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Synthesis and Antibacterial Activity of Some Aryloxyacetic Acid Derivatives Containing Aryl Sulfonate Moiety

Aril Sülfonat Parçası İçeren Bazı Ariloksiasetik Asit Türevlerinin Sentezi ve Antibakteriyel Aktivitesi

[1]Sevil ŞENKARDEŞ, [2]Tuğçe KOYUNCU, [3]Hilal Başak EROL, [3]Banu KAŞKATEPE

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye
[2]Faculty of Pharmacy, Marmara University, Istanbul, Türkiye
[3]Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Ankara University, Ankara, Türkiye

Sevil Şenkardeş: https://orcid.org/0000-0002-0523-459X
Tuğçe Koyuncu: https://orcid.org/0000-0002-9395-9522
Hilal Başak Erol: https://orcid.org/0000-0002-7943-755X
Banu Kaşkatepe: https://orcid.org/0000-0002-9722-4267

ABSTRACT

Objective: Today, the development of antibiotic resistance is increasing rapidly. This makes it necessary to discover new antibiotics; therefore, this research aims to find new antibacterial agents.

Materials and Methods: Structures of the newly synthesised compounds (4a-d, 5a-d) were elucidated by elemental analyses and spectroscopic data. Their *in vitro* antibacterial activities were tested using a micro-dilution technique against *Escherichia coli, Pseudomonas aeruginosa*, *Staphylococcus aureus,* methicillin-resistant *Staphylococcus aureus*, and *Enterococcus faecalis.* Ciprofloxacin was used as the control drug in this study, which was carried out in accordance with the guidelines of the European Committee on Antimicrobial Susceptibility Testing.

Results: The antimicrobial activities of the compounds were found in a wide range with minimum inhibitory concentration (MIC) values of 15.62-125 µg/mL. Particularly, 4-((2-(2-(4-chloro-3-methyl)acetyl) hydrazineylidene)methyl)phenyl p-methyl benzenesulfonate (4b) was found to be most effective against *Enterococcus faecalis* with MIC value of 15.62 µg/mL.

Conclusion: The findings of this study display that the different derivatives of the molecules in this study may be considered important candidates for future research. Considering the results, it is planned to reach more effective new compounds with modifications to be made by changing the substituents on the aromatic rings.

Keywords: Aldehyde, antimicrobial activity, hydrazide, hydrazone, sulfonate

ÖZ

Amaç: Günümüzde antibiyotik direnci gelişimi hızla artmaktadır. Bu da yeni antibiyotiklerin keşfedilmesini gerekli kılmaktadır. Dolayısıyla bu araştırmanın amacı yeni antibakteriyel ajanlar bulmaktır.

Materyal ve Metot: Yeni sentezlenen bileşiklerin (4a-d, 5a-d) yapıları elemental analiz ve spektroskopik verilerle aydınlatıldı. *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, metisiline dirençli *Staphylococcus aureus* and *Enterococcus faecalis*'e karşı mikrodilüsyon tekniği kullanılarak *in vitro* antibakteriyel aktiviteleri test edildi. Avrupa Antibiyotik Duyarlılık Komitesi standartlarına uygun olarak yapılan bu çalışmada, kontrol ilaç olarak siprofloksazin kullanıldı.

Bulgular: Bileşiklerin antimikrobiyal aktivite sonuçları minimum inhibitör konsantrasyon (MİK)=15,62-125 µg/mL olarak geniş bir aralıkta bulundu ve özellikle 4-((2-(2-(4-kloro-3-metil)asetil)hidraziniliden)metil)fenil p-metilbenzensülfonat (4b)' nin 15,62 µg/mL MİK değeri ile *Enterococcus faecalis*'e karşı en etkili olduğu tespit edildi.

Sonuç: Bu çalışmanın bulguları, bu çalışmadaki moleküllerin farklı türevlerinin gelecekteki araştırmalar için önemli adaylar olarak kabul edilebileceğini göstermektedir. Sonuçlar göz önüne alındığında; aromatik halkaların üzerindeki sübstitüentler değiştirilerek yapılacak modifikasyonlarla daha etkin yeni bileşiklere ulaşılması planlanmaktadır.

Anahtar Kelimeler: Aldehit, antimikrobiyal aktivite, hidrazit, hidrazon, sülfonat

Sorumlu Yazar / Corresponding Author:
Sevil Şenkardeş
Marmara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 34854, İstanbul, Türkiye.
Tel: +90(216) 777 52 00
E-mail: sevil.aydin@marmara.edu.tr

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INTRODUCTION

Hydrazones possessing an azomethine -NHN=CH- proton constitute a considerable class of compounds for new drug development and have beneficial roles in treating many bacterial infections.[1] Nitrofurazone, furazolidone and nitrofurantoin are known to contain typical hydrazide-hydrazone moiety, in which the carbonyl group and nitrogen atom are included in the oxazolidine or imidazolidine ring.

In recent years, much attention has been devoted to the synthesis of new hydrazones and to testing these molecules for antibacterial activity.[2–5] In this direction, Nabizadeh et al.[6] reported nitro benzylidene (quinazoline-4-yl) hydrazine scaffold as an antimicrobial agent. Balasubramaniyan et al.[7] reported the synthesis of 2r,6c-diaryl-3t-methylpiperidin-4-one arylsulphonylhydrazones and showed that they exhibit significant activity against bacteria. The 2-(2-(1 -(furan-2-yl)ethylidene) hydrazine) quinazoline-4 (3H)-one was identified as *Escherichia coli (E. coli)* DNA gyrase inhibitor.[8] Similarly, Tekin et al.,[9] in 2023, synthesised a novel series of hydrazide–hydrazones of bis-substituted isovanillin and assessed their antibacterial activity. Some hydrazones showed great inhibition properties against *E. coli* bacterial strains. Recently, several hydrazones discovered in our laboratory have shown potent anti-*Pseudomonas aeruginosa* (*P. aeruginosa)* activity.[10] Besides, sulfonate moiety is known to possess several antimicrobial activities.[11–14]

Because a new series of 4-((2-(2-(aryloxy)acetyl) hydrazineylidene)methyl)phenyl 4-methyl benzenesulfonate and 2-methoxy-4-((2-(2-(aryloxy)acetyl) hydrazineylidene)methyl)phenyl 4-methyl benzenesulfonate was designed and synthesised as potential antibacterial agents.

Thus, we aim to discover new compounds with high antibacterial activity by combining sulfonate and hydrazone groups, each with an antimicrobial effect. These derivatives were evaluated *in vitro* for their activity against *E. coli, P. aeruginosa*, *Staphylococcus aureus (S. aureus)*, methicillin-resistant Staphylococcus aureus (MRSA), and *Enterococcus faecalis (E. faecalis)*.

MATERIALS AND METHODS

Ethical Status: Ethical approval for the study is not required.

Chemistry: Melting points were determined using Schmelzpunktbestimmer SMP II. NMR spectra were recorded on the BRUKER Ultrashield TM spectrometer. Microanalyses were determined by LECO CHNS-932. FTIR spectra were recorded on a Shimadzu 8400S spectrometer. Compounds 2a-d and 3a -b were prepared according to the reported procedure.[15–19]

Synthesis of Compounds 4a-d and 5a-d: A suspension of the hydrazides (2 mmol) 2a-d in absolute ethanol (20 ml) was treated with the 3a-b (2 mmol) catalytic amount of gl. acetic acid and mixture were refluxed for 2-5 h. After completion of reflux, the precipitate formed was collected, dried and recrystallised from ethanol (Figure 1).

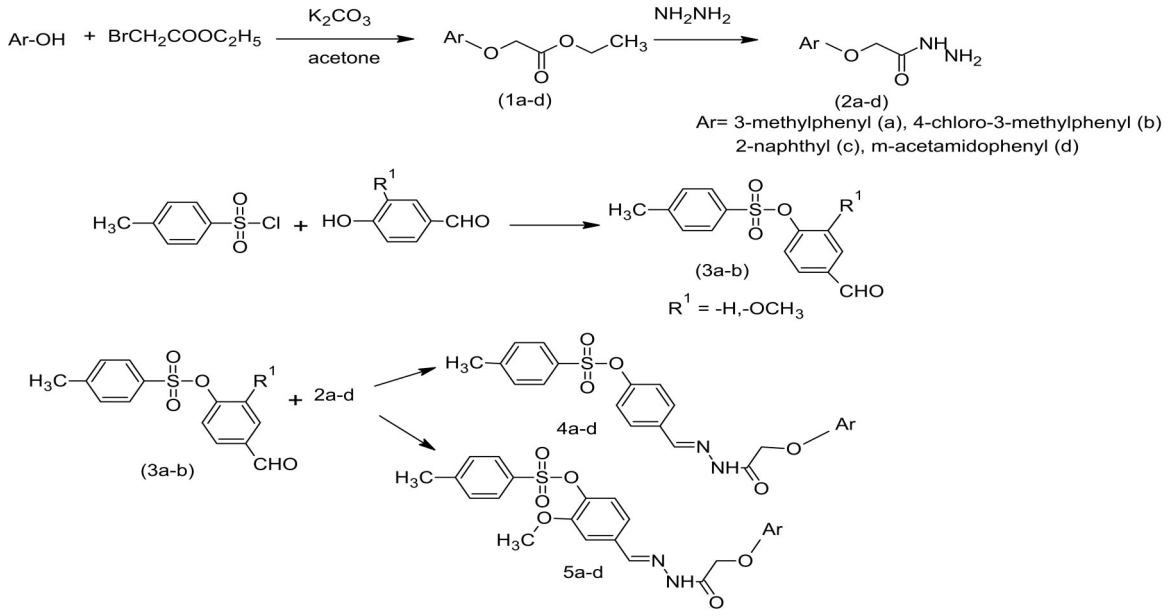

Figure 1. Synthesis of sulfonate-based hydrazones.

4-((2-(2-(m-tolyloxy)acetyl)hydrazineylidene) methyl)phenyl p-methylbenzenesulfonate (4a): Melting point: 143-144°C; FTIR u_{max} (cm^{-1}): 3319 (N-H); 1674 (C=O amide); 1369, 1151 (SO_2). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.26 (s, 3H, -CH_3); 2.28 (s, 3H, -CH_3); 4.63 and 5.09 (2s, 2H, O-CH_2); 6.76-7.76 (m, 12H, aromatic-H); 7.96 and 8.31 (2s, 1H, hydrazone -CH=); 11.62 and 11.63 (2s, 1H, -NH). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.6 (-CH_3), 64.9 and 66.8 (CH_2), 111.8, 112.0, 115.6, 115.8, 121.9, 122.4, 122.9, 123.0, 128.9, 129.1, 129.5, 129.7, 130.7, 131.6, 133.6, 133.7, 139.5, 142.6, 146.4 and 146.8 (CH=N), 150.2 and 150.4 (C-OSO_2), 158.2 and 158.6 (C-O-CH_2), 164.9 and 169.7 (CO). Anal. Calcd for $C_{23}H_{22}N_2O_5S$. 1/3 H_2O: C 62.15%; H 5.14%; N 6.30%; S, 7.21% Found: C 62.35%; H 4.98%; N 6.23%; S 7.43%.

4-((2-(2-(4-chloro-3-methylphenoxy)acetyl) hydrazineylidene)methyl)phenyl p-methylbenzenesulfonate (4b): Melting point: 145-146°C; FTIR u_{max} (cm^{-1}): 3329 (N-H); 1685 (C=O amide); 1371, 1172 (SO_2). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.26 (s, 3H, -CH_3); 2.28 (s, 3H, -CH_3); 4.65 and 5.11 (2s, 2H, O-CH_2); 7.05-7.75 (m, 11H, aromatic-H); 7.95 and 8.27 (s, 1H, hydrazone -CH=); 11.63 (s, 1H, -NH). ^{13}C-NMR-DEPT (150 MHz, DMSO-d_6) δ: 20.2 (-CH_3), 21.6 (-CH_3), 65.3 and 67.0 (CH_2), 114.0, 114.2, 117.7, 117.9, 122.9, 123.0, 128.7, 128.9, 129.1, 129.9, 130.7, 142.7, 146.9 (CH=N). Anal. Calcd for $C_{23}H_{21}ClN_2O_5S$. 1/2 H_2O: C 58.41%; H 4.48%; N 5.92%; 6.78% Found: C 57.43%; H 4.42%; N 5.72%; S 6.81%.

4-((2-(2-(naphthalen-2-yloxy)acetyl) hydrazineylidene)methyl)phenyl p-methylbenzenesulfonate (4c): Melting point: 172-173°C; FTIR u_{max} (cm^{-1}): 3319 (N-H); 1689 (C=O amide); 1375, 1174 (SO_2). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.41 (s, 3H, -CH_3); 4.79 and 5.25 (2s, 2H, O-CH_2); 7.28-7.89 (m, 15H, aromatic-H); 7.99 and 8.30 (s, 1H, hydrazone -CH=); 11.68 and 11.74 (s, 1H, -NH). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.6 (-CH_3), 65.2 (CH_2), 107.4, 107.6, 119.0, 122.0, 123.0, 124.1, 124.4, 126.8, 127.0, 127.1, 127.9, 128.7, 129.0, 129.1, 129.7, 129.9, 130.7, 131.6, 133.6, 134.5, 142.7, 146.4 and 146.9 (CH=N), 150.2 (C-OSO_2), 156.0 and 156.5 (C-O-CH_2), 164.7 and 169.4 (CO). Anal. Calcd for $C_{26}H_{22}N_2O_5S$: C 65.80%; H 4.67%; N 5.90%; S 6.76% Found: C 65.38%; H 4.74%; N 5.91%; S 6.76%.

4-((2-(2-(3-acetamidophenoxy)acetyl) hydrazineylidene)methyl)phenyl p-methylbenzenesulfonate (4d): Melting point: 180-181°C; FTIR u_{max} (cm^{-1}): 3263 (N-H); 1685 (C=O amide); 1352, 1155 (SO_2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.19 (s, 3H, $NHCOCH_3$); 2.47 (s, 3H, -CH_3); 4.66 and 5.14 (2s, 2H, O-CH_2); 6.67-7.76 (m, 13H, aromatic-H and hydrazone -CH=); 8.24 (s, 1H, $NHCOCH_3$); 9.54 and 9.61 (s, 1H, -NH). Anal. Calcd for $C_{24}H_{23}N_3O_6S$.1/3H_2O: C 59.13%; H 4.89%; 8.62%; S 6.58% Found: C 59.25%; H 4.72%; N 8.62%; S 6.62%.

2-methoxy-4-((2-(2-(m-tolyloxy)acetyl) hydrazineylidene)methyl)phenyl p-methylbenzenesulfonate (5a): Melting point: 138-140°C; FTIR u_{max} (cm^{-1}): 3198 (N-H); 1687 (C=O amide); 1371, 1161 (SO_2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3H, CH_3); 2.46 (s, 3H, -CH_3); 3.58 (s, 3H, Ar-OCH_3); 4.67 and 5.14 (2s, 2H, O-CH_2); 7.10-7.79 (m, 11H, aromatic-H); 8.81 (s, 1H, hydrazone -CH=); 9.53 and 9.71 (2s, 1H, -NH). Anal. Calcd for $C_{24}H_{24}N_2O_5S$.1/3H_2O: C 60.75%; H 5.07%; N 5.95%; S 6.79% Found: C 60.75%; H 5.24%; N 5.90%; S 6.76%.

2-methoxy-4-((2-(2-(4-chloro-3-methylphenoxy) acetyl)hydrazineylidene)methyl)phenyl p-methylbenzenesulfonate (5b): Melting point: 165-167°C; FTIR u_{max} (cm^{-1}): 3320 (N-H); 1695 (C=O amide); 1373, 1174 (SO_2). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.28 (s, 3H, -CH_3); 2.42 (s, 3H, -CH_3); 3.54 (O-CH_3); 4.66 and 5.14 (2s, 2H, O-CH_2); 7.16-7.74 (m, 10H, aromatic-H); 7.94 and 8.27 (s, 1H, hydrazone -CH=); 11.68 (s, 1H, -NH). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 20.2 (-CH_3), 21.6 (-CH_3), 56.1 and 56.4 (OCH_3), 65.3 and 67.0 (CH_2), 110.8, 111.4, 114.0, 114.2, 117.7, 117.9, 120.0, 120.8, 124.3, 125.1, 125.7, 128.7, 129.9, 130.3, 130.4, 132.3, 132.5, 134.6, 136.7, 136.9, 138.9, 139.2, 142.8, 146.1 and 147.2 (CH=N), 152.0 (C-OSO_2), 156.9 (OCH_3), 157.4 (C-O-CH_2), 164.6 and 169.5 (CO). Anal. Calcd for $C_{24}H_{23}ClN_2O_6S$: C 57.31%; H 4.61%; N 5.57%; S 6.38% Found: C 57.23%; H 4.87%; N 5.43%; S 6.75%.

2-methoxy-4-((2-(2-(napthalen-2-yloxy)acetyl) hydrazineylidene)methyl)phenyl p-methylbenzenesulfonate (5c): Melting point: 175-176°C; FTIR u_{max} (cm^{-1}): 3209 (N-H); 1703 (C=O amide); 1355, 1178 (SO_2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.46 (s, 3H, -CH_3); 3.58 (s, 3H, OCH_3); 4.82 and 5.26 (2s, 2H, O-CH_2); 7.07-7.85 (m, 14H, aromatic-H); 8.18 (s, 1H, hydrazone -CH=); 9.56 and 9.68 (s, 1H, -NH). Anal. Calcd for $C_{27}H_{24}N_2O_6S$.1/4H_2O: C 63.70%; H 4.85%; N 5.50%; S 6.30% Found: C 63.67%; H 5.07%; N 5.51%; S 6.36%.

4-((2-(2-(3-acetamidophenoxy)acetyl) hydrazineylidene)methyl)-2-methoxyphenyl p-methylbenzenesulfonate (5d): Melting point: 177-179°C; FTIR u_{max} (cm^{-1}): 3313 (N-H); 1697 (C=O amide); 1363, 1157 (SO_2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.19 (s, 3H, $NHCOCH_3$); 2.46 (s, 3H, -CH_3); 3.53 (OCH_3); 4.63 and 5.14 (2s, 2H, O-CH_2); 6.65-7.81 (m, 12H, aromatic-H and hydrazone -CH=); 8.19 (s, 1H, $NHCOCH_3$); 9.81 and 9.95 (s, 1H, -NH). Anal. Calcd for $C_{25}H_{25}N_3O_7S.H_2O$: C

56.70%; H 5.14%; N 7.93%; S 6.30 % Found: C 56.32%; H 5.45%; N 7.48%; S 6.31%.

Determination of the Minimum Inhibitory Concentration: The antibacterial activity of all synthesised compounds was determined by using the micro-dilution method according to The European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations against a group of bacteria, including *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, MRSA ATCC 43300, and *E. faecalis* ATCC 29212.[20] For the micro-dilution method, briefly, double-fold dilutions of compounds were prepared by adding 100 µl (1000 µg/ml) to the first well of the microplate containing 100 µl of cation adjusted Mueller Hinton Broth (Becton Dickinson) in each well. Then, bacterial suspensions, prepared from fresh cultures of bacteria, equal to McFarland 0.5 turbidity were prepared from fresh cultures, the concentrations were diluted at a ratio of 1/100, and 100 µL was added to all wells. Microplates were incubated at 37°C for 16-20 h, and the lowest concentration that inhibited bacterial growth was determined as the minimum inhibitory concentration (MIC) value. Ciprofloxacin (Himedia, Mumbai, India) was used as the control and the results of ciprofloxacin MIC were evaluated according to the EUCAST quality control.[20]

Statistical Analysis: Data are expressed as means ±SDs. Concerning the MIC values, the experiments were performed in triplicate, the concordance degree was 3/3, and the ±SD was zero.

RESULTS

Hydrazones showed carbonyl amide stretching at 1674-1703 cm^{-1} and N-H bands in 3198-3320 cm^{-1} region. ^{1}H-NMR data were also in agreement with the formation of hydrazones. The ^{13}C-NMR spectra showed the carbonyl signals at 169.48-169.67 ppm, and imine signals at 146.4-147.2 ppm.

The antibacterial activity of the compounds 4a-d and 5a-d were assayed using the micro-dilution method against Gram-negative *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) and Gram-positive (MRSA ATCC 43300, *S. aureus* ATCC 29213 *and E. faecalis* ATCC 29212*)* strains. The results of MICs are presented in Table 1.

The result revealed that none of the compounds displayed better activity than the standard drug Ciprofloxacin. All of them exhibited moderate inhibitory activities (MIC= 62.5 µg/ml) against *P. aeruginosa*. Also, it displayed broad antibacterial spectra with MIC values ranging from 62.5-125 µg/mL against MRSA. Compound 4b bearing 4-chloro-3-methylphenoxy moiety was the most effective molecule having the least MIC value (MIC= 15.62 µg/ml) as compared to the other compounds against *E. faecalis*.

DISCUSSION AND CONCLUSION

The synthesis method is outlined in Figure 1. The synthesis of hydrazide (2a-d) derivatives was prepared according to the literature.[15–19] We have previously reported the synthesis of aldehydes (3a-b).[18] Hydrazones 4a-d and 5a-d were obtained into good yield by coupling 2a-d compounds with the 3a-b aldehydes in ethanol. All the new products gave corrected analytical data. When the ^{1}H-NMR spectra are examined, the absence of the $–NH_2$ peak belonging to the $-NHNH_2$ group proves that our compounds are formed. We also observed two signals for CH_2-CO- and some of the –CONH- protons believed to be due to their presence as conformational or geometrical isomers.[21–23] When the ^{1}H-NMR spectra of the flurbiprofen hydrazide-hydrazones were examined, it was determined that -CH, -CONH, -CH=N groups gave two separate peaks.[24] When viewed in ^{13}C-NMR spectra, the hydrazone structures were supported by the resonance of carbonyl groups in the lower field. Han et al.[25] confirmed that the peak around 169 ppm corresponds to a carbonyl

Table 1. *In vitro* antimicrobial activity of the synthesised compounds, MIC in µg/mL.

Compounds	MIC (mg/mL)*				
	***Pseudomonas aeruginosa* ATCC 27853**	***Escherichia coli* ATCC 25922**	***Enterococcus faecalis* ATCC 29212**	***Staphylococcus aureus* ATCC 29213**	**Methicillin resistant *Staphylococcus aureus* ATCC 43300**
4a	62.5	125	62.5	125	62.5
4b	62.5	125	15.62	125	62.5
4c	62.5	125	31.25	125	62.5
4d	62.5	125	62.5	125	125
5a	62.5	125	62.5	125	125
5b	62.5	125	62.5	125	125
5c	62.5	125	62.5	125	62.5
5d	62.5	125	62.5	125	62.5
Ciprofloxacin	0.25	0.008	0.5	0.5	-

*: MIC: Minimum inhibitory concentration (MIC was determined in three independent experiments).

group. According to the antibacterial activity results, it was understood that compound 4b showed a remarkable effect. When the activity results of all the compounds are examined, they are not better than the antibacterial effect results of the hydrazone compounds mentioned in the information section.

In conclusion, a series of novel hydrazide-hydrazone derivatives incorporating different aryloxy moieties were synthesised and characterised by elemental analysis and spectral methods. All new compounds were evaluated for their antibacterial activity against five bacteria (including three gram-positive and two gram-negative) found as medium to good (MIC=15.62-125 µg/mL) compared with the reference drug. These outcomes propose that further modification of these compounds may give beneficial agents acting as antimicrobial drug candidates.

Ethics Committee Approval: There is no need for ethics committee approval for this work.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – SŞ, TK; Supervision – SŞ, BK; Materials – TK, HBE, BK; Data Collection and/or Processing – SŞ, TK, HBE, BK; Analysis and/or Interpretation – SŞ, HBE, BK; Writing – SŞ, TK, HBE, BK.

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