Progress in COX-2 Inhibitors: A Journey So Far

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Abstract: The non-steroidal anti-inflammatory drugs (NSAIDs) are diverse group of compounds used for the treatment of inflammation, since the introduction of acetylsalicylic acid in 1899. Traditional (first generation) NSAIDs exert anti-inflammatory, analgesic, and antipyretic effects through the blockade of prostaglandin synthesis *via* non-selective inhibition of cyclooxygenase (COX-1 and COX-2) isozymes. Their use is associated with side effects such as gastrointestinal and renal toxicity. A number of selective (second generation) COX-2 inhibitors (rofecoxib, celecoxib, valdecoxib etc.) were developed as safer NSAIDs with improved gastric safety profile. Observation of increased cardiovascular risks in APPROVe (Adenomatous Polyp Prevention on Vioxx) study sent tremors and led to voluntary withdrawn of Vioxx (rofecoxib) by Merck from the market in September 2004 followed by Bextra (valdecoxib) in 2005 raising a question on the safety of selective COX-2 inhibitors. This leads to the belief that these effects are mechanism based and may be class effect. However, some studies suggested association of traditional NSAIDs with similar effects requiring a relook into the whole class of NSAIDs rather than simply victimizing the selective COX-2 inhibitors. Recognition of new avenues for selective COX-2 inhibitors such as cancer, Alzheimer's disease, Parkinson's disease, schizophrenia, major depression, ischemic brain injury and diabetic peripheral nephropathy has kindled the interest in these compounds. This review highlights the various structural classes of selective COX-2 inhibitors developed during past seven years (2003-2009) with special emphasis on diaryl-hetero/carbo-cyclic class of compounds. Molecular modeling aspects are also briefly discussed.

Keywords: NSAIDs, Cyclooxygenase, Selective COX-2 Inhibitors, Rofecoxib, Lumiracoxib, Advancements, Analogs, Molecular Modeling.

1. INTRODUCTION

Inflammation is the most important defense mechanism of an organism. Elevated levels of prostaglandins (PGs) are associated with inflammation and pain. Non-steroidal anti-inflammatory drugs (NSAIDs) constitute a diverse group of compounds that have been primarily used for the treatment of pain and inflammation. They exert their action by the inhibition of PG biosynthesis (Fig. **1**). Cyclooxygenase (COX) was identified as the molecular target for NSAIDs by John R.Vane in 1971 [1].

Though the PGs (especially PGE_2) are responsible for the inflammatory symptoms, they have cytoprotective effects in the gastrointestinal tract and also control the renal functions in kidney [2]. Hence, inhibition of PGs by aspirin and other classical NSAIDs causes gastric ulceration, bleeding [3] and renal dysfunction [4]. After the discovery of a second COX isoform, COX-2 [5], the dual role of prostaglandins as mediators of physiological and pathological functions was clarified. Both the isozymes carry out essentially the same catalytic biotransformation of arachidonic acid, but differ in their structure, expression and function [6-8].

The COX-1 is constitutively expressed in most of the tissues and plays an important role in maintaining the homeostasis. On the other hand, COX-2 is inducible which is activated by pro-inflammatory stimuli and is involved in the inflammatory processes. These findings led to the hypothesis that the inhibition of COX-1 is associated with the adverse effects of classical NSAIDs (Fig. **2**) whereas inhibition of COX-2 is responsible for their anti-inflammatory effects [9,10].

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The aggressive explorations in the search of safer selective COX-2 inhibitors lead to the introduction of rofecoxib, celecoxib, valdecoxib and etoricoxib (Fig. **3**). Rofecoxib (Vioxx) was withdrawn voluntarily by Merck from the market in September 2004 following the increased cardiovascular risks observed in APPROVe (Adenomatous Polyp Prevention on Vioxx) study. Subsequently the sale of Bextra (valdecoxib) was also suspended by Pfizer in 2005. This raised a question on the safety of selective COX-2 inhibitors. However, no increased risk of cardiovascular thrombotic events was evident in CLASS (Celecoxib Long Term Arthritis Safety Study) trial conducted on celecoxib [11] which is the only selective COX-2 inhibitor available in U.S. market. A meta-analysis of published and unpublished tabular data from randomized trials revealed that selective COX-2 inhibitors and traditional NSAIDs (high dose regimens of ibuprofen and diclofenac) have similar incidence of adverse cardiovascular events [12]. Various studies suggest that the cardiovascular toxicity associated with the use of selective COX-2 inhibitors might be dependent on the dose as well as on the duration of treatment [13-16].

The mechanism underlying the adverse cardiovascular effects associated with the use of COX inhibitors is due to an imbalance between COX-1 derived thrombotic thromboxane A_2 (TXA_2) in platelets and COX-2 derived vasoprotective prostacyclin (PGI_2) in endothelium [11]. There should be >95% suppression of the platelet COX-1 before it can be translated into clinically relevant platelet inhibition [17]. All NSAIDs significantly inhibit COX-2 at therapeutic dose but only few traditional NSAIDs (aspirin and naproxen) are able to show >95% suppression of the platelet COX-1 at such dose. This explains why selective COX-2 inhibitors as well as traditional NSAIDs show adverse cardiovascular effects [18].

Lumiracoxib [19], the most selective COX-2 inhibitor [7 times more potent than rofecoxib in the human whole blood

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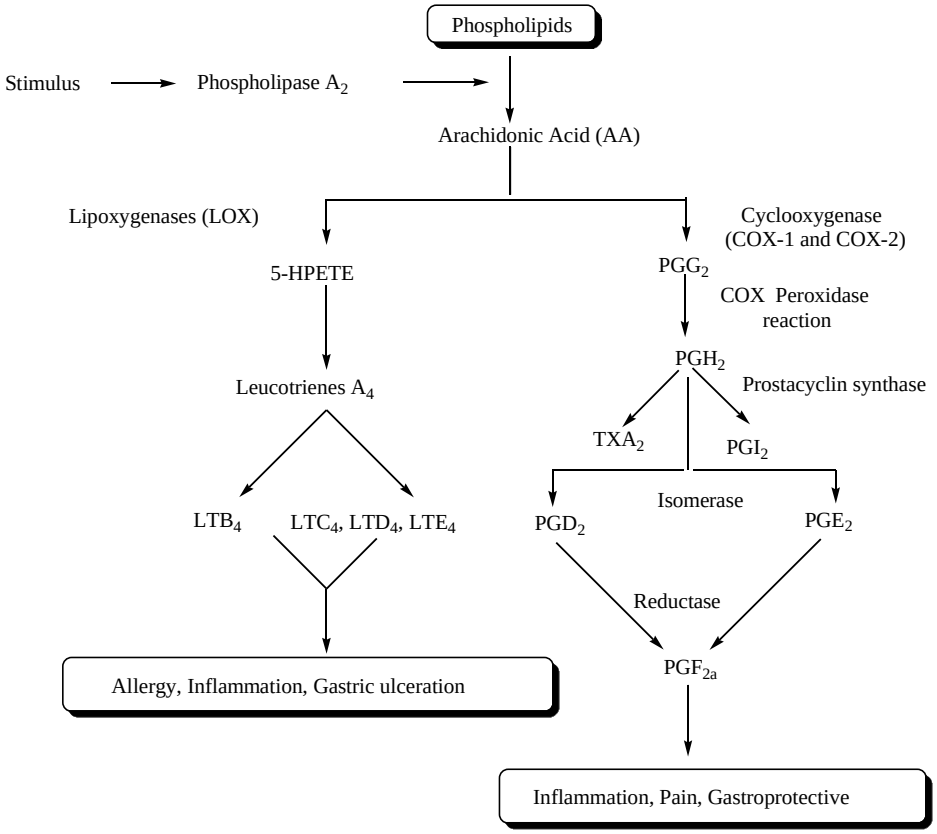


Fig. (1). Arachidonic acid pathway.

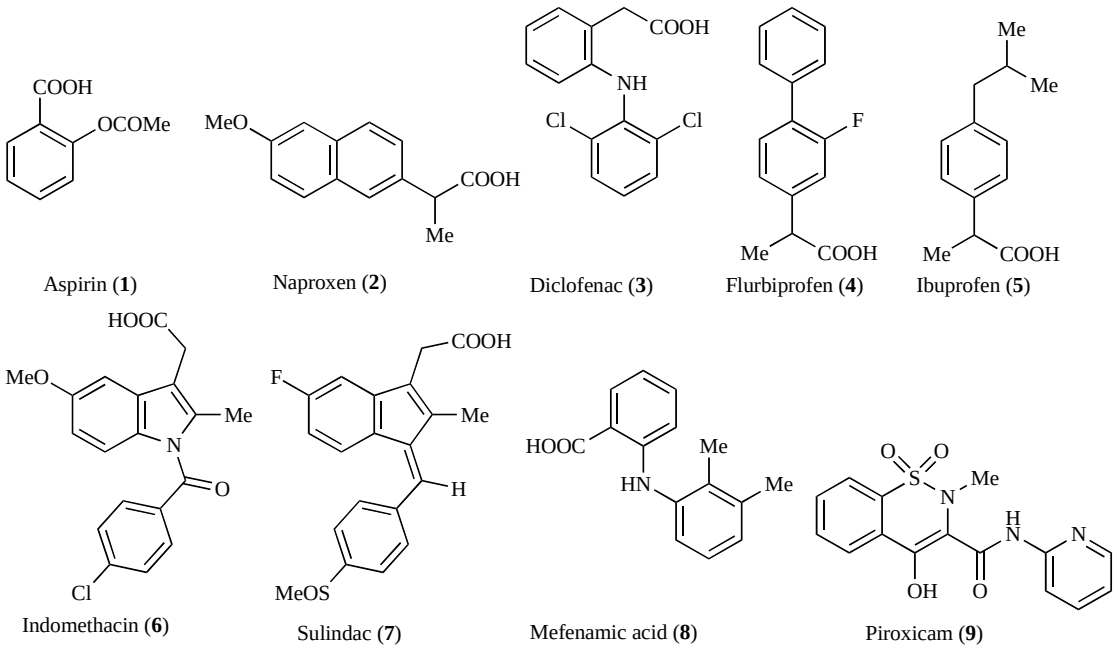


Fig. (2). Classical NSAIDs.

(HWB) assay] did not demonstrate significant cardiovascular side effects in TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial) [20]. However, reports of serious hepatic side effects associated with use of lumiracoxib, resulted in its withdrawal from Australian market followed by European Market. In a recent study, lumiracoxib elicited similar COX-2 inhibitory profile at 50, 100, and 200 mg and indeed was found to completely inhibit COX-2 at 50 mg dose [21]. Is it possible that lower doses of lumiracoxib can be used to avoid hepatic side effects? This emphasizes the need for dose-dependent clinical study of selective COX-2 inhibitors to find out the lowest effective therapeutic dose,

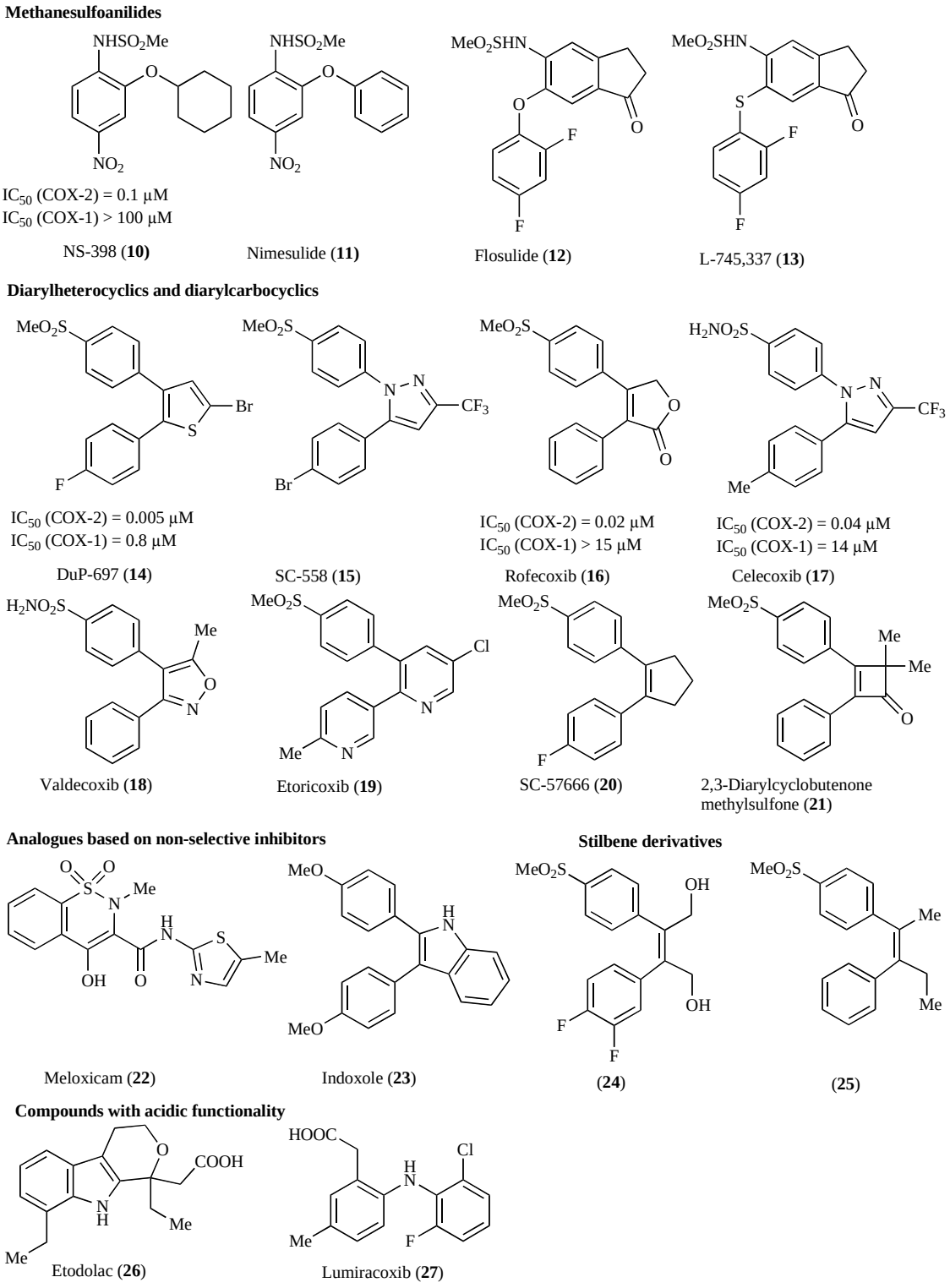


Fig. (3). Structures of representative selective COX-2 inhibitors.

thereby minimizing the side effects and their renaissance as anti-inflammatory agents [22,23].

Inflammation has been suggested as a new hallmark of cancer [24]. COX-2 expression is upregulated in several human cancers [25] suggesting that it plays an important role in pathophysiology of various cancers such as lung [26], breast [27], colorectal [28], genitourinary [29] and cervical [30]. Celecoxib has been approved by FDA (Food and Drug Administration) as an adjunct for the treatment of familial adenomatous polyposis (FAP) [31]. In a recent case report, a patient with attenuated FAP on long-term treatment with selective COX-2 inhibitors (rofecoxib and subsequently celecoxib) showed no evidence of progression of polyposis or development of colorectal cancer after nine-years of fol-

low-up [32]. Moreover, during the follow-up period, no adverse effects of the drug were reported.

Alzheimer's disease (AD), a neurodegenerative disorder, is the most common cause of dementia in the elderly. Epidemiological studies show that the long-term use of NSAIDs is associated with reduced risk of developing AD and delaying its onset [33]. It has been postulated that beneficial effects of non-selective and selective NSAIDs in AD might be due to anti-inflammatory (inhibition of COX) or anti-amyloidogenic or synergistic mechanisms [34]. However, clinical trials with non-selective NSAIDs and selective COX-2 inhibitors on AD have failed to show any beneficial effect on progression of AD [35]. Recent finding suggests that COX-2 plays a role in oxidative stress in AD and rofecoxib may be beneficial in AD management through reduction of AD-related oxidative stress [36]. Further studies need to be undertaken on selective COX-2 inhibitors to unfold their exact mechanism of action in the prevention or delay of onset of AD.

Parkinson's disease (PD) is a neurodegenerative disorder. Inflammatory processes are involved in the pathogenesis of PD as COX-2 expression was found to be up-regulated in brain dopaminergic neurons of various experimental models of PD [37]. Data from several experimental and epidemiological studies revealed that NSAIDs including preferential COX-2 inhibitors have neuroprotective effects on the pathogenesis of PD and may be useful in delaying the onset and slowing down the progression of the disease [38]. Further animal experiments and clinical trials with selective COX-2 inhibitors are required to clarify their neuroprotective role in the pathogenesis of PD.

Up-regulation of COX-2 expression has also been implicated with a number of other pathophysiological conditions such as schizophrenia and major depression [39], epilepsy [40], ischemic brain injury [41], diabetic peripheral nephropathy [42] etc. COX-2 has been identified as therapeutic target by researchers to intervene with various disease conditions, indicating that the future of selective COX-2 inhibitors is not limited to management of inflammation and pain; new therapeutic avenues are emerging where they can play a vital role.

Nitric oxide (NO) has a significant role in the cytoprotection of gastric mucosa. Hybrid molecules comprising of NSAID and nitric oxide donor moieties have reduced gastrointestinal and cardiovascular toxicity compared to selective and non-selective COX inhibitors [43].

The detailed aspects related to the biology of COX isozymes [44-50] and a number of previously developed classes of selective COX-2 inhibitors are described in some of the excellent reviews [51-56]. This review will highlight the recent developments in diverse structural classes of selective COX-2 inhibitors with brief discussion on molecular modeling studies.

2. RECENT ADVANCEMENTS IN THE DEVELOPMENT OF SELECTIVE COX-2 INHIBITORS

Over a decade, a large number of selective COX-2 inhibitors with diverse chemical characteristics have been designed but only a few have emerged as drugs (Fig. **3**). The prototypical COX-2 inhibitors NS-398 (**10**) and DuP-697 (**14**) led to the development of methanesulfoanilides (sulides) [57] and diaryl heterocycle (coxibs) [58] class of selective COX-2 inhibitors respectively.

2.1. Analog Based Approaches

These include either a novel class or a previously developed class on which various chemical modifications have been performed. Since, major advancements have occurred in the field of diaryl hetero/carbo-cyclic class of compounds, the focus will be first on this class followed by others.

A. Diaryl Hetero/Carbo-Cyclics

Several series of selective COX-2 inhibitors belonging to the 1,2-diaryl class of compounds containing different heterocyclic and carbocyclic moieties as a central scaffold have been developed.

Furans

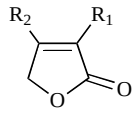
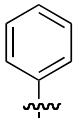
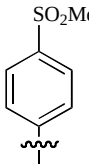
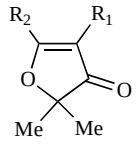
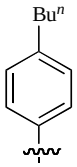
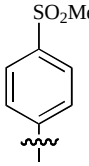
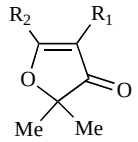
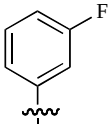
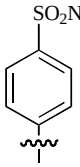
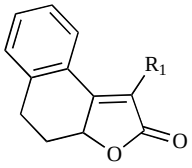
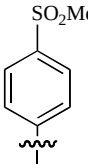
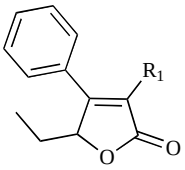
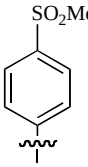
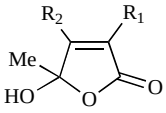
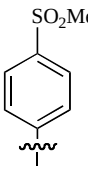
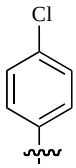
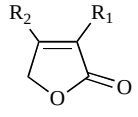
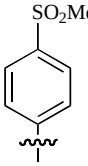
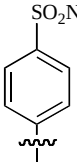
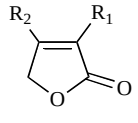
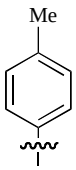
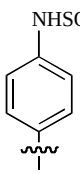
Diarylfuranone derivatives have been extensively investigated as selective COX-2 inhibitors [59] and the blockbuster drug rofecoxib (**16**) belongs to this class containing the basic structural framework of 3,4-diarylfuranone [60]. Since then this molecular fragment has been the target of continuous efforts in designing new chemical entities as selective COX-2 inhibitors.

Shin *et al.* reported a novel series of 5-aryl-2,2-dialkyl-4-phenyl-3(2*H*)furanone derivatives with improved gastric safety profiles [61]. Methyl sulfone derivative **28** with *para-n*-butyl substituent on the 4-phenyl ring (Table **1**) exhibited very high selectivity comparable to rofecoxib (COX-2, IC_{50} = 0.06 μM; SI > 1667**)**. Replacement of the methyl sulfone moiety with sulfonamide decreased selectivity but improved the inhibitory potency. Sulfonamide derivative **29** with *meta*-fluoro substituent on 4-phenyl ring is one of the most potent COX-2 inhibitor (ED_{50} = 0.1 mg/kg/day) ever reported [even more potent than rofecoxib (ED_{50} = 0.74 mg/kg/day) and etoricoxib (ED_{50} = 0.7 mg/kg/day)] in adjuvant-induced arthritis animal model.

In order to ascertain the effect of linking the furanone ring to the phenyl group of the diarylfuranone, Pal *et al.* synthesized conformationally restricted 3,4-diarylfuranones (naphthofuranones) [62] and observed that the naphthofuranone derivative **30** (Table **1**) exhibited COX-2 inhibitory potency comparable to rofecoxib (COX-2, IC_{50} = 0.329 μM; SI > 1519). Restricted conformation was found to be a prerequisite for COX-2 inhibition in case of methanesulfonyl derivatives as freely rotating analog **31** of **30** was found to be inactive (Table **1**).

Introduction of a hydroxyl group into the 5-position of the 3,4-diarylfuranone system resulted in highly selective COX-2 inhibitors which can be easily converted into their water soluble open chain sodium salts under basic conditions making them suitable for intravenous formulation [63]. However, hydroxyl-substituted compounds were found to be less potent than their alkoxy analogs. The compound **32** with 4-chlorophenyl substitution (Table **1**) emerged as a highly potent COX-2 inhibitor with *in vivo* anti-inflammatory activity (ED_{50} = 1.4 mg/kg) comparable to rofecoxib (ED_{50} = 1.5 mg/kg) in carrageenan-induced rat paw edema assay.

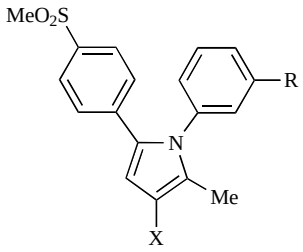
Table 1. Furan Derivatives as Selective COX-2 Inhibitors

Compd.	Central Scaffold	R_1	R_2	COX-2 IC_{50}, μM	COX-1 IC_{50}, μM	Refs.
16				0.02[a]	>15[a]	[60]
28				0.002[b]	5[b]	[61]
29				0.003[b]	0.3[b]	[61]
30			—	0.562[c]	>45[c]	[62]
31			—	14% inhibition at 100 μM[c]	20% inhibition at 100 μM[c]	[62]
32				0.11[d]	105[d]	[63]
33				0.05[e]	>100[e]	[64]
34				0.9[e]	>100[e]	[65]

[a]*In vitro* evaluation was carried out by using human COX-1 and COX-2 enzymes derived from CHO cells. [b]*In vitro* evaluation was carried out by using mouse macrophage method. [c]*In vitro* evaluation was carried out by using recombinant human COX-2 enzyme and COX-1 derived from microsomal fraction of ram seminal vesicles. [d]*In vitro* evaluation was carried out by using HWB assay method. [e]*In vitro* evaluation was carried out by using ovine COX-1/COX-2 assay kit.

Knaus *et al.* reported a novel group of regioisomeric rofecoxib derivatives with an additional SO_2NH_2/ $SO_2NHCOMe/SO_2N_3$ substituent at the *para*-position of either of the phenyl rings [64]. Substitution with an additional SO_2NH_2/SO_2N_3 group resulted in inactive/moderately active compounds whereas substitution with an additional $SO_2NHCOMe$ group resulted in highly active compounds and the rofecoxib regioisomeric analog **33** (Table **1**) exhib-

Table 2. Pyrrole Derivatives as Selective COX-2 Inhibitors



Compd.	X	R	COX-2 IC_{50}, μM	COX-1 IC_{50}, μM	Refs.
35	CH_2COOEt	H	0.04[a]	>100[a]	[66]
36	CH_2COOEt	F	0.010[a]	>100[a]	[67]
37	$CH_2CH_2O(CH_2)_2CH_3$	H	0.018[b]	>100[b]	[68]
38	CH(OH)COOEt	F	0.12[a]	>100[a]	[69]

[a]*In vitro* evaluation was carried out by using murine macrophage method. [b]*In vitro* evaluation was carried out by using HWB assay method.

ited higher potency and selectivity than rofecoxib (COX-2, IC_{50} = 0.43 μM; SI > 1162).

Anticipating that adverse cardiovascular effects of rofecoxib might be due to its higher COX-2 selectivity, Knaus *et al.* modified the rofecoxib template [65] by replacement of its SO_2Me group with $MeSO_2NH$ moiety of nimesulide in order to reduce its COX-2 selectivity. Replacement of the SO_2Me group with $MeSO_2NH$ moiety in general resulted in compounds with decreased COX-2 potency and selectivity and **34** possessing a methyl group at *para* position of C-3 phenyl ring (Table **1**) emerged as the most promising compound with reduced selectivity than rofecoxib (COX-2, IC_{50} = 0.5 μM; SI > 200).

Pyrroles

Biava *et al.* extensively studied 1,5-diarylpyrroles by varying the substitution at 3-position of the pyrrole ring. Various substitutions such as acetic acid and its esters [66,67], ethers [68], *α*-hydroxy/alkoxy esters [69] were tried, amongst them the ester derivatives were more potent and selective COX-2 inhibitors and **35** exhibited potency comparable to celecoxib (COX-2, IC_{50} = 0.079 μM; SI = 64.5) and selectivity better than rofecoxib (COX-2, IC_{50} = 0.012 μM; SI >800) (Table **2**).

Pyrazoles

Since celecoxib (**17**) belongs to 1,5-diarylpyrazole class of selective COX-2 inhibitors, much attention was paid to this class of compounds [70]. Pal *et al.* reported a series of 1,5-diarylpyrazoles with benzenesulfonamide moiety [71]. In this series, **39** exhibited good *in vitro* inhibitory potency with selectivity better than celecoxib (COX-2, IC_{50} = 0.07 μM; SI = 219) (Table **3**) and its sodium salt showed good *in vivo* anti-inflammatory activity (ED_{50} = 6.0 mg/kg). Replacement of the benzenesulfonamide group with fused heterocycles resulted in COX-1 selective compounds whereas polar substitutions such as hydroxyalkyl/acylaminoalkyl on *N*-1 benzenesulfonamide ring increased the COX-2 selectivity [72]. Hydroxymethyl derivative **40** was most selective (Table **3**) with less potency than celecoxib (COX-2, IC_{50} = 0.036 μM). Repositioning of sulfonamide group from *N*-1 phenyl ring to *C*-5 phenyl ring resulted in compounds with improved potency and selectivity [73] and **41** (Table **3**) exhibited potency and selectivity comparable to celecoxib (COX-2, IC_{50} = 0.036 μM).

Recently, Szabo *et al.* synthesized a new series of 1,5-diarylpyrazoles containing benzenesulfonamide moiety as anti-inflammatory agents [74]. None of these compounds showed *in vitro* COX-1/COX-2 inhibitory activity at 10 μM concentration but interestingly *in vivo* studies using carrageenan-induced rat paw edema assay identified **42** (ED_{30} = 5.7 mg/kg) as better anti-inflammatory agent than celecoxib (ED_{30} = 23 mg/kg) (Fig. **4**).

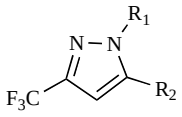
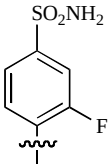
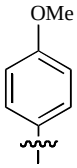
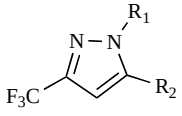
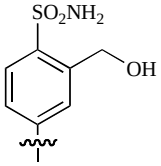
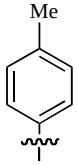
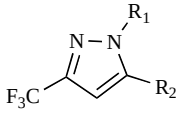
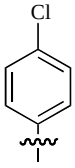
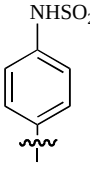
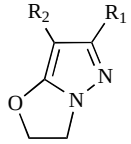
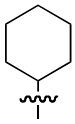
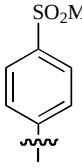
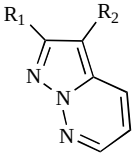
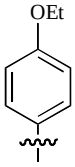
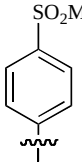
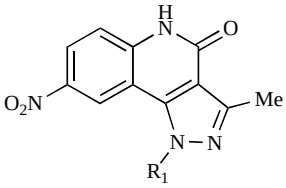
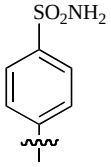
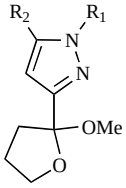
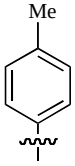
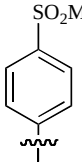
Ranatunge *et al.* [75] synthesized three novel series of bicyclic-pyrazoles (pyrazolo[5,1-*b*]1,3-oxazolidines, pyrazolo[5,1-*b*]1,3-oxazines and imidazolidino[1,2-*d*]pyrazoles) by activation of hydroxyalkyl group attached to the pyrazole ring with subsequent cyclization and **43** was identified as the most promising compound with potency comparable to celecoxib (COX-2, IC_{50} = 1.2 μM) (Table **3**).

Several novel series of 2,3-diaryl-pyrazolo[5,1-*b*]-pyridazines [76], pyrazolo[4,3-*c*]quinoline-4-ones [77] and 3-(2-methoxytetrahydrofuran-2-yl)pyrazoles [78] have also been reported as selective COX-2 inhibitors with compounds GW40681 (**44**), **45**, and **46** respectively were the best from each series (Table **3**).

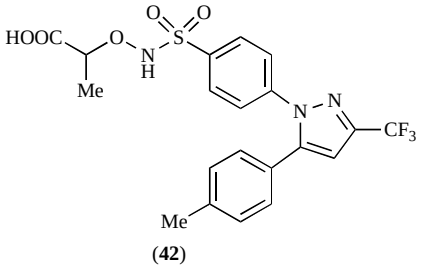
Imidazoles

Heterocyclic compounds with vicinal diaryl substitution having imidazole ring as central scaffold have been investigated earlier as selective COX-2 inhibitors [79,80]. Almansa *et al.* reported a new series of 1,5-diarylimidazoles [81]. The structure-activity relationship (SAR) studies of two regioisomeric imidazoles, 1-methylsulfonylimidazole and 5-methylsulfonylimidazole resulted in identification of **47** as more potent and selective inhibitor than celecoxib (COX-2, IC_{50} = 0.079 μM) (Table **4**) exhibited high potency in various *in vivo* inflammation tests (carrageenan-induced rat paw edema test, air pouch model and hyperalgesia test).

Table 3. Pyrazole Derivatives as Selective COX-2 Inhibitors

Compd.	Central scaffold	R_1	R_2	COX-2 IC_{50} μM	COX-1 IC_{50} μM	Refs.
39				0.15[a]	>30[a]	[71]
40				0.76[a]	278[a]	[72]
41				0.030[a]	15.6[a]	[73]
43				1.3[b]	>100[b]	[75]
44				0.003[c]	>84.2[c]	[76]
45			—	0.24[a]	4.7[a]	[77]
46				1.2[b]	>100[b]	[78]

[a]*In vitro* evaluation was carried out by using recombinant human COX-2 enzyme and COX-1 derived from microsomal fraction of ram seminal vesicles. [b]*In vitro* evaluation was carried out by using HWB assay method. [c]*In vitro* evaluation was carried out by using recombinant human COX-1/COX-2 enzymes.

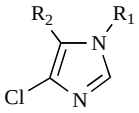
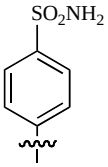
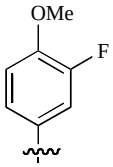
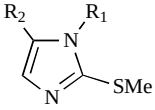
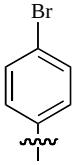
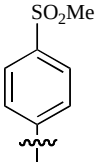
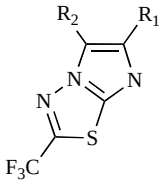
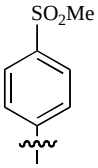
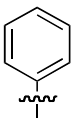
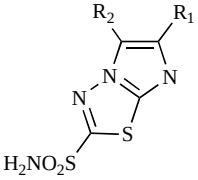
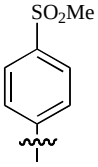
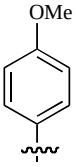
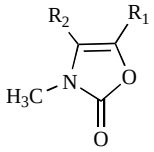
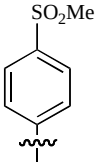
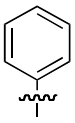
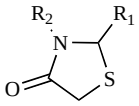
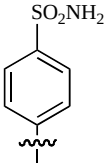
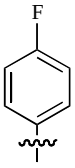
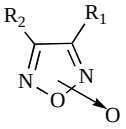
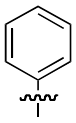
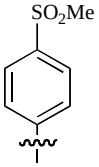
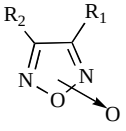
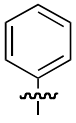
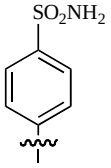
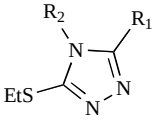
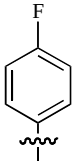
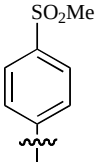


(**42**)

Fig, (4).

Recently, Navidpour *et al.* described a new series of 2-alkylthio substituted 1,5-diarylimidazoles [82]. The COX-2 selectivity and potency was governed by steric properties of the 2-alkylthio substituent as well as electronic properties of the *para*-substituent of 1-phenyl ring. The compound **48** exhibited COX-2 potency comparable to celecoxib (COX-2, IC_{50} = 0.21 μM) (Table **4**) with good *in vivo* anti-inflammatory activity in carrageenan-induced rat paw edema assay.

Table 4. Imidazole, Oxazole, Thiazole, Oxadiazole, and Triazole Derivatives as Selective COX-2 Inhibitors

Compd.	Central scaffold	R_1	R_2	COX-2 IC_{50}, μM	COX-1 IC_{50}, μM	Refs.
47				0.005[a]	3.3[a]	[81]
48				0.43[b]	>25[b]	[82]
49				4.79[c]	>50[c]	[83]
50				3.24[c]	>50[c]	[83]
51				70.14% inhibition at 10 μM[c]	3.56% inhibition at 10 μM[c]	[84]
52				0.12[c]	>100[c]	[85]
53				0.12[c]	11.6[c]	[86]
54				0.78[c]	9.8[c]	[86]
55				0.0018[c]	0.0205[c]	[87]

[a]*In vitro* evaluation was carried out by using human cell lines. [b]*In vitro* evaluation was carried out by using purified COX-2 enzyme and ovine COX-1 enzyme. [c]*In vitro* evaluation was carried out by using ovine COX-1/COX-2 assay kit.

Gadad *et al*. reported a novel class of 2-trifluoromethyl/sulfonamido-5,6-diaryl substituted imidazo[2,1-*b*]1,3,4-thiadiazoles [83] and observed that **49** and **50** exhibited potent COX-2 inhibitory activities (Table **4**) but were inferior to celecoxib (COX-2, IC_{50} = 0.04 μM). However, these compounds exhibited good *in vivo* anti-inflammatory activity comparable to celecoxib in carrageenan-induced rat paw edema assay.

Oxazoles

The *in vitro* COX inhibitory activities of a new series of 4,5-diphenyloxazolone derivatives [84] were found to be discouraging and only **51** exhibited noticeable COX-2 selectivity (Table **4**).

Thaizoles

In the novel series of 2,3-diaryl-1,3-thiazolidine-4-ones possessing methylsulfonyl moiety [85], **52** emerged as most selective and potent COX-2 inhibitor with selectivity higher than celecoxib (COX-2, IC_{50} = 0.06 μM; SI > 403) (Table **4**).

Oxadiazoles

Knaus *et al.* [86] isosterically replaced the 2-(5*H*)furanone central ring present in rofecoxib with 1,2,5-oxadiazole-2-oxide projecting 3,4-diphenyl-1,2,5-oxadiaz-ole-2-oxides as hybrid COX-2 inhibitor/nitric oxide (NO) donor agents. The compound **53**, a hybrid of methanesulfonyl regioisomers and **54**, a hybrid of aminosulfonyl regioisomers exhibited good *in vitro* COX-2 inhibitory potency and selectivity but were inferior to celecoxib (COX-2, IC_{50} = 0.07 μM; SI = 472) (Table **4**).

Triazoles

Navidpour *et al.* [87] reported that in the newly designed 3-thio/alkylthio substituted-4,5-diaryl-4*H*-1,2,4-triazoles, the alkylthio analog **55** was more potent and selective inhibitor than celecoxib (COX-2, IC_{50} = 2.2 μM; SI = 1.68) (Table **4**) and also exhibited good *in vivo* anti-inflammatory activity compared to celecoxib in a carrageenan-induced rat paw edema assay.

Pyrans

Joo *et al*. reported a new series of 2,3-diarylbenzopyrans [88]. Derivatives bearing a halogen atom on the 3-aryl ring showed improved COX-2 potency, *e.g*., **56** exhibited potency comparable to celecoxib (COX-2, IC_{50} = 0.01 μM) (Table **5**). However, it was ineffective in carrageenan-induced rat paw edema assay indicating its poor bioavailability due to the presence of three lipophilic aromatic rings. An approach of replacing 3-aryl ring with pyridine ring afforded **57** with improved bioavailability, but also led to decreased potency (Table **5**). Further approach of truncating the benzopyran scaffold to γ-pyrone resulted in compounds with weaker COX-2 inhibitory activities than celecoxib (COX-2, IC_{50} = 0.01 μM) [89]. The compound **58** with 3,4-difluoro substitution exhibited oral *in vivo* anti-inflammatory activity comparable to celecoxib in carrageenan-induced rat paw edema assay. Replacement of the 3-phenyl group in the γ-pyrone series with 3-pyridyl moiety (**59**) resulted in significant reduction of COX-2 inhibitory activity along the lines of the earlier observations with benzopyran scaffold containing COX-2 inhibitors [88].

Catrula *et al*. reported 2-phenylpyran-4-ones as a new class of orally active COX-2 inhibitors [90]. Exploration of various substitutions at 3-position of 2-phenylpyran-4-one scaffold led to identification of 3-phenoxypyran-4-ones as potent and selective COX-2 inhibitors. Halogen substitution on 3-phenoxy ring further enhanced the COX-2 activity and selectivity. The *para*-chloro derivative **60** emerged as the most selective compound of this series exhibiting five-fold COX-2 SI compared to etoricoxib (COX-2, IC_{50} = 0.81 μM; SI = 122) (Table **5**). The dihalo substitution on the 3-phenoxy ring resulted in further increase in potency. Difluoro substituted compound **61** was most potent COX-2 inhibitor (Table **5**) and exhibited potency (ED_{50} = 0.015 mg/kg) higher than that of rofecoxib (ED_{50} = 0.300 mg/kg) and etoricoxib (ED_{50} = 0.440 mg/kg) in adjuvant-induced arthritis model.

Rao *et al.* designed a group of 6-alkyl/alkoxy/alkylthio-substituted 3-(4-methanesulfonylphenyl)-4-aryl-pyran-2-ones [91] and **62, 63** and **64** from C-6 alkyl, alkoxy and alkylthio series respectively were identified as highly potent and selective COX-2 inhibitors (Table **5**). Although **62** exhibited excellent *in vitro* COX-2 selectivity even higher than celecoxib (COX-2, IC_{50} = 0.057 μM; SI >401) and rofecoxib (COX-2, IC_{50} = 0.43 μM; SI >1162) yet it demonstrated only weak *in vivo* anti-inflammatory activity suggesting more susceptibility of alkylthio group to metabolic inactivation as compared to C-6 alkyl/alkoxy analogs when administered orally. They further designed 6-phenyl substituted 3-(4-methanesulfonylphenyl)-4-aryl-pyran-2-ones [92], **65** exhibited potency and selectivity better than that of celecoxib (COX-2, IC_{50} = 0.07 μM; SI = 474) and rofecoxib (COX-2, IC_{50} = 0.50 μM; SI >200) (Table **5**) along with potent oral *in vivo* anti-inflammatory activity (ID_{50} = 5.6 mg/kg) than celecoxib (ID_{50} = 10.8 mg/kg) in carrageenan-induced rat paw edema assay.

Indoles

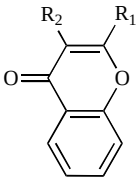
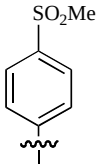
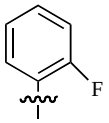
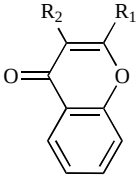
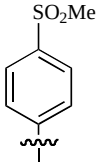
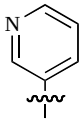
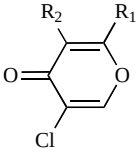
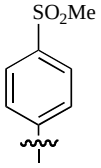
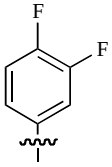
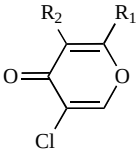
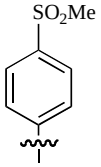
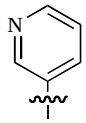
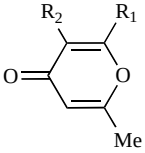
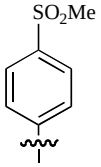
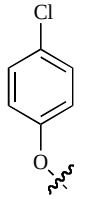
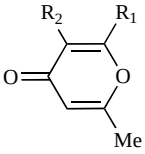
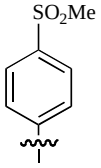
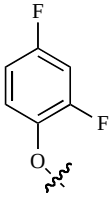
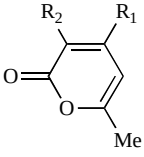
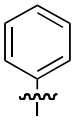
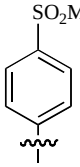
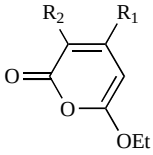
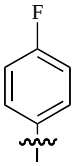
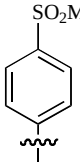
Indole ring present in classical NSAID indomethacin (**6**) constitutes an important scaffold for the design of selective COX-2 inhibitors. A new series of substituted 2-sulfonyphenyl-3-phenylindoles was reported by Hu *et al.* [93]. Most of the compounds exhibited *in vitro* COX-2 inhibitory potency and selectivity higher than celecoxib (COX-2, IC_{50} = 0.52 μM), **66** exhibiting higher potency and selectivity than celecoxib both *in vitro* and *in vivo*. They further reported 2-phenyl-3-sulfonylphenyl-indoles, the regioisomeric analogs of the above series [94], **67** and **68** emerged as the most promising compounds exhibiting potency and selectivity higher than celecoxib (Table **6**).

Campbell *et al*. reported a series of 6-methylsulfonylindoles [95]. The conformationally more rigid analogs (3-aroyl/sulfinyl/sulfonyl) were although selective but less potent than conformationally flexible analogs (3-arylmethyl/aryloxy/arylthio). The analog **69** with 3-aryloxy substitution displayed good *in vitro* COX-2 inhibitory potency and selectivity (Table **6**) and also exhibited reasonable *in vivo* efficacy in rat carrageenan air pouch model.

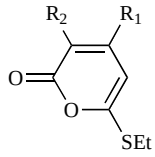
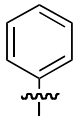
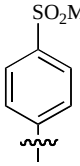
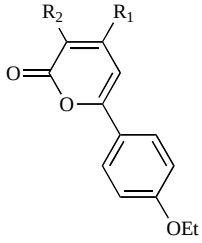
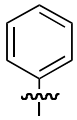
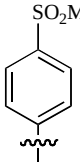
Pyrazines and Quinoxalines

Singh *et al.* reported series of 2,3-diarylpyrazines and 2,3-diarylquinoxalines having methylsulfone/sulfonamide

Table 5. Pyran Derivatives as Selective COX-2 Inhibitors

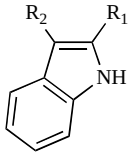
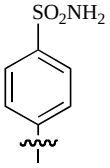
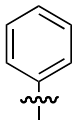
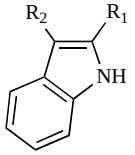
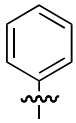
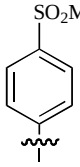
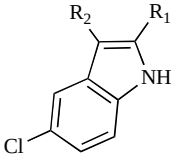
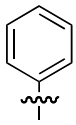
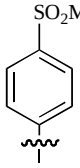
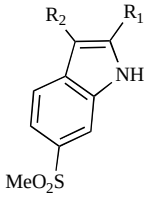
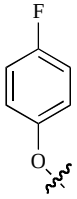
Compd.	Central scaffold	R_1	R_2	COX-2 IC_{50}, μM	COX-1 IC_{50}, μM	Refs.
56				0.03[a]	<5% inhibition at 10 μg/mL[a]	[88]
57				0.5[a]	13% inhibition at 10 μg/mL[a]	[88]
58				0.49[a]	20% inhibition at 10 μg/mL[a]	[89]
59				2.55[a]	<5% inhibition at 10 μg/mL[a]	[89]
60				0.32[b]	207[b]	[90]
61				0.08[b]	22.3[b]	[90]
62				0.68[c]	614.8[c]	[91]
63				0.1[c]	288[c]	[91]

(Table 5). Contd…..

Compd.	Central scaffold	R_1	R_2	COX-2 IC_{50}, μM	COX-1 IC_{50}, μM	Refs.
64				0.0032[c]	386.2[c]	[91]
65				0.05[c]	>100[c]	[92]

[a]*In vitro* evaluation was carried out by using mouse macrophage method. [b]*In vitro* evaluation was carried out by using HWB assay method. [c]*In vitro* evaluation was carried out by using ovine COX-1/COX-2 assay kit.

Table 6. Indole Derivatives as Selective COX-2 Inhibitors

Compd.	Central scaffold	R_1	R_2	COX-2 IC_{50}, μM	COX-1 IC_{50}, μM	Refs.
66				0.09[a]	>10[a]	[93]
67				0.22[a]	>10[a]	[94]
68				0.27[a]	>10[a]	[94]
69		Me		2.0[b]	37.0[b]	[95]

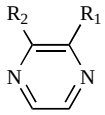
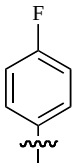
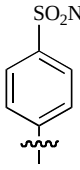
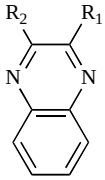
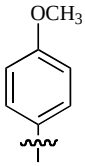
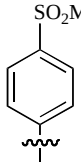
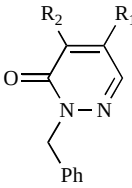
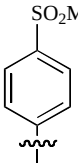
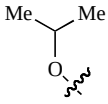
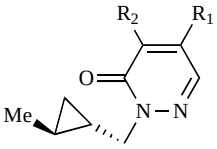
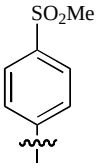
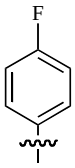
[a]*In vitro* evaluation was carried out by using mouse macrophage method. [b]*In vitro* evaluation was carried out by using HWB assay method.

group [96]. Benzenesulfonamide derivative **70** was most selective (Table **7**) and was converted to the water soluble sodium salt **71** in order to have a better drug candidate for animal studies. Both exhibited *in vivo* anti-inflammatory activities comparable to celecoxib in the carrageenan-induced rat paw edema assay. 2,3-Diarylquinoxalines showed similarity to 2,3-diarylpyrazines except the *in vivo* anti-inflammatory profile and **72** was identified as most selective COX-2 inhibitor (Table **7**).

Pyridazinones

Li *et al.* reported a new class of pyridazinones [97]. Among various *N*-substituted analogs, the *N*-benzyl derivative **73** and *N*-cyclopropylmethyl derivative **74** were most potent and selective COX-2 inhibitors *in vitro* (Table **7**) and exhibited excellent *in vivo* anti-inflammatory activity in carrageenan-induced rat paw edema assay [**73** (ED_{50} <0.3 mg/kg) and **74** (ED_{50} = 0.7 mg/kg)].

Table 7. Pyrazine, Quinoxaline and Pyridazinones as Selective COX-2 Inhibitors

Compd.	Central scaffold	R_1	R_2	COX-2 IC_{50}, μM	COX-1 IC_{50}, μM	Refs.
70				1.07[a]	>300[a]	[96]
72				0.40[a]	>30[a]	[96]
73				0.02[b]	>10[b]	[97]
74				0.06[b]	3-10[b]	[97]

[a]*In vitro* evaluation was carried out by using recombinant human COX-2 enzyme and COX-1 derived from microsomal fraction of ram seminal vesicles. [b]*In vitro* evaluation was carried out by using human COX-2 enzyme derived from CHO cells and Microsomal COX-1 enzyme.

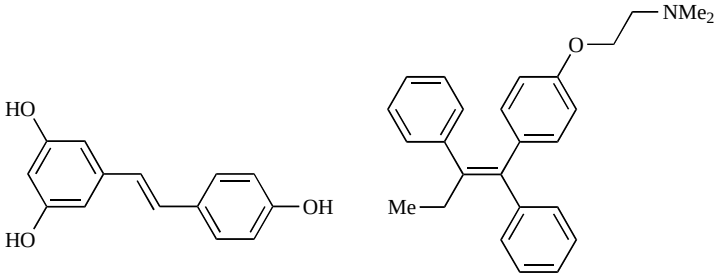


Fig. (5).

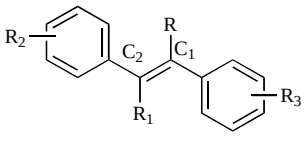
B. 1,2-Diarylethenes and 1,1,2-Triarylethenes

Based on naturally occurring *trans*-stilbene, the anti-inflammatory resveratrol (**75**) [98] and acyclic triaryl olefin, tamoxifen (**76**)[99] (Fig. **5**), various 1,2-diarylethenes and 1,1,2-triarylethenes have been reported as selective COX-2 inhibitors respectively (Fig. **6**).

1,2-Diarylethenes

Various resveratrol analogs have been reported as selective COX-2 inhibitors [100]. The methoxylated derivatives were less potent than the hydroxylated resveratrol derivatives. The hexahydroxy compound **77** and tetrahydroxy analog piceatannol (**78**), a natural compound found in grapes and red wine were the most potent and selective exhibiting better potency than celecoxib (COX-2, IC_{50} = 0.03482 μM; SI = 546.41) (Table **8**).

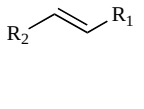
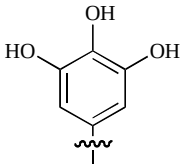
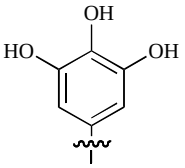
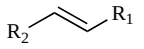
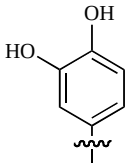
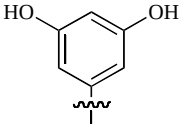
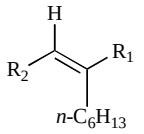
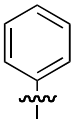
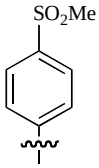
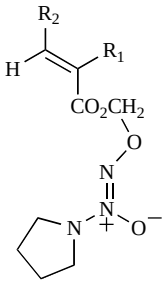
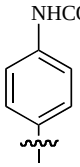
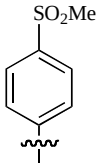
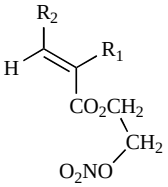
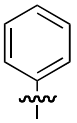
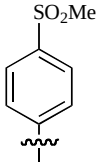
Knaus *et al.* reported a new class of 2-alkyl-1,2-diaryl (*E*)-olefins [101]. C-2 alkyl substituent chain length deter-



R = H or aryl;
R_1 = H or alkyl;
R_2, R_3 = SO_2Me, $NHSO_2Me$, Me, N_3, H, F or Cl

Fig. (6).

Table 8. 1,2-Diarylethene Derivatives as Selective COX-2 Inhibitors

Compd.	Central scaffold	R_1	R_2	COX-2 IC_{50},μM	COX-1 IC_{50}, μM	Refs.
77				0.00104[a]	0.748[a]	[100]
78				0.0113[a]	4.713[a]	[100]
79				0.77[a]	>100[a]	[101]
80				0.94[a]	>100[a]	[102]
81				0.18[a]	6.2[a]	[103]

[a]*In vitro* evaluation was carried out by using ovine COX-1/COX-2 assay kit.

mined the COX-2 inhibitory potency and selectivity, *n*-hexyl substituted compound **79** exhibited reasonable potency and selectivity compared to reference standard celecoxib (COX-2, IC_{50} = 0.07 μM; SI = 472) (Table **8**).

Knaus *et al*. also reported a novel series of (*E*)-2-(aryl)-3-(4-methanesulfonylphenyl)acrylic ester prodrugs as hybrid NO releasing anti-inflammatory agents [102]. The hybrid compounds were potent *in vitro* inhibitors of COX-2 and released significant amount of NO when incubated in rat serum. The compound **80** was identified as most potent and selective COX-2 inhibitor (Table **8**) with good NO releasing ability but was found less promising than celecoxib (COX-2, IC_{50} = 0.07 μM; SI = 473) and rofecoxib (COX-2, IC_{50} = 0.50 μM; SI >200). They recently reported a novel series of (*E*)-2-(aryl)-3-(4-methanesulfonylphenyl)acrylic acid prodrugs containing O^2-acetoxymethyl-1-(*N*-ethyl-*N*-methylamino)diazen-1-ium-1,2-diolate and nitrooxyethyl NO donor ester moiety [103]. Hybrid nitrooxyethyl ester prodrugs exhibited moderate to high COX-2 inhibitory activities with **81** showing the best COX-2 SI (Table **8**).

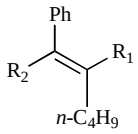
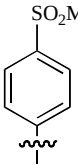
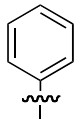
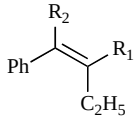
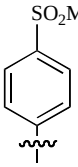
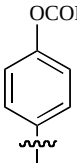
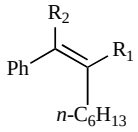
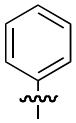
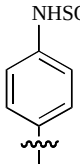
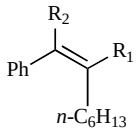
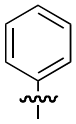
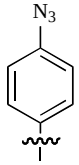
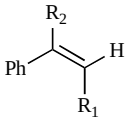
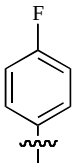
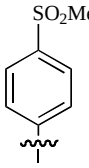
1,1,2-Triarylethenes

New classes of acyclic triaryl olefins devoid of traditional central heterocyclic or carbocyclic ring scaffold have been developed [104-107]. In a series of triaryl (*Z*)-olefins, COX-2 inhibitory potency and selectivity increased considerably with the increase in 2-alkyl chain length (up to 4 carbons) [104]. *n*-Butyl substituted compound **82** exhibited excellent potency and selectivity better than celecoxib (COX-2, IC_{50} = 0.057 μM; SI = 403) (Table **9**).

Introduction of *para*-acetoxy substituent on C-1 phenyl ring offered (*Z*)-1-(4-acetoxyphenyl)-1-phenyl-2-(4-methylsulfonylphenyl)but-1-ene (**83)** as potent and selective COX-2 inhibitor (Table **9**) with *in vivo* anti-inflammatory activity (ID_{50} = 4.1 mg/kg) superior to celecoxib (ID_{50} = 10.8 mg/kg) in carrageenan-induced rat paw edema assay [105].

From a series of 2-alkyl-1,1,2-triaryl (*Z*)-olefins possessing *para*-$MeSO_2NH/N_3$ as COX-2 pharmacophoric feature on the C-1 phenyl ring [106], **84** and **85** were the best exhibiting potency comparable to celecoxib (COX-2, IC_{50} = 0.07

Table 9. 1,1,2-Triarylethene Derivatives as Selective COX-2 Inhibitors

Compd.	Central scaffold	R_1	R_2	COX-2 IC_{50}, μM	COX-2 IC_{50}, μM	Refs.
82				0.014[a]	>100[a]	[104]
83				0.03[a]	2.4[a]	[105]
84				0.03[a]	>100[a]	[106]
85				0.11[a]	>100[a]	[106]
86				0.0316[a]	>100[a]	[107]

[a]*In vitro* evaluation was carried out by using ovine COX-1/COX-2 assay kit.

μM) and selectivity better than celecoxib (COX-2, SI = 472) (Table **9**). They also exhibited superior *in vivo* anti-inflammatory activity [**84** (ID_{50} = 2.8 mg/kg); **85** (ID_{50} = 5.0 mg/kg)] than celecoxib (ID_{50} = 10.8 mg/kg) in carrageenan-induced rat paw edema assay.

A series of 1,1,2-triaryl (*E*)-ethenes having *para*-methylsulfonyl moiety on the C-1 phenyl ring exhibited good COX-2 inhibitory potency and selectivity [107]. Substitution at the C-2 phenyl ring with 4-fluoro substituent afforded **86** with better inhibitory potency and selectivity than celecoxib (COX-2, IC_{50} = 0.07 μM; SI = 472) (Table **9**).

C. Acetylenes

Knaus *et al.* designed a novel class of phenylacetylenes in order to determine the effect of the replacement of the double bond of acyclic olefinic compounds by linear acetylene on the COX-2 selectivity and *in vivo* anti-inflammatory activity [108]. The SAR data revealed that COX-2 inhibitory potency and selectivity was dependent upon the position of SO_2Me group on C-1 phenyl ring as well as upon the nature and position of C-2 phenyl substituent. The compound **87** emerged as potent and selective COX-2 inhibitor (Table **10**) compared to rofecoxib (COX-2, IC_{50} = 0.50 μM; SI >200) but was found to be inferior to celecoxib both in terms of potency and selectivity (COX-2, IC_{50} = 0.07 μM; SI = 472). The *in vivo* anti-inflammatory activity of **87** was quite discouraging (ED_{50} = 129.3 mg/kg) compared to celecoxib (ED_{50} = 10.8 mg/kg) in carrageenan-induced rat paw edema assay. A new series of phenylacetylenes designed by replacement of 'SO_2Me' with 'SO_2NH_2' was reported by the same group [109]. Surprisingly, SO_2NH_2 derivatives were less potent and selective than earlier reported SO_2Me derivatives [108]. The analog **88** exhibited the best COX-2 inhibitory potency and selectivity (Table **10**) but displayed inferior *in vivo* anti-inflammatory activity than celecoxib in a carrageenan-induced rat paw edema assay.

Recently, Knaus *et al.* reported a class of regioisomeric 1-(phenyl)-2-(pyridyl)acetylenes by bioisosteric replacement of one of the phenyl ring of 1,2-diphenylacetylene with pyridyl ring [110] and **89** and **90** emerged as most potent and selective COX-2 inhibitors (Table **10**). These compounds were less potent for *in vivo* anti-inflammatory activity [**89** (ID_{50} = 76.4 mg/kg); **90** (ID_{50} = 59.9 mg/kg)] compared to celecoxib (ID_{50} = 10.8 mg/kg) in carrageenan-induced rat paw edema assay.

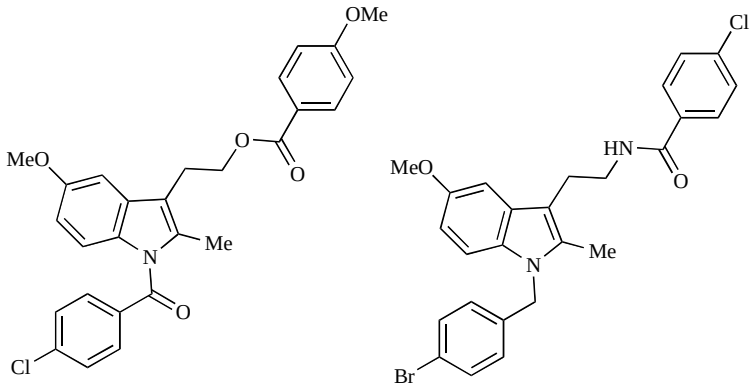
D. Modifications of Classical NSAIDs

Many efforts have been made in search of novel selective COX-2 inhibitors by functional group modifications of well-known classical NSAIDs. These include modifications of

Table 10. Acetylene Derivatives as Selective COX-2 Inhibitors

Compd.	Central scaffold	R_1	R_2	COX-2 IC_{50}, μM	COX-1 IC_{50}, μM	Refs.
87	R_2—≡—R_1	SO_2Me	Me	0.32[a]	>100[a]	[108]
88	R_2—≡—R_1	SO_2NH_2		0.45[a]	>31.6[a]	[109]
89	R_2—≡—R_1	N	SO_2Me	0.20[a]	31.6[a]	[110]
90	R_2—≡—R_1	N	SO_2Me	0.04[a]	3.2[a]	[110]

[a]*In vitro* evaluation was carried out by using ovine COX-1/COX-2 assay kit.



IC_{50} (COX-2) = 0.040 μM
(human COX-2)
IC_{50} (COX-1) > 66 μM
(Ovine COX-1)

(**91**)
Reverse esters of indomethacin

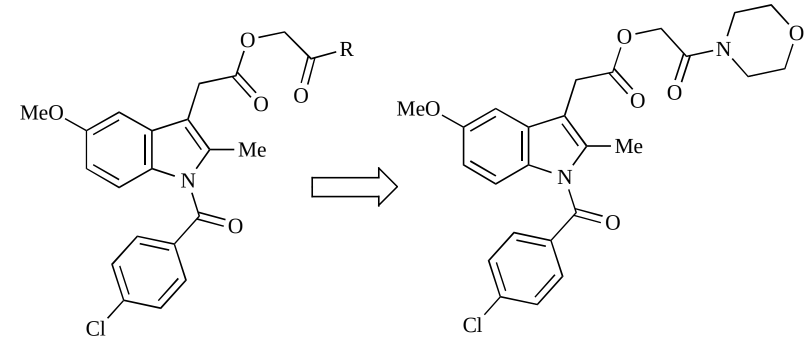
IC_{50} (COX-2) = 0.04 μM
(human COX-2)
IC_{50} (COX-1) > 66 μM
(Ovine COX-1)

(**92**)
Reverse amides of indomethacin

Fig. (7).

aspirin (**1**) [111,112], diclofenac (**3**) [113], flurbiprofen (**4**) [114], indomethacin (**6**) [115-119], and meclofenamic acid (**8**) [120]. Modification of the carboxylic acid moiety of indomethacin to esters or amides resulted in compounds with increased COX-2 selectivity as well as potency [117]. However, it was anticipated that these esters and possibly some amides may undergo hydrolysis *in vivo*. Therefore, the synthesis of 'reverse' esters **91** and 'reverse' amides **92** of indomethacin were synthesized (Fig. **7**) to retain the selectivity as well as potency [121].

Khanna *et al.* have recently described modifications of indomethacin leading to selective COX-2 inhibitors in which the acid moiety has been converted to *N*-substituted glycolamide ester [122]. The compound **93** with *N*-morpholinyl substituent was most potent inhibitor compared to celecoxib (COX-2, IC_{50} = 0.07 μM; SI ~ 219). It also exhibited *in vivo* anti-inflammatory activity (ED_{50} = 5.3 mg/kg) better than celecoxib (ED_{50} = 7.9 mg/kg) in carrageenan-induced rat paw edema assay (Fig. **8**).



Indomethacin glycolamide esters

IC_{50} (COX-2) = 0.30 μM
(human COX-2)
IC_{50} (COX-1) = 25 μM
ramseminal vesicles)

(**93**)

Fig. (8).

The *N*-acetyl-2-carboxybenzesulfonamides were synthesized by isosteric replacement of acetoxy group of aspirin by $SO_2NHCOMe$ moiety [123] and **94** was identified as potent non-selective inhibitor of COX isozymes than aspirin (COX-1, IC_{50} = 0.35 μM; COX-2, IC_{50} = 2.4 μM) (Fig. **9**). *N*-Acetyl-2-carboxybenzesulfonamide analogs having substituted phenyl ring at C-4/C-5 position were also synthesized and it was observed that **95** and **96** were potent and selective COX-2 inhibitors. The compound **96** was less potent but more selective inhibitor than celecoxib (COX-2, IC_{50} = 0.07 μM; SI ~ 472), whereas **94** exhibited better *in vivo* anti-inflammatory activity (ED_{50} = 49 mg/kg) than **95** (ED_{50} = 91 mg/kg) in a carrageenan-induced rat paw edema assay although the latter was more potent and selective inhibitor of COX-2 *in vitro*.

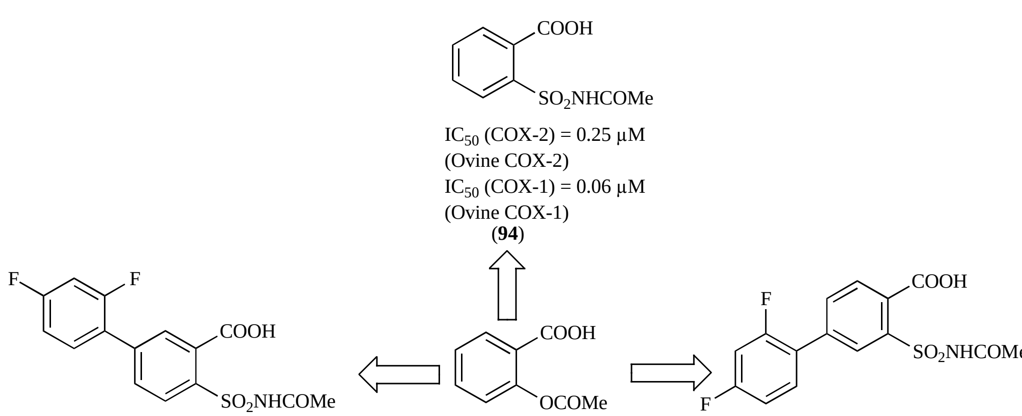
E. Other Novel Structural Classes

Benzo-1,3-dioxolanes

Khanapure *et al.* reported a series of benzo-1,3-dioxolane meth-aryl/cycloalkyl as selective COX-2 inhibitors [124]. Incorporation of one-carbon spacer group (methylene/carbonyl/methylidene) between central benzo-1,3-dioxolane ring and cycloalkyl or aryl substituent provided additional flexibility and resulted in more potent and selective inhibitors and **97** was identified as a potent and selective inhibitor with potency comparable to celecoxib (COX-2, IC_{50} = 1.2 μM) (Fig. **10**). Due to poor oral *in vivo* anti-inflammatory activity of **97** in air pouch model of inflammation, pyridyl ring was explored as the central scaffold in an attempt to enhance its bioavailability [125]. The compound **98** was identified as potent and selective inhibitor with *in vivo* anti-inflammatory activity comparable to etoricoxib in rat carrageenan-induced air pouch inflammation model (Fig. **11**).

Benzothiazoles, Benzimidazoles and Benzoxazoles

Paramashivappa *et al.* [126] synthesized a new series of benzimidazoles, benzothiazoles, and benzoxazoles from anacardic acid (Fig. **12**), **99** and **100** were more selective but less potent inhibitors than rofecoxib (COX-2, IC_{50} = 0.057 μM; SI = 200) in HWB assay.



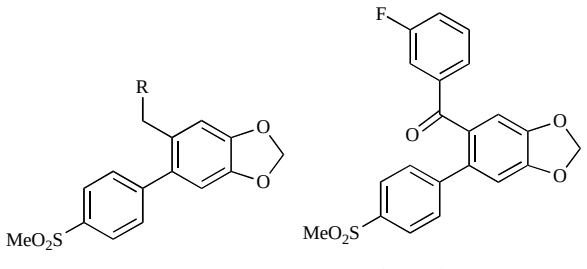
IC_{50} (COX-2) = 0.25 μM
(Ovine COX-2)
IC_{50} (COX-1) = 0.06 μM
(Ovine COX-1)
(**94**)

IC_{50} (COX-2) = 0.087 μM
(Ovine COX-2)
IC_{50} (COX-1) > 100 μM
(Ovine COX-1)
(**95**)

Aspirin (**1**)

IC_{50} (COX-2) = 0.77 μM
(Ovine COX-2)
IC_{50} (COX-1) > 100 μM
(Ovine COX-1)
(**96**)

Fig. (9).



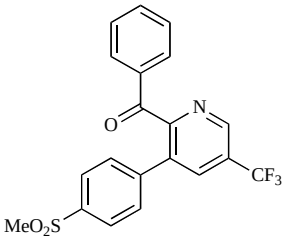
R = aryl/cycloalkyl

Benzo-1,3-dioxolane meth-aryl/cycloalkyl derivatives

IC_{50} (COX-2) = 1.0 μM (HWB)
IC_{50} (COX-1) = 20 μM (HWB)

(**97**)

Fig. (10).



IC_{50} (COX-2) = 0.25 μM (HWB)
IC_{50} (COX-1) = 14 μM (HWB)

(**98**)

Fig. (11).

1,3-Diarylprop-2-en-1-ones

Knaus *et al.* reported a new class of regioisomeric (*E*)-1,3-diarylprop-2-en-1-ones [127,128]. Compounds possessing *p*-SO_2Me (**101**)/$NHSO_2Me$ (**102**)/N_3 (**103**) moiety on C-1 ring exhibited selective and potent *in vitro* COX-2 inhibitory activities (Fig. **13**).

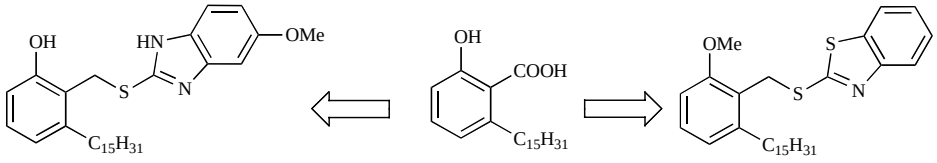
1,3-Diarylureas

Recently, Zarghi *et al.* reported a group of 1,3-diarylureas [129], **104** emerged as most potent and selective COX-2 inhibitor (Fig. **14**).

Phenylazo/Benzylideneamino/Phenyliminomethyl-Benzenesulfonamides

Yang *et al.* designed a series of phenylazobenzenesulfonamides as selective COX-2 inhibitors by bioisosteric replacement of ethylenic linkage of resveratrol with an azo *N,N*-double bond [130] and **105** was identified as most potent and selective COX-2 inhibitor from this series (Fig. **15**).

They further developed new benzenesulfonamides by isosteric replacement of the central -N=N- with -N=C- or -C=N- and reported two series of 4-benzylideneamino- and 4-phenyliminomethyl-benzenesulfonamides as selective COX-2 inhibitors [131]. 4-Benzylideneaminobenzenesulfonamides were more potent and selective inhibitors than 4-phenyliminomethylbenzenesulfonamides and **106** and **107** emerged as most potent and selective COX-2 inhibitors among 4-benzylideneaminobenzenesulfonamides and 4-phenyliminomethylbenzenesulfonamides respectively (Fig. **16**) and **106** exhibited selectivity comparable to the reference standard celecoxib (COX-2, IC_{50} = 0.30 μM; SI = 78).



IC_{50} (COX-2) = 1.0 μM (HWB)
IC_{50} (COX-1) = 384 μM (HWB)

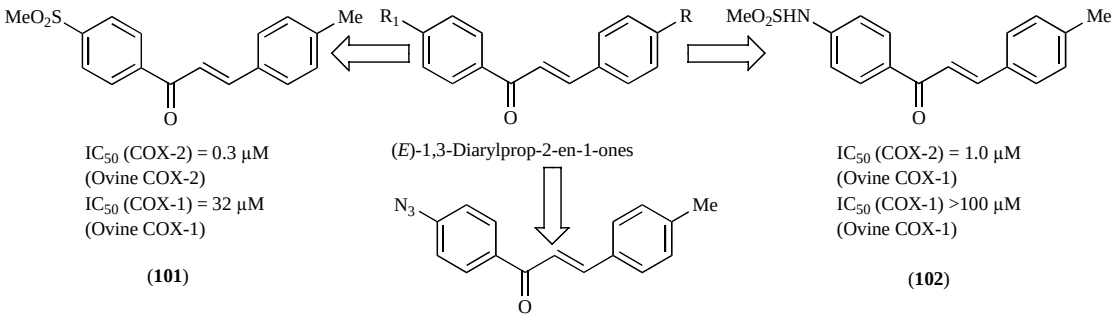
(**99**)

Anacardic acid

IC_{50} (COX-2) = 1.06 μM (HWB)
IC_{50} (COX-1) > 500 μM (HWB)

(**100**)

Fig. (12).



IC_{50} (COX-2) = 0.3 μM (Ovine COX-2)
IC_{50} (COX-1) = 32 μM (Ovine COX-1)

(**101**)

(*E*)-1,3-Diarylprop-2-en-1-ones

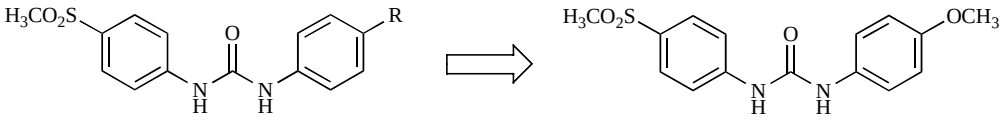
IC_{50} (COX-2) = 1.0 μM (Ovine COX-1)
IC_{50} (COX-1) >100 μM (Ovine COX-1)

(**102**)

IC_{50} (COX-2) = 0.3μM (Ovine COX-1)
IC_{50} (COX-1) >22.2 μM (Ovine COX-1)

(**103**)

Fig. (13).



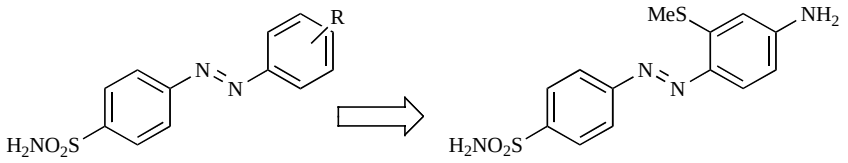
1,3-Diphenylureas

R = H, F, Cl, CH_3, OCH_3

IC_{50} (COX-2) = 0.11 μM
(Ovine COX-2)
IC_{50} (COX-1) = 22.4 μM
(Ovine COX-1)

(**104**)

Fig. (14).

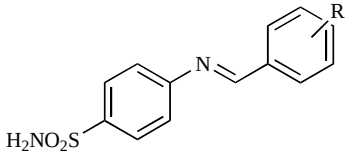


R = H, OH , OMe, NH_2, SMe, Cl etc.
Phenylazobenzenesulfonamides

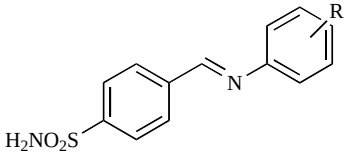
IC_{50} (COX-2) = 2.04 μM
(HWB)
IC_{50} (COX-1) = 23.28 μM
(HWB)

(**105**)

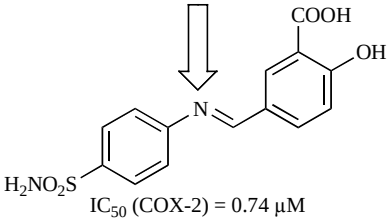
Fig. (15).



R = H, OH , OMe,COOH, NH_2, NO_2, NMe_2, F etc.
4-Benzylideneaminobenzenesulfonamides

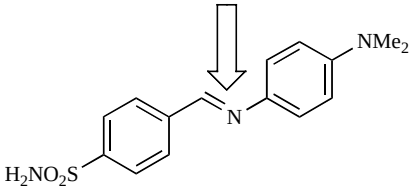


R = H, OH , OMe,COOH, COOMe, NH_2, F etc.
4-Phenyliminomethylbenzenesulfonamides



IC_{50} (COX-2) = 0.74 μM
(HWB)
IC_{50} (COX-1) = 85.13 μM
(HWB)

(**106**)



IC_{50} (COX-2) = 1.95 μM
(HWB)
IC_{50} (COX-1) = 64.42 μM
(HWB)

(**107**)

Fig. (16).

Styryls

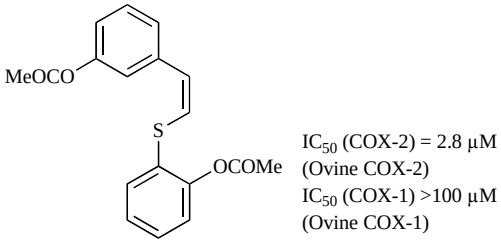
Reddy *et al.* described a series of (*E*)- and (*Z*)-styryl-2-acetoxyphenyl sulfides and sulfones [132]. Only sulfides with (*Z*)-configuration exhibited potential COX-2 inhibitory activity whereas the corresponding sulfones were less active (Fig. **17**), **108** exhibited *in vitro* potency comparable to celecoxib (COX-2, IC_{50} = 1.7 μM).

Thioxoimidazolin-4-ones

Gauthier *et al.* designed a new series of (±)-3,5-diphenyl-2-thioxoimidazolin-4-ones (Fig. **18**) characterized by a 3,5-diaryl substitution [133]. Substitution at *para* position of phenyl ring resulted in compounds with increased COX-2 inhibitory potency, **109** emerged as most active compound but exhibited poor inhibitory potency in HWB assay which could be ascribed to its poor aqueous stability.

Thiazinanones

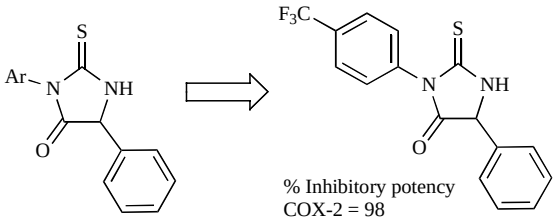
Zarghi *et al.* have reported a new series of 3-alkyl-2-aryl-1,3-thiazinan-4-ones [134]. All synthesized compounds were potent and selective COX-2 inhibitors, **110** exhibited best potency and selectivity and was equipotent to celecoxib (COX-2, IC_{50} = 0.06 μM; SI = 405) (Fig. **19**). They recently



IC_{50} (COX-2) = 2.8 μM
(Ovine COX-2)
IC_{50} (COX-1) >100 μM
(Ovine COX-1)

(**108**)

Fig. (17).



3,5-Diphenyl-2-thioxo
imidazolidin-4-ones

% Inhibitory potency
COX-2 = 98
(Human recombinant COX-2)
COX-1 = 67
(Ovine COX-1)

(**109**)

Fig. (18).

reported a new series of 1,3-benzthiazinan-4-ones [135] and identified **111** as more potent and selective inhibitor compared to celecoxib (Fig. **19**).

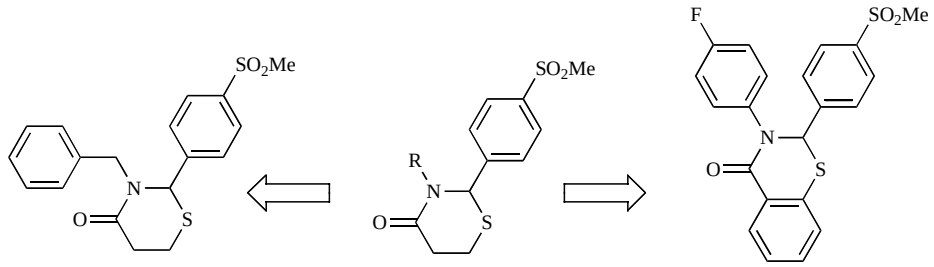
Quinolines

Recently, Zarghi *et al.* reported a new series of 4-carboxyl quinoline derivatives [136], **112** with cyclohexyl substitution emerged as best compound with potency better than celecoxib (COX-2, IC_{50} = 0.060 μM; COX-2 SI = 405) (Fig. **20**).

Analysis of Structural Features of Selective COX-2 Inhibitors

Considering the structural diversity of reported selective COX-2 inhibitors it seems impossible to generalize the common structural features present in them. However, a scrupulous analysis of the majority of compounds investigated as selective COX-2 inhibitors suggests the presence of vicinal diaryl/arylheteroaryl rings on the central heterocyclic/carbocyclic/acyclic scaffold (with one of the aryl rings substituted with 4-methylsulfonyl/sulfonamide moiety and the other aryl/heteroaryl ring bearing a halogen atom/small lipophilic group) as a basic template for exhibiting good COX-2 selectivity and potency (Fig. **21**). In general, the presence of methylsulfonyl group was attributed to increased selectivity but decreased COX-2 potency compared to sulfonamide group.

However, the use of a variety of *in vitro* assay methods employing different reference standards makes it difficult to compare the COX-2 selectivity and potency data of reported inhibitors in the literature and rationalize their SAR studies.



IC_{50} (COX-2) = 0.06 μM
(Ovine COX-2)
IC_{50} (COX-1) = 17.5 μM
(Ovine COX-1)

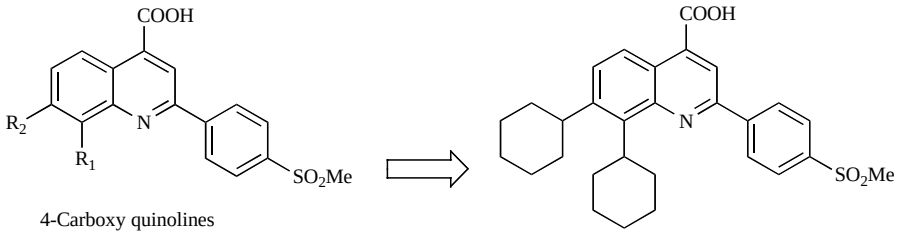
(**110**)

Thiazinan-4-ones

IC_{50} (COX-2) = 0.05 μM
(Ovine COX-2)
IC_{50} (COX-1) = 12.95 μM
(Ovine COX-1)

(**111**)

Fig. (19).



4-Carboxy quinolines

IC_{50} (COX-2) = 0.043 μM
(Ovine COX-2)
IC_{50} (COX-1) = 22.1 μM
(Ovine COX-1)

(**112**)

Fig. (20).

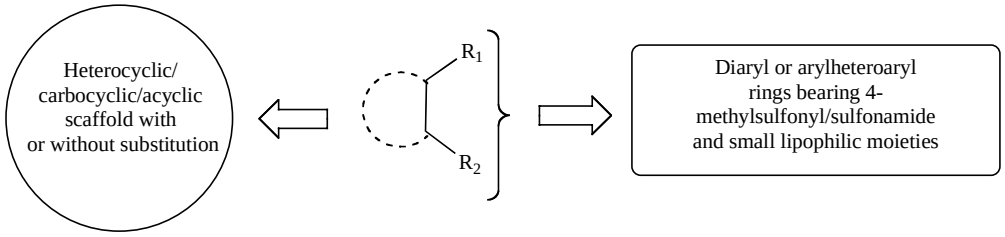


Fig. (21).

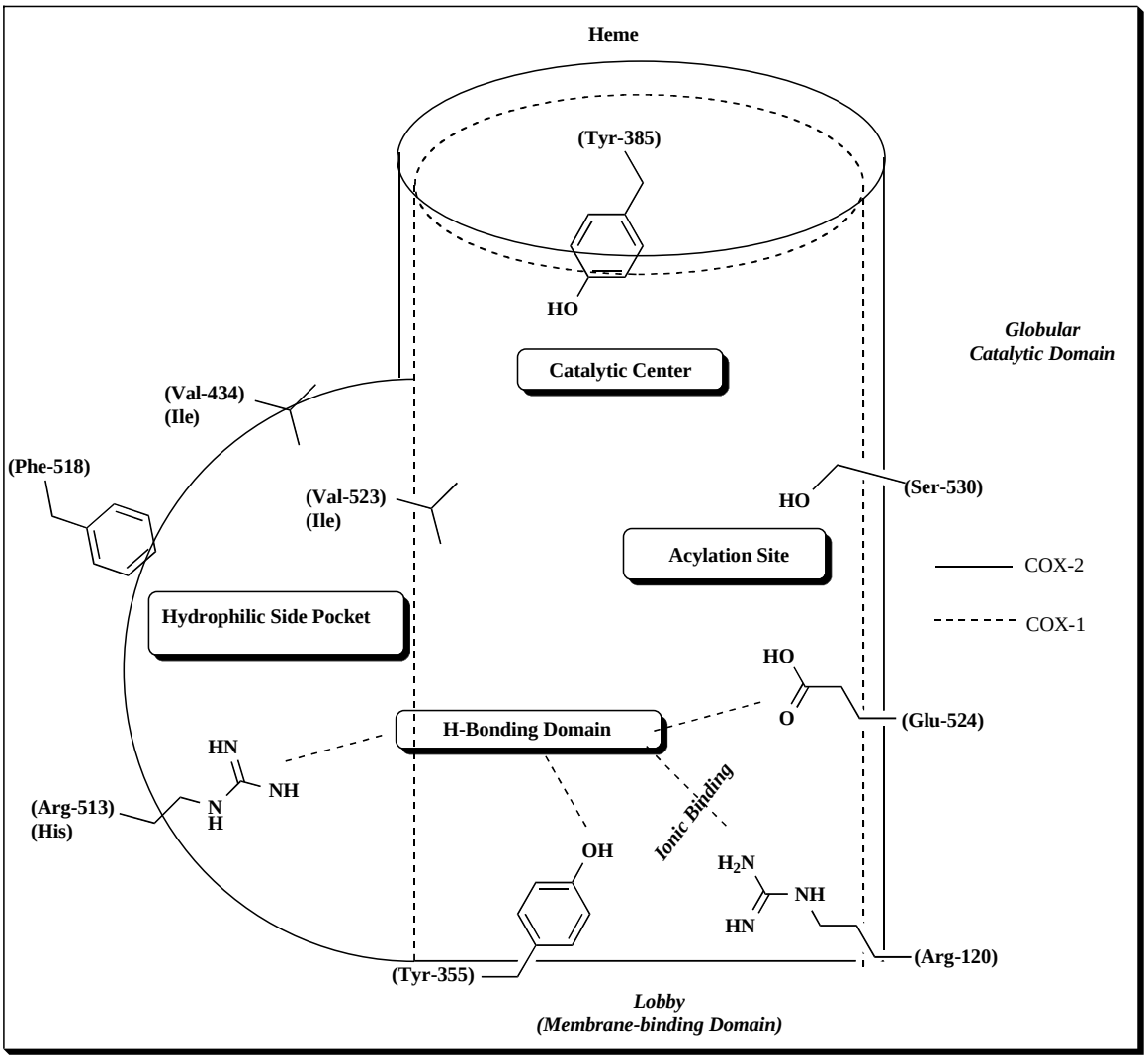


Fig. (22).

2.2. Molecular Modeling Based Approaches

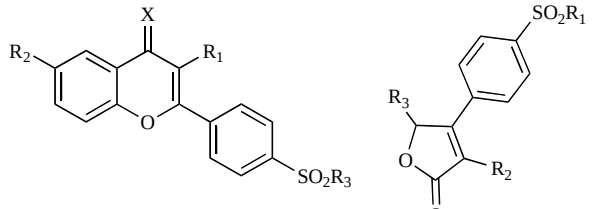
The advent of three-dimensional structures of COX-1 and COX-2 isozymes with the substrate and inhibitors provide rationale for COX-2 specificity of the selective inhibitors [137-141]. Both the isozymes are homodimeric proteins. Apart from the catalytic center, acylation site, ionic binding and H-bonding domain present in both COX-1 and COX-2 active site, there is a side pocket adjacent to the central channel in COX-2 active site which is generated due to the replacement of **Ile 523** in COX-1 by the smaller **Val 523** (Fig. **22**). The other key difference in COX-1 and COX-2 active site is the mutation of **His 513** in COX-1 by **Arg 513** in COX-2 (sulfonyl and sulfonamidic NSAIDs interact with this residue). These differences provide the basis for selectivity of COX inhibition.

A. QSAR Studies: An Overview

Diverse classes of compounds such as flavones, and diaryl hetero/carbo-cycles have been focused for the design of new selective COX-2 inhibitors. Extensive efforts have been made to find out the important pharmacophoric features required for the selective inhibition of COX-2 using the feasible and available molecular modeling methods of drug de-

signing. There are some excellent reviews on quantitative structure-activity relationship (QSAR) studies performed on COX inhibitors [142-144].

Chaturvedi *et al.* [145] performed a QSAR analysis on 26 compounds of 2,3-diaryl benzopyran series **113** which were already reported as selective COX-2 inhibitors (Fig. **23**). QSAR models developed in the study showed good predictive ability. QSAR analysis suggested that the sulfur atom at position X is important for enhancing the activity and bulkier R_1, X, R_2 and R_3 interacting groups were not tolerated at COX-2 receptor site. They also created a pharmacophore query employing pharmacophore Query Editor of Molecular Operating Environment (MOE) and identified two aromatic probes, an acceptor probe and a sulfonyl probe as the important pharmacophoric structural features of the COX-2 selective ligands. Chaturvedi *et al.* also carried out a QSAR study on a series of 43 diaryl furanones **114** using MOE [146]. The QSAR models gave good correlations of physical property, connectivity and conformation of the molecule with selective COX-2 inhibitory activity.



(**113**) (**114**)

Fig. (23).

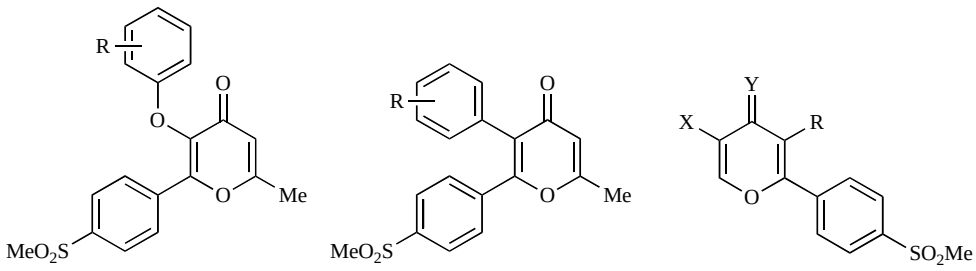
Another QSAR analysis [147] based on classical Hansch approach using conventional two-dimentional descriptors on two series [**series-1**: 3-phenoxypyran-4-ones (**115**) and 3-phenylpyran-4-ones (**116**); **series-2**: 5-halo-2-phenylpyran derivatives (**117**)] of total 54 molecules illustrated the effect of hydrophobic and electronic interactions primarily responsible for COX-2 binding (Fig. **24**). For instance, 2-fluoro substituent on 3-phenoxypyran-4-ones, 4-fluoro substituent on 3-phenylpyran-4-ones and a bulkier hydrophobic ring substituent like biphenyl on series-2 seem to improve COX-2 inhibition. This QSAR model was explored for selective inhibition of COX-2 over COX-1 and showed that selectivity could be influenced by the size and lipophilicity of substituents.

In continuation of finding the important parameters for the selective COX-2 inhibition, statistically significant QSAR models were derived [148] on the series of 15 conformationally restricted 1,5-diaryl pyrazoles (**118**) using correlation analysis of conformationally dependent and independent descriptors. Geometries of the compounds were optimized using semi-empirical Austin Model 1 (AM1) and Wang-Ford charges on non-hydrogen common atoms were calculated (Fig. **25**). Wang-Ford charges calculated suggest that substitution at C-7 position is important in determining the COX-1 selectivity whereas substitution at C-8 influences COX-2 selectivity.

3D-QSAR studies on diarylheterocycles and diarylcarbocycles have been carried out by various research groups [149-153]. A combination of ligand-based and structure-based 3D-QSAR study was attempted on 88 molecules [154] belonging to three chemical classes [triaryl rings (**119**), diaryl cycloalkanopyrazoles (**120**), and diphenyl hydrazides (**121**)] using Comparative Molecular Field Analysis (CoMFA), Comparative Molecular Similarity Index Analysis (CoMSIA) and molecular docking (Fig. **26**). The QSAR models came out with statistically significant r^2_{cv} (cross-validated correlation) values. CHARMM program was used to carry out the flexible docking into active site in continuum solvation environment. A good correlation of binding energies with inhibitory activities was observed for all the three chemical classes using the least-squares fit method.

Terphenyl methyl sulfones and sulfonamides (Fig. **27**) have also been studied for the development of statistically acceptable QSAR models [155] to explore the selectivity requirements for COX-2 versus COX-1 binding using electro-topological (E-state: an atom level descriptor) state index. The final analysis from the derived model suggested three important sites: A (methylsulfone or sulfonamide moiety), B (central phenyl ring), and C (terminal phenyl ring containing different substituents). All three sites play an important role in COX-2 binding whereas for COX-1 binding sites B and C are important. Only site C is important for COX-2 selectivity.

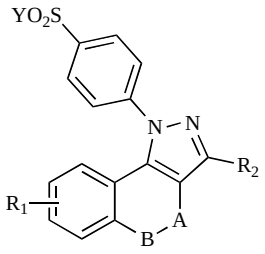
Molecular docking of structurally diverse 82 COX-1/COX-2 inhibitors were performed in this laboratory using FlexX program in order to differentiate between the active and inactive compounds based on the docking score [156]. Encouraging results were obtained that could be useful in building structure-based 3-D QSAR models.



3-Phenoxypyran-4-ones (**115**) 3-Phenylpyran-4-ones (**116**) 5-Halo-2-phenylpyran derivatives (**117**)

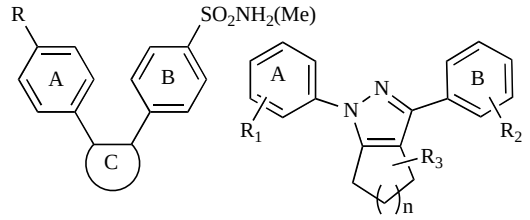
Series-1 **Series-2**

Fig. (24).



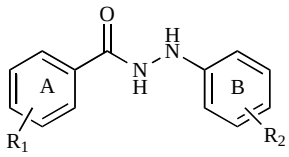
(**118**)

Fig. (25).



Triayl rings
(**119**)

Diaryl cycloalkanopyrazoles
(**120**)



Diphenyl hydrazides

(**121**)

Fig. (26).

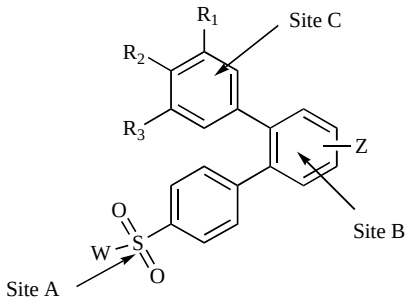


Fig. (27).

Though most of the COX-2 inhibitors contain sulfonyl moiety, recently reported COX-2 inhibitors devoid of sulfonyl group [157,158] encouraged us to search for new pharmacophoric requirements for selective COX-2 inhibitory activity and further designing of the molecules. CoMFA and CoMSIA models were developed on a series of 35 molecules of 1,3-diaryl isoindoles (Fig. **28**) in this laboratory [159]. An improved CoMFA model was obtained (r^2_{cv} = 0.536, r^2_{conv} = 0.968, r^2_{pred} = 0.6564) by taking into account the CMR as additional descriptor.

3D-QSAR models for 34 molecules of 1,5-diaryl pyrazoles have been derived in this laboratory using two different alignment methods (atom based alignment method and alignment method involving the docked conformations) to find out the importance of alignment of molecules in deriving 3D-QSAR models [160]. The atom based alignment method provided better CoMFA and CoMSIA models.

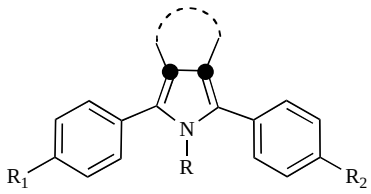


Fig. (28).

B. Success Stories of Molecular Modeling

Chavatte *et al.* [161] synthesized 5 molecules (**122-126**) designed on the basis of 3D-QSAR study [150] that could be considered as new leads for chemical optimization (Table **11**).

Another successful example of molecular modeling based designing and synthesis was reported by Palomer *et al.* [162]. A pharmacophore model was developed using three-dimentional structure of four selective COX-2 inhibitors (**15, 16**, **127** and **128**) (Fig. **29**). Sulfonyl S atom (characteristic of phenylsulfonyl tricyclic compounds), aromatic ring A (normal to plane A), aromatic ring B (plane B), dihedral angles (angle between the two planes) and excluded volume were the five important characteristic features of the pharmacophore model. The model was then applied for the design and synthesis of *N*-benzyl/benzoyl-5-sulfonylindole analogs of indomethacin as selective COX-2 inhibitors. Compound **129** emerged as a potent and selective COX-2 inhibitor (*in vitro* and *in vivo* evaluation) that could be taken for further lead optimization.

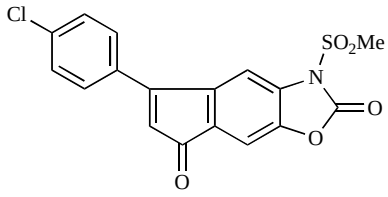
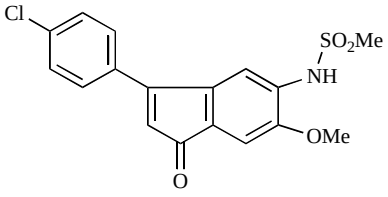
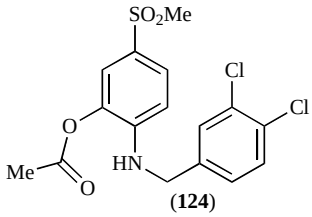
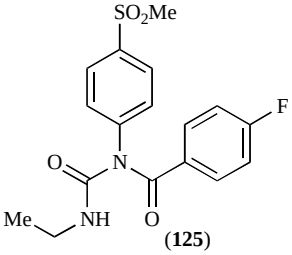
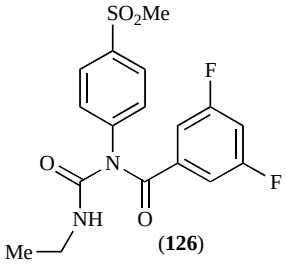
A set of potential COX-2 pharmacophoric points (planar hydrophobic and H-bond acceptors) were obtained (Fig. **30**) after extracting and visualizing the important features using support vector machines (SVM) [163]. Interestingly, the developed pharmacophore was in accordance with the pharmacophore developed by Palomer *et al.* [162]. In the study, SVM identified the promising screening candidates and predicted their activities which were tested for COX-2 inhibitory activity, benzimidazole derivative **130** showed higher potency than rofecoxib **16** and celecoxib **17** in cellular activity assay and was considered as a lead molecule.

Bijev group [164] performed 3D-QSAR (CoMFA and CoMSIA) modeling studies for *in vitro* and *in vivo* prediction of anti-inflammatory activities. Based on the prediction of 3D-QSAR models they synthesized nine derivatives of *N*-pyrrolylcarboxylic acid (**131-139**) which were tested for *in vivo* anti-inflammatory activity. Six compounds were found to be active (Table **12**).

3. CONCLUSIONS

The journey of selective COX-2 inhibitors begun in early 1990's with the identification of second isoform of COX enzyme (COX-2) which was thought to be responsible for inflammation. This gave the impetus for the search of selective COX-2 inhibitors as safer NSAIDs. Extensive libraries of compounds with diverse structural features were investigated for selective COX-2 inhibition. The main emphasis

Table 11. Predicted and Experimental IC_{50} Values of Compounds Studied by Chavatte *et al.*

Compd.	Predicted IC_{50}, μM COX-2	Experimental IC_{50}, μM		COX-1/COX-2 ratio
		COX-1	COX-2	
 (**122**)	0.002	>5	0.96	>5.2
 (**123**)	0.27	26	0.37	70
 (**124**)	0.03	24	0.54	44
 (**125**)	0.50	4.16	0.27	15.4
 (**126**)	0.66	170	0.57	298
Aspirin (**1**)		13.70	98.10	0.1
Ibuprofen (**5**)		31.40	81.40	0.4
Nimesulide (**11**)		297.0	1.52	195.4

was on diaryl hetero/carbo-cyclic class of compounds and within a decade various selective COX-2 inhibitors (rofecoxib, celecoxib, valdecoxib, etoricoxib etc.) belonging to this class were in the market and became blockbuster drugs. This lead to a notion that search for safer NSAIDs is completed. Withdrawal of Vioxx (rofecoxib) in 2004 and Bextra (valdecoxib) in 2005 from the market due to the associated adverse cardiovascular events raised a question on the safety of this class of drugs and gave a setback to the journey of selective COX-2 inhibitors. Celebrex (celecoxib) is the only drug of this class in US market with apparent cautions of cardiac risks.

Lumiracoxib, the most selective COX-2 inhibitor with structure different from other coxibs did not demonstrate

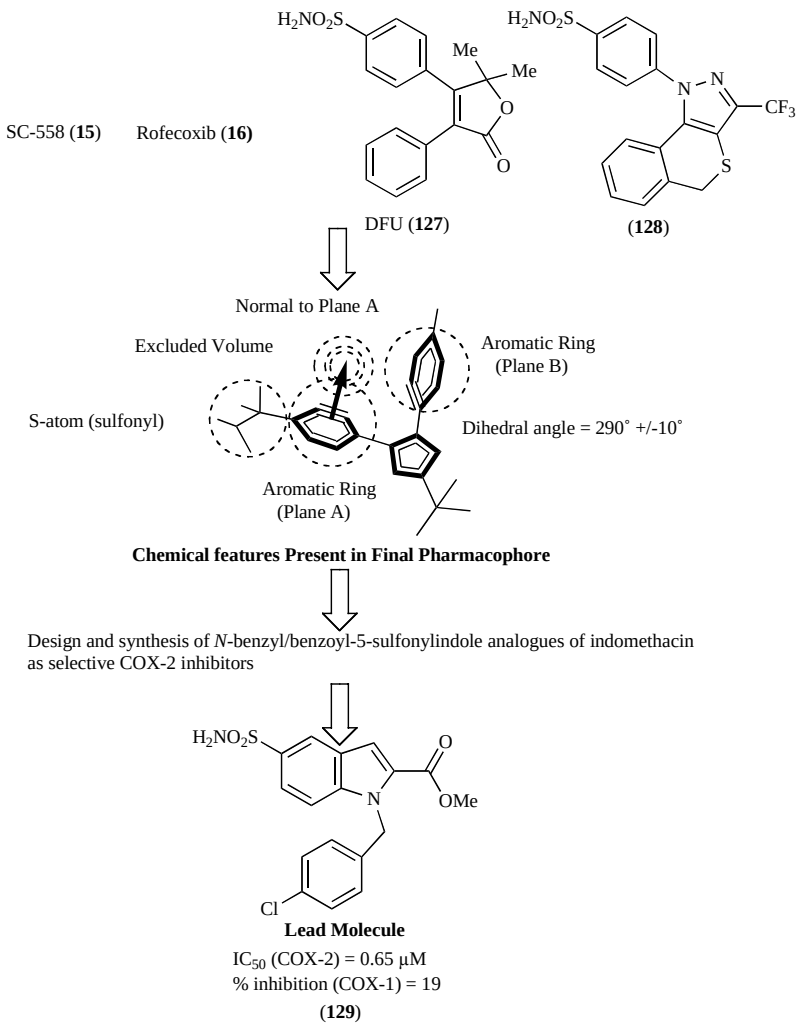

SC-558 (**15**)
Rofecoxib (**16**)
DFU (**127**)
(**128**)
Normal to Plane A
Excluded Volume
Aromatic Ring (Plane B)
S-atom (sulfonyl)
Dihedral angle = 290˚ +/-10˚
Aromatic Ring (Plane A)
Chemical features Present in Final Pharmacophore
Design and synthesis of *N*-benzyl/benzoyl-5-sulfonylindole analogues of indomethacin as selective COX-2 inhibitors
Lead Molecule
IC_{50} (COX-2) = 0.65 μM
% inhibition (COX-1) = 19
(**129**)

Fig. (29).

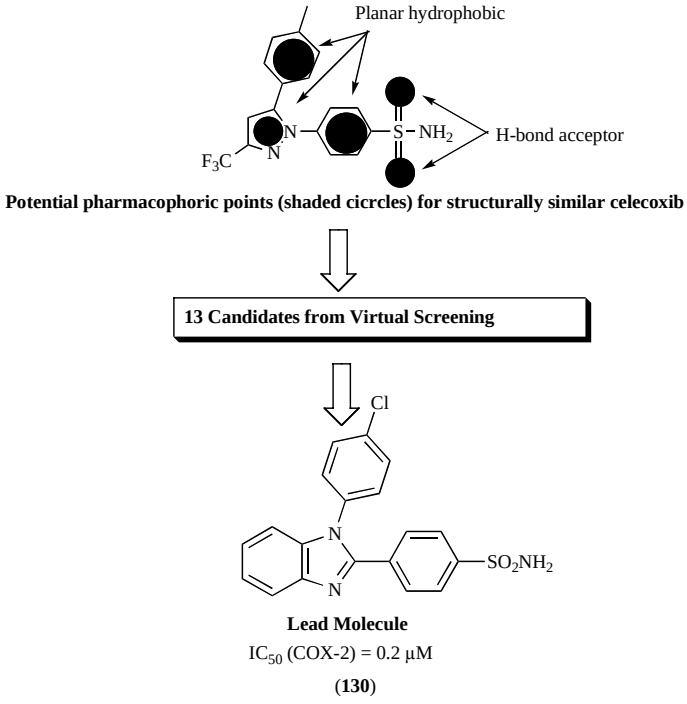
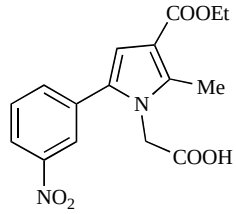
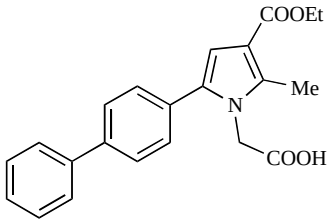
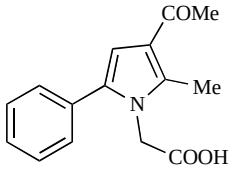
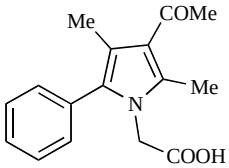
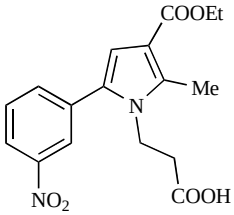
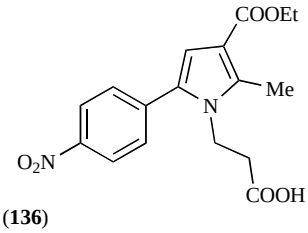
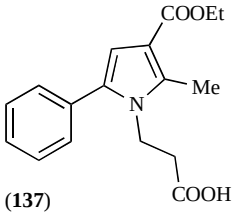
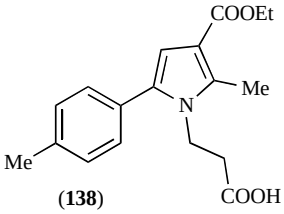
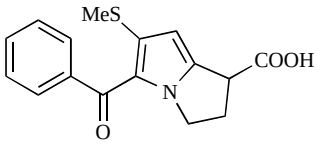

Planar hydrophobic
H-bond acceptor
Potential pharmacophoric points (shaded cicrcles) for structurally similar celecoxib
13 Candidates from Virtual Screening
Lead Molecule
IC_{50} (COX-2) = 0.2 μM
(**130**)

Fig. (30).

Table 12. Predicted and Observed Activities of *N*-Pyrrolylcarboxylic Acids

Compound	Predicted *in vitro* activity				Predicted *in vivo* activity	Observed activity	
	EF		SF	HF	SF	i.p.	p.o.
	COX-1	COX-2	COX-1	COX-2			
 (**131**)	I	I	A	A	M	I	I
 (**132**)	M	A	A	A	M	I	I
 (**133**)	M	A	M	M	I	A	I
 (**134**)	M	A	M	M	I	M	I
 (**135**)	I	I	A	A	M	A	A
 (**136**)	I	I	A	A	A	A	A

(Table 12). Contd…..

Compound	Predicted *in vitro* activity				Predicted *in vivo* activity	Observed activity	
	EF		SF	HF	SF	i.p.	p.o.
	COX-1	COX-2	COX-1	COX-2			
 (**137**)	A	A	M	M	M	A	A
 (**138**)	A	A	M	M	A	M	A
 (**139**)	A	M	I	I	M	M	A

A: Active; I: Inactive; M: Moderate activity, EF: Electrostatic field, SF: Steric field, HF: Hydrophobic field, p.o.: per oral, i.p.: intra peritonial.

significant cardiovascular side effects in TARGET. Moreover, both traditional NSAIDs and selective COX-2 inhibitors were found to have similar risk of adverse cardiovascular events. Recent findings have also highlighted an important role of COX-2 in several pathophysiological processes such as Alzheimer's disease, Parkinson's disease and various cancers. Celecoxib was approved by FDA as an adjunct for the treatment of FAP. Thus, COX-2 has attracted the attention of researchers as emerging therapeutic target in various other areas of biomedical sciences beyond its current applications in the treatment of inflammatory disorders. Probably it is required to further unravel the biology involved in PG biosynthesis with respect to COX enzyme and to have a relook in to the design of selective COX-2 inhibitors. Moreover, emphasis should be given to find the lowest effective dose of various selective COX-2 inhibitors in order to avoid/minimize side effects. Hopefully, the journey of selective COX-2 inhibitors will continue and deliver fruitful outcomes in future not only in the field of inflammation but also in other therapeutic areas.

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ABBREVIATIONS

AD = Alzheimer's Disease

AM1 = Austin Model 1

APPROVe = Adenomatous Polyp Prevention on Vioxx

CMR = Calculated Molar Refractivity

CLASS = Celecoxib Long Term Arthritis Safety Study

CoMFA = Comparative Molecular Field Analysis

CoMSIA = Comparative Molecular Similarity Index Analysis

COX = Cyclooxygenase

3D-QSAR = Three-dimensional Structure-Activity Relationship

ED = Effective Dose

FAP = Familial Adenomatous Polyposis

FDA = Food and Drug Administration

HWB = Human Whole Blood

IC_{50} = Inhibitory Concentration 50

ID_{50} = Inhibitory Dose 50

μM = Micromolar

MOE = Molecular Operating Environment

NO = Nitric Oxide

NSAIDs = Non Steroidal Anti-Inflammatory Drug(s)

PD = Parkinson's disease

PGs = Prostaglandins

QSAR = Quantitative Structure-Activity Relationship

SAR = Structure-Activity Relationship

SI = Selectivity Index

SVM = Support Vector Machines

TARGET = Therapeutic Arthritis Research and Gastrointestinal Event Trial

TXA_2 = Thromboxane A_2

VIGOR = Vioxx Gastrointestinal Outcomes Research

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