General chemistry methods

Analysis

NMR spectra were recorded on Bruker AV400 spectrometer. The chemical shifts (δ) are given in ppm relative to $CDCl_3$ (7.26 ppm for ^1H NMR), acetone-d_6 (2.09 ppm for ^1H NMR) or TMS (0 ppm for ^1H NMR) and $CDCl_3$ (77.0 ppm for ^{13}C NMR) or acetone-d_6 (30.6 ppm for ^{13}C NMR). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, ddd = doublet of doublet of doublet, t = triplet, td = triple doublet, m = multiplet), coupling constants (Hz) and integration.

Chemicals

All reagents were used without further purification unless noted otherwise.

Reagent and resource	Source	Identifier
2-*tert*-butylphenol	Innochem	88-18-6
3-(*tert*-butyl)-2-hydroxybenzaldehyde	Bidepharm	24623-65-2
tert-butyl bromoacetate	Ouhechem	5292-43-3
hydroxylamine hydrochloride	Ouhechem	5470-11-1
sodium acetate	Tgreag	127-09-3
formic acid	J&K	64-18-6
aniline	Tgreag	62-53-3
4-aminophenol	Macklin	123-30-8
Cs_2CO_3	Ouhechem	534-17-8
TFA	Aladdin	76-05-1
$(COCl)_2$	Energy	79-37-8
DMF	Energy	68-12-2
Et_3N	Energy	121-44-8
THF	Energy	109-99-9

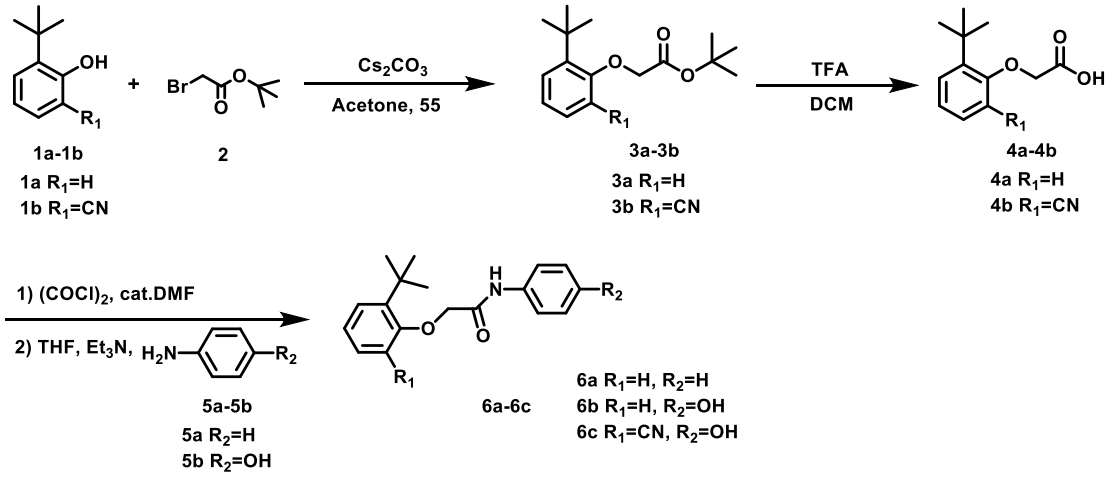
DCM	Aladdin	75-09-2
Acetone	Tgreag	67-64-1

Chromatography

For chromatographic purifications, silica gel (Haiyangchem Inc., 200 - 300 mesh) was used. Thin-layer chromatography was performed on a GF-254 silica gel plate (Haiyangchem Inc.) using a 254 nm UV analyzer.

General procedures for the synthesis of NAT and its analogs

Compound NAT and its analogs were synthesized through the general procedure outlined in the scheme below. Besides, the detailed methods for the synthesis of **NAT** (**6b**), NAT-1a (**6a**), and NAT-5r (**6c**) are provided in this work.



3-(*tert*-butyl)-2-hydroxybenzonitrile (1b)

Compound **1b** was synthesized according to the literature method[1]: A solution of 3-(*tert*-butyl)-2-hydroxybenzaldehyde (1.48 g, 8.29 mmol), hydroxylamine hydrochloride (0.69 g, 9.9 mmol), and sodium acetate (0.8 g, 9.9 mmol) in formic acid (20 mL) was heated at reflux overnight. The solvent was evaporated under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic phase was washed with saturated NaCl and was dried with anhydrous Na_2SO_4, then filtered and evaporated to dryness. The mixture was purified by silica gel chromatography to afford compound **1b** as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 6.93 (td, J = 7.8, 1.5 Hz, 1H), 6.03 (s, 1H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.00, 137.78, 132.25, 129.77, 120.92, 116.76, 100.21, 34.98, 29.27.

***tert*-butyl 2-(2-(*tert*-butyl)phenoxy)acetate (3a)**

The titled compound was synthesized according to a modified method[2]: To a mixture of **1a** (0.92 g, 6 mmol) and Cs_2CO_3 (3.9 g, 12 mmol) in acetone (6 mL) was added compound **2** (2.39 g, 12 mmol). The mixture was then stirred at reflux overnight, After the completion of the reaction, the mixture was filtered, the filtrate was evaporated to dryness and purified by silica gel chromatography to afford compound **3a** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 7.7, 1.7 Hz, 1H), 7.18 (ddd, J = 8.0, 7.3, 1.7 Hz, 1H), 6.95 (td, J = 7.5, 1.2 Hz, 1H), 6.74 (dd, J = 8.1, 1.2 Hz, 1H), 4.56 (s, 2H), 1.52 (s, 9H), 1.45 (s, 9H).

***tert*-butyl 2-(2-(tert-butyl)-6-cyanophenoxy)acetate (3b)**

The titled compound was prepared as a brown solid from **1b** (1.05 g, 6 mmol) and **2** (2.39 g, 12 mmol) using the same procedure applicable for compound **3a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 4.84 (s, 2H), 1.53 (s, 9H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.81, 159.64, 143.74, 132.32, 132.24, 123.66, 117.49, 105.06, 82.60, 70.24, 35.26, 30.08, 28.10.

2-(2-(*tert*-butyl)phenoxy)acetic acid (4a)

To a solution of **3a** (0.79 g, 3 mmol) in 2 mL DCM was added TFA (1 mL) slowly. After stirring at room temperature for about 2 h, the solution was concentrated and compound **4a** was obtained without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 7.8, 1.7 Hz, 1H), 7.22-7.14 (m, 1H), 6.97 (td, J = 7.6, 1.2 Hz, 1H), 6.75 (dd, J = 8.1, 1.2 Hz, 1H), 4.72 (s, 2H), 1.42 (s, 9H).

2-(2-(*tert*-butyl)-6-cyanophenoxy)acetic acid (4b)

The titled compound was prepared as a brown oil from **3b** (0.87 g, 3 mmol) using the same procedure applicable for compound **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 4.98

(s, 2H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.10, 159.18, 144.07, 132.53, 132.30, 124.33, 117.07, 105.64, 69.53, 35.28, 30.27.

2-(2-(*tert*-butyl)phenoxy)-*N*-phenylacetamide (6a)

Compound **4a** (42 mg, 0.2 mmol) was added to 0.5 mL $(COCl)_2$, followed by a catalytic amount of DMF. The mixture was stirred at room temperature for about 2 h, and then evaporated to dryness. Dry THF (1 mL) was added to the residue, followed by compound **5a** (23 mg, 0.24 mmol) and Et_3N (33 μL, 0.24 mmol). After stirring for 0.5 h, the mixture was evaporated to dryness and purified by silica gel chromatography to afford compound **6a** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.66-7.58 (m, 2H), 7.40 (td, J = 7.3, 1.6 Hz, 3H), 7.28-7.23 (m, 1H), 7.22-7.16 (m, 1H), 7.05 (td, J = 7.6, 1.2 Hz, 1H), 6.93 (dd, J = 8.2, 1.2 Hz, 1H), 4.71 (s, 2H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.43, 155.80, 138.12, 136.99, 129.21, 127.64, 127.30, 124.85, 122.31, 119.69, 113.21, 68.07, 34.77, 30.17.

2-(2-(*tert*-butyl)phenoxy)-*N*-(4-hydroxyphenyl)acetamide (6b)

The title compound was obtained as a white solid using the same procedure applicable for compound **6a**. ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.86 (s, 1H), 7.57-7.45 (m, 2H), 7.32 (dd, J = 7.7, 1.6 Hz, 1H), 7.20 (ddd, J = 8.1, 7.2, 1.7 Hz, 1H), 7.05-6.89 (m, 2H), 6.81 (d, J = 8.9 Hz, 2H), 4.70 (s, 2H), 1.45 (s, 9H).

2-(2-(*tert*-butyl)-6-cyanophenoxy)-*N*-(4-hydroxyphenyl)acetamide (6c)

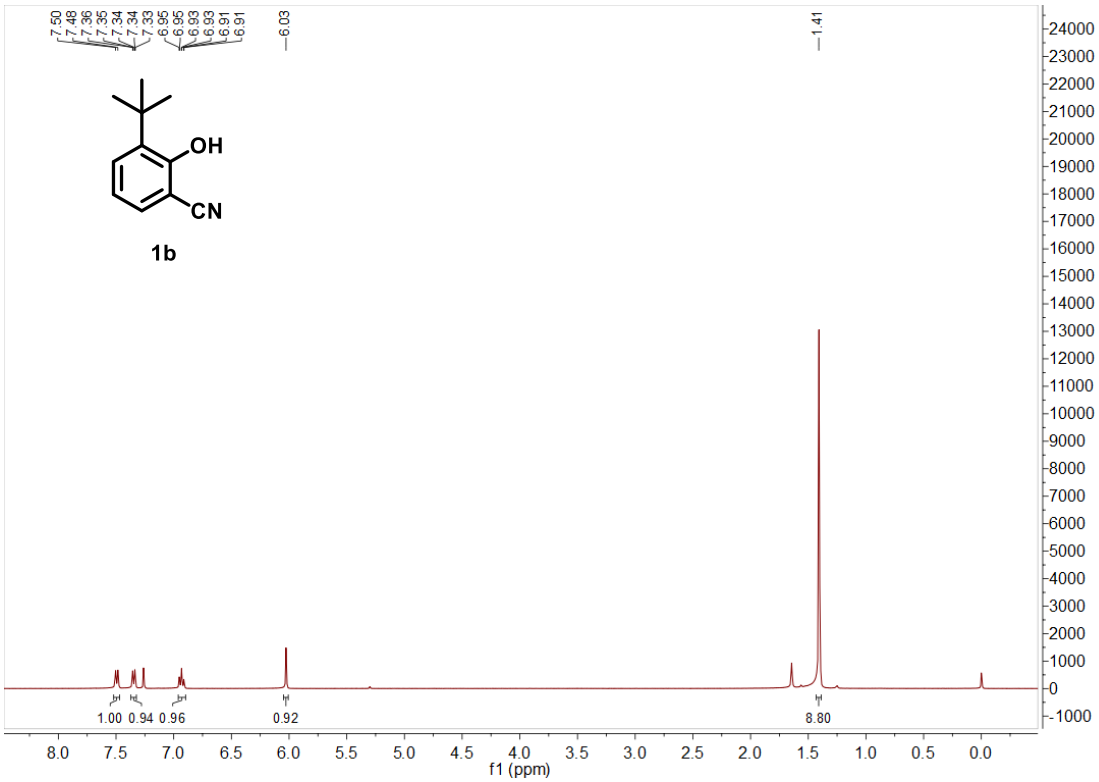
The title compound was obtained as a white solid using the same procedure applicable for compound **6a**. ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.24 (s, 1H), 8.30 (s, 1H), 7.75 (dd, J = 8.0, 1.9 Hz, 1H), 7.65 (dd, J = 7.6, 1.9 Hz, 1H), 7.62-7.57 (m, 2H), 7.30 (t, J = 7.8 Hz, 1H), 6.87-6.80 (m, 2H), 4.87 (s, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 164.83, 159.36, 154.16, 143.94, 132.68, 132.42, 130.37, 124.70, 121.98, 116.68, 115.11, 106.65, 72.99, 34.96, 30.00.

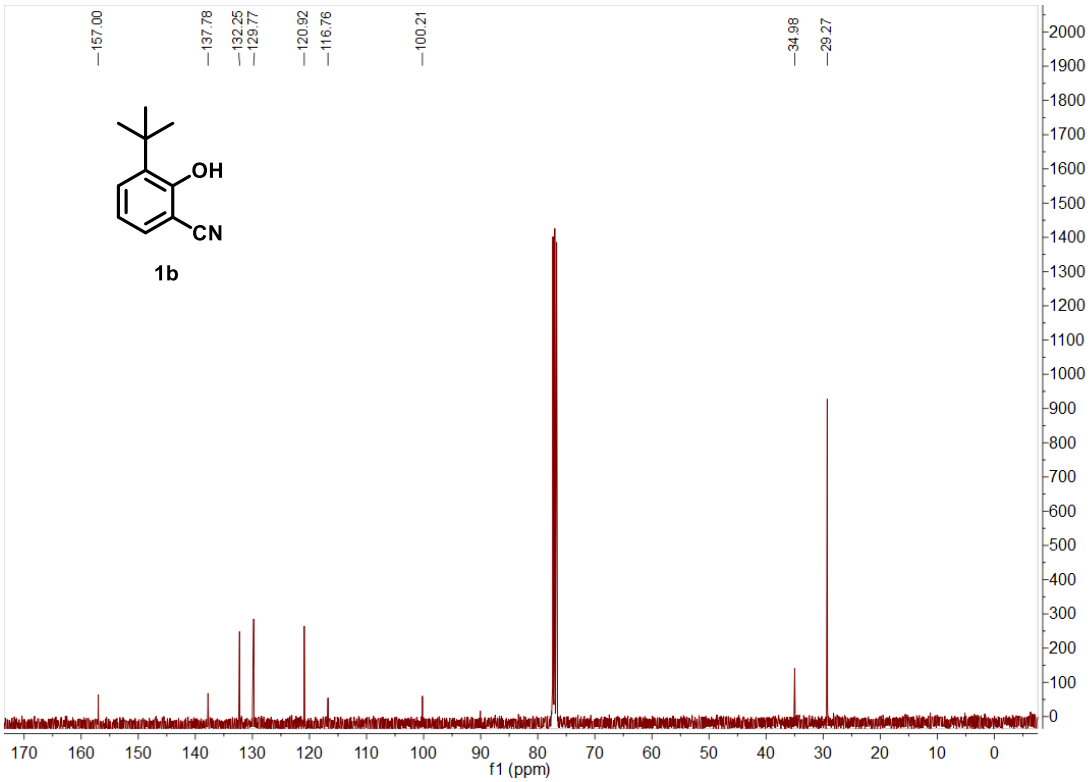
Reference:

[1] Dow; Robert L. Cyano containing oxamic acids and derivatives as thyroid receptor ligands. US6194454.

[2] Takahashi, E.; Hirano, N.; Nagahara, T.; Yoshikawa, S.; Momen, S.; Yokokawa, H.; Hayashi, R. Discovery of Potent Transient Receptor Potential Vanilloid 1 Antagonists: Design and Synthesis of Phenoxyacetamide Derivatives. Bioorganic & Medicinal Chemistry Letters 2013, 23 (11), 3154-3156.

NMR Spectra of Representative Compounds

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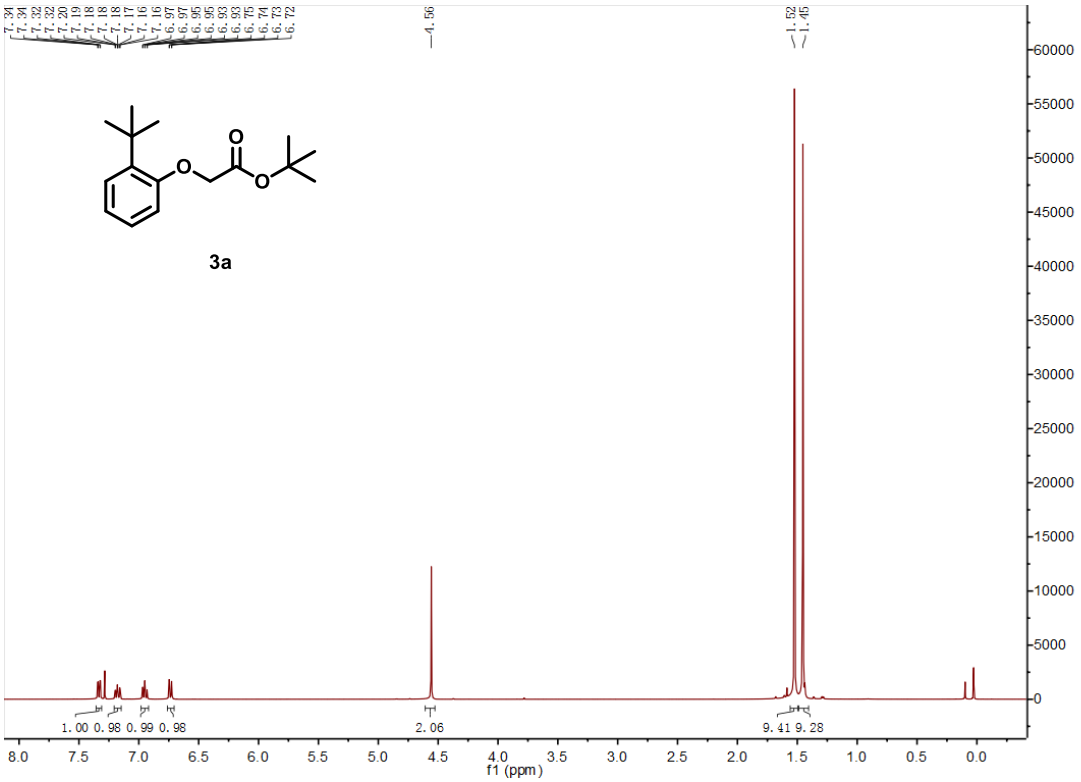
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9.41 9.28
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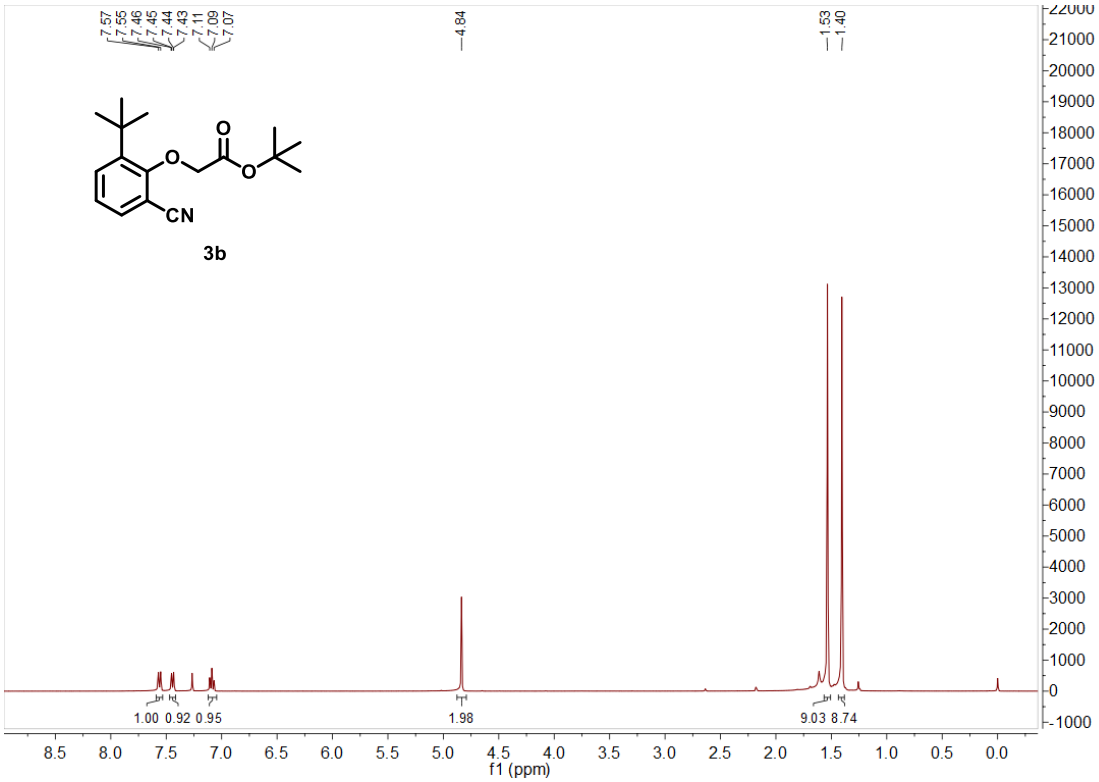
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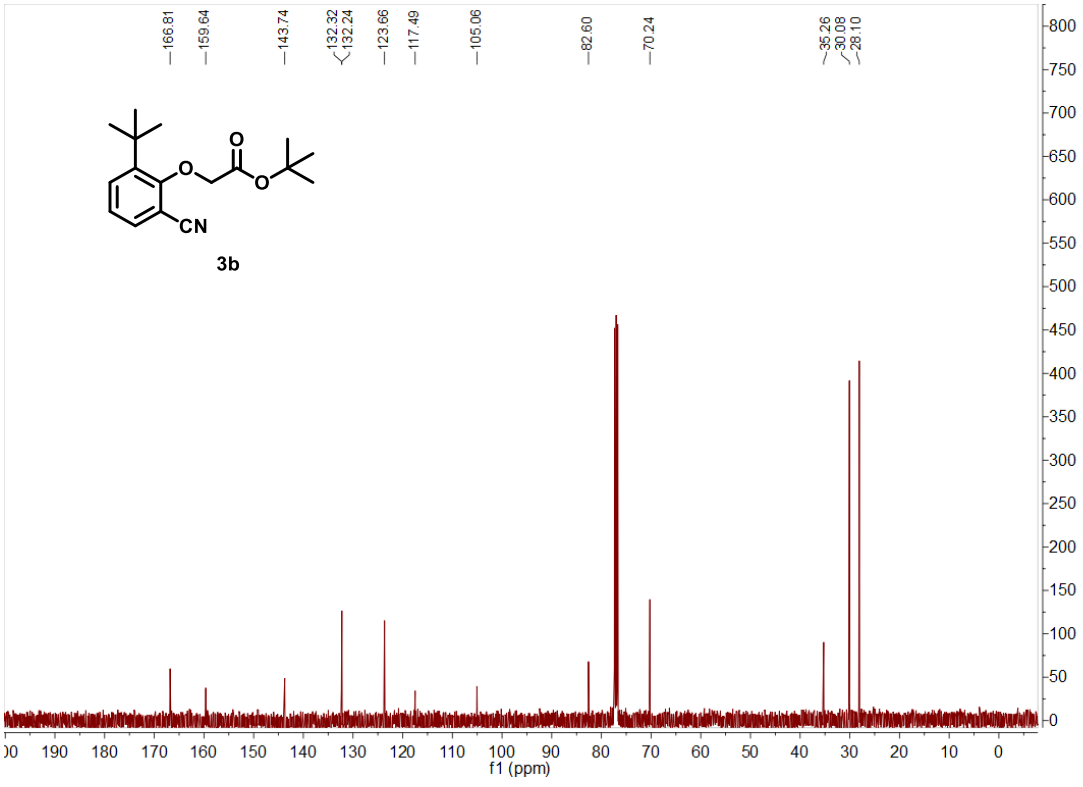
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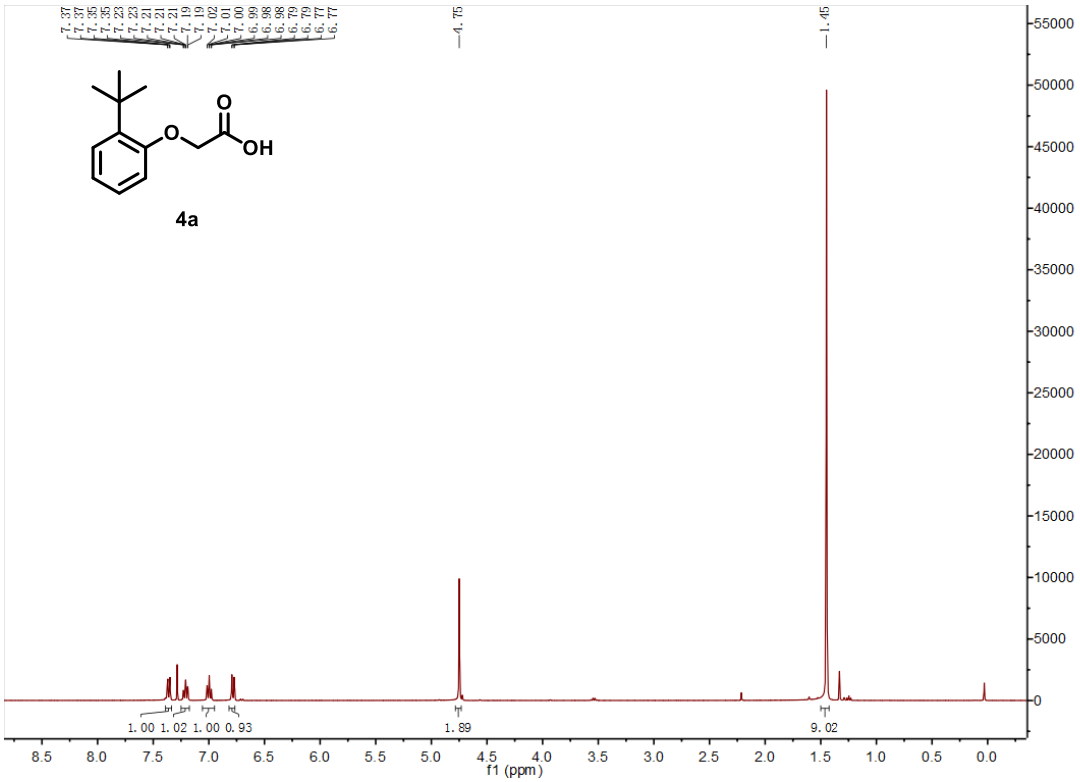
3b
f1 (ppm)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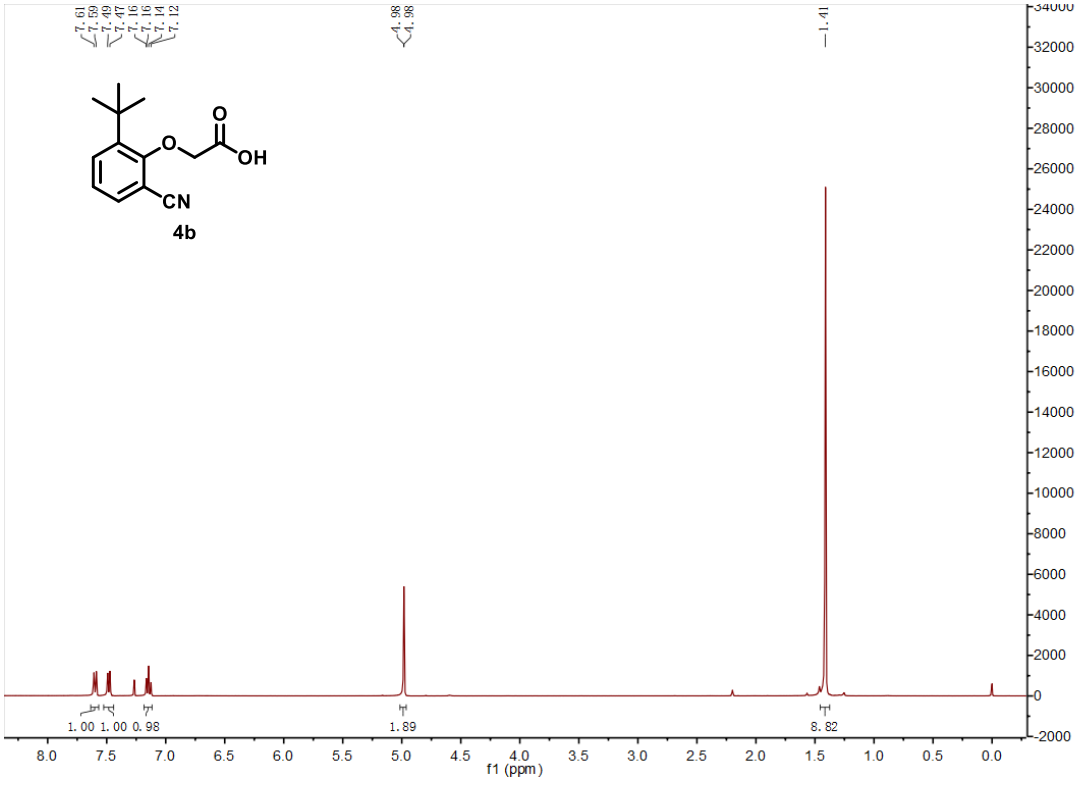
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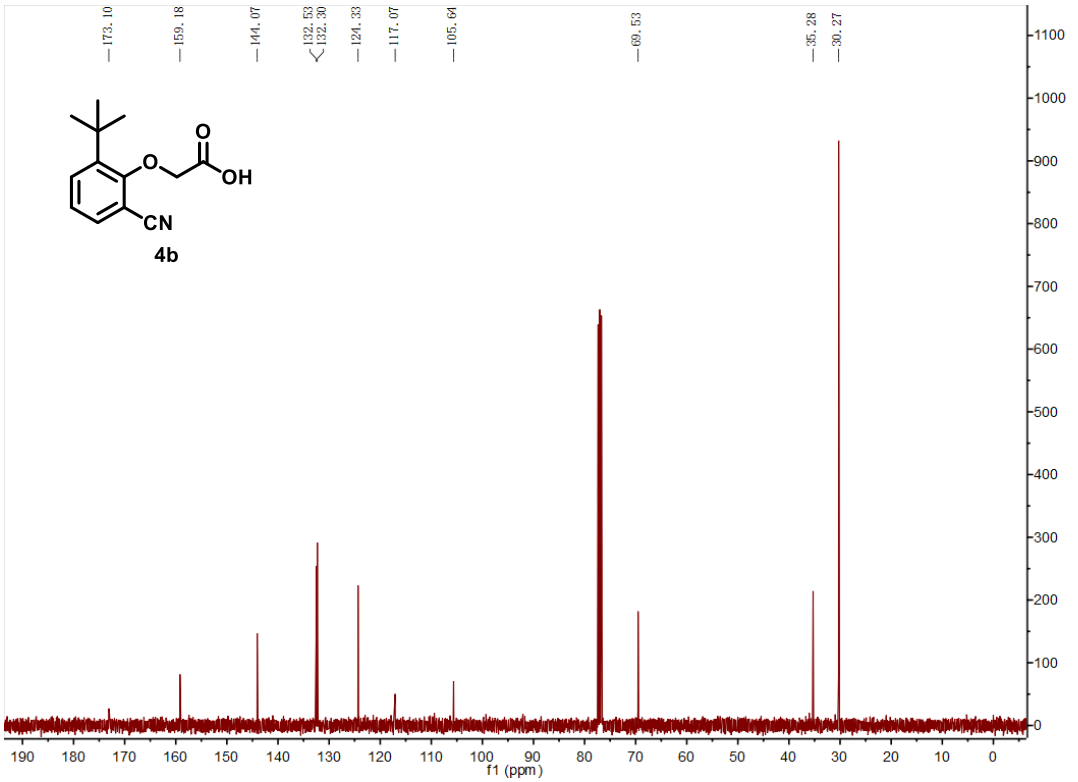
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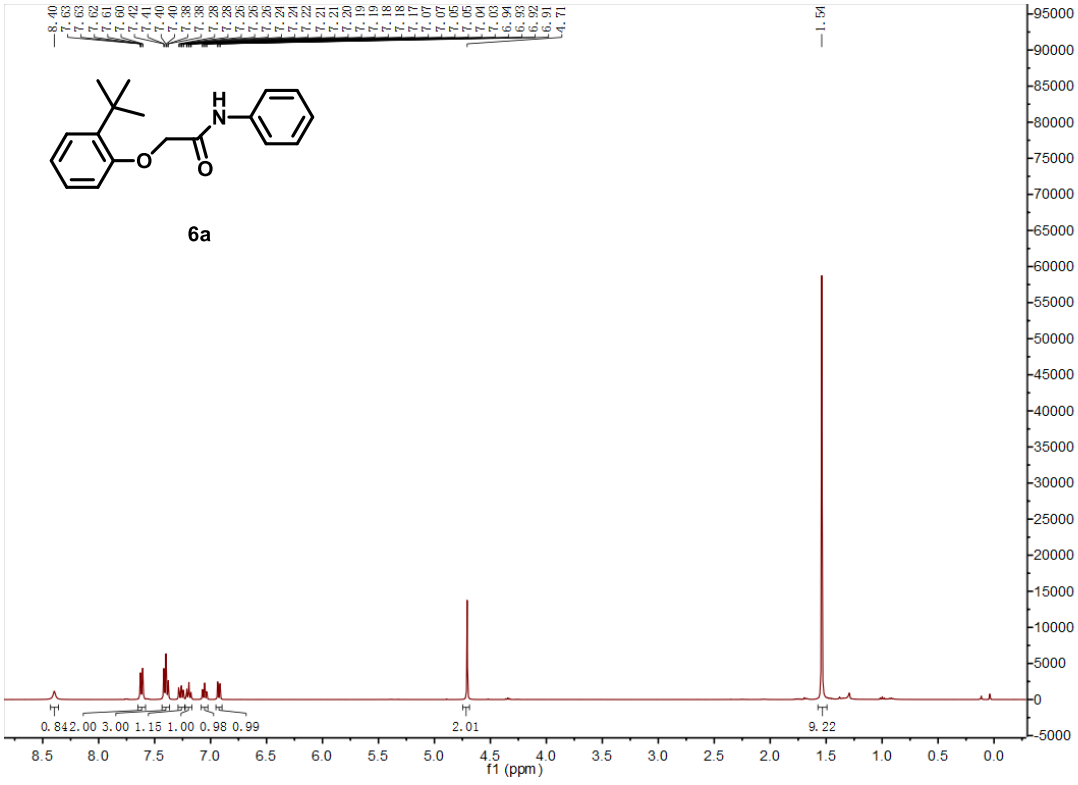
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7.05
7.05
7.04
7.03
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6.92
6.91
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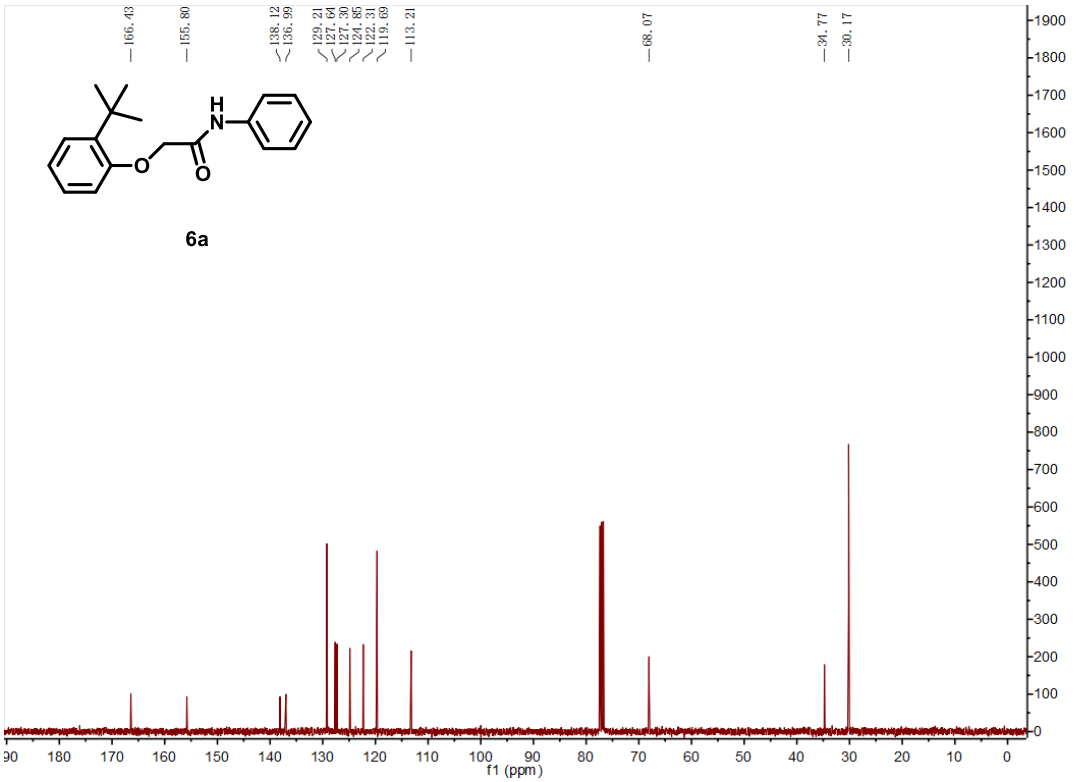
f1 (ppm)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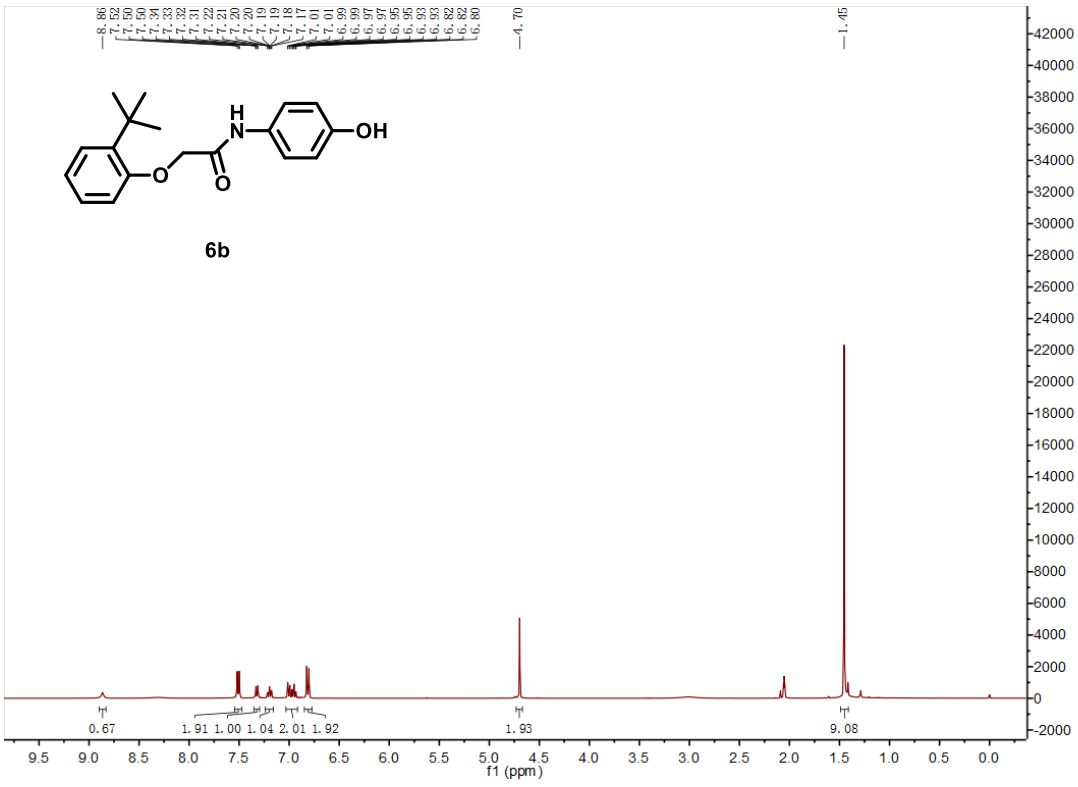
6a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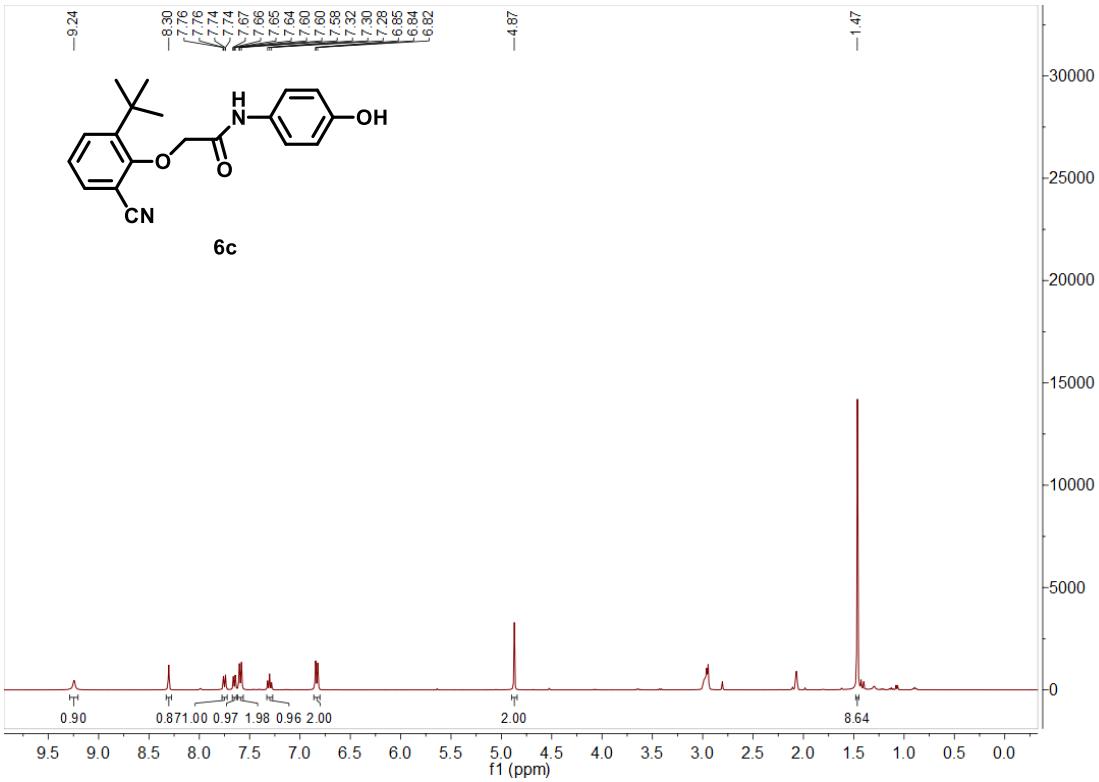
6b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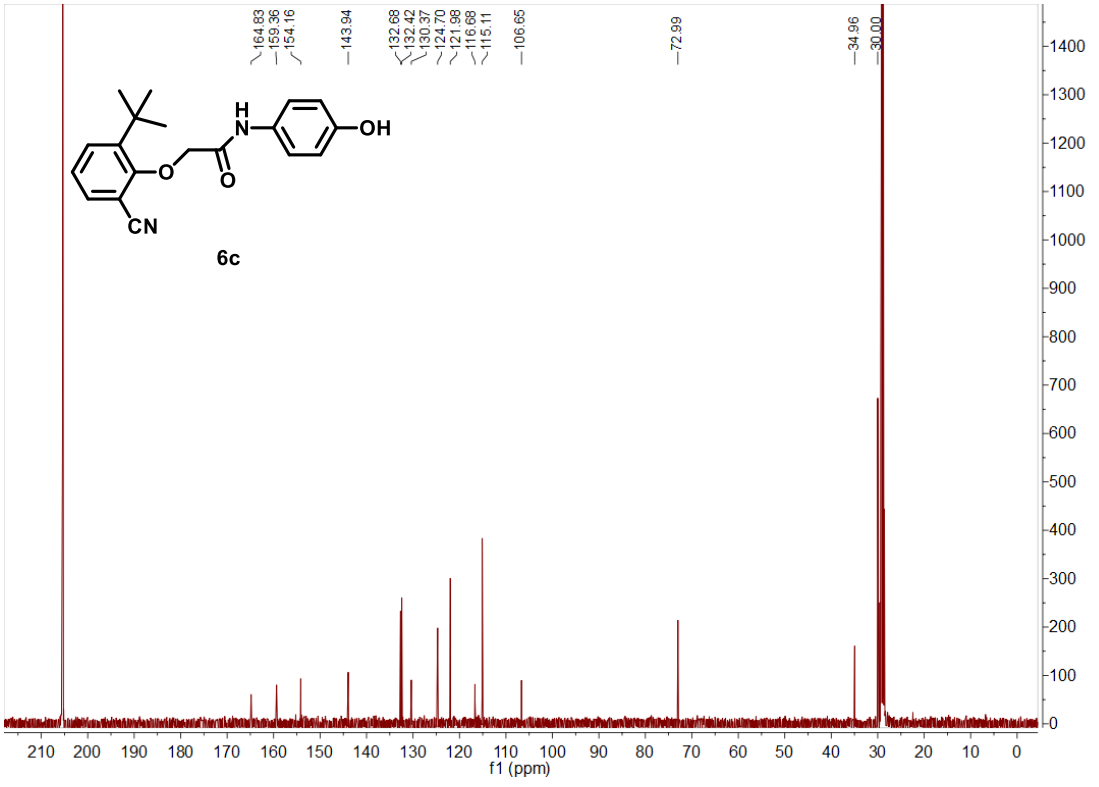
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1300
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1100
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f1 (ppm)