https://doi.org/10.33472/AFJBS.6.13.2024.1318-1336

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

'Microwave Assisted Synthesis, Design Including Docking of Benzimidazole Substituted 4-Thiazolidinone Derivatives'

Ashutosh Pathak[1*], Neetu Soni[2], Bharat Mishra[3], Pawan Kumar[4], Sugat Shukla[5], Salman Ahmad Khan[6], Desh Deepak Pandey[7], Sanjay Kumar Yadav[8], Ashutosh Yadav[9], Aadaya Raj Pandey[10]

[2]Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology & Sciences, Allahabad, Uttar Pradesh, India – 211007

[1,3,6,8,9]Institute of Pharmacy, Dr. Shakuntala Misra National Rehabilitation University, Mohan Rd, Sarosa Bharosa, Lucknow, Uttar Pradesh India – 226017.

[4]Institute of Engineering and Technology, Dr. Shakuntala Misra National Rehabilitation University, Mohan Rd, Sarosa Bharosa, Lucknow, Uttar Pradesh India – 226017.4

[7]Department of Pharmaceutical Chemistry, City School of Pharmacy Bajha, Pratapganj, Ayodhya Rd Barabanki, Uttar Pradesh India -225001.

[10]Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University, A Central University,Lucknow, 226025 Uttar Pradesh, India.

[5]Institute of Pharmacy, Sitapur Shiksha Sans than, Resora Uttar Pradesh, India – 261001

***Corresponding author:** (Dr.) Ashutosh Pathak
Institute of Pharmacy Department of Pharmaceutical Chemistry, Dr. Shakuntala Misra National Rehabilitation University, Mohan Rd, Sarosa Bharosa, Lucknow, Uttar Pradesh India – 226017.
Email: rrscopashu1986@gmail.com

Article Info

Volume 6, Issue 13, July 2024

Received: 02 June 2024

Accepted: 30 June 2024

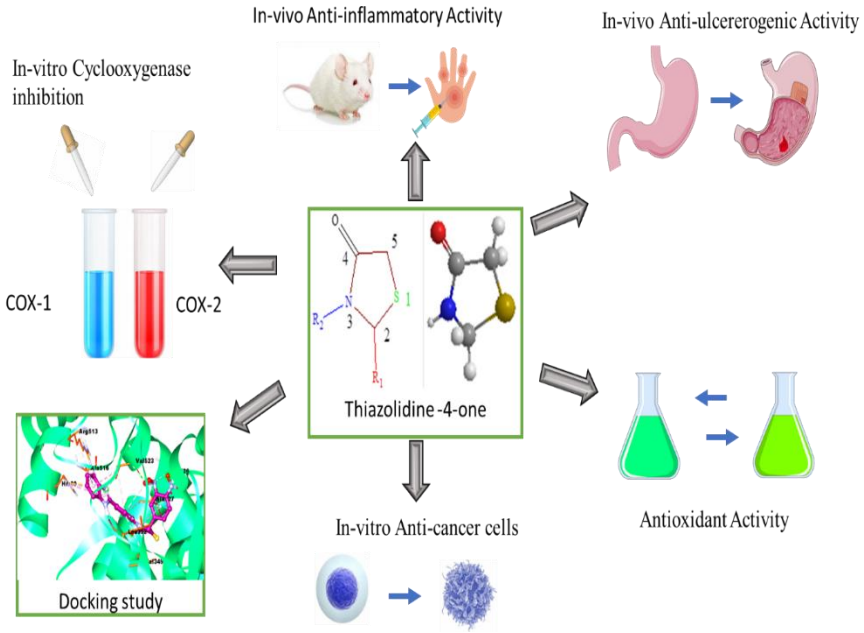
Published: 24 July 2024

doi: 10.33472/AFJBS.6.13.2024.1318-1336

ABSTRACT:

Application of green chemistry methods for synthesizing these derivatives aligns well with current environmental concerns and the need for sustainable practices in chemical synthesis. It's great to see efforts directed towards minimizing waste and ensuring the safety and quality of products. The process of synthesizing six derivatives of substituted phenyl thiazolidine-4-ones seems thorough, especially with the utilization of spectral analysis techniques like Mass, IR and NMR spectroscopy, along with results from elemental analyses. These analyses provide essential insights into the structural characteristics and purity of the synthesized compounds. Moreover, employing molecular docking studies to evaluate the affinity of these derivatives towards target enzymes COX-1 as well as COX-2 is a commendable approach. Acknowledging the collaboration of these compounds through their biological targets through computational methods like Auto Dock Vina can offer valuable predictive insights into their potential efficacy as anti-inflammatory agents. Overall, this study appears to be situated a comprehensive exploration of the biochemical properties of thiazolidine -4 one's derivatives, with a focus on their anti-inflammatory activity. It holds promise for contributing to the development of innovative medicinal substances that are less harmful and more effective.

Keywords: Thiazolidin-4-one, anti-inflammatory activity, molecular docking, indomethacin, docking studies, para-amino benzoic acid (PABA).



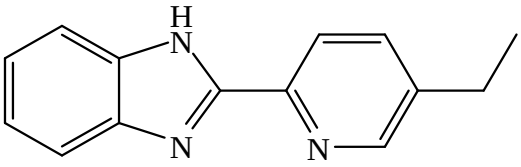
GRAPHICAL ABSTRACT (Fig. 1)

1. Introduction

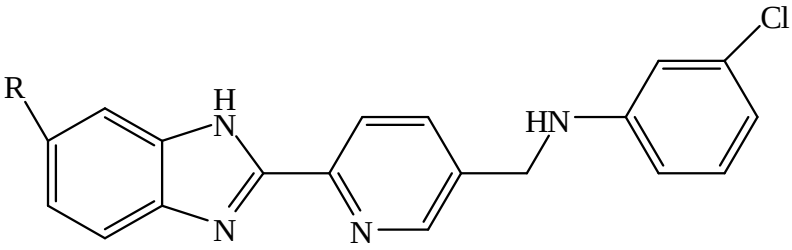
Under the influence of different noxious causes, such as infections, damaged cells, and toxic substances, inflammation is a defence mechanism that preserves equilibrium within tissues and facilitates survival. Numerous crucial inflammatory mediators, Tissues normally secrete a variety of substances to regulate inflammation, including various hormone [prostaglandin, thromboxane, the neurotransmitter histamine, leukotrienes, nitric oxide, tumour proliferation factor-(TNF-), interleukins (IL), chemokines, and colony stimulating factors (CSF) [1-4]. Vascular tissues' complicated biochemical reaction to opposed stimuli like infections, irritants, or injured cells is inflammation. It comprises a series of biochemical processes involves different cell types, the immunological system, and the local vascular system present in the wounded tissue and can be either acute or chronic. The initial reaction, known as acute inflammation, is characterised by an increase in the flow of bloodstream that enters injured tissues carrying plasma and primitive adaptive immune cells like macrophages as well as neutrophils. The hallmarks of persistent inflammation include the progressive change in the kind of cells present at the location of the inflammatory response and concurrent devastation and healing of the injured tissue [5-9]. NSAIDs are among the furthermost frequently prearranged medications designed for the intervention of inflammation. These drugs' main mode of action is based on the suppression of COXs, or cyclooxygenase enzymes. NSAIDs able to split into two subclasses according to their selectivity. Ibuprofen and indomethacin, which show stronger selectivity towards constitutional COX-1 than the inducible COX-2, are examples of nonselective COX inhibitors in the initial class.

Nonselective COX inhibitor usage, however, was linked to several of negative side effects, including ulceration, acute renal failure, and allergic skin responses [10-15]. Since thiazolidinediones (TZDs) play part in the control of several physiological processes, they have been the focus of substantial investigation. By functioning as antagonists for the receptors known as PPARs (γ- peroxisome proliferator-activated), TZDs that lower serum glucose concentration includes pioglitazone and rosiglitazone. Additionally, this family of substances offers a number of additional possible positive benefits, such as an enhancement of lipid composition, a reduction regulating hypertension, including anti-inflammatory actions. To halt

the production of cell adhesion molecules and stimulate the production of nitric oxide in addition to the generation of pro-inflammatory cytokines, TZDs 12 target vascular cells13, monocytes/macrophages14, and macrophages. [16-22]. An important heterocyclic ring system is thiazolidine-2,4-dione (TZD), which has a number of pharmacological effects, such as those that are anti-hyperglycaemic anti-inflammatory, antibacterial, anti-cancer, and anti-arthritic, among other properties. Bansal et al 2012, reported because of the well-known anthelmintic benzimidazole's modest anti-inflammatory and analgesic properties, the Centre for P.R. at Japan's Kanebo Ltd. Has created a sequence relative to benzimidazoles 2-[2-pyridinyl] through isometric substitution about thiazole at that forefront loop in the pharmacophore. Beginning a sequence of molecules, benzimidazole 2-(5-ethyl 2-pyridinyl) as shown in **Fig. 2** was discovered to exhibit superior antipyretic, analgesic, and anti-inflammatory properties than tiaramide and phenylbutazone. Additionally, it irritates the gastrointestinal tract Compared to cite substances, tolerability is marginally lower and therapeutic efficacy is 2-3 times higher. [23]. Newly, Vasava et al 2020, having created innovative 2- (Supplanted Phenol) amino methyl benzimidazoles as well as assessed by a model of paw oedema generated by carrageenan. The molecule in **Fig. 3** has proven to be a powerful compound (81% preservation), and adding a bromo group at position 6 (as indicated in Fig. 4) further improves the action (89% inhibition) as shown in **Fig. 4 and 5** [24-26].

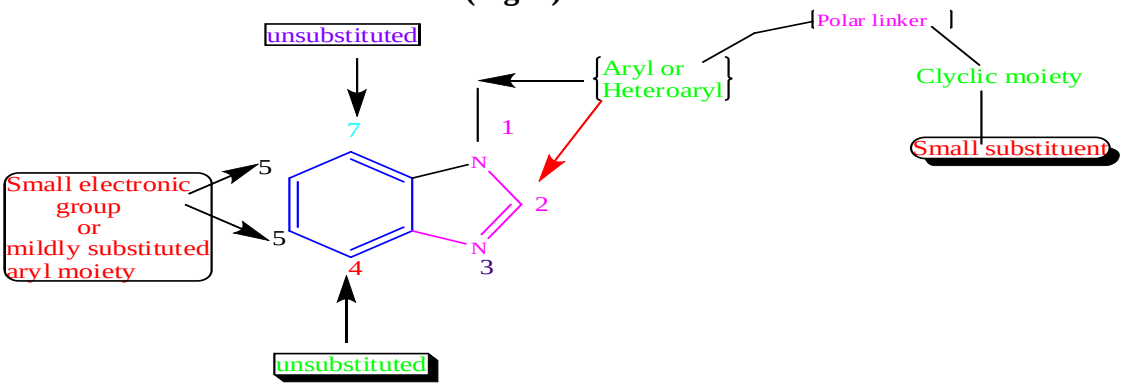


(Fig. 2)



(Fig. 3) R =H

(Fig. 4) R = Br



(Fig. 5) CHEMICALS AND INSTRUMENTS

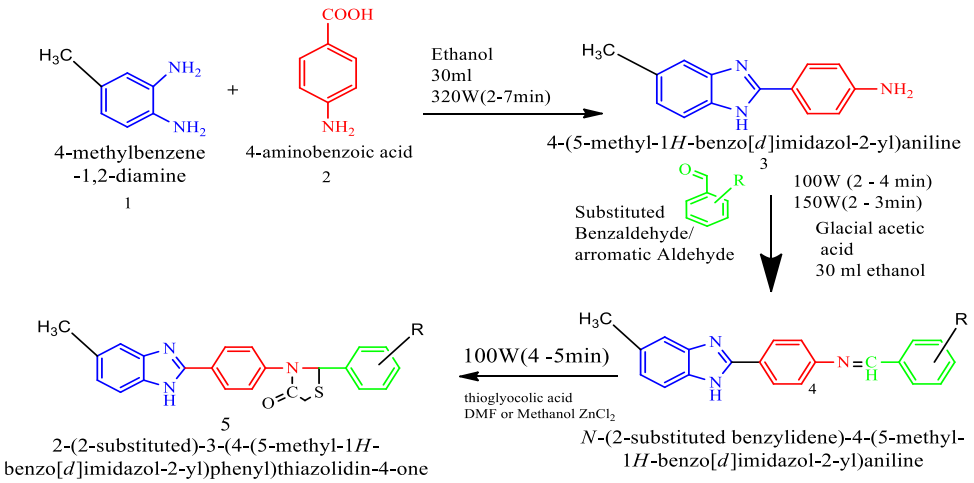
The sources of the chemicals and reagents were Sigma Aldrich Pvt. Ltd., SD-Fine Ltd., and Hi-media Chem. Ltd. The melting temperatures were ascertained using means of the open capillaries temperature device that is not adjusted. Using silica gel G, (TLC) was used to track reaction's progress. Solvent system (chloroform: methanol, ethyl acetate: n-hexane) together with an ultraviolet (UV) cell to see dots. ^{1}H captured at 400 MHz on a Bruker WM-400 analyser. ppm (δ value) chemical modifications were documented via DMSO (δ 0 ppm for ^{1}H

NMR). Applying the Perkin Elmer 2400 elemental detector, the pureness of the constituents was confirmed based on analysis of the elements. A scientific (green tech.) microwave machine oven called the Ceramic Catalyst System was used to carry out the electromagnetic-irradiated synthesis (Functioning in between 140–700 W) [27-28].

GENERAL METHOD OF MICROWAVE SUPPORTED HYBRIDATION

A microwave source at 320W was used to irradiate an equimolar amount of PABA and Four-methylbenzene-1, 2- diamine for 2–7 minutes. Utilising the phase that is mobile (petroleum ether and ethyl acetate) (7:3), the TLC technique was employed to track the development of the reaction. After cooling, gently add a solution containing 10% sodium hydroxide while stirring to make the product alkaline to precipitate. The product was subsequently filtrated, rinsed with ice-cold water, and decoloured with charcoal. Following drying, ethanol was used to reassemble the crude amorphous product. **[A1]**. Substituted The mixture received 0.07 mol of benzaldehyde administered compound A1 (0.07 mol), which was already dissolved in (ethanol) 30 ml and included a few of droplets of glacial acidic solution. The mixture was then microwaved at 100 W for 2–5 minutes. TLC was used to keep an eye on the reaction's progress. After cooling, it was then put over ice that had been crushed, filtered, dried, cleaned, and reconstituted from ethanol **[2I-2N].** Thioglycolic acid (0.005 mol/0.43 g), substituted Schiff base [2I-2N] (1.5 gm, 0.005 mol), and a tiny quantity of anhydrous $ZnCl_2$ in 250 ml of RBF. Then thoroughly fraternization the mixture, it stood microwave-irradiated for two minutes at 150 W and seven minutes at 100 W. Petroleum ether and ethyl acetate (3:4) were used as the mobile phase to track the reaction's endpoint on TLC. When the reaction was finished, the RBF was taken out of the micro-oven. Then cool the mixture before the result stood recrystallized from ethanol to remove the chemical **[3I-3N].**

Scheme I: Synthesis of 4- thiazolidinone derivatives (**3I-3N**)



Where R=Cl, NO_2, Br, OH

CHARACTERIZATION OF SYNTHESIZED COMPOUNDS

Table.1. PHYSICAL DATA OF compound (IA, 2I-2Nand 3I-3N) (MICROWAVE ASSISTED SYNTHESIS)

Compound code	R (Substituent')	Chemical formula	Mol. Wt.	% Yield	Colour	M. p. (^{0}C)	Solubility	R_f value
1A		$C_{14}H_{13}N_3$	223.12	87%	Dark brown	97-98 ^{0}C	Ethanol	0.59
2I	3-Cl	$C_{21}H_{16}ClN_3$	345.82	74%	Light Yellow	117-118^0 C	Ethanol, Methanol	0.67
2J	4- NO_2	$C_{21}H_{16}N_4O_2$	356.13	68%	Dark Yellow	121-123^0 C	Ethanol DMSO	0.65
2K	2-Br,4- NO_2	$C_{21}H_{15}BrN_4O_2$	435.27	79%	Light Brown	115-117^0 C	DMSO, Methanol	0.68
2L	3-Br, 4- NO_2	$C_{21}H_{15}BrN_4O_2$	435.27	72%	Light Yellow	119-120^0 C	Ethanol Methanol	0.61
2M	3-OH, 4- NO_2	$C_{21}H_{16}N4O_3$	372.38	82%	Dark Yellow	125-126^0 C	Ethanol	0.57
2N	3, 4- di NO_2	$C_{21}H_{15}N_5O_4$	401.37	74%	Light Brown	113-114^0 C	Ethanol Methanol	0.68
3I	3-Cl	$C_{23}H_{18}ClN_3OS$	419.93	61%	Dark Green	117-118^0 C	Ethanol, Methanol	0.63
3J	4- NO_2	$C_{23}H_{18}N_4O_3S$	430.48	65%	Brown	98-99^{0}C	Ethanol	0.62
3K	2-Br,4- NO_2	$C_{23}H_{17}BrN_4O_3S$	509.38	74%	Light Yellow	112-113^0 C	Ethanol Methanol	0.74
3L	3-Br, 4- NO_2	$C_{23}H_{17}BrN_4O_3S$	509.38	67%	Brown	120-121^0 C	Methanol DMSO	0.56
3M	3-OH, 4- NO_2	$C_{23}H_{18}N_4O_4S$	446.10	65%	White	111-112^0 C	DMSO, Methanol	0.59
3N	3, 4- di NO_2	$C_{23}H_{17}N_5O_5S$	475.48	70%	Cream white	104-105^0 C	Ethanol, Methanol	0.65

SYNTHESES OF ANALOGUES

4-((5-methyl – 1 H – benzo [d] imidazole - 2 - yl) aniline [A1]

Equimolar quantity of 4 – methyl benzene - 1,2-diamine (0.1 mol) and (PABA) para-amino benzoic acid (0.1 mol) was microwave-irradiated to feed two to seven minutes beginning at 320 Watt using alcohol as the medium. TLC was employed to monitor the reaction's end while the solvent phase consisted of petroleum-based ether and acetate of ethyl. (7:4). Subsequently cooling added 10% sodium hydroxide solution gradually while mixing to made alkaline to the end result with precipitation, filtering, icy water washing, and charcoal decolorization and after being dried, the amorphous result was recrystallized using ethanol to form 4-(5-methyl- 1- H-benzo [d] imidazole – 2 - yl) aniline [**A1]**. Dark (Deep) Brown, Solid, $R_{f.}$ 0.59, Yield: 87%, mp: (97-98 ^{o}C), FTIR (cm-1, KBr): N-H (Stretching) 3559.37, N-H bending (NH_2) 1594.65, (C=N) 1638.24, (C-N) 1125.74, Aromatic C-H stretching: 3095.43, m/z: 223.11 (100.0%), 224.11 (16.3%), 225.12 (1.1%) Anal. calcd for $C_{14}H_{13}N_3$ (223.12) C, 74.32; H, 4.78; N, 17.81, Found. C, 74.33; H, 4.77; N, 17.80.

Standard Protocol for Microwave-Assisted Synthesis to get substituted Schiff bases [2I-2N]

To the compound 4 - ((5- methyl – 1 - H - benzo [d] imidazole – 20) - yl) aniline A1 (.07 mole) in 30ml of C_2H_5OH holding 3-4 drops of GAA, substituted (.07 mole) benzaldehyde was supplementary & the combination was treated within microwave at 320W for Two- five min. The achievement feedback was watched via TLC, formerly cooled, emptied crazy about child ice, then filtered, wash, dehydrated & recrystallized as of C_2H_5OH (ethanol) to form [2I-3N].

Synthesis of N - (3-Chloro- benzylidene)- 4 – ((5-methyl-1H) – benzo [d] imidazole – 2 - yl) aniline [2I]

(Light)Yellow, Solid, $R_{f.}$ 0.67, Yield: 74%, mp: (117-118 ^{o}C), FTIR (cm-1, KBr): N-H (Stretching) 3485.92, N-H bending (NH_2) 1622.93, (C=N) 1682.38, (C-N) 1142.45, Aromatic C-H stretching: 3086.17, (C-Cl) 724.64, (C=N) 778.22 m/z: 345.10 (100.0%), 347.10 (32.2%), 346.11 (22.9%), 348.10 (7.6%), 347.11 (2.5%), 346.10 (1.1%), Anal. calcd for $C_{20}H_{15}N_3O$ (345.82) C, 71.97; H, 3.99; Cl, 09.89; N, 11.24, Found. C, 71.08; H, 3.65; Cl, 10.45; N, 11.78

Synthesis of 4 - ((5- methyl – 1- H - benzo [d] imida- zol-2-yl)-N-(4-nitrobenzylidene) aniline [2J]

Dark Yellow, Solid, $R_{f.}$ 0.65, Yield: 68%, mp: (121-123 ^{o}C), FTIR (cm-1, KBr): N-H (Stretching) 3557.37, N-H bending (NH_2) 1618.65, (C=N) 1682.38, (C-N) 1233.38, Aromatic C-H stretching: 3095.28, m/z: 356.13 (100.0%), 357.13 (23.0%), 358.13 (3.2%), 357.12 (1.5%), Anal. calcd for $C_{21}H_{16}N_4O_2$ (356.13) C, 69.55; H, 3.37; N, 14.62; O, 7.89, Found. C, 69.76; H, 3.92; N, 14.99; O, 7.96

Synthesis of N-(2-bromo-4-nitrobenzylidene)-4-(5-methyl- 1(H) -benzo-[d] imidazol-2) - yl) aniline [2K]

Lightbrown, Solid, $R_{f.}$ 0.68, Yield: 79%, mp: (115-117^{o}C), FTIR (cm-1, KBr): N-H (Stretching) 3554.32, N-H bending (NH_2) 1615.54, (C=N) 1682.38, (C-N) 1233.38, Aromatic C-H stretching: 3095.28, m/z: 356.13 (100.0%), 357.13 (23.0%), 358.13 (3.2%), 357.12 (1.5%), Anal. calcd for $C_{21}H_{15}BrN_4O_2$ (435.27) C, 56.97; H, 2.98; Br, 17.96; N, 11.91; O, 6.87, Found. C, 56.95; H, 2.97; Br, 17.36; N, 11.87; O, 6.35.

Synthesis of N-(3-bromo-4-nitrobenzylidene)-4-((5 – methyl – 1- (H) -benz [d] imida zol-2-yl) aniline [2L]

Lightyellow, Solid, $R_{f.}$ 0.68, Yield: 72%, mp: (119-120^{o}C), FTIR (cm-1, KBr): N-H (Stretching) 3554.32, N-H bending (NH_2) 1615.54, (C=N) 1682.38, (C-N) 1233.38, Aromatic C-H stretching: 3095.28, m/z: 436.04 (100.0%), 434.04 (99.5%), 435.04 (22.9%), 437.04 (22.3%), 438.04 (3.1%).435.03 (1.5%), 437.03 (1.4%) Anal. calcd for $C_{21}H_{15}BrN_4O_2$ (434.04) C, 56.93; H, 2.74; Br, 17.63; N, 11.78; O, 6.53, Found. C, 56.97; H, 2.48; Br, 17.86; N, 11.7; O, 6.53.

Synthesis of 5-(4 -(5 – (methyl -1 (H-) benz - [d] imida -zol- 2-yl) phenyl) imino) methyl)-2-nitrophenol [2M]

Darkyellow, Solid, $R_{f.}$ 0.57, Yield: 82%, mp: (124-126^{o}C), FTIR (cm-1, KBr): N-H (Stretching) 3294.73, N-H bending (NH_2) 1519.54, (C=N) 1674.48, (C-N) 1184.38, Aromatic C-H stretching: 3045.87, (N=O) 1472.42, (-CH_3) 1329.74 m/z: 372.12 (100.0%), 373.13 (23.0%), 374.13 (3.1%), 373.12 (1.5%) Anal. Cal. for $C_{21}H_{16}N_4O3$ (371.47) C, 66.37; H, 3.44; N, 14.95; O, 12.89, found. C, 66.37; H, 3.33; N, 14.94; O, 12.89.

Synthesis of N-(3 -(4-dinitrobenzylidene)-4 - (5 -methyl – 1(H) – benzo [d] imida - zol-2-yl) aniline [2N]

Lightbrown, Solid, $R_{f.}$ 0.68, Yield: 74%, mp: (113-114^{o}C), FTIR (cm-1, KBr): m/z: 401.11 (100.0%), 402.12 (23.0%), 403.12 (3.4%), 402.11 (1.8%) Anal. calcd $C_{21}H_{15}N_5O_4$ (401.37) C, 61.48; H, 2.97; N, 16.54; O, 14.49, found. C, 61.49 ; H, 2.99 ; N, 16 .67 ; O, 16.97.

The general process for synthesis with microwave assistance to get substituted Schiff bases [3I-3N]

Equimolar amount of synthesized compound (2I-2N) (0.6M) substituted (relieved) Schiff base with (thioglycolic acid) $SHCH_2COOH$ and (0.6M) with anhydrous $ZnCl_2$ was taken in 250 ml RBF, in green synthesis reaction (assortment) mixture was irradiation at (100 W-150 W, 2-7 min.). TLC was done by taking solvent system (mobile phase) using chloroform and ethanol or (chloroform: methanol). removed from the oven, then allowed to cool to form solid crystals (3I-3N) or powders, washed through water and dried, recrystallized (ethanol) (Upadhyay et al. 2010, Patil Swaraj et al. 2011)

2-(3-chlorophenyl)-3-(4-(6- (-methyl- 1 H – benzo [d] imida zol-2 - yl) phenyl) thiazolidinone-4 (3I)

Dark Green, Solid, $R_{f.}$ 0.63, Yield: 61%, m p: (117-118^{o}C), FTIR (cm-1, KBr): Aromatic (OH) 3623.78, Aromatic N-H stretching 3218.20, Ketone C=O stretching 1784.29, C=N (imine) 1688.35, N-H bending 1618.69, Aromatic (C=C) 1532.89, C-N (bending) 1198.37, (C-O) 1122.37, m/z: 419.09 (100.0%), 421.08 (36.5%), 420.09 (25.9%), 422.09 (9.3%), 421.09 (3.7%), 423.08 (1.6%), 423.09 (1.2%), 420.08 (1.1%)Anal. calcd $C_{23}H_{18}ClN_3OS$ (419.93) C, 61.48; H, 2.98; N, 16.54; O, 14.49, found. C, 61.81; H, 2.73; N, 16.41; O, 16.93.1HNMR, ppm (DMSO): $_1$H NMR ($CDCl_3$), $_1$H NMR ($CDCl_3$), 11.345 (d, 1 H), 9.686(s, 1H), 8.207-8.201(d, J=1.8Hz, 2H), 7.598-7.592 (1.8Hz) 7.339-7.332(d, J=2.1Hz, 2H), 7.228-7.214(d, J=4.2Hz, 2H), 7.094-7.083 (t, J=3.3, 1H), 7.064-7.052(d, J= 3.6Hz, 1H), 6.897-6.882(t, J=4.5Hz, 1H), 6.834-6.821(d, J=3.9Hz,1H), 6.448(s, 1H), 3.992-3.986(d, J=1.8, 1H), 3.906-3.901(d, J=1.5Hz, 1H).

3-(4-(5-methyl- 1 (H)- benzo [d] imida – zol - 2 – yl) phenyl))- 2 - (4-nitrophenyl)thiazolidine – 4 - Sone (3J) Brown , Solid, $R_{f.}$ 0.62, Yield: 65%, mp: (98-99^{o}C), m p: (98-99^{o}C), FTIR (cm-1, KBr): Aromatic (OH) 3635.62, Aromatic N-H stretching 3362.13, Ketone C=O stretching 1785.67, C=N (imine) 1684.78, N-H bending 1607.43, Aromatic (C=C) 1512.56, C-N (bending) 1392.93, (C-O) 1193.37 m/z: 430.11 (100.0%), 431.11 (27.3%), 432.11 (5.7%), 432.12 (3.0%), 433.11 (1.2%) Anal. calcd $C_{23}H_{18}N_4O_3S$ (430.48) C, 64.17; H, 4.21; N, 13.01; O, 11.15; S, 7.45, Found. C, 64.15; H, 4.19; N, 12.91; O, 11.12; S, 7.44**.** $_1$H NMR ($CDCl_3$), 12.568 (s, 1H), 9.438(s, 1H), 8.209-8.202 (d, J=2.1Hz, 2H), 7.786-7.782 (d,1.2Hz, 2H) 7.595-7.591(d, J=1.2Hz, 2H), 7.338-7.321(d, J=5.1Hz, 2H), 7.338-7.321 (d, J=5.1, 2H), 7.228-7.221(d, J= 2.1Hz, 2H), 6.637-6.631(d, J=1.8Hz, 1H), 6.442(s, ,1H), 3.993-3.982(d, J=3.3Hz, 1H), 3.906-3.901(d, J=1.5, 1H).

2-(2-bromo-4-nitrophenyl)-(- 3 -(4 - (5 – methyl – 1(H) – benzo [d] imida – zol – 2 -yl) phenyl) thiazolidin-4-one (3K) Lightyellow, Solid, $R_{f.}$ 0.74, Yield: 74%, mp: (112-113^{o}C), FTIR (cm-1, KBr): Aromatic (OH) 3623.35, Aromatic N-H stretching 3367.38, Ketone C=O stretching 1784.32, C=N (imine) 1686.35, N-H (bending) 1596.31, Aromatic (C=C) 1522.32, , (C-O) 1248.31. m/z: 510.02 (100.0%), 508.02 (97.1%), 511.02 (27.1%), 509.02 (26.5%),

512.01 (4.3%), 510.03 (3.0%), 512.03 (2.9%), 512.02 (1.3%), 513.02 (1.2%) Anal. Cal. $C_{23}H_{17}BrN_4O_3S$ (509.38) C, 54.22; H, 3.23; Br, 15.56; N, 09.11 ; O, 9.42; S, 6.29, Found. C, 54.21; H, 3.31; Br, 15.67; N, 11.01; O, 9.44; S, 6.30. 1HNMR, ppm (DMSO): $_1$H NMR ($CDCl_3$), 12.765 (s , 1 H), 8.765 (s , 1H), 8.745-8.945 (d , J = 1.4 Hz, 2 H), 7.863-7.891 (d ,4 .1 Hz, 2H) 7.307 -7.494 (d , J = 2.2 H), 7.327-7.563 (d , J = 3 .5 Hz, 2H), 7.117-7.387 (t, J = 3.7 , 2 H), 6.717 (s , 1 H), 6.698 -6.712 (d , J = 1 Hz, 1H), 6.123 (s, ,1H) , 3.862 – 3.949(d, J = 1.7 Hz, 1 H), 3.849-3.899 (d , J =2.3 Hz, 1 H),), 3.564 (s , 3H).

2-(3-bromo-4-nitrophenyl)-3(-(4 -(5 – methyl – 1 (H) – benzo [d] imida – zol - 2-yl) phenyl) thiazolidin-4-one (3L) Brown, Solid, R_f 0.56, Yield: 67%, mp: (120-121^{o}C), FTIR (cm-1, KBr): Aromatic (OH) 3623.35, Aromatic N-H stretching 3367.38, Ketone C=O stretching 1784.32, C=N (imine) 1686.35, N-H (bending) 1596.31, Aromatic (C=C) 1522.32, (C-O) 1248.31 m/z: 510.02 (100.0%), 508.02 (97.1%), 511.02 (27.1%), 509.02 (26.5%), 512.01 (4.3%), 510.03 (3.0%), 512.03 (2.9%), 512.02 (1.3%), 513.02 (1.2%) Anal. calcd $C_{23}H_{17}BrN_4O_3S$ (509.38) C, 53.22; H, 3.27; Br, 14.78; N, 11.22; O, 9.42; S, 6.21, Found. C, 55.32; H, 3.37; Br, 14.65 ; N, 11.25; O, 9.76; S, 5.54. 1HNMR, ppm (DMSO): $_1$H NMR ($CDCl_3$), 11.743 (s ,1 H), 8.769 (s , 1H), 8.129-8.403 (d , J = 1.4 Hz, 2 H), 7.863-7.891 (d ,4 .1 Hz, 2H) 7.307 -7.494 (d , J = 2.2 H), 7.327-7.389 (d , J = 3 .5 Hz, 2H), 7.117-7.387 (t, J = 3.7 , 2 H), 6.717 (s , 1 H), 6.698 -6.712 (d , J = 1 Hz, 1H), 6.127 (s, ,1H) , 3.862 – 3.949(d, J = 1.7 Hz, 1 H), 3.849-3.899 (d , J =2.3 Hz, 1 H),), 3.789 (s , 3H).

2-(3-hydroxy-4-nitrophenyl)-3- ((4 -(5 – methyl – 1 (H) – benzo [d]imida – zol - 2-yl)) phenyl) thiazolidine -4-one (3M) White, Solid, R_f .59, Yield: 65%, mp: (111-112^{o}C), FTIR (cm-1, KBr): Aromatic (N-H) stretching 3412.72, Ketone (C=O) stretching 1784.32, C=N (imine) 1622.37, N-H (bending) 1584.35, Aromatic (C=C) 1527.47, (C-N) bending 1407.32, Aromatic NO_2, 1494.69 m/z: 446.10 (100.0%), 447.11 (25.2%), 448.10 (4.5%), 448.11 (4.4%), 447.10 (2.3%), 449.10 (1.2%) Anal. calcd $C_{23}H_{18}N_4O_4S$ (446.10) C, 61.87; H, 4.17; N, 12.48; O, 14.24; S, 7.18, found. C, 61.86; H, 4.04; N, 12.53; O, 14.31; S, 7.19.1HNMR, ppm (DMSO): $_1$H NMR ($CDCl_3$), 12.567 (s, 1H), 8.123-8.168(d, J= 1.8 Hz, 2H), 7.768-7.895 (d , J=1.2Hz, 1H), 7.724-7.116 (t, 2.4Hz, 1H) 7.592-7.576(t, J=4.8 Hz, 2H), 7.552-7.542(t, J=3.3Hz, 1H), 7.138-7.348 (d , J = 1.4, 1H), 7.279-7.442 (d , J = 1.3 Hz, 2H), 7.158-7.249 (t, J=2.7Hz, 2H), 6.642 (s , ,1 H), 3.792 -3.972 (d , J = 1.2 Hz, 1 H), 3.756-3.889 (d , J =1 .8, 1 H).

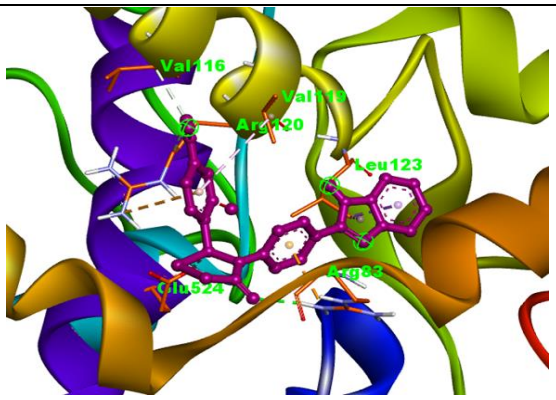
2. Results and Discussion

By using mass spectrum analysis, 1HNMR, and infrared spectroscopy, synthesised structure of amalgams was ascertained. IR 1783 cm^{-1} & (C = S) extending in series of 2278-2294 cm^{-1}. The existence of 4-thiazolidinone Further confirmation of the ring system was obtained.by ^{1}H NMR exhibited characteristic top most series of 3.97-4.11 δ. ppm corroborative the occurrence of CH_2, ^{1}H & C = N extending in series of 1683-1695 cm^{-1}in compounds **3I-3N**. The substances acquired trendy phase 1 (**C_1 - C_8**)) displayed a distinctive ultimate aimed at (–C = O) & (-C = C) amongst 1716-1738 cm^{-1} & 1609-1641 cm^{-1} correspondingly & stage 2 (**3I-3N)** revealed typical peak used for 1^0 amino & (C = S) flanked by 3309-3384 cm^{-1} & 1019-1109 cm^1 respectively [13,14]. Compounds **3K, 3L**, **3N, 3J** and **3I** showed a notable reduction in inflammation as compared to indomethacin as shown (Fig. 6,7,8,9 & 10) in protein docking investigations.

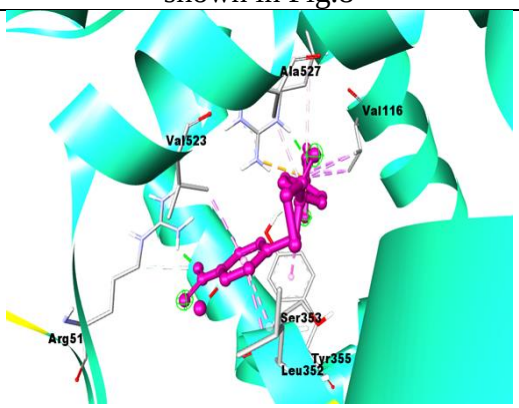
PROTEIN DOCKING INVESTIGATIONS

According to docking experiments, each chemical was marked by a distinct shade and latched in identical affinity site of the enzyme COX-1 as shown in Fig.6 and 7.

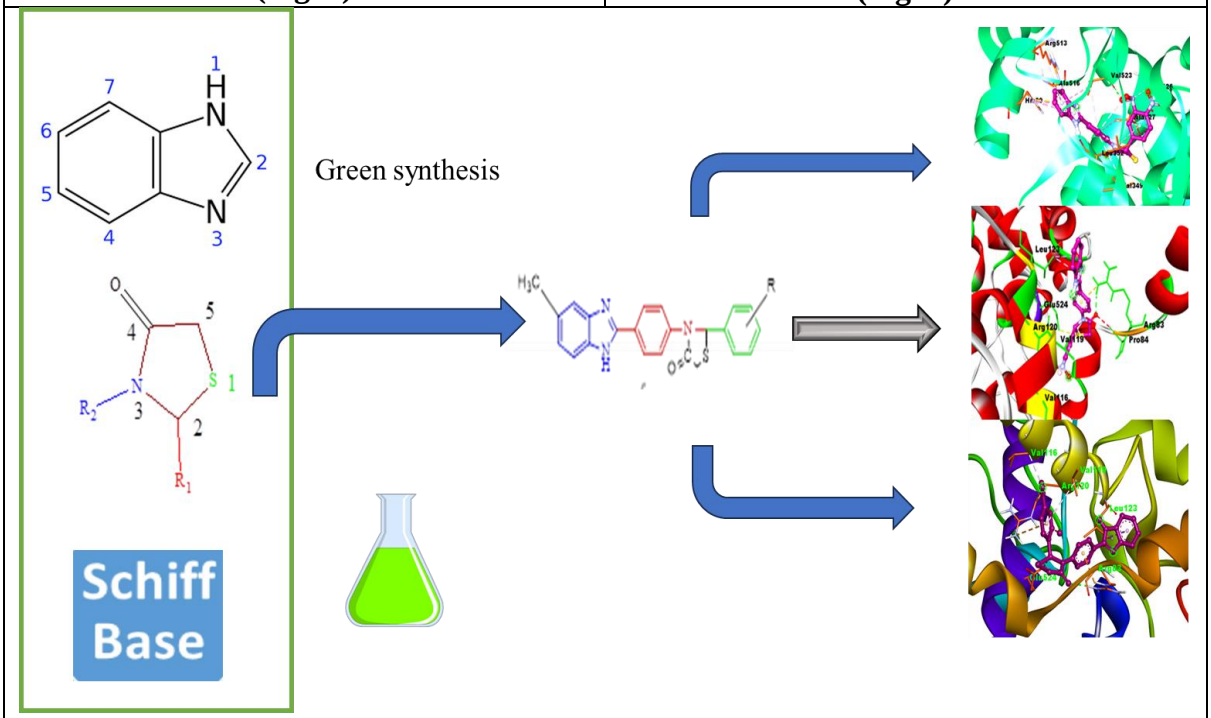
standard drug exhibited inferior docking oomph of -6.5 kcal per mol as related to synthesized amalgams which illustrations advanced docking oomph from -9.2 to -8.2 kcal per moles publicized in Table 2 also shown in Fig.8



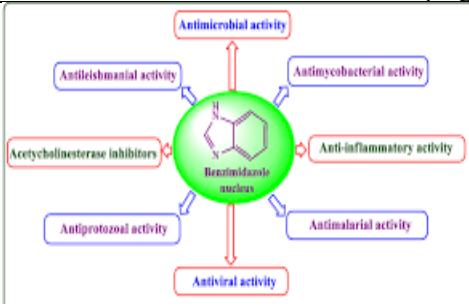
(Fig. 6)



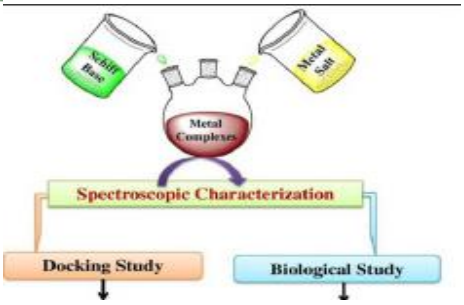
(Fig. 7)



(Fig. 8)

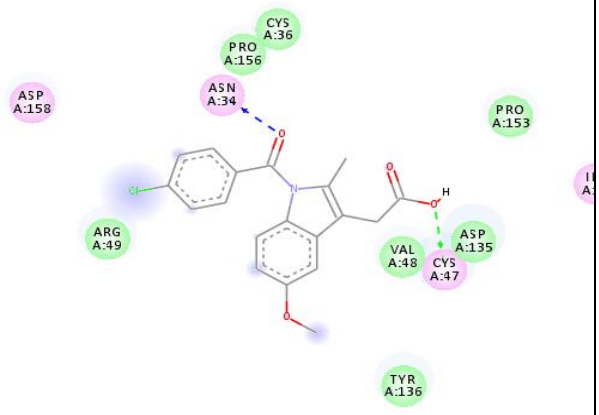
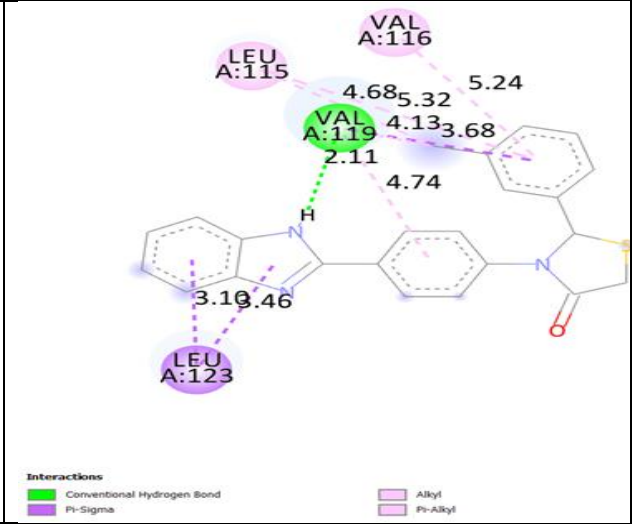


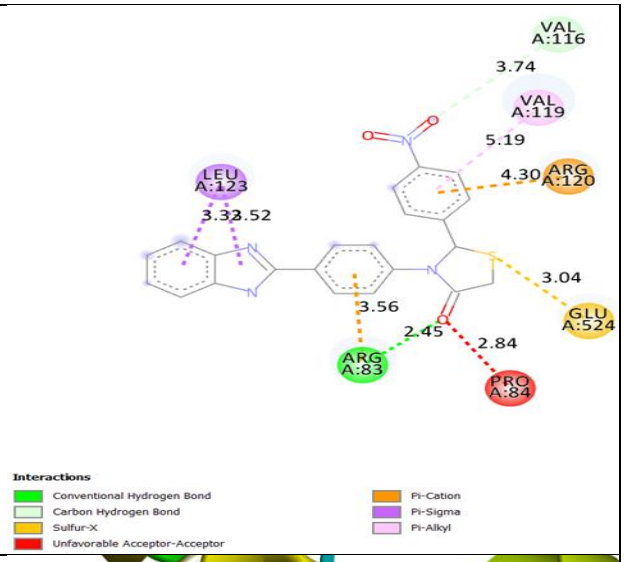
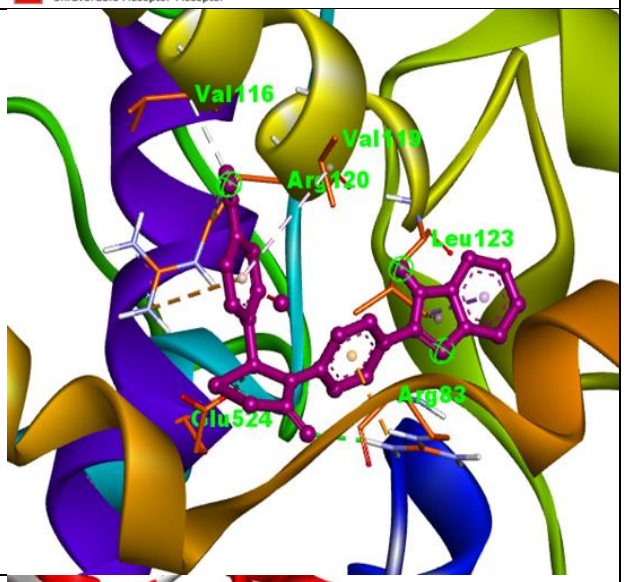
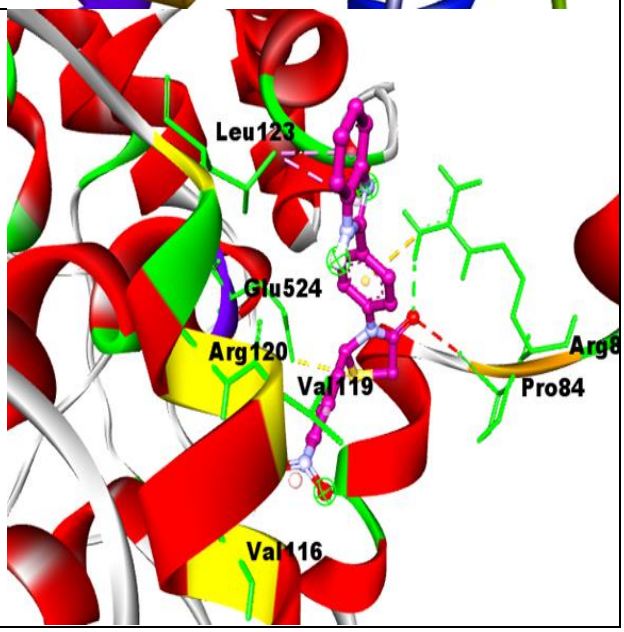
(Fig. 9)



(Fig. 10)

Table2. COX-1's atomic docking positions when coupled with generated substances

Sr.No.	Compounds	Kinetic Coupling Kcal. Per Mole	The bonding of hydrogen in proximity of 4Å	Pictures
1	Standard (Indomethacin)	-6.64	A S N A : 34 C Y S A : 47 P R O A :156 A S P A : 135 V A L A : 48 C YS A : 47 T Y R A:136 A R G A : 49 A S P A : 158	
2	3I	-6.71	L E U A :115 V A L A :119 L E U A :123 V A L A:116 V A L A:4.13	

3	3J	-6.96	L E U A :123 V A L A :119 A R G A :120 G L U A : 524 P R O A :84 A R G A :83 V A L A :116	
4	3K	-7.59	Val 116 Arg 120 Leu 123 Arg 123 Arg 83 Leu 524 V A L 119	
5	3L	-7.52	L E U 123 G L U 524 A R G 120 P R O 84 VAL119 VAL116 ARG83	

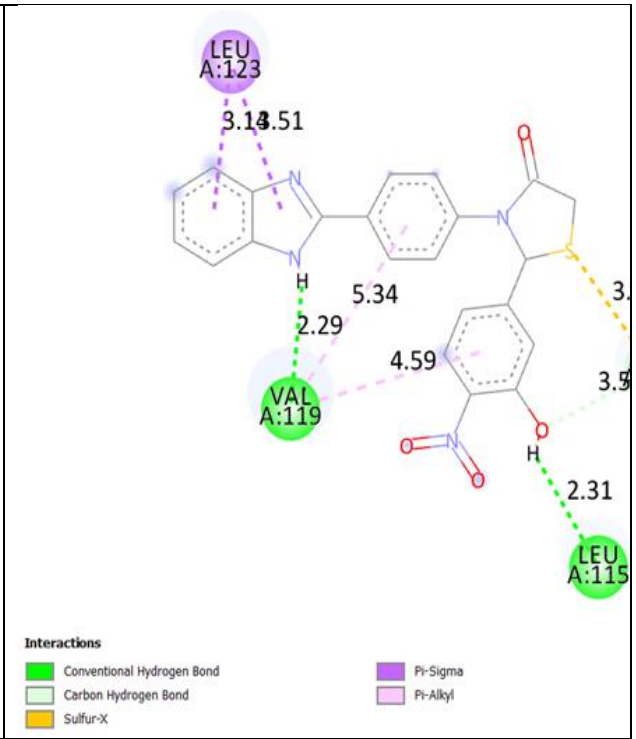
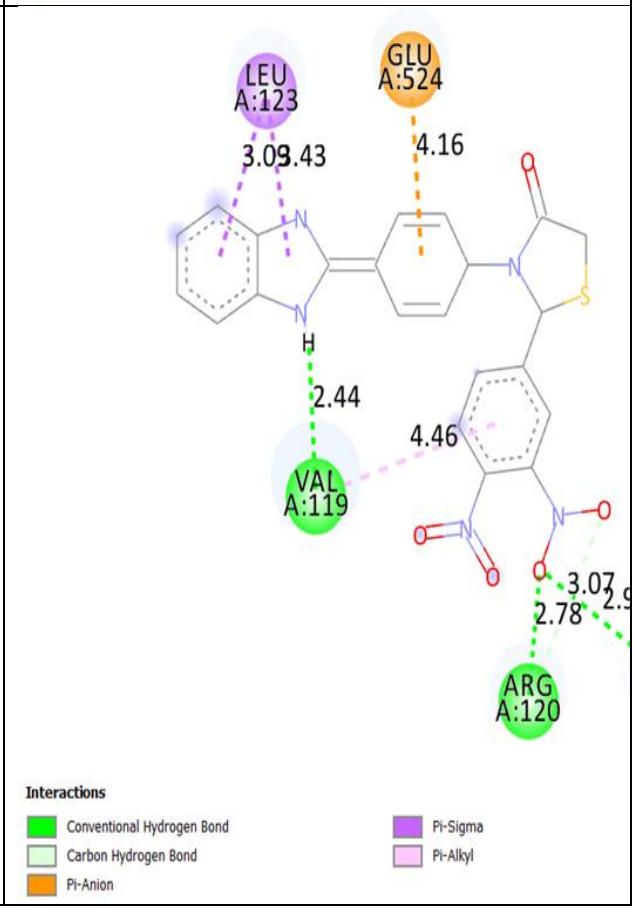
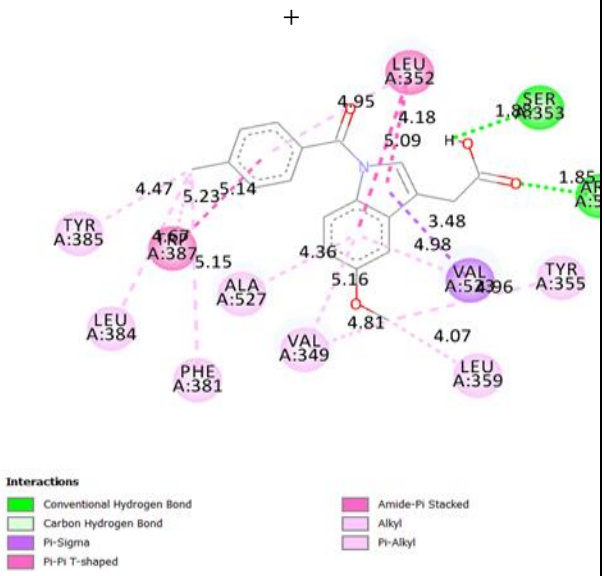
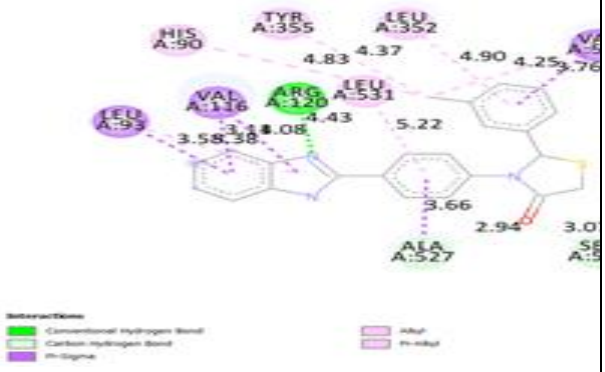
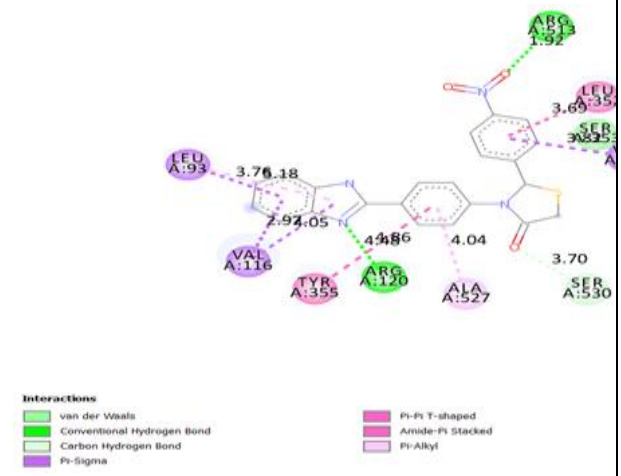
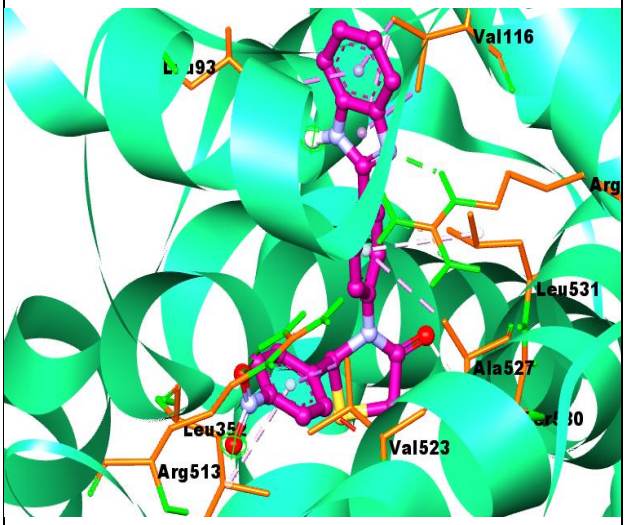
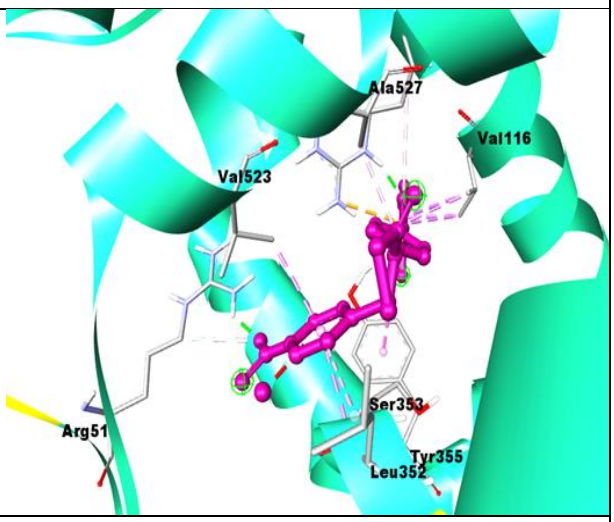
6	3M	-6.61	LE U A:123 V A L A :119 L E U A :115 A R G A:120	
7	3N	-7.11	L E U A :123 G L U A : 524 V A L A :119 A R G A :120 V A L A :116	

Table 3 displays the alignment of frequency along with hydrogen bonds amino acids used for COX-2 (PDB ID: 5KIR) in 2D postures.

Sr.No.	Compounds	Kinetic Coupling Kcal. Per Mole	The bonding of hydrogen in proximity of 4Å	Pictures
1	Standard (Indomethacin)	-8.96	TYR A : 385 LEU A : 384 PHE A : 381 VAL A : 349 ALA A : 527 LEU A : 359 VAL A : 523 TYR A : 355 ARG A : 513 SER A : 353 LEU A : 352	
2	3I	-9.45	HIS A: 90 T Y R A : 355 L E U A : 352 V A L A : 523 L E U A : 531 A R G A : 120 VAL A : 116 LEU A : 93	

3	3J	-9.74	A R G A: 513 L E U A : 352 V A L A : 523 A L A A : 527 A R G A : 120 T Y R A :355 VAL A : 116 LEU A : 93	
4	3K	-9.87	Val116 Arg120 Leu531 Ala527 Arg 513 Val153 Leu 352	
5	3L	-9.79	Ala 527 Val 523 Arg 51 Ser 353 Leu 352	
6	3M	-9.61	LEU A : 93 A R G A :120	

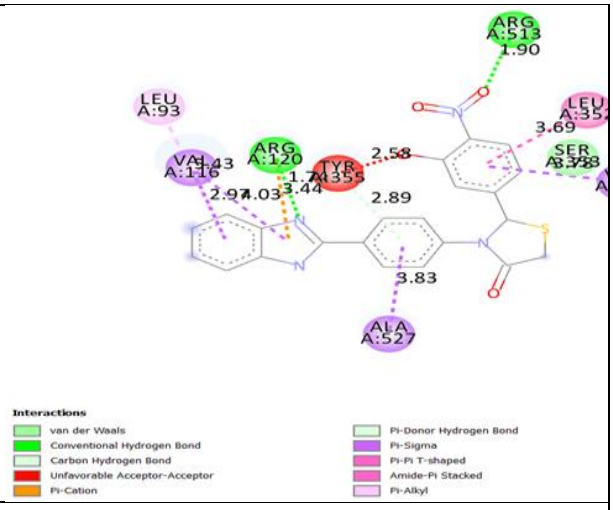
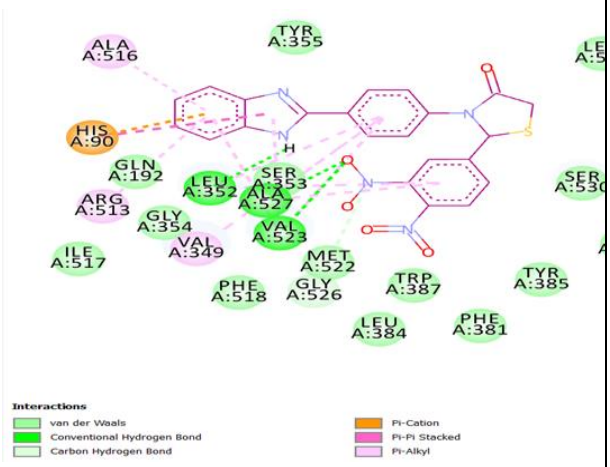
			TYR A : 355 S E R A : 393 V A L A : 523 L E U A : 352 SERA A : 418	
7	3N	-10.03	A L A A : 516 T Y R A : 355 L E U A : 531 S E R A : 530 T R P A : 387 P H E A : 381 G L Y A : 354 G L N A : 192 I L E A : 517 H I S A : 90	

Fig. 2 illustration of tethered chemicals inside an identical affinity groove of the COX-2 exploratory framework (P. D. B.- I.D. 5KIR)

RESEARCH ON DOCKING OF MOLECULES

To determine the affinity configuration of drugs that engage the anti-inflammatory goals COX-1 & COX-2, DNA docking experiments were conducted. The RCSB PDB polypeptide information bank provided the PDB structures of COX-1 (PDB ID: 3KK6; Crystal Structure of Cyclooxygenase-1 in association with celecoxib) and COX-2 (PDB ID: 5KIR; crystal structure of the drug Vioxx coupled to mammalian COX-2). Chem sketch Ultra 7.0 was utilised to sketch the substances employed in the docking study, and Chem3D Pro 7.0 was used to run the compounds until they reached their minimised state. In order to evaluate the correctness of the docking programme, the drug compounds included inside the protein structures COX-1 and COX-2 were removed and re-docked. The protein frameworks became then set up for docking investigation by inserting hydrogen bonds in place of water molecules.

3. Conclusion

Throughout the current study, eight byproducts of 2-((3- (N -phenyl)-5-(N -substituted -phenyl)) – 4 , 5- di- hydro-1(H) – pyra-zol -1 - yl) 4-thiazol 5(H) - one (3I-3N) were produced using a three-step process. Many contemporary medical systems manage the signs and symptoms of pain and inflammation using a variety of synthetic substances. In comparison to the reference medicine indomethacin (10 mg/kg, p.o.), the complete range of synthesised substances shown considerable to excellent anti-inflammatory effectiveness. Molecule with the $-OCH_3$ group had stronger anti-inflammatory effect in the para position than in the ortho and meta positions. F group had more activity in the para position as well. One may take the conclusion that groups that donated electrons performed better than those that drew electrons. Due of the exceptional results for docking with COX-2 ligands, it can also be said that synthetic derivatives connect with COX-2 receptors more frequently than COX-1 receptors.

The created compounds (3I-3N) can therefore act as effective COX-2 inhibitors. The selectivity is explained by computational molecular docking research, which also offers a binding model for future chemotype refining. As a result, the development of these 4 - thiazolidinone derivatives (3I-3N) as possible anti-inflammatory drugs holds great promise. The excellent docking score with COX-2 receptors led to the conclusion that synthesised analogues engage more with COX-2 ligands than COX-1 ligands. The synthetic derivatives (3I to 3N) are shown to be strong COX-2 inhibitors. The order of reactivity for COX-1 (3K>3L>3N>3J>3I>3M) and COX-2 (3N>3K>3L>3J>3M>3I)

ACKNOWLEDGEMENTS
The authors are thankful to Dr. Shakuntala Misra National Rehabilitation University in Lucknow's Institute of Pharmacy for providing the resources needed for the research. The Central Drugs Research Institute in Lucknow, India, is well appreciated for giving the advanced diagnostic equipment facilities and library.

CONFLICT OF INTEREST
No conflict of interest is reported by the authors.

4. References

1. Vieira SF, Reis RL, Ferreira H, Neves NM. Plant-derived bioactive compounds as key players in the modulation of immune-related conditions. Phytochemistry Reviews. 2024 Apr 16:1-18. https://doi.org/10.1007/s11101-024-09955-7
2. Galvão I, Sugimoto MA, Vago JP, Machado MG, Sousa LP. Mediators of inflammation. Immunopharmacology and inflammation. 2018:3-2. https://doi.org/10.3390/microorganisms10020405
3. Baral P, Udit S, Chiu IM. Pain and immunity: implications for host defence. Nature Reviews Immunology. 2019 Jul;19(7):433-47. doi: 10.1038/s41577-019-0147-2
4. Otimenyin SO. Anti-inflammatory medicinal plants: a remedy for most disease conditions? In Natural Products and Drug Discovery 2018 Jan 1 (pp. 411-431) Elsevier. https://doi.org/10.1016/B978-0-08-102081-4.00015-0
5. Mediators PP. Acute and Chronic Inflammation. Robbins and Cotran Pathologic Basis of Disease, Professional Edition E-Book. 2009 Jun 10:43.
6. Actor JK, Smith KC. Translational inflammation. In Translational Inflammation 2019 Jan 1 (pp. 1-22). Academic Press. https://doi.org/10.1016/B978-0-12-813832-8.00001-7

7. Basu S, Shukla V. Complications of wound healing. Measurements in Wound Healing: Science and Practice. 2013:109-44.
8. Damjanov I, Perry AM, Perry K. Pathology for the Health Professions-E-Book. Elsevier Health Sciences; 2021 Mar 31. 2021•books.google.com
9. Gusev E, Zhuravleva Y. Inflammation: A new look at an old problem. International Journal of Molecular Sciences. 2022 Apr 21;23(9):4596. https://doi.org/10.3390/ijms23094596
10. Goncharov EN, Koval OA, Nikolaevich Bezuglov E, Engelgard M, Igorevich EI, Velentinovich Kotenko K, Encarnacion Ramirez MD, Montemurro N. Comparative Analysis of Stromal Vascular Fraction and Alternative Mechanisms in Bone Fracture Stimulation to Bridge the Gap between Nature and Technological Advancement: A Systematic Review. Biomedicines. 2024 Feb 1;12(2):342. https://doi.org/10.3390/biomedicines12020342
11. Eren E, Ellidag HY, Aydin O, Yilmaz N. HDL functionality and crystal-based sterile inflammation in atherosclerosis. Clinica Chimica Acta. 2015 Jan 15;439:18-23. https://doi.org/10.1016/j.cca.2014.09.024
12. Vasconcelos DP, Águas AP, Barbosa MA, Pelegrín P, Barbosa JN. The inflammasome in host response to biomaterials: Bridging inflammation and tissue regeneration. Acta Biomaterialia. 2019 Jan 1;83:1-2. https://doi.org/10.1016/j.actbio.2018.09.056
13. Prakash M, Bodas M, Prakash D, Nawani N, Khetmalas M, Mandal A, Eriksson C. Diverse pathological implications of YKL-40: answers may lie in 'outside-in'signaling. Cellular signalling. 2013 Jul 1;25(7):1567-73. https://doi.org/10.1016/j.cellsig.2013.03.016
14. Gupta PK, Gupta PK. Target organ toxicity. Problem Solving Questions in Toxicology: A Study Guide for the Board and other Examinations. 2020:83-117.
15. Duarte J, Mascarenhas-Melo F, Pires PC, Veiga F, Paiva-Santos AC. Multifunctional hydrogels-based therapies for chronic diabetic wound healing. European Polymer Journal. 2024 Apr 8:113026. https://doi.org/10.1016/j.eurpolymj.2024.113026
16. Walter H, Lübben G. Potential role of oral thiazolidinedione therapy in preserving β-cell function in type 2 diabetes mellitus. Drugs. 2005 Jan;65:1-3.
17. Chiazza F, Collino M. Peroxisome proliferator-activated receptors (PPARs) in glucose control. Molecular nutrition and diabetes. 2016 Jan 1:105-14. https://doi.org/10.1016/B978-0-12-801585-8.00009-9
18. Basak S, Murmu A, Matore BW, Roy PP, Singh J. Thiazolidinedione an Auspicious Scaffold as PPAR-γ Agonist: its Possible Mechanism to Manoeuvre against Insulin Resistant Diabetes Mellitus. European Journal of Medicinal Chemistry Reports. 2024 Apr 20:100160. https://doi.org/10.1016/j.ejmcr.2024.100160
19. Wu D, Eeda V, Undi RB, Mann S, Stout M, Lim HY, Wang W. A novel peroxisome proliferator-activated receptor gamma ligand improves insulin sensitivity and promotes browning of white adipose tissue in obese mice. Molecular Metabolism. 2021 Dec 1;54:101363. https://doi.org/10.1016/j.molmet.2021.101363
20. Decara J, Rivera P, López-Gambero AJ, Serrano A, Pavón FJ, Baixeras E, Rodríguez de Fonseca F, Suárez J. Peroxisome proliferator-activated receptors: Experimental targeting for the treatment of inflammatory bowel diseases. Frontiers in pharmacology. 2020 May 27;11:493292. | https://doi.org/10.3389/fphar.2020.00730
21. Wang N, Yin R, Liu Y, Mao G, Xi F. Role of Peroxisome Proliferator-Activated Receptor-γ in Atherosclerosis–An Update–. Circulation Journal. 2011;75(3):528-35. https://doi.org/10.1253/circj.CJ-11-0060

22. Wang N, Yin R, Liu Y, Mao G, Xi F. Role of Peroxisome Proliferator-Activated Receptor-γ in Atherosclerosis–An Update–. Circulation Journal. 2011;75(3):528-35. https://doi.org/10.1253/circj.CJ-11-0060
23. Jain VS, Vora DK, Ramaa CS. Thiazolidine-2, 4-diones: Progress towards multifarious applications. Bioorganic & medicinal chemistry. 2013 Apr 1;21(7):1599-620.
24. PATHAK A, NEETU S, SINGH R, KUMAR S, KUSHWAHA S, RANA P, SHALU AK, PANDEY DD, VERMA D, SINGH S, BHATT P. A Short Review Of Current Trends, Impending Obstacles, Modern Synthetic Approach, Structure Activity Relationship And Numerous Biological Activities Of Benzimidazole. Latin American Journal of Pharmacy. 2023 Jul 29;42(3):1089-104.
25. Banerjee S, Mukherjee S, Nath P, Mukherjee A, Mukherjee S, Kumar SA, De S, Banerjee S. A critical review of benzimidazole: Sky-high objectives towards the lead molecule to predict the future in medicinal chemistry. Results in Chemistry. 2023 Jun 22:101013. https://doi.org/10.1016/j.rechem.2023.101013
26. Mor S, Khatri M, Punia R, Nagoria S, Sindhu S. A new insight into the synthesis and biological activities of pyrazole-based derivatives. Mini-Reviews in Organic Chemistry. 2022 Sep 1;19(6):717-78. https://doi.org/10.2174/1570193X19666220118111614
27. Holam MR. Synthesis and antimicrobial activity of some novel coumarin derivatives (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).
28. Habib T. Effect of antimicrobial agents for the prevention of Streptococcus mutans biofilm formation (Doctoral dissertation, University of Rajshahi). http://rulrepository.ru.ac.bd/handle/123456789/1093
29. Pathak A, Gupta A, Gautam A, A brief overview of 4-Thiazolidinone's biological activity, SAR, current advancements, and impending challenges, Eur. Chem. Bull. 2023, 12 (Special Issue 4), 17085-17106. DOI: 10.2174/1385272043369773
30. Patel D, Kumari P, Patel N. Synthesis and biological evaluation of some thiazolidinones as antimicrobial agents. European journal of medicinal chemistry. 2012 Feb 1;48:354-62. https://doi.org/10.1016/j.ejmech.2011.11.041
31. Abhinit M, Ghodke M, Pratima NA. Exploring potential of 4-thiazolidinone: a brief review. Int J Pharm Pharm Sci. 2009 Jan;1(1):47-64. https://www.researchgate.net/profile/Anna-Nikalje/publication/250535504_ChemInform_Abstract_Exploring_Potential_of_4-Thiazolidinone/links/5d01299f299bf13a3850dec7/ChemInform-Abstract-Exploring-Potential-of-4-Thiazolidinone.pdf
32. Tripathi AC, Gupta SJ, Fatima GN, Sonar PK, Verma A, Saraf SK. 4-Thiazolidinones: the advances continue…. European Journal of Medicinal Chemistry. 2014 Jan 24;72:52-77. https://doi.org/10.1016/j.ejmech.2013.11.017
33. Kumar RA, Patil SH. Biological prospective of 4-thiazolidinone: a review. Hygeia: Journal for Drugs and Medicines. 2017 Jul;9(1):80-97. DOI:10.15254/H.J.D.Med.9.2017.166
34. Chawla PA, Wahan SK, Negi M, Faruk A, Chawla V. Synthetic strategies and medicinal perspectives of 4-thiazolidinones: Recent developments and structure–activity relationship studies. Journal of Heterocyclic Chemistry. 2023 Aug;60(8):1248-86. https://doi.org/10.1002/jhet.4596
35. Chawla PA, Wahan SK, Negi M, Faruk A, Chawla V. Synthetic strategies and medicinal perspectives of 4-thiazolidinones: Recent developments and structure–activity relationship studies. Journal of Heterocyclic Chemistry. 2023 Aug;60(8):1248-86. | https://doi.org/10.3389/fphar.2020.00730