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Synthesis, Characterization and Antibacterial Studies of Fe(II) and Mn(II) Complexes of 2-[({4-[(1,3-thiazol-2-ylamino)sulfonyl]phenyl}amino)carbonyl]benzoicacid

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Abstract

2-[({4-[(1,3-thiazol-2-ylamino)sulfonyl]phenyl}amino)carbonyl] benzoicacid commonly known as phthalylsulfathiazole, belongs to the group of drugs called sulfonamides. The drug is a broad spectrum antimicrobial that can treat different types of infections including intestinal infections. The drug is indicated in treatment of dysentery, colitis, gastroenteritis and intestinal surgery. Fe(II) and Mn(II) complexes of this drug have been synthesized. The melting point, solubility, colour and yield were determined. The metal complexes were characterized based on electonic and infrared spectroscopy. Electronic spectrum of the phthalylsulfathiazole showed intraligand charge transfer transition (ILCT). The electronic spectra of the metal complexes showed intraligand charge transfer transition (ILCT), ligand to metal charge transfer (LMCT) and d-d transition. Infrared spectra studies suugested coordination through the C-O, OH and C=N functionalities in Fe(II) complex. Suggested coordination in Mn(II) complex was through C-O and OH. Metal:ligand ratio for Fe(II) and Mn(II) complexes were 1:2 and 1:1 respectively. Phthalylsulfathiazole showed no inhibitory activity against *Escherichia coli and Stapylococcus aureus*. Inhibition was observed in iron and manganese complexes. Iron showed the highest inhibition zone diameter and minimum inhibition concentration against *Stapylococcus aureus* at 20.67±0.58mm and 1.56±3.61 mg/ml respectively. Manganese complex showed higher inhibition zone diameter and minimum inhibition concentration against *Escherichia coli* at 20.00±0.00 mm and 12.83±0.29 mg/ml respectively. These showed that both metal ions were able to introduce a new feature into the drug.
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***Keywords**: Phthalylsulfathiazole, infrared, electronic, spectra, antibacterial.*

1. Introduction

The Applications and pharmacological applications of metal complexes are of increasing clinical and commercial importance. Literature publications testify to the growing importance of the discipline [1–11]. Relevant reviews have been published, for example Metal Ions in Biological Systems [12] and Coordination Chemistry Reviews [13]. Lists of clinically used complexing agents may be found in most pharmacopoeia [14] while new coordination compounds continue to be sought [14,15]. The use of complexing agents in the treatment of Wilson's disease is a good example of how excess (CuII) toxicity may be ameliorated by chelating agents [16]. The application of chelating agents in medicine may even be traced to a collaboration research between Werner (the father of coordination chemistry) and Ehrlich (the father of chemotherapy) to find less toxic complexes to replace arsenic compounds for the treatment of syphilis [14]. An interesting aspect of the role of metal complexes in medicine is the role of nitroprusside ion conplex [17,18]. The nitroprusside ion, $[Fe(NO)(CN)_5]^{2-}$ is a vasodilator used in emergency situations to treat hypertensive patients in operating theaters [19,20]. The complex is 30–100 times more potent than simple nitrites. The toxicology of metal complexes in biological use, especially those containing the heavy metals, confronts the ''stigma'' of heavy metal toxicity; but therapeutic windows are rigorously defined to minimize such side effects—the usefulness of any drug is a balance between its activity and toxicity [21]. Transition metals complexes offer advantages over the more common organic – based drugs, because the transition metal ion provide an alternative route in the drug receptor mechanism. Medicinal Inorganic chemistry is a thriving area of research [22], which was initially fueled by the discovering of the metallopharmaceutical cisplatin about 45 years ago. Several years after the approval of cisplatin as a chemotherapeutic agent, it is still one of the world's best-selling anticancer drugs [22].

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2-[({4-[(1,3-thiazol-2-ylamino)sulfonyl]phenyl}amino)carbonyl]benzoic acid (phthalylsulfathiaz ole) belongs to the group of drugs called sulfonamides [23]. The drug is a broad spectrum antimicrobial that can treat different types of intestinal infections [23]. The mechanism of action depends is based on competitive antagonism with para-aminobenzoic acid and inhibition of dihydropteroate synthetase activity, that in turn leads to impaired synthesis of dihydrofolic acid and as a result its active metabolite that is necessary for the synthesis of purine and pyrimidine [23]. The drug is indicated in treatment of dysentery, colitis, gastroenteritis and intestinal surgery [23]. Adverse effects may include allergic reactions, vitamin B insufficiency, agranulocytosis and aplastic anemia[23]. The structure of 2-[({4-[(1,3-thiazol-2-ylamino)sulfonyl]phenyl}amino) carbonyl]benzoic acid (phthalylsulfathiazole) is shown in Figure 1 .

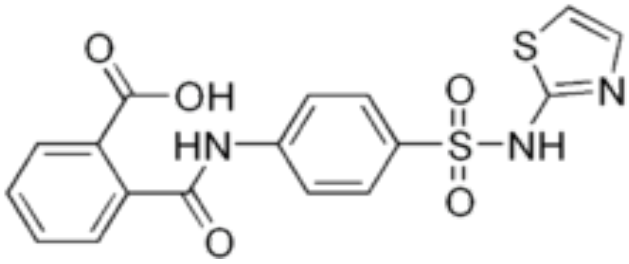

Figure 1: Structure of 2-[({4-[(1,3-thiazol-2-ylamino)sulfonyl]phenyl}amino)carbonyl]benzoic acid (phthalylsulfathiazole)

Due to the biological importance of this drug, we have decided to synthesize, characterize and determine the antibacterial activity of its iron and manganese complexes

2. Materials and Methods

2.1 All reagent used were of analytical grade. Phthalylsulfathiazole was purchased from, Fe(II) chloride and Manganese (II) chloride were purchased fron BDH Chemical Ltd Poole England. UV-visible 2500PC Series Spectrophotometer was used for electronic studies while SHIMADZU FTIR-8400S Fourier Transform Infrared Spectrophotometer was employed for the functional group studies.

2.2 Synthesis of Iron (II) phthalylsulfathiazole complex: methanolic solution (50ml) of phthalylsulfathiazole (8.06g) was prepared. Methanolic solution (50ml) of iron compound (2.54g) was added to the phthalylsulfathiazole solution and stirred gently for 45 minutes, the mixture was refluxed for 4 hours. The precipitate was dried in a desiccator and the yield was recorded.

2.3 Synthesis of Manganese (II) phthalylsulfathiazole complex: methanolic solution of (50ml) of phthalylsulfathiazole (8.06g) was prepared. Methanolic solution (50ml) of manganese compound(3.96g) was added to the phthalylsulfathiazole solution and stirred gently for 45 minutes, the mixture was refluxed for 4 hours. The precipitate was dried in a desiccator and the yield was recorded.

2.4 Stoichiometric determination: Metal: ligand ratio was determine using Job's method of continuous variation method[24]

2.5 Media preparation: The media used for the antimicrobial sensitivity testing was Muller Hinton agar. It was prepared by weighing out 38g of the powered agar into 100ml of distilled water in a conical flask. This was sterilized in an autoclave at 121^{o} C for 15 minutes, after autoclave, the media was poured into sterile petri dish and allowed to gel (cool).

2.6 Determination of antimicrobial activity.The organisms used are Escherichia coli ((2 strains) from the family of Enterobactriaceae and Staphylococcus aureus (2 strains) from the family of bacillales gotten from stock culture in microbiology lab was inoculated into the already prepared Muller Hinton agar. Using a cork borer, well (7mm in diameter and 2.5mm deep) was bored into the inoculated agar and 50µl of each of the complex at a concentration of 1g/ml was delivered into the wells. The plates were incubated and read after 18 -24 hours. The diameter zone of inhibition produced by the complexes were measured with a transparent meter rule in mm

2.7 Determination of minimum Inhibitory Concentration (MIC) : The minimum inhibitory concentration (MIC) is the lowest concentration of antimicrobial extract that can be able to inhibit the visible growth of a microorganism after overnight incubation. To determine the MIC 0.95 mL of Mueller Hinton Broth was transferred into 9 test tubes.1ml of the complex at 50mg/ml was pipetted into the first tube and properly mixed.1ml was taken from the first test tube into the second test tube and mixed. This was continued up to the 7th tube to give concentrations of 50, 25, 12.5, 6.25, 3.12 and 0.78mg/ml. The 8th tube was labeled the organism control which contained only the organisms and Mueller Hinton Broth but no complex. The 9th tube was labeled antibiotic control which contained the organism, Mueller Hinton Broth and antibiotic. 0.05ml (50ul) of the organism suspension was transferred into each test tube using a micropipette. The tubes were incubated and result read

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after 18-24 hours. The MIC was the tube that prevented visible growth of the organism after the period of incubation.

3. Results and Discussion

Physical data of the ligand and complexes are shown in Table 1. The solubility data is shown in Table 2. Inhibition zone diameter (IZD) (mm) of the ligand and complexes are shown in Table 3. Minimum inhibition concentration (mg/ml) for the ligand and complexes against the bacterial strains are presented in Table 4. Figures 2 – 7 shows the FTIR and electronic spectra of the ligand and complexes.

Table 1: Physical data for the ligand and complexes.

Properties	L	[FeL_2]	[MnL]
Appearance	Solid	Solid	Solid
Melting point (^oC)	272-277	283-285	310-312
Color	White	Brown	Pinkish
Yield (%)	-	55	90

L = Phthalylsulfathiazole

Table 2: Solubility data for the ligand and metal complexes

Compound	C_6H_{14}	C_2H_5OH	**H_2O**	$CHCl_3$	DMSO
L	IS	SS	SS	IS	S
[FeL_2]	IS	SS	SS	IS	S
[MnL]	IS	SS	SS	IS	S

IS = insoluble, SS = sparingly soluble, S = soluble, L = Phthalylsulfathiazole,

Table 3: Inhibition zone diameter (IZD) (mm) of the ligand and complexes

Bacteria strains	L	[MnL]	[FeL_2]
Escherichia coli	0.00 ± 0.00	20.00±0.00	14.00±1.73
Stapylococcus aureus	0.00 ± 0.00	1.56±1.35	20.67±0.58

L = Phthalylsulfathiazole

Table 4: Minimum inhibition concentration (mg/ml) for the ligand and complexes against the bacterial strains

Bacteria strains	L	[MnL]	[FeL_2]
Escherichia coli	0.00 ± 0.00	12.83±0.29	8.33±3.61
Stapylococcus aureus	0.00 ± 0.00	16.67±7.21	1.56±3.61

L = Phthalylsulfathiazole

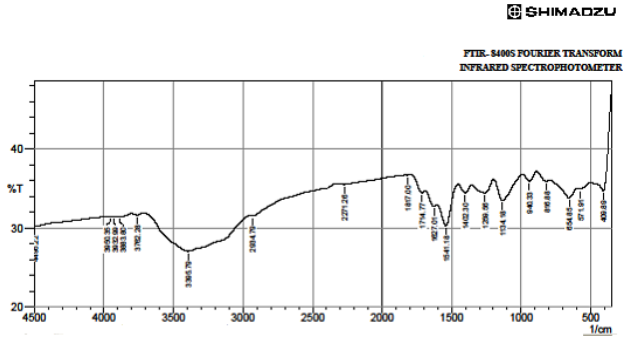

Figure 2: FTIR spectrum of *phthalylsulfathiazole*

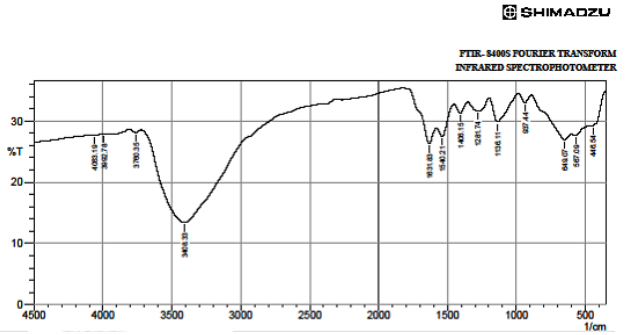

Figure 3: FTIR spectrum of Iron(II)*phthalylsulfathiazole* complex

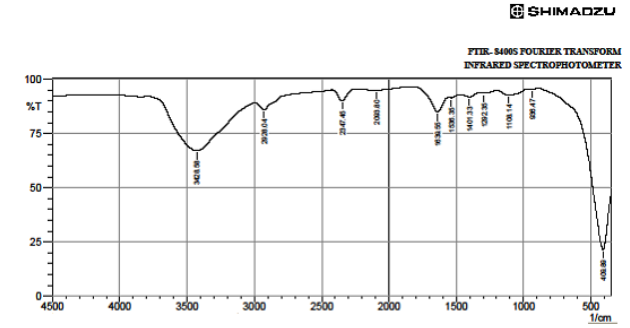

Figure 4: FTIR spectrum of manganese(II)*phthalylsulf athiazole* complex

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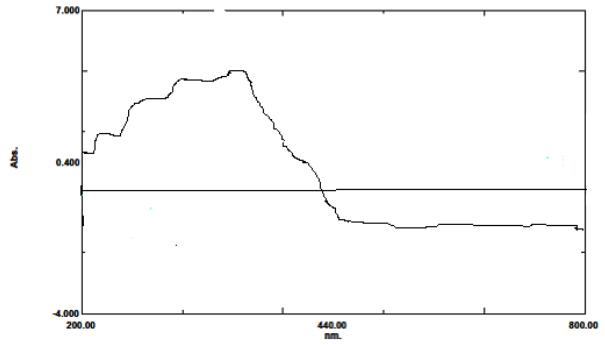

Figure 5: UV-visible of phthalylsulfathiazole

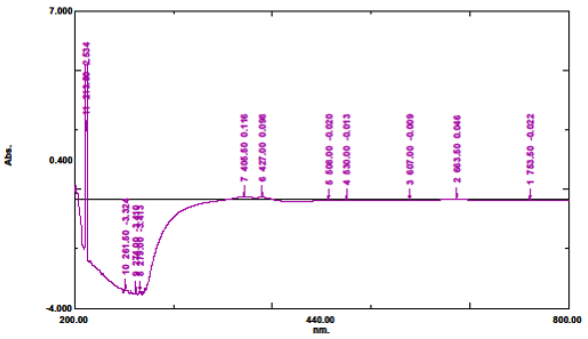

Figure 6: UV-visible of iron(II) phthalylsulfathiazole complex

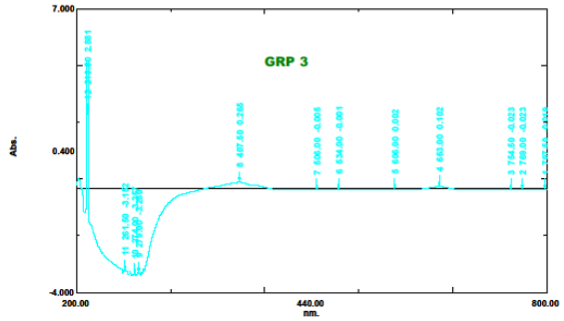

Figure 7: UV-visible of manganese c(II) *phthalylsulfa thiazole* complex

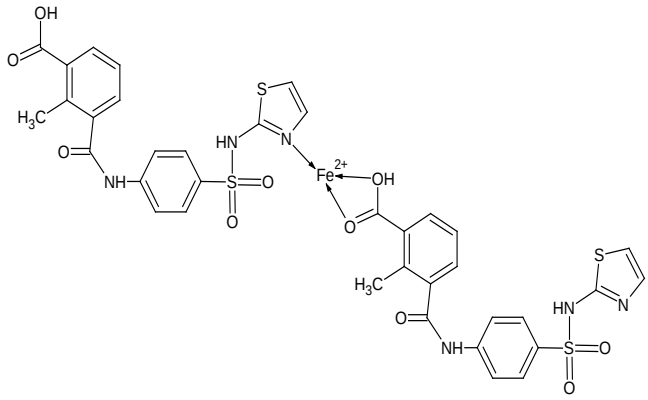

Figure 8. Suggested structure for iron (II) phthalylsulfa thiazole complex

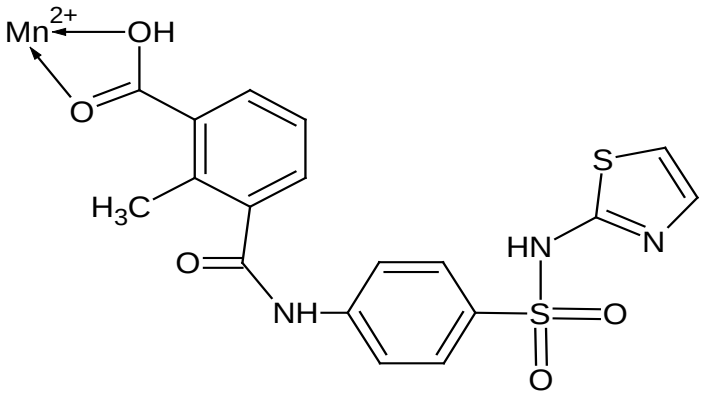

Figure 9. Suggested structure for manganese(II) phthalylsulfathiazole complex

3.2. Product Color : The color of Iron complex is brownish while that of manganese complex is pinkish. The change in color indicates complexation, since transition metals are colored compounds. (Nicholls, 1973)

3.3. Melting Point: The melting point of thalazole is within the range of 272 - 277^{o}C, the melting point of Iron complex is 283 - 285^{o}C while that of manganese complex is 310 - 312^{o}C. This increase in melting point is an indication that complexation occurred.

3.4 The infrared spectrum of phthalylsulfathiazole was compared with the spectra of the metal complexes. The infrared spectra of the ligand and metal complexes are showed in Figures 2,3 and 4 respwctively. The C-O stretch of ligand was found to be 1259.56cm^{-1} .The C-O vibrational frequency shifted in the metal complexes (1281.74cm^{-1} in Mn and 1292.35cm^{-1} in Fe). These shifts suggest the involvement of C-O in coordination which is as a result of decrease in electron density which decreases

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the C-O bond length and consequently increased in vibrational frequency. In the infrared spectrum of the ligand the O-H stretch of carboxylic acid was found to be 3395.79cm^{-1} .In the spectra of the metal complexes the O-H vibrational frequency shifted up field in both complexes, (3408.33cm^{-1} in Mn and 3428.58cm^{-1} in Fe complex). These shifts suggest the involvement of O-H group of thalazole in complexation. The C=N vibrational frequency appeared at 1627.01cm^{-1} for the ligand, there was no significant shift in Mn complex but in Fe complex there was a shift. It shifted to 1639.55cm^{-1} suggesting the involvement of C=N in coordination with iron.

3.5 In the electronic spectrum of the ligand (Figure 5), the λ maximum was found at 365 nm. This band has been assigned intraligand charge transfer transition (ILCT). This π— π* transition transition could be as a result of the chromophore in the ligand. The chromophore are S═O, C═O, C═C, C═N. There was no positive transition in the visible region i.e 400 - 800nm. In the metal complexes three types of transition has been assigned, the first is intraligand charge transfer transition, the second is ligand to metal charge transfer (LMCT) and the third is d-d transition confirming the coordination of metal with the ligand. In manganese complex, λ maximum was observed in the region of 213.50, 407.50, 663.00 (nm) and this bands were assigned ILCT, LMCT and d – d transition respectively. In iron complex, λ maximum was observed in the region of 213.50, 405.50 and 663.50 (nm) and these bands were assigned ILCT, LMCT and d – d transition respectively.

3.6 Stoichiometric ratio base on Jobs method of continous varation [24] showed that the Metal:ligand ratio for Fe(II) and Mn(II) complexes were 1:2 and 1:1 respectively.

Based on the electronic and infrared characterization, the following structures (Figures 8 and 9) have been suggested for the metal complexes.

Phthalylsulfathiazole showed no inhibitory activity against *Escherichia coli and Stapylococcus aureus* (Table 3). Inhibition was observed in iron and manganese complexes. Iron showed the highest inhibition zone diameter and minimum inhibition concentration against *Stapylococcus aureus* at 20.67±0.58mm and 1.56±3.61 mg/ml respectively. Manganese complex showed higher inhibition zone diameter and minimum inhibition concentration against *Escherichia coli* at 20.00±0.00 mm and 12.83±0.29 mg/ml respectively. These showed that both metal ions were able to introduce a new feature into the drug.

4.0 Conclusion

With respect to the FT-IR spectra, electronic characterization, stoichiometric determination, solubility, and melting point a tentative structure was proposed for the complexes. The ability of phthalylsulfathiazole to coordinate Fe(II) and Mn(II) has been assured. A new antibacterial feature was also introduced into the drug due to coordination with the Mn(II) and Fe(II) in the complexes. The complexes were more potent than phthalylsulfathiazole.

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