Research Article

Synthesis and Evaluation of Novel Fluorinated 2-Styrylchromones as Antibacterial Agents

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A range of fluorinated 2-styrylchromones (**5a–g**) of which six were new (**5a–f**) were prepared in three steps using the Baker-Venkataraman rearrangement along with two methoxylated derivatives (**5h–i**) and a methylenedioxy derivative (**5j**) and screened for their antibacterial activity using Gram-positive bacteria (*Staphylococcus aureus*, *sciuri*, and *xylosus* as well as *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumonia*). The compounds were most effective against *B. subtilis* followed by *S. aureus* and a single strain of *E. coli* (ATCC 25922). Difluorination on the phenyl ring was shown to enhance antibacterial activity, and fluorine substitution at the 6 position was shown to be far superior to substitution at the 7 position. In comparison to tetracycline, the activity indices of the fluorinated styrylchromones ranged from 0.50 to 0.75 against *B. subtilis*. The crystal structure of 2'-fluoro-2-styrylchromone is also presented, and the molecule was shown to be planar.

1. Introduction

Fluorinated compounds have a wide range of medical applications such as anti-inflammatory, antiviral, anti-HIV, antibacterial, anticancer, antimalarial, antidepressants, antipsychotics, anaesthetics, and steroids [1, 2]. Introducing fluorine atoms into drugs can also alter the rate and route of drug metabolism [1], and stereoelectronic factors associated with the fluorine atom can lead to changes in the biological action of molecules in comparison to its hydroxyl or hydrogen analogues [3]. The substitution of fluorine for hydrogen or hydroxy groups can lead to changes in the mechanism of the drug as well as enzyme inhibition [3]. The small size of the fluorine atom, the enhanced lipophilicity it imparts to the molecules, and the electronegativity of the atom often result in improved therapeutic drugs [2]. As part of an ongoing study on fluorinated pharmaceutical compounds, we have chosen to explore the antibacterial effects of fluorinated 2-styrylchromones.

The biological activities of 2-styrylchromones have recently been reviewed by Gomes et al. [4]. The 2-styrylchromones were shown to be A₃ adenosine receptor antagonists [5], have hepatoprotective activity [6], be potent antioxidants [7], have antiallergic properties [8], antiviral activity [9], and anticancer activity [10–12], and display xanthine oxidase inhibition to treat, for example, gout, hypertension, and hepatitis linked to xanthine oxidase activity [13].

The synthesis of these compounds has been reviewed by Silva et al. [14]. In one synthetic approach, it involves the aldol condensation between cinnamaldehydes and 2'-hydroxyacetophenones followed by an oxidative cyclisation [15]. It was also synthesised by the Baker-Venkataraman rearrangement, involving the O-acylation of 2'-hydroxyacetophenones with cinnamic acids, followed by rearrangement of the ester and then cyclisation into the styrylchromone [16]. They can also be made directly from 2'-hydroxyacetophenones with cinnamoyl chlorides [17].

FIGURE 1: The preparation of 2-styrylchromones **5a–j** from their corresponding acetophenones and benzaldehydes (i) malonic acid, piperidine, pyridine, 80–90°C, 4–5 h, (ii) pyridine, POCl₃, rt. 4–5 h, (iii) DMSO, KOH, rt. 2 h, and (iv) DMSO, PTSA, 90–95°C, 2–3 h.

The 2-styrylchromones have a structure analogous to the flavonoids, with an extra two-carbon olefinic bond between the chromone and the phenyl rings. Thus, instead of a phenyl group attached to the chromone portion as in the flavonoids, a styryl group is inserted instead (see **5** in Figure 1). Due to the double bond in the backbone of the structure, 2-styrylchromones are reactive molecules, being able to take part in pericyclic reactions acting as dienes forming xanthenes [18] and as dienophiles forming flavones with *ortho*-benzoquinodimethane [19]. They can also be transformed into pyrazolines [20, 21], 1,2,3-triazoles [22], pyrazoles [23–25], and pyrimidines [26].

To our knowledge, there have only been two studies on fluorinated styrylchromones, where the 6-fluoro styrylchromones have shown antirhinovirus activity [27] and the 4'-fluoro-, the 4'-trifluoromethyl-, and 4'-trifluoromethoxy-styrylchromones were shown to have antitumor activity [28]. We report here on the synthesis and antibacterial activity of a series of fluorinated 2-styrylchromones as well as the crystal structure for the 2'-fluoro-2-styrylchromone.

2. Material and Methods

2.1. General Experimental Procedures. Reagents and chemicals used in this study were purchased from Sigma Aldrich via Capital Laboratories, South Africa, and were reagent grade. All organic solvents were redistilled and dried according to

standard procedures. NMR spectra were recorded using a Bruker Avance^{III} 400 MHz spectrometer at room temperature with chemical shifts (δ) recorded against the internal standard, tetramethylsilane (TMS). 2D NMR spectroscopy (COSY, NOESY, HSQC, and HMBC) were used for the structural elucidation of the synthesised compounds. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with universal ATR sampling accessory. For GC-MS analyses, the samples were analysed on an Agilent GC-MSD apparatus equipped with DB-5SIL MS (30 m $\times$ 0.25 mm i.d., 0.25 μ m film thickness) fused-silica capillary column. Helium (at 2 mL min⁻¹) was used as a carrier gas. The MS was operated in the EI mode at 70 eV. Optical rotation was recorded using a Perkin Elmer, Model 341 Polarimeter. Melting points were recorded on an Ernst Leitz Wetzlar microhot stage melting point apparatus.

2.2. Typical Procedure for the Preparation of Cinnamic Acids.

For the preparation of the cinnamic acids **2a–c** and **2h–i**, the procedure in Qian et al. [29] was adopted with slight modifications. The required aromatic aldehydes (3.2 mmol), malonic acid (3.87 mmol), and piperidine (0.387 mmol) were dissolved in pyridine (10 mL) and stirred at 80–90°C for 4–5 hours. The pyridine was removed under vacuum, and the reaction mixture was poured into water (25 mL) and washed with HCl (3 $\times$ 10 mL). A precipitate formed which was filtered and washed thrice with hexane (3 $\times$ 10 mL), after which it

was dried under vacuum to afford the cinnamic acids **2a-c** and **2h-i** (Figure 1), whose ^1H NMR was consistent with that in the literature [30–34]. The cinnamic acids **2d-g** and **2j** were purchased from Sigma Aldrich via Capital Laboratories, South Africa.

2'-Fluorocinnamic acid (2a) yield 91%; mp 175–176°C (lit. 176.5–177°C [30]); **3'-fluorocinnamic acid (2b)** yield 84%, mp 166–167°C (lit. 167°C [35]); **4'-fluorocinnamic acid (2c)** yield 88%, mp 206–208°C (lit. 208°C [32]); **4'-methoxycinnamic acid (2h)** yield 92%, mp 172–173°C (lit. 173–175°C [33]); **3',4'-dimethoxycinnamic acid (2i)** yield 83%, mp 181–183°C (lit. 182–184°C [36]).

2.3. Typical Procedure for the Synthesis of Substituted 2-(Cinnamoyloxy) Acetophenones (3a-j). POCl₃ (15.6 mmol, 2.39 g) was added to a solution of the appropriate 2-hydroxyacetophenone (12.0 mmol) and the appropriate cinnamic acid (15.6 mmol) in dry pyridine (10 mL). The solution was stirred at 60–70°C for 3 h and then poured into ice and water (20 mL), and the reaction mixture acidified with HCl (pH 3–4). The obtained solid was removed by filtration, dissolved in EtOAc (100 mL), and purified by silica gel column chromatography using a 7 : 3 mixture of EtOAc : *n*-hexane as the eluent. The solvent was evaporated to dryness, and the residue recrystallized from EtOH, resulting in compounds **3a-j**.

2'-(2-Fluorocinnamoyloxy) Acetophenone (3a). Brown solid residue (90% yield); mp 68–70°C; IR (KBr) ν_{max} : 1682 (br C=O), 1627 (C=C), 1612 (aromatic C–C), 1483, 1456, 1284 (C–F), 1227 cm^{−1}; ^1H NMR (CDCl₃, 400 MHz) δ 8.00 (1H, d, J = 16.2 Hz, H- β), 7.85 (1H, dd, J = 7.9, 1.6 Hz, H-6'), 7.59 (1H, td, J = 7.9, 1.7 Hz, H-6''), 7.54 (1H, td, J = 7.6, 1.6 Hz, H-4'), 7.39–7.40 (1H, m, H-4''), 7.33 (1H, td, J = 7.6, 0.8 Hz, H-5'), 7.19 (1H, dd, J = 8.0, 0.8 Hz, H-3'), 7.18 (1H, t, J = 7.5 Hz, H-5''), 7.11 (1H, dd, J = 10.3, 8.8 Hz, H-3''), 6.76 (1H, d, J = 16.2 Hz, H- α), 2.55 (3H, s, CH₃-2); ^{13}C NMR (CDCl₃, 100 MHz) δ 197.7 (C-1), 165.1 (C=O), 161.8 (d, J_{CF} = 252.6 Hz, C-2''), 149.1 (C-2'), 140.0 (d, J = 2.7 Hz, C- β), 133.4 (C-4'), 132.2 (d, J = 14.2 Hz, C-4''), 131.3 (C-1'), 130.2 (C-6'), 129.4 (d, J = 2.7 Hz, C-6''), 126.1 (C-5'), 124.6 (d, J = 3.6 Hz, C-5''), 123.8 (C-3'), 122.2 (d, J = 11.6 Hz, C-1''), 119.4 (d, J = 6.9 Hz, C- α), 116.3 (d, J = 21.7 Hz, C-3''), 29.8 (C-2); ^{19}F NMR (CDCl₃, 376.5 MHz) δ −113.57; EIMS (probe) 70 eV, m/z (rel. int.): 284 M⁺ (3), 149 (100), 121 (63), 101 (65), 75 (15); calculated molecular mass: 284.28.

2'-(3-Fluorocinnamoyloxy) Acetophenone (3b). Brown solid residue (68% yield); mp 55–56°C; IR (KBr) ν_{max} : 1733 and 1673 (C=O), 1637 (C=C), 1444, 1136 (C–F), 1073 cm^{−1}; ^1H NMR (CDCl₃, 400 MHz) δ 7.83 (1H, dd, J = 7.6, 1.6 Hz, H-6'), 7.82 (1H, d, J = 16.0 Hz, H- β), 7.55 (1H, td, J = 7.8, 1.6 Hz, H-4'), 7.35–7.37 (2H, m, H-5', H-6''), 7.33 (1H, td, J = 7.7, 0.8, H-5''), 7.27 (1H, d, J = 9.6 Hz, H-2''), 7.17 (1H, dd, J = 8.0, 0.7 Hz, H-3'), 7.10 (1H, tt, J = 8.2, 2.0 Hz, H-4''), 6.55 (1H, d, J = 16.0 Hz, H- α), 2.55 (3H, s, CH₃-2); ^{13}C NMR (CDCl₃, 100 MHz) δ 197.7 (C-1), 164.9 (C=O), 163.0 (d, J_{CF} = 245.6 Hz, C-3''), 149.0 (C-2'), 145.8 (d, J = 2.7 Hz, C- β), 136.3 (d, J = 7.9 Hz, C-1''), 133.4 (C-4'), 131.2 (C-1'), 130.6 (d, J = 8.0 Hz, C-5''), 130.2 (C-6'), 126.2 (C-5'), 124.4 (d, J = 2.9 Hz, C-6''), 123.8 (C-3'), 118.3

(C- α), 117.7 (d, J = 21.3 Hz, C-4''), 114.6 (d, J = 21.9 Hz, C-2''), 30.0 (C-2); ^{19}F NMR (CDCl₃, 376.5 MHz) δ −112.27; EIMS (probe) 70 eV, m/z (rel. int.): 284 M⁺ (3), 149 (100), 121 (60), 101 (55), 75 (11); calculated molecular mass: 284.28.

2'-(4-Fluorocinnamoyloxy) Acetophenone (3c). Cream solid residue (72% yield); mp 80–82°C; IR (KBr) ν_{max} : 1729 (C=O), 1670 (C=O), 1624 (C=C), 1590, 1446, 1221 (C–F), 1202, 1159, 1050 cm^{−1}; ^1H NMR (CDCl₃, 400 MHz) δ 7.84 (1H, d, J = 16.0 Hz, H- β), 7.81 (1H, dd, J = 8.0, 1.6 Hz, H-6'), 7.58 (2H, dd, J = 8.6, 5.4 Hz, H-2''/6''), 7.53 (1H, dd, J = 8.0, 1.5 Hz, H-4'), 7.33 (1H, td, J = 8.1, 0.7 Hz, H-5'), 7.17 (1H, dd, J = 8.1, 0.7 Hz, H-3'), 7.09 (2H, t, J = 8.6 Hz, H-3''/5''), 6.58 (1H, d, J = 16.0 Hz, H- α), 2.54 (s, 3H, CH₃-2); ^{13}C NMR (CDCl₃, 100 MHz) δ 197.8 (C-1), 165.1 (C=O), 164.3 (d, J_{CF} = 250.7 Hz, C-4''), 149.1 (C-2'), 146.0 (C- β), 133.4 (C-4'), 131.3 (C-1'), 130.4 (d, J = 8.4 Hz, C-2''/6''), 130.32 (d, J = 3.6 Hz, C-1''), 130.2 (C-6'), 126.1 (C-5'), 123.8 (C-3'), 116.6 (d, J = 2.4 Hz, C- α), 116.2 (d, J = 21.9 Hz, C-3''/5''), 29.7 (C-2); ^{19}F NMR (CDCl₃, 376.5 MHz) δ −108.54; EIMS (probe) 70 eV, m/z (rel. int.): 284 M⁺ (21), 149 (100), 121 (25), 101 (20); calculated molecular mass: 284.28.

2'-(3,5-Difluorocinnamoyloxy) Acetophenone (3d). Brown solid residue (70% yield); mp 58–59°C; IR (KBr) ν_{max} : 1729 (C=O), 1682 (C=O), 1249 (C–F), 1201, 1122 cm^{−1}; ^1H NMR (CDCl₃, 400 MHz) δ 7.82 (1H, dd, J = 7.9, 1.0 Hz, H-6'), 7.75 (1H, d, J = 16.0 Hz, H- β), 7.55 (1H, td, J = 7.6, 1.1 Hz, H-4'), 7.34 (1H, t, J = 7.6 Hz, H-5'), 7.16 (1H, dd, J = 7.9, 0.8 Hz, H-3'), 7.08–7.10 (2H, m, H-2''/6''), 6.85 (1H, tt, J = 8.7, 2.3 Hz, H-4''), 6.64 (1H, d, J = 16.0 Hz, H- α), 2.54 (3H, s, CH₃-2); ^{13}C NMR (CDCl₃, 100 MHz) δ 197.6 (C-1), 164.6 (C=O), 163.2 (dd, J_{CF} = 248.3, 12.8 Hz, C-3''/5''), 148.9 (C-2'), 144.5 (t, J = 2.8 Hz, C- β), 137.3 (d, J = 9.5 Hz, C-1''), 133.5 (C-4'), 131.0 (C-1'), 130.3 (C-6'), 126.3 (C-5'), 123.7 (C-3'), 119.7 (C- α), 111.0 (dd, J = 18.8, 7.2 Hz, C-2''/6''), 105.9 (t, J = 25.4 Hz, C-4''), 29.5 (C-2); ^{19}F NMR (CDCl₃, 376.5 MHz) δ −108.75; EIMS (probe) 70 eV, m/z (rel. int.): 302 M⁺ (3), 167 (100), 139 (79), 119 (60); calculated molecular mass: 302.27.

4'-Fluoro-2'-(4-fluorocinnamoyloxy) Acetophenone (3e). Off-white solid residue (68% yield); mp 60–62°C; IR (KBr) ν_{max} : 1724 (C=O), 1679 (C=O), 1361 (C–O), 1225 (C–F), 1143 cm^{−1}; ^1H NMR (CDCl₃, 400 MHz) δ 7.87 (1H, dd, J = 8.8, 6.3 Hz, H-6'), 7.84 (1H, d, J = 16.0 Hz, H- β), 7.58 (2H, dd, J = 5.4, 2.0 Hz, H-2''/6''), 7.10 (2H, dd, J = 8.7, 2.5 Hz, H-3''/5''), 7.03 (1H, td, J = 8.8, 2.5 Hz, H-5'), 6.92 (dd, J = 8.9, 2.5 Hz, H-3'), 6.56 (1H, d, J = 16.0 Hz, H- α), 2.53 (3H, s, CH₃-2); ^{13}C NMR (CDCl₃, 100 MHz) δ 196.1 (C-1), 165.1 (C=O), 165.0 (d, J_{CF} = 254.1 Hz, C-4'), 164.4 (d, J_{CF} = 251.0 Hz, C-4''), 151.0 (d, J = 11.2 Hz, C-2'), 146.6 (C- β), 132.2 (d, J = 10.1 Hz, C-6'), 130.5 (d, J = 8.5 Hz, C-2''/6''), 130.2 (d, J = 3.0 Hz, C-1''), 127.6 (d, J = 3.5 Hz, C-1'), 116.3 (d, J = 21.9 Hz, C-3''/5''), 116.1 (d, J = 2.2 Hz, C- α), 113.3 (d, J = 21.2 Hz, C-5'), 111.7 (d, J = 24.0 Hz, C-3'), 29.7 (C-2); ^{19}F NMR (CDCl₃, 376.5 MHz) δ −103.81, −103.17; EIMS (probe) 70 eV, m/z (rel. int.): 302 M⁺ (3), 149 (100), 121 (92), 101 (75); calculated molecular mass: 302.27.

4'-Fluoro-2'-cinnamoyloxy Acetophenone (3f). Brown solid residue (86% yield); mp 98–100°C; IR (KBr) ν_{max} : 1730 (C=O),

1678 (C=O), 1634, 1598, 1247 (C–F), 1100, 886 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.88 (1H, d, J = 15.9 Hz, H- β), 7.86 (1H, dd, J = 8.6, 5.4 Hz, H-6'), 7.58 (2H, dd, J = 7.5, 1.9 Hz, H-2''/6''), 7.43–7.45 (3H, m, H-3''/4''/5''), 7.03 (1H, ddd, J = 8.6, 7.9, 2.5 Hz, H-5'), 6.94 (1H, dd, J = 8.9, 2.5 Hz, H-3'), 6.63 (1H, d, J = 15.9 Hz, H- α), 2.53 (3H, s, CH_3 -2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 196.1 (C-1), 166.4 (d, J_{CF} = 255.8 Hz, C-4'), 164.8 (C=O), 151.0 (C-2'), 145.4 (C- β), 133.9 (C-1''), 132.3 (d, J = 10.2 Hz, C-6'), 131.1 (C-4''), 129.0 (C-2''/6''), 128.5 (C-3''/5''), 127.0 (C-1'), 116.3 (C- α), 113.4 (d, J = 21.1 Hz, C-3'), 111.7 (d, J = 24.1 Hz, C-5'), 29.8 (C-2); ^{19}F NMR (CDCl_3 , 376.5 MHz) δ –103.91; EIMS (probe) 70 eV (m/z , rel. int.) 284 M^+ (3), 131 (100), 103 (71), 77 (39), 51 (11); calculated molecular mass: 284.28.

5'-Fluoro-2'-cinnamoyloxy Acetophenone (3g). Brown solid residue (90% yield); mp 81–83°C; IR (KBr) ν_{max} : 1731 (C=O), 1681 (C=O), 1632, 1581, 1131 (C–F), 983 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.88 (1H, d, J = 15.9 Hz, H- β), 7.58–7.59 (2H, m, H-2''/6''), 7.49 (1H, dd, J = 8.7, 3.0 Hz, H-3'), 7.39–7.41 (3H, m, H-3''/4''/5''), 7.23 (1H, dd, J = 7.8, 3.0 Hz, H-4'), 7.15 (1H, dd, J = 8.7, 4.7 Hz, H-6'), 6.64 (1H, d, J = 15.9 Hz, H- α), 2.53 (3H, s, CH_3 -2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 196.4 (C-1), 165.2 (C=O), 159.9 (d, J_{CF} = 245.1 Hz, C-5'), 147.8 (C-2'), 145.0 (C- β), 133.9 (C-1''), 132.6 (d, J = 6.1 Hz, C-1'), 131.0 (C-4''), 129.0 (C-3''/5''), 128.5 (C-2''/6''), 125.4 (d, J = 8.0 Hz, C-3'), 120.1 (d, J = 23.3 Hz, C-6'), 116.5 (d, J = 20.5 Hz, C-4'), 116.6 (C- α), 29.8 (C-2); ^{19}F NMR (CDCl_3 , 376.5 MHz) δ –115.35; EIMS (probe) 70 eV (m/z , rel. int.) 284 M^+ (30), 266 (8), 145 (25), 131 (100), 103 (44), 77 (21); calculated molecular mass: 284.28.

2'-(4-Methoxycinnamoyloxy) Acetophenone (3h). Off-white solid residue (91% yield); mp 97–99°C (lit. 103–105°C [20]); IR (KBr) ν_{max} : 1711 (C=O), 1680 (C=O), 1600 (C=C), 1509, 1581, 1246, 1189 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.83 (1H, d, J = 15.9 Hz, H- β), 7.80 (1H, dd, J = 8.0, 1.6 Hz, H-6'), 7.53 (2H, d, J = 8.7 Hz, H-2''/6''), 7.51 (1H, td, J = 7.6, 1.6 Hz, H-4'), 7.31 (1H, td, J = 8.0, 0.8 Hz, H-5'), 7.17 (1H, d, J = 8.0 Hz, H-3'), 6.91 (dd, J = 8.7, 2.6 Hz, H-3''/5''), 6.52 (1H, d, J = 15.9 Hz, H- α), 3.84 (3H, s, OCH_3), 2.54 (3H, s, CH_3 -2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 197.9 (C-1), 165.5 (C=O), 161.9 (C-4''), 149.3 (C-2'), 147.2 (C- β), 133.3 (C-4'), 131.5 (C-1'), 130.2 (C-2''/6''), 130.0 (C-6'), 126.8 (C-1''), 126.0 (C-5'), 123.8 (C-3'), 114.5 (C-3''/5''), 114.1 (C- α), 55.4 (OCH_3), 29.9 (C-2); EIMS (probe) 70 eV (m/z , rel. int.) 296 M^+ (7), 161 (100), 133 (49), 118 (16), 90 (15), 77 (16); calculated molecular mass: 296.10.

2'-(3,4-Dimethoxycinnamoyloxy) Acetophenone (3i). Off-white solid residue (56% yield); mp 99–101°C (lit. 97–99°C [37]); IR (KBr) ν_{max} : 1728 (C=O), 1683 (C=O), 1633 (C=C), 1515, 1254 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.82 (1H, d, J = 15.9 Hz, H- β), 7.81 (1H, dd, J = 7.8, 1.7 Hz, H-6'), 7.54 (td, J = 7.9, 1.6 Hz, H-4'), 7.31 (1H, td, J = 7.6, 0.9 Hz, H-5'), 7.17 (1H, d, J = 8.0 Hz, H-3'), 7.16 (1H, dd, J = 8.2, 1.9 Hz, H-6''), 7.10 (1H, d, J = 1.9 Hz, H-2''), 6.87 (1H, d, J = 8.2 Hz, H-5''), 6.52 (1H, d, J = 15.9 Hz, H- α), 3.91 (6H, s, 2 x OCH_3), 2.55 (3H, s, CH_3 -2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 197.9 (C-1), 165.5 (C=O), 151.7 (C-2'), 149.3 (C-4''), 149.2 (C-3''), 147.4 (C- β),

133.3 (C-4'), 131.5 (C-1'), 130.1 (C-6'), 127.0 (C-1''), 126.0 (C-5'), 123.8 (C-3'), 123.3 (C-6''), 114.4 (C- α), 111.1 (C-5''), 109.8 (C-2''), 55.9 (OCH_3), 56.0 (OCH_3), 29.9 (C-2); EIMS (probe) 70 eV (m/z , rel. int.) 326 M^+ (20), 191 (100), 163 (36), 148 (19), 77 (22); calculated molecular mass: 326.10.

2'-(3,4-Methylenedioxcinnamoyloxy) Acetophenone (3j). Off-white solid residue (59% yield); mp 99–100°C, IR (KBr) ν_{max} : 1715 (C=O), 1679 (C=O), 1600 (C=C), 1449, 1202 (C–F), 925 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.80 (1H, dd, J = 7.9, 1.6 Hz, H-6'), 7.78 (1H, d, J = 15.9 Hz, H- β), 7.53 (1H, td, J = 7.9, 1.6 Hz, H-4'), 7.31 (1H, td, J = 7.9, 1.6 Hz, H-5'), 7.16 (1H, d, J = 7.9 Hz, H-3'), 7.08 (1H, dd, J = 7.9, 1.6 Hz, H-6''), 7.05 (1H, dd, J = 7.9, 1.6 Hz, H-2''), 6.82 (1H, d, J = 7.9 Hz, H-5''), 6.47 (1H, d, J = 15.9 Hz, H- α), 6.01 (2H, s, OCH_2O), 2.54 (3H, s, CH_3 -2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 197.8 (C-1), 165.4 (C=O), 150.2 (C-2'), 149.2 (C-4''), 148.5 (C-3''), 147.1 (C- β), 133.3 (C-4'), 131.5 (C-1'), 130.1 (C-6'), 128.5 (C-1''), 126.0 (C-5'), 125.2 (C-3'), 123.8 (C-6''), 114.6 (C- α), 108.6 (C-5''), 106.7 (C-2''), 101.7 (OCH_2O), 29.9 (C-2); EIMS (probe) 70 eV (m/z , rel. int.) 310 M^+ (12), 175 (100), 145 (64), 117 (24), 89 (40), 63 (16); calculated molecular mass: 310.30.

2.4. Typical Procedure for the Synthesis of Substituted 3-Hydroxy-1-(2-hydroxyphenyl)-5-(phenyl)-2,4-pentadien-1-ones (4a-j). KOH powder (0.05 mmol, 2.8 g) was added to a solution of 2-cinnamoyloxy acetophenones **3a-j** (10.0 mmol) in Me_2SO (15 mL). The solution was stirred at room temperature until complete disappearance of the starting material, which was monitored by TLC. A typical reaction time was 2 h. The solution was then poured into ice water and HCl (20 mL) and the pH adjusted to 5. The obtained solid was removed by filtration, dissolved in EtOAc (150 mL), and purified by silica gel chromatography using EtOAc : *n*-hexane (7 : 3) as the eluent. The solvent was evaporated to dryness, and the residue recrystallized from EtOH, resulting in **4a-j**.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one (4a). Pale yellow solid residue (93% yield); mp 158–160°C, IR (KBr) ν_{max} : 1680 (C=O), 1626, 1581, 1483, 1283 (C–F), 1227 (C–O) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 14.55 (s, 3-OH), 12.17 (s, 2'-OH), 7.73 (1H, d, J = 16.0 Hz, H-5), 7.69 (1H, dd, J = 8.0, 1.4 Hz, H-6'), 7.54 (1H, td, J = 7.7, 1.5 Hz, H-6''), 7.43 (1H, ddd, J = 8.5, 7.1, 1.4 Hz, H-4'), 7.31–7.32 (1H, m, H-4''), 7.16 (1H, td, J = 7.6 Hz, H-5''), 7.09 (1H, t, J = 8.2 Hz, H-3''), 6.97 (1H, dd, J = 8.5, 0.7 Hz, H-3'), 6.88 (1H, t, J = 8.1 Hz, H-5'), 6.70 (1H, d, J = 16.0 Hz, H-4), 6.32 (1H, s, H-2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 196.5 (C-1), 174.0 (C-3), 162.6 (C-2'), 161.4 (d, J_{CF} = 253.8 Hz, C-2''), 136.1 (C-4'), 132.6 (d, J = 2.2 Hz, C-5), 131.4 (d, J = 8.8 Hz, C-4''), 129.2 (d, J = 3.0 Hz, C-6''), 128.6 (C-6'), 124.8 (d, J = 7.8 Hz, C-4), 124.5 (d, J = 3.5 Hz, C-5''), 123.1 (d, J = 11.5 Hz, C-1''), 119.06 (C-5'), 119.04 (C-1'), 118.7 (C-3'), 116.3 (d, J = 21.9 Hz, C-3''), 97.4 (C-2); ^{19}F NMR (CDCl_3 , 376.5 MHz) δ –114.18; EIMS (probe) 70 eV (m/z , rel. int.) 284 M^+ (26), 264 (7), 149 (100), 121 (59), 101 (20); calculated molecular mass: 284.28.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-pentadien-1-one (4b). Yellow solid residue (72% yield), mp

115–117°C, IR (KBr) $\nu_{\max}$: 1641 (C=O), 1626 (C=C), 1581, 1488, 1429, 1294 (C–F), 1236 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 14.55 (s, 3-OH), 12.15 (s, 2'-OH), 7.68 (1H, dd, J = 8.0, 2.0 Hz, H-6'), 7.58 (1H, d, J = 15.8 Hz, H-5), 7.44 (1H, ddd, J = 8.5, 7.1, 1.5 Hz, H-4'), 7.34 (1H, dd, J = 7.9, 5.7 Hz, H-5''), 7.30 (1H, d, J = 7.8 Hz, H-6''), 7.24–7.25 (1H, m, H-2''), 7.06–7.07 (1H, m, H-4''), 6.89 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, H-5'), 6.97 (1H, dd, J = 7.9, 0.9 Hz, H-3'), 6.56 (1H, d, J = 15.8 Hz, H-4), 6.32 (1H, s, H-2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 196.3 (C-1), 173.6 (C-3), 164.9 (d, J_{CF} = 247.2 Hz, C-3''), 162.7 (C-2'), 138.3 (d, J = 2.5 Hz, C-5), 137.3 (d, J = 7.8 Hz, C-1''), 136.0 (C-4'), 130.5 (d, J = 8.23 Hz, C-5''), 128.5 (C-6'), 124.1 (d, J = 2.8 Hz, C-6''), 123.5 (C-4), 119.1 (C-5'), 119.0 (C-1'), 118.8 (C-3'), 116.9 (d, J = 21.6 Hz, C-4''), 114.1 (d, J = 20.0 Hz, C-2''), 97.4 (C-2); ^{19}F NMR (CDCl_3 , 376.5 MHz) δ -112.32; EIMS (probe) 70 eV (m/z , rel. int.) 284 M^+ (25), 149 (100), 265 (8), 121 (88), 101 (17); calculated molecular mass: 284.28.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one (4c). Pale yellow solid residue (92% yield); mp 130–132°C, IR (KBr) $\nu_{\max}$: 1683 (C=O), 1627 (C=C), 1598, 1572, 1489, 1156 (C–F) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 14.62 (s, 3-OH), 12.17 (s, 2'-OH), 7.68 (1H, dd, J = 8.0, 1.4 Hz, H-6'), 7.60 (1H, d, J = 16.0 Hz, H-5), 7.52 (2H, dd, J = 8.9, 5.4 Hz, H-2''/6''), 7.44 (1H, ddd, J = 8.5, 7.1, 1.4 Hz, H-4'), 7.08 (2H, t, J = 8.9 Hz, H-3''/5''), 6.97 (1H, dd, J = 8.5, 0.9 Hz, H-3'), 6.88 (1H, ddd, J = 8.1, 7.1, 0.9 Hz, H-5'), 6.49 (1H, d, J = 16.0 Hz, H-4), 6.29 (1H, s, H-2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 196.0 (C-1), 174.3 (C-3), 163.8 (d, J_{CF} = 250.3 Hz, C-4''), 162.6 (C-2'), 138.5 (C-5), 135.9 (C-4'), 130.2 (d, J = 3.5 Hz, C-1''), 129.8 (d, J = 8.2 Hz, C-2''/6''), 128.5 (C-6'), 121.9 (C-4), 119.04 (C-1'/5'), 118.8 (C-3'), 116.2 (d, J = 21.9 Hz, C-3''/5''), 97.0 (C-2); ^{19}F NMR (CDCl_3 , 376.5 MHz) δ -109.55; EIMS (m/z , rel. int.) 284 M^+ (21), 149 (100), 121 (71), 265 (4), 163 (16), 101 (18); calculated molecular mass: 284.28.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,5-difluorophenyl)-2,4-pentadien-1-one (4d). Light brown solid residue (91% yield); mp 130–132°C, IR (KBr) $\nu_{\max}$: 1698 (C=O), 1658 (C=C), 1119 (C–F), 962, 843 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 14.46 (s, 3-OH), 12.10 (s, 2'-OH), 7.67 (1H, dd, J = 8.0, 1.4 Hz, H-6'), 7.51 (1H, d, J = 15.7 Hz, H-5), 7.45 (1H, ddd, J = 8.5, 7.2, 1.6 Hz, H-4'), 7.04 (1H, dd, J = 8.2, 2.2 Hz, H-2''/6''), 6.98 (1H, dd, J = 8.5, 1.1 Hz, H-3'), 6.89 (1H, ddd, J = 8.1, 7.2, 1.1 Hz, H-5'), 6.80 (1H, tt, J = 8.8, 2.2 Hz, H-4''), 6.55 (1H, d, J = 15.7 Hz, H-4), 6.32 (1H, s, H-2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 196.4 (C-1), 172.8 (C-3), 163.3 (d, J_{CF} = 247.8 Hz, C-3''/5''), 162.7 (C-2'), 138.3 (t, J = 9.5 Hz, C-1''), 137.0 (C-5), 136.2 (C-4'), 128.6 (C-6'), 124.8 (C-4), 119.1 (C-5'), 118.94 (C-1'), 118.85 (C-3'), 110.5 (dd, J = 18.5, 6.8 Hz, C-2''/6''), 105.1 (d, J = 25.6 Hz, C-4''), 97.9 (C-2); ^{19}F NMR (CDCl_3 , 376.5 MHz) δ -109.10; EIMS (m/z , rel. int.) 302 M^+ (28), 167 (100), 121 (76), 285 (10), 139 (29), 121 (76); calculated molecular mass: 302.27.

3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one (4e). Yellow solid residue (82% yield); mp 143–145°C; IR (KBr) $\nu_{\max}$: 1726 (C=O), 1629 (C=C), 1234 (C–F), 1157, 975, 824, 803, 789 cm^{-1} ; ^1H NMR (CDCl_3 ,

400 MHz) δ 14.42 (s, 3-OH), 12.47 (s, 2'-OH), 7.60 (1H, d, J = 15.9 Hz, H-5), 7.68 (1H, dd, J = 9.0, 6.4 Hz, H-6'), 7.52 (1H, dd, J = 8.7, 5.4 Hz, H-2''/6''), 7.08 (2H, t, J = 8.6 Hz, H-3''/5''), 6.65 (1H, dd, J = 10.4, 2.5 Hz, H-3'), 6.60 (1H, ddd, J = 8.8, 8.2, 2.2 Hz, H-5'), 6.51 (1H, d, J = 15.9 Hz, H-4), 6.20 (1H, s, H-2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 194.9 (C-1), 174.2 (C-3), 166.4 (d, J_{CF} = 212.1 Hz, C-4'), 165.2 (d, J = 14.1 Hz, C-2'), 163.0 (d, J_{CF} = 252.6 Hz, C-4''), 138.7 (C-5), 130.7 (d, J = 11.9 Hz, C-1''), 130.4 (d, J = 10.8 Hz, C-6'), 129.9 (d, J = 8.6 Hz, C-2''/6''), 121.7 (C-4), 116.2 (d, J = 21.9 Hz, C-3''/5''), 116.0 (C-1'), 107.3 (d, J = 22.6 Hz, C-5'), 105.3 (d, J = 23.6 Hz, C-3'), 96.7 (C-2); ^{19}F NMR (CDCl_3 , 376.5 MHz) δ -100.64, -109.57; EIMS (m/z , rel. int.) 302 M^+ (41), 149 (100), 283 (18), 207 (11), 163 (35), 139 (95), 121 (37), 101 (35); calculated molecular mass: 302.27.

3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-1-one (4f). Yellow solid residue (64% yield); mp 143–145°C; IR (KBr) $\nu_{\max}$: 1632 (C=O), 1579 (C=C), 1178 (C–F) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 14.48 (s, 3-OH), 12.55 (s, 2'-OH), 7.68 (1H, dd, J = 8.9, 6.4 Hz, H-6'), 7.64 (1H, d, J = 15.8 Hz, H-5), 7.53 (dd, J = 8.1, 2.1 Hz, H-2''/6''), 7.37–7.39 (3H, m, H-3''/4''/5''), 6.65 (dd, J = 10.3, 2.5 Hz, H-3'), 6.60 (1H, td, J = 8.0, 2.50 Hz, H-5'), 6.57 (1H, d, J = 15.8 Hz, H-4), 6.21 (1H, s, H-2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 194.9 (C-1), 174.4 (C-3), 165.2 (d, J_{CF} = 209.2 Hz, C-4'), 165.1 (d, J = 14.1 Hz, C-2'), 140.1 (C-5), 134.9 (C-1''), 130.5 (d, J = 11.7 Hz, C-6'), 130.2 (C-4''), 129.0 (C-3''/5''), 128.0 (C-2''/6''), 122.0 (C-4), 116.0 (C-1'), 107.3 (d, J = 22.7 Hz, C-5'), 105.3 (d, J = 23.4 Hz, C-3'), 96.8 (C-2); ^{19}F (CDCl_3 , 376.5 MHz) δ -100.72; EIMS (m/z , rel. int.) 284 M^+ (33), 131 (100), 265 (14), 139 (64), 103 (42), 77 (39), 51 (11); calculated molecular mass: 284.28.

3-Hydroxy-1-(5-fluoro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-1-one (4g). Yellow solid residue (90% yield); mp 118–120°C; IR (KBr): 1632 (C=O), 1550, 1487, 1248, 1180, 960, 781, 754 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 14.59 (s, 3-OH), 11.94 (s, 2'-OH), 7.66 (1H, d, J = 15.8 Hz, H-5), 7.54 (2H, dd, J = 7.9, 2.2 Hz, H-2''/6''), 7.39–7.41 (3H, m, H-3''/4''/5''), 7.34 (1H, dd, J = 9.0, 3.0 Hz, H-6'), 7.17 (1H, ddd, J = 9.2, 3.0, 1.3 Hz, H-4'), 6.93 (1H, dd, J = 9.1, 4.7 Hz, H-3'), 6.58 (1H, d, J = 15.8 Hz, H-4), 6.20 (1H, s, H-2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 194.8 (d, J = 2.7 Hz, C-1), 175.2 (C-3), 158.7 (C-2'), 155.1 (d, J_{CF} = 236.8 Hz, C-5'), 140.6 (C-5), 134.8 (C-1''), 130.4 (C-4''), 129.0 (C-3''/5''), 128.1 (C-2''/6''), 123.2 (d, J = 23.4 Hz, C-4'), 121.9 (C-4), 120.0 (d, J = 7.41 Hz, C-3'), 118.7 (d, J = 6.5 Hz, C-1'), 113.46 (d, J = 23.5 Hz, C-6'), 96.8 (C-2); ^{19}F (CDCl_3 , 376.5 MHz) δ -124.33; EIMS (probe) 70 eV (m/z , rel. int.) 284 M^+ (5), 131 (100), 103 (80), 77 (35); calculated molecular mass: 284.28.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-2,4-pentadien-1-one (4h). Yellow solid residue (90% yield); mp 167–169°C (lit. 162–164°C [38]); IR (KBr) $\nu_{\max}$: 1645 (C=O), 1599, 1514, 1462, 1258, 963, 828, 749 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 14.72 (s, 3-OH), 12.24 (s, 2'-OH), 7.67 (1H, dd, J = 8.0, 1.6 Hz, H-6'), 7.61 (1H, d, J = 15.8 Hz, H-5), 7.49 (2H, d, J = 8.8 Hz, H-2''/6''), 7.42 (1H, ddd, J = 8.5, 7.5, 1.6 Hz, H-4'),

6.96 (1H, dd, $J = 8.5$, 2.1 Hz, H-3'), 6.91 (2H, d, $J = 8.8$ Hz, H-3''/5''), 6.88-6.89 (1H, m, H-5'), 6.45 (d, $J = 15.8$ Hz, H-4), 6.26 (1H, s, H-2), 3.83 (s, 3H, OCH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 195.3 (C-1), 174.9 (C-3), 162.3 (C-2'), 161.1 (C-4''), 139.5 (C-5), 135.3 (C-4'), 129.8 (C-1''), 129.4 (C-2''/6''), 128.8 (C-6'), 119.4 (C-4), 118.9 (C-1'), 118.7 (C-5'), 118.44 (C-3'), 114.2 (C-3''/5''), 96.1 (C-2), 55.2 (OCH₃); EIMS (probe) 70 eV (m/z , rel. int.) 296 M⁺ (14), 161 (100), 207 (18), 133 (77), 118 (29); calculated molecular mass: 296.10.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-2,4-pentadien-1-one (4i). Yellow solid residue (84% yield); mp 130–132°C (lit. 136–138°C [37]); IR (KBr): 1685 (C=O), 1621, 1564, 1488, 1252, 1161; ¹H NMR (CDCl₃, 400 MHz) δ 14.71 (s, 3-OH), 12.23 (s, 2'-OH), 7.67 (1H, dd, $J = 8.1$, 1.5 Hz, H-6'), 7.59 (1H, d, $J = 15.8$ Hz, H-5), 7.42 (1H, ddd, $J = 8.5$, 8.3, 1.5 Hz, H-4'), 7.11 (dd, $J = 8.3$, 1.9 Hz, H-6''), 7.1 (d, $J = 1.8$ Hz, H-2''), 6.96 (1H, dd, $J = 8.4$, 0.7 Hz, H-3'), 6.87 (1H, d, $J = 8.3$ Hz, H-5''), 6.85 (1H, td, $J = 8.3$, 0.7 Hz, H-5'), 6.45 (1H, d, $J = 15.8$ Hz, H-4), 6.28 (1H, s, H-2), 3.92 (3H, s, 4'-OCH₃), 3.91 (3H, s, 3'-OCH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 195.6 (C-1), 175.0 (C-3), 162.5 (C-2'), 151.1 (C-3''), 149.3 (C-4''), 140.0 (C-5), 135.6 (C-4'), 128.4 (C-6'), 128.0 (C-1''), 122.6 (C-6''), 119.9 (C-4), 119.1 (C-1'), 119.0 (C-5'), 118.7 (C-3'), 111.2 (C-5''), 109.7 (C-2''), 96.5 (C-2), 56.0 (3''-OCH₃), 55.93 (4''-OCH₃); EIMS (probe) 70 eV (m/z , rel. int.) 326 M⁺ (15), 191 (100), 207 (16), 163 (49), 148 (19), 133 (18), 77 (23); calculated molecular mass: 326.12.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-methylenedioxyphenyl)-2,4-pentadien-1-one (4j). Light yellow solid residue (94% yield); mp 165–167°C; IR (KBr) $\nu_{\max}$: 1693 (C=O), 1621, 1602, 1566, 1484, 1446, 1239 (C-O), 1171, 1035, 925 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 14.68 (s, 3-OH), 12.21 (s, 2'-OH), 7.66 (1H, dd, $J = 8.0$, 1.6 Hz, H-6'), 7.55 (1H, d, $J = 15.8$ Hz, H-5), 7.42 (1H, ddd, $J = 8.5$, 8.0, 1.6 Hz, H-4'), 7.04 (1H, bd, $J = 0.35$ Hz, H-2''), 7.02 (1H, dd, $J = 8.0$, 1.2 Hz, H-6''), 6.96 (1H, dd, $J = 8.5$, 0.5 Hz, H-3'), 6.87 (1H, td, $J = 8.0$, 0.5 Hz, H-5'), 6.81 (1H, d, $J = 8.0$ Hz, H-5''), 6.39 (1H, d, $J = 15.8$ Hz, H-4), 6.26 (1H, s, H-2), 6.00 (2H, s, OCH₂O); ¹³C NMR (CDCl₃, 100 MHz) δ 195.7 (C-1), 174.8 (C-3), 162.6 (C-2'), 149.6 (C-3''), 148.5 (C-4''), 139.7 (C-5), 135.7 (C-4'), 129.5 (C-1''), 128.4 (C-6'), 124.6 (C-6''), 120.1 (C-4), 119.1 (C-1'), 119.0 (C-5'), 118.73 (C-3'), 108.7 (C-5''), 106.3 (C-2''), 101.6 (OCH₂O), 96.6 (C-2); EIMS (probe) 70 eV (m/z , rel. int.) 310 M⁺ (18), 175 (100), 207 (28), 145 (87), 157 (42), 117 (44), 89 (52), 43 (62); calculated molecular mass: 310.30.

2.5. Typical Procedure for the Synthesis of Substituted 2-Styrylchromones (5a–j). *p*-Toluenesulfonic acid (3.42 mmol, 0.59 g) was added to a solution of the appropriate 3-hydroxy-1-(2-hydroxyphenyl)-5-(phenyl)-2,4-pentadien-1-ones **4a–j** (6.5 mmol) in Me₂SO (20 mL). The reaction mixture was heated at 90°C for 2 h and then poured into ice and water (20 mL) and stirred for 10 min. The obtained solid was removed by filtration, dissolved in CHCl₃ (100 mL), and washed with a 20% aqueous solution of sodium thiosulphate (3 × 10 mL). The solvent was evaporated to dryness, and

the residue was purified by silica gel chromatography, using CHCl₃ : *n*-hexane (7 : 3) as the eluent, to produce **5a–j**.

2'-Fluoro-2-styrylchromone (5a). Light yellow solid residue (68% yield); mp 150–152°C; UV $\lambda_{\max}$ (CH₃OH) nm (log ϵ): 325 (3.37); IR (KBr) $\nu_{\max}$: 1682 (C=O), 1625, 1589 (C–C), 1562, 1464, 1391 (C–F), 1125, 968 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.17 (1H, dd, $J = 7.9$, 1.6 Hz, H-5), 7.72 (1H, d, $J = 16.2$ Hz, H- β), 7.66 (1H, ddd, $J = 8.6$, 7.2, 1.6 Hz, H-7), 7.59 (1H-td, $J = 7.6$, 1.5 Hz, H-6'), 7.53 (1H, d, $J = 8.3$ Hz, H-8), 7.37 (1H, td, $J = 7.9$, 0.8 Hz, H-6), 7.31-7.32 (1H, m, H-4'), 7.17 (1H, t, $J = 7.9$ Hz, H-5'), 7.11 (1H, ddd, $J = 9.2$, 8.2, 2.4 Hz, H-3'), 6.87 (1H, d, $J = 16.2$ Hz, H- α), 6.32 (1H, s, H-3); ¹³C NMR (CDCl₃, 100 MHz) δ 178.5 (C-4), 161.5 (C-2), 161.2 (d, $J_{\text{CF}} = 253.3$ Hz, C-2'), 156.0 (C-9), 133.9 (C-7), 131.3 (d, $J = 8.7$ Hz, C-4'), 129.5 (d, $J = 3.1$ Hz, C- β), 128.4 (d, $J = 2.7$ Hz, C-6'), 125.7 (C-5), 125.1 (C-6), 124.6 (d, $J = 3.6$ Hz, C-5'), 124.1 (C-10), 123.1 (d, $J = 11.7$ Hz, C-1'), 122.7 (d, $J = 6.5$ Hz, C- α), 117.9 (C-8), 116.2 (d, $J = 21.8$ Hz, C-3'), 111.2 (C-3); ¹⁹F NMR (CDCl₃, 376.5 MHz) δ -115.39; EIMS (m/z , rel. int.) 265 (M⁺-1) (100), 237 (12), 207 (20), 146 (36), 92 (25); HRMS (m/z) M⁺ 266.0733 (calculated for C₁₇H₁₁FO₂: 266.0743).

3'-Fluoro-2-styrylchromone (5b). Brown solid residue (62% yield), mp 105–108°C; UV $\lambda_{\max}$ (CH₃OH) nm (log ϵ): 325 (3.34); IR (KBr) $\nu_{\max}$: 1694 (C=O), 1622, 1579 (C–C), 1465, 1389 (C–F), 1247, 1122, 967, 775 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.18 (dd, $J = 7.9$, 1.6 Hz, H-5), 7.68 (dt, $J = 8.6$, 1.6 Hz, H-7), 7.52 (d, $J = 8.3$ Hz, H-8), 7.55 (1H, d, $J = 16.0$ Hz, H- β), 7.35–7.37 (3H, m, H-5'/6'/6), 7.26-7.27 (1H, m, H-2'), 7.06 (1H, d, $J = 6.8$ Hz, H-4'), 6.77 (1H, d, $J = 16.0$ Hz, H- α), 6.34 (1H, s, H-3); ¹³C NMR (CDCl₃, 100 MHz) δ 178.5 (C-4), 163.2 (d, $J_{\text{CF}} = 245.5$ Hz, C-3'), 161.2 (C-2), 156.0 (C-9), 137.3 (d, $J = 7.8$ Hz, C-1'), 135.6 (d, $J = 2.8$ Hz, C- β), 133.9 (C-7), 130.5 (d, $J = 8.3$ Hz, C-5'), 125.8 (C-5), 125.1 (C-6), 124.1 (C-10), 123.61 (d, $J = 2.7$ Hz, C-6'), 121.7 (C- α), 117.9 (C-8), 116.7 (d, $J = 21.6$ Hz, C-4'), 114.0 (d, $J = 22.0$ Hz, C-2'), 111.2 (C-3); ¹⁹F NMR (CDCl₃, 376.5 MHz) δ -108.99; EIMS (m/z , rel. int.) 265 (M⁺-1) (100), 237 (6), 209 (8), 173 (16), 146 (40), 121 (20), 92 (27); HRMS (m/z): 266.0726 M⁺ (calculated for C₁₇H₁₁FO₂: 266.0743).

4'-Fluoro-2-styrylchromone (5c). Off-white solid residue (70% yield), mp 158–160°C; UV $\lambda_{\max}$ (CH₃OH) nm (log ϵ): 328 (3.39); IR (KBr): 1691 (C=O), 1623, 1594, 1506, 1466, 1391 (C–F), 1224, 969, 817 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.01 (1H, dd, $J = 7.9$, 1.4 Hz, H-5), 7.81-7.82 (1H, m, H-7), 7.79 (2H, m, H-2'/6'), 7.70 (1H, d, $J = 16.2$ Hz, H- β), 7.69 (1H, d, $J = 8.5$ Hz, H-8), 7.47 (1H, t, $J = 7.4$ Hz, H-6), 7.28 (2H, t, $J = 8.8$ Hz, H-3'/5'), 7.16 (1H, d, $J = 16.2$ Hz, H- α), 6.46 (1H, s, H-3); ¹³C NMR (CDCl₃, 100 MHz) δ 177.1 (C-4), 162.88 (d, $J_{\text{CF}} = 240.6$ Hz, C4'), 161.7 (C-2), 155.4 (C-9), 135.4 (C- β), 134.4 (C-7), 131.6 (d, $J = 3.2$ Hz, C-1'), 130.0 (d, $J = 8.1$ Hz, C-2'/6'), 125.3 (C-6), 124.8 (C-5), 123.4 (C-10), 120.4 (C- α), 118.2 (C-8), 116.0 (d, $J = 24.3$ Hz, C-3'/5'), 110.1 (C-3); ¹⁹F NMR (CDCl₃, 376.5 MHz) δ -110.72; EIMS (m/z , rel. int.) 265 (M⁺-1) (100),

237 (8), 207 (13), 173 (10), 146 (39), 120 (18), 92 (20); HRMS (m/z): 266.0721 M^+ (calculated for $C_{17}H_{11}FO_2$: 266.0743).

3',5'-Difluoro-2-styrylchromone (5d). Light brown solid residue (92% yield); mp 114–116°C; UV $\lambda_{\max}$ (CH_3OH) nm ($\log \epsilon$) 322 (3.49); IR (KBr) $\nu_{\max}$: 1701 (C=O), 1615, 1586, 1465, 1390 (C–F), 1309, 1272, 1117 (C–F), 966, 847, 751 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (1H, dd, $J = 7.9, 1.6$ Hz, H-5), 7.72 (1H, ddd, $J = 8.5, 7.2, 1.6$ Hz, H-7), 7.51 (1H, d, $J = 8.3$ Hz, H-8), 7.49 (1H, d, $J = 16.0$ Hz, H- β), 7.39 (1H, td, $J = 7.9, 0.7$ Hz, H-6), 7.08 (2H, dd, $J = 8.1, 1.9$ Hz, H-2'/6'), 6.76 (1H, d, $J = 16.0$ Hz, H- α), 6.81 (1H, tt, $J = 8.7, 2.4$ Hz, H-4'), 6.34 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3 (C-4), 163.4 (dd, $J_{CF} = 247.8, 12.9$ Hz, C3'/5'), 160.6 (C-2), 156.0 (C-9), 138.3 (t, $J = 11.2$ Hz, C-1'), 134.0 (C-7), 134.2 (t, $J = 3.0$ Hz, C- β), 125.8 (C-5), 125.3 (C-6), 124.1 (C-10), 123.0 (C- α), 117.9 (C-8), 111.7 (C-3), 110.3 (dd, $J = 18.5, 7.2$ Hz, C-2'/6'), 105.0 (t, $J = 25.4$ Hz, C-4'); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -109.31; EIMS (m/z , rel. int.) 284 M^+ (100), 267 (82), 191 (40), 164 (63), 121 (58), 92 (65), 64 (21); HRMS (m/z): 284.0633 M^+ (calculated for $C_{17}H_{10}F_2O_2$: 284.0649).

7,4'-Difluoro-2-styrylchromone (5e). Pale yellow solid residue (45% yield); mp 182–184°C; UV $\lambda_{\max}$ (CH_3OH) nm ($\log \epsilon$) 322 (3.54); IR (KBr) $\nu_{\max}$: 1659 (C=O), 1621 (C=C), 1598, 1511, 1438, 1377 (C–F), 1233, 1140, 1112, 967 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (1H, dd, $J = 8.8, 6.4$ Hz, H-5), 7.56 (2H, dd, $J = 8.6, 5.6$ Hz, H-2'/6'), 7.53 (1H, d, $J = 16.0$ Hz, H- β), 7.20 (1H, dd, $J = 9.0, 2.4$ Hz, H-8), 7.11–7.12 (1H, m, H-6), 7.10 (2H, t, $J = 8.6$ Hz, H-3'/5'), 6.67 (1H, d, $J = 16.0$ Hz, H- α), 6.28 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4 (C-4), 167.1 (d, $J_{CF} = 210.1$ Hz, C-7), 165.0 (d, $J_{CF} = 251.6$ Hz, C-4'), 161.8 (C-2), 156.9 (C-9), 135.8 (C- β), 131.2 (d, $J = 3.6$ Hz, C-1'), 129.5 (d, $J = 8.2$ Hz, C-2'/6'), 128.2 (d, $J = 10.5$ Hz, C-5), 121.0 (C-10), 119.7 (C- α), 116.2 (d, $J = 21.9$ Hz, C-3'/5'), 113.7 (d, $J = 22.5$ Hz, C-6), 110.6 (C-3), 104.6 (d, $J = 25.5$ Hz, C-8); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -102.96, -109.89; EIMS (m/z , rel. int.) 283 (M^+ -1) (100), 267 (56), 255 (8), 227 (13), 173 (13), 146 (50), 120 (10); HRMS (m/z): 284.0642 (calculated for $C_{17}H_{10}F_2O_2$: 284.0649).

7-Fluoro-2-styrylchromone (5f). Off-white solid residue (94% yield); mp 116–118°C; UV $\lambda_{\max}$ (CH_3OH) nm ($\log \epsilon$) 312 (3.35); IR (KBr) $\nu_{\max}$: 1667 (C=O), 1599, 1538, 1438, 1382 (C–F stretch), 1143, 1012, 960 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ 8.19 (1H, dd, $J = 8.9, 6.4$ Hz, H-5), 7.59 (1H, d, $J = 16.0$ Hz, H- β), 7.58 (2H, dd, $J = 8.1, 1.5$ Hz, H-2'/6'), 7.39–7.41 (3H, m, H-3'/4'/5'), 7.21 (1H, dd, $J = 9.1, 2.4$ Hz, H-8), 7.10 (1H, td, $J = 8.6, 2.4$ Hz, H-6), 6.76 (1H, d, $J = 16.0$ Hz, H- α), 6.29 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.5 (C-4), 164.5 (d, $J_{CF} = 240.0$ Hz, C-7), 162.0 (C-2), 157.1 (d, $J = 13.2$ Hz, C-9), 137.2 (C- β), 134.9 (C-1'), 130.0 (C-4'), 129.05 (C-3'/5'), 128.2 (d, $J = 10.6$ Hz, C-5), 127.7 (C-2'/6'), 121.0 (C-10), 119.9 (C- α), 113.7 (d, $J = 22.6$ Hz, C-6), 110.6 (C-3), 104.6 (d, $J = 25.4$ Hz, C-8); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -103.04; EIMS (m/z , rel. int.) 265 (M^+ -1) (100), 250 (36), 237 (5), 209 (7), 128 (29), 102 (8); HRMS (m/z): 266.0730 (calculated for $C_{17}H_{11}FO_2$: 266.0743).

6-Fluoro-2-styrylchromone (5g). Light green solid residue (89% yield); mp 108–110°C; IR (KBr): 1710 (C=O), 1628, 1567, 1478, 1445, 1378, 1284, 1172, 967, 818, 751 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ 7.85 (1H, dd, $J = 8.2, 3.2$ Hz, H-5), 7.60 (1H, d, $J = 16.1$ Hz, H- β), 7.56 (2H, d, $J = 8.0$ Hz, H-2'/6'), 7.52 (1H, dd, $J = 9.10, 4.15$ Hz, H-8), 7.39–7.41 (4H, m, H-3'/4'/5'/7), 6.77 (1H, d, $J = 16.1$ Hz, H- α), 6.31 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.6 (d, $J = 2.3$ Hz, C-4), 162.0 (C-2), 159.5 (d, $J_{CF} = 245.1$ Hz, C-6), 152.20 (C-9), 137.4 (C- β), 134.9 (C-1'), 130.0 (C-4'), 129.1 (C-3'/5'), 127.7 (C-2'/6'), 125.5 (d, $J = 7.1$ Hz, C-10), 121.8 (d, $J = 25.13$ Hz, C-7), 120.03 (C- α), 119.9 (d, $J = 7.9$ Hz, C-8), 110.7 (d, $J = 23.4$ Hz, C-5), 109.9 (C-3); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -115.51; EIMS (m/z , rel. int.) 265 (M^+ -1) (100), 249 (43), 237 (9), 209 (12), 128 (56); calculated molecular mass: 266.67.

4'-Methoxy-2-styrylchromone (5h). Yellow solid residue (90% yield); mp 140–141°C (lit. 139–140 [11]); UV $\lambda_{\max}$ (CH_3OH) nm ($\log \epsilon$) 354 (3.33); IR (KBr) $\nu_{\max}$: 1645 (C=O), 1599, 1514, 1462, 462, 1258, 963, 828, 749 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (1H, dd, $J = 8.0, 1.6$ Hz, H-5), 7.65 (1H, ddd, $J = 8.6, 7.1, 1.6$ Hz, H-7), 7.55 (1H, d, $J = 16.0$ Hz, H- β), 7.52 (1H, d, $J = 8.6$ Hz, H-8), 7.48 (2H, d, $J = 8.7$ Hz, H-2'/6'), 7.36 (1H, t, $J = 8.0$ Hz, H-6), 6.92 (2H, d, $J = 8.7$ Hz, H-3'/5'), 6.64 (1H, d, $J = 16.0$ Hz, H- α), 6.28 (1H, s, H-3), 3.84 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.5 (C-4), 162.3 (C-2), 161.1 (C-4'), 156.0 (C-9), 136.7 (C- β), 133.6 (C-7), 131.0 (C-1'), 129.3 (C-2'/6'), 125.7 (C-5), 124.9 (C-6), 124.2 (C-10), 117.90 (C- α), 117.85 (C-8), 114.5 (C-3'/5'), 109.9 (C-3), 55.4 (OCH_3); EIMS (m/z , rel. int.) 277 (M^+ -1) (100), 247 (21), 207 (19), 158 (38), 115 (55); calculated molecular mass: 278.30.

3',4'-Dimethoxy-2-styrylchromone (5i). Yellow solid residue (55% yield); mp 162–163°C (lit. 163–164°C [11]); UV $\lambda_{\max}$ (CH_3OH) nm ($\log \epsilon$) 367 (3.18); IR (KBr) $\nu_{\max}$: 1682 (C=O), 1617, 1558, 1509, 1464, 1381, 1261, 1138, 1025, 965, 780, 759 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ 8.01 (1H, dd, $J = 7.9, 1.7$ Hz, H-5), 7.81 (1H, ddd, $J = 8.2, 7.2, 1.7$ Hz, H-7), 7.70 (1H, d, $J = 8.2$ Hz, H-8), 7.65 (1H, d, $J = 16.0$ Hz, H- β), 7.47 (1H, ddd, $J = 7.9, 7.2, 0.7$ Hz, H-6), 7.36 (1H, d, $J = 1.7$ Hz, H-2'), 7.27 (1H, dd, $J = 8.3, 1.7$ Hz, H-6'), 7.11 (1H, d, $J = 16.0$ Hz, H- α), 7.02 (1H, d, $J = 8.3$ Hz, H-5'), 6.40 (1H, s, H-3), 3.80 (3H, s, 3'- OCH_3), 3.83 (s, 3H, 4'- OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0 (C-4), 162.3 (C-2), 155.4 (C-9), 150.5 (C-4'), 149.0 (C-3'), 136.9 (C- β), 134.2 (C-7), 127.8 (C-1'), 125.2 (C-6), 124.7 (C-5), 123.4 (C-10), 122.3 (C-6'), 118.1 (C-8), 118.0 (C- α), 111.7 (C-5'), 109.9 (C-2'), 109.2 (C-3), 55.5 (2 $\times$ OCH_3); EIMS (m/z , rel. int.) 308 (M^+) (100), 277 (22), 250 (10), 221 (14), 188 (70), 121 (19); calculated molecular mass: 308.33.

3',4'-Methylenedioxy-2-styrylchromone (5j). Yellow solid residue (92% yield); mp 209–210°C (lit. 209–210°C [11]); UV $\lambda_{\max}$ (CH_3OH) nm ($\log \epsilon$) 329 (3.36); IR (KBr) $\nu_{\max}$: 1694 (C=O), 1625, 1461, 1499, 1447, 1383, 1251, 845 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ 8.17 (1H, d, $J = 7.6$ Hz, H-5), 7.65 (1H, ddd, $J = 8.1, 7.1, 1.0$ Hz, H-7), 7.51 (1H, d, $J = 7.8$ Hz, H-8), 7.50 (1H, d, $J = 16.1$ Hz, H- β), 7.37 (1H, t, $J = 7.5$, H-6), 7.08 (1H, s, H-2'), 7.05 (1H, d, $J = 8.1$ Hz, H-6'), 6.81 (1H, d,

$J = 8.1$ Hz, H-5'), 6.59 (1H, d, $J = 16.1$, H- α), 6.28 (1H, s, H-3), 6.01 (2H, s, OCH₂O); ¹³C NMR (CDCl₃, 100 MHz) δ 178.5 (C-4), 162.0 (C-2), 156.0 (C-9), 149.3 (C-3'), 148.5 (C-4'), 136.7 (C- β), 133.7 (C-7), 129.5 (C-1'), 125.7 (C-5), 125.0 (C-6), 123.9 (C-6'), 123.3 (C-10), 118.4 (C- α), 117.8 (C-8), 110.2 (C-3), 108.7 (C-5'), 106.2 (C-2'), 101.6 (OCH₂O); EIMS (m/z , rel. int.) 291 ($M^+ - 1$) (100), 275 (55), 233 (18), 205 (24), 172 (67), 114 (29); calculated molecular mass: 292.29.

2.6. X-Ray Crystallographic Study. Single-crystal X-ray diffraction data were collected on a Bruker KAPPA APEX II DUO diffractometer using graphite-monochromated Mo-K α radiation ($\chi = 0.71073$ Å). Data collection was carried out at 173(2) K. Temperature was controlled by an Oxford Cryostream cooling system (Oxford Cryostat). Cell refinement and data reduction were performed using the program SAINT [39]. The data were scaled, and absorption correction was performed using SADABS [40]. The structure was solved by direct methods using SHELXS-97 [40] and refined by full-matrix least-squares methods based on F^2 using SHELXL-97 [40] and using the graphics interface program X-Seed [41, 42]. The programs X-Seed and POV-Ray were both used to prepare molecular graphic images. All nonhydrogen atoms were refined anisotropically, and all hydrogen atoms could be found in the difference electron density maps but were placed in idealised positions and refined in riding models with U_{iso} set at 1.2 times those of their parent atoms and at a distance (C-H) of 0.95 Å. The structure was refined to a R factor of 0.0503.

CCDC 897969 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

2.7. Antibacterial Assay. *In vitro* evaluation of antibacterial activity was carried out on all synthesized, fluorinated, and oxygenated 2-styrylchromones by the disc diffusion method as described by Bauer et al. [43] against the Gram-positive bacteria, *Bacillus subtilis*, *Enterococcus faecium*, and three *Staphylococcus* species, *aureus*, *sciuri*, and *xylosus*, and the Gram-negative bacteria, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. The standard antibiotics, tetracycline (Te) and ampicillin (Amp), were used as controls and for comparison. Briefly, Mueller Hilton agar was prepared (38 g in 1 L of water) and poured into prelabeled sterile Petri dishes, which were then allowed to set and dry at room temperature. The bacterial organisms were standardized using a 0.5 McFarland standard turbidity and then swabbed onto the agar plates. Paper discs with dissolved sample and a control disc was placed onto the agar plates, which were inverted and incubated at 35–37°C for 24 hours. The diameter of the inhibition zones were then measured in mm. The tests were done in triplicate, and the results were reported as means of at least three determinations. The results are summarized in Tables 2 and 3.

The activity index of the product 2-styrylchromones was calculated as follows: Activity index (A.I.) = zone of inhibition

of compound/Zone of inhibition obtained for the standard antibiotic drug.

3. Results and Discussion

3.1. Chemistry. Seven fluorinated 2-styrylchromones of which six (**5a–f**) were novel were prepared in good overall yields of between 60 and 90% with only one compound (**5e**) having a yield of 45%. The synthesis was carried out according to the three-step sequence shown in Figure 1 and based on the Baker-Venkataraman rearrangement [16]. This involved the formation of the desired 2'-cinnamoyloxyacetophenones from substituted *ortho*-hydroxyacetophenones and cinnamic acid derivatives in pyridine using POCl₃ as a condensing agent. A strong base such as potassium hydroxide abstracts a proton from the methyl ketone, and the resultant carbanion attacks the ester carbonyl resulting in the conversion of the cinnamoyloxyacetophenones to the ketoenols. A ring chain tautomerism then occurs in this intermediate which is subsequently protonated by the strong catalyst *para*-toluene sulfonic acid, and attack by the 2'-hydroxy group ultimately results in the more stable chromone product by elimination. The cinnamic acids, **2a–c** and **2h–i**, were prepared by an aldol condensation and elimination reaction from the corresponding benzaldehydes and malonic acid before being reacted with the corresponding acetophenones.

The series of 2-styrylchromones synthesized contained a single fluorine atom on the *ortho*-, *meta*-, and *para*-positions (**5a–c**) of the phenyl ring, two fluorine atoms at the 3' and 5' positions on the phenyl ring (**5d**), fluorine atoms on both of the aromatic rings (at the 7 and 4' positions) (**5e**), and a single fluorine atom on the 6 (**5f**) and 7 (**5g**) positions on the chromone ring. These substitution patterns were chosen to observe the effect of fluorine at different positions on the phenyl ring as well as the effect of fluorine on the chromone ring. The difluorinated compounds would provide information on multiple sites of the molecule as well as substitution on both the phenyl and chromone rings simultaneously. Two methoxylated 2-styrylchromones, the 4'-methoxy- and the 3',4'-dimethoxy-2-styrylchromones as well as the 3',4'-methylenedioxy-2-styrylchromone (**5h–j**) were also synthesized to test alongside the fluorinated styrylchromones for comparison.

The structures of the prepared compounds were elucidated using 1D and 2D NMR spectroscopies along with mass spectrometry and IR spectroscopy. Compounds **5g–j** and their intermediates were all prepared previously [11, 27]; however only the NMR data for **4g** and **5g** [27], **3h** and **4h** [20] and **3i** and **4i** [37] is available in the literature. Furthermore, only the ¹H NMR data is given for **5g** [27], and only the ethylene resonance is reported for **5h–j** [11]. The NMR data for **3g**, **3j**, **4j**, and **5g–j** is therefore also reported here along with the new compounds **5a–f** and their intermediates **3a–f** and **4a–f**, to provide a complete set of NMR data for all the synthesized 2-styrylchromones and their intermediates.

The cinnamoyloxyacetophenone (**3a**) was established by the presence of α and β unsaturated proton resonances in the ¹H NMR spectrum at δ_H 6.76 and 8.00 as two doublets

with large coupling constants of 16.2 Hz, typical of *trans* olefinic protons, a methyl singlet at δ_{H} 2.55, and aromatic protons between δ_{H} 7.11 and 7.85. The structure of **3a** was further supported by two carbonyl resonances in the ^{13}C NMR spectrum at δ_{C} 197.7 for the ketone and δ_{C} 165.1 for the ester carbonyl. The aromatic carbon to which fluorine was attached was detected at δ_{C} 161.8 ($J = 252.6$ Hz). The fluorine NMR resonance at $\delta = -113.57$ was used to confirm the presence of fluorine on the aromatic ring, and the structure was confirmed by the detection of the molecular ion at m/z 284 in the EIMS. The other intermediates **3b–j** had similar NMR data, and the structures were elucidated in the same manner as **3a**. The aromatic oxygenated carbon resonance in **3h** was recorded at δ_{C} 161.91 with similar resonances occurring in **3i–j**.

Conversion to the ketoenol (**4a**) was indicated by the disappearance of the methyl singlet resonance and the appearance of a singlet proton resonance at δ_{H} 6.32 for the olefinic α proton. This was supported by the enol carbon resonance at approximately δ_{C} 173.6 and the keto resonance at δ_{C} 196.3. The fluorinated carbon resonance could be seen at δ_{C} 164.9 with a coupling constant of 247.2 Hz and the olefinic C–O resonance at δ_{C} 162.7. The ^{19}F NMR resonance at $\delta = -112.32$ and the molecular ion at m/z 284 in the MS spectrum further confirmed the structure. The other intermediates, **4b–j**, were elucidated in a similar manner.

Cyclisation to the 2-styrylchromones was indicated by a marked shift in the H-5 resonance from δ_{H} 7.69 in **4a** to δ_{H} 8.17 in **5a**. Further to this, only a single pyran carbonyl resonance could be seen at δ_{C} 178.4 in the ^{13}C NMR spectrum. The C-2 resonance was evident at δ_{C} 161.5 and the doublet C–F resonance at 161.2 ($J = 253.3$), which was supported by the ^{19}F NMR resonance at $\delta = -115.39$. The structures of **5b–j** were confirmed similarly. All intermediates and final products were further confirmed by 2D NMR spectroscopy and by the presence of the molecular ion using mass spectrometry.

In addition, the crystal structure of **5a** was carried out to determine the extent to which the molecule was planar. As can be seen in Figure 2 and from the data in Table 1, the molecule is almost planar with bond angles between 116 and 124°. The compound crystallizes with four planar molecules in the symmetric unit and contains four molecules per unit cell. The molecule has a C–F bond distance of 1.336 Å and a C=O distance of 1.237 Å (Table 2). The fluorine atom is 0.392 Å from the plane, and the H α and H β hydrogen atoms are 0.958 and 1.082 Å from the plane, respectively.

3.2. Antibacterial Activity. The fluorinated derivatives (**5a–g**) were most effective against Gram-positive bacteria, particularly *B. subtilis* and *S. aureus*, with that against *B. subtilis* being more predominant (Table 2). The two methoxy derivatives (**5h** and **5i**) were only effective against *B. subtilis*, with the dimethoxy derivative (**5i**) also being active against a strain of *S. aureus* (ATCC 29212), while the dioxole derivative (**5j**) displayed no antibacterial activity against both Gram-negative and Gram-positive bacteria. Thus, in comparing the methoxy (**5h–i**) and fluoro derivatives (**5a–g**), the fluoro derivatives were far superior in their activity to the methoxy

FIGURE 2: ORTEP diagram of a crystal of 2'-fluoro-2-styrylchromone at 50% probability level.

TABLE 1: Selected bond angles and bond lengths of 2'-fluorostyrylchromone.

No.	Atom1	Atom2	Atom3	Angle	Atoms	Length
1	C17	O1	C9	118.7 (2)	C2–F1	1.366
2	F1	C2	C1	117.4 (2)	C9–O1	1.369
3	C3	C2	F1	118.1 (2)	C11–O2	1.237
4	C10	C11	O2	123.9 (2)	C17–O1	1.384
5	C12	C11	O2	122.4 (2)	C7–C8	1.335
6	O1	C17	C12	121.8 (2)	C7–C1	1.460
7	O1	C17	C16	116.1 (2)	C8–C9	1.448

compounds. Limited antibacterial activity was observed with Gram-negative bacteria (Table 2), with *K. pneumoniae* and *P. aeruginosa* being completely resistant to all the tested compounds. Although the addition of fluorine to the benzene ring resulted in antibacterial action against *E. coli* ATCC 25922, it was not effective against the *E. coli* ATCC 35218 strain (Table 2) and the activity appeared to be strain-specific. The difluorinated styrylchromones showed a broader spectrum, with only **5d** and **5e** being effective against both *E. coli* strains tested (Table 2), indicating that multiple fluorinations on the 2-styrylchromone backbone could lead to enhanced activity against *E. coli*. However, fluorination on the chromone ring only resulted in no activity against *E. coli*.

The 3',5' derivative (**5d**) showed the greatest activity from all the compounds substituted on the phenyl ring. This compound also showed activity against both *E. coli* strains tested. This could therefore indicate that the activity of the 2-styrylchromones increases with increased fluorine substitution on the phenyl ring. Fluorination at position 7 on the chromone ring resulted in the compound being active against *B. subtilis* alone. This activity increased slightly with additional fluorine substitution at the 4' position, as activity was now experienced with *S. sciuri* and both the *E. coli* strains with **5e**. However, both compounds with fluorine substitution at position 7 did not show activity

TABLE 2: *In vitro* antibacterial activity of 2-styrylchromone derivatives using the disk diffusion method.

Comp.	Conc. mM	<i>B. subtilis</i> ATCC 6633	<i>E. faecium</i> ATCC 51299	<i>S. aureus</i> ATCC 29212	<i>S. aureus</i> ATCC 43300	<i>S. sciuri</i> ATCC 29062	Diameter of inhibition zone (mm)*					<i>E. coli</i> ATCC 25218	<i>K. pneumoniae</i> ATCC 700603	<i>P. aeruginosa</i> ATCC 35032
							<i>S. aureus</i> ATCC 43300	<i>S. sciuri</i> ATCC 29062	<i>S. xyloso</i> ATCC 35033	<i>E. coli</i> ATCC 25922	<i>E. coli</i> ATCC 25218			
5-a	0.75	20 ± 0.06	—	14 ± 0.00	10 ± 0.06	—	10 ± 0.06	—	—	14 ± 0.06	—	—	—	—
5-b	0.75	22 ± 0.12	—	15 ± 0.06	16 ± 0.00	—	16 ± 0.00	—	—	12 ± 0.12	—	—	—	—
5-c	0.75	24 ± 0.12	—	8 ± 0.06	8 ± 0.15	—	8 ± 0.15	—	—	12 ± 0.06	—	—	—	—
5-d	0.70	25 ± 0.15	—	19 ± 0.12	13 ± 0.06	—	13 ± 0.06	—	—	14 ± 0.00	10 ± 0.12	—	—	—
5-e	0.70	27 ± 0.12	—	—	—	12 ± 0.06	—	12 ± 0.06	—	12 ± 0.06	14 ± 0.06	—	—	—
5-f	0.75	18 ± 0.17	—	—	—	—	—	—	—	—	—	—	—	—
5-g	0.75	20 ± 0.12	10 ± 0.06	12 ± 0.00	11 ± 0.15	8 ± 0.06	11 ± 0.15	8 ± 0.06	10 ± 0.06	—	—	—	—	—
5-h	0.72	21 ± 0.06	—	—	—	—	—	—	—	—	—	—	—	—
5-i	0.65	23 ± 0.00	—	9 ± 0.12	—	—	—	—	—	—	—	—	—	—
5-j	0.68	—	—	—	—	—	—	—	—	—	—	—	—	—
*AMP10 ^a	0.57	38 ± 0.06	24 ± 0.12	25 ± 0.00	20 ± 0.15	34 ± 0.06	20 ± 0.15	34 ± 0.06	32 ± 0.00	20 ± 0.06	0	0	0	0
**TE30 ^b	0.45	36 ± 0.12	22 ± 0.00	28 ± 0.00	32 ± 0.12	25 ± 0.06	32 ± 0.12	25 ± 0.06	36 ± 0.00	27 ± 0.17	23 ± 0.17	12 ± 0.06	14 ± 0.17	14 ± 0.17

^a AMP10: ampicillin control, ^b TE30: tetracycline control, and “—” represents no activity.

TABLE 3: Activity indices of 200 µg/mL 2-styrylchromone derivatives in comparison to tetracycline.

Comp.	Conc. mM	<i>B. subtilis</i> ATCC 6633	<i>E. faecium</i> ATCC 51299	<i>S. aureus</i> ATCC 29212	<i>S. aureus</i> ATCC 43300	<i>S. sciuri</i> ATCC 29062	<i>S. xyloso</i> ATCC 35033	<i>E. coli</i> ATCC 25922	<i>E. coli</i> ATCC 35218	<i>K. pneumoniae</i> ATCC 700603	<i>P. aeruginosa</i> ATCC 35032
5-a	0.75	0.56 ± 0.02	0	0.50 ± 0.00	0.31 ± 0.02	0	0	0.52 ± 0.02	0	0	0
5-b	0.75	0.61 ± 0.01	0	0.54 ± 0.01	0.50 ± 0.00	0	0	0.44 ± 0.01	0	0	0
5-c	0.75	0.67 ± 0.01	0	0.29 ± 0.01	0.02 ± 0.01	0	0	0.44 ± 0.01	0	0	0
5-d	0.70	0.69 ± 0.01	0	0.68 ± 0.01	0.41 ± 0.01	0	0	0.42 ± 0.00	0.44 ± 0.01	0	0
5-e	0.70	0.75 ± 0.01	0	0	0	0.48 ± 0.01	0	0.44 ± 0.01	0.61 ± 0.01	0	0
5-f	0.75	0.50 ± 0.01	0	0	0	0	0	0	0	0	0
5-g	0.75	0.56 ± 0.01	0.46 ± 0.01	0.43 ± 0.00	0.34 ± 0.01	0.32 ± 0.01	0.27 ± 0.01	0	0	0	0
5-h	0.72	0.58 ± 0.01	0	0	0	0	0	0	0	0	0
5-i	0.65	0.64 ± 0.00	0	0.32 ± 0.01	0	0	0	0	0	0	0
5-j	0.68	0	0	0	0	0	0	0	0	0	0
*TE30	0.45	36 ± 0.12	22 ± 0.00	28 ± 0.00	32 ± 0.12	25 ± 0.06	36 ± 0.00	27 ± 0.17	23 ± 0.17	12 ± 0.06	14 ± 0.17

*TE30: tetracycline inhibition zone (mm).

against *S. aureus*. In contrast, the **5g** derivative, with fluorine at position 6 of the chromone ring, was the most effective of all the tested compounds, with an observable inhibitory effect against 100% of the Gram-positive bacteria (Table 2). In fact, it was the only compound that showed any activity against *E. faecium*. This compound however did not show any activity to any of the Gram-negative bacteria. In another study, the **5g** derivative (6-fluorinated) also showed antirhinovirus activity by interfering with the replication of the HRV serotype 14 and serotype 1B [27].

Although an activity index of greater than or equal to 1 relative to tetracycline susceptibility is ideal, in the present study activity indices ranged from 0 (no activity) to 0.75 (Table 3). Activity indices ranging from 0.27–0.56 were obtained following testing of the 6-F derivative (**5g**) against Gram-positive bacteria. Gram-positive organisms appeared to be more susceptible to the fluorine and methoxy derivatives compared to Gram-negative bacteria.

This may be related to their mode of antimicrobial action, which remains to be elucidated. The low activity indices do not preclude the use of these derivatives with antibacterial activity, and these compounds may have the potential to be used as mild antibiotics.

4. Conclusion

Several new fluorinated 2-styrylchromones (**5a–5f**) were synthesized along with a known fluorinated compound (**5g**), two methoxylated compounds (**5h–i**), and a methylenedioxy derivative (**5j**). The compounds were characterized and screened for their antibacterial activity. In general, the fluorinated compounds displayed antibacterial activity against Gram-positive bacteria more than Gram-negative bacteria, with the fluorinated styrylchromones being most active against *B. subtilis* followed by *S. aureus* and then a single strain of *E. coli* (ATCC 25922), but not the *E. coli* (ATCC 35218) strain, indicating that their activity toward *E. coli* is strain specific. However, the styrylchromones with two fluorine substitutions showed activity against both *E. coli* strains, indicating that a broader spectrum could be obtained with multiple fluorinations on the styrylchromone backbone. Furthermore, the 3',5'-difluorostyrylchromone (**5d**) showed the best activity from all the compounds fluorinated on the phenyl ring, also indicating that more fluorine substitutions on the styrylchromone could lead to enhanced activity.

Activity of the styrylchromones substituted on the chromone ring was specific to fluorination at position 6, which showed the best activity amongst all the compounds tested. Fluorination at position 7 was only active against one bacterial strain, *B. subtilis*. Thus, the position and number of fluorine substituents on either the phenyl or the chromone ring have an effect on the antibacterial activity of the 2-styrylchromones. It is worthwhile exploring the effect of hydroxy, methoxy, and fluorine substitutions on the phenyl ring together with fluorine substitution at position 6, as these compounds may show enhanced activity.

Conflict of Interests

The authors declare that they do not have any financial relations with any of the commercial entities mentioned in the paper that could lead to a conflict of interests.

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