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RESEARCH ARTICLE

ANTIMICROBIAL ACTIVITY of (*E*)-3-(4-SULFAMOYLPHENYLCARBAMOYL) ACRYLIC ACID DERIVATIVES

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ABSTRACT

In this study, proton transfer salts {$(Hap)^+(samal)^-$ (**4**) and $(HBI)^+(samal)^-$ (**5**)} were synthesized from the reaction of (*E*)-3-(4-sulfamoylphenylcarbamoyl)acrylic acid (Hsamal, **1**) with 1*H*-benzimidazole (BI, **3**) or 2-aminopyridine (ap, **2**), metal complexes of **1** {Fe(II) {$[Fe(samal)(H_2O)_2][Fe(OH)_3(H_2O)]$ (**6**) and $[(H_2O)(OH)_2Fe(samal)Fe(H_2O)_2]$ (**7**)}, Co(II) {$[(H_2O)(OH)_2Co(samal)Co(H_2O)_2]$ (**8**)}, Ni(II) {$[Ni(samal)_2(H_2O)_2]$ (**9**)} and Cu(II) {$[Cu(samal)_2(H_2O)_2]$ (**10**)}}, of **4** {Ni(II) {$[(H_2O)(OH)Ni(samal)Ni(OH)_2(ap)(H_2O)_2]$ (**11**)}, Cu(II) {$[Cu(samal)(OH)(ap)_2]$ (**12**)} and of **5** {Co(II) {$[(HO)_2Co(samal)Co(BI)_2]$ (**13**)}, Ni(II) {$[(H_2O)_2(HO)_3Ni(samal)Ni(BI)_2]$ (**14**)} and Cu(II) {$[(H_2O)_2(HO)_3Cu(samal)Cu(BI)_2(OH)]$ (**15**)}} by the methods found in the literature. Antimicrobial activities of **1**-**15** and metal salts {iron(II) sulfate heptahydrate (**16**), cobalt(II) acetate tetrahydrate (**17**), nickel(II) acetate tetrahydrate (**18**) and copper(II) acetate dihydrate (**19**)} against *Enterococcus faecalis (*ATCC 29212*)* (Gram positive), *Pseudomonas aeruginosa (*ATCC 27853), *Bacillus subtilis* (*wild type), Staphylococcus aureus* (NRRL B-767), *Listeria monocytogenes (*ATCC 7644), *Escherichia coli* (ATCC 25922) (Gram negative) and *Candida albicans* (ATCC 14053) (yeast) microorganisms has been tested. The MIC (Minimum Inhibitory Concentration) values of **1**-**19** were compared with those of reference antimicrobial compounds Vancomycin, Cefepime, Levofloxacin and Fluconazole. Compounds with the best activity are **12** (15.60 µg/mL) for *C. albicans*, **1** and **2** (31.25 µg/mL) for *B. subtilis*, **13** (31.25 µg/mL) for *E. faecalis*, **13** (15.60 µg/mL) for *S. aureus*, **4** and **12** (15.60 µg/mL) for E. Coli, **3** and **8**-**12** (31.25 µg/mL) for *L. monocytogens*, and **8** (31.25 µg/mL) for *P. aeruginoa.*

Keywords: *3-(4-sulfamoylphenylcarbamoyl)acrylic acid, 2-Aminopyridine, Salt, Metal Complexes, Antimicrobial activity*

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1. INTRODUCTION

Proton transfer reactions are unique among numerous chemical processes in which a proton is transferred from one binding site to another, either intermolecularly or intramolecularly. These only involve the transport of a nucleus without any auxiliary electrons. Such reactions can occur without serious disorder in the bonding electrons and without introducing repulsive forces between the non-bonding electrons [1]. Proton transfer is one of the most fundamental processes that plays an important role in many biochemical and chemical reactions [2,3]. Recently, research on proton transfer has been mainly focused on catalytic reactions [4], crystal engineering [5,6], energetic materials [7-9], organic ferroelectrics [10,11],hydrogen storage [12-15], nonlinear optical materials [16,17] and pharmaceutical industry [18,19]. Proton transfer is also known as an important step in many biochemical processes [20-24]. Aromatic/aliphatic carboxylic acids and aromatic/aliphatic bases are generally used in the synthesis of proton transfer salts. In these reactions, the proton of the acid is transferred by the base to form compounds with (+) and (-) charges. These compounds are water-soluble compounds [25].

The biological activity of (*E*)-3-(4-sulfamoylphenylcarbamoyl) acrylic acid (**1**) derivatives are known such as antimicrobial activity [26], dielectric properties [27], anti-inflammatory [28] and antiglaucoma [29,30]. In the literature, proton transfer salts of **1** with 2-aminopyridine [30], 1*H*-benzimidazole [30], 3-aminopyridine, 2-amino-4/5/6-methylpyridines [31] and Ni(II), Co(II), Cu(II) and Fe(II) metal complexes of **1** have been synthesized.

Nowadays, it becomes useless because bacteria that cause diseases gain resistance to the chemicals used in the treatment of diseases. Therefore, there is a need for new chemicals obtained in an effective and inexpensive way to eliminate microorganisms harmful to human health [32-36]. Finding that the compounds obtained in this study have antimicrobial activity against bacteria and yeasts will shed light on future studies. It is obvious that proton transfer salts obtained from 3-(4-sulfamoylphenylcarbamoyl) acrylic acid and its derivatives with antifungal and antibacterial activity and other organic ligands will show similar properties in co-crystal and mixed ligand metal complexes [26-30].

In this study, proton transfer salts **4** and **5** were synthesized from the reaction of 3-(4-sulfamoylphenylcarbamoyl) acrylic acid (**1**) with 2-aminopyridine (**2**) or 1*H*-benzimidazole (**3**), simple metal complexes (**6-10**) of **1** and metal complexes (**11-15**) of salts by the methods found in the literature. Antimicrobial activities of **1-15** and metal salts (**16-19**) against *E. faecalis* (Gram +), *B. subtilis* (*wild type), L. monocytogenes*, *E. coli*, *P. aeruginosa*, *S. aureus* (Gram -) and *C. albicans* (yeast) microorganisms has been tested. The MIC values of the **1-19** were compared with those of control compounds Vancomycin, Cefepime, Levofloxacin and Fluconazole.

2. EXPERIMENTAL

2.1. Materials and Methods

This study, maleic anhydride, sulphanilamide, 2-aminopyridine, 1*H*-benzimidazole, iron(II) sulfate heptahydrate, cobalt(II) acetate tetrahydrate, nickel(II) acetate tetrahydrate and copper(II) acetate dihydrate were obtained from Sigma Aldrich.

2.2. Synthesis of 4-15.

The compounds (**4-15**) were synthesized and characterized by methods found in the literature [30, 31]. The structures of **1-15** are given in Figure 1.

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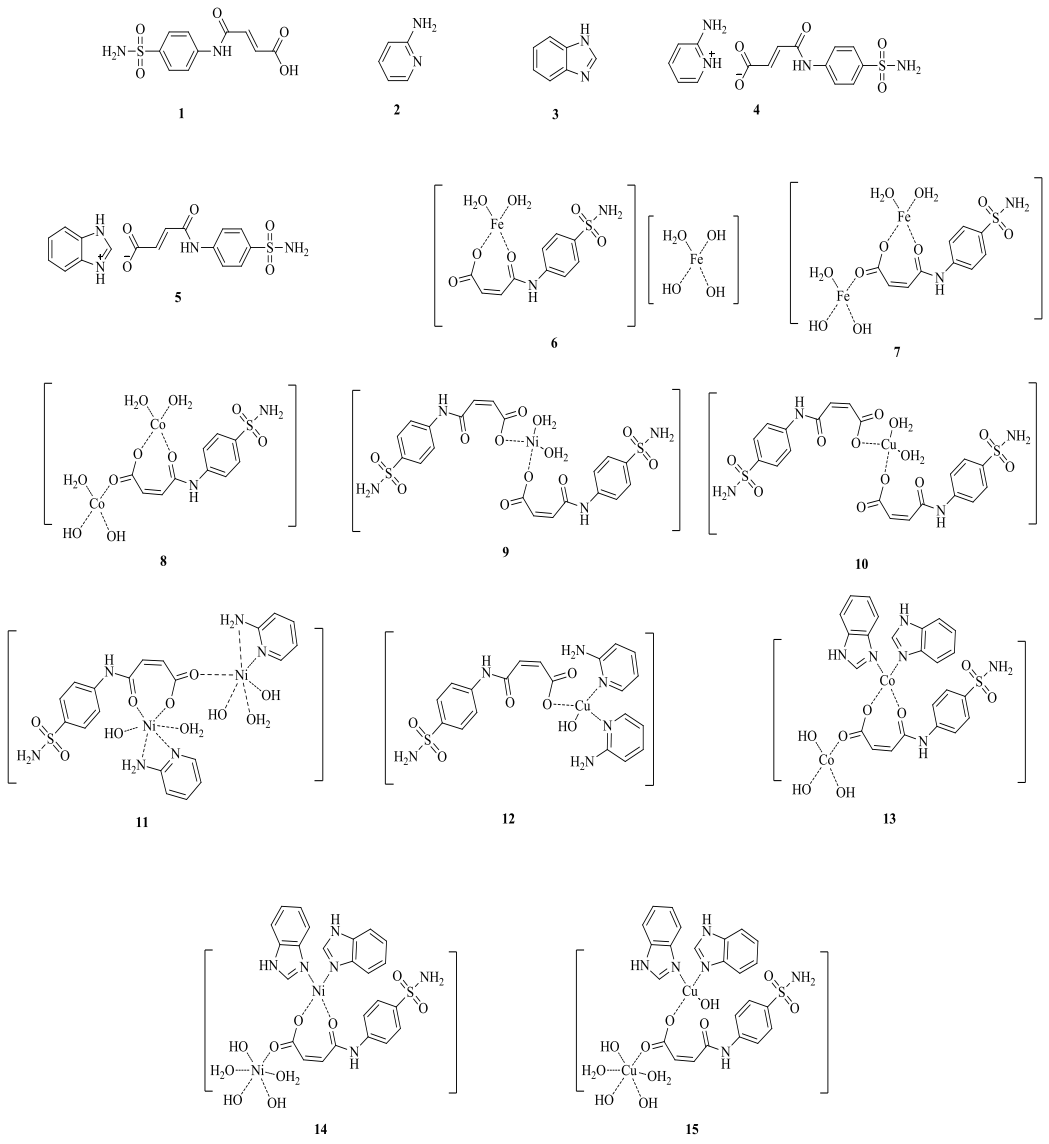

Figure 1. Structures of **1-15**.

2.3. Antimicrobial Assay

E. coli (ATCC 25922) and *E. faecalis* (ATCC 29212) has been obtained from Eskişehir Osmangazi University, Faculty of Medicine *and S. aureus* (NRRL B-767), *B. subtilis*, *P. aeruginosa* (ATCC 27853), *L. monocytogenes* (ATCC 7644) and *C. albicans* (ATCC 14053) from Eskişehir Technical

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University, Biology Department. Microdilution susceptibility test was used to evaluate the antimicrobial activities of **1-19**.

2.3.1. Microorganism

Microbroth dilution susceptibility test was used for antimicrobial analysis of the compounds [37]. MHB medium was prepared as single and double force. The **1-19** and reference antimicrobial compounds (4 mg) were dissolved in 2 mL of DMSO solution. The fungal and bacterial species used were incubated overnight on single-strength MHB medium and their fresh cultures were prepared. Suspensions of the cultures were prepared, and cell densities were adjusted to 0.5 Mc Farland tube turbidity {$1.0x10^8$ CFU/mL} [38,39].

3. RESULTS AND DISCUSSION

3.1. Antifungal and Antibacterial Activities of Compounds

In this work, antifungal and antibacterial activity of all compounds (**1-19**) were tested by microdilution method. MIC values of **1-19** are given in Table 1. **1-19** were observed to have antibacterial and antifungal activity properties. The antifungal and antibacterial activity results obtained are in agreement with similar studies in the literature [26,27,40-43].

Against *C. albicans* yeast species, the compounds **12** (15.60 µg/mL), **7** and **13-15** (31.25 µg/mL) showed a higher effect than the control compound Fluconazole (62.50 µg/mL) while other compounds (except **5**, **8**, **16,** and **19**) had similar effects with Fluconazole. The compounds **5**, **8**, **16,** and **19** (125.00 µg/mL) showed less activity than Fluconazole.

Against *E. faecalis* bacteria, compound **13** was more effective than Vancomycin and Levoflaxacin while the other compounds (except **3**, **8,** and **10**) had similar effects with Vancomycin and Levofloxacin (62.50 µg/mL). The compounds **3**, **8,** and **10** (125.00 µg/mL) showed less activity than Vancomycin and Levofloxacin. The compound **13** (31.25 µg/mL) had similar effects with Cefepime while other compounds showed less activity (62.50-125.00 µg/mL) than Cefepime.

Against B. subtilis bacteria, all compounds were found to have higher activity than the Vancomycin. It was determined that compounds **1** and **2** (31.25 µg/mL) had the highest activity against bacteria. The compounds **1** and **2** were more effective than Levofloxacin and Cefepime while the other compounds (except **10**) had similar effects with Levofloxacin and Cefepime. The compound **10** (125.00 µg/mL) showed less activity than Levofloxacin and Cefepime.

Against *S. aureus* bacteria, the compounds **1**, **2, 4-9**, **12,** and **15-18** were determined to have similar effects (62.50 µg/mL) with Cefepime while the compounds **3**, **10,** and **11** showed less activity (125.00 µg/mL) than Cefepime. The others compound **13** (15.60 µg/mL), **14,** and **19** (32.25 µg/mL) were more effective than Cefepime. The **14** and **19** (31.25 µg/mL) were determined to have similar effects with Levofloxacin and Vancomycin while other compounds showed less activity (62.50-125.00 µg/mL) than Vancomycin and Levofloxacin.

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Against *E. coli* bacteria, compounds **4** and **12** (15.60 µg/mL) had higher activity than all control compounds. Compounds **1**, **2**, **5**, **11**, **15,** and **16** (31.25 µg/mL) for Vancomycin and Levofloxacin and **3**, **6**, **9**, **10**, **13**, **14,** and **17-19** (62.50 µg/mL) for Cefepime have similar effects with control compounds.

Against *L. monocytogens*, all compounds had higher activity than Vancomycin. The **3** and **8-12** were determined to have similar effects (31.25 µg/mL) with Levofloxacin and Cefepime while the other compounds showed less activity than Levofloxacin and Cefepime.
Against *P. aeruginoa* bacteria, the compound **8** showed a higher effect (15.60 µg/mL) than the control compounds. The compounds **1-5**, **7**, **10,** and **13-19** were determined to have similar effects (62.50 µg/mL) with Vancomycin while the compound **11** showed similar activity (31.25 µg/mL) than Levofloxacin and Cefepime. The compounds **6** and **9** showed less activity (125.00 µg/mL) than all the control compounds.

Table 1. Antibacterial and antifungal activity values (µg/mL) of compounds

Compound	***C. albicans***	***B. subtilis***	***E. faecalis***	***S. aureus***	***E. coli***	***L. monocytogens***	***P. aeruginoa***
Cefepime	Not tested	62.50	31.25	62.50	62.50	31.25	31.25
Vancomycin	Not tested	250	62.50	31.25	31.25	125.00	62.50
Levofloxacin	Not tested	62.50	62.50	31.25	31.25	31.25	31.25
Fluconazole	62.50	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
1	62.50	31.25	62.50	62.50	31.25	62.50	62.50
2	62.50	31.25	62.50	62.50	31.25	62.50	62.50
3	62.50	62.50	125.00	125.00	62.50	31.25	62.50
4	62.50	62.50	62.50	62.50	15.60	62.50	62.50
5	125.00	62.50	62.50	62.50	31.25	62.50	62.50
6	62.50	62.50	62.50	62.50	62.50	62.50	125.00
7	31.25	62.50	62.50	62.50	125.00	62.50	62.50
8	125.00	62.50	125.00	62.50	125.00	31.25	15.60
9	62.50	62.50	62.50	62.50	62.50	31.25	125.00
10	62.50	125.00	125.00	125.00	62.50	31.25	62.50
11	62.50	62.50	62.50	125.00	31.25	31.25	31.25
12	15.60	62.50	62.50	62.50	15.60	31.25	62.50
13	31.25	62.50	31.25	15.60	62.50	62.50	62.50
14	31.25	62.50	62.50	31.25	62.50	62.50	62.50
15	31.25	62.50	62.50	62.50	31.25	62.50	62.50
16	125.00	62.50	62.50	62.50	31.25	62.50	62.50
17	62.50	62.50	62.50	62.50	62.50	62.50	62.50
18	62.50	62.50	62.50	62.50	62.50	62.50	62.50

19	125.00	62.50	62.50	31.25	62.50	62.50	62.50

4. CONCLUSIONS

All compounds (**1-19**) showed antimicrobial activity against *S. aureus*, *E. faecalis*, *B. subtilis*, *E. coli*, *C. albicans*, *L. monocytogenes* and *P. aeroginosa* microorganisms. **1-19** with the best activity are **12** (15.60 µg/mL) for *C. albicans*, **1** and **2** (31.25 µg/mL) for *B. subtilis*, **13** (31.25 µg/mL) for *E. faecalis*, **13** (15.60 µg/mL) for *S. aureus*, **4** and **12** (15.60 µg/mL) for *E. Coli*, **3** and **8-12** (31.25 µg/mL) for *L. monocytogens* and **8** (15.60 µg/mL) for *P. aeruginoa*. In general, metal complexes showed better activity results than proton transfer salts and starting materials.

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