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Palladium-catalyzed coupling reactions on functionalized 2-trifluoromethyl-4-chromenone scaffolds. Synthesis of highly functionalized trifluoromethyl-heterocycles

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Abstract

The chromenone core is a ubiquitous group in biologically-active natural products and has been extensively used in organic synthesis. Fluorine derived compounds, including those with a trifluoromethyl group (-CF₃), have shown enhanced biological activities in numerous pharmaceuticals compared with their non-fluorinated analogs. We have found that 2-trifluoromethyl chromenones can be readily functionalized in the 8- and 7-positions, providing chromenones cores of high structural complexity which are excellent precursors for numerous trifluoromethyl-heterocycles.

Graphical Abstract

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Primary Data

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Keywords

Fluorine; chromenone; trifluoromethyl-; heterocycle synthesis; palladium-catalyzed coupling

Incorporation of fluorine into molecules is gaining interest as a modification strategy for many pharmaceuticals, agrochemicals and functional materials.¹ Among the fluorine functionalities utilized, the trifluoromethyl group (-CF₃) has attracted substantial attention since it has been used as an isostere for the methyl group.² The addition of this moiety onto a molecular platform leads to remarkable enhancements of lipophilicity, metabolic stability, and bioavailability of the resulting compound. Besides these changes in biological properties, the strong electron-withdrawing nature and large hydrophobic domain of this moiety leads to important changes in the physical properties.³ Fluorine appears in > 20 % of pharmaceuticals and agrochemicals, most commonly as a trifluoromethyl group, including the drugs efavirenz, mefloquine, sorafenib and teriflunomide among others. However, in spite of the utility of fluorine in synthetic molecules, fluorine atoms have been only identified in approximately a dozen naturally-occurring organic compounds such as fluoroacetone, nucleocidin or ω -fluoro-oleic acid (Figure 1)⁴.

Isoflavones (3-aryl-chromen-4-ones) are a large class of natural products present in legumes (*Fabaceae*) such as soya, lentils chick pea, fenugreek, clovers and alfalfa which have a large number of biological activities such as anti-viral, anti-cancer, anti-oxidative, anti-hyperglycemic, anticataracts, antiinflammatory, antifertility, insecticidal, anti-fungal, and anti-microbial.⁵ 2-Trifluoromethyl isoflavones and chromenones have also been identified as promising therapeutic agents against cancer, inflammation or neurological disorders.⁶ Moreover, the chromen-4-one scaffold has also been used as an intermediate building block and can be an intermediate for the synthesis of a large number of other heterocycles such as oxazoles,⁷ pyrimidines,⁸ and pyrazoles.⁹ We hypothesized that introducing a trifluoromethyl group in the structure would increase the metabolic stability of the parent 4-chromenone scaffold and alter the electronics of the heterocycle and derived compounds. 2-CF₃-chromen-4-one derivatives have been synthesized previously by Khilya et al.¹⁰ but their reactivity and biological activity has been poorly studied. Here we report new advances in the synthesis of 2-CF₃-chromen-4-ones as well as their palladium-catalyzed coupling reactions.

As a part of our effort to develop new small molecules with enhanced biological activity and to extend previous studies using the chromenone scaffold,¹¹ we focused our attention on the synthesis and functionalization of the 2-CF₃-chromen-4-one scaffold. This platform was envisaged as a building block for the synthesis of more complex molecules with increased and interesting bioactivity. 7-hydroxy-2-CF₃-chromen-4-one **1** was chosen as our basic starting point template. Using a previously published synthesis of **1** allowed the production of the CF₃-chromenone in gram-scale without the need for chromatographic purification.¹² Two strategies were designed in order to increase the complexity of template chromenone **1** (Scheme 1). In one approach, triflylation of the 7-phenolic oxygen provided chromenone **2** in excellent yield by following a general procedure for phenolic triflylation with Tf₂O, pyridine in dichloromethane.¹³ In the second approach, a direct iodination protocol used for the

synthesis of 3-iodo chromenones,¹⁴ provided exclusively 8-iodo-chromenone which was confirmed by the X-rays structure of a directly closed analogue (Compound 7. Scheme 5). It is worth noting the high selectivity of this reaction at this position since neither a different isomer nor a poly-iodinated compound were detected in spite of the excess of iodine used in the reaction conditions and the desired iodo-chromenone **3** was obtained in high purity after titration.

To functionalize the CF₃-chromen-4-ones, the Suzuki coupling reaction of compound **2** with diverse aryl boronic acids was investigated. Several conditions were screened by varying the palladium sources (See Supporting Information). Pd(dppf)Cl₂ was found to be the most reactive species of palladium, with reaction proceeding to completion in less than half an hour for most substrates. Moreover, this palladium species also showed a high reactivity with alkyl boronic acids (**4i**). Alternative Pd(0) species such as Pd(PPh₃)₄, were less active and needed longer reaction times with ranges between 3 to 16 h for a high conversion. Moreover, Pd(0) sources were completely ineffective with alkyl boronic acids. These reaction conditions were found to be very robust for the synthesis of aryl chromenones **4**, affording high reactivity for both electron-rich and electron-poor aromatic as well as alkyl boronic acids, furnishing the desired products, generally, in excellent yields (Scheme 2).

Because of the high potential biological utility of the 2-CF₃-chromen-4-one scaffold and the success that we achieved with Suzuki reactions of the triflate, we set out to further diversify this platform by investigating Pd-catalyzed aminations. In particular, it was important to develop a general protocol for the Buchwald-type reaction of anilines with 7-triflate chromenone derivatives **2** since there is no general methodology for this transformation. A small number of 7-amino-chromenones have been reported by Pd-catalyzed benzophenone-imine coupling reaction with bromides followed by hydrolysis¹⁵ and 7-(alkyl)amino-chromenones by Nucleophilic Aromatic Substitution (S_NAr) of activated chromenones.¹⁶ After screening several sets of reaction conditions, it was found that Pd(OAc)₂ with BINAP as ligand lead to the most efficient transformations and reproducibility (Scheme 3). These conditions provided excellent yields with electron-rich anilines as well as with hydrazines (**5k**).

Moreover, to generate ether-linked 2-CF₃-chromen-4-ones, additional reaction screening led to the identification of conditions that enabled Pd-catalyzed coupling with phenols. The most effective conditions consisted of Pd₂dba₃ in the presence of JohnPhos ligand, which afforded 7-phenoxyaryl chromenone ethers **6** in good to excellent yields with both electron-rich and electron-poor phenols, as well as thiols (Scheme 4). Notably, the conditions that have been developed allow selective coupling of phenols in the presence of anilines, and *vice versa* (see compounds **5b** and **6c**).

Next, we explored the functionalization of 2-CF₃-chromenones at position 8. It was found that chromenone **3**, with a 7-OH, underwent direct Suzuki coupling only with the highly electron-withdrawing 3,5-trifluoromethyl boronic acid using the conditions previously described to give compound **9** in excellent yield. Unfortunately, no other boronic acids that were screened were reactive enough for this direct Suzuki reaction with the unprotected OH. Chromenones **7** and **8** were synthesized by alkylation of chromenone **3** and screened with

substituted aryl boronic acids of diverse nature: electron-rich, electron-poor and heterocycles furnishing 3-aryl chromenones in good yields (Scheme 5). These substrates were not found to react with alkyl boronic acids, instead furnishing the deiodinated chromenone, likely due to a more favorable β -hydride elimination process than the desired reductive elimination.

Trifluoromethyl heterocycles are important substructures for pharmaceutical, agrochemicals and material sciences.¹⁷ We envisaged that the chromenones synthesized in this study could lead to new types of highly functionalized heterocycles. It was found that CF₃-containing heterocycles were readily obtained in excellent yields under mild and general conditions independent of the substituents of the chromenone scaffold. Utilizing diverse chromenones **10c**, **4f**, and **6d**, synthesis of pyrazole **12a**, 2-thioneimidine **12b**, and 2-aminopyrimidine **12c** respectively all took place rapidly and in high yield to afford the CF₃-heterocycles (Scheme 6).

In summary, we have developed an extensive and highly efficient methodology for the functionalization of 2-CF₃-4-chromenones at the 7 and 8 positions which provides a new approach to prepare these complex heterocyclic systems. The trifluoromethyl group modifies the physicochemical properties of the chromenones enabling the production of more diverse structures. In addition, it was found that incorporation of the CF₃ group increases the reactivity of the chromenone core towards Pd-catalyzed Suzuki and other coupling reactions in comparison with the 2-H scaffold. We have also demonstrated the high utility of these compounds by preparing a small library of CF₃-containing heterocycles. Further studies involving the combination of derivatives at both positions 8 and 7 are underway. Moreover, the biological activities of these new 4-chromenones, isoflavones as well as some of the derived-heterocycles are being currently studied.

All chemical reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Anhydrous solvents were purchased from Sigma-Aldrich, and dried over 3 Å molecular sieves when necessary. DCM, DMF and THF were purified by passage through a bed of activated alumina. Normal phase flash column chromatography was performed using Biotage KP-Sil 50 μ m silica gel columns and ACS grade solvents on a Biotage Isolera flash purification system. Analytical thin layer chromatography (TLC) was performed on EM Reagent 0.25 mm silica gel 60 F₂₅₄ plates and visualized by UV light. Proton (¹H), and carbon (¹³C) NMR spectra were recorded on a 500 MHz Bruker Avance III with direct cryoprobe spectrometer. Chemical shifts were reported in ppm (δ) and were referenced using residual non-deuterated solvent as an internal standard (CDCl₃ at 7.26 ppm for ¹H NMR and 77.16 for ¹³C NMR. CD₃OD at 3.31 ppm for ¹H NMR and 49.00 for ¹³C NMR). The chemical shifts for ¹H NMR and ¹³C NMR are reported to the second and first decimal place respectively. Proton coupling constants are expressed in hertz (Hz). The following abbreviations were used to denote spin multiplicity for proton NMR: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublets, dt = doublet of triplets, quin = quintet, tt = triplet of triplets. In some cases, overlapping signals occurred in the ¹³C NMR spectra and C-F coupling constants could also be reported (Hz). Low resolution liquid chromatography/mass spectrometry (LCMS) was performed on a Waters Acquity-H UPLC/MS system with a 2.1 mm x 50 mm, 1.7 μ m, reversed phase BEH C18 column and LCMS grade solvents. A

gradient elution from 95% water +0.1% formic acid/5% acetonitrile +0.1% formic acid to 95% acetonitrile +0.1% formic acid/5% water +0.1% formic acid over 2 min plus a further minute continuing this mixture at a flow rate of 0.85 mL/min was used as the eluent. Total ion current traces were obtained for electrospray positive and negative ionization (ESI+/ESI-). High-resolution mass spectra were obtained using an Agilent 6210 LC-TOF spectrometer in the positive ion mode using electrospray ionization with an Agilent G1312A HPLC pump and an Agilent G1367B autoinjector at the Integrated Molecular Structure Education and Research Center (IMSERC), Northwestern University. Melting point ranges were measured with a Buchi Melting Point M-565 apparatus and are uncorrected.

General procedure for the synthesis of 7-hydroxy-2-(trifluoromethyl)-4H-chromen-4-one (1)

Over a suspension of 1-(2,4-dihydroxyphenyl)ethan-1-one (5.00 g, 32.89 mmol) in trifluoroacetic anhydride (18.50 mL, 131.56 mmol) placed in a high-pressure tube, sodium 2,2,2-trifluoroacetate (9.84 g, 72.36 mmol) was added and the system was capped and stirred at 110 °C for 24 h. The reaction was allowed to cool down to approximately 70 °C and then was diluted with 200 mL of EtOAc. The mixture was neutralized by adding saturated aqueous K₂CO₃ solution until no more bubbling was observed. Layers were separated and the aqueous phase was extracted with more EtOAc (3 × 150 mL). The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. The solution was then concentrated to 100–150 mL of EtOAc. Then the flask was capped and kept at room temperature for 1–2 days, obtaining a solid which was filtrated and dried under vacuum to obtain 4.09 g of pure 1 as a white solid in 54% yield.

¹H NMR (500 MHz, CD₃OD) δ 8.02 (d, *J* = 8.9 Hz, 1H), 7.01 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 6.74 (s, 1H) ppm.

¹³C NMR (126 MHz, CD₃OD) δ 178.0, 166.0, 159.2, 153.2 (*q*, ²*J*(C,F) = 37.8 Hz), 128.3, 120.2 (*q*, ¹*J*(C,F) = 273.4 Hz) 117.6, 117.5, 116.9, 111.2, 111.2, 103.5 ppm.

LCMS (ESI): *m/z* [M+H]⁺ calcd for C₁₀H₆F₃O₃⁺: 231.0; found: 231.1.

General procedure for the synthesis of 4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl trifluoromethanesulfonate (2)

Over an ice-bath cold solution of compound **1** (2 g, 8.70 mmol) and pyridine (2.81 mL, 34.8 mmol) in 18 mL of CH₂Cl₂ under nitrogen atmosphere, Tf₂O (2.20 mL, 13.06 mmol) was added dropwise for 15 min. Then, the mixture stirred from 0 °C to room temperature for 16 h. The reaction was quenched by adding 15 mL of water. The organic layer was separated and the aqueous one was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography (*n*-hexanes / ethyl acetate = 10:1 to 4:1) providing compound **2**.

Yellow solid in 95% yield (3.0 g); mp 46 – 48 °C.

^1H NMR (500 MHz, DMSO- d_6) δ 8.32 – 8.20 (m, 2H), 7.74 (dd, J = 8.8, 2.4 Hz, 1H), 7.17 (s, 1H) ppm.

^{13}C NMR (126 MHz, DMSO- d_6) δ 175.4, 155.6, 152.4, 151.4 (q , $^2J(\text{C},\text{F})$ = 38.8 Hz), 128.2, 123.7, 120.1, 118.5 (q , $^1J(\text{C},\text{F})$ = 274.7 Hz), 112.9, 111.5, 111.4 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_5\text{F}_6\text{O}_5\text{S}^+$: 362.9756; found: 362.9758.

General procedure for the synthesis of 7-hydroxy-8-iodo-2-(trifluoromethyl)-4H-chromen-4-one (3)

Over a solution of 7-hydroxy-2-(trifluoromethyl)-4H-chromen-4-one (**1**) (4 g, 17.31 mmol) and iodine (17.57 g, 69.24 mmol) in 110 mL of CHCl_3 , pyridine (5.59 mL, 69.24 mmol) were added. The resulting solution was stirred at room temperature for 16 h. Then, 120 mL of saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ were added and the resulting mixture stirred for one hour. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . Solvent was then removed under reduced pressure and the residue was triturated with diethyl ether several times. Compound **3**.

White solid in 90% yield (5.55 g, 15.60 mmol); mp 205 – 206 °C.

^1H NMR (500 MHz, CDCl_3) δ 8.11 (dd, J = 8.9, 1.0 Hz, 1H), 7.15 (dd, J = 8.9, 1.0 Hz, 1H), 6.77 – 6.69 (m, 1H), 6.36 (s, 1H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 175.8, 161.5, 156.0, 152.5 (q , 2J = 39.1 Hz), 128.1, 119.0, 118.6 (q , 1J = 272.2 Hz), 117.5, 114.7, 110.9 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_5\text{F}_3\text{IO}_3^+$: 356.9230; found: 356.9230.

General procedure for the synthesis of Suzuki cross-coupling of compound 2

A suspension of compound **2** (150 mg, 0.41 mmol, 1 equiv.), with the corresponding boronic acid (0.46 mmol), Na_2CO_3 (87 mg, 0.82 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (23 mg, 0.03 mmol) in 4 mL of a mixture 1:2:6 of EtOH:water:toluene was bubbled with nitrogen gas for 10 minutes. Then, the flask was capped, and the mixture was heated at 90 °C for 20 min. The dark solution was cool down to room temperature and diluted with EtOAc. The organic layer was separated and the aqueous one was extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

7-(4-fluorophenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4a)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 1:1). White solid in 80% yield (102 mg); mp 111 – 114 °C.

^1H NMR (500 MHz, CDCl_3) δ 8.28 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 1.7 Hz, 1H), 7.72 – 7.65 (m, 3H), 7.24 (t, J = 8.5 Hz, 2H), 6.78 (s, 1H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 176.8, 164.6, 162.6, 156.2, 152.5 (q , $^2J(\text{C},\text{F})$ = 38.9 Hz), 147.4, 134.8, 134.7, 129.4, 129.3, 126.7, 125.4, 122.8, 118.7 (q , $^1J(\text{C},\text{F})$ = 274.7 Hz), 116.5, 116.4, 116.31, 110.9 (q , $^3J(\text{C},\text{F})$ = 3.1 Hz) ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_9\text{F}_4\text{O}_2^+$: 309.0533; found: 309.0531.

7-(4-hydroxyphenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4b)

Purified by silica gel column chromatography [n -hexanes / ethyl acetate = 4:1 to 1:2). Pale brown solid in 79% yield (99 mg); mp 224 – 226 °C.

^1H NMR (500 MHz, CDCh) δ 8.23 (d, J = 8.3 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.61 – 7.52 (m, 2H), 7.02 – 6.93 (m, 2H), 6.74 (s, 1H) ppm.

^{13}C NMR (126 MHz, CDCh) δ 176.9, 156.9, 156.3, 152.5 (q , $^2J(\text{C},\text{F})$ = 39.1 Hz), 148.0, 131.2, 129.0, 126.5, 125.1, 122.3, 118.8 (q , $^1J(\text{C},\text{F})$ = 282.2 Hz), 116.3, 115.6, 110.8 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{10}\text{F}_3\text{O}_3^+$: 307.0577; found: 307.0579.

4-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)benzonitrile (4c)

Purified by silica gel column chromatography (n -hexanes / ethyl acetate = 4:1 to 1:2). White solid in 41% yield (53 mg); mp 189 – 191 °C.

^1H NMR (500 MHz, CDCh) δ 8.31 (d, J = 8.3 Hz, 1H), 7.85 – 7.74 (m, 4H), 7.73 – 7.66 (m, 1H), 7.26 (s, 1H), 6.78 (s, 1H) ppm.

^{13}C NMR (126 MHz, CDCh) δ 176.5, 156.1, 152.7 (q , $^2J(\text{C},\text{F})$ = 35.3 Hz), 146.1, 143.0, 133.1, 133.0, 128.3, 128.1, 127.2, 125.5, 123.7, 118.7 (q , $^1J(\text{C},\text{F})$ = 275.9 Hz), 118.4, 117.1, 113.1, 111.1 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_9\text{F}_3\text{NO}_2^+$: 316.0580; found: 316.0582.

7-(3,5-bis(trifluoromethyl)phenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4d)

Purified by silica gel column chromatography (n -hexanes / ethyl acetate = 10:1 to 3:1). White solid in 71% yield (125 mg); mp 137 – 139 °C.

^1H NMR (500 MHz, CDCh) δ 8.35 (d, J = 8.3 Hz, 1H), 8.09 (d, J = 1.7 Hz, 2H), 7.98 (s, 1H), 7.82 (d, J = 1.7 Hz, 1H), 7.74 (dd, J = 8.3, 1.7 Hz, 1H), 6.79 (s, 1H) ppm.

^{13}C NMR (126 MHz, CDCh) δ 176.5, 156.2, 152.8 (q , $^2J(\text{C},\text{F})$ = 39.1 Hz), 145.0, 140.8, 132.9 (q , $^2J(\text{C},\text{F})$ = 33.6 Hz), 127.7, 127.5, 125.5, 124.3, 123.9, 122.8, 122.1, 118.7 (q , $^1J(\text{C},\text{F})$ = 274.7 Hz), 117.2, 111.1 (q , $^3J(\text{C},\text{F})$ = 3.8 Hz) ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_8\text{F}_9\text{O}_2^+$: 427.0375; found: 427.0379.

3-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)benzamide (4e)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 4:1 to 1:1). White solid in 99% yield (135 mg); mp 232 – 233 °C.

¹H NMR (500 MHz, CD₃OD) δ 8.29 (d, *J* = 1.8 Hz, 1H), 8.26 (d, *J* = 8.3 Hz, 1H), 8.03 (d, *J* = 1.8 Hz, 1H), 7.98 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.92 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 6.88 (s, 1H) ppm.

¹³C NMR (126 MHz, CD₃OD) δ 178.4, 171.7, 157.7, 153.8 (*q*, ²*J*(C,F) = 39.1 Hz), 148.9, 140.0, 136.1, 131.8, 130.6, 129.4, 127.8, 127.3, 126.7, 124.0, 122.4 (*q*, ¹*J*(C,F) = 279.7 Hz), 117.6, 111.7 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₇H₁₁F₃NO₃⁺: 334.0686; found: 334.0694.

7-(2-chlorophenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4f)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1). Pale yellow oil in 99% yield (132 mg).

¹H NMR (500 MHz, CDCl₃) δ 8.14 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 1.5 Hz, 1H), 7.46 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.41 (ddd, *J* = 4.6, 3.4, 1.3 Hz, 1H), 7.29 – 7.23 (m, 3H), 7.14 (s, 1H), 6.65 (d, *J* = 1.9 Hz, 1H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 176.8, 155.5, 152.7 (*q*, ²*J*(C,F) = 39.1 Hz), 146.6, 138.2, 132.4, 131.2, 130.5, 130.1, 128.1, 127.4, 125.8, 123.2, 119.4, 118.8 (*q*, ¹*J*(C,F) = 274.7 Hz), 117.7, 110.9 (*q*, ³*J*(C,F) = 2.5 Hz) ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₆H₉ClF₃O₂⁺: 325.0238; found: 325.0232.

7-(2-(trifluoromethoxy)phenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4g)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 8:1). White solid in 97% yield (149 mg); mp 86 – 88 °C.

¹H NMR (500 MHz, CDCl₃) δ 8.26 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.60 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.47 – 7.39 (m, 2H), 6.77 (s, 1H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 176.8, 155.6, 152.7 (*q*, ²*J*(C,F) = 40.3 Hz), 146.2, 144.2, 133.0, 131.4, 130.5, 127.8, 127.6, 126.1, 123.2, 121.9, 121.5, 119.0, 118.8 (*q*, ¹*J*(C,F) = 274.7 Hz), 110.9 (*q*, ³*J*(C,F) = 2.5 Hz) ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₇H₉F₆O₃⁺: 375.0450; found: 375.0458.

7-(thiophen-3-yl)-2-(trifluoromethyl)-4H-chromen-4-one (4h)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1). White solid in 88% yield (107 mg); mp 113 – 116 °C.

^1H NMR (500 MHz, CDCl_3) δ 8.21 (d, $J = 8.2$ Hz, 1H), 7.76 – 7.64 (m, 3H), 7.52 – 7.42 (m, 2H), 6.73 (s, 1H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 176.7, 156.4, 152.5 (q , $^2J(\text{C},\text{F}) = 39.0$ Hz), 142.7, 139.9, 127.5, 126.7, 126.1, 124.8, 123.6, 122.6, 118.8 (q , $^1J(\text{C},\text{F}) = 274.7$ Hz), 115.3, 110.9 (q , $^3J(\text{C},\text{F}) = 2.5$ Hz) ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_8\text{F}_3\text{O}_2\text{S}^+$: 297.0192; found: 297.0198.

7-cyclopropyl-2-(trifluoromethyl)-4H-chromen-4-one (4i)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1). White solid in 95% yield (99 mg); mp 57 – 59 °C.

^1H NMR (500 MHz, CDCl_3) δ 8.06 (d, $J = 8.2$ Hz, 1H), 7.19 – 7.15 (m, 2H), 6.68 (s, 1H), 2.07 – 1.99 (m, 1H), 1.21 – 1.08 (m, 2H), 0.91 – 0.81 (m, 2H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 176.8, 156.2, 153.7, 152.2 (q , $^2J(\text{C},\text{F}) = 37.8$ Hz), 125.9, 124.4, 121.8, 119.9, 117.7, 116.1 (q , $^1J(\text{C},\text{F}) = 273.4$ Hz), 114.3, 110.7 (q , $^3J(\text{C},\text{F}) = 2.5$ Hz), 16.2, 11.2 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{10}\text{F}_3\text{O}_2^+$: 255.0627; found: 255.0629.

General procedure for the Pd-catalyzed cross-coupling of chromenone 2 with aromatic amines

Over a suspension of compound **2** (150 mg, 0.41 mmol), with Cs_2CO_3 (202 mg, 0.62 mmol), BINAP (25 mg, 0.04 mmol) and PdOAc_2 (4.5 mg, 0.02 mmol) in 4 mL of toluene was bubbled with nitrogen gas for 10 minutes. Then, the flask was capped, and the mixture was heated at 90 °C for 16 h. The dark solution was cool down to room temperature and diluted with 5 mL of EtOAc and 5 mL of water. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 $\times$ 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

7-((4-chlorophenyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5a)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 95:5). Light brown solid in 62% yield (135 mg); mp 186 – 188 °C.

^1H NMR (500 MHz, DMSO- d_6) δ 9.35 (s, 1H), 7.92 (d, $J = 8.8$ Hz, 1H), 7.45 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 8.8$ Hz, 2H), 7.15 (dd, $J = 8.8, 2.2$ Hz, 1H), 7.04 (d, $J = 2.2$ Hz, 1H), 6.88 (s, 1H) ppm.

^{13}C NMR (126 MHz, DMSO) δ 174.5, 157.3, 150.4, 150.0 (q , $^2J(\text{C},\text{F}) = 37.8$ Hz), 139.2, 129.5, 126.8, 126.8, 122.1, 118.7 (q , $^1J(\text{C},\text{F}) = 273.6$ Hz), 115.5, 115.3, 110.8, 110.7, 98.9 ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{10}ClF_3NO_2^+$: 340.0347; found: 340.0349.

7-((4-hydroxyphenyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5b)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 9:1).
Yellow solid in 16% yield (22 mg); mp 217 – 219 °C.

1H NMR (500 MHz, CD_3OD) δ 7.88 (d, J = 8.9 Hz, 1H), 7.12 – 7.05 (m, 2H), 6.95 (dd, J = 8.9, 2.2 Hz, 1H), 6.88 – 6.78 (m, 2H), 6.72 (d, J = 2.2 Hz, 1H), 6.64 (s, 1H), 2.16 (s, 1H) ppm.

^{13}C NMR (126 MHz, CD_3OD) δ 177.5, 159.9, 156.3, 155.4, 152.6 (q , $^2J(C,F)$ = 38.6 Hz), 132.7, 127.8, 126.3, 120.1 (q , $^1J(C,F)$ = 254.5 Hz), 117.2, 115.8, 115.3, 111.1, 98.1 ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{11}F_3NO_3^+$: 322.0686; found: 322.0694.

7-(o-tolylamino)-2-(trifluoromethyl)-4H-chromen-4-one (5 c)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 95:5).
Yellow solid in 59% yield (77 mg); mp 94 – 96 °C.

1H NMR (500 MHz, $DMSO-d_6$) δ 8.81 (s, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.34 – 7.27 (m, 2H), 7.22 (ddd, J = 7.5, 5.6, 3.0 Hz, 1H), 6.98 (dd, J = 8.9, 2.2 Hz, 1H), 6.83 (s, 1H), 6.53 (d, J = 2.2 Hz, 1H), 2.24 (s, 3H) ppm.

^{13}C NMR (126 MHz, $DMSO-A_1$) δ 174.3, 157.4, 152.8, 149.7 (q , $^2J(C,F)$ = 38.0 Hz), 137.9, 133.4, 131.3, 127.0, 126.7, 125.8, 125.2, 118.7 (q , $^1J(C,F)$ = 273.4 Hz), 114.3, 114.2, 110.6, 110.6, 97.4, 17.6 ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{13}F_3NO_2^+$: 320.0893; found: 320.0894.

7-((2,6-dimethylphenyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5d)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 95:5).
Yellow solid in 71% yield (97 mg); mp 93 – 95 °C.

1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.7 Hz, 1H), 7.24 – 7.14 (m, 3H), 6.79 – 6.67 (m, 1H), 6.57 (s, 1H), 6.23 (s, 1H), 2.22 (s, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 158.5, 152.9, 151.4 (q , $^2J(C,F)$ = 38.8 Hz), 136.9, 135.7, 129.1, 127.8, 127.6, 118.8 (q , $^1J(C,F)$ = 274.7 Hz), 115.5, 113.8, 110.6 (q , $^3J(C,F)$ = 2.8 Hz), 97.7, 18.3 ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{15}F_3NO_2^+$: 334.1049; found: 334.1057.

2-(trifluoromethyl)-7-((3,4,5-trimethoxyphenyl)amino)-4H-chromen-4-one (5e)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 95:5). Yellow solid in 70% yield (113 mg); mp 162 – 165 °C.

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.16 (s, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.94 (d, *J* = 2.1 Hz, 1H), 6.84 (s, 1H), 6.58 (s, 2H), 3.82 (s, 6H), 3.39 (s, 3H) ppm.

¹³C NMR (126 MHz, DMSO-*d*₆) δ 174.3, 157.4, 153.5, 153.3, 151.6, 149.8 (*q*, ²*J*(C,F) = 38.0 Hz), 135.8, 134.1, 126.7, 118.7 (*q*, ¹*J*(C,F) = 273.7 Hz), 114.9, 114.7, 110.7, 110.6, 100.0, 98.5, 91.6, 60.1, 55.9 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₉H₁₇F₃NO₅⁺: 396.1056; found: 396.1058.

7-((3,4-dichlorophenyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5f)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 95:5). Light brown solid in 80% yield (123 mg); mp 197 – 199 °C.

¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, *J* = 9.3 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.32 (d, *J* = 2.6 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.08 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.94 (h, *J* = 2.2 Hz, 2H), 6.62 (s, 1H), 6.32 (s, 1H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 177.5, 159.4, 153.0 (*q*, ²*J*(C,F) = 39.1 Hz), 151.9, 141.9, 134.1, 132.3, 131.5, 128.1, 127.1, 123.0, 121.1, 120.18 (*q*, ¹*J*(C,F) = 273.4 Hz), 117.2, 117.0, 115.7, 111.3, 101.1 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₆H₉Cl₂F₃NO₂⁺: 373.9957; found: 373.9965.

7-(1H-indol-1-yl)-2-(trifluoromethyl)-4H-chromen-4-one (5g)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 95:5). White solid in 63% yield (85 mg); mp 104 – 106 °C.

¹H NMR (500 MHz, CDCl₃) δ 8.35 (d, *J* = 8.4 Hz, 1H), 7.76 – 7.64 (m, 3H), 7.42 (d, *J* = 3.4 Hz, 1H), 7.32 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1H), 7.26 (d, *J* = 4.1 Hz, 2H), 6.79 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.77 (s, 1H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 176.2, 156.7, 152.6 (*q*, ²*J*(C,F) = 37.8 Hz), 145.8, 135.4, 130.3, 129.0, 127.2, 123.7, 121.9, 121.7, 121.5, 120.9 (*q*, ¹*J*(C,F) = 277 Hz), 119.8, 111.8, 111.1, 110.7, 106.5 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₈H₁₁F₃NO₂⁺: 330.0736; found: 330.0743.

7-(indolin-1-yl)-2-(trifluoromethyl)-4H-chromen-4-one (5h)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 95:5). Yellow solid in 99% yield (134 mg); mp 138 – 140 °C.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.99 (d, *J* = 9.0 Hz, 1H), 7.52 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.23 (d, *J* = 2.3 Hz, 1H), 7.22 – 7.16 (m, 1H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.91 (s, 1H), 4.09 (t, *J* = 8.3 Hz, 2H), 3.18 (t, *J* = 8.3 Hz, 2H) ppm.

¹³C NMR (126 MHz, DMSO-*d*₆) δ 174.5, 156.9, 148.9, 150.1 (*q*, ²*J*(C,F) = 38.2 Hz), 143.7, 132.7, 127.15, 126.3, 125.5, 121.4, 118.7 (*q*, ¹*J*(C,F) = 273.8 Hz), 115.6, 115.2, 110.8, 110.8, 110.4, 101.7, 51.7, 27.2 ppm.

HRMS (ESI): *m/z* [M+H]⁺⁺ calcd for C₁₈H₁₃F₃NO₂⁺: 332.0893; found: 332.0896.

7-(pyridin-2-ylamino)-2-(trifluoromethyl)-4H-chromen-4-one (5i)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 9:1). Yellow solid in 64% yield (80 mg); mp 216 – 218 °C.

¹H NMR (500 MHz, CD₃OD) δ 8.49 (d, *J* = 2.0 Hz, 1H), 8.33 (dd, *J* = 5.2, 2.0 Hz, 1H), 8.03 – 7.93 (m, 1H), 7.68 (ddd, *J* = 8.9, 7.2, 1.9 Hz, 1H), 7.44 (dd, *J* = 8.9, 2.0 Hz, 1H), 6.98 – 6.89 (m, 2H), 6.73 (s, 1H) ppm.

¹³C NMR (126 MHz, CD₃OD) δ 177.9, 159.1, 156.2, 153.1 (*q*, ²*J*(C,F) = 43.9 Hz), 150.2, 148.5, 139.1, 126.9, 118.5, 117.9, 117.5, 113.6, 111.2, 104.2 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₅H₁₀F₃N₂O₂⁺: 307.0689; found: 307.0691.

7-((4-bromophenyl)(methyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5j)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 95:5). White solid in 86% yield (141 mg); mp 151 – 152 °C.

¹H NMR (500 MHz, CDCl₃) δ 7.93 (t, *J* = 6.9 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.14 – 7.10 (m, 2H), 6.78 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.59 (s, 1H), 3.39 (s, 3H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 175.9, 157.8, 154.0, 151.8 (*q*, ²*J*(C,F) = 39.1 Hz), 145.5, 133.5, 128.4, 126.9, 120.1, 118.8 (*q*, ¹*J*(C,F) = 273.4 Hz), 115.3, 114.0, 110.7, 110.7, 100.0, 40.6 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₇H₁₂BrF₃NO₂⁺: 397.9998; found: 397.9989.

7-(2-(*m*-tolyl)hydrazinyl)-2-(trifluoromethyl)-4H-chromen-4-one (5k)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 95:5). Yellow solid in 64% yield (88 mg); mp 164 – 167 °C.

^1H NMR (500 MHz, CDCl_3) δ 7.94 (d, J = 8.9 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.16 – 7.04 (m, 4H), 6.60 (s, 1H), 4.26 (s, 2H), 2.40 (s, 3H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 175.9, 157.7, 155.2, 151.8 (q , $^2J(\text{C},\text{F})$ = 37.8 Hz), 146.4, 140.5, 130.1, 127.9, 125.9 (q , $^1J(\text{C},\text{F})$ = 281.0 Hz), 126.5, 125.7, 122.1, 115.6, 113.9, 110.5, 100.1, 21.5 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_2\text{O}_2^+$: 335.1002; found: 335.1000.

General procedure for the Pd-catalyzed cross-coupling of chromenone **2** with phenols

Over a suspension of compound **2** (150 mg, 0.41 mmol), with K_2CO_3 (113 mg, 0.82 mmol), JohnPhos (12 mg, 0.04 mmol) and Pd_2dba_3 (19 mg, 0.02 mmol) in 4 mL of toluene, nitrogen gas was bubbled for 10 minutes. Then, the flask was capped, and the mixture was heated at 90 °C for 16 h. The dark solution was cool down to room temperature and diluted with 5 mL of EtOAc and 5 mL of water. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 $\times$ 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

7-(4-chlorophenoxy)-2-(trifluoromethyl)-4H-chromen-4-one (**6a**)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1). White solid in 71% yield (99 mg); mp 68 – 70 °C.

^1H NMR (500 MHz, CDCl_3) δ 8.17 (d, J = 8.9 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.12 (dd, J = 8.9, 2.3 Hz, 1H), 7.07 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 2.4 Hz, 1H), 6.69 (s, 1H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 176.1, 163.6, 157.2, 153.1, 152.3 (q , $^2J(\text{C},\text{F})$ = 36.6 Hz), 131.2, 130.6, 128.2, 122.2, 119.4, 117.1, 110.9, 110.9, 104.9 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_9\text{GF}_3\text{O}_3^+$: 341.0187; found: 341.0194.

7-(4-acetylphenoxy)-2-(trifluoromethyl)-4H-chromen-4-one (**6b**)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1). White solid in 71% yield (101 mg); mp 120 – 122 °C.

^1H NMR (500 MHz, CDCl_3) δ 8.21 (d, J = 8.9 Hz, 1H), 8.09 – 8.01 (m, 2H), 7.20 – 7.11 (m, 3H), 7.03 (d, J = 2.3 Hz, 1H), 6.71 (s, 1H), 2.63 (s, 3H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 196.6, 176.0, 162.4, 158.8, 157.1, 152.4 (q , $^2J(\text{C},\text{F})$ = 39.1 Hz), 134.3, 131.1, 128.3, 120.0, 119.9, 118.6 (q , $^1J(\text{C},\text{F})$ = 273.4 Hz), 117.7, 110.9, 110.9, 106.2, 26.7 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{12}\text{F}_3\text{O}_4^+$: 349.0682; found: 349.0688.

7-(4-aminophenoxy)-2-(trifluoromethyl)-4H-chromen-4-one (6c)

Purified by silica gel column chromatography (dichloromethane / methanol = 99:1 to 9:1). Yellow solid in 78% yield (103 mg); mp 184 – 186 °C.

¹H NMR (500 MHz, CD₃OD) δ 7.85 (d, *J* = 8.9 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.69 (s, 1H), 6.61 (s, 1H) ppm.

¹³C NMR (126 MHz, CD₃OD) δ 177.5, 159.9, 156.2, 155.3, 153.5 (*q*, ²*J*(C,F) = 38.7 Hz), 132.7, 127.8, 126.2, 120.2 (*q*, ¹*J*(C,F) = 272.2 Hz), 117.2, 115.8, 115.3, 111.1 (*q*, ³*J* = 2.5 Hz), 98.1 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₆H₁₁F₃NO₃⁺: 322.0686; found: 322.0694.

7-(o-tolyloxy)-2-(trifluoromethyl)-4H-chromen-4-one (6d)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1). Pale brown solid in 72% yield (95 mg); mp 86 – 87 °C.

¹H NMR (500 MHz, CDCl₃) δ 8.15 (d, *J* = 8.9 Hz, 1H), 7.33 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.29 (td, *J* = 7.6, 1.8 Hz, 1H), 7.23 (td, *J* = 7.6, 1.3 Hz, 1H), 7.09 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.05 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.67 (s, 1H), 2.19 (s, 3H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 176.2, 164.1, 157.4, 152.3, 152.2 (*q*, ²*J*(C,F) = 40.3 Hz), 132.2, 130.8, 128.0, 128.0, 126.3, 121.5, 118.8, 118.8 (*q*, *V* (C,F) = 287.3 Hz), 116.4, 110.9, 110.8, 103.5, 16.1 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₇H₁₂F₃O₃⁺: 321.0733; found: 321.0738.

7-(3,4-dimethoxyphenoxy)-2-(trifluoromethyl)-4H-chromen-4-one (6e)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 4:1 to 1:1). Yellow solid in 56% yield (84 mg); mp 100 – 103 °C.

¹H NMR (500 MHz, CDCl₃) δ 8.15 (d, *J* = 8.9 Hz, 1H), 7.11 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.93 – 6.89 (m, 1H), 6.87 (d, *J* = 2.5 Hz, 1H), 6.69 (d, *J* = 2.5 Hz, 1H), 6.67 (d, *J* = 1.4 Hz, 2H), 3.92 (s, 3H), 3.87 (s, 3H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 176.2, 164.7, 157.4, 152.2 (*q*, ²*J*(C,F) = 36.5 Hz), 150.5, 147.9, 147.1, 127.9, 118.9, 118.7 (*q*, ¹*J*(C,F) = 274.7 Hz), 116.7, 112.4, 112.0, 110.9, 105.3, 104.0 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₈H₁₄F₃O₅⁺: 367.0788; found: 367.0790.

(7-(phenylthio)-2-(trifluoromethyl)-4H-chromen-4-ylidene)oxonium (6f)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1). White solid in 69% yield (91 mg); mp 113 – 116 °C.

^1H NMR (500 MHz, CDCl_3) δ 8.02 (d, J = 8.5 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.49 (dd, J = 5.0, 1.8 Hz, 3H), 7.21 (dd, J = 8.5, 1.8 Hz, 1H), 7.09 (d, J = 1.8 Hz, 1H), 6.66 (s, 1H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 176.3, 156.2, 152.1 (q , $^2J(\text{C},\text{F})$ = 39.0 Hz), 149.4, 135.1, 130.3, 130.1, 126.2, 124.9, 121.4, 118.7 (q , $^1J(\text{C},\text{F})$ = 274.7 Hz), 114.9, 110.9 (q , $^3J(\text{C},\text{F})$ = 1.9 Hz) ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{10}\text{F}_3\text{O}_2\text{S}^+$: 323.0348; found: 323.0351.

General procedure for the synthesis of 8-iodo-7-methoxy-2-(trifluoromethyl)-4H-chromen-4-one (7)

Over a suspension of 7-hydroxy-3-iodo-2-(trifluoromethyl)-4H-chromen-4-one (3) (1 g, 2.8 mmol) and K_2CO_3 (0.77 g, 5.6 mmol) in 28 mL of THF, iodomethane (0.35 μL , 5.6 mmol) was added dropwise and the solution was heated at 60 °C for 20 h. The reaction was filtrated and the solvent removed under reduced pressure. The crude residue was purified by silica gel chromatography column (*n*-hexanes / ethyl acetate = 10:1 to 3:1) providing compound 7.

White solid in 93% yield (0.98 g); mp 135 – 138 °C.

^1H NMR (500 MHz, CDCl_3) δ 8.20 (d, J = 8.9 Hz, 1H), 7.01 (d, J = 8.9 Hz, 1H), 6.71 (s, 1H), 4.06 (s, 3H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 176.2, 164.2, 152.8 (q , $^2J(\text{C},\text{F})$ = 37.8 Hz), 156.4, 128.0, 119.0, 118.7 (q , $^1J(\text{C},\text{F})$ = 273.4 Hz), 110.5 (q , $^3J(\text{C},\text{F})$ = 2.5 Hz), 110.0, 57.4 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_7\text{F}_3\text{IO}_3^+$: 370.9386; found: 370.9392.

General procedure for the synthesis of 7-(benzyloxy)-8-iodo-2-(trifluoromethyl)-4H-chromen-4-one (8)

Over a suspension of 7-hydroxy-3-iodo-2-(trifluoromethyl)-4H-chromen-4-one (3) (1 g, 2.8 mmol) and K_2CO_3 (0.77 g, 5.6 mmol) in 28 mL of acetone, benzyl chloride (0.37 μL , 3.4 mmol) was added dropwise and the solution was heated at 60 °C for 16 h. The reaction was filtered through a funnel and the solvent removed under reduced pressure. The crude residue was triturated with water and dried under reduced pressure until dry. Compound 8.

White solid in 89% yield (1.13 g, 2.5 mmol); mp 186 – 187 °C.

^1H NMR (500 MHz, CDCl_3) δ 8.13 (d, J = 8.9 Hz, 1H), 7.49 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.36 (d, J = 7.3 Hz, 1H), 7.02 (d, J = 8.9 Hz, 1H), 6.70 (s, 1H), 5.33 (s, 2H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 176.1, 163.2, 156.4, 152.7 (q , $^2J(\text{C},\text{F})$ = 39.4 Hz), 135.3, 128.9, 128.5, 127.8, 127.1, 119.1, 117.6 (q , $^1J(\text{C},\text{F})$ = 274.7 Hz), 111.4, 110.6, 110.5 (q , $^3J(\text{C},\text{F})$ = 2.7 Hz), 71.7 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{11}\text{F}_3\text{IO}_3^+$: 446.9705; found: 446.9705.

General procedure for the synthesis of 8-(3,5-bis(trifluoromethyl)phenyl)-7-hydroxy-2-(trifluoromethyl)-4H-chromen-4-one (9)

A suspension of compound **3** (355 mg, 1 mmol), with the corresponding boronic acid (284 mg, 1.1 mmol), Na₂CO₃ (212 mg, 2 mmol, 2 equiv.) and Pd(dppf)Cl₂ (55 mg, 0.08 mmol) in 10 mL of a mixture 1:2:6 of EtOH:water:toluene was bubbled with nitrogen gas for 10 minutes. Then, the flask was capped, and the mixture was heated at 90 °C for 20 min. The dark solution was cool down to room temperature and diluted with EtOAc. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography (*n*-hexanes / ethyl acetate = 4:1 to 1:1).

White solid in 85% yield (376 mg); mp 222 – 225 °C.

¹H NMR (500 MHz, CD₃OD) δ 8.12 (d, *J* = 1.6 Hz, 2H), 8.07 (d, *J* = 8.9 Hz, 1H), 7.98 (s, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 6.75 (s, 1H) ppm.

¹³C NMR (126 MHz, CD₃OD) δ 178.0, 162.5, 155.8, 153.1 (*q*, ²*J*(C,F) = 39.1 Hz), 135.08, 132.7 (*q*, ³*J*(C,F) = 3.8 Hz), 132.6 (*q*, ²*J*(C,F) = 21.4 Hz), 128.3, 126.0, 123.8, 122.3 (*q*, ³*J*(C,F) = 3.8 Hz), 120.0 (*q*, ¹*J*(C,F) = 272.2 Hz), 118.0, 117.0, 115.0, 111.2 (*q*, ³*J*(C,F) = 2.5 Hz) ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₈H₈F₈O₃⁺: 443.324; found: 443.0329.

General procedure for the Suzuki cross-coupling of chromenones 7 or 8

A suspension of compound **7** or **8** (0.34 mmol, 1 equiv.), with the corresponding boronic acid (0.37 mmol, 1.1 equiv.), Na₂CO₃ (0.68 mmol, 2 equiv.) and Pd(dppf)Ch (0.026 mmol, 0.08 equiv.) in 3.5 mL of a mixture 1:2:6 of EtOH: water: toluene was bubbled with nitrogen gas for 10 minutes. Then, the flask was capped, and the mixture was heated at 90 °C for 2 h. The dark solution was cool down to room temperature and diluted with EtOAc. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

8-(3,5-bis(trifluoromethyl)phenyl)-7-methoxy-2-(trifluoromethyl)-4H-chromen-4-one (10a)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1).

White solid in 80% yield (124 mg); mp 157 – 160°C.

¹H NMR (500 MHz, CDCl₃) δ 6.30 (d, *J* = 9.0 Hz, 1H), 7.92 (s, 3H), 7.23 (d, *J* = 9.0 Hz, 1H), 6.68 (s, 1H), 3.96 (s, 3H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 176.2, 161.4, 153.6, 152.3 (q , $^2J(\text{C},\text{F}) = 39.3$ Hz), 132.7, 131.6 (q , $^2J(\text{C},\text{F}) = 32.8$ Hz), 131.3 (q , $^3J(\text{C},\text{F}) = 3.9$ Hz), 131.3, 128.4, 124.5, 122.4, 122.0, 122.0, 121.9, 118.5 ($J(\text{C},\text{F}) = 273.4$), 118.3, 116.0, 110.7, 110.5 (q , $^3J(\text{C},\text{F}) = 2.7$ Hz), 56.8 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{10}\text{F}_9\text{O}_3^+$: 457.0481; found: 457.0486.

4-(7-methoxy-4-oxo-2-(trifluoromethyl)-4H-chromen-8-yl)benzamide (10b)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 4:1 to 1:1). White solid in 78% yield (117 mg); mp 196 – 199°C.

^1H NMR (500 MHz, CDCl_3) δ 8.26 (d, $J = 9.0$ Hz, 1H), 7.92 (d, $J = 8.1$ Hz, 2H), 7.49 (d, $J = 8.1$ Hz, 2H), 7.19 (d, $J = 9.0$ Hz, 1H), 6.67 (s, 1H), 3.91 (s, 3H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 176.6, 169.2, 161.6, 153.8, 152.4 (q , $^2J(\text{C},\text{F}) = 39.0$ Hz), 134.6, 133.0, 131.1, 127.5, 127.3, 118.6 (q , $^1J(\text{C},\text{F}) = 273.4$ Hz), 118.3, 118.2, 110.6, 110.3 (q , $^3J(\text{C},\text{F}) = 2.9$ Hz), 56.7 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{13}\text{F}_3\text{NO}_4^+$: 364.0791; found: 364.0794.

3-(7-methoxy-4-oxo-2-(trifluoromethyl)-4H-chromen-8-yl)benzonitrile (10c)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 4:1 to 1:1). Orange solid in 57% yield (67 mg); mp 201 – 202°C.

^1H NMR (500 MHz, CDCl_3) δ 8.29 (d, $J = 9.0$ Hz, 1H), 7.77 – 7.70 (m, 2H), 7.67 (t, $J = 10.5, 5.3$ Hz, 1H), 7.61 (t, $J = 7.7$ Hz, 1H), 7.23 (d, $J = 9.0$ Hz, 1H), 6.68 (s, 1H), 3.84 (s, 3H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 176.2, 161.5, 153.6, 152.2 (q , $^2J(\text{C},\text{F}) = 39.2$ Hz), 135.2, 134.5, 132.0, 131.7, 129.1, 127.8, 118.7, 118.5 (q , $^1J(\text{C},\text{F}) = 274.7$ Hz), 118.2, 116.8, 112.5, 110.6, 110.4, 110.4, 56.7 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{11}\text{F}_3\text{NO}_3^+$: 346.0686; found: 346.0693.

8-(2-chlorophenyl)-7-methoxy-2-(trifluoromethyl)-4H-chromen-4-one (10d)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1). White solid in 76% yield (92 mg); mp 125 – 128°C.

^1H NMR (500 MHz, CDCl_3) δ 8.28 (d, $J = 9.0$ Hz, 1H), 7.53 (dt, $J = 7.0, 3.7$ Hz, 1H), 7.42 – 7.34 (m, 2H), 7.31 – 7.27 (m, 1H), 7.19 (d, $J = 9.0$ Hz, 1H), 6.65 (s, 1H), 3.92 (s, 3H) ppm.

^{13}C NMR (126 MHz, CDCl_3) δ 176.7, 162.0, 154.1, 152.4 (q , $^2J(\text{C},\text{F}) = 39.2$ Hz), 134.6, 132.2, 130.2, 129.9, 129.7, 127.6, 126.7, 118.6 (q , $^1J(\text{C},\text{F}) = 274.7$ Hz), 118.1, 116.9, 110.5, 110.3, 110.3, 56.7 ppm.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{11}\text{ClF}_3\text{NO}_3^+$: 355.0343; found: 355.0343.

7-(benzyloxy)-8-(3,5-bis(trifluoromethyl)phenyl)-2-(trifluoromethyl)-4H-chromen-4-one (11a)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1). White solid in 76% yield (137 mg); mp 167 – 168°C.

¹H NMR (500 MHz, CDCl₃) δ 8.19 (d, *J* = 9.0 Hz, 1H), 7.89 (s, 2H), 7.82 (s, 1H), 7.29 – 7.13 (m, 6H), 6.59 (s, 1H), 5.15 (s, 2H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 176.1, 160.5, 153.6, 152.3 (*q*, ²*J*(C,F) = 39.3 Hz), 135.0, 132.6, 131.5 (*q*, ³*J*(C,F) = 5.0 Hz), 131.5 (*q*, ²*J*(C,F) = 34.0 Hz), 128.9, 128.7, 128.3, 127.2, 124.5, 122.3, 122.0 (*q*, ³*J*(C,F) = 4.0 Hz), 118.5, 118.5 (*q*, ¹*J*(C,F) = 273.4 Hz), 116.5, 112.1, 110.6 (*q*, ³*J*(C,F) = 2.8 Hz), 71.5 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₅H₁₄F₉O₃⁺: 533.0794; found: 533.0784.

4-(7-(benzyloxy)-4-oxo-2-(trifluoromethyl)-4H-chromen-8-yl)benzamide (11b)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 4:1 to 1:1). White solid in 70% yield (105 mg); mp 217 – 221°C.

¹H NMR (500 MHz, CDCl₃) δ 8.21 (d, *J* = 9.0 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.23 (dd, *J* = 7.8, 4.3 Hz, 3H), 6.67 (s, 1H), 5.22 (s, 2H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 176.4, 169.0, 160.5, 153.7, 151.3 (*q*, ²*J*(C,F) = 39.1 Hz), 135.4, 134.6, 132.8, 131.0, 128.7, 128.3, 127.2, 127.1, 126.7, 118.8, 118.4 (*q*, ¹*J*(C,F) = 274.7 Hz), 118.3, 112.1, 110.2, 71.0 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₄H₁₇F₃NO₄⁺: 440.1104; found: 440.1113.

7-(benzyloxy)-8-(4-hydroxyphenyl)-2-(trifluoromethyl)-4H-chromen-4-one (11c)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 4:1 to 1:1). White solid in 70% yield (98 mg); mp 208 – 209°C.

¹H NMR (500 MHz, CDCl₃) δ 8.19 (d, *J* = 9.0 Hz, 1H), 7.41 – 7.25 (m, 8H), 7.22 (d, *J* = 9.0 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.70 (s, 1H), 5.45 (s, 1H), 5.24 (s, 2H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 177.1, 160.9, 155.7, 154.2, 152.5 (*q*, ²*J*(C,F) = 39.1 Hz), 135.9, 132.2, 128.8, 128.2, 126.8, 126.3, 122.7, 119.9, 118.7 (*q*, ¹*J*(C,F) = 274.7 Hz), 118.4, 115.2, 112.4, 110.1, 71.0 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₃H₁₆F₃O₄⁺: 413.0995; found: 413.1002.

7-(benzyloxy)-8-(3-methoxyphenyl)-2-(trifluoromethyl)-4H-chromen-4-one (11d)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1). White solid in 76% yield (105 mg); mp 83 – 85°C.

¹H NMR (500 MHz, CDCl₃) δ 8.45 (d, *J* = 9.0 Hz, 1H), 7.69 – 7.63 (m, 1H), 7.62 – 7.51 (m, 5H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.27 – 7.23 (m, 1H), 6.93 (s, 1H), 5.50 (s, 2H), 4.09 (s, 3H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 176.7, 160.8, 159.4, 154.0, 152.5 (*q*, ²*J*(C,F) = 38.9 Hz), 135.9, 131.8, 129.1, 128.8, 128.2, 126.8, 126.6, 123.3, 120.1, 118.7 (*q*, ¹*J*(C,F) = 274.7 Hz), 116.0, 114.4, 112.3, 110.2 (*q*, ³*J*(C,F) = 2.8 Hz), 71.0, 55.4 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₄H₁₈F₃O₄⁺: 427.1152; found: 427.1158.

7-(benzyloxy)-8-(pyridin-4-yl)-2-(trifluoromethyl)-4H-chromen-4-one (11e)

Purified by silica gel column chromatography (*n*-hexanes / ethyl acetate = 4:1 to 1:1). Brown crystals in 76% yield (103 mg); mp 174 – 177°C.

¹H NMR (500 MHz, CDCl₃) δ 8.74 (d, *J* = 5.1 Hz, 1H), 8.25 (d, *J* = 9.0 Hz, 1H), 7.42 – 7.23 (m, 4H), 6.69 (s, 1H), 5.25 (s, 1H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 176.2, 160.5, 152.3 (*q*, ²*J*(C,F) = 39.2 Hz), 153.6, 149.8, 139.1, 135.3, 128.9, 128.5, 127.9, 126.9, 125.7, 118.5 (*q*, ¹*J*(C,F) = 274.7 Hz), 118.4, 117.2, 112.2, 110.5 (*q*, ³*J*(C,F) = 2.7 Hz), 71.2 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₂H₁₅F₃NO₄⁺: 398.0999; found: 398.0998.

General procedure for the synthesis of 2'-hydroxy-6'-methoxy-3'-(3-(trifluoromethyl)-1H-pyrazol-5-yl)-(1,1'-biphenyl) –3 -carbonitrile (12a)

A solution of compound **10c** (64 mg, 0.19 mmol) with hydrazine (30 μL, 0.19 mmol) in 2 mL of EtOH was heated at 70 °C for 20 minutes. The solution was cooled down to room temperature and concentrated. The solid residue was directly purified by silica gel chromatography (*n*-hexanes / ethyl acetate = 5:1 to 1:1) providing compound **12a**.

White solid in 97% yield (66 mg g, 0.18 mmol); mp 158 – 159 °C.

¹H NMR (500 MHz, CDCl₃) δ 7.71 (d, *J* = 1.7 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.59 (dd, *J* = 12.0, 8.5 Hz, 2H), 6.89 (s, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 3.78 (s, 3H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 157.8, 152.0, 135.8, 135.0, 131.5, 129.6, 128.3, 120.8 (*q*, ¹*J*(C,F) = 268.4 Hz), 118.8, 116.2, 112.9, 109.3, 103.9, 101.1, 56.1 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₈H₁₃F₃N₃O₂⁺: 360.0954; found: 360.0958.

General procedure for the synthesis of 4-(2-amino-6-(trifluoromethyl)pyrimidin-4-yl)-2'-chloro-(1,1'-biphenyl)-3-ol (12b)

A solution of compound **4f** (100 mg, 0.31 mmol) with guanidine hydrochloride (89 mg, 0.93 mmol) and K₂CO₃ (86 mg, 0.62 mmol) in 3 mL of EtOH was heated at 70 °C for 20 minutes. The solution was cooled down to room temperature and concentrated. The solid residue was directly purified by silica gel chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1) providing compound **12d**.

Light yellow solid in 81% yield (92 mg g, 0.25 mmol); mp 212 – 214 °C.

¹H NMR (500 MHz, CDCl₃) δ 13.17 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.41 – 7.29 (m, 3H), 7.12 (d, *J* = 1.8 Hz, 1H), 7.07 (dd, *J* = 8.3, 1.8 Hz, 1H), 5.50 (s, 2H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 168.1, 161.0, 160.8, 157.7 (*q*, ²*J*(C,F) = 35.3 Hz), 145.6, 139.3, 132.4, 131.1, 130.3, 129.4, 127.3, 127.1, 120.6 (*q*, ¹*J*(C,F) = 275.9 Hz), 121.1, 120.0, 115.9, 101.7 (*q*, ³*J*(C,F) = 2.5 Hz) ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₇H₁₂ClF₃N₃O⁺: 366.0616; found: 366.0620.

General procedure for the synthesis of 6-(2-hydroxy-4-(*o*-tolylloxy)phenyl)-4-(trifluoromethyl)pyrimidine-2(1H)-thione (12c)

A solution of compound **6d** (95 mg, 0.30 mmol) with thiourea (69 mg, 0.90 mmol) and K₂CO₃ (83 mg, 0.60 mmol) in 3 mL of EtOH was heated at 70 °C for 20 minutes. The solution was cooled down to room temperature and concentrated. The solid residue was directly purified by silica gel chromatography (*n*-hexanes / ethyl acetate = 10:1 to 3:1) providing compound **12 c**.

Orange solid in 97% yield (110 mg g, 0.29 mmol); mp 162 – 164 °C.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.95 (d, *J* = 8.9 Hz, 1H), 7.43 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.36 (td, *J* = 7.7, 1.6 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.60 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.39 (d, *J* = 2.5 Hz, 1H), 2.17 (s, 3H) ppm.

¹³C NMR (126 MHz, DMSO-*d*₆) δ 180.5, 163.0, 160.0 (*q*, ²*J*(C,F) = 34.0 Hz), 152.0, 132.3, 131.9, 130.1, 127.9, 125.9, 121.4, 119.9 (*q*, ¹*J*(C,F) = 275.9 Hz), 109.7, 108.5, 103.2, 102.8, 15.6 ppm.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₈H₁₄F₃N₂O₂S⁺: 379.0723; found: 379.0726.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Fluorine-containing (A) FDA-approved drugs and (B) natural products

Scheme 1. Synthesis of 2-trifluoromethyl-4-chromenone precursors **2** and **3**

Scheme 2.

Substrate scope for the palladium-catalyzed coupling reactions of 7-triflic-4-chromenones **2** with boronic acids.

Scheme 3.

Substrate scope for the palladium-catalyzed coupling reactions of 7-triflic-4-chromenones **2** with aromatic amines

Scheme 4.

Substrate scope for the palladium-catalyzed coupling reactions of 7-triflic-4-chromenones **2** with phenol derivatives

Scheme 5.

Scope for the palladium-catalyzed Suzuki reactions of 3-iodo-4-chromenones **3**, **7** and **8**

Scheme 6.

Synthesis of trifluoromethyl-heterocycles. **Conditions:** K_2CO_3 (not necessary for **12a**), EtOH, 70 °C, 20 min.