

Supporting Information
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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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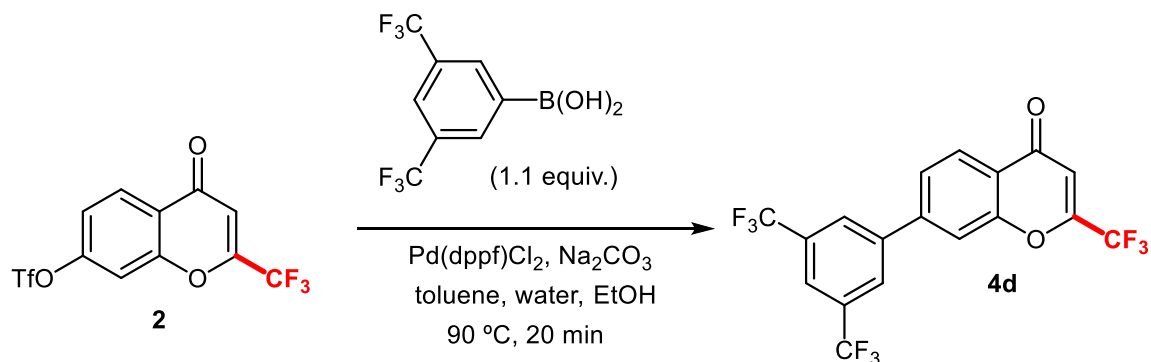
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General Information.

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 µm 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 µm, 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 Büchi Melting Point M-565 apparatus and are uncorrected.

Optimization table for the Pd-catalyzed Suzuki reaction of compounds **4**, **10** and

11.



| Entry | Conditions | Yield^a |
|--------------|--|--------------------------|
| 1 | Standard | 71% |
| 2 | Pd(PPh ₃) ₄ instead of Pd(dppf)Cl ₂ | 10% ^b |
| 3 | Pd(PPh ₃) ₄ instead of Pd(dppf)Cl ₂ and 16 h instead of 20 min | 56% |
| 4 | Dioxane:water instead of toluene:EtOH:water | 58% |
| 5 | NaOAc instead of Na ₂ CO ₃ | NR |
| 6 | Compound 7 instead of 2 ^c | 65% ^b |
| 7 | Compound 7 instead of 2 ^c and 2h instead of 20 min | 80% |
| 8 | Compound 8 instead of 2 ^d and 2h instead of 20 min | 76% |

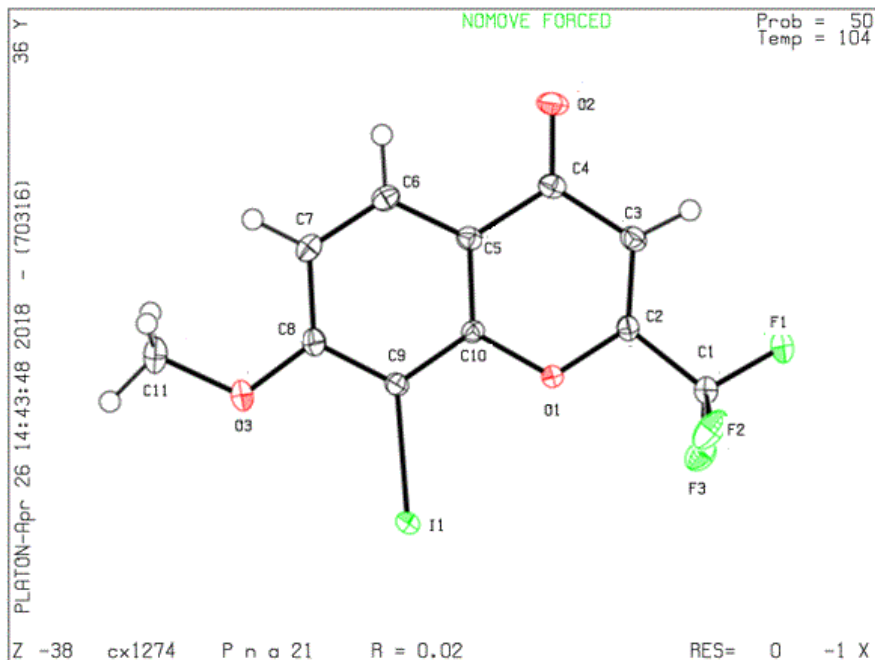
^aIsolated yield for **4d**, **10a** (entry 7) and **11a** (entry 8). ^bConversion measured by LCMS.

^cCompound **10a** was obtained instead of compound **4d**. ^dCompound **11a** was obtained instead of compound **4d**

Crystal data and refinement parameters

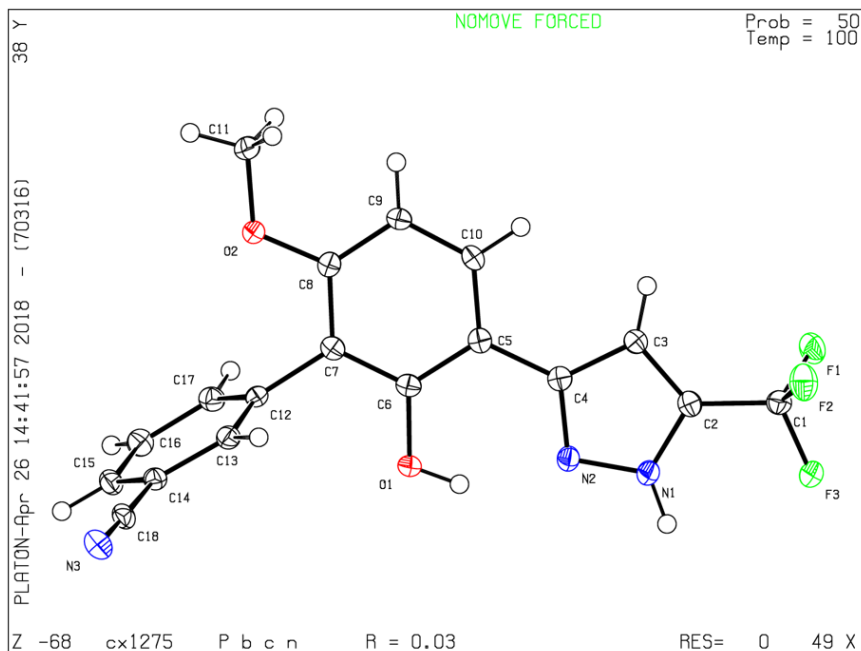
Crystal data and structure refinement for compound **7** (CCDC 1840656)

| Table S1: Crystal data and structure refinement for cx1274 | |
|--|---|
| Identification code | cx1274 |
| Empirical formula | C ₁₁ H ₆ F ₃ IO ₃ |
| Formula weight | 370.06 |
| Temperature / K | 103.57 |
| Crystal system | orthorhombic |
| Space group | Pna2 ₁ |
| a / Å, b / Å, c / Å | 15.1829(6), 17.1979(7), 4.4846(2) |
| α/°, β/°, γ/° | 90, 90, 90 |
| Volume / Å ³ | 1170.99(8) |
| Z | 4 |
| ρ _{calc} / mg mm ⁻³ | 2.099 |
| μ / mm ⁻¹ | 2.771 |
| F(000) | 704 |
| Crystal size / mm ³ | 0.287 × 0.073 × 0.016 |
| 2θ range for data collection | 3.578 to 66.64° |
| Index ranges | -23 ≤ h ≤ 23, -26 ≤ k ≤ 26, -6 ≤ l ≤ 5 |
| Reflections collected | 29060 |
| Independent reflections | 4148[R(int) = 0.0288] |
| Data/restraints/parameters | 4148/1/164 |
| Goodness-of-fit on F ² | 1.064 |
| Final R indexes [I > 2σ (I)] | R ₁ = 0.0206, wR ₂ = 0.0552 |
| Final R indexes [all data] | R ₁ = 0.0216, wR ₂ = 0.0564 |
| Largest diff. peak/hole / e Å ⁻³ | 0.722/-1.027 |



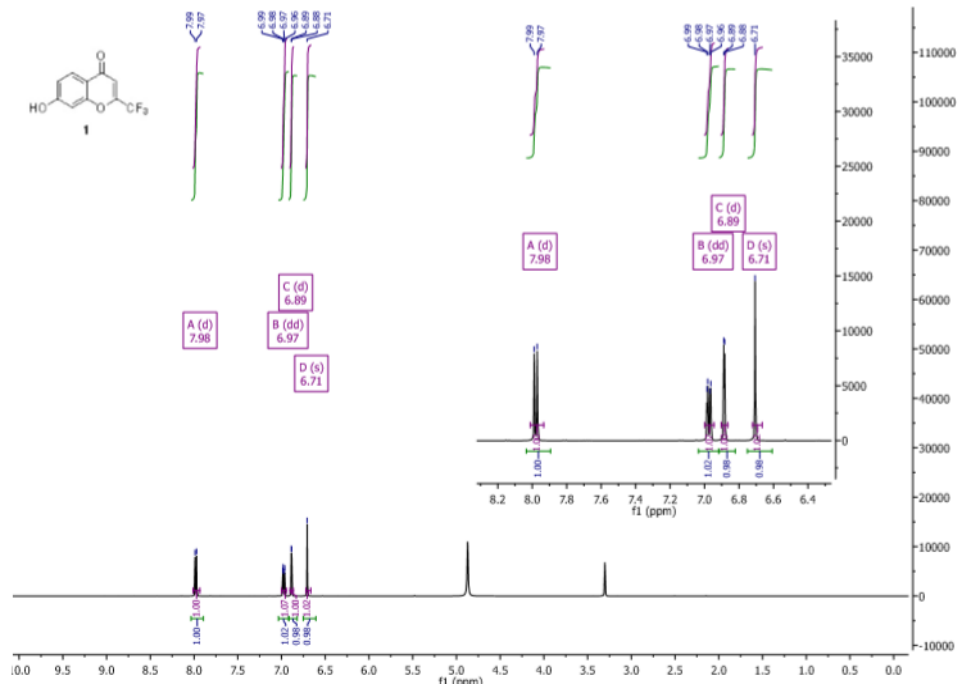
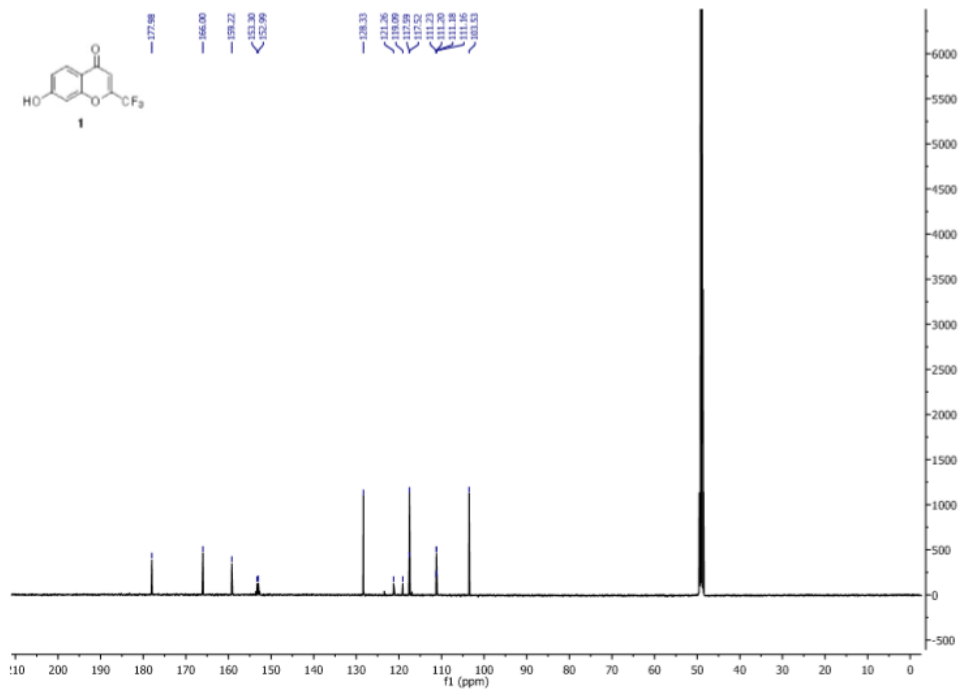
Crystal data and structure refinement for compound **12a** (CCDC 1840657)

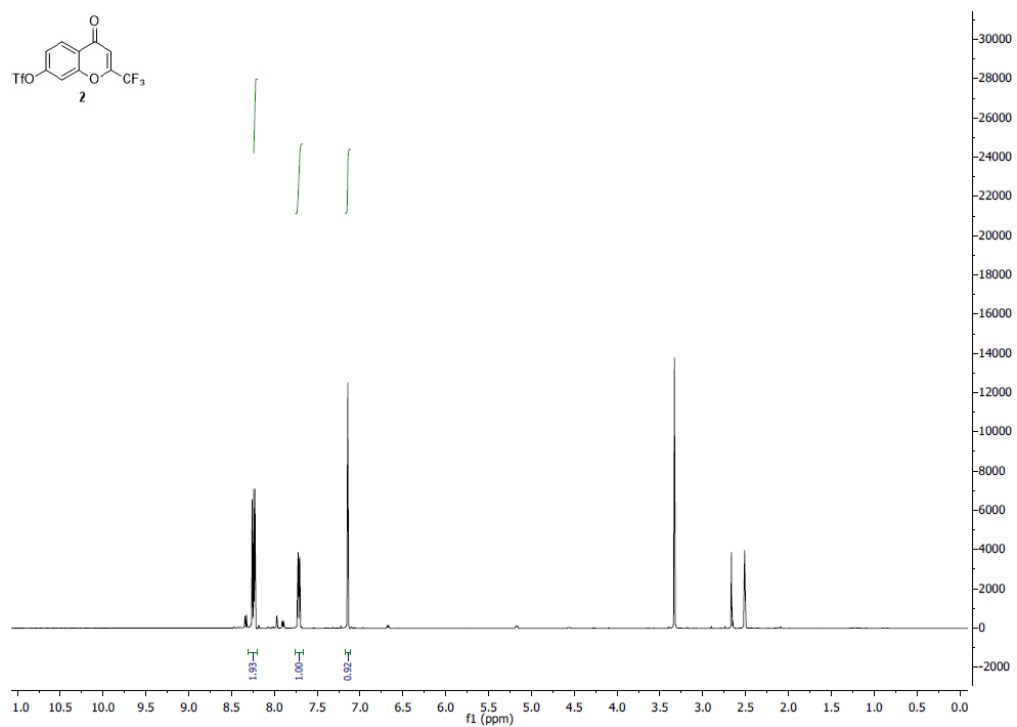
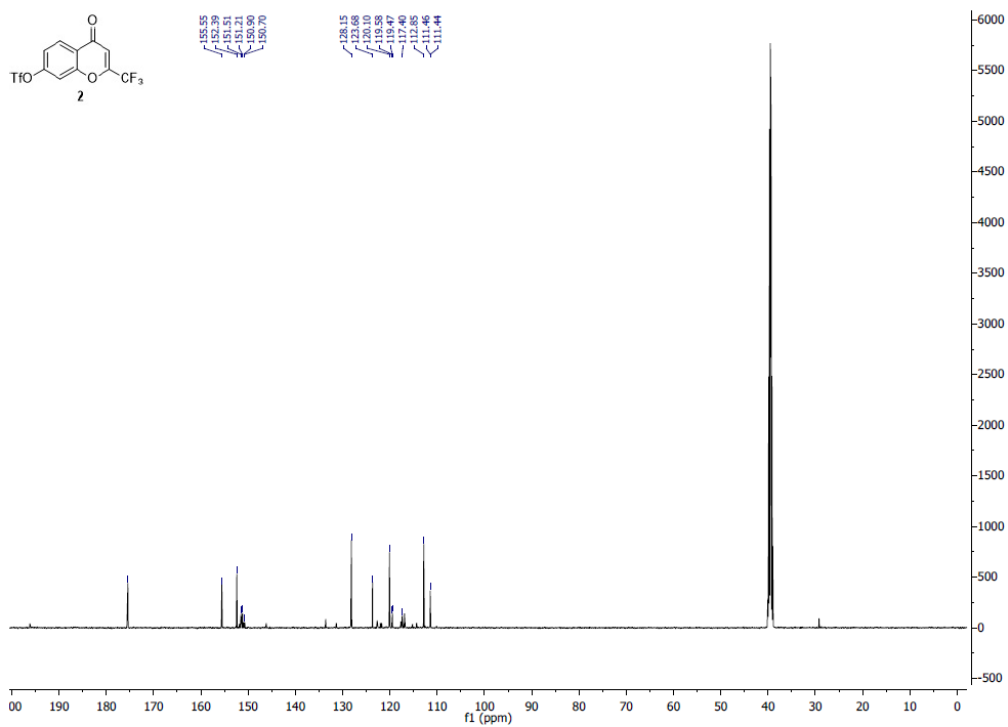
| Table S2: Crystal data and structure refinement for cx1275 | |
|---|--|
| Identification code | cx1275 |
| Empirical formula | C ₁₈ H ₁₂ N ₃ O ₂ F ₃ |
| Formula weight | 359.31 |
| Temperature / K | 100.01 |
| Crystal system | orthorhombic |
| Space group | Pbcn |
| a / Å, b / Å, c / Å | 27.8356(9), 5.13030(10), 21.0337(6) |
| α / °, β / °, γ / ° | 90, 90, 90 |
| Volume / Å ³ | 3003.72(14) |
| Z | 8 |
| ρ _{calc} / mg mm ⁻³ | 1.589 |
| μ / mm ⁻¹ | 1.131 |
| F(000) | 1472 |
| Crystal size / mm ³ | 0.119 × 0.099 × 0.034 |
| 2θ range for data collection | 8.408 to 130.242° |
| Index ranges | -19 ≤ h ≤ 32, -5 ≤ k ≤ 6, -24 ≤ l ≤ 16 |
| Reflections collected | 7133 |
| Independent reflections | 2531 [R(int) = 0.0279] |
| Data/restraints/parameters | 2531/0/244 |
| Goodness-of-fit on F ² | 1.043 |
| Final R indexes [I > 2σ (I)] | R ₁ = 0.0325, wR ₂ = 0.0864 |
| Final R indexes [all data] | R ₁ = 0.0347, wR ₂ = 0.0887 |
| Largest diff. peak/hole / e Å ⁻³ | 0.208/-0.261 |

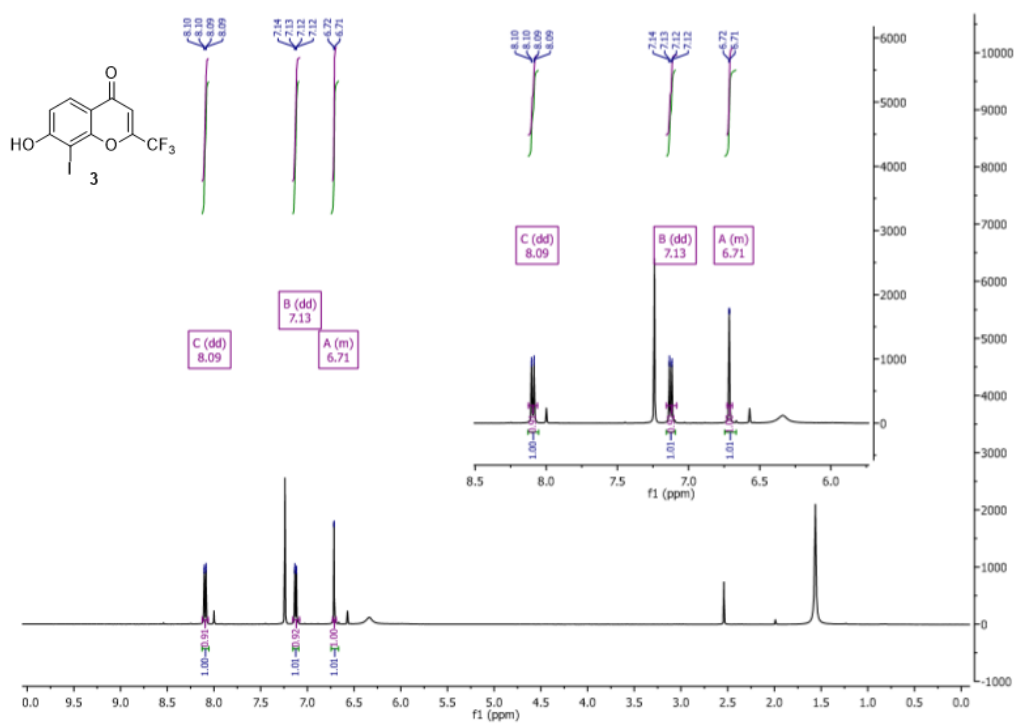
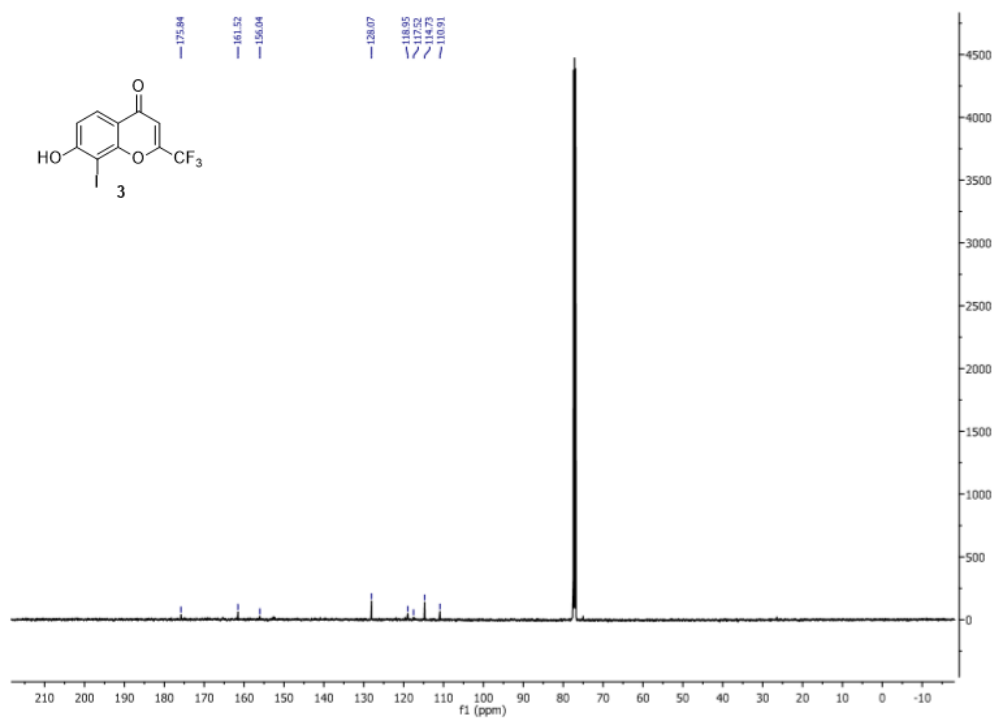


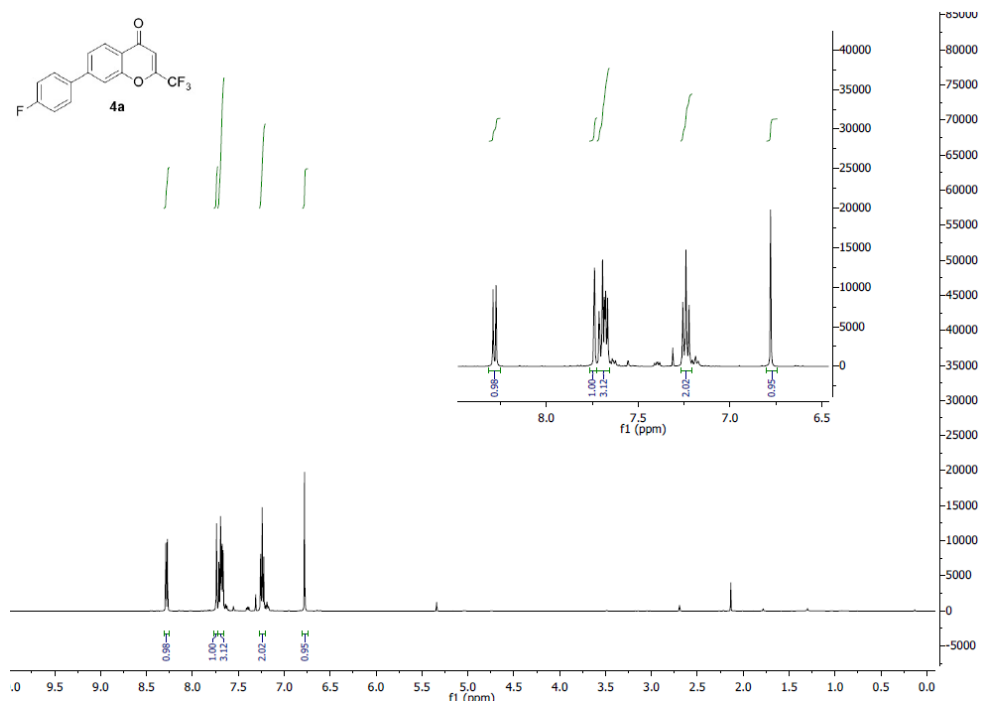
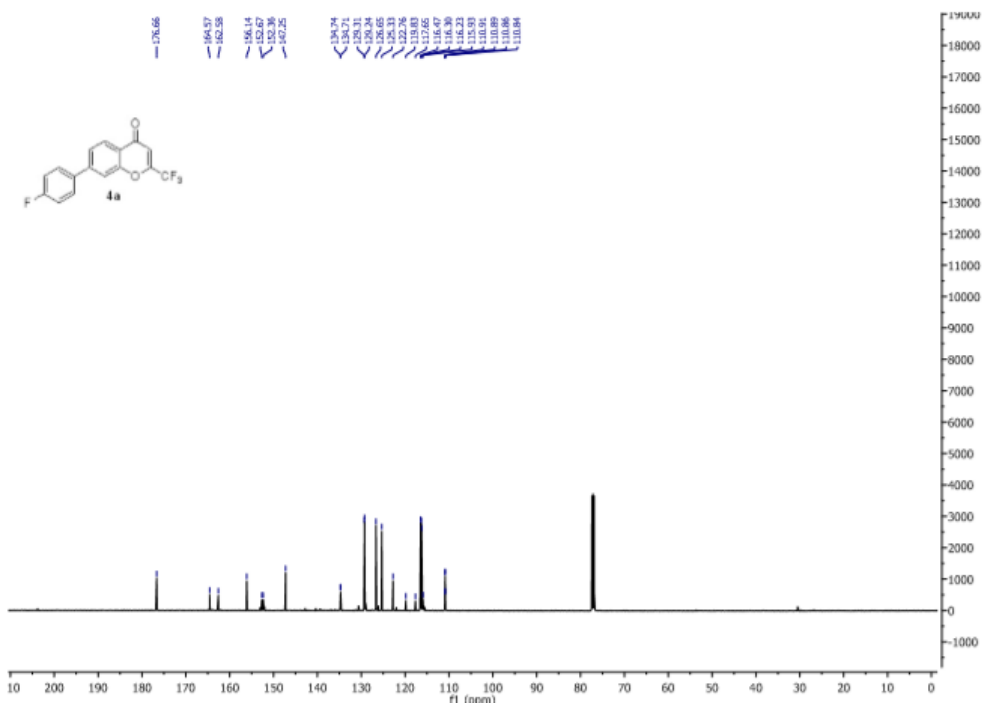
NMR SPECTRA

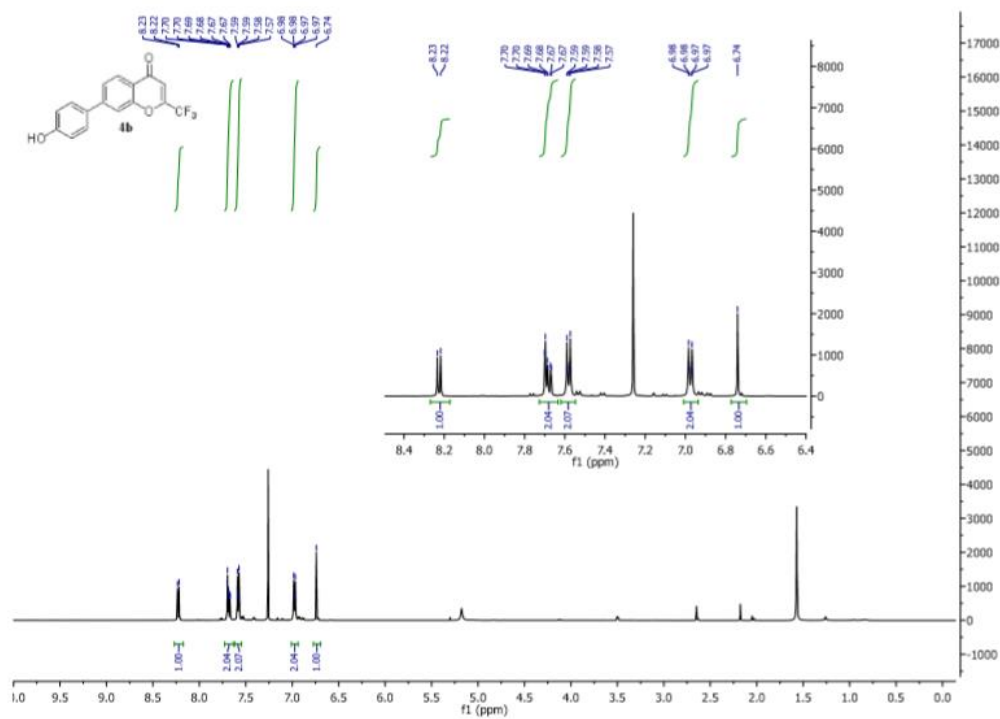
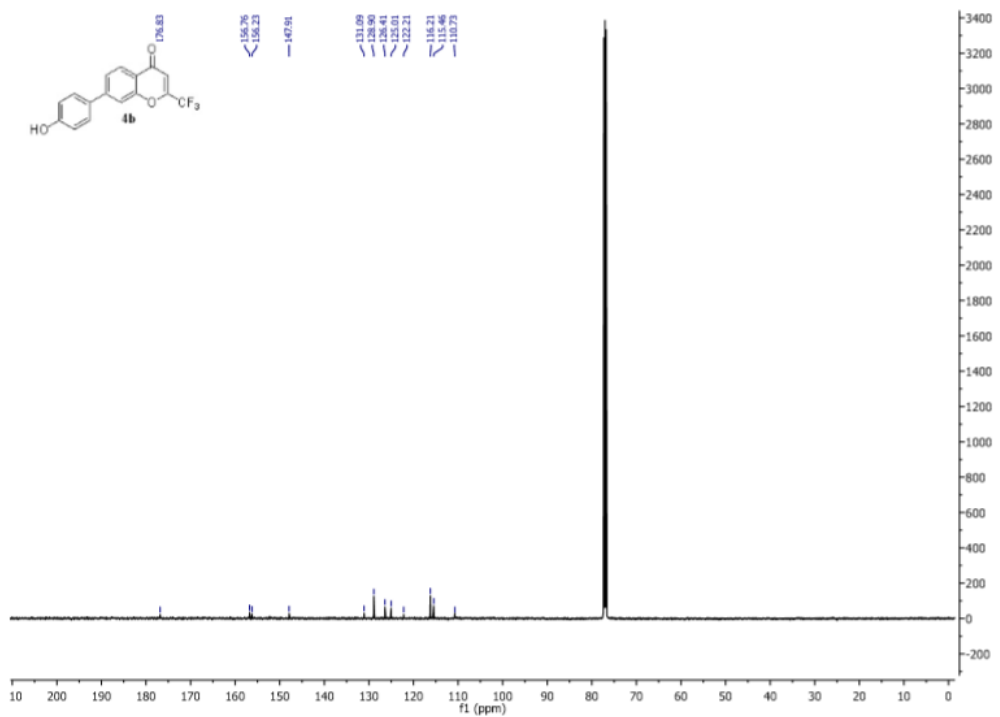
7-hydroxy-2-(trifluoromethyl)-4H-chromen-4-one (1)

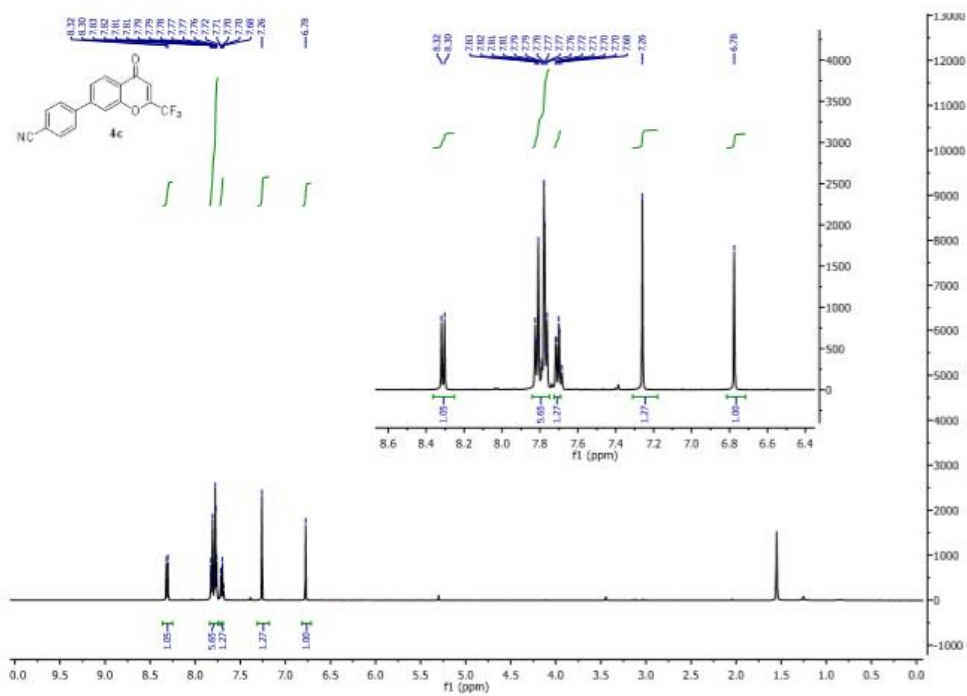
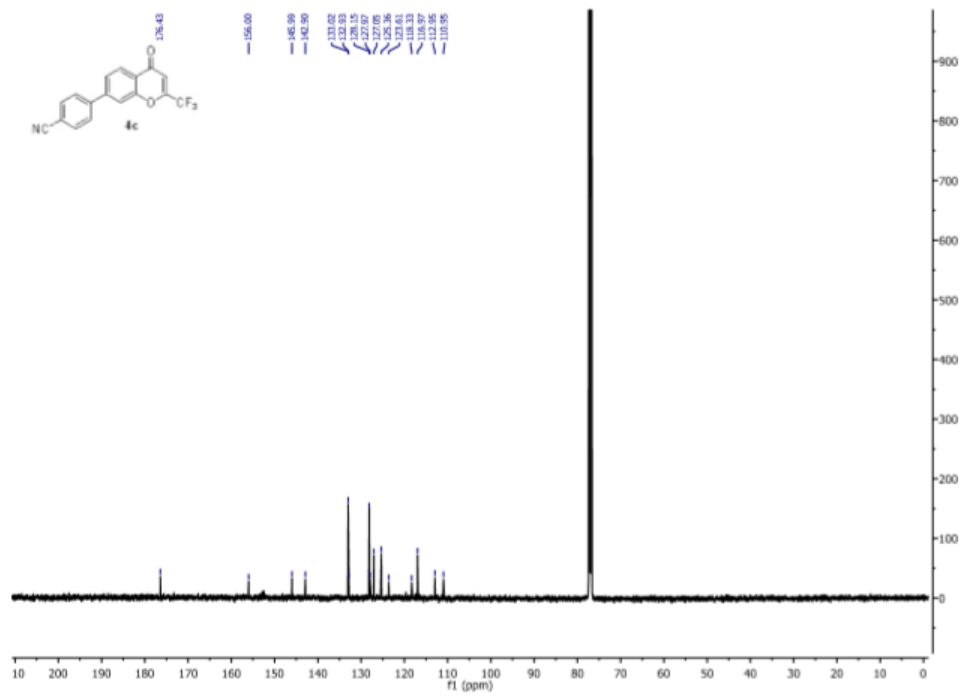
¹H NMR¹³C NMR

4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl trifluoromethanesulfonate (2)**¹H NMR****¹³C NMR**

7-hydroxy-8-iodo-2-(trifluoromethyl)-4H-chromen-4-one (3)**¹H NMR****¹³C NMR**

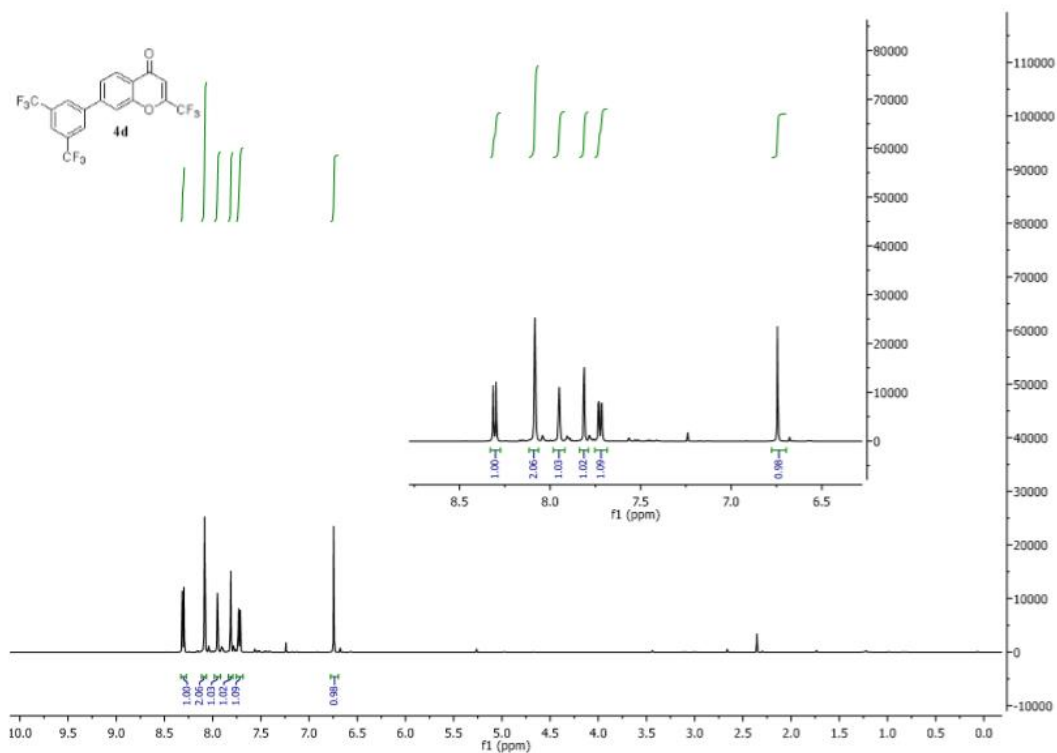
7-(4-fluorophenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4a)**¹H NMR****¹³C NMR**

7-(4-hydroxyphenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4b)**¹H NMR****¹³C NMR**

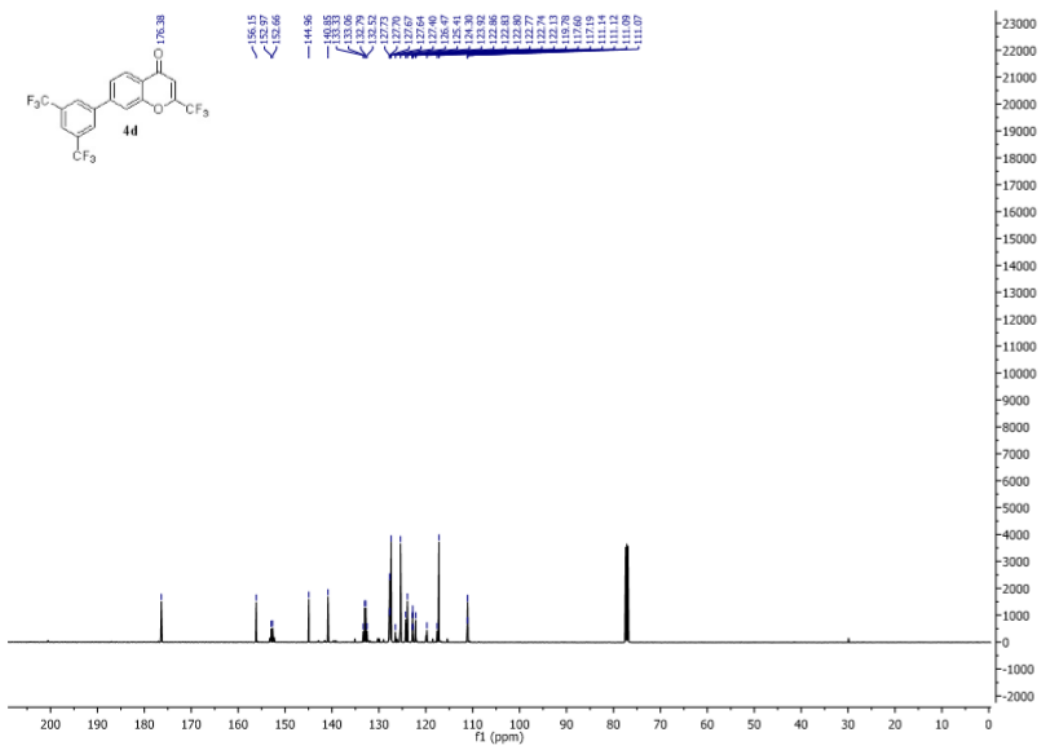
4-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)benzonitrile (4c)**¹H NMR****¹³C NMR**

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

¹H NMR

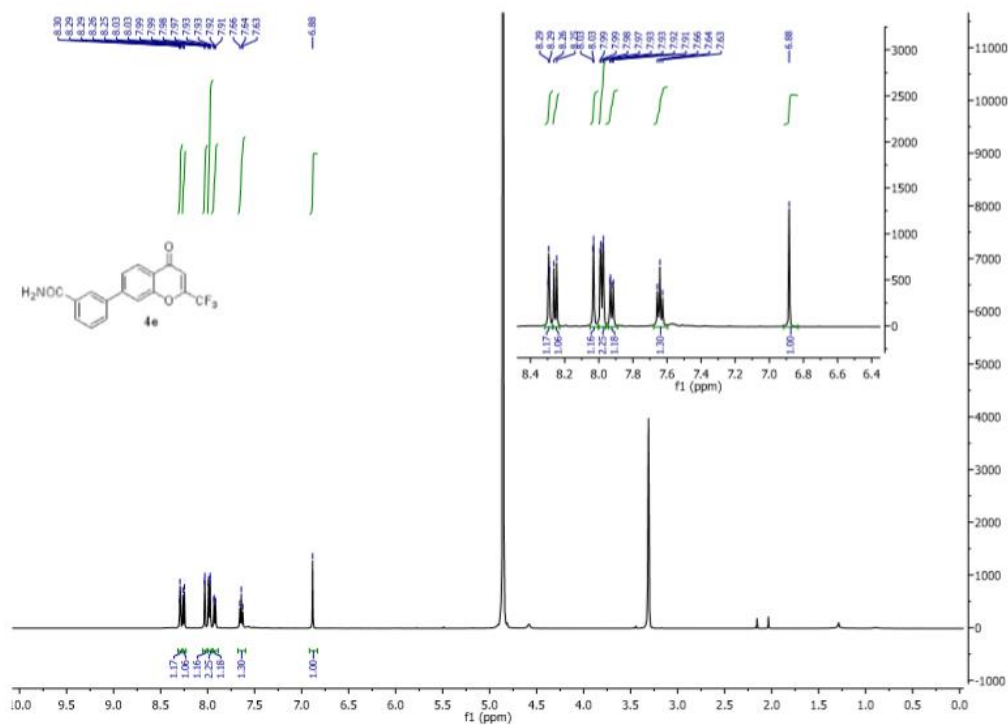


¹³C NMR

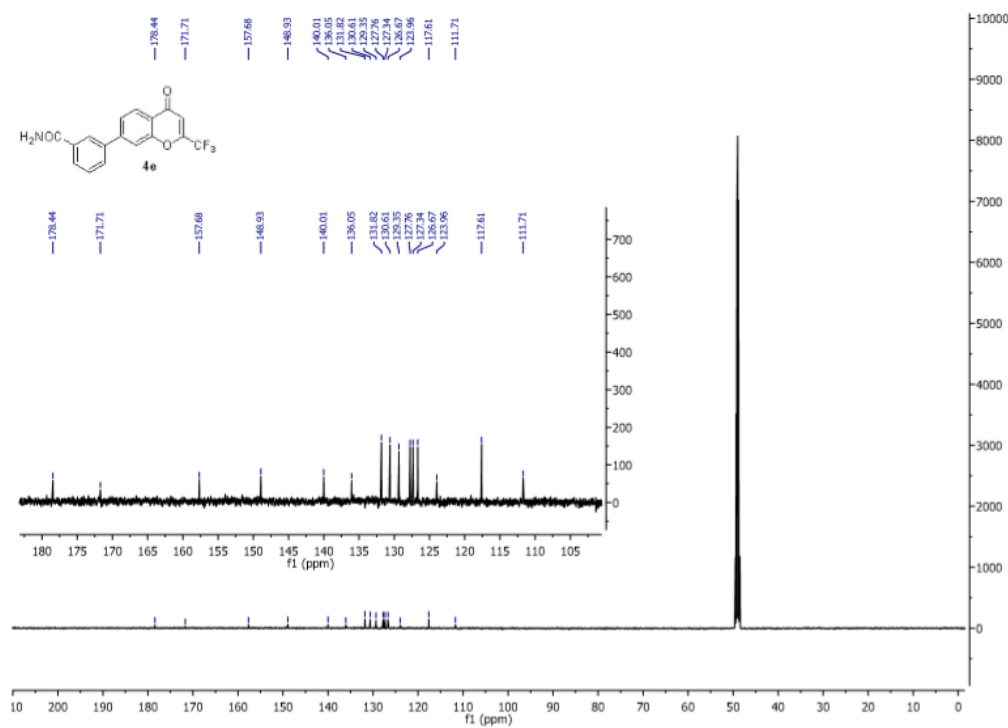


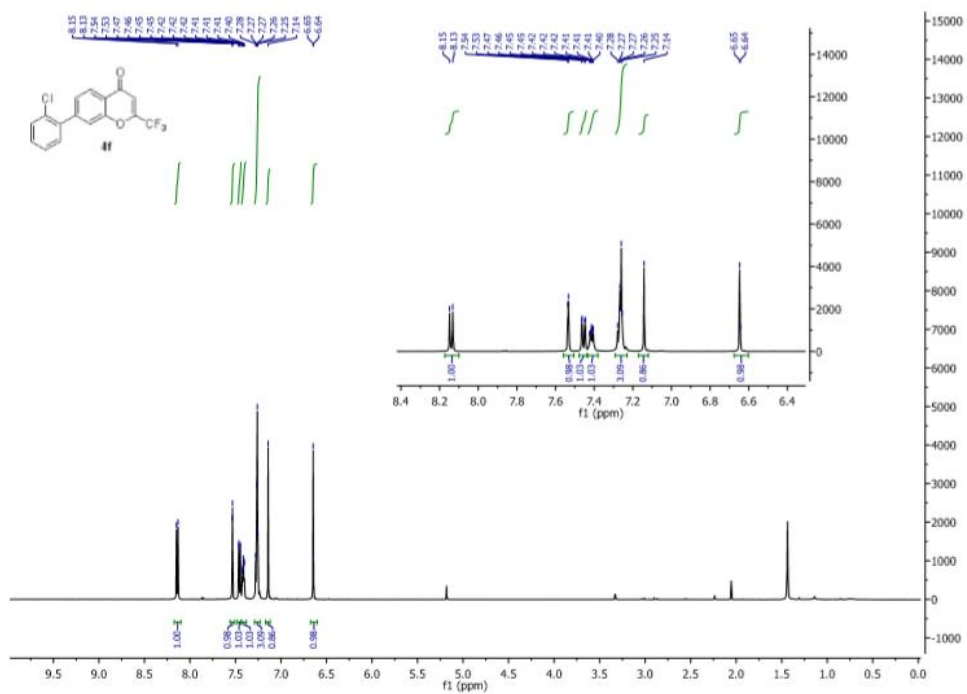
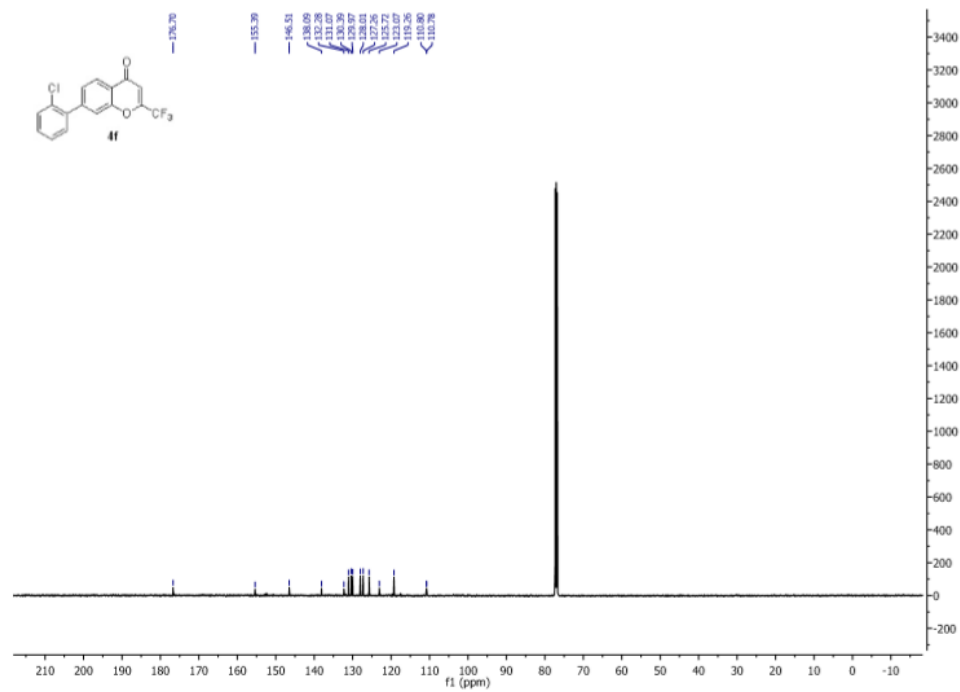
3-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)benzamide (4e)

¹H NMR

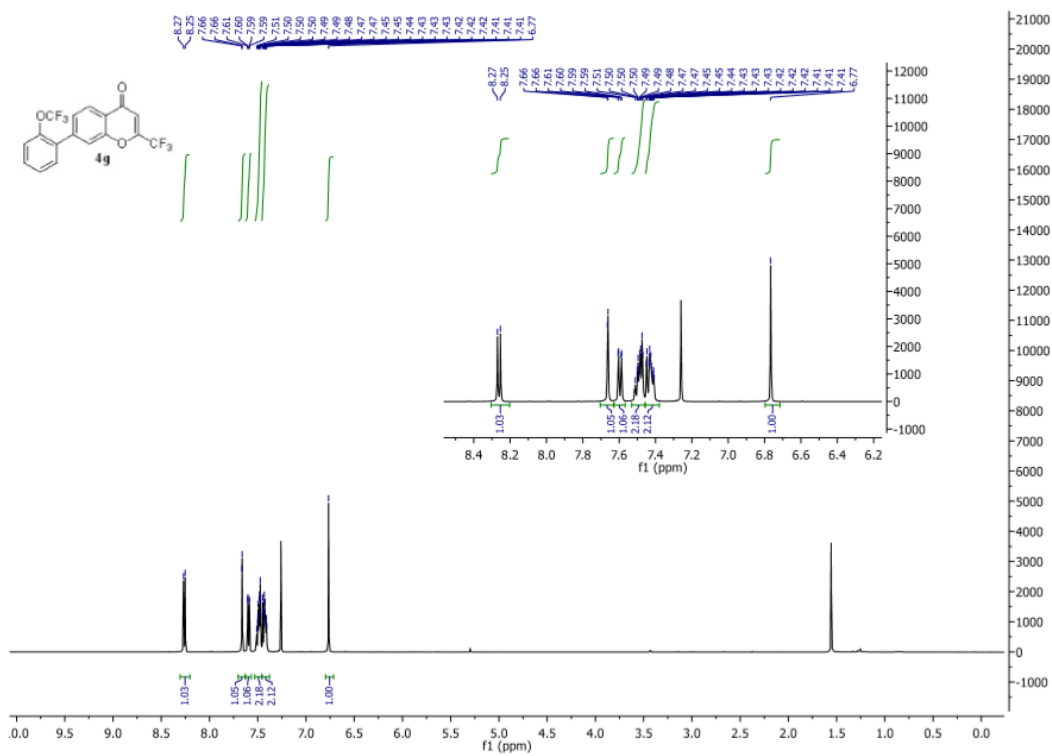
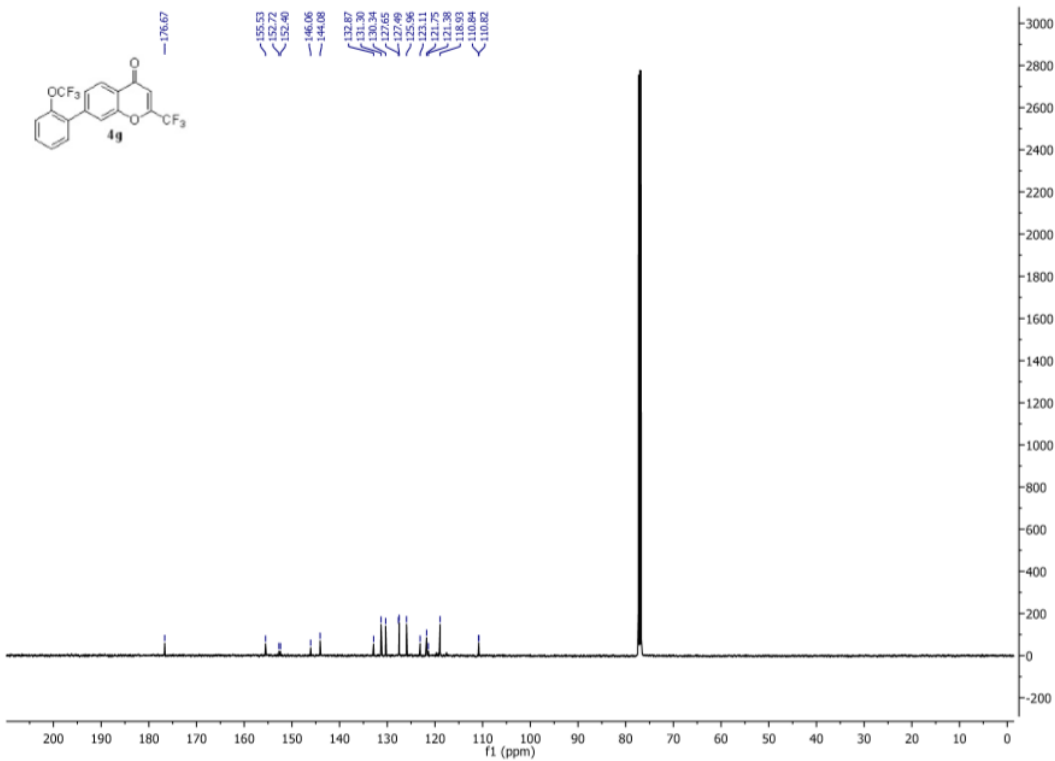


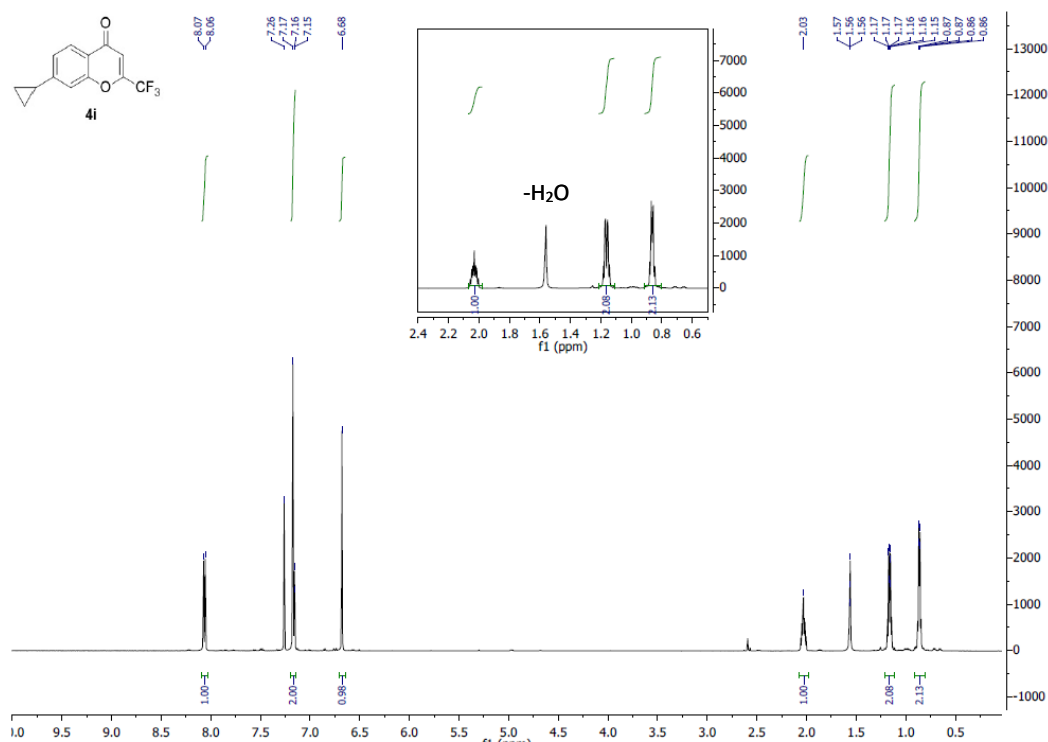
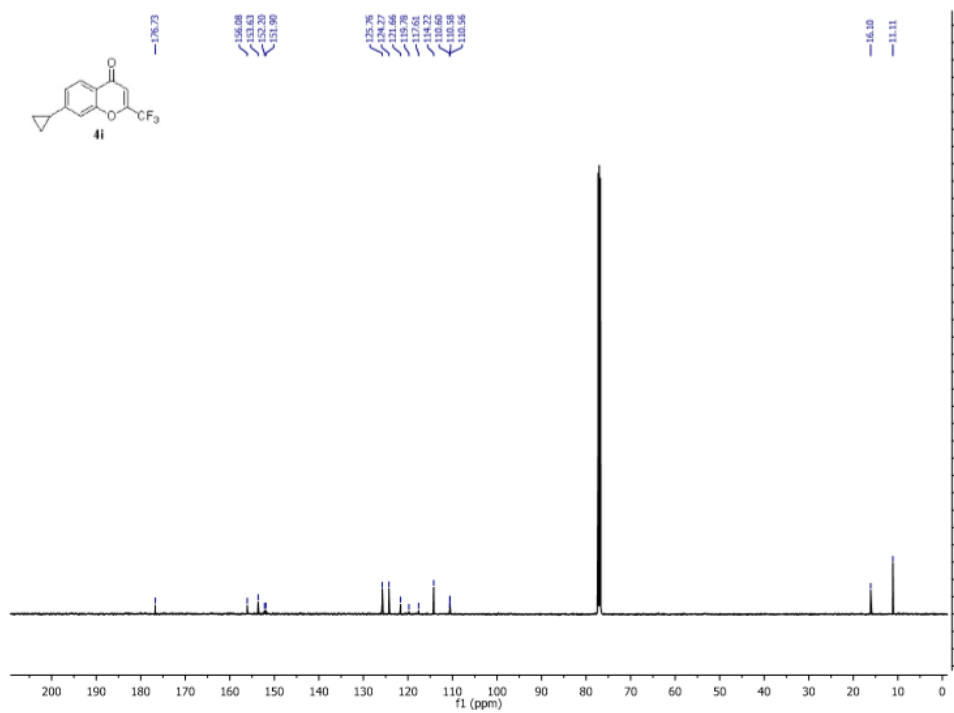
¹³C NMR

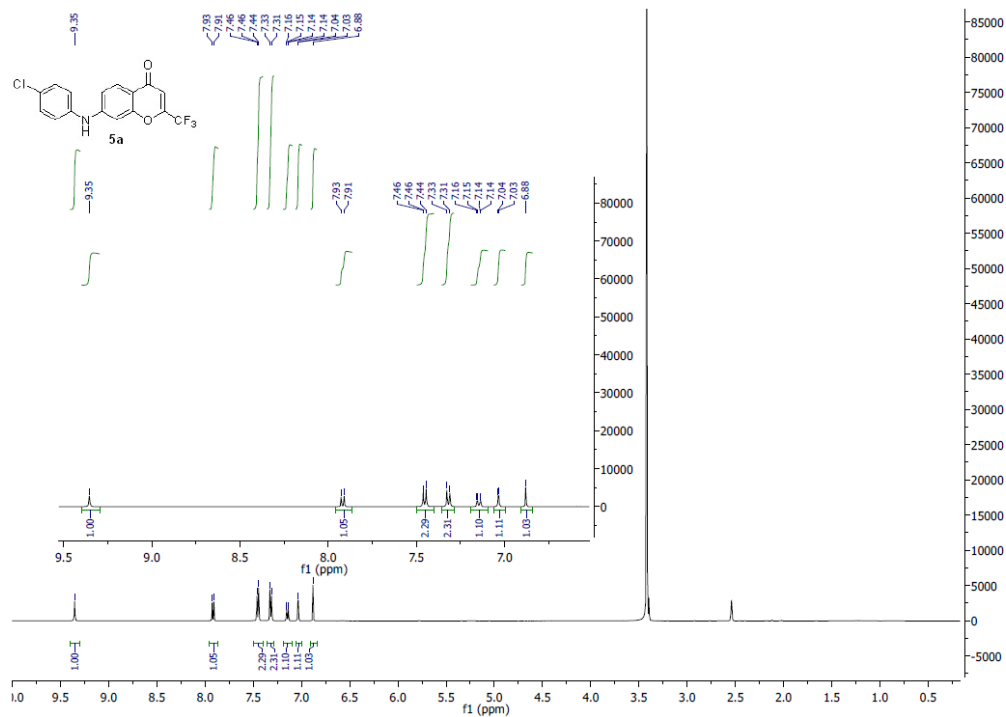
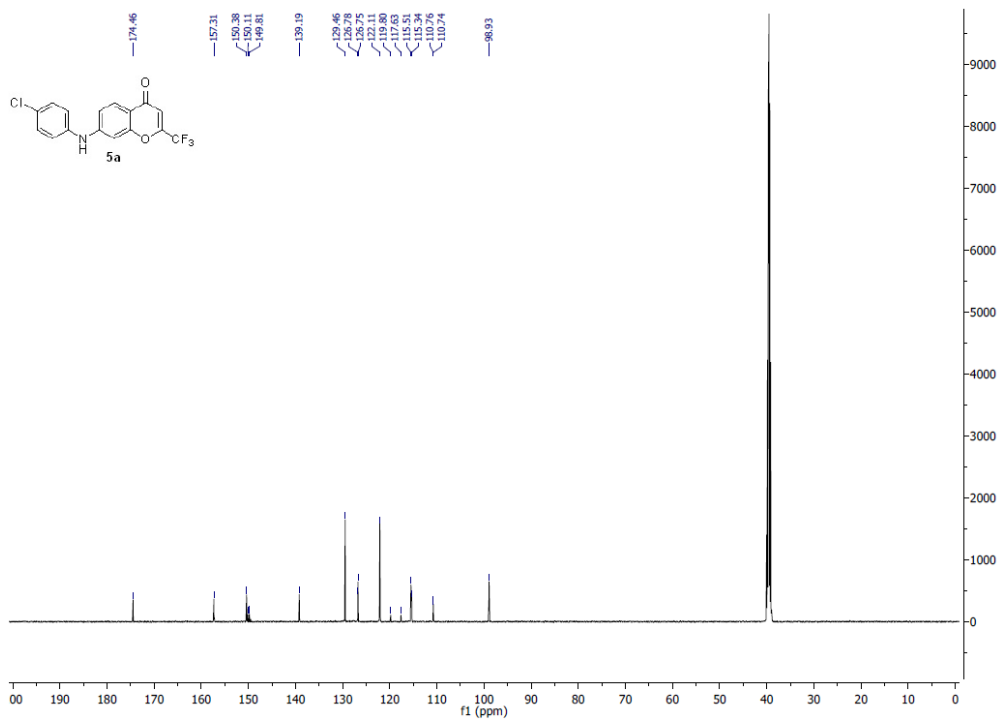


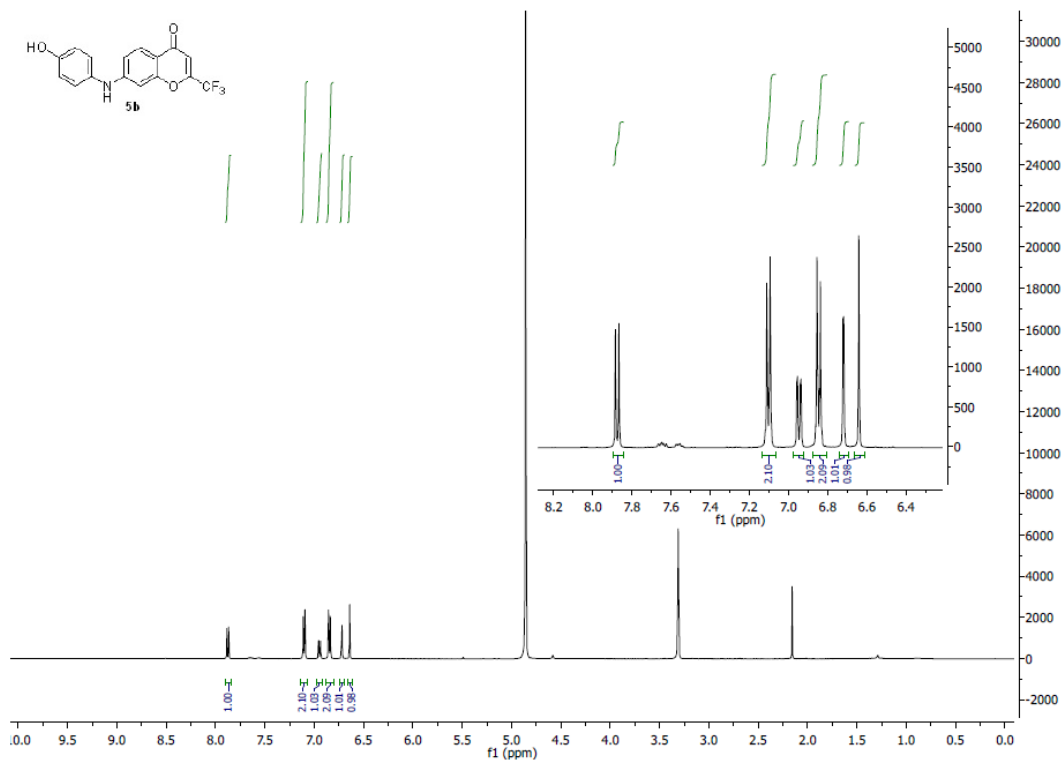
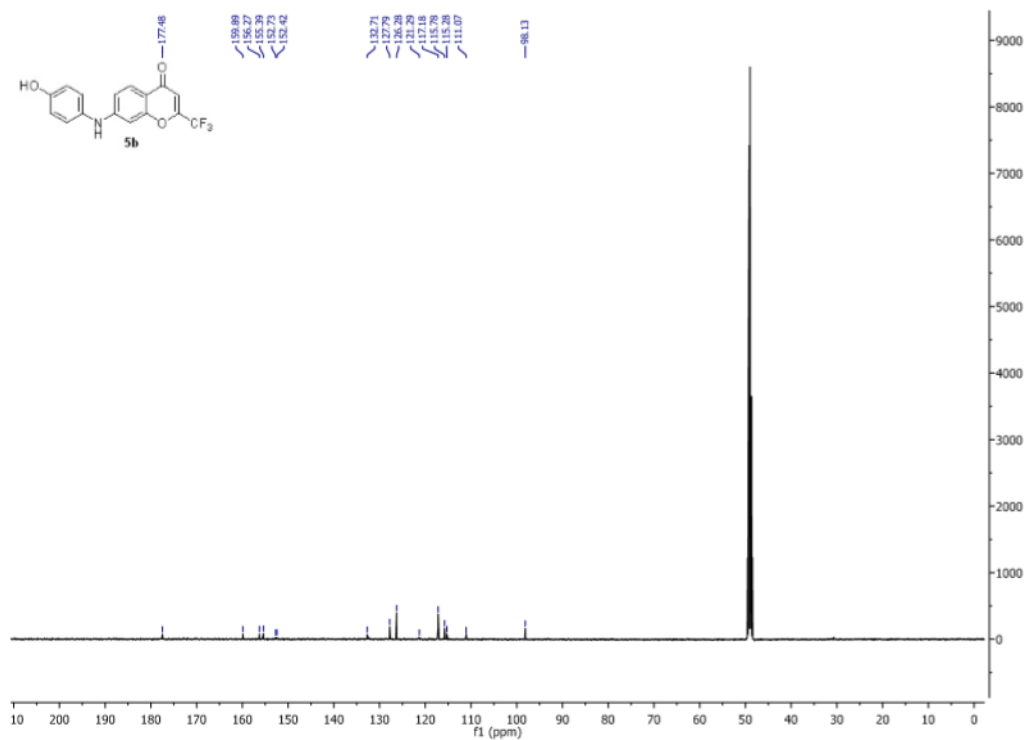
7-(2-chlorophenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4f)**¹H NMR****¹³C NMR**

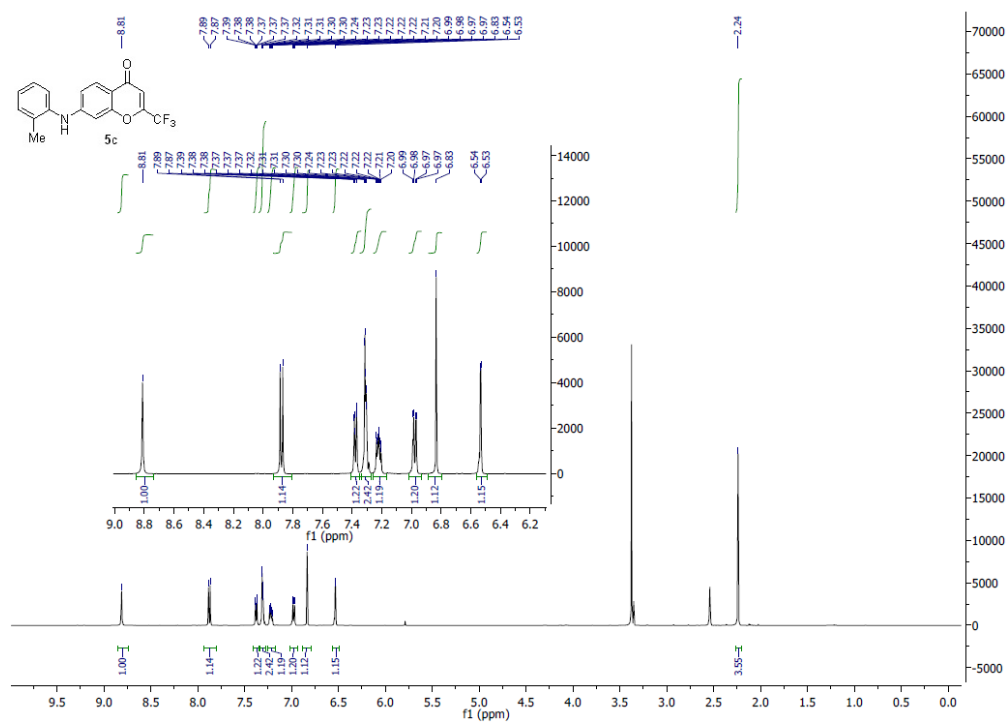
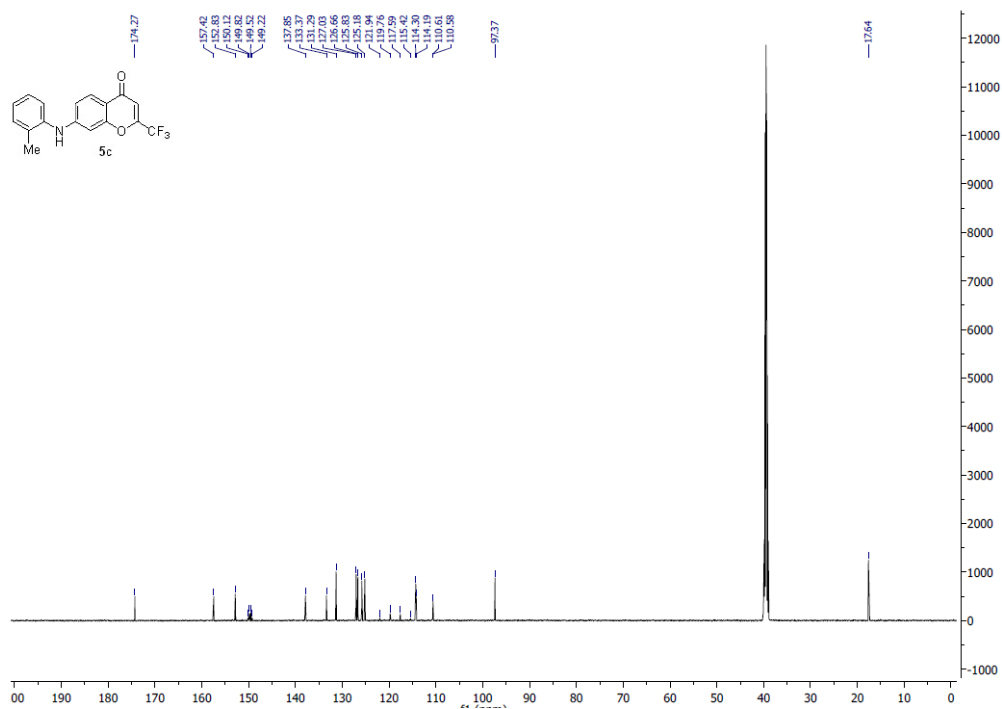
7-(2-(trifluoromethoxy)phenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4g)

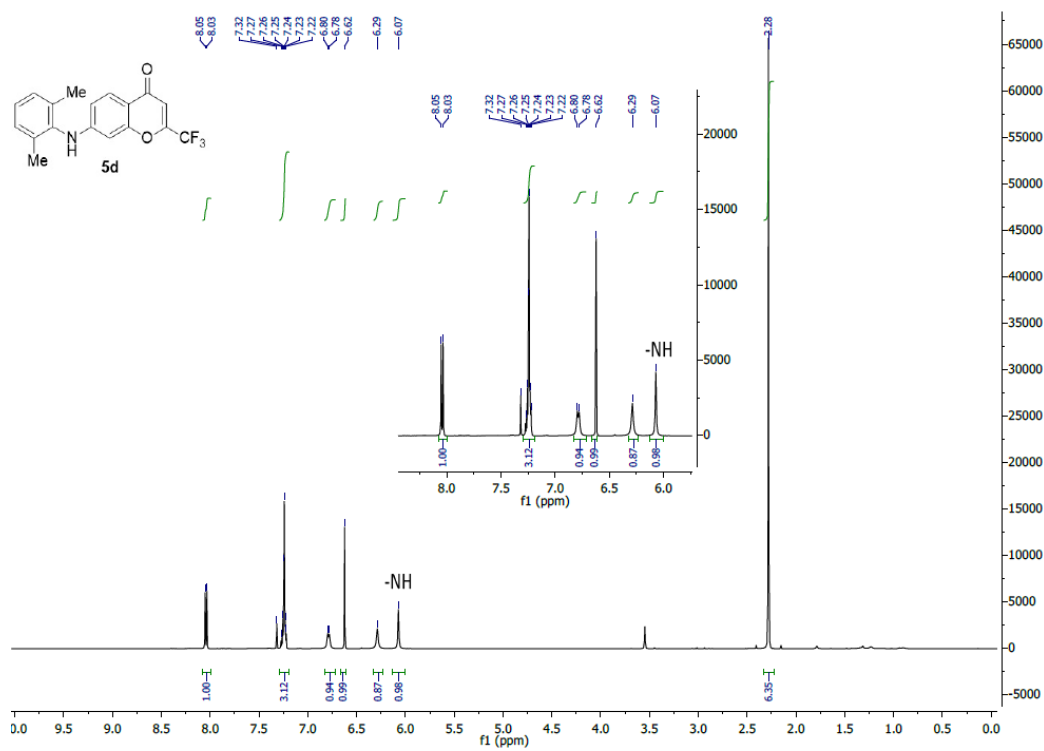
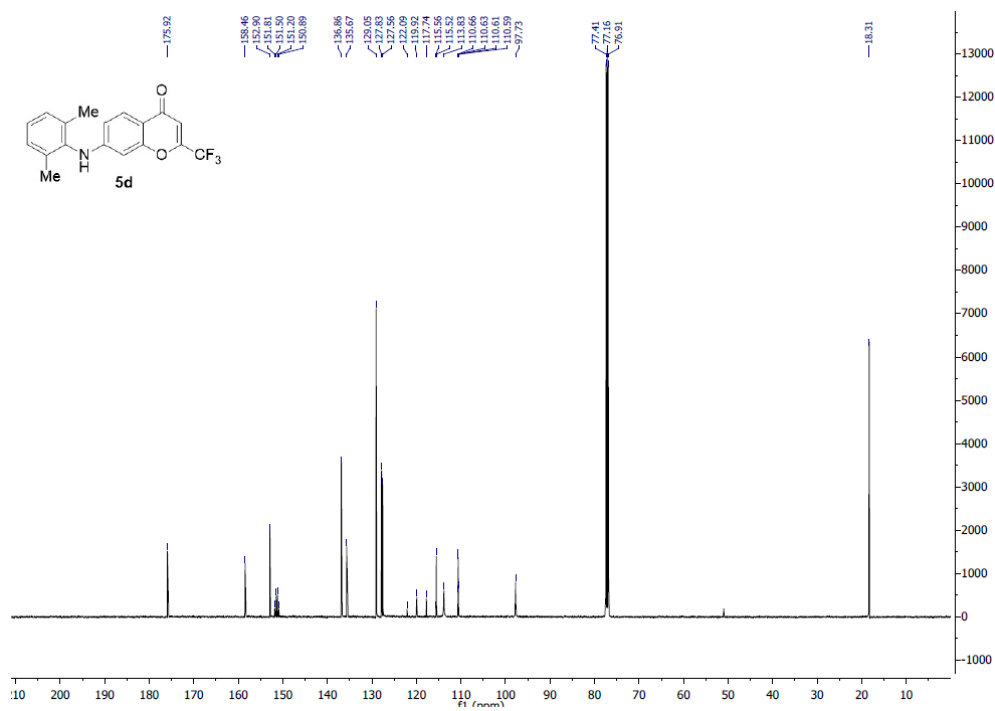
¹H NMR¹³C NMR

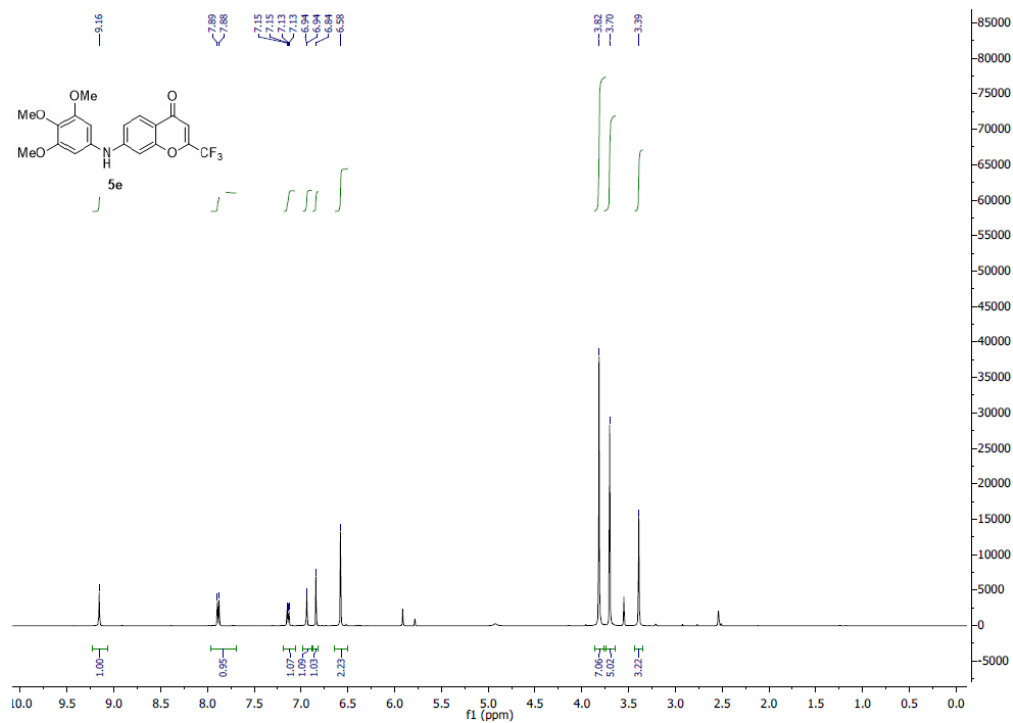
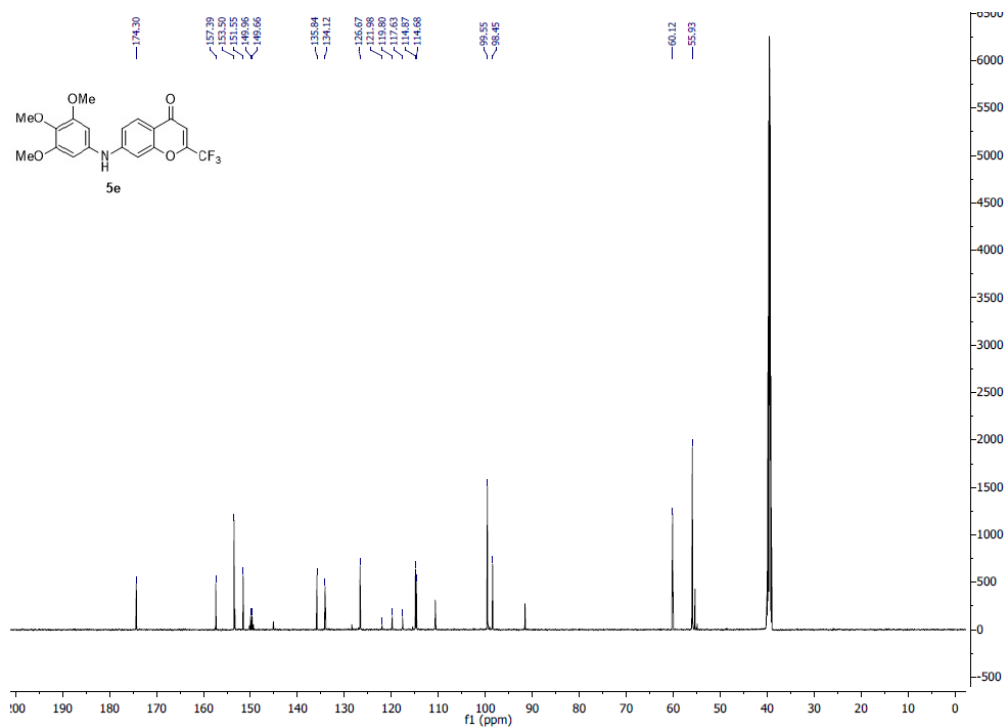
7-cyclopropyl-2-(trifluoromethyl)-4H-chromen-4-one (4i)**¹H NMR****¹³C NMR**

7-((4-chlorophenyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5a)**¹H NMR****¹³C NMR**

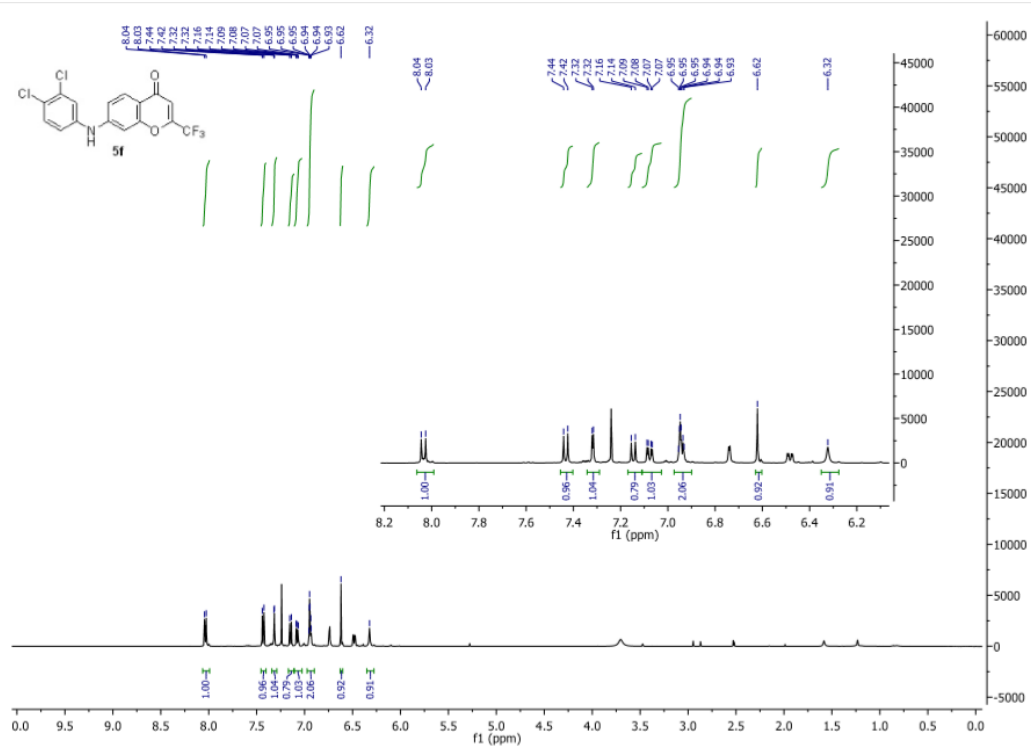
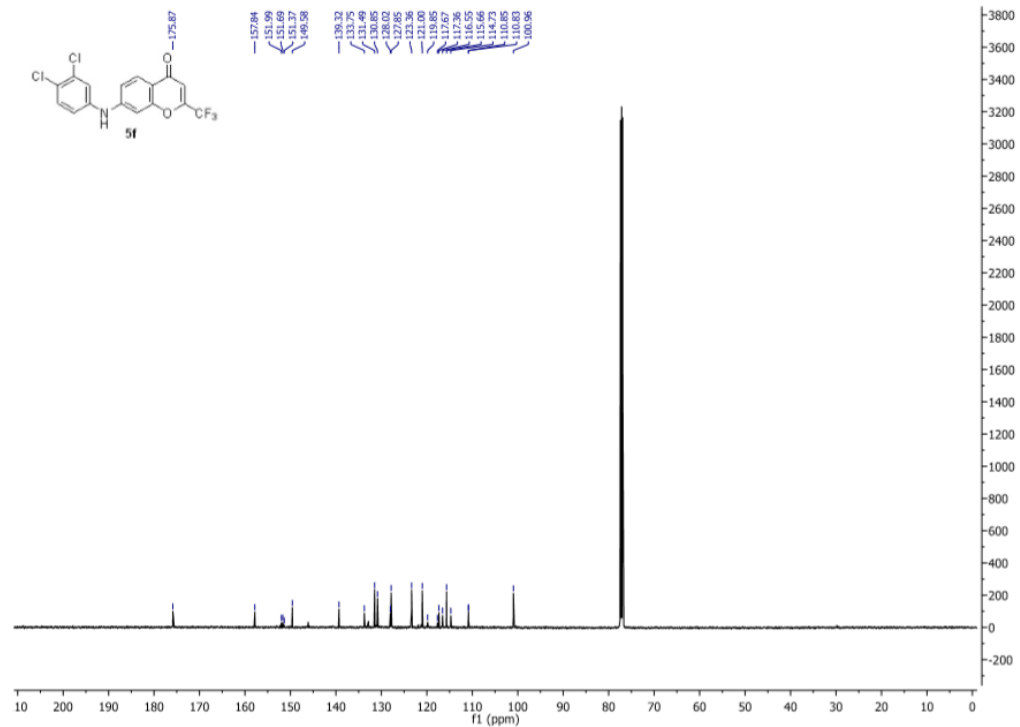
7-((4-hydroxyphenyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5b)**¹H NMR****¹³C NMR**

7-(o-tolylamino)-2-(trifluoromethyl)-4H-chromen-4-one (5c)**¹H NMR****¹³C NMR**

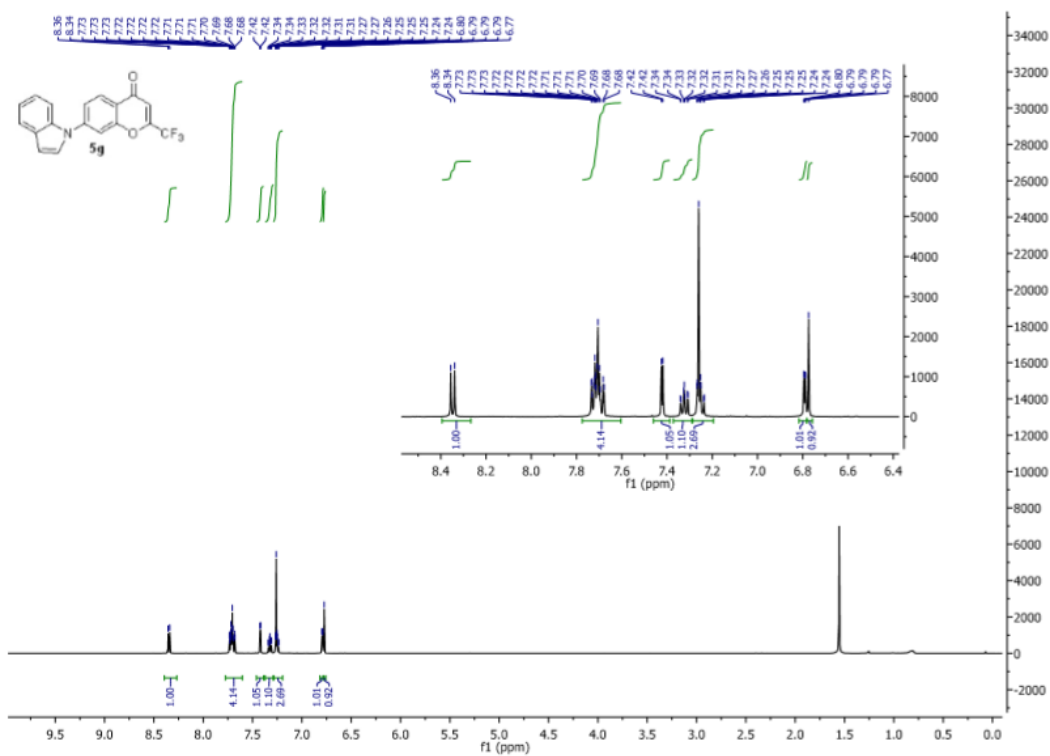
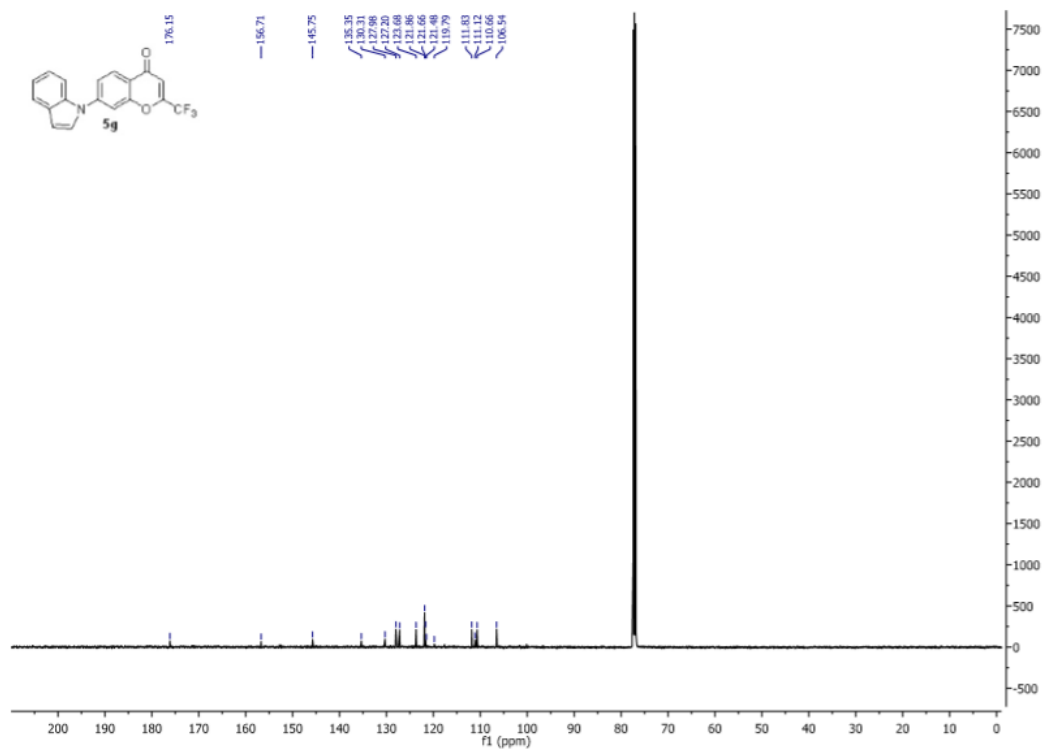
7-((2,6-dimethylphenyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5d)**¹H NMR****¹³C NMR**

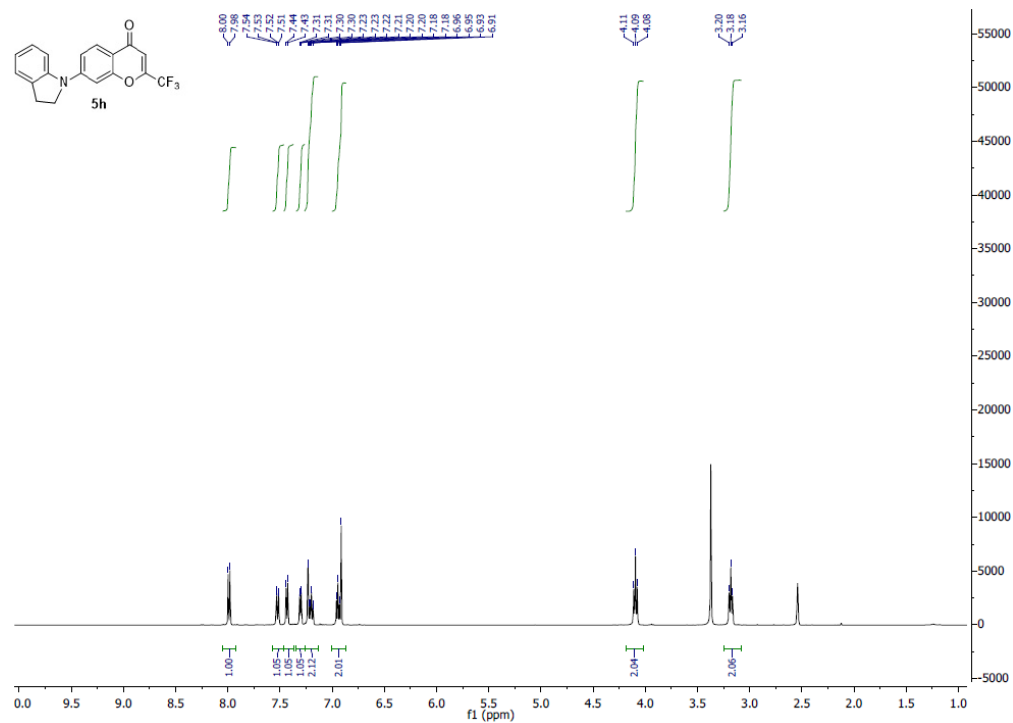
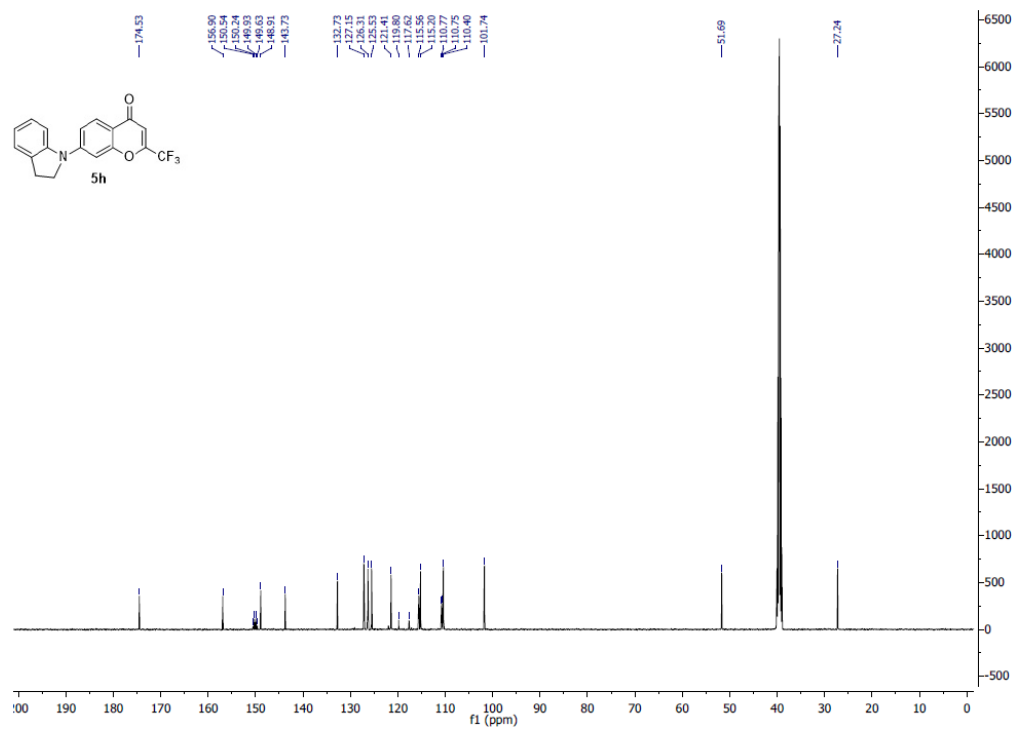
2-(trifluoromethyl)-7-((3,4,5-trimethoxyphenyl)amino)-4H-chromen-4-one (5e)**¹H NMR****¹³C NMR**

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

¹H NMR¹³C NMR

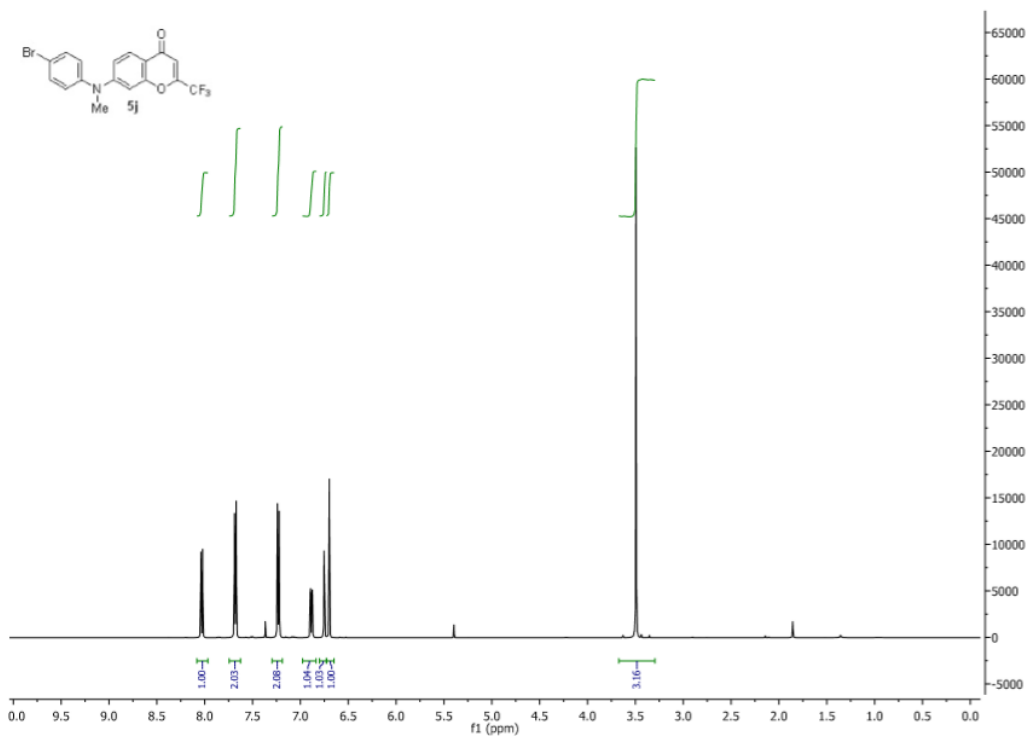
7-(1H-indol-1-yl)-2-(trifluoromethyl)-4H-chromen-4-one (5g)

¹H NMR¹³C NMR

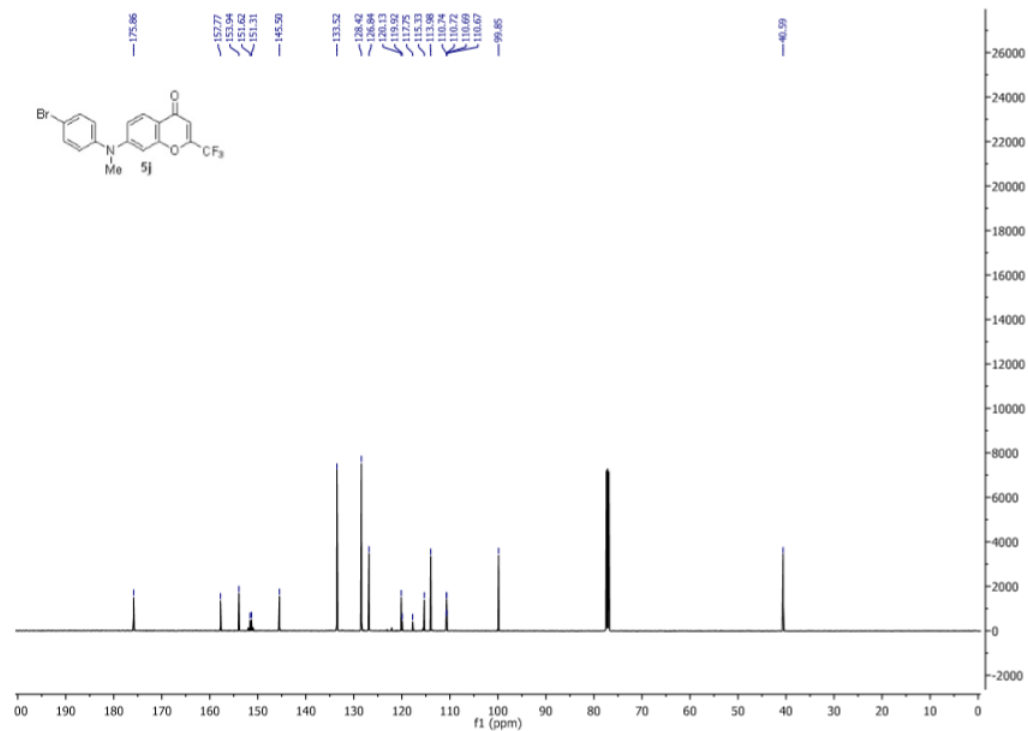
7-(indolin-1-yl)-2-(trifluoromethyl)-4H-chromen-4-one (5h)**¹H NMR****¹³C NMR**

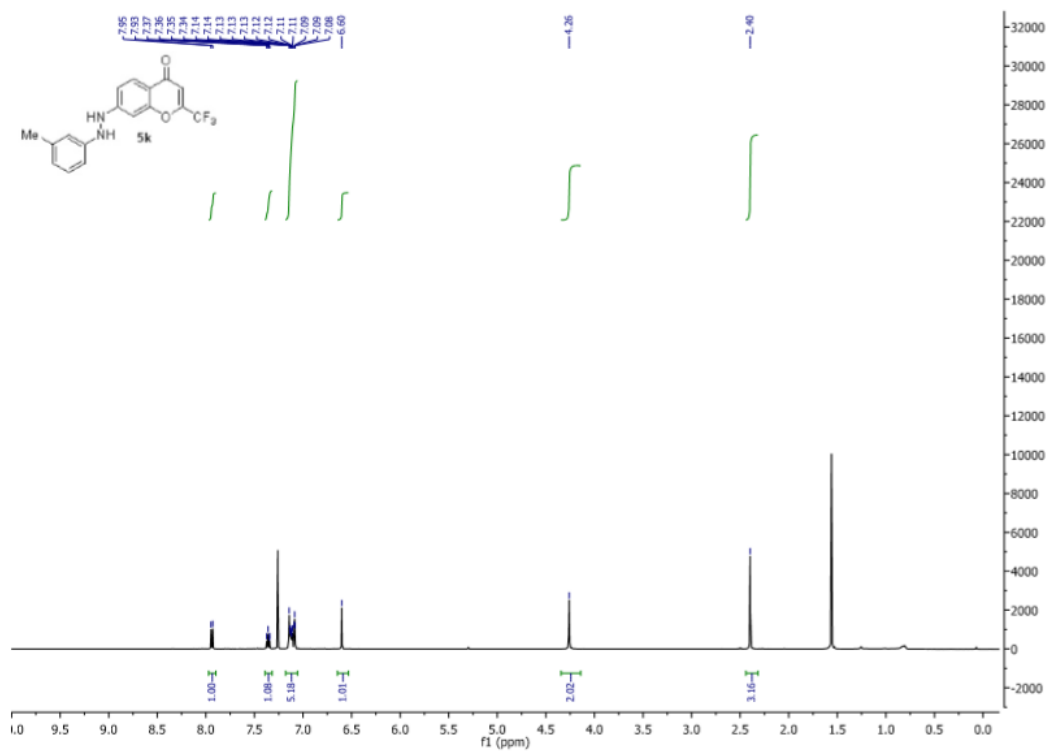
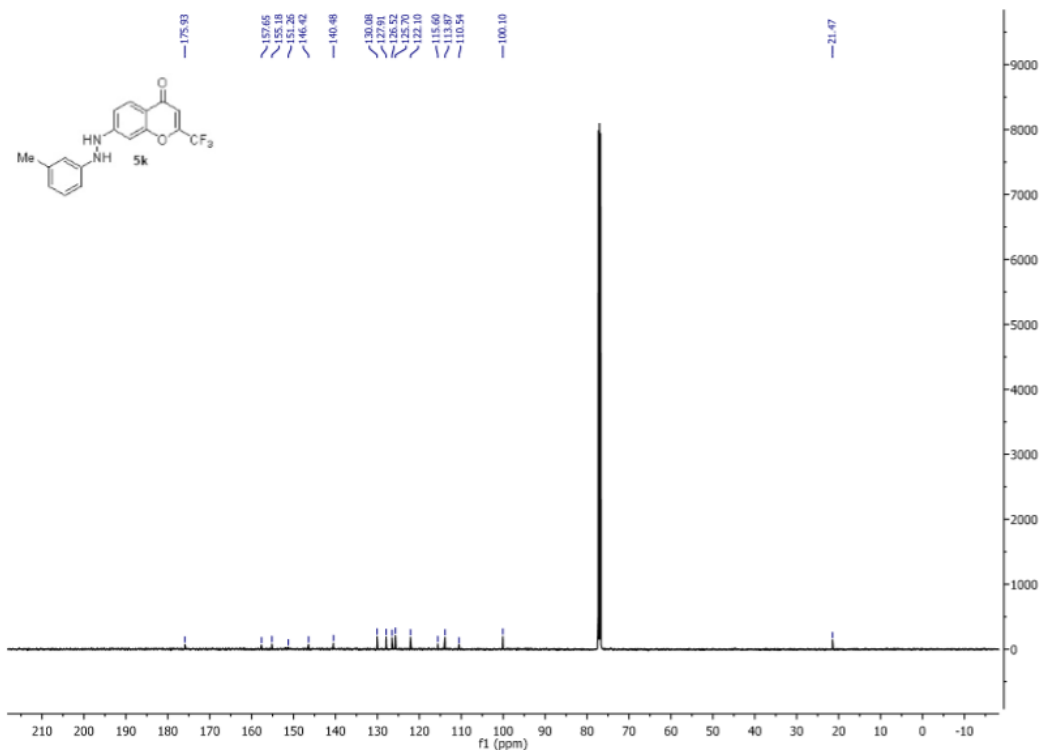
7-((4-bromophenyl)(methyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5j)

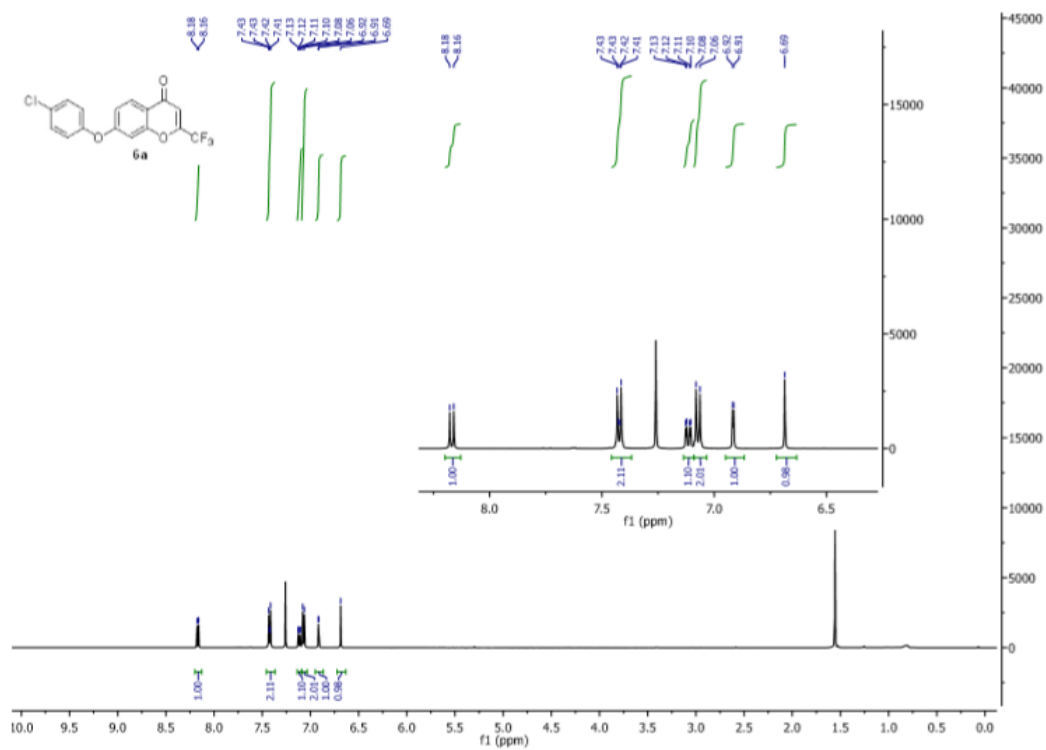
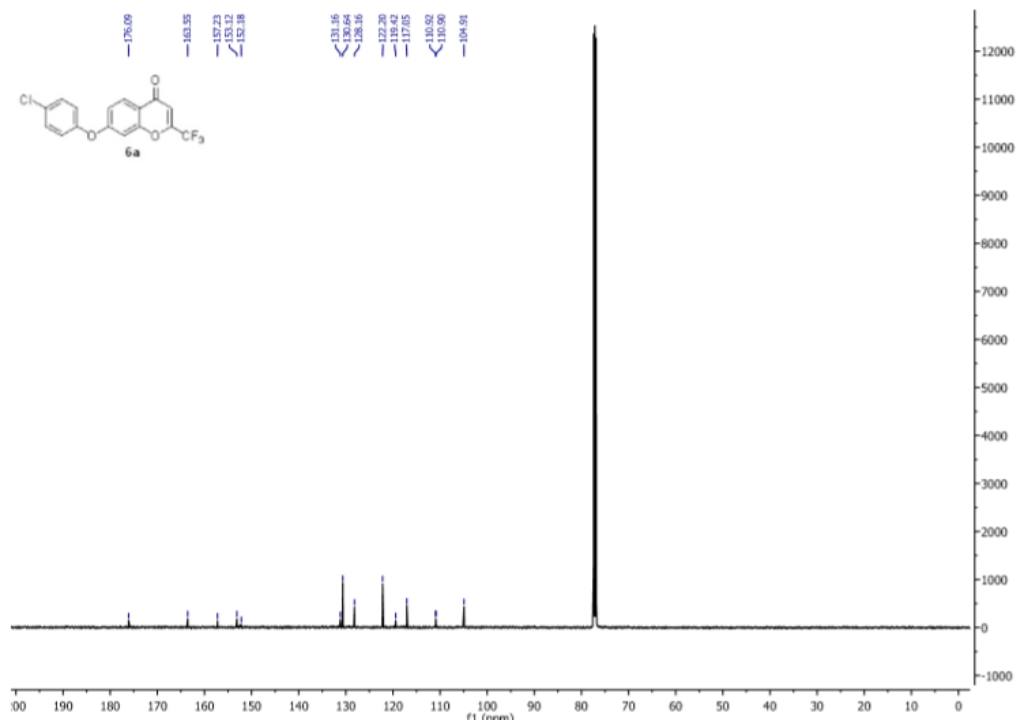
¹H NMR



¹³C NMR

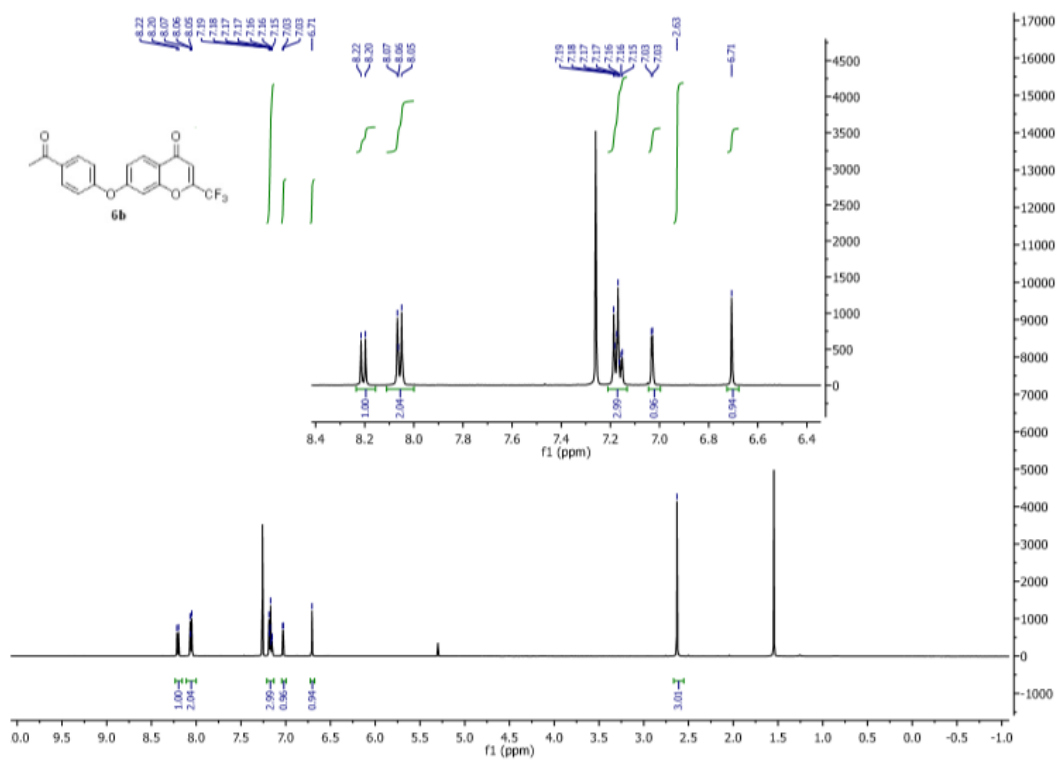


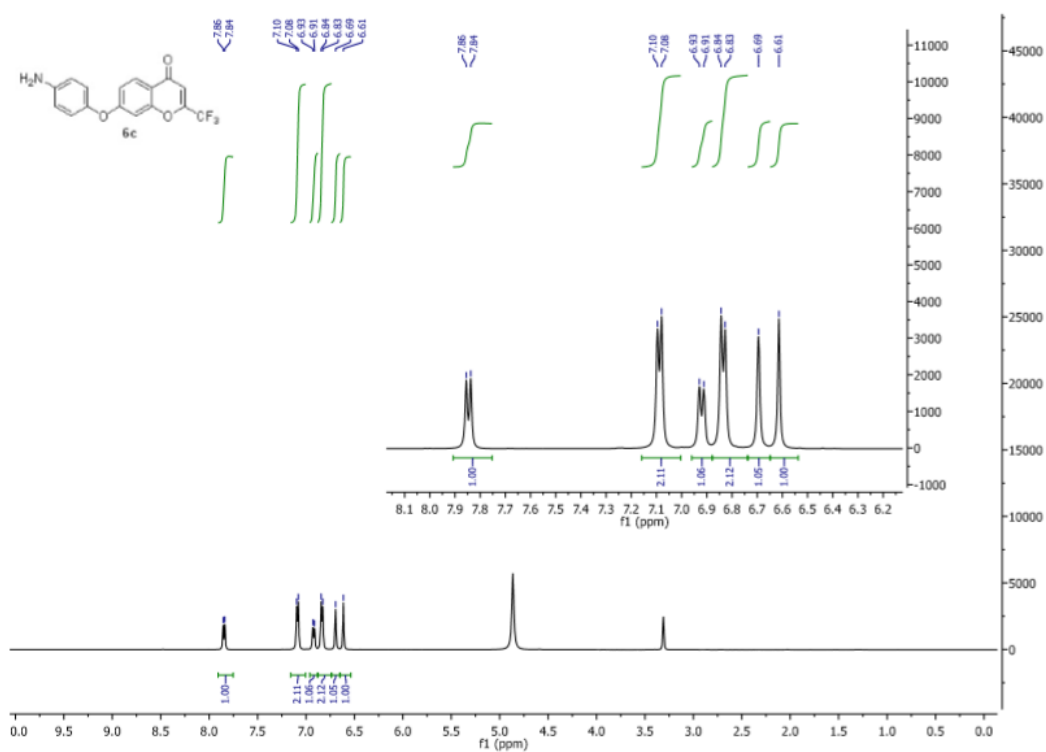
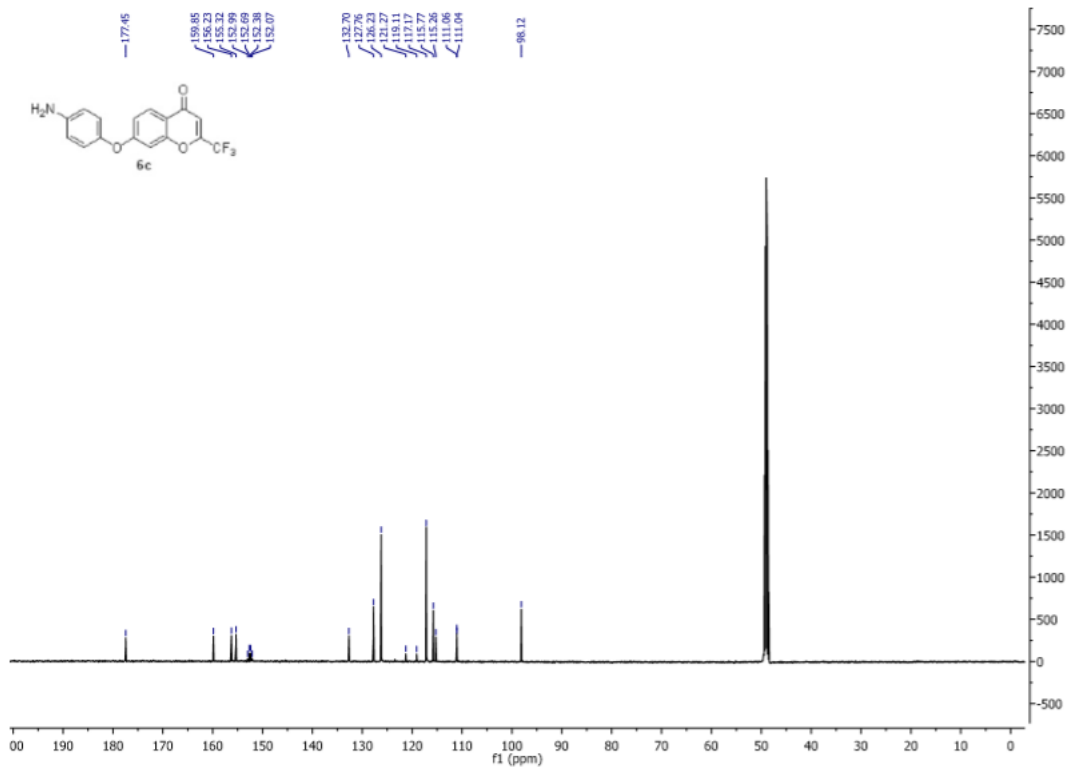
7-(2-(m-tolyl)hydrazinyl)-2-(trifluoromethyl)-4H-chromen-4-one (5k)**¹H NMR****¹³C NMR**

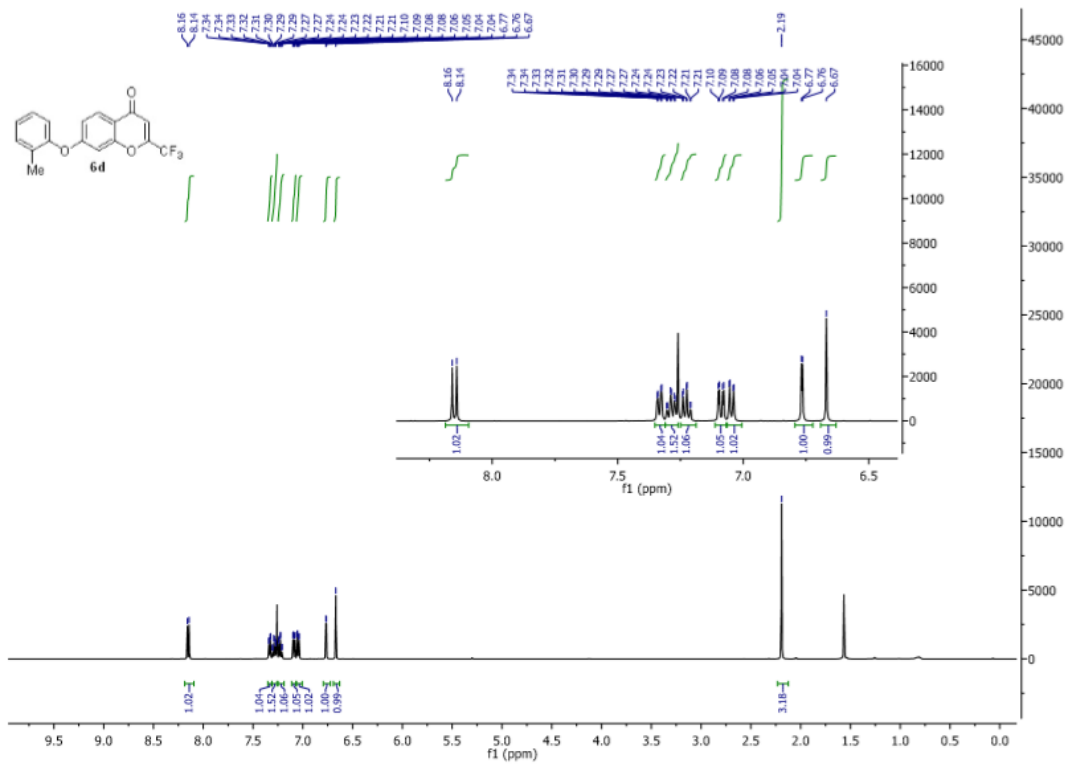
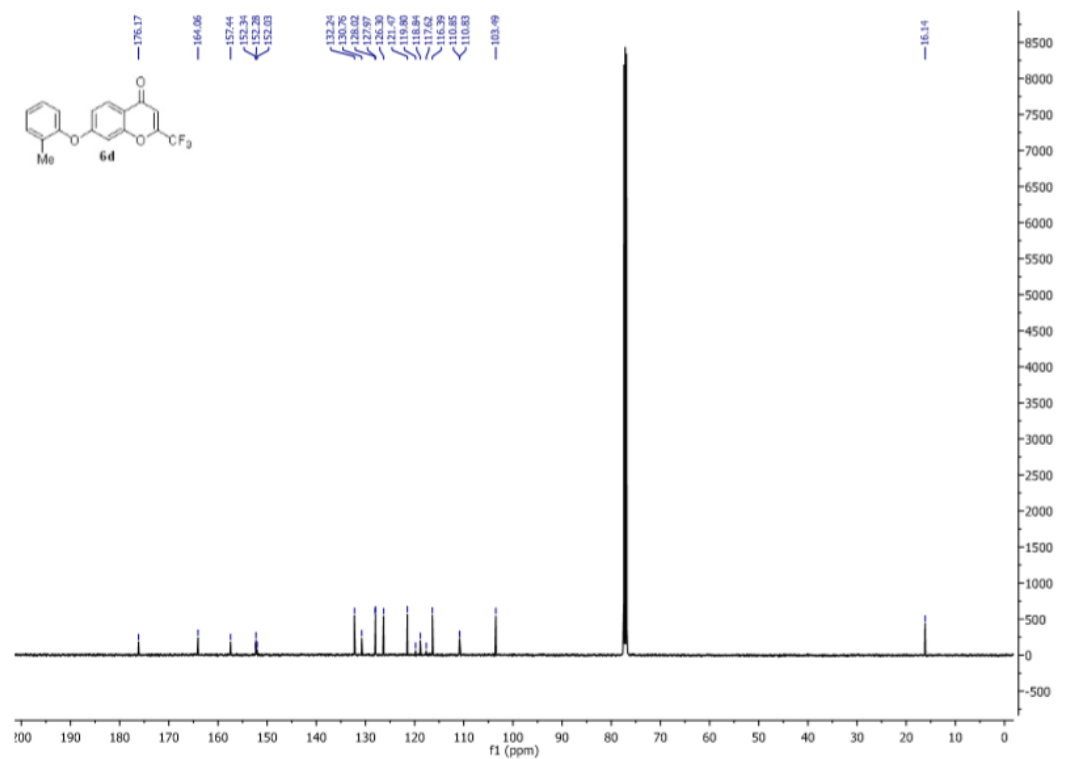
7-(4-chlorophenoxy)-2-(trifluoromethyl)-4H-chromen-4-one (6a)**¹H NMR****¹³C NMR**

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

¹H NMR

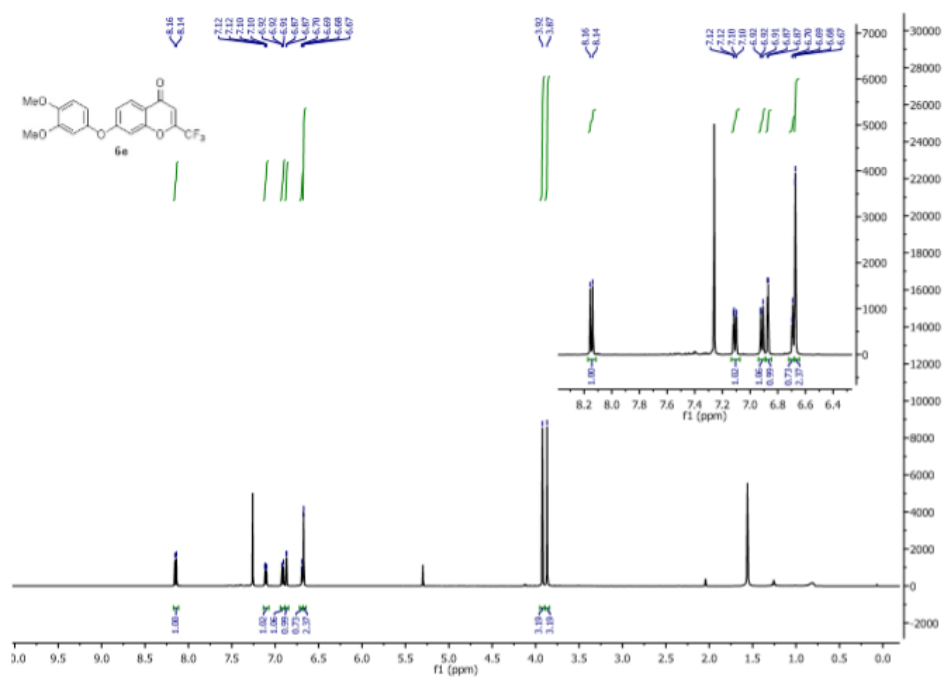


7-(4-aminophenoxy)-2-(trifluoromethyl)-4H-chromen-4-one (6c)**¹H NMR****¹³C NMR**

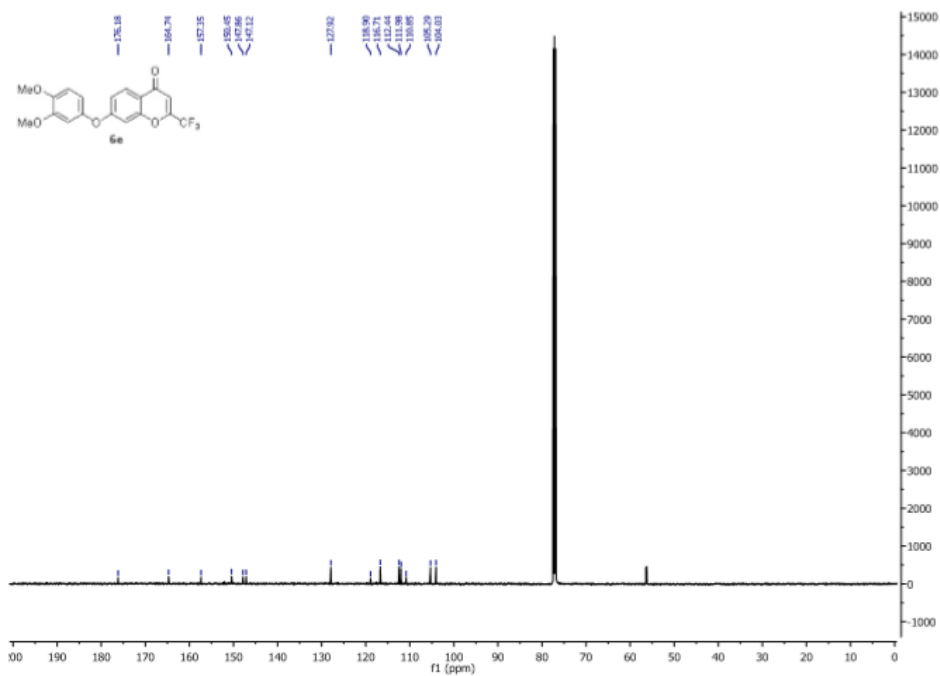
7-(*o*-tolyoxy)-2-(trifluoromethyl)-4*H*-chromen-4-one (6d)¹H NMR¹³C NMR

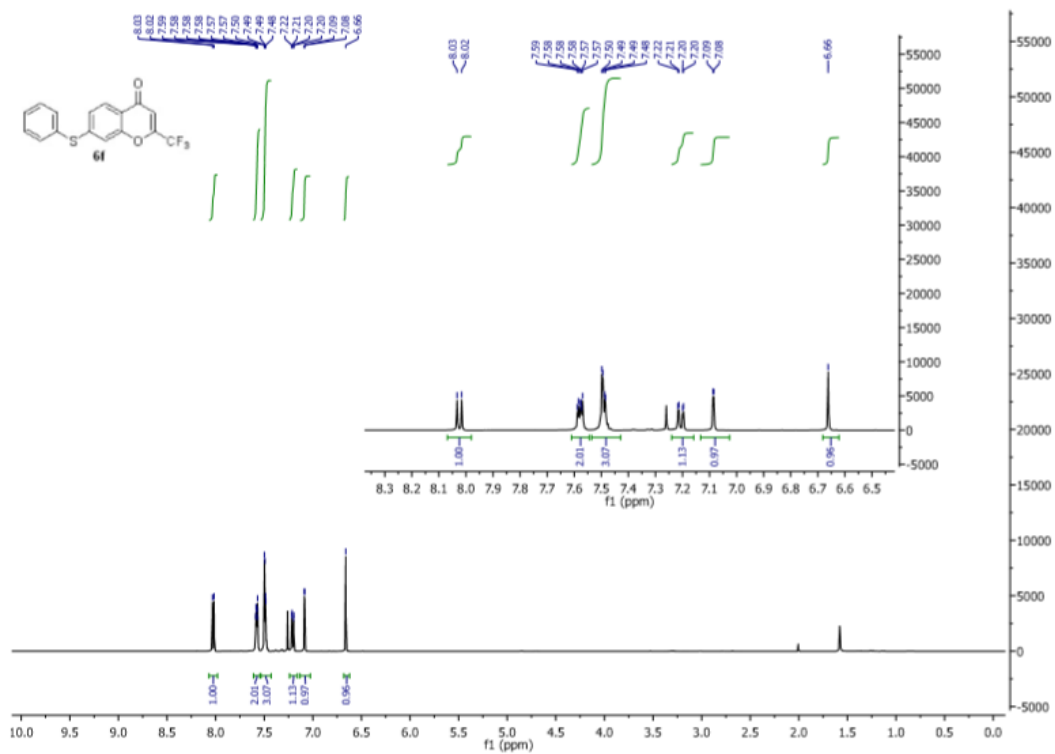
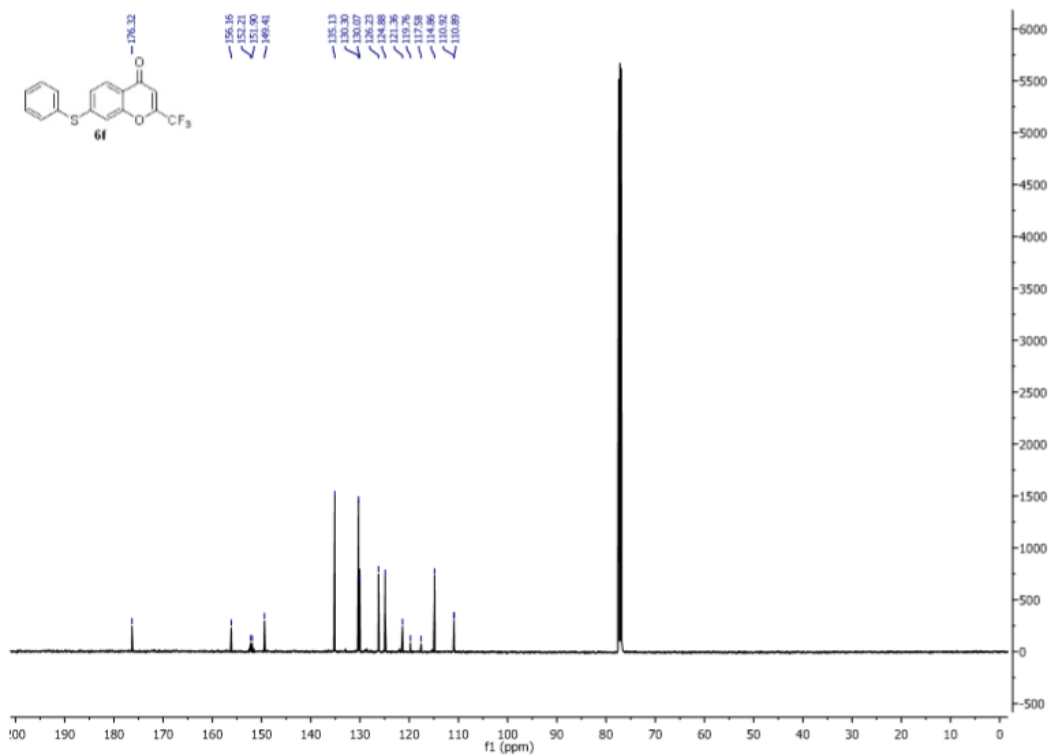
7-(3,4-dimethoxyphenoxy)-2-(trifluoromethyl)-4H-chromen-4-one (6e)

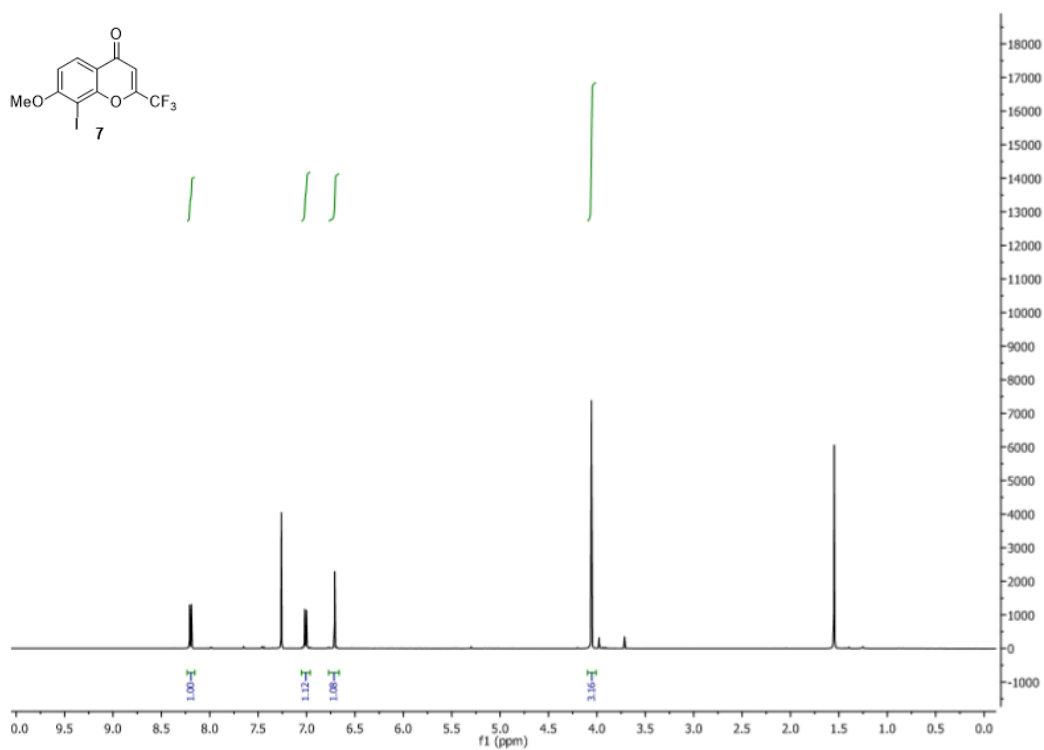
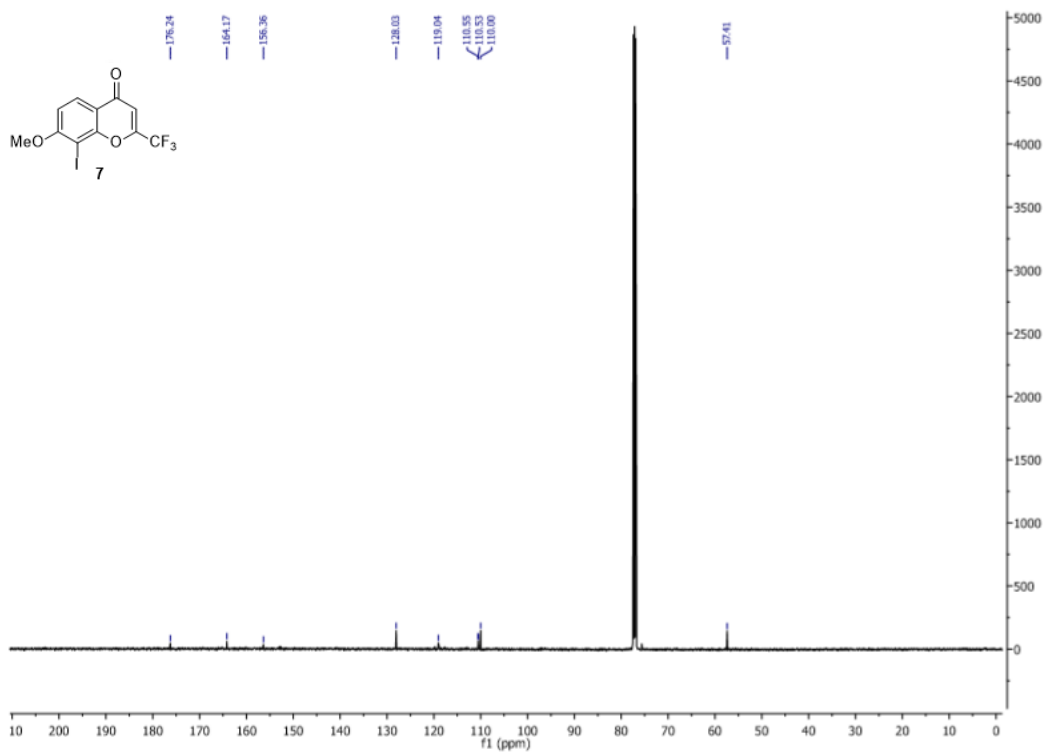
¹H NMR



¹³C NMR

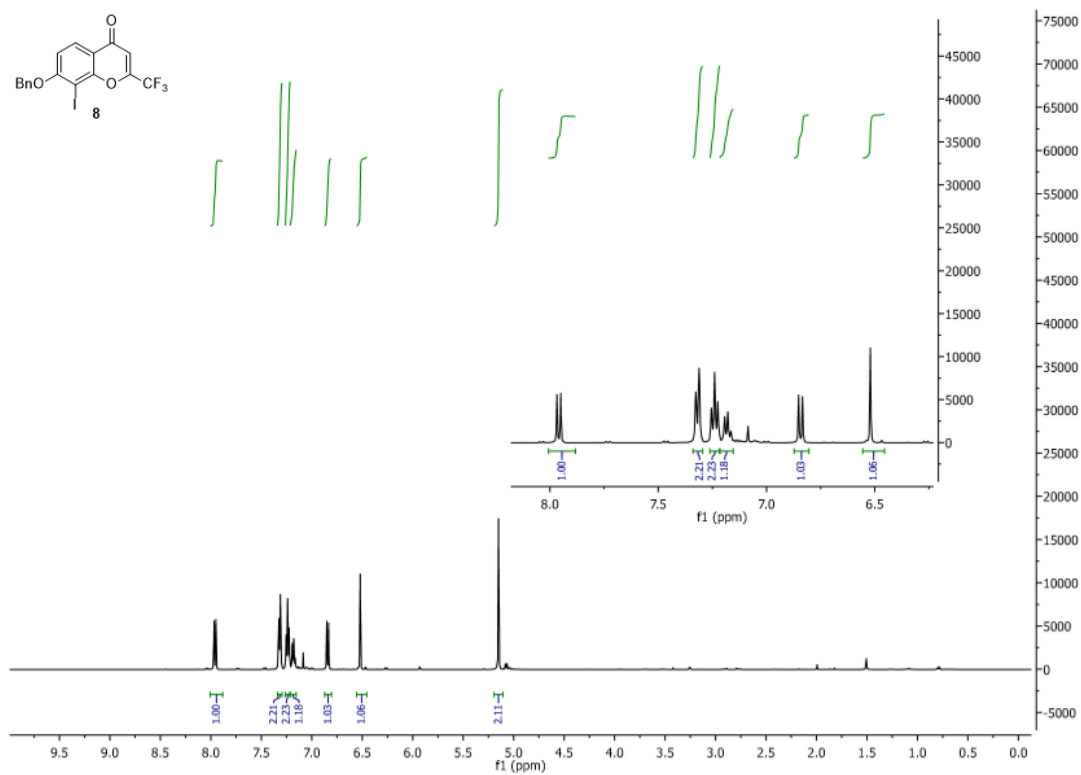


(7-(phenylthio)-2-(trifluoromethyl)-4H-chromen-4-ylidene)oxonium (6f)**¹H NMR****¹³C NMR**

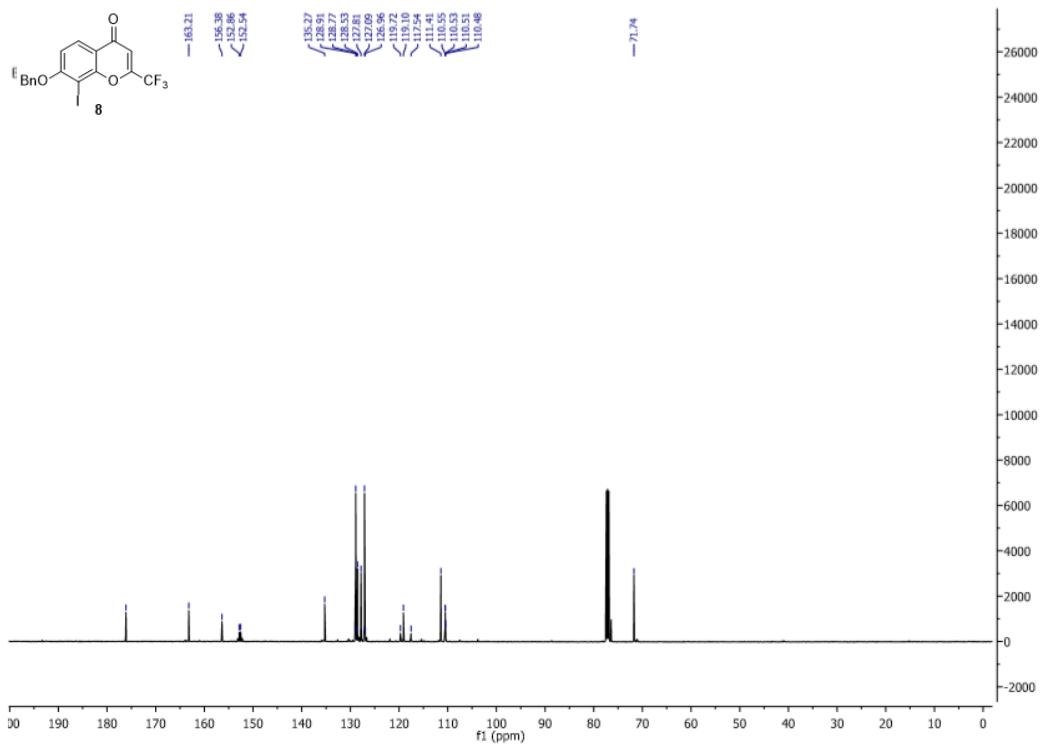
8-iodo-7-methoxy-2-(trifluoromethyl)-4H-chromen-4-one (7)**¹H NMR****¹³C NMR**

7-(benzyloxy)-8-iodo-2-(trifluoromethyl)-4H-chromen-4-one (8)

¹H NMR

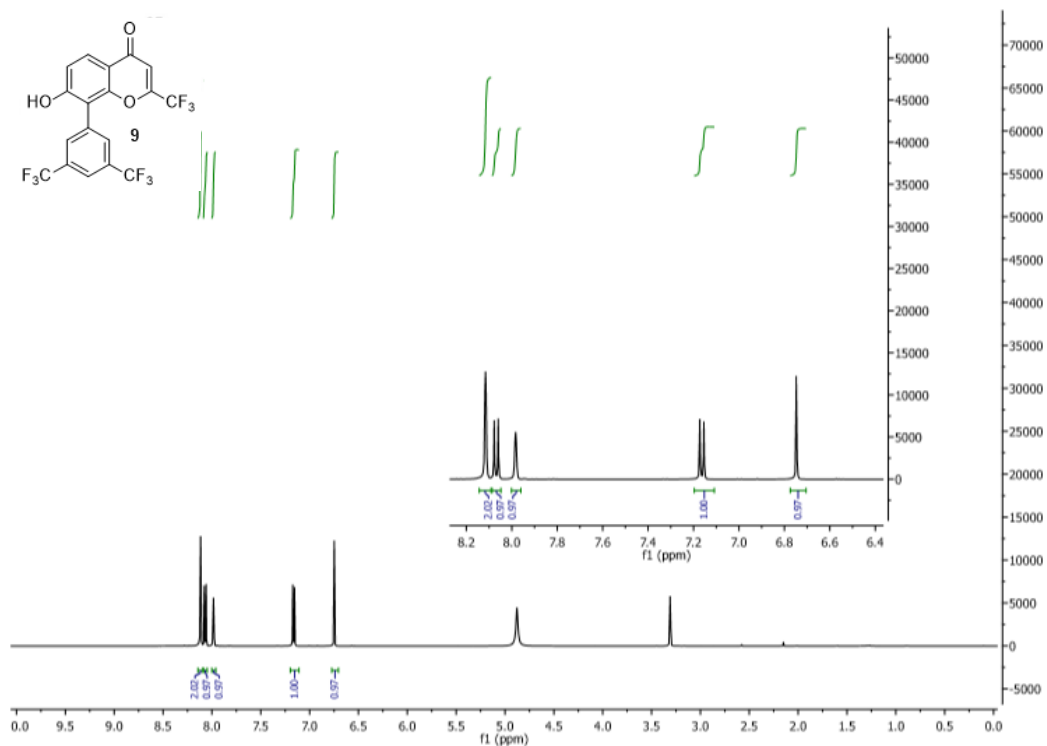


¹³C NMR

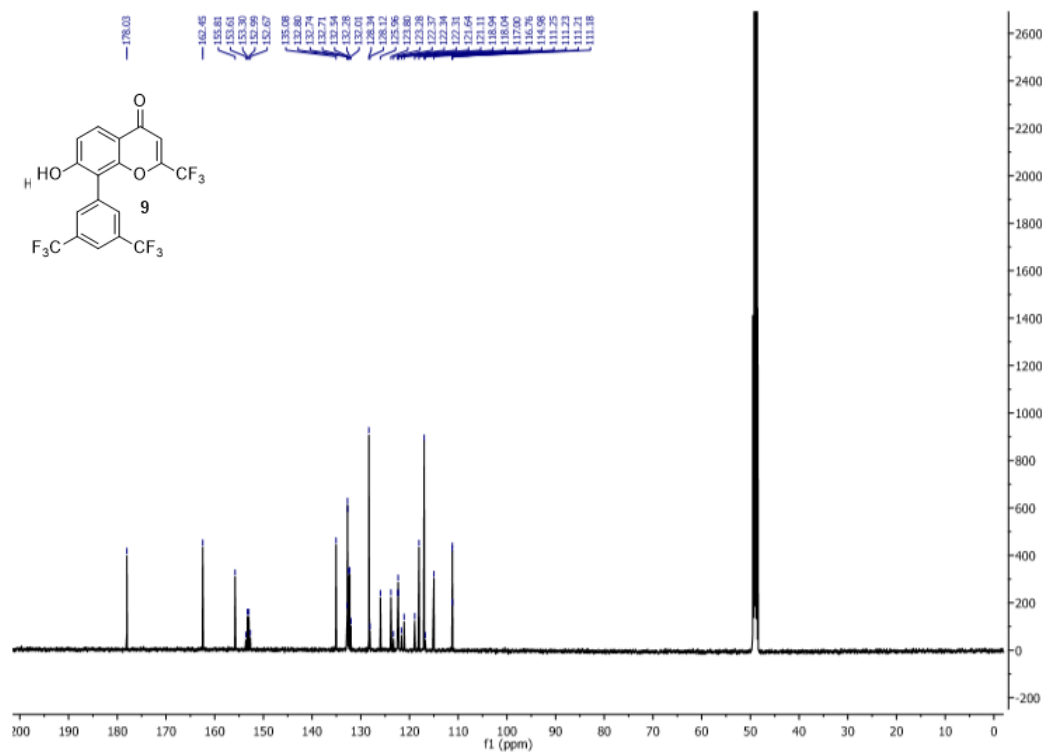


8-(3,5-bis(trifluoromethyl)phenyl)-7-hydroxy-2-(trifluoromethyl)-4H-chromen-4-one (9)

¹H NMR

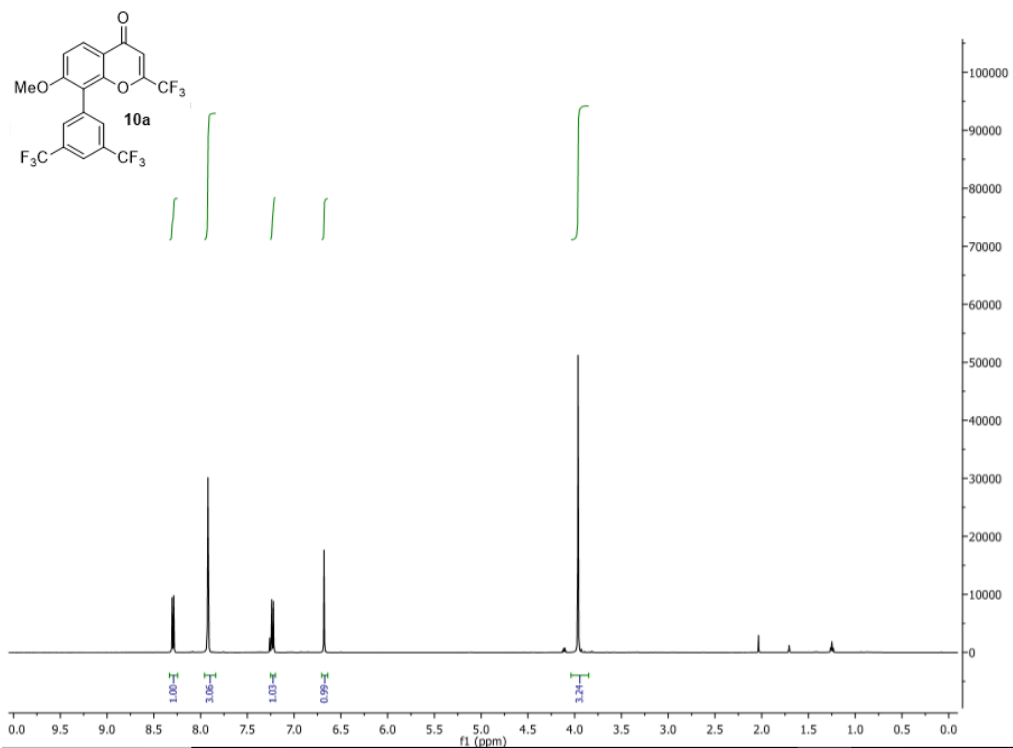


¹³C NMR

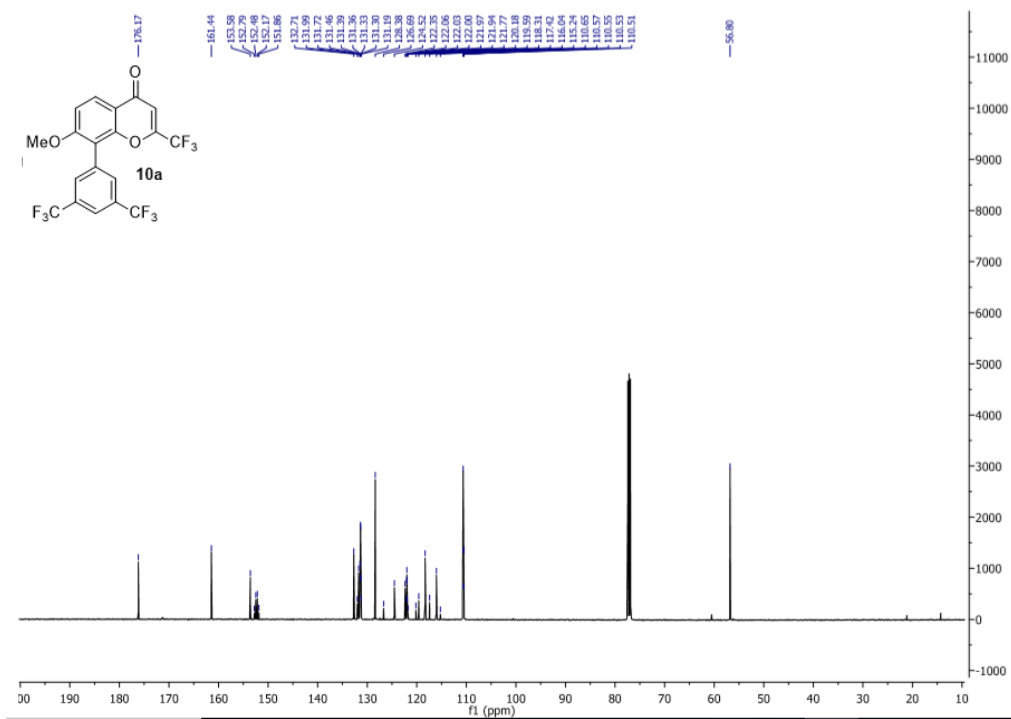


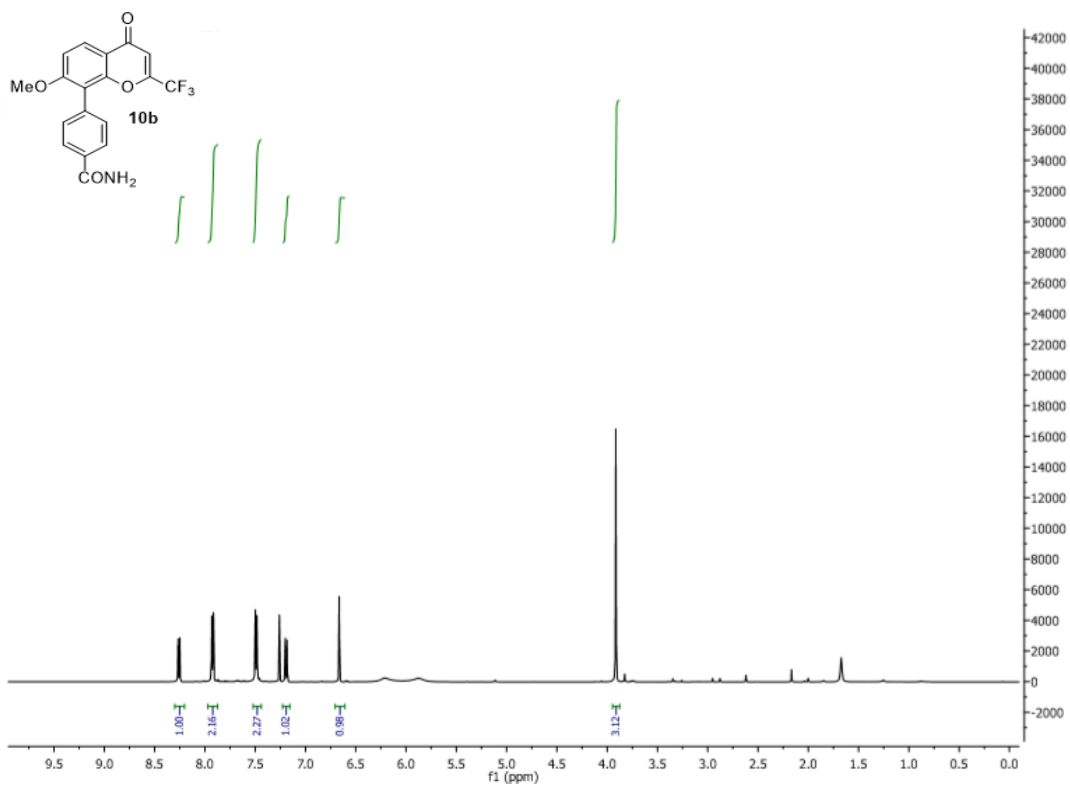
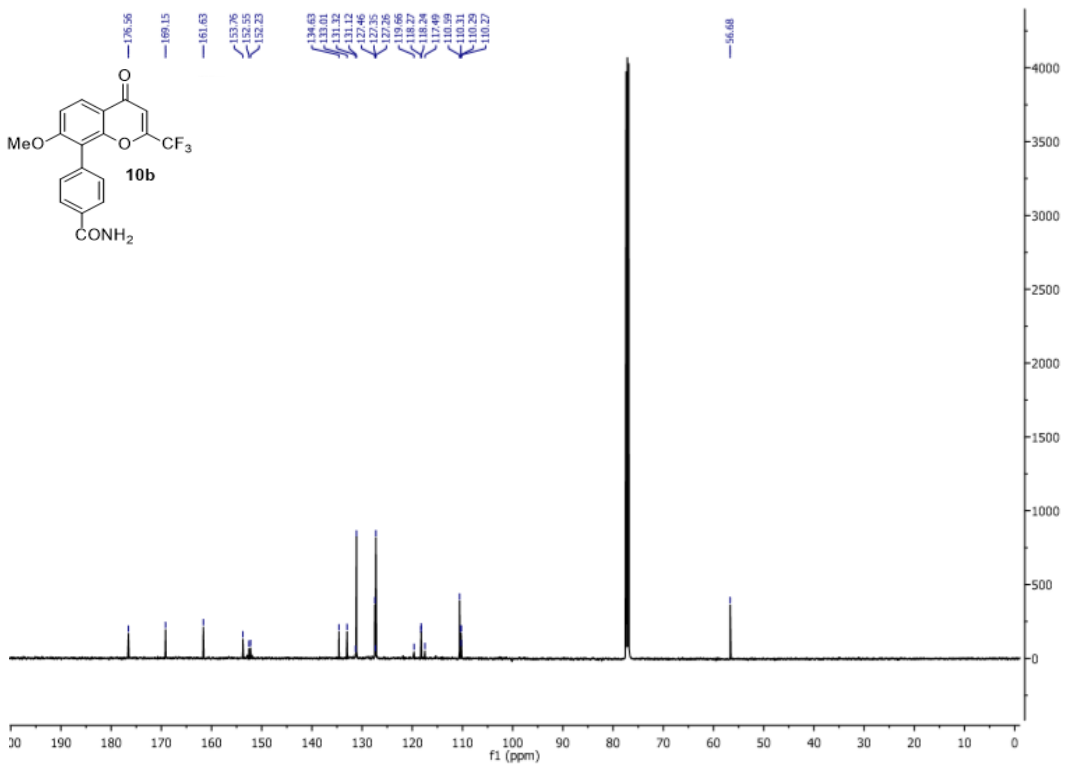
8-(3,5-bis(trifluoromethyl)phenyl)-7-methoxy-2-(trifluoromethyl)-4H-chromen-4-one (10a)

¹H NMR



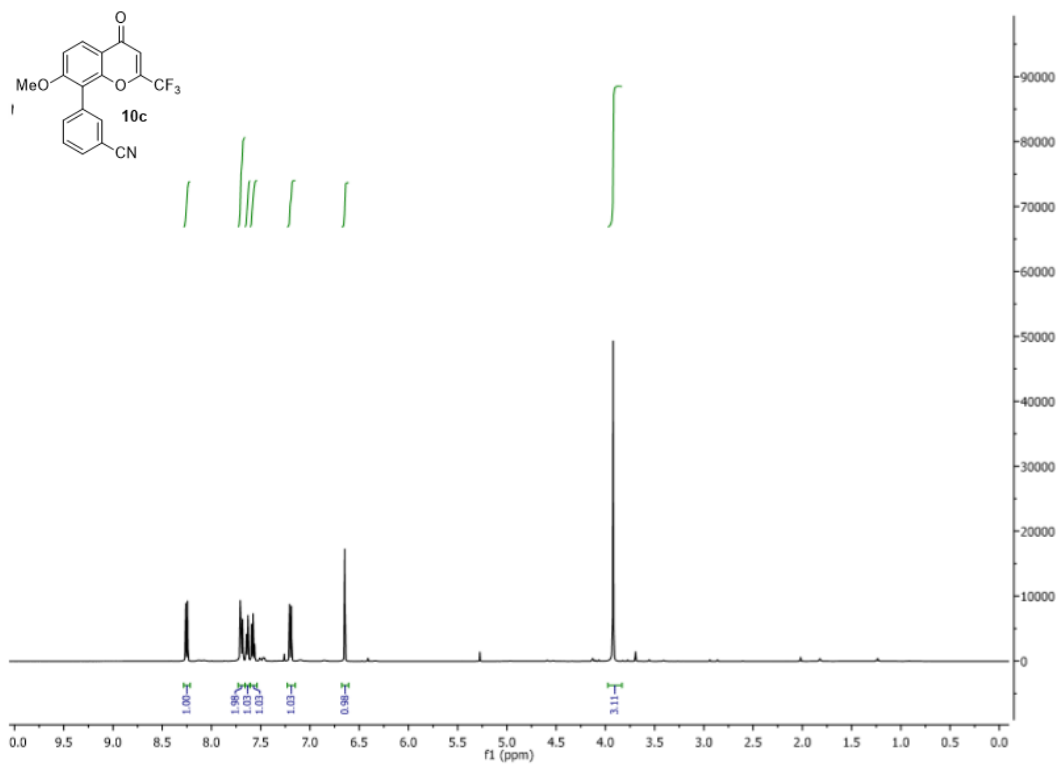
¹³C NMR



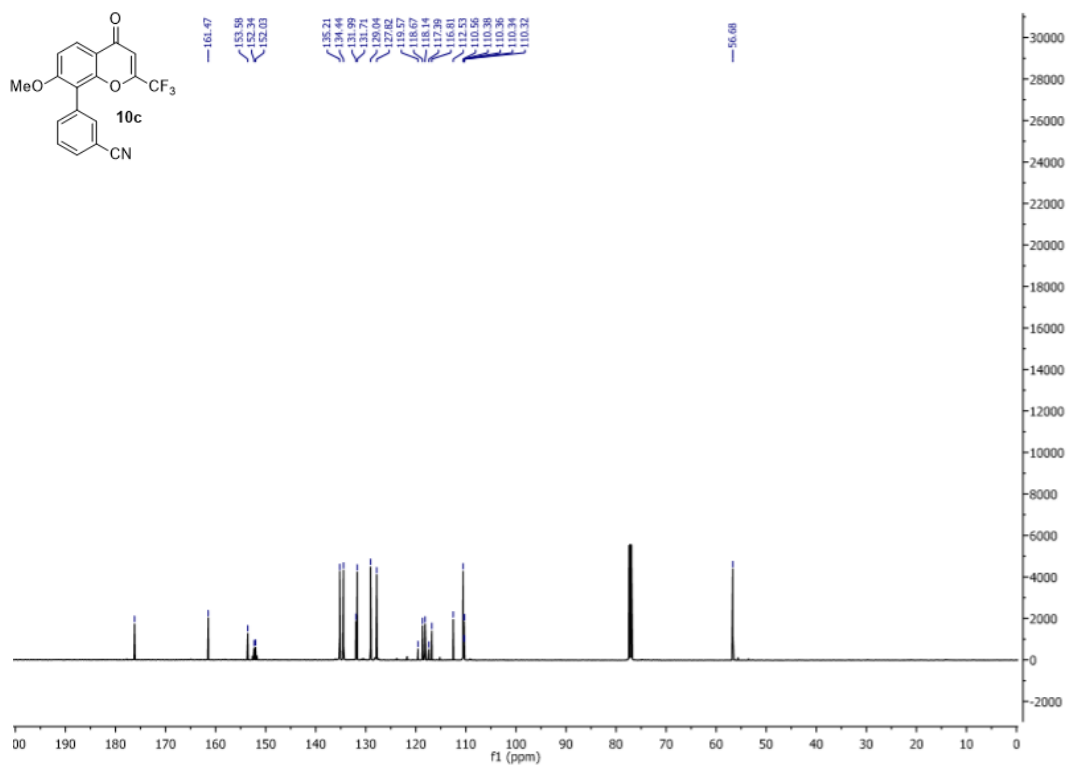
4-(7-methoxy-4-oxo-2-(trifluoromethyl)-4H-chromen-8-yl)benzamide (10b)**¹H NMR****¹³C NMR**

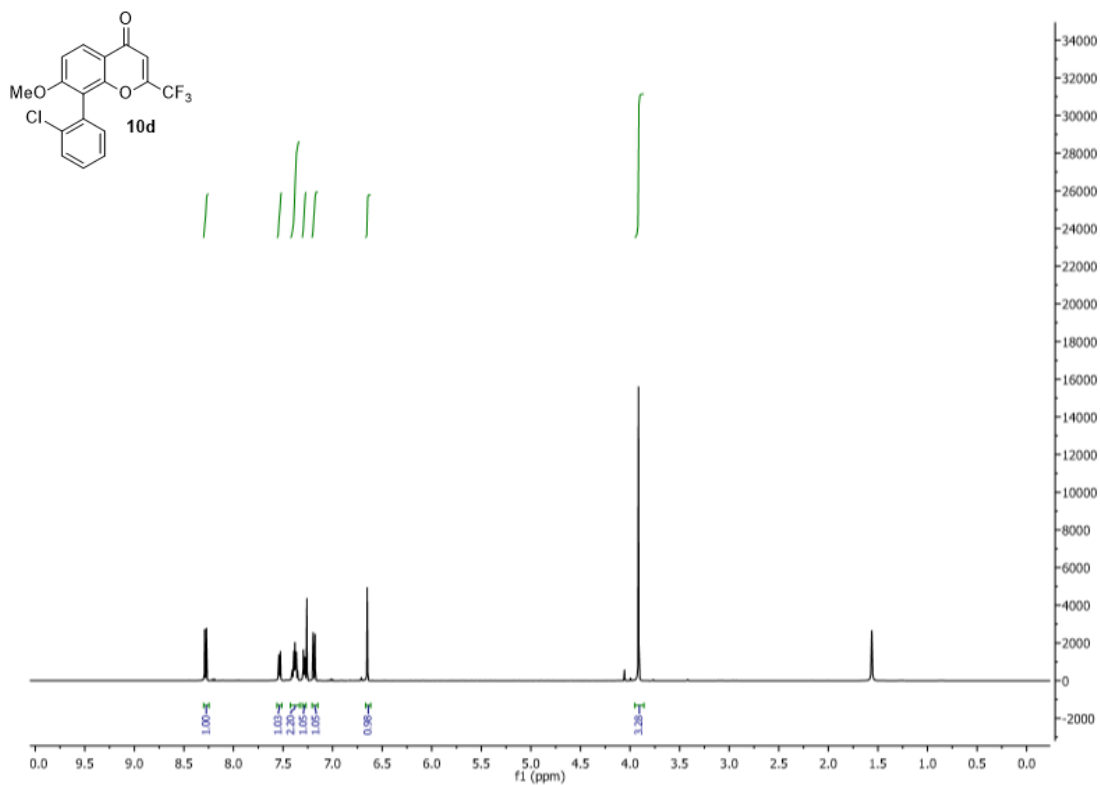
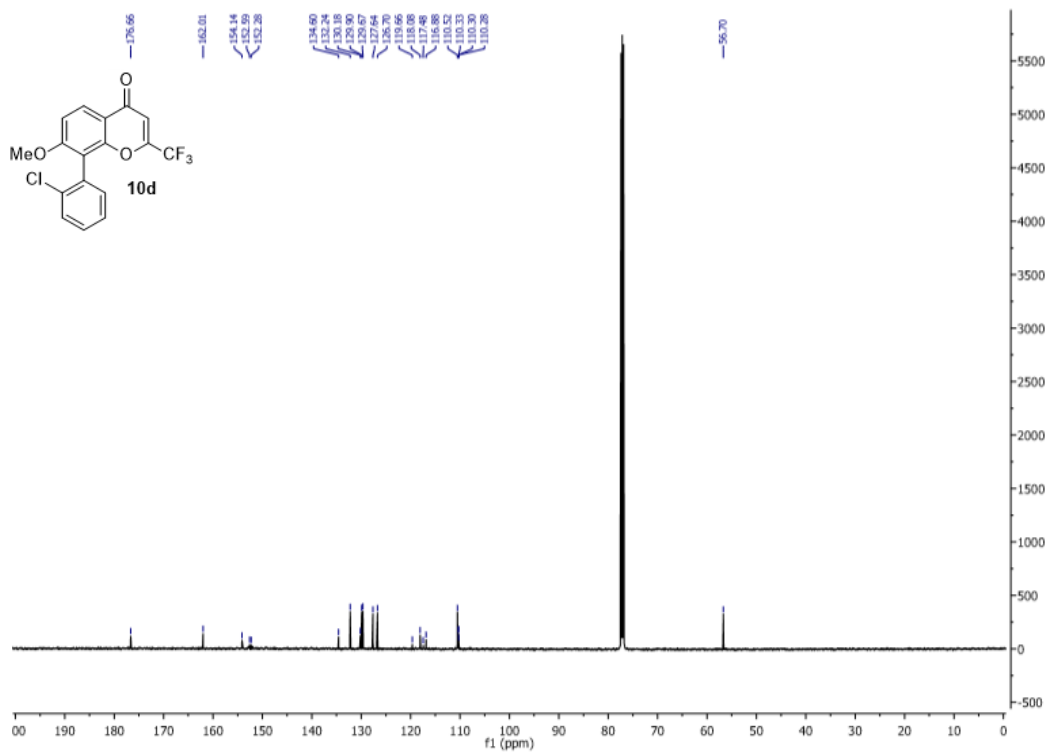
3-(7-methoxy-4-oxo-2-(trifluoromethyl)-4H-chromen-8-yl)benzonitrile (10c)

¹H NMR



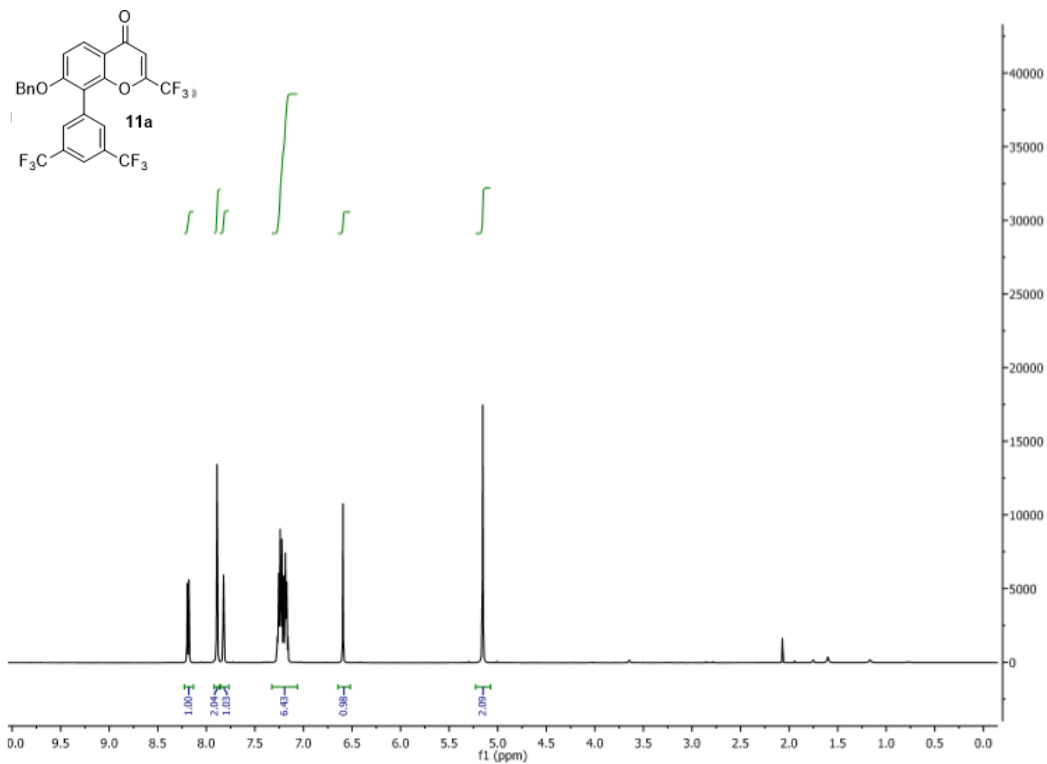
¹³C NMR



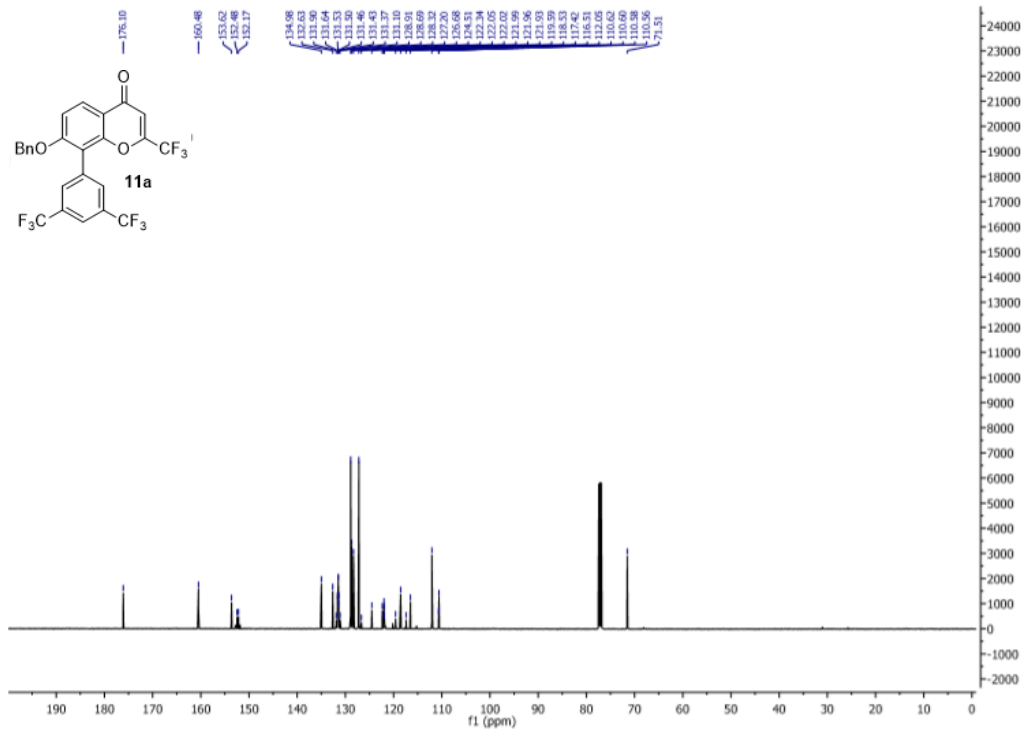
8-(2-chlorophenyl)-7-methoxy-2-(trifluoromethyl)-4H-chromen-4-one (10d)**¹H NMR****¹³C NMR**

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

¹H NMR

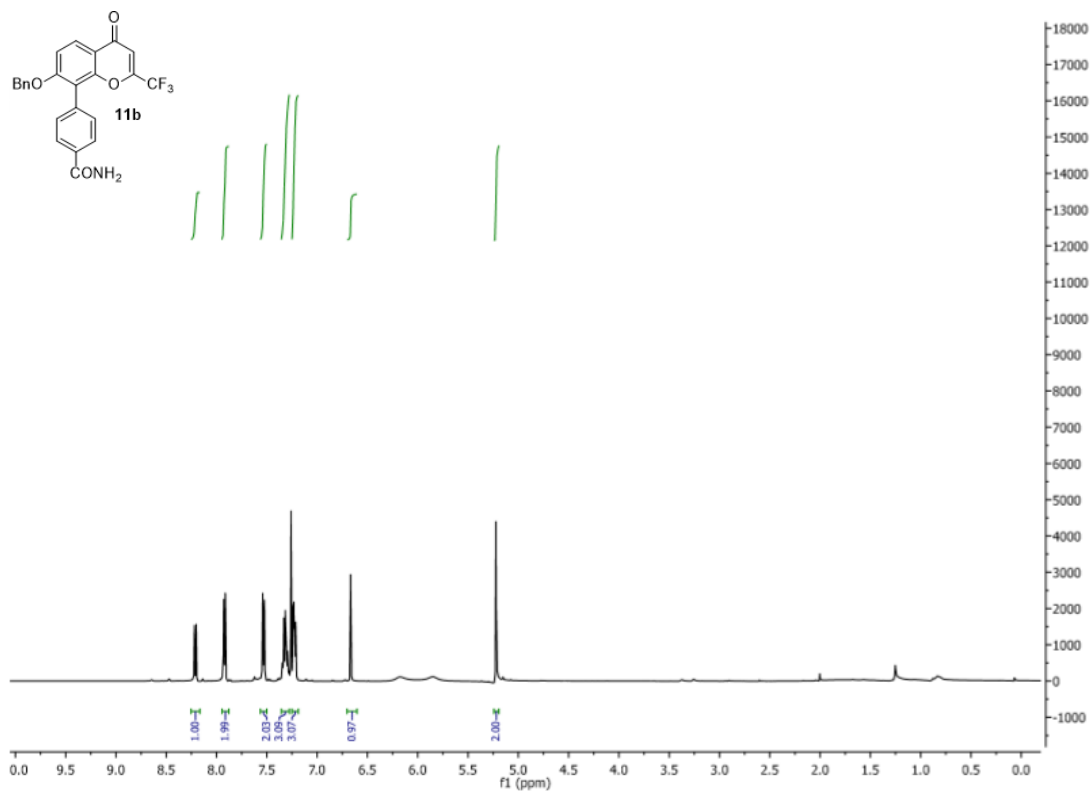


¹³C NMR

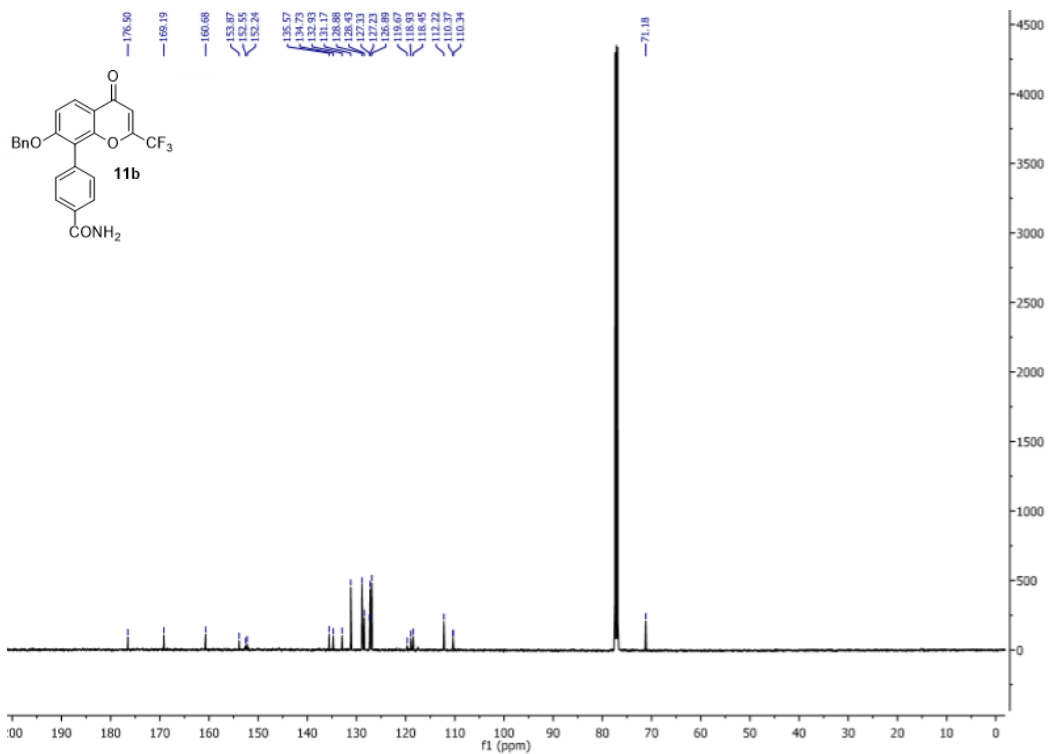


4-(7-(benzyloxy)-4-oxo-2-(trifluoromethyl)-4H-chromen-8-yl)benzamide (11b)

¹H NMR

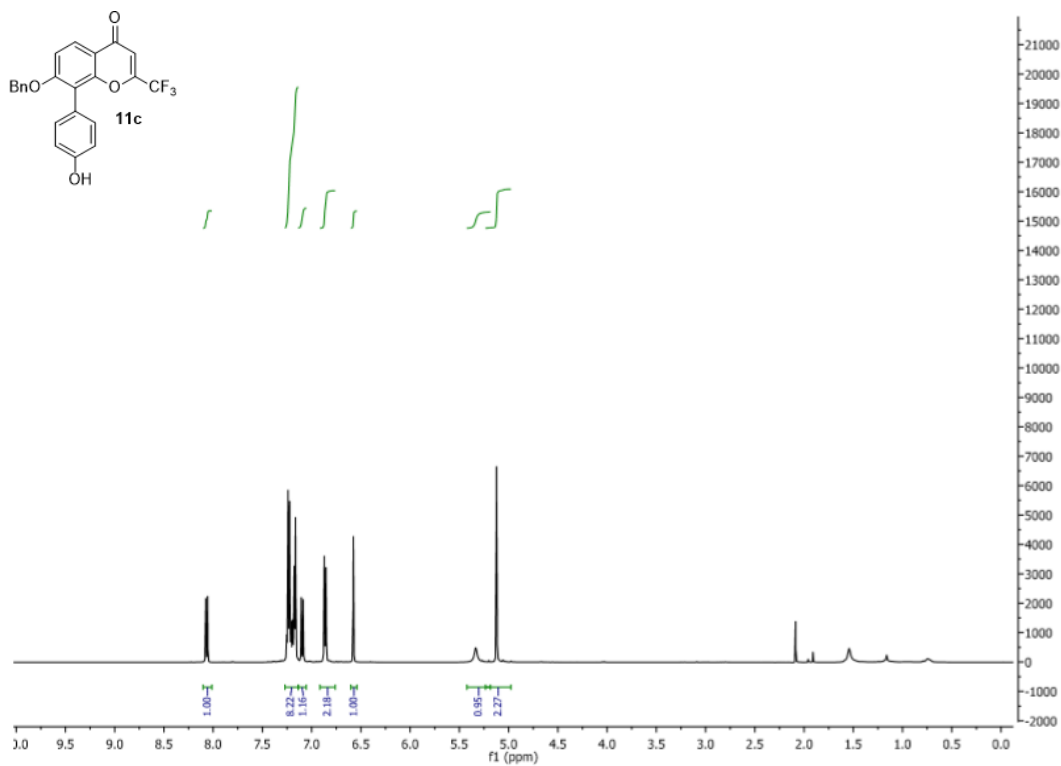


¹³C NMR

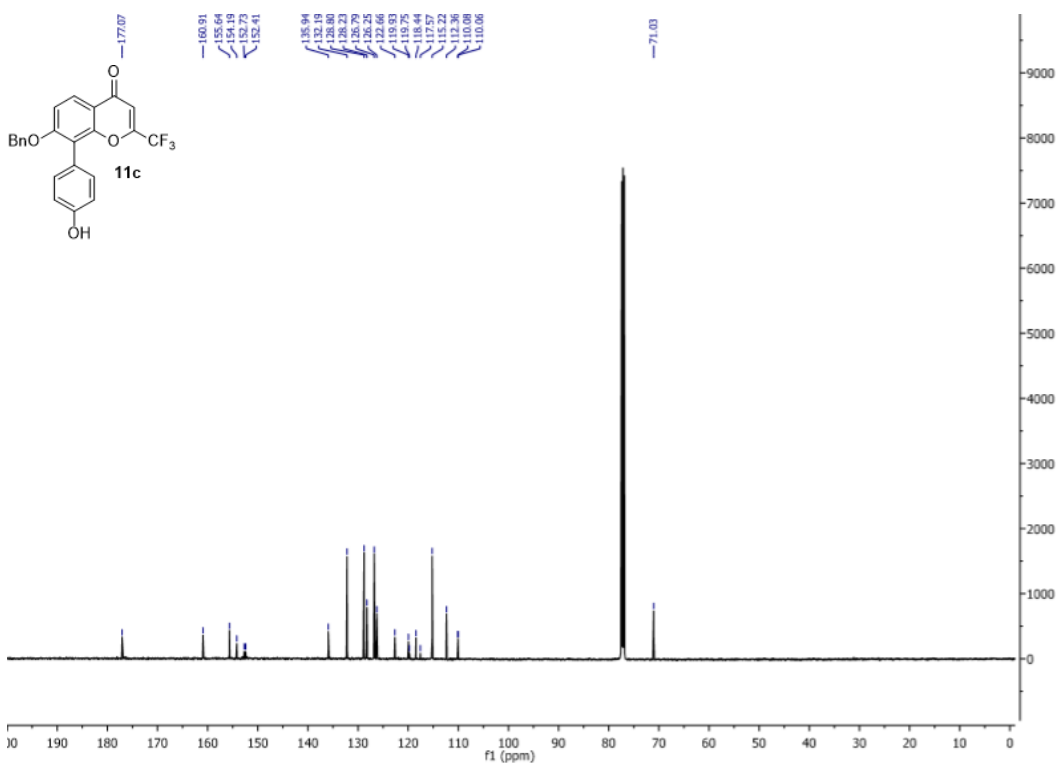


7-(benzyloxy)-8-(4-hydroxyphenyl)-2-(trifluoromethyl)-4H-chromen-4-one (11c)

¹H NMR

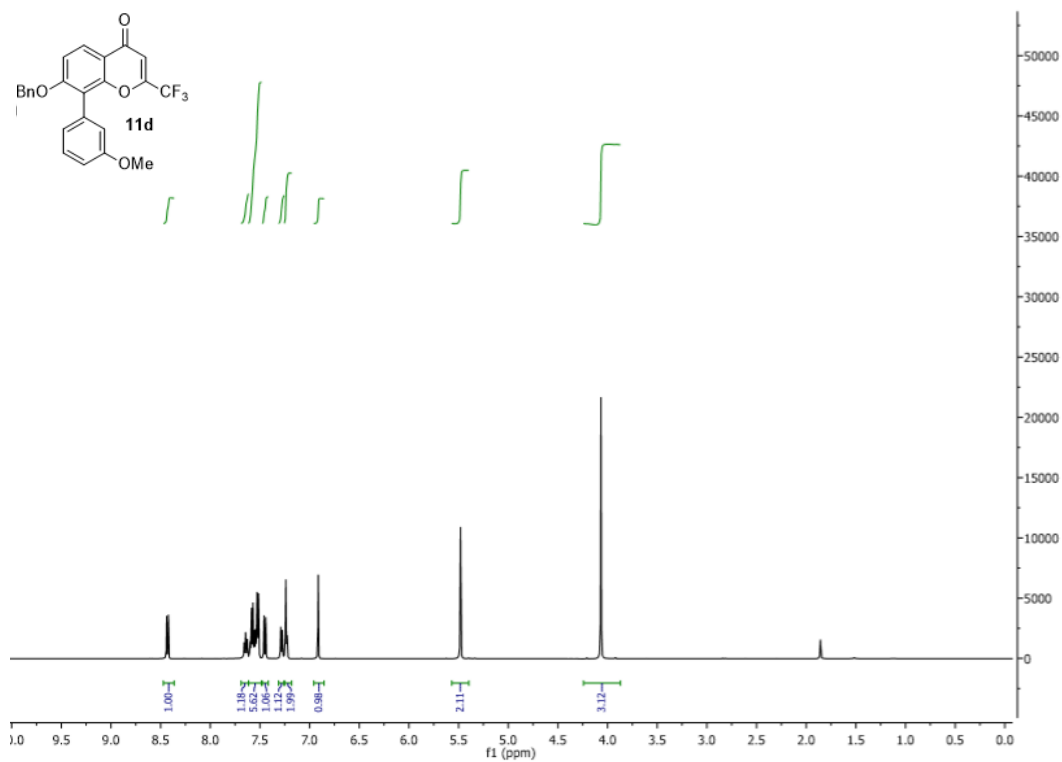


¹³C NMR

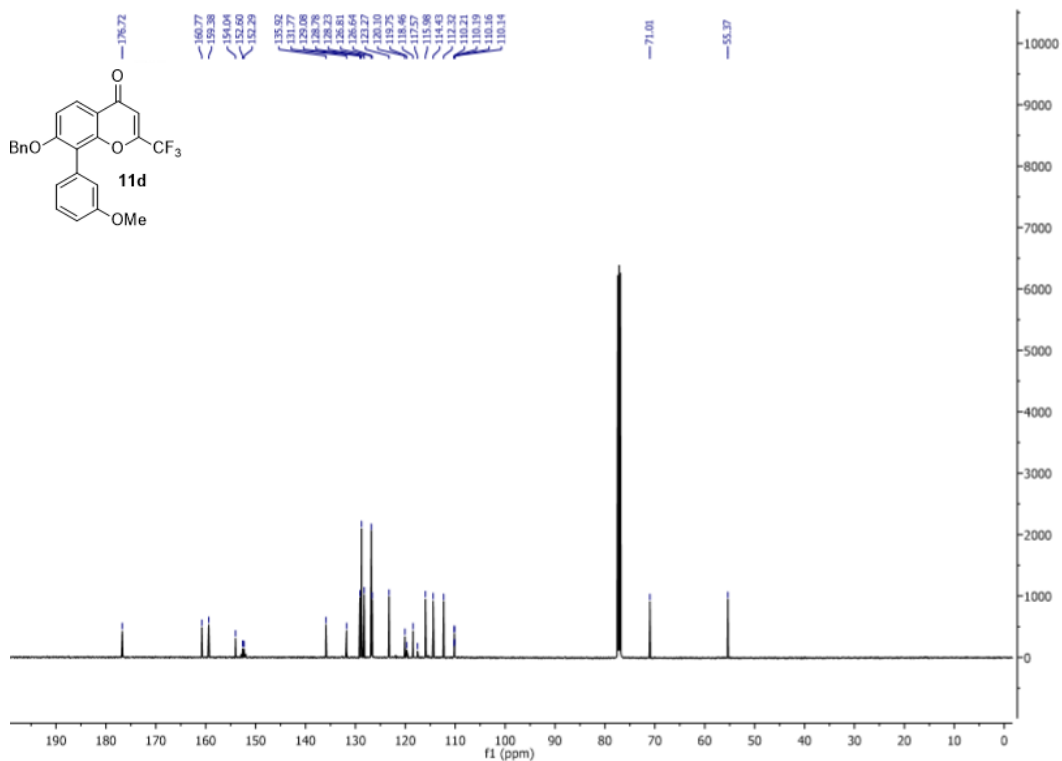


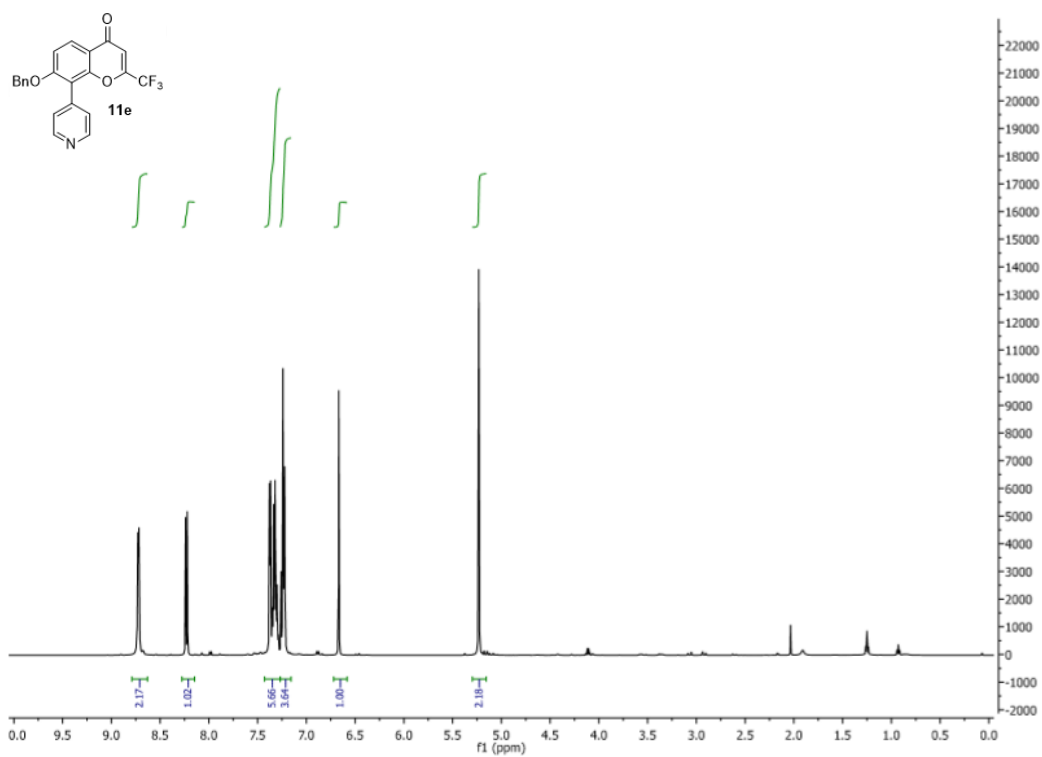
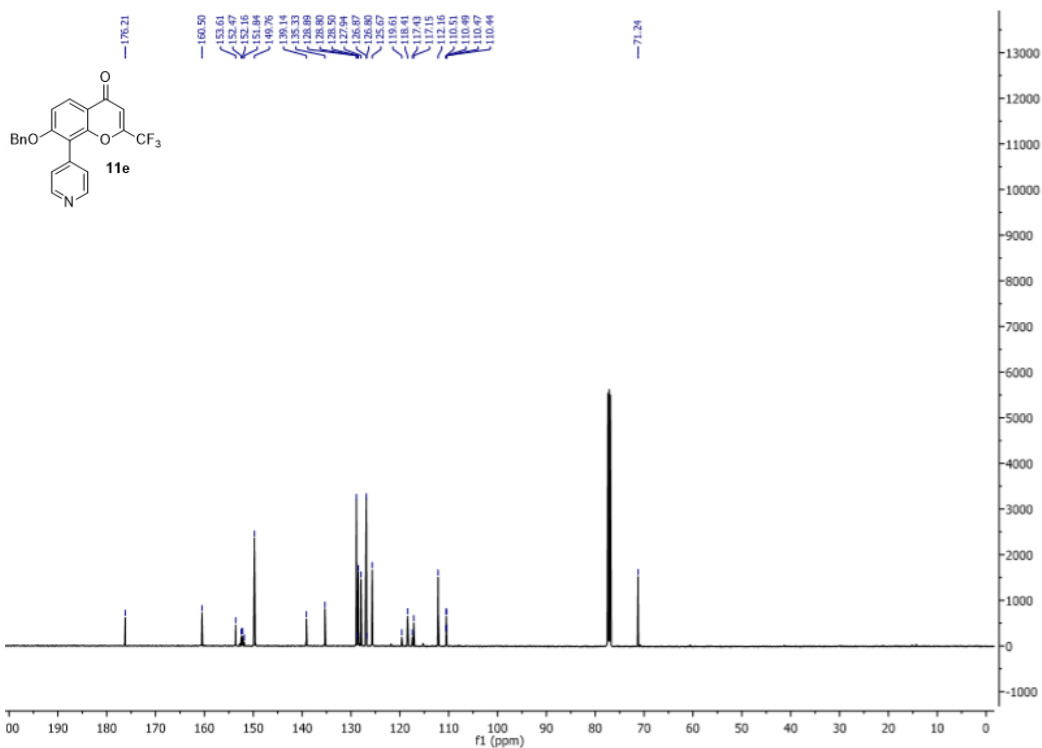
7-(benzyloxy)-8-(3-methoxyphenyl)-2-(trifluoromethyl)-4H-chromen-4-one (11d)

¹H NMR



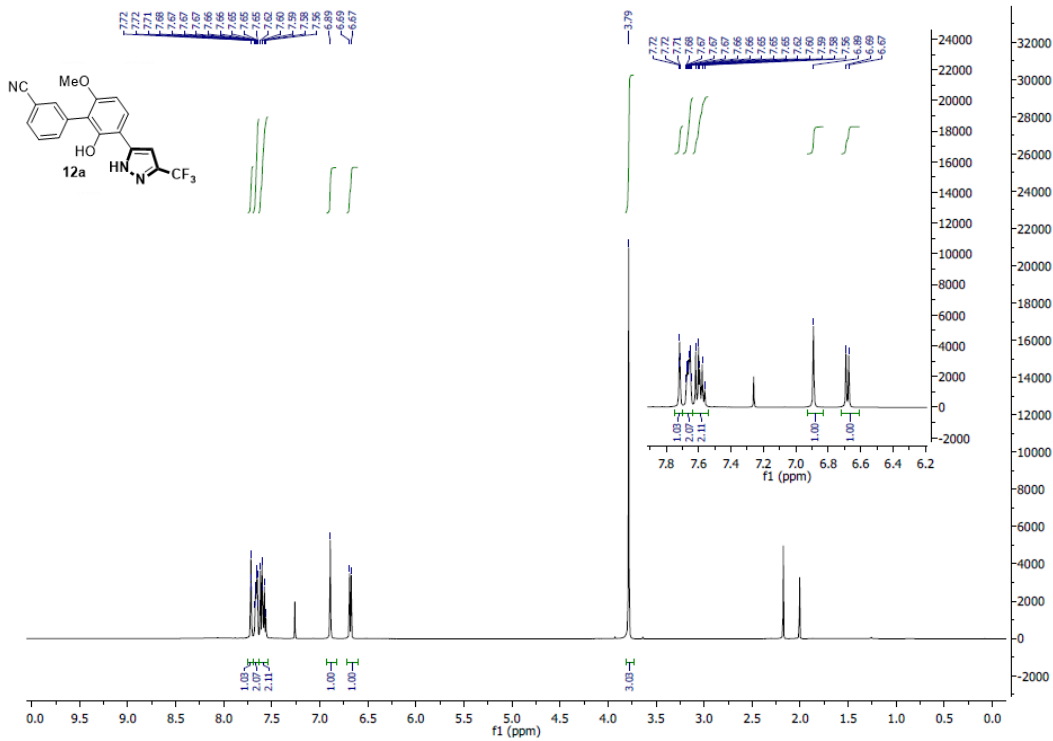
¹³C NMR



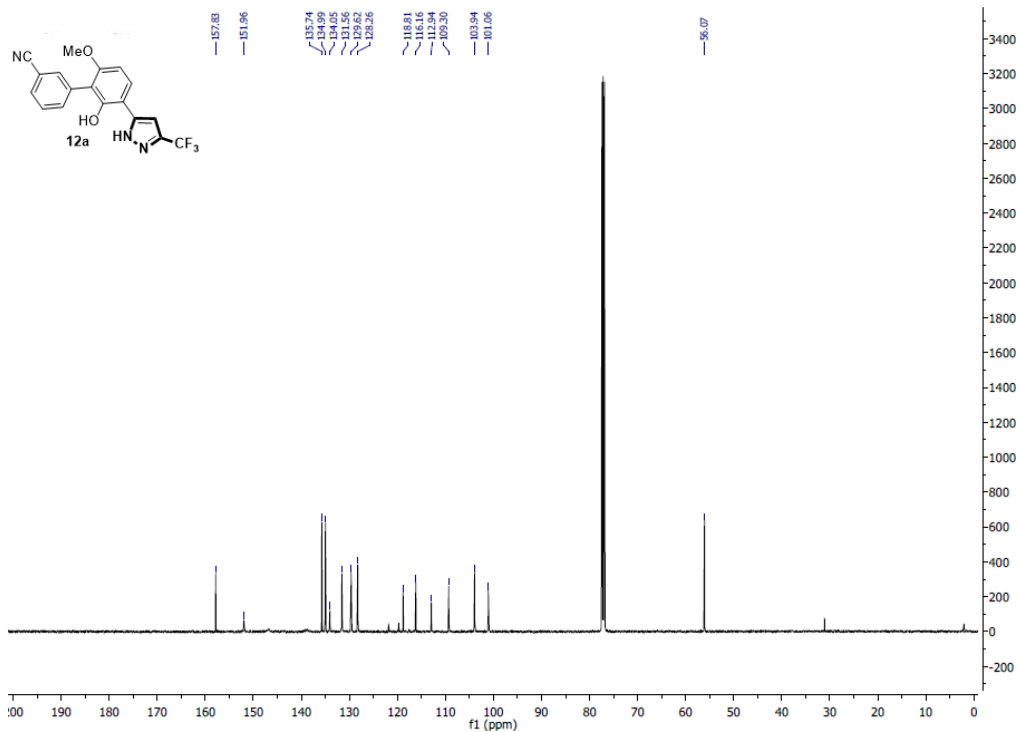
7-(benzyloxy)-8-(pyridin-4-yl)-2-(trifluoromethyl)-4H-chromen-4-one (11e)**¹H NMR****¹³C NMR**

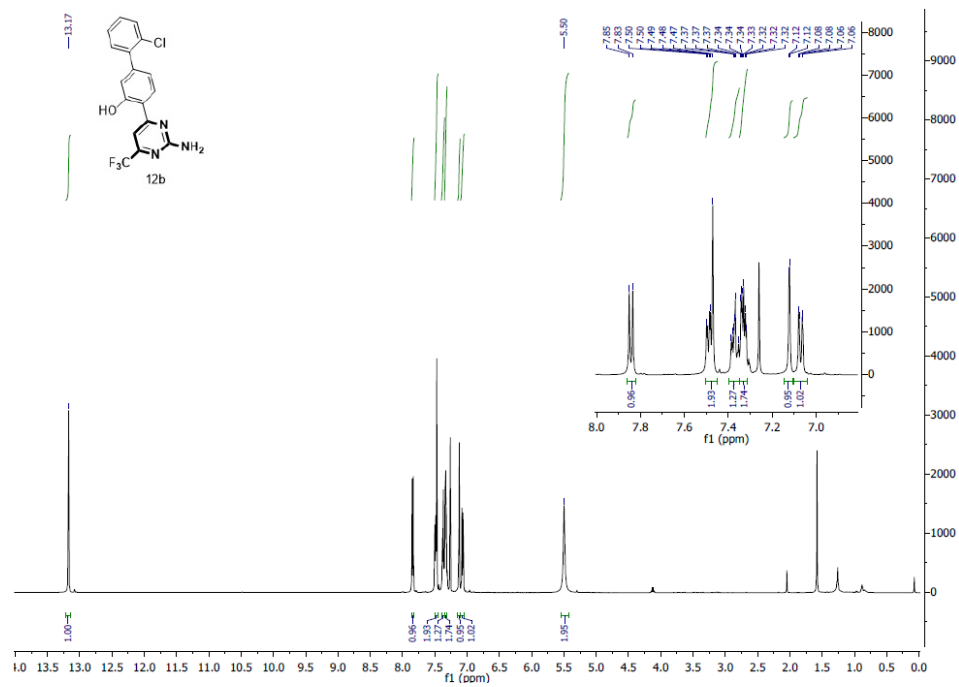
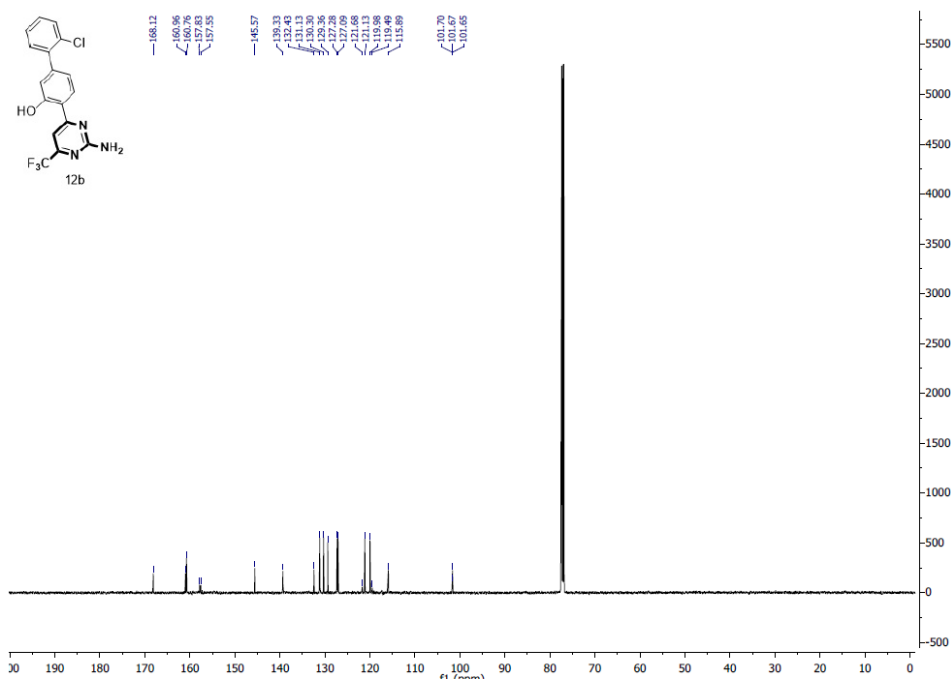
2'-hydroxy-6'-methoxy-3'-(3-(trifluoromethyl)-1H-pyrazol-5-yl)-[1,1'-biphenyl]-3-carbonitrile (12a)

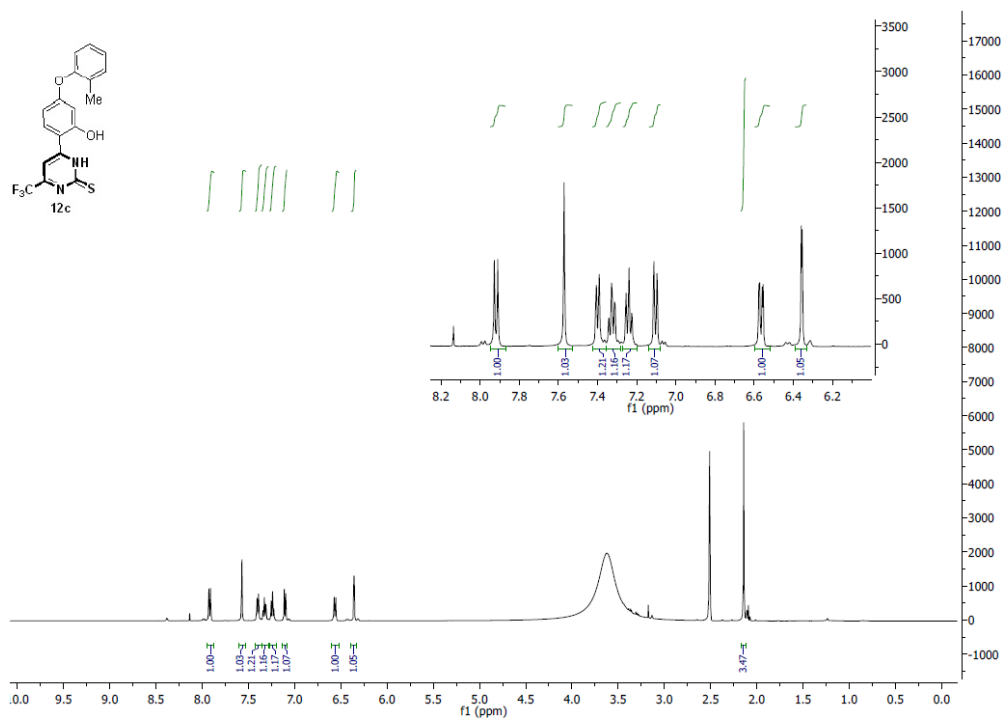
¹H NMR



¹³C NMR



4-(2-amino-6-(trifluoromethyl)pyrimidin-4-yl)-2'-chloro-[1,1'-biphenyl]-3-ol (12b)**¹H NMR****¹³C NMR**

6-(2-hydroxy-4-(*o*-tolxyloxy)phenyl)-4-(trifluoromethyl)pyrimidine-2(1H)-thione (12c)**¹H NMR****¹³C NMR**