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RESEARCH ARTICLE

ANTIMICROBIAL ACTIVITY OF PROTON SALTS OF 3-(SULFAMOYLPHENYLCARBAMOYL)ACRYLIC ACID DERIVATIVES WITH AMINOPYRIDINE DERIVATIVES

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ABSTRACT

Ten proton transfer salts (**9-18)** were synthesized from the reaction of 2-aminopyridine (**1**), 2-amino-3/4/5/6-methylpyridines (**2-5**) and 3-aminomethylpyridine (**6**) with (*E*)-3-(3/4-sulfamoylphenylcarbamoyl)acrylic acid (**7** and **8**), respectively. *Bacillus subtilis* (*wild culture)*, *Candida albicans* (ATCC 14053) (yeast), *Enterococcus faecalis (*ATCC 29212*)* (Gram positive), *Escherichia coli* (ATCC 25922), *Listeria monocytogenes (*ATCC 7644), *Pseudomonas aeruginosa* (ATCC 27853*)*, *Staphylococcus aureus* (NRRL B-767) (Gram negative) bacterial microorganisms have been tested against the antimicrobial evaluation of compounds (**1–18**). Vancomycin, Cefepime, Levofloxacin and the antifungal substance Fluconazole were used as antibacterial reference compounds for comparing the MIC values of **1-18**. Compounds **1**, **3-6**, **8-13**, **15**, **17** and **18** for *E. faecalis*, **5** for *B. subtilis*, **1**, **3-12**, **15**, **17** and **18** for *S. aureus*, **3**, **9**, **10**, **13**, **15** and **17** for *L. monocytogenes*, **16** for *E. Coli* and **4** for *P. aeruginosa* the best effect are observed. Proton transfer salts {**9**, **14, 15** and **17**} were showed higher effect than Fluconazole while other compounds (except compounds **2** and **4**) had similar effects with Fluconazole. The compounds **2** and **4** showed less activity than Fluconazole.

Keywords: *2-Aminopyridine derivatives, 3/4-(Sulfamoylphenylcarbamoyl) acrylic acid, Proton transfer salt, Antibacterial and antifungal activity.*

1. INTRODUCTION

Proton transfer is one of the most fundamental processes that plays an important role in many chemical and biochemical reactions [1-7]. Proton transfer reactions are unique among numerous chemical processes in which a proton is transferred from one binding site to another, either intermolecular or intramolecular. These only involve the transport of a nucleus without any auxiliary

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electrons. Such reactions can occur without serious disorder in the bonding electrons and without introducing repulsive forces between the non-bonding electrons [8]. Recently, research on proton transfer has been mainly focused on crystal engineering [9,10], catalytic reactions [11,12], organic ferroelectrics [13,14], energetic materials [15-17], nonlinear optical materials [18,19], hydrogen storage [20-23] and pharmaceutical industry [24,25] focused on other related areas. 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 [26].

The biological activity of acrylic acid derivatives which are the acid compound of this study are known such as anti-inflammatory [27], dielectric properties [28], antimicrobial activity [28,29], virus type 1 (HIV-1) [30] and antiglaucoma [31,32]. In the literature, 2-amino-3/4/5/6-methylpyridines [34], 2-aminopyridine [33], 2-aminobenzothiazole and 2-amino-6-ethoxybenzothiazole [35] proton transfer salts with (*E*)-3-(3-sulfamoylphenylcarbamoyl)acrylic acid (**7**) while 1*H*-benzimidazole, 2-aminopyridine [32], 2-amino-3/4/5/6-methylpyridine, 3-aminopyridine [36] proton transfer salts are synthesized with (*E*)-3-(4-sulfamoylphenylcarbamoyl)acrylic acid (**8**) have been synthesized. The antimicrobial properties of metal complexes of **8** are investigated [37].

2-Aminopyridine derivatives which are the basic components of this study, have known biological activities such as antiviral, antiparasitic, antibacterial, anticonvulsant, antihistamine, antifungal, anti-inflammatory, antidiabetic, analgesic and anti-Alzheimer's. In the literature, abundant salts of 2-aminopyridine derivatives with other compounds continue to be synthesized.

In this study, salts **9-13** of between **7** and **1-5**, and **14-18** of between **8** and **1-6** were synthesized by methods found in the literature [32-36]. The antimicrobial activities of the compounds **1-6** and **8** [37] and **9-18** were tested against *C. albicans* (yeast) and *E. coli*, *L. monocytogenes*, *B. subtilis*, *P. aeruginosa*, *E. faecalis*, and *S. aureus* bacterial microorganisms. The antimicrobial test results of all compound substances (**1-18**) were compared with the control compounds.

2. EXPERIMENTAL

2. 1. Synthesis of 9-18.

Proton transfer salts **9-18**, which we synthesized and characterized in our previous studies [32-36]. The structures of free ligands (**1-8**) and proton transfer salts (**9-18**) are given in Figure 1.

The ethanol solution of 10 mmol **7** (50 mL) was added to 10 mmol **1** for **9**, **2** for **10**, **3** for **11**, **4** for **12** and **5** for **13** (50 mL). The ethanol solution of 10 mmol **8** (50 mL) was added to 10 mmol **1** for **14**, **3** for **15**, **4** for **16**, **5** for **17** and **6** for **18** (50 mL). The white solids resulting from the reaction mixture were filtered and dried (m.p 207 ^{o}C for **7**, d.p 189 ^{o}C for **9**, d.p 190 ^{o}C for **10**, d.p 182 ^{o}C for **11**, d.p 200 ^{o}C for **12**, d.p 180 ^{o}C for **13**, m.p 209 ^{o}C for **8**, d.p 191 ^{o}C for **14**, d.p 210 ^{o}C for **15**, d.p 180 ^{o}C for **16**, d.p 190 ^{o}C for **17** and d.p 145 ^{o}C for **18**).

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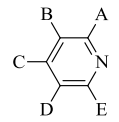
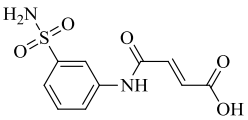
2. 2. Microbiological Test

In this study, Eskişehir Osmangazi University, Faculty of Medicine provided the *E. faecalis* and *E. coli* bacteria utilized and the biology department of Eskişehir Technical University provided the *C. albicans*, *B. subtilis*, *L. monocytogenes*, *S. aureus* and *P. aeruginosa* microorganisms. All compounds (**1–18**) had their antibacterial activity assessed using a microdilution susceptibility test. In DMSO solution, the sample solutions had previously been separated.

The compounds' antibacterial investigation was conducted using a microbroth dilution susceptibility test [38]. The samples' stock solutions in DMSO were created. In 4 mL of DMSO solution, antibiotics (8 mg) and synthesized substances (8 mg) were dissolved. Using McFarland No. 0.5 standard solution, overnight-grown bacterial and yeast suspensions in double-strength Mueller-Hinton broth were standardized to 10^8 Colony Forming Units/mL. The wells then received 100 µL of each microbe suspension. As a negative control, the last well chain without a microorganism was employed. The medium and sterile distilled water acted as a positive growth control. The first well without turbidity was chosen as the MIC following an 18–24 h incubation period at 37 °C [39,40].



A = NH_2, B = H, C = H, D = H, E = H (**1**)
A = NH_2, B = CH_3, C = H, D = H, E = H (**2**)
A = NH_2, B = H, C = CH_3, D = H, E = H (**3**)
A = NH_2, B = H, C = H, D = CH_3, E = H (**4**)
A = NH_2, B = H, C = H, D = H, E = CH_3 (**5**)
A = H, B = CH_2NH_2, C = H, D = H, E = H (**6**)



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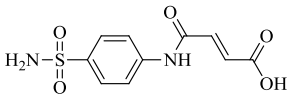

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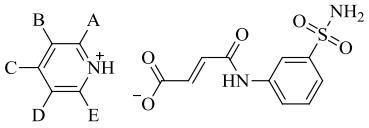
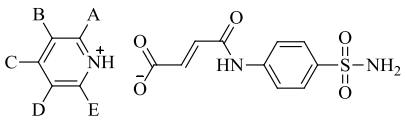


A = NH_2, B = H, C = H, D = H, E = H (**9**)
A = NH_2, B = CH_3, C = H, D = H, E = H (**10**)
A = NH_2, B = H, C = CH_3, D = H, E = H (**11**)
A = NH_2, B = H, C = H, D = CH_3, E = H (**12**)
A = NH_2, B = H, C = H, D = H, E = CH_3 (**13**)



A = NH_2, B = H, C = H, D = H, E = H (**14**)
A = NH_2, B = H, C = CH_3, D = H, E = H (**15**)
A = NH_2, B = H, C = H, D = CH_3, E = H (**16**)
A = NH_2, B = H, C = H, D = H, E = CH_3 (**17**)
A = H, B = CH_2NH_2, C = H, D = H, E = H (**18**)

Figure 1. Structures of **1-18**.

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3. RESULTS AND DISCUSSION

In this work, antimicrobial activity of **1-18** were tested by microdilution method. MIC values of **1-18** are given in Table 1. According to MIC values it was observed that the all compounds have antibacterial and antifungal activity properties.

It was determined that compound **5** (7.80 µg/mL) had the highest activity against *B. subtilis* bacteria. All compounds found to have higher efficacy against this bacterium than the Vancomycin control compound. The compounds **5**, **8**, **9**, **12** and **17** were more effective than Levofloxacin, and Cefepime control compounds while the compounds **1-4**, **6**, **7**, **10**, **11**, **13-15** and **18** were showed similar effects with the compounds. The compound **16** showed less activity than Levofloxacin, and Cefepime.

Table 1. Antimicrobial activity values of compounds (µg/mL).

Compound	***S. aureus***	***E. faecalis***	***E. coli***	***B. subtilis***	***P. aeruginosa***	***L. monocytogenes***	***C. albicans***
Vancomycin	31.25	62.50	31.25	250	62.50	125.00	-
Levofloxacin	31.25	62.50	31.25	62.50	31.25	31.25	-
Cefepime	62.50	31.25	62.50	62.50	31.25	31.25	-
Fluconazole	-	-	-	-	-	-	62.50
1	62.50	62.50	15.60	62.50	62.50	62.50	62.50
2	125.00	125.00	125.00	62.50	62.50	62.50	125.00
3	62.50	62.50	31.25	62.50	62.50	31.25	62.50
4	62.50	62.50	31.25	62.50	15.60	62.50	125.00
5	62.50	62.50	62.50	7.80	62.50	62.50	62.50
6	62.50	62.50	62.50	62.50	125.00	62.50	62.50
7	62.50	125.00	62.50	62.50	62.50	62.50	62.50
8	62.50	62.50	31.25	31.25	62.50	62.50	62.50
9	62.50	62.50	62.50	31.25	31.25	31.25	15.60
10	62.50	62.50	125.00	62.50	62.50	31.25	62.50
11	62.50	62.50	31.25	62.50	62.50	62.50	62.50
12	62.50	62.50	31.25	31.25	62.50	62.50	62.50
13	125.00	62.50	62.50	62.50	62.50	31.25	62.50
14*	125.00	125.00	31.25	62.50	125.00	62.50	31.25
15	62.50	62.50	31.25	62.50	62.50	31.25	31.25
16	125.00	125.00	7.80	125.00	62.50	62.50	62.50
17	62.50	62.50	31.25	31.25	62.50	31.25	31.25
18	62.50	62.50	62.50	62.50	62.50	62.50	62.50

*[37]

Against *E. faecalis* bacteria, all compounds (expect compounds **2**, **7**, **14** and **16**) were determined to have similar effects (62.50 µg/mL) with Vancomycin and Levofloxacin. The compounds **2**, **7**, **14** and

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16 showed less activity (125.00 µg/mL) than Vancomycin and Levofloxacin. The all showed less activity (62.50-125.00 µg/mL) than Cefepime.

Against *S. aureus* bacteria, the compounds **1**, **3-12**, **15**, **17** and **18** were determined to have similar effects (62.50 µg/mL) with Cefepime while the compounds **2**, **14** and **16** showed less activity (125.00) than Cefepime. The all compounds showed less activity (62.50-125.00 µg/mL) than Vancomycin and Levofloxacin (31.25 µg/mL).

Against *E. coli* bacteria, compounds **1** (15.60 µg/mL) and **16** (7.80 µg/mL) had higher activity than all control compounds. Compounds **3**, **4**, **8**, **11**, **12**, **14**, **15** and **17** for Vancomycin and Levofloxacin and **5**, **6**, **7**, **9**, **13** and **18** for Cefepime have similar effects with control compounds.
Against *L. monocytogenes*, the compounds **3**, **9**, **10**, **13**, **15** and **17** showed the same effect as Levofloxacin and Cefepime, and all other substances were found to be more effective against this bacterium than the Vancomycin control compound.

Against *P. aeruginosa* bacteria, the compound **4** showed a higher effect (15.60 µg/mL) than the control compounds. The compounds **1-3**, **5**, **7**, **8**, **10-13** and **15-18** were determined to have similar effects (62.50 µg/mL) with Vancomycin while the compound **9** showed similar activity (31.25 µg/mL) than Levofloxacin and Cefepime. The compounds **6** and **14** showed less activity (125.00 µg/mL) than all the control compounds.

Against *C. albicans* yeast species, the compounds **9** (15.60 µg/mL), **14, 15** and **17** (31.25 µg/mL) showed a higher effect than Fluconazole (62.50 µg/mL) while other compounds (except compounds **2** and **4**) had similar effects (62.50 µg/mL) with Fluconazole. The compounds **2** and **4** showed less activity (125.00 µg/mL) than Fluconazole.

In the antimicrobial activity studies of compounds containing sulphanilamide and maleic acid, only studies conducted by our group were found in the literature as salt [37]. In addition, the activities of some monomeric or polymeric structures were examined and it was observed that they showed activity against bacteria and yeasts [28,29]. When the antimicrobial activities of the synthesized salts were compared with similar compounds found in the literature, it was observed that they had similar activity [28,29,37].

4. CONCLUSIONS

All compounds showed antimicrobial activity against *E. coli*, *B. subtilis*, *P. aeruginosa*, *S. aureus*, *E. faecalis*, *L. monocytogenes* and *C. albicans* microorganisms. In general, the synthesized compounds showed similar properties with the control compounds against bacteria (*P. aeruginosa*, *S. aureus*, *E. coli*, *L. monocytogenes*, *B. subtilis* and *E. faecalis*). Compounds **1**, **3-6**, **8-13**, **15**, **17** and **18** for *E. faecalis*, **5** for *B. subtilis*, **1**, **3-12**, **15**, **17** and **18** for *S. aureus*, **3**, **9**, **10**, **13**, **15** and **17** for *L. monocytogenes*, **16** for *E. Coli* and **4** for *P. aeruginosa* the best effect are observed. Proton transfer salts {**9**, **14, 15** and **17**} were showed higher effect than Fluconazole while other compounds (except compounds **2** and **4**) had similar effects with Fluconazole. The compounds **2** and **4** showed less activity than Fluconazole.

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