

# Metal Complexes of Heterocyclic Sulphonamide: Synthesis, Characterization and Biological Activity

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**Abstract:** The metal complex of heterocyclic sulphonamide with aminopyridine is a substantial class of pharmaceutical drugs used to treat infection, diabetes, anti-inflammatory issues and neurological disorders in the field of medicinal chemistry. The research reports the synthesis, characterization and biological activity of metal complexes of heterocyclic sulphonamide of aminopyridine. Sulphonamide of heterocyclic pyridine was synthesized by reacting 2-aminopyridine and tosyl chloride in an aqueous alkaline solution at ambient temperature. The iron (II) and copper (II) complexes of the ligand were also synthesized and recrystallized with suitable solvents, and the purity levels were ascertained with melting point and thin layer chromatographic pattern. Structural elucidation of the compounds was done via Nuclear Magnetic Resonance (NMR), Ultraviolet-Visible Spectroscopy (UV-VIS) Infrared (IR), Electrospray Ionization Mass Spectrometry (ESI-MS) Micro elemental analysis. Some absorption bands in the IR spectrum of heterocyclic sulphonamide derivatives were found to shift either to higher or lower wavenumbers in the complexes, indicating the involvement of azomethine nitrogen in coordination with the metal ion. The synthesized ligand and its metal complexes were screened for antimicrobial activity against Gram (-) *Escherichia coli*, Gram (-) *Salmonella typhi*, Gram (+) *Staphylococcus aureus*, *Aspergillus flavus*, *Aspergillus niger* and *Saccharomyces cerevisiae*. The ligand did not show activity against the selected bacterial and fungal strains whereas; some of the coordinated ligands gave a substantial improvement on their bactericidal and fungicidal activity. The complex of copper (II) was not bioactive to all the bacteria strains but sensitive to all the fungi strains. The complex of iron (II) was susceptible to the bacteria and fungi strains, except *Aspergillus flavus* that was inactive. When compared to Ciprofloxacin and Ketoconazole, with a broad-spectrum antibiotic, the standard antimicrobial agents were better in sensitivity than the synthesized compound.

**Keywords:** Biological Activity, Metal Complexes, Sulphonamide, Synthesis

## 1. Introduction

Bacteria and fungi resistance to common antimicrobial therapies has become a major public health concern in clinical settings. This worldwide medical challenge is associated with the shortage of effective drugs and the lack of successful prevention measures. The concept of multi-drug resistance with bacteria and fungi could sometimes be associated with the extensive use and abuse of classical antimicrobial agents [1-3].

Metal complexes are increasingly and commonly used as therapeutic compounds to treat several human diseases, such as infection, diabetes, anti-inflammatory issues and

neurological disorders. Significant interest in the synthesis of metal complex-based drugs is currently observed in medicinal organic chemistry to address unique research, therapeutic and diagnostic opportunities [4-6].

Metal complexes of sulphonamide derivatives have numerous applications including antibacterial, antifungal and other biological applications. Such complexes are used in clinical, analytical, and industrial sectors, as well as corrosion and catalysis [7-9]. On the other hand, many organic drugs, which possess modified pharmacological and toxicological properties administered in the form of metallic complexes, have the potential to act as ligands and the resulting metal-drug complexes are particularly important

both in coordination chemistry and biochemistry [5, 7], however, the study of metal–drug complexes is still in its early stages, thus representing a great challenge in current synthetic chemistry.

Sulphonamide nuclei containing pyridine based ligands have been reported in numerous biochemical reactions used to design and develop molecular systems of biological and medical importance. Sulpha drugs have attracted special attention for their therapeutic importance, as they were used against a wide spectrum of bacterial ailments and in the treatment of cancer, malaria, leprosy and tuberculosis [9-12].

Some of the sulphonamide derivatives used as ligands and drug are N-(salicylidene) sulphadiazine [10], ketene N,S-acetal-substituted sulphonamide [13], 4-(benzylideneamino)- and 4-(benzylamino)-benzenesulphonamide derivatives [14], 4-amino-N-(5-methyl-3-isoxazolyl)benzenesulphonamide [15], N-(quinolin-8-yl)-4-chloro-benzenesulphonamide [16], N-heterocyclic sulphonamide derivatives [17], alkyl-2-(4-(N-(substituted)sulphamoyl)phenyl)diazene-3-oxo-3-(2-henylhydrazinyl)propanoates [18], 2-substituted phenyl-2-oxo-, 2-hydroxyl- and 2-acyloxyethylsulfonamides [19].

Sulphonamide with heterocyclic aromatic core has been valued extremely in medicinal chemistry. This is on the basis that their antimicrobial activities have been established by researchers, thus, evident with most drugs sold on the market. It is on this credence, that the paper describes the coordination behaviour of sulphonamide derived from the action of toluenesulphonyl chloride on 4-aminopyridine towards some transition elements, which may help in more understanding of the mode of chelation of ligands towards metals (like copper (II) and iron (II) ions). The research further evaluates the biological activity of some microorganisms.

The choice of 4-aminopyridine ( $C_5H_6N_2$ ) and toluenesulphonyl chloride as a precursor is associated with essential functional moieties of the aromatic pyridine and benzene nucleus. In drug chemistry, both moieties are capable of eliciting electrophilic and nucleophilic reactions at different conditions. It is an important intermediate in the chemical industry, as well as in medicine manufacturing companies; owing to its usage in perfume, fragrances, dyes, pharmaceuticals, etc [11, 20]. It is also an important transformation in medicinal chemistry because of the production of a drug molecule having multifunctional moieties (such as pyridine ring, benzene nucleus and sulphonamide) with vast applications [4].

## 2. Materials and Methods

### 2.1. Equipment Used in This Study

The chemicals 2-aminopyridine, tosyl chloride ethanol, acetic acid, acetone, sodium trioxocarbonate (IV) and others were of analytical grade and were used without further purification. Thin-layer chromatography (TLC) was carried out using a Merck pre-coated silica gel plate (10x10 cm); the  $R_f$  value was obtained using a solvent mixture of acetic acid

and ethanol in a ratio of 1:2. The chromatogram was visualized using an ultraviolet lamp at 256nm. The melting point was recorded with Digital Melting Point Electrothermal IA9300X1. The IR spectra were obtained from the FTIR-8400S Fourier Transform Infrared spectrophotometer at NARICT Zaria using an ATR disc. It was used to identify the functional groups, Liquid Chromatography/Mass Spectrometer was used for molecular formula/mass identification, and Proton Nuclear Magnetic Resonance ( $^1H$ NMR) and Carbon-13 Nuclear Magnetic Resonance ( $^{13}C$ NMR) were recorded on a JEOL-400 MHz-NMR Spectrophotometer at the University of Strathclyde, United Kingdom.

### 2.2. Experimental Methods

#### 2.2.1. Synthesis of Heterocyclic Sulphonamide Derivative of Aminopyridine

The method adopted for the heterocyclic sulphonamide derivative of 2-aminopyridine was by Abdul Qadir *et al.*, [3] and Rehman *et al.*, [12] with minor modification. 2-aminopyridine (0.053mol, 5g) and sodium trioxocarbonate (IV) (1M, 20ml) were placed in distilled water (25ml) in a 250 mL round bottom flask and stirred vigorously for 15 minutes in a fume chamber. Thereafter, tosyl chloride (0.053mol, 10g) was gradually added to the mixture and stirred vigorously at room temperature for 4 hours. The end of the reaction was marked by the change of pH from alkaline to acidic range and a TLC analysis. The addition of few drops of concentrated HCl adjust the pH of the solution and led to the precipitation of the product which was washed severally with distilled water until it was acid-free and recrystallized with a mixed solvent system of ethanol and water at a ratio of 1:5. The resulting crystal was collected via filtration, washed with distilled water and dried (figure 1).

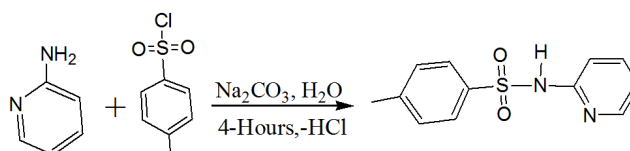


Figure 1. Synthesis of heterocyclic Sulphonamide.

#### 2.2.2. Complexation of Heterocyclic Sulphonamide Derivatives of 2-aminopyridine

The method adopted for the complexation of monotosylated 2-aminopyridine was by Orié *et al.*, [4] and Duru *et al.*, [5] with some modification. A hot ethanolic sulphonylated aminopyridine solution,  $C_{12}H_{12}N_2O_2S$  (2.0g, 806mmol) was placed in a boiled ethanolic solution of  $Cu(NO_3)_2 \cdot 6H_2O$  (1.19g, 404mmol), /  $Fe(NO_3)_3 \cdot 9H_2O$  (1.16g, 403mmol) in a 250 mL round bottom flask respectively. The mixture was stirred for 2 hours and allowed to stand for 2 hours. The precipitate formed was filtered and washed severally with ethanol. The products were recrystallized with a mixed solvent of DMSO and ethanol (1:6) and allowed to dry at room temperature (figure 2).

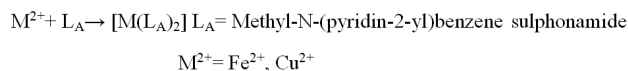


Figure 2. Complexation of heterocyclic sulphonamide.

### 2.2.3. Bacteria Sensitivity Test

The well in agar diffusion method (Mueller Hinton Agar test) used was by Andrews [21]. The medium was prepared according to the manufacturer's standard. The test organism used was refreshed by streaking on a freshly prepared nutrient agar medium for 24hr at 37°C, thereafter, suspended in nutrient broth overnight at 37°C, diluted using sterile water to match a 0.5 standard McFarland solution, seeded on Mueller Hinton Agar and allowed for a while for acclimatization. A cork-borer was sterilized by dipping in ethanol and passed through a Bunsen flame and used to create wells in the medium. Several dilutions of the bioactive compounds prepared with 50% dimethyl sulphoxide DMSO were introduced in the wells. The Petri dishes were incubated at 37°C for 18-24hr. Finally, the plates were observed, the diameter of the zone of inhibition around the well was measured in millimetres (mm).

### 2.2.4. Fungal Sensitivity Test

The well in Agar diffusion method with Dextrose Agar was used for this test. The medium was prepared according to the manufacturer's standard. The fungal isolates were refreshed on a freshly medium and incubated at room temperature for 120hr. The spores were harvested from a well-sporulated colony into a tube of sterile distilled water, introduced into the molten medium, gently agitated to homogenize, poured into sterile Petri dishes and allowed to solidify. Cork borer was used to create wells in the medium and several dilutions of the bioactive compounds prepared with dimethyl sulphoxide DMSO were introduced into the wells. All inoculated plates were incubated at room temperature for 5-7 days. Thereafter, plates were observed for the zone of inhibition around the wells.

### 2.2.5. Minimum Inhibitory Concentration (MIC) Screen

The method adopted was in line with Vedel [22]. This screening was done to determine the least concentration of the test agents that is capable of inhibiting the growth of each microbial test pathogen using the well-in-agar diffusion method. For each test pathogen that was screened, a cell concentration of  $10^8$  cells was first inoculated into Mueller Hinton agar plates, after which wells (5 mm diameter) were dug and filled (10  $\mu$ L) with the different concentrations of each of the test agents. The plates were then incubated for 12 - 24 hours at 37°C. After incubation, the observed zones of inhibition for each concentration of each test agent on each test pathogen were recorded. MIC concentration was then determined by looking out for that particular minimum concentration of the test agent that was capable of inhibiting the growth of a given test pathogen.

### 2.2.6. Antimicrobial Test Agent Preparation

Different concentrations (1000 mg/mL, 640 mg/mL, 320

mg/mL, 80 mg/mL and 40 mg/mL) of the antimicrobial test agents (both ligands and complexes) were prepared using serial dilution method with 50%v/v DMSO contained in different sterile test tubes and labelled appropriately.

## 3. Results and Discussions

### 3.1. Solubility Analysis of Ligand and Its Complexes

The solubility of the ligand and the complexes were conducted in eight different solvents. The ligand was insoluble in water, hexane, acetone and ethyl acetate, whereas soluble in DMSO, DMF, Acetic acid and ethanol. The complexes were soluble in DMSO, DMF, Acetic acid and ethanol whereas insoluble in water, hexane, acetone and ethyl acetate. This finding corroborates the investigation of [3, 4]. The solubility of the compounds synthesized in some solvents depicts the interaction between the hydrogen ion in the complexes and the oxygen atom in the solvents which indicates the formation of a hydrogen bond (4).

### 3.2. Physicochemical Analysis of Ligand and Complexes

The compounds shade colour ranging from offwhite, white and light blue for the ligand and the complexes of Fe (II) and Cu (II) respectively. The melting point of the compound that served as the ligand, 4-Methyl-N-(pyridin-2-yl)benzene sulphonamide was 180°-182°C, and their metal(II) complexes of Fe (II) and Cu (II) have the melting points of 265-267°C and 155-157°C. The sharp melting points indicate fairly pure isolated compounds. These values were consistent with the melting points analysis of amidine sulphonamides and benzene sulphonamides by Abdul Qadir *et al.*, [3] and the complexes of monotosylated 4-aminopyridine by Orie *et al.*, [4]. The molar conductance of the complexes was determined in DMSO (10<sup>-3</sup>M). It was found to be 13.2, 14.7 and 16.2  $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$  for the ligand, Fe (II) and Cu (II) complexes respectively. The values indicate the absence of anions outside the coordination sphere in all the complexes. Thus, suggest the non-electrolytic nature of the synthesized compounds [18, 19]. The synthesis of sulphonamide and its metal (II) complexes were successful based on a 50-80% yield [10]. The anticipated molecular weight of the ligand was estimated at 248.3 while the molecular ion peak of the ligand from the ESI-MS analysis was 249.1. The complexes have the molecular weight of 553.4 and 560.8 for iron (II) and copper (II) complexes respectively. The molecular mass obtained from ESI-MS analysis agreed with the anticipated proposed product and is confirmed by the FTIR and NMR analysis structural elucidation.

### 3.3. Elemental Analysis of the

#### 4-Methyl-N-(pyridin-2-yl)benzene Sulphonamide and Its Complexes

Elemental analysis of the ligand and its complexes are listed in Table 4. The percentage compositions of the element in both the experimental and calculated formulas of the complexes were highly consistent, and this depicts the purity and success of the coordinated compounds. The data

reveal a chelation ratio of metals to ligand to be 1:2 (M:2L). The data of the elemental analysis of the ligand corroborates with Abdul-Qadir et al. [3] and Orie et al. [4]

that has earlier work on montosylated 2-aminopyridine and 4-aminopyridine.

**Table 1.** Elemental Analysis of the Ligand and Complexes.

compounds	Mol. weight	Analysis Found (calculated)%					
		M	C	H	N	O	S
C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S	249.1	-	57.59 (57.81)	5.06 (4.82)	11.86 (11.24)	13.40 (12.85)	11.89 (12.85)
[Fe(C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S) <sub>2</sub> ]	553.4	11.60 (10.09)	52.27 (52.00)	4.62 (4.33)	10.37 (10.19)	10.64 (11.56)	10.55 (11.56)
[Cu(C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S) <sub>2</sub> ]	560.8	11.56 (11.42)	52.44 (51.40)	4.47 (4.28)	10.53 (10.00)	10.59 (11.43)	10.60 (11.42)

### 3.4. Electronic Analysis of

#### 4-Methyl-N-(pyridin-2-yl)benzene Sulphonamide and Its Complexes

The electronic spectra of the pure sulfonamide, and the Fe(II) and Cu(II) complexes were measured in DMSO solution between 200 and 1100 nm at room temperature. The absorption band at 224–200 nm corresponds to the  $\pi \rightarrow \pi^*$  transition of the benzene rings, and the absorptions at 290–253 nm and 341–300 nm were assigned to the  $\pi \rightarrow \pi^*$  of the double-bonded carbons and  $n \rightarrow \pi^*$  transitions and the azomethine group (HC=N) of 2-aminopyridine respectively. The prominent band at 330 nm is associated with ligand–metal charge transfer of Cu (II) complex and the broadband at the 599 nm region corresponds to the d–d transition of the Cu(II) complexes [23, 24]. The band at 334.09–375.25 nm was assigned to ligand-metal charge transfer transition (LMCT) of iron (II) complex and the broad electronic

band at 612 nm region corresponds to the d-d transition of the Iron (II) complex [4, 23].

### 3.5. NMR Analysis of 4-Methyl-N-(pyridin-2-yl)benzene Sulphonamide

The <sup>1</sup>H NMR data in Table 2 represents the chemical shift and coupling constant values of the heterocyclic sulphonamide, 4-methyl-N-(pyridin-2-yl)benzene sulphonamide. The chemical shift within the range of 6.5 to 8.5 ppm confirms the aromatic region [13–15]. The proton with the peak, 2.28 ppm was assigned to the proton of the methyl in tosyl moieties, and the proton with the chemical shift, 11.03 ppm was assigned to the proton of the sulphonamide moieties. The observed data were consistent with the results of Abdul Qadir *et al.*, [3], Dojer *et al.*, [9] and Rehman *et al.*, [12], which have researched different sulphonamide derivatives. Other <sup>1</sup>H NMR details of the synthesized product are shown in Table 2 below;

**Table 2.** Selected Chemical Shift and Coupling Constant Methyl-N-(pyridin-2-yl)benzene sulphonamide.

Experimental		Literature (ref) [3, 12, 13, 15]	
<sup>1</sup> H (δ ppm)	<sup>13</sup> C (δ ppm)	<sup>1</sup> H (δ ppm)	<sup>13</sup> C (δ ppm)
11.03 (br, s, one H, NH), 8.05 (dd, J=5.63 Hz, 1.88 Hz, one H), 7.76 (m, J=8.41 Hz, one H), 7.15 (d, J=7.85.11 Hz, one H), 7.19 (d, J=8.8.68 Hz, one H), 7.33 (d, J=8.03 Hz one H), 7.52 (m, one H), 6.91 (ddd, J=6.83 Hz, 5.63 Hz, 1.88 Hz, one H), 2.32-I, 2.29 (s, three H)	21.33, 114.32, 116.60, 125.94, 126.50, 126-129.65, 139.13, 141.31, 143.13, 145.14, 152.89	11.43, (br, s, 1H, NH), 7.97 (d, J = 8.11 Hz, 1H, CH), 7.61 (d, J = 8.31 Hz, 1H, CH), 7.25 (t, J = 7.21 Hz, 1H, CH), 7.20 (s, 1H, CH), 7.11 (t, J = 8.41 Hz, 1H, CH), 7.15 (d, J = 8.39 Hz, 1H, CH), 2.48 (s, 3H, CH <sub>3</sub> )	22, 113, 117, 125 138, 148, 150

### 3.6. FTIR Investigations of Synthesized Ligand and Metal Complexes

The important IR spectral bands of the ligand and its metal complexes were given in Table 3. The heterocyclic nitrogen of azomethine, the oxygen of sulphonamide and the nitrogen of sulphonamide are the likely viable sites for coordination [4, 24]. The IR frequency band of the ligand at 3286.81 cm<sup>-1</sup> was assigned to nitrogen of the sulphonamide, the band at 1003.03 cm<sup>-1</sup> was assigned to the sulphonamide oxygen and

the vibration frequency at 1689.70 cm<sup>-1</sup> was assigned to the heterocyclic azomethine nitrogen [3, 6]. The coordination of imine to zinc (II) ion was assigned to the vibration frequency band of 1674.30 cm<sup>-1</sup> and that of the nickel (II) was assigned to the vibration frequency band of 1615.12 cm<sup>-1</sup>. This observation corroborates the azomethine (C = N) frequency range of 1683.41 –1575 cm<sup>-1</sup> estimated by Jisha and Isac Sobana raj, [7] and Sobola & Watkins, [23]. Other important frequency bands of the ligand and their complexes are shown in Table 3.

**Table 3.** Selected FT IR Absorption Bands for Ligand and complexes.

Ligand/Complex	Experimental	Literature (ref)
	Vibration Frequency (cm <sup>-1</sup> )	Vibration Frequency (cm <sup>-1</sup> )
C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S	3286.81, NH, 2918.47 CH, 1689.70 C=N, 1134.18 (C-N), 1003.03 (S=O), 1519.96, 933.58, 846.71 (C=C)	3328 (NH), 1665 (C=N), 1019 (S=O), 1161 (-N-S=O), 1455 (C=C), Abdul Qadir <i>et al.</i> , [3]; Deng, & Mani, [6]
[Cu(C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S) <sub>2</sub> ]	3294.53, 3610.55 NH, 2931.90 CH, 1674.27 C=N, 1134.18 C – N 1010.73 (S=O), 1519.95, 848.71 Aromatic C=C	3461 (NH), 1648 (C=N), 1558 (C=C), 1155 (-N-S=O), 1261 (C-N) (Duru <i>et al.</i> , [5]; Pervaiz <i>et al.</i> , [15])
[Fe(C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S) <sub>2</sub> ]	3286.81, 3603.15 NH, 2931.90 CH, 1615.12 (C=N), 1134.18 (C-N), 1010.73 (S=O), 1519.99, 925.86, 840.99 aromatic C=C	3380 (NH), 1620 (C=N), 1573 (C=C), 1157 (-N-S=O), Al-Noor, [20]; Sobola & Watkins, [23]

### 3.7. Activity of Tosylated Aminopyridine and Its Complexes Against Some Bacteria and Fungi Strains

The bioactivity of aminopyridine sulphonamide and its complexes is shown in Table 4. This result showed that the synthesized compounds were susceptible to some of the six microbes that were investigated at 1000 mg/mL. Other concentrations of the ligand and its complexes considered were inactive. The ligand was not active against all the pathogens tested, whereas, its complexes enhanced the activity against some microorganisms. The complex of copper (II) was not susceptible to bacterial strain considered while the complex of iron (II) has the highest zone inhibition for Gram (-) *Escherichia coli* as 23 mm, and the lowest for Gram (+) *Staphylococcus aureus* as 10 mm. These findings corroborate the activity test of Duru *et al.*, [5], where complexes of imidazole derivative were more bioactive than the ligands. Ciprofloxacin used as a standard has the lowest zone inhibition of 34 mm for Gram (-) *Escherichia coli* and the highest zone inhibition of 36 mm for Gram (+)

*Staphylococcus aureus*. This implies that the standard drug however showed higher activity for all the bacterial strains than the synthesized compound. Consistent with this observation was the phenyl sulphonamide sensitivity test conducted by Ijeomah and Tseeka [25]. The standard drug, ciprofloxacin was better against Gram (+) *Escherichia coli* when compared to the synthesized compound.

The complex of copper (II) has the highest zone inhibition for *S cerevisiae* as 20 mm, and the lowest for *A flavus* as 10 mm. The complex of iron (II) also has the highest zone inhibition for *S cerevisiae* as 24 mm, and the lowest for *A niger* as 10 mm. The complex of iron (II) and copper (II) inhibited the growth of the organism more than the standard drug (ketoconazole) having 16 mm for the same microbe, therefore, showing lesser activity. Both complexes were less sensitive than the standard drug (Table 4). The finding was in line with Andrew [21] and Lakrout *et al.*, [26], with the reports that standard drug was better than sulphonamide derivatives of aniline.

**Table 4.** Activity of Tosylated Aminopyridine and its complexes against some bacteria and fungi strains.

variables	Antibacterial activity			Antifungal activity		
Zone of inhibition (mm)						
compounds	Gram(-) <i>E. coli</i>	<i>S typhi</i>	Gram (+) <i>S aureus</i>	Fungal <i>A flavus</i>	<i>A niger</i>	<i>S cerevisiae</i>
C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S	-	-	-	-	-	-
[Cu(C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S) <sub>2</sub> ]	-	-	-	10	18	20
[Fe(C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S) <sub>2</sub> ]	23	18	10	-	10	24
Ciprofloxacin	34	36	36	-	-	-
ketoconazol	-	-	-	20	26	16

## 4. Conclusion

Heterocyclic sulphonamide derivatives of 2-aminopyridine and their complexes were synthesized and characterized based on various physicochemical properties and analytical tools. Screening of these compounds against pathogenic microorganisms reveals that the sulphonamide derivative was not active against bacterial and fungal strains considered, but its sensitivity improved when coordinated with some metals. The methods employed and the compounds synthesized are viable potential sources of knowledge for chemical and pharmaceutical chemists. In the view of recommendation, the compound synthesized should be tested against other pathogens.

## Competing Interests

All the authors do not have any possible conflicts of interest.

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