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Synthesis, Characterization and antimicrobial activity of Metal Complexes of 4-Nitro-*N*-(6-sulfamoylbenzothiazol-2-yl)benzamide

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4-Nitro-*N*-(6-sülfamoilbenzotiazol-2-il)benzamidin Metal Komplekslerinin Sentezi, Karakterizasyonu ve Antimikrobiyal Aktivitesi

ABSTRACT

In this study, the new Fe(II) {$[Fe(abt)_2(SO_4)].H_2O$ (**1**)}, Ni(II) {$[Ni(abt)_2(Ac)_2].4H_2O$ (**2**)} and Cu(II) {$[Cu(abt)_2(Ac)_2].4H_2O$ (**3**)} complexes of 4-nitro-*N*-(6-sulfamoylbenzothiazol-2-yl)benzamide (abt) were synthesized. The structures (**1-3**) were suggested by elemental analysis, AAS, molar conductivity, and magnetic susceptibility methods. 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), *E. faecalis, E. coli, L. monocytogenes, S. aureus, P. aeruginosa,* and *B. subtilis* (bacteria) were thoroughly investigated. The antimicrobial activities were contrasted with those of Ketoconazole, Fluconazole, Levofloxacin, Chloramphenicol, Vancomycin, and Cefepime. Compounds abt and **2** showed better activity in *S. aureus* and *B. subtilis* bacteria, while compounds **1-3** showed the same activity in E. coli and E. faecalis bacteria and C. albicans yeast. Complex **3** showed better activity in L. monocytogenes bacteria.

Keyword: 4-Nitro-N-(6-sulfamoylbenzothiazol-2-yl)benzamide, metal complex, tetrahedral complex, antimicrobial activity.

ÖZ

Bu çalışmada, 4-nitro-*N*-(6-sülfamoilbenzotiazol-2-il)benzamid'in (abt) yeni Fe(II) {$[Fe(abt)_2(SO_4)].H_2O$ (**1**)}, Ni(II) {$[Ni(abt)_2(Ac)_2].4H_2O$ (**2**)} ve Cu(II) {$[Cu(abt)_2(Ac)_2].4H_2O$ (**3**)} kompleksleri sentezlendi. **1-3**'ün yapıları, element analizi, AAS, molar iletkenlik ve manyetik duyarlılık yöntemleri ile önerildi. Spektroskopik değerlendirmenin bir sonucu olarak, **1-3** bileşiklerinin iyonik olmayan ve tetrahedral bir konformasyon sergilediği belirlendi. Tüm maddelerin *C. albicans* (maya), *E. faecalis*, *E. coli, L. monocytogenes*, S. *aureus*, *P. aeruginosa* ve *B. subtilis* (bakteri) duyarlılığına ilişkin kapsamlı bir inceleme yürütüldü ve kapsamlı bir şekilde araştırıldı. Antimikrobiyal aktiviteler Ketokonazol, Flukonazol, Levofloksasin, Kloramfenikol, Vankomisin ve Sefepim ile karşılaştırıldı. Bileşikler abt ve **2**, S. aureus ve B. subtilis bakterilerinde daha iyi aktivite gösterirken, bileşikler **1-3**, *E. coli* ve *E. faecalis* bakterilerinde ve *C. albicans* mayasında aynı aktiviteyi gösterdi. Kompleks **3**, *L. monocytogenes* bakterilerinde daha iyi aktivite gösterdi.

Anahtar Kelimeler: 4-Nitro-N-(6-sülfamoilbenzotiazol-2-il)benzamid, metal kompleksi, tetrahedral kompleks, antimikrobiyal aktivite.

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INTRODUCTION

Amide derivatives are a wide variety of bioactive molecules prepared both naturally and synthetically.[1] Amide derivatives are found as sources of both carbonyl and amine groups in various transformation reactions. Amide bond formation can be achieved by ribosomal synthesis, ATP-dependent amide ligation mechanisms, and other enzymatic pathways based on hydrolases, proteases, and acylases.[2-4]

Sulfonamide derivatives are five or six membered heterocycles containing -SO_2NH_2 and/or -SO_2NH- groups.[5] The sulfonamide and benzothiazole derivatives are considered as a fundamental building block in the search of a novel class of drug molecules with diverse pharmacological activities.[6-9] Sulfamoyl and benzothiazole derivatives have antibacterial, anticonvulsant, anti-inflammatory, antituberculosis, therapeutic, protease and carbonic anhydrase inhibitory effects.[10-12]

N-(benzothiazol-2-yl)benzamide derivatives have antifungal[13], antiproliferative[14], antibacterial[15-22], antioxidant[16,17,23,24], anticancer[16,25-27], anti-Zika virus[28], antituberculosis[29], antiviral[30-32], anti-inflammatory[33,34], antiHIV[35], antiarteriosclerotic[36,37] and antitumor[38-40] activities. While 2-aminobenzothiazole-benzamide derivatives are synthesized abundantly in the literature[1-9,41], 2-amino-6-sulfonamidebenzothiazole-benzamide is very rare.[42] The simple or metal mixed-ligand complexes of *N*-(benzothiazol-2-yl)benzamide derivatives have been successfully synthesized[16,43-46], whereas the metal complexes of 2-amino-6-sulfonamidebenzothiazole-benzamide remain unsynthesized.

In this study, novel Fe(II) (**1**), Ni(II) (**2**) and Cu(II) (**3**) complexes of 4-nitro-*N*-(6-sulfamoylbenzothiazol-2-yl)benzamide were synthesized. The structures were suggested by elemental analysis, 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.

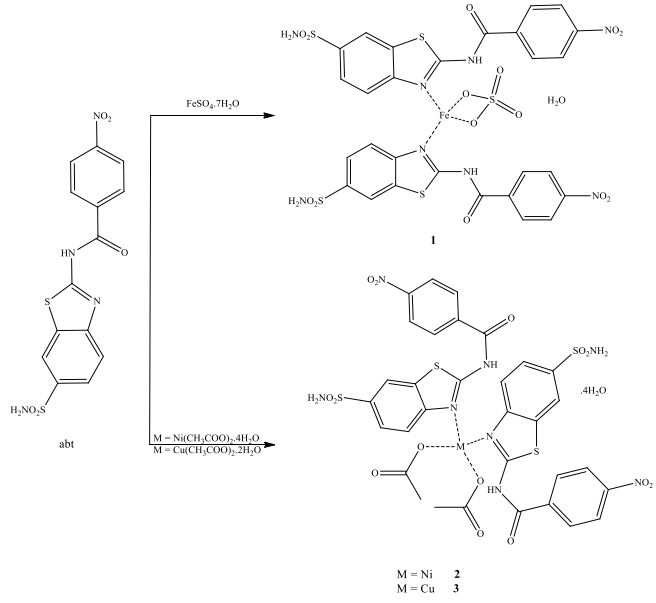
METHODS

General methods and materials

All chemicals used were purchased from Chemazone and Aldrich. Elementar Vario III EL for elemental analyses, Perkin Elmer PinAAcle 900T for AAS analysis, Bruker Optics Vertex 70 (using KBr) for IR, SHIMADZU UV-2550 for UV-vis (200–900 nm and in DMSO), WTW Cond 315i/SET for molar conductances and Sherwood Scientific Magway MSB MK1 for magnetic susceptibility were used for spectral and analytical measurements.

Preparation of 1-3.

0.7568 g (2 mmol) abt and 1 mmol (0.278 g) $FeSO_4.7H_2O$ for **1**, 1 mmol (0.248 g) $Ni(Ac)_2.4H_2O$ for **2,** and 1 mmol (0.200 g) $Cu(Ac)_2.H_2O$ for **3** were dissolved in ethanol (50%) (50 mL) with stirring one week. The powdered solids obtained from the mixtures were filtered and dried {orange, 0.3538 g, 65% yield, m.p. >350 °C for **1**, green 0.3677 g, 65% yield, m.p. >350 °C for **2**, and brown 0.3409 g, 60% yield, m.p. >350 °C for **3**} (Scheme 1). Complexes **1-3** are soluble in DMSO and DMF.



Scheme 1. The structures of **1-3**.

Antimicrobial study

The assessment of the antimicrobial characteristics of the compounds was executed through the application of a microbroth dilution susceptibility assay. Stock solutions were formulated utilizing DMSO as a solvent. Each compound, with a total mass of 4 mg, was solubilized in 2 mL of dimethyl sulfoxide. Bacterial and yeast suspensions, cultivated overnight, were standardized to a concentration of 10^8 Colony Forming Units/mL using the McFarland No. 0.5 standard solution in double-strength Mueller-Hinton broth. Subsequently, 100 µL of each microbial suspension was introduced into the wells. A well-chain that lacked microbial presence functioned as the negative control. The positive growth control comprised the medium along with sterile distilled water. The minimum inhibitory concentration (MIC) was established as the initial well exhibiting the absence of turbidity following an incubation period of 18-24 hours at a temperature of 37 °C.

RESULTS AND DISCUSSION

AAS and Elemental analysis results

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

Table 1. Elemental analysis and AAS results of the studied substances.

Comp.	Formula	Found% Anal. Cald.%				
		C	H	N	S	M
1	$C_{28}H_{22}FeN_8O_{15}S_5$	36.30(36.29)	2.40(2.39)	12.10(12.09)	17.35(17.30)	6.05(6.03)
2	$C_{32}H_{34}N_8NiO_{18}S_4$	38.20(38.22)	3.45(3.41)	11.15(11.14)	12.80(12.75)	5.80(5.84)
3	$C_{32}H_{34}N_8NiO_{18}S_4$	38.00(38.04)	3.40(3.39)	11.10(11.09)	12.70(12.69)	6.30(6.29)

IR results

Table 2. IR data of all compounds (cm^{-1})

	abt	1	2	3
ν(OH)	-	3549(br)	3569(br)	3553(br)
ν(NH)	3470(m)	3468(m)	3470(m)	3483(m)
	3385(m)	3390(m)	3415(m)	3414(m)
	3238(m)	3238(m)	3232(m)	3239(m)
$\nu(CH)_{Ar}$	3115(w)	3050(w)	3163(w)	3080(w)
$\nu(CH)_{Alf.}$	-	-	2926(w)	2923(w)
			2855(w)	2856(w)
				2710(w)
$\nu(C=O)_{asit}$	-	-	1637(s)	1638(s)
			1437(s)	1445(s)
$\nu(C=O)_{amit}$	1671(s)	1660(s)	1658(s)	1682(s)
ν(C=N)	1618(s)	1621(s)	1619(s)	1605(s)
ν(C=C)	1547(s)	1527(s)	1513(s)	1528(s)
	1470(s)	1493(s)	1458(s)	1498(s)
	1444(s)	1449(s)		1404(s)
		1403(s)		
$\nu(NO_2)$	1598(s)	1543(s)	1560(s)	1540(s)
ν(C-O)	-	-	1382(s)	1349(s)
			1316(s)	1284(s)
			1158(s)	1169(s)
ν(S=O)	1278(s)	1281(s)	1254(s)	1248(s)
	1154(s)	1152(s)	1206(s)	1106(s)
	1100(s)	1106(s)	1105(s)	1086(s)
ν(M-O)	-	613(w)	609(w)	614(w)
ν(M-N)	-	490(w)	475(w)	453(w)

The IR spectra of **1-3** in Figures 1-3 and the IR data results of **1-3** are given in Table 2. The ν(N-H) vibrations observed 3470, 3385, and 3238 cm^{-1} for abt, 3468, 3390, and 3238 cm^{-1} for **1**, 3470, 3415, and 3232 cm^{-1} for **2**, and 3483, 3414, and 3239 cm^{-1} for **3**. The differential results (Δυ) between the symmetric and asymmetric vibrations of compounds **2** and **3** in the acetate group were found to be 200 (1637 and 1437 cm^{-1}) for **2** and 193 (1638 and 14445 cm^{-1}) for **3**. These observations indicate that the acetate group is bound to the metal ion in a monodentate manner.[47] The observed bands in the spectra of **1-3** are observed region of 3549-3569 cm^{-1} for ν(O-H), 3050-3163 cm^{-1} for aromatic *ν*(C-H), 2710-2926 cm^{-1} for aliphatic *ν*(C-H) for **2** and **3**, 1658-1682 cm^{-1} for $\nu(C=O)_{amide}$, 1540-1543 cm^{-1} for $\nu(NO_2)$, 1403-1621 cm^{-1} for *ν*(C=N)/*ν*(C=C), 1188-1382 cm^{-1} for *ν*(C-O) for **2** and **3**, 1086-1281 cm^{-1} for *ν*(S=O), 609-614 cm^{-1} for *ν*(M-O) and 453-490 cm^{-1} for *ν*(M-N).

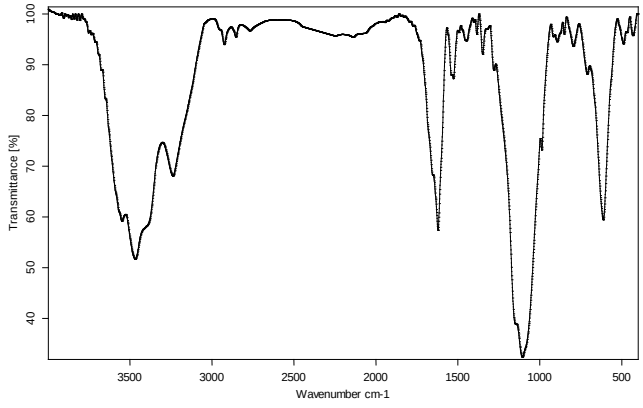


Figure 1. IR spectrum of **1.**

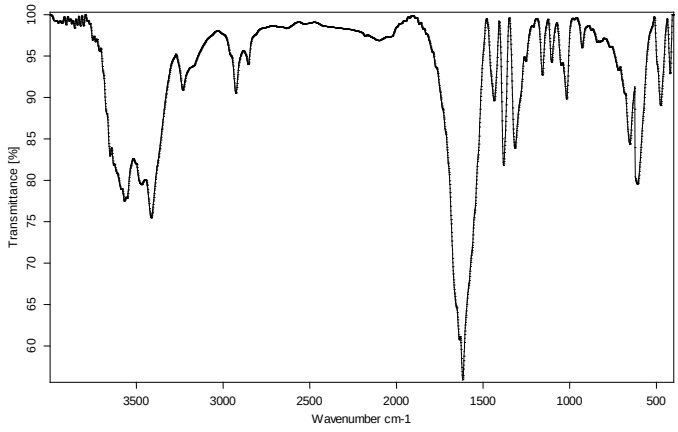


Figure 2. IR spectrum of **2.**

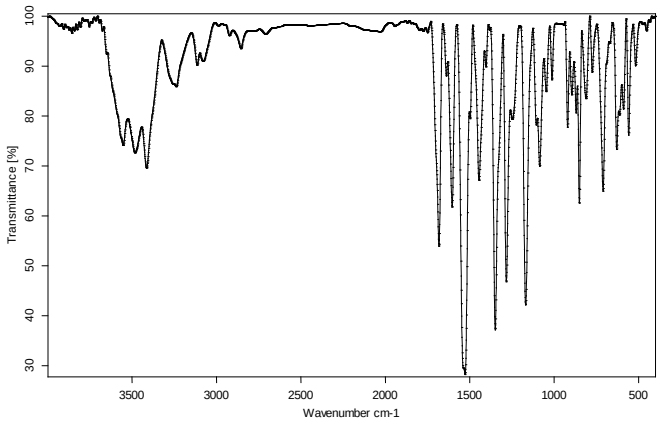


Figure 3. IR spectrum of **3**.

Magnetic susceptibilities

The magnetic susceptibility measurements for compounds **1-3** were recorded as 4.85, 2.80, and 1.65 BM, respectively. These values indicate the presence of four, two, and one unpaired electrons 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]

Molar conductivity

Conductivity assessments of compounds **1-3** (in DMSO) yielded values of 5.1, 4.0, and 3.1, respectively; consequently, these results indicate non-ionic behaviour for **1-3**.[50]

Antimicrobial activity

The antimicrobial efficacy of Levofloxacin, Vancomycin, Chloramphenicol, Cefepime, Ketoconazole, Fluconazole, abt {substances that can be used in the synthesis of abt are sulfanilamide (sa), KSCN, 4-thioureidobenzenesulfonamide (tbs), 2-amino-6-sulfamoylbenzothiazole and 4-iodobenzoyl chloride}sulfanilamide (sa), KSCN, 4-thioureidobenzenesulfonamide (tbs), 2-amino-6-sulfamoylbenzothiazole and 4-iodobenzoyl chloride (Clbz)} and **1-3** were systematically examined utilizing the microdilution methodology. The Minimum Inhibitory Concentration (MIC) values for all compounds exhibiting antimicrobial activity against both bacterial and yeast strains are delineated in Table 3.

Cefepime, Levofloxacin, Vancomycin, and Chloramphenicol (antibacterial drugs), and all compounds have activity against *S. aureus:* sa, KSCN, abt, and **2** showed the same activity as Vancomycin and Levofloxacin, while other compounds showed the same effect as Cefepime and Chloramphenicol.

B. subtilis; while abt, tbs, and **2** found the same effect as Vancomycin and Levofloxacin, other compounds showed Cefepime and Chloramphenicol the other compounds found equally activity. *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.

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.

Table 3. MIC values of 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
Clbz	62.50	62.50	62.50	62.50	62.50	62.50	62.50
abt	31.25	31.25	62.50	62.50	31.25	62.50	62.50
1	62.50	62.50	62.50	62.50	62.50	31.25	62.50
2	31.25	31.25	62.50	62.50	62.50	62.50	62.50
3	62.50	62.50	62.50	62.50	31.25	15.62	62.50

L. monocytogenes; all compounds exhibited enhanced activity when compared to Vancomycin. All compounds (except sa, KSCN, abt, and **3**) showed greater activity according to the other drug while sa, KSCN, abt, and **3** showed the same activity according to the other drug.

P. aeruginosa; **3** exhibited a level of activity surpassing that of all tested drugs. all compounds (except Clbz, abt, and **2**) exhibited superior activity in comparison to Vancomycin, while compounds Clbz, abt, and **2** were found to be equally effective. Although all compounds (apart from Clbz, abt, and **2**) demonstrated equivalent efficacy, compounds Clbz, abt, and **2** 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.

CONCLUSIONS

In this study, the novel Fe(II), Ni(II), and Cu(II) complexes 4-nitro-*N*-(6-sulfamoylbenzothiazol-2-yl)benzamide were synthesized. The structural elucidation of these compounds was accomplished through a combination of elemental analysis, AAs, IR, 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. Compounds abt and **2** showed better activity in *S. aureus* and *B. subtilis* bacteria, while compounds **1-3** showed the same activity in E. coli and E. faecalis bacteria and C. albicans yeast. Complex **3** showed better activity in L. monocytogenes bacteria.

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