

One-Pot Synthesis of 1,5-Diketones from 3-acetyl-4-Hydroxycoumarin and Effective Cyclization to Unexpected 3, 4-dihydropyridines

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1) General procedure for the synthesis of 1,5-diketone and 3,4-Dihydropyridine

2) ¹H and ¹³C NMR spectra for the compounds prepared

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General remarks

The chemicals were purchased from commercial sources and used without further purification. All reactions were monitored by TLC using pre-coated silica gel aluminum plates. Visualization of TLC plates was accomplished with an UV lamp. The column chromatography was performed using silica gel 60–120 mesh size with EtOAc–hexane as eluent. All products were characterized by NMR, IR HRMS and x-ray spectral data. ^1H and ^{13}C NMR spectra were recorded in deuterated chloroform (CDCl_3) on a 400 MHz and 101 MHz spectrometer respectively. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br).

Crystallographic data of compound **1b**:

Crystal data for ligand **1b** were obtained using a Bruker Kappa Apex Four Circle CCD diffractometer, $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), graphite monochromator, $\text{C}_{29}\text{H}_{29}\text{NO}_7$, monoclinic, space group P-1, $a = 7.7460 (3) \text{ \AA}$, $b = 11.9902 (4) \text{ \AA}$, $c = 12.4618 (4) \text{ \AA}$, $V = 1051.15 (6) \text{ \AA}^3$, $Z = 2$, $D_c = 1.278 \text{ mg/m}^3$, crystal size $0.23 \times 0.23 \times 0.23 \text{ mm}$, $F(000) = 428.0$, $\mu = 0.088 \text{ mm}^{-1}$. Data were collected at $296 (2) \text{ K}$ using ω - 2θ scans in the ranges 1.77 – 28.40° . A total of 5230 reflections were collected, 3082 were unique ($R_{\text{int}} = 0.0762$). The structure was refined by full-matrix least-squares on F^2 . The final refinement [$> 2\sigma(I)$] gave $R_1 = 0.0311$, $wR_2 = 0.2420$.

Crystallographic data of compound **1b** have been deposited at the Cambridge Crystallographic Data Center with deposition number: CCDC 1816147. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic data of compound **2a**:

Crystal data for ligand **2a** were obtained using a Bruker Kappa Apex Four Circle CCD diffractometer, $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), graphite monochromator, $\text{C}_{29}\text{H}_{29}\text{NO}_7$,

monoclinic, space group P-1, $a = 8.0151(4) \text{ \AA}$, $b = 11.4152(5) \text{ \AA}$, $c = 12.7980(6) \text{ \AA}$, $V = 1109.52(9) \text{ \AA}^3$, $Z = 2$, $D_c = 1.235 \text{ mg/m}^3$, crystal size $0.23 \times 0.23 \times 0.23 \text{ mm}$, $F(000) = 436$, $\mu = 0.081 \text{ mm}^{-1}$. Data were collected at $296(2) \text{ K}$ using ω - 2θ scans in the ranges 1.67 - 28.34° . A total of 5535 reflections were collected, 2545 were unique ($R_{\text{int}} = 0.0701$). The structure was refined by full-matrix least-squares on F^2 . The final refinement [$>2\sigma(I)$] gave $R_1 = 0.0418$, $wR_2 = 0.2155$.

Crystallographic data of compound **2a** have been deposited at the Cambridge Crystallographic Data Center with deposition number: CCDC 1814354. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the synthesis of 1, 5 diketones (1a-1q):

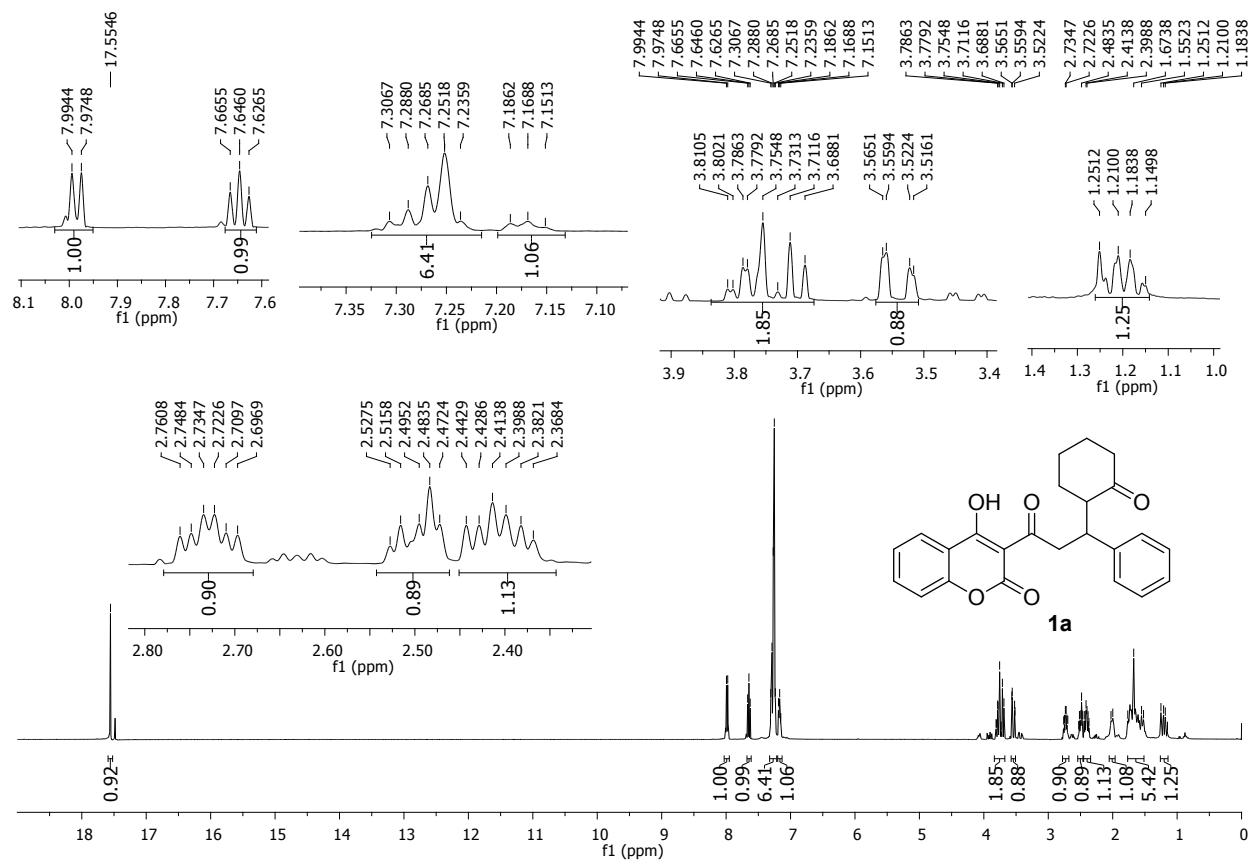
A mixture of 3-Acetyl 4-Hydroxycoumarin (1 mmol), aromatic aldehyde (1 mmol), and L-Proline (10 mol %) in ethanol (5 ml) was refluxed for 6-8 hours. After completion of starting materials (monitor by TLC), cyclohexanone/cyclopentanone (1.2 mmol) was added to the reaction mixture and remaining solution was refluxed. After completion of starting materials as monitor by TLC, solvent was removed under pressure. Water (10 ml) was added to the reaction mixture and extracted with ethyl acetate (3 x 10 ml). The combined organic layer was dried with anhyd. Na_2SO_4 and the solvent was concentrated in vacuum to obtain a light yellow solids. The residue was purified by silica gel column chromatography (5-10% EtOAc in hexane) to afford the corresponding pure products.

General procedure for the synthesis of 3,4-dihydropyridine (2a-2n):

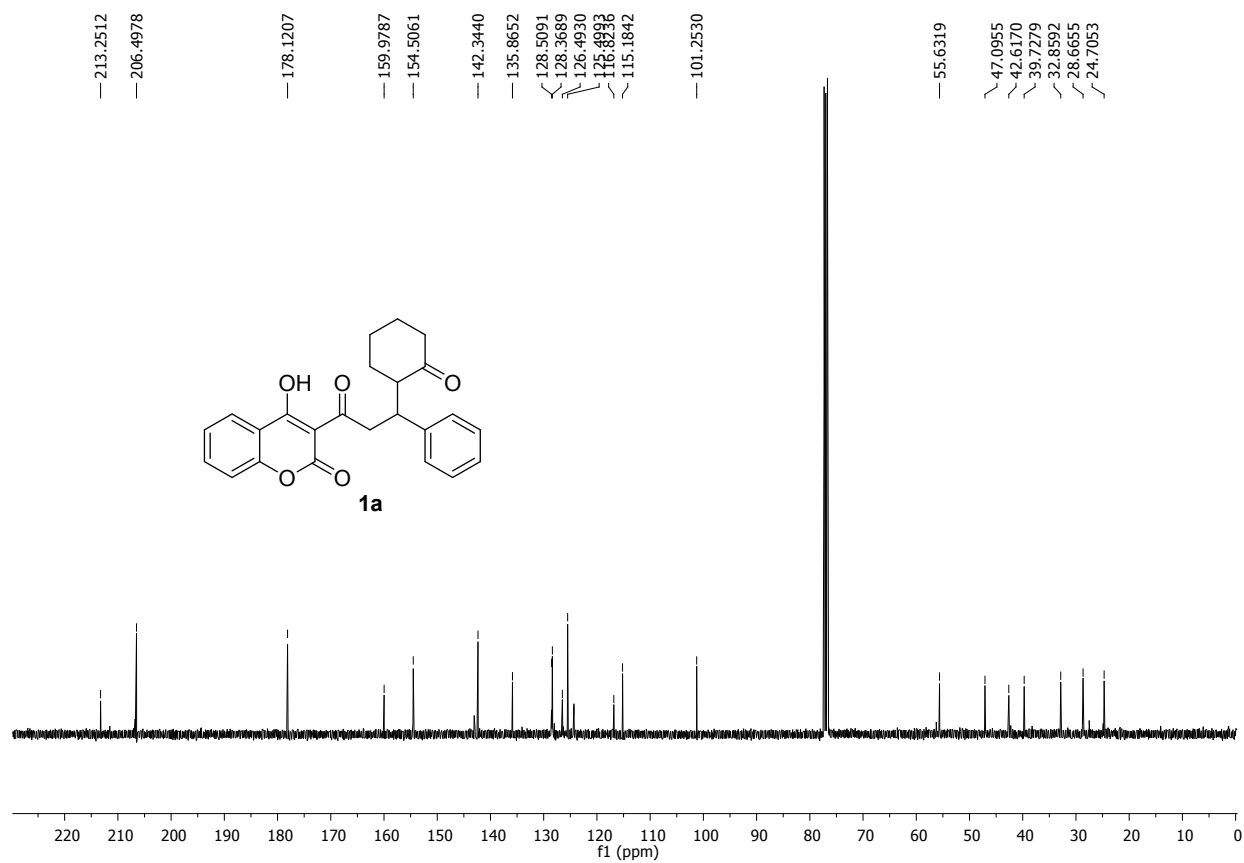
A mixture of 1, 5 diketones (0.5 mmol) and ammonium acetate (1 mmol) in acetic acid (5 ml) was refluxed for one hour. After completion of starting materials as monitor by TLC, mixture was cooled at room temperature. Resultant cooled mixture was poured in ice cooled water gave yellow precipitate. Precipitate was collected by filtration and purified by silica gel column chromatography (5-10% EtOAc in hexane) to afford the corresponding pure products.

SPECTRA

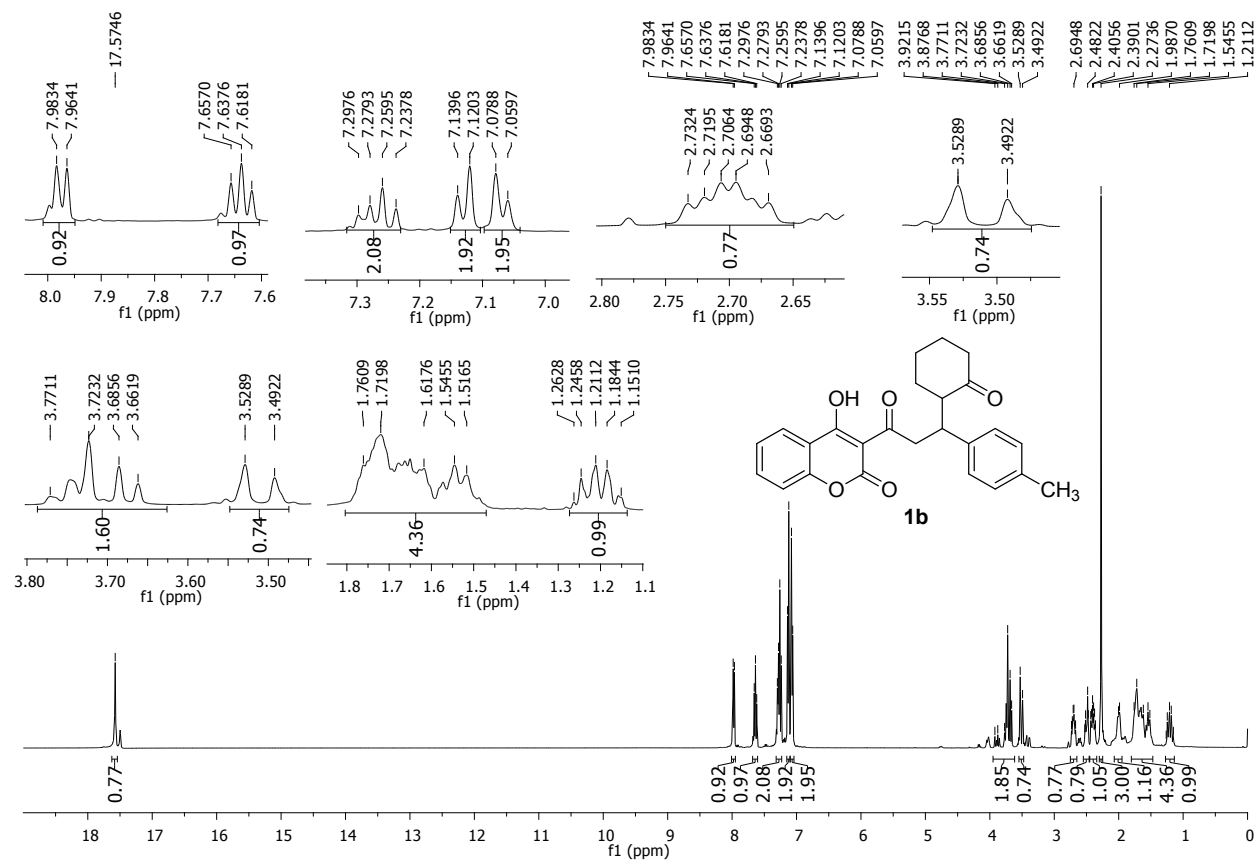
4-hydroxy-3-(3-(2-oxocyclohexyl)-3-phenylpropanoyl)-2H-chromen-2-one (1a): ¹H NMR



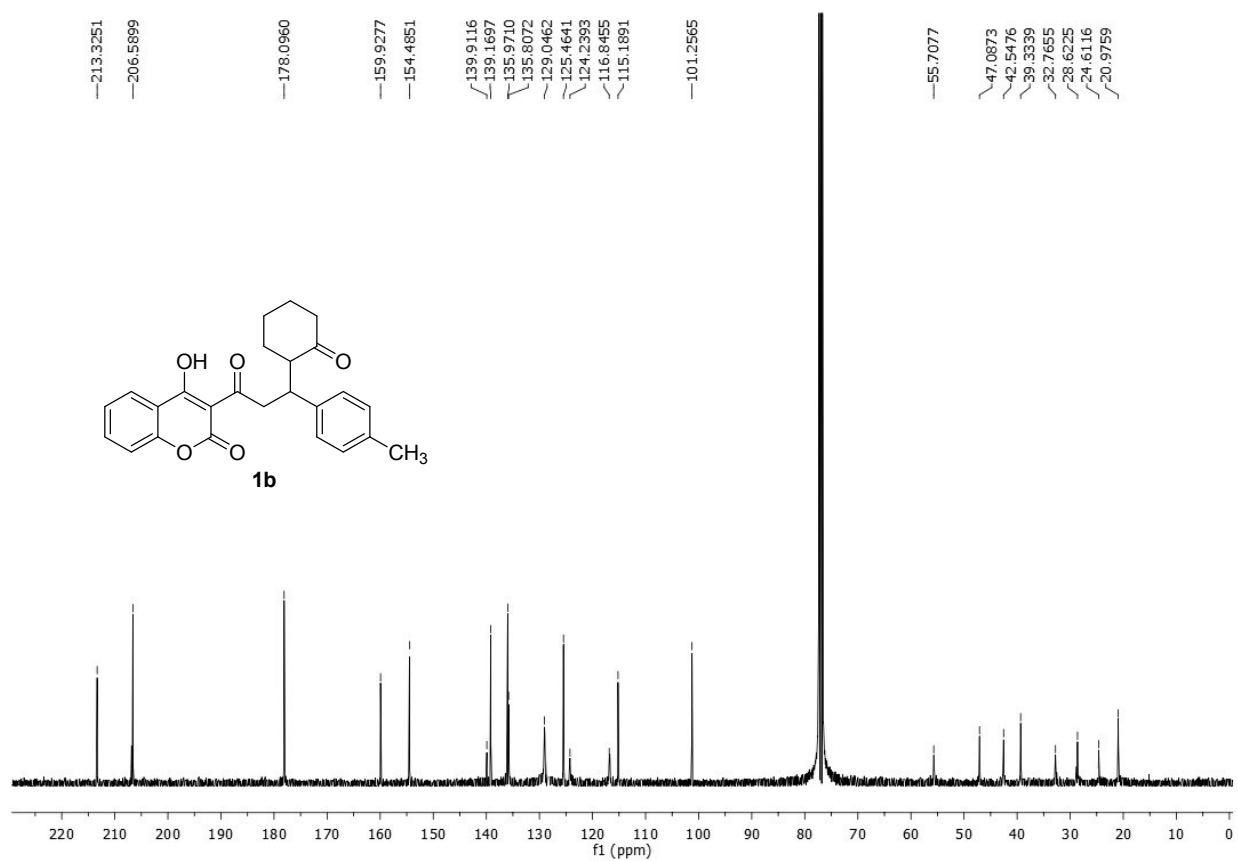
4-hydroxy-3-(3-(2-oxocyclohexyl)-3-phenylpropanoyl)-2H-chromen-2-one (1a): ^{13}C NMR



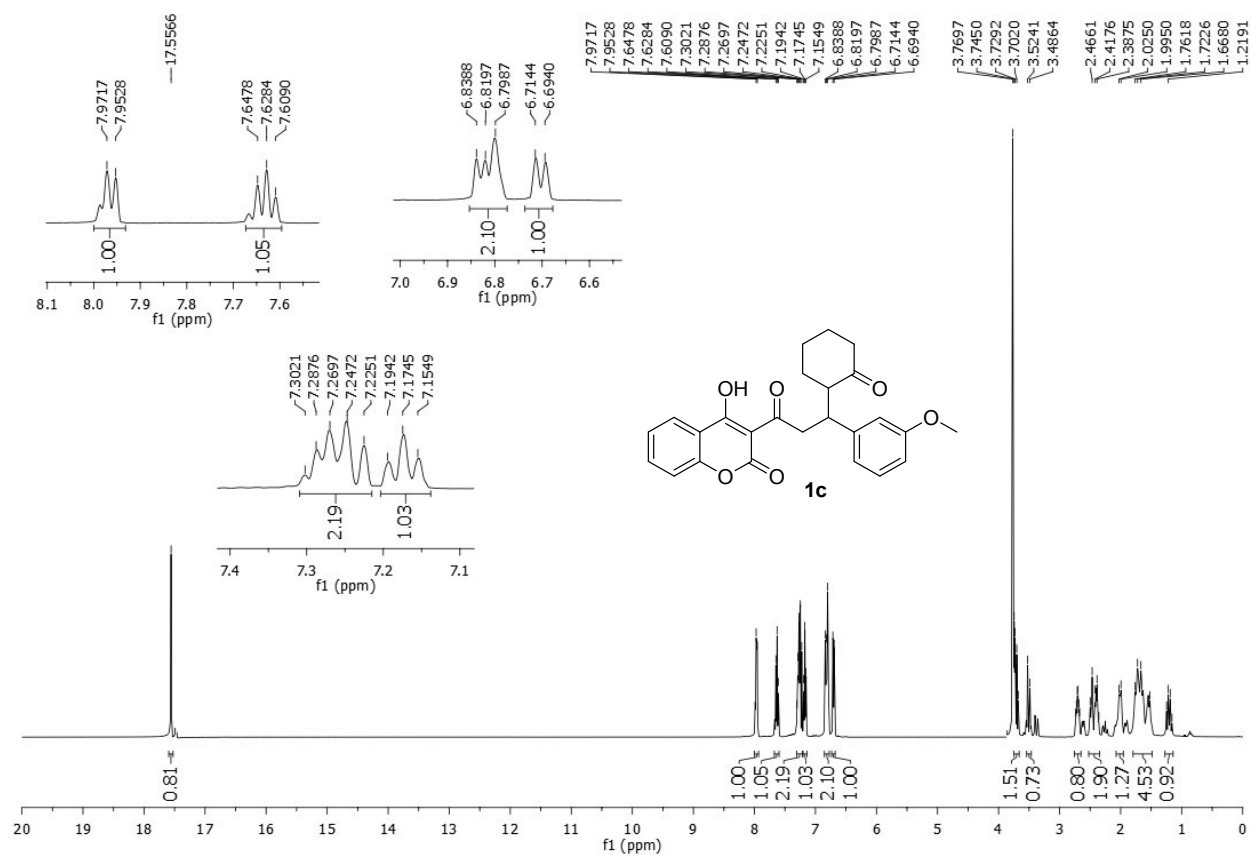
4-hydroxy-3-(3-(2-oxocyclohexyl)-3-(p-tolyl)propanoyl)-2H-chromen-2-one (1b): ^1H NMR



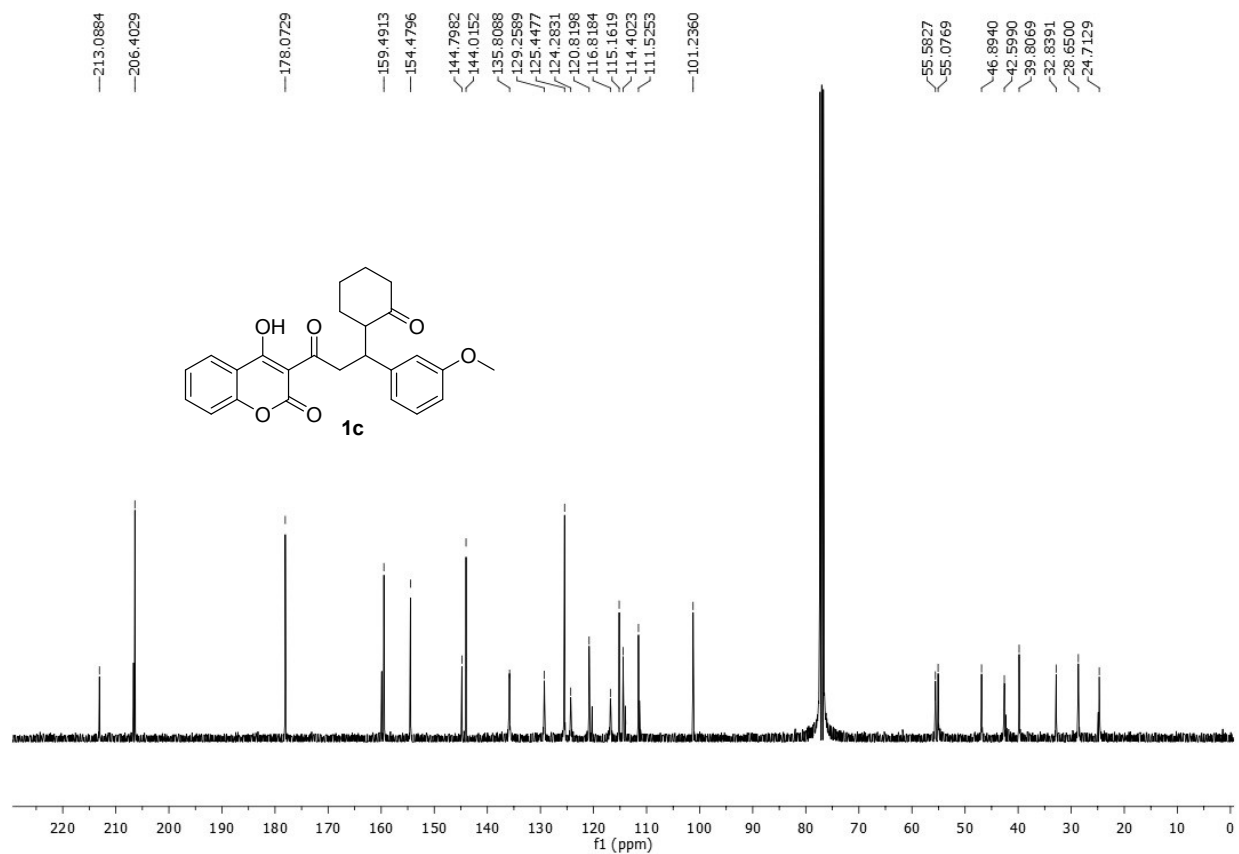
4-hydroxy-3-(3-(2-oxocyclohexyl)-3-(p-tolyl)propanoyl)-2H-chromen-2-one (1b): ^{13}C NMR



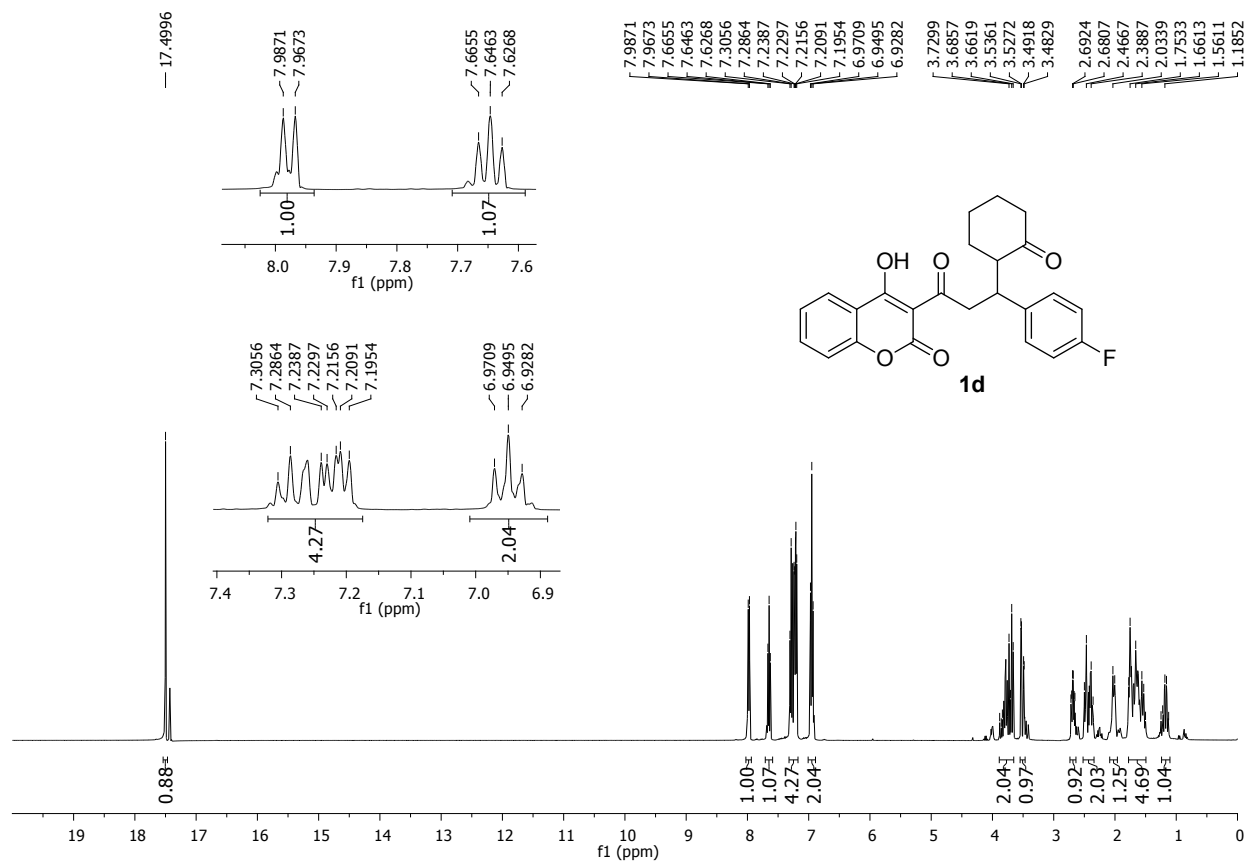
4-hydroxy-3-(3-(3-methoxyphenyl)-3-(2-oxocyclohexyl)propanoyl)-2H-chromen-2-one (1c):
¹H NMR



4-hydroxy-3-(3-(3-methoxyphenyl)-3-(2-oxocyclohexyl)propanoyl)-2H-chromen-2-one (1c):
¹³C NMR

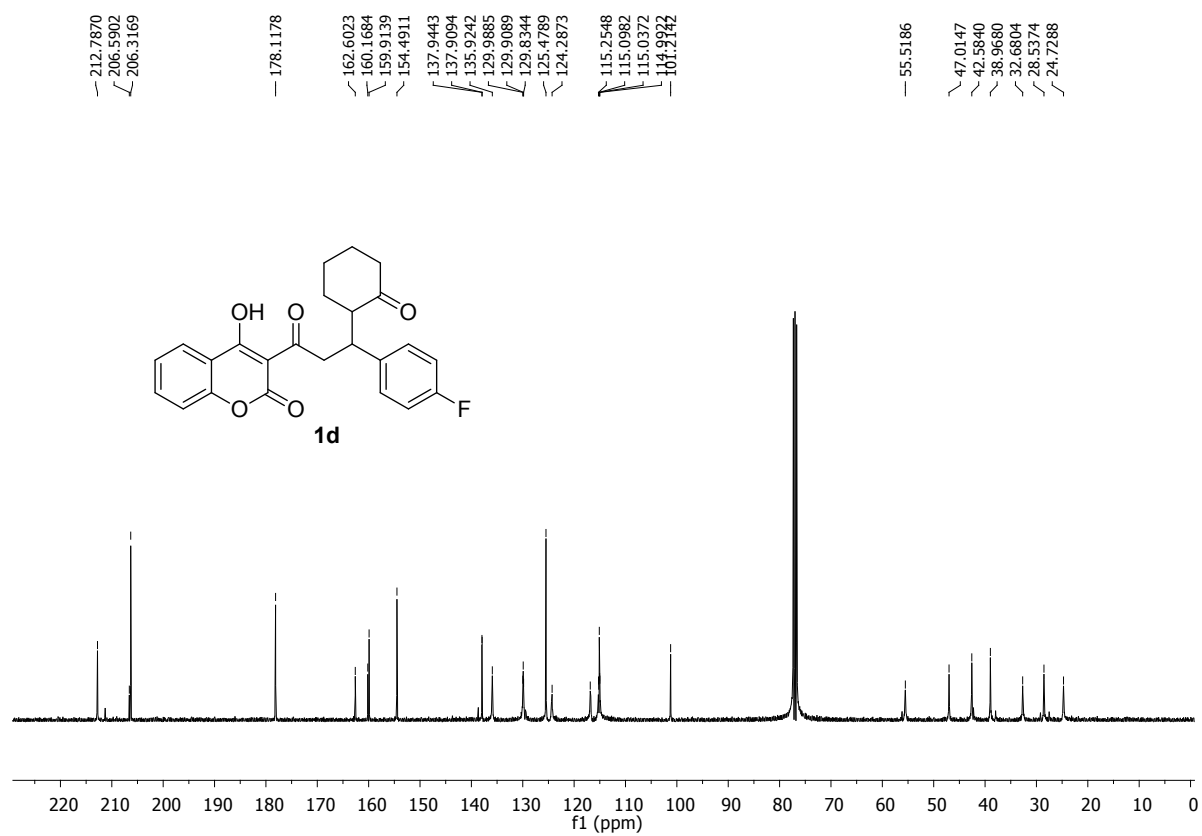


**3-(3-(4-fluorophenyl)-3-(2-oxocyclohexyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1d):
¹H NMR**



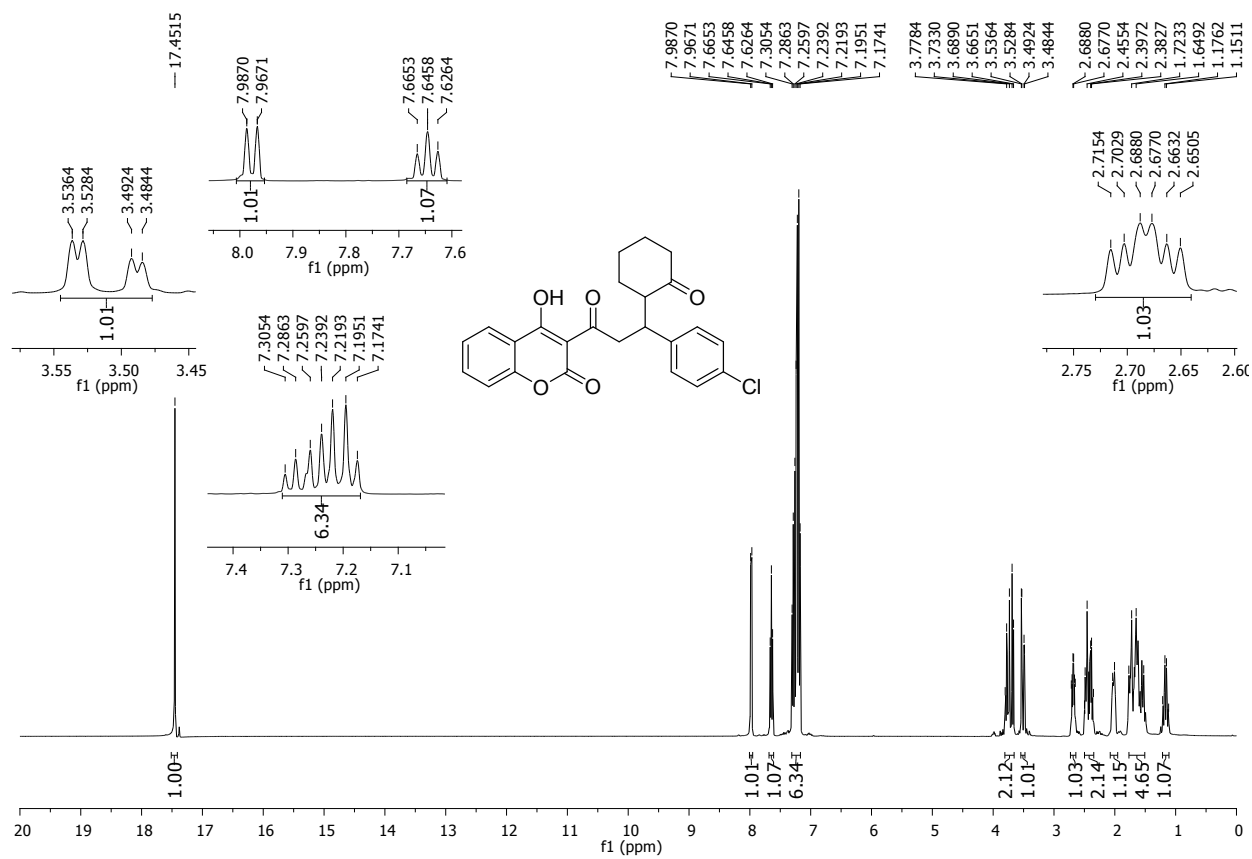
3-(3-(4-fluorophenyl)-3-(2-oxocyclohexyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1d):

¹³C NMR



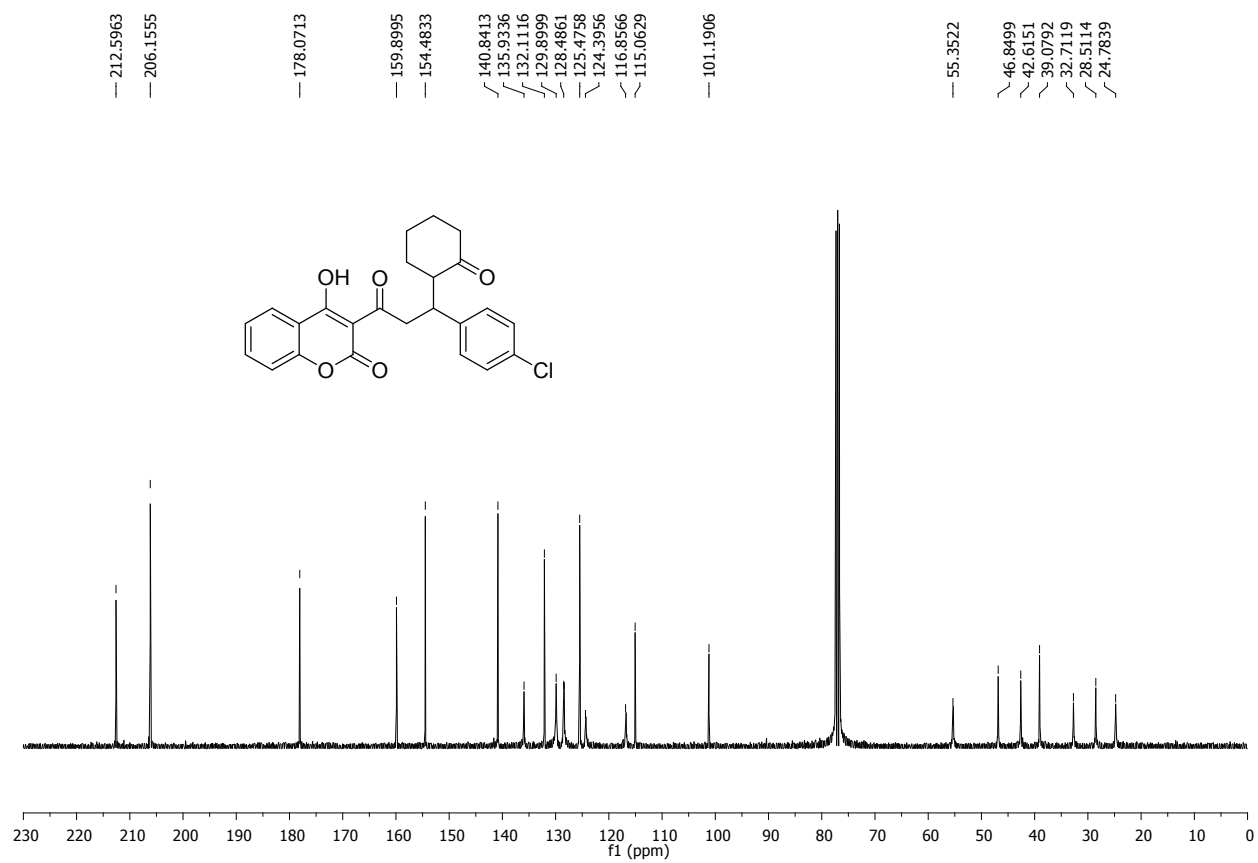
3-(3-(4-chlorophenyl)-3-(2-oxocyclohexyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1e):

¹H NMR

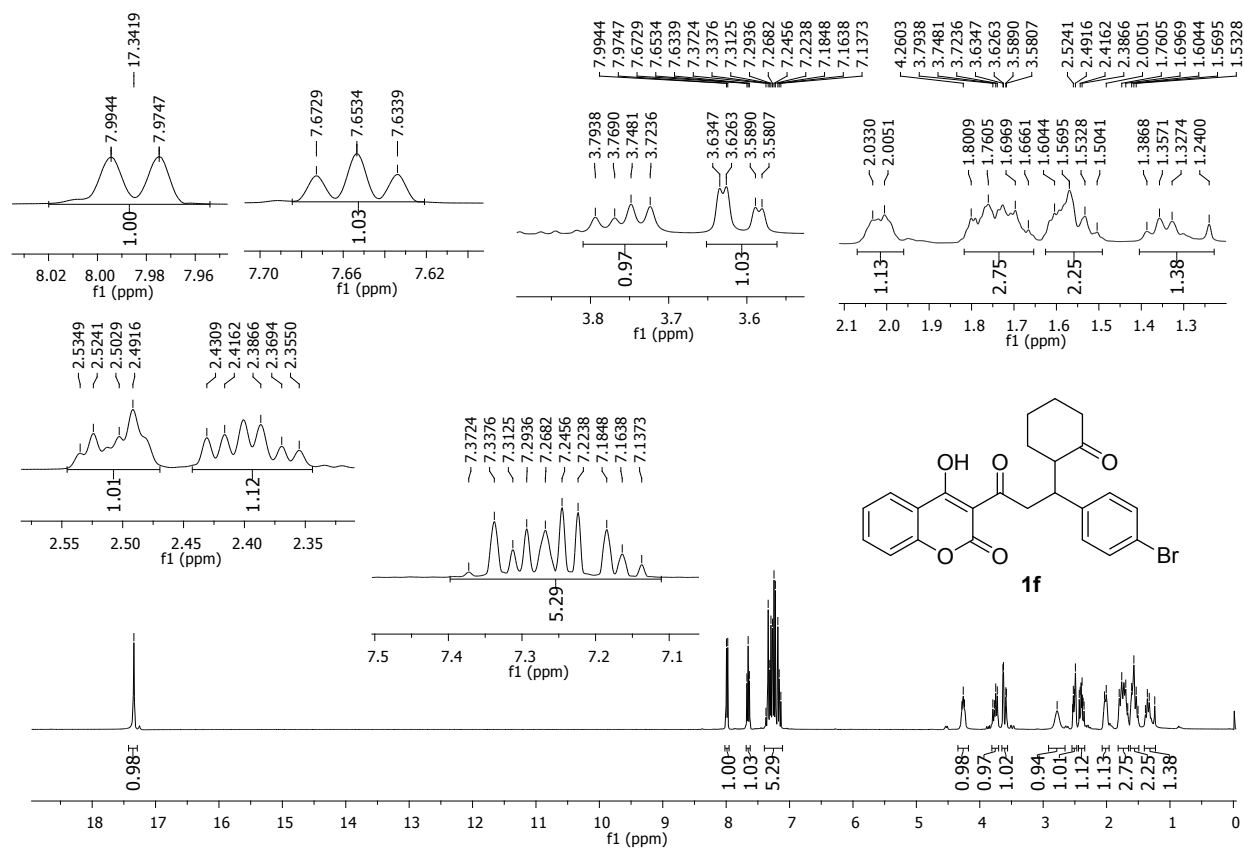


3-(3-(4-chlorophenyl)-3-(2-oxocyclohexyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1e):

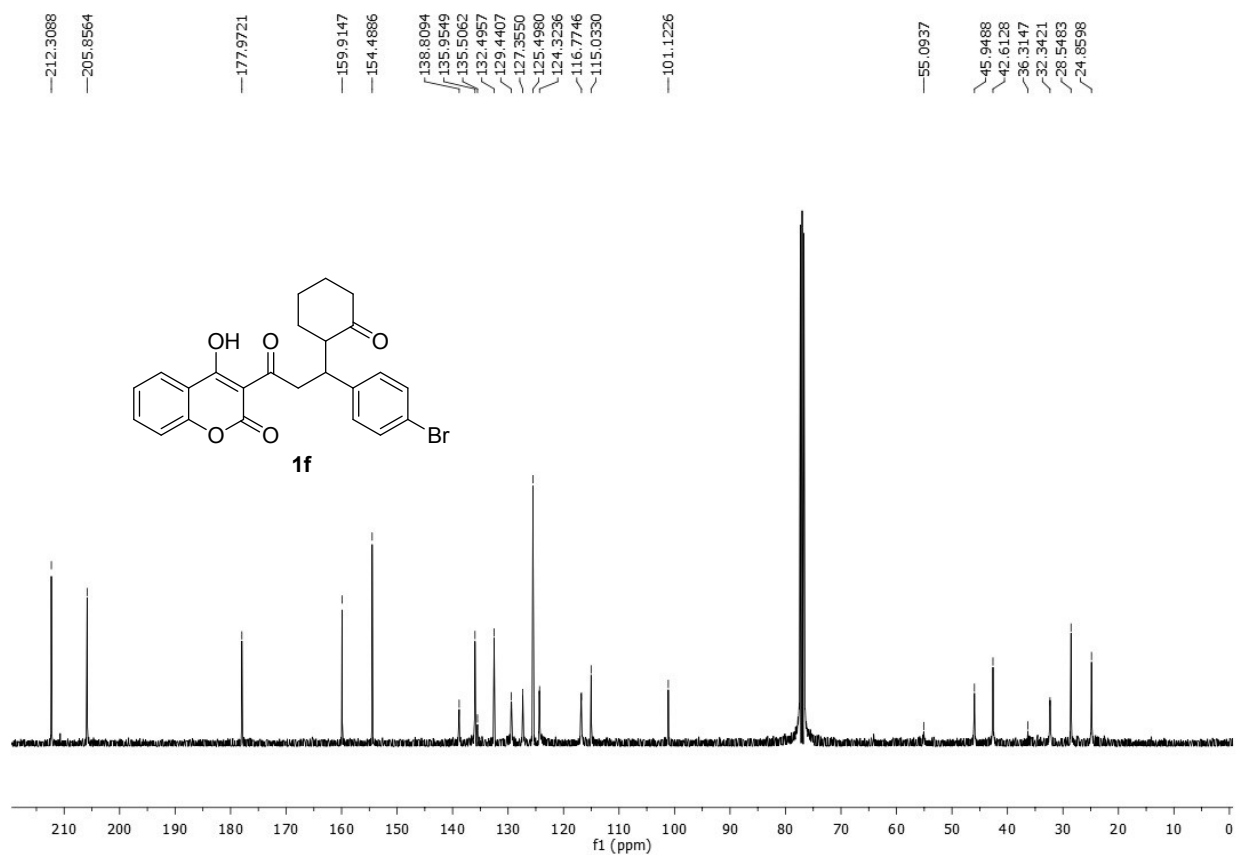
¹³C NMR



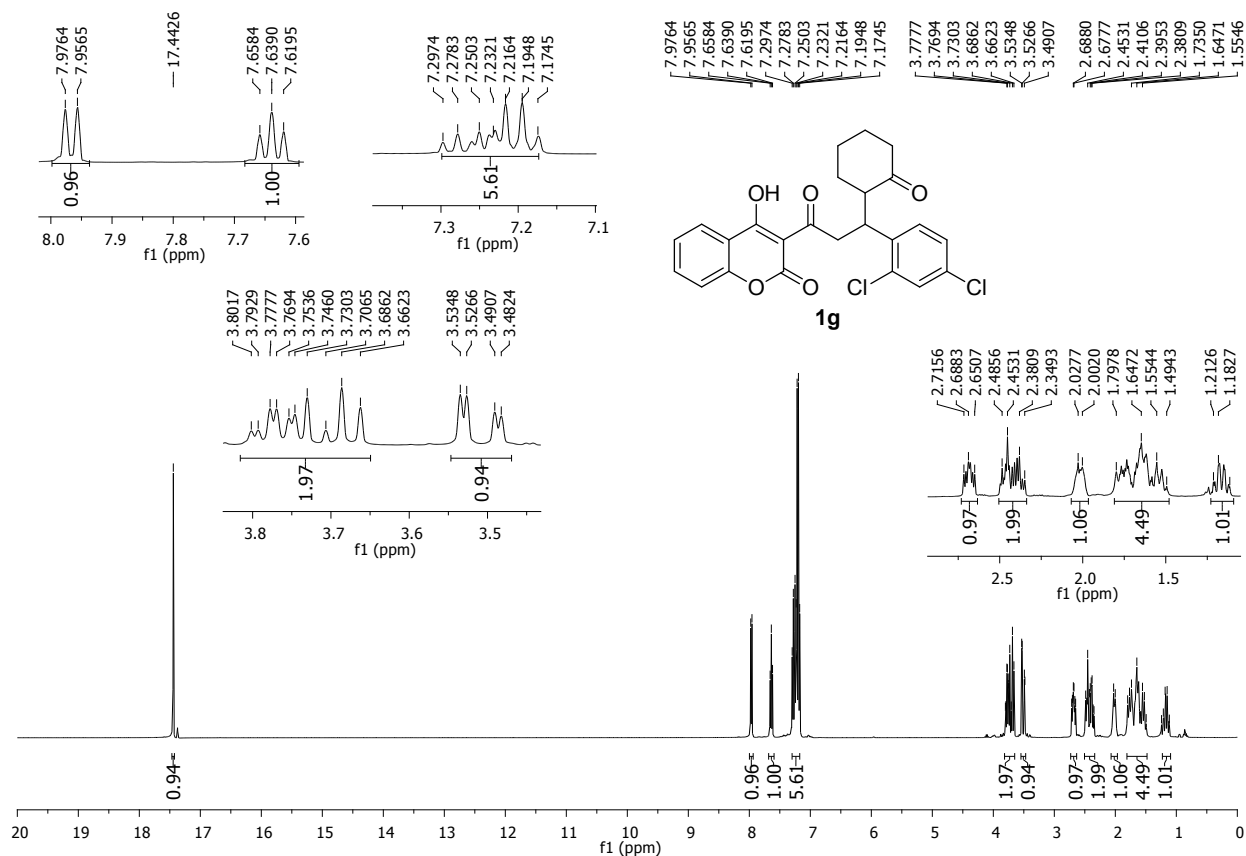
**3-(3-(4-bromophenyl)-3-(2-oxocyclohexyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1f):
¹H NMR**



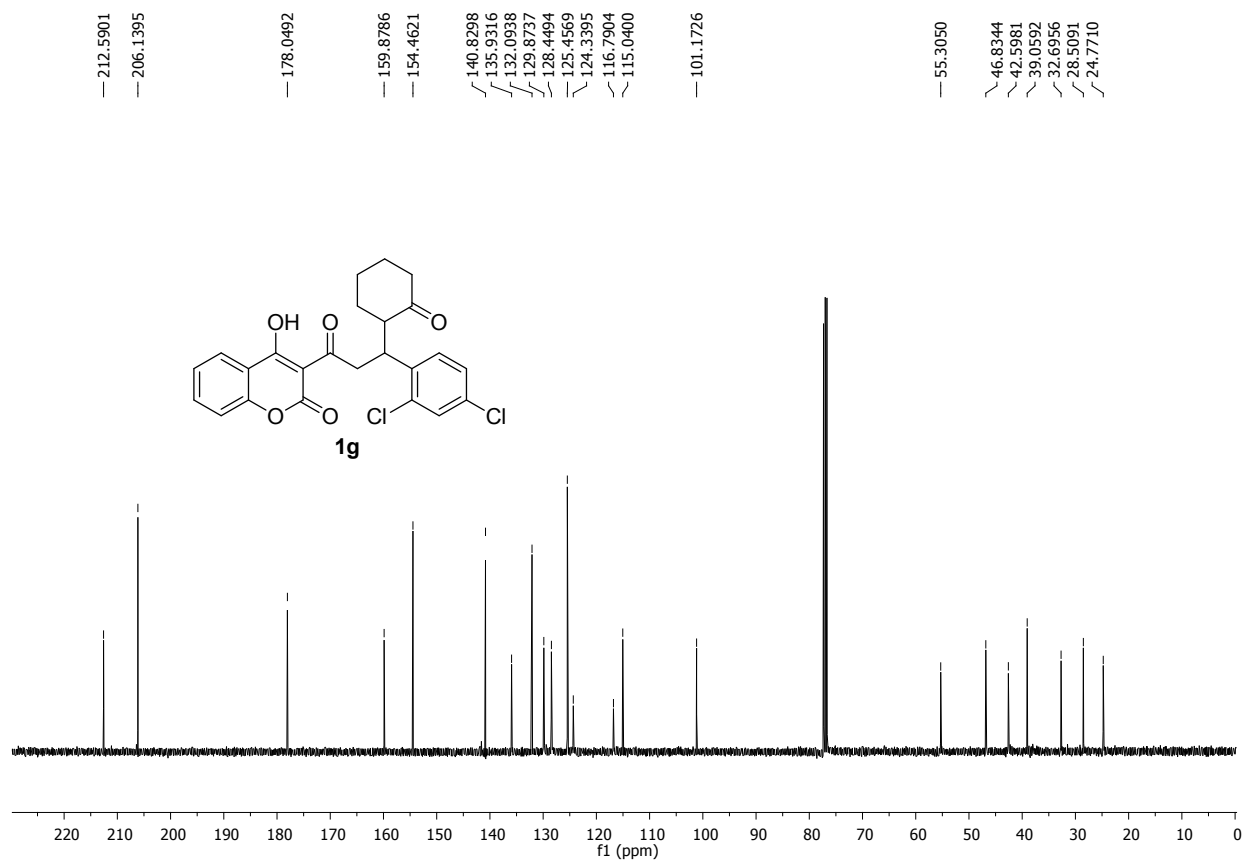
3-(3-(4-bromophenyl)-3-(2-oxocyclohexyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1f):
¹³C NMR



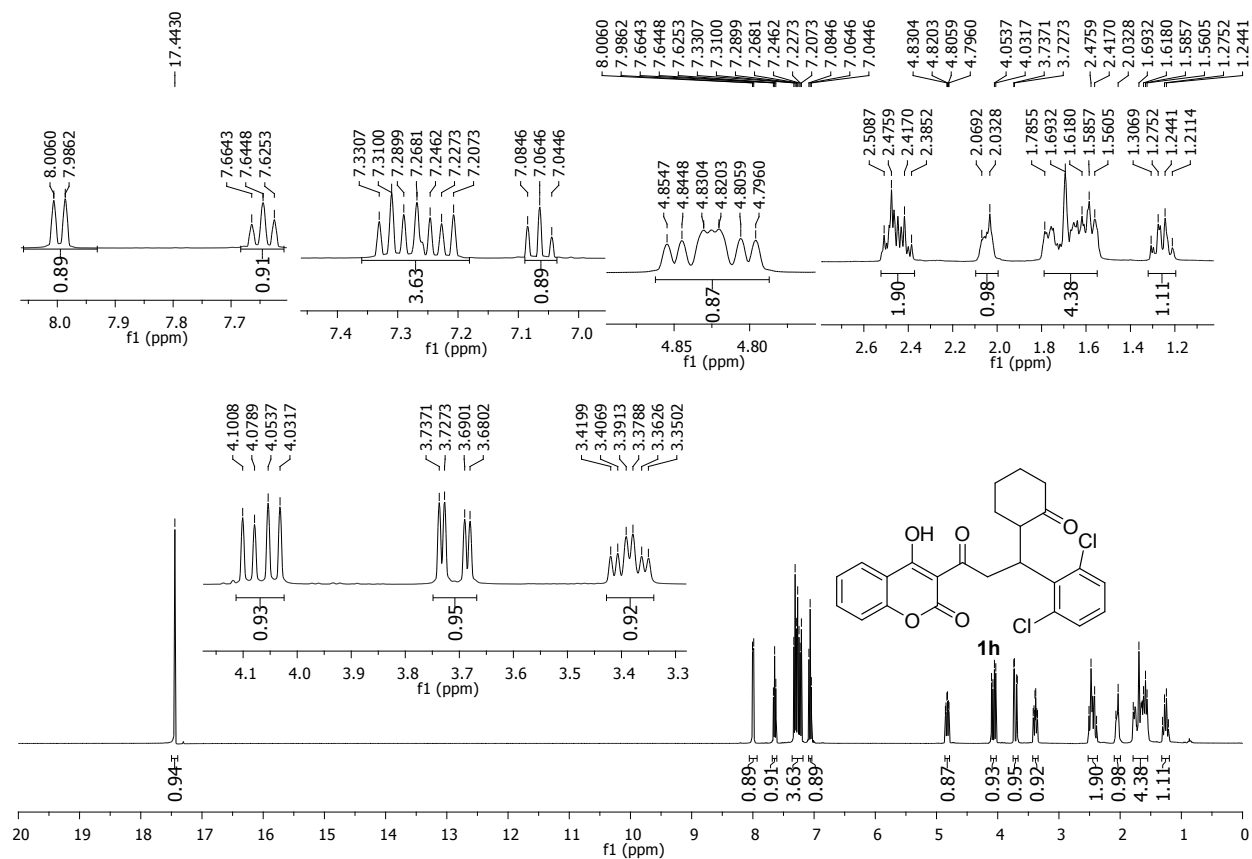
3-(3-(2,4-dichlorophenyl)-3-(2-oxocyclohexyl)propanoyl)-4-hydroxy-2H-chromen-2-one
(1g): ^1H NMR



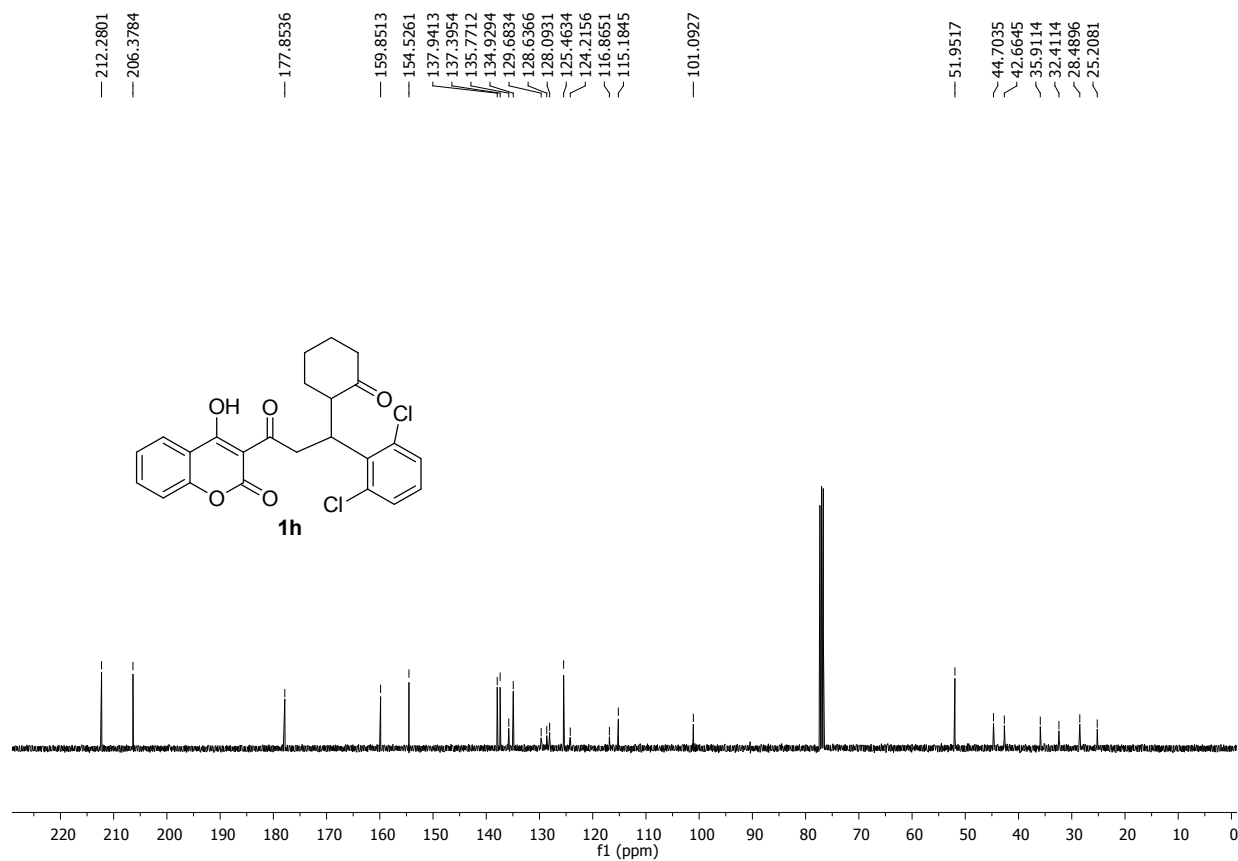
**3-(3-(2,4-dichlorophenyl)-3-(2-oxocyclohexyl)propanoyl)-4-hydroxy-2H-chromen-2-one
(1g): ^{13}C NMR**



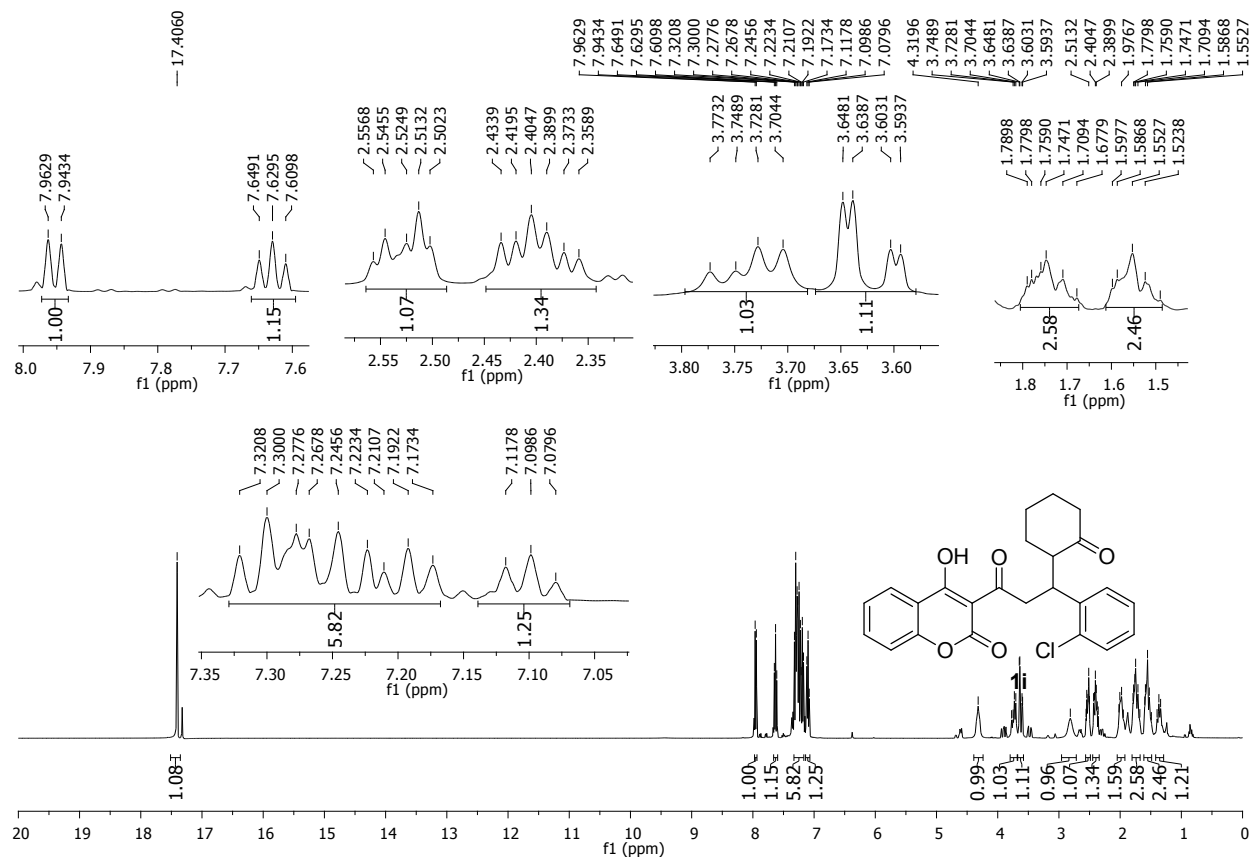
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(1h): ^1H NMR



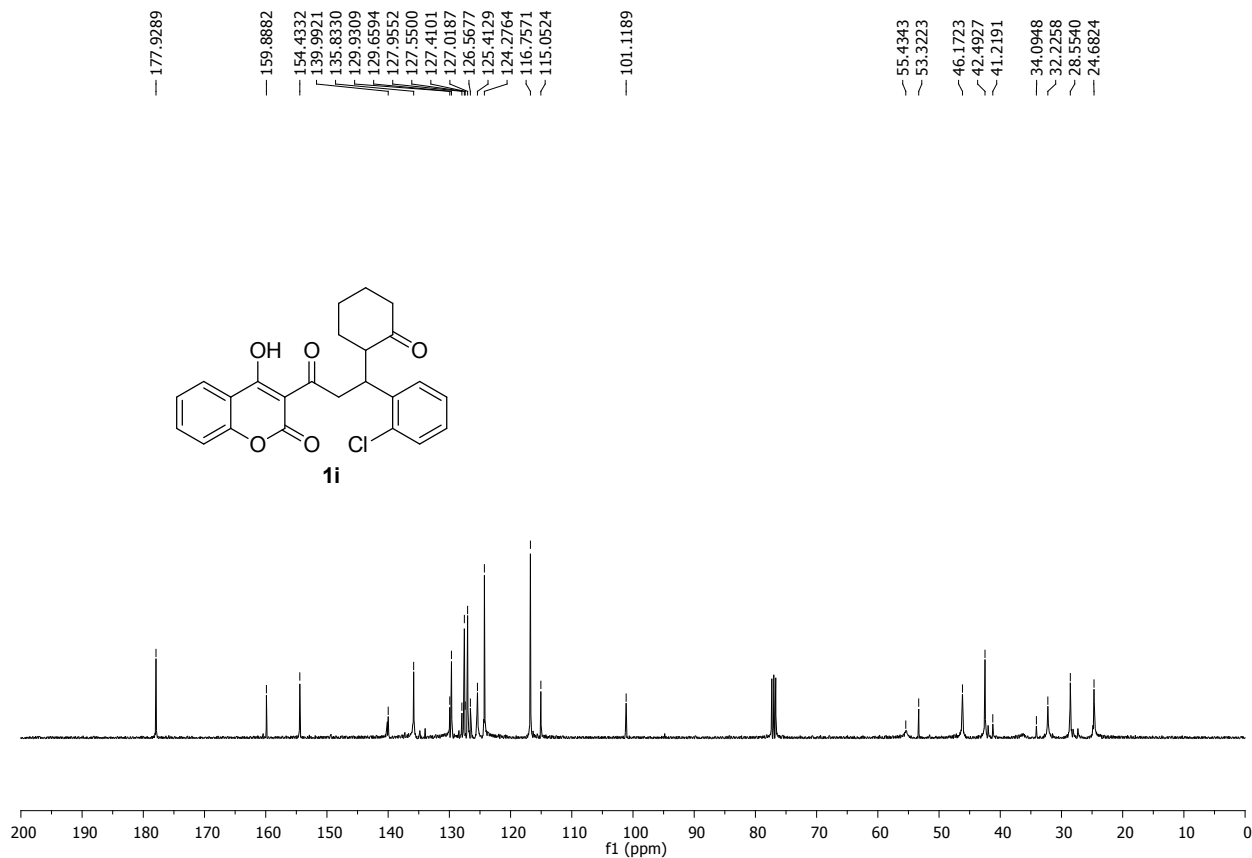
**3-(3-(2,6-dichlorophenyl)-3-(2-oxocyclohexyl)propanoyl)-4-hydroxy-2H-chromen-2-one
(1h): ^{13}C NMR**



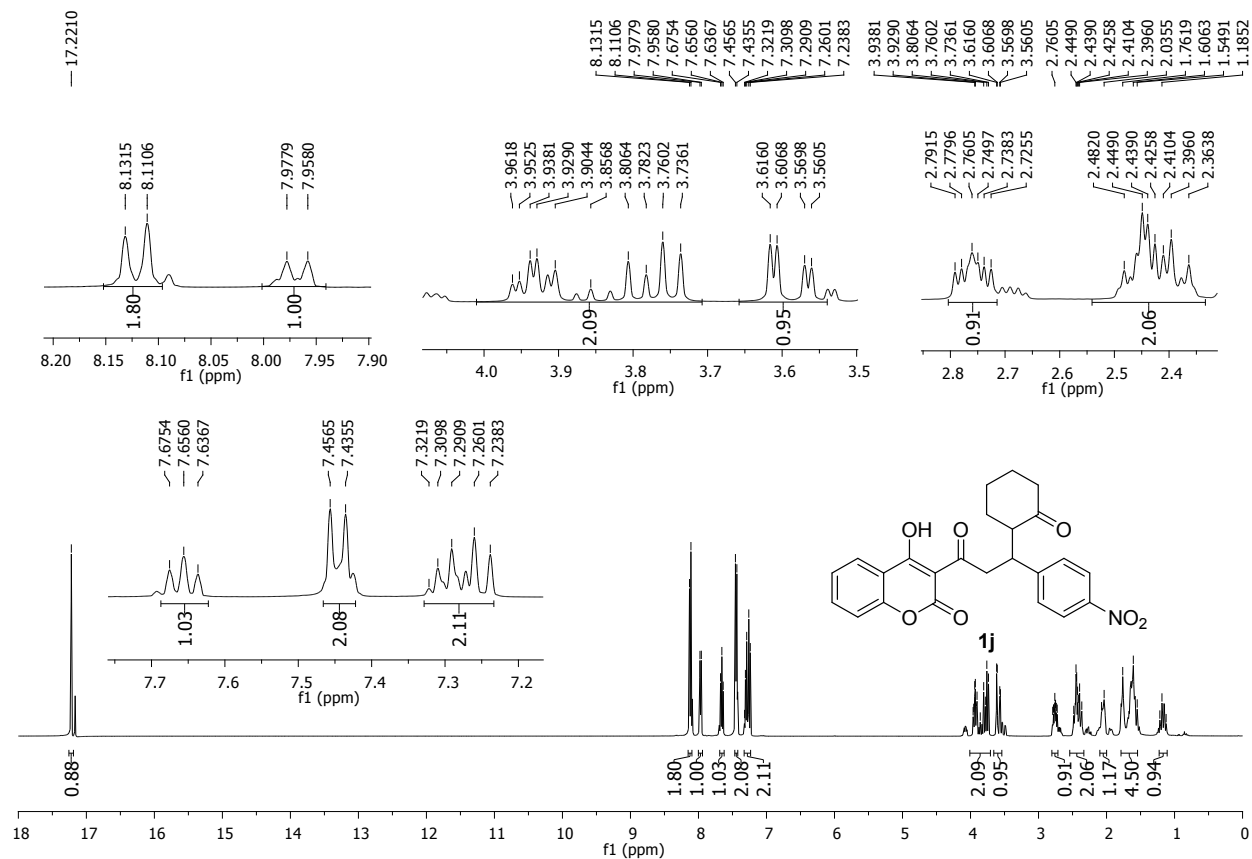
3-(3-(2-chlorophenyl)-3-(2-oxocyclohexyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1i): ¹H NMR



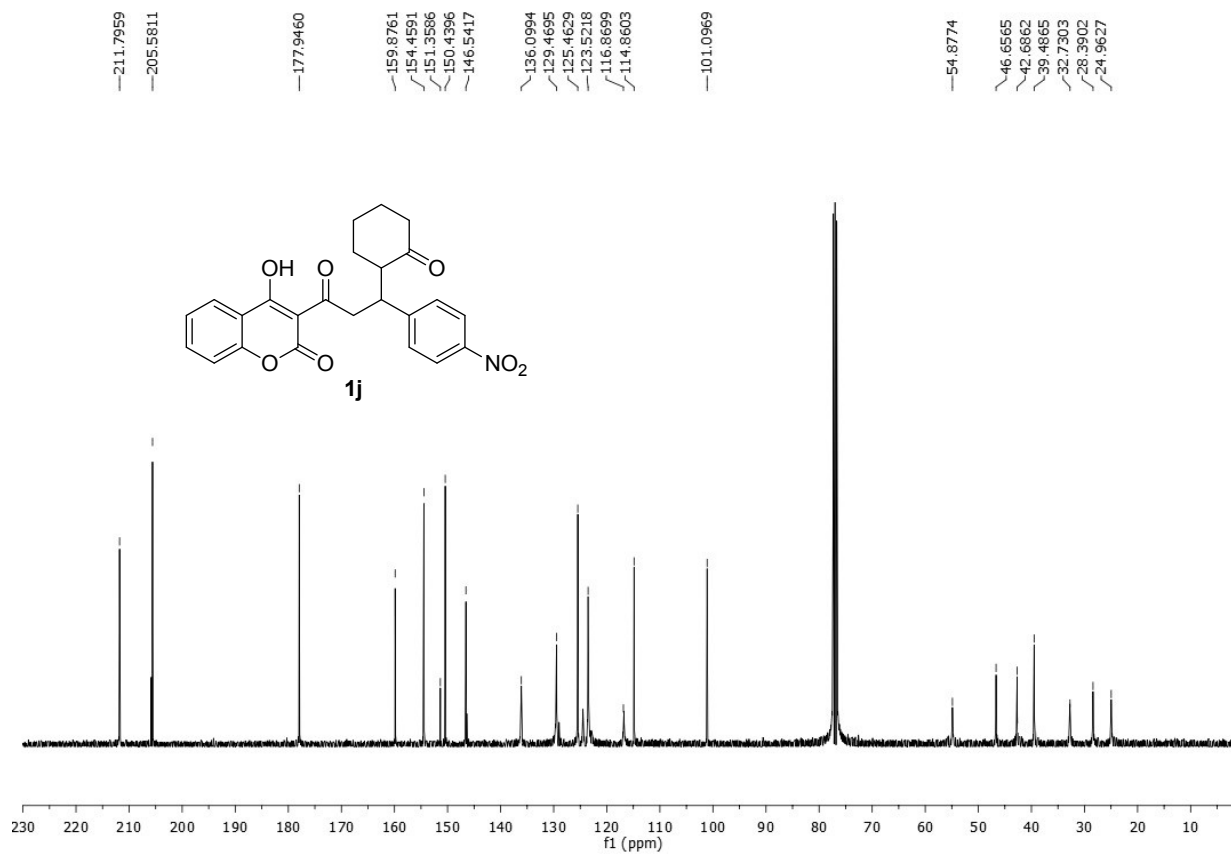
**3-(3-(2-chlorophenyl)-3-(2-oxocyclohexyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1i):
¹³C NMR**



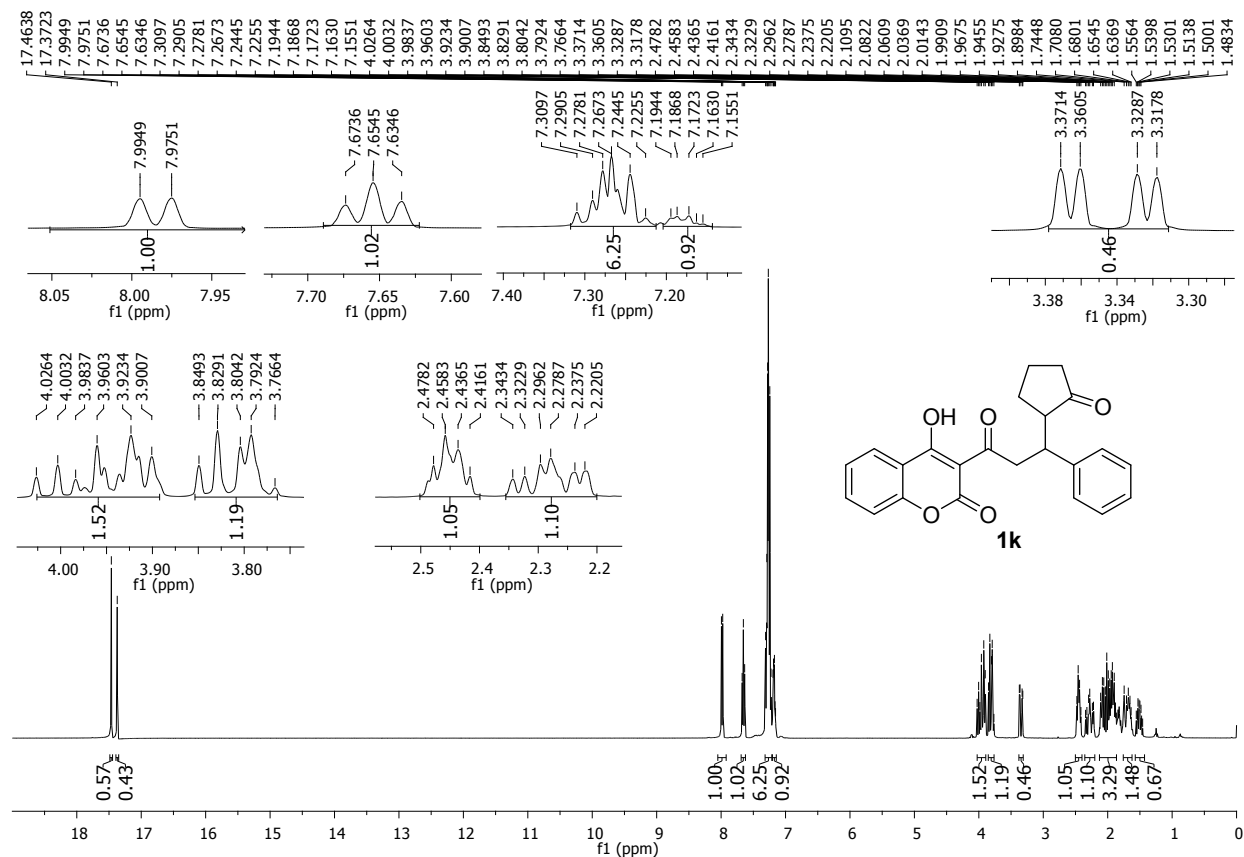
**4-hydroxy-3-(3-(4-nitrophenyl)-3-(2-oxocyclohexyl)propanoyl)-2H-chromen-2-one (1j): ¹H
NMR**



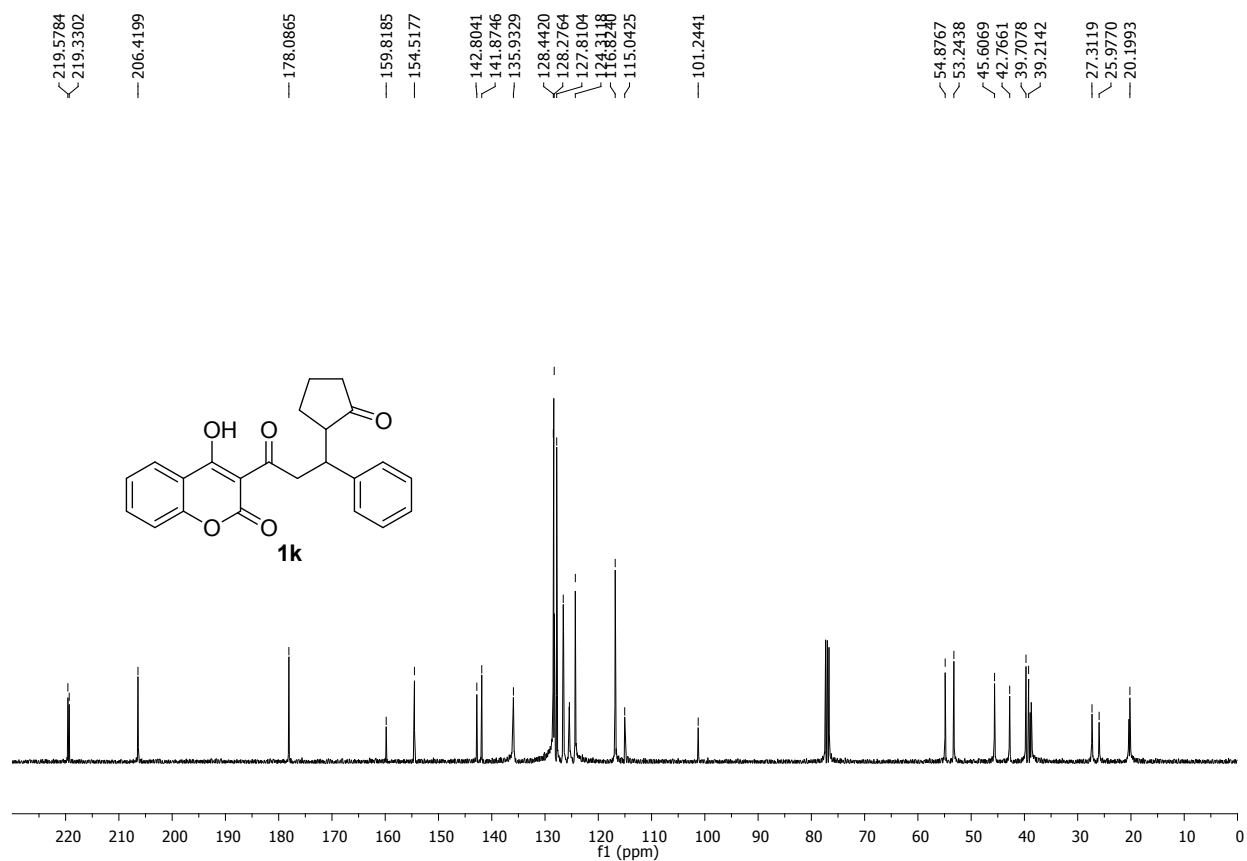
4-hydroxy-3-(3-(4-nitrophenyl)-3-(2-oxocyclohexyl)propanoyl)-2H-chromen-2-one (1j): ^{13}C NMR



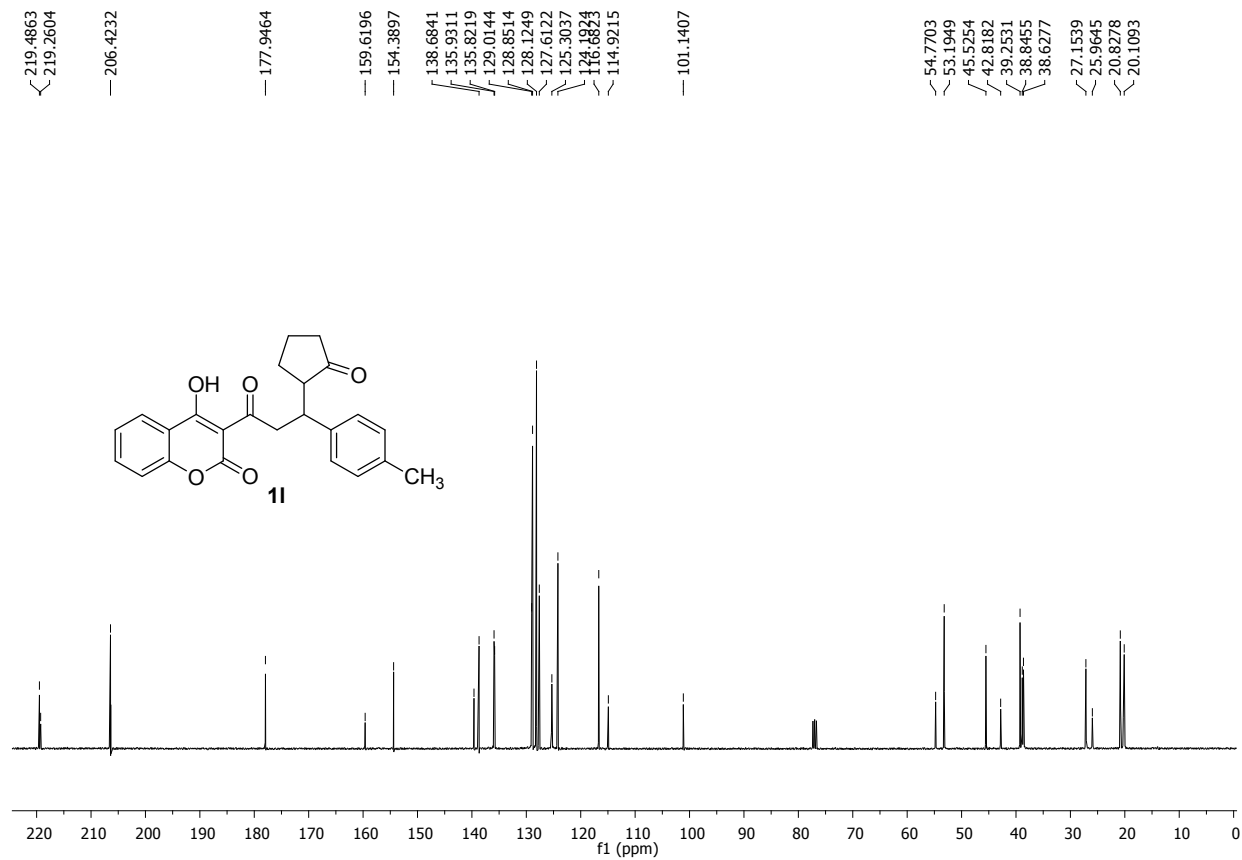
4-hydroxy-3-(3-(2-oxocyclopentyl)-3-phenylpropanoyl)-2H-chromen-2-one (1k): ^1H NMR



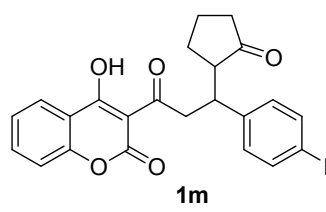
4-hydroxy-3-(3-(2-oxocyclopentyl)-3-phenylpropanoyl)-2H-chromen-2-one (1k): ^{13}C NMR



4-hydroxy-3-(3-(2-oxocyclopentyl)-3-(p-tolyl)propanoyl)-2H-chromen-2-one (11): ^{13}C NMR

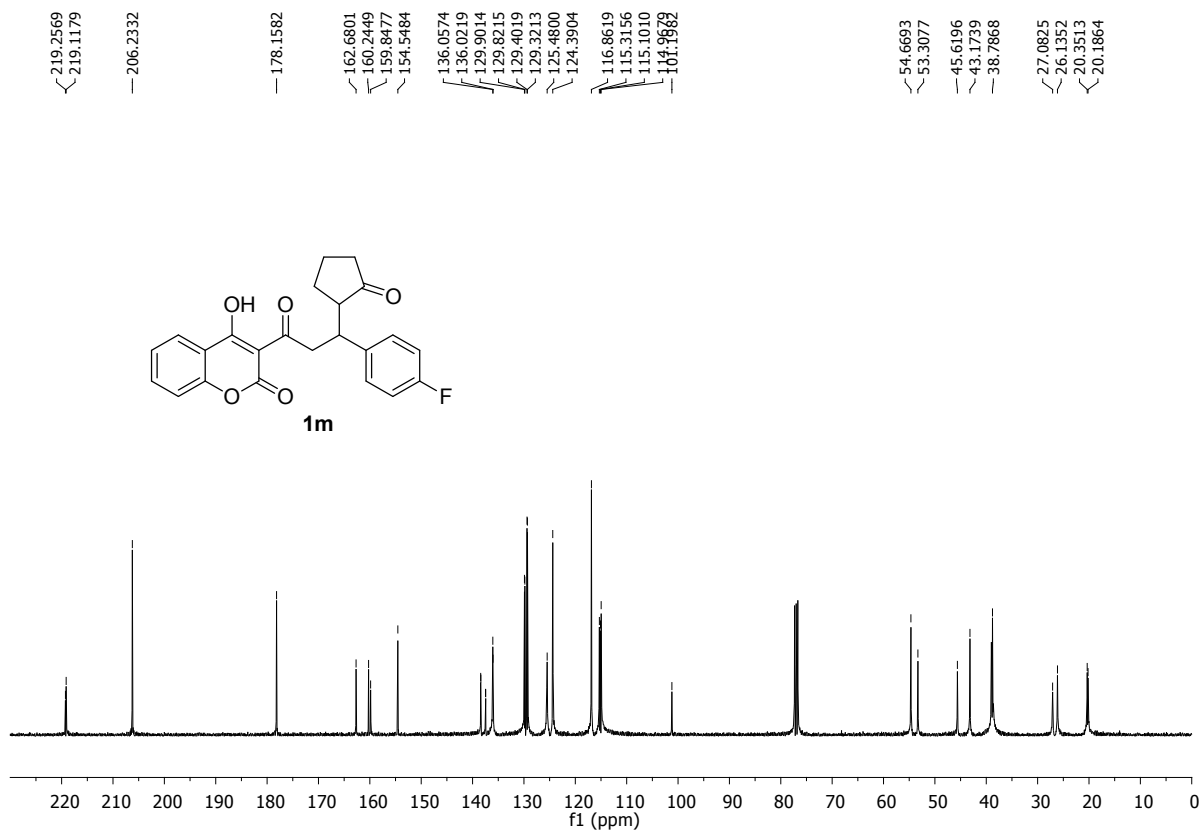


¹H NMR

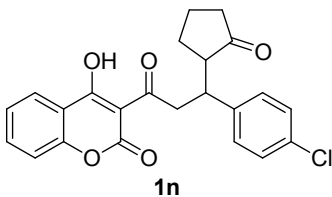


3-(3-(4-fluorophenyl)-3-(2-oxocyclopentyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1m):

¹³C NMR

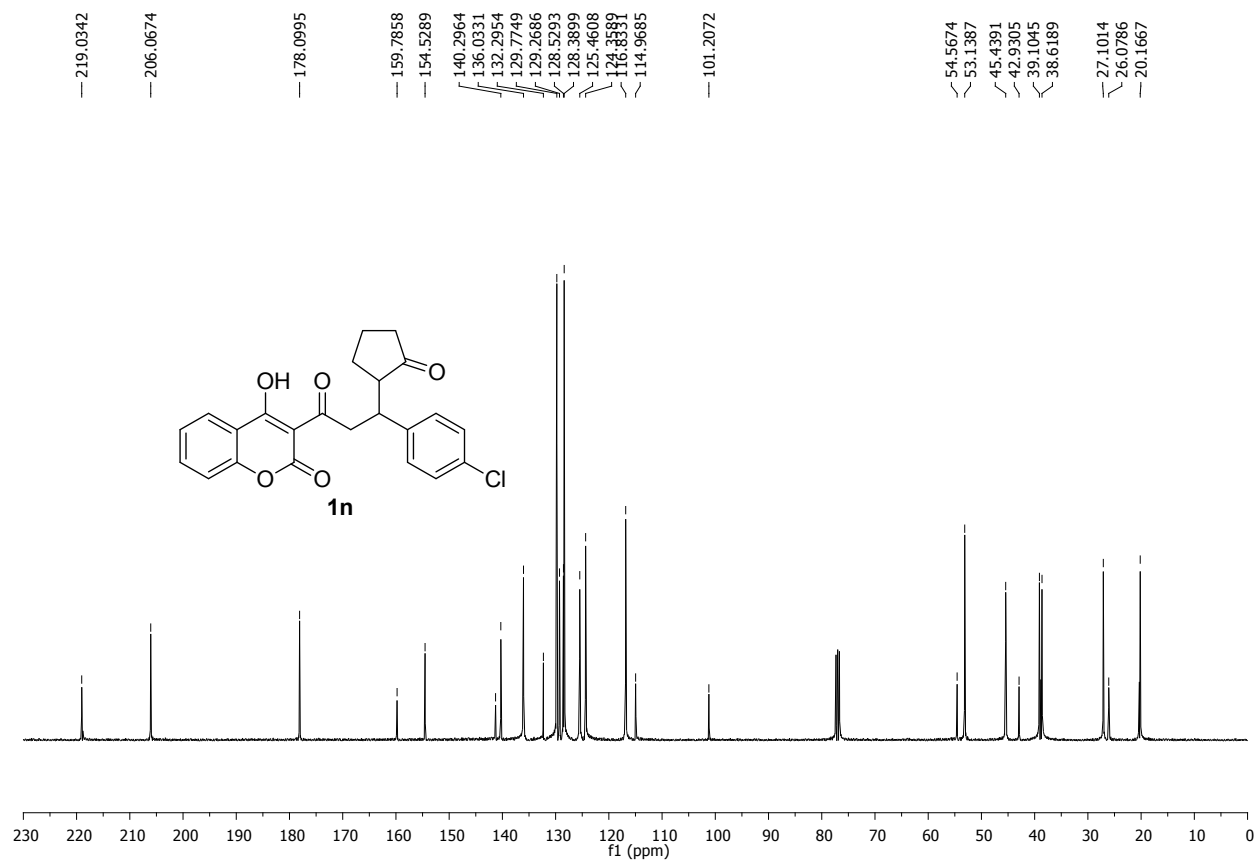


¹H NMR

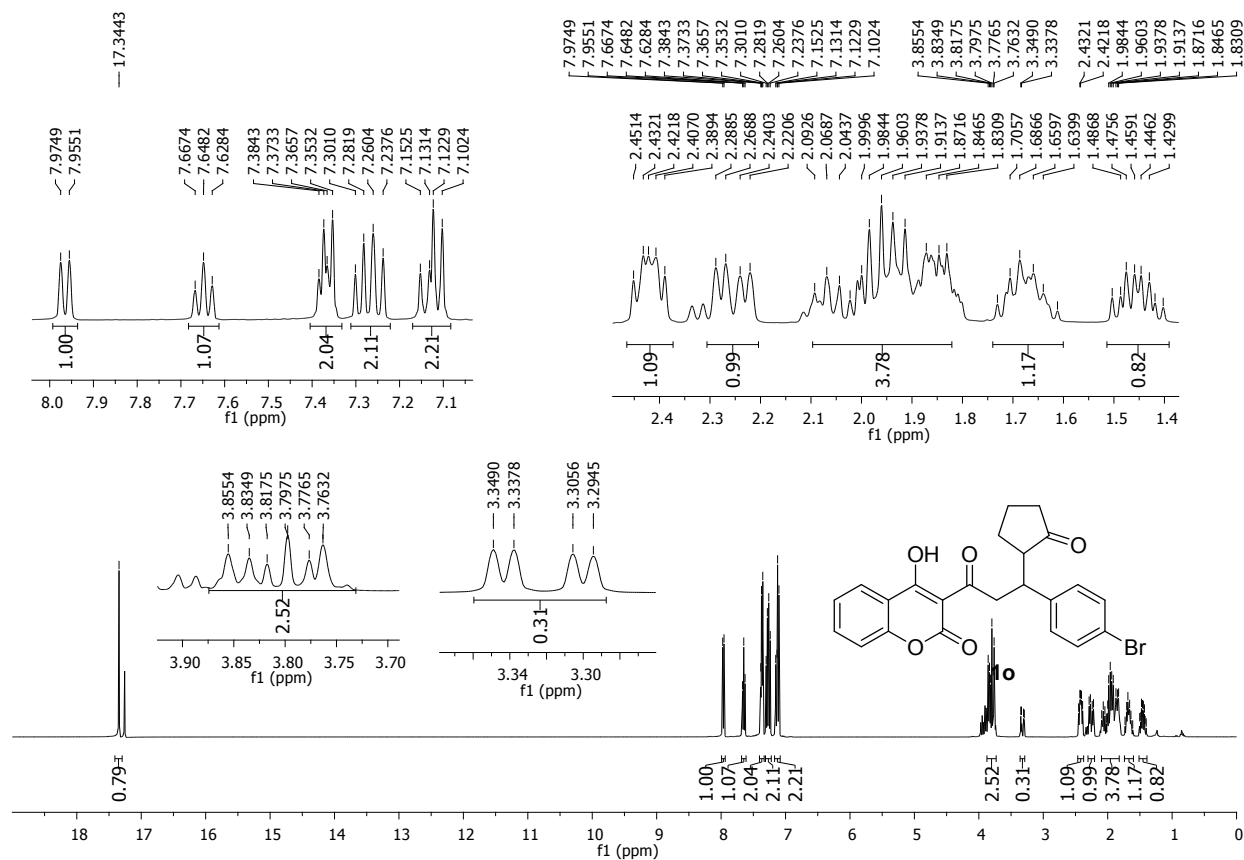


3-(3-(4-chlorophenyl)-3-(2-oxocyclopentyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1n):

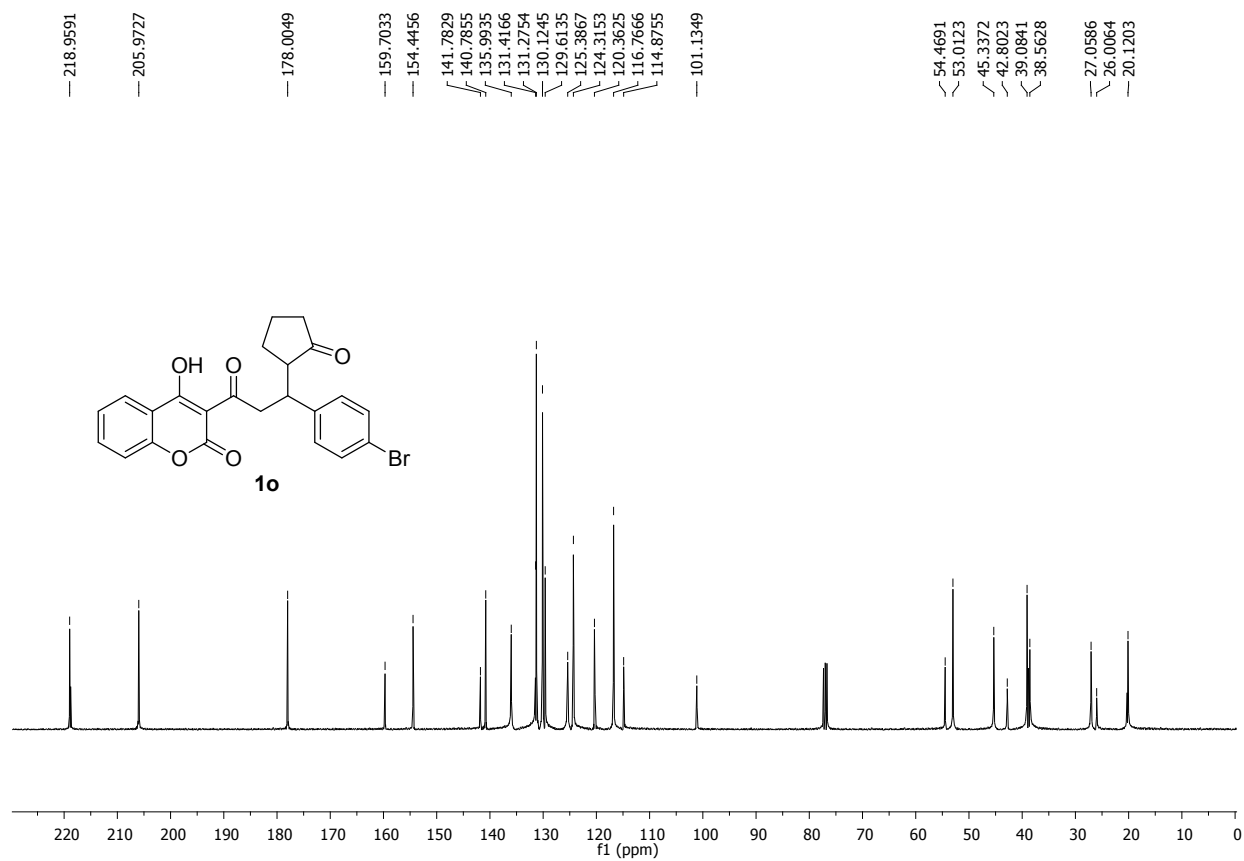
^{13}C NMR



**3-(3-(4-bromophenyl)-3-(2-oxocyclopentyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1o):
¹H NMR**

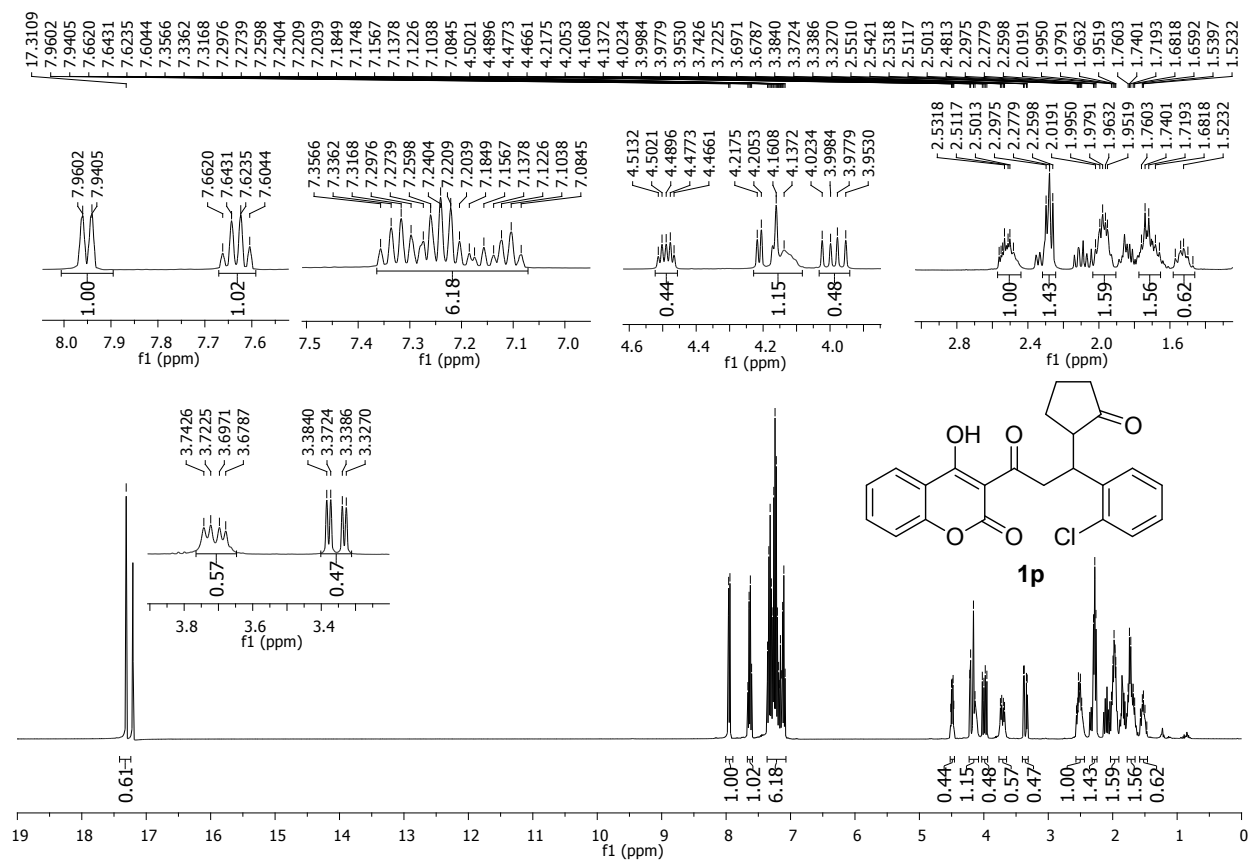


3-(3-(4-bromophenyl)-3-(2-oxocyclopentyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1o):
¹³C NMR

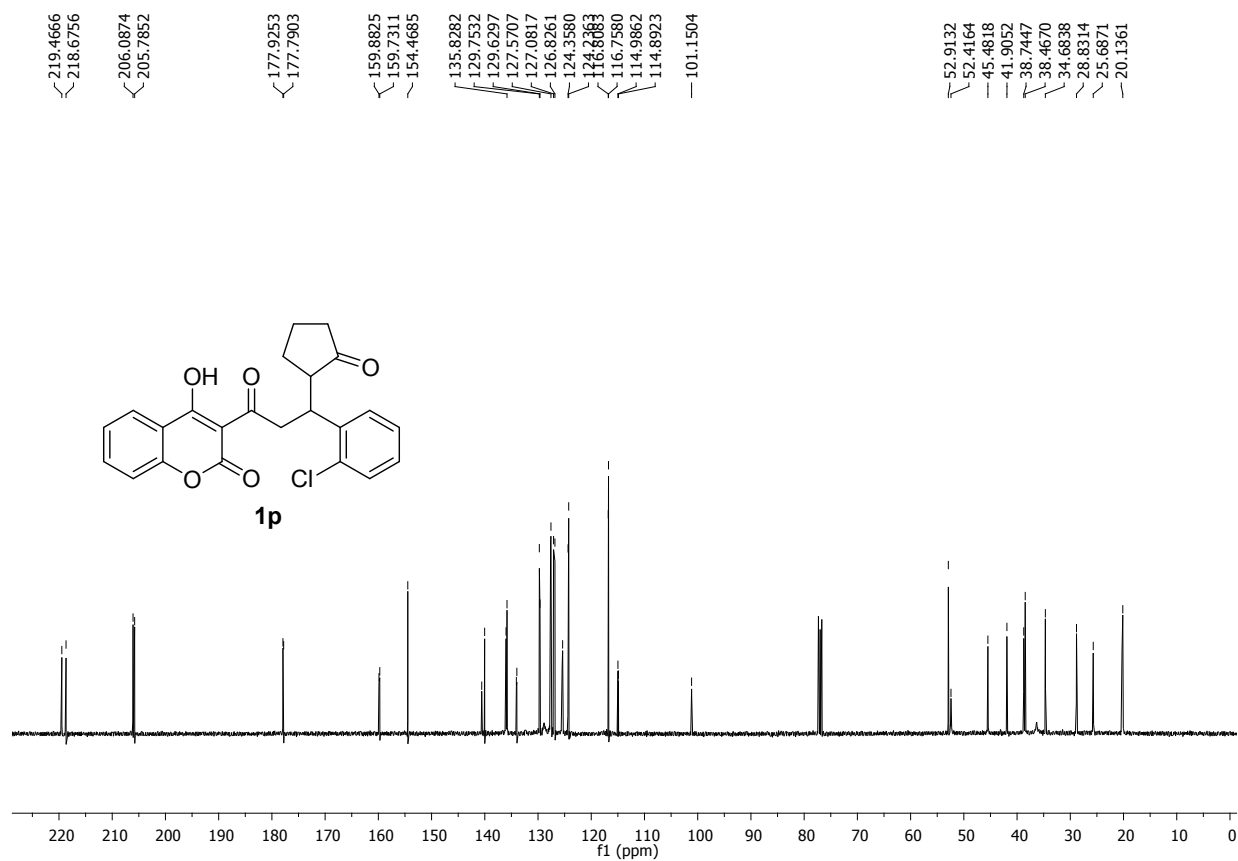


3-(3-(2-chlorophenyl)-3-(2-oxocyclopentyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1p):

¹H NMR

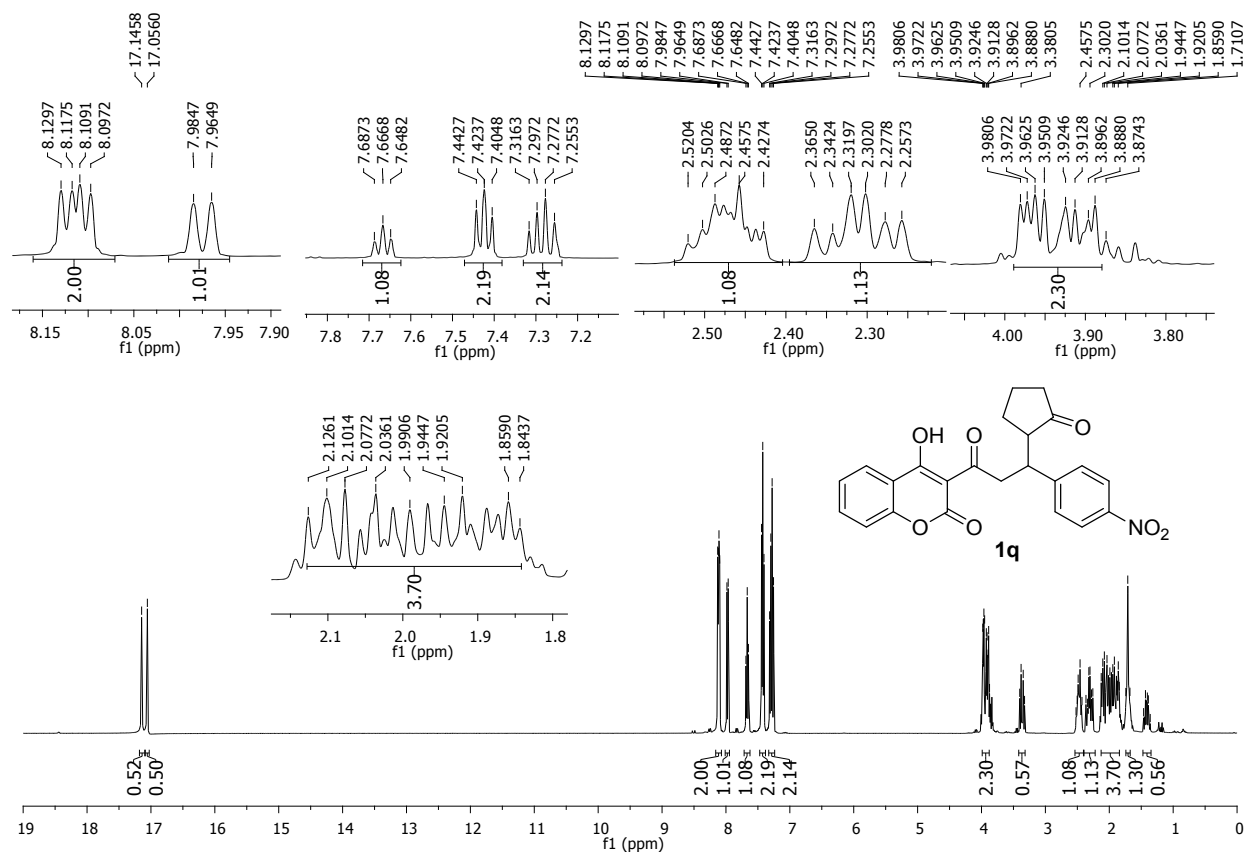


3-(3-(2-chlorophenyl)-3-(2-oxocyclopentyl)propanoyl)-4-hydroxy-2H-chromen-2-one (1p):
¹³C NMR



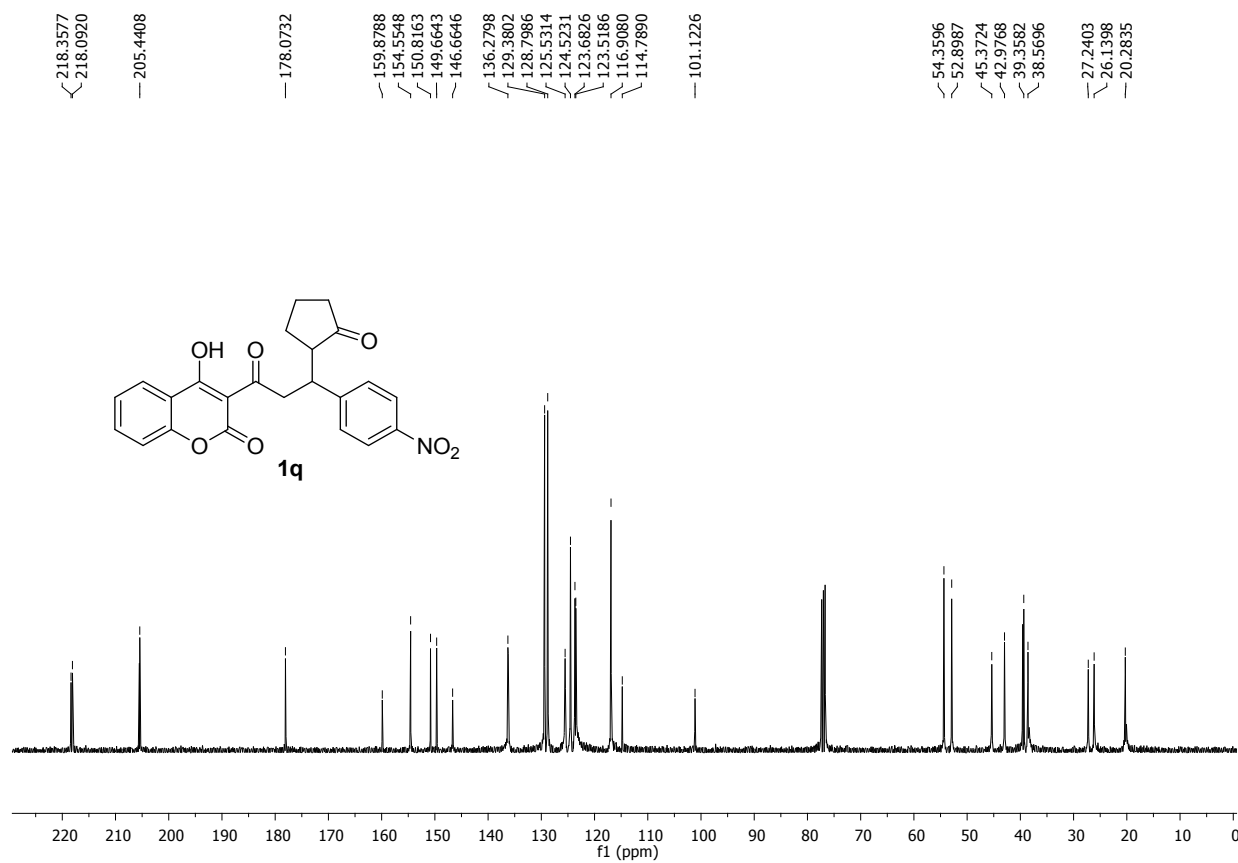
4-hydroxy-3-(3-(4-nitrophenyl)-3-(2-oxocyclopentyl)propanoyl)-2H-chromen-2-one (1q): ^1H

NMR



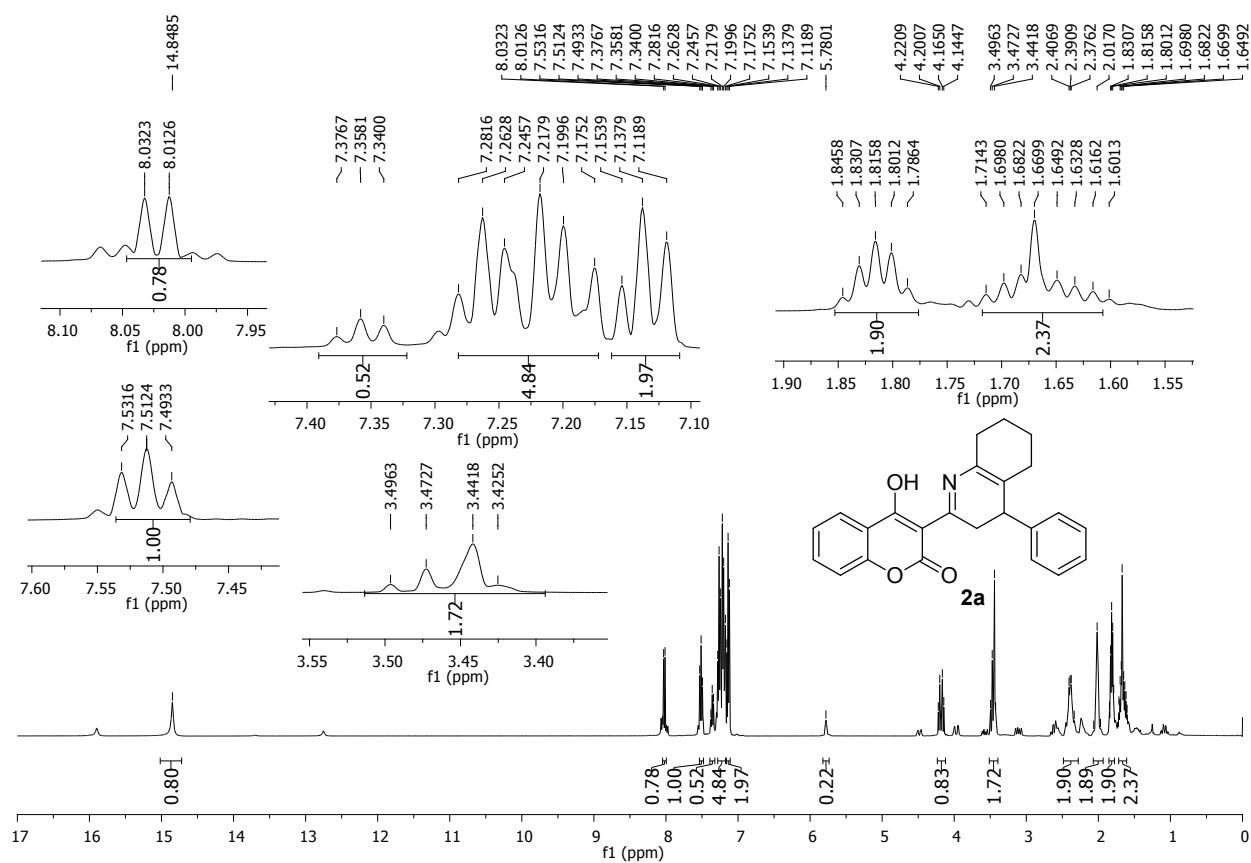
4-hydroxy-3-(3-(4-nitrophenyl)-3-(2-oxocyclopentyl)propanoyl)-2H-chromen-2-one (1q):

¹³C NMR

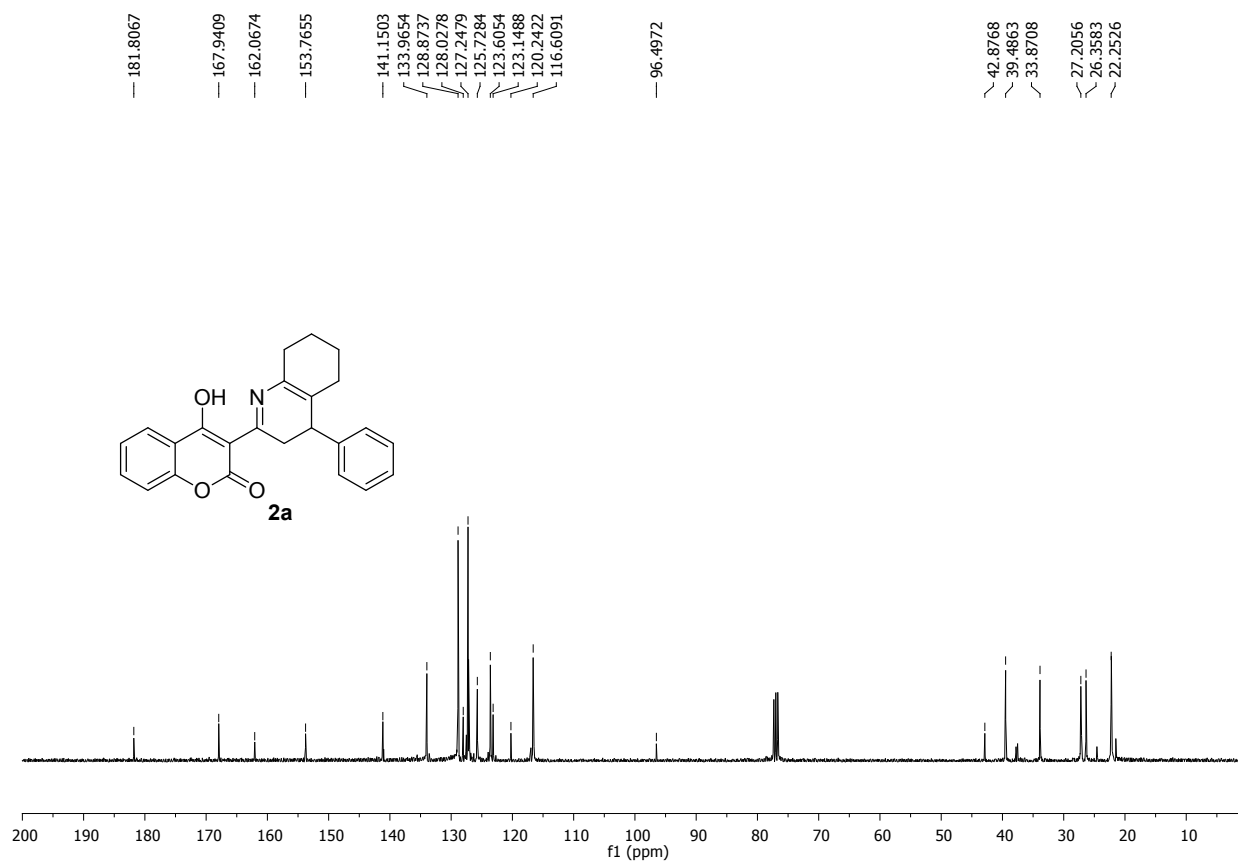


Spectra of Cyclization of 1,5-diketones

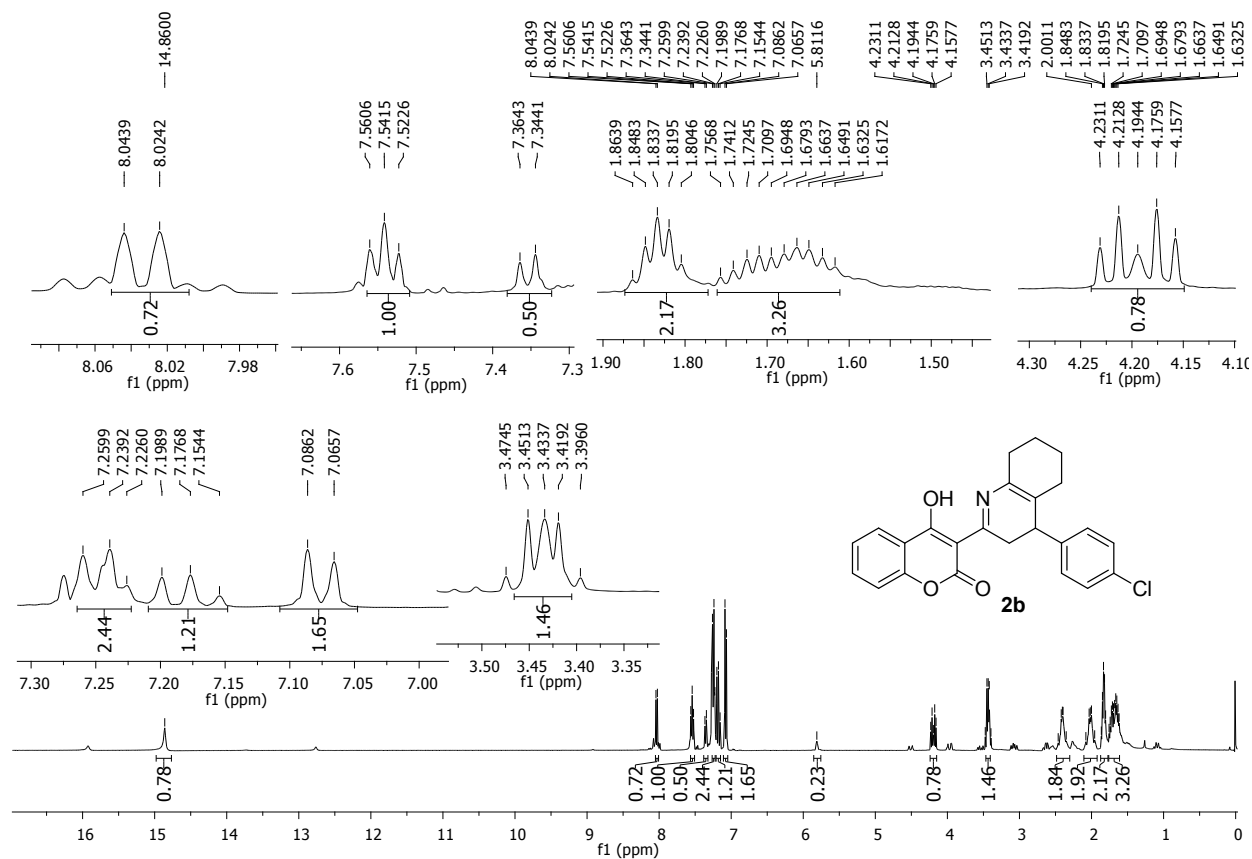
4-hydroxy-3-(4-phenyl-3,4,5,6,7,8-hexahydroquinolin-2-yl)-2H-chromen-2-one (2a): ¹H NMR



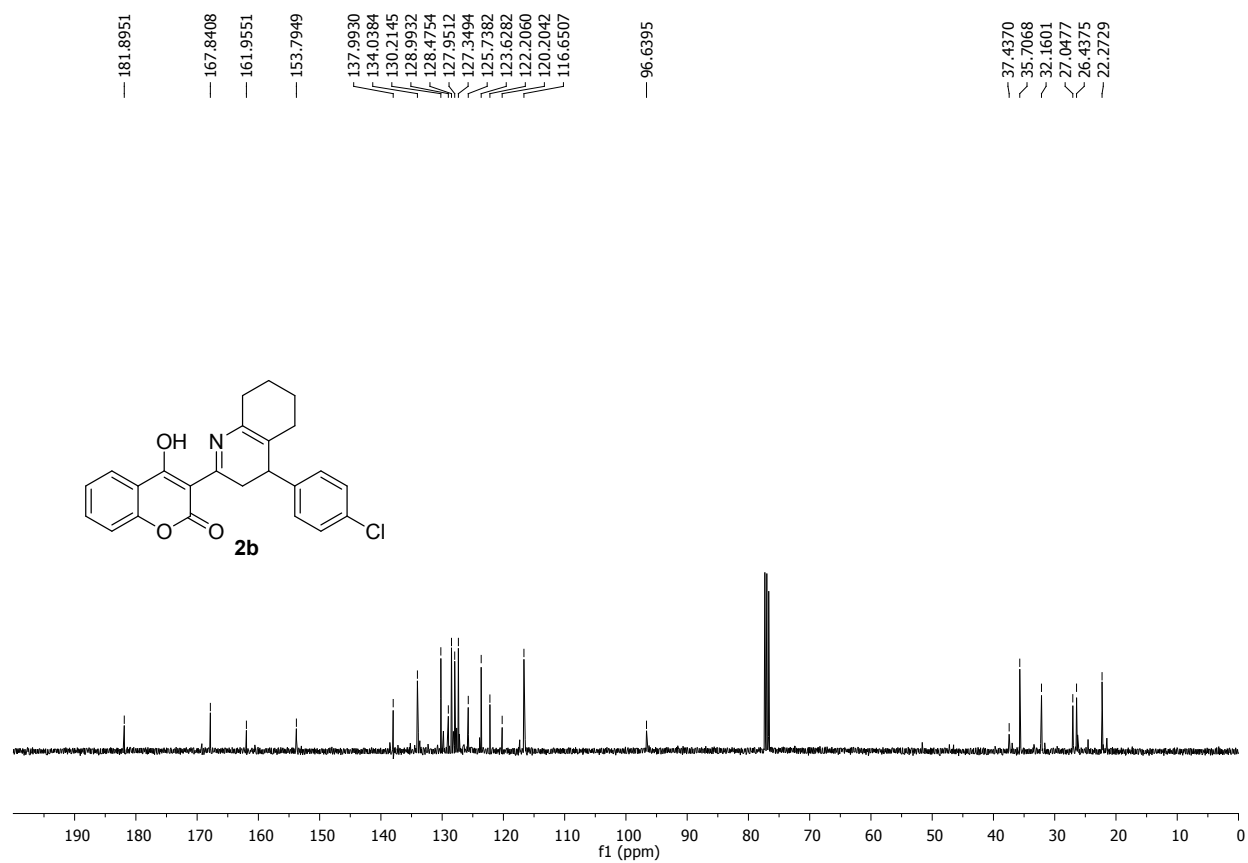
4-hydroxy-3-(4-phenyl-3,4,5,6,7,8-hexahydroquinolin-2-yl)-2H-chromen-2-one (2a): ^{13}C NMR



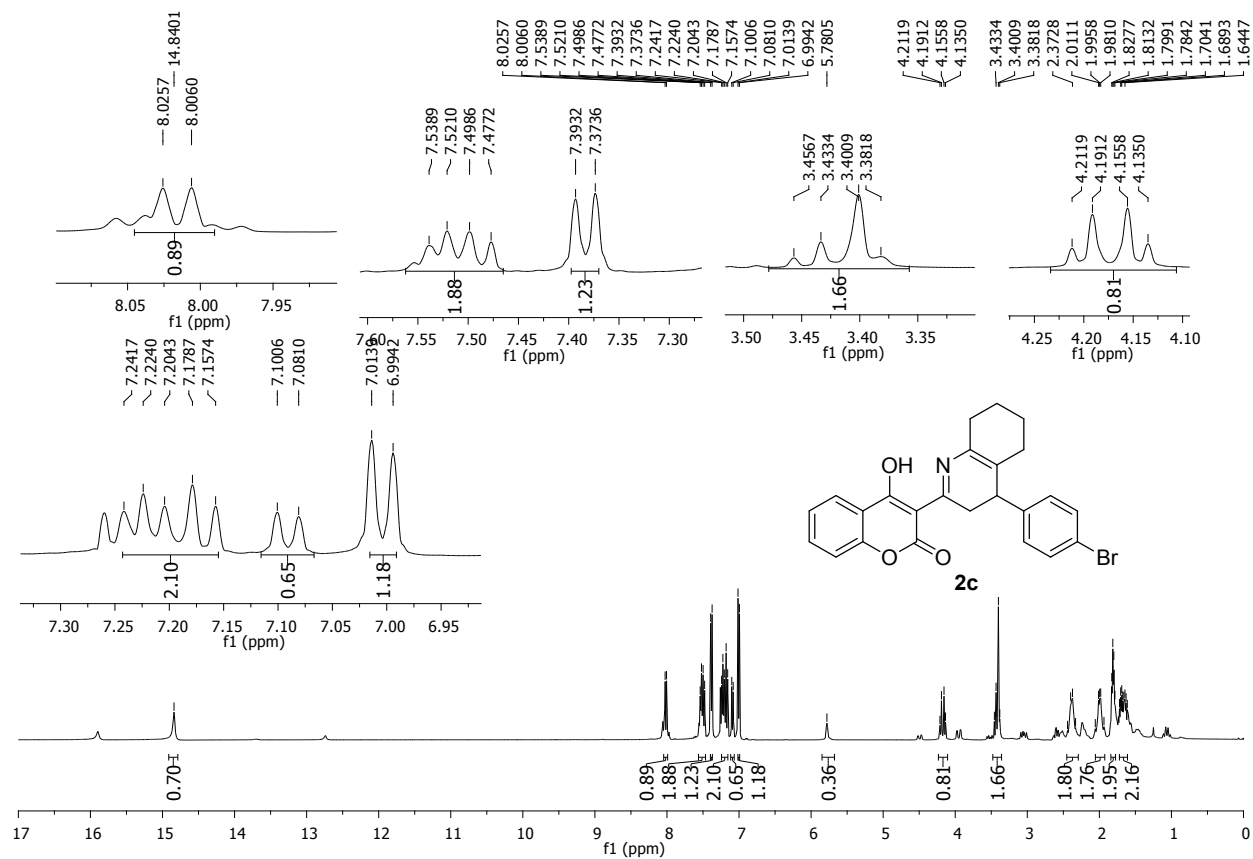
3-(4-(4-chlorophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one (2b): ^1H NMR



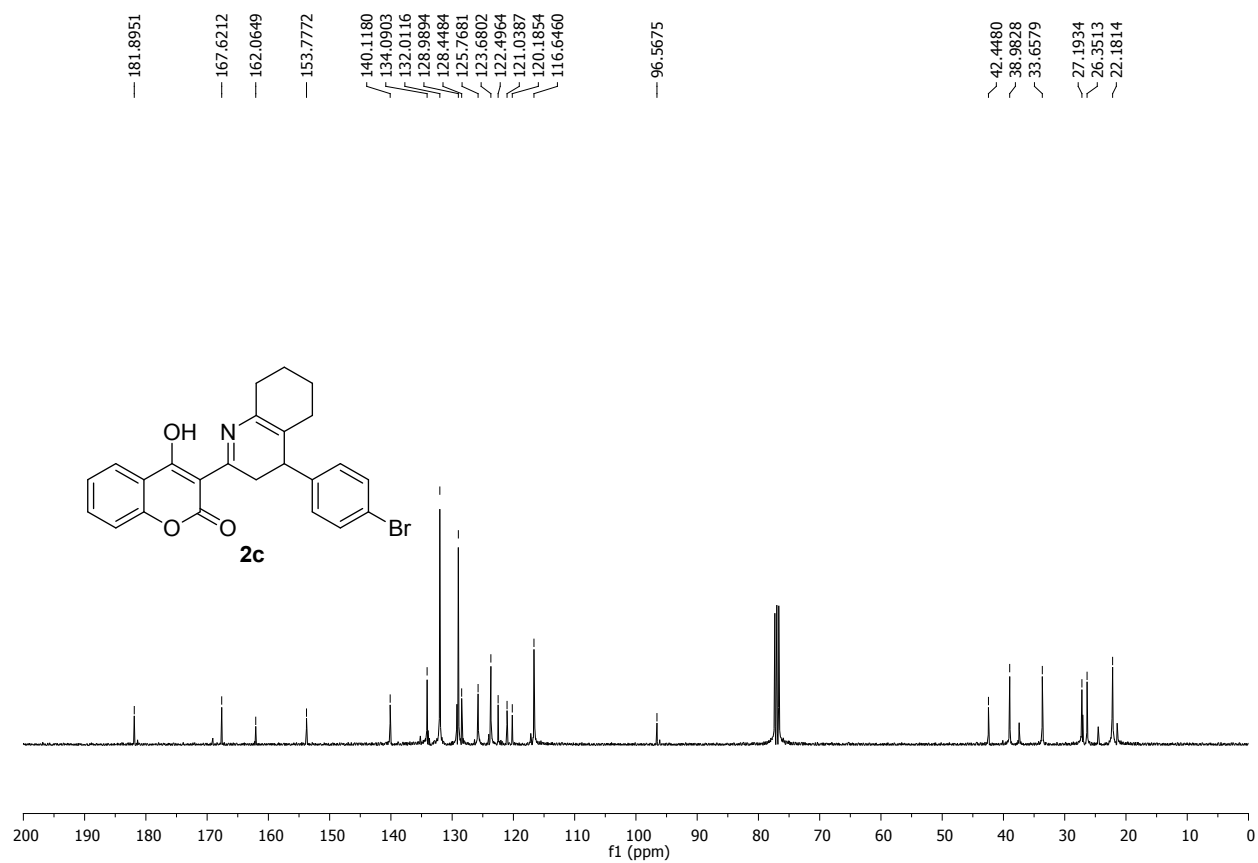
3-(4-(4-chlorophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one (2b): ^{13}C NMR



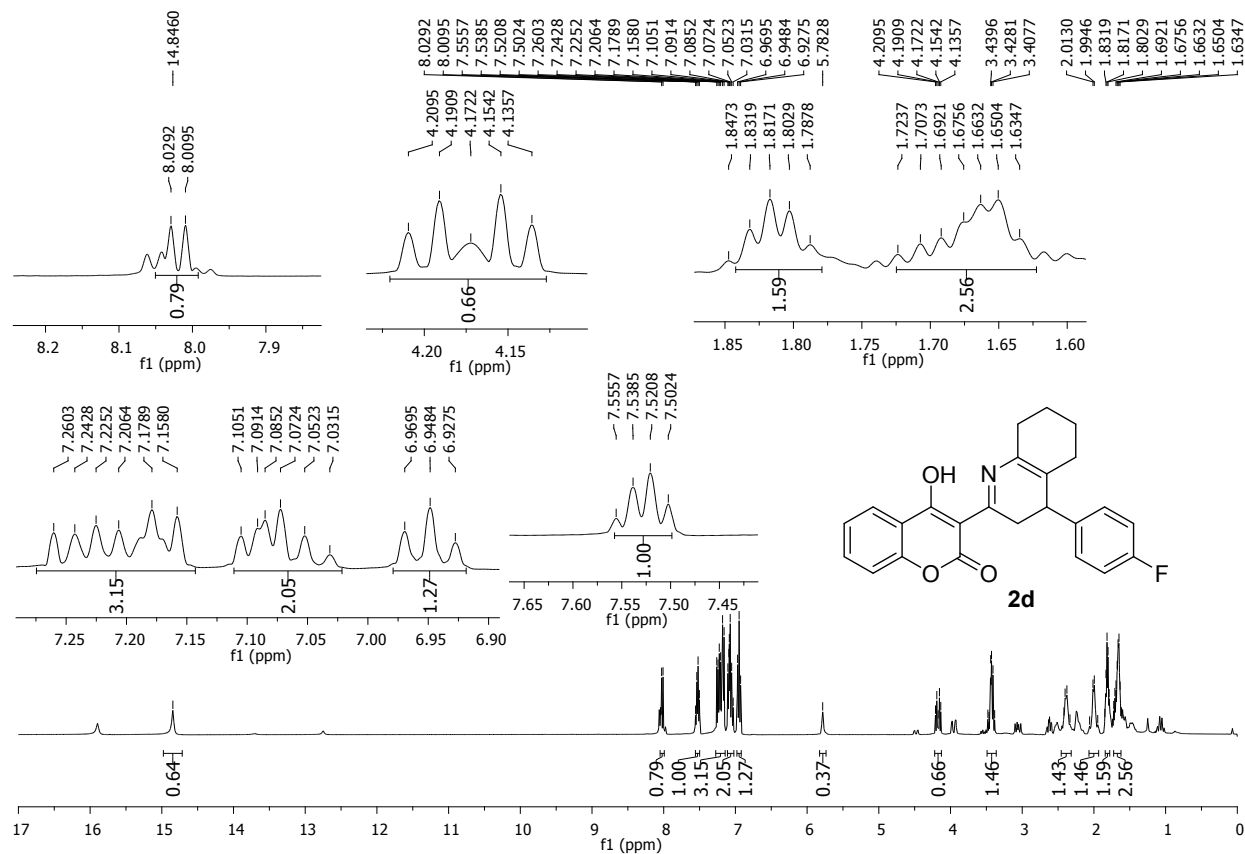
3-(4-(4-bromophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one (2c): ^1H NMR



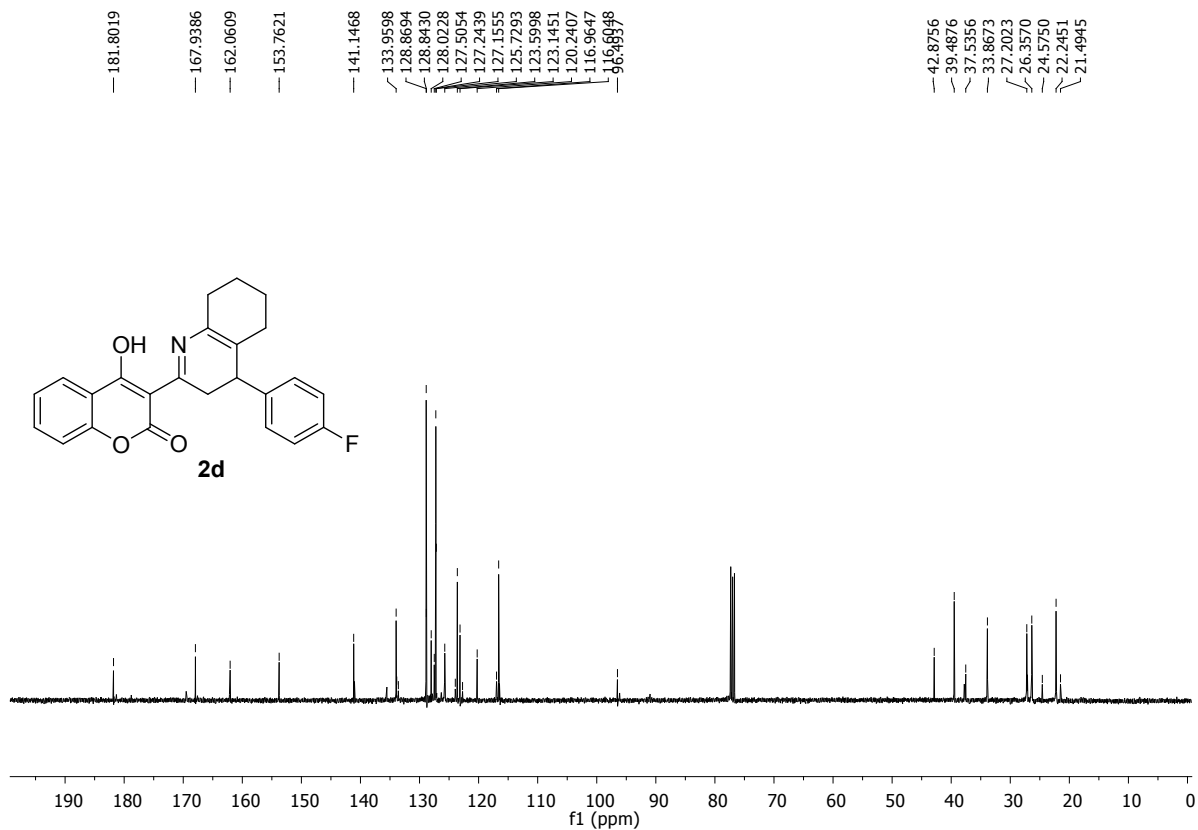
3-(4-(4-bromophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one (2c): ^{13}C NMR



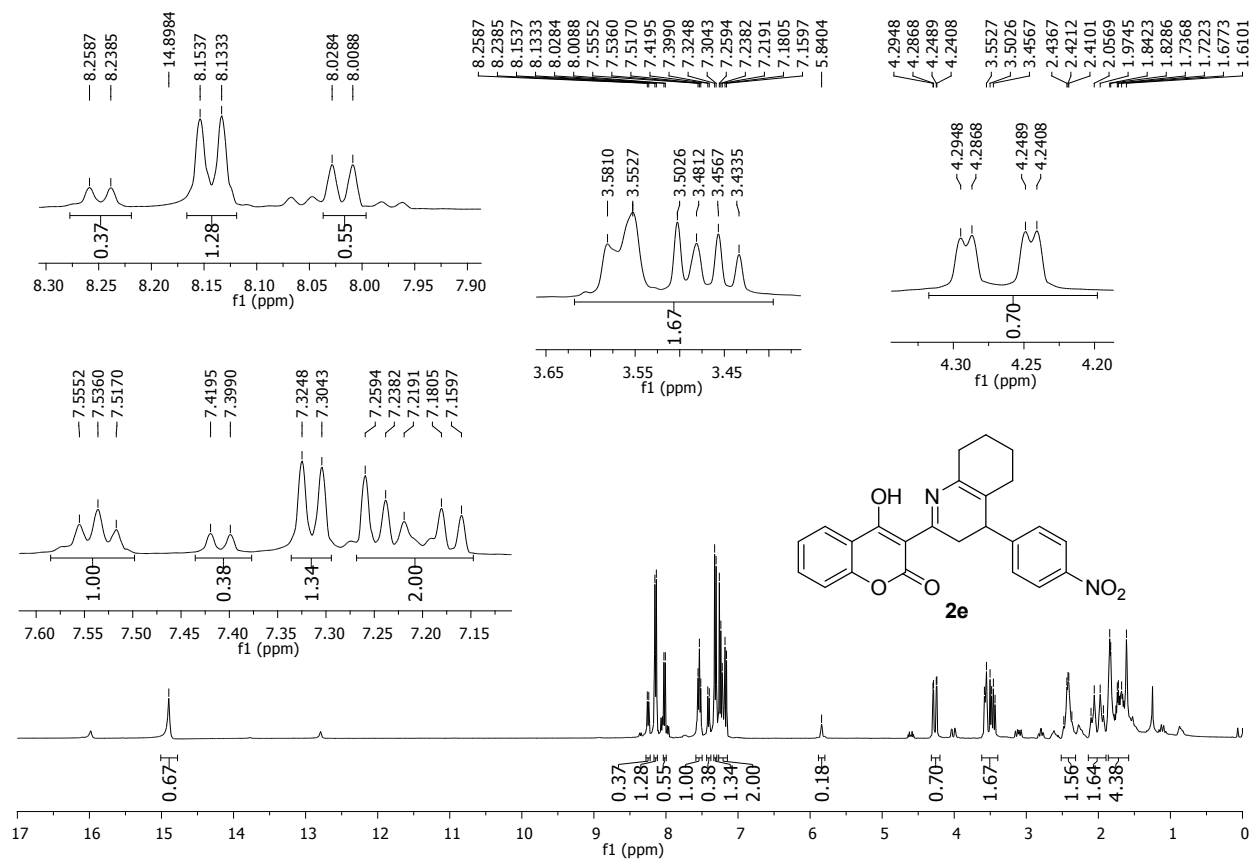
3-(4-(4-fluorophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one (2d): ^1H NMR



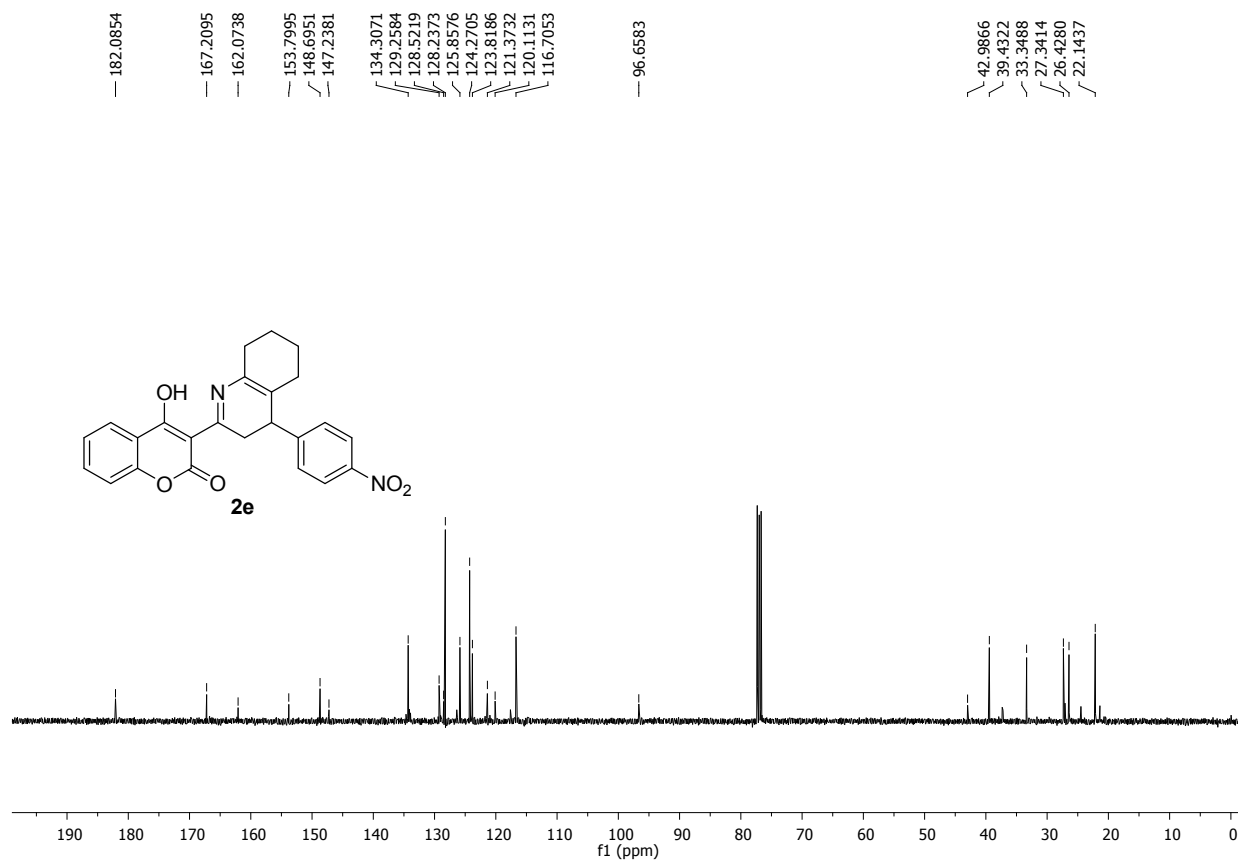
3-(4-(4-fluorophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one (2d): ^{13}C NMR



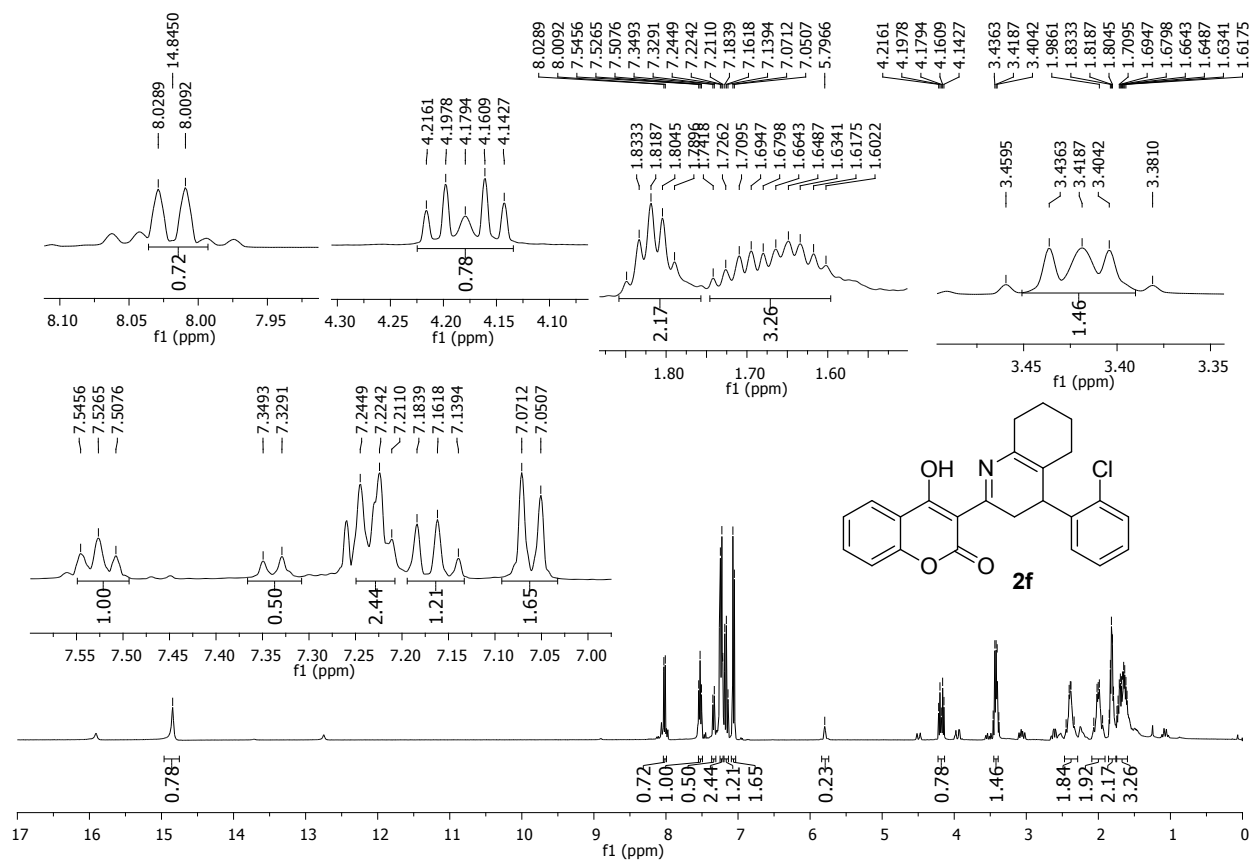
4-hydroxy-3-(4-(4-nitrophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-2H-chromen-2-one
(2e): ^1H NMR



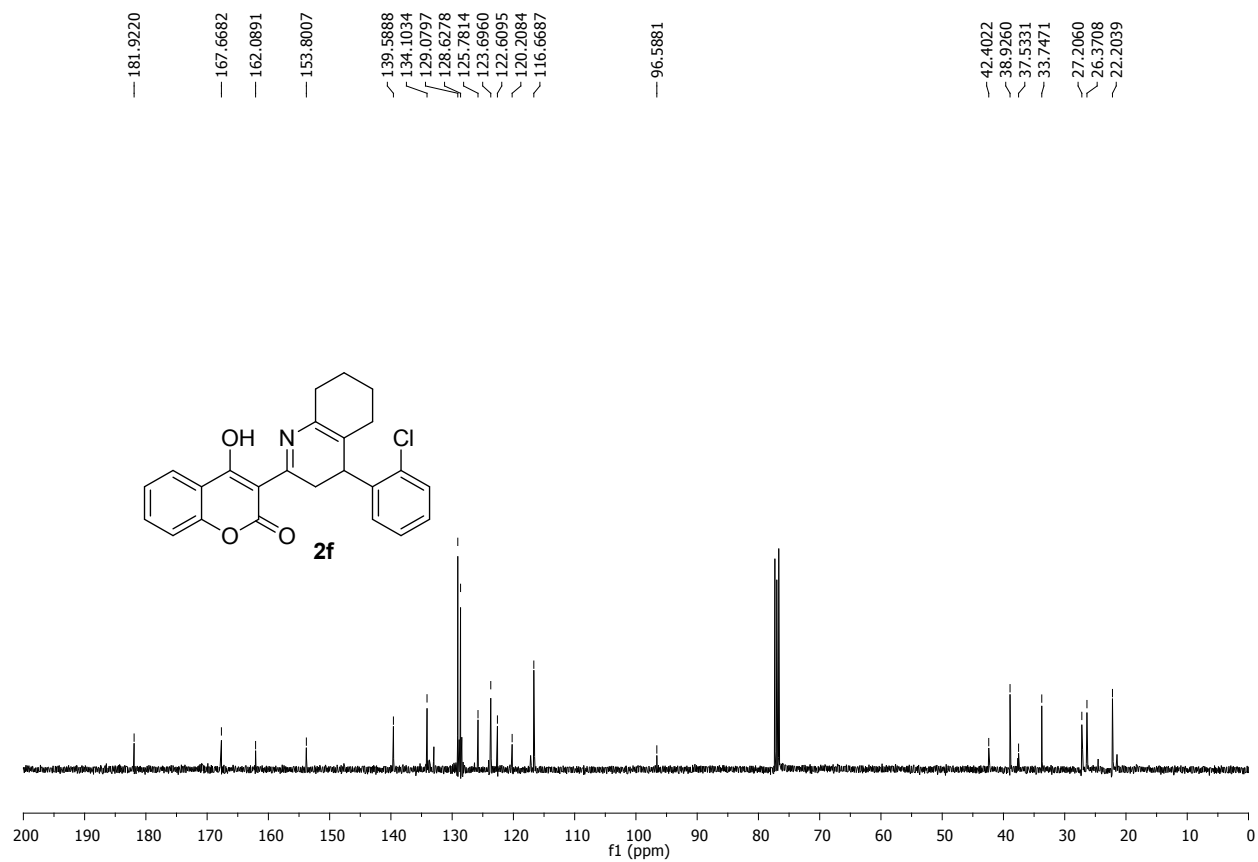
4-hydroxy-3-(4-(4-nitrophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-2H-chromen-2-one
(2e): ^{13}C NMR



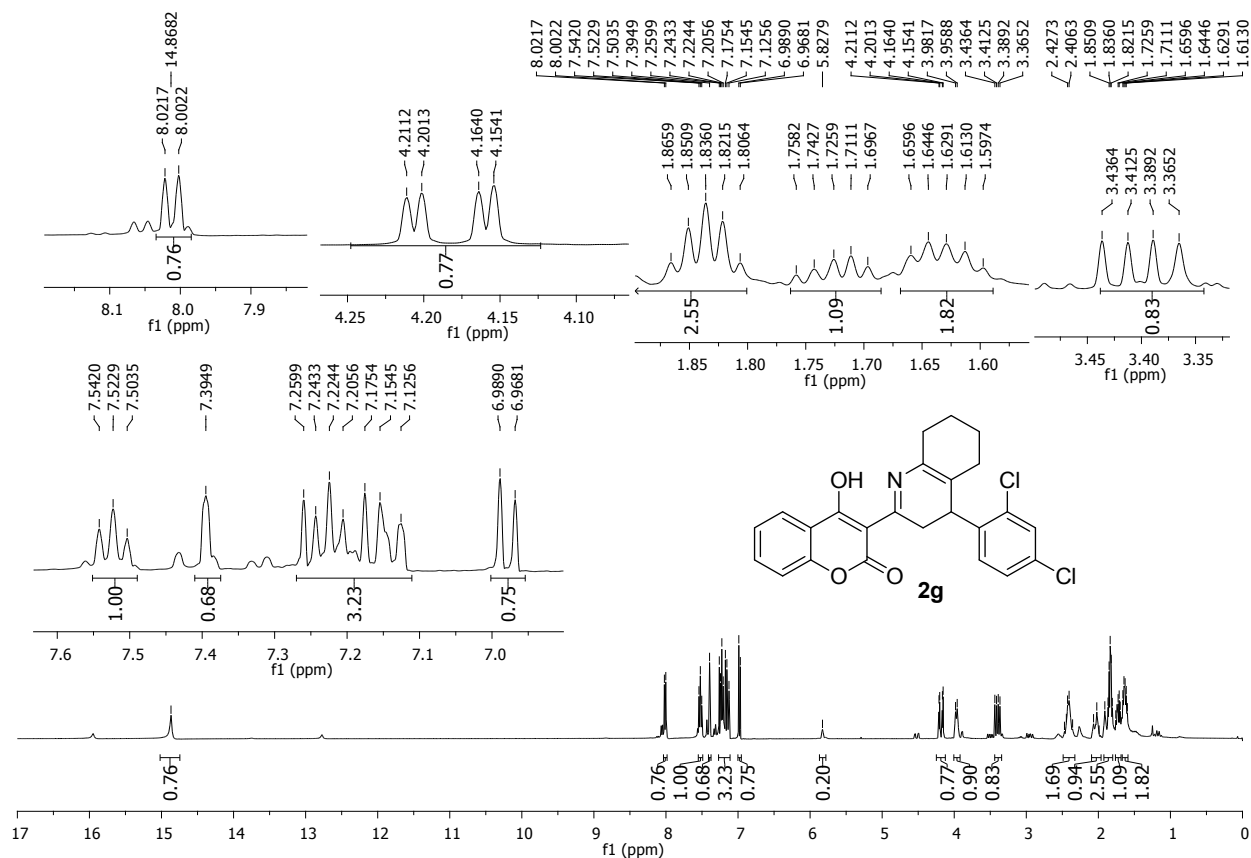
3-(4-(2-chlorophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one
(2f): ^1H NMR



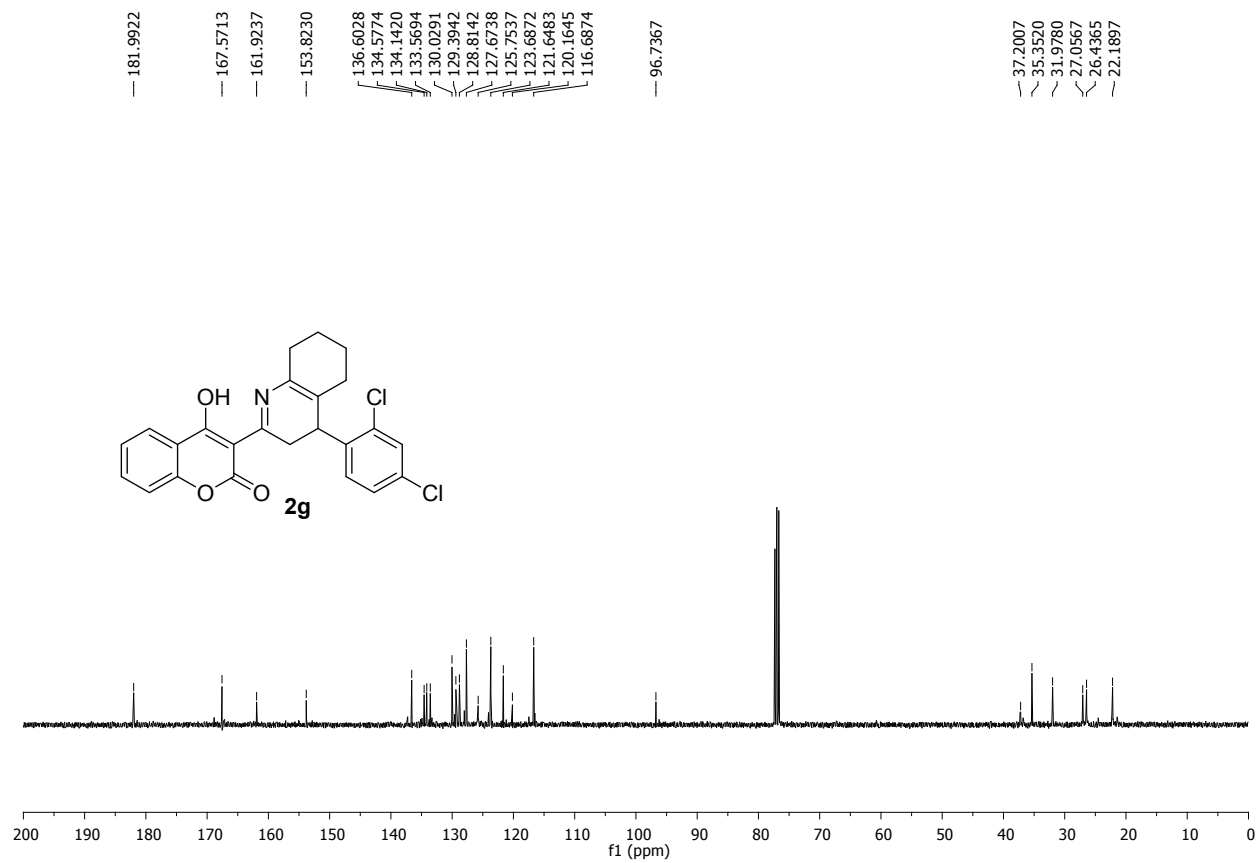
3-(4-(2-chlorophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one
(2f): ^{13}C NMR



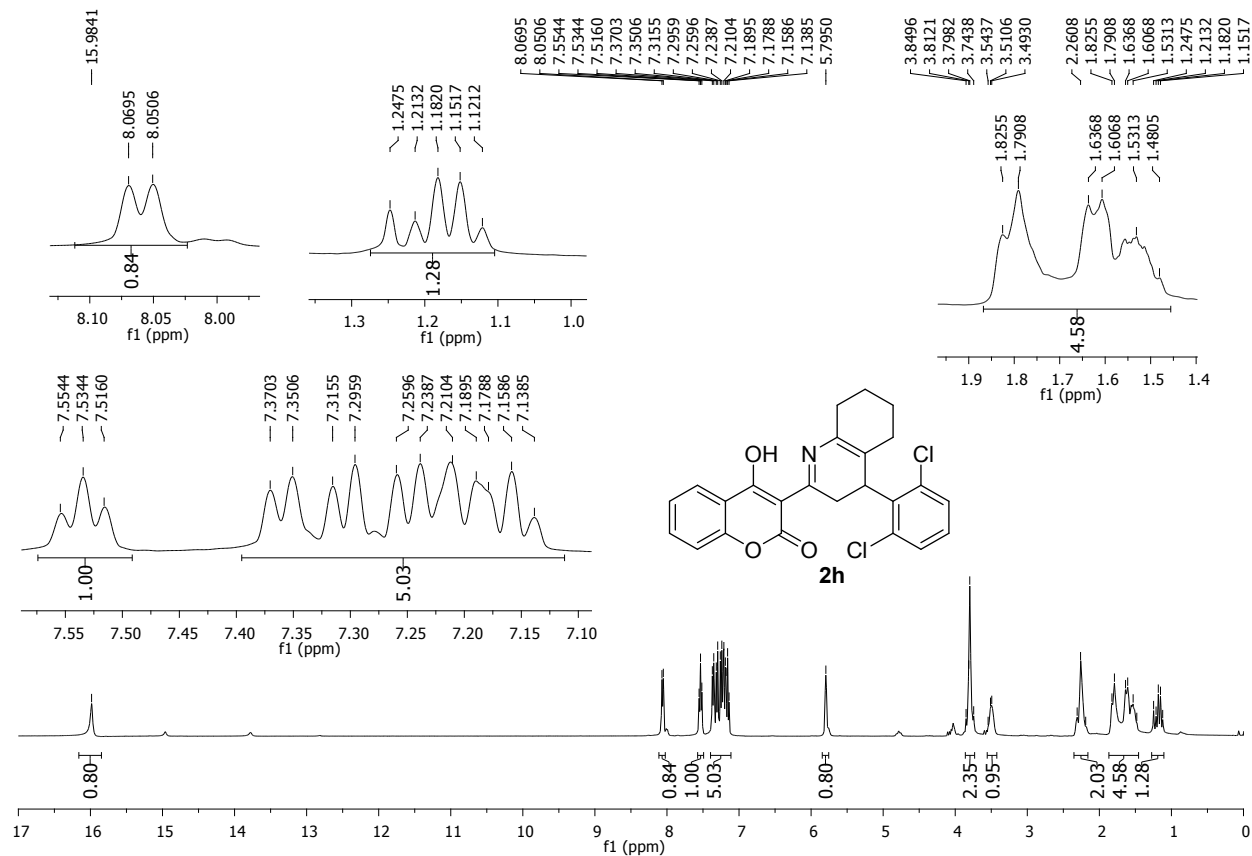
3-(4-(2,4-dichlorophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one (2g): ^1H NMR



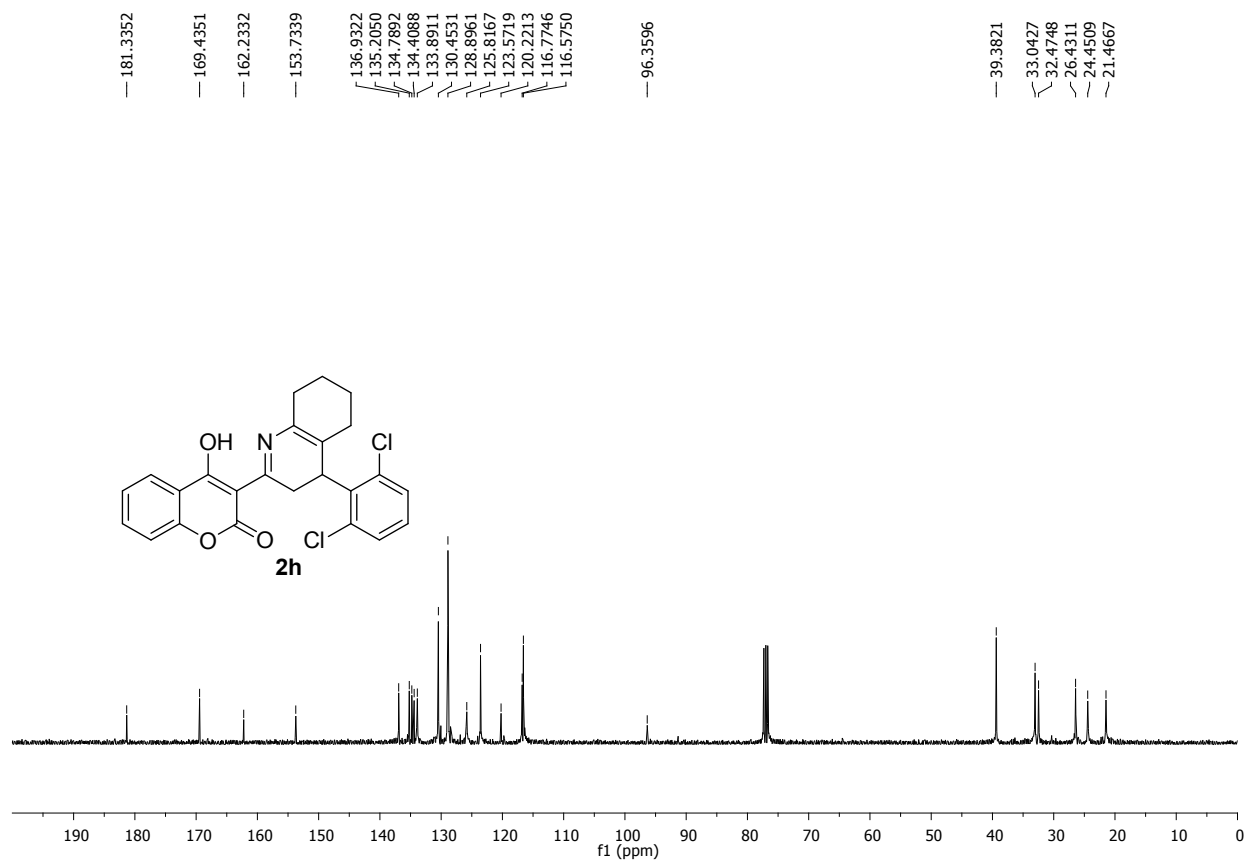
3-(4-(2,4-dichlorophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one (2g): ^{13}C NMR



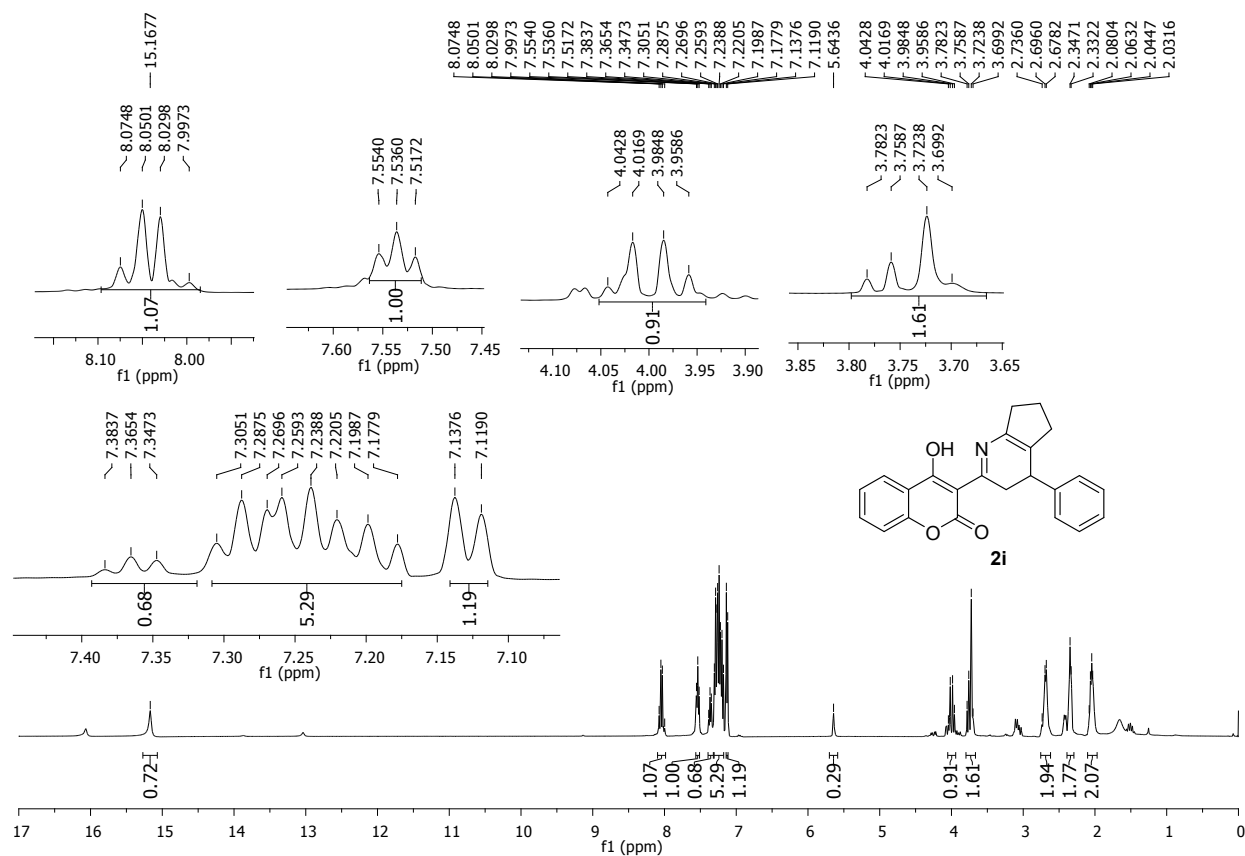
3-(4-(2,6-dichlorophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one (h): ^1H NMR



3-(4-(2,6-dichlorophenyl)-3,4,5,6,7,8-hexahydroquinolin-2-yl)-4-hydroxy-2H-chromen-2-one (h): ^{13}C NMR



4-hydroxy-3-(4-phenyl-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-2-yl)-2H-chromen-2-one (1i): ^1H NMR



4-hydroxy-3-(4-phenyl-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-2-yl)-2H-chromen-2-one (1i): ^{13}C NMR

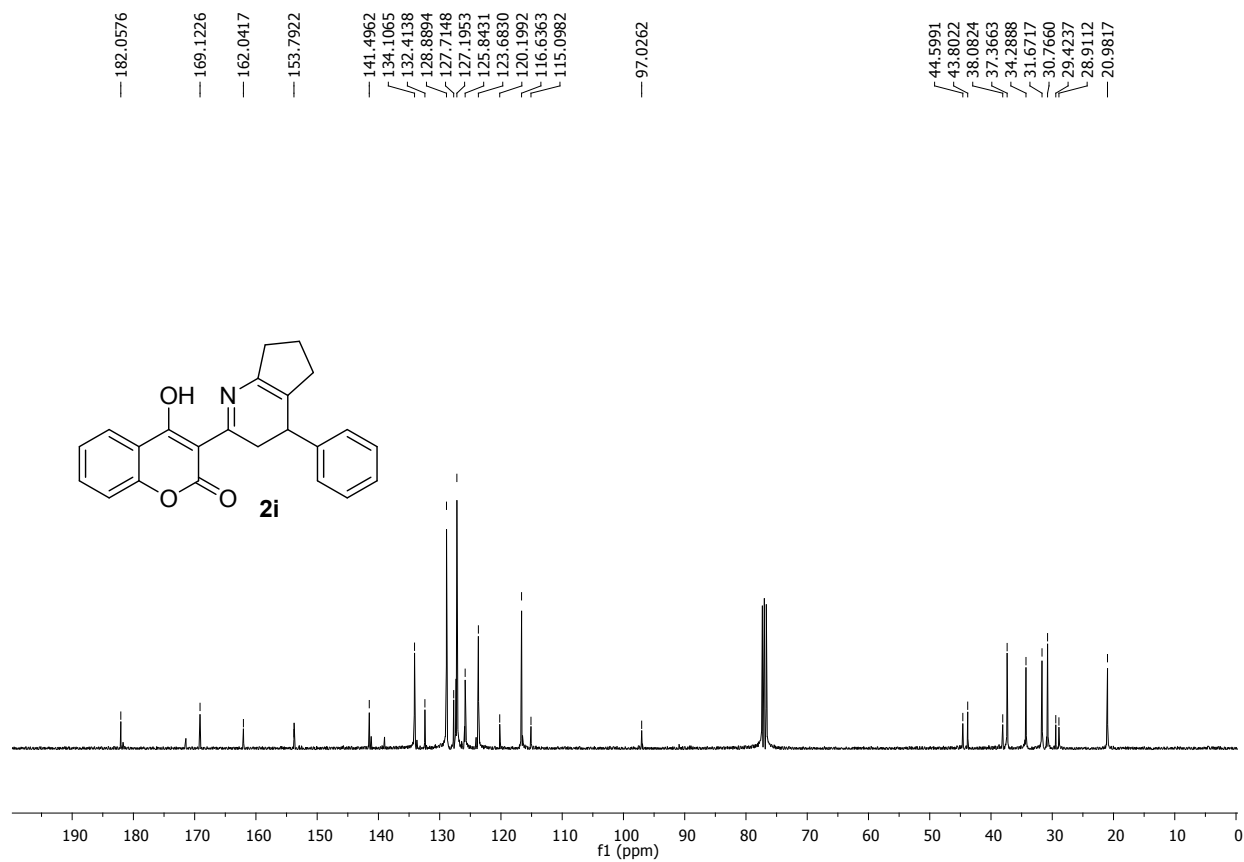


Figure S10 displays the ^1H and ^{13}C NMR spectra of compound **2j**. The chemical structure of **2j** is shown in the center.

The ^{13}C NMR spectrum (top) shows peaks at 15.1350, 8.0439, 8.0204, 8.0001, 7.9706, 7.5503, 7.5410, 7.5233, 7.5026, 7.4822, 7.4616, 7.4330, 7.3988, 7.3781, 7.2223, 7.2029, 7.1788, 7.1581, 7.1183, 7.0976, 6.9951, 6.9743, 5.6237, 3.9945, 3.9674, 3.9345, 3.9052, 3.7340, 3.7107, 3.6710, 3.6419, 2.6702, 2.6575, 2.3063, 2.2626, 2.0675, 2.0244, and 1.9869 ppm.

The ^1H NMR spectrum (middle) shows peaks at 8.15, 8.10, 8.05, 8.00, 7.95, and 7.90 ppm. Integration values are 1.00 and 1.33.

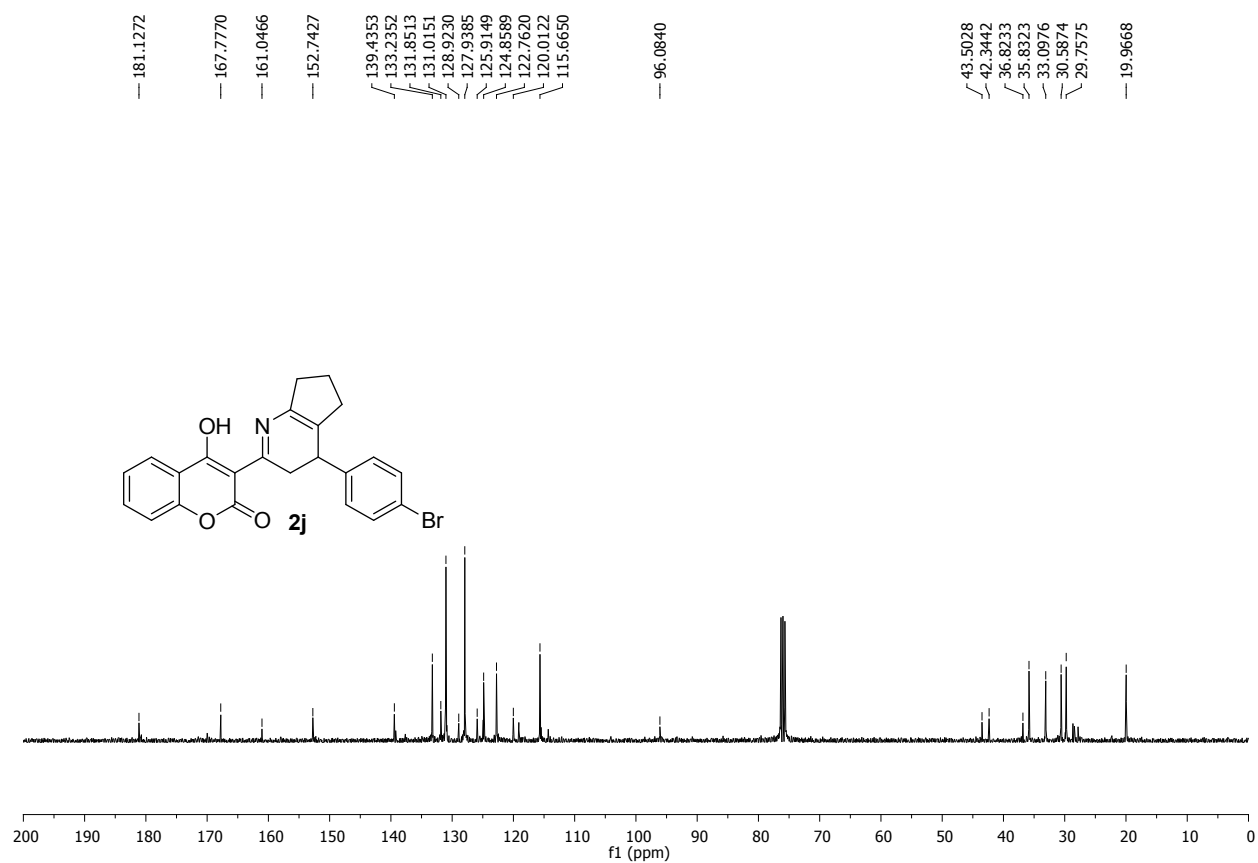
The ^1H NMR spectrum (bottom left) shows peaks at 7.30, 7.25, 7.20, 7.15, 7.10, 7.05, 7.00, and 6.95 ppm. Integration values are 1.86, 0.58, and 1.32.

The ^1H NMR spectrum (bottom middle) shows peaks at 4.00, 3.95, 3.90, and 3.85 ppm. Integration values are 0.93 and 1.33.

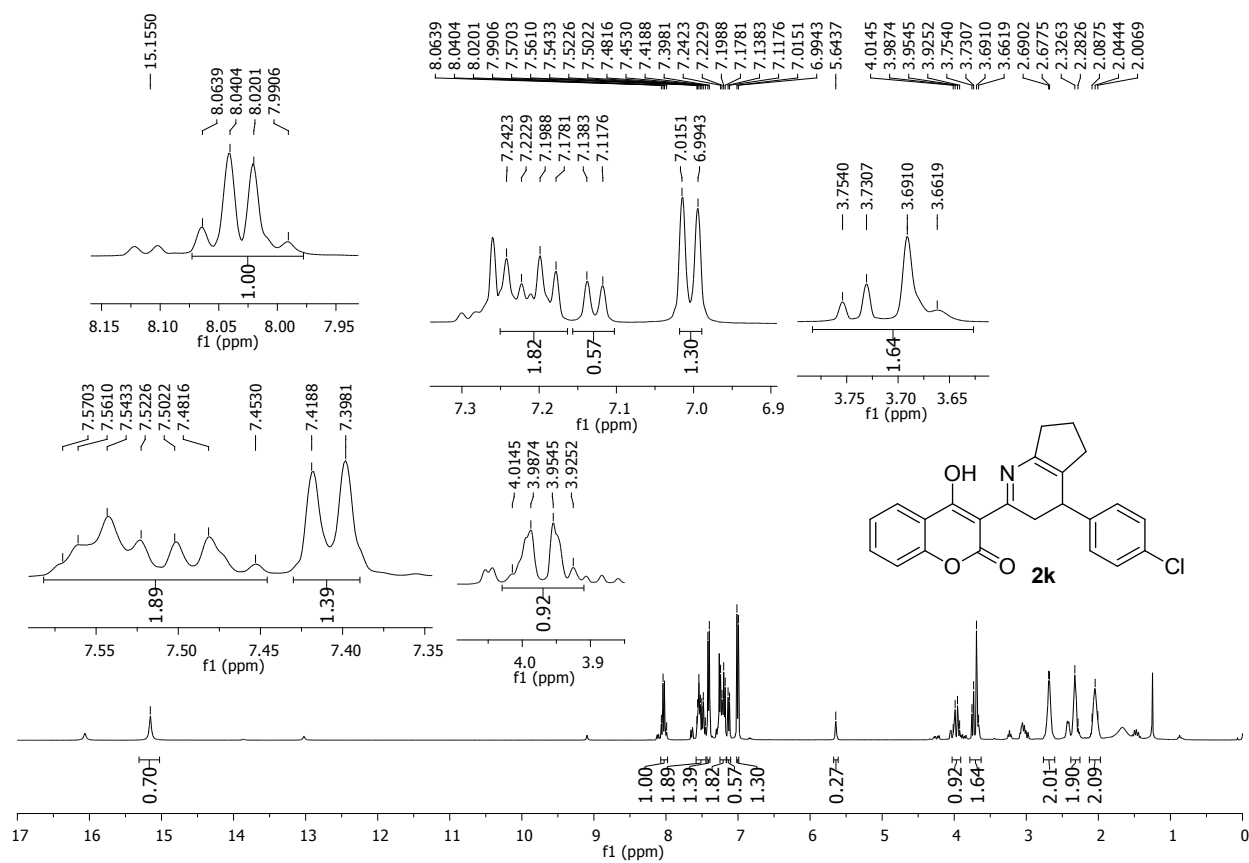
The ^1H NMR spectrum (bottom right) shows peaks at 3.80, 3.75, 3.70, 3.65, and 3.60 ppm. Integration values are 1.67 and 1.33.

The full ^1H NMR spectrum (bottom) shows peaks from 17 to 0 ppm. Integration values are 0.71, 1.00, 1.93, 1.33, 1.86, 0.58, 1.32, 0.27, 0.93, 1.67, 2.05, 1.94, and 2.13.

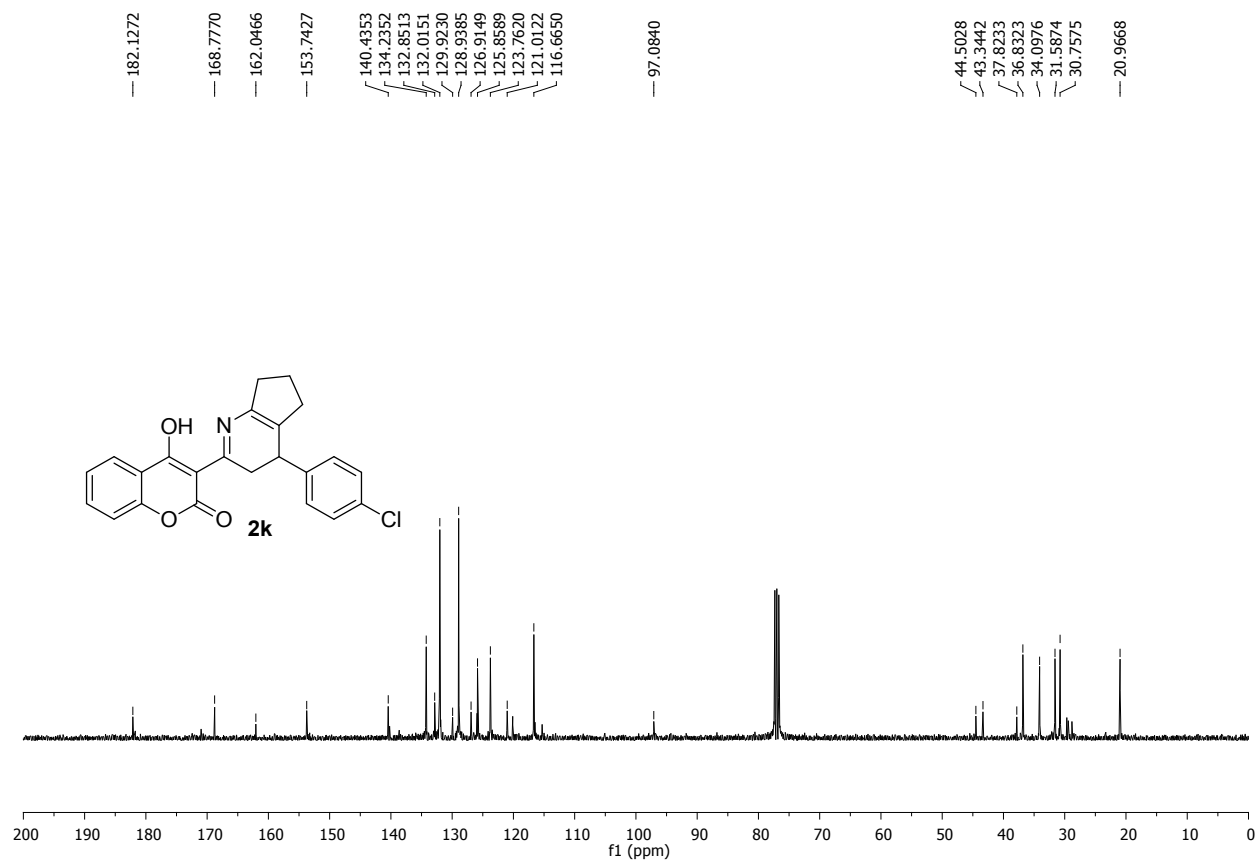
3-(4-(4-bromophenyl)-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-2-yl)-4-hydroxy-2H-chromen-2-one (2j): ^{13}C NMR



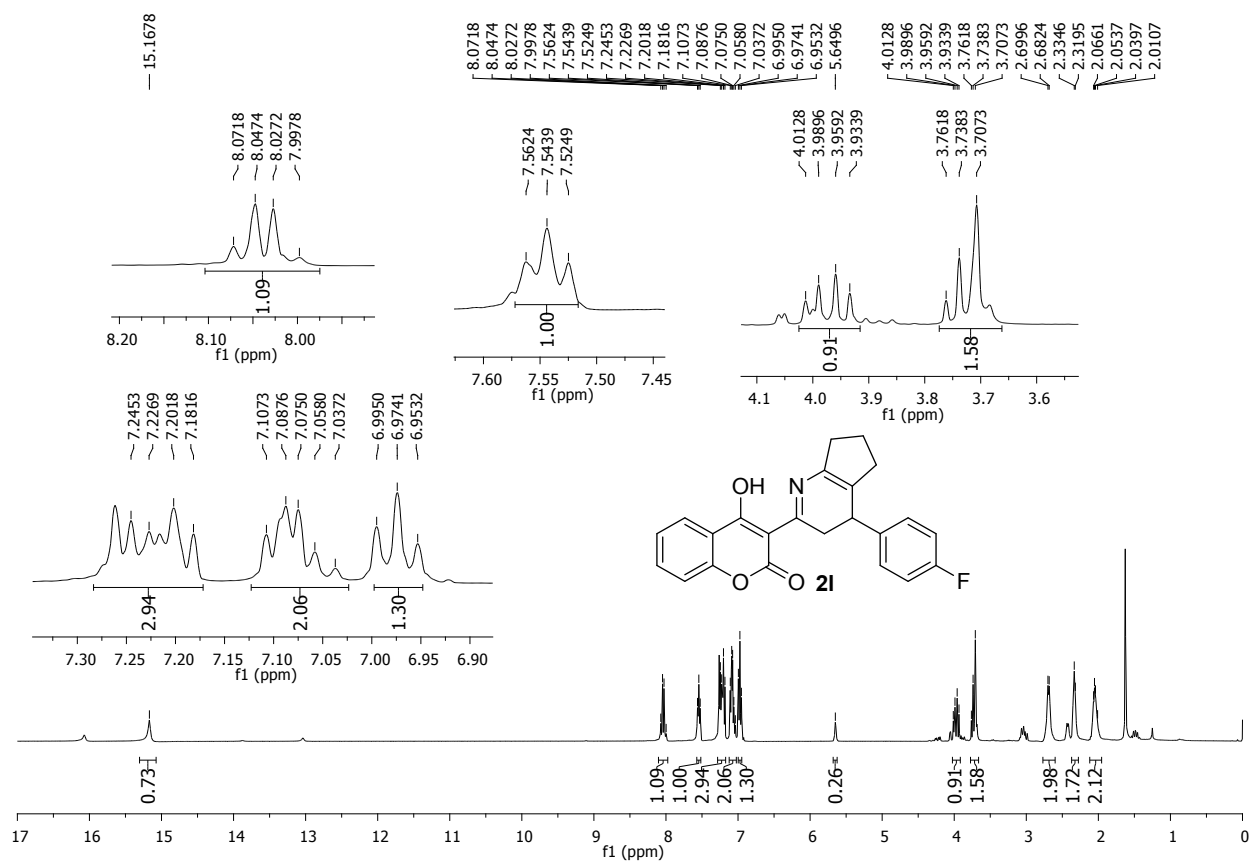
3-(4-(4-chlorophenyl)-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-2-yl)-4-hydroxy-2H-chromen-2-one (2k): ^1H NMR



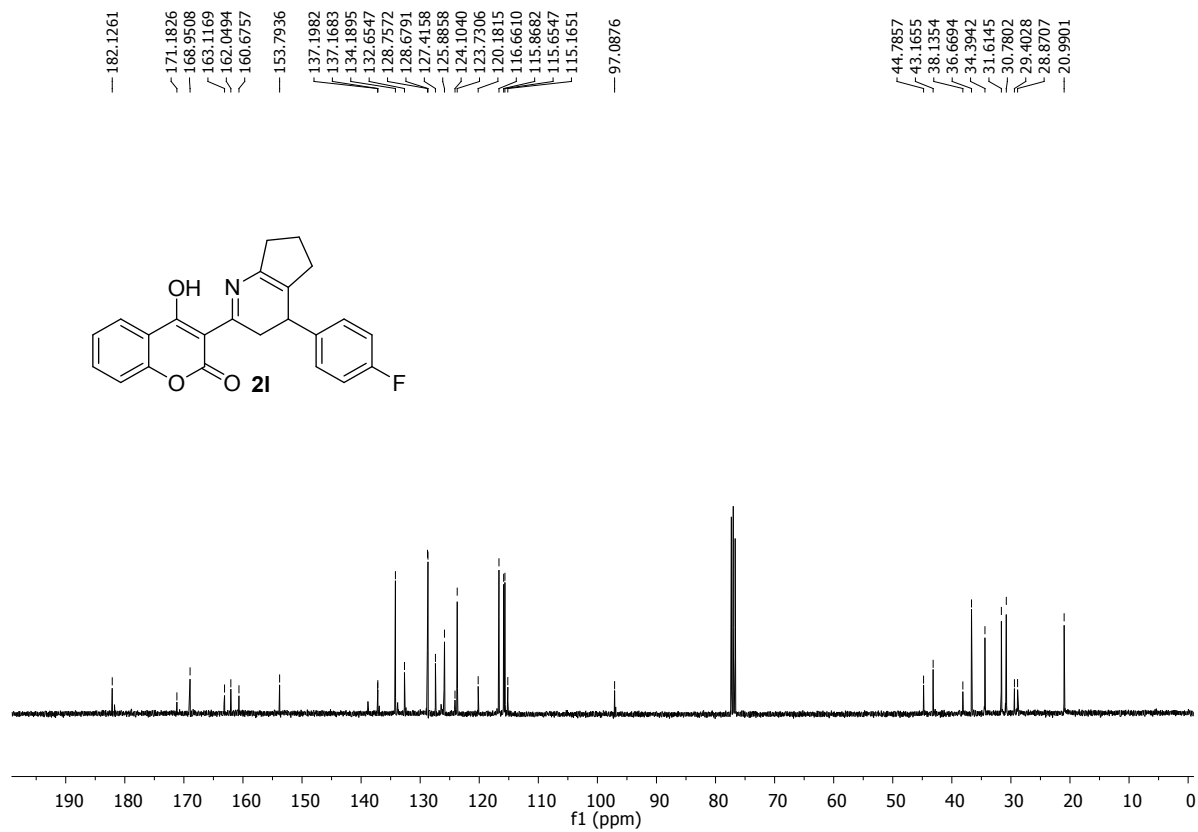
3-(4-(4-chlorophenyl)-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-2-yl)-4-hydroxy-2H-chromen-2-one (2k): ^{13}C NMR



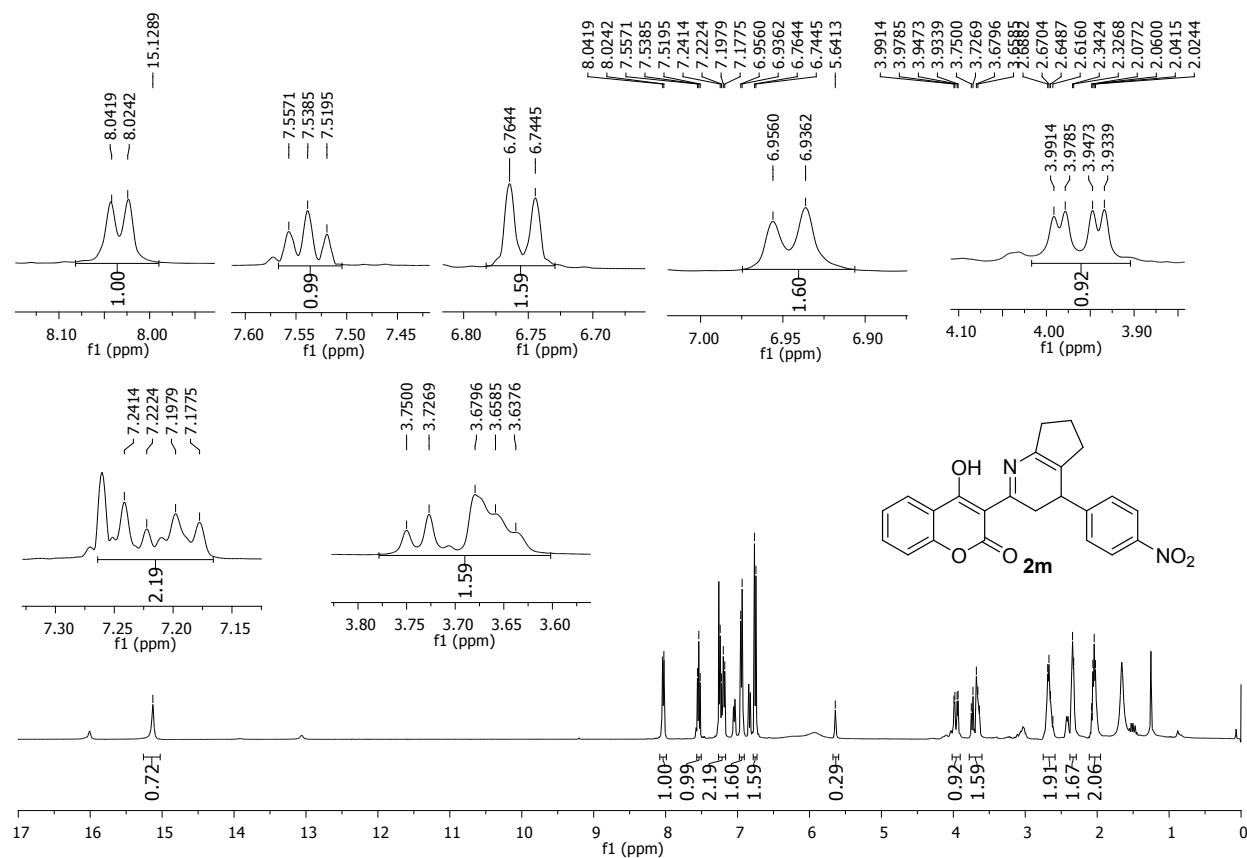
3-(4-(4-fluorophenyl)-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-2-yl)-4-hydroxy-2H-chromen-2-one (2l): ¹H NMR



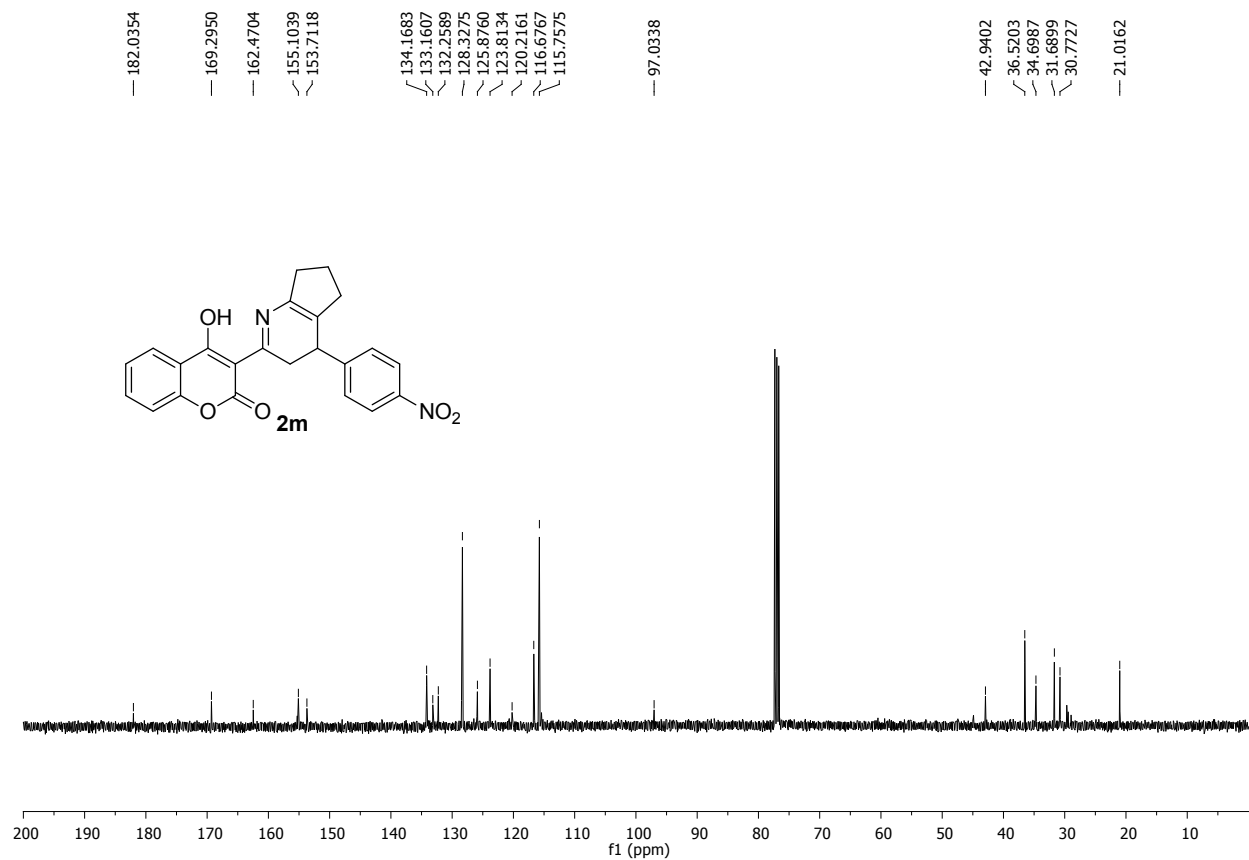
3-(4-(4-fluorophenyl)-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-2-yl)-4-hydroxy-2H-chromen-2-one (2l): ^{13}C NMR



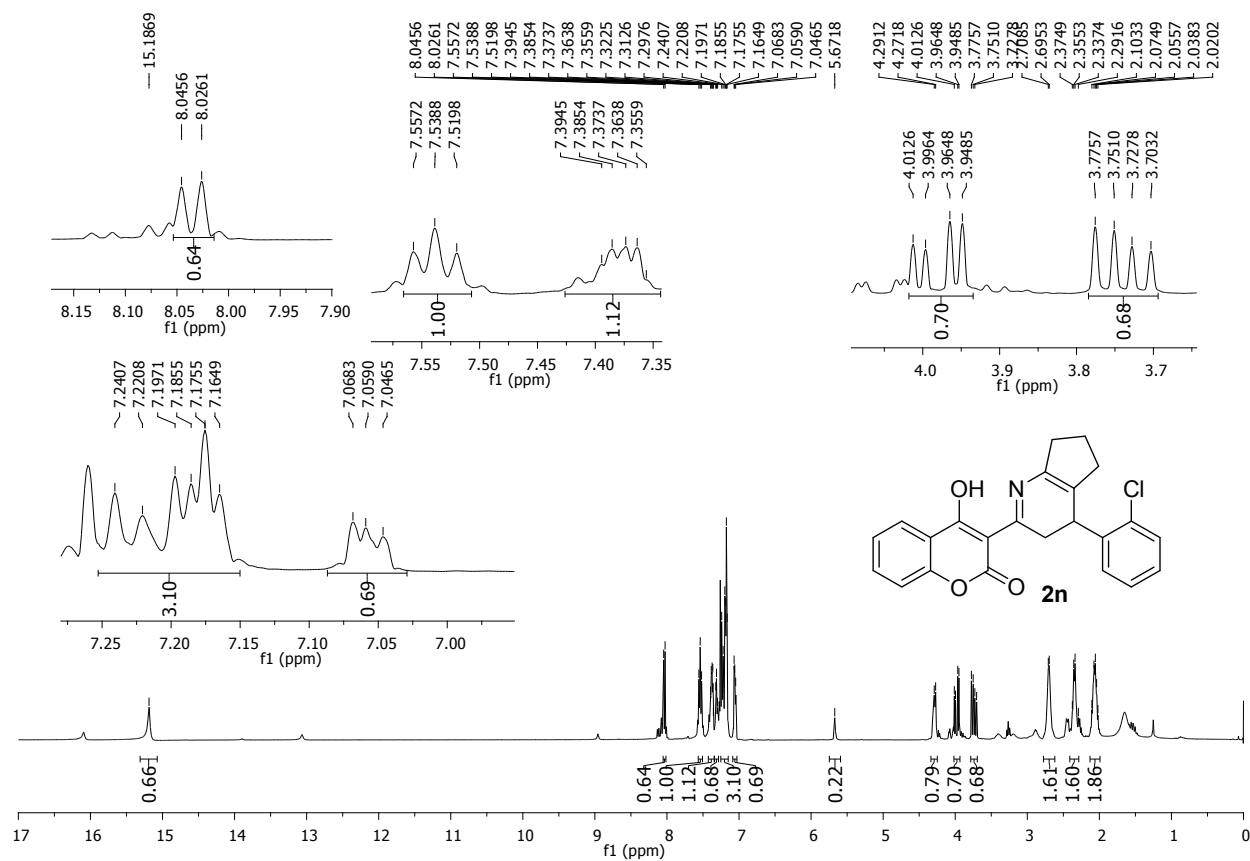
4-hydroxy-3-(4-(4-nitrophenyl)-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-2-yl)-2H-chromen-2-one (2m): ^1H NMR



4-hydroxy-3-(4-(4-nitrophenyl)-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-2-yl)-2H-chromen-2-one (2m): ^{13}C NMR



3-(4-(2-chlorophenyl)-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-2-yl)-4-hydroxy-2H-chromen-2-one (2n): ¹H NMR



3-(4-(2-chlorophenyl)-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-2-yl)-4-hydroxy-2H-chromen-2-one (2n): ^{13}C NMR

