Supporting Information

Alkoxycarbonyl radicals from alkyloxalyl chlorides: photoinduced synthesis of isoquinolinediones under visible-light irradiation

Mingjuan Ji,[‡a] Liang Xu,[‡a] Xiangxiang Luo,[a] Minghui Jiang,[a] Siyu Wang,[a] Jian-Qiang Chen,*[a] and Jie Wu*[a,b,c]

[a] School of Pharmaceutical and Materials Engineering & Institute for Advanced Studies, Taizhou University, Taizhou 318000, China.
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China.
[c] School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, China.
Corresponding author: chenjq@tzc.edu.cn; jie_wu@fudan.edu.cn

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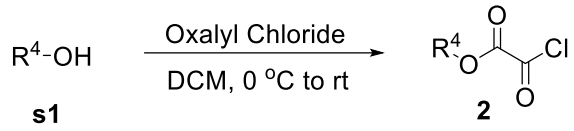
1. General information

All glassware was thoroughly oven-dried. Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Thin-layer chromatography plates were visualized by exposure to ultraviolet light and/or staining with phosphomolybdic acid followed by heating on a hot plate. Flash chromatography was carried out using silica gel (200−300 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz). The spectra were recorded in deuterochloroform ($CDCl_3$) as solvent at room temperature, ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual solvent peak. The residual solvent signals were used as references and the chemical shifts were converted to the TMS scale ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet, br = broad), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported as chemical shift. HRMS were performed on a Bruker Apex II mass instrument (ESI).

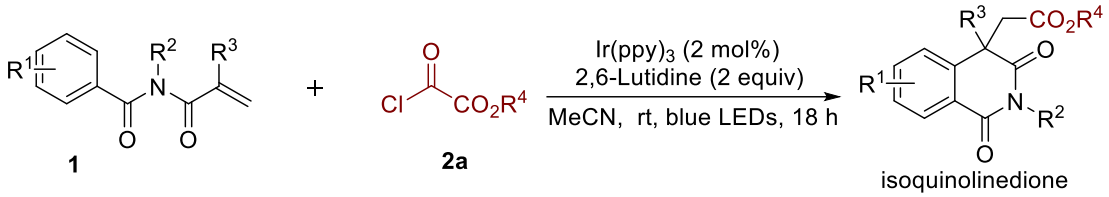
2. General procedure for the synthesis of substrates 2.[1]



Into a 100 mL round-bottom flask equipped with a magnetic stir-bar was added solution of oxalyl chloride (20 mmol, 2 equiv.) in DCM (20 mL). The mixture was stirred at 0 ℃, and a solution of an appropriate alcohol **s1** (10 mmol) in dry DCM (20 ml) was added drop-wise over 30 min. When the addition was completed, the mixture was allowed to warm to room temperature for 2 h. Excess oxalyl chloride was removed by vacuum distillation. The alkyloxyoxalyl chloride **2** was used for the next step without purification.

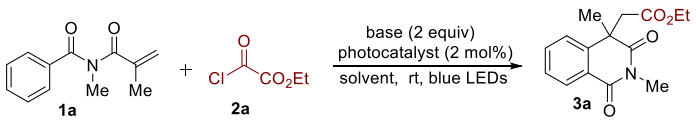
Ethyl chlorooxoacetate **2a** and methyl chloroglyoxylate are commercially available.

3. General procedure for isoquinolinediones.



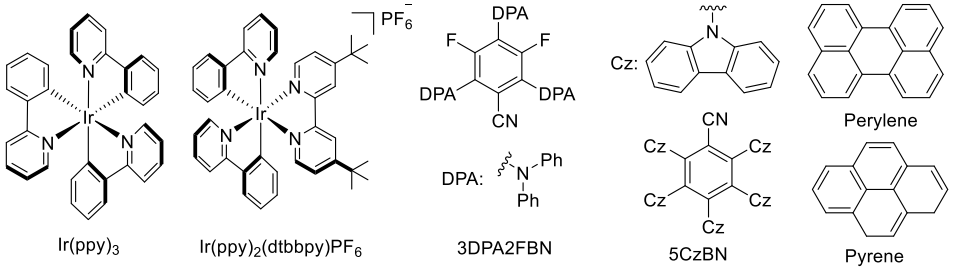
All optimization reactions were set up in a glove box under N_2 atmosphere. Substrate **1** (0.2 mmol), alkyloxyoxalyl chloride **2** (0.6 mmol) and 2,6-lutidine (0.4 mmol) were added to a solution of photocatalyst $Ir(ppy)_3$ (2 mol %) in dry MeCN (4 mL) at room temperature. The heterogenous mixture was placed in the irradiation apparatus equipped with 36 W blue LEDs. The resulting mixture was stirred at rt for 18 h. Upon completion of the reaction, the mixture was diluted with ethyl acetate (30 mL), washed with brine (10 x 3 mL), dried with Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography on silica gel to afford the desired product.

4. Initial studies and the reaction optimization.



Entry	Photocatalyst	Solvent	Base	Time	Yield (%)[a,b]
1	$Ir(ppy)_3$	DMF	2,6-Lutidine	12 h	70
2	$Ir(ppy)_2(dtbbpy)PF_6$	DMF	2,6-Lutidine	12 h	37
3	5CzBN	DMF	2,6-Lutidine	12 h	24
4	3DPA2FBN	DMF	2,6-Lutidine	12 h	47
5	$Ir(ppy)_3$	DMA	2,6-Lutidine	24 h	31
6	$Ir(ppy)_3$	MeCN	2,6-Lutidine	18 h	76
7	Perylene	MeCN	2,6-Lutidine	18 h	20
8	Pyrene	MeCN	2,6-Lutidine	18 h	0
9	Eosin Y	MeCN	2,6-Lutidine	18 h	0
10	$Ir(ppy)_3$	THF	2,6-Lutidine	36 h	14
11	$Ir(ppy)_3$	Xylenes	2,6-Lutidine	36 h	trace
12	$Ir(ppy)_3$	DCE	2,6-Lutidine	48 h	47
13	$Ir(ppy)_3$	DCM	2,6-Lutidine	48 h	30
14	$Ir(ppy)_3$	$CHCl_3$	2,6-Lutidine	48 h	25
15	$Ir(ppy)_3$	EA	2,6-Lutidine	48 h	17
16	$Ir(ppy)_3$	Acetone	2,6-Lutidine	48 h	trace
17	$Ir(ppy)_3$	MeCN	-	18 h	29
18	$Ir(ppy)_3$	MeCN	2,6-di^{t}Bu-Py	18 h	70
19	$Ir(ppy)_3$	MeCN	K_2HPO_4	18 h	51
20	$Ir(ppy)_3$	MeCN	Na_2HPO_4	18 h	19
21	$Ir(ppy)_3$	MeCN	$KHCO_3$	18 h	16
22	-	MeCN	2,6-Lutidine	18 h	0
23[c]	$Ir(ppy)_3$	MeCN	2,6-Lutidine	18 h	0
24[d]	$Ir(ppy)_3$	MeCN	2,6-Lutidine	18 h	75

[a] Unless otherwise noted, reaction conditions are as follows: **1a** (0.2 mmol), **2a** (0.6 mmol), photocatalyst (0.004 mmol), base (0.4 mmol), solvent (4 mL), 36 W blue LEDs, under a N_2 atmosphere. [b] Yield determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene an internal standard. [c] In the dark. [d] 72 W blue LEDs.



5. Devices for the photocatalytic reactions

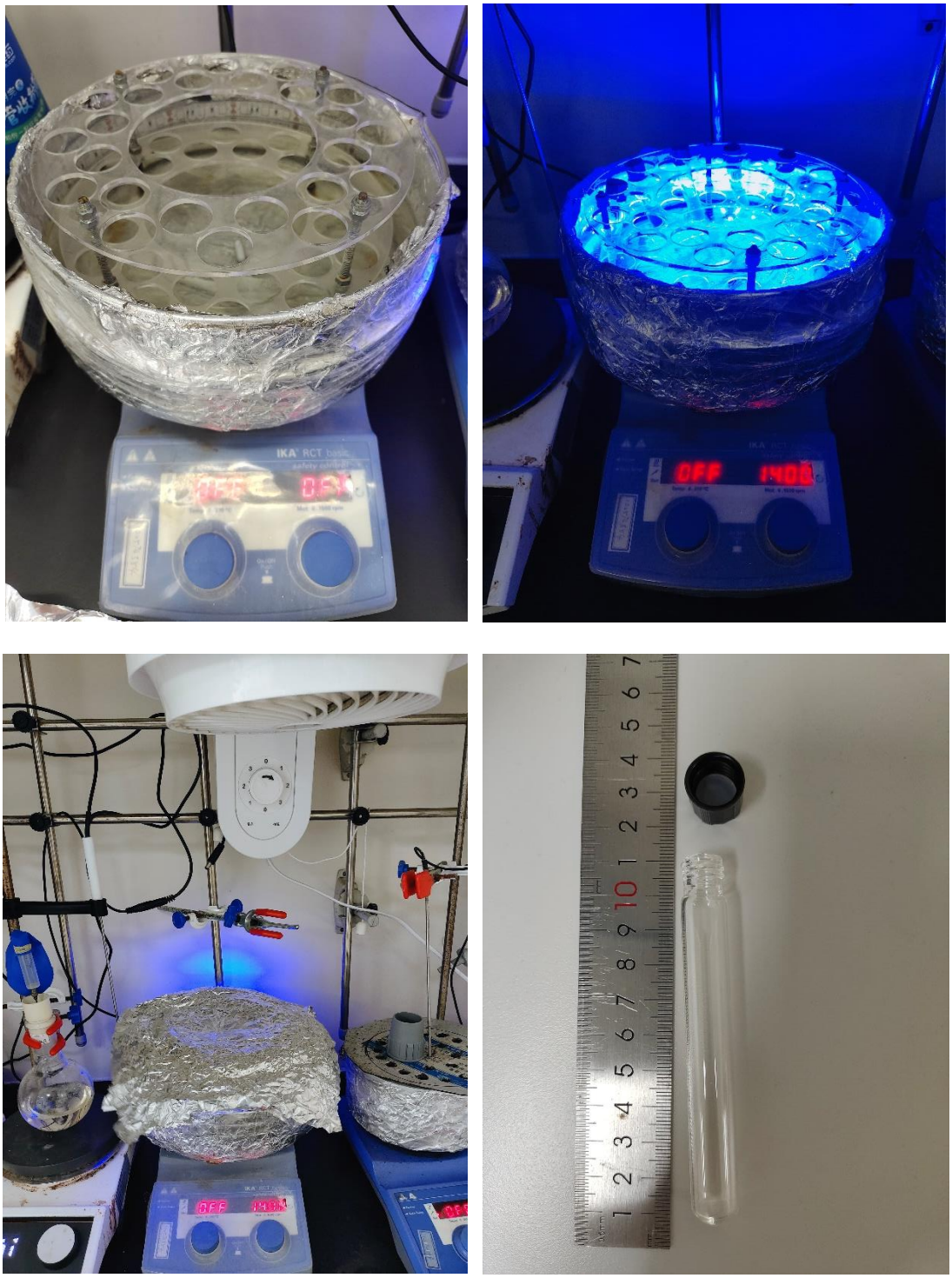
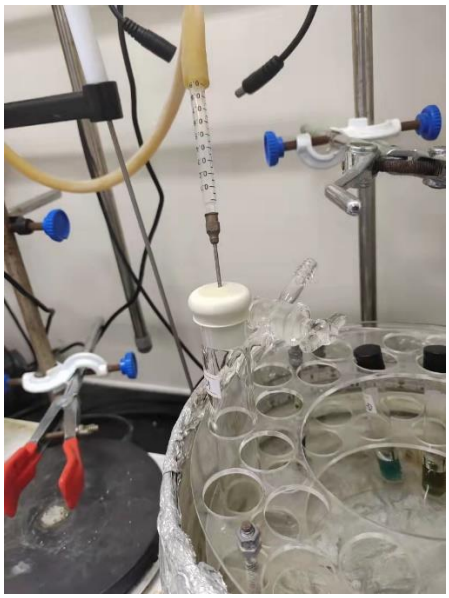
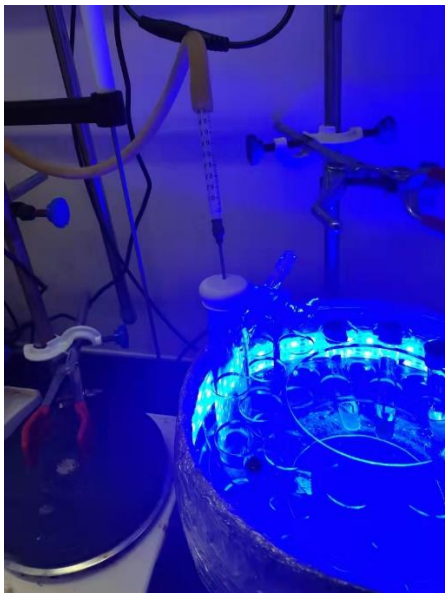


Figure S1 Devices for the photocatalytic reactions

6. Further investigations





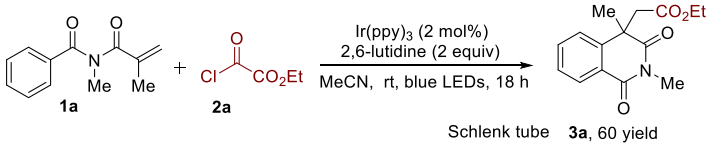


Figure S2 When the reaction was conducted in a Schlenk tube (open with a weak N_2 flow), the yield of **3a** was decreased to 60%.

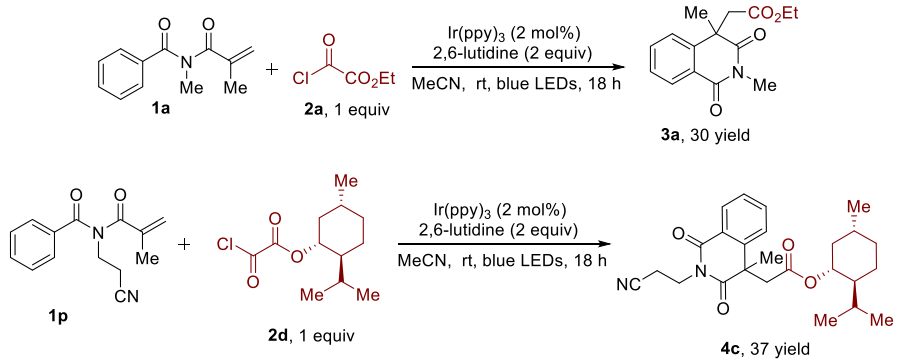
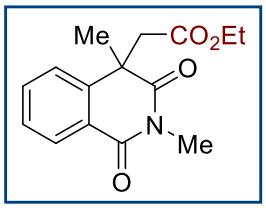


Figure S3 By using alkyloxalyl chloride as the limiting reagent, the reaction efficiency was decreased.

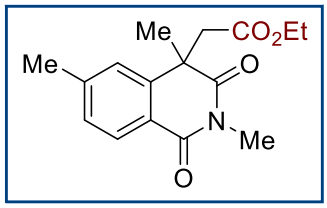
7. Characterization of products

ethyl 2-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3a)



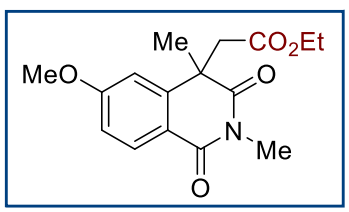
Purification by flash chromatography (PE/EA = 6/1) afforded **3a.** Colorless oil; 40.2 mg, 73% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.98 (t, *J* = 7.1 Hz, 3H), 1.56 (s, 3H), 3.05 (d, *J* = 16.9 Hz, 1H), 3.42 (s, 3H), 3.61 (d, *J* = 16.9 Hz, 1H), 3.79−3.91 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.43 (td, *J* = 7.9, 1.1 Hz, 1H), 7.62 (td, *J* = 7.9, 1.5 Hz, 1H), 8.27 (dd, *J* = 7.9, 1.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.7, 27.3, 30.5, 44.8, 44.9, 60.7, 124.2, 124.8, 127.5, 129.1, 133.9, 142.8, 164.3, 169.8, 176.2; HRMS (ESI) for $C_{15}H_{17}NO_4Na$ $[M+Na]^+$ calcd. 298.1050, found 298.1063.

ethyl 2-(2,4,6-trimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3b)



Purification by flash chromatography (PE/EA = 6/1) afforded **3b.** Colorless oil; 22.5 mg, 39% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.97 (t, *J* = 7.1 Hz, 3H), 1.54 (s, 3H), 2.43 (s, 3H), 3.03 (d, *J* = 16.9 Hz, 1H), 3.40 (s, 3H), 3.59 (d, *J* = 16.9 Hz, 1H), 3.80−3.92 (m, 2H), 7.12 (s, 1H), 7.23 (dd, *J* = 8.0, 0.8 Hz, 1H), 8.15 (d, *J* =8.0 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.8, 21.9, 27.2, 30.6, 44.8, 44.9, 60.7, 122.3, 124.7, 128.6, 129.2, 142.8, 144.7, 164.3, 169.9, 176.4; HRMS (ESI) for $C_{16}H_{19}NO_4Na$ $[M+Na]^+$ calcd. 312.1206, found 312.1216.

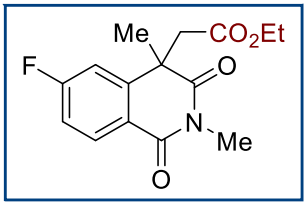
ethyl 2-(6-methoxy-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3c)



Purification by flash chromatography (PE/EA = 6/1) afforded **3c.** Colorless oil; 30.5 mg, 50% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 1.00 (t, *J* = 7.2 Hz, 3H), 1.54 (s, 3H), 3.00 (d, *J* = 16.9 Hz, 1H), 3.39 (s, 3H), 3.60 (d, *J* = 16.9 Hz, 1H), 3.81−3.94 (m, 5H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 8.8, 2.4

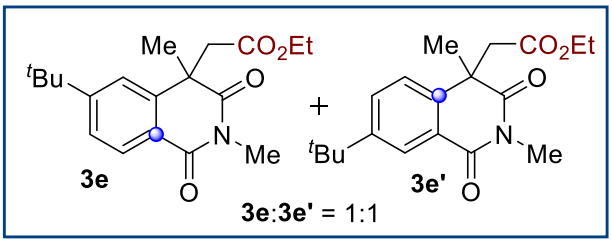
Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ (ppm) = 13.8, 27.1, 30.7, 44.7, 45.1, 55.5, 60.7, 109.9, 112.9, 117.8, 131.5, 145.0, 164.0, 164.0, 169.8, 176.3; HRMS (ESI) for $C_{16}H_{19}NO_5Na$ $[M+Na]^+$ calcd. 328.1155, found 328.1167.

ethyl 2-(6-fluoro-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3d)



Purification by flash chromatography (PE/E = 6/1) afforded **3d.** Colorless oil; 37.5 mg, 64% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) = 1.04 (t, J = 7.1 Hz, 3H), 1.55 (s, 3H), 2.98 (d, J = 17.2 Hz, 1H), 3.41 (s, 3H), 3.62 (d, J = 17.2Hz, 1H), 3.83−3.95 (m, 2H), 7.02 (dd, J = 9.3, 2.3 Hz, 1H), 7.10−7.1 (m, 1H), 8.30 (dd, J = 8.7, 5.9 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ (ppm) = 13.8, 27.3, 30.4, 44.6, 45.1, 60.9, 111.3 (J = 22.9 Hz), 115.3 (J = 21.9 Hz), 121.3 (J = 2.6 Hz), 132.2 (J = 9.6 Hz), 145.9 (J = 8.2 Hz), 163.4, 166.2 (J = 253.9 Hz), 169.7, 175.8; HRMS (ESI) for $C_{15}H_{16}FNO_4Na$ $[M+Na]^+$ calcd. 316.0956, found 316.0970.

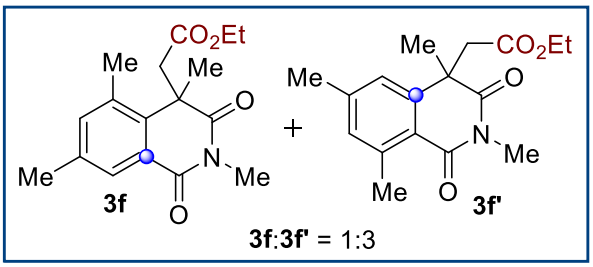
ethyl 2-(6-(tert-butyl)-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3e) + ethyl 2-(7-(tert-butyl)-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3e')



Purification by flash chromatography (PE/EA = 6/1) afforded **3e** + **3e'.** Colorless oil; 49.0 mg, 74% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) = 0.92−0.98 (m, 6H), 1.34−1.35 (m, 18H), 1.54−1.56 (m, 6H), 3.01−3.08 (m, 2H), 3.41−3.42 (m, 6H), 3.56−3.65 (m, 2H), 7.28 (d, J = 8.2 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H), 7.46 (dd, J = 8.4, 1.8 Hz, 1H), 7.64 (dd, J = 8.2, 2.2 Hz, 1H), 8.17 (d, J = 8.3 Hz, 1H), 8.27 (d, J = 2.2 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ (ppm) = 13.7, 13.8, 27.2, 27.3, 30.5, 30.7, 31.0, 31.1, 34.7, 35.3, 44.6, 44.8, 45.3, 60.5, 60.6, 120.8, 122.2, 124.1, 124.3, 124.8, 125.7, 128.9, 131.2, 139.8, 142.4, 150.6, 157.6, 164.3, 164.7, 169.9,

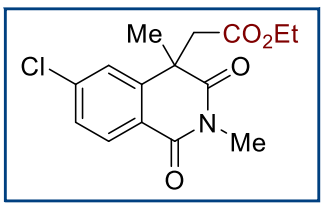
169.9, 176.4; HRMS (ESI) for $C_{19}H_{25}NO_4Na$ $[M+Na]^+$ calcd. 354.1676, found 354.1690.

ethyl 2-(2,4,5,7-tetramethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3f) + ethyl 2-(2,4,6,8-tetramethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3f')



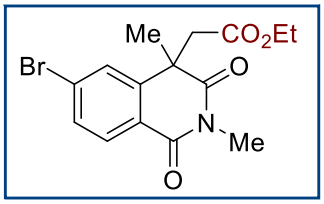
Purification by flash chromatography (PE/EA = 6/1) afforded **3f + 3f'.** Colorless oil; 53.4 mg, 88% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.95 (t, *J* = 7.1 Hz, 1H), 1.00 (t, *J* = 7.1 Hz, 3H), 1.53 (s, 3H), 1.64 (s, 1H), 2.36 (s, 1H), 2.37 (s, 3H), 2.56 (s, 1H), 2.75 (s, 3H), 3.03 (d, *J* = 17.0 Hz, 1H), 3.38 (s, 3H), 3.39−3.43 (m, 1.33H), 3.61 (d, *J* = 17.0 Hz, 1H), 3.70 (d, *J* = 16.9 Hz, 0.33H), 3.78−3.94 (m, 2.67H), 7.00 (s, 1H), 7.03 (d, *J* = 0.5 Hz, 1H), 7.22 (dd, *J* = 1.4, 0.6 Hz, 0.33H), 8.04 (dd, *J* = 1.3, 0.5 Hz, 0.33H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.7, 13.8, 20.6, 21.6, 22.4, 23.8, 26.7, 27.1, 27.5, 31.1, 42.9, 44.8, 44.9, 46.2, 60.5, 60.5, 120.5, 122.9, 125.8, 128.2, 132.5, 134.4, 136.7, 137.1, 139.4, 142.6, 143.2, 144.2, 164.7, 164.8, 170.0, 170.2, 176.0, 177.3; HRMS (ESI) for $C_{17}H_{21}NO_4Na$ $[M+Na]^+$ calcd. 326.1363, found 326.1372.

ethyl 2-(6-chloro-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3g)



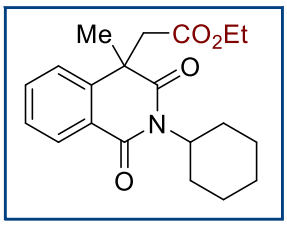
Purification by flash chromatography (PE/EA = 6/1) afforded **3g.** Colorless oil; 34.7 mg, 56% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 1.04 (t, *J* = 7.2 Hz, 3H), 1.55 (s, 3H), 3.00 (d, *J* = 17.2 Hz, 1H), 3.41 (s, 3H), 3.61 (d, *J* = 17.2 Hz, 1H), 3.84−3.96 (m, 2H), 7.32 (d, *J* = 1.9 Hz, 1H), 7.41 (dd, *J* = 8.5, 1.9 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.8, 27.4, 30.4, 44.6, 45.0, 60.9, 123.4, 124.5, 128.1, 130.8, 140.4, 144.6, 163.5, 169.7, 175.6; HRMS (ESI) for $C_{15}H_{16}ClNO_4Na$ $[M+Na]^+$ calcd. 332.0660, found 332.0673.

ethyl 2-(6-bromo-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3h)



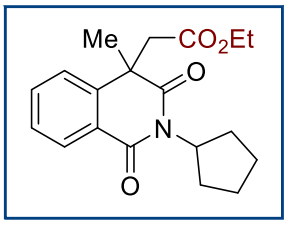
Purification by flash chromatography (PE/EA = 6/1) afforded **3h.** Colorless oil; 31.1 mg, 44% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 1.04 (t, *J* = 7.1 Hz, 3H), 1.55 (s, 3H), 3.00 (d, *J* = 17.2 Hz, 1H), 3.40 (s, 3H), 3.60 (d, *J* = 17.2 Hz, 1H), 3.84−3.96 (m, 2H), 7.48 (d, *J* = 1.8 Hz, 1H), 7.57 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.8, 27.4, 30.4, 44.6, 44.9, 60.9, 123.8, 127.5, 129.0, 130.8, 131.1, 144.7, 163.7, 169.7, 175.6; HRMS (ESI) for $C_{15}H_{16}BrNO_4Na$ $[M+Na]^+$ calcd. 376.0155, found 376.0168.

ethyl 2-(2-cyclohexyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3i)



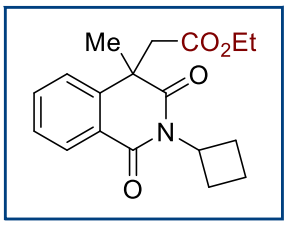
Purification by flash chromatography (PE/EA = 6/1) afforded **3i.** Colorless oil; 30.2 mg, 44% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.96 (t, *J* = 7.1 Hz, 3H), 1.21−1.32 (m, 1H), 1.33−1.46 (m, 2H), 1.53 (s, 3H), 1.64−1.74 (m, 3H), 1.83−1.87 (m, 2H), 2.35−2.48 (m, 2H), 3.00 (d, *J* = 16.9 Hz, 1H), 3.59 (d, *J* = 16.9 Hz, 1H), 3.77−3.93 (m, 2H), 4.77−4.85 (m, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.41 (td, *J* = 8.0, 1.0 Hz, 1H), 7.58 (td, *J* = 8.0, 1.4 Hz, 1H), 8.22 (dd, *J* = 7.9, 1.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 25.4, 26.4, 26.5, 28.6, 29.1, 30.6, 44.4, 45.3, 54.0, 60.6, 123.9, 125.5, 127.4, 129.2, 133.6, 142.7, 164.4, 169.8, 176.3; HRMS (ESI) for $C_{20}H_{25}NO_4Na$ $[M+Na]^+$ calcd. 366.1676, found 366.1686.

ethyl 2-(2-cyclopentyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3j)



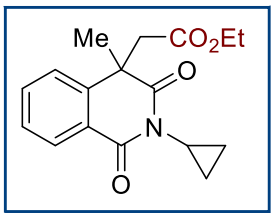
Purification by flash chromatography (PE/EA = 10/1) afforded **3j.** Colorless oil; 32.9 mg, 50% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.96 (t, *J* = 7.1 Hz, 3H), 1.54 (s, 3H), 1.60−1.65 (m, 2H), 1.82−1.93 (m, 2H), 1.96−2.14 (m, 4H), 3.01 (d, *J* = 16.8 Hz, 1H), 3.60 (d, *J* = 16.8 Hz, 1H), 3.78−3.92 (m, 2H), 5.34−5.42 (m, 1H), 7.32 (dd, *J* = 7.9, 0.5 Hz, 1H), 7.42 (td, *J* = 7.6, 1.1 Hz, 1H), 7.59 (td, *J* = 7.6, 1.4 Hz, 1H), 8.25 (dd, *J* = 7.6, 1.1 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.8, 26.0, 26.0, 28.5, 28.7, 30.5, 44.5, 45.2, 53.0, 60.6, 124.1, 125.4, 127.4, 129.2, 133.6, 142.7, 164.5, 169.8, 175.9; HRMS (ESI) for $C_{19}H_{23}NO_4Na$ $[M+Na]^+$ calcd. 352.1519, found 352.1530.

ethyl 2-(2-cyclobutyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3k)



Purification by flash chromatography (PE/EA = 10/1) afforded **3k.** Colorless oil; 41.0 mg, 65% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.97 (t, *J* = 7.2 Hz, 3H), 1.55 (s, 3H), 1.73−1.86 (m, 1H), 1.87−1.97 (m, 1H), 2.361.73−2.47 (m, 2H), 2.63−2.77 (m, 2H), 3.00 (d, *J* = 16.9 Hz, 1H), 3.58 (d, *J* = 16.9 Hz, 1H), 3.79−3.91 (m, 2H), 5.05−5.14 (m, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.41 (td, *J* = 7.6, 1.1 Hz, 1H), 7.59 (td, *J* = 7.6, 1.4 Hz, 1H), 8.22 (dd, *J* = 7.9, 1.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.7, 15.6, 28.3, 28.6, 30.3, 44.4, 45.3, 48.7, 60.6, 124.1, 125.5, 127.4, 129.0, 133.6, 142.7, 164.5, 169.8, 176.2; HRMS (ESI) for $C_{18}H_{21}NO_4Na$ $[M+Na]^+$ calcd. 338.1363, found 338.1374.

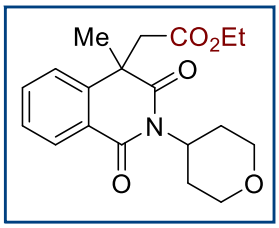
ethyl 2-(2-cyclopropyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3l)



Purification by flash chromatography (PE/EA = 10/1) afforded **3l.** Colorless oil; 41.0 mg, 68% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.63−0.71 (m, 1H), 0.74−0.83 (m, 1H), 0.99 (t, *J* = 7.1 Hz, 3H), 1.11−1.22 (m, 2H), 1.52 (s, 3H), 2.75−2.81

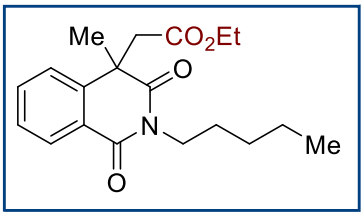
(m, 1H), 3.02 (d, J = 16.9 Hz, 1H), 3.58 (d, J = 16.9 Hz, 1H), 3.79−3.93 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 8.2, 8.6, 13.8, 24.5, 30.2, 44.5, 45.2, 60.7, 124.2, 125.4, 127.4, 129.0, 133.7, 142.7, 165.2, 169.9, 177.0; HRMS (ESI) for $C_{17}H_{19}NO_4Na$ $[M+Na]^+$ calcd. 324.1206, found 324.1212.

ethyl 2-(4-methyl-1,3-dioxo-2-(tetrahydro-2H-pyran-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3m)



Purification by flash chromatography (PE/EA = 6/1) afforded **3m.** Colorless oil; 36.6 mg, 53% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.98 (t, J = 7.1 Hz, 3H), 1.54−1.62 (m, 5H), 2.74−2.87 (m, 2H), 3.02 (d, J = 16.9 Hz, 1H), 3.47−3.55 (m, 2H), 3.59 (d, J = 16.9 Hz, 1H), 3.79−3.93 (m, 2H), 4.05−4.10 (m, 2H), 5.02−5.11 (m, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.42 (td, J = 7.6, 1.0 Hz, 1H), 7.60 (td, J = 7.6, 1.4 Hz, 1H), 8.25 (dd, J = 7.9, 1.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.8, 28.8, 29.3, 30.5, 44.6, 45.3, 51.0, 60.7, 68.0, 68.1, 124.1, 125.3, 127.5, 129.3, 133.8, 142.7, 164.4, 169.9, 176.3; HRMS (ESI) for $C_{19}H_{23}NO_5Na$ $[M+Na]^+$ calcd. 368.1468, found 368.1477.

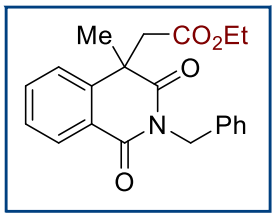
ethyl 2-(4-methyl-1,3-dioxo-2-pentyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3n)



Purification by flash chromatography (PE/EA = 10/1) afforded **3n.** Colorless oil; 45.0 mg, 68% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.90 (t, J = 6.9 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H), 1.31−1.40 (m, 4H), 1.61−1.69 (m, 2H), 3.05 (d, J = 16.9 Hz, 1H), 3.62 (d, J = 16.9 Hz, 1H), 3.78−3.93 (m, 2H), 3.95−4.08 (m, 2H), 7.34 (d, J = 7.8 Hz, 1H), 7.42 (td, J = 7.6, 1.1 Hz, 1H), 7.60 (td, J = 7.6, 1.4 Hz, 1H), 8.26 (dd, J = 7.9, 1.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.8, 14.0, 22.3, 27.3, 29.1, 30.7, 40.6, 44.5, 44.9, 60.6, 124.1, 124.9, 127.4, 129.2, 133.8, 142.9, 164.0, 169.8, 175.9; HRMS (ESI) for $C_{19}H_{25}NO_4Na$ $[M+Na]^+$

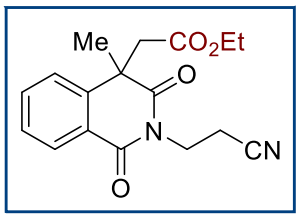
calcd. 354.1676, found 354.1683.

ethyl 2-(2-benzyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3o)



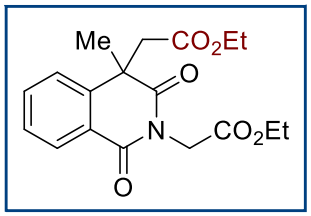
Purification by flash chromatography (PE/EA = 6/1) afforded **3o.** Colorless oil; 44.3 mg, 63% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.85 (t, *J* = 7.2 Hz, 3H), 1.53 (s, 3H), 3.06 (d, *J* = 17.0 Hz, 1H), 3.61−3.73 (m, 2H), 3.81−3.89 (m, 1H), 5.19−5.27 (m, 2H), 7.19−7.24 (m, 1H), 7.25−7.30 (m, 2H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.39−7.45 (m, 3H), 7.60 (td, *J* = 7.6, 3.6 Hz, 1H), 8.26 (dd, *J* = 7.9, 1.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.6, 30.7, 43.7, 44.4, 45.2, 60.6, 124.1, 124.8, 127.2, 127.5, 128.3, 128.5, 129.3, 134.0, 137.1, 142.9, 164.0, 169.7, 176.0; HRMS (ESI) for $C_{21}H_{21}NO_4Na$ $[M+Na]^+$ calcd. 374.1363, found 374.1369.

ethyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3p)



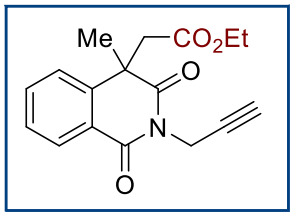
Purification by flash chromatography (PE/EA = 3/1) afforded **3p.** Colorless oil; 59.7mg, 95% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 1.00 (t, *J* = 7.1 Hz, 3H), 1.60 (s, 3H), 2.69−2.84 (m, 2H), 3.07 (d, *J* = 17.0 Hz, 1H), 3.58 (d, *J* = 17.0 Hz, 1H), 3.79−3.95 (m, 2H), 4.26−4.33 (m, 1H), 4.39−4.46 (m, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.45 (td, *J* = 7.6, 1.1 Hz, 1H), 7.65 (td, *J* = 7.6, 1.4 Hz, 1H), 8.27 (dd, *J* = 7.9, 1.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.8, 16.0, 30.3, 35.7, 44.9, 45.0, 60.8, 117.3, 124.3, 124.4, 127.7, 129.3, 134.3, 142.7, 163.7, 170.0, 175.8; HRMS (ESI) for $C_{17}H_{18}N_2O_4Na$ $[M+Na]^+$ calcd. 337.1159, found 337.1170.

diethyl 2,2'-(4-methyl-1,3-dioxo-3,4-dihydroisoquinoline-2,4(1H)-diyl)diacetate (3q)



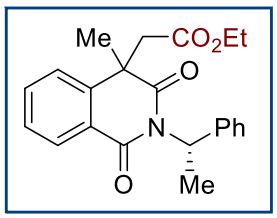
Purification by flash chromatography (PE/EA = 6/1) afforded **3q.** Colorless oil; 38.2 mg, 55% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) = 0.97 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.60 (s, 3H), 3.10 (d, *J* = 17.1 Hz, 1H), 3.63 (d, *J* = 17.1 Hz, 1H), 3.81−3.97 (m, 2H), 4.16−4.27 (m, 2H), 4.75 (d, *J* = 16.7 Hz, 1H), 4.85 (d, *J* = 16.7 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 8.27 (d, *J* = 7.9 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ (ppm) = 13.8, 14.1, 30.8, 41.4, 43.9, 45.3, 60.8, 61.4, 124.1, 124.4, 127.5, 129.4, 134.2, 143.0, 163.6, 167.9, 169.8, 175.7; HRMS (ESI) for $C_{18}H_{21}NO_6Na$ $[M+Na]^+$ calcd. 370.1261, found 370.1268.

ethyl 2-(4-methyl-1,3-dioxo-2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3r)



Purification by flash chromatography (PE/EA = 10/1) afforded **3r.** Colorless oil; 36.7 mg, 61% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) = 0.96 (t, *J* = 7.1 Hz, 3H), 1.58 (s, 3H), 2.17 (t, *J* = 2.4 Hz, 1H), 3.07 (d, *J* = 17.0 Hz, 1H), 3.64 (d, *J* = 17.0 Hz, 1H), 3.77−3.94 (m, 2H), 4.81 (d, *J* = 2.4 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.45 (td, *J* = 7.6, 1.1 Hz, 1H), 7.64 (td, *J* = 7.6, 1.5 Hz, 1H), 8.29 (dd, *J* = 7.9, 1.2 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ (ppm) = 13.7, 29.6, 30.4, 44.6, 45.2, 60.8, 70.4, 78.3, 124.3, 124.5, 127.6, 129.3, 134.2, 142.8, 163.2, 169.6, 175.1; HRMS (ESI) for $C_{17}H_{17}NO_4Na$ $[M+Na]^+$ calcd. 322.1050, found 322.1062.

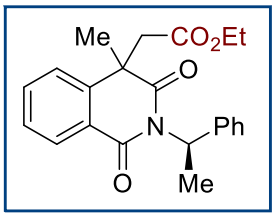
ethyl 2-(4-methyl-1,3-dioxo-2-((S)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3s)



Purification by flash chromatography (PE/EA = 10/1) afforded **3s.** Colorless oil; 36.7 mg, 50% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) = 0.90−0.95 (m, 6H), 1.43 (s, 3H), 1.59 (s, 3H), 1.87−1.90 (m, 6H), 3.00−3.05 (m, 2H), 3.56−3.63 (m, 2H), 3.72−3.99 (m, 4H), 6.32 (q, *J* = 7.1 Hz, 2H), 7.18−7.23 (m, 2H), 7.28−7.32 (m, 6H),

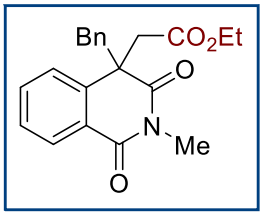
7.38−7.43 (m, 6H), 7.56−7.61 (m, 2H), 8.18−8.25 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.8, 13.8, 15.9, 16.0, 30.5, 30.8, 44.0, 44.3, 45.3, 50.3, 50.3, 60.6, 60.7, 123.9, 124.0, 125.2, 125.3, 126.7, 126.7, 127.4, 127.4, 128.0, 129.3, 129.4, 133.8, 133.8, 140.7, 140.9, 142.8, 143.0, 163.8, 164.1, 169.8, 169.9, 175.5, 176.0; HRMS (ESI) for $C_{22}H_{23}NO_4Na$ $[M+Na]^+$ calcd. 388.1519, found 388.1523.

ethyl 2-(4-methyl-1,3-dioxo-2-((R)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3t)



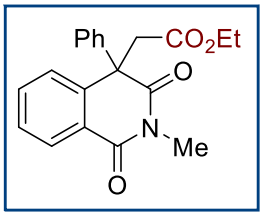
Purification by flash chromatography (PE/EA = 10/1) afforded **3t.** Colorless oil; 35.2 mg, 48% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.90−0.95 (m, 6H), 1.43 (s, 3H), 1.59 (s, 3H), 1.87−1.90 (m, 6H), 3.00−3.05 (m, 2H), 3.56−3.63 (m, 2H), 3.72−3.98 (m, 4H), 6.32 (q, *J* = 7.1 Hz, 2H), 7.18−7.23 (m, 2H), 7.28−7.32 (m, 6H), 7.38−7.43 (m, 6H), 7.56−7.61 (m, 2H), 8.18−8.25 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.8, 13.8, 15.9, 16.0, 30.5, 30.8, 44.0, 44.3, 45.3, 50.3, 50.3, 60.6, 60.7, 124.0, 124.0, 125.2, 125.3, 126.7, 126.7, 127.4, 127.4, 128.0, 129.3, 129.4, 133.8, 133.8, 140.7, 140.9, 142.8, 143.0, 163.9, 164.1, 169.8, 169.9, 175.5, 176.0; HRMS (ESI) for C22H23NO4Na [M+Na]+ calcd. 388.1519, found 388.1528.

ethyl 2-(4-benzyl-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3u)



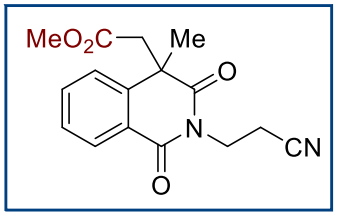
Purification by flash chromatography (PE/EA = 10/1) afforded **3u.** Colorless oil; 39.4 mg, 56% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.96 (t, *J* = 7.2 Hz, 3H), 2.99 (d, *J* = 12.6 Hz, 1H), 3.16 (s, 3H), 3.23 (d, *J* = 16.9 Hz, 1H), 3.32 (d, *J* = 12.6 Hz, 1H), 3.79−3.92 (m, 3H), 6.45 (d, *J* = 7.1 Hz, 2H), 7.00 (t, *J* = 7.7 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.40−7.45 (m, 2H), 7.64−7.68 (m, 1H), 8.04−8.07 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.7, 26.7, 43.8, 50.0, 51.1, 60.7, 124.5, 126.6, 127.4, 127.6, 127.8, 128.6, 129.1, 133.5, 133.9, 140.3, 163.6, 169.7, 174.9; HRMS (ESI) for $C_{21}H_{21}NO_4Na$ $[M+Na]^+$ calcd. 374.1363, found 374.1368.

ethyl 2-(2-methyl-1,3-dioxo-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3v)



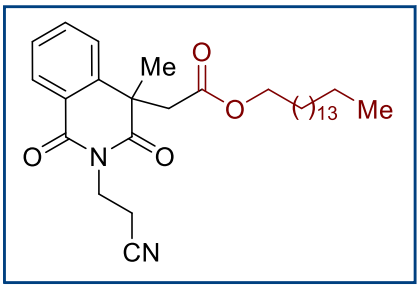
Purification by flash chromatography (PE/EA = 10/1) afforded **3v.** Colorless oil; 33.7 mg, 50% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 1.01 (t, *J* = 7.1 Hz, 3H), 3.36−3.42 (m, 4H), 3.83−3.96 (m, 2H), 4.26 (d, *J* = 16.5 Hz, 1H), 7.05−7.07 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.22−7.28 (m, 3H), 7.49 (td, *J* = 7.6, 1.0 Hz, 1H), 7.58 (td, *J* = 7.6, 1.4 Hz, 1H), 8.34 (dd, *J* = 7.8, 1.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.8, 27.6, 43.6, 52.7, 60.9, 126.2, 126.8, 127.9, 127.9, 128.9, 129.0, 133.9, 141.4, 141.5, 164.5, 169.9, 174.3; HRMS (ESI) for $C_{20}H_{19}NO_4Na$ $[M+Na]^+$ calcd. 360.1206, found 360.1216.

methyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4a)



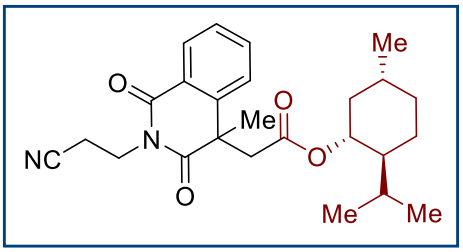
Purification by flash chromatography (PE/EA = 3/1) afforded **4a.** Colorless oil; 50.9 mg, 85% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 1.60 (s, 3H), 2.69−2.84 (m, 2H), 3.10 (d, *J* = 17.2 Hz, 1H), 3.45 (s, 3H), 3.59 (d, *J* = 17.2 Hz, 1H), 4.26−4.33 (m, 1H), 4.40−4.47 (m, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.46 (td, *J* = 7.6, 0.6 Hz, 1H), 7.65 (td, *J* = 7.7, 1.3 Hz, 1H), 8.27 (dd, *J* = 7.9, 1.1 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 15.9, 30.3, 35.7, 44.6, 44.9, 51.9, 117.3, 124.2, 124.3, 127.7, 129.3, 134.4, 142.6, 163.6, 170.5, 175.8; HRMS (ESI) for $C_{16}H_{16}N_2O_4Na$ $[M+Na]^+$ calcd. 323.1002, found 323.1011.

hexadecyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4b)



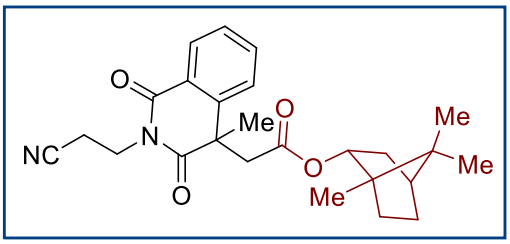
Purification by flash chromatography (PE/EA = 4/1) afforded **4b.** Colorless oil; 91.0 mg, 89% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.88 (t, *J* = 6.6 Hz, 3H), 1.08−1.30 (m, 28H), 1.59 (s, 3H), 2.67−2.83 (m, 2H), 3.08 (d, *J* = 17.0 Hz, 1H), 3.59 (d, *J* = 17.0 Hz, 1H), 3.75−3.87 (m, 2H), 4.26−4.32 (m, 1H), 4.39−4.46 (m, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.45 (td, *J* = 7.6, 0.6 Hz, 1H), 7.64 (td, *J* = 7.7, 1.3 Hz, 1H), 8.26 (dd, J = 7.9, 1.1 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ (ppm) = 14.1, 15.9, 22.6, 25.6, 28.3, 29.1, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 30.3, 31.9, 35.7, 44.9, 45.0, 65.0, 117.3, 124.3, 124.4, 127.6, 129.3, 134.3, 142.7, 163.7, 170.1, 175.8; HRMS (ESI) for $C_{31}H_{46}N_2O_4Na$ [M+Na]+ calcd. 533.3350, found 533.3356.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4c)



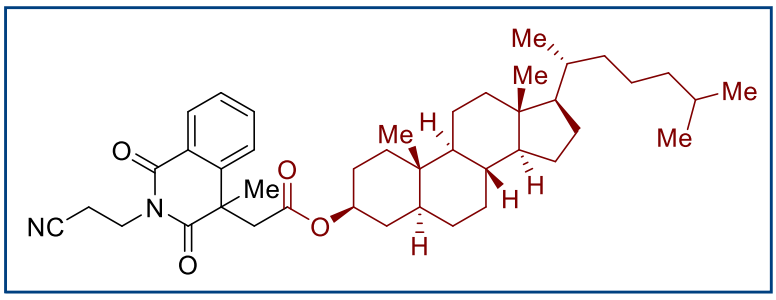
Purification by flash chromatography (PE/EA = 4/1) afforded **4c.** Colorless oil; 67.9 mg, 80% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.32−0.56 (m, 3H), 0.58−0.67 (m, 1H), 0.71−0.94 (m, 8H), 1.05−1.13 (m, 1H), 1.22−1.35 (m, 2H), 1.42−1.61 (m, 6H), 2.68−2.84 (m, 2H), 3.00−3.08 (m, 1H), 3.57−3.63 (m, 1H), 4.25−4.47 (m, 3H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.43−7.47 (m, 1H), 7.61−7.67 (m, 1H), 8.23−8.28 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 15.8, 15.9, 16.0, 20.6, 20.8, 21.8, 21.8, 23.0, 23.0, 25.8, 25.9, 30.1, 30.5, 31.1, 31.2, 33.9, 35.6, 35.7, 40.3, 40.6, 45.0, 45.1, 45.6, 46.8, 46.8, 74.8, 74.9, 117.3, 117.3, 124.3, 124.4, 124.5, 127.6, 127.6, 129.2, 129.4, 134.2, 134.3, 142.7, 142.9, 163.7, 169.5, 169.5, 175.7, 175.8; HRMS (ESI) for $C_{25}H_{32}N_2O_3Na$ $[M+Na]^+$ calcd. 447.2254, found 447.2254.

(2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4d)



Purification by flash chromatography (PE/EA = 4/1) afforded **4d.** Colorless oil; 48.8 mg, 58% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.39−0.61 (m, 4H), 0.74−0.78 (m, 6H), 0.93−1.02 (m, 1H), 1.11−1.20 (m, 1H), 1.52−1.69 (m, 6H), 2.02−2.11 (m, 1H), 2.70−2.84 (m, 2H), 3.11 (d, *J* = 16.1 Hz, 1H), 3.60−3.69 (m, 1H), 4.25−4.32 (m, 1H), 4.40−4.47 (m, 1H), 4.59−4.64 (m, 1H), 7.38−7.47 (m, 2H), 7.63−7.68 (m, 1H), 8.26 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 13.0, 13.2, 16.0, 16.0, 18.6, 19.5, 26.8, 26.9, 27.8, 27.8, 30.6, 30.8, 35.6, 35.7, 36.0, 36.3, 44.5, 44.5, 44.7, 44.8, 45.3, 47.6, 47.7, 48.5, 48.6, 80.5, 80.7, 117.3, 117.3, 124.2, 124.2, 124.3, 124.4, 127.7, 129.4, 134.3, 134.4, 142.7, 142.8, 163.6, 163.7, 170.3, 170.4, 175.7, 175.7; HRMS (ESI) for $C_{25}H_{30}N_2O_4Na$ $[M+Na]^+$ calcd. 445.2098, found 445.2102.

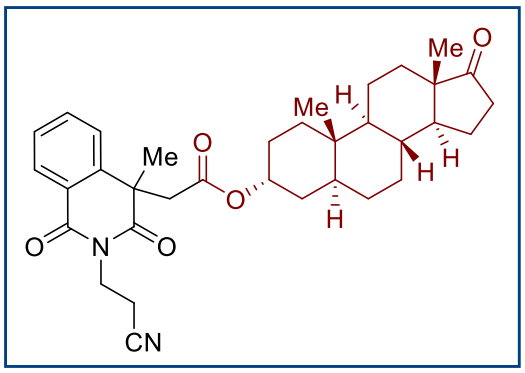
(3S,5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4e)



Purification by flash chromatography (PE/EA = 4/1) afforded **4e.** Colorless oil; 109.7 mg, 83% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.50−0.56 (m, 1H), 0.62 (s, 3H), 0.72 (s, 3H), 0.84−1.42 (m, 32H), 1.45−1.62 (m, 8H), 1.73−1.83 (m, 1H), 1.91−1.94 (m, 1H), 2.69−2.83 (m, 2H), 3.01−3.05 (m, 1H), 3.55−3.59 (m, 1H), 4.25−4.46 (m, 3H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.42−7.47 (m, 1H), 7.62−7.66 (m, 1H), 8.25−8.27 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 12.0, 12.1, 16.0, 18.6, 21.1, 22.5, 22.8, 23.8, 24.1, 26.9, 27.0, 27.9, 28.2, 28.4, 30.3, 31.8, 33.4, 33.6, 35.2, 35.3, 35.7, 35.7, 36.1, 36.4, 39.4, 39.8, 42.5, 44.3, 44.3, 45.1, 45.3, 54.0, 56.2, 56.3, 74.4, 117.3, 124.3, 124.3, 124.4, 127.6, 129.2,

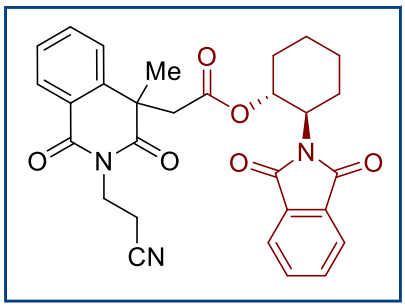
134.3, 142.8, 142.8, 163.7, 169.4, 169.4, 175.8; HRMS (ESI) for $C_{42}H_{60}N_2O_4Na$ $[M+Na]^+$ calcd. 679.4445, found 679.4446.

(3R,5S,8R,9S,10S,13S,14S)-10,13-dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4f)



Purification by flash chromatography (PE/EA = 1.5/1) afforded **4f.** Colorless oil; 90.5 mg, 81% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.57−0.70 (m, 4H), 0.76−0.89 (m, 4H), 0.92−1.13 (m, 5H), 1.21−1.37 (m, 6H), 1.39−1.54 (m, 4H), 1.59−1.60 (m, 3H), 1.74−1.84 (m, 2H), 2.43−2.50 (m, 1H), 2.71−2.85 (m, 2H), 3.08−3.13 (m, 1H), 3.63−3.67 (m, 1H), 4.26−4.32 (m, 1H), 4.37−4.33 (m, 1H), 4.73−4.76 (m, 1H), 7.38−7.47 (m, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 8.25−8.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 11.0, 11.1, 13.8, 13.8, 16.1, 19.8, 20.0, 21.7, 25.5, 25.8, 27.8, 27.9, 30.4, 30.5, 31.0, 31.2, 31.5, 31.6, 32.1, 32.4, 32.5, 32.6, 34.8, 34.8, 35.5, 35.6, 35.6, 35.8, 39.9, 40.0, 44.4, 44.6, 45.3, 47.8, 51.5, 51.5, 53.9, 54.1, 70.8, 71.2, 117.2, 117.2, 124.2, 124.2, 124.3, 127.6, 127.7, 129.4, 129.6, 134.4, 143.0, 143.2, 163.6, 169.2, 169.3, 175.7, 175.7; HRMS (ESI) for $C_{34}H_{42}N_2O_5Na$ $[M+Na]^+$ calcd. 581.2986, found 581.2986.

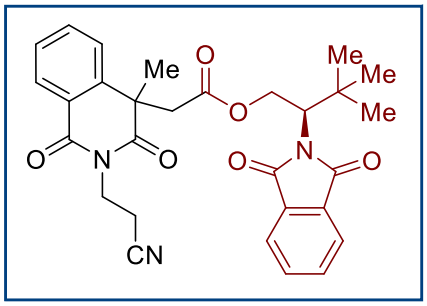
(1R,2R)-2-(1,3-dioxoisoindolin-2-yl)cyclohexyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4g)



Purification by flash chromatography (PE/EA = 1.5/1) afforded **4g.** Colorless oil; 82.1 mg, 80% yield; ***Product 1***, **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 1.05−1.15 (m, 1H), 1.24−1.34 (m, 2H), 1.45 (s, 3H), 1.68−1.82 (m, 4H), 2.13−2.23 (m, 1H), 2.68−2.84 (m, 2H), 2.88 (d, *J* = 17.2 Hz, 1H), 3.49 (d, *J* = 17.2 Hz,

1H), 3.95−4.02 (m, 1H), 4.22−4.29 (m, 1H), 4.37−4.44 (m, 1H), 5.20−5.27 (m, 1H), 6.95−6.99 (m, 2H), 7.07−7.14 (m, 1H), 7.73−7.76 (m, 4H), 8.04 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) =16.0, 23.5, 24.7, 28.4, 30.6, 31.2, 35.6, 44.3, 44.8, 53.2, 72.2, 117.4, 123.2, 123.4, 124.0, 127.2, 129.0, 131.5, 133.7, 133.8, 142.4, 163.5, 167.6, 169.0, 175.5; ***Product 2***, **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 1.21−1.22 (m, 3H), 1.42 (s, 3H), 1.67−1.76 (m, 4H), 2.22−2.41 (m, 2H), 2.54−2.63 (m, 1H), 2.96 (d, *J* = 17.2 Hz, 1H), 3.29 (d, *J* = 17.2 Hz, 1H), 3.97 (t, *J* = 7.5 Hz, 2H), 4.02−4.09 (m, 1H), 5.20−5.26 (m, 1H), 7.26−7.28 (m, 1H), 7.35−7.38 (m, 1H), 7.56−7.60 (m, 1H), 7.78−7.81 (m, 2H), 7.85−7.88 (m, 1H), 8.15 (dd, *J* = 7.9, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 15.5, 23.6, 24.8, 28.3, 30.2, 31.2, 35.4, 44.4, 44.8, 53.5, 72.4, 117.3, 123.2, 124.1, 124.2, 127.5, 129.2, 131.7, 134.0, 134.2, 142.5, 163.5, 168.1, 169.6, 175.2; HRMS (ESI) for $C_{29}H_{27}N_3O_6Na$ $[M+Na]^+$ calcd. 536.1792, found 536.1798.

(R)-2-(1,3-dioxoisoindolin-2-yl)-3,3-dimethylbutyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4h)



Purification by flash chromatography (PE/EA = 1.5/1) afforded **4h.** Colorless oil; 90.0 mg, 87% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 0.94−0.96 (m, 9H), 1.47−1.49 (m, 3H), 2.63−2.82 (m, 2H), 2.92−2.99 (m, 1H), 3.42−3.49 (m, 1H), 4.04−4.13 (m, 1H), 4.16−4.43 (m, 3H), 4.72−4.82 (m, 1H), 7.14−7.25 (m, 1H), 7.31−7.64 (m, 2H), 7.77−7.90 (m, 4H), 8.11−8.15 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 15.8, 15.9, 27.6, 27.7, 30.4, 30.5, 35.1, 35.2, 35.6, 35.6, 44.0, 44.2, 44.8, 44.9, 59.0, 59.0, 60.7, 60.8, 117.3, 123.1, 123.2, 123.4, 123.4, 124.0, 124.0, 124.1, 127.5, 127.6, 129.2, 129.3, 131.1, 131.2, 131.8, 133.9, 134.0, 134.1, 134.2, 134.2, 134.4, 142.4, 142.4, 163.5, 163.5, 168.5, 168.6, 168.8, 169.0, 169.9, 169.9, 175.5, 175.5; HRMS (ESI) for $C_{29}H_{29}N_3O_6Na$ $[M+Na]^+$ calcd. 538.1949, found 538.1952.

8. References

(1) Zhao, Y.; Wang, G.; Li, Y.; Wang, S.; Li, Z. *Chin. J. Chem*. **2010**, *28*, 475.

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(3) Arjomandia, O. K.; Kavoosic, M.; Adibi, H. *Bioorg. Chem.* **2019***, 92,* 103277.

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(5) Canestrari, D.; Lancianesi, S.; Badiola, E.; Strinna, C.; Ibrahim, H.; Adamo, M. F. A. *Org. Lett.* **2017**, *19*, 918.

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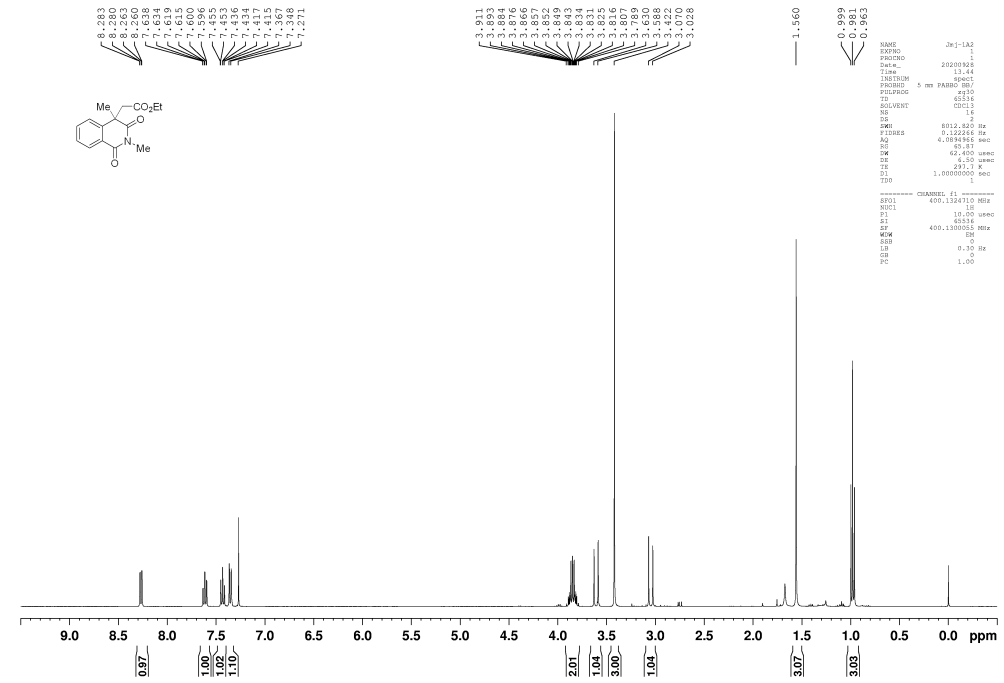
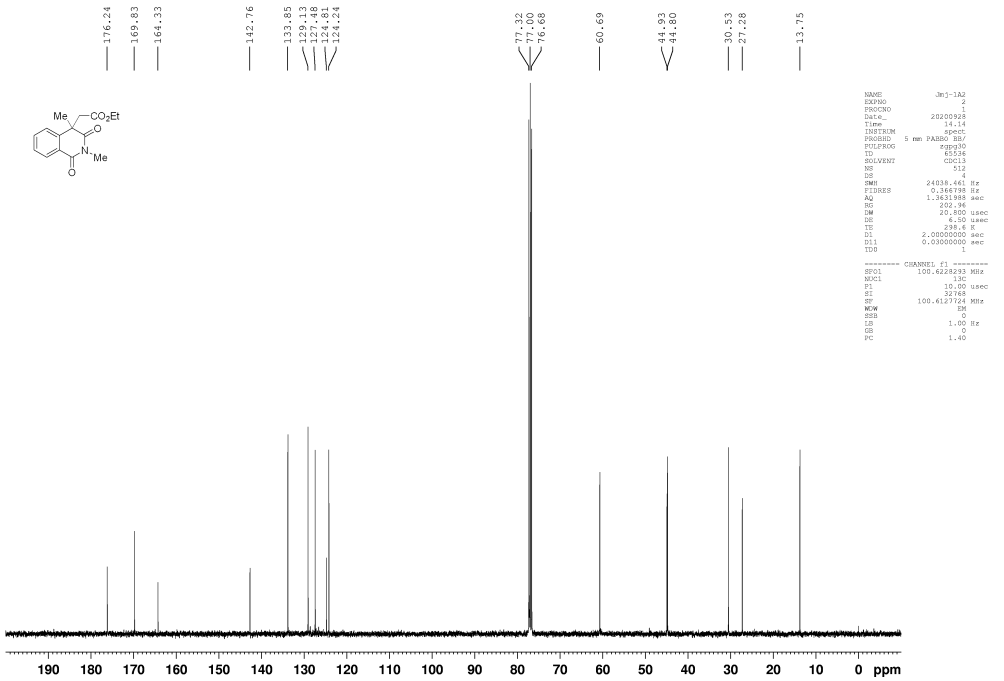
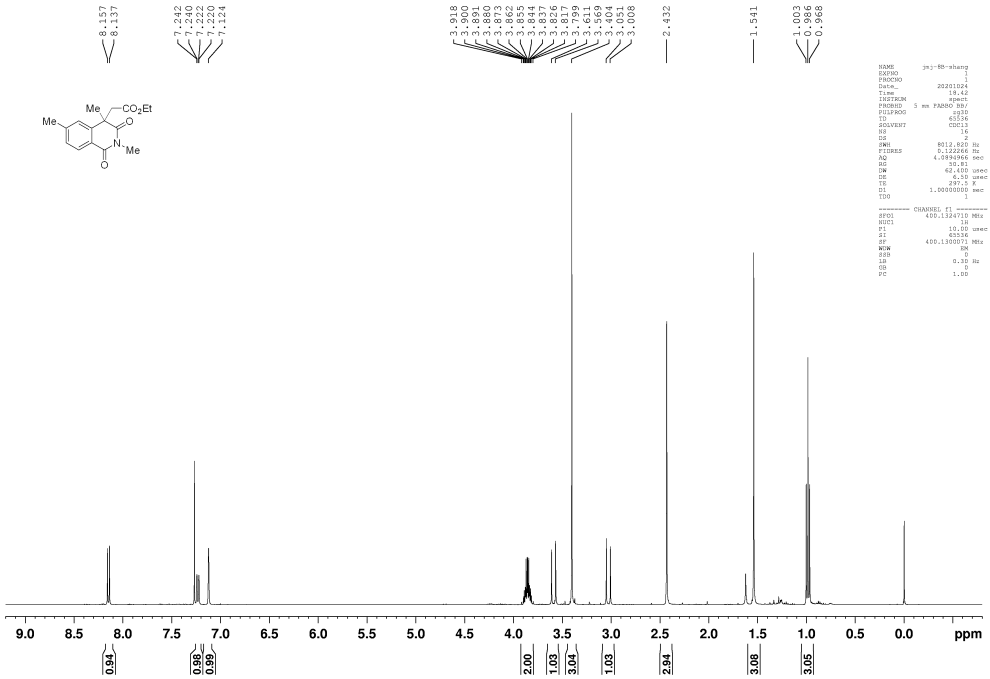
9. NMR spectra of compounds

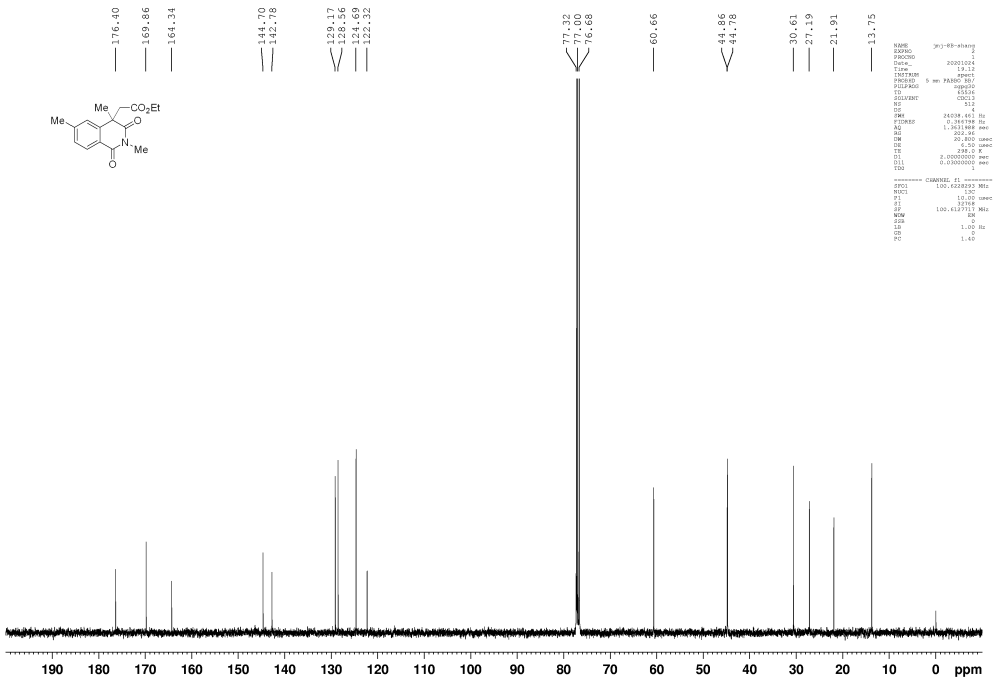
ethyl 2-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3a)



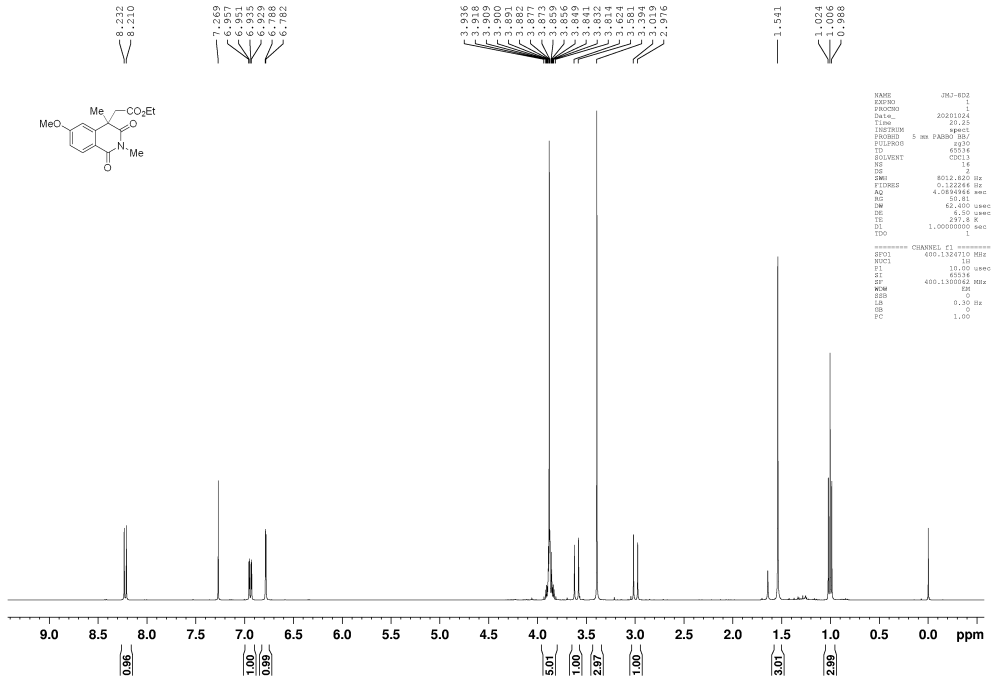


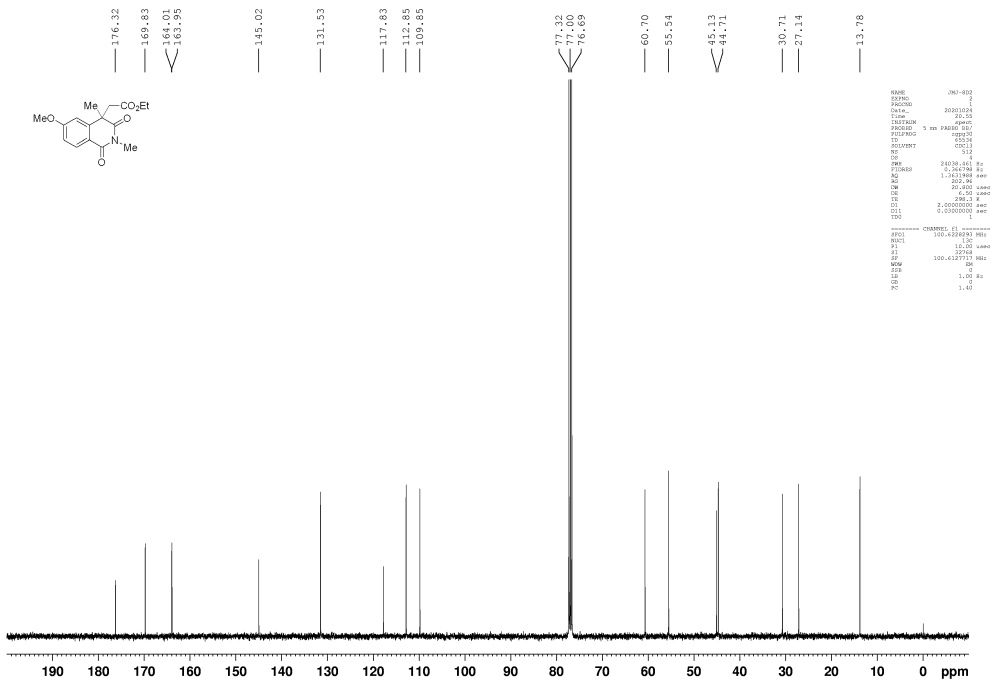
ethyl 2-(2,4,6-trimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3b)



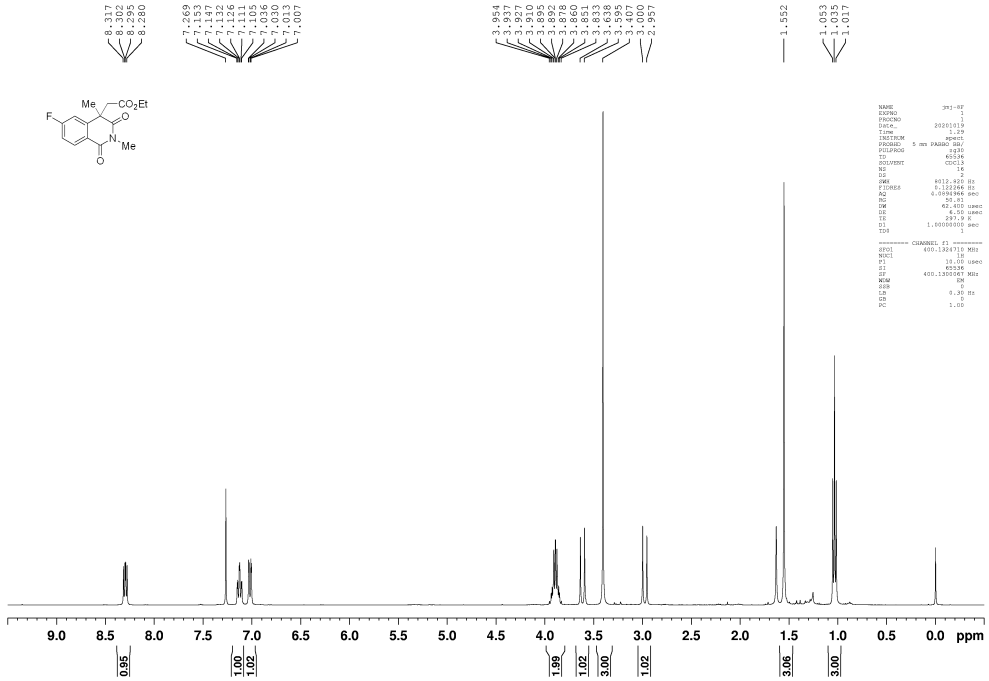


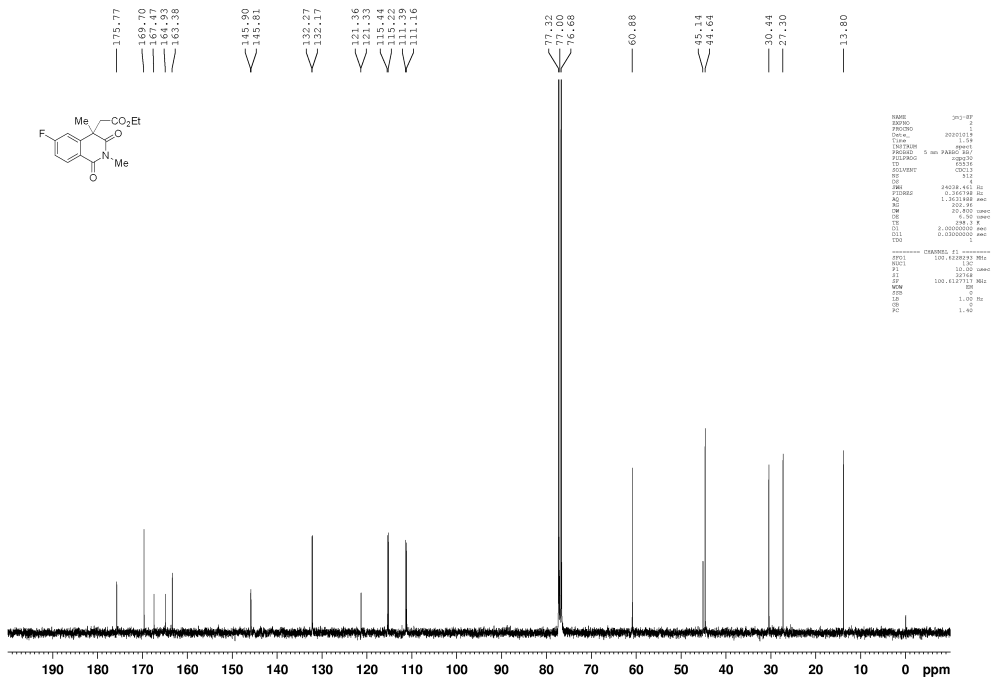
ethyl 2-(6-methoxy-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3c)



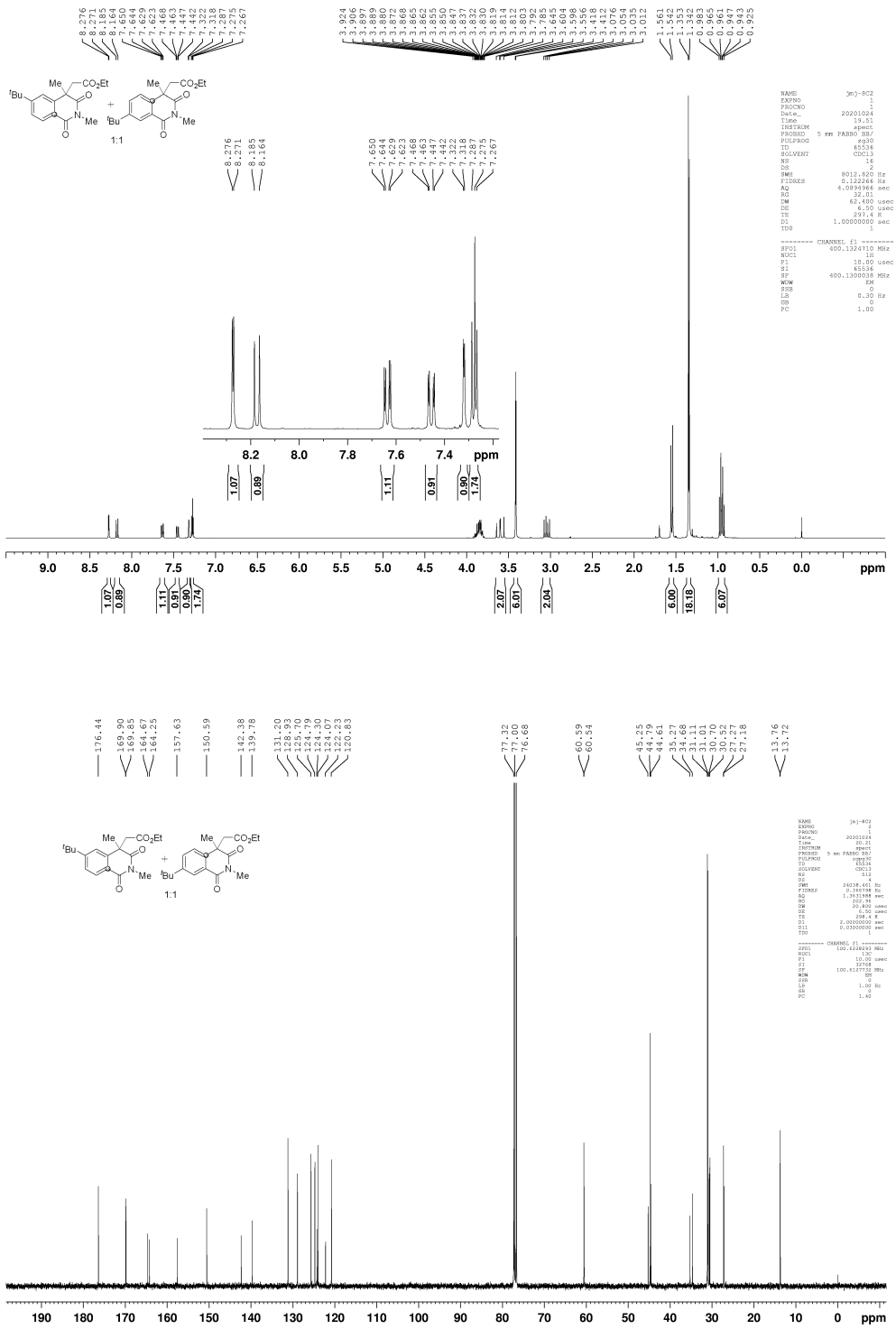


ethyl 2-(6-fluoro-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3d)

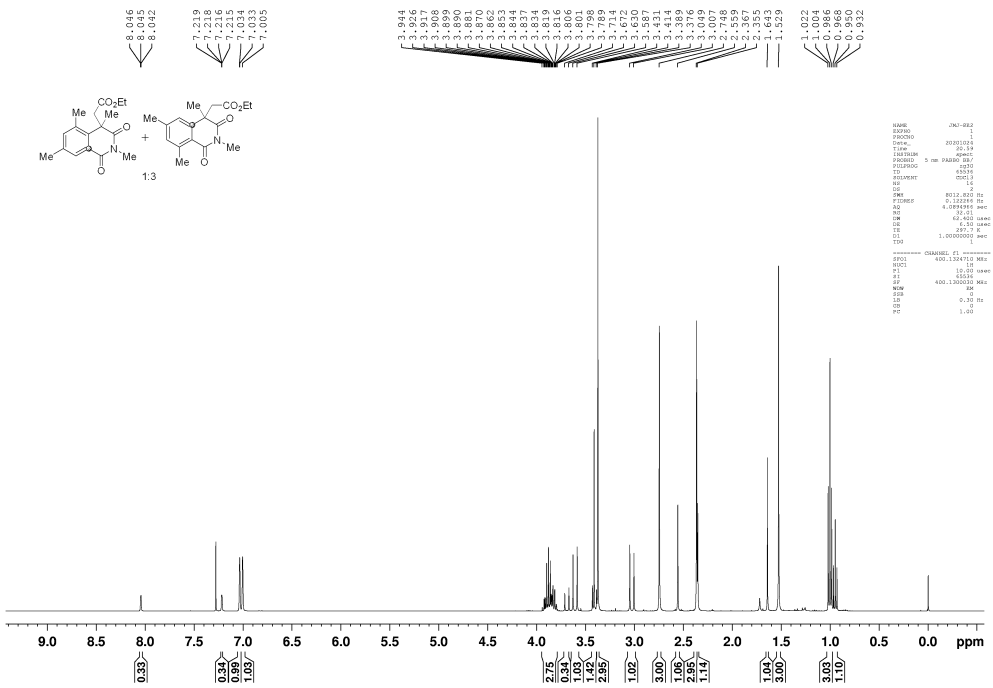


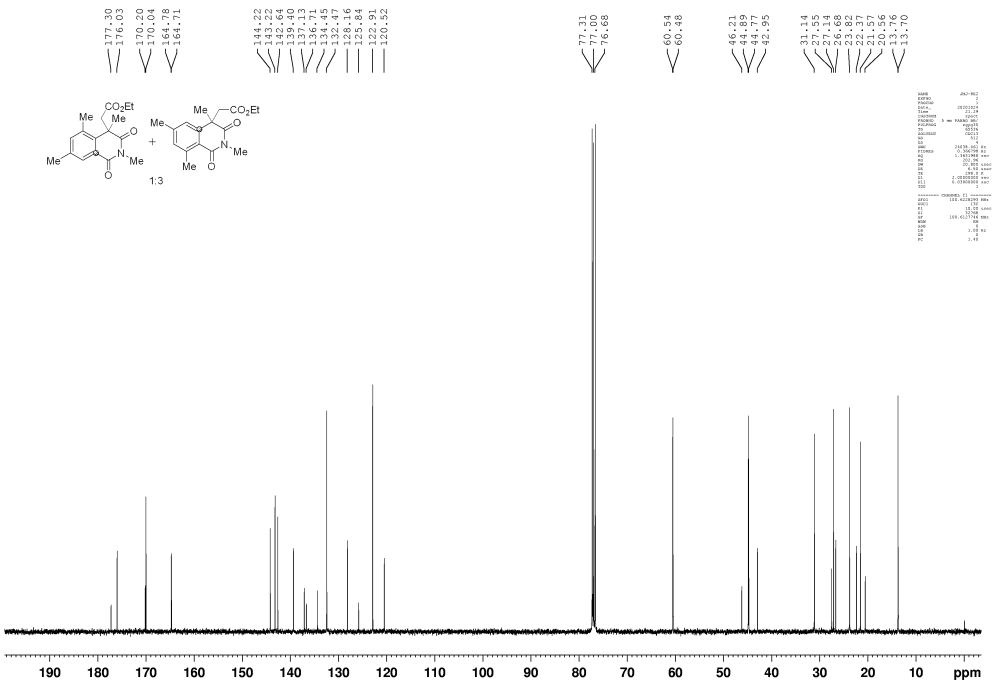


ethyl 2-(6-(tert-butyl)-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3e) + ethyl 2-(7-(tert-butyl)-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3e')

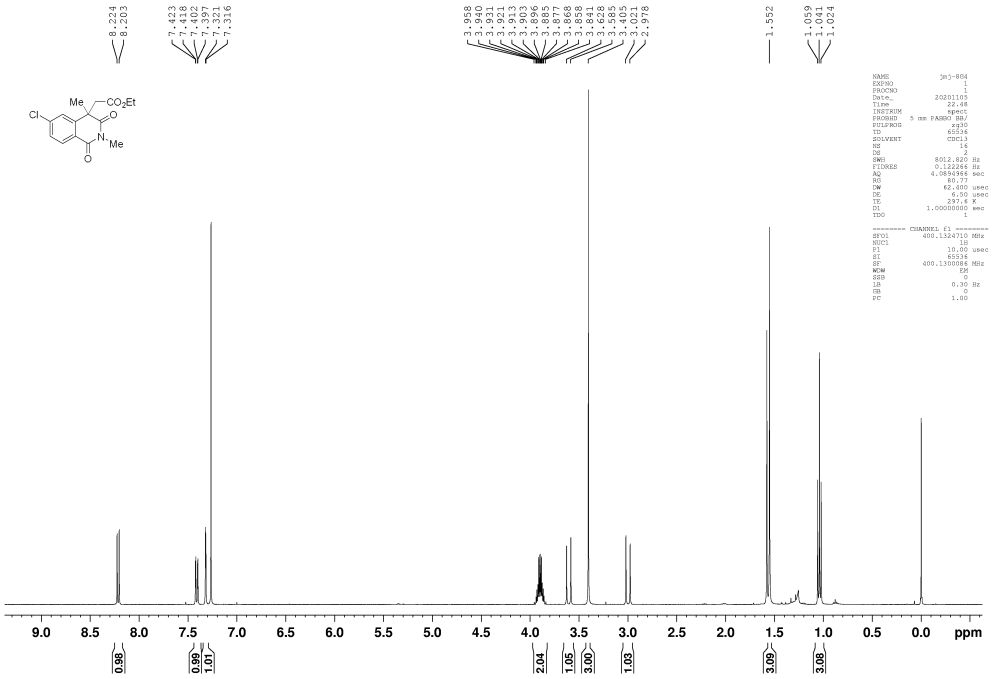


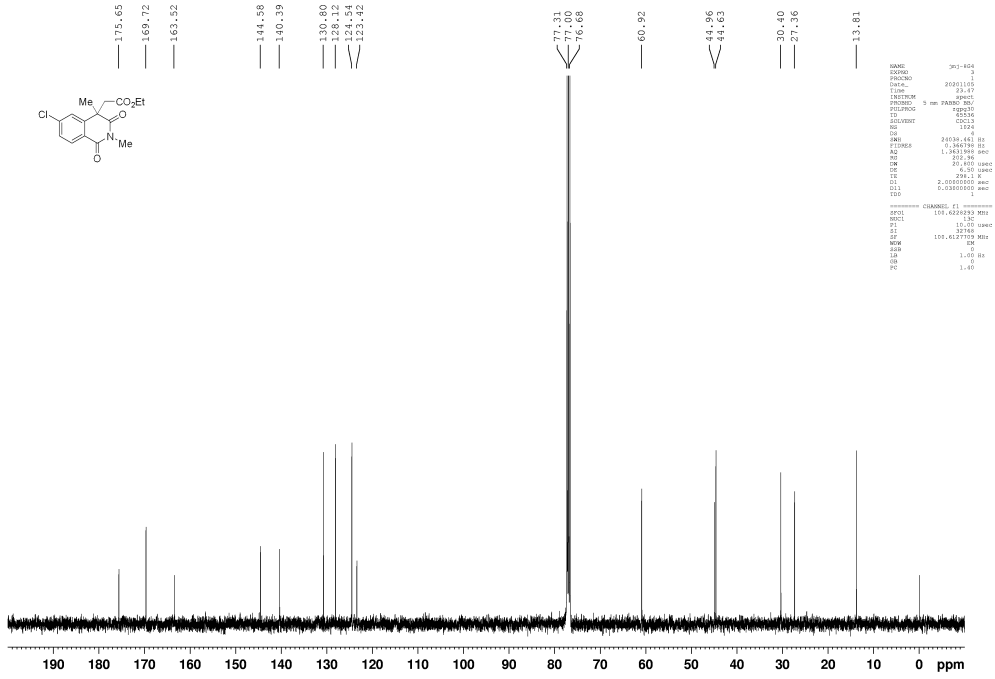
ethyl 2-(2,4,5,7-tetramethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3f) + ethyl 2-(2,4,6,8-tetramethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3f')



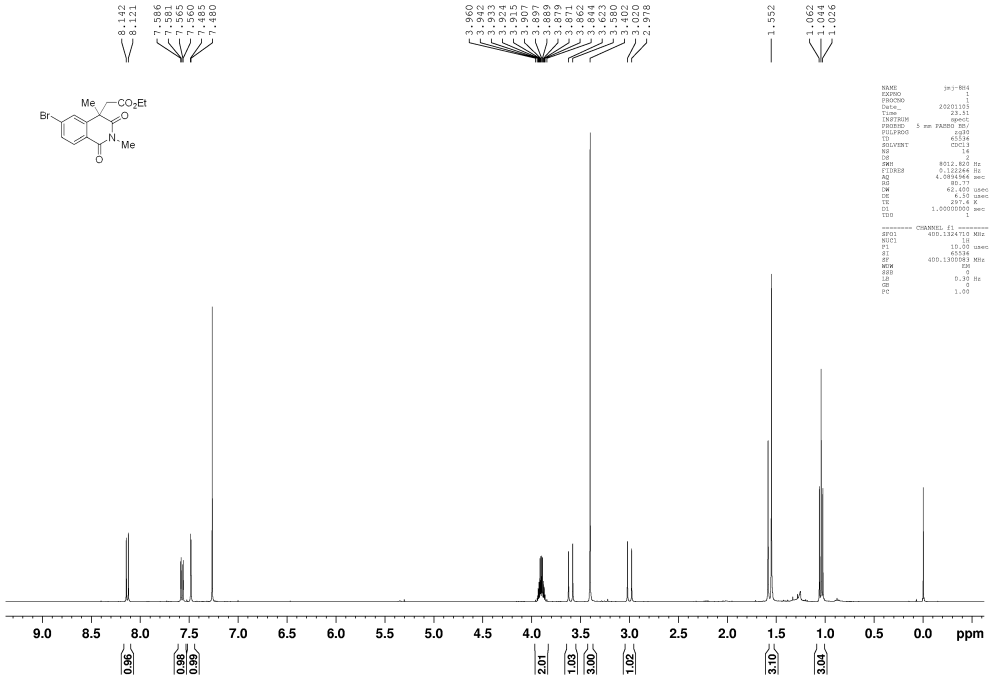


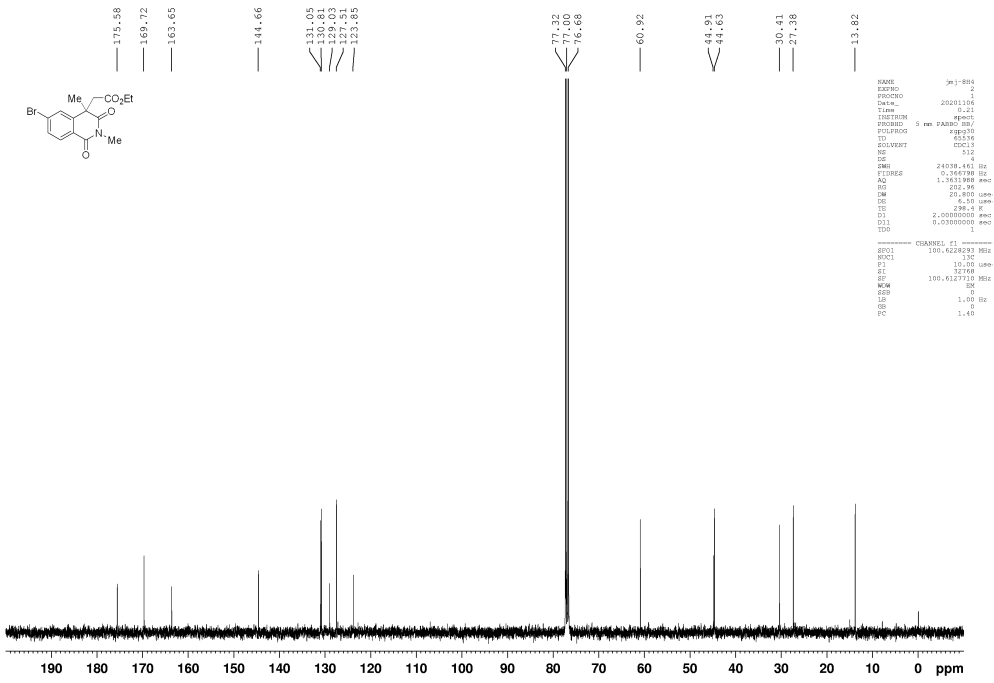
ethyl 2-(6-chloro-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3g)



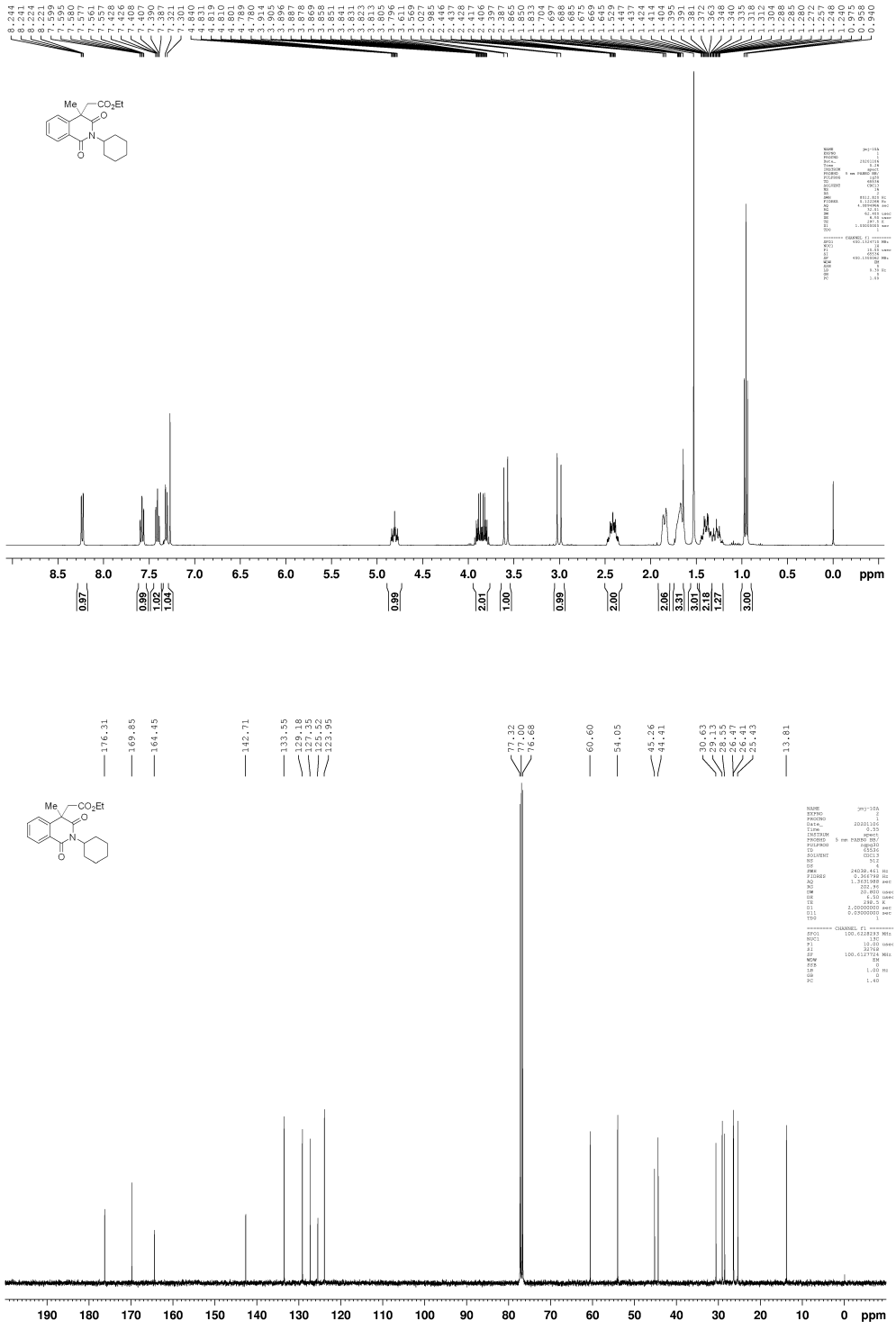


ethyl 2-(6-bromo-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3h)

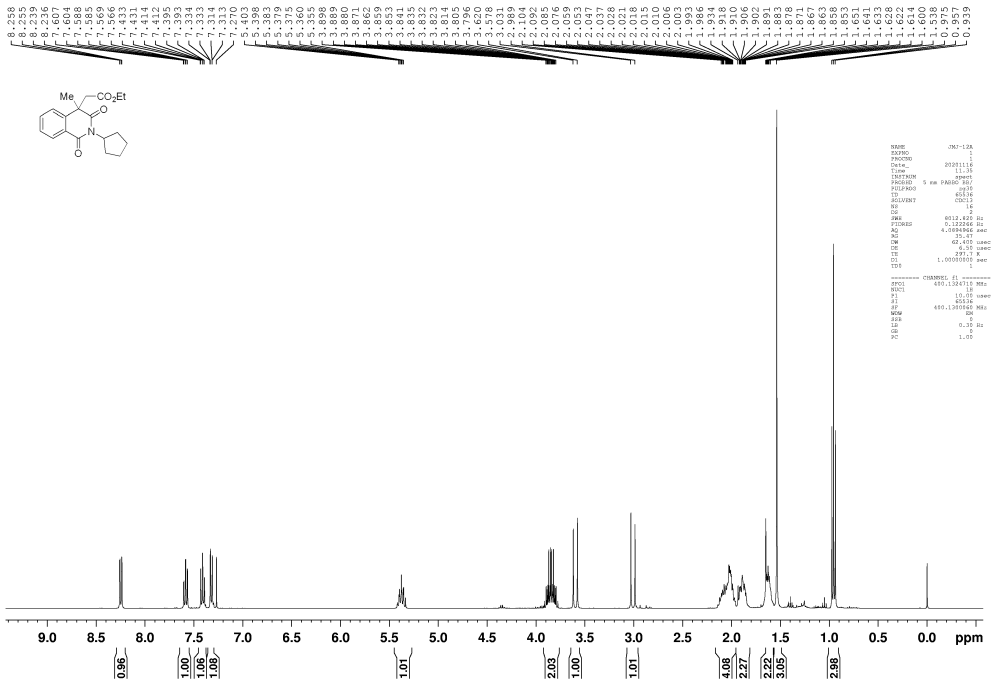


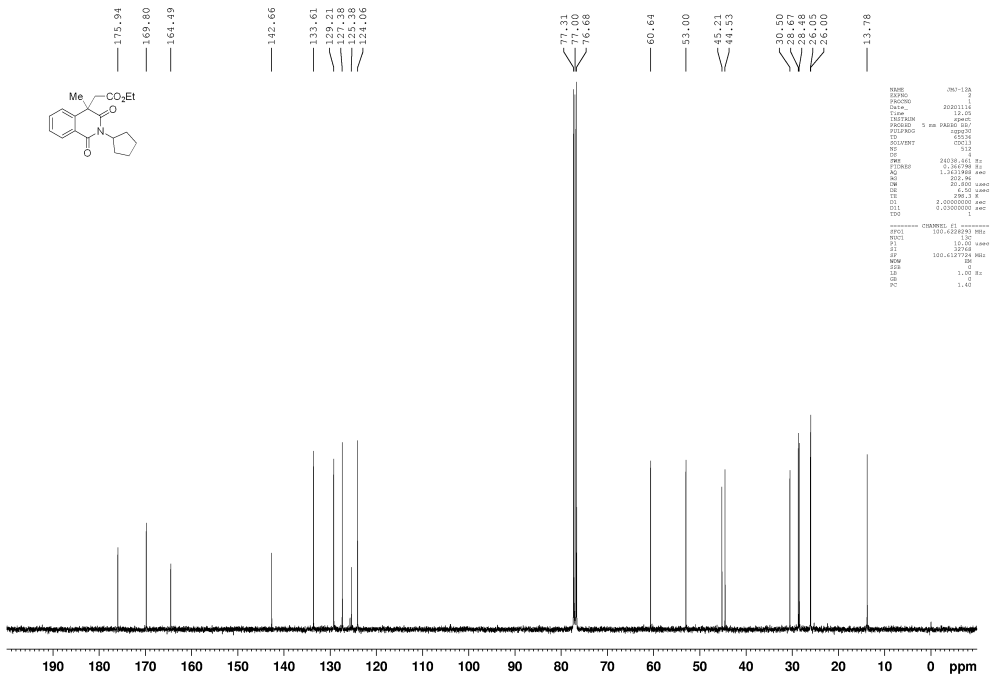


ethyl 2-(2-cyclohexyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3i)

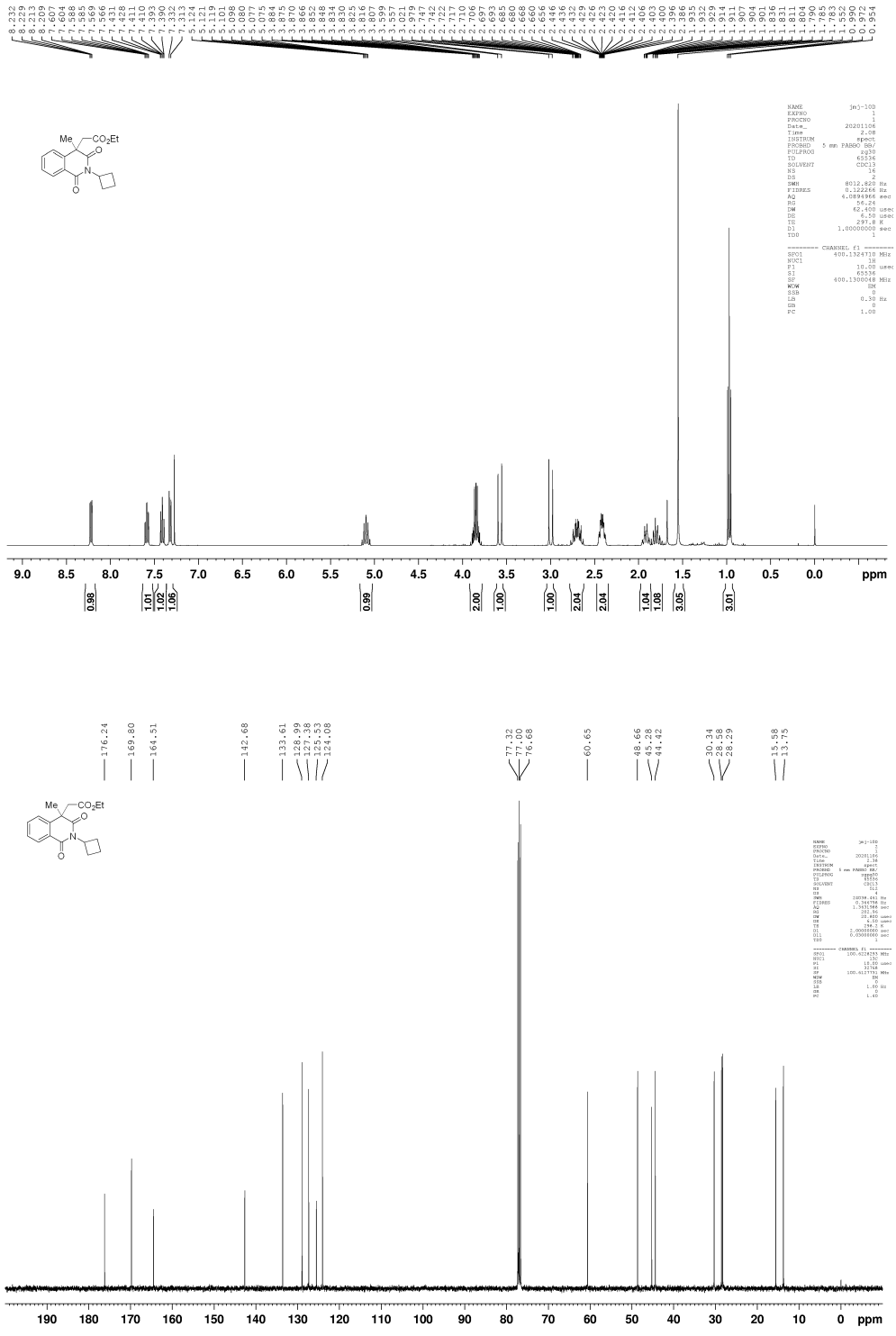


ethyl 2-(2-cyclopentyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3j)

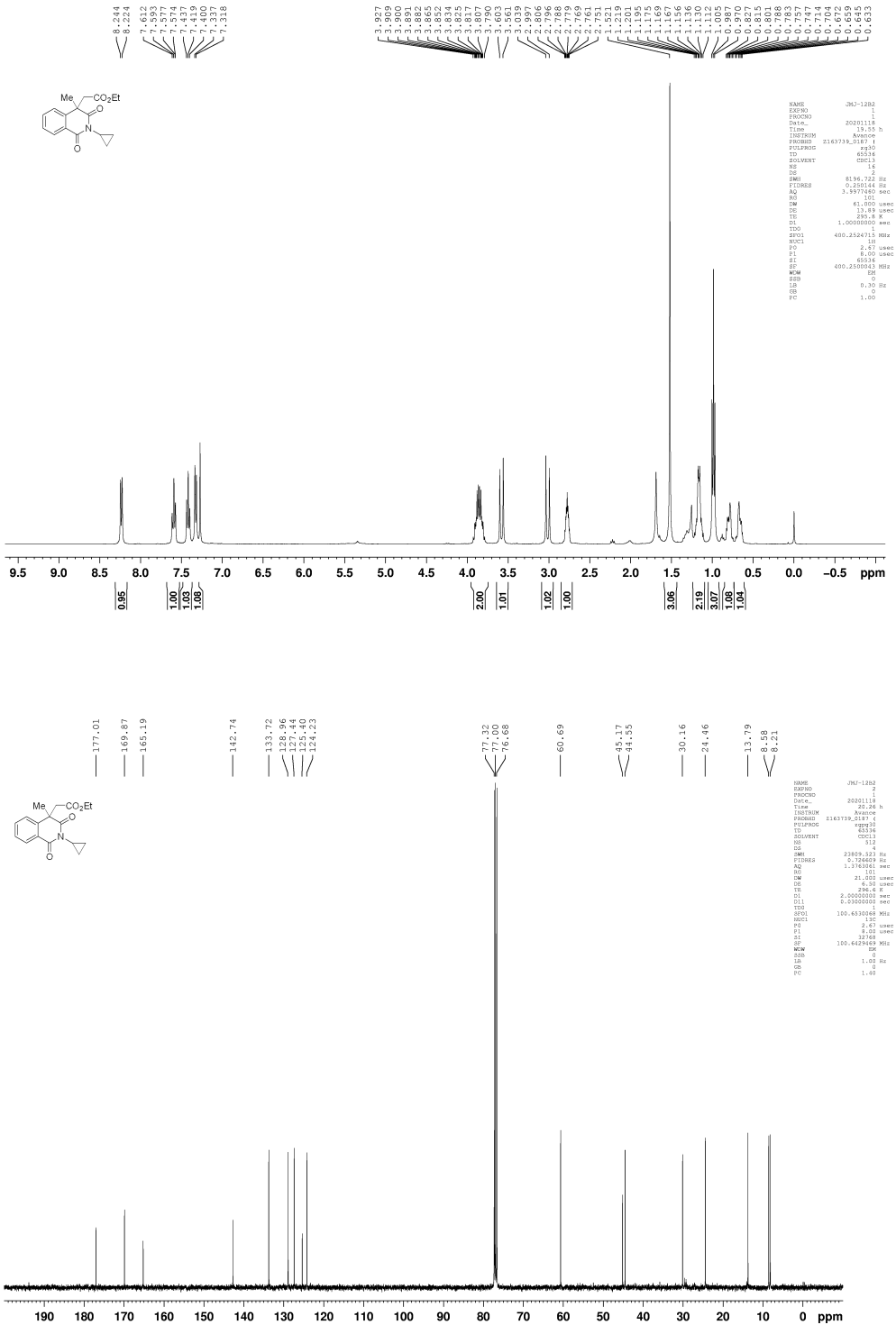




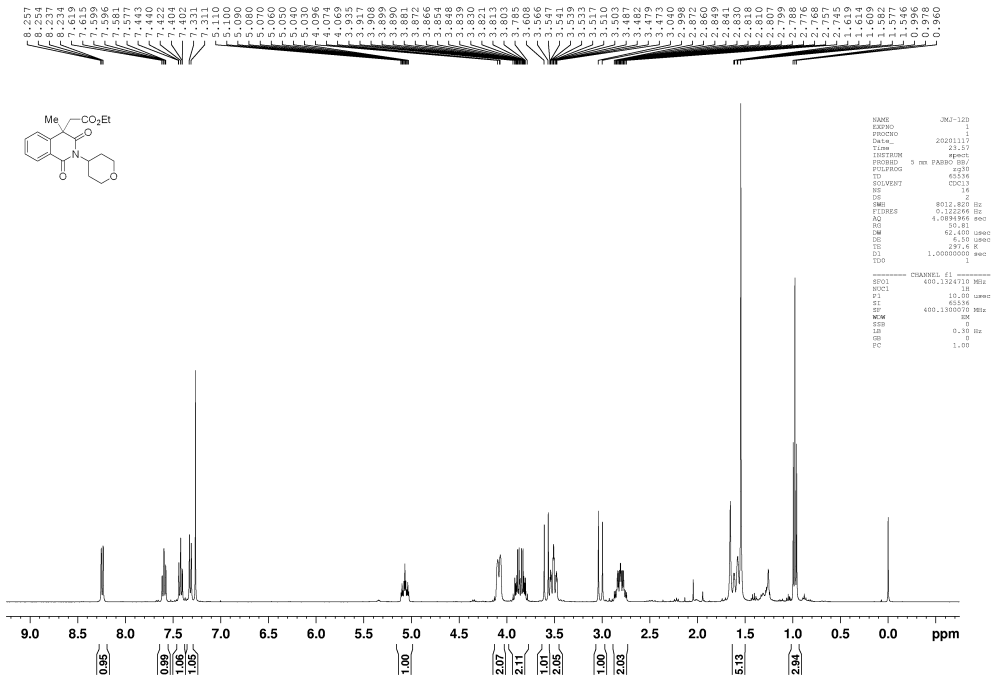
ethyl 2-(2-cyclobutyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3k)

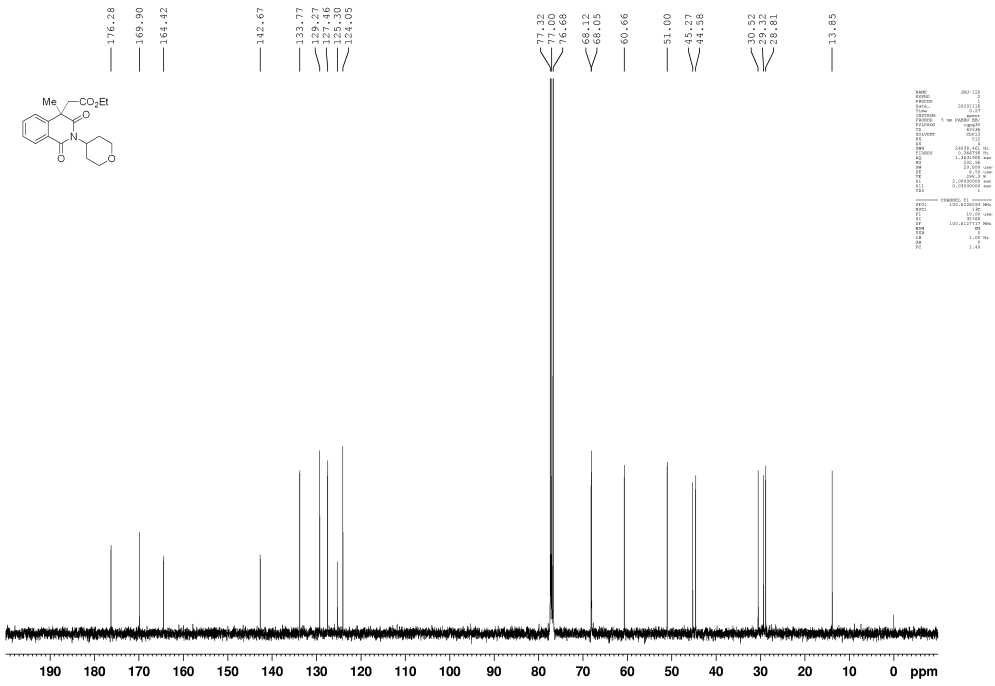


ethyl 2-(2-cyclopropyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3l)

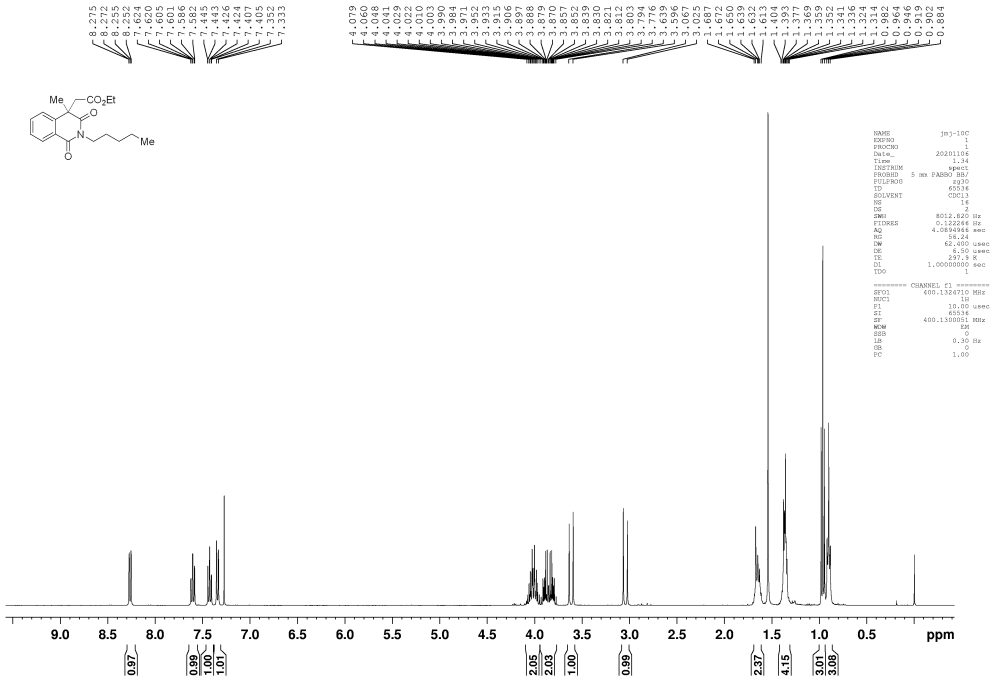


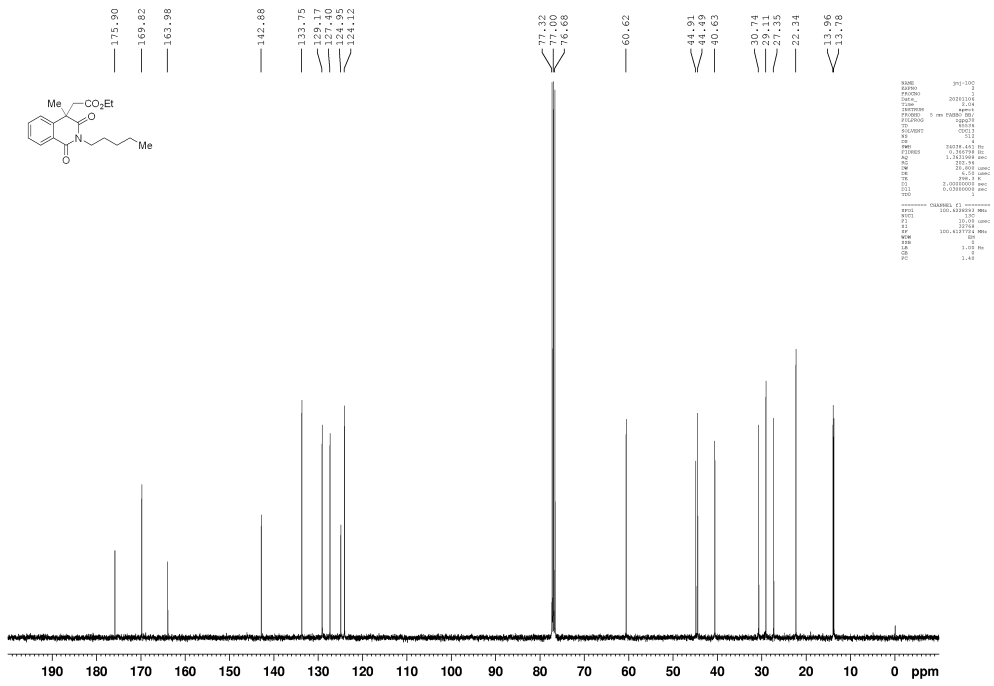
ethyl 2-(4-methyl-1,3-dioxo-2-(tetrahydro-2H-pyran-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3m)



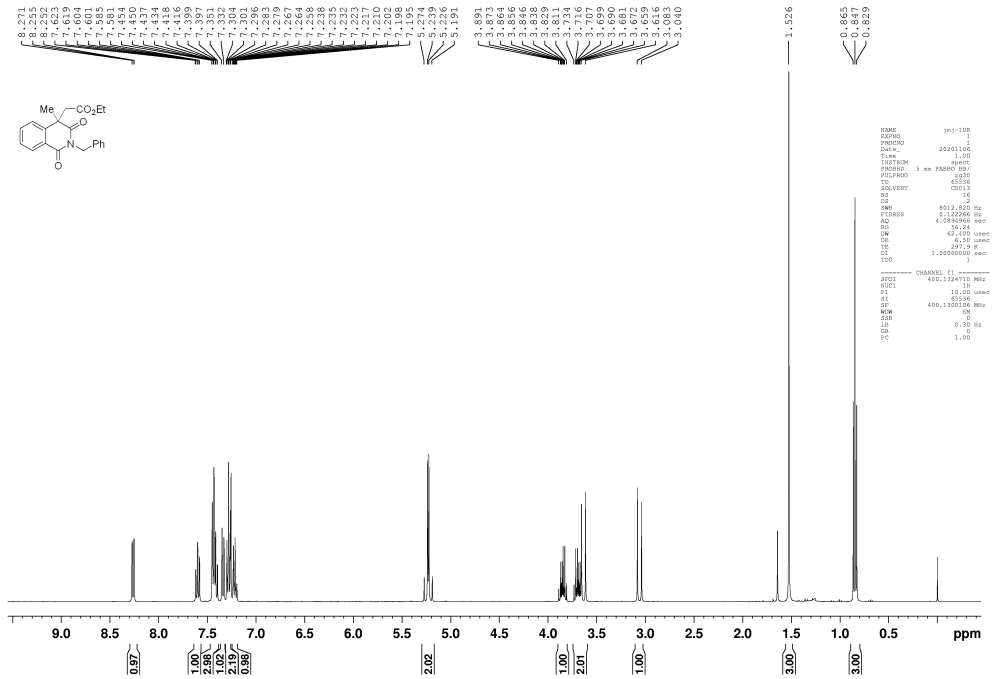


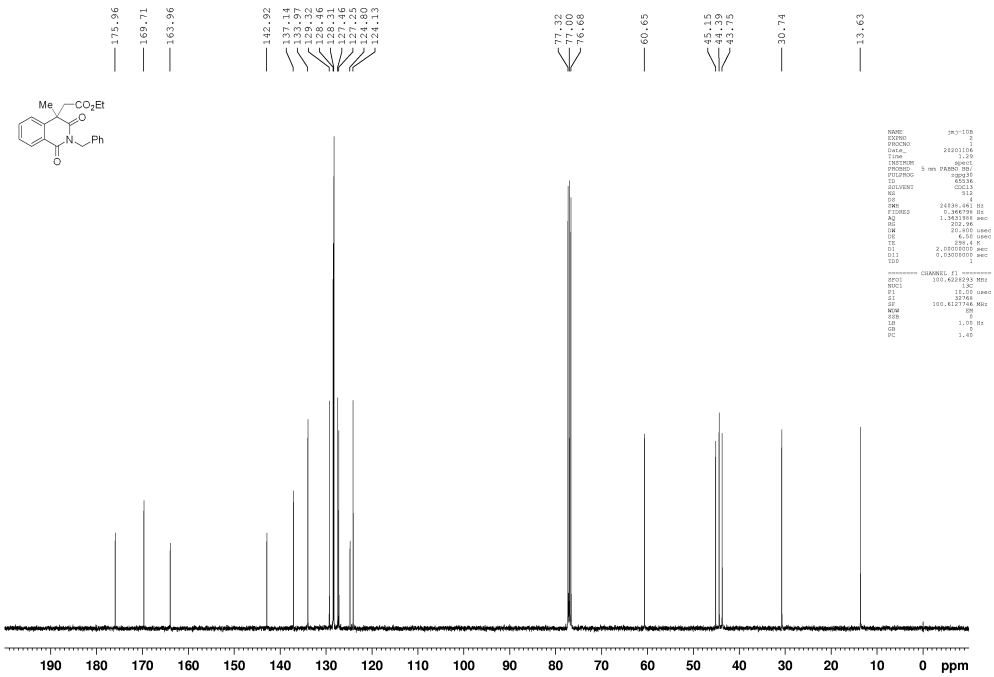
ethyl 2-(4-methyl-1,3-dioxo-2-pentyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3n)



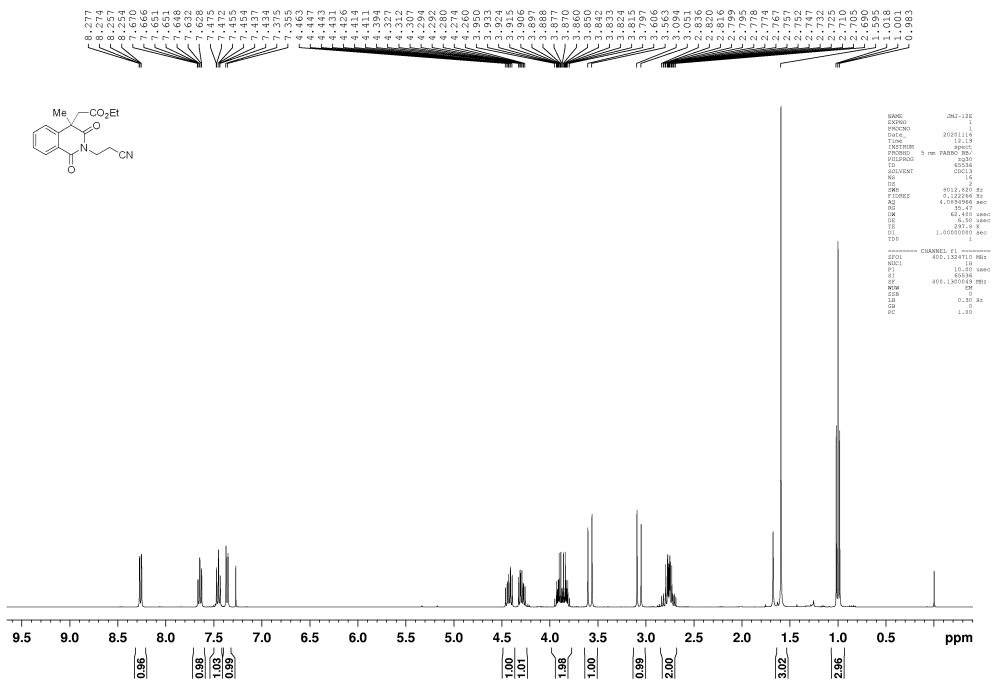


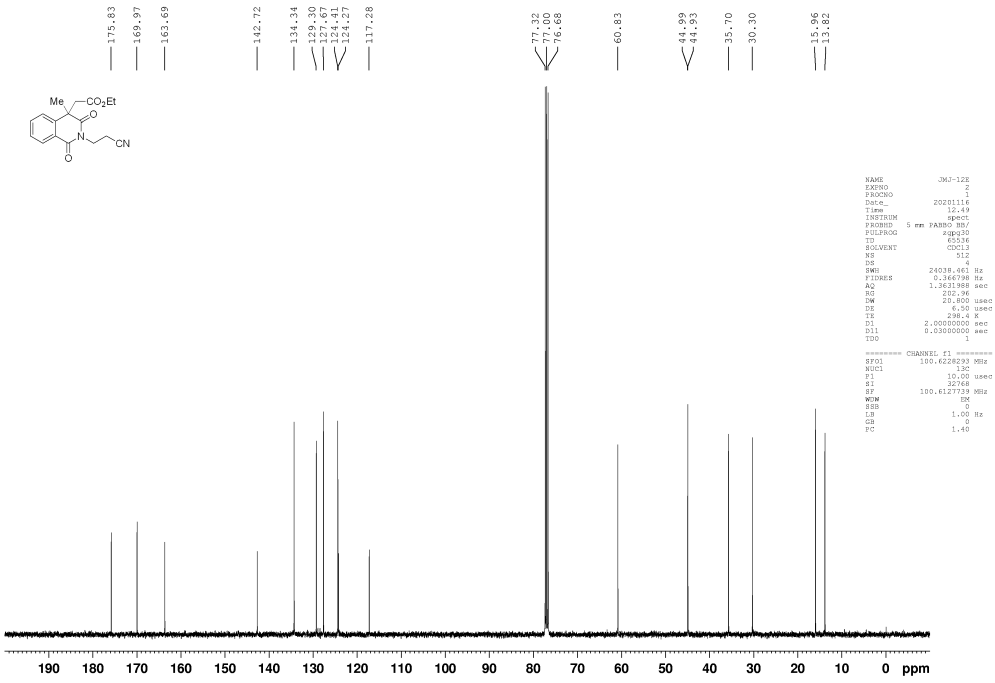
ethyl 2-(2-benzyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3o)



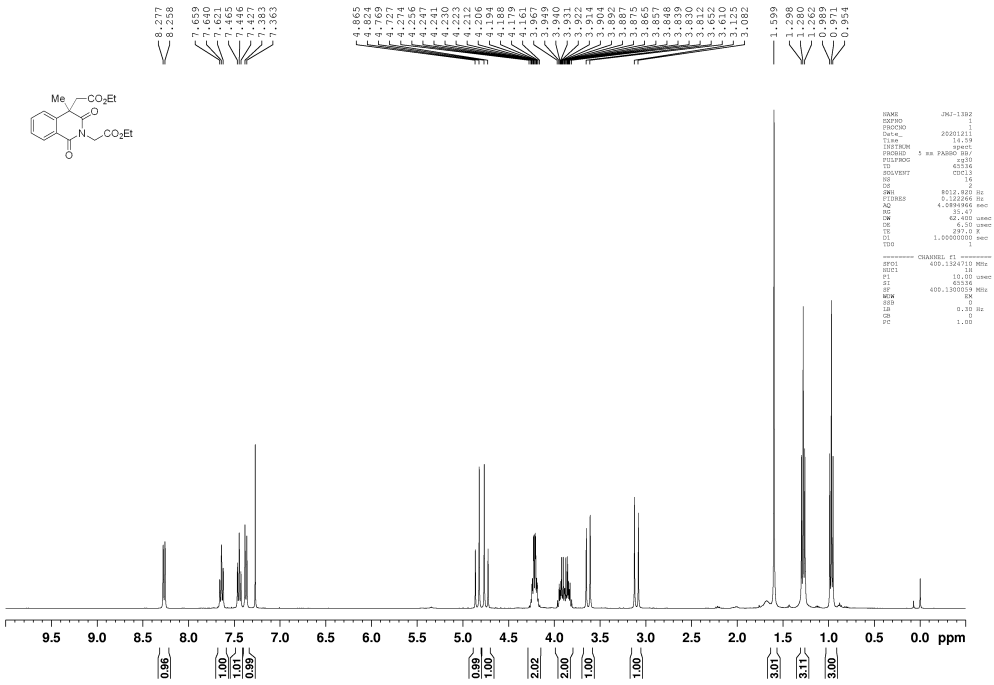


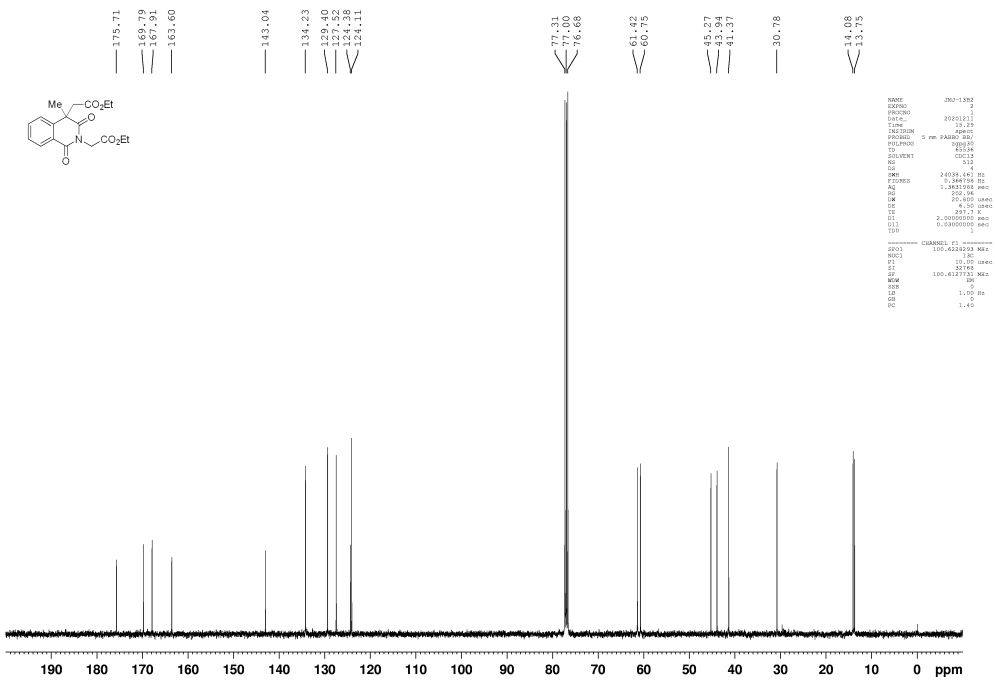
ethyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3p)



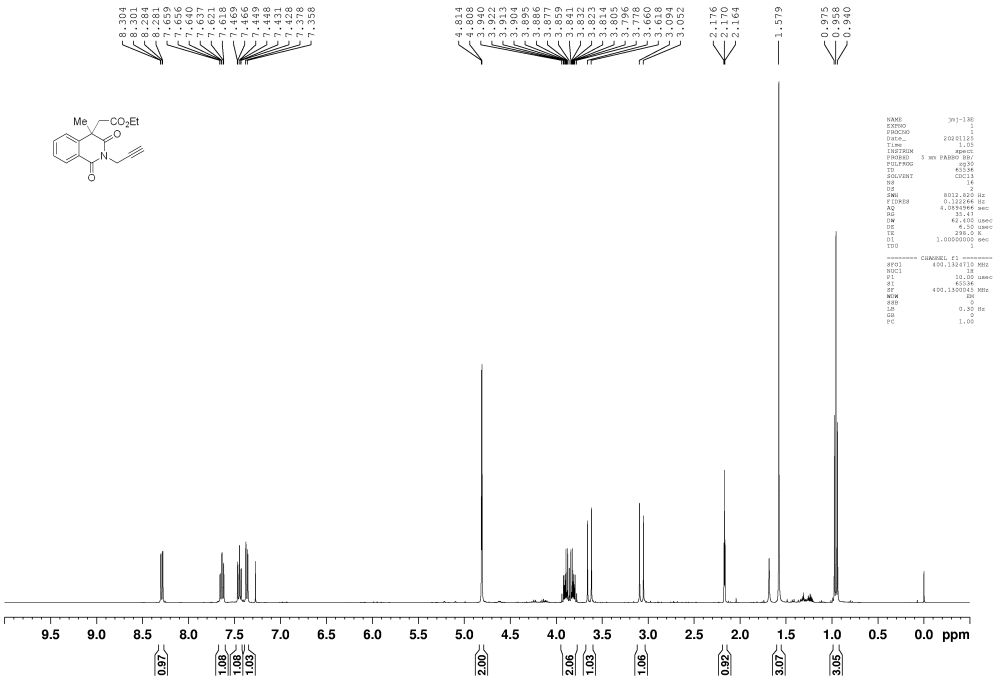


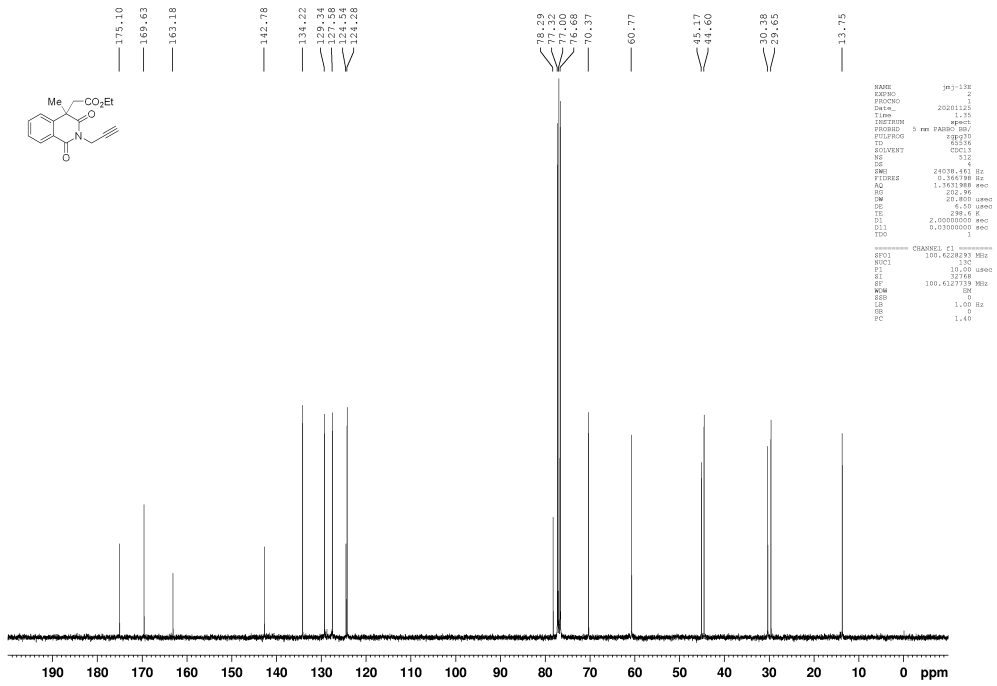
diethyl 2,2'-(4-methyl-1,3-dioxo-3,4-dihydroisoquinoline-2,4(1H)-diyl)diacetate (3q)



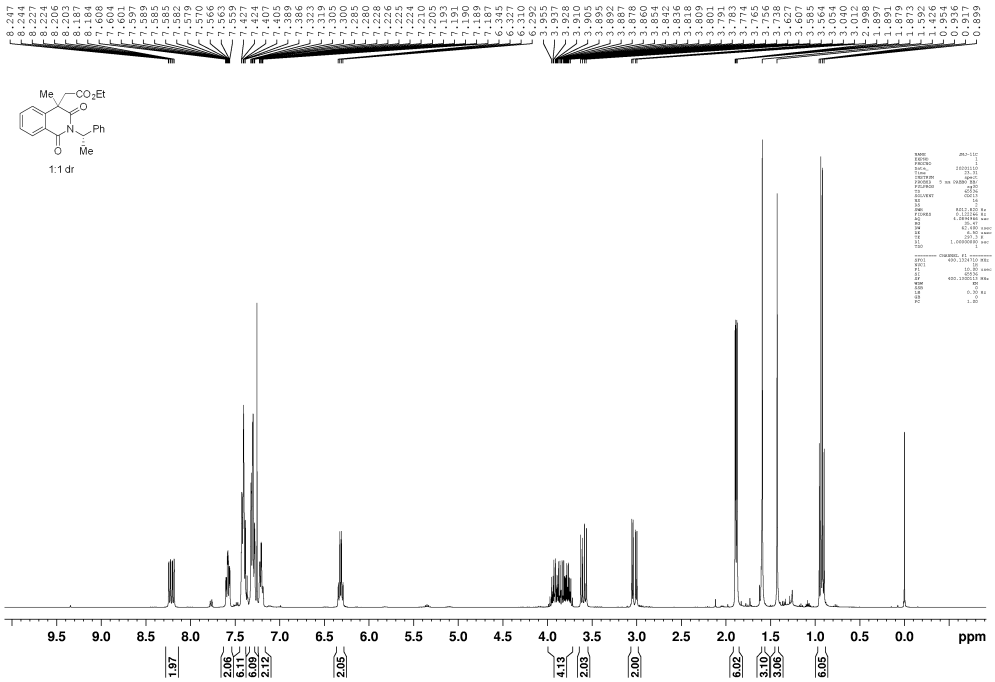


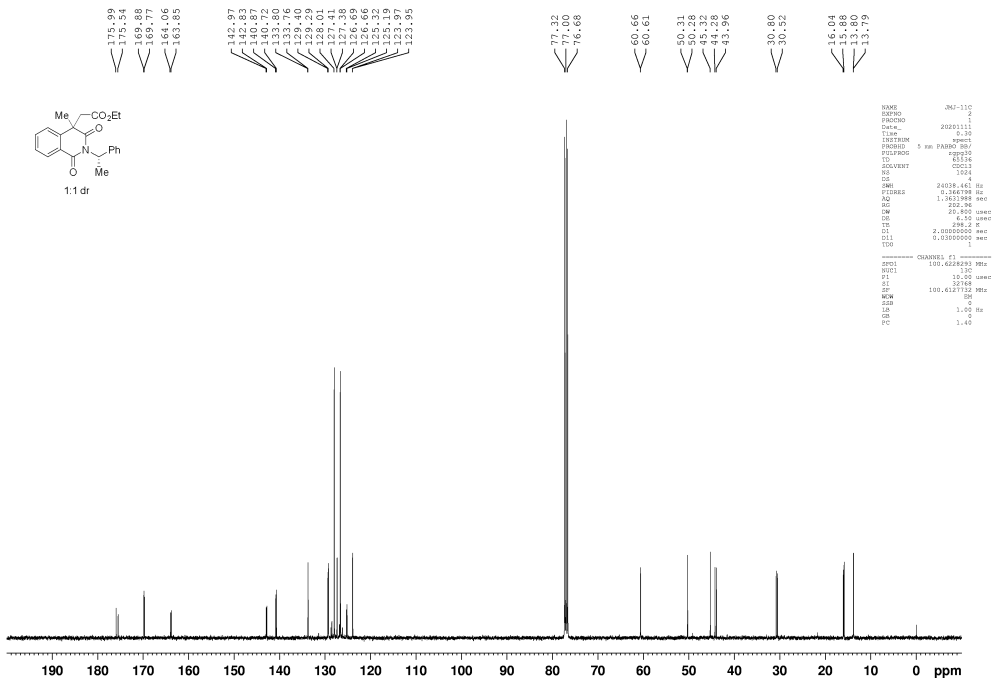
ethyl 2-(4-methyl-1,3-dioxo-2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3r)



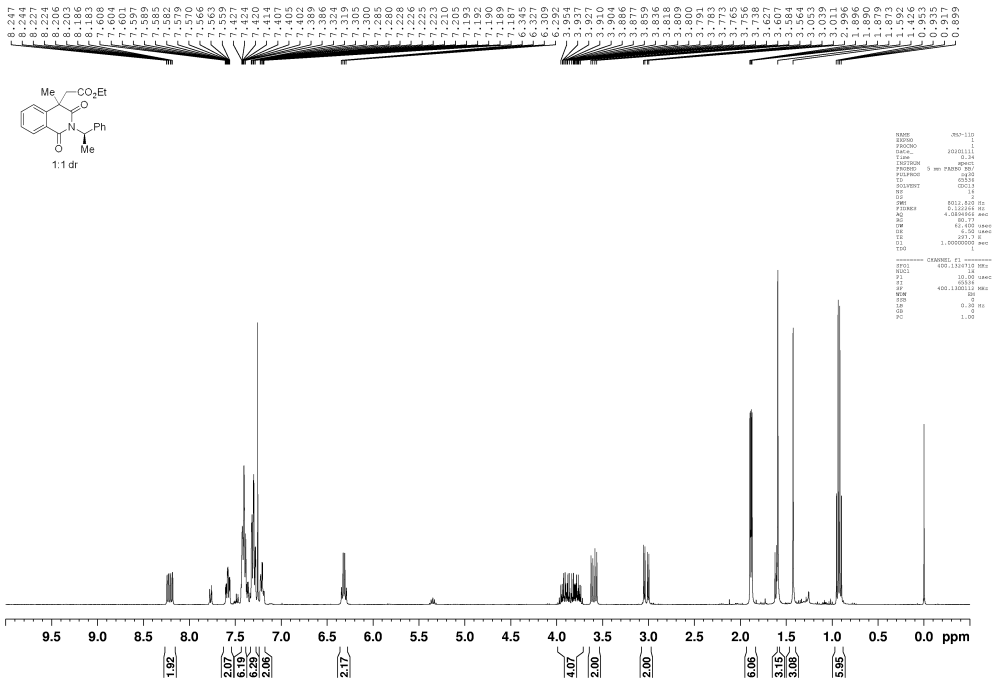


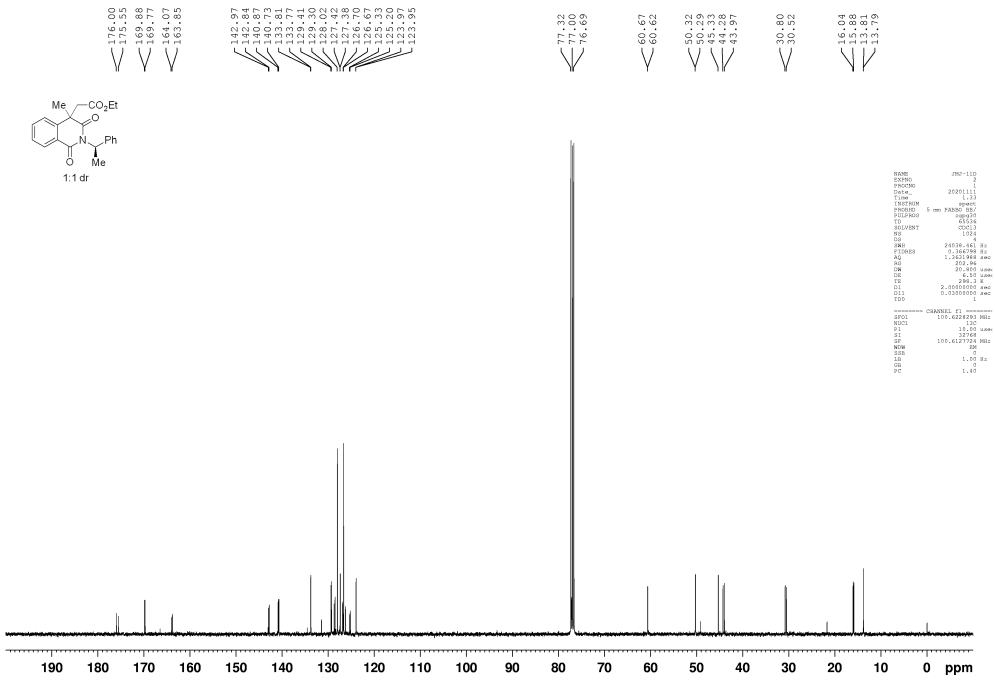
ethyl 2-(4-methyl-1,3-dioxo-2-((S)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3s)



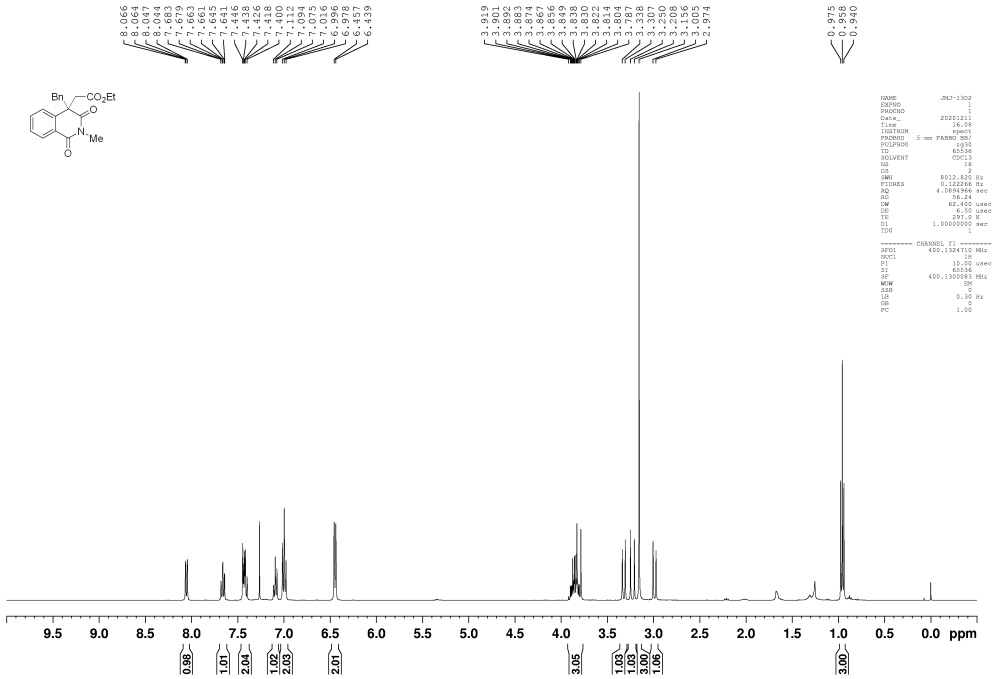


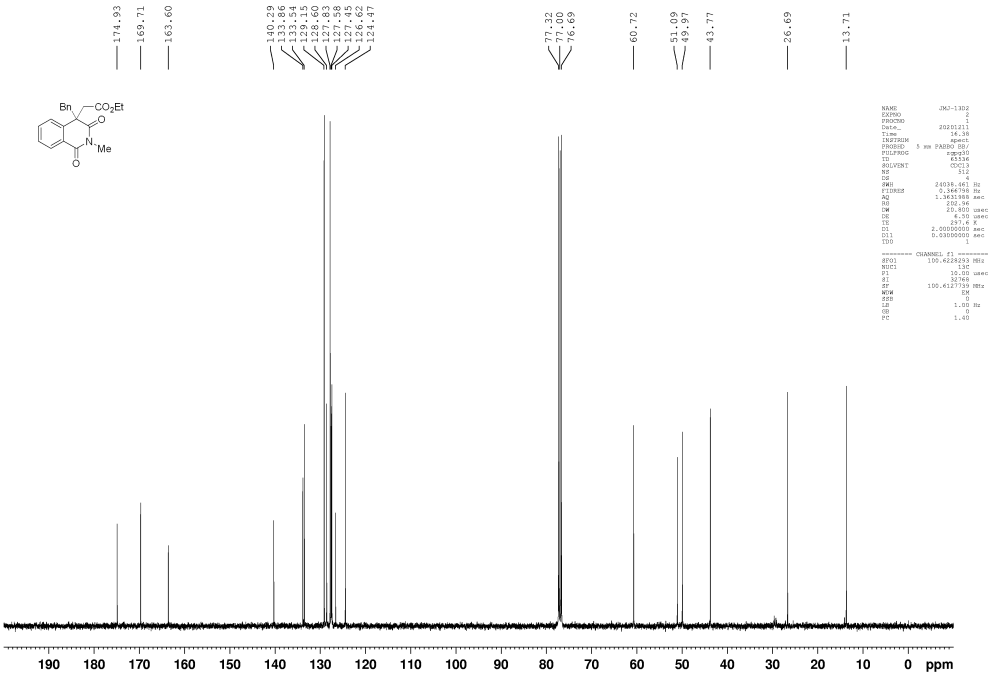
ethyl 2-(4-methyl-1,3-dioxo-2-((R)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3t)



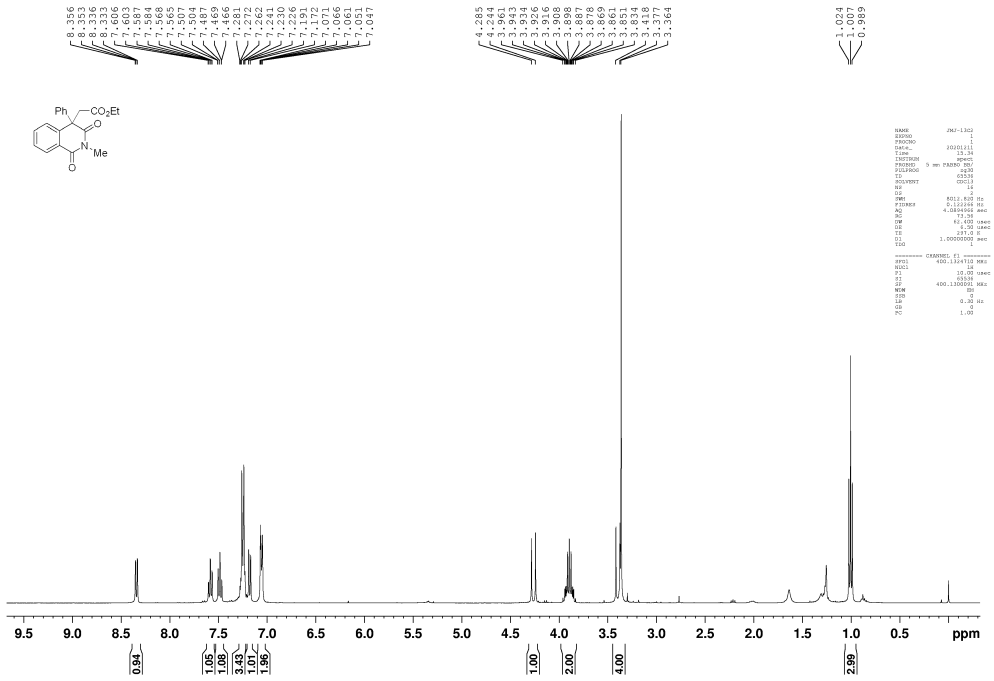


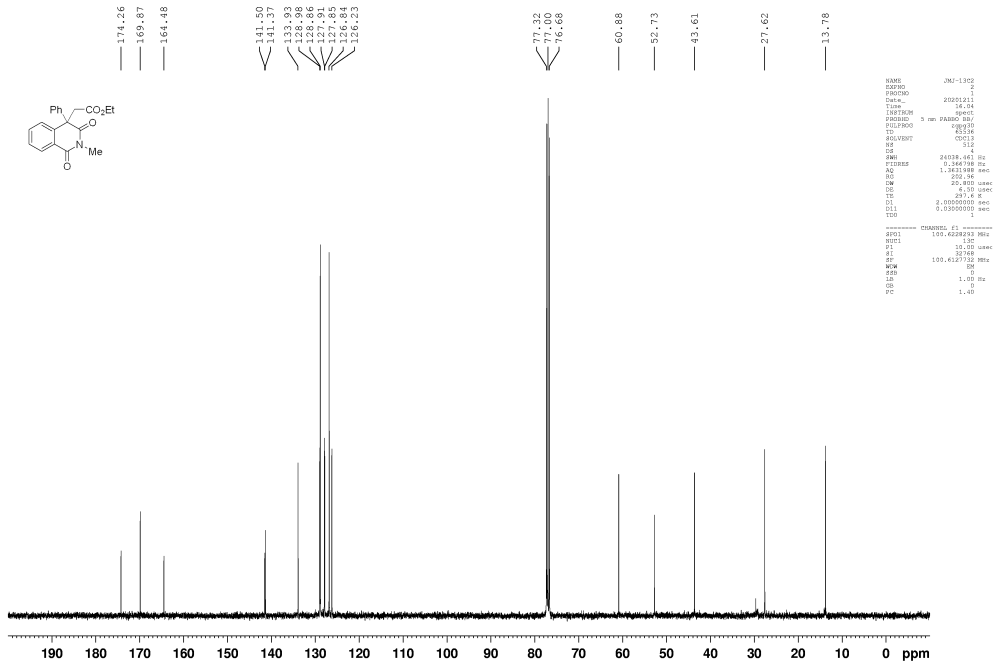
ethyl 2-(4-benzyl-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3u)



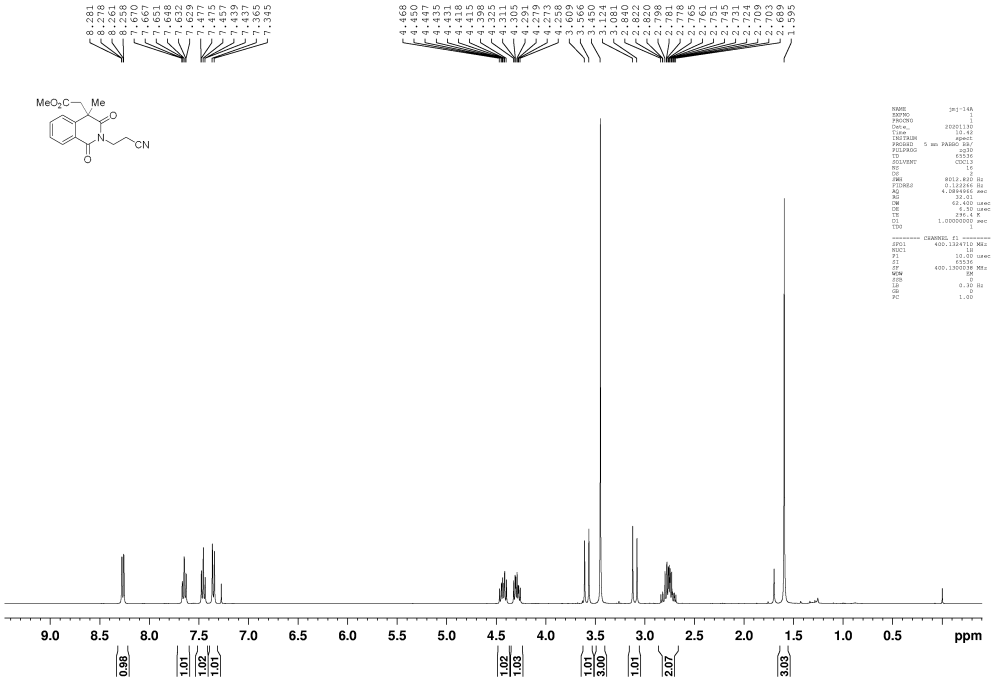


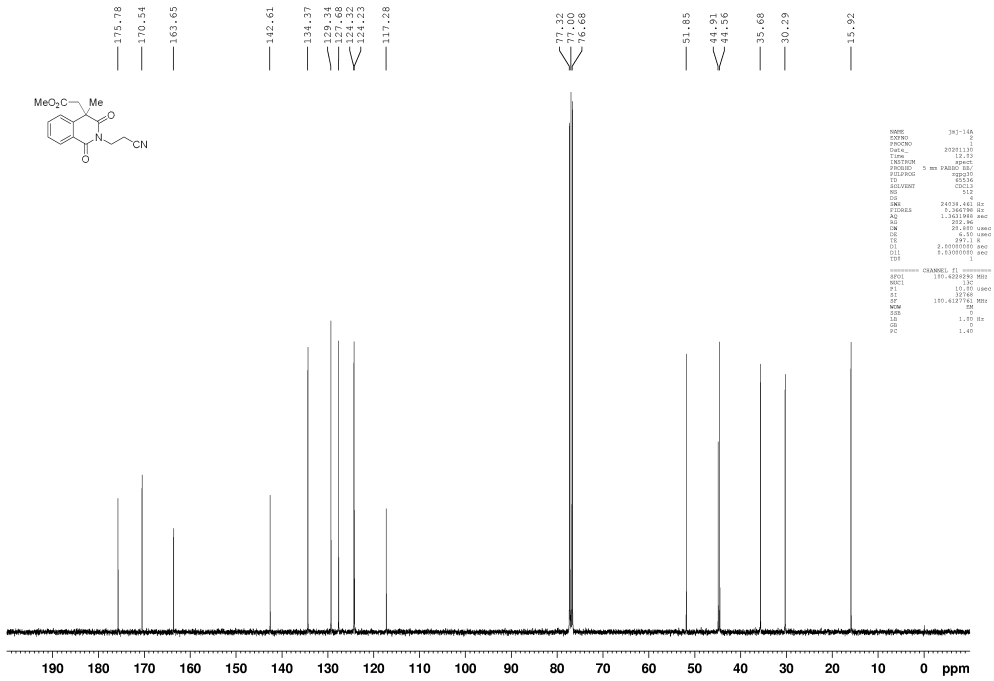
ethyl 2-(2-methyl-1,3-dioxo-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (3v)



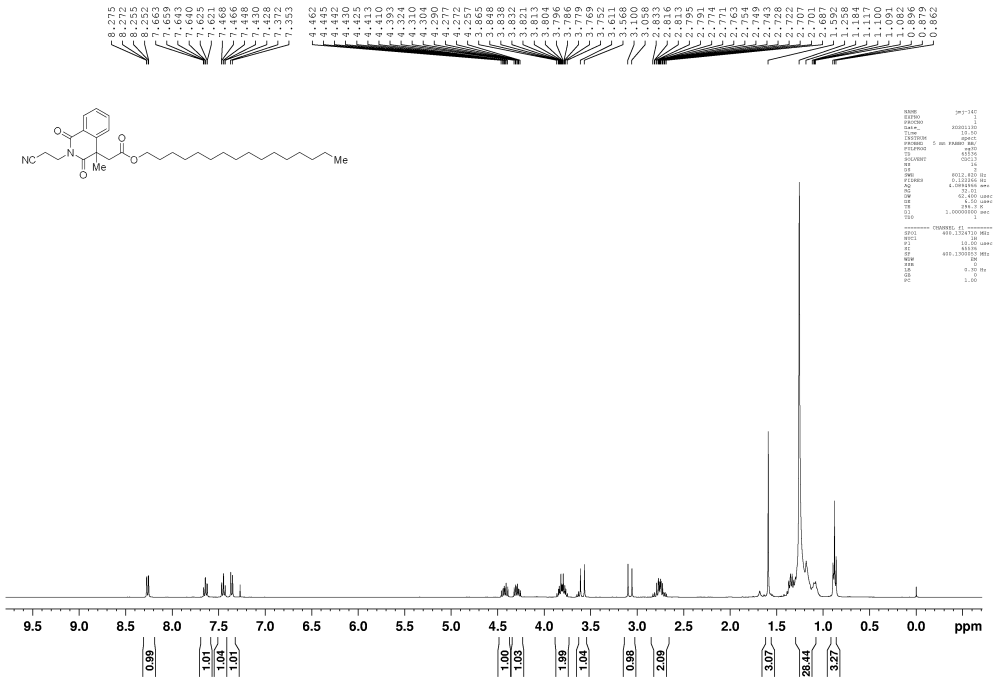


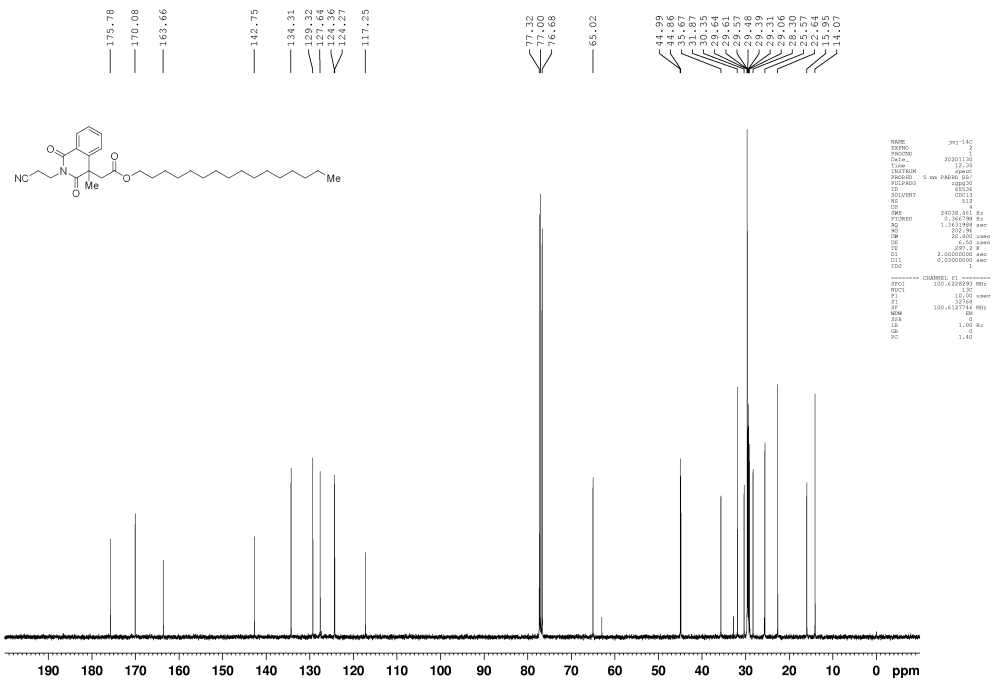
methyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4a)



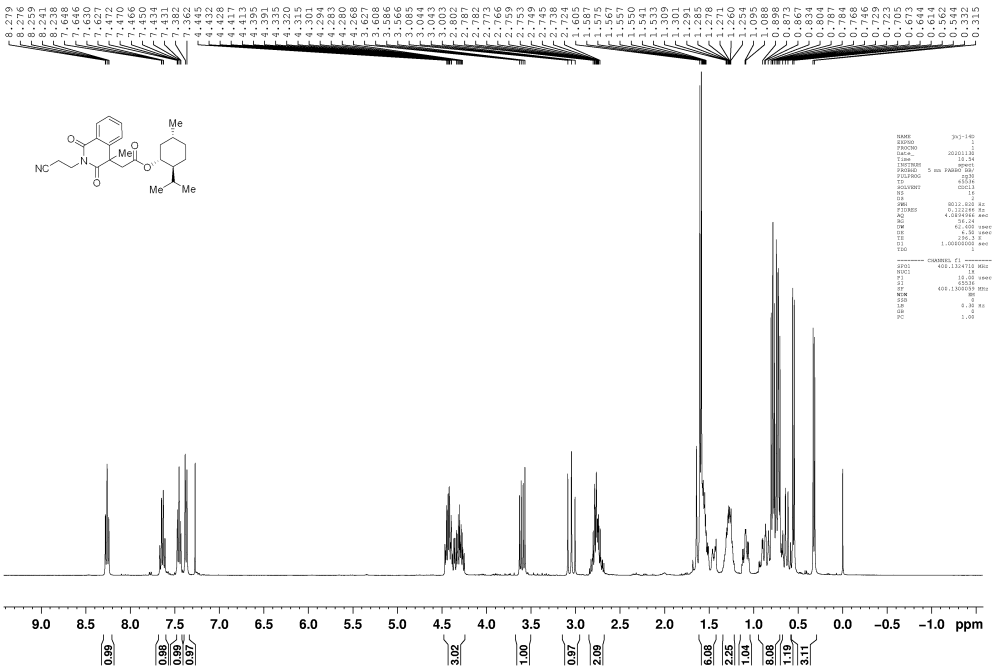


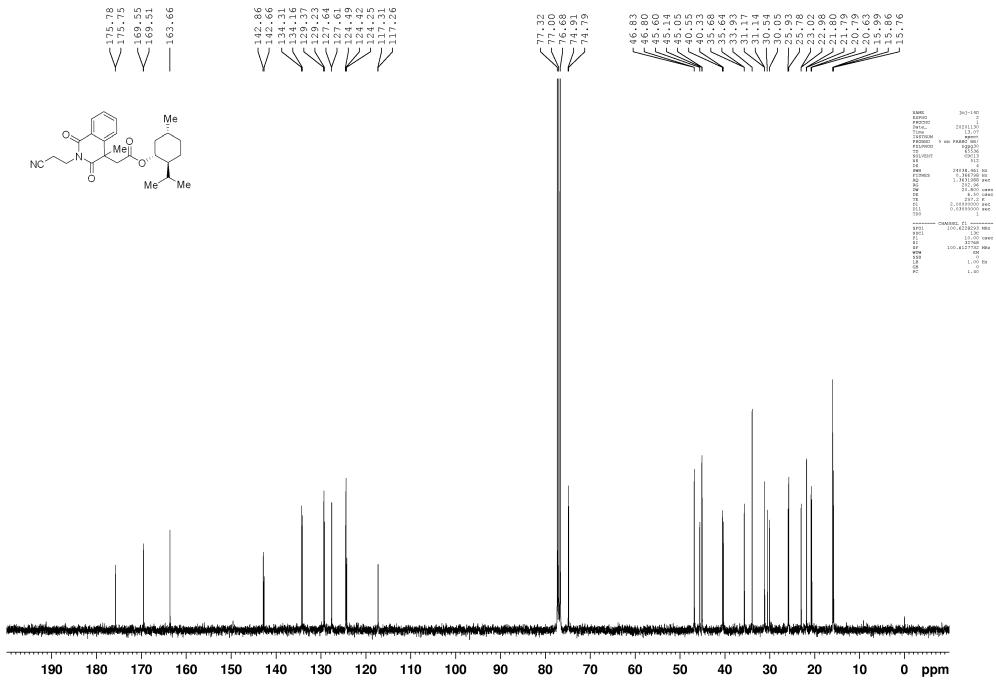
hexadecyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4b)



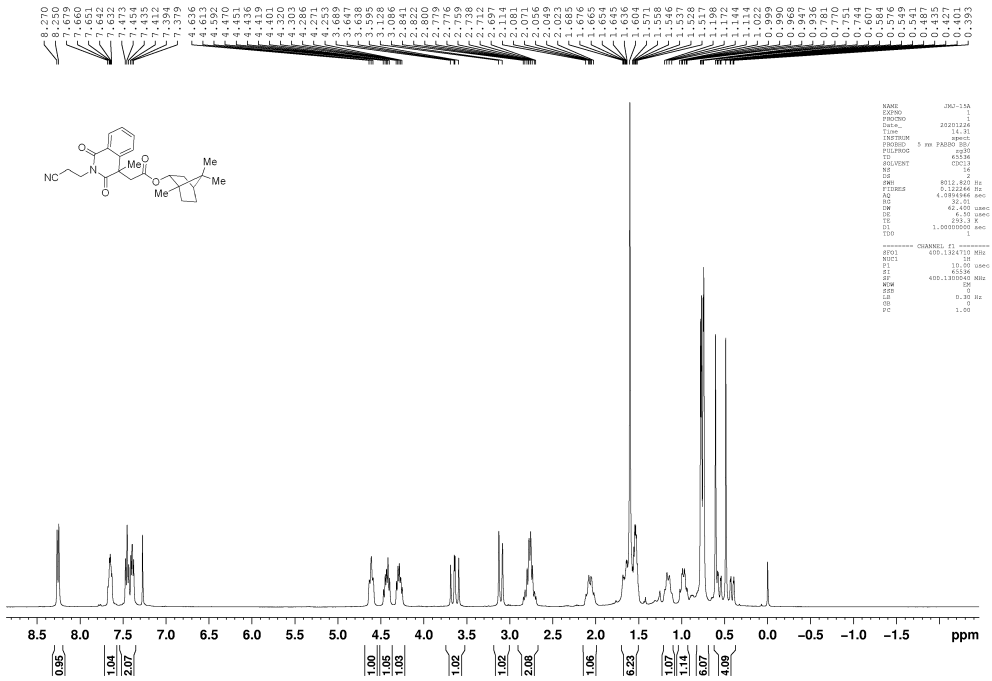


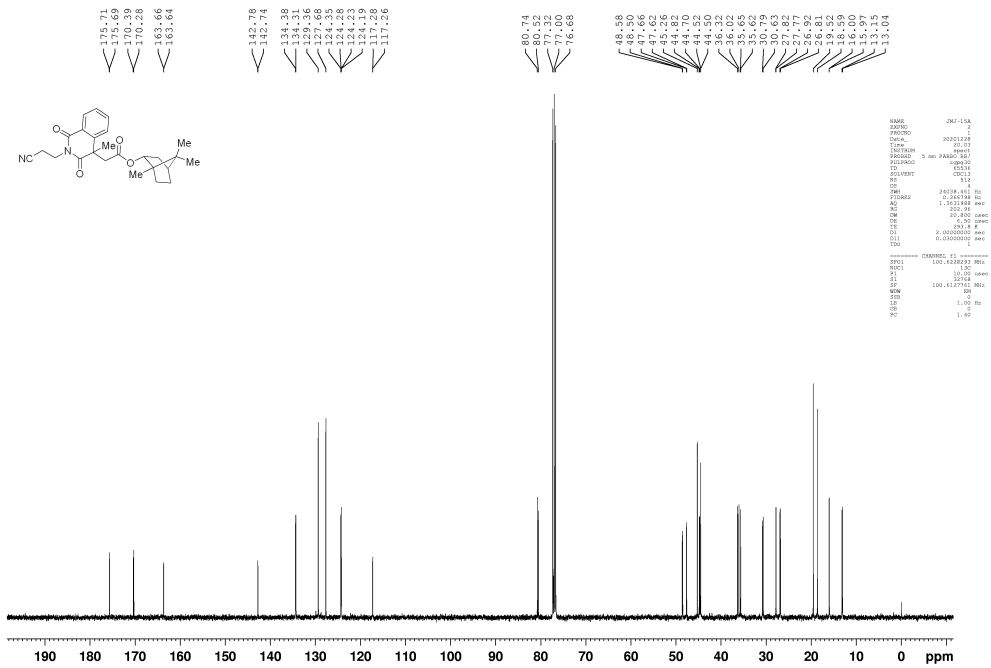
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4c)



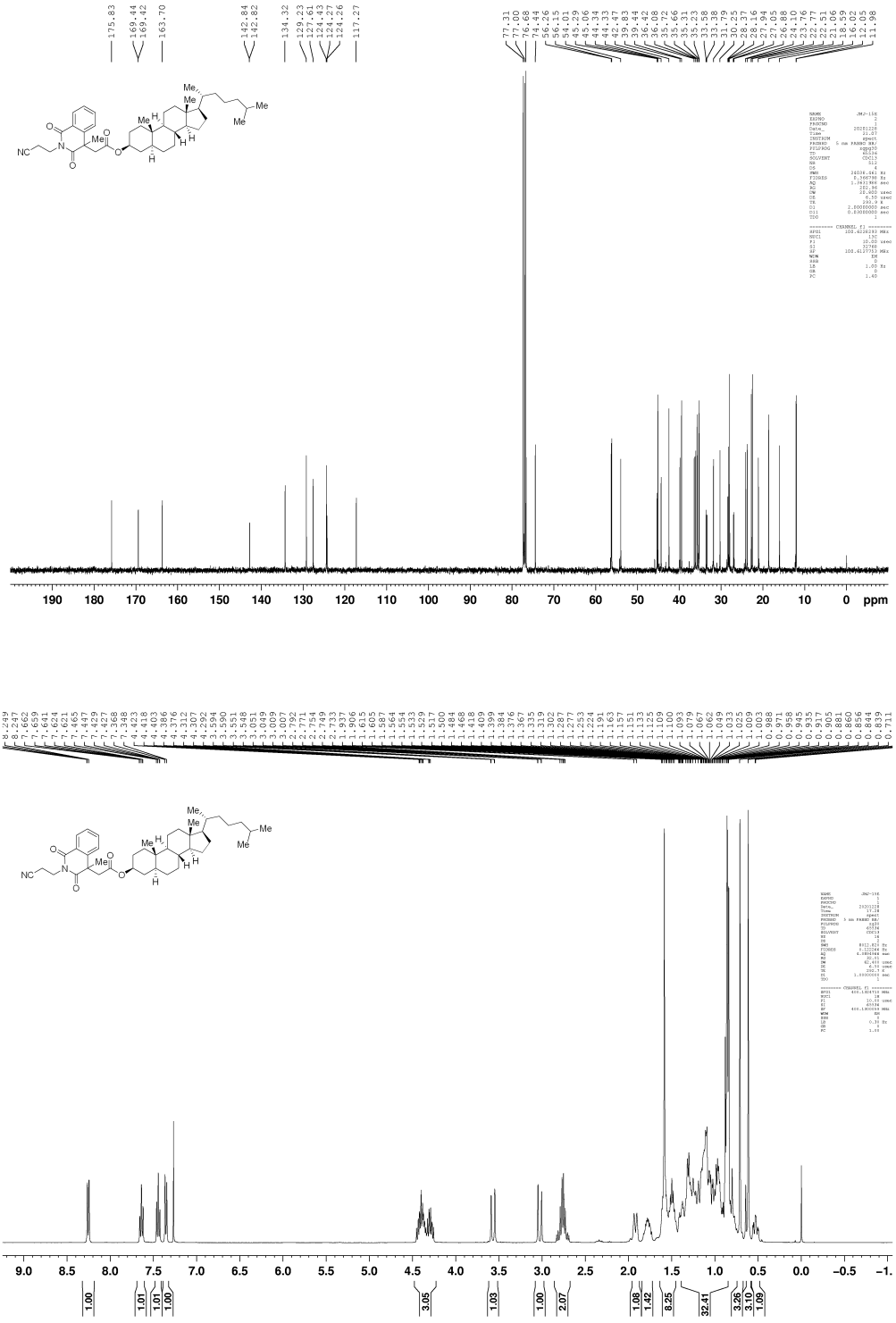


(2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4d)

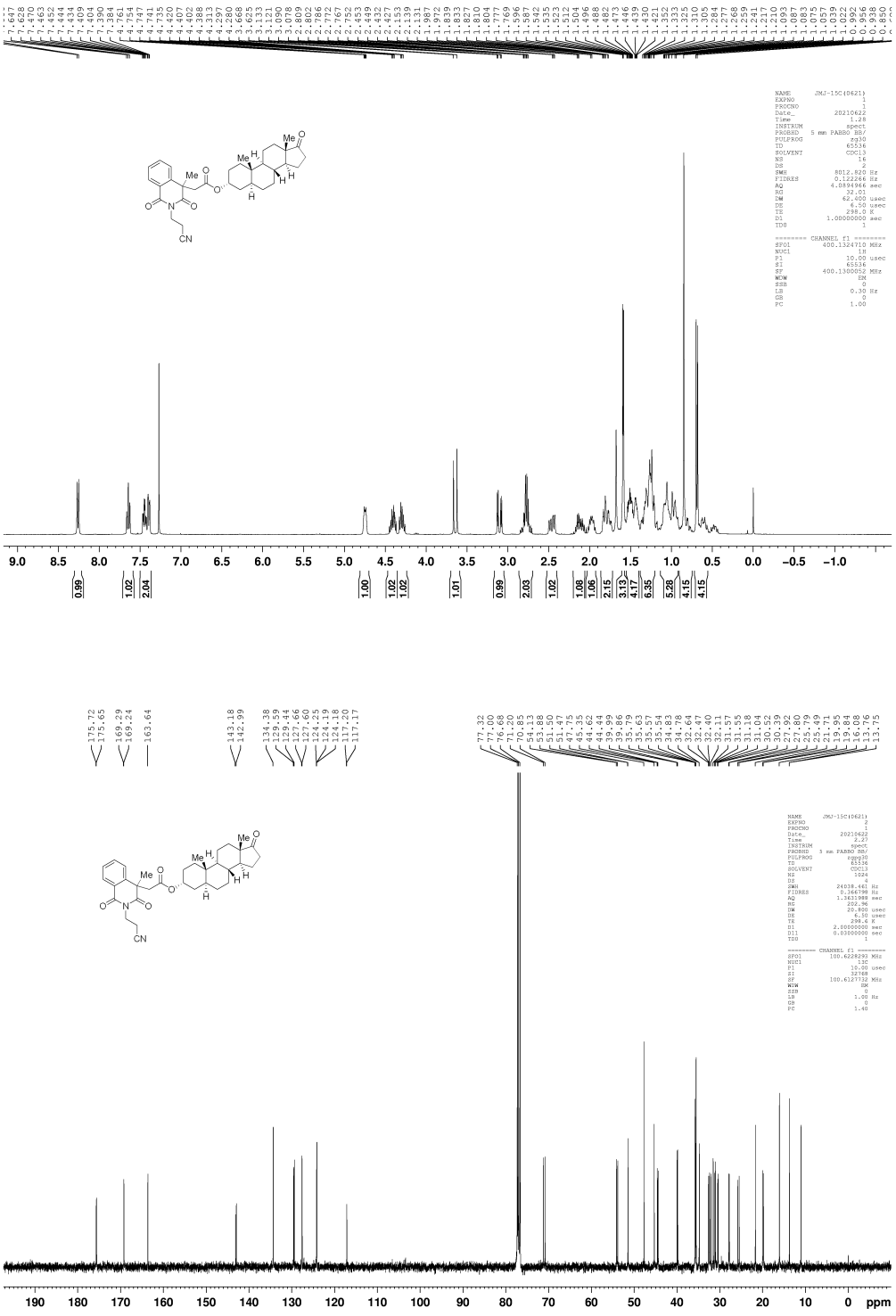




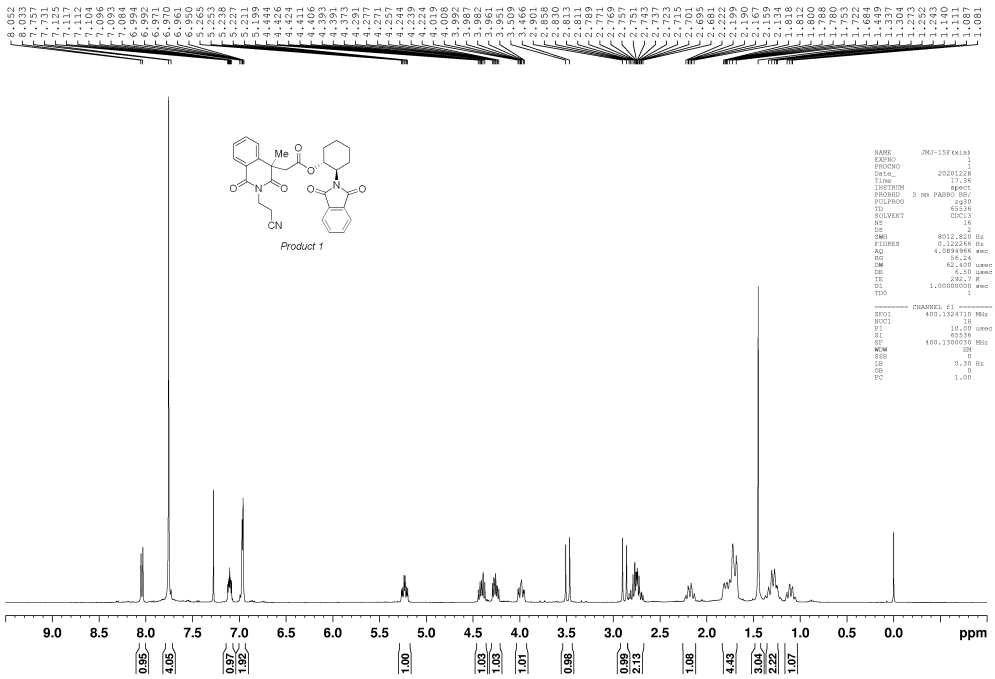
(3S,5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4e)

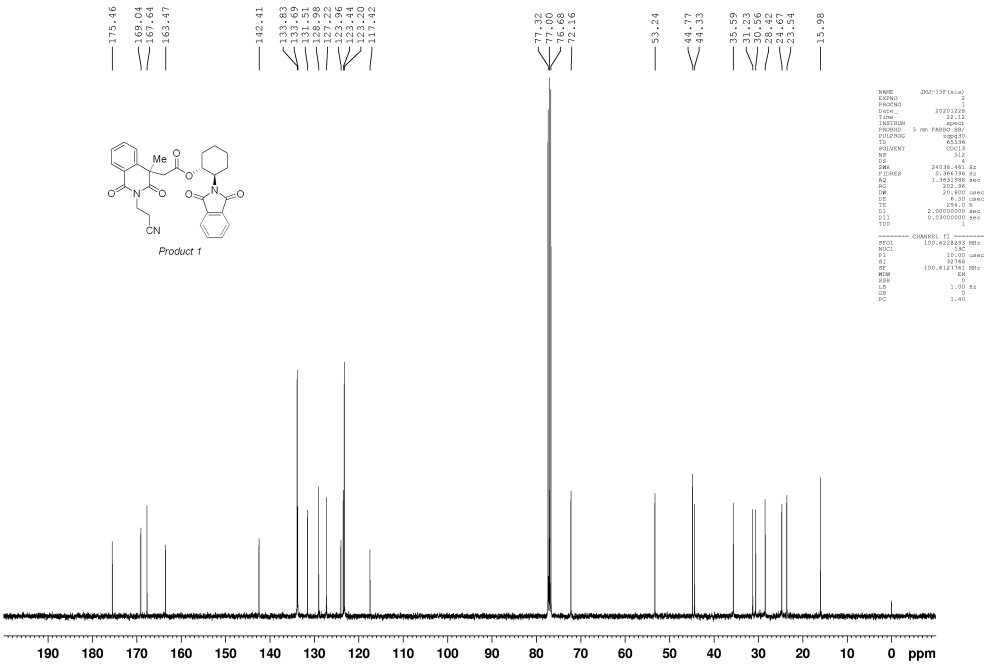


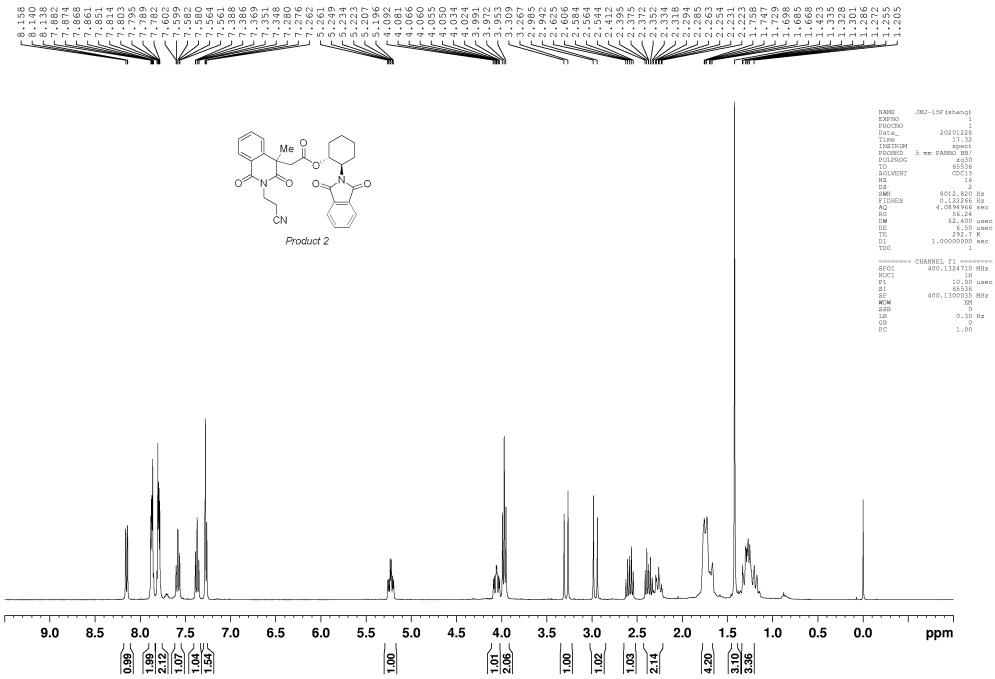
(3R,5S,8R,9S,10S,13S,14S)-10,13-dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4f)

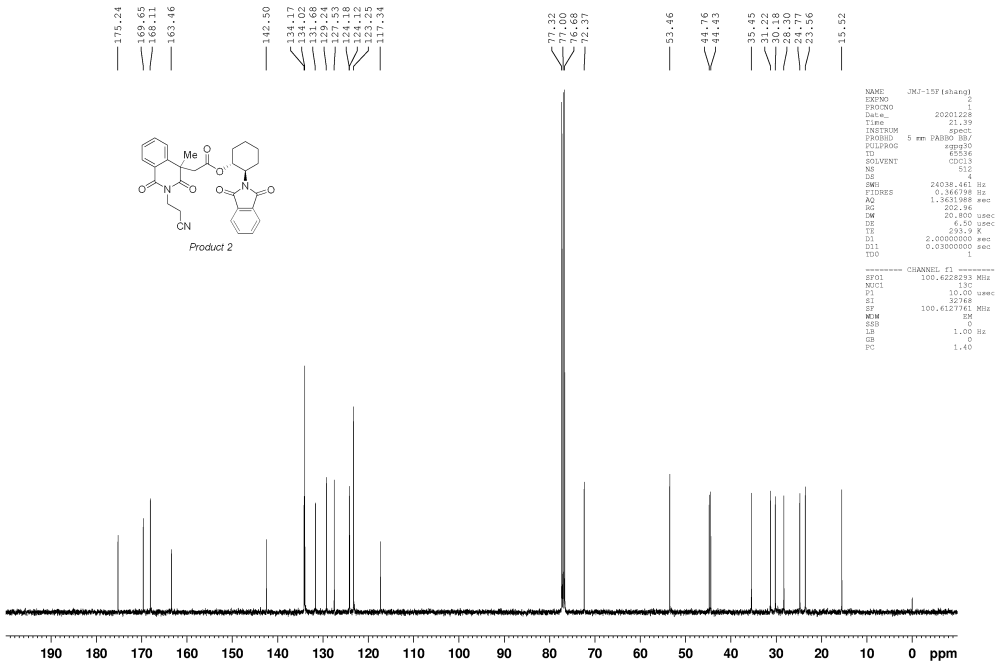


(1R,2R)-2-(1,3-dioxoisoindolin-2-yl)cyclohexyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4g)






Product 2
ppm


Product 2
ppm

(R)-2-(1,3-dioxoisoindolin-2-yl)-3,3-dimethylbutyl 2-(2-(2-cyanoethyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (4h)