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COMPUTATIONAL DESIGN, SYNTHESIS, ANALYSIS AND EVALUATION OF NEW SPIRO [INDOLINE-THIAZOLIDINE] DERIVATIVES FOR ANTI-INFLAMMATORY AND ANTIOXIDANT PROPERTIES

N. Saritha Devi ^{*1}, Ragunath Chevva ², Kiranmai Mandava ¹, Divya Sreepada ³ and Neeradi Dinesh ⁴

Department of Pharmaceutical Chemistry ¹, St. Pauls College of Pharmacy, Turkayamjal - 501510, Telangana, India.

Department of Pharmaceutical Chemistry ², Sri Indu College of Pharmacy, Sheriguda - 501510, Telangana, India.

Department of Pharmaceutical Chemistry ³, Dnyansadhana College of Pharmacy, Dharmapuri Tq. & Parbhani - 431401, Maharashtra, India.

Department of Pharmacology ⁴, Telangana State Veterinary, Rajendranagar, Hyderabad - 500030, Telangana, India.

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Correspondence to Author:

Dr. N. Saritha Devi

Associate Professor,
Department of Pharmaceutical
Chemistry, St. Pauls College of
Pharmacy, Turkayamjal - 501510,
Telangana, India.

E-mail: nellutlasaritha@gmail.com

ABSTRACT: In this study, a series of novel N-(2,4'-dioxospiro[indoline-3,2'-thiazolidin]-3'-yl) isonicotinamide derivatives (VIa-l) were synthesized by cyclizing N1- (2-mercaptoacetyl) isonicotinohydrazide with various 5,6,7-substituted isatins. Structural confirmation of the new compounds was achieved using IR, Mass, H1, and C13 NMR spectroscopy techniques. *In-silico* molecular docking studies were conducted to identify the binding affinity of the synthesized compounds to the COX-2 enzyme (PDB ID: 3LN1), using PyRx software. The compounds were evaluated for *in-vitro* and *in-vivo* anti-inflammatory and antioxidant activities. For the *in-vitro* anti-inflammatory study, Cayman's COX (ovine) colorimetric inhibitor screening assay kit was utilized, while for the *in-vivo* anti-inflammatory activity, the carrageenan-induced rat paw edema method was employed. The *in-vitro* antioxidant activity of the new derivatives was determined using the DPPH assay method with ascorbic acid as a standard drug. Regarding docking, most compounds exhibited good binding affinity, equal to or greater than that of the standard. All derivatives demonstrated moderate to good anti-inflammatory activity both *in-vitro* and *in-vivo*. They showed mild to moderate antioxidant activity compared to ascorbic acid. In conclusion, N-(7 - nitro - 2, 4'- dioxospiro [indoline - 3, 2'-thiazolidin] - 3'-yl) isonicotinamide could be further investigated in search of potent anti-inflammatory agents.

INTRODUCTION: Inflammation is a tissue reaction or biological response to harmful stimuli such as injection, injury, irritation, or a foreign substance like a pathogen, and plays a pivotal role in the body's defense mechanism ^{1,2}.

Ageing is also considered to be an inflammatory response. These responses mainly include release of histamine, prostaglandins and bradykinin which play an important role in tissue repair.

Inflammation represents a complex cascade of biochemical episodes involving different types of cells and molecular mediators. The basic symptoms of inflammatory reaction include redness of the skin, swelling, heat, and increased sensitivity to pain, occur immediately after injury as a protective mechanism in the body. Though necessary for healing and protection, if not regulated or

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controlled properly, it may lead to harmful diseases like arthritis, heart related diseases and certain types of cancer^{3, 4}. Synthesis of non-steroidal anti-inflammatory agents (NSAIDs) in recent years has contributed to alleviating human suffering, such as arthritis, and enhancing the understanding of the tissue mechanisms involved in Inflammation.

NSAIDs are often the primary option for alleviating pain and inflammation. Medications such as indomethacin and diclofenac are widely used therapeutic agents, primarily for addressing pain, inflammation, and arthritis. The advantageous anti-inflammatory and pain-relieving properties of NSAIDs stem from their ability to inhibit the action of cyclooxygenase (COX) enzymes, resulting in a reduction in prostaglandin production. Among the different forms of COX, the inducible COX-2 is linked to inflammatory disorders, whereas the COX-1 isoform, which is constantly expressed, provides cytoprotective benefits through prostaglandins. Despite their primary action in relieving pain, they also have side effects affecting the gastrointestinal tract (GIT), blood coagulation, and kidney function, partly due to inhibition of essential COX-1 enzymes^{5, 6}. Thus, there is an urgent need to develop novel drug molecules that exhibit significant anti-inflammatory activity with fewer or no adverse effects.

Indole derivatives are widely found in nature, and their various derivatives have been recognized for their range of pharmacological effects, such as anti-inflammatory, antibacterial, antiviral, and anticancer properties. An example is Indomethacin, a well-established anti-inflammatory medication, which has indole as its core structure⁷⁻¹⁰. Thiazolidinone is a five-membered ring containing sulfur and features an additional ketone group, making it significant due to its wide array of pharmacological effects, including anticancer, antimicrobial, antifungal, anti-inflammatory, hypoglycemic, and anticonvulsant activities. *In-silico* molecular docking study is a computational methods that help predict the perfect orientation of a ligand molecule to target enzymes when they form stable complex. These tools assist chemists in identifying lead compounds, predicting binding affinities, and facilitating structure-based drug design. Molecular docking studies provide insights into various interactions between protein and

ligand, such as interactions involving hydrogen bonding interactions, non polar interactions, and vander Waals forces, which are crucial for analyzing ligand activity¹¹.

The molecular docking analyses were performed using PyRx 0.8 (GUI version 0.8), a virtual screening application that enables the simultaneous screening of multiple ligands against target proteins. The PyRx software includes tools such as Open Babel, AutoDock 4, and AutoDock Vina, which offer important insights into the potential therapeutic uses of new compounds.

Owing to the notable anti-inflammatory properties of indoles and Thiazolidinones, we have designed and synthesized novel N-(2,4'-dioxospiro[indoline-3,2'-thiazolidin]-3'-yl) isonicotinamide derivatives. The aim is to evaluate these compounds for their anti-inflammatory and antioxidant activity both in *in-vitro* and *in-vivo*.

MATERIALS AND METHODS:

General: All analytical grade chemicals from SD fine chemicals were used for synthesis of derivatives. E-Merck 0.25mm TLC plates were used to find out the progress and completion of reaction. Melting points of synthesized compounds were noted using BioTechnics India melting point apparatus and the values were uncorrected.

Animals: Adult male albino wistar rats (150-350g) were bought from Jeeva Life Sciences, Hyderabad. Animals were acclimatized for 14 days with continuous supply of food and water. After 14days of acclimatization they were divided to groups each group containing 6 animals. Animals were fasted overnight before the experiment. IAEC approval was obtained prior to conducting of experiment with ID number CCSEA/IAEC/JLS/22/10/24/014.

Chemistry:

General Procedure:

Synthesis of Indole-2,3-Diones (Isatins) (IIIa-I): The synthesis of Isatins was done according to the standard procedure¹².

Synthesis of N'-(2-mercaptoacetyl) isonicotinohydrazide (V): In a round-bottom flask (RBF), an equimolar mix of isoniazid (0.01 M) and thioglycolic acid (0.01 M) was combined with a pinch of ZnCl₂ and about 4 to 5 drops of glacial

acetic acid, then refluxed in ethyl alcohol (40 ml) using a water bath for 7 hours. Once the reaction was complete, the mixture from the flask was poured over crushed ice. A 10% Na₂CO₃ was added for acid neutralization. The resulting compound was filtered, washed thoroughly with cold water, and dried. Finally, the compound obtained was recrystallized using an appropriate solvent to eliminate impurities.

Synthesis of N-(2,4'-dioxospiro[indoline-3,2'-thiazolidin]-3'-yl)isonicotinamide (VI a-l): A solution of an appropriate indole-2,3-dione (0.01M) and N'-(2-mercaptoacetyl) isonicotinohydrazide (0.01M) was prepared in a flask containing 50ml of ethanol, with 4-5 drops of piperidine added, and then refluxed in a water bath for 6-7 hours. The colored compound obtained after cooling was filtered, rinsed with little amount of cold methanol, and then dried. The compound was further purified through recrystallization using alcohol.

The scheme of the synthesized compounds N-(2,4'-dioxospiro [indoline-3, 2'-thiazolidin]-3'-yl) isonicotinamide (VIa-l) and their physical data are depicted in **Fig. 1** and **Table 1**. The synthesized compounds were characterized using IR, NMR, and mass spectroscopy.

Biological Activities:

In-vitro Antioxidant Activity: DPPH is a “stable” synthetic free radical that receives a hydrogen radical or an electron to convert into a stable diamagnetic compound¹³⁻¹⁵. When DPPH encounters antioxidants, its free radical nature is lost and colour changes from violet to yellow. The reduction capacity of the DPPH radical was evaluated by the decrease in its absorbance at 517 nm (λ_{max}).

Antioxidants cause a reduction in the absorbance of the DPPH radical due to the reaction between the radical molecule and the antioxidant molecule, resulting in the scavenging of the radical through hydrogen donation. A visual change from purple to yellow can be easily observed. Therefore, DPPH is commonly used to assess various chemical compounds' antioxidant activity. The reduction in absorbance is expressed as a percentage inhibition.

$$\% \text{ Inhibition} = \frac{(\text{Absorbance of Blank} - \text{Absorbance of Test})}{(\text{Absorbance of Blank})} \times 100$$

Preparation of 0.5mM DPPH Solution: 2.45mg of DPPH dissolved in 12.5 mL of methanol.

Preparation of 0.1M Tris buffer (pH 7.2): 0.605g of Tris buffer dissolved in 50 mL of distilled water.

In-vitro Anti-Inflammatory Activity: Colorimetric COX (ovine) inhibitor screening assay kit from Cyaman Chemical, Michigan, USA was used to determine *in-vitro* anti-inflammatory activity of new derivatives. This colorimetric assay relies on the peroxidase function of ovine cyclooxygenase to oxidize the colorimetric substrate, N, N, N', N' - tetramethyl - p - phenylenediamine (TMPD). 220 μ l of sample solution was used for the procedure. The background wells and inhibitor wells were prepared according to kit's guidelines and later at 25°C temperature it is preincubated for 5 min. The reaction starts with the addition of 20 μ l of TMPD solution and arachidonic acid (10 μ l) to all wells. The assay mixture was mixed and incubated at 25°C for 5 minutes. Using UV Spectrophotometer, the enzyme activity was measured at 590 nm. The resulting activity data are illustrated in **Fig. 3** and **Table 3**.

Acute Toxicity Studies: All newly developed Isatin derivatives, which exhibit excellent COX-2 inhibitory properties, underwent acute toxicity assessments prior to conducting *in-vivo* anti-inflammatory evaluations. None of the six Isatin derivatives tested showed signs of toxicity or adverse effects, even at a high dosage of 1000 mg/kg body weight when administered orally as suspensions in 0.1% CMC.

The activity results, expressed as the percentage of inhibition in rat paw volume, are illustrated in **Fig. 4** and **5**, as well as in **Table 4** and **5**, using Indomethacin as the standard reference drug at a dosage of 31.4 μ g/ml (10 mg)/kg body weight.

In-vivo Anti-Inflammatory Activity: Albino rats, weighing between 150-200g and of either sex, were separated into various groups, each consisting of six animals. Prior to the experiment, the animals were fasted for 12 hours and were allowed to drink only water. The first group served as the control and received Tween 80 in propylene glycol (10% v/v), at a dosage of 0.5ml per rat, while the second group was given a vehicle¹⁶⁻²¹.

Molecular Docking Studies of Synthesized Novel Spiro Compounds against COX-2: The 3D X-ray crystal structure of Cyclooxygenase II (COX-2) (3LN1) was sourced from the RCSB protein data bank (<http://www.rcsb.org/pdb>). The macromolecule was processed and purified with the help of the Dassault Systèmes BIOVIA Discovery Studio visualizer. Initially, water molecules, co-crystallized ligands, additional protein chains, and cofactors were removed. Subsequently, polar hydrogens were introduced, and the prepared protein was saved in PDB format on the desktop. For ligand preparation, the designed ligands were illustrated using ChemSketch/ChemDraw software and stored in CDX format on the desktop. For docking calculations in PyRx, the macromolecule

is first loaded and converted to PDBQT format, followed by the step of loading ligands individually from the desktop. After that, using the open babel tool, energy minimization is performed on all ligands to refine their geometry before docking into the protein. All ligands are then transformed into PDBQT format for molecular docking simulations using AutoDock Vina in the following step. Once both the ligand and protein are prepared, the vina wizard is used to draw a grid box encompassing the entire macromolecule, and the docking program is executed. The binding affinity values are reported as RMSD values²²⁻²⁵. The docking interactions, including hydrogen bond interactions and hydrophobic interactions, were examined with the Discovery Studio Visualizer.

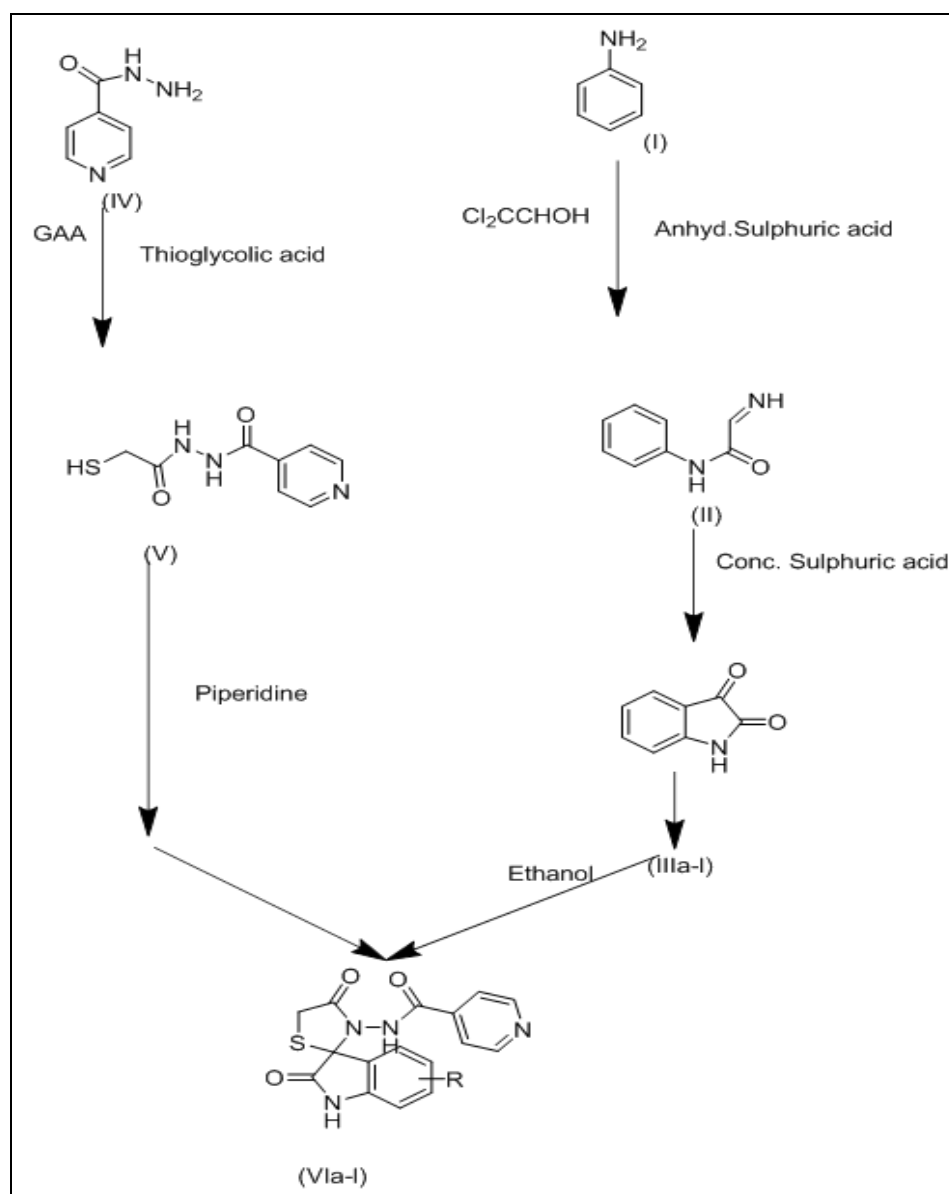


FIG. 1: SCHEME: SYNTHESIS OF N-(2, 4' - DIOXOSPIRO [INDOLINE - 3, 2' - THIAZOLIDIN] - 3' - YL) ISO-NICOTINAMIDE DERIVATIVES

TABLE 1: PHYSICAL DATA OF N-(2, 4'-DIOXOSPIRO[INDOLINE-3, 2'-THIAZOLIDIN]-3'-YL) ISO-NICOTINAMIDE (VIAL)

S. no.	Compound	R	Mol. Formula	Chemdraw structure	Smile notations	Binding interactions (Hydrogen bonds, Hydrophobic-interactions)	Binding affinities
1	Via	H	C ₁₆ H ₁₂ N ₄ O ₃ S		O=C1Nc2cccc2C21SCC(=O)N2NC(=O)c1ccncc1	SER B:457; LYS B:64 THR B:61 ARG B:29 LEU B:65 PHE B:49	-7.5
2	Vib	5-Cl	C ₁₆ H ₁₁ ClN ₄ O ₃ S		O=C1Nc2ccc(Cl)cc2C21SCC(=O)N2NC(=O)c1ccncc1	ASN B:72 LYS B:497 ARG B:499 PRO B:500 HIS B: 75	-7.1
3	Vic	7-Cl	C ₁₆ H ₁₁ ClN ₄ O ₃ S		O=C1Nc2c(Cl)cccc2C21SCC(=O)N2NC(=O)c1ccncc1	TYR B:341 HIS B:337 GLN B:569 LYS B:344	-7.8
4	Vid	5-CH ₃	C ₁₇ H ₁₄ N ₄ O ₃ S		O=C1Nc2ccc(C)cc2C21SCC(=O)N2NC(=O)c1ccncc1	ASN B:567 TYR B:341 HIS B:337	-8.0
5	Vie	7-CH ₃	C ₁₇ H ₁₄ N ₄ O ₃ S		O=C1Nc2c(cccc2C)C21SCC(=O)N2NC(=O)c1ccncc1	TYR B:341 HIS B:337 HIS B:342 GLN B:336	-7.5
6	Vif	5-F	C ₁₆ H ₁₁ FN ₄ O ₃ S		O=C1Nc2ccc(F)cc2C21SCC(=O)N2NC(=O)c1ccncc1	ASN B:72 LYS B:497 ARG B:499 PRO B:500	-7.6
7	VIg	7-F	C ₁₆ H ₁₁ FN ₄ O ₃ S		O=C1Nc2c(F)cccc2C21SCC(=O)N2NC(=O)c1ccncc1	GLN B: 336 GLN B:569 LYS B:344	-7.3
8	VIh	5-Br	C ₁₆ H ₁₁ BrN ₄ O ₃ S		O=C(NN1C(=O)CSC11C(=O)Cc2ccc(Br)cc21)c1ccncc1	HIS B:193 HIS B:372	-7.1
9	VII	5,6-Dichloro	C ₁₆ H ₁₀ Cl ₂ N ₄ O ₃ S		O=C(NN1C(=O)CSC11C(=O)Cc2cc(Cl)c(Cl)cc21)c1ccncc1	THR B:198 ASN B:368 TYR B:134 HIS B:200 LYS B:197 VAL B:277	-7.8
10	VIj	5-NO ₂	C ₁₆ H ₁₁ N ₅ O ₅ S		[O-][N+](=O)c1cccc2c1CC(=O)C12SCC(=O)N1NC(=O)c1ccncc1	HIS B: 337 GLN B:336	-7.3

11	VIIk	7- NO ₂	C ₁₆ H ₁₁ N ₅ O ₅ S	[O-][N+](=O)c1c c2c(CC(=O)C 32SCC(=O)N 3NC(=O)c2cc ncc2)cc1	SER B:457 LYS B:64 THR B:61 ARG B: 29 LEU B: 65 PHE B: 49	-8.2
12	VII	7-OH	C ₁₆ H ₁₂ N ₄ O ₄ S	O=C(NN1C(= O)CSC11C(= O)Cc2ccc(O)c c21)c1ccncc1	ASN B:567 HIS B:337 TYR B:341 GLN B:336 HIS B:342	-7.4
13	Indomethaci n		C ₁₉ H ₁₆ Cl NO ₄	Clc1ccc(cc1)C (=O)n1c([*])c(CC(=O)O)c2c c(ccc21)OC	PHE B:566 HIS B:337 ASN B: 567 ILE B: 550	-8.0

ANALYTICAL DISCUSSION:

Spectral data

Spectral data of the synthesized compounds:

VIa N-(2, 4'-dioxospiro [indoline-3, 2'-thiazolidin]-3'-yl) isonicotinamide: IR (KBR, cm⁻¹): 3285 (Aromatic-CH), 1686(NH-C=O), 1604 (C=N), 1340(C-N), 1713(C=O), 1508(Ar C=C). ¹H-NMR(CDCl₃-D) δppm: 3.62(d, 1H, CH₂ Thiazolidine), 3.75(d, 1H, CH₂ Thiazolidine), 7.05(t, 1H, Ar-H), 7.19(d, 1H Ar-H), 7.34(t, 1H, Ar-H), 7.51(d,1H, Ar-H), 7.78(d, 2H, Ar-H), 8.77(d, 2H, Ar-H), 8.44(s, 1H N-H Indole), 9.60(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 340.

VIb N-(5-chloro-2,4'-dioxospiro[indoline-3,2'-thiazolidin]-3'-yl) isonicotinamide: IR(KBR, cm⁻¹): 3263(Aromatic-CH), 1642(NH-C=O), 1635 (C=N), 1351(C-N), 1695(C=O), 1522(Ar C=C), 738(C-Cl). ¹H-NMR(CDCl₃-D) δppm: 3.70(d, 1H, CH₂ Thiazolidine), 3.81(d,1H, CH₂ Thiazolidine), 7.37(d, 1H, Ar-H), 7.56(s, 1H Ar-H), 7.6(t, 1H, Ar-H), 7.72(d, 2H, Ar-H), 8.71(d, 2H, Ar-H),8.74(s, 1H N-H Indole), 9.9(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 374 and M⁺¹ peak at 376.

VIc N-(7-chloro-2, 4'-dioxospiro [indoline-3, 2'-thiazolidin]-3'-yl)isonicotinamide: IR(KBR, cm⁻¹): 3247(Aromatic-CH), 1635(NH-C=O), 1612 (C=N), 1336(C-N), 1702(C=O), 1519(Ar C=C), 727(C-Cl). ¹H-NMR(CDCl₃-D) δppm: 3.71(d, 1H, CH₂ Thiazolidine), 3.83(d,1H, CH₂ Thiazolidine),

7.26(d, 1H, Ar-H), 7.19(t, 1H Ar-H), 7.60(d, 1H, Ar-H), 7.81(d, 2H, Ar-H), 8.78(d, 2H, Ar-H), 9.22(s, 1H N-H Indole), 10.36(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 374 and M⁺¹ peak at 376.

VIId N-(5-methyl-2,4'-dioxospiro[indoline-3,2'-thiazolidin]-3'-yl) isonicotinamide IR (KBR, cm⁻¹): 3235(Aromatic-CH), 1312(Aromatic Alkyl C-H), 1660(NH-C=O), 1624(C=N), 1347(C-N), 1691(C=O), 1510(Ar C=C). ¹H-NMR(CDCl₃-D) δppm:2.31(s, 3H, Methyl CH₃), 3.65(d, 1H, CH₂ Thiazolidine), 3.76(d,1H, CH₂ Thiazolidine), 7.02(d, 1H, Ar-H), 7.23(d, 1H Ar-H), 7.29(s, 1H, Ar-H), 7.76(d, 2H, Ar-H), 8.75(d, 2H, Ar-H), 9.52(s, 1H N-H Indole), 10.26(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 354.

VIe N-(7-methyl-2, 4'-dioxospiro [indoline-3, 2'-thiazolidin]-3'-yl) isonicotinamide IR (KBR, cm⁻¹): 3246(Aromatic-CH),1319(Aromatic Alkyl C-H), 1696(NH-C=O), 1630(C=N), 1355(C-N), 1711(C=O), 1504(Ar C=C). ¹H-NMR(CDCl₃-D) δppm:2.16(s, 3H, Methyl CH₃), 3.65(d, 1H, CH₂ Thiazolidine), 3.78(d,1H, CH₂ Thiazolidine), 7.12(d, 1H, Ar-H), 7.28(d, 1H Ar-H), 7.35(t, 1H, Ar-H), 7.78(d, 2H, Ar-H), 8.77(d, 2H, Ar-H), 9.49(s, 1H N-H Indole), 10.37(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 354.

VIIf N-(5-fluoro-2, 4'-dioxospiro [indoline-3, 2'-thiazolidin]-3'-yl) isonicotinamide: IR(KBR, cm⁻¹): 3285(Aromatic-CH), 1686(NH-C=O), 1604

(C=N), 1340(C-N), 1713(C=O), 1508(Ar C=C), 1113(C-F Str). ¹H-NMR(CDCl₃-D) δppm: 3.68(d, 1H, CH₂ Thiazolidine), 3.76(d, 1H, CH₂ Thiazolidine), 7.07(s, 1H, Ar-H), 7.18(d, 1H Ar-H), 7.66(d, 1H, Ar-H), 7.78(d, 2H, Ar-H), 8.77(d, 2H, Ar-H), 8.94(s, 1H N-H Indole), 10.07(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 358 and M⁺¹ peak at 360.

VIg N-(7-fluoro-2, 4'-dioxospiro [indoline-3, 2'-thiazolidin]-3'-yl) isonicotinamide: IR(KBR, cm⁻¹): 3238(Aromatic-CH), 1622(NH-C=O), 1611(C=N), 1326(C-N), 1702(C=O), 1521(Ar C=C), 1097(C-F Str). ¹H-NMR(CDCl₃-D) δppm: 3.62(d, 1H, CH₂ Thiazolidine), 3.75(d, 1H, CH₂ Thiazolidine), 7.15(d, 1H, Ar-H), 7.17(d, 1H Ar-H), 7.28(t, 1H, Ar-H), 7.78(d, 2H, Ar-H), 8.77(d, 2H, Ar-H), 8.76(s, 1H N-H Indole), 9.89(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 358 and M⁺¹ peak at 360.

VIh N-(5-bromo-2,4'-dioxospiro[indoline-3,2'-thiazolidin]-3'-yl)isonicotinamide: IR(KBR, cm⁻¹): 3231(Aromatic-CH), 1674(NH-C=O), 1617(C=N), 1325(C-N), 1701(C=O), 1503(Ar C=C), 601(C-Br Str). ¹H-NMR(CDCl₃-D) δppm: 3.71(d, 1H, CH₂ Thiazolidine), 3.83(d, 1H, CH₂Thiazolidine), 6.70(d, 1H, Ar-H), 7.33(d, 1H Ar-H), 7.54(s, 1H, Ar-H), 7.78(d, 2H, Ar-H), 8.77(d, 2H, Ar-H), 8.97(s, 1H N-H Indole), 10.06(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 419 and M⁺¹ peak at 421.

VII N-(5, 6-dichloro-2, 4'-dioxospiro [indoline-3,2'-thiazolidin]-3'-yl)isonicotinamide: IR (KBr, cm⁻¹): 3068(Aromatic-CH), 1640.99(N-H-C=O), 1642(C=N), 1421(C-N), 1742(C=O), 744.90(C-Cl). ¹H-NMR(CDCl₃-D) δppm: 3.32(d, 1H, CH₂ Thiazolidine), 3.45(d, 1H, CH₂ Thiazolidine), 7.51(d, 1H, Ar-H), 7.56(s, 1H, Ar-H), 7.78(d, 2H,

Ar-H), 8.77(d, 2H, Ar-H), 8.81(s, 1H N-H Indole), 9.92(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 409 and M⁺¹ peak at 411.

VIj N-(5-nitro-2, 4'-dioxospiro[indoline-3, 2'-thiazolidin]-3'-yl) isonicotinamide: IR (KBr, cm⁻¹): 3292(Aromatic-CH), 1645(NH-C=O), 1667(C=N), 1418(C-N), 1410(Nitro N-O), 1736(C=O), 1538(Ar C=C). ¹H-NMR (CDCl₃-D) δppm: 3.62(d, 1H, CH₂ Thiazolidine), 3.75(d, 1H, CH₂ Thiazolidine), 7.19(d, 1H Ar-H), 7.63(d, 1H, Ar-H), 8.18(d, 1H, Ar-H), 7.83(s, 2H, Ar-H), 8.77(d, 2H, Ar-H), 8.99(s, 1H N-H Indole), 9.61(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 385.

VIk N-(7-nitro-2, 4'-dioxospiro[indoline-3, 2'-thiazolidin]-3'-yl)isonicotinamide: IR (KBR, cm⁻¹): 3285(Aromatic-CH), 1637(NH-C=O), 1652(C=N), 1413(C-N), 1402(Nitro N-O), 1720(C=O), 1527(Ar C=C). ¹H-NMR (CDCl₃-D) δppm: 3.63(d, 1H, CH₂ Thiazolidine), 3.75(d, 1H, CH₂ Thiazolidine), 7.48(t, 1H Ar-H), 7.77(d, 1H, Ar-H), 8.03(d, 1H, Ar-H), 7.82(d, 2H, Ar-H), 8.78(d, 2H, Ar-H), 9.11(s, 1H N-H Indole), 9.87(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 385.

VII N-(7-hydroxy-2, 4'-dioxospiro[indoline-3, 2'-thiazolidin]-3'-yl)isonicotinamide: IR (KBR, cm⁻¹): 3275(Aromatic C-H), 1686(NH-C=O), 1640(C=N), 1340(C-N), 1713(C=O), 1508(Ar C=C), 3224(Aromatic O-H). ¹H-NMR (CDCl₃-D) δppm: 3.65(d, 1H, CH₂ Thiazolidine), 3.77(d, 1H, CH₂Thiazolidine), 6.86(d, 1H Ar-H), 6.92(s, 1H, Ar-H), 7.51(d, 1H, Ar-H), 7.82(d, 2H, Ar-H), 8.77(d, 2H, Ar-H), 9.29(s, 1H, Aromatic O-H), 9.68(s, 1H, N-H Indole), 10.29(s, 1H, N-H). Mass Spectrum (EI-MS): M⁺ peak observed at 356.

In-vitro Antioxidant Activity:

TABLE 2: IN-VITRO ANTI-OXIDANT ACTIVITY DATA OFN-(2, 4'-DIOXOSPIRO [INDOLINE-3, 2'-THIAZOLIDIN]-3'-YL)ISONICOTINAMIDE (VI A-L)

Compound	R	IC ₅₀ (μM) Trail-1	IC ₅₀ (μM) Trail-2	IC ₅₀ (μM) Trail-3	Average (μM)
Via	H	68.31	68.48	68.42	68.40
Vib	5-Cl	41.49	41.55	41.57	41.54
Vic	7-Cl	54.14	54.24	54.34	54.24
Vid	5-CH ₃	72.34	72.28	72.46	72.36
Vie	7-CH ₃	79.45	79.67	79.56	79.56
VI f	5-F	35.58	35.67	35.76	35.67
VIg	7-F	57.54	57.63	57.68	57.62

Vlh	5-Br	49.98	50.54	50.5	50.34
Vii	5,6-Dichloro	23.61	24.66	25.67	24.65
Vij	5-NO ₂	66.09	66.12	66.21	66.14
Vik	7-NO ₂	31.97	31.85	31.76	31.86
Vil	5-OH	61.17	61.23	61.25	61.22
Standard	Ascorbic acid	6.03	6.04	6.02	6.03

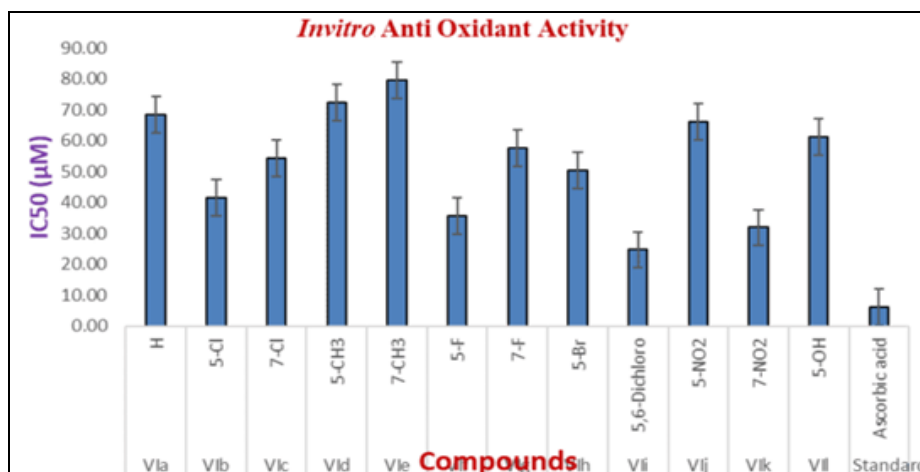


FIG. 2: IN-VITRO ANTI-OXIDANT ACTIVITY DATA OF N-(2,4'-DIOXOSPIRO[INDOLINE-3,2'-THIAZOLIDIN]-3'-YL) ISONICOTINAMIDE (VI A-L)

The *in-vitro* antioxidant activity of N-(2,4'-dioxospiro [indoline-3, 2'-thiazolidin]-3'-yl) isonicotinamide derivatives (VIa-l) was assessed by comparing their IC₅₀ values with that of a standard reference, ascorbic acid (IC₅₀ = 6.03 µM). The findings indicate that the considerable differences in antioxidant effectiveness among the compounds are linked to the type and positioning of substituents on the fundamental structure.

The parent compound VIa (R = H) exhibited moderate activity, presenting an average IC₅₀ of 68.40 µM, indicating a weak capacity for radical scavenging when compared to ascorbic acid. Among the derivatives that were tested, VII (5,6-dichloro) showed the most effective activity (IC₅₀ = 24.65 µM), followed by VIF (5-fluoro; IC₅₀ = 35.67 µM) and VIK (7-nitrophenyl; IC₅₀ = 31.86 µM). The increased effectiveness of these derivatives implies that electron-withdrawing groups such as chlorine, fluorine, and nitro at specific positions enhance antioxidant capability by facilitating radical scavenging or stabilizing intermediate radicals. The effect of substituent position was evident: VIF (5-F) demonstrated greater activity than the 7-Cl variant (VIC, IC₅₀ = 54.24 µM), underscoring the significance of substituent arrangement near the reactive site. Likewise, the introduction of chlorine substitutions at positions 5 and 6 in VII likely enhanced electron

delocalization or the stability of radical intermediates, resulting in the lowest IC₅₀ seen among non-standard compounds. In contrast, the introduction of alkyl groups (e.g., VID, 5-methyl; VIE, 7-methyl) notably decreased the activity, indicating that larger substituents might obstruct access to reactive sites or interfere with beneficial interactions with free radicals. The differing impacts of nitro groups at positions 5 and 7 further emphasize the importance of positional specificity: while VIK (7-NO₂) exhibited enhanced activity, VIJ (5-NO₂) demonstrated lower efficacy (IC₅₀ = 66.14 µM), which could be attributed to steric hindrance or modified electronic influences.

Ultimately, the data suggest that electron-withdrawing groups like halogens and nitro groups can enhance antioxidant activity when appropriately placed on the molecule, especially at position 5 for fluorine and at positions 5 and 6 for chlorine. These results underline the significant influence of the type and positioning of substituents in maximizing the antioxidant capacity of spiro[indoline-thiazolidinyl] derivatives, with compound VII standing out as a noteworthy candidate that warrants further exploration for practical uses. However, despite these progressions, all compounds are still less effective than ascorbic acid, highlighting the potential for future structural improvements to narrow the performance gap.

In-vitro Anti -inflammatory Activity:

TABLE 3: IN-VITRO ANTI-INFLAMMATORY ACTIVITY DATA OF N-(2,4'-DIOXOSPIRO [INDOLINE-3,2'-THIAZOLIDIN]-3'-YL) ISONICOTINAMIDE (VI A-L)

S. no.	Compound	R	% of COX-2		% of COX-2		Average
			Inhibition Trial-1		Inhibition Trial-2	Inhibition Trial-3	
1	Via	H	47.34		47.52	47.38	47.41
2	Vib	5-Cl	58.29		58.33	58.35	58.32
3	Vic	7-Cl	61.42		61.43	61.45	61.43
4	Vid	5-CH ₃	66.22		66.24	66.18	66.21
5	Vie	7-CH ₃	50.21		49.2	48.31	49.24
6	Vif	5-F	46.25		48.23	47.2	47.23
7	VIg	7-F	57.04		57.11	57.03	57.06
8	VIh	5-Br	60.11		60.23	60.24	60.19
9	Vli	5,6-Dichloro	62.06		62.1	62.23	62.13
10	Vij	5-NO ₂	52.13		54.15	53.16	53.15
11	Vik	7-NO ₂	69.16		69.1	69.14	69.13
12	Vil	5-OH	58.16		58.22	58.17	58.18
13	Indomethacin		74.31		72.4	73.26	73.32

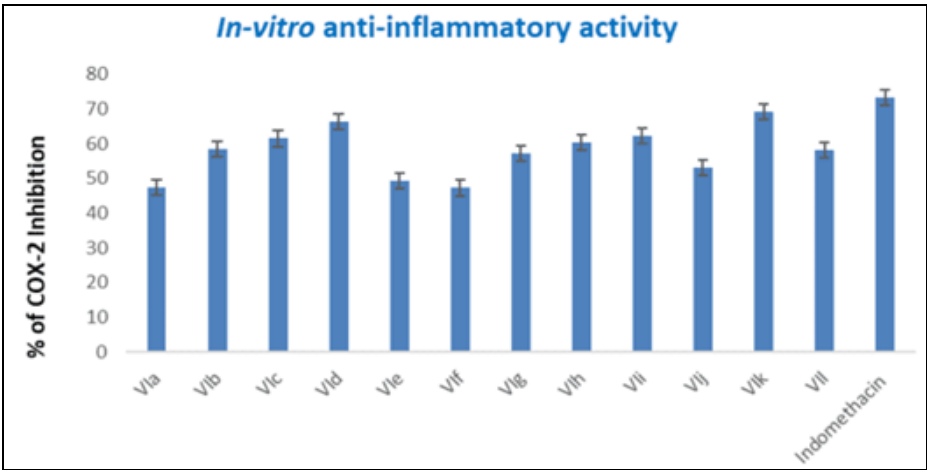


FIG. 3: IN-VITRO ANTI-INFLAMMATORY ACTIVITY DATA OF N-(2,4'-DIOXOSPIRO [INDOLINE-3,2'-THIAZOLIDIN]-3'-YL) ISONICOTINAMIDE (VIA-L)

In-vitro anti-Inflammatory Activity of N-(2,4'-Dioxospiro [indoline-3, 2'-thiazolidin]-3'-yl) isonicotinamide Derivatives (VIa-l): COX-2 Inhibition Analysis. The anti-inflammatory properties of a range of synthesized compounds (VIa–VII), which are derived from N-(2,4'-dioxospiro [indoline-3, 2'-thiazolidin]-3'-yl) isonicotinamide, were assessed by measuring their ability to inhibit cyclooxygenase-2 (COX-2), an important enzyme involved in inflammation. These compounds were distinguished by different substituents (R groups) on the benzyl ring at the 5 and 7 positions, encompassing halogens (Cl, F, Br), alkyl groups (Me), nitro (NO₂), hydroxyl (OH), and dichloro groups. Indomethacin, a widely recognized inhibitor of COX-2, was used as the reference standard, demonstrating an average inhibition rate of 73.32%. The findings demonstrated considerable variability in the COX-2

inhibitory activity across the different derivatives, emphasizing the significant role of both the type and location of substituents. The compound VIk (7-nitro derivative) showed the greatest effectiveness among the compounds tested, achieving an average inhibition of 69.13%, with VID (5-methyl group: 66.21%) and VII (5,6-dichloro: 62.13%) following closely behind. These results highlight the critical nature of substituent positioning and electronic characteristics, with position 7 identified as a particularly responsive site for enhancing anti-inflammatory activity, especially when modified with electron-withdrawing groups like nitro or halogens. Interestingly, electron-donating groups such as methyl at position 7 (VIE: 49.24%) significantly decreased efficacy when compared to those at position 5 (VID), highlighting the importance of steric and electronic influences in enzyme interactions.

The nitro group (NO₂) at position 7, in particular, exhibited remarkable potency, probably due to its strong electron-withdrawing characteristics and its ability to engage in hydrogen bonding or π - π stacking with residues in the COX-2 active site. In contrast, compounds featuring smaller substituents like fluorine (VI_f: ~47%) or chlorine at position 5 (VI_b) displayed moderate inhibition, indicating that the size and polarizability of substituents play vital roles in enhancing activity. Although Indomethacin was found to be the most potent, with an efficacy of 73.32%, various derivatives, especially those

featuring 7-NO₂ or 5-Me, showed encouraging anti-inflammatory activity, nearly reaching 90% of Indomethacin's effectiveness. These findings suggest that strategic alterations at the 7 position, incorporating large, electronegative groups such as nitro, could further improve COX-2 inhibition, possibly matching commercial benchmarks. This research offers valuable insights for the development of new anti-inflammatory compounds aimed at COX-2 through thoughtful structural optimization.

TABLE 4: IN-VIVO ANTI-INFLAMMATORY ACTIVITY DATA OF N-(2,4'-DIOXOSPIRO[INDOLINE-3,2'-THIAZOLIDIN]-3'-YL)ISONICOTINAMIDE (VI A-L)

S. no.	Compound (100 mg /kg body weight)	R	Mean Paw Edema Volume in ml ± SD			
			1h	2h	3h	4h
1	Vib	5-Cl	0.48± 0.076	0.42± 0.021	0.40± 0.012	0.38 ±0.032
2	Vic	7-Cl	0.45 ±0.023	0.38± 0.043	0.36± 0.020	0.34± 0.021
3	Vid	5-CH ₃	0.43± 0.021	0.37± 0.065	0.33± 0.062	0.24± 0.052
4	VIh	5-Br	0.47 ±0.034	0.43± 0.090	0.40 ±0.038	0.39 ±0.068
5	Vii	5,6 Dichloro	0.42± 0.045	0.39 ±0.052	0.36 ±0.070	0.33 ±0.090
6	Vik	7-NO ₂	0.34 ±0.035	0.30 ±0.070	0.47 ±0.054	0.21 ±0.043
7	Control Group (carrageenan induced)		0.58±0.080	0.62±0.016	0.68±0.035	0.72±0.080
8	Indomethacin(100mg/kg Body wt)		0.36± 0.070	0.34 ±0.120	0.31±0.080	0.28±0.062

The anti-inflammatory properties of N-(2,4'-dioxospiro [indoline-3, 2'-thiazolidin]-3'-yl) isonicotinamide derivatives (VIa-l) were evaluated *in-vivo* using a rat model of paw edema caused by carrageenan. The compounds were administered at a dosage of 100 mg/kg of body weight, and their anti-inflammatory efficacy was assessed by measuring the reduction in paw volume compared to the control group (which did not receive any treatment for carrageenan-induced inflammation) and the reference drug, Indomethacin (100mg/kg).

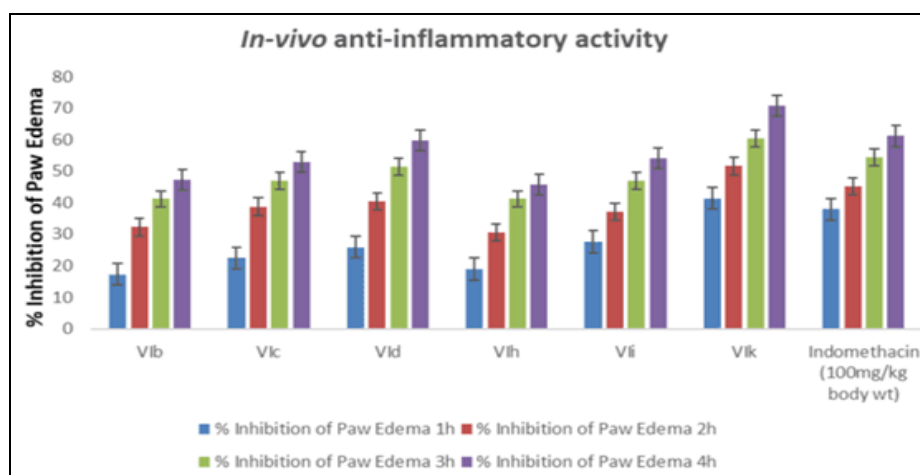
Inhibition of edema = (Mean edema of control group-Mean edema of treated group) / (Mean edema of control group) × 100

The anti-inflammatory effects of N-(2,4'-dioxospiro [indoline-3,2'-thiazolidin]-3'-yl) isonicotinamides (compounds VIa-l) were evaluated *in vivo* using the carrageenan-induced paw edema model in rats. The compounds were given at a dosage of 100 mg/kg of body weight, and indomethacin (100 mg/kg) served as the reference standard. The percentage decrease in paw swelling was measured at 1, 2, 3, and 4 hours post-treatment to assess the effectiveness over time. Among the compounds evaluated, VI_k (with a 7-nitro substituent) demonstrated the strongest anti-inflammatory

effect, showing a steady increase in its inhibitory impact over time: it reached 41.38% at the 1-hour mark and surged to an impressive 70.83% at 4 hours. This level of performance surpassed that of indomethacin, which recorded 61.11% at the 4-hour interval, indicating that VI_k has superior long-lasting effectiveness. The exceptional activity of VI_k is likely linked to the electron-withdrawing nature of the nitro group (NO₂) at the 7 position, which probably enhances polar interactions or radical scavenging abilities due to its high electronegativity and capacity to produce reactive intermediates that inhibit inflammatory processes such as cyclooxygenase (COX) and the production of prostaglandins. Other significant compounds included VI_d (with a 5-methyl group), which exhibited a consistent rise in performance from 25.86% inhibition at 1 hour to 59.72% at the 4-hour mark, underscoring the advantageous effect of a methyl group at position 5 in influencing activity. Likewise, both VI_c (7-chloro) and VI_i (5,6-dichloro) displayed increases over time, with VI_i achieving 54.17% inhibition after 4 hours, indicating that halogen substitutions at certain positions might also boost anti-inflammatory effectiveness through enhanced lipophilicity or π - π stacking interactions with the target enzymes.

TABLE 5: IN-VIVO ANTI-INFLAMMATORY ACTIVITY DATA OF N-(2,4'-DIOXOSPIRO[INDOLINE-3,2'-THIAZOLIDIN]-3'-YL) ISONICOTINAMIDE (VI A-L)

S. no.	Compound (100mg / kg body weight)	R	% Inhibition of Paw Edema			
			1h	2h	3h	4h
1	Vib	5-Cl	17.24	32.26	41.18	47.22
2	Vic	7-Cl	22.41	38.71	47.06	52.78
3	Vid	5-CH ₃	25.86	40.32	51.47	59.72
4	Vih	5-Br	18.97	30.65	41.18	45.83
5	Vii	5,6-Dichloro	27.59	37.10	47.06	54.17
6	Vik	7-NO ₂	41.38	51.61	60.29	70.83
7	Indomethacin(100mg/kg body wt)		37.93	45.16	54.41	61.11

**FIG. 4: IN-VIVO ANTI-INFLAMMATORY ACTIVITY DATA OF N-(2, 4'-DIOXOSPIRO [INDOLINE-3,2'-THIAZOLIDIN]-3'-YL) ISONICOTINAMIDE (VI A-L)**

The data indicates a distinct relationship between the type and position of substituents and their efficacy: compounds that contain electron-withdrawing groups (such as Cl, Br, NO₂) typically exhibited higher activity than those without substitutions, especially when located at the 7th carbon of the thiazolidin ring.

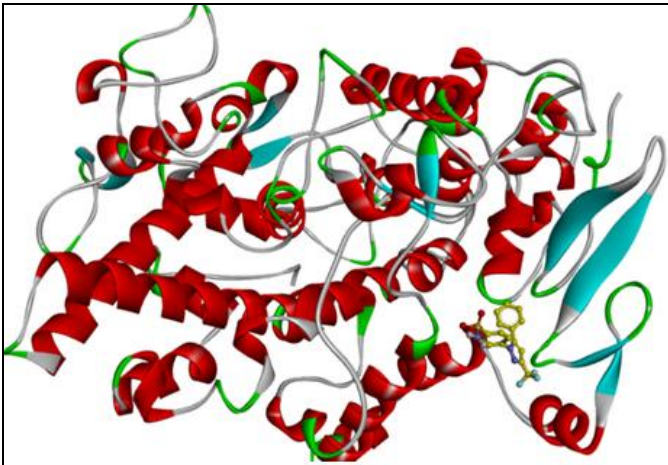
Interestingly, Vib (5-chloro) and Vih (5-bromo) showed comparatively lower inhibition when compared to similar compounds with substituents in different positions, implying that spatial arrangement and electronic influences play a crucial role in biological activity.

In general, Vik, characterized by its 7-nitro group, proved to be the most favorable option because of its enhanced and extended anti-inflammatory effects compared to indomethacin at later intervals, which may provide better therapeutic benefits for chronic inflammatory diseases while minimizing the requirement for frequent dosing. These results highlight the importance of choosing the right substituents and optimizing their positions within the spiro[indoline-thiazolidin] framework to improve the drug's effectiveness and stability.

**FIG. 5: CARRAGENAN INDUCED EDEMA IN THE RIGHT HIND PAW(*) OF THE RAT**

Statistical Analysis: The statistical analysis revealed that the average IC₅₀ value for in vitro antioxidant activity was 49.97, with a standard deviation of 21.13. An average of 58.69 with a standard deviation of 8.08 was found for the in vitro anti-inflammatory activity. When a one-way ANOVA was used to assess the in vivo anti-inflammatory activity, the p-value was less than 0.0001. We consider this result to be statistically significant.

In-silico Molecular Docking Studies:



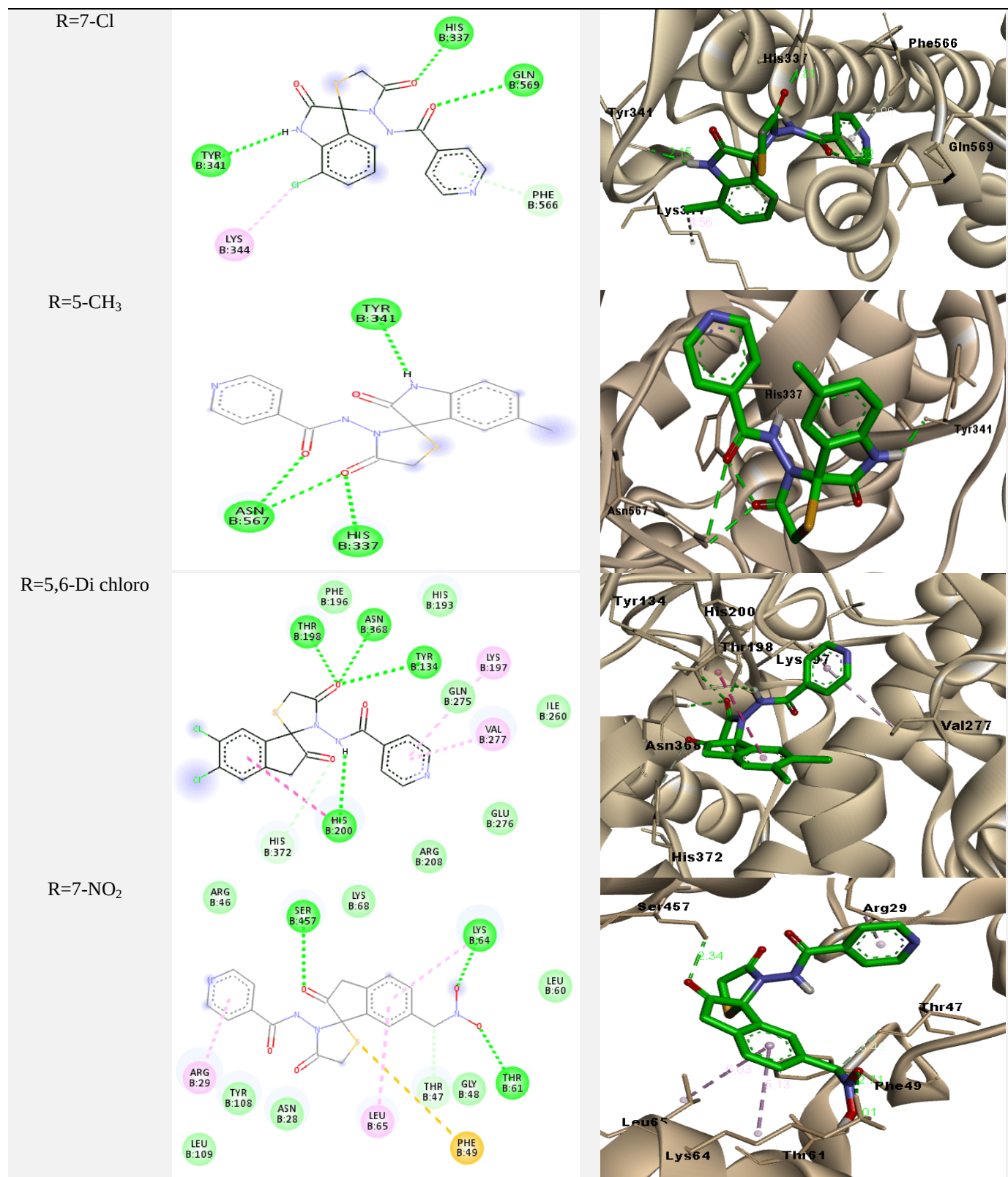
PDB DOI: <https://doi.org/10.2210/PDB3LN1/PDB>
FIG. 6: 3LN1 (STRUCTURE OF CELECOXIB BOUND AT THE ACTIVE SITE OF COX-2)

TABLE 6: BINDING FREE ENERGY OF LIGANDS WITH 3LN1

S. no.	Compound	Binding Affinity
1	H	-7.5
2	5-Cl	-7.1
3	7-Cl	-7.8
4	5-CH ₃	-8.0
5	7-CH ₃	-7.5
6	5-F	-7.6
7	7-F	-7.3
8	5-Br	-7.1
9	5,6-Dichloro	-7.8
10	5-NO ₂	-7.3
11	7-NO ₂	-8.2
12	5-OH	-7.4
13	Celecoxib	-7.9
14	Indomethacin	-8.0

TABLE 7: THE CYCLOOXYGENASE II ACTIVE SITE (PDB:3LN1) SHOWS THE PROJECTED BINDING ORIENTATIONS OF INDOMETHACIN AS WELL AS THE EXPECTED TWO- AND THREE-DIMENSIONAL BINDING INTERACTIONS OF COMPOUNDS 4, 6, 11, 14, AND 17; THE LIGANDS ARE SHOWN IN GREEN

Ligand	2D Receptor interaction	3D Receptor interaction
Indomethacin		
Celecoxib		



Interactions			
	van der Waals		Pi-Pi Stacked
	Conventional Hydrogen Bond		Pi-Pi T-shaped
	Pi-Sigma		Pi-Alkyl

ADME Studies and DrugLikeness: The evaluation of potential drug-likeness attributes was conducted utilizing Swiss ADME software; this stage is vital to the advancement of the drug discovery process and must be taken into account. The Swiss ADME tool was employed to analyze

various physical and chemical characteristics, including molecular weight, the number of hydrogen bond donors, the number of hydrogen bond acceptors, solubility, lipophilicity, and the bioavailability score²⁶⁻³⁰. Illustrated in **Table 8**.

TABLE 8: ADME PROPERTIES AND DRUGLIKENESS OF LEAD COMPOUNDS

Molecule	H-bond acceptors	H-bond donors	TPSA	QLog P	ESOL Log S	GI absorption	BBB permeability	CYP3A4 inhibitor	Lipinski violations	Bioavailability Score
Via	4	2	116.7	0.8	-2.67	High	No	No	0	0.55
Vib	4	2	116.7	1.36	-3.27	High	No	Yes	0	0.55
Vic	4	2	116.7	1.33	-3.27	High	No	Yes	0	0.55
Vid	4	2	116.7	1.17	-2.98	High	No	No	0	0.55
Vie	4	2	116.7	1.13	-2.98	High	No	No	0	0.55
Vif	5	2	116.7	1.14	-2.83	High	No	No	0	0.55
VIg	5	2	116.7	1.12	-2.83	High	No	No	0	0.55
VIh	4	2	116.7	1.44	-3.58	High	No	Yes	0	0.55
VIIi	4	2	116.7	1.84	-3.86	High	No	Yes	0	0.55
Vij	6	2	162.5	0.08	-2.74	Low	No	No	0	0.55
Vik	6	2	162.5	0.04	-2.74	Low	No	No	0	0.55
VII	5	3	136.9	0.45	-2.53	High	No	No	0	0.55

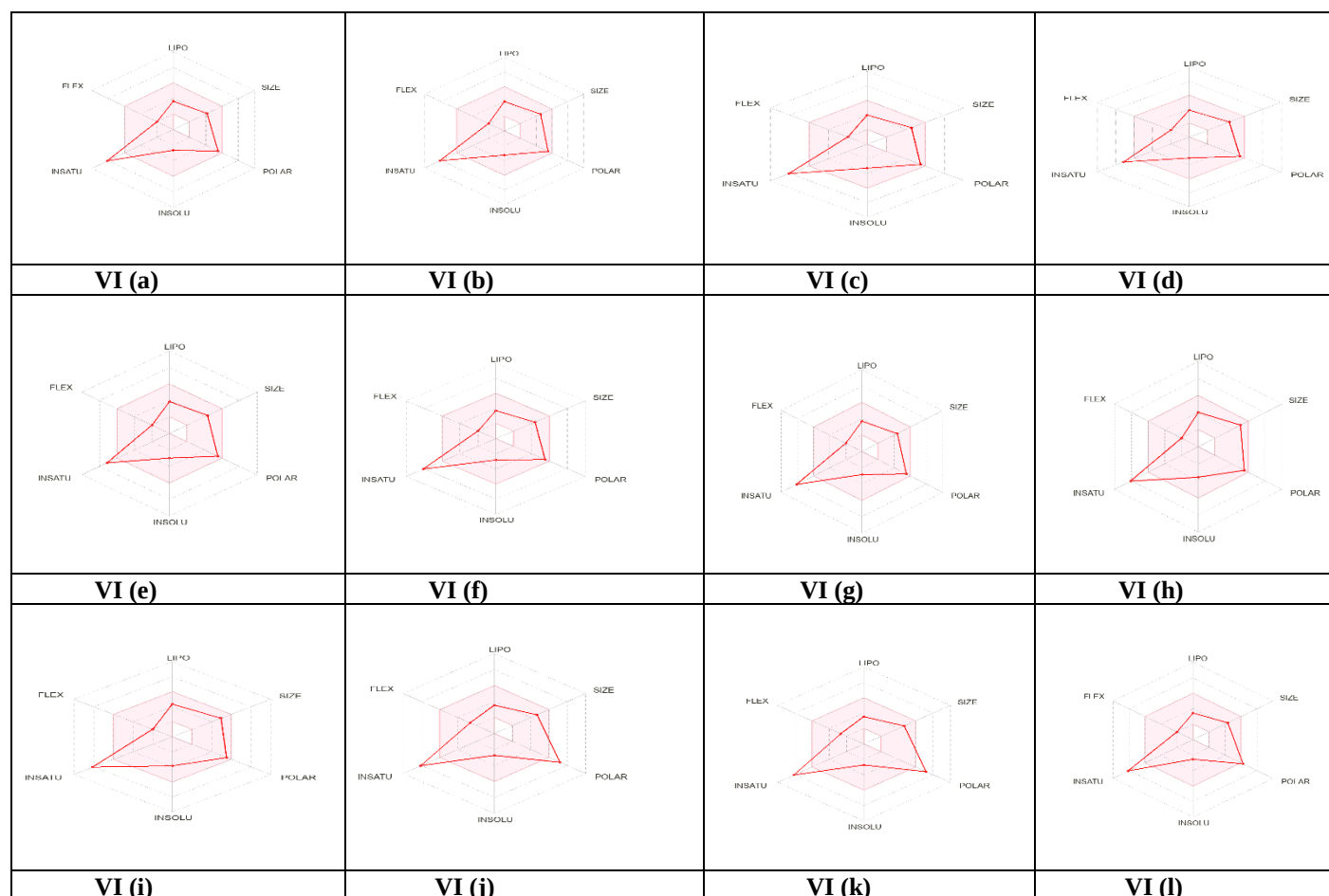


FIG. 7: SWISS ADME RADAR FOR DRUG-LIKENESS OF ALL IDENTIFIED COMPOUND

ADME and Drug-Likeness Studies: *In-silico* ADME (Absorption, Distribution, Metabolism, and Excretion) and drug-likeness evaluations were

performed for the synthesized derivatives. Interestingly, compounds VIj (R=5-NO₂) and Vik (R=7-NO₂), which showed promising anti-

inflammatory and antioxidant activities, exhibited low gastrointestinal absorption according to the ADME predictions. Despite this limitation, compound VIk (R=7-NO₂) demonstrated notable antioxidant activity, indicating potential need for formulation strategies to enhance oral bioavailability.

TABLE 9: COMPARISON OF COX-2 INHIBITION, ANTI-INFLAMMATORY ACTIVITY, AND BINDING AFFINITY OF SYNTHESIZED COMPOUNDS AND THE STANDARD DRUG INDOMETHACIN

S. no.	Compound	R	COX-2 Inhibition	In-vivo % Inhibition of paw edema at 4h	Binding affinity towards COX-2 (PDBID:3LN1)
1	VI c	7-Cl	61.43	52.78	-7.8
2	VI d	5-CH ₃	66.21	59.72	-8.0
3	VI i	5,6-Dichloro	62.13	54.17	-7.8
4	VI k	7-NO ₂	69.13	70.83	-8.2
	Indomethacin		73.32	61.11	-8.0

Upon reviewing the findings, it is evident that including a nitro group amplifies the compound's anti-inflammatory effectiveness. Prior studies conducted by Neha Krishnarth *et al.*³¹ indicate that the electron-withdrawing characteristic of the nitro group contributes to its increased potency. Our research similarly reveals that compounds with nitro substitutions demonstrate the strongest *in-vitro* and *in-vivo* anti-inflammatory activity, thereby confirming the significance of the nitro group.

CONCLUSION: The data indicates that VI d (5-methyl) and VI k (7-nitro) show particular promise because of their prolonged and rapid anti-inflammatory effects, respectively. Additional research into the mechanisms behind their actions and long-term safety could further their application in treating inflammatory diseases. Furthermore, the results highlight the significance of refining substituent positioning and functional groups to improve therapeutic effectiveness while reducing side effects.

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CONFLICT OF INTEREST: The authors declare no conflict of interest

REFERENCES:

1. Barbosa da Silva SE, Moura JAS, Branco Júnior JF, de Souza BSS, da Silva TG and Santos-Filho OA: Synthesis and *in-vitro* and *in-silico* anti-inflammatory activity of new thiazolidinedione-quinoline derivatives. *Curr Top Med Chem* 2024; 24(14): 1264–1277. <https://doi.org/10.2174/1568026624666231214113618>

2. Patel K and Rana AM: Review on thiazolidinone possessing heterocyclic analogues, their potential binding

sites with cyclooxygenase and lipoxygenase; their Sar and docking studies for anti-inflammatory activity. *Int J Sci Res Arch* 2024; 11(2): 879–892. <https://ijsra.net/index.php/ijrsra/article/view/841>

3. Gupta V, Yadav D, Kumar R and Sharma A: Medicinal perspective of 2,4-thiazolidinediones derivatives: an insight into recent advancements. *Chemistry Open* 2024. <https://doi.org/10.1002/open.202402043>

4. Kamboj P, Anjali, Imtiyaz K, Rizvi MA, Verma A and Singh SK: Design, synthesis, biological assessment and molecular modeling studies of novel imidazothiazole-thiazolidinone hybrids as potential anticancer and anti-inflammatory agents. *Sci Rep* 2024; 14: 8457. <https://doi.org/10.1038/s41598-024-55351>

5. Mekhlef YO, Aboul Magd AM and Gouda AM: Design, synthesis, modeling studies and biological evaluation of novel 2,3-diaryl-1,3-thiazolidine-4-one derivatives as potential anti-inflammatory and cytotoxic agents. *Bioorg Chem* 2023; 133: 106411. [doi:10.1016/j.bioorg.2023.106411](https://doi.org/10.1016/j.bioorg.2023.106411)

6. Süzgün P, Şenkardeş S, Gürboğa M, Bingöl Özakpınar Ö and Küçükgül ŞG: Synthesis and biological evaluation of new 4-oxothiazolidin-3-yl flurbiprofen derivatives. *Org Commun* 2023; 1(1-3): 11–23. [doi:10.25135/acg.oc.144.2212.2653](https://doi.org/10.25135/acg.oc.144.2212.2653)

7. Singh VJ and Chawla P: Exploring the role of 4-thiazolidinone-pyridine hybrids as potential COX-2 inhibitors and free-radical scavenging agents. Presented at: ScholarWorks, UTRGV Research Symposium 2023.

8. Archana, Chawla PA, Teli G, Pathania S, Singh S and Srivastava V: Exploration of antioxidant, anti-inflammatory and anticancer potential of substituted 4-thiazolidinone derivatives: synthesis, biological evaluation and docking studies. *Polycycl Aromat Compd* 2023; 43(1): 597–618. [doi:10.1080/10406638.2021.2019796](https://doi.org/10.1080/10406638.2021.2019796)

9. Al-Omar MA, Alrashood KA, Al-Ajmi MF, Ola ARB and Abdel-Aziz HA: Discovery of 5-methylthiazole-thiazolidinone conjugates as selective cox-1 inhibitors with anti-inflammatory activity and gastric safety. *Mol Basel Switz* 2022; 27(23): 8226. <https://doi.org/10.3390/molecules27238226>

10. Al-Omar MA, Alrashood KA, Al-Ajmi MF, Ola ARB and Abdel-Aziz HA: Benzothiazole-based thiazolidinones as potent anti-inflammatory and lox-inhibiting agents: *in-vivo* and *in-silico* studies. *Med Chem Res* 2022; 31: 1616–1627. <https://doi.org/10.1007/s00044-022-02823>

11. El-Gamal MI, Aljulaih AA, Abdel-Aziz HA and Oh CH: Synthesis, preliminary pharmacological evaluation, molecular docking, and ADME studies of new

- 4-thiazolidinone derivatives bearing ketoprofen moiety targeting cyclooxygenase enzyme. Egypt J Chem 2021; 64(12): 7339–7350. <https://doi.org/10.21608/ejchem.2021.91135.4192>
12. Devi and Divya Sreepada Manda Sarangapani: "Synthesis and screening of N-(2,4'-Dioxo-1,2-Dihydro-3'H-Spiro (Indole-3,2'-(1,3) thiazolidin)-3'-yl) Hydroxy benzamides for antibacterial activity", International Journal of Pharmaceutical Sciences and Research 2019; 10(8): 3850-3855.
 13. Desai S, Patel D and Dave R: Design, synthesis, and biological evaluation of 4-thiazolidinone derivatives as potential dual anti-inflammatory and antioxidant agents. J Heterocycl Chem 2022; 59(9): 1479–1490. <https://doi.org/10.1002/jhet.4445>
 14. Mahdi AA, Nawar NA and Saleh AI: Design, synthesis, and acute anti-inflammatory assessment of new 2-methyl benzimidazole derivatives having 4-thiazolidinone nucleus. Iraqi J Pharm Sci 2022; 31(1): 60–71. <https://doi.org/10.31351/vol31iss1pp60-71>
 15. Tomašić T, Zidar N, Mravljak J, Kikelj D and Časar Z: Synthesis, antiulcerative, and anti-inflammatory activities of new campholenic derivatives-1,3-thiazolidin-4-ones. Chem Pap 2021; 5: 5503–5514. <https://doi.org/10.1007/s11696-021-01636-1>
 16. Ibrahim MA, Abdelrahman MH, Ahmed RF, El-Moghazy SA and Ahmed SM: Synthesis, design, and anti-inflammatory activity of novel 5-(Indol-3-yl) thiazolidinone derivatives as COX-2 inhibitors. Lett Drug Des Discov 2021; 18(6): 597–604. <https://doi.org/10.2174/1570180818666210322151804>
 17. Mahdi AA, Nawar NA and Saleh AI: Synthesis, characterization and acute anti-inflammatory evaluation of new mefenamic acid derivatives having 4-thiazolidinone nucleus. Iraqi J Pharm Sci 2021; 30(2): 75–84. <https://doi.org/10.31351/vol30iss2pp75-84>
 18. Shahan M, Rashad AE, Kamel GM and Abdel-Aziz HA: Design, synthesis and molecular docking of new pyrazole-thiazolidinones as potent anti-inflammatory and analgesic agents with TNF α inhibitory activity. Bioorg Chem 2021; 111: 104827. <https://doi.org/10.1016/j.bioorg.2021.104827>
 19. Rosy PJ, Jebastin Sonia JAS, Sankar S and Mahalakshmi S: Green synthesis, biological evaluation and DFT calculations of thiazolidinone derivatives – a review. Asian J Pharm Clin Res 2020; 13(1): 10–20.
 20. Abdu-Allah HHM, Abdelmoez AAB, Tarazi H, El-Shorbagi AA and El-Awady R: Conjugation of 4-aminosalicylate with thiazolidinones afforded non-cytotoxic potent *in-vitro* and *in-vivo* anti-inflammatory hybrids. Bioorg Chem 2020; 94: 103378.
 21. Omar YM, Abdel-Moty SG and Abdu-Allah HHM: Further insight into dual COX-2 and 15-LOX anti-inflammatory activity of 1,3,4-thiadiazole-thiazolidinone hybrids: substituent effects. Bioorg Chem 2020; 97: 103657.
 22. Fadaly WAA, Elshaier YAMM, Hassanein EHM and Abdellatif KRA: Pyrazolyl-thiazolidinone derivatives as celecoxib/dasatinib analogues with selective COX-2, HER-2 and EGFR inhibitory effects: design, synthesis, anti-inflammatory/anti-proliferative activities, molecular modelling and ADME studies. Bioorg Chem 2020; 98: 103752.
 23. Haroun M, Fesatidou M, Petrou A, Tratat C, Kolokotroni A and Zagaliotis P: Discovery of 5-methylthiazole-thiazolidinone conjugates as potential anti-inflammatory agents: molecular target identification and *in-silico* studies. Molecules 2022; 27(23): 8137.
 24. Nassiri Koopaei M, Shojaei S, Dehpour AR and Khoshneviszadeh M: Synthesis and *in-silico* ADMET evaluation of new thiazole and thiazolidine-4-one derivatives as non-ulcerogenic analgesic and anti-inflammatory agents. J Serb Chem Soc 2024; 89(12): 1411–22.
 25. Omar YM, Abutaleb NS, Al-Hamzawi MS and Soliman WE: Dual COX-2 and 15-LOX anti-inflammatory activity of 1,3,4-thiadiazole-thiazolidinone hybrids: synthesis, biological evaluation and molecular docking. Bioorg Chem 2020; 97: 103657.
 26. El-Karim SSA, El-Sayed WA, Badria FA, Fattah AA, Rashed HE and Taha M: Pyrazole-thiazolidinones as potent anti-inflammatory and analgesic agents with TNF α inhibitory activity. Bioorg Chem 2021; 111: 104827.
 27. Shepeta Y, Shchukina M, Zhuravska O, Savych A and Lesyk R: Thiazolidinone-diclofenac hybrid molecules: synthesis and *in-silico* anti-inflammatory activity. Phosphorus Sulfur Silicon Relat Elem 2020; 195(7): 836–41.
 28. Ram VJ, Shukla R, Saxena A and Srivastava V: Design, synthesis and biological evaluation of thiazolidinone derivatives with pyrazole core as potential anti-inflammatory COX-2 selective inhibitors. Bioorg Chem 2019; 82: 86–99.
 29. Patel R and Shah S: Antiinflammatory activity of triazine-thiazolidinone derivatives: in silico docking and pharmacophore modeling. Indian J Pharm Sci 2021; 83(4): 674–81.
 30. Mohassab AM, El-Gamal MI, Abdel-Maksoud MS, Hamed MI and Bekhit AA: New quinoline/1,2,4-triazole hybrids as dual inhibitors of COX-2/5-LOX and inflammatory cytokines: design, synthesis, and docking studies. J Mol Struct 2021; 1244: 1309.
 31. Neha Krishnarth, Santosh Kumar Verma and Anurag Chaudhary: "Synthesis and anti-inflammatory activity of some novel quinazolinone derivatives". ABAD J Pharm Sci 2020; 3: 205-210.

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