Synthesis and antibacterial activity of C-7 acylhydrazone derivatives of dehydroabietic acid

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Seven new C-7 acylhydrazone derivatives of dehydroabietic acid were synthesised from dehydroabietic acid through benzylic oxidation, condensation with hydrazine hydrate, followed by nucleophilic substitution reactions with a variety of substituted aromatic acids. The structures of the synthesised compounds were characterised by IR, ^{1}H NMR and MS. The antibacterial activities of the synthesised compounds were evaluated by the disk diffusion method. Antibacterial activity studies showed that C-7 acylhydrazone derivatives of dehydroabietic acid exhibited inhibitory activities against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*. Among the seven compounds, dehydroabietic acid *p*-fluorobenzoyl hydrazone showed the strongest inhibitory activity against *B. subtilis* and *S. aureus*.

Keywords: dehydroabietic acid, acylhydrazone, synthesis, antibacterial activity

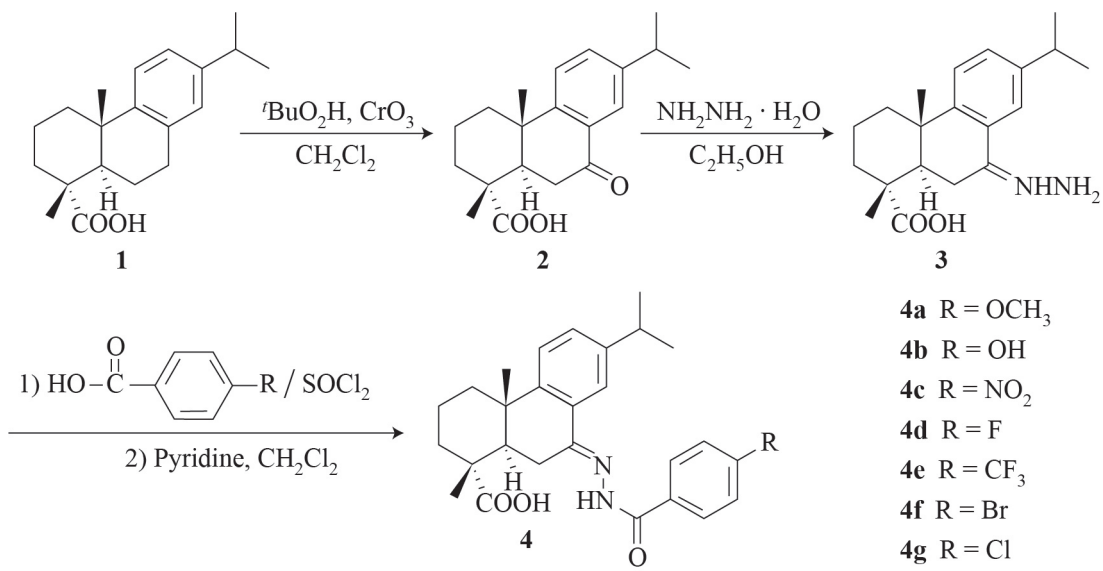
Dehydroabietic acid **1**, which possesses an aromatic diterpene structure with three rings and three chiral carbon atoms, can be extracted from commercial disproportionated rosin. Dehydroabietic acid and its derivatives have attracted considerable interest due to their potential biological activities, including antimicrobial,[1,2] antiviral,[3] antitumour,[4–6] antiulcer[7] and anti-inflammatory activity.[8] Reports of the biological activity of dehydroabietic acid and its derivatives prompted us to search for new rosin acid derivatives. Li *et al.*[9] utilised transformation of the carboxyl group to synthesise dehydroabietic acid-based acylhydrazone derivatives, many of which showed moderate to high levels of anticancer activity, and some displayed similar potent inhibitory activities comparable to commercial anticancer drugs. Gu *et al.*[10] synthesised a series of dehydroabietic acid acylhydrazone derivatives by means of carboxyl halogenation, reaction with hydrazine hydrate to generate an acylhydrazine, followed by condensation with a variety of substituted aromatic aldehydes, some of which exhibited pronounced antimicrobial activity. The majority of studies on acylhydrazone derivatives of dehydroabietic acid have focused on the carboxyl group, and acylhydrazone derivatives at other centres have seldom been reported. In this paper, we report the synthesis of seven new C-7 acylhydrazone derivatives of dehydroabietic acid from dehydroabietic acid through benzylic oxidation, condensation with hydrazine hydrate, followed by nucleophilic substitution reactions with a variety of substituted aromatic acids. The antibacterial activities of the target compounds were then tested.

Results and discussion

The general procedure for the synthesis of C-7 acylhydrazone derivatives of dehydroabietic acid (**4a–g**) is shown in Scheme 1.

Dehydroabietic acid **1**, the starting material, was oxidised with *t*-BuOOH to give compound **2**. The traditional methods for C-7 benzylic oxidations of dehydroabietic acid have involved the use of very large excesses of chromium(VI) reagents, such as CrO_3 and Na_2CrO_4,[11–14] in a mixed solvent of Ac_2O/AcOH. This has led to considerable amounts of toxic effluents and low yields (56.7%). When dehydroabietic acid was treated with an excess of *t*-BuOOH (8 equiv.) as an oxidant and CrO_3/pyridine mixture as a catalyst in CH_2Cl_2 the yields of compound **2** increased significantly (70.5%). Subsequently, the reactions of compound **2** with hydrazine hydrate yielded the corresponding 7-oxodehydroabietic acid hydrazone **3**.

Dehydroabietic acid acylhydrazone derivatives **4a–g** were prepared by the following procedure. First, substituted aromatic acids were reacted with thionyl chloride ($SOCl_2$) in dry toluene for 30 min at room temperature. The products were dissolved in dry CH_2Cl_2 and cooled to 0 °C, a solution of compound **3** and



Scheme 1 Synthesis of C-7 acylhydrazone derivatives of dehydroabietic acid (**4a–g**).

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Table 1 Antimicrobial activities of the tested compounds (units: diameter of inhibition zone/cm)

Compound no.	4a	4b	4c	4d	4e	4f	4g	Ciprofloxacin
Escherichia coli	0.78	0.85	1.21	1.26	1.18	1.03	1.23	2.93
Staphylococcus aureus	0.86	1.02	1.34	1.45	1.24	0.94	1.42	3.01
Bacillus subtilis	0.95	0.83	1.40	1.68	1.29	1.07	1.39	3.39

pyridine in dry CH_2Cl_2 was added, and the mixture was then stirred for 2 h at room temperature.

Antibacterial activity

The results for the antimicrobial activities of acylhydrazone derivatives of dehydroabietic acid are listed in Table 1.

As shown in Table 1, all of the compounds **4a–g** that were tested showed some inhibitory activity against three bacterial strains. Dehydroabietic acid *p*-nitrobenzoyl hydrazone **4c**, dehydroabietic acid *p*-fluorobenzoyl hydrazone **4d** and dehydroabietic acid *p*-chlorobenzoyl hydrazone **4g** exhibited considerably higher inhibitory activity against two bacterial strains, including *Bacillus subtilis* and *Staphylococcus aureus*. Among the seven compounds, dehydroabietic acid *p*-fluorobenzoyl hydrazone showed the strongest inhibitory activity against *B. subtilis* and *S. aureus*, the diameters of antibacterial rings reaching 1.68 and 1.45 cm, respectively.

Conclusion

We have prepared a series of C-7 acylhydrazone derivatives of dehydroabietic acid by benzylic oxidation, condensation with hydrazine hydrate, followed by nucleophilic substitution reactions with a variety of substituted aromatic acids. Their antibacterial activities against *E. coli*, *S. aureus* and *B. subtilis* were evaluated by the disk diffusion method. The results showed that C-7 acylhydrazone derivatives of dehydroabietic acid possessed good antibacterial activities, among which dehydroabietic acid *p*-fluorobenzoyl hydrazone showed the highest activity against *B. subtilis* and *S. aureus*.

Experimental

All chemicals and solvents were obtained from commercial sources and were used as received or dried according to standard procedures. Column chromatography was performed on silica gel (ZCXII, 100~200 mesh). Chemical reactions were monitored by thin-layer chromatography (TLC) using pre-coated silica gel GF254 plates. Melting points were determined on an RY-1G melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance AV-500 spectrometer at 500 MHz. Chemical shifts are reported in δ (parts per million) relative to tetramethylsilane (TMS) and coupling constants (*J*) are given in hertz (Hz). Infrared spectra were recorded using KBr pellets on a Nicolet 360 FT-IR spectrometer. ESI mass spectra were obtained on an Agilent 1100 Capillary LC/Micromass Q-TOF micromass spectrometer. Microanalytical data were obtained on an Elementar Vario EL III elemental analyser.

*Preparation of 7-oxodehydroabietic acid (**2**)*

A suspension of CrO_3 (74 mg, 0.74 mmol) in CH_2Cl_2 (120 mL) was treated with 65% *t*-BuOOH (19 mL, 118.4 mmol) and pyridine (0.12 mL, 1.48 mmol). The mixture was stirred for 3 min at room temperature. Dehydroabietic acid **1** (4.45 g, 14.8 mmol) was added and stirring continued for 24 h at room temperature, The resulting solution was then washed successively with saturated solutions of $Na_2S_2O_3$ (2 × 40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (chloroform/ethylacetate, 10:1) to give compound **2**: Light yellow solid; yield: 70.5%; m.p. 158–160 °C (lit.[15] 160–161.5 °C); FTIR (KBr, ν_{max}/cm^{-1}): 2955, 2929, 2868 (CH_{alkyl}), 1722, 1693 (C=O), 1604, 1497, 1458 ($C{=}C_{arom}$); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.87 (d, *J* = 2.0 Hz, 1H), 7.41 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 2.92 (septet, *J* = 7.0 Hz, 1H), 2.75 (dd, *J* = 13.9 Hz, 13.9 Hz, 1H), 2.70 (d, *J* = 13.9 Hz, 1H), 2.49 (d, *J* = 13.9 Hz, 1H), 2.36 (br d, *J* = 13.0 Hz, 1H), 2.90–1.39 (m, 3H), 1.35 (s, 3H), 1.26 (s, 3H), 1.24 (d, *J* = 7.0 Hz, 6H); TOF MS *m/z*: 314.2 [M$^+$]; Anal. calcd for $C_{20}H_{26}O_3$ (314.42): C, 76.40; H, 8.33; found: C, 76.51; H, 8.58%.

*Preparation of 7-oxodehydroabietic acid hydrazone (**3**)*

Compound **2** (10 g, 31.80 mmol) was dissolved in ethanol (160 mL) and the mixture was stirred and heated to reflux. Next, 98% hydrazine hydrate (2.08 g, 41.34 mmol) was added dropwise and the mixture was stirred and heated at reflux for 1 h. The solvent was evaporated under reduced pressure and the residue was recrystallised from ethanol to give compound **3**: Light yellow solid; yield: 85.5%; m.p. 164–166 °C; FTIR (KBr, ν_{max}/cm^{-1}): 3358, 3243 (NH), 2954, 2925, 2863 (CH_{alkyl}), 1721 (C=O), 1657 (C=N), 1608, 1501, 1453 ($C{=}C_{arom}$); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56 (d, *J* = 2.0 Hz, 1H), 7.27 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 5.34 (br s, 2H), 2.87 (septet, *J* = 7.0 Hz, 1H), 2.72 (dd, *J* = 13.8 Hz, 13.8 Hz, 1H), 2.67 (d, *J* = 13.8 Hz, 1H), 2.45 (d, *J* = 13.8 Hz, 1H), 2.35 (br d, *J* = 13.0 Hz, 1H), 2.89–1.37 (m, 3H), 1.34 (s, 3H), 1.25 (s, 3H), 1.23 (d, *J* = 7.0 Hz, 6H); TOF MS *m/z*: 330.2 [M+H]$^+$; Anal. calcd for $C_{20}H_{29}N_2O_2$ (329.46): C, 72.91; H, 8.87; N, 8.50; found: C, 72.76; H, 8.83; N, 8.39%.

*Preparation of dehydroabietic acid acylhydrazone derivatives (**4a–g**)*

Thionyl chloride (2.34 g, 19.71 mmol) was added slowly with stirring to a solution of *p*-methoxybenzoic acid (2.00 g, 13.14 mmol) in dry toluene (20 mL) at 0 °C. The mixture was then stirred at 23 °C for 30 min. After cooling, the solvent and excess $SOCl_2$ were removed *in vacuo* to yield *p*-methoxybenzoyl chloride as a colourless oily product. This was then dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C, then a solution of compound **3** (2.16 g, 6.57 mmol) and pyridine (1.56 g, 19.71 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise with stirring. The mixture was stirred for 2 h at room temperature and the precipitate that formed was collected by filtration and washed with CH_2Cl_2 (10 mL) and acetone (10 mL). The solid was then added to cold water (20 mL) and stirred for 1 h, then filtered, washed with distilled water (3 × 10 mL) and recrystallised from ethanol to give compound **4a**: White solid; yield: 54.5%; m.p. 183–185 °C; FTIR (KBr, ν_{max}/cm^{-1}): 3241 (NH), 2955, 2926, 2863 (CH_{alkyl}), 1725 (C=O), 1646 (C=N), 1603, 1510, 1461 ($C{=}C_{arom}$); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 11.08 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.22 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 2.97 (dd, *J* = 17.6 Hz, 12.8 Hz, 1H), 2.87 (septet, *J* = 7.0 Hz, 1H), 2.68–2.49 (m, 2H), 2.45 (d, *J* = 11.9 Hz, 1H), 2.38 (br d, *J* = 11.8 Hz, 1H), 2.19–1.98 (m, 2H), 1.65–1.58 (m, 1H), 1.56 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 6H), 1.22 (s, 3H); TOF MS *m/z*: 463.2 [M+H]$^+$; Anal. calcd for $C_{28}H_{34}N_2O_4$ (462.58): C, 72.70; H, 7.41; N, 6.06; found: C, 72.57; H, 7.36; N, 5.95%.

Compounds **4b–g** were prepared by the same procedure as used for the synthesis of compound **4a**.

Compound **4b**: White solid; yield: 57.4%; m.p. 174–176 °C; FTIR (KBr, ν_{max}/cm^{-1}): 3271 (NH), 2956, 2862 (CH_{alkyl}), 1722 (C=O), 1651 (C=N), 1602, 1531, 1453 ($C{=}C_{arom}$); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 11.35 (s, 1H), 10.85 (s, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.21 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 2.95 (dd, *J* = 17.6 Hz, 12.8 Hz, 1H), 2.89 (septet, *J* = 7.0 Hz, 1H), 2.71–2.50 (m, 2H), 2.42 (d, *J* = 11.9 Hz, 1H), 2.37 (br d, *J* = 11.8 Hz, 1H), 2.17–1.95 (m, 2H), 1.62–1.57 (m, 1H), 1.53 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 6H), 1.23 (s, 3H); TOF MS *m/z*: 449.2 [M+H]$^+$; Anal. calcd for $C_{27}H_{32}N_2O_4$ (448.55): C, 72.30; H, 7.19; N, 6.25; found: C, 72.25; H, 7.16; N, 6.19%.

Compound **4c**: Light yellow solid; yield: 60.7%; m.p. 195–197 °C; FTIR (KBr, ν_{max}/cm^{-1}): 3254 (NH), 2967, 2925, 2846 (CH_{alkyl}), 1721 (C=O), 1649 (C=N), 1602 (C=C_{arom}), 1528 (NO_2), 1471 (C=C_{arom}), 1351 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 11.59 (s, 1H), 8.32 (d, *J* = 8.5 Hz, 2H), 8.12 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 2.95 (dd, *J* = 17.6 Hz, 12.8 Hz, 1H), 2.88 (septet, *J* = 7.0 Hz, 1H), 2.73–2.52 (m, 2H), 2.45 (d, *J* = 11.9 Hz, 1H), 2.39 (br d, *J* = 11.8 Hz, 1H), 2.18–1.94 (m, 2H), 1.64–1.58 (m, 1H), 1.54 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 6H), 1.24 (s, 3H); TOF MS *m/z*: 478.2 [M+H]$^+$; Anal. calcd for $C_{27}H_{31}N_3O_5$ (477.55): C, 67.91; H, 6.54; N, 8.80; found: C, 67.87; H, 6.58; N, 8.71%.

Compound **4d**: White solid; yield: 58.3%; m.p. 181–183 °C; FTIR (KBr, ν_{max}/cm^{-1}): 3256 (NH), 2953, 2930, 2869 (CH_{alkyl}), 1727 (C=O), 1651 (C=N), 1604, 1508 (C=C_{arom}); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 11.50 (s, 1H), 8.30 (d, *J* = 8.5 Hz, 2H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 2.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 2.91 (dd, *J* = 17.6 Hz, 12.8 Hz, 1H), 2.84 (septet, *J* = 7.0 Hz, 1H), 2.76–2.54 (m, 2H), 2.46 (d, *J* = 11.9 Hz, 1H), 2.35 (br d, *J* = 11.8 Hz, 1H), 2.25–1.96 (m, 2H), 1.69–1.60 (m, 1H), 1.53 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 6H), 1.23 (s, 3H); TOF MS *m/z*: 451.2 [M+H]$^+$; Anal. calcd for $C_{27}H_{31}FN_2O_3$ (450.55): C, 71.98; H, 6.94; N, 6.22; found: C, 71.92; H, 6.92; N, 6.18%.

Compound **4e**: White solid; yield: 55.2%; m.p. 187–189 °C; FTIR (KBr, ν_{max}/cm^{-1}): 3268 (NH), 2943, 2927, 2861 (CH_{alkyl}), 1719 (C=O), 1643 (C=N), 1603, 1512 (C=C_{arom}); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 11.57 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 2.89 (dd, *J* = 17.6 Hz, 12.8 Hz, 1H), 2.83 (septet, *J* = 7.0 Hz, 1H), 2.74–2.55 (m, 2H), 2.47 (d, *J* = 11.9 Hz, 1H), 2.37 (br d, *J* = 11.8 Hz, 1H), 2.30–1.98 (m, 2H), 1.71–1.64 (m, 1H), 1.54 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 6H), 1.22 (s, 3H); TOF MS *m/z*: 501.2 [M+H]$^+$; Anal. calcd for $C_{28}H_{31}F_3N_2O_3$ (500.55): C, 67.19; H, 6.24; N, 5.60; found: C, 67.13; H, 6.22; N, 5.54%.

Compound **4f**: White solid; yield: 60.3%; m.p. 178–180 °C; FTIR (KBr, ν_{max}/cm^{-1}): 3265 (NH), 2958, 2929, 2837 (CH_{alkyl}), 1715 (C=O), 1653 (C=N), 1607, 1536, 1481 (C=C_{arom}); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 10.97 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 2.87 (dd, *J* = 17.5 Hz, 12.6 Hz, 1H), 2.82 (septet, *J* = 6.9 Hz, 1H), 2.78–2.59 (m, 2H), 2.43 (d, *J* = 11.7 Hz, 1H), 2.35 (br d, *J* = 11.3 Hz, 1H), 2.28–2.01 (m, 2H), 1.70–1.64 (m, 1H), 1.52 (s, 3H), 1.27 (d, *J* = 6.7 Hz, 6H), 1.23 (s, 3H); TOF MS *m/z*: 511.1, 513.1 [M+H]$^+$; Anal. calcd for $C_{27}H_{31}BrN_2O_3$ (511.45): C, 63.41; H, 6.11; N, 5.48; found: C, 63.37; H, 6.18; N, 5.35%.

Compound **4g**: Light yellow solid; yield: 56.9%; m.p. 174–176 °C; FTIR (KBr, ν_{max}/cm^{-1}): 3242 (NH), 2971, 2934, 2865 (CH_{alkyl}), 1726 (C=O), 1650 (C=N), 1598, 1539, 1491 (C=C_{arom}); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 11.29 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 2H), 8.15 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 7.9 Hz, 2.0 Hz, 1H), 2.81 (dd, *J* = 17.6 Hz, 12.5 Hz, 1H), 2.78 (septet, *J* = 6.9 Hz, 1H), 2.83–2.64 (m, 2H), 2.38 (d, *J* = 11.5 Hz, 1H), 2.34 (br d, *J* = 11.3 Hz, 1H), 2.30–2.18 (m, 2H), 1.78–1.67 (m, 1H), 1.51 (s, 3H), 1.26 (d, *J* = 6.5 Hz, 6H), 1.21 (s, 3H); TOF MS *m/z*: 467.2, 469.2 [M+H]$^+$; Anal. calcd for $C_{27}H_{31}ClN_2O_3$ (467.00): C, 69.44; H, 6.69; N, 6.00; found: C, 69.37; H, 6.75; N, 5.94%.

Antibacterial activity studies

The antibacterial activities of the synthesised compounds were evaluated against three test bacteria: *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*. The antimicrobial screening of the prepared compounds was performed according to the disk diffusion method.[16] Filter paper disks of 7 mm diameter were sterilised by autoclaving for 15 min at 121°C. Compounds **4a–g** were dissolved in dimethylformamide (DMF) to give a 30 mg mL^{-1} solution, and the sterile disks were impregnated with the prepared solution for 10 min. Agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. The impregnated disks were placed on the medium, suitably spaced apart, and the plates were incubated at 5 °C for 1 h to permit good diffusion and then transferred to an incubator at 35 °C for 48 h to grow the bacteria, which were then examined for the inhibition zones resulting from the action of the prepared compounds on the microorganisms. The zone of inhibition was measured in cm and compared with the reference standard, ciprofloxacin.

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