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Synthesis and structure elucidation of a series of pyranochromene chalcones and flavanones using 1D and 2D NMR spectroscopy and X-ray crystallography

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A series of novel pyranochromene chalcones and corresponding flavanones were synthesized. This is the first report on the confirmation of the absolute configuration of chromene-based flavanones using X-ray crystallography. These compounds were characterized by 2D NMR spectroscopy, and their assignments are reported herein. The 3D structure of the chalcone 3b and flavanone 4g was determined by X-ray crystallography, and the structure of the flavanone was confirmed to be in the *S* configuration at C-2. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: NMR; ¹H; ¹³C; X-ray crystallography; pyranochromene; chalcones; flavanones

Introduction

Chalcones and flavanones form a large and important group of naturally occurring secondary metabolites.^[1] Chalcones are important intermediates for the synthesis of biologically active compounds such as flavone, flavonol, flavanone, isoflavone and their derivatives.^[2] Besides having a physiological role in plants, flavonoids have also been reported to have a wide variety of biological activities, including anti-inflammatory, antiviral, antiprotozoal, antioxidant, cardiovascular and anticarcinogenic properties.^[2]

A five-membered prenyl moiety on a benzene ring cyclized with an oxygen atom on an adjacent position leads to a benzopyran or chromene molecule with a second such cyclization leading to a pyranochromene such as the naturally occurring octandrenolone,^[3,4] O-methyloctandrenolone,^[4,5] trans-3"',4"'dihydro-3"',4"'-dihydroxy-O-methyloctandrenolone,[4] trans-3",4"dihydro-3",4"-dihydroxy-O-methyloctandrenolone,^[4] flemiculosin,^[6] laxichalcone,^[7] 3-deoxy-MS-II^[3,8,9] and MS-II.^[3,8] The flavanone (4a) 3-deoxy-MS-II (Scheme 1), which incorporates pyranochromene moieties, was isolated from the methanolic extracts of the bark and leaf of Mundulea chapelieri and exhibited activity against a human ovarian cancer cell line.^[8] Shortly afterward, its synthesis was reported.^[3] The synthesis of six chalcones with an octandrenolone moiety was also reported.^[10] Several other pyranochromene chalcones and flavonoids were isolated from Mundulea suberosa and Mundulea sericea and have exhibited interesting biological activities including antimicrobial and ornithine decarboxylase activity.^[8,11-17] A pyranochromene chalcone, (-)-rubranine with prenyl groups on the pyran rings, was also isolated from Aniba rosaeodora.[18] Two series of prenylated chromenochalcones were also synthesized and tested for their antileishmanial and antimalarial activity where several compounds showed good activity.^[19,20]

In our ongoing study on synthesizing fluorinated pharmaceuticals, we have prepared several fluorinated chalcones and flavanones with the pyranochromene moiety. Herein, we report the NMR elucidation of these fluorinated pyranochromene chalcones and flavanones, which is slightly more complicated than the oxygenated or chlorinated molecules because of the fluorine atom being NMR active and coupling with both hydrogen and carbon. We used X-ray crystallography and NMR studies to provide a full structural elucidation of these novel pyranochromene chalcones and flavanones.

Experimental

Reagents and chemicals used in this study were purchased from Sigma-Aldrich via Capital Lab, South Africa and were reagent grade. All organic solvents were redistilled and dried according to standard procedures. Optical rotations were recorded using a PerkinElmer[™] Model 341 Polarimeter with a 10-cm flow tube. Melting points were measured using a Stuart scientific melting point apparatus SMP3. IR spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer with universal attenuated total reflectance sampling accessory. UV spectra were obtained on a Varian Cary UV-VIS spectrophotometer in chloroform. Highresolution mass data were obtained using a Bruker microTOF-O II ESI instrument operating at ambient temperatures, with a sample concentration of approximately 1 ppm. Thin-layer chromatography was performed using Merck Kieselgel 60F₂₅₄ plates. Crude compounds were purified with column chromatography using silica gel (60–120 mesh) as the stationary phase and varying combinations of solvents depending on the sample to be purified.

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Scheme 1. Synthetic scheme for the synthesis of pyranochromene flavanones **4a–h**. (i) 3-methyl-2-butenal, pyridine, 110 °C, reflux; (ii) substituted benzaldehydes, KOH, EtOH/H₂O, rt; and (iii) NaOAc, EtOH, 80 °C, reflux.

The ¹H and ¹³C NMR spectra were recorded at 298 K with 5- to 10-mg samples dissolved in 0.5 ml of CDCl₃ in 5-mm NMR tubes using a Bruker Avance^{III} 400-MHz NMR spectrometer (9.4 T; Bruker, Germany) (400.22 MHz for ¹H, 100.63 MHz for ¹³C and 376.58 Hz for ¹⁹F). The digital digitizer resolution was set at 22 for both the ¹H and ¹³C NMR experiments. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. The 1 H and ¹³C chemical shifts of the deuterated solvent were 7.24 and 77.0, respectively, referenced to the internal standard, TMS. For the ¹⁹F NMR spectra, the chemical shift of trifluorotoluene (0.05% in CDCl₃) was referenced at -62.73. For the ¹H NMR analyses, 16 transients were acquired with a 1-s relaxation delay using 32 K data points. The 90° pulse duration was 10.0 µs, and the spectral width was 8223.68 Hz. The ¹³C NMR spectra were obtained with a spectral width of 24 038.46 Hz using 64 K data points. The 90° pulse duration was of 8.40 µs. For the ¹⁹F NMR spectra, the spectral width was 89285.71 Hz using131 K data points, and the 90° pulse duration was 12.50 µs. For the 2D experiments including COSY, NOESY, HSQC and HMBC, all data were acquired with 4K×128 data points $(t_2 \times t_1)$. The mixing time for the NOESY experiment was 0.3 s, and the long range coupling time for the HMBC experiment was 65 ms. All data were analyzed using Bruker TopSpin 2.1 (2008) software.

Materials

The prenylated flavanones (**4a–h**) were prepared in rather moderate overall yields (30–55%) in a three-step reaction (Scheme 1) where 2',4',6'-trihydroxyacetophenone was prenylated at the 2' and 4' positions with 3-methyl-2-butenal in basic conditions under reflux resulting in the dichromene acetophenone intermediate 2,^[21] which then underwent a Claisen–Schmidt condensation reaction with various substituted benzaldehydes to produce chalcones **3a–h** in good yields (60–90%) before being cyclized to their corresponding flavanones **4a–h**.

For the synthesis of octandrenolone (1-(5-hydroxy-2,2,8,8-tetramethyl-2H,8H-pyrano[2,3-f]chromen-6-yl)ethanone) (**2**), the method in Pawar *et al.*^[21] was followed, and the NMR data were compared with that of an authentic sample prepared earlier.^[21]

The pyranochromene chalcones **3a–3h** were synthesized according to the methods reported earlier in Pawar *et al.*^[22], and the compounds were purified by flash column chromatography to produce pure brown solids. For the ¹H and ¹³C NMR data, refer to Tables 1 and 2.

1-(5-Hydroxy-2,2,8,8-tetramethyl-2H,8H-pyrano[2,3-f]chromen-6-yl)-3-phenylpropenone (3a)

Yield 90%; mp 99–100 °C. IR (neat) v_{max} = 2970, 2928, 1631, 1582, 1546 and 1132 cm⁻¹.

3-(2-Fluorophenyl)-1-(5-hydroxy-2,2,8,8-tetramethyl-2H,8Hpyrano[2,3-f]chromen-6-yl)-propenone (3b)

Yield 64%; mp 110–111 °C. ¹⁹F NMR (376 MHz, CDCl₃) δ –112.95; IR (neat) v_{max} = 2963, 2923, 1627, 1583, 1539, 1339, 1181, 1137 and 1109 cm⁻¹; HRMS *m/z* 429.1476 [M+Na]⁺ (calcd. for C₂₅H₂₃O₄FNa 429.1478).

3-(3-Fluorophenyl)-1-(5-hydroxy-2,2,8,8-tetramethyl-2H,8Hpyrano[2,3-f]chromen-6-yl)-propenone (3c)

Yield 90%; mp 150–151 °C. ¹⁹F NMR (376 MHz, CDCl₃) δ –112.63; IR (neat) υ_{max} = 2971, 2928, 1630, 1584, 1451, 1135 and 1112 cm⁻¹; HRMS *m/z* 429.1472 [M + Na]⁺ (calcd. for C₂₅H₂₃O₄FNa 429.1478).

3-(4-Fluorophenyl)-1-(5-hydroxy-2,2,8,8-tetramethyl-2H,8Hpyrano[2,3-f]chromen-6-yl)-propenone (3d)

Yield 90%; mp 143–144 °C. ¹⁹F NMR (376 MHz, CDCl₃) δ –109.92; IR (neat) υ_{max} = 2971, 2928, 1631, 1585, 1468, 1135 and 1113 cm⁻¹; HRMS *m/z* 429.1477 [M + Na]⁺ (calcd. for C₂₅H₂₃O₄FNa 429.1478).

3-(2,4-Difluorophenyl)-1-(5-hydroxy-2,2,8,8-tetramethyl-2H,8Hpyrano[2,3-f] chromen-6-yl)-propenone (3e)

Yield 74%; mp 154–155 °C. ¹⁹F NMR (376 MHz, CDCl₃) δ –106.57 and –108.54; IR (neat) υ_{max} = 2977, 2931, 1630, 1612, 1582 and 1136 cm⁻¹; HRMS *m/z* 447.1393 [M + Na]⁺ (calcd. for C₂₅H₂₂O₄F₂Na 447.1384).

1-(5-Hydroxy-2,2,8,8-tetramethyl-2H,8H-pyrano[2,3-f]chromen-6-yl)-3-(3-methoxyphenyl)-propenone (3f)

Yield 77%; mp 95–96 °C. IR (neat) v_{max} = 2975, 2924, 1640, 1625, 1586, 1534, 1465, 1153, 1131 and 1112 cm⁻¹; HRMS *m/z* 441.1671 [M + Na]⁺ (calcd. for C₂₆H₂₆O₅Na 441.1678).

1-(5-Hydroxy-2,2,8,8-tetramethyl-2H,8H-pyrano[2,3-f]chromen-6-yl)-3-(4-methoxyphenyl)-propenone (3g)

Yield 85%; mp 125–126 °C. IR (neat) $\upsilon_{max}\!=\!2977,\;2968,\;1602,\;1578,\;1532,\;1509,\;1145,\;1131$ and $1110\;cm^{-1}.$

Table 1.	¹ H NMR shifts of th	e pyranochromene	e acetophenone interme	ediate 2 and pyrano	chromene chalcones 3	la–3h			
					δ of ¹ H (J, Hz)				
No.	2*	3a*	Зb	Зс	3d	Зе	зf	3g	Зh
Ы	14.00 (s)	14.37 (s)	14.36 (s)	14.24 (s)	14.31 (s)	14.32 (s)	14.34 (s)	14.49 (s)	14.33 (s)
OCH ₃		I	Ι	I	Ι	Ι	3.84 (s)	3.85 (s)	3.91 (s)
GH₃	2.65 (s)	I	I	Ι	Ι	Ι	Ι	I	I
2	Ι	7.60 (s)	Ι	7.29–7.26 (m)	7.57 (dd, 8.6, 5.5)	Ι	7.13 (d, 1.7)	7.55 (d, 8.3)	Ι
e	I	7.40 (s)	7.12 (dd, 11.0, 8.8)	I	7.10 (t, 8.6)	6.95–6.85 (m)	I	6.93 (d, 8.3)	I
4	I	7.40 (s)	7.36-7.32 (m)	7.10-7.05 (m)	Ι	Ι	6.94 (dd, 8.08, 2.08)		6.98 (dt, 8.0, 1.2)
5	I	7.40 (s)	7.18 (t, 7.6)	7.38–7.34 (m)	7.10 (t, 8.6)	6.95–6.85 (m)	7.32 (t, 7.9)	6.93 (d, 8.3)	7.09 (t, 8.2)
9	I	7.60 (s)	7.57 (td,7.6, 1.4)	7.38–7.34 (m)	7.57 (dd, 8.6, 5.5)	7.54 (ddd, 8.5, 8.5, 6.4)	7.19 (d, 7.6)	7.55 (d, 8.3)	7.14 (dt, 7.3, 1.3)
7	Ι	7.76 (d, 15.7)	7.83 (d, 15.9)	7.68 (d, 15.7)	7.71 (d, 15.6)	7.76 (d, 15.9)	7.73 (d, 15.6)	7.76 (d, 15.6)	7.84 (d, 15.8)
8	I	8.10 (d, 15.7)	8.23 (d, 15.9)	8.06 (d, 15.7)	8.01 (d, 15.6)	8.17 (d, 15.9)	8.08 (d, 15.6)	8.00 (d, 15.6)	8.19 (d, 15.8)
1"	6.58 (d, 10.1)	6.61 (bs)	6.60 (d, 10.0)	6.61 (d, 10.0)	6.61 (d, 10.0)	6.60 (d, 9.9)	6.61 (d, 10.0)	6.61 (d, 9.9)	6.60 (d, 9.9)
2 "#	5.45 (d, 10.1)	5.48 (bs)	5.48 (d, 10.0)	5.49 (d, 10.0)	5.48 (d, 10.0)	5.48 (d, 9.9)	5.48 (d, 10.0)	5.47 (d, 9.9)	5.46 (d, 9.9)
4"/5" [†]	1.49 (s)	1.55 (s)	1.54 (s)	1.54 (s)	1.54 (s)	1.53 (s)	1.55 (s)	1.55 (s)	1.54 (s)
"L	6.65 (d, 10.1)	6.69 (bs)	6.69 (d, 9.9)	6.68 (d, 10.0)	6.68 (d, 10.0)	6.68 (d, 9.9)	6.69 (d, 10.0)	6.69 (d, 9.9)	6.68 (d, 9.9)
2 ‴#	5.43 (d, 10.1)	5.48 (bs)	5.47 (d, 9.9)	5.47 (d, 10.0)	5.47 (d, 10.0)	5.46 (d, 9.9)	5.47 (d, 10.0)	5.47 (d, 9.9)	5.47 (d, 9.9)
4‴/5 ^{‴†}	1.43 (s)	1.45 (s)	1.45 (s)	1.46 (s)	1.45 (s)	1.45 (s)	1.45 (s)	1.45 (s)	1.45 (s)
* NMR at	600 MHz; [#] and [†] ir	idicate resonances	that can be interchang	ed.					

3-(2-Fluoro-3-methoxyphenyl)-1-(5-hydroxy-2,2,8,8-tetramethyl-2H,8H-pyrano[2,3-f]chromen-6-yl)-propenone (3h)

Yield 65%; mp 122–123 °C. ¹⁹F NMR (376 MHz, CDCl₃) δ –136.22; IR (neat) υ_{max} = 2968, 2926, 1632, 1605, 1581, 1276, 1151, 1132 and 1113 cm⁻¹; HRMS *m/z* 459.1579 [M+Na]⁺ (calcd. for C₂₆H₂₅O₅FNa 459.1584).

General Procedure for the Synthesis of Pyranochromene Flavanones 4a-h

To a solution of sodium acetate (188 mg, 3.0 mmol) in ethanol (10 ml), pyranochromene chalcones **3a-h** (0.3 mmol) were added at room temperature. The reaction mixture was refluxed for 48 h at 80 °C. The solvent was distilled off under reduced pressure, and the residue was dissolved in water (20 ml). After acidifying with 2 M HCI (20 ml), the mixture was extracted with ethyl acetate (3 × 30 ml), washed with water and dried over anhydrous MgSO₄. Removal of the solvent followed by flash column chromatography on silica gel afforded the pure pyranochromene flavanones as yellow solids. For the ¹H and ¹³C NMR data, refer to Tables 3 and 4.

6,6,10,10-Tetramethyl-2-phenyl-2,3-dihydro-6H,10H-dipyrano [2,3-f;2',3'-h]chromen-4-one (4a)

Yield 55%; mp 144–145 °C. IR (neat) v_{max} =2923, 2853, 1729, 1677, 1637, 1571, 1434, 1363, 1136 and 1116 cm⁻¹.

2-(2-Fluorophenyl)-6,6,10,10-tetramethyl-2,3-dihydro-6H,10Hdipyrano[2,3-f;2',3'-h]chromen-4-one (4b)

Yield 38%; mp 148–150 °C. ^{19}F NMR (376 MHz, CDCl₃) δ –118.38; IR (neat) υ_{max} =2966, 2922, 1677, 1637, 1571, 1433, 1364, 1135 and 1117 cm $^{-1}$; HRMS m/z 429.1476 $[\text{M}+\text{Na}]^+$ (calcd. for C₂₅H₂₃O₄FNa 429.1478).

2-(3-Fluorophenyl)-6,6,10,10-tetramethyl-2,3-dihydro-6H,10H-dipyrano[2,3-f;2',3'-h]chromen-4-one (4c)

Yield 46%; mp 92–93 °C. ¹⁹F NMR (376 MHz, CDCl₃) δ –112.06; IR (neat) v_{max} = 2968, 2923, 1678, 1643, 1571, 1162, 1136 and 1118 cm⁻¹; HRMS *m*/*z* 429.1471 [M + Na]⁺ (calcd. for C₂₅H₂₃O₄FNa 429.1478).

2-(4-Fluorophenyl)-6,6,10,10-tetramethyl-2,3-dihydro-6H,10Hdipyrano[2,3-f;2',3'-h]chromen-4-one (4d)

Yield 36%; mp 112–113 °C. ¹⁹F NMR (376 MHz, CDCl₃) δ –113.29; IR (neat) v_{max} = 2968, 2924, 2854, 1681, 1638, 1572, 1512, 1462, 1436, 1132 and 1116 cm⁻¹; HRMS *m/z* 429.1475 [M + Na]⁺ (calcd. for C₂₅H₂₃O₄FNa 429.1478).

2-(2,4-Difluorophenyl)-6,6,10,10-tetramethyl-2,3-dihydro-6H,10H-dipyrano[2,3-f;2',3'-h]chromen-4-one (4e)

Yield 31%; mp 158–159°C. ¹⁹F NMR (376 MHz, CDCl₃) δ –109.62 and –114.22; IR (neat) υ_{max} = 2978, 2925, 1679, 1641, 1590, 1570, 1132 and 1113 cm⁻¹; HRMS *m/z* 447.1384 [M + Na]⁺ (calcd. for C₂₅H₂₂O₄F₂Na 447.1384).

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Table 2. ¹³	C NMR shifts of	pyranochrome	ne chalcones 2 and 3a–3	ßh					
					δ of ¹³ C (J,Hz)				
	2*	3a	Зb	Зс	3d*	Зе	Зf	39	Зһ
-	I	135.8	123.8 (d, 11.4)	138.2 (d, 7.6)	132.1 (d, 3.2)	120.3 (dd, 11.6, 3.8)	137.2	128.6	124.5 (d, 9.2)
7		129.1	161.9 (d, 252.6)	114.3 (d, 21.6)	130.1 (d, 8.6)	162.1 (dd, 243.4, 12.1)	113.1	130.1	151.8 (d, 252.7)
ñ		128.4	116.5 (d, 21.9)	163.3 (d, 245.0)	116.3 (d, 21.8)	104.6 (t, 25.6)	160.1	114.5	148.5 (d, 10.6)
4		130.2	131.4 (d, 8.8)	117.0 (d, 20.4)	163.9 (d, 249.6)	163.8 (dd, 239.5, 12.3)	116.8	161.7	114.6 (d, 2.1)
5		128.4	124.7 (d, 3.6)	130.6 (d, 8.3)	116.3 (d, 21.8)	112.2 (dd, 21.6,3.6)	130.1	114.5	124.2 (d, 4.8)
9		129.1	130.5 (d, 8.3)	124.5 (d, 2.8)	130.1 (d, 8.6)	131.5 (dd, 9.9, 5.0)	121.2	130.1	121.0 (d, 2.1)
7		142.3	135.4	140.5 (d, 2.5)	140.9	134.4	142.2	142.4	135.0 (d, 2.4)
8		127.8	130.5	129.1	127.6 (d, 1.7)	130.0 (dd, 8.6, 2.4)	128.0	124.9	130.6 (d, 7.7)
6	203.5	193.1	193.1	192.7	192.9	192.9	193.0	193.0	193.0
1,	105.7	106.1	106.1	106.1	106.1	106.1	106.1	106.1	106.1
7 ,	160.7	161.6	161.7	161.6	161.6	161.7	161.6	161.5	161.7
M,	102.5	102.8	102.8	102.8	102.8	102.8	102.8	102.8	102.8
4	155.2	155.5	155.6	155.7	155.5	155.7	155.5	155.3	155.6
Ω	102.4	102.7	102.7	102.7	102.7	102.7	102.7	102.7	102.7
6'	156.9	156.4	156.5	156.4	156.3	156.4	156.4	156.3	156.5
1″	116.6	116.8	116.6	116.7	116.8	116.6	116.4	116.8	116.6
2"#	125.5	125.6	125.2	125.6	125.6	125.6	125.6	125.5	125.5
3″‡	78.4	78.6	78.7	78.6	78.5	78.6	78.5	78.4	78.7
4 "/5" [†]	28.5	28.6	28.6	28.6	28.6	28.6	28.6	28.6	28.6
1‴	116.3	116.4	116.4	116.3	116.4	116.4	116.3	116.5	116.4
2‴#	124.9	124.9	125.5	125.0	124.9	125.1	124.9	125.4	125.1
3‴‡	78.3	78.5	78.6	78.5	78.4	78.5	78.4	78.3	78.5
4 ‴/5‴†	28.2	28.3	28.0	28.3	28.3	28.1	28.3	28.3	28.1
OCH ₃	33.4		Ι	Ι	Ι	Ι	55.4	55.6	55.6
* NMR at 6C	00 MHz; # , [‡] an	d [†] indicate tha	ıt assignments may be in	ıterchangeable.					

No. 4a 4b 4c 4d 4e 4					δ of ¹ H (/, Hz)			
2 5.39 (dd, 13.1, 28) 5.69 (dd, 12.9, 3.1) 5.39 (dd, 16.5, 2.8) 5.63 (dd, 16.5, 3.0) 5.36 (dd, 16.5, 3.0) 5.36 (dd, 16.5, 3.0) 5.37 (dd, 16.5, 3.0) 5.37 (dd, 16.5, 3.0) 5.37 (dd, 16.5, 3.0) 5.37 (dd, 16.5, 3.0) 2.77 (dd, 16.5, 13.1) 2.93 (dd, 16.5, 12.9) 2.94 (dd, 16.5, 13.1) 2.93 (dd, 16.5, 12.9) 2.94 2.94 2.02	ō	4a	4b	4c	4d	4e	4f*	49	4h
3a 2.77 (dd, 165, 2.8) 2.81 (dd, 16.6, 3.1) 2.77 (dd, 16.5, 2.9) 2.81 (dd, 16.6, 12.9) 2.93 (dd, 16.5, 13.0) 2.77 (dd, 16.5, 13.0) 2.77 (dd, 16.5, 13.0) 2.94 (dd, 16.5) 2 $7.42-736$ (m) $7.11-7.06$ (m) $ 7.09$ (t, 86.5) 6.85 (dd, 16.5, 2.5) 2.94 (dd, 16.5) 4 $7.42-736$ (m) $7.37-7.31$ (m) $7.07-7.02$ (m) $ 7.09$ (t, 86.5) 6.95 (dt, 10.2) 6.95 (dt, 10.2) 7.32 (dd, 13.9, 7.8) 7.09 (t, 86.6) $6.90-6.89$ (d, 10.3) 6 $7.42-736$ (m) $7.37-7.31$ (m) $7.07-7.02$ (m) 7.37 (dd, 13.9, 7.8) 7.09 (t, 8.6) $6.90-6.89$ (d, 10.3) 6 $7.42-7.36$ (m) 7.37 (dd, 13.9, 7.8) 7.09 (t, 8.6) 6.95 (dt, 10.2, 1.6) 7.32 (t, 8.2) 6 $7.42-7.36$ (m) 7.32 (dt, 13.9, 7.8) 7.09 (t, 8.6) 6.95 (dt, 10.0) 7.32 (t, 8.2)	2	.39 (dd, 13.1, 2.8)	5.69 (dd, 12.9, 3.1)	5.39 (dd, 12.8, 3.1)	5.37 (dd, 13.0, 2.9)	5.63 (dd, 12.9, 3.0)	5.36 (dd, 13.3, 2.9)	5.33 (dd, 13.1, 2.8)	5.70 (dd, 12.9, 2.9)
3b $2.96 (dd, 16.5, 13.1)$ $2.93 (dd, 16.6, 12.9)$ $2.93 (dd, 16.5, 12.8)$ $2.93 (dd, 16.5, 12.9)$ $2.94 (dd, 16.5)$ $7.37 (2dd, 8.5, 5.4)$ $7.21 (dt, 3.2, 5.4)$ $7.21 (dt, 3.2, 5.4)$ $7.22 (dt, 7.3)$ $7.37 (dd, 13.9, 7.8)$ $7.90 (t, 8.6)$ $6.90 - 6.89 (d, 10.0)$ $6.56 (d, 10.0)$ $6.57 (dd, 8.5, 5.4)$ $7.22 (d, 7.3)$ $7.32 (d, 7.3)$ $7.42 - 7.36 (m)$ $7.22 (m, 3.5, 7.3)$ $7.37 (dd, 13.9, 7.8)$ $7.09 (t, 8.6)$ $6.95 (dt, 10.0)$ $6.56 (d, 0.10.0)$ $5.46 (d, 10.0)$ $5.54 (d, 10.0)$ $5.57 (d, 9.9)$ $5.46 (d, 10.0)$ 7^{-1} $1.33 (s)$ $1.22 (s)$ $1.148 (s)$ $1.148 (s)$ $1.148 (s)$ 1.148	a 2	.77 (dd, 16.5, 2.8)	2.81 (dd, 16.6, 3.1)	2.77 (dd, 16.5, 3.1)	2.75 (dd, 16.5, 2.9)	2.78 (dd, 16.5, 3.0)	2.77 (dd, 16.5, 2.9)	2.73 (dd, 16.5, 2.8)	2.80 (dd, 16.6, 2.9)
2' $7.42-7.36$ (m) - 7.19 (d, 7.5) 7.42 (dd, 8.5 , 5.4) - 7.01 (s) 3' $7.42-7.36$ (m) $7.11-7.06$ (m) - 7.09 (r, 8.6) 6.85 (dr, 9.6 , 2.5) - - 4' $7.42-7.36$ (m) $7.37-7.31$ (m) $7.07-7.02$ (m) - - 6.90-6.89 (r) 5' $7.42-7.36$ (m) $7.37-7.31$ (m) $7.07-7.02$ (m) - - - 6.90-6.89 (r) 6' $7.42-7.36$ (m) $7.37-7.31$ (m) 7.09 (r, 8.6) 6.95 (dr, 10.2) 6.59 (dr, 10.2) 7.32 (r, 8.2) 7.32 (r, 8.2) 6' $7.42-7.36$ (m) 7.22 (r, 7.3) 7.37 (dd, $13.9, 7.8$) 7.09 (r, 8.6) 6.56 (dr, 10.0) 6.57 (dr, 10.0) 6.57 (dr, 10.0) 5.54 (dr, 10.0) 5.57 (dr, 9.9) 5.46 (dr, 10.0) 5.54 (dr, 10.0) 5.57 (dr, 10.0) 5.57 (dr, 10.0) 5.57 (dr, 9.9) 5.56 (dr, 9.9	b 2	.96 (dd, 16.5, 13.1)	2.93 (dd, 16.6, 12.9)	2.93 (dd, 16.5, 12.8)	2.93 (dd, 16.5, 13.0)	2.91 (dd, 16.5, 12.9)	2.94 (dd, 16.5, 13.3)	2.97 (dd, 16.5, 13.1)	2.93 (dd, 16.6, 12.9)
3' $7.42-7.36$ (m) $7.11-7.06$ (m) $ 7.09$ (t, 86) 6.85 (dt, 96, 2.5) $-$ 4' $7.42-7.36$ (m) $7.37-7.31$ (m) $7.07-7.02$ (m) $ 6.90-6.89$ (t, $10.2, 1.5$) 7.32 (t, 8.2) 5' $7.42-7.36$ (m) 7.22 (t, 7.3) 7.37 (dd, $13.9, 7.8$) 7.09 (t, 8.6) 6.95 (dt, $10.2, 1.5$) 7.32 (t, 8.2) 6' $7.42-7.36$ (m) 7.22 (t, 7.3) 7.37 (dd, $8.5, 5.4$) 7.57 (ddd, $8.4, 8.4, 6.4$) 7.02 (d, 7.3) 6' $7.42-7.36$ (m) 7.60 (td, $8.6, 1.5$) 7.19 (d, 7.5) 7.42 (dd, $8.5, 5.4$) 7.57 (dd, $8.4, 8.4, 6.4$) 7.02 (d, 7.3) 6' $7.42-7.36$ (m) 7.56 (td, 10.00) 6.57 (d, 10.00) 6.57 (d, 10.00) 5.54 (d, 10.00) 5.54 (d, 10.00) 5.54 (d, 10.00) 5.57 (d, 1	. 7	.42–7.36 (m)	I	7.19 (d, 7.5)	7.42 (dd, 8.5, 5.4)	Ι	7.01 (s)	7.37 (d, 8.6)	Ι
4' $7.42-7.36$ (m) $7.37-7.31$ (m) $7.07-7.02$ (m) $ 6.90-6.89$ (r) 5' $7.42-7.36$ (m) $7.37-7.31$ (m) $7.07-7.02$ (m) $ 6.90-6.89$ (r) 6' $7.42-7.36$ (m) 7.22 (t, $7.3)$ 7.37 (dd, $13.9, 7.8)$ 7.09 (t, 8.6) 6.95 (dt, $10.2, 1.6$) 7.32 (t, 8.2) 6' $7.42-7.36$ (m) 7.60 (rd, $8.6, 1.5$) 7.19 (d, 7.5) 7.42 (dd, $8.5, 5.4$) 7.57 (ddd, $8.4, 8.4, 6.4$) 7.02 (d, 7.3) 7'' 6.60 (d, 10.00) 6.58 (d, 10.00) 6.57 (d, 10.00) 6.57 (d, 10.00) 5.46 (d, 10.01) 5.546 (d, 10.01) 5.57 (d, 9.99) 5.546 (d, 10.01) 5.57 (d, 10.00)		.42–7.36 (m)	7.11–7.06 (m)	Ι	7.09 (t, 8.6)	6.85 (dt, 9.6, 2.5)	Ι	6.93 (d, 8.7)	Ι
5' 7.42-7.36 (m) 7.22 (t, 7.3) 7.37 (dd, 13.9, 7.8) 7.09 (t, 8.6) 6.95 (dt, 10.2, 1.6) 7.32 (t, 8.2, 7.3) 6' 7.42-7.36 (m) 7.60 (td, 8.6, 1.5) 7.19 (d, 7.5) 7.42 (dd, 8.5, 5.4) 7.57 (ddd, 8.4, 8.4, 6.4) 7.02 (d, 7.3) 7'' 6.60 (d, 10.0) 6.58 (d, 10.0) 6.57 (d, 10.0) 6.56 (d, 9.9) 6.60 (d, 10.0) 7^{**} 5.46 (d, 10.0)		.42–7.36 (m)	7.37-7.31 (m)	7.07–7.02 (m)	Ι	Ι	6.90–6.89 (m)	Ι	7.15–7.11 (m)
6' $7.42-7.36$ (m) 7.60 (td, 8.6, 1.5) 7.19 (d, 7.5) 7.42 (dd, 8.5, 5.4) 7.57 (ddd, 8.4, 6.4) 7.02 (d, 7.3) 1"# 6.60 (d, 10.0) 6.58 (d, 10.0) 6.57 (d, 10.0) 6.56 (d, 9.9) 6.60 (d, 10.1) 2" 5.46 (d, 10.0) 5.546 (d, 10.0) 5.547 (d, 9.9) 5.46 (d, 10.1) $4"^{\dagger}$ 1.53 (s) 1.52 (s) 1.52 (s) 1.52 (s) 1.52 (s) 1.52 (s) $4"^{\dagger}$ 1.53 (s) 1.49 (s) 1.48 (s) 1.49 (s) 1.46 (s) 5.50 (d, 10.0) 5.51 (d, 10.0) 5.57 (d, 10.0) 5.57 (d, 10.0) 5.57 (d, 9.9) <t< th=""><th>. 7</th><td>.42–7.36 (m)</td><td>7.22 (t, 7.3)</td><td>7.37 (dd, 13.9, 7.8)</td><td>7.09 (t, 8.6)</td><td>6.95 (dt, 10.2, 1.6)</td><td>7.32 (t, 8.2)</td><td>6.93 (d, 8.7)</td><td>6.99–6.95 (m)</td></t<>	. 7	.42–7.36 (m)	7.22 (t, 7.3)	7.37 (dd, 13.9, 7.8)	7.09 (t, 8.6)	6.95 (dt, 10.2, 1.6)	7.32 (t, 8.2)	6.93 (d, 8.7)	6.99–6.95 (m)
1^{**} 6.60 (d, 10.0) 6.58 (d, 10.0) 6.57 (d, 10.0) 6.57 (d, 10.0) 5.46 (d, 10.0) 5.57 (d, 9.9) 5.60 (d, 9.9) 5.56 (d, 9.9) 5.57 (d, 9.9) 5.56 (d, 9.9) 5.57 (d	. 7	.42–7.36 (m)	7.60 (td, 8.6, 1.5)	7.19 (d, 7.5)	7.42 (dd, 8.5, 5.4)	7.57 (ddd, 8.4, 8.4, 6.4)	7.02 (d, 7.3)	7.37 (d, 8.6)	7.15–7.11 (m)
2" 5.46 (d, 10.0) 5.46 (d, 10.0) 5.48 (d, 10.0) 5.46 (d, 10.0) 5.47 (d, 9.9) 5.46 (d, 10.0) 4" 1.53 (s) 1.52 (s) 1.52 (s) 1.52 (s) 1.52 (s) 1.52 (s) 1.52 (s) 5" 1.49 (s) 1"" 6.57 (d, 9.9) 6.57 ("# 6	.60 (d, 10.0)	6.58 (d, 10.0)	6.59 (d, 10.0)	6.57 (d, 10.0)	6.56 (d, 9.9)	6.60 (d, 10.0)	6.57 (d, 10.0)	6.57 (d, 10.0)
4^{*1} 1.53 (s) 1.52 (s) 1.49 (s) 1.40 (s) 5.50 (d, 9.9) 5.51 (d, 10.0) 5.51 (d	" 5	.46 (d, 10.0)	5.46 (d, 10.0)	5.48 (d, 10.0)	5.46 (d, 10.0)	5.47 (d, 9.9)	5.46 (d, 10.0)	5.44 (d, 10.0)	5.45 (d, 10.0)
5^{+1} 1.49 (s) 1.49 (s) 1.49 (s) 1.49 (s) 1.49 (s) 1^{m*} 6.57 (d, 9.0) 6.57 (d, 9.9) 5.50 (d, 9.9) 5.51 (d, 10.0) 5.51 (d, 9.9) 5.50 (d, 9.9) 5.51 (d, 9.9) 5.50	Ҡ 1	.53 (s)	1.52 (s)	1.52 (s)	1.51 (s)	1.52 (s)	1.52 (s)	1.52 (s)	1.51 (s)
$1^{m#}$ 6.57 (d, 10.0) 6.57 (d, 9.9) 2^{m} 5.50 (d, 10.0) 5.51 (d, 9.9) 5.51 (d, 9.9) 5.51 (d, 10.0) 5.50 (d, 9.9) 2^{m+} 1.46 (s)	Ҡ 1	.49 (s)	1.49 (s)	1.48 (s)	1.48 (s)	1.49 (s)	1.49 (s)	1.49 (s)	1.49 (s)
2 ^{<i>w</i>} 5.50 (d, 10.0) 5.51 (d, 9.9) 5.51 (d, 9.9) 5.49 (d, 10.0) 5.51 (d, 10.0) 5.50 (d, 9.9) $4^{w^{\dagger}}$ 1.46 (s) 1.46 (s) 1.46 (s) 1.46 (s) 1.46 (s) 1.44 (s)	<i>""</i> # 0	.57 (d, 10.0)	6.57 (d, 9.9)	6.57 (d, 9.9)	6.57 (d, 10.0)	6.55 (d, 10.0)	6.57 (d, 9.9)	6.56 (d, 10.0)	6.56 (d, 10.0)
4^{m+} 1.46 (s) 1.46 (s) 1.46 (s) 1.46 (s) 1.46 (s) 1.46 (s) 5^{m+} 1.44 (s) 1.44 (s) 1.44 (s) 1.44 (s) 1.44 (s) 1.44 (s)	" 5	.50 (d, 10.0)	5.51 (d, 9.9)	5.51 (d, 9.9)	5.49 (d, 10.0)	5.51 (d, 10.0)	5.50 (d, 9.9)	5.49 (d, 10.0)	5.50 (d, 10.0)
5^{m^+} 1.44 (s) 1.44 (s) 1.44 (s) 1.43 (s) 1.43 (s) 1.44 (s) 1.44 (s) 1.44 (s)	Ҡ 1	.46 (s)	1.46 (s)	1.46 (s)	1.45 (s)	1.46 (s)	1.46 (s)	1.45 (s)	1.45 (s)
	Ҡ 1	.44 (s)	1.44 (s)	1.44 (s)	1.43 (s)	1.44 (s)	1.44 (s)	1.43 (s)	1.43 (s)
OCH ₃ – – – – – – 3.83 (s)	ĞH₃	I	I	I	Ι	I	3.83 (s)	3.82 (s)	3.90 (s)

Table 4. ¹³C NMR shifts of pyranochromene flavanones 4a-h $\delta \text{ of}^1 \text{H} (J, \text{Hz})$ No. 4a 4b 4c **4**d 4e 4f* 4g 4h 2 791 78.5 79.0 78.9 73.5 (d, 3.1) 78.3 (d, 1.3) 73.1 (d, 2.6) 73.4 (d, 4.28) 3 46.1 45.0 46.0 46.0 44 9 46.2 45.9 44 9 188.9 4 188.9 188.5 188.3 188.6 188.3 189.1 188.6 5 154.5 154.5 154.5 154.4 155.4 154.5 154.4 154.5 6 102.5 102.6 102.5 102.5 102.5 102.6 102.5 102.6 7 156.1 156.1 156.1 156.2 156.1 156.2 156.1 156.2 8 104.8 104.9 104.9 104.8 105.0 104.9 104.7 104.9 9 157.6 157.5 157.2 157.4 157.3 157.6 157.7 157.5 10 105.7 105.7 105.6 105.7 105.6 105.8 105.7 105.7 139.3 126.7 (d, 12.9) 141.8 (d, 7.2) 135.1 (d, 3.3) 122.7 (dd, 13.1, 3.8) 127.5 (d, 10.2) 1' 140.9 131.3 2 1261 159.8 (d, 246.2) 113.1 (d, 22.5) 127.9 (d, 8.2) 163.0 (dd, 236.3, 12.0) 1277 149.6 (d, 246.4) 1184 3 1289 115.8 (d, 21.1) 163.1 (d, 245.0) 115.8 (d, 21.6) 104.3 (t, 25.3) 147.9 (d, 10.2) 160 1 114.2 4 128.6 130.1 (d, 8.2) 115.5 (d, 21.0) 162.8 (d, 245.7) 160.0 (dd, 237.0, 12.0) 159.9 124.5 (d, 4.9) 113.9 5' 128.8 124.6 (d, 3.6) 130.5 (d, 8.1) 115.8 (d, 21.6) 111.8 (dd, 21.2, 3.6) 130.0 114.2 113.4 (d, 1.6) 6' 126.1 127.4 (d, 3.7) 121.6 (d, 2.9) 127.9 (d, 8.2) 128.5 (dd, 9.7, 5.3) 111.9 127.7 118.3 (d, 2.6) 1″# 116.4 116.3 116.3 116.3 116.2 116.5 116.5 116.4 2″ 126.4 126.9 126.9 126.5 126.6 126.5 126.3 126.5 3″ 78.1 78.1 78.1 78.1 78.1 78.1 78.0 78.1 **4**"[†] 28.6 28.6 28.6 28.6 28.7 28.7 28.6 28.7 **5**"[†] 28.4 28.4 28.4 28.4 28.4 28.4 28.4 28.4 1‴# 1160 1160 1160 116.0 1159 116.0 1160 1160 2‴ 126.8 126.5 126.6 126.9 126.8 126.7 126.9 126.8 3‴ 77.9 78.0 78.0 77.9 78.0 77.9 77.9 77.9 4""† 28.3 28.3 28.3 28.3 28.3 28.3 28.3 28.3 **5**‴[†] 28.1 28.1 28.0 28.1 28.1 28.1 28.0 28.1 OCH₃ 55.4 55.5 56.5

* NMR frequency at 600 MHz; [#] and [†] indicate resonances that can be interchanged.

2-(3-Methoxyphenyl)-6,6,10,10-tetramethyl-2,3-dihydro-6H,10Hdipyrano[2,3-f;2',3'-h]chromen-4-one (4f)

Yield 40%; mp 80–81 °C. IR (neat) υ_{max} = 2969, 2923, 2853, 1678, 1638, 1570, 1431, 1361, 1134 and 1115 cm⁻¹; HRMS *m/z* 441.1672 $[M + Na]^+$ (calcd. for C₂₆H₂₆O₅Na 441.1678).

2-(4-Methoxyphenyl)-6,6,10,10-tetramethyl-2,3-dihydro-6H,10Hdipyrano[2,3-f;2',3'-h]chromen-4-one (4g)

Yield 46%; mp 141–142 °C. IR (neat) v_{max} =2975, 2923, 2853, 1684, 1634, 1613. 1592, 1571, 1245, 1136 and 1115 cm⁻¹; HRMS m/z 441.1674 [M + Na]⁺ (calcd. for C₂₆H₂₆O₅Na 441.1678).

2-(2-Fluoro-3-methoxyphenyl)-6,6,10,10-tetramethyl-2,3dihydro-6H,10H-dipyrano[2,3-f;2',3'-h]chromen-4-one (4h)

Yield 54%; mp 100–101 °C. ¹⁹F NMR (376 MHz, CDCl₃) δ –140.91; IR (neat) v_{max} = 2969, 2926, 1681, 1634, 1590, 1572, 1135, 1115 and 1088 cm⁻¹; HRMS m/z 459.1576 [M + Na]⁺ (calcd. for C₂₆H₂₅O₅FNa 459.1584).

Single Crystal X-ray Diffraction Analysis

A cube-shaped single crystal was selected and glued onto the tip of a glass fiber and mounted in a stream of cold nitrogen at 100 (1) K and centered in the X-ray beam using a video camera. The crystal evaluation and data collection were performed on a

Bruker Smart APEX II diffractometer with Mo Ka radiation $(\lambda = 0.71073 \text{ Å})$. The diffractometer to crystal distance was set at 4.00 cm. The initial cell matrix was obtained from three series of scans at different starting angles. Each series consisted of 12 frames collected at intervals of 0.5° in a 6° range with the exposure time of 10s per frame. The reflections were successfully indexed by an automated indexing routine built in the APEX II program suite. The final cell constants were calculated from a set of 6460 strong reflections from the actual data collection. Data collection method involved ω scans of width 0.5°. Data reduction was carried out using the program System Administrator's Integrated Network Tool+. The structure was solved by direct methods using SHELXS and refined. Non-H atoms were first refined isotropically and then by anisotropic refinement with full-matrix least-squares calculations based on F^2 using SHELXS. All H atoms were positioned geometrically and allowed to ride on their respective parent atoms. All H atoms were refined isotropically. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. The final least-squares refinement of 286 parameters against 5126 data resulted in residuals R (based on F2 for $l \ge 2\sigma$) and wR (based on F^2 for all data) of 0.0404 and 0.1035, respectively. The final difference Fourier map was featureless. The programs Olex-2 and Ortep-3 were used within the WinGX software package to prepare artwork representation. The molecular diagram is drawn with 50% probability ellipsoids.

Results and Discussion

The full characterization (¹H and ¹³C NMR assignments) of the pyranochromene chalcones **3a–h** and flavanones **4a–h** is presented in Tables 1–4, and the ¹H spectra of a representative fluorinated chalcone and fluorinated flavanone are presented in Figs 1 and 2. The spectra of these compounds were well resolved. With the aid of HSQC, HMBC, COSY and NOESY data as well as multiplicity patterns, the unambiguous chemical shift assignments were made.

For the pyranochromene chalcones, typical ¹H and ¹³C NMR resonances can be observed for the pyran rings and the α , β -unsaturated ketone moiety. Taking the 2-fluoro derivative (**3b**) as an example, the double bond of the α , β -unsaturated ketone moiety occurs as a distinct pair of doublets at δ 8.23 (H-7) and 7.83 (H-8) with a coupling constant of 15.9 Hz, typical of *trans* olefinic protons (Fig. 1). The carbonyl resonance (C-9) is distinctly separated from the other carbon resonances at δ 193.1 and shows HMBC correlations to both H-7 and H-8 (Fig. 3), confirming the assignments of the α , β -unsaturated ketone moiety. Because of conjugation between

the double bond and the carbonyl group, C-8 ($\delta_{\rm C}$ 130.5) is more shielded than C-7 ($\delta_{\rm C}$ 135.4) and is therefore assigned further upfield than C-7. This is, however, not the case for H-7 and H-8, and HSQC correlations show that H-8 appears more deshielded than H-7. A ³*J* correlation in the HMBC spectrum can also be observed between H-7 and C-2 and C-6, verifying the assignment of H-7. The H-8 resonance is more deshielded because of the through space deshielding effect of the oxygen on the nearby pyran ring.



Figure 3. HMBC correlations of compound 3b, the 2-fluoropyranochromene chalcone.



Figure 1. ¹H NMR spectrum of 2'-fluoropyranochromene chalcone (3b).



Figure 2. ¹H NMR spectrum of 2'-fluoropyranochromene flavanone (4b).

MRC

There are four resonances between 7.10 and 7.60. These are attributed to the aromatic proton resonances of the fluorinated aromatic ring B. C-7 shows an HMBC correlation to the doublet of triplets (dt) at $\delta_{\rm H}$ 7.57 (H-6). This doublet of triplets arises from the coalescing of the doublet of doublet of doublets (ddd) brought about by coupling with the fluorine atom and H-5 ($J_{H6, F} = J_{H6,H5} = 7.6$ Hz) and the meta coupling with H-4 ($J_{H4,H6} = 1.4$ Hz). The H-6 proton resonance shows a COSY correlation to another triplet also arising because of coalescing of the doublet doublet that arises by coupling with both H-6 and H-4 with $J_{H6,H5} = J_{H5,H4} = 7.5$ Hz. No meta coupling between H-5 and H-3 is observed. The other two aromatic resonances at $\delta_{\rm H}$ 7.32–7.36 (m) and $\delta_{\rm H}$ 7.12 (dd, J = 11.0 and 8.8 Hz) were assigned to H-4 and H-3, respectively, and could be distinguished by HMBC correlations between C-1 (d, J=11.4 Hz) and H-3. C-1 also showed HMBC correlations to H-5. $J_{H3,F}$ (11.0 Hz) was larger than $J_{H3,H4}$ (8.8 Hz). The C-3 carbon resonance was identified by an HSQC correlation with H-3 and was seen overlapping with C-1" and C-1" as a doublet at δ_{C} 116.5 (J=21.9 Hz). C-4, C-5 and C-6 were all identified similarly at $\delta_{\rm C}$ 131.4 (d, J = 8.8 Hz, meta C-F coupling), 124.7 (d, J = 3.6 Hz, para C-F coupling) and 130.5 (d, J = 8.3 Hz, meta C-F coupling), respectively. The fluorine bonded C-2 showed HMBC correlations with H-7, H-6, H-4 and H-3 and was identified as a large doublet at δ_{C} 162.0 (J = 252.5 Hz).

For the two pyran rings on the A ring (closer to the ketone), the H-2''/2''' resonances overlap as a pair of doublets, with four peaks for the two doublet resonances, the first and the third peak being assigned to H-2" and the second and fourth peak being assigned to H-2". These doublets occur at $\delta_{\rm H}$ 5.48 and $\delta_{\rm H}$ 5.47 and have coupling constants of 10.0 Hz, characteristic of *cis* olefinic protons and can be interchanged. The H-1" and H-1" proton resonances, although occurring close to each other, do not overlap and can be distinguished as two separate resonances at $\delta_{\rm H}$ 6.60 and $\delta_{\rm H}$ 6.69 (J = 10.0 Hz). The H-1" and H-2" and H-1" and H-2" resonances show clear coupling in the COSY spectrum. Both H-2" and H-2" show HMBC correlations to C-3' and C-5', respectively, at δ_{C} 102.80 and δ_{C} 102.76. However, both these sets of resonances can be interchanged as they occur so close to each other that it is difficult to tell them apart. The H-1" resonance was distinguished from the H-1" resonance by an HMBC correlation between H-1" and C-2' at $\delta_{\rm C}$ 161.8. The identification of H-1" and H-1" allowed the unambiguous assignments of C-4' (through an HMBC with

H-1"') and C-6' (HMBC with H-1"). The C-1' resonance at δ_C 106.17 was detected by an HMBC correlation to the 2'-hydroxy resonance at δ_H 14.36.

The corresponding carbon resonances of H-1" and H-1" were found at $\delta_{\rm C}$ 116.4 (C-1") and $\delta_{\rm C}$ 116.7 (C-1") in the HSQC spectrum. There are two methyl proton resonances for the four methyl groups because the methyl groups on each of the pyran rings are equivalent because of the planar nature of the molecule. Thus, H-4"/5" occurs at δ 1.54, and H-4"/5" occurs at δ 1.46. These methyl resonances show HMBC correlations to C-2"/C-2" and C-3" and C-3", the latter two carbon resonances occuring at $\delta_{\rm C}$ 78.7 and 78.6, which can be interchanged. The C-4"/5" and C-4"/5" and C-4"/5" are reflected in Fig. 3.

A crystal structure of **3b** (Fig. 4) was solved in the monoclinic space group P21/c, with one molecule in the asymmetric unit. The bond length and angles are in agreement with the expected average values for related compounds.^[21,22] The *trans* double bond is clearly evident for C-7 and C-8, and the 2'-hydroxy group is on the same side of the carbonyl group with weak intramolecular hydrogen bonds being experienced by the 2'-hydroxy and C-9 carbonyl group. Each of the methyl groups on a particular pyran ring is in a similar chemical environment being on different sides of the planar molecule. The fluorine atom is seen pointing toward the angular pyran ring. Both pyranochromene rings exist in a half chair conformation with $\Phi = 0.3779$ (11) Å, $\theta = 112.14$ (18)°, $\Psi = 219.32$ (19)°and $\Phi = 0.3460$ (11) Å, $\theta = 113.85$ (18)° and $\Psi = 146.4$ (2)°, respectively. This is similar to our previous reports on similar structures.^[21,22]

The cyclization of the chalcones to the flavanones is carried out with sodium acetate under reflux at 80 °C in ethanol. The spectra of the flavanones using **4b** as an example (Fig. 2) are typified by a doublet doublet at $\delta_{\rm H}$ 5.69 (H-2) deshielded by the oxygen and two double doublets at $\delta_{\rm H}$ 2.93 (H-3a) and 2.81(H-3b), respectively. The two protons at C-3 and the one proton at C-2 all couple with each other with $J_{\rm H-3a,H-3b}$ = 16.6 Hz, $J_{\rm H-3a,H-2}$ = 3.2 Hz and $J_{\rm H-3b,H-2}$ = 12.9 Hz. These coupling constants indicate that the H-2/H-3a dihedral angle is closer to 90° and the H-2/H-3b dihedral angle closer to 180°. These occurrences take place with the concomitant disappearance of the distinctive H-7 and H-8 pair of doublets discussed previously.

Interestingly enough, the change in structure from the pyranochromene chalcone to the flavanone led to differences in the NMR resonances of the pyran rings. In particular, whereas





Figure 5. ORTEP diagram of 4g.

H-2" and H-2" overlapped in the chalcones and H-1" and H-1" could clearly be distinguished, the opposite now occurs with the flavanones. As with the H-2"/H-2" resonances previously mentioned, the H-1"/H-1" resonances appear as a series of four peaks, the first and the third being the doublet of H-1" and the second and the fourth being the doublet of H-1". These occur at $\delta_{\rm H}$ 6.58 and $\delta_{\rm H}$ 6.57, respectively, with $J_{\rm H-1",2"}$ = 10.0 Hz and $J_{\rm H-1",2"}$ = 9.9 Hz. These coupling constants were used to distinguish the olefinic methine resonances on each of the rings.

Unlike in the chalcones where there was a clear correlation between H-1^{*m*} and C-2' that allowed us to assign each of the pyran ring resonances unambiguously, there is no correlation between H-1^{*m*} and C-9 in the flavanones to make this distinction. Therefore, each of the pyran ring resonances as well as C-5 and C-7 and C-6 and C-8 may be interchangeable. Nevertheless, H-1^{*m*} shows an HMBC correlation to C-6 and H-1^{*m*} an HMBC correlation to C-8. Because the planarity of the molecule changes in forming the flavanone, each of the methyl resonances in both the ¹H and ¹³C NMR spectra appears as separate resonances at $\delta_{\rm H}$ 1.52, 1.50, 1.46 and 1.44 and $\delta_{\rm C}$ 28.7, 28.4, 28.3 and 28.1. However, it is impossible to assign any one of these resonances to a specific methyl group, and these resonances are interchangeable. The chemical shifts and splitting patterns of the fluorinated aromatic ring of **4b** were very similar to that of the chalcone **3b**.

The crystal structure of a related flavanone **4g** (Fig. 5) with a *para* methoxy group on the phenyl ring shows the absolute stereochemistry to be in the S configuration at C-2. The dihedral angle between the axial H-2 and the axial H-3b is 137.8 (4)°, whereas the dihedral angle between the axial H-2 and the equatorial H-3a is 94.8 (3)°, which explains the coupling constants previously mentioned. Both the pyran rings are now in an angular position with the phenyl ring being out of the plane of the benzopyranone ring with the dihedral angle between the least-squares plane of the pyranochromene ring system and the phenyl ring being 40.65 (19)°. The flavanone core ring exists in the half chair conformation ($\Phi = 0.453$ (5) Å, $\theta = 53.8$ (6)° and $\Psi = 284.5$ (7)°.

Conclusion

A series of pyranochromene chalcones and flavanones were synthesized and characterized by 1D and 2D NMR spectroscopy and X-ray crystallography. The stereochemistry of C-2 for **4g** was shown to be in the *S* configuration for the flavanones, and because the NMR spectra of all the other compounds prepared with the same method are similar, the series of compounds is deduced to have the *S* configuration for C-2. The ¹H and ¹³C NMR assignments of the pyranochromene chalcones and flavanones were made with the aid of HSQC and HMBC data and will provide a reference point for other pyranochromene chalcones synthesized or isolated.

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