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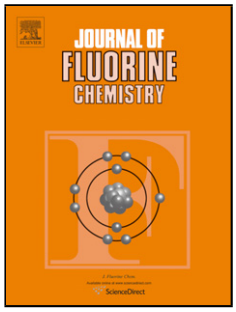

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Synthesis of 8-carbo substituted 2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-ones and their thienoangelicin derivatives

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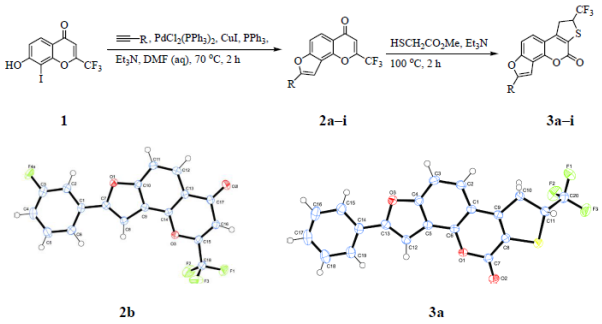
Highlights:

- Tandem alkynylation-cycloisomerization of 7-hydroxy-8-iodo-2-(trifluoromethyl)chromen-4-one afforded the 2-(trifluoromethyl)furochromen-4-ones.
- Redox reaction of the 2-(trifluoromethyl)furochromen-4-ones with methyl mercaptoacetate afforded dihydrothienocoumarin derivatives.
- The X-ray crystal structures of representative compounds from each series were determined.

Graphical Abstract

Synthesis of 8-carbo substituted 2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-ones and their thienoangelicin derivatives



Abstract

Tandem Sonogashira cross-coupling and heteroannulation of 7-hydroxy-8-iodo-2-(trifluoromethyl)chromen-4-one with terminal acetylenes afforded the 8-carbo–substituted 2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-ones **2a**–**i**. The latter were reacted with methyl mercaptoacetate in the presence of triethylamine to afford the corresponding 7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one derivatives **3a**–**i**. The structures of the prepared compounds were characterized using a combination of NMR (^{1}H-, ^{13}C & ^{19}F-), IR and mass spectroscopic techniques, and confirmed by single X-ray crystal structures of 8-(3-fluorophenyl)-2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-one (**2b**) and 2-phenyl-7-(trifluoromethyl)-7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one (**3a**). The highlight of this investigation is the conversion of 2-(trifluoromethyl)–substituted 4*H*-furo[2,3-*h*]chromen-4-ones into trifluoromethyl–substituted thienoangelicin analogues.

Keywords: chromen-4-ones; Sonogashira cross-coupling; furochromen-4-ones; dihydrothienoangelicins; thienoangelicins; X-ray crystal structures

1. Introduction

The naturally occurring khellin (**A**) and visnagin (**B**) shown in Figure 1 exhibit anti-inflammatory properties [1] and these furo[3,2-*c*]chromones are used clinically for the treatment of bronchial asthma and renal colics [2]. The analogous furocoumarins, on the other hand, exhibit a wide range of biological properties including photochemotherapeutic [3,4], antitumor [5], antioxidant [6] and anti-inflammatory [7] activities. Angelicin (**D**) [8] and sphondin (**E**) [9] represented in Figure 1, for example, are angular furocoumarins with therapeutic potential as anti-inflammatory drugs on airway inflammation. The propensity for the pyrone and furan rings to undergo photocycloaddition reactions in the case of the linear furocoumarins such as psoralen (**C**) and to a lesser extend angelicin derivatives has been suggested to cause undesirable side effects in their medical use [10]. However, annulation of an additional ring onto the photoreactive pyrone double bond has been found to generally reduce the phototoxicity of the furocoumarin derivatives [11].

The two main approaches towards the synthesis of furocoumarins involve either construction of the furan ring onto a suitably functionalized pyrone scaffold [12] or construction of the six-membered heterocyclic ring onto an *ortho*-hydroxy carbonylbenzofuran framework [13]. Among these strategies, the methodology of fusing a furan ring on a coumarin nucleus of allyloxy- or propargyloxycoumarins [14], 7-(2-oxopropoxy)- or 7-(2-hydroxyethoxy)-2*H*-chromen-2-ones [15], and *ortho*-hydroxy styrylcoumarins [16], for example, has been widely applied for the synthesis of linear or angular furocoumarins and their difurocoumarin derivatives. Tandem copper catalysed cross-coupling of 8-iodo-7-hydroxycoumarin with terminal acetylenes has also been employed for the synthesis of angular furocoumarins [17,18].

Fluorinated organic compounds often show unique physical and chemical behaviour that can be utilized in pharmaceutics and materials science. A trifluoromethyl group, for example, is known to enhance lipid solubility and metabolic stability of a molecule, and to lead to reduced side effects [19]. Moreover, the presence of this strongly electron-withdrawing group on the 2-

position of a chromen-4-one skeleton has been found to have a major impact on the reactivity of the pyrone ring towards nitrogen-, sulfur- and carbon-based nucleophiles [20]. The reaction of 2-(trifluoromethyl)chromen-4-one or 7-(trifluoromethyl)norkhellin with alkyl mercaptoacetates, for example, has been found to promote 1,4-nucleophilic ring addition instead of ring fission to afford trifluoromethyl–substituted dihydrothienocoumarins or dihydrothienopsoralens, respectively [20-22]. We considered the molecular framework of the readily accessible 7-hydroxy-8-iodo-2-(trifluoromethyl)chromen-4-one, which has recently been shown to undergo palladium catalysed Suzuki cross-coupling with arylboronic acids to afford the 8-carbo–substituted 7-hydroxy-2-(trifluoromethyl)chromen-4-ones [23]. We envisaged that this *ortho*-iodohydroxychromenone derivative would undergo tandem palladium catalysed Sonogashira cross-coupling and cycloisomerization with terminal acetylenes to afford the 8-carbo–substituted 4*H*-furo[2,3-*h*]chromen-4-ones. In our view, the presence of the 2-trifluoromethyl group on the resulting furochromenone framework would facilitate subsequent 1,4-nucleophilic ring addition reaction with methyl mercaptoacetate to afford novel trifluoromethyl–substituted dihydrothienoangelicin analogues.

2. Results and Discussion

In order to proof the above assumptions, we synthesised 7-hydroxy-8-iodo-2-(trifluoromethyl)chromen-4-one (**1**) from commercially available 2,4-dihydroxyacetophenone following literature protocol [23,24]. This was achieved via initial condensation of 2,4-dihydroxyacetophenone with trifluoroacetic anhydride in the presence pyridine (1.0 equivalent) at 80 °C for 10 h [24]. Site-selective halogenation of the intermediate 7-hydroxy-2-(trifluoromethyl)chromen-4-one with iodine in chloroform in the presence of pyridine afforded

1 in analogy with the literature precedent [23]. The proximity of the Csp^2–I bond to the nucleophilic hydroxyl group was exploited by subjecting compound **1** to terminal acetylenes in the presence of dichlorobis(triphenylphosphine)palladium(II) and copper(I) iodide catalyst mixture, triphenylphosphine as ligand and triethylamine as a base in dimethyl formamide under reflux for 2 h (Scheme 1). Aqueous work-up and purification by column chromatography on silica gel afforded in each case in sequence, a homocoupled dimer and a cross-coupled product. A combination of nuclear magnetic resonance (NMR), infrared (IR) and mass spectroscopic data confirmed the structures of the cross-coupled products as the 8-carbo–substituted 2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-ones **2a**–**i** (refer to Table 1 for substitution pattern). The signal for the trifluoromethyl group resonates as a singlet around δ -71.3 ppm in ^{19}F-NMR spectra of the corresponding substrates **2a–i**. The ^{1}H- and ^{13}C-NMR spectra of compounds **2a**–**h**, for example, revealed the presence of increased number of signals in the aromatic region. Likewise, the `^{1}H-NMR spectrum of **2i** revealed set of multiplets in the aliphatic region 1.70–2.70 ppm corresponding to the cyclohexenyl ring. The absence of a set of carbon singlets in the region δ 80–100 ppm of the ^{13}C-NMR spectra of compounds **2a**–**i**, which are typical for the acetylene moiety ruled out the possibility of the intermediate 8-alkynylated derivatives. Moreover, the accurate calculated m/z values of these products were consistent with the assigned structures.

The strong electron-withdrawing property of the trifluoromethyl group (–CF_3) has been found to enhance the electrophilic character at cationic sites in superelectrophiles resulting in greater positive-charge delocalisation [25]. Its presence on the C2 position of a chromen-4-one scaffold causes activation of the pyrone ring towards sulfur-based nucleophiles to convert the chromen-4-one scaffold into a chromen-2-one ring and at the same time append an additional ring on the pyrone double bond [20-22]. These literature precedents encouraged us to subject compounds **2a**–**i** to methyl mercaptoacetate (3 equiv.) in the presence of triethylamine as

catalyst at 100 °C with thin layer chromatography (tlc) monitoring (Scheme 2). The reaction was found to be complete within 2 h and the mixtures were in each case quenched with aqueous ethanol followed by filtration of the precipitate and recrystallization. Characteristic signals in the ^{1}H-NMR spectra of these products recorded as $CDCl_3$ or DMSO-d_6 solutions at 300 MHz are a set of doublet of doublets (dd) in the region δ 3.90–4.00 ppm integrating for two protons and another multiplet around δ 5.10 ppm integrating for a single proton. The long range coupling of the chemically non-equivalent (diastereotopic) methylene protons to fluorine atoms ($^{4}J_{HF}$) was not observed and these protons resonate as a pair of doublet of doublets at this frequency. The multiplet for the methine proton resonates significantly downfield due to the combined electronegativity of sulphur and strong electron withdrawing inductive effect of the trifluoromethyl group. Their ^{19}F-NMR spectra confirmed the presence of an intense doublet around δ -73.1 ppm with coupling constant value J = 8.9 Hz corresponding to the trifluoromethyl group. The structures of these compounds were assigned based on combination of NMR, IR and mass spectroscopic data as the 7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one (dihydrothienoangelicin) derivatives **3a**–**i**.

Single crystals suitable for X-ray diffraction (XRD) analysis were obtained for compounds **2b** and **3a**, respectively, and the structures of the 8-carbo–substituted 2-(trifluoromethyl)-4H-furo[2,3-h]chromen-4-ones **2a**–**i** and 7,8-dihydro-5H-furo[2,3-h]thieno[2,3-c]chromen-5-one (dihydrothienoangelicin) derivatives **3a**–**i** were thus distinctly confirmed by X-ray analysis (Figure 2). The crystallographic numbering for both compounds has been used in the context of the X-ray analysis, and differs with the systematic numbering for series **2a**–**i** and **3a**–**i**. The furochromenone framework of **2b** (Figure 2a) is essentially co-planar with the 3-fluorophenyl substituent slightly twisted out of the plane of planarity with torsion angle C(2)-C(1)-C(7)-O(1) of 10.1°. There is disorder of fluorine atom of the phenyl group with a site occupancy of 0.56:0.44. This positional disorder, which brings the position of fluorine atom at two sites, one

with a higher occupancy and the other with lower occupancy is known to be prevalent when fluorine atom is present in an *ortho* or *meta* position with any given functional group in an organic molecule [27,28]. The phenyl substituent of **3a**, on the other hand, is coplanar with the tetracyclic framework with torsion angle C(12)-C(13)-C(14)-C(19) of 1.6° (Figure 2b). Disorder in both cases has not been observed for the trifluoromethyl (–CF_3) group, which is more prone to disorder [29]. Crystallographic parameters for compounds **2b** and **3a** are summarized in Table 3 [26].

In summary, tandem Sonogashira cross-coupling and heteroannulation of 7-hydroxy-8-iodo-2-(trifluoromethyl)chromen-4-one with terminal acetylenes afforded novel 8-carbo substituted 2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-ones. The presence of trifluoromethyl group at the 2-position of the pyrone ring facilitated 1,4-nucleophilic ring addition with methyl mercaptoacetate to afford series of trifluoromethyl–substituted dihydrothienoangelicin analogues. These results represent the first synthesis of thienoangelicin analogues and, more so angular furocoumarin derivatives substituted at position-2 of the furan ring with a carbon-based group. The X-ray crystal structures of compounds **2b** and **3a** were determined. The results of this study corroborate previous studies which indicated that the fluorine atom tends to get disordered over different positions in the molecule, particularly when this atom is present in an *ortho* or *meta* position with any given functional group in an organic molecule. The trifluoromethyl substituted heterocycles prepared in this investigation represent suitable candidates for further studies of chemical transformation and biological activity.

3. Experimental

3.1. General

The melting points (mp.) were recorded on a Thermocouple digital melting point apparatus (Mettler Toledo LLC, Columbus, OH, USA). The infrared (IR) spectra were recorded as powders using a Bruker VERTEX 70 FT-IR Spectrometer (Bruker Optics, Billerica, MA, USA) with a diamond ATR (attenuated total reflectance) accessory by using the thin-film method. Merck kieselgel 60 (0.063–0.200 mm) (Merck KGaA, Frankfurt, Germany) was employed as a stationary phase for column chromatography. The NMR (^{1}H-, ^{13}C- and ^{19}F-) spectra were recorded using Varian Mercury 300 MHz NMR spectrometer (Varian Inc., Palo Alto, CA, USA) and the chemical shifts are quoted relative to the solvent peaks. The low- and high-resolution mass spectra were recorded at an ionization potential of 70 eV using Micromass Autospec-TOF (double focusing high resolution) instrument (Waters Corp., Milford, MA, USA).

3.2. Synthesis of 7-hydroxy-8-iodo-2-(trifluoromethyl)chromene-4-one (1).

3.2.1. 7-Hydroxy-2-(trifluoromethyl)chromen-4-one

A stirred solution of 2,4-dihydroxyacetophenone (5.00 g, 32.9 mmol) in trifluoroacetic anhydride (10 mL) was treated with pyridine (2.60 g, 32.9 mmol) and the mixture was heated at 80 °C for 4 h. The cooled reaction mixture was treated with 1 M hydrochloric acid (5 mL) and the product was extracted with chloroform. The combined organic phases were washed with water, dried over anhydrous $MgSO_4$, and then concentrated *in vacuo* on a rotary evaporator. The crude product was purified by column chromatography on using silica gel using 9:1 toluene-ethyl acetate mixture (v/v) as an eluent to afford 7-hydroxy-2-(trifluoromethyl)chromen-4-one as a yellow solid (4.80 g, 63%), mp. 210–212 °C (Lit. [31] 208–210 °C); ν_{max} (ATR) 634, 724, 830, 847, 868, 925, 1074, 1132, 1164, 1191, 1230, 1250, 1278, 1395, 1557, 1660 cm^{-1} ; δ_H (300 MHz, DMSO-*d*$_6$) 6.86 (1H, s, H-3), 6.91 (1H, d, *J* = 2.2 Hz, H-8), 6.98 (1H, dd, *J* = 2.2 and 8.8 Hz, H-6), 7.89 (1H, d, *J* = 8.8 Hz, H-5), 11.14 (1H, br s, OH); δ_C (75 MHz, DMSO-*d*$_6$) 102.9, 111.0 (q, $^{3}J_{CF}$ = 2.6 Hz), 116.5, 116.7, 119.1 (q, $^{1}J_{CF}$ =

273.8 Hz), 127.4, 150.6 (q, $^{2}J_{CF}$ = 38.3 Hz), 157.4, 164.3, 175.4; δ_F (282 MHz, DMSO-*d*$_6$) -70.5 (s, -CF_3); HRMS (ES^+): m/z $[M - H]^-$ calc for $C_{10}H_4O_3F_3$: 229.0113; found 229.0110.

3.2.2. 7-Hydroxy-8-iodo-2-(trifluoromethyl)chromen-4-one (**1**)

A stirred mixture of 7-hydroxy-2-(trifluoromethyl)chromen-4-one (2.00 g, 8.69 mmol) and iodine (8.82 g, 34.8 mmol) in chloroform (30 mL) in a round-bottomed flask was treated with pyridine (2.75 g, 34.8 mmol). The reaction mixture was stirred at room temerature 16 h and then quenched with saturated aqueous solution of $Na_2S_2O_3$ (60 mL). The resulting precipitate was filtered and purified using silica gel column chromatography with 3:1 toluene-ethyl acetate mixture (v/v) as an eluent to afford **2** as an off-white solid (2.38 g, 77%); mp. 208–209 °C (lit. [23] 205–206 °C); ν_{max} (ATR) 528, 765, 827, 867, 930, 1148, 1163, 1192, 1216, 1265, 1283, 1407, 1514, 1549, 1578, 1652 cm^{-1}; δ_H (300 MHz, DMSO-*d*$_6$) 6.98 (1H, s, H-3), 7.07 (1H, d, *J* = 8.8 Hz, H-6), 7.90 (1H, d, *J* = 8.8 Hz, H-5), 11.95 (1H, br s, OH); δ_C (75 MHz, DMSO-*d*$_6$) 74.8, 111.1 (q, $^{3}J_{CF}$ = 2.6 Hz), 115.0, 117.4, 119.1 (q, $^{1}J_{CF}$ = 273.9 Hz), 127.1, 151.0 (q, $^{2}J_{CF}$ = 38.6 Hz), 156.7, 164.3, 175.6; δ_F (282 MHz, DMSO-*d*$_6$) -70.3 (s, -CF_3); HRMS (ES^+): m/z $[M - H]^-$ calc for $C_{10}H_3O_3F_3I$: 354.9079; found 354.9062.

3.3. Typical procedure for the tandem Sonogashira cross-coupling and cycloisomerization of 2.

A mixture of **2** (0.50 g, 1.40 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.05 g, 0.07 mmol), copper(I) iodide (0.03 g, 0.14 mmol), triphenylphosphine (0.02 g, 0.08 mmol) and triethylamine (0.17 g, 1.68 mmol) in 4:1 DMF-water (v/v, 20 mL) was placed in a two necked round-bottomed flask equipped with a stirrer bar, condenser and a rubber septum. The mixture was flushed with argon gas for 30 minutes and a solution of phenylacetylene derivative (1.2 equiv.) in DMF (2 mL) was introduced *via* a rubber septum by means of a syringe. A balloon filled with argon was connected to the top of the condenser and the mixture was left to stir at 70 °C for 2 h. The mixture was allowed to cool and then poured into crushed ice. The product

was extracted into chloroform and the combined organic phases were washed with water and dried over anhydrous $MgSO_4$. The salt was filtered off and the solvent was evaporated under reduced pressure on a rotary evaporator. The residue was purified by column chromatography on using silica gel using 9:1 toluene-ethyl acetate mixture (v/v) as an eluent. The following compounds were prepared in this fashion.

8-Phenyl-2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-one (**2a**)

Yellow solid (0.32 g, 69%), mp. 195–196 ℃; ν_{max} (ATR) 545, 653, 689, 736, 756, 905, 919, 975, 1085, 1120, 1136, 1161, 1192, 1215, 1263, 1281, 1316, 1334, 1414, 1463, 1613, 1668 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.80 (1H, s, H-3), 7.36 (1H, s, H-9), 7.42–7.53 (3H, m, H-3′,4′,5′), 7.63 (1H, d, *J* = 8.8 Hz, H-6), 7.90 (2H, d, *J* = 8.3 Hz, H-2′,6′), 8.11 (1H, d, *J* = 8.8 Hz, H-5); δ_C (75 MHz, $CDCl_3$) 98.2, 111.1, 111.2 (q, $^3J_{CF}$ = 2.6 Hz), 118.7 (q, $^1J_{CF}$ = 273.9 Hz), 119.1, 119.7, 121.5, 125.2, 129.0, 129.1, 129.6, 149.8, 151.6 (q, $^2J_{CF}$ = 39.2 Hz), 157.8, 158.4, 176.5; δ_F (282 MHz, DMSO-d_6) -71.3 (s); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{18}H_{10}O_3F_3$: 331.0582; found 331.0585.

8-(3-Fluorophenyl)-2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-one (**2b**)

Brown solid (0.35 g, 72%), mp. 200–201 ℃; ν_{max} (ATR) 515, 652, 683, 736, 768, 821, 846, 911, 1075, 1085, 1117, 1139, 1183, 1213, 1264, 1282, 1330, 1412, 1482, 1572, 1596, 1613, 1672 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.80 (1H, s, H-3), 7.11 (1H, td, *J* = 8.4 and 2.5 Hz, H-4′), 7.38 (1H, s, H-9), 7.46 (1H, td, *J* = 5.8 and 8.1 Hz, H-6′), 7.55–7.72 (3H, overlapping signals, H-6 and H-2′,5′), 8.12 (1H, d, *J* = 8.8 Hz, H-5); δ_C (75 MHz, $CDCl_3$) 99.3, 111.1, 111.3 (q, $^3J_{CF}$ = 2.6 Hz), 112.1 (d, $^2J_{CF}$ = 23.9 Hz), 116.5 (d, $^2J_{CF}$ = 21.3 Hz), 118.7 (q, $^1J_{CF}$ = 274.0 Hz), 118.9, 119.8, 120.8 (d, $^4J_{CF}$ = 3.1 Hz), 122.0, 130.7 (d, $^3J_{CF}$ = 8.4 Hz), 131.1 (d, $^3J_{CF}$ = 8.5 Hz), 149.9, 151.7 (q, $^2J_{CF}$ = 39.2 Hz), 156.4 (d, $^4J_{CF}$ = 3.2 Hz), 158.4, 163.1 (d, $^1J_{CF}$ = 246.7 Hz), 176.4; δ_F (282 MHz, $CDCl_3$) -71.3 (s, $-CF_3$), -111.8 (td, J_{FH} = 5.8 and 9.0 Hz, 3-F); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{18}H_9O_3F_4$: 349.0488; found 349.0489.

8-(4-Fluorophenyl)-2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-one (**2c**)

Pale green solid (0.33 g, 67%), mp. 215–216 °C; ν_{max} (ATR) 530, 613, 657, 737, 771, 808, 912, 977, 1083, 1119, 1139, 1155, 1191, 1213, 1282, 1334, 1411, 1467, 1502, 1616, 1672 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.78 (1H, s, H-3), 7.17 (2H, t, *J* = 8.7 Hz, H-3′,5′), 7.26 (1H, s, H-9), 7.59 (1H, d, *J* = 8.8 Hz, H-6), 7.86 (2H, t, *J* = 8.7 Hz, H-2′,6′), 8.09 (1H, d, *J* = 8.8 Hz, H-5); δ_C (75 MHz, $CDCl_3$) 97.9, 111.0, 111.2 (q, $^3J_{CF}$ = 2.6 Hz), 116.2 (d, $^2J_{CF}$ = 22.1 Hz), 118.7 (q, $^1J_{CF}$ = 274.0 Hz), 119.0, 119.7, 121.5, 125.4 (d, $^4J_{CF}$ = 3.4 Hz), 127.1 (d, $^3J_{CF}$ = 8.5 Hz), 149.8, 151.6 (q, $^2J_{CF}$ = 39.2 Hz), 156.9, 158.3, 163.4 (d, $^1J_{CF}$ = 250.7 Hz), 176.4; δ_F (282 MHz, $CDCl_3$) -71.3 (s, $-CF_3$), -110.4 (tt, J_{FH} = 5.2 and 8.4 Hz, 4-F); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{18}H_9O_3F_4$: 349.0488; found 349.0480.

8-(3-Chlorophenyl)-2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-one (**2d**)

Pale yellow solid (0.29 g, 57%), mp. 212–213 °C; ν_{max} (ATR) 533, 657, 684, 738, 767, 830, 871, 925, 977, 1085, 1119, 1147, 1184, 1204, 1279, 1325, 1414, 1458, 1472, 1612, 1651, 1667 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.80 (1H, s, H-3), 7.34–7.46 (3H, overlapping signals, H-9, H-4′,5′), 7.61 (1H, d, *J* = 8.8 Hz, H-6), 7.76 (1H, dt, *J* = 1.6 and 7.3 Hz, H-6′), 7.87 (1H, t, *J* = 1.6 Hz, H-2′), 8.12 (1H, d, *J* = 8.8 Hz, H-5); δ_C (75 MHz, $CDCl_3$) 99.3, 111.1, 111.3 (q, $^3J_{CF}$ = 2.6 Hz), 118.6 (q, $^1J_{CF}$ = 274.0 Hz), 118.8, 119.8, 122.0, 123.1, 125.1, 129.5, 130.3, 130.7, 135.2, 149.9, 151.7 (q, $^2J_{CF}$ = 39.3 Hz), 156.2, 158.4, 176.3; δ_F (282 MHz, $CDCl_3$) -71.3 (s, $-CF_3$); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{18}H_9O_3ClF_3$: 365.0192; found 365.0190.

8-(4-Chlorophenyl)-2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-one (**2e**)

Yellow solid (0.32 g, 63%), mp. 229–231 °C; ν_{max} (ATR) 528, 656, 736, 770, 808, 912, 976, 1081, 1118, 1144, 1191, 1213, 1280, 1334, 1406, 1468, 1590, 1617, 1669 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.79 (1H, s, H-3), 7.32 (1H, s, H-9), 7.44 (2H, d, *J* = 8.6 Hz, H-3′,5′), 7.60 (1H, d, *J* = 8.8 Hz, H-6), 7.80 (2H, d, *J* = 8.6 Hz, H-2′,6′), 8.10 (1H, d, *J* = 8.8 Hz, H-5); δ_C (75 MHz, $CDCl_3$) 98.6, 111.0, 111.2 (q, $^3J_{CF}$ = 2.6 Hz), 118.7 (q, $^1J_{CF}$ = 274.0 Hz), 119.0, 119.8, 121.8,

126.3, 127.5, 129.3, 135.5, 149.8, 151.6 (q, $^{2}J_{CF}$ = 39.2 Hz), 156.6, 158.3, 176.4; δ_F (282 MHz, $CDCl_3$) -71.3 (s, -CF_3); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{18}H_9O_3ClF_3$: 365.0192; found 365.0189.

8-(*p*-Tolyl)-2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-one (**2f**)

Light brown solid (0.35 g, 72%), mp. 193–194 ℃; ν_{max} (ATR) 529, 658, 737, 767, 817, 914, 975, 1083, 1117, 1139, 1163, 1191, 1215, 1262, 1283, 1333, 1415, 1465, 1504, 1615, 1651 cm^{-1}, 1672; δ_H (300 MHz, $CDCl_3$) 2.41 (3H, s, CH_3), 6.78 (1H, s, H-3), 7.26–7.29 (3H, s overlapping d, H-3′,5′ and H-9), 7.59 (1H, d, *J* = 8.8 Hz, H-6), 7.76 (2H, d, *J* = 8.0 Hz, H-2′, 6′), 8.07 (1H, d, *J* = 8.8 Hz, H-5); δ_C (75 MHz, $CDCl_3$) 21.4, 97.4, 110.9, 111.1 (q, $^{3}J_{CF}$ = 2.7 Hz), 118.7 (q, $^{1}J_{CF}$ = 273.9 Hz), 119.2, 119.6, 121.1, 125.1, 126.3, 129.7, 139.8, 149.7, 151.6 (q, $^{2}J_{CF}$ = 39.0 Hz), 158.1, 158.2, 176.5; δ_F (282.2 MHz, $CDCl_3$) -71.3 (s, -CF_3); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{19}H_{12}O_3F_3$: 345.0739; found 345.0741.

8-(4-Methoxyphenyl)-2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-one (**2g**)

Yellow solid (0.31 g, 61%), mp. 196–197 ℃; ν_{max} (ATR) 737, 763, 802, 833, 917, 976, 1024, 1087, 1117, 1147, 1176, 1188, 1208, 1254, 1277, 1335, 1418, 1503, 1589, 1614, 1645, 1667 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 6.79 (1H, s, H-3), 7.00 (2H, d, *J* = 8.8 Hz, H-3′,5′), 7.21 (1H, s, H-9), 7.59 (1H, d, *J* = 8.8 Hz, H-6), 7.82 (2H, d, *J* = 8.8 Hz, H-2′,6′), 8.07 (1H, d, *J* = 8.8 Hz, H-5); δ_C (75 MHz, $CDCl_3$) 55.4, 96.5, 110.9, 111.1 (q, $^{3}J_{CF}$ = 2.6 Hz), 114.5, 118.7 (q, $^{1}J_{CF}$ = 274.0 Hz), 119.3, 119.7, 120.9, 121.8, 126.7, 149.7, 151.6 (q, $^{2}J_{CF}$ = 39.1 Hz), 158.0, 158.2, 160.7, 176.6; δ_F (282 MHz, $CDCl_3$) -71.3 (s, -CF_3); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{19}H_{12}O_4F_3$: 361.0688; found 361.0685.

8-(3,5-Dimethoxyphenyl)-2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-one (**2h**)

Yellow solid (0.38 g, 69%), mp. 230–231 ℃; ν_{max} (ATR) 530, 655, 736, 767, 815, 884, 943, 1032, 1087, 1114, 1146, 1193, 1212, 1270, 1329, 1413, 1461, 1571, 1603, 1667 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.88 (6H, s, 2 × OCH_3), 6.51 (1H, d, *J* = 1.8 Hz, H-4′), 6.79 (1H, s, H-3),

7.01 (2H, d, J = 1.8 Hz, H-2′,6′), 7.31 (1H, s, H-9), 7.60 (1H, d, J = 8.8 Hz, H-6), 8.09 (1H, d, J = 8.8 Hz, H-5); δ_C (75 MHz, $CDCl_3$) 55.5, 98.6, 101.9, 103.2, 111.0, 111.2 (q, $^3J_{CF}$ = 2.7 Hz), 118.7 (q, $^1J_{CF}$ = 273.9 Hz), 119.0, 119.7, 121.5, 130.7, 149.8, 151.6 (q, $^2J_{CF}$ = 39.2 Hz), 157.6, 158.2, 161.2, 176.4; δ_F (282 MHz, $CDCl_3$) -71.3 (s, -CF_3); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{20}H_{14}O_5F_3$: 391.0793; found 391.0788.

8-(Cyclohex-1-en-1-yl)-2-(trifluoromethyl)-4*H*-furo[2,3-*h*]chromen-4-one (**2i**)

Brown solid (0.32 g, 68%), mp. 179–180 °C; ν_{max} (ATR) 525, 652, 737, 764, 826, 863, 1084, 1112, 1144, 1186, 1201, 1252, 1266, 1326, 1415, 1460, 1609, 1647, 1668 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.67–1.75 (2H, m, H-5′), 1.76–1.89 (2H, m, H-4′), 2.18–2.34 (2H, m, H-3′), 2.36–2.49 (2H, m, H-6′), 6.70 (1H, t, J = 4.0 Hz, H-2′), 6.76 (1H, s, H-3), 6.79 (1H, s, H-9), 7.50 (1H, d, J = 8.7 Hz, H-6), 8.03 (1H, d, J = 8.7 Hz, H-5); δ_C (75 MHz, $CDCl_3$) 21.9, 22.1, 24.8, 25.5, 96.8, 110.7, 111.0 (q, $^3J_{CF}$ = 2.7 Hz), 118.7 (q, $^1J_{CF}$ = 274.0 Hz), 118.9, 119.4, 121.0, 126.4, 128.5, 149.7, 151.6 (q, $^2J_{CF}$ = 39.0 Hz), 158.1, 159.3, 176.6; δ_F (282 MHz, $CDCl_3$) -71.3 (s, -CF_3); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{18}H_{14}O_3F_3$: 335.0895; found 335.0895.

4.4. Typical procedure for reaction of **2a**–**i** with methyl mercaptoacetate to afford **3a**–**i**.

A mixture of **2a** (0.20 g, 0.61 mmol), methyl mercaptoacetate (0.33 g, 3.10 mmol) and Et_3N (0.1 mL) was heated at 100 °C for 2 h. After cooling, the reaction mixture was diluted with 25% aqueous ethanol (10 mL) and filtered on a sintered funnel. The solid product was washed with cold aqueous ethanol and then purified by column chromatography on silica gel using 9:1 toluene-ethyl acetate mixture (v/v) as an eluent to afford **3a** as a solid. The following compounds were prepared in this fashion.

2-Phenyl-7-(trifluoromethyl)-7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one (**3a**)

White solid (0.16 g, 68%), mp. 263–264 °C; ν_{max} (ATR) 451, 689, 757, 794, 1079, 1113, 1148, 1269, 1358, 1608, 1702 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.96 (1H, dd, J = 4.0 and 19.0 Hz, 8-H_a), 4.04 (1H, dd, J = 9.9 and 19.0 Hz, 8-H_b), 5.05–5.24 (1H, m, H-7), 7.41–7.56 (3H,

m, H-3′,4′,5′), 7.65 (1H, d, *J* = 8.7 Hz, H-10), 7.72 (1H, d, *J* = 8.7 Hz, H-9), 7.80 (1H, s, H-3), 7.98 (2H, d, *J* = 7.2 Hz, H-2′,6′); δ_C (75 MHz, DMSO-*d*$_6$) 36.5, 47.1 (q, $^2J_{CF}$ = 30.5 Hz), 99.3, 109.4, 113.0, 118.2, 122.0, 122.2, 125.4, 126.7 (q, $^1J_{CF}$ = 277.9 Hz), 129.3, 129.6, 129.9, 146.6, 148.8, 156.0, 156.1, 157.0; δ_F (282 MHz, DMSO-*d*$_6$) -73.1 (d, J_{FH} = 8.9 Hz, -CF_3); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{20}H_{12}O_3F_3S$: 389.0459; found 389.0460.

2-(3-Fluorophenyl)-7-(trifluoromethyl)-7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one (**3b**)

Pale yellow solid (0.15 g, 64%), mp. 270–271 ℃; ν_{max} (ATR) 456, 688, 746, 761, 788, 854, 1081, 1114, 1151, 1183, 1267, 1353, 1568, 1608, 1705 cm^{-1}; δ_H (300 MHz, DMSO-*d*$_6$) 3.93 (1H, dd, *J* = 4.0 and 18.8 Hz, 8-H_a), 4.02 (1H, dd, *J* = 9.9 and 18.8 Hz, 8-H_b), 5.06–5.20 (1H, m, H-7), 7.24 (1H, t, *J* = 8.5 Hz, H-4′), 7.53 (1H, td, *J* = 6.2 and 8.1 Hz, H-2′), 7.62(1H, d, *J* = 8.7 Hz, H-10), 7.66 (1H, d, *J* = 8.7 Hz, H-9), 7.70–7.78 (2H, m, H-5′,6′), 7.82(1H, s, H-3); δ_C (75 MHz, DMSO-*d*$_6$) 36.5, 47.1 (q, $^2J_{CF}$ = 30.2 Hz), 100.6, 109.3, 112.0 (d, $^2J_{CF}$ = 23.8 Hz), 113.0, 116.5 (d, $^2J_{CF}$ = 21.1 Hz), 118.0, 121.3, 122.3, 122.4, 126.7 (q, $^1J_{CF}$ = 278.3 Hz), 131.5 (d, $^3J_{CF}$ = 8.9 Hz), 131.7 (d, $^3J_{CF}$ = 8.4 Hz), 146.6, 148.6, 155.5 (d, $^4J_{CF}$ = 3.0 Hz), 155.9, 156.1, 162.9 (d, $^1J_{CF}$ = 243.7 Hz); δ_F (282 MHz, DMSO-*d*$_6$) -73.0 (d, J_{FH} = 8.9 Hz), -112.19 to -112.10 (m, 3-F); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{20}H_{11}O_3F_4S$: 407.0365; found 407.0365.

2-(4-Fluorophenyl)-7-(trifluoromethyl)-7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one (**3c**)

White solid (0.17 g, 73%), mp. 226–227 ℃; ν_{max} (ATR) 449, 594, 609, 758, 795, 958, 1076, 1106, 1157, 1193, 1237, 1265, 1505, 1606, 1707 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.77 (1H, dd, *J* = 4.2 and 18.2 Hz, 8-H_a), 3.85 (1H, dd, *J* = 9.9 and 18.2 Hz, 8-H_b), 4.37–4.54 (1H, m, H-7),7.16 (2H, t, *J* = 8.6 Hz, H-3′,5′), 7.21–7.26 (2H, overlapping signals, H-3, H-10), 7.47 (1H, d, *J* = 8.6 Hz, H-9), 7.82 (2H, t, *J* = 8.6 Hz, H-2′,6′); δ_C (75 MHz, $CDCl_3$) 36.4, 47.7 (q, $^2J_{CF}$ = 31.6 Hz), 97.9, 108.9, 112.6, 116.2 (d, $^2J_{CF}$ = 22.1 Hz), 118.8, 119.6, 123.6, 125.62 (d, $^4J_{CF}$ = 3.4

Hz), 125.63 (q, $^{1}J_{CF}$ = 278.1 Hz), 127.0 (d, $^{3}J_{CF}$ = 8.4 Hz), 146.2, 146.7, 156.1, 156.2, 156.5, 163.3 (d, $^{1}J_{CF}$ = 250.2 Hz); δ_F (282 MHz, $CDCl_3$) -74.1 (d, $J_{H,F}$ = 8.1 Hz, -CF_3), -110.78 to -110.69 (m, 4-F); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{20}H_{11}O_3F_4S$: 407.0365; found 407.0352.

2-(3-Chlorophenyl)-7-(trifluoromethyl)-7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one (**3d**)

White solid (0.19 g, 82%), mp. 277–278 ℃; ν_{max} (ATR) 455, 563, 663, 685, 761, 790, 948, 1019, 1074, 1108, 1159, 1187, 1267, 1353, 1474, 1557, 1605, 1704 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.95 (1H, dd, *J* = 3.9 and 19.0 Hz, 8-H_a), 4.03 (1H, dd, *J* = 9.9 and 19.0 Hz, 8-H_b), 5.06–5.20 (1H, m, H-7), 7.42–7.57 (2H, m, H-4′,5′), 7.64 (1H, d, *J* = 8.7 Hz, H-10), 7.69 (1H, d, *J* = 8.7 Hz, H-9), 7.87–7.92 (2H, overlapping signals, H-6′, H-3), 7.99 (1H, t, *J* = 1.6 Hz, H-2′); δ_C (75 MHz, DMSO-d_6) 36.5, 47.2 (q, $^{2}J_{CF}$ = 30.7 Hz), 100.7, 109.4, 113.1, 118.1, 122.3, 122.4, 123.9, 124.9, 126.7 (q, $^{1}J_{CF}$ = 278.5 Hz), 128.6, 131.3, 131.4, 134.4, 146.7, 148.6, 155.3, 155.9, 156.2; δ_F (282.2 MHz, DMSO-d_6) -73.0 (d, J_{FH} = 8.9 Hz, -CF_3); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{20}H_{11}O_3ClF_3S$: 423.0070; found 423.0070.

2-(4-Chlorophenyl)-7-(trifluoromethyl)-7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one (**3e**)

White solid (0.21 g, 91%), mp. 240–241 ℃; ν_{max} (ATR) 481, 745, 799, 953, 1010, 1076, 1095, 1106, 1159, 1195, 1263, 1345, 1492, 1606, 1709 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.93 (1H, dd, *J* = 3.9 and 18.8 Hz, 8-H_a), 4.02 (1H, dd, *J* = 10 and 18.8 Hz, 8-H_b), 5.06–5.13 (1H, m, H-7), 7.53 (2H, d, *J* = 8.6 Hz, H-3′,5′), 7.61(1H, d, *J* = 8.7 Hz, H-10), 7.65 (1H, d, *J* = 8.7 Hz, H-9), 7.75(1H, s, H-3), 7.92 (2H, d, *J* = 8.6 Hz, H-2′,6′); δ_C (75 MHz, DMSO-d_6) 36.5, 47.1 (q, $^{2}J_{CF}$ = 30.3 Hz), 99.9, 109.3, 113.0, 118.1, 122.1, 122.2, 126.7 (q, $^{1}J_{CF}$ = 277.9 Hz), 126.9, 128.1, 129.5, 134.3, 146.5, 148.6, 155.7, 155.9, 156.1; δ_F (282 MHz, DMSO-d_6) -73.0 (d, $J_{H,F}$ = 8.9 Hz, -CF_3); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{20}H_{11}O_3ClF_3S$: 423.0070; found 423.0060.

2-(*p*-Tolyl)-7-(trifluoromethyl)-7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one (**3f**)

White solid (0.15 g, 64%), mp. 261–262 ℃; ν_{max} (ATR) 493, 644, 746, 793, 957, 1014, 1031, 1077, 1105, 1157, 1193, 1262, 1351, 1506, 1606, 1622, 1706 cm^{-1}; δ_H (300 MHz, DMSO-*d*$_6$) 2.36 (3H, s, CH_3), 3.94 (1H, dd, *J* = 3.9 and 18.8 Hz, 8-H_a), 4.03 (1H, dd, *J* = 10.0 and 18.8 Hz, 8-H_b), 5.04–5.21 (1H, m, H-7),7.31 (2H, d, *J* = 8.1 Hz, H-3′,5′), 7.61(1H, d, *J* = 8.7 Hz, H-10), 7.65–7.70 (2H, overlapping signals, H-3 and H-9), 7.84 (2H, d, *J* = 8.1 Hz, H-2′,6′); δ_C (75 MHz, DMSO-*d*$_6$) 21.4, 36.5, 47.1 (q, $^2J_{CF}$ = 30.4 Hz), 98.4, 109.3, 113.0, 118.3, 121.7, 122.1, 125.3, 126.6, 126.7 (q, $^1J_{CF}$ = 278.3 Hz), 130.1, 139.7, 146.5, 148.8, 156.0, 157.2; δ_F (282 MHz, DMSO-*d*$_6$) -73.0 (d, J_{FH} = 8.9 Hz, -CF_3); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{21}H_{14}O_3F_3S$: 403.0616; found 403.0616.

2-(4-Methoxyphenyl)-7-(trifluoromethyl)-7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one (**3g**)

Pale Yellow solid (0.15 g, 65%), mp. 253–254 ℃; ν_{max} (ATR) 447, 612, 754, 767, 784, 953, 1023, 1040, 1072, 1107, 1168, 1198, 1253, 1268, 1342, 1484, 1590, 1609, 1716 cm^{-1}; δ_H (300 MHz, DMSO-*d*$_6$) 3.82 (3H, s, OCH_3), 3.94 (1H, dd, *J* = 4.0 and 19.0 Hz, 8-H_a), 4.02 (1H, dd, *J* = 9.9 and 19.0 Hz, 8-H_b), 5.04–5.20 (1H, m, H-7), 7.06 (2H, d, *J* = 8.8 Hz, H-3′,5′), 7.56–7.60 (2H, overlapping signals, H-3, 10), 7.65 (1H, d, *J* = 8.6 Hz, H-9), 7.89 (2H, d, *J* = 8.8 Hz, H-2′, 6′); δ_C (75 MHz, DMSO-*d*$_6$) 36.5, 47.1 (q, $^2J_{CF}$ = 30.8 Hz), 55.8, 97.3, 109.2, 113.0, 115.0, 118.5, 121.3, 121.9, 122.0, 126.7 (q, $^1J_{CF}$ = 277.9 Hz), 127.0, 146.4, 148.7, 155.9, 156.0, 157.2, 160.7; δ_F (282.2 MHz, DMSO-*d*$_6$) -73.0 (d, J_{FH} = 8.9 Hz, -CF_3); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{21}H_{14}O_4F_3S$: 419.0565; found 419.0563.

2-(3,5-Dimethoxyphenyl)-7-(trifluoromethyl)-7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one (**3h**)

Pale yellow solid (0.16 g, 70%), mp. 256–258 ℃; ν_{max} (ATR) 469, 744, 792, 818, 853, 953, 1014, 1032, 1060, 1080, 1104, 1157, 1192, 1205, 1258, 1335, 1429, 1567, 1592, 1606, 1711

cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.82 (6H, s, 2 × OCH_3), 3.94 (1H, dd, J = 4.0 and 19.0 Hz, 8-H_a), 4.03 (1H, dd, J = 9.9 and 19.0 Hz, 8-H_b), 5.05–5.21 (1H, m, H-7), 6.54 (1H, t, J = 2.1 Hz, H-4′), 7.10 (2H, d, J = 2.1 Hz, H-2′,6′), 7.62 (1H, d, J = 8.7 Hz, H-10), 7.69 (1H, d, J = 8.7 Hz, H-9), 7.86 (1H, s, H-3); δ_C (75 MHz, DMSO-d_6) 36.5, 47.1 (q, $^2J_{CF}$ = 30.7 Hz), 55.9, 100.0, 102.1, 103.1, 109.3, 113.0, 118.2, 122.0, 122.1, 126.7 (q, $^1J_{CF}$ = 278.0 Hz), 131.0, 146.6, 148.7, 156.97, 156.01, 156.8, 161.3; δ_F (282 MHz, DMSO-d_6) -73.0 (d, J_{FH} = 8.9 Hz, -CF_3); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{22}H_{16}O_5F_3S$: 449.0671; found 449.0663.

2-(Cyclohex-1-en-1-yl)-7-(trifluoromethyl)-7,8-dihydro-5*H*-furo[2,3-*h*]thieno[2,3-*c*]chromen-5-one (**3i**)

White solid (0.16 g, 68%), mp. 235–236 ℃; ν_{max} (ATR) 445, 636, 746, 794, 959, 1009, 1073, 1103, 1154, 1193, 1263, 1350, 1374, 1554, 1606, 1620, 1643, 1706 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.52–1.69 (2H, m, H-5′), 1.69–1.83 (2H, m, H-4′), 2.14–2.31 (2H, m, H-3′), 2.32–2.45 (2H, m, H-6′), 3.93 (1H, dd, J = 4.0 and 19.0 Hz, 8-H_a), 4.02 (1H, dd, J = 9.9 and 19.0 Hz, 8-H_b), 5.03–5.20 (1H, m, H-7), 6.60 (1H, t, J = 3.7 Hz, H-2′), 7.02 (1H, s, H-3), 7.57 (2H, s, H-9,10); δ_C (75 MHz, DMSO-d_6) 21.9, 22.1, 24.6, 25.4, 36.5, 47.1 (q, $^2J_{CF}$ = 30.6 Hz), 97.6, 109.0, 112.8, 118.0, 121.6, 121.9, 126.7 (q, $^1J_{CF}$ = 277.8 Hz), 126.8, 127.9, 146.4, 148.8, 155.8, 156.0, 158.4; δ_F (282.2 MHz, DMSO-d_6) -73.0 (d, J_{FH} = 8.9 Hz); HRMS (ES^+): m/z $[M + H]^+$ calc for $C_{20}H_{16}O_3F_3S$: 393.0772; found 393.0770.

3.5. Data Collection and Refinement of **2b** and **3a**.

Intensity data were determined on a Bruker Venture D8 Photon CMOS diffractometer (Bruker AXS, Madison, WI, USA) with graphite-monochromated MoKα_1 (λ = 0.71073 Å) radiation at 173 K using an Oxford Cryostream 600 cooler. Data reduction was performed using the program SAINT+, version 6.02 [31]. Data reduction was carried out using the program SAINT+, version 6.02 and empirical absorption corrections were made using SADABS [31]. The space group assignments were made using XPREP [31]. The structures were solved in the

WinGX [32] Suite of programs using direct methods through using SHELXS-97 [33], and refined using full-matrix least-squares/difference Fourier techniques on F^2 using SHELXL-2017 [33]. All C-bound H atoms were placed at idealized positions and refined as riding atoms with isotropic parameters 1.2 times those of their parent atoms. The positional disorder of the F atom (labelled F4A and F4B) of **2b** was resolved by finding alternative positions in the difference Fourier map and their site occupancies refined to 0.560(5) and 0.440(5). Diagrams and publication material for **2b** and **3a** were generated using ORTEP-3 [32] and PLATON [34].

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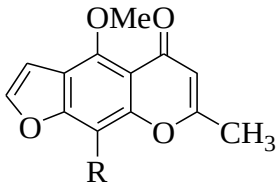
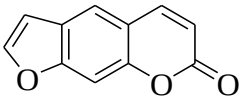
Figures

Figure 1: Structures of naturally occurring furo[3,2-*c*]chromones and furocoumarin analogues.

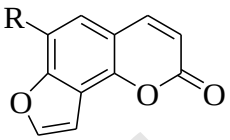


Khellin, R = OCH_3 (**A**)

Visnagin, R = H (**B**)



Psoralen (**C**)



Angelicin, R = H (**D**)

Sphondin, R = OCH_3 (**E**)

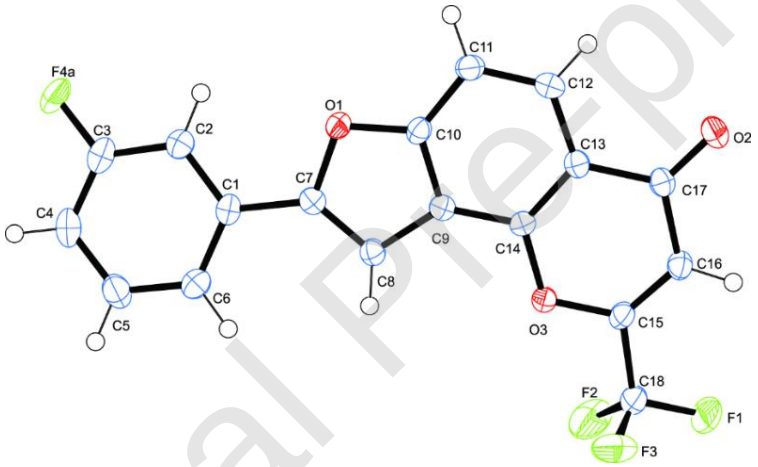


Figure 2(a)

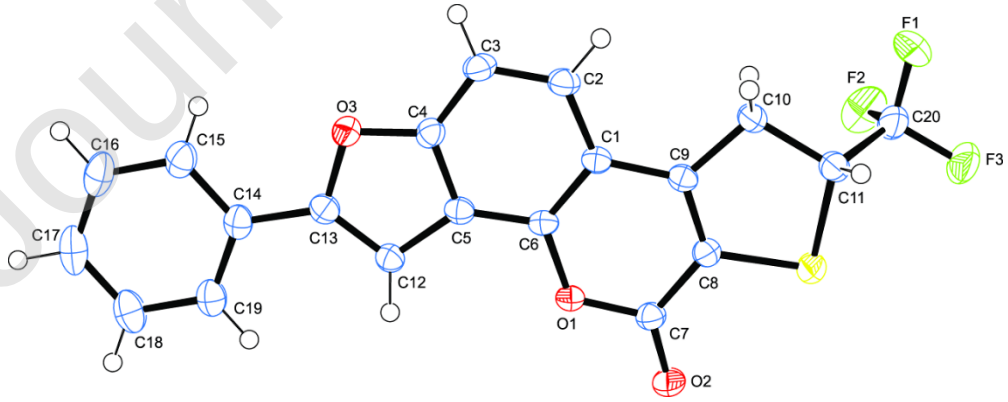
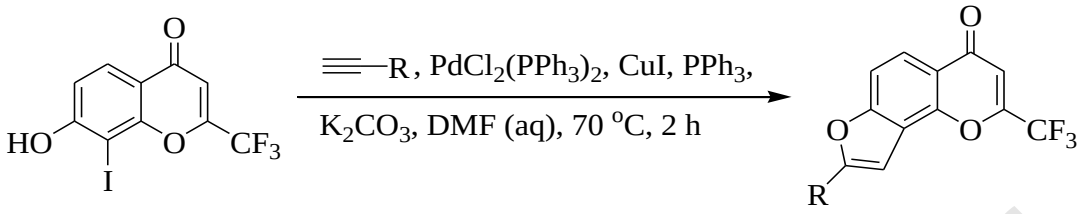


Figure 2(b)

Figure 2: Oak Ridge Thermal Ellipsoid Plot (ORTEP) diagrams (50% probability level) of **2b** (Figure 2a) and **3a** (Figure 2b). For clarity, hydrogen atoms are not labelled.

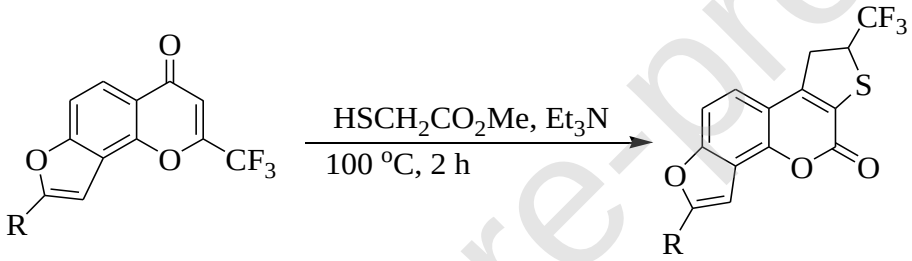
Scheme

Scheme 1: Synthesis of the 2,5-dicarbo substituted 4*H*-furo[2,3-*h*]chromen-4-ones **2a**–**i**.



1 **2a**–**i**

Scheme 2: Synthesis of dihydrothienoangelicin analogues **3a**–**i**.



2a–**i** **3a**–**i**

Tables

Table 1: Designation of R for **2a**–**i** and corresponding percentage yields.

Entry	Designation of R	%Yield of 2
1	C_6H_5-	69 (**2a**)
2	3-FC_6H_4-	72 (**2b**)
3	4-FC_6H_4-	67 (**2c**)
4	3-ClC_6H_4-	57 (**2d**)
5	4-ClC_6H_4-	63 (**2e**)
6	4-MeC_6H_4-	72 (**2f**)
7	4-MeOC_6H_4-	61 (**2g**)
8	3,5-MeO(C_6H_3)-	69 (**2h**)
9	Cyclohex-1-en-1-yl	68 (**2i**)

Table 2: Designation of R and the corresponding percentage yields for **3a**–**i**.

Entry	Designation of R	%Yield of 3
1	C_6H_5-	68 (**3a**)
2	3-FC_6H_4-	64 (**3b**)
3	4-FC_6H_4-	73 (**3c**)
4	3-ClC_6H_4-	82 (**3d**)
5	4-ClC_6H_4-	91 (**3e**)
6	4-MeC_6H_4-	64 (**3f**)
7	4-MeOC_6H_4-	65 (**3g**)
8	3,5-MeO(C_6H_3)-	70 (**3h**)
9	-Cyclohex-1-en-1-yl	68 (**3i**)

Table 3. Crystal data and structure refinement for **2b** and **3a**.

	CCDC-1954710	**CCDC-1954888**
Formula	$C_{18}H_8F_4O_3$	$C_{20}H_{11}F_3O_3S$
Formula weight	348.24	388.35
Temperature	173(2) K	173(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Monoclinic
Space group	*P*-1	$P2_1/n$
Unit cell dimensions	a = 4.8321(4) Å b = 9.8738(9) Å c = 15.1458(12) Å α = 100.432(3)° β = 97.039(3)° γ = 93.871(3)°	a = 7.3355(3) Å b = 29.0389(10) Å c = 8.3463(3) Å α= 90° β= 108.811(2)° γ = 90°
Volume	702.34(10) $Å^3$	1682.92(11) $Å^3$
Z	2	4
Density (calculated)	1.647 Mg/m^3	1.533 Mg/m^3
Absorption coefficient	0.147 mm^{-1}	0.243 mm^{-1}
F(000)	352	792
Crystal size	0.746 x 0.096 x 0.054 mm^3	0.359 x 0.213 x 0.090 mm^3
Theta range for data collection	3.137 to 27.999°	2.672 to 28.000°
Data/ restraints/ parameters	3331/0/236	4050/0/244
Measured reflections	15487	22573
$\theta_{min}/\theta_{max}$	3.137/27.999°	2.672/28.000°.
R_{int}	0.0390	0.0267
Goodness-of-fit on F^2	1.044	1.043
Final R indices [I > 2sigma(I)]	R_1 = 0.0541, wR_2 = 0.1228	R_1 = 0.0329, wR_2 = 0.0833

R indices (all data)	R_1 = 0.0745, wR2 = 0.1331	R_1 = 0.0399, wR_2 = 0.0869
Extinction coefficient	n/a	n/a
Largest diff. peak and hole	0.318/-0.270 e.Å^{-3}	0.343/-0.233 e.Å^{-3}