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DESIGN AND CHARACTERIZATION OF NEWLY SYNTHESIZED ZINC COMPLEXES OF AMINOTHIOPHENE SCHIFF BASES FOR ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT:

Following a 1:1 molar ratio condensation of ethyl 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate with various aryl aldehydes, tridentate Schiff bases were produced. These novel aminothiophene Schiff bases were synthesised as zinc chloride complexes using a metal:ligand ratio of 1:1. Molar conductivity, elemental analysis, IR, and UV-visible spectroscopy were used to characterise these compounds. Tetrahedral complexes were generated by Schiff bases exhibiting monobasic tridentate interaction with the central Zn(II) ion. In comparison to the parent Schiff bases, these complexes were assessed for their anti-inflammatory properties and for their enhanced biological activity.

Keywords:

Zinc complex; Inflammation; Schiff base; Biological activity

INTRODUCTION:

A host's response to a range of stimuli, including pathogens, infections brought on by trauma or biological reactions, damaged cells, or toxic compounds, can set off an immune response known as inflammation, which can lead to the release of cytokines, the generation of reactive oxygen and nitrogen species, and ultimately tissue damage. (1) Acute inflammation brought on by a persistent injury or unique circumstances (such as diabetes, obesity, corticosteroid use, blood problems, etc.) can progress to chronic inflammation. (2) Numerous uncomfortable symptoms and illnesses, including rheumatoid arthritis, inflammatory bowel disease, cardiovascular events, neurological diseases, cancer, COVID-19, and others, are brought on by inflammation. (3, 4, 5). Therefore, the creation of innovative, safe compounds with anti-inflammatory properties is currently one of the primary goals in the field of drug discovery. Pain and inflammation are frequently treated with nonsteroidal anti-inflammatory medications (NSAIDs). (6) In terms of anti-inflammatory activity, medications created to treat inflammation aim to block inflammatory pathways (MAPK, NF-Kb, and JAK-STAT), inflammatory proteins (C-reactive protein, haptoglobin, alpha 1-acid glycoprotein, etc.), or enzymes (COX-2, LOX, PDE4, etc.). (7, 8)

Hugo Schiff was the first to report on the condensation reaction between a primary amine and a carbonyl molecule. Products with the distinctive azomethine group are commonly referred to as Schiff bases (9, 10). The research of Schiff bases and their metal complexes has increased dramatically over the past few decades because of these compounds' wide range of biological activity, variety of interactions, and ease of synthesis (11, 12, 13). The biological characteristics and the coordination of the metal complex are significantly influenced by the azomethine linkage and the presence of N, S, and O donor atoms. (14, 15) If metal ions are attached to such physiologically active compounds, their biological activities might be amplified. After iron, zinc is the most prevalent necessary trace mineral in the human body. (16, 17) Zinc is essential for the correct expression of genes, the metabolism of RNA and DNA, and the physiological growth, reproduction, and regular operation of the brain and central nervous system. (18 and 19) Zinc is an essential trace element that is vital to the correct operation of many enzymes that are involved in preserving the equilibrium between the interaction of oxidative and antioxidative processes (20). More and more research is pointing to zinc's role in the immune system, namely in promoting the healthy growth and operation of immune response cells and serving as a second messenger. (21, 22) According to recent research, the body's low zinc levels cause a systemic rise in a specific protein complex that plays a big part in the inflammatory

response, like NF-κB activation. Zinc inhibits these protein complexes, hence lowering the inflammatory state. One of the major signalling channels that are triggered in cells as part of the body's response to inflammation is this intricate system. (23, 24) The current study focuses on the biological activity and production of Zn(II) complexes of our previously described aminothiophene Schiff bases, which are obtained from ethyl 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate.

EXPERIMENTAL:

Materials and methods: All chemicals were purchased from Merck and sigma–Aldrich as 'synthesis grade' and used without similarly purification. melting factors have been determined by way of open tube capillary technique and are uncorrected using HECO melting factor equipment. Purity of the compounds was checked via thin layer chromatography (TLC) on silica gel g plates and the spots were placed either beneath extremely violet light. The IR spectra had been measured the use of a SHIMADZU FTIR-8400S spectrophotometer. ELICO Digital conductivity meter was used for molar conductance measurement with DMF (10-3 M solution) as a solvent. The elemental analysis was done by standard methods.

Synthesis of Ligand: According to the described procedure, ethyl 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate was condensation-bonded in a 1:1 molar ratio with an o-hydroxyl aldehyde derivative to yield the Schiff bases. (25)

Synthesis of metal complexes: Drop by drop, and with continuous stirring, zinc chloride (0.01 mol) dissolved in the least amount of ethanol was added to an ethanolic solution of the Schiff base ligand (0.01 mol). After adjusting the pH to 6-7, the liquid was cooked in a water bath under reflux for four to five hours. The solid complex precipitated as a fine yellow precipitate, which was then dried in a vacuum and refined by washing in aqueous ethanol and ether. (26, 27)

In vitro Anti-inflammatory Assays:

Albumin denaturation Assays:

Reagents: In order to prepare the bovine serum albumin (1%) solution, 1 gramme of bovine serum was placed in a volumetric flask, and the remaining space was filled with water to create 100 millilitres.

Instruments: U.V, Incubator

Procedure: One of the most well-known causes of inflammation is protein denaturation. Eight test samples were examined for their anti-inflammatory qualities as part of the inquiry. The assay for protein denaturation was run. (28) Three separate people carried out the experiment. Test samples were made at different concentrations (100, 200, 300, 400, and 500 µg/mL). Each reaction mixture was prepared by mixing 0.5 mL of 1.5 mg/mL bovine serum albumin (BSA) and then incubating for 20 minutes at 37 °C. Then, the reaction mixtures were heated to 57 °C for three minutes. Each combination was properly mixed before 250 µL of phosphate buffer (0.5 M, pH 6.3) was added. Following an equal dispersion of molecules throughout each reaction mixture, 100 µL of each mixture was put into a different test tube, and the same volume of Folin-Ciocalteu's reagent was added. The tubes were allowed to cool after being incubated for 10 minutes at 55 °C. The absorbance was then measured at 650 nm using a Multimode Microplate Reader (Tecan Sunrise, USA). As a reference medication, aspirin (100 µg/mL) was utilised to assess the collected values. (29, 30) Using the following formula, the inhibition % of protein denaturation was determined.

Calculation:

$$\%\text{inhibition} = \frac{\text{Abs control} - \text{Abs sample}}{\text{Abs control}} \times 100$$

$$IC_{50} = \frac{\text{Concentration}}{\text{\% inhibition}} \times 50\ \text{\% of population}$$

RESULTS AND DISCUSSION:

Zinc complexes had a 1:1 metal-ligand stoichiometry, according to physicochemical study. Each complex has a distinct colour, is stable, and has outstanding keeping quality. Aside from DMF and DMSO, the complexes demonstrated insolubility in typical organic solvents. The complexes' non-electrolyte origin was suggested by the molar conductance values. The data from the elemental analysis agrees with the suggested molecular formula (Table 1).

Table 1: Physico-chemical data of Zn(II) complexes

Complex	Colour	M.W.	Elemental analysis (%) found (calc.)						Molar conductance in DMF (Ω^{-1} cm^2 mol^{-1})
			C	H	S	N	Cl	Zn	
[Zn(L_1)Cl]	Yellowish brown	418.65	47.75 (49.13)	3.98 (4.43)	8.34 (7.65)	4.56 (4.77)	8.11 (8.47)	16.32 (16.75)	4.11
[Zn(L_2)Cl]	Yellowish brown	445.78	46.56 (47.32)	3.99 (4.65)	7.76 (6.87)	4.65 (4.98)	16.23 (17.34)	13.67 (14.03)	1.65
[Zn(L_3)Cl]	Yellowish brown	487.32	45.54 (41.28)	4.11 (4.76)	8.54 (7.21)	3.32 (4.13)	7.98 (8.18)	13.78 (14.11)	2.43
[Zn(L_4)Cl]	Yellowish brown	474.34	52.32 (53.76)	4.11 (4.79)	7.76 (7.11)	3.96 (4.76)	7.65 (8.11)	15.65 (15.97)	4.11

Figure 1 displays the suggested structures of the Zn(II) complexes based on FTIR, elemental analysis, molar conductance, electronic spectra, and magnetic susceptibility.

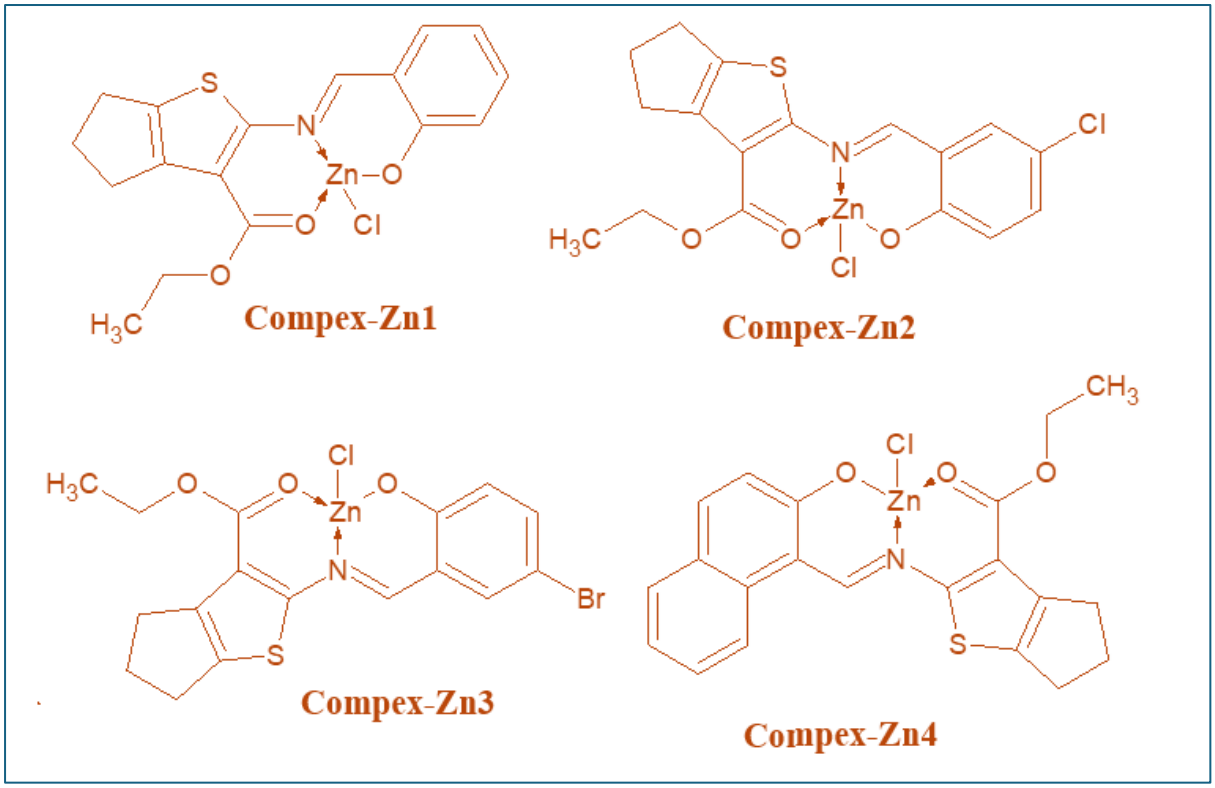

Figure 1: Proposed structures of Zn(II) complexes

The identification of the various functional groups contained in the complex and their method of bonding with the central metal atom can be accomplished with the use of the infrared spectra. The bonding of Schiff base with the central zinc atom was understood by comparing the infrared spectra of the zinc complex and the free ligands. Table 2 shows the major infrared bands and their allocations.

- The phenolic –OH band at 3000-3200 cm^{-1} present in the Schiff base ligand spectra does not appear in metal complexes spectra indicating the participation of phenolic oxygen in the coordination with central Zn(II) atom.
- This is confirmed by the upward shifting of phenolic ν(C-O) band from the region 1312-1368 cm^{-1} in Schiff base spectra to higher wave number by 28-30 cm^{-1} in the metal complexes spectra.
- The involvement of ester carbonyl group in the bonding is indicated by the downward shifting of the absorption band in the region 1665-1843 cm−1 in the Schiff base spectra due to ν(C=O) to lower wavenumber region by 38-66 cm-1 in the metal complexes spectra.
- Further prominent band due to azomethine group 1553-1632 cm^{-1} in the Schiff base spectra is shifted to lower frequency by 19-27 cm-1 in metal complexes spectra confirming the involvement of azomethine nitrogen in coordination with zinc atom.
- The stretching vibrations due to υ(C=S) band showed no significant change in the complex spectra, indicating non-participation of thiophene sulfur in the coordination.
- The presence of the two medium intensity non-ligand band around 534-565 cm−1 and 413-477 cm−1 due to ν(M-O) and to ν(M-N) stretching vibrations respectively confirms the coordination of phenolic oxygen and azomethine nitrogen atoms with the zinc atom.

Table 2: FTIR spectral data

Compound	υ(O-H) phenolic	υ(C=O) ester	υ(C=N) azomethine	υ(C-O) phenolic	υ(C=S) thiophene	υ(M←O)	υ(M←N)
T1	3200-3000	1675	1564	1365	642	-	-
T2	3200-3000	1755	1632	1323	646	-	-
T3	3200-3000	1843	1612	1368	676	-	-
T4	3200-3000	1753	1623	1335	643	-	
Complex-Zn1	-	1687	1553	1354	641	564	477
Complex-Zn1	-	1665	1612	1322	653	545	466
Complex-Zn1	-	1665	1601	1317	652	565	432
Complex-Zn1	-	1687	1553	1312	653	534	413

The π→π* transitions in the zinc complex electronic spectra were somewhat red-shifted (Figure 2) in contrast to the Schiff base spectra, suggesting that the ligand was coordinated to

the zinc atom without altering its structural arrangement. Since the Zn(II) complexes lack d-d transitions and are diamagnetic with d10 configuration, it is possible to argue that the ligand molecules around Zn(II) have a tetrahedral geometry.

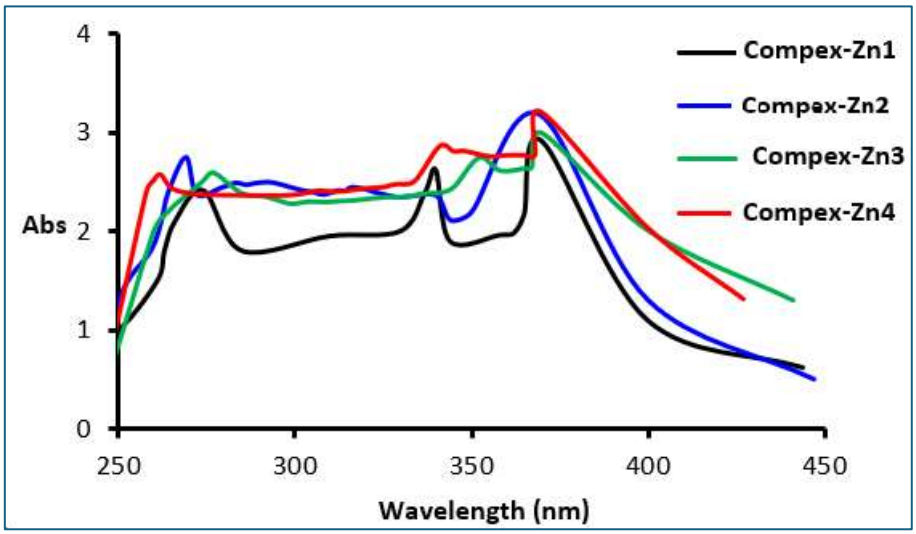

Figure 2: Electronic spectrum of Zn(II) complexes

Anti-Inflammatory Activity: The Protein Denaturation Assay was used to test the synthetic derivatives' anti-inflammatory properties. The assay's findings were as follows.:

Table 3: In-vitro Anti-inflammatory activity of test samples by protein denaturation assay.

Con (µg/ml)	%inhibition								
	T1	T2	T3	T4	Compex-Zn1	Compex-Zn2	Compex-Zn3	Compex-Zn4	Aspirin
100	20%	24%	39%	30%	26%	32%	23%	21%	68%
200	34%	34%	37%	42%	37%	47%	43%	39%	68%
300	46%	47%	55%	47%	48%	57%	49%	47%	72%
400	53%	47%	55%	50%	58%	65%	59%	47%	65%
500	58%	55%	61%	62%	65%	71%	71%	65%	79%

Table 4: IC_{50} values of standard and Zn complexes.

S. no	Compound	IC_{50} values
1	T1	302.1
2	T2	278.1
3	T3	319.1
4	T4	299.7
5	Complex-Zn1	276.1
6	Complex-Zn2	223.5
7	Complex-Zn3	218.65
8	Complex-Zn4	276.5

9	Aspirin	208.3

CONCLUSION:

Schiff bases were used to create zinc (II) metal complexes, which were then characterised. Schiff base ligand connected in a tridentate manner with the central zinc atom via carboxylic oxygen, azomethine nitrogen, and phenolic oxygen. Zn(II) complexes were ascribed tetrahedral geometry based on the spectroscopic analysis. When compared to the parent ligands, zinc complexes exhibited stronger anti-inflammatory properties. This work could serve as a foundation for the subsequent synthesis of a zinc complex derived from aminothiophene Schiff bases.

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