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DESIGN, SYNTHESIS, AND METAL COORDINATION BEHAVIOR OF 2-(4-METHYLPHENOXYMETHYL) BENZOIC ACID

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Abstract

A series of phenoxymethylbenzoic acid derivatives were synthesized through the reaction of p-cresol with phthalide. The resulting phenoxymethylbenzoic acid was subsequently converted into its corresponding acid chloride using cyanuric chloride. These phenoxymethylbenzoyl chlorides were then reacted with various aminobenzenesulfonamides to yield a new set of sulfonamide derivatives.

The synthesized sulfonamides were structurally characterized using modern spectroscopic techniques, including UV–Visible and FT-IR spectroscopy. The presence of a characteristic absorption band around 3400 cm⁻¹ confirmed the existence of the amide functionality, while a broad peak near 1250 cm⁻¹ indicated the presence of the sulfone group within the molecular structure.

1. INTRODUCTION

Cresols are derivatives of Sulfonamides. The molecules having a methyl group substituted onto the phenol ring are called Cresols. Sulfonamides are important function groups (-SO2-NH2) and the basic constituent of several groups of sulfa drugs (RSO2NH3). Sulfa drugs are important compounds in the pharmaceutical industry as they are a family of broad-spectrum antibiotics. 4-Aminobenzenenesulfonamide derivatives are one of the large groups of organ sulfur compounds and structure analogs of p-amino benzoic acid (PABA). The derivatives of 4- 4-amino benzene sulfonamide having a wide range of clinical applications are called sulfa drugs. In their basic chemical structure, these compounds contain the RSO2NH2 group. They are used against many microorganisms including bacteria, some fungi, and protozoa. In the treatment of urinary tract infections sulfa drugs are primarily used, they are also frequently used in combination with Trimethoprim for the treatment of antibiotics, bronchitis, sinusitis, and pneumocystis carinii pneumonia.[1] Some examples of sulfonamide-based sulfa drugs that are in clinical use are sulfadiazine (1), Sulfadimidine (2), sulfamethoxazole (3), salfamethopyrazine (4), sulfadoxine (5), sulfasalazine (6), (Fig.3) where (1) and (2) are short-acting drugs, (3) is intermediate-acting, (4) and (5) Are long-acting drugs and (6) is a drug which absorbs poorly in the gastrointestinal tract and (3) is a drug which is given with Trimethoprim and the combination is collectively called co-trimoxazole which is used against pneumocystis carinii.[2]

Sulfa drugs are broad-spectrum antibiotics, and they are classified into different groups based on the rapidity with which they are absorbed and based on their uses and duration of action.[3] These are the group of sulfa drugs that show their action in a short interval of time as compared to other sulfa drugs. They act for 4-8 hours and include (1), Sulfisoxazole (7), sulfaamerazine (8), Sulfisomidine (9), and (2).4 These are the group of sulfa drugs which show intermediate action for 8-12 hours and

include (3), sulfaphenazole (10).1 These are the group of sulfa drugs that show their action for a long time i.e. for 7 days which include (5), sulfamethoxypyridazine (11), and sulfadimethoxine (12).4 Drugs that are absorbed and excreted rapidly include (6), (3), and (1).2 Some sulfonamides are poorly absorbed but active in the bowel of humans and are included in (6).1 Some sulfa drugs are used topically. This class includes sulfaacetamide (13) and silver sulfadiazine (14).5 Sulfa Drugs are broad antibiotics that show their activity against different species of bacteria, fungi, and some protozoan. Sulfa drugs are very effective against different species of (bacteria) Streptococcus, Escherichia coli, and Actimyces.6Mechanism of Action

4-Aminobenzenesulfonamides are the structural analogues of amino benzoic acid (PABA). To synthesize folic acid in bacteria PABA is very essential. Folate is required for the synthesis of nucleic acids as it is the precursor of DNA and RNA in both bacteria and mammals. Still, mammals obtain their folic acid from their diet whereas bacteria need to synthesize it. Folic acid is reduced to tetrahydrofolate, and 4- aminobenzene sulfonamide derivative inhibits the enzyme dihydropteroate synthetase (DHPS) responsible for the formation of folic acid. They are competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS).

If the tetrahydrofolate is no longer synthesized, the biosynthesis of thymine is disrupted. Thus, the biosynthesis of nucleic acid is inhibited. The main function of sulfonamide is to inhibit the growth of the bacteria, i.e. they are bacteriostatic rather than bactericidal, and prevent the bacterial cells from dividing and multiplying. The body's defense system then wipes out the bacteria.[7]

These drugs are also active against the causative agents of some of the infections, such as shigellosis salmonellosis and meningococcal meningitis.[8] There is some evidence that this drug is more effective than soluble sulfonamides or other antimicrobial agents.[9] Bacillary dysentery and sexually transmitted diseases can be treated by using sulfa drugs and sometimes by using malaria and toxoplasmosis a combination of 4- amino benzene sulfonamide and Trimethoprim is widely used.[11,12]

Borras et al (1999) [17] synthesized a series of new derivatives of water-soluble sulfonyl chloride. Supuran et al (2000) [13] synthesized derivatives of aromatic and heterocyclic sulfonamide are reacted with trisubstituted pyridinium methiocarb moieties, and then their substitution was done with amino, amino hydrazine, and the hydroxyl group of these compounds. Scozzafava et al (2000) [14] synthesized various new derivatives of sulfonamides by reaction 0 or p-hydroxybenzaldehyde's with sulfanilamide s and homosulfonamide p-(2- aminoethyl) benzene sulfonamides and the new derivatives were subsequently reacted and derivative at the hydroxyl phenol moiety by reacting with aryl sulfonyl isocyanates. Supuran et al (2001) [15] synthesized novel sulfonamides by reaction of aromatic or heterocyclic sulfonamides, with N, N-dialkylditkldithiocarbamates in the presence of sodium hypochlorite or iodine. Scozzafava et al (2000) [14] synthesized various new derivatives of sulfonamides by reacting o or p-hydroxybenzaldehyde with sulfonamide and homosulfanilamide p- (2-aminoethyl) benzene sulfonamides and the new derivatives were subsequently reacted and derivatized at the hydroxyl phenolic moiety by reacting with arylsulfonylisocyanates. Supuran et al (2001) [15] synthesized novel sulfonamides by reacting aromatic or heterocyclic sulfonamides, with N, N-dialkyl dithiocarbamates in the presence of sodium hypochlorite or iodine. Arslan et al (2002) [16] synthesized 4 new derivatives of aromatic sulfonamides by reacting 4-carboxy benzene-sulfonamide with triethleneglycol and 1,2-bis (aminooxy)ethane to produce 1,2 – bis [(4-sulfonamide benzamide) ethoxy]ethane. Daniela et al (2003) [17] synthesized many derivatives of aromatic and heterocyclic sulfonamide and investigated their activity against tumor-associated transmembrane carbonic anhydrase IX. Wilkinson et al (2007) 18 synthesized a series of benzene sulfonamides having triazole-o-glycoside-tails. Bulbul et al (2008) 19 synthesized pyrazole carboxylic acid amides of 5-amino-1, 3,4-thiadiazole-2-sulfonamide by reacting 4-benzoyl- 1,5-diphenyl-1 H-Pyrazole-3-carbonyl chloride and 4-benzoyl-1-(-3-nitrophenyl)-5-phenyl-1H-pyrazol-3-carbonyl chloride with aminobenzene sulfonamide. Kasimogullari et al (2009) 20 synthesized pyrazole carboxylic acid amides of 5- amino-1,3,4-thiadiazole-2- sulfonamide from 4-benzoyl-l-(4-nitrophenyl)-5-

phenyl-1H-pyrazole-3-carbonyl chloride and 4-benzoyl- 1-(3-nitrophenyl)-5-phenyl-1H-pyrazole-3-carbonyl chloride compound. Nadeem et al (2009) 21 synthesized 2-(2-Iodobenzenzenesulfonamido) acetate by the reaction of a benzene sulfonyl chloride with glycine methyl ester hydrochloride. Kasimogullari et al (2011) 22 synthesized many derivatives of sulfonamides by the reaction of 4-benzoyl-1-(4-nitrophenyl)-5-phenyl-1-H-pyrazole-3-carbonyl chloride with 5-amino-1,3,4-thiadiazole-2-sulphonamide. Gitto et al (2012) 23 synthesized a series of aryl sulfonamides, and their structural characterization was carried out through spectral analysis like IR, H- NMR, (13) Crerand MS. Alafeefy et al (2013) 24 synthesized a series of benzenesulfonamides introduction cyanoacrylate moieties (tyrphostin analogs).

MATERIALS AND METHODS

1.1 Materials Required

Distilled water, round bottom flask (500mL), separating funnel, reflex beakers (250mL,500mL), hot plate, magnetic stirrer, funnel, spatula, pH paper, aminobenzene sulfonamide (E. Merck), para-cresol(E.Merck), aminomethylbenzenesulfonamide (E.Merck), methanol, ethanol (E.Merck), xylene (E.Merck), acetone (E.Merck), DMF (E.Merck), triethylamine TEA (E.Merck), phthalid (E.Merck), cyanuric chloride (E.Merck), para-nitro phenol (E.Merck), KOH (E.Merck).

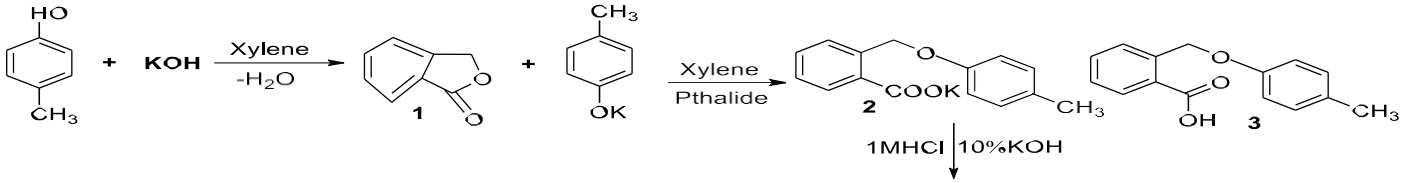
1.2 SYNTHESIS OF PARA-CRESOL DERIVATIVE

1.2.1. Step 1: Synthesis of 2 (4-methyl-phenoxy methyl) benzoic acid

A solution having 0.05 Mol (5.4 g) of freshly Distilled Para-Cresol in 30 ml xylene in a Round Bottom Flask. Then 0.055 mol (2.5 g) of KOH - Solution. The reaction mixture was refluxed for 30 min at temp 60-70 °C. The Para-Cresolate layer is formed at the bottom of the round bottom flask.

In the next step 0.05 mol (6.7g) of phthalide was added to the mixture and the reaction for 3 her with constant Stirring at a temperature of 150-200°C. Monitored the reaction through the TLC [ethyl acetate: ethanol 1:3]. The bottom layer now becomes more prominent (the color becomes dark brown). Stop the reaction and separate the transparent upper layer (xylene solvent) by using the separating funnel.

Then 50 ml of 10% KOH-solution in the lower dark layer. Then the mixture with 1 M HCl until the mixture becomes acidic (pH 3). The precipitate of the corresponding acid formed immediately in the solution. Filter out the product by using filter paper (To increase the yield of the product keep the solution overnight and then filter it out). The crude product is recrystallized by using ethanol.



Scheme 1. The synthesis of 2-(4-methyl-phenoxymethyl) benzoic acid

2.2.2 Step 2: Synthesis of 2 (4-Mathyl-Phenoxymethyl) benzoyl chlorides

Take 0.01mol (1.845g) cyanuric chloride (c.c) in 15 ml acetone and 5 ml DMF (dimethyl furan) in a round bottom flask a clear solution formed then added 0.02mole (4.8452g) of 2 (4-Mathyl-Phenoxymethyl) benzoic acid and stirred the solution for 10 min until a clear solution formed. Then add 0.02 mol (2.02g) of triethyl amine TEA in the reacting mixture. Reflux the brownish color clear mixture for 3 hr. at 50-60 °C. Stop the reaction when no c.c remains in the reacting mixture monitor this with the help of TLC [ethyl acetate: methanol 3:1] acetone and DMF remove by reducing the pressure. 20 ml of water was added, and the acid chloride was precipitated out in the aq. Medium. Filter out the precipitate by using filter paper. Wash the precipitate with CCl 4 to remove

the unreacted cyanuric chloride (c.c). Dichlorohydroxytriazine was the by-product obtained from the filtrate.

Scheme 2. Synthesis of 2 (4-Mathyl-Phenoxymethyl) benzoyl chlorides

After synthesizing 2 (4-Mathyl-Phenoxymethyl) benzoyl chlorides, we made metal coordinate complexes of Gd, Zn, Cu, Co, and Ni by reacting these metals with phenoxymethylbenzoic acid. Complexes were easily obtained with high yield by the procedure described in the experimental section. These compounds were successfully characterized by elemental analysis, solubility, melting point, electronic absorption spectrum, and Fourier transform inferred spectrum.

2. METAL COORDINATION COMPLEX

2.1 Synthesis of gadolinium complex

Take 0.05 mol (12.1g) of ligand (compound 3) and 0.025 mol (8.5g) of Gadolinium nitrate. Add sodium bicarbonate pinch by pinch in 30 ml of Ethanol: water (1:1) solvent and to make pH alkaline continuously stir the solution at a temperature of 50-60 °C for 1 hr. The precipitate of the complex is formed and then centrifuged the complex. The resulting precipitate is crystallized from acetonitrile.

2.2 Synthesis of zinc complex

Take 0.05 mol (12.1g) of ligand (compound 3) and 0.025 mol (5.4g) of zinc acetate dehydrate *[Zn (CH3COO)2].2H2O*. Add sodium bicarbonate pinch by pinch in 30 ml of Ethanol: water (1:1) solvent and to make PH alkaline continuously stir the solution at a temperature of 50-60 °C for 1 hr. The precipitate of the complex is formed so the complex. The resulting precipitate is crystallized from acetonitrile.

2.3 Synthesis of nickel complex

Take 0.05 mol (12.1g) of ligand (compound 3) and 0.025 mol (7.0g) of nickel sulfate [NiSO4.7H2O]. Add sodium bicarbonate NaHCO3 pinch by pinch in 30 ml of Ethanol: water (1:1) solvent and to make pH alkaline continuously stir the solution at a temperature 50-60 °C for 1 hr. The precipitate of the complex is formed and then centrifuged the complex. The resulting precipitate is crystallized from acetonitrile.

2.4 Synthesis of copper complex

Take 0.05 mol (12.1g) of ligand (compound 3) and 0.025 mol (5.9g) of copper chloride [CuCl2.6H2O]. Add sodium bicarbonate pinch by pinch in 30 ml of Ethanol: water (1:1) solvent and to make PH alkaline continuously stir the solution at a temperature of 50-60 °C for 1 hr. The precipitate of the complex is formed and then centrifuged the complex. The resulting precipitate is crystallized from acetonitrile.

2.5 Synthesis of cobalt complex

Take 0.05 mol (12.1g) of ligand (compound 3) and 0.025 mol (5.9g) of cobalt chloride CoCl2.6H2O. Add sodium bicarbonate NaHCO3 pinch by pinch in 30 ml of Ethanol: water (1:1) solvent and to make pH alkaline continuously stir the solution at a temperature 50-60 °C for 1 hr. The precipitate of the complex is formed and then centrifuged the complex. The resulting precipitate is crystallized from acetonitrile.

3. RESULT AND DISCUSSION

This research work was aimed at the synthesis of

the derivatives of different amino benzene sulfonamide and their characterization via, IR spectroscopic, UV-visible spectrometric, and elemental techniques and also synthesis of the metal co-ordinate complex with the phenoxymethylbenzoic acid. Following the conventional method, already reported in the literature [s]. The synthesis has been economized in terms of the time taken, conditions, and the reaction medium, they all are optimized in terms of the product's purity and overall yield of the product. The structural characterization of the synthesized compound was confirmed by the spectral data obtained from FTIR and UV-visible spectrometer.

3.1 PARA–CRESOL DERIVATIVE

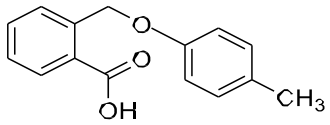
4.1.1 Synthesis of 2 (4-Methyl-Phenoxymethyl) benzoic acid

White color crystal, M.P 122.5 °C, 45% yield, soluble in ethanol, λ Max 240 cm $^{-1}$, carbon% 63.699(64.678), Hydrogen % 5.3806(5.01), carbonyl peak at 1745.56 cm^{-1}, -OH peak at 3143.71cm^{-1}, ether linkage peak at 1048.01cm^{-1}

3.2 Fourier Transformer Infrared spectrum: (FT IR)

Structural characterization was carried out using FT-IR spectroscopic techniques. The IR spectrum showed that the compound was synthesized successfully.

Figure 1.



The reported values of peaks of functional groups like O-H stretch at 3400-2400 cm^{-1}, C=O stretch at 1725- 1700 cm^{-1}, C-O-C stretch at 1300-1000. The IR spectrum of the given compound showed the functional group like –OH at 3143 cm^{-1}, carbonyl carbon peak of carboxylic acid at 1745 cm$^{-1,}$ and -O- peak at 1048 cm^{-1}.

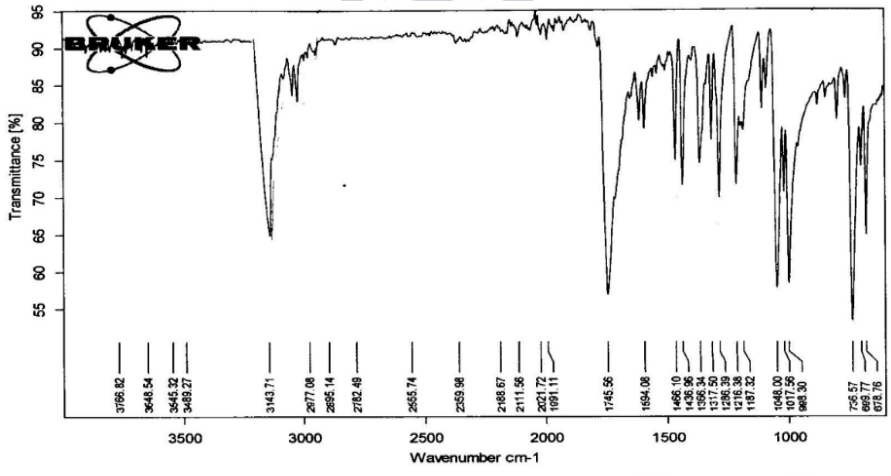


Figure 2. IR spectrum of 2-(4- methylphenoxmethyl benzoic acid).

3.3 General procedure for the synthesis of metal coordination complexes Table 1. Physical data of metal complex with compound

S #	Comp code	Expected molecular formula	Expected molecular formula	Color	Physical state	Melting point °C	% yield

1	Zn	C30H26O6Zn	547.9321	WHITE	SOLID	> 300	85
2	Gd	C45H43GdO11	917.06632	WHITE	SOLID	> 300	85
3	Cu	C30H30CuO8	582.1004	BLUE	SOLID	> 300	75
4	Ni	C30H30NiO8	577.24	PURPLE	SOLID	> 300	85
5	Co	C30H30CoO8	577.4875	GREEN	SOLIDE	> 300	75

Metal complexes with Gd, Zn, Cu, Co, and Ni were synthesized by reacting with phenoxymethylbenzoic acid in a 2:1 ratio by the mechanochemical method. The reaction is carried out in ethanol: water (1:1) by simple stirring at 70 °C temperature Gd and Zn complexes formed showed no color change and Cu, Co, Ni showed color change. During the complex formation hydrochloric acid HCl evolved which makes the solution acidic, so to make the environment alkaline the NaHCO3 is added into the reacting mixture. Complexes were easily obtained with high yield by the procedure described in the experimental section. These compounds were successfully characterized by elemental analysis, solubility, melting point, electronic absorption spectrum, and Fourier transform inferred spectrum. The new compounds were purified by recrystallization using methanol and acetonitrile.

4.3.1 Physical data of metal complexes

The physical data of the compound showed that the compound was synthesized successfully and as each compound has a melting point higher than 300 it showed that the compound was successfully synthesized. All compounds were synthesized with good yield. All are solid, having specific color and all complexes are insoluble in ethanol.

The summary of the physical data and characterization of the organic compounds is given below, Zn means Zinc formed complex with compound 3 [*2-(4- methylphenoxmethyl benzoic acid*.

3.4 Electronic Absorption Spectra of metal complexes

The UV-visible spectrum of metal displayed a sharp peak. The maximum absorption is shown by the different metal complexes (Gd, Zn, Co, Cu, Ni) in the given table no1. This absorption is due to π -π^* and n- π^* transition in the ligand. This indicates the presence of ligand moiety in the complex.

Zn^{+2} being a d^{10} system with electronic configuration $4s^0$ $3d^{10}$ does not involve d-d transition. Gd^{+3} belongs to the lanthanide series and f block. Mostly lanthanide showed a high co-donation number.

Table 2. UV-visible metal complex

S #	Compound code	λ Max (nm)
1	Zn	**290**
2	Gd	**290**
3	Cu	**440**
4	Ni	**245**
5	Co	**245**

3.5 Fourier TRANSFORMER INFRARED SPECTRUM OF METAL COMPLEXES

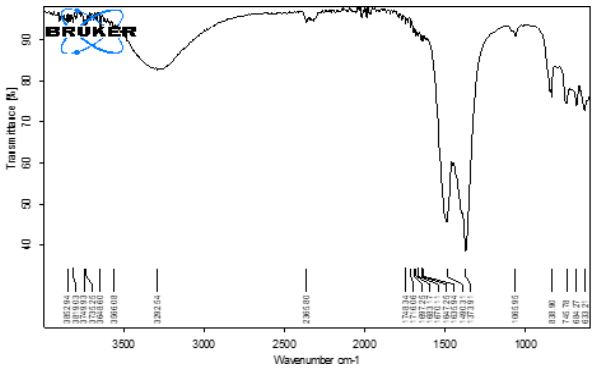


Figure 3. IR spectrum of Gd complex

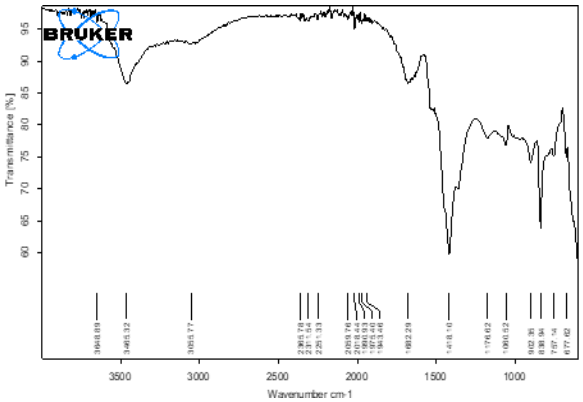


Figure 4. IR spectrum of Zn complex

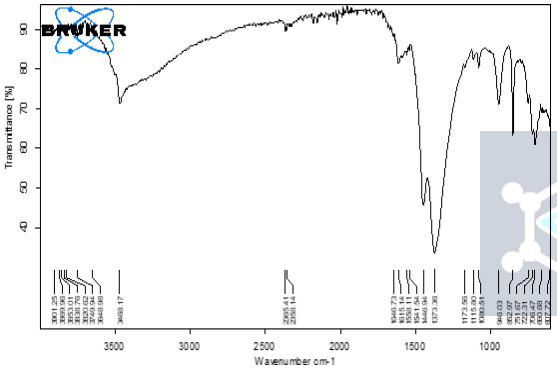


Figure 5. IR spectrum of co-complex

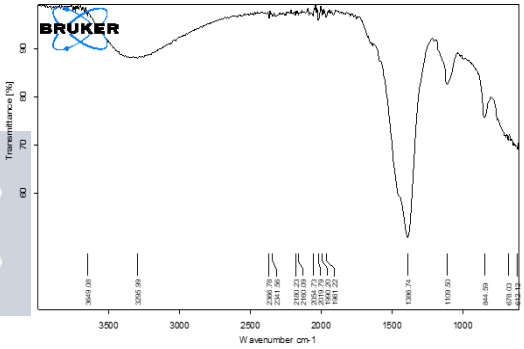


Figure 6. IR spectrum of Ni complex

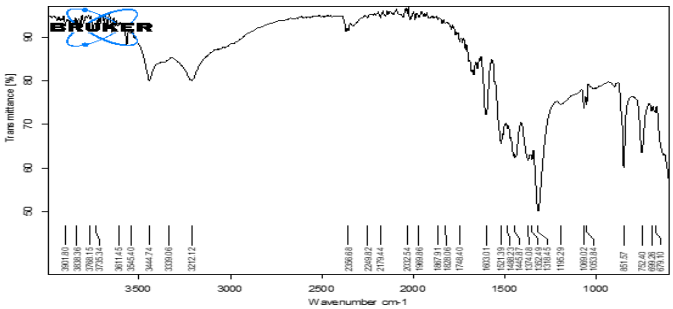


Figure 7. IR spectrum of Cu complex

4.5 THERMAL ANALYSIS OF METAL COMPLEXES (TGA/DSC)

4.5.1 TGA of Gd complex

The Thermogram of the Gd complex is shown in Fig. 2 the relevant data is presented in Table 1. The TGA curve showed two-stage decomposition with a weight loss of 12% at 150°C and 20 % weight loss at 550°C. This value corresponds to the calculated value of 11.3 % which correlated with the decomposition of two water and one nitro group. Thus, through TGA it was proved that 2 H_2O and NO_2 moieties coordinated with metal.

4.5.2 TGA of Zn complex

The Thermogram of the complex is shown in Fig. 3 and the relevant date is presented.

The TGA curve showed single-stage decomposition with a weight loss of 26% weight loss at 275°C. This value corresponds with the decomposition of ligands.

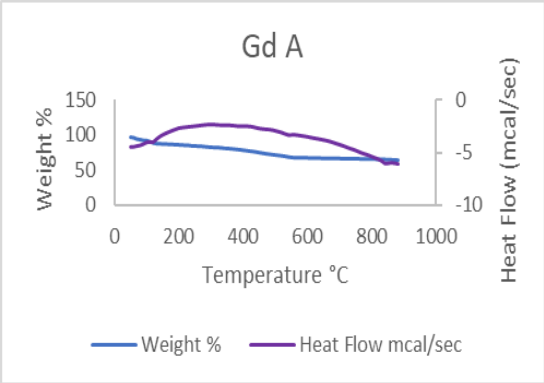


Figure 8. Thermogram of Gd complex

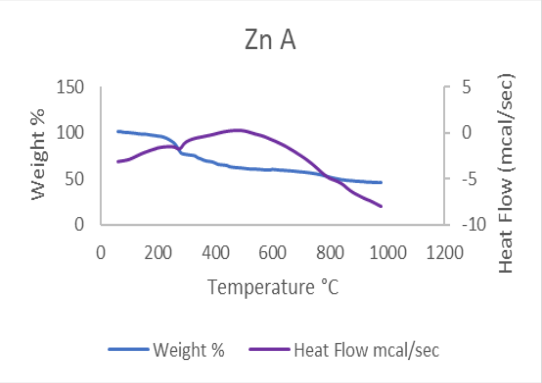


Figure 9. Thermogram of Zn complex

4. CONCLUSION

By reacting p-cresol with phthalide, several derivatives of phenoxymethylbenzoic acid were produced. The resultant phenoxymethyl benzoic acid reacted with cyanuric chloride to produce the equivalent acid chloride. After reacting with different aminobenzenesulfonamides, these phenoxymethyl benzoyl chlorides produced novel sulfonamide derivatives. C, H, and N elemental analysis as well as UV-visible and infrared spectroscopic data were used for structural characterization. Gd, Zn, Cu, Co, and Ni metal complexes were created by interacting with phenoxymethylbenzoic acid. High yields of complexes were achieved with ease. Elemental analysis, solubility, melting point, electronic absorption spectrum, and Fourier transform inferred spectrum were all used to successfully characterize these substances.

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