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Synthesis and Biological Activity of Some Novel Benzimidazole Derivatives

***Trivedi Vipul V., [1] Shinde Kiran K., [2] Shah Darshan V, [3] Hapse Sandip A.**
*Research Scholar,Department of Pharmacy, Shubham University, Bhopal, Madhya Pradesh (MP)
[1]Associate Professor, Vidya Niketan Institute of Pharmacy and Research Center, Bota (MS)
[2]Professor, Anekant Education Society's College of Pharmacy, Baramati (MS)
[3]Assistant Professor, Dr. V. V. P. F's College of Pharmacy, Vilad Ghat, Ahmednagar (MS)
Corresponding Author Email id: **vipulvtrivedi@gmail.com**

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ABSTRACT:
In medicinal chemistry, benzimidazole, a heterocyclic aromatic chemical molecule, has been a significant pharmacophore and preferred structure. As compounds having a broad range of biological action and minimal toxicity, substituted benzimidazoles are of great interest. The biological effects of various substituted benzimidazoles are diverse and include antiviral, antifungal, antimicrobial, antiprotozoal, anti-inflammatory, anticancer, antioxidant, anticoagulant, antidiabetic, and antihypertensive properties. Infectious diseases are those that have become more common in people over the last few decades. They result in a great deal of financial hardship as well as pain and death. Antimicrobial medications have saved millions of lives. However, the sharp rise in drug-resistant bacteria threatens the advancements made in medicine over the past 50 years. When it comes to their ability to suppress germs, benzimidazoles are highly effective substances. Studies in pharmacology and biochemistry have demonstrated the effectiveness of these compounds against a variety of microorganism strains. In the present study, 15 derivatives of substituted benzimidazoles were synthesized and evaluated for antimicrobial activity against *E. coli* and S. aureus. Compounds 2a-o were obtained through a multistep synthesis involving the incorporation of substituted benzaldehydes with diamine and sodium bisulfite. The evaluation of antimicrobial activity by the cup plate method on the *E. coli* and S. aureus species shows significant activity. The compounds **2a, 2b, 2c,** and **2o** exhibit significant antimicrobial activity against Gram-positive and Gram-negative species.

INTRODUCTION:
Imidazole and a benzene ring with nitrogen, sulphur, and oxygen unite to form the heterocyclic molecule benzimidazole. Owing to its many medicinal uses and biological activities, its derivatives are of considerable interest. Due to their high selectivity ratios and inhibitory activity, they are considered the most effective chemical compounds. They show a range of activities, including antibacterial, antiviral, antifungal, antiparasitic, anthelminthic, and anticonvulsant. They can also be used to treat intestinal cystitis. A large number of natural

products and pharmacologically active compounds possess benzimidazole as a common moiety. Benzimidazole and its derivatives are among the most important heterocyclic compounds from both biological and industrial standpoints. Benzimidazole derivatives are also used in the treatment of several neurological disorders[1–3]. The benzimidazole scaffold is a functional moiety for the development of novel pharmacological compounds. The benzimidazole nucleus possesses diverse pharmacological activities, including antiulcer, antihypertensive, antiviral, antifungal, anticancer, antihistaminic, antimicrobial, anti-inflammatory, anticonvulsant, antidepressant, antioxidant, radioprotective, and antileishmanial activities [4–8].

MATERIALS AND METHODS:

All chemicals required for the synthesis were brought from Spectrochem Chemicals, Loba Chemicals, S. D. Fine Chemicals, and Sigma Alardrich Chemicals.

Synthesis of Substituted Benzimidazole Derivatives:

A series of substituted benzimidazoles 2a-o was synthesized in the laboratory. The purity of the compound and the completeness of the reaction were monitored by thin-layer chromatography (TLC) using Silica gel 60 F254 (Merck), and the results were identified under UV light. The Gallencamp electric melting point apparatus was used for determining melting points, which were uncorrected. All synthesized compounds were analyzed by KBr disc FT-IR spectroscopy (Jasco Infrared Affinity-1 Spectrophotometer). The ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-D_6 using a Bruker 500 MHz spectrometer (Bruker Biosciences, Billerica, MA, USA), with tetramethylsilane (TMS) used as the internal standard. A Waters Q-TOF Premier mass spectrometer was used to record an HR-MS spectrum, revealing that the molecular ion is M+1.

General Procedure:

The equimolar amounts (0.1 mmol) of *o*-phenylenediamine and 0.1 mmol of substituted aromatic benzaldehyde were thoroughly mixed in 2 mL of N, N-dimethylformamide. Then, 0.1 mmol of sodium bisulfite was added, and the mixture was stirred at 80-90°C for 30 min until the reaction was complete, as indicated by TLC data. The mixture was cooled to room temperature and added dropwise to 20 ml of water under continuous stirring. The product separated as a solid; it was collected by filtration, washed with warm water, and dried. [9-10]

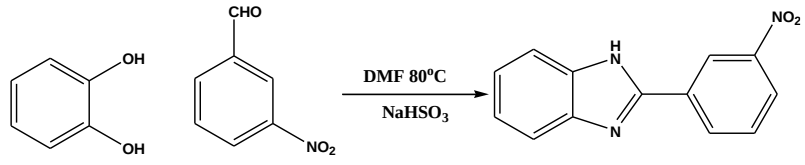
Ethyl [2-(3-nitrophenyl)-1H-benzimidazole-1-Yl] acetate:

A mixture of equimolar alkaline solution (0.5 mL, 4 N NaOH) and substituted benzimidazole (0.01 mol) in 50 mL of methanol, along with 0.01 mol of ethyl chloroacetate in methanol (20 mL), was heated gently on a boiling water bath for 30 min. The solid thus obtained on cooling was recrystallized from alcohol to give the product.

Substituted 2-[2-(3-nitrophenyl)-1H-benzimidazole-1-yl] acetamide analogues:

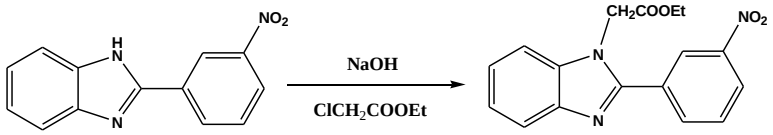
To a solution of *ethyl* [2-(3-nitrophenyl)-1H-benzimidazole-1-yl*] acetate* (0.01 mol) dissolved in dry methanol (20 ml), primary amines, substituted hydrazine (1 ml) was added, and the mixture was allowed to stand for reflux for 3-4 hrs. The reaction mixture was cooled, and the solid obtained was filtered and washed with a small quantity of cold methanol to give the product.

STEP 1:



o-phenylenediamine 3-Nitro-benzaldehyde 2-(3-nitrophenyl)-1H-benzimidazole

STEP 2:



2-(3-nitrophenyl)-1H-benzimidazole [2-(3-Nitro-phenyl)-benzoimidazol-1-yl]-acetic acid ethyl ester

STEP 3:

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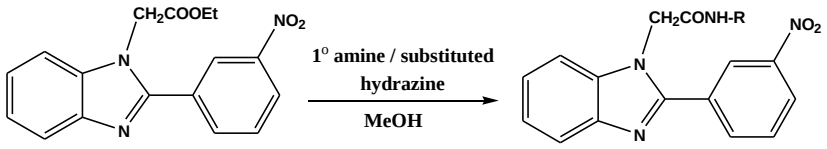

[2-(3-Nitro-phenyl)-benzoimidazol-1-yl]-acetic acid ethyl ester

Substituted 2[2-(3-Nitro-phenyl)-1H-benzoimidazol-1-yl]-acetamide

Scheme 1: Synthesis of Benzimidazole Derivatives

EXPERIMENTAL PROCEDURE FOR ANTIMICROBIAL ACTIVITY

All the title compounds synthesized were tested against gram-positive bacterial strains S. *aureus* and gram-negative bacterial strains E. *coli* by the cup-plate method for antimicrobial activity. The solutions of the test compounds at a concentration of 1000 µg/mL were prepared in dimethylsulphoxide (solvent) for the study. Streptomycin was used as the standard for antibacterial and antifungal activity, respectively. Standard drug and solvent controls were maintained throughout the study. Regarding antibacterial activity, the zone of inhibition ranged from 08 to 29 mm and 09 to 27 mm for gram-positive and gram-negative bacterial strains, respectively. At the same time, compounds **2a, 2b, 2c,** and **2o** showed significant activity against Gram-positive and Gram-negative bacteria. [11-17]

RESULTS AND DISCUSSION

PHYSICOCHEMICAL AND SPECTRAL ANALYSIS OF SYNTHESIZED COMPOUNDS

From scheme 1 fifteen compounds were synthesized. The physicochemical data of the compounds are tabulated in **Table 1**.

Table 1: The physicochemical data of the synthesized compounds

Code	Molecular formula	Molecular weight (gm/mol)	M.P. (^{0}C)	% Yield	Rf value
2a	C19H20N2O4	340.37	169-172	0.58	0.58
2b	C17H14Cl2N2O4	381.21	180-182	0.61	0.62
2c	C17H14Cl2N2O3	365.21	195-196	0.64	0.71
2d	C17H15N3O5	341.31	174-176	0.67	0.58
2e	C20H22ClN3O2	371.86	155-157	0.72	0.63
2f	C20H21ClN2O2	356.84	161-163	0.56	0.55
2g	C17H16N2O4	312.31	167-170	0.59	0.58
2h	C17H16N2O5	328.31	171-175	0.54	0.61
2i	C17H15ClN2O4	346.76	180-183	0.69	0.58
2j	C16H11Cl3N2O2	369.62	179-182	0.67	0.59
2k	C16H12Cl2N2O3	351.18	169-174	0.63	0.57
2l	C16H14N2O3	282.29	176-178	0.59	0.56
2m	C16H13ClN2O2	300.73	180-182	0.57	0.54
2n	C15H10ClN3O4	331.71	190-193	0.68	0.53
2o	C15H9Cl2N3O4	366.15	186-189	0.57	0.57

STRCTURAL ELUCIDATION:

Ethyl 2-(2-(3,4-dihydroxyphenyl)-4,5-dimethyl-1H-benzo[d]imidazol-1-yl) acetate (2a)

MS (m/e): 339.11, 340.01 (m+1), 341.81(m+2). FTIR (cm^{-1}): 3287.5 (-NH str.), 3026.6 (Ar –CH str.), 2960.0 (-CH3 str.), 1498.4 (-C=N str.), 1271.0 (-C-N str.). ^{1}H-NMR (ppm): 6.89-7.56 (m, Ar-H), 5.42 (s, –OH); 2.47- 2.59 (t, –CH3); 1.48(d, methylene protons).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm:15.56, 17.79, 19.89, 52.16, 62.01, 62.68, 112.56, 114.61, 116.99, 117.45, 123.88, 124.46, 125.31, 125.89, 129.99, 130.73, 137.82, 145.56, 146.89, 152.67, 165.89, 166.34.

Ethyl 2-(4,5-dichloro-2-(3,4-dihydroxyphenyl)-1H-benzo[d]imidazol-1-yl) acetate (2b)

MS (m/e): 380.98, 381.78 (m+1), 383.17 (m+2). FTIR (cm^{-1}): 3384.4 (-NH str.), 3276.3 (Ar –CH str.), 2795.5 (-CH3 str.), 1591.6 (-C=N str.), 1271.0 (-C-N str.). ^{1}H-NMR (ppm): 6.80-7.45(m, Ar-H), 5.38(s, –OH); 1.39-1.45(t, –CH3) and 2.21(d, methylene protons).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm:15.37, 51.88, 61.76, 115.12, 115.73, 117.31, 122.18, 124.19, 125.34, 126.02, 129.15, 134.21, 140.45, 147.37, 148.08, 154.29, 168.09.

Ethyl 2-(2-(3,4-dichlorophenyl)-4-hydroxy-1H-benzo[d]imidazol-1-yl)acetate (2c)

MS (m/e): 365.39, 366.27 (m+1), 367.89 (m+2). FTIR (cm^{-1}): 3287.5 (-NH str.), 3026.6 (Ar –CH str.), 2851.4 (-CH3 str.), 1621.4 (-C=N str.), 1271.0 (-C-N str.), 693.3, 741.7, 831.2 (aromatic region). ^{1}H-NMR (ppm): 7.33-7.98(m, Ar-H), 5.35(s, –OH), 4.22(q, of –CH2); 1.09-1.15(t, -CH3).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm:14.47,

50.76, 60.03, 98.82, 102.98, 121.45, 126.31, 128.12, 129.38, 130.06, 132.09, 133.23, 134.53, 147.54, 153.04, 166.76.

Ethyl 2-(4-hydroxy-2-(4-nitrophenyl)-1H-benzo[d]imidazol-1-yl) acetate (2d)
MS (m/e): 340.08, 342.67 (m+2), 344.23 (m+4).FTIR (cm^{-1}): 3287.5 (-NH str.), 3030.3 (Ar –CH str.), 2668.8 (-CH3 str.), 1621.4 (-C=N str.), 1271.0 (-C-N str.), 961.7, 741.7, 827.5 (aromatic region). ^{1}H-NMR (ppm): 6.88-7.18 (m, Ar-H), 5.35(s, –OH); 4.19- 4.24 (q,–CH2) 1.41-1.46(t, -CH3).^{13}CNMR (CHCl3-*d6*400 MHz) δ ppm: 15.77, 51.66, 61.76, 98.20, 102.18, 120.71, 123.33, 125.42, 133.28, 134.09, 135.55, 145.67, 145.99, 151.56, 165.69.

Ethyl 2-(5-chloro-2-(4-(dimethylamino)phenyl)-4-methyl-1H-benzo[d]imidazol-1- yl)acetate (2e)
MS: (m/e):372.81, 373.78 (m+1). FTIR (cm^{-1}): 3287.2 (-NH str.), 3030.3 (Ar –CH str.), 2922.2, 2668.8 (-CH3 str.), 1498.4. (-C=N str.), 1271 (-C-N str.), 670.9, 742.7, 823.7.^{1}H-NMR (ppm): 6.78-7.32 (m, Ar-H), 4.18-4.25 (q,–CH2), 2.47 (d, dimethylamino proton), 1.41-1.45(t, -CH3).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm:13.55, 15.68, 41.71, 50.51, 61.02, 112.30, 113.76, 120.12, 124.08, 125.09, 128.03, 129.45, 132.08, 140.02, 153.62, 155.65, 167.98.

Ethyl 2-(5-chloro-2-(3,5-dimethylphenyl)-4-methyl-1H-benzo[d]imidazol-1- yl)acetate (2f)
MS (m/e): 357.34, 358.13 (m+1), 361.98 (m+3).FTIR (cm^{-1}): 3256.45 (-NH str.), 3015.24 (Ar –CH str.); 2865.34 (-CH3 str.), 1578.34 (-C=N str.), 1265.35 (-C-N str.) 670.9, 742.7, 823.7. ^{1}H-NMR (ppm): 7.07-7.83 (m, Ar-H), 4.08-4.17 (q,–CH2) 2.40 (s, -CH3), 1.30-1.39 (t, -CH3).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm:15.28, 17.13, 23.12, 51.19, 61.11, 113.12, 123.88, 124.17, 128.01, 129.76, 130.31, 131.18, 134.09, 138.61, 139.39, 152.49, 166.63.

Methyl 2-(2-(2,4-dihydroxyphenyl)-4-methyl-1H-benzo[d]imidazol-1-yl)acetate (2g)
MS (m/e): 314.19, 316.56 (m+2), 320.21 (m+4).FTIR (cm^{-1}): 3324.8 (-NH str.), 3056.4 (Ar –CH str.), 2929.7 (-CH3 str.), 1520.8 (-C=N str.), 1241.2 (-C-N str.), 823.7, 894.6, 928.1, 689.6. ^{1}H-NMR (ppm): 6.28-7.82 (m, Ar-H), 5.35(s, –OH); 3.64 (s,–CH2) 2.36(t, -CH3).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm:16.00, 50.08, 51.76, 105.04, 106.78, 109.02, 110.91, 122.67, 123.98, 125.38, 129.67, 133.88, 138.01, 152.24, 155.78, 159.23, 165.34.

Methyl 2-(2-(3,4-dihydroxyphenyl)-4-methoxy-1H-benzo[d]imidazol-1-yl)acetate (2h)
MS (m/e): 330.10, 331.99 (m+1), 333.17 (m+3).FTIR (cm^{-1}): 3324.8 (-NH str.), 3060.1 (Ar –CH str.), 2851.4 (-CH3 str.), 1625.1 (-C=N str.), 1241.2 (-C-N str.), 715.6, 820.0, 928.1. ^{1}H-NMR (ppm): 7.10-7.55 (m, Ar-H), 5.35(s, –OH); 3.60, 3.88 (q,–CH3).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm:49.87, 51.09, 55.31, 101.45, 109.11, 113.61, 115.62, 120.16, 122.18, 123.81, 132.01, 134.20, 145.13, 146.02, 148.09, 152.12, 164.64.

Methyl 2-(5-chloro-2-(3,4-dihydroxyphenyl)-4-methyl-1H-benzo[d]imidazol-1-yl) acetate (2i)
MS (m/e): 348.10, 349.02 (m+1), 350.08 (m+3).FTIR (cm^{-1}): 3183.1 (-NH str.),2926.0 (Ar –CH str.), 2847.7 (-CH3 str.), 1572.9 (-C=N str.), 1241.2 (-C-N str.), 715.6, 823.7, 928.1, 894.6. ^{1}H-NMR (ppm): 7.10-7.85 (m, Ar-H), 5.35(s, –OH); 3.70, 3.84 (s,– CH3).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm:16.09, 50.37, 52.10, 113.11, 113.88, 115.82, 123.03, 123.78, 124.01, 124.23, 128.03, 132.10, 139.18, 145.01, 146.71, 153.27, 165.66.

Methyl 2-(4,5-dichloro-2-(3-chlorophenyl)-1H-benzo[d]imidazol-1-yl)acetate (2j)
MS (m/e): 368.11, 371.78 (m+3). FTIR (cm^{-1}): 33.24.8 (-NH str.); 3063.9 (Ar –CH str.); 2847.7(-CH3 str.); 1520.8 (-C=N str.); 1285.9 (-C-N str.), 708.2, 820.0, 928.1. ^{1}H-NMR (ppm): 7.33-8.10 (m, Ar-H), 4.66 (d, methylene protons) 3.84 (t, -CH3).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm:49.68, 50.08, 112.10, 119.67, 123.89, 125.10, 126.66, 127.27, 130.09, 131.72, 133.71, 137.72, 151.19, 164.08.

Methyl 2-(2-(2,4-dichlorophenyl)-5-hydroxy-1H-benzo[d]imidazol-1-yl)acetate (2k)
MS (m/e): 351.23, 352.78 (m+1), 354.09 (m+3). FTIR (cm^{-1}): 3324.8 (-NH str.); 3056.4 (Ar –CH str.); 2926.0 (-CH3 str.); 1576.7 (-C=N str.); 1271.0 (-C-N str.), 704.5, 820.0, 890.8, 931.8. ^{1}H-NMR (ppm): 7.01-8.10 (m, Ar-H), 5.40(s, –OH); 4.08-4.11(q,–CH2).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm:50.04, 52.05, 102.06, 111.01, 113.12, 126.02, 126.41, 129.31, 130.03, 132.56, 135.11, 135.81, 139.67, 151.09, 152.48, 165.41.
2-(2-(4-hydroxyphenyl)-5-methyl-1H-benzo[d]imidazol-1-yl) acetic acid (2l)
MS (m/e): 282.09, 283.65 (m+1), 285.18 (m+3).FTIR (cm^{-1}): 3324.8 (-NH str.); 2974.4 (Ar –CH str.); 2851.5 (-CH3 str.); 1625.1 (-C=N str.); 1431.3 (-C-N str.), 864.7, 823.7, 685.8, 898.3. ^{1}H-NMR (ppm): 7.02-7.49 (m, Ar-

H), 5.35(s, –OH); 4.06-4.11(q,– CH2) 2.37(t, -CH3).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm:20.18, 49.89, 109.42, 110.05, 117.12, 119.45, 123.93, 124.18, 125.77, 131.08, 144.21, 150.03, 165.23.

2-(2-(3-chlorophenyl)-5-methyl-1H-benzo[d]imidazol-1-yl) acetic acid (2m)
MS (m/e): 302.32, 305.28 (m+3), 306.01 (m+4).FTIR (cm^{-1}): 3285.48 (-NH str.); 3015.45 (Ar –CH str.); 2864.26 (-CH3 str.); 1590.35 (-C=N str.); 1265.32 (-C-N str.). ^{1}H-NMR (ppm): 7.29-8.10 (m, Ar-H), 4.06-4.13(q,–CH2) 2.38(t, -CH3).^{13}C NMR (CHCl3- *d6*400 MHz) δ ppm:26.40, 56.02, 115.04, 115.41, 125.34, 126.10, 128.18, 129.12, 130.23, 131.21, 132.00, 134.08, 137.89, 151.57, 172.10.

2-(2-(4-chlorophenyl)-5-nitro-1H-benzo[d]imidazol-1-yl) acetic acid (2n)
MS (m/e): 332.16, 333.67 (m+1), 336.76 (m+4).FTIR (cm^{-1}): 3245.28 (-NH str.); 3025.65 (Ar –CH str.); 2850.26 (-CH3 str.); 1585.35 (-C=N str.); 1252.64 (-C-N str.). ^{1}H-NMR (ppm): 7.02-8.54 (m, Ar-H), 4.06-4.13 (q,–CH2).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm: 55.55, 110.04, 112.32, 117.82, 127.01, 127.67, 132.57, 137.38, 138.18, 142.09, 150.03, 171.01.

2-(2-(2,4-dichlorophenyl)-5-nitro-1H-benzo[d]imidazol-1-yl)acetic acid (2o)
MS (m/e): 367.99, 370.02 (m+1). FTIR (cm^{-1}): 3228.26 (-NH str.); 3010.65 (Ar –CH str.); 2865.30 (-CH3 str.); 1590.35 (-C=N str.); 1265.38 (-C-N str.). ^{1}H-NMR (ppm): 7.33-7.81 (m, Ar-H), 3.46-4.11(q,–CH2).^{13}C NMR (CHCl3-*d6*400 MHz) δ ppm: 54.98, 109.43, 112.05, 117.45, 125.78, 128.18, 129.04, 131.65, 134.06, 134.76, 137.89, 138.02, 142.11, 150.21, 170.32.

ANTIMICROBIAL ACTIVITY:

The antimicrobial activity of compounds 2a-o was determined by the cup plate method with *S. aureus* and *E. Coli* species. The antimicrobial drug Streptomycin was used as the reference standard. The zone of inhibition (mm) of synthesized compounds on *S. aureus* and *E. Coli* species was also illustrated in **Table 2**.

Table 2: Antimicrobial activity of title compounds on *S. aureus* and *E. Coli*.

Sr. No.	Compound Code	Zone of Inhibition (mm)	
		S. aureus	***E. Coli***
1.	2a	31	28
2.	2b	27	30
3.	2c	29	30
4.	2d	26	25
5.	2e	24	16
6.	2f	23	25
7.	2g	16	24
8.	2h	22	20
9.	2i	14	18
10.	2j	22	18
11.	2k	22	18
12.	2l	19	23
13.	2m	25	25
14.	2n	22	20
15.	2o	29	31
16.	**Streptomycin (Standard)**	36	34

CONCLUSION:

In the present study, compounds 2a-o were obtained through a multistep synthesis involving the incorporation of substituted benzaldehydes with diamine and sodium bisulfite. The evaluation of antimicrobial activity by the cup plate method against *S. aureus* and *E. coli* shows significant activity. The evaluation of antimicrobial activity using the cup plate method on the *S. aureus* and *E. Coli* shows significant activity. The compounds **2a, 2b, 2c,** and **2o** exhibit significant antimicrobial activity against Gram-positive and Gram-negative species.

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