Current Status of COX-2 Inhibitors

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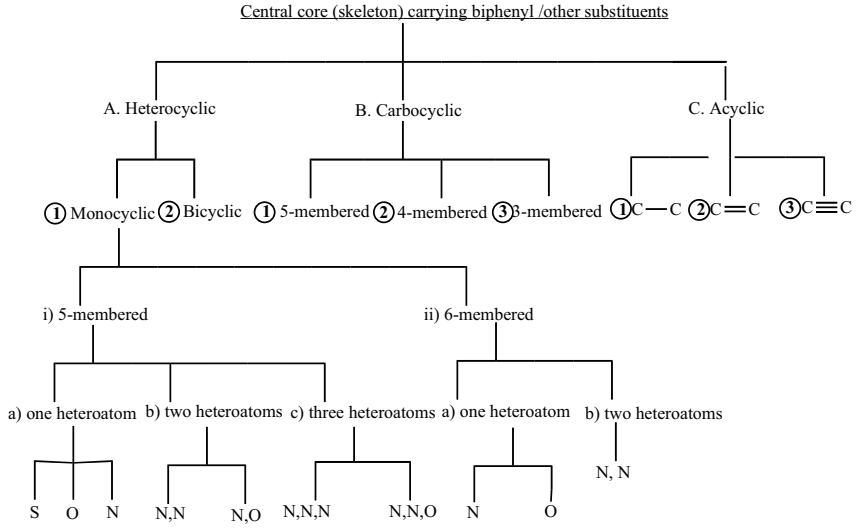
Abstract: The two isoforms of enzyme cyclooxygenase viz. COX-1 and COX-2 play key roles in the metabolism of arachidonic acid. The enzyme COX-2, when over expressed, leads to more production of prostaglandins causing inflammation and it also participates in the propagation of cancer. Therefore, COX-2 becomes the cellular target of a number of chemical entities for the treatment of inflammatory diseases as well as for the chemotherapy of cancer.

In the present review, an up to date status of the compounds investigated for COX-2 inhibition has been given so that a collective view of the existing COX-2 inhibitors could be helpful for the design of safer anti-inflammatory drugs. In order to cover the maximum reported COX-2 inhibitors, a unique classification on the basis of the central core of the molecule (carrying mostly the phenyl moieties) has been followed, an outline of which has been given below:



Each category of compounds has been discussed with suitable examples giving the IC_{50} (for COX-2) values and the selectivity towards COX-2 over COX-1 of most potent compounds.

Key words: Inflammation, arachidonic acid, COX-2, prostaglandins, COX-2 inhibitors, vicinal diaryl rings, heterocyclic, carbocyclic and acyclic template.

INTRODUCTION

Inflammation, symptomized as irritation, swelling, tenderness, redness or soreness, occurs in response to certain stimuli during which the three enzymes of arachidonic acid metabolism viz, phospholipases (PLA_2), cyclooxygenases (COX) and lipoxygenases (LOX) get over expressed resulting in over production of arachidonic acid and its metabolites like prostaglandins and leukotrienes. Due to its common prevalence, (even a small cut or a burn on some part of the body), the drugs associated with inflammation (such as aspirin, ibuprofen, coxibs) are widely prescribed and millions of people take them over-the-counter each day. The history of anti-inflammatory drugs, starting from the use of steroids to the use of aspirin, ibuprofen and coxibs has been well described [1, 2].

Of the three enzymes of arachidonic acid metabolism, most of the anti-inflammatory drugs target cyclooxygenases. The side effects associated with these drugs, mainly their gastro-intestinal (GI) toxicity, led to the identification of two isoforms of cyclooxygenase viz. COX-1 and COX-2 [3, 4] and heralded the era of selective COX-2 inhibitory anti-inflammatory drugs [5-7].

A large number of compounds with a common structural feature i.e., the presence of two aryl rings on adjacent carbons of a cyclic/acyclic moiety have been investigated for COX-2 inhibition. Amongst such compounds, ones like ro-

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fecoxib, celecoxib, valdecoxib were put to the market. However, too much inhibition of COX-2 by the use of these drugs blocks the formation of vasodilators (PGD_2, PGE_2 and PGI_2) and shifts the arachidonic acid metabolism to lipoxygenase pathway which is the major cause of their cardiac toxicity. These facts are substantiated by the withdrawal of rofecoxib and valdecoxib from the market and trigger an intensive search for the development of safe COX-2 inhibitors.

With the presently available long list of compounds investigated for COX-2 inhibition, it is difficult to review them collectively and rationalize their structure activity relationships. In the present review, categorization of COX-2 inhibitors has been made based on the various structural features and attempts have been made to rationalize the central core of the molecules so that a collective view of these compounds could be helpful for the design of more potent and safe anti-inflammatory drugs.

Since the presence of two substituted / unsubstituted aryl rings on a central template is a common feature of most of the COX-2 inhibitors, their classification has been made on the basis of structure of central core of the molecule. An outlay of the arrangement of COX-2 inhibitors discussed in this review has been shown in Scheme **1**.

Each category of COX-2 inhibitors has been discussed with examples of the most potent compounds indicating their IC_{50} values (investigated under particular conditions) as mentioned in the original paper and their COX-2 selectivity.

A. HETEROCYCLIC BASED COX-2 INHIBITORS

Heterocycles constitute an important class of organic compounds and due to their compatibility in the living systems, form an integral part of large number of biologically useful molecules. A number of molecules based upon the monocyclic or bicyclic heterocyclic template have been investigated for their COX-2 inhibitory activities.

1. Monocyclic Heterocycles as the Central Core of COX-2 Inhibitors

The optimum molecular volume and the compatibility of the molecule in the active site of COX-2 make an exclusive use of 5- and 6-membered heterocycles as the central core of a number of COX-2 inhibitors.

i) COX-2 Inhibitors Based on 5-Membered Heterocycles

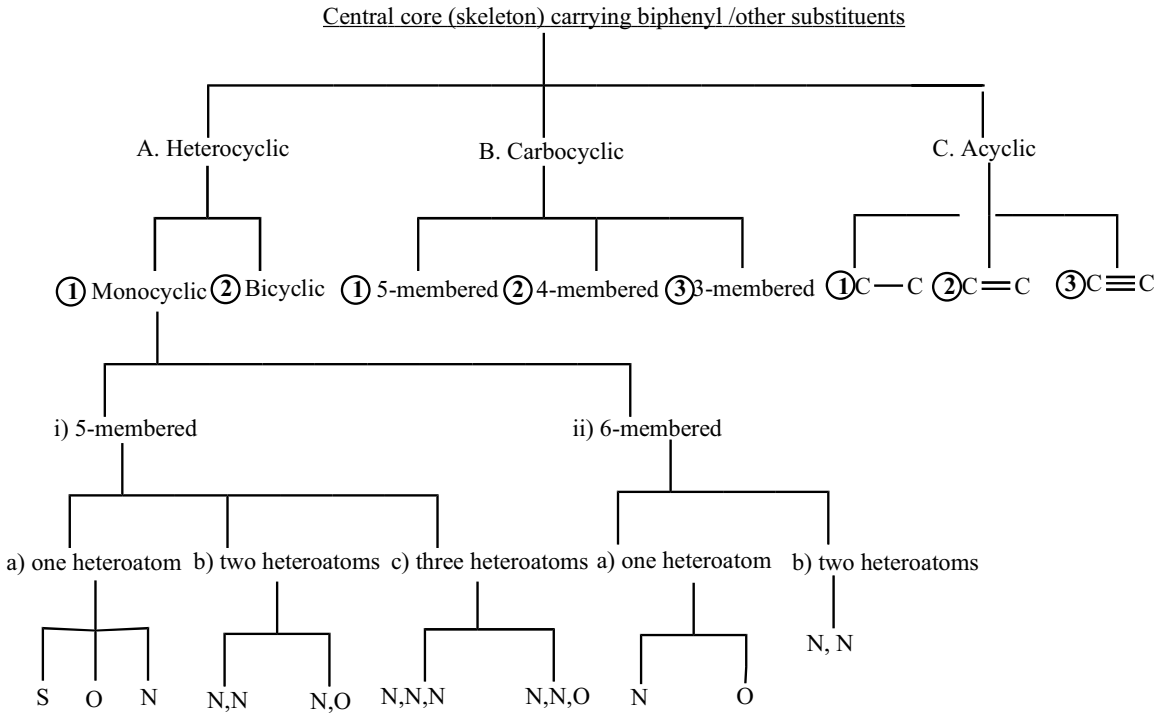
Based upon the number (one, two and three) and nature of the heteroatom viz. oxygen, nitrogen and sulphur, each category of compounds has been discussed one by one.

a) One Heteroatom in the 5-Membered Ring

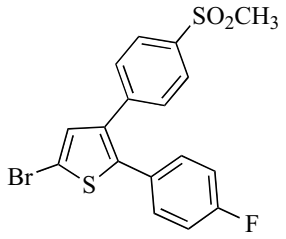
S-Containing 5-Membered Heterocycles

After the identification of two isoforms of cyclooxygenases viz. COX-1 and COX-2, du Pont & Co. developed a novel orally active prostaglandin synthesis inhibitor DUP 697 (**1**, Chart **1**). Its differential effects on PG synthesis by various tissues account for its high potency as an anti-inflammatory and antipyretic agent [8].

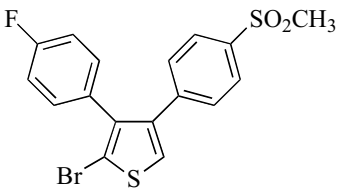
To study the structure activity relationship around the thiophene template, a number of analogues of DUP 697 have been obtained by altering the position of two phenyl substituents and varying the substituents present thereon [9,10]. Compound **2** (Chart **1**), with the same substituents as in DUP 697 but placed at different positions of thiophene core viz.



Scheme 1. Schematic representation of the arrangement of COX-2 inhibitors discussed in this review.



1. DUP 697



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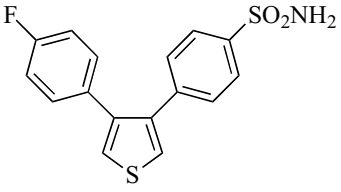


3

IC_{50} (for COX-2)	0.014 μM	0.015 μM	0.008 μM
Selectivity for COX-2 over COX-1	58	347	225

Chart 1.

aryl groups at 3, 4-carbons of thiophene is as potent as DUP 697 but more selective for COX-2 over COX-1. Replacement of methyl sulphonyl group with sulphonamide and removal of Br from the thiophene moiety (**3**, Chart **1**) increases the activity for COX-2 inhibition but less selectivity.

O-containing 5-Membered Heterocycles

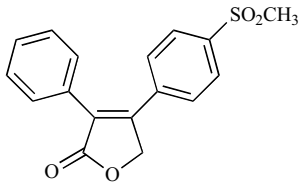
The low oral bioavailability was one of the major drawbacks of DUP 697 and its analogues. The lactone moiety has been found to be suitable replacement of thiophene (present in DUP 697) and led to the development of oxygen containing 5-membered heterocyclic based COX-2 inhibitors with good bio-availability. A major achievement was the launch of rofecoxib (**4**, Chart **2**) where phenyl and *p*-methylsulphonyl phenyl moieties are present at 3, 4-carbons of the lactone ring [11]. However, too much inhibition of COX-2 by rofecoxib and the slow oxidation of the lactone ring to maleic anhydride [12], which seems to be responsible for its cardiac toxicity, led to its withdrawal from the market [13]. Some other highly potent and selective COX-2 inhibitors with lactone template (**5** [14] and **6** [15], Chart **2**) have been reported.

More analogues of **6**, obtained by replacing the isopropoxy group with phenyl /substituted phenyl and replacing oxygen of the alkoxy group with S, NH, CO, CH_2, have been investigated for COX-2 inhibition [16]. Among these compounds, **7** and **8** (Chart **3**) have been identified as the highly potent but less selective than **6** towards COX-2. Further to improve the COX-2 inhibitory activity and selectivity, a number of heterocyclic moieties have been introduced in place of *O*-linked phenyl group of **8**. Out of these compounds, one with 5-bromopyridine moiety linked through oxygen at C-3 of lactone (**9**, Chart **3**) has been found to be more potent and selective than compounds **7** and **8** [17].

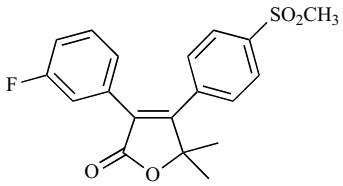
With the advantage of making the alkoxy substituted furanones as water soluble salts, a hydroxyl group has been introduced at C-5 of furanone (**10**, Chart **4**). Compound **11**, the sodium salt of **10**, suitable for oral dosing, is equally potent as the neutral cyclic form **10** [18] and provides the advantage for the preparation of stable aqueous solutions that may be suitable for intravenous formulation. In order to provide conformational restrictions to the furanone moiety, naphthofuranone derivatives (**12**, Chart **4**) have been investigated for COX-2 inhibition. They do not possess much potency or selectivity [19].

In order to improve the GI toxicity profile of selective COX-2 inhibitors, a remarkable modification has been made in the basic furanone system of above discussed COX-2 inhibitors through the synthesis of 3-furanone derivatives **13** (Chart **5**). Amongst these compounds, one with n-butyl chain on one of the two phenyl rings has been found to be highly potent and selective for COX-2 [20].

Compounds **14** (Chart **6**), obtained by the replacement of methyl sulphone moiety of **13** with sulphonamide, are more active but less selective for COX-2. The most potent com-



4, Rofecoxib



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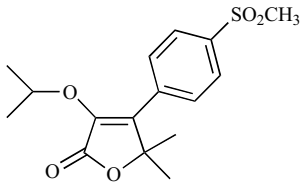
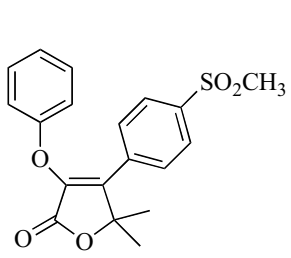


6

IC_{50} (for HWB COX-2)	0.5 μM	0.3 μM	0.3 μM
IC_{50} (Whole cells COX-2)	0.02 μM		
Selectivity for COX-2 over COX-1	>750 (at whole cells) 19 (at HWB)	>200	>330

Chart 2.



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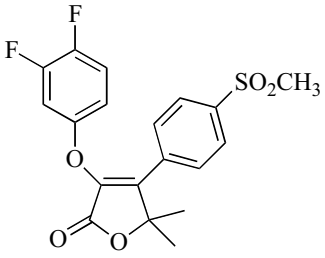

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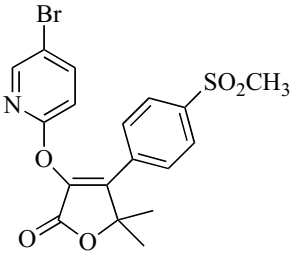
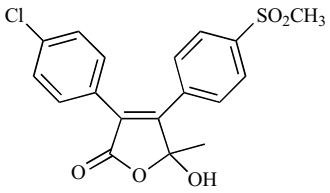


9

IC_{50} (for HWB COX-2)	0.04 μM	0.06 μM	0.03 μM
Selectivity for COX-2 over COX-1	115	130	187

Chart 3.



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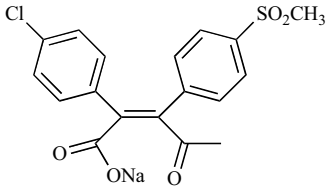

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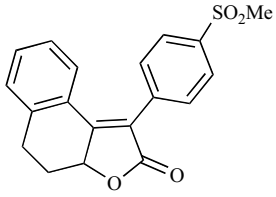
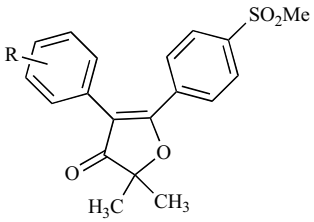


12

IC_{50} (for HWB COX-2)	1.7 μM		
IC_{50} (Whole cells COX-2)	0.11 μM		0.56 μM
COX-2 Selectivity	60/1000		>80

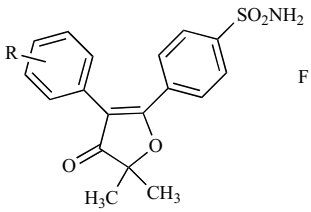
Chart 4.



13

R	3-F	3-Cl	4-Br	3,5-diF	3-ispropyl	4-n-butyl	3-acetyl	rofecoxib
IC_{50} (μM)	0.02	0.01	0.03	0.05	0.03	0.002	0.05	0.06
COX-2 selectivity	250	200	1	400	1000	2500	1000	>1667

Chart 5.



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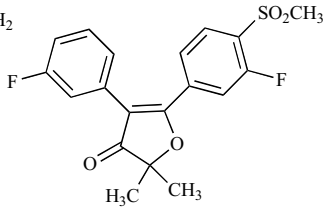

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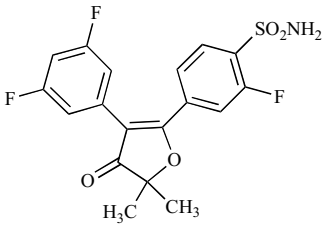

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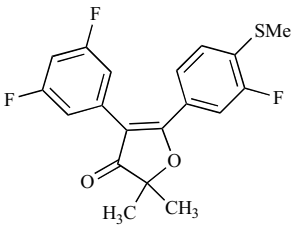


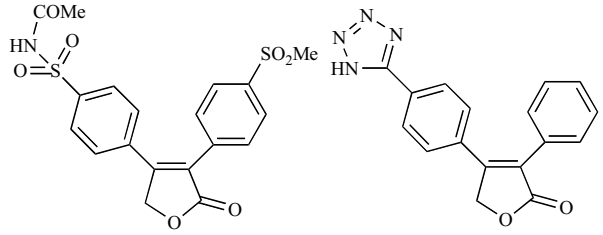
17

IC_{50}		0.03 μM	0.02 μM
COX-2 selectivity		6667	5000

Chart 6.

pound among this category i.e., with 3-fluorophenyl group at C-4 of furanone exhibits IC_{50} 0.003 μM for COX-2 with a selectivity order of 100 only. The COX-2 selectivity of **13** and **14** has been increased several fold by introducing a halide moiety to the phenyl ring substituted with sulfonylmethyl / sulphonamide group (**15**, **16;** Chart **6**) [20].

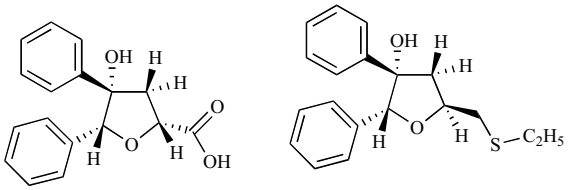
Despite its strong anti-inflammatory potency, compound **16** showed poor bio-availability in dogs which could pose a technical issue relating to its oral intake by humans. Therefore, a pro-drug approach has been used where compound **17**, with good bio-availability, after administration in the body get transformed to the parent sulphone. The sulphoxide prodrugs could also reduce gastro-intestinal burden of COX-2 inhibitors [21]. Introduction of N-acetylsulphonamide /sulphonamide moieties onto the phenyl rings of rofecoxib has identified a highly potent and selective COX-2 inhibitor **18** (Chart **7**) [22].



	18	**19**
IC_{50}	0.05 μM	0.0018 μM
COX-2 selectivity	>2000	2.11

Chart 7.

Further modification of methyl sulphonyl group of rofecoxib to tetrazole ring provided water soluble and highly potent COX-2 inhibitor **19** (Chart **7**) [23]. The preliminary investigations carried out with 5-substituted-2,3-diphenyltetrahydrofurans for COX-1 and COX-2 inhibition shows the potential of compounds **20** and **21** (Chart **8**) as moderately selective COX-2 inhibitors and could be utilized for the design of new molecules [24].

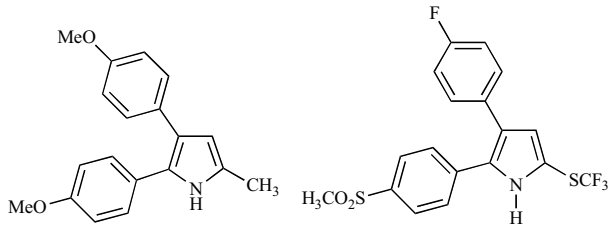


	20	**21**
IC_{50}	<1 μM	<1 μM
COX-2 selectivity	>10	>10

Chart 8.

N-Containing 5-Membered Heterocycles as COX-2 Inhibitors

Based upon the anti-inflammatory and analgesic properties of bimetopyrol (**22**, Chart **9**) [25] and 2-[(trifluoromethyl)thio]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (**23**, Chart **9**) [26] , the structural analogues of DUP 697, with pyrrole in place of thiophene, have been investigated for COX-2 inhibition activities.



22, Bimetopyrole **23**

Chart 9.

Amongst 2, 3-disubstituted-4, 5-diarylpyrroles (**24**, Chart **10**) [27], 3-substituted-4-methyl-1,2-diarylpyrroles [28] and 1,5-diarylpyrrole-3-acetic acid esters [29], the most potent compounds with appreciable selectivity for COX-2 are **25-30** (Chart **10**).

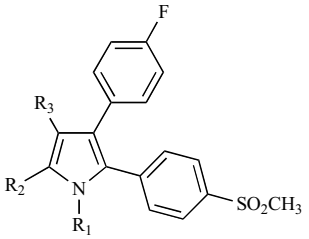
Further, out of these compounds, desmethyl compound **27** is the most active COX-2 inhibitor with IC_{50}14 nM.

b) Two Heteroatoms in the 5-Membered Ring

N, *N*-Containing Molecules

In order to further improve the drug profile of 1,2-diarylpyrroles by replacing the pyrrole moiety with pyrazole, the research group from Searle Research Development modified their own molecules SC-58125 (**31**, Chart **11**) [30]. A detailed investigation on the different substituents present on the pyrazole template (**32**, Chart **11**) led to the search for highly potent molecule with good bio-availability and excellent safety profile [31] which is clinically used now-a-days in the name of celecoxib (**33**, Chart **11**) for the treatment of rheumatoid arthritis and osteoarthritis.

Further modifications of celecoxib do not lead to much improvement in the COX-2 inhibitory activities of the molecules. Introduction of an oxime moiety at C-5 carbon in **34** [32], 4-substituted-1, 5-diarylpyrazoles with different substituents at C-5 aryl ring (**35**-**38**, Chart **12**) [33] have been studied for COX-2 inhibition. Replacement of sulphonamide pharmacophore with a sulphonylazide bioisostere [34] as in molecule **39** lowers COX-2 inhibition potency of the molecule (IC_{50} 5.16 μM). Introduction of F-, CH_3- and CH_2OH groups etc. onto the most vital 4-sulfamoyl (SO_2NH_2)-phenyl ring of celecoxib provided compounds **40**, **41** and **42** (Chart **13**). Compound **40** shows 75% and 13% inhibitions of COX-2 and COX-1 respectively at 10 μM concentrations [35] while celecoxib exhibits 100% and 0% inhibitions of COX-2 and COX-1 at same concentrations. Remarkably, in this contribution [35] a water soluble prodrug (**41**) with good *in-vivo* activity has been developed. Compound **42** has been reported to be superior to celecoxib on the basis of its anti-inflammatory, antipyretic, analgesic and anti-arthritic potential [36-39]. Like compound **41**, through a prodrug approach, the in-vivo efficacy, pharmacokinetic properties and water solubility of **42** has been improved [38, 39]. Moreover, the replacement of methyl group present at C-5 phenyl of cele-



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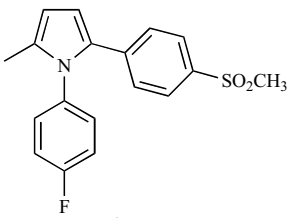

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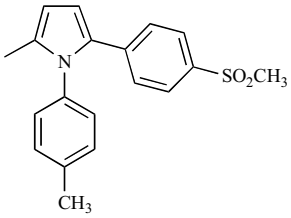

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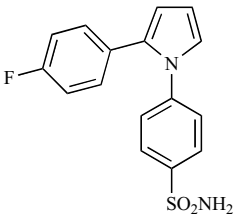

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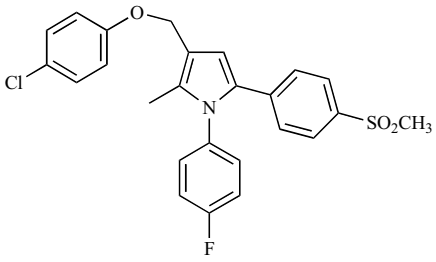
IC_{50}	0.06 μM	0.04 μM	0.014 μM
COX-2 selectivity	>1700	>2500	750



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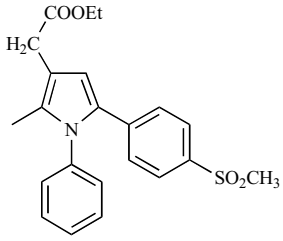

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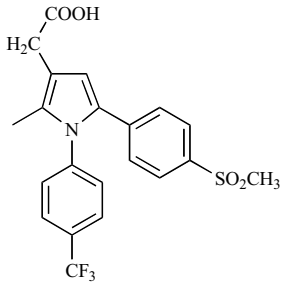
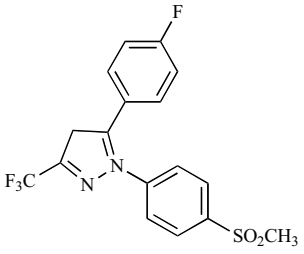


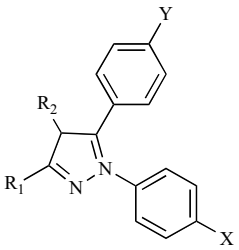
30

IC_{50}	0.03 μM	0.04 μM	0.11 μM
COX-2 selectivity	>3333	>2500	>900

Chart 10.



31, SC-58125



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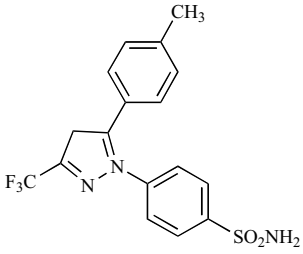
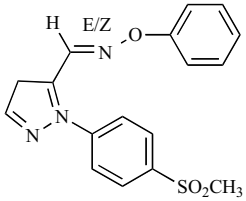


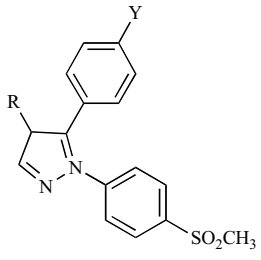
33, Celecoxib

IC_{50}	0.05 μM	0.04 μM
COX-2 selectivity	>200	~400

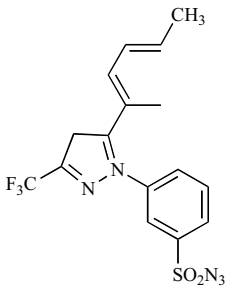
Chart 11.



34



35, R=CN, CO_2Et
36, R=COOH
37, R=CH_2OH
38, R=CHO



39

Chart 12.

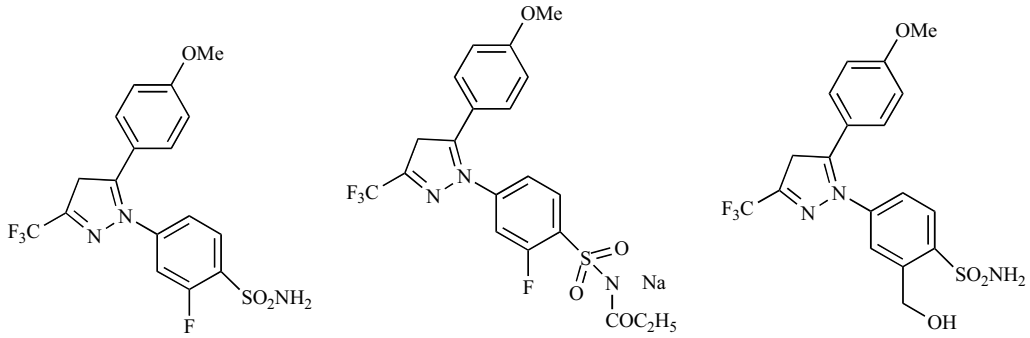
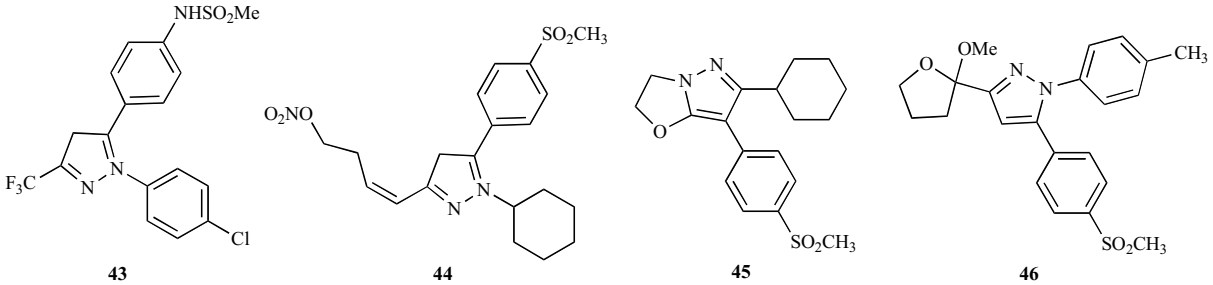


Chart 13.

coxib with methansulfonamide and varying the substituents at *N*-1 phenyl ring along with the variation in *C*-3 substituent provided some highly potent compounds out of which **43** (Chart **14**) exhibits IC_{50} for COX-2 at 0.03 μM concentration with COX-2 over COX-1 selectivity index 520 [40]. Among a series of nitric oxide donor-containing pyrazoles investigated for COX-2 inhibitory activities, **44** (Chart **14**) has been identified as the most potent compound [41].

Pyrazole and isoxazole derivatives like **50** and **51** (Chart **16**) obtained by replacing the β-diketo fragment of curcumin, the isolates of *Curcuma longa* have been found to possess antioxidant and COX-1/COX-2 inhibitory activities [49].

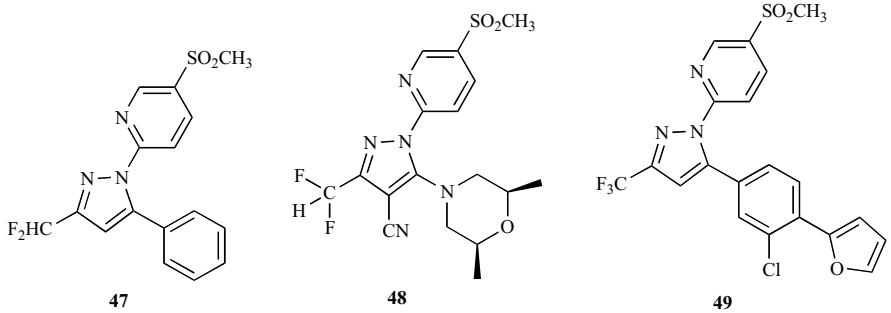


IC_{50}	0.03 μM	0.5 μM	1.3 μM	1.2 μM
COX-2 selectivity	520	2000	>80	>80

Chart 14.

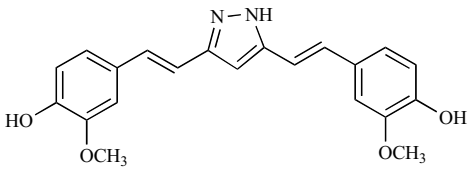
A few bicyclic pyrazole derivatives like **45** [42] and tetrahydrofuranone substituted pyrazoles **46** (Chart **14**) [43] have been reported but their COX-2 potency as well as the selectivity is not very encouraging. With an aim to develop orally active canine COX-2 inhibitors, the modifications have been made at the *N*-1, *C*-3, *C*-4 and *C*-5 positions of pyrazole to get the lead compounds **47**, **48** and **49** (Chart **15**) [44-48].

Regioisomeric imidazoles viz. 1,2-diaryl-/ 4,5-diaryl- and 1,5-diaryl-imidazoles (**52**-**54**, Chart **17**) have been explored for COX-2 inhibition. Some of these compounds show excellent potency (**52**:X=3-Cl, R=CH_3 IC_{50}=0.06μM, SI=6000;

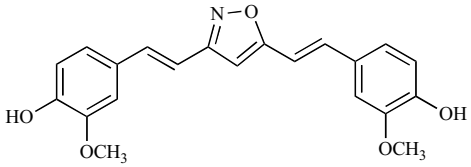


IC_{50}	0.31 μM	0.24 μM	0.012 μM
COX-2 selectivity	155	186	>4167

Chart 15.



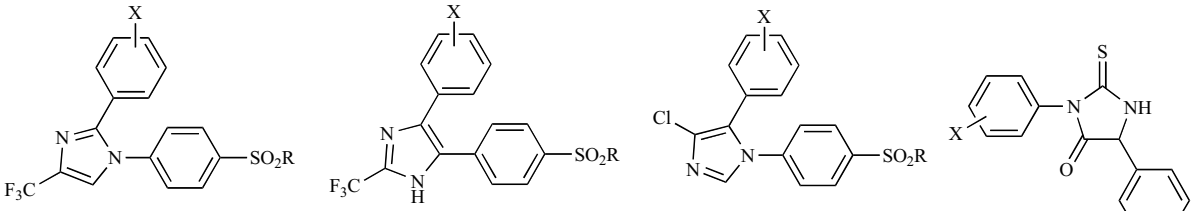
50



51

% inhibition (100 μM)		
COX-1	87	81
COX-2	61	58

Chart 16.



52 **53** **54** **55**

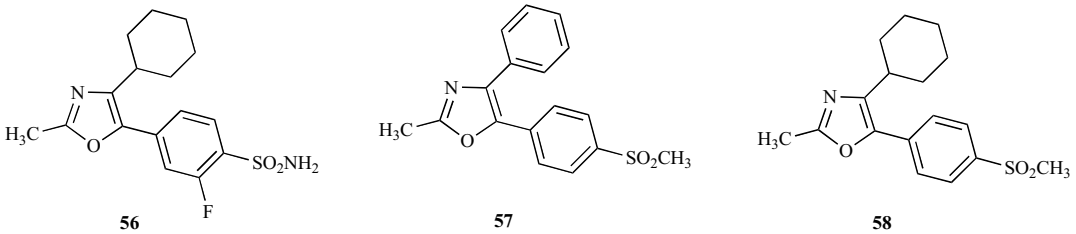
Chart 17.

X=3-Cl, R=NH_2 IC_{50} = 0.008μM, SI =775 [50], **53**: X=3-Cl, R=CH_3 IC_{50}=0.08μM, SI =6750 [51], **54**:X=4-OMe-3-F, R=NH_2 IC_{50}=0.005 μM, SI=660 [52]) against COX-2 but none of them could reach the market. 3,5-Diphenyl-2-thioxo-imidazolidin-4-ones (**55**, Chart **17**) exhibit appreciable inhibition of COX-2 at 50 μM concentration but poor selectivity over COX-1 [53].

N, *O*-containing molecules

Oxazole and isoxazole based compounds have been investigated in detail for their COX-2 inhibitory activities. Out of a series of oxazole derivatives (**56-58**, Chart **18**), compound **56** (JTE-522) has been identified as promising COX-2 inhibitor with low GI toxicity [54, 55].

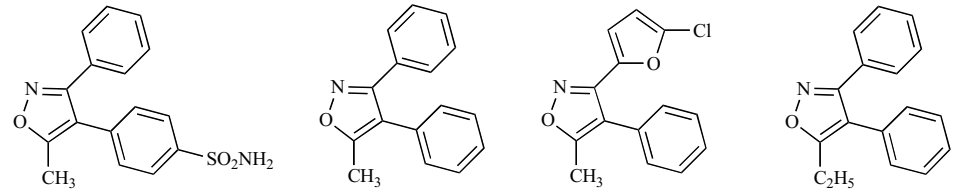
The use of an isoxazole moiety, bearing two aryl rings on adjacent carbons, led to the identification of a clinically used anti-inflammatory drug, valdecoxib (**59**, Chart **19**) [56]. Analogues of valdecoxib obtained by removing the sulphonamide group have been prepared and found to exhibit reversal of COX-2 selectivity and compounds **60**, **61**, **62** (Chart **19**) are highly COX-1 selective which could represent an ade-



56 **57** **58**

IC_{50}	0.085 μM	0.09 μM	0.07 μM
COX-2 selectivity	>1176	>1100	>1400

Chart 18.



59 **60** **61** **62**

IC_{50}	0.005 μM	IC_{50} (COX-1)	0.09 μM	0.5 μM	0.05 μM
COX-2 selectivity	28000	COX-1 selectivity	27	>200	29

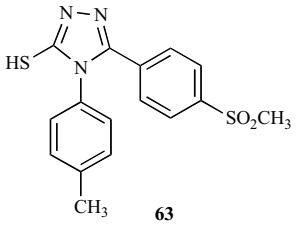
Chart 19.

quate tool to study the involvement of COX-1 in cancer development and pain [57].

c) Three Heteroatoms in the 5-Membered Ring

N, N, N-Containing Molecules

The high potency of celecoxib for COX-2 inhibition led to the investigations of triazole based COX-2 inhibitors. A recent report [58], studying the structure activity relationship studies of alkylthio-substituted-5-(4-methylsulfonylphenyl)-4-phenyl (or cyclohexyl) triazoles and alkylthio-substituted-4-(4-methylsulfonylphenyl)-5-phenyltriazoles, identifies compounds **63** and **64** (Chart **20**) as more potent and selective than celecoxib towards COX-2.



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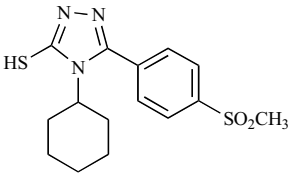
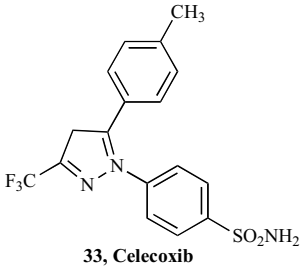


64



33, Celecoxib

IC_{50}	0.0006 μM	0.0006 μM	0.002 μM
COX-2 selectivity	5.17	4.0	1.68

Chart 20.

N, N, O-Containing Molecules

After the withdrawal of rofecoxib and valdecoxib, more emphasis has been laid on the development of hybrid molecules devoid of adverse cardiovascular effects associated with the use of selective COX-2 inhibitors. Since NO donor drugs are expected to reduce blood pressure and prevent artherosclerosis, based upon the NO donor activity of 1,2,5-oxadiazole-2-oxides, a group of 3,4-diphenyl-1,2,5-oxadiazole-2-oxides (**65**, Chart **21**) and the corresponding desoxy 3,4-diphenyl-1,2,5-oxadiazoles (**66**, Chart **21**) have been investigated for COX-2 inhibition and NO release [59].

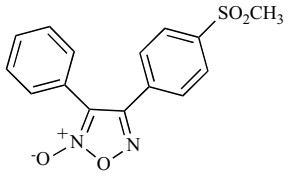
ii) COX-2 Inhibitors Based on 6-Membered Heterocycles

In this category of COX-2 inhibitors, 6-membered heterocycles with one heteroatom viz. *N*- / *O*- and two heteroatoms viz. *N*, *N* have been discussed.

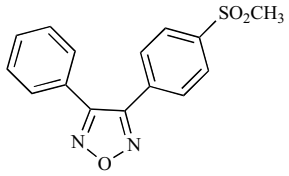
a) One Heteroatom in the 6-Membered Ring

N-Containing 6-Membered Heterocyclic Based COX-2 Inhibitors

Highly selective COX-2 inhibitors (**67**, **68**, Chart **22**) have been obtained by replacing the thiophene moiety of DUP 697 with pyridine [60-62] but their *in-vivo* potency is poor. A detailed exploration of 2-pyridinyl-3-(4-methylsulfonyl)phenylpyridines led to the identification of a selective and orally active COX-2 inhibitor, etoricoxib (**69**, Chart **22**) (IC_{50} 0.081 μM (CHO), 1.1 μM (HWB) [63-64]. The investigations of pyridone and pyridine derivatives fused with steroidal structure as COX-2 inhibitors identify some promising anti-inflammatory agents (**70**, Chart **22**) with more than 90% inhibition of PGE_2 [65].



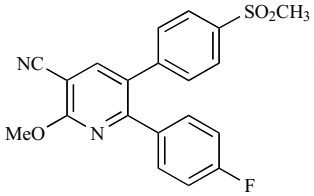
65



66

IC_{50}	0.12 μM	0.74 μM
COX-2 selectivity	97	2

Chart 21.



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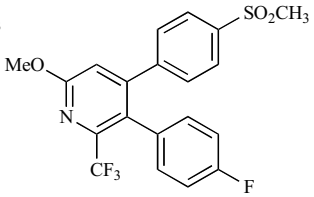
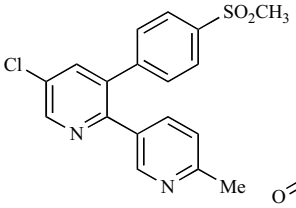
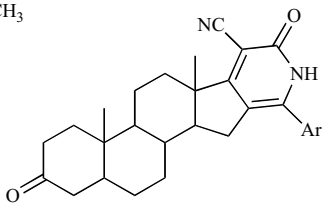


68



69, Etoricoxib

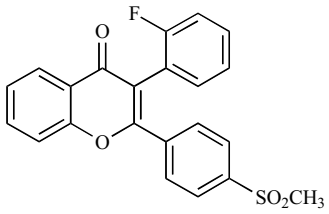


70

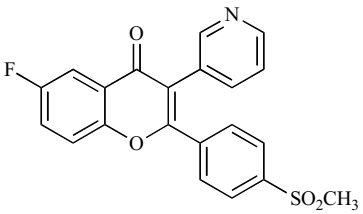
Chart 22.

***O*-Containing 6-Membered Heterocyclic Based COX-2 Inhibitors**

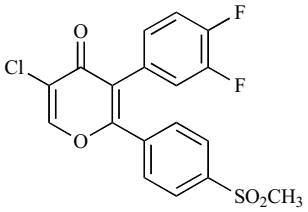
2,3-Diarylbenzopyrans (e.g. **71**, Chart **23**), having the central scaffold with naturally occurring flavonoids, have been found to be highly potent COX-2 inhibitors [66] but their poor oral bioavailability led to the screening of pyridine substituted benzopyrans and 2,3-diarylpyran-4-ones for COX-2 inhibition and identification of **72** and **73** (Chart **23**) as orally potent COX-2 inhibitors [67].



71



72



73

IC_{50}	0.03 μM	0.5μM	0.49 μM
COX-2 selectivity	>167	24	41

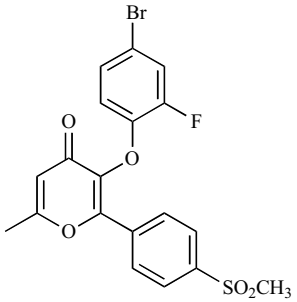
Chart 23.

A series of 2-phenylpyran-4-ones have been prepared and evaluated for their ability to inhibit COX-2 and the compounds carrying a 3-phenoxy group (e.g., **74**, Chart **24**), on the basis of their *in-vivo* profile and lack of gastrointestinal toxicity, have been selected for preclinical and clinical evaluations [68]. Investigations of 6-substituted-3-(4-methansulfonylphenyl)-4-phenylpyran-2-ones led to the identification of compounds **75** and **76** (Chart **24**) as highly potent and selective for COX-2 [69-70].

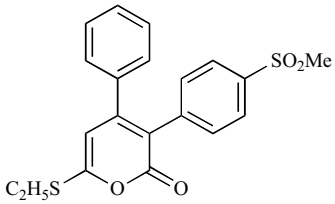
b) Two Heteroatoms in the 6-Membered Ring

COX-2 inhibitory activity of 3-aroyl benzyl pyridazinones led to the synthesis and investigations of 3-*O*-substituted benzyl pyridazinones for COX-2 inhibition [71] and identified compound **77** (Chart **25**) as the most potent among this series. In another report, the *in-vitro* and *in-vivo* studies on variously substituted pyridazinone template has identified two potent and selective COX-2 inhibitors **78** and **79** (Chart **25**) [72].

Based upon the COX-2 inhibitory profile of etoricoxib and bringing the two nitrogen atoms of the two pyridyl rings



74



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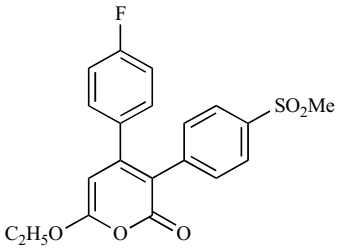
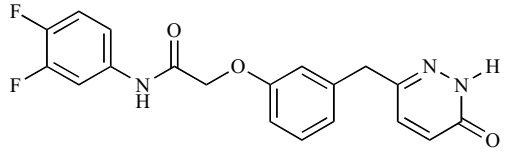


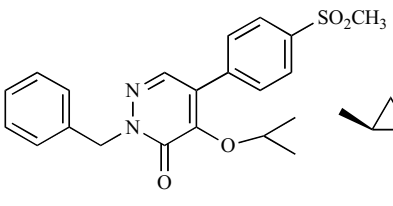
76

IC_{50}	0.15 μM	0.0032 μM	0.10 μM
COX-2 selectivity	~150	>120687	2880

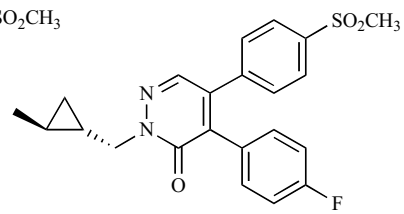
Chart 24.



77



78



79

IC_{50}	0.45 μM	0.02 μM	0.06 μM
COX-2 selectivity	>100	>500	~50

Chart 25.

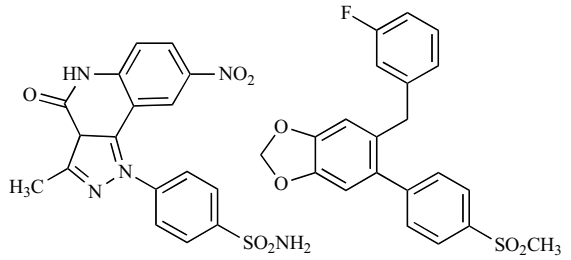
of etoricoxib in one, six membered nitrogen containing heterocycles such as pyrazine and quinoxalines have been explored for their COX-2 inhibitory activities. Compound **80** and its prodrug **81** (Chart **26**) have shown excellent *in-vivo* activity [73].

2. Bicyclic Heterocycles as the Central Core of COX-2 Inhibitors

The clinical efficacy and much improved gastric safety profile of celecoxib, rofecoxib, valdecoxib etc., which carry 1,2-diaryl substituents on monocyclic heterocyclic rings, has drawn the attention for the synthesis of COX-2 inhibitors with a bicyclic template. These agents were expected to demonstrate increased selectivity for the COX-2 isoform by more efficient occupation of the larger active site available in the COX-2 isoform relative to COX-1. Among a series of pyrazolo[1,5-a]pyrimidines [74], pyrazolo[1,5-b] pyridazines [75] and pyrazolo[3,4-d]pyrimidines [76], compounds **82**, **83** and **84** (Chart **27**) have been found to be most potent and selective towards COX-2 inhibition. Amongst a series of pyrazolo [4,3-c] quinolone-4-ones, compound **85** (Chart **28**) has been found to exhibit 100% and 40% inhibitions of COX-2 and COX-1 respectively at 10 μM concentrations [77]. Similarly, the investigations of a series of disubstituted metharyl benzo-1,3-dioxolanes has identified compound **86** (Chart **28**) as exhibiting 40% and 90% inhibition of HWB COX-2 at 1 μM and 10 μM concentrations respectively [78].

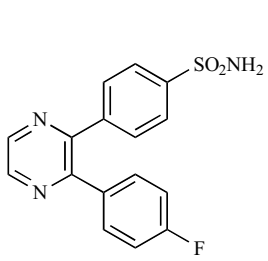
Based upon the biological activities of anacardic acid (pentadecyl salicylic acid), its benzimidazole, benzothiazole and benzoxazole derivatives were investigated for COX-2 inhibitory activities [79], among which compound **87** (IC_{50} = 1.06 μM, SI, >470) has been identified as the most active and selective towards COX-2 but it is less potent than rofecoxib in human whole blood assay. Similarly, a combination of benzofuran and benzotriazole with pyrazole and thiadiazole derivatives has found **88** (Chart **29**) as highly potent anti-inflammatory compound [80].

Since the transformation of indomethacin (**89**, Chart **30**), a non-steroidal anti-inflammatory drug, into COX-2 selective inhibitor [81, 82], modifications have been made at *N*-1 and *C*-3 substituent of indomethacin to get highly potent and selective COX-2 inhibitors. One such detailed investigation on indomethacin ester and amide derivatives identified compounds **90** and **91** (Chart **30**) to exhibit anti-inflammatory activity [83] but suffer from the limitation of *in-vivo* hy-

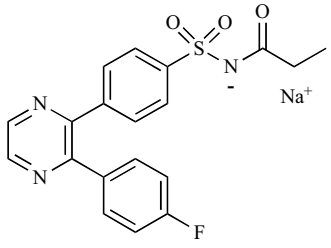


85 **86**

Chart 28.



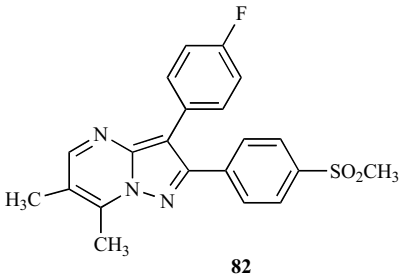
80



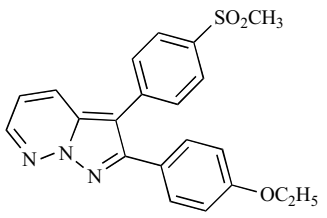
81

IC_{50}	1.07 μM
COX-2 selectivity	>300

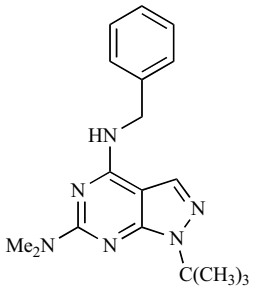
Chart 26.



82



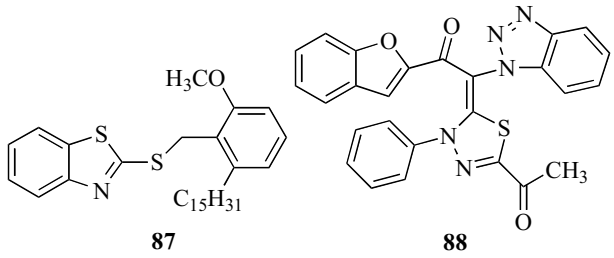
83



84

IC_{50}	0.012 μM	0.003 μM	0.0009 μM
COX-2 selectivity	>800	>28067	~50

Chart 27.



87 **88**

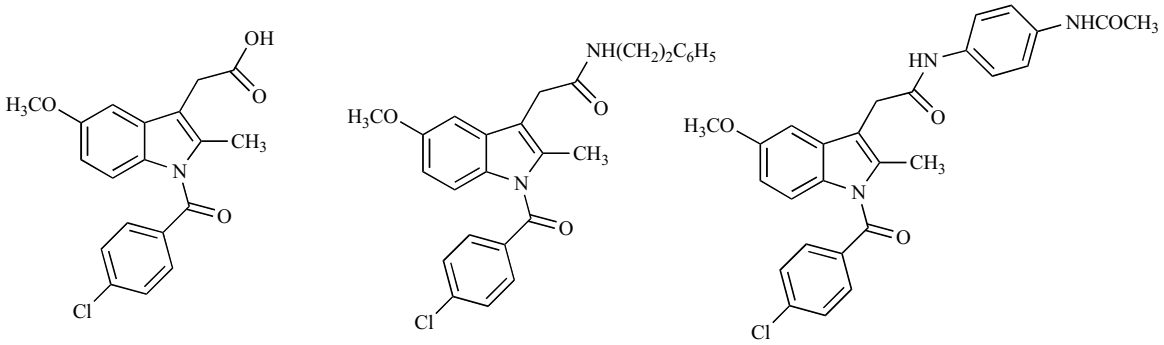
Chart 29.

drolysis to indomethacin [84]. The investigations on reverse ester/amide derivatives of indomethacin (e.g. **92**, **93**, Chart **31**) displayed time dependent COX-2 inhibition with IC_{50} values in low nanomolar range [85].

In a recent report, the above mentioned strategy of modification of non-selective agents for the development of novel COX-2 inhibitors has been used for introducing substituted glycolamide ester in place of acid side chain of indomethacin [86]. Compound **94** (Chart **31**) with 93% and 0% inhibition of COX-2 and COX-1 respectively at 10 μM concentration has been identified as a promising candidate in this class of indomethacin derivatives. The replacement of *N*-1 substituent of indomethacin with cyclopropyl methyl, cyclopropyl ethyl, *o*-tolyl groups etc. does not improve the COX-2 efficacy profile of these compounds [87]. Using indole as the central template, a series of 2-sulfonylphenyl-3-phenyl- [88] and 2-phenyl-3-sulfonylphenyl- indoles [89] have been synthesized and investigated for COX-2 inhibitory activities and led to the discovery of compounds **95**, **96** and **97** (Chart **32**) as highly potent COX-2 inhibitors. Using the molecular overlays of celecoxib, rofecoxib, valdecoxib and 3-aryloxy-6-methylsulfonyl-2-methylindole, a series of compounds have been prepared and tested for inhibition against COX-2 and COX-1 out of which compound **98** (Chart **32**) showed excellent *in-vitro* COX-2 enzyme potency and selectivity over COX-1 [90].

B. CARBOCYCLIC BASED COX-2 INHIBITORS

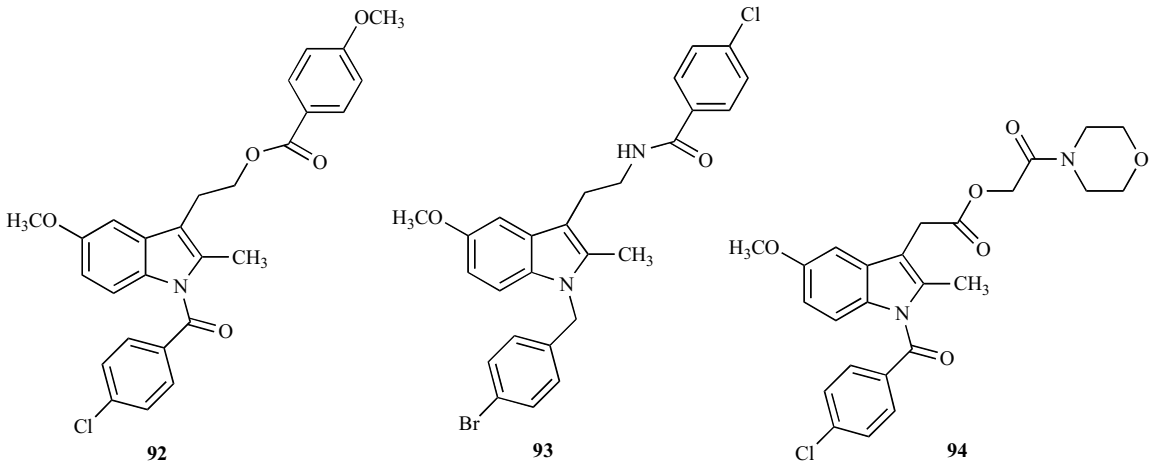
A variety of central three-, four- or five- membered carbocyclic templates provide a scaffold to act as selective



89, Indomethacin **90** **91**

IC_{50} (COX-2 selectivity) 0.75 μM (0.067) 0.06 μM (>1000) 0.12 μM (>550)

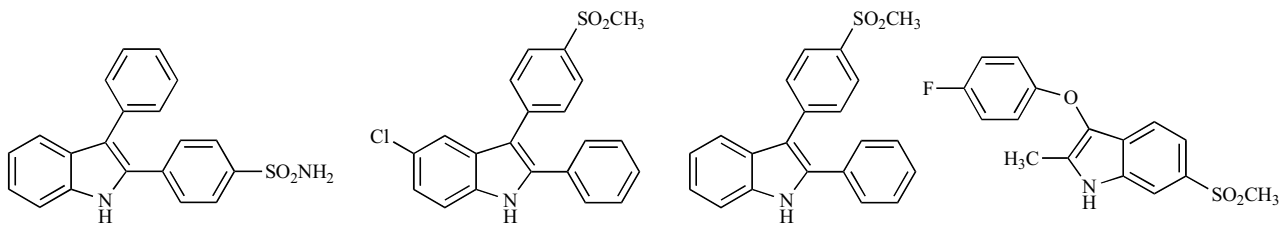
Chart 30.



92 **93** **94**

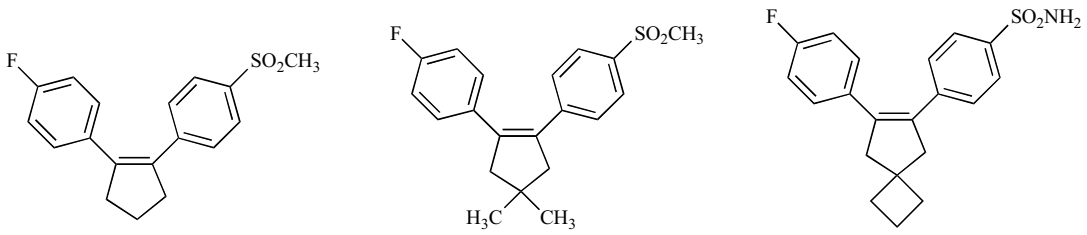
IC_{50}	0.04 μM	0.04 μM
COX-2 selectivity	>1500	>1650

Chart 31.



	95	**96**	**97**	**98**
IC_{50}	0.09 μM	0.27 μM	0.22 μM	0.03 μM
COX-2 selectivity	>111	>37	>45	>1300

Chart 32.



	99	**100**	**101**
IC_{50}	0.026 μM	0.015 μM	0.002 μM
COX-2 selectivity	>38000	1220	415

Chart 33.

COX-2 inhibitors. This tricyclic class of compounds generally possesses diaryl substituents on adjacent carbons of cycloprop-2-ene, cyclobutene or cyclopentene.

1. 5-Membered Carbocycles as the Central Core of COX-2 Inhibitors

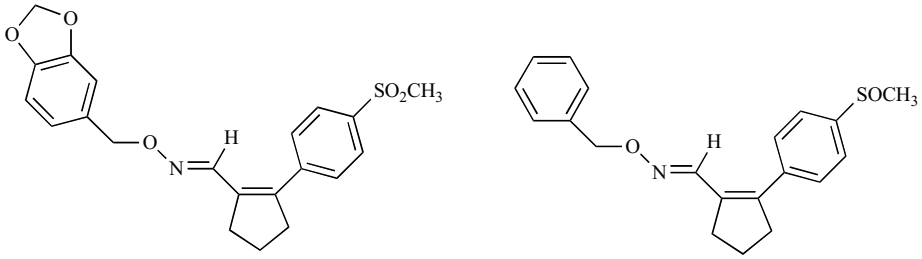
1,2-Diarylcyclopentenes, 1,2-diarylcyclopentenes with geminal methyl groups at C-4 and their spiro analogues have been investigated for COX-2 inhibition and compounds **99**, **100** and **101** (Chart **33**) have been found to be highly selective and active against COX-2 [91].

Replacement of *p*-fluorophenyl ring of **99** with methyleneaminoxymethyl moiety provided compound **102** and **103** (Chart **34**) possessing the highest *in-vitro* activity against COX-2, modest anti-inflammatory activity when given intraperitoneally but lack of activity after oral administration which might be due to limited gastrointestinal stability, poor absorption, and /or rapid first pass metabolism [92, 93].

2. 4-Membered Carbocycles as the Central Core of COX-2 Inhibitors

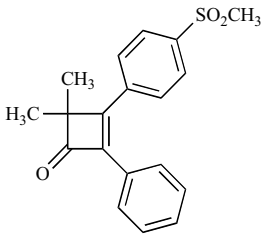
Among a series of novel, potent and selective cyclobutenone COX-2 inhibitors, compound **104** (Chart **35**) has been identified as a very selective COX-2 inhibitor *in vitro* [94].

Enhanced COX-2 selectivity of these compounds has been attributed to larger dihedral angle between the two aryl rings relative to five membered ring templates.

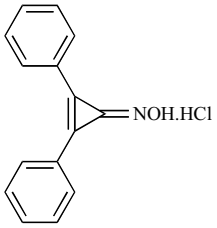


	102	**103**
IC_{50}	0.41 μM	0.1 μM
COX-2 selectivity	66	320

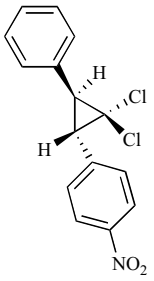
Chart 34.



104



105



106

	104	105	106
IC_{50}	0.0028 μM	2.94 μM	80.5 μM
COX-2 selectivity	714	>34	3.5

Chart 35.

3. 3-Membered Carbocycles as the Central Core of COX-2 Inhibitors

The spatial disposition of the 2,3-diaryl rings relative to the C=C of the cycloprop-2-ene ring could be an important determinant of COX-2 selectivity. Based upon this hypothesis, compounds with vicinal diaryl rings on cycloprop-2-en-1-one have been investigated as COX-2 inhibitors. *In-vitro* COX-1 and COX-2 inhibition studies showed that 2,3-diphenylcycloprop-2-en-1-one oxime **105** (Chart **35**) is a selective COX-2 inhibitor [95]. Among a group of (*Z*)- and (*E*)-1,1-dihalo-2-(4-substituted-phenyl)-3-phenylcyclopropanes evaluated for analgesic and anti-inflammatory properties, compound **106** (Chart **35**) with *E*-configuration inhibited COX-1 (IC_{50} = 278.8 μM) and COX-2 (IC_{50} = 80.5 μM) for a COX-2 selectivity index of 3.5 [96].

C. COX-2 INHIBITORS WITH VICINAL DIARYL RINGS ON ACYCLIC TEMPLATE

In this category of compounds, the appropriate pharmacophores for COX-2 inhibition in the form of diaryl rings are separated from each other through a C-C, C=C or C≡C bond.

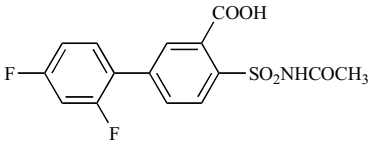
1. COX-2 Inhibitors with Diaryl Rings Joined Through C-C Bond

In this category of COX-2 inhibitors, *N*-acetyl-2-carboxybenzenesulfonamides possessing an appropriately substituted-phenyl group at *C*-4 or *C*-5 position have been investigated. In these compounds, $SO_2NHCOCH_3$ moiety is a suitable bioisostere of the OAc substituent present in aspirin and incorporation of 2,4-difluorophenyl substituent at the *C*-4 position of *N*-acetyl-2-carboxybenzenesulfonamide [97] and 4-isopropoxyphenyl substituent at *C*-4 of *N*-acetyl-3-carboxymethylbenzensulfonamide [98] provided the most potent compound **107** and **108** (Chart **36**).

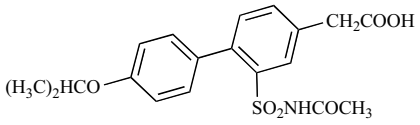
2. COX-2 Inhibitors with Aryl Rings at C=C Bond

The COX-1 selectivity and good chemopreventive properties of resveratrol (**109**) [99] and tamoxifen (**110**) [100] (Chart **37**) led to the design of acyclic triaryl olefinic compounds as selective COX-2 inhibitors.

Amongst a series of acyclic triaryl olefins (with *Z*- and *E*-configurations) carrying different alkyl chains at one of the doubly bonded carbons, compounds **111**, **112**, **113** and **114**



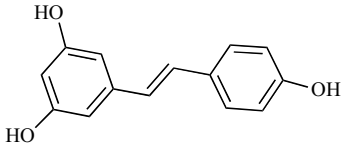
107



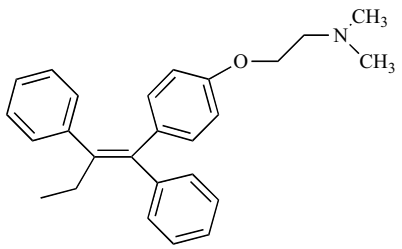
108

	107	108
IC_{50}	0.087 μM	0.15 μM
COX-2 selectivity	>1149	>667

Chart 36.

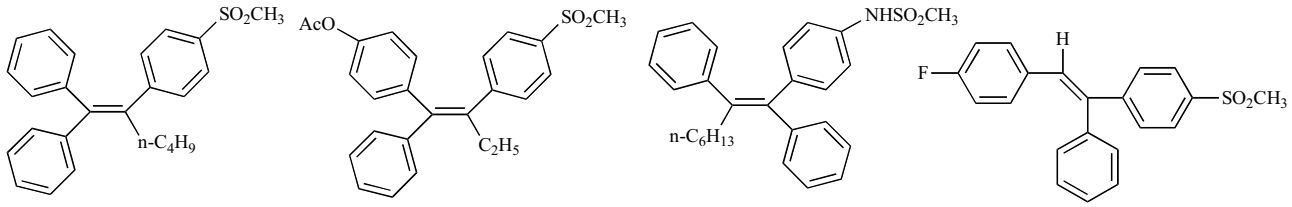


109, Resveratrol



110, Tamoxifen

Chart 37.



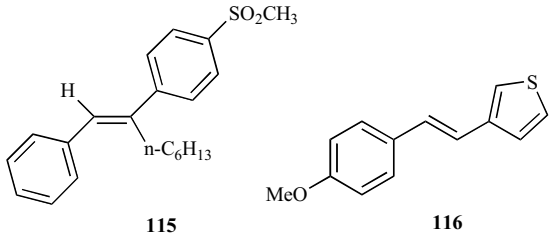
111 **112** **113** **114**

IC_{50}	0.014 μM	0.03 μM	0.03 μM	0.0316 μM
COX-2 selectivity	>7142	81	>3333	>3164

Chart 38.

(Chart **38**) have been identified as highly active and selective for COX-2 [101-104].

The acyclic diaryl olefins, possessing a *trans*-stilbenoid template with *E*-stereochemistry, exhibit selective COX-2 inhibition when a 4-methanesulfonylphenyl substituent is incorporated at the *C*-2 position and compound **115** (Chart **39**) exhibits the best combination of COX-2 inhibitory potency and selectivity [105]. Another *trans*-stilbenoid viz. 3-[2-(4-methoxy-phenyl)-vinyl]-thiophene **116** (Chart **39**) has an appreciable inhibitory activity against the overproduction of the inflammatory mediator PGE_2 in the sub-micromolar range (IC_{50} = 0.1 μM) [106].



115 **116**

IC_{50}	0.77 μM
COX-2 selectivity	>130

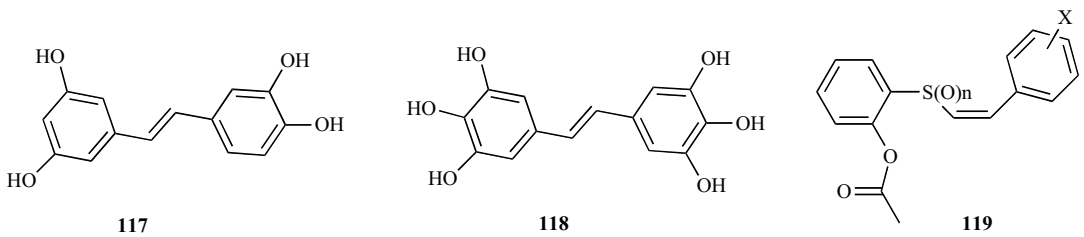
Chart 39.

Amongst a series of hydroxylated resveratrol, compounds **117** and **118** (Chart **40**) are selective COX-2 inhibitors with their potencies comparable or better than the clinically established celecoxib [107]. A series of (*Z*)- and (*E*)-styryl acetoxyphenyl sulfides and sulfones (**119**, Chart **40**) have been examined for their COX-1 and COX-2 inhibitory activities and have been found to act mechanistically similar to aspirin by covalently modifying the Ser^{516} residue of COX-2 enzyme [108]. In the chalcone class of compounds, the *p*-$MeSO_2NH$ and N_3 moieties proved to be suitable COX-2 pharmacophores and compounds **120** and **121** (Chart **41**) have been identified as exhibiting good COX-2 inhibitory potency and selectivity [109]. Among a series of novel phenylazobenzensulfonamides, the most potent compound **122** (Chart **41**) exhibits IC_{50} = 4.28 μM and a selectivity order of 14.42 for COX-2 [110].

3. COX-2 Inhibitors with Aryl Rings at C≡C Bond

Based upon the excellent *in-vitro* inhibitory potency against COX-2 of acyclic olefins, where compound **111** has been identified as a lead molecule, the double bond in these acyclic olefins has been replaced with linear acetylene. Among a class of 1-(4-,3- or 2-methylsulfonylphenyl / bezenesulfonamide)-2-phenylacytelens, 1-(3-methylsulfonyl-phenyl)-2-(4-methyl-phenyl) acetylene **123** and 3-(2-phenyl-ethynyl) benzenesulfonamide **124** (Chart **42**) have been found to be selective *in-vitro* COX-2 inhibitors [111, 112].

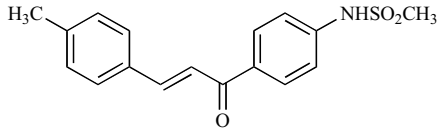
Therefore, the whole discussion of COX-2 inhibitors exemplified by various molecules points towards the presence of an aryl / substituted aryl and a methylsulfonylphenyl/ phenylsulfonamide groups on the adjacent carbons of a suitable template as the ultimate pharmacophore for COX-2 inhibition. The choice of the template depends upon the factors like the overall volume of the molecule, solubility which in turn affects the bio-availability of the compound and the stability and acceptability of the central core of the molecule under physiological conditions.



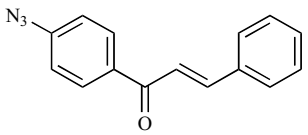
117 **118** **119**

IC_{50}	0.0113 μM	0.00104 μM
COX-2 selectivity	417	719

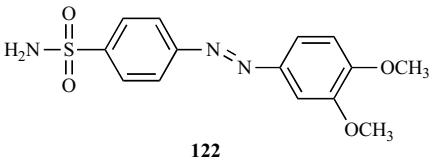
Chart 40.



120



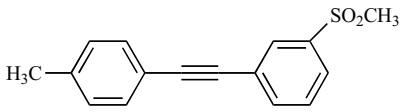
121



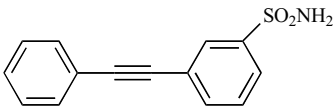
122

IC_{50}	1.0 μM	3.4 μM	4.28 μM
COX-2 selectivity	>100	>29	14.42

Chart 41.



123



124

IC_{50}	0.32 μM	0.45 μM
COX-2 selectivity	>320	70

Chart 42.

We are hopeful that this overall view of the current status of COX-2 inhibitors could provide a platform for the design of new molecules (as COX-2 inhibitors) devoid of side effects, one of the major drawbacks of presently available anti-inflammatory drugs.

ACKNOWLEDGEMENTS

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