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Synthesis, Characterization and Antibacterial Activity of Azomethine Derivatives Derived from 2-Formylphenoxyacetic Acid

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Abstract: A series of eight new azomethine derivatives were synthesized by reacting 2-formylphenoxyacetic acid with aromatic amines. The chemical structures of these compounds were confirmed by means of ^{1}H-NMR, ^{13}C-NMR, MS and elemental analysis. The compounds were assayed by the disc diffusion method for antibacterial against *Staphylococcus aureus* and *Escherichia coli*. Among the compounds tested, **2a**, **2b, 2e, 2g** and **2h** exhibited good antibacterial activity, almost equal to that of Ciprofloxacin used as standard.

Keywords: 2-Formylphenoxyacetic acid, picoline, N-phenylhydrazine, *p*-toluidine, *o*-bromobenzylamine, 2,3-dichloroaniline, *p*-aminoacetanilide, imidazole, thiazole, antibacterial activity

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Introduction

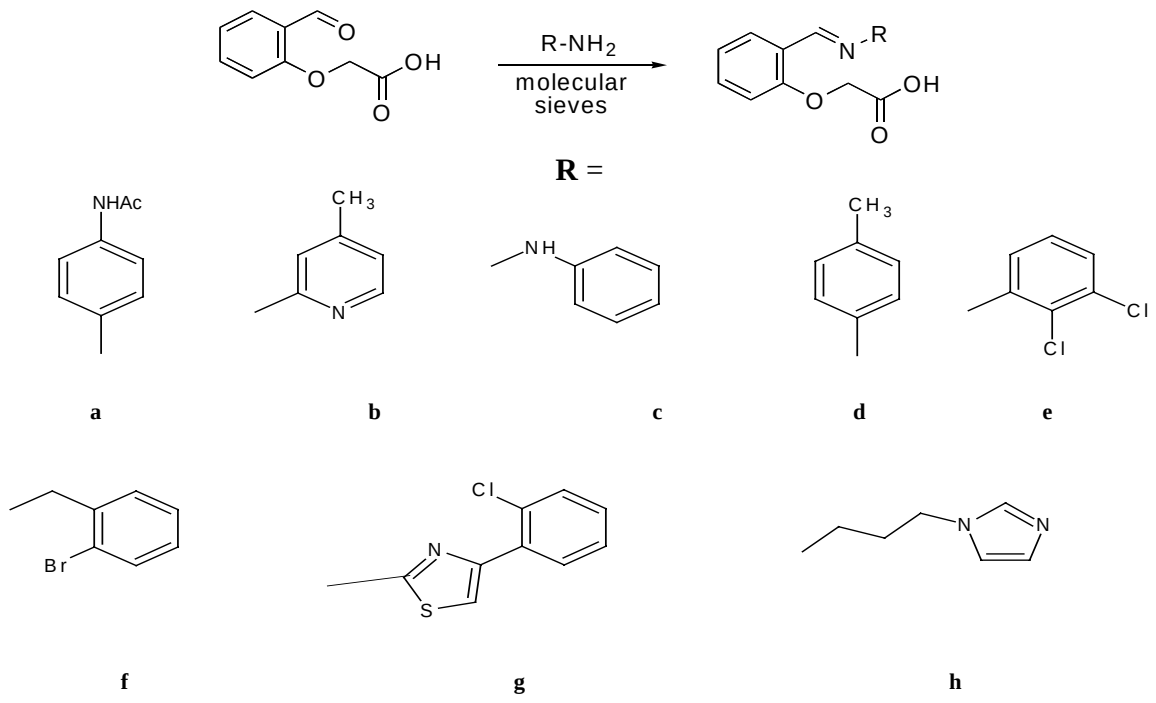
It is evident that in azomethine derivatives the C=N linkage is an essential structural requirement for biological activity. These compounds are readily hydrolyzed under acidic conditions leading to active

aldehydes which can act as alkylating agents [1]. Besides, several azomethines have been reported to possess remarkable antibacterial [2-6], antifungal [7-9], anticancer [10-13], and diuretic activities [14]. The action of aryloxyaliphatic acids on the permeability of blood vessels [15], and the antimicrobial activity against human pathogens [16] of *o*-substituted phenoxyacetic acid have been reported. The azomethine derivatives and their complexes derived from *o*-formylphenoxyacetic acid with aminothiazoles, a number of aminobenzene derivatives, some heterocyclic and aliphatic amines have revealed biological significance such as antimetabolites of pyridoxal phosphate [17], bacteriostatic activity [18], chorismate synthase inhibition [19] and antitumor activity [20]. Many attempts have been made to synthesize, characterize and to study structure-activity relationship (SAR) of Schiff bases [21-24]. In view of our ongoing preliminary investigation of the remarkable binding of azomethines derived from *o*-formylphenoxyacetic acid with proteins, we decided to synthesize some new azomethines. This study was aimed at exploring the potential antibacterial activity resulting from the combination of pharmacophores in one structure. The results of this study may be useful to researchers attempting to gain more insight into the antibacterial activity of azomethine derivatives.

Results and Discussion

The azomethine derivatives **2a-h** were synthesized in good yields (65 to 90%) by condensation of *o*-formylphenoxyacetic acid with various substituted primary aromatic amines in hot ethanol, benzene or dichloromethane (DCM) using molecular sieves as the dehydrating agent (Scheme 1).

Scheme 1 Synthesis of Azomethine derivatives



It is known that condensation of amines with aldehydes is favoured by a polar medium [20]. The addition of ytterbium triflate was also found to be beneficial, as in some experiments the reaction was found not to go to completion, even after extended heating times. This may be due to the acid-base reaction occurring between the amine and phenoxyacetic acid groups in the starting materials. Addition of the Lewis acid catalyst resulted in greater conversion to product (70%) in the case of compound **2h**.

The structures of the title compounds were determined by IR, ^{1}H- and ^{13}C-NMR, and FAB mass spectrometry and the spectroscopic properties and analytical data were in accord with the proposed structures. Compounds **2a,b,d-h** showed in the IR spectra an absorption band at 1630-1680 cm^{-1}, typical of the stretching vibrations of the C=N double bond, while the value for the hydrazone **2c** was lower, at 1600 cm^{-1}, as expected for the electron donating amino substituent on the imine nitrogen. Two more absorption bands in the 3580-3425 cm-1 (br) and 1711-1682 range were also observed, due to -OH and C=O groups of the carboxylic acid substituent in each compound.

The ^{1}H-NMR spectra of **2a-h** contained multiplet signals due to aromatic protons in the δ 6.39-8.31 ppm regions and singlets at δ 8.29 - 9.37 ppm from the C-H protons of the CH=N groups. In the DEPT spectra of **2a-h**, the peak at δ 189.8 ppm, due to the -CHO group, disappeared and was observed shifted to δ 154.2, 157.8, 154.8, 154.9, 158.5, 160.76 164.9 and 160.9, respectively, indicating the formation of CH=N groups. The signals at δ 23.9, 20.7, and 20.6 ppm showed the presence of CH_3 groups in compounds **2a, 2b** and **2d** respectively. Similarly, one signal each appeared at δ 65.1, 65.5, 64.9, 65.2, 65.1 65.0 and 66.4 ppm in compounds **2a-g**, while one more signal at δ 41.9, in addition to a signal at δ 65.0 in compound **2f**, were due to CH_2 groups. In the ^{1}H-NMR spectrum of compound **2h** four methylene signals were observed at δ 2.15, 2.91, 4.20 and 5.04, while the singlet of HC=N- group was observed at δ 8.37. The phenyl and imidazole protons gave rise to overlapping multiplets in the range δ 6.94-7.78. The compound exhibited three quaternary carbon signals at δ 166.0, 157.7, 124.46, four methylene signals at δ 68.9, 45.5, 37.9, 29.9, and eight CH signals in the DEPT spectrum.

Biological activity

All the synthesized compounds were screened for antibacterial activity against *Staphylococcus aureus* (AMJ-2005) and *Escherichia coli* (AMJ-2006) by the disc diffusion method. Ciprofloxacin was used as a standard. The bacterial inhibition zone values are summarized in Table 1. The MICs (minimum inhibitory concentrations) and MBCs (minimum bacterial concentrations) are presented in Table 2.

Table1 Bacterial Inhibition Zone values.

Compound	***Staphylococcus aureus* (AMJ-2005)**	***Escherichia coli* (AMJ-2006)**
2a	25[a]	27
2b	23	22
2c	18	19

Table 1. Cont.

Compound	*Staphylococcus aureus* (AMJ-2005)	*Escherichia coli* (AMJ-2006)
2d	13	12
2e	24	26
2f	20	21
2g	25	27
2h	26	30
Standard	25	30

[a] Diameter of zone of inhibition in mm

Table 2. MIC and MBC results of azomethine derivatives.

Compound	*Staphylococcus aureus* (AMJ-2005)		*Escherichia coli* (AMJ-2006)	
	MIC	**MBC**	**MIC**	**MBC**
2a	6.25	12.5	6.25	12.5
2b	6.25	6.25	6.25	12.5
2c	12.5	50	12.5	50
2d	12.5	100	12.5	100
2e	6.25	25	6.5	6.5
2f	12.5	25	25	50
2g	6.25	6.25	6.25	6.25
2h	6.25	6.25	6.25	6.25
Standard	6.25	12.5	12.5	25

MIC (ug/mL) = minimum inhibitory concentration that is lowest concentration to completely inhibit bacterial growth
MBC (ug/mL) = minimum bacterial concentration that is lowest concentration to completely kill bacteria.

The screening data revealed that most of the tested compounds showed good bacterial inhibition. The compounds **2a**, **2b**, **2e**, **2g** and **2h** exhibited good antibacterial activity, almost equal to that of the standard. The MBC of compound **2b**, **2g** and **2h** were found to be the same as the MIC, but in most of the compounds it was two to four fold higher than the corresponding MIC result. The synthesis and bioassay of similar other azomethine derivatives and their complexes are under study.

Experimental

General

2-Formylphenoxyacetic acid, picoline, N-phenylhydrazine, *p*-toluidine, *o*-bromobenzylamine, 2,3-dichloroaniline, *p*-aminoacetanilide, 3-imidazol-1-yl-propylamine were obtained commercially from Lancaster Research Chemicals. 2-Amino-4-(2'-chlorophenyl)thiazole was prepared from 1-bromo-2'-chloroacetophenone and thiourea by standard methods. Solvents used were of analytical grade. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DPX-400 instrument at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm reference to the residual solvent signal. Mass spectra were recorded on a JEOL SX-102 instrument and IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer. Melting points were recorded on a Stuart Scientific-SMP3 apparatus and are uncorrected.

2-(4-Acetamido phenyliminomethyl)phenoxyacetic acid (**2a**).

2-Formylphenoxy acetic acid (0.5 mmol, 0.09 g) was added to 4-aminoacetanilide (0.5 mmol, 0.075 g) in dioxane (10 mL) in addition to molecular sieves and the mixture heated under reflux for 3 h under N_2 (g). After filtration, evaporation and recrystallisation from EtOH, the yield of **2a** was found to be 80%; m.p. 216 ºC; HRMS (FAB, MH+) calcd. $C_{17}H_{16}N_2O_4$ 313.1188, found 313.1193; IR (ν_{max}, KBr, cm^{-1}) 3390, 1702, 1677, 1550; *Anal*. Found: C, 65.13; H, 5.17; N, 8.90. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.15; H, 5.15; N, 8.94; ^{1}H-NMR (DMSO-d_6) 2.60 (s,CH_3), 4.85 (s, CH_2), 7.09 (2H, t, *J*, 7.6 Hz), 7.20 (2H, d, *J* 8.0 Hz), 7.47 (1H, dd, *J* 7.6, 14.8 Hz), 7.63, (2H, d, *J* 8.4 Hz), 8.02 (1H, d, *J* 7.6 Hz), 8.93 (1H, s, CH=N); ^{13}C-NMR (DMSO-d_6) 23.97 (CH_3), 65.11 (CH_2), 113.13 (CH), 119.62 (2CH), 121.27 (2CH), 121.32 (CH), 124.42 (C), 126.74 (CH), 132.69 (CH), 137.62 (C), 146.75 (C), 154.22 (C=N), 157.76 (C), 168.16 (C), 170.05 (COOH).

2-(4-Methylpyridin-2-yliminomethyl)phenoxyacetic acid (**2b**).

2-Formylphenoxy acetic acid (0.5 mmol, 0.09 g) was added to 2-amino-4-methylpicoline (0.5 mmol, 0.054 g) in benzene (10 mL) containing molecular sieves and the mixture heated under reflux for 4 h under N_2 (g). After filtration, evaporation and recrystallisation from EtOH, the yield of **2b** was found to be 75%; m.p. 118 ºC; HRMS (FAB, MH^+) calcd. $C_{15}H_{14}N_2O_3$ 271.1083, found 271.1088; IR (ν_{max}, KBr, cm^{-1}) 3390, 1706, 1683, 1598; *Anal*. Found: C, 66.44; H, 5.17; N, 10.35. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.39; H, 5.20; N, 10.32; ^{1}H-NMR (DMSO-d_6) 2.17 (s, 3H), 4.82 (s, 2H), 6.36 (1H, *s*), 6.39 (1H, d, *J* 1.2 Hz), 7.47 (1H, dd, *J* 7.6, 14.8 Hz), 7.63, (2H, d, *J* 8.4 Hz), 8.02 (1H, d, *J* 7.6 Hz), 8.93 (1H, s, CH=N); ^{13}C-NMR (DMSO-d_6) 20.71 (Me), 65.52 (CH_2), 108.92 (CH), 113.38 (CH), 113.82 (CH), 121.03 (CH), 124.41 (C), 127.43 (CH), 136.18 (CH), 144.29 (CH), 148.45 (C), 158.53 (C), 157.76 (C=N), 160.47 (C), 170.48 (COOH).

2-(2-phenyl hydrazonomethyl)phenoxyacetic acid (**2c**).

2-Formylphenoxy acetic acid (0.5 mmol, 0.09 g) was added to N-phenylhydrazine (0.5 mmol, 0.049 g) in EtOH (10 mL) in addition to molecular sieves and stirred at room temp. for 15 min. under N_2 (g). After filtration, evaporation and recrystallisation from EtOH, the yield of **2c** was found to be 90%; m.p. 102 ºC; HRMS (FAB, M^+) calcd. $C_{15}H_{14}N_2O_3$ 270.1004, found 270.1002; IR (ν_{max}, KBr, cm^{-1}) 3440, 1712, 1600, 1566, 1516; *Anal*. Found: C, 66.60; H, 5.19; N, 10.33. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.64; H, 5.22; N, 10.36; ^{1}H-NMR (DMSO-d_6) 4.78 (s, CH2), 6.74 (1H ,m), 6.95 (1H, d, *J* 8.0 *HZ*), 7.01 (1H, t, *J* 7.6 *Hz*), 7.09, (2H, dd, *J* 1.6, 7.6 Hz), 7.18 - 7.27 (4H, m), 8.29 (1H, s, CH=N); ^{13}C-NMR, (DMSO-d_6) 64.87 (CH_2), 111.87 (CH), 111.88 (CH), 112.39 (CH), 118.56 (CH), 121.18 (CH), 124.24 (CH), 124.61 (C), 128.91 (CH), 129.07 (CH), 129.09 (CH), 131.86 (CH), 145.37 (C), 154.87 (CH=N), 170.16 (COOH).

2-(4-Methyl phenyliminomethyl)phenoxyacetic acid (**2d**).

2-Formylphenoxy acetic acid (0.5 mmol, 0.09 g) was added to *p*-toluidine (0.5 mmol, 0.054 g) in EtOH (10 mL) in addition to molecular sieves and stirred at room temp. for 3 h under N_2 (g). After filtration, evaporation and recrystallisation from EtOH, **2d** was obtained in 65% yield; m.p. 148 ºC; HRMS (FAB, M^+) calcd. $C_{16}H_{15}NO_3$ 270.1130, found 270.1133; *Anal*. Found: C, 71.00; H, 5.62; N, 5.16. Calcd. for $C_{16}H_{15}NO_3$: C, 71.08; H, 5.59; N, 5.18; IR (ν_{max}, KBr, cm^{-1}) 3406, 1710, 1682, 1598; ^{1}H-NMR (DMSO-d_6) 2.32 (s, 3H), 4.84 (s, 2H), 7.06 – 7.18 (4H, m), 7.22 (2H, d, *J* 7.6 *Hz*), 7.49, (1H, t, *J* 7.6 Hz), 8.03 (1H, d, *J* 7.3 *Hz)*, 8.94 (1H, s, CH=N); ^{13}C-NMR (DMSO-d_6) 20.55 (Me-H), 65.16 (CH_2), 113.14 (CH), 120.75 (2CH), 121.25 (CH), 124.36 (C), 126.70 (CH), 129.20 (CH), 129.73 (CH), 132.75 (CH), 135.18 (C), 146.01 (C), 154.88 (CH=N), 157.82 (C), 170.05 (COOH).

2-(2,3-Dichloro phenyliminomethyl)phenoxyacetic Acid (**2e**).

2-Formylphenoxy acetic acid (0.5 mmol, 0.09 g) was added to 2,3-dichloroaniline (0.5 mmol, 0.06 ml) in benzene (10 mL) in addition to molecular sieves and refluxed at 85 ºC for 5 h under N_2 (g). After filtration, evaporation and recrystallisation from EtOH, the yield of the viscous compound was found to be 84%; HRMS (FAB, M^+) calcd. $C_{15}H_{11}NO_3Cl_2$ 324.0199, found 324.0189; *Anal*. Found: C, 55.53; H, 3.40; N, 4.29. Calcd. for $C_{15}H_{11}NO_3Cl_2$: C, 55.55; H, 3.42; N, 4.32; ^{1}H-NMR (DMSO-d_6) 4.83 (s, CH_2), 6.74 (1H, m), 7.01 (1H, t, *J* 8.0 Hz), 7.12, (2H, dd, *J* 1.6, 7.6 Hz), 7.39 - 7.47 (3H, m), 8.97 (1H, *s*, CH=N); ^{13}C-NMR (DMSO-d_6) 65.11 (CH_2), 113.56 (CH), 116.69 (CH), 121.22 (CH), 123.65 (C), 127.26 (CH), 127.50 (CH), 131.52 (C), 133.84 (CH), 136.21 (CH), 146.71 (C), 146.73 (C), 158.48 (CH=N), 160.25 (C), 170.02 (COOH).

2-(2-Bromobenzyl iminomethyl)phenoxyacetic acid (**2f**).

2-Formylphenoxy acetic acid (0.5 mmol, 0.09 g) was added to *o*-bromobenzylamine (0.5 mmol, 0.112 g) in EtOH (10 mL) in addition to molecular sieves and refluxed at 85 ºC for about 4 h under N_2 (g). After

filtration, evaporation and recrystallisation from EtOH, the yield of the title compound **2f** was 70%; m.p. 166 ºC; HRMS (FAB, MH^+) calcd. $C_{16}H_{14}NO_3Br$, 348.0235 found; 348.0237; IR (ν_{max}, KBr, cm^{-1}) 3400, 1708, 1650, 1573; *Anal*. Found: C, 55.12; H, 4.09; N, 4.05. Calcd. for $C_{16}H_{14}NO_3Br$: C, 55.16; H, 4.05; N, 4.02; ^{1}H-NMR (DMSO-d_6) 5.05 (s, CH_2), 5.19 (s, CH_2), 7.29 - 7.83 (7H, m), 8.31 (1H, dd, *J* 1.2, 8.0 Hz*)*, 9.37 (1H, s, CH=N); ^{13}C-NMR (DMSO-d_6) 41.89 (CH_2), 65.05 (CH_2), 113.80 (CH), 121.27 (CH), 123.27 (C), 124.46 (C), 127.51 (CH), 127.99 (CH), 130.39 (CH), 130.44 (CH), 132.68 (CH), 133.25 (CH), 136.22 (C), 160.76 (CH=N), 160.81 (CH), 169.76 (COOH).

(2-{[4-(2′-chlorophenyl)-thiazole-2-yl imino]methyl}phenoxy)acetic acid (**2g**).

2-Formylphenoxyacetic acid (0.001 mol, 0.18 g) was added to a solution of 2-amino-4-(2′-chlorophenyl)thiazole (0.001 mol, 0.211 g) in absolute alcohol (20 mL), in addition to molecular sieves and Na_2SO_4 (*anhydr.*). The mixture heated under reflux for one week under N_2. The product was purified by crystallisation from EtOH and the yield of **2g** was 40%; m.p. 191-193 °C. HRMS (FAB, MH^+) calcd. for $C_{18}H_{13}O_3N_2SCl$ 372.604 found 372.58. IR (ν_{max}, KBr cm^{-1}): 3030, 1735, 1680, 1550, 1240; *Anal*. Found: C, 58.0; H, 3.86; N, 7.31. Calcd. for $C_{18}H_{13}O_3N_2SCl$: C, 57.99; H, 3.51; N, 7.51. ^{1}H-NMR, (400 MHz, MeOH-d_4): δ 4.98 (2H, s, CH_2), 6.77 (1H, d, *J* 8.0 Hz, ArH), 6.90-7.49 (8H, m, ArH and thiazole-H), 7.99 (1H, s, CH=N); ^{13}C-NMR (100 MHz, MeOH-d_4): δ 66.4 (CH_2), 164.9 (CH=N), 169.4 (2′-C), 113.3 (5′-C), 141.0 (4′-C), 122.2, 122.5, 126.2, 128.4, 129.8, 130.2, 130.8, 130.9, 135.4, 141.0, 156.3, 157.2, 172.0 (CO_2H).

2-{2-[(3-imidazol-1-yl-propylimino)methyl]phenoxy}acetic acid (**2h**).

2-Formylphenoxyacetic acid (0.002 mol, 0.360 g) was added to 3-imidazol-1-yl-propylamine (0.002 mol, 0.250 g) in dichloromethane (10.0 ml) in addition to 10% mmol of $Yb(OTf)_3$ as Lewis catalyst, and molecular sieves as dehydrating agent. The mixture was heated under reflux for 10 h under N_2. The reaction mixture was filtered through a column of silica gel, charcoal and Celite® to remove the catalyst. The product obtained after concentration under vacuum, as viscous oil in 70% yield; HRMS: found MH^+ 288.1344, $C_{15}H_{18}N_3O_3$ requires 288.1348; IR (ν_{max}, nujol, cm^{-1}): 3200-2900 (br), 1652, 1557, 1490, 1380; *Anal*. Found: C, 62.41; H, 6.32; N, 14.53 Calcd. for $C_{15}H_{18}N_3O_3$: C, 62.47; H, 6.29; N, 14.57; ^{1}H-NMR (MeOH-d_4): 2.15 (2H, quin, *J* 7 Hz, CH_2), 2.91 (2H, t, *J* 7 Hz, CH_2), 4.20 (2H, t, *J* 7 Hz, CH_2), 5.04 (2H, s, CH_2), 6.94-7.78 (7H, m, ArH and ImH), 8.37 (1H, s, CH=N); ^{13}C-NMR (MeOH-d_4): 29.9 (CH_2), 37.9 (CH_2), 45.5 (CH_2), 68.9 (CH_2O), 114.8, 121.2, 121.6, 122.8, 128.4, 130.9, 137.8, 138.1 (ImC-2), 157.7, 160.9 (C=N), 166.0 (CO_2H).

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against locally isolated *Escherichia coli* (AMJ-2006) and *Staphylococcus aureus* (AMJ-2005) bacterial strains by the disc diffusion method [25-26]. Overnight incubated cultures of these bacteria were introduced onto the surface

of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculum. The discs measuring 6.25 mm in diameter were prepared from Whatman No. 1 filter paper and sterilized by dry heat at 140 °C for an hour. The sterile discs previously soaked in a 100 µg/ml of the test compound dissolved in DMSO were placed on the inoculated nutrient agar medium. The plates were inverted and incubated for one day at 37 °C. Ciprofloxacin was used as a standard drug. Growth inhibition zones were measured and compared with the controls. The bacterial inhibition zone values are summarized in Table 1 Minimum inhibitory concentrations (MIC) were determined by the broth dilution technique. The Nutrient Broth, which contained logarithmic serially two fold diluted amount of test compound and controls, were inoculated with approx. 5 x 10^5 c.f.u. of actively dividing bacterial cells. The cultures were incubated for 24 h at 37 °C, and the growth was monitored visually and spectrophotometrically. To obtain the minimum bacterial concentration (MBC), 0.1 mL vol. was taken from each test and spread on agar plates. The number of c.f.u was counted after 18-24 hrs of incubation at 37 °C. The MIC and MBC are given in Table 2

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Sample Availability: Samples of the compounds are available from authors