

Synthesis, Characterization and Molecular Docking Studies of Mn (II) Complex of Sulfathiazole

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Abstract

Sulfathiazole (SFTZ) is an antibacterial drug that contains organosulfur compound. It is used as a short-acting sulfa drug. The metal complexes of sulfa-drug have gained considerable importance due to their pronounced biological activity. The sulfa-drugs have received great attentions because of their therapeutic applications against bacterial infections. Mn(II) complex of sulfathiazole was synthesized by reaction of sulfathiazole with $MnCl_2 \cdot 4H_2O$. The Mn (II) complex was characterized based on UV, IR, 1H NMR Spectroscopy and x-ray powder diffraction. The electronic spectrum of the ligand showed intra charge transfer which were assigned to the chromophores present in the ligand, while that of the complex suggested intra ligand charge transfer (ILCT) and ligand to metal charge transfer (LMCT). In the IR spectrum of sulfathiazole the $N-H$ stretch of SO_2NH appeared at $3255.23cm^{-1}$. In the IR spectrum of the metal complex this band was absent. This suggested the deprotonation of the $N-H$ of SO_2NH during complexation reaction. This showed that sulfathiazole acted as a monodentate ligand. 1H NMR spectrum of $[Mn(SFTZ)]$ complex showed the involvement of nitrogen atom of SO_2NH . The crystal structure of $[Mn(SFTZ)]$ complex belongs to monoclinic system, space group P1, with cell parameters of $a = 4.519 \text{ \AA}$, $b = 8.704 \text{ \AA}$, $c = 12.608 \text{ \AA}$, $V = 493.5 \text{ \AA}^3$, $\beta = 95.69^\circ$. Molecular docking suggested that the ligand/complex binded effectively with the *E.coli* and *S.aureus* because their global binding energies were negative. The binding interactions of ligand/complex with *E. coli* and *S. aureus* were predicted. Molecular docking predicted the feasibility of the biochemical reactions before experimental investigation. It was concluded that sulfathiazole behaved as a monodentate ligand towards Mn (II) ion. The binding energy and interaction of $[Mn(SFTZ)]$ with *E.coli* and *S. aureus* have also shown that inhibition of the bacterial species are feasible. The mechanism of action of $[Mn(SFTZ)]$ with *E. coli* and *S. aureus* is now well understood.

Keywords: Sulfathiazole, Spectra Bacteria, Complex, Docking

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1. Introduction

Sulfathiazole (Figure 1) was the first therapeutic agents used systematically for the cure and prevention of bacterial infections. Furthermore, sulfadruugs and their metal complexes, pos-

sess many applications as diuretic, antiglaucoma or antiepileptic drugs, among others. Sulpha drugs show important biological activity e.g mechanism of action is based on the competitive antagonism of PABA (p-aminobenzoic acid) and the sulfanilamide [1, 2]. It has been reported that the activity of the metal complex is much better than the ligand alone [3, 4]. Studies on their metal chelates have much physiological and pharmacological relevance because the metal chelates of sulfadruugs have

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been found to be more bacteriostatic than the drugs themselves [5, 6].

The role of metal ions in living systems has been well established in recent years. The use of transition metal complexes as medicinal compounds has become more and more prominent. These complexes offer a great diversity in their action; they do not only have anti-cancer properties but have also been used as anti-inflammatory, anti-infective and anti-diabetic compounds [7].

Metal ions play pivotal roles in many biological processes, and the study of the roles of these metal ions in biological systems falls into the rapidly developing interdisciplinary field known as bioinorganic chemistry. When compared to other branches of natural sciences, bioinorganic chemistry seems to be a young discipline. However, there is a copious amount of information on the effects of metals on biological systems. For instance, the toxicities of metal ions such as mercury, lead and chromium on the environment have been well publicized [8, 9].

Metal complexes containing the sulphonamide group has found importance because of their applications as biological, biochemical, analytical, antimicrobial, anticancer, antibacterial, antifungal and antitumor activity [10, 11, 12]. They also find application as antibiotics, anti-inflammatory agents and in the industry as anticorrosion agents [13-17].

Molecular complexes of sulfonamides have been reported [18]. Syntheses, Characterization, thermal and antimicrobial studies of binuclear metal complexes of Sulfa-guanidine Schiff bases have been reported [19]. The metal complexes of Sulfa-guanidine were assessed to be more potent than the free ligand [19]. It is in view of this pharmacological importance of sulphonamide that we have reported the synthesis, characterization and molecular docking studies of Mn-sulphathiazole.

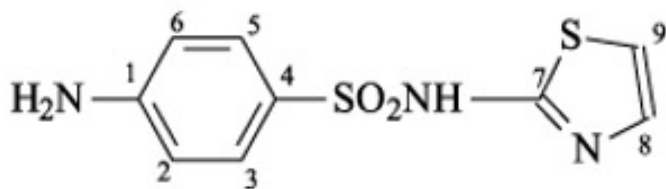


Figure 1: Structure of sulfathiazole

2. Material and Methods

All chemicals and reagent used in this experimental work were of analytical grade. Pure sulfathiazole, and $MnCl_2 \cdot 4H_2O$ salt were all imported from Sigma–Aldrich Laboratories. The solvents are ethanol, methanol, acetone, chloroform, sodium hydroxide, benzene and dimethyl sulfoxide.

Synthesis of [Mn(SFTZ)]: The complex was prepared following a reported procedure [21]. Mn (II) salt solution was prepared by dissolving 3.96 g (0.02 mol) $MnCl_2 \cdot 4H_2O$ in 25 ml of distilled water. The solution of the metal salt was added slowly with stirring in a separate 20 ml of distilled water containing 5.1 g of sulfathiazole (0.02 mol) at room temperature maintaining the PH between 6.0 - 6.5 by adding dilute solution of KOH.

The synthesis was carried out with stirring at room temperature. After 1 hour, the complex separated out. The complexes were washed well with distilled water, recrystallized, filtered and finally dried in vacuum and weighed and melting point recorded.

Melting points of the complex was determined using MPA 160 melting point apparatus. Atomic absorption spectroscopy was carried out on Duck-2010 spectrometer (Duck instrumental company) [20]. Infrared spectrum was collected on Perkin Elmer Paragon 1000 FT-IR spectrophotometer (spectrum BX) equipped with cesium iodide window ($4000 - 350cm^{-1}$) in KBr pellets. The UV-Visible spectrum was obtained on a Perkin Elmer (lambda 25) spectrometer (200–800 nm) using distilled water as solvent.

The 1H Nuclear Magnetic Resonance (NMR) spectra were obtained using Varian 400 MHz Unity INOVA, using DMSO as solvent. In the Crystallographic studies, appropriate amounts of the crystal was collected and deposited on Bruker D8 diffractometer operating in transmission mode using Germanium monochromated $CuK_{\alpha 1}$ radiation, $\lambda = 1.5406 \text{ \AA}$, linear position-sensitive detector covering 12° in 2θ , 2θ mode range $3.5^\circ - 70^\circ$, step size 0.017° and 17 h data collection time. FOX software was used for structure determination and refinement.

Molecular docking: The three-dimensional structure of *Escherichia coli* and *Staphylococcus aureus* and were obtained from the Protein Data Bank, PDB 1E91 and 1STN respectively. The protein structures were subjected to a refinement protocol using Molegro Molecular Viewer. Molecular docking was performed using PatchDock Server: an automatic server for molecular docking [22]. Refinement was done in FireDock Server: An automatic server for fast interaction refinement in molecular docking and processed with Molegro molecular viewer [23-26].

3. Results and Discussion

Crystallographic data and structure refinement parameters for [Mn(SFTZ)] is given in Table 1, whereas the powdered X-ray diffraction is shown in Figure 2

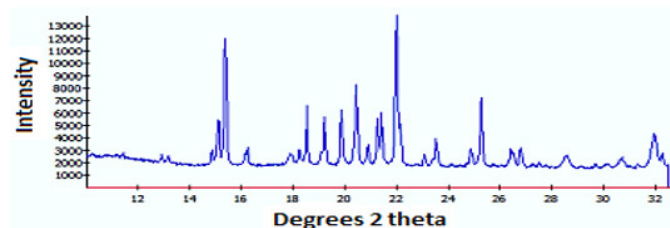


Figure 2: Powdered x-ray diffraction of [Mn(SFTZ)].

The crystal structure of [Mn(SFTZ)] complex belongs to monoclinic system, space group P1, with cell parameters of $a = 4.519 \text{ \AA}$, $b = 8.704 \text{ \AA}$, $c = 12.608 \text{ \AA}$, $V = 493.5 \text{ \AA}^3$, $\beta = 95.69^\circ$. Elemental and physical properties of sulfathiazole and its metal complex are shown in Table 2

The elemental analysis of sulfathiazole and its Mn(II) complex showed that the experimental values are in agreement with the calculated values. The colour of the new product suggested the formation of complex because transition metal complexes

Table 1: Crystal data and structure refinement for sulfathiazole and its (Mn(II) complex

Parameters	[Mn(SFTZ)]
Temperature (K)	298
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 1
a(Å)	4.519
b(Å)	8.704
c(Å)	12.608
α (°)	90
β (°)	95.69
γ (°)	90
Volume (Å ³)	493.51 (1.0V)

Table 2: Elemental and physical properties of SFTZ and [Mn(SFTZ)]

Ligand/complex	% Mn Found (Calculated)	Colour	Melting point °C	Yield (%)
SFTZ	—	White	202 – 202.5	—
[Mn(SFTZ)]	17.50 (17.77)	Pink	141 - 142	86

are coloured. The change in melting point also indicated the formation of new complex. The infrared spectra data of sulfathiazole and its *Mn(II)* complex are presented in Table 3

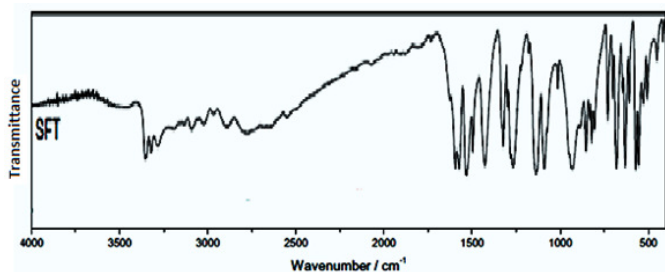


Figure 3: IR spectrum of sulfathiazole [21].

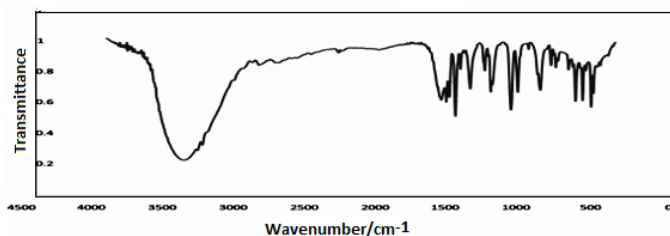


Figure 4: IR spectrum of [Mn(SFTZ)].

A comparison of IR spectrum of SFTZ and that of the complex was made (Figures 3 and 4). The infrared spectrum of SFTZ showed a broad band at 3354.00 and 3321.00 cm^{-1} [21]. This band was assigned *N – H* stretch of the primary amine due to asymmetric and symmetric stretching vibrations of the two *N – H* bonds. In the IR spectra of the *Mn(II)* complex,

this vibration frequency remained unchanged. This suggested that *NH*₂ was not involved in complexation. Vibration frequency 1323.00 cm^{-1} and 1140.00 cm^{-1} were assigned to $V_{as}(O=S=O)$ and $V_s(O=S=O)$ in SFTZ. In the complex, these frequencies showed up at 1319.79 and 1138.39 cm^{-1} in [Mn(SFTZ)]. It is evident that sulfonyl group was not involved in coordination to *Mn*. In SFTZ spectrum *C – N* stretching vibration was observed at 1497.00 cm^{-1} . In the spectrum of the complex, this functional group was observed at 1494.05 cm^{-1} [Mn(SFTZ)]. This observation suggest that coordination did not occurred through *C – N* in [Mn(SFT)]. The *N – H* stretch of *SO*₂*NH* appeared at 3255.23 cm^{-1} in the free ligand. In the IR spectrum of the metal complex this band was absent. This suggested the deprotonation of the *N – H* of *SO*₂*NH* during complexation reaction.

The UV spectral data of sulfathiazole and its *Mn(II)* complex are presented in Table 4, while the spectra are present in Figures 5 and 6.

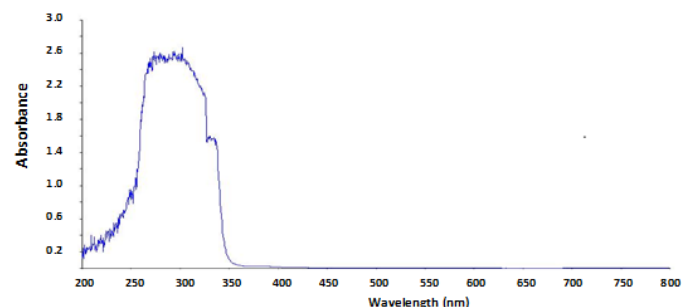


Figure 5: UV-Vis spectrum of sulfathiazole.

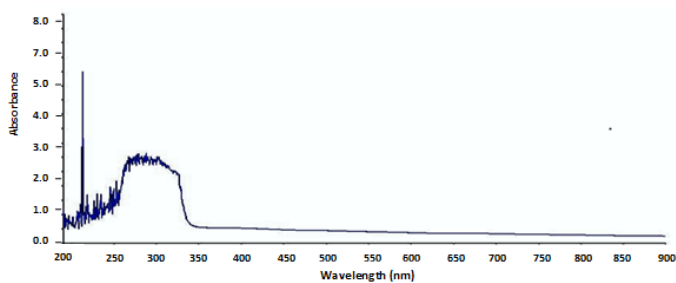
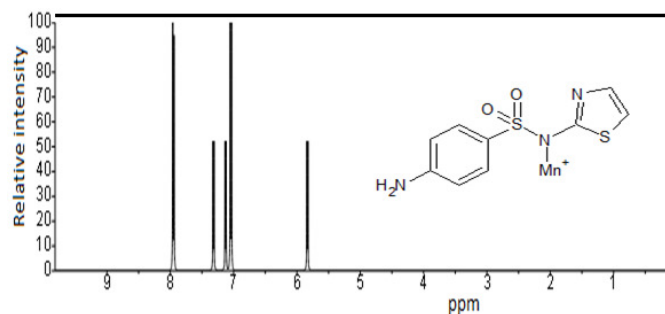
The UV-Vis spectrum of SFTZ showed a band centered at 269 nm. It was assigned $\pi - \pi^*$ due to intra-ligand charge

Table 3: Infrared spectral data of sulfathiazole and its *Mn(II)* complex

Ligand/complex	$V_{as}(\text{O}=\text{S}=\text{O})$ (cm^{-1})	$V_s(\text{O}=\text{S}=\text{O})$ (cm^{-1})	$V(\text{NH})$ (cm^{-1}) (primary amine)	$V(\text{CN})$ (cm^{-1})	$(\text{N} - \text{H})$ (cm^{-1}) ($\text{S O}_2\text{NH}$)
SFTZ	1323.00	1140.00	3354.00, 3321.00	1497.00	3255.23
[<i>Mn</i> (SFTZ)]	1319.79	1136.39	3350.32, 3320.10	1494.05	Absent

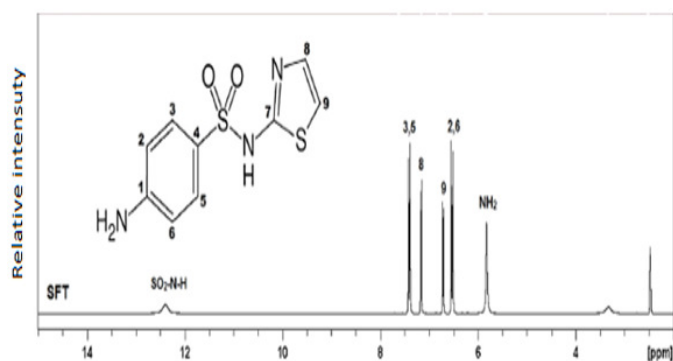
Table 4: The UV spectral data of sulfathiazole and its complex.

Ligand/Metal complex	$\lambda_{max}(\text{nm})$	Assignment
SFT	269	$\pi - \pi^*$ (ILCT)
[<i>Mn</i> (SFTZ)]	270	$\pi - \pi^*$ (ILCT)
	230	LMCT

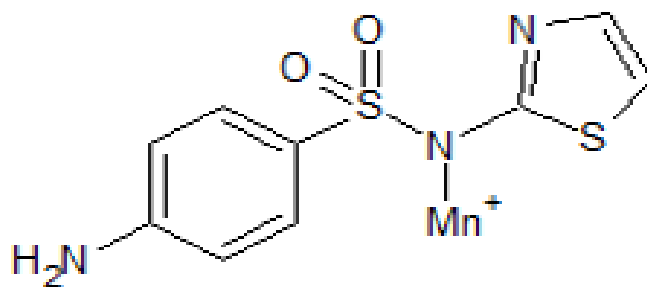
Figure 6: UV-vis spectrum of [*Mn*(SFTZ)].Figure 8: ^1H NMR spectrum of [*Mn*(SFTZ)].

transfer (ILCT). The UV-Vis spectrum of [*Mn*(SFTZ)] showed a band centered at 270 nm which has been assigned ILCT due to $\pi - \pi^*$. The chromophores that may exhibit this transition are S=O and C=N. A sharp peak centered at 230 nm suggested ligand to metal charge transfer (LMCT). The $^1\text{H} - \text{NMR}$ spectral data of sulfathiazole and its *Mn(II)* complex are presented in Table 5. The spectra are shown in Figures 7 and 8.

the ($\text{O}_2\text{S} - \text{N} - \text{H}$) group of SFTZ when coordination occurred through the nitrogen to the metal centre. Based on the UV, IR, ^1H NMR spectra and x-ray powder diffraction, the structure (Figure 9) has been proposed for [*Mn*(SFTZ)].

Figure 7: ^1H NMR spectrum of sulfathiazole [21].

In the ^1H NMR spectrum of SFTZ, the aromatic protons appeared at 6.51 and 7.43 ppm while the thiazole protons are observed between 6.71 and 7.18 ppm [21]. NH_2 protons were observed at 5.80 ppm. In the spectrum of the metal complex, these chemical shifts remained relatively unchanged. In the ^1H NMR spectrum of SFTZ, the hydrogen that appeared as a singlet at 12.4 ppm is no longer observed in the spectra of the metal complex. This is attributed to the loss of hydrogen atom of

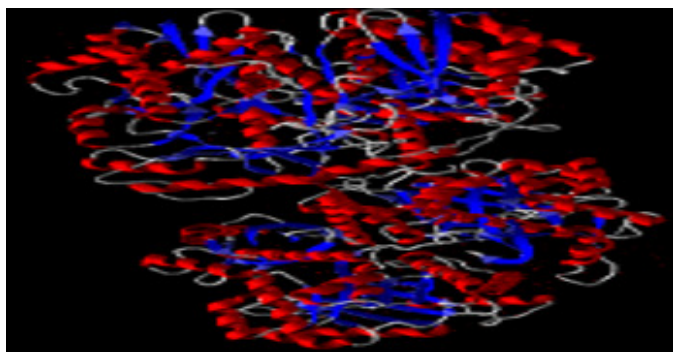
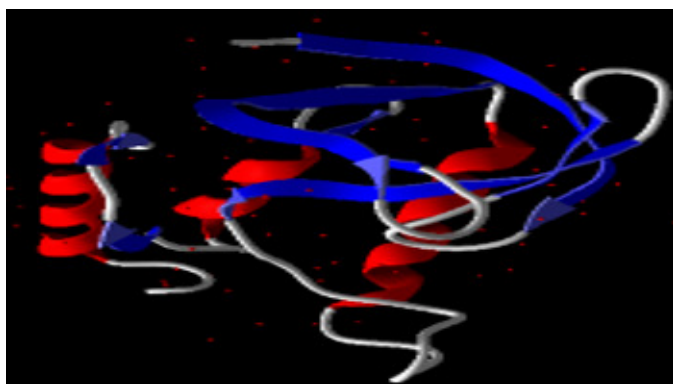
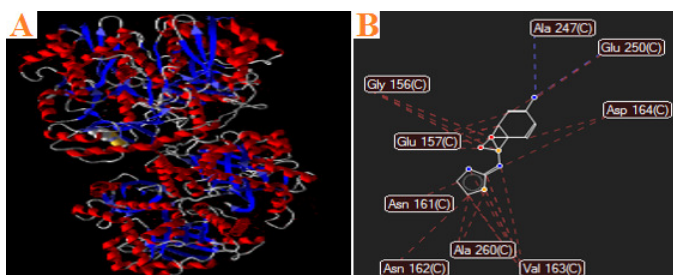
Figure 9: Proposed structure of [*Mn*(SFTZ)].

The solutions Tables of the molecular docking are shown in Tables 6 - 9. The crystal structure of the *E. coli* RNA degradosome component enolase and *S. aureus* nuclease are shown in Figures 10 and 11 respectively. The crystal structure of *E. coli* contains four protein chains (A, B, C and D) and 506 water molecules. The crystal structure of *S. aureus* nuclease is made up of one protein chain (A) and 83 water molecules. The molecular docking and molecular interactions of sulfathiazole with *E. coli* are presented in Figures 12a and 12b. The molecular docking and molecular interactions of [*Mn*(SFTZ)] with *E. coli* are presented in Figures 13a and 13b. The molecular docking and molecular interactions of sulfathiazole with *S. aureus*

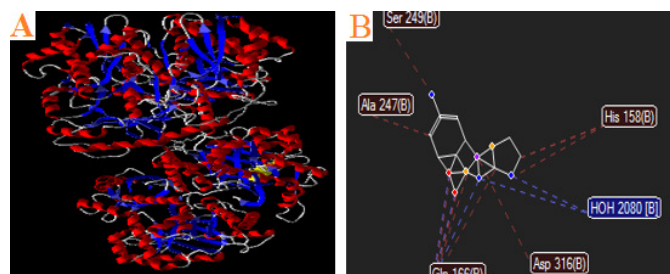
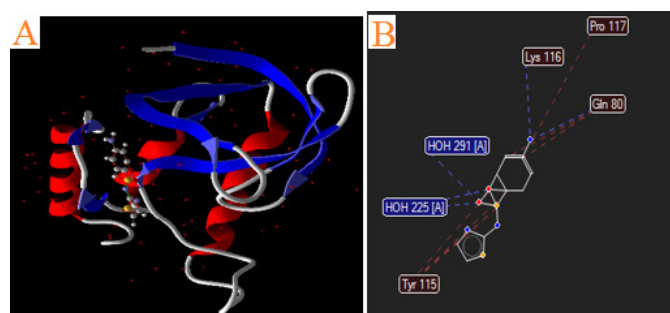
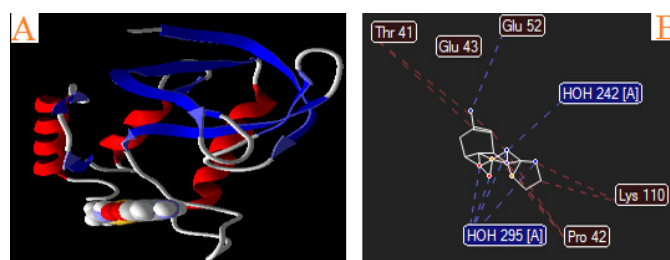
Table 5: 1H – NMR spectral data of sulfathiazole and its complex.

Ligand/ complex	Thiazole protons (δ ppm)	$O_2S - N - H$ (δ ppm)	NH (δ ppm)	Aromatic (δ ppm)
SFTZ	6.71 - 7.18	12.4	5.80	6.51-7.43
[Mn(SFTZ)]	7.02 -7.45	Absent	5.80	6.51-7.43

nuclease are presented in Figures 14a and 14b. . The molecular docking and molecular interactions of [Mn(SFTZ)] with *S. aureus* nuclease are presented in Figures 15a and 15b.

Figure 10: Crystal structure of *E. coli* RNA degradosome component enolase.Figure 11: Crystal structure of *S. aureus* nuclease.Figure 12: (A) Crystal structure of *E. coli* RNA degradosome component enolase docked with sulfathiazole. (B) Molecular interactions of sulfathiazole with *E. coli* RNA degradosome component enolase.

The best ranking in Table 6 is solution 2 with global energy -46.74 Kcal/mol. This suggested that sulfathiazole has the

Figure 13: (A) Crystal structure of *E. coli* RNA degradosome component enolase docked with [Mn(SFTZ)]. (B) Molecular interactions of [Mn(SFTZ)] with *E. coli* RNA degradosome component enolase.Figure 14: (A) Crystal structure of *S. aureus* nuclease docked with sulfathiazole. (B) Molecular interactions of sulfathiazole with *S. aureus* nuclease.Figure 15: (A) Crystal structure of *S. aureus* nuclease docked with [Mn(SFTZ)]. (B) Molecular interactions of [Mn(SFTZ)] with *S. aureus* nuclease.

ability to inhibit *E. coli*. The attractive Vander waals and atomic contact energy (ACE) showed negative values. These suggested that sulfathiazole docked effectively with *E. coli*. The molecular interactions (Figure 12b) show that *E. coli* formed hydrogen bonding with sulfathiazole using Ala 247(C) and Glu 250(C). Steric interaction between *E. coli* and sulfathiazole were observed with Gly 156(C), Glu 157(C), Asn 161(C), Ala 260(C), Asn 162(C), Val 163(C), and Asp 164(C).

The best global energy in Table 7 is -40.08 Kcal/mol (so-

Table 6: Solution Table of SFTZ docked with *E. coli*(VdW = Vanderwaals; ACE = Atomic Contact Energy).

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol)
1	2	-46.74	-15.12	1.68	-16.11
2	5	-39.59	-14.83	1.49	-12.46
3	9	-34.11	-12.29	1.08	-10.99
4	10	-25.97	-13.63	0.99	-4.88
5	6	-21.88	-13.34	3.23	-3.65
6	1	-21.72	-12.16	0.20	-2.46
7	4	-17.18	-13.71	3.19	0.16
8	7	-11.34	-8.06	2.10	-2.04
9	3	-5.73	-12.05	18.51	-2.15
10	8	3.31	-12.71	29.59	-1.56

Table 7: Solution Table of [Mn(SFTZ)] docked with *E. coli*(VdW = Vanderwaals; ACE = Atomic Contact Energy).

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol)
1	9	-40.08	-11.96	3.61	-15.77
2	4	-38.68	-14.27	2.68	-12.57
3	1	-35.93	-13.63	2.29	-11.48
4	6	-33.85	-11.60	1.10	-11.54
5	8	-29.70	-11.47	1.62	-9.17
6	10	-29.18	-9.28	0.71	-10.35
7	3	-20.15	-10.26	1.42	-5.76
8	5	-19.49	-10.86	3.63	-6.83
9	7	-18.03	-12.44	4.59	-2.38
10	2	-10.31	-13.92	8.90	1.35

Table 8: Solution Table of SFTZ docked with *S. aureus* (VdW = Vanderwaals; ACE = Atomic Contact Energy).

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol)
1	1	-25.35	-11.53	3.66	-7.77
2	9	-24.36	-13.36	1.42	-5.00
3	2	-21.31	-9.73	2.95	-6.32
4	6	-19.93	-8.76	1.77	-7.08
5	3	-19.27	-6.79	0.61	-7.54
6	8	-18.63	-11.33	1.99	-3.87
7	7	-16.25	-9.00	2.49	-5.05
8	10	-10.07	-5.26	2.43	-3.60
9	5	-9.98	-8.36	5.39	-4.11
10	4	-9.65	-5.51	2.56	-4.53

Table 9: Solution Table of [Mn(SFTZ)] docked with *S. aureus* (VdW = Vanderwaals; ACE = Atomic Contact Energy).

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol)
1	4	-23.56	-9.86	4.80	-9.09
2	8	-23.48	-10.23	1.83	-7.94
3	1	-22.65	-11.19	4.93	-8.21
4	5	-16.39	-9.69	1.59	-3.65
5	9	-13.64	-6.72	4.14	-6.44
6	2	-13.17	-6.45	5.68	-5.97
7	6	-11.25	-7.38	2.10	-3.20
8	7	-7.27	-4.41	2.60	-4.43
9	10	-5.71	-4.97	2.29	-1.96
10	3	0.59	-11.04	38.87	-9.47

lution 9). This suggested that [Mn(SFTZ)] has the ability to inhibit *E. coli*. The attractive Vander waals and atomic contact energy (ACE) were also predicted. Their negative value predicted effective binding. The molecular interactions (Figure 13b) showed that *E. coli* formed hydrogen bonding with [Mn(SFTZ)] through Gly 166(B) and HOH 208(B). Steric interactions between [Mn(SFTZ)] and *E. coli* occurred with His 158(B), Ala 247(B), Ser 249(B), Gln 166(B) and Asp 316(B).

The best ranking in Table 8 is solution 1 with global energy -23.56 Kcal/mol. This suggested that sulfathiazole has the ability to inhibit *S. aureus*. The attractive Vander waals and atomic contact energy (ACE) showed negative values. These suggested that sulfathiazole docked effectively with *S. aureus*. The molecular interactions (Figure 14b) showed that *S. aureus* formed hydrogen bonding with sulfathiazole using HOH 225(A) and HOH 291(A). Steric interaction between *S. aureus* and sulfathiazole were observed with Gln 80, Lys 116, Tyr 115 and Pro 117. The best ranking in Table 9 is solution 4 with global energy -23.56 Kcal/mol. This suggested that [Mn(SFTZ)] has the ability to inhibit *S. aureus*. The attractive Vander waals and atomic contact energy (ACE) showed negative values. These suggested that [Mn(SFTZ)] docked effectively with *S. aureus*. The molecular interactions (Figure 15b) show that *S. aureus* formed hydrogen bonding with [Mn(SFTZ)] using HOH 295(A), HOH 242(A) and Glu 52. Steric interaction between *S. aureus* and [Mn(SFTZ)] were observed with Pro 42, Lys 110, Tyr 41, Glu 43 and Glu 52.

4. Conclusion

Complex of manganese ion with sulfathiazole was successfully synthesized. The colour, IR, UV ¹H NMR spectra and x-ray powder diffraction suggested that new products were formed. This also shows that sulfathiazole can be used to remove toxic metals from the environment or from the biological system. This is because they can be complexed with sulfathiazole. Molecular docking study predicted the binding energies and interactions between the compounds and bacterial strains. It helped us to understand the mechanism of action of the proposed complex. A thorough investigation should be carried out to find out

whether the synthesized drugs can be safely used as a metal based anti-bacterial drug for the treatment of bacterial infections. We also recommend toxicology test for the complexes.

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References

- [1] G. M. H. Golzar, "Synthesis and characterisation of cobalt complex of sulfathiazole with acetic acid", *J. Saudi Chemical Society* **17** (2013) 253.
- [2] B. Sebastian, H. Estela, T. Marcela, R. Marcela, S. Emma, S. Mirna & M. Virtudes, "The interaction between mercury(II) and sulfathiazole", *Quim. Nova* **26** (2003) 2.
- [3] A. B. Corradi, E. Gozzoli, L. Menabue, M. Saladini, L. P. Battaglia & P. Sgarabotto, "Palladium(II) complexes of N-sulfonylamino acids. Part 1. Solid-state behaviour of binary and ternary 2,2'-bipyridine-containing systems", *J. Chemical. Society Dalton Trans* (1994) 273.
- [4] T. N. Drebuschak, E. V. Boldyreva & M. A. Mikhailenko, "Crystal structures of sulfathiazole polymorphs in the temperature range 100 K: A comparative analysis", *Journal of Structural Chemistry* **49** (2008) 84.
- [5] J. Casanova, G. Alzuet, S. Ferrer, J. Borrás, S. García-Granda & E. Perez-Carreno, "Synthesis and characterisation of cobalt complex of sulfathiazole with acetic acid", *Journal of Inorganic. Biochemistry* **51** (1993) 689.
- [6] F. Blasco, L. Perello, J. Latorre, J. Borrás & S. Garcia-Granda, "Cobalt(II), Nickel(II), and Copper(II) complexes of sulfanilamide derivatives: Synthesis, spectroscopic studies, and antibacterial activity, *Journal of Inorganic. Biochemistry* **61** (1996) 143.
- [7] C. Pieter, A. Bruijninx & P. J. Sadler, "New Trends for Metal Complexes with Anticancer Activity", *Curr. Opin. Chem. Biol* **12** (2) (2008) 197.
- [8] P. B. Tchounwou, C. G. Yedjou, A.K. Patolla & D. J. Sutton, "Heavy Metal Toxicity and the Environment", *Springer* **101** (2012) 133.
- [9] J. J. Silva & R. J. Williams, *The Biological Chemistry of the Elements, The Inorganic Chemistry of Life, (2nd ed.)* Oxford University Press, London (2001) 20.
- [10] C. Spinu, M. Pleniceanu & C. Tigae, "Biologically activetransition metal chelates with 2- thiophene carboxaldehyde- Derived Schiff base: Synthesis, characterization and antibacterial properties", *Turkish Journal of Chemistry* **32** (2008) 487.
- [11] B. K. Singh, H. K. Rajour & A. Prakash, "Synthesis, characterization and biological activity of transition metal complexes with Schiff bases derived from 2-nitrobenzaldehyde with glycine and methionine", *Spectrochimica Acta A* **94** (2012) 143.
- [12] V. Singh, N. K. Kaushik & R. Singh "Metallosulphadriugs: Synthesis and Bioactivity", *Asian Journal of Research in Chemistry* **4** (2011) 339.

- [13] G. Vellaiswamy & S. Ramaswamy, "Synthesis, spectral characterization and antimicrobial screening of Novel Schiff bases from sulfa drugs", *International Journal of Pharmacy and Pharmaceutical Sciences* **6** (2014) 487.
- [14] D. M. Boghaei & S. Mohebi, "Non-symmetrical tetradentate vanadyl Schiff base derived from 1, 2, phenylenediamine and 1,3- naphthalene diamine as catalysts for the oxidation of cyclohexene", *Tetrahedron* **58** (2002) 5357.
- [15] G. Valarmathy & R. Subbalakshmi, "Synthesis, spectral characterization of biologically active Novel Schiff base complexes derived from 2- sulphanilamidopyridine", *International Journal of Pharmaceutical and Biological Sciences* **4** (2013) 1019.
- [16] A. Budakoti, M. Abid & A. Azam, "Synthesis and antiamoebic activity of new 1-N- substituted thiocarbonyl- 3-5 diphenyl-2- pyrazoline derivatives and their Pd (II) complexes", *European Journal of Medicinal Chemistry* **41** (2006) 63.
- [17] V. X. Jin, S. I. Tan & J. D. Ranford, "Platinum (II) triammine antitumor complexes; structure- activity relationship with guanosine 5'- monophosphate (5' GMP)", *Inorganic Chimica Acta* **358** (2005) 677.
- [18] M. R. Caira, "Molecular complexes of sulfonamides. 2.1:1 complexes between drug molecules: Sulfadimidine-acetylsalicylic acid and sulfadimidine-4-aminosalicylic acid", *Journal of Chemical Crystallography* **22** (1992) 193.
- [19] R. M. Issa, S. A. Azim, A. M. Khedr & D. F. Draz, Synthesis, "Characterization, thermal and antimicrobial studies of binuclear metal complexes of Sulfa-guanidine Schiff bases", *Journal of Coordination Chemistry* **62** (2009) 1859.
- [20] G. H. Jeffery, J. Bassett & R. C. Denney, *Vogel's Text book of Quantitative Chemical Analysis (5th Ed.)*, Pearson Education Publisher, Singapore, (1989) 473
- [21] H. Julia, N. Bormio, E. F. P. Raphael, C. Alexandre, R. L. Wilton & P. C. Pedro, "Silver complexes with sulfathiazole and sulfamethoxazole: synthesis, spectroscopic characterization, crystal structure and antibacterial assays", *Polyhedron*, **85** (2015) 437.
- [22] R. M. A. Knegtel, I. D. Kuntz & C. M. Oshiro, "Molecular docking to ensembles of protein structures", *Journal of Molecular Biology* **266** (1997) 424.
- [23] O. V. Ikpeazu, K. K. Igwe, & I. E. Otuokere, "In Silico Structure-Activity Relationship and Virtual Screening of Monosubstituted Doxycycline with *Pseudomonas Aeruginosa* Lipase", *IJAEMS* (2017) 233.
- [24] N. Andrusier, R. Nussinov & H. J. Wolfson, "FireDock: Fast interaction refinement in molecular docking", *Proteins*, **69** (2007) 139.
- [25] E. Mashlach, D. Schneidman-Duhovny, N. Andrusier, R. Nussinov, H. J. Wolfson, "FireDock: a web server for fast interaction refinement in molecular docking", *Nucleic Acids Res.*, **36** (2008) 29.
- [26] M. Zacharias "Accounting for conformational changes during protein-protein docking", *Current Opin Structural Biology* **20** (2010) 180.