

Synthesis, characterization, and antimicrobial activity of some new coumarin derivatives

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Abstract A number of new [(4-methyl-2-oxo-2H-chromen-7-yl)amino]methylcoumarins (**5a–c**), benzofuran (**6**), and benzoxazol (**7**) were synthesized through the reaction of 7-amino-4-methylcoumarin (**1**) with a number of organic halides. In addition, series of *N*-substituted 2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (**11a–h**) and (**12a–d**) were prepared from the reaction of 2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (**8**) with corresponding heteroaryl/alkyl halides (**2–4**, **9**, and **10**). The synthesized compounds were characterized by elemental analysis and by spectroscopic techniques such as ¹H-NMR, ¹³C-NMR, and mass spectrometry and were tested for their in vitro antimicrobial activity. The newly synthesized compounds exerted significant inhibitory activity against the growth of tested bacterial strains and a few of them are found to be potent antimicrobial agents.

Keywords 7-Amino-4-methylcoumarin ·
Acetohydrazide · Spectral analysis · Antimicrobial activity

Introduction

Coumarins form an important class of benzopyrones several derivatives of which are found in nature (Borges *et al.*, 2005). Recently, many of the isolated prenyloxy coumarins were shown to exhibit in vitro and in vivo remarkable anti-tumoral, anti-inflammatory, and anti-viral effects (Curini *et al.*, 2006). In addition, coumarins and related derivatives have continued to attract attention for their interesting biological activities. Their anticoagulant, antithrombotics, antifungal, antiinflammatory, and antiviral activities including human immunodeficiency virus activities are well known (Al-Zghoul *et al.*, 2005).

The natural occurrence, antimicrobial, antiinflammatory, anticancer, and other properties of different coumarins have been recently reviewed (Kulkarni *et al.*, 2006). Kalkhambkar *et al.* (2008) have quite recently prepared a series of new fluorinated coumarins and 1-aza coumarins and studied their antimicrobial, antiinflammatory, and analgesic activities. They discovered that these newly synthesized compounds exhibit moderate analgesic and excellent inflammatory and potential anti-bacterial and anti-fungal activities compared to other halogenated compounds. In addition, interest in coumarins and 1-aza coumarins as antibiotics is due to recent observations that these compounds are potent inhibitors of bacterial DNA gyrase (Kalkhambkar *et al.*, 2008).

Similarly, the biological importance of substituted coumarins and acetohydrazide stimulated an intensive research work for the synthesis of many members of this class of compounds (Maczynski *et al.*, 2008; Mubarak and Ayoub, 2007). Among the various coumarin derivatives, 7-substituted coumarins constitute an important group of compounds that show various bioactivities along with other applications (Kuznetsova *et al.*, 2003). Moreover, 7-amino

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4-methyl coumarin is also used as laser dye and intermediate for the synthesis of bioactive compounds (Nowakowska *et al.*, 2001) and the 4-methylcoumarin derivatives present in various naturally occurring compounds, are known to exhibit a wide range of biological and pharmaceutical activities (Ramesh and Raghunathan, 2008). In addition, coumarin moieties containing hydrazide and sulfonamide groups act as anti-malarial, antiviral activity, anti-HIV, and anticancer agents (Havaladar and Patil, 2008; Hwu *et al.*, 2008; Azizian *et al.*, 2008; Georgieva *et al.*, 2007).

In view of the wide continued interest in the activity spectrum and profile of coumarins (Kontogiorgis and Hadjipavlou-Litina 2003; Satyanarayana *et al.*, 2008; Burbuliene *et al.*, 2005; Brzozowski *et al.*, 2007), and in continuation of our work in the synthesis of new compounds of pharmacological and biological interest (Al-Zghoul *et al.*, 2005; Salih *et al.*, 2006; Salih *et al.*, 2007; Al-Soud *et al.*, 2008; Abu-Shaireh *et al.*, 2009; Saadeh *et al.*, 2010), we report, herein, on the synthesis and characterization of some newly substituted [(4-methyl-2-oxo-2*H*-chromen-7-yl)amino]methylcoumarins and *N*-substituted 2-[(4-methyl-2-

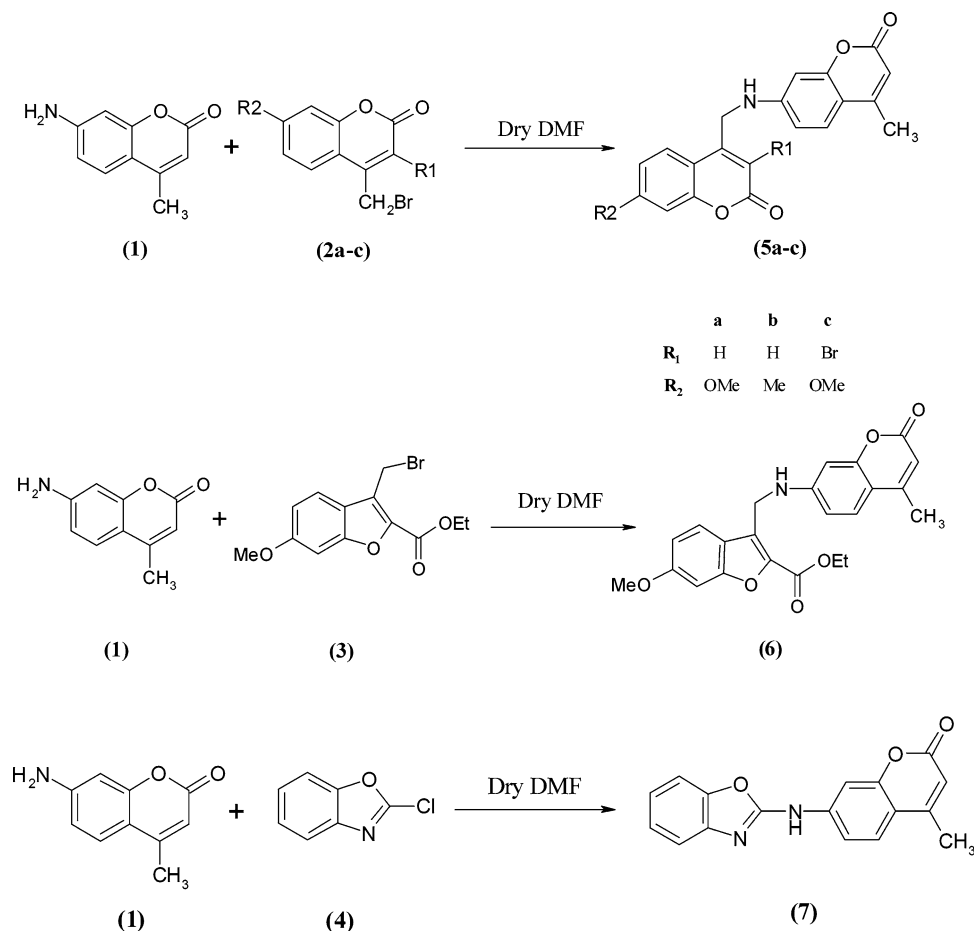
oxo-2*H*-chromen-7-yl)oxy]acetohydrazide. The antibacterial activity of these newly synthesized compounds was evaluated.

Results and discussion

Chemistry

The key starting material, 7-amino-4-methylcoumarin (**1**) was synthesized according to published procedures (Pozdnev, 1990) through the reaction of *m*-aminophenol, methoxycarbonyl chloride, and acetoacetic ester, using concentrated sulfuric acid. Compound **1** was reacted with 4-(bromomethyl)-2*H*-chromen-2-one (**2a-c**), 3-bromomethyl-6-methoxy-benzofuran-2-carboxylic acid ethyl ester (**3**), and 2-chlorobenzoxazole (**4**) in the presence of dry DMF to afford the substituted [(4-methyl-2-oxo-2*H*-chromen-7-yl)amino]methylcoumarins (**5a-c**), ethyl-6-methoxy-3-[[[(4-methyl-2-oxo-2*H*-chromen-7-yl)amino]methyl]-1-benzofuran-2-carboxylate (**6**) and 7-[(1,3-benzoxazol-2-yl)amino]-4-methyl-2*H*-chromen-2-one (**7**), respectively, in good yields

Scheme 1 Synthesis of compounds **5a-c**, **6**, and **7**

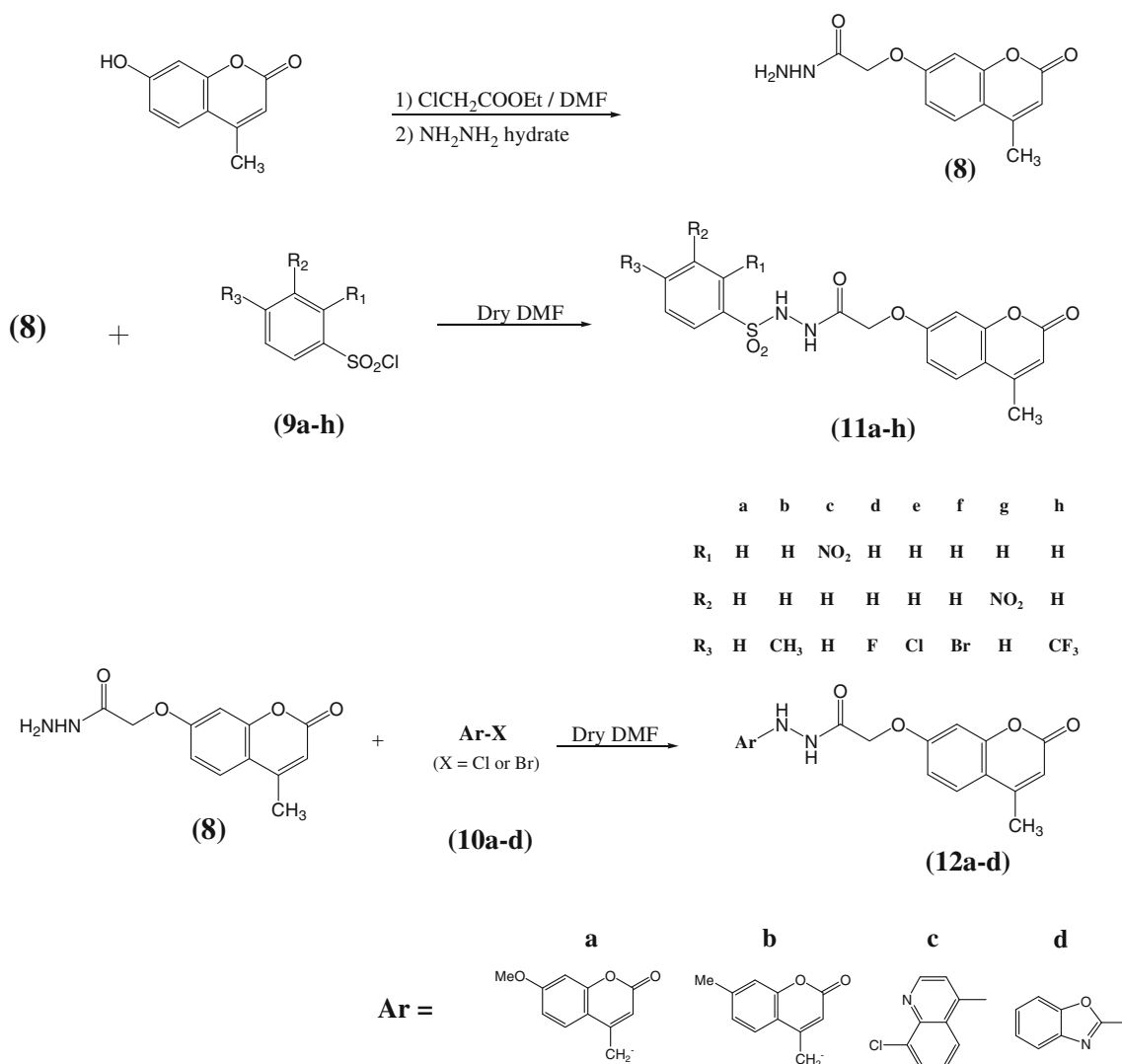


(Scheme 1). Purity of the prepared compounds was checked by TLC and their structures were confirmed by means of ^1H NMR, ^{13}C NMR, mass spectrometry, IR, and elemental analysis; the spectral data are in total agreement with the proposed structures. All the compounds were screened for anti-bacterial activities.

Since many benzenesulfonylhydrazide derivatives display a variety of interesting activities as antibacterial agents (Salih *et al.*, 2007), it was of interest to react the parent 2-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetohydrazide (**8**) with appropriate benzene sulfonyl chlorides (**9a–h**) and aryl halides (**10a–d**) to obtain new *N*-substituted 2-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetohydrazides (**11a–h**) and (**12a–d**) (Scheme 2). Compound **8** itself was prepared according to published procedures outlined by Satyanarayana *et al.* that involves reacting 7-hydroxy-4-methylcoumarin with ethyl chloroacetate in DMF followed

by the addition of hydrazine hydrate (Satyanarayana *et al.*, 2008).

^1H -NMR and ^{13}C -NMR spectra of all prepared compounds are in total agreement with the suggested structures; the ^1H NMR spectra of compounds (**5a–c**, **6**, and **7**), (**11a–h**), and (**12a–d**) showed signals corresponding to hydrazide, sulfonamide, aromatic, and NH protons. DEPT experiments were employed to differentiate between secondary and quaternary carbons from primary and tertiary carbons. Moreover, the infrared spectra of the prepared compounds showed characteristics of absorption bands of NH group in addition to other absorptions correlated to the assigned structures. Mass spectral data of the synthesized compounds are also in total agreement with the assigned structures and show the expected molecular ions, M^+ as suggested by their molecular formulas.



Scheme 2 Synthesis of compounds **11a–h** and **12a–d**

Biological activity

Antibacterial activity

A number of the newly synthesized compounds were screened for their antibacterial activity against Gram-negative microorganism (*K.pneumoniae* and *E.coli*) and Gram-positive bacteria (*Staphylococcus aureus*). In vitro antibacterial screening of the compounds **5a**, **5c**, **6**, **11b**, **11d–h**, and **12c** indicates that all of them produce antibacterial activity against Gram-negative microorganism (*K.pneumoniae* and *E.coli*) and Gram-positive bacteria (*Staphylococcus aureus*) in general (Table 1). Results (Tables 1, 2) reveal that these compound have significant influence on antibacterial profile of Gram-negative bacteria. The compounds also showed moderate to good inhibitory results against Gram-positive bacteria. The Minimum inhibitory concentrations of the synthesized compounds ranged from 22.9 to 57.8 µg/ml against *K. pneumoniae* and 24.1–98.4 µg/ml against *E.coli*. The MIC values were more than 85 µg/ml against *Staphylococcus aureus* (Table 2). Compounds **5a**, **5c**, **11b**, **11d**, **11f**, and **11h** showed good antibacterial activity while compounds **6**, **11e**, **11g**, and **12c** showed moderate antibacterial activity against Gram-positive microorganism as compared to ciprofloxacin. It is generally assumed that the more lipophilic compound can penetrate better the lipophilic cell membrane of Gram-positive bacteria, while less lipophilic compound are more liable to penetrate the cell wall of Gram-negative bacteria. It has been noted that the compounds which are less lipophilic (lower log *P* values, Table 1) in nature are more effective against Gram-negative microorganism, on the other hand, these compounds are less effective against Gram-positive microorganism. In the

Table 2 Minimum inhibitory concentrations (µg/ml) for the synthesized compound (**5a**, **5c**, **6**, **11b**, **11d–h**, and **12c**) against *K. pneumoniae*, *E. coli*, and *S. aureus*

SN	Compound	<i>K. pneumoniae</i> Minimum inhibitory concentration (µg/ml)	<i>E. coli</i>	<i>S. aureus</i>
1	5a	22.9	45.9	91.9
2	5c	46.4	46.4	92.8
3	6	25.8	51.6	>100
4	11b	49.2	98.4	98.4
5	11d	48.3	24.1	96.6
6	11e	27.7	55.3	>100
7	11f	42.6	42.6	85.1
8	11g	52.0	26.0	>100
9	11h	44.5	44.5	89.1
10	12c	57.8	28.9	>100
11	Ciprofloxacin	1.3	0.6	0.6

Ph–SO₂–NH–NH–CO–O series, compounds with electron-withdrawing groups have more activity than compounds with electron-donating functional groups. In the case of amino-coumarin series, it was noted that the introduction of *o*-bromo group, reduces the antibacterial activity against Gram-negative microorganism; this could be due to changes in the lipophilicity of the compound. Compound **5c** is more lipophilic than compound **5a** (Table 1). Isosteric replacement (benzofuran instead of coumarin), does not reduce the antibacterial activity significantly.

Conclusions

We reported on the synthesis and characterization of new coumarin derivatives and new *N*-substituted 2-[(4-methyl-

Table 1 In-vitro antibacterial activity of compounds (**5a**, **5c**, **6**, **11b**, **11d–h**, and **12c**) at 50 µg/ml concentration

Sn	Compound	Log <i>P</i> (c Log <i>P</i>) ^a	Gram negative		Gram positive
			<i>K. pneumoniae</i>	<i>E. coli</i>	<i>S. aureus</i>
			Diameter of inhibition zone in mm at 50 µg/ml		
1	5a	1.03 (1.88)	20	12	10
2	5c	1.34 (2.74)	14	11	10
3	6	0.56 (3.31)	14	11	11
4	11b	1.79 (2.65)	10	11	10
5	11d	1.52 (2.30)	12	12	9
6	11e	2.00 (2.87)	10	12	9
7	11f	2.27 (3.02)	11	12	14
8	11g	1.34 (1.90)	14	13	10
9	11h	2.36 (3.04)	15	13	11
10	12c	2.55 (3.92)	13	13	10
11	Ciprofloxacin (1.0 µg/ml)		20	22	24

Note: diameter of wells = 6 mm

^a Log *P* (cLog *P*) were calculated using CambridgeSoft Chem Draw Ultra Ver. 8.0

2-oxo-2*H*-chromen-7-yl)oxy]acetohydrazide. The antimicrobial activity showed that the synthesized compounds exerted significant inhibitory activity against the growth of tested bacterial strains and a few of them are potent antimicrobial agents.

Experimental

Chemistry

All reagents were used as received from commercially sources without further purification. Progress of reactions was monitored by thin layer chromatography (TLC) using glass plates pre-coated with silica gel (E. Merck Kiesegel 60 F₂₅₄ layer thickness 0.25 mm). Melting points of the newly synthesized compounds were determined with a Stuart melting point apparatus and were uncorrected. ¹H and ¹³C NMR spectra were recorded with the aid of Bruker-DPX 300 MHz spectrometers and are reported in ppm (δ) relative to TMS as an internal standard and with DMSO-*d*₆ as solvent. Infrared (IR) spectra were recorded as KBr discs on a Nicolet-MAGNA-IR-560 instrument. High resolution mass spectral data were acquired with a Bruker APEX (IV) mass spectrometer (Bremen, Germany). Elemental analyses were obtained using a Eurovector Euro EA3000, CHNS-O elemental analyzer.

7-Amino-4-methylcoumarin (**1**)

The title compound was synthesized according to published procedure by reacting *m*-aminophenol (22.0 g, 202 mmol) and methoxycarbonyl chloride (18.0 ml, 234 mmol), followed by the addition of acetoacetic ester (25.0 ml) and concentrated sulfuric acid. The reaction mixture was then filtered to give 7-amino-4-methylcoumarin (**1**), mp 224–226°C (28.5 g, 80% yield), [lit., 222–223°C, Pozdnev (1990)].

2-[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetohydrazide (**8**)

This compound was synthesized according to the procedure outlined by Satyanarayana *et al.* (2008), which involved the reaction of 7-hydroxy-4-methylcoumarin (0.057 mol, 10.0 g) and ethylchloroacetate, followed by the addition of hydrazine hydrate (0.014 mol). The reaction mixture was filtered to give 2-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetohydrazide (**8**), mp 203–205°C (Yield 90%), [lit. 202–204°C, (Satyanarayana *et al.*, 2008)].

General procedure for preparation of compounds (**5a–c**, **6**, and **7**)

A mixture of 7-amino-4-methylcoumarin (**1**) (0.25 g, 1.43 mmol) and corresponding halides (**2a–c**, **3**, and **4**) (1.43 mmol) in dry DMF (5–10 ml) was heated at 70°C for 5–15 h depending on the halide. Disappearance of the starting material and completion of the reaction were confirmed by TLC. The reaction mixture was poured onto crushed ice (100 ml) and stirred for 10 min. The precipitate was filtered, washed with cold water, and recrystallized from ethanol to give the desired products (**5a–c**, **6**, and **7**).

7-Methoxy-4-[[[(4-methyl-2-oxo-2*H*-chromen-7-yl)amino]methyl]-2*H*-chromen-2-one (**5a**)

Yield = 0.292 g (56.3%), mp = 268–270°C. ¹H NMR (DMSO-*d*₆): δ 7.79 (d, *J* = 8.7 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.21(t, *J* = 5.4 Hz, 1H), 6.99 (dd, *J* = 2.5, 8.7 Hz, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 6.68 (dd, *J* = 2.1, 8.7 Hz, 1H), 6.47 (d, *J* = 2.1 Hz, 1H), 6.08 (s, 1H), 5.92 (s, 1H), 4.62 (d, *J* = 5.4 Hz, 2H), 3.83 (s, 3H), 2.28 (s, 3H). ¹³C NMR (DMSO-*d*₆): δ 162.97, 161.06, 160.74, 155.97, 155.54, 154.19, 153.92, 152.25, 126.73, 126.49, 112.70, 111.74, 110.87, 110.09, 108.98, 108.71, 101.37, 97.65, 56.47, 43.11, 18.52. IR (KBr): 1710, 3381, 1614, 1291 cm⁻¹. HRMS *m/z*: calcd for C₂₁H₁₇NO₅ [M]⁺ 363.11067, found 363.11122. Anal. Calcd for C₂₁H₁₇NO₅: C, 69.41; H, 4.72; N, 3.85. Found: C, 69.53; H, 4.96; N, 3.47.

7-Methyl-4-[[[(4-methyl-2-oxo-2*H*-chromen-7-yl)amino]methyl]-2*H*-chromen-2-one (**5b**)

Yield = 0.298 g (60.1%), mp = 216–219°C. ¹H NMR (DMSO-*d*₆): δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.23 (br s, 1H), 7.23 (d, *J* = 2.8 Hz, 1H), 7.21 (dd, *J* = 2.8, 8.0 Hz, 1H), 6.68 (dd, *J* = 1.9, 8.7 Hz, 1H), 6.48 (d, *J* = 1.9 Hz, 1H), 6.18 (s, 1H), 5.92 (s, 1H), 4.64 (d, *J* = 4.6 Hz, 2H), 2.39 (s, 3H), 2.27 (s, 3H). ¹³C NMR (DMSO-*d*₆): δ 161.04, 160.53, 155.98, 154.15, 153.74, 153.67, 152.22, 143.49, 126.71, 125.91, 125.09, 117.13, 115.91, 111.23, 110.87, 110.13, 108.74, 97.69, 43.09, 21.57, 18.51. IR (KBr) 1707, 3375, 1616, 1266, 3071 cm⁻¹. HRMS *m/z*: calcd for C₂₁H₁₇NO₄Na [M + Na]⁺ 370.10553, found 370.10498. Anal. Calcd for C₂₁H₁₇NO₄: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.53; H, 4.53; N, 4.08.

3-Bromo-7-methoxy-4-[(4-methyl-2-oxo-2H-chromen-7-yl)amino]methyl]-2H-chromen-2-one (5c)

Yield = 0.359 g (56.8%), mp = 252–254°C. ¹H NMR (DMSO-d₆): δ 7.74 (d, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.04 (dd, *J* = 2.3, 8.21 Hz, 1H), 6.99 (t, *J* = 2.5 Hz, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 6.65 (dd, *J* = 1.8, 8.7 Hz, 1H), 6.58 (d, *J* = 1.8 Hz, 1H), 5.94 (s, 1H), 4.63 (d, *J* = 2.5 Hz, 2H), 3.83 (s, 3H), 2.28 (s, 3H). ¹³C NMR (DMSO-d₆): δ 163.14, 161.09, 157.18, 156.03, 154.19, 154.08, 152.12, 150.39, 127.59, 126.64, 113.56, 112.38, 111.09, 110.93, 110.09, 108.73, 101.32, 97.46, 56.62, 44.97, 18.53. IR (KBr): 1706, 3303, 1621, 1284, 3080, 631 cm⁻¹. HRMS *m/z*: calcd for C₂₁H₁₅Br NO₅ [M - H]⁺ 440.01336, found 440.01391. Anal. Calcd for C₂₁H₁₆BrNO₅: C, 57.03; H, 3.65; N, 3.17. Found: C, 56.43; H, 3.26; N, 3.31.

Ethyl-6-methoxy-3-[(4-methyl-2-oxo-2H-chromen-7-yl)amino]methyl]-1-benzofuran-2-carboxylate (6)

Yield = 0.253 g (43.4%), mp = 164–167°C. ¹H NMR (DMSO-d₆): δ 7.80 (d, *J* = 8.7 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.32 (t, *J* = 5.9 Hz, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 6.92 (dd, *J* = 2.1, 8.7 Hz, 1H), 6.63 (dd, *J* = 2.1, 8.7 Hz, 1H), 6.45 (d, *J* = 2.1 Hz, 1H), 5.87 (s, 1H), 4.81 (d, *J* = 5.9 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 2.23 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (DMSO-d₆): δ 161.07, 160.99, 159.95, 155.96, 155.89, 154.15, 152.42, 140.48, 127.61, 126.65, 123.34, 120.66, 114.17, 110.58, 109.68, 108.38, 97.05, 96.32, 61.57, 56.26, 37.45, 18.47, 14.67. IR (KBr): 1712, 3370, 1624, 1272, 3078 cm⁻¹. HRMS *m/z*: calcd for C₂₃H₂₁NO₆Na [M + Na]⁺ 430.12666, found 430.12611. Anal. Calcd for C₂₃H₂₁NO₆: C, 67.80; H, 5.20; N, 3.44. Found: C, 67.34; H, 6.15; N, 3.78.

7-[(1,3-Benzoxazol-2-yl)amino]-4-methyl-2H-chromen-2-one (7)

Yield = 0.239 g (57.2%), mp = 335–336°C. ¹H NMR (DMSO-d₆): δ 11.16 (s, 1H), 7.96 (d, *J* = 1.8 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.55 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.20 (m, 4H), 6.21 (s, 1H), 2.37 (s, 3H). ¹³C NMR (DMSO-d₆): δ 160.58, 157.66, 154.60, 153.72, 147.44, 142.58, 126.67, 124.78, 122.88, 117.66, 114.46, 112.18, 109.78, 104.39, 18.54. IR (KBr): 1686, 3253, 1596, 1271, 3077, 1567 cm⁻¹. HRMS *m/z*: calcd for C₁₇H₁₂N₂O₃Na [M + Na]⁺ 315.07456, found 315.07401. Anal. Calcd for C₁₇H₁₂N₂O₃: C, 69.86; H, 4.14; N, 9.58. Found: C, 70.01; H, 4.39; N, 10.04.

N-Substituted-2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (11a–h)

General procedure

A mixture of substituted sulfonyl chloride (**9a–h**) (1.37 mmol) and 2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (**8**) (0.34 g, 1.37 mmol) was stirred at room temperature in (5–10 ml) dry DMF in the presence of TEA as base. The progress of reaction and disappearance of the starting material was monitored by TLC. The reaction mixture was poured onto crushed ice (100 ml) and stirred for 10 min. The precipitate was collected by suction filtration, washed with cold water and further purified by crystallization from ethanol to give compounds (**11a–h**).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N-(phenylsulfonyl)acetohydrazide (11a)

Yield = 0.198 g (37%), mp = 195–196°C. ¹H NMR (DMSO-d₆): δ 10.21 (br s, 1H), 9.85 (br s, 1H), 7.66 (m, 5H), 7.50 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.77 (s, 1H), 6.19 (s, 1H), 4.57 (s, 2H), 2.36 (s, 3H). ¹³C NMR (DMSO-d₆): δ 166.56, 161.07, 160.55, 154.94, 153.84, 139.37, 133.54, 129.37, 128.07, 126.91, 114.16, 113.00, 111.98, 101.96, 66.24, 18.61. IR (KBr): 1724, 3308, 1618, 1206, 3061, 1686 cm⁻¹. HRMS *m/z*: calcd for C₁₈H₁₅N₂O₆S [M-H]⁺ 387.06508, found 387.06563. Anal. Calcd for C₁₈H₁₆N₂O₆S: C, 55.66; H, 4.15; N, 7.21. Found: C, 56.04; H, 4.42; N, 7.67.

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N-[(4-methylphenyl)sulfonyl]acetohydrazide (11b)

Yield = 0.196 g (35.6%), mp = 217–218°C. ¹H NMR (DMSO-d₆): δ 10.32 (br., 1H), 9.84 (br., 1H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.77 (s, 1H), 6.20 (s, 1H), 4.57 (s, 2H), 2.31 (s, 3H), 2.24 (s, 3H). ¹³C NMR (DMSO-d₆): δ 166.45, 161.09, 160.55, 154.95, 153.85, 143.81, 136.40, 129.81, 128.15, 126.89, 114.14, 113.05, 111.97, 101.95, 66.18, 21.49, 18.61. IR (KBr): 1737, 3291, 1613, 1285, 3076, 1690, 1334 cm⁻¹. HRMS *m/z*: calcd for C₁₉H₁₈N₂NaO₆S [M + Na]⁺ 425.07832, found 425.07778. Anal. Calcd for C₁₉H₁₈N₂O₆S: C, 56.71; H, 4.51; N, 6.96. Found: C, 56.65; H, 4.81; N, 6.29.

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N-[(2-nitrophenyl)sulfonyl]acetohydrazide (11c)

Yield = 0.212 g (35.7%), mp = 203–205°C. ¹H NMR (DMSO-d₆): δ 10.58 (br s, 1H), 10.27 (br s, 1H), 8.02 (d, *J* = 7.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.79 (m, 2H),

7.64 (d, $J = 8.8$ Hz, 1H), 6.88 (dd, $J = 2.0, 8.2$ Hz, 1H), 6.79 (d, $J = 2.0$ Hz, 1H), 6.19 (s, 1H), 4.63 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (DMSO- d_6): δ 167.06, 161.02, 160.53, 154.92, 153.82, 148.15, 135.16, 132.96, 132.23, 131.35, 126.92, 124.87, 114.19, 112.92, 112.01, 102.04, 66.23, 18.60. IR (KBr): 1700, 3299, 1614, 1281, 3171, 1683, 1352, 1542 cm^{-1} . HRMS m/z : calcd for $\text{C}_{18}\text{H}_{14}\text{N}_3\text{O}_8\text{S}$ [M - H] $^+$ 432.05016, found 432.05071. Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_8\text{S}$: C, 49.88; H, 3.49; N, 9.70. Found: C, 50.31; H, 3.63; N, 9.11.

N-[(4-Fluoro phenyl)sulfonyl]-2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (**11d**)

Yield = 0.312 g (55.9%), mp = 238–240°C. ^1H NMR (DMSO- d_6): δ 10.45 (br s, 1H), 10.09 (br s, 1H), 7.81 (m, 2H), 7.64 (d, $J = 8.8$ Hz, 1H), 7.32 (t, $J = 8.7$ Hz, 2H), 6.85 (dd, $J = 2.2$ Hz, 8.84 Hz, 1H), 6.78 (d, $J = 2.2$ Hz, 1H), 6.21 (s, 1H), 4.57 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (DMSO- d_6): δ 166.63, 163.42, 160.99, 160.54, 154.89, 153.87, 135.64, 131.30, 126.93, 116.69, 114.12, 112.95, 111.98, 101.91, 66.13, 18.64. IR (KBr): 1735, 3318, 1622, 1307, 3057, 1686, 1078 cm^{-1} . HRMS m/z : calcd for $\text{C}_{18}\text{H}_{16}\text{FN}_2\text{O}_6\text{S}$ [M + H] $^+$ 407.07131, found 407.07076. Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{FN}_2\text{O}_6\text{S}$: C, 53.20; H, 3.72; N, 6.89. Found: C, 52.81; H, 4.07; N, 6.46.

N-[(4-Chloro phenyl)sulfonyl]-2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (**11e**)

Yield = 0.347 g (59.8%), mp = 236–238°C. ^1H NMR (DMSO- d_6): δ 10.47 (br s, 1H), 10.18 (br s, 1H), 7.75 (d, $J = 8.5$ Hz, 2H), 7.65 (d, $J = 8.8$ Hz, 1H), 7.55 (d, $J = 8.5$ Hz, 2H), 6.85 (dd, $J = 2.2, 8.8$ Hz, 1H), 6.79 (d, $J = 2.2$ Hz, 1H), 6.21 (s, 1H), 4.58 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (DMSO- d_6): δ 166.66, 160.98, 160.56, 154.89, 153.88, 138.43, 138.21, 130.07, 129.51, 126.95, 114.12, 112.92, 111.99, 101.93, 66.05, 18.66. IR (KBr): 1734, 3324, 1625, 1307, 3055, 1699, 832 cm^{-1} . HRMS m/z : calcd for $\text{C}_{18}\text{H}_{16}\text{ClN}_2\text{O}_6\text{S}$ [M + H] $^+$ 423.04176, found 423.04121. Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{O}_6\text{S}$: C, 51.13; H, 3.58; N, 6.63. Found: C, 51.63; H, 3.86; N, 6.96.

N-[(4-Bromo phenyl)sulfonyl]-2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (**11f**)

Yield = 0.378 g (58.9%), mp = 234–235°C. ^1H NMR (DMSO- d_6): δ 10.48 (br s, 1H), 10.18 (br s, 1H), 7.67 (d, $J = 5.4$ Hz, 2H), 7.64 (d, $J = 5.4$ Hz, 2H), 7.64 (d, $J = 8.7$ Hz, 1H), 6.84 (dd, $J = 2.3, 8.7$ Hz, 1H), 6.79 (d, $J = 2.3$ Hz, 1H), 6.21 (s, 1H), 4.59 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (DMSO- d_6): δ 166.68, 160.97, 160.56, 154.89, 153.87, 138.64, 133.07, 130.48, 127.49, 126.94,

114.13, 112.89, 112.00, 101.94, 66.04, 18.68. IR (KBr): 1733, 3324, 1621, 1307, 3054, 1696, 656 cm^{-1} . HRMS m/z : calcd for $\text{C}_{18}\text{H}_{16}\text{BrN}_2\text{O}_6\text{S}$ [M + H] $^+$ 466.99124, found 466.99070. Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{BrN}_2\text{O}_6\text{S}$: C, 46.27; H, 3.24; N, 5.99. Found: C, 47.04; H, 3.67; N, 6.06.

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-*N*-[(3-nitro phenyl)sulfonyl]acetohydrazide (**11g**)

Yield = 0.330 g (55.6%), mp = 247–249°C. ^1H NMR (DMSO- d_6): δ 10.60 (br s, 1H), 10.50 (br s, 1H), 8.47 (s, 1H), 8.43 (d, $J = 8.0$ Hz, 1H), 8.17 (d, $J = 8.0$ Hz, 1H), 7.79 (t, $J = 8.0$ Hz, 1H), 7.63 (d, $J = 8.7$ Hz, 1H), 6.83 (dd, $J = 2.3, 8.7$ Hz, 1H), 6.77 (d, $J = 2.3$ Hz, 1H), 6.21 (s, 1H), 4.57 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (DMSO- d_6): δ 166.94, 160.87, 160.54, 154.87, 153.85, 147.99, 141.22, 134.26, 131.45, 128.16, 126.93, 122.92, 114.19, 112.75, 112.04, 101.97, 66.21, 18.64. IR (KBr): 1729, 3309, 1616, 1280, 3080, 1710, 1533 cm^{-1} . HRMS m/z : calcd for $\text{C}_{18}\text{H}_{16}\text{N}_3\text{O}_8\text{S}$ [M + H] $^+$ 434.06581, found 434.06526. Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_8\text{S}$: C, 49.88; H, 3.49; N, 9.70. Found: C, 50.09; H, 3.40; N, 9.68.

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-*N*-[[4-(trifluoromethyl)phenyl]sulfonyl]acetohydrazide (**11h**)

Yield = 0.378 g (60.4%), mp = 245–247°C. ^1H NMR (DMSO- d_6): δ 10.52 (br s, 1H), 10.35 (br s, 1H), 7.97 (d, $J = 8.3$ Hz, 2H), 7.86 (d, $J = 8.3$ Hz, 2H), 7.65 (d, $J = 8.8$ Hz, 1H), 6.86 (d, $J = 2.3, 8.8$ Hz, 1H), 6.79 (d, $J = 2.3$ Hz, 1H), 6.21 (s, 1H), 4.59 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (DMSO- d_6): δ 166.82, 160.95, 160.54, 154.89, 153.86, 143.51, 129.52, 129.08, 126.94, 126.51, 114.13, 112.91, 111.98, 101.92, 66.04, 18.62. IR (KBr): 1736, 3328, 1623, 1306, 3049, 1702, 1164 cm^{-1} . HRMS m/z : calcd for $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_6\text{S}$ [M + H] $^+$ 457.06812, found 457.06757. Anal. Calcd for $\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_6\text{S}$: C, 50.00; H, 3.31; N, 6.14. Found: C, 50.45; H, 3.01; N, 6.45.

General procedure for preparation of compounds (**12a–d**)

A mixture of 2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (**8**) (0.34 g, 1.37 mmol) and other required reactants (**10a–d**) (1.37 mmol) in dry DMF (5–10 ml) and TEA was heated at 70°C. Completion of the reaction was checked by TLC. The reaction mixture was poured onto crushed ice (100 ml) and stirred for 10 min. The precipitate was collected by suction filtration, washed with cold water and further purified by crystallization from ethanol to give the desired products (**12a–d**).

N-[(7-Methoxy-2-oxo-2H-chromen-4-yl)methyl]-2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (**12a**)

Yield = 0.278 g (44.6%), mp = 219–222°C. ¹H NMR (DMSO-d₆): δ 9.60 (br s, 1H), 7.86 (d, *J* = 6.5 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 6.5 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.69 (s, 1H), 6.32 (s, 1H), 6.12 (s, 1H), 4.54 (s, 1H), 4.27 (s, 2H), 3.81 (s, 3H), 3.26 (d, *J* = 6.7 Hz, 2H), 2.31 (s, 3H). ¹³C NMR (DMSO-d₆): δ 166.68, 162.63, 160.63, 160.36, 155.40, 154.66, 153.46, 151.56, 127.03, 126.69, 114.10, 112.71, 112.34, 112.08, 111.81, 102.10, 101.09, 67.08, 56.93, 56.34, 18.52. IR (KBr): 1724, 3298, 1615, 1284, 3077, 1699 cm⁻¹. HRMS *m/z*: calcd for C₂₃H₂₀N₂O₇Na [M + Na]⁺ 459.11682, found 459.11627. Anal. Calcd for C₂₃H₂₀N₂O₇: C, 63.30; H, 4.62; N, 6.42. Found: C, 63.46; H, 5.14; N, 7.11.

N-[(7-Methyl-2-oxo-2H-chromen-4-yl)methyl]-2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (**12b**)

Yield = 0.303 g (50.5%), mp = 215–217°C. ¹H NMR (DMSO-d₆): δ 9.70 (br s, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.10 (s, 1H), 6.77 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.69 (d, *J* = 2.3 Hz, 1H), 6.43 (s, 1H), 6.12 (s, 1H), 4.55 (s, 2H), 4.30 (d, *J* = 6.0 Hz, 2H), 2.35 (s, 3H), 2.29 (s, 3H). ¹³C NMR (DMSO-d₆): δ 166.73, 160.66, 160.42, 154.68, 153.63, 153.34, 151.39, 143.06, 126.65, 125.61, 125.55, 116.92, 116.20, 114.13, 114.01, 112.23, 112.05, 102.20, 67.17, 56.85, 21.51, 18.45. IR (KBr): 1717, 3272, 1619, 1282, 3070, 1693 cm⁻¹. HRMS *m/z*: calcd for C₂₃H₂₀N₂O₆Na [M + Na]⁺ 443.12191, found 443.12136. Anal. Calcd for C₂₃H₂₀N₂O₆: C, 65.71; H, 4.79; N, 6.66. Found: C, 66.55; H, 5.66; N, 7.46.

N-(8-Chloroquinolin-4-yl)-2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (**12c**)

Yield = 0.309 g (55.0%), mp = 290–292°C. ¹H NMR (DMSO-d₆): δ 11.23 (br s, 1H), 8.63 (d, *J* = 6.8 Hz, 1H), 8.57 (d, *J* = 9.1 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.81 (dd, *J* = 8.4, 9.1 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.05 (s, 1H), 6.95 (d, *J* = 6.8 Hz, 1H), 6.23 (s, 1H), 4.99 (s, 2H), 2.38 (s, 3H). ¹³C NMR (DMSO-d₆): δ 167.47, 161.02, 160.56, 156.54, 155.02, 153.90, 144.73, 139.68, 138.74, 128.11, 127.14, 125.79, 120.39, 114.30, 113.05, 112.10, 102.22, 99.75, 66.82, 18.68. IR (KBr): 1767, 3209, 1614, 1281, 3085, 1698, 816 cm⁻¹. HRMS *m/z*: calcd for C₂₁H₁₆ClN₃O₄Na [M + Na]⁺ 432.07270, found 432.07215. Anal. Calcd for C₂₁H₁₆ClN₃O₄: C, 61.54; H, 3.94; N, 10.25. Found: C, 61.95; H, 3.33; N, 10.37.

N-1,3-Benzoxazol-2-yl-2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (**12d**)

Yield = 0.291 g (58.1%), mp = 239–241°C. ¹H NMR (DMSO-d₆): δ 9.80 (br s, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.12 (s, 1H), 7.09 (m, 4H), 6.23 (s, 1H), 4.81 (s, 2H), 2.38 (s, 3H). ¹³C NMR (DMSO-d₆): δ 167.74, 163.40, 162.62, 161.05, 160.62, 155.04, 153.95, 148.67, 127.01, 124.57, 121.81, 116.99, 114.21, 113.31, 112.00, 109.72, 102.15, 66.74, 18.68. IR (KBr): 1705, 3238, 1611, 1281, 3055, 1656 cm⁻¹. HRMS *m/z*: calcd for C₁₉H₁₅N₃O₅Na [M + Na]⁺ 388.09094, found 388.09039. Anal. Calcd for C₁₉H₁₅N₃O₅: C, 62.46; H, 4.14; N, 11.50. Found: C, 62.87; H, 4.34; N, 11.07.

Biological evaluation

Antibacterial studies

The synthesized compounds were dissolved to prepare a stock solution of 5 mg/ml using DMSO. All the chemical compounds were tested for antibacterial activity against human pathogens Gram-negative (*K. pneumoniae*, *E. coli*) and Gram-positive bacteria (*Staphylococcus aureus*). The minimal inhibitory concentration (MICs) of the chemical compound assays were carried out as described by Foroumadi *et al.* (2003a, b) with minor modification. Ciprofloxacin was used as reference antibacterial agent.

Determination of inhibition zones (agar diffusion method): a drop of bacteria was added to sterile nutrient agar (20 ml), poured into a plate (9 cm in diameter) and allowed to solidify to obtain the seeded agar. The final concentration of the microorganisms in the agar plate was 1–4 × 10⁵ cfu ml⁻¹ (checked by viable counting in normal saline). Aliquots of 50 μl of the freshly prepared solutions of the synthesized compounds (50 μg/ml) were poured in wells (6 mm in diameter). Plates were then incubated at 37°C for 24 h. The zones of inhibition were determined as the diameter of the zone of inhibition around the well solution for each compound at its saturated concentration (Table 1). Solvent (DMSO) was included in every experiment of determining zones of inhibition as a control to ensure that it has no effect on the bacterial growth. Each experiment was done in duplicate.

Determination of minimum inhibitory concentration, MIC, (serial dilution method): stock solutions were prepared by dissolving each pure compound (5 mg) in 1 ml of DMSO, then 1 ml of the compound stock solution was added to nutrient broth (4 ml). Progressive two fold serial dilutions of the stock solutions were made in nutrient broth starting from ~1000 μg/ml concentrations in the first test tubes and ending with a concentration of 1.9 μg/ml. The standardization of bacterial test suspension was carried out

according to the McFarland standard method as described by the National Committee for Clinical Laboratories Standard (NCCLS 1993). One drop of bacterial suspension was added to the test tubes containing graded concentrations of test compounds to yield final concentration of $1-4 \times 10^6$ cfu ml⁻¹. Test tubes were incubated at 37°C for 24 h and were checked for turbidity. Each experiment was done in duplicate. Control tests for each experiment were performed. Positive growth control was performed by adding one drop of each micro-organism suspensions to a test tube of the culture medium without the test compound. Negative growth control was also performed using uninoculated tube of medium without the test compound. Both were incubated for 24 h at 37°C for both types of bacteria following reported procedures. Positive and negative controls were performed with DMSO at the same dilutions as in the experiment to ensure that it is incapable of inhibiting the growth of bacteria. Test tubes were incubated at 37°C for 24 h and found to have no effect on microbial growth at tested concentrations. This procedure was modified from reported literature procedures (Foroumadi *et al.*, 2003a, b; Sarma *et al.*, 2001).

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