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A simple and convenient synthesis of 2-(perfluoroalkyl)-4*H*-chromenes from salicyl *N*-tosylimines or salicylaldehydes and methyl 2-perfluoroalkynoates

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ABSTRACT

Et_3N-catalyzed reactions of salicyl *N*-tosylimines or salicylaldehydes with methyl 2-perfluoroalkynoates proceed smoothly at room temperature in dichloromethane (DCM) or dimethyl sulfoxide (DMSO) to give the corresponding fluorinated chromenes in good to excellent yields with high regioselectivity.

1. Introduction

4*H*-Chromenes are an important class of compounds being the main components of many biologically active compounds, and are widely employed as key intermediates in the synthesis of numerous natural products and medicinal reagents.[1] For example, substituted 4*H*-chromenes have displayed high antibacterial activity and powerful anticancer properties by affecting tumor vasculature progression and inducing tumor necrosis in vivo.[1e,i] Thus, the development of new efficient processes for their construction has been the subject of increasing attention over the last couple of years.[2] Although it is well known that the introduction of polyfluoroalkyl groups into organic molecules can bring about some remarkable changes in the properties of the derived fluorinated compounds, and selective perfluoroalkylation has been recognized as an important tool in developing new biologically important compounds,[3] methods for preparing polyfluoroalkyl-substituted 4*H*-chromenes remain very limited.[4]

2-Perfluoroalkynoates have been widely used in synthesizing fluorinated organic compounds especially as a modulator to enhance the yield and regioselectivity of Michael-type conjugate additions.[5]

As part of our ongoing efforts in developing synthetic approaches for the synthesis of novel fluorinated heterocycles with potential biological applications, we built upon the recent reports by Shi's group on the synthesis of the chromenes.[2d,6] It was found that although the amine-catalyzed reaction between ethyl 2-butynoate and salicyl *N*-tosylimine did not give the substituted chromenes in satisfactory yield under various reaction conditions, the reaction of diethyl acetylenedicarboxylate with salicyl *N*-tosylimines or salicylaldehydes proceeded smoothly because of the substitution of the methyl group in ethyl 2-butynoate for the electron-withdrawing ester group.[6c] On considering the high electronegativity of polyfluoroalkyl groups, we developed a new general and efficient methodology for the preparation of perfluoroalkyl containing substituted 4*H*-chromenes from the Et_3N-catalyzed reaction of salicyl *N*-tosylimines or salicylaldehydes with methyl 2-perfluoroalkynoates. The structures of these compounds were confirmed by IR, ^1H NMR, ^{13}C NMR, ^{19}F NMR, MS, and X-ray diffraction analysis as well.

2. Results and discussion

Perfluoroalkyl containing substituted 4*H*-chromenes were obtained from the Et_3N-catalyzed reaction of salicyl *N*-tosylimines

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or salicylaldehydes with methyl 2-perfluoroalkynoates (Scheme 1). The structures of the producs were confirmed by IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and MS as well.

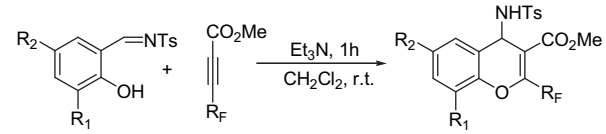
1 or **4** **2** **3** or **5**

1, 3 X=NTs, **4, 5** X=O; R_F=CF_3, C_2F_5, n-C_3F_7; R_1=H, Me, OMe; R_2=H, Cl, NO_2

Scheme 1. Preparation of perfluoroalkyl containing 4*H*-chromenes.

Different solvents were first examined by using the reaction of salicyl *N*-tosylimine **1a** (1.0 equiv) with methyl 4,4,5,5,6,6,6-heptafluorohex-2-ynoate **2a** (1.2 equiv) as a model. Using Et_3N (10 mol %) as catalyst and performing the reaction in different solvents, the reaction could be completed in CH_2Cl_2 within 1 h at room temperature giving the corresponding chromene **3a** in 91% yield (Table 1, entry 1). Both $CHCl_3$ and DMSO proved to be good (90% yield in $CHCl_3$, 90% yield in DMSO, Table 1, entries 2 and 3), while in THF, the yield was only 75% (Table 1, Entry 4). The reaction yield remained unchanged when increased the amount of Et_3N but lower the yield while decreased the amount of Et_3N. As a consequence, we chose CH_2Cl_2 as the best solvent. We found optimal reaction conditions were 1.0 equiv of **1**, 1.2 equiv of **2**, 10 mol % of Et_3N, and performing the reaction in CH_2Cl_2 at room temperature (20 °C) for 1 h.

Table 1
Reaction of other salicyl *N*-tosylimines **1** (1.0 equiv) with methyl 2-perfluoroalkynoates **2** (1.2 equiv) in the presence of 10 mol % of Et_3N



1 **2** **3**

Entry	1	R_1	R_2	2	R_F	Product	Solvent	Yield[a] (%)
1	**1a**	H	H	**2c**	*n*-C_3F_7	**3a**	CH_2Cl_2	91
2	**1a**	H	H	**2c**	*n*-C_3F_7	**3a**	$CHCl_3$	90
3	**1a**	H	H	**2c**	*n*-C_3F_7	**3a**	DMSO	90
4	**1a**	H	H	**2c**	*n*-C_3F_7	**3a**	THF	75
5	**1b**	OCH_3	H	**2c**	*n*-C_3F_7	**3b**	CH_2Cl_2	92
6	**1c**	H	Cl	**2c**	*n*-C_3F_7	**3c**	CH_2Cl_2	86
7	**1b**	OCH_3	H	**2a**	CF_3	**3d**	CH_2Cl_2	90
8	**1c**	H	Cl	**2a**	CF_3	**3e**	CH_2Cl_2	79[b]
9	**1d**	CH_3	H	**2c**	*n*-C_3F_7	**3f**	CH_2Cl_2	88
10	**1b**	OCH_3	H	**2b**	C_2F_5	**3g**	CH_2Cl_2	89
11	**1c**	H	Cl	**2b**	C_2F_5	**3h**	CH_2Cl_2	77
12	**1d**	CH_3	H	**2a**	CF_3	**3i**	CH_2Cl_2	90

[a] Isolated yield.
[b] The reaction was carried out at 0 °C.

Under these optimized reaction conditions, the reactions of several other salicyl *N*-tosylimines **1** with methyl 2-perfluoroalkynoates **2** were also examined (Table 1, entries 5–12). The corresponding fluorinated chromenes **3** were obtained in good to excellent yields. The structure of final product was confirmed by X-ray diffraction of **3b** (Fig. 1[7]). It is noteworthy that the yield of **3e** was rather low under these reaction conditions because the reaction system was complicated and made the isolation difficult. But at 0 °C, the reaction proceeded smoothly giving the sole product **3e** in the yield of 79%. Another distinguishing feature of the reaction is its high regioselectivity: only one regioisomer containing stronger electron-withdrawing substituent at position

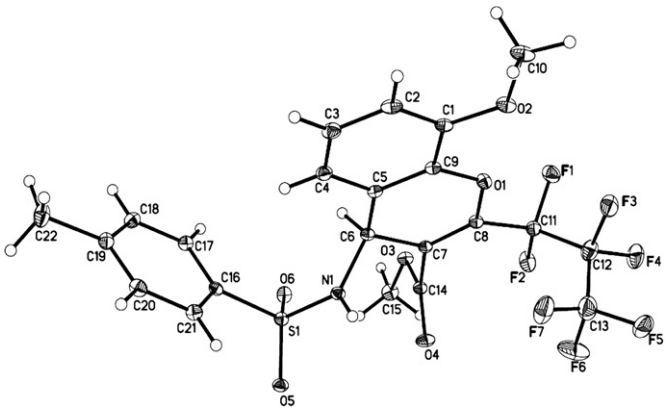
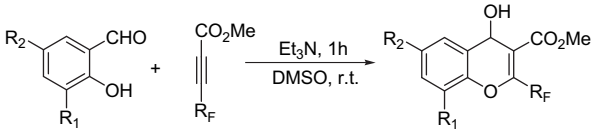


Figure 1. X-ray diffraction of **3b**.

2 of the 4*H*-chromenes is formed, which could be explained by our previous reported result.[8]

To test the generality of this methodology, we further subjected the less reactive salicylaldehyde to the reaction. Performing the reaction in CH_2Cl_2, the reaction of 2-hydroxybenzaldehyde **4a** with methyl 4,4,5,5,6,6,6-heptafluorohex-2-ynoate **2a** became disordered and **5a** was isolated only in low yield (50%). However, when the solvent was changed to DMSO, a high yield of **5a** was observed in 1 h. Under the revised optimal reaction conditions, several other salicylaldehydes can also react with methyl 2-perfluoroalkyl propiolates **2** to give the corresponding chromenes **5** as the sole regioisomer in good to excellent yields (Table 2).

Table 2
Reactions of salicylaldehydes **4** (1.0 equiv) with methyl 2-perfluoroalkynoates **2** (1.2 equiv) in the presence of 10 mol % of Et_3N

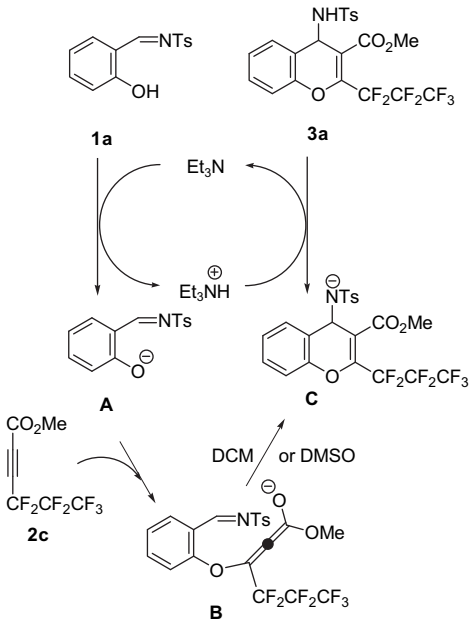


4 **2** **5**

Entry	4	R_1	R_2	2	R_F	Product	Yield[a] (%)
1	**4a**	H	H	**2c**	*n*-C_3F_7	**5a**	93
2	**4b**	OCH_3	H	**2c**	*n*-C_3F_7	**5b**	92
3	**4c**	H	Cl	**2c**	*n*-C_3F_7	**5c**	89
4	**4a**	H	H	**2a**	CF_3	**5d**	87
5	**4b**	OCH_3	H	**2a**	CF_3	**5e**	90
6	**4c**	H	Cl	**2a**	CF_3	**5f**	85
7	**4d**	CH_3	H	**2a**	CF_3	**5g**	91
8	**4d**	CH_3	H	**2c**	*n*-C_3F_7	**5h**	89
9	**4e**	H	NO_2	**2b**	C_2F_5	**5i**	77

[a] Isolated yield.

On the basis of the previous reports,[6,9,10] the proposed mechanism is shown in Scheme 2. We consider the reaction of **1a** with **2c** as an example. Et_3N first abstracts a proton from imine **1a** to generate the anion **A** and release Et_3NH^+. Then, Michael addition occurs between intermediate **A** and **2c** to give intermediate **B**. Then, intramolecular Mannich reaction occurs in intermediate **B** to afford intermediate **C** and subsequent protonation gives product **3a** and regenerates Et_3N. The reason why the reaction of the less reactive salicylaldehyde with methyl 2-perfluoroalkynoates became complicated in DCM is not known. One reasonable explanation is that the proton transfer step for the conversion of intermediate **C** to **3a** is rate determining and the intramolecular Mannich reaction is a reversible one.[8] Proton transfer in DMSO is much faster than in DCM, which allows the Mannich reaction to be predominant.



Scheme 2. Mechanism for the formation of product **3a**.

3. Conclusions

In conclusion, we developed a new efficient process for the synthesis of 4-functional 2-trifluoromethylated or perfluoroalkylated 4*H*-chromenes by reaction of methyl 2-perfluoroalkynoates with salicyl *N*-tosylimines or salicylaldehydes. Compared to previous methods, this technique is simple, experimentally convenient and proceeds smoothly under mild conditions in the presence of Et_3N. The corresponding fluorinated chromenes were obtained in good to excellent yields with high regioselectivity. Efforts to explore further applications of these products are currently in progress in our laboratory.

4. Experimental

4.1. General information

All reagents and solvents were purchased from commercial sources and used without further purification, except that salicyl *N*-tosylimines **1** and methyl 2-perfluoroalkynoates **2** were prepared according to reported literature.[11,12] Melting points were uncorrected. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded on 500 MHz spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard: C_6F_6 for ^{19}F, TMS for ^1H and ^{13}C NMR spectra. IR spectra were obtained on an FT-IR spectrometer. Elemental analysis was performed on an elemental analysis instrument. MS was run on a mass spectrometer. X-ray analysis was performed on an X-ray spectrometer. Preparative TLC on silica gel was performed by using self-coated GF_{254} plates, which were activated immediately before use.

4.2. General procedure for preparation of compound 3

To the solution of salicyl *N*-tosylimines (1.0 mmol) in CH_2Cl_2, methyl 2-perfluoroalkynoates (1.2 mmol) and Et_3N (10 mmol%) were added and the mixture was stirred at room temperature for 1 h. After the completion of the reaction (monitored by TLC), the products were purified by preparative TLC [eluent: petroleum ether (60–90 °C)/ethyl acetate] and recrystallized from dichloromethane and petroleum ether (60–90 °C) to give pure product **3**.

*4.2.1. Methyl 2-(heptafluoropropyl)-4-(tosylamino)-4H-chromene-3-carboxylate **3a**.* A white solid: mp: 130.4–131.2 °C; ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.45 (3H, s, CH_3), 3.46 (3H, s, OCH_3), 5.10 (1H, d, J=9.0 Hz, CH), 5.65 (1H, d, J=9.0 Hz, NH), 7.05–7.75 (8H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −80.75 (t, J=9.4 Hz, 3F), −114.88 (m, 2F), −125.49 (m, 2F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 21.7, 48.5, 52.8, 108.1 (CF_2, tt, $^1J_{F-C}$=243.8 Hz, $^2J_{F-C}$=38.8 Hz), 110.3 (CF_2, m), 113.1, 116.8, 117.6 (CF_3, qt, $^1J_{F-C}$=275.0 Hz, $^2J_{F-C}$=31.0 Hz), 118.7, 126.2, 127.3, 129.6, 129.8, 130.2, 138.2, 140.1 (CCF_2, t, $^2J_{F-C}$=27.0 Hz), 143.9 148.9, 164.8. MS (ESI) m/z: 550.0 $(M+Na)^+$. IR (KBr, cm^{-1}): ν 3302, 2953, 1739, 1693, 1459, 1339. Anal. Calcd for $C_{21}H_{16}F_7NO_5S$: C, 47.82; H, 3.06; N, 2.66. Found: C, 48.02; H, 3.31; N, 2.42.

*4.2.2. Methyl 2-(heptafluoropropyl)-8-methoxy-4-(tosylamino)-4H-chromene-3-carboxylate **3b**.* A white solid: mp: 149.2–151.7 °C; ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.44 (3H, s, CH_3), 3.47 (3H, s, OCH_3), 3.85 (3H, s, CH_3), 5.16 (1H, d, J=8.8 Hz, CH), 5.62 (1H, d, J=8.8 Hz, NH), 6.84–7.74 (7H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −80.75 (t, J=9.4 Hz, 3F), −114.70 (m, 2F), −125.51 (m, 2F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 21.8, 48.7, 52.9, 56.6, 108.9 (CF_2, tt, $^1J_{F-C}$=258.8 Hz, $^2J_{F-C}$=32.5 Hz), 110.3 (CF_2, m), 112.3, 113.0, 117.7 (CF_3, qt, $^1J_{F-C}$=286.3 Hz, $^2J_{F-C}$=33.8 Hz), 119.7, 120.3, 125.9, 127.4, 129.9, 138.3, 139.3, 140.2 (t, CCF_2, $^2J_{F-C}$=28.0 Hz), 143.9, 148.1, 164.9. MS (EI) m/z (%): 557 (M^+, 1), 402 (100), 387 (87), 370 (25), 210 (16), 155 (10), 91 (60). IR (KBr, cm^{-1}): ν 3261, 2960, 1742, 1692, 1489, 1334. Anal. Calcd for $C_{22}H_{18}F_7NO_6S$: C, 47.40; H, 3.25; N, 2.51. Found: C, 47.66; H, 3.51; N, 2.46.

*4.2.3. Methyl 6-chloro-2-(heptafluoropropyl)-4-(tosylamino)-4H-chromene-3-carboxylate **3c**.* A white solid: mp: 135.7–136.4 °C; ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.46 (3H, s, CH_3), 3.55 (3H, s, OCH_3), 5.22 (1H, d, J=9.0 Hz, CH), 5.54 (1H, d, J=9.0 Hz, NH), 6.99–7.74 (7H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −80.73 (t, J=9.4 Hz, 3F), 114.96 (m, 2F), 125.49 (m, 2F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 21.8, 52.9, 56.6, 109.3 (CF_2, tt, $^1J_{F-C}$=260.0 Hz, $^2J_{F-C}$=32.5 Hz), 110.9 (CF_2, m), 112.3, 113.1, 118.3 (CF_3, qt, $^1J_{F-C}$=285.0 Hz, $^2J_{F-C}$=33.8 Hz), 119.7, 120.3, 125.9, 127.4, 129.9, 138.3, 139.3, 140.2 (t, CCF_2, $^2J_{F-C}$=28 .0 Hz), 143.9, 148.1, 164.9. MS (EI) m/z (%): 406 (100), 407 (16), 391 (70), 392 (10), 374 (35), 257 (16), 155 (12), 91 (36). IR (KBr, cm^{-1}): ν 3259, 2973, 1733, 1673, 1458, 1362. Anal. Calcd for $C_{21}H_{15}ClF_7NO_5S$: C, 44.89; H, 2.69; N, 2.49. Found: C, 44.71; H, 2.83; N, 2.35.

*4.2.4. Methyl 8-methoxy-2-(trifluoromethyl)-4-(tosylamino)-4H-chromene-3-carboxylate **3d**.* A white solid: mp: 191.4–193.2 °C; ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.44 (3H, s, CH_3), 3.50 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.05 (1H, d, J=9.0 Hz, CH), 5.66 (1H, d, J=9.0 Hz, NH), 6.86–7.73 (7H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −67.14 (s, 3F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 21.7, 48.2, 52.8, 56.5, 110 (d, CCF_3, $^3J_{F-C}$=2.5 Hz), 112.1, 118.9 (CF_3, q, $^1J_{F-C}$=273.0 Hz), 119.8, 120.5, 126.0, 126.6, 127.3, 129.7, 129.9, 138.3, 139.2, 142.5 (q, CCF_3, $^2J_{F-C}$=37.0 Hz), 143.7, 147.9, 164.8. MS (EI) m/z (%): 457 (M^+, 1), 302.1 (81), 287 (100), 270 (20), 243 .1 (10), 203 (11), 155 (9), 91 (29). IR (KBr, cm^{-1}): ν 3313, 2959, 1737, 1697, 1487, 1340. Anal. Calcd for $C_{20}H_{18}F_3NO_6S$: C, 52.51; H, 3.97; N, 3.06. Found: C, 52.39; H, 3.82; N, 3.22.

*4.2.5. Methyl 6-chloro-2-(trifluoromethyl)-4-(tosylamino)-4H-chromene-3-carboxylate **3e**.* A white solid: mp: 155.4–156.8 °C; ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.45 (3H, s, CH_3), 3.58 (3H, s, OCH_3), 5.29 (1H, d, J=8.0 Hz, CH), 5.54 (1H, d, J=8.0 Hz, NH), 7.04–7.68 (7H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −67.46 (s, 3F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 21.7, 47.9, 53.0, 109.9 (d, CCF_3, $^3J_{F-C}$=1.3 Hz), 118.4, 118.7 (CF_3, q, $^1J_{F-C}$=275.0 Hz), 119.9, 127.2, 129.2, 129.9, 130.4, 131.1, 138.1, 142.5 (q, CCF_3, $^2J_{F-C}$=37.0 Hz), 144.1, 147.7, 164.5. MS (EI) m/z (%): 461 (M^+, 1), 306 (100), 307 (30), 291 (60), 292 (18), 274 (40). IR (KBr, cm^{-1}): ν 3285, 2924, 1728, 1682, 1483,

1342. Anal. Calcd for $C_{19}H_{15}F_3NO_5S$: C, 49.41; H, 3.27; N, 3.03. Found: C, 49.66; H, 3.18; N, 3.15.

4.2.6. Methyl 2-(heptafluoropropyl)-8-methyl-4-(tosylamino)-4H-chromene-3-carboxylate ***3f***. A white solid: mp: 154.1–155.6°C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.26 (3H, s, CH_3), 2.45 (3H, s, CH_3), 3.49 (3H, s, OCH_3), 5.11 (1H, br s, CH), 5.63 (1H, br s, NH), 7.01–7.74 (7H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −80.77 (t, J=9.4 Hz, 3F), −114.75 (m, 2F), −125.56 (m, 2F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 15.4, 21.7, 48.8, 52.8, 109.1 (CF_2, tt, $^1J_{F-C}$=260.0 Hz, $^2J_{F-C}$=32.5 Hz), 110.9 (CF_2, m), 113.1, 118.3, 118.9 (CF_3, qt, $^1J_{F-C}$=285.0 Hz, $^2J_{F-C}$=33.8 Hz), 125.6, 126.4, 126.9, 127.3, 129.8, 131.3, 138.3, 140.2 (t, *C*CF_2, $^2J_{F-C}$=27 .5 Hz), 143.8, 147.5, 164.9. MS (EI) *m*/*z* (%): 510 (3), 386 (100), 371 (93), 354 (29). IR (KBr, cm^{-1}): ν 3305, 2957, 1722, 1688, 1474, 1335. Anal. Calcd for $C_{22}H_{18}F_7NO_5S$: C, 48.80; H, 3.35; N, 2.59. Found: C, 48.65; H, 3.43; N, 2.37.

4.2.7. Methyl 8-methoxy-2-(pentafluoroethyl)-4-(tosylamino)-4H-chromene-3-carboxylate ***3g***. A white solid: mp: 135.1–136.1 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.45 (3H, s, CH_3), 3.48 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.01 (1H, d, J=8.5 Hz, CH), 5.64 (1H, d, J=8.5 Hz, NH), 6.85–7.75 (7H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −82.22 (s, 3F), 116.69 (m, 2F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 21.7, 48.5, 52.9, 56.5, 108.8 (CF_2, qt, $^1J_{F-C}$=260.5 Hz, $^2J_{F-C}$=32.5 Hz), 112.3, 112.6, 117.5 (CF_3, qt, $^1J_{F-C}$=280.0 Hz, $^2J_{F-C}$=33.8 Hz), 119.6, 120.3, 125.9, 127.3, 129.8, 138.2, 139.2, 140.5 (t, *C*CF_2, $^2J_{F-C}$=28.0 Hz), 143.8, 148.0, 164.9. MS (EI) *m*/*z* (%): 476 (3), 388 (3), 352 (91), 337 (100), 320 (25), 293 (11). IR (KBr, cm^{-1}): ν 3310, 2957, 1737, 1685, 1488, 1339. Anal. Calcd for $C_{21}H_{18}F_5NO_6S$: C, 49.71; H, 3.58; N, 2.76. Found: C, 49.53; H, 3.39; N, 2.54.

4.2.8. Methyl 6-chloro-2-(pentafluoroethyl)-4-(tosylamino)-4H-chromene-3-carboxylate ***3h***. A white solid: mp:143.5–145.3 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.46 (3H, s, CH_3), 3.56 (3H, s, OCH_3), 5.21 (1H, d, J=9.0 Hz, CH), 5.54 (1H, d, J=9.0 Hz, NH), 6.99–7.73 (7H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −82.25 (s, 3F), −117.11 (m, 2F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 21.7, 48.2, 53.1, 108.8 (CF_2, qt, $^1J_{F-C}$=260.5 Hz, $^2J_{F-C}$=32.5 Hz), 112.7, 117.1 (CF_3, qt, $^1J_{F-C}$=280.0 Hz, $^2J_{F-C}$=33.8 Hz), 118.3, 119.9, 127.3, 129.1, 130.0, 130.4, 131.1, 137.9, 140.4 (t, *C*CF_2, $^2J_{F-C}$=28.0 Hz), 144.3, 147.6, 164.5. MS (EI) *m*/*z* (%): 480 (4), 358 (31), 356 (100), 341 (77), 324 (37). IR (KBr, cm^{-1}): ν 3321, 2962, 1731, 1688, 1482, 1340. Anal. Calcd for $C_{20}H_{15}ClF_5NO_5S$: C, 46.93; H, 2.95; N, 2.74. Found: C, 46.88; H, 2.86; N, 2.61.

4.2.9. Methyl 8-methyl-2-(trifluoromethyl)-4-(tosylamino)-4H-chromene-3-carboxylate ***3i***. a white solid: mp:148–149.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.31 (3H, s, CH_3), 2.44 (3H, s, CH_3), 3.52 (3H, s, OCH_3), 4.99 (1H, d, J=8.5 Hz, CH), 5.65 (1H, d, J=8.5 Hz, NH), 7.02–7.71 (7H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −67.42 (s, 3F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 15.5, 21.7, 48.5, 52.8, 110.0 (d, *C*CF_3, $^3J_{F-C}$=2.5 Hz), 116.8 (CF_3, q, $^1J_{F-C}$=270.0 Hz), 118.5, 125.7, 126.5, 127.1, 127.3, 129.7, 131.3, 138.4, 142.7 (q, *C*CF_3, $^2J_{F-C}$=37.0 Hz), 143.7, 147.6, 164.8. MS (EI) *m*/*z* (%): 441 (M^+, 1), 410 (3), 372 (25), 286 (71), 271 (100), 254 (21). IR (KBr, cm^{-1}): ν 3302, 2927, 1737, 1693, 1473, 1377. Anal. Calcd for $C_{20}H_{18}F_3NO_5S$: C, 54.42; H, 4.11; N, 3.17. Found: C, 54.26; H, 4.08; N, 3.23.

4.3. General procedure for preparation of compounds 5

To the solution of salicyaldehyde (1.0 mmol) in DMSO (2 mL), methyl 2-perfluoroalkynoates (1.2 mmol) and Et_3N (10 mmol%) were added and the mixture was stirred at room temperature for 1 h. After the completion of the reaction (monitored by TLC), the products were purified by preparative TLC [eluent: petroleum ether 60–90 °C/ethyl acetate] and recrystallized from dichloromethane and petroleum ether (60–90 °C) to give pure product **5**.

4.3.1. Methyl 2-(heptafluoropropyl)-4-hydroxy-4H-chromene-3-carboxylate ***5a***. A white solid: mp: 109.0–109.6 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.89 (1H, d, J=7.3 Hz, OH), 3.87 (3H, s, OCH_3), 5.66 (1H, d, J=7.3 Hz, CH), 7.13–7.54 (4H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −81.90 (t, J=9.4 Hz, 3F), −115.36 (m, 2F), −126.39 (m, 2F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 53.1, 62.6, 109.0 (CF_2, tt, $^1J_{F-C}$=270.0 Hz, $^2J_{F-C}$=32.5 Hz), 110.5 (CF_2, m), 114.6, 116.8, 119.0 (CF_3, qt, $^1J_{F-C}$=285.0 Hz, $^2J_{F-C}$=33.8 Hz), 120.5, 125.9, 129.4, 130.3, 141.1 (t, *C*CF_2, $^2J_{F-C}$=29.0 Hz), 148.7, 166.1. MS (ESI) *m*/*z*: 397 $(M+Na)^+$. IR (KBr, cm^{-1}): ν 3451, 2959, 1720, 1675, 1458, 1337. Anal. Calcd for $C_{14}H_9F_7O_4$: C, 44.93; H, 2.42. Found: C, 45.18; H, 2.66.

4.3.2. Methyl 2-(heptafluoropropyl)-4-hydroxy-8-methoxy-4H-chromene-3-carboxylate ***5b***. A white solid: mp: 113.9–114.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 3.22 (1H, d, J=3.5 Hz, OH), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 5.61 (1H, d, J=3.5 Hz, CH), 6.89–7.18 (3H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −80.81 (t, J=9.4 Hz, 3F), −114.05 (m, 2F), −125.27 (m, 2F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 53.0, 56.5, 62.5, 108.9 (CF_2, tt, $^1J_{F-C}$=270.0 Hz, $^2J_{F-C}$=32.5 Hz), 110.7 (CF_2, m), 112.3, 114.5, 117.8 (CF_3, qt, $^1J_{F-C}$=272.0 Hz, $^2J_{F-C}$=38.0 Hz), 120.2, 121.5, 125.6, 138.8, 140.9 (t, *C*CF_2, $^2J_{F-C}$=29.0 Hz), 148.0, 166.2. MS (ESI) *m*/*z*: 427 $(M+Na)^+$. IR (KBr, cm^{-1}): ν 3473, 2958, 1720, 1675, 1488, 1336. Anal. Calcd for $C_{15}H_{11}F_7O_5$: C, 44.57; H, 2.74. Found: C, 44.36; H, 2.70.

4.3.3. Methyl 6-chloro-2-(heptafluoropropyl)-4-hydroxy-4H-chromene-3-carboxylate ***5c***. A white solid: mp: 97.7–99.3 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 3.18 (1H, d, J=7.3 Hz, OH), 3.87 (3H, s, OCH_3), 5.61 (1H, d, J=7.3 Hz, CH), 7.08–7.51 (3H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −80.77 (t, J=9.4 Hz, 3F), −144.22 (m, 2F), −125.27 (m, 2F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 53.2, 62.2, 108.9 (CF_2, tt, $^1J_{F-C}$=270.0 Hz, $^2J_{F-C}$=32.5 Hz), 110.7 (CF_2, m), 114.5, 117.8 (CF_3, qt, $^1J_{F-C}$=285.0 Hz, $^2J_{F-C}$=34.0 Hz), 118.3, 122.0, 129.1, 130.5, 131.0, 140.9 (t, *C*CF_2, $^2J_{F-C}$=28.0 Hz), 147.1, 165.8. MS (ESI) *m*/*z*: 431 $(M+Na)^+$. IR (KBr, cm^{-1}): ν 3334, 2925, 1731, 1692, 1482, 1335. Anal. Calcd for $C_{14}H_8ClF_7O_4$: C, 41.15; H, 1.97. Found: C, 41.12; H, 1.92.

4.3.4. Methyl 4-hydroxy-2-(trifluoromethyl)-4H-chromene-3-carboxylate ***5d***. A white solid: mp: 86.6–88.1 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 3.17 (1H, d, J=6.0 Hz, OH), 3.88 (3H, s, OCH_3), 5.69 (1H, d, J=6.0 Hz, CH), 7.16–7.50 (4H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −66.96 (s, 3F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 53.0, 62.0, 111.3 (d, *C*CF_3, $^3J_{F-C}$=1.2 Hz), 116.9, 119.1 (CF_3, q, $^1J_{F-C}$=273.8 Hz), 120.5, 126.0, 129.6, 130.2, 143.5 (q, *C*CF_3, $^2J_{F-C}$=37.9 Hz), 148.6, 166.0. MS (EI) *m*/*z* (%): 304 (M^+, 43), 287 (66), 271 (61), 245 (44), 203 (100). IR (KBr, cm^{-1}): ν 3383, 2951, 1732, 1677, 1590, 1490, 1380. Anal. Calcd for $C_{12}H_9F_3O_4$: C, 52.56; H, 3.31. Found: C, 52.53; H, 3.26.

4.3.5. Methyl 4-hydroxy-8-methoxy-2-(trifluoromethyl)-4H-chromene-3-carboxylate ***5e***. A white solid: mp: 118.1–118.8 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 3.04 (1H, d, J=5.8 Hz, OH), 3.89 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 5.69 (1H, d, J=5.8 Hz, CH), 6.92–7.21 (3H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −66.58 (s, 3F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 53.0, 56.5, 62.1, 111.2 (d, *C*CF_3, $^3J_{F-C}$=2.5 Hz), 112.2, 119.2 (CF_3, q, $^1J_{F-C}$=273.8 Hz), 120.5, 121.5, 125.9, 138.7, 143.6 (q, *C*CF_3, $^2J_{F-C}$=38.3 Hz), 148.0, 166.0. MS (EI) *m*/*z* (%): 274 (M^+, 8), 273 (15), 257 (4), 241 (32), 215 (39), 173 (100). IR (KBr, cm^{-1}): ν 3411.15, 2963, 1722, 1682, 1486, 1373. Anal. Calcd for $C_{13}H_{11}F_3O_5$: C, 51.32; H, 3.64. Found: C, 51.08; H, 3.57.

4.3.6. Methyl 6-chloro-4-hydroxy-2-(trifluoromethyl)-4H-chromene-3-carboxylate ***5f***. A white solid: mp: 124.7–126.4 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 3.22 (1H, d, J=5.8 Hz, OH), 3.89 (3H, s, OCH_3), 5.66 (1H, d, J=5.8 Hz, CH), 7.12–7.51 (3H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): δ −66.87 (s, 3F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 53.2, 61.8, 111.1 (d, *C*CF_3, $^3J_{F-C}$=2.5 Hz), 118.4, 118.9 (CF_3, q,

$^1J_{F-C}$=273.8 Hz), 121.9, 129.3, 130.5, 131.0 143.5 (q, *C*CF$_3$, $^2J_{F-C}$=38.3 Hz), 147.1, 165.8. MS (EI) *m*/*z* (%): 308 (M$^+$, 38), 307 (44), 291 (73), 275 (90), 249 (97), 207 (100). IR (KBr, cm^{-1}): *ν* 3505, 2955, 1721, 1678, 1483, 1372. Anal. Calcd for $C_{12}H_8ClF_3O_4$: C, 46.70; H, 2.61. Found: C, 46.58; H, 2.64.

4.3.7. Methyl 4-hydroxy-8-methyl-2-(trifluoromethyl)-4H-chromene-3-carboxylate ***5g***. A white solid: mp: 88–89.7 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): *δ* 2.35 (3H, CH_3), 3.01 (1H, d, *J*=6.0 Hz, OH), 3.89 (3H, s, OCH_3), 5.70 (1H, d, *J*=6.0 Hz, CH), 7.15–7.35 (3H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): *δ* −66.88 (s, 3F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): *δ* 15.6, 52.9, 62.4, 111.1 (d, *C*CF$_3$, $^3J_{F-C}$=2.5 Hz), 119.2 (CF$_3$, q, $^1J_{F-C}$=273.8 Hz), 120.2, 125.5, 126.5, 127.1, 131.4, 143.9 (q, *C*CF$_3$, $^2J_{F-C}$=38.3 Hz), 147.1, 166.1. MS (EI) *m*/*z* (%): 288 (M$^+$, 20), 287 (25), 271 (48), 255 (44), 229 (48), 187 (100). IR (KBr, cm^{-1}): *ν* 3367, 2953, 1731, 1672, 1470, 1377. Anal. Calcd for $C_{13}H_{11}F_3O_4$: C, 54.17; H, 3.85. Found: C, 54.01; H, 4.01.

4.3.8. Methyl 4-hydroxy-8-methyl-2-(heptafluoropropyl)-4H-chromene-3-carboxylate ***5h***. A white solid: mp: 92–92.8 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): *δ* 2.30 (3H, CH_3), 3.05 (1H, d, *J*=6.0 Hz, OH), 3.86 (3H, s, OCH_3), 5.63 (1H, d, *J*=6.0 Hz, CH), 7.13–7.33 (3H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): *δ* −80.80 (t, *J*=9.4 Hz, 3F), −144.07 (m, 2F), −125.26 (m, 2F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): *δ* 15.4, 52.9, 62.8, 108.7 (CF_2, tt, $^1J_{F-C}$=270.0 Hz, $^2J_{F-C}$=32.5 Hz), 111.4 (CF_2, m), 114.4, 118.9 (CF_3, qt, $^1J_{F-C}$=285.0 Hz, $^2J_{F-C}$=34.0 Hz), 120.2, 125.4, 126.4, 126.8, 131.4, 141.1 (t, *C*CF$_2$, $^2J_{F-C}$=28 .0 Hz), 147.1, 166.2. MS (EI) *m*/*z* (%): 388 (M$^+$, 17), 371 (46), 357 (22), 355 (41), 329 (59), 187 (100). IR (KBr, cm^{-1}): *ν* 3473, 2961, 1722, 1674, 1472, 1363. Anal. Calcd for $C_{15}H_{11}F_7O_4$: C, 46.41; H, 2.86. Found: C, 46.40; H, 2.88.

4.3.9. Methyl 4-hydroxy-6-nitro-2-(pentafluoroethyl)-4H-chromene-3-carboxylate ***5i***. A white solid: mp: 105.7–106.7 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): *δ* 3.47 (1H, br s, OH), 3.91 (3H, s, OCH_3), 5.75 (1H, br s, CH), 7.29–8.49 (3H, m, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz, ppm): *δ* −82.05 (s, 3F), −116.48 (m, 2F). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): *δ* 53.5, 61.7, 109.0 (CF_2, qt, $^1J_{F-C}$=270.0 Hz, $^2J_{F-C}$=32.5 Hz), 114.8, 118.0, 118.2 (CF_3, qt, $^1J_{F-C}$=285.0 Hz, $^2J_{F-C}$=34.0 Hz), 121.6, 125.6, 125.9, 140.8 (t, *C*CF$_2$, $^2J_{F-C}$=28 .0 Hz), 145.1, 152.4, 165.3. MS (EI) *m*/*z* (%): 369 (M$^+$, 8), 368 (23), 352 (24), 338 (23), 317 (32), 310 (100). IR (KBr, cm^{-1}): *ν* 3492, 2964, 1721, 1684, 1483, 1350. Anal. Calcd for $C_{13}H_8F_5O_6$: C, 42.29; H, 2.18; N, 3.79. Found: C, 42.43; H, 2.25; N, 3.63.

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7. CCDC-683461 (**3b**) contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/consts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk. Unit cell parameters: *a*: 9.5269 Å; *b*: 11.2132 Å; *c*: 12.9275 Å; *α*: 72.580; *β*: 76.271; *γ*: 67.682; space group: *P*-1.
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