REVIEW ARTICLE

An Overview of Arachidonic Acid Metabolic Pathway and Recent Updates on a Few Heterocyclic Derivatives showing COX-2 Inhibition

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ABSTRACT

Inflammation crucial part of the immune response associated with a broad range of immunological diseases. The arachidonic acid (AA) pathway, which is an essential inflammatory mediator present at the internal surface of the cellular matrix, is hydrolyzed by phospholipase A2, which leads to the development of metabolites such as cytochrome P450 (CYP), lipoxygenases (LOXs), cyclooxygenases (Coxs) and enzymes which further develops into bioactive mediators such as prostanoids, leukotrienes (LTs) and more. Cyclooxygenases produce prostaglandins, available as 2 isomorphs, COX-1(constitutive) & COX-2(inducible), targeted by NSAIDs used to treat inflammation. Yet, they have a number of negative effects that lead to market withdrawal. Research has been done to look at novel COX-2 inhibitors and safety precautions. By structural alteration at COX-2 strong receiving site, structural along with functional research on a number of selective COX-2 blockers results in the creation of novel structures that are more potent and selective against inflammation while having a very low risk of side effects. This is made possible by computer-assisted medication design. This review gives an explanation regarding the biological functionalization of several COX-2 derivatives obtained by the help of in vitro, in vivo & molecular docking for better understanding of the structures and bonding accountable for an action.

Keywords: Inflammation, COX-2 inhibitors, Arachidonic acid, Cyclooxygenases

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INTRODUCTION

Arachidonic acid (AA), along with its biproducts are concerned with infection & diseases related to inflammation.[1,2] The AA is metabolized across 3 distinct enzymatic processes, such as lipoxygenases LOXs, cytochrome P450 (CYP enzyme), and cyclooxygenases COXs, generating active metabolites acting in inflammation.[3] Prostaglandin belongs to a class of biologically active compounds acquired from AA in the cyclooxygenase pathway, also known as eicosanoids. COX-1 and COX-2 enzymes bring eicosanoids closer to completion. All tissues have the constitutional COX-1 enzyme, however, only explicit COX-2 enzyme is intimated at the site of inflammation. COX-1 controls functions correlated with housekeeping, whereas COX-2, associated with the maintenance of cardio and renovascular health and platelet aggregation, produces pro-inflammatory prostaglandins.[4,5] Leukotrienes (LTs), a biologically active metabolite, were described by Bengt I. Samuelsson.[6] LT receptor antagonists and arachidonate 5-LOX (or ALOX5) were discovered to treat illnesses related to type one hypersensitivity reactions, including allergies and asthma.

Eicosanoid pathways (COX and LOX) constitute key therapeutic targets since they've been implicated in various clinical disorders via recognized receptors and metabolites.[7,8] The cytochrome CYP family contains enzymes of several subclasses.[9] Nonetheless, AA's metabolism includes a very noticeable class. Despite the fact that many CYP enzymes perform both hydroxylase and epoxygenase functions and produce a variety of final derivatives. The CYP enzymes' -hydroxylase activity get conversion of AA into hydroxyeicosatetraenoic acids (HETEs). 20-hydroxyeicosatetraenoics by-product, primarily associated with vascular activity, however, it is also associated with inflammation and possesses pro-inflammatory properties. The CYP2J and 2C families produce[10] CYP enzymes. Epoxyeicosatrienoic acid (EETs; 5,6,8,9,11,12, along with 14,15-EET) or AA epoxides are found inside hepatocytes and

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cardiomyocytes. The solvent Epoxide Hydrolase (sEH) enzyme produces Dihydroxyeicosatrienoic acids (DHET), or diols, from the transformation of EETs.[11,12]

Pathway and Their Metabolites

The COX Pathway

In the above context, COX is expressed in most cells and is not the limiting factor. But due to high reactivity towards oxidation, free arachidonic acid is unavailable. AA exists in the form of phosphatidylethanolamine, phosphatidylcholine, and phosphatidylinositides.[13] The COX enzymes, producing such as prostaglandins (PGs), Prostanoids, and Thromboxane A2 (TXA2), became initial enzymes to be identified as metabolizing AA. AA is liberated through a semi-permeable plasma membrane with the enzyme Phospholipase A2 (PLA2) support and metabolized through COX to PGG2 and PGH2. These are further converted into PGs using particular PG synthases. All of the NSAIDs inhibited the COX pathway (Figure 1), which led to a substantial decrease in PG production.[14] Although considerable arachidonic acid is capable of being generated by the effects of phospholipase C on diacylglycerol. More than 30 distinct isoforms of PLA2 are known to exist, and they can be broadly categorized as (i) cytosolic (cPLA2), which is activated by calcium concentrations of M, (ii) calcium-independent (iPLA2), or (iii) secretory (sPLA2), which is activated by mM concentrations of Ca. The COX enzyme catalyzes the second stage of prostanoid production. COX-1, as well as COX-2 are both isoforms. COX-1, the main source of prostanoid synthesis during housekeeping, is naturally produced in all cells. COX-2 (also identified as PTGS2) is a protein that is activated by stimuli generated by inflammation, growth factors, and hormones and is believed to be the principal origin of prostanoid synthesis throughout proliferative disorders like cancer and inflammation.[15] Though not cleared for autoregulation, both contribute equally during inflammation. The only difference present is the spatial arrangement among COX-1 and COX-2 within the energetic site. However, similarity exists for converting arachidonic acid into prostanoids, oxidation forming PGG_2 followed by peroxidation forming PGH_2. $PGH_2$is further broken by synthase/isomerase enzymes to prostanoids. PGH2 as well as PGG2 were substrates enabling the production of certain PGs such as PGE2, PGI2, PGD2, PGF2, and TXA2.[16-18] The nature of prostanoids synthesis is established from the varying levels of the above-discussed metabolic enzymes inside the cells detected at places of inflammation. PGD2 is largely produced by mast cells, while macrophages produce PGE2 and TXA2.[19] Whereas PGF synthase, thromboxane synthase, as well as the cytosolic (c) PGE synthase (PGES) isozymes exist in three different partners with whom COX-1 most regularly pairs, there are various advantages in partnering among COX as well as downstream synthases. The (PGIS) prostaglandin I synthase as well as microsomal (m) PGES isozymes, as both are significantly activated by COX-2, cytokines, including tumor promoters, feed PGG2/H2.[20-23] Among the initial investigations revealed upon the discovery of 2 COX isoforms consist of a screened of presently found NSAIDs those were associated with different impacts on COX-1 versus. COX-2 inhibition, and a few were discovered having a 20- to 70-fold greater degree of selectivity preferences[24] known today. The oxidative cyclization that occurs to the central 5 carbon molecules in PUFA produces prostaglandins.[25] By interfering with PGI2 production, resulting in the absence of COX-2, which regulates systolic blood pressure, homeostasis, as well as thrombogenesis. Following the process, NO-dependent vascular dysfunction occurs.[26] The COX-3 isoform, COX-3, is created by the same COX-1 gene; however is silent in humans due to splicing alternatives.[27-28] In accordance with research, COX-3 appears more frequently in the brain as well as heart microvesicles compared to the major arteries.[29,30] Prostaglandin (PG) endoperoxide H synthases are critical enzymes in the AA cascade that catalyses the conversion of AA to PGs as well as thromboxane (TXA).[31,32] Diet can influence prostaglandin as well as thromboxane production. Adding linoleic acid six supplements into your diet increases PG biosynthesis.[33] COX-1, including its physiologically active PGs ensure the integrity of the mucosal epithelium of the intestines and stomach, and their suppression can result in gastric injury, hemorrhage, and ulceration, just like it does with typical NSAIDs.[34,35] COX-2, in conjunction with COX-1, defends the mucosa of the digestive tract. The repeated administration of NSAIDs, causes a slew of issues in the digestive tract [36] including burning and ulceration.[37] However, COX-2 selective inhibitors tend to cause lesser gastrointestinal damage than standard NSAIDs.[38]

In fact, aspirin along with nonsteroidal anti-inflammatory medicines (NSAIDs), especially COX-2 inhibitors, are effective for both inflammation and pain medications.[39,40] Furthermore, endothelial suppression of PGI2 synthesis may provide adverse effects of COX-2 inhibitors related to cardiovascular disorder. PGI2 is produced by endothelial cells, whereas platelets produce TXA2.[41,42] Aspirin is hypothesised to lessen the risk of ischemic events that include strokes and cardiac arrest by inhibiting blood clotting. Pneumovascular hypertension is treated with prostaglandin derivatives. The 1st generation COX-2 inhibitors such as valdecoxib along with rofecoxib, were introverted from the trade[43]due to a effects that included cardiovascular issues, a higher likelihood of stroke, as well as cardiac arrest.[44] Giannella *et al.*[45] reported that indomethacin may successfully inhibit fast intestinal fluid secretion as well as Salmonella infection in rhesus monkeys. Eckmann *et al.*[46] just found and showed that incubating intestinal epithelial cells using *Salmonella* significantly increases COX-2 initiation.

The Lox Pathway

Four different hydroperoxy-eicosatetraenoic acids (HPETEs; 5, 8, 12, and 15-HPETEs) produced from the resulting LOX Enzymes, which are 15-LOX, 12-LOX, 8-LOX, as well as 5-LOX, depending on, where the molecular oxygen is inserted into the AA. The HPETEs are subsequently converted into molecules those are biologically active such, lipoxins (LXs), hepoxilins, and LTs or reduced to monohydroxy eicosatetraenoic acids (HETEs) through peroxidases enzymes.[47]

The majority of research has focused on the LOX enzyme 5-LOX, which adds O_2 to AA at C-5 position producing 5-HPETE as well as LTA4, the precursor to the LTs (LTB4, LTC4, LTD4, as well as LTE4) [48]. Moreover 5-LOX, were previously believed to be in the cytosol, it was later shown that it had the ability to traverse the nuclear envelope when phosphorylated.[49,50] Since then, it has been established that the main site of LT synthesis is the nuclear membrane. 5-HPETE is broken down through LTA4 hydrolase to synthesize LTB4.[51] FLAP, an activating protein[52] is a membrane-spanning protein having three transmembrane domains that is a group of the membrane-associated proteins, in the eicosanoid as well as glutathione metabolism group, and contains LTC4 synthase as well as microsomal PGE2 synthase, are essential for the catalytic action of 5-LOX.[53] Although it is generally believed that transformation of AA into 5-LOX by FLAP &/or acts like set, for 5-LOX, it is not quite clear what FLAP performs in 5-LOX reactions.[54] 5-LOX-derived active mediators particularly oxo-ETEs are produced from the HETEs through microsomal dehydrogenase in form of polymorphonuclear leukocytes (PMNLs), being considered as a strongly active eosinophillic chemoattractant.[55] Increasingly LTs are recognised such as a significant contributor to inflammation.[56] They are produced by an enzyme called as LTA4 hydrolase, a cytosolic protein additionally each zinc-dependent peptidase along with LTA4 hydrolase activity. Though LTA_4 hydrolase acts as a peptide biologically, is not understood yet, and it restricts inflammation in pulmonary system by degradation of chemotactic peptide along with proline-glycine-proline (PGP).[57] Consequently, during a period of inflammation, degradation of chemotactic peptide PGP occurs by LT4 hydrolase while also producing the chemotactic lipid mediator LTB4. There are two known primary deactivation mechanisms for LTB4 inactivation. LTB4 is deactivated by granulocytes and hepatocytes oxidising its C-20 via the -oxidation pathway,[58] which is carried out by the CYP enzymes CYP4F3 within granulocytes & CYP4F1 or two within hepatocytes.[59] The 12-hydroxydehydrogenase LTB4 enzyme,[60] also included in the deactivation of other eicosanoids like LXA4 & PG48, converts 12-keto-LTB4 into inactive LTB4 in other organs. In terms of signalling, LTC4 works on smooth muscle contraction via the CysLT1 and CysLT2 receptors. LTB4, unlike LTC4, operates through the LTB4R2 (BLT2) and LTB4R (BLT1) receptors.[61] Additionally their capability to produce dihydroxyeicosatetraenoics. Additionally, 5-LOX, 12-LOX, and 15-LOX, all create dihydroxyeicosatetraenoic acids (diHETEs), oxo-ETEs, and LXs.[62] Similarly 12-LOX, transforms 5(S)-HETE into 14(R),15(S)-diHETE, and 5(S),12(S)-diHETE to produce extra-platelet LTA4.[63,64] 5-LOX produces LTA4 in neutrophils which is getting converted into platelets, at the same time, 12-LOX produces either LXB4 / LXA4.[65,66] There are having 2 isomorphs of 15-LOX present in mammalian cells, those are 15-LOX-2 along with 15-LOX-1. Arachidonate 15-lipoxygenase gene as well as the functional enzyme metabolizes AA into LXB_4, LXA_4, & 15- oxo-ETEs is encoded by 15-LOX-1. Additionally, 15-LOX-2, produces 8S-HETE and 15-oxo-ETE.[67,68] When 15-diHPETE is used as a substrate, 15-LOX-1's efficiency is 20 times more than 12-LOX's, resulting in LXB4 as the catalytic product.[69]

The Cytochrome Phosphate-450 Pathway

The CYP genes conceal for a group of mixed-functional monooxygenase enzymes, including individual enzymes more than 6000.[70]

The metabolism of xenobiotics which are lipophilic in nature is the most-explained role of the Cytochrome Phosphate pathway. Till-date important biological activity of EETs in heart, liver, endothelial cells, and kidney. A lots of genetic & external factors change the CYP expression and the function of their bioactive products.[71] The cardiovascular system is regarded as producing CYP enzymes from hydroxylated HETEs (6-, 17-,8-,19-, and 20-HETE).

AA epoxides, also known as EETs, exhibit anti-inflammatory, cardioprotective, and vasodilatory properties. They can also affect vascular smooth muscle migration, a crucial stage in atherosclerosis and vascular remodelling. Every one of the four EET regioisomers are having stereoisomers, for example, 11,12-EETs has 11®,12(S)-EET & 11(S),12®-EET, along with the various stereoisomers describe varied effects.[72] It is already considered that the cardiovascular system is shielded by CYP-derived EETs from transient ischemia-reperfusion damage, persistent non-ischemic cardiomyopathy, and hypertensive.[73]

In-silico Approaches (Computer-Aided Drug Designing)

Before manufacturing, an essential computational evaluation of the affinity towards the binding of enzyme blockers is being included in Computer-Aided Drug Design (CADD) models.[74] *In-silico* assisted drug designing aspects were implemented for development of COX-2 blockers strongly, creating stable anti-inflammatory along with anticancer drug entities.[75] There are so many CADD methods, employed for modeling and visualizing potent COX-2 inhibitors. It helps in studying and altering the ligand or substrate analog interacting with the enzyme or receptor more precisely and occupying important sites, obtaining in better specificity and potency. The approach is termed as drug design based on structure. Advanced CADD procedures are being used in the choosing and designing of the best correspondent.[76] Recently, implementing the aspects based on structure for regular screening and molecule designing resembles to be intricate. The chance of using such techniques for the creation of appropriate and strongly active blockers is made possible by the availability of numerous crystal arrangements of atoms complexed with COX-2 inhibitors. Upon comparing the experimental and calculated relative binding affinities towards structurally similar inhibitors with COX-2 infers that QSAR, computational technology along with FEP methods provided semi-quantitative, qualitative as well as quantitatively agreement sequentially with obtained results. CADD methodology thereby speeds ups the drug discovery along with the development procedure and makes it as affordable cost.[77]

Heterocyclic Derivatives Showing Cox-2 Inhibition

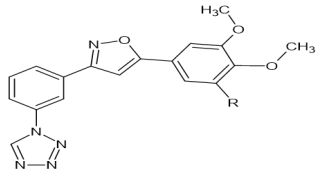
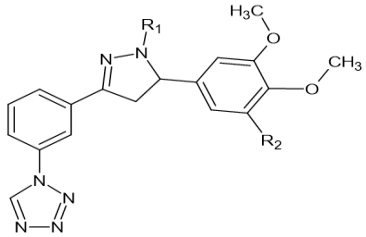
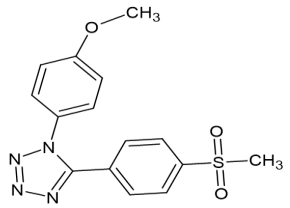
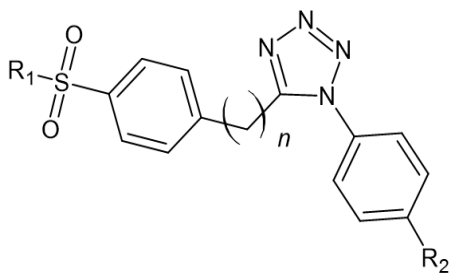
Tetrazole based derivatives

Synthetic organic heterocyclic compounds contain tetrazole, a five-membered ring with 4 nitrogen and 1 carbon atoms. Tetrazole has a broad spectrum of biologically and pharmacologically active implementations because of its highly consistency of Nitrogen, and multi-electron conjugating system.[78]

Depending upon isosteric replacement of group SO_2NH_2 biologically in Celecoxib and Rofecoxib with less acidic tetrazole moiety many tetrazole derivatives are designed by Labib *et al.* and team. Two different divisions of compounds were planned namely isoxazoles (1, 2) along with pyrazoles (3,4,5,6,7) given in Table 1, Compound 1 to 7 shows potencies of vitro COX-2 inhibition in an Enzyme-linked immunosorbent assays (ELISA assay) with in vivo anti-inflammatory activity, in vitro selectivity, and high water solubility. Compound 2, 4, 6 with the remarkable COX-2 selectivity index discussed in table 1 shows closeness with reference drug celecoxib and compound 2 and 6 have shown extremely less ulcerative properties among one of the most known side effects of NSAIDS. Through proper analysis and research it was concluded that Methoxy groups on the benzene ring are more efficient than hydrogen groups.[79]

Further experiments and updates in technology lead to the development of more tetrazole-based derivatives showing remarkable inhibition of COX-2 activity Al-Hourani *et al.* reported several derivatives of tetrazoles, in the span of 7 years showing potent activity. Compound **7** showed potent inhibition of COX-2 though the potency was found less than the already existing marketed drug celecoxib.[80] Modifications in the methyl sulfonyl unit CH_3SO_2X of the tetrazole derivatives lead to the development of new compounds 8,9,10 on researching the potency of these compounds, compound 8,9showed moderate inhibition of COX-2 activity.[81] Anita *et. al* reported EIA assay

Table 1: Tetrazole derivatives showing anti- inflammatory activity selectivity towards COX-2

S No.	*Compound name*	*Structure*	*IC_{50} (µmol/L)*	*SI*
1	1 R = H	Isoxazole 	0.045	251.11
2	2 R = -OCH_3		0.041	302.44
3	3 R_1 = H R_2= H	Pyrazole 	0.064	164.06
4	4 R_1 = H R_2= -OCH_3		0.043	297.67
5	5 R_1=-$COCH_3$ R_2 = H		0.065	167.69
6	6 R_1=-$COCH_3$ R_2 = -OCH_3		0.039	317.95
7	7		2.0	210
8	8 R_1 =-NH_2 R_2=-CH_2OH n = 0		24	0.87
9	9 R_1 =CH_3 R_2=CH_2OH n = 1		5.2	
10	10 R_1 = -CH_3 R_2=-NH_2 n = 1		> 67	

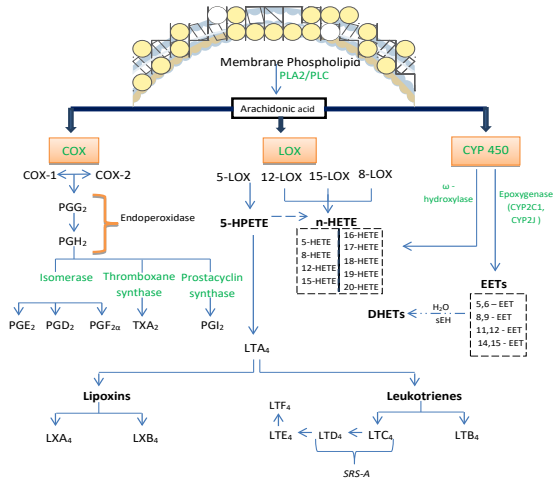


Figure 1: AA metabolizing pathway

compound 10 which has increased its activity and selectivity towards COX-2. Due to the methylene spacer at the C-1, position their activities have increased towards enzyme COX-2 up to 200-folds.[82]

Indole based derivatives

Indole is a heterocyclic aromatic organic compound with the general formula C_8H_7N. A five-membered pyrrole ring, and six membered benzene rings are fused together to form a bicyclic fused structure. It is a substance with significant pharmacological value and is used to screen a variety of receptors.[83] Hayashi *et al.* reported that, as a selective COX-2 inhibitor, compound 11 (Table 2) derived from indomethacin considered as a basic structure which showed strong selective COX-2 blocking activity in human cells. Also, it has effective as an anti-inflammating agent when administered orally and with it is potent within a living organism showing inhibition in fluid retention (edema) [84]Compound 12 (Table 2) synthesized by Kaur *et al.* was containing substitution on the C-3 position of indole which resulted in selective COX-2 inhibition. Using molecular docking techniques, the C = N bonded with phenyl CF_3 substituent remains present close by the COX-2 action site and an essential hydrogen bond was formed with amino acid His90, very important for COX-2 blocking.[85]Compounds 13,14,15, (Table 3) were also reported which were containing toluene sulfonyl *group at the position* N-1 and *presence of* dipeptide groups at position C-3, for checking COX-2 inhibition. Compounds 13 and 14 were reported for the same in vivo anti-inflammation-based activity as such of diclofenac. Compound 15 was reported to be more potent.[86]On adding sulfonamide, at the C-5 position of indomethacin and two 4-Fluro benzyls provided derivatives of indole with selective COX-2 inhibiting moeities were substituted at C-2 and C-3 positions.[87]A novel C-3, N-1 substituted derivative of indole 16 (Table 2) was designed using bio isosteric replacement drug design strategy. The indole-containing analogs or derivatives were mainly modified on the basis of the arrangement of atoms of indomethacin. As a consequence, the successor of Acetic Acid at the position C-3 of indomethacin with different other groups is considered to be an efficacious approach to improve these potency and perceptiveness. Moreover, changes at C-2 and N-1 positions have shown positivity as well. The above-discussed compounds derived from indole were tested and evaluated for their selectivity and IC_{50} values tabulated below.

Pyrazole derivatives

Pyrazole contains π-electrons in excess. It is being identified as primary compound in synthesis of chemicals, specifically for the invention of novel COX-2 inhibitors. Medicinal entities used clinically contain pyrazole as the basic structure are celecoxib, antipyrine, aminopyrine, and metamizole.[88] Celecoxib (as a COX-2 inhibitor containing pyrazole base) was discovered for first time using Claisen condensation following a cyclo-condensation reaction to give an overall production of 50%.[89]

Bansal *et al.* have synthesized a compound[22] (Table 3) containing pyrazole fragment in its basic structure, it had shown more affinity towards COX-2 inhibition. Molecular docking suggested formation of a vital H-bond among O_2, $-No_2^-$ group & the H^+ content of aminoacid Arg120, essential for interacting with COX-2 enzymes.[90] Xu *et al.* and team[91] by considering a typical sulphonamide fragment containing selective COX-2 inhibitor celecoxib, derived few pyrazole analogs with N-aryl sulfonate, compound 25–29 (Table 3) showed strong COX-2 inhibitory activity through both in vitro and in vivo researches. In the year span from 2011 to 2012 El-Sayed *et al.*[92,93] derived various pyrazole derivatives namely 23,24and 30 (Table 4) increased anti-inflammatory activity along with COX-2 inhibitory activity. Molecular docking studies indicate that compound 23 and 24 bind to the reactive site of COX-2, as a selective COX-2 blocker, SC-558. Whereas compound 30 forms deep bond within the pocket of COX-2 and forms a hydrogen bond with Arg513, and Gln192, consequently with COX-2 inhibition. By using molecular docking for calculating the strength between the ligand and Arg513, required for COX-2 inhibition were examined through unusual flexible fragments by Tewari *et al.* and group[94] selectivity index (Table 4) for compounds 31and 32. In 2020, various halogenated tri-aryl-pyrazoles were produced based on the arrangement of celecoxib's atoms. Due to the availability of a halogenated aryl ring, which influences the selectivity and activity and is absent in celecoxib, three fluorinated compounds—numbers 33, 34, and 35—exerted good efficacies in COX-2 inhibition assay when performed in *in-vitro* manner.[95] In order to inhibit COX-2 and 15-lipoxygenase, an unique class of 1,5-diaryl pyrazoles was created. Specifically, 36 exhibited strong anti-inflammatory action.[96] Compound 37 designed by Mohammed *et al.* contains an acylamino linker in the compound, responsible for COX-2 inhibition and potent edema inhibition (Table 3).[97] A hybridization strategy aiming for dual inhibitory action towards COX-2/5- LOX. Celecoxib, licofelone, sulindacsulfide, pyridone, and their combined active groups were used to create the pyrazole sulfonamide derivative compound 38, which was created to meet the binding specifications for both enzymes. Leu338 and Tyr341

Table 2: Indole derivatives showing anti-inflammatory activity selectivity towards COX-2

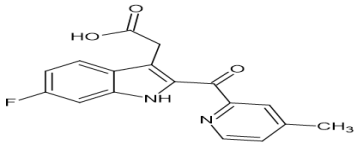
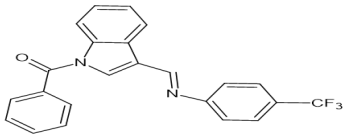
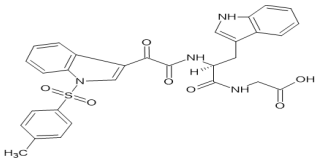
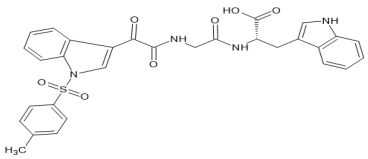
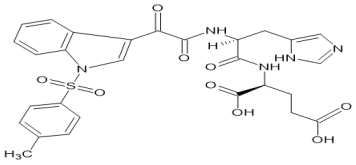
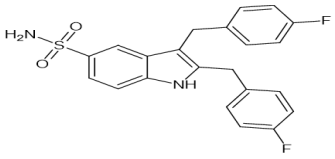
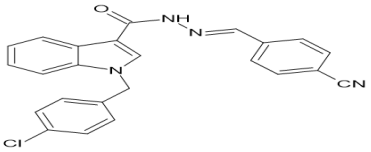
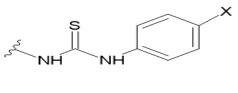
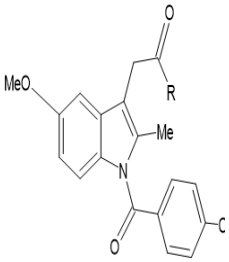
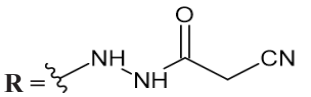
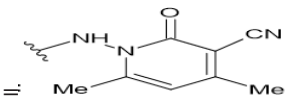
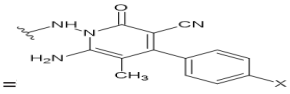
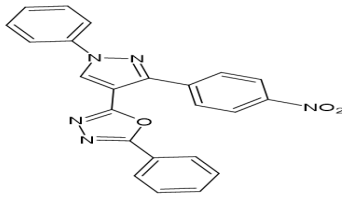
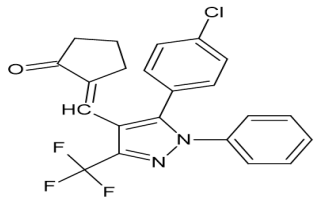
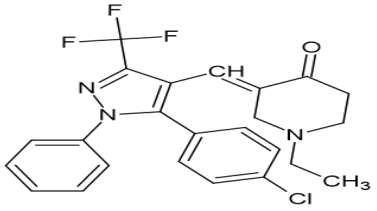
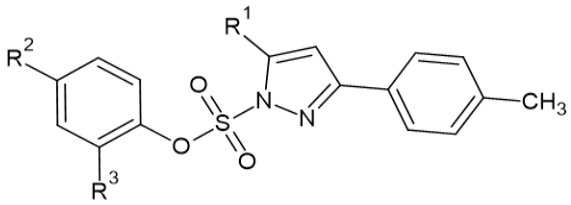
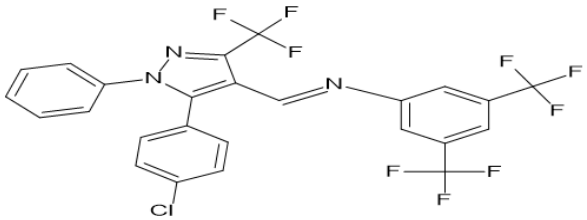
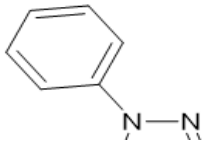
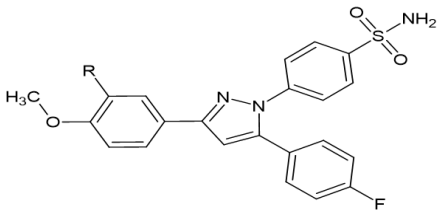
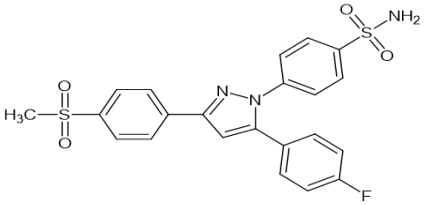
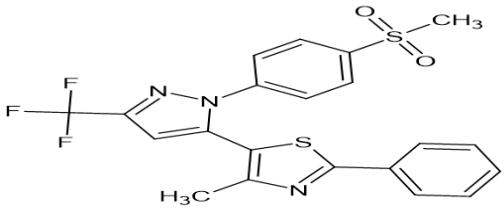
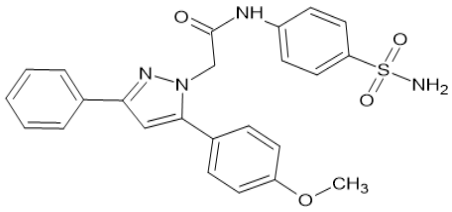
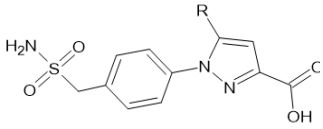
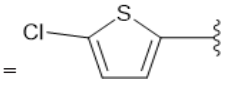
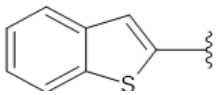
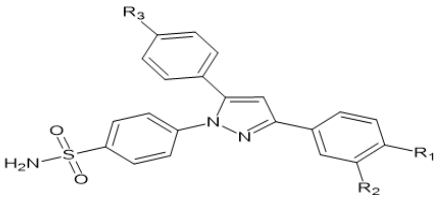
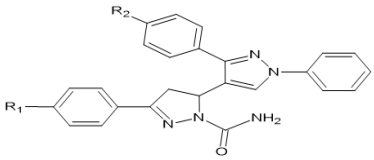
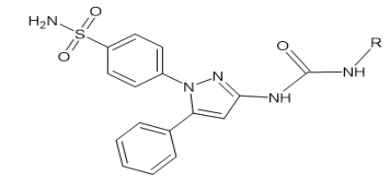
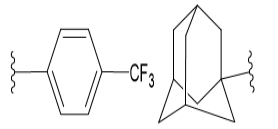
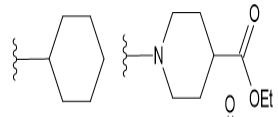
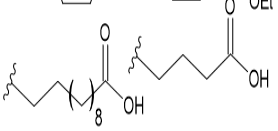
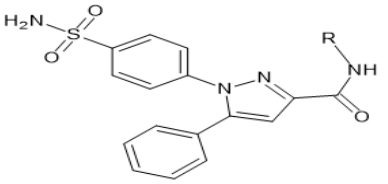
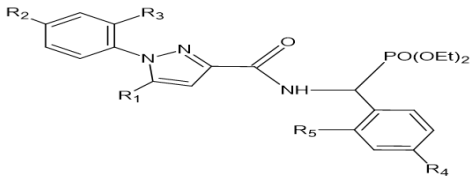
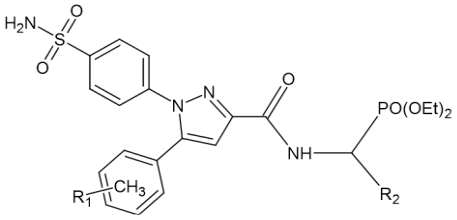
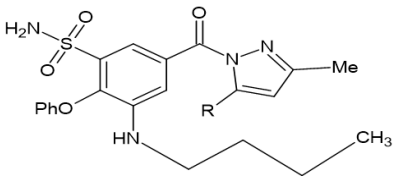
SNo.	*Compound*	*Structure*	*IC_{50} (µmol/L)*	*SI*
1	11		0.009	-
2	12		0.32	>312
4	13		0.006	351
5	14		0.099	440
6	15		0.54	24
7	16		67± 6% (50 µmol/L)	-
8	17		7.59	5.16
9	18 (X = H, F, Cl, Me,OMe,COOMe, COOEt)	**R =** 	0.09–0.27	4.07–6.33
10	19	 **R =** 	0.4	
11	20	**R =** 	0.31	
12	**21** **X** = H, Cl	**R =** 	0.15 (X = H) 0.09 (X = Cl)	

Table 3: Pyrazole derivatives showing anti-inflammatory activities and selective COX-2 blocking

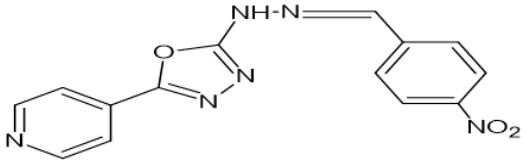
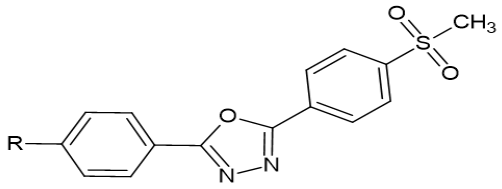
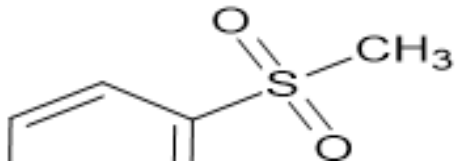
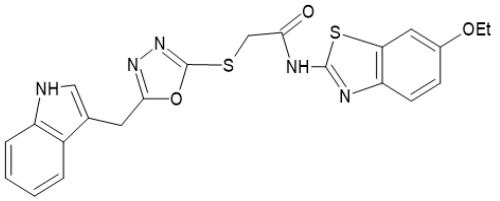
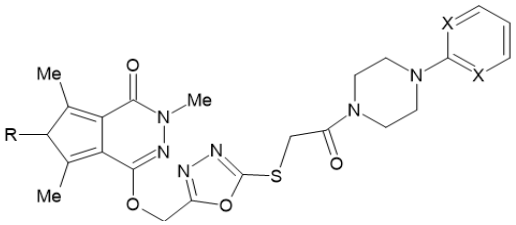
SNo.	*COMPOUND*	*STRUCTURE*	***IC_{50} (μmol/L)***	***SI***
1	22		0.31	> 222
2	23		0.45	111.1
3	24			
4	25 R_1 = -CH_3 R_2 = H R_3 = H		0.0011	455
5	26 R_1 =-CH_3 R_2 = I R_3 = H			
6	27 R_1 = -CH_3 R_2 = H R_3 = I			
7	28 R_1 = -CH_3 R_2 = H R_3 = Cl			
8	29 R_1 = -Ph R_2 = H R_3 = H			
9	30		0.26	192.3
10	31 R = H		16.8	0.5100
11	32 R = CH_3			

12	33 R = H		0.049	253.1
13	34 R = -OCH_3			
14	35		0.054	214.8
15	36		-	4.89
16	37		1.76	11.1
17	38	 **R =** 	0.4	29.73
		R = 	0.01	344.56
18	39 R_1 = OMe, SO_2Me, OEt R_2 = H, OMe R_3 = Cl, F, Br		0.043–0.17	50.6–311.6
19	40 R_1 = H, F, Cl, Me, OMe R_2 = H, F, Cl		1.09–2.10	63.56–80.03

21	41	 **R =**   	1.24 – 4.12	2.85 – 7.03
22	42				
23	43 R_1=thiophene-2-yl, naphthalen-1-yl R_2 = H, F, Br, SO_2NH_2 R_3 = H, F R_4 = H, Cl, Br, OMe R_5 = H,OMe			0.22 – 5.84	5.84 - 179.18
24	44 R_1=Br, F, Cl, OMe, Me, CF_3 R_2 = phenyl, 4-bromophenyl phenyl, 4-bromophenyl methyl			0.28–6.32	5.41– 172.32
25	45		R = Ph R = Me	0.32 4.75	4.84– 115.82

were hydrophobic targets for the aryl ring, and the amino acids Tyr341, and Arg106 were targets for the -COOH group, which interacted with the ASC of COX-2 in H-bond, & ionic path ways, successfully. The H-bond was developed by the sulfonamide connecting to residue of Ser339.[98] The researchers found that compared to indomethacin, fluorinated pyrazole derivative 39 had improved gastrointestinal profile and higher anti-inflammatory effectiveness. Also, they looked at the effects of para-halogen substitution, methylsulfonyl (-SO2Me) and alkoxy substitutes (on ortho and para positions) upon COX-2's phenyl ring blocking activity. Those alterations resulted in strong interactions with the main amino acid present at the ASC of COX-2. Impact of change in the electron-donating & electron- withdrawing groups of the phenyl rings on blocking action was studied, and fluorinated pyrazole displayed outstanding efficacy similar to celecoxib but with a higher SI. The nitrogen atom of the pyrazole ring, -SO2Me, and -SO2NH2 groups were first implicated in multiple H-bond interactions inside the ASC,[99] according to molecular docking of the tri aryl pyrazoles. Anti-inflammatory entities having dual inhibitory action may inhibit COX-2 or LOXs. Deracoxib, Celecoxib, Tepoxalin, and Lonazolac are examples of NSAIDs used in treating cancer & inflammation.[100,101] Abdelazeem *et al.* inferred urea- &- amide-linked derivatives of diaryl-pyrazole 41, 42 having double inhibition effectiveness towards COX-2 & HER-2, they possess high anti-inflammatory functions against edema synthesized in treating inflammation and cardiovascular disorders by degrading EETs. The strong pharmacophores 12-(3-adamantan-1-yl-ureido)-dodecanoic acid, celecoxib, SC-558, & GSK2256294 are joined to create a hybrid diaryl-pyrazole molecule that has a diarylpyrazole group with urea and amide connections. This compound has a more favourable cardiovascular profile which is more potent than that of celecoxib and less risk of cardiovascular toxicity.[102] A sequence of pyrazole derivatives linked to amino-phosphonate group 43 replacing R alongwith naphthalene on the pyrazole ring, in place of thiophene leads high blocking effectiveness, especially when the N-1 pyrazole phenyl ring situated in p-position (–F > –SO_2NH_2> –Br).[103] The researchers evaluated

TABLE 4: Oxadiazole derivatives showing anti-inflammatory activities and COX-2 inhibition selectively

S No	*Compound*	*Structure*	*IC_{50} (μmol/L)*	*SI*
1	46		0.041 μmol/L	89.72
4	47 R = Cl		0.74	74.31
5	48 R = NO_2		0.48	132.83
6	49 R = NO_2		0.81	67.96
7	50 R = ^{t}Bu		0.89	68.10
8	51		37.5	1.96
9	52 X = C, N R = Ph, pentyl		6.8–15.0	-

These few drugs have been formed and are still on going works over them for better results.

numerous substituted compounds 44,45 those are having several substitutions but the substituent of 4-bromophenyl phenyl at R_2 position & methoxy group (R_1) on meta position monitored higher blocking effectivity towards COX-2.[104]

Oxadiazole Derivatives

Oxadiazole exists in three isomers, namely 1,2,4, 1,2,5-& 1,3,4-oxadiazole, having several pharmacological effectiveness like anti-viral, antibacterial, anti-tumor, and antioxidant effects. Three groups have previously detailed how COX-2 inhibitors with an oxadiazole group are made.[105] As summarized in (Table 4), El-Sayed *et al.* designed new oxadiazole compound 46, which showed well known COX-2 selectivity & blocking upon comparision with celecoxib.[106] Grover *et al.* discovered a series of oxadiazole-comprising derivatives namely47,48,49,50. These results ensured that tert-butyl is an essential group for increasing COX-2 inhibition along with selectivity, an alternative aspect for studies.[107]

Among several derivatives 2-[(5-((1Hindol) methyl)-1,3,4-oxadiazol-2-yl) thiol] N-(6-ethoxybenzothiazol2-yl) acetamide 51 containing benzothiazole & thiazole moieties showing COX-2 inhibition selectively[108] which shown significant inhibition of EGFR expression when compared with that using erlotinib.[109]

Derivative of Pyrrolo[3,4-d]pyridazinone 52 possessing 4-aryl1-(1-oxoethyl)piperazine as active site was documented by Szczukowski *et al.* Molecular docking and spectroscopic analysis clearly indicating the interactions of H-bond among the COX-2 ACS having, Arg208, and Lys211 were commonly by the nitrogen atom, & carbonyl group of the pyridazine moiety, sequentially.[110]

CONCLUSION

The AA, along with its byproducts, are of huge concern with relation to inflammatory processes. COX-2 is an enzyme that catalyzes the synthesis of PGs during inflammation and is an essential pharmaceutical focus regarding anti-inflammatory moieties. The main objective of this review is to bring light on synthetic heterocyclic derivatives having effective COX-2 inhibition as well as other enzymes active during inflammation

such as LOX, EGFR, PDE_5 and anti-inflammatory effectiveness. Molecular designing of COX-2 inhibitors synthetically with the assistance of CADD has accelerated the process. Studies on the chemistry of these structures helped in guessing the higher potency, selectivity and minimal adverse effects as noted from traditionally marketed NSAIDs. However, further studies and investigations are essential for the better understanding required for market approval and mass application.

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