaryl-substituted-based COX-2 inhibitors. For instance, valdecoxib and parecoxib bear an isoxazole central ring while etoricoxib is a pyridine diaryl-substituted-based COX-2 inhibitor (Fig. (**4**)).

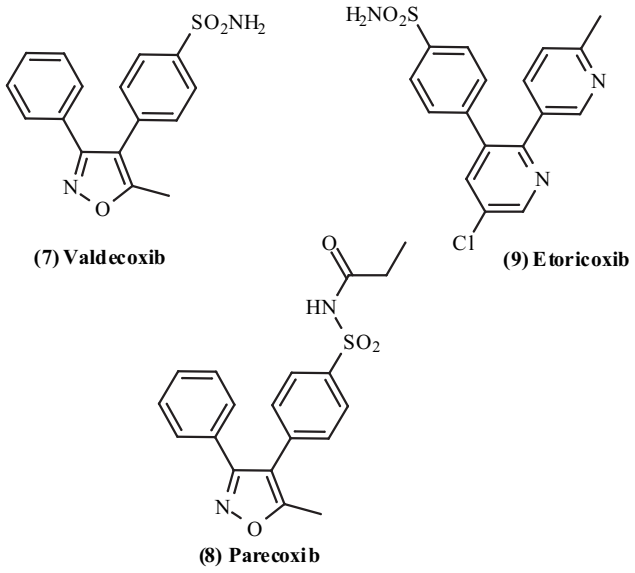


**Fig. (4).** Chemical structures of the second generation of COX-2 inhibitors.

### 1. Valdecoxib and Parecoxib

Valdecoxib (**7**) and parecoxib (**8**) are two recently developed COX-2 inhibitors displaying potent and selective COX-2 inhibitory potencies [30-32]. Indeed, Hood and co-workers demonstrated, using $^3H$ valdecoxib, that this drug displayed a highly specific and saturable binding to COX-2. Under the same assay conditions, little or no specific binding to COX-1 could be detected. The measured $K_D$ of $^3H$ Valdecoxib for COX-2 was 2.3 nM and the binding to COX-2 seemed to be both rapid and slowly reversible with association rates of 4.5 x $10^6$/M/min and dissociation rates of 7.0 x $10^{-3}$/min ($t_{1/2}$ = 98 min) for $^3H$ valdecoxib [33]. Valdecoxib was also found to possess an $IC_{50}$ COX-1 over COX-2 ratio of 61.5 in a human whole blood assay *in vitro* by Tacconelli *et al*. while celecoxib and rofecoxib exhibited, in the same test, ratios of 29.6 and 272, respectively [34]. Finally, Ouellet *et al*. recently reported that valdecoxib was able to block the inactivation of COX-1 by aspirin (10 μM), suggesting a competition between these two drugs for the access to the COX-1 active site and, therefore, an interaction of valdecoxib with COX-1, although the $EC_{50}$ measured with valdecoxib was quite low compared to non-selective inhibitors such as ibuprofen [35].

Parecoxib has also been demonstrated to display a potent and selective inhibitory potency against COX-2 after metabolisation [31]. Indeed, this compound administered to rodent, dog or monkey is rapidly and completely converted to valdecoxib. The main advantage of this compound, under the sodium salt form, is its enhanced water solubility (22 mg/mL in PBE at 25°C) which allows the intra-venous and intra-muscular injection. Pharmacological data obtained *in vivo* with this compound demonstrated that it displayed a potent anti-inflammatory activity in the adjuvant arthritis model in rats ($ED_{50}$ = 0.08 mg/kg) and in the carrageenan air pouch assay (78% inhibition at the dose of 0.3 mg/kg). Finally, this compound, possessing a great anti-

inflammatory and analgesic potency as well as a good water solubility, would be ideal for a parenteral use. Clinical trials performed with this compound demonstrated its usefulness in the management of post-operative pain [36-38] and its lack of GI toxicity compared to ketorolac and naproxen [39].

### Etoricoxib

Etoricoxib (MK-0663) (**9**) has been characterized in a human whole blood mode *in vitro* by a COX-2/COX-1 selectivity ratio of 344 [34]. Riendeau *et al*. [10] who evaluated the preclinical profile of etoricoxib also reported a high selectivity *in vitro* using whole blood assays and sensitive COX-1 enzyme assays at low substrate concentration. Indeed, Etoricoxib selectively inhibited COX-2 in human whole blood assays *in vitro*, with an $IC_{50}$ value of 1.1 +/- 0.1 μM for COX-2 compared with an $IC_{50}$ value of 116 +/- 8 μM for COX-1. Subsequently, they estimated that the selectivity ratio for the inhibition of COX-2 by etoricoxib in the human whole blood assay was 106, compared with values of 35, 30, 7.6, 7.3, for rofecoxib, valdecoxib, celecoxib and nimesulide, respectively. In the same study, etoricoxib did not inhibit platelet or human recombinant COX-1 under most assay conditions ($IC_{50}$ > 100 μM). In a highly sensitive assay for COX-1 with U937 microsomes where the arachidonic acid concentration was lowered to 0.1 μM they measured an $IC_{50}$ values of 12 μM while the $IC_{50}$ measured for rofecoxib, valdecoxib and celecoxib were, respectively, 2, 0.25, and 0.05 μM. *In vivo*, etoricoxib was a potent inhibitor in models of carrageenan-induced paw oedema with an $ID_{50}$ of 0.64 mg/kg, carrageenan-induced paw hyperalgesia with an $ID_{50}$ of 0.34 mg/kg, LPS-induced pyresis with an $ID_{50}$ of 0.88 mg/kg, and adjuvant-induced arthritis with an $ID_{50}$ of 0.6 mg/kg/day in rats, without effects on gastrointestinal permeability at doses up to 200 mg/kg/day for 10 days. In squirrel monkeys, etoricoxib reversed LPS-induced pyresis by 81% within 2 hours of administration at a dose of 3 mg/kg and showed no effect in a fecal $^{51}Cr$ excretion model of gastropathy at 100 mg/kg/day for 5 days, in contrast to lower doses of diclofenac or naproxen.

## DISCUSSION AND CONCLUSIONS

The discovery of two cyclooxygenase isoenzymes, a constitutive COX-1, responsible for the homeostatic prostanoid synthesis, and an inducible COX-2, responsible for pro-inflammatory prostanoid production, led to the development of new non-steroidal, anti-inflammatory drugs (NSAIDs), the selective COX-2 inhibitors, thought to display minimal, NSAID-typical toxicity with full anti-inflammatory efficacy. So far, the strategy of selective COX-2 inhibition has been successful. Indeed, selective COX-2 inhibitors, although they should be called COX-2 preferential inhibitors, discussed in this issue display a good COX-2 over COX-1 selectivity ratio. It is worthy to note that the selectivity ratio estimated by different research groups, even in the same test, can be quite different. Therefore, it seems very important to consider this kind of data only when other reference drugs are also evaluated in the same test, which permit to rank the investigated drugs in terms of selectivity. Furthermore, the COX-2 selective inhibitors display potent anti-inflammatory, antipyretic and analgesic effects in several animal models of inflammation, pyresis or hyperalgesia. Finally, these compounds have significantly less gastro-intestinal toxicity and, at therapeutic dose, no effects on platelet aggregation compared to classical NSAIDs.

These pre-clinical data clearly demonstrate the potential therapeutic benefit of these drugs, which appear at least also potent in reducing inflammation compared to classical NSAIDs while causing less GI side-effects. These compounds are classified as “first” or “second” generation of COX-2 inhibitors in regard to their COX-2 selectivity. In general terms, most recent compounds such as valdecoxib, parecoxib and etoricoxib possess, compared to nimesulide, celecoxib and rofecoxib, an enhanced COX-2 selectivity while a strong inhibitory potency is conserved. Of special interest is the development of parecoxib, a parenteral, highly selective COX-2 inhibitor which has the potential to become the NSAID of choice for treatment of postoperative pain. Consequently, pre-clinical data regarding these new COX-2 inhibitors suggest the interest of such drugs in the therapeutic approach of inflammation, pyresis and pain, although clinical trials are actually performed in order to assess the efficacy and therapeutic interest of the second generation of COX-2 selective inhibitors.

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