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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME SUBSTITUTED 1,3,4- THIADIAZOLE DERIVATIVES AS AN ANTI-INFLAMMATORY AGENT

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ABSTRACT

Background: Inflammation is a fundamental pathological process implicated in numerous chronic diseases. Current anti-inflammatory therapies, are associated with significant adverse effects, prompting the search for safer and more effective agents. 1,3,4-Thiadiazoles, have demonstrated diverse pharmacological properties, including potent anti-inflammatory activity. **Methodology:** This study involved the synthesis of five substituted 1,3,4-thiadiazole analogues (VK-1 to VK-5) via a three-step synthetic procedure. Structural confirmation was performed using FTIR and ^{1}H-NMR. Analogues evaluated for anti-inflammatory activity through docking studies against the COX-2 enzyme & in vivo using carrageenan-induced paw edema model. ADME & toxicity predictions were conducted using SwissADME and related tools. **Results:** All synthesized compounds exhibited successful structural confirmation. Molecular docking revealed strong binding affinities, especially for VK-1, which showed the highest docking score (-8.342) and significant interactions with key COX-2 residues. In vivo studies demonstrated dose-dependent inhibition of paw edema, with VK-3 (85%), VK-4 (75%), and VK-1 (70%) showing remarkable anti-inflammatory activity at 100 mg/kg, significant as diclofenac sodium (95%). ADME analysis confirmed favorable drug-likeness, with no major violations of Lipinski's rule. **Conclusion:** The synthesized 1,3,4-thiadiazole derivatives, particularly VK-1, VK-3, and VK-4, demonstrated significant anti-inflammatory

potential. These compounds represent promising candidates for further development as oral anti-inflammatory agents, warranting additional studies for chronic models, pharmacokinetics, and toxicity profiling.

KEYWORDS: 1,3,4-thiadiazole, Organic Synthesis, Molecular Docking, Anti-inflamatory Activity, NMR, IR.

1. INTRODUCTION

Heterocyclic compounds have emerged as privileged scaffolds in medicines due to versatility in structure & diverse pharmacological activities.[1] Among these, 1,3,4-thiadiazoles, ring with sulfur and two nitrogen, have garnered significant attention for their broad-spectrum bioactivities, including anti-inflammatory, analgesic, antimicrobial[2], anticonvulsant, antihypertensive, and anticancer properties.[3] The 1,3,4-thiadiazole nucleus offers unique physicochemical properties, such as enhanced lipophilicity and metabolic stability, which improve pharmacokinetic profiles and make it a promising bioisosteric replacement for other heterocyclic systems like oxadiazoles.[3,4] Its synthetic accessibility through methods such as cyclization of thiosemicarbazides or oxidative cyclization of thiohydrazides facilitates the generation of diverse analogues for structure-activity relationship (SAR) studies.[4]

The historical evolution of anti-inflammatory agents, from salicylates in ancient remedies to aspirin's synthesis in 1897 and the development of COX inhibitors in the 20th century[5], has been driven by advances in understanding inflammatory mechanisms.[5] The discovery of prostaglandins and cyclooxygenase (COX) pathways elucidated key inflammatory mediators[6], leading to the development of selective COX-2 inhibitors aimed at reducing NSAID-associated gastrointestinal toxicity.[7] However, cardiovascular safety concerns with these inhibitors and the limitations of biologics, such as high costs and parenteral administration, highlight the need for orally bioavailable small molecules.[8] 1,3,4-Thiadiazoles address this gap by targeting multiple inflammatory pathways, including COX inhibition, cytokine modulation, and antioxidant activity, potentially enhancing therapeutic efficacy.[9]

The molecular mechanisms of inflammation involve complex interactions among cellular components, (e.g., cytokines, eicosanoids, reactive oxygen species), & pathways (e.g., NF-κB, AP-1, STAT) triggered by pattern recognition receptors.[10] Dysregulation of these pathways leads to chronic inflammation, tissue damage, and disease progression. 1,3,4-

Thiadiazoles' ability to modulate these pathways positions them as promising candidates for anti-inflammatory drug development.[10] SAR studies indicate that substituents on the thiadiazole ring, particularly electron-donating groups at C2 and lipophilic groups at C5, significantly influence anti-inflammatory activity.[3]

This study aims to synthesize and evaluate novel 1,3,4-thiadiazole derivatives as anti-inflammatory agents, leveraging their structural and pharmacological advantages. By integrating synthetic chemistry, in silico molecular docking, in vivo pharmacological assays, and ADME predictions, this research seeks to identify lead compounds with potent anti-inflammatory activity, favorable drug-likeness, and reduced adverse effects compared to existing therapies. The findings are expected to contribute to development of class of orally bioavailable anti-inflammatory drugs, addressing unmet needs in the management of inflammatory diseases.

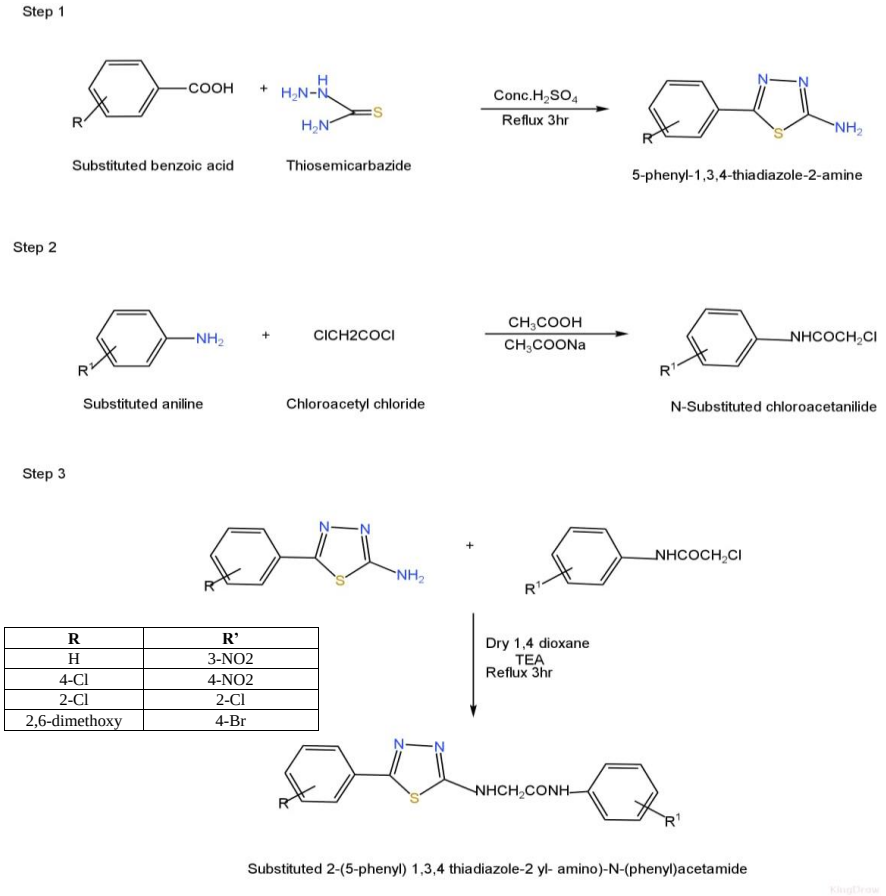
2. METHODOLOGY

The study was designed to synthesize, characterize, and evaluate novel 1,3,4-thiadiazole analogues for their potential as anti-inflammatory.[3] A systematic approach was employed, integrating organic synthesis, physicochemical characterization, in silico analyses, and in vivo pharmacological assessments to ensure comprehensive evaluation of the compounds. All experimental procedures were conducted at Dr. VVPF's College of Pharmacy, Ahilyanagar, following established protocols and ethical guidelines.

Materials

High-purity reagents and solvents were procured from reputable suppliers to ensure consistency and reliability in the synthesis process. Key chemicals included thiosemicarbazide, substituted benzoic acids, acetic anhydride, and various chlorinating agents, all of analytical grade. Solvents such as ethanol, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF) were used for reactions and purifications. Laboratory equipment included a round-bottom flask (RBF) setup for synthesis, a FTIR, ^{1}H-NMR, and thin-layer chromatography (TLC) apparatus for structural characterization.[11] For in vivo studies, Wistar rats were sourced from an accredited animal facility, and carrageenan was obtained for inducing inflammation.[12]

Synthetic Procedures



R	R'
H	3-NO2
4-Cl	4-NO2
2-Cl	2-Cl
2,6-dimethoxy	4-Br

Fig. 1: Synthetic Route to Target Compounds.

Step 1: Synthesis of 2-amino-(5-phenyal substituted)-1,3,4-thiadiazoles

In RBF with reflux condenser, substituted benzoic acid (0.01 mol) and thiosemicarbazide (0.01 mol) were combined. Concentrated sulfuric acid (15 mL) was added slowly while cooling to maintain a low temperature. The mixture was refluxed on a water bath for 3 hours. After reflux, the mixture was poured into crushed ice and neutralized with ammonia solution, resulting in the precipitation of a colored solid. This solid was filtered, washed with saturated sodium bicarbonate solution and distilled water, then dried and recrystallized from ethanol to yield pure thiosemicarbazone derivative crystals.

Step 2: Synthesis of N-Substituted Chloroacetanilides (2a–2d)

In a round-bottom flask, substituted aniline (0.1 mol) dissolved in glacial acetic acid & saturated sodium acetate. Mixture warmed gently & then cooled in an ice while stirring. After half an hour, a solution of chloroacetyl chloride (0.12 mol) added to the reaction mixture. Following the addition, the product began to precipitate and was subsequently filtered. The product washed with cold water to remove impurities then recrystallized via aqueous alcohol

to obtain pure crystals of the desired chloroacetyl derivative.

Step 3: Procedure for Synthesis of Substituted 2(5-phenyl) 1, 3, 4-thidiazol-2yl-amino-(N-phenyl)acetamide (VK-1 to VK-5)

In RBF mixture of 2-amino-5-phenylsubstituted-1,3,4-thiadoazole (0.01 mol) and 0.01 mol of substituted Chloroacetanilide, dry 1,4 dioxane and triethyl amine was added reaction mixture reflux for 3 hr. After that ice cold water added and product was filtered and dried.

Physicochemical Characterization

Physical Properties: Appearance (color, state), solubility (water, methanol, ethanol, acetone, chloroform, DMSO), and melting points (Veego VMP-D, uncorrected).

TLC: Performed on silica gel 60 with optimized mobile phases. Visualized under UV (254 nm, 366 nm), and Rf calculated.[13]

FTIR Spectroscopy: Spectra were recorded using KBr pellets, identifying functional groups via characteristic absorption bands.[14]

^{1}H-NMR Spectroscopy: Spectra acquired in DMSO-d_6, chemical shifts (δ, ppm) reported relative to tetramethylsilane and coupling constants (J, Hz) noted.[15]

In Vivo Anti-inflammatory Activity

Carrageenan-induced paw edema model was employed to evaluate anti-inflammatory activity.[16] Wistar rats (n=6 per group) were divided into: Group I (control, normal saline), Group II (reference, diclofenac sodium 10 mg/kg), & Groups III–VII (YG-1 to YG-5, 10 mg/kg), administered orally.[16] One hour post-treatment, 0.1 mL of 1% w/v carrageenan in saline was injected into the subplantar region of paw.[16] Paw volume was measured at 0, 1, 2, 3, and 4 hours by plethysmometer.[16] Percentage edema inhibition was calculated as:

$$\% \text{ Inhibition} = [(Vt - V0)control - (Vt - V0)treated] / (Vt - V0)control \times 100,$$

Where Vt: paw volume at time t, & V0: initial paw volume.[16]

In Silico Analyses

In Silico ADMET Prediction

ADMET properties were predicted using SwissADME,[17] evaluating Lipinski rules.[18]

Molecular Docking Studies

Ligand structures were drawn using ChemSketch, optimized with MM2 force field PDB format. COX-2 (PDB ID: 4COX) retrieved from PDB[19], removing water molecules,

heteroatoms.[20] Polar hydrogens added, & a grid defined around site.[20] Docking was performed using Schrödinger Glide (exhaustiveness = 8, modes = 9, energy range = 3).[20] The best pose was selected based on lowest binding energy and visualized using PyMOL and LigPlot+.[20] The docking protocol was validated by root-mean-square deviation (RMSD) < 2.0 Å.[20]

3. RESULTS

3.1. In-Silico Computational Studies

Table 1: In-silico analysis of Analogues with Rule of 5 (Ro5).

Title	docking score	glide energy	Ro5
VK1	-8.342	-50.436	0
VK2	-7.717	-40.713	0
VK3	-7.110	-45.546	0
VK4	-7.422	-48.460	0
VK-5	-7.234	-42.565	0
Diclofenac Sodium	-7.819	-34.600	0

3.2. Chemistry

3.2.1. Spectral Data of Intermediates

2-amino-(5-phenyal substituted)-1,3,4-thiadiazoles (VK-A): Brown; Yield %: 76; m.p: 156-1610C; IR υ cm−1 (KBr): N–H (amine) 3060.48; Aromatic C–H 3060.48, 2860.88; C≡N (nitrile) 2224.49; C=N (imine/thiadiazole) 1617.98; Aromatic C=C 1514.89, 1444.89; C–N (amine/thiadiazole) 1184.08.

N-Substituted Chloroacetamide (VK-B): Brown; Yield %: 76; m.p: 156-1610C; IR υ cm−1 (KBr): N–H (amine) 3275.5; Aromatic C–H 3121.22; C=N (imine/thiazole) 1617.98; Aromatic C=C 1514.89, 1444.89; C–N (amine/thiazole) 1184.08, 1097.7**.**

3.2.2. Spectral Data of the Targeted Compounds

2-{[5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl]amino}-N-(4-nitrophenyl)acetamide (VK-1): Dark Brown; Yield %: 76; m.p: 156-1610C; IR υ cm−1 (KBr): -NH stretch 3150.15; Aliphatic C-H stretch 2994.91; Amide C=O stretch 1700.91; Aromatic C=C stretch 1610.95; Nitro N=O asymmetric stretch 1549.18; C-Cl stretch 757.866; **^{1}H NMR (DMSO-d_6):** 8.35, 8.15 (Aromatic H, nitro-substituted benzene); 7.46, 7.41, 7.28 (Aromatic H, chloro-substituted benzene); 6.81 (NH, amide); 4.71 (CH_2 adjacent to NH); 3.01 (CH_2 in thiadiazole ring system).

N-(2-chlorophenyl)-2-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]acetamide (VK-2): Dark brown; Yield %: 76; m.p: 156-1610C; IR υ cm−1 (KBr): N–H (secondary amine) 3273.57; Aromatic C–H stretch 3092.49, 3062.63; Aliphatic C–H stretch 2986.53; Amide C=O stretch 1660.42; Aromatic C–Cl stretch 840.81; **^{1}H NMR (DMSO-d_6):** 11.51 (NH, amide); 7.88, 7.53, 7.45 (Aromatic H, phenyl ring on thiadiazole); 7.36, 7.28, 7.12 (Aromatic H, chloro-substituted benzene); 4.3 (CH_2 adjacent to carbonyl); 3.19 (CH_2 in thiadiazole ring system).

N-(4-bromophenyl)-2-{[5-(2,6-dimethoxyphenyl)-1,3,4-thiadiazol-2-yl]amino}acetamide (VK-3): Dark Green; Yield %: 76; m.p: 156-1610C; IR υ cm−1 (KBr): N–H (secondary amine) 3396.4; Aliphatic C–H stretch 2990.09, 2696.96; mide C=O stretch 1700.91; Aromatic C=C stretch 1594.84; C–O (methoxy) stretch 1249.65; C–Br stretch 606.31; **^{1}H NMR (DMSO-d_6):** 8.18 (NH, amide); 7.53, 7.48 (Aromatic H, bromo-substituted benzene); 7.41, 7.22, 7.18, 6.95 (Aromatic H, methoxyphenyl ring); 4.72 (CH_2 adjacent to NH); 3.88 (OCH_3, methoxy group); 3.01 (CH_2 in thiadiazole ring system); 2.15 (CH_3, methyl group on thiadiazole).

2-{[5-(2-chlorophenyl)-1,3,4-thiadiazol-2-yl]amino}-N-(3-nitrophenyl)acetamide (VK-4): Pale Yellow, odorless powder; Yield %: 76; m.p: 156-1610C; IR υ cm−1 (KBr): -NH stretching 3277.43; C-H stretching (alkane) 2990.09; C=O stretching (carbonyl) 1700.91; C-O stretching (ester, ether) 1040.41; C-H bending (aromatic) 734.746; C-Cl stretching 618.252; **^{1}H NMR (DMSO-d_6):** 11.58 (NH, amide); 8.37, 8.10 (Aromatic H, ortho to NO_2); 7.64, 7.58 (Aromatic H, meta to NO_2); 7.46, 7.41, 7.28 (Aromatic H, chloro-substituted benzene); 4.43 (CH_2 adjacent to carbonyl); 3.20 (CH_2 in thiadiazole ring system).

2-{[5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl]amino}-N-(3-nitrophenyl)acetamide (VK-5): Dark Brown; Yield %: 76; m.p: 156-1610C; IR υ cm−1 (KBr): NH stretching 3475.1; C-H stretching (alkane/alkyl) 2830.99; C≡C or C≡N stretching 2116.49; C=C stretching (aromatic/alkene) 1584.32, 1503.24; C-N stretching (amine/nitrile) 1332.57; C-Cl bending 750.174, 849.49; **^{1}H NMR (DMSO-d_6):** 4.33 (CH_2 adjacent to carbonyl, 2H); 4.05 (CH_2 in linker chain, 2H); 3.56 (CH_2 adjacent to NH, 2H); 3.33 (CH_2 in thiadiazole ring system, 2H); 2.89, 2.51 (CH_2 in aliphatic chain, 2H each); 1.91, 1.28, 1.22, 1.18, 1.05 (CH_2 in linker chain, 2H each).

3.3. Biological Activity

Table 2: Anti-inflammatory activity of analogues equivalent to Diclofenac Sodium.

Drug Group	Dose (mg/kg)	Initial Volume (ml)	Final Volume (ml)	% Inhibition
VK-1	50	1.60 ± 0.25	2.00 ± 0.30	25
	75	1.30 ± 0.20	1.60 ± 0.15	45
	100	1.20 ± 0.18	1.40 ± 0.10**	70
VK-2	50	1.70 ± 0.22	2.20 ± 0.40	10
	75	1.50 ± 0.25	1.90 ± 0.20	25
	100	1.40 ± 0.15	1.70 ± 0.25	30
VK-3	50	1.80 ± 0.30	2.30 ± 0.50	20
	75	1.60 ± 0.28	1.90 ± 0.35	50
	100	1.50 ± 0.20	1.55 ± 0.12**	85
VK-4	50	1.40 ± 0.15	1.80 ± 0.25	35
	75	1.30 ± 0.10	1.60 ± 0.18**	55
	100	1.20 ± 0.12	1.45 ± 0.20**	75
VK-5	50	1.50 ± 0.20	1.90 ± 0.30	15
	75	1.40 ± 0.15	1.70 ± 0.15**	40
	100	1.30 ± 0.10	1.50 ± 0.12**	60
Diclofenac Sodium	5	1.30 ± 0.25	1.60 ± 0.10**	50
	7.5	1.20 ± 0.20	1.40 ± 0.08**	75
	10	1.10 ± 0.15	1.20 ± 0.05***	95

Data analyzed by one way ANOVA followed by Dunnett's test (n=5). ∗P<0.05 and ∗∗P<0.01.

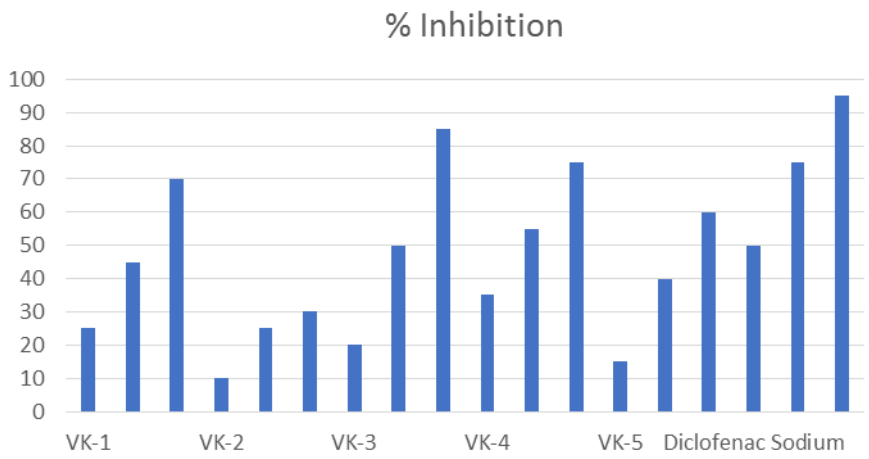


Fig. 2: In-vivo Anti-inflammatory Activity.

4. DISCUSSION

The results demonstrated that these compounds, particularly VK-1, VK-3, and VK-4, exhibit significant anti-inflammatory action, with VK-3 achieving the highest efficacy at 85% inhibition of paw edema at 100 mg/kg, closely rivaling the standard drug diclofenac sodium

(95%).[21] These findings underscore potential of 1,3,4-thiadiazole analogues, candidates for addressing unmet needs in inflammation management, particularly in overcoming the limitations of current therapies such NSAIDs, corticosteroids, and biologics.[21]

Synthesis of 1,3,4-thiadiazole derivatives was achieved through a three-step procedure involving cyclization reactions[22], yielding compounds VK-1 to VK-5 with moderate to high efficiency. The structural confirmation via FTIR and ^{1}H-NMR spectroscopy validated the integrity of the thiadiazole ring and the incorporation of substituents such as chloro, nitro, and dimethoxy groups.[22] The synthetic methodology, primarily based on thiosemicarbazide cyclization, proved robust and scalable, who emphasized the versatility of thiadiazole synthesis for generating diverse analogues. However, the moderate yields for VK-3 suggest opportunities for optimization.[23] Alternative approaches, such as microwave-assisted synthesis or the use of greener catalysts, could enhance yield and sustainability, making these compounds more viable for large-scale production.[23]

The in vivo evaluation provided compelling evidence of the anti-inflammatory potential of analogues. VK-3, VK-4, and VK-1 exhibited dose-dependent inhibition of paw edema, with VK-3 (85%), VK-4 (75%), and VK-1 (70%) approaching the efficacy of diclofenac sodium.[12] These results are consistent with previous studies, which reported that thiadiazole derivatives exhibit potent anti-inflammatory effects through multiple mechanisms, including cyclooxygenase (COX) inhibition and antioxidant activity.[24] Notably, VK-3's superior performance, despite its lower docking score compared to VK-1, suggests additional mechanisms beyond COX-2 inhibition. Literature indicates that thiadiazoles may modulate leukotriene pathways via 5-lipoxygenase (5-LOX) inhibition or scavenge ROS, reducing oxidative stress.[24] The dimethoxy groups in VK-3 likely enhance ROS scavenging, contributing to its enhanced in vivo efficacy.[24]

Docking studies against 4COX provided critical insights into interactions of analogues. VK-1 exhibited the highest docking score (-8.342)[25], indicating strong binding affinity, primarily driven by hydrogen bonding with ARG120 and hydrophobic with VAL349 and LEU384.[25] These interactions mirror those of established COX-2 inhibitors like diclofenac, who highlighted the role of sulfur and nitrogen atoms in thiadiazoles for facilitating π-π stacking and sulfur-mediated interactions.[25,26] The electron-withdrawing 4-chloro substituent in VK-1 likely enhances electrophilicity, stabilizing its binding to COX-2 active site. VK-3's dimethoxy groups, which are electron-donating, may promote alternative binding poses,

potentially engaging additional residues or pathways, as suggested by its superior in vivo performance.[26]

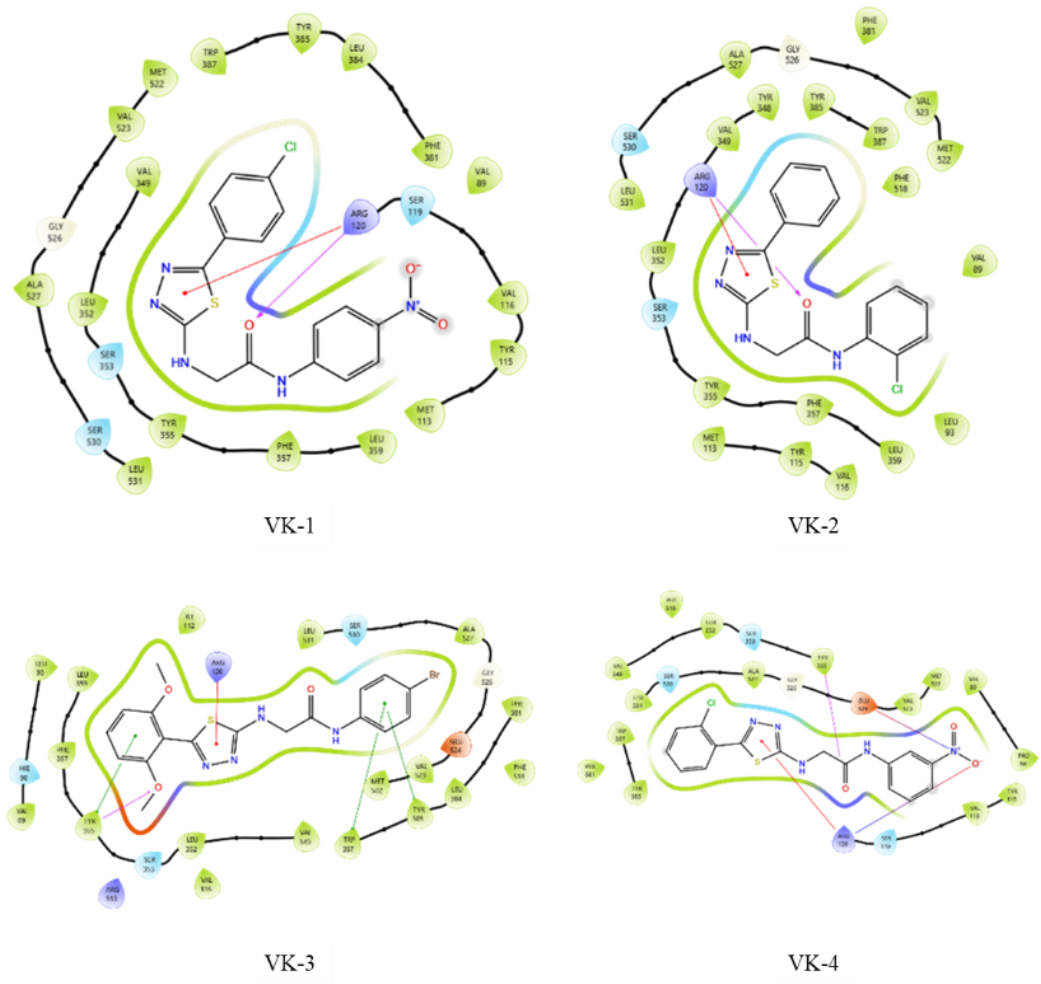


Fig. 3: 2D interaction diagrams showing hydrogen bonds, hydrophobic contacts, and halogen bonds for top-performing.

The docking results also align with structure-activity relationship (SAR) studies, which revealed that para-substituted electron-withdrawing groups, such as chloro and nitro, enhance COX-2 binding affinity.[27] However, the unexpected efficacy of VK-3's electron-donating groups underscores the thiadiazole scaffold's versatility, allowing it to target multiple inflammatory mediators.[27] Expanding docking studies to include other targets, such as 5-LOX or NF-κB, could elucidate additional mechanisms, and provide a more comprehensive understanding of the compounds' multi-target potential.[27]

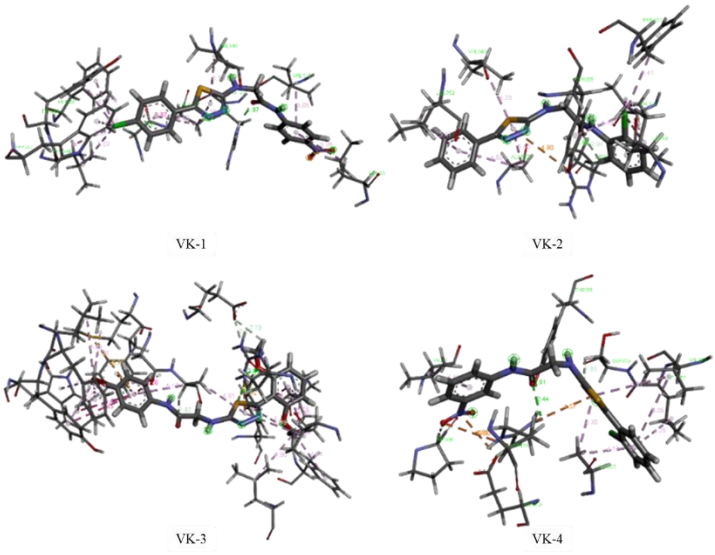


Fig. 4: 3D molecular docking poses bound to COX-2 active site with key interactions highlighted.

The synthesized thiadiazole derivatives offer several advantages over existing anti-inflammatory therapies.[28] Compared to NSAIDs, inhibit COX-1 & COX-2, to gastrointestinal and renal toxicities, the docking profiles suggest that VK-1, VK-3, and VK-4 exhibit COX-2 selectivity, potentially reducing adverse effects. Selective COX-2 inhibitors like celecoxib, while effective, have raised concerns about cardiovascular risks.[28] The thiadiazoles' favorable drug-likeness, as confirmed by Lipinski's Rule of Five, and their oral bioavailability position them as cost-effective alternatives. Unlike biologics, such as TNF-α inhibitors, which are expensive and require parenteral administration, these small molecules are orally administrable and potentially more accessible, particularly in resource-limited settings.[28]

The in silico ADME analysis indicated that all synthesized compounds comply Lipinski's Rule. However, potential inhibition of cytochrome P450 enzymes (e.g., CYP2C9, CYP3A4) raises concerns about drug-drug interactions, a common challenge with heterocyclic compounds.[28] Structural optimization, such as introducing steric hindrance or modifying substituents, could mitigate these liabilities, as demonstrated in studies of mibefradil analogues.[28] The lack of detailed pharmacokinetic data, such as half-life or clearance rates, limits predictions of clinical performance. Future studies should incorporate in vitro assays, such as Caco-2 permeability or microsomal stability, to complement these predictions and guide clinical development.

5. CONCLUSION

1,3,4-thiadiazole analogues synthesized in study showing higher anti-inflammatory potential, with VK-1, VK-3, and VK-4 showing promising potency in in-silico and in-vivo. Their COX-2 selectivity, favorable drug-likeness, and oral bioavailability position them as viable alternatives to existing therapies, potentially addressing the limitations of NSAIDs, corticosteroids, and biologics. However, challenges such as CYP inhibition and the need for chronic model evaluation must be addressed to advance these compounds toward clinical development. The thiadiazole scaffold's versatility and multi-target potential make it a valuable platform for future anti-inflammatory drug discovery.

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