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Update on COX-2 Selective Inhibitors: Chemical Classification, Side Effects and their Use in Cancers and Neuronal Diseases

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Abstract: Inflammation is a complex phenomenon necessary in human defense mechanisms but also involved in the development of some human diseases. The discovery of cyclooxygenase-2 (COX-2) improved the pharmacology of nonsteroidal anti-inflammatory drugs (NSAID) giving a clear mechanism for prostaglandin regulation *in vivo* and providing a new target for the development of COX-2-selective drugs without gastrointestinal side-effects. Keeping in view the importance of this pharmacological class, several literature reports have underlined the impact of these anti-inflammatory compounds in therapeutics. The present review considers the most recently published literature concerning COX-2 inhibitors until 2016. Through a wide chemical classification, the last developments concerning this therapeutic family by highlighting structure-activity relationships insights and mechanisms are presented. A summary of the principal adverse effects observed and an overview of the new potential therapeutic indications for COX-2 inhibitors are also reported.

Keywords: COX-2 inhibitors, Inflammation, Non-steroidal anti-inflammatory Drugs, Cyclooxygenase, COX-1/COX-2 inhibition, Structure-activity relationship.

1. INTRODUCTION

Inflammation is a complex phenomenon essential in human defense mechanisms but is also involved in the development of some human diseases. The inflammation process is characterized by four cardinal signs: redness, heat, pain and swelling. Among all the mediators participating in the inflammation process, the Prostaglandins (PG) remain the major target of anti-inflammatory therapy since non-steroidal anti-inflammatory drugs (NSAIDs) mechanism of action lies in the inhibition of PG biosynthesis. The story started in 1971 when Vane [1, 2] demonstrated that the blockade of prostaglandin synthesis by aspirin was due to the inhibition of a Prostaglandin G/H Synthase (PGHS) enzyme that he proposed to name Cyclooxygenase (COX). Twenty years later, a second COX isoform was discovered [3, 4]. The first COX isoform, identified by Vane and isolated in 1976 by Hemler [2, 5], was renamed COX-1 whereas the second one unknown until 1991 was named COX-2. These two isoforms catalyze the same biotransformation of arachidonic acid but present some differences, notably in terms of expression, function and structure (Fig. 1, Table A) [6, 7].

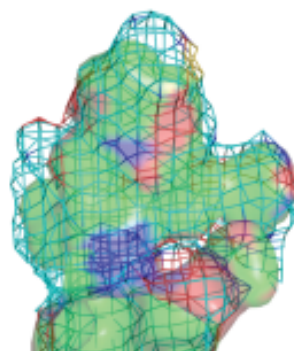


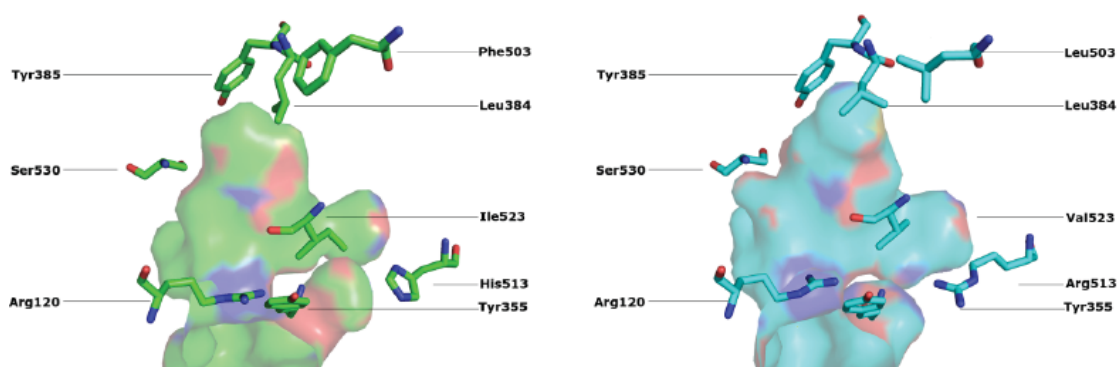
Fig. (1). Representation of COX.

COX-1 is constitutively expressed in most tissues and exerts housekeeping functions such as maintaining the homeostasis or gastric cytoprotection [8]. On the opposite, COX-2 is inducible, usually undetectable under physiological conditions in most tissues except prostate, kidney, brain and smooth muscle [8]. The COX-2 isoform is notably activated by pro-inflammatory stimuli and presents mainly a pro-inflammatory function. However, evidences for COX-2 involvement in gastric mucosal defense, renal homeostasis and vascular systems have been made [9-15]. COX-1 and COX-2 share a sequence identity of 60%, present closely similar three-dimensional structure [16] but their active sites

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Table A. Respiratory tract (adapted Pairet *et al* [196]).

	COX-1	COX-2
Location on chromosome	9q32-q33.3	1q25
Enzyme location	Endoplasmic reticulum	Nuclear envelope
Enzyme size (weight kDa)	600-602 AA (70-72)	603-604 AA (70-72)
Regulation	Constitutive	Inductible
Induced gene expression	2-4 folds	10-80 folds
Function	Homeostasis, organs protection	Inflammation
Tissue expression	Ubiquitous (particularly in stomach, kidney and platelet)	Quasi-undetectable at basal condition Induced by inflammatory stimuli (macrophages, monocytes...)

**Fig. (2).** Active sites of COX-1 (left) and COX-2 (right)/ picture from Pymol.

are not identical (Fig. 2). Indeed, some mutations in the active site between COX-1 and COX-2 have been observed: I434V, F503L, H513R and I523V [16-18] and result in a COX-2 binding site more flexible and 25% larger than COX-1 binding site, with the emergence of a side pocket not available in the COX-1 binding site. These differences in binding site size and amino acids composition enable to develop ligands selective for COX-2. Indeed, COX-1 inhibition was thought to be blamed for the adverse effects (gastric damage, blood thinning and renal dysfunction) associated with classical and non-selective NSAIDs such as aspirin, diclofenac or ibuprofen whereas COX-2 inhibition was associated with anti-inflammatory effects [19, 20]. Even if this dogma is tending to change, it fully explains the discovery story of the anti-inflammatory drugs targeting COX pathways and notably the intensive efforts made upon producing selective, and therefore safer, COX-2 inhibitors. A large number of compounds, belonging to several chemical families have been proposed, and sometimes marketed. These inhibitors present different mechanisms and kinetics of inhibition (irreversible or reversible, competitive, slow time-dependent, selective or non-selective COX-2 inhibitors) [16]. However, a common classification of NSAIDs uses their selectivity to separate the inhibitors in 4 groups [18, 20]. The first group is formed by non-selective NSAIDs, among which aspirin (**1**), ibuprofen (**16**) or piroxicam (**30**) that can completely inhibit both COX-1 and COX-2. The second class includes NSAIDs with moderate COX-2 selectivity (with an IC50 COX-1 / IC50 COX-2 ratio ranging from 5 to 50) like

etodolac (**150**) or meloxicam (**32**). The third category gathers NSAIDs presenting a high selectivity for COX-2, with a COX-2 inhibition potency over 50 fold superior to the COX-1 potency. Finally, NSAIDs that are only weak inhibitors of both COX-1 and COX-2 isoforms formed the last group of this classification.

This review will retrace as extensively as possible the state of the art of these compounds, with a focus on the last developments of this therapeutic family of compounds since 2010 referenced as “recent compounds”. The description of the major compounds, some insights about structure-activity relationships and about mechanism of COX inhibition are provided for each chemical class of COX-2 inhibitors. Finally, a summary of the different types of adverse effects observed together and a brief overview of potential new therapeutic indications for COX-2 inhibitors conclude this review.

2. EVALUATION METHODS OF COX-2 INHIBITORS

Various methods have been developed to evaluate drugs inhibitory activity against COX-1 and COX-2. *In vitro* assays use both enzymes and cells. The most frequently used enzymatic methods are based on purified or recombinant enzymes [21, 22], or microsomal preparation of cell line U937 [23]. Cellular methods include human whole blood [2], [24], insect cells [21, 25], various mammalian cells [21, 22, 26] and platelets [27]. However, the use of different and non-standardized methods for the evaluation of COX-1 and COX-2 IC50 jeopardizes the comparison of these data be-

tween studies [2, 28-31]. To ensure a solid evaluation of COX-2 potency, at least one enzymatic and one cellular experiment using as reference known COX-2 inhibitors should be combined [32]. Four main *in vivo* assays are used: carrageenan-induced paw oedema assay ([33-36], carrageenan-induced analgesia models in rats [26, 36, 37], adjuvant-induced arthritis model ([36, 38-40] and endotoxin –induced pyretic response in rats [30, 41]. These assays enable to quantify respectively the anti-inflammatory, the analgesic, the chronic anti-inflammatory and the antipyretic properties of compounds.

3. COX-2 INHIBITORS: FROM 1900 TO 2016

3.1. Classical NSAIDs Agents (1900-1970)

Classical NSAIDs (Tables 1-8) were the first drugs marketed to reduce inflammation. They represent a structural heterogeneous class of compounds and can be classified into 7 groups [42]: (1) salicylates, (2) anthranilates (3) pyrazolinone derivatives, (4) arylacetic acids, (5) arylpropionic acids, (6) para-aminophenol derivatives, (7) acidic enolic compounds (pyrazolidine-3,5-diones, oxicams). These drugs bear a carboxylic acid function as common structural characteristic. They are non-selective drugs and share a common binding mode: the carboxylate moiety is involved in hydrogen bonds and/or ionic interactions with Arg 120 and Tyr 355.

Salicylates (Table 1): The major compound of salicylates group is acetylsalicylic acid (1), also known as aspirin, the first marketed drug to relieve pain and inflammation. This drug inactivates COX-1 and COX-2 by acetylation of the COX residue Ser 530. This covalent modification is more important (10-100 times) in COX-1 than in COX-2 [43]. Other members of the salicylates group are also marketed, such as ethenzamide (2), salicylamide (3) or diflunisal (4).

Anthranilates and pyrazolinone derivatives (Tables 2, 3): Two anthranilate compounds (niflumic (5a) and mefenamic (6b) acids) and one pyrazolinone compound (metamizol, 7) are marketed drugs. However, the therapeutic use of anthranilates and pyrazolinone compounds has been largely reduced due to poor risk-benefit ratio [20, 44]

Arylacetic acids (Tables 4, 5): These compounds are time- and concentration-dependent inhibitors of PGs synthesis [43]. Indomethacin (11b), its prodrug acemetacin (11a) [45] and diclofenac (9b) are marketed and widely used in anti-inflammation therapy. Indomethacin presents a time-dependent inhibition linked to its 2'-methyl group which binds into a small hydrophobic area formed by Val 349, Ala 527, Ser 530 and Leu 531. The 2'-des-methyl indomethacin analogue is a poor inhibitor of COX-2 [43]. Conversely, diclofenac adopts an inverted binding mode compared to other classical NSAIDs, in which the carboxylate part is involved in hydrogen bonds with Ser 530 and Tyr 385 of the COX-2 active site. Diclofenac also displays a better COX-2 selectivity than the other classical NSAIDs [46].

Arylpropionic acids (Table 6): This group of compounds includes the commercial drugs (S)-ibuprofen (16), (S)-flurbiprofen (15) and (S)-naproxen (18). Despite their structural similarity, these compounds present different mechanisms of inhibition: single-step competitive, rapid and reversible inhibition; two-steps irreversible inhibition slow and

reversible; and weak inhibition respectively [43]. (R)-stereoisomers are inactive since their 2'-methyl functions clashes with the Tyr 355 of the COX-2 active site [47].

p-aminophenol derivatives (Table 7): Acetaminophen, also known as paracetamol (21), and its prodrug proparacetamol (23), are two main representatives of this group. Currently, the COX-2 binding potency remains unclear and controversial [48-51]. Paracetamol presents a very weak anti-inflammatory activity, and is rather used as an analgesic and antipyretic drug [52]. However, its analogues are able to inhibit COX like phenidine, a preferential COX-1 inhibitor [53].

Acidic enolic compounds (pyrazolidine-3,5-diones, oxicams) (Table 8): These compounds, including the commercially available and widely used piroxicam (30) and meloxicam (32), combine a thiazine ring and a carboxamide moiety and have several tautomers. Their binding mode, never seen with other NSAIDs, is characterized by hydrogen bonds between hydroxyl group of thiazine and carboxamide group and Ser 530 and Tyr 385 from one part and between nitrogen atom of the thiazine and carboxamide group and Arg-120 and Tyr-355 on the other part, both through two highly coordinated water molecules. The binding of oxicams induces changes in the protein conformation rarely observed in the NSAIDs class, with a rotation of the side chain of Leu 531 and opening of a new pocket [54]. The anti-inflammatory mechanism of action of piroxicam is still controversial [55], but meloxicam is proved to be a modest selective COX-2 inhibitor since its 4'-methyl group clash with the COX-1 Phe-518 due to I434V mutation [54].

The currently marketed classical NSAIDs are both COX-1 and COX-2 inhibitors, resulting in undesirable side effects, such as gastrointestinal disorder and bleeding. The research for new NSAIDs is currently focused on selective COX-2 inhibitors, supposed to display an improved tolerance profile.

3.2. COX-2 Selective Agents (1970-2016)

3.2.1. Analogues of Classical NSAIDs

Numerous analogues of classical NSAIDs were synthesized with the aim to preserve or enhance their potency and to improve their selectivity. (Tables 9-19)

Salicylates Derivatives (Table 9): Numerous analogues of aspirin have been developed; among them the substitution of the acetate group by a sulfonamide moiety increased the COX-2 selectivity by 1000- to 10000-fold [33].

Meclofenamic acid modified compounds (Table 10): The replacement of meclofenamic acid carboxylate group with amides enabled to increase the COX-2 selectivity by 900 to 1400-fold (34) [56]. Other compounds were complexed with metals and demonstrated potent and selective COX-2 inhibition [57]. Arylacetic acids (Tables 11, 12): Several analogues of indomethacin [35-37] displayed great potency and selectivity against COX-2. The indomethacin structure modifications included the synthesis of ortho-carborane derivatives (SI>152381, 37d), replacing the Me (R1) of the parent drug with a CF3 group (SI > 375, 37a) or the acid carboxylic moiety by large and complex substituents (SI up to 333000 and IC50 = 0.3 nM for compounds 36r and 36s). SAR stud-

ies on the diclofenac scaffold (Tables 13, 14) indicate that the introduction of halogen atoms (Cl or F) enhance the selectivity. The same effect was observed with an alkyl group in meta-position on the phenyl bearing the COOH moiety [43] (38, 39). Particularly, lumiracoxib (38c) exhibited a high COX-2 potency (IC₅₀ = 7 nM) and selectivity (SI > 1428) explained by its methyl group that enabled a better insertion in the COX-2 active site [43]. However, lumiracoxib was withdrawn from the market in several countries, according to severe liver side effects. Concerning etodolac derived compounds (Table 15), they have shown poor COX-2 selectivity (40b, SI > 45) compared to his molecule parent (40a, SI = 142). Indeed, replacing the oxygen atom of etodolac by a methyl moiety drives to a decrease of COX-2 selectivity [42, 58]. Arylpropionic acids (Tables 16, 17): Flurbiprofen derivatives modified on the phenyl ring attached to the arylpropionic acid (41) presented enhanced COX-2 selectivity and inhibition potency. Some ketoprofen analogues (42b-c) displayed a strong enhancement of selectivity (COX-2 SI > 1100) [59] by replacing the R₃ substituent (N₃ >> SO₂Me > NHCOMe). This can be explained by the insertion and stabilization of this 4-N₃Ph group into the COX-2 side pocket. Oxicams modified analogues (Table 18): (44) enhance COX-2 selectivity by >200-fold with IC₅₀ = 0.06 μM.

3.2.2. COX-2 Selective Agents with Original Structures

The chemical structures of this group of COX-2 inhibitors are significantly different to those of the classical NSAIDs, mainly due to the absence of the typical carboxylic group. Consequently, these new structures present binding mode in the COX-2 active site distinct to those observed with classical NSAIDs, mainly because of the absence of salt bridge between the carboxylic group and Arg 120 and Tyr 355 [42]. Therefore, the selectivity and the affinity of these new compounds for COX-2 are enhanced: these augmentations were mainly explained by their ability to reach the COX-2 additional pocket and establish interactions with its specific residues [42, 60].

Methanesulfonanilide inhibitors (Sulides class, Table 20): This class of COX-2 inhibitors was developed from two potent and selective compounds: nimesulide (46) and NS-398 (47) (COX-2 SI of 25.64 and 164.3 respectively), designed by an isosteric replacement of the carboxylic acid group of NSAIDs by a sulfonamide group. The sulides inhibitors present three main features [32]: a substituent (R = methyl, trifluoromethyl...) on the sulfonyl group; an aryl, a cycloalkyl or even a heterocyclic ether or thioether on position 2; and an electron withdrawing group (EWG) (carboxy, nitro, trifluoromethyl groups...) on position 4. Improvement of the selectivity against COX-2 was obtained with flusulide (51) (SI = 263.15) and its thioether analogue L-745,337 (52) [61, 62] leading to the synthesis of other analogues such as ethylthiazolyl (53) or lactone (54) analogues (COX-2 SI > 1000-2000). The EWG in position 4, particularly a cyano or an acetyl group [63], the acidic hydrogen of the sulfonamide and the carbonyl group of the indanone [61, 62] are essential for COX-2 activity. The acidic character of sulfonamides controls the COX-2 inhibition mechanism: sulfonamides having a pK_a between 3 and 5 acted as competitive inhibitors while those having a pK_a > 7 acted as reducing

drugs enabling conversion of PGG₂ into PGH₂. Compounds with intermediates pK_a (6.5-7) are mixed inhibitors [12, 64]. Sulides compounds present a time-dependent inhibition [65-67] and the binding in the COX-2 active site, with the methyl sulfonamide group stabilized in the COX-2 side pocket [43, 68], induced subtle conformational changes of the enzyme conformation, causing its inactivation [24, 69].

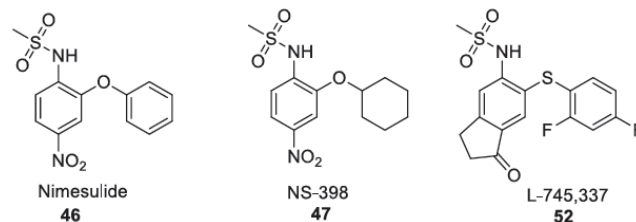


Fig. (3). Some examples of methanesulfonanilide compounds.

Diaryl hetero/carbo-cyclic compounds: The first compounds of this diaryl-substituted heterocycles class, synthesized in the 1960's, were indoxole and oxaprozin. Extensive SAR studies [43] identified the main features responsible of COX-2 selective inhibition: a central ring surrounded by two phenyl groups that must be adjacent in the central scaffold and one of the phenyl rings bearing a 4-sulfonamido or a 4-methylsulfonyl group. The importance of this para-substitution is explained by the binding mode of these compounds in which the sulfonamide or 4-methylsulfonyl group is fitted into the COX-2 specific side pocket and stabilized by a hydrogen bonds network [43]. Between 1970 and 1980, a large number of structures have been developed, differing in size and nature of the central ring [32] and most of these inhibitors display time-dependent inhibition (Fig. 3).

3.2.3. Diaryl-substituted Cycles with a Central 4-membered Ring

These COX-2 inhibitors present a cyclobutene (Table 21) as central ring with a phenyl or a 4-substituted phenyl (on one side, and a methylsulfonylphenyl on the other side). For the phenyl 4-substitution, alkyls, halogens, ketones, and ethene (60) or NOH (62) groups provide highly selective and potent COX-2 inhibitors (SI = 450 and 557.4 respectively, IC₅₀ COX-2 = 0.0012 and 0.061 μM respectively [70]). More recently, the azetidins (Table 22), a four-membered scaffold containing a nitrogen atom and a ketone moiety has been derivated with different groups displaying relatively good selectivity against COX-2 (65). SAR studies [71] indicate that large and lipophilic substituents on the nitrogen atom and para-substitution are favorable to the activity (Fig. 4).

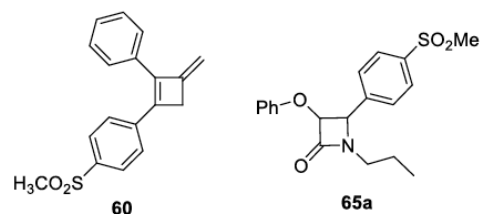


Fig. (4). Some examples of cyclobutene (60) and azetidins (65a) derivatives.

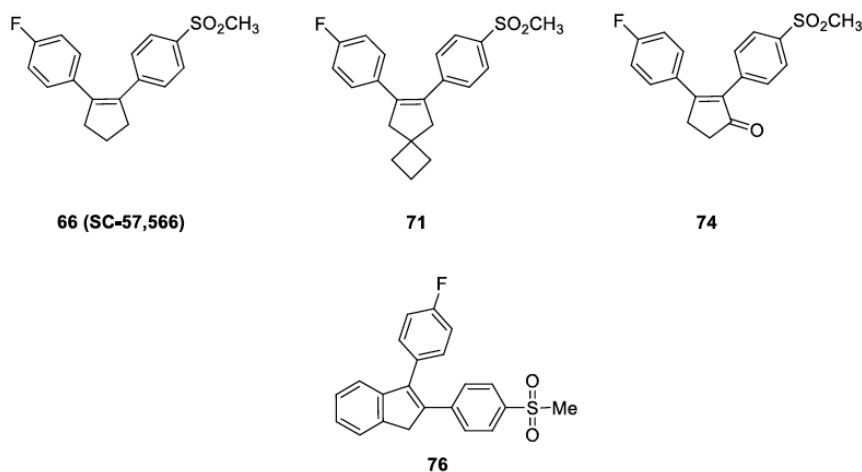


Fig. (5). Some examples of cyclobutene (66, 71, 76) and cyclopentenone (74) derivatives

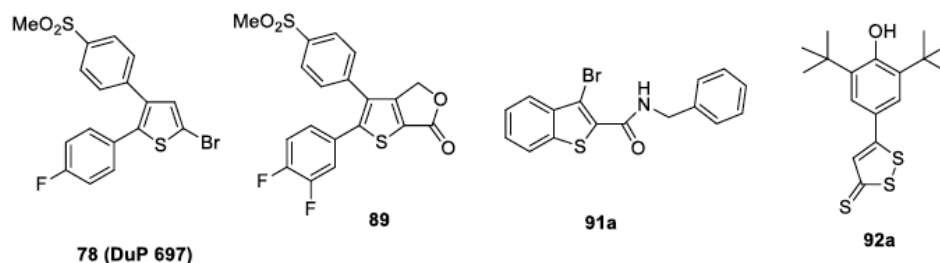


Fig. (6). Some examples of thiophene (78, 88, 91a, 92a) derivatives

3.2.4. Diaryl-substituted Cycles with a Central 5-membered Ring

Cyclopentenes (Tables 23-26) are characterized by a cyclopentene central ring, surrounded by a mono or di-substituted phenyl on one side and a methylsulfonylphenyl or a phenyl sulfonamide on the other side. This class of compounds includes several highly selective and potent COX-2 inhibitors such as SC-57,566 (66) and its chloro analogue (67) (SI of 38461 and 33333 and IC₅₀ (COX-2) = 26 nM and 3 nM respectively). Spirocyclic compounds derived on cyclopentene ring (Table 24, 70-73), cyclopentenone (Table 25, 74, 75) and benzene fused on cyclopentene ring substituted by a methylsulfonylphenyl (Table 26, 76) display great inhibitory potency and selectivity against COX-2 (SI >600 to 25000 and IC₅₀ = 4-62 nM). Cyclopentene spirocyclic compounds with n superior to 2 are associated with a decreased selectivity and potency [32, 72-74]. Table 24, (Fig. 5).

Thiophenes (Tables 27, 28) are mainly substituted in position 4 and 5 of the central ring but others substitutions have also been studied (3,4; 2,4; 2,5; 2,4,5) [32] [75-77]. This group is led by DuP 697 (78) (SI = 120, IC₅₀ = 5 nM) bearing a 4-SO₂MePh (R4), a 4-FPh (R5) and a bromine (R2). Increased selectivity could be obtained by replacing the bromine by an hydrogen (SI >400, IC₅₀ = 0.25 μM, 79) or by fusing the thiophene with cycle ring (Table 29) display (SI = 627, IC₅₀ (COX-2) = 30 nM, 88). 2,4- and 2,5- disubstituted compounds are less potent than 2,3 and 3,4- disubstituted products [58]. For 3, 4-diarylthiophene derivatives, 4-

amino or 4-methyl sulphonyl group is required for selectivity and replacement of 4-fluoro group by 4-OMe or 4-SMe group reverses the selectivity in favor of COX-1 [78]. Recently, benzothiophenes substituted by combination of bromine and benzoyl groups (91) and dithiolethiones (Table 30) substituted by alkyl groups (92) were synthesized and displayed a micromolar activity on COX-2 and a very poor COX-1 inhibition potency [79] (Fig. 6).

Furans and furanones (Tables 31-33): The 3, 4-diaryl-substituted furan derivatives are less active than their thiophene analogues. However, some furanones present an interesting potency on COX-2, such as the rofecoxib (96), a member of the coxibs family and time dependent irreversible COX-2 selective inhibitor (96, SI >750). Rofecoxib is substituted by a Ph (R3) and a 4-SO₂MePh (R5) and was marketed during 5 years before being withdrawn for cardiovascular safety concerns. SAR studies demonstrated that di-substitution of rofecoxib at position 5 with alkyl, alkoxy or cycloalkoxy groups lead to compounds more stable after metabolizations with metabolites preserving the potency and selectivity against COX-2 [58]. DFU (98) and UR-8962 (105) are highly selective and potent compounds (SI >1000 and 4546, IC₅₀ (COX-2) = 41 μM and 22 nM respectively) and were used together with rofecoxib to synthesize new analogues (122, 368, 369). The most potent and selective compound was obtained by introducing a 4-OAc moiety to the phenyl adjacent to the 4-SO₂MePh in the rofecoxib scaffold (368f, IC₅₀ = 1.26 nM, SI = 79865). According to the nature of R2 and R3 groups, furanones and benzofuranones compounds display poor to strong COX-2 inhibition (0-25%

at 10 μM). Some furanones and benzofuranones derived by alkenes give very poor COX-2 inhibitory (SI = 20, **116-121** and **123a**) whereas benzofuranones containing pyrazole scaffold possess a 100 fold COX-2 selectivity (**123b-c**) (Fig. 7).

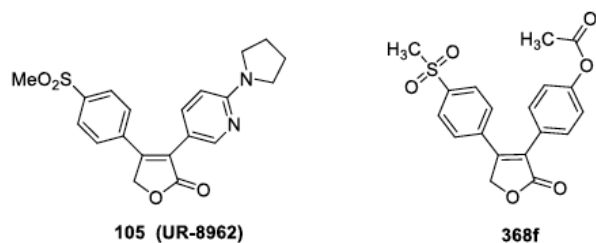


Fig. (7). Some examples of furanone (**105**) derivatives and Rofecoxib analogue (**368f**).

Pyrroles (Tables **34-39**) can present very high selectivity and inhibition potency against COX-2 (SI >1000-6666, IC_{50} = 5 μM -16 nM (**125**, **127**, **134**, **138**, **142**, **147a-e**) (Fig. 8). Minor modifications on size and/or the nature of R1 groups bore by the N-aromatic ring can dramatically affect the selectivity against COX-2 (R1 = trifluorophenyl, SI >10000 (**133**)). Tetrasubstituted pyrroles are the most potent compounds [32], a EWG in position 5 enhancing the potency against COX-2 [78]. Zomepirac (**144** SI = 0.15, IC_{50} = 2 μM), a former commercial drug, inspired the synthesis of numerous analogues, notably by replacing the COOH moiety by a pyridazin-3-one (**148**, SI = 1667, IC_{50} = 0.6 μM). In 2008, Biava *et al.* [80] developed a series of compounds (**147b-e**) exhibiting high potency and selectivity against COX-2 (SI = 900-6600, IC_{50} (COX-2) >0.015-0.040 μM) with an ether group acting as the COOH function of classical NSAIDs. Pyrroles compounds with fused indole ring and bearing a 4-SO₂NH₂Ph or 4-SO₂MePh moiety are also highly selective COX-2 inhibitor (SI >30000-1.6.10⁶, IC_{50} : 0.006-0.3 nM) (**152**, **153**, **159,160**, **162**). SAR studies indicate that replacing the indole N-H hydrogen by a methyl leads to a decreased COX-2 selectivity [81] (**164-166**). More recently, pyrroles derivated by acid, amide or ester functions (**36a-e**) were synthesized with high selectivity and potency [82]. The highly COX-2 potency and selectivity of ester derivatives are explained by the hydrogen bonds and hydrophobic interaction between the ester function and the binding site [83]. Additionally, esters derivatives containing hydroxyl or NO₂ groups increase the ability to create several intramolecular and intermolecular hydrogen bonds to enhance compounds stability and thus their COX-2 selectivity and inhibition potency (SI >700-4000, 149k-n). Pyrrole-2-ones (**167a-c**) and even more pyrrole-2,5-diones (**168a-h**) compounds display

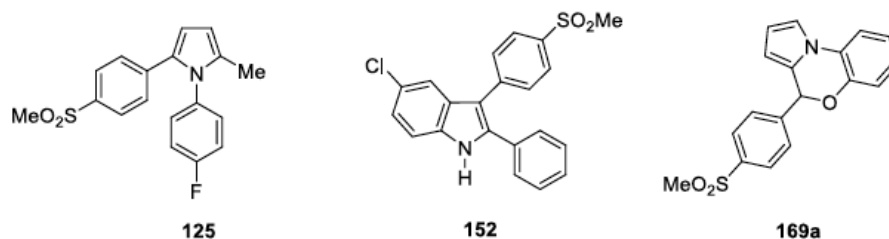


Fig. (8). Some examples of pyrrole derivatives compounds (**125**, **152**, **169a**).

strong COX-2 selectivity (SI >100-1000) [84-87]. Taking into account the differences in binding site volume, series of indoles containing larger substituents (SI = 1000-5000 (**158h-l**, n)), pyrroles and pyrrolidines fused with heterocyclic ring system (SI >100-200, 169) were synthesized and presented high COX-2 selectivity.

Pyrazoles (Tables **40-43**): The first potent COX-2 inhibitor with a pyrazole ring was the SC-58125 (**171**). To avoid SC-58125 metabolic concerns, the 4-fluoro-phenyl group was replaced by a 4-methyl substituent, providing the celecoxib (**172**, SI = 325, IC_{50} (COX-2) = 0.04 μM) [32], a drug currently marketed to treat pain and inflammation mainly in rheumatic affection. Celecoxib displays a three-step mechanism for the inhibition of COX-2 in which the third step is responsible for the selectivity against COX-2 by the formation of a tightly bound between the enzyme and the drug [43]. The sulfonamide moiety of celecoxib is stabilized in the COX-2 specific additional pocket by electrostatic interactions with Asn 192, Leu 352 and Arg 513 [88]. The remaining structure interacts through Van der Waals contacts with the binding site [88, 89] and an electrostatic interaction between the nitrogen atom of the pyrazole ring and the Arg 120 (Fig. 9). Another interesting compound of this family is SC-558 (**173**, SI = 1903, IC_{50} = 9.3 nM) (Fig. 10). Pyrazole compounds with phenylsulfonamide and CF₃ groups display great selectivity against COX-2 (**175**, **180**, **191**, **193-196**, SI >1000, IC_{50} = 3.7-84 nM). Other compounds present a 4-FPh substituent and a 4-SO₂CH₃Ph group rather than a 4-SO₂NH₂Ph group (**198**, **199**, SI = 10000, IC_{50} = 0.10 μM and 41 nM respectively). Additionally, pyrazole fused with aromatic ring also display great COX-2 selectivity, particularly when this aromatic ring is a pyridine (**202**, SI = 33333, IC_{50} = 3 nM). More recently, pyrazole derivatives with large bulkier groups were elaborated and reached great COX-2 selectivity (**200j** and **m**, SI = 450, 1350 respectively) and the substitution with groups favoring hydrogen bonds: 4-SO₂MePh, -(CH₂)₂-ONO₂ and -CH₂OH (**200 q-r**) was favorable to the activity. Associated with heterocycle ring system, compounds display interesting COX-2 inhibitory potency (SI >500, **207c**) thanks to the oxygen atom that makes hydrogen bonds at COX-2 active site. Pyrazolone derivatives (208, SI >100-400, Table 44) and pyrazoline compounds (**209d-e**, % inhibition at 100 μM : 83.69% and 88.43% respectively, Table 45) are also potent COX-2 selective inhibitors [90-92].

Imidazoles (Tables **46-48**) derivatives display great up to 8000 fold COX-2 selectivity (**211**, **224**, **230**, SI > 8000, IC_{50} = 0.08-0.12 μM) (Fig. 11). These molecules are substituted in R4 by a halogenated group (CF₃ or a Cl) and in R1 by a 4-NH₂SO₂Ph or a 4-CH₃SO₂Ph group, essential for the

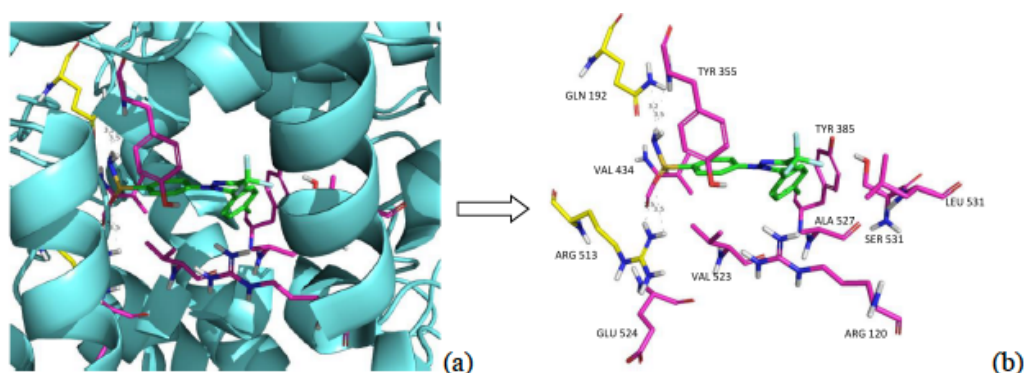


Fig. (9). (a) Celecoxib (green) inserts in the COX-2 active site (cyan). (b) Main interactions between celecoxib and hydrophobic residues (pink) and residues making hydrogen bonds (yellow) (adapted [43]). (The color version of the figure is available in the electronic copy of the article).

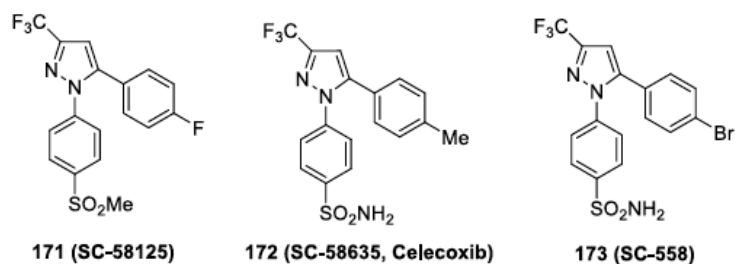


Fig. (10). Some examples of pyrazole derivatives (171, 172, 173).

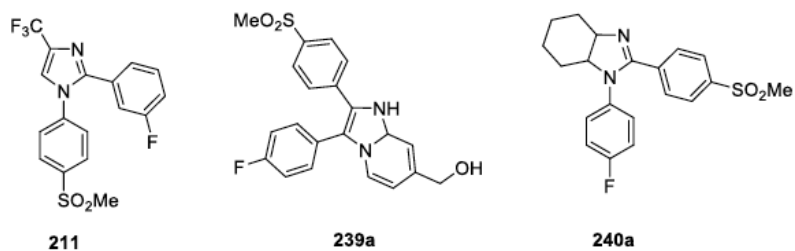


Fig. (11). Some examples of imidazole derivatives (211, 239a, 240a).

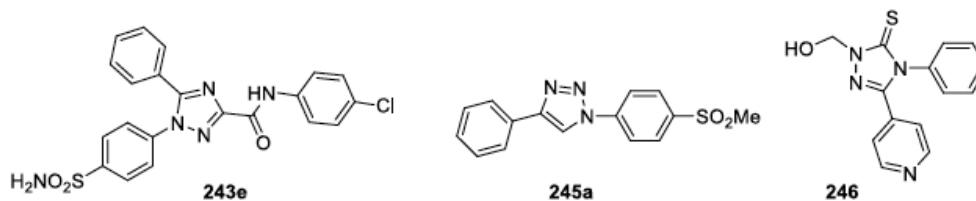


Fig. (12). Some examples of triazole derivatives (243e, 245a, 246).

COX-2 selectivity [93]. Electrophilicity and hydrophobic properties of substituents also play a role in the COX-2 selectivity. For 4,5 diarylimidazoles family, R4 substitutions with SO_2NH_2 or 4- SO_2N_3 or EWG (NO_2 , COOH) are associated with the best results in COX-2 inhibition [94]. For both R4 and R5, if the substituent is a phenyl, small hydrophobic and electronegative groups introduced in para position increase the selectivity while electropositive group in R2 (SO_2 -alkyl > SO -alkyl > S-alkyl) is required for inhibitory potency. Imidazole compounds fused with aromatic rings (Table 48) also display good selectivity (241, 242, SI >625, 715 IC_{50} = 0.16 μM , 0.14 respectively). Recently, imidazole derivatives

substituted on one of the two nitrogen atoms of the central scaffold have been described to display good COX-2 selectivity (SI: 100-200, 237). The same range of selectivity is observed when imidazole is fused with benzene or non-aromatic rings (238-240). Inversely, 1,2-disubstituted imidazoles are poor COX-2 inhibitors [95] (Tables 47, 48).

Triazole compounds (Tables 49-51) COX-2 inhibitory potency and selectivity are mainly dependent of the size and the nature of substituents attached in C-3 and C-4: thiol groups (SH > SMe > SEt) and moieties with electronic properties increase the COX-2 selectivity. The most selective compounds are fused with thiazole rings (SI >1600-4300,

IC₅₀ = 6-20 nM (**248a-e**). Recently, new compounds with high COX-2 selectivity (SI >1000-2000 (**243c-f**)) were obtained, bearing 4-NH₂SO₂Ph and amide groups essential for the activity. Triazole-5(4H)-thione derivatives were evaluated but displayed a poor COX-2 selectivity (SI >4, 246) [96-98] (Fig. 12).

Tetrazole (Table 52) compounds (**249a** and **d**) possess only weak COX-2 inhibition potency (IC₅₀ (COX-2) >30 μM) justifying the lack of interest for this class of compounds. More recently, tetrazoles with a 200-fold COX-2 selectivity were synthesized (**249b, c**) by introducing a mono-substitution in para position of the phenyl group. [99, 100] (Fig. 13).

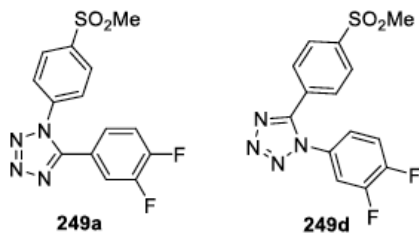


Fig. (13). Some examples of tetrazole derivatives (**249a**, **249d**).

Oxazole (Tables 53-55) compounds were inspired by Oxaprozin (**250**) [101, 102]. Oxazole, isoxazole and oxazoline derivatives (Table 53) possess the stronger COX-2 selectivity with a SI reaching 10000-64500 (**251n**, **252b**, **253a** IC₅₀ = 4nM-97nM) for the most selective. Valdecoxib (**252b**, SI = 28000, IC₅₀ = 5 nM) and its prodrug Parecoxib (**252c**), a commercially available drug, are potent and selective COX-2 inhibitors. Regioisomers of these two compounds display better selectivity against COX-2 (**252e** and **252f** SI >105 and 1113) [103] (Fig. 14). The position 2 of the oxazole ring can support a large variety of substituents without altering the selectivity for COX-2 [78]. Replacing 4-SO₂MePh or 4-SO₂NH₂Ph by a cyclohexyl substituent lead to JTE-522 (**251e**, SI >1176, IC₅₀ = 85 nM) [58, 104-106]. Oxazol-2-one, 1,3-dioxol-2-one and 1,2,5-oxadiazole derivatives (Table 54) are also selective COX-2 inhibitors (254, 255, 257 SI <100, IC₅₀ = 0.06 to >30 μM). SAR studies [107] demon-

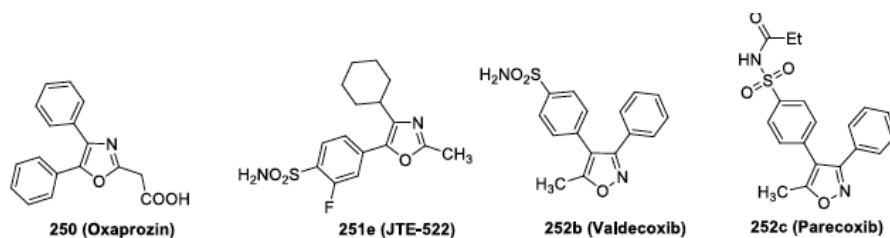


Fig. (14). Some examples of oxazoles derivatives (**250**, **251e**, **252b**, **252c**).

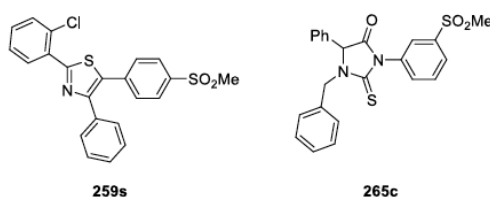


Fig. (15). Some examples of thiazole (**259s**) and thioimidazoline(**265c**) compounds.

strate that a para- SO₂MePh or a para- SO₂NH₂Ph attached to C-3 or C-4 on the central ring is essential for COX-2 selectivity, while unsubstituted C-3 or C-4 positions give selective COX-1 inhibitors. Recent isoxazole (Table 53) and oxadiazole (Table 55) derivatives display quite COX-2 selectivity (SI >100, **252h-j**, **256a-j**). For isoxazole scaffold, small groups in R3 (CH₃, CF₃...) instead of hydrogen bond donor or acceptor groups enhance strongly the COX-2 potency and selectivity (SI>10000, IC₅₀ = 6 nM **252j**).

Benzoxazole derivatives (Table 56) substituted by larger substituents, such as isoxazoles, thiazoles, display good COX-2 selectivity (SI >300-500, **258g-i**, **k-l**). Others compounds, substituted by diaryl groups (**258 c** and **d**) have been synthesized but they have displayed a lower COX-2 selectivity (COX-2 SI <100)

Thiazole, isothiazole, 1,2,3-thiadiazole, dithiolethione, and thiazolidinone derivatives (Tables 57-58) display great COX-2 inhibition and selectivity with a SI reaching 10000 (**259s, t**) whereas thioimidazolinones display interesting inhibition but weak selectivity (**265c**) (Fig. 15). Compounds presenting aromatic rings fused with thiazoles and diathiazoles (Table 59) show important COX-2 selectivity: (SI >3000-4000 and IC₅₀ <20 nM, **266a-e**). Thiazolones series with benzylidene substituents display weak potency against COX-2 [108]. Recently it has been shown that oxazolidinones substituted by triazoles ring system and thiazolidines derivatives (Table 60) present good COX-2 inhibitory potency and selectivity (SI >300-500, IC₅₀(COX-2) ≤ 5.6 μM, **267a-h** except for **267d** the % inhibition at 10 μM is 70.14%).

Hydantoin derivatives (Table 61) bearing a methylsulfonyl function at the para position of the phenyl ring have been described as interesting COX-2 inhibitors. *In vitro* COX-1/COX-2 inhibition studies indicated that hydantoin compounds were selective inhibitors of the COX-2 with IC₅₀ values in the highly potent 0.077 to 0.171 μM range, and COX-2 SI in the 70.2 to > 1298 range (**268a-d**) (Fig. 16). These results also revealed the effect of different alkyl substituents at the N-3 hydantoin ring. A modeling study showed that the most stable enzyme-ligand complex of un-

substituted compound was not docked into the active site of COX-1 justifying the high COX-2 inhibitory activity and selectivity [109].



Fig. (16). Example of hydantoin derivative (268a).

3.2.5. Diaryl-substituted Cycles with a Central 6-membered Ring

Benzene derivatives (Tables 62) substituted in R1 by a 4-SO₂MePh or a 4-SO₂NH₂Ph and in R3 and R4 by halogens, in particular fluorine, are associated with potent and selective COX-2 inhibition (SI >7000-20000, IC₅₀ <15 nM, 269i, 269l-s) (Fig. 17). For naphthalene derivatives (Tables 63) substituted by a SO₂Me in R4 and by a phenyl in R2, lipophilicity and large ortho-substituent on the R2-phenyl ring are critical for COX-2 activity while hydrophobic substituents are essential for COX-2 selectivity [110]. Recently benzene, naphthalene (270), benzoyl (271) derivatives compounds (Tables 63, 64) were developed by incorporating sulfonamides with mono-substituted phenyl (269t-u), alkene groups (trans stereoisomer, 269v-w), or pyridine moiety (271e). Those compounds failed to ameliorate the COX-2 selectivity (SI = 100-200) [111-113].

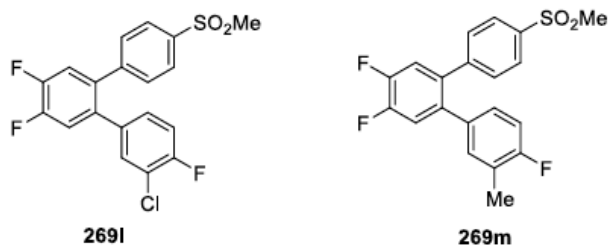


Fig. (17). Some examples of benzene derivatives (269l, 269m).

Pyridines family (Table 65) is led by the marketed drug etoricoxib, metabolized (272 d-g) in less potent and selective structures. SAR studies reveal that a wide range of substituents can be attached to the pyridine ring leading to selective COX-2 inhibitors (SI >800-1100, 272 q-s). Bulkier and larger substituents were added to pyridine and pyridinone derivatives (Table 66), but the resulting compounds have proven to be poor COX-2 selective inhibitors (SI: 20, 272t-ab, 273). Quinolines (SI >300-1200, 274) and tetrahydroquinolinone (SI = 62.3; 97.6, 275 a and b) derivatives (Table 67) present good COX-2 selectivity. The most potent compounds (SI >100-514, IC₅₀ <25 μM, 274h-k) present a COOH moiety and thus a similar binding mode than classical NSAIDs. The COX-2 selectivity varies according to the position of the substituent in the central scaffold (274c-d, 275a-b). More recently, new pyridazinone derivatives (Table 68) bearing various ring systems such as isoxazoles or triazole-5(4H)-

thiones (SI = 10-333, 276a-c) were designed without gain in COX-2 selectivity and inhibition potency [114] (Fig. 18).

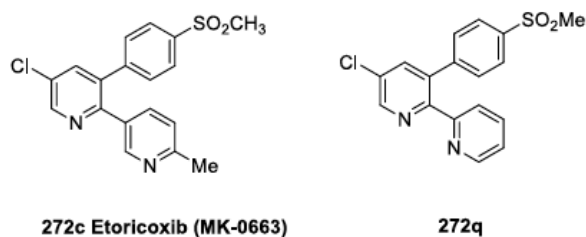


Fig. (18). Some examples of pyridine derivatives (272c, 272q).

Pyrazine, pyridazinone and quinolaxine derivatives (Tables 69-70) display good (SI <300) to great selectivity against COX-2 (SI >500-3333, 279a, b, f). Most of these structures contain a 4-SO₂MePh or a 4-SO₂NH₂Ph substituent. For the pyrazine scaffold, a 4-FPh (278a) increases the selectivity by 2 fold compared to a methyl analogue (278b), and the IC₅₀ by 8 fold. For the pyridazinone derivatives (279), the best compound is substituted by a 1-methoxycyclopropane in R2 and a benzyl in R3 (SI >33333, IC₅₀ (COX-2) = 3 nM, 279a), whereas replacing the R2 by a methoxypropane (279b) decreases the selectivity and the COX-2 inhibition potency. The quinolaxines (280) describe good COX-2 selectivity (SI <100) but poor COX-2 potency (IC₅₀ ~ 40 μM) [115, 116] (Fig. 19).

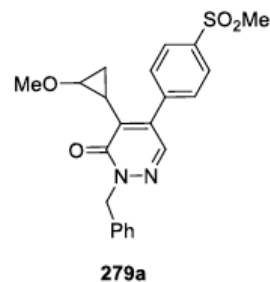


Fig. (19). Example of pyridazinone derivatives (279a).

Pyrimidines (Table 71) compounds can present a very high COX-2 selectivity (>400000 (281 g, i)) (Fig. 20). SAR studies suggested that an electron donating group (-OMe, -OEt) at R2 position increases the potency better than an EWG (281r-t IC₅₀ = 0.3-0.4 nM) and that CH₃SO₂Ph (R4) gives better selectivity than other sulfonyl moieties [117]. Molecules with 4-CH₃SO₂Ph (R4) group associated with a benzylamine moiety (R1) exhibit the higher COX-2 selectivity (281g, i). Recently it has been shown that pyrimidine derivatives bearing 4-SO₂MePh and CF₃ groups are highly selective against COX-2 (SI >1000-350000, 281w-ay) [118].

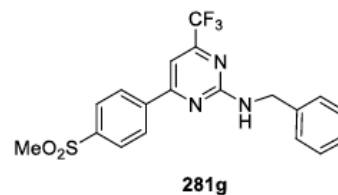


Fig. (20). One example of pyrimidine derivatives (281g).

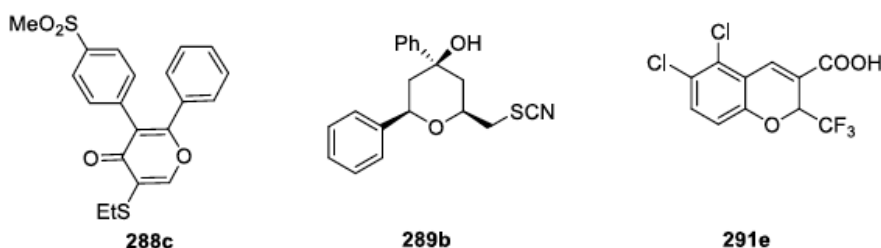


Fig. (21). Some examples of pyrans derivatives (**288c**, **289b**, **291e**)

Pyrimidinone derivatives (Table 72) and pyrimidines or pyrimidinones fused with aromatic rings (Table 73) are poor COX-2 selective inhibitors (**282a-c**, **285**) [119-121], nevertheless certain compounds display good COX-2 selectivity (SI = 400-600, **286a-b**). The substitution of these groups by an amide or a smaller group such as H, Me decreases dramatically the COX-2 selectivity (SI = 2-4.35, **282**, **283**).

Pyran derivatives (Table 74) can display great potency with SI value superior 120000 for the most selective compound (**288c**, IC₅₀ = 3.2 nM). SAR study [122] specify that R3 substituents such as alkyl-, alkoxy-, alkylthio- or para-substituted phenyl orientate the central pyranone ring close to the COX-2 selective side pocket and are thus critical for COX-2 inhibition potency and selectivity (Fig. 21).

Recently, chiral pyrans (Table 75, SI > 1000-41000, **289**, **290**) and benzofurans substituted by the combination of -COOH and CF₃ (Table 76, SI >1000-4700, **291a**, **c-f**, **k**, **l**, and **o**) demonstrate an enhanced COX-2 selectivity, whereas coumarins (Table 77) substituted by pyrazole scaffold display a weak COX-2 selectivity (SI < 20, **292**) [89, 118, 123, 124-127]

Thiazinanone compounds (Table 78-79) display average COX-2 inhibition and selectivity (IC₅₀ = 0.05-0.08 μM, SI >100-200, **293a-c**, **294a-d**). Recent thiazinanone and benzothiazinanone derivatives exhibit similar COX-2 selectivity (SI >200, **293d**, **294a-b**) than the former member of this series [118, 128, 129] (Fig. 22).

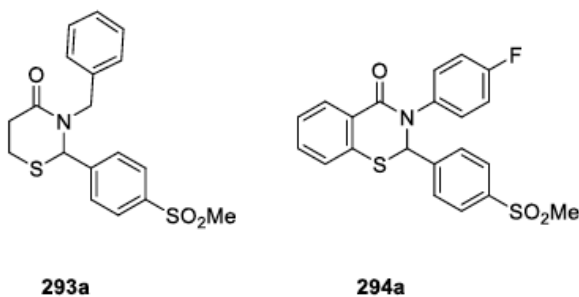


Fig. (22). Some examples of thiazinanone (**293a**) and benzothiazinanone derivatives (**294a**).

1,2 diarylethenes and 1,1,2-triarylethenes compounds (Tables 80, 81) forming the stilbenes family were inspired from the natural product resveratrol (**295a**) a selective COX-1 inhibitor [115]. Various analogues were designed to enhance the COX-2 inhibition and decrease the COX-1 potency. 1,2 diarylethenes derivatives (trans-stilbenes) exhibit good inhibition and selectivity against COX-2 (SI >400-700, IC₅₀ = 1-11 nM, **295b,c**). Acyclic diaryl (E)-olefins are also

potent inhibitors of COX-2 and their selectivity is dependent of the size and length of acyclic substituent attached to C-2 position [130]. 1, 1, 2- triarylethenes derivatives (trans- and cis- stilbenes), synthesized by analogy with the tamoxifen (**297a**) exhibit greater COX-2 selectivity (SI >7000, IC₅₀ = 14 nM, **298a,d**) than 1,2 diarylethenes compounds. Acyclic substituents play a key role in the COX-2 inhibition (**298a** with nBu substituent) for these compounds [131] (Fig. 23).

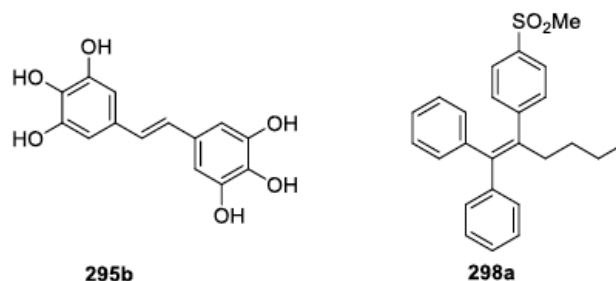


Fig. (23). Examples of 1,2 diarylethenes (**295b**) and 1,1,2-triarylethenes derivatives (**298a**).

Di-tert-butylphenol compounds (Table 82) present a quite good COX-2 inhibition and selectivity (IC₅₀ = 140 and 64 nM for **299d**, **g**, **i** with SI >700). The phenolic OH group surrounded by tert-butyl substituents is essential for COX-2 selectivity. Many of these compounds inhibit both COX and lipoxygenase (LOX) active sites, such as Darbufelone (**299a**) and BF-389 (**299b**) but their COX-2 mechanism of inhibition remains unsolved [132] (Fig. 24).

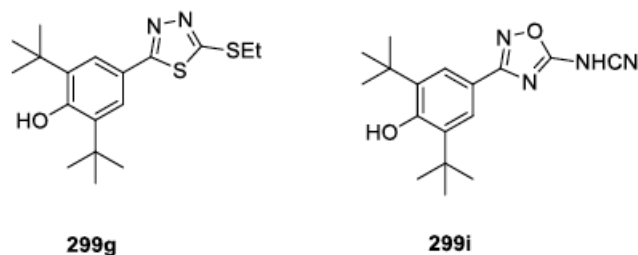


Fig. (24). Some examples of di-tert-butylphenol derivatives (**299g** and **299i**).

Triazines and benzotriazinones (Table 83) are recent compounds, with a poor to good COX-2 selectivity (SI >5-400, **300**, **301**) [133, 134] (Fig. 25).

Piperidine derivatives (Table 84) were recently synthesized and compounds exhibit quite good COX-2 selectivity (SI > 100, **302**). The substitution of the central scaffold nitrogen atom by large groups promote hydrogen bonds and to prevent the insertion in COX-1 binding site [135] (Fig. 26).

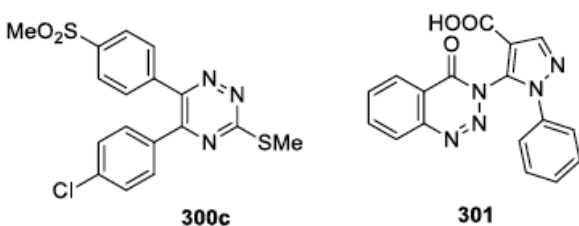


Fig. (25). Some examples of triazine and benzotriazinone derivatives (300c and 301).

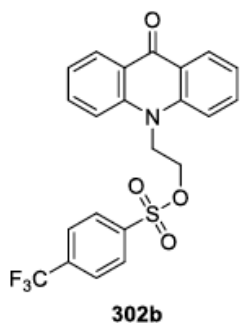


Fig. (26). One example of piperidinone derivative (302b).

3.2.6. Diaryl-substituted Cycles with a Central Acetylene (Table 85)

COX-2 inhibitors display quite good COX-2 inhibition and selectivity (SI >100-300, IC₅₀ = 0.89 μM-50 nM, **303**). Compounds substituted in R2 with 4-MeSO₂Ph are selective COX-2 inhibitors whereas the 3-MeSO₂Ph and 2-MeSO₂Ph substituents lead to respectively mixed COX inhibitors and selective COX-1 inhibitors. Similarly, for the R1 substitution, the best selectivity is obtained with 3-SO₂NH₂Phe group, and the worst with 4-SO₂NH₂Phe [136] (Fig. 27).

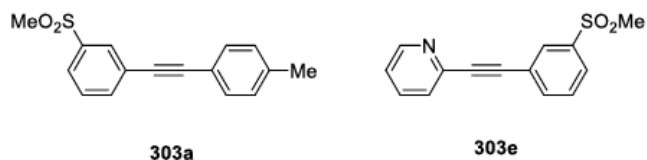


Fig. (27). Examples of acetylene derivatives (303a and 303e).

3.2.7. Others Compounds

Chromene compounds (Tables **86**, **87**) can exhibit high selectivity and inhibition potency against COX-2 (SI >1000, IC₅₀ = 40-110 nM, **304e**, **f**, **k**), and chromen-4-one derivatives present good COX-2 inhibition *in vivo* (**305f** 0.03 μg/mL). Recently, new chromene compounds were prepared with larger substituents such as cyclooctane or mono-substitution of phenyl introduced in α-position of the chromenes ketone and presented poor COX-2 selectivity (SI >2-60, **305a**, **e**). Additionally, smaller groups (H, Me) introduced in R4 display good COX-2 selectivity (SI >200-600, **305b**, **d**)

Chalcone derivatives (Table **88**), display weaker COX-2 potency (SI >100, IC₅₀ <1 μM, **306h**, **j**). The potency and selectivity of these compounds are mainly explained by the insertion of 4-MeSO₂Ph into the COX-2 secondary pocket. For chalcone derivatives the alkene trans stereochemistry

controls the optimal insertion and binding of the compounds into the COX-2 active site [137]. New chalcone derivatives with the phenyl substituted by a piperidyl moiety associated with halogens incorporated on the other phenyl display interesting COX-2 selectivity (**306 d,f,g**) [138] (Fig. 28).

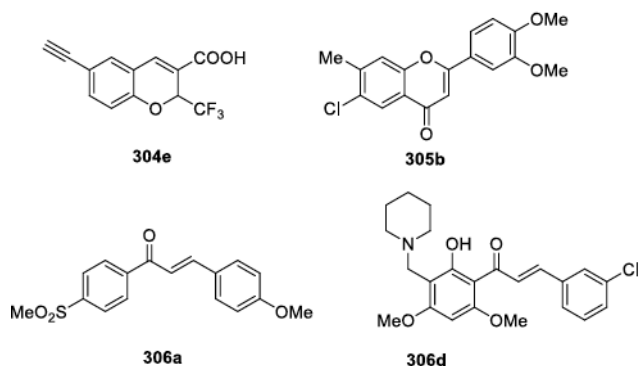


Fig. (28). Examples of chromene (304e and 305b) and chalcone derivatives (306a,d).

Heteroalkenes (Table **89**) are recent and original structures, but the currently compounds of this family show poor COX-2 selectivity (SI > 5-100, **307**, **308**) [118, 139-141] (Fig. 29).

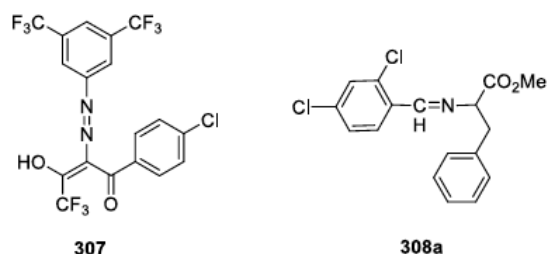
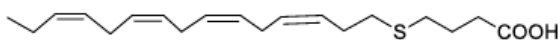


Fig. (29). Examples of heteroalkene derivatives (307 and 308a).

Natural compounds (Tables **90**, **91**) are the starting point in the development of new potent COX-2 selective inhibitors since the National Cancer Institute [142] tested for COX inhibition the 6% of the marketed drug that are natural products. These natural compounds exhibit a great variety of structures: alkaloids, terpenoids, stilbenes, flavonoids, chalcones, phenolic derivatives and most of them are specifically selective COX-1 inhibitors and show poor selectivity against COX-2.

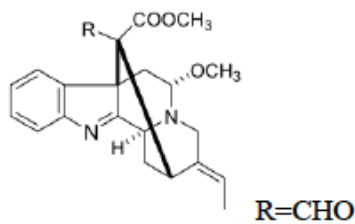
Fatty acids extracted from natural compounds (Table **92**) such as 5-thia-8, 11, 14, 17-eicosatetraenoic acid (**348**) show some inhibitory against COX-2 (SI = 6.7, IC₅₀ = 3.9 μM) (Fig. 30).

Miscellaneous compounds [349-365] (Table **93**), COX-2 selective inhibitors that do not belong to the COX-2 inhibitor classes previously described, display potent COX-2 inhibitory up to SI >3000-125000. Recently, some natural compounds extracted from *Alstonia rupestris* (**330**, **331**, 92-96% of COX-2 inhibition against 37-39% of COX-1 inhibition at 100 μM), Cryptotanshinone (**333**, 31% of COX-2 inhibition with none COX-1 inhibition at 10 μM), Senkyunolide O (**334**, 52% of COX-2 inhibition with none COX-1 inhibition at 10 μM) demonstrated great COX-2 selectivity (Fig. 31).



5-thia-8,11,14,17-eicosatetraenoic acid (348)

Fig. (30). Example of a fatty acid derivative (5-thia-8,11,14,17-eicosatetraenoic acid, 346) from *Plantago major*.

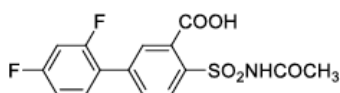


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Fig. (31). Example of a compound isolated (331) from *Alstonia rupestris* displaying a selective inhibition towards COX-2.

Analogues of known drugs have been also studied. Benzenesulfonamides modified (Table 94) by the introduction of an *N*-acetylsulfonamido group have a great COX-2 selectivity (SI >1100, 366, IC₅₀ = 87 nM). Sulindac (367a) and zomepirac (367 d-e) modified compounds (Table 95) exhibit from 300 to 1000-fold better COX-2 selectivity than their parent compounds and a better inhibition potency. The selectivity gain of flusulide analogues (367 b,c) is limited (1-fold better) without alter the potency [58, 143, 144] (Figs. 32, 33).

Analogues of rofecoxib (368, 369, Table 96) and celecoxib (370, Table 97) were synthesized by replacing the sulfoalkyl moiety by a sulfonamide group able to interact through hydrogen bonds with residues of the COX-2 active site [145]. Celecoxib analogues exhibit good anti-inflammatory activity (ED₅₀ = 42.3 mg/kg) which is lower than celecoxib (ED₅₀ = 10.8 mg/kg), but greater than ibuprofen (ED₅₀ = 67.4 mg/kg) and aspirin (ED₅₀ = 128.7 mg/kg) [145] whereas some rofecoxib analogues display similar activity compared to their parent compound. Mono- or di-substitutions by halogens or other functional groups (amines, esters) decrease the COX-2 selectivity compared to the parent structures (368-370) [103, 145-151] (Fig. 7).



366

Fig. (32). Example of a benzenesulfonamide modified compound (366).

4. OTHER ALTERNATIVES THERAPIES TO TREAT INFLAMMATION

To reduce the Gastrointestinal Tract (GI) side effects of COX-2 inhibitors, gastroprotective agents such as antisecretory agents are often used as omeprazole, ranitidine or cimetidine. However, some studies suggest that these compounds neutralize gastric acidity resulting in a decrease of NSAIDs bioavailability [152, 153]. Several strategies were thus developed to obtain COX-2 inhibitors with less GI toxicity.

4.1. CINODS (COX Inhibitor-Nitric Oxide Donors) and H₂S Releasing Compounds

Nitric oxide and hydrogen sulfide present protective effects in gastric mucosa. NSAIDs able to release NO and H₂S were thus developed to decrease the NSAIDs GI side effects. Several NSAIDs (diclofenac, aspirin, ibuprofen...) were coupled with NO or H₂S moiety (compounds 371, 372 see Tables 98, 99) and the resulting compounds present better GI tolerability than classical selective COX-2 inhibitors [154] (Fig. 34). Cyclooxygenase Inhibitor-Nitric Oxide Donors (CINODS) [155] were synthesized by modifying coxibs with introduction of a NO-donor group and displayed a reduced cardiovascular risk compared to selective COX-2 compounds [156-164]. Since NO and H₂S act in concert for the maintenance of gastric mucosa, dual H₂S-NO releasing compounds were also elaborated [156, 165] (compounds 372 g-j, see Table 99) (Fig. 35).

4.2. Dual COX-2/5-LOX Compounds

Since leukotrienes participate in gastric mucosa injuries and inhibitors of 5-LOX demonstrated their protective effect in gastric mucosa [156], dual COX-2/5-LOX inhibitors were developed. This class of compounds present enhance anti-inflammatory activity [166] and good inhibition potency for the 2 active sites (IC₅₀ (μM)/ CI-986 (373a): 0.86/5.7, Lico-felone (373b): 0.37/0.21, Darbufelone (373c): 0.48/0.77). (compounds 373, see Table 100) (Fig. 36).

4.3. Zwitterionic Phospholipids Compounds

Combination of zwitterionic phospholipids like DPPC (374, Fig. 37) and NSAIDs enables to prevent the interaction of NSAIDs with the mucosa avoiding GI side effects since the interaction with NSAIDs decreases the protective ability of the mucosa. [167]. Some zwitterionic phospholipids compounds associated with NSAIDs have been developed: phosphatidylcholine-associated with aspirin (PL2200), phosphatidylcholine-associated with ibuprofen (PL1100) [165].

The process of inflammation is very complex, and several approaches to reduce and relieve inflammation exist. Current trend is to develop molecules that act on one of the multiple signaling pathways of inflammation: NFκB, MAPKs, Lipopolysaccharides (LPS), Microsomal Prostaglandin E2 Synthase Inhibitors (mPGHES-1), TNFα. In the literature, a great numbers of papers and reviews refer to these kinds of inhibitors [165, 168].

5. ADVERSE EFFECTS OF COX INHIBITORS

Both selective and non-selective COX-2 inhibitors are associated with adverse side effects affecting particularly the gastro-intestinal and cardiovascular systems (Table B).

5.1. Gastrointestinal Tract

GI injuries caused by COX inhibition, is one of the major side effects of anti-inflammatory drugs leading to hospitalizations and deaths. These side effects range from diarrhea, nausea, abdominal pain and flatulence to severe complications such as perforations, ulcerations, bleeding and obstruction

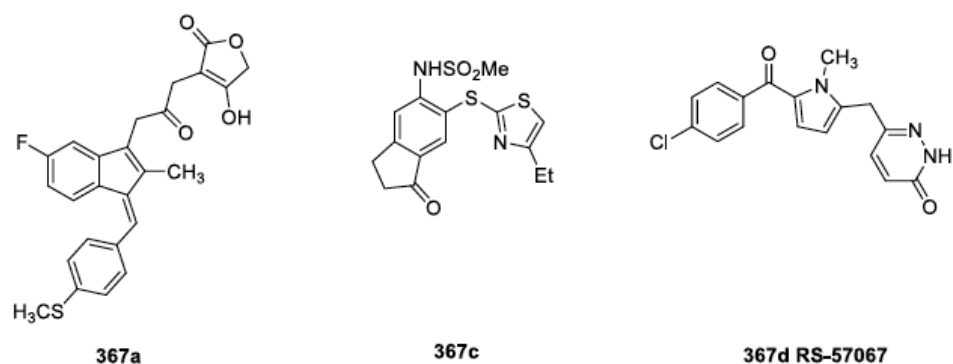


Fig. (33). Examples of sulindac (**367a**), fluosulide (**367c**) and zomepirac (**367d RS-57067**) modified compounds.

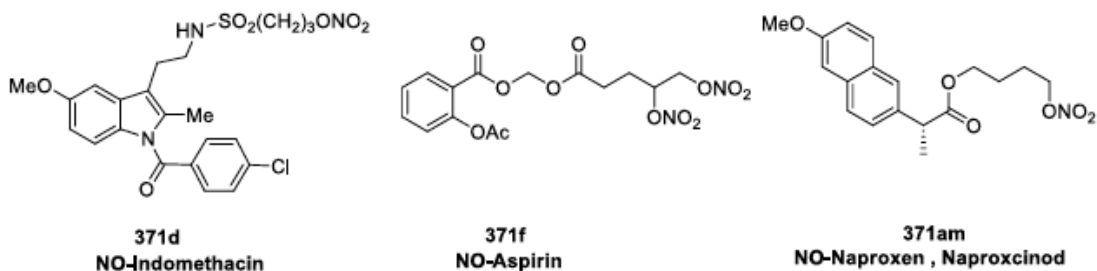


Fig. (34). Some examples of CINODs derived from NSAIDs (**371d**, **371f**, **371a**)

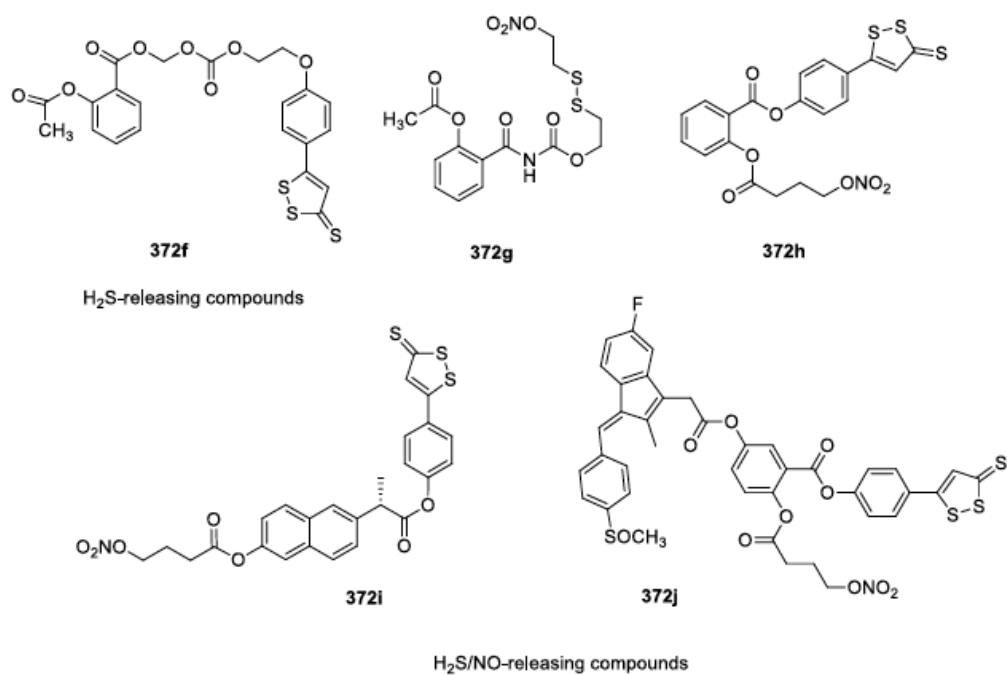


Fig. (35). Some examples of H₂S-(**372f**) and H₂S/NO-releasing (**372 g-j**) compounds.

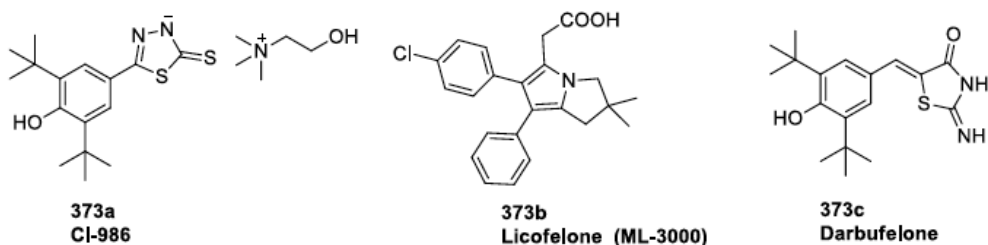
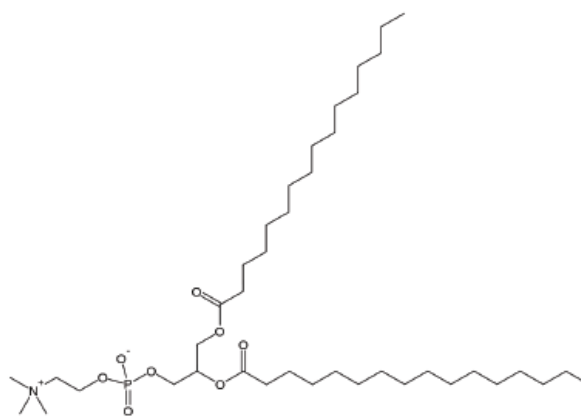


Fig. (36). Examples of some COX-2/5-LOX (**373a-c**) compounds.



1,2-dipalmitoylphosphatidylcholine (DPPC)(374)

Fig. (37). Zwitterionic phospholipids compound

[161]. These GI adverse effects can be explained mainly by two features. The first one is the acidic character of the classical NSAIDs [169]: these inhibitors are present in a non-ionized state in the highly acidic medium of the stomach, facilitating their migration through the gastric mucosa barrier where they are metabolized. Their ionized metabolites are responsible of several injuries in GI [170, 171]. The second risk factor for GI side effects is the inhibition of the synthesis of protective prostaglandins associated with the COX inhibition. For a long time, only the COX-1 inhibition was held responsible for the GI damages, through the inhibition of the synthesis of TXA₂. However, inhibition of COX-2 induces a delay in healing and an exacerbation of inflammation on the GI tract [11]. Furthermore, COX-2 assists COX-1 in the maintenance and the protection of gastric mucosa integrity [10, 172]. Experiences *in vivo* have demonstrated that selective inhibitors that only inhibit one COX isoform (either COX-1 or COX-2), are not associated with GI damages [156, 173]. However, these findings and the involvement of COX-2 inhibition in GI damages remain controversial [164, 174]. Despite the relative low rate of GI side effects associated with selective COX-2 inhibitors such as coxibs in several clinical studies [160, 161, 175, 176], efforts are still made to enhance GI tolerability of AINS. The current solutions include the use of NSAIDs or coxibs in combination with proton-pump inhibitor [177, 178], and the development of new drugs with NO or H₂S releasing parts added to the structure of known NSAIDs.

5.2. Cardiovascular Tract (CV)

The second most important side effects of selective COX-2 inhibitors are their adverse cardiovascular effects as illustrated by several clinical studies (VIGOR, CLASS, TARGET...)[161]. These side effects are the consequence of an over aggregation of platelets, obstructing arterials and vessels, [179] and can result in myocardial infarction, atherosclerosis, chronic heart failure and hypertension [177, 180-183]. They led to the withdrawal from the market of several coxibs, notably rofecoxib in 2004 and valdecoxib in 2005 [155, 184]. The CV adverse effects were first associated with the disequilibrium of the balance between the COX-1 TXA₂ prothrombotic effects and the COX-2 PGI₂ antithrombotic effects [177, 179, 184]. However, in 2013, Mitchell's group [185] found that COX-1 controls the synthesis of PGI₂ in

CV system and is responsible of CV events. The CV side effects of the coxibs were then linked to their sulfone moiety which oxidation releases free radicals [186]. To counterpart the CV events, several propositions have been made: the use of meloxicam that presents better GI and CV profiles; the use of NO-NSAIDs; the combination with low dose of aspirin to reduce the synthesis of platelets [29, 182], or a proton pump inhibitor, and a change of lifestyle for patients susceptible to develop CV events [182].

5.3. Kidney

About 1 to 5% of patients develop renal side effects due to the use of NSAIDs [178]. PGs inhibition by COX-2 selective or non-selective NSAIDs induce a decrease in water, sodium and potassium excretion, a decrease of the glomerular filtration rate, and changes in the release of renin, resulting in hypertension, edema, renal insufficiency and failure [161, 180, 186-190].

5.4. Reproductive Tract

PG such as PGE₂ and PGF_{2α} are involved in all stages of the pregnancy and in reproductive process [191] and PGE₂ inhibition prevents infertility [180]. The PGs synthesized by COX-1 appear to be essential for survival of fetus during the pregnancy and COX-1 inhibition can result in premature child death [2, 172]. The PGs synthesized by COX-2 act particularly in the delivery process [191]. Non-selective NSAIDs, such as indomethacin, associated with delay in the delivery and high child mortality [61] should be avoided during the pregnancy. COX-2 selective drugs may lead to failures in ovulation, fertilization, implantation [11] but can be useful in reducing preterm labor [49, 155, 192] and to treat endometriosis [193].

5.5. Central Nervous System (CNS)

COX-1 and COX-2 are expressed in the CNS and a large range of adverse effects affecting the CNS can be observed with the use of NSAIDs, from headaches and confusion to the aggravation of psychiatric illness such as epilepsy and Parkinson disease [194]. However, studies suggested that NSAIDs could reduce cerebral edema to prevent cerebral cardiovascular accident and reduce neuronal death [195].

5.6. Respiratory Tract

COX-2 seems to be implied in the pathogenesis of asthma based on its over-expression in asthmatic patients [196, 197] by promoting inflammation and airways constriction [180]. Classical NSAIDs may aggravate asthma by inducing bronchoconstriction and edema, whereas selective COX-2 inhibitors can be used to reduce asthma [49, 171].

5.7. Other Organs

All NSAIDs can damage the liver, resulting in asymptomatic transaminase elevation to clinical hepatitis [194] and more particularly sulindac, diclofenac and aspirin [198]. Skin allergic reactions can be observed with classical NSAIDs and selective drugs: urticaria, alopecia, photosensitivity, erythema multiform, Stevens-Johnson syndrome and rarely necrosis of epidermal [188, 199]. Other events have been also observed such as in bone healing, dizziness, headache, flu symptoms, fatigue and insomnia [161].

The prescription of NSAIDs, and particularly the determination of the therapeutic dose and the duration of the treatment, must be adapted to each patient susceptibility to minimize adverse events [176, 178].

6. COX INHIBITORS: FUTURE THERAPIES FOR CANCERS AND NEURONAL DISEASES

COX inhibitors were developed to treat inflammation and can thus be used in a large number of inflammatory diseases. However, for more than twenty years, the use of COX inhibitors to treat cancers and neuronal diseases such as Alzheimer's and Parkinson's is investigated.

6.1. Cancer

The involvement and the over-expression of COX-2 in cancers have been reported [180]. Evidence suggests that NSAIDs tumor inhibition could be mediated by their ability to inhibit angiogenesis [11, 180] and to restore apoptosis in APC-deficient cells [200, 201]. However, the knowledge of the anti-oncogenic mechanism remains uncompleted and the involvement of LOX and COX- independent pathways were also highlighted [195]. NSAIDs could be used to prevent and to participate in tumor decrease in several cancers [202-204]. The COX-2 over-expression in colorectal cancer reaches 80% [180]. Several clinical studies revealed that NSAIDs could be used for the prevention (long-term use of aspirin [157]) and treatment of colon cancer (SC-58125 [157], celecoxib and rofecoxib [205]). In animal models, other NSAIDs like piroxicam, indomethacin, sulindac, ibuprofen or ketoprofen decrease 40-50% the risk to develop the colon cancer [202, 205, 206]. Similarly, in familial adenomatous polyposis (FAP), celecoxib [11, 180, 205] or the combination of aspirin and sulindac [11] inhibits significantly the growth of adenomatous polyps and leads to the regression of existing polyps [11, 167, 180, 205, 207]. Several studies described the potency of aspirin and NSAIDs in the prevention of esophageal cancer [11, 180, 208, 209]. Coxibs and particularly celecoxib are used to prevent tobacco-related cancers [157, 210] or to reduce tumoral growth [11, 180]. Celecoxib and its derivatives are efficient antiproliferative agents in prostate and breast cancer [202, 208, 211]. Nimesulide is used in the treatment of breast cancer [212] where COX-2 is overexpressed up to 40% [213].

Table B. Summary of some adverse effects associated with the use of COX-2 selective inhibitors (adapted Puhlmann *et al.* [155]).

Localisation	Adverse effects
Cardiovascular	Myocardial infarction Thrombosis events, stroke Hypertension
Renal	Reduced glomerular filtration rate and renal plasma flow Sodium retention Acute interstitial nephritis Acute renal failure
Gastrointestinal	Inhibition of ulcer healing Hepatic complications
Regenerative	Retarded wound healing Slowing of fracture healing Retarded ligament healing
Neuropsychiatric	Depression Confusion and hallucination Somnolence or insomnia Abnormal thinking
Reproductive	Delayed follicular rupture Reduction of preterm labour
Cutaneous	Hypersensitivity reactions Fatal skin reactions Allergy

6.2. Alzheimer's Disease (AD)

Several epidemiological studies suggest an association between the long term use of NSAIDs and a reduced risk of AD [214-216]. However, this protection differs according to the NSAIDs used. Some NSAIDs such as ibuprofen and naproxen demonstrated significantly reduced AD risk [216]. However, rofecoxib in a 12-18 month clinical trial of in patients with mild cognitive impairment showed on the contrary no protective effect on AD development and was even suspected to increase the rate of conversion to AD [217]. In fact, several factors seem to be essential for NSAIDs protection effect against AD: early NSAIDs chronic exposition, earlier onset subjects, ApoE4 carriers, a COX-1 inhibition potency... [218]. The initial hypothesis that the COX-2 inhibition could be responsible for a reduced neuro-inflammation and thus the protective effect is now refuted but the complete mechanisms of amyloid accumulation reduction are still unclear.

6.3. Parkinson's Disease (PD)

Patients suffering from PD present an over-expression of COX-2 in the brain [202]. Several evidences indicate that COX-2 is involved in the pathogenesis of PD and could be an interesting target to delay the apparition of PD or to stop its progression [219]. Rofecoxib and Parecoxib are notably considered as neuroprotective agents [103, 220].

CONCLUSION

Since its discovery in 1990's, COX-2 enzyme has aroused the development of a great number of selective inhibitors with chemical diversity, different in inhibitory potency, contrasting in their ability to reduce side effects and enhancing tolerability compared to classical NSAIDs. Recently, an important effort has been focused on COX-2 selective drugs as future therapies for a wide kind of cancers and neuronal diseases. Currently, new researches have turned toward nanotechnology where selective drugs will be associated with nanoparticles.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

All authors contributed to the drafting and revision of the article and approved the final version. The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers web site along with the published article. Tables 1-99 are mentioned in the supplementary material.

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