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Review article

Recent advancement in the discovery and development of COX-2 inhibitors: Insight into biological activities and SAR studies (2008–2019)

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ABSTRACT

Cyclooxygenase-2 is a very important physiological enzyme playing key roles in various biological functions especially in the mechanism of pain and inflammation, among other roles, making it a molecule of high interest to the pharmaceutical community as a target. COX 2 enzyme is induced only during inflammatory processes or cancer and reflects no role in the guarding stomach lining. Thus, selective COX-2 inhibition can significantly reduce the adverse effects including GI tract damage and hepatotoxic effects of traditional NSAIDs like aspirin, ibuprofen, etc. Recent developments on COX-2 inhibitors is primarily focused on improving the selectivity index of the drug towards COX-2 along with enhancing the potency of the drug by modifying the scaffolds of Coxibs currently in the market like Celecoxib, Indomethacin, Oxaprozin, etc. We have reported the progress on new COX-2 inhibitors in the last decade (2008–2019) focussing on five heterocyclic rings- Pyrazole, Indole, Oxazole, Pyridine and Pyrrole. The addition of various moieties to these core rings and their structure-activity relationship along with their molecular modelling data have been explored in the article. This review aims to aid medicinal chemists in the design and discovery of better COX-2 inhibitors constructed on these five heterocyclic pharmacophores.

1. Introduction

Prostaglandin-endoperoxide synthase (PTGS), more commonly recognized as Cyclooxygenase (COX) is a family of isozymes which is responsible for the catalysis of the reaction forming prostaglandins and related compounds from Arachidonic acid [1]. Till now, there are currently 3 identified isoforms of the COX enzyme, namely: COX-1, COX-2 and COX-3.

COX-1(cyclooxygenase-1) serves a homeostatic function in most tissues where it is constitutively present, thus known as the housekeeping enzyme. The COX-1 enzyme is produced under normal physiological conditions where it is responsible for prostaglandins synthesis, thus showing cytoprotective action along with regulation of platelet activity, renal and gastric functions [2]. COX-3 is an enzyme that was first described by Simmons and group in 2002. It is the most recently discovered enzyme and is most abundantly present in spinal cord and brain [3]. COX-2 is induced due to inflammatory stimuli and does not have a constitutive presence like COX-1 [4]. COX-2 is unexpressed under normal physiological environment in the body. It is

Abbreviations: **μM**, Micromolar; **A549**, Cell line-Lung Adenocarcinoma; **ACE**, Angiotensin-converting-enzyme; **ADME-T**, Absorption, Distribution, Metabolism, Excretion-Toxicity; **AI%**, % Anti-inflammatory activity; **Ala**, Alanine; **Arg**, Arginine; **Asp**, Aspartic acid; **B16-F10**, murine tumor cell line; **BAS**, Biological activity score; **CCK-8**, Cell counting kit-8; **CEM**, Lymphoid cell lines; **COPD**, Coronary obstructive pulmonary disease; **COX**, Cyclooxygenase; **DENV**, Dengue virus; **DFT**, Density Functional Theory; **DMF**, Dimethylformamide; **EAC**, Ehrlich ascites carcinoma cell mouse model; **ED_{50}**, Effective dose for 50% of the population; **G1**, Gap 1 phase; **MIA**, Monoiodoacetate; **MS**, Mass spectrometry; **MTT**, Colorimetric assay; **NAG**, *N*-acetylglucosamine; **NIH/3T3**, Murine embryonic fibroblast cell line; **nM**, Nanomolar; **NMR**, Nuclear magnetic resonance spectroscopy; **NSAIDs**, Nonsteroidal anti-inflammatory drugs; **PASS**, Prediction of activity spectra for substances; **PGE2**, Prostaglandin E2; **PGG2**, Prostaglandin G2; **PGH2**, Prostaglandin H2; **PGI2**, Prostaglandin I2; **Gln**, Glutamine; **Glu**, Glutamic acid; **Gly**, Glycine; **HaCaT**, Keratinocyte cell line; **Hela**, Cervical cancer cell line; **HepG2**, Human liver cancer cell line; **His**, Histidine; **HRBC**, Human red blood cell; **HWB**, Human whole blood; **IC_{50}**, Half maximal inhibitory concentration; **IL**, Interleukin; **Ile**, Isoleucine; **IP**, Intraperitoneal; **IR**, Infra red; **J774**, Murine macrophage cell line; **LD_{50}**, Lethal dose, 50%; **Leu**, Leucine; **LOX**, Lipoxygenase; **LPS**, Lipopolysaccharide; **MCF-7**, Breast carcinoma cell line; **Phe**, Phenylalanine; **PTGS**, Prostaglandin-endoperoxide synthase; **RAW264.7**, Murine macrophage cell line; **Ser**, Serine; **SI**, Selectivity Index; **SPF/VAF**, Specific-pathogen-free/Viral antibody free; **SD**, Sprague Dawley; **Thr**, Threonine; **TNF-α**, Tumor necrosis factor α; **Trp**, Tryptophan; **TXA2**, Thromboxane A2; **Tyr**, Tyrosine; **Val**, Valine

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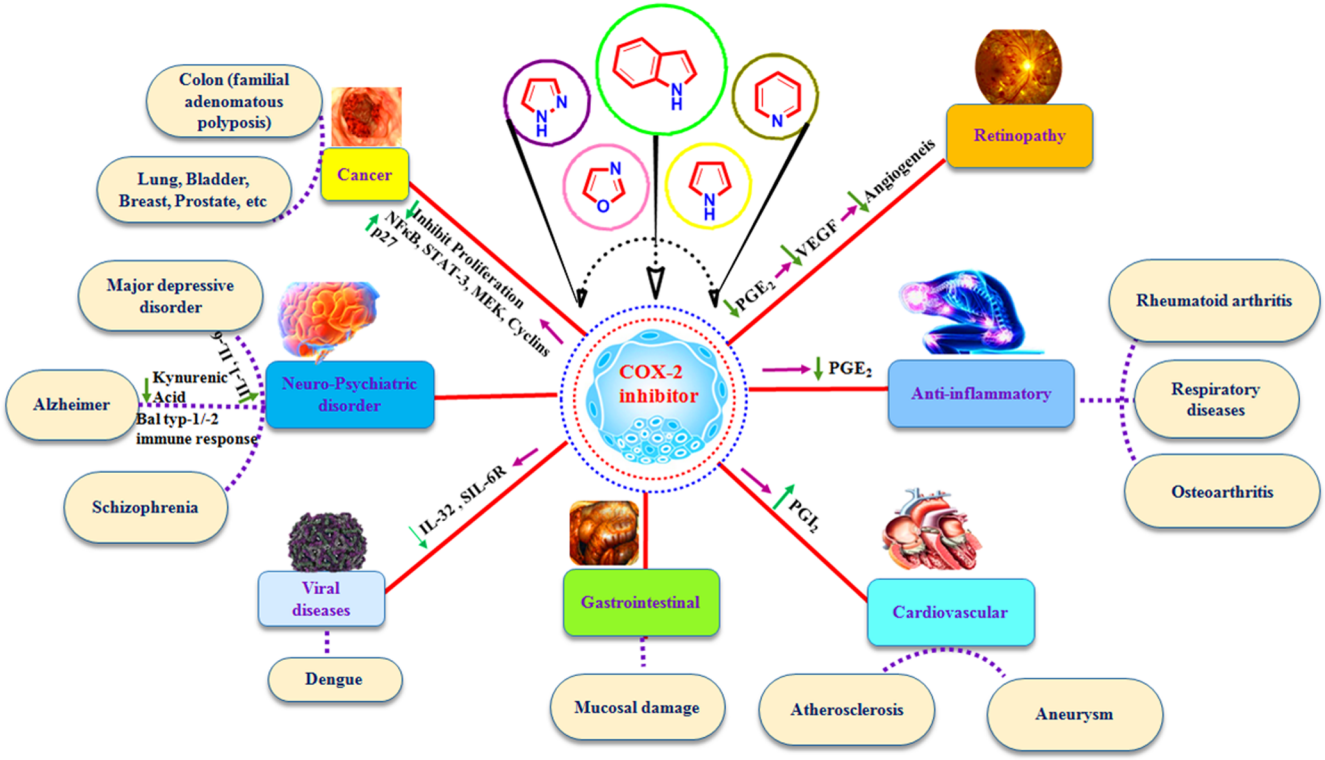


Fig. 1. Pharmacological applications of COX-2 inhibitors.

usually found in cells where increased level of prostaglandin is observed during inflammatory reactions [5]. Other functions of COX-2 have also been suggested in recent studies.

CNS: According to a study performed in rats, COX-2 was predominantly found in the lumbar segment of spinal cord [6] in turn showing effect on the Central Nervous System to produce hyperalgesia.

GI: Zimmerman and co-workers first demonstrated the COX-2 mRNA expression and protein in gastric mucosa of healthy human and rabbit [7] and studies on rats showed that it becomes up-regulated during gastric erosions and ulcers [8] suggesting involvement in healing process [9].

Kidney: Studies have shown the expression of COX-2 in macula densa region of rat kidney and an increase in its presence on the restriction of salt. Also, renin secretion was shown to be inhibited on the administration of COX-2 specific inhibitors (no effect was observed when COX-1 specific inhibitors were used) [10].

CVS: The effect of COX-2 on the cardiovascular system is majorly due to one of its major product being prostacyclin, a vasoprotective molecule. Evidence has been collected suggesting the role of COX-2 in atherosclerosis and its anti-atherogenic activity [11,12]. A recent study also showed the protective effect of COX-2 on blood vessels independent of its role in the synthesis of prostacyclin by using a systems biology approach [13].

Reproductive System: Studies have suggested COX-2 role of in the female reproductive system showing that the enzyme is necessary for processes like ovulation, fertilization, implantation and decidualization [14] although exact mechanisms remain elusive. Inhibition of cyclooxygenase by Aspirin (non-specific NSAID) showed a decreased quantity of spermatids and surge in size of spermatocyte nuclei [15].

Inflammation: Rheumatoid arthritis, osteoporosis, Alzheimer's disease, Cancer, etc. COX enzyme is required during the catalysis of arachidonic acid to prostanoids, which includes molecules like prostanoids, prostacyclins, and thromboxane [16]. Studies conducted on patients with COPD (chronic obstructive pulmonary disease) have indicated that there is an upregulation of the COX 2 enzyme leading to an increased level of PGE2 during chronic inflammatory diseases like COPD [17]. PGE2 can have an anti-inflammatory and bronchoprotective action along with its pro-inflammatory action. The strategic modulation of the metabolites of the COX 2 enzyme could thus be therapeutically used to control the progression of inflammatory diseases.

1.1. COX-2 inhibitors and their applications

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) are drugs that function by the inhibition of COX-1 as well as COX-2 enzymes [18]. These include aspirin, ibuprofen, naproxen, etc. Specific COX-2 inhibitors belongs to a newer class of NSAIDs that are responsible for the blockage of the COX-2 enzyme in the body but plays no role in the inhibition of the COX-1 enzyme. Various symptoms have been linked with the use of traditional NSAIDs including gastrointestinal tract damage, bleeding, ulcers, etc. These symptoms were mainly due to the blockage of the protective action that the COX-1 enzyme has on the stomach lining [19]. With the advent of COX-2 inhibitors, the side effects related to the gastrointestinal tract have been significantly reduced, as the COX-2 is induced only during inflammatory processes or cancer and plays no role in the protection of gastric lining. COX-2 inhibitors find role in several diseases as mentioned below in Fig. 1 along with their mechanism of action in Fig. 2. Natural compounds possessing COX-2 inhibition potential have been given in Table 1 and COX-2 inhibitors currently in the market have been included in Table 2.

1.1.1. COX-2 inhibitors in inflammation

Respiratory diseases: -Elevated levels of prostanoid metabolites and COX 2 protein were seen during asthma, bronchoconstriction, COPD and thus COX 2 enzyme plays a significant role in their pathogenesis. According to a study performed on mouse models, administration of COX 2 inhibitors on a short-term basis was able to alleviate the respiratory conditions like asthma [36]. COX 2 inhibitors can also be used as drugs of choice for reducing the severity of an irreversible respiratory disease such as COPD [17].

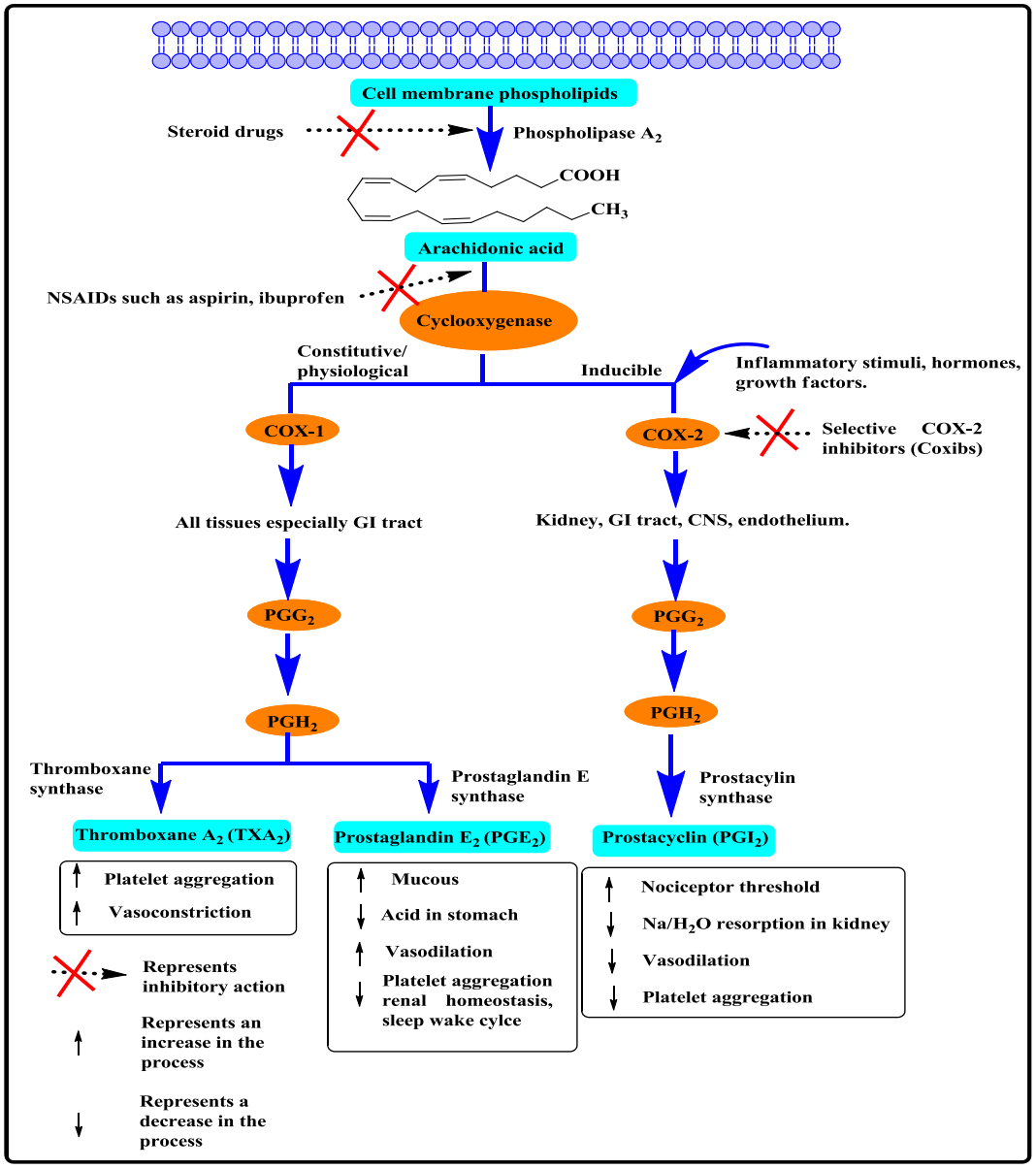


Fig. 2. Mechanism of action.

Rheumatoid Arthritis and Osteoarthritis: - Chronic inflammation of the tissues present in synovial joints is seen during these diseases. The overexpression of the COX 2 enzyme has shown to irreversibly advance the disease and thereby plays a vital role in its pathogenesis. Administration of COX 2 inhibitors led to a decrease in the synovial inflammation and thus can be therapeutically used to suppress the progression of the disease [37].

1.1.2. COX-2 inhibitors in cancer

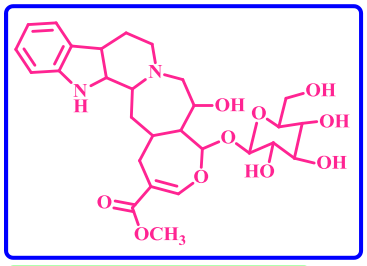
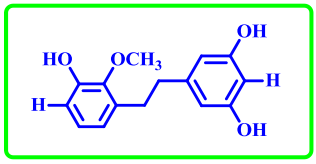
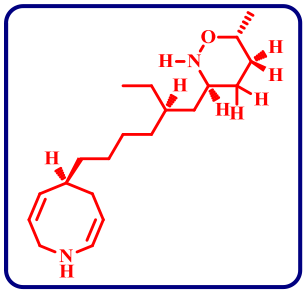
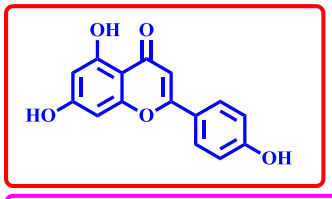
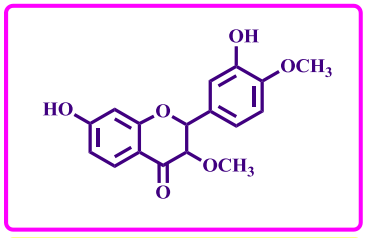
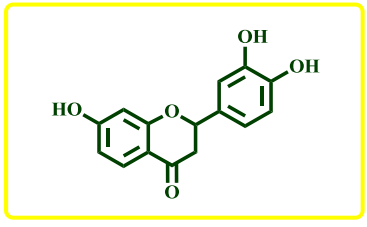
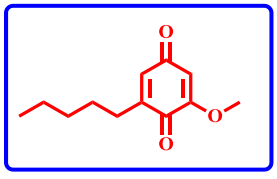
The major enzymatic product of COX-2 is prostaglandin E2 (PGE2). Both COX-2, as well as PGE2, play a role in "inflammo genesis of cancer" which suggests that chronic inflammation may be a probable cause for cancer. COX-2 plays a role as an oncogene [38]. Elevated levels of COX-2 have been shown to promote carcinogenesis. PGE2 also has an ability to inhibit natural killer cells thereby leading to immunosuppression [39]. Studies performed during the late 1980s had demonstrated the role of non-specific NSAIDs in reducing the mortality due to colorectal cancer [40]. Further studies performed in rats have explored the possibility of specific COX-2 inhibitors in reducing immune evasion as well as providing chemo preventive action [41]. Thus, specific COX-2 inhibitors can be used along with cytotoxic therapy for treating cancer.

1.1.3. COX-2 inhibitors in neuropsychiatric disorders

Alzheimer's disease: Cyclooxygenase plays an important role in spatial learning and memory by inhibiting the brain derived neurotrophic factor. Clinical trials have shown that the level of COX-2 was significantly greater in Alzheimer's patient in comparison to the control group. It has been demonstrated that continuous NSAIDs use prevents the development of Alzheimer's disease suggesting the possible role of COX-2 in neurodegenerative mechanisms. Thus, specific COX-2 inhibitors can be therapeutically used in Alzheimer's disease [42,43].

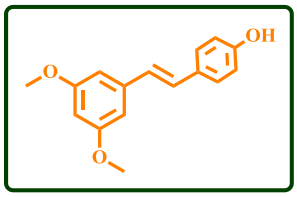
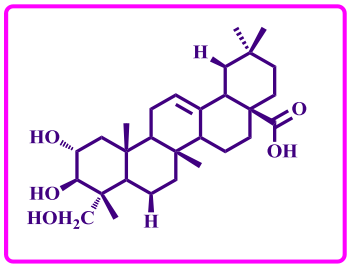
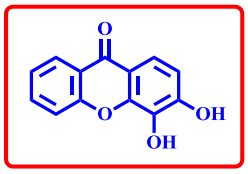
Schizophrenia: An amplified expression of the COX 2 enzyme and PGE2 (one of the metabolites produced from arachidonic acid) was reported in Schizophrenia [44]. A double-blinded study performed using Celecoxib and Risperidone drugs revealed that these drugs provided symptomatic relief from positive and negative indications of Schizophrenia [45]. Studies performed on animal models as well as during clinical trials have revealed the therapeutic efficacy of the COX 2 inhibitors during the early stages of Schizophrenia.

Table 1
Natural compounds having COX-2 inhibitory activity.

S.NO.	Biological Source	Structure of the most potent compound	COX-2 inhibitory activity	References
A.	**Alkaloids as COX-2 inhibitors**			
	Anthocephalus cadamba		% of COX-2 inhibition = 37.91%	[20]
2.	*Dioscorea opposita* (Dioscoreaceae)		Selectivity for COX-2 inhibition > 55.6	[21]
3.	*Gracilaria opuntia*		IC_{50} = 0.84 μM	[22]
B.	**Flavanoids as COX-2 inhibitors**			
1.	Apigenin		IC_{50} = 50 μM	[23]
2.	Centaureidin		IC_{50} for COX-2 = 45 μmol L^{-1}	[24]
3.	Luteolin		IC_{50} = 36.6 μmol L^{-1}	[24]
C.	**Quinones as COX-2 inhibitors**			
	Primin from *Medicago wildenowii*		IC_{50} = 0.09 μM	[25]
D.	**Stilbenes as COX-2 inhibitors**			

(*continued on next page*)

Table 1 (*continued*)

S.NO.	Biological Source	Structure of the most potent compound	COX-2 inhibitory activity	References
1.	Pterostilbene		IC_{50} = 83.9 μM	[26]
E.	**Terpenoids as COX-2 inhibitors**			
1.	*Picrorhiza kurroa*		Inhibitory % at 100 μg/ml = 49.6%	[27]
F.	**Xanthines as COX-2 inhibitors**			
1.	3,4-dihydroxyxanthone from *Calophyllum membranaceum*		IC_{50} = 1.80 mM	[28]

Major Depressive Disorder: COX 2 inhibitors have the ability to affect the CNS serotonergic system. Studies performed on rats have shown that the administration of COX 2 inhibitors leads to an increased serotonin levels in frontal and temporoparietal cortex. Along with this, inhibition of IL 1 and IL 6 also contributes to COX 2 inhibitors antidepressant action. Thus, COX 2 inhibitors can be clinically used for their antidepressant action [46].

1.1.4. COX-2 inhibitors in viral diseases like Dengue

COX 2 enzyme acts as a mediator during the process of viral replication. An elevated COX 2 enzyme level observed in patients suffering from Dengue fever. According to a study performed on murine models, the administration of COX 2 inhibitors suppressed the DENV (Dengue virus) replication process and thus protected the mice from DENV infection [47].

1.2. Limitations and challenges in the development of COX-2 inhibitors

Pain management has always been a complex and interesting challenge for scientists worldwide. COX-2, an inducible enzyme has presented a lucrative drug target in the reduction of pain to medicinal chemists and leads to the development of a number of drugs like the coxibs (Celecoxib, Etoricoxib). However, side effects like gastrointestinal bleeding, dyspepsia, duodenal ulcers, arterial hypertension, stroke etc. pose challenges in the improvement of pain inhibitors, their therapeutic relevance and development of selective COX-2 inhibitors. Presented below are some of the primary problems faced:-

1.2.1. Physiological COX-2 and side effects

The initial theory that COX-1 only was the constitutively expressed physiological enzyme while COX-2 was only inducible has an increasing amount of evidence presented against it. Recent studies have suggested its constitutive presence and function in the kidney [48], brain [49] reproductive system [50,51] and the gastric mucosa [52]. A recent systematic study of constitutive COX-2 expression by Kirkby et al. [53] showed multiple transcriptional regulatory pathways for constitutive expression of COX-2 and that inflammation-inducible expression of COX-2 follows a different transcriptional pathway than the physiological expression of COX-2 at various discrete locations throughout the body and suggested transcriptional targeting of the NFAT (Nuclear Factor of activated *T*-cells) pathway to avoid cardiovascular side effects. Various strategies of drug design to bypass side effects of selective COX-2 inhibition include NO and other gaseous mediator releasing drugs to improve gastric safety and low cardiovascular effects [54] and mPGES-1 inhibitors among others [55]. There are still some gaps in the knowledge of the exact presence and function of COX-2 and requires more body of evidence to establish concrete facts.

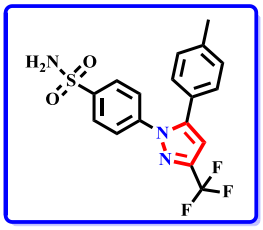
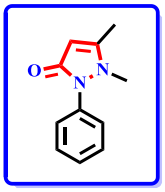
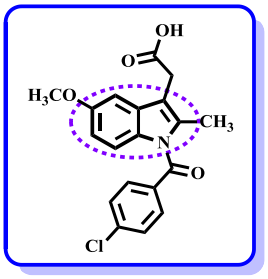
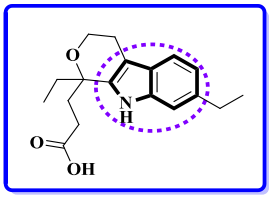
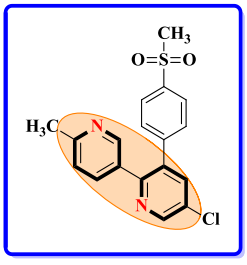
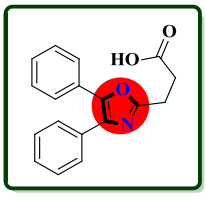
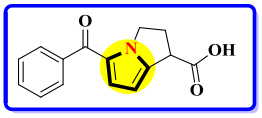
1.2.2. COX-1 and COX-2 role in inflammation

Conflicting evidence against both the pro-inflammatory and anti-inflammatory actions of COX-2 and COX-1 are present as some research suggested that COX-2 is intricated in the synthesis of PGD2 which is anti-inflammatory in nature [56,57] but it is also widely hypothesized that COX-3 might be responsible for the same [56,58,59]. Other evidence showed that COX-1 is involved in pro-inflammatory pathways [60–63] while others suggest COX-2 as the primary source in different models [64,65]. It is suggested that the difference in the experimental model results in different enzyme or its products being expressed as prostaglandins derived from COX-1 were expressed in one [63] while a different model showed that deletion of COX-2 gene independent of the immune response significantly contributed to suppression of the pathogenesis of arthritis [66]. This suggests the presence of complex regulatory pathways in the induction of pain and its causative reason.

1.2.3. Structural selectivity of drugs

Three primary structural domains characterize this enzyme – the epidermal growth factor domain (*N*-terminal) present between residues ranging from 34 to 72, between 73 and 116 lies the membrane binding domain and the catalytic C-terminal domain which shares a great deal of homology with mammalian myeloperoxidase [67]. The homology

Table 2
COX 2 inhibitors currently in the market.

S.NO.	Name of the marketed drug	Structure	IC_{50} for COX-2	References
A.	**Marketed drugs possessing pyrazole moiety**			
1.	Celecoxib		0.52 nM	[29]
2.	Antipyrine		> 1000 μM	[30]
B.	**Marketed drugs possessing indole moiety**			
1.	Indomethacin		5.9 nM	[31]
2.	Etodolac		60 μg/mL	[32]
C.	**Marketed drugs possessing pyridine moiety**			
1.	Etoricoxib		1.1 μg/mL	[33]
D.	**Marketed drug possessing Oxazole moiety**			
1.	Oxaprozin		36 μg/mL	[34]
E.	**Marketed drug possessing Pyrrole moiety**			
1.	Ketorolac		0.12 μg/mL	[35]

between the amino acid sequences of the COX isozymes poses an obstacle with respect to making safe and effective NSAIDs with low ulcerogenic properties. COX-1 and COX-2 enzymes revealed 60% sequence homology between them but the substitution of Val 523 in COX-2 in place of the bulky Ile 523 in COX-1 exposes a lateral binding adjacent pocket in COX-2 not available in COX-1 which can be exploited for drug design [68]. Other differences like Val 434 in place of Ile 434 which displaces Phe 518 to expose the side pocket. Various other differences in amino acids do not contribute directly to the binding site but do alter the chemical properties of the enzyme with respect to its environment [69,70]. Design of COX-2 and 5-LOX dual inhibitors is also being explored to synthesize stronger anti-inflammatory compounds [71].

2. Pyrazole as COX 2 inhibitor

Pyrazole as a heterocycle is a 5-membered ring consisting of three carbon and two consecutive nitrogen atoms. Celecoxib is a branded COX-2 inhibitor drug which contains 1,5-diarylpyrazole moiety. Antipyrine is an analgesic, antipyretic and non steroidal anti-inflammatory drug containing pyrazolone nucleus. It is 1,2-dihydropyrazol-3-one derivative substituted with methyl groups at C-1 and C-5 and with a phenyl group at N-2 (Table 2) along with synthetic methods for its preparation are mentioned in Fig. 3 and patents in Table 3.

Pyrazole or isoxazole derivatives can be prepared by a palladium catalyzed four component coupling of a terminal alkyne, hydrazine, carbon monoxide and an aryl iodide leading to the formation of substituted pyrazole [72].

In Pechmann Pyrazole synthesis [73], pyrazoles are formed by the reaction of acetylenes with diazomethane. Pyrazole-carboxylic acid derivatives are formed by the analogous addition of diazoacetic esters to the triple bonds.

1,3-dinitroalkanes are synthetically equivalent to 1,3-dicarbonyl compounds, and therefore could be used to synthesize substituted pyrazoles [74].

The most important synthesis of pyrazole is Knorr pyrazole synthesis [75] which involves condensation reaction of hydrazines with 1,3-dicarbonyl compounds.

Wiley et al. synthesized 3,5-disubstituted pyrazoles by the reaction of a diketone with hydrazinehydrate in ethanol [76].

Alam et al. [89] reported hybrid pyrazole analogs and assessed for ulcerogenicity, cytotoxicity and TNF-α assay. Compound **"1"** presented maximum half-minimal inhibition (IC_{50} = 1.79 μM, SI = 72.73) in comparison to Celecoxib (IC_{50} = 0.31 μM, SI = 78.06). Evaluation of *in vivo* anti-inflammatory activity was carried out using the carrageenan-induced rat-paw edema method where compound **"1"** (% inhibition = 78.09%) displayed comparable inhibition to Ibuprofen (% inhibition = 79.23%). Compound **"1"** also showed (%inhibition = 73.72%) analgesic activity comparable Ibuprofen (% inhibition = 74.72%) and less ulcerogenicity (Severity index = 0.81) than Ibuprofen (Severity index = 1.16). *In vitro* TNFα activity showed 73.72% inhibition for the compound **"1"** which is almost similar to ibuprofen (% inhibition of 74.12%). Compound **"1"** decreased the NO level to 7.97 mmol/mg while in Celecoxib it was 7.53 mmol/mg. MTT assay was performed to evaluate cytotoxicity which demonstrated that compound **"1"** possessed 91% cell viability similar Celecoxib possessing 93% cell viability. SAR analysis revealed that the presence of sulfonamide derivatives possessed better *in-vitro* and *in-vivo* analysis. Methyl at *para* position showed higher COX-2 inhibitory potential as compared to Cl/F substituents (Fig. 4).

Ren et al. [90] designed and synthesized diarylpyrazole compounds unified with chrysin. Compound **"2"** showed most potent antiproliferative activity against Hela cell line with an IC_{50} = 1.12 μM, better than Celecoxib (IC_{50} = 15.69 μM) and Chrysin (IC_{50} = 25.05 μM) as positive controls and highest inhibitory potential against COX-2 with an IC_{50} = 0.23 μM, similar to Celecoxib (IC_{50} = 0.36 μM). On further investigations, it was revealed that this compound through mitochondrial depolarization can bring about apoptosis of Hela cells and cell cycles G1 phase could be blocked in a dose dependant manner (Fig. 5).

Qiu et al. [91] reported dihydropyrazole derivatives as novel COX-2 inhibitors. Compound **"3"** appeared as potential COX-2 enzyme inhibitor (COX-2 IC_{50} = 0.08 μM, SI = 451) against the standard Celecoxib (Celebrex) (COX-2 IC_{50} = 0.07 μM, SI = 415) which is a marketed drug possessing anticancer potential. In silico scaffold modification strategy along with docking simulation was used to obtain the modified lead compounds and then evaluated using bioassays. It could reduce cell adhesion of A549 cells and expression of COX-2. It was observed that the potent molecule had a lower AlogP and a higher binding affinity to COX-2, anti-proliferative activity with lower IC_{50} value (1.63 ± 0.97 μM) when compared with celecoxib (2.21 ± 1.31 μM) (Fig. 6).

Abdelgawad et al. [92] prepared a new series of benzothiazole/benzoxazole and/or benzimidazole substituted pyrazole derivatives and evaluated them for their antiproliferative potential against the MCF-7 and A549 cell lines. Compound, **"4"** appeared as the most potential derivative against MCF-7 (IC_{50} = 6.42 μM) and A549 cell lines (IC_{50} = 8.46 μM) as compared to reference drug doxorubicin (IC_{50} for MCF-7 = 2.11 μM; IC_{50} for A549 = 2.74 μM). Results showed that the benzothiazolopyrazolone derivative of **"4"** displayed most potential COX-2 inhibition (IC_{50} = 0.10 μM, S.I. = 101.1), while 5-acetylbenzimidazolylpyrazolone derivative showed maximum COX-2 selectivity (S.I. = 104.67) against celecoxib (IC_{50} = 1.11 μM, S.I. = 13.33) (Fig. 7).

Abdellatif et al. [93] reported a series of diarylpyrazoles as novel COX-2 inhibitors and evaluated for anti-inflammatory activity using Celecoxib as the standard drug. The synthesized derivatives possessed vicinal diaryl rings attached to a central five-membered heterocyclic ring. A lipophilic group, methanesulfonyl (-SO_2CH_3) attached to one of the aryl rings delivered the COX-2 selectivity. The potency increased with the attachment of carboxylic (–COOH) or sulphonamide (-SO_2NH_2) groups at the *p*-position of the other aryl ring. *In vitro* inhibition studies indicated that compound **"5"** displayed good COX-2 enzyme inhibition with IC_{50} values of 1.11 μM as compared to the reference drug Celecoxib with an IC_{50} value of 0.87 μM. The selectivity index (SI) was found to be 4.77 as compared to 7.8 for the reference drug Celecoxib. The *in vivo* anti-inflammatory results was assessed using carrageenan on murine models. After 3 h, the highest anti-inflammatory activity was shown by **"5"** with 63% inhibition as compared to Celecoxib with 51% inhibition (Fig. 8).

Abdellatif and co-workers [94] synthesized newer 1,3,4-trisubstituted-pyrazole derivatives owning two COX-2 pharmacophoric moieties (SO_2Me or/and SO_2NH_2) and assessed for inhibition of COX, anti-inflammatory potential and ulcerogenic study. The derivatives of bisaminosulphonyl showed maximum COX-2 selectivity (S.I. = 9.87) and good anti-inflammatory potency (ED_{50} = 15.06 mol/kg) against celecoxib (COX-2 S.I. = 8.61, ED_{50} = 82.2 μmol/kg), reduced ulcerogenicity (ulcer indexes = 2.72–3.72) than ibuprofen (ulcer index = 20.25) and equivalent to celecoxib (ulcer index = 2.93). The chloro derivative of bisaminosulphonyl series i.e. compound **"6"** displayed maximum COX-2 inhibition (COX-2 IC_{50} = 0.39 μM) (Fig. 9).

Nossier et al. [95] reported a novel series of pyrazole substituted rings in which various heterocyclic ring systems were substituted at the C4 position and evaluated using carrageenan-induced rat paw edema method for their anti-inflammatory activity. The presence of electron releasing groups (methoxy group) at the 4th position of pyrazole moiety showed a higher activity than their congeners that had an electron withdrawing group (Bromo group). The cyclization of α,β-unsaturated ketone possessing methoxyphenyl at 4th position of pyrazole, led to increased activity whereas cyclization of chalcone possessing a bromophenyl group at 4th position of pyrazole resulted in decreased activity. Investigations revealed that the cyanopyridone derivative **"7"** exhibited a better anti-inflammatory activity (89.57% inhibition of

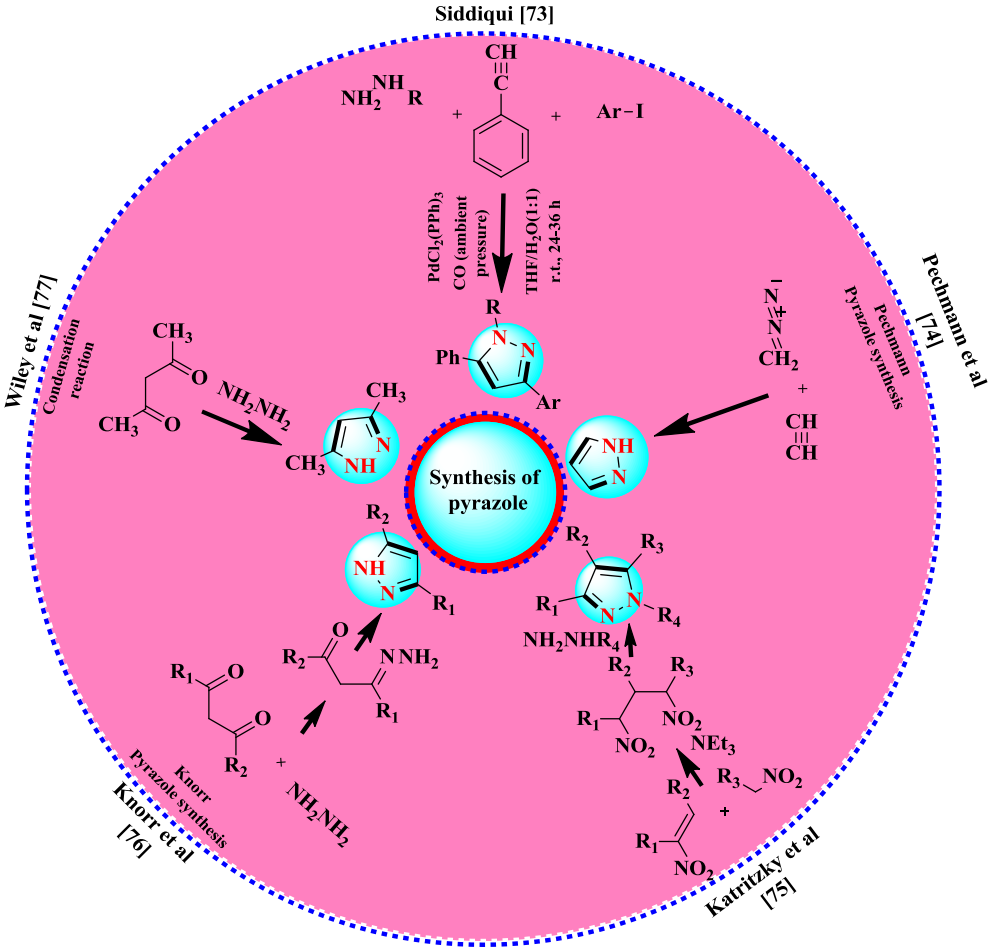


Fig. 3. Synthesis of pyrazole.

edema) as compared to indomethacin and celecoxib (%inhibition of edema was 72.99% and 83.76% respectively) (Fig. 10).

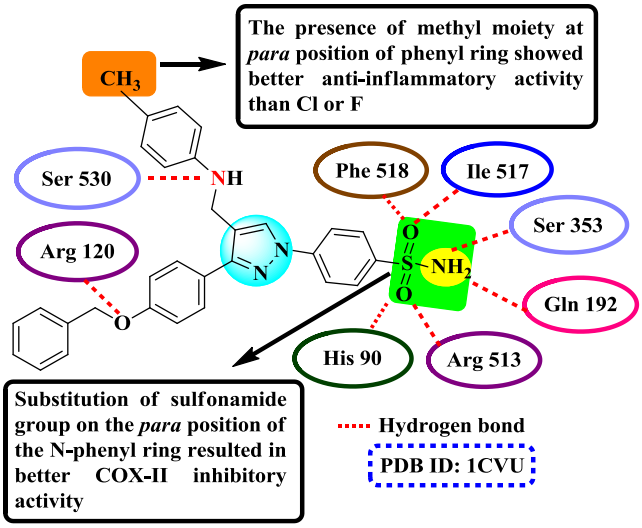
Alegaon et al. [96] synthesized a series of twenty-two 1,3,4-trisubstituted pyrazole derivatives and evaluated for anti-inflammatory activity using carrageenan-induced rat paw edema technique. 1,3,4-thiadiazole derivatives loaded with acetamide group **"8"** showed most potent COX 2 inhibitory activity (%AI = 87.25%, IC_{50} = 14 μM and SI = 5.21) against diclofenac sodium (%AI = 86.72%). The cytotoxic activity for the most potent 1,3,4-thiadiazole derivatives was also evaluated using MTT cell proliferation assay against HeLa and MCF-7 cell lines and compared using Doxorubicin as the standard drug. Compound **"8"** showed IC_{50} values of 12 ± 1.5 and 6.5 ± 1.2 against HeLaand MCF-7 cell lines respectively as compared to doxorubicin with IC_{50} value of 3.33 ± 0.57 μM (HeLa) and 2.0 ± 0.8 μM (MCF-7) (Fig. 11).

El-Sayed et al. [97] reported pyrazole and pyrazoline containing derivatives and evaluated for inhibition of ovine COX-1/COX-2 isozymes and anti-inflammatory activity (Carrageenan-induced foot paw edema model). Compound **"9"** appeared as the most potential derivative (IC_{50} = 0.26 and SI = > 192.31) as compared to the standard drugs, Diclofenac (IC_{50} = 3.1, SI = 0.07) and Celecoxib (IC_{50} = 0.28, SI = > 178.57). Compound **"9"** also showed potential antiinflammatoey activity (% Inhibition of edema = 89.3% following 200 mg/kg IP, ED_{50} = 96 ± 4.3 mg/kg) as compared to the standard drugs diclofenac (% Inhibition of edema = 87.3% following 200 mg/kg IP, ED_{50} = 63 ± 7.5 mg/kg) and celecoxib (% Inhibition of edema = 83.0%following 200 mg/kg IP, ED_{50} = 70.4 ± 0.8 mg/kg). 3,5-ditrifluoromethyl groups on phenyl ring at C4 increased the COX 2 inhibitory activity as well as the selectivity of **"9"** as compared to Celecoxib. It was observed that COX-2 potency and selectivity increased in the cyclized derivatives. The replacement of the benzylidene fragment with a benzyl moiety led to a drastic decrease in the COX-2 activity. Molecular docking studies were performed which further revealed that selectivity of COX 2 of **"9"** was due to the presence of trifluoromethyl moieties that inserted deep inside the COX-2 2°pocket. Thus **"9"** appeared as a promising anti-inflammatory agent (Fig. 12).

Faidallah and Rustom [98] synthesized and evaluated the anti-inflammatory activity of some structure hybrids comprising basically of 5-hydroxy-3-methyl-1-phenyl-4-substituted-1H-pyrazole scaffold directly linked to a variety of heterocycles and functionalities, or annulated as pyrano[2,3-*c*]pyrazoles. According to the *in vivo* results (carrageenan induced paw edema bioassay in rats) and a comprehensive structure–activity relationship study, five analogs displayed remarkable anti-inflammatory profiles showing distinctive % protection and ED_{50} values, especially **"10"** (ED_{50} = 35.7 μM/kg) which was nearly equiactive to celecoxib (ED_{50} = 32.1 μM/kg). It was revealed in these studies that the anti-inflammatory activity was greatly influenced by the type of substituent at C4 of the main pyrazole scaffold. It is worth noting that a significant improvement in the anti-inflammatory potential was obtained via cyclization of the pyrazole into the corresponding bipyrazole structure **"10"**, stemmed as the most active member in this study (% protection = 74.2% , AI% relative to celecoxib = 98.5%, IC_{50} for COX-2 = 0.72 μM, SI = 7.83), being more potent *in vivo* than indomethacin (%protection = 70.8, IC_{50} = 3.73 μM, SI = 0.95) and nearly equiactive to celecoxib(% protection = 75.3%, IC_{50} = 0.84 μM, SI = 8.68). Further derivatization of the sulfonamido group of **"10"** led to a noticeable lowering of the anti-inflammatory potential. Such dramatic collapse in the bioactivity of the analogs could be attributed to

Table 3
Patents on Pyrazole moiety related to anti-inflammatory activity.

S. No.	Patent number	Patent date	Inventors	Description
1.	US6603008B1 [77]	05 July 2003	Kazuo Ando, Kiyoshi Kawamura	Sulfamoylheleroaryl pyrazole compounds as anti-inflammatory/ analgesic agents
2.	US6506747B1 [78]	14 January 2003	Rajashekhar Betageri, Charles L. Cywin, Karl Hargrave, Mary Ann Hoermann Thomas M. Kirrane, Thomas M. Parks, Usha R. Patel, John R. Proudfoot, Rajiv Sharma, Sanxing Sun, Xiao-Jun Wang	Substituted 1-(4-aminophenyl)pyrazoles and their use as anti-inflammatory agents
3.	US6900230B2 [79]	31 May 2005	Subas M. Sakya, Bryson Rast	Heterocyclo-alkylsulfonyl pyrazoles as anti-inflammatory/ analgesic agents
4.	WO2001064669A1 [80]	07 September 2001	Hengmiao Cheng, Jason Kenneth Dutra, Subas Man Sakya	Pyrazole ether derivatives as anti-inflammatory/analgesic agents
5.	US6531492B1 [81]	11 March 2003	Kristin M. Lundy, Hengmiao Cheng, Subas M. Sakya, Jin Li, Martha L. Minich, Chikara Uchida	Heterocyclo-alkylsulfonyl pyrazole derivatives as anti-inflammatory/analgesic agents
6.	US6649636B1 [82]	18 November 2003	Kazuo Ando, Martha L. Minich, Jin Li, Subas M. Sakya, Kristin M. Lundy, Hengmiao Cheng, Brian S. Bronk, Kiyoshi Kawamura, Tomoki Kato	Heteroaryl phenyl pyrazole compounds as anti-inflammatory/ analgesic agents
7.	US4349558A [83]	14 September 1982	Malcolm R. Bell	Anti-inflammatory 8H-phenanthro-[2,3-c]pyrazole derivatives
8.	US5434178A [84]	18 July 1995	John J. Talley, Donald J. Rogier, Jr.	1,3,5 trisubstituted pyrazole compounds for treatment of inflammation
9.	US5486534A [85]	23 January 1996	Len F. Lee, Thomas D. Penning, Steven W. Kramer	3,4-substituted pyrazoles for the treatment of inflammation
10.	US7001917B2 [86]	12 April 2002	Misato Hirano, Kazunari Nakao, Seiji Nuki, Tatsuya Yamagishi.	Pyrazole compounds as anti-inflammatory and analgesic agents
11.	WO1996014302A1 [87]	17 May 1996	Hirotoshi Numata, Yasushi Okamoto,Masanobu Shinoda Naoki Kobayashi, Shuhei Miyazawa,Tetsuya kawahara Hiroshi Shirota, Naoki Nagakura,Tatsuo Horizoe, Shinya Abe,Seiichi Kobayashi, Takashi Yamanaka	Pyrazole derivatives exhibiting anti-inflammatory and analgesic effects
12.	US5760068A [88]	02 June 1998	John J. Talley, Thomas D. Penning, Paul W. Collins Donald J. Rogier, Jr. James W. Malecha, Julie M. Miyashiro, Stephen R. Bertenshaw, Ish K. Khanna, Matthew J. Graneto, Roland S. Rogers,Jeffery S. Carter, Stephen H. Docter, Stella S. Yu	Substituted pyrazolyl benzenesulfonamides for the treatment of inflammation



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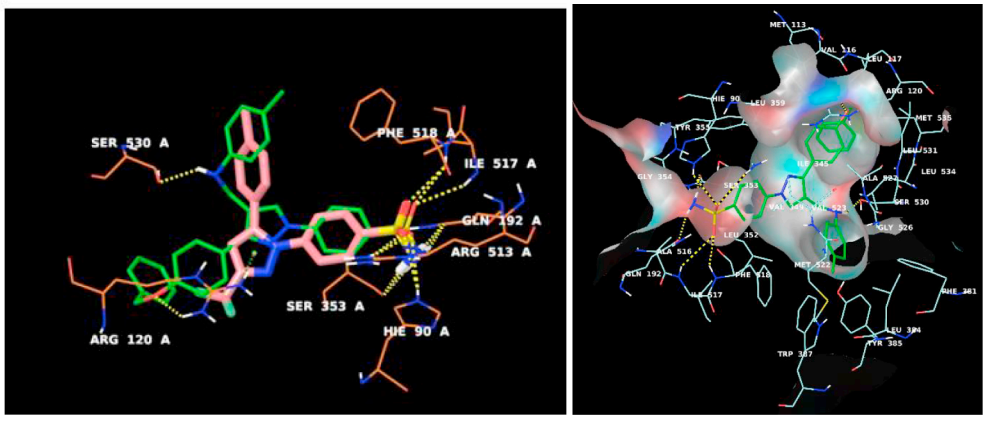

Fig. 4. Upper panel: Structure and SAR of N-((3-(4-(benzyloxy)phenyl)-1-phenyl-1H-pyrazol-4-yl) methyl)aniline derivatives. **Lower left panel**: superimposed structures of most potent compound 1 (green color) with celecoxib (pink color). **Lower right panel**: Receptor surfaceof COX-2 complexed with most potent compound 1.

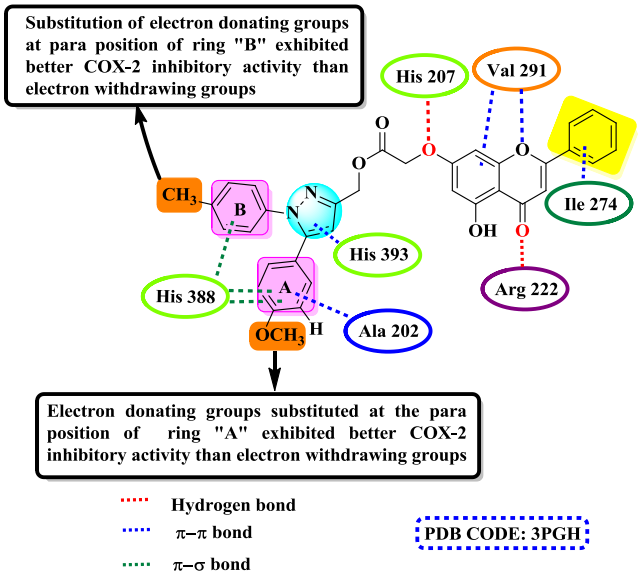

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Fig. 5. Structure, SAR and molecular docking of (5-(4-Methoxyphenyl)-1-(p-tolyl)-1H-pyrazol-3-yl)methyl 2-((5-hydroxy-4-oxo-2-phenyl-4H-chromen-7-yl) oxy)acetate.

their steric bulkiness which would probably affect bioavailability and/or binding with COX enzymes. On the other hand, annulation of the parent pyrazolyl butane-1,3-diones into the corresponding bicyclic substituted 3,6-dimethyl-1-phenylpyrano[2,3-*c*]pyrazole-4(1H)-ones furnished four active compounds, which carry some structural relevance to the vicinal diarylheterocycles template of COX-2 inhibitors represented by celecoxib. The anti-inflammatory profile of these derivatives was modulated by the type of substituent at position 5. Additionally, the five most potent analogs identified proved to be gastrointestinal tract safe (0–20% ulceration) and non-toxic, when treated at a dose of 80 mg/kg parenterally and 250 mg/kg orally. Collectively, the *in vivo* ED_{50} values agree with their *in vitro* COX-2 selectivity indices. The bipyrazole **"10"** could be considered as the potential member in this study, being nearly equiactive to celecoxib, besides its obvious selective COX-2 inhibition, high safety margin, and predicted pharmacokinetic (ADME-T) suitability for oral use (Fig. 13).

Tewari et al. [99] synthesized a novel pyrazole derivatives and aasessed for anti-inflammatory activity using carrageenan-induced rat paw edema model. Ccompound **"11"** showed worthy anti-inflammatory potential and optimum COX-2 inhibition (IC_{50} = 14.3 μM, SI = 0.44) with respect to reference drug Nimesulide. Results revealed that control group showed 38.7% paw edema growth which reduced to 19.4% in rats treated with **"11"** against nimesulide treated rats with 23.4% paw edema growth (Fig. 14).

Shen et al. [100] designed and synthesized novel dual inhibitors of

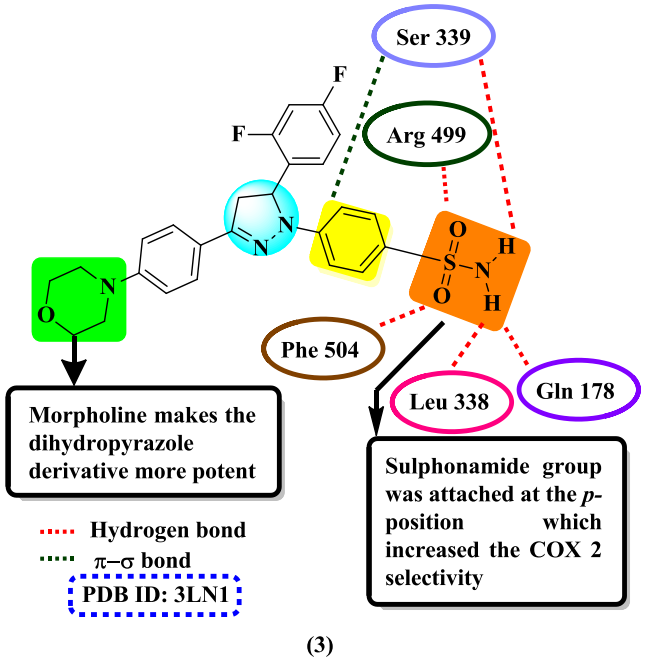

Fig. 6. Structure, SAR and molecular docking of the most potent compound of the novel series of dihydropyrazole sulphonamide derivatives.

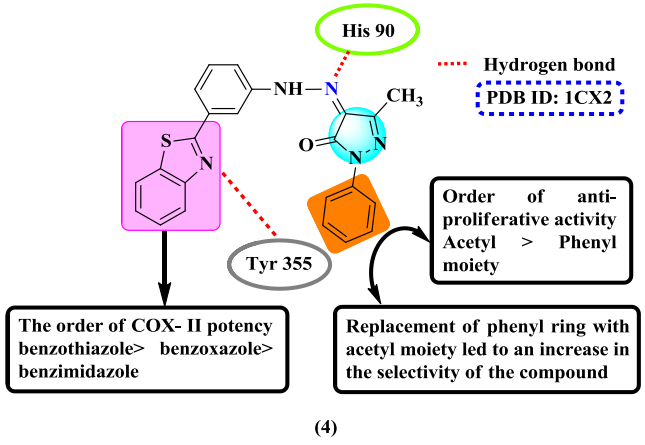

Fig. 7. Structure, SAR and molecular docking of 4-[3-(Benzothiazol-2-yl)-phenyl)hydrazono]-5-methyl-2-phenyl-2,4-dihydropyrazol-3-one.

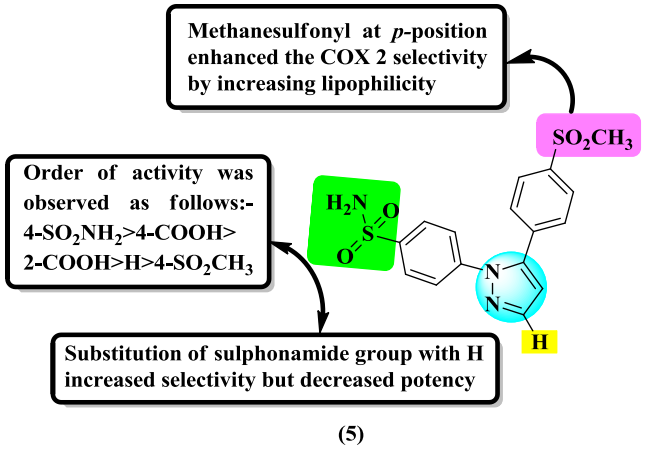

Fig. 8. Structure and SAR of 4-[5-(4-Methylsulfonylphenyl)-1H-pyrazol-1-yl]-benzene sulfonamide.

cyclooxygenase (COX-2) and Lipooxygenase (5-LOX) by hybridizing pyrazole with substituted coumarin. Compound **"12"** with IC_{50} = 0.23 ± 0.16 μM for COX-2, IC_{50} = 0.87 ± 0.07 μM for 5-LOX and IC_{50} = 4.48 ± 0.57 μM against A549 cell lines, presented advantage against celecoxib with IC_{50} = 0.41 ± 0.28 μM for COX-2 and IC_{50} = 7.68 ± 0.55 μM against A549 cell lines and Zileuton with IC_{50} = 1.35 ± 0.24 μM for 5-LOX (Fig. 15).

Ghareb et al. [101] prepared a series of pyrazoles and pyrazolo[1,2-*a*]pyridazines with selective inhibition of COX-2 and *in vivo* anti-inflammatory potential. Compound **"13"** showed a decent IC_{50} of 16.2 nM and a selectivity ratio of 4.35. Docking studies revealed that aniline moiety at C3 of pyrazole moiety docked efficiently deep inside the crystal structure if COX-2 (Fig. 16).

Bashir et al. [102] reported newer 2-pyrazoline derivatives equipped with benzenesulfonamide moiety and assessed for anticancer and anti-inflammatory potential. Compound **"14"** (95.2% inhibition after 5 h) showed the most potent anti-inflammatory activity against celecoxib (85.7% inhibition after 5 h) and showed higher GI safety than celecoxib when evaluated for their ulcerogenic potential. SAR study revealed that introduction of electron releasing substituents in 5-aryl ring of pyrazolines improved the anti-inflammatory activity (Fig. 17).

Amir et al. [103] synthesized 3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines and 1-benzoyl-3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines and evaluated for anti-inflammatory and analgesic action. Compound **"15"** displayed potential anti-inflammatory and analgesic action along with lower ulcerogenic potential against fliubiprofen as standard drug. Results indicated that derivatives with 4-methyl and 2,4,6-trimethoxy group attached to the phenyl ring present at C-5 of pyrazoline moiety owns the maximum anti-inflammatory activity (% inhibition = 82.45%) and analgesic activity (%inhibition = 72.90%) superior than flurbiprofen (%inhibition = 80.69%). However derivative with 2,4,6-trimethoxy group indicated sharp reduction in analgesic potential (%inhibition = 28.60%) (Fig. 18).

Fioravanti et al. [104] prepared newer 1-*N*-substituted-3,5-diphenyl-2-pyrazoline derivatives and assessed for cyclooxygenase inhibition (COX-1 and COX-2) but none of the new derivatives showed enhanced COX-1 inhibition and only some of them showed a good COX-2 inhibition. Compound **"16"** was the most poent compound with an IC_{50} of 3.20 μM when compared with Indomethacin (IC_{50} = 35.20 μM) and Diclofenac (IC_{50} = 23.62 μM) (Fig. 19).

Bandgar et al. [105] synthesized a series of 3-(substituted)-aryl-5-(9-methyl-3-carbazole)-1H-2-pyrazolines and evaluated for COX-1 and COX-2 inhibition. Compound **"17"** appeared as the most potent derivative of the series (COX-2% inhibition = 88.43%, selectivity ratio = 3.66). The *in vitro* inhibition assay revealed that it was more potent as compared to the reference drug Indomethacin (COX-2 %inhibition = 28.43%). *In vivo* inhibition was calculated using the standard carrageenan induced rat paw edema model and the results obtained were consistent with the *in vitro* assay (%inhibition of "19" = 60.3%, %inhibition of indomethacin = 47%). Molecular docking studies performed for the potent compound **"17"** depicted that the oxygen atoms of the methoxy group led to an increase in selectivity for the COX-2 enzyme by the formation of hydrogen bonds with the active site. Similarly, the nitrogen atoms on the pyrazoline ring facilitated the embedding of the compound **"17"** into the active site by the help of hydrogen bonding. Selective COX-2 inhibition significantly raised the protection of the active compound **"17"** (65%) as compared to the reference drug indomethacin (47%) at an equivalent dose (Fig. 20).

Razik et al. [106] reported benzodioxole–pyrazole hybrids and examined for dual *in vitro* inhibition of COX (COX-1 and COX-2) and 5-LOX (5-lipoxygenase) using their IC_{50} values. *In vitro* evaluation revealed that compound **"18"** (COX-2 IC_{50} = 0.33, selectivity Index = 12.06) appeared as more potent derivative than celecoxib (COX-2 IC_{50} = 0.88) with %inhibition of rat paw edema = 50.9%, 1 h after the administration of the dose than the reference drug diclofenac sodium (%inhibition of rat paw edema = 30.17%, 1 h after the

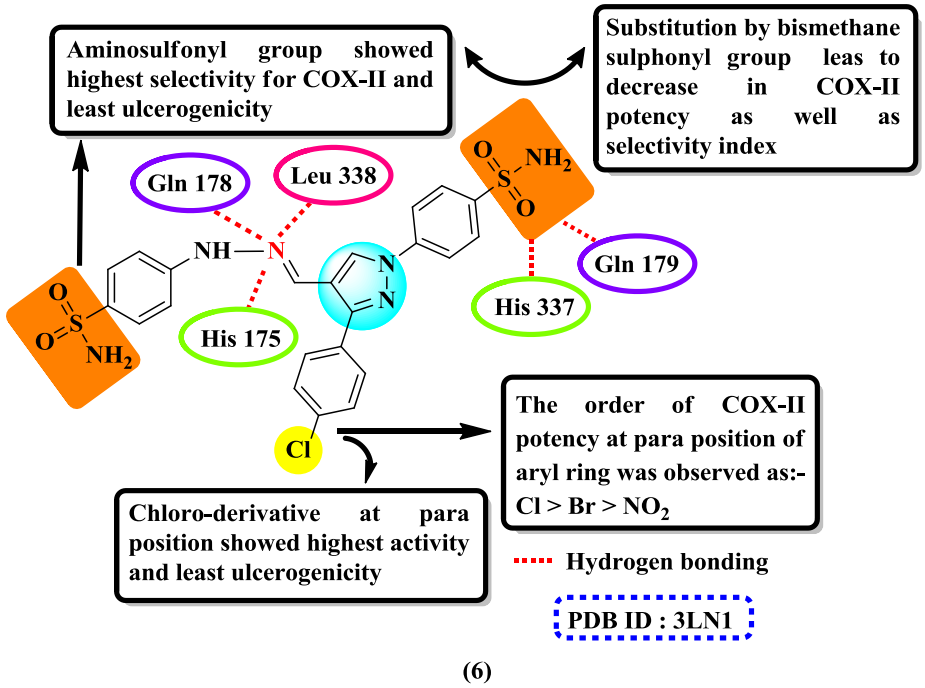

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Fig. 9. Structure, SAR and molecular docking of 4-{3-(4-Bromophenyl)-4-[(4-sulfamoyl phenyl)hydrazonomethyl]-pyrazol-1-yl}benzenesulfonamide.

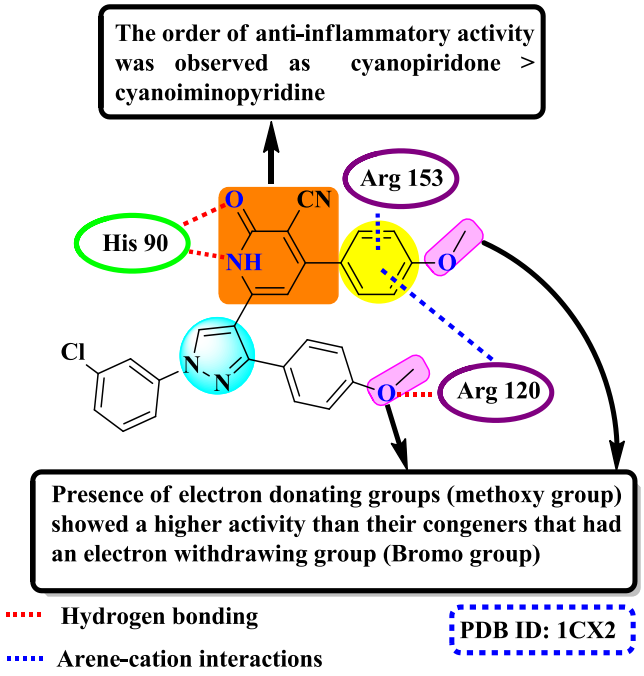

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Fig. 10. Structure, SAR and molecular docking of 6-(4-Methoxyphenyl)-4-(1-(3-chloro phenyl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)-1,2-dihydro-2-oxo-pyridine-3-carbonitrile.

administration of the dose). *In vivo* evaluation of analgesic activity was carried out using a model of inflammatory pain in which the reduction of writhes was measured after administration of intraperitoneal injections of acetic acid solution in mice. The potency of the compound **"18"** (%Inhibition of writhes = 57%) was comparable with the reference drug diclofenac sodium (% Inhibition of writhes = 65.7%). 1,3-diarylpyrazoles showed maximum anti-inflammatory activity. Benzodioxole also enhanced the COX-2 inhibitory activity by forming H-bonds with the active site. Sulfonamide derivatives showed potent COX-2 inhibition due to H-bonding with the active site.. Molecular docking revealed the same binding site for the potent compounds as that of the reference drug "Celecoxib" and could thus be further investigated and derivatized in order to potentiate their biological activity (Fig. 21).

El-Feky et al. [107] synthesized trisubstitutedquinoline derivatives linked to pyrazoles and assesed using ovine COX-1/COX-2 assay kit. It was found that the chlorine substituents displayed most potent COX-2 inhibition activity and selectivity (IC_{50} = 0.26 μM, SI = > 192.33) even higher than the reference drug celecoxib ((IC_{50} = 0.28 μM, SI = > 178.57). Compound **"19"** (paw thickness = 0.68 mm after 3 h) possessed almost as potent anti-inflammatory activity as that of the reference drug celecoxib (paw thickness = 0.65 mm after 3 h). Ulcerogenic study revealed that compound **"19"** possessed ulcer index = 0 against indomethacin with an ulcer index of 440. Molecular docking showed that compound **"19"** potently binds to the active site with the help of hydrophobic interactions and hydrogen bonding. Amino group and the quinoline ring also stabilize the binding by the formation of hydrogen bonds. The *p*-chlorophenyl group interacts with the amino acid on the active site via cation-pi interactions. Thus, the compound **"19"** showed potent anti-inflammatory activity by better binding abilities (Fig. 22).

Thore et al. [108] synthesized a novel ethyl-5-amino-3-methylthio-1H-pyrazole-4-carboxylates and evaluated for *in vivo* analgesic and anti-inflammatory activity. Compounds **"20"** (%inhibition = 38.80% after 3 h) showed similar anti-inflammatory activity as standard drug diclofenac (%inhibition = 40.56% after 3 h) and its analgesic activity (% inhibition = 56.57%) was found equivalent to diclofenac sodium (% inhibition = 63.15%) and found less ulcerogenic (ulcer index = 1.12) against diclofenac sodium (ulcer index = 3.10). The presence of the substituent sulfonamidophenyl for **"20"** at the N-1 position of pyrazole led to an increase in the analgesic and anti-inflammatory activities (Fig. 23).

Bakr et al. [109] synthesized 1-phenylpyrazolo[3,4-*d*]pyrimidine derivatives and evaluated for *in vitro* COX-2 inhibition potential. Compound **"21(a)"** was the most potent compound of the series (COX-2 IC_{50} = 0.56 μM, selectivity index = 7.09) than celecoxib (COX-2

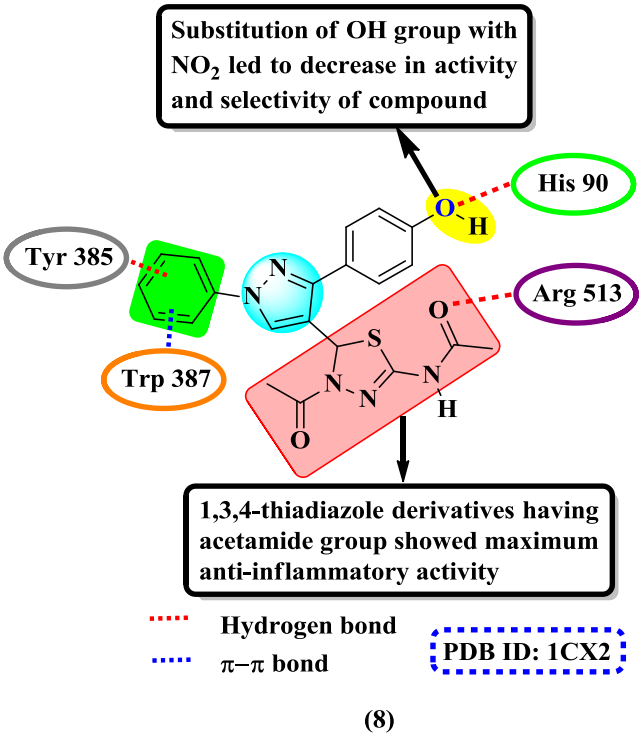


Fig. 11. Structure, SAR and molecular docking of -acetyl-5-(3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide.

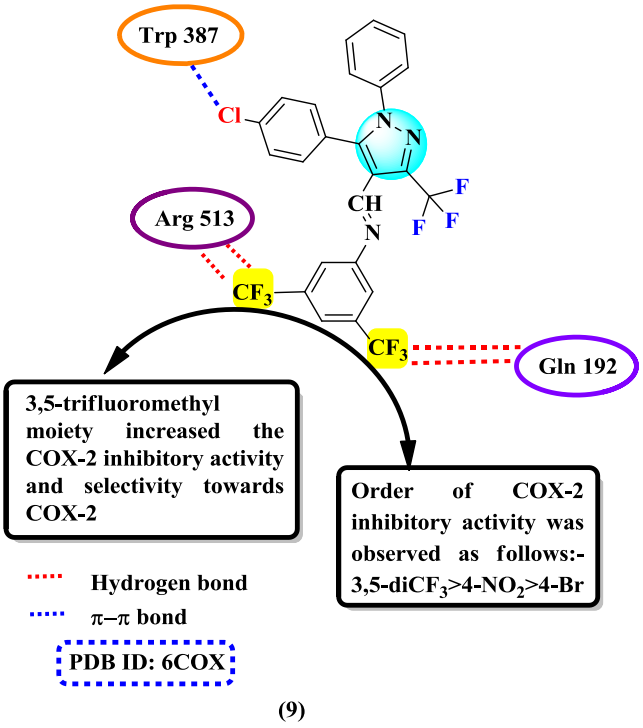


Fig. 12. Structure, SAR and molecular docking of 3,5-bi(Trifluoromethyl)-N-((5-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene) aniline.

IC_{50} = 1.11 μM, selectivity index = 6.61). Compound **"21(b)"** was found to be more potent (ED_{50} = 87.9 mol/kg) than the reference drug celecoxib (ED_{50} = 91.9 μmo l/kg). Compounds possessing pyrazolyl moiety with pyrazolo[3,4-*d*]pyrimidine scaffold displayed greater anti-

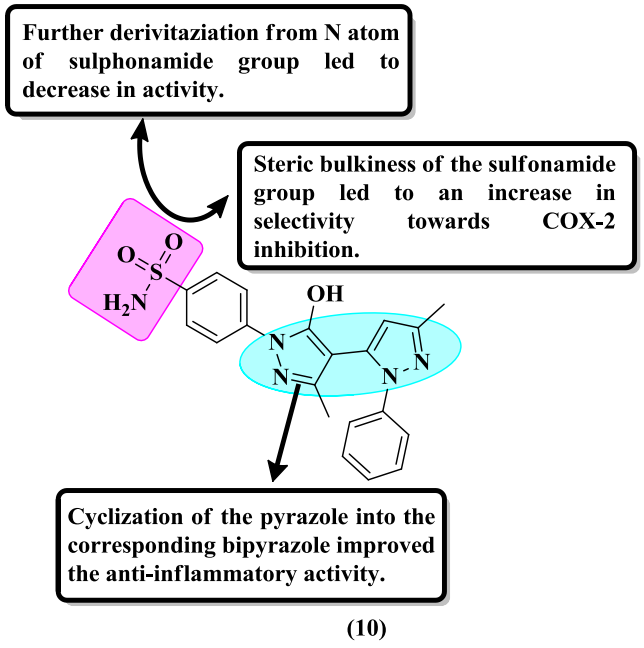


Fig. 13. Structure and SAR of 5-Hyroxy-3-methyl-1-(4-sulfamylphenyl)-4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-1H-pyrazole.

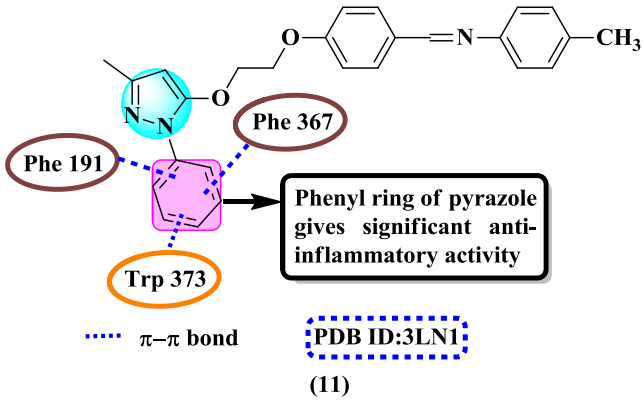


Fig. 14. Structure, SAR and molecular docking of 4-[2-(5-Methyl-2-phenyl-2H-pyrazol-3-yloxy)-ethoxy]-benzylidine}-p-tolylamine.

inflammatory potential. The presence of the amino group in the compound **"21(b)"** increased the potency of the compound (Figs. 24a and 24b).

Abdellatif et al. [110] reported novel series of compounds possessing pyrazole ring having vicinal diaryl rings that were asessed for *in-vitro* and *in-vivo* COX-2 inhibition along with COX-2 selectivity. Compound **"22"** with COX-2 IC_{50} = 0.62 μM and S.I. = 8.85 was found to be more potent than Celecoxib as reference drug having COX-2 IC_{50} = 0.84 μM and S.I. = 8.60. The compounds when assesed for anti-inflammatory potential based on changes in paw-edema volume, it was found that **"22"** with 97.68% inhibition was more active than the standard Celecoxib with 80.38% inhibition (evaluation done after 3 h). Carrageenan induced rat paw edema assay was carried out for the novel series using a dose of 50 mg/kg where it was revealed that compound **"22"** with 91% inhibition and ED_{50} = 38.37 μmol/kg showed more potency than Celecoxib with 80% inhibition and ED_{50} = 82.20 μmol/kg. Ulcerogenic effect was also determined for the novel series where **"22"** was found to possess comparable ulcer index = 3.12 as Celecoxib (ulcer index = 2.93) and offered more protectiveness than Indomethacin (ulcer index = 20.25). Shape alignment studies along with molecular docking were carried out in order to determine their

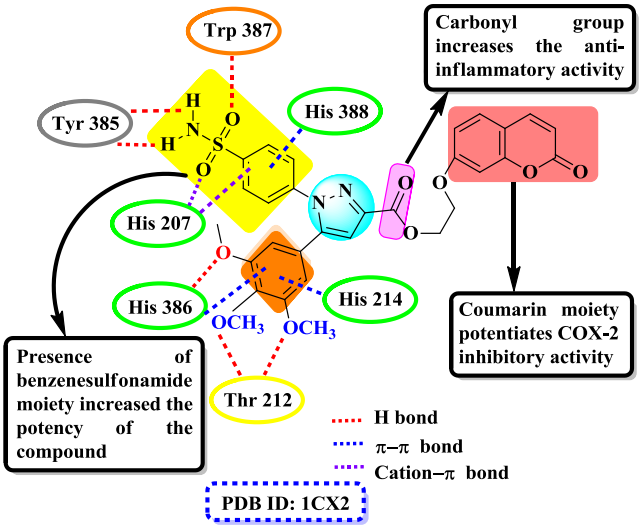


Fig. 15. Structure, SAR and molecular docking of the most active compound of the novel series of novel hybrids of pyrazole and coumarin.

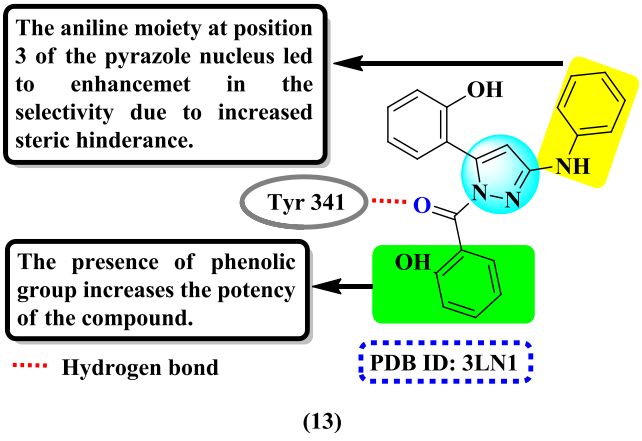


Fig. 16. Structure, SAR and molecular docking of the most active compound of Novel series of pyrazoles and pyrazolo[1,2-*a*]pyridazines.

interaction and compare their similarity with the known drugs (Fig. 25).

Abdelal et al. [111] reported a new series pyrazolopyrimidine series containing substitution of pyrazole, oxazole, triazole and Schiff base at the *para* position whose *in-vitro* and *in-vivo* assessment was performed to compare their anti-inflammatory potential against standard drugs like Celecoxib. Triazole derivative **"23"** was found to be the most potent compound of the series having COX-2 IC_{50} = 0.10 μM and Selectivity index = 113.20. The activity of compound was found comparable with Celecoxib (IC_{50} = 0.049 μM and Selectivity index = 165.30) and was found more potent as compared to Indomethacin (IC_{50} = 0.51 μM and Selectivity index = 0.080) and Diclofenac Sodium (IC_{50} = 0.84 μM and Selectivity index = 4.52). *In-vivo* studies were done with the help of carrageenan-induced rat paw edema model where the compound **"23"** was found to possess greater anti-inflammatory activity (90% after 5 h) than the reference drugs Celecoxib (89% after 5 h) and Indomethacin (74% after 5 h). Further, molecular docking studies were done where selected compounds were docked into active site of COX-2 where the binding studies on **"23"** revealed the presence of 3 hydrogen bonds (Fig. 26).

Abdelgawad et al. [112] synthesized novel 4-aryl-hydrazonopyrazolones and subjected to *in-vitro* evaluation for inhibition of COX-2 and 5-LOX along with *in-vivo* assessment of anti-inflammatory and

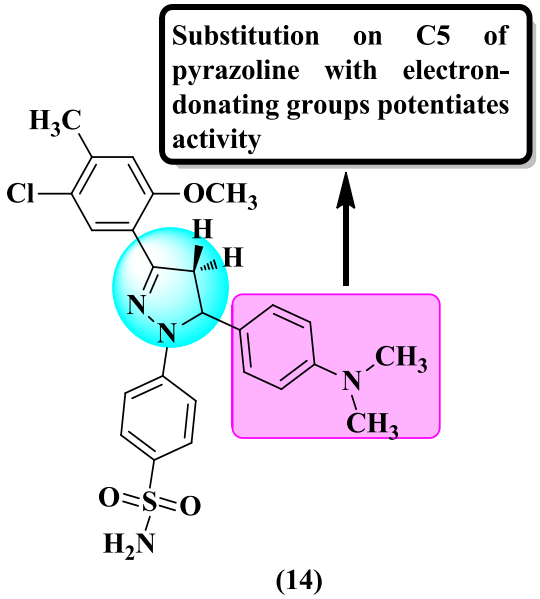


Fig. 17. Structure and SAR of a novel series of 2-pyrazoline derivatives bearing benzenesulfonamide moiety.

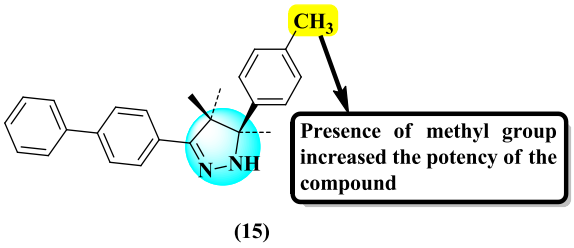


Fig. 18. Structure, SAR and molecular docking of 3-(4-biphenyl)-5-(40-methyl phenyl)-2-pyrazoline.

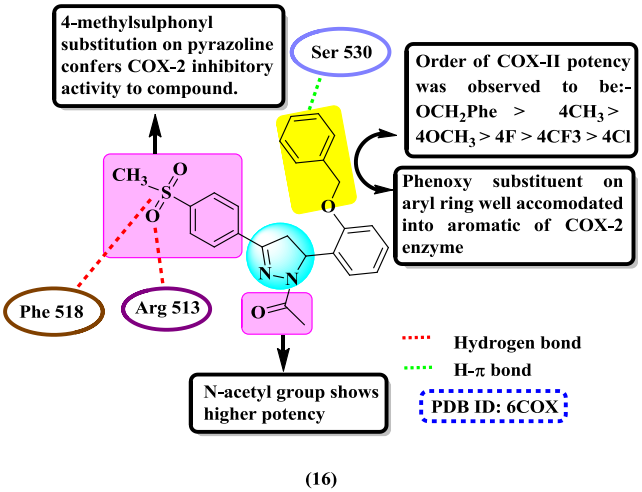
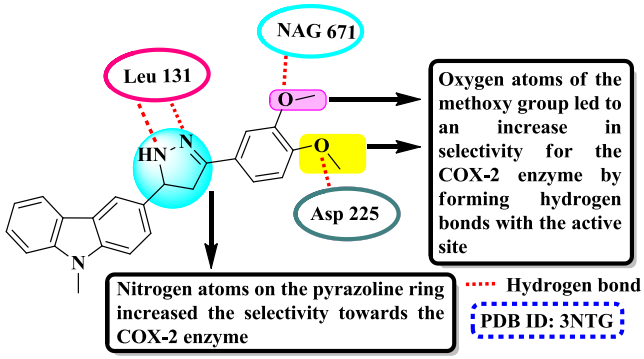


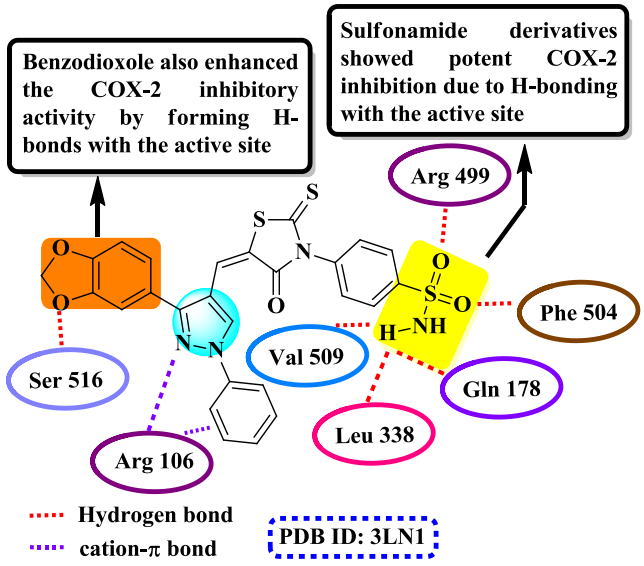
Fig. 19. Structure, SAR and molecular docking of the most active compound of *N*-substituted -3,5-diphenyl-2-pyrazoline derivatives.

analgesic activities. Compound **"24"** appeared most potent derivative of the series with COX-2 IC_{50} = 0.72 μM and S.I. = 5.29 and was found more potent than Celecoxib as standard drug (COX-2 IC_{50} = 0.89 μM and S.I. = 3.52) and Indomethacin (COX-2 IC_{50} = 7.24 μM and S.I. = 0.15). *In-vivo* evaluation using Carrageenan-induced rat paw edema assay model was consistent with *in-vitro* evaluation where **"24"** showed 1.5 ± 0.09 mm increase in paw thickness and



(17)

Fig. 20. Structure, SAR and molecular docking of the most potent compound of the novel series of 3-(substituted)-aryl-5-(9-methyl-3-carbazole)-1H-2-pyrazolines.



(18)

Fig. 21. Structure, SAR and molecular docking of 4-{5-{[3-(benzo[d]-[1,3]dioxol-5-yl)-1-(4-substitutedphenyl)-1H-pyrazol-4-yl]-methylene}-4-oxo-2-thioxothiazolidin-3-yl}-benzenesulfon amides.

ED_{50} = 0.044 mmol/kg after 2 h as compared to Celecoxib that showed 1.8 ± 0.08 mm increase in paw thickness and ED_{50} = 0.032 mmol/kg after 2 h. Binding interactions of **"24"** were seen by the help of molecular docking where it was observed that it fitted well inside the pocket by the help of 3H-bond interactions (Fig. 27).

Tageldin et al. [113] synthesized newer pyrazolopyrimidines by substituting different functional groups or by attaching them with substituted pyrazole ring through various linkages. *In-vitro* evaluation of the series revealed that compound **"25"** was the most potent compound with COX-2 IC_{50} = 0.22 μM and S.I. = 12.45 and was found to be more potent than the reference drugs Celecoxib (COX-2 IC_{50} = 0.78 μM and S.I. = 7.23) and Diclofenac Sodium (COX-2 IC_{50} = 1.10 μM and S.I. = 6.12). Cotton pellet-induced granuloma assay was carried out to investigate anti-inflammatory effect where **"25"** with % granuloma inhibition = 85.3% appeared more potent than Celecoxib (% granuloma inhibition = 8.6%) and Diclofenac sodium (% granuloma inhibition = 36.1%) as reference drugs (Fig. 28).

El-Shoukrofy et al. [114] designed and synthesized pyrazole derivatives containing thienopyrimidine, thienotriazolopyrimidine and thiophene moieties and assesses for COX-1/COX-2 inhibition (*in-vitro*)

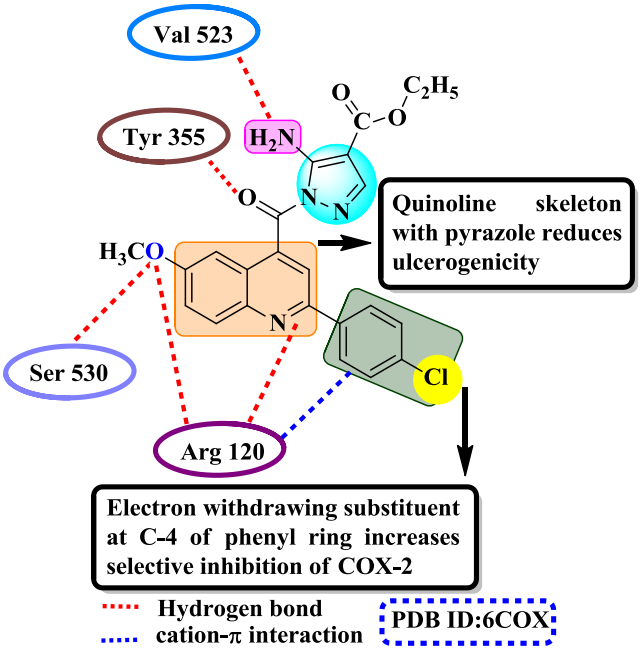


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Fig. 22. Structure, SAR and molecular docking of Ethyl 5-amino-1-(2-(4-chlorophenyl)-6-methoxyquinoline-4-carbonyl)-1Hpyrazole-4-carboxylate.

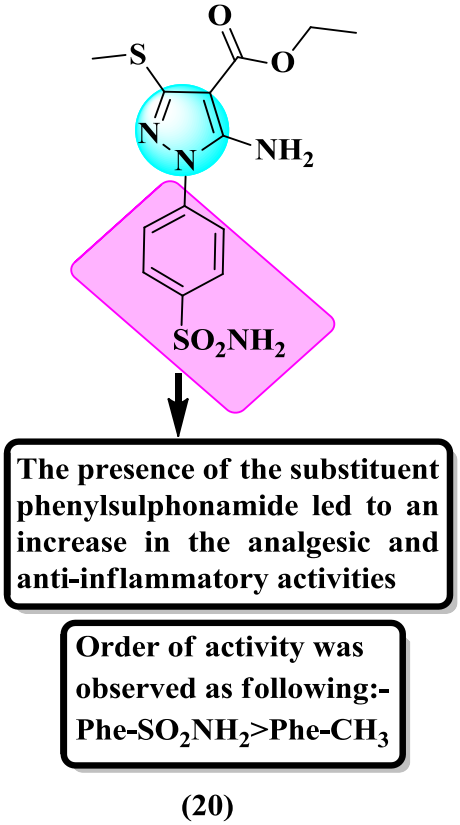

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Fig. 23. Structure and SAR of Ethyl-5-amino-3-methylthio-1-(4-sulfonamidophenyl)-1H-pyrazole −4-carboxylate.

and anti-inflammatory activity *(in-vivo)*. Thienopyrimidine derivative **"26"** was seen as a potent COX-2 inhibitor. According to *in-vitro* studies, **"26"** (IC_{50} = 0.059 μM and S.I. = 190.34) showed comparable COX-2 inhibition to Celecoxib as the reference drug (IC_{50} = 0.045 μM and

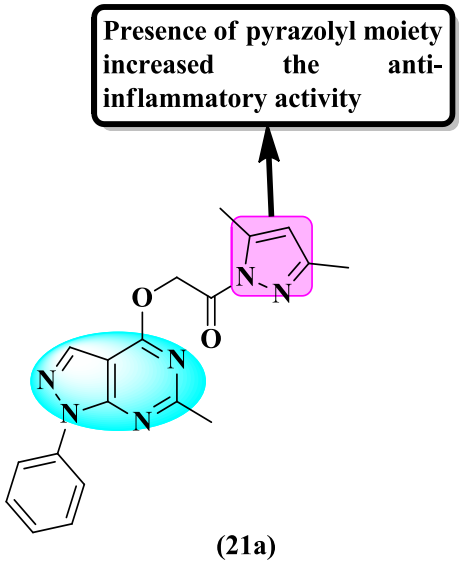

Fig. 24a. Structure and SAR of 1-(3,5-Dimethylpyrazol-1-yl)-2-(6-methyl-1-phenyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-yloxy)-ethanone.

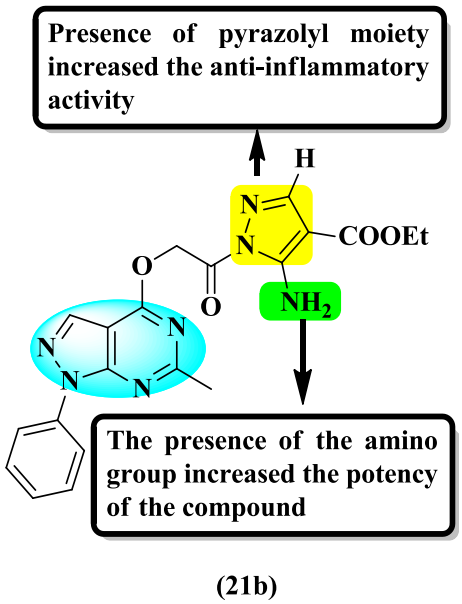

Fig. 24b. Structure and SAR of Ethyl 5-amino-1-[2-(6-methyl-1-phenyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-yloxy)acetyl]-1H-pyrazole-4-carboxylate.

S.I. = 326.67) and was more potent than Indomethacin (IC_{50} = 0.080 μM and S.I. = 1.25). Sub acute anti-inflammatory activity was calculated using formalin induced paw edema bioassay where **"26"** showed promising results (Edema inhibition% = 42%) similar to Diclofenac sodium (Edema inhibition% = 42%) and Celecoxib (Edema inhibition% = 51%). The potent compounds were checked for ulcerogenecity where **"26"** showed a high safety margin (10% ulceration) (Fig. 29).

Ren et al. [115] reported a new series of ferocene-pyrazole derivatives as inhibitors of COX-2 enzyme that were also evaluated biologically for their use in cancer therapy. *In-vitro* evaluation for COX-2 inhibition revealed that **"27"** was the most potent compound with IC_{50} = 0.28 μM and S.I. = 142.96 and was even more potent than Celecoxib as reference drug with COX-2 IC_{50} = 0.38 μM and S.I. = 97.29. Compound **"27"** possessed anti-tumor activity when tested against HeLa cell line where it was observed that apoptosis (percentage of apoptotic cells after 36 h = 78.10%) led to a suppression

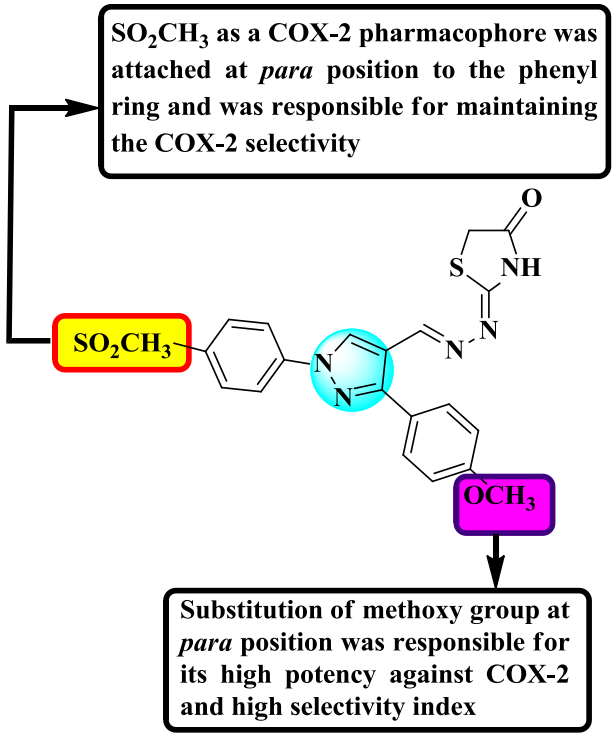

Fig. 25. Structure and SAR of (E)-2-((E)-((3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)methylene)-hydrazono)thiazolidin-4-one.

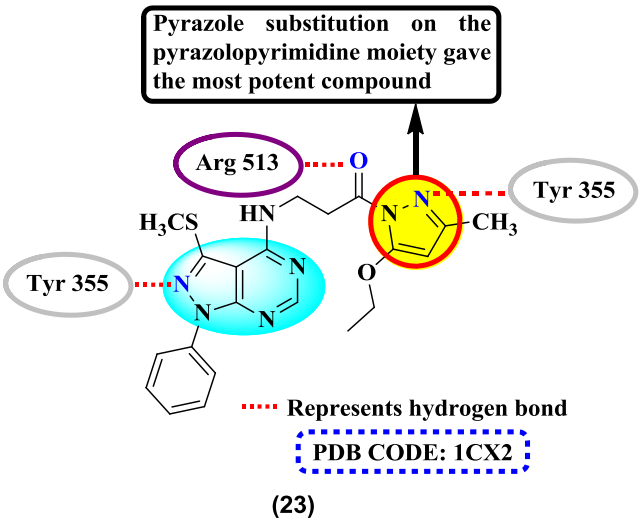

Fig. 26. Structure, SAR and Molecular docking of 1-(5-Ethoxy-3-methyl-1H-pyrazol-1-yl)-2-[3-methythio-1-phenyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-ylamino]ethanone.

in the growth of HeLa cells. The anti-cancer activity was directly correlated with NO release by the selected compound (Fig. 30).

Inceler et al. [116] reported novel pyrazole derivatives possessing two aryl rings and assessed *in-vitro* for COX-2 inhibition where compound **"28"** appeared most potent inhibitor with 66.27% COX-2 inhibition as compared to Indomethacin with 84.27% inhibition as the standard drug. Inhibition of platelet aggregation using arachidonic acid and collagen protein was also studied for the series where the most potent COX-2 inhibitor showed 90.69% and 78.66% inhibition respectively. Combined inhibition of COX-2 enzyme and platelet

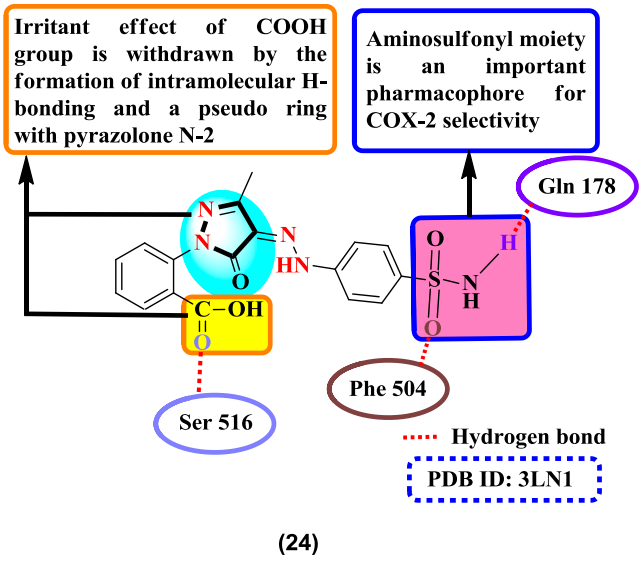

Fig. 27. Structure, SAR and Molecular docking of 2-[3-methyl-5-oxo-4-[2-(4-sulfamoylphenyl)hydrazin-1-ylidene]-4,5-dihydro-1H-pyrazol-1-yl]benzoic acid.

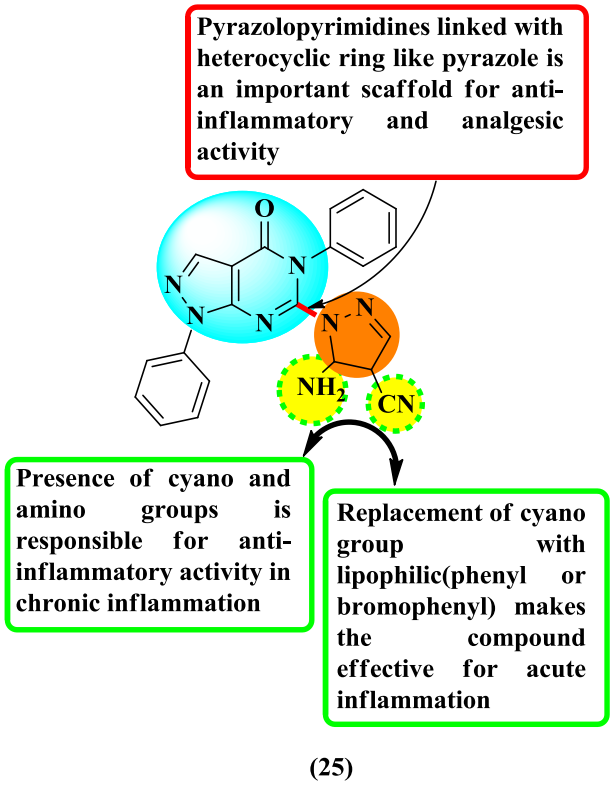

Fig. 28. Structure, SAR and Molecular docking of 5-Amino-1-(4-oxo-1,5-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)-1H-pyrazole-4-carbonitrile.

aggregation was correlated with the activity against Huh7, MCF7 and HCT116 cancer cell lines where **"28"** showed a good activity against MCF7 cell line (IC_{50} = 14.3 μM) (Fig. 31)

Mohamed et al. [117] synthesized novel pyrazoles and pyrazolo [3,4-*b*] pyridines and evaluated *in vitro* for COX-2 inhibition and *in vivo* for anti-inflammatory activity. *In vitro* tests revealed that compound "**29**" (COX-2 IC_{50} = 0.048 μM S.I. = 258.33) was more potent than reference compound celecoxib (COX-2 IC_{50} = 0.049 μM S.I. = 308.163). *In vivo* tests also gave promising results with a

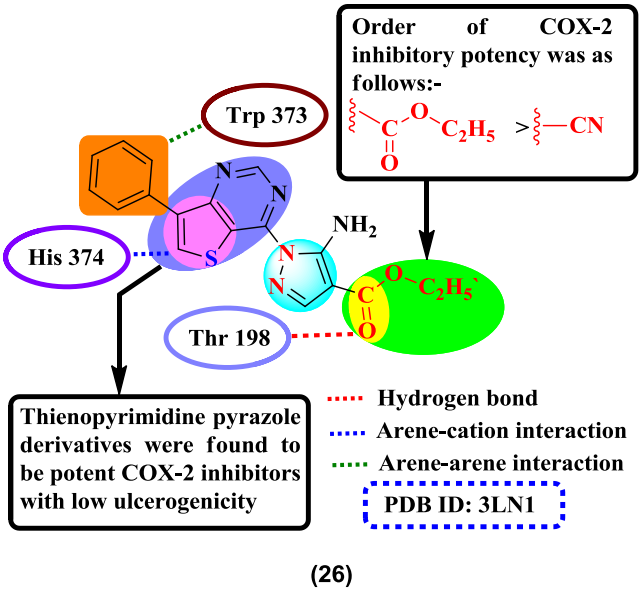

Fig. 29. Structure, SAR and Molecular docking of Ethyl-5-amino-1-(7-phenylthieno[3,2-*d*]pyrimidin-4-yl)-1H-pyrazole-4-carboxylate.

percentage protection of 64% from paw edema as compared to 69% for celecoxib and 70% for indomethacin. Ulcerogenic tests were also performed in which compound "**29**" (%ulceration = 20%) was found less safe than celecoxib (%ulceration = 10%) but safer than indomethacin (%ulceration = 100%). From the tests, it is observed that pyrazole ring derivatives were more potent than the pyrazolo[3,4-*b*] pyridine derivatives and bulkier compounds showed higher activity due to better fit in the selectivity pocket of COX-2 (Fig. 32).

Da Silva et al. [118] designed and synthesized compound "**30**" by molecular hybridization of paracetamol and celecoxib. *In-vitro* assay of COX-2 exhibited an IC_{50} of 5.8 μM and S.I. for COX-2 was observed to be 341.7. Inhibition of 5-LOX enzyme was also seen (IC_{50} = 91.6 μM). Anti-inflammatory evaluation using carrageenan induced paw edema method showed a reduction in edema by 35.1% as compared to celecoxib (30.7%) in the 4th hour. On treatment with repeated doses, chronic anti-inflammatory activity was observed to be 66.6% reduction in ear edema induced by croton oil for compound Lqfm-102. For Paracetamol, it was 39.6% and 53.4% for celecoxib. (Fig. 33).

Hassan et al. [119] synthesized novel pyrazole derivatives and assessed for COX-1 and COX-2 inhibition anti-inflammatory activity. Compound "**31**" exhibited highest S.I. of 22.21 and an IC_{50} of 39.43 ± 1.13 nM against COX-2 which was comparable to Celecoxib used as positive control (COX-2 IC_{50} = 35.56 ± 1.02 nM SI: 3.71). In the *in-vivo* paw edema assay, "**31**" showed highest inhibitory percentage at 27.51% after 2 h while Celecoxib displayed 8.99% inhibition in the same time. Plasma PGE_2 levels in rats were also determined. "**31**" showed 76.17% inhibition which was the highest while Celecoxib showed 69.61% inhibition. Replacement with propionamide morpholine derivative with chloroethyl group led to decrease in selectivity but increase in potency of compound (Fig. 34).

3. Indole as a COX 2 inhibitor

Indole is a bicyclic assembly comprising of a benzene ring fused to a pyrrole ring. Indomethacin is a potent non-steroidal indole derative that selectively inhibits cyclooxygenase-2. It is prescribed in moderate to severe rheumatoid arthritis. Acemetacin is a carboxymethyl ester of indomethacin. It has a better gastric tolerability than Indomethacin which is its active metabolite. Lenalidomide is a thalidomide derative possessing indole moiety. It is an immunomodulatory and anti-neoplastic activity. Lenalidomide inhibits COX-2 expression but not

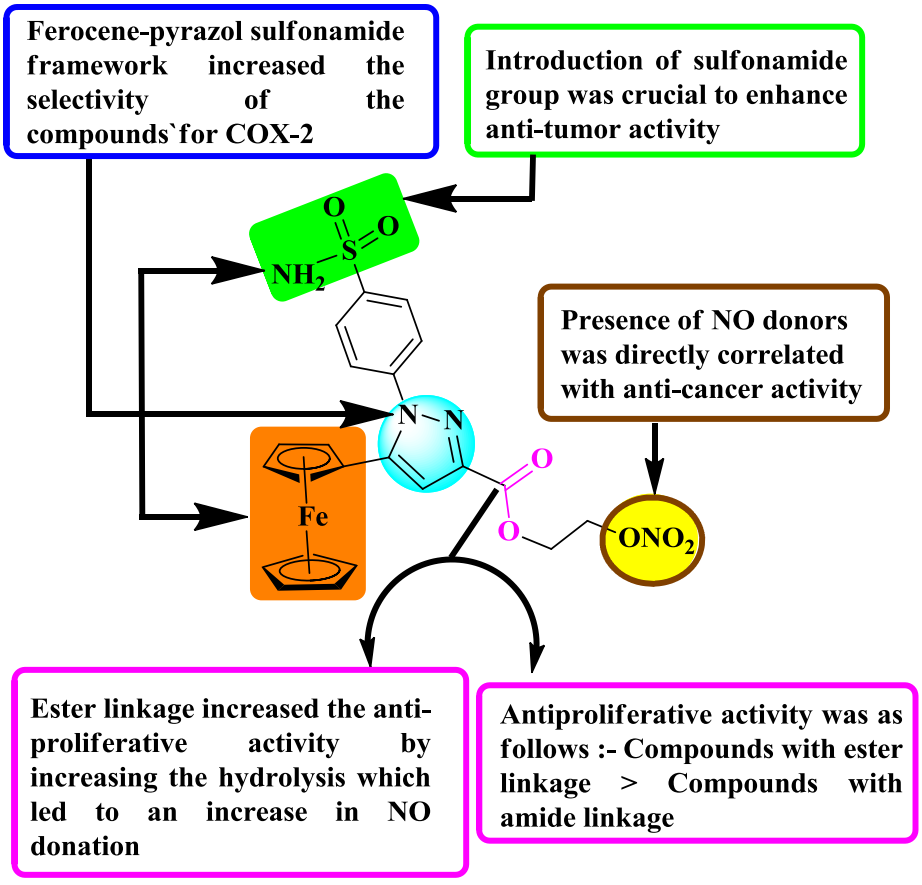

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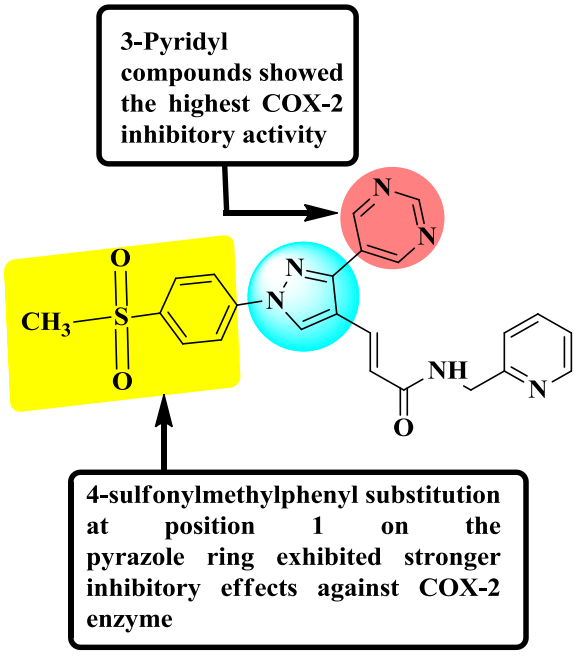
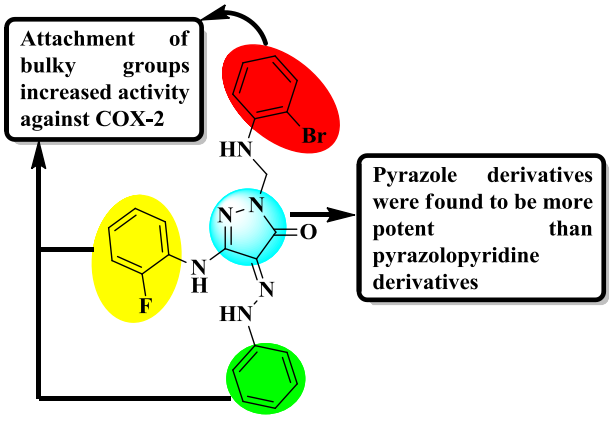
Fig. 30. Structure and SAR of the most potent compound of the series of ferocene-pyrazole derivatives.



(28)

Fig. 31. Structure and SAR of (2E)-3-[1-(4-Methanesulfonylphenyl)-3-(pyridin-3-yl)-1Hpyrazol-4-yl]-N-(2-pyridin-2-ylethyl)acrylamide.



(29)

Fig. 32. Structure and SAR and 4-(2-(2-Bromophenyl)hydrazono)-3-((2-fluorophenyl)amino) −1-((phenylamino)methyl)-1H-pyrazol-5(4H)-one.

COX-1. Etodolac is a pyranocarboxylic acid possessing indole moiety. It inhibits the synthesis of prostaglandins and is used in the treatment of osteoarthritis (Table 2). Synthetic procedures for indole synthesis are mentioned in Fig. 35 and patents on indole are mentioned in Table 4.

Fischer indole synthesis is the most commonly used synthesis which was first given by Emil Fishcher. Here, phenylhydrazine reacts with aldehyde or ketone under acidic condition leading to the synthesis of substituted indole [120].

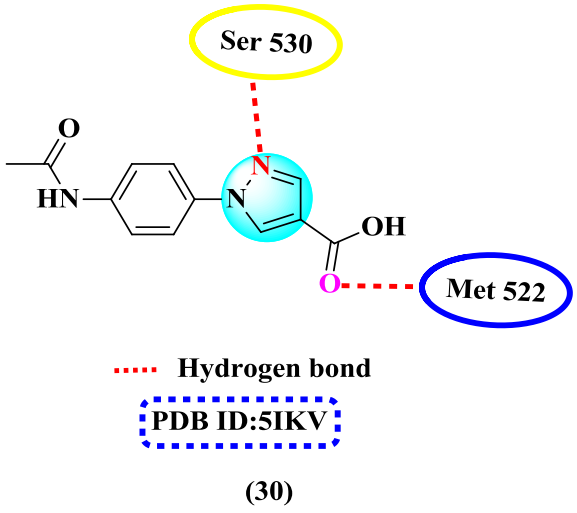


Fig. 33. Structure and Molecular docking of 1-(4-acetamidophenyl)-1H- pyrazole-4-carboxylic acid.

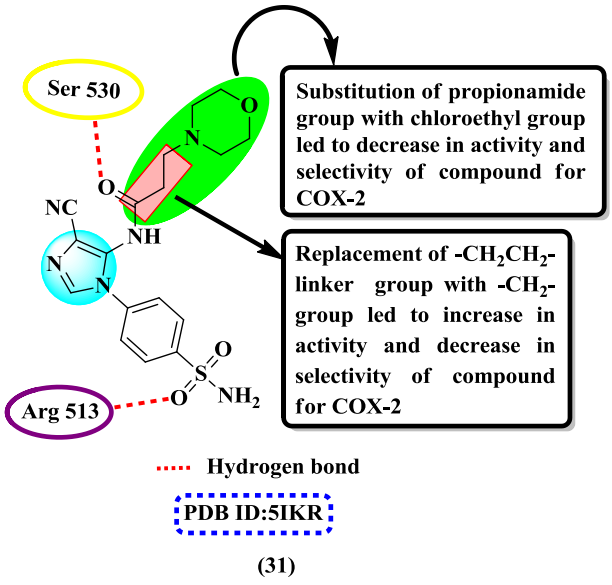


Fig. 34. Structure, SAR and Molecular docking of N-[4-Cyano-1-(4-sulfamoyl-phenyl)-1H-pyrazol-5-yl]-3-morpholino-propionamide.

Fukuyama indole synthesis involves formation of 2,3-disubstituted indoles by radical cyclization of *ortho*-isocyanostyrene using tributyltin hydride as the reducing agent [121].

In Bischler–Möhlau indole synthesis, α -bromo-acetophenone and aniline in excess react to form a 2-aryl-indole [122].

In Leimgruber–Batcho indole synthesis, indoles are produced by reductive cyclisation of o-nitrotoluenes, N,N-dimethylformamide dimethyl acetal and pyrrolidine [123].

5-hydroxyindole derivatives are produced from benzoquinone and β-aminocrotonic esters during Nenitzescu indole synthesis [124].

In Baeyer–Emmerling indole synthesis, indole is synthesized from *ortho*-nitrocinnamic acid using iron powder under strongly alkaline conditions [125].

In Madelung synthesis, intramolecular cyclization of *N*-phenylamides is performed in strong base at high temperature conditions in order to synthesize substituted indoles [126].

Gassman indole synthesis involves addition of an aniline and a ketone finally leading to substituted indoles formation [127].

During Bartoli indole synthesis, substituted indoles are formed by vinyl Grignard reagents reaction with *ortho*-substituted nitroarenes [128].

Hemetsberger indole synthesis involves thermal decomposition of 3-aryl-2-azido-propenoic ester leading to the synthesis of indole-2-carboxylic ester [129].

Larock indole synthesis involves heteroannulation reaction during which indoles are synthesized from *ortho*-iodoaniline and a disubstituted alkyne. The reaction is catalysed with the help of palladium [130].

Lamie et al. [143] reported *N*-substituted indole derivatives and evaluated to determine *in vitro* anti-inflammatory potency. Compound **"32"** appeared as most potential member of the series to inhibit COX-2 with IC_{50} = 0.98 μM and selectivity index equal to 8.05 against celecoxib (IC_{50} = 1.54 μM, SI = 7.16) (Fig. 36).

Kaur et al. [144] synthesized N-1 and C-3 disubstituted-indole Schiff bases bearing an indole N-1 (R′ = H, CH_2Ph, COPh) substituent in combination with a C-3–CH = N–C_6H_4–4-X (X = F, Me, CF3, Cl) substituent and assesed them as cyclooxygenase inhibitors (COX-1/COX-2). Compound **"33"** appeared as the most powerful (COX-2 IC_{50} = 0.32 μM) and selective (SI > 312) inhibitor of COX-2 against indomethacin (COX-2 IC_{50} = 6.9 μM, SI = 0.02) (Fig. 37).

Singh et al. [145] synthesized a series of indoles possessing a tosyl (toluene-4-sulfonyl) radical at the N-1 position and a dipeptide group at the C-3 position. These compounds were then screened for their anti-inflammatory and anti-hyperalgesic activities using Swiss albino mice. Compounds **"34"** appeared as most potential derivative when evaluated for its anti-inflammatory activity (IC_{50} = 0.0063 μM; Selectivity index = 351) using the standard drug diclofenac (IC_{50} = 0.63 μM, SI = ~1). The IC_{50} of **"34"** was much better than other drugs available in the market including wogonin (IC_{50} = 40 μM), indomethacin (IC_{50} = 0.96 μM, SI = 0.08), celecoxib (IC_{50} = 0.04 μM, SI = 0.08), and SC-558(IC_{50} = 0.05, SI = > 200). The anti-inflammatory activity of **"34"** (47% reduction in paw thickness after a dose of 5 mg/Kg) was similar to diclofenac (42% reduction in paw thickness after a dose of 10 mg/Kg). Compounds **"34"** also showed a remarkable anti-hyperalgesic effect (96% reduction in paw lickings) against diclofenac (90% reduction in paw lickings). The presence of Gly-Trp dipeptides and a combination of these amino acids at the C-3 substituent as well as tosyl group at the N position led to an increase in the COX-2 inhibitory and anti-inflammatory activity. Molecular docking was also performed which showed that S- configuration at the Cα position of amino acids increased the interactions with COX-2 active site. No toxicity was observed in the animals during the study and thus compound **"34"** was identified as a promising lead for anti-inflammatory drugs (Fig. 38).

Kassab et al. [146] designed new analogs of indomethacin that had an improved selectivity against the COX-2 enzyme. A number of methods were adopted to decrease the interaction between the molecule and COX-1 enzyme and thereby increasing the selectivity towards the COX-2 enzyme. Ring extension of indomethacin was carried out resulting in a reduction of the interaction between the molecule and the narrow hydrophobic tunnel of the COX-1 enzyme. Carboxylic groups were removed in order to prevent COX-1 inhibition. Methyl sulfonyl groups increased the COX-2 inhibition by facilitating the interaction of the molecule with the polar side pockets. Three novel series of tetrahydrocarbazoles were synthesized out of which **"35"** was found to be a more potent and selective compound (IC_{50} = 0.23 μM, SI = 452) as compared to Celecoxib (IC_{50} = 0.3 μM, SI = 333) and Indomethacin (IC_{50} = 2.63 μM, SI = 0.098). The anti-inflammatory action of **"35"** was assessed through *in-vivo* Carrageenan-induced rat paw edema bioassay and it was found to be very potent (%protection = 88%, ED_{50} = 12.4 μM) as compared to the reference drugs Celecoxib (% protection = 96.7%, ED_{50} = 86.1 μM) and Indomethacin (%protection = 74.5%, ED_{50} = 9.5 μM). Molecular docking was performed that revealed a similar docking score to the reference drugs, minimal gastric irritation, and significantly lesser ulcerogenic activity. Thus, the newly synthesized compounds could be developed as potential selective COX-2 inhibitors beyond the commonly used diarylsulfonamides (Fig. 39).

Bhat et al. [147] synthesized 2-(5-methoxy-2-methyl-1H-indol-3-

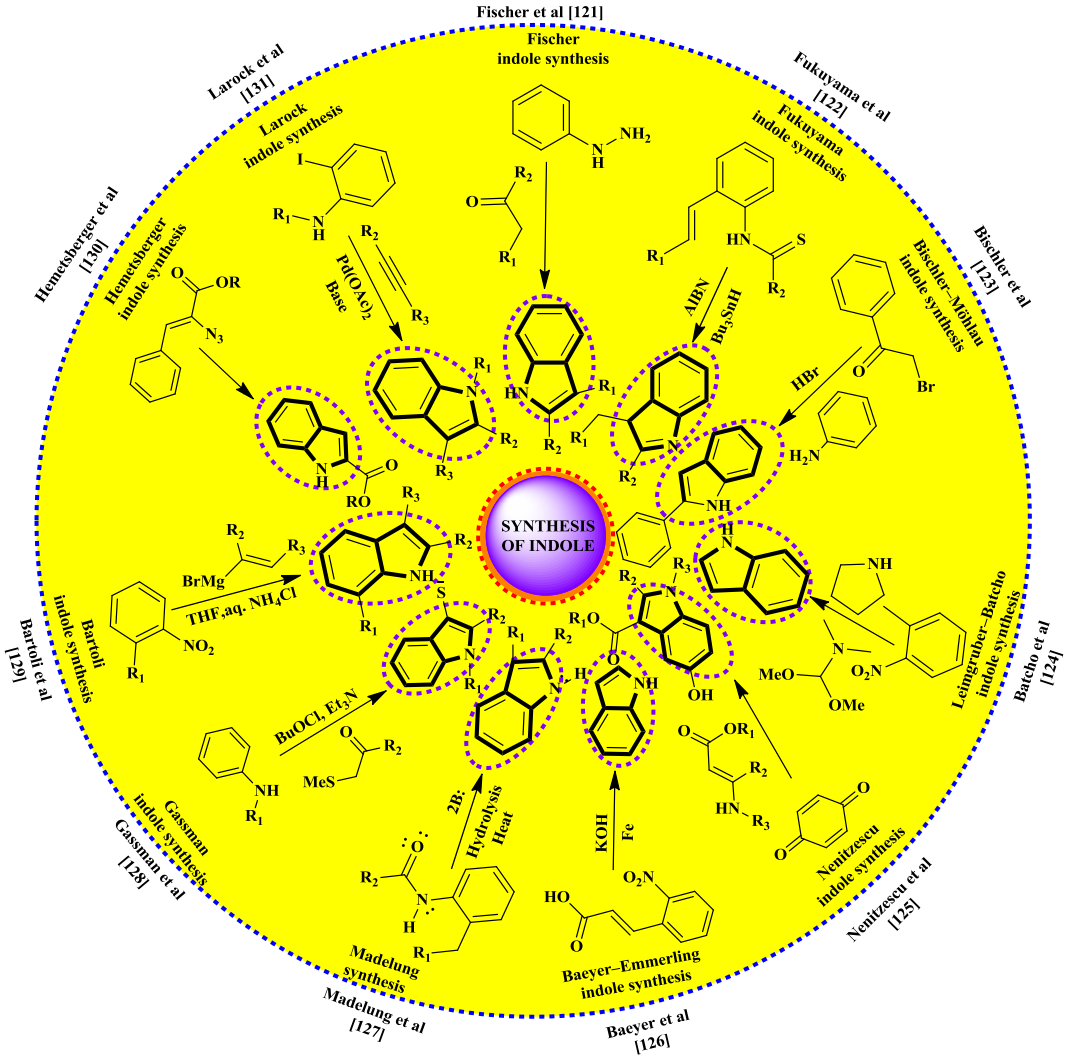


Fig. 35. Synthesis of indole.

yl)-N0-[(E)-(substituted phenyl)methylidene] acetohydrazide derivatives and evaluate their anti-inflammatory and analgesic activity. Compound **"36"** was the most potent compound with significant analgesic and anti-inflammatory activity along with a good COX-2 selectivity which showed 62% inhibition of inflammation (using rat paw edema method) as compared to 77% by indomethacin. The analgesic activity was evaluated using the hot plate method in which **"36"** expressed 61.3% inhibition as compared to indomethacin with 84%inhibition. **"36"** also showed a significant gastric sparing activity which was evaluated by their ulcerogenicity and lipid peroxidation activity. **"36"** showed the ulcerogenic index of 0.116 as compared to 0.948 for indomethacin. Karber method was used to calculate LD_{50} where it was found that **"36"** showed a very low toxicity (Fig. 40).

Estevao et al. [148] reported new indolic compounds with two dissimilar substituent at indole scaffold and evaluated for COX-1 and COX-2 inhibition. Compound **"37"** was found to be potent at 50 μM with 67% COX-2 inhibition and 18% COX-1 inhibition (Fig. 41).

Abdellatif et al. [149] synthesized 3-methyl-2-phenyl-1-substituted-indole derivatives as analogs of indomethacin and evaluated for anti-inflammatory activity, analgesic activity and gastric irritancy. The aim was to retain the main scaffold of indomethacin in order to maintain the potency while modifying the side groups to enhance selective COX-2 inhibition. It was seen through *in vitro* COX inhibition assay that compound **"38"** was a potent COX-2 inhibitor (IC_{50} = 1.65 μM and S.I. = 25.65) than the standard drug indomethacin (COX-2 IC_{50} = 11.36 μM, S.I. = 0.055). It was 467 times more potent (%inhibition = 73.5% after 1 h) than indomethacin (%inhibition = 71.2% after 1 h) due to the presence of pharmacophore of COX-2 (methanesulfonyl moiety, SO_2Me) in addition to indomethacin as a chlorobenzoyl moiety. The anti-inflammatory potency was evaluated using carrageenan-induced rat paw edema assay and analgesic activity by using acetic acid-induced writhing test and results obtained were parallel to the anti-inflammatory activity (Fig. 42).

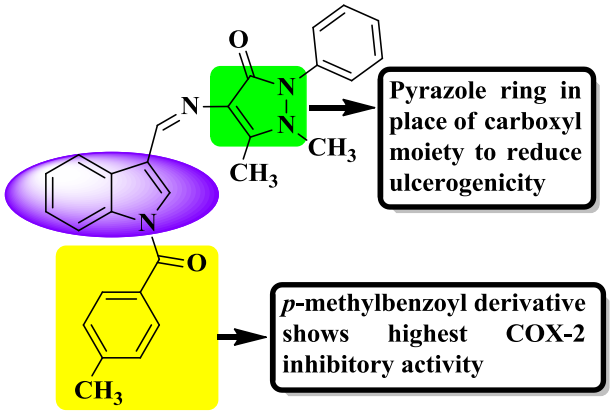
Ozdemir et al. [150] synthesized newer indole-centred chalcone derivatives and investigated for *in vitro* COX-1 and COX-2 inhibition. Compound **"39"** bearing 5-bromo-1H-indol-3-yl and 4-cyanophenyl moieties displayed COX-2 inhibition with an IC_{50} value of 9.5 ± 0.8 mg/mL against indomethacin (IC_{50} = 10.0 ± 4.2 mg/ml) (Fig. 43).

Shaveta et al. [151] screened chromone-indole and chromone-pyrazole conjugates for COX-2, COX-1 and 5-LOX inhibitory. Compound **"40"** was recognised as preferred COX-2 inhibitor with IC_{50} of 20 nM and selectivity index (SI) of 337 against celecoxib (IC_{50} = 40 nM and SI = 375). Compound **"40"** also exhibited analgesic potential comparable to diclofenac (Fig. 44).

Zarghi et al. [152] reported 5-substituted-2-(4-azido or (methylsulfonyl)phenyl)-1H-indoles and evaluated for *in vitro* COX-1/COX-2 inhibition using chemiluminescent enzyme assay. *In vitro* studies revealed that **"41"** was the most potential compound of the series (COX-2 IC_{50} = 0.08 μM, SI = > 291) while Celecoxib as the reference drug had

Table 4
Patents on Indole moiety relating to anti-inflammatory activity.

S. No.	Patent number	Patent date	Inventors	Description
1.	US6303628B1 [131]	16 October 2001	Kazunari Nakao, Shigeo Hayashi, Rodney W. Stevens	Bicycliccarbonyl indole compounds as anti-inflammatory/analgesic agents
2.	US6277878B1 [132]	21 August 2001	Kazunari Nakao, Rodney W. Stevens, Kiyoshi Kawamura, Chikara Uchida	Substituted indole compounds as anti-inflammatory and analgesic agents
3.	US6872744B2 [133]	29 March 2005	Chris Allen Broka, Jeffrey Allen Campbell	Indole derivatives as anti-inflammatory agents
4.	WO2000046195A1 [134]	10 August 2001	Alan Wellington Faull, Jason Kettle	Anti-inflammatory indole derivatives
5.	US6353007B1 [135]	05 March 2002	Rajiv Sharma	Substituted 1-(4-aminophenyl)indoles and their use as anti-inflammatory agents
6.	WO1994019343A2 [136]	01 September 1994	Oliver J. McConnell, Gabriel Saucy, Robert Jacobs	Novel use as anti-inflammatory agents for bis-heterocyclic compounds and pharmaceutical compositions thereof
7.	US5508026A [137]	16 April 1996	William H. Gerwick, Richard Castenholz, Ferran Garcia-Pichel, Philip J. Proteau	Indole alkaloids useful as UV protective and anti-inflammatory agents
8.	US5962498A [138]	05 October 1999	Paul E. Driedger, James Quick	Protein kinase C modulators. C. indolactam structural-types with anti-inflammatory activity
9.	US6300363B1 [139]	09 October 2001	Rodney William, Stevens Kasumari Nakao Kiyoshi Kawamura Chikara Uchida Shinya Fujiwara	Indole compounds as COX-2 inhibitors
10.	US5521171A [140]	28 May 1996	John R. J. Sorenson	Anti-inflammatory and anti-ulcer compounds and process.
11.	WO1998018466A2 [141]	07 May 1998	Robert S. Jacobs, Shirley Pomponi, Sarath Gunasekera, Amy Wright	Anti-neurogenic inflammatory compounds and compositions and methods of use thereof
12.	US7074939B2 [142]	11 July 2006	Chris Allen Broka, Jeffrey Allen Campbell	Indole derivatives as anti-inflammatory agents



(32)

Fig. 36. Structure and SAR of N-[(1-(p-Methylbenzoyl)-1H-indol-3yl)methylene)-4H-1,2,4-triazol-4-amine.

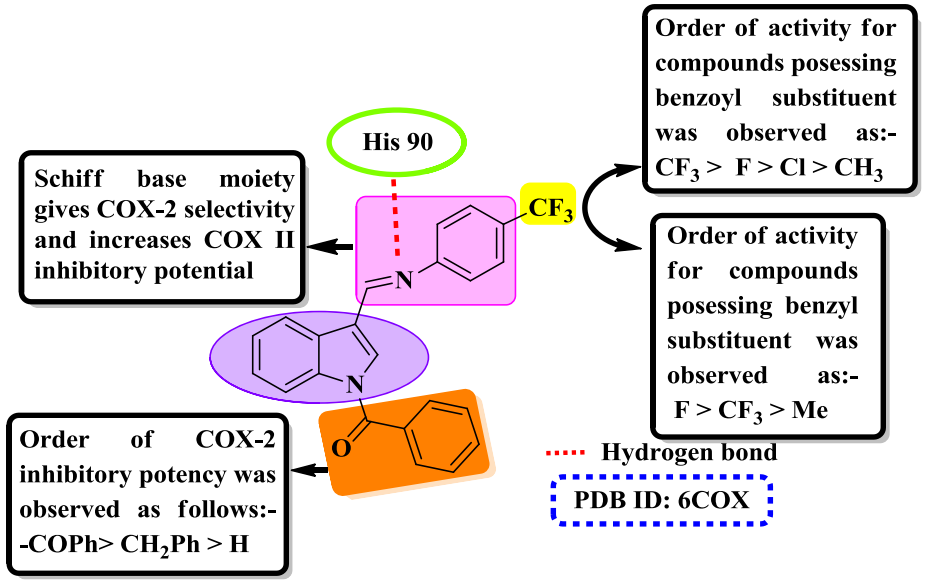
a COX-2 IC_{50} = 0.06 μM and SI = 405. It was observed that methylsulfonyl substituent binds with COX-2 by inserting into the subordinate pocket of the COX-2. O-atoms of *p*-SO_2Me further led to an increase in the potency by the help of H-bonding. The NH group of the central indole ring also increases the potency by forming H-bonds with the active site. The oxygen atom of the o-methyl group present in the active compound **"41"** further increased the COX-2 inhibitory activity by hydrogen bonding interaction (Fig. 45).

Labib et al. [153] synthesized isoindoline hybrids by substituting oxime, hydrazone, pyrazole, chalcone or aminosulfonyl and were evaluated using biological assays for its *in vitro* COX-1/COX-2 inhibition. Compound **"42"** was the most potent compound of the series (COX-2 IC_{50} = 0.11, selectivity index = 103) and found to be more potent than indomethacin (COX-2 IC_{50} = 0.51, selectivity index = 0.08), diclofenac sodium (COX-2 IC_{50} = 0.84 μM, selectivity index = 6.07) and had similar potency to celecoxib (COX-2 IC_{50} = 0.09 μM, selectivity index = 167.78). The standard method of formalin-induced rat paw edema model was used to evaluate the *in vivo* anti-inflammatory activity and the results obtained were consistent with the *in vitro* analysis. Compund **"42"** (% Edema inhibition = 59.30% after 3 h) was found more potent than diclofenac sodium (% Edema inhibition = 22.20% after 3 h). Compound **"42"** exhibited greater central analgesic activity (92.85% latency change) at 1 h and was more potent than piroxicam (75% latency change). Molecular docking studies were performed to evaluate the binding interactions of the potent compounds with the active site. The presence of methoxy substituents (hydrogen acceptors) potentiated the activity of **"42"** due to its similar activity to the aminosulfonyl moiety. Thus, molecular hybridization of chalcone pharmacophore was a useful technique to improve the COX-2 inhibitory potential with decreased side effects (Fig. 46).

Hayashi et al. [154] designed and synthesised {2-[(2-, 3- and/or 4-substituted)-benzoyl, (bicyclic heterocycloalkanophenyl) carbonyl or cycloalkanecarbonyl]-(5- or 6-substituted)-1H-indol-3-yl}acetic acid analogues and examined to recognise several chemotypes of selective and potential COX-2 inhibitors using peripheral-inflammation model rats. In the *in vitro human* cell-based COX-2 assay, compound **"43"** showed lowest IC_{50} of 0.01569 μM and high selectivity (SI = 509). It was observed in SAR studies that the relatively electronegative groups showed higher potency and selectivity like 6-fluoro analogue **"43"**. Replacement with electron-releasing and/or bulkier groups resulted in reduced potency (Fig. 47).

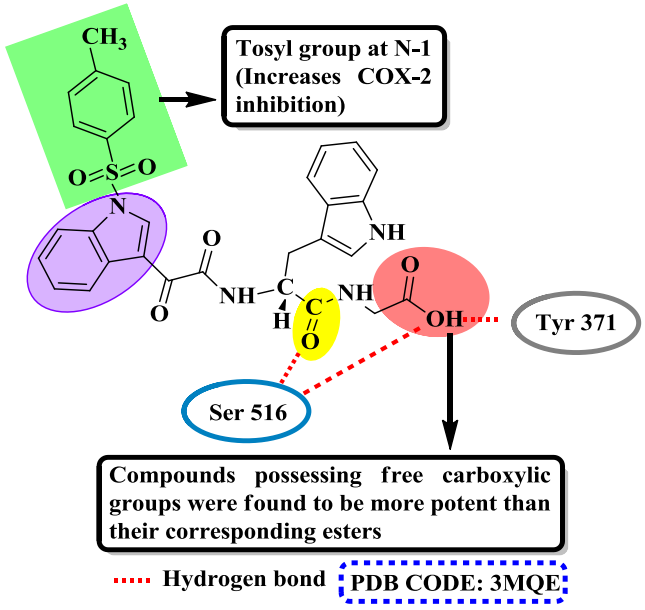
Hayashi et al. [155] reported [2-{[(4-substituted or 4,5-disubstituted)-pyridin-2-yl]carbonyl}-(5- or 6-substituted or 5,6-disubstituted)-1H-indol-3-yl]acetic acids and evaluated for *in vitro* COX-2 inhibition and carrageenan-induced oedema *in vivo*. Compound **"44"** appeared as an effective and selective COX-2 inhibitor (IC_{50} = 9.81 nM SI = 33.5). While studying SAR, fluoro group showed maximum potency at 5- and 6- position of indole core. This revealed that electron-withdrawing/attracting groups were preferred over electron-donating/releasing/electron-rich (Fig. 48).

Lai et al. [156] synthesized newer 3-[4-(amino/methylsulfonyl) phenyl]methylene-indolin-2-one derivatives and evaluated for COX-1/2 and 5-LOX inhibition. Compound **"45"** displayed excellent inhibition with IC_{50} = 0.10–0.56 μM and 29.41% inhibition after 6 h in paw volume of rat showed similar or higher anti-inflammatory and analgesic



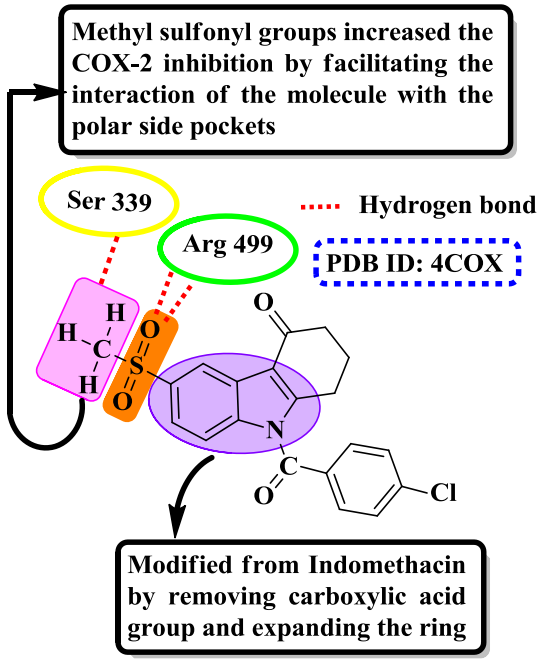
(33)

Fig. 37. Structure, SAR and molecular modeling of 1-benzoyl-3-[(4-trifluoromethylphenyl imino)methyl]indole.



(34)

Fig. 38. Structure, SAR and molecular modeling of 3-(1*H*-indol-2-yl)-2-(2-{2-oxo-2-[1-(tolu ene-4-sulfonyl)-1*H*-indol-3-yl]-acetylamino}-acetylamino)-propionic acid.



(35)

Fig. 39. Structure, SAR and molecular modeling of 9-(4-chlorobenzoyl)-6-(methylsulfonyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one.

activities followed by enhanced gastric tolerability *in vivo* when compared with standard drugs darbufelonemesilate (17.65%) and tenidap sodium (19.61%). Structure–activity relationship (SAR) studies discovered that compounds equipped with methylsulfonyl groupo resulted in greater inhibition (COX-1/2 and 5-LOX) than corresponding sulfamoyl analogs (Fig. 49).

Kaur et al. [157] reported a series of hybrid compounds by the combination of different heterocyclic moieties like piperidine, pyrrolidine, pyrazole, morpholine and oxindole. *In-vitro* evaluation against COX-1 and COX-2 revealed that compound **"46"** was the most potent with IC_{50} for COX-2 = 0.02 μM and S.I. = 150 and was found to be more potent than the standard drugs Diclofenac (IC_{50} for COX-2 = 0.02 μM and S.I. = 3.5), Celecoxib (IC_{50} for COX-2 = 0.04 μM and S.I. = 375) and Indomethacin (IC_{50} for COX-2 = 0.96 μM and S.I. = 0.08). *In-vivo* studies were performed using carrageenan induced rat paw edema model and formalin-induced analgesia to evaluate anti-inflammatory and analgesic activity respectively. Compound **"46"** decreased the paw thickness by 18% after 30 min with significant analgesic effect (%inhibition of analgesia = 68.24%) as compared to Indomethacin that decreased it by 30% after 30 min. Toxicity studies revealed that compound **"46"** showed absence of any significant lesions even after the animals were given a high dose of 2000 mg/kg. Further, the compounds were subjected to molecular docking where **"46"**

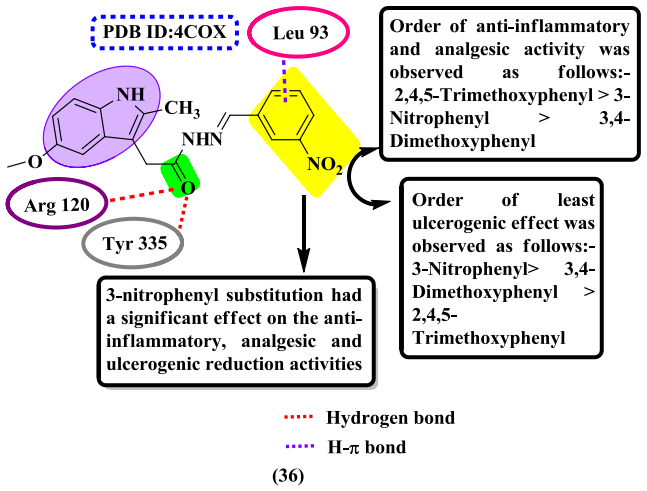


Fig. 40. Structure, SAR and molecular docking of 2-(5-Methoxy-2-methyl-1H-indol-3-yl)-N0-[(E)-(3-nitrophenyl)methylidene]acetohydrazide.

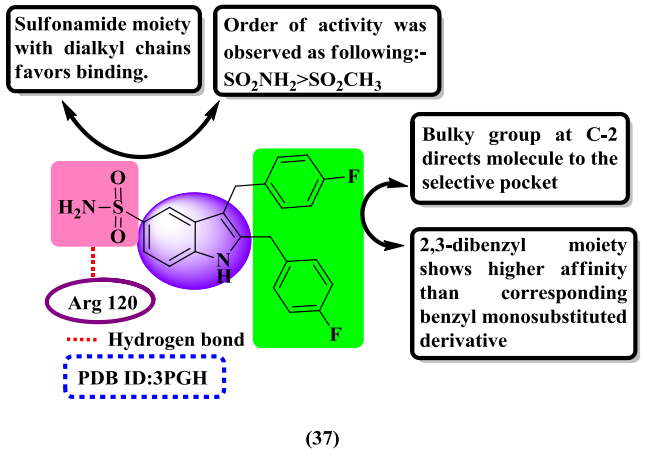


Fig. 41. Structure, SAR and Molecular docking of 2,3-Bis(4-fluorobenzyl)-1H-indole-5-sulfonamide.

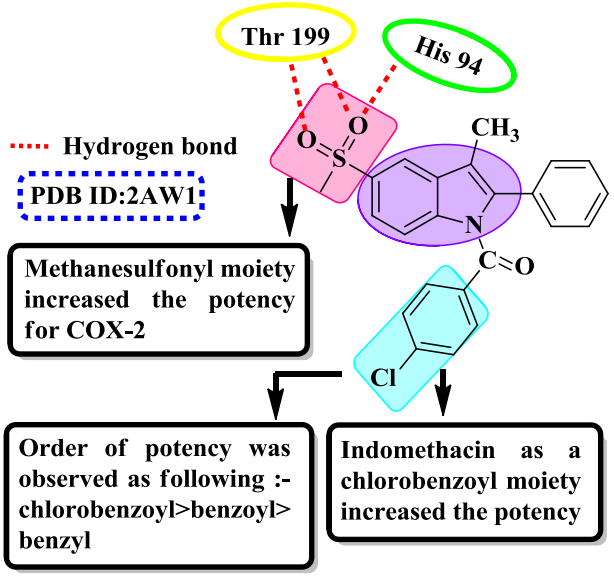


Fig. 42. Structure, SAR and molecular docking of (4-Chlorophenyl)-(5-methanesulfonyl-3-methyl-2-phenyl-indol-1-yl)-methanone.

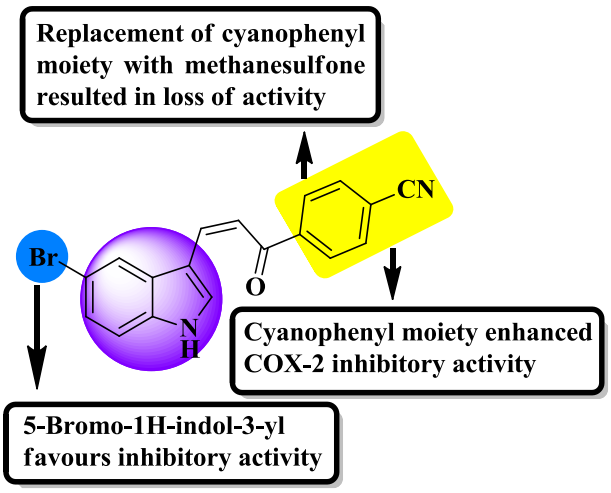


Fig. 43. Structure and SAR of 3-(5-Bromo-1H-indol-3-yl)-1-(4-cyanophenyl) prop-2-en-1-one.

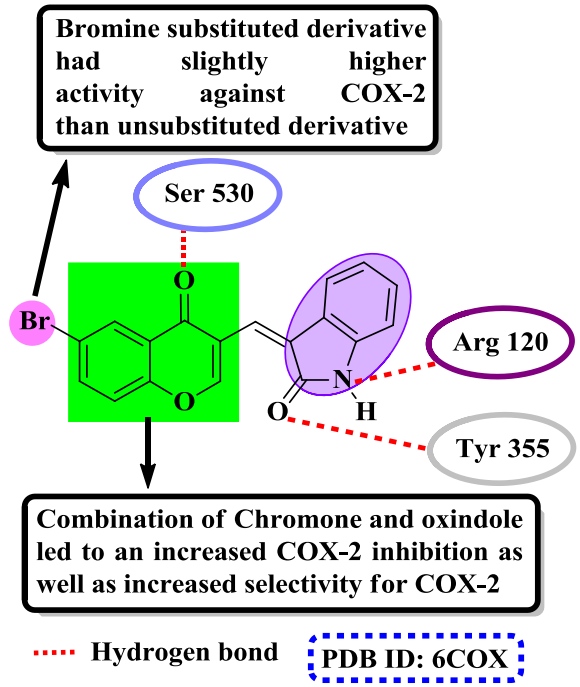
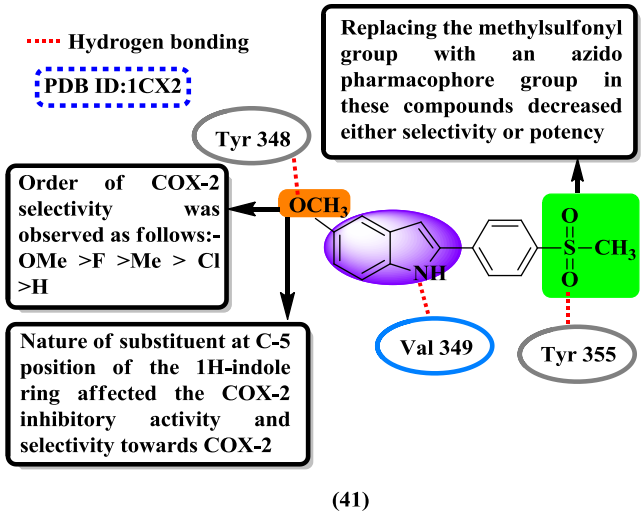


Fig. 44. Structure, SAR and molecular docking of 3-(4-Oxo-4H-chromen-3-yl-methylene)-1,3-dihydroindol-2-one.

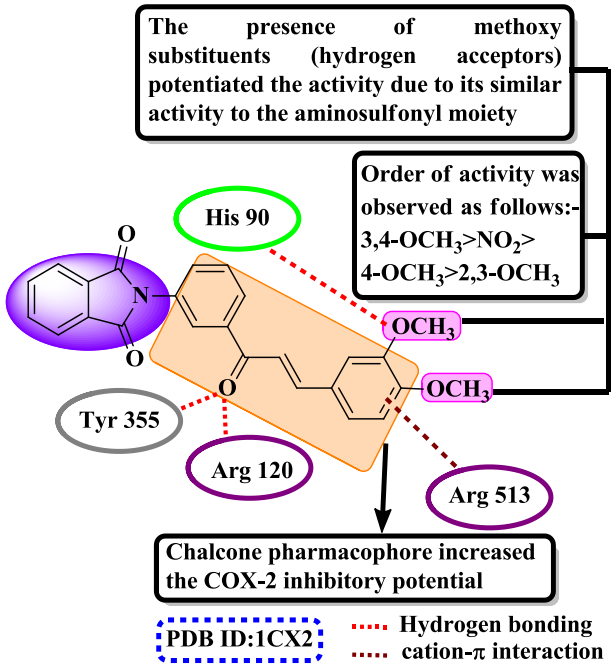
showed significant binding with COX-2 with the help of H-bonding, π-π and cation-π interactions (Fig. 50).

Amin et al. [158] reported indole derivatives and assessed for COX-2 inhibitory activity by *in-vivo* evaluation followed by biological assay to determine *in-vivo* anti-inflammatory activity. *In-vitro* assesment revealed that compound **"47"** (COX-2 IC_{50} = 0.14 μM and S.I. = 65.71) was more potent than Indomethacin (COX-2 IC_{50} = 0.49 μM and S.I. = 0.079) and had comparable potency to Celecoxib (COX-2 IC_{50} = 0.08 μM and S.I. = 157.5). Rat paw edema model showed that **"47"** (%AI = 90.5% after 3 h) was a potent compound comparable to Indomethacin (%AI = 86.7% after 3 h). A significant reduction in ulcerogenicity was observed for **"47"** (Ulcer Index = 7.30) in comparison with Indomethacin (Ulcer Index = 20.20). Further, molecular docking



(41)

Fig. 45. Structure, SAR and molecular docking of 5-Methoxy-2-[4-(methylsulfonyl)phenyl]-1H-indole.

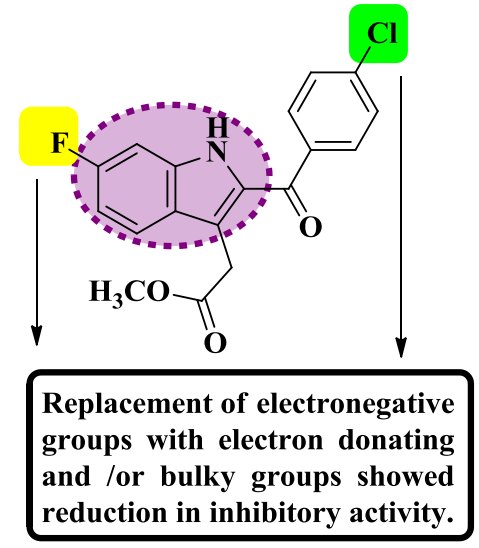


(42)

Fig. 46. Structure, SAR and molecular docking of (E)-2-{3-[3-(3,4-Dimethoxyphenyl) acryloyl]phenyl}isoindoline-1,3-dione.

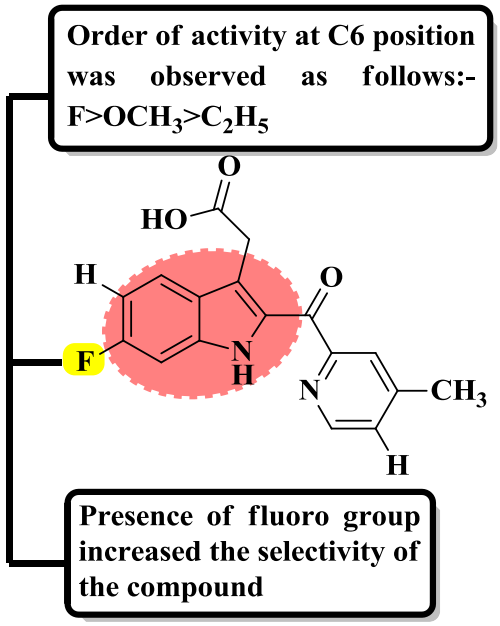
was done which showed significant hydrophobic bonding with the help of methylsulfone, fluorophenyl moiety and phenyl ring with side pockets and amino acids in the active site (Fig. 51).

Shrivastava et al. [159] reported novel indolizine derivatives by altering imidazopyridine that were proposed to be COX-2 and LOX dual inhibitors. *In-vitro* evaluation showed that compound **"48"** was most potent compound of the series with COX-2 IC_{50} = 14.91 μM (IC_{50} values for standard drugs, Celecoxib = 0.87 μM and for diclofenac sodium = 0.05 μM). *In-vivo* anti-inflammatory evaluation showed that **"48"** had a comparable mean protection (90.5% after 4 h) to diclofenac sodium (91.6% after 4 h). Compound **"48"** was found a lot safer (ulcer index = 10) in comparison with standard drugs Celecoxib (ulcer index = 53) and Diclofenac (ulcer index = 46). Molecular docking of **"48"** suggested its similarity to the Celecoxib with respect to the



(43)

Fig. 47. Structure and SAR of 2-(4-chlorobenzoyl)-(6-fluoro)-1H-indol-3-yl] acetic acid.

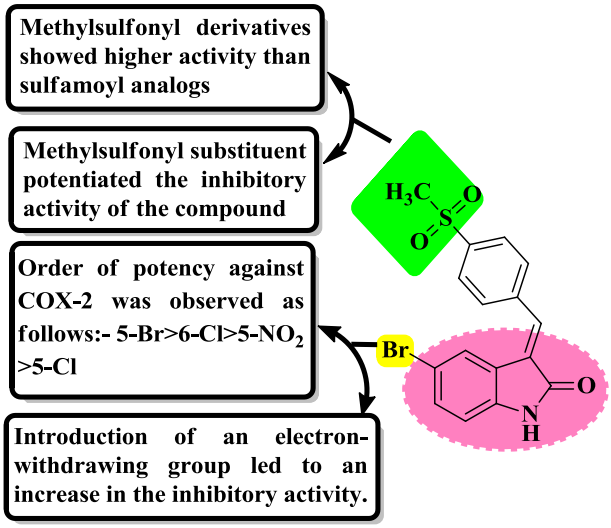


(44)

Fig. 48. Structure and SAR of 2-{6-fluoro-2-[(4-methyl-2-pridinyl)carbonyl]-1H-indol-3-yl}acetic acid.

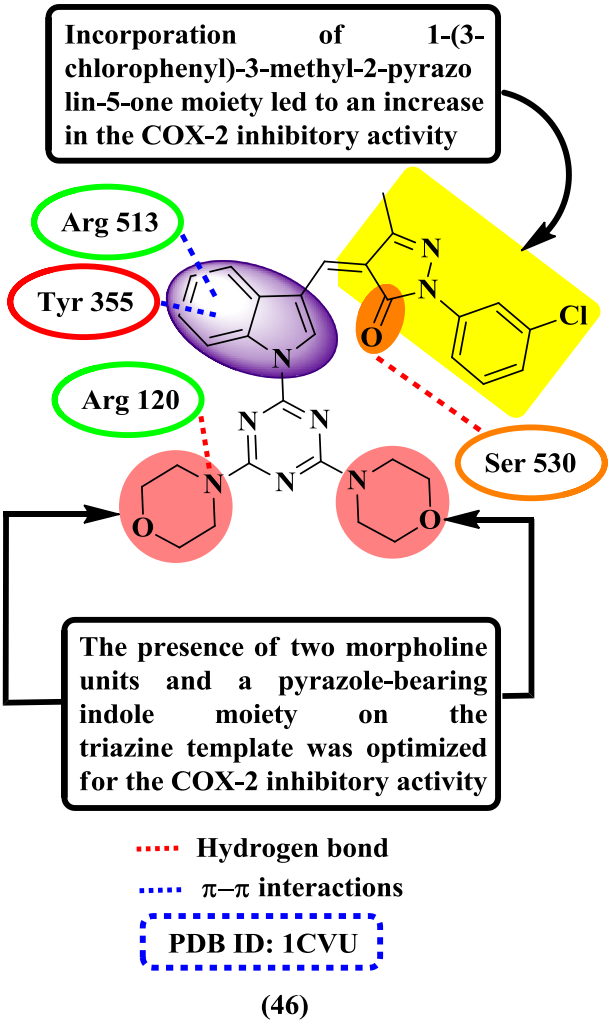
binding pose on COX-2 (Fig. 52).

Naaz et al. [160] reported two novel series of Indole-3-glyoxamide derivatives containing 1,2,3-triazole ring and tested for *in-vitro* evaluation of COX-1, COX-2 and 5-LOX inhibition and *in-vivo* anti-proliferative activity. *In-vitro* evaluation revealed that compound **"49"** appeared most potent compound (COX-2 IC_{50} = 0.12 μM and S.I.(COX-2/COX-1) = 0.058) with comparable COX-2 inhibition to reference drugs Celecoxib (COX-2 IC_{50} = 0.041 μM and S.I.(COX-2/COX-1) = 0.0027) and Indomethacin (COX-2 IC_{50} = 0.049 μM and S.I.(COX-2/COX-1) = 7.2). Through carrageenan induced rat paw edema model, compound **"49"** with %inhibition = 82.80% was found to be more potent than Indomethacin with %inhibition = 77.94% (evaluated after 5 h). Compound **"49"** also showed remarkable activity against DU145



(45)

Fig. 49. Structure and SAR of the most potent compound of the novel series of 3-[4-(amino/methylsulfonyl)phenyl]methylene-indolin-2-one derivatives.



(46)

Fig. 50. Structure, SAR and Molecular docking of (4Z)-1-(3-Chlorophenyl)-3-methyl-4-((1-(4,6-dimorpholino-1,3,5-triazin-2-yl)-1H-indol-3-yl)methylene)-1Hpyrazol-5(4H)-one.

(IC_{50} = 8.17 μM). Molecular docking studies were also carried out for the synthesized compounds where **"49"**showed similar binding patterns as that of the standard drug celecoxib (Fig. 53).

Blobaum et al. [161], in an effort to improve the selectivity of indomethacin while retaining its potency, synthesized trifluoromethyl analogue of indomethacin by substituting the methyl group at position-2 with trifluoromethyl group. *In-vitro* studies revealed that compound **"50"** became a lot more COX-2 selective by the substitution of methyl group with trifluoromethyl group while retaining its inhibitory potential towards COX-2 (COX-2 IC_{50} = 267 nM and COX-1 IC_{50} = > 100 μM) as compared to indomethacin (COX-2 IC_{50} = 127 nM and COX-1 IC_{50} = 27 nM). *In-vivo* anti-inflammatory results revealed that CF_3 analogue of indomethacin (ED_{50} = 1.7 mg/kg) showed comparable results to indomethacin (ED_{50} = 1.0 mg/kg) (Fig. 54).

Moraes et al. [162] synthesized 10 novel compounds as indole-*N*-acylhydrazone derivatives and evaluated for COX-2 enzyme inhibition and lymphocyte proliferation where compound **"51"** appeared most potent with 50.7% inhibition against lymphocyte proliferation and good selectivity (but less potency) against COX-2 (IC_{50} = 1.02 μM and S.I. = 1.51) as compared to celecoxib (IC_{50} = 0.26 μM and S.I. = 11.88). *In-vivo* anti-inflammatory data showed significant results for all the administered doses for the compound **"51"** (%inhibition after 5 h at a dose of 30 mg/kg = 100%) (Fig. 55).

Swathi et al. [163] developed new indole derivatives as dialkyl amino alkoxy indole diones and evaluated for anti-inflammatory potential by carrageenan induced rat paw edema assay that showed very promising results for the compound **"52"** with 75.4% inhibition of COX-2 after 4 h that was comparable with the standard drug Indomethacin that had 76.1% inhibition after 4 h. Anti-inflammatory activity was also evaluated using TMPD (*N*-tetramethyl-*p*-phenylenediamine) method which showed 75% inhibition of COX-2 at 100 μM that was more promising than the standard drugs etoricoxib with 67.74% inhibition and celecoxib with 58.06% inhibition (Fig. 56).

4. Pyridine as a COX 2 inhibitor

Pyridine is a basic heterocyclic organic compound basically interrelated to benzene, with one C atom replaced by N atom. Etoricoxib (Table 2) is a pyridine derivative that is used as a NSAID for treating rheumatoid arthritis and dental pain. Synthetic procedures for pyridine synthesis are mentioned in Fig. 57 and patents on indole are mentioned in Table 5.

In Hantzsch pyridine synthesis, first a double hydrogenated pyridine is obtained by refluxing a β-keto acid with aldehyde and ammonia for an hour which is then oxidized to pyridine derivative by the help of an oxidizing agent like $FeCl_3$ [164].

Ciamician–Dennstedt rearrangement involves pyrrole ring-expansion to yield 3-chloropyridine by using dichlorocarbene [165].

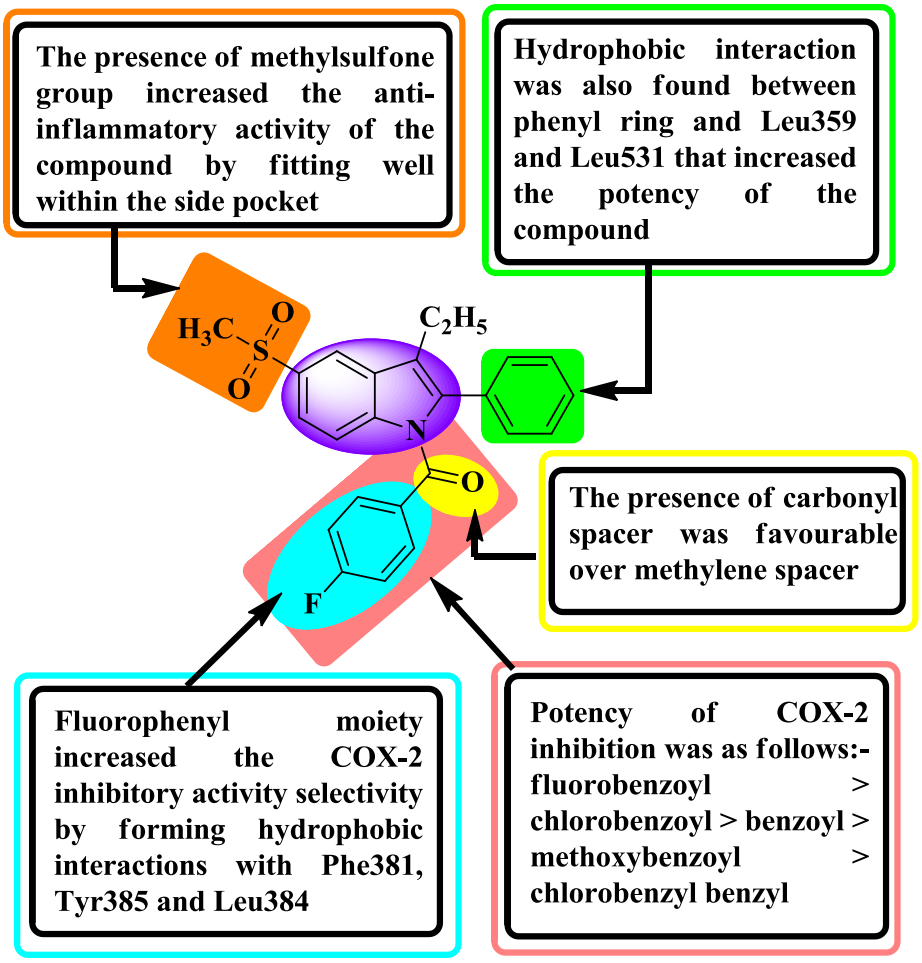
Bönnemann cyclization involves trimerization of nitrile molecule and two acetylene molecules into pyridine [166].

The Kröhnke pyridine synthesis is used to synthesize substituted pyridines using pyridine, α-bromoesters as the reagents which undergo Michael reaction followed by closure of ring in the presence of ammonium acetate generating targeted substituted pyridines [167].

Gattermann–Skita synthesis involves the synthesis of pyridine by reacting malonate ester salt with dichloromethylamine [168].

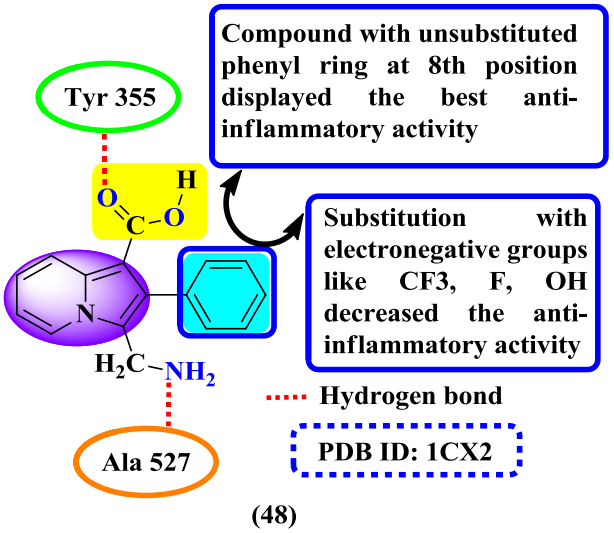
Chichibabin pyridine synthesis is commonly used in the industries and involves condensation of substituted aldehydes, ketones and α,β-unsaturated carbonyl compounds in ammonia or ammonia derivatives [169].

Lu et al. [182] prepared pyridine acyl sulfonamide derivatives and assessed for COX-2 inhibition. Compound **"53"** demonstrated potent COX-2 inhibition with IC_{50} of 0.8 μM. Also antitumor and anti-inflammatory results showed that **"53"** possessed good antiproliferative potential against B16-F10, HepG2 and MCF-7 cell lines and PGE2 inhibition of murine macrophage RAW 264.7 cell line with IC_{50} values of



(47)

Fig. 51. Structure and SAR of (3-ethyl-5-(methanesulfonyl)-2-phenyl-indol-1-yl)(4-fluorophenyl)methanone.



(48)

Fig. 52. Structure, SAR and Molecular docking of 3-(aminomethyl)-2-phenylindolizine-1-carboxylic acid.

2.8, 1.2, 1.8 and 0.15 μM, respectively

SAR studies displayed that electron-withdrawing/attracting group enhanced COX-2 inhibition while electron donating/releasing alkyl substituents showed negative results (Fig. 58).

Badrey et al. [183] prepared imidazopyrazolopyridines as potential inhibitors of COX-2 using colorimetric screening assay. Compound **"54"** appeared as potential COX-2 inhibitor of the series (%inhibition = 75.9, COX-2/COX-1 selectivity = 19.4) as compared to the reference drugs Diclofenac (%inhibition = 7.88 COX-2/COX-1 selectivity = 0.13), Valdecoxib (%inhibition = 76.1, COX-2/COX-1 selectivity = 6.26) and Ibuprofen (%inhibition = 5.23, COX-2/COX-1 selectivity = 0.06). Compound **"54"** also showed good anti-inflammatory activity with complete edema protection (% Protection against edema = 97% with dose 5 mg/kg) against Diclofenac sodium (% Protection against edema = 72% with dose 5 mg/kg) and Valdecoxib (% Protection against edema = 87% with dose 5 mg/kg) (Fig. 59).

Renard et al. [184] synthesized a series of novel COX-2 inhibitors by replacing the nitrobenzene ring of the nimesulide with pyridine nucleus to enhance the COX-2 selectivity and thereby reducing the side effects (acute liver failure, gastric irritation and cardiovascular problems) caused by nimesulide. *In vivo* evaluation using the λ carrageenan-induced pleurisy model revealed that compound **"55"** (IC_{50} = 0.09 μM, selectivity ratio = 15.35) appeared more potent than Nimesulide (IC_{50} = 0.7 μM, selectivity ratio = 5.37) and Celecoxib (IC_{50} = 0.35, selectivity ratio = 7.46). Plasma assays further revealed the potency of **"55"**. It was observed that the substitution of the methyl group in methanesulfonamide moiety with trifluoro group led to enhancement of

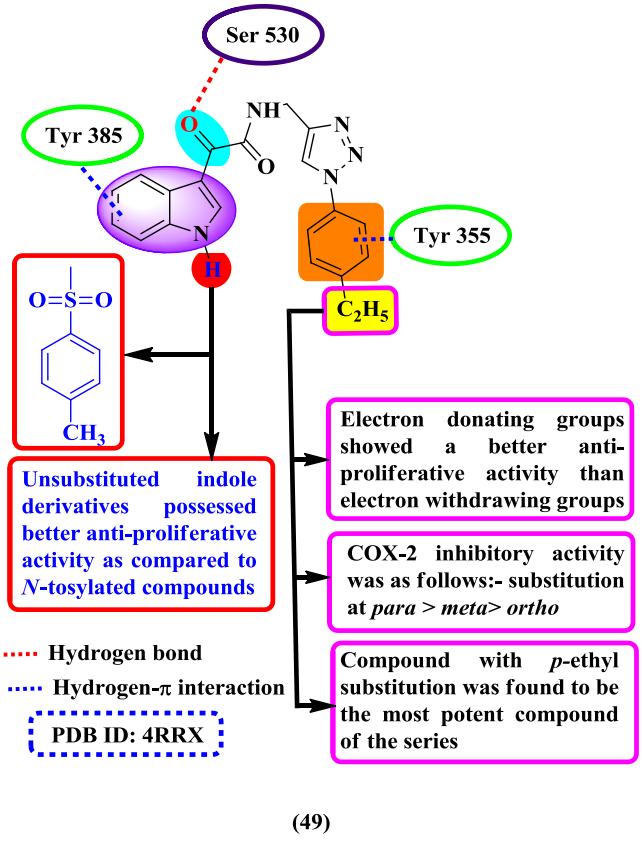


Fig. 53. Structure, SAR and Molecular docking of N-((1-(4-ethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(1H-indol-3-yl)-2-oxoacetamide.

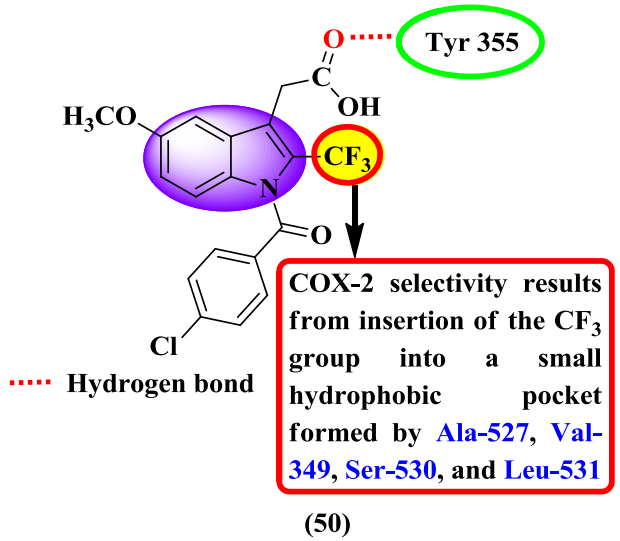


Fig. 54. Structure, SAR and Molecular docking of 2-trifluoromethyl analogue of Indomethacin.

inhibitory potency. Also, the selectivity ratio towards COX-2 was increased by the presence of alkyl chain or halogen atoms (Cl/Br) at *meta* or *para* position due to the steric hindrance caused by their introduction (Fig. 60).

Krejcova et al. [185] tested the anti-inflammatory and neurological potential of pyrithione and sulfur-containing pyridine *N*-oxides as important ingredients of *Allium stipitatum*. Compound **"56"** showed very high anti-inflammatory effect (COX-2 IC_{50} = 15.4 μM, %inhibition = 47% at 100 μM concentration) in comparison to Nimesulide (%

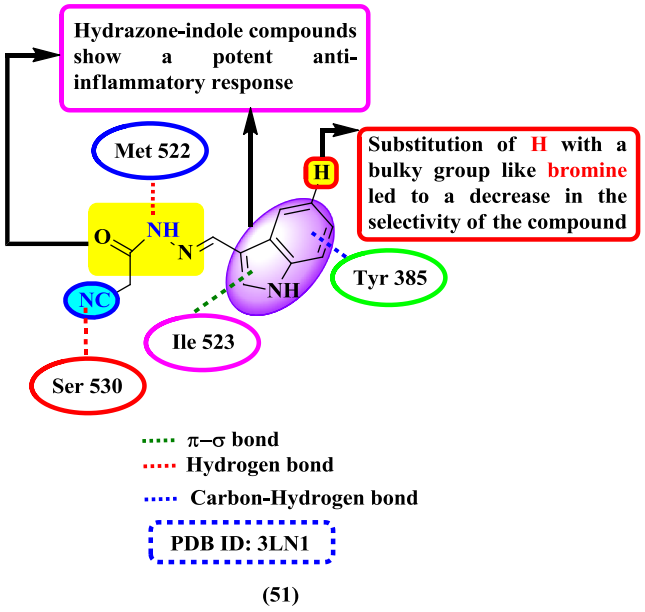


Fig. 55. Structure, SAR and Molecular docking of 2-Cyano-N'-((1H-indol-3-yl) methylene)acetohydrazide.

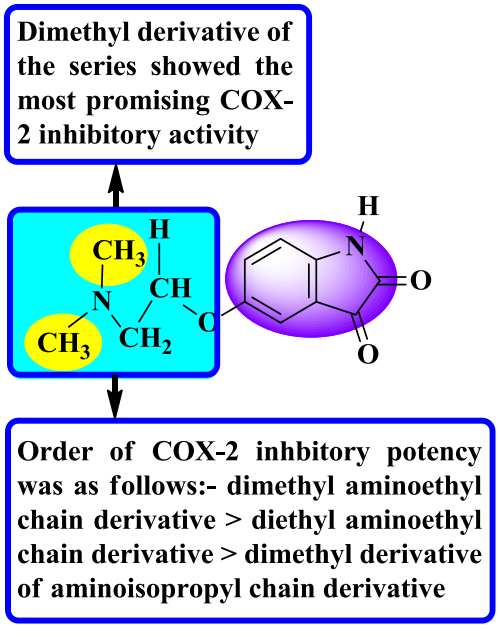


Fig. 56. Structure and SAR of 5-(2-(dimethylamino)ethoxy)indoline-2,3-dione.

inhibition = 47%). The results also indicated that the anti-inflammatory activity of the compounds tested is not related to the presence of the *N*-oxide group. It rather seemed to be linked to the (methylthio)methyl disulfide moiety (CH_3SCH_2SS) which is present only in the active compound (Fig. 61).

Abdelgawad et al. [186] prepared pyrimidine-pyridine hybrids containing pyrido[2,3-*d*:6,5*d*0]dipyrimidine-4,5-diones, tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitriles and 6-(4-acetylphenyl)-2-thioxo-2,3,5,6,7,8-hexahydro-1H-pyrimido[4,5-*d*]pyrimidin-4-one. Compound **"57"** revealed superior COX-2 inhibition (IC_{50} = 0.25 μM, S.I. = 17.08) as compared to standard drug celecoxib (IC_{50} = 1.11 μM, S.I. = 6.61). Compound **"57"** showed an edema inhibition upto 76% after two hours that was higher than Celecoxib with 63% edema inhibition using *in vivo* carrageenan-induced rat paw oedema model. In

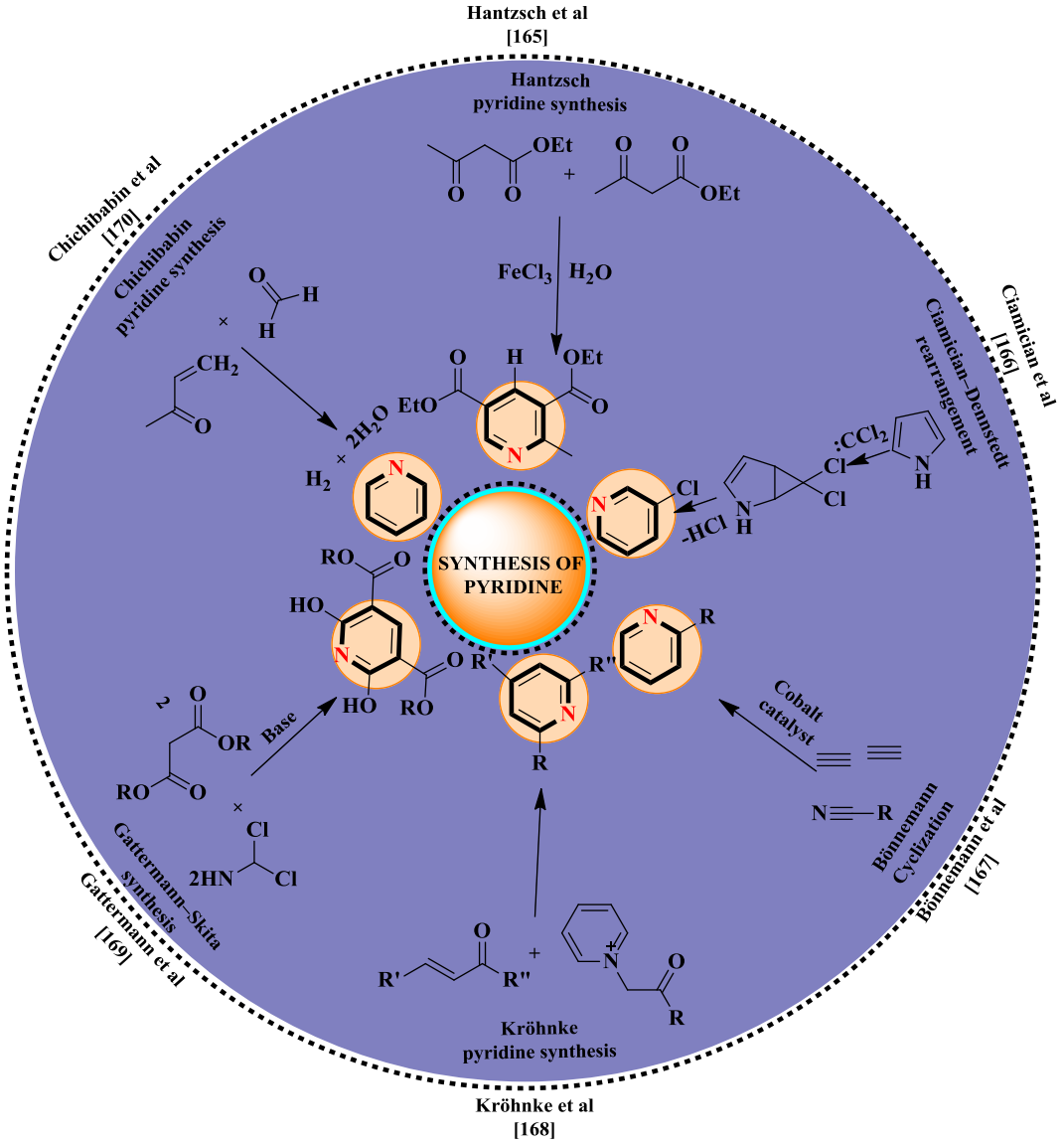


Fig. 57. Synthesis of pyridine.

the pyridodipyrimidine series, compounds having electron donating/releasing groups showed superior edema inhibition than those equipped with electron withdrawing/attracting groups. Regarding ulcerogenic liability, the compound **"57"** (ulcer index = 1.5) was less ulcerogenic than the standard drug Indomethacin (ulcer index = 42) (Fig. 62).

Renard et al. [187] synthesized pyridine analogs of Nimesulide bearing a trifluoromethane sulfonamide moiety and assessed for anti-inflammatory activity using carrageenan-induced pleurisy model. Compound **"58"** appeared as most potential derivative (COX-2 IC_{50} = 0.12, selectivity ratio = 7.48) as compared to the reference drugs. The substitution of chlorine atom on the phenyl ring displayed increased COX-2 inhibition. Presence of bromine atom in place of chlorine atom further increased COX-2 inhibition due to improved steric hindrance and lipophilicity. Substitution of the phenyl ring with alkyl chains led to increased selectivity towards COX-2 enzyme. Compounds having methyl sulfonamide moiety in place of trifluoromethanesulfonamide moiety displayed weaker COX-2 inhibition. *In vivo* evaluation of **"58"** displayed significant anti-inflammatory action at a dose 20 mg/kg (%inhibition of exudate = 64.5%). Significant reduction in hepatotoxicity was observed in case of **"58"** as compared to nimesulide (Fig. 63).

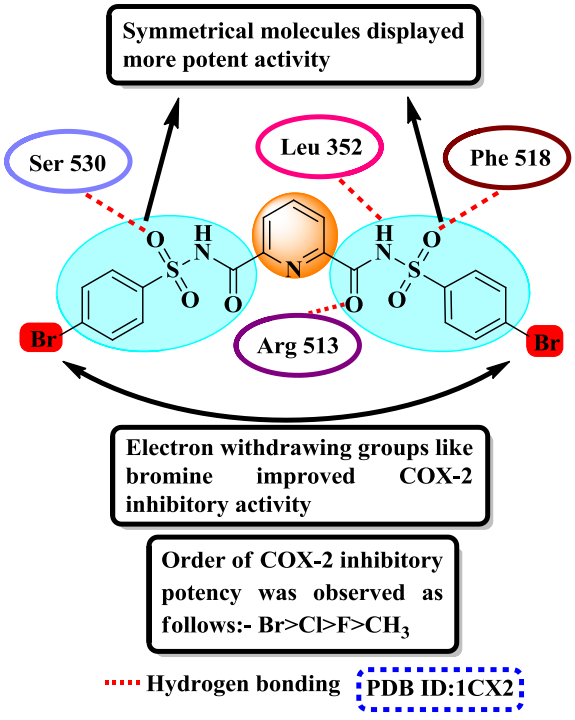
Marquez-Flores et al. [188] prepared and performed a molecular docking exploration on imidazo[1,2-*a*]pyridine carboxylic acid derivatives and evaluated for anti-inflammatory activity and COX inhibition along with their binding to COX-1 and COX-2 active pockets. *In vitro* results revealed that compound **"59"** favourably inhibited COX-2. These compounds were assessed (at a dose = 10 mg/kg) against acute and chronic anti-inflammatory action. Compound **"59"** showed more efficient inhibition (%inhibition = 80.3% at 3 h) than indomethacin (% inhibition = 77.3% at 3 h) and did not produce gastroduodenal damage. Chronic anti-inflammatory activity was found in derivative **"59"** and indomethacin-treated groups in the granuloma model (Fig. 64).

Pandit et al. [189] prepared imidazo[1,2-*a*]pyridine derivatives and were computationally analysed for binding into COX-1 and COX-2 pockets and assessed for anti-inflammatory action using carrageenan-induced rat paw oedema model. Compound **"60"** inhibition (%inhibition = 52.90%) was found closer to indomethacin (%inhibition = 54.66%) and showed moderate ulceration (Ulcer index = 5) 100 mg/kg against indomethacin (Ulcer index = 10) (Fig. 65).

Ahmed et al. [190] synthesized derivatives of curcumin possessing different heterocyclic moieties like pyrazole, isoxazole and pyrimidine out of which pyrimidine containing compounds revealed potential anti-inflammatory results. These derivatives were subjected to *in-vitro*

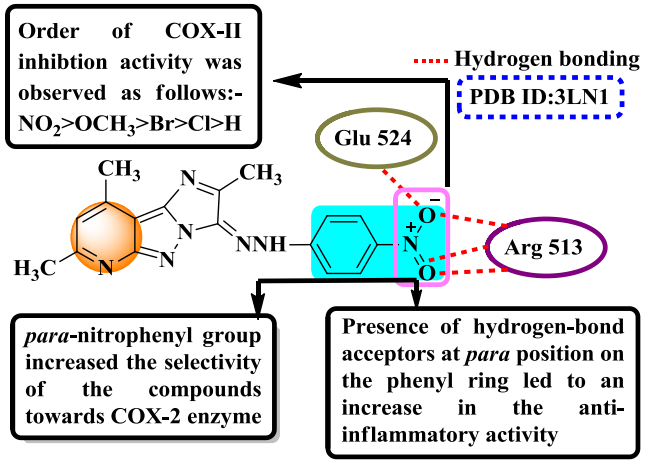
Table 5
Patents on pyridine moiety relating to anti-inflammatory activity.

S. No.	Patent number	Patent date	Inventors	Description
1.	US7060715B2 [170]	13 June 2006	Daniel Dube, Rejean Fortin, Richard Friesen, Zhaoyin Wang, Jacques Yves Gauthier	Substituted pyridines as selective cyclooxygenase − 2 inhibitors
2.	US6369275B1 [171]	09 April 2002	Ian W. Davies, Michel Journet, Linda Gerena, Robert D. Larsen, Philip J. Pye, Kai Rossen	Process for making diaryl pyridines useful as cox-2-inhibitors
3.	US7172769B2 [172]	06 February 2007	Tugrul T. Kararli, Mark J. Kontny, Subhash Desai, Michael J. Hageman, Royal J. Haskell	Cyclooxygenase-2 inhibitor compositions having rapid onset of therapeutic effect
4.	WO2003055874A1 [173]	10 July 2003	Il-Hwan Cho, Jee-Woong Lim, Ji-Young Noh, Jong-Hoon Kim, Sang-Wook Park, Hyung-Chul Ryu, Je-Hak Kim, Jong-Ho Kim, So-Young Wang, Dal-Hyun Kim	Bipyridinyl derivatives as a highly selective cyclooxygenase-2 inhibitor
5.	US6046217A [174]	04 April 2000	Richard Friesen, Rejean Fortin, Daniel Dube, Denis Deschenes	2,3,5-trisubstituted pyridines as inhibitors of cyclooxygenase-2
6.	US7446117B2 [175]	04 November 2008	Paul Beswick, Neil Pegg, Martin Swarbrick, John Skidmore, Sandeep Modi	Cox-2 inhibiting pyridine derivatives
7.	US8877782B2 [176]	04 November 2014	Bernd Buettelmann, Roland Jakob-Roetne, Henner Knust, Matthew C. Lucas, Andrew Thomas	Isoxazolo-pyridine derivatives
8.	US5922742A [177]	13 July 1999	Cameron Black, Zhaoyin Wang, Greg Hughes	Pyridinyl-2-cyclopenten-1-ones as selective cyclooxygenase-2 inhibitors
9.	US5916905A [178]	29 June 1999	Richard M. Weier, Len F. Lee, Richard A. Partis, Francis J. Koszyk	2,3-substituted pyridines for the treatment of inflammation.
10.	US7223772B1 [179]	29 May 2007	Ian Baxter Campbell, Alan Naylor	Pyrazolopyridine derivatives as selective cox-2 inhibitors.
11.	US7585875B2 [180]	08 September 2009	Federico C. A. Gaeta, Matthew Gross, Kirk W. Johnson	Substituted pyrazolo[1,5-*a*]pyridine compounds and their methods of use
12.	US6130334A [181]	10 October 2000	Philip J. Pye, Ashok Maliakal, Kai Rossen, Ralph P. Volante, Jess Sager	Process for making 2-aryl-3-aryl-5-halo pyridines useful as COX-2 inhibitors



(53)

Fig. 58. Structure, SAR and molecular docking of N^2,N^6-Bis(4-bromophenylsulfonyl) pyridine-2,6-dicarboxamide.



(54)

Fig. 59. Structure, SAR and molecular docking of 2,7,9-Trimethyl-3-[(4-nitrophenyl) diazenyl]-1H-imidazo[1′,2′:1,5]pyrazolo[3,4-b]pyridine.

studies where compound **"61"** was found to be the most potent compound with % inhibition at 10 μM dose for COX-2 = 75.3%, comparable to Celecoxib (% inhibition at 10 μM dose for COX-2 = 76.5%). Anti-inflammatory data showed that **"61"** possessed significant inhibitory activity (75.9% inhibition after 3 h) that was more than Curcumin (71.6% inhibition after 3 h) and comparable to Indomethacin as standard drug (84.4% inhibition after 3 h). Anti-nociceptive activity was evaluated by recording writhing responses induced with the help of acetic acid where **"61"** (%inhibition = 71.8%) showed better activity than Curcumin (%inhibition = 58.1%) and standard drug Diclofenac (%inhibition = 67.1%). Ulcerogenicity of the compounds was also evaluated where **"61"** (ulcer index = 1.0) was found to be a safer compound as compared to diclofenac sodium (ulcer index = 5.0) (Fig. 66).

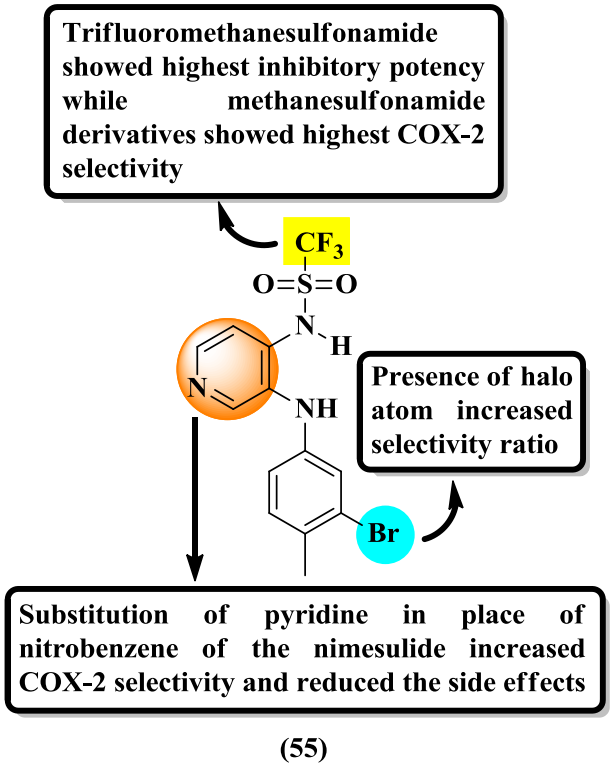


Fig. 60. Structure and SAR of N-[3-(3-Bromo-4-methylphenylamino)pyridin-4-yl]trifluoro methanesulfonamide.

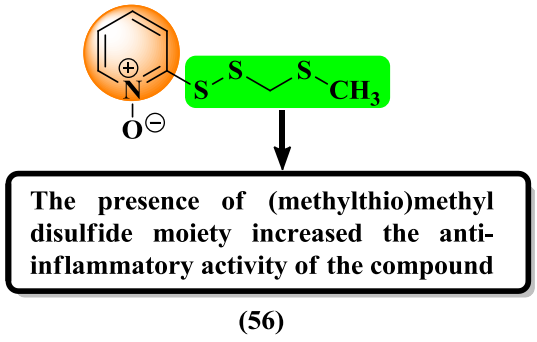


Fig. 61. Structure and SAR of 2-[(Methylthio)methyldithio]pyridine *N*-oxide.

Graziano et al. [191] synthesized a series of eight thieno-pyrimidinone methanesulphonamide thio-derivatives that were studied using in-silico techniques in order to evaluate COX-1 and COX-2 inhibition (*in vitro*) and biologically evaluated with the help of inflammation models (interleukin-1beta at a dose of 10 ng/mL using human cartilaginous tissues along with cultures of chondrocytes). Western blot technique was used to analyse the expression of various inflammatory markers including COX-2 where **"62"** showed remarkable anti-inflammatory activity. The results suggested that the structure of the compound with central pyrimidine along with two other aryl rings bearing sulfonamide or methylsulfonyl moiety provided the proper orientation to the compound that aided in its binding with the active site. Hydrophobic interaction of fluorine with binding sites added to the strong interactions of the compound with the amino acids of the receptor (Fig. 67).

Atatreh et al. [192] reported a new series of pyrazolopyrimidine compounds that were subjected to *in-vitro* evaluation for assessing COX-2 inhibition where compound **"63"** (IC_{50} = 23.8 μM and % inhibition at 40 μM = 91.25%) was found to be more effective than Diclofenac Sodium but comparable to Celecoxib (IC_{50} = 11.7 μM and % inhibition at

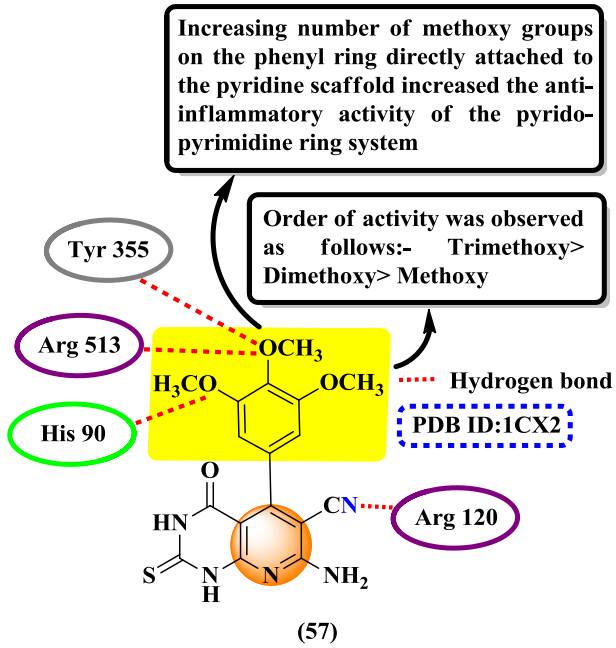


Fig. 62. Structure, SAR and molecular modeling of 7-Amino-5-(3,4,5-trimethoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile.

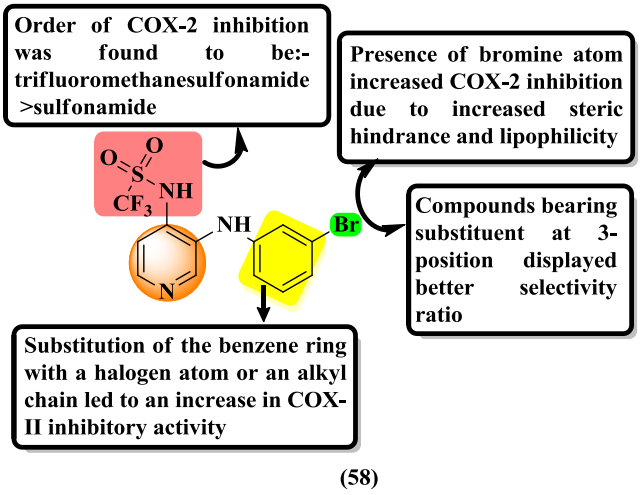


Fig. 63. Structure and SAR of N-[3-(3-Bromophenylamino)-4-pyridinyl]trifluoromethane sulfonamide.

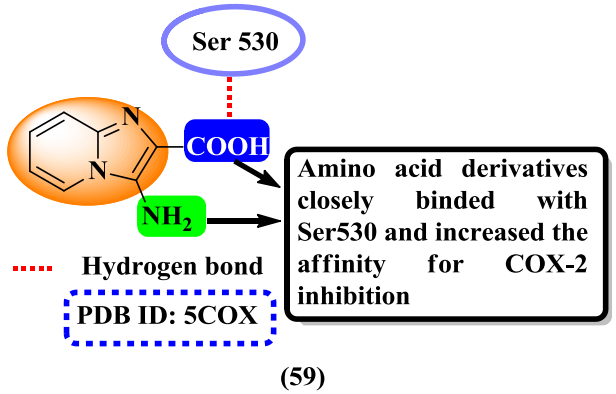
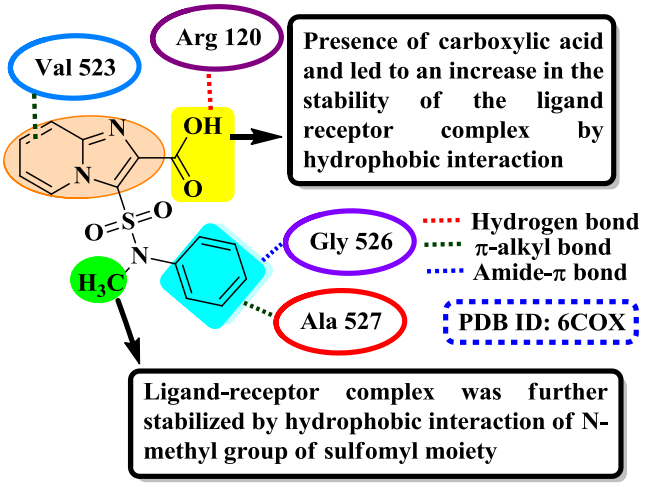
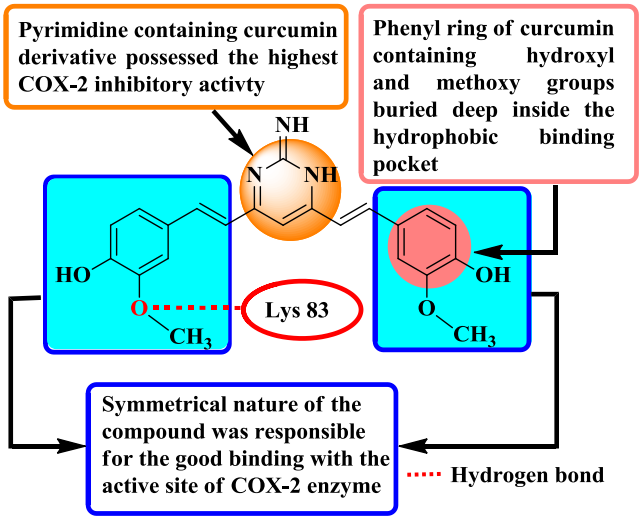


Fig. 64. Structure, SAR and molecular docking of the amino acid derivative as most potent inhibitor.



(60)

Fig. 65. Structure, SAR and molecular modeling of 3-(*N*-methyl-*N*-phenylsulfamoyl)imidazo [1,2-*a*]pyridine-2-carboxylic acid.



(61)

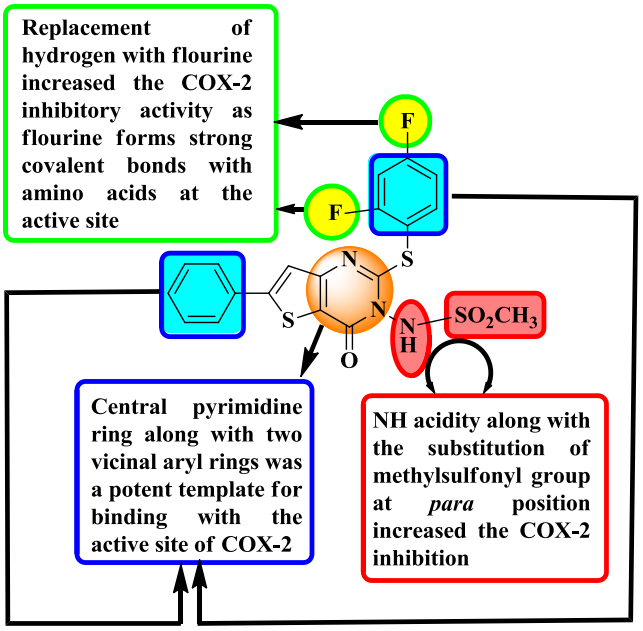
Fig. 66. Structure, SAR and Molecular docking of pyrimidine containing analogue of curcumin derivative.

40 μM = 96.61%) as standard drugs. Carrageenan induced rat paw edema model was used to assess the *in-vivo* anti-inflammatory activity where **"63"** showed significant inhibition (AI = 65% after 2 h and ED_{50} = 7.6 mg/kg) when compared against standard drugs Celecoxib (AI = 68% after 2 h and ED_{50} = 7.2 mg/kg) and diclofenac sodium (AI = 53% after 2 h). Sub acute inflammatory model showed similar results where **"63"** showed AI = 64%, Celecoxib showed AI = 69% and diclofenac sodium showed AI = 57% on the first day (Fig. 68).

Roscales et al. [193] synthesized valdecoxib based derivatives possessing 3,4-diaryl derivatives of isoxazole ring and assesed for their COX-1/COX-2 inhibition by using *in-vitro* analysis. Compound **"64"** (COX-2 IC_{50} = 0.042 μM and S.I. = > 2400) was the most potent compound of the series and was found even more potent than valdecoxib (COX-2 IC_{50} = 0.052 μM and S.I. = > 2000) (Fig. 69)

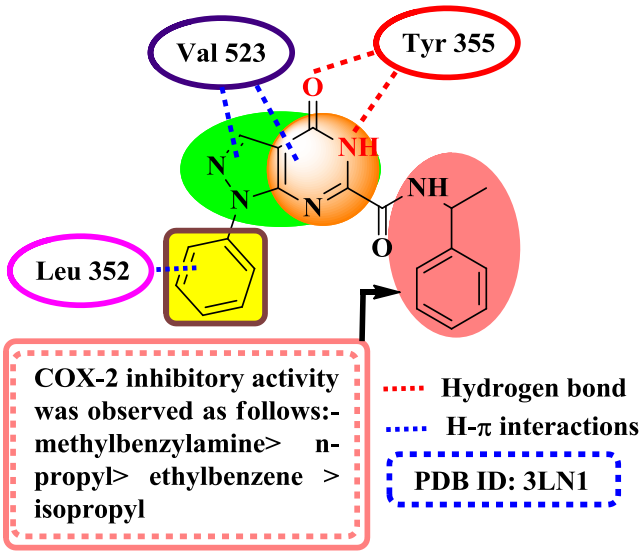
5. Oxazole as a COX 2 inhibitor

Oxazole is a weakly basic heterocyclic compound which is the parent compound for a number of other heterocyclic compounds called



(62)

Fig. 67. Structure and SAR of N-[2-[2,4-difluorophenyl)thio]-4-oxo-6-phenylthieno[3,2-*d*]pyridine-3-4*H*-yl]methanesulfonemide.

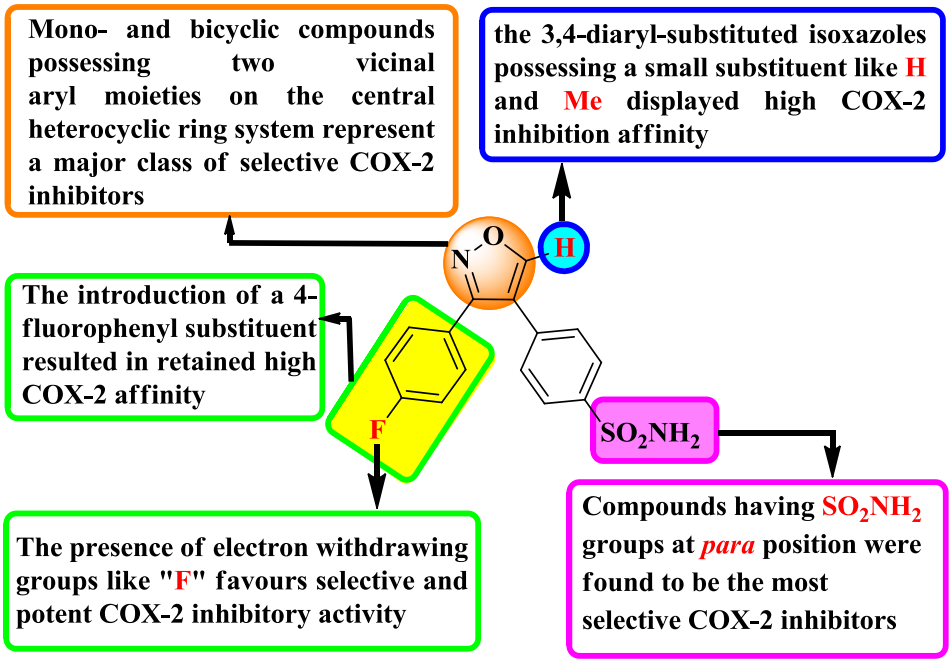


(63)

Fig. 68. Structure, SAR and molecular docking of S-(-)-4-oxo-1-phenyl-N-(1-phenylethyl)-4,5-dihydro-1H-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide.

azoles which are five-membered heterocycles having a carbon between the heterocyclic oxygen and nitrogen atom. Oxaprozin (Table 2) is an accepted COX-2 inhibitor currently in market which is a trisubstitutedoxazole. Synthetic procedures for Oxazole synthesis are mentioned in Fig. 70 and patents are mentioned in Table 6.

Sir Robert Robinson and Siegmund Gabriel described a reaction in which a 2-acylamino-ketone reacts intramolecularly followed by a dehydration giving an oxazole as product. The Van-Leusen reaction allows the preparation of oxazoles from aldehydes by reaction with tosylmethyl isocyanide (TosMIC). Although, in contrast to Van-Leusen reaction, the existence of a proton in the β-position to the sulfinyl group allows a base-promoted elimination. Originally, the reaction was proposed by Cornforth and Cornforth which involved the reaction of



(64)

Fig. 69. Structure and SAR of 4-(3-(4-fluorophenyl)isoxazol-4-yl)benzenesulfonamide compound with ethane.

amides with α-hydroxyketones. Upon heating formamide with ethyl α-hydroxyketosuccinate, diethyl oxazole-4,5-dicarboxylate is obtained. Hydrolysis of the diester with ether-ethanolic NaOH or aq. Ba(OH)2 and decarboxylation of the acid salt is affected by heating it in quinoline in the presence of quinoline sulfate and copper or copper oxide to give oxazole in 30–50% overall yield. The reaction of an acid imide and an α-halogenoketone yields oxazole. In the presence of anhydrous hydrochloride, a 2,5-disubstituted oxazole can be synthesized from the reaction of a cyanohydrin and an aldehyde [194–198].

Mohamed et al. [211] prepared oxazolones and triazinones and evaluated for *in vitro* COX-1/COX-2 inhibition. The assay revealed that compound **"65"** (COX-2 IC_{50} = 0.019 μM) appeared as the most potential derivative of oxazolone series even more potent than celecoxib (COX-2 IC_{50} = 0.05 μM) (Fig. 71).

Shakya et al. [212] synthesized N-(2-(4-chlorobenzyl)benzo[*d*]oxazol-5-yl)-3-substituted-propanamide derivatives and assessed them for anti-inflammatory activity using carrageen an-induced paw edema. Compound **"66"** (20 mg/kg b.wt. p.o.) exhibited 81.7% protection against paw inflammation as compared to diclofenac sodium (69.5%) and ibuprofen (64.7%). It also showed 44.0% protection against cotton pellets-induced granuloma as compared to diclofenac sodium (60.2%). Compound **"66"** (severity index = 1.60) was found to be less ulcerogenic than ibuprofen (severity index = 2.80) (Fig. 72).

Dundar et al. [213] prepared 3-unsubstituted/substituted-4,5-diphenyl-2-oxo-3H-1,3-oxazole derivatives as selective COX-2 inhibitors. Compound **"67"** presented 70.14% (2 μM) inhibition in purified enzyme (PE) assay with a selectivity index of > 50 and found to be more potent than rofecoxib (%inhibition = 66.78%). *N*-methyl group unsubstituted phenyl moiety is placed well into hydrophobic cavity of COX-2 whereas the sulfonamide group is sited into the selectivity pocket (Fig. 73).

Rakesh et al. [214] synthesized isoxazole derivatives and assessed them for anti-inflammatory potential via COX and LOX inhibitory activity. Compound **"68"** displayed inhibition (COX-2 IC_{50} = 9.56 μM) comparable to Indomethacin (COX-2 IC_{50} = 6.78 μM). In silico studies discovered that compound **"68"** binds more strongly to catalytic domain of COX-2 with high atomic contact energy (ACE) score in comparison to indomethacin. The inhibitory activity of **"68"** may possibly be due to aryl groups with strong electron releasing/donating substituent and moderately electron rich hetero aryl substituent like indole (Fig. 74).

Abraham et al. [215] synthesized 2-phenyl-1,3-oxazole derivatives and evaluated for *in vitro* anti inflammatory activity by human RBC (HRBC) stabilization method. The compounds were also subjected to in silico prioritization using PASS server for biological activity score (BAS). *In vivo* assessment for anti-inflammatory activity and ulcerogenic effects was carried out for molecules having acceptable BAS and with good HRBC stabilization activity. Compound **"69"** exhibited good anti inflammatory activity (carrageenan- induced rat paw edema model) with very low ulcerogenicity (%inhibition = 77.4%; ulcer index = 0.59) compared with the standard drug diclofenac sodium (% inhibition = 73.2% ; ulcer index = 2.34) (Fig. 75).

Zhou et al. [216] synthesized 4,5-diaryloxazole analogs and screened for their analgesic and anti-inflammatory activity using oxaprozin as the reference drug. Compound **"70"** was the most potent derivative of the series. Anti-inflammatory potential was assessed using carrageenan-induced paw edema test using murine models (For **"70"**, anti-inflammatory activity = 31.7% and for oxaprozin, anti-inflammatory activity = 47.6%). Murine models were used to assess the analgesic activity using acetic acid-induced writhing response (For **"70"**, %inhibition = 54% and for oxaprozin, %inhibition = 65.2%). Ulcerogenicity of **"70"** (Mucosal lesion area = 1.04 mm^2) was compared with oxaprozin by using a dose of 800 mg/kg (Mucosal lesion area = 10.34 mm^2). Presence of an aminosulfonyl substituent led to an increased selective COX-2 inhibition along with a reduction in the number of gastric lesions (Fig. 76).

Srinivas [217] synthesized methyl-2-(2-(arylideneamino)thiazole-4-ylamino)benzoxazole-5-carboxylate derivatives and assessed for COX-1 and COX-2 inhibition. The IC_{50} values were determined by using the method of Copeland et al. Compound **"71"** appeared as most potential derivative (COX-2 IC_{50} value = 1 mM; selectivity index = 379) using rofecoxib as the reference drug. The presence of a nitro group on the phenyl ring enhanced COX-2 inhibitory activity and selectivity (Fig. 77).

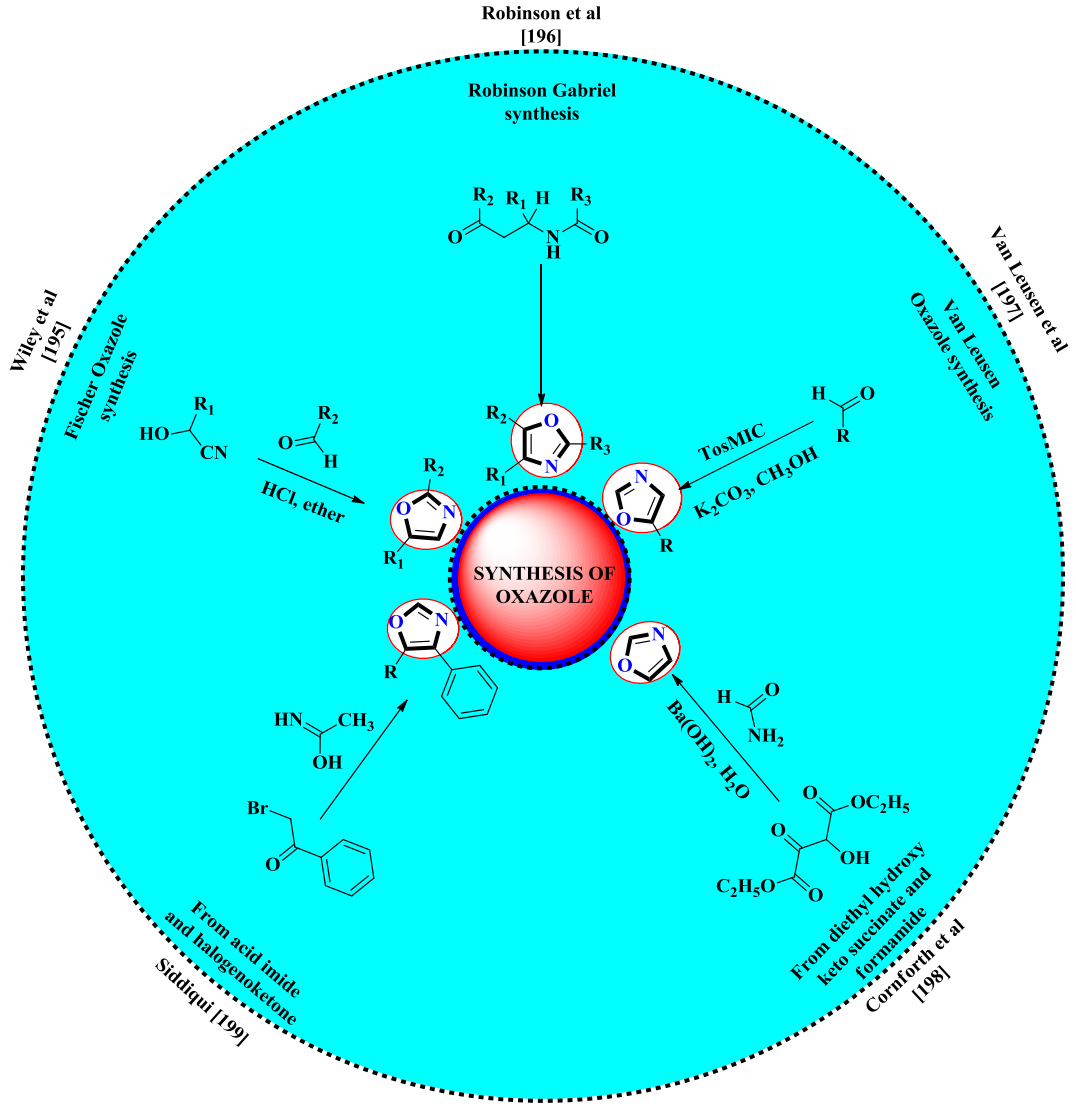


Fig. 70. Synthesis of oxazole.

Kaur et al. [218] synthesized substituted-N-(3,4-dimethoxyphenyl)-benzoxazole derivatives and evaluated for *in vitro* COX-1 and COX-2 inhibition where it was revealed that **"72"** was the most potent compound of the series (COX-2 IC_{50} = 0.04 μM, selectivity index = 25.5) using Celecoxib (COX-2 IC_{50} = 0.15 μM , selectivity index = 41.33) and Ibuprofen (COX-2 IC_{50} = 1.08 μM, selectivity index = 1.31) as the standard drugs. *In vivo* anti-inflammatory potential was assessed using carrageenan-induced rat paw edema model where **"72"** showed better inhibition (%inhibition = 84.09%) as compared to ibuprofen (%inhibition = 65.9%). Compound **"72"** (severity index = 0.8) displayed improved safety margin on gastric mucosa than the standard drug Ibuprofen (severity index = 2.2). The substitution of the phenyl ring with electron attracting/withdrawing groups such as chloro at ortho, nitro group at para position led to an increased activity (Fig. 78).

Kankala et al. [219] performed a regioselective synthesis of isoxazole–mercaptobenzimidazole hybrids and assessed for *in vivo* analgesic and anti-inflammatory activity. Ccompound **"73"** showed potent anti-inflammatory activity (60.76% paw oedema inhibition) activity as compared to diclofenac (45.76% oedema inhibition). Evaluation of *in vivo* analgesic activity revealed that compounds comprising electron withdrawing/attracting groups on benzimidazole 5th position (bromine in case of compound **"73"**) exhibited greater activity (Fig. 79).

Chilumula et al. [220] synthesized substituted methyl-2-(2-(arylideneamino)oxazole-5-ylamino) benzoxazole-5-carboxylate derivatives. Compound **"74"** (COX-2 IC_{50} = 1 mM, selectivity towards COX-2 = 368) was the most potent compound of the series. The presence of methoxy group in the **"74"** increased the potency of the compound. Groups such as 2-(dialkylamino)acetamido were responsible for increasing COX-2 inhibition. The synthesized compounds were found to be more selective in comparison to rofecoxib (Fig. 80).

6. Pyrrole as a COX 2 inhibitor

Pyrrole is a five-membered heterocyclic aromatic organic compound consisting of a nitrogen atom. A common example of COX-2 inhibitors which are derivatives of Pyrrole is Ketorolac (Table 2). Ketorolac is an NSAID structurally related to Indomethacin. It is used principally for its analgesic activity. It is a pyrrolizine carboxylic acid derivative having anti-inflammatory and anti-pyretic activity as well. Synthetic procedures for pyrrole synthesis are mentioned in Fig. 81 and patents are mentioned in Table 7.

Barton–Zard synthesis involves the reaction of an isocyanoacetate with a nitroalkene which is followed by cyclization, elimination of nitro group and tautomerization leading to the formation of pyrroles [221].

Trofimov Synthesis involves formylation of 1-Vinylpyrroles by the

Table 6
Patents on Oxazole moiety relating to anti-inflammatory activity.

S. No.	Patent number	Patent date	Inventors	Description
1.	US7019006B2 [199]	28 March 2006	Pier F. Cirillo, Steffen Breitfelder, Usha R. Patel, John R. Proudfoot, Alan D. Swinamer, Hidenori Takahashi, Thomas A. Gilmore, Rajiv Sharma	Compounds useful as anti-inflammatory agents
2.	US5945539A [200]	31 August 1999	Junichi Haruta, Hiromasa Hashimoto, Mutsuyoshi Matsushita	Oxazole derivatives and use thereof
3.	WO1996036617A1 [201]	21 November 1996	John J. Talley, Stephen Bertenshaw, Donald J. Rogier, Jr. Matthew Graneto David L. Brown Balekudru Devadas Lu Hwang-Fun James A. Sikorski	Substituted oxazoles for the treatment of inflammation
4.	US9597318B2 [202]	21 March 2017	George Kokotos, Berit Johansen, Victoria Magrioti Michael Tsakos	2-oxothiazole compounds and method of using same for chronic inflammatory disorders
5.	US5403852A [203]	04 April 1995	Michel Barreau, Michel Kryvenko, Marc-Pierre Lavergne, Auguste Techer	Oxazole derivatives, their preparation and pharmaceutical compositions containing them
6.	US5859257A [204]	12 January 1999	John J. Talley	Isoxazole compounds as cyclooxygenase inhibitors
7.	US5994381A [205]	30 November 1999	Junichi Haruta, Hiromasa Hashimoto, Mutsuyoshi Matsushita	Heterocyclic aromatic oxazole compounds and use thereof
8.	WO1994027980A1 [206]	08 December 1994	Bryan H. Norman, Len F. Lee, Jaime L. Masferrer, John J. Talley	Substituted oxazolyl compounds for the treatment of inflammation
9.	US6090834A [207]	18 July 2000	John J. Talley, Stephen R. Bertenshaw, Donald J Rogier, Jr. Matthew J. Graneto	Substituted oxazoles for the treatment of inflammation
10.	WO2001092238A1 [208]	06 December 2001	Thomas W. Schultz, Daniel Korey	Amorphous oxazole coumpound and its use as cox-2 inhibitor
11.	US7087630B2 [209]	08 August 2006	Upul K. Bandarage, Richard A. Earl, Maiko Ezawa, Xinqin Fang, David S. Garvey, Subhash P. Khanapure, Ramani R. Ranatunga, Stewart K. Richardson Joseph D. Schroeder, Cheri A. Stevenson, Shiow-Jyi Wey	Cyclooxygenase 2 selective inhibitors, compositions and methods of use
12.	US7163952B2 [210]	16 January 2007	Takashi Inaba, Tomoyuki Ikemoto, Shohei Sakata, Hiroshi Maegawa, Atsunori Kashiwagi	Azole compound and medicinal use thereof

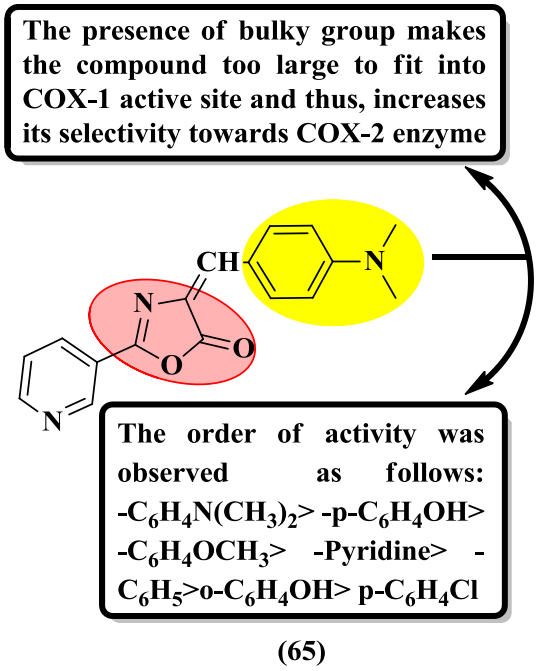


Fig. 71. Structure and SAR of the most potent compound of the novel series of oxazolones.

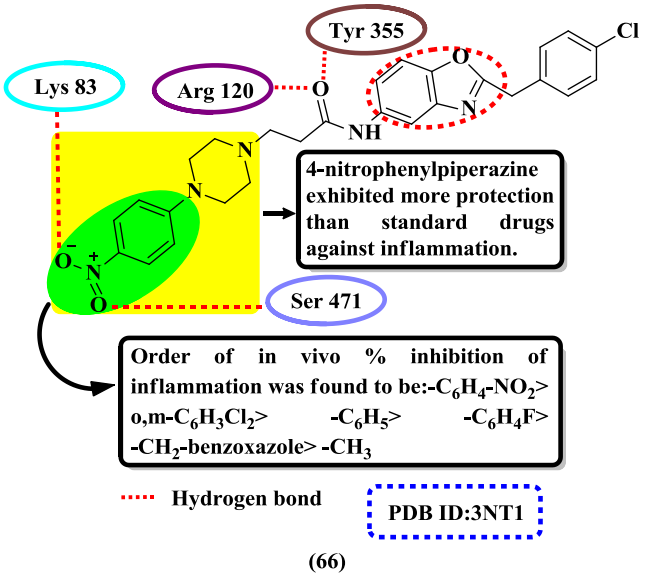


Fig. 72. Structure, SAR and molecular modeling of N-(2(4-chloro-benzyl)-benzo[*d*]oxazol-5-yl)-3-(4-(4-nitrophenyl)-piperazin-1-yl)propanamide.

N,*N*-dimethylformamide/oxalyl chloride reagent leading to the formation of substituted pyrroles [222].

In the synthesis given by Zavyalov and colleagues, 2-carbonyl-substituted azirines are reacted with 2-diazo-3,3,3-trifluoropropionate or ethyl 2-cyano-2-diazoacetate leading to the formation of an intermediate 2-azabuta-1,3-diene which isomerizes into 2*H*-1,3-oxazine, finally giving 1*H*-pyrrol-3(2*H*)-one as the only product at elevated temperatures [223].

Knorr pyrrole is an important method for the synthesis of pyrroles where α-amino-β-ketoester or α-amino ketone is reacted with an activated methylene compound [224].

In Paal Knorr synthesis, 1,4-dicarbonyl compound is reacted with NH_3 or 1° amine producing a substituted pyrrole [225].

The Van Leusen reaction has been used to synthesize pyrroles by

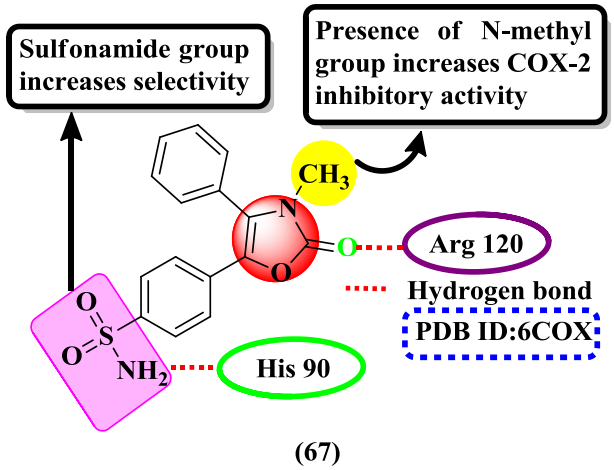


Fig. 73. Structure, SAR and molecular docking of 4-(4-Phenyl-3-methyl-2-oxo-3H-1,3-oxazol-5-yl)benzenesulfonamide.

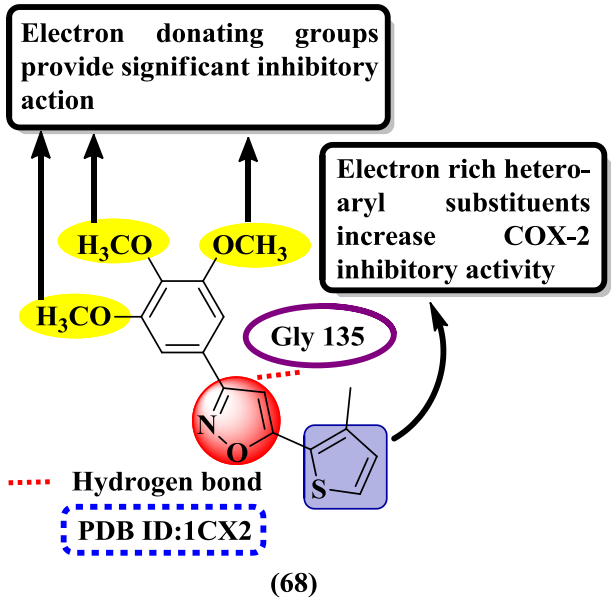


Fig. 74. Structure, SAR and molecular docking of 3-(3-methylthiophen-2-yl)-5-(3,4,5-trimethoxyphenyl)isoxazole.

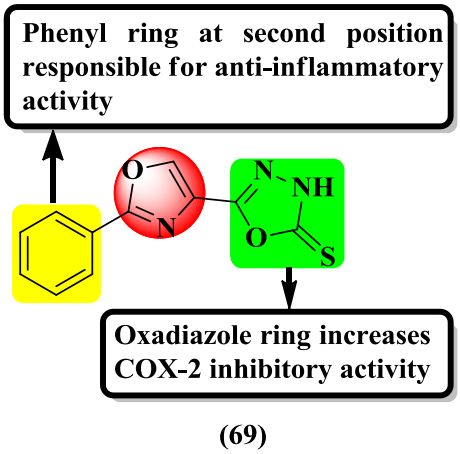


Fig. 75. Structure and SAR of 5-(2-Phenyl-1,3-oxazole-4-yl)-1,3,4oxadiazol-2(3H)-thione.

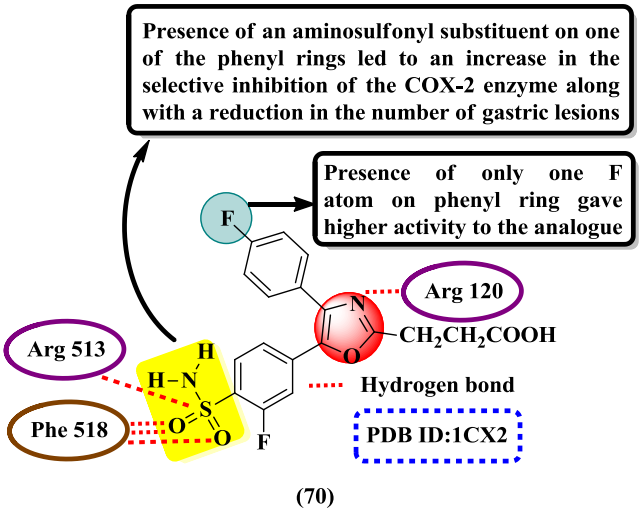


Fig. 76. Structure, SAR and molecular docking of 3-[4-(4-Fluorophenyl)-5-(4-aminosulfonyl-3-fluorophenyl)oxazole-2-yl] Propanoic Acid.

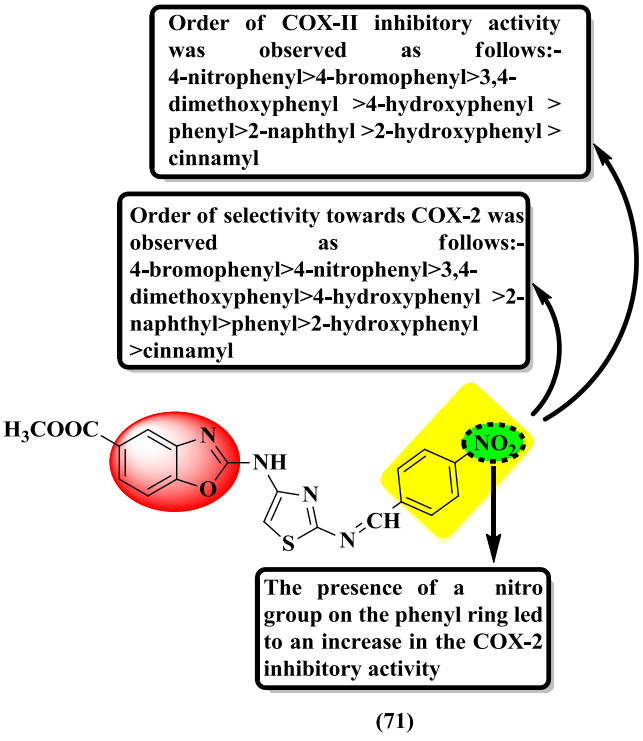


Fig. 77. Structure and SAR of most active methyl 2-(2-(arylideneamino) thiazole-4-ylamino) benzoxazole-5-carboxylate derivative.

reacting tosylmethyl isocyanide (TosMIC) with an enone. This reaction involves Michael addition followed by cyclization and tautomeriztion. The reaction takes place in the presence of a base [226].

Substituted pyrrole can be produced by the reaction of an aldehyde with hydrazine with the help of Piloty–Robinson pyrrole synthesis [227].

The synthesis discovered by Huisgen involves reacting α-amino acid with a carboxylic acid and an alkyne reacts to form a substituted pyrrole [228].

Battilocchio et al. [241] synthesized pyrrole derivatives featuring carbaldehyde, oxime, and nitrile on the central core. Compound **"75"** (IC_{50} = 0.0022 μM, SI > 454.5) displayed *in vivo* anti-nociceptic profile comparable to Celecoxib (IC_{50} = 0.06 μM, SI = 62.9). All synthesized compounds were assessed for *in vitro* study at various

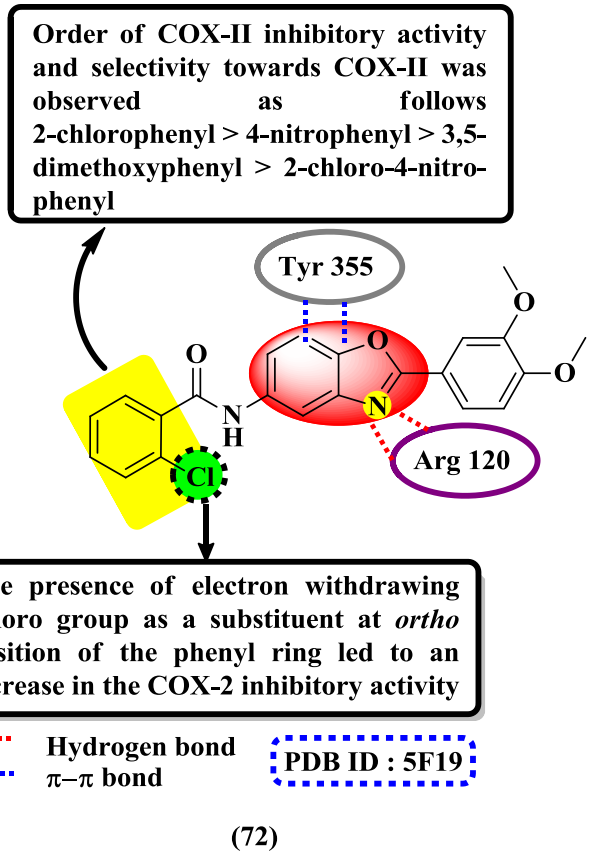


Fig. 78. Structure, SAR and molecular docking of 2-Chloro-N-(2-(3,4-dimethoxyphenyl)-benzoxazol-5-yl)-benzamide.

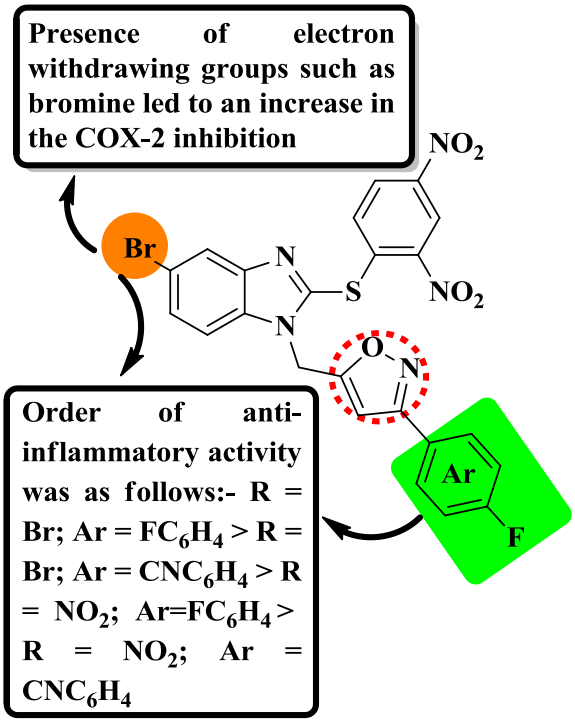


Fig. 79. Structure and SAR of most potent 2-mercaptobenzimidazole containing 3,5-disubstituted isoxazole derivative.

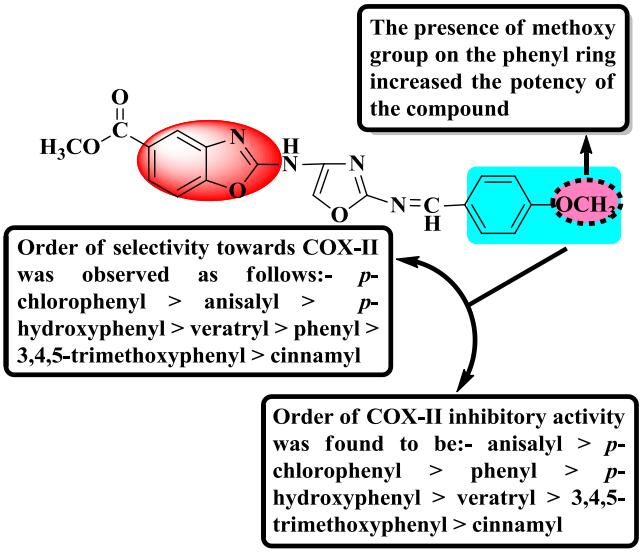


Fig. 80. Structure and SAR of Methyl-2-(2-(4-chlorobenzylideneamino) oxazol-5-ylamino) benzoxazole-5 carboxylate.

concentrations upto 10 μM, to evaluate their COX-1 and COX-2 inhibition expressed in murine monocyte/macrophage J774 cell line. Compound **"75"** was found to be 36 times more potent than the reference drug celecoxib. The anti-nociceptic activity of the nitrile derivative **"75"** (%writhe reduction = 57%) was comparable with that of the reference drug Celecoxib (%writhe reduction = 69%) (Fig. 82).

Kim et al. [242] prepared 1H-pyrrole-2,5-dione derivatives and assessed for the inhibitory action on LPS-induced PGE2 production in RAW 264.7 macrophage cells as well as the COX-1 and COX-2 inhibition. Compound **"76"** showed more potent and selective inhibition of COX-2 [COX-2 IC_{50} = 6.0 nM; COX-2 selectivity index (SI) = > 168] than celecoxib (COX-2 IC_{50} = 72 nM). Results revealed that *N*-methyl group was a determining factor of COX-2 inhibition potential and selectivity alongwith the electron withdrawing Chloro group (Fig. 83).

Anzini et al. [243] synthesized 3-substituted 1,5-diarylpyrroles bearing a nitro-oxyalkyl side chain linked to different spacers and assessed for selective COX-2 inhibition. Compound **"77"**, showed most potent COX-2 inhibition which may be due to an electronic interaction at the inner hydrophobic channel COX-2 and appears to be independent of the presence or position of the fluorine but not from the number of substituents. 3',4'-difluoro compound is less active (IC_{50} = 0.920 μM) than the corresponding un-substituted or mono-halogenated derivatives **"77"** (IC_{50} = 0.0073 μM SI = 150.7) (Fig. 84).

Anzini et al. [244] synthesized substituted 1,5-diarylpyrrole-3-

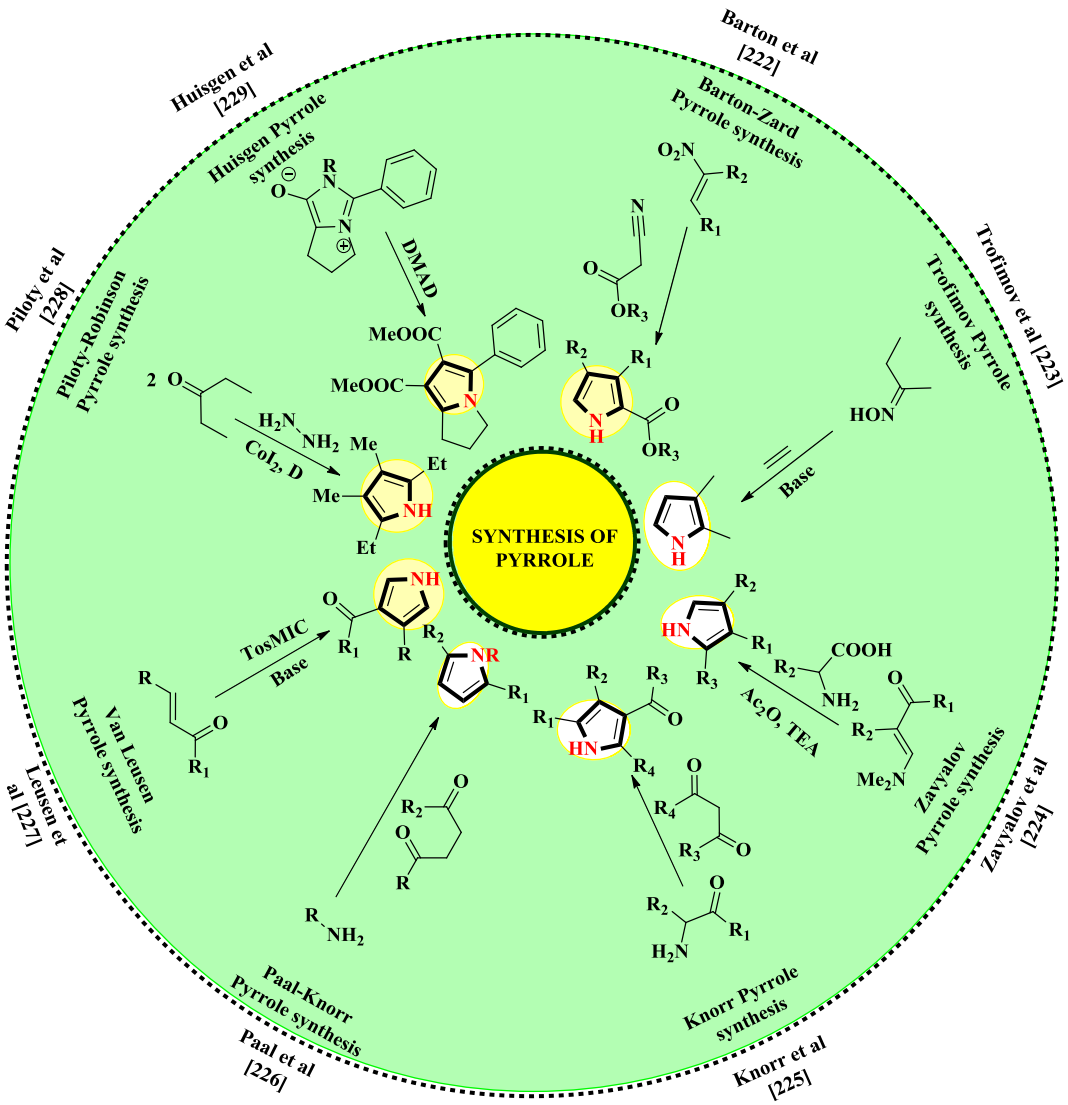


Fig. 81. Synthesis of pyrrole.

Table 7
Patents on Pyrrole moiety relating to anti-inflammatory activity.

S. No.	Patent number	Patent date	Inventors	Description
1.	US6887893B1 [229]	03 May 2005	Shinichi Kurakata, Masaharu Hanai, Saori Kanai, Tomio Kimura	Methods and compositions for treatment and prevention of tumors, tumor-related disorders and cachexia
2.	WO2008140251A2 [230]	20 November 2008	Jae Yeol Lee, Dong Joon Choo, Kyung Tae Lee, Jong Taik Moon, Ji Young Jeon	Cyclooxygenase-2 inhibitors
3.	US6936632B2 [231]	30 August 2005	Hans-Guenter Striegel, Stefan Laufer, Karola Tollmann, Susanne Tries	Fused pyrrole compounds, pharmaceutical agents containing the same, and the use thereof
4.	US5908858A [232]	01 June 1999	Tomio Kimura, Yasuo Noguchi, Akira Nakao, Keisuke Suzuki, Shigeru Ushiyama, Akihiro Kawara, Masaaki Miyamoto	1,2-diphenylpyrrole derivatives, their preparation and their therapeutic uses
5.	US7906551B2 [233]	15 March 2011	Andrea Cappelli, Maurizio Anzini, Mariangela Biava, Francesco Makovec, Antonio Giordani, Gianfranco Caselli, Lucio Claudio Rovati	3-substituted-1,5-diarly-2-alkyl-pyrroles highly selective and orally effective COX-2 inhibitors
6.	US5935990A [234]	10 August 1999	Ish K. Khanna, Richard M. Weier, Yi Yu	Substituted pyrrolyl compounds for the treatment of inflammation
7.	US6180643B1 [235]	30 January 2001	Jeffery A. Zablocki, Eugene Tarlton, Jr., James P. Rizzi, Nathan B. Mantlo	Aryl and heteroaryl substituted fused pyrrole antiinflammatory agents
8.	US9162979B2 [236]	20 October 2015	Antonio Giordani, Mariangela Biava, Maurizio Anzini, Vincenzo Calderone, Lucio Claudiao Rovati	1,5-Diaryl-2-alkylpyrrole-3-substituted nitro esters, selective COX-2 inhibitors and nitric oxide donors
9.	US6867211B2 [237]	15 March 2005	Hans-Guenter Striegel, Stefan Laufer, Karola Tollmann, Susanne Tries	4-Pyridyl-and 2,4-pyrimidinyl-substituted pyrrole derivatives and their use in pharmacy
10.	USRE39420E1 [238]	05 December 2006	Tomio Kimura, Yasuo Noguchi, Akira Nakao, Keisuke Suzuki, Shigeru Ushiyama, Akihiro Kawara, Masaaki Miyamoto	1,2-Diphenylpyrrole derivatives, their preparation and their therapeutic uses
11.	WO2004029040A1 [239]	08 April 2004	James L. Bullington, Xiaodong Fan, Paul F. Jackson, Yue-Mei Zhang	3,4-disubstituted pyrroles and their for use in treating inflammatory diseases
12.	US5700947A [240]	23 December 1997	Piero Del Soldato	Nitric esters having anti-inflammatory and/or analgesic activity and process for their preparation

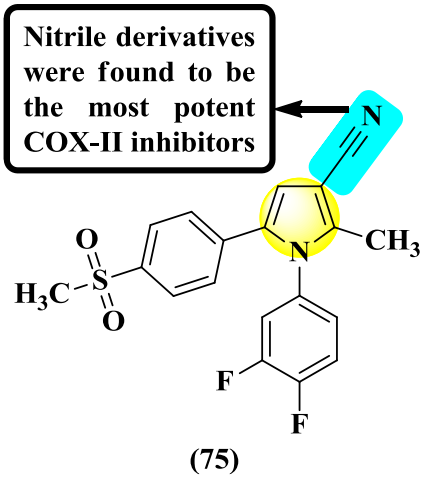


Fig. 82. Structure and SAR of 2-Methyl-5-[4-(methylsulfonyl)phenyl]-1-[3,4-difluoro-phenyl]-1H-pyrrole-3-carbonitrile.

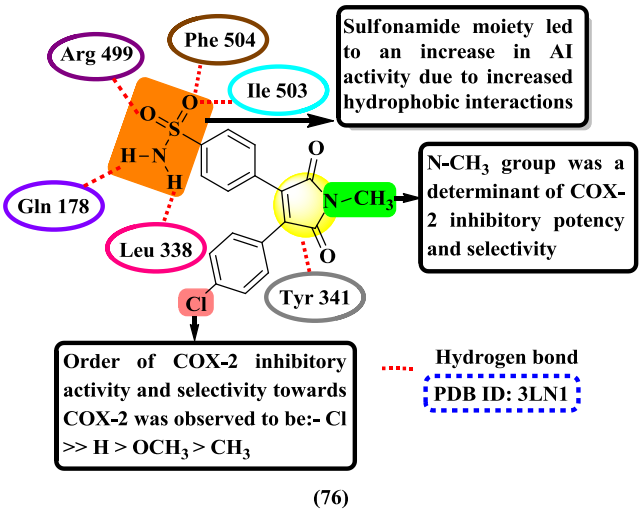


Fig. 83. Structure, SAR and molecular docking of the most potent compound of the 1-methy-1H-pyrrole-2,5-dione series.

alkoxyethyl ethers and evaluated *in vitro* for COX-2 inhibition. Compound **"78"** (COX-2 IC_{50} = 0.015 μM SI = > 6666) showed equivalent COX-2 selectivity to valdecoxib, but more selective than celecoxib and less selective than rofecoxib (Fig. 85).

Biava et al. [245] synthesized substituted 1,5-diarylpyrrole derivatives. *In vivo* anti-inflammatory and analgesic activity evaluation revealed that **"79"** as the most potential compound of the series (COX-2 IC_{50} = 0.010 μM, selectivity index= > 10,000, %inhibition = 91% for a dose of 1 μM). Its activity was compared using celecoxib (COX-2 IC_{50} = 0.06 μM, selectivity index = 61.7, %inhibition = 80% for the same dose of 1 μM). Murine models were used in order to carry out paw pressure test and paw volume test. The % of paw-edema suppression for **"79"** (95.5%) was comparable with that of the reference drug, celecoxib (95.5%). Ester derivatives displayed better COX-2 inhibition. Presence of fluorine atom at *meta* position in **"79"** increased the COX-2 inhibitory activity as well as selectivity of the compounds (Fig. 86).

Biava et al. [246] synthesized newer substituted 1,5-diarylpyrrole derivatives and assessed for anti-inflammatory and analgesic activity. Compound **"80"** was the most potent compound (COX-2 IC_{50} = 0.0073 μM, selectivity index = > 13600) in comparison to celecoxib as the reference drug (COX-2 IC_{50} = 0.079 μM, selectivity index = 65). Standard carrageenan induced rat paw edema model was used to check the anti-inflammatory activity of the synthesized series

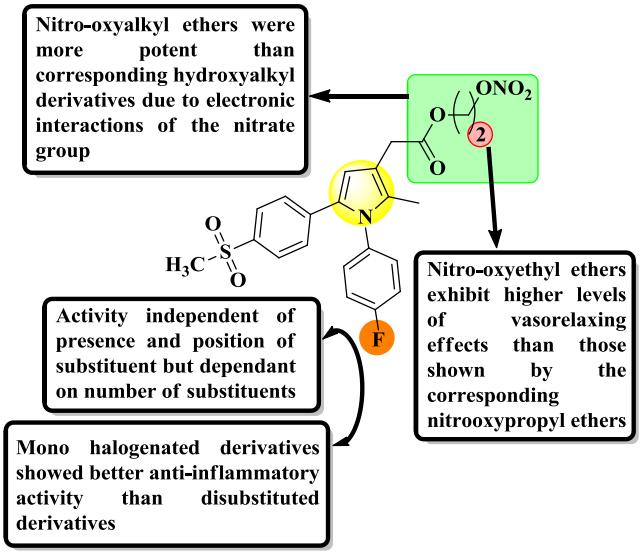


Fig. 84. Structure and SAR of 2-(2-(1-(4-Fluorophenyl)-2-methyl-5-(4-(methylsulfonyl) phenyl)-1H-pyrrol-3-yl)ethoxy)ethylnitrate.

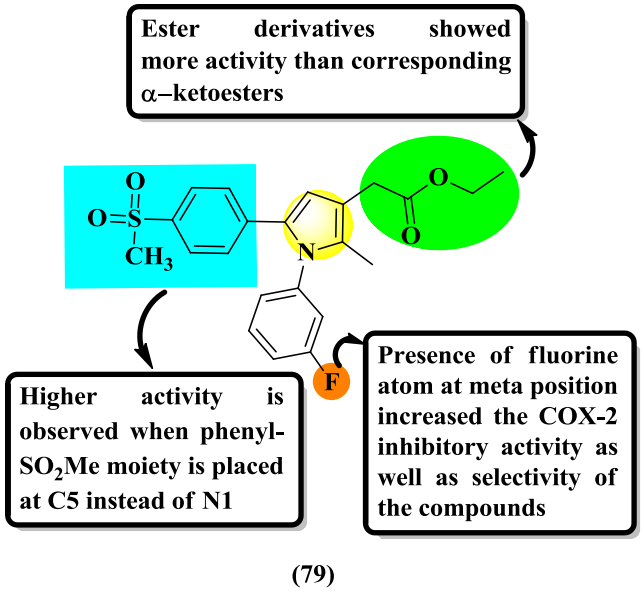


Fig. 86. Structure, SAR and molecular docking of ethyl-2-methyl-5-[4-(methylsulfonyl) phenyl]-1-[3-fluorophenyl]-1H-pyrrol-3-acetate.

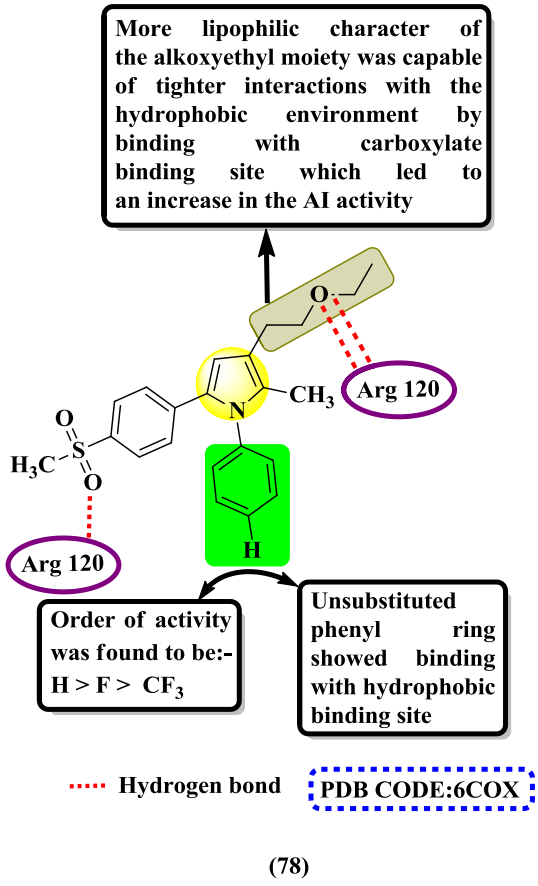


Fig. 85. Structure, SAR and molecular modeling of the most potent compound of the novel series of 1,5-diarylpyrrole-3-alkoxyethyl ethers.

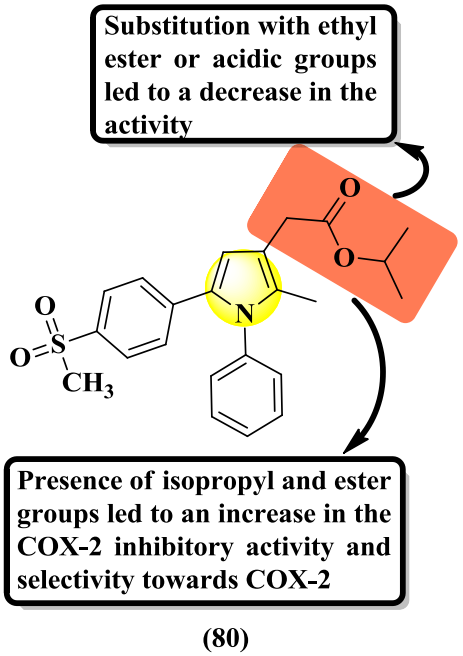


Fig. 87. Structure and SAR of Isopropyl-2-methyl-5-[4-(methylsulfonyl) phenyl]-1-phenyl-1H-pyrrole-3-acetate.

where **"80"** (%inhibition = 100% using a dose of 1 μM) showed added potentcy than celecoxib (%inhibition = 80% using a dose of 1 μM). Randall-Selitto model of zymosan-induced hyperalgesia in rats was used to check the hyperagesia where **"80"** (ED_{50} = 2.2 mg/kg) appeared more potent than celecoxib (ED_{50} = 9.0 mg/kg). Presence of longer side chains such as isopropyl at C3 led to a better interaction with hydrophobic residues of the receptor and thus increasing the selectivity towards COX-2. The presence of *n*-butylester as a substituent was found to increase the COX-2 inhibition (Fig. 87).

Harrak et al. [247] synthesized 1,4-benzodioxine or pyrrole derivatives and evaluated for *in vitro* and *in vivo* anti-inflammatory potential. Derivative **"81"** (COX-2 IC_{50} = 2.4 μM, SI = 4.4) was found to be more potent. The *in vitro* activity and *in vivo* activity (using rat paw oedema model induced by carrageenan) showed that compound **"81"** was more active than the reference drug ibuprofen (COX-2 IC_{50} = 6.2 μM, SI = 1.1). SAR analysis showed that pyrrole ring as core nucleus showed best anti-inflammatory activity. The carboxylic acid moiety conferred greater activity both *in vivo* and *in vitro* in the respective tests. The *N*-substituent and the importance of its position was also noteworthy. When the substituent was 2-flourophenyl at C3, it

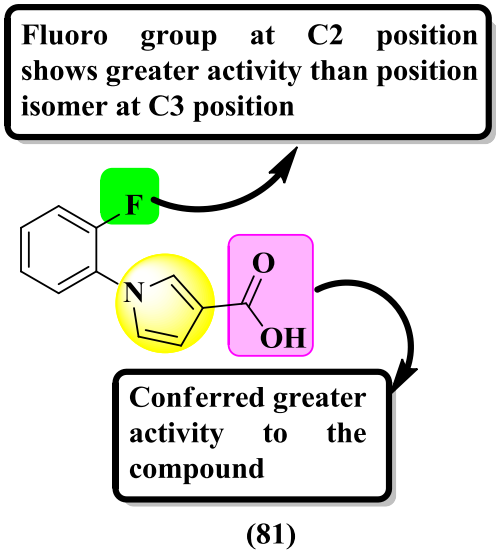


Fig. 88. Structure and SAR of 2-(N-(2-Fluorophenyl)pyrrol-3-yl) acetic acid.

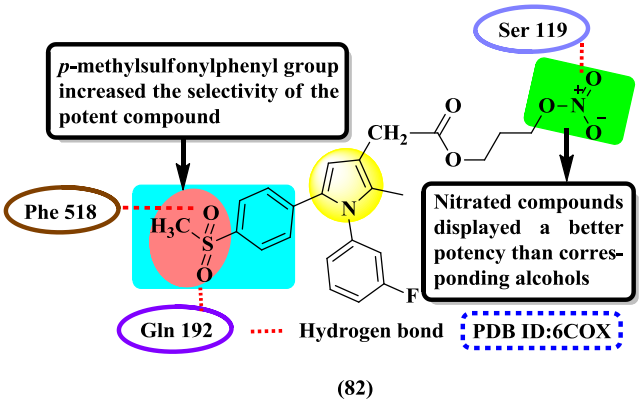


Fig. 89. Structure, SAR and molecular docking of the most potent compound of 1,5-Diarylpyrrole-3-acetic Nitroxyalkyl and Hydroxylalkyl Esters series.

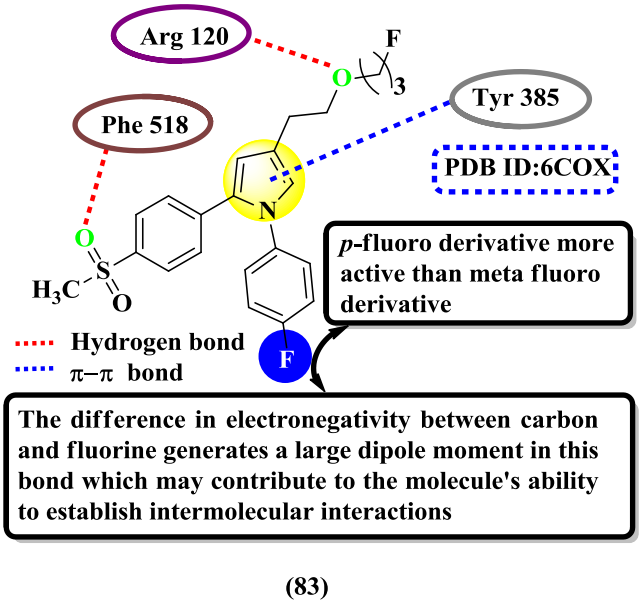


Fig. 90. Structure, SAR and molecular docking of the most potent compound of novel series of substituted 1,5-diarylpyrrole-3-alkoxyethyl ethers.

exhibited greater activity than its position isomer whihad the same group substituted at *C*2 (Fig. 88).

Biava et al. [248] reported pyrrole-derived nitrooxy esters that had a combined ability to inhibit COX enzyme as well as release NO which overall had the ability to reduce the side effects of COX-2 inhibitors. The inhibitory activity and selectivity was tested using murine models where **"82"** was found as potent compound (COX-2 IC_{50} = 0.0073 μM, selectivity index = 150.7) as compared to celecoxib (COX-2 IC_{50} = 0.0610 μM; selectivity index = > 63). HWB assay was used to check the preferential inhibitors of COX-2. Carrageenan-induced rat paw edema model used to check the %inhibition for the two compounds revealed satisfactory results (%inhibition = 97%) in comparison to the reference drug celecoxib (%inhibition = 100%). Here, the nitrated compounds displayed good potency. The increase in the length of the side chain in case of *meta*-fluorine substituted derivatives led to an increase in the inhibitory activity. *p*-methylsulfonylphenyl at 5th position group of the diarylpyrrole ring increased the selectivity of the potent compounds (Fig. 89).

Capua et al. [249] synthesized substituted 1,5-diarylpyrrole-3-alkoxyethyl ethers out of which the fluorinated derivatives were found to possess an improved pharmacokinetic profile. Compound **"83"** appeared 11 times more potent (COX-2 IC_{50} = 0.007 μM), selectivity index = > 14,285) than celecoxib (COX-2 IC_{50} = 0.079 μM, selectivity index = 65). The intraplantar administration of carrageenan was carried out in a rat model for evaluation of anti-inflammatory activity of the potent compound **"83"** which showed significant reduction in paw volume. The presence of fluorine atom resulted in increased intramolecular bonding especially at the para position which led to an increase in the COX-2 inhibitory activity. The stereoisomeric electronic effects, as well as metabolic obstruction due to fluorine atom led to a reduction in the first-pass effect. Intra-articular injection of monoiodoacetate (MIA), was administered to check the potency of the compound in osteoarthritis. MIA dependent hyperalgesia was significantly reduced by the repeated administration of **"83"** (Fig. 90).

7. Highlights of past review papers on COX-2

Bertolini et al. [57], had summarized about the role of COX-2 along with the shortcomings of COX-2 specific inhibitors. They had also discussed about the role of 5-LOX enzyme. Detailed discussion about the dual inhibition of COX-2 and 5-LOX enzymes and the importance of dual inhibition in ensuring high anti-inflammatory activity was done. Bertolini et al. concluded that it is the concurrent inhibition of the two enzymes which facilitates the anti-inflammatory activity and summarized the COX-2/5-LOX dual inhibitors that had been developed till 2002. Chakraborti et al. [250], in their 2010 review paper discussed about the progress of COX-2 inhibitors during the period of 2003–2009 and summarized the recent advancements on COX-2 inhibitors of the following structural classes:- furans, pyrroles, pyrazoles, Imidazole, Oxazole, Thiazole, Oxadiazole, Triazole, pyran, Indole, pyrazine, quinoxaline, pyridazinones, 1,2-Diarylethene, 1,1,2-Triarylethene and acetyline. Broad analysis of the general structural features of the selective COX-2 inhibitors had been carried out. An overview about selectivity of COX-2 inhibitors was also given by using the molecular modelling techniques. Zarghi et al. [70] in their 2011 review paper had summarized the selective COX-2 inhibitors based on two broad structural classes: - tricyclics (4-,5-,6- membered and fused bicyclic core) and non-tricyclics with 2- and 3- membered central template. The structural activity relationship was also discussed for the compounds that had emerged in the then last decade. Hemlatha et al. [251] had written a mini-review discussing the importance of indole nucleus in the development of anti-inflammatory drugs up till 2013. They had highlighted the potency of indomethacin and discussed the possibility of improving the selectivity towards COX-2 inhibition by changing the indole as core ring. The potency and choosiness of the derivatives was correlated with the presence of different substitution patterns. They had thus

established the importance of indole nucleus in the future development of COX-2 inhibitors. Carullo et al. [252] had summarized selective COX-2 inhibitors that were developed in the period 2009–2016. The chemical features of different series of compounds were explored and the importance of pharmacophore's feature in developing a potent COX-2 inhibitors was discussed. Jacob et al. [253] in their 2018 review paper had attempted to highlight the importance of dual COX-2/5-LOX inhibitors. Different derivatives having dual inhibition were explored along with various pharmacophoric modifications that could be done in those derivatives for improving the potency and selectivity. This was done by studying the binding interactions of marketed drugs with COX-2 and 5-LOX and then analyzing the inhibitory activity along with safety profile of selected derivatives (COX-2/5-LOX dual inhibitors). Suthar et al. [55] had explored the various approaches that have been used in the recent years for developing safer NSAIDs with a higher potential. The advantages and side effects of various NSAIDs derivatives were realized by evaluating their COX-1, COX-2 and 5-LOX (*in-vitro*) inhibition along with *in-vivo* anti-inflammatory and analgesic activities. They concluded that development of conjugated NSAIDs could be a promising option ensuring safety along with efficacy.

In our review paper, we have aimed to summarize the recent developments (2008–2019) on COX-2 inhibitors based on 5 heterocyclic ring systems (pyrazole, indole, oxazole, pyrrole and pyridine) that have shown great scope of progress in future. We have given a detailed diagrammatic representation about the structure-activity relationship of each compound which has not been given in any other recent review paper and have tried to understand the role of different substituents in establishing the COX-2 inhibition and selectivity of compounds for COX-2 over COX-1. The molecular modelling done for the compounds has also been presented along with the structures which would benefit the pharmaceutical chemists in developing potent and selective COX-2 inhibitors with stumpy GI side effects.

8. Conclusion

Recent efforts in the design of novel COX-2 inhibitors have led to the discovery of potential leads for the development of new anti-inflammatory, analgesic and anti-proliferative drugs. Pyrazole and indole as a core ring have been extensively studied as a potential drug scaffold by medicinal chemists in the last few decades. Other rings which have shown potential are oxazole, pyridine and pyrrole whose derivatives have been evaluated for COX-2 enzyme inhibition potency. Along with COX-2 inhibitory activity, drugs have been so designed which confer them anti-proliferative activity, also making this class of drugs as potential ant-cancer agents. The SARs presented along with the given structure should help scientists come up with newer molecules capable of more potent and selective action along with a better safety profile.

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