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RESEARCH ARTICLE

Synthesis and antibacterial activity of new hydrazide-hydrazones derived from Benzocaine

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ABSTRACT

A novel series of new eleven benzocaine hydrazide derivatives, *N*-(4-{[2-(nonsubstituted/ substitutedfuryl/ phenyl/ pyridinyl/ thienyl/ pyrrole)methylidene]hydrazinyl] carbonyl}phenyl) benzamides [**3a-k**] have been synthesized in this study. The structures of the new compounds were determined by spectral (FT-IR and ^{1}H-NMR) methods and their purity was proven by elemental analysis and thin layer chromatography. These compounds were evaluated for *in vitro* antibacterial activity by using micro-well dilution method against *Escherichia coli* ATCC 10536, *Escherichia coli* ATCC 15442, *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 15442, *Acinetobacter baumannii* , *Klebsiella pneumonia ATCC 13883*.

Key words: Antibacterial activity; Benzocaine; hydrazide-hydrazone; azomethine.

1. Introduction

In recent years, many species of bacteria have improved resistance as a consequence of erroneous and unnecessary use of antibiotics. Lack of new drug molecules and synthesis of molecules with significant effects canalized researchers to develop new molecules in this area. Previously synthesized molecules with hydrazide-hydrazone structure have been found to have antibacterial activity of a significant level. Benzocaine (ethyl 4-amino-benzoate) is a local anesthetic drug which contains esther funcionality. Hydrazide-hydrazones have diverse biological activities [1-12].

In this study, benzocaine hydrazide-hydrazones have been synthesized. The purity of the synthesized compounds have been proven by elementel analysis and melting point assay. Their structure elucidation have been characterized by ^{1}H-NMR and FT-IR spectroscopic methods. The antibacterial activity of the synthesized compounds were studied against Gram positive and Gram negative bacteria, *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumonia* .

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2. Results and Discussion

2. 1. Chemistry

Ethyl 4-amino benzoate (Benzocaine) was used as the starting compound to design several novel hydrazide-hydrazones. Firstly *p*-(benzoylamino)benzoic acid hydrazide was prepared. That compound **1** was prepared by benzocaine which was solved in diethylether and benzoyl chloride in cold medium. The reaction of compound **1** with hydrazine-hydrate in ethanol resulted in *N*-[4-(hydrazinylcarbonyl) phenyl]benzamide. Compound **2** was condensed with substituted aldehydes in ethanolic medium in the presence of a few drops of glacial acetic acid with refluxed to obtain new *N*-(4-{[2-(nonsubstituted/substituted furyl/phenyl/ pyridinyl/thienyl/pyrrole)methylidene]hydrazinyl]carbonyl} phenyl)benzamides (**3a-k**) (Scheme 1).

The structures of compounds **3a-k** were confirmed by elemental analyses and spectral techniques such as FT-IR and ^{1}H-NMR.

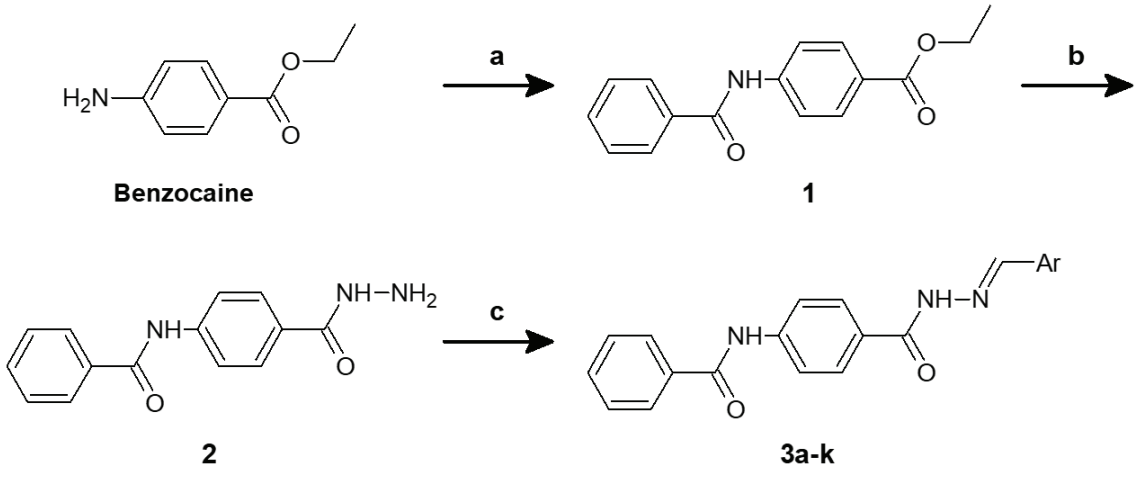
FT-IR spectral data of our novel hydrazide-hydrazones **3a-k** were observed amide N-H, hydrazone N-H amide C=O, hydrazone C=O and C=N streching data between 3360-3269, 3198-3045, 1687-1680, 1653-1643 and 1620-1600 cm^{-1}, respectively.

^{1}H-NMR spectral data of compounds **3a-k** revealed supporting evidence to identify their structures. The singlet signals belonging to azomethine proton in compounds **3a-k** were detected at 8.39-8.93 ppm respectively. The chemical shift of the azomethine proton in compounds **3c** were detected in the range of 8.17 and 8.40 ppm as two singlet peaks. The –NH-proton of acylhydrazone moiety of compounds **3a-k** was detected in the range of 10.51-10.56 ppm. In the ^{1}H-NMR spectra of compounds **3a-k** the NH-proton of benzamide was detected in the range of 11.48-12.24 ppm.

In the ^{1}H-NMR spectra of compounds **3d**, characteristic signals for CH_3 moiety have been detected 3.38 ppm as signal proton. The $–CH_2$-CH_3 protons of compound **3f** was detected for CH_3 moiety at 1.26 ppm as triplet and for CH_2 2.83 ppm as quartet signals. In the ^{1}H-NMR spectra of compounds **3k** which were derived from piperidine aldehyde, characteristic signals for CH moiety were detected in the range of 1.58-3.27 ppm.

2.2 Biological Activity

The antimicrobial activities of all compounds were evaluated in the Department of Genetics and Bioengineering, Faculty of Engineering, Yeditepe University. The sensitivity of the bacterial strains towards the compounds was evaluated from the minimal inhibitory concentration (MIC) values obtained by the micro-well dilution method. The antibacterial activity of the compounds were evaluated against 5 bacterial cultures. The microorganisms used were *Escherichia coli* ATCC 10536, *Escherichia coli* ATCC 15442, *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 15442, *Acinetobacter baumannii , Klebsiella pneumonia ATCC 13883.* The results of antibacterial activity of synthesized compounds **3a-k** are given Table 1.



Scheme 1. Synthetic route to benzocaine hydrazide-hydrazones (**3a-k**). **a)** C_6H_5COCl, Et_2O; **b)** $NH_2NH_2.H_2O$, EtOH **c)** Ar-CHO, EtOH.

Table 1. Antibacterial activity results of the synthesized compounds **3a-k**

COMPOUND ID (LAB CODE)	Antibacterial activity (MIC, µg/µl)				
	Escherichia coli ATCC 10536-ATCC 15442	*Staphylococcus aureus* ATCC 6538	*Pseudomonas aeruginosa* ATCC 15442	*Acinetobacter baumannii*	*Klebsiella pneumoniae* ATCC 13883
3a (SGK 581)	8.192	4.096	> 8.192	> 8.192	8.192
3b (SGK 582)	8.192	2.048	4.096	> 8.192	8.192
3c (SGK 583)	8.192	8.192	4.096	> 8.192	8.192
3d (SGK 584)	4.096	2.048	2.048	8.192	4.096
3e (SGK 585)	4.096	2.048	2.048	8.192	4.096
3f (SGK 587)	2.048	2.048	2.048	4.096	4.096
3g (SGK 588)	2.048	2.048	2.048	8.192	4.096
3h (SGK 589)	> 8.192	> 8.192	> 8.192	> 8.192	> 8.192
3i (SGK 590)	> 8.192	> 8.192	> 8.192	> 8.192	> 8.192
3j (SGK 591)	> 8.192	> 8.192	> 8.192	> 8.192	> 8.192
3k (SGK 592)	> 8.192	> 8.192	> 8.192	> 8.192	> 8.192

3. Conclusion

Through condensation of *N*-[4-(hydrazinylcarbonyl) phenyl]benzamide (**2**) and selected aldehydes, 11 new acylhydrazone derivatives were synthesized and evaluated for their antibacterial activity. None of the compounds tested (compounds **3a-k**) were found to be active against both Gram (+) and Gram (-) bacterial strains.

4. Materials and Methods

Benzocaine was liberally ensured Merck. All aldehydes were purchased from Fluka and Aldrich. All other chemicals were purchased from Merck. Melting points were taken on Schmelzpunktbestimmer 9300 SMP II apparatus and are uncorrected. Synthesis of these compounds were carried out in Memmert WNB14 instrument and Heidolph MR Plug radley. Elemental analyses were performed on VarioMICRO V1.5.7.* instrument. FT-IR spectra were run on Schimadzu FTIR-8400S spectrophotometer. ^{1}H-NMR spectra were obtained on a BRUKER AVANCE-DPX 400* instrument (*This instruments exist in İnönü University Scientific and Technological Research Center).

4.1. Chemistry

Preparation of ethyl 4-[(phenylcarbonyl)amino]benzoate (1) and *N*-[4-(hydrazinylcarbonyl) phenyl]benzamide (2)

Benzocaine (0.05 mol, 8.25 g) was dissolved in diethylether (50 mL). Simultaneously solution of benzoylchloride (0.05 mol, 6 mL) was added dropwise to that liquid with stirring. This reaction becomes in cold atmosphere and it cooled with ice bath (approximately 5-10 °C). Almost the mixture was stirred 45 minutes. The solid which was fell down filtered and washed with cold water. Extra benzoyl chloride go away from the solid with water. The compound (**1**) was crystallized from ethanol (M.p. 139 °C, Lit. M.p. 140 °C [13]).

Compound **1** (0.04 mol,10.77g) and hydrazine-hydrate (%80, 7,5 ml) was heated under the reflux in 50 mL ethanol for 2 hours. The mixture was cooled at room temperature after stopped the reaction. The precipitate was filtered and washed with water. The yield crystallized from ethanol (M.p 237 °C, Lit. M.p. 240 °C [13]).

General procedure for the synthesis of arylhydrazones of *N*-[4-(hydrazinylcarbonyl) phenyl]benzamide (3a-k)

A solution of compound **2** (0.001 mol, 0.255 g) in 20 mL ethanol and appropriate aldehyde (0.001 mol) were heated (100 °C) under reflux for 8 hours. After the mixture was cooled at room temperature and ethanol was evaporated. The product was dried and crystallized with ethanol.

***N*-(4-{[2-(4-bromothiophene-2-yl)methylidene] hydrazinyl]carbonyl}phenyl)benzamide (3a)**

Yield %81; M.p. 294 °C; Rf 0.67; FT-IR ν_{max} (cm^{-1}): 3360 (amide NH str.), 3198 (hydrazone NH str.), 3003 (arom. CH str.), 1680 (amide CO str.), 1645 (hydrazone CO str.), 1606 (hydrazone C=N str.), 1593, 1541, 1500, 1489 (aromatic C=C str., amide CN str., amide and hydrazone NH bending), 1058 (arom. C-Br str.); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 7.53-7.99 (11H, m, Ar-H), 8.63 (1H, s, -N=CH), 10.53 (1H, s, CO-NH), 11.90 (1H, s, CO-NH-N). Anal. Calcd for $C_{19}H_{14}BrN_3O_2S$: C, 53.28; H, 3.29; N, 9.81; S, 7.49. Found: C, 53.97; H, 3.72; N, 9.94; S, 7.40.

_N_-(4-{[2-(5-nitrofuran-2-yl) methylidene]hydrazinyl] carbonyl}phenyl)benzamide (3b)

Yield %83; M.p. 307-308 °C; Rf 0.38; FT-IR v_{max} (cm^{-1}): 3321 (amide NH str.), 3144 (hydrazone NH str.), 3003 (arom. CH str.), 1687 (amide CO str.), 1651 (hydrazone CO str.), 1612 (hydrazone CN str.), 1599, 1541, 1508, 1469, 1402 (aromatic C=C str., amide CN str., nitro N=O asm. str., amide and hydrazone NH bending), 1346 (nitro N=O sym str.) ; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 7.26-7.99 (11H, m, Ar-H), 8.40 (1H, s, -N=CH), 10.56 (1H, s, CO-NH), 12.21 (1H, s, CO-NH-N). Anal. Calcd for $C_{19}H_{14}N_4O_5$: C, 60.32; H, 3.73; N, 14.81. Found: C, 60.09; H, 3.65; N, 14.59.

_N_-(4-{[2-(furan-3-yl) methylidene]hydrazinyl]carbonyl} phenyl)benzamide (3c)

Yield %62; M.p. 308-309 °C; Rf 0.43 FT-IR v_{max} (cm^{-1}): 3335 (amide NH str.), 3184 (hydrazone NH str.), 3003 (arom. CH str.), 1680 (amide CO str.), 1643 (hydrazone CO str.), 1600 (hydrazone CN str.), 1570, 1527, 1508, 1489 (aromatic C=C str., amide CN str., amide and hydrazone NH bending); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.82-7.99 (12H, m, Ar-H), 8.17, 8.40 (1H, s, -N=CH), 10.52 (1H, s, CO-NH), 11.67 (1H, s, CO-NH-N). Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 67.77; H, 4.48; N, 12.44.

_N_-(4-{[2-(1-methyl-1_H_-pyrrole-2-yl)methylidene] hydrazinyl]carbonyl}phenyl)benzamide (3d)

Yield %63; M.p. 254-255 °C; Rf 0.64; IR v_{max} (cm^{-1}): 3292 (amide NH str.), 3080 (hydrazone NH str.), 3003 (arom. CH str.), 2933 (alif. CH str.), 1680 (amide CO str.), 1651 (hydrazone CO str.), 1620 (hydrazone CN str.), 1602, 1543, 1506, 1489 (aromatic C=C, amide CN str., amide and hydrazone NH bending); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.88 (3H, s, Ar-CH_3) 6.10-7.99 (12H, m, Ar-H), 8.38 (1H, s, -N=CH), 10.51 (1H, s, CO-NH), 11.48 (1H, s, CO-NH-N). Anal. Calcd for $C_{20}H_{18}BrN_4O_2$.1/2 C_2H_5OH: C, 68.22; H, 5.68; N, 15.16. Found: C, 68.16; H, 4.86; N, 15.96.

_N_-(4-{[2-(2,6-difluorobenzylidene)hydrazinyl]carbonyl} phenyl)benzamide (3e)

Yield %90; M.p. 283-285 °C; Rf 0.50; FT-IR v_{max} (cm^{-1}): 3271 (amide NH str.), 3045 (hydrazone NH str.), 3001 (arom. CH str.), 1689 (amide CO str.), 1645 (hydrazone CO str.), 1602 (hydrazone CN str.), 1591, 1545, 1510, 1489 (aromatic C=C str., amide CN str., amide and hydrazone NH bending), 1122 (arom C-F str.); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 7.24-7.99 (12H, m, Ar-H), 8.63 (1H, s, -N=CH), 10.54 (1H, s, CO-NH), 11.94 (1H, s, CO-NH-N). Anal. Calcd for $C_{21}H_{15}F_2N_3O_2$: C, 66.49; H, 3.99; N, 11.08. Found: C, 67.30; H, 4.14; N, 10.82.

_N_-[4-({2-[(5-ethylthiophene-2-yl)methylidene] hydrazinyl}carbonyl)phenyl]benzamide (3f)

Yield %36; M.p. 237 °C; Rf 0.55; FT-IR v_{max} (cm^{-1}): 3335 (amide NH str.), 3157 (hydrazone NH str.), 3003 (arom. CH str.), 2933 (aliphatic CH str.), 1680 (amide CO str.), 1653 (hydrazone CO str.), 1604 (hydrazone CN str.), 1587, 1556, 1502, 1487 (aromatic C=C str., amide CN str., amide and hydrazone NH bending); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.26 (3H, t, -CH_2-CH_3) 2.83 (2H, q, -CH_2-CH_3) 6.87-7.98 (11H, m, Ar-H), 8.57 (1H, s, -N=CH), 10.52 (1H, s, CO-NH), 11.69 (1H, s, CO-NH-N). Anal. Calcd for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.07; N, 11.13; S, 8.49. Found: C, 66.44; H, 4.93; N, 10.92; S, 8.08.

_N_-[4-({2-[4-(trifluoromethoxy)benzylidene]hydrazinyl} carbonyl)phenyl]benzamide (3g)

Yield %77; M.p. 311 °C; Rf 0.55; FT-IR v_{max} (cm^{-1}): 3327 (amide NH str.), 3159 (hydrazone NH str.), 2997 (arom. CH str.), 1680 (amide CO str.), 1653 (hydrazone CO str.), 1606 (hydrazone CN str.) 1581, 1543, 1506, 1489 (aromatic C=C str., amide CN str., amide and hydrazone NH bending), 1151 (ether CO str.); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 7.53-8.00 (13H, m, Ar-H), 8.49 (1H, s, -N=CH), 10.54 (1H, s, CO-NH), 11.91 (1H, s, CO-NH-N). Anal. Calcd for $C_{22}H_{16}F_3N_3O_3$: C, 61.83; H, 3.77; N, 9.83. Found: C, 61.00; H, 3.62; N, 9.74.

_N_-(4-{[2-(4-cyanobenzylidene)hydrazinyl]carbonyl} phenyl)benzamide (3h)

Yield %88; M.p. 303-304 °C; Rf 0.51; FT-IR v_{max} (cm^{-1}): 3323 (amide NH str.), 3126 (hydrazone NH str.), 3022 (arom. CH str.), 2225 (cyano CN str.) 1680 (amide CO str.), 1653 (hydrazone CO str.), 1606 (hydrazone CN str.), 1589, 1541, 1502, 1487 (aromatic C=C str., amide CN str., amide and hydrazone NH bending); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 7.53-7.99 (13H, m, Ar-H), 8.51 (1H, s, -N=CH), 10.55 (1H, s, CO-NH), 12.05 (1H, s, CO-NH-N). Anal. Calcd for $C_{22}H_{16}N_4O_2$.1/2 C_2H_5OH: C, 70.51; H, 4.85; N, 14.30. Found: C, 70.49; H, 4.40; N, 14.82.

_N_-[4-({2-[3,5-_bis_(trifluoromethyl)benzylidene] hydrazinyl}carbonyl)phenyl]benzamide (3i)

Yield %88; M.p. 297 °C; Rf 0.55; FT-IR v_{max} (cm^{-1}): 3298 (amide NH str.), 3124 (hydrazone NH str.), 3030 (arom. CH str.), 1680 (amide CO str.), 1641 (hydrazone CO str.), 1610 (hydrazone CN str.), 1600, 1533, 1508, 1487 (aromatic C=C str., amide CN str., amide and hydrazone NH bending); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 7.54-8.61 (12H, m, Ar-H, 1H, s, -N=CH), 10.56 (1H, s, CO-NH), 12.24 (1H, s, CO-NH-N). Anal. Calcd for $C_{23}H_{15}F_6N_3O_2$: C, 57.63; H, 3.15; N, 8.77. Found: C, 57.52; H, 3.12; N, 8.63.

_N_-[4-({2-[(5-(2-nitrophenyl)furan-2-yl)methylidene] hydrazinyl}carbonyl)phenyl] benzamide (3j)

Yield %91; M.p. 265-266 °C; Rf 0.69; FT-IR v_{max} (cm^{-1}): 3327 (amide NH str.), 3134 (hydrazone NH str.), 2997 (arom. CH str.), 1683 (amide CO str.), 1654 (hydrazone CO str.), 1608 (hydrazone CN str.), 1591, 1545, 1508, 1489, 1404 (aromatic C=C str., nitro NO_2 asm. str., amide CN str., amide and hydrazone NH bending) 1404 (nitro NO_2 sym. str.); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 7.10-7.99 (15H, m, Ar-H), 8.39 (1H, s, -N=CH), 10.54 (1H, s, CO-NH), 11.83 (1H, s, CO-NH-N). Anal. Calcd for $C_{25}H_{18}N_4O_3$: C, 66.08; H, 3.99; N, 12.33. Found: C, 65.84; H, 3.91; N, 12.14.

_N_-(4-{[2-(4-(piperidine-1-yl)benzylidene)hydrazinyl] carbonyl}phenyl)benzamide (3k)

Yield %75; M.p. 299 °C; Rf 0.48; FT-IR v_{max} (cm^{-1}): 3317 (amide NH str.), 3163 (hydrazone NH str.), 3034 (arom. CH str.), 1680 (amide CO str.), 1653 (hydrazone CO str.), 1604 (hydrazone CN str.), 1597, 1543, 1506, 1489 (aromatic C=C str., amide CN str., amide and hydrazone NH bending); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.58 (5H, s, piperidine $-CH_2$), 3.27 (5H, s, piperidine $-CH_2$) 6.96-8.32 (15H, m, Ar-H; 1H, s, -N=CH), 10.51 (1H, s, CO-NH), 11.55 (1H, s, CO-NH-N). Anal. Calcd for $C_{26}H_{26}N_4O_2$: C, 71.64; H, 6.19; N, 12.85. Found: C, 71.38; H, 5.92; N, 12.52.

4.2. Antibacterial activity

All synthesized compounds were evaluated for antibacterial activity. Activity experiments were carried out in Yeditepe University, Faculty of Engineering, Department of Genetic and Bioengineering. Gram positive and Gram negative bacteria, *Escherichia coli* ATCC 10536, *Escherichia coli* ATCC 15442, *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 15442, *Acinetobacter baumannii* , *Klebsiella pneumonia ATCC 13883* were used in activity studies. Antibacterial activities of the compounds tested against that bacteria species based on micro-well dilution assay. The sensitivity of the bacterial strains towards the compounds was quantitively evaluated from the minimal inhibitory concentration (MIC) values obtained by the micro-well dilution method. The inocula of the bacterial strains were prepared from 12 h broth cultures and suspensions were adjusted to 0.5 McFarland standard turbidity. Compounds dissolved in DMSO were first prepared at the highest concentration to be tested (200 µg/mL), and then serial two-fold dilutions were made in order to obtain a concentration range from 6.25 to 200 µg/mL, in 15 mL sterile test tubes containing nutrient broth. The 96-well plates were prepared by dispensing into each well 95 µL of nutrient broth and 5 µL of the inoculum. 200 µL of nutrient broth without inoculum was transferred into the first wells as positive control. Aliquots, (100 µL) taken from the 200 µg/mL stock solution, were added to the second well. 100 µL from the respective serial dilutions was transferred into 5 consecutive wells. The last well containing 195 µL of nutrient broth without compound and 5 µL of the inoculum on each strip was used as negative control. Contents of each well were mixed on plate shaker at 300 rpm for 20 s and then incubated at appropriate temperatures for 24 h. Microbial growth in each medium was determined by reading the absorbance (Abs) at 630 nm using the ELx 800 universal microplate reader (Biotek Instrument inc, Highland Park, Vermont, USA) and confirmed by plating 5 µL samples from clear wells on nutrient agar medium. The MIC was defined as the lowest concentration of the compounds to inhibit the growth of microorganisms. Ampisillin was used as the positive sensitivity reference standard for bacteria [14,15].

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