Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Synthesis of Difluorinated 3-Oxo-*N*,3-Diarylpropanamides from 4-Arylamino Coumarins Mediated by Selectfluor

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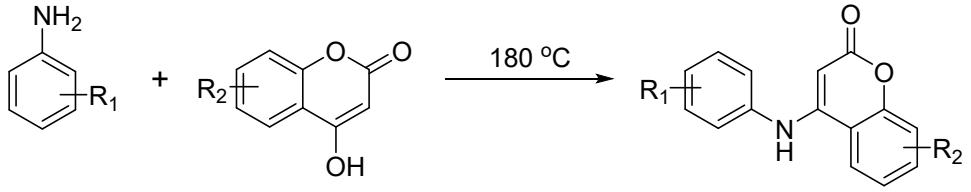
2. General Information

All reactions were carried out under an atmosphere of air except noted. The solvents were distilled prior to use under a nitrogen atmosphere. Silica gel (200–300 mesh) was used for flash chromatography. The 4-arylamino coumarins were prepared according to the literature procedures, and other reagents were purchased from commercial sources and used directly. High-resolution mass spectra (HRMS) were recorded by using an Electrothemal LTQ-Orbitrap mass spectrometer. Melting points were measured by using a Gongyi X-5 microscopy digital melting point apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded with a Bruker Avance III 400 MHz NMR spectrometer with $CDCl_3$ as solvent. The chemical shifts are reported in ppm relative to $CDCl_3$ (δ = 7.26) and DMSO-*d* (δ 2.5) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0) and DMSO-*d* (δ 40.0) for ^{13}C NMR. Coupling constants (*J*) are quoted in Hz. NMR data of known compounds is in agreement with literature values.[1-5] Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), and multiplet (m).

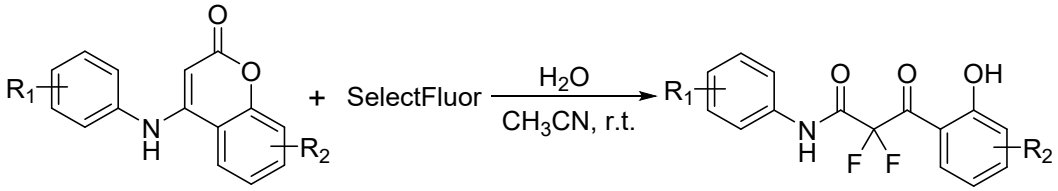
3. Experimental Procedures

3.1 General procedure for the synthesis of 4-arylamino coumarins [1-5]



A mixture of 4-hydroxy-2*H*-chromen-2-ones (1.0 mmol) and anilines (3.0 mmol, 3.0 equiv) (without solvent) in a 10 mL flask was heated at 180 °C till the end of reaction. After being cooled to room temperature, the reaction mixture was washed with methanol (5 mL) at 60 °C for 0.5 h and then filtered and washed with methanol to give the desired 4-arylamino coumarins without further purification.

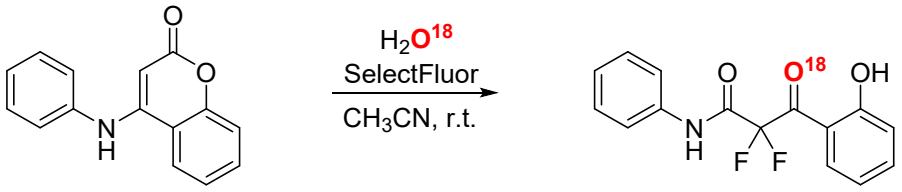
3.2 General Procedure for the Synthesis of **2**



1 **2**

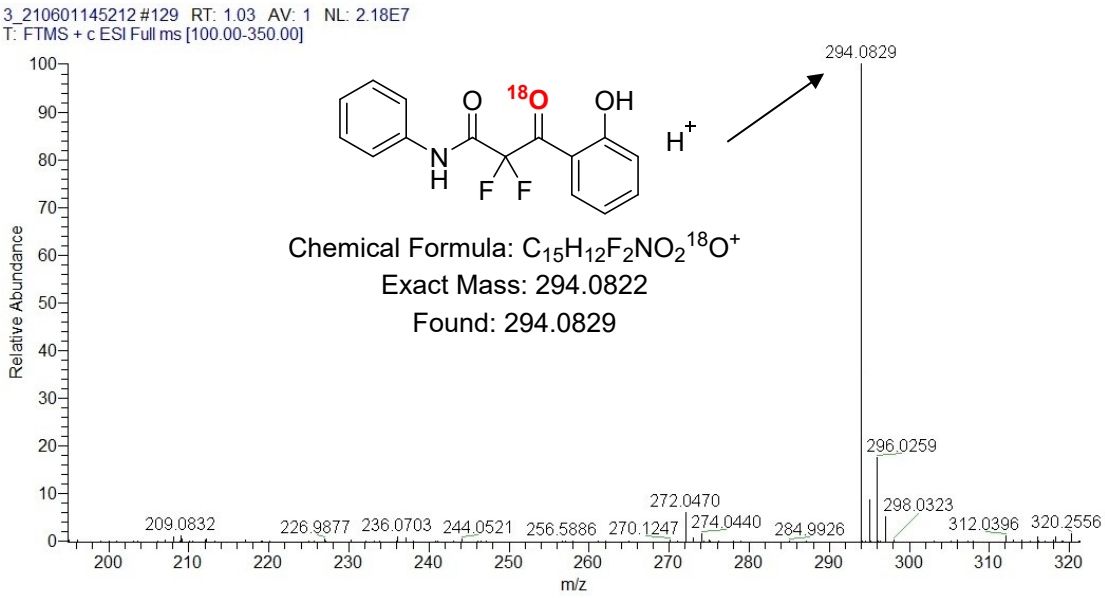
The mixture of4-arylamino coumarins **1** (1.0 equiv., 0.3 mmol), SelectFluor (0.66 mmol), and H_2O (5.0 equiv., 1.5 mmol) in CH_3CN (2.0 mL) was stirred at room temperature for 3.0 h. The reaction mixture was quenched with saturated $NaHCO_3$. H_2O (5 mL) was added to the mixture and extracted with CH_2Cl_2 (10 mL × 3). Combined organic phase was washed with brine and dried over Na_2SO_4, and then filtered, the solvent was removed in a rotary evaporator. The residue was purified by flash chromatography (ethyl acetate/petroleum ether mixtures) to give the desired product **2**.

3.3 Verification experiment for the Synthesis of **2a-O^{18}**



1a **2a-O^{18}**

MS-analytical Results:

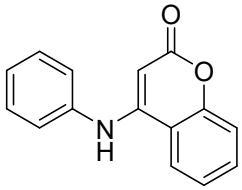


3.4 Cell viability and antidiabetic assay

Hep G2 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10 % FBS and 1 % penicillin/streptomycin. Hep G2 cells were seeded in 96-well plates at the concentrition of 1 × 10^4 cells/well. After incubation for 24 h, cells were exposed to several types of compounds at three concentritions (0.4 μg/mL, 2 μg/mL, 10 μg/mL) for 24 h. The cell viability of treatment was assayed by MTT method.[6] To induce insulin resistance, the cells were treated as the previous method of our group with some modification.[7] Briefly, cells were seeded in 96-well plates at the concentrition of 1 × 10^4 cells/well. After 24 h, glucosamine (18 mM) was added to the medium for 18 h. The above compounds were added and incubated with 100 nM insulin for 24 h. The glucose content in the supernant was measured using a commercial POD-GOD kit (Jiancheng Co., Ltd., Nanjing, China).

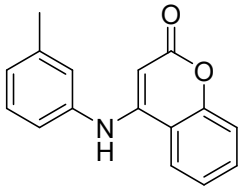
4. Characterization Data of the substrates and products

4.1 Spectral Data of Substrates **1**



4-(phenylamino)-2*H*-chromen-2-one (1a)

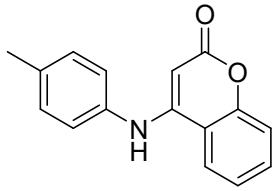
Synthesis carried out according to the General Procedure, compound **1a** was obtained in 80% yield as a yellowish solid after purification. mp 265–266 °C (lit.[1] mp 267–268 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.32 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.2Hz, 2H), 7.39 (s, 4H), 7.29 (t, J = 6.8 Hz, 1H), 5.31 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.9, 153.9, 152.9, 138.7, 132.8, 130.0, 126.5, 125.6, 124.1, 123.3, 117.5, 115.0, 84.9. These spectral data correspond to previously reported data.[2]



4-(*m*-tolylamino)-2*H*-chromen-2-one (1b)

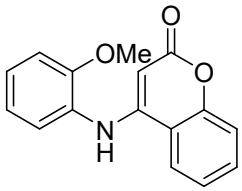
Synthesis carried out according to the General Procedure, compound **1b** was obtained in 82% yield as a yellowish solid after purification. mp 209–210 °C (lit. mp 212 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.27 (s, 1H), 8.24 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.41–7.34 (m, 3H), 7.17 (t, J = 9.2Hz, 2H), 7.10 (t, J = 7.6 Hz, 1H), 5.31 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.0, 153.9,

152.9, 139.5, 138.6, 132.8, 129.8, 127.2, 126.0, 124.1, 123.3, 122.6, 117.5, 115.0, 84.8, 21.4. These spectral data correspond to previously reported data.[3]



4-(*p*-tolylamino)-2*H*-chromen-2-one (1c)

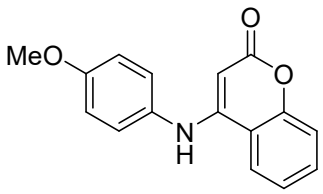
Synthesis carried out according to the General Procedure, compound **1c** was obtained in 79% yield as a yellowish solid after purification. mp 253–254 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.26 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.41–7.36 (m, 2H), 7.30–7.24 (m, 4H), 5.22 (s, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.9, 153.9, 153.2, 136.0, 135.9, 132.8, 130.5, 125.7, 124.0, 123.2, 117.5, 115.0, 84.4, 21.1. These spectral data correspond to previously reported data.[2]



4-((2-methoxyphenyl)amino)-2*H*-chromen-2-one (1d)

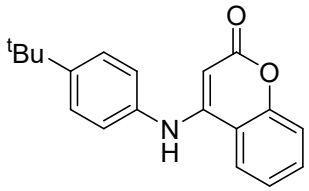
Synthesis carried out according to the General Procedure, compound **1d** was obtained in 73% yield as a yellowish solid after purification. mp 249–250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.07 (s, 1H), 8.27 (d, J = 8.0 Hz, 1H), 7.66–7.62 (m, 1H), 7.41–7.36 (m, 3H), 7.33–7.30 (m, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 4.75 (s, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.0, 155.1, 153.8, 153.7, 132.7, 129.2, 129.0, 126.3, 124.1, 123.3, 121.4, 117.5, 114.9, 113.1, 84.5,

56.1. These spectral data correspond to previously reported data.[2]



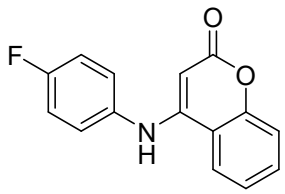
4-((4-methoxyphenyl)amino)-2*H*-chromen-2-one (1e)

Synthesis carried out according to the General Procedure, compound **1e** was obtained in 71% yield as a yellow solid after purification. mp 261–262 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.22 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.40–7.34 (m, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 5.10 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.0, 158.0, 153.9, 153.7, 132.8, 131.1, 127.6, 124.0, 123.2, 117.5, 115.2, 114.9, 84.0, 55.8. These spectral data correspond to previously reported data.[2]



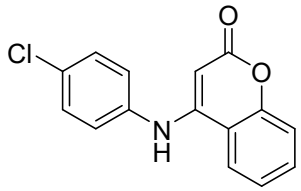
4-((4-(*tert*-butyl)phenyl)amino)-2*H*-chromen-2-one (1f)

Synthesis carried out according to the General Procedure, compound **1f** was obtained in 54% yield as a white solid after purification. mp 243–244 °C (lit. mp 247–248 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.26 (s, 1H), 8.24 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.41–7.36 (m, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.27 (s, 1H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.9, 153.9, 153.0, 149.0, 136.0, 132.8, 126.7, 125.2, 124.0, 123.2, 117.5, 115.0, 84.5, 34.8, 31.6. These spectral data correspond to previously reported data.[4]



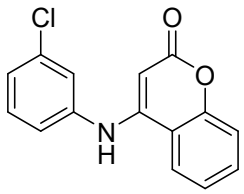
4-((4-fluorophenyl)amino)-2*H*-chromen-2-one (1g)

Synthesis carried out according to the General Procedure, compound **1g** was obtained in 61% yield as a yellowish solid after purification. mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.29 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.43–7.37 (m, 4H), 7.35–7.29 (m, 2H), 5.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.9,160.4 ($J_{C\text{-}F}$ = 241.8 Hz), 153.9, 153.3, 134.9 ($J_{C\text{-}F}$ = 2.6 Hz), 132.8, 128.0 ($J_{C\text{-}F}$ = 8.5 Hz), 124.1, 123.2, 117.5, 116.8 ($J_{C\text{-}F}$ = 22.4 Hz), 114.9, 84.8. These spectral data correspond to previously reported data.[2]



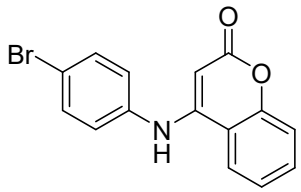
4-((4-chlorophenyl)amino)-2*H*-chromen-2-one (1h)

Synthesis carried out according to the General Procedure, compound **1h** was obtained in 66% yield as a yellowish solid after purification. mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.33 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 7.4 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.42–7.37 (m, 4H), 5.36 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.8, 153.8, 152.6, 137.8, 132.9, 130.2, 130.0, 127.0, 124.1, 123.3, 117.5, 114.9, 85.5. These spectral data correspond to previously reported data.[2]



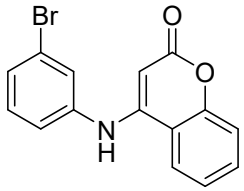
4-((3-chlorophenyl)amino)-2*H*-chromen-2-one (1i)

Synthesis carried out according to the General Procedure, compound **1i** was obtained in 69% yield as a yellow solid after purification. mp 259–260 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.34 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.51–7.45 (m, 2H), 7.42–7.36 (m, 3H), 7.32 (d, J = 8.0 Hz, 1H), 5.34 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.8, 153.9, 152.4, 140.5, 134.1, 132.9, 131.6, 125.9, 124.7, 124.1, 123.6, 123.3, 117.5, 114.9, 86.1. HRMS (ESI) *m/z*: Calcd for $C_{15}H_{11}ClNO_2$ $[M + H]^+$: 272.0473, found 272.0469.



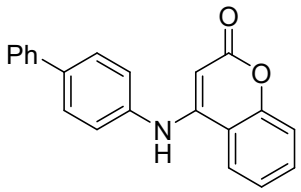
4-((4-bromophenyl)amino)-2*H*-chromen-2-one (1j)

Synthesis carried out according to the General Procedure, compound **1j** was obtained in 73% yield as a yellow solid after purification. mp 272–273 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.31 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 3H), 7.42–7.34 (m, 4H), 5.38 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.8, 153.8, 152.4, 138.3, 132.9, 132.8, 127.2, 124.1, 123.3, 118.3, 117.5, 114.9, 85.6. These spectral data correspond to previously reported data.[2]



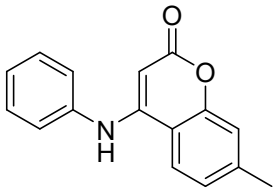
4-((3-bromophenyl)amino)-2*H*-chromen-2-one (1k)

Synthesis carried out according to the General Procedure, compound **1k** was obtained in 70% yield as a yellow solid after purification. mp 277–278 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.34 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 8.4 Hz, 1H), 7.59 (s, 1H), 7.47–7.37 (m, 5H), 5.42 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.8, 153.8, 152.4, 140.6, 133.0, 131.8, 128.8, 127.6, 124.2, 124.0, 123.3, 122.5, 117.5, 114.9, 86.0. HRMS (ESI) *m/z*: Calcd for $C_{15}H_{11}BrNO_2$ $[M + H]^+$: 315.9968, found 315.9973.



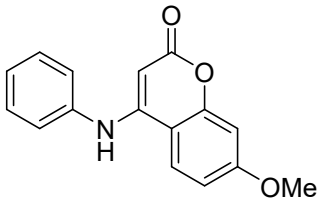
4-([1,1'-biphenyl]-4-ylamino)-2*H*-chromen-2-one (1l)

Synthesis carried out according to the General Procedure, compound **1l** was obtained in 62% yield as a yellow solid after purification. mp 328–329 °C (lit. mp 330–331 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.38 (s, 1H), 8.27 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 7.6 Hz, 2H), 7.73–7.66 (m, 3H), 7.51–7.38 (m, 7H), 5.44 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.9, 153.9, 152.7, 139.8, 138.2, 137.9, 132.9, 129.5, 128.2, 128.0, 127.0, 125.6, 124.1, 123.3, 117.6, 115.0, 85.3. These spectral data correspond to previously reported data.[4]



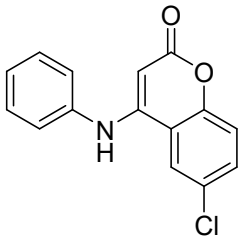
7-methyl-4-(phenylamino)-2*H*-chromen-2-one (1m)

Synthesis carried out according to the General Procedure, compound **1m** was obtained in 66% yield as a yellow solid after purification. mp 259–260 °C (lit. mp 253–254 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.26 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.23–7.19 (m, 2H), 5.27 (s, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.0, 154.0, 153.0, 143.5, 138.8, 130.0, 126.3, 125.5, 125.1, 123.0, 117.5, 112.5, 84.2, 21.4. These spectral data correspond to previously reported data.[4]



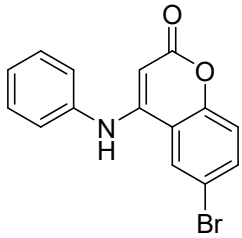
7-methoxy-4-(phenylamino)-2*H*-chromen-2-one (1n)

Synthesis carried out according to the General Procedure, compound **1n** was obtained in 69% yield as a yellow solid after purification. mp 262–263 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.23 (s, 1H), 8.15 (d, J = 8.8 Hz, 1H), 7.48 (t, J = 7.4 Hz, 2H), 7.36 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 7.0 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 5.18 (s, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.0, 162.3, 155.7, 153.2, 138.8, 130.0, 126.3, 125.5, 124.5, 111.9, 108.1, 101.4, 82.8, 56.3. These spectral data correspond to previously reported data.[5]



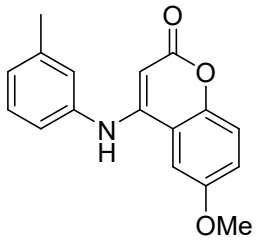
6-chloro-4-(phenylamino)-2*H*-chromen-2-one (1o)

Synthesis carried out according to the General Procedure, compound **1o** was obtained in 73% yield as a yellow solid after purification. mp 279–280 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.36 (s, 1H), 8.40 (d, J = 2.0 Hz, 1H), 7.71–7.68 (m, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.42–7.36 (m, 3H), 7.30 (t, J = 7.4 Hz, 1H), 5.35 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.5, 152.6, 151.9, 138.5, 132.5, 130.1, 128.4, 126.5, 125.3, 123.0, 119.5, 116.5, 85.3. These spectral data correspond to previously reported data.[4]



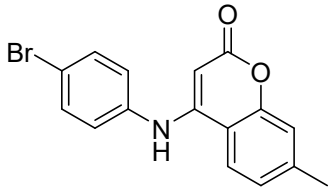
6-bromo-4-(phenylamino)-2*H*-chromen-2-one (1p)

Synthesis carried out according to the General Procedure, compound **1p** was obtained in 69% yield as a yellow solid after purification. mp 290–291 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.35 (s, 1H), 8.51 (d, J = 2.0 Hz, 1H), 7.82–7.79 (m, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.36 (t, J = 9.2 Hz, 3H), 7.29 (t, J = 7.2 Hz, 1H), 5.34 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.4, 153.0, 151.8, 138.5, 135.3, 130.0, 126.5, 125.8, 125.3, 119.8, 116.9, 116.1, 85.3. HRMS (ESI) *m/z*: Calcd for $C_{15}H_{11}BrNO_2$ [M + H]$^{+}$: 315.9968, found 315.9971.



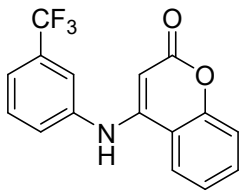
6-methoxy-4-(*m*-tolylamino)-2*H*-chromen-2-one (1q)

Synthesis carried out according to the General Procedure, compound **1q** was obtained in 73% yield as a yellowish solid after purification. mp 236–237 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.22 (s, 1H), 7.75 (s, 1H), 7.39–7.10 (m, 6H), 5.29 (s, 1H), 3.85 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.4, 155.9, 152.9, 148.2, 139.7, 138.6, 129.9, 127.3, 126.1, 122.7, 120.4, 118.7, 115.3, 106.0, 85.0, 56.5, 21.5. HRMS (ESI) *m/z*: Calcd for $C_{17}H_{16}NO_3$ $[M + H]^+$: 282.1125, found 282.1129.



4-((4-bromophenyl)amino)-7-methyl-2*H*-chromen-2-one (1r)

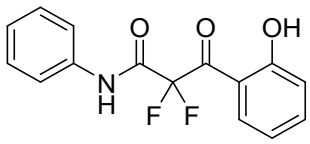
Synthesis carried out according to the General Procedure, compound **1r** was obtained in 61% yield as a yellow solid after purification. mp 287–288 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.27 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.25–7.21 (m, 2H), 5.34 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.0, 153.9, 152.5, 143.6, 138.3, 132.9, 127.2, 125.2, 123.1, 118.2, 117.5, 112.4, 84.9, 21.5. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{13}BrNO_2$ $[M + H]^+$: 330.0124, found 330.0129.



4-((3-(trifluoromethyl)phenyl)amino)-2*H*-chromen-2-one (1s)

Synthesis carried out according to the General Procedure, compound **1s** was obtained in 61% yield as a yellowish solid after purification. mp 270–271 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.43 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.73–7.68 (m, 3H), 7.64 (t, J = 8.0 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.41–7.34 (m, 2H), 5.45 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.9, 153.9, 152.3, 140.0, 132.9, 131.2, 130.8 (q, J = 31.9 Hz), 128.7, 125.7, 124.2, 123.3, 123.0, 122.4 (q, J = 3.7 Hz), 121.3 (q, J = 3.7 Hz), 117.5, 115.0, 86.2. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{11}F_3NO_2$ $[M + H]^+$: 306.0736, found 306.0739.

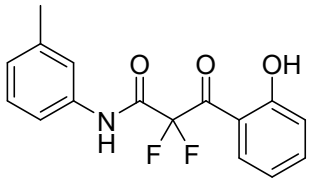
4.2 Spectral Data of products **2**



2,2-difluoro-3-(2-hydroxyphenyl)-3-oxo-*N*-phenylpropanamide (2a)

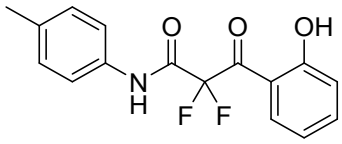
Synthesis carried out according to the General Procedure, compound **2a** was obtained in 79% yield as a yellowish solid after purification by a silica gel column chromatography. mp 70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.25 (s, 1H), 8.13–8.11 (m, 2H), 7.61–7.57 (m, 3H), 7.37 (t, J = 8.0 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.06–7.04 (m, 1H), 7.00–6.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.4 ($J_{C\text{-}F}$ = 26.6 Hz), 164.3, 158.8 ($J_{C\text{-}F}$ = 27.1 Hz), 138.6, 135.5, 131.7 ($J_{C\text{-}F}$ = 5.8 Hz),

129.3, 126.1, 120.3, 119.8, 118.8, 115.4, 110.5 ($J_{C\text{-}F}$ = 265.3 Hz). HRMS (ESI) *m/z*: Calcd for $C_{15}H_{12}F_2NO_3$ $[M + H]^+$: 292.0780, found 292.0783.



2,2-difluoro-3-(2-hydroxyphenyl)-3-oxo-*N*-(*m*-tolyl)propanamide (2b)

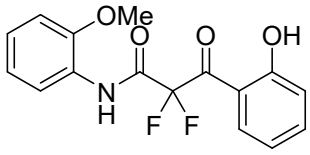
Synthesis carried out according to the General Procedure, compound **2b** was obtained in 81% yield as a yellow solid after purification by a silica gel column chromatography. mp 67–68 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.26 (s, 1H), 8.13–8.11 (m, 1H), 8.07 (s, 1H), 7.60–7.56 (m, 1H), 7.43 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.04 (t, *J* = 7.8 Hz, 2H), 6.98 (t, *J* = 8.2 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.5 ($J_{C\text{-}F}$ = 26.6 Hz), 164.2, 158.7 ($J_{C\text{-}F}$ = 27.2 Hz), 139.4, 138.6, 135.4, 131.8 ($J_{C\text{-}F}$ = 5.9 Hz), 129.1, 126.9, 120.9, 119.7, 118.8, 117.4, 115.4, 110.5 ($J_{C\text{-}F}$ = 265.2 Hz), 21.4. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{14}F_2NO_3$ $[M + H]^+$: 306.0936, found 306.0941.



2,2-difluoro-3-(2-hydroxyphenyl)-3-oxo-*N*-(*p*-tolyl)propanamide (2c)

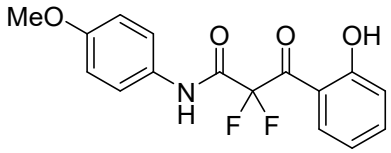
Synthesis carried out according to the General Procedure, compound **2c** was obtained in 82% yield as a yellowish solid after purification by a silica gel column chromatography. mp 79–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.26 (s, 1H),

8.12–8.10 (m, 2H), 7.60–7.55 (m, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 7.05–7.03 (m, 1H), 6.99–6.95 (m, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.5 ($J_{C\text{-}F}$ = 26.7 Hz), 164.2, 158.7 ($J_{C\text{-}F}$ = 27.1 Hz), 138.5, 135.9, 133.0, 131.7 ($J_{C\text{-}F}$ = 5.8 Hz), 129.7, 120.3, 119.7, 118.7, 115.4, 110.5 ($J_{C\text{-}F}$ = 265.2 Hz), 20.9. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{14}F_2NO_3$ $[M + H]^+$: 306.0936, found 306.0940.



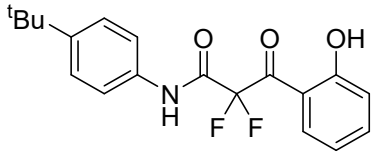
2,2-difluoro-3-(2-hydroxyphenyl)-*N*-(2-methoxyphenyl)-3-oxopropanamide (2d)

Synthesis carried out according to the General Procedure, compound **2d** was obtained in 78% yield as a yellow solid after purification by a silica gel column chromatography. mp 79–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.29 (s, 1H), 8.75 (s, 1H), 8.32–8.30 (m, 1H), 8.13–8.10 (m, 1H), 7.60–7.56 (m, 1H), 7.17–7.13 (m, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.98 (t, J = 7.2 Hz, 2H), 6.93 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.5 ($J_{C\text{-}F}$ = 26.6 Hz), 164.2, 158.4 ($J_{C\text{-}F}$ = 27.0 Hz), 148.3, 138.5, 131.7 ($J_{C\text{-}F}$ = 5.7 Hz), 125.7, 125.4, 121.1, 120.1, 119.7, 118.8, 115.5, 110.4 ($J_{C\text{-}F}$ = 265.1 Hz), 110.2, 55.9. HRMS (ESI) m/z: Calcd for $C_{16}H_{14}F_2NO_4$ $[M + H]^+$: 322.0885, found 322.0890.



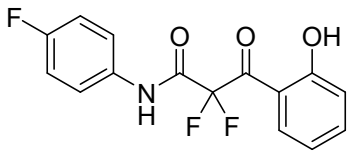
2,2-difluoro-3-(2-hydroxyphenyl)-*N*-(4-methoxyphenyl)-3-oxopropanamide (2e)

Synthesis carried out according to the General Procedure, compound **2e** was obtained in 87% yield as a yellow solid after purification by a silica gel column chromatography. mp 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.26 (s, 1H), 8.13–8.11 (m, 1H), 8.03 (s, 1H), 7.60–7.56 (m, 1H), 7.48 (d, J = 9.2 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.98 (t, J = 7.8 Hz, 1H), 6.88 (d, J = 9.2 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.5 ($J_{C\text{-}F}$ = 26.7 Hz), 164.2, 158.6 ($J_{C\text{-}F}$ = 27.0 Hz), 157.6, 138.6, 131.8 ($J_{C\text{-}F}$ = 5.8 Hz), 128.5, 122.1, 119.7, 118.8, 118.7, 115.4, 114.4, 110.6 ($J_{C\text{-}F}$ = 264.9 Hz). HRMS (ESI) m/z: Calcd for $C_{16}H_{14}F_2NO_4$ $[M + H]^+$: 322.0885, found 322.0891.



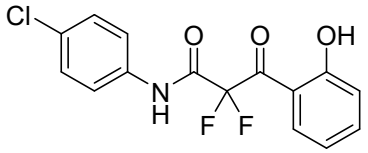
***N*-(4-(*tert*-butyl)phenyl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2f)**

Synthesis carried out according to the General Procedure, compound **2f** was obtained in 85% yield as a yellow oil after purification by a silica gel column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.25 (s, 1H), 8.13–8.10 (m, 1H), 8.06 (s, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.98 (t, J = 7.8 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.5 ($J_{C\text{-}F}$ = 26.5 Hz), 164.2, 158.7 ($J_{C\text{-}F}$ = 27.2 Hz), 149.3, 138.6, 132.9, 131.8 ($J_{C\text{-}F}$ = 5.8 Hz), 126.1, 120.0, 119.7, 118.8, 115.4, 110.5 ($J_{C\text{-}F}$ = 265.1 Hz), 34.5, 31.2. HRMS (ESI) m/z: Calcd for $C_{19}H_{20}F_2NO_3$ $[M + H]^+$: 348.1406, found 348.1411.



2,2-difluoro-*N*-(4-fluorophenyl)-3-(2-hydroxyphenyl)-3-oxopropanamide (2g)

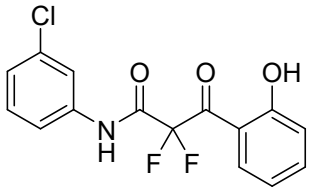
Synthesis carried out according to the General Procedure, compound **2g** was obtained in 73% yield as a yellowish solid after purification by a silica gel column chromatography. mp 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.22 (s, 1H), 8.17 (s, 1H), 8.11–8.09 (m, 1H), 7.61–7.53 (m, 3H), 7.06 (t, J = 8.4 Hz, 3H), 6.98 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.3 ($J_{C\text{-}F}$ = 26.6 Hz), 164.3, 161.5, 159.1, 158.9 ($J_{C\text{-}F}$ = 27.3 Hz), 138.7, 131.7 ($J_{C\text{-}F}$ = 5.9 Hz), 131.5 ($J_{C\text{-}F}$ = 3.0 Hz), 122.3 ($J_{C\text{-}F}$ = 8.1 Hz), 119.8, 118.8, 116.1 ($J_{C\text{-}F}$ = 22.6 Hz), 115.3, 110.6 ($J_{C\text{-}F}$ = 265.3 Hz). HRMS (ESI) m/z: Calcd for $C_{15}H_{11}F_3NO_3$ $[M + H]^+$: 310.0686, found 310.0690.



***N*-(4-chlorophenyl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2h)**

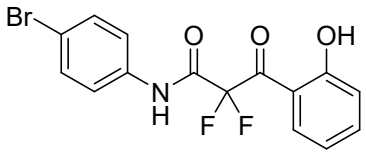
Synthesis carried out according to the General Procedure, compound **2h** was obtained in 75% yield as a yellowish solid after purification by a silica gel column chromatography. mp 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.21 (s, 1H), 8.15 (s, 1H), 8.10–8.08 (m, 1H), 7.61–7.57 (m, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.98 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.2 ($J_{C\text{-}F}$ = 26.5 Hz), 164.3, 158.9 ($J_{C\text{-}F}$ = 27.5 Hz), 138.8, 134.1, 131.6 ($J_{C\text{-}F}$ = 6.0 Hz), 131.3, 129.3, 121.6, 119.8, 118.8, 115.3, 110.5 ($J_{C\text{-}F}$ = 265.5 Hz).

HRMS (ESI) *m/z*: Calcd for $C_{15}H_{11}ClF_2NO_3$ $[M + H]^+$: 326.0390, found 326.0396.



***N*-(3-chlorophenyl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2i)**

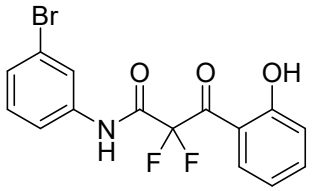
Synthesis carried out according to the General Procedure, compound **2i** was obtained in 73% yield as a yellow solid after purification by a silica gel column chromatography. mp 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.21 (s, 1H), 8.17 (s, 1H), 8.11–8.09 (m, 1H), 7.71 (t, *J* = 2.0 Hz, 1H), 7.62–7.57 (m, 1H), 7.44–7.41 (m, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.20–7.18 (m, 1H), 7.07–7.04 (m, 1H), 7.01–6.97 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.2 ($J_{C\text{-}F}$ = 26.6 Hz), 164.3, 158.9 ($J_{C\text{-}F}$ = 27.4 Hz), 138.8, 136.7, 135.0, 131.7 ($J_{C\text{-}F}$ = 6.0 Hz), 130.3, 126.2, 120.5, 119.8, 118.9, 118.3, 115.3, 110.5 ($J_{C\text{-}F}$ = 265.4 Hz). HRMS (ESI) *m/z*: Calcd for $C_{15}H_{11}ClF_2NO_3$ $[M + H]^+$: 326.0390, found 326.0395.



***N*-(4-bromophenyl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2j)**

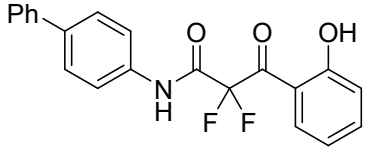
Synthesis carried out according to the General Procedure, compound **2j** was obtained in 79% yield as a yellow solid after purification by a silica gel column chromatography. mp 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.21 (s, 1H), 8.12–8.09 (m, 2H), 7.62–7.58 (m, 1H), 7.49 (s, 4H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ (ppm): 190.3 ($J_{C\text{-}F}$ = 26.6 Hz), 164.3, 158.8 ($J_{C\text{-}F}$ = 27.3 Hz), 138.8, 134.6, 132.3, 131.7 ($J_{C\text{-}F}$ = 6.0 Hz), 121.8, 119.8, 119.0, 118.9, 115.3, 110.5 ($J_{C\text{-}F}$ = 265.4 Hz). HRMS (ESI) *m/z*: Calcd for $C_{15}H_{11}BrF_2NO_3$ $[M + H]^+$: 369.9885, found 369.9890.



***N*-(3-bromophenyl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2k)**

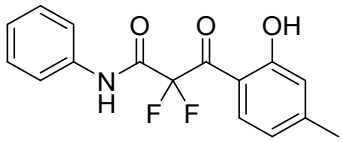
Synthesis carried out according to the General Procedure, compound **2k** was obtained in 77% yield as a yellow solid after purification by a silica gel column chromatography. mp 75–76 °C. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.21 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.85 (s, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.49–7.47 (m, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.2 ($J_{C\text{-}F}$ = 26.6 Hz), 164.3, 158.9 ($J_{C\text{-}F}$ = 27.9 Hz), 138.8, 136.7, 131.7 ($J_{C\text{-}F}$ = 5.9 Hz), 130.5, 129.1, 123.3, 122.9, 119.8, 118.9, 118.8, 115.3, 110.5 ($J_{C\text{-}F}$ = 265.5 Hz). HRMS (ESI) *m/z*: Calcd for $C_{15}H_{11}BrF_2NO_3$ $[M + H]^+$: 369.9885, found 369.9891.



***N*-([1,1'-biphenyl]-4-yl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2l)**

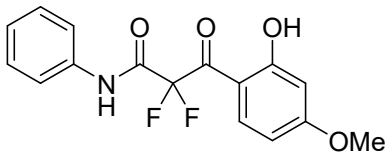
Synthesis carried out according to the General Procedure, compound **2l** was obtained

in 79% yield as a yellow solid after purification by a silica gel column chromatography. mp 125–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.26 (s, 1H), 8.14 (d, J = 6.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.62–7.56 (m, 5H), 7.44 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.4 ($J_{C\text{-}F}$ = 26.5 Hz), 164.3, 158.8 ($J_{C\text{-}F}$ = 27.6 Hz), 140.0, 139.0, 138.7, 134.8, 131.8 ($J_{C\text{-}F}$ = 5.7 Hz), 128.9, 127.9, 127.5, 126.9, 120.6, 119.8, 118.8, 115.4, 110.5 ($J_{C\text{-}F}$ = 265.2 Hz). HRMS (ESI) *m/z*: Calcd for $C_{21}H_{16}F_2NO_3$ $[M + H]^+$: 368.1093, found 368.1099.



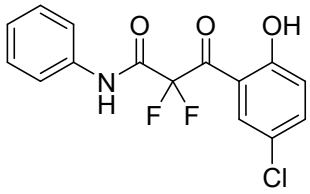
2,2-difluoro-3-(2-hydroxy-4-methylphenyl)-3-oxo-*N*-phenylpropanamide (2m)

Synthesis carried out according to the General Procedure, compound **2m** was obtained in 73% yield as a yellow solid after purification by a silica gel column chromatography. mp 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.32 (s, 1H), 8.14 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 6.85 (s, 1H), 6.78 (d, J = 8.4 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 189.6 ($J_{C\text{-}F}$ = 26.5 Hz), 164.5, 158.9 ($J_{C\text{-}F}$ = 27.4 Hz), 151.0, 135.6, 131.5 ($J_{C\text{-}F}$ = 5.9 Hz), 129.2, 126.0, 121.3, 120.3, 118.7, 115.1, 110.6 ($J_{C\text{-}F}$ = 266.1 Hz), 22.2. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{14}F_2NO_3$ $[M + H]^+$: 306.0936, found 306.0941.



2,2-difluoro-3-(2-hydroxy-4-methoxyphenyl)-3-oxo-*N*-phenylpropanamide (2n)

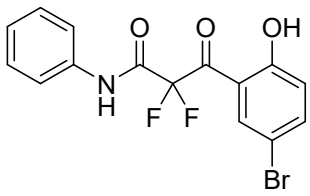
Synthesis carried out according to the General Procedure, compound **2n** was obtained in 69% yield as a yellowish solid after purification by a silica gel column chromatography. mp 69–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.81 (s, 1H), 8.15 (s, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H), 6.52–6.50 (m, 1H), 6.45 (d, J = 2.4 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 188.0 ($J_{C\text{-}F}$ = 26.4 Hz), 168.0, 167.7, 159.1 ($J_{C\text{-}F}$ = 27.3 Hz), 135.7, 133.6 ($J_{C\text{-}F}$ = 6.3 Hz), 129.2, 125.9, 120.3, 110.7 ($J_{C\text{-}F}$ = 264.3 Hz), 109.6, 109.2, 101.0, 55.8. HRMS (ESI) m/z: Calcd for $C_{16}H_{14}F_2NO_4$ $[M + H]^+$: 322.0885, found 322.0891.



3-(5-chloro-2-hydroxyphenyl)-2,2-difluoro-3-oxo-*N*-phenylpropanamide (2o)

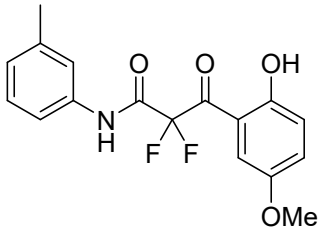
Synthesis carried out according to the General Procedure, compound **2o** was obtained in 61% yield as a yellow solid after purification by a silica gel column chromatography. mp 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.16 (s, 1H), 8.12 (s, 1H), 8.04 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.55–7.53 (m, 1H), 7.39 (t, J = 8.0 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.1

($J_{C\text{-}F}$ = 27.0 Hz), 162.8, 158.4 ($J_{C\text{-}F}$ = 26.9 Hz), 138.7, 135.4, 130.8 ($J_{C\text{-}F}$ = 6.5 Hz), 129.4, 126.3, 124.7, 120.4, 118.7, 116.0, 110.3 ($J_{C\text{-}F}$ = 265.7 Hz). HRMS (ESI) *m/z*: Calcd for $C_{15}H_{11}ClF_2NO_3$ $[M + H]^+$: 326.0390, found 326.0397.



3-(5-bromo-2-hydroxyphenyl)-2,2-difluoro-3-oxo-*N*-phenylpropanamide (2p)

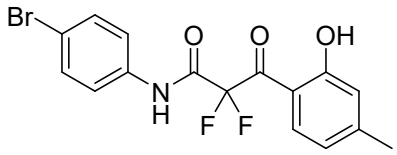
Synthesis carried out according to the General Procedure, compound **2p** was obtained in 63% yield as a yellow oil after purification by a silica gel column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.18 (s, 1H), 8.25 (s, 1H), 8.12 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.0 ($J_{C\text{-}F}$ = 27.1 Hz), 163.2, 158.5 ($J_{C\text{-}F}$ = 27.0 Hz), 141.3, 137.0, 135.4, 133.9 ($J_{C\text{-}F}$ = 6.4 Hz), 129.3, 126.3, 120.5, 118.8, 116.6, 110.3 ($J_{C\text{-}F}$ = 265.7 Hz). HRMS (ESI) *m/z*: Calcd for $C_{15}H_{11}BrF_2NO_3$ $[M + H]^+$: 369.9885, found 369.9889.



2,2-difluoro-3-(2-hydroxy-5-methoxyphenyl)-3-oxo-*N*-(*m*-tolyl)propanamide (2q)

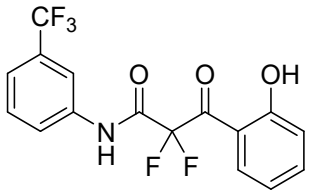
Synthesis carried out according to the General Procedure, compound **2q** was obtained in 82% yield as a yellow oil after purification by a silica gel column chromatography.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.98 (s, 1H), 7.98 (s, 1H), 7.60 (s, 1H), 7.41 (s, 1H), 7.36–7.32 (m, 1H), 7.30–7.22 (m, 3H), 7.03 (d, J = 7.2 Hz, 1H), 6.99 (d, J = 9.2 Hz, 1H), 3.82 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 189.9 ($J_{C\text{-}F}$ = 26.3 Hz), 159.3, 158.7 ($J_{C\text{-}F}$ = 27.3 Hz), 152.1, 139.4, 135.5, 129.1, 128.2, 126.9, 120.9, 119.7, 117.4, 114.7, 112.6 ($J_{C\text{-}F}$ = 5.6 Hz), 110.6 ($J_{C\text{-}F}$ = 264.8 Hz), 55.9, 21.4. HRMS (ESI) m/z: Calcd for $C_{17}H_{16}F_2NO_4$ [M + H]$^+$: 336.1042, found 336.1050.



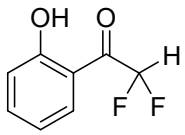
***N*-(4-bromophenyl)-2,2-difluoro-3-(2-hydroxy-4-methylphenyl)-3-oxopropanamide (2r)**

Synthesis carried out according to the General Procedure, compound **2r** was obtained in 71% yield as a yellow solid after purification by a silica gel column chromatography. mp 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.27 (s, 1H), 8.07 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.48 (s, 4H), 6.85 (s, 1H), 6.79 (d, J = 8.4 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 189.4 ($J_{C\text{-}F}$ = 26.5 Hz), 164.6, 159.0 ($J_{C\text{-}F}$ = 27.4 Hz), 151.2, 134.7, 132.3, 131.5 ($J_{C\text{-}F}$ = 6.0 Hz), 121.8, 121.3, 118.9, 118.8, 116.7, 110.6 ($J_{C\text{-}F}$ = 263.3 Hz), 22.3. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{13}BrF_2NO_3$ [M + H]$^+$: 384.0041, found 384.0045.



2,2-difluoro-3-(2-hydroxyphenyl)-3-oxo-*N*-(3-(trifluoromethyl)phenyl)propanamide (2s)

Synthesis carried out according to the General Procedure, compound **2s** was obtained in 29% yield as a yellow oil after purification by a silica gel column chromatography.. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.20 (s, 1H), 8.39 (s, 1H), 8.11–8.09 (m, 1H), 7.91 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.62–7.57 (m, 1H), 7.53–7.46 (m, 2H), 7.05 (d, J = 7.6 Hz, 1H), 6.99 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.2 ($J_{C\text{-}F}$ = 26.6 Hz), 164.4, 159.2 ($J_{C\text{-}F}$ = 27.5 Hz), 138.8, 136.2, 133.8, 131.8 ($J_{C\text{-}F}$ = 32.7 Hz), 131.6 ($J_{C\text{-}F}$ = 5.9 Hz), 129.9, 123.4, 122.7 ($J_{C\text{-}F}$ = 3.7 Hz), 119.8, 118.9, 117.2 ($J_{C\text{-}F}$ = 3.8 Hz), 115.3, 110.5 ($J_{C\text{-}F}$ = 265.7 Hz). HRMS (ESI) *m/z*: Calcd for $C_{16}H_{11}F_5NO_3$ $[M + H]^+$: 360.0654, found 360.0657.



2,2-difluoro-1-(2-hydroxyphenyl)ethan-1-one (3)

Synthesis carried out according to the General Procedure, compound **3** was obtained in 31% yield as a yellow oil after purification by a silica gel column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.29 (s, 1H), 7.90–7.88 (m, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.33 (t, J = 53.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 191.6 ($J_{C\text{-}F}$ = 25.0 Hz), 164.0, 138.3, 130.4 ($J_{C\text{-}F}$ = 4.3 Hz), 119.7, 118.9, 115.3, 110.8 ($J_{C\text{-}F}$ = 251.8 Hz). HRMS (ESI) *m/z*: Calcd for $C_8H_7F_2O_2$ $[M + H]^+$: 173.0409, found 173.0413.

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5. X-ray Crystallographic Data for 2a

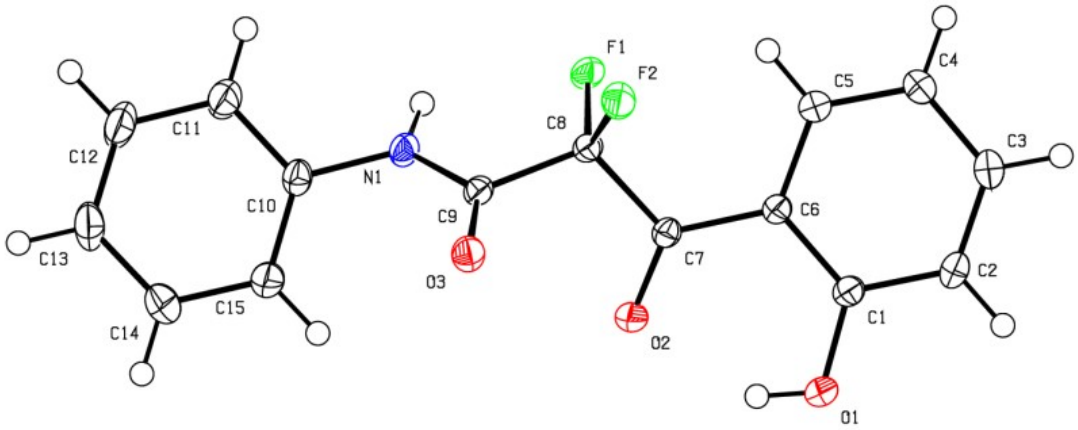


Figure S1. *X*-Ray crystal structure of **2a**

Table 1. Crystal Data and Structure Refinement for **2a**

CCDC number	2084177
Identification code	r20210507a
Empirical formula	C15 H11 F2 N O3
Formula weight	291.25
Temperature	113.15 K
Wavelength	0.71073
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a= 5.1636(2) Å α= 90°. b= 17.4283(6) Å β= 95.475(4)°. c= 14.1357(5) Å γ= 90°.
Volume	1266.31(8) Å3
Z	4
Density (calculated)	1.528 g/cm^3
Absorption coefficient	0.126 mm^{-1}
F(000)	600.0

Theta range for data collection	3.72 to 65.68°
Index ranges	$-7 \leq h \leq 7$, $-25 \leq k \leq 26$, $-19 \leq l \leq 20$
Reflections collected	15726
Independent reflections	4361 [R_{int} = 0.0648, R_{sigma} = 0.0519]
Max. and min. transmission	1.000 and 0.613
Data / restraints / parameters	4361/0/192
Goodness-of-fit on F^2	1.039
Final R indices [I>=2σ (I)]	R_1 = 0.0513, wR_2 = 0.1258
R indices (all data)	R_1 = 0.0698, wR_2 = 0.1444
Largest diff. peak and hole	0.43 and -0.28 e $Å^{-3}$

Table 2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for r20210507a. U(eq) is defined as 1/3 of of the trace of the orthogonalised U^{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
F1	7438.3(16)	6205.9(5)	4059.1(6)	22.0(2)
F2	4146.2(18)	6926.0(4)	3522.1(6)	22.6(2)
O1	113(2)	5938.7(6)	6255.7(8)	23.7(2)
O2	2353(2)	5408.1(5)	4775.5(7)	20.6(2)
O3	1683.8(19)	5633.0(6)	2711.8(7)	21.2(2)
N1	5945(2)	5264.1(6)	2672.4(8)	18.4(2)
C1	1835(3)	6518.6(7)	6226.5(10)	18.1(3)
C2	1885(3)	7060.2(8)	6958.5(10)	24.3(3)
C3	3613(3)	7665.4(8)	6987.6(11)	24.0(3)
C4	5312(3)	7755.8(8)	6286.3(10)	22.4(3)
C5	5255(3)	7234.3(8)	5549.1(10)	20.2(3)
C6	3517(3)	6604.0(7)	5501.7(9)	16.0(2)
C7	3454(3)	6029.1(7)	4745.0(9)	15.5(2)
C8	4805(3)	6204.1(7)	3836.9(9)	16.0(2)
C9	3987(3)	5651.0(7)	3009.7(9)	15.9(2)
C10	5600(3)	4736.8(8)	1890.2(10)	19.1(3)
C11	7336(4)	4768.1(12)	1203.2(13)	39.3(5)
C12	7066(4)	4247.6(14)	451.8(15)	47.3(6)

C13	5107(3)	3710.6(10)	386.2(12)	30.6(4)
C14	3397(4)	3683.6(9)	1079.1(12)	31.5(4)
C15	3634(3)	4196.4(8)	1838.5(12)	28.3(3)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for r20210507a. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	13.5(4)	31.0(4)	22.0(4)	-5.0(3)	4.2(3)	-3.4(3)
F2	32.5(5)	15.4(4)	20.7(4)	1.9(3)	6.2(3)	0.3(3)
O1	26.1(6)	23.2(5)	23.6(5)	-3.3(4)	11.5(4)	-7.2(4)
O2	22.6(5)	17.5(4)	22.6(5)	-1.4(3)	7.1(4)	-4.1(4)
O3	15.8(5)	24.9(5)	22.7(5)	-4.4(4)	1.3(4)	1.4(4)
N1	14.7(5)	21.9(5)	19.1(5)	-3.9(4)	3.5(4)	1.8(4)
C1	17.9(6)	18.2(5)	18.9(6)	0.0(4)	4.6(5)	-0.6(4)
C2	28.3(8)	25.7(6)	20.4(7)	-5.0(5)	10.4(6)	-1.9(5)
C3	27.9(8)	23.1(6)	21.4(7)	-6.5(5)	4.3(6)	-0.8(5)
C4	22.8(7)	20.8(6)	23.8(7)	-4.8(5)	2.9(5)	-3.7(5)
C5	20.1(7)	20.6(6)	20.3(6)	-1.4(5)	4.8(5)	-2.8(5)
C6	16.2(6)	15.8(5)	16.5(6)	-0.7(4)	3.7(5)	-0.4(4)
C7	14.2(6)	16.0(5)	16.6(6)	-0.7(4)	3.0(4)	1.2(4)
C8	15.8(6)	15.7(5)	17.0(6)	0.0(4)	4.1(4)	-0.2(4)
C9	16.5(6)	16.6(5)	15.0(6)	0.6(4)	3.7(4)	-0.1(4)
C10	17.7(6)	21.9(6)	17.8(6)	-3.4(4)	2.0(5)	3.4(5)
C11	26.4(9)	60.5(11)	32.7(9)	-23.3(8)	12.2(7)	-16.3(8)
C12	32.0(10)	75.0(14)	37.8(10)	-32.1(10)	18.4(8)	-15.0(9)
C13	27.7(8)	36.7(8)	27.2(8)	-15.7(6)	1.2(6)	5.0(6)
C14	39.9(10)	22.0(6)	33.6(8)	-7.9(6)	8.7(7)	-6.0(6)
C15	36.3(9)	22.4(6)	28.6(8)	-5.3(5)	14.5(6)	-6.1(6)

Table 4. Bond Lengths for r20210507a.

Atom	Atom	Length/ Å
1	C8	1.3660(15)
F2	C8	1.3666(14)
O1	C1	1.3494(16)
O2	C7	1.2251(15)
O3	C9	1.2234(17)
N1	C9	1.3406(16)

N1	C10	1.4357(17)
C1	C2	1.3990(18)
C1	C6	1.4128(18)
C2	C3	1.379(2)
C3	C4	1.394(2)
C4	C5	1.3811(19)
C5	C6	1.4160(18)
C6	C7	1.4637(17)
C7	C8	1.5488(18)
C8	C9	1.5429(18)
C10	C11	1.384(2)
C10	C15	1.382(2)
C11	C12	1.394(2)
C12	C13	1.375(3)
C13	C14	1.381(2)
C14	C15	1.393(2)

Table 5. Bond Angles for r20210507a.

Atom	Atom	Atom	Angle/°
C9	N1	C10	123.60(12)
O1	C1	C2	116.65(12)
O1	C1	C6	123.61(12)
C2	C1	C6	119.73(12)
C3	C2	C1	120.28(13)
C2	C3	C4	120.96(13)
C5	C4	C3	119.50(13)
C4	C5	C6	120.93(13)
C1	C6	C5	118.56(12)
C1	C6	C7	119.04(11)
C5	C6	C7	122.38(12)
O2	C7	C6	123.86(12)
O2	C7	C8	116.77(11)
C6	C7	C8	119.37(11)
F1	C8	F2	106.52(10)
F1	C8	C7	109.09(10)
F1	C8	C9	111.74(10)
F2	C8	C7	109.47(10)
F2	C8	C9	106.66(10)
C9	C8	C7	113.11(10)
O3	C9	N1	127.31(12)
O3	C9	C8	117.64(11)
N1	C9	C8	114.99(11)

C11	C10	N1	118.29(13)
C15	C10	N1	120.91(13)
C15	C10	C11	120.76(13)
C10	C11	C12	118.99(16)
C13	C12	C11	120.94(16)
C12	C13	C14	119.45(14)
C13	C14	C15	120.64(15)
C10	C15	C14	119.22(14)

Table 6. Torsion Angles for r20210507a.

A	B	C	D	Angle/°
F1	C8	C9	O3	-175.97(11)
F1	C8	C9	N1	1.33(15)
F2	C8	C9	O3	-59.94(15)
F2	C8	C9	N1	117.35(12)
O1	C1	C2	C3	179.17(14)
O1	C1	C6	C5	-179.63(13)
O1	C1	C6	C7	-1.3(2)
O2	C7	C8	F1	-110.94(13)
O2	C7	C8	F2	132.87(12)
O2	C7	C8	C9	14.08(17)
N1	C10	C11	C12	178.44(18)
N1	C10	C15	C14	-178.58(14)
C1	C2	C3	C4	0.8(2)
C1	C6	C7	O2	-12.7(2)
C1	C6	C7	C8	166.39(12)
C2	C1	C6	C5	1.2(2)
C2	C1	C6	C7	179.53(13)
C2	C3	C4	C5	0.4(2)
C3	C4	C5	C6	-0.8(2)
C4	C5	C6	C1	0.0(2)
C4	C5	C6	C7	-178.30(13)
C5	C6	C7	O2	165.62(13)
C5	C6	C7	C8	-15.33(19)
C6	C1	C2	C3	-1.6(2)
C6	C7	C8	F1	69.95(14)
C6	C7	C8	F2	-46.25(16)
C6	C7	C8	C9	-165.03(11)
C7	C8	C9	O3	60.45(15)
C7	C8	C9	N1	-122.25(12)
C9	N1	C10	C11	136.12(16)
C9	N1	C10	C15	-45.8(2)

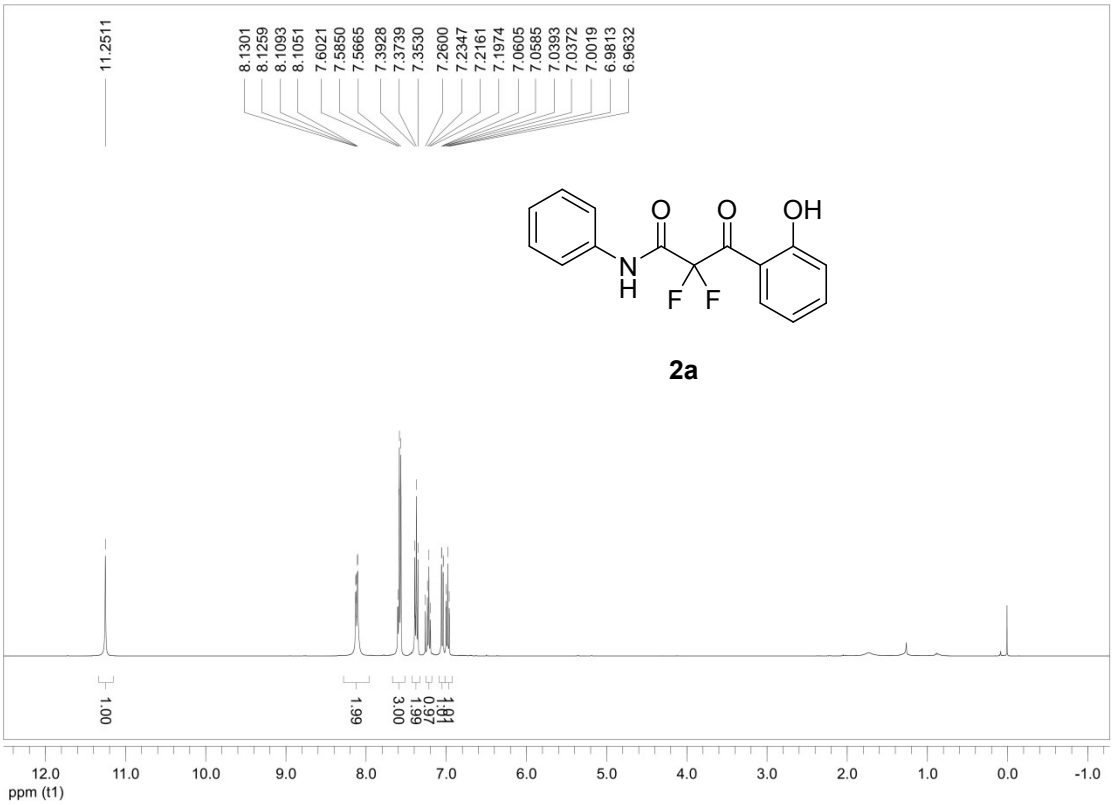
C10	N1	C9	O3	-1.4(2)
C10	N1	C9	C8	-178.41(11)
C10	C11	C12	C13	0.2(3)
C11	C10	C15	C14	-0.6(3)
C11	C12	C13	C14	-0.5(3)
C12	C13	C14	C15	0.3(3)
C13	C14	C15	C10	0.2(3)
C15	C10	C11	C12	0.4(3)

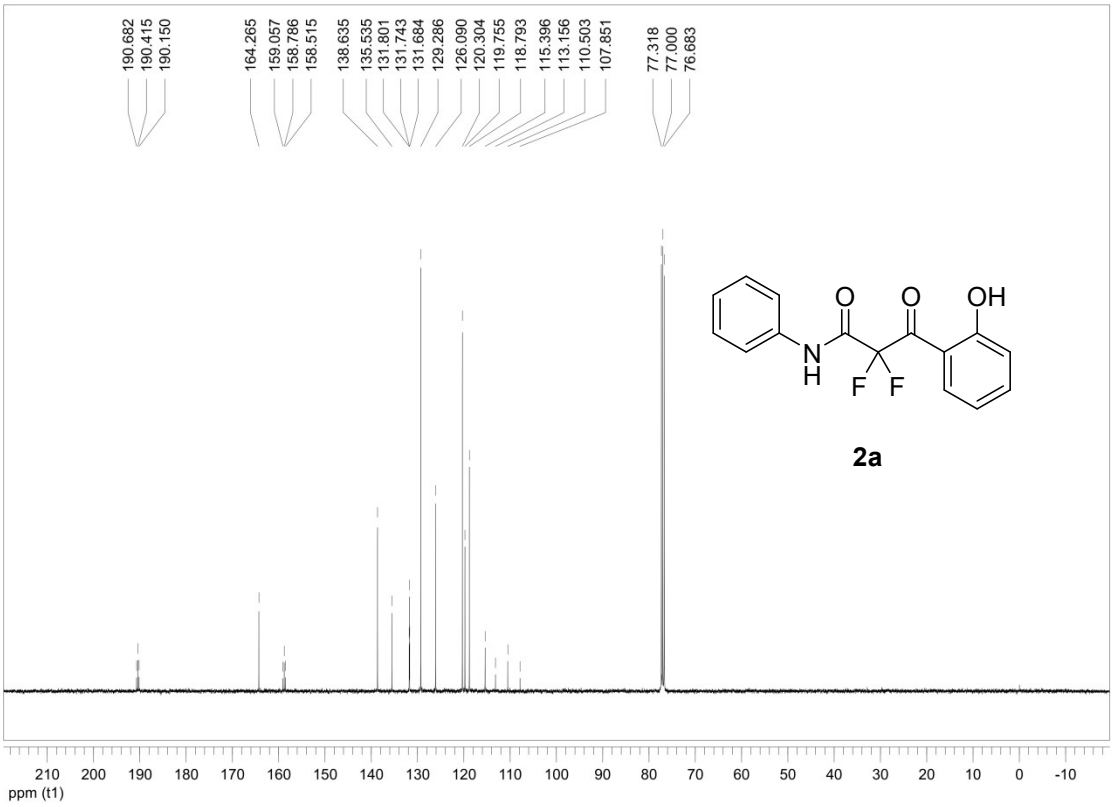
Table 7. Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for r20210507a.

Atom	x	y	z	U(eq)
H1	273.39	5636.32	5802.22	36
H1A	7529.94	5337.33	2945.39	22
H2	725.12	7010.94	7437.65	29
H3	3644.34	8025.77	7492.71	29
H4	6501.08	8173.11	6315.48	27
H5	6398.22	7299.31	5066.89	24
H11	8691.49	5138.61	1243.32	47
H12	8251.95	4264.12	-21.77	57
H13	4931.09	3361.02	-131.58	37
H14	2045.67	3311.72	1037.63	38
H15	2457.3	4174.8	2315.09	34

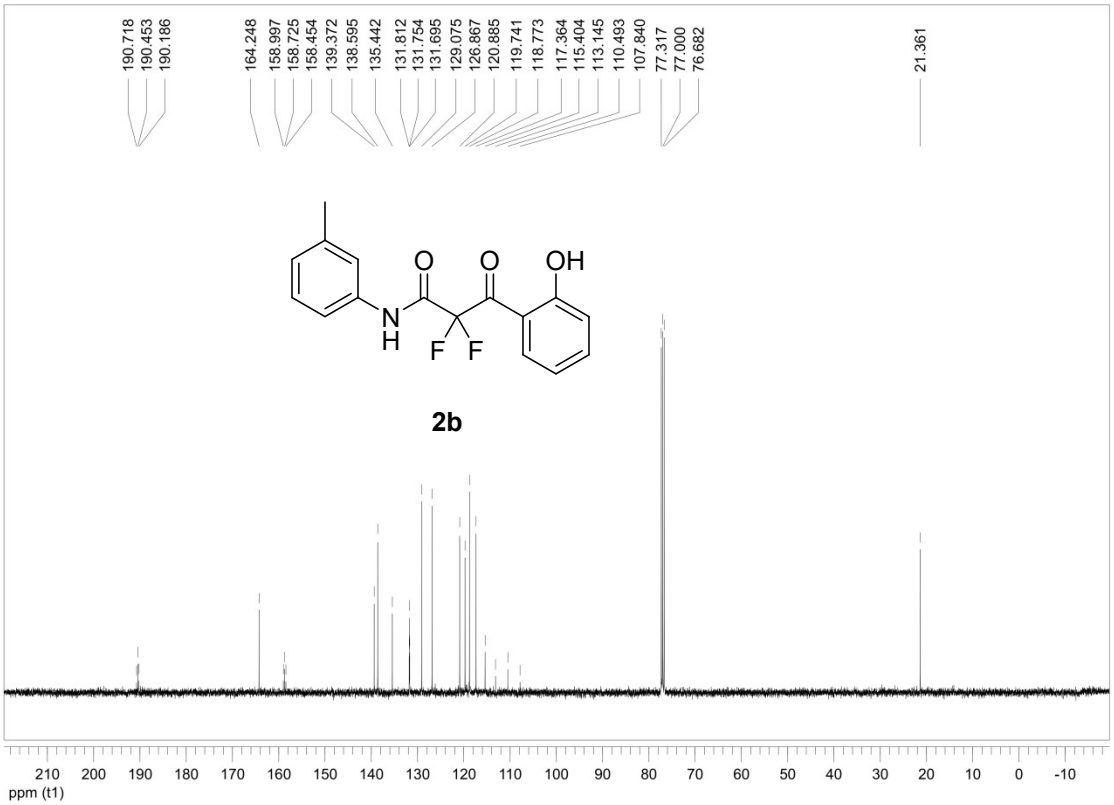
6. NMR Spectra for Products

2,2-difluoro-3-(2-hydroxyphenyl)-3-oxo-*N*-phenylpropanamide (2a)

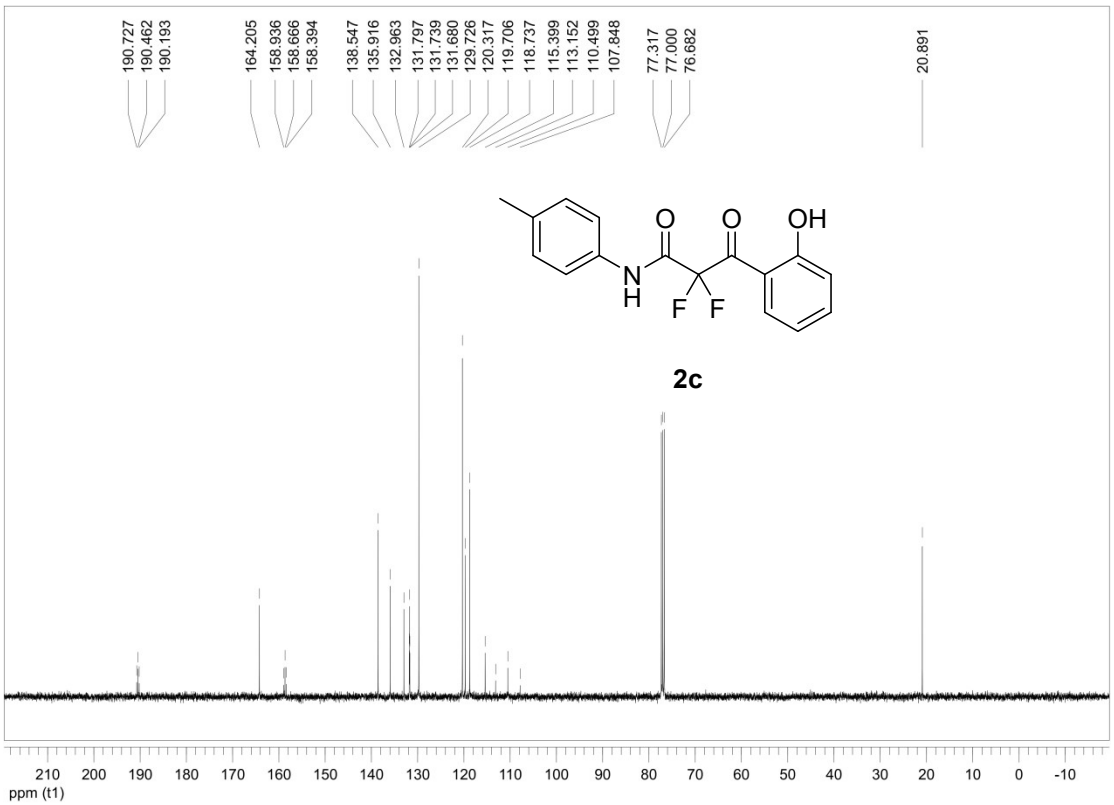




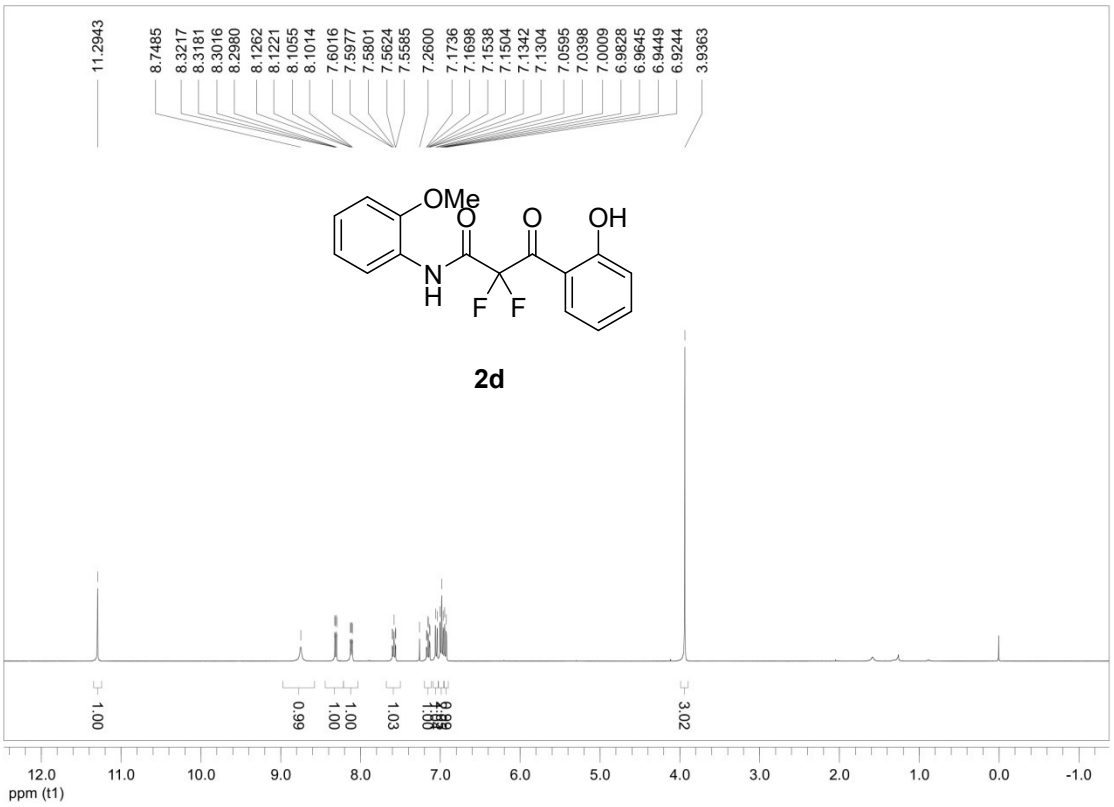
2,2-difluoro-3-(2-hydroxyphenyl)-3-oxo-*N*-(*m*-tolyl)propanamide (2b)

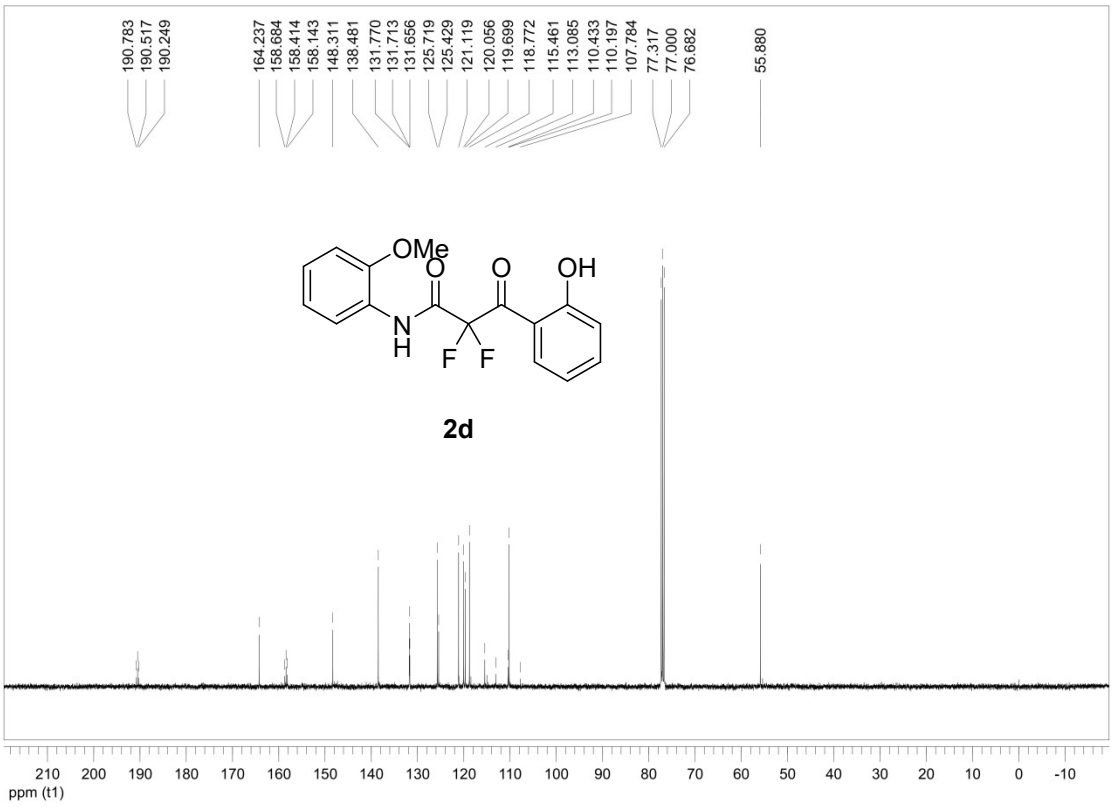


2,2-difluoro-3-(2-hydroxyphenyl)-3-oxo-*N*-(*p*-tolyl)propanamide (2c)

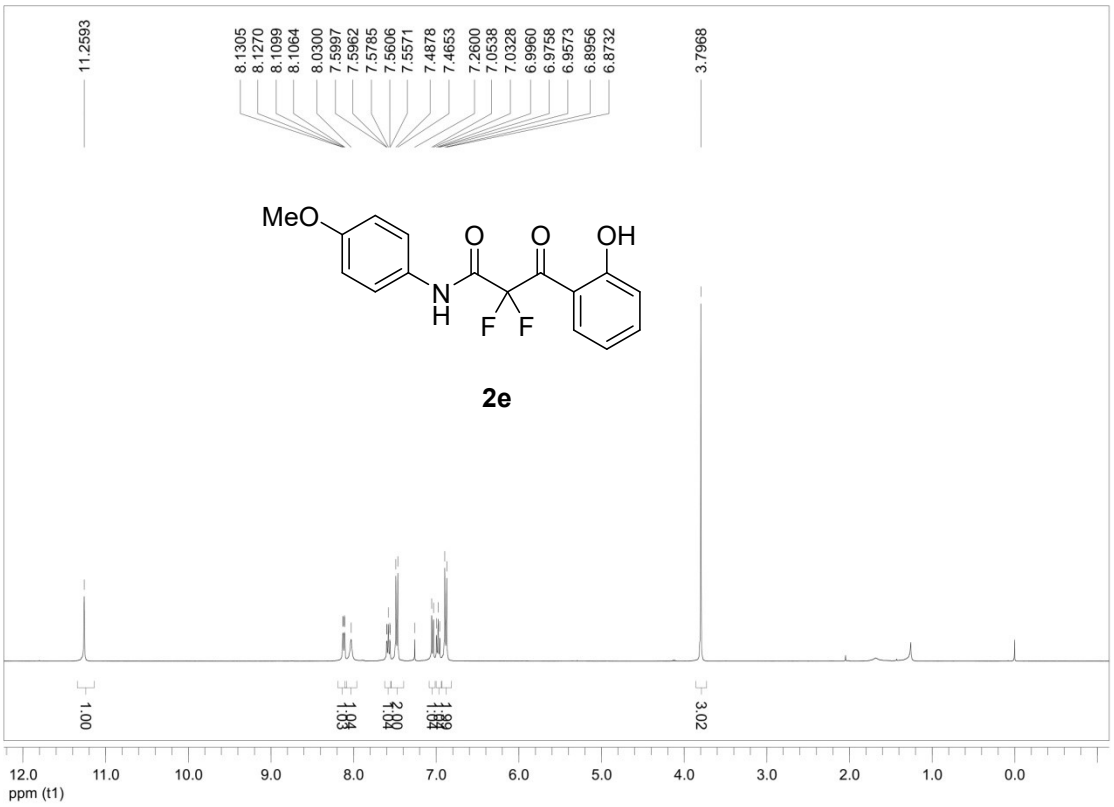


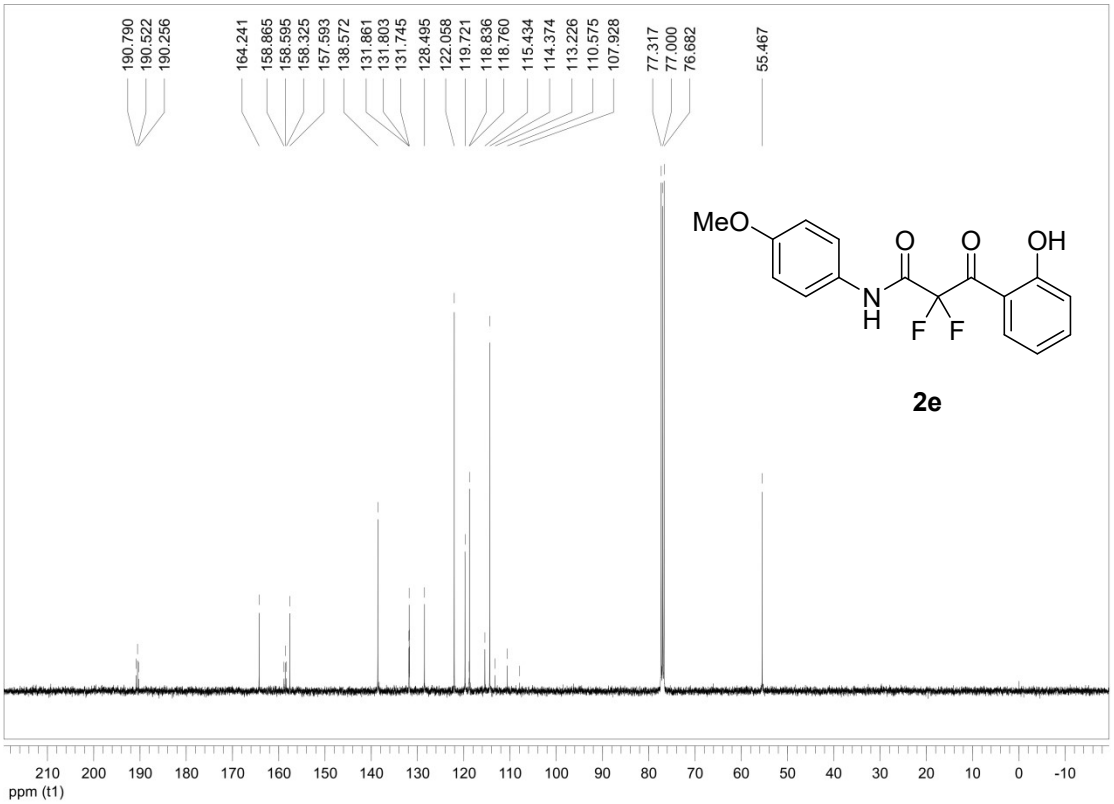
2,2-difluoro-3-(2-hydroxyphenyl)-*N*-(2-methoxyphenyl)-3-oxopropanamide (2d)



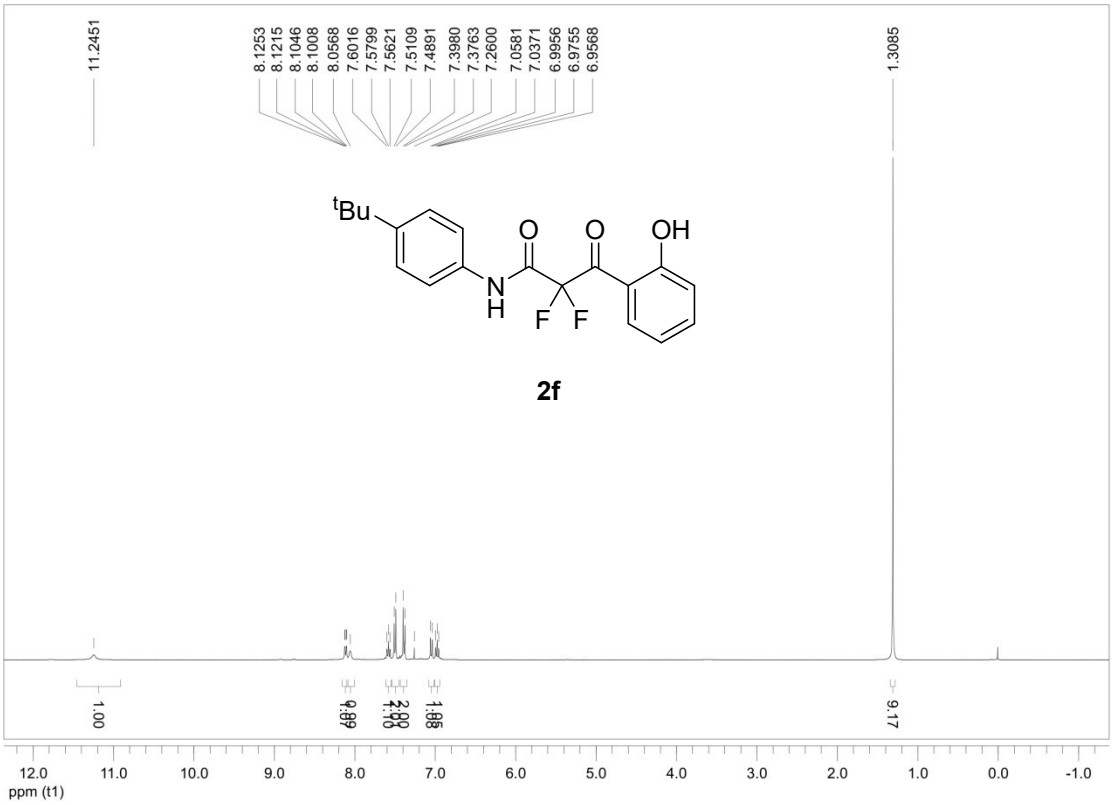


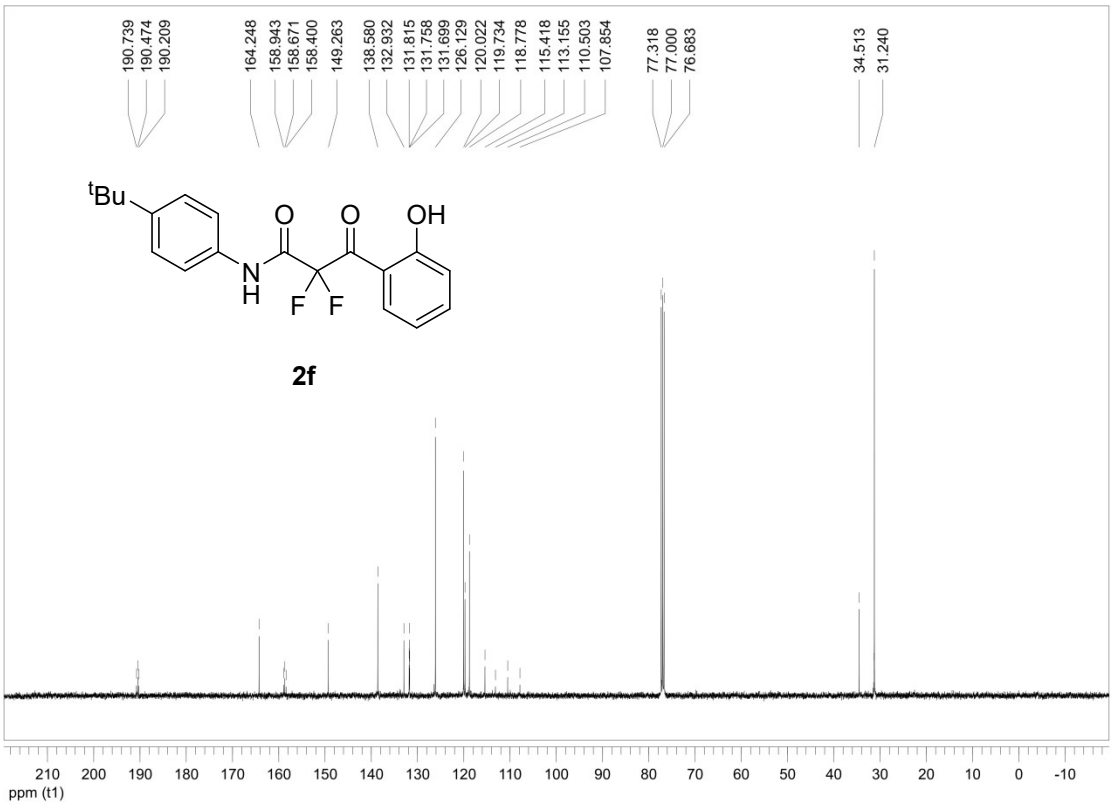
2,2-difluoro-3-(2-hydroxyphenyl)-*N*-(4-methoxyphenyl)-3-oxopropanamide (2e)



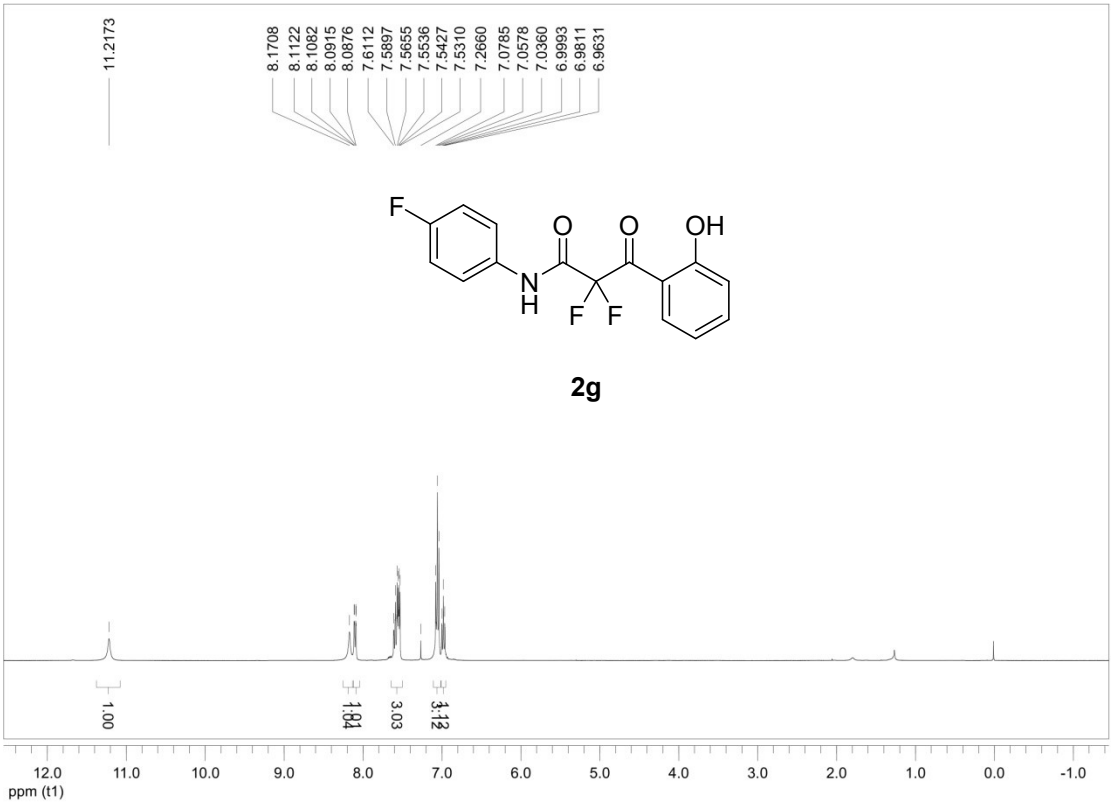


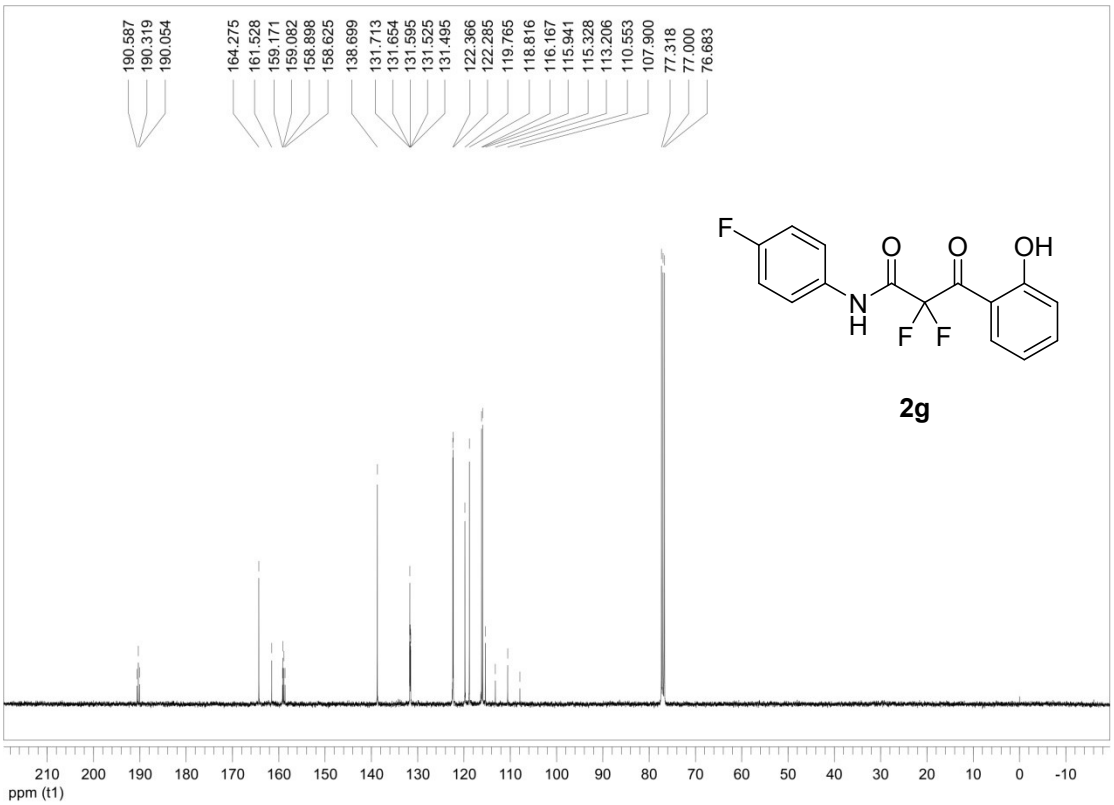
N-(4-(*tert*-butyl)phenyl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2f)



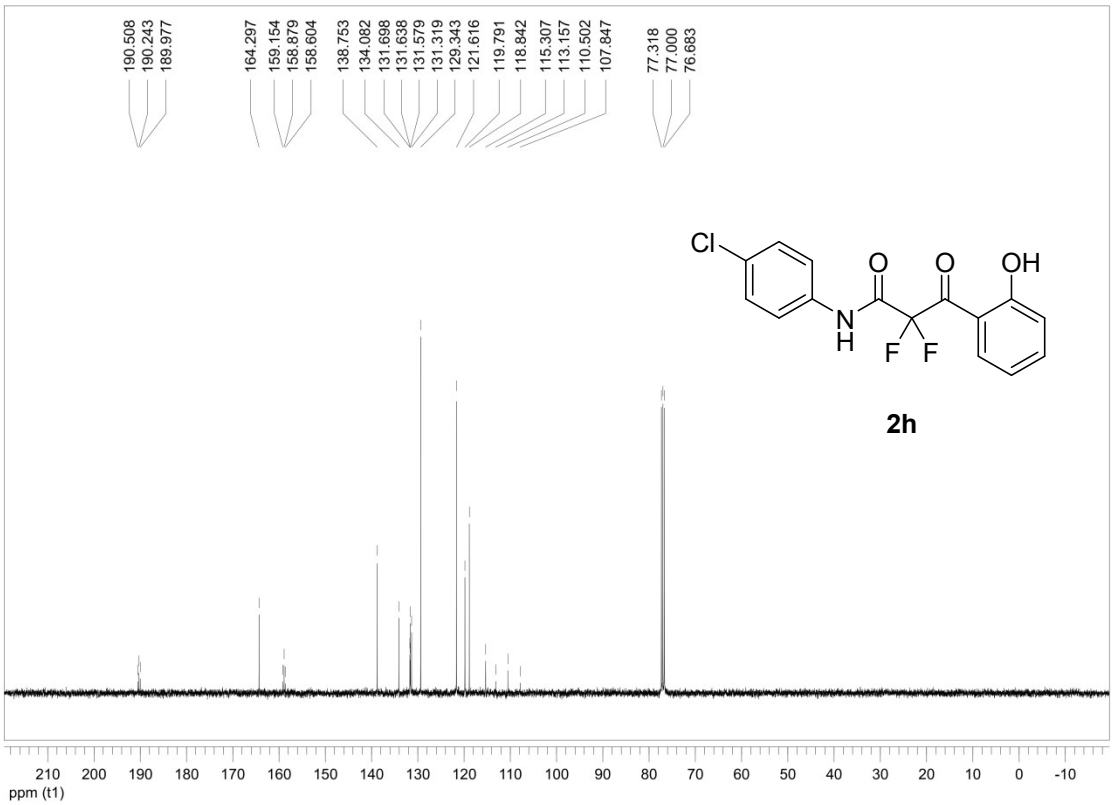


2,2-difluoro-*N*-(4-fluorophenyl)-3-(2-hydroxyphenyl)-3-oxopropanamide (2g)

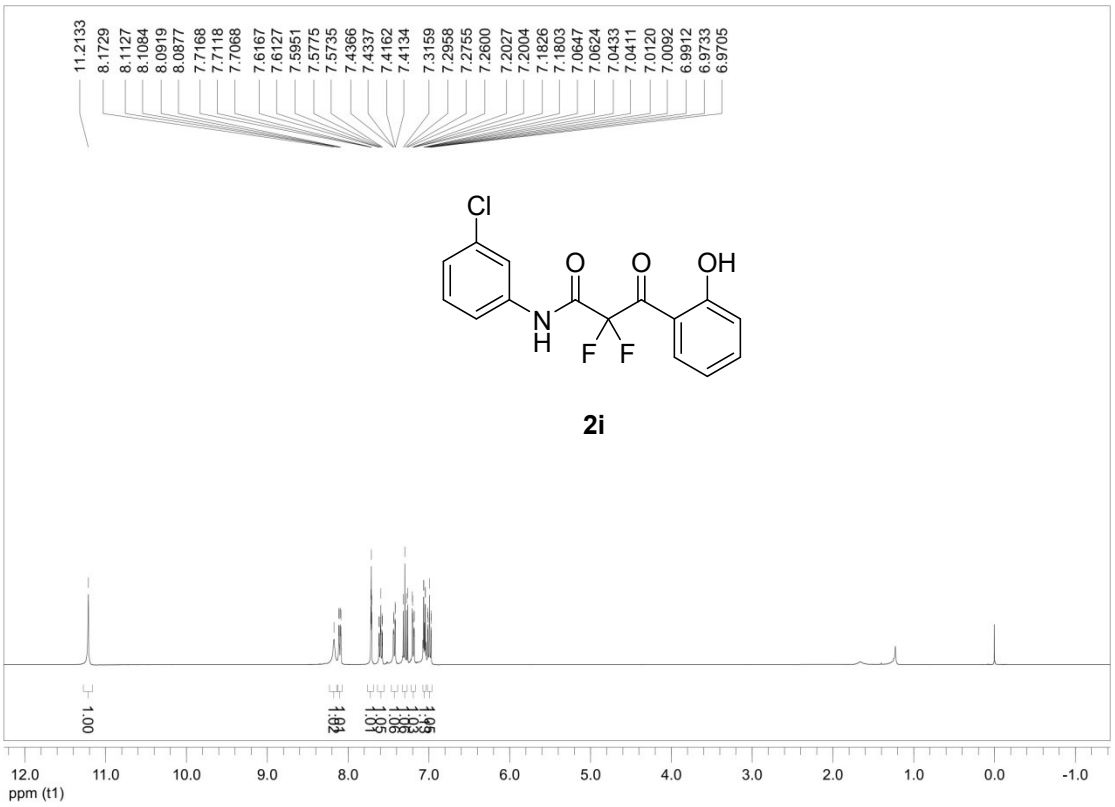


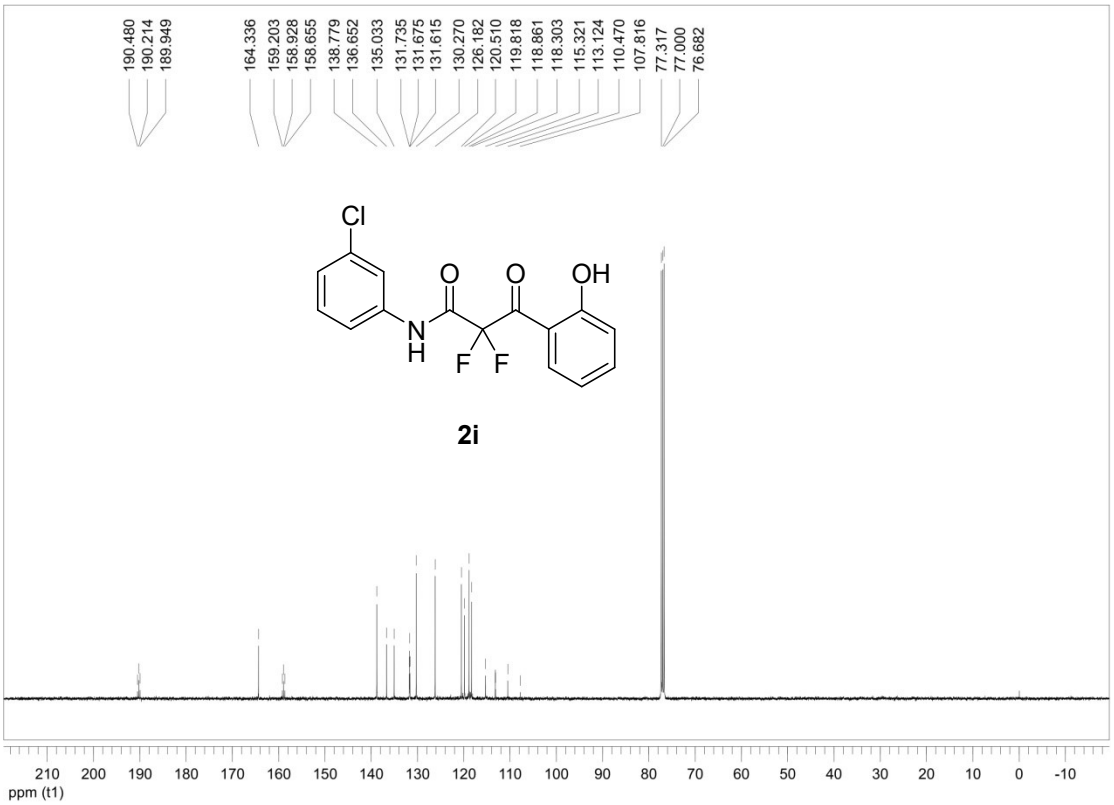


N-(4-chlorophenyl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2h)

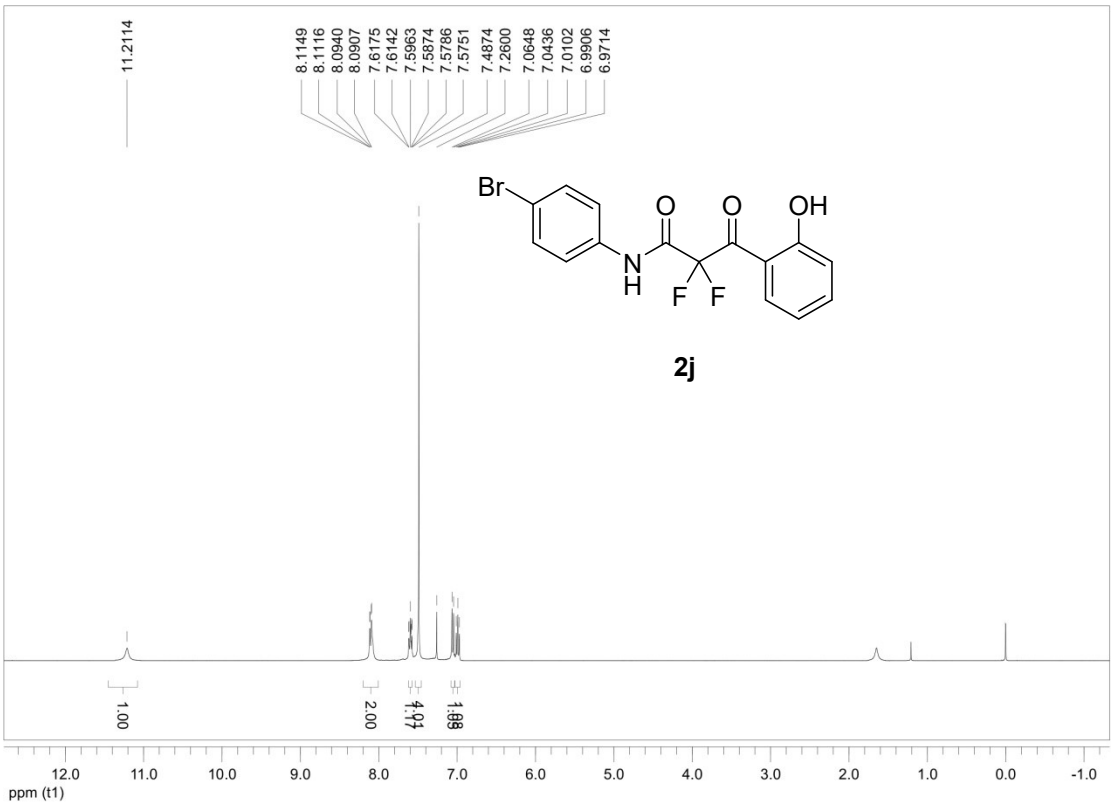


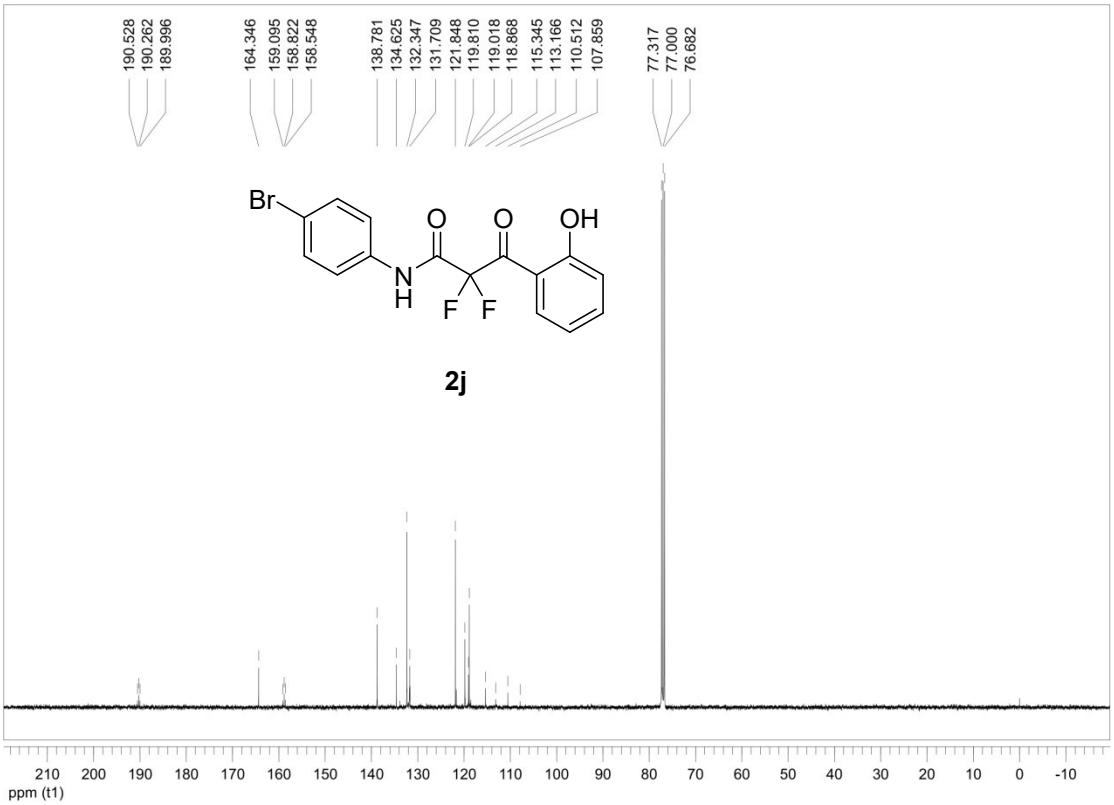
N-(3-chlorophenyl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2i)



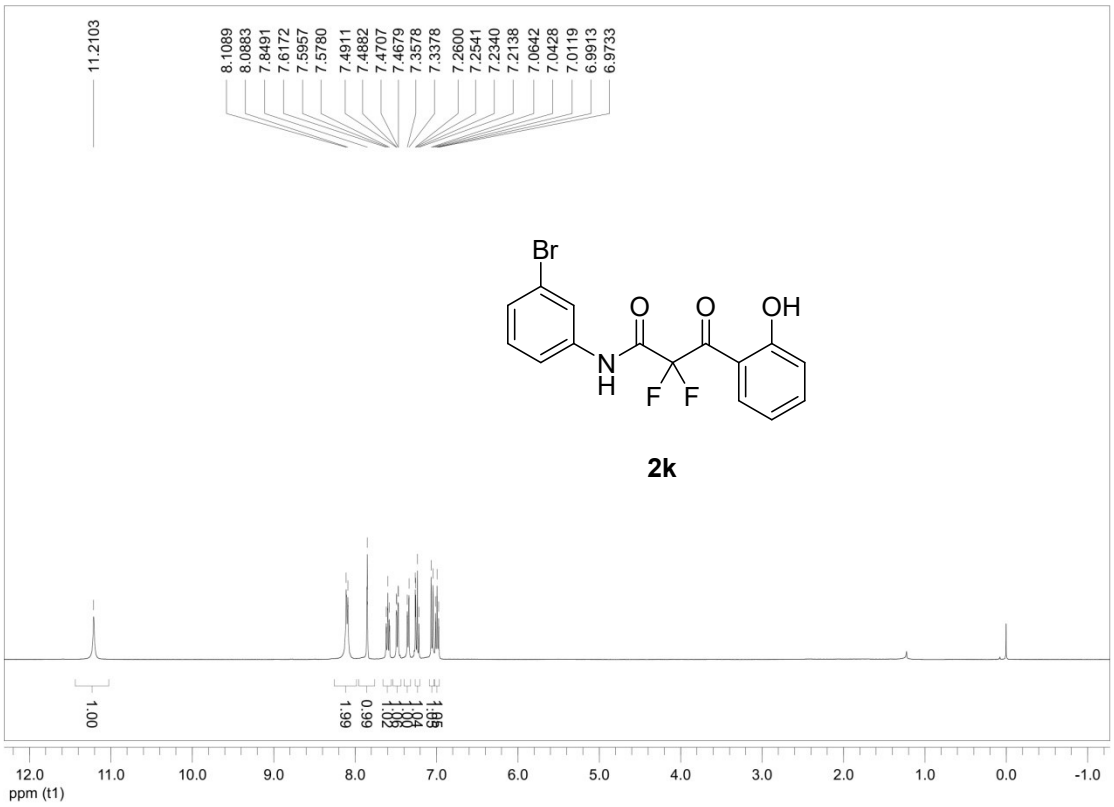


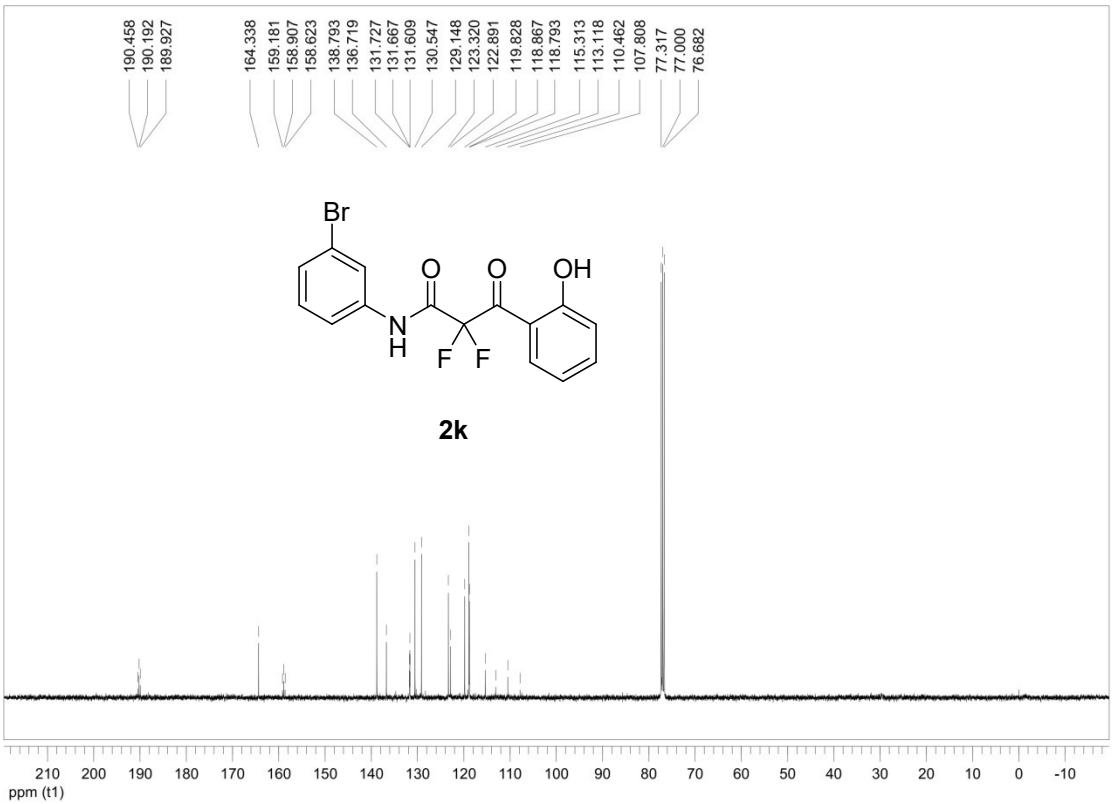
N-(4-bromophenyl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2j)



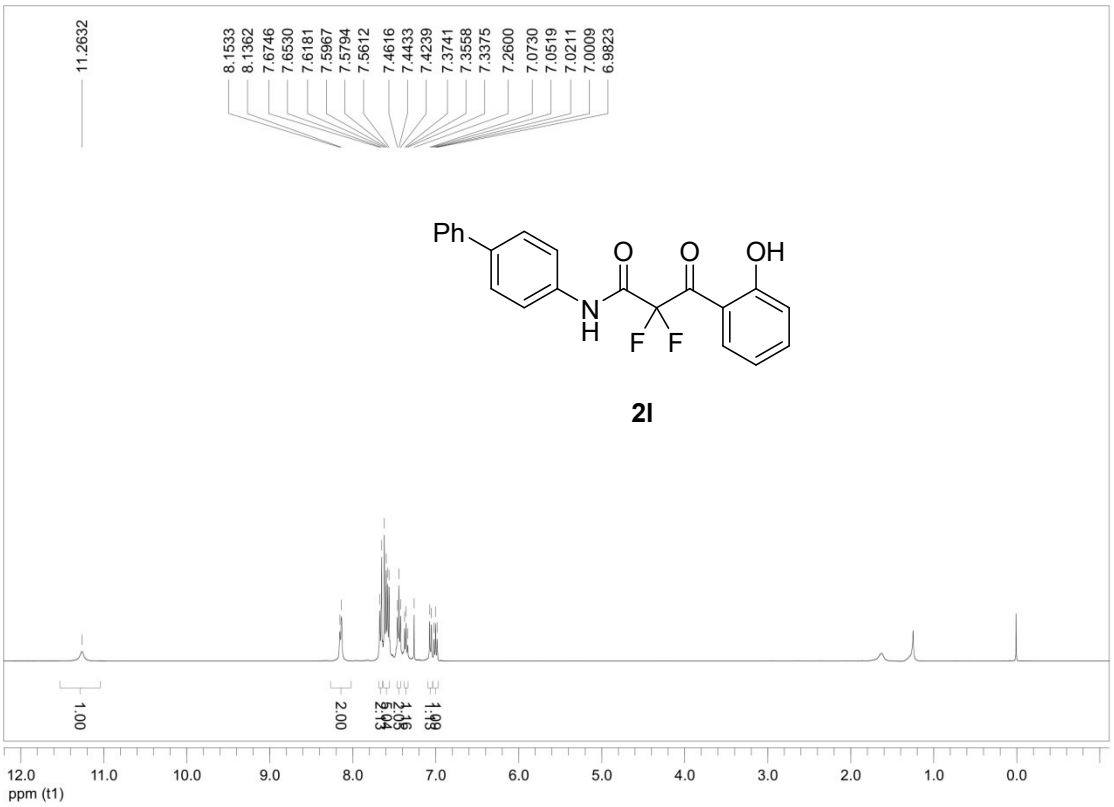


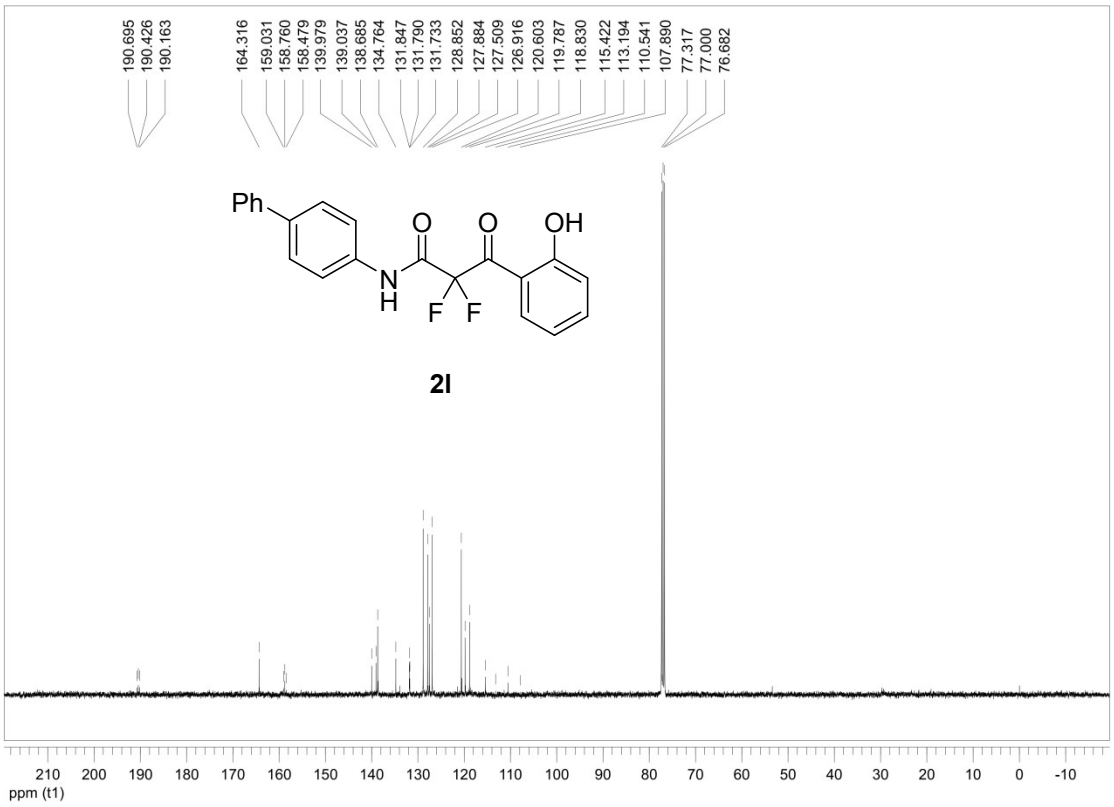
N-(3-bromophenyl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2k)



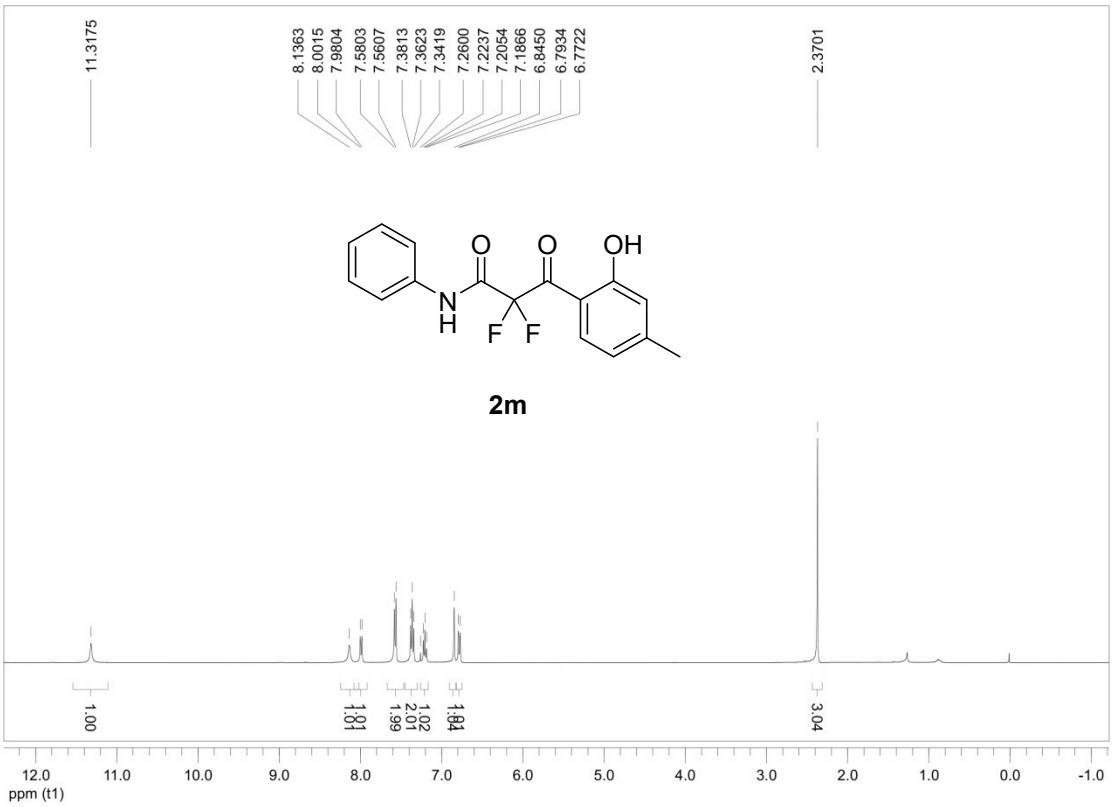


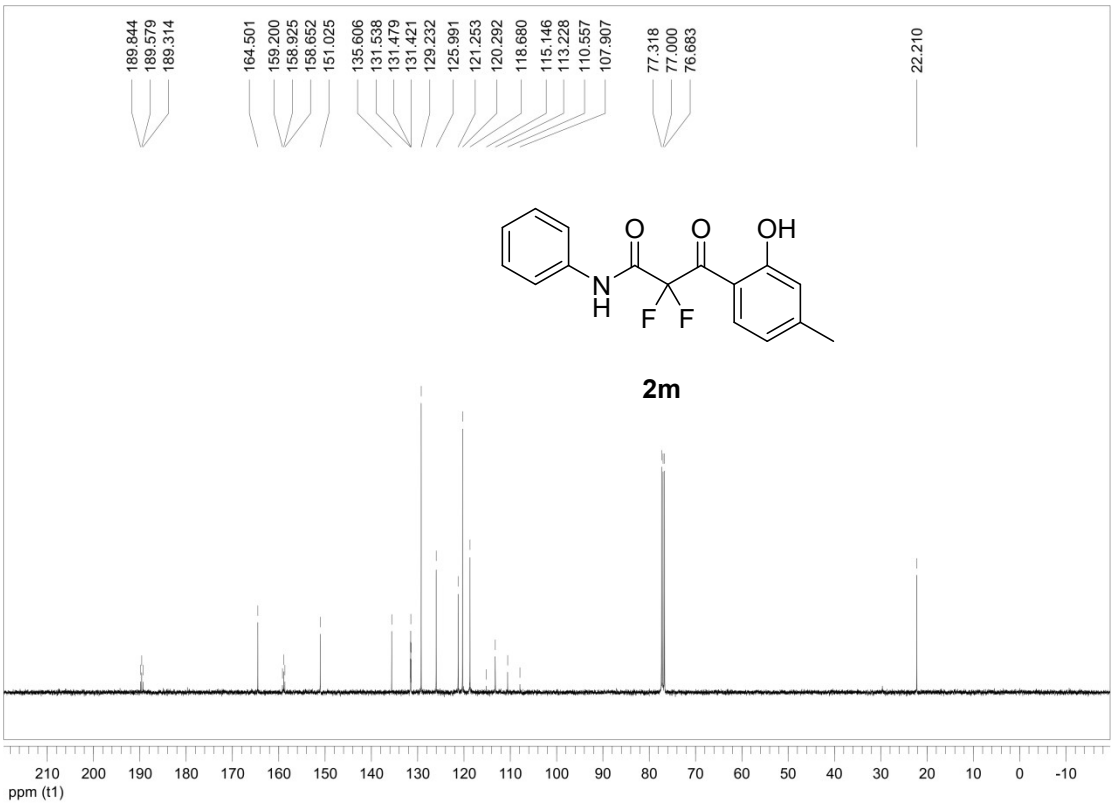
N-([1,1'-biphenyl]-4-yl)-2,2-difluoro-3-(2-hydroxyphenyl)-3-oxopropanamide (2l)



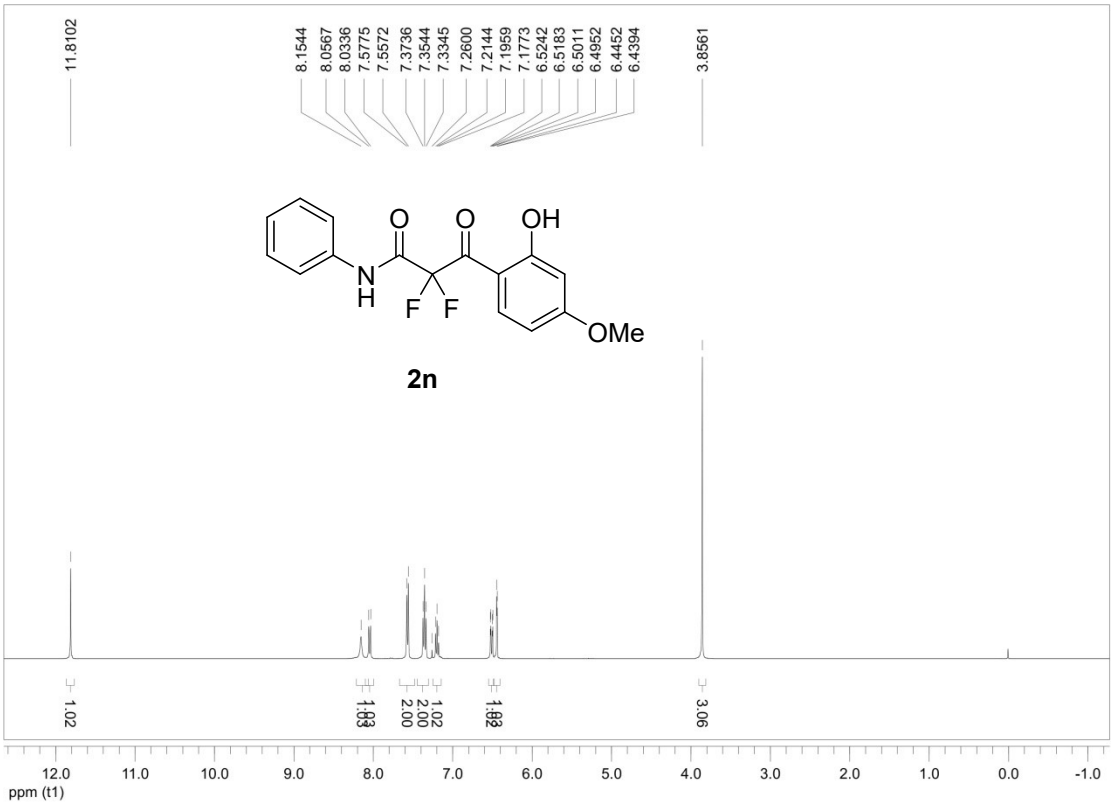


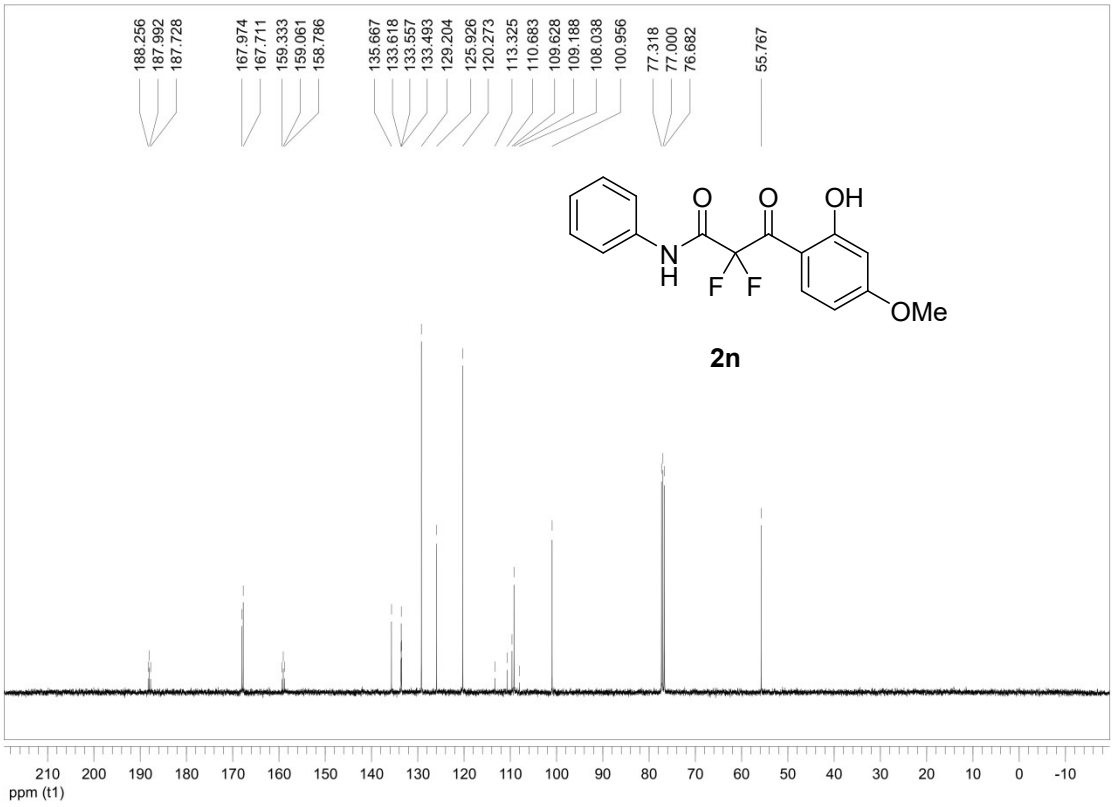
2,2-difluoro-3-(2-hydroxy-4-methylphenyl)-3-oxo-*N*-phenylpropanamide (2m)



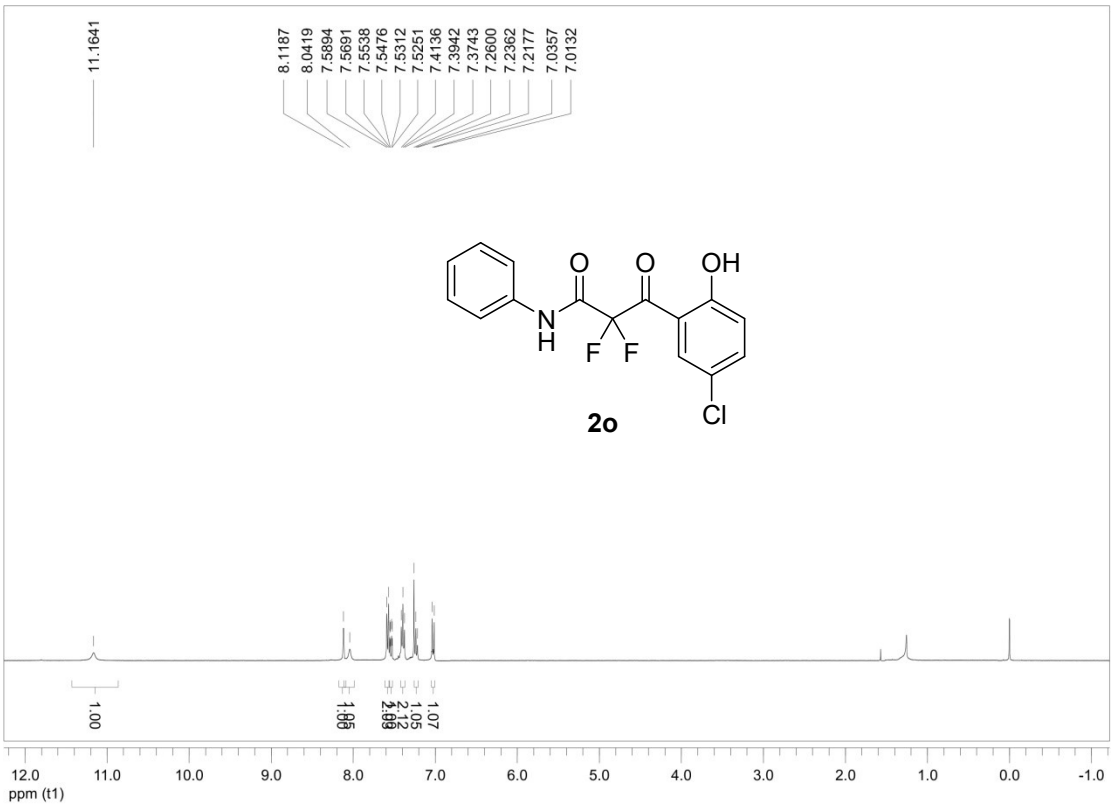


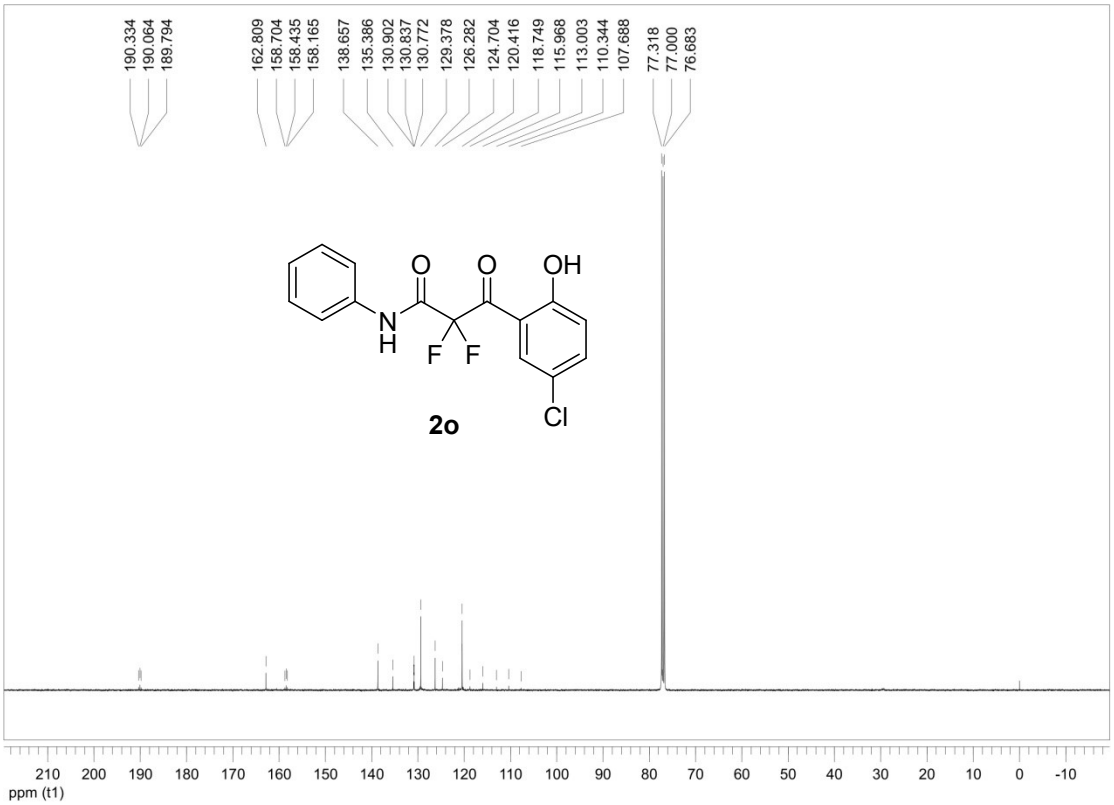
2,2-difluoro-3-(2-hydroxy-4-methoxyphenyl)-3-oxo-*N*-phenylpropanamide (2n)



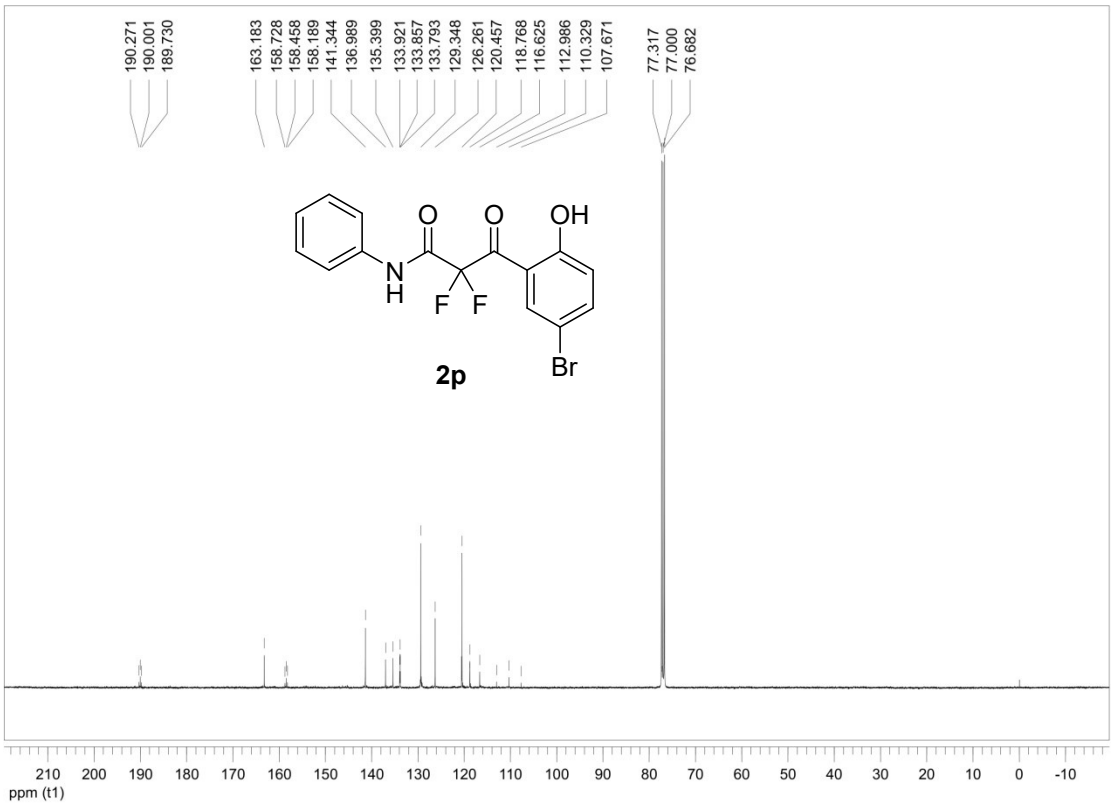


3-(5-chloro-2-hydroxyphenyl)-2,2-difluoro-3-oxo-*N*-phenylpropanamide (2o)

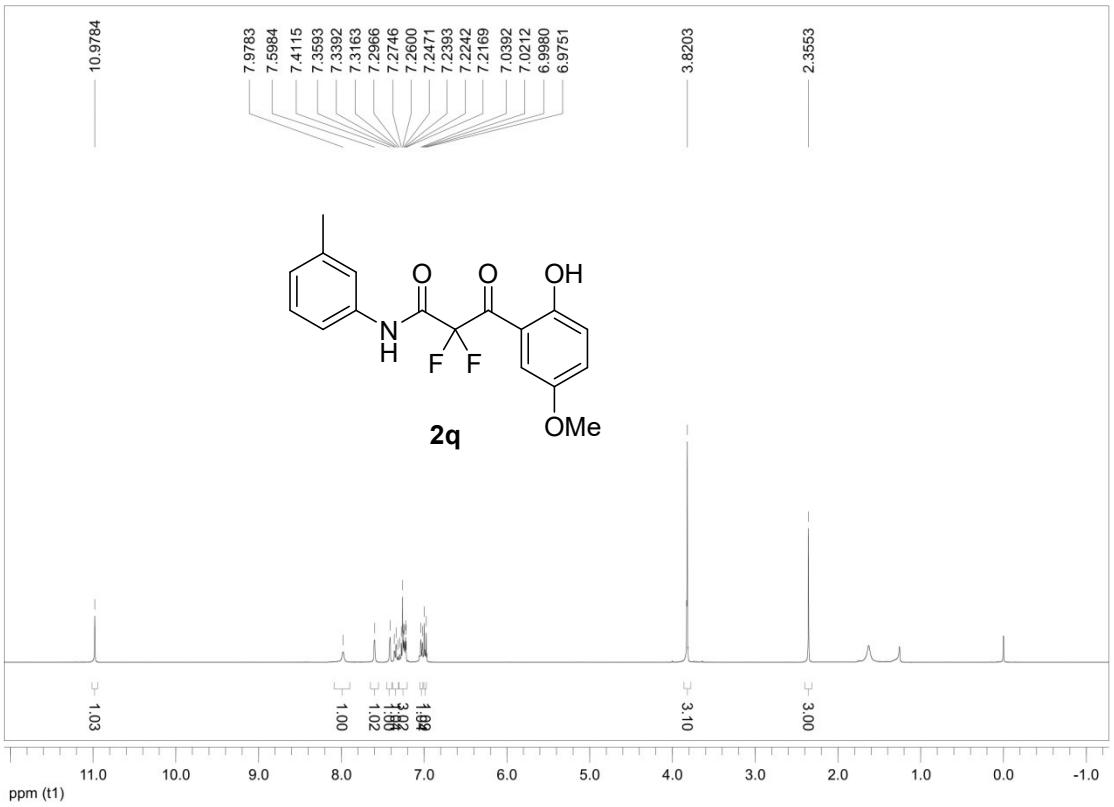


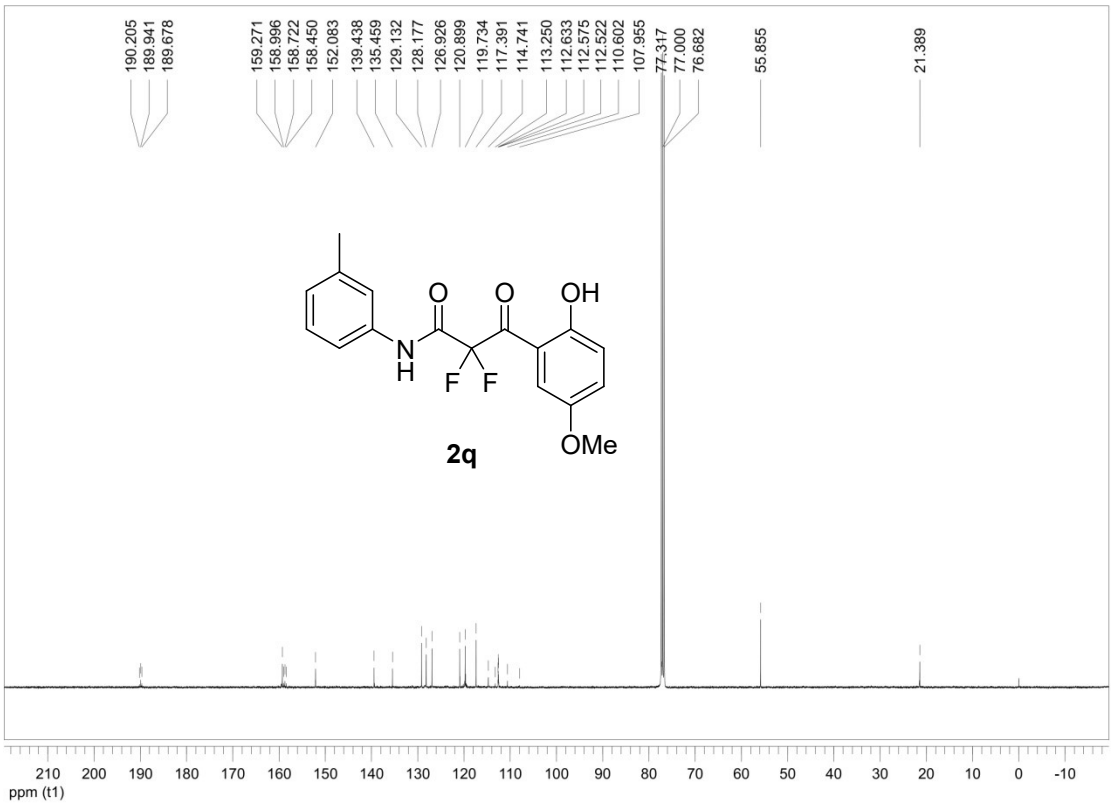


3-(5-bromo-2-hydroxyphenyl)-2,2-difluoro-3-oxo-N-phenylpropanamide (2p)

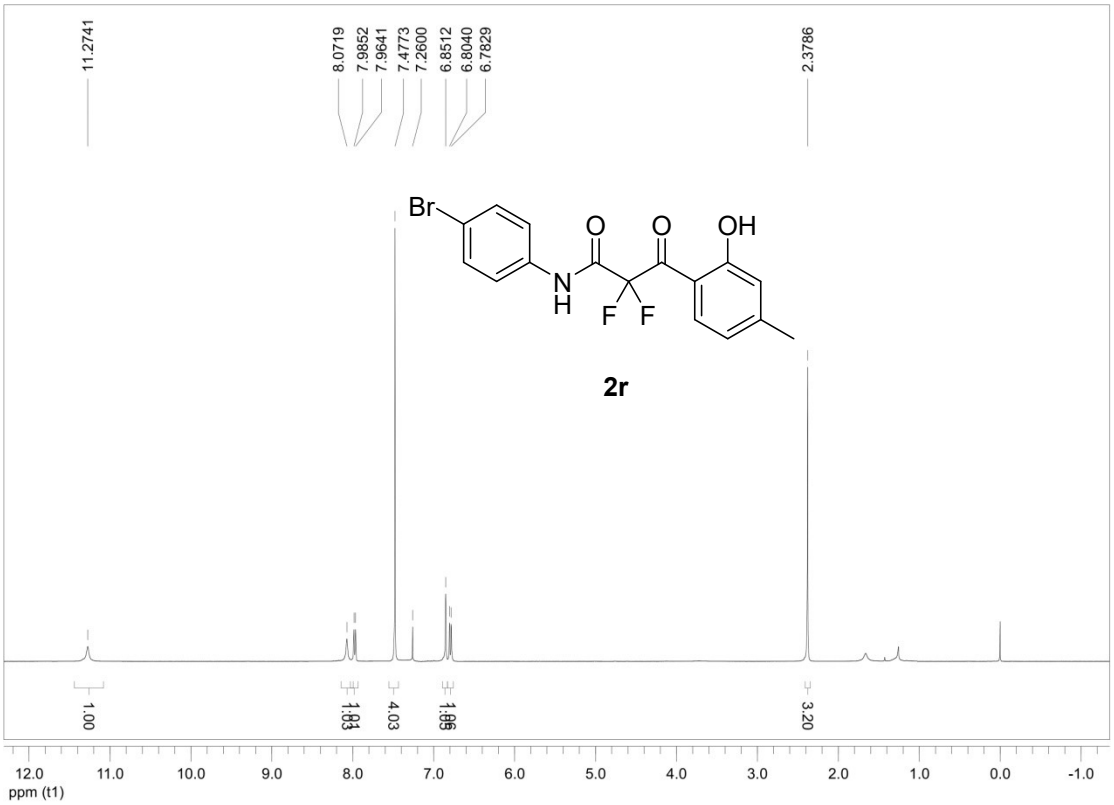


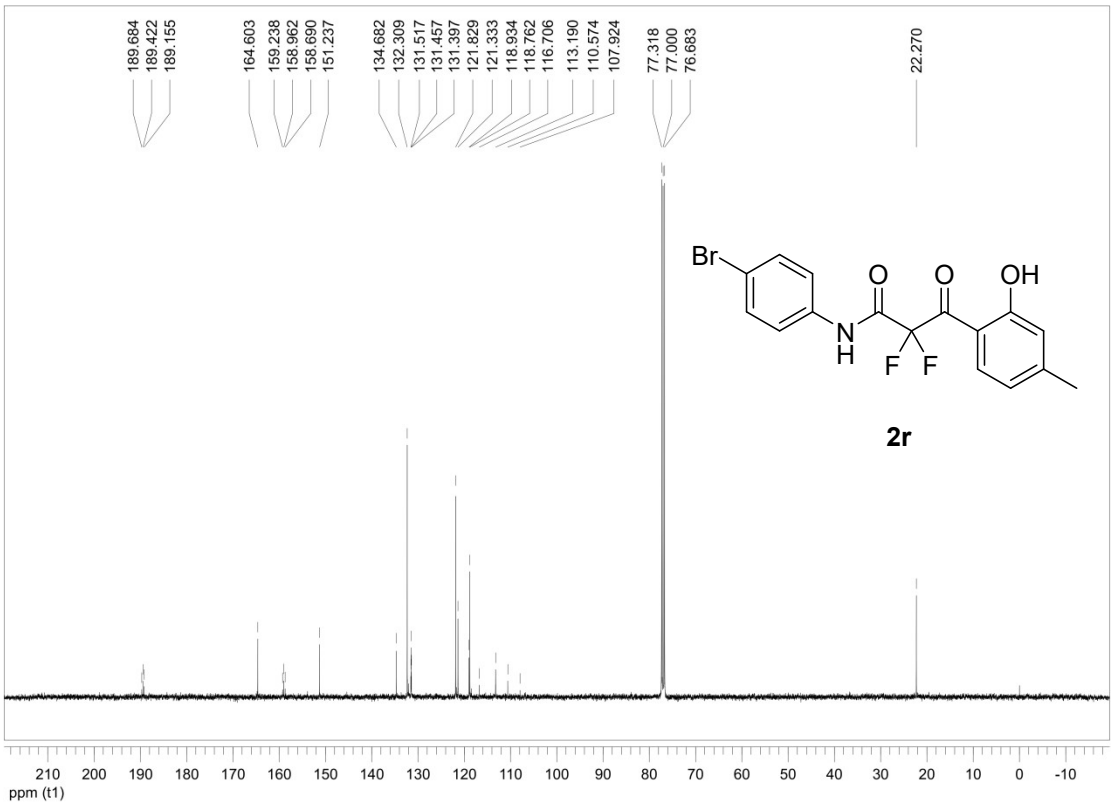
2,2-difluoro-3-(2-hydroxy-5-methoxyphenyl)-3-oxo-*N*-(*m*-tolyl)propanamide (2q)





***N*-(4-bromophenyl)-2,2-difluoro-3-(2-hydroxy-4-methylphenyl)-3-oxopropanamide (2r)**





2,2-difluoro-3-(2-hydroxyphenyl)-3-oxo-*N*-(3-(trifluoromethyl)phenyl)propanamide (2s)