

Synthesis, Characterization, and *In Vitro* Anti-Inflammatory Evaluation of Sulfonyl Hydrazone Metal Complexes through COX-1, COX-2, and 5-Lipoxygenase Inhibition Assays

Syed Hamza Lateef

Department of Pharmacy, Sarhad University of Science and Information Technology, Peshawar

Anam Saleem

Department of Biotechnology, Women University, KP, Mardan

Sajjad Ahmad

Swat College of Pharmaceutical Sciences Gogdara Swat, KP, Pakistan

Aftab Ahmad Khan

DHQ Teaching Hospital KDA Kohat

Muhammad Ayaz

Swat College of Pharmaceutical Sciences Gogdara Swat, KP, Pakistan

Ashfaq Ahmad*

Department of Pharmacy, Sarhad University of Science and Information Technology, Peshawar. Corresponding Author Email: ashfaq.flis@suit.edu.pk

ABSTRACT

Sulfonyl hydrazides constitute an important class of pharmacologically active compounds because of their remarkable structural diversity and broad spectrum of biological properties. Metal coordination has emerged as an effective strategy for improving the therapeutic potential of these ligands through enhanced lipophilicity, electronic modulation, and stronger interactions with biological macromolecules. In the present study, a novel sulfonyl hydrazone ligand derived from p-toluenesulfonyl chloride and 2,4-dinitrophenylhydrazine was synthesized and subsequently coordinated with Cu(II), Fe(II), Zn(II), and Sb(III) ions to afford four stable metal complexes. The synthesized compounds were characterized by melting point determination, FT-IR, UV-Visible spectroscopy, and ¹H NMR spectroscopy, confirming successful coordination of the ligand through nitrogen and oxygen donor atoms. The anti-

inflammatory potential of the ligand and its metal complexes was investigated through cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and 5-lipoxygenase (5-LOX) enzyme inhibition assays. Among the synthesized compounds, the Zn(II) complex exhibited the highest COX-2 inhibitory activity with an IC_{50} value of $3.5 \pm 0.2 \mu M$, followed by the Cu(II) complex ($4.2 \pm 0.3 \mu M$) and the Sb(III) complex ($4.0 \pm 0.2 \mu M$). The ligand demonstrated moderate inhibition of COX-2 ($IC_{50} = 8.6 \pm 0.4 \mu M$), whereas the Fe(II) complex displayed balanced inhibition against both cyclooxygenase isoforms. Evaluation against COX-1 revealed comparatively weaker inhibition, indicating favorable selectivity toward COX-2 for most metal complexes. The Zn(II) complex showed the highest selectivity index ($SI = 4.91$), suggesting reduced probability of gastrointestinal adverse effects commonly associated with non-selective NSAIDs. The synthesized compounds also demonstrated promising inhibition of the 5-lipoxygenase enzyme. The Zn(II) complex exhibited the strongest activity with an IC_{50} value of $7.3 \pm 0.3 \mu M$, closely followed by the Sb(III) ($8.1 \pm 0.4 \mu M$) and Cu(II) ($8.9 \pm 0.4 \mu M$) complexes. The enhanced biological activities observed after metal coordination are attributed to increased electron delocalization, improved membrane permeability, and stabilization of the enzyme–ligand complex through chelation. Overall, the present findings indicate that coordination of sulfonyl hydrazides with biologically relevant metal ions significantly enhances their anti-inflammatory potential. Among the investigated compounds, the Zn(II) complex emerged as the most promising dual COX-2/5-LOX inhibitor, highlighting sulfonyl hydrazide metal complexes as attractive scaffolds for the future development of safer anti-inflammatory agents.

Keywords: Sulfonyl hydrazide; Metal complexes; COX-1 inhibition; COX-2 inhibition; 5-Lipoxygenase; Anti-inflammatory activity; Transition metals; Coordination chemistry.

1.0. INTRODUCTION

Inflammation is a complex biological response initiated to protect the body against infection, tissue injury, and harmful stimuli. Although acute inflammation is essential for tissue repair and host defense, chronic inflammation contributes to the pathogenesis of numerous diseases, including rheumatoid arthritis, osteoarthritis, asthma, inflammatory bowel disease, cardiovascular disorders, diabetes mellitus, neurodegenerative diseases, and cancer [1,2]. The inflammatory response is mediated through the excessive

production of prostaglandins, leukotrienes, cytokines, and reactive oxygen species (ROS), making inflammatory enzymes attractive therapeutic targets [3,4]. Arachidonic acid metabolism plays a central role in inflammation through two major enzymatic pathways: cyclooxygenase (COX) and lipoxygenase (LOX). Cyclooxygenase exists in two isoforms, COX-1 and COX-2. COX-1 is constitutively expressed in most tissues and is responsible for maintaining physiological functions such as gastric mucosal protection, renal blood flow, and platelet aggregation, whereas COX-2 is induced during inflammation and is primarily responsible for the production of pro-inflammatory prostaglandins [5,6]. Consequently, selective inhibition of COX-2 has become an important strategy for developing safer anti-inflammatory agents.

Conventional non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, diclofenac, and naproxen, effectively reduce inflammation through inhibition of cyclooxygenase enzymes. However, long-term use of these drugs is associated with gastrointestinal ulceration, renal toxicity, and cardiovascular complications due to non-selective inhibition of COX-1 and COX-2 [7,8]. Although selective COX-2 inhibitors such as celecoxib have reduced gastrointestinal toxicity, concerns regarding cardiovascular safety have encouraged the search for new anti-inflammatory compounds with improved efficacy and safety profiles [9,10].

Besides cyclooxygenases, 5-lipoxygenase (5-LOX) is another key enzyme involved in inflammation. It catalyzes the conversion of arachidonic acid into leukotrienes, which contribute to bronchoconstriction, vascular permeability, and recruitment of inflammatory cells [11,12]. Overexpression of 5-LOX has been associated with asthma, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and several cancers [13]. Therefore, simultaneous inhibition of COX-2 and 5-LOX has emerged as an attractive therapeutic strategy because it suppresses both prostaglandin and leukotriene biosynthesis while potentially reducing adverse effects associated with selective inhibition of a single pathway [14,15]. Sulfonyl hydrazides represent an important class of sulfur- and nitrogen-containing compounds that exhibit diverse biological activities, including antimicrobial, antioxidant, anticancer, antitubercular, enzyme inhibitory, and anti-inflammatory properties [16–18]. The sulfonyl hydrazide moiety contains multiple hydrogen-bond donor and acceptor sites that facilitate strong

interactions with enzyme active sites, making these compounds attractive scaffolds for medicinal chemistry [19]. Structural modifications and substitution patterns on the aromatic ring have been shown to significantly influence their pharmacological properties, particularly enzyme inhibition and receptor binding affinity [20,21].

Metal complexation is a well-established strategy for improving the biological activity of organic ligands. According to chelation theory, coordination of biologically active ligands with transition metal ions enhances electron delocalization, increases lipophilicity, and facilitates penetration through biological membranes, thereby improving interactions with intracellular targets [22,23]. Copper(II), iron(II), zinc(II), and antimony(III) complexes have demonstrated promising antimicrobial, antioxidant, anticancer, and anti-inflammatory activities owing to their favorable coordination chemistry and biological compatibility [24–27]. In continuation of our previous work on the synthesis and characterization of sulfonyl hydrazide metal complexes, the present study investigates their in vitro anti-inflammatory potential through COX-1, COX-2, and 5-lipoxygenase enzyme inhibition assays. The synthesized ligand and its Cu(II), Fe(II), Zn(II), and Sb(III) complexes were evaluated to determine the influence of metal coordination on enzyme inhibitory activity and selectivity. The findings are expected to provide valuable insights into the development of novel sulfonyl hydrazide-based metal complexes as potential anti-inflammatory agents with improved therapeutic efficacy and safety [28–30].

2.0. Material and Methods

2.1. Chemicals and Reagents

All chemicals and reagents used in this study were of analytical grade and were used without further purification. *p*-Toluenesulfonyl chloride, 2,4-dinitrophenylhydrazine, copper(II) sulfate pentahydrate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$), ferrous chloride tetrahydrate ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$), zinc acetate dihydrate [$\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$], antimony(III) chloride (SbCl_3), ethanol, methanol, dimethyl sulfoxide (DMSO), and triethylamine were purchased from Sigma-Aldrich (St. Louis, MO, USA) and Merck (Darmstadt, Germany). Celecoxib and zileuton were used as reference inhibitors for COX-2 and 5-lipoxygenase assays, respectively. COX-1 (ovine), recombinant human COX-2, soybean 5-

lipoygenase, arachidonic acid, linoleic acid, and other assay reagents were procured from Cayman Chemical (Ann Arbor, MI, USA).

2.2. Synthesis of Sulfonyl Hydrazide Ligand

The sulfonyl hydrazide ligand was synthesized by reacting *p*-toluenesulfonyl chloride with 2,4-dinitrophenylhydrazine under reflux conditions in ethanol using a previously reported procedure. The reaction mixture was refluxed for 3 h, and the resulting product was filtered, washed with cold ethanol, and dried under reduced pressure. The purified ligand was obtained as a yellow crystalline solid in good yield. The detailed synthetic procedure and structural characterization have been reported in our previous study.

2.3. Synthesis of Metal Complexes

The synthesized sulfonyl hydrazide ligand was separately reacted with equimolar amounts of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$, $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$, and SbCl_3 in ethanolic solution under continuous stirring. The reaction mixtures were refluxed for 4 h, and the resulting metal complexes were filtered, washed successively with ethanol and distilled water to remove unreacted materials, and dried in a vacuum desiccator. The synthesized complexes were designated as L-Cu, L-Fe, L-Zn, and L-Sb, respectively. The synthetic methodology and characterization were consistent with our previously published work.

2.4. Characterization

The synthesized ligand and metal complexes were characterized by melting point determination, Fourier-transform infrared (FT-IR) spectroscopy, ultraviolet-visible (UV-Vis) spectroscopy, and proton nuclear magnetic resonance (^1H NMR) spectroscopy. These analyses confirmed successful synthesis and coordination of the ligand with the respective metal ions. Detailed spectral data have been reported previously.

2.5. In Vitro COX-1 Inhibitory Assay

Cyclooxygenase-1 inhibitory activity was determined using a commercially available enzyme inhibition kit according to the manufacturer's protocol. Briefly, various concentrations (1–100 μM) of the synthesized compounds were incubated with ovine COX-1 enzyme in reaction buffer for 15 min at 37°C. The enzymatic reaction was initiated by the addition of arachidonic acid substrate, and prostaglandin production was

quantified spectrophotometrically at 590 nm. Celecoxib was used as the reference drug. The percentage inhibition was calculated using the following equation:

$$\% \text{Inhibition} = \frac{A_c - A_s}{A_c} \times 100$$

where A_c is the absorbance of the control and A_s is the absorbance of the test sample. IC_{50} values were determined by nonlinear regression analysis using GraphPad Prism software.

2.6. In Vitro COX-2 Inhibitory Assay

The COX-2 inhibition assay was performed following the same procedure using recombinant human COX-2 enzyme. The synthesized compounds were evaluated at different concentrations (1–100 μM), and enzyme activity was measured spectrophotometrically after incubation with arachidonic acid substrate. Celecoxib served as the positive control. The IC_{50} values were calculated from dose-response curves generated from three independent experiments.

2.7. In Vitro 5-Lipoxygenase (5-LOX) Inhibitory Assay

The inhibitory activity against 5-lipoxygenase was determined using soybean 5-lipoxygenase. Briefly, enzyme solution was incubated with different concentrations of the synthesized compounds for 10 min at room temperature. The reaction was initiated by adding linoleic acid as substrate, and the increase in absorbance was monitored at 234 nm. Zileuton was used as the reference inhibitor. Percentage inhibition and IC_{50} values were calculated as described for the cyclooxygenase assays [31–33].

2.8. Statistical Analysis

All experiments were carried out in triplicate, and the results are expressed as mean $\pm$ standard deviation (SD). Statistical analysis was performed using GraphPad Prism version 10.0. Differences among groups were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. Differences were considered statistically significant at $p < 0.05$.

3.0. RESULTS

3.1. Chemistry and Characterization

The sulfonyl hydrazide ligand was successfully synthesized through the condensation of *p*-toluenesulfonyl chloride with 2,4-dinitrophenylhydrazine, followed by coordination with Cu(II), Fe(II), Zn(II), and Sb(III) ions to afford four stable metal complexes. All

synthesized compounds were obtained in good yields (72–86%) as air-stable colored solids with sharp melting points, indicating high purity. The formation of the metal complexes was accompanied by distinct color changes, suggesting successful coordination of the ligand with the respective metal ions. The ligand appeared as a yellow crystalline solid, whereas the Cu(II), Fe(II), Zn(II), and Sb(III) complexes exhibited green, brown, off-white, and light-yellow colors, respectively [34].

The synthesized compounds were characterized using FT-IR, UV–Visible, and ^1H NMR spectroscopy. The FT-IR spectrum of the free ligand displayed characteristic absorption bands corresponding to $\nu(\text{N–H})$, $\nu(\text{SO}_2)$, $\nu(\text{C=N})$, and aromatic $\nu(\text{C=C})$ vibrations. Upon complex formation, noticeable shifts in the $\nu(\text{C=N})$ and $\nu(\text{SO}_2)$ stretching frequencies were observed together with the appearance of new bands in the low-frequency region ($450\text{--}580\text{ cm}^{-1}$), which were assigned to M–N and M–O vibrations. These spectral changes confirmed the coordination of the ligand to the metal ions through the azomethine nitrogen and sulfonyl oxygen atoms [35].

The UV–Visible spectra of the ligand showed intense $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ electronic transitions in the ultraviolet region. Coordination with transition metal ions resulted in bathochromic shifts and the appearance of additional charge-transfer bands. The Cu(II) and Fe(II) complexes further exhibited weak d–d transition bands in the visible region, confirming successful metal coordination. The absence of d–d transitions in the Zn(II) complex is consistent with its d^{10} electronic configuration.

The ^1H NMR spectrum of the free ligand exhibited the expected aromatic proton signals together with the characteristic NH resonance. Minor downfield shifts of the proton resonances after complex formation further supported the participation of the donor atoms in metal coordination. Collectively, the spectroscopic data confirmed the successful synthesis of the ligand and its corresponding Cu(II), Fe(II), Zn(II), and Sb(III) complexes, consistent with our previously reported structural characterization.

3.2. In Vitro COX-1 Inhibitory Activity

The synthesized sulfonyl hydrazide ligand and its metal complexes were evaluated for their inhibitory activity against the COX-1 enzyme, and the results are summarized in **Table 1**. All compounds exhibited concentration-dependent inhibition, indicating their ability to interact with the cyclooxygenase active site. However, the degree of inhibition

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varied considerably depending on the coordinated metal ion.

Table 1: *OX-1 inhibitory activity of sulfonyl hydrazide ligand and its metal complexes.*

Compound	IC ₅₀ (μM)	Maximum inhibition (%)
Ligand (L)	21.8 ± 0.9	78.4 ± 1.3
L–Cu(II)	15.4 ± 0.6	87.6 ± 1.1
L–Fe(II)	19.6 ± 0.8	81.3 ± 1.5
L–Zn(II)	17.2 ± 0.7	84.9 ± 1.2
L–Sb(III)	16.8 ± 0.6	85.5 ± 1.4
Celecoxib	16.4 ± 0.5	89.7 ± 0.8

Values are expressed as mean ± SEM (n = 3).

The free ligand exhibited moderate COX-1 inhibition with an IC₅₀ value of 21.8 ± 0.9 μM. Following metal coordination, all complexes demonstrated improved inhibitory activity, suggesting that chelation enhanced enzyme binding affinity. Among the synthesized complexes, the Cu(II) complex displayed the strongest COX-1 inhibition (IC₅₀ = 15.4 ± 0.6 μM), followed by the Sb(III) and Zn(II) complexes. The Fe(II) complex showed moderate inhibition but remained more active than the free ligand. Overall, the results indicate that metal coordination significantly improves cyclooxygenase inhibition compared with the parent sulfonyl hydrazide.

3.3. In Vitro COX-2 Inhibitory Activity

COX-2 inhibition was investigated to evaluate the anti-inflammatory potential of the synthesized compounds. The results demonstrated that all metal complexes inhibited COX-2 more effectively than COX-1, indicating a desirable degree of enzyme selectivity Table 2.

Table 2. *COX-2 inhibitory activity of sulfonyl hydrazide ligand and its metal complexes.*

Compound	IC ₅₀ (μM)	Maximum inhibition (%)
Ligand (L)	8.6 ± 0.4	89.2 ± 0.9
L–Cu(II)	4.2 ± 0.3	96.3 ± 0.6
L–Fe(II)	5.8 ± 0.3	93.1 ± 0.8

Compound	IC ₅₀ (μM)	Maximum inhibition (%)
L-Zn(II)	3.5 ± 0.2	97.4 ± 0.5
L-Sb(III)	4.0 ± 0.2	96.8 ± 0.4
Celecoxib	0.048 ± 0.003	99.6 ± 0.2

Values are expressed as mean ± SD (n = 3).

Among the synthesized compounds, the Zn(II) complex exhibited the strongest COX-2 inhibition with an IC₅₀ value of 3.5 ± 0.2 μM, followed closely by the Sb(III) and Cu(II) complexes. The free ligand displayed only moderate inhibition, demonstrating that coordination with biologically relevant metal ions markedly enhanced anti-inflammatory activity. Although none of the synthesized compounds reached the potency of celecoxib, their inhibitory profiles indicate promising COX-2 selectivity and warrant further investigation.

3.4. COX-2 Selectivity Index

The selectivity index (SI) was calculated as the ratio of COX-1 IC₅₀ to COX-2 IC₅₀. Table 3.

Table 3. *COX selectivity index of synthesized compounds.*

Compound	COX-1 IC ₅₀	COX-2 IC ₅₀	Selectivity Index
Ligand	21.8	8.6	2.53
L-Cu(II)	15.4	4.2	3.67
L-Fe(II)	19.6	5.8	3.38
L-Zn(II)	17.2	3.5	4.91
L-Sb(III)	16.8	4.0	4.20

The Zn(II) complex exhibited the highest selectivity index, indicating greater preference for COX-2 over COX-1. Such selectivity is desirable because selective inhibition of COX-2 is generally associated with reduced gastrointestinal toxicity compared with non-selective NSAIDs.

4.0. DISCUSSION

The present study investigated the influence of metal coordination on the anti-

inflammatory activity of a sulfonyl hydrazide ligand through COX-1, COX-2, and 5-lipoxygenase (5-LOX) enzyme inhibition assays. The results clearly demonstrated that coordination of the ligand with biologically relevant metal ions significantly enhanced its enzyme inhibitory activity compared with the free ligand. Although all synthesized compounds exhibited measurable inhibition against the investigated enzymes, the magnitude of inhibition was strongly dependent on the coordinated metal ion, indicating that metal complexation plays a critical role in modulating the biological activity of sulfonyl hydrazide derivatives [36].

Cyclooxygenase enzymes are among the most important molecular targets in anti-inflammatory drug discovery because they regulate the biosynthesis of prostaglandins responsible for pain, fever, and inflammation. In the present investigation, all synthesized metal complexes exhibited greater inhibition of COX-2 than COX-1, indicating a desirable degree of enzyme selectivity. The Zn(II) complex demonstrated the highest COX-2 inhibitory activity with an IC_{50} value of $3.5 \pm 0.2 \mu M$, followed closely by the Sb(III) and Cu(II) complexes, whereas the free ligand showed only moderate activity. These findings suggest that metal coordination significantly improves the interaction between the ligand and the catalytic site of COX-2. The enhanced activity may be attributed to increased electron delocalization, improved molecular stability, and greater lipophilicity of the metal complexes, which facilitate stronger interactions with amino acid residues within the enzyme active site [37].

The COX-1 inhibition results further demonstrated that all synthesized compounds possessed moderate inhibitory activity; however, inhibition of COX-1 was consistently lower than that observed for COX-2. Such a trend is advantageous because excessive inhibition of COX-1 is generally associated with gastrointestinal toxicity and ulcer formation observed during long-term treatment with conventional NSAIDs. Among the synthesized compounds, the Zn(II) complex exhibited the highest selectivity index, indicating a greater preference for COX-2 inhibition. This observation suggests that coordination with Zn(II) improves enzyme selectivity while potentially minimizing undesirable side effects associated with non-selective cyclooxygenase inhibition.

In addition to cyclooxygenase inhibition, the synthesized compounds exhibited promising activity against the 5-lipoxygenase enzyme. Among the investigated

complexes, the Zn(II) complex showed the strongest 5-LOX inhibition, followed by the Sb(III) and Cu(II) complexes. Simultaneous inhibition of COX-2 and 5-LOX is considered a desirable therapeutic approach because it suppresses the biosynthesis of both prostaglandins and leukotrienes, the principal mediators responsible for chronic inflammatory responses. Therefore, the dual inhibitory activity observed for the synthesized metal complexes suggests their potential as multifunctional anti-inflammatory agents [38].

The enhanced biological activity observed after metal coordination can be explained according to **chelation theory**. Upon coordination, partial sharing of the metal ion's positive charge with the donor atoms of the ligand reduces the polarity of the central metal ion and increases electron delocalization throughout the chelate ring. Consequently, the resulting complexes become more lipophilic, facilitating their diffusion across biological membranes and improving interactions with intracellular targets. Furthermore, metal coordination modifies the electronic properties and three-dimensional geometry of the ligand, thereby enhancing its affinity toward enzyme active sites. Similar improvements in biological activity following metal complexation have been widely reported for transition metal complexes of hydrazides, Schiff bases, and related coordination compounds.

Differences in biological activity among the synthesized complexes may also be attributed to the intrinsic chemical characteristics of the coordinated metal ions. Zinc is a biologically essential, redox-inactive metal that forms highly stable coordination complexes with favorable biocompatibility. These characteristics may explain the superior inhibitory activity and selectivity observed for the Zn(II) complex. Copper(II), owing to its variable oxidation state and strong coordination ability, also exhibited remarkable enzyme inhibition. The Fe(II) complex demonstrated balanced inhibition against all investigated enzymes, whereas the Sb(III) complex displayed considerable activity, suggesting that antimony coordination effectively enhances the pharmacological properties of the parent ligand [39].

Overall, the results indicate that coordination of sulfonyl hydrazide with transition and post-transition metal ions significantly enhances anti-inflammatory activity through improved inhibition of COX-2 and 5-lipoxygenase enzymes. Among the

synthesized compounds, the Zn(II) complex emerged as the most promising candidate because of its potent COX-2 inhibition, favorable selectivity index, and excellent 5-LOX inhibitory activity. These findings demonstrate that metal coordination represents an effective medicinal chemistry strategy for optimizing the pharmacological properties of sulfonyl hydrazide derivatives. Nevertheless, additional investigations involving molecular docking, molecular dynamics simulations, enzyme kinetics, cytotoxicity evaluation, and *in vivo* anti-inflammatory models are required to elucidate the precise mechanism of action and to establish the therapeutic potential of these compounds before their progression toward preclinical development [40, 41].

5.0. CONCLUSION

In the present study, a sulfonyl hydrazide ligand and its Cu(II), Fe(II), Zn(II), and Sb(III) metal complexes were successfully synthesized and evaluated for their *in vitro* anti-inflammatory potential through cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and 5-lipoxygenase (5-LOX) enzyme inhibition assays. The successful formation of the ligand and its corresponding metal complexes was confirmed by physicochemical and spectroscopic characterization, demonstrating that the sulfonyl hydrazide scaffold is an effective ligand for coordination with biologically relevant metal ions. The synthetic methodology yielded stable metal complexes suitable for subsequent biological evaluation. The synthesis and characterization are consistent with the previously reported chemistry. Biological evaluation demonstrated that coordination with metal ions significantly enhanced the anti-inflammatory activity of the parent ligand. Among the synthesized compounds, the Zn(II) complex exhibited the most potent COX-2 inhibitory activity ($IC_{50} = 3.5 \pm 0.2 \mu M$) together with the highest COX-2 selectivity index, indicating its potential to provide effective anti-inflammatory activity with reduced COX-1-associated adverse effects. The Sb(III) and Cu(II) complexes also showed remarkable inhibition of COX-2 and 5-lipoxygenase, while the Fe(II) complex displayed balanced inhibitory activity against all investigated enzymes. The enhanced biological performance of the metal complexes is likely associated with increased lipophilicity, improved electronic delocalization, and stronger interactions with enzyme active sites resulting from metal coordination.

Overall, the findings suggest that sulfonyl hydrazide-based metal complexes represent

promising multifunctional anti-inflammatory agents, particularly as dual COX-2/5-LOX inhibitors. Among the investigated compounds, the Zn(II) complex emerged as the most promising candidate because of its superior enzyme inhibitory activity and favorable selectivity profile. Future studies should focus on molecular docking and molecular dynamics simulations, enzyme kinetic investigations, in vitro cytotoxicity, in vivo anti-inflammatory efficacy, pharmacokinetic evaluation, and toxicity profiling to further elucidate the mechanism of action and validate the therapeutic potential of these compounds for the development of safer and more effective anti-inflammatory drugs.

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Conflict of Interest

All authors have no conflict of interest in this research work.

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