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Synthesis and Antibacterial Activity of Some Imidazole-5-(4*H*)one Derivatives

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In the present study, several substituted oxazolones were synthesized by condensation of benzoylglycine with different aldehydes. From such oxazolones, substituted imidazolones were synthesized by condensation with ethylenediamine, urea and 4-*N,N*-dimethylaminoaniline. All these synthesized compounds produced significant antibacterial activities. Furthermore, compounds containing $-CH_2CH_2NH_2$, $-CONH_2$ and $-C_6H_4-N(CH_3)_2$ groups as substitutents on the imidazolones were found to be potent antibacterial agents. Thus, among the twelve compounds, 1-(2-aminoethyl)-2-phenyl-4-(4-(dimethylamino)benzylidene)imidazole-5-(4*H*)one (**4d**), 1-carboxamido-2-phenyl-4-(4-(dimethylamino)benzylidene)imidazole-5-(4*H*)one (**4e**) and 1-(4-(*N,N*-dimethylamino)phenyl)-2-phenyl-4-(4-(dimethylamino)benzylidene)imidazole-5-(4*H*)one (**4f**) were found to have a significant higher antibacterial activity than the other substituted imidazolones. Compound **4e** was the most active one in this series.

Keywords: Synthesis; Oxazolones; Imidazoleones; Antibacterial activity

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Introduction

Imidazole derivatives have been found to be associated with several biological activities [1–4] like CNS depressant, monoamine oxidase (MAO) inhibitory, anticonvulsant [5–7], antibacterial activities [8] and others. This observation prompted us to extend our earlier synthetic work to synthesize some substituted imidazolones and to evaluate their antimicrobial activity.

Twelve imidazolones substituted at the 1-, 2- and 4-position were synthesized by treating the precursor oxazolones with some amine or amino derivative in the presence of acetic anhydride and sodium acetate. The oxazolones were prepared in our laboratory by reacting benzoyl glycine with aromatic aldehydes [9]. The synthesized compounds were tested for their antibacterial activity by the agar dilution method.

Results and discussion

The title imidazolone derivatives were synthesized by the reaction of 4-substituted oxazolone (**3**) under reflux conditions with the appropriate amines in dioxine/pyridine. Analytical data for structure elucidation are given in the Experimental section. The preparation of the resulting imidazolone derivatives **4a–l** is outlined in Scheme 1.

The compounds were tested *in vitro* for their antibacterial activity against ten microorganisms belonging to both gram-positive and gram-negative bacteria. It was observed that more than 80% of the total samples tested showed good antibacterial activities. Most of the compounds inhibited bacterial growth at concentrations of 50 μg/mL and 100 μg/mL for seven out of ten organisms. However, for *S. typhimurium* NCTC 74, *K. pneumoniae* 14 and *Ps. aeruginosa* APC 1, minimum inhibitory concentration (MIC) values were 100, 200 and >200 μg/mL. A close observation of the MIC values obtained for the twelve compounds under investigation indicates the importance of different chemical moieties in the two specific positions, namely 1 and 4, of the imidazolone ring while keeping a phenyl group in the 2-position. Thus, the presence of a dimethylaminophenyl group either in the 1- or 4-position on the imidazolone ring yielded active compounds, *e.g.* **4c**, **4d**, **4e**, **4f**, **4i** and **4l**; out of these, compound **4e** containing a $-C_6H_4-N(CH_3)_2$ group in the 4-position and a $-CONH_2$ group in the 1-position had maximum antibacterial activity.

Other substituents present in the 4-position of the imidazolone ring that impart activity are 4-hydroxy-3-methoxyphenyl and furfuryl. Thus, compounds having $-CH_2CH_2NH_2$ and $-CONH_2$ groups in the 1-position and 3-hydroxy-4-

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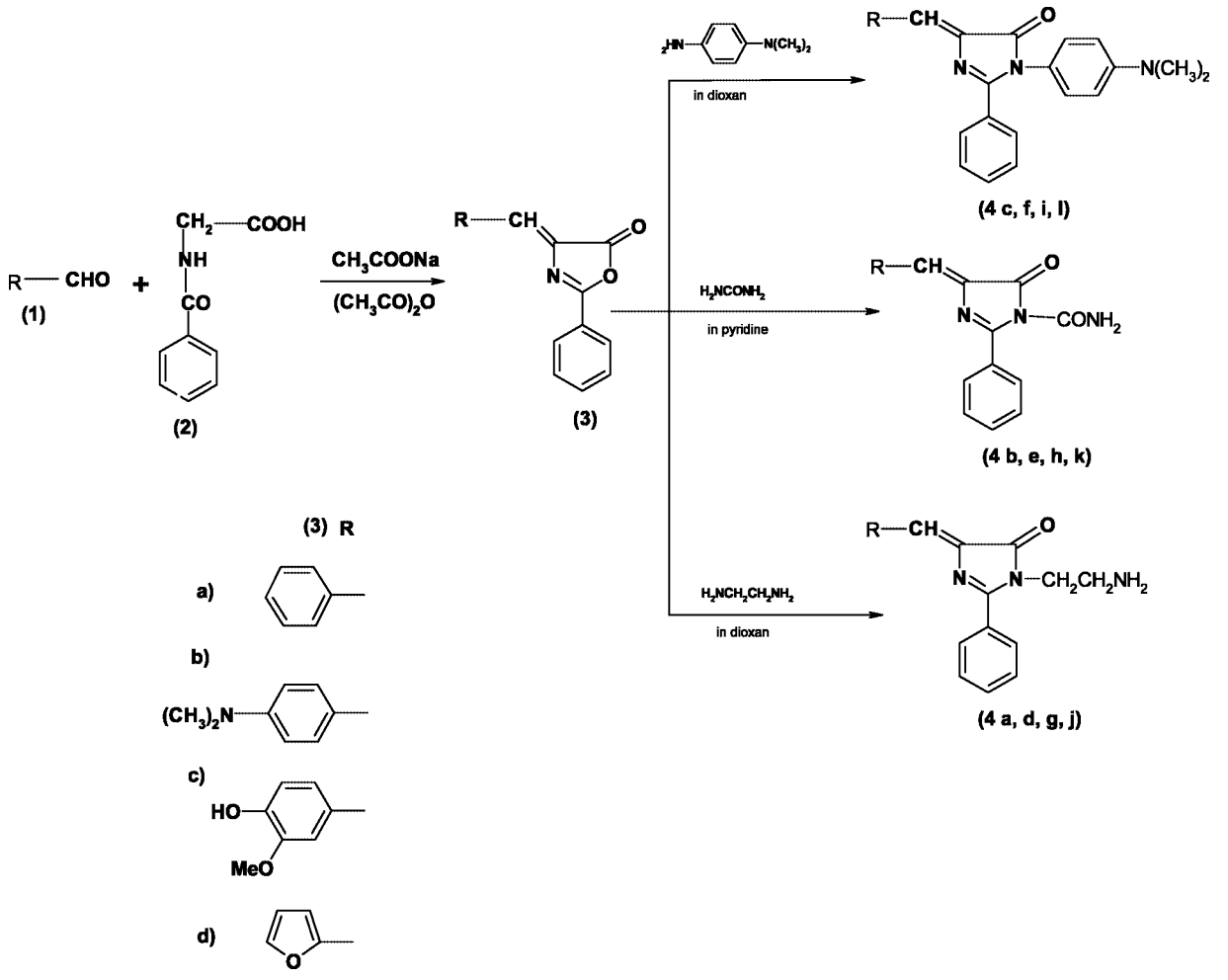

Scheme 1. Preparation of the resulting imidazolone derivatives **4a**–**l**.

methoxyphenyl or a furfuryl group in the 4-position are moderately active. It is interesting to note that other compounds having the same two substitutents, *i.e.* $-CH_2CH_2NH_2$ and $-CONH_2$ in the 1-position and $-C_6H_5$ only in the 4-position, yielded less active compounds. Another point of interest is that compounds having a $-CONH_2$ group in the 1-position are found to exhibit different degrees of activity, depending on the nature of the other group in the 4-position; thus, a $-C_6H_4-N(CH_3)_2$ group in the 4-position yielded the most active compound, while the activity gradually subsided, in descending order, with the 4-hydroxy-3-methoxyphenyl, furfuryl and benzene groups.

Finally, on the basis of the observed MIC values of these compounds, it can be concluded that the $-C_6H_4-N(CH_3)_2$ group exerts distinct antibacterial activity that is independent of the presence of other substituents, and compound **4e** was found to be the most active compound of this series and could therefore serve as a lead molecule for further modification to obtain clinically useful antibacterial agents.

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Experimental

Chemistry

The melting points of the synthesized compounds were taken in open capillary tubes on an ADCO melting point apparatus and are uncorrected. The IR spectra of the compounds were recorded in the 4000–400 cm^{-1} range using (KBr) disks on a Perkin-Elmer 297 spectrophotometer. The ^{1}H-NMR spectra were recorded on a

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Varian Gemini 200 MHz spectrometer in $CDCl_3$. Microanalyses for C, H, and N were performed in a Heraeus CHN Rapid Analyzer. All the compounds gave satisfactory elemental analyses (±0.4%).

*General procedure for the synthesis of oxazolones (**3**)*

4-substituted-2-phenyloxazol-5-(4*H*)ones (**3**) were prepared by refluxing benzoylglycine [10] (**2**) (hippuric acid; 0.25 mol) and appropriate aldehydes (**4**) (0.25 mol) in acetic anhydride (0.75 mol) with freshly fused sodium acetate (0.25 mol) for 2 h. After cooling, ethanol (10 mL) was added and the mixture kept overnight at 5°C; then, the solid obtained was filtered, washed with alcohol, dried in vacuum and recrystallized from benzene (Scheme 1).

*4-Benzylidene-2-phenyl-oxazol-5-(4H)one (**3a**)*

Yield = 97%, mp 166–167°C. ^{1}H-NMR ($CDCl_3$) δ: 6.5–6.9 (m, 10H, $(C_6H_5)_2$), 5.8 (s, 1H, CH=C). IR (KBr) cm^{-1}: 1652 (C=O), 1628 (C=N), 1592 (C=C), 1121 (C–O–C). (Calc. for $C_{16}H_{11}NO_2$: 249.26). *Anal.* Calc. for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.49; N, 5.61. Found: C, 76.58; H, 4.78; N, 5.48.

*4-(4-(Dimethylamino)benzylidine)-2-phenyl-oxazol-5-(4H)one (**3b**)*

Yield = 62%, mp 216–217°C. ^{1}H-NMR ($CDCl_3$) δ: 6.3–6.9 (m, 9H, Ar–H), 5.7 (s, 1H, CH=C), 2.8 (s, 6H, $-N(CH_3)_2$). IR (KBr) cm^{-1}: 1660 (C=O), 1618 (C=N), 1612 (C=C), 1136 (C–O–C). (Calc. for $C_{18}H_{16}N_2O_2$: 292.33). *Anal*. Calc. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.51; N, 9.58. Found: C, 73.26; H, 5.72; N, 9.12.

*4-(4–-Hydroxy-3′-methoxy benzylidine)-2-phenyl-oxazol-5-(4H)-one (**3c**)*

Yield = 95%, mp 192–193°C. ^{1}H-NMR ($CDCl_3$) δ: 9.7 (s, 1H, Ar–OH), 6.8–7.8 (m, 8H, Ar-H), 6.1 (s, 1H, CH=C), 4.1 (s, 3H, OCH_3). IR (KBr) cm^{-1}: 3680 (OH), 1674 (C=O), 1622 (C=N), 1596 (C=C), 1120 (C–O–C). (Calc. for $C_{17}H_{13}NO_4$: 295.29). *Anal*. Calc. for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.43; N, 4.74. Found: C, 68.76; H, 4.12; N, 4.92.

*4-(Furfur-2-yl)-2-phenyl-oxazol-5-(4H)one (**3d**)*

Yield = 78%, mp 168–169°C. ^{1}H-NMR ($CDCl_3$) δ: 6.3–6.8 (m, 8H, Ar–H), 5.7 (s, 1H, CH=C). IR (KBr) cm^{-1}: 1660 (C=O), 1620 (C=N), 1590 (C=C), 1132 (C–O–C), (Calc. for $C_{14}H_{10}NO_3$: 239.23). *Anal*. Calc. for $C_{14}H_{10}NO_3$: C, 70.29; H, 3.79; N, 5.85. Found: C, 70.02; H, 3.12; N, 5.24.

*General procedure for the synthesis of 1,4-disubstituted imidazolones (**4**)*

The respective 4-substituted oxazolones (**3**) (0.1 mol) were refluxed with an equimolar quantity (0.1 mol) of ethylenediamine in dioxan (10 mL) in a water bath for 6 h, with *N,N*-dimethylaminobenzene in dioxan (10 mL) in a water bath for 6 h, and with urea in pyridine (10 mL) in an oil bath at 150°C for 6 h, separately, to yield the respective 1-substituted imidazolones. The excess of solvent was distilled off from the reaction mixture in vacuum. The mixture was cooled and poured into crushed ice. The solid obtained was filtered and recrystallized from rectified spirit **4a–l** (Scheme 1).

*1-Aminoethyl-2-phenyl-4-benzylidene imidazole-5-(4H)one (**4a**)*

Yield = 58%, mp 171–172°C. ^{1}H-NMR ($CDCl_3$) δ: 6.6–7.1 (m, 10H, $(C_6H_5)_2$), 5.8 (s, 1H, CH=C), 3.2 (s, 2H, NH_2), 2.6 (m, 4H, NCH_2CH_2). IR (KBr) cm^{-1}: 1655 (C=O), 1622 (C=N), 1590 (C=C). (Calc. for $C_{18}H_{17}NO_3$: 291.35). *Anal*. Calc. for $C_{18}H_{17}NO_3$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.02; H, 5.62; N, 14.26.

*1-Carboxamido-2-phenyl-4-benzylidene imidazole-5-(4H)one (**4b**)*

Yield = 96%, mp 272–273°C. ^{1}H-NMR ($CDCl_3$) δ: 6.7–7.1 (m, 10H, Ar–H), 6.3 (s, 2H, $CONH_2$), 5.3 (s, 1H, CH=C). IR (KBr) cm^{-1}: 3226 (NH), 1655 (C=O), 1635 (C=N), 1580 (C=C). (Calc. for $C_{17}H_{13}N_3O_2$: 291.30). *Anal*. Calc. for $C_{17}H_{13}N_3O_2$: C, 71.80; H, 4.49; N, 14.42. Found: C, 71.62; H, 4.34; N, 14.28.

*1-(4′-(N,N-Dimethylamino)phenyl)-2-phenyl-4-benzylidene imidazole-5-(4H)one (**4c**)*

Yield = 94%, mp 152–153°C. ^{1}H-NMR ($CDCl_3$) δ: 6.9–7.5 (m, 14H, Ar–H), 5.7 (s, 1H, CH=C), 2.85 (s, 6H, $N(CH_3)_2$). IR (KBr) cm^{-1}: 1654 (C=O), 1610 (C=N), 1550 (C=C). (Calc. for $C_{24}H_{21}N_3O$: 367.45). *Anal*. Calc. for $C_{24}H_{21}N_3O$: C, 78.44; H, 5.76; N, 11.43. Found: C, 78.10; H, 5.54; N, 11.28.

*1-(2-Aminoethyl)-2-phenyl-4-(4-(dimethylamino)benzylidene)-imidazole-5-(4H)one (**4d**)*

Yield = 57%, mp 250–251°C. ^{1}H-NMR ($CDCl_3$) δ: 6.5–7.2 (m, 9H, Ar–H), 3.8 (s, 2H, NH_2), 3.2–3.4 (m, 4H, NCH_2CH_2), 2.4 (s, 6H, $(CH_3)_2$). IR (KBr) cm^{-1}: 1645 (C=O), 1605 (C=N), 1580 (C=C). (Calc. for $C_{20}H_{22}N_4O$: 334.42). *Anal*. Calc. for $C_{20}H_{22}N_4O$: C, 71.83; H, 6.63; N, 16.75. Found: C, 71.66; H, 6.42; N, 16.56.

*1-Carboxamido-2-phenyl-4-(4-(dimethylamino)benzylidene)-imidazole-5-(4H)one (**4e**)*

Yield = 47%, mp 265–266°C. ^{1}H-NMR ($CDCl_3$) δ: 6.8–7.1 (m, 9H, Ar–H), 6.1 (s, 2H, $CONH_2$), 5.5 (s, 1H, CH=C), 2.98 (s, 4H, $N(CH_3)_2$). IR (KBr) cm^{-1}: 1655 (C=O), 1620 (C=N), 1610 (C=C). (Calc. for $C_{19}H_{18}N_4O_2$: 334.37). *Anal*. Calc. for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.42; N, 16.75. Found: C, 68.02; H, 5.12; N, 17.06.

*1-(4′-(N,N-Dimethylamino)phenyl)-2-phenyl-4-(4-dimethylamino-benzylidene)imidazole-5-(4H)one (**4f**)*

Yield = 71%, mp 243–244°C. ^{1}H-NMR ($CDCl_3$) δ: 6.8–7.4 (m, 13H, Ar-H), 5.8 (s, 1H, CH=C), 2.8 (s, 6H, $N(CH_3)_2$). IR (KBr) cm^{-1}: 1652 (C=O), 1622 (C=N), 1595 (C=C). (Calc. for $C_{26}H_{26}N_4O$: 410.51). *Anal*. Calc. for $C_{26}H_{26}N_4O$: C, 76.07; H, 6.38; N, 13.64. Found: C, 75.82; H, 6.12; N, 13.72.

*1-(2-Aminoethyl)-2-phenyl-4-(4′-hydroxy-3′-methoxybenzylidene)-imidazole-5-(4H)one (**4g**)*

Yield = 53%, mp 181–182 sC. ^{1}H-NMR ($CDCl_3$) δ: 9.8 (s, 1H, Ar–OH), 7.1–7.4 (m, 8H, Ar–H), 6.2 (s, 1H, CH=C), 3.9 (s, 3H, OCH_3), 3.1 (s, 2H, NCH_2CH_2). IR (KBr) cm^{-1}: 3680 (OH) 1654 (C=O), 1628 (C=N), 1590 (C=C). (Calc. for $C_{19}H_{19}N_3O_3$: 334.37). *Anal*. Calc. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.67; N, 12.45. Found: C, 67.44; H, 5.78; N, 12.04.

*1-Carboxamido-2-phenyl-4-(4′-hydroxy-3′-methoxybenzylidene)-imidazole-5-(4H)one (**4h**)*

Yield = 95%, mp 198–199°C. ^{1}H-NMR ($CDCl_3$) δ: 9.5 (s, 1H, Ar–H), 7.3–8.2 (m, 8H, Ar–H), 6.2 (s, 2H, $CONH_2$), 3.8 (s, 3H, OCH_3). IR (KBr) cm^{-1}: 3782 (OH), 1645 (C=O), 1610 (C=N), 1595 (C=C). (Calc. for $C_{18}H_{15}N_3O_4$: 337.33). *Anal*. Calc. for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.45. Found: C, 63.82; H, 4.52; N, 12.18.

*1-(4′-(N,N-Dimethylamino)phenyl)-2-phenyl-4-(4′-hydroxy-3′-methoxybenzylidene)imidazole-5-(4H)one (**4i**)*

Yield = 97%, mp 210–211 °C. ^{1}H-NMR ($CDCl_3$) δ: 9.9 (s, 1H, Ar–OH), 6.9–7.6 (m, 12H, Ar–H), 5.9 (s, 1H, CH=C), 3.9 (s, 3H, OCH_3), 2.95 (s, 6H; $N(CH_3)_2$). IR (KBr) cm^{-1}: 3705 (OH), 1655 (C=O), 1630 (C=N), 1595 (C=C). (Calc. for $C_{25}H_{23}N_3O_3$: 413.47). *Anal*. Calc. for $C_{25}H_{23}N_3O_3$: C, 72.62; H, 5.28; N, 10.16. Found: C, 72.12; H, 5.28; N, 10.42.

1-(2-Aminoethyl)-2-phenyl-4-(furfur-2-yl)imidazole-5-(4H)one (**4j**)
Yield = 82%, mp 166–167 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.2–7.6 (m, 8H, Ar–H), 5.8 (s, 1H, CH=C), 3.4 (s, 2H, NH_2), 2.6–2.9 (m, 4H, NCH_2CH_2). IR (KBr) cm^{-1}: 1665 (C=O), 1640 (C=O), 1580 (C=C). (Calc. for $C_{16}H_{15}N_3O_2$: 281.31). *Anal*. Calc. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37, N, 14.93. Found: C, 62.98; H, 5.18; N, 15.12.

*1-Carboxamido-2-phenyl-4-(furfur-2-yl)imidazole-5-(4H)one (**4k**)*

Yield = 81%, mp 258–259 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.7–7.1 (m, 8H, Ar–H), 6.1 (s, 2H, $CONH_2$), 5.3 (s, 1H, CH=C). IR (KBr) cm^{-1}: 1665 (C=O), 1622 (C=N), 1592 (C=C). (Calc. for $C_{15}H_{11}N_3O_3$: 281.27). *Anal*. Calc. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.93. Found: C, 64.28; H, 3.64; N, 14.28.

*1-(4′-(N,N-Dimethylamino)phenyl)-2-phenyl-4-(furfur-2-yl-imidazole-5-(4H)one (**4l**)*

Yield = 95%, mp 190–191 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.9–7.4 (m, 12H, Ar–H), 5.8 (s, 1H, CH=C), 2.95 (s, 6H, NCH_2CH_2). IR (KBr) cm^{-1}: 1636 (C=N), 1580 (C=C), 1645 (C=O). (Calc. for $C_{22}H_{20}N_3O_2$: 357.32). *Anal*. Calc. for $C_{22}H_{20}N_3O_2$: C, 73.92; H, 5.35; N, 11.75. Found: C, 73.54; H, 5.02; N, 11.92.

Antibacterial activity

The MIC values of the synthesized compounds (**4a–l**) were determined by following the agar dilution method [11–14]. The standard ATCC strains and the pathological strains were procured from the Central Drugs Laboratory (Kolkata, India) and the Division of Microbiology, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India. The antibacterial activities of the synthesized compounds were screened against the following bacterial stains: *Staphylococcus aureus* ATCC 25923, *Staphylococcus aureus* NCTC 6571, *Bacillus pumilus* NCTC 8241, *Salmonella typhimurium* NCTC 74, *Shigella sonnei* NCTC 9774, *Shigella dysenteriae* 7 NCTC 519/66, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* 14, *Pseudomonas aeruginosa* APC 1, *Vibrio cholerae* ATCC 14033. The test drugs were added at concentrations of 0 (control), 25, 50, 100, 200 μg/mL in molten nutrient agar (oxoid) and poured into petri dishes. The organisms were grown in peptone water, and the overnight culture corresponding to 0.5 McFarland standard was spot-inoculated on the nutrient agar plates such that each inoculum contained 2×10^6 colony forming units (CFU). The plates were incubated at +37 °C, examined after 24 h and incubated for a further 72 h, if necessary. The lowest concentration of the compounds (**4a–l**) in a plate that failed to show any visible macroscopic growth was considered as its MIC. MIC determination was performed in duplicate for each organism, and the experiment was repeated when necessary. The MIC values for a given isolate were either identical or within one dilution. The MIC of the test compounds were compared with the reference drug Ciprofloxacin. The results of antibacterial screening (MIC values) of the synthesized compounds are given in Table 1.

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Table 1. Antimicrobial screening data of the synthesized compounds.

Bacterial strains tested	MIC (μg/mL)												
	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l	Std.†
S. aureus ATCC 25923	100	50	50	50	50	50	50	100	50	50	100	100	2
S. aureus NCTC 6571	100	50	50	50	50	50	100	50	50	100	50	50	2
B. pumilus NCTC 8241	100	100	50	100	50	100	50	100	100	50	100	50	2
S. typhimurium NCTC 74	200	200	100	100	100	200	200	100	200	100	> 200	100	2
S. sonnei NCTC 9774	100	100	50	100	100	100	50	50	100	50	50	50	2
Sh. dysenteriae 7 NCTC 519/66	100	> 200	100	50	50	50	50	50	100	50	50	50	2
E. coli ATCC 25922	50	100	50	50	50	50	100	50	200	100	100	100	2
K. pneumoniae 14	200	> 200	200	200	100	200	100	100	> 200	200	200	200	5
P. aeruginosa APC 1	200	200	200	100	100	100	200	200	> 200	200	100	100	5
V. cholerae ATCC 14033	100	50	100	50	50	50	50	100	50	100	50	100	2

† Standard compound Ciprofloxacin.

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