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

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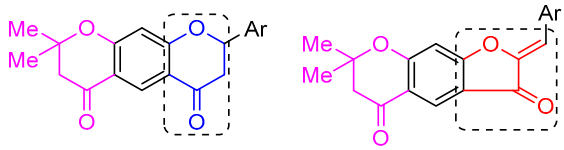


A series of novel 8-aryl-2,2-dimethyl-2,3,7,8-tetrahydropyrano[3,2-*g*]chromene-4,6-dione and 2-arylidene-7,7-dimethyl-6,7-dihydro-2*H*-furo[3,2-g]chromene-3,5-dione derivatives have been synthesized by oxidation of the corresponding chalcones under microwave irradiation. All newly synthesized compounds were characterized by IR, ^{1}H, ^{13}C NMR, and mass spectra and valuated for their *in vitro* antibacterial and antifungal activities.

Keywords: aurones, chromanones, flavanones, antimicrobial activity, antioxidant activity.

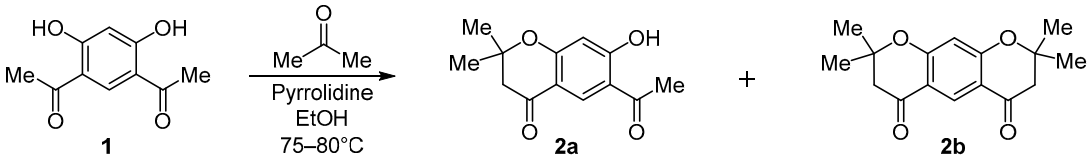
Synthesis of heterocyclic compounds has emerged as a powerful technique for generating new molecules useful for drug design.[1] In particular, five- and six-membered heterocycles occupy a unique position due to dominant pharmacological applications.[2] Flavonoids and their subclass flavanones occur in nature as polyphenolic compounds that have been reported to possess anticancer or anticarcinogenic (antimutagenic) activities.[3,4] In this family, flavanones have been widely employed as important intermediates in the synthesis of many natural products and medicinal agents. They are widely distributed in nature displaying diverse range of biological activities. Aurones, containing a 1-benzofuran ring system, constitute a less studied subclass of flavonoids, which occur rarely in nature. Aurones are biologically important compounds due to their anticancer,[5] antibacterial,[6] and anti-inflammatory[7] activities.

Chroman-4-ones and chromen-4-ones (chromones) that contain a 1-benzopyran ring system and constitute the principal structural motif of flavonoids have been also used as scaffolds for the development of peptidomimetics. Depending on the substitution pattern these chromene derivatives show different biological effects.[8–10] In addition, the 2,2-dimethyl-substituted chromane ring system is found in many widely varied natural compounds. For example, vitamin E (D-α-tocopherol)[11] is a natural radical scavenger that suppresses cellular membrane phospholipid degradation and also exhibits antioxidant, anticancer, and cardioprotective activities.[12] This has determined our interest in the synthesis and evaluation of the antimicrobial activity of diverse classes of compounds containing condensed pyran framework.

In recent years, microwave-assisted organic synthesis has attracted the attention of synthetic chemists as a new tool in organic synthesis.[13] This technique offers simple, clean, fast, and efficient synthesis of a large number of organic molecules.

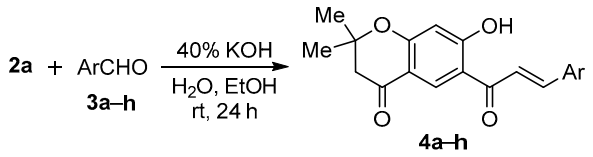
In view of the biological importance of chromanone, flavanones, and aurones, we describe in this report the synthesis of a series of substituted flavanones (8-aryl-2,2-dimethyl-2,3,7,8-tetrahydropyrano[3,2-*g*]chromene-4,6-diones) and aurones ((*Z*)-2-arylidene-7,7-dimethyl-6,7-dihydro-2*H*-furo-[3,2-*g*]chromene-3,5-diones) under solvent-free microwave (MW) irradiation, as well as preliminary tests of their antimicrobial activity. The target flavanones and aurones were obtained in three steps. The chromene synthons

Scheme 1



6-acetyl-7-hydroxy-2,2-dimethylchroman-4-one (**2a**)[14] and 2,2,8,8-tetramethyl-2,3,7,8-tetrahydropyrano[3,2-*g*]chromene-4,6-dione (**2b**)[14] were prepared from 4,6-diacetylresorcinol-(1,1'-(4,6-dihydroxybenzene-1,3-diyl)diethanone) (**1**) and acetone in the presence of pyrrolidine and ethanol as shown in Scheme 1. Compounds **2a** and **2b** were isolated by column chromatography in the ratio of 3:1. Compound **2a** was then subjected to the Claisen–Schmidt condensation with different aromatic aldehydes **3a**–**h** in 40% aq KOH and ethanol to yield the corresponding chalcones **4a**–**h** (Scheme 2).

Scheme 2



3, **4** **a** Ar = Ph, **b** Ar = 4-FC_6H_4, **c** Ar = 4-ClC_6H_4, **d** Ar = 4-BrC_6H_4, **e** Ar = 4-MeC_6H_4, **f** Ar = 4-$MeOC_6H_4$, **g** Ar = 4-(*i*-Pr)C_6H_4, **h** Ar = 1-naphthyl

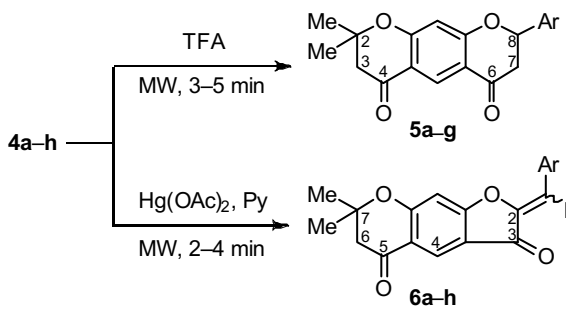
Further, chalcones **4a**–**h** were cyclized in the presence of trifluoroacetic acid (TFA) under MW irradiation to afford the corresponding flavanones **5a**–**g** in good yields. Aurones **6a**–**h** were synthesized by the oxidation of chalcones **4a**–**h** with mercuric acetate under MW irradiation in moderate to good yields (Table 1).

The structures of compounds **5a**–**g** and **6a**–**h** were characterized by IR, ^{1}H and ^{13}C NMR, and mass spectroscopy, as well as elemental analysis. IR spectra of compounds **5a**–**g** featured the signal of carbonyl groups at 1679–1704 cm^{-1}. The ^{1}H NMR spectra of compounds **5a**–**g** showed three signals characteristic of an ABX proton system consisting of diastereotopic protons of the 7-CH_2 group and 8-CH proton at the chiral carbon atom of the flavanone pyran ring. The methylene proton which is *cis*-oriented relative to the 8-CH proton is observed as a doublet of doublets (J_{AB} = 16.9, J_{AX} = 2.6–3.2 Hz) at a higher field (2.92–2.87 ppm) than the *trans*-oriented methylene proton (J_{BA} = 16.9, J_{BX} = 12.5–12.9 Hz) (3.08–3.00 ppm). The 8-CH proton (5.46–5.53 ppm) signal had both matching vicinal spin-spin interaction constants (J_{AX} and J_{BX}). The proposed structure of compounds **5a**–**g** was further supported by the ^{13}C NMR spectrum, which contained the signals at 42.7–44.3 and 48.6–48.8 ppm that could be attributed to the 7-CH_2 and 3-CH_2 groups, respectively (only the latter signal is observed in the spectra of compounds **4a**–**h** and **6a**–**h**).

The IR spectra of compounds **6a**–**h** showed a characteristic absorption band carbonyl groups (1671–1709 cm^{-1}). The ^{1}H NMR spectra of the representative compounds **6a**–**h** showed a characteristic singlet at 6.72–6.85 ppm due to the benzylidene methine proton. In the ^{13}C NMR spectrum, the signal of carbonyl carbon in the aurone five-membered ring appeared at 181.0–186.5 ppm. The NMR spectroscopic data of the synthesized aurones prove that this oxidative cyclization procedure yields one isomer. The GC-MS spectra of all compounds **5a**–**g** and **6a**–**h** exhibited $[M+H]^+$ peaks with the expected *m*/*z* values.

All synthesized compounds **5a**–**g** and **6a**–**h** were screened for *in vitro* antibacterial activity against two Gram-positive bacterial strains *Staphylococcus aureus* (ATCC-6538), *Bacillus subtilis* (ATCC-6633) and two Gram-negative bacterial strains *Escherichia coli* (ATCC-25922) and

Table 1. Synthesis of flavanones **5a**–**g** and **6a**–**h**



Compound	Ar	Mp, °C	Microwave irradiation	
			Time, min	Yield, %
5a	Ph	134–136	3.5	92
5b	4-Fluorophenyl	158–160	3.0	63
5c	4-Chlorophenyl	166–168	3.5	89
5d	4-Bromophenyl	185–187	3.5	90
5e	4-Methylphenyl	128–130	4.0	88
5f	4-Methoxyphenyl	132–134	4.5	89
5g	4-Isopropylphenyl	124–126	5.0	85
6a	Ph	188–190	2.0	93
6b	4-Fluorophenyl	236–238	3.0	90
6c	4-Chlorophenyl	252–254	3.0	89
6d	4-Bromophenyl	248–250	3.5	88
6e	4-Methylphenyl	238–240	2.5	90
6f	4-Methoxyphenyl	226–228	3.0	91
6g	4-Isopropylphenyl	180–182	4.0	82
6h	1-Naphthyl	194–196	4.0	80

Table 2. Antimicrobial and antifungal activity of aurones **5a**–**g** and **6a**–**h** (zone of inhibition, mm)

Compound	*Bacillus subtilis* (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
5a	12.0	12.0	10.0	15.5	20.5	29.0	20.0	27.5	10.5	14.5
5b	10.0	22.5	8.5	11.0	13.5	25.5	15.0	26.5	8.0	13.5
5c	9.5	21.0	8.0	10.5	13.0	24.0	14.5	25.5	8.5	14.0
5d	10.5	23.5	9.0	11.5	15.0	26.5	18.5	28.0	9.5	15.0
5e	12.5	30.0	12.8	20.0	22.8	33.5	23.5	30.5	10.0	16.8
5f	13.0	31.5	13.0	20.5	23.2	34.8	24.5	33.8	10.5	17.2
5g	12.5	26.5	12.0	19.5	22.5	30.6	21.5	29.5	7.5	11.0
6a	13.8	24.5	12.5	19.0	22.6	31.5	19.5	24.6	8.6	15.6
6b	9.5	26.5	8.0	15.5	10.5	21.0	7.0	11.5	3.5	5.0
6c	8.5	20.0	7.5	12.5	5.0	9.5	6.2	10.5	2.5	5.5
6d	6.8	11.5	8.0	14.5	4.5	12.5	7.8	15.8	8.0	11.0
6e	12.0	28.5	10.5	16.0	21.5	30.5	22.5	31.0	11.5	14.5
6f	14.5	33.0	12.5	20.0	22.5	33.5	19.5	30.5	15.0	12.5
6g	10.5	25.5	10.5	19.5	20.5	33.0	23.1	34.5	14.5	16.0
6h	11.5	32.0	12.6	20.0	25.0	34.0	26.0	34.0	11.5	13.5
Ciprofloxacin	15.2	33.4	13.2	20.2	24.5	35.8	25.5	33.5	–	–
Amphotericin B	–	–	–	–	–	–	–	–	13.4	18.6
Hymexazol	–	–	–	–	–	–	–	–	17.2	23.6

Klebsiella pneumoniae (ATCC-13883) by the disc diffusion method[15] at different concentrations (20 and 40 μg/ml). Nutrient agar medium was used for the antibacterial screening. The zone of inhibition (in mm) was compared with that of standard drug ciprofloxacin. The results are presented in Table 2.

All the synthesized compounds showed a better activity against Gram-negative bacterial strains than Gram-positive bacterial strains at the concentrations 20 and 40 μg/ml. Flavanones **5a**,**e**–**g** and aurones **6a**,**e**–**h** containing an aryl group with electron donor properties showed a promising activity against all bacterial strains. Compounds **5b**–**d** and **6b**–**d** with electron-withdrawing halogen substituents at the phenyl ring showed moderate zone of inhibition against all the bacterial strains. Compounds **5f**, **6f**, and **6h** showed zone of inhibition (31.5, 33.0, and 32.0 mm, respectively) comparable to the standard drug ciprofloxacin (33.4 mm) against *B. subtilis* at the concentration 40 μg/ml. Compounds **5f** (23.2 mm) and **6h** (25.0 mm) showed a good activity against the Gram-negative bacterial strain *K. pneumoniae* at the concentration 20 μg/ml.

All the synthesised compounds were screened for their antifungal activity against two pathogenic fungi, *Aspergillus niger* and *Fusarium oxysporum* by the poison plate technique.[16] The results of the antifungal screening were compared with standard antifungal drugs amphotericin B and hymexazol. All the compounds showed moderate activity against the tested fungal strains. The activity of compounds **6f**,**g** against *A. niger* was slightly higher than that of standard drug amphotericin B.

In summary, we have successfully developed synthesis of novel aurone and flavanone derivatives under solvent-free microwave irradiation. The present method should be economically feasible because the products can be obtained through a facile, two-step reaction with commercially available and relatively inexpensive chemicals. Some of the synthesized compounds show promising antimicrobial activities compared with commercial drugs while all the rest show moderate activity against the tested organisms. Electron-donating substituents on the flavanone or aurone phenyl group appear to diminish the antimicrobial activity compared to other substituents.

Experimental

FT-IR spectra were recorded in KBr pellets on a Perkin Elmer spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker DRX-400 instrument (400 and 100 MHz, respectively) in $CDCl_3$. Chemical shift values are reported relative to TMS as internal reference. Mass spectra were obtained on a Jeol SX-102 mass spectrometer (ESI). Elemental analyses were recorded on a Karlo Erba 1106 elemental analyzer. Melting points were determined

in open capillary tubes and are uncorrected. Microwave reactions were carried out in a Milestone multi SYNTH series (ATC-FO 300) multimode microwave reactor with a twin magnetron (2 × 800 W, 2.45 GHz) and the maximum delivered power of 1,000 W in 10 W increments (pulsed irradiation). All the reactions were monitored by TLC on Merck Kieselgel 60 F524, visualized by UV light and/or spraying a 5% H_2SO_4 in EtOH followed by heating. Column chromatography was performed on Silica Gel 60 (60–120 mesh). All the available reagent grade chemicals were purchased from Sigma-Aldrich or Spectrochem Pvt. Ltd. and used without further purification. Solvents were dried according to standard methods.

Synthesis of 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**) followed a published procedure.[14]

6-Acetyl-7-hydroxy-2,2-dimethylchroman-4-one (**2a**). ^{1}H NMR spectrum, δ, ppm: 1.40 (6H, s, $2CH_3$); 2.40 (3H, s, CH_3); 2.74 (2H, s, CH_2); 6.50 (1H, s, H Ar); 7. 55 (1H, s, H Ar).

2,2,8,8-Tetramethyl-2,3,7,8-tetrahydropyrano[3,2-*g*]-chromene-4,6-dione (2b). ^{1}H NMR spectrum, δ, ppm: 1.45 (12H, s, $4CH_3$); 2.60 (4H, s, $2CH_2$); 6.30 (1H, s, H Ar); 8.33 (1H, s, H Ar).

Synthesis of chalcones 4a–h by Claisen–Schmidt condensation (General method). 6-Acetyl-7-hydroxy-2,2-dimethylchroman-4-one (**2a**) (0.5 g, 0.002 mol) and an aromatic aldehyde **3a**–**h** (0.002 mol) were dissolved in minimum amount of ethanol. Aqueous potassium hydroxide solution (40%, 1.2 ml, 0.015 mol) was added slowly, and the reaction mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC (eluent n-hexane–AcOEt, 6:4). After completion of reaction, the reaction mixture was poured onto crushed ice, carefully neutralized with 3 N HCl, and extracted with EtOAc (15 ml). The organic layer was concentrated in vacuum and purified by column chromatography on silica gel (eluent *n*-hexane–AcOEt, 3:1).

7-Hydroxy-6-[(2*E*)-3-phenylprop-2-enoyl]-2,2-dimethyl-chroman-4-one (4a). Yield 65%, yellow solid, mp 148–150°C. IR spectrum, ν, cm^{-1}: 1203, 1367, 1564 (C=C), 1637 (C=O), 1683, 2970 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (6H, s, $2CH_3$); 2.75 (2H, s, CH_2); 6.46 (1H, s, H Ar); 7.45–7.46 (3H, m, H Ar); 7.69–7.71 (3H, m, =CH, H Ar); 7.94 (1H, d, *J* = 15.6, =CH); 8.58 (1H, s, H Ar); 13.54 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 26.8; 48.6; 80.2; 105.9; 113.4; 114.1; 118.0; 122.3; 127.5; 128.5; 130.8; 135.2; 145.1; 167.8; 170.3; 190.8; 192.8. Mass spectrum, *m*/*z*: 323 $[M+H]^+$. Found, %: C 74.50; H 5.60. $C_{20}H_{18}O_4$. Calculated, %: C 74.52; H 5.63.

6-[(2*E*)-3-(4-Fluorophenyl)prop-2-enoyl]-7-hydroxy-2,2-dimethylchroman-4-one (4b). Yield 77%, yellow solid, mp 195–197°C. IR spectrum, ν, cm^{-1}: 1201, 1359, 1558 (C=C), 1636 (C=O), 1679, 2974 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (6H, s, $2CH_3$); 2.74 (2H, s, CH_2); 6.46 (1H, s, H Ar); 7.19 (2H, s, H Ar); 7.71 (2H, s, H Ar); 7.56 (1H, d, *J* = 15.3, =CH); 8.04 (1H, d, *J* = 15.6, =CH); 8.55 (1H, s, H Ar); 13.62 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 26.8; 48.6; 80.2; 105.9; 113.4; 114.1; 115.4; 118.7; 130.8 (2C); 131.0; 135.2; 145.1; 162.1; 167.8; 170.3; 190.9, 192.8. Mass spectrum, *m*/*z*: 341 $[M+H]^+$.

6-[(2*E*)-3-(4-Chlorophenyl)prop-2-enoyl]-7-hydroxy-2,2-dimethylchroman-4-one (4c). Yield 67%, yellow solid, mp 220–222°C. IR spectrum, ν, cm^{-1}: 1204, 1368, 1569 (C=C), 1632 (C=O), 1691, 2971 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (6H, s, $2CH_3$); 2.74 (2H, s, CH_2); 6.46 (1H, s, H Ar); 7.44 (2H, s, H Ar); 7.59–7.68 (3H, m, =CH, H Ar); 8.05 (1H, d, *J* = 15.5, =CH); 8.57 (1H, s, H Ar); 13.55 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 26.8; 48.6; 80.2; 105.7; 113.4; 114.1; 118.7; 128.7; 129.0; 130.7; 133.3; 133.5; 145.1; 162.1; 168.8; 170.3; 190.9; 192.8. Mass spectrum, *m*/*z*: 357 $[M(^{35}Cl)+H]^+$. Found, %: C 67.30; H 4.75. $C_{20}H_{17}ClO_4$. Calculated, %: C 67.32; H 4.80.

6-[(2*E*)-3-(4-Bromophenyl)prop-2-enoyl]-7-hydroxy-2,2-dimethylchroman-4-one (4d). Yield 90%, yellow solid, mp 215–217°C. IR spectrum, ν, cm^{-1}: 1211, 1375, 1572 (C=C), 1645 (C=O), 1689, 2978 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (6H, s, $2CH_3$); 2.74 (2H, s, CH_2); 6.44 (1H, s, H Ar); 7.50 (2H, s, H Ar); 7.59–7.61 (3H, m, =CH, H Ar); 7.98 (1H, d, *J* = 15.5, =CH); 8.56 (1H, s, H Ar); 13.64 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 26.8; 48.6; 80.2; 105.7; 113.1; 114.1; 118.7; 122.3; 128.7; 130.7; 131.3; 134.2; 145.1; 168.8; 170.3; 190.9; 192.8. Mass spectrum, *m*/*z*: 401 $[M(^{79}Br)+H]^+$. Found, %: C 59.80; H 4.82. $C_{20}H_{17}BrO_4$. Calculated, %: C 59.87; H 4.27.

7-Hydroxy-2,2-dimethyl-6-[(2*E*)-3-(4-methylphenyl)-prop-2-enoyl]chroman-4-one (4e). Yield 70%, yellow solid, mp 180–183°C. IR spectrum, ν, cm^{-1}: 1204, 1370, 1568 (C=C), 1640 (C=O), 1689, 2971 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (6H, s, $2CH_3$); 2.41 (3H, s, CH_3); 2.74 (2H, s, CH_2); 6.46 (1H, s, H Ar); 7.25–7.27 (2H, m, H Ar); 7.59–7.65 (3H, m, =CH, H Ar); 7.92 (1H, d, *J* = 15.3, =CH); 8.57 (1H, s, H Ar); 13.52 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 21.3; 26.8; 48.6; 80.2; 105.9; 113.4; 114.1; 118.5; 128.5; 128.9; 130.7; 132.2; 137.6; 145.1; 167.8; 170.3; 190.8; 192.8. Mass spectrum, *m*/*z*: 337 $[M+H]^+$. Found, %: C 74.92; H 5.94. $C_{21}H_{20}O_4$. Calculated, %: C 74.98; H 5.99.

7-Hydroxy-6-[(2*E*)-3-(4-methoxyphenyl)prop-2-enoyl]-2,2-dimethylchroman-4-one (4f). Yield 75%, yellow solid, mp 176–178°C. IR spectrum, ν, cm^{-1}: 1207, 1369, 1552 (C=C), 1633 (C=O), 1687, 2972 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (6H, s, $2CH_3$); 2.74 (2H, s, CH_2); 3.88 (3H, s, OCH_3); 6.45 (1H, s, H Ar); 6.91 (2H, d, *J* = 8.8, H Ar); 7.55 (1H, d, *J* = 15.3, =CH); 7.66 (2H, d, *J* = 8.8, H Ar); 7.91 (1H, d, *J* = 15.3, =CH); 8.57 (1H, s, H Ar); 13.71 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 26.8; 48.6; 55.8; 80.2; 105.7; 113.4; 114.1; 114.2; 118.7; 127.7; 130.2; 130.7; 145.2; 168.8; 170.3; 190.9; 192.8. Mass spectrum, *m*/*z*: 353 $[M+H]^+$. Found, %: C 71.54; H 5.70. $C_{21}H_{20}O_5$. Calculated, %: C 71.58; H 5.72.

7-Hydroxy-6-[(2*E*)-3-(4-isopropylphenyl)prop-2-enoyl]-2,2-dimethylchroman-4-one (4g). Yield 70%, yellow solid, mp 153–155°C. IR spectrum, ν, cm^{-1}: 1213, 1364,

1555 (C=C), 1643 (C=O), 1678, 2984 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (6H, d, *J* = 6.8, $(C\underline{H}_3)_2CH$); 1.52 (6H, s, $2CH_3$); 2.78 (2H, s, CH_2); 2.96 (1H, sept, *J* = 6.8, $(CH_3)_2C\underline{H}$); 6.79 (1H, s, H Ar); 7.32 (2H, d, *J* = 7.9, H Ar); 7.82 (2H, d, *J* = 7.9, H Ar); 7.90 (1H, d, *J* = 15.3, =CH); 7.52 (1H, d, *J* = 15.3, =CH); 8.58 (1H, s, H Ar); 13.72 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 23.3; 26.7; 33.2; 48.3; 80.2; 105.7; 113.4; 114.1; 118.7; 126.0; 128.3; 130.7; 132.4; 145.1; 147.6; 168.8; 170.3; 190.9; 192.8. Mass spectrum, *m*/*z*: 365 $[M+H]^+$. Found, %: C 75.76; H 6.60. $C_{23}H_{24}O_4$. Calculated, %: C 75.80; H 6.64.

7-Hydroxy-2,2-dimethyl-6-[(2*E*)-3-(naphthalen-1-yl)-prop-2-enoyl]chroman-4-one (4h). Yield 66%, yellow solid, mp 169–171°C. IR spectrum, ν, cm^{-1}: 1201, 1367, 1556 (C=C), 1631 (C=O), 1683, 2978 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (6H, s, $2CH_3$); 2.75 (2H, s, CH_2); 6.47 (1H, s, H Ar); 6.92 (2H, d, *J* = 8.7, H Ar); 7.48–7.51 (3H, m, H Ar); 7.55 (1H, d, *J* = 15.3, =CH); 7.91 (1H, d, *J* = 15.3, =CH); 8.21 (1H, d, *J* = 8.4, H Ar); 8.28 (1H, d, *J* = 7.3, H Ar); 8.57 (1H, s, H Ar); 13.71 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 26.8; 48.6; 80.7; 105.7; 113.4; 114.1; 121.3; 122.6; 124.0; 126.0; 126.3; 126.9; 126.9; 128.3; 128.8; 130.7; 132.0; 133.5; 133.6; 135.6; 168.8; 170.3; 190.9; 192.8. Mass spectrum, *m*/*z*: 373 $[M+H]^+$. Found, %: C 77.35; H 5.35. $C_{24}H_{20}O_4$. Calculated, %: C 77.40; H 5.41.

Synthesis of flavanones 5a–g (General method). A mixture of chalcone **4a–g** (10 mmol) and TFA (2 ml) was placed in a quartz tube which was inserted into a screw-capped Teflon vial and then was subjected to microwave irradiation at 320 W for 3–5 min. After completion of the reaction (as indicated by TLC), the reaction mixture was poured into ice-cold water, extracted with dichloromethane (2×30 ml), and the organic layer was dried over Na_2SO_4, purified by column chromatography (eluent *n*-hexane–AcOEt, 9:1).

2,2-Dimethyl-8-phenyl-2,3,7,8-tetrahydro-4*H*,6*H*-pyrano[3,2-*g*]chromene-4,6-dione (5a). IR spectrum, ν, cm^{-1}: 2981, 1688 (C=O), 1600, 1464, 1229, 1149. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (3H, s, CH_3); 1.48 (3H, s, CH_3); 2.72 (2H, s, CH_2); 2.89 (1H, dd, *J* = 16.9, *J* = 3.1) and 3.06 (1H, dd, *J* = 16.9, *J* = 12.8, 7-CH_2); 5.50 (1H, dd, *J* = 12.8, *J* = 3.0, 8-CH); 6.53 (1H, s, H Ar); 7.40–7.48 (5H, m, H Ph); 8.56 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.6; 27.0; 44.3; 48.7; 79.9; 80.5; 105.4; 115.9; 126.2; 128.4; 128.9; 129.0; 129.7; 138.2; 165.3; 166.5; 189.8; 190.3. Mass spectrum, *m*/*z*: 323 $[M+H]^+$. Found, %: C 74.48; H 5.60. $C_{20}H_{18}O_4$. Calculated, %: C 74.52; H 5.63.

8-(4-Fluorophenyl)-2,2-dimethyl-2,3,7,8-tetrahydro-4*H*,6*H*-pyrano[3,2-*g*]chromene-4,6-dione (5b). IR spectrum, ν, cm^{-1}: 2990, 1690 (C=O), 1605, 1469, 1231, 1165. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (3H, s, CH_3); 1.48 (3H, s, CH_3); 2.72 (2H, s, CH_2); 2.87 (1H, dd, *J* = 16.9, *J* = 3.1) and 3.03 (1H, dd, *J* = 16.9, *J* = 12.7, 7-CH_2); 5.48 (1H, dd, *J* = 12.7, *J* = 3.0); 6.52 (1H, s, H Ar), 7.09–7.17 (2H, m, H Ar); 7.42–7.48 (2H, m, H Ar); 8.56 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.6; 27.0; 44.3; 48.6; 79.2; 80.6; 105.4; 115.8; 116.0; 128.1; 128.4; 134.0; 134.1; 161.7; 164.2; 165.4; 166.3; 189.6; 190.4. Mass spectrum, *m*/*z*: 341 $[M+H]^+$. Found, %: C 70.51; H 5.00. $C_{20}H_{17}FO_4$. Calculated, %: C 70.58; H 5.03.

8-(4-Chlorophenyl)-2,2-dimethyl-2,3,7,8-tetrahydro-4*H*,6*H*-pyrano[3,2-*g*]chromene-4,6-dione (5c). IR spectrum, ν, cm^{-1}: 2983, 1704 (C=O), 1602, 1461, 1227, 1157. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (3H, s, CH_3); 1.48 (3H, s, CH_3); 2.72 (2H, s, CH_2); 2.88 (1H, dd, *J* = 16.9, *J* = 3.2) and 3.01 (1H, dd, *J* = 16.9, *J* = 12.5, 7-CH_2); 5.48 (1H, dd, *J* = 12.5, *J* = 3.2, 8-CH); 6.52 (1H, s, H Ar); 7.36–7.45 (4H, m, H Ar), 8.56 (s, 1H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 26.7; 27.0; 42.7; 48.6; 79.8; 80.8; 104.6; 115.9; 116.8; 126.9; 128.0; 128.6; 129.0; 133.2; 136.4; 166.4; 167.6; 189.9; 190.6. Mass spectrum, *m*/*z*: 357 $[M+H]^+$. Found, %: C 67.30; H 4.75. $C_{20}H_{17}ClO_4$. Calculated, %: C 67.32; H 4.80.

8-(4-Bromophenyl)-2,2-dimethyl-2,3,7,8-tetrahydro-4*H*,6*H*-pyrano[3,2-*g*]chromene-4,6-dione (5d). IR spectrum, ν, cm^{-1}: 2963, 1679 (C=O), 1604, 1463, 1231, 1160. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (3H, s, CH_3); 1.48 (3H, s, CH_3); 2.73 (2H, s, CH_2); 2.88 (1H, dd, *J* = 16.9, *J* = 3.2) and 3.00 (1H, dd, *J* = 16.9, *J* = 12.5, 7-CH_2); 5.47 (1H, dd, *J* = 12.5, *J* = 3.2, 8-CH); 6.52 (1H, s, H Ar); 7.32–7.36 (2H, m, H Ar); 7.56–7.59 (2H, m, H Ar); 8.55 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.7; 27.0; 42.7; 48.6; 80.8; 81.8; 105.1; 116.0; 116.3; 122.0; 127.2; 128.8; 131.8; 137.3; 166.6; 167.8; 189.9; 190.6. Mass spectrum, *m*/*z*: 401 $[M(^{79}Br)+H]^+$. Found, %: C 59.82; H 4.22. $C_{20}H_{17}BrO_4$. Calculated, %: C 59.87; H 4.27.

2,2-Dimethyl-8-(4-methylphenyl)-2,3,7,8-tetrahydro-4*H*,6*H*-pyrano[3,2-*g*]chromene-4,6-dione (5e). IR spectrum, ν, cm^{-1}: 2981, 1691 (C=O), 1604, 1467, 1229, 1158. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (3H, s, CH_3); 1.48 (3H, s, CH_3); 2.39 (3H, s, CH_3); 2.72 (2H, s, CH_2); 2.87 (1H, dd, *J* = 16.9, *J* = 2.9) and 3.06 (1H, dd, *J* = 16.9, *J* = 12.8, 7-CH_2); 5.46 (1H, dd, *J* = 12.7, *J* = 2.6, 8-CH); 6.51 (1H, s, H Ar); 7.24 (2H, d, *J* = 8.1, H Ar); 7.34 (2H, d, *J* = 8.0, H Ar); 8.55 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.1; 26.6; 27.0; 44.2; 48.7; 79.9; 80.5; 105.4; 115.8; 115.8, 126.2; 128.3; 129.5; 135.2; 138.9; 165.3; 166.6; 190.0; 190.4. Mass spectrum, *m*/*z*: 337 $[M+H]^+$. Found, %: C 74.93; H 5.96. $C_{21}H_{20}O_4$. Calculated, %: C 74.98; H 5.99.

8-(4-Methoxyphenyl)-2,2-dimethyl-2,3,7,8-tetrahydro-4*H*,6*H*-pyrano[3,2-*g*]chromene-4,6-dione (5f). IR spectrum, ν, cm^{-1}: 2979, 1690 (C=O), 1602, 1459, 1230, 1145. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (3H, s, CH_3); 1.48 (3H, s, CH_3); 2.71 (2H, s, CH_2); 2.88 (1H, dd, *J* = 16.9, *J* = 2.9) and 3.08 (1H, dd, *J* = 16.9, *J* = 12.8); 3.25 (3H, s, OCH_3); 5.53 (1H, dd, *J* = 12.7, *J* = 2.6, 8-CH); 6.51 (1H, s, H Ar); 7.24 (2H, d, *J* = 8.1, H Ar); 7.35 (2H, d, *J* = 8.0, H Ar); 8.57 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.6; 27.0; 44.2; 48.8; 53.8; 79.8; 80.4; 105.4; 115.4; 115.7; 126.5; 128.1; 129.4; 135.2; 139.0; 165.1; 166.8; 189.9; 190.7. Mass spectrum, *m*/*z*: 353 $[M+H]^+$. Found, %: C 71.52; H 5.69. $C_{21}H_{20}O_5$. Calculated, %: C 71.58; H 5.72.

8-(4-Isopropylphenyl)-2,2-dimethyl-2,3,7,8-tetrahydro-4*H*,6*H*-pyrano[3,2-*g*]chromene-4,6-dione (5g). IR spectrum,

ν, cm^{-1}: 2964, 1690 (C=O), 1601, 1465, 1224, 1152. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (6H, d, *J* = 6.3, $(C\underline{H}_3)_2CH$); 1.46 (3H, s, CH_3); 1.48 (3H, s, CH_3); 2.72 (2H, s, CH_2); 2.88 (1H, dd, *J* = 16.9, *J* = 2.9) and 3.08 (1H, dd, *J* = 16.9, *J* = 12.9, CH_2); 2.95 (1H, sept, *J* = 6.3, $(CH_3)_2C\underline{H}$); 5.47 (1H, dd, *J* = 12.9, *J* = 2.8, 8-CH); 6.51 (1H, s, H Ar); 7.30 (2H, d, *J* = 8.2, H Ar); 7.38 (2H, d, *J* = 8.1, H Ar); 8.56 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.8; 26.6; 27.0; 33.9; 44.2; 48.7; 79.9; 80.5; 105.4; 115.1, 115.8, 126.3; 126.9; 128.4; 135.4; 149.9; 165.3; 166.7; 190.1; 190.4. Mass spectrum, *m*/*z*: 365 $[M+H]^+$. Found, %: C 75.77; H 6.60. $C_{23}H_{24}O_4$. Calculated, %: C 75.80; H 6.64.

Synthesis of aurones 6a–h (General method). A mixture of chalcone **4a**–**h** (10 mmol), mercuric acetate (35 mg, 11.0 mmol), and pyridine (2 ml) was taken up in a quartz tube which was inserted into a screw-capped Teflon vial and then subjected to microwave irradiation at 320 W for 2–4 min. After completion of the reaction (as indicated by TLC), the reaction mixture was poured into ice-cold water and extracted with dichloromethane (2×30 ml). The organic phase was dried over Na_2SO_4 and purified by column chromatography (eluent *n*-hexane–AcOEt, 9:1).

2-Benzylidene-7,7-dimethyl-6,7-dihydro-5*H*-furo[3,2-*g*]-chromene-3,5(2*H*)-dione (6a). IR spectrum, ν, cm^{-1}: 2928, 1671 (C=O), 1605, 1326, 1242, 1138. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.44 (6H, s, $2CH_3$); 2.71 (2H, s, CH_2); 6.73 (1H, s, H Ar); 6.78 (1H, s, CH); 7.32–7.41 (3H, m, H Ar); 7.81 (2H, d, *J* = 7.3, H Ar); 8.35 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.7; 48.5; 87.5; 102.8; 112.8; 113.9; 115.0; 127.9; 128.5; 128.6; 130.0; 132.3; 146.7; 168.3; 171.2; 182.7; 190.9. Mass spectrum, *m*/*z*: 321 $[M+H]^+$. Found, %: C 74.90; H 5.00. $C_{20}H_{16}O_4$. Calculated, %: C 74.99; H 5.03.

2-(4-Fluorobenzylidene)-7,7-dimethyl-6,7-dihydro-5*H*-furo[3,2-*g*]chromene-3,5(2*H*)-dione (6b). IR spectrum, ν, cm^{-1}: 2935, 1698 (C=O), 1604, 1330, 1240, 1150. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.45 (6H, s, $2CH_3$); 2.72 (2H, s, CH_2); 6.72 (1H, s, H Ar); 6.79 (1H, s, CH); 7.29 (2H, d, *J* = 8.5, H Ar); 7.54 (2H, d, *J* = 8.5, H Ar); 8.36 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.8; 48.5; 81.2; 101.2; 111.6; 115.9; 116.0; 116.3; 117.4; 125.4; 128.2; 133.4; 146.9; 162.2; 164.7; 166.6; 169.6; 182.5; 190.4. Mass spectrum, *m*/*z*: 339 $[M+H]^+$. Found, %: C 70.95; H 4.40. $C_{20}H_{15}FO_4$. Calculated, %: C 71.00; H 4.47.

2-(4-Chlorobenzylidene)-7,7-dimethyl-6,7-dihydro-5*H*-furo[3,2-*g*]chromene-3,5(2*H*)-dione (6c). IR spectrum, ν, cm^{-1}: 2925, 1699 (C=O), 1605, 1328, 1238, 1137. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.45 (6H, s, $2CH_3$); 2.72 (2H, s, CH_2); 6.72 (1H, s) and 6.73 (1H, s, CH, H Ar); 7.35 (2H, d, *J* = 8.5, H Ar); 7.74 (2H, d, *J* = 8.5, H Ar); 8.35 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.7; 48.3; 87.3; 102.3; 111.6; 113.2; 115.7; 128.7; 129.0; 130.0; 130.4; 133.5; 146.9; 168.1; 170.2; 182.6; 190.9. Mass spectrum, *m*/*z*: 355 $[M+H]^+$. Found, %: C 67.67; H 4.20. $C_{20}H_{15}ClO_4$. Calculated, %: C 67.71; H 4.26.

2-(4-Bromobenzylidene)-7,7-dimethyl-6,7-dihydro-5*H*-furo[3,2-*g*]chromene-3,5(2*H*)-dione (6d). IR spectrum, ν, cm^{-1}: 2964, 1700 (C=O), 1607, 1250, 1016. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.45 (6H, s, $2CH_3$); 2.72 (2H, s, CH_2); 6.70 (1H, s, H Ar); 6.72 (1H, s, CH); 7.49–7.53 (2H, m, H Ar); 7.64–7.67 (2H, m, H Ar); 8.35 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.7; 48.3; 87.3; 102.8; 111.6; 113.6; 115.0; 122.3; 128.7; 130.0; 131.5; 146.9; 168.3; 171.2; 182.8; 191.2. Mass spectrum, *m*/*z*: 399 $[M(^{79}Br)+H]^+$. Found, %: C 60.10; H 3.72. $C_{20}H_{15}BrO_4$. Calculated, %: C 60.17; H 3.79.

7,7-Dimethyl-2-(4-methylbenzylidene)-6,7-dihydro-5*H*-furo[3,2-*g*]chromene-3,5(2*H*)-dione (6e). IR spectrum, ν, cm^{-1}: 2968, 1705, 1601, 1254, 1011. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.52 (6H, s, $2CH_3$); 2.41 (3H, s, CH_3); 2.78 (2H, s, CH_2); 6.80 (1H, s, H Ar); 6.85 (1H, s, CH); 7.27–7.28 (2H, m, H Ar); 7.78 (2H, d, *J* = 7.8, H Ar); 8.42 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.3; 26.7; 48.3; 87.3; 102.8; 112.4; 113.9; 115.0; 128.5; 128.9; 129.3; 130.0; 137.6; 146.9; 168.2; 171.2; 182.6; 191.2. Mass spectrum, *m*/*z*: 335 $[M+H]^+$. Found, %: C 75.40; H 5.40. $C_{21}H_{18}O_4$. Calculated, %: C 75.43; H 5.43.

2-(4-Methoxybenzylidene)-7,7-dimethyl-6,7-dihydro-5*H*-furo[3,2-*g*]chromene-3,5(2*H*)-dione (6f). IR spectrum, ν, cm^{-1}: 2969, 1701 (C=O), 1607, 1253, 1020. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.52 (6H, s, $2CH_3$); 2.78 (2H, s, CH_2); 3.88 (3H, s, OCH_3), 6.78 (1H, s, H Ar); 6.84 (1H, s, CH); 6.97 (2H, d, *J* = 8.6, H Ar); 7.84 (2H, d, *J* = 8.6, H Ar); 8.41 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.7; 48.3; 55.8; 87.3; 102.1; 112.4; 113.8; 114.2; 115.0; 124.6; 131.3; 132.8; 146.9; 159.8; 168.5; 171.2; 182.6; 190.7. Mass spectrum, *m*/*z*: 351 $[M+H]^+$. Found, %: C 71.92; H 5.13. $C_{21}H_{18}O_5$. Calculated, %: C 71.99; H 5.18.

2-(4-Isopropylbenzylidene)-7,7-dimethyl-6,7-dihydro-5*H*-furo[3,2-*g*]chromene-3,5(2*H*)-dione (6g). IR spectrum, ν, cm^{-1}: 2962, 1702 (C=O), 1606, 1353, 1138. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (6H, d, *J* = 6.8, $(C\underline{H}_3)_2CH$); 1.52 (6H, s, $2CH_3$); 2.78 (2H, s, CH_2); 2.96 (1H, sept, *J* = 6.8, $(CH_3)_2C\underline{H}$); 6.79 (1H, s, H Ar); 6.85 (1H, s, CH); 7.32 (2H, d, *J* = 7.9, H Ar); 7.82 (2H, d, *J* = 7.9, H Ar); 8.42 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.3; 26.7; 33.2; 48.3; 86.5; 102.6; 112.3; 113.9; 115.0; 126.0; 128.3; 129.5; 130.4; 147.0; 147.6; 168.4; 171.5; 181.0; 190.8. Mass spectrum, *m*/*z*: 363 $[M+H]^+$. Found, %: C 76.18; H 6.09. $C_{23}H_{22}O_4$. Calculated, %: C 76.22; H 6.12.

7,7-Dimethyl-2-(naphthalen-1-ylmethylidene)-6,7-dihydro-5*H*-furo[3,2-*g*]chromene-3,5(2*H*)-dione (6h). IR spectrum, ν, cm^{-1}: 2986, 1709 (C=O), 1610, 1386, 1025. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.44 (6H, s, $2CH_3$); 2.71 (2H, s, CH_2); 6.73 (1H, s, CH); 7.51–7.53 (3H, m, H Ar); 7.60 (1H, s, H Ar); 7.83 (2H, t, *J* = 9.1, H Ar); 8.21 (1H, d, *J* = 8.4, H Ar); 8.30 (1H, d, *J* = 7.3, H Ar); 8.38 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.7; 48.3; 87.4; 102.6; 112.8; 112.9; 113.9; 115.0; 122.9; 124.0; 126.0; 126.3; 126.9; 128.8; 130.0; 132.0; 133.5; 135.6; 147.2; 169.5; 171.2; 186.5; 191.8. Mass spectrum, *m*/*z*: 371 $[M+H]^+$. Found, %: C 77.80; H 4.85. $C_{24}H_{18}O_4$. Calculated, %: C 77.82; H 4.90.

Biological assay. For the antibacterial activity test, the cultures were grown in nutrient agar media and subcultured for log phase cultures in a liquid nutrient broth medium for zone of inhibition test and further subcultured onto media in Petri plates for the experimental purposes. The broth

cultures were diluted with sterilized saline to bring the final size of inoculum to 10^5–10^6 CFU/ml. The compounds were diluted in acetone, DMSO, and diethyl ether for biological assays. Among the three solvents, diethyl ether was taken as the best one. The bacterial cultures were placed on the media and incubated at 37°C for 24–48 h along with the diluted compounds introduced through discs dipped and placed over the nutrient media. The bacterial growth inhibition on the media was expressed as zone of inhibition in mm.

For the antifungal activity test, the synthesized 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 to be 500 μg/ml. The cultures of fungi were incubated in PDA at 25±1°C for 48–72 h to get long mycelium for antifungal assay. The mycelia disc of approximately 0.45 cm in diameter was cut from the PDA medium with a sterilized inoculation needle and inoculated in the center of PDA plate. The inoculated plates were incubated at 27±1°C for 3 days. Diethyl ether in sterilized distilled water was taken as blank control, while hymexazol was used as positive control. The growth of the fungal colonies was measured on the third day and the data were statistically analyzed.

The Supplementary information file containing ^{1}H NMR spectra of compounds **5a**–**e**,**g**, **6a**,**c**–**h** and ^{13}C NMR spectra of compounds **5a**,**b** is available at http://link.springer.com/journal/10593.

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