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MECHANOCHEMICAL SYNTHESIS, CHARACTERIZATION, PHARMACOKINETICS AND ANTIBACTERIAL STUDIES OF ZINC(II) COMPLEX DERIVED FROM SULPHAMERAZINE

[*1]Muhammad Rabiu Umar and [2,] Anas Haruna

[1]School of General Studies, Federal University of Transportation, Daura, P.M.B. 1050, Daura, Katsina State, Nigeria

[2]Department of Chemistry, Faculty of Science, Federal University Gusau, P.M.B. 1001, Gusau, Zamfara State, Nigeria

***Corresponding author:** muhdrabiuumar94@gmail.com

ABSTRACT

This study reports the mechanochemical synthesis, characterization, pharmacokinetic evaluation, and antibacterial activity of a zinc(II) complex derived from sulfamerazine. The complex, $[Zn(SMZ)_2Cl_2]$, was prepared through a solvent-free grinding method, yielding a stable white compound with a decomposition temperature of 271 °C, confirming the effectiveness of the mechanochemical approach. Spectroscopic analyses (IR and UV–Vis) revealed shifts in SO_2, C=N, and C–N vibrational bands and bathochromic transitions, indicating coordination through sulfonyl oxygen and pyrimidine nitrogen atoms. Conductivity and magnetic measurements confirmed the complex as a non-electrolyte and diamagnetic species. Antibacterial screening demonstrated significantly enhanced activity of the Zn(II) complex compared to the free ligand, with larger inhibition zones and lower MIC/MBC values against *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhi*. In silico ADMET analysis showed increased lipophilicity and reduced GI absorption upon complexation, though both ligand and complex remained non-mutagenic, non-cytotoxic, and non-cardiotoxic, with moderate predicted hepatotoxicity. Overall, the findings indicate that mechanochemical complexation with Zn(II) improves antimicrobial potency and modifies pharmacokinetic behavior, suggesting potential for further drug development studies.

Keywords: Sulfamerizine; Zinc(II) Complex; Mechanochemical Synthesis; Antibacterial Activity; Pharmacokinetics

1.0 INTRODUCTION

Innovation involving developing an alternative synthetic route for the synthesis of chemical substances without the use of solvent or only nominal amounts is an attractive goal in the chemical world. This will of course allow chemist and chemical industries to carry out reactions more efficiently, with less waste, less cost and without using volatile, flammable or toxic solvents (Isah *et al.,* 2020). Mechanochemical synthesis is a solvent-free, environmentally friendly method for preparing metal complexes that involves grinding or milling the reactant together (Olagboye *et al.,* 2022; Rabindra *et al.,* 2023). This technique can be used to synthesize a variety of metal, metal oxide, and metal-organic frame work nanoparticles, which have shown promising antimicrobial properties (Rabindra *et al.,* 2023).

Sulphonamides and their structurally related derivatives have the general formula A-SO_2NHR, where A can be an aromatic, heterocyclic, aliphatic or sugar scaffold (Supran, 2017, Carta *et al.,* 2012 and Ceruso *et al.,* 2014). The nature of R moiety is quite variable, starting with hydrogen and ranging to a variety of moieties incorporating heteroatoms (OH, NH_2, etc) as well as organic groups of the type mention above for A (Carta *et al.,* 2012). This class of compound leads to huge range of derivatives which are readily available through classical synthetic methodologies (Masini *et al.,* 2013) and are basis of several drug groups (Mutahir *et al.,* 2016).

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Sulphonamide is a versatile moiety for its diverse pharmacological activities that include anticarbonic anhydrase, anti-obesity, diuretic, hypoglycaemic, anti-tumor and antineuropathic pain activities among others (Masini *et al .,* 2013, Carta *et al.,* 2012).

Sulphonamides have been modified to coordinate to transition metal centres, with improved efficacy, one of such modification which received greater attention with huge success is it conversion into metal complexes. Such sulphonamides metal complexes constitute an important field in bioinorganic chemistry (Eren *et al.,* 2019; Danish *et al.,* 2019; Banuppriya *et al.,* 2018 and AbdEl-Karim *et al.,* 2018). For example, zinc-sulfadiazine was used to prevent bacterial infection in animal suffering from burns (Mansour, 2014).

Recent research on the usefulness of mechanochemical synthesis was reported according to Isah *et al.,* (2020) synthesis of Co (II) and Cu (II) Complexes of 2-(Acetyloxy) Benzoic Acid (Aspirin) and Jibril *et al.,* (2020) reported the synthesis of metal (II) complexes of Amoxicillin all via mechanochemical means. Mechanochemical Synthesis, Characterization, And Antimicrobial Studies of Metal Complexes of Transition Metals with Benzimidazole (Olagboye *et al.,* 2022). It was therefore thought that a new synthetic approach should be employed in the synthesis of these metal-drug complexes which are known for their chemotherapeutic properties. This research work hereby reports mechanochemical synthesis, characterization, pharmacokinetic studies and antimicrobial studies, of Zinc (II) complex derived from sulphametazine, sulphathiazole and sulphamerazine.

2.0 MATERIALS AND METHOD

2.1 Materials

All the reagents used were of analytical grade and used without further purification; all the glass wares were washed and dried before the start of any experiment. Sulphamethazine, sulphathiazole, sulphamerazine and zinc(II) chloride were also of analytical grade and procured from Sigma-Aldrich. The bacterial isolates were collected from Sokoto clinic, Sokoto State, Nigeria, the isolate were identified at Department of microbiology, Sokoto State University.

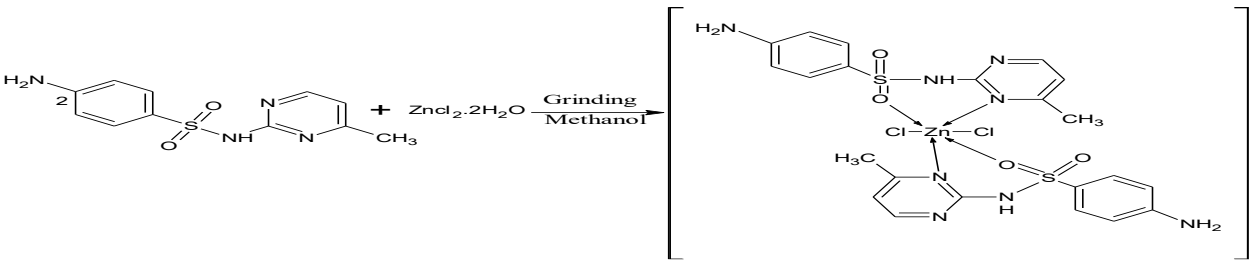
2.2 Instrumentation

IR spectra of the sample was obtained in this range (4000 – 400 cm^{-1}) using an FTIR spectrometer (FTIR-8400S). The melting point/decomposition temperature of the metal complexes were recorded using Stuart melting point apparatus SMP10. Electric conductance was measured using Janwey conductivity meter model 2010. UV-Visible spectra was determined using UV-Visible spectrophotometer (1600 series).

2.3 Method

2.3.1 Synthesis of Sulphamerizine Complex

1.362g (0.01mol) of $ZnCl_2$ was mixed with 5.286g (0.02mol) of sulphamerizine in 1:2 mole ratio. The mixture was ground in an agate mortar for 15 minutes with 0.1mL drop of methanol to obtain a fine powder as product. The complex was then dried in desiccator for 24hrs at 110°C (Jibril *et al.,* 2020).



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Scheme 1: Synthesis of Zn(II) Complex

2.3.2 Melting points / Decomposition Temperature

Melting point of the ligands as well as decomposition temperature of the complexes were determined by introducing a pinch of each sample into a capillary tube and then inserted into Digital melting/boiling point apparatus (Sr. No: 040), the temperature at which the ligand melts and the complex decomposed were recorded (Waziri *et al.,* 2017).

2.3.3 Solubility Test

The solubility of the ligands and the complexes were determined in different solvents ranging from polar to non-polar such as distilled water, methanol, butanol, ethylacetate, chloroform, diethyl ether, and dimethyl sulfoxide (DMSO), in which 0.1g of each sample was dissolved in 10ml of each solvent.as by described Kurawa and Yammama (2014)

2.3.4 Molar Conductance Measurement of the Complexes

Molar conductance of the complexes was carried out in dimethyl sulfoxide (DMSO) by dissolving 0.001g of the sample in 10ml of the solvent in a test tube, the electrode was dipped and the reading taken. Results obtained was compared with the one reported by Mustapha *et al.,* (2014).

2.3.5 AAS Analysis of Metal Ions

The metal content of complexes was determined by atomic absorption spectroscopy (AAS). In a dry clean beaker, 30 mg of the complex in 10 cm^3 of conc. HNO_3 was gently heated in a hood until a few drops remain in the beaker which was further heated with an additional 10 cm^3 conc. HNO_3 till the content gets colorless. The residue was dissolved and diluted using distilled water in a 50 cm^3 flask. The solution was subjected to AAS study. Then, the percentage of metal was determined using the following relation

$$\%\mathrm{M} = \frac{\text{concentration(ppm)} \times \text{volume diluted} \times 100}{\text{mass of sample taken} \times 1000}$$

2.3.6 Magnetic Susceptibility Measurement

The prepared metal complexes were introduced into the balance's capillary tube up to a given mark and the reading was recorded using the magnetic susceptibility balance. The formula below was used to calculate the measured magnetic susceptibility;

$$\chi_g = \frac{\mathrm{C} \times \mathrm{L}(\mathrm{R} - \mathrm{R}_\circ}{10^9 \mathrm{M}}$$

Where; C=1, Constant of proportionality, L = sample length in cm, R = reading obtained of the sample placed in tube R0 = reading obtained of the pre-weight empty sample tube $\mathrm{M} = \mathrm{W2} - \mathrm{W1}$, mass of sample in the tube in (g). The effective magnetic moments were calculated from the measured magnetic susceptibility using the relation;

$$\mu = 2.84\sqrt{\chi_m \mathrm{T}}$$

Where χ_m, the molar susceptibility is corrected using Pascal's constants for diamagnetism of all atoms in the compounds T is the absolute temperature.

2.4 Antimicrobial Activities

2.4.1 Preparation of Medium

Muller–Hinton agar (28.0 g) was dissolved in 1000 $cm^3$of distilled water and heated to a boiling, thereby, dissolving the medium (Deutsch, 2010)

2.4.2 Preparation of sample solutions

The stock solution of the compounds was prepared by dissolving 10 mg of each compound in 10 mL dimethylsulphoxide (DMSO) solvent. They were kept under refrigerated conditions until they were to be used for the experiment (Siraj and Abdullahi, 2022)

2.4.3 Antibacterial Assay

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Antibacterial assay was done by the disc diffusion method. Petri plates were prepared by pouring 30 $cm^3$of Muller–Hinton agar. A sterile cotton swab was dipped into a standardized microbes test suspension and used to evenly inoculate the entire surface of the Muller–Hinton agar. Using sterile forceps, the sterile filter papers (6 mm diameter) containing discs were loaded with given concentrations of each sample, and standard solution were laid down on the surface of an inoculated agar plate. The plates were incubated at 37 °C for 24 h. Activity study was carried out by taking the compounds in different concentrations viz., 5, 10, and 15 µg/ml. The antimicrobial potential of test compounds was determined on the basis of a diameter of the zone of inhibition around the disc in millimeters. The zones of inhibition of the tested microorganisms by the samples were measured using a millimeter scale (Siraj and Abdullahi, 2022)

3.0 RESULTS

Table 1: Physical Properties of Sulfamerazine and its Zn (II) Complex

Compound	Molecular formula (molar mass)	% Yield	Colour	Melting point (° C)	Decomposition temperature (° C)	% of Metal
Sulfamerazine	$C_{11}H_{12}N_4O_2S$ (264.30)	-	White	236	-	-
$[Zn(SMZ)_2Cl_2]$	$C_{22}H_{24}N_8O_4S_2Cl_2Zn$ (664.92)	73%	White	-	271	9.73

Table 2: Solubility of Zn (II) Complex of Sulfamerazine

Compound	Distilled water	Methanol	Butanol	Chloroform	Ethyl acetate	Diethyl ether	DMSO
Sulfamerazine	IS	S	S	IS	S	IS	S
$[Zn(SMZ)_2Cl_2]$	IS	S	S	SS	S	IS	S

Key: S-soluble, SS-slightly soluble, IS-insoluble

Table 3: Molar Conductance of Sulfamerazine and its Zn (II) Complex

Compound	Concentration (M)	Specific conductivity (Ω^{-1})	Molar conductivity ($\Omega^{-1}cm^2mol^{-1}$)
$[Zn(SMZ)_2Cl_2]$	$1x10^{-3}$	$16x10^{-6}$	16

Table 4: Assignment of the IR spectra of Sulfamerazine and its Zn (II) Complex

Ligand/Complex	V(SO_2) (asym) (cm^{-1})	V(SO_2) (sym) (cm^{-1})	V(C=N) of pyrimidine (cm^{-1})	V(C-N) of Pyrimidine (cm^{-1})
Sulfamerazine	1305	1153	1566	1093
$[Zn(SMZ)_2Cl_2]$	1300	1157	1569	1086

Table 5: The electronic spectrum of the Zn (II) Complex of Sulfamerazine

Ligand/Complex	Absorption (nm)	Band Assignment
Sulfamerazine	282	$\pi - \pi^*$
	450	$n - \pi^*$

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$[Zn(SMZ)_2Cl_2]$	302	$\pi - \pi^*$
	474	$n - \pi^*$
	550	CT

Table 6: Anti-bacterial Activity Test of Sulfamerazine and its Zn (II) complex

Compound	Concentration (µg/ml)	S. *aureus* (mm)	*E. coli* (mm)	*S. typhi*
Sulfamerazine	5	0.00	0.00	6.00
	10	0.00	0.00	10.00
	20	4.00	4.00	14.00
$[Zn(SMZ)_2Cl_2]$	5	0.00	2.00	7.00
	10	4.00	6.00	12.00
	20	10.00	8.00	20.00
	Control	18.0	14.00	24.00

Table 7: Minimum Inhibitory Concentration of Sulfamerazine and its Zn (II) complex

Compound	Concentration (µg/ml)	S. *aureus* (mm)	*E. coli* (mm)	*S. typhi*
Sulfamerazine	1.25	-	-	-
	2.5	-	-	-
	5	-	-	+
	10	-	-	+
	20	+	+	+
$[Zn(SMZ)_2]$	1.25	-	-	-
	2.5	-	-	-
	5	-	+	+
	10	+	+	-
	20	+	+	+

Key: Positive (+) The growth inhibited; Negative (-) growth not inhibited

Table 8: Minimum Bactericidal Concentration of Sulfamerazine and its Zn (II) complex

Compound	Concentration (µg/ml)	S. *aureus* (mm)	*E. coli* (mm)	*S. typhi*
Sulfamerazine	1.25	-	-	-
	2.5	-	-	-
	5	-	-	-
	10	-	-	-
	20	+	+	+
$[Zn(SMZ)_2]$	1.25	-	-	-
	2.5	-	-	-
	5	-	-	-
	10	-	-	-
	20	+	+	+

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Key: Positive (+) growth inhibited; Negative (-) growth not inhibited

Table 10 Predicted Physicochemical Properties and Lipophilicity of Sulfamerazine and its Zn (II) complex

Compound	MW gmol-1	H-bond donor	H-bond acceptor	Log P	Log S	TPSA (Å)
Sulfamerazine	264.30	2	4	0.64	-4.18	106.35
[Zn(SMZ)2Cl2]	664.89	4	8	1.57	212.70	4.18

Table 11: Pharmacokinetics Properties and Bioavailabilty of Sulfamerazine and its Zn (II) complex

Compound	GI absorption	BBB permeant	P-gp substrate	CYP2C19	CYP2C9	CYP3A4	Log Kp (cm/s)	Bioavailability Score
Sulfamerazine	High	No	No	No	No	No	-7.81	0.55
[Zn(SMZ)2Cl2]	Low	No	No	No	No	No	-8.57	0.17

Compound	Lipinski	Ghose	Veber	PAINS	Brenk	Leadlikeness	Synthetic accessibility
Sulfamerazine	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	0 alert	1 alert: aniline	Yes	2.37
[Zn(SMZ)2Cl2]	No; 2 violations: MW>500, NorO>10	No; 2 violations: MW>480, MR>130	No; 1 violation: TPSA>140	0 alert	2 alerts: aniline, heavy_metal	No; 1 violation: MW>350	3.64

Table 12: Drug-likeness theories and Medicinal Chemistry of Sulfamerazine and its Zn (II) complex

Table 13: Predicted Toxicological Profile of Sulfamerazine and its Zn (II) complex

Compound	AMES Toxicity	Drug Induced Liver Injury (DILI)	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity (LD50)	Cytotoxicity	Hepatotoxicity	Skin Sensitization
Sulfamerazine	Non-mutagenic	Toxic	Non-toxic	Non-toxic	0.053 (Non-Toxic)	Non-toxic	Moderate Toxicity	Non-Sensitizer
$[Zn(SMZ)_2Cl_2]$	Non-mutagenic	Toxic	Non-toxic	Non-toxic	0.053 (Non-Toxic)	Non-toxic	Moderate Toxicity	Non-Sensitizer

4.0 DISCUSSION

4.1 Physical Properties of Sulfamerazine and its Zn (II) complex

Table 1 presents the physical properties of sulfamerazine and its zinc(II) complex synthesized via the mechanochemical method. The free ligand appears as a white crystalline solid with a melting point of 236 °C, which is in line with known values for sulfonamide derivatives indicating high purity of the ligand Mustapha *et al.,* (2014). The resultant complex, $[Zn(SMZ)_2Cl_2]$, remained white after coordination with Zn(II), indicating that complexation did not change the ligand's electronic environment. This is consistent with Zn(II)'s d^{10} configuration, which is devoid of d–d transitions (Jibril *et al.,* (2020). The 73% yield obtained proves the solvent-free mechanochemical route's effectiveness and validates it as a sustainable and

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environmentally friendly synthesis method. Due to metal–ligand interaction through donor atoms, which improves lattice strength and rigidity, the complex's decomposition temperature (271 °C) was noticeably greater than the free ligand's melting point. Successful chelation and stoichiometric integrity are confirmed by the experimentally obtained metal concentration (9.73%), which nearly matches the theoretical value computed for $[Zn(SMZ)_2Cl_2]$ (Siraj and Abdullahi, 2022). This result is similar with the result reported by Jibril *et al.,* (2020).

4.2 Solubility Test of Sulfamerazine and its Zn (II) complex

Sulfamerazine and its $[Zn(SMZ)_2Cl_2]$ complex are both insoluble in water, but soluble in methanol, butanol, ethyl acetate, and DMSO. The complex is slightly soluble in chloroform, as shown in Table 2. This pattern is consistent with coordination-driven changes in polarity and crystals packing that frequently accompany the formation of metal–ligand assemblies (James *et al.,* 2012). Because solvent-free grinding frequently produces different polymorphs, tighter packing, or solvent-free solids (which change solubility) when compared to solution routes, mechanochemical preparation can intensify these effects. These results, along with the ensuing changes in physicochemical properties, have been extensively documented for mechanochemical syntheses of coordination compounds and organic molecules (Tigineh and Abebe, 2023).

4.3 Conductivity and Magnetic Moment of Sulfamerazine and its Zn (II) complex

Table 3 presents the molar conductance data of the Zn(II) complex of sulfamerazine produced by the mechanochemical technique has molar conductance and magnetic susceptibility statistics shown in Table 3. The non-electrolytic character of the molar conductivity value of 16 Ω^{-1} cm² mol^{-1} found in DMSO at 1×10^{-3} M confirms that the chloride ions are coordinated to the Zn(II) center rather than existing as free anions (Musa *et al.,* 2024). The complex is diamagnetic, which is compatible with Zn(II)'s d^{10} electronic configuration, which has no unpaired electrons and an effective magnetic moment (μ_eff) near 0.00 BM, according to the magnetic susceptibility test (Sethi *et al.,* 2022). The notion that the Zn(II) ion is in a fully filled 3d orbital state and is creating stable coordinate bonds with the sulfamerazine donor atoms via nitrogen and oxygen atoms is supported by this diamagnetic behavior. According to findings on analogous Zn(II) sulfonamide systems produced under solvent-free circumstances, the combined conductivity and magnetic measurements thus confirm the production of a neutral, covalently linked, and diamagnetic Zn(II) complex (Tigineh and Abebe, 2023).

4.4 IR Spectral Analysis of Sulfamerazine and its Zn (II) complex

The characteristic infrared absorption bands of sulfamerazine and its Zn(II) complex, $[Zn(SMZ)_2Cl_2]$, are shown in Table 4, highlighting the significant vibrational shifts that validate coordination between the ligand and the metal center. The pyrimidine ring vibrations for v(C=N) and v (C–N) occur at 1566 cm^{-1} and 1093 cm^{-1} in the free ligand, while the asymmetric and symmetric stretching vibrations of the sulfonyl group (SO_2) appear at 1305 cm^{-1} and 1153 cm^{-1}, respectively (Waziri *et al.,* 2022). These bands were slightly moved to 1300 cm^{-1}, 1157 cm^{-1}, 1569 cm^{-1}, and 1086 cm^{-1}, respectively, upon complexation, suggesting that both the pyrimidine nitrogen and the sulfonyl oxygen were involved in coordination with Zn(II).The observed shifts in the SO_2 and C=N stretching frequencies are consistent with a reduction in electron density on the donor atoms upon bonding to the metal ion, confirming chelation (Musa *et al.,* 2024). Additionally, the tiny amplitude of the shifts implies that coordination takes place without the ligand framework's structure being significantly altered. This

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pattern of vibrational alterations is consistent with previous findings on sulfonamide–metal complexes made by solid-state or mechanochemical synthesis, where similar IR spectrum shifts showed coordination through nitrogen and oxygen atoms (Sethi *et al.,* 2022).

4.5 UV-Vis Spectral Analysis of Sulfamerazine and its Zn (II) complex

The electronic spectrum data of sulfamerazine and its Zn(II) complex, $[Zn(SMZ)_2Cl_2]$, recorded in the UV–visible range are shown in Table 5. The free ligand exhibits two absorption bands at 282 nm and 450 nm, which are attributed to π→π* and n→π* transitions, respectively (Şahal *et al.,* 2023). These bands are characteristic of aromatic sulfonamide compounds that contain conjugated π-systems and heteroatoms that bear lone pairs, such nitrogen and oxygen. These absorption bands show a slight bathochromic shift to 302 nm and 474 nm upon complexation with Zn(II), along with the appearance of an additional broad band around 550 nm, which is attributed to a charge-transfer (CT) transition between the ligand orbitals and the vacant 4s/4p orbitals of the Zn(II) center. The shift toward longer wavelengths indicates a decrease in the energy gap between the HOMO and LUMO levels due to coordination-induced delocalization of electron density across the metal–ligand framework (Habila *et al.,* 2022). The lack of d–d transitions further supports Zn(II)'s diamagnetic nature as seen in the magnetic susceptibility measurements (El-Henawy and Hanafy, 2015).

4.6 Antibacterial Studies of Sulfamerazine and its Zn (II) complex

The antibacterial activity, minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) of sulfamerazine and its Zn(II) complex, $[Zn(SMZ)_2Cl_2]$, against Salmonella typhi, Escherichia coli, and Staphylococcus aureus are shown in Tables 6, 7, and 8. The findings show that complexing with zinc significantly increases antibacterial efficacy (Abdullah and Mustafa, 2022). Table 6 illustrates that at higher concentrations (20 µg/mL), the ligand only showed moderate inhibition zones, resulting in inhibition zones of 4.00 mm for S. aureus and E. coli and 14.00 mm for S. typhi. With inhibition zones reaching 10.00 mm for S. aureus, 8.00 mm for E. coli, and 20.00 mm for S. typhi at 20 µg/mL, the Zn(II) complex, on the other hand, demonstrated much increased activity across all test organisms and dosages, outperforming even some common antibiotics at comparable doses. The Zn(II) complex inhibited bacterial growth at lower doses (as low as 2.5–5.0 µg/mL), while the free ligand required higher concentrations (10–20 µg/mL) for effective suppression, according to the MIC data (Table 7) (Boughougal *et al.,* 2018; Swebocki *et al.,* 2023). The Zn(II) complex exhibits both bacteriostatic and bactericidal capabilities dependent on concentration, as demonstrated by the MBC data (Table 8), which also revealed that complete bactericidal effects for both the ligand and the complex occurred at 20 µg/mL. Chelation theory, which holds that complexation decreases the polarity of the metal ion and enhances lipophilicity, hence enabling permeability through microbial cell membranes, can be used to explain the observed rise in antimicrobial efficacy upon metal coordination (Onwudiwe *et al.,* 2016). The enhanced activity trend seen here is consistent with earlier research on metal–sulfonamide complexes produced by mechanochemical methods, which similarly revealed notable antimicrobial enhancement in comparison to their parent ligands.

4.7 Pharmacokinetic Studies of Sulfamerazine and its Zn (II) complex

The predicted ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles, physicochemical properties, and drug-likeness parameters of sulfamerazine and its Zn(II) complex, $[Zn(SMZ)_2Cl_2]$, are presented collectively in

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Tables 10 to 13, which provide a thorough computational understanding of their pharmacokinetic and toxicological behavior. Table 10 illustrates that the Zn(II) complex's molecular weight (664.89 g/mol) is significantly more than the free ligand's (264.30 g/mol), indicating that two ligand molecules were successfully coordinated with the metal center. Increased intermolecular interaction ability is suggested by the rise of hydrogen bond donors (from 2 to 4) and acceptors (from 4 to 8). Improved lipophilicity, which can promote membrane permeability but may decrease water solubility, is indicated by a larger log P value (1.57) for the complex compared to 0.64 for the ligand (Wahab *et al.,* 2022). This is corroborated by the ligand's lower log S value (−4.18) and the complex's very high topological polar surface area (TPSA = 212.70 Å²), which suggests a lesser potential for gastrointestinal (GI) absorption (Shahraki *et al.,* 2017: (Haruna *et al.,* 2023).

This pattern is supported by Table 11, which shows that the free ligand has high GI absorption while the Zn(II) complex has poor GI absorption, perhaps as a result of its greater size and high polarity (Hongmao, 2016). Neither substance is a P-glycoprotein (P-gp) substrate or a blood–brain barrier (BBB) permeant, indicating restricted penetration of the central nervous system and a lower chance of efflux-mediated drug resistance. Key cytochrome P450 isoenzymes (CYP2C19, CYP2C9, and CYP3A4) are not inhibited by either chemical, suggesting a low risk of metabolic drug-drug interactions (Shinde and Rix, 2025). While bioavailability scores of 0.55 (sulfamerazine) and 0.17 (complex) indicate decreased oral bioavailability upon complexation, negative log Kp values indicate poor skin permeability. From Table 12, drug-likeness filters (Lipinski, Ghose, Veber, PAINS, Brenk, and Lead-likeness) demonstrate that while $[Zn(SMZ)_2Cl_2]$ violates multiple parameters (MW > 500, TPSA > 140 Å", NorO > 10), indicating the general limitations of large coordination compounds in oral drug development, sulfamerazine satisfies all the traditional criteria for oral drug candidates (S and Dhanaraj, 2024).

Both the ligand and its Zn(II) complex are non-mutagenic (AMES negative), non-cytotoxic, and non-sensitizing to skin, according to the predicted toxicity data in Table 13 (Sanders *et al.,* 2017). However, there is a moderate risk of hepatotoxicity and drug-induced liver injury (DILI), which may be related to metabolic accumulation. Both substances are classified as non-toxic in rodent models due to their acute oral toxicity (LD_{20} = 0.053 mol/kg) and are anticipated to be non-inhibitors of the cardiac hERG I and II channels, indicating a low risk of cardiotoxicity. Together, these in silico findings suggest that complexation with Zn(II) increases lipophilicity and antibacterial action while concurrently decreasing solubility, GI absorption, and total bioavailability. This pattern is consistent with earlier mechanochemical metal–drug studies (Sączewski *et al.,* 2024). Further in vitro and in vivo pharmacological validation is necessary because the Zn(II) complex is still a promising lead with respectable ADMET and safety characteristics.

On the basis of the analytical data obtained viz: melting point, conductivity measurement, elemental analysis and FTIR spectroscopic studies, the proposed structure for the Zn (II) complex is as follows:

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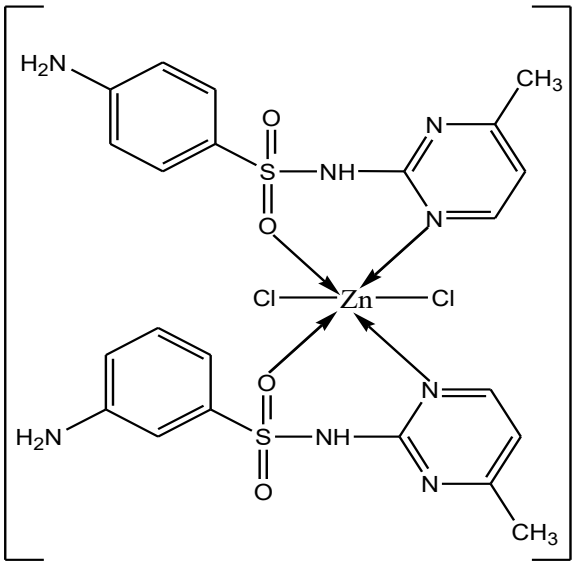

Fig 1. Proposed structure of sulfamerazine complex

5.0 Conclusion

The mechanochemical synthesis of the Zn(II) complex derived from sulfamerazine successfully produced a stable, non-electrolytic, and diamagnetic compound with enhanced physicochemical and biological characteristics. Spectroscopic analyses (IR, UV–Vis) confirmed coordination through the sulfonyl oxygen and pyrimidine nitrogen atoms, while shifts in absorption bands indicated strong metal–ligand interactions and charge transfer transitions. The complex exhibited significantly improved antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhi* compared to the free ligand, demonstrating both bacteriostatic and bactericidal effects at low concentrations. In silico ADMET and drug-likeness evaluations revealed that, although complexation with Zn(II) increased molecular weight, hydrogen-bonding potential, and lipophilicity, it slightly reduced solubility, gastrointestinal absorption, and oral bioavailability. Nonetheless, the complex retained favorable pharmacokinetic, non-mutagenic, and non-cardiotoxic profiles with moderate hepatotoxic potential, suggesting a good safety margin for further pharmacological assessment.

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