Supporting Information for:

Aerobic oxidative cyclization of benzamides via *meta*-selective C-H *tert*-alkylation: Rapid entry to 7-alkylated isoquinolinediones

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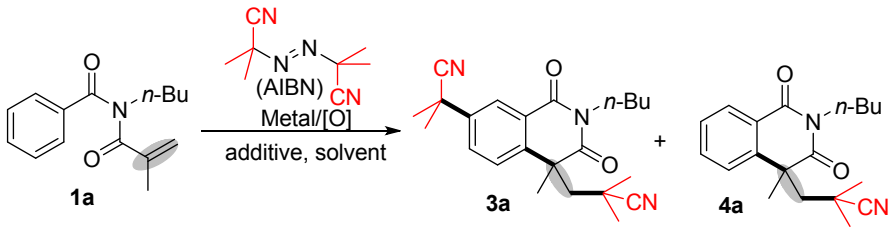
1. General

All manipulations of oxygen- and moisture-sensitive materials were conducted with a Schlenk technique under a nitrogen or argon atmosphere. Solvent were purified and dried in a standard manner. Flash column chromatography was performed using EM Silica gel

60 (200-400 mesh). Visualization was accomplished with UV light (254 nm) and/or an aqueous alkaline $KMnO_4$ solution followed by heating. ^1H NMR, ^{13}C NMR spectra were recorded on 400 or 500 MHz NMR spectrometer with trimethylsilane resonance as the internal standard. Unless otherwise noted, reagents were commercially available and were used without further purification. Preparation of *N*-alkyl-*N*-methacryloyl benzamides **1** were prepared according to literature procedures.[1]

2. Optimization of Reaction Conditions

Table S1 Screening of optimal conditions[a]



entry	metal/[O]	base/additive	solvent	yield **3a** (%)[b]	yield **4a** (%)[b]
1	CuI/DTBP	none	DMF	trace	13
2	CuI/TBHP	none	DMF	trace	9
3[c]	CuI/H_2O_2	none	DMF	trace	11
3	CuI/air	K_3PO_4	DMF	11	75
4	CuI/air	K_3PO_4	DMSO	13	62
5	CuI/air	K_3PO_4	dioxane	58	11
6	CuI/air	K_3PO_4	THF	12	17
7	CuI/air	K_3PO_4	CH_3CN	27	23
8	CuI/air	K_3PO_4	*t*-AmylOH	45	16
9	CuI/air	K_3PO_4	DCM	23	11
10	CuI/air	K_3PO_4	ethyl acetate	8	15
11	CuCl/air	K_3PO_4	dioxane	51	10
12	CuBr/air	K_3PO_4	dioxane	53	14
13	$FeBr_2$/ air	K_3PO_4	dioxane	28	9
14	AgOAc/ air	K_3PO_4	dioxane	23	7
15	$Mn(OAc)_2.4H_2O$ /air	K_3PO_4	dioxane	14	16
16	$NiCl_2.6H_2O$/air	K_3PO_4	dioxane	10	12

Continued (Table S1)

17	CuI/O_2	K_3PO_4	dioxane	54	15
18[d]	CuI	K_3PO_4	dioxane	21	10
19[e]	CuI/air	K_3PO_4/KF	dioxane	65	16
20	CuI/air	K_3PO_4/KF	dioxane	73	13
21[f]	CuI/air	K_3PO_4/KF	dioxane	71	17
22	CuI/air	K_3PO_4/NaF	dioxane	61	15
23	CuI/air	K_3PO_4/CaF_2	dioxane	36	9
24	CuI/air	K_3PO_4/CsF	dioxane	53	14
25	CuI/air	K_2CO_3/KF	dioxane	19	12
26	CuI/air	K_2HPO_4/KF	dioxane	35	10
27	CuI/air	Cs_2CO_3/KF	dioxane	18	13
28[g]	CuI/air	K_3PO_4/KF	dioxane	22	8
29[h]	CuI/air	K_3PO_4/KF	dioxane	67	15
30[i]	CuI/1,10-Phenanthroline/air	K_3PO_4/KF	dioxane	66	16
31[i]	CuI /2,2'-bipyridine/air	K_3PO_4/KF	dioxane	51	18
32[j]	CuI/air	K_3PO_4/KF	dioxane	64	15

[a] Reaction conditions: **1a** (0.3 mmol), AIBN (4 equiv.), metal (20 mol %), oxidant (2 equiv.) or O_2/air (1 atm), base (2 equiv.), additive (2 equiv.) and solvent (2 mL) at 90 °C for 10 h. DTBP = Di-*tert*-butyl peroxide, DMF = Dimethyl formamide, DMSO = Dimethyl sulfoxide, THF = Tetrahydrofuran, DCM = Dichloromethane.[b] Yield of the isolated product. [c] H_2O_2 (30% aqueous solution). [d] Under N_2 atmosphere. [e] Using 2 equiv. of KF. [f] Using 4 equiv. of KF. [g] Using 2 equiv. of AIBN. [h] Using 5 equiv. of AIBN. [i] In the presence of *N*-containing ligand (20 mol %). [j] Using 10 mol % of CuI.

3. Calculations

General: All calculations presented in this paper were performed using unrestricted density functional theory (DFT) with the hybrid functional B3LYP[2–4] as implemented in Gaussian 09 package.[5] Geometry optimizations were carried out with the 6-31G(d,p) basis set. On the basis of the optimized geometries, more accurate energies were with the 6-31G (d,p) basis set. On the basis of the optimized geometries, more accurate energies were obtained by performing single-point calculations with a larger 6-311+G (2d, 2p)

basis set. It should be noted that the lack of dispersion (van der Waals effects) in DFT theory should lead to exaggerated repulsive interactions when atoms are forced closer to each other, especially for systems with large groups or ligands.[7-9] In the present work, dispersion corrections were taken into account using an empirical formula by Grimme et al,[10-13] which has recently been successfully applied to a number of massive systems, such as semirigid supramolecular systems,[14] dicopper complexes,[8,15] cobalamin-dependent enzymes,[6,7] Ni-containing enzyme,[15] and α-Keggin-type polyoxometalates.[17,18] It is worth stressed here that dispersion effects were taken into account in all calculations including geometry optimizations and single-point calculations. Solvation effects were also considered by performing single-point calculations at the same theory level as optimizations, using a conductor-like polarizable continuum model (CPCM)[19-21] method with a dielectric constant of 2.2 (the solvent is dioxane). Frequency calculations were performed at the same level of theory as in the optimizations to further confirm the nature of stationary points and to obtain zero-point energies (ZPE) and entropy effects. The energies reported in this paper are the free energies which have been corrected for dispersion, solvation, ZPE, and entropy effects.

Results and Discussion: A reactant-state complex of intermediate **E** with the radical **A** has been optimized and named by **React** here (Figure 1). The two molecules are weakly bound. The unpaired spin density is delocalized at the xxx radical so that the one at the central carbon (C_R) is 0.79. From **React**, a transition state (see **TS** in Figure 1) for hydrogen transfer from the substrate to the xxx radical has been optimized and confirmed to be a first-order saddle point with an imaginary frequency of 1740*i* cm^{-1}. At **TS**, the distances of the transferred hydrogen (H_P) to the two carbons are 1.43 and 1.34 Å, respectively. The very small spin at the H_P atom (-0.08), along with the spins at the two

carbons (0.47 and 0.37), indicates that this is an electron-coupled proton transfer process. The free energy barrier for this step is calculated to be accessible (14.4 kcal/mol). This step results in a product state of intermediate **E** with a radical **A** (see **Prod** in Figure 1). The **Prod** is much more stable than the **React** (by -14.7 kcal/mol), since the spin in the substrate are delocalized by a larger π-conjugated system than in the radical **A**. This implies that the reaction is irreversible, that is, the reverse hydrogen transfer from the radical **A** to the substrate radical is unreachable.

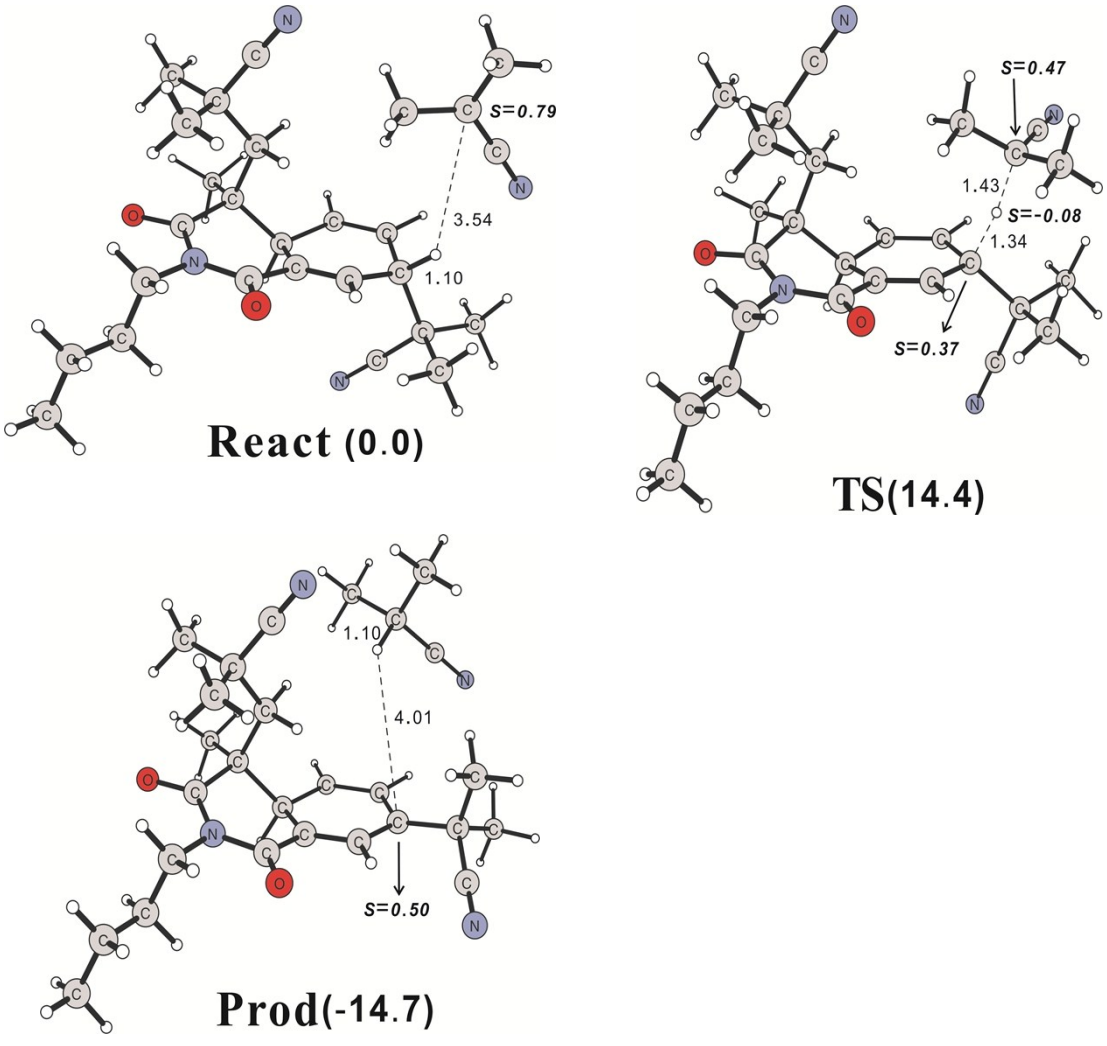
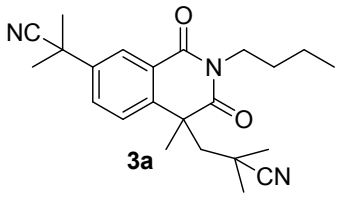


Figure S1. Optimized structures of stationary points. All distances are given in angstrom (Å). The unpaired spin populations are also shown. The free energies (in kcal/mol) are provided in parentheses with the **React** as the energy reference (0.0 kcal/mol).

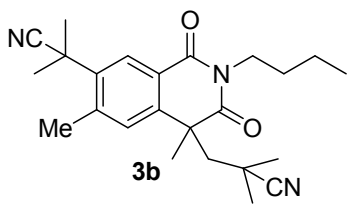
4. Typical Experimental Procedures

General procedure for the synthesis of isoquinolinediones. To a mixture of methacryloyl benzamide **1** (0.3 mmol), CuI (20 mol%), azo compound **2** (4.0 equiv.) , K_3PO_4 (2 equiv.), KF (3 equiv.) was added dioxane (2 mL), and then the resulting solution was stirred at 90 ^oC under air atmosphere (1 atm.) for 10-12 h. The solvent was evaporated under reduced pressure and the resulted mixture was filtered through a Florisil pad, diluted with Et_2O, and washed with water and then brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel to afford the corresponding 7-alkylated isoquinolinediones (**3a-3w**) in a yield listed in **Scheme 2** and **3**.



3a

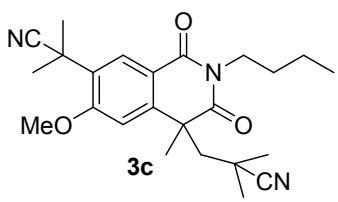
3-(2-Butyl-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (**3a**)**.** Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.35 (d, *J* = 2.2 Hz, 1H), 7.85 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 4.10 – 3.94 (m, 2H), 2.77 (d, *J* = 14.6 Hz, 1H), 2.34 (d, *J* = 14.6 Hz, 1H), 1.80 (s, 3H), 1.78 (s, 3H), 1.63 – 1.54 (m, 5H), 1.45 – 1.36 (m, 2H), 1.16 (s, 6H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 175.1, 163.2, 142.0, 140.6, 131.1, 127.5, 125.5, 125.4, 123.8, 123.2, 49.5, 45.9, 40.7, 37.0, 33.4, 30.5, 29.8, 29.6, 29.1, 28.8, 27.4, 20.3, 13.7; HRMS *m/z* (ESI) calcd for $C_{23}H_{30}N_3O_2$ $[M+H]^+$ 380.2333, found: 380.2330.



3b

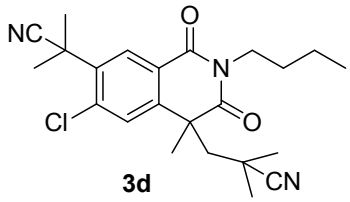
3-(2-Butyl-7-(2-cyanopropan-2-yl)-4,6-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-

dimethylpropanenitrile (3b). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (s, 1H), 7.34 (s, 1H), 4.04 – 3.95 (m, 2H), 2.77 (s, 3H), 2.75 (d, *J* = 14.7 Hz, 1H), 2.34 (d, *J* = 14.7 Hz, 1H), 1.89 (s, 3H), 1.80 (s, 3H), 1.61 – 1.52 (m, 5H), 1.46 – 1.37 (m, 2H), 1.19 (s, 3H), 1.11(s, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.4, 163.4, 143.3, 140.2, 138.8, 131.1, 125.8, 124.0, 123.5, 122.9, 49.0, 45.6, 40.7, 34.6, 33.4, 30.6, 30.0, 29.6, 28.3, 28.1, 26.8, 21.6, 20.3, 13.8; HRMS *m/z* (ESI) calcd for $C_{24}H_{32}N_3O_2$ $[M+H]^+$ 394.2490, found: 394.2494.



3c

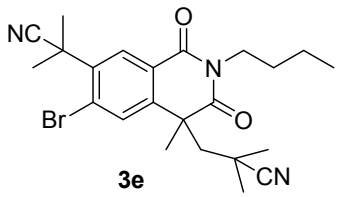
3-(2-Butyl-7-(2-cyanopropan-2-yl)-6-methoxy-4-methyl-1,3-dioxo1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3c). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (s, 1H), 6.99 (s, 1H), 4.08 (s, 3H), 4.04 – 3.95 (m, 2H), 2.81 (d, *J* = 14.8 Hz, 1H), 2.39 (d, *J* = 14.8 Hz, 1H), 1.84 (s, 3H), 1.78 (s, 3H), 1.64 – 1.54 (m, 5H), 1.44–1.35 (m, 2H), 1.27 (s, 3H), 1.10 (s, 3H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.4, 163.1, 161.6, 142.9, 129.8, 127.4, 123.9, 123.8, 117.3, 109.5, 56.1, 48.8, 46.2, 40.6, 33.8, 33.6, 30.6, 30.2, 29.6, 27.0, 26.0, 20.3, 13.8; HRMS *m/z* (ESI) calcd for $C_{24}H_{32}N_3O_3$ $[M+H]^+$ 410.2439, found: 410.2442.



3d

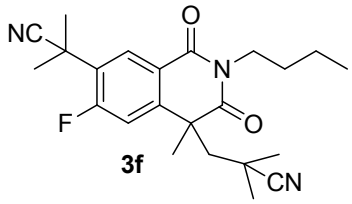
3-(2-Butyl-6-chloro-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3d). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.36 (s, 1H), 7.59 (s, 1H), 4.05 – 3.98 (m, 2H), 2.76 (d, *J* = 14.7 Hz, 1H), 2.29 (d, *J* = 14.7 Hz, 1H), 1.95 (s, 3H), 1.90 (s, 3H), 1.66 – 1.57 (m, 5H), 1.46 – 1.37 (m, 2H), 1.21 (s, 3H), 1.17 (s, 3H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:

174.5, 162.6, 142.0, 139.6, 137.9, 130.2, 127.9, 123.8, 123.1, 122.6, 49.4, 45.8, 40.8, 35.5, 33.2, 30.5, 29.9, 29.5, 27.5, 27.3, 27.1, 20.3, 13.7; HRMS *m/z* (ESI) calcd for $C_{23}H_{29}ClN_3O_2$ $[M+H]^+$ 414.1943, found: 414.1941.



3e

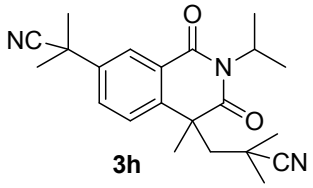
3-(6-Bromo-2-butyl-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3e). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (s, 1H), 7.81 (s, 1H), 4.08 – 3.95 (m, 2H), 2.76 (d, *J* = 14.7 Hz, 1H), 2.30 (d, *J* = 14.7 Hz, 1H), 1.97 (s, 3H), 1.92 (s, 3H), 1.64 – 1.56 (m, 5H), 1.39 (dd, *J* = 10.3, 4.6 Hz, 2H), 1.20 (s, 3H), 1.18 (s, 3H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.5, 162.7, 141.9, 139.1, 134.0, 129.4, 127.8, 124.3, 123.1, 122.6, 49.3, 45.7, 40.9, 36.8, 33.2, 30.5, 29.9, 29.5, 27.8, 27.4, 20.3, 13.8; HRMS *m/z* (ESI) calcd for $C_{23}H_{29}BrN_3O_2$ $[M+H]^+$ 458.1438, found: 458.1436.



3f

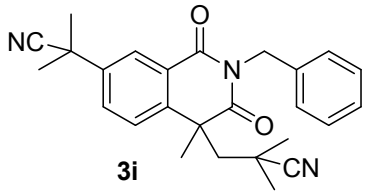
3-(2-Butyl-7-(2-cyanopropan-2-yl)-6-fluoro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3f). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 11.6 Hz, 1H), 4.07 – 3.95 (m, 2H), 2.75 (d, *J* = 14.7 Hz, 1H), 2.27 (d, *J* = 14.7 Hz, 1H), 1.87 (s, 3H), 1.83 (s, 3H), 1.65 – 1.50 (m, 5H), 1.49 – 1.34 (m, 2H), 1.20 (s, 3H), 1.17 (s, 3H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.6, 164.0 (d, *J* = 260.6 Hz), 162.4, 143.7 (d, *J* = 4.7 Hz), 129.2 (d, *J* = 26.4 Hz), 128.9 (d, *J* = 5.3 Hz), 122.9 (d, *J* = 17.8 Hz), 121.5 (d, *J* = 1.4 Hz), 115.3, 115.0, 49.7, 45.9, 40.8, 33.9, 33.3, 30.5, 30.0, 29.6, 27.0, 26.9, 20.3, 13.8; HRMS

m/z (ESI) calcd for $C_{23}H_{29}FN_3O_2$ $[M+H]^+$ 398.2239, found: 398.2237.



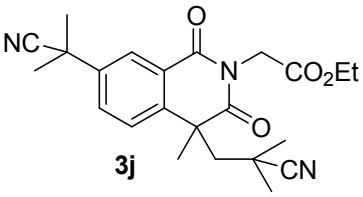
3h

3-(7-(2-Cyanopropan-2-yl)-2-isopropyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3h). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (d, *J* = 2.2 Hz, 1H), 7.83 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 5.29 – 5.12 (m, 1H), 2.76 (d, *J* = 14.7 Hz, 1H), 2.32 (d, *J* = 14.6 Hz, 1H), 1.80 (s, 3H), 1.78 (s, 3H), 1.57 (d, *J* = 7.0 Hz, 6H), 1.54 (s, 3H), 1.19 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.3, 163.5, 141.9, 140.4, 130.9, 127.4, 125.5, 123.9, 123.4, 121.1, 49.0, 46.2, 45.9, 33.5, 30.5, 30.4, 30.0, 29.1, 28.8, 27.3, 19.5, 19.2; HRMS *m/z* (ESI) calcd for $C_{22}H_{28}N_3O_2$ $[M+H]^+$ 366.2177, found: 366.2179.



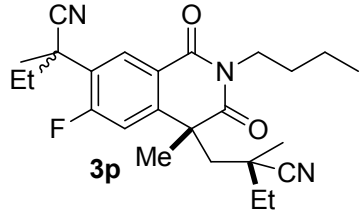
3i

3-(2-Benzyl-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3i). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.38 (d, *J* = 2.2 Hz, 1H), 7.87 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.33 – 7.24 (m, 3H), 5.32 (d, *J* = 13.7 Hz, 1H), 5.16 (d, *J* = 13.7 Hz, 1H), 2.73 (d, *J* = 14.6 Hz, 1H), 2.34 (d, *J* = 14.6 Hz, 1H), 1.80 (s, 3H), 1.79 (s, 3H), 1.62 (s, 3H), 1.12 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 175.0, 163.3, 142.1, 140.5, 136.5, 131.3, 129.2, 128.4, 127.6, 125.7, 125.3, 123.8, 123.2, 49.8, 46.0, 44.0, 37.0, 33.3, 30.5, 29.7, 29.2, 28.8, 26.9; HRMS *m/z* (ESI) calcd for $C_{26}H_{28}N_3O_2$ $[M+H]^+$ 414.2177, found: 414.2173.



3j

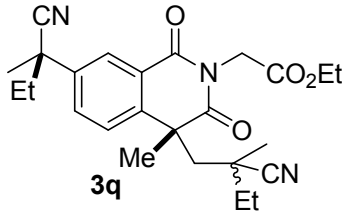
Ethyl 2-(4-(2-Cyano-2-methylpropyl)-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (3j). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.35 (d, *J* = 2.2 Hz, 1H), 7.89 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 4.86 (d, *J* = 16.7 Hz, 1H), 4.69 (d, *J* = 16.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 1H), 2.77 (d, *J* = 14.7 Hz, 1H), 2.38 (d, *J* = 14.7 Hz, 1H), 1.80 (s, 3H), 1.78 (s, 3H), 1.66 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 3H), 1.15(s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 174.8, 167.7, 162.8, 142.1, 140.7, 131.5, 127.7, 124.8, 123.7, 123.4, 61.6, 49.2, 46.1, 41.7, 37.0, 33.4, 30.6, 29.7, 29.1, 28.8, 27.4, 14.1; HRMS *m/z* (ESI) calcd for $C_{23}H_{28}N_3O_4$ $[M+H]^+$ 410.2075, found: 410.2076.



3p

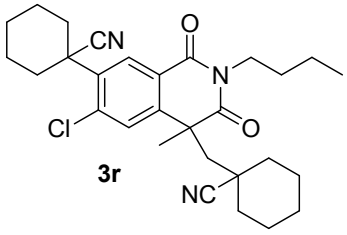
2-(2-Butyl-4-(2-cyano-2-methylbutyl)-6-fluoro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methylbutanenitrile (3p). Yellowish oil; d.r. = 1:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (d, *J* = 8.1 Hz, 0.5 H), 8.41 (d, *J* = 8.1 Hz, 0.5 H), 7.25 (d, *J* = 3.5 Hz, 0.5H), 7.22 (d, *J* = 3.4 Hz, 0.5H), 4.08 – 3.89 (m, 2H), 2.64 (d, *J* = 8.1 Hz, 1H), 2.32 (d, *J* = 14.7 Hz, 1H), 2.27 – 1.97 (m, 2H), 1.82 (s, 1.5H), 1.80 (s, 1.5H), 1.64 – 1.53 (m, 5H), 1.46 – 1.34 (m, 4H), 1.05 – 0.93 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.0, 163.9 (d, *J* = 260.3 Hz), 162.4, 143.4 (dd, *J* = 17.6, 7.9 Hz), 130.4 (dd, *J* = 40.9, 5.6 Hz), 128.1 (dd, *J* = 25.9, 12.1 Hz), 122.3, 122.0 (d, *J* = 14.7 Hz), 121.3, 115.4 (dd, *J* = 25.1, 11.7 Hz), 48.0, 47.9, 45.6, 40.8, 35.6, 35.3, 33.5, 33.4, 29.5, 25.5, 24.4, 23.2, 20.3, 13.8, 9.9, 9.7, 8.9; HRMS *m/z* (ESI) calcd for $C_{25}H_{33}FN_3O_2$ $[M+H]^+$ 426.2552, found:

426.2550.



3q

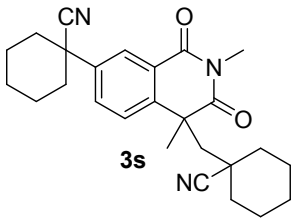
Ethyl 2-(4-(2-Cyano-2-methylbutyl)-7-(2-cyanobutan-2-yl)-4-methyl-1,3-dioxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (3q). Colorless oil; d.r. = 1:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 – 8.31 (m, 1H), 7.89 –7.78 (m, 1H), 7.63 – 7.54 (m, 1H), 4.88 (d, *J* = 16.8 Hz, 0.5H), 4.86 (d, *J* = 16.8 Hz, 0.5H), 4.70 (d, *J* = 16.8 Hz, 0.5H), 4.68 (d, *J* = 16.8 Hz, 0.5H), 4.26 – 4.20 (m, 2H), 2.83 (d, *J* = 14.6 Hz, 0.5H), 2.68 (d, *J* = 14.8 Hz, 0.5H), 2.47 (d, *J* = 14.8 Hz, 0.5H), 2.25 (d, *J* = 14.6 Hz, 0.5H), 2.08 – 1.95 (m, 2H), 1.80 – 1.72 (m. 3H), 1.67 (s, 1.5H), 1.66 (s, 1.5H), 1.33-1.24 (m, 5H), 1.08 (s, 1.5H), 1.02 – 0.94 (m, 7.5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.3, 174.7, 167.9, 167.7, 162.9, 141.0, 140.9, 140.7, 140.3, 132.1, 131.9, 128.7, 127.9, 127.4, 127.1, 126.3, 126.0, 125.0, 124.6, 122.6, 122.3, 61.7, 61.6, 48.5, 47.3, 46.0, 45.9, 43.2, 43.1, 41.7, 41.6, 35.6, 35.5, 35.3, 35.0, 33.8, 33.7, 33.4, 27.4, 27.0, 25.8, 23.5, 14.2, 9.8, 9.7, 9.0, 8.9; HRMS *m/z* (ESI) calcd for $C_{25}H_{32}FN_3O_4$ $[M+H]^+$ 438.2388, found: 438.2392.



3r

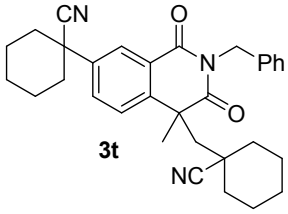
1-(2-Butyl-4-((1-cyanocyclohexyl)methyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-7-yl)cyclohexanecarbonitrile (3r). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (s, 1H), 7.57 (s, 1H), 4.08 – 3.88 (m, 2H), 2.72 (d, *J* = 14.7 Hz, 1H), 2.26 (d, *J* = 14.7 Hz, 1H), 2.00 – 1.83 (m, 7H), 1.68 – 1.56 (m, 15H), 1.45 – 1.33 (m, 5H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)

δ: 174.7, 162.8, 142.1, 139.8, 137.9, 130.2, 128.1, 123.7, 121.3, 120.5, 49.6, 45.5, 41.9, 40.8, 38.3, 36.9, 35.9, 35.2, 34.8, 33.5, 29.5, 24.9, 24.7, 23.1, 23.0, 22.6, 22.5, 20.3, 13.8; HRMS *m/z* (ESI) calcd for $C_{29}H_{37}ClN_3O_2$ $[M+H]^+$ 494.2569, found: 494.2573.



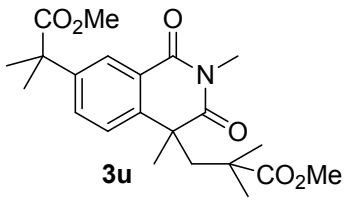
3s

1-((7-(1-Cyanocyclohexyl)-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)cyclohexanecarbonitrile (3s). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 (d, *J* = 2.2 Hz, 1H), 7.86 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 3.41 (s, 3H), 2.73 (d, *J* = 14.6 Hz, 1H), 2.28 (d, *J* = 14.5 Hz, 1H), 2.23 – 2.15 (m, 2H), 1.92 – 1.16 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.5, 163.7, 141.8, 141.1, 131.6, 127.4, 125.9, 125.2, 122.2, 121.3, 50.5, 45.6, 44.1, 38.0, 37.4, 37.1, 36.9, 36.2, 33.2, 27.5, 24.8, 24.7, 23.5, 22.8, 22.5; HRMS *m/z* (ESI) calcd for $C_{26}H_{32}N_3O_2$ $[M+H]^+$ 418.2490, found: 418.2489.



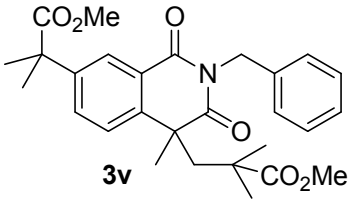
3t

1-(2-Benzyl-4-((1-cyanocyclohexyl)methyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-7-yl)cyclohexanecarbonitrile (**3t**). Colorless solid; m.p. 128-129 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36 (s, 1H), 7.85 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.56 – 7.44 (m, 3H), 7.35 – 7.20 (m, 3H), 5.32 (d, *J* = 13.7 Hz, 1H), 5.11 (d, *J* = 13.7 Hz, 1H), 2.66 (d, *J* = 14.6 Hz, 1H), 2.32 (d, *J* = 14.6 Hz, 1H), 2.25 – 2.14 (m, 2H), 1.94 – 1.17 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.2, 163.5, 141.9, 140.8, 136.5, 131.8, 129.4, 128.4, 127.6, 126.1, 125.0, 122.2, 121.4, 50.1, 45.6, 44.1, 44.0, 38.2, 37.5, 36.9, 35.2, 33.5, 29.5, 25.6, 24.8, 24.6, 23.5, 22.5, 22.4; HRMS *m/z* (ESI) calcd for $C_{32}H_{36}N_3O_2$ $[M+H]^+$ 494.2803, found: 494.2805.



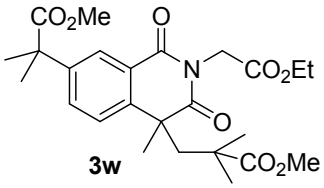
3u

Methyl 3-(7-(1-methoxy-2-methyl-1-oxopropan-2-yl)-2,4-dimethyl-1,3 -dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl) -2,2-dimethylpropanoate (**3u**)**.** Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (d, *J* = 2.2 Hz, 1H), 7.55 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 3.66 (s, 3H), 3.38 (s, 3H), 3.12 (s, 3H), 2.64 (d, *J* = 14.5Hz, 1H), 2.55 (d, *J* = 14.5 Hz, 1H), 1.62 (s, 6H), 1.56 (s, 3H), 1.00 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.9, 176.6, 176.3, 164.2, 144.1, 140.2, 131.1, 127.0, 125.7, 124.6, 52.3, 51.5, 51.2, 46.4, 45.7, 41.6, 33.3, 28.9, 27.3, 26.4, 23.3; HRMS *m/z* (ESI) calcd for $C_{22}H_{30}NO_6$ $[M+H]^+$ 404.2068, found: 404.2071.



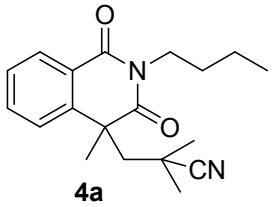
3v

Methyl 3-(2-Benzyl-7-(1-methoxy-2-methyl-1-oxopropan -2-yl)-4- methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin -4-yl)-2,2-dimethylpropanoate (3v). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, *J* = 2.0 Hz, 1H), 7.53 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.34 – 7.19 (m, 4H), 5.25 (d, *J* = 13.7 Hz, 1H), 5.13 (d, *J* = 13.7 Hz, 1H), 3.64 (s, 3H), 3.11 (s, 3H), 2.64 (d, *J* = 14.4 Hz, 1H), 2.59 (d, *J* = 14.4 Hz, 1H), 1.61 (s, 6H), 1.53 (s, 3H), 1.00 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.0, 176.5, 176.0, 163.9, 144.1, 140.2, 136.8, 131.3, 129.2, 128.3, 127.1, 125.9, 124.6, 52.4, 51.4, 50.6, 46.4, 46.0, 43.9, 41.6, 33.7, 29.2, 26.4, 26.3, 23.1; HRMS *m/z* (ESI) calcd for $C_{28}H_{34}NO_6$ $[M+H]^+$ 480.2381, found: 480.2384.



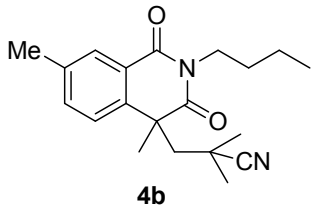
3w

Methyl 3-(2-(2-Ethoxy-2-oxoethyl)-7-(1-methoxy-2-methyl -1-oxopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-Tetrahydro -isoquinolin-4-yl)-2,2-dimethylpropanoate (3w). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (d, *J* = 2.1 Hz, 1H), 7.57 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 4.86 (d, *J* = 16.6 Hz, 1H), 4.63 (d, *J* = 16.6 Hz, 1H), 4.2 – 4.1 (m, 2H), 3.66 (s, 3H), 3.15 (s, 3H), 2.69 (d, *J* = 14.6 Hz, 1H), 2.63 (d, *J* = 14.6 Hz, 1H), 1.62 (s, 6H), 1.58 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3H), 1.04 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.1, 176.5, 175.8, 167.9, 163.5, 144.2, 140.4, 131.5, 127.1, 126.0, 124.1, 61.5, 52.4, 51.5, 50.0, 46.4, 46.0, 41.6, 41.5, 33.8, 29.0, 26.4, 26.3, 23.5, 14.1; HRMS *m/z* (ESI) calcd for $C_{25}H_{34}NO_8$ $[M+H]^+$ 476.2279, found: 476.2283.



4a

3-(2-Butyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (4a). Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 – 8.27 (m, 1H), 7.75 – 7.64 (m, 1H), 7.57 – 7.46 (m, 2H), 4.09 – 3.95 (m, 2H), 2.77 (d, *J* = 14.6 Hz, 1H), 2.36 (d, *J* = 14.6 Hz, 1H), 1.65 – 1.50 (m, 5H), 1.45 – 1.36 (m, 2H), 1.16 (s, 3H), 1.15 (s, 3H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.4, 163.6, 140.6, 133.7, 129.4, 128.2, 125.7, 124.7, 123.4, 49.5, 45.9, 40.7, 33.6, 30.6, 29.7, 29.6, 27.2, 20.3, 13.8; HRMS *m/z* (ESI) calcd for $C_{19}H_{25}N_2O_2$ $[M+H]^+$ 313.1911, found: 313.1907.



4b

3-(2-Butyl-4,7-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (4b). Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 7.48 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 4.07 – 3.94 (m, 2H), 2.75 (d, *J* =

14.6 Hz, 1H), 2.45 (s, 3H), 2.33 (d, J = 14.6 Hz, 1H), 1.67 – 1.52 (m, 5H), 1.45 – 1.36 (m, 2H), 1.14 (s, 3H), 1.13 (s, 3H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.3, 164.1, 143.2, 142.2, 132.6, 132.2, 125.0, 123.5, 123.1, 49.8, 45.9, 40.6, 34.0, 30.6, 29.8, 29.6, 27.1, 24.3, 20.4, 13.8; HRMS *m/z* (ESI) calcd for $C_{20}H_{27}N_2O_2$ $[M+H]^+$ 327.2068, found: 327.2067.

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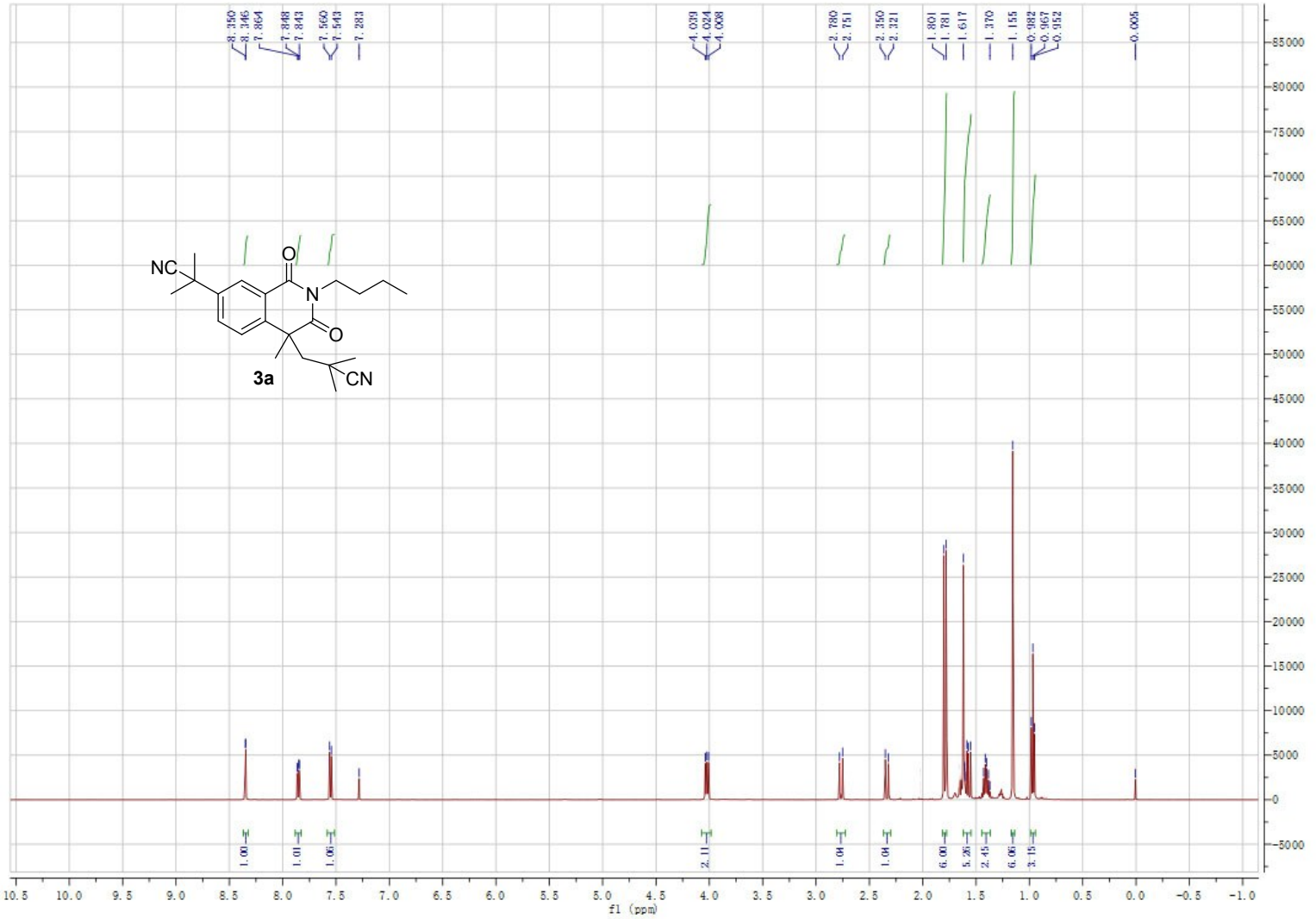
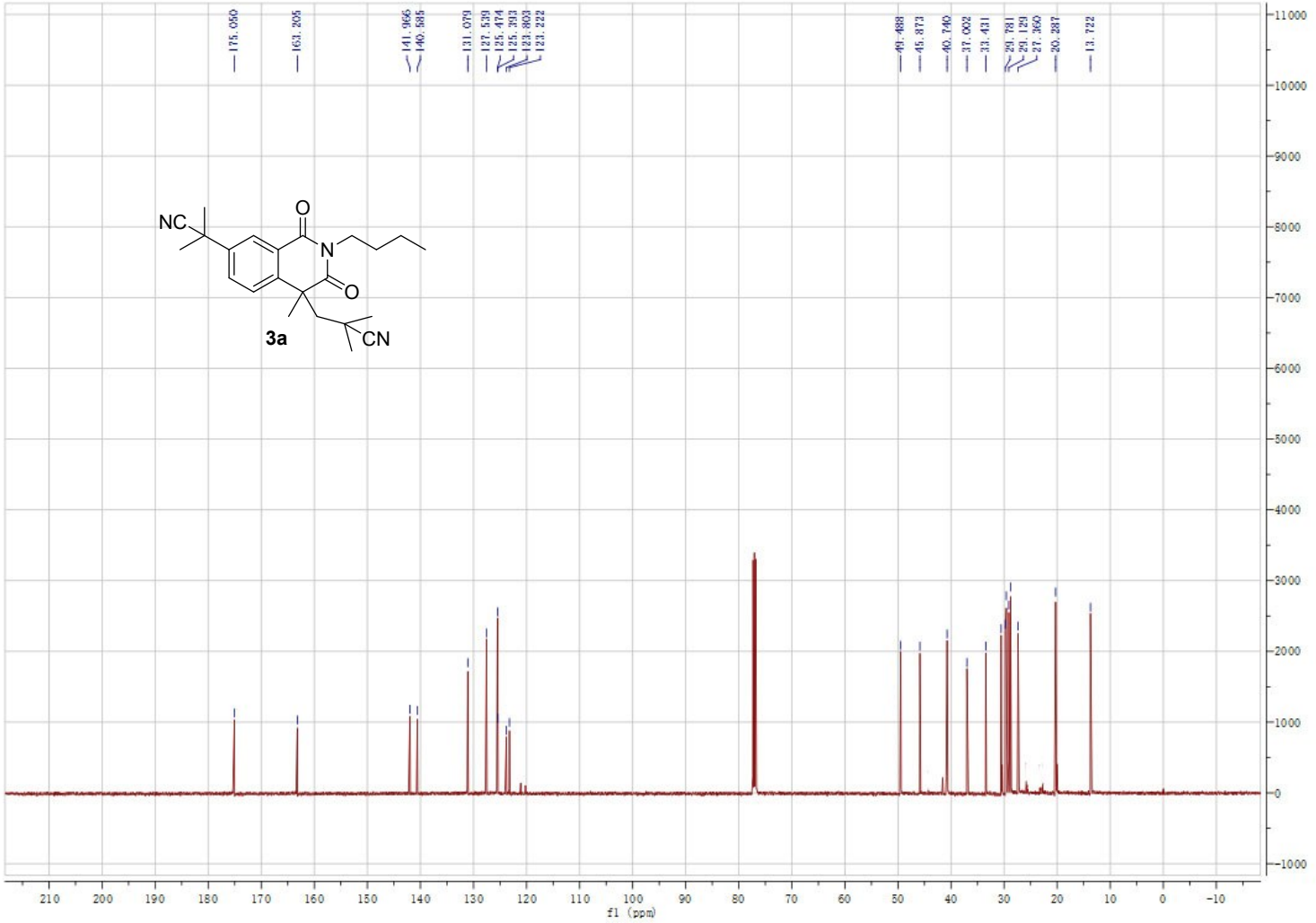
5 Copies of ^{1}H NMR and ^{13}C NMR spectra

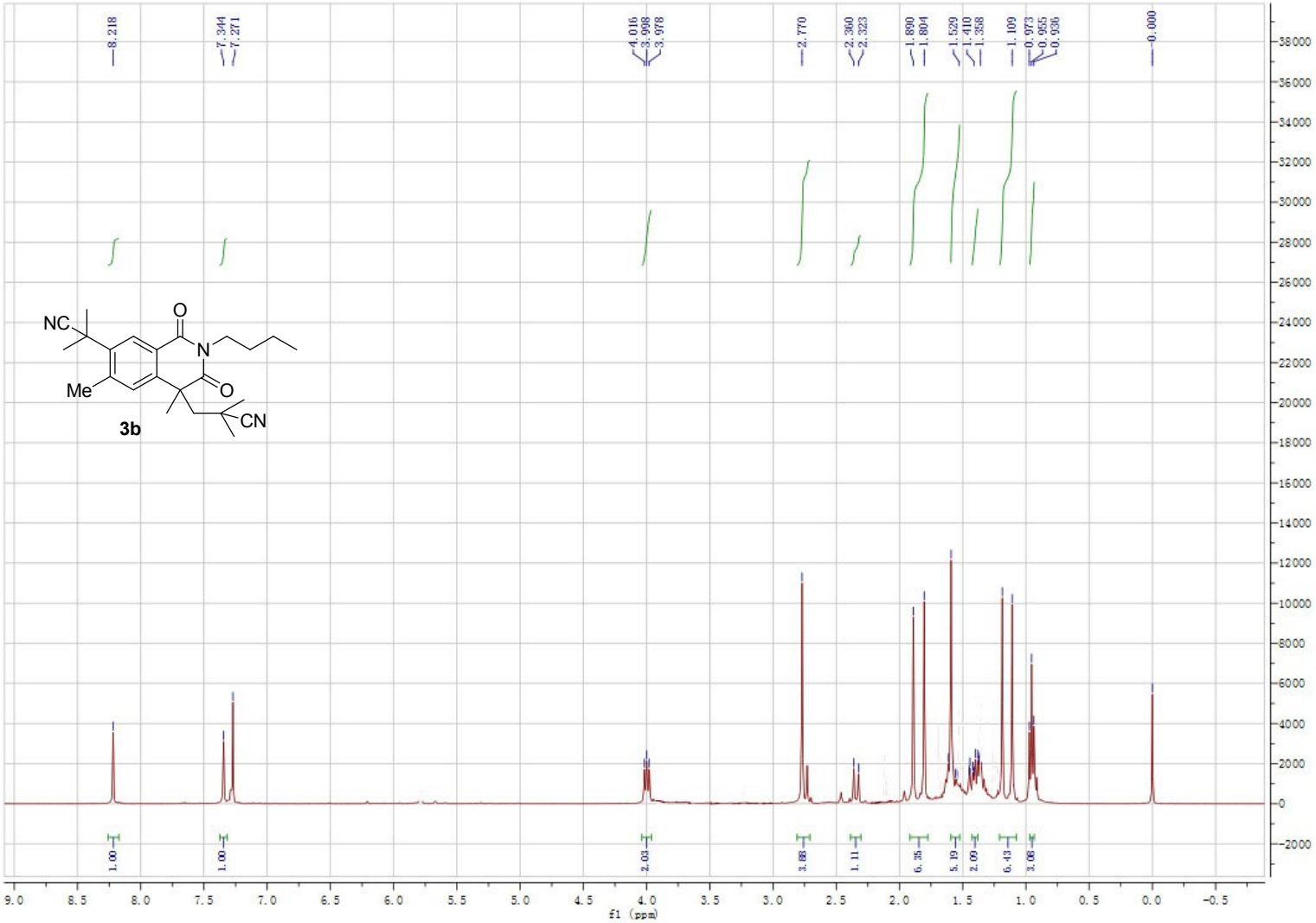
3-(2-Butyl-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3a)



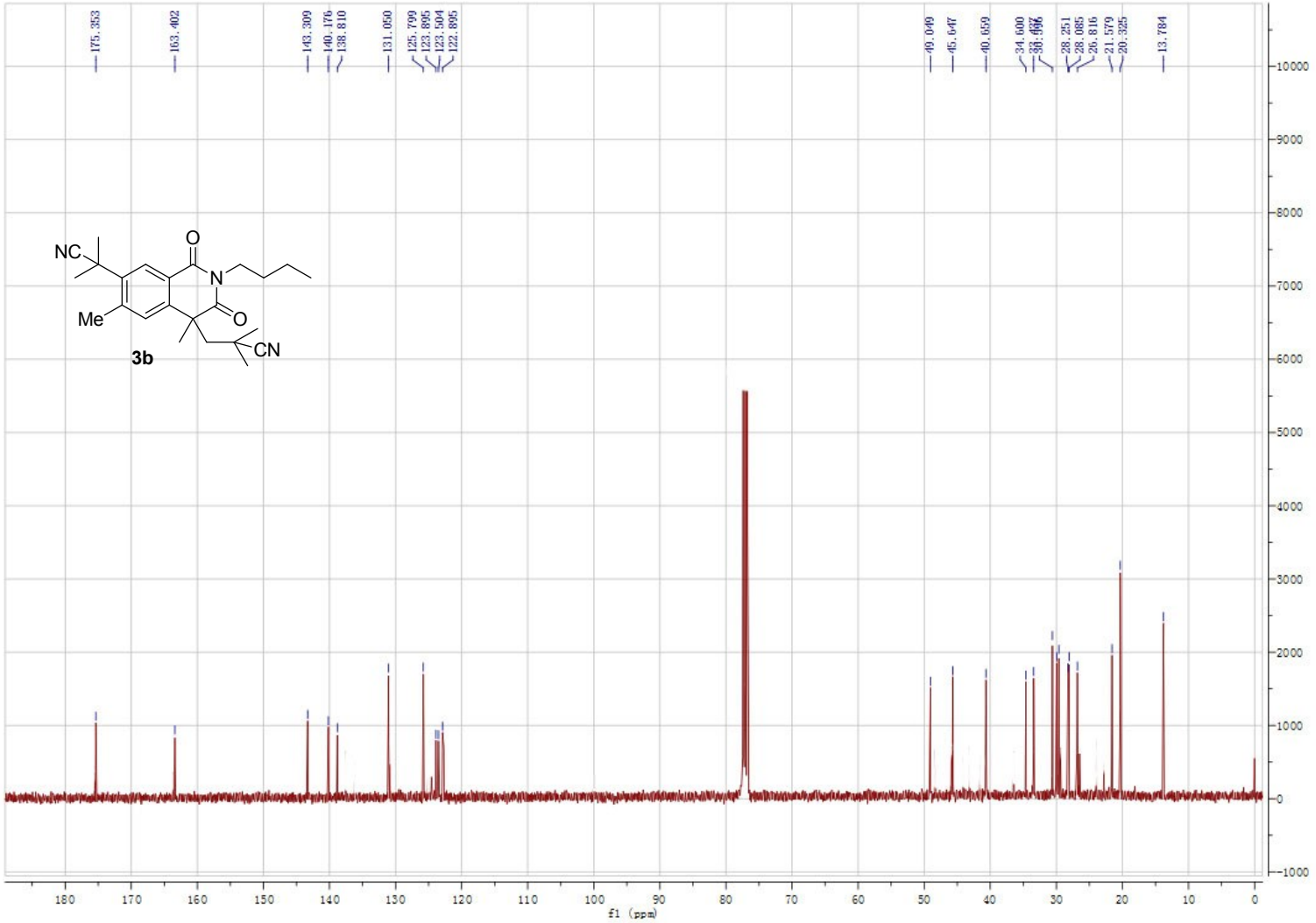
3-(2-Butyl-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3a)



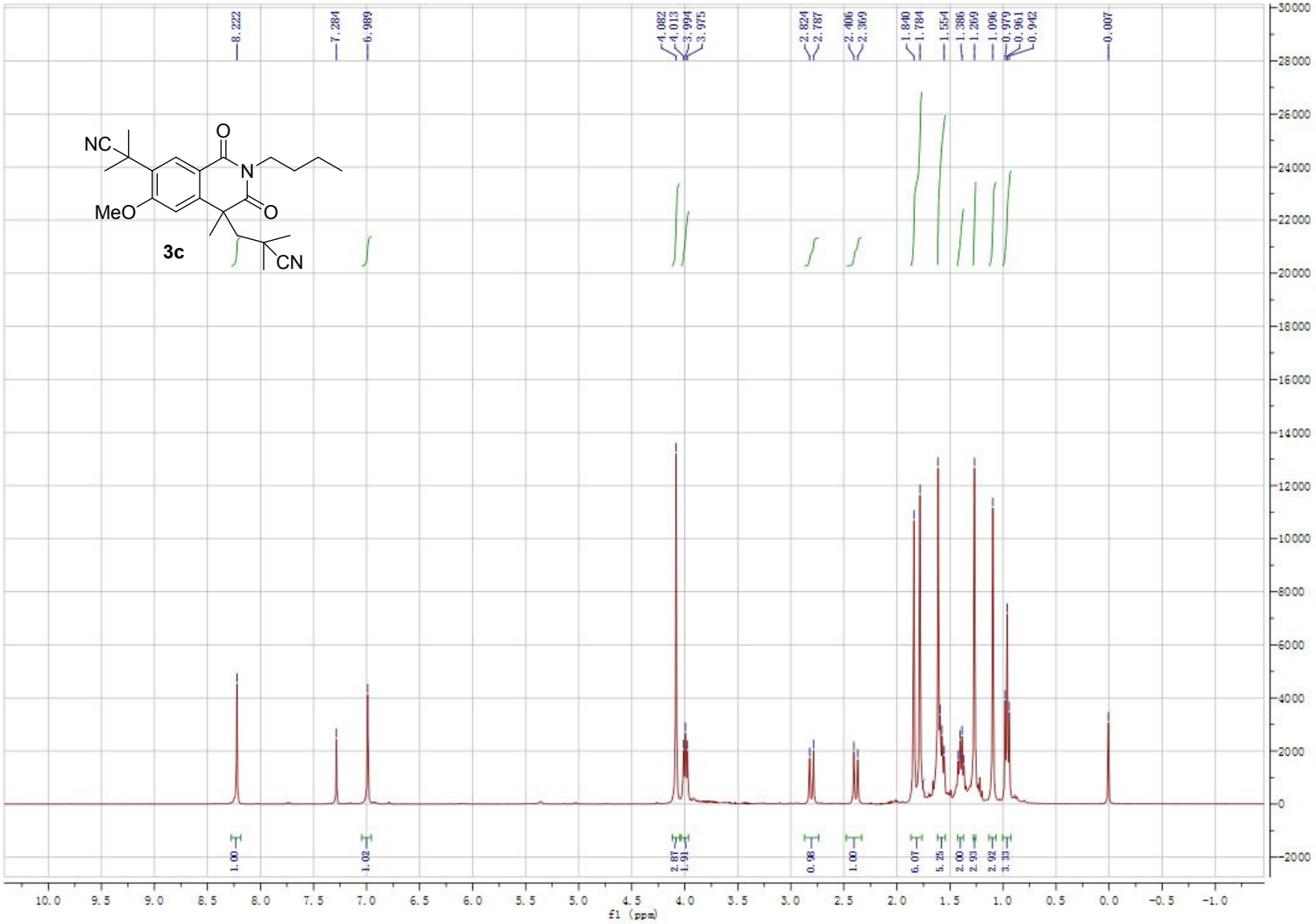
3-(2-Butyl-7-(2-cyanopropan-2-yl)-4,6-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3b)



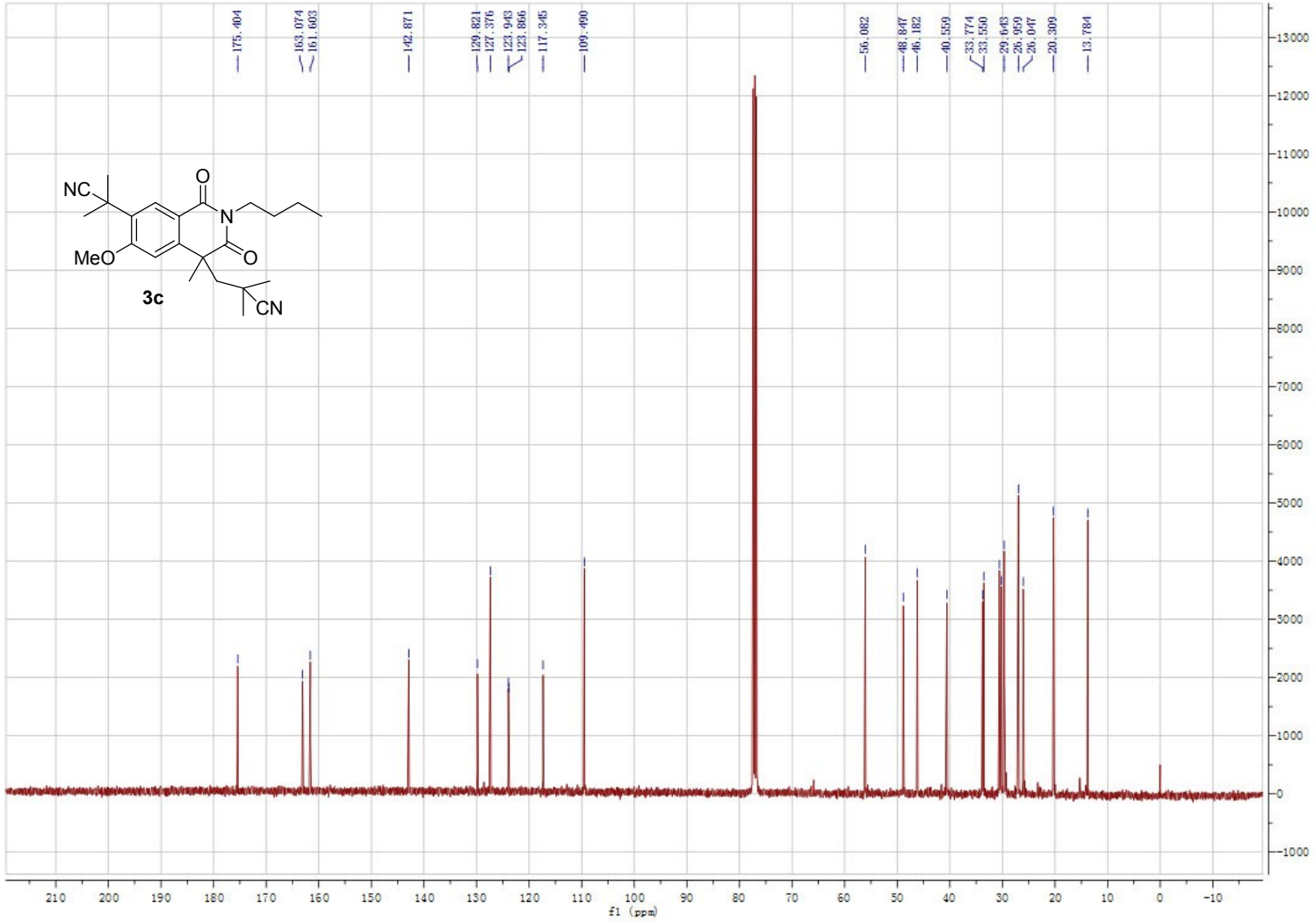
3-(2-Butyl-7-(2-cyanopropan-2-yl)-4,6-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3b)



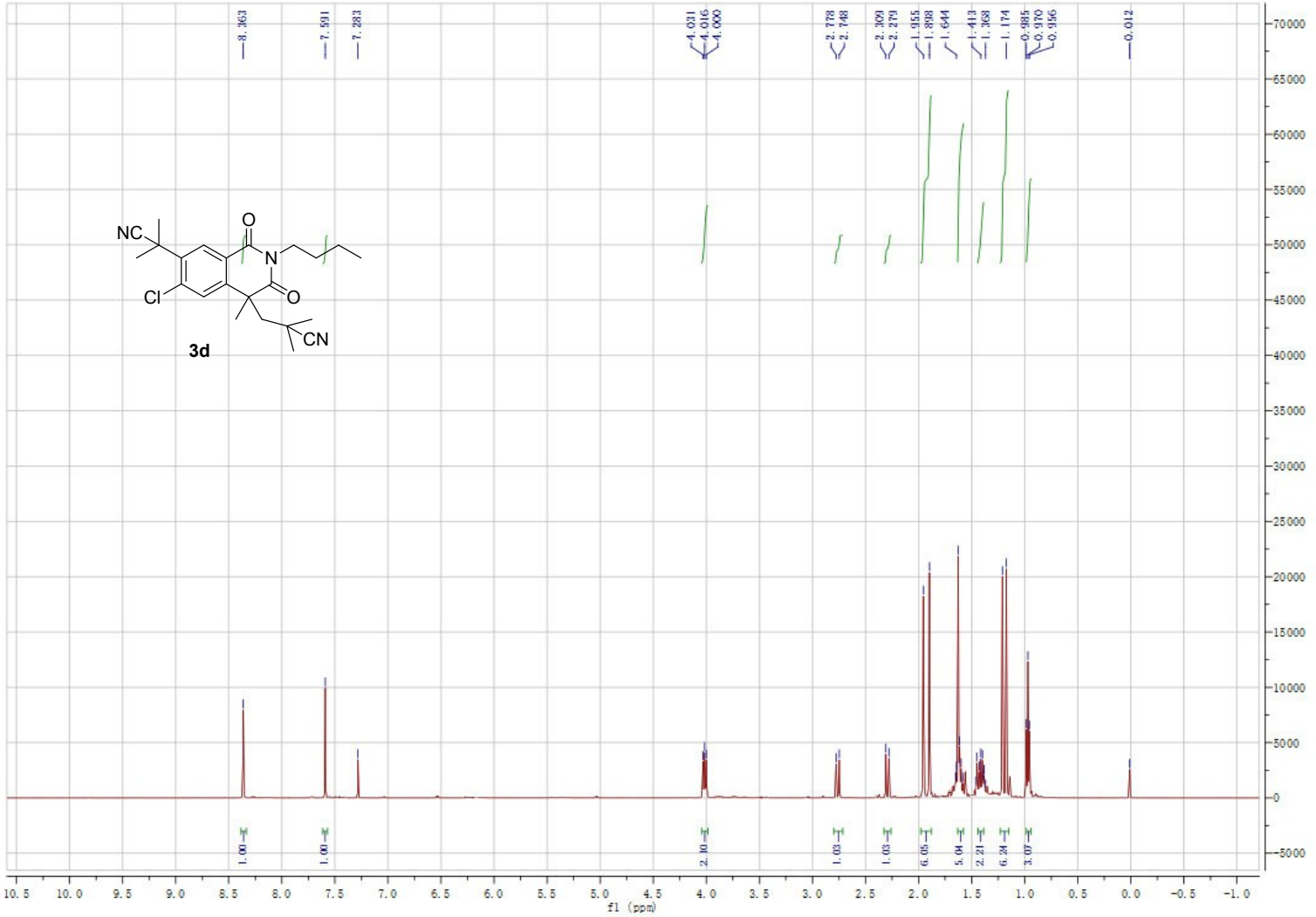
3-(2-Butyl-7-(2-cyanopropan-2-yl)-6-methoxy-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3c)



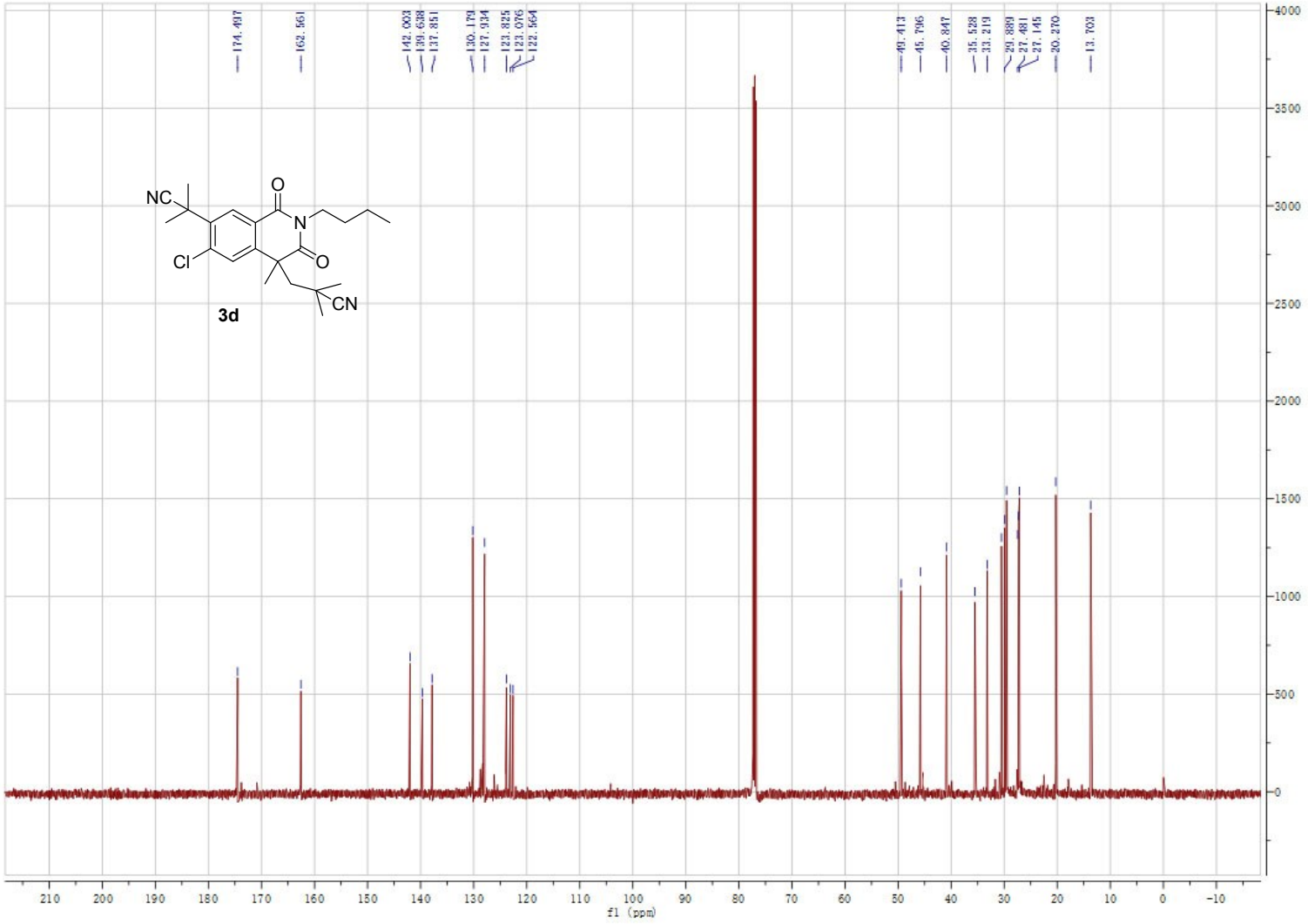
3-(2-Butyl-7-(2-cyanopropan-2-yl)-6-methoxy-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3c)



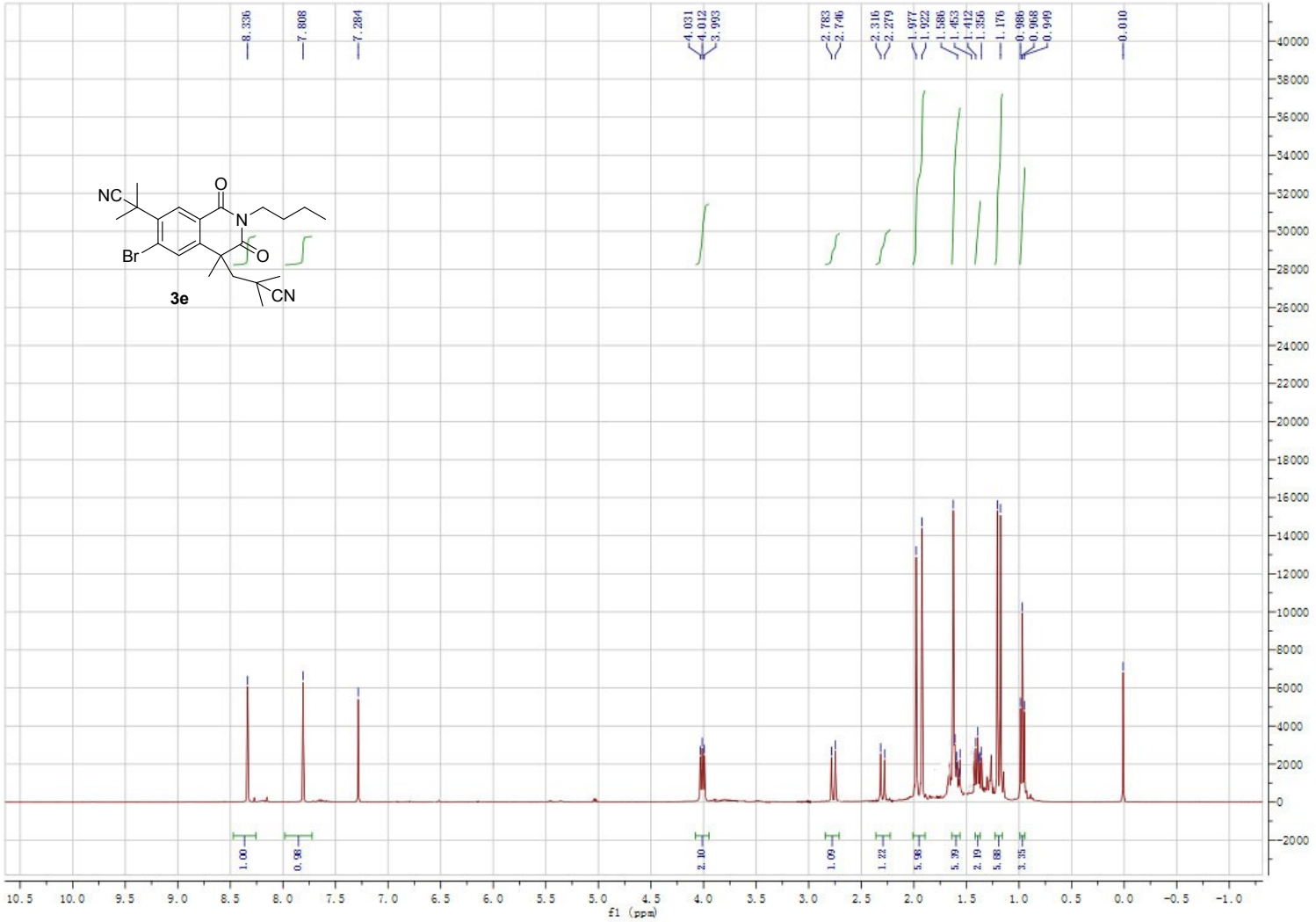
3-(2-Butyl-6-chloro-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3d)



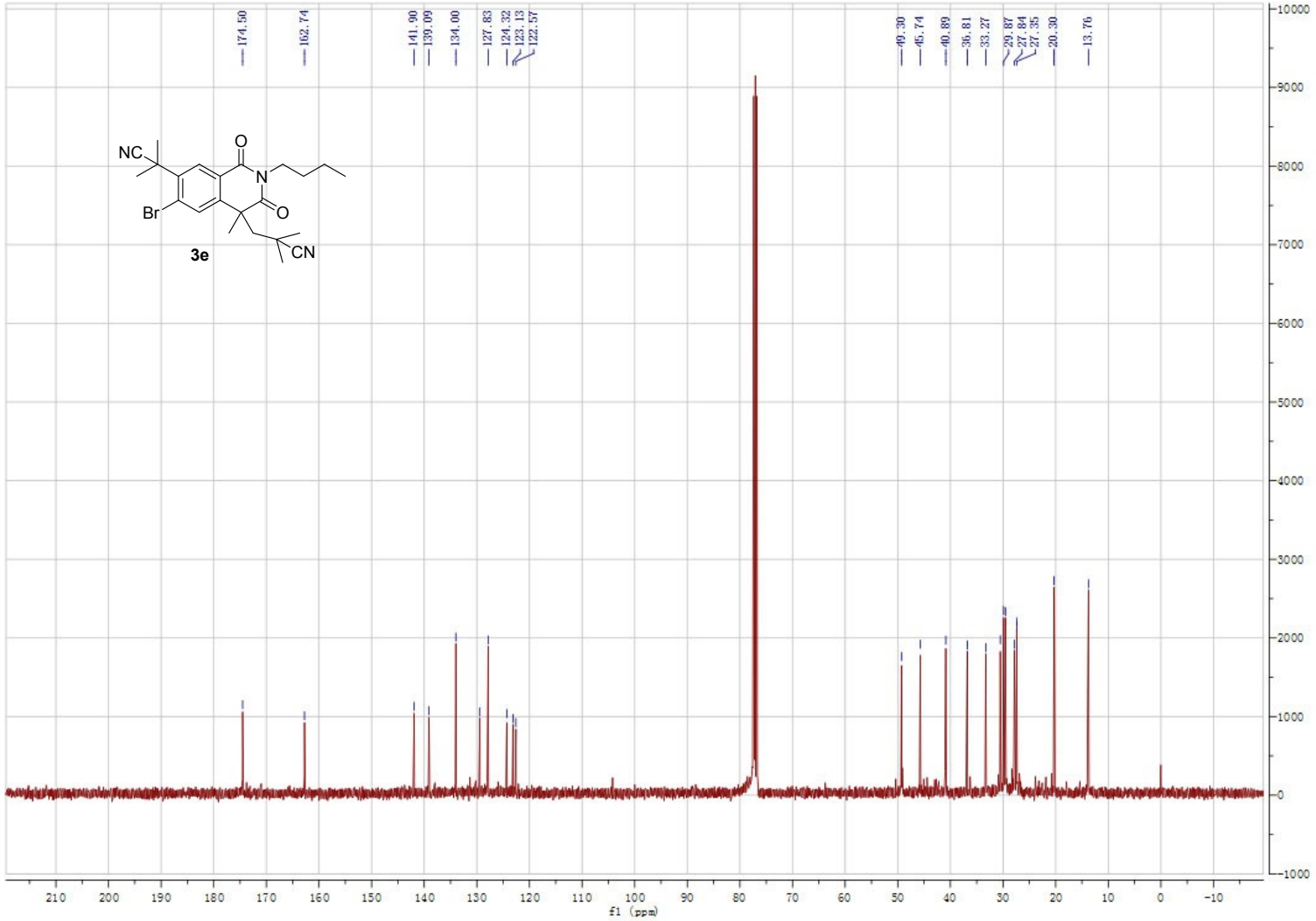
3-(2-Butyl-6-chloro-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3d)



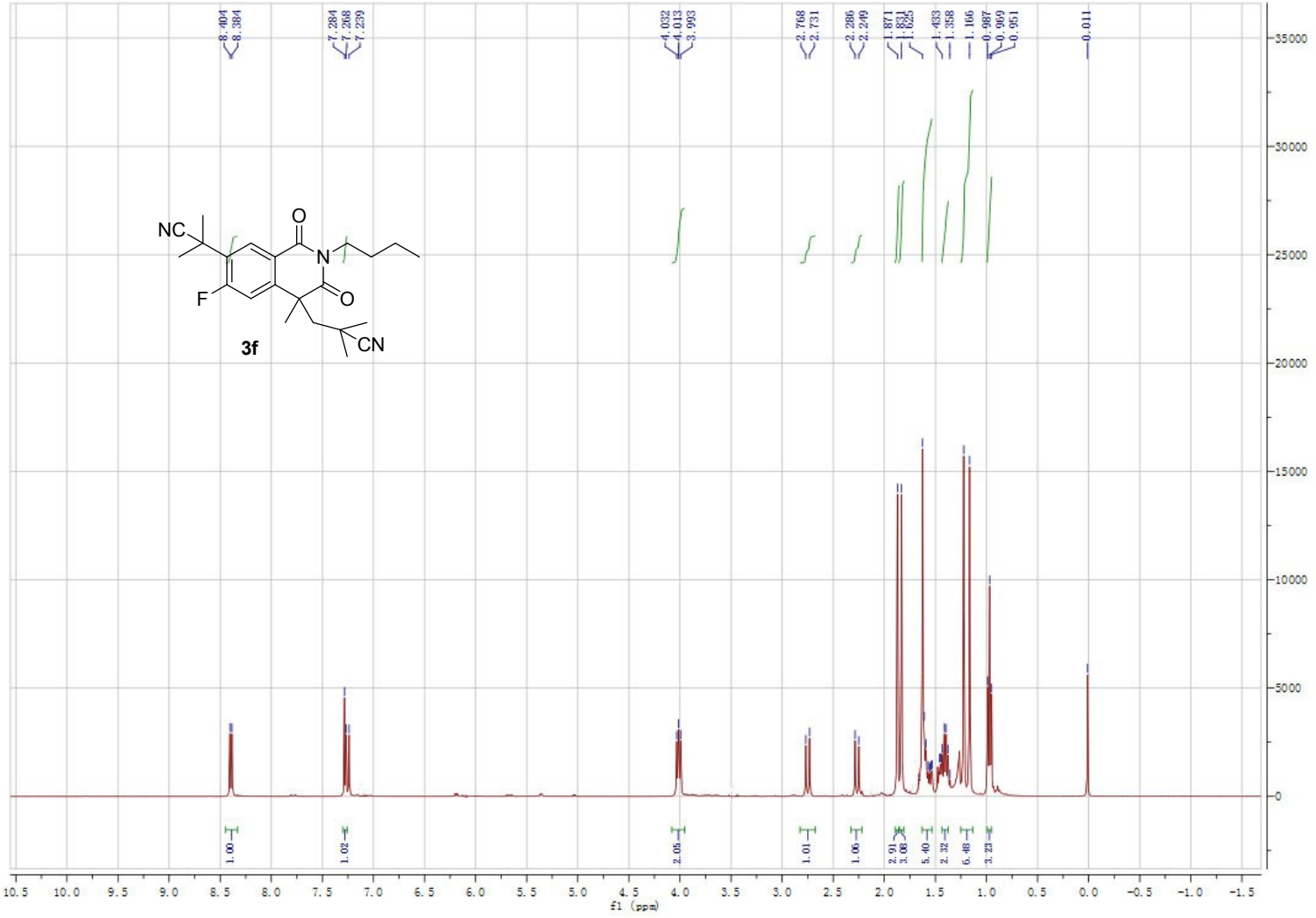
3-(2-Butyl-6-bromo-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3e)



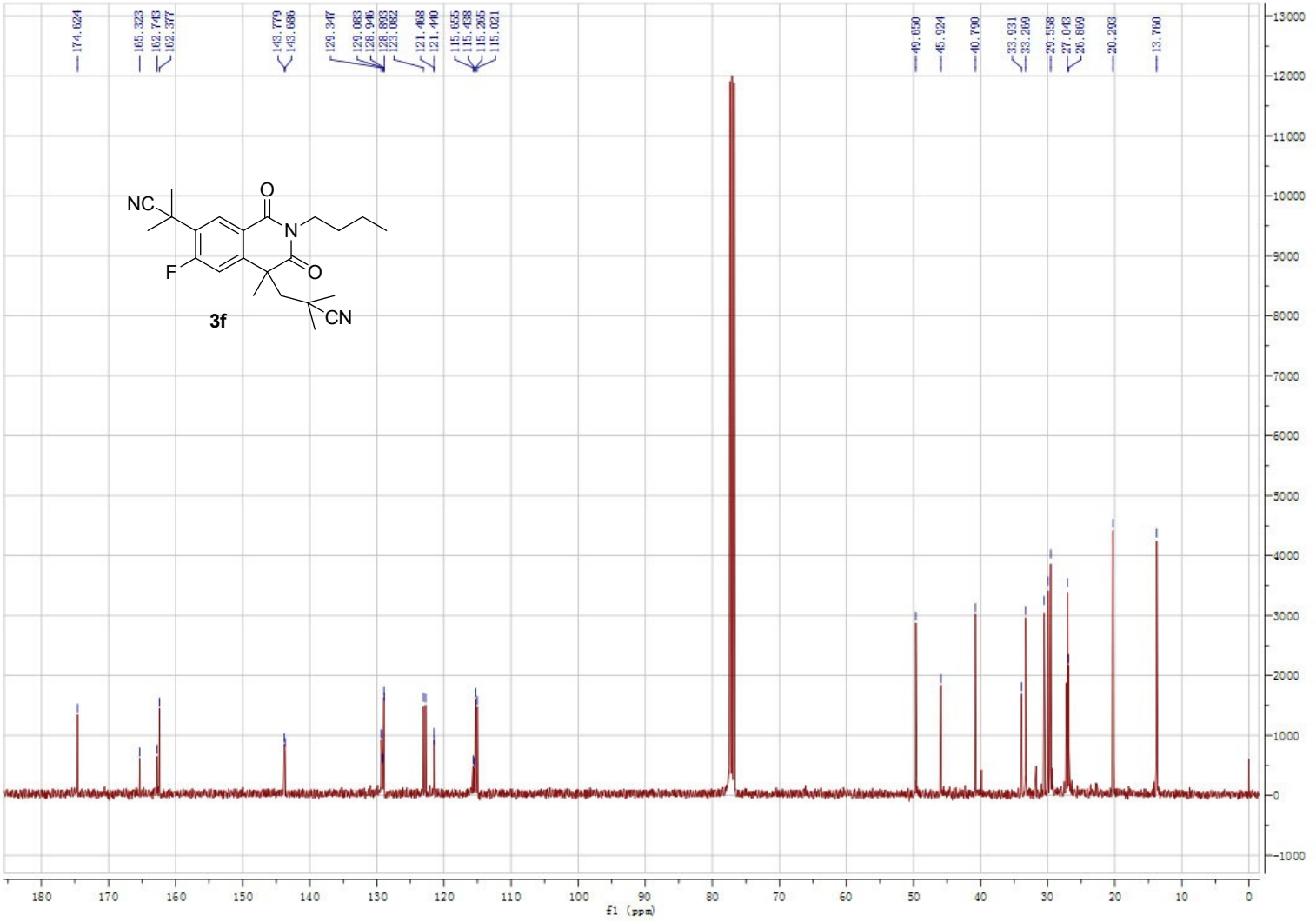
3-(2-Butyl-6-bromo-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3e)



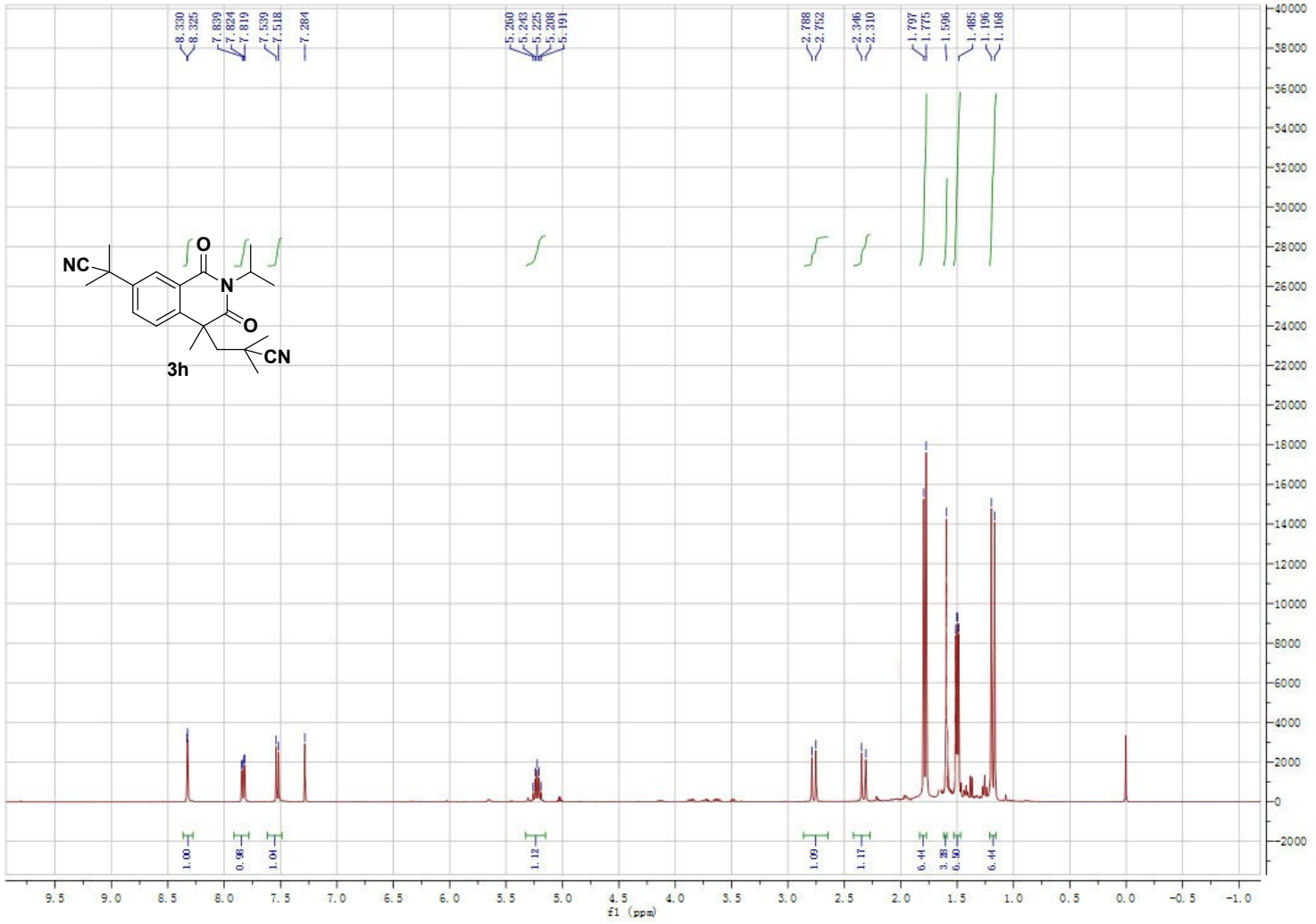
3-(2-Butyl-7-(2-cyanopropan-2-yl)-6-fluoro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3f)



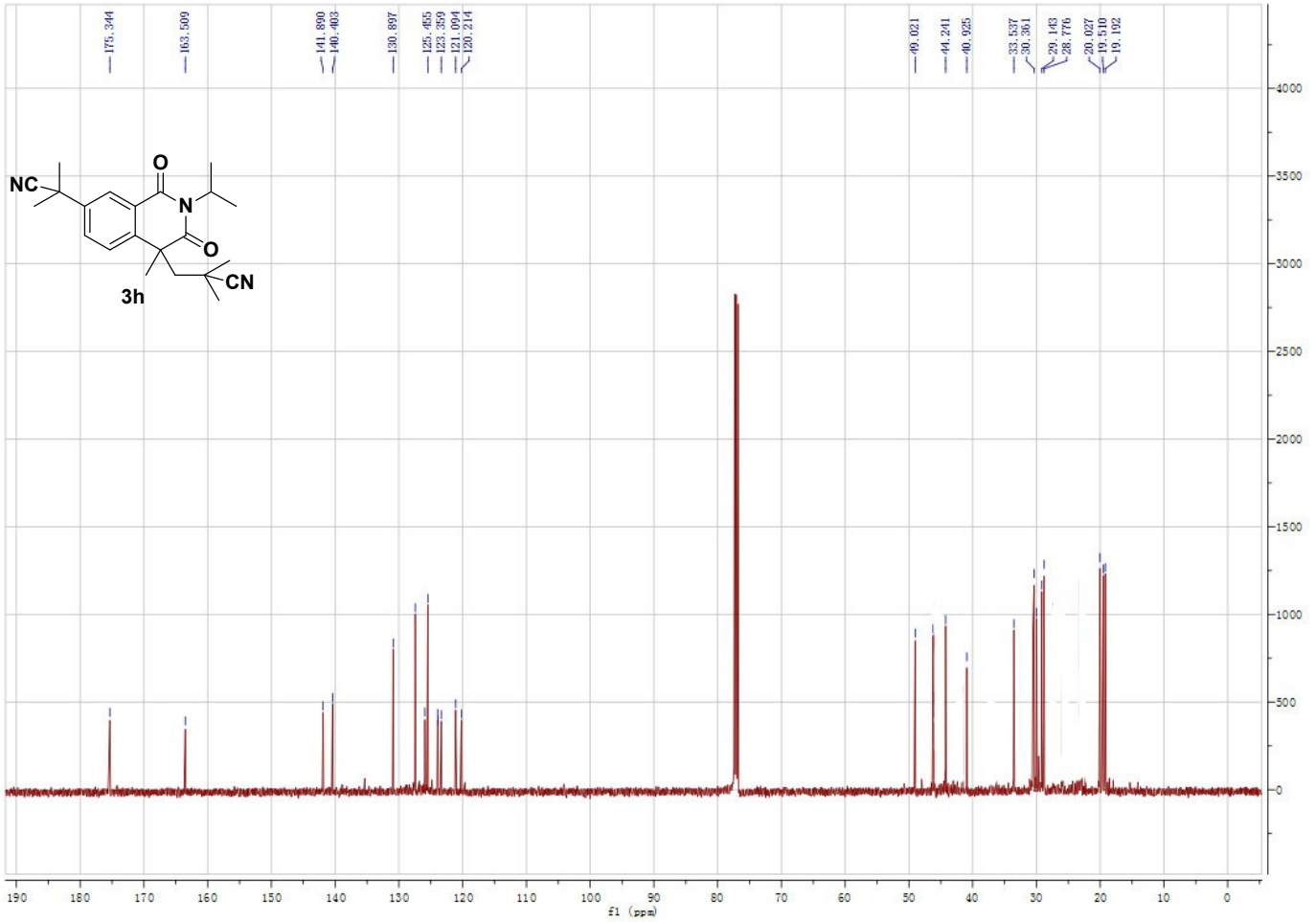
3-(2-Butyl-7-(2-cyanopropan-2-yl)-6-fluoro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3f)



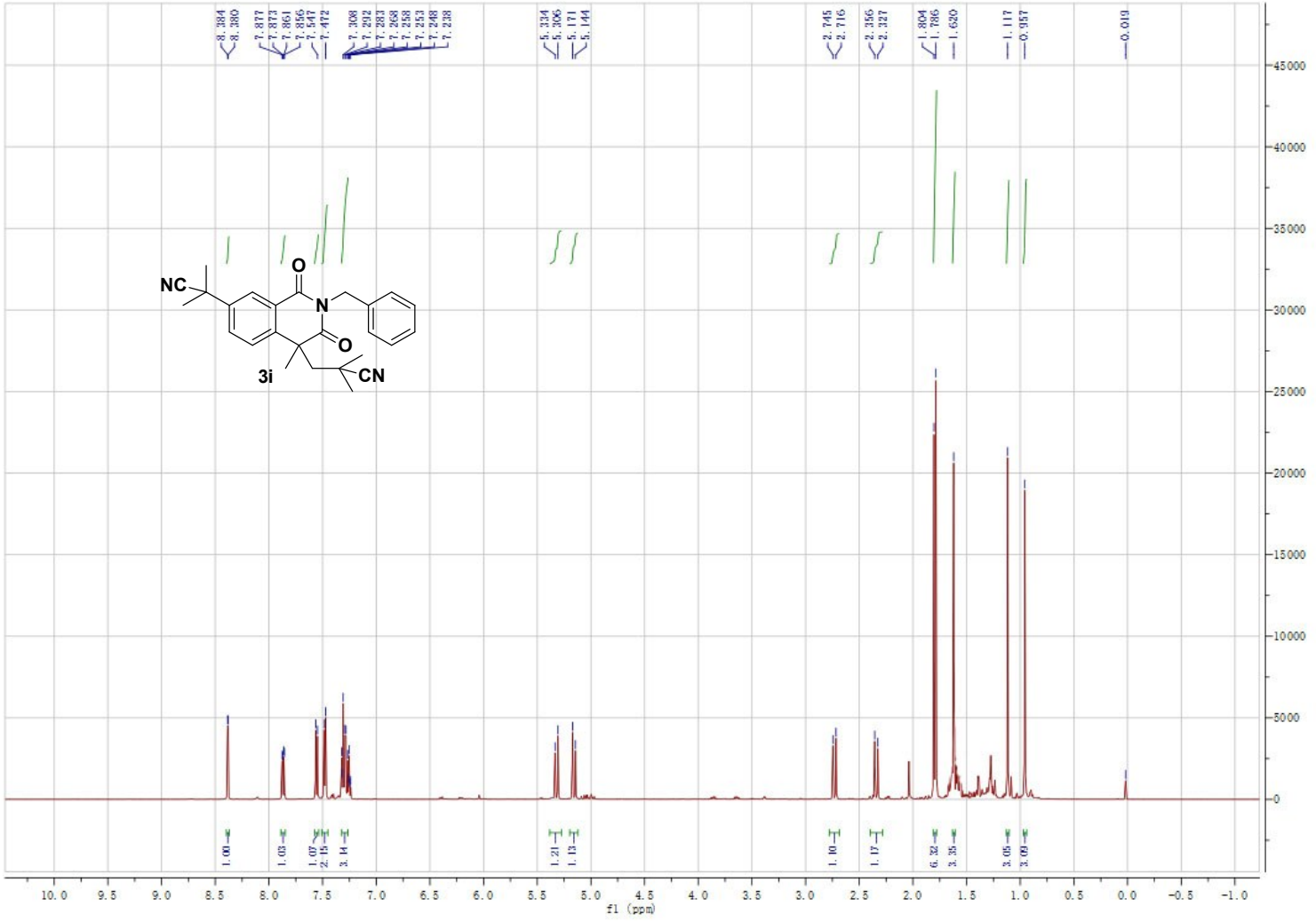
3-(7-(2-Cyanopropan-2-yl)-2-isopropyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3h)



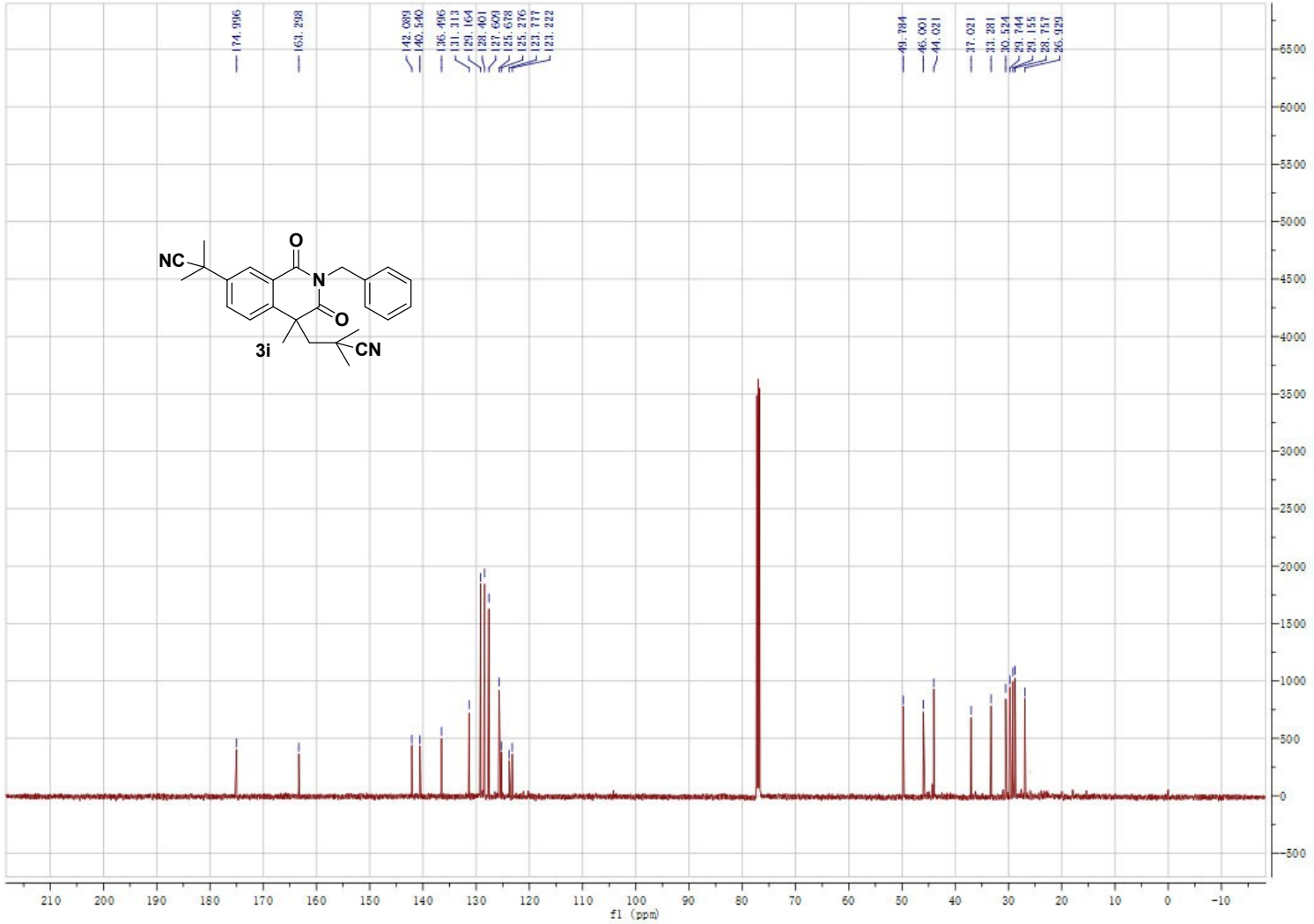
3-(7-(2-Cyanopropan-2-yl)-2-isopropyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3h)



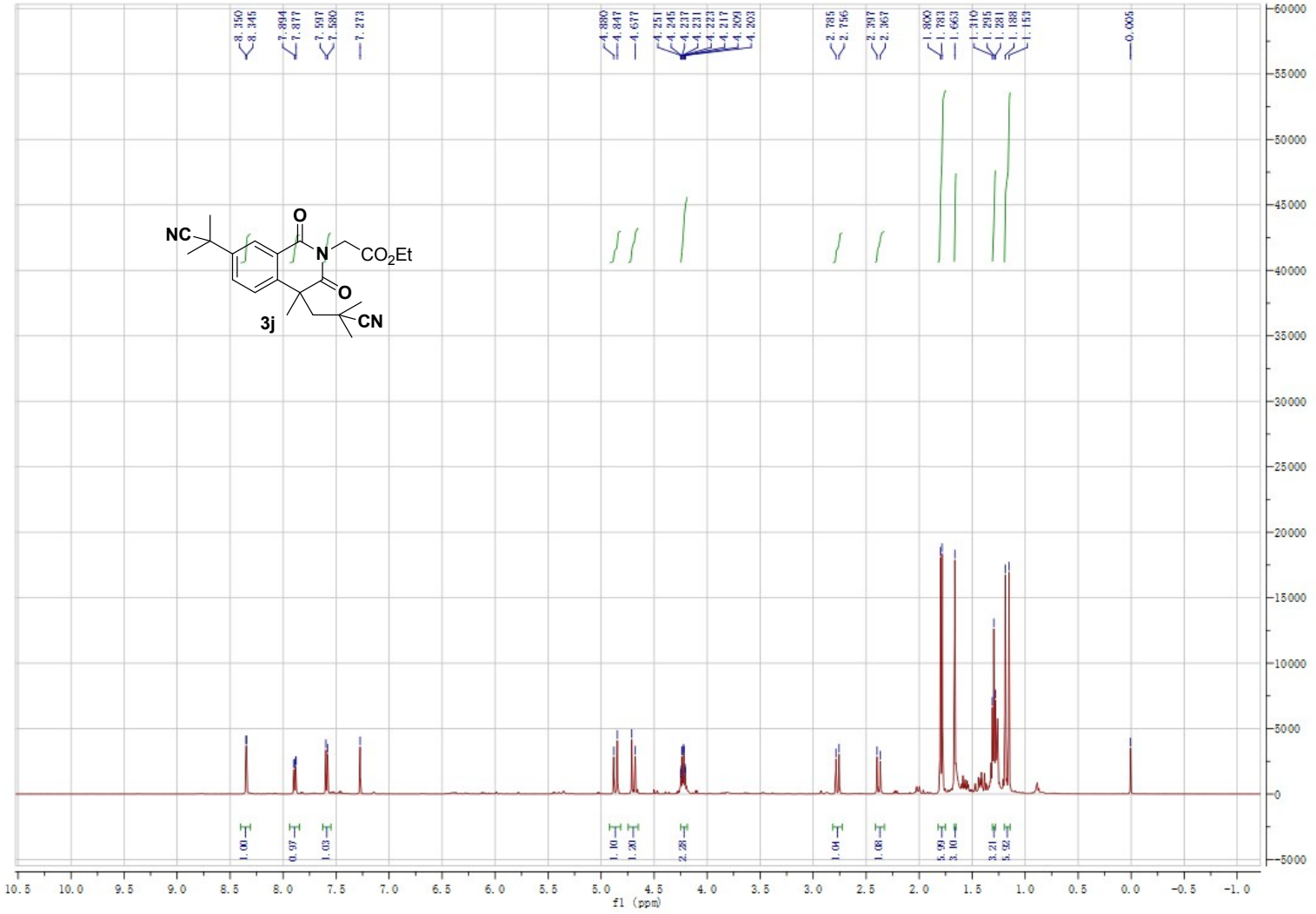
3-(2-Benzyl-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3i)



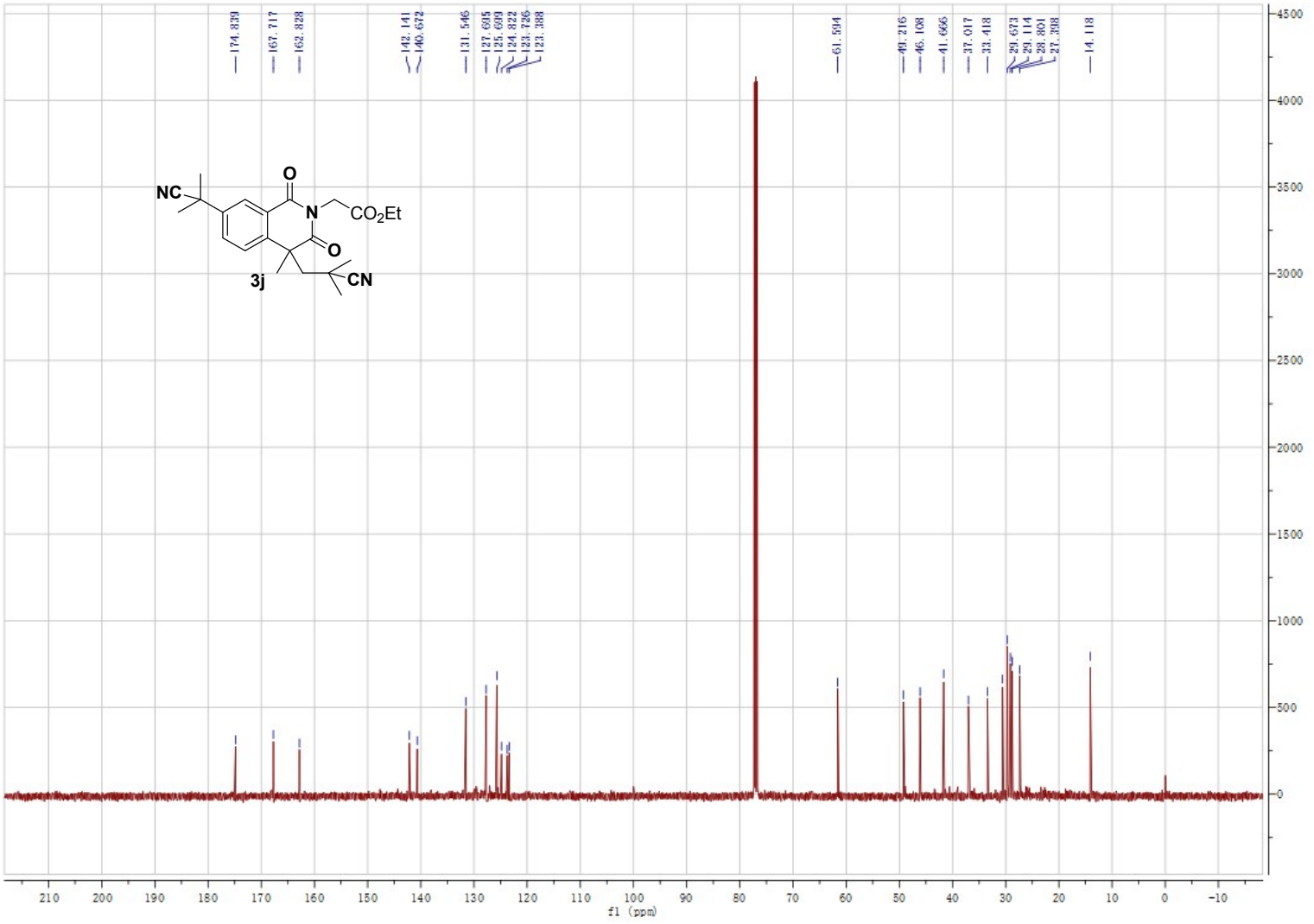
3-(2-Benzyl-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (3i)



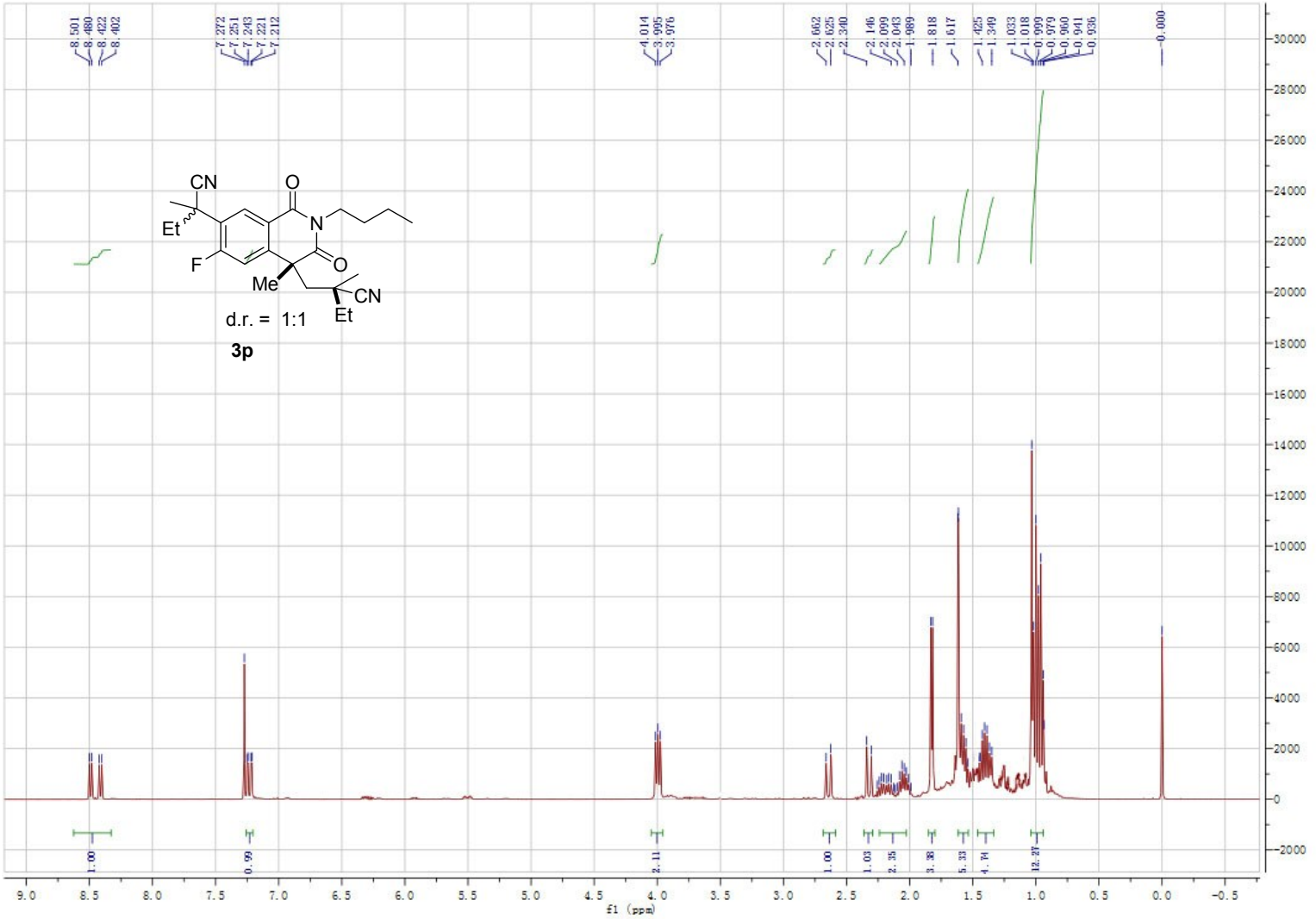
Ethyl 2-(4-(2-cyano-2-methylpropyl)-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate （3j）



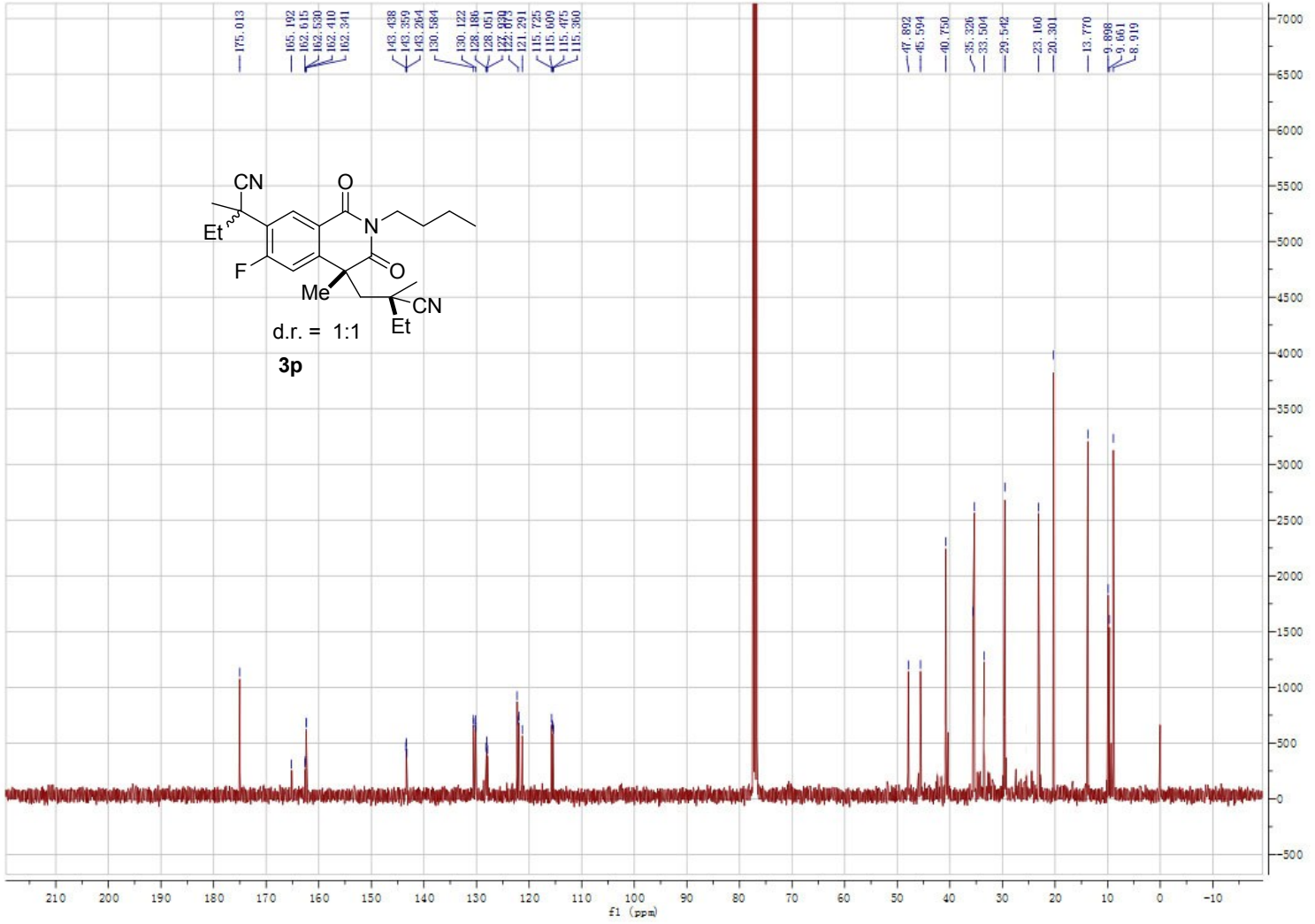
Ethyl 2-(4-(2-cyano-2-methylpropyl)-7-(2-cyanopropan-2-yl)-4-methyl-1,3-dioxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate （3j）



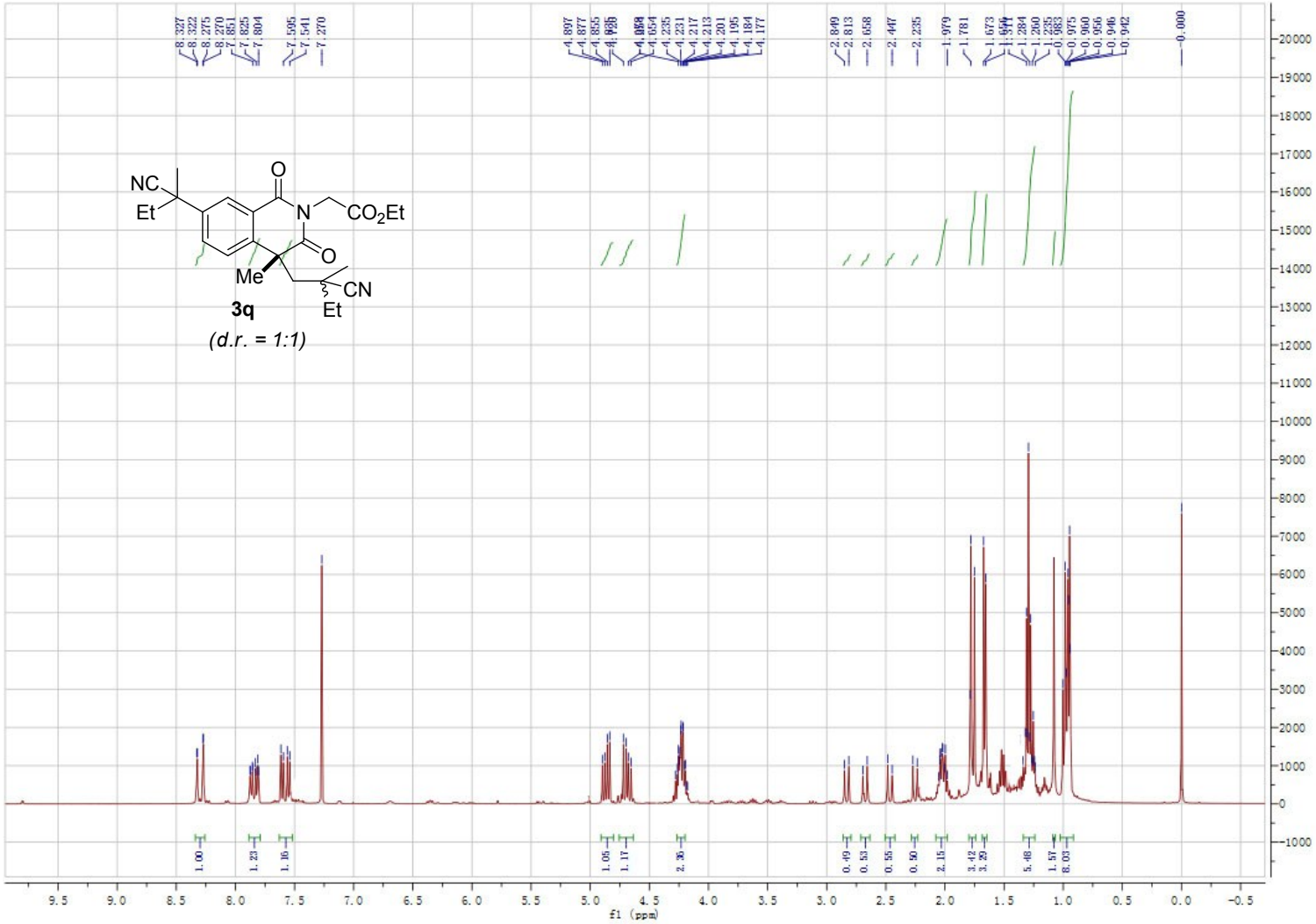
2-(2-Butyl-4-(2-cyano-2-methylbutyl)-6-fluoro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methylbutanenitrile (3p)



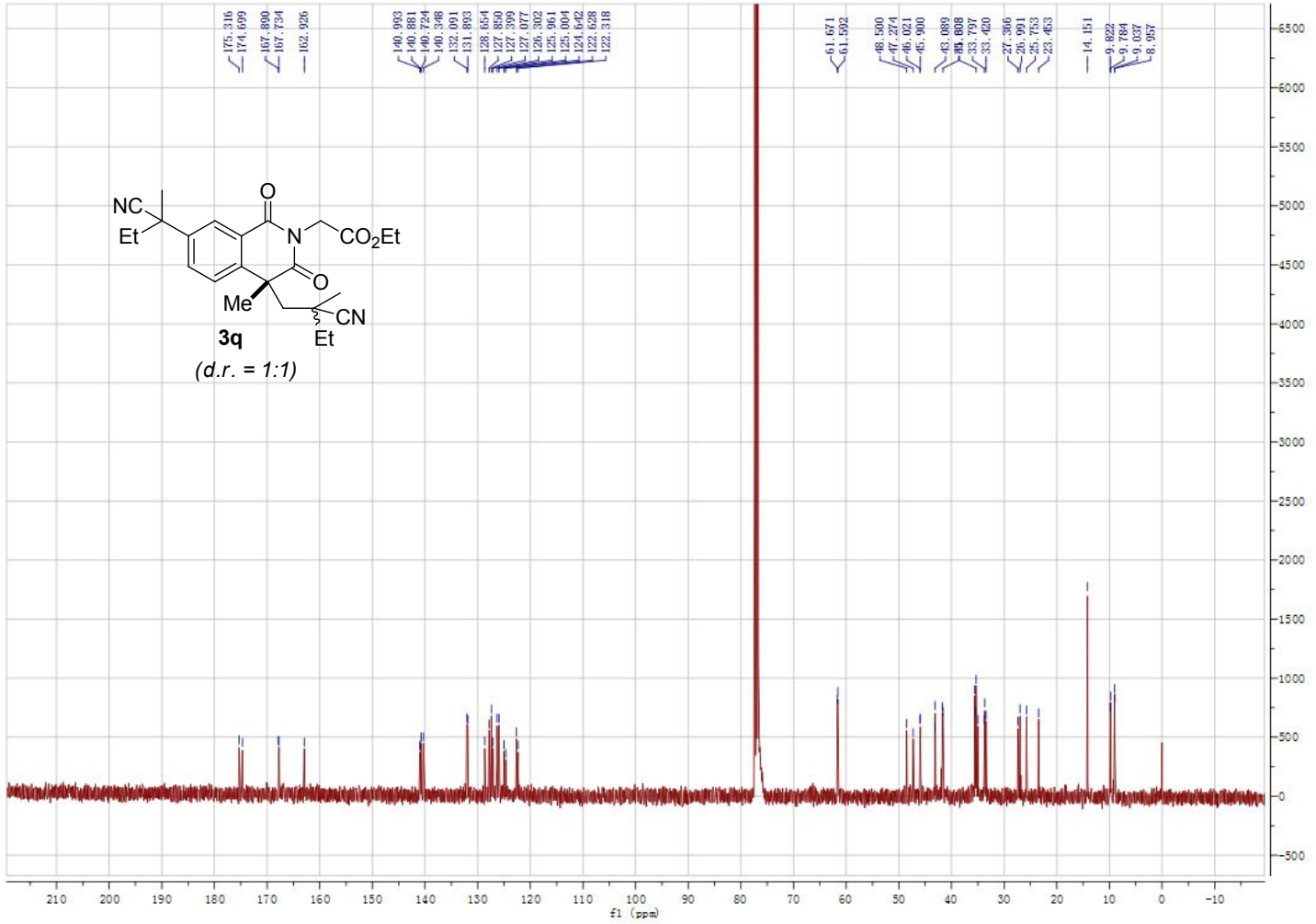
2-(2-Butyl-4-(2-cyano-2-methylbutyl)-6-fluoro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methylbutanenitrile (3p)



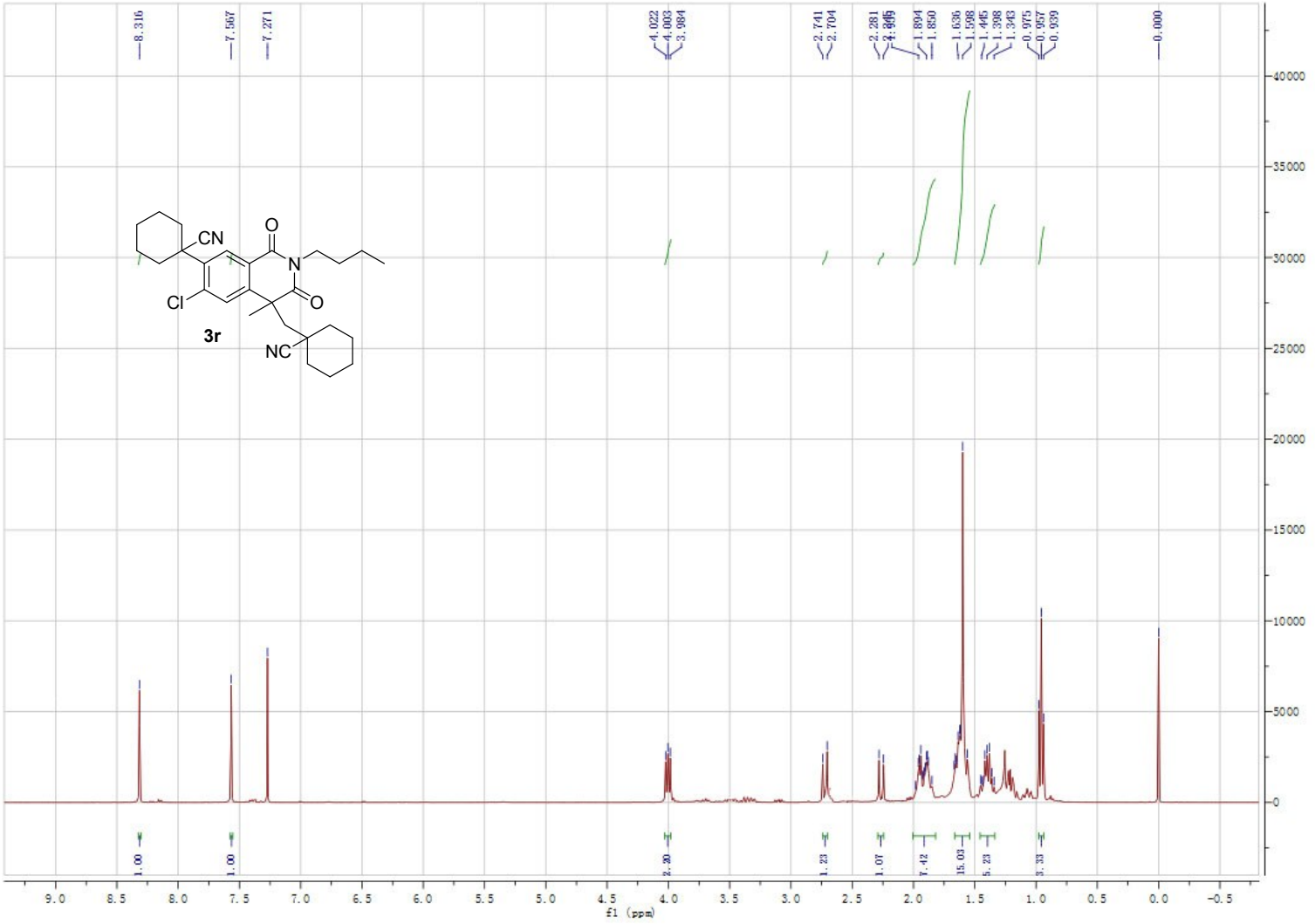
Ethyl 2-(4-(2-cyano-2-methylbutyl)-7-(2-cyanobutan-2-yl)-4-methyl-1,3-dioxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (3q)



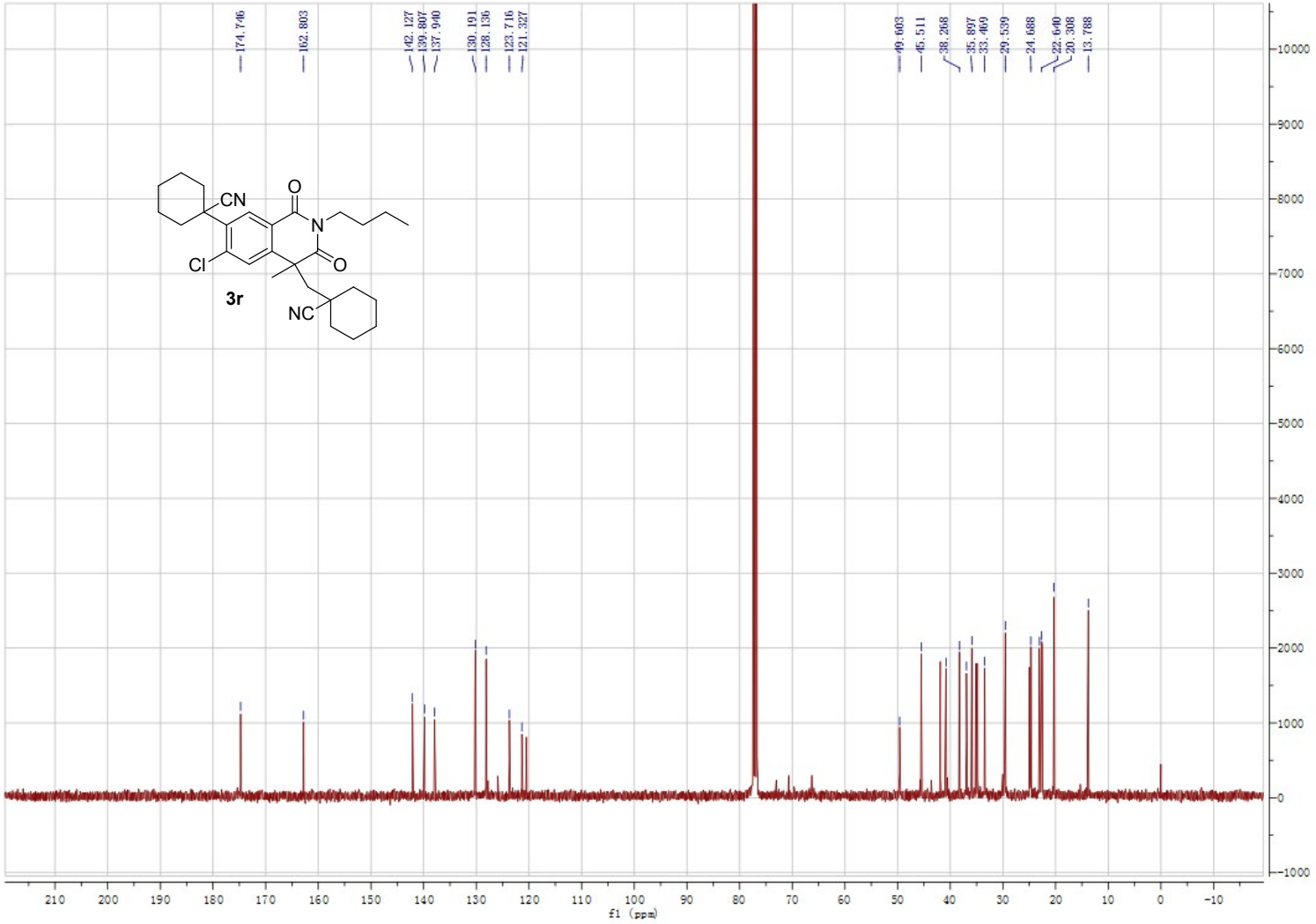
Ethyl 2-(4-(2-cyano-2-methylbutyl)-7-(2-cyanobutan-2-yl)-4-methyl-1,3-dioxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (3q)



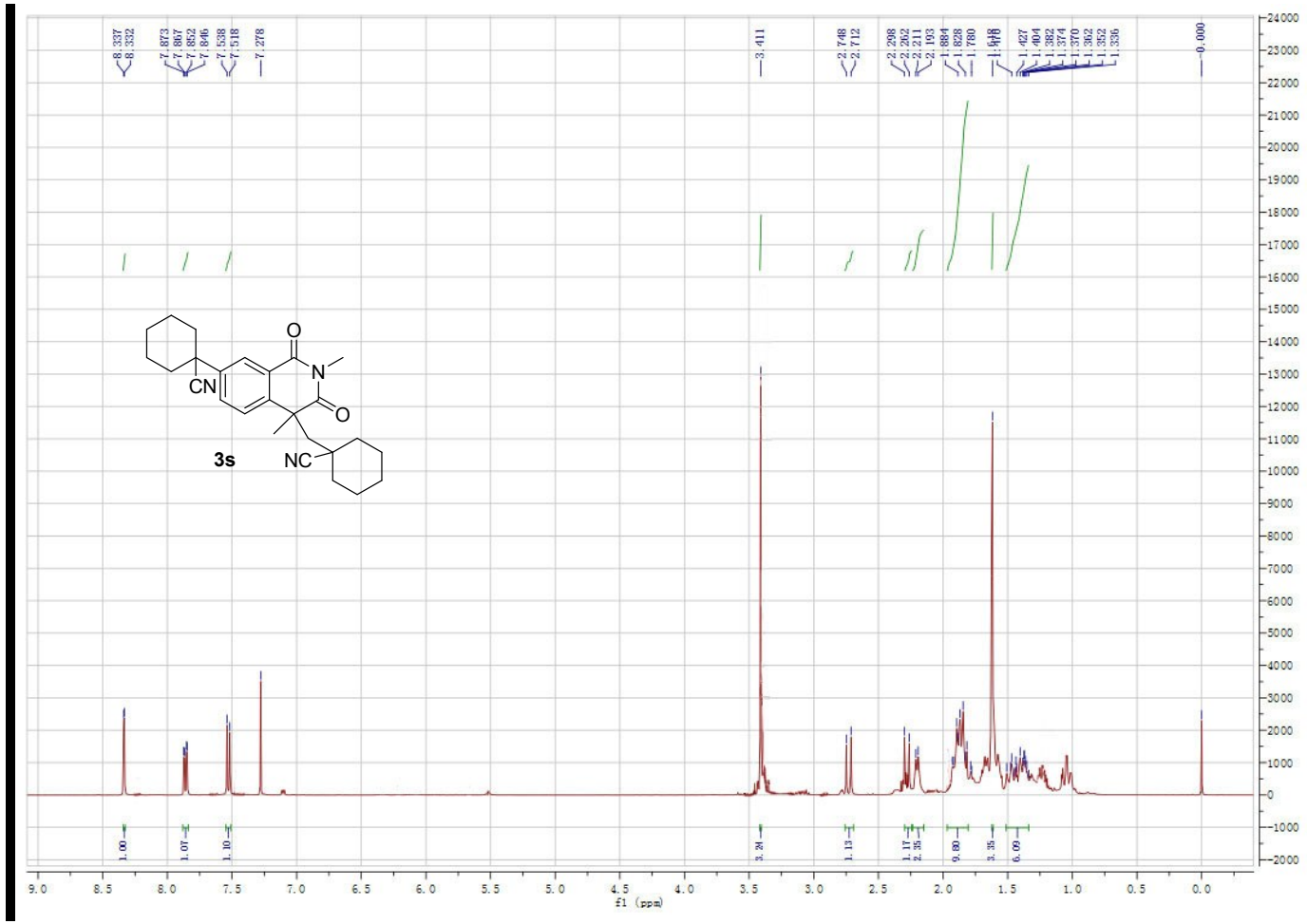
1-(2-butyl-6-chloro-4-((1-cyanocyclohexyl)methyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-7-yl)cyclohexanecarbonitrile (3r)



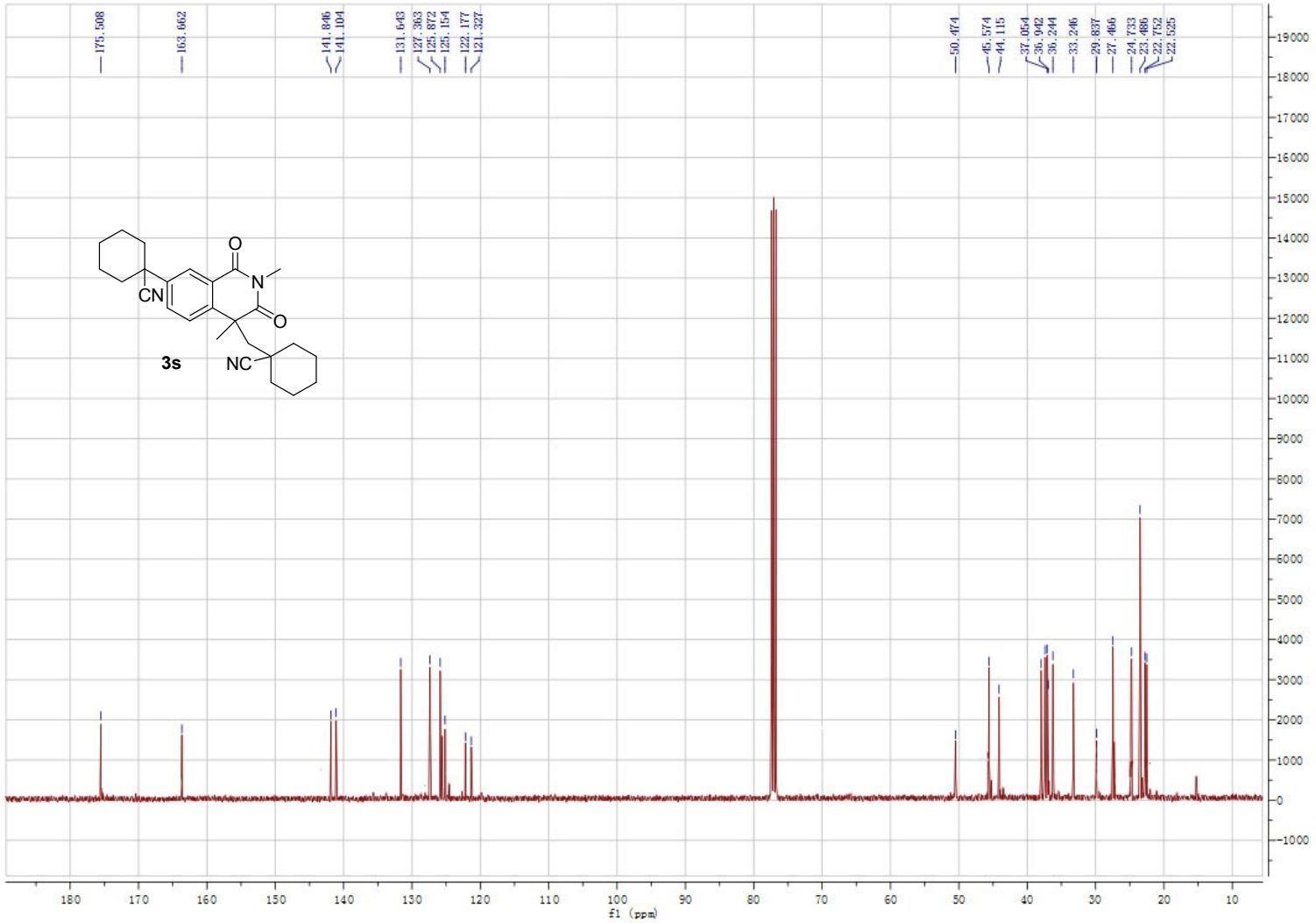
1-(2-butyl-6-chloro-4-((1-cyanocyclohexyl)methyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-7-yl)cyclohexanecarbonitrile (3r)



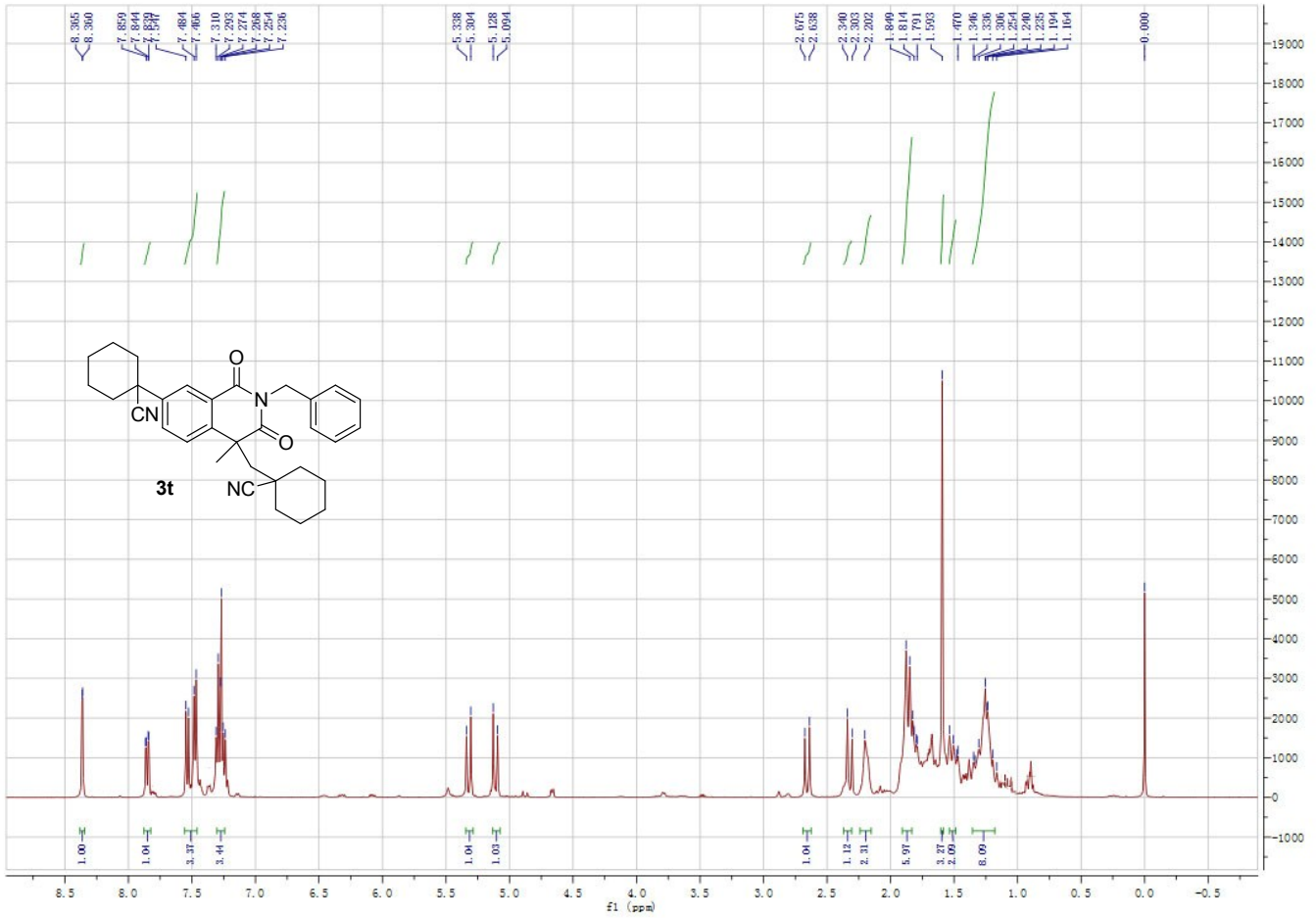
1-((7-(1-Cyanocyclohexyl)-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)cyclohexanecarbonitrile (3s)



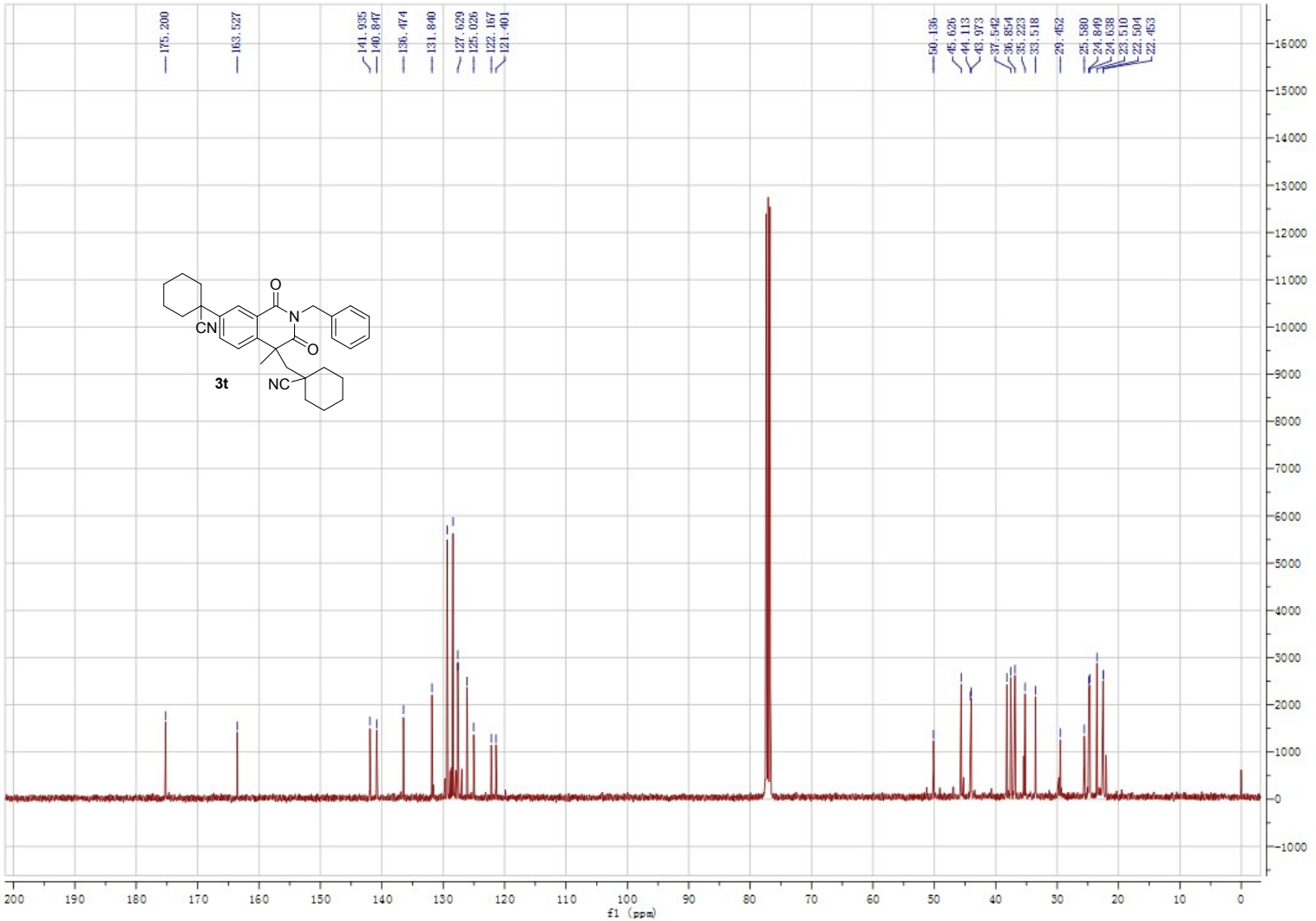
1-((7-(1-Cyanocyclohexyl)-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)cyclohexanecarbonitrile (3s)



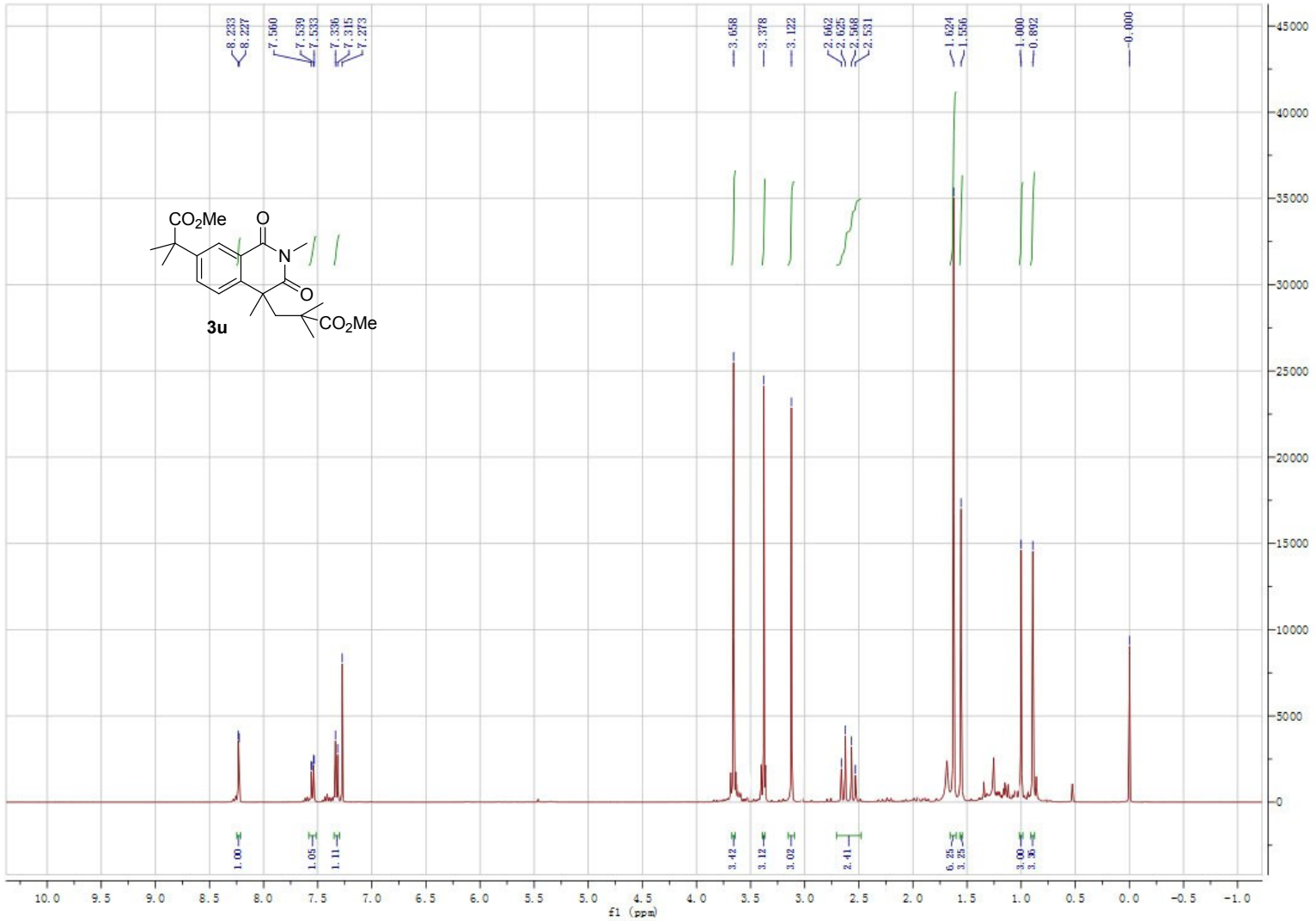
1-(2-Benzyl-4-((1-cyanocyclohexyl)methyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-7-yl)cyclohexanecarbonitrile (3t)



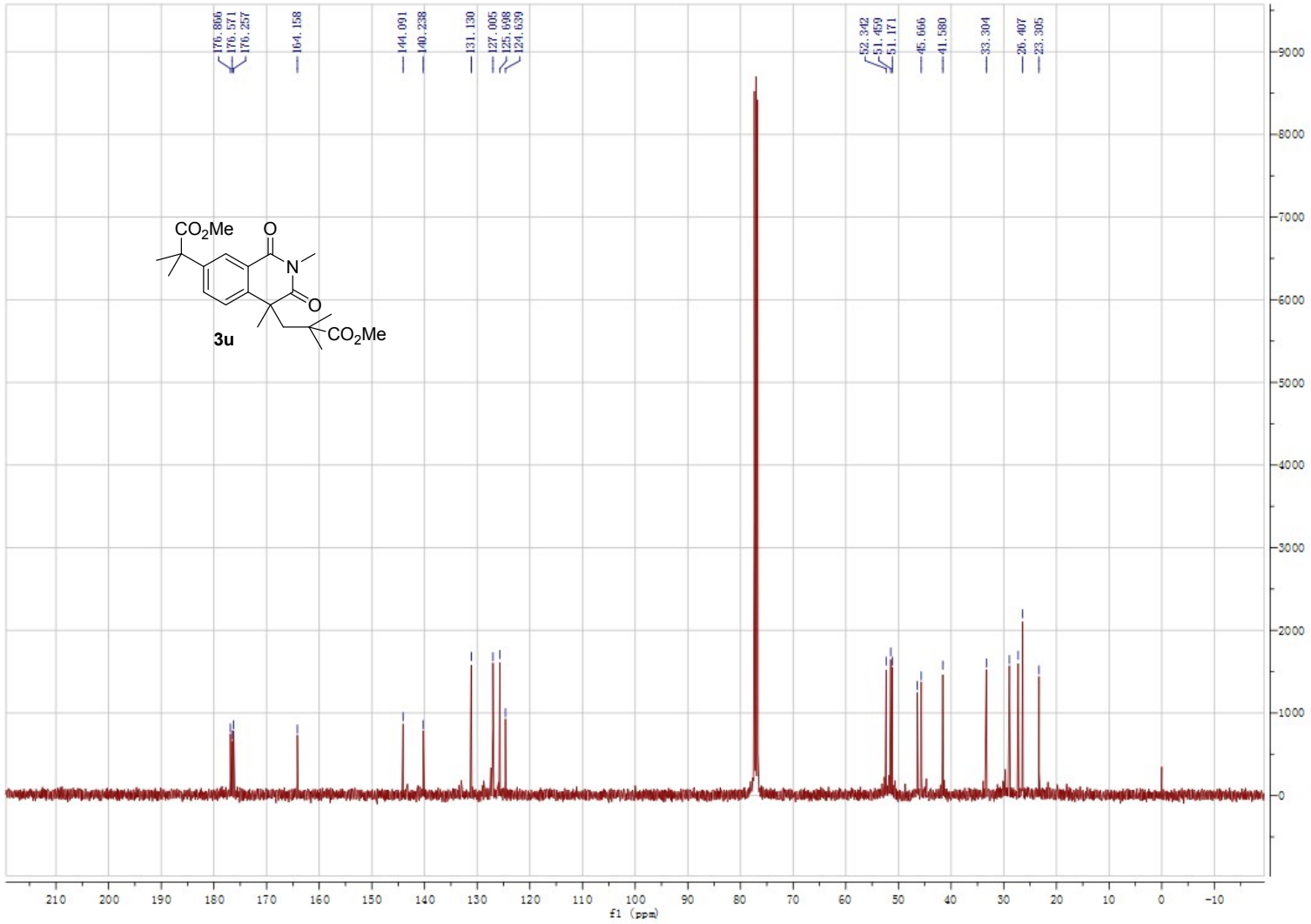
1-(2-Benzyl-4-((1-cyanocyclohexyl)methyl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-7-yl)cyclohexanecarbonitrile (3t)



Methyl 3-(7-(1-methoxy-2-methyl-1-oxopropan-2-yl)-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanoate (3u)

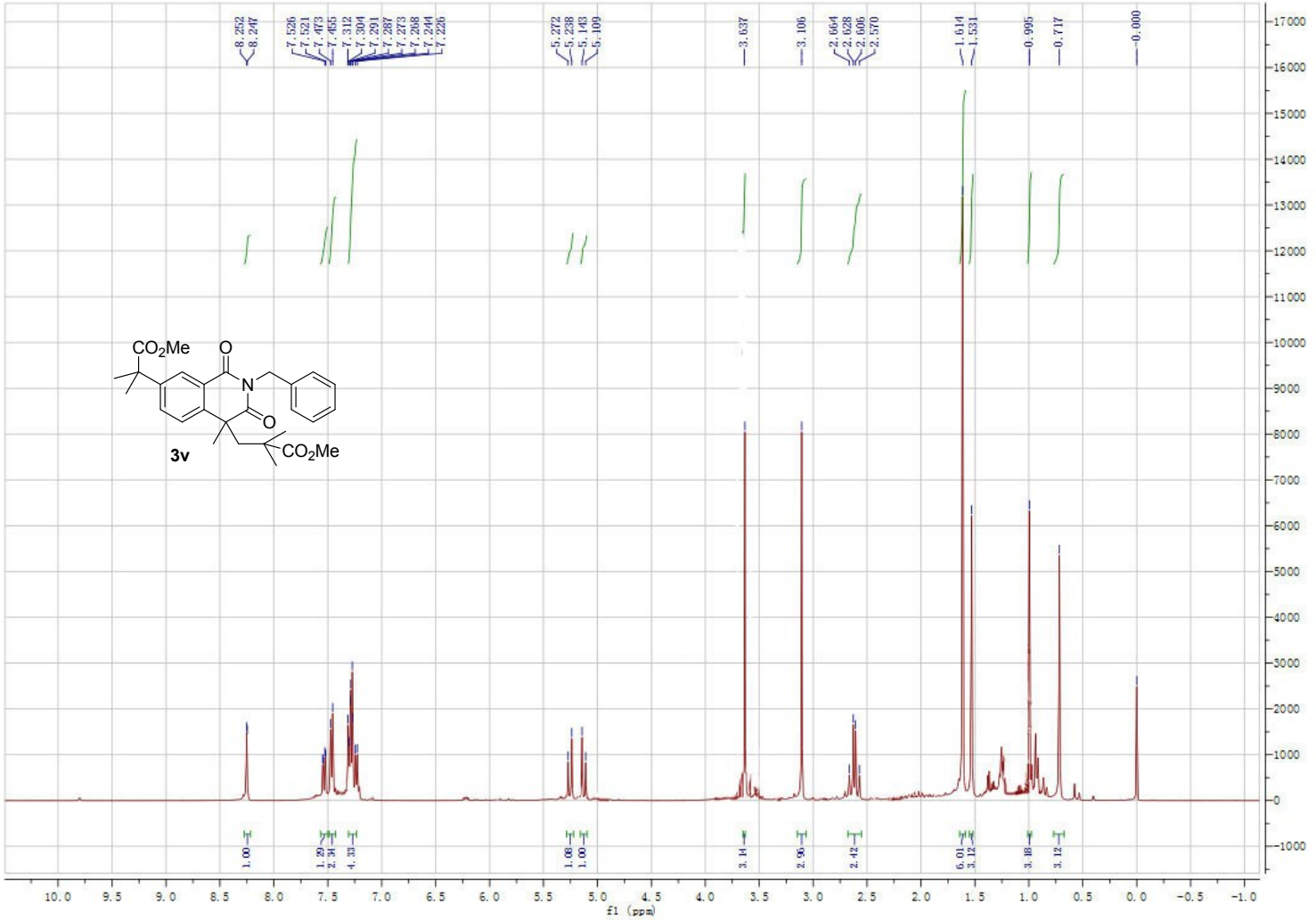


Methyl 3-(7-(1-methoxy-2-methyl-1-oxopropan-2-yl)-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanoate (3u)



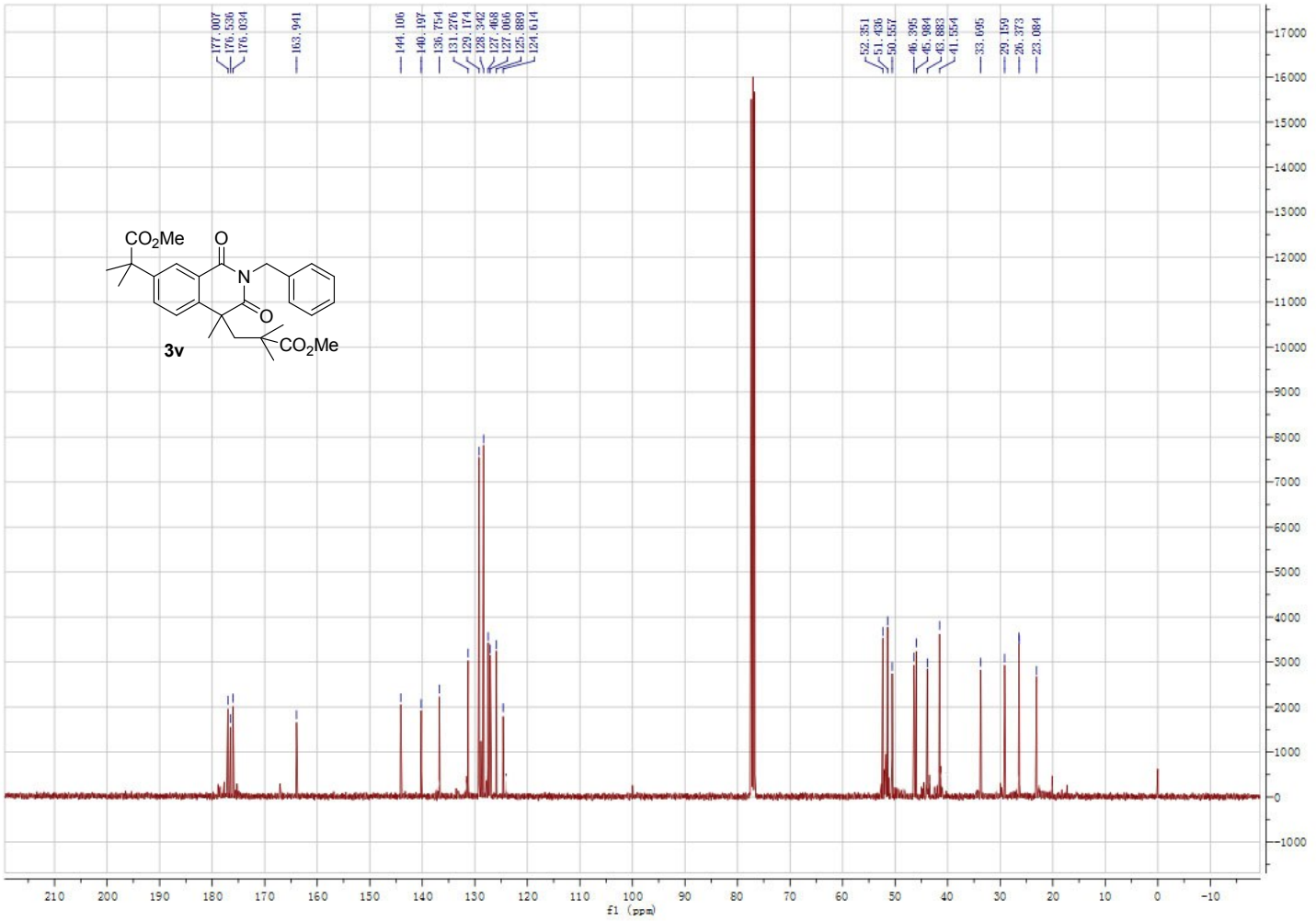
Methyl 3-(2-benzyl-7-(1-methoxy-2-methyl-1-oxopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanoate

(3v)



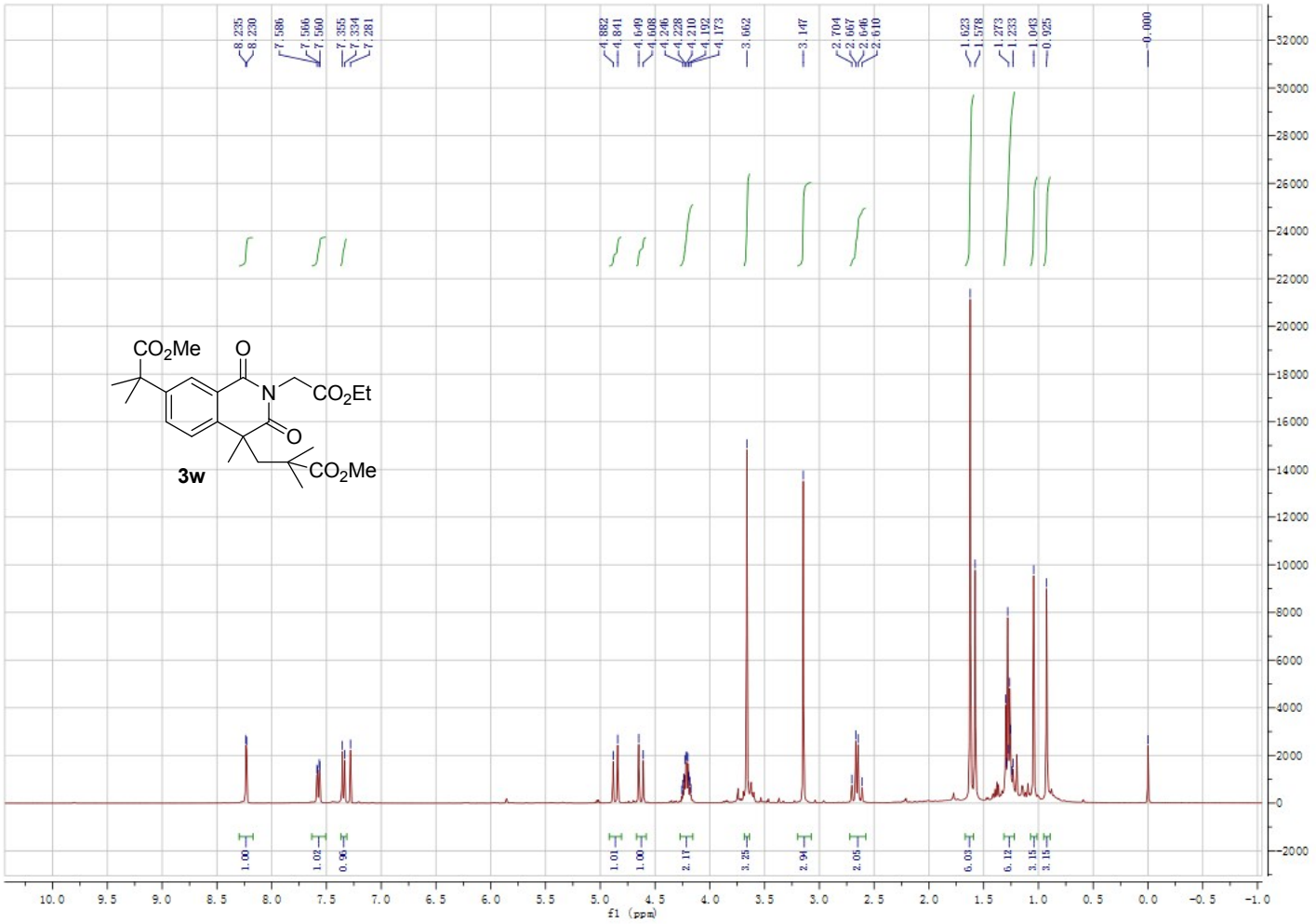
Methyl 3-(2-benzyl-7-(1-methoxy-2-methyl-1-oxopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanoate

(3v)



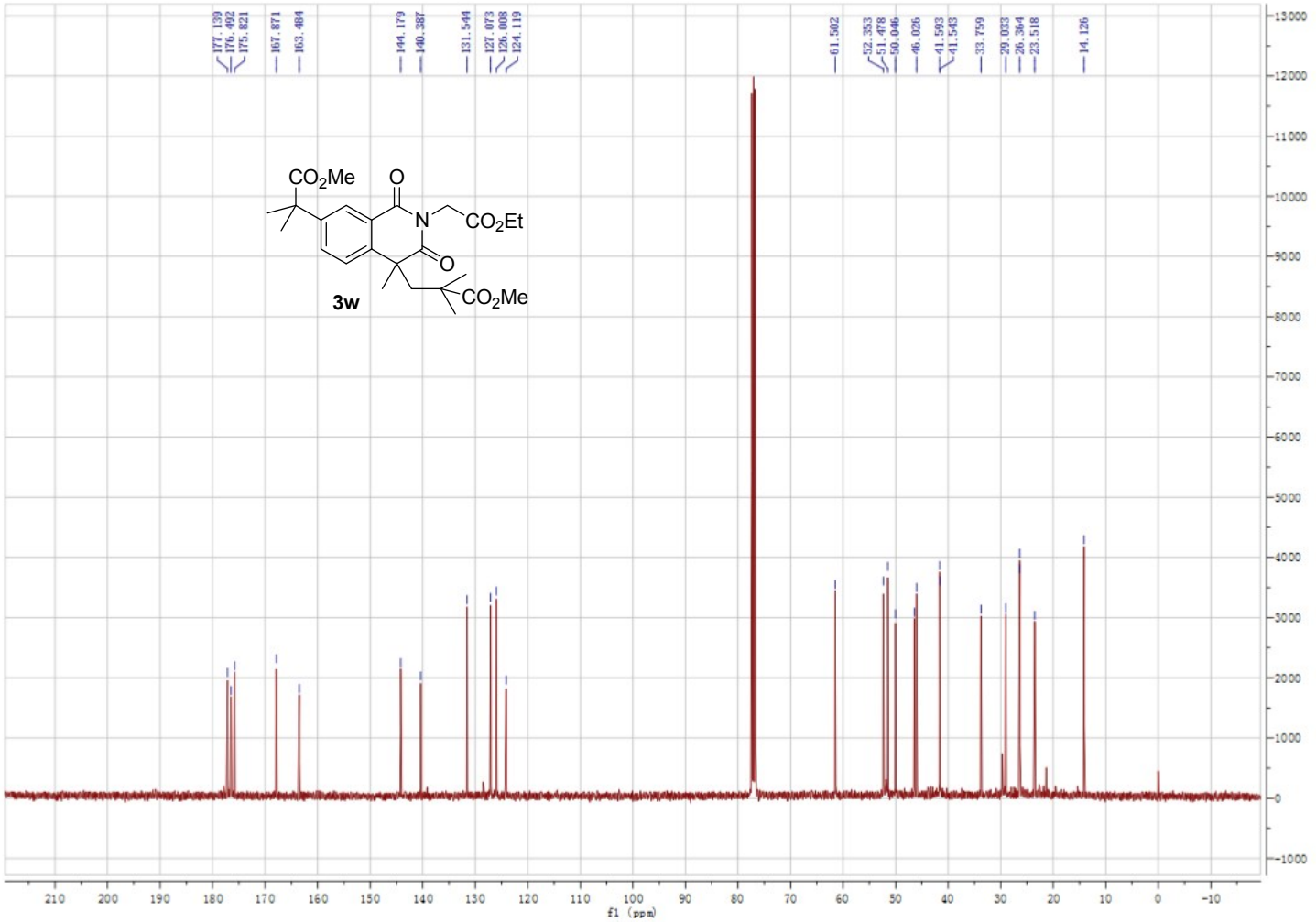
Methyl 3-(2-(2-ethoxy-2-oxoethyl)-7-(1-methoxy-2-methyl-1-oxopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)

-2,2-dimethylpropanoate (3w)

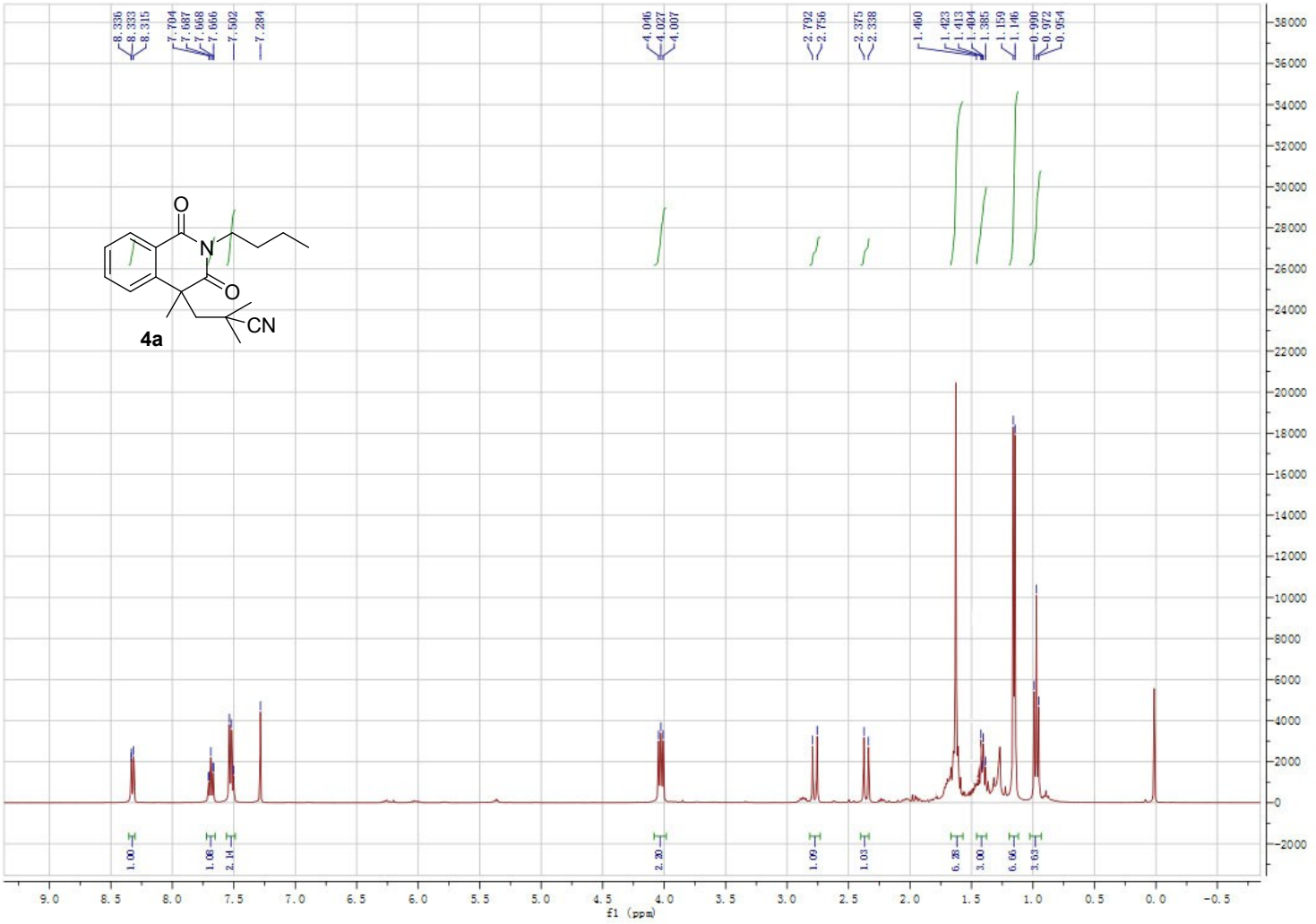


Methyl 3-(2-(2-ethoxy-2-oxoethyl)-7-(1-methoxy-2-methyl-1-oxopropan-2-yl)-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)

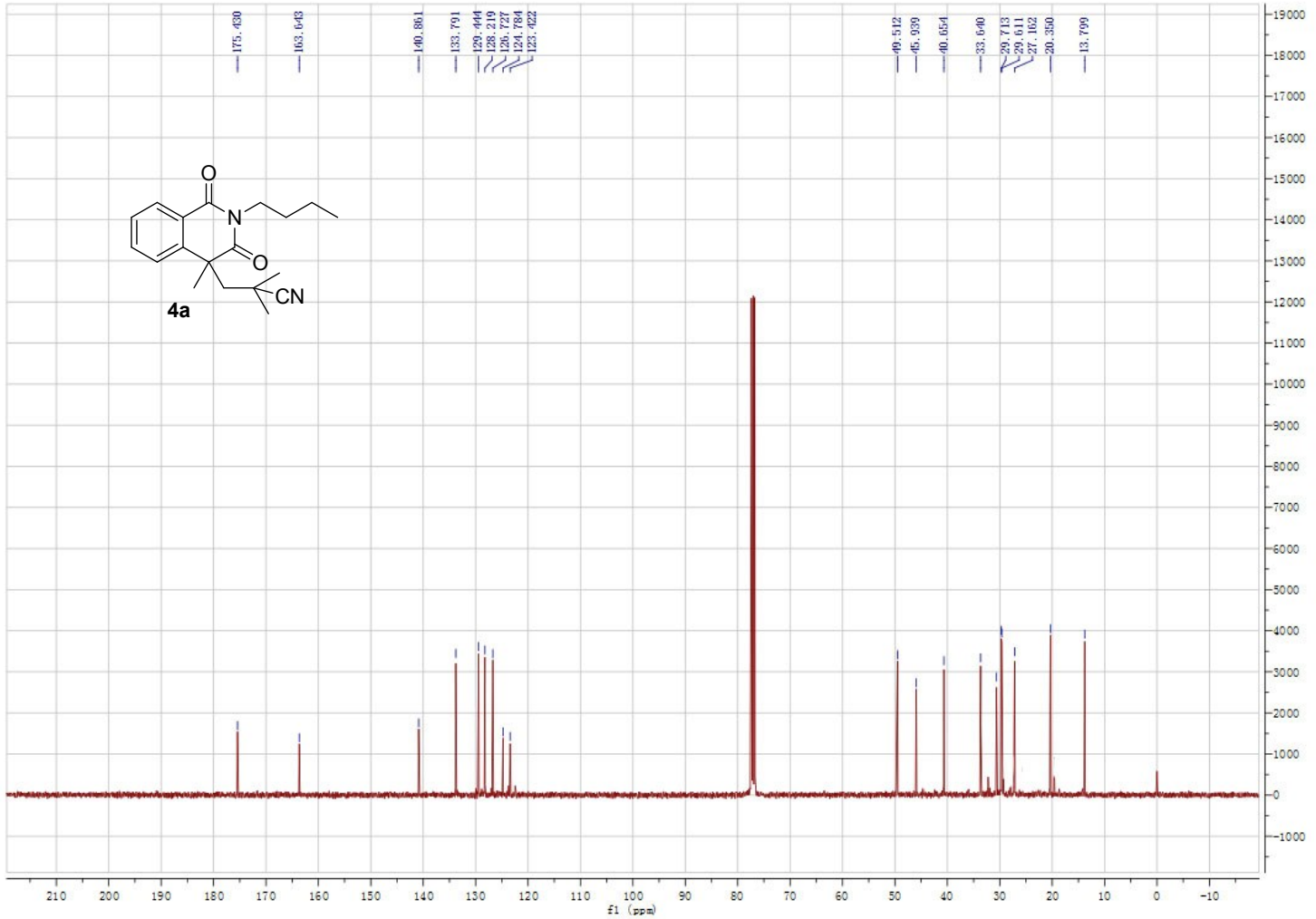
-2,2-dimethylpropanoate （3w）



3-(2-butyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (4a)



3-(2-butyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (4a)



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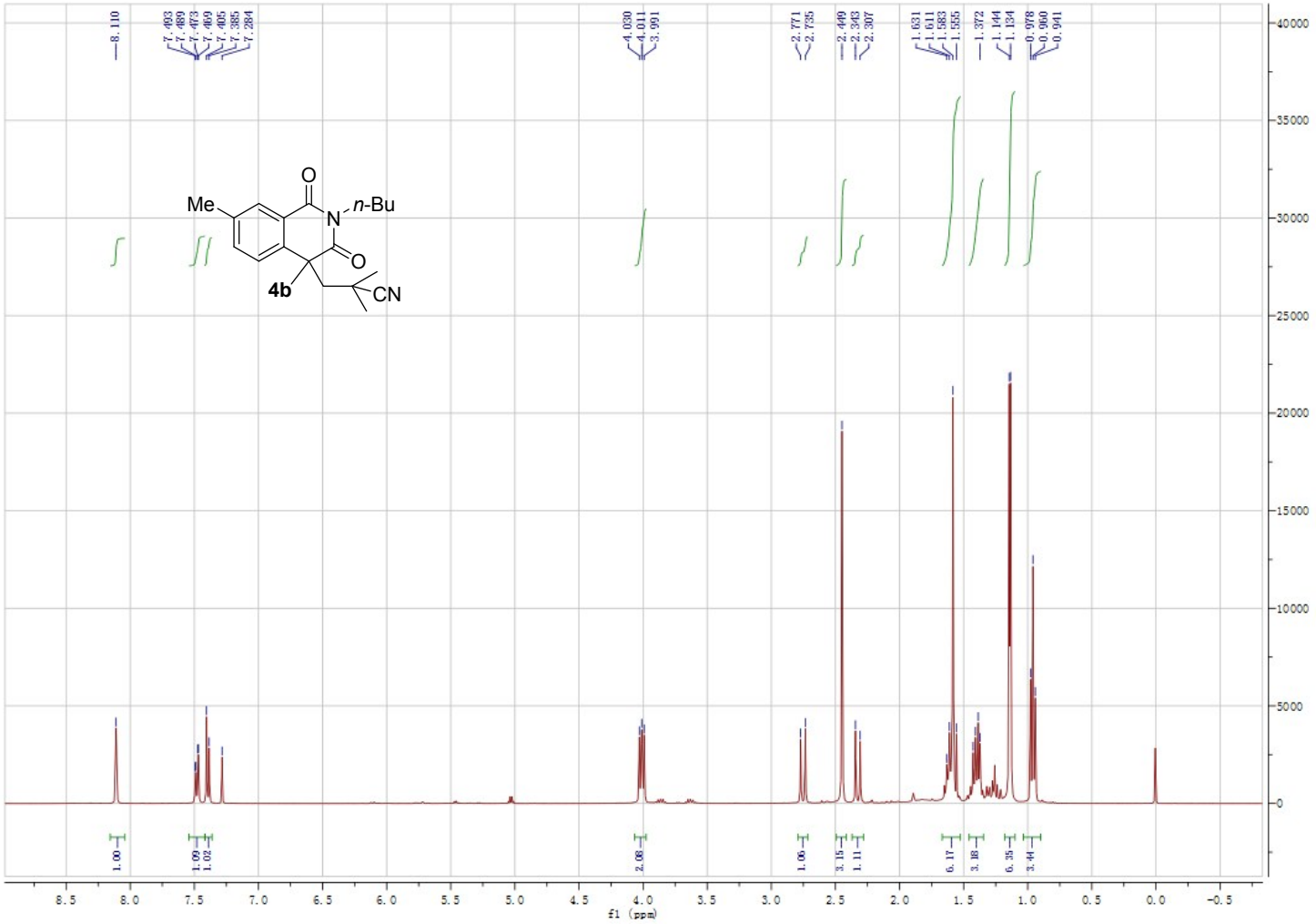
3-(2-Butyl-4,7-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (4b)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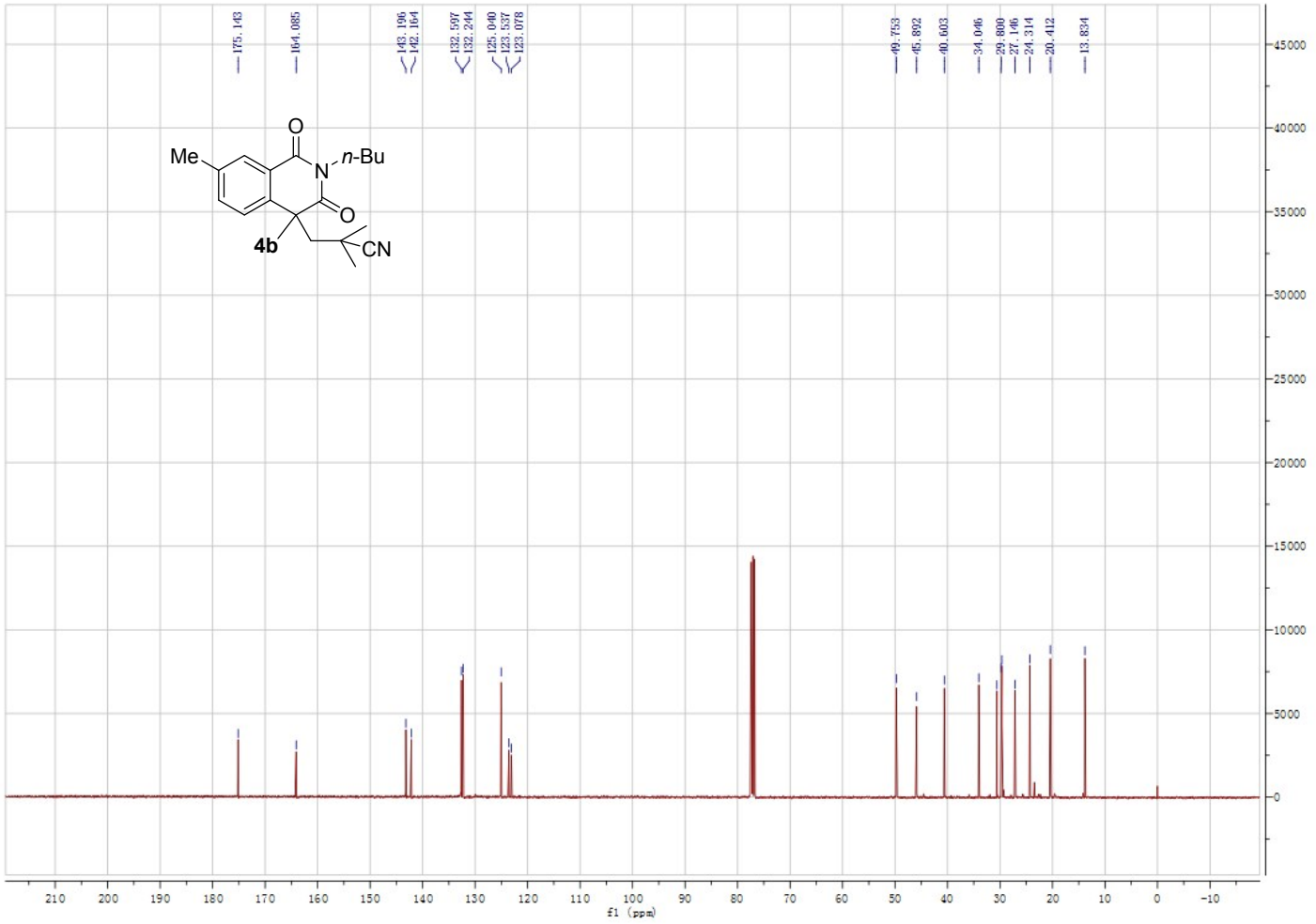
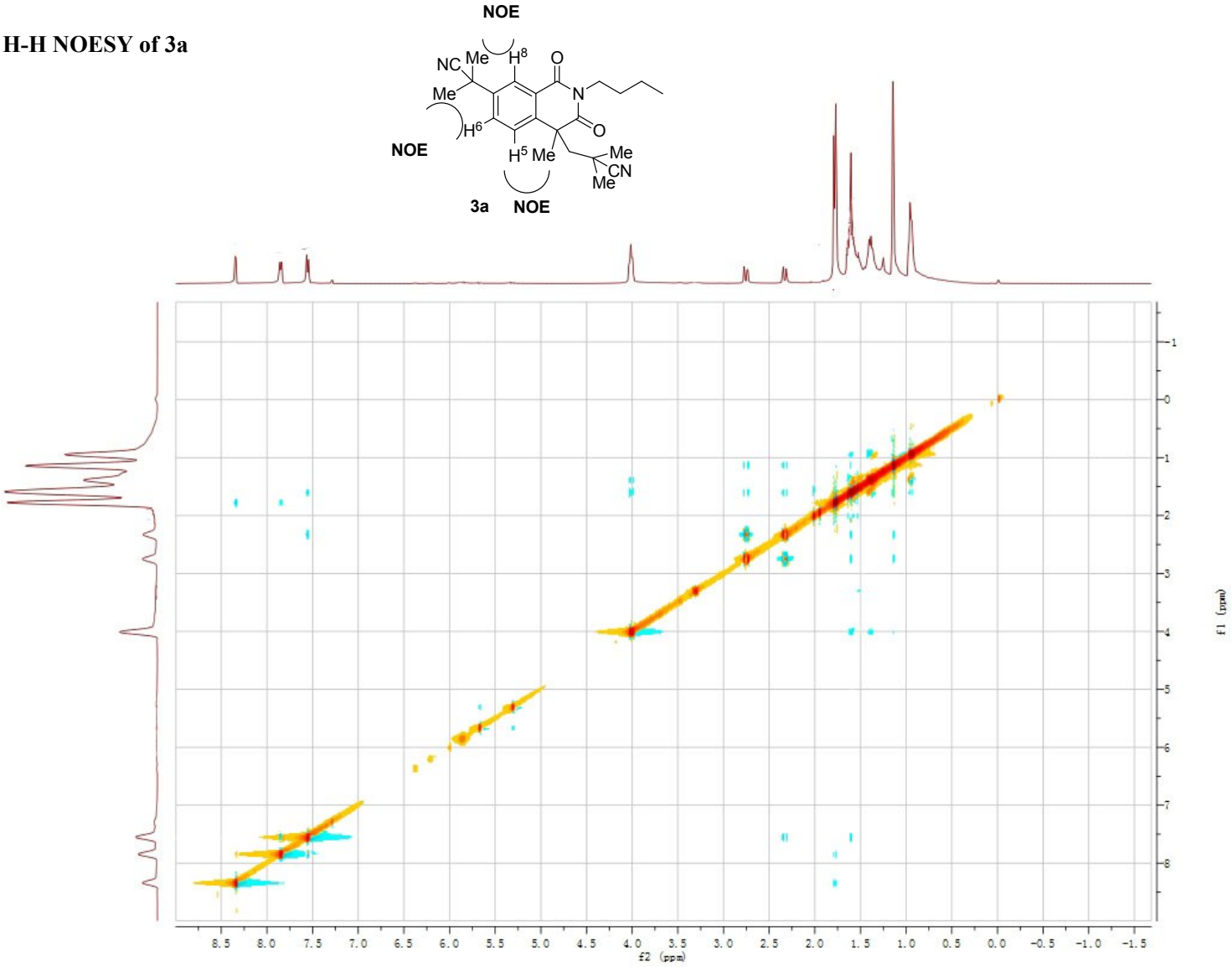
7.473
7.469
7.405
7.385
7.284
4.030
4.011
3.991
2.771
2.735
2.449
2.343
2.307
1.631
1.611
1.583
1.555
1.372
1.144
1.134
0.978
0.960
0.941
Me
n-Bu
N
O
O
4b
CN
f1 (ppm)

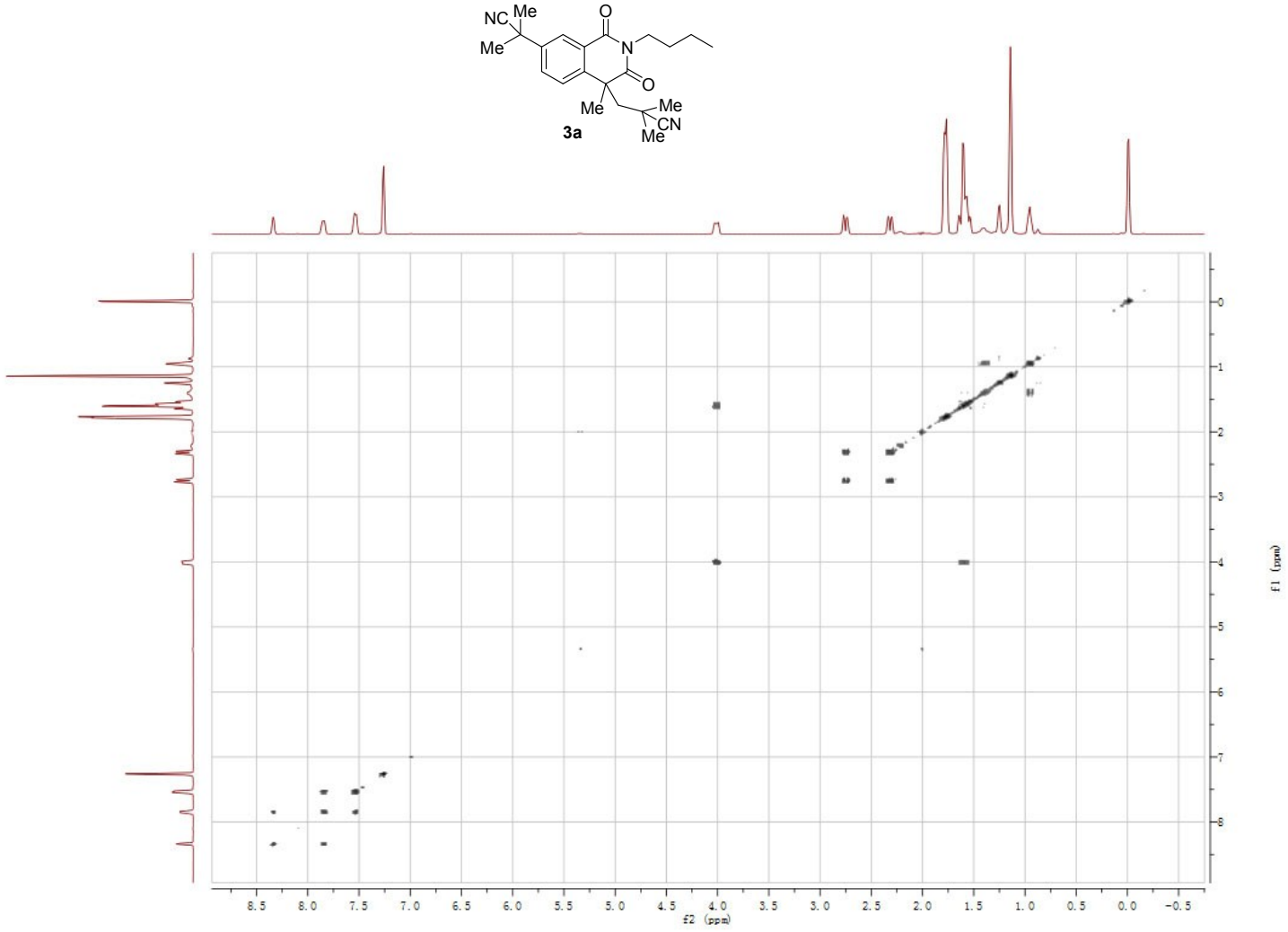
3-(2-Butyl-4,7-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-dimethylpropanenitrile (4b)



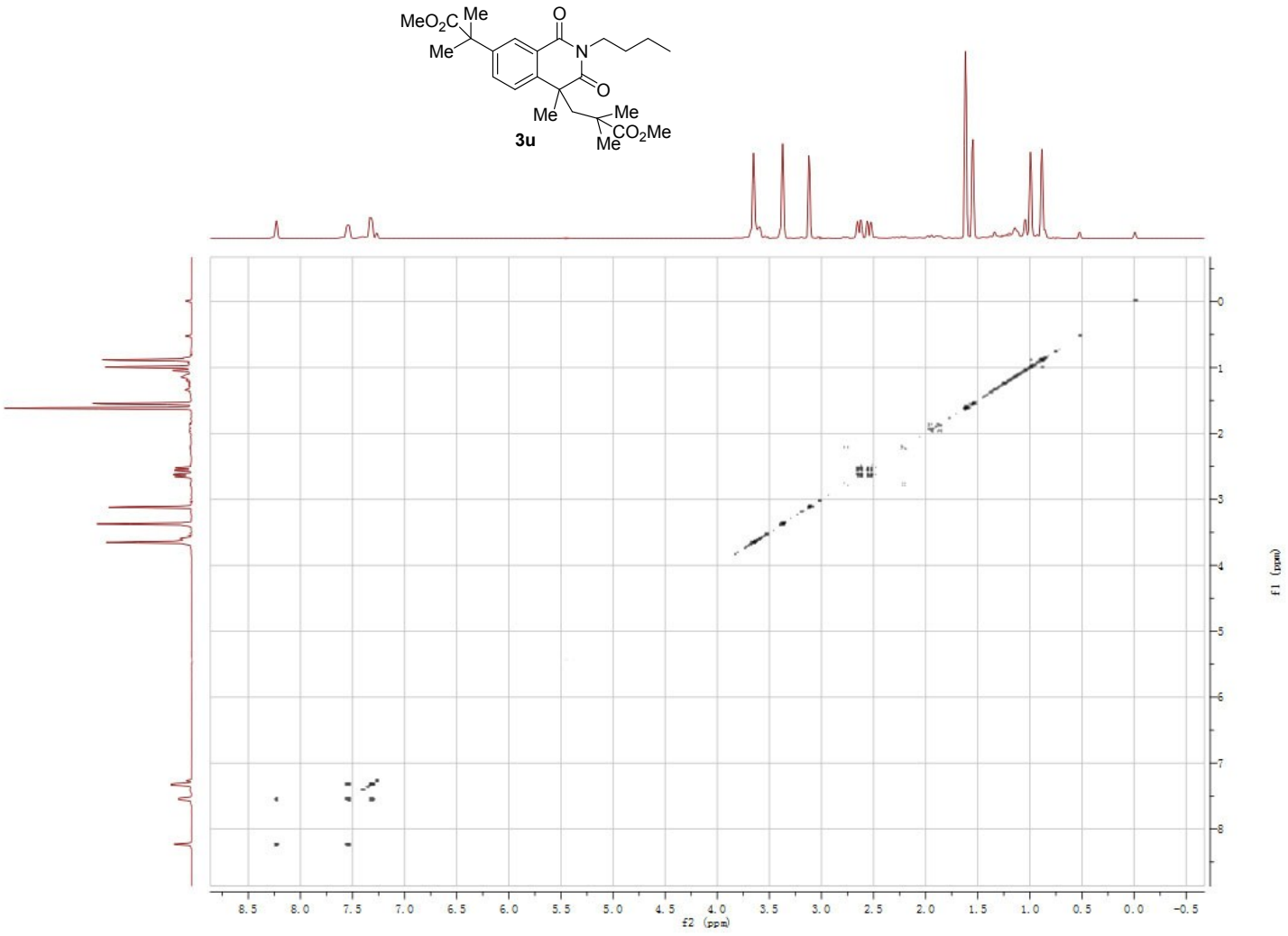
5 H-H NOESY of 3a



5 H-H COSY of 3a



H-H COSY of 3u



6. Observation of side-product isobutyronitrile (Me_2CHCN)