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Solvent-free microwave-assisted synthesis and biological evaluation of 2,2-dimethylchroman-4-one based benzofurans

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Abstract: A series of novel chroman-4-one fused benzofurans were synthesized by cyclization of the corresponding chalcones under microwave irradiation. All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data and were evaluated for their *in vitro* antimicrobial and antioxidant activities.

Keywords: antimicrobial; antioxidant; benzofurans; 4-chromanone.

Introduction

Chroman-4-ones and chromones are used as scaffolds for the development of bioactive compounds. These frameworks are naturally occurring derivatives containing an oxa-pyran ring [1, 2]. The most frequently found chromone-based natural products are 2-aryl substituted chromones (flavonoids) carrying hydroxy and/or methoxy groups on the A and/or B rings [3, 4]. They are constituents of pigments in leaves and are present in a range of food sources such as olive oil, tea, fruits and red wine. The substitution pattern of the chroman-4-one and chromone scaffolds determines their different biological effects. Known effects of these types of compounds are antioxidant [5, 6], antiviral [7], antibacterial activities [8] or kinase inhibition [9, 10]. On the other hand, benzofuran derivatives possess a wide range of biological activities such as antitumor [11, 12], antibacterial [13], antifungal [14], antidepressant [15], analgesic [16] and hypoglycemic [17] activities. Hybrid compounds containing both chroman-4-ones and furan moieties, called furochromanones may exhibit better biological activity. Such compounds may be prepared using microwave assisted organic synthesis (MAOS) [18–22]. This technique offers simple, clean, fast and efficient synthesis of a large number of organic molecules.

Encouraged by the biological importance of chromanones and benzofurans, in this report, we describe the synthesis of (*E*)-7,7-dimethyl-2-pivaloyl-3-aryl-6,7-dihydro-5*H*-furo-[3,2-*g*]chromen-5-ones **6a–j** under microwave irradiation in good yields. The products were evaluated for their antimicrobial and antioxidant activities.

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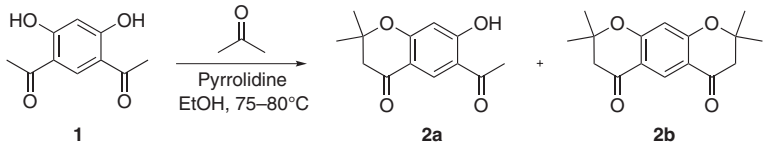
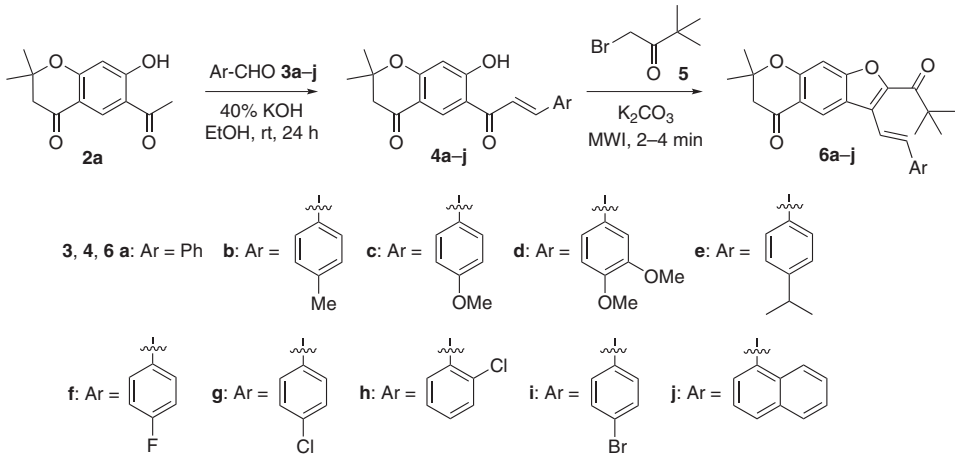
Results and discussion

Chemistry

Synthesis of benzofurans **6a–j** was accomplished in two steps as shown below. The starting materials 6-acetyl-7-hydroxy-2,2-dimethylchroman-4-one (**2a**) and 2,2,8,8,-tetramethyl-2,3,7,8-tetrahydropyrano[3,2-*g*] chromene-4,6-dione (**2b**) were prepared as previously described [23] (Scheme 1). The precursor chalcones **4a–j** (Scheme 2) were synthesized by the Claisen-Schmidt condensation of 6-acetyl-7-hydroxy-2,2-dimethylchroman-4-one (**2a**) and substituted aromatic aldehydes **3a–j** in the presence of potassium hydroxide in ethanol. The chalcones were subjected to cyclization with 1-bromo-3,3-dimethylbutan-2-one (**5**) to give the 2,2-dimethylchroman-4-one based benzofurans **6a–j** in good yields. All these compounds were thoroughly characterized by spectroscopic techniques and elemental analysis.



Scheme 1 Synthesis of 7-hydroxy-2,2-dimethylchroman-4-one (**2a**) and 2,2,8,8,-tetramethyl-2,3,7,8-tetrahydropyrano[3,2-*g*]chromene-4,6-dione (**2b**).



Scheme 2 Synthetic route to 7-hydroxy-2, 2-dimethylchroman-4-one derived chalcones **4a–j** and benzofurans **6a–j**.

Antimicrobial activity

Compounds **6a–j** were screened for their *in vitro* antibacterial activity against two Gram-positive bacterial strains *Staphylococcus aureus* (ATCC-6538), *Bacillus faecalis* (ATCC-6633) and two Gram-negative bacterial strains *Escherichia coli* (ATCC-25922) and *Klebsiella pneumonia* (ATCC-13883) by the disc diffusion method [24] at concentrations of 20 μg/mL and 40 μg/mL. The zones of inhibition (in mm) were compared with that for the standard drug ciproflaxin. As can be seen from Table 1, among newly synthesized benzofurans, compound **6f** (4-fluorophenyl derivative) shows good activity against *S. aureus*, *K. pneumonia* and *E. coli* bacterial strains. The inhibitory efficiencies of compounds **6h** and **6i** against *K. pneumonia* are close to that of standard. Compounds with withdrawing groups (4-F, 4-Cl and 4-Br) at the phenyl ring show zones of inhibition that are comparable to that of the standard against all the bacterial strains.

All synthesized compounds were also screened for their antifungal activity against two pathogenic fungi, *Fusarium oxysporum* and *Aspergillus flavus* by the poison plate technique [25] (Table 1). The results of the antifungal screening were compared with the activities of the

Table 1 Antimicrobial activity of benzofurans **6a–j** by zone of inhibition (mm).

Cmpd	*Bacillus faecalis* (ATCC-6633)		*Staphylococcus aureus* (ATCC-6538)		*Klebsiella pneumoniae* (ATCC-13883)		*Escherichia coli* (ATCC-25922)		*Aspergillus niger*	*Fusarium oxysporum*
	20 μg/mL	40 μg/mL	20 μg/mL	40 μg/mL	20 μg/mL	40 μg/mL	20 μg/mL	40 μg/mL	500 μg/mL	500 μg/mL
6e	11.4	20.9	11.2	18.6	19.8	30.5	21.2	25.6	11.2	10.9
6f	13.2	26.2	12.5	20.1	22.4	35.3	24.6	30.5	13.2	12.8
6h	12.4	22.4	11.8	19.8	20.6	32.2	22.4	31.5	12.8	15.4
6i	13.0	24.2	10.4	18.2	18.6	28.6	20.7	28.6	10.5	14.2
Std-1	15.2	33.4	13.2	20.2	24.5	35.8	25.5	33.5	–	–
Std-2	–	–	–	–	–	–	–	–	13.4	18.6
Std-3	–	–	–	–	–	–	–	–	17.2	23.6

Std-1, ciprofloxacin; **Std-2**, amphotericin-B; **Std-3**, hymexazol.

Table 2 Antioxidant activity (DPPH inhibition percent) of benzofurans **6a–j.**

Cmpd	DPPH radical scavenging	Cmpd	DPPH radical scavenging
6a	55.58 ± 1.85	**6f**	70.34 ± 1.46
6b	60.68 ± 1.36	**6g**	70.22 ± 1.45
6c	78.22 ± 1.25	**6h**	67.47 ± 1.24
6d	80.86 ± 1.18	**6i**	68.67 ± 1.24
6e	65.58 ± 1.84	**6j**	56.37 ± 1.34
		Std	84.45 ± 2.42

The results are expressed as mean percent of inhibition of three independent measurements.

standard antifungal drugs amphotericin-B and hymexazol. All compounds show moderate activity against the tested fungal strains.

Antioxidant activity

In vitro antioxidant activities of the benzofurans **6a–j** were determined using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay [22]. The DPPH radical scavenging activity evaluation is a rapid and convenient screening technique. The results are shown in Table 2. As can be seen, the best compounds are **6d** and **6c**, the radical scavenging abilities of which compare favorably with that of the standard. The remaining compounds show moderate activities.

Conclusion

The synthesized compounds **6a–j** were evaluated for their antimicrobial and antioxidant activities. Compounds **6f** and **6h** show promising antimicrobial activities compared with the standard. Compounds **6c** and **6d** show better antioxidant activities than the standard.

Experimental

All reactions were monitored by TLC on Merck Kieselgel 60 F524. Visualization was done by UV light irradiation and/or spraying with a solution of a 5% sulfuric acid in ethanol followed by heating. Column chromatography was performed on Silica Gel 60 (60–120 mesh). Melting points were determined in open capillary tubes and are uncorrected. FT-IR spectra were recorded in KBr pellets on a Perkin-Elmer spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker DRX-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$. Mass spectra were recorded using a Jeol SX-102 mass spectrometer.

General procedure for the synthesis of benzofurans 6a–j

A mixture of substituted 2′-hydroxychalcone **4a–i** (10.0 mmol), 1-bromo-3,3-dimethylbutan-2-one (15.0 mmol) and potassium carbonate (25.0 mmol) was placed in a quartz tube and inserted into a Teflon vial that was screw capped and subjected to microwave irradiation at 320 W for 2–4 min. After completion of reaction (as indicated by TLC), the mixture was poured into ice water, extracted with dichloromethane (2×30 mL), dried over Na_2SO_4, and purified by column chromatography eluting with *n*-hexane/ethyl acetate (9 : 1).

(*E*)-7,7-dimethyl-2-pivaloyl-3-styryl-6,7-dihydro-5*H*-furo-[3,2-*g*]chromen-5-one (6a) Pale yellow solid; mp 134–136°C; reaction time 3.5 min; yield 92%; IR: 2928, 1738, 1625, 1475, 1360, 1230, 1008 cm^{-1}; ^{1}H NMR: δ 8.64 (s, 1H, Ar-H_5), 8.04 (d, J = 16.8 Hz, 1H, H_β), 7.68–7.63 (m, 2H, Ar-H), 7.55–7.48 (m, 1H, Ar-H), 7.40 (dd, J = 10.2 Hz and 4.7 Hz, 2H), 7.33–7.29 (m, 1H, Ar-H), 7.05 (s, 1H, Ar-H_8), 2.82 (s, 2H, CH_2), 1.51 (s, 6H, 2×CH_3), 1.42 (s, 9H, 3×CH_3); ^{13}C NMR: δ 198.2, 192.0, 160.1, 158.7, 148.1, 136.9, 135.7, 128.7, 128.5, 127.1, 126.9, 122.5, 120.3, 119.8, 118.4, 100.5, 79.9, 48.9, 44.4, 26.7, 26.4; ESI-MS: 403 (M + H)$^+$. Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 77.54; H, 6.45.

(*E*)-7,7-dimethyl-3-(4-methylstyryl)-2-pivaloyl-6,7-dihydro-5*H*-furo-[3,2-*g*]chromen-5-one (6b) White solid; mp 158–160°C; reaction time 3.0 min; yield 93%; IR: 2930, 1740, 1624, 1474, 1358, 1229, 1009 cm^{-1}; ^{1}H NMR: δ 8.64 (s, 1H, Ar-H_5), 8.01 (d, J = 16.8 Hz, 1H, H_β), 7.53 (dd, J = 20.1 Hz and 12.5 Hz, 3H), 7.20 (d, J = 8.0 Hz, 2H), 7.04 (s, 1H, Ar-H_8), 2.81 (s, 2H, CH_2), 2.38 (s, 3H, CH_3), 1.51 (s, 6H, 2×CH_3), 1.42 (s, 9H, 3×CH_3); ^{13}C NMR: δ 198.6, 192.9, 160.6, 152.7, 151.5, 137.6, 134.5, 133.4, 133.2, 128.7, 128.5, 127.4, 122.1, 120.1, 119.1, 100.0, 79.9, 48.5, 44.4, 26.7, 26.4, 21.3; ESI-MS: 417 (M + H)$^+$. Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.86; H, 6.78. Found: C, 77.81; H, 6.72.

(*E*)-3-(4-methoxylstyryl)-7,7-dimethyl-2-pivaloyl-6,7-dihydro-5*H*-furo-[3,2-*g*]chromen-5-one (6c) Pale yellow solid; mp 166–168°C; reaction time 3.5 min; yield 89%; IR: 2929, 1741, 1625, 1473, 1356, 1230, 1010 cm^{-1}; ^{1}H NMR: δ 8.64 (s, 1H, Ar-H_5), 7.94 (d, J = 16.8 Hz, 1H, H_β), 7.60 (d, J = 8.7 Hz, 2H, Ar-H), 7.49 (d, J = 16.8 Hz, 1H, H_α), 7.04 (s, 1H, Ar-H_8), 6.92 (d, J = 8.7 Hz, 2H, Ar-H), 3.85 (s, 3H, O-CH_3), 2.81 (s, 2H, CH_2), 1.51 (s, 6H, 2×CH_3), 1.42 (s, 9H, 3×CH_3); ^{13}C NMR: δ 198.0, 191.9, 159.8, 157.9, 151.1, 149.7, 134.3, 133.2, 130.2, 129.8, 127.4, 122.6, 120.8, 117.8, 114.1, 100.4, 79.8, 55.8, 48.3, 44.3, 26.7, 26.4; ESI-MS: 433 (M+H)$^+$. Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.95; H, 6.50.

(*E*)-3-(3,4-dimethoxylstyryl)-7,7-dimethyl-2-pivaloyl-6,7-dihydro-5*H*-furo-[3,2-*g*]chromen-5-one (6d) Yellow solid; mp 185–187°C; reaction time 3.5 min; yield 90%; IR: 2928, 1745, 1628, 1478, 1356, 1230, 1005 cm^{-1}; ^{1}H NMR: δ 8.64 (s, 1H, Ar-H_5), 7.93 (d, J = 16.8 Hz, 1H, H_β), 7.47 (d, J = 16.8 Hz, 1H, H_α), 7.24–7.15 (m, 2H, Ar-H), 7.04 (s, 1H, Ar-H_8), 6.89 (d, J = 8.3 Hz, 1H, Ar-H), 3.99 (s, 3H, O-CH_3), 3.94 (s, 3H, O-CH_3), 2.82 (s, 2H, CH_2), 1.52 (s, 6H, 2×CH_3), 1.42 (s, 9H, 3×CH_3); ^{13}C NMR: δ 198.2, 192.1, 160.1, 158.8, 149.7, 149.1, 147.8, 135.7, 130.1, 127.2, 122.6, 120.6, 120.4, 118.3, 117.8, 111.1, 109.3, 100.5, 79.8, 56.0, 48.9, 44.3, 26.7, 26.4; ESI-MS: 463 (M + H)$^+$. Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.69; H, 6.50.

(*E*)-3-(4-isopropylstyryl)-7,7-dimethyl-2-pivaloyl-6,7-dihydro-5*H*-furo-[3,2-*g*]chromen-5-one (6e) Pale yellow solid; mp 128–130°C; reaction time 4.0 min; yield 88%; IR: 2965, 1740, 1695, 1623, 1474, 1359, 1226, 1009 cm^{-1}; ^{1}H NMR: δ 8.64 (s, 1H, Ar-H_5), 8.01 (d, J = 16.8 Hz,

1H, H_β), 7.59 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 16.8 Hz, 1H, H_α), 7.24 (m, 2H, Ar-H), 7.04 (s, 1H, Ar-H_8), 2.93 (d, J = 13.8, 6.9 Hz, 1H), 2.81 (s, 2H, CH_2), 1.51 (s, 6H, 2×CH_3), 1.42 (s, 9H, 3×CH_3), 1.28 (d, J = 6.9 Hz, 6H); ^{13}C NMR: δ 198.1, 192.0, 160.1, 158.8, 149.6, 148.0, 135.7, 134.6, 127.1, 126.8, 122.6, 120.4, 118.9, 118.3, 100.5, 79.8, 48.9, 44.3, 34.0, 26.7, 26.4, 23.9; ESI-MS: 437 $(M+H)^+$. Anal. Calcd for $C_{29}H_{32}O_4$: C, 78.35; H, 7.26. Found: C, 78.31; H, 7.22.

(*E*)-3-(4-fluorostyryl)-7,7-dimethyl-2-pivaloyl-6,7-dihydro-5*H*-furo-[3,2-*g*]chromen-5-one (6f) Pale yellow solid; mp 132–134°C; reaction time 4.5 min; yield 89%; IR: 2972, 1740, 1625, 1474, 1359, 1225, 1150, 1008 cm^{-1}; ^{1}H NMR: δ 8.61 (s, 1H, Ar-H_5), 7.96 (d, J = 16.8 Hz, 1H, H_β), 7.66–7.59 (m, 2H, Ar-H), 7.47 (d, J = 16.8 Hz, 1H, H_α), 7.12–7.02 (m, 3H, Ar-H), 2.82 (s, 2H, CH_2), 1.51 (s, 6H, 2×CH_3), 1.42 (s, 9H, 3×CH_3); ^{13}C NMR : δ 198.6, 192.0, 162.1, 160.1, 158.1, 150.2, 135.4, 134.3, 134.1, 130.4, 128.2, 122.2, 120.4, 120.0, 118.4, 115.4, 100.6, 79.9, 48.3, 43.5, 26.7, 26.3; ESI-MS: 421 $(M+H)^+$. Anal. Calcd for $C_{26}H_{25}FO_4$: C, 74.27; H, 5.99. Found: C, 74.23; H, 5.94.

(*E*)-3-(2-chlorostyryl)-7,7-dimethyl-2-pivaloyl-6,7-dihydro-5*H*-furo-[3,2-*g*]chromen-5-one (6g) White solid; mp 133–135°C; reaction time 4.5 min; yield 89%; IR: 2971, 1741, 1688, 1623, 1470, 1231, 1003; ^{1}H NMR : δ 8.70 (s, 1H, Ar-H_5), 7.98 (d, J = 16.8 Hz, 1H, H_β), 7.90 (d, J = 16.8 Hz, 1H, H_α), 7.83 (dd, J = 7.7 Hz and 1.8 Hz, 1H, Ar-H), 7.42 (dd, J = 7.8 Hz and 1.4 Hz, 1H, Ar-H), 7.32–7.27 (m, 1H, Ar-H), 7.24 (dd, J = 7.5 Hz and 1.8 Hz, 1H, Ar-H), 7.06 (s, 1H, Ar-H_8), 2.81 (s, 2H, CH_2), 1.51 (s, 6H, 2×CH_3), 1.42 (s, 9H, 3×CH_3); ^{13}C NMR: δ 198.8, 192.9, 159.8, 153.4, 150.2, 135.0, 133.4, 133.2, 133.0, 129.9, 129.3, 128.5, 127.8, 126.6, 122.0, 120.2, 117.8, 100.6, 79.9, 48.9, 44.3, 26.7, 26.3; ESI-MS: 437 $(M+H)^+$. Anal. Calcd for $C_{26}H_{25}ClO_4$: C, 71.47; H, 5.77. Found: C, 71.42; H, 5.71.

(*E*)-3-(4-chlorostyryl)-7,7-dimethyl-2-pivaloyl-6,7-dihydro-5*H*-furo-[3,2-*g*]chromen-5-one (6h) Pale yellow solid; mp 134–136°C; reaction time 4.5 min; yield 89%; IR: 2973, 1740, 1692, 1624, 1472, 1357, 1230, 1006 cm^{-1}; ^{1}H NMR: δ 8.61 (s, 1H, Ar-H_5), 8.02 (d, J = 16.8 Hz, 1H, H_β), 7.58 (d, J = 8.5 Hz, 2H, Ar-H), 7.45 (d, J = 16.8 Hz, 1H), 7.39–7.32 (m, 2H, Ar-H), 7.06 (s, 1H, Ar-H_8), 2.82 (s, 2H, CH_2), 1.51 (s, 6H, 2×CH_3), 1.42 (s, 9H, 3×CH_3); ^{13}C NMR: δ 198.3, 192.0, 160.2, 158.7, 148.2, 135.5, 134.2, 134.1, 128.9, 128.2, 126.6, 122.4, 120.4, 120.1, 118.4, 100.6, 79.9, 48.9, 44.4, 26.7, 26.3; ESI-MS: 437 $(M+H)^+$. Anal. Calcd for $C_{26}H_{25}ClO_4$: C, 71.47; H, 5.77. Found: C, 71.42; H, 5.71.

(*E*)-3-(4-bromostyryl)-7,7-dimethyl-2-pivaloyl-6,7-dihydro-5*H*-furo-[3,2-*g*]chromen-5-one (6i) Pale yellow solid; mp 124–126°C; reaction time 5.0 min; yield 85%; IR: 2972, 1740, 1689, 1623, 1472, 1230, 1004 cm^{-1}; ^{1}H NMR: δ 8.60 (s, 1H, Ar-H_5), 8.03 (d, J = 16.8 Hz, 1H, H_β), 7.51 (s, 4H, Ar-H), 7.44 (d, J = 16.8 Hz, 1H, H_α), 7.06 (s, 1H, Ar-H_8), 2.82 (s, 2H, CH_2), 1.51 (s, 6H, 2×CH_3), 1.42 (s, 9H, 3×CH_3); ^{13}C NMR: δ 198.4, 192.9, 160.2, 158.6, 149.0, 136.5, 134.2, 133.1, 133.0, 129.9, 128.6, 126.6, 122.4, 120.4, 120.0, 117.4, 99.8, 79.9, 48.3, 44.5, 27.7, 26.3; ESI-MS: 481 $(M+H)^+$. Anal. Calcd for $C_{26}H_{25}BrO_4$: C, 64.87; H, 5.23. Found: C, 64.82; H, 5.18.

(*E*)-7,7-dimethyl-3-(2-(napthalen-1-yl)vinyl)-2-pivaloyl-6,7-dihydro-5*H*-furo-[3,2-*g*]chromen-5-one (6j) Pale yellow solid; mp 194–196°C; reaction time 4.0 min; yield 80%; IR: 2974, 1742, 1691, 1623, 1475, 1228, 1009 cm^{-1}; ^{1}H NMR: δ 8.75 (s, 1H, Ar-H_5), 8.28 (dd, J = 18.1 Hz and 12.5 Hz, 2H), 8.06 (d, J = 16.5 Hz, 1H, H_β), 7.95–7.81 (m, 3H, Ar-H), 7.66–7.61 (m, 1H, Ar-H), 7.52–7.54 (m, 2H, Ar-H), 7.09 (s, 1H, Ar-H_8), 2.83 (s, 2H, CH_2), 1.53 (s, 6H, 2×CH_3), 1.43 (s, 9H, 3×CH_3); ^{13}C NMR: δ 198.1, 191.9, 160.2, 158.8, 148.3, 134.5, 133.7, 132.8, 131.2, 128.9, 128.6, 127.1, 126.5, 125.9, 125.7, 124.4, 123.6, 122.4, 122.4, 120.4, 118.5, 100.6, 79.9, 48.9, 44.3, 26.8, 26.4; ESI-MS: 453 $(M+H)^+$. Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24. Found: C, 79.58; H, 6.20.

Biological assays

Antibacterial activity

Compounds **5a–j** were screened for their *in vitro* antibacterial activity against the bacterial cultures *S. aureus*, *B. subtilis* (Gram-positive) and *E. coli* and *Klebsiella* (Gram-negative) by the disc diffusion method at concentrations of 20 μg/mL and 40 μg/mL. The cultures were grown in nutrient agar media and sub-cultured for log phasic cultures in a liquid nutrient broth medium for zone of inhibition and further sub-cultured onto media in Petri plates. The broth cultures were diluted with a sterilized saline to bring the final size of inoculum approximately to 10^5–10^6 CFU/mL. The compounds were dissolved in acetone, DMSO and diethyl ether for biological assays. Diethyl ether was the preferred solvent. The bacterial cultures were placed on the media and incubated at 37°C for 24 h–48 h along with the diluted compounds introduced through discs dipped and placed over the nutrient media. The zones of bacterial growth inhibitions were measured using the diameter of the zone. All the results were expressed as zone of inhibition (ZOI) in mm. The results were compared with the activity of the standard antibiotic ciproflaxin (20 μg/mL and 40 μg/mL). For the disc diffusion method, the diluted test compounds were introduced onto the disc and once the disc was found completely saturated it was immediately transferred on to surface of the medium with bacterial inoculums spread on the plate evenly. The Petri dishes were incubated at 37°C for 24 h. Bioactivity was determined by measuring diameter of the inhibition zone (DIZ) in mm.

Antifungal activity

The antifungal activity of synthesized compounds was tested against two pathogenic fungi, *F. oxysporum* and *A. flavus*, by the poison plate technique. Test compounds were dissolved in diethyl ether (10 mL) before mixing with potato dextrose agar medium (PDA, 90 mL). The final concentration of compounds in the medium was maintained at 500 μg/mL. The fungi were incubated in PDA at 25 ± 1°C for 48–72 h to get long mycelium for antifungal assay. The

mycelia disks of approximately 0.45 cm in diameter were cut from the PDA medium with a sterilized inoculation needle and inoculated in the center of a PDA plate. The inoculated plates were incubated at 27 ± 1°C for 3 days. Diethyl ether in sterilized distilled water was taken as control, while hymexazole was used as positive control for the treatment. The growth of the fungal colonies was measured on the third day and the data were statistically analyzed. The *in vitro* inhibition effects of the test compounds on the fungi were calculated by the given formula CV = (A – B)/A, where A represents the diameter of fungi growth on untreated PDA, B represents the diameter of the fungi growth on treated PDA, and CV represents the rate of inhibition.

DPPH radical scavenging

DPPH radical scavenging activity was measured by the method of Cotelle [26] after standardization with some modifications. A mixture containing 0.2 mL of DPPH (100 μM in methanol) and 2.0 mL of the test solution containing the compound (50, 100, 200 μg/mL) was incubated at 37°C for 30 min. Absorbance of the mixture was measured at 517 nm using a Beckman model DU-40 spectrophotometer. The percentage inhibition of DPPH radical was calculated by comparing the result of the test with that of the control (not treated with extract) using the following equation:

$$\text{Percent inhibition} = \text{Absorbance of test}/(\text{Absorbance of control} \times 100)$$

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