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SYNTHESIS AND CHARACTERIZATION OF Cu(II) COMPLEXES OF PROTON TRANSFER SALTS DERIVED FROM PIPERAZINE DERIVATIVES AND 5-SULFOSALICYLIC ACID

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In this study, proton transfer salts (H_2Etpip)(Hssa), (H_2HOEtpip)(Hssa) and (HAcpip)(H_2ssa), have been obtained by reactions between 1-ethylpiperazine (Etpip), 1-(2-hydroxyethyl)piperazine (HOEtpip) and 1-acetylpiperazine (Acpip) and 5-sulfosalicylic acid (H_3ssa). Also, Cu(II) complexes of proton transfer salts (H_2Etpip)[Cu(Hssa)$_2$]·5H_2O, (H_2HOEtpip)[Cu(Hssa)$_2$]·5H_2O and (H_2Acpip)[Cu(Hssa)$_2$]·5H_2O) have been synthesized. The structures of proton transfer salts have been proposed by using FT-IR, ^{1}H and ^{13}C NMR spectroscopy, and elemental analysis. The structures of the amorphous metal complexes have been proposed by atomic absorption spectrometry, FT-IR, magnetic susceptibility, molar conductivity techniques, and elemental analysis. Antimicrobial activities of compounds have been tested against *Staphylococcus aureus* (ATCC 29213) (Gram-positive), *Escherichia coli* (ATCC 25922) (Gram-negative), *Candida krusei* (ATCC 6258) (yeast), and *Candida parapsilosis* (ATCC 22019) (yeast) microorganisms. For *S. aureus*, the minimum inhibitory concentration (MIC) values of the synthesized salts were between 31.25 and 62.50 μg/ml, and 15.60 μg/ml for complexes. The MIC values of salts and complexes for *E. coli* were in the range 125.00–500.00 μg/ml and 31.25–62.50 μg/ml, respectively. The MIC values of the salts for *C. krusei* were 62.50 μg/ml, and for the complexes in the range 15.60–31.25 μg/ml. For *C. parapsilosis*, these values were 31.25 μg/ml for all salts and in the range 15.60–62.50 μg/ml for complexes.

Keywords: 5-sulfosalicylic acid; 1-piperazine derivatives; proton transfer salt; metal complexes; antimicrobial activity

СИНТЕЗА И КАРАКТЕРИЗАЦИЈА НА Cu(II)-КОМПЛЕКСИ НА СОЛИТЕ ПРЕНОСИТЕЛИ НА ПРОТОН ДОБИЕНИ ОД ПИПЕРАЗИНСКИ ДЕРИВАТИ НА 5-СУЛФОСАЛИЦИЛНА КИСЕЛИНА

Во оваа студија се добиени соли за пренос на протон трансфер (H_2Etpip)(Hssa), (H_2HOEtpip)(Hssa) и (HAcpip)(H_2ssa) при реакција на 1-етилпиперазин (Etpip), 1-(2-хидроксиетил)пиперазин (HOEtpip) и 1-ацетилпиперазин (Acpip) со 5-сулфосалицилна киселина (H_3ssa). Покрај тоа беа синтетизирани и Cu(II)-комплекси на соли за пренос на протон (H_2Etpip)[Cu(Hssa)$_2$]·5H_2O, (H_2HOEtpip)[Cu(Hssa)$_2$]·5H_2O и (H_2Acpip)[Cu(Hssa)$_2$]·5H_2O). Структурите на солите за пренос на протон се предложени врз основа на FT-IR, на ^{1}H и ^{13}C NMR спектроскопија и на елементна анализа. Структурите на аморфните и метални комплекси се предложени врз основа на атомска апсорпциона спектрометрија, FT-IR, магнетен сусцептибилитет, техники на моларна спроводливост и елементна анализа. Антимикорбните активности на соединенијата беа тестирани со микроорганизми на *Staphylococcus aureus* (ATCC 29213) (Грам-позитивни), *Escherichia coli* (ATCC 25922) (Грам-негативни), *Candida krusei* (ATCC 6258) (квасец) и *Candida parapsilosis* (ATCC 22019) (квасец). За *S. aureus* вредностите на минималната инхибиторна концентрација (MIC) на синтетизираните соли беа меѓу 31,25 и 62,50 μg/ml, и 15,60 μg/ml за комплексите. Вредностите на MIC солите и на комплексите за *E. coli* беа во опсег од 125,00 до 500,00 μg/ml и 31,25–62,50 μg/ml, соодветно. MIC-вредностите на солите за *C. krusei* беа 62,50 μg/ml,

додека за комплексите беа во опсегот од 15,60 до 31,25 μg/ml. За *C. parapsilosis* овие вредности изнесуваа 31,25 μg/ml за сите соли, а за комплексите од 15,60–62,50 μg/ml.

Клучни зборови: 5-сулфосалицилна киселина; 1-пиперазин деривати; соли за пренос на протон; комплекси на метали; антимикробна активност

1. INTRODUCTION

Among the aromatic sulfonic acids, 5-sulfosalicylic acid is especially important because it has three functional groups: –OH, –COOH, and $–SO_3H$. These groups react with organic bases (aliphatic and aromatic amines and heterocyclic N-containing compounds) to form supramolecular sequences through strong hydrogen bonding interactions [1–3]. 5–Sulfosalicylic acid acts as a multichelated ligand in complex formation. It contains a sulfonyl group ($–SO_3H$), a carboxyl group (–COOH) and a phenolic group (–OH) and has a total of six donor sites for coordination with the metal. Crystallographic examinations of the complexes of 5-sulfosalicylic acid containing alkali, alkaline earth and main-group metals show that the structures of these compounds are substantially polymeric [4–14]. Complexes containing mixed metals have also been found [5, 15, 16]. Furthermore, the 5-sulfosalicylate anion can be present as a complementary ion without coordination to a metal [17]. Many complexes have been reported in which the central metal atom coordinates to one [5, 10], two [18], three [5] or four [10, 19, 20] 5-sulfosalicylate anions. Although 5-sulfosalicylic acid is known to have biological activity, metal complexes have been found to exhibit more antimicrobial activity than free 5-sulfosalicylic acid [21, 22]. The chemistry of Cu(II) carboxylate complexes with ligands containing an *N*-donor has been extensively studied [23–26]. The Cu(II) complex of 5-sulfosalicylate and 2,2'-bipyridine features a charge-transfer type with two cationic and anionic chains in which both carboxyl and sulfonyl are coordinated to Cu atoms [27]. Copper complexes of substituted benzothiazole and 5-sulfosalicylic acid have been synthesized and their anti-inflammatory and analgesic activities investigated [28]. Piperazine can coordinate through one or two N atoms to the metal as well as bonding to metal centers as a bridging ligand. The metal complexes of proton transfer salts, including piperazine, and some mono- and dicarboxylic acids, have been reported [29–31]. In the Cu(II) complex of the proton transfer salt of pyridine-2,6-dicarboxylic acid and 2-(piperazin-1-yl)ethanol it is present only as a complementary ion in the structure [32]. Studies have shown that piperazine and its derivatives have many biological activities [33–36].

In this study, the proton transfer compounds **1**–**3** and Cu(II) complexes **4**–**6** have been synthesized. The structures of the proton transfer salts **1**–**3** were determined by elemental and spectral (FT-IR, ^1H and ^{13}C NMR) analyses. Elemental analysis, atomic absorption spectrometry (AAS), FT-IR, magnetic susceptibility and molar conductivity techniques have been used to elucidate proposed structures of the amorphous metal complexes **4**–**6**. We have studied the antimicrobial activities of **1**–**6**, H_3ssa, Etpip, HOEtpip, Acpip on the growth of *Staphylococcus aureus*, *Escherichia coli*, *Candida krusei*, and *Candida parapsilosis* cultures.

2. EXPERIMENTAL

2.1. *Materials and methods*

The chemicals used in this study were obtained from Sigma Aldrich and used without further purification.

Elemental analysis was carried out by Thermo Finnigan Flash model EA 1112 elemental analyzer. AAS studies were carried out using Perkin Elmer model PinAAcle 900T. ^1H and ^{13}C NMR spectra of the synthesized compounds were recorded in DMSO using a 500 MHz UltraShield NMR spectrometer. FT-IR studies were carried out using a Bruker Optics Vertex 70 instrument using ATR. A Sherwood Scientific Magway MSB MK1 instrument was used for magnetic susceptibility studies. Molar conductivity measurements were performed using a WTW Cond model 315i/ ET instrument using 10^{-3} M solutions in DMSO.

2.2. *General procedure for synthesis of proton transfer salts 1–3*

In a 1:1 ratio, 5-sulfosalicylic acid (2.18 g, 10.0 mmol) was dissolved in 15 ml of pure ethanol and added dropwise to 15 ml of base solution (Etpip, HOEtpip and Acpip) dissolved in ethanol. The white proton transfer salts (H_2Etpip)(Hssa) (**1**), (H_2HOEtpip)(Hssa) (**2**) and (H_2Acpip)(Hssa) (**3**) were obtained by stirring the reaction mixture at room temperature for 24 h. The white solids were filtered, washed with ethanol, and dried. The physical properties of proton transfer salts **1**–**3** are given in Table 1.

2.3. *General procedure for synthesis of metal complexes 4–6*

The proton transfer salt (**1**–**3**) (1 mmol) was dissolved in 10 ml of water/ethanol (1:1). An aqueous solution (10 ml) of $Cu(CH_3COO)_2 \cdot H_2O$ (1 mmol, 0.200 g) was added to the proton transfer salt (**1**–**3**) solution and the reaction mixture stirred at room temperature for 72 h. The resulting amorphous Cu(II) metal complexes $(H_2Etpip)[Cu(Hssa)_2] \cdot 5H_2O$ (**4**), $(H_2HOEtpip)[Cu(Hssa)_2] \cdot 5H_2O$ (**5**) and $(H_2Acpip)[Cu(Hssa)_2] \cdot 5H_2O$ (**6**) were filtered and dried in air. The physical properties of complexes **4**–**6** are given in Table 1.

T a b l e 1

*The physical properties of salts **1**–**3** and metal complexes **4**–**6***

Compound	Closed formula	MW* (g/mol)	Color	Yield (%)	m.p. (˚C)
1	$C_{13}H_{20}N_2O_6S$	332.32	White	85	249.5
2	$C_{13}H_{20}N_2O_7S$	348.37	White	90	218.8
3	$C_{13}H_{18}N_2O_7S$	346.36	White	85	245.0
4	$C_{20}H_{34}CuN_2O_{17}S_2$	702.16	Green	65	280.5
5	$C_{20}H_{34}CuN_2O_{18}S_2$	718.16	Green	70	227.8
6	$C_{20}H_{32}CuN_2O_{18}S_2$	716.15	Green	65	295.7

*Estimated MW

Analysis. Calcd. for **1** ($C_{13}H_{20}N_2O_6S$): C, 47.00 %; H, 6.10 %; N, 8.40 %; S, 9.65 %. Found: C, 46.98 %; H, 6.07 %; N, 8.43 %; S, 9.65 %. Calcd. for **2** ($C_{13}H_{20}N_2O_7S$): C, 44.81%; H, 5.75 %; N, 8.02 %; S, 9.27 %. Found: C, 44.82 %; H, 5.79 %; N, 8.04 %; S, 9.20 %. Calcd. for **3** ($C_{13}H_{18}N_2O_7S$): C, 45.08 %; H, 5.25 %; N, 8.10 %; S, 9.23 %. Found: C, 45.08 %; H, 5.24 %; N, 8.09 %; S, 9.26 %. Calcd. for **4** ($C_{20}H_{34}CuN_2O_{17}S_2$): C, 34.21 %; H, 4.88 %; N, 3.99 %; S, 9.13 %; Cu 9.05 %. Found: C, 34.20 %; H, 4.90; N, 4.00 %; S, 9.10 %; Cu, 9.05 %. Calcd. for **5** ($C_{20}H_{34}CuN_2O_{18}S_2$): C, 33.45 %; H, 4.77 %; N, 3.90 %; S, 8.93 %; Cu, 8.85 %. Found: C, 33.45 %; H, 4.75 %; N, 3.91 %; S, 8.95 %; Cu, 8.87 %. Calcd. for **6** ($C_{20}H_{32}CuN_2O_{18}S_2$): C, 33.54 %; H, 4.50 %; N, 3.91; S, 8.95 %; Cu, 8.87 %. Found: C, 33.50 %; H, 4.57 %; N, 3.93 %; S, 8.90 %; Cu, 8.89 %.

2.4. *Antimicrobial assay*

In this study, microorganisms of *Staphylococcus aureus* (ATCC 29213; Gram-positive), *Escherichia coli* (ATCC 25922; Gram-negative), *Candida krusei* (ATCC 6258; yeast) and *Candida parapsilosis* (ATCC 22019; yeast) were used. Microorganisms were obtained from Eskişehir Osmangazi University Faculty of Medicine.

2.4.1. *Determination of antimicrobial effect by microdilution method*

The minimum inhibitory concentrations (MICs) of the starting materials (H_3ssa, Etpip, HOEtpip and Acpip) and synthesized compounds **1**–**6** against bacterial strains (*S. aureus* and *E. coli*) and yeasts (*C. krusei* and *C. parapsilosis*) were determined. The MICs of reference antibiotics levofloxacin, cefepime, vancomycin and flucanazole were compared with the newly synthesized compounds **1**–**6**. For this purpose, U-shaped 96-well microplates were used in the microdilution method.

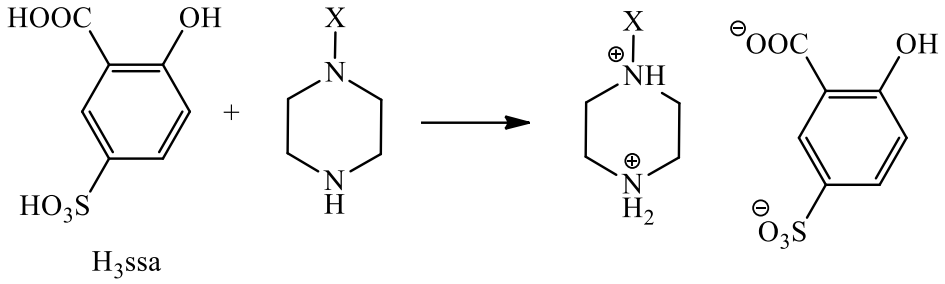
2.4.1.1. *Microdilution method*

MHB medium was prepared at single and double strength. The synthesized compounds (4 mg) and antibiotics (4 mg) were dissolved in 2 ml of DMSO. The bacteria and fungi used were incubated overnight in single-strength MHB medium and their cultures freshly prepared. Suspensions of the cultures were prepared and cell densities were adjusted to 0.5 McFarland tube turbidity (1.0×10^8 (kob)/ml).

3. RESULTS AND DISCUSSION

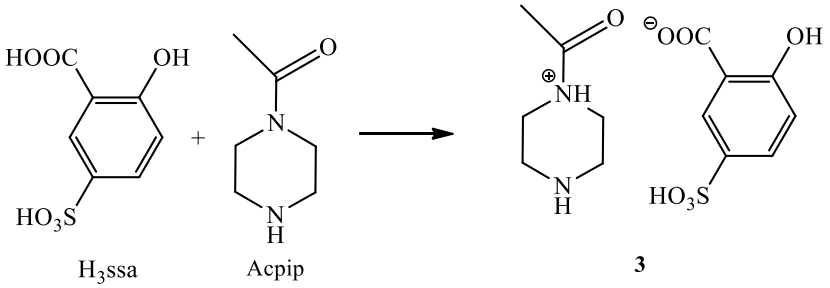
The syntheses of proton transfer salts **1** and **2** obtained by the reactions of Etpip (C_2H_5) and HOEtpip (C_2H_4OH) with H_3ssa are shown in Figure 1a. Treatment of Acpip ($COCH_3$) with H_3ssa yielded the proton transfer salt **3**, as shown in Figure 1b.

The three metal complexes **4**–**6** were synthesized as a result of the reaction of the obtained proton transfer salts **1**–**3** with $Cu(Ac)_2 \cdot H_2O$. The proposed structures of Cu(II) complexes are shown in Figure 2.



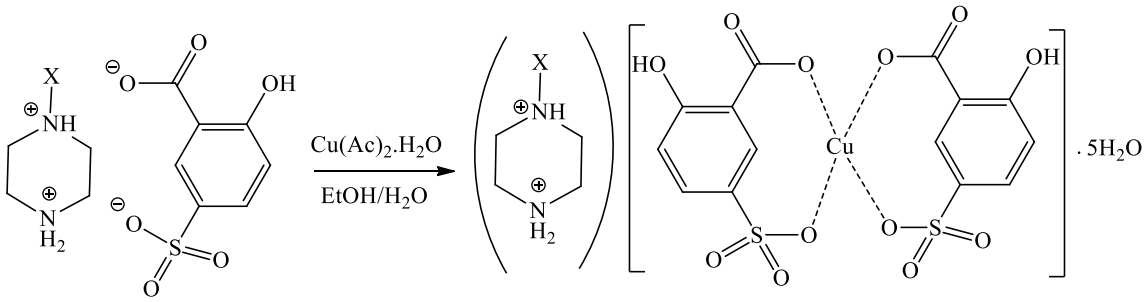
X = C_2H_5 (**1**); X = C_2H_4OH (**2**)

a



b

Fig. 1. Syntheses of proton transfer salts **1**–**3**. (**a** for **1** and **2**, **b** for **3**)



X = C_2H_5(**4**), C_2H_4OH (**5**), $COCH_3$ (**6**)

Fig. 2. Syntheses of metal complexes (**4**–**6**)

3.1. *NMR (^{1}H and ^{13}C) spectra*

3.1.1. *NMR (^{1}H and ^{13}C) spectra of (H_2Etpip)(Hssa)* **(1)**

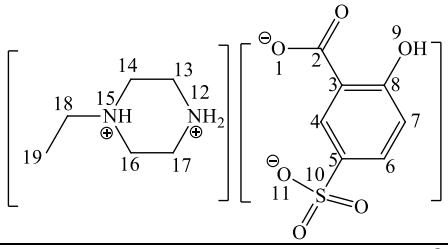
The ^{1}H and ^{13}C NMR (DMSO-d_6, 25 °C) spectra of the synthesized proton transfer salt (**1**) are given in Figures S1 and S2, respectively, and the data of these spectra are given in Table 2. The signals in ^{1}H NMR spectrum of **1** are assigned as follows:

The two doublets for the protons H^6 and H^7 of $Hssa^{2-}$ ring, both with 1H intensity, are observed at 7.58 ppm (H^6, $^3J_{H6\text{-}H7}$ = 7.43 Hz) and 6.77 ppm (H^7, $^3J_{H7\text{-}H6}$ = 8.14 Hz), respectively. A singlet with 1H intensity is observed at 8.07 ppm corresponding to proton H^4. The two singlets, both with 4H intensity, at 3.29 ppm (H^{13} and H^{17}) and at 3.07 ppm (H^{14} and H^{16}) arise from the piperazine ring (H_2Etpip^{2+}) protons. The ethyl group protons of the piperazine ring are observed at 2.85 ppm for the H^{18} proton and at 1.10 ppm for the H^{19} proton, both as singlets. In salt formation, protons of –COOH (H^1) and $–SO_3H$ (H^{11}) are not observed in the ^{1}H NMR spectrum of **1** since they are transferred to the base (Etpip).

As expected, 11 carbon signals are observed in the ^{13}C NMR spectrum of **1**. The peak at 173.035 ppm is assigned to the carboxyl group carbon (–C^2OO). The six signals in the range 109.988–162.402 ppm belong to aromatic carbon atoms (C^3 and C^8). The carbon atoms of the piperazine ring are observed at 41.721 (C^{13} and C^{17}) and 48.327 ppm (C^{14} and C^{16}) and the ethyl group C^{18} and C^{19} carbons attached to the piperazine group are observed at 51.423 and 10.225 ppm, respectively.

T a b l e 2

^{1}H NMR and ^{13}C NMR chemical shifts (ppm) with coupling constants (Hz) and assignments for compound ***1***



H^{1}	–	C^{2}	173.035
H^{4}	8.07 (1H, s)	C^{3}	109.988
H^{6}	7.58 (1H, d) ($^{3}J_{H6-H7}$ = 7.43 Hz)	C^{4}	128.296
H^{7}	6.77 (1H, d) ($^{3}J_{H7-H6}$ = 8.14 Hz)	C^{5}	137.785
H^{9}	8.30 (1H, s)	C^{6}	131.395
H^{11}	–	C^{7}	116.003
H^{12}	–	C^{8}	162.402
H^{13}, H^{17}	3.29 (4H, s)	C^{13}, C^{17}	41.721
H^{14}, H^{16}	3.07 (4H, s)	C^{14}, C^{16}	48.327
H^{15}	–	C^{18}	51.423
H^{18}	2.85 (2H, s)	C^{19}	10.225
H^{19}	1.10 (3H, s)		

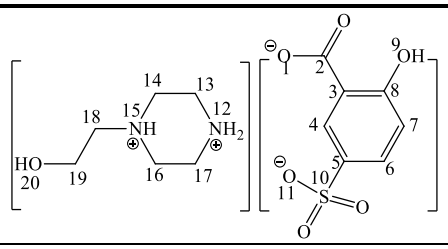
3.1.2. *NMR (^{1}H and ^{13}C) spectra of (H_2HOEtpip)(Hssa)* **(2)**

The ^{1}H and ^{13}C NMR (DMSO-d_6, 25 °C) spectra of the synthesized proton transfer salt **2** are given in Figures S3 and S4, respectively, and the data of these spectra are given in Table 3.

The ^{1}H NMR spectrum of **2** shows three signals for $Hssa^{2-}$ ring protons in the aromatic region. Two doublets for protons H^{6} and H^{7}, both with 1H intensity, are observed at 7.65 ppm (H^{6}, $^{3}J_{H6-H7}$ = 7.71 Hz) and 6.85 ppm (H^{7}, $^{3}J_{H7-H6}$ = 7.93 Hz), respectively. The third proton (H^{4}) signal of the $Hssa^{2-}$ ring is observed as a singlet at 8.07 ppm with 1H intensity.

T a b l e 3

^{1}H and ^{13}C NMR chemical shifts (ppm) with coupling constants (Hz) and assignments for compound ***2***



H^{1}	–	C^{2}	172.882
H^{4}	8.07 (1H, s)	C^{3}	115.764
H^{6}	7.65 (1H, d) ($^{3}J_{H6-H7}$ = 7.71 Hz)	C^{4}	128.296
H^{7}	6.85 (1H, d) ($^{3}J_{H7-H6}$ = 7.93 Hz)	C^{5}	137.815
H^{9}, H^{20}	8.69 (2H, s)	C^{6}	131.508
H^{11}	–	C^{7}	116.175
H^{12}	–	C^{8}	162.405
H^{13}, H^{17}	3.29 (4H, s)	C^{13}, C^{17}	41.668
H^{14}, H^{16}	3.14 (4H, s)	C^{14}, C^{16}	49.294
H^{15}	–	C^{18}	56.817
H^{18}	2.91 (2H, s)	C^{19}	58.882
H^{19}	3.63 (2H, s)		

The two singlets for protons H^{13}-H^{17} and H^{14}-H^{16}, each of 4H intensity, were observed at 3.29 ppm and 3.14 ppm respectively. The two singlets for protons H^{18} and H^{19}, with 2H intensity each, are seen at 2.91 ppm and 3.63 ppm, respectively. A singlet with intensity of 2H is observed at 8.69 ppm, corresponding to the protons OH (H^9 and H^{20}). The absence of –COOH (H^1) and $–SO_3H$ (H^{11}) protons in the NMR spectrum of **2** is evidence of salt formation. These protons are thought to be transferred to the N^{12} and N^{15} atoms of the piperazine ring.

The ^{13}C NMR spectrum of **2** is in good agreement with that expected. It exhibits 11 signals. The peak at 172.882 ppm corresponds to the carboxyl group carbon ($–C^2OO$). Six signals in the range of 162.405–15.764 ppm belong to aromatic carbon atoms (C^3 and C^8). The piperazine carbons C^{13}-C^{17} and C^{14}-C^{16}, each with 2C intensity, are seen at 41.668 and 49.294 ppm, respectively. The carbon atoms in the ethyl group bound to the piperazine ring are observed at 56.817 for C^{18} and 58.882 ppm for C^{19}.

3.1.3. *NMR (^1H and ^{13}C) spectra of (HAcpip)(H_2ssa)* **(3)**

The ^1H and ^{13}C NMR (DMSO-d_6, 25 °C) spectra of the synthesized proton transfer salt (**3**) are given in Figures S5 and S6, respectively, and the data of these spectra are given in Table 4.

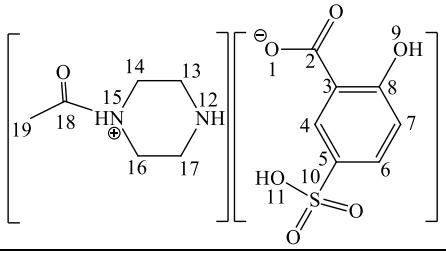
The proton of –COOH (H^1) group is not observed in the ^1H NMR spectrum of **3**. This proton is thought to be transferred to the nitrogen (N^{15}) atom of the piperazine ring in salt formation. Two broad singlets at 11.47 ppm with 1H intensity and at 8.76 ppm with 2H intensity correspond the protons $–SO_3H$ (H^{11}) and OH + NH (H^9 and H^{12}), respectively. The protons –OH (H^9) and $–SO_3H$ (H^{11}) have remain nonionized. The protons H^6 and H^7 of the H_2ssa ring, with intensity of 1H each, are observed as doublets at 7.71 ppm ($^3J_{H6\text{-}H7}$ = 8.55 Hz) and 6.91 ppm ($^3J_{H7\text{-}H6}$ = 8.51 Hz), respectively. The singlet with 1H intensity at 8.05 ppm corresponds to the proton H^4. The signals observed as a triplet with 4H intensity for protons H^{13}–H^{17} ($^3J_{H13/H17\text{-}H14/H16}$ = 4.99 Hz) and a singlet+singlet with 4H intensity for protons H^{14}-H^{16} are seen at 3.59 ppm and at 3.10 ppm, respectively. The acetyl methyl group protons (H^{19}) are observed as a singlet at 1.99 ppm with 3H intensity.

The ^{13}C NMR spectrum of **3** displays 11 resonances. The peak at 172.047 ppm corresponds to carboxyl group carbon ($–C^2OO$). The six resonances in the aromatic region in the range 161.772–112.258 ppm belong to aromatic carbons (C^3 and C^8). The signals at 38.031 (C^{13} and C^{17}) and 43.318 ppm (C^{14} and C^{16}) are from the piperazine ring carbons. The acetyl group carbons C^{18} and C^{19} attached to the piperazine ring are observed at 169.080 and 21.421 ppm, respectively.

The ratio of acid (H_3ssa) to base (Etpip, HOEtpip, or Acpip) was found to be 1:1 from the ^1H and ^{13}C NMR spectra data of the prepared salts **1**–**3**. These results are in good agreement with the structures proposed in Figure 1.

T a b l e 4

*^1H and ^{13}C NMR chemical shifts (ppm) with coupling constants (Hz) and assignments for compound **3***



H^1	–	C^2	172.047
H^4	8.05(1H, s)	C^3	112.258
H^6	7.71 (1H, d) ($^3J_{H6\text{-}H7}$ = 8.55 Hz)	C^4	127.996
H^7	6.91 (1H, d) ($^3J_{H7\text{-}H6}$ = 8.51 Hz)	C^5	139.255
H^9, H^{12}	8.76 (2H, s)	C^6	133.331
H^{11}	11.47 (1H, s)	C^7	117.096
H^{13}, H^{17}	3.59 (4H, t) ($^3J_{H13/H17\text{-}H14/H16}$ = 4.99 Hz)	C^8	161.772
H^{14}, H^{16}	3.10 (4H, s+s)	C^{13}, C^{17}	38.031
H^{15}	–	C^{14}, C^{16}	43.318
H^{19}	1.99 (3H, s)	C^{18}	169.080
		C^{19}	21.421

3.2. *FT-IR measurements*

The FT-IR spectra and data of the compounds **1**–**6** are given in Table 5 and Figures S7–S12, respectively. The phenolic –OH vibration bands of compounds **1** and **2** are observed at 3448 and 3309 cm^{-1}, respectively, while the OH vibration of the –COOH and $–SO_3H$ groups of 5-sulfosalicylate are not observed. The FT-IR spectrum of proton transfer salt **3** shows a very broad absorption band in the range of 3000–2500 cm^{-1} attributed to the ν(O–H) vibration of the $–SO_3H$ group. The broad bands at 3420 cm^{-1} for **4**, at 3372–3325 cm^{-1} for **5** and at 3449 cm^{-1} for **6** are attributed to the ν(OH) vibrations of uncoordinated H_2O molecules and phenolic OH in complexes **4**–**6**. The band due to ν(N–H) stretching vibration for **3** was observed at 3352 cm^{-1}, but not for proton transfer salts **1** and **2** and also complexes **4**–**6**, which confirms that only one nitrogen atom is protonated in compound **3.** In the high-frequency region, weak bands at 2978–2742 cm^{-1} and 3153–3011 cm^{-1} are attributed to the stretching vibrations of aliphatic ν(C–H) and aromatic ν(C–H) vibrations for all compounds **1**–**6**. For compounds containing the –COOH group, the ν(C=O) stretching band is the most characteristic band in the FT-IR spectra and is expected to be in the range of 1660–1700 cm^{-1} [37]. The absence of characteristic ν(C=O) vibration band for the –COOH group in the FT-IR spectra of compounds **1**–**6** indicates that these groups are deprotonated [27]. The strong asymmetrical stretching and weak symmetrical vibration bands of carboxylate ions are observed at 1634 and 1423 cm^{-1} for **1**, at 1617 and 1430 cm^{-1} for **2**, and at 1612 and 1432 cm^{-1} for **3**, respectively [38]. These bands confirm the proton transfer from the –COOH group of 5-sulfosalicylic acid to the nitrogen atoms of the piperazine rings. These bands are observed at 1602 and 1423 cm^{-1} for **4**, at 1601 and 1440 cm^{-1} for **5** and at 1606 and 1431 cm^{-1} for **6** [39, 40]. Also, the strong ν(C=O) stretching vibration band is observed at 1680 and 1647 cm^{-1} for the acetyl group of the piperazine rings of **3** and **6**, repectively. According to the literature [41], the differences between asymmetric and symmetric stretches of carboxylate groups higher than 200 cm^{-1} are monodentate. The Δ-values are 179 cm^{-1} for **4**, 161 cm^{-1} for **5** and 180 cm^{-1} for **6**, which suggests bidentate coordination of the carboxylate and sulfonyl group of 5-sulfosalicylate to the metal ion. The relatively weak and broad band in the range of 2717–2633 cm^{-1} is attributed to the ν(N^+–H) vibration for both proton transfer salts **1**–**3** and complexes **4**–**6** [28].

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*FT-IR spectral data (cm^{-1}) of proton transfer salts **1**–**3** and complexes **4**–**6***

	1	**2**	**3**	**4**	**5**	**6**
ν(O-H)	3448(b)	3309(b)	3000(b)	3420(b)	3372-3325(b)	3449(b)
ν(NH)	–	–	3352(m)	–	–	–
$\nu(C–H)_{ar.}$	3153(w)	3125(w)	3073(w)	3011(w)	3030(w)	3026(w)
$\nu(C–H)_{aliph..}$	2978(w)	2956(w)	2965(w)	2914(w)	2976(w)	2956(w)
	2814(w)	2884(w)	2808(w)	2861(w)	2928(w)	2809(w)
		2745(w)		2742(w)	2777(w)	2751(w)
$\nu(N^+–H)$	2679(w)	2717(w)	2633(w)	2699(w)	2707(w)	2643(w)
	2485(w)	2504(w)	2495(w)	2484(w)	2501(w)	2477(w)
$\nu(C=O)_{acetyl}$	–	–	1680(s)	–	–	1647(s)
$\nu(C=O)_{as}$	1634(s)	1617(s)	1612(s)	1602(s)	1601(s)	1606(s)
$\nu(C=O)_{sym}$	1423(s)	1430(s)	1432(s)	1423(s)	1440(s)	1431(s)
ν(C=C)	1588(s)	1591(s)	1584(s)	1566(s)	1565(s)	1558(s)
	1572(s)	1555(s)	1519(s)	1530(s)	1558(s)	1525(s)
	1479(s)	1476(s)	1471(s)	1475(s)	1517(s)	1471(s)
	1456(s)	1463(s)			1477(s)	
ν(C-O)	1372(s)	1382(s)	1371(s)	1322(s)	1338(s)	1390(s)
	1238(s)	1258(s)	1233(s)	1201(s)	1203(s)	1250(s)
	1076(s)	1078(s)	1078(s)	1086(s)	1085(s)	1086(s)
$\nu_{as}(S=O)$	1264(s)	1299(s)	1289(s)	1222(s)	1271(s)	1271(s)
$\nu_{sym}(S=O)$	1164(s)	1150(s)	1141(s)	1138(s)	1150(s)	1159(s)
ν(Cu–O)	–	–	–	609(w)	606(w)	607(w)

(b: broad, s: sharp, m: medium, w: weak)

The aromatic ν(C=C) stretching vibrations are seen in the of range 1591–1456 and 1566–1471 cm^{-1} for salts **1**–**3** and metal complexes **4**–**6**, respectively. The SO_2 asymmetric vibration for sodium 5-sulphosalicylate dihydrate [5], is reported at 1300 cm^{-1}. The FT-IR spectra of compounds show characteristic ν_{as}(S=O) and ν_{sym}(S=O) vibration bands at 1264 and 1164 cm^{-1} for **1**, at 1299 and 1150 cm^{-1} for **2**, at 1289 and 1141 cm^{-1} for **3**, at 1222 and 1138 cm^{-1} for **4**, at 1271 and 1150 cm^{-1} for **5** and at 1271 and 1159 $cm^{-1}$for **6**, respectively [42,43]. The shift of these absorptions to lower frequency indicates salt formation for **1**–**3** and coordination with copper for **4**–**6** [43]. The Cu–O vibration bands for metal complexes **4**, **5** and **6** are observed at 609, 606 and 607 cm^{-1}, respectively [44]. All these FT-IR data suggest the proposed structures of proton transfer salts **1**–**3** and coordination complexes **4**–**6**, as shown in Figures 1 and 2, respectively.

3.3. *Magnetic susceptibility and molar conductivity of metal complexes* **4–6**

The experimental and theoretical magnetic susceptibility and molar conductivity results of the synthesized metal complexes **4**–**6** are given in Table 6. It is seen that the experimentally obtained values are consistent with the theoretical values and support the structures proposed in Figure 2. Magnetic susceptibilities of metal complexes **4**–**6** were found experimentally as 1.67, 1.61 and 1.65 BM, respectively. These magnetic moment values of the Cu(II) complexes (**4**–**6**) indicate the presence of one unpaired electron (d^9) [45].

The molar conductivity data in DMSO are 50.20 for **4**, 48.80 for **5** and 45.10 $\Omega^{-1}cm^2\ mol^{-1}$ for **6**, indicating that all complexes are ionic [46].

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*Magnetic susceptibility of metal complexes **4–6***

Complexes	$M_{Experimantally}$	$M_{Theoretical}$	n	d^x	Ω
4	1.67	1.73	1	d^9	50.20
5	1.61	1.73	1	d^9	48.80
6	1.65	1.73	1	d^9	45.10

*(BM: Bohr magneton, n: number of unpaired electrons)

3.4. *Atomic absorption spectra of metal complexes* **4–6**

The AAS data of of the metal complexes **4**–**6** are given in Table 1. According to the AAS results, the metal/acid/base ratio in the synthesized metal complexes **4**–**6** is 1:2:1. These results are in good agreement with the proposed structures for the metal complexes **4**–**6** (Fig. 2).

Single X-ray diffraction studies could not be applied to identify the structures of complexes **4**–**6** due to their powder forms. Using elemental analysis, the formulas of the complexes were proposed with the help of FT-IR spectra and magnetic susceptibility and molar conductivity studies (Fig. 2).

3.5. *Antimicrobial activity results*

In this study, the antibacterial and antifungal activities of the starting materials (H_3ssa, Etpip, HOEtpip, Acpip) and synthesized compounds **1**–**6** were measured by a microdilution method. The MIC values of the synthesized compounds **1**–**6** are given in Table 7. When the results were evaluated, it was observed that most of the compounds showed antibacterial and antifungal properties, but the antibacterial activities were more pronounced than the antifungal activities. The antimicrobial activity results obtained are in agreement with similar studies in the literature [47–49]. Most of the compounds were found to be effective against *S. aureus* (Gram-positive) and *E. coli* (Gram-negative) bacteria. In terms of antifungal activity, the compounds were shown to be more effective against the *C. parapsilosis* yeast strain than the *C. krusei* yeast.

The MIC values of the synthesized compounds against *S. aureus* were compared with vancomycin as control compound, when it was observed that the complexes **4**–**6** are more effective than vancomycin, and the proton transfer salt **1** has similar activity to that of vancomycin. The other compounds were observed to have lower activity. Proton transfer salt **1** (31.25 μg/ml) and synthesized complexes **4**–**6** (15.60 μg/ml) showed better activity against *S. aureus* than the control compounds levofloxacin and cefepime (62.50), while free ligands (H_3ssa, Etpip, HOEtpip and Acpip) and proton transfer salts **2** and **3** were determined to have similar activity to those of levofloxacin and cefepime. Complexes **4** and **5** had similar activity to that of levofloxacin (31.25 μg/ml), while other compounds (62.50–500.0 μg/ml) were found to have less effect on the bacterial growth of *E. coli* (31.25 μg/ml) culture than did levofloxacin. Complexes **4** and **5** showed better activity than the control antibiotics vancomycin (62.50 μg/ml) and cefepime (62.50 μg/ml), while complex **6** showed similar activity to those of vancomycin and cefepime.

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MIC values of the compounds (μg/ml)

Compound	*S. aureus*	*E. coli*	*C. krusei*	*C. parapisilosis*
Vancomycin	31.25	62.50	–	–
Levofloxacin	62.50	31.25	–	–
Cefepime	62.50	62.50	–	–
Fluconazole	–	–	–	62.50
H_3ssa	62.50	250.00	62.50	31.25
Etpip	62.50	125.00	125.00	31.25
HOEtpip	62.50	500.00	250.00	31.25
Acpip	62.50	125.00	31.25	31.25
1	31.25	500.00	62.50	31.25
2	62.50	125.00	62.50	31.25
3	62.50	125.00	62.50	31.25
4	15.60	31.25	15.60	15.60
5	15.60	31.25	31.25	62.50
6	15.60	62.50	15.60	15.60

The starting compounds (H_3ssa, Etpip, HOEtpip, and Acpip), proton transfer salts **1**–**3** and metal complexes **4**–**6** were observed to have antifungal activity against *C. krusei*, while the control compound fluconazole showed no activity. Complexes **4** and **6** with MIC values of 15.60 μg/ml were found to have the highest activity of all the compounds. Newly synthesized complexes **4** and **6** (15.60 μg/ml) showed higher antimicrobial effect against *C. parapsilosis* compared to the control antibiotic fluconazole (62.50 μg/ml), proton transfer salts **1**–**3** and free ligands (31.25 μg/ml).

4. CONCLUSIONS

In the present work, three new proton transfer salts (H_2Etpip)(Hssa) (**1**), (H_2HOEtpip)(Hssa) (**2**), (HAcpip)(H_2ssa) (**3**) and their Cu(II) complexes **4**–**6** were synthesized. All measurements showed good agreement with the proposed structures of metal complexes **4**–**6**. Antimicrobial activities of all new compounds **1**–**6** were tested against *S. aureus* (Gram-positive), *E. coli* (Gram-negative), *C. krusei* (yeast) and *C. parapsilosis* (yeast). When the results of antibacterial and antifungal tests of the synthesized compounds **1**–**6** were compared with the control antimicrobial compounds (vancomycin, levofloxacin, cefepime and fluconazole), complexes **4**–**6** showed higher activity against yeasts (*C. krusei* and *C. parapsilosis*) than against bacteria (*S. aureus* and *E. coli*).

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