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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Developmental perspectives of the drugs targeting enzyme-instigated inflammation: a mini review

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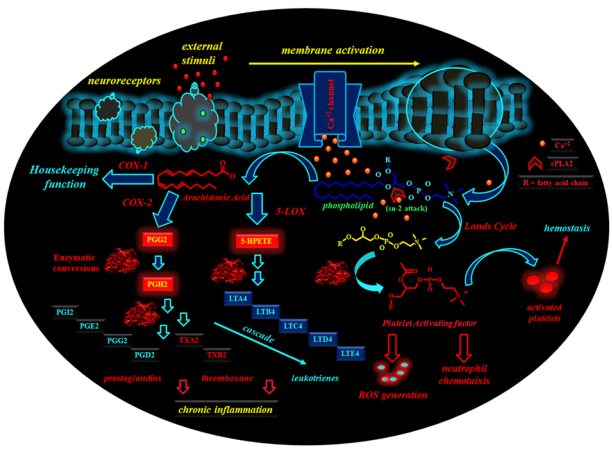
Abstract

The instigation of chronic inflammation begins with the release of arachidonic acid (AA) from the membranous phospholipids through a biochemical reaction catalyzed by cytosolic phospholipase A_2, which selectively hydrolyzes the arachidonyl phospholipid at the sn-2 position, thereby releasing a lysophospholipid and AA into the cytosol. This intracellular event swiftly progresses to the production of pro-inflammatory leukotrienes and prostaglandins by the catalytic action of the enzymes lipoxygenases and cyclooxygenases (COXs) on AA, respectively, whose anomalous production may manifest into chronic inflammation and related disorders. Despite several developments from aspirin to non-steroidal anti-inflammatory drugs and COX-2 inhibitors, the anti-inflammatory therapy, due to its associated side effects even in the advanced formulations, has suffered frequent setbacks and commercial withdrawals. The contemporary research therefore aims at designing novel candidate molecules with superior viability and an enhanced acceptability towards biological systems with a minimum conceivable side effect.

Graphical Abstract



Keywords $cPLA_2$ · AA · COX-1/2 · 5-LOX · COXIBs · NSAIDs

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Abbreviations

AA	arachidonic acid
$cPLA_2$	cytosolic phospholipase A_2
COX	cyclooxygenase
LOX	lipoxygenase
NSAIDs	non-steroidal anti-inflammatory drugs

Introduction

Inflammation is an intrinsic immunity response to the contacted stimuli in the form of a microbial attack, allergen, or a pathogen or due to an intracellular metabolic breakdown (Barton 2008; Mogensen 2009). When switched on, this innate immune response assures of eliminating the invading agent by initiating the cellular repair mechanisms for restoring the tissue homeostasis (Colaco and Moita 2016). The physiological response for an effective elimination of the inducing stimuli produces only transient after effects, but failure to exterminate the invading agent effectually coupled with slumping cellular repair mechanism ostensibly expresses into a protracted inflammatory response causing perpetual failure of biochemical machinery apparently causing chronic ailments (Prasher 2015). The release of arachidonic acid (AA) from the membrane phospholipids by a site-specific attack of cytosolic phospholipase A_2 ($cPLA_2$) enzyme to counter the cellular stress promotes such events (Balsinde et al. 2002). When acted upon by cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, AA acts as a precursor for the production of a cascade of pro-inflammatory metabolites (Fig. 1), whose overproduction abnormally expresses as severe conditions (Needleman et al. 1986). COX-2 isoform of COX family of enzymes inflicts the biosynthesis of pro-inflammatory prostaglandins, whereas another channel of AA pathway mediated by LOX enzyme (5-lipoxygenase (5-LOX)) manifests into the production of inflammation causing leukotrienes, both of which play a critical role in the development of acute asthma and related disorders, atherosclerosis, arteriosclerosis, irritable bowel syndrome, and cancer (Prasher and Pooja 2014). The discovery of aspirin in 1887 and its successful commercialization in 1899 saw an advent of anti-inflammatory drug discovery (Desborough and Keeling 2017) that sustained until the latter half of twentieth century with the discovery and popularization of drugs like acetaminophen in 1956 and ibuprofen in 1962 with a superior anti-inflammatory profile. Subsequently, the identification of the substrate binding sites in the two COX isoforms COX-1 and COX-2 in 1972 led to the contemporary development of drugs tagged as the selective COX-2 inhibitors (COXIBs) (Blobaum and Marnett 2007) presenting a grander inhibitory profile vis-a-vis other mainstream anti-inflammatory drugs. By the end of twentieth century, the identification of side effects associated with the available classes of anti-inflammatory drugs led to their withdrawal from the market (Arellano 2005). The contemporary period also witnessed an extensive exploration on molecular motifs and scaffolds focused on designing the prevalent "hits" and "leads" against the inflammation epidemiology with numerous active pharmaceutical ingredients in the pipeline of becoming the potential drugs (Singh et al. 2015). However, limited solutions are available for mitigating the disorders related to the COX-2 inhibition therapy that comprise critical cardiovascular events and gastric mucosa erosion (Pepine and Gurbel 2017). The present status of the anti-inflammatory drug discovery demands for a target-specific polypharmacological approach (Bolognesi and Cavalli 2016) for the potential candidates by incorporating the profile of parent molecules into a single hybrid that could target multiple disease pathways eventually overcoming the side effects associated with the drug, thereby raising its efficacy (Prasher and Sharma 2018). Nitric oxide-releasing non-steroidal anti-inflammatory drugs (NSAIDs) present an imperative development in this regard presenting substantial evidence of physiological tolerance (Fiorucci et al. 2001). Additionally, the hybrid molecules incorporating the beneficial ulcerogenic and antioxidant activities of parent molecules with NSAIDs and COXIBs are also under development. In this review, we compendiously discuss the developmental perspectives and current progress in anti-inflammatory medication.

PLA_2 enzyme family

With their discovery as a major component in snake venom a few decades ago, 15 different groups of enzymes of PLA_2 family have been reported. Broadly, the PLA_2 enzymes could be categorized into four parts: secreted PLA_2s (sPLA2s), $cPLA_2$s, calcium (Ca^{+2})-independent ($iPLA_2$s), and platelet-activating factor (PAF) acetyl hydrolase/oxidized lipid lipoprotein-associated PLA_2s (LpPLA2s), each having a diverse implication in the lipid metabolism and disease advancement (Burke and Dennis 2009).

Secreted PLA_2s

Having a low molecular weight of 14–18 kDa, $sPLA_2$s catalyze the hydrolysis reaction characteristic of their family, by the abstraction of proton from the water molecule activated by the bounded histidine-aspartic acid dyad in the active site in the presence of Ca^{+2}. The ion helps to stabilize the transition state by coordinating the carbonyl group and negative charge on the oxygen of phosphate group. The $sPLA_2$s, reportedly, have a poor selectivity towards the sn-2

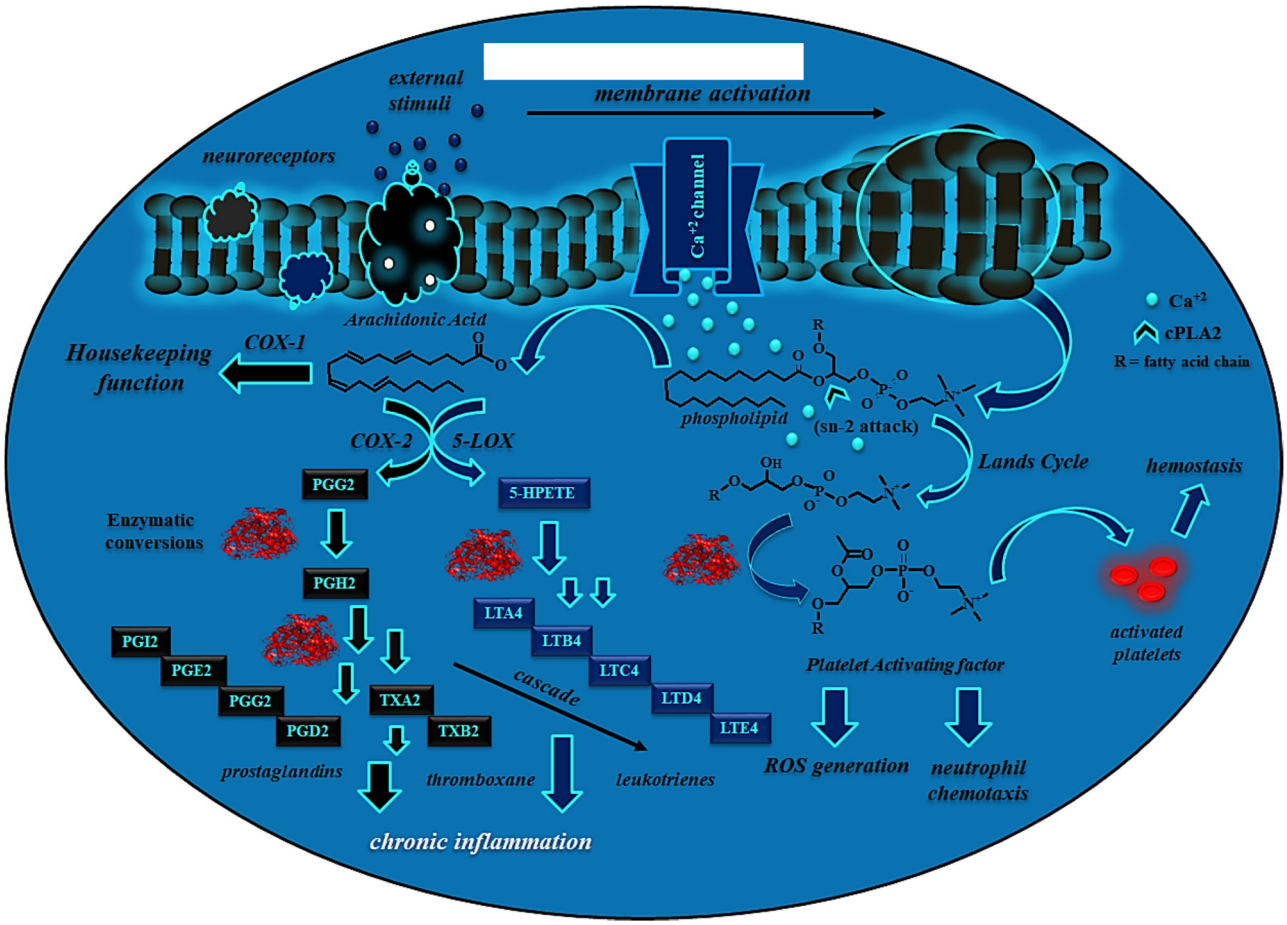


Fig. 1 Events and metabolites involved in the instigation of chronic inflammation

attack on a specific fatty acid substrate (Sato et al. 2016). The molecular modeling experiments establish that during the hydrolysis of phospholipid substrate by $sPLA_2$s, only the 50% carbons of the *sn*-2 acyl chain interact with the enzyme and rest of the chains remain buried in the lipid-water interface. The activity of $sPLA_2$s depends on the interfacial interactions of the active site residues of the enzyme with the target phospholipid aggregates (Murakami et al. 2015). The $sPLA_2$ class of enzymes displays a similar activity towards the phospholipids with diverse fatty acids appendage at the sn-2 position, but the preferences vary with the charge on the lipid surface and with the types of surface residues.

Ca^{+2}-independent PLA_2

These class of enzymes belong to the group VI of PLA_2s and they do not require Ca^{+2} ions for their catalytic activity; however, their activity is regulated by the intracellular Ca^{+2} ions. Any depletion in the intracellular Ca^{+2} by calmodulin, zymosan, reactive oxygen species (ROS), or PKC-α (protein kinase C-α) activity leads to their activation and interaction with the phospholipid to release AA eventually (Winstead et al. 2000). They are also involved in the generation of lysophospholipids as an acceptor for the assimilation of AA to change into phospholipids, thereby playing a housekeeping role in the phospholipid remodeling.

Lipoprotein-associated PLA_2

The PAF acetyl hydrolase/oxidized lipid $LpPLA_2$ belongs to the group VII family of PLA_2 enzymes. A characteristic feature of $LpPLA_2$ enzyme is that unlike the other PLA2s, it can access the phospholipid substrate in the aqueous phase. Another typical feature of $LpPLA_2$ is that its active site is composed of a serine, histidine, and aspartic acid hydrolase triad, whereas the other PLA_2s have dyads. Some reports on $LpPLA_2$ establish its anti-inflammatory potential by stopping the pro-inflammatory roles of PAF, but after numerous clinical investigations on the role of group VIIA PLA_2 levels in patients with heart risks, this enzyme was considered as a definitive marker of coronary heart disease, thereby making it a very attractive drug target (Packard 2009).

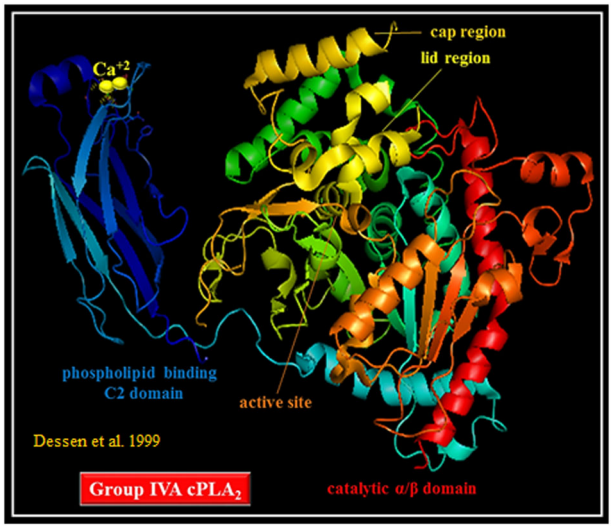


Fig. 2 Crystal coordinates of cytosolic phospholipase A_2 ($cPLA_2$) (pdb ID 1CJY) Dessen et al. (1999)

Cytosolic PLA_2

The trigger of AA cascade lies with group IVA $cPLA_2$ (GIVA $cPLA_2$) enzymes, which during the cellular stress directs a site-specific attack on membrane-based arachidonyl phospholipids in the presence of Ca^{+2} ions, thereby releasing the AA and a lysophospholipid into the cytoplasm. Since AA is the precursor for the generation of several eicosanoids, the GIVA $cPLA_2$s were regarded as the sole perpetrators in the progression of inflammatory diseases (Sun et al. 2014). Mechanistically, out of the several classes of phospholipases, during the phospholipid hydrolysis catalyzed by $sPLA_2$, the catalytic Ca^{+2} ion that is optimally bound to the conserved calcium-binding loop interacts simultaneously with water molecules and specific amino acid residues present at the enzyme active site. Ca^{+2} ion ensures an appropriate orientation of polar headgroup of the phospholipid substrate molecule to encourage the redistribution of the *p*-orbital electron density at the sn-2 carbonyl, leading to polarization of the carbonyl carbon-oxygen double bond. This polarization at the carbonyl functional group creates an electron-deficient carbonyl carbon atom at the scissile sn-2 ester linkage, thereby promoting the nucleophilic attack by the oxygen atom of an adjacent water molecule at the electron-deficient carbonyl carbon atom, leading to the formation of a tetrahedral transition state intermediate. This tetrahedral transition state simultaneously generates the lysophospholipid and fatty acid products. To ensure optimal spatial relationships for all the interacting active site elements, a conformational flexibility of the $sPLA_2$ protein molecule needs restrain. This is ensured by the formation of disulfide bonds that assist in stabilizing protein tertiary structure and may represent the principal reason $sPLA_2$ possesses such a large number of disulfide bonds that are required for enzyme activity (Heinrikson 1991; Verheij and de Haas 1991). However, unlike the $sPLA_2$s, the $cPLA_2$s belonging to GIVA exhibit a substantial selectivity towards the phospholipids with AA appendage at the sn-2 position (Fig. 1). Since AA is the precursor for the generation of several eicosanoids, the GIVA $cPLA_2$s are the major contributors in the development of inflammatory diseases. The crystal structure of GIVA $cPLA_2$ enzyme determined by Dessen et al. (1999) reveals a phospholipid-binding Ca^{+2}-dependent domain and a catalytic α/β domain (Fig. 2). Both these domains ensure a full contribution towards the enzyme activity. Multiple lipases ensure a conserved basic structure of cPLA2. The presence of a $CAP^{370–548}$ region is characteristic only to the GIVA $cPLA_2$. Within the $CAP^{370–548}$ region, an $LID^{413–57}$ region is present due to which the modeling of a phospholipid substrate in the active site is restrained (Kramer and Sharp 1993). In the presence of Ca^{+2}, this enzyme is employed to the phospholipid membrane of the invaded cell by the translocation of the C2 domain. The activation of the enzyme is eventually enabled either through the phosphorylation on residues 505, 515, and 727 or in the presence of second lipid messengers: ceramide-1-phosphate and phosphatidylinositol (4, 5) bisphosphate. Reportedly, the elevated PLA_2 catalytic activities in synovial fluid of patients suffering with rheumatoid arthritis, osteoarthritis, and crystal-associated arthritis assert the association of phospholipases with chronic inflammation and related disorders. Additionally, in patients with systemic sclerosis, obstinately subnormal amounts of PLA_2 levels and activity persists (Stephanski et al. 1986; Nevalainen 1993). Reportedly, the activity of PLA_2 in serum, sepsis, and septic shock interrelated with the concentration of synovial-type PLA_2-II. However, no such correlation occurs with pancreatic PLA_2-I. Apparently, the therapeutic indications claimed for $sPLA_2$ and $cPLA_2$ inhibitors encompass several inflammatory conditions, such as rheumatoid arthritis, osteoarthritis, inflammatory diseases of the skin and the gastrointestinal (GI) tract, and lung disorders such as asthma and bronchitis. The role of GIVA $cPLA_2$ enzymes in switching on the AA cascade to produce pro-inflammatory metabolites makes it one of the potential drug targets in capping chronic inflammation and the related disorders (Soubhye et al. 2018).

Arachidonoyl trifluoromethyl ketone (**1**; Fig. 3) was the first reported non-selective class of $cPLA_2$ inhibitors (Trimble et al 1993; Street et al. 1993). Besides the potency of trifluoromethyl ketone analogs of palmitic acid (**2**; Fig. 3), γ-linolenic acid (**3**; Fig. 3) and linoleic acid (**4**; Fig. 3) was reported at par with their AA counterpart 1 (Ghomashchi et al. 1999; Conde-Frieboes et al. 1996). Methyl arachidonyl fluorophosphonate (**5**; Fig. 3) was the

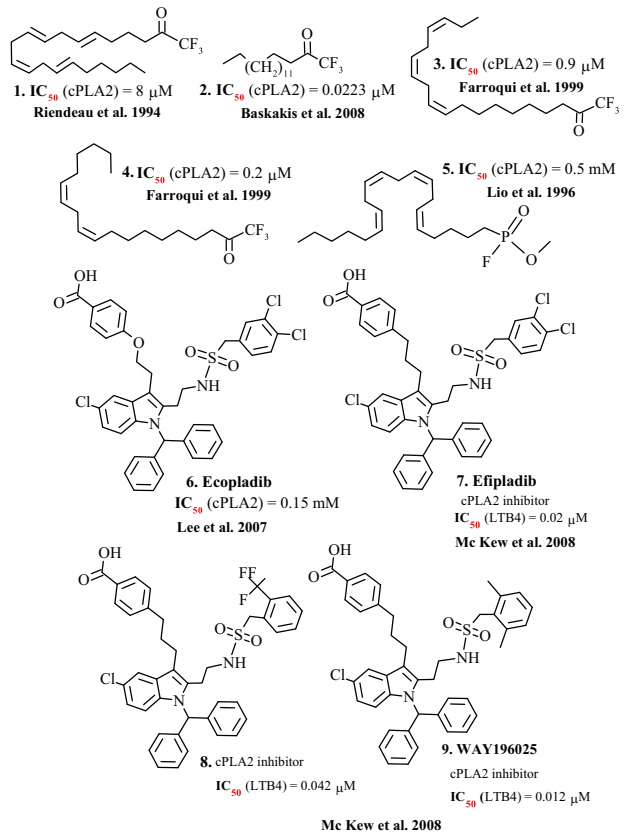


Fig. 3 Cytosolic phospholipase A2 ($cPLA_2$) inhibitors

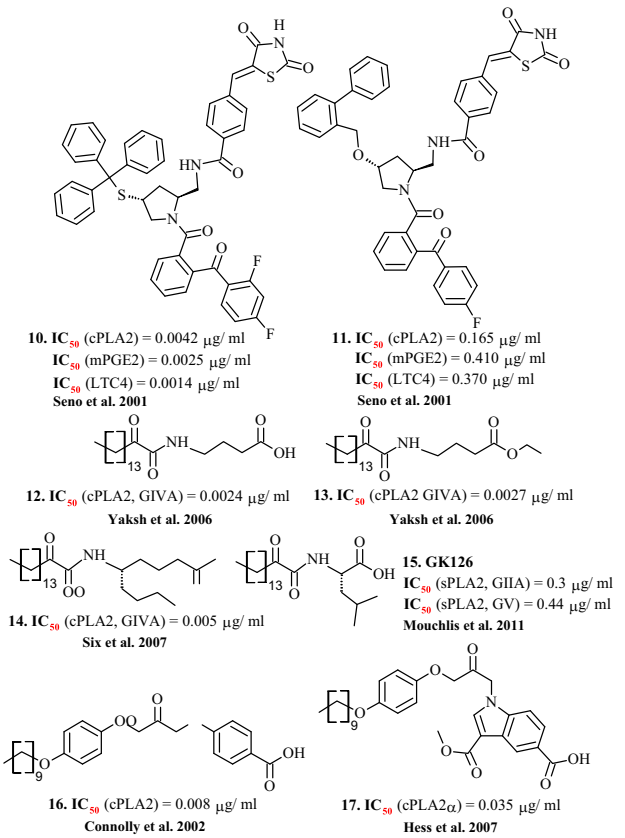


Fig. 4 Cytosolic phospholipase A_2 ($cPLA_2$) inhibitors

first reported irreversible and highly potent $cPLA_2$ inhibitor (Lio et al. 1996), but it cannot be distinguished from $iPLA_2$. Wyeth reported the first highly selective and commercial indole-based $cPLA_2$ inhibitors (**6–9**, Fig. 3). The testing of the inhibitory profile for the compounds was done by using glutamate (GLU) assay and rabbit antibody-derived whole blood (RWB) assay. Compound **6**, clinically known as *ecopladib*, strongly inhibited $cPLA_2$ activity with a substantial half-maximal inhibitory concentration (IC_{50}) value of 0.15 μM using a GLU assay and 0.11 μM using an RWB assay (Lee et al. 2007). Its functional analog compound **7**, clinically named as *efipladib*, exhibited an IC_{50} value of 0.04 and 0.07 μM in a GLU assay in an RWB assay, respectively (McKew et al. 2008 a, b). The $cPLA_2$ inhibition potency was found to be strongest for compound **9**, clinically known as *WAY-196025*.

The reported minimum inhibitory concentration of compound **9** for 50% inhibition of the target enzyme activity was found to be 0.01 and 0.03 μM in a GLU assay and an RWB assay, respectively. The clinical inflammation models for compound **6** indicated a good oral efficacy for the drug, which led to its advancement to phase I clinical trials. The same was applicable for its functional analogs, compound **7**, which displayed a decent in vivo oral efficacy. Additionally, it was also found to decline the nociceptive responses in the mouse models without affecting the prostaglandin E2 (PGE2) levels (Nickerson-Nutter et al. 2011). Like other compounds of the series, compound **8**, clinically designated as *giripladib* due to its significant $cPLA_2$ efficacy, also advanced to phase II clinical trial for osteoarthritis, but the trials were soon terminated concerning the GI toxicity associated with the compound ((http://clinicaltrials.gov/, Identifier: NCT00396955). Another set of potent, pyrrolidine-based $cPLA_2$ inhibitors were identified (**10**, **11**, Fig. 4; Seno et al. 2000; Ghomashchi et al. 2001). The studies revealed that compound **11** reversibly inhibits the activity of human $cPLA_2$ with an IC_{50} 4.2 nM, thereby affecting the release of AA, resulting in a low production of PGE2, thromboxane B2, and leukotriene B4 (LTB4) formation in the human whole blood assay (Seno et al. 2001; Ono et al. 2002). Its functional analog compound **11** displayed a similar inhibitory profile exhibiting an IC_{50} value of 0.078 μM against $cPLA_2$ and suppressing the release of AA and biosynthesis of PGE2 from the A23187-stimulated THP-1 cells. Additionally, compound **10** also displayed anti-arthritic and antibone destructive action in the in vitro mouse arthritis models (Tai et al. 2010). Another novel class of 2-oxoamide-based inhibitors to target the active site serine residue of $cPLA_2$ was introduced (Kokotos et al. 2002, 2004; Constantinou-Kokotou et al. 2005; Stephens

et al. 2006; Six et al. 2007). The free carboxylic group on the long-chain 2-oxoamide-based γ- or δ-amino acids as in compound **12** (Fig. 4) induces a $cPLA_2$-selective inhibition, whereas the selectivity was found to be lost on esterifying the free –COOH as in compound **13**. The inhibition profile for compound **13** was effective against both $cPLA_2$ and $iPLA_2$, but reportedly it efficiently blocks the release of PGE2 from the spinal cells and displayed a significant anti-hyperalgesic effect (Yaksh et al 2006). Interestingly, the compounds **14** and **15** with a free carboxylic group exhibited selective $cPLA_2$ inhibitory activity and stimulate the production of regulatory T cells in the in vitro inflammation rat models. Six et al. (2007) targeted GIVA $cPLA_2$, a key supplier of substrates that regulate the production of eicosanoids and PAF. While identifying the structure–activity relationship of 2-oxoamide-based compounds and GIVA cPLA2 inhibition, the most persuasive inhibitors identified were from δ- and γ-amino acid-based 2-oxoamides (**14**, Fig. 4). A short nonpolar aliphatic chain as a side-chain moiety was optimum for the activity of compounds. The resulting 2-oxoamides on testing with the human group V secreted PLA2 (GV sPLA2) and the human GVIA iPLA2 (GVIA iPLA2) gave compound **14** with a considerable inhibition of GIVA cPLA2. Group IIA sPLA2 (GIIA sPLA2), which is a member of the mammalian sPLA2 enzyme family, is reportedly associated with various inflammatory disorders. Mouchlis et al. (2011) carried the synthesis of 2-oxoamides based on α-amino acids and performed *in vitro* assessment against the sPLA2s (GIIA and GV). The long-chain 2-oxoamide GK126 based on the amino acid (S)-leucine displayed substantial inhibition of human and mouse GIIA sPLA2s (IC_{50} 300 and 180 nM, respectively). It also inhibited human GV sPLA2 with similar potency; however, it did not inhibit human GX sPLA2 (Mouchlis et al. 2011; Yang et al. 2014). A novel series of potential cPLA2 inhibitors based on a 1,3-disubstituted propan-2-one framework were designed by Connolly et al. (2002) at the AstraZeneca pharmaceutical company. Compound **16** containing a decyloxy-lipophilic side chain and a benzoic acid substituent displayed a selective cPLA2 inhibition with an IC_{50} value of 0.008 µM in a bilayer assay, 0.03 µM in a soluble assay, and 2.8 µM in a whole-cell assay. In the subsequent years, a series of 1,3-disubstituted propan-2-one derivatives tethered with an indole ring were introduced (Hess et al 2007; Fritsche et al. 2008; Forster et al. 2010; Drews et al. 2010; Ludwig et al. 2006). The structure–activity relationship (SAR) analysis for the effect of the position of carboxylic group, the nature of the substituent on indole ring, and the replacement of octyl chain by decyloxy appendage led to compound **17** (Fig. 4), which exhibited an IC_{50} of 0.0043 µM in a vesicle assay with isolated cPLA2 enzyme. However, compared to cPLA2, microsomal PGES-1 (mPGES-1), which is an inducible enzyme, is a more promising, superlative target for designing anti-inflammatory drugs, as the inhibition of mPGES-1 eventually disables the PGE2 production. In contrast to COX-1/2 inhibition, the inhibition of terminal mPGES-1 blocks the production of PGE2 without upsetting the normal production of other prostaglandins. Hence, mPGES-1 inhibitors expectedly retain the anti-inflammatory activities of COX-1/2 inhibitors without causing the associated side effects displayed by the COX-1/2 inhibitors. Compounds **10** and **11** (Fig. 4) displayed significant inhibition activity against the mPGE2 enzyme with IC_{50} values 0.0025 and 0.410 µg/ml, respectively.

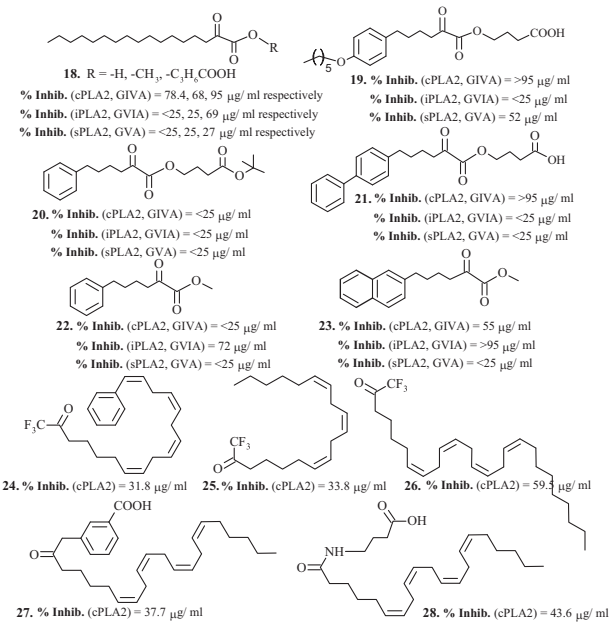


Fig. 5 Recently reported cytosolic phospholipase A_2 ($cPLA_2$) inhibitors

Kokotou et al. (2017) developed novel $cPLA_2$ inhibitors based on the 2-oxoester functionality (**18–23**, Fig. 5) tethered with a long aliphatic chain or a chain appended with an aromatic system and a free carboxyl group. The resultant molecules exhibited a high selectivity towards the inhibition of GIVA $cPLA_2$. Compound **23** appended with a short chain carrying a naphthalene ring and a methyl 2-oxoester functionality displayed the most significant inhibition for $cPLA_2$. This compound also resulted in over 50% decrease in KLA (Kdo2 lipid A)-elicited prostaglandin D2 production in RAW264.7 macrophages, which further supports its anti-inflammatory candidature. A novel class of AA analogs were designed (**24–28**, Fig. 5) and the results were compared with arachidonyl trifuoromethyl ketone (AACOCF3: compound **1**, Fig. 3). The best results for the $cPLA_2$ inhibition were achieved with compounds **27** and **28**, which displayed an $IC_{50} = 11.5$ and 15.5 µM, respectively. For the compounds **24**, **25**, and **26**, the inhibition was much more potent compared to the reference AACOCF3. The

experimental investigations supported the candidature of compound **27**, which was found to be a $cPLA_2$-selective, non-cytotoxic, cell and brain penetrant and capable of reducing ROS and NO production in stimulated microglial cells (Ng et al. 2017). Table 1 highlights the most recently patented $cPLA_2$ inhibitors.

Cycloxygenase enzyme and prostaglandins

The appreciation of prostaglandin synthase enzyme in early 1990s led to the recognition of two discrete isoforms of COX enzyme viz. COX-1 and COX-2. Both the isoforms reportedly held a high homology in the amino acid sequence at the active site (60%), but the presence of Valine523, Arginine513, and Valine434 residues in the COX-2 isoform in place of isoleucine523, histidine513, and isoleucine434 residues (Fig. 6) in the COX-1 isoform leads to a 25% larger active site for COX-2 isozyme (Rouzer and Marnett 2009). The small-sized valine523 residue in COX-2 allows an easy access to a hydrophobic side pocket accompanying the active site. This has substantiated the designing of selective COXIBs where the presence of a bulkier group (sulfonyl) limits the access to the active site of COX-1 isozyme (Michaux and Charlier 2004). However, the same drug for accessing the active site of COX-2 isozyme counters no such constraint. Of the two isozymes, COX-1 is implicated in the bioconversion of AA to homeostatic prostaglandins, a part of the innate immunity mechanism, and it acts as a housekeeping enzyme. COX-2, on the other hand, is involved in the production of prostaglandins, which leads to the escalation of chronic inflammation. Looking into the mechanism of action of COX, a free radical-based Tyr 385 residue is crucial for the abstraction of 13-pro-S hydrogen from AA to yield a pentadienyl free radical delocalized between C11 and C15 (Marnett 2000). The radical reacts with one molecule of oxygen at C11 to yield a peroxide radical, which facilitates cyclization after forming a bond between the free radical oxygen and C9 yielding a five-membered heterocycle followed by a bicycle formation forming a bond between C8 and C12 (Fig. 7). The resultant molecule reacts with another molecule of oxygen at C15 to yield a stable hydroperoxide (van der Donk et al. 2002), PGG2, which is a precursor for the biosynthesis of other prostaglandins (Fig. 8).

Inhibition of cycloxygenase pathway

Starting from hypertension, asthma, atherosclerosis, and arteriosclerosis to cancers, an abnormal production of the metabolites of AA pathway display severe life-threatening implications (Ricciotti and Fitzgerald 2011; Haeggstrom and Funk 2011). The capping of ensuing detrimental effects has been achieved by the introduction of NSAID therapeutics, a category of drugs that restrain the prostaglandin synthesis mediated by COX isozyme, thereby checking the progression of chronic inflammation (Ong et al. 2007). However, due to a poor selectivity towards the perpetrator COX-2 isozyme, the consumption of NSAIDs is associated with severe complications, mainly related to the GI tract (Bjarnason et al. 2018). The identification of NSAIDs' arbitrated side effects led to the recognition of the structural dissimilarity between the COX-1 and COX-2 isozymes, consequently leading to the development of selective COXIBs, with COXIBs holding a representative bulkier group as a main functional characteristic to limit its access to the active site of housekeeping COX-1 isozyme (Limongelli et al. 2010). Being a therapeutic breakthrough, however, the popularity of COXIBs saw a momentary decline due to their association with the development of chronic heart ailments (Funk and Fitzgerald 2007; Martinez-Gonzalez 2007). Apparently, the pharma giants like Merck and Pfizer lost a quarter of their value with the dawn of twenty-first century (www.reuters.com). These events led to the contemporary development of second-generation COXIBs like lumiracoxib (Prexige by Novartis), etoricoxib (Arcoxia by Merck), and parecoxib (Dynastat by Pfizer), which reportedly have a high vigor and several folds high selectivity towards COX-2, but still with a dubious toxicity profile (Stichtenoth and Frolich 2003). Therefore, the search for a potential drug candidate continues. In this report, we will understand the COXIBs under six broad categories.

Salicylate-derived COXIBs

The acetylayed and non-acetylated salicylates form the two categories of this class of anti-inflammatory therapeutics that are effectively used in treating arthritis pain. One of the earliest used drug, aspirin (**29**, Fig. 9), which was first discovered from the bark of willow tree in 1763 and was first synthesized in the year 1897, belongs to the acetylated subset of the salicylates (Higgs et al. 1987). Quite lately after its consistent use as a common analgesic and anti-inflammatory agent, its mechanism of action came into limelight. The COX-2 selectivity for aspirin was later established where it reportedly displayed around a 25-fold superior inhibition profile against the COX-1 isozyme compared to the COX-2 variant (Mitchell et al. 1994). Aspirin suppresses the production of prostaglandins and thromboxanes by irreversibly inhibiting the COXs (Vane and Botting 2003). The success of aspirin led to the contemporary development of other drugs in the class, including salsalate (**30**, Cryer et al. 1990; Goldfine et al 2008), trolamine salicylate (**31**, Rothacker et al. 1994,

Table 1 Patented $cPLA_2$ inhibitors

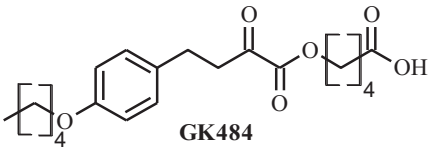
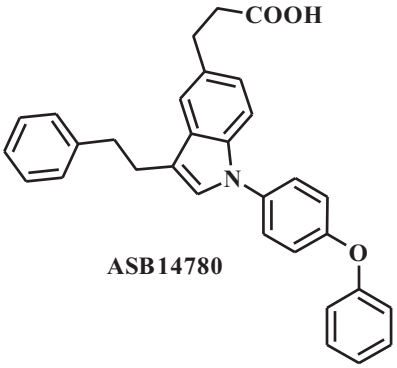
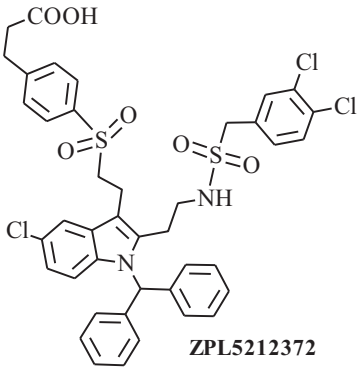
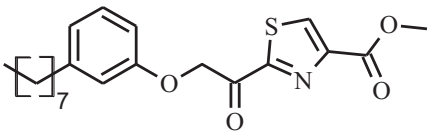
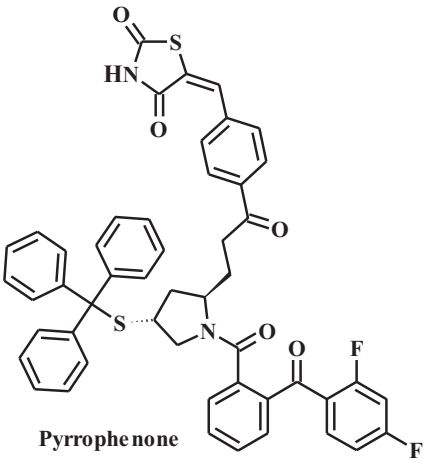
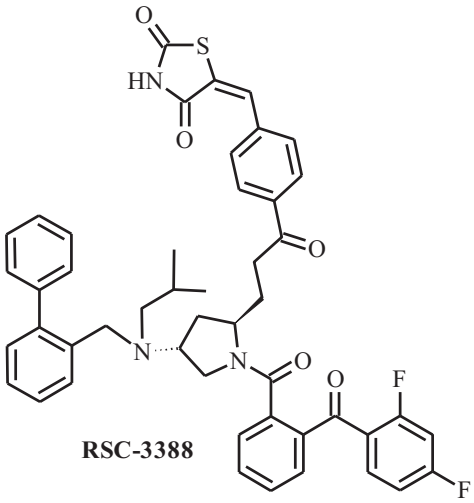
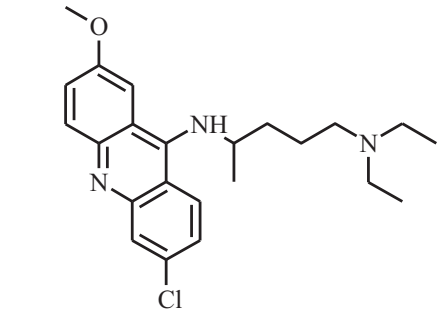
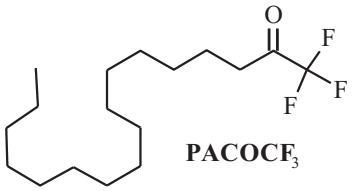
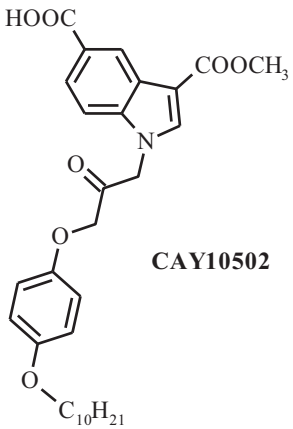
Compound	Inhibition profile	Ref.
 GK484	(a) GIVA $cPLA_2$, $[Xi(50)] = 1.9 \times 10^{-5}$ % Inhib. >95% (b) GIVA $cPLA_2$ % inhib. 86% (c) GIVA $cPLA_2$ <25%	Psarra et al. (2018)
 ASB14780	Potent inhibitor of GIVA $cPLA_2$, used in the treatment of hepatic fibrosis and non-alcoholic fatty liver disease	Kanai et al. (2016)
 ZPL5212372	GIVA $cPLA_2$ $[IC_{50}] = 7$ nM in GLU assay	Hewson et al. (2012)
 AVX235	$cPLA_2\alpha$ inhibitor, anti-angiogenic properties	Eugene et al. (2016)
 Pyrrophenone	(a) Inhibitor of $cPLA_2\alpha$, $IC_{50} = 4.2$ nM (b) Inhibition for interleukin-1-induced prostaglandin E2 synthesis, $IC_{50} = 0.0081$ μM	ONO et al. (2002)

Table 1 (continued)

Compound	Inhibition profile	Ref.
 **RSC-3388**	Inhibitor of $cPLA_2\alpha$, $IC_{50} = 1.8$ nM	Yamamoto et al. (2008)
 **Quinacrine dihydrochloride dihydrate**	Inhibitor of $cPLA_2\alpha$, $IC_{50} = 4.4$ µM	Holscher (1995)
 **$PACOCF_3$**	(a) Ca^{2+}-dependent cytosolic $cPLA_2$ ($IC_{50} = 45$ µM) (b) Ca^{2+}-independent group VI $iPLA_2$ (phospholipases A_2 $iPLA_2$, $IC_{50} = 3.8$ µM)	Ackermann et al. (1995)
 **CAY10502**	Inhibitor of $cPLA_2\alpha$ $IC_{50} = 4.3$ nM	Ludwig et al. (2006)

$cPLA_2$ cytosolic phospholipase A_2, *IC_{50}* half-maximal inhibitory concentration, *GIVA* group IVA, *GLU* glutamate, *$iPLA_2$* calcium-independent PLA_2

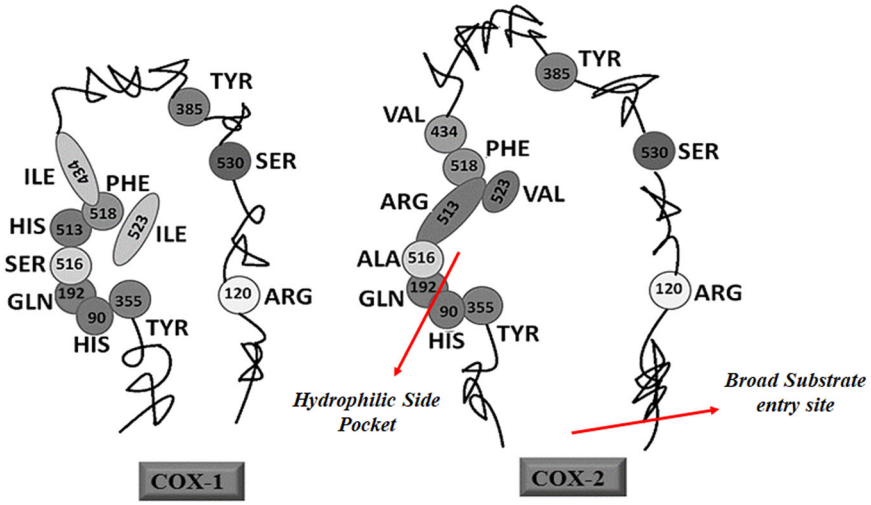


Fig. 6 Structural dissimilarity between cyclooxygenase isoforms

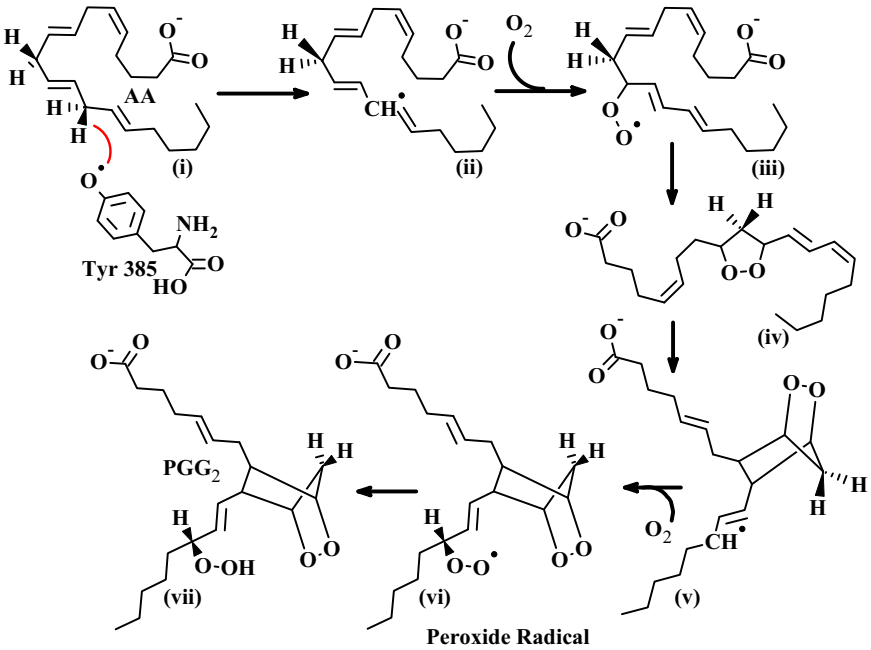


Fig. 7 Mechanism of COX-1/2 enzyme

1998), and trilisate (**32**, Ehrlich et al. 1980; Blechman and Lechner 1979; Kilander and Dotevall 1983) (Fig. 9).

Acid-derived COXIBs

This class of COXIBs comprises the most commonly used anti-inflammatory drugs, including indomethacin (**33**, Fig. 10), which was discovered in 1963 and was approved in the USA by the Food and Drug Administration (FDA) in 1965 (Shen 1982). Another important drug belonging to this class includes diclofenac (**34**, Fig. 9), which was first discovered in 1973 (Sallmann 1986) and is one of the most widely used non-selective COXIB for pain, fever, and swelling. Other important drugs belonging to this class includes sulindac (**35**), Shen 1995), ketorolac (**36**, Resman-Targoff 1990), etodolac (**37**, Humber 1987), aceclofenac (**38**, González-Álvaro et al. 1996), and tolmetin (**39**, Grindel 1981). Another sister class of these drugs incorporate a propionic acid skeleton, leading to the development of some of the core medicines as declared by the World Health Organization. One such example is ibuprofen (**40**, Fig. 10), which was derived from propionic acid in 1960s (Rainsford 2015). Other clinically used members of the family include naproxen (**41**, Harrington and Lodewijk 1997), ketoprofen (**42**, Kantor 1986), and flurbiprofen (**43**, Agrawal et al. 2015), and oxaprazin (**44**, Miller 1992) as shown in Fig. 10.

Another class of COXIBs includes the "oxicam" class of anti-inflammatory drugs (Xu et al. 2014), of which piroxacam (**45**, Fig. 11) is one of the representative members (Ando and Lombardino 1983; Dahl and Ward 1982). It

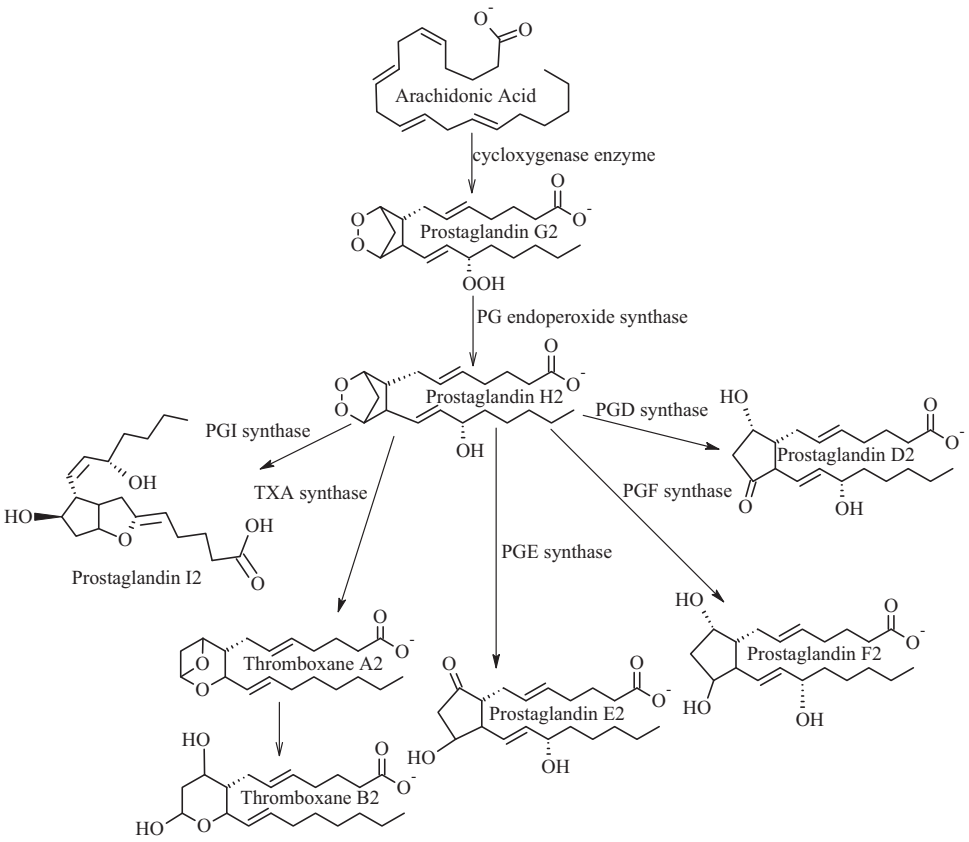


Fig. 8 Arachidonic acid metabolism by cyclooxygenase enzyme

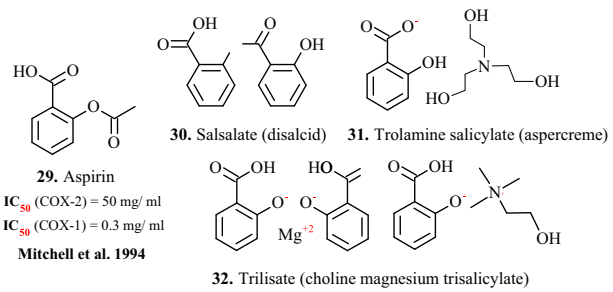


Fig. 9 Cycloxygenase inhibitors based on salicylic acid

shows both analgesic and anti-pyretic effects and is a non-selective NSAID. Meloxicam (**48**, Fig. 11) is another integral member of this class of anti-COX therapeutics, but reportedly show lesser side effects than piroxicam (Yocum et al. 2000). This class also includes the sister drugs tenoxicam (**46**, Fig. 11) and lornoxicam (**47**, Fig. 11) (Facino et al. 1996; Zarski et al. 1998; Leigh et al 1989; Yakhno et al. 2006; Buritova and Besson 1997). Isoxicam (**49**, Fig. 11) is clinically exploitable; however, its marketing suffered a ban because of its fatal skin reactions (Yakatan 1982). Several piroxicam derivatives developed as its prodrugs (Redasani et al. 2017) display reduced GI side effects (Redasani et al. 2014). The prodrugs like ampiroxicam (Carty et al. 1993; Falkner et al. 1989) and droxicam (Martinez and Sanchez 1991) that were found to be stable under gastric conditions have been successfully marketed. The anti-COX compounds based on *N*-arylanthranilic acid skeleton, better known as "fenamates" form another important class of NSAID family (Kankaanranta et al. 1994; 1996; Rees et al. 1988; Orlando and Malkowski 2016). Meclofenamic acid (**50**, Fig. 11) remains the prevalent drug in this category ever since its approval by the FDA in 1980. It is a non-selective NSAID and is used for the treatment of inflammatory pain associated with arthritis by inhibiting the production of prostaglandins (Stadler et al. 1994; Kalgutkar et al. 2002; Levy and Lindner 1971). Other important members of this family include flufenamic acid (**51**, Fig. 11; Lentjes and van Ginneken 1987), tolfenamic acid (**52**, Fig. 10; Pentikainen et al. 1981), and mefenamic acid (**53**, Fig. 11; Ito et al. 1994; Li et al. 2013).

Anilide and sulfnilide-derived COXIBs

After administration, acetanilide is ring hydroxylated to yield acetaminophen, which is an active analgesic/anti-pyretic. On the contrary, phenacetin undergoes oxidative-O-dealkylation, thereby generating acetaminophen (Merrill and Adams 1917). Due to the absence of carboxylic acid functional group, the anilides possess a meager inhibitory activity against COX enzyme (Brodie and Axelrod 1948).

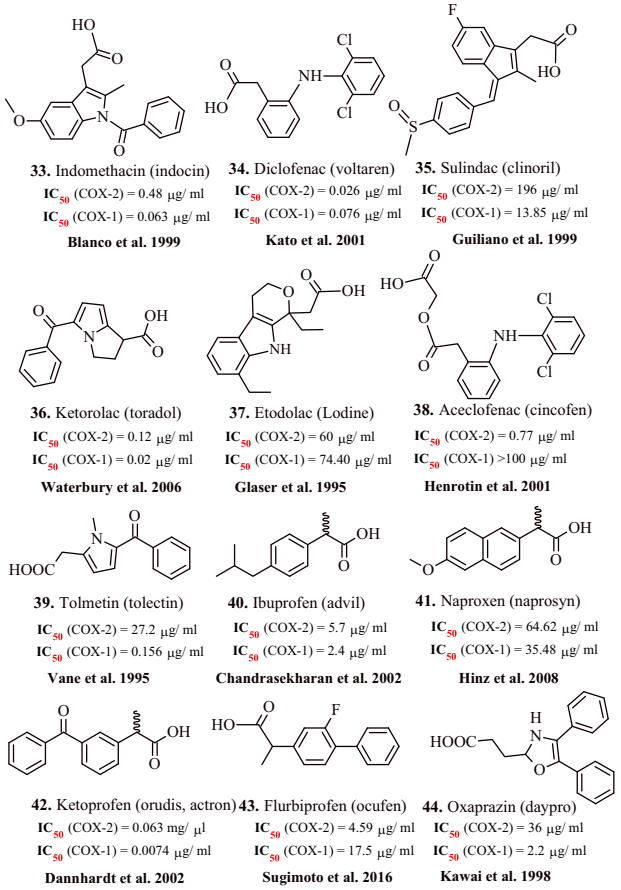


Fig. 10 Acetic/propionic acid-based cyclooxygenase inhibitors

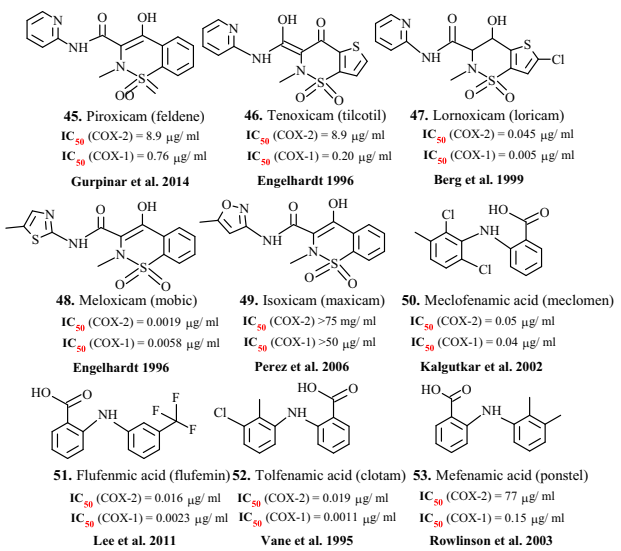


Fig. 11 Enolic and fenamic acid-based cyclooxygenase inhibitors

Anilides act as scavengers of hydroperoxide radicals generated by invading leukocytes having a stimulating effect on COX (Fig. 12) (Hinson 1983). However, an elevated leukocyte activity raises the concentration of hydroperoxides

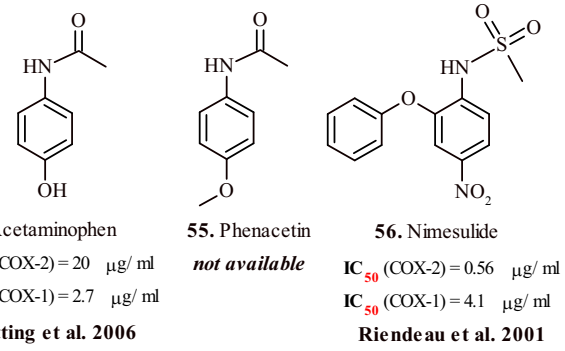


Fig. 12 Anilide- and sulfoanilide-based cyclooxygenase inhibitors

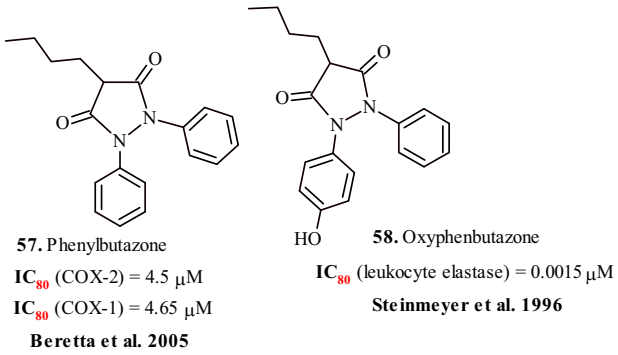


Fig. 13 Phenylpyrozolone-based cyclooxygenase inhibitors

that are able to overcome the anilides eventually producing prostaglandins in the due course (Prescott 1980). This restricts the anti-inflammatory action of anilides only in the uninflamed areas. The absence of carboxylic acid functionality and a limited COX inhibitory activity impart several advantages to anilides, which include partial gastric irritation and ulceration, imperfect cardiovascular, and respiratory effects (McClean 1978). However, being aromatic amines, the anilides manifest several glitches: methemoglobinemia, anemia, hepatoxicity, and nephrotoxicity (McClelland and Patel 1981).

Phenylpyrozolone-derived COXIBs

The presence of 1-aryl-3, 5-pyrazolidinedione scaffold typify this class of NSAIDs (Carty 1973). The acidity of phenylpyrozolones is due to the presence of a proton flanked by the two electron-withdrawing carbonyl groups (Fig. 13). Phenylbutazone and oxyphenbutazone, used predominantly for the treatment of rheumatoid arthritis and osteoarthritis (Gulati et al. 1969), causes adverse reactions that include GI irritation, retention of Na^+ and H_2O, and blood dyscrasias (Tobin et al. 1986). Characteristic to NSAIDs, these agents are comprehensively bound to protein, resulting in numerous drug interactions with other acidic drugs, such as anticoagulants, hypoglycemics,

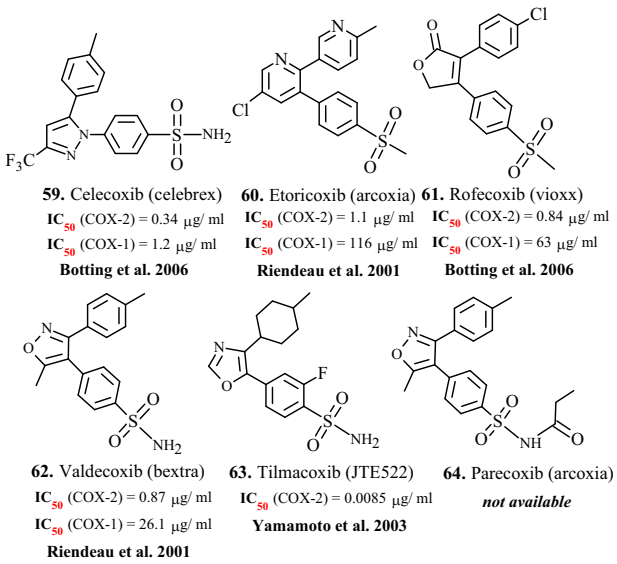


Fig. 14 Selective cyclooxygenase-2 (COX-2) inhibitors

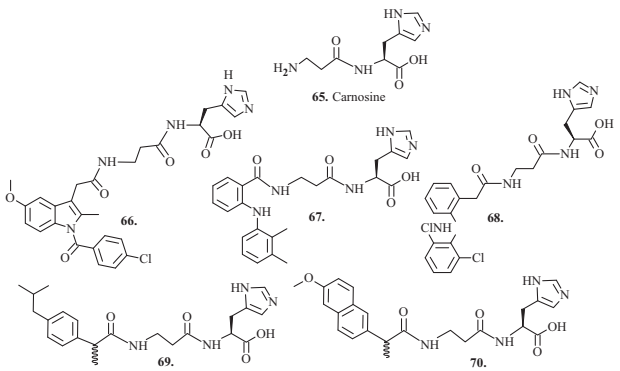


Fig. 15 Conjugates of non-steroidal anti-inflammatory drugs (NSAIDs) with carnosine

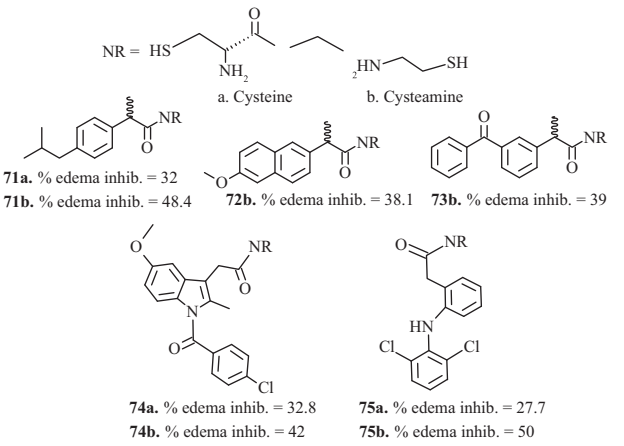


Fig. 16 Conjugates of non-steroidal anti-inflammatory drugs (NSAIDs) with –SH group containing antioxidants

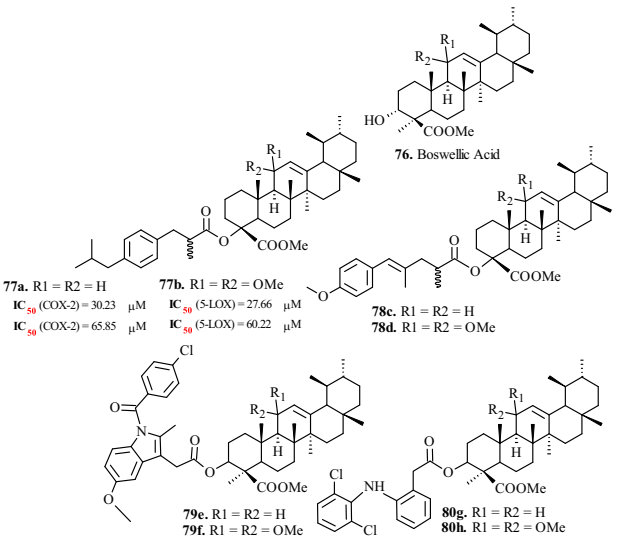


Fig. 17 Boswellic acid–non-steroidal anti-inflammatory drug (NSAID) conjugates

sulfonamides, other NSAIDs, and glucocorticoids. Phenylbutazone metabolizes to para (oxyphenbutazone) and omega-1 metabolites in the liver (Aarbakke 1978).

COX-2-selective inhibitors (COXIBs)

Unlike nfon-selective NSAIDs, the COXIBs selectively cap the activity of COX-2 enzyme. The preliminary drugs: DUP697 (Gans et al. 1990) and NS398 (Futaki et al. 1993) laid the foundation for the discovery of selective COXIBs. The launch of celecoxib (**59**, Fig. 14; Goldenberg 1999) and rofecoxib (**61**, Fig. 14; Prasit et al. 1999) in the late 1990s was considered a historical breakthrough, as unlike NSAIDs, these drugs did not produce any GI ulcerogenic effects. The contemporary release of valdecoxib (**62**, Fig. 14; Alsalameh et al. 2003) in the market as selective COXIB fortified the COXIBs regime until the associated cardiovascular side effects were recognized. This apparently led to the withdrawal of rofecoxib and valdecoxib from the market. After the exclusion of rofecoxib and valdecoxib, celecoxib remains the only legally available selective COXIB. Etoricoxib (**60**, Fig. 14; Takemoto et al. 2008) and parecoxib (**64**, Fig. 14; Karim et al. 2001) are the other selective COXIBs used in around 80 countries all over the world, but have not still been approved by FDA. Tilmacoxib (**63**, Fig. 14; Yamamoto et al. 2003) has also been reported as a COX-2-selective inhibitor and is used against osteoarthritis and rheumatoid arthritis.

The side effects associated with NSAIDs and selective COXIBs on the GI tract and the cardiovascular system demand an urgency for the development of novel potent and safe anti-inflammatory drugs. mPGES-1 inhibitors may present superior safety in comparison to existing anti-inflammatory drugs. After the discovery of first mPGES-1

synthetic inhibitor in 2001, the contemporary era has witnessed the development of a variety of structurally different inhibitors. However, only a few inhibitors entered clinical trials and none has reached yet the market. Table 2 displays some of the recently patented molecules with anti-mPGES-1 activity. However, extended preclinical investigations and clinical trials are required to realize therapeutic potency of mPGES-1 as the potential target for the treatment of inflammation and related disorders.

The lesson learnt from the NSAID and COXIB episode clearly raises the aspirations for a novel class of therapeutics or an upgradation of the prevailing drugs as they have faced frequent withdrawals owing to their ostensible toxicity profile (Table 1). From masking the free carboxylic group to their tethering with intracellular NO-releasing probes, a numerous strategies have been adopted to counter the severities associated with NSAIDs and COXIBs, still only a limited success has been experienced. The practice of polypharmacology could solve the NSAID riddle, where the introduction of hybrid molecules combining the desired profile of the parent therapeutics gets the expected outcome. This practice extended to the anti-inflammatory drug discovery has already started delivering, though not proving to be a decisive retort against the offensive NSAIDs.

L-carnosine (β-alanine L-histidine) is an endogenous dipeptide, which acts as a cytosolic buffering agent (Quinn et al. 1992) and is known to maintain a healthy gastric mucosa by capping the ailments such as lesions in gastric mucosa, erosion of mucosal cell by histamine, aspirin, and indomethacin, and duodenal ulcers induced by mepirizole (Nishiwaki et al. 1997; Ohkawara et al. 2006; Ueda et al. 2009). Additionally, carnosine reportedly have antioxidant and anti-inflammatory properties (Tsai et al 2010). Sahu et al. (2013) reported an efficient method to synthesize the hybrid compounds based on L-carnosine scaffold conjugated to the NSAIDs (**65–70**, Fig. 15). The basic idea behind this design was to create potential hybrids, which could combine the gastro-protective properties of carnosine nucleus with the conventional NSAIDs. A critical relationship between the generation of ROS and inflammation-related disorders is well recognized. Investigations indicate that the indomethacin-induced gastric ulcerations develop due to the oxidative stress created by the latter. Several antioxidant nuclei display substantial anti-inflammatory activity in conjugation with classical NSAIDs to get an enhanced anti-inflammatory effect and overcoming the gut-related problems created by the latter.

Kourounakis et al. (1999) synthesized the conjugates of anti-inflammatory drugs, such as indomethacin, diclofenac, and ibuprofen, with cysteamine, a polar antioxidant molecule through an amide linkage (**71–75**, Fig. 16). The conjugates displayed a remarkable antioxidant activity by inhibiting the lipid peroxidation and an enhanced anti-inflammatory potency compared to the parent drug (Kourounakis et al. 1999). The sulfhydryl group present on cysteamine provides antioxidant property to the compounds, which also substantially reduced their ulcerogenic potency and improved their lipophilicity compared to the parent drug. Retaining a similar antioxidant profile of sulfhydryl group, L-cysteine ethyl ester replaced cysteamine, resulting in a considerably lower GI toxicity (Galanakis et al. 2004).

Alkaloids obtained from *Boswellia serrata* have been widely acknowledged for their anti-inflammatory properties by inhibiting the generation of tumor necrosis factor-α (TNF-α) by human monocytes (Syrovets et al. 2005) as well as against the ulcerative colitis (Gupta et al. 1997a, b; 2001). Shenvi et al. (2015) subjected the methyl esters of the β-boswellic acid and 11-keto-β-boswellic acid obtained from *Boswellia serrata* resin to Steglich esterification with NSAIDs, such as naproxen, ibuprofen, indomethacin, and diclofenac, to get NSAID–boswellate conjugates (**76–80**, Fig. 17). A significant inhibition of carrageenan-induced paw edema was observed when testing compounds. A synergistic effect was observed for the conjugates containing ibuprofen in the appendages, with minor signs of toxicity compared to the parent drug. These conjugates were highly effective anti-arthritic agents in the Wistor albino rat model (Shenvi et al. 2015).

Caffeic acid phenylethyl ester (CAPE) is a naturally occurring anti-inflammatory agent (**81**, Fig. 18), which is reportedly a specific inhibitor of nuclear factor-κβ (Natarajan et al. 1996). CAPE is known to inhibit the formation of superoxide ion produced during the autoxidation of β-mercaptoethanol. It inhibits the activity of xanthine oxidase, a physiological source of superoxide ions in the eukaryotic cells. Additionally, the histological investigations reveal the anti-ulcerative potency of CAPE in the mice with dextran sulfate sodium-induced colon injury (Khan et al. 2018). The CAPE–NSAID conjugates (**81–83**, Fig. 18) have been instrumental in reducing the PGE2 and TNF-α levels in the aqueous humor, as well as proteins and polymorphonucleosides. Any event relating to ocular irritation reduced with the CAPE–indomethacin hybrid, **82**. CAPE–aspirin conjugates, **83**, reportedly displayed a significant anti-inflammatory potential in the ocular inflammation experimental model along with an optimal pharmacological and safety profile (Pittala et al. 2015), thereby presenting a useable and benign new chemical entity expedient for the management of ocular inflammation.

Del Soldato et al. (1996) synthesized NO-releasing NSAIDs (**84–91**, Fig. 19), which unlike the parent drug were reported to have a high bio-tolerability coupled with a retained selective COX-2 inhibitory profile. The mechanistic investigations have revealed that the non-ulcerogenic activity of these hybrids is due to the intracellular release of

Table 2 Recently patented mPGES-1 inhibitors

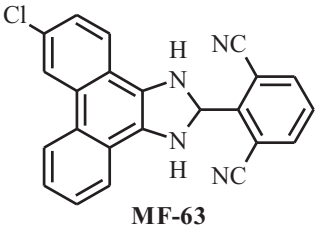
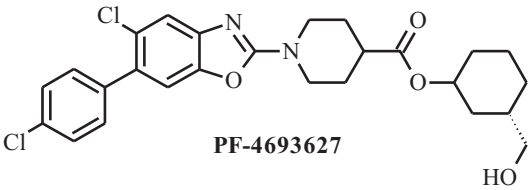
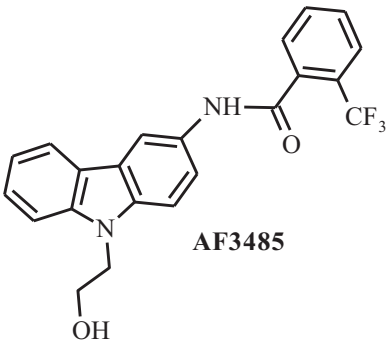
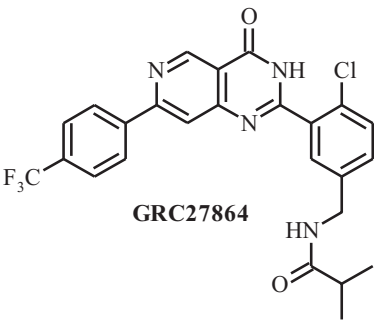
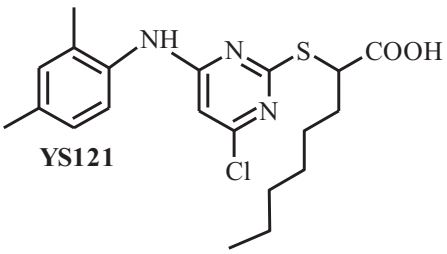
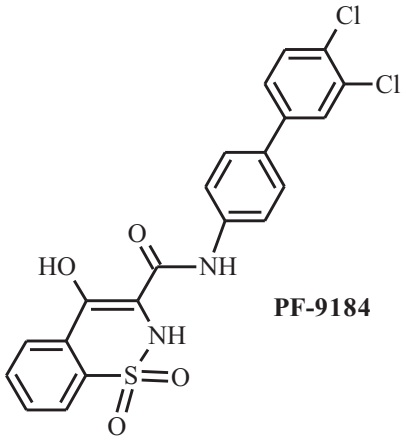
Compound	Inhibition profile	Ref.
 **MF-63**	mPGES-1 (IC_{50}) = 0.42 μM	Nakanishi and Rosenberg (2013)
 **PF-4693627**	mPGES-1 (IC_{50}) = 0.109 μM	Arhancet et al. (2013)
 **AF3485**	mPGES-1 (IC_{50}) = 2.55 μM	Finetti et al. (2012)
 **GRC27864**	mPGES-1 (IC_{50}) = 12 nM	Banerjee et al. (2014)
 **YS121**	mPGES-1 (IC_{50}) = 3.4 μM	Koeberle et al. (2010)

Table 2 (continued)

Compound	Inhibition profile	Ref.
 **PF-9184**	mPGES-1 (IC_{50}) = 16.5 nM	Mbalaviele et al. (2010)

IC_{50} half-maximal inhibitory concentration, *mPGES* microsomal PGES-1

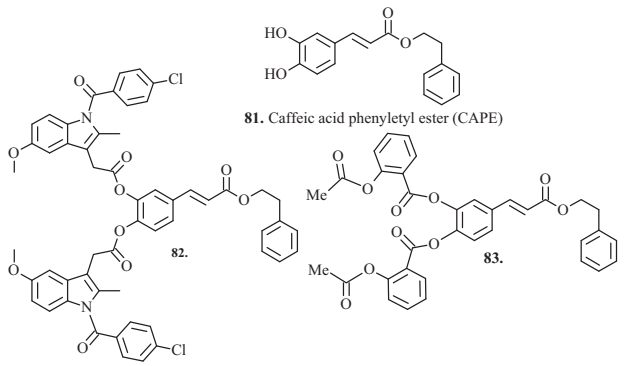


Fig. 18 Caffeic acid–non-steroidal anti-inflammatory drug (NSAID) conjugates

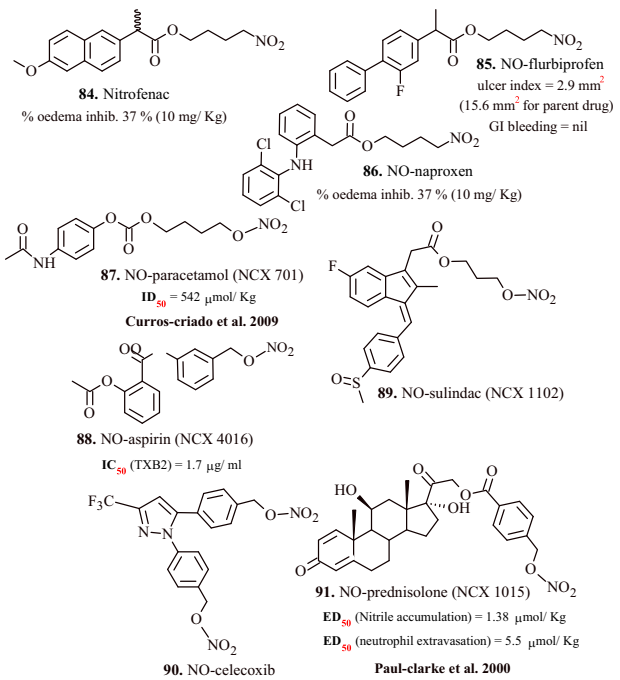


Fig. 19 Nitric oxide-releasing non-steroidal anti-inflammatory drugs (NSAIDs) and steroidal anti-inflammatory drugs (SAIDs)

NO, which plays a protective role on the tissue integrity due to its vasodilatory properties and an ability to inhibit the neutrophil adherence to the vascular endothelium (Moncada et al. 1991). However, such an event would lead to the cellular activation, consequently redeeming the oxygen-derived free radicals and proteases, leading to capillary blockade inevitably reducing the blood flow to the gastric mucosa, thereby exposing the mucosa to damage (Watanabe et al. 2002). This mechanism restrains in the presence of NO. The popularization of the new concept of NO donor NSAIDs to mimic the physiological intracellular release of NO has gained momentum in the recent decades, leading to the commercialization of several NSAID–NO hybrids. NCX4016, a NO-releasing aspirin derivative, releases NO intracellularly at a rate that is comparable to the endothelial NO synthase (Fulton et al. 2002). Additionally, the antithrombotic activity of NCX4016 (**88**, Fig. 19) has been reported to be significant compared to the parent drug (Wallace et al. 1999). The most substantial effects of NCX4016 include the initiation of local vasodilation, inhibiting the release of cytokines leading to the optimizing of oxidative stress and inflammation, and improving the vascular cell regeneration (Fiorucci et al. 2000). Nitrosulindac NCX1102 reportedly brings forward the antitumour potency of the NSAIDs, demonstrating a greater antiproliferative potency of NCX1102 compared to its parent molecule sulindac (Huguenin et al. 2004). In vivo

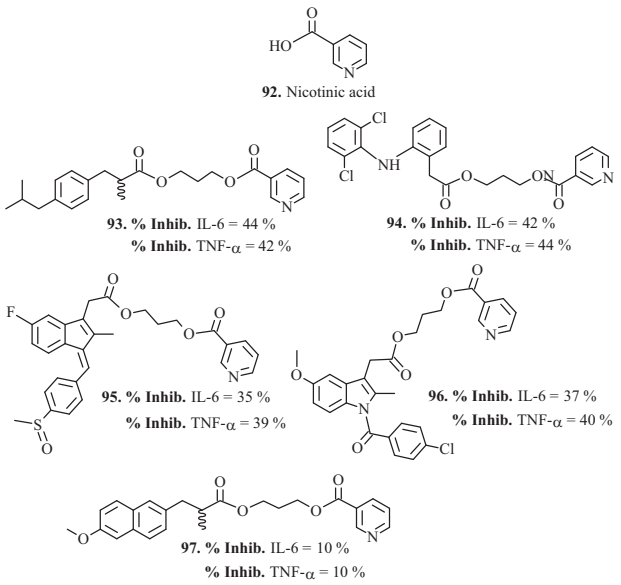


Fig. 20 Nicotinic acid–non-steroidal anti-inflammatory drug (NSAID) conjugates

investigations on NO-flurbiprofen (**85**, Fig. 19) and flurbiprofen in the perfused cirrhotic liver reveal that both drugs improved the dysfunctioning of endothelium and hyperresponsiveness associated with a decreased hepatic thromboxane A2-production and an increased intrahepatic nitrate/nitrite level. Another significant observation was the appearance of severe GI ulcerations in flurbiprofen-treated rats, and nefrotoxicity, which was not observed in NO-flurbiprofen-treated cirrhotic rats (Laleman et al. 2007).

Gund et al. (2013) designed a new series of nicotinic acid conjugates with NSAIDs (**92–97**, Fig. 20). Experimental investigations revealed a substantial improvement in the anti-inflammatory activity over the parent drug. The investigations were mainly done on human TNF-α and interleukin-6. The quantification of pro-inflammatory chemokines and cytokines by an enzyme-linked immunosorbent assay investigations revealed the toxicity profile for these compounds to be within the acceptable limits, thereby making NSAID–nicotinic acid conjugation a leading combination in the anti-inflammatory drug discovery (Table 3).

Moller et al. (1989) developed a series of 5-aminosalicylic acid–NSAID conjugates (**98–102**, Fig. 21) and subjected them to various biological assays for evaluating their anti-inflammatory activity and GI toxicity. These conjugates substantially inhibited the in vitro release of prostaglandins and presented significant anti-LOX activities by inhibiting the in vitro leukotriene production as well. A similar trend occurred in both the in vivo rat carrageenan paw edema and rat adjuvant-induced arthritis models. The in vivo acute toxicity analysis for determining the GI toxicity in rats displayed that the number of observed lesions was insignificant compared to the parent NSAIDs acting as controls. Hence, the 5-aminosalicyclic acid–NSAID combination could be a useful discovery for designing the lead molecules that could overcome the representative shortcomings associated with most NSAIDs.

Bansal and Silakari (2014) synthesized the novel hybrids containing 2-amino benzimidazole and NSAIDs (**103–105**, Fig. 22) and evaluated their anti-inflammatory and immunomodulatory activities. Importantly, the investigation on their antioxidant and ulcerogenic potency provided substantial results. Chiefly, the compounds **99** and **100** displayed a significant safety towards the gastric mucosa and did not lead to the development of gastric ulcers, thereby validating the candidature of these conjugates as potential anti-inflammatory leads with an enhanced safety.

5-LOX enzyme and leukotrienes

The crystal structure of LOX enzyme comprises of a non-heme Iron cofactor present as Fe^{+2} ion in its inactive state (Pistorius and Axelrod 1973 and Pistorius et al. 1974). Five amino acid residues including three histidines in addition to a single isoleucine and asparagine together form distorted bipyramidal (octahedral) geometry around the Fe^{+2} ion (Boyington et al. 1993). An activated water molecule occupies the sixth position in this geometry. Leukotrienes are a direct manifestation of the catalytic action of LOX enzyme on AA via a stable hydroperoxide intermediate. On approaching a hydroperoxide radical, the oxidation state of iron in the inactive form of LOX, Fe (II)-H_2O, changes to ferric, Fe (III)-OH, thereby activating the enzyme. Fe (III)-OH performs a stereospecific attack on the bis-allylic pro-*S* hydrogen of the pentadiene sub-system of the fatty acid through a proton-coupled electron transfer mechanism, which eventually generates a carbon-centered free radical delocalized via π-type electron system. The molecular oxygen could therefore attack on the fatty acid backbone either through R or S face of the free radical generating a peroxide radical, which again acts as an activating agent for the Fe (II)-H_2O, which protonates the peroxide radical to generate a stable hydroperoxide. If the precursor polyunsaturated fatty acid is AA, then the stabilized hydroperoxide formed is termed as 5-HPETE (5(*S*)-hydroperoxyeicosatetraenoic acid), which is actually AA with hydroperoxide functional group at the fifth position. The catalytic activity of dehydrase enzyme triggers the bioconversion of 5-HPETE to leukotriene A4 (LTA4), which acts as a precursor for the formation of other pro-inflammatory leukotrienes (Andreou and Feussner 2009). The redox state of iron therefore shuffles between the inactive Fe (II)-H_2O and the active Fe(III)-OH during the whole catalytic cycle of LOX enzyme (Figs. 23, 24).

Table 3 List of withdrawn NSAIDs and COXIBs

Drug	Trade name	Target	Adverse effects	Manufactured by	Introduction year	Withdrawl ear
Etodolac	Lodine	Hyperalgesic, treatment of osteoarthritis and rheumatoid arthritis	Hypersensitivity, gastrointestinal defects	Wyeth Pharmaceuticals Inc.	January 1991	Not available
Ketoprofen	Orudis KT and Actron	Analgesic, Anti-pyretic	Gastrointestinal effects, sleeplessness	AA Pharma Inc.	July 1973	September 2016
Nabumetone	Relafen, Relifex, Gambaran	Pain associated with osteoarthritis and rheumatoid arthritis	Hypersensitivity	Smithcline Beecham	December 1991	Not available
Sulindac	Tolmetin& Clinoril	Preterm labor, Alzheimers, inflammation	Peptic ulcers	Merck	March 1972	Not available
Bromfenac	Duract	Pain killer	Hepatotoxic	Wyeth-Ayerst Laboratories	July 1997	June 1998
Valdecoxib	Bextra	Pain relief	Cardiovascular defects, gastrointestinal problems, skin problems: epidermal necrolysis	G.D. Searle & Co.	November 2001	April 2005
Rofecoxib	Vioxx	Pain relief	Cardiovascular defects	Merck	May 1999	September 2004
Ketorolac	Toradol	Analgesic	Cardiovascular risk, hypersensitivity, renal impairment, hepatotoxic	Syntex Corp.	May 1989	Not available
Lumiracoxib	Prexige	Analgesic	Hepatotoxic	Novartis	November 2006	August 2007

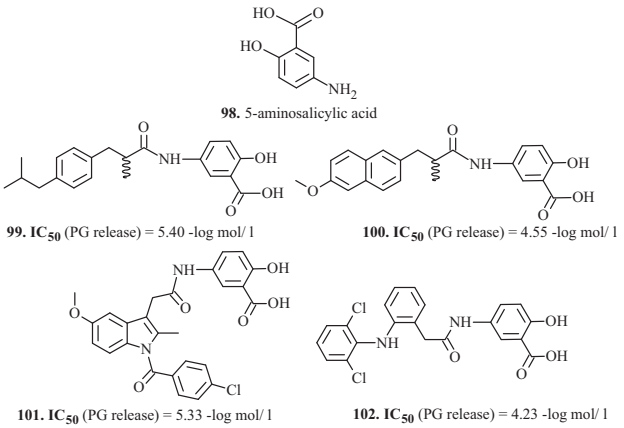


Fig. 21 5-Aminosalicylic acid–non-steroidal anti-inflammatory drug (NSAID) conjugates

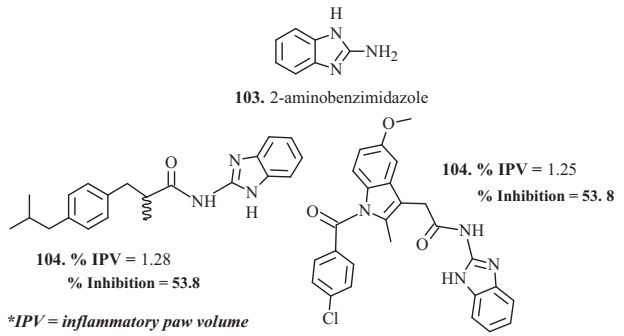


Fig. 22 2-Amino benzimidazole–non-steroidal anti-inflammatory drug (NSAID) conjugates

Five LOX-activating protein targeting drugs

Upon an immune, allergic, or inflammatory stimulation, the leukotriene synthesis by leukocytes begins stimulating the translocation of $cPLA_2$ and 5-LOX to endoplasmic reticulum, Golgi apparatus, and nuclear membranes. Five LOX-activating protein (FLAP) embedded in the membrane selectively transfers the substrate, AA to the active site of 5-LOX enzyme, followed by the sequential oxygenation of AA to 5-HPETE and dehydration to LTA4, which is implicated in inflammation and related complications (Evans et al. 2008). The cellular leukotriene synthesis can therefore be completely inhibited by the compounds that bind to FLAP. In the year 1988, an indole-based leukotriene synthesis inhibitor MK886 (**109**, Fig. 25) (Rouzer et al. 1990) was identified, but while deciphering its mechanism, it was found inactive towards the 5-LOX enzyme or phospholipases. It was followed by a subsequent identification of another quinolone class leukotriene synthesis inhibitor DG031 (Muller-Pedinghaus et al. 1993; Hatzelmann et al. 1993) with a similar mode of action. While determining the molecular targets of MK886 and DG031, 18 kDa integral membrane protein was discovered, and because of its ability

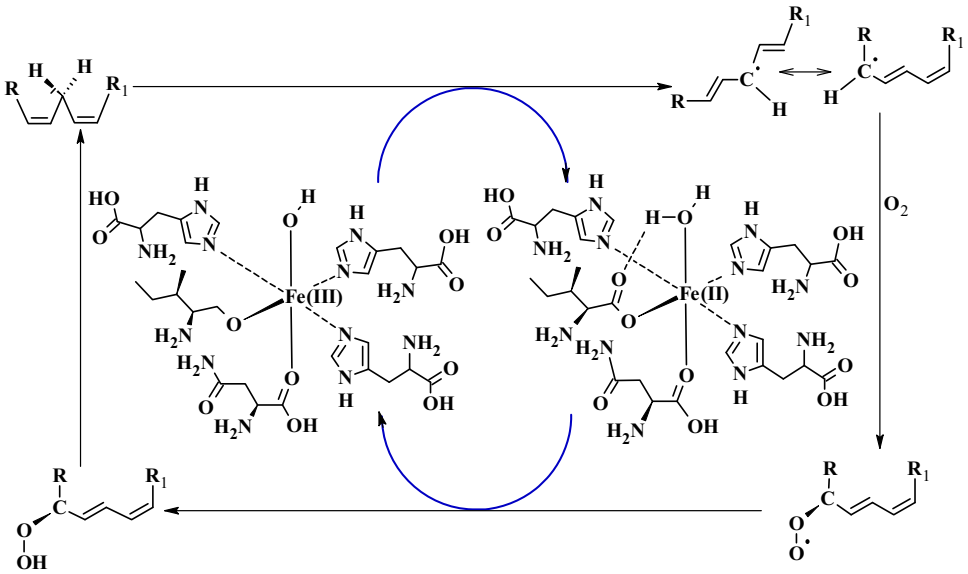


Fig. 23 Role of iron cofactor in 5-lipoxygenase (5-LOX) enzyme activity

to influence the cellular activity of 5-LOX, this protein was named FLAP. With the identification of active site of FLAP, an indole-quinoline hybrid compound MK591 (**108**, Fig. 25) (Prasit and Vickers 1995; Diamant et al. 1995) was developed, which is also regarded as a second-generation leukotriene biosynthesis inhibitor. Figure 25 represents other classes of FLAP inhibitors.

5-LOX inhibitors with iron-chelating properties

Inhibition of 5-LOX occurs by the replacement of one of the ligands of octahedral Fe^{2+} to create a new complex. Molecules with iron-chelating functionalities such as hydroxamic acid or *N*-hydroxyurea are potent inhibitors for 5-LOX. Zileuton (**114**, Fig. 25) (Bell et al. 1992) is one of the 5-LOX iron chelator inhibitors that is commercially available for the treatment of asthma under the trade name "zyflo." Despite its effectiveness, zileuton is not the first choice therapy due to its side effects, such as nausea and idiosyncratic effects on the liver. Further development of this class of inhibitors led to the identification of atreleuton (**115**, Fig. 26), which inhibits LTB4 and cys-LTE4 production and has a potency that is about 5-fold enhanced in comparison to zileuton. Atreleuton (Gaztanaga et al. 2015), which has entered clinical trials for atherosclerosis and cardiovascular diseases, is one of the leading 5-LOX inhibitors in clinical development (Fig. 26).

Leukotriene antagonist drugs

A new class of compounds, known as leukotriene receptor antagonists, have laudable properties against the leukotriene biosynthesis. Pranlukast (Keam et al. 2003), Zafirlukast (Lynch et al. 1999; Bernstein 1999), and Montelukast (Young 2012) (Fig. 27) are the most popular leukotriene receptor antagonists known for their effectiveness in the treatment of asthma. The mode of action of these drugs involve the blocking of the binding of leukotriene D4 and also LTC4 and LTE4 to the cysLTR1 in the lungs and bronchial tubes, which resulted in the reduction of airway constriction, and mucus accumulation in the lungs. Reportedly, Montelukast (**117**, Fig. 27) suppresses the leukotriene biosynthesis by selective inhibition of 5-LOX and gives no effect on the other enzymes involved in the leukotrienes biosynthesis pathway, such as LTA4 hydrolase and LTC4 synthase. Despite its efficacy against asthma, the safe use of Montelukast is still under question as they cause liver-related problems (Harugeri et al. 2009).

Redox and non-redox inhibitors

Redox inhibitors have a limiting effect on the expression of LOX enzyme by acting as antioxidants. Phenidone, BW755C (Parellada and Carnonell 1985), and AA-861 (Ashida et al. 1983) are well-known reducing agents. Reportedly, the redox potency lipophilicity is also important. New molecules such as trimer or tetramer of caffeoyl and cinnamoyl clusters having a potential for redox inhibition for 5-LOX are one of the recent developments in anti-LOX therapeutics (Doiron et al. 2009; Boudreau et al. 2009). It is important to mention that redox inhibitors have a low selectivity for 5-LOX inhibition compared to COXs' inhibition. Apart from their appreciable potential to inhibit leukotriene biosynthesis, their major drawback is that these interfere with biological redox processes. The formation of methemoglobin is one of the problems associated with the

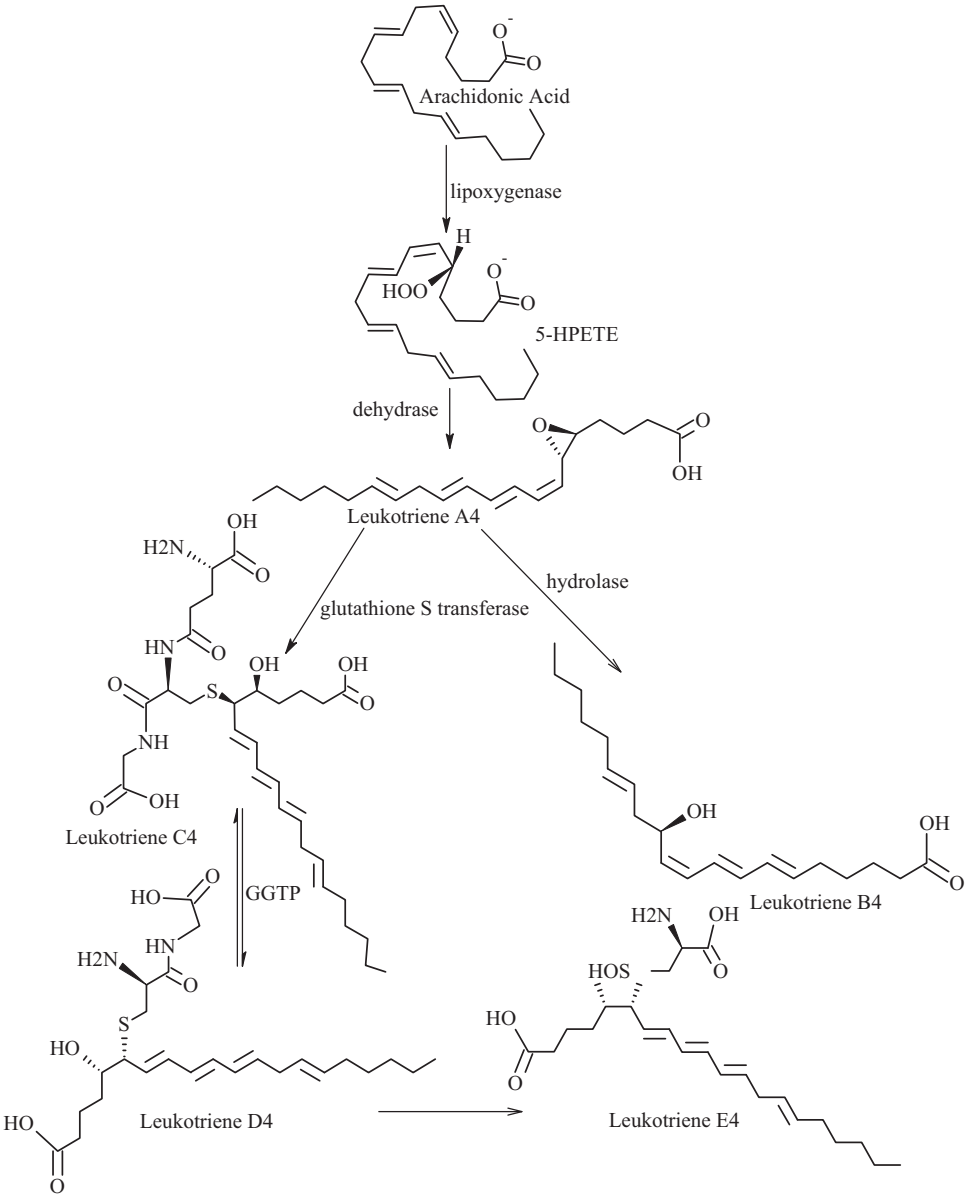


Fig. 24 Arachidonic acid metabolism by lipoxygenase enzyme

application of redox inhibitors. Non-redox inhibitors have mode of action different from redox inhibitors, FLAP inhibitors, and iron chelation inhibitors. These do not interfere with the oxidation reaction of LOXs nor do they have iron-binding properties. These inhibitors act by competitively binding to the active site of LOX enzyme. Binding may occur to an allosteric binding site, which regulates the activity of the enzyme. The non-redox inhibitor like (methoxyalkyl) thiazole (ICI211965) selectively inhibits 5-LOX activity, which reduces LTC4 and LTB4 synthesis in animals as well as in human blood samples (**121**, Fig. 28). Although ICI211965 is a highly potent 5-LOX inhibitor from a novel structural class, it has a low oral potency (Bird et al. 1991; Crawley et al. 1992).

Hybrid molecules for dual COX-2/5-LOX inhibition

Reportedly, an inhibition of COX pathway by NSAIDs results in an upregulation of AA pathway by LOX enzyme, thereby augmenting the leukotriene production and increasing the severity of its associated disorders (Gilroy et al. 1998). The counter productivity of NSAIDs led to the emergence of a novel category of hybrid anti-inflammatory molecules, which incorporate the inhibitory profile against both 5-LOX and COX-2 enzymes (Pelletier et al. 2003). Licofelone, containing a pyrrolizine scaffold, which initially popularized as anti-osteoarthritis medication (Cicero and Laghi 2007) eventually established as the first dual inhibitor

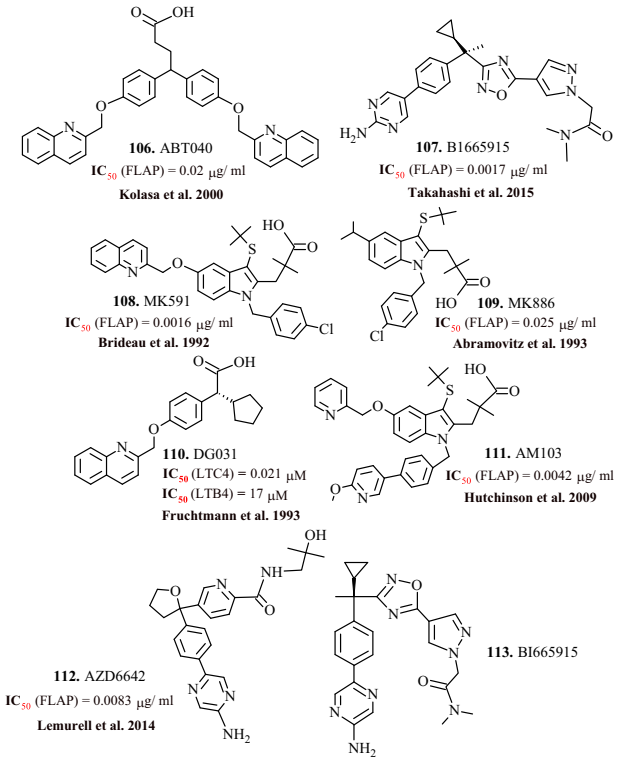


Fig. 25 Commercial five LOX-activating protein (FLAP) inhibitors

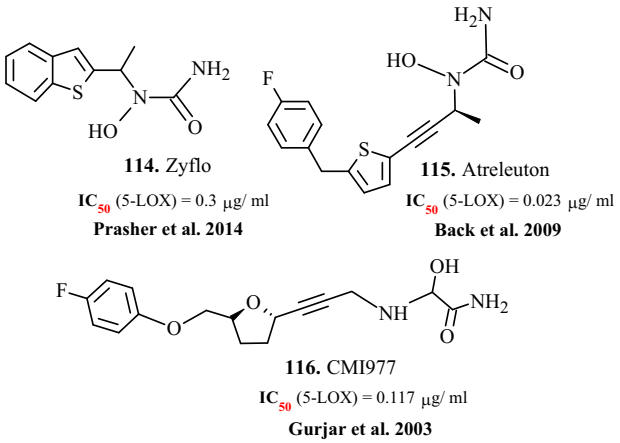


Fig. 26 Iron chelator inhibitors

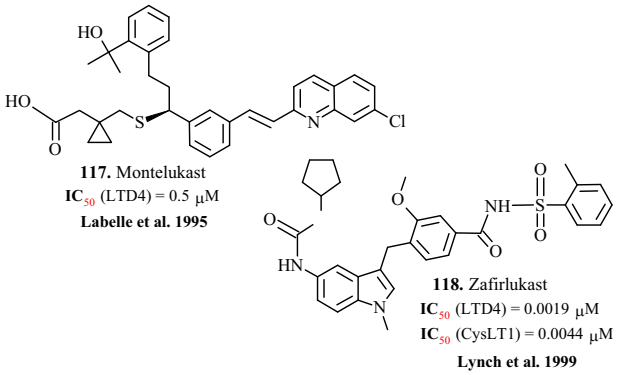


Fig. 27 Leukotriene receptor antagonists

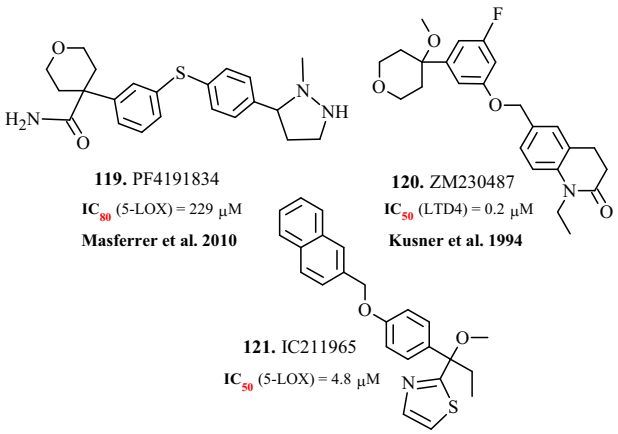
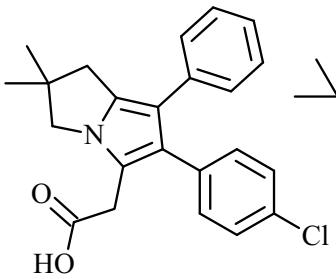


Fig. 28 Redox and non-redox inhibitors

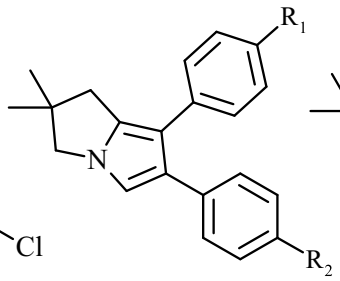
anti-inflammatory drug against 5-LOX and COX-2 enzymes (**122**, Fig. 29a). Presenting minimal GI side effects (Wallace et al. 1994), licofelone offers a superior inhibitory profile against 5-LOX enzyme compared to the inhibition of COX-1 (Leval et al. 2002). However, even after a successful entry to the phase III clinical trials, this molecule has no regulatory approval granted till date (Fischer et al. 2007; Vidal et al. 2007; Alvaro-Gracia 2004).

The licofelone episode realized the therapeutic prominence of dual inhibitors with rising aspirations for designing multi-target hitting molecules in a single medication. This not only spared the available resources but also raised the activity profile without compromising on toxicity (Charlier and Michaux 2003). Moreover, going by the practice of polypharmacology in designing the hybrid molecules, the dual targeting anti-inflammatory agents could be the next-generation therapeutics sidelining all the conventional medics in the category. The dual inhibitors act by blocking the production of both pro-inflammatory prostaglandins and leukotrienes without altering the lipoxin production due to which these are not alarming for the gastric mucosa (Pelletier-Martel et al. 2003). Ulbrich et al. (2002) designed a series of 6, 7-diaryl-2, 3-1*H*-dihydropyrrolizines as dual inhibitors of COX-1/COX-2 and 5-LOX enzymes (**123** and **124**, Fig. 29a). The SAR analysis confirmed that the COX-1/COX-2 and 5-LOX inhibition for the test compounds varied with the nature of substituent. The presence of a thiophene or a furan moiety in place of a phenyl substituent at the C-6 position presented a humble COX-1/2 or 5-LOX inhibitory activity. The presence of a lipophilic substituent at the C-7 position amplified COX-2 selectivity, whereas the presence of methyl sulfide group at the C-6 position produced the best COX-1 inhibition profile. Additionally, a combination of a methyl sulfonyl group or methane

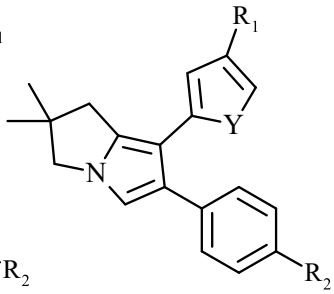
a



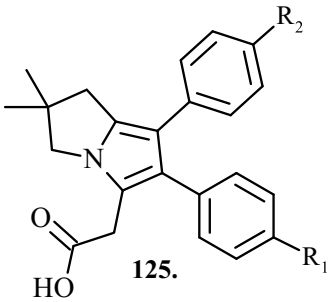
122. Licofelone (ML3000)
IC$_{50}$ (COX-2) = 0.00037 mM
IC$_{50}$ (5-LOX) = 0.00021 mM



123. R_1 = -$NHSO_2CH_3$, R_2 = H
IC$_{50}$ (COX-2) = 0.0036 mM
IC$_{50}$ (5-LOX) = 0.0034 mM

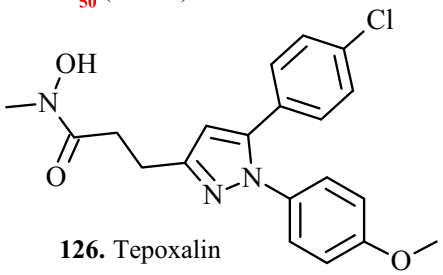


124. R_1, R_2 = H, Y = S
IC$_{50}$ (COX-2) = 20% inhibition
IC$_{50}$ (5-LOX) = 10% inhibition

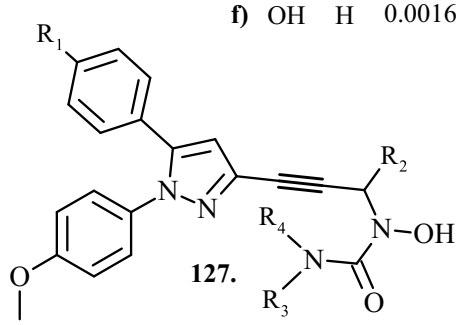


125.

	R_1	R_2	**IC$_{50}$** (COX-2)	**IC$_{50}$** (5-LOX)
a)	H	H	0.0001 mM	0.004 mM
b)	Cl	H	0.00021 mM	0.00018 mM
c)	NO_2	H	0.00003 mM	0.0015 mM
d)	NH_2	H	0.001 mM	0.006 mM
e)	OCH_3	H	0.0001 mM	0.00024 mM
f)	OH	H	0.0016 mM	0.0077 mM

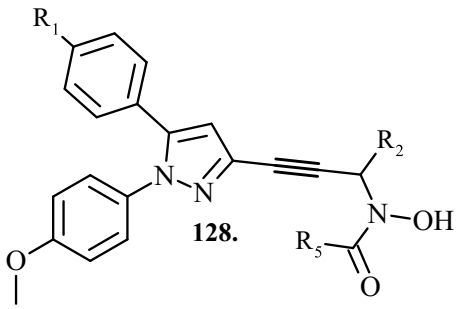


126. Tepoxalin
IC$_{50}$ (COX-2) = 0.0042 mM
IC$_{50}$ (5-LOX) = 0.0017 mM



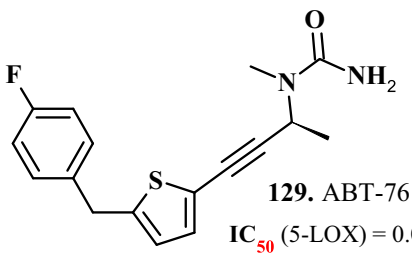
127.

	R_1	R_2	R_3	R_4	**IC$_{50}$** (COX-2)	**IC$_{50}$** (5-LOX)
a)	CH_3	CH_3	H	H	0.0094 mM	0.00037 mM
b)	CH_3	H	H	H	0.00031 mM	0.00007 mM
c)	CH_3	iPr	H	H	0.0046 mM	0.00024 mM



128.

	R_1	R_2	R_5	**IC$_{50}$** (COX-2)	**IC$_{50}$** (5-LOX)
a)	CH_3	CH_3	CH_3	0.0001 mM	0.0008 mM
b)	CH_3	CH_3	iPr	0.00004 mM	0.0001 mM
c)	CH_3	C_2H_5	CH_3	0.00001 mM	0.00007 mM



129. ABT-761
IC$_{50}$ (5-LOX) = 0.023 μM
Chen et al. 2012

sulfonamide with a lipophilic moiety exhibited triple inhibition of COX-1/2 and 5-LOX. Laufer et al. (1994) developed novel nonantioxidant dual inhibitors of both COX and LOX enzymes. The poise between the activity against COX-2 and 5-LOX can be budged by adjusting the substitution pattern of the phenyl moiety at the sixth position of

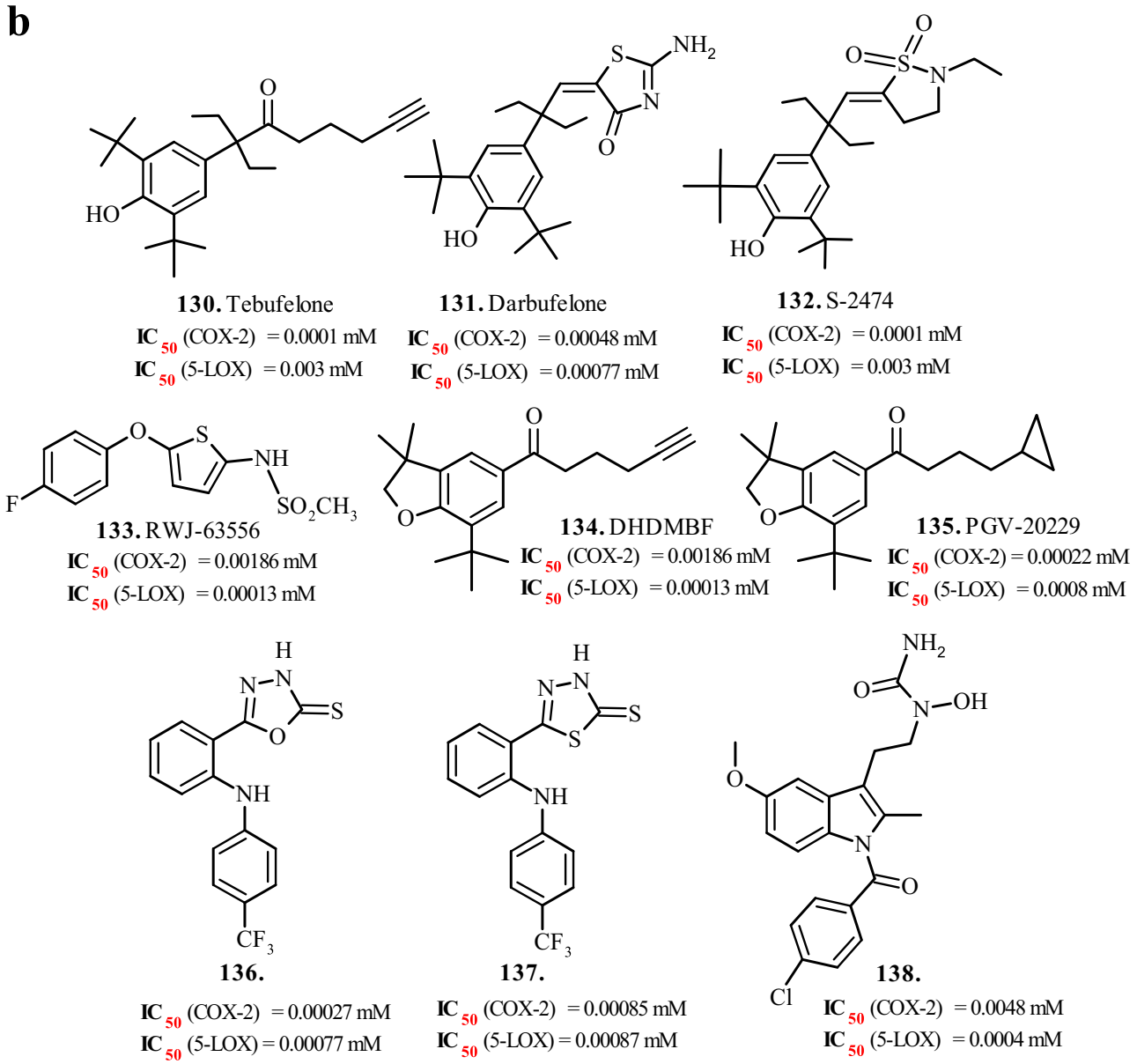


Fig. 29 **a**, **b** Molecular scaffolds for dual inhibition of 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2) enzymes

the pyrrolizine ring (**125a–f**, Fig. 29a). Connolly et al. (1999) performed SAR analysis on tepoxalin-based *N*-hydroxyurea and hydroxamic acid derivatives for their dual inhibition of 5-LOX and COX-2 enzymes (**127–128a–c**, Fig. 29a). Tepoxalin, a pyrazole-containing hydroxamic acid, which is a dual COX/5-LO inhibitor, has undergone clinical evaluation for psoriasis and rheumatoid arthritis (**126**, Fig. 29a) (Argentieri et al. 1994) Reportedly, its in vivo 5-LO inhibitory activity is not promising due to a rapid metabolism of the hydroxamate functionality into the corresponding carboxylate (Waldman et al. 1996). The reported compounds incorporated the structural features of both tepoxalin and the in vivo-active 5-LO inhibitor ABT-761 (**129**, Fig. 29a).

Unangst et al. (1992 a, b) studied di-*tert*-butylphenol derivatives for their activity against COX/5-LOX enzymes (**130–132**, Fig. 29b). The SAR analysis optimized a common structure of 2,6-di-*tert*-butyl-1-hydroxy-benzene at the fourth position for a prime dual activity. The phenol moiety assured antioxidant property to the molecule, which validates the anti-inflammatory potency and a low ulcerogenic potential. Similar to darbufelone (**131**, Fig. 29b), S-2474 (**132**, Fig. 29b) is also a selective inhibitor of COX-2/5-LOX enzymes, which in addition to its anti-inflammatory

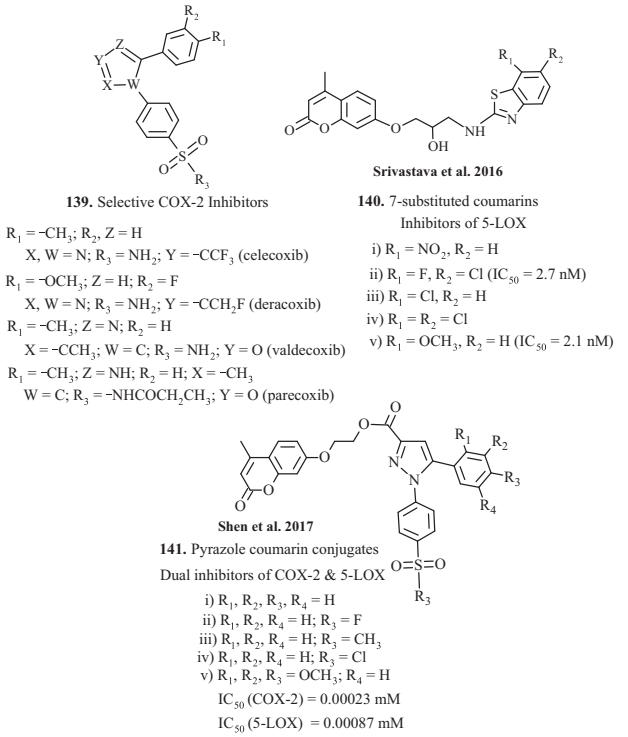


Fig. 30 Pyrazole-coumarin based hybrid compounds for dual inhibition of 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2) enzymes

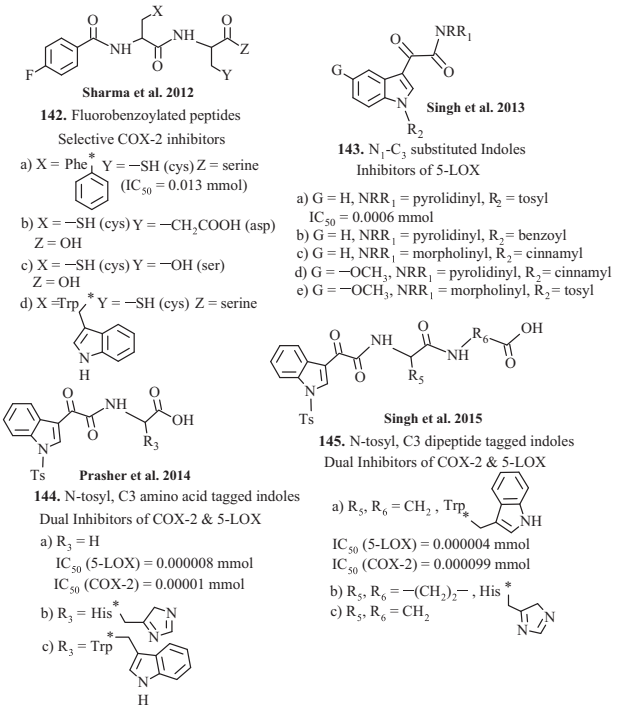


Fig. 31 Indole-peptide based hybrid compounds for dual inhibition of 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2) enzymes

efficacy also warrants cytokine-modulating properties. Among the metabolites of tebufelone (**130**, Fig. 29b), the dihydrodimethyl-benzofuran (DHDMBF) (**134**, Fig. 29b) displays predominantly interesting properties. Though it lacks phenol moiety with antioxidant properties, it presents an anti-inflammatory activity equal to tebufelone in the rat carrageenan paw-edema model. Reportedly, DHDMBF, conversely to tebufelone, selectively inhibits both 5-LOX and COX-2 enzymes. Structural optimizations of the tebufelone metabolites yielded a series of dihydrobenzofurans, exemplified by PGV20229 (**135**, Fig. 29b) that reportedly provides analgesic efficacy and excellent gastric safety in a variety of in vivo investigations (Janusz et al. 1992, 1998a, b). Boschelli et al. (1992) attempted to transform selective COX inhibitors into dual inhibitors of both COX and 5-LOX by replacing the carboxylic acid functionality of several fenamates with 1,3,4-oxadiazole-2-thiones and 1,3,4-thiadiazole-2-thiones (**136–137**, Fig. 29b). Kolasa et al. (1997) in an attempt to find effective dual inhibitors introduced structural alterations to the conventional NSAIDs and selective COXIBs. The resulting compounds designed by this approach validated a dual inhibitory activity against both 5-LOX and COX enzymes (**138**, Fig. 29b). Shen et al. (2017) reported hybrid compounds incorporating classical NSAIDs (**139**, Fig. 30) with 7-substituted coumarins (**140**, Fig. 30). The resulting pyrazole-coumarin conjugates displayed admirable dual inhibitory activity against 5-LOX and COX-2 (**141**, Fig. 30). Sharma et al. (2012) identified fluorobenzoylated di/tri peptides as selective inhibitors of COX-2 isoform. The experimental investigations shortlisted cysteine, serine, tryptophan, and phenylalanine as active amino acid residues for designing dual inhibitors.

The tripeptide with phenylalanine, cysteine and serine sequences displayed the most promising activity against both the target enzymes (**142**, Fig. 31). Singh and Pooja (2014) identified N_1-C_3-substituted indoles for effective inhibition of 5-LOX enzyme. The SAR analysis recognized cyclic amine substitution at the C_3 position of indole and tosyl group at N_1 for an optimum 5-LOX inhibitory activity (**143**, Fig. 31). Prasher and Pooja (2014) and Singh et al. (2015) attempted to combine the efficacy of peptide chain and indoles for designing dual inhibitors of inflammation-causing enzymes. Indole nucleus appended with a peptide arm at the C_3 position, and the tosyl group at N_1 displayed substantial COX-2/5-LOX inhibitory proficiency (**144–145**, Fig. 31). The physicochemical investigations revealed a satisfactory lipophilicity and energy of association with the active site of target enzymes. In vivo studies on Swiss albino mice with induced hyperalgesia followed by oral administration of test compounds in the presence/absence of substance-P justified a dual mode of action for the compounds with competitive mode of inhibition as the most probable mechanism.

Conclusion

Inflammation capping is a multi-dimensional aspect where triumph over one pathway may activate another one of an equal significance. The journey of anti-inflammatory therapeutics has seen many vicissitudes because of the multi-dimensional characteristics of the participating inflammatory pathways. Much of the trademarks have already faced backlash in the past. An upgradation of the conventional therapeutics is therefore the need of the time. Another optimistic approach could be to focus on the expansion of multi-targeting molecules that could tap these pathways without compromising on toxicity, activity, and selectivity overall.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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