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Synthesis, characterization and biological studies of metal complexes of 4-iodo-*n*-(6-sulfamoylbenzothiazol-2-yl)benzamide

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Abstract

In this study, the new 4-iodo-*N*-(6-sulfamoylbenzothiazol-2-yl)benzamide (**L3**) obtained from 2-amino-6-sulfamoylbenzothiazole (**L1**) and 4-iodobenzoyl chloride (**L2**) and Fe(II) {[Fe(**L3**)$_2$(SO$_4$)].H$_2$O (**1**)}, Ni(II) {[Ni(**L3**)$_2$(Ac)$_2$].2H$_2$O (**2**)} and Cu(II) {[Cu(**L3**)$_2$(Ac)$_2$].2H$_2$O (**3**)} complexes were synthesized. The structures were synthesized by elemental analysis for **L3** and **1-3**, infrared spectroscopy (IR) for **L3** and **1-3**, nuclear magnetic resonance (NMR) for **L3**, atomic absorption spectroscopy (AAS), molar conductivity, and magnetic susceptibility methods for **1-3**. As a consequence of spectroscopic evaluation, it was determined that compounds **1-3** exhibited a non-ionic and tetrahedral conformation. A comprehensive examination was conducted on the susceptibility of all substances to *C. albicans* (yeast), *L. monocytogenes, E. faecalis, E. coli, P. aeruginosa, S. aureus*, and *B. subtilis* (bacteria) were thoroughly investigated. The antimicrobial activities were contrasted with those of Ketoconazole, Fluconazole, Levofloxacin, Chloramphenicol, Vancomycin, and Cefepime.

Keywords: 4-Iodo-N-(6-sulfamoylbenzothiazol-2-yl)benzamide, 2-amino-6-sulfamoylbenzothiazole, 4-iodobenzoyl chloride, metal complex.

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1. Introduction

Amides are well-known important functional groups in biology and chemistry, and the formation of amide bonds is of great importance, especially in the synthesis of complex homogeneous glycoproteins [1]. Amides are extremely useful functional groups in organic synthesis. They also serve as precursors for many valuable compounds, including pharmaceuticals, agrochemicals, polymers, and organic materials [2]. Sulfonamides are generally expressed with the formula NH_2SO_2R and are bioisosteric derivatives of sulfamide group compounds. Compounds containing sulfonamide group have a very wide field of study in pharmaceutical chemistry [3-6]. The sulfonamide and benzothiazole derivatives are considered as a fundamental building block in the search for a novel class of drug molecules with diverse pharmacological activities [3-6]. *N*-(benzothiazol-2-yl)benzamide derivatives have antifungal [7], antiproliferative [8], antibacterial [9-16], antioxidant [5,6,17,17], anticancer [6,19-21], anti-Zika virus [22], antituberculosis [23], antiviral [24-26], anti-inflammatory [27,28], antiHIV [29], antiarteriosclerotic [30,31] and antitumor [32-34] activities. While 2-aminobenzothiazole-benzamide derivatives are synthesized abundantly in the literature [3-6,35], 2-amino-6-sulfonamidebenzothiazole-benzamide is very rare [36]. The simple or metal mixed-ligand complexes of *N*-(benzothiazol-2-yl)benzamide are few reports such as Cu(II) and Zn(II) of *N*-(benzothiazol-2-yl)benzamide [37], BF_2 of *N*-(benzothiazol-2-yl)benzamide, *N*-(benzothiazol-2-yl)-4-methoxybenzamide, *N*-(benzothiazol-2-yl)-4-(diphenylamino)benzamide and *N*-(benzothiazol-2-yl)-4-(dimethylamino)benzamide [38], Fe(III), Co(II) and Cr(III) of *N*-(benzothiazol-2-ylcarbamothioyl)benzamide [**Hata! Yer işareti tanımlanmamış.**], Pd(II) and Zn(II) of *N*-(benzothiazol-2-yl)-4-(octyloxy)benzamide [39], Pd(II) of *N*-(benzothiazol-2-yl)benzamide with 1,2-bis(diphenylphosphino)ethane [40] and Ru, Rh and Ir of *p*-isopropyltoluene, cyclopentadienyl and azide with *N*-(benzothiazol-2-yl)benzamide [5]. The metal complexes of 2-amino-6-sulfonamidebenzothiazole-benzamide have not been synthesized.

In this study, novel 4-iodo-*N*-(6-sulfamoylbenzothiazol-2-yl)benzamide (**L3**) of 2-amino-6-sulfamoylbenzothiazole (**L1**) and 4-iodobenzoyl chloride (**L2**) and the metal complexes were synthesized. The structures were suggested by elemental analysis for **L3** and **1-3**, IR for **L3** and **1-3**, NMR for **L3**, AAS, magnetic susceptibility and molar conductivity methods for **1-3**. The antimicrobial properties of all compounds against yeast and bacteria were thoroughly investigated. The antimicrobial efficacies were contrasted with those of Ketoconazole, Fluconazole, Levofloxacin, Chloramphenicol, Vancomycin, and Cefepime.

2. Experimental

*2.1. Preparation of **L1** and **L3***

According to the literature, for the synthesis of 2-amino-6-sulfamoylbenzothiazole (**L1**), firstly 4-thioureidobenzenesulfonamide (tbs) was obtained from the reaction of sulfanylamide (sa) with KSCN. Then, it was synthesized from the reaction of 4-thioureidobenzenesulfonamide with Br_2 [41].

1.1464 g (5 mmol) **L1** was dissolved in 50 mL of tetrahydrofuran in a flask. 1.3323 g (5 mmol) **L2** was added by dropwise in an ice bath at -5 degrees. After stirring at 25 ºC for three days, the solid precipitated in the reaction medium were filtered by using filter paper, washed with dry toluene, and dried at 25 ºC (**L3**, 1.8369 g, 80% yield, M = 459.28 g/mol) (Fig. 1).

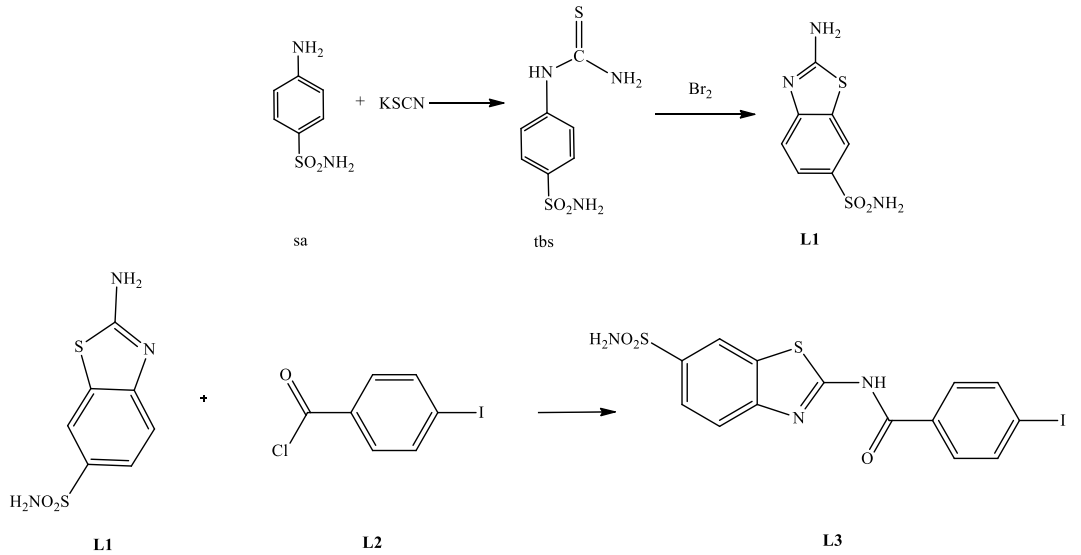
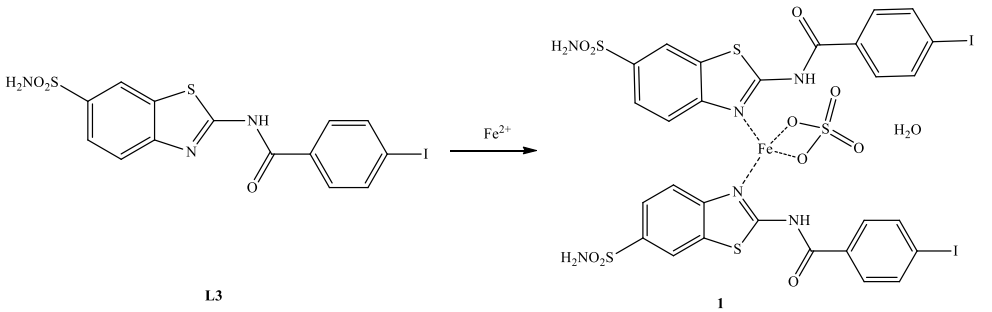


Fig. 1. The structure of **L3**.

*2.2. Preparation of **1-3***

0.278 g (1 mmol) $FeSO_4.7H_2O$ for **1** or 0.248 g (1 mmol) $Ni(Ac)_2.4H_2O$ for **2** or0.200 g (1 mmol) $Cu(Ac)_2.H_2O$ for **3** and 0.4593 g (1 mmol) **L3** was dissolved in water:ethanol (1:1) (50 mL) with stirring one week. The powdered solids obtained from the mixtures were filtered and dried {orange, 0.3538 g, 65% yield, M = 1088.49 g/mol for **1**, green 0.3677 g, 65% yield, M = 1131.38 g/mol for **2**, and brown, 0.3409 g, 60% yield, M = 1136.23 g/mol for **3**} (Fig. 1).



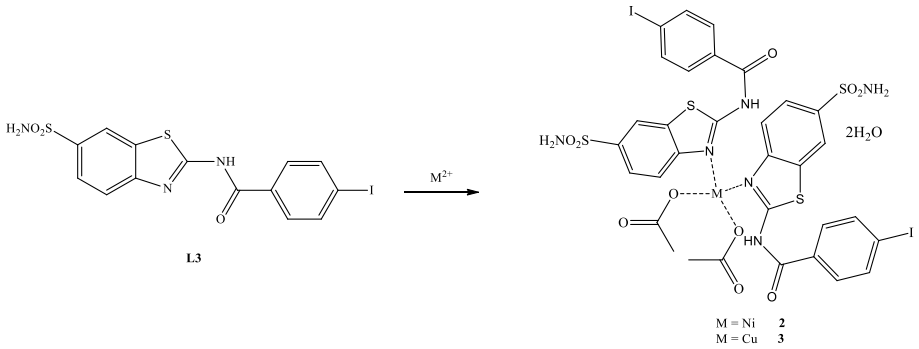


Fig. 2. The structures of **1**-**3**.

2.3. Antimicrobial study

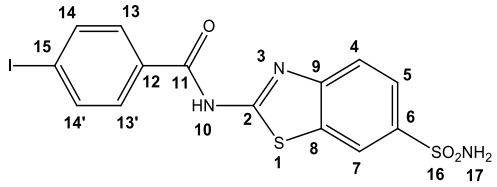
In determining the antibacterial and antifungal activities of all compounds, the micro-tube dilution technique was applied to determine the lowest concentration value (MIC) that inhibits the growth of microorganisms [42,43]. Each microorganism culture was incubated in Müller Hinton Broth at 37 ºC overnight and adjusted to a concentration of approximately 10^8 cfu/mL (with 0.5 McFarland) in tubes containing 15 mL of double-strength Müller Hinton Broth (MBH). Dilutions of the compounds were prepared at a 1:1 ratio with 1000 µL of DMSO solution and 1000 µL of sterile distilled water, and 11 dilutions were made. Then, 100 µL of sterile distilled water was transferred to the 12th row of horizontal wells from 1 to 12 of sterile 96-well micro plates from top to bottom, and 100 µL of previously prepared dilutions were transferred to wells 11-1 from top to bottom, respectively, and 100 µL of single strength MHB medium was transferred to the wells in the last row of the horizontal row [42,43]. Finally, 100 µL of the microorganism suspension was added to each well. Reference antibiotic dilutions (Cefepime, Vancomycin, Levofloxacin, Chloramphenicol for bacteria and Fluconazole and Ketoconazole for yeast) were also performed in the same manner. The plates were incubated at 37 °C for 24 hours and the lowest concentration at which turbidity (growth) was not observed was determined as the MIC.

3. Results and discussion

*3.1. NMR result of **L3***

The NMR results of **L3** are given in Figures 3 and 4, and Table 1. In the ^{1}H NMR spectrum of **L3** (Fig. 3, Table 1), the protons were observed at 7.94 ppm (H^4 and H^5, 2H, doublet, $^3J_{H4\text{-}H5}$ = 7.59 Hz), 8.51 ppm (H^7, 1H, singlet), 13.15 ppm (H^{10}, 1H, singlet), 7.88 ppm (H^{13}, $H^{13'}$, H^{14} and $H^{14'}$, 4H, multiplet) and 7.36 ppm (H^{17}, 2H, singlet).

Table 1. ^{1}H-NMR and ^{13}C-NMR spectra peaks of **L3**.



^{1}H NMR		^{13}C NMR	
H^4/H^5	7.94 (2H, d) [$^3J_{H4\text{-}H5}$ = 7.59 Hz]	C^2	166.346
H^7	8.51 (1H, s)	C^4	131.525

H^{10}	13.15 (1H, s)	C^{5}	124.432
$H^{13}/H^{13'}/H^{14}/H^{14'}$	7.88 (4H, m)	C^{6}	130.609
H^{17}	7.36 (2H, s)	C^{7}	120.918
		C^{8}	120.899
		C^{9}	120.668
		C^{11}	162.297
		C^{12}	138.038
		$C^{13}/C^{13'}$	131.963
		$C^{14}/C^{14'}$	131.591
		C^{15}	101.917

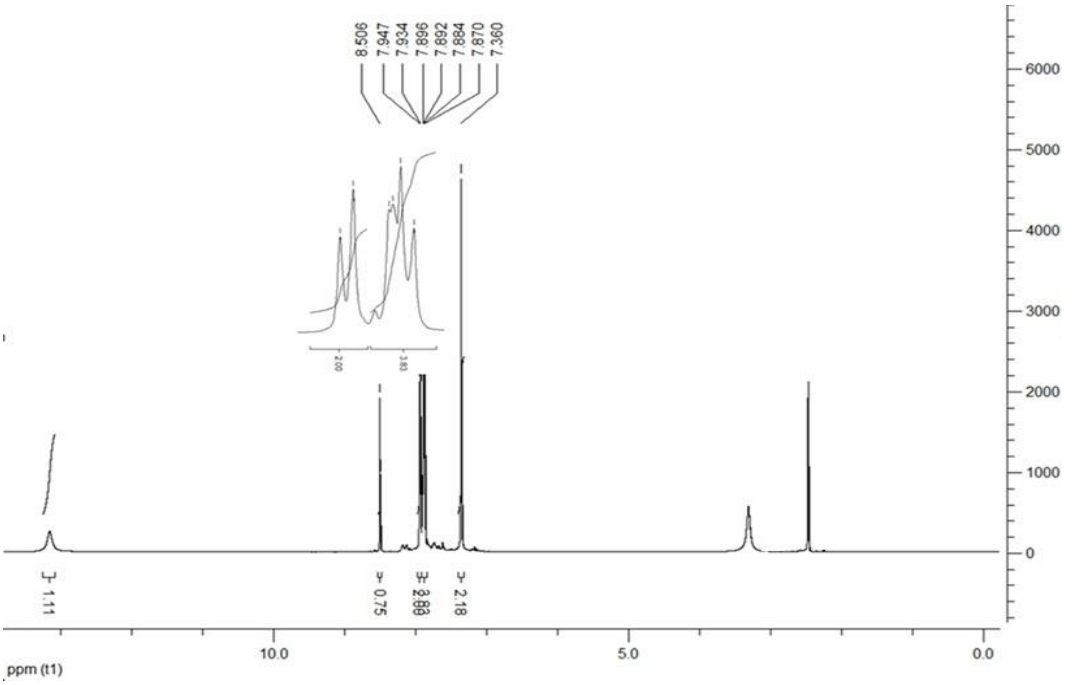


Fig. 3. ^{1}H NMR spectrum of **L3**.

^{13}C NMR spectrum of **L3** exhibits twelve signals (Fig. 4, Table 1) at 166.346 ppm (C^{2}), 131.525 ppm (C^{4}), 124.432 ppm (C^{5}), 130.609 ppm (C^{6}), 120.918 ppm (C^{7}), 120.899 ppm (C^{8}), 120.668 ppm (C^{9}), 162.297 ppm (C^{11}), 138.038 ppm (C^{12}), 131.963 ppm (C^{13}, $C^{13'}$), 131.591 ppm (C^{14}, $C^{14'}$) and 101.917 ppm (C^{15}).

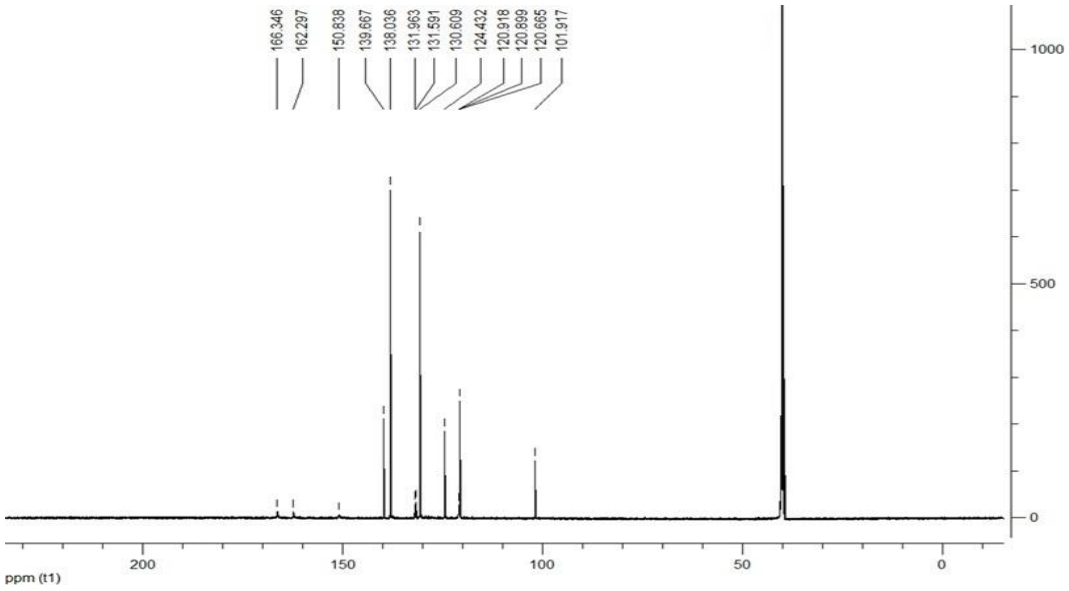


Fig. 4. ^{13}C NMR spectrum of **L3**.

3.2. AAS and Elemental analysis results

Results of AAS for **1-3** and elemental analysis for **L3** and **1-3** indicated that the metal:**L3** ratios for **1-3** were 1:1 (Table 2).

Table 2. Elemental analysis and AAS results of compounds **L3-3**.

Compound	Formula	Found% (Calculated%)				
		C	H	N	S	M
L3	$C_{14}H_{10}IN_3O_3S_2$	36.65(36.61)	2.20(2.19)	9.20(9.15)	13.95(13.96)	-
1	$C_{28}H_{22}FeI_2N_6O_{11}S_5$	30.90(30.90)	2.05(2.04)	7.75(7.72)	14.75(14.73)	5.10(5.13)
2	$C_{32}H_{30}I_2N_6NiO_{14}S_4$	33.90(33.97)	2.65(2.67)	7.45(7.43)	11.35(11.34)	5.20(5.19)
3	$C_{32}H_{34}CuI_2N_6O_{12}S_4$	33.80(33.83)	2.60(2.66)	7.50(7.40)	11.25(11.29)	5.60(5.59)

3.3. IR results

The IR spectra and IR data of **L3** and **1-3** are given in Figure 5 and Table 3, respectively. The ν(N-H) vibrations observed at 3424, 3314, and 3268 cm^{-1} for compound **L3**, 3483, 3411, and 3233 cm^{-1} for compound **1**, 3486, 3418, 3313, and 3265 cm^{-1} for compound **1**, and 3483, 3414, 3310, and 3270 cm^{-1} for compound **3**. The differential results (Δυ) between the symmetric and asymmetric vibrations of compounds **1** and **3** in the acetate group were found to be 218 (1618 and 1400 cm-1) for **1** and 219 (1619 and 1400 cm^{-1}) for **3**. These values indicate that the acetate group is monodentately bound to the metal ion [44]. The observed bands in the spectra of **L3** and **1-3** are observed region of 3551-3553 cm^{-1}, 3074-3114 cm^{-1}, 2852-2973 cm^{-1}, 1673-1676 cm^{-1}, 1448-1639 cm^{-1}, 1188-1390 cm^{-1}, 1056-1278 cm^{-1}, 607-630 cm^{-1} and 460-496 cm^{-1} for ν(O-H), aromatic *ν*(C-H), aliphatic *ν*(C-H) for compounds **1** and **3,** for $\nu(C{=}O)_{amide}$, *ν*(C=N)/*ν*(C=C), *ν*(C=O) for compounds **1** and **3**, *ν*(S=O), *ν*(M-O) (except compound **L3**) and *ν*(M-N) (except compound **L3**), respectively.

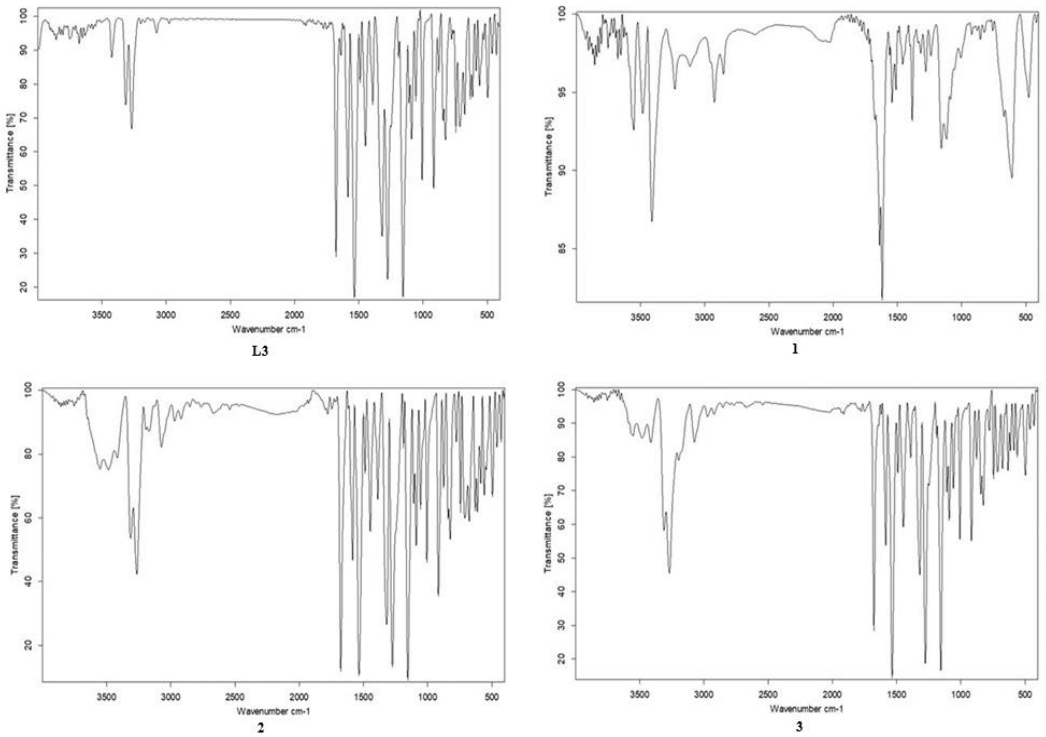


Fig. 5. IR spectra of **L3** and **1-3**.

Table 3. IR data of **L3** and **1-3** (cm^{-1})

	L3	**1**	**2**	**3**
ν(OH)	-	3553(br)	3551(br)	3552(br)
$\nu(NH_2)$	3424(m)	3483(m)	3486(m)	3483(m)
	3314(m)	3411(m)	3418(m)	3414(m)
	3268(m)	3233(m)	3313(m)	3310(m)
			3265(m)	3270(m)
$\nu(CH)_{Ar}$	3074(w)	3114(w)	3074(w)	3074(w)
$\nu(CH)_{Alp.}$	-	-	2971(w)	2973(w)
			2921(w)	2922(w)
			2852(w)	2852(w)
$\nu(C{=}O)_{acetate}$	-	-	1618(s)	1619(s)
			1400(s)	1400(s)
$\nu(C{=}O)_{amide}$	1676(s)	1673(s)	1676(s)	1676(s)
ν(C=N)	1639(s)	1638(s)	1584(s)	1584(s)
ν(C=C)	1619(s)	1618(s)	1535(s)	1535(s)
	1584(s)	1560(s)	1447(s)	1490(s)
	1534(s)	1541(s)		1447(s)
	1489(s)	1511(s)		
	1448(s)	1458(s)		
ν(C-O)	-	-	1388(s)	1390(s)
			1319(s)	1319(s)
			1188(s)	1188(s)
ν(S=O)	1275(s)	1278(s)	1274(s)	1275(s)

	1155(s)	1157(s)	1154(s)	1155(s)
	1056(s)	1118(s)	1089(s)	1090(s)
ν(M-O)	-	607(w)	630(w)	614(w)
ν(M-N)	-	477(w)	460(w)	496(w)

3.4. Results of UV-Vis measurements

The electronic spectra of **L3** and **1-3** (Fig. 6, in DMSO), π-π* and n-π* transitions are observed 285 nm (30900 $Lmol^{-1}cm^{-1}$) and 300 nm (37060 $Lmol^{-1}cm^{-1}$) for **L3**, 289 nm (28900 $Lmol^{-1}cm^{-1}$) and 300 nm (37000 $Lml^{-1}cm^{-1}$) for **1**, 285 nm (15900 $Lmol^{-1}cm^{-1}$) for **2** and 300 nm (38900 $Lmol^{-1}cm^{-1}$) for **3.** The sands for d-d transitions of tetrahedral complexes are observed at 702 nm (200 $Lmol^{-1}cm^{-1}$) for **1** [45], 6603nm (150 $Lmol^{-1}cm^{-1}$) for **2** [46] and 690 nm (100 $Lmol^{-1}cm^{-1}$) for **3** [47].

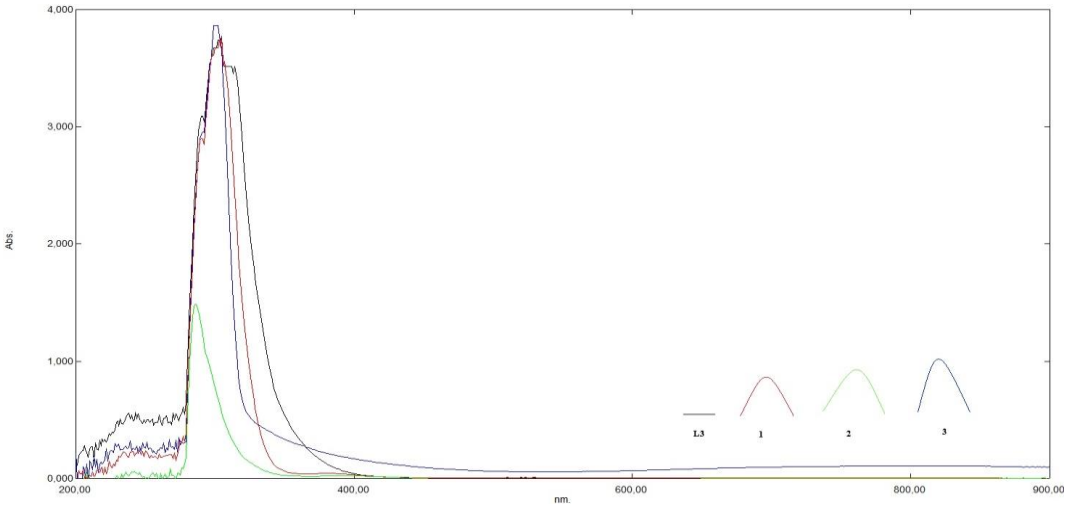


Fig. 6. UV-Vis spectra of **L3** and **1-3**.

*3.5. Magnetic susceptibilities and Molar Conductivity for **1-3***

The magnetic susceptibility measurements for compounds **1-3** were recorded as 4.80, 2.15, and 1.61 BM, respectively. These values indicate the presence of 4, 2, and 1 unpaired electron within the respective complexes. The magnetic moment associated with the metal ion in the tetrahedral configuration is also in agreement with these findings [48,49].

Conductivity assessments of compounds **1-3** (dissolved in DMSO) yielded values of 2.1, 5.0, and 2.1, respectively; consequently, these results indicate non-ionic behaviour for compounds **1-3** [50].

The highly effective technique of single-crystal X-ray diffraction analyses is not applicable for elucidating the structures of complexes **1–3** as a result of their particulate nature. The molecular formulas of the above mentioned complexes are elucidated based on the results from elemental analysis, AAS, spectral analyses (IR, UV-Vis), magnetic susceptibility and molar conductivity (Fig. 2).

3.6. Antimicrobial activity

The antimicrobial efficacy of Levofloxacin, Vancomycin, Chloramphenicol, Cefepime, Ketoconazole,

Fluconazole, sa, KSCN, tbs, and **L1-L3** and **1-3** were systematically examined utilizing the microdilution methodology. Minimum Inhibitory Concentration (MIC) values of the compounds against yeast and bacteria are given in Table 4.

Table 4. MIC values of all compounds (µg/mL)

	S. aureus	***B. subtilis***	***E. Coli***	***E. faecalis***	***L. monocytogenes***	***P. aeruginosa***	***C. albicans***
Vancomycin	31.25	31.25	125.00	31.25	125.00	62.50	
Levofloxacin	62.50	31.25	31.25	31.25	62.50	31.25	
Cefepime	31.25	62.50	31.25	62.50	62.50	31.25	
Chloramphenicol	62.50	62.50	62.50	62.50	62.50	125.00	
Fluconazole	-	-	-	-	-	-	62.50
Ketoconazole	-	-	-	-	-	-	62.50
sa	31.25	62.50	31.25	15.62	31.25	31.25	62.50
KSCN	31.25	62.50	31.25	62.50	31.25	31.25	62.50
tbs	62.50	31.25	62.50	62.50	62.50	31.25	62.50
L1	62.50	62.50	62.50	62.50	31.25	31.25	62.50
L2	62.50	62.50	62.50	62.50	62.50	62.50	62.50
L3	31.25	31.25	62.50	62.50	31.25	62.50	62.50
1	62.50	62.50	62.50	62.50	31.25	31.25	62.50
2	62.50	62.50	62.50	62.50	31.25	31.25	62.50
3	62.50	62.50	62.50	62.50	31.25	31.25	62.50

Cefepime, Levofloxacin, Vancomycin, and Chloramphenicol (antibacterial drugs) and all compounds have activity against *S. aureus:* sa, KSCN, and **L3** showed the same activity as Vancomycin and Levofloxacin, while other compounds showed the same effect as Cefepime and Chloramphenicol.

B. subtilis; while tbs and **L3** found the same effect as Vancomycin and Levofloxacin, other compounds showed Cefepime and Chloramphenicol, the other compounds found equally active.

E. coli; sa and KSCN were found to demonstrate activity comparable to that of Cefepime and Levofloxacin, while the remaining compounds exhibited effects akin to those of Chloramphenicol. Notably, all compounds demonstrated superior activity relative to Vancomycin.

L. monocytogenes; all compounds exhibited enhanced activity when compared to Vancomycin. All compounds (except tbs and **L2**) showed greater activity according to the other drug while tbs and **L2** showed the same activity according to the other drug.

E. faecalis; faecalis, sa exhibited a level of activity surpassing that of all tested drugs. The remaining compounds exhibited activity comparable to Cefepime and Chloramphenicol, while other compounds were determined to possess a lesser degree of efficacy relative to both Levofloxacin and Vancomycin.

P. aeruginosa; all compounds (except **L2** and **L3**) exhibited superior activity in comparison to Vancomycin, while compounds **L2** and **L3** were found to be equally effective. Although all compounds (apart from **L2** and **L3**) demonstrated equivalent efficacy, compounds **L2** and **L3** were identified as having a lesser degree of activity compared to Cefepime and Levofloxacin. Furthermore, all compounds exhibited greater activity than that observed with Chloramphenicol.

Ketoconazole and Fluconazole (antifungal drugs) both classified as antifungal agents, along with all other compounds, demonstrated efficacy against Candida albicans when the MIC values were compared; all compounds exhibited effects analogous to those of Ketoconazole and Fluconazole.

4. Conclusions

In this study, the novel compound 4-iodo-*N*-(6-sulfamoylbenzothiazol-2-yl)benzamide (**L3**) was synthesized from 2-amino-6-sulfamoylbenzothiazole, 4-iodobenzoyl chloride, and the complexes of Fe(II), Ni(II), and Cu(II) derived from compound **L3**. The structural elucidation of these compounds was accomplished through a combination of elemental analysis, IR, NMR, AAS, magnetic susceptibility measurements, and molar conductivity assessments. The results obtained from the spectroscopic analysis indicated that compounds **1-3** exhibited a non-ionic nature and a tetrahedral geometry. All synthesized compounds demonstrated antimicrobial activity against a spectrum of both bacterial and fungal microorganisms. Compound **L3** showed better activity in *S. aureus* and *B. subtilis* bacteria, while compounds **L3** and **1-3** showed the same activity in *E. coli* and *E. faecalis* bacteria and *C. albicans* yeast. Complex compounds (**1-3**) showed better activity in L. monocytogenes bacteria.

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Author contributions

H.I: Investigation, Writing- Reviewing and Editing, T.O: Investigation**,** C.Y: Investigation, and A.G: Activity Study.

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