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

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REVIEW ARTICLE

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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].

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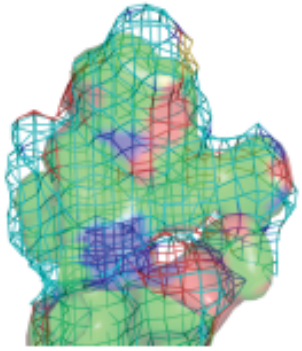


Fig. (1). Representation of COX.

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 inductible, 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

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…)

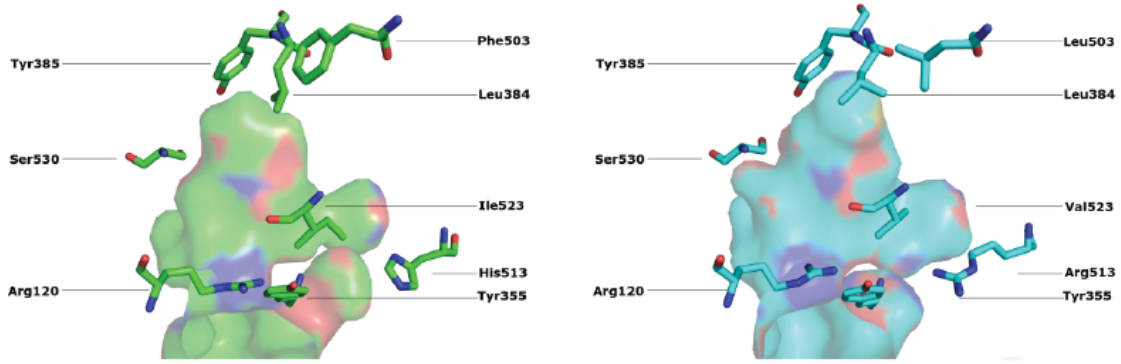


Fig. (2). Active sites of COX-1 (left) and COX-2 (right)/ picture from Pymol.

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 improve 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-carbaborane 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 (N_3 >> SO_2Me > NHCOMe). This can be explained by the insertion and stabilization of this 4-N_3Ph group into the COX-2 side pocket. Oxicams modified analogues (Table **18**): (**44**) enhance COX-2 selectivity by >200-fold with IC_{50} = 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 fluosulide (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 pKa between 3 and 5 acted as competitive inhibitors while those having a pKa > 7 acted as reducing drugs enabling conversion of PGG2 into PGH2. Compounds with intermediates pKa (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].

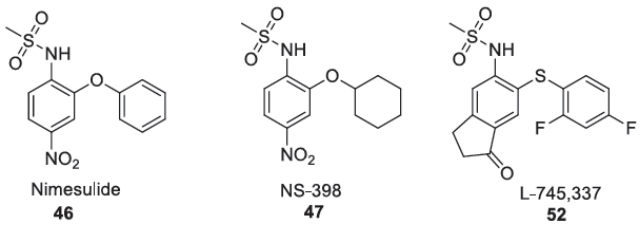


Fig. (3). Some examples of methanesulfonanilide compounds.

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 azetidin (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**).

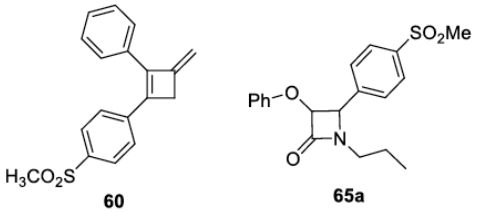


Fig. (4). Some examples of cyclobutene (**60**) and azetidin (**65a**) derivatives.

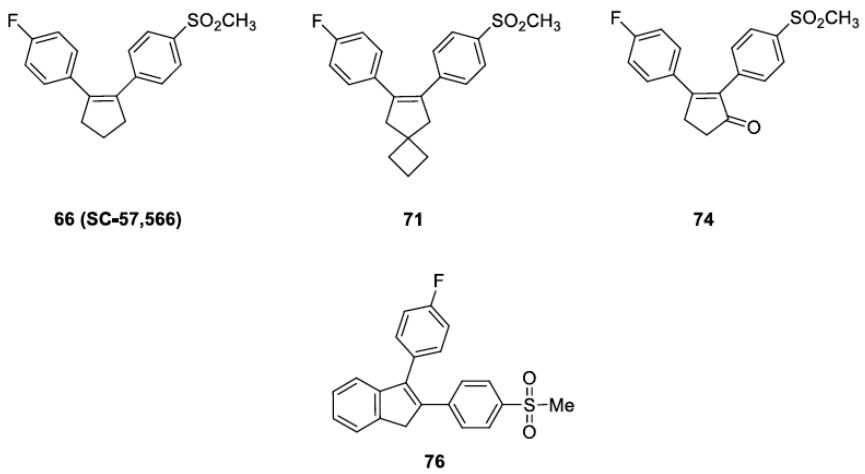


Fig. (5). Some examples of cyclobutene (**66**, **71**, **76**) and cyclopentenone (**74**) derivatives

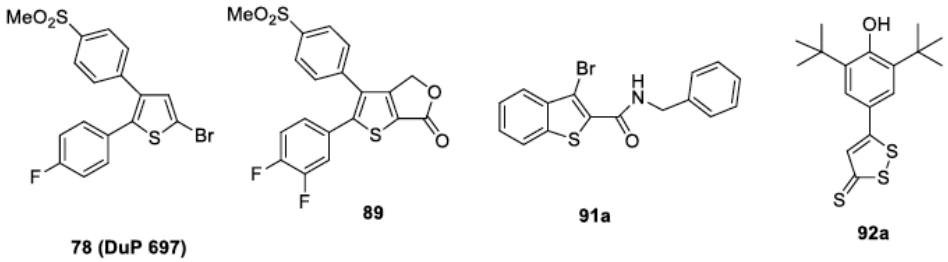


Fig. (6). Some examples of thiophene (**78**, **88**, **91a, 92a**) derivatives

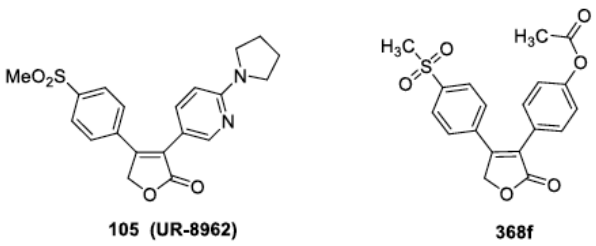
3.2.4. Diaryl-substituted Cycles with a Central 5-membered Ring

Cyclopentenes (Tables **23-26**) are characterized by a cyclopentene central ring, surrounded by a mono or disubstituted 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 derivated on cyclopentene ring (Table **24**, 70-73), cyclopentenone (Table **25**, 74, 75) and benzene fused on cyclopentene ring substituted by a methylsulphonylphenyl (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-SO_2MePh (R5) and was marketed during 5 years before being withdrawn for cardiovascular safety concerns. SAR studies demonstrated that disubstitution 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, IC_{50} (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-SO_2MePh in the rofecoxib scaffold (**368f**, IC_{50} = 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**).



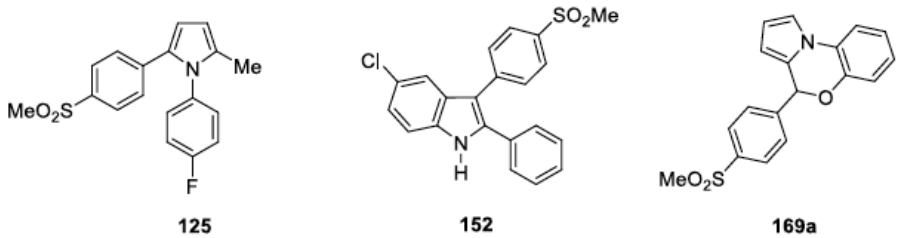
105 (UR-8962) 368f

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, IC50 = 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-SO_2NH_2Ph or 4-SO_2MePh moiety are also highly selective COX-2 inhibitor (SI >30000-1.6.10^6, 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 NO_2 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 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-SO_2CH_3Ph group rather than a 4-SO_2NH_2Ph 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-SO_2MePh, -$(CH_2)_2$-ONO_2 and -CH_2OH (**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, IC50= 0.08-0.12 μM) (Fig. **11**). These molecules are substituted in R4 by a halogenated group (CF_3 or a Cl) and in R1 by a 4-NH_2SO_2Ph or a 4-CH_3SO_2Ph group, essential for the



125 152 169a

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

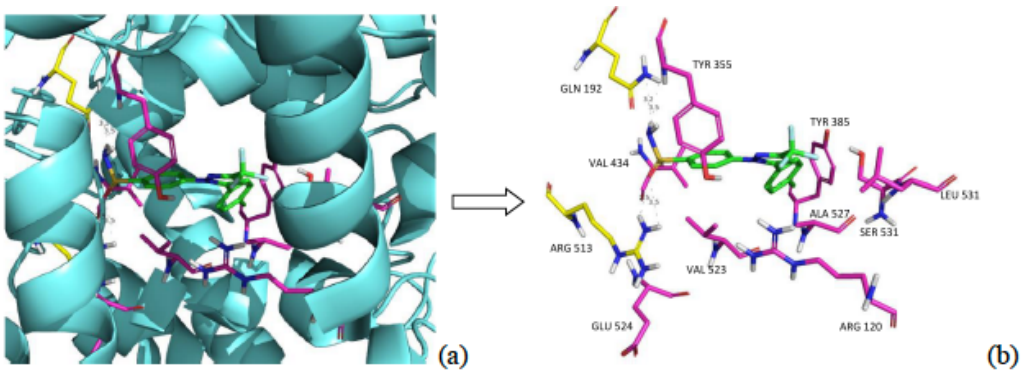


Fig. (9). (**a**) Celecoxib (green) inserts in the COX-2 active site (cyan). (**b**) Main interactions between celecoxib and hydrophobic residues (pink) and residues making hydrogen bonds (yellow) (adapted [43]). *(The color version of the figure is available in the electronic copy of the article).*

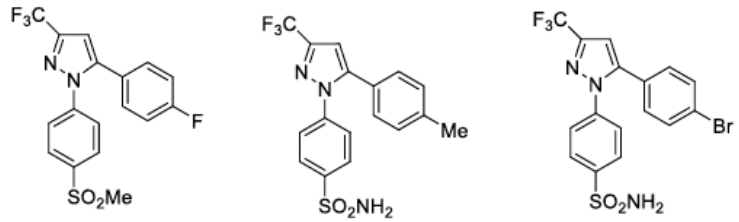


Fig. (10). Some examples of pyrazole derivatives (**171, 172, 173**).

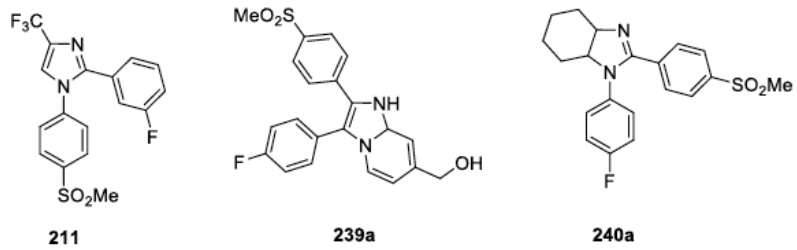


Fig. (11). Some examples of imidazole derivatives (**211**, **239a**, **240a**).

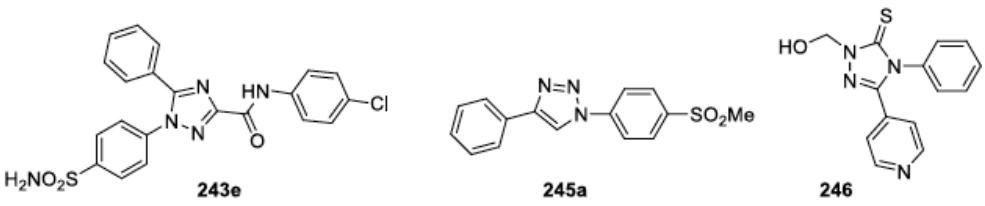


Fig. (12). Some examples of triazole derivatives (**243e, 245a, 246).**

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 imizadole 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-NH_2SO_2Ph 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 (IC_{50} (COX-2) >30μM) 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**).

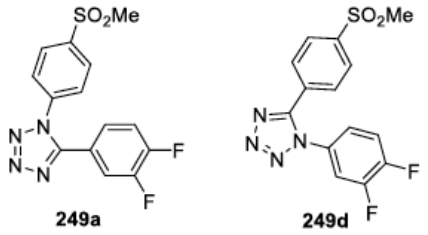


Fig. (13). Some examples of tetrazole derivatives (**249a**, **249d**).

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** IC_{50} = 4nM-97nM) for the most selective. Valdecoxib (**252b**, SI = 28000, IC_{50} = 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-SO_2MePh or 4-SO_2NH_2Ph by a cyclohexyl substituent lead to JTE-522 (**251e**, SI >1176, IC_{50} = 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, IC_{50} = 0.06 to >30 uM). SAR studies [107] demonstrate that a para- SO2MePh or a para- SO_2NH_2Ph 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 (CH_3, CF_3…) instead of hydrogen bond donor or acceptor groups enhance strongly the COX-2 potency and selectivity (SI>10000, IC_{50} = 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 synthetized 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 IC_{50} <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, IC_{50}(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-

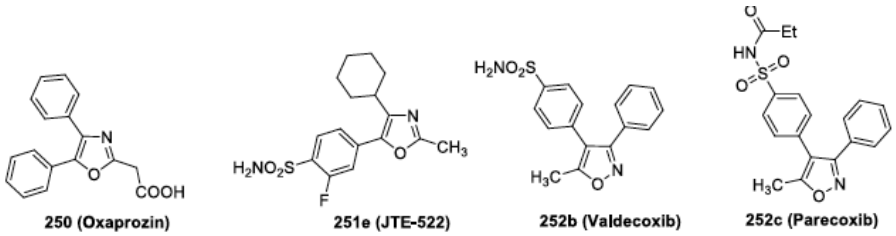


Fig. (14). Some examples of oxazoles derivatives (**250**, **251e, 252b, 252c**).

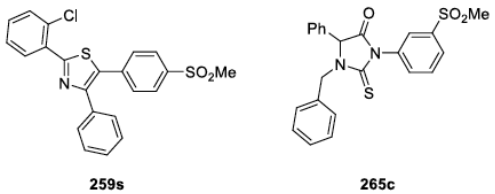
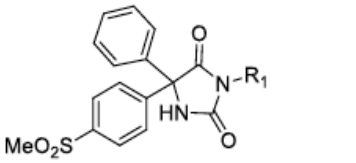


Fig. (15). Some examples of thiazole (**259s**) and thioimidazoline(**265c**) compounds.

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

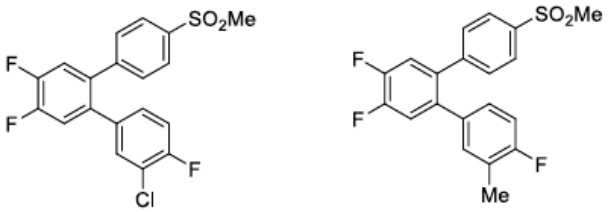


268a–d

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

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

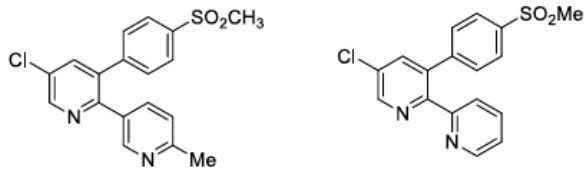
Benzene derivatives (Tables **62**) substituted in R1 by a 4-SO_2MePh or a 4-SO_2NH_2Ph and in R3 and R4 by halogens, in particular fluorine, are associated with potent and selective COX-2 inhibition (SI >7000-20000, IC_{50} <15 nM, 269i, **269l-s**) (Fig. **17**). For naphathalene derivatives (Tables **63**) substituted by a SO_2Me 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].



269l **269m**

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

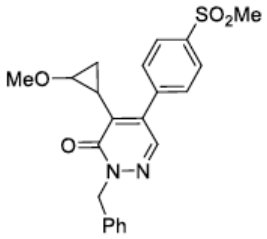
Pyridines family (Table **65**) is led by the marketed drug etoricoxib, metabolized (**272 d-g**) in less potent and selective structures. SAR studies reveal that a wide range of substituents can be attached to the pyridine ring leading to selective COX-2 inhibitors (SI >800-1100, **272 q-s**). Bulkier 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**).



272c Etoricoxib (MK-0663) **272q**

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

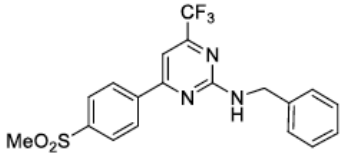
Pyrazine, pyridazinone and quinolaxine derivatives (Tables **69-70**) display good (SI <300) to great selectivity against COX-2 (SI >500-3333, **279a, b, f**). Most of these structures contain a 4-SO_2MePh or a 4-SO_2NH_2Ph substituent. For the pyrazine scaffold, a 4-FPh (**278a**) increases the selectivity 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, IC_{50} (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**).



279a

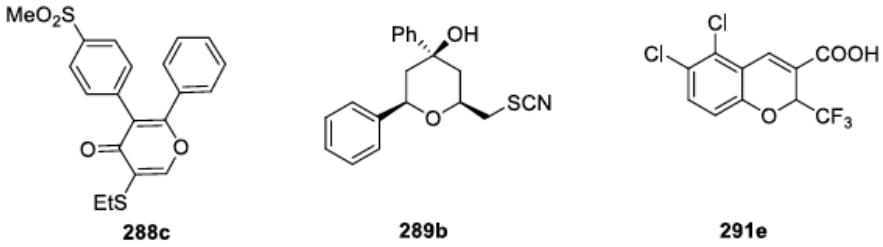
Fig. (19). Example of pyridazinone derivatives (**279a**).

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 IC_{50} = 0.3-0.4 nM) and that CH_3SO_2Ph (R4) gives better selectivity than other sulfonyl moieties [117]. Molecules with 4- CH_3SO_2Ph (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-SO_2MePh and CF_3 groups are highly selective against COX-2 (SI >1000-350000, 281w-ay) [118].



281g

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



288c **289b** **291e**

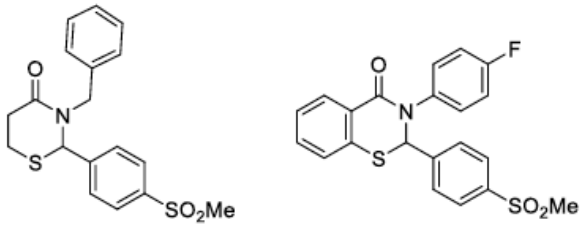
Fig. (21). Some examples of pyrans derivatives (**288c, 289b, 291e**)

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, IC_{50} = 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 CF_3 (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]

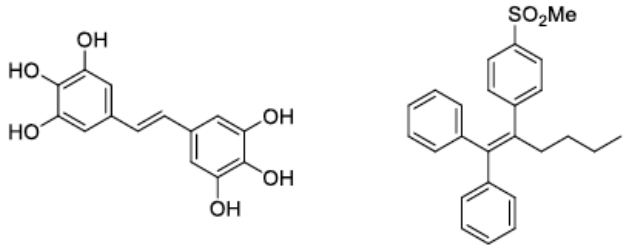
Thiazinanone compounds (Table **78-79**) display average COX-2 inhibition and selectivity (IC_{50} = 0.05-0.08 μM, SI >100-200, **293a-c, 294a-d**). Recent thiazinanone and benzothiazinanone derivatives exhibit similar COX-2 selectivity (SI >200, **293d, 294a-b**) than the former member of this series [118, 128, 129] (Fig. **22**).



293a **294a**

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

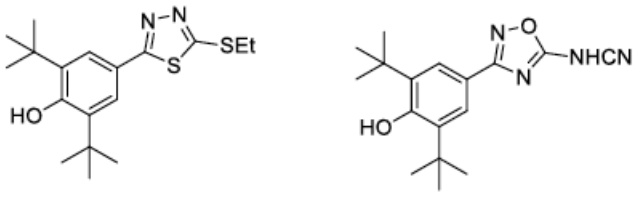
1,2 diarylethenes and 1,1,2-triarylethenes compounds (Tables **80, 81**) forming the stilbenes family were inspired from the natural product resveratrol (**295a**) a selective COX-1 inhibitor [115]. Various analogues were designed to enhance the COX-2 inhibition and decrease the COX-1 potency. 1,2 diarylethenes derivatives (trans-stilbenes) exhibit good inhibition and selectivity against COX-2 (SI >400-700, IC_{50} = 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, IC_{50} = 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**).



295b **298a**

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 (IC_{50} = 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**).



299g **299i**

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**).

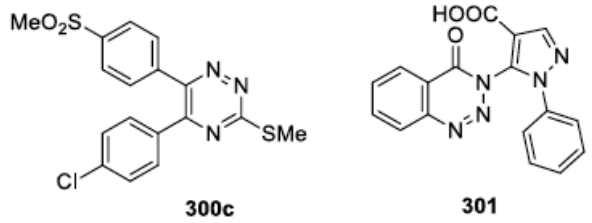


Fig. (25). Some examples of triazine and benzotriazinone derivatives (**300c** and **301**).

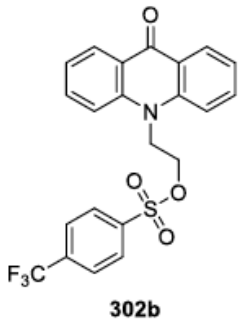


Fig. (26). One example of piperidinone derivative (**302b**).

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, IC_{50} = 0.89 µM-50 nM, **303**). Compounds substituted in R2 with 4-$MeSO_2$Ph are selective COX-2 inhibitors whereas the 3-$MeSO_2$Ph and 2-$MeSO_2$Ph substituents lead to respectively mixed COX inhibitors and selective COX-1 inhibitors Similarly, for the R1 substitution, the best selectivity is obtained with 3-SO_2NH_2Phe group, and the worst with 4-SO_2NH_2Phe [136] (Fig. **27**).

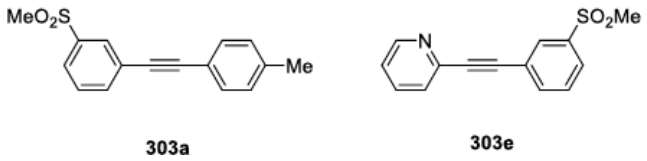


Fig. (27). Examples of acetylene derivatives (**303a** and **303e**).

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, IC_{50} <1µM, **306h,j**). The potency and selectivity of these compounds are mainly explained by the insertion of 4-$MeSO_2$Ph 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**).

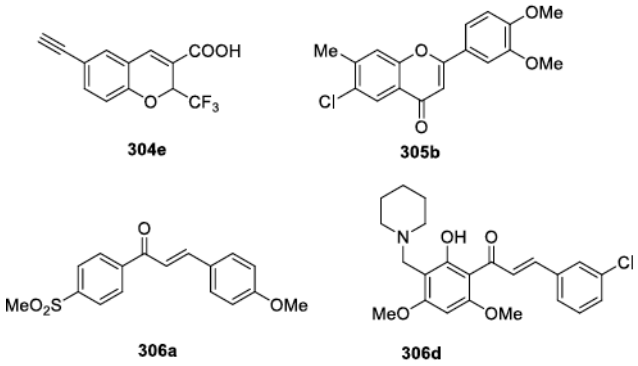


Fig. (28). Examples of chromene (**304e** and **305b**) and chalcone derivatives (**306a,d).**

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**).

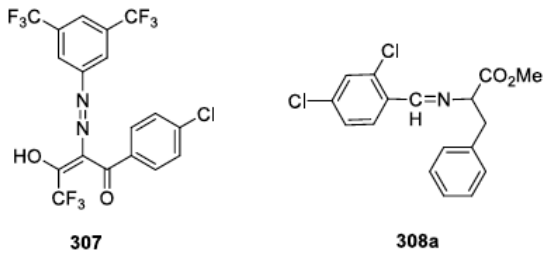
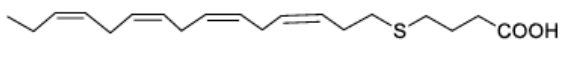


Fig. (29). Examples of heteroalkene derivatives (**307** and **308a**).

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 selectively against COX-2.

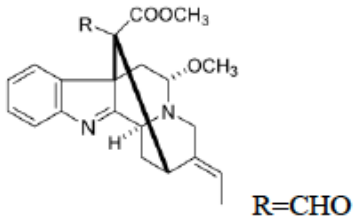
Fatty acids extracted from natural compounds (Table **92**) such as 5-thia-8, 11, 14, 17-eicosatetraenoic acid (**348**) show some inhibitory against COX-2 (SI = 6.7, IC_{50} = 3.9 µM) (Fig. **30**).

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*.

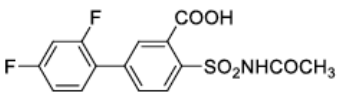


331

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 fluosulide 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 sulfonamine group able to interact through hydrogen bonds with residues of the COX-2 active site [145]. Celecoxib analogues exhibite good anti-inflammatory activity (ED_{50} = 42.3 mg/kg) which is lower than celecoxib (ED_{50} = 10.8 mg/kg), but greater than ibuprofen (ED_{50} = 67.4 mg/kg) and aspirin (ED_{50} = 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 benzosulfonamide 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 H_2S Releasing Compounds

Nitric oxide and hydrogen sulfide present protective effects in gastric mucosa. NSAIDS able to release NO and H_2S were thus developed to decrease the NSAIDS GI side effects. Several NSAIDS (diclofenac, aspirin, ibuprofen…) were coupled with NO or H_2S 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 H_2S act in concert for the maintenance of gastric mucosa, dual H_2S-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, Licofelone (**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

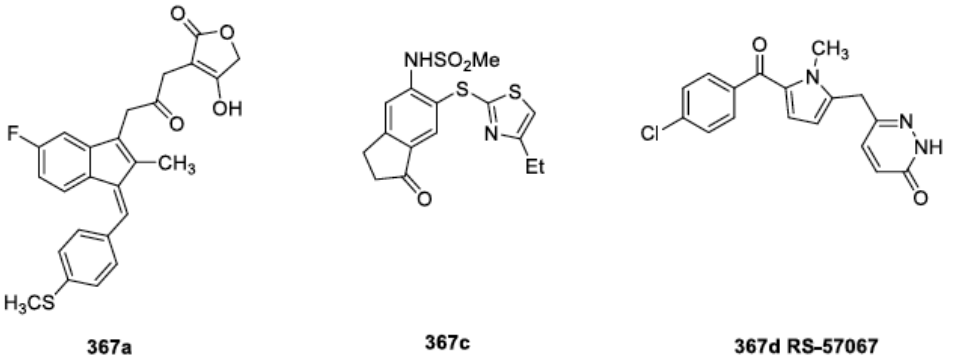


Fig. (33). Examples of sulindac (**367a**), fluosulide (**367c**) and zomepirac (**367d RS-57067**) modified compounds.

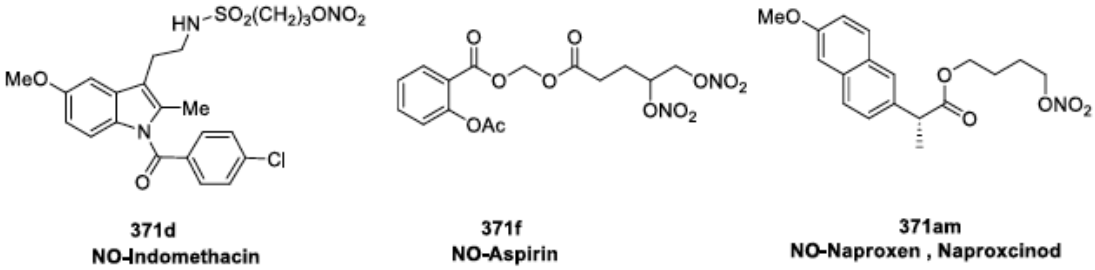


Fig. (34). Some examples of CINODs derivated from NSAIDS (**371d, 371f, 371al**)

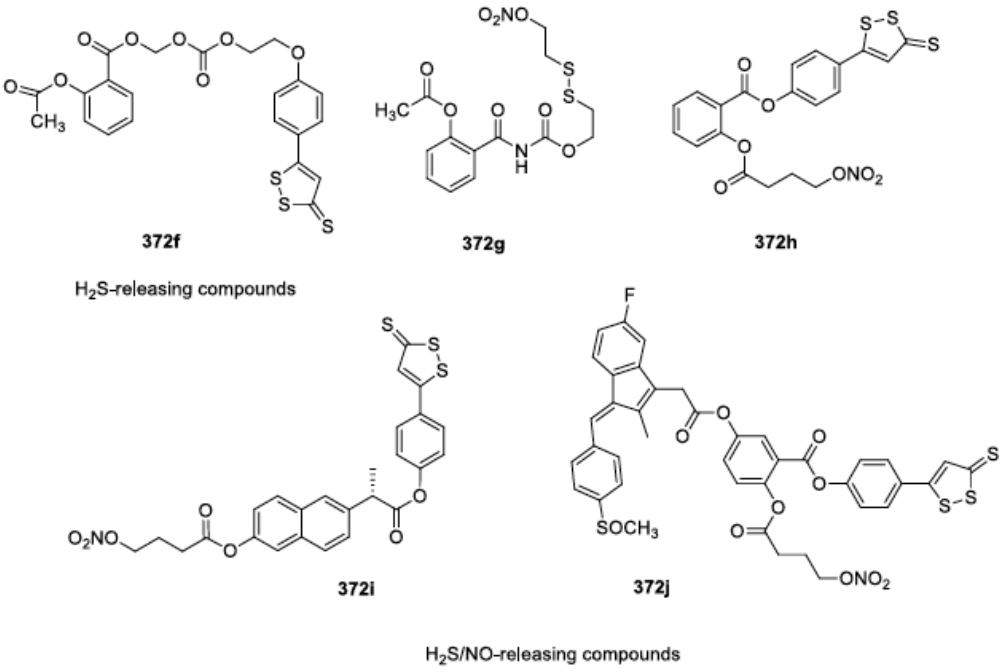


Fig. (35). Some examples of H_2S-(**372f**) and H_2S/NO-releasing (**372 g-j**) compounds.

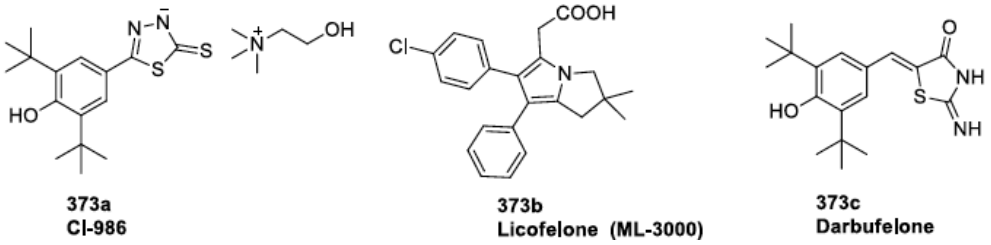
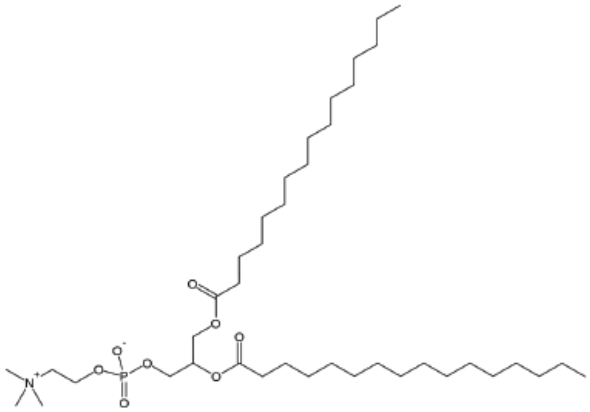


Fig. (36). Examples of some COX-2/5-LOX (**373a-c)** compounds.



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 NDAIDS [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 PGF2α 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, dicloflenac 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 overexpression 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 neuroinflammation 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.

REFERENCES

[1] Vane, J.R. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature (London), New Biol*., **1971**, *231*(25), 232-235.

[2] Vane, J.R. The mechanism of action of anti-inflammatory drugs In: *Advances in Eicosanoid Research*; Ernst Schering Res. Found. Workshop, **2000**, 31, 1-23.

[3] Xie, W.; Chipman, J.G.; Robertson, D.L.; Erikson, R.L.; Simmons, D.L. 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.

[4] Kujubu, D.A.; Fletcher, B.S.; Varnum, B.C.; Lim, R.W.; Herschman, H.R. 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, W.E.M.; Smith, W.L. 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, D.L.; Simmons, D.L. Mitogen-inducible prostaglandin G/H synthase: a new target for nonsteroidal antiinflammatory drugs. *Drug Dev. Res.,* **1992**, *25*(4), 249-265.

[7] Smith, W.L.; DeWitt, D.L.; Garavito, R.M. Cyclooxygenases: structural, cellular, and molecular biology. *Annu. Rev. Biochem.,* **2000**, *69,* 145-182.

[8] Crofford, L.J. 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, B.D.; Abramson, S.B. Selective cyclooxygenase-2 inhibitors. *Rheum Dis Clin North Am*., **1999**, *25*(2), 359-378.

[10] Penglis, P.S.; James, M.J.; Cleland, L.G. 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, D.E.; Adams, J.L. 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, D.A.; Abou-Zeid, L.A.; Shehata, I.A.; Al-Omar, M.A. 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, M.-l.; 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, R.G.; Stevens, A.M.; Gierse, J.K.; McDonald, J.J.; Stegeman, R.A.; Pak, J.Y.; Gildehaus, D.; Miyashiro, J.M.; Penning, T.D.; Seibert, K.; Isakson, P.C.; Stallings, W.C. Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory 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), 109-126.

[18] Flower, R.J. 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), 215-216.

[20] Warner, T.D.; Giuliano, F.; Vojnovic, I.; Bukasa, A.; Mitchell, J.A.; Vane, J.R. Nonsteroid drug selectivities for cyclo-oxygenase-1 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.; Nguyen, B.; Tsing, S.; Bach, C.; Freirec, J.; Chana, H.; Sigalb, E.; Ramesha, c. 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.,* **1996**, *51*(1), 21-28.

[23] Li, C.-S.; Black, W.C.; Brideau, C.; Chan, C.C.; Charleson, S.; Cromlish, W.A.; Claveau, D.; Gauthier, J.Y.; Gordon, R.; Greig, G.; Grimm, E.; Guay, J.; Lau, C.K.; Riendeau, D.; Therien, M.; Visco, D.M.; Wong, E.; Xu, L.; Prasit, P. A new structural variation on the methanesulfonylphenyl class of selective cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem. Lett*., **1999**, *9*(22), 3181-3186.

[24] Panara, M.R.; Greco, A.; Santini, G.; Sciulli, M.G.; Rotondo, M.T.; 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-(2,4-difluorothiophenyl)-1-indanone (L-745,337), on the cyclo-oxygenase activity of human blood prostaglandin endoperoxide synthases. *Br. J. Pharmacol.*, **1995**, *116*(5), 2429-2434.

[25] Gierse, J.K.; Hauser, S.D.; Creely, D.P.; Koboldt, C.; Rangwala, S.H.; Isakson, P.C.; Seibert, K. 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, M.L.; Mauleon, D. Stereoselective inhibition of inducible cyclooxygenase by chiral nonsteroidal antiinflammatory drugs. *J. Clin. Pharmacol.,* **1996**, *36*(6), 505-512.

[27] Grossman, C.J.; Wiseman, J.; Lucas, F.S.; Trevethick, M.A.; Birch, P.J. 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, M.L.; Tacconelli, S.; Di Francesco, L.; Sacchetti, A.; Sciulli, M.G.; 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), 109-126.

[31] Jouzeau, J.-Y.; 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.; Dogne, J.-M. Recent advances in inducible cyclooxygenase (COX-2) inhibition. *Curr. Med. Chem*., **2000**, *7*(10), 1041-1062.

[33] Winter, C.A.; Risley, E.A.; Nuss, G.W. 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, I.G.; Moore, P.F. Carrageenan foot edema test. *Methods Enzymol.,* **1988**, *162,* 320-327.

[35] Seibert, K.; Zhang, Y.; Leahy, K.; Hauser, S.; Masferrer, J.; Perkins, W.; Lee, L.; Isakson, P.; 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, T.D.; Talley, J.J.; Bertenshaw, S.R.; Carter, J.S.; Collins, P.W.; Docter, S.; Graneto, M.J.; Lee, L.F.; Malecha, J.W.; Miyashiro, J.M.; Rogers, R.S.; Rogier, D.J.; Yu, S.S.; Anderson, G.D.; Burton, E.G.; Cogburn, J.N.; Gregory, S.A.; Koboldt, C.M.; Perkins, W.E.; Seibert, K.; Veenhuizen, A.W.; Zhang, Y.Y.; Isakson, P.C. Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1h-pyrazol-1-yl]benzenesulfonamide (SC-58635, celecoxib). *J. Med. Chem*., **1997**, *40*(9), 1347-1365.

[37] Richardson, J.D.; Kilo, S.; Hargreaves, K.M. Cannabinoids reduce hyperalgesia and inflammation *via* interaction with peripheral CB1 receptors. *Pain*, **1998**, *75*(1), 111-119.

[38] Anderson, G.D.; Hauser, S.D.; McGarity, K.L.; Bremer, M.E.; Isakson, P.C.; Gregory, S.A. 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, B.D.; Kerr, J.S.; Jones, E.A.; Giannaras, J.V.; McGowan, M.; Ackerman, N.R. The effect of immunomodulating drugs on adjuvant-induced arthritis in Lewis rats. *Agents Actions*, **1989**, *27*(3-4), 344-346.

[40] Simon, L.S.; Lanza, F.L.; Lipsky, P.E.; Hubbard, R.C.; Talwalker, S.; Schwartz, B.D.; Isakson, P.C.; Geis, G.S. 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, J.A.; Akarasereenont, P.; Thiemermann, C.; Flower, R.J.; Vane, J.R. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc. Natl. Acad. Sci. U.S.A.*, **1993**, *90*(24), 11693-11697.

[42] Christoph, T.; Buschmann, H. *Cyclooxygenase inhibition: From NSAIDs to selective COX-2 inhibitors*. Wiley-VCH Verlag GmbH & Co. KGaA, **2002**.

[43] Blobaum, A.L.; Marnett, L.J. Structural and Functional Basis of Cyclooxygenase Inhibition. *J. Med. Chem.,* **2007**, *50*(7), 1425-1441.

[44] Campos, C.; De Gregorio, R.; Garcia-Nieto, R.; Gago, F.; Ortiz, P.; Alemany, S. Regulation of cyclooxygenase activity by metamizol. *Eur. J. Pharmacol*., **1999**, *378*(3), 339-347.

[45] Sanphui, P.; Bolla, G.; Nangia, A.; Chernyshev, V. Acemetacin cocrystals and salts: structure solution from powder X-ray data and form selection of the piperazine salt. *IUCrJ*, **2014**, *1*(2), 136-150.

[46] Rowlinson, S.W.; Kiefer, J.R.; Prusakiewicz, J.J.; Pawlitz, J.L.; Kozak, K.R.; Kalgutkar, A.S.; Stallings, W.C.; Kurumbail, R.G.; Marnett, L.J. A novel mechanism of cyclooxygenase-2 inhibition involving interactions with Ser-530 and Tyr-385. *J. Biol. Chem.,* **2003**, *278*(46), 45763-45769.

[47] Picot, D.; Loll, P.J.; Garavito, R.M. The X-ray crystal structure of the membrane protein prostaglandin H2 synthase-1. *Nature*, **1994**, *367*(6460), 243-249.

[48] Hinz, B.; Cheremina, O.; Brune, K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J*., **2008**, *22*(2) 383-390.

[49] Warner, T.D.; Mitchell, J.A. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. *FASEB J*., **2004**, *18*(7), 790-804. doi:10.1096/fj.03-0645rev.

[50] Kis, B.; Snipes, J.A.; Busija, D.W. Acetaminophen and the cyclooxygenase-3 puzzle: Sorting out facts, fictions, and uncertainties. *J. Pharmacol. Exp. Ther*., **2005**, *315*(3), 1415-1416.

[51] Botting, R.M. Mechanism of action of acetaminophen: Is there a cyclooxygenase 3? *Clin. Infect. Dis.,* **2000**, *31*(Suppl. 5), S202-S210.

[52] Chandrasekharan, N.V.; Dai, H.; Roos, K.L.T.; Evanson, N.K.; Tomsik, J.; Elton, T.S.; Simmons, D.L. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc. Natl. Acad. Sci. U.S.A*., **2002**, *99*(21), 13926-13931.

[53] Buschmann, H.H.; Gutierrez, S.B.; Holenz, J.; Farre, G.A. Analgesic anti-inflammatory combination comprising a carbinol and an NSAID. **2005**, Laboratorios del Dr. Esteve, S.A., Spain. p. 84 pp.

[54] Xu, S.; Hermanson, D.J.; Banerjee, S.; Ghebreselasie, K.; Clayton, G.M.; Garavito, R.M.; Marnett, L.J. Oxicams bind in a novel mode to the cyclooxygenase active site *via* a two-water-mediated H-bonding network. *J. Biol. Chem.,* **2014**, *289*(10), 6799-6808.

[55] Carty, T.J.; Stevens, J.S.; Lombardino, J.G.; Parry, M.J.; Randall, M.J. Piroxicam, a structurally novel antiinflammatory compound. Mode of prostaglandin synthesis inhibition. *Prostaglandins,* **1980**, *19*(5), 671-682.

[56] Kalgutkar, A.S.; Rowlinson, S.W.; Crews, B.C.; Marnett, L.J. Amide derivatives of meclofenamic acid as selective cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem. Lett*., **2002**, *12*(4), 521-524.

[57] Iqbal, M.S.; Khurshid, S.J.; Muhammad, B. Anti-inflammatory and selective COX-2 inhibitory activities of metal complexes of Schiff bases derived from aldoses. *Med. Chem. Res.,* **2013**, *22*(2), 861-868.

[58] Marnett, L.J.; Kalgutkar, A.S. Structural diversity of selective COX-2 inhibitors. Birkhaeuser Verlag, Switzerland, **2004**.

[59] Zarghi, A.; Ghodsi, R. Design, synthesis, and biological evaluation of ketoprofen analogs as potent cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem.*, **2010**, *18*(16), 5855-5860.

[60] Randy, L.B.; Richard, R.H.; Andrew, O.S. COX-2 inhibitors and leukotriene modulators. In: *Burger's Medicinal Chemistry and Drug Discovery,* **2003.**

[61] Kam, P.C.A.; See, A.U.L. Cyclo-oxygenase isoenzymes: physiological and pharmacological role. *Anaesthesia,* **2000**, *55*(5), 442-449.

[62] Chan, C.-C.; Rodger, I.W. Selective cyclooxygenase-2 inhibitors as potential therapeutic agents for inflammatory diseases. (Eicosanoids and other bioactive lipids in cancer, inflammation, and radiation injury. *Adv. Exp. Med. Biol.*, **1997**, *407,* 407157-407161.

[63] Talley, J.J. Selective inhibitors of cyclooxygenase-2. *Expert Opin. Ther. Pat*., **1997**, *7*(1), 55-62.

[64] Rufer, C.; Schillinger, E.; Boettcher, I.; Repenthin, W.; Herrmann, C. Nonsteroidal antiinflammatories. XII. Mode of action of anti-inflammatory methane sulfonanilides. *Biochem. Pharmacol.,* **1982**, *31*(22), 3591-3596.

[65] Vigdahl, R.L.; Tukey, R.H. Mechanism of action of novel anti-inflammatory drugs diflumidone and R-805. *Biochem. Pharmacol.,* **1977**, *26*(4), 307-311.

[66] Guo, Q.; Wang, L.-H.; Ruan, K.-H.; Kulmacz, R.J. Role of Val509 in time-dependent inhibition of human prostaglandin H synthase-2 cyclooxygenase activity by isoform-selective agents. *J. Biol. Chem.,* **1996**, *271*(32), 19134-19139.

[67] Gierse, J.K.; McDonald, J.J.; Hauser, S.D.; Rangwala, S.H.; Koboldt, C.M.; Seibert, K. A single amino acid difference between cyclooxygenase-1 (COX-1) and -2 (COX-2) reverses the selectivity of COX-2 specific inhibitors. *J. Biol. Chem*., **1996**, *271*(26), 15810-15814.

[68] Wu, K.K.-Y. Biochemical pharmacology of nonsteroidal anti-inflammatory drugs. *Biochem. Pharmacol.,* **1998**, *55*(5), 543-547.

[69] Copeland, R.A.; Williams, J.M.; Giannaras, J.; Nurnberg, S.; Covington, M.; Pinto, D.; Pick, S.; Trzakos, J.M. Mechanism of selective inhibition of the inducible isoform of prostaglandin G/H synthase. *Proc. Natl. Acad. Sci. U.S.A*., **1994**, *91*(23), 11202-11206.

[70] Friesen, R.W.; Dube, D.; Fortin, R.; Frenette, R.; Prescott, S.; Cromlish, W.; Greig, G.M.; Kargman, S.; Wong, E.; Chan, C.C.; Gordon, R.; Xu, L.J.; Riendeaut, D. Novel 1,2-diarylcyclobutenes: selective and orally active COX-2 inhibitors. *Bioorg. Med. Chem. Lett.*, **1996**, *6*(22), 2677-2682.

[71] Arefi, H.; Zarghi, A. Synthesis and biologic evaluation of new 3-phenoxyazetidin-2-one derivatives as selective cyclooxygenase-2 inhibitors. *Med. Chem. Res*., **2013**, *22*(8), 3881-3887.

[72] Talley, J.J.; Bertenshaw, S.R.; Brown, D.L.; Carter, J.S.; Graneto, M.J.; Koboldt, C.M.; Masferrer, J.L.; Norman, B.H.; Rogier, D.J.; Zweifel, B.S.; Seibert, K. 4,5-Diaryloxazole inhibitors of cyclooxygenase-2 (COX-2). *Med. Res. Rev.,* **1999**, *19*(3), 199-208.

[73] Reitz, D.B.; Huang, H.-C.; Li, J.J.; Garland, D.J.; Anderson, G.D.; Gregory, S.A.; Koboldt, C.M.; Perkins, W.E.; Seibert, K.; Isakson, P.C. Selective cyclooxygenase inhibitors: novel diarylspirocycloalkenes are potent and orally active COX-2 inhibitors. *Bioorg. Med. Chem. Lett.,* **1995**, *5*(8), 867-872.

[74] Huang, H.-C.; Li, J.J.; Garland, D.J.; Chamberlain, T.S.; Reinhard, E.J.; Manning, R.E.; Seibert, K.; Koboldt, C.M.; Gregory, S.A.; Anderson, G.D.; Veenhuizen, A.W.; Zhang, Y.; Perkins, W.E.; Burton, E.G.; Cogburn, J.N.; Isakson, P.C.; Reitz, D.B. Diarylspiro[2.4]heptenes as orally active, highly selective cyclooxygenase-2 inhibitors: synthesis and structure-activity relationships. *J. Med. Chem.,* **1996**, *39*(1), 253-266.

[75] Leblanc, Y.; Gauthier, J.Y.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Prasit, P. Synthesis and biological evaluation of 2,3-diarylthiophenes as selective Cox-2 and Cox-1 inhibitors. *Bioorg. Med. Chem. Lett.,* **1995**, *5*(18), 2123-2128.

[76] Pinto, D.J.P.; Copeland, R.A.; Covington, M.B.; Pitts, W.J.; Batt, D.G.; Orwat, M.J.; Lam, G.N.; Joshi, A.; Chan, Y.-C.; Wang, S.; Trzaskos, J.M.; Magolda, r.L.; Kornhauser, D.M. Chemistry and pharmacokinetics of diarylthiophenes and terphenyls as selective cox-2 inhibitors. *Bioorg. Med. Chem. Lett.*, **1996**, *6*(24), 2907-2912.

[77] Bertenshaw, S.R.; Talley, J.J.; Rogier, D.J.; Graneto, M.J.; Rogers, R.S.; Kramer, S.W.; Penning, T.D.; Koboldt, C.M.; Veenhuizen, A.W.; Zhang, Y; Perkins, W.E. 3,4-Diarylthiophenes are selective COX-2 inhibitors. *Bioorg. Med. Chem. Lett.*, **1995***, 5*(23), 2919-2922.

[78] Talley, J.J. Selective inhibitors of cyclooxygenase-2 (COX-2). *Prog. Med. Chem*., **1999**, *36,* 201-234.

[79] Zanatta, S.D.; Jarrott, B.; Williams, S.J. Synthesis and preliminary pharmacological evaluation of aryl dithiolethiones with cyclooxygenase-2-selective inhibitory activity and hydrogen sulfide-releasing properties. *Aust. J. Chem.,* **2010**, *63*(6), 946-957.

[80] Anzini, M.; Rovini, M.; Cappelli, A.; Vomero, S.; Manetti, F.; Botta, M.; Sautebin, L.; Rossi, A.; Pergola, C.; Ghelardini, C.; Norcini, M.; Giordani, A.; Makovec, F.; Anzellotti, P.; Patrignani, P.; Biava, M. Synthesis, biological evaluation, and enzyme docking simulations of 1,5-diarylpyrrole-3-alkoxyethyl ethers as selective cyclooxygenase-2 inhibitors endowed with anti-inflammatory and antinociceptive activity. *J. Med. Chem.,* **2008**, *51*(15), 4476-4481.

[81] Campbell, J.A.; Bordunov, V.; Broka, C.A.; Browner, M.F.; Kress, J.M.; Mirzadegan, T.; Ramesha, C.; Sanpablo, B.F.; Stabler, R.; Takahara, P.; Villasenor, A.; Walker, K.A.M.; Wang, J.-H.; Welch, M.; Weller, P. Rational design of 6-methylsulfonylindoles as selective cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem. Lett.,* **2004**, *14*(18), 4741-4745.

[82] Consalvi, S.; Alfonso, S.; Di Capua, A.; Poce, G.; Pirolli, A.; Sabatino, M.; Ragno, R.; Anzini, M.; Sartini, S.; La Motta, C.; Di Cesare, M.L.; Ghelardini, C.; Biava, M. Synthesis, biological evaluation and docking analysis of a new series of methylsulfonyl and sulfamoyl acetamides and ethyl acetates as potent COX-2 inhibitors. *Bioorg. Med. Chem*., **2015**, *23*(4), 810-820.

[83] Biava, M.; Porretta, G.C.; Poce, G.; Battilocchio, C.; Manetti, F.; Botta, M.; Forli, S.; Sautebin, L.; Rossi, A.; Pergola, C.; Ghelardini, C.; Galeotti, N.; Makovec, F.; Giordani, A.; Anzellotti, P.; Patrignani, P.; Anzini, M. Novel ester and acid derivatives of the 1,5-diarylpyrrole scaffold as anti-inflammatory and analgesic agents. Synthesis and *in vitro* and *in vivo* biological evaluation. *J. Med. Chem*., **2010**, *53*(2), 723-733.

[84] Kim, K.J.; Choi, M.J.; Shin, J.-S.; Kim, M.; Choi, H.-E.; Kang, S.M.; Jin, J.H.; Lee, K.-T.; Lee, J.Y. Synthesis, biological evaluation, and docking analysis of a novel family of 1-methyl-1H-pyrrole-2,5-diones as highly potent and selective cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem. Lett.,* **2014**, *24*(8), 1958-1962.

[85] Al-Suwaidan, I.A.; Alanazi, A.M.; El-Azab, A.S.; Al-Obaid, A.M.; ElTahir, K.E.H.; Maarouf, A.R.; Abu El-Enin, M.A.; Abdel-Aziz, A.A.M. Molecular design, synthesis and biological evaluation of cyclic imides bearing benzenesulfonamide fragment as potential COX-2 inhibitors. Part 2. *Bioorg. Med. Chem. Lett.,* **2013**, *23*(9), 2601-2605.

[86] Abdel-Aziz, A.A.M.; El Tahir, K.E.H.; Asiri, Y.A. Synthesis, anti-inflammatory activity and COX-1/COX-2 inhibition of novel substituted cyclic imides. Part 1: Molecular docking study. *Eur. J. Med. Chem*., **2011**, *46*(5), 1648-1655.

[87] Alanazi, A.M.; El-Azab, A.S.; Al-Suwaidan, I.A.; El Tahir, K.E.H.; Asiri, Y.A.; Abdel-Aziz, N.I.; Abdel-Aziz, A.A.M. Structure-based design of phthalimide derivatives as potential cyclooxygenase-2 (COX-2) inhibitors: Anti-inflammatory and analgesic activities. *Eur. J. Med. Chem*., **2015**, *92*, 115-123.

[88] Soliva, R.; Almansa, C.; Kalko, S.G.; Luque, F.J.; Orozco, M. Theoretical studies on the inhibition mechanism of cyclooxygenase-2. is there a unique recognition site? *J. Med. Chem.,* **2003**, *46*(8), 1372-1382.

[89] Wang, J.L.; Limburg, D.; Graneto, M.J.; Springer, J.; Hamper, J.R.B.; Liao, S.; Pawlitz, J.L.; Kurumbail, R.G.; Maziasz, T.; Talley, J.J.; Kiefer, J.R.; Carter, J. The novel benzopyran class of selective cyclooxygenase-2 inhibitors. Part 2: The second clinical candidate having a shorter and favorable human half-life. *Bioorg. Med. Chem. Lett.,* **2010**, *20*(23), 7159-7163.

[90] Fioravanti, R.; Bolasco, A.; Manna, F.; Rossi, F.; Orallo, F.; Ortuso, F.; Alcaro, S.; Cirilli, R. Synthesis and biological evaluation of N-substituted-3,5-diphenyl-2-pyrazoline derivatives as cyclooxygenase (COX-2) inhibitors. *Eur. J. Med. Chem.,* **2010**, *45*(12), 6135-6138.

[91] Abdellatif, K.R.A.; Elshemy, H.A.H.; Azoz, A.A. 1-(4-Methane(amino)sulfonylphenyl)-3-(4-substituted-phenyl)-5-(4-trifluoromethylphenyl)-1H-2-pyrazolines/pyrazoles as potential anti-inflammatory agents. *Bioorg. Chem.,* **2015**, *63,* 13-23.

[92] Bandgar, B.P.; Adsul, L.K.; Chavan, H.V.; Jalde, S.S.; Shringare, S.N.; Shaikh, R.; Meshram, R.J.; Gacche, R.N.; Masand, V. Synthesis, biological evaluation, and docking studies of 3-(substituted)-aryl-5-(9-methyl-3-carbazole)-1H-2-pyrazolines as potent anti-inflammatory and antioxidant agents. *Bioorg. Med. Chem. Lett.,* **2012**, *22*(18), 5839-5844.

[93] Yadav, M.R.; Puntambekar, D.S.; Sarathy, K.P.; Vengurlekar, S.; Giridhar, R. Quantitative structure activity relationship studies of diarylimidazoles as selective COX-2 inhibitors. *Indian J. Chem.,* Sect. B: *Org. Chem. Incl. Med. Chem*., **2006**, *45B*(2), 475-482.

[94] Bhandari, S.; Bothara, K.; Pawar, V.; Lokwani, D.; Devale, T. Design of new chemicals entities as selective COX-2 inhibitors using structure optimization by molecular modeling studies. *Internet Electron. J. Mol. Des.*, **2009**, *8*(2), 14-28.

[95] Handler, N.; Jaeger, W.; Kuen-Krismer, B.; Erker, T. Cyclooxygenase-1 and cyclooxygenase-2 inhibition of novel 1,2-

disubstituted imidazoles. *Arch. Pharm. (Weinheim, Ger.),* **2005**, *338*(12), 602-604.

[96] Abuo-Rahma, G.E.-D.A.A.; Abdel-Aziz, M.; Farag, N.A.; Kaoud, T.S. Novel 1-[4-(Aminosulfonyl)phenyl]-1H-1,2,4-triazole derivatives with remarkable selective COX-2 inhibition: Design, synthesis, molecular docking, anti-inflammatory and ulcerogenicity studies. *Eur. J. Med. Chem.*, **2014**, *83*, 398-408.

[97] Radwan, A.A.; El Tahir, K.E.H. Synthesis and in-silico studies of some diaryltriazole derivatives as potential cyclooxygenase inhibitors. *Arch. Pharmacal Res.*, **2013**, *36*(5), 553-563.

[98] Roy, P.L.Y.; Gall, R.G.; Brideau, C.; Chan, C.C.; Chauret, N.; Cromlish, W.; Ethier, D.; Gauthier, J.Y.; Gordon, R.; Greig, G.; Guay, J.; Kargman, S.; Lau, C.K.; O'Neill, G.; Silva, J.; Therien, M.; van Staden, C.; Wong, E.; Xu, L.; Prasit, P. A new series of selective COX-2 inhibitors: 5,6-diarylthiazolo[3,2-b][1,2,4]triazoles. *Bioorg. Med. Chem. Lett.,* **1997**, *7*(1), 57-62.

[99] Al-Hourani, B.J.; Sharma, S.K.; Mane, J.Y.; Tuszynski, J.; Baracos, V.; Kniess, T.; Suresh, M.; Pietzsch, J.; Wuest, F.; Synthesis and evaluation of 1,5-diaryl-substituted tetrazoles as novel selective cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem. Lett.,* **2011**, *21*(6), 1823-1826.

[100] Jawabrah Al-Hourani, B.; Sharma, S.K.; Kaur, J.; Wuest, F. Synthesis, bioassay studies, and molecular docking of novel 5-substituted 1H tetrazoles as cyclooxygenase-2 (COX-2) inhibitors. *Med. Chem. Res.,* **2015**, *24*(1), 78-85.

[101] Kawai, S.; Nishida, S.; Kato, M.; Furumaya, Y.; Okamoto, R.; Koshino, T.; Mizushima, Y. Comparison of cyclooxygenase-1 and -2 inhibitory activities of various nonsteroidal anti-inflammatory drugs using human platelets and synovial cells. *Eur. J. Pharmacol.,* **1998**, *347*(1), 87-94.

[102] Rainsford, K.D.; Omar, H.; Ashraf, A.; Hewson, A.T.; Bunning, R.A.D.; Rishiraj, R.; Shepherd, P.; Seabrook, R.W. Recent pharmacodynamic and pharmacokinetic findings on oxaprozin. *Inflammopharmacology*, **2002**, *10*(3), 185-239.

[103] Praveen, R.P.N.; Knaus, E.E. Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond. *J. Pharm. Pharm. Sci.,* **2008**, *11*(2), 81s-110s.

[104] Hashimoto, H.; Imamura, K.; Haruta, J.-i.; Wakitani, K. 4-(4-Cycloalkyl/aryl-oxazol-5-yl)benzenesulfonamides as selective cyclooxygenase-2 inhibitors: enhancement of the selectivity by introduction of a fluorine atom and identification of a potent, highly selective, and orally active COX-2 inhibitor JTE-522. *J. Med. Chem*., **2002**, *45*(7), 1511-1517.

[105] Hashimoto, H.; Maeda, K.; Ozawa, K.; Haruta, J.-I.; Wakitani, K. 4-Aryl/cycloalkyl-5-phenyloxazole derivatives as selective COX-2 inhibitors. *Bioorg. Med. Chem. Lett.*, **2002**, *12*(1), 65-68.

[106] Wakitani, K.; Nanayama, T.; Masaki, M.; Matsushita, M. Profile of JTE-522 as a human cyclooxygenase-2 inhibitor. *Jpn. J. Pharmacol.,* **1998**, *78*(3), 365-371.

[107] Velazquez, C.; Rao, P.N.P.; McDonald, R.; Knaus, E.E. Synthesis and biological evaluation of 3,4-diphenyl-1,2,5-oxadiazole-2-oxides and 3,4-diphenyl-1,2,5-oxadiazoles as potential hybrid COX-2 inhibitor/nitric oxide donor agents. *Bioorg. Med. Chem*., **2005**, *13*(8), 2749-2757.

[108] Song, Y.; Connor, D.T.; Doubleday, R.; Sorenson, R.J.; Sercel, A.D.; Unangst, P.C.; Roth, B.D.; Gilbertsen, R.B.; Chan, K.; Schrier, D.J.; Guglietta, A.; Bornemeier, D.A.; Dyer, R.D. Synthesis, structure-activity relationships, and *in vivo* evaluations of substituted di-tert-butylphenols as a novel class of potent, selective, and orally active cyclooxygenase-2 inhibitors. 1. Thiazolone and oxazolone series. *J. Med. Chem.*, **1999**, *42*(7), 1151-1160.

[109] Zarghi, A.; Javid, F.S.; Ghodsi, R.; Dadrass, O.G.; Daraei, B.; Hedayati, M. Design, synthesis and biological evaluation of new 5,5-diarylhydantoin derivatives as selective cyclooxygenase-2 inhibitors. *Sci. Pharm.*, **2011**, *79*(3), 449-460.

[110] Pinto, D.J.P.; Batt, D.G.; Pitts, W.J.; Petraitis, J.J.; Orwat, M.J.; Wang, S.; Jetter, J.W.; Sherk, S.R.; Houghton, G.C.; Copeland, R.A.; Covington, M.B.; Trzaskos, J.M.; Magolda, R.L. Terphenyl cyclooxygenase-2 (COX-2) inhibitors: optimization of the central ring and o-biphenyl analogs. *Bioorg. Med. Chem. Lett*., **1999**, *9*(7), 919-924.

[111] Negi, V.J.; Sharma, A.K.; Ram, V. Synthesis and biological evaluation of 4-(substituted phenylsulfamoyl)-2-hydroxyphenyl acetate derivatives as potent anti-inflammatory and selective COX-2 inhibitors. *Pharma. Chem.,* **2013**, *5*(3), 18-25.

[112] Adel Moallem, S.; Hadizadeh, F.; Yavar, I. New N-aryl-4-(methysulfony)aminobenzenesulfonamides as selective COX-2 inhibitors. *J. Biol. Sci. (Faisalabad, Pak.)*, **2011**, *11*(8), 496-499.

[113] Silva, T.; Borges, F.; Edraki, N.; Alizadeh, M.; Miri, R.; Saso, L.; Firuzi, O. Hydroxycinnamic acid as a novel scaffold for the development of cyclooxygenase-2 inhibitors. *RSC Adv.,* **2015**, *5*(72), 58902-58911.

[114] Zarghi, A.; Ghodsi, R.; Azizi, E.; Daraie, B.; Hedayati, M.; Dadrass, O.G. Synthesis and biological evaluation of new 4-carboxyl quinoline derivatives as cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem*., **2009**, *17*(14), 5312-5317.

[115] Chakraborti, A.K.; Garg, S.K.; Kumar, R.; Motiwala, H.F.; Jadhavar, P.S. Progress in COX-2 inhibitors: a journey so far. *Curr. Med. Chem.*, **2010**, *17*(15), 1563-1593.

[116] Singh, S.K.; Saibaba, V.; Ravikumar, V.; Rudrawar, S.V.; Daga, P.; Rao, C.S.; Akhila, V.; Hegde, P.; Rao, Y.K. Synthesis and biological evaluation of 2,3-diarylpyrazines and quinoxalines as selective COX-2 inhibitors. *Bioorg. Med. Chem*., **2004**, *12*(8), 1881-1893.

[117] Shah, U.A.; Deokar, H.S.; Kadam, S.S.; Kulkarni, V.M. Pharmacophore generation and atom-based 3D-QSAR of novel 2-(4-methylsulfonylphenyl)pyrimidines as COX-2 inhibitors. *Mol. Diversity*, **2010**, *14*(3), 559-568.

[118] Jawabrah Al-Hourani, B.; Sharma, S.K.; Suresh, M.; Wuest, F. Cyclooxygenase-2 inhibitors: a literature and patent review (2009 - 2010). *Expert Opin. Ther. Pat*., **2011**, *21*(9), 1339-1432.

[119] Devesa, I.; Alcaraz, M.J.; Riguera, R.; Ferrandiz, M.L. A new pyrazolo pyrimidine derivative inhibitor of cyclooxygenase-2 with anti-angiogenic activity. *Eur. J. Pharmacol*., **2004**, *488*(1-3), 225-230.

[120] Santagati, A.; Granata, G.; Marrazzo, A.; Santagati, M. Synthesis and effects on the COX-1 and COX-2 activity in human whole blood ex vivo of derivatives containing the [1]benzothienol[3,2-d]pyrimidin-4-one heterocyclic system. *Arch. Pharm. (Weinheim, Ger.),* **2003**, *336*(9), 429-435.

[121] Raffa, D.; Maggio, B.; Plescia, F.; Cascioferro, S.; Raimondi, M.V.; Plescia, S.; Cusimano, M.G. Pyrazolo[3,4-d]pyrimidine derivatives as COX-2 selective inhibitors: synthesis and molecular modelling studies. *Arch. Pharm. (Weinheim, Ger.),* **2009***, 342*(6), 321-326.

[122] Rao, P.N.P.; Uddin, M.J.; Knaus, E.E. Design, synthesis, and structure-activity relationship studies of 3,4,6-triphenylpyran-2-ones as selective cyclooxygenase-2 inhibitors. *J. Med. Chem*., **2004**, *47*(16), 3972-3990.

[123] Zhang, Y.; Tortorella, M.D.; Wang, Y.; Liu, J.; Tu, Z.; Liu, X.; Bai, Y.; Wen, D.; Lu, X.; Lu, Y.; Talley, J.J. Synthesis of deuterated benzopyran derivatives as selective cox-2 inhibitors with improved pharmacokinetic properties. *ACS Med. Chem. Lett*., **2014**, *5*(10), 1162-1166.

[124] Wang, J.L.; Aston, K.; Limburg, D.; Ludwig, C.; Hallinan, A.E.; Koszyk, F.; Hamper, B.; Brown, D.; Graneto, M.; Talley, J.; Maziasz, T.; Masferrer, J.; Carter, J. The novel benzopyran class of selective cyclooxygenase-2 inhibitors. Part III: The three microdose candidates. *Bioorg. Med. Chem. Lett*., **2010**, *20*(23), 7164-7168.

[125] Wang, J.L.; Carter, J.; Kiefer, J.R.; Kurumbail, R.G.; Pawlitz, J.L.; Brown, D.; Hartmann, S.J.; Graneto, M.J.; Seibert, K.; Talley, J.J. The novel benzopyran class of selective cyclooxygenase-2 inhibitors-part I: The first clinical candidate. *Bioorg. Med. Chem. Lett*., **2010**, *20*(23), 7155-7158.

[126] Grover, J.; Kumar, V.; Sobhia, M.E.; Jachak, S.M. Synthesis, biological evaluation and docking analysis of 3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-ones as potential cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem. Lett.*, **2014**, *24*(19), 4638-4642.

[127] Begum, T.; Mohammed, T.; Khan, S.A. Mannich bases of 7-hydroxy coumarins and their biological activity. World *J. Pharm. Pharm. Sci*., **2015**, *4*(1), 26-37.

[128] Zebardast, T.; Zarghi, A.; Daraie, B.; Hedayati, M.; Dadrass, O.G. Design and synthesis of 3-alkyl-2-aryl-1,3-thiazinan-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors. *Bioorg. Med. Chem. Lett*., **2009**, *19*(12), 3162-3165.

[129] Zarghi, A.; Zebardast, T.; Daraie, B.; Hedayati, M. Design and synthesis of new 1,3-benzthiazinan-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors. *Bioorg. Med. Chem*., **2009**, *17*(15), 5369-5373.

[130] Uddin, M.J.; Rao, P.N.P.; Rahim, M.A.; McDonald, R.; Knaus, E.E. A new class of acyclic 2-alkyl-1,2-diaryl (E)-olefins as selective cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem. Lett*., **2004**, *14*(19), 4911-4914.

[131] Uddin, M.J.; Rao, P.N.P.; McDonald, R.; Knaus, E.E. Design and synthesis of (E)-1,1,2-triarylethenes: novel inhibitors of the cyclooxygenase-2 (COX-2) isozyme. *Bioorg. Med. Chem. Lett.*, **2005**, *15*(2), 439-442.

[132] Johnson, A.R.; Marletta, M.A.; Dyer, R.D. Slow-binding inhibition of human prostaglandin endoperoxide synthase-2 with darbufelone, an isoform-selective antiinflammatory di-tert-butyl phenol. *Biochemistry*, **2001**, *40*(25), 7736-7745.

[133] Dadashpour, S.; Kucukkilinc, T.T.; Tan, O.U.; Ozadali, K.; Irannejad, H.; Emami, S. Design, Synthesis and *in vitro* study of 5,6-diaryl-1,2,4-triazine-3-ylthioacetate derivatives as COX-2 and β-amyloid aggregation inhibitors. *Arch. Pharm. (Weinheim, Ger.),* **2015**, *348*(3), 179-187.

[134] Irannejad, H.; Kebriaieezadeh, A.; Zarghi, A.; Montazer-Sadegh, F.; Shafiee, A.; Assadieskandar, A.; Amini, M.; Synthesis, docking simulation, biological evaluations and 3D-QSAR study of 5-Aryl-6-(4-methylsulfonyl)-3-(metylthio)-1,2,4-triazine as selective cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem*., **2014**, *22*(2), 865-873.

[135] Bhardwaj, A.; Kaur, J.; Sharma, S.K.; Huang, Z., Wuest, F.; Knaus, E.E. Hybrid fluorescent conjugates of COX-2 inhibitors: Search for a COX-2 isozyme imaging cancer biomarker. *Bioorg. Med. Chem. Lett.,* **2013**, *23*(1), 163-168.

[136] Chen, Q.-H.; Rao, P.N.P.; Knaus, E.E. Design, synthesis, and biological evaluation of linear 1-(4-, 3- or 2-methylsulfonylphenyl)-2-phenylacetylenes: A novel class of cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem.*, **2005**, *13*(23), 6425-6434.

[137] Zarghi, A.; Arfaee, S.; Rao, P.N.P.; Knaus, E.E. Design, synthesis, and biological evaluation of 1,3-diarylprop-2-en-1-ones : A novel class of cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem*., **2006**, *14*(8), 2600-2605.

[138] Bandgar, B.P.; Patil, S.A.; Gacche, R.N.; Korbad, B.L.; Hote, B.S.; Kinkar, S.N.; and Jalde, S.S.; Synthesis and biological evaluation of nitrogen-containing chalcones as possible anti-inflammatory and antioxidant agents. *Bioorg. Med. Chem. Lett*., **2010**, *20*(2), 730-733.

[139] El-Sayed, M.A.A.; Abdel-Aziz, N.I.; Abdel-Aziz, A.A.M.; El-Azab, A.S.; Asiri, Y.A.; El Tahir, K.E.H. Design, synthesis, and biological evaluation of substituted hydrazone and pyrazole derivatives as selective COX-2 inhibitors: Molecular docking study. *Bioorg. Med. Chem*., **2011**, *19*(11), 3416-3424.

[140] Palkar, M.B.; Praveen, D.M.; Ronad, P.M.; Viswanathswamy, A.H.M.; Rane, R.A.; Patel, H.M.; Shaikh, M.S.; Hampannavar, G.A.; Jain, K.S.; Karpoormath, R. Novel series of phenylalanine analogs endowed with promising anti-inflammatory activity: synthesis, pharmacological evaluation, and computational insights. *Med. Chem. Res*., **2015**, *24*(5), 1988-2004.

[141] Che, H.; Tuyen, T.N.; Kim, H.P.; Park, H. 1,5-Diarylimidazoles with strong inhibitory activity against COX-2 catalyzed PGE2 production from LPS-induced RAW 264.7 cells. *Bioorg. Med. Chem. Lett*., **2010**, *20*(14), 4035-4037.

[142] Newman, D.J.; Cragg, G.M.; Snader, K.M. Natural products as sources of new drugs over the period 1981-2002. *J. Nat. Prod*., **2003**, *66*(7), 1022-1037.

[143] Barnett, J.W.; Dunn, J.P.; Kertesz, D.J.; Miller, A.B.; Morgans, D.J.; Jr.; Ramesha, C.S.; Sigal, C.E.; Sjogren, E.B.; Smith, D.B.; Talamas, F.X. Pyrrole derivatives. Ed. F. Hoffmann-La Roche Ag, Switzerland, **1996**, p. 55.

[144] Ouimet, N.; Chan, C.-C.; Charleson, S.; Claveau, D.; Gordon, R.; Guay, D.; Li, C.-S.; Ouellet, M.; Percival, D.M.; Riendeau, D.; Wong, E.; Zamboni, R.; Prasit, P. Substituted heterocyclic analogs as selective COX-2 inhibitors in the flosulide class. *Bioorg. Med. Chem. Lett*., **1999**, *9*(2), 151-156.

[145] Abdur Rahim, M.; Praveen Rao, P.N.; Bhardwaj, A.; Kaur, J.; Huang, Z.; Knaus, E.E. Isomeric acetoxy analogs of celecoxib and their evaluation as cyclooxygenase inhibitors. *Bioorg. Med. Chem. Lett*., **2011**, *21*(20), 6074-6080.

[146] Zarghi, A.; Rao, P.N.P.; Knaus, E.E. Synthesis and biological evaluation of methanesulfonamide analogues of rofecoxib: Replacement of methanesulfonyl by methanesulfonamido decreases cyclooxygenase-2 selectivity. *Bioorg. Med. Chem*., **2007**, *15*(2), 1056-1061.

[147] Zarghi, A.; Rao, P.N.P.; Knaus, E.E. Design and synthesis of new rofecoxib analogs as selective cyclooxygenase-2 (COX-2) inhibitors: replacement of the methanesulfonyl pharmacophore by an N-acetylsulfonamido bioisostere. *J. Pharm. Pharm. Sci*., **2007**, *10*(2), 159-167.

[148] Abdur Rahim, M.; Praveen Rao, P.N.; Knaus, E.E. Isomeric acetoxy analogues of rofecoxib: A novel class of highly potent and selective cyclooxygenase-2 inhibitors. Bioorg. *Med. Chem. Lett*., **2002**, *12*(19), 2753-2756.

[149] Abdellatif, K.R.A.; Abdelgawad, M.A.; Helmy, N.A. Synthesis of new rofecoxib analogs of expected anti-inflammatory activity. *Eur. J. Exp. Biol.*, **2013**, *3*(2), 524-534.

[150] Bhardwaj, A.; Huang, Z.; Kaur, J.; Knaus, E.E. Rofecoxib analogues possessing a nitric oxide donor sulfohydroxamic acid (so2nhoh) cyclooxygenase-2 pharmacophore: synthesis, molecular modeling, and biological evaluation as anti-inflammatory agents. *ChemMedChem*, **2012**, *7*(1), 62-67.

[151] Kim, S.-H.; Margalit, O.; Katoh, H.; Wang, D.; Wu, H.; Xia, D.; Holla, V.R.; Yang, P.; DuBois, R.N. CG100649, a novel COX-2 inhibitor, inhibits colorectal adenoma and carcinoma growth in mouse models. *Invest. New Drugs*, **2014**, *32*(6), 1105-1112.

[152] Lichtenberger, L.M.; Ulloa, C.; Romero, J.J.; Vanous, A.L.; Illich, P.A.; Dial, E.J. Nonsteroidal anti-inflammatory drug and phospholipid prodrugs: Combination therapy with antisecretory agents in rats. *Gastroenterology*, **1996**, *111*(4), 990-995.

[153] Giraud, M.N.; Sanduja, S.K.; Felder, T.B.; Illich, P.A.; Dial, E.J.; Lichtenber Ger, L.M. Effect of omeprazole on the bioavailability of unmodified and phospholipid-complexed aspirin in rats. *Aliment. Pharmacol. Ther.*, **1997**, *11*(5), 899-906.

[154] Wolfe, M.M. Future trends in the development of safer nonsteroidal anti-inflammatory drugs. *Am. J. Med.,* **1998**, *105*(5A), 44S-52S.

[155] Puhlmann, U.; Schaefer, D.; Ziemann, C. Update on COX-2 inhibitor patents with a focus on optimised formulation and therapeutic scope of drug combinations making use of COX-2 inhibitors. *Expert Opin. Ther. Pat.*, **2006**, *16*(4), 403-430.

[156] Coruzzi, G.; Venturi, N.; Spaggiari, S. Gastrointestinal safety of novel nonsteroidal antiinflammatory drugs: selective COX-2 inhibitors and beyond. *Acta Bio Med. Atenei Parmensis*, **2007**, *78*(2), 96-110.

[157] Marnett, L.J. The COXIB experience: a look in the rearview mirror. *Annu. Rev. Pharmacol. Toxicol*., **2009**, *49,* 265-290.

[158] Rainsford, K.D. Anti-inflammatory drugs in the 21st century. *Subcell Biochem.*, **2007***, 42,* 3-27.

[159] Patrignani, P.; Tacconelli, S.; Sciulli, M.G.; Capone, M.L. New insights into COX-2 biology and inhibition. *Brain Res. Rev*., **2005**, *48*(2), 352-359.

[160] Casturi, S.R.; Hegde, P.; Ramanujam, R. Development of COX-2 selective inhibitors - therapeutic perspectives. *Curr. Med. Chem.: Immunol., Endocr. Metab. Agents,* **2005**, *5*(3), 241-248.

[161] Shi, S.; Klotz, U. Clinical use and pharmacological properties of selective COX-2 inhibitors. *Eur. J. Clin. Pharmacol.,* **2008**, *64*(3), 233-252.

[162] Yuan, Y.; Hunt, R.H. Assessment of the safety of selective cyclooxygenase-2 inhibitors: where are we in 2003? *Inflammopharmacology,* **2003**, *11*(4-6), 337-354.

[163] Khanna, D.; Khanna, P.P.; Furst, D.E. COX-2 controversy: where are we and where do we go from here? *Inflammopharmacology*, **2005**, *13*(4), 395-402.

[164] Cirino, G. Nitric oxide releasing drugs: from bench to bedside. *Dig. Liver Dis.*, **2003**, *35*(Suppl. 2), p. S2-S8.

[165] Suthar, S.K.; Sharma, M. Recent developments in chimeric NSAIDs as safer anti-inflammatory agents. *Med. Res. Rev*., **2015**, *35*(2), 341-407.

[166] Charlier, C.; Michaux, C. Dual inhibition of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) as a new strategy to provide safer non-steroidal anti-inflammatory drugs. *Eur. J. Med. Chem.*, **2003**, *38*(7-8), 645-659.

[167] Lichtenberger, L.M.; Wang, Z.-M.; Romero, J.J.; Ulloa, C.; Perez, J.C.; Giraud, M.-N.; Barreto, J.C. Non-steroidal anti-inflammatory drugs (NSAIDs) associate with zwitterionic phospholipids: insight into the mechanism and reversal of NSAID-induced gastrointestinal injury. *Nat. Med. (N.Y.),* **1995**, *1*(2), 154-158.

[168] De Leval, X.; Julemont, F.; Delarge, J.; Sanna, V.; Pirotte, B.; Dogne, J.-M. Advances in the field of COX-2 inhibition. *Expert Opin. Ther. Pat.,* **2002**, *12*(7), 969-989.

[169] Rainsford, K.D. Structure-activity relationships of non-steroid antiinflammatory drugs 1. Gastric ulcerogenic activity. *Agents Actions*, **1978**, *8*(6), 587-605.

[170] Simon, L.S. The COX 2 selective inhibitors: what the newspapers have not told you. *Bull NYU Hosp Jt Dis*, **2007**, *65*(3), 229-241.

[171] Green, G.A. Understanding NSAIDs: from aspirin to COX-2. *Clin Cornerstone*, **2001**, *3*(5), 50-60.

[172] Botting, R.M. Cyclooxygenase: past, present and future. A tribute to John R. Vane (1927-2004). *J. Therm. Biol*., **2006**, *31*(1-2), 208-219.

[173] Parente, L.; Perretti, M. Advances in the pathophysiology of constitutive and inducible cyclooxygenases: two enzymes in the spotlight. *Biochem. Pharmacol*., **2003**, *65(*2), 153-159.

[174] Wallace, J.L. Distribution and expression of cyclooxygenase (COX) isoenzymes, their physiological roles, and the categorization of nonsteroidal anti-inflammatory drugs (NSAIDs). *Am. J. Med*., **1999**, *107*(6A), 11S-17S.

[175] Black, W.C. Selective cyclooxygenase-2 inhibitors. *Annu. Rep. Med. Chem*., **2004**, *39*, 125-138.

[176] Bjarnason, I., Thjodleifsson, B. The murky world of the COX-2-selective agents. *Inflammopharmacology*, **2005**, *13*(4), 381-393.

[177] Gatti, D.; Adami, S. Coxibs: a significant therapeutic opportunity. *Acta Biomed*, **2010**, *81*(3), 217-224.

[178] Harirforoosh, S.; Asghar, W.; Jamali, F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. *J. Pharm. Pharm. Sci.,* **2013**, *16*(4), 821-847, 27 pp.

[179] Ong, C.K.S.; Lirk, P.; Tan, C.H.; Seymour, R.A. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin. Med. Res*., **2007**, *5*(1), 19-34.

[180] Simmons, D.L.; Botting, R.M.; Hla, T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. *Pharmacol. Rev.,* **2004**, *56*(3), 387-437.

[181] Kawai, S.; Kojima, F.; Kusunoki, N. Recent advances in nonsteroidal anti-inflammatory drugs. *Allergol. Int*., **2005**, *54*(2), p. 209-215.

[182] Fosslien, E. Review: cardiovascular complications of non-steroidal anti-inflammatory drugs. *Ann. Clin. Lab. Sci*., **2005**, *35*(4), 347-385.

[183] Hermann, M.; Ruschitzka, F. Coxibs, non-steroidal anti-inflammatory drugs and cardiovascular risk. *Intern. Med. J.,* **2006**, *36*(5), 308-319.

[184] Zarghi, A.; Arfaei, S. Selective COX-2 inhibitors: a review of their structure-activity relationships. *Iran. J. Pharm. Res*., **2011**, *10*(4), 655-683.

[185] Kirby, N.S.; Lundberg, M.H.; Harrington, L.S.; Leadbeater, P.D.M.; Milne, G.L.; Potter, C.M.F.; Al-Yamani, M.; Adeyemi, O.; Warner, T.D.; Mitchell, J.A. Cyclooxygenase-1, not cyclooxygenase-2, is responsible for physiological production of prostacyclin in the cardiovascular system. *Proc. Natl. Acad. Sci. U.S.A., Early Ed*., **2012**, *109*(43), 17597-17609.

[186] Mattia, C.; Coluzzi, F. COX-2 inhibitors: pharmacological data and adverse effects. *Minerva Anestesiol.*, **2005**, *71*(7-8), 461-470.

[187] Grosser, T. The pharmacology of selective inhibition of COX-2. *Thromb. Haemostasis*, **2006**, *96*(4), 393-400.

[188] Bennett, A.; Tavares, I.A. COX-2 inhibitors compared and contrasted. *Expert Opin. Pharmacother.,* **2001**, *2*(11), 1859-1876.

[189] Jackson, L.M.; Hawkey, C.J. COX-2 selective nonsteroidal anti-inflammatory drugs: Do they really offer any advantages? *Drugs*, **2000**, *59*(6), 1207-1216.

[190] Harris, R.C.; Breyer, M.D. Update on cyclooxygenase-2 inhibitors. *Clin. J. Am. Soc. Nephrol.,* **2006**, *1*(2), 236-245.

[191] Katori, M.; Majima, M. Cyclooxygenase-2: its rich diversity of roles and possible application of its selective inhibitors. *Inflammation Res.,* **2000**, *49*(8), 367-392.

[192] Kumar, A.; Gaur, A. Remembering cyclooxygenases: a brief review. *Asian J. Pharm. Technol. Innovation*, **2014**, *2*(4), 1-8.

[193] Kilico, I.; Kokcu, A.; Kefeli, M.; Kandemir, B. Regression of experimentally induced endometriosis with a new selective cyclooxygenase-2 enzyme inhibitor. *Gynecol. Obstet. Invest*., **2014**, *77*(1), 35-39.

[194] Sharma, J.N.; Jawad, N.M. Adverse effects of COX-2 inhibitors. *TheScientificWorld*, **2005**, *5*, 629-645.

[195] Blain, H.; Jouzeau, J.Y.; Netter, P.; Jeandel, C. Non-steroidal anti-inflammatory agents with selective inhibitory activity on cyclooxygenase-2. Interest and future prospects. *Rev. Med. Interne.,* **2000**, *21*(11), 978-988.

[196] Pairet, M.; Engelhardt, G. Distinct isoforms (COX-1 and COX-2) of cyclooxygenase: Possible physiological and therapeutic implications. *Fundam. Clin. Pharmacol*., **1996**, *10*(1), 1-15.

[197] Vane, J.R.; Botting, R.M. Anti-inflammatory drugs and their mechanism of action. *Inflamm. Res*., **1998**, *47*(Suppl.2), S78-S87.

[198] Savage, R. Cyclo-oxygenase-2 inhibitors: when should they be used in the elderly? *Drugs Aging*, **2005**, *22*(3), 185-200.

[199] Hilario, M.O.E. Terreri, M.T. Len, C.A. Nonsteroidal anti-inflammatory drugs: cyclooxygenase 2 inhibitors. *J. Pediatr. (Rio J),* **2006**, *82*(5 Suppl), S206-212.

[200] Tsujii, M.; DuBois, R.N. Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2. *Cell,* **1995**, *83*(3), 493-501.

[201] He, T.-C.; Chan, T.A.; Vogelstein, B.; Kinzler, K.W. PPARδ is an APC-regulated target of nonsteroidal anti-inflammatory drugs. *Cell (Cambridge, Mass.),* **1999**, *99*(3), 335-345.

[202] Luan, Y.; Xu, W. The function of the selective inhibitors of cyclooxygenase 2. *Mini-Rev. Med. Chem.,* **2006**, *6*(12), 1375-1381.

[203] Hayashi, S.; Ueno, N.; Murase, A.; Takada, J. Design, synthesis and structure-activity relationship studies of novel and diverse cyclooxygenase-2 inhibitors as anti-inflammatory drugs. *J. Enzyme Inhib. Med. Chem.*, **2014**, *29*(6), 846-867.

[204] Thun, M.J.; Henley, S.J.; Pairono, C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J. Natl. Cancer Inst.,* **2002**, *94*(4), 252-266.

[205] Turini, M.E.; DuBois, R.N. Cyclooxygenase-2: a therapeutic target. *Annu. Rev. Med*., **2002**, *53,* 35-57.

[206] Bovill, J.G. Pharmacology and clinical action of COX-2 selective NSAIDs. (Advances in modelling and clinical application of intravenous anaesthesia), *Adv. Exp. Med. Biol*., **2003**, 523201-523214.

[207] Williams, G.W. An update on nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors. *Curr. Pain. Headache Rep.*, **2005**, *9*(6), 377-389.

[208] Chung, S.; Lim, K.M.; Shin, S.S. Profiles of COX-2 inhibitors: present and future. *Expert Opin. Ther. Pat*., **2005**, *15*(1), 9-32.

[209] Corley, D.A.; Kerlikowske, K.; Verma, R.; and Buffler, P. Protective association of aspirin/NSAIDs and esophageal cancer: A systematic review and meta-analysis. *Gastroenterology,* **2003**, *124*(1), 47-56.

[210] Xiao, J.; Tan, Y.; Pan, Y.; Liang, G.; Qu, C.; Zhang, X.; Zhang, Y.; Li, X.; Yang, H. A new cyclooxygenase-2 inhibitor, (1E,4E)-1,5-bis(2-bromophenyl)penta-1,4-dien-3-one (GL63) suppresses cyclooxygenase-2 gene expression in human lung epithelial cancer cells: coupled mRNA stabilization and posttranscriptional inhibition. *Biol. Pharm. Bull*., **2010**, *33*(7), 1170-1175.

[211] Vosooghi, M.; Amini, M. The discovery and development of cyclooxygenase-2 inhibitors as potential anticancer therapies. *Expert Opin. Drug Discovery*, **2014**, *9*(3), 255-267.

[212] Carvalho, W.A.; Carvalho, R.D.S.; Rios-Santos, F. Specific cyclooxygenase-2 inhibitor analgesics: therapeutic advances. *Rev. Bras. Anestesiol.*, **2004**, *54*(3), 448-464.

[213] Takeda, S.; Okazaki, H.; Ikeda, E.; Abe, S.; Yoshioka, Y.; Watanabe, K.; Aramaki, H.; Down-regulation of cyclooxygenase-2 (COX-2) by cannabidiolic acid in human breast cancer cells. *J. Toxicol. Sci*., **2014**, *39*(5), 711-716.

[214] Akiyama, H.; Barger, S.; Barnum, S.; Bradt, B.; Bauer, J.; Cole, G.M.; Cooper, N.R.; Eikelenboom, P.;; Emmerling, M.; Fiebich, B.L.; Finch, C.E.; Frautschy, S.; Griffin, W.S.T.; Hampel, H.; Hull, M.; Landreth, G.; Lue, L.F.; Mrak, R.; Mackenzie, I.R.; McGeer, P.L.; O'Banion, M.K.; Pachter, J.; Pasinetti, G.; Plata-Salaman, C.; Rogers, J.; Rydel, R.; Shen, Y.; Streit, W.; Strohmeyer, R.; Tooyoma, I.; Van Muiswinkel, F.L.; Veerhuis, R.; Walker, D.; Webster, S.; Wegrzyniak, B.; Wenk, G.; Wyss-Coray, T. Inflammation and Alzheimer's disease. *Neurobiol. Aging,* **2000**, *21*(3), 383-421.

[215] McGeer, P.L.; McGeer, *E.G.;* NSAIDs and Alzheimer disease: Epidemiological, animal model and clinical studies. *Neurobiol. Aging,* **2007**, *28*(5), 639-647.

[216] Vlad, S.C.; Miller, D.R.; Kowall, N.W.; Felson, D.T. Protective effects of NSAIDs on the development of Alzheimer disease. *Neurology,* **2008**, *70*(19, Pt. 1), 1672-1677.

[217] Aisen, P.S.; Thal, L.J.; Ferris, S.H.; Assaid, C.; Nessly, M.L.; Giuliani, M.J.; Lines, C.R.; Norman, B.A.; Potter, W.Z. Rofecoxib in patients with mild cognitive impairment: further analyses of data

from a randomized, double-blind, trial. *Curr. Alzheimer Res*., **2008**, *5*(1), 73-82.

[218] Cole, G.M.; Frautschy, S.A. Mechanisms of action of non-steroidal anti-inflammatory drugs for the prevention of Alzheimer's disease. *CNS Neurol. Disord.: Drug Targets*, **2010**, *9*(2), 140-148.

[219] Teismann, P. COX-2 in the neurodegenerative process of Parkinson's disease. *BioFactors*, **2012**, *38*(6), 395-397.

[220] Teismann, P.; Tieu, K.; Choi, D.-K.; Wu, D.-C.; Naini, A.; Hunot, S.; Vila, M.; Jackson-Lewis, V.; Przedborski, S. Cyclooxygenase-2 is instrumental in Parkinson's disease neurodegeneration. *Proc. Natl. Acad. Sci. U.S.A.*, **2003**, *100*(9), 5473-5478.