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Microwave-assisted synthesis of 10-aryl-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehydes by Suzuki coupling and their antimicrobial activity

Dongamanti Ashok[1]*, Bommidi Vijaya Lakshmi[1], Sidda Ravi[1], Arram Ganesh[1], Shaik Adam[2]

[1] *Department of Chemistry, Osmania University, Hyderabad-500 007, India; e-mail: ashokdou@gmail.com*

[2] *Nanotechnology laboratory, Regional Agricultural Research Station, ANGRAU, Tirupati-517502, India; e-mail: shaikadam@gmail.com*

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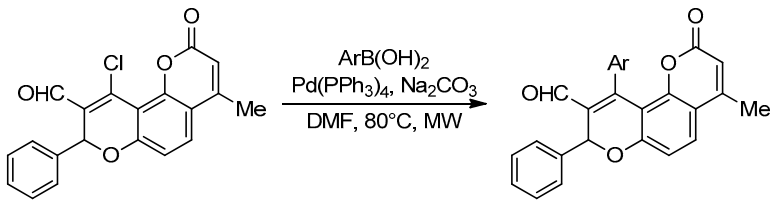


A series of new pyranochromenes has been synthesized by conventional and microwave irradiation methods from 10-chloro-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehyde using the Suzuki coupling. All the synthesized compounds were characterized by standard spectroscopic methods and elemental analysis and screened for their antibacterial and antifungal activities.

Keywords: chromene, chromenecarbaldehyde, coumarin, pyranocoumarin, Suzuki coupling.

Synthesis of heterocyclic compounds has emerged as a powerful technique for generating new molecules useful for drug discovery.[1] Coumarin derivatives have been reported to exhibit anti-inflammatory,[2] antimicrobial,[3] antioxidant,[4] anticancer,[5] and antiviral[6] activities. Naturally occurring coumarins are of great interest due to their diverse pharmacological properties, and this attracts attention of many medicinal chemists to further derivatization of the heterocycle backbone and screening the resulting compounds for their biological activity. Chromenes and fused chromenes are biologically important compounds with antiHIV,[7] antifungal,[8] antitumor,[9] and antiviral[10] activities. It is reported in the literature that when one biodynamic heterocyclic system is coupled with another heterocyclic system, biological activity increases.[11] Thus, pyrane ring condensed with coumarin ring system gives polycyclic molecules, called pyranochromenes or pyranocoumarins which may exhibit better biological activity.

Many of the natural compounds containing a pyranochromene moiety are known for various biological activities[12] (Fig. 1). Among them xanthyletin, a linear pyranocoumarin, posseses antitubercular activity.[13] Seselin, an angular pyranocoumarin isolated from citrus roots, has shown activity against skin cancer.[14] A large variety of natural products have been described as antiHIV agents, and pyranocoumarin derivatives are also among them. The

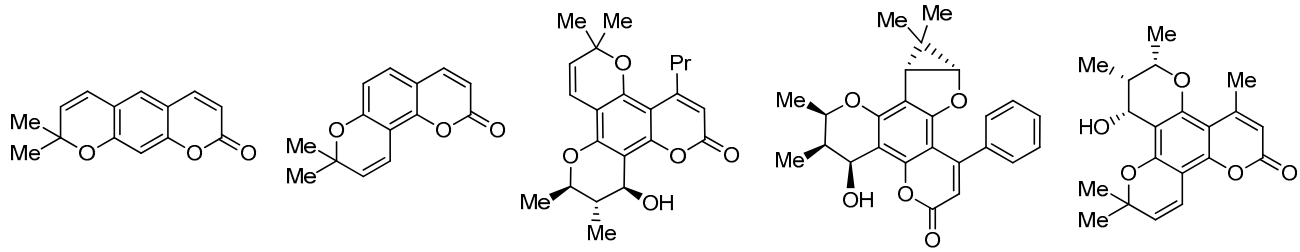
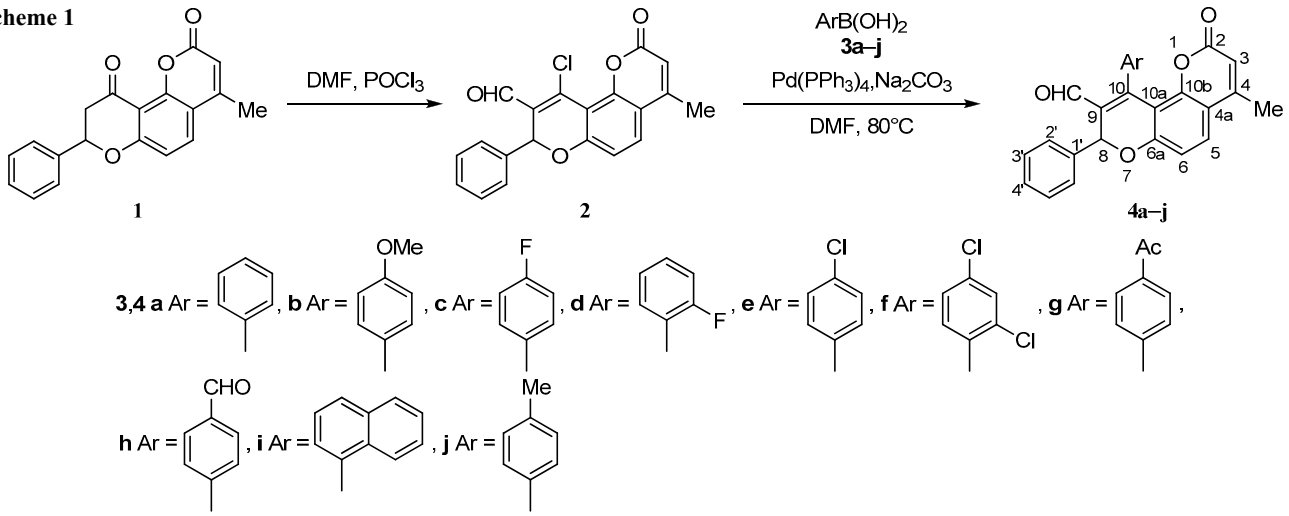


Figure 1. Structures of some naturally occurring pyranochromenes.

Scheme 1



pyranocoumarins (+)-calanolide A,[15] inophyllum G-1,[16] and pseudocordatolide C[17] have their potential application for treating HIV infection. The present work describes synthesis of some new arylpyranocoumarins and their antimicrobial activity.

Aryl–aryl and aryl–vinyl bond formation is very important in organic synthesis and has a wide range of applications of industrial interest, including the synthesis of pharmaceuticals, herbicides, polymers, and other materials.[18,19] The coupling of aryl and vinyl halides with organoboronic acids is one of the most important metal-catalyzed cross-coupling reactions, known as the Suzuki or Suzuki–Miyaura coupling. This palladium-catalyzed reaction is certainly one of the most attractive methods for preparing biaryl and arylated compounds because of its functional-group tolerance, the use of stable and non-toxic organoboron reagents, and the possibility of using aqueous solvents as reaction medium.[20]

The application of microwave irradiation (MW) can provide enhanced reaction rate and improved product yield in the formation of a variety of carbon–heteroatom bonds. During recent years, microwaves have been extensively used for carrying out chemical reactions and have become a useful non-conventional energy source for performing organic synthesis.[21] Our research group has been making considerable efforts towards designing and carrying out innovative synthetic protocols in organic synthesis adopting a more environmentally friendly approach.[22–24]

Earlier we have reported some 4-chlorochromone derivatives which showed potential biological activity.[25] In view of the potential bioactivity of pyranocoumarins, we have carried out the synthesis of some new 10-aryl-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehydes **4a**–**j** using the Suzuki coupling under microwave irradiation. The synthesized compounds were screened for their antibacterial and antifungal activity.

The synthetic route to compounds **4a**–**j** is shown in Scheme 1. The reaction of flavanone **1** with Vilsmeier reagent (DMF/$POCl_3$) by microwave irradiation for 5 min gave 10-chloro-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano-[2,3-*f*]chromene-9-carbaldehyde (**2**)[26] with 80% yield. Subsequently compound **2** underwent the Suzuki coupling with arylboronic acids **3a**–**j**, yielding 10-aryl-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehydes **4a**–**j**. Na_2CO_3 was chosen as the base and $Pd(PPh_3)_4$ was used as the catalyst.[27] Initially, we optimized the Suzuki coupling conditions by running the synthesis of compound **4a** at different catalyst loadings (Table 1). The use of 10 mol % $Pd(PPh_3)_4$ was found to be the optimal condition. The proposed structure of compound **4a** was confirmed by spectral data as 4-methyl-2-oxo-8,10-diphenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehyde. The base peak in the mass spectrum of compound **4a** at *m*/*z* 395 corresponding to $[M+H]^+$ confirms the Suzuki coupled product. We observed that the use of MW irradiation instead of conventional heating brought further improvement of the reaction yield along with a significant decrease of the reaction time (Tables 1, 2).

Table 1. Yields of compound **4a** at different catalyst loads and heating methods

$Pd(PPh_3)_4$ concentration, mol %	Conventional heating		MW heating	
	Time, h	Yield, %	Time, min	Yield, %
1	5	8	4	10
3	5	13	4	18
5	5	24	4	28
8	5	44	4	48
10	5	52	4	60

Table 2. Yields of the synthesized compounds **4a**–**j**

Compound	Conventional heating*		MW heating*	
	Time, h	Yield, %	Time, min	Yield, %
4a	6	68	5	87
4b	6	65	6	85
4c	7	62	6	85
4d	6	65	6	80
4e	7	60	5	80
4f	6	65	6	80
4g	6	68	5	84
4h	8	65	8	83
4i	6	64	6	82
4j	8	62	7	80

* Compound **2** (1.0 mmol), compound **3** (1.2 mmol), $Pd(PPh_3)_4$ (0.10 mmol), Na_2CO_3 (3.0 mmol), DMF (3–5 ml), 80°C.

Table 3. Antibacterial activity of compounds **2**, **4a**–**j**

Compound	Zone of inhibition, mm			
	Gram-positive bacteria		Gram-negative bacteria	
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
2	20	08	22	08
4a	28	10	26	12
4b	24	12	33	15
4c	29	07	25	13
4d	26	11	23	12
4e	25	08	26	14
4f	29	09	28	10
4g	36	15	36	12
4h	28	08	25	11
4i	26	08	23	08
4j	28	10	24	08
Amoxicillin	30	12	30	10

The synthesized novel compounds **4a**–**j** (Table 3) were screened for their antibacterial activity against different types of bacterial Gram-positive and Gram-negative strains at a concentration of 100 μg/ml.

From the screening studies it is evident that the replacement of chlorine atom by an aryl group enhanced the activity of compounds against all tested bacteria. Compounds **4a**,**c**,**f**–**j** showed high activity against Gram-positive *Staphylococcus aureus*, and compounds **4a**,**b**,**g** showed better activity against Gram-positive *Bacillus subtilis*, compound **4g** being more active than the standard drug amoxicillin against both strains.

The activity of compounds **4b**,**f**,**g** was high against Gram-negative *Escherichia coli*, and compounds **4a**–**h** had high activity against Gram-negative *Pseudomonas aeruginosa* compared to the standard drug. It was observed that compound **4g** exhibited broad spectrum of antibacterial activity against all the tested strains.

The antifungal activity of the synthesized compounds **4a**–**j** (Table 4) was tested against three pathogenic fungi at a concentration of 100 μg/ml. Replacement of chlorine atom by aryl group enhanced the activity of compounds against *Aspergillus niger, Penicillium italicum*. In case of *Fusarium oxysporum,* there was a minor enhancement of activity in comparison to compound **2**. Compounds **4a**–**h** showed high activity against *Aspergillus niger*, compounds **4a**,**b**,**e**,**g** showed high activity against *Penicillium italicum*, and compounds **4a**,**b**,**c**,**d**,**g** had high activity against *Fusarium oxysporum* compared to standard drug mycostatin at a concentration of 100 μg/ml. It was observed that compounds **4a**,**b**,**g** showed broad spectrum of antifungal activity against all tested fungal species.

Table 4. Antifungal activity of compounds **2**, **4a**–**j**

Compound	Zone of inhibition, mm		
	Aspergillus niger	*Penicillium italicum*	*Fusarium oxysporum*
2	08	16	22
4a	13	20	26
4b	10	18	23
4c	12	17	25
4d	13	16	23
4e	11	18	18
4f	10	17	20
4g	16	23	28
4h	10	13	20
4i	09	14	21
4j	10	16	20
Mycostatin	13	20	26

An efficient microwave synthesis of pyranocoumarin derivatives have been carried out successfully under mild reaction conditions. All the final compounds were investigated for their *in vitro* antimicrobial activity. Substitution of chlorine atom at pyranocoumarin ring by an aryl group enhanced the antibacterial activity. The *p*-acetylphenyl derivative exhibited broad spectrum of antibacterial activity against all the tested bacterial and fungal strains, and two other compounds showed a promising antifungal activity against tested strains compared to the standard drug mycostatin. The microwave irradiation process proved to be a simple environmentally friendly technique with high yields and short reaction times.

Experimental

IR spectra were recorded in KBr on a Shimadzu FTIR 8400S spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 mass spectrometer. The elemental analysis was carried out on a Vario-11 CHN analyzer. Melting points were determined in open glass capillaries on a Stuart SMP30 apparatus and are uncorrected. Purity of the compounds was checked by TLC on silica gel 60 F_{254} (Merck). All the microwave irradiation experiments were performed in a CEM Discover microwave system and reaction temperatures were monitored by an equipped IR sensor.

Synthesis of 10-aryl-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehydes 4a–j. Conventional heating (General method). 10-Chloro-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehyde (**2**) (353 mg, 1.0 mmol), $Pd(PPh_3)_4$ (115 mg, 0.10 mmol), arylboronic acid (1.2 mmol), and Na_2CO_3 (318 mg, 3.0 mmol) were sequentially added into a round-bottomed flask. The mixture was dissolved in DMF (5 ml) and degassed with nitrogen over 15 min. The reaction mixture was stirred at 80°C for 6–8 h (Table 2) under nitrogen atmosphere. After the reaction was completed, the mixture was diluted with EtOAc and washed with H_2O and brine solution. The organic layer was washed with H_2O (10 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by using silica gel column chromatography (hexane–AcOEt, 3:1).

Synthesis of 10-aryl-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehydes 4a–j. Microwave heating (General method). A degassed mixture of 10-chloro-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]-chromene-9-carbaldehyde (**2**) (353 mg, 1.0 mmol), $Pd(PPh_3)_4$

(115 mg, 0.10 mmol), arylboronic acid (1.2 mmol), Na_2CO_3 (318 mg, 3.0 mmol), and DMF (3 ml) was introduced into a microwave reaction vessel equipped with a magnetic stirrer. The vessel was sealed and then placed into the microwave cavity. Initial microwave irradiation of 180 W was used, the temperature being ramped from room temperature to the desired 80°C temperature. The reaction mixture was heated at this temperature under continuous stirring for the appropriate time (Table 2). The reaction mixture was then cooled to room temperature, diluted with EtOAc (20 ml), and washed with H_2O and brine solution. The organic layer was washed with water (10 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by using silica gel column chromatography (hexane–AcOEt, 3:1).

4-Methyl-2-oxo-8,10-diphenyl-2,8-dihydropyrano[2,3-*f*]-chromene-9-carbaldehyde (4a). Yield 87%, pale-yellow solid, mp 160–162°C. IR spectrum, ν, cm^{-1}: 1078 (C–O–C), 1749 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, d, *J* = 1.0, CH_3); 5.97 (1H, d, *J* = 1.0, H-3); 6.54 (1H, s, 8-CH); 6.82–6.93 (2H, m, H-2',6'); 6.99 (1H, d, *J* = 8.8, H-6); 7.21–7.41 (8H, m, H-3',4',5' H Ph); 7.53 (1H, d, *J* = 8.8, H-5); 9.68 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 18.9 (CH_3); 73.2; 111.8; 112.3; 114.2 (C-3); 114.9; 121.6; 126.9; 128.4; 128.5; 128.6; 128.9; 129.2; 129.7; 134.2; 137.6; 148.7; 152.0; 152.3; 157.9 (C-6a); 158.7 (C=O); 190.5 (CHO). Mass spectrum, *m/z* (I_{rel}, %): 395 $[M+H]^+$ (100). Found, %: C 79.21; H 4.57. $C_{26}H_{18}O_4$. Calculated, %: C 79.17; H 4.60.

10-(4-Methoxyphenyl)-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehyde (4b). Yield 85%, pale-yellow solid, mp 154–156°C. IR spectrum, ν, cm^{-1}: 1084 (C–O–C), 1745 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, d, *J* = 1.0, CH_3); 3.88 (3H, s, OCH_3); 5.97 (1H, d, *J* = 1.0, H-3); 6.52 (1H, s, 8-CH); 6.98–7.00 (3H, m, H-6, 2H Ar); 7.24–7.39 (7H, m, 2H Ar, H Ph); 7.53 (1H, d, *J* = 8.8, H-5); 9.70 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 18.9 (CH_3); 55.4; 73.2 (C-8); 112.3; 113.3; 114.1 (2C); 114.5; 114.9; 126.2; 126.9 (2C); 128.4 (2C); 128.5 (2C); 129.5; 134.3; 137.6; 142.1; 148.5; 151.9; 152.3; 158.0; 158.8; 160.6 (C=O); 190.7 (CHO). Mass spectrum, *m/z* (I_{rel}, %): 425 $[M+H]^+$ (100). Found, %: C 76.44; H 4.78. $C_{27}H_{20}O_5$. Calculated, %: C 76.40; H 4.75.

10-(4-Fluorophenyl)-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehyde (4c). Yield 85%, pale-yellow solid, mp 175–177°C. IR spectrum, ν, cm^{-1}: 1080 (C–O–C), 1742 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, d, *J* = 1.0, CH_3); 5.97 (1H, d, *J* = 1.00, H-3); 6.54 (1H, s, 8-CH); 6.98–7.00 (3H, m, H-6, 2H Ar), 7.27–7.29 (3H, m, H-3',4',5'); 7.36–7.38 (2H, m, H-2',6'); 7.53–7.55 (3H, m, H-5, H Ar); 9.66 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 19.3 (CH_3); 73.7 (C-8); 112.7; 114.0; 115.2; 115.5; 120.2; 121.3; 121.6; 122.0; 122.3; 122.9; 124.5; 126.9; 128.6; 129.0; 129.1; 129.6; 134.4; 136.1; 150.4; 152.4; 158.4; 159.3; 160.2 (C=O); 161.2; 190.8 (CHO). Mass spectrum, *m/z* (I_{rel}, %): 413 $[M+H]^+$ (100). Found, %: C 75.74; H 4.16. $C_{26}H_{17}FO_4$. Calculated, %: C 75.72; H 4.15.

10-(2-Fluorophenyl)-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehyde (4d). Yield 80%, pale-yellow solid, mp 170–172°C. IR spectrum, ν, cm^{-1}: 1080 (C–O–C), 1742 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, d, *J* = 1.0, CH_3); 6.01 (1H, d, *J* = 1.0, H-3); 6.67 (1H, s, 8-CH); 6.90 (1H, d, *J* = 8.8, H-6); 7.25–7.50 (9H, m, H Ar, H Ph); 7.55 (1H, d, *J* = 8.8, H-5); 9.68 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 19.3 (CH_3); 73.7 (C-8); 112.7; 114.0; 115.2; 115.4; 120.2; 121.3; 121.6; 122.0; 122.3; 122.9; 124.0; 124.5; 125.3; 126.0; 126.9; 128.6; 129.0; 129.1; 129.6; 134.4; 136.1; 150.8; 152.4; 158.4; 159.3; 161.2; 160.2 (C=O); 190.7 (CHO). Mass spectrum, *m/z* (I_{rel}, %): 413 $[M+H]^+$ (100). Found, %: C 75.75; H 4.17. $C_{26}H_{17}FO_4$. Calculated, %: C 75.72; H 4.15.

10-(4-Chlorophenyl)-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehyde (4e). Yield 80%, pale-yellow solid, mp 170–172°C. IR spectrum, ν, cm^{-1}: 1082 (C–O–C), 1742 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (3H, d, *J* = 1.0, CH_3); 6.20 (1H, d, *J* = 1.0, H-3); 6.78 (1H, s, 8-CH); 6.96 (1H d, *J* = 8.8, H-6); 7.33–7.75 (9H, m, H Ar, H Ph); 7.86 (1H, d, *J* = 8.8, H-5); 9.53 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 19.3 (CH_3); 73.7 (C-8); 112.7; 114.0; 115.2 (C-3); 115.4; 120.2; 121.6; 122.9; 124.5; 126.9; 128.6; 129.0; 129.1; 129.6; 134.4; 136.8; 150.3; 152.4; 158.4; 159.3; 160.2 (C=O); 161.2; 190.5 (CHO). Mass spectrum, *m/z* (I_{rel}, %): 429 $[M+H]^+$ (100). Found, %: C 72.85; H 4.03. $C_{26}H_{17}ClO_4$. Calculated, %: C 72.82; H 4.00.

10-(2,4-Dichlorophenyl)-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehyde (4f). Yield 80%, pale-yellow solid, mp 181–183°C. IR spectrum, ν, cm^{-1}: 1082 (C–O–C), 1742 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.36 (3H, d, *J* = 1.0, CH_3); 6.08 (1H, d, *J* = 1.0, H-3); 6.69 (1H, s, 8-CH); 6.88 (1H, d, *J* = 8.8, H-6); 7.27–7.49 (8H, m, H Ar, H Ph); 7.61 (1H, d, *J* = 8.8, H-5); 9.74 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 19.3 (CH_3); 73.7 (C-8); 112.7; 114.0; 114.7 (C-3); 115.2; 120.2; 122.3; 122.9; 124.5; 126.9; 128.6; 129.0; 129.1; 129.6; 134.4; 136.1; 150.3; 152.4; 158.4 (C-6a); 159.3; 161.2; 162.4 (C=O); 190.5 (CHO). Mass spectrum, *m/z* (I_{rel}, %): 463 $[M+H]^+$ (100). Found, %: C 67.44; H 3.51. $C_{26}H_{16}C_{l2}O_4$. Calculated, %: C 67.40; H 3.48.

10-(4-Acetylphenyl)-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehyde (4g). Yield 84%, pale-yellow solid, mp 156–158°C. IR spectrum, ν, cm^{-1}: 1084 (C–O–C), 1745 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, d, *J* = 1.0, CH_3); 3.68 (3H, s, $COCH_3$); 5.95 (1H, d, *J* = 1.0, H-3); 6.54 (1H, s, 8-CH); 7.01 (1H, d, *J* = 8.8, H-6); 7.29–7.69 (10H, m, H-5, H Ar, H Ph); 9.62 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 19.0 (CH_3); 24.3; 76.4 (C-8); 112.0; 112.8; 114.3 (C-3); 114.5; 114.9; 121.5; 122.2 (2C); 123.8; 126.6; 126.8; 128.4; 129.0; 137.8; 150.2; 151.6; 152.3; 157.3 (C-6a); 160.0; 160.2 (C=O); 190.6 (CHO). Mass spectrum, *m/z* (I_{rel}, %): 437 $[M+H]^+$ (100). Found, %: C 77.08; H 4.64. $C_{28}H_{20}O_5$. Calculated, %: C 77.05; H 4.62.

10-(4-Formylphenyl)-4-methyl-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehyde (4h). Yield 80%, pale-yellow solid, mp 168–170°C. IR spectrum, ν, cm^{-1}:

1084 (C–O–C), 1749 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (3H, d, *J* = 1.0, CH_3); 6.21 (1H, d, *J* = 1.0, H-3); 6.92 (1H, s, 8-CH); 6.95 (1H, d, *J* = 8.8, H-6); 7.05 (2H, d, *J* = 9.0, H Ar); 7.35–7.86 (8H, m, H-5, H Ar, H Ph); 9.96 (1H, s, CHO); 10.24 (1H, s, ArCHO). ^{13}C NMR spectrum, δ, ppm: 18.9 (CH_3); 73.2 (C-8); 111.8; 112.3; 114.2 (C-3); 114.9; 121.9; 128.4; 128.5; 128.6; 128.9; 129.2; 129.7; 134.2 (C-3); 137.6; 148.7; 152.0; 152.3; 157.9 (C-6a); 158.7; 162.2 (C=O); 188.9; 190.5 (CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 423 $[M+H]^+$ (100). Found, %: C 76.79; H 4.31. $C_{27}H_{18}O_5$. Calculated, %: C 76.77; H 4.29.

4-Methyl-10-(naphthalen-1-yl)-2-oxo-8-phenyl-2,8-dihydropyrano[2,3-*f*]chromene-9-carbaldehyde (4i). Yield 82%, pale-yellow solid, mp 152–154°C. IR spectrum, ν, cm^{-1}: 1083 (C–O–C), 1746 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (3H, d, *J* = 1.0, CH_3); 5.79 (1H, d, *J* = 1.0, H-3); 6.62 (1H, s, 8-CH); 7.03 (1H, d, *J* = 8.8, H-6); 7.37–7.99 (13H, m, H-5, H Ar, H Ph), 9.33 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 18.8 (CH_3); 73.5 (C-8); 112.1; 112.4; 113.9 (C-3); 114.9; 124.7; 125.1; 125.5; 126.2; 126.6, 126.9; 128.6; 128.7 (3C); 128.8; 129.2; 131.5; 132.0; 133.5; 133.6; 138.4; 145.3; 146.5; 151.3; 152.1; 157.9 (C=O); 190.5 (CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 445 $[M+H]^+$ (100). Found, %: C 81.10; H 4.57. $C_{30}H_{20}O_4$. Calculated, %: C 81.07; H 4.54.

4-Methyl-2-oxo-8-phenyl-10-(*p*-tolyl)-2,8-dihydropyrano-[2,3-*f*]chromene-9-carbaldehyde (4j). Yield 80%, pale-yellow solid, mp 178–180°C. IR spectrum, ν, cm^{-1}: 1078 (C–O–C), 1731 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.43 (3H, s, CH_3); 2.44 (3H, d, *J* = 1.0, 4-CH_3); 6.20 (1H, d, *J* = 1.0, H-3); 6.85 (1H, s, 8-CH); 6.95 (1H, d, *J* = 8.8, H-6); 7.31–7.86 (10H, m, H-5, H Ar, H Ph); 10.02 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 19.0 (CH_3); 55.3 ($ArCH_3$); 76.4 (C-8); 112.3; 113.3; 114.1 (C-3); 114.5; 114.9; 121.5; 122.2; 123.8; 124.0; 126.6; 127.5; 128.4; 129.0; 137.8; 150.2; 151.6; 152.3; 157.3 (C-6a); 159.4 (C=O); 190.2 (CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 409 $[M+H]^+$ (100). Found, %: C 79.44; H 4.97. $C_{27}H_{20}O_4$. Calculated, %: C 79.40; H 4.94.

Biological activity tests. All the prepared compounds were screened for their antimicrobial activity against two strains of Gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), two strains of Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*), as well as three strains of fungi (*Aspergillus niger*, *Penicillium italicum*, and *Fusarium oxysporum*). Standard antibiotic drugs amoxicillin for bacteria and mycostatin for fungi were used for comparison. The biological activity of these compounds has been evaluated by filter paper disc method[28] on the test compounds and standards dissolved in DMF to obtain concentration 100 μg/ml. The inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimeters at the end of an incubation period of 4 days at 47°C for *Escherichia coli* and at 28°C for other bacteria and fungi. Pure solvent DMF showed no inhibition zone.

Supporting material to this article containing ^{1}H NMR spectra of compounds **2**, **4a**–**e**,**g**–**j**, ^{13}C NMR spectra of compounds **2**, **4a**,**b**,**i**, and mass spectra of compounds **3**, **4a**,**b** is available for the authorized users.

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