Synthesis of novel fluorinated flavonols via Algar-Flynn-Oyamada reaction

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Abstract:

Flavonols have attracted considerable attention due to their diverse biological effects. However, naturally occurring flavonols are typically present only in low concentrations, with fluorine-containing flavonols being especially rare. In that respect, the construction of diverse flavonol analogues is attractive to synthetic chemists. As part of our efforts to develop fluorinated flavonols, a series of fifteen fluorinated flavonols (1-15) were synthesised via the oxidative cyclisation of 2′-Hydroxychalcones with hydrogen peroxide in an alkaline ethanol solution, using the Algar-Flynn-Oyamada (AFO) reaction. Despite the relative simplicity and convenience of the AFO reaction, the isolated yields of the fluoro-substituted flavonols were relatively modest, ranging from 16 to 51%. The cyclisation yields of flavonols were found to be favourable in the presence of fluorine substituents at the 2′- or 3′-position in the B ring. The structures of the fluorinated flavonols were elucidated by Nuclear Magnetic Resonance (NMR) and Mass Spectrometry (MS) data. It is of interest to note that this work, for the first time, demonstrates the synthesis of six novel fluorinated flavonols (7, 8, 12-15) through the application of the AFO approach.

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1. Introduction

Flavonols, also known as 3-Hydroxyflavones, are a subgroup of flavonoids that occur abundantly in a wide variety of plants. Chemically, flavonols possess a 15-carbon skeleton (C6-C3-C6), composed of two phenyl rings (A and B) and a heterocyclic ring (C). The classification of flavonoids depends on the degree of unsaturation/oxidation of the C ring and the position of the carbon atom bearing the B ring. Flavonols are characterised by a C2=C3 double bond and a ketone group at C4 in the C ring, with the B ring linked in position C2. Compared with flavones, flavonols additionally contain a hydroxyl group attached at position C3 in the C ring (Fig. 1).

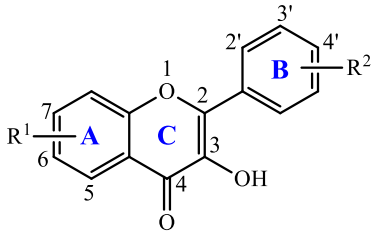


Fig. 1. Skeleton of flavonols [1]**.**

The synthesis of the target flavonols has been reported via four main approaches: the Baker-Venkataraman synthesis [2], Auwers synthesis [3], flavone oxidation by 3,3-dimethyldioxirane (DMDO) [4], and the AFO reaction [5-7]. Owing to its simplicity and convenience, the AFO reaction has been widely accepted for the synthesis of flavonols rather than the previous routes. This reaction involves the oxidation of 2′-Hydroxychalcones by the action of hydrogen peroxide (H_2O_2) in the presence of alkali. The synthetic yields of the AFO reaction are dependent on several factors including the position of the substituents on 2′-Hydroxychalcones, base, solvent, and temperature. For

example, the presence of a methoxy (-OCH_3) group at 6′-position of a 2′-Hydroxychalcone or 2′-tosyloxychalcone favors the formation of aurones as the main product, rather than the desired 5-methoxyflavonol [7-9].

X. Shen, et al. (2017) [10] investigated the effects of base and solvent on flavonol yields using 2′-hydroxy-6′-methoxychalcone as a model substrate. A range of inorganic and organic bases was screened for the AFO reaction and the best result was obtained when the chalcone was treated with Na_2CO_3 (5.0 eq.)/H_2O_2 (2.5 eq.) in a binary solvent methanol/H_2O (2/1, v/v) at 27^{o}C, affording the desired flavonol in 33% yield. The reaction was also found to be temperature-dependent: at 0-10°C only small amounts of flavonol were produced, whereas at 27°C the yield improved to 33%.

From a biological point of view, flavonols exhibit a diversity of interesting effects including anti-cancer [11], anti-viral, anti-tumour [12, 13], anti-inflammatory, and anti-oxidant [14, 15] activities. Remarkably, the most studied flavonols such as kaempferol, quercetin, myricetin, which are diverse in hydroxylation patterns exhibited a wide range of health benefits [16-18]. Interestingly, fluoro-substituted flavonols have been found to enhance biological activities due to the effects of fluorine atoms on the physicochemical properties and metabolic stability [19-21]. However, fluorinated flavonols are rarely isolated from natural resources. Consequently, various synthetic strategies have been developed to construct structurally diverse flavonols containing fluorine, using 2′-Hydroxychalcone as a key intermediate in the synthetic procedure. Recently, our group reported the synthetic approach to 2′-Hydroxychalcone derivatives containing fluorine [22]. Thus, as part of our ongoing research into the preparation of novel fluorinated flavonols, we herein present a solution to the fluoro-substituted flavonols synthesis by applying the AFO conversion under mild conditions using H_2O_2/NaOH in ethanol.

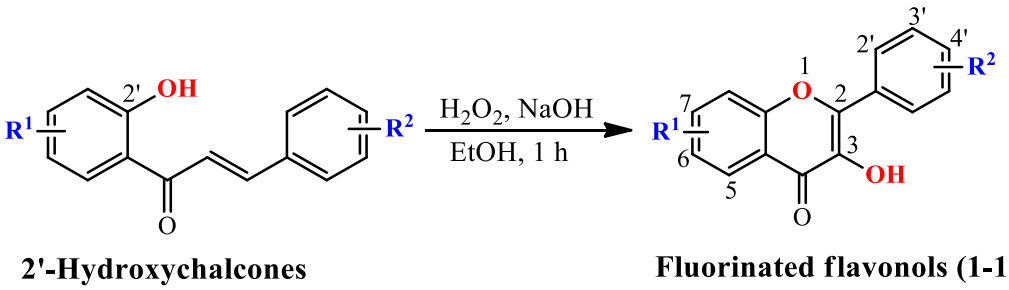
2. Materials and methods

2.1. General

Commercially available chemicals: hydrogen peroxide solution (H_2O_2, 3% (w/w) in H_2O, China), sodium hydroxide (NaOH, >95%, China), and ethanol (EtOH, >96%, J. T. Baker, USA) were used without further purification. 2′-Hydroxychalcone derivatives used as starting materials were obtained as previously reported by our group [22]. The progress of the AFO reactions was monitored by thin-layer chromatography (TLC, silica gel 60 F254, Merck, Germany). Thin layer chromatography (TLC) spots were visualized by the UV detection at λ=254 and 365 nm. Silica gel 0.035-0.070 mm (Merck, Germany) was used for flash column chromatography (CC). Melting points of fluorinated flavonols were determined using the melting point meter (M5000, Krüss, Germany) with a heating rate of 2.0°C/min. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance (500 or 600 MHz for ^{1}H NMR, 125 or 150 MHz for ^{13}C NMR). Multiplicities were abbreviated as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), dt (doublet of triplets). Coupling constants (*J*) were given in hertz. High-resolution mass spectrometry (HRMS)/mass spectrometry (MS) measurements were performed on an AGILENT 1200 series LC-MSD.

2.2. Synthesis of fluorinated flavonols (1-15) using the AFO reaction

In a 10 ml round-bottom flask 2′-Hydroxychalcones containing fluorine (0.67 mmol), 30% v/v H_2O_2 (410 µl), 20% w/v NaOH (2.0 ml) were added in EtOH (2.0 ml) (Scheme 1). A rubber stopper was used instead of a glass stopper. After folding septum flaps over the joint, a needle was inserted into the reagent flask to release gas during the reaction. The reaction mixture was stirred at ambient temperature (32°C). A full conversion was detected by TLC after 1 hour. The reaction mixture was extracted with dichloromethane (3×10 ml). The resulting organic phase was dried over Na_2SO_4. The solvent was removed using a rotary evaporator. The crude product was purified via flash CC (silica gel, eluent: *n*-hexane (Hex)/ethyl acetate (EtOAc)=90/10→85/15).



Scheme 1. Synthesis of fluorinated flavonols (1-15) under the AFO condition.

3-Hydroxy-2-phenyl-4H-chromen-4-one (1): Yield 16%, yellow solid, $C_{15}H_{10}O_3$ [238.1 g/mol]; R_f=0.51 (Hex/EtOAc=9/1); m.p. 170.6°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.02 (s, 1H, OH), 7.42 (td, ^3J (H,H)=8.4 Hz, ^4J (H,H)=1.2 Hz, 1H, H4'), 7.48 (m, 1H, H6), 7.54 (t, ^3J (H,H)=7.2 Hz, 2H, H3',5'), 7.60 (d, ^3J (H,H)=8.4 Hz, 1H, H8), 7.71 (m, 1H, H7), 8.26 (dd, ^3J(H,H)=7.8 Hz, ^4J(H,H)=3.0 Hz, 1H, H5), 8.26 (d, ^3J (H,H)=8.4 Hz, 2H, H2',6') ppm. ^{13}C-NMR (150 MHz, $CDCl_3$): δ=118.3 (C8), 120.7 (C10), 124.5 (C4'), 125.5 (C5'), 127.8 (C2',6'), 128.6 (C3',5'), 130.2 (C6), 131.1 (C1'), 133.7 (C7), 138.5 (C3), 145.0 (C2), 155.5 (C9), 173.5 (C4) ppm. ESI-MS calc'd for $[M+H]^+$: 239.1; found: *m/z* 238.9 $[M+H]^+$.

2-(2′-Fluorophenyl)-3-hydroxy-4H-chromen-4-one (2): Yield 33%, grey solid, $C_{15}H_9FO_3$ [256.1 g/mol]; R_f=0.46 (Hex/EtOAc=85/15); m.p. 171.8°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.24 (t, ^3J(H,H)=^3J(H,F)=9.0 Hz, 1H, H3′), 7.31 (t, ^3J(H,H)=7.8 Hz, 1H, H5′), 7.44 (t, ^3J(H,H)=7.2 Hz, 1H, H6), 7.52 (m, 1H, H4′), 7.55 (d, ^3J(H,H)=8.4 Hz, 1H, H8), 7.71 (td, ^3J(H,H)=7.8 Hz, ^4J(H,H)=1.2 Hz, 1H, H7), 7.81 (td, ^3J(H,H)=^4J(H,F)=7.8 Hz, ^4J(H,H)=1.8 Hz, 1H, H6′), 8.28 (dd, ^3J(H,H)=7.8 Hz, ^4J(H,H)=1.2 Hz, 1H, H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ=116.6 (d, ^2J(C,F)=21.3 Hz, C3′), 118.5 (C8), 118.8 (d, ^2J(C,F)=13.8 Hz, C1′), 121.1 (C10), 124.1 (d, ^4J(C,F)=2.5 Hz, C5′), 124.7 (C6), 125.6 (C5), 130.9 (d, ^3J(C,F)=2.5 Hz, C6′), 132.4 (d, ^3J(C,F)=8.7 Hz, C4′), 133.8 (C7), 139.0 (C3), 143.0 (C2), 156.0 (C9), 160.0 (d, ^1J(C,F)=253.8 Hz, C2′), 173.3 (C4) ppm. ESI-MS calc'd for $[M+H_2O]^+$: 274.1; found: *m/z* 274.1 $[M+H]^+$.

2-(3′-Fluorophenyl)-3-hydroxy-4H-chromen-4-one (3): Yield 30%, white-light yellow solid, $C_{15}H_9FO_3$ [256.1 g/mol]; R_f=0.29 (Hex/EtOAc=9/1); m.p. 169.7°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.09 (s, 1H, OH), 7.18 (m, 1H, H4'), 7.44 (td, ^3J (H,H)=7.2 Hz, ^4J (H,H)=1.2 Hz, 1H, H6), 7.51 (m, 1H, H5'), 7.61 (d, ^3J (H,H)=8.4 Hz, 1H, H8), 7.73 (m, 1H, H7), 8.00 (m, 1H, H2'), 8.08 (dd, ^3J (H,H)=7.8 Hz, ^4J (H,H)=1.2 Hz, 1H, H6'), 8.26 (dd, ^3J (H,H)=8.4 Hz, ^4J (H,H)=1.8 Hz, 1H, H5) ppm. ^{13}C-NMR (150 MHz, $CDCl_3$): δ=114.7 (d, ^2J(C,F)=25 Hz, C2'), 117.1 (d, ^2J(C,F)=21.3 Hz, C4'), 118.3 (C8), 120.6 (C10), 123.4 (d, ^4J(C,F)=2.5 Hz, C6'), 124.7 (C6), 125.6 (C5), 130.2 (d, ^3J(C,F)=7.5 Hz, C5'), 133.1 (d, ^3J(C,F)=8.7 Hz, C1'), 134.0 (C7), 139.0 (C3), 143.3 (C2), 155.4 (C9), 162.8 (d, ^1J(C,F)=243.8 Hz, C3'), 173.55 (C4) ppm. ESI-MS calc'd for $[M+H]^+$: 257.1; found: *m/z* 256.9 $[M+H]^+$.

2-(4′-Fluorophenyl)-3-hydroxy-4H-chromen-4-one (4): Yield 24%, white-light yellow solid, $C_{15}H_9FO_3$ [256.1 g/mol]; R_f=0.53 (Hex/EtOAc=8/2); m.p. 153.4°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.00 (s, 1H, OH), 7.23 (td, ^3J(H,H)=^3J(H,F)=9.0 Hz, 2H, H3′,5′), 7.43 (td, ^3J(H,H)=7.8 Hz, ^4J(H,H)=0.6 Hz, 1H, H6), 7.59 (d, ^3J(H,H)=8.4 Hz, 1H, H8), 7.72 (td, ^3J(H,H)=9.0 Hz, ^4J(H,H)=1.8 Hz, 1H, H7), 8.26 (dd, ^3J(H,H)=7.8 Hz, ^4J(H,H)=1.2 Hz, 1H, H5), 8.28 (dd, ^3J(H,H)=9.0 Hz, ^4J(H,F)=5.4 Hz, 2H, H2′,6′) ppm. ^{13}C-NMR (150 MHz, $CDCl_3$): δ=115.8 (d, ^2J(C,F)=22.5 Hz, C3′,5′), 118.2 (C8), 120.7 (C10), 124.6 (C6), 125.5 (C5), 127.3 (d, ^4J(C,F)=3.0 Hz, C1′), 130.0 (d, ^3J(C,F)=9.0 Hz, C2′,6′), 133.7 (C7), 138.2 (C3), 145.0 (C2), 155.4 (C9), 163.7 (d, ^1J(C,F)=251 Hz, C4′), 173.43 (C4) ppm. ESI-MS calc'd for $[M-HF+8H_2O+H]^+$: 381.1; found: *m/z* 380.7 $[M-HF+8H_2O+H]^+$.

2-(3′,4′-Difluorophenyl)-3-hydroxy-4H-chromen-4-one (5): Yield 23%, white-light yellow solid, $C_{15}H_8F_2O_3$ [274.0 g/mol]; R_f=0.46 (Hex/EtOAc=8/2); m.p. 156.6°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.07 (s, 1H, OH), 7.32 (td, ^3J(H,H)=^4J(H,F)=8.4 Hz, ^3J(H,F)=9.6 Hz, 1H, H5′), 7.44 (td, ^3J(H,H)=7.8 Hz, ^4J(H,H)=0.6 Hz, 1H, H6), 7.59 (d, ^3J(H,H)=8.4 Hz, 1H, H8), 7.68 (td, ^3J(H,H)=8.4 Hz, ^4J(H,H)=1.8 Hz, 1H, H7), 8.06 (m, 1H, H6′), 8.15 (ddd, ^3J(H,F)=7.8 Hz, ^4J(H,F)=2.4 Hz, ^4J(H,H)=1.8 Hz, 1H, H2′), 8.26 (dd,

^{3}J(H,H)=8.4 Hz, ^{4}J(H,H)=1.8 Hz, 1H, H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ=117.1 (d, ^{2}J(C,F)=21.2 Hz, C2′), 117.6 (d, ^{2}J(C,F)=17.5 Hz, C5′), 118.3 (C8), 120.6 (C10), 124.4 (d, ^{3}J(C,F)=6.3 Hz, C6′), 124.8 (C6), 125.6 (C5), 132.6 (C1′), 134.0 (C7), 138.5 (C3), 142.6 (C2), 150.3 (C3′,4′), 155.4 (C9), 173.5 (C4) ppm. ESI-MS calc'd for $[M+H]^+$: 275.0; found: *m/z* 274.8 $[M+H]^+$.

6-Fluoro-3-hydroxy-2-phenyl-4H-chromen-4-one (6): Yield 20%, yellow solid, $C_{15}H_9FO_3$ [256.1 g/mol]; R_f=0.52 (Hex/EtOAc=95/5); m.p. 161.3°C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ=6.96 (s, 1H, OH), 7.44 (m, 1H, H7), 7.49 (m, 1H, H4′), 7.55 (d, ^{3}J(H,H)=7.0 Hz, 2H, H3′,5′), 7.61 (dd, ^{3}J(H,H)=9.5 Hz, ^{4}J(H,F)=4.0 Hz, 1H, H8), 7.88 (dd, ^{3}J(H,F)=8.0 Hz, ^{4}J(H,H)=3.0 Hz, 1H, H5), 8.24 (d, ^{3}J(H,H)=7.5 Hz, 2H, H2′,6′) ppm. ^{13}C-NMR (150 MHz, $CDCl_3$): δ=110.0 (d, ^{2}J(C,F)=24.0 Hz, C5), 120.5 (d, ^{3}J(C,F)=9.0 Hz, C8), 121.6 (C10), 122.3 (d, ^{2}J(C,F)=27.0 Hz, C7), 127.8 (C2′,6′), 128.7 (C3′,5′), 130.4 (C4′), 130.8 (C1′), 138.2 (C3), 145.4 (C2), 151.8 (C9), 159.1 (d, ^{1}J(C,F)=246.0 Hz, C6), 172.9 (C4) ppm. ESI-MS calc'd for $[M+H]^+$: 257.1; found: *m/z* 256.8 $[M+H]^+$.

6-Fluoro-2-(2′-fluorophenyl)-3-hydroxy-4H-chromen-4-one (7): Yield 35%, white solid, $C_{15}H_8F_2O_3$ [274.0442 g/mol]; R_f=0.52 (Hex/EtOAc=9/1); m.p. Not determined; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.24 (m, 1H, H3′), 7.31 (td, ^{3}J(H,H)=7.8 Hz, ^{4}J(H,H)=1.8 Hz, 1H, H5′), 7.44 (m, 1H, H7), 7.52 (m, 1H, H4′), 7.56 (dd, ^{3}J(H,H)=9.6 Hz, ^{4}J(H,F)=4.2 Hz, 1H, H8), 7.79 (td, ^{3}J(H,H)=7.8 Hz, ^{4}J(H,F)=1.8 Hz, 1H, H6′), 7.90 (dd, ^{3}J(H,F)=8.4 Hz, ^{4}J(H,H)=3.0 Hz, 1H, H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ=110.0 (d, ^{2}J(C,F)=22.5 Hz, C5), 116.6 (d, ^{2}J(C,F)=21.2 Hz, C3′), 118.5 (d, ^{2}J(C,F)=13.8 Hz, C1′), 120.7 (d, ^{3}J(C,F)=7.5 Hz, C8), 122.0 (d, ^{3}J(C,F)=7.5 Hz, C10), 122.4 (d, ^{2}J(C,F)=26.2 Hz, C7), 124.2 (d, ^{4}J(C,F)=3.8 Hz, C5′), 130.9 (d, ^{3}J(C,F)=2.5 Hz, C6′), 132.6 (d, ^{3}J(C,F)=8.8 Hz, C4′), 138.7 (C3), 143.2 (C2), 152.3 (C9), 159.1 (d, ^{1}J(C,F)=246.2 Hz, C2′), 160.0 (d, ^{1}J(C,F)=253.8 Hz, C6), 172.63 (C4) ppm. ESI-HRMS calc'd for $[M+H]^+$: 275.0520; found: *m/z* 275.0524 $[M+H]^+$.

6-Fluoro-2-(3′-fluorophenyl)-3-hydroxy-4H-chromen-4-one (8): Yield 51%, white solid, $C_{15}H_8F_2O_3$ [274.0442 g/mol]; R_f=0.35 (Hex/EtOAc=95/5); m.p. 124.3°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.04 (s, 1H, OH), 7.19 (td, ^3J(H,F)=^3J(H,H)=7.8 Hz, ^4J(H,H)=2.4 Hz, 1H, H4′), 7.47 (m, 1H, H7), 7.51 (m, 1H, H5′), 7.62 (dd, ^3J(H,H)=9.6 Hz, ^4J(H,F)=4.2 Hz, 1H, H8), 7.88 (dd, ^3J(H,F)=7.8 Hz, ^4J(H,H)=3.0 Hz, 1H, H5), 7.98 (dd, ^3J(H,F)=8.4 Hz, ^4J(H,H)=1.2 Hz, 1 H, H2′), 8.06 (dd, ^3J(H,H)=7.8 Hz, ^4J(H,H)=1.2 Hz, 1H, H6′). ^{13}C-NMR (125 MHz, $CDCl_3$): δ=110.0 (d, ^2J(C,F)=23.8 Hz, C5), 114.7 (d, ^2J(C,F)=23.8 Hz, C4′), 117.3 (d, ^2J(C,F)=21.3 Hz, C4′), 120.50 (d, ^3J(C,F)=8.8 Hz, C8), 121.5 (d, ^3J(C,F)=8.8 Hz, C10), 122.6 (d, ^2J(C,F)=25.0 Hz, C7), 123.5 (d, ^4J(C,F)=2.5 Hz, C6′), 130.3 (d, ^3J(C,F)=7.5 Hz, C5′), 132.9 (d, ^3J(C,F)=8.8 Hz, C1′), 138.50 (C3), 143.8 (C2), 151.8 (C9), 159.2 (d, ^1J(C,F)=245.0 Hz, C3′), 161.87 (d, ^1J(C,F)=250 Hz, C6), 172.94 (C4) ppm. ESI-HRMS calc'd for $[M+H]^+$: 275.0520; found: *m/z* 275.0524 $[M+H]^+$.

6-Fluoro-2-(4′-fluorophenyl)-3-hydroxy-4H-chromen-4-one (9): Yield 20%, white-light yellow solid, $C_{15}H_8F_2O_3$ [274.0 g/mol]; R_f =0.59 (Hex/EtOAc=9/1); m.p. 184.2°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.24 (t, ^3J (H,F)=^3J (H,H)=8.4 Hz, 2H, H3',5'), 7.45 (m, 1H, H7), 7.60 (dd, ^3J (H,H)=9.0 Hz, ^4J (H,F)=3.6 Hz, 1H, H8), 7.88 (dd, ^3J (H,F)=7.8 Hz, ^4J (H,H)=3.0 Hz, 1H, H5), 8.26 (d, ^3J (H,H)=9.0 Hz, 1H, H2′), 8.27 (d, ^3J (H,H)=9.0 Hz, 1H, H6′) ppm.^{13}C-NMR (125 MHz, $CDCl_3$): δ=110.0 (d, ^2J(C,F)=22.5 Hz, C5), 115.90 (d, ^2J(C,F)=21.3 Hz, C3',5'), 120.4 (d, ^3J(C,F)=8.8 Hz, C8), 121.3 (C10), 122.33 (d, ^2J(C,F)=25 Hz, C7), 127.0 (C1'), 130.09 (d, ^3J(C,F)=7.5 Hz, C2',6'), 137.9 (C3), 144.6 (C2), 151.7 (C9), 159.2 (d, ^1J(C,F)=246.3 Hz, C4′), 163.2 (d, ^1J(C,F)=251.3 Hz, C6'), 172.8 (C4) ppm. ESI-MS calc'd for $[M+H]^+$: 275.1; found: *m/z* 275.0 $[M+H]^+$.

2-(3′,4′-Difluorophenyl)-6-fluoro-3-hydroxy-4H-chromen-4-one (10): Yield 22%, white-light yellow solid, $C_{15}H_7F_3O_3$ [292.0 g/mol]; R_f=0.51 (Hex/EtOAc=9/1); m.p. 168.5°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.33 (td, ^3J(H,H)=^4J(H,F)=9.6 Hz, ^3J(H,F)=8.4 Hz, 1H, H5′), 7.47 (m, 1H, H7), 7.61 (dd, ^3J(H,H)=9.6 Hz, ^4J(H,F)=4.2 Hz, 1H, H8), 7.85 (dd, ^3J(H,F)=8.4 Hz, ^4J(H,H)=3.0 Hz, 1H, H5), 8.05 (m, 1H, H6′), 8.14 (m, 1H, H2′) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ=110,1 (d, ^2J(C,F)=22.5 Hz, C5), 117.2 (d, ^2J(C,F)=20 Hz, C2′), 117.7 (d, ^2J(C,F)=17.5 Hz, C5′), 120.4 (d, ^3J(C,F)=6.3 Hz, C8), 121.5 (C10), 122.6 (d, ^2J(C,F)=25 Hz, C7), 124.6 (m, C6′), 138.3 (C3), 143.2 (C2), 151.8 (C9), 159.2 (d, ^1J(C,F)=245 Hz, C6), 172.9 (C4) ppm. ESI-MS calc'd for $[M+H]^+$: 293.0; found: *m/z* 293.0 $[M+H]^+$.

7-Fluoro-3-hydroxy-2-phenyl-4H-chromen-4-one (11): Yield 19%, white-light yellow solid, $C_{15}H_9FO_3$ [256.1 g/mol]; R_f=0.47 (Hex/EtOAc=9/1); m.p. 165.4°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=6.98 (s, 1H, OH), 7.16 (dd, ^3J(H,F)=9.0 Hz, ^3J(H,H)=9.0 Hz, ^4J(H,H)=2.4 Hz, 1H, H6), 7.28 (dd, ^3J(H,F)=9.0 Hz, ^4J(H,H)=2.4 Hz, 1H, H8), 7.48 (m, 1H, H4′), 7.54 (t, ^3J(H,H)=8.4 Hz, 2H, H3′,5′), 8.23 (d, ^3J(H,H)=8.4 Hz, 2H, H2′,6′), 8.27 (dd, ^3J(H,H)=9.0 Hz, ^4J(H,F)=6.0 Hz, 1H, H5) ppm. ^{13}C-NMR (150 MHz, $CDCl_3$): δ=104.8 (d, ^2J(C,F)=25.5 Hz, C8), 113.9 (d, ^2J(C,F)=22.5 Hz, C6), 117.6 (C10), 127.7 (C2′,6′), 128.0 (d, ^3J(C,F)=10.5 Hz, C5), 128.7 (C3′,5′), 130.4 (C4′), 130.8 (C1′), 138.4 (C3), 145.3 (C2), 156.5 (C9), 165.8 (d, ^1J(C,F)=253.5 Hz, C7), 172.8 (C4) ppm. ESI-MS calc'd for $[M+H]^+$: 257.1; found: *m/z* 256.9 $[M+H]^+$.

7-Fluoro-2-(2′-fluorophenyl)-3-hydroxy-4H-chromen-4-one (12): Yield 36%, white-light yellow solid, $C_{15}H_8F_2O_3$ [274.0 g/mol]; R_f =0.48 (Hex/EtOAc=8/2); m.p. 152.6°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.16 (ddd, ^3J (H,H)=^3J (H,F)=8.4 Hz, ^4J (H,H)=2.4 Hz, 1H, H6), 7.21 (dd, ^3J (H,F)=9.0 Hz, ^4J (H,H)=2.4 Hz, 1 H, H8), 7.23 (m, 1 H, H3'), 7.30 (td, ^3J (H,H)=7.8 Hz, ^4J (H,H)=1.2 Hz, 1H, H5'), 7.51 (m, 1H, H4'), 7.78 (td, ^3J (H,H)=^4J (H,F)=7.2 Hz, ^4J (H,H)=1.8 Hz, 1H, H6'), 8.29 (dd, ^3J (H,H)=9.0 Hz, ^4J (H,F)=6.6 Hz, 1H, H5) ppm. ^{13}C-NMR (150 MHz, $CDCl_3$): δ=105.0 (d, ^2J(C,F)=25.5 Hz, C8), 114.0 (d, ^2J(C,F)=22.5 Hz, C6), 116.6 (d, ^2J(C,F)=22.5 Hz, C3'), 118.0 (C10), 118.5 (d, ^2J(C,F)=13.5 Hz, C1'), 124.2 (d, ^4J(C,F)=3.0 Hz, C5'), 128.1 (d, ^3J(C,F)=10.5 Hz, C5), 130.8 (C6'), 132.5 (d, ^3J(C,F)=9.0 Hz, C4'), 139.0 (C3), 143.1 (C2), 157.0 (d, ^3J(C,F)=13.5 Hz, C9), 159.9 (d, ^1J(C,F)=255.0 Hz, C2'), 165.9 (d, ^1J(C,F)=255.0 Hz, C7), 172.59 (C4) ppm. ESI-MS calc'd for $[M+H]^+$: 275.1; found: *m/z* 274.9 $[M+H]^+$.

7-Fluoro-2-(3′-fluorophenyl)-3-hydroxy-4H-chromen-4-one (13): Yield 29%, white-light yellow solid, $C_{15}H_8F_2O_3$ [274.0 g/mol]; R_f=0.34 (Hex/EtOAc=9/1); m.p. 137.2°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.06 (s, 1H, OH), 7.18 (td, ^3J (H,H)=8.4 Hz, ^3J (H,F)=8.4 Hz, ^4J (H,H)=2.4 Hz, 2H, H6,4'), 7.28 (dd, ^3J (H,F)=9.0 Hz, ^4J (H,H)=2.4 Hz, 1H, H8), 7.51 (td, ^3J (H,H)=7.8 Hz, ^4J (H,F)=6.0 Hz, 1H, H5'), 7.96 (dt, ^3J (H,F)=10.8 Hz, ^4J (H,H)=2.4 Hz, 1H, H2'), 8.04 (d, ^3J (H,H)=8.4 Hz, 1H, H6'), 8.27 (dd, ^3J (H,H)=9.0 Hz, ^4J (H,F)=6.6 Hz, 1H, H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ=104.8 (d, ^2J(C,F)=26.3 Hz, C8), 114.1 (d, ^2J(C,F)=23.8 Hz, C6), 114.6 (d, ^2J(C,F)=23.8 Hz, C2'), 117.2 (d, ^2J(C,F)=20.0 Hz, C4'), 117.5 (C10), 123.3 (d, ^4J(C,F)=2.5 Hz, C6'), 128.1 (d, ^3J(C,F)=11.3 Hz, C5), 130.3 (d, ^3J(C,F)=7.5 Hz, C5'), 132.80 (d, ^3J(C,F)=7.5 Hz, C1'), 138.7 (C3), 143.7 (C2), 156.4 (C9), 162.9 (d, ^1J(C,F)=243.8 Hz, C3'), 166.0 (d, ^1J(C,F)=253.8 Hz, C7), 172.8 (C4) ppm. ESI-MS calc'd for $[M-H]^-$: 273.0; found: *m/z* 272.7 $[M-H]^-$.

7-Fluoro-2-(4′-fluorophenyl)-3-hydroxy-4H-chromen-4-one (14): Yield 19%, white-light yellow solid, $C_{15}H_8F_2O_3$ [274.0 g/mol]; R_f =0.27 (Hex/EtOAc=9/1); m.p. 194.6°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=6.99 (s, 1H, OH), 7.18 (td, ^3J (H,H)=^3J(H,F)=8.4 Hz, ^4J (H,H)=2.0 Hz, 1H, H6), 7.23 (t, ^3J(H,H)=^3J(H,F)=8.5 Hz, 2H, H3',5'), 7.27 (dd, ^3J (H,F)=8.0 Hz, ^4J (H,H)=2.0 Hz, 1H, H8), 8.25 (d, ^3J (H,H)=9.0 Hz, 2H, H2',6'), 8.27 (dd, ^3J (H,H)=9.0 Hz, ^4J (H,F)=6.0 Hz, 1H, H5) ppm. ^{13}C-NMR (150 MHz, $CDCl_3$): δ=104.7 (d, ^2J(C,F) = 25.5 Hz, C8), 114.0 (d, ^2J(C,F)=24.0 Hz, C6), 115.9 (d, ^2J(C,F)=24.0 Hz, C3′,5′), 117.6 (C10), 127.0 (C1'), 128.1 (d, ^3J(C,F)=12.0 Hz, C5), 129.9 (d, ^3J(C,F)=9.0 Hz, C2',6'), 138.0 (C3), 144.5 (C2), 156.4 (d, ^3J(C,F)=13.5 Hz, C9), 163.7 (d, ^1J(C,F)=250.5 Hz, C4'), 165.9 (d, ^1J(C,F)=255.0 Hz, C7), 172.73 (C4) ppm. ESI-MS calc'd for $[M+H]^+$: 275.1; found: *m/z* 274.8 $[M+H]^+$.

2-(3′,4′-Difluorophenyl)-7-fluoro-3-hydroxy-4H-chromen-4-one (15): Yield 37%, yellow solid, $C_{15}H_7F_3O_3$ [292.0 g/mol]; R_f =0.37 (Hex/EtOAc=9/1); m.p. 169.2°C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ=7.06 (s, 1H, OH), 7.19 (td, ^3J (H,F)=^3J (H,H)=8.4 Hz, ^4J (H,H)=1.8 Hz, 1H, H6), 7.27 (dd, ^3J (H,F)=9.0 Hz, ^4J (H,H)=1.8 Hz, 1H, H8), 7.33 (td, ^3J(H,H)=^4J(H,F)=9.0 Hz, ^3J(H,F)=9.0 Hz, 1H, H5′), 8.02 (m, 1H, H6'), 8.11 (ddd, ^3J

(H,F)=11.4 Hz, ^{4}J (H,F)=7.8 Hz, ^{4}J (H,H)=1.8 Hz, 1H, H2'), 8.27 (dd, ^{3}J (H,H)=8.4 Hz, ^{4}J (H,F)=6.0 Hz, 1H, H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ=104.8 (d, ^{2}J(C,F)=25 Hz, C8), 114.2 (d, ^{2}J(C,F)=22.5 Hz, C6), 117.0 (d, ^{2}J(C,F)=21.3 Hz, C2'), 117.5 (C10), 117.7 (d, ^{2}J(C,F)=17.5 Hz, C5'), 124.3 (m, C6'), 127.7 (C1'), 128.2 (C5), 138.40 (C3), 142.99 (C2), 150.2-152.3 (d, ^{1}J(C,F)=252.5 Hz, C3',4′), 156.4 (d, ^{3}J(C,F)=12.5 Hz, C9), 166.0 (d, ^{1}J(C,F)=253.8 Hz, C7), 172.7 (C4) ppm. ESI-MS calc'd for $[M-H]^-$: 291.0; found: *m/z* 290.8 $[M-H]^-$.

3. Results and discussion

Subjecting the 2′-Hydroxychalcones containing fluorine to oxidative intramolecular cyclization using 30% v/v H_2O_2 and 20% w/v NaOH afforded fifteen fluorinated flavonols (1-15) in yields of 16-51%, six of which are novel fluoro-substituted flavonols (7, 8, 12-15) (Fig. 2). In terms of the synthesis of flavonols via the AFO, the synthetic yields are dependent on several factors such as base, solvent, and temperature [10]. Therefore, the progress of the reaction was monitored at 30-minute intervals. Complete conversion of fluorinated 2′-Hydroxychalcones was observed after 1 hour. Nevertheless, fluoro-substituted flavonols (1-15) were obtained after purification via flash CC with low to moderate isolated yields.

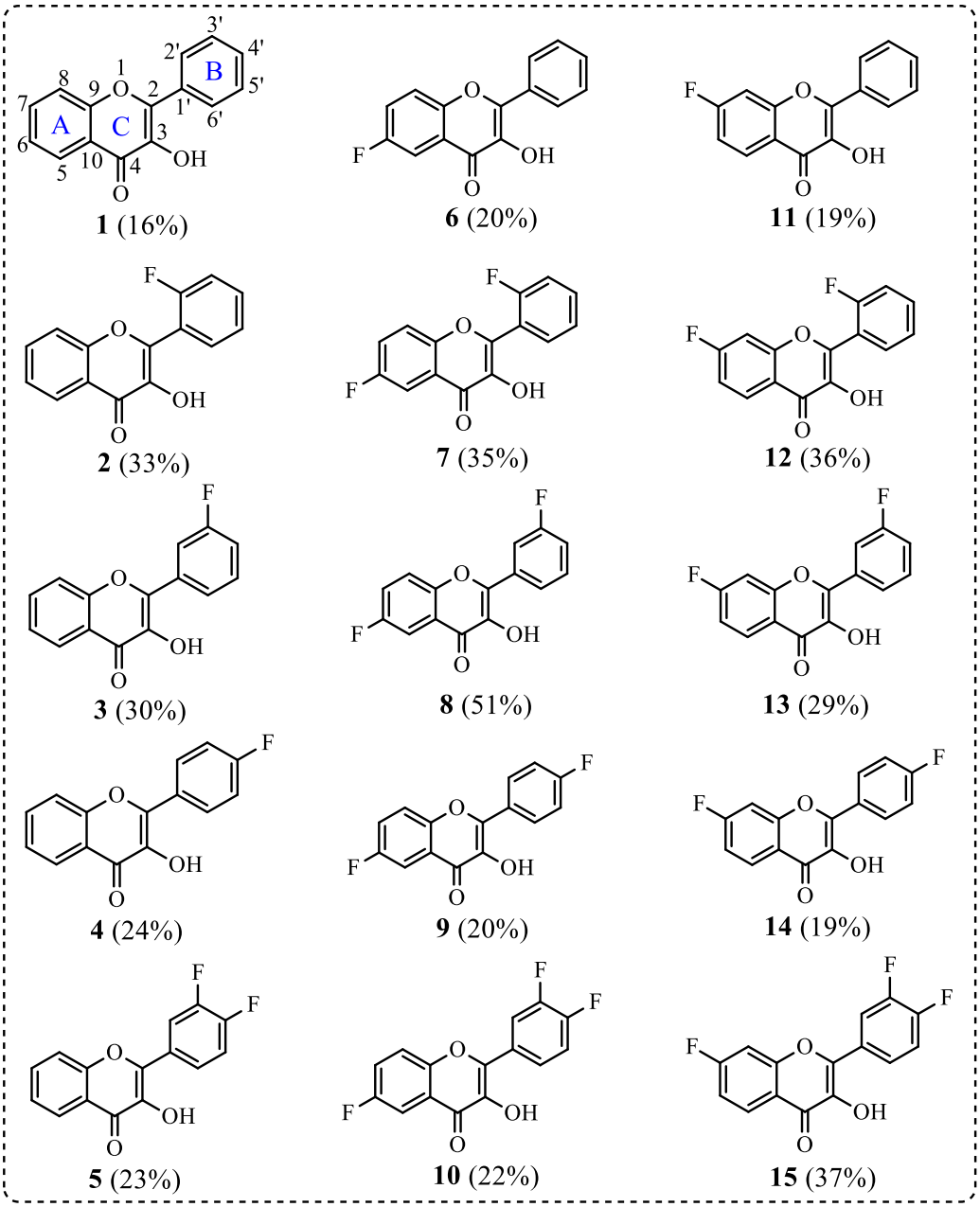
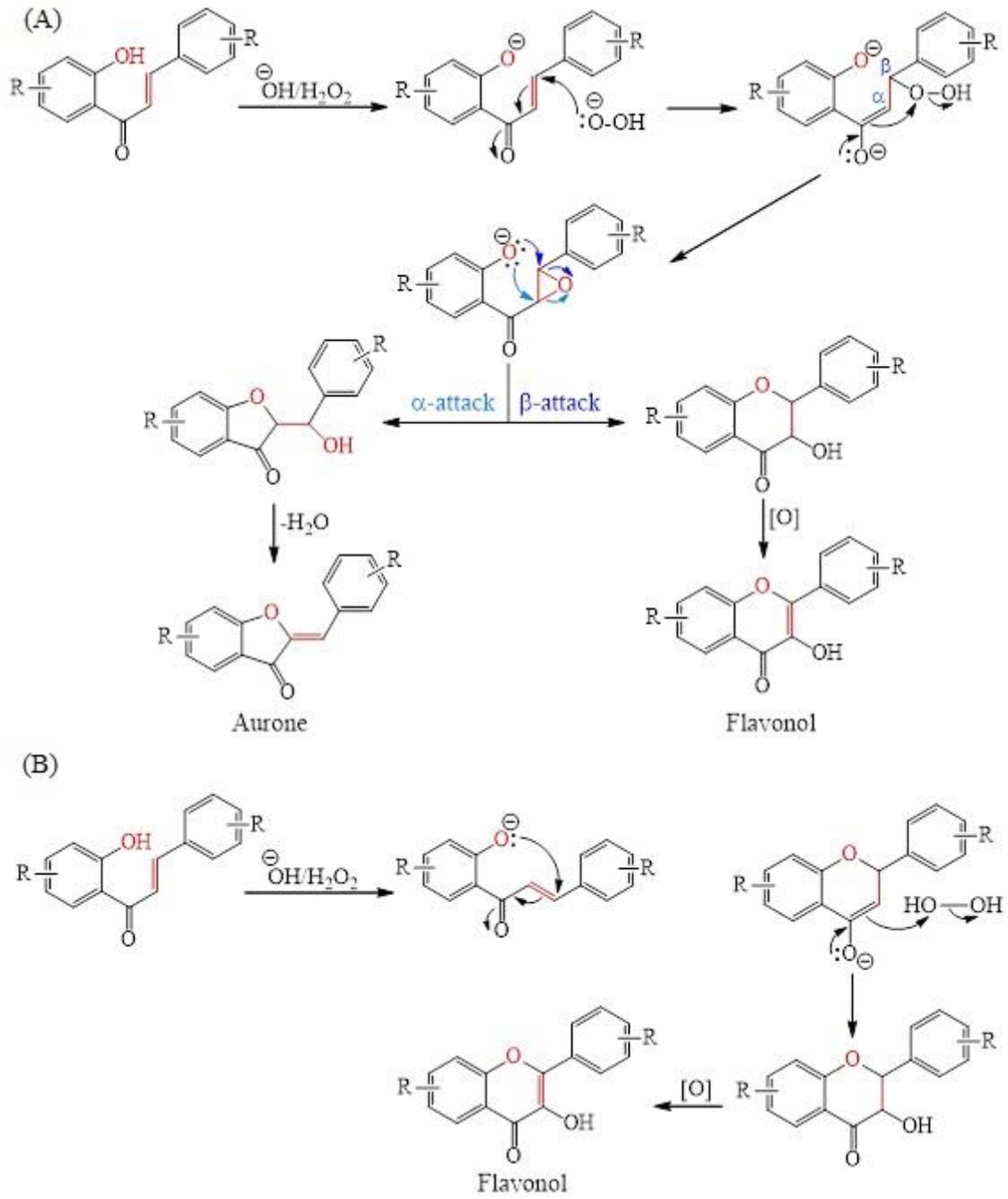


Fig. 2. Chemical structures of fluorinated flavonols (1-15) synthesised by the AFO reaction. The isolated yields are in parentheses.

In fact, oxidation of 2′-Hydroxychalcones under the AFO conditions often led to flavonols with relatively low yields [9, 10]. The effects of the strength of base and temperature on the efficiency of the flavonol synthesis were investigated. X. Shen, et al. (2017) [10] screened the conditions of the conversion of 2′-hydroxy-5′-methoxychalcone

to 5-methoxyflavonol, the yield of the AFO reaction was only 13% under H_2O_2/NaOH conditions. In comparison, the yield improved to 32% when the reaction was carried out under optimal conditions using H_2O_2/Na_2CO_3 at 27^oC.

It is therefore necessary to review the mechanism of the AFO reaction in the present work. To date, both computational and experimental studies have been conducted to elucidate its mechanism. In general, efforts have aimed at identifying intermediates. The first possible reaction mechanism suggested that the chalcone epoxide serves as a key intermediate [7, 8]. An epoxide can further undergo ring opening by the nucleophilic attack at either the α- or β-position, leading to aurone or 3-Hydroxyflavanone, respectively (Scheme 2A). Finally, oxidation of 3-Hydroxyflavanone yields the product of 3-Hydroxyflavone.



(A) The first possible reaction mechanism suggested that the chalcone epoxide serves as a key intermediate; (B) The second hypothesis proposed that the formation of 3-Hydroxyflavanone starts with the cyclisation of the phenolate ion at the β-position.

Scheme 2. Two proposed mechanisms of the AFO reaction for the flavonol synthesis [10].

Later, a second hypothesis for the formation of 3-Hydroxyflavanone suggested that the AFO reaction starts with the cyclisation of the phenolate ion at the β-position rather than via epoxide formation [23, 24]. A consequence of the electrophilic attack by H_2O_2 on the resulting intermediate anion generates 3-Hydroxyflavanone, which is subsequently oxidized to 3-Hydroxyflavone (Scheme 2B). Consistent with this view, J.F. O′Sullivan, et al. (1955) [25] also demonstrated that the AFO reaction involves a process of cyclisation and oxidation rather than through an epoxide intermediate. i.e., the cyclisation of chalcone anion, followed by the attack of H_2O_2 at C3 carbon atom of the intermediate to afford 3-Hydroxyflavanone.

In this context, the authors argued that the conversion of 2′-Hydroxychalcone to its anion under alkaline conditions leads to Coulombic repulsion with the hydroperoxide anion ($^-$O-OH), thereby increasing the activation energy of the reaction. As a consequence, epoxide formation was disfavoured. However, to account for the formation of aurone as the main product in the AFO reaction of 2′-Hydroxychalcones substituted at the 6′-position, J.F. O′Sullivan, et al. (1955) [25] also accepted that the involvement of an epoxide pathway in the synthesis of 5-substituted flavonols [7].

The presence of a 6′-substituted chalcone forces the carbonyl group out of the aromatic plane due to steric interactions. In addition, the negative charge on the 2′-O^- group is less effectively delocalised onto the >C=O group because of steric inhibition of resonance. In other words, the displacement of the carbonyl group from planarity enhances the nucleophilicity of the 2′-O^- group and the distance of the phenolate oxygen from the β-carbon. Consequently, α-cyclisation leading to aurone formation becomes favoured. Recently, to probe the AFO reaction mechanism, X. Shen, et al. (2017) [10] synthesised 5-substituted flavonols under mild conditions of H_2O_2/Na_2CO_3 in methanol. Despite the stereo-electronical inhibition of β-cyclisation of the epoxide, experimental evidence from LC-MS and *in situ* ^{1}H NMR analyses indicated that the synthetic mechanism of 5-substituted flavonols involves an epoxide intermediate under alkaline hydrogen peroxide conditions.

In our experiments, all AFO reactions were monitored by TLC and stopped when 2′-Hydroxychalcones were completely consumed after 1 hour. Based on TLC analysis, the highest conversion toward the expected fluorinated flavonols was observed without detectable side products. Therefore, we suggest that when an epoxide intermediate was involved in the AFO reaction pathway, aurone formation was absent in our experiments. Unexpectedly, the use of the AFO reaction for the preparation of fluorinated flavonols resulted in low yields. As previously reported, the formation of flavonol is affected by reaction temperature. In our present experiments, cyclisation reactions were stirred under alkaline/hydrogen peroxide conditions, which cause an exotherm. As a result, in the course of an exothermic process, the corresponding flavonols are of lower yielding, consistent with previous literature that flavonol synthesis is unfavourable above 30^{o}C [10].

Moreover, we herein found that the yields of the fluorinated flavonol synthesis seem to be dependent on the positions of fluorine substituents of the B ring. Fluorine atoms at the 2 or 3-position in B ring acting as an electron-withdrawing group were favourable for the flavonol formation with the yields of 29-51% (Fig. 2, compounds 2, 3, 7, 8, 12, 13). As illustrated in Scheme 2, flavonol formation occurred via the nucleophilic attack of the 2′-O-group to the β-position in both proposed mechanisms. Thus, in our present work, the mechanisms for the formation of fluorinated flavonols, i.e., through an epoxide or/and an intramolecular oxa-Michael addition can be rationalised by the increased electrophilicity of the β-carbon induced by the electron-withdrawing inductive effect of fluorine at the 2- or 3-position of the B ring. As a result, the 2′-O attack at the β-carbon was facilitated, leading to the formation of fluorinated flavonols. By contrast, fluorine substitution at the 4-position of the B ring was prone to lowering the yields of flavonols (Fig. 2, compounds 4, 9, 14), in agreement with previous observations [10].

4. Conclusions

A simple and convenient AFO reaction for the synthesis of fluorinated flavonols from fluoro-substituted 2′-Hydroxychalcones was established. Under the alkaline hydrogen peroxide conditions, fifteen fluorinated flavonols including six novel structures

were successfully synthesised in isolated yields of 16-51%. With the observations shown above, we suggest that aurone formation, i.e., phenolate attack at the α-carbon, was absent in our experiments. Furthermore, *ortho*/*meta*-fluoro substitution on the B ring probably favors the synthesis of fluorinated flavonols, whereas the presence of the electron-withdrawing group of fluorine at *para*-position gives lower isolated yields of fluorinated flavonols. We expect that the synthetic results reported here will be useful for the synthesis of novel fluorinated flavonols with potential applications in biochemistry and organic chemistry.

CRediT author statement

Le Thanh Huy, Vo Thi Dien, Huynh Van Khang, Phan Phuoc Hoai Nhan, Ho Phuong: AFO synthesis, Purification; Ho Phuong, Pham Thi Bich Van, Nguyen Linh Nham: NMR elucidation, Discussion; Hoang Minh Hao: Conceptualisation, Methodology, Supervision, NMR elucidation, Writing original draft, Writing-Reviewing and Editing.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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