Organocatalytic Diastereoselective [3+2] Cyclization of MBH Carbonates with Dinucleophiles: Synthesis of Bicyclic Imidazoline Derivatives that Inhibit MDM2-p53 Interaction

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Supplementary Information

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1. General Information

General Procedures

- All reactions were performed in oven-dried or flame-dried reaction vessels, modified Schlenk flasks, or round-bottom flasks. The flasks were fitted with Teflon screw caps and reactions were conducted under an atmosphere of argon if needed. Gas-tight syringes with stainless steel needles were used to transfer air- and moisture-sensitive liquids. All moisture and/or air sensitive solid compounds were manipulated inside normal desiccators. Flash column chromatography was performed using silica gel (40–63 μm, 230–400 mesh).
- Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum plates (Merck) containing a 254 nm fluorescent indicator. TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and I_2.
- Organic solutions were concentrated at 30-50 °C on rotary evaporators at ~10 torr followed by drying on vacuum pump at ~1 torr. Reaction temperatures are reported as the temperature of the bath surrounding the vessel unless otherwise stated.

Materials

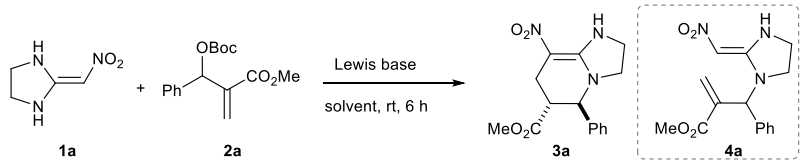
- Commercial reagents and solvents were were purchased from Adamas-beta, Aldrich Chemical Co., Alfa Aesar, Macklin and Energy Chemical and used as received with the following exceptions: THF, Et_2O and toluene were purified by refluxing over Na-benzophenone under positive argon pressure followed by distillation.[1] The HKA **1**[2] and MBH carbonates **2**[3] were prepared according to literature procedure.

Instrumentation

- Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with JEOL-600M. Proton chemical shifts are reported in parts per million (δ scale), and are referenced using residual protium in the NMR solvent ($CDCl_3$: δ 7.26 ($CHCl_3$)). Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant(s) (Hz), integration].
- Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with JEOL 150 MHz spectrometers. Carbon chemical shifts are reported in parts per million (δ scale), and are referenced using the carbon resonances of the solvent (δ 77.0 ($CHCl_3$)). Data are reported as follows: chemical shift [multiplicity (if not singlet), assignment (C_q = fully substituted carbon)].
- High resolution mass spectra (HRMS) were recorded on a Waters SYNAPT G2 using an electrospray (ESI) ionization source.
- Melting points were recorded on WRX-X-4A melting point apparatus.

2. Optimization of the annulation of HKA 1 with MBH carbonate 2a

Table S1. Optimization of the reaction of **1** with **2a**[a]



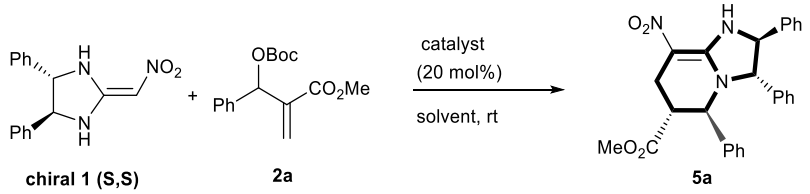
entry	catalyst	solvent	yield of **3a**/**4** (%)[b]	dr of **3a**[c]
1	DABCO	DCM	40/53	14:1
2	DABCO	toluene	<5/12	/
3	DABCO	MeCN	63/<5	12:1
4	DABCO	THF	<5/36	/
5	DMAP	MeCN	<5/<5	
6	PPh_3	MeCN	<5/<5	
7[d]	**DABCO**	**DCM**	**89/<5**	**14:1**
8[e]	DABCO	DCM	36/49	13:1
9[f]	DABCO	DCM	mess	/
10[g]	DABCO	DCM	mess	/

[a] Unless noted otherwise, the reactions were carried out with **1a** (0.12 mmol), **2a** (0.1 mmol) and Lewis base (20 mol %) in solvent (1 mL) at room temperature for 6 h. [b] Isolated yield. [c] *d.r.* was determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] K_2CO_3(1 equiv.) was added. [e] DIPEA (1 equiv.) was added. [f] DBU (1 equiv.) was added. [g] TMG (1 equiv.) was added.

Initially, heterocyclic ketene aminal (HKA) **1a** and the readily available Morita-Baylis-Hillman (MBH) carbonate **2a** were chosen as model substrates to investigate the feasibility of desired [3+3] cyclization conditions that should deliver **3a** as the target product. As shown in Table **S1**, solvents were screened in the presence of DABCO as a Lewis base catalyst, (entries 1–4) and DCM was found able to afford the desired adduct **3a**, along with an unclosed intermediate **4** in 53% yield (entry 1). This intermediate was not detected when MeCN as the solvent, but afford moderate yield (entry 3). Then, we screened other Lewis base catalysts, such as DMAP and PPh_3; however, no desired products were observed (entries 5 and 6). To improve the yield of this reaction, we envisioned that the intermediate **4** in the reaction in DCM might convert to the desired product **3** by the addition of a Brønsted base. Fortunately, after screening several Brønsted bases in DCM, we found K_2CO_3 could promote the cyclization to deliver **3a** in excellent yield without the observation of **4** (entries 7–10).

3. Optimization of the Asymmetric cycloaddition of HKA chiral 1 with 2a

Table S2. Optimization of the reaction of **1c** with **5a**[a]



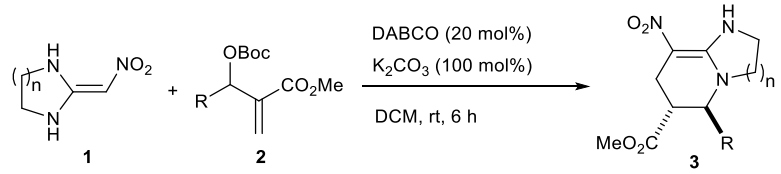
entry	catalyst	solvent	yield (%)[b]	dr[c]
1	DABCO	toluene	52	10:1
2	**DABCO**	**DCM**	**90**	**17:1**
3	DABCO	MeCN	33	13:1
4	DABCO	THF	75	17:1
5	DABCO	DMF	18	/
6	DMAP	DCM	<5	/
7	PPh_3	DCM	<5	/
8[d]	DABCO	DCM	72	16:1
9[e]	DABCO	DCM	33	16:1

[a] Unless noted otherwise, the reactions were carried out with **chiral 1** (0.10 mmol), **2a** (0.12 mmol), catalyst (20 mol %) and in solvent (1.0 mL) at room temperature for 2 h. [b] Isolated yield. [c] Dr was determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] 10 mol % of DABCO was used. [e] at 0 °C.

To prove the feasibility of our proposal, readily available HKA chiral **1** and MBH carbonate **2a** were chosen as substrates. The reaction was conducting in toluene in the presence of 20 mol% DABCO, providing desired chiral bicyclic imidazoline derivative **5a** in 52% yield with 10:1 *d.r.* (entry 1). Different solvents and Lewis bases were screened to improve the yield and diastereoselectivity. As shown in Table **S2**, dichloromethane was the best solvent for this [3+3] cycloaddition, delivering adduct 5a in 90% yield with 17:1 *d.r.*, while other solvents gave inferior results (entry 2-5). Then, we screened other Lewis base catalysts, such as DMAP and PPh_3; however, no desired products were observed (entries 6 and 7). Reducing the catalyst loading or lowering the reaction temperature had negative effects on the yields (entries 8 and 9). Thus, the optimal conditions were identified as 20 mol% DABCO in CH_2Cl_2 at room temperature.

4. General Procedure for the Preparation of the products 3 and 5

*General procedure A for the synthesis of products **3***

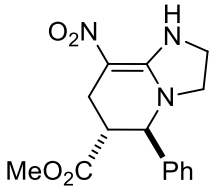


A glass tube was charged with heterocyclic ketene aminal **1** (0.1 mmol), MBH carbonate **2** (0.12 mmol), DABCO (0.02 mmol) and K_2CO_3 (0.1 mmol) in DCM (1 mL). The mixture was stirred at room temperature for 6 hour. Then the mixture was directly purified by column chromatography on silica gel (DCM/ethyl acetate = 10/1 to 3/1) to afford the corresponding product **3**.

*General procedure B for the asymmetric synthesis of products **5***

A glass tube was charged with chiral heterocyclic ketene aminal **chiral 1**(*S, S*) (0.1 mmol), MBH carbonate **2** (0.12 mmol) and DABCO (0.02 mmol) in DCM (1 mL). The mixture was stirred at room temperature for 2 hour. Then the mixture was directly purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to 2/1) to afford the corresponding product **5**.

<u>methyl 8-nitro-5-phenyl-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-6-carboxylate 3a</u>



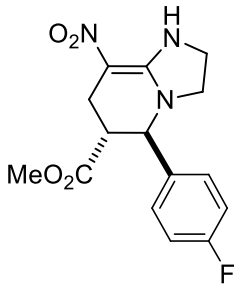
Prepared according to the general procedure A to afford **3a** (26.3 mg) in 87% yield as white solid. The diastereomeric ratio was determined to be 14:1 by crude ^{1}H NMR analysis; the relative configuration was determined by NOEDS analysis; m.p. 183 – 188 ^{o}C.

NMR and HRMS data for the product **3a**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.69 (brs, 1H), 7.41 – 7.34 (m, 3H), 7.19 (d, *J* = 7.2 Hz, 2H), 4.74 (d, *J* = 4.8 Hz, 1H), 3.86 – 3.75 (m, 2H), 3.65 (s, 3H), 3.61 – 3.54 (m, 2H), 3.25 (dd, *J* = 15.6 Hz, *J* = 5.4 Hz, 1H), 3.01 (dd, *J* = 16.8 Hz, *J* = 5.4 Hz, 1H), 2.83 (dd, *J* = 15.6 Hz, *J* = 5.4 Hz, 1H).

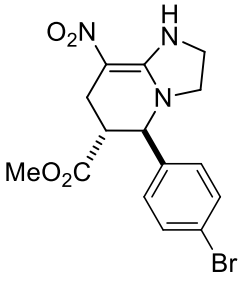
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.2, 157.0, 137.2, 129.2, 128.7, 126.5, 102.1, 59.2, 52.5, 48.2, 45.4, 42.3, 22.5.
HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{15}H_{17}N_3O_4Na^+$: 326.1111, found: 326.1115.

methyl 5-(4-fluorophenyl)-8-nitro-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-6-carboxylate 3b



Prepared according to the general procedure A to afford **3b** (23.4 mg) in 73% yield as white solid. The diastereomeric ratio was determined to be 10:1 by crude ^{1}H NMR analysis; m.p. 192 – 194 °C.
NMR and HRMS data for the product **3b**:
^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.68 (brs, 1H), 7.20 – 7.18 (m, 2H), 7.11 – 7.07 (m, 2H), 4.70 (d, *J* = 5.4 Hz, 1H), 3.86 – 3.81 (m, 1H), 3.77 (dd, *J* = 19.8 Hz, *J* = 9.6 Hz, 1H), 3.64 (s, 3H), 3.56 – 3.50 (m, 2H), 3.21 (dd, *J* = 15.6 Hz, *J* = 6.0 Hz, 1H), 2.98 (dd, *J* = 11.4 Hz, *J* = 5.4 Hz, 1H), 2.87 (dd, *J* = 15.6 Hz, *J* = 6.0 Hz, 1H).
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.1, 162.7 (d, J_{C-F} = 246.9 Hz), 156.9, 133.0, 128.4 (d, J_{C-F} = 7.2 Hz), 116.2 (d, J_{C-F} = 21.6 Hz), 102.0, 58.8, 52.5, 48.2, 45.6, 42.3, 22.8.
HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{15}H_{16}FN_3O_4Na^+$: 344.1017, found: 344.1014.

methyl 5-(4-bromophenyl)-8-nitro-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-6-carboxylate 3c



Prepared according to the general procedure A to afford **3c** (29.0 mg) in 76% yield as white solid. The diastereomeric ratio was determined to be 12:1 by crude ^{1}H NMR analysis; m.p. 105

– 109 °C.

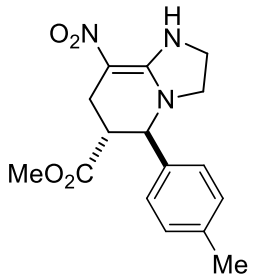
NMR and HRMS data for the product **3c**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.68 (brs, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.69 (d, *J* = 4.8 Hz, 1H), 3.86 – 3.82 (m, 1H), 3.78 (dd, *J* = 19.8 Hz, *J* = 9.6 Hz, 1H), 3.65 (s, 3H), 3.57 – 3.50 (m, 2H), 3.22 (dd, *J* = 16.2 Hz, *J* = 6.0 Hz, 1H), 2.98 (dd, *J* = 17.4 Hz, *J* = 5.4 Hz, 1H), 2.84 (dd, *J* = 16.2 Hz, *J* = 6.0 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.0, 156.8, 136.3, 132.3, 128.3, 122.7, 101.9, 58.8, 52.5, 48.2, 45.3, 42.3, 22.7.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{15}H_{16}{}^{79}BrN_3O_4Na^+$: 404.0222, found: 404.0218; calculated for $C_{15}H_{16}{}^{81}BrN_3O_4Na^+$: 406.0201, found: 406.0199.

<u>methyl 8-nitro-5-(p-tolyl)-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-6-carboxylate 3d</u>



Prepared according to the general procedure A to afford **3d** (28.2 mg) in 89% yield as white solid. The diastereomeric ratio was determined to be 4:1 by crude ^{1}H NMR analysis; m.p. 93 – 98 °C.

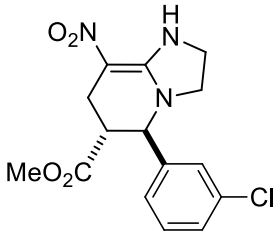
NMR and HRMS data for the product **3d**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.70 (brs, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 4.69 (d, *J* = 4.8 Hz, 1H), 3.82 – 3.72 (m, 2H), 3.65 (s, 3H), 3.57 – 3.53 (m, 2H), 3.24 (dd, *J* = 16.2 Hz, *J* = 5.4 Hz, 1H), 2.98 (dd, *J* = 10.8 Hz, *J* = 5.4 Hz, 1H), 2.85 (dd, *J* = 16.2 Hz, *J* = 5.4 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.3, 157.0, 138.7, 134.1, 129.9, 126.5, 102.1, 59.0, 52.5, 48.2, 45.5, 42.3, 22.6, 21.1.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{16}H_{19}N_3O_4Na^+$: 340.1268, found: 340.1270.

<u>methyl 5-(3-chlorophenyl)-8-nitro-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-6-carboxylate 3e</u>



Prepared according to the general procedure A to afford **3e** (32.0 mg) in 95% yield as white solid. The diastereomeric ratio was determined to be 14:1 by crude ^{1}H NMR analysis; m.p. 164 – 167 ºC.

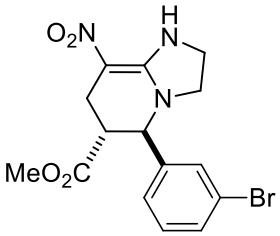
NMR and HRMS data for the product **3e**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.68 (brs, 1H), 7.35 – 7.34 (m, 2H), 7.19 (s, 1H), 7.10 – 7.08 (m, 1H), 4.73 (d, *J* = 4.2 Hz, 1H), 3.87 – 3.78 (m, 2H), 3.67 (s, 3H), 3.62 – 3.56 (m, 2H), 3.28 (dd, *J* = 16.2 Hz, *J* = 5.4 Hz, 1H), 2.98 (dd, *J* = 10.8 Hz, *J* = 5.4 Hz, 1H), 2.84 (dd, *J* = 16.2 Hz, *J* = 5.4 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.0, 156.7, 139.5, 135.2, 130.5, 129.0, 126.7, 124.7, 101.8, 58.8, 52.6, 48.3, 45.2, 42.3, 22.3.

HRMS (ESI-TOF) m/z: **[M + Na]$^{+}$** calculated for $C_{15}H_{16}{}^{35}ClN_3O_4Na^{+}$: 360.0722, found: 360.0724; calculated for $C_{15}H_{16}{}^{37}ClN_3O_4Na^{+}$: 362.0698, found: 362.0693.

<u>methyl 5-(3-bromophenyl)-8-nitro-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-6-carboxylate 3f</u>



Prepared according to the general procedure A to afford **3f** (30.9 mg) in 81% yield as white solid. The diastereomeric ratio was determined to be 8:1 by crude ^{1}H NMR analysis; m.p. 113 – 117 ºC.

NMR and HRMS data for the product **3f**:

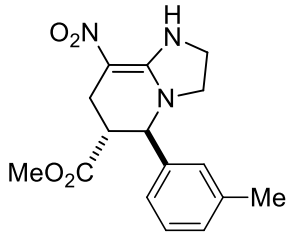
^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.68 (brs, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.34 (s, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 4.72 (d, *J* = 4.2 Hz, 1H), 3.88 – 3.78 (m, 2H), 3.67 (s, 3H), 3.62 – 3.55 (m, 2H), 3.28 (dd, *J* = 16.2 Hz, *J* = 5.4 Hz, 1H), 2.99 (dd, *J* = 10.2 Hz, *J* = 5.4 Hz, 1H), 2.81 (dd, *J* = 16.2 Hz, *J* = 5.4 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.0, 156.8, 139.8, 131.9, 130.8, 129.6, 125.1, 123.3, 101.9, 58.8, 52.6, 48.4, 45.3, 42.4, 22.4.

HRMS (ESI-TOF) m/z: **[M + Na]$^{+}$** calculated for $C_{15}H_{16}{}^{79}BrN_3O_4Na^{+}$: 404.0222, found:

404.0218; calculated for $C_{15}H_{16}{}^{81}BrN_3O_4Na^+$: 406.0201, found: 406.0195.

methyl 8-nitro-5-(m-tolyl)-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-6-carboxylate 3g



Prepared according to the general procedure A to afford **3g** (24.4 mg) in 77% yield as white solid. The diastereomeric ratio was determined to be 4:1 by crude ^{1}H NMR analysis; m.p. 94 – 98 °C.

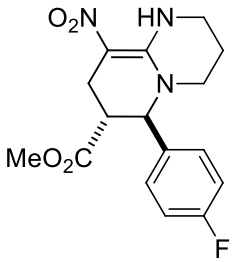
NMR and HRMS data for the product **3g**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.68 (brs, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.98 (s, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 4.72 (d, *J* = 4.8 Hz, 1H), 3.84 – 3.76 (m, 2H), 3.66 (s, 3H), 3.60 – 3.57 (m, 2H), 3.27 (dd, *J* = 16.2 Hz, *J* = 5.4 Hz, 1H), 3.00 (dd, *J* = 10.2 Hz, *J* = 5.4 Hz, 1H), 2.82 (dd, *J* = 15.6 Hz, *J* = 5.4 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.3, 156.9, 139.0, 137.2, 129.4, 129.0, 127.0, 123.5, 102.0, 59.1, 52.4, 48.2, 45.3, 42.3, 22.4, 21.4.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{16}H_{19}N_3O_4Na^+$: 340.1268, found: 340.1269.

methyl 6-(4-fluorophenyl)-9-nitro-2,3,4,6,7,8-hexahydro-1H-pyrido[1,2-a]pyrimidine-7-carboxylate 3h



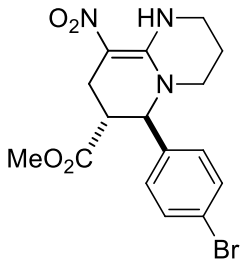
Prepared according to the general procedure A to afford **3h** (25.0 mg) in 79% yield as white solid. The diastereomeric ratio was determined to be 13:1 by crude ^{1}H NMR analysis; m.p. 169 – 172 °C.

NMR and HRMS data for the product **3h**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 11.79 (brs, 1H), 7.16 – 7.07 (m, 4H), 4.84 – 4.82 (m, 1H), 3.73 (s, 3H), 3.56 – 3.47 (m, 4H), 3.32 – 3.28 (m, 1H), 2.92 – 2.90 (m, 1H), 2.59 (dd, *J* = 16.8 Hz, *J* = 6.0 Hz, 1H), 2.10 – 2.06 (m, 1H), 2.00 – 1.95 (m, 1H).

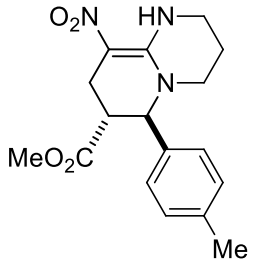
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.3, 162.6 (d, J_{C-F} = 247.1 Hz), 152.8, 133.3, 127.7 (d, J_{C-F} = 8.7 Hz), 116.3 (d, J_{C-F} = 21.6 Hz), 103.6, 63.1, 52.7, 47.0, 43.1, 38.3, 21.8, 20.1.
HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{16}H_{18}FN_3O_4Na^+$: 358.1174, found: 358.1174.

methyl 6-(4-bromophenyl)-9-nitro-2,3,4,6,7,8-hexahydro-1H-pyrido[1,2-a]pyrimidine-7-carboxylate 3i



Prepared according to the general procedure A to afford **3i** (32.8 mg) in 83% yield as white solid. The diastereomeric ratio was determined to be 9:1 by crude ^{1}H NMR analysis; m.p. 105 – 108 °C.
NMR and HRMS data for the product **3i**:
^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 11.77 (brs, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.04 (d, *J* = 9.6 Hz, 2H), 4.82 – 4.81 (m, 1H), 3.74 (s, 3H), 3.57 – 3.47 (m, 4H), 3.31 – 3.24 (m, 1H), 2.93 – 2.90 (m, 1H), 2.57 (dd, *J* = 16.8 Hz, *J* = 6.0 Hz, 1H), 2.10 – 2.06 (m, 1H), 2.00 – 1.96 (m, 1H).
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm):172.2, 152.7, 136.6, 132.4, 127.7, 122.5, 103.6, 63.2, 52.7, 47.1, 42.9, 38.3, 21.8, 20.1.
HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{16}H_{18}{}^{79}BrN_3O_4Na^+$: 418.0373, found: 418.0373; calculated for $C_{16}H_{18}{}^{81}BrN_3O_4Na^+$: 420.0358, found: 420.0356.

methyl 8-nitro-5-(p-tolyl)-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-6-carboxylate 3j



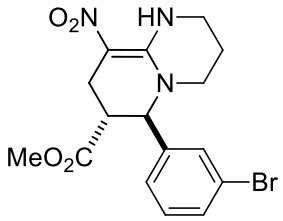
Prepared according to the general procedure A to afford **3j** (28.5 mg) in 86% yield as white solid. The diastereomeric ratio was determined to be 3:1 by crude ^{1}H NMR analysis; m.p. 98 – 102 °C.
NMR and HRMS data for the product **3j**:
^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 11.80 (brs, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 4.80 (brs, 1H), 3.72 (s, 3H), 3.56 – 3.45 (m, 4H), 3.38 – 3.28 (m, 2H), 2.93 – 2.90

(m, 1H), 2.60 (dd, *J* = 16.2 Hz, *J* = 5.4 Hz, 1H), 2.35 (s, 3H), 2.08 – 2.05 (m, 1H), 1.99 – 1.92 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.5, 152.8, 138.4, 134.4, 129.9, 125.8, 103.9, 63.5, 52.5, 47.0, 43.2, 38.3, 21.9, 21.0, 20.0.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{17}H_{21}N_3O_4Na^+$: 354.1424, found: 354.1423.

methyl 6-(3-bromophenyl)-9-nitro-2,3,4,6,7,8-hexahydro-1H-pyrido[1,2-a]pyrimidine-7-carboxylate 3k



Prepared according to the general procedure A to afford **3k** (29.2 mg) in 74% yield as white solid. The diastereomeric ratio was determined to be 12:1 by crude ^{1}H NMR analysis; m.p. 83 – 87 °C.

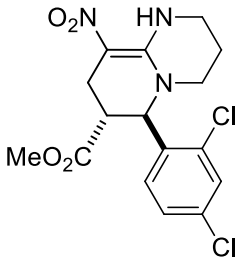
NMR and HRMS data for the product **3k**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 11.79 (brs, 1H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.29 – 7.28 (m, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 4.82 – 4.81 (m, 1H), 3.74 (s, 3H), 3.59 – 3.48 (m, 4H), 3.33 – 3.29 (m, 1H), 2.96 – 2.94 (m, 1H), 2.57 (dd, *J* = 17.4 Hz, *J* = 6.0 Hz, 1H), 2.11 – 2.07 (m, 1H), 2.03 – 1.98 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm):172.2, 152.7, 140.0, 131.8, 130.9, 129.1, 124.4, 126.4, 103.5, 63.2, 52.7, 47.2, 43.0, 38.3, 21.8, 20.1.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{16}H_{18}{}^{79}BrN_3O_4Na^+$: 418.0373, found: 418.0374; calculated for $C_{16}H_{18}{}^{81}BrN_3O_4Na^+$: 420.0358, found: 420.0363.

methyl 6-(2,4-dichlorophenyl)-9-nitro-2,3,4,6,7,8-hexahydro-1H-pyrido[1,2-a]pyrimidine-7-carboxylate 3l



Prepared according to the general procedure A to afford **3l** (26.9 mg) in 70% yield as white solid. The diastereomeric ratio was determined to be 9:1 by crude ^{1}H NMR analysis; m.p. 217

– 219 °C.

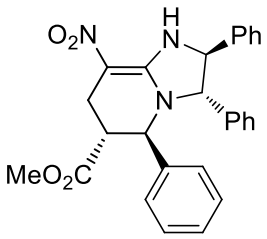
NMR and HRMS data for the product **3l**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 11.78 (brs, 1H), 7.47 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 5.19 – 5.18 (m, 1H), 3.76 (s, 3H), 3.59 – 3.49 (m, 4H), 3.27 – 3.22 (m, 1H), 3.07 – 3.05 (m, 1H), 2.46 (dd, *J* = 17.4 Hz, *J* = 6.0 Hz, 1H), 2.12 – 2.08 (m, 1H), 2.00 – 1.94 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.0, 153.0, 135.2, 133.3, 133.0, 130.4, 127.9, 127.9, 103.2, 60.8, 52.8, 47.3, 39.9, 38.3, 21.8, 20.1.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{16}H_{17}Cl_2N_3O_4Na^+$: 408.0488, found: 408.0490.

(2*S*,3*S*,5*R*,6*R*)-methyl 8-nitro-2,3,5-triphenyl-1,2,3,5,6,7-hexahydroimidazo[1,2-a] pyridine-6-carboxylate 5a



Prepared according to the general procedure B to afford **5a** (40.9 mg) in 90% yield as white solid. The diastereomeric ratio was determined to be 17:1 by crude ^{1}H NMR analysis; m.p. 96 – 100 °C.

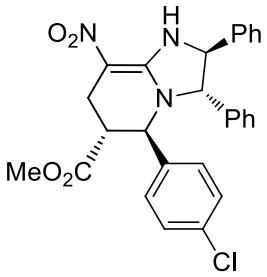
NMR and HRMS data for the product **5a**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.12 (brs, 1H), 7.44 – 7.38 (m, 3H), 7.36 – 7.31 (m, 6H), 7.22 – 7.19 (m, 2H), 7.11 (d, *J* = 6.6 Hz, 2H), 7.02 – 7.01 (m, 2H), 4.97 (d, *J* = 9.0 Hz, 1H), 4.56 (d, *J* = 3.6 Hz, 1H), 4.41 (d, *J* = 9.0 Hz, 1H), 3.69 (s, 3H), 3.41 (dd, *J* = 16.2 Hz, *J* = 3.6 Hz, 1H), 2.98 – 2.96 (m, 1H), 2.82 (dd, *J* = 16.8 Hz, *J* = 6.0 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm):171.7, 156.1, 137.9, 136.6, 135.5, 129.6, 129.5, 129.3, 129.2, 129.1, 128.9, 128.7, 127.9, 126.5, 126.3, 102.2, 71.9, 67.8, 56.4, 52.4, 44.6, 21.1.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{27}H_{25}N_3O_4Na^+$: 478.1737, found: 478.1733.

(2*S*,3*S*,5*R*,6*R*)-methyl 5-(4-chlorophenyl)-8-nitro-2,3-diphenyl-1,2,3,5,6,7-hexahydro-imidazo[1,2-a]pyridine-6-carboxylate 5b



Prepared according to the general procedure B to afford **5b** (45.0 mg) in 92% yield as white solid. The diastereomeric ratio was determined to be 16:1 by crude ^{1}H NMR analysis; m.p. 205 – 210 ºC.

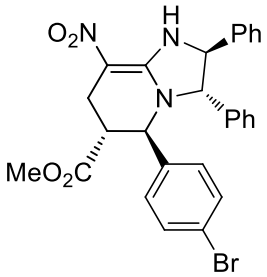
NMR and HRMS data for the product **5b**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.10 (brs, 1H), 7.43 – 7.39 (m, 3H), 7.37 – 7.35 (m, 3H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.20 – 7.18 (m, 2H), 7.10 (d, *J* = 6.0 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 4.96 (d, *J* = 8.4 Hz, 1H), 4.53 (d, *J* = 3.6 Hz, 1H), 4.34 (d, *J* = 7.2 Hz, 1H), 3.68 (s, 3H), 3.39 (dd, *J* = 16.2 Hz, *J* = 3.6 Hz, 1H), 2.96 – 2.93 (m, 1H), 2.84 (dd, *J* = 16.8 Hz, *J* = 6.0 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.5, 155.9, 137.8, 135.3, 135.1, 134.7, 129.6, 129.5, 129.2, 129.2, 129.0, 128.0, 127.8, 126.2, 102.0, 71.8, 67.7, 56.0, 52.5, 44.6, 21.3.

HRMS (ESI-TOF) m/z: **[M + Na]$^{+}$** calculated for $C_{27}H_{24}{}^{35}ClN_3O_4Na^{+}$: 512.1348, found: 512.1349; calculated for $C_{27}H_{24}{}^{37}ClN_3O_4Na^{+}$: 514.1324, found: 514.1320.

(2*S*,3*S*,5*R*,6*R*)-methyl 5-(4-bromophenyl)-8-nitro-2,3-diphenyl-1,2,3,5,6,7-hexahydro-imidazo[1,2-a]pyridine-6-carboxylate 5c



Prepared according to the general procedure B to afford **5c** (50.1 mg) in 94% yield as white solid. The diastereomeric ratio was determined to be >19:1 by crude ^{1}H NMR analysis; m.p. 105 – 110 ºC.

NMR and HRMS data for the product **5c**:

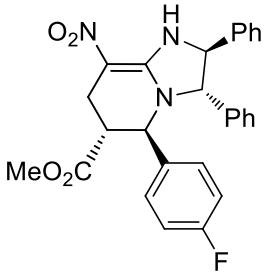
^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.10 (brs, 1H), 7.47 – 7.38 (m, 5H), 7.36 – 7.32 (m, 3H), 7.20 – 7.18 (m, 2H), 7.10 (d, *J* = 6.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 4.96 (d, *J* = 8.4 Hz, 1H),

4.51 (d, *J* = 3.6 Hz, 1H), 4.34 (d, *J* = 8.4 Hz, 1H), 3.68 (s, 3H), 3.39 (dd, *J* = 16.2 Hz, *J* = 3.6 Hz, 1H), 2.96 – 2.93 (m, 1H), 2.84 (dd, *J* = 16.8 Hz, *J* = 5.4 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.5, 155.9, 137.8, 135.7, 135.3, 132.4, 129.6, 129.3, 129.2, 129.0, 128.3, 127.8, 126.2, 122.8, 102.0, 71.8, 67.7, 56.0, 52.5, 44.6, 21.3.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{27}H_{24}{}^{79}BrN_3O_4Na^+$: 556.0842, found: 556.0844; calculated for $C_{27}H_{24}{}^{81}BrN_3O_4Na^+$: 558.0827, found: 558.0825.

(2*S*,3*S*,5*R*,6*R*)-methyl 5-(4-fluorophenyl)-8-nitro-2,3-diphenyl-1,2,3,5,6,7-hexahydro imidazo[1,2-a]pyridine-6-carboxylate 5d



Prepared according to the general procedure B to afford **5d** (41.1 mg) in 87% yield as white solid. The diastereomeric ratio was determined to be 15:1 by crude ^{1}H NMR analysis; m.p. 236 – 239 °C.

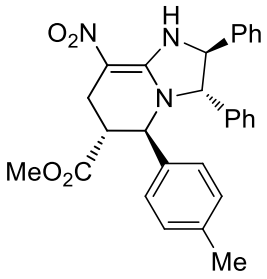
NMR and HRMS data for the product **5d**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.10 (brs, 1H), 7.46 – 7.35 (m, 6H), 7.20 – 7.19 (m, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.05 – 6.97 (m, 4H), 4.96 (d, *J* = 7.8 Hz, 1H), 4.53 (d, *J* = 3.0 Hz, 1H), 4.34 (d, *J* = 8.4 Hz, 1H), 3.68 (s, 3H), 3.38 (dd, *J* = 16.2 Hz, *J* = 3.0 Hz, 1H), 2.96 – 2.85 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.6, 156.0, 137.9, 135.4, 132.3, 129.6, 129.2, 129.2, 129.0, 128.4, 128.4, 127.8, 126.2, 116.3 ($J_{C\text{-}F}$ = 21.6 Hz), 102.0, 71.8, 67.7, 56.0, 52.4, 44.8, 21.4.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{27}H_{24}FN_3O_4Na^+$: 496.1643, found: 496.1644.

(2*S*,3*S*,5*R*,6*R*)-methyl 8-nitro-2,3-diphenyl-5-(p-tolyl)-1,2,3,5,6,7-hexahydroimidazo [1,2-a]pyridine-6-carboxylate 5e



Prepared according to the general procedure B to afford **5e** (38.0 mg) in 81% yield as white solid. The diastereomeric ratio was determined to be 16:1 by crude ^{1}H NMR analysis; m.p. 215 – 218 °C.

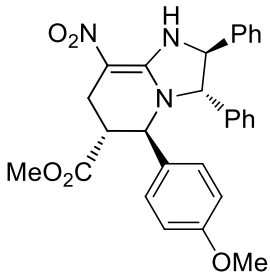
NMR and HRMS data for the product **5e**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.12 (brs, 1H), 7.42 – 7.35 (m, 6H), 7.21 – 7.19 (m, 2H), 7.14 – 7.10 (m, 4H), 6.90 (d, *J* = 7.2 Hz, 2H), 4.95 (d, *J* = 9.0 Hz, 1H), 4.52 (d, *J* = 3.6 Hz, 1H), 4.40 (d, *J* = 9.0 Hz, 1H), 3.68 (s, 3H), 3.39 (dd, *J* = 16.2 Hz, *J* = 3.6 Hz, 1H), 2.96 – 2.93 (m, 1H), 2.83 (dd, *J* = 16.2 Hz, *J* = 6.0 Hz, 1H), 2.32 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.8, 156.1, 138.5, 138.0, 135.6, 133.5, 129.9, 129.4, 129.1, 129.1, 128.9, 127.8, 126.4, 126.3, 102.2, 71.8, 67.7, 56.2, 52.3, 44.7, 21.1, 21.0.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{28}H_{27}N_3O_4Na^+$: 492.1894, found: 492.1899.

(2*S*,3*S*,5*R*,6*R*)-methyl 5-(4-methoxyphenyl)-8-nitro-2,3-diphenyl-1,2,3,5,6,7-hexahydro imidazo[1,2-a]pyridine-6-carboxylate 5f



Prepared according to the general procedure B to afford **5f** (41.2 mg) in 85% yield as white solid. The diastereomeric ratio was determined to be 12:1 by crude ^{1}H NMR analysis; m.p. 100 – 104 °C.

NMR and HRMS data for the product **5f**:

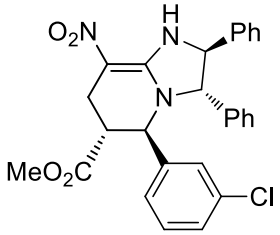
^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.11 (brs, 1H), 7.43 – 7.33 (m, 6H), 7.20 – 7.19 (m, 2H), 7.11 – 7.09 (m, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 4.94 (d, *J* = 8.4 Hz, 1H),

4.49 (d, *J* = 3.6 Hz, 1H), 4.38 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.38 (dd, *J* = 16.2 Hz, *J* = 3.6 Hz, 1H), 2.96 – 2.93 (m, 1H), 2.89 (dd, *J* = 16.2 Hz, *J* = 6.0 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.8, 159.7, 156.1, 138.0, 135.7, 129.4, 129.2, 129.1, 128.9, 128.3, 127.8, 127.8, 126.3, 114.6, 102.2, 71.8, 67.7, 56.1, 55.3, 52.3, 44.9, 21.5.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{28}H_{27}N_3O_5Na^+$: 508.1843, found: 508.1846.

(2*S*,3*S*,5*R*,6*R*)-methyl 5-(3-chlorophenyl)-8-nitro-2,3-diphenyl-1,2,3,5,6,7-hexahydro-imidazo[1,2-a]pyridine-6-carboxylate 5g



Prepared according to the general procedure B to afford **5g** (40.0 mg) in 90% yield as white solid. The diastereomeric ratio was determined to be 17:1 by crude ^{1}H NMR analysis; m.p. 115 – 120 °C.

Notably, according to the same reaction condition, a 2.5mmol-scale reaction has been performed, which afford **5g** (1.05 grams) in 86% yield as white solid.

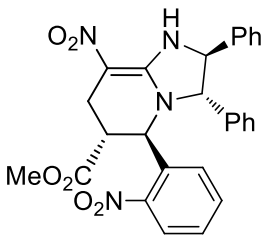
NMR and HRMS data for the product **5g**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.11 (brs, 1H), 7.47 – 7.35 (m, 7H), 7.27 – 7.26 (m, 1H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 6.6 Hz, 2H), 6.99 (s, 1H), 6.94 – 6.93 (m, 1H), 4.98 (d, *J* = 9.0 Hz, 1H), 4.54 – 4.53 (m, 1H), 4.39 (d, *J* = 8.4 Hz, 1H), 3.69 (s, 3H), 3.42 (d, *J* = 16.2 Hz, 1H), 2.98 – 2.97 (m, 1H), 2.79 (dd, *J* = 16.8 Hz, *J* = 4.8 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.4, 155.9, 138.8, 137.9, 135.4, 135.3, 130.6, 129.6, 129.3, 129.2, 129.0, 128.9, 127.8, 126.7, 126.2, 124.4, 101.9, 71.9, 67.8, 55.9, 52.5, 44.5, 21.0.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{27}H_{24}{}^{35}ClN_3O_4Na^+$: 512.1348, found: 512.1352; calculated for $C_{27}H_{24}{}^{37}ClN_3O_4Na^+$: 514.1324, found: 514.1318.

(2*S*,3*S*,5*R*,6*R*)-methyl 8-nitro-5-(2-nitrophenyl)-2,3-diphenyl-1,2,3,5,6,7-hexahydro imidazo[1,2-a]pyridine-6-carboxylate 5h



Prepared according to the general procedure B to afford **5h** (39.5 mg) in 79% yield as white solid. The diastereomeric ratio was determined to be 13:1 by crude ^{1}H NMR analysis; m.p. 130 – 133 °C.

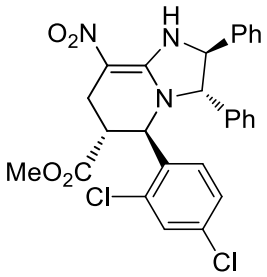
NMR and HRMS data for the product **5h**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.06 (brs, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.44 – 7.32 (m, 7H), 7.20 – 7.18 (m, 2H), 7.12 (d, *J* = 6.6 Hz, 2H), 5.18 – 5.17 (m, 1H), 5.07 (d, *J* = 9.6 Hz, 1H), 4.27 (d, *J* = 10.2 Hz, 1H), 3.74 (s, 3H), 3.62 (d, *J* = 10.8 Hz, 1H), 3.27 – 3.25 (m, 1H), 2.69 (dd, *J* = 16.8 Hz, *J* = 6.0 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.1, 156.0, 148.2, 137.4, 134.0, 133.9, 132.1, 130.0, 129.7, 129.3, 129.1, 129.0, 128.2, 127.7, 126.3, 125.9, 101.7, 72.0, 67.7, 52.6, 51.3, 42.4, 20.4.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{27}H_{24}N_4O_6Na^+$: 523.1588, found: 523.1584.

(2*S*,3*S*,5*R*,6*R*)-methyl 5-(2,4-dichlorophenyl)-8-nitro-2,3-diphenyl-1,2,3,5,6,7-hexahydro imidazo[1,2-a]pyridine-6-carboxylate 5i



Prepared according to the general procedure B to afford **5i** (40.0 mg) in 86% yield as white solid. The diastereomeric ratio was determined to be 17:1 by crude ^{1}H NMR analysis; m.p. 195 – 198 °C.

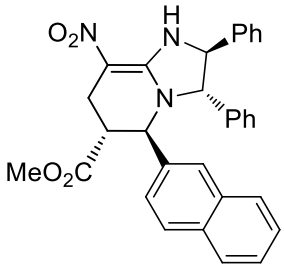
NMR and HRMS data for the product **5i**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.06 (brs, 1H), 7.46 – 7.30 (m, 8H), 7.22 – 7.20 (m, 2H), 7.17 – 7.14 (m, 2H), 7.04 (s, 1H), 5.05 – 4.99 (m, 1H), 5.04 (d, *J* = 9.6 Hz, 1H), 4.36 (d, *J* = 9.6 Hz, 1H), 3.71 (s, 3H), 3.54 – 3.50 (m, 1H), 3.03 – 2.98 (m, 1H), 2.61 – 2.57 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.1, 1 56.0, 137.6, 135.2, 134.6, 133.5, 132.5, 130.6, 129.7, 129.7, 129.3, 129.2, 129.1, 128.1, 127.8, 127.7, 127.6, 126.2, 101.8, 71.9, 67.8, 52.5, 52.4, 41.7, 20.3.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{27}H_{23}Cl_2N_3O_4Na^+$: 546.0958, found: 546.0963.

(2*S*,3*S*,5*R*,6*R*)-methyl 5-(naphthalen-2-yl)-8-nitro-2,3-diphenyl-1,2,3,5,6,7-hexahydro imidazo[1,2-a]pyridine-6-carboxylate 5j



Prepared according to the general procedure B to afford **5j** (42.9 mg) in 85% yield as white solid. The diastereomeric ratio was determined to be 17:1 by crude ^{1}H NMR analysis; m.p. 133 – 138 ºC.

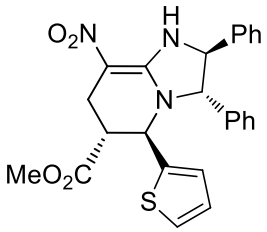
NMR and HRMS data for the product **5j**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.12 (brs, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.45 – 7.34 (m, 7H), 7.28 (d, *J* = 6.6 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 6.6 Hz, 2H), 5.48 – 5.47 (m, 1H), 5.07 (d, *J* = 9.6 Hz, 1H), 4.60 (d, *J* = 9.0 Hz, 1H), 3.78 (s, 3H), 3.48 (d, *J* = 16.2 Hz, 1H), 3.18 – 3.17 (m, 1H), 2.49 (dd, *J* = 16.8 Hz, *J* = 6.0 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.7, 156.6, 137.9, 135.6, 134.2, 131.4, 129.7, 129.6, 129.3, 129.2, 129.1, 129.0, 127.9, 127.1, 126.3, 126.2, 125.1, 122.8, 121.5, 102.0, 71.8, 67.9, 52.5, 42.7, 20.2.

HRMS (ESI-TOF) m/z: **[M + Na]$^+$** calculated for $C_{27}H_{25}N_3O_4Na^+$: 478.1737, found: 478.1733.

(2*S*,3*S*,5*R*,6*R*)-methyl 8-nitro-2,3-diphenyl-5-(thiophen-2-yl)-1,2,3,5,6,7-hexahydro imidazo[1,2-a]pyridine-6-carboxylate 5k



Prepared according to the general procedure B to afford **5k** (35.0 mg) in 76% yield as white solid. The diastereomeric ratio was determined to be 10:1 by crude ^{1}H NMR analysis; m.p. 115 – 117 ºC.

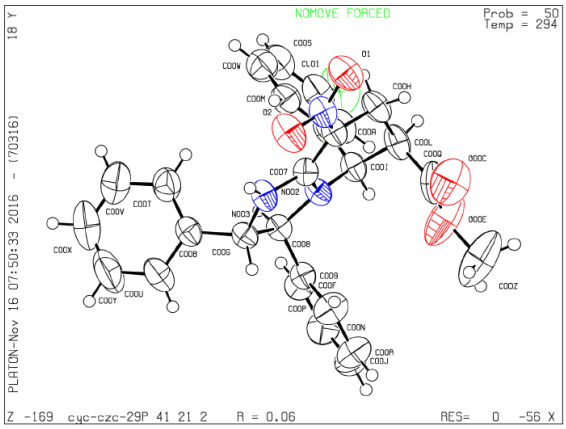
NMR and HRMS data for the product **5k**:

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.06 (brs, 1H), 7.45 – 7.40 (m, 3H), 7.34 – 7.30 (m, 3H), 7.30 (d, *J* = 4.2 Hz, 1H), 7.18 – 7.14 (m, 4H), 6.95 (dd, *J* = 6.0 Hz, *J* = 3.0 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 4.90 – 4.87 (m, 2H), 4.41 (d, *J* = 9.0 Hz, 1H), 3.72 (s, 3H), 3.50 (d, *J* = 16.2 Hz, 1H), 3.09 – 3.02 (m, 2H).

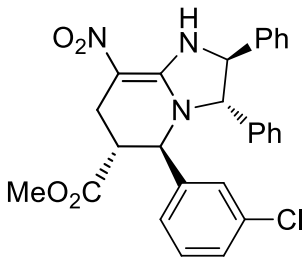
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.4, 155.4, 139.1, 137.6, 135.3, 129.6, 129.5, 129.2, 129.1, 129.0, 129.0, 127.9, 127.0, 126.8, 126.6, 126.5, 126.3, 102.2, 71.8, 67.7, 52.5, 52.5, 44.5, 21.3.

HRMS (ESI-TOF) m/z: **$[M + Na]^+$** calculated for $C_{25}H_{23}N_3O_4SNa^+$: 484.1301, found: 484.1302.

5. Crystal Data and Structure Refinement for the Representative Product 5g



≡



5g ccdc 1920648

Identification code	**5g**
Empirical formula	$C_{27}H_{24}ClN_3O_4$
Formula weight	489.94
Temperature/K	293.9(3)
Crystal system	tetragonal
Space group	$P4_12_12$
a/Å	10.62565(16)
b/Å	10.62565(16)
c/Å	43.3437(17)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	4893.7(2)
Z	8
ρcalcg/cm^3	1.330
μ/mm-1	1.703
F(000)	2048.0
Crystal size/mm^3	0.7 × 0.5 × 0.3
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.16 to 134.156
Index ranges	-12 ≤ h ≤ 10, -12 ≤ k ≤ 6, -50 ≤ l ≤ 51
Reflections collected	11517
Independent reflections	4209 [R_{int}= 0.0351, R_{sigma}= 0.0313]
Data/restraints/parameters	4209/0/317
Goodness-of-fit on F2	1.085
Final R indexes [I>=2σ (I)]	R_1= 0.0647, wR_2= 0.1701
Final R indexes [all data]	R_1 = 0.0682, wR_2= 0.1743
Largest diff. peak/hole / e Å^{-3}	0.40/-0.37
Flack parameter	0.009(12)

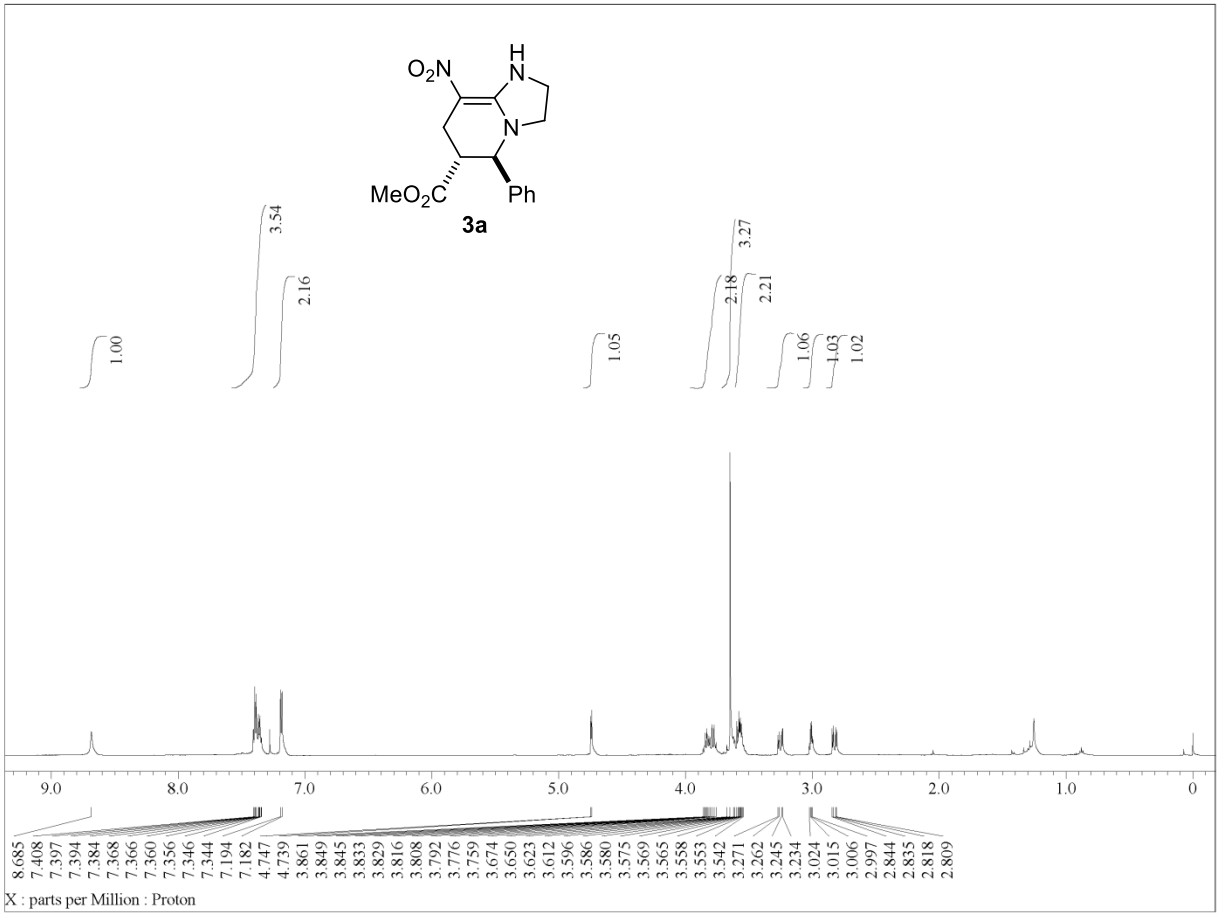
6. References and Notes

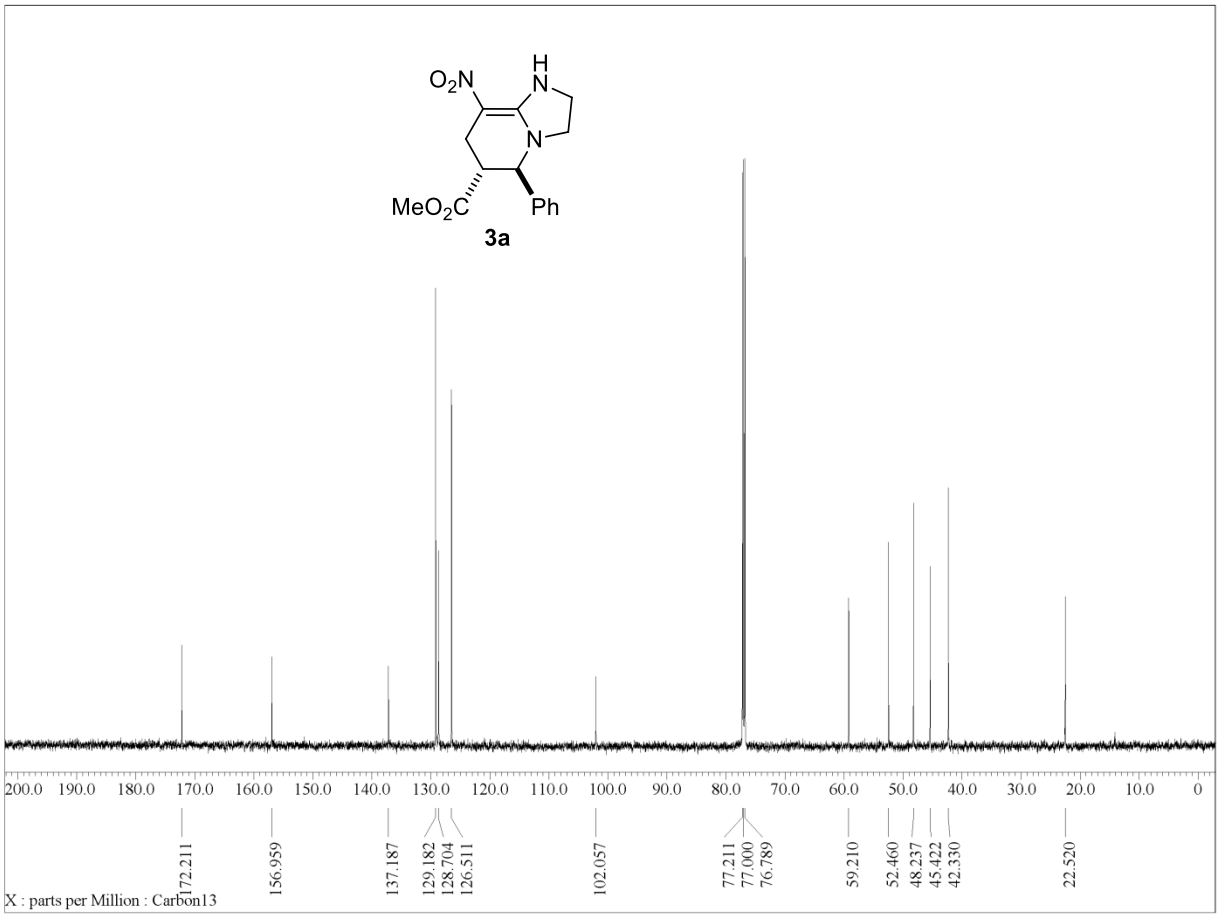
1 (*a*) E. Krell, *Handbook of Laboratory Distillation*, Elseriver Publishing Company, Amsterdam-London-New York, 1963; (*b*) M. J. Rosengart, *The Technique of Distillation and Rectification in the Laboratory*, VEB Verlag Technik, Berlin, 1954; (*c*) F. Stage, *Angew. Chem.* 1947, **19**, 175.

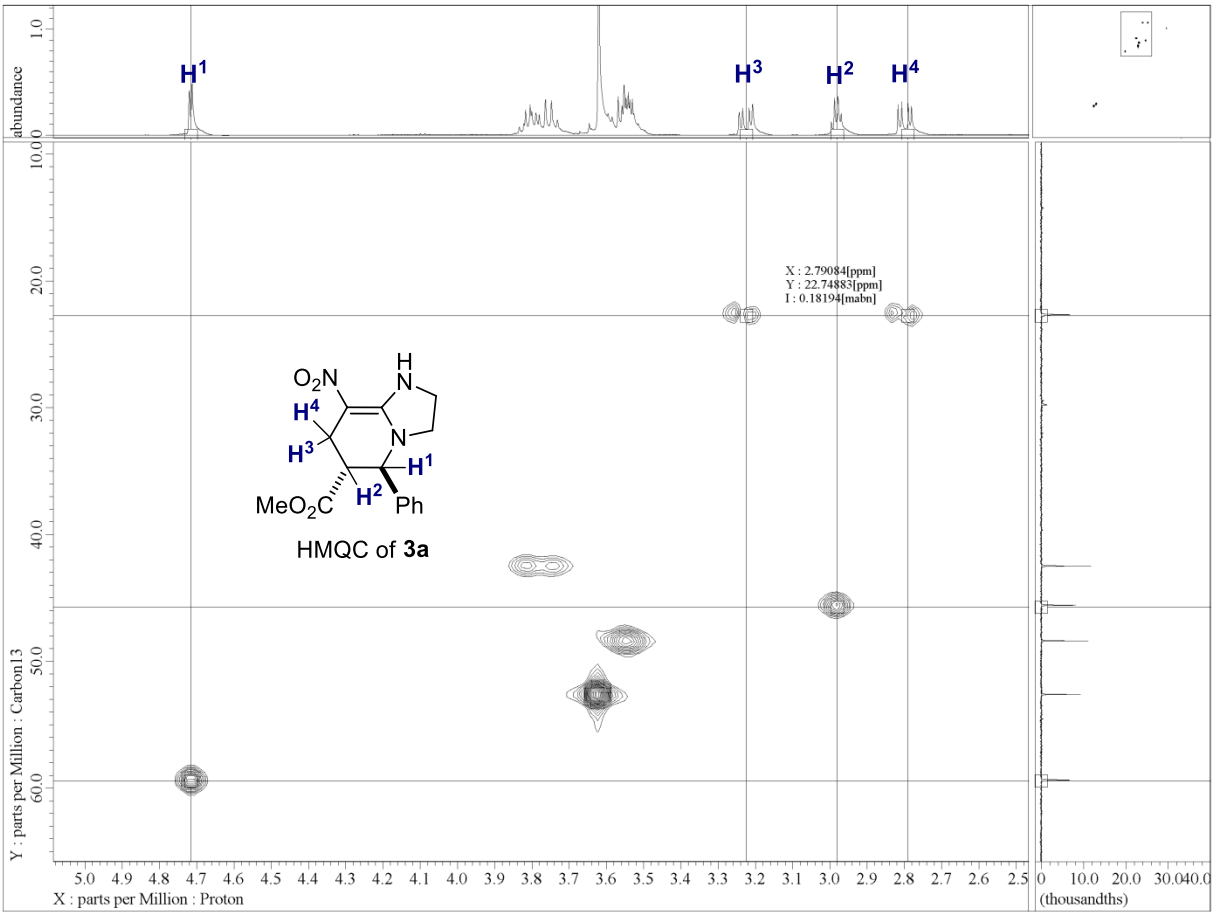
2 E. Safari, A. Maryamabadi and A. Hasaninejad, *RSC Adv.* 2017, **7**, 39502.

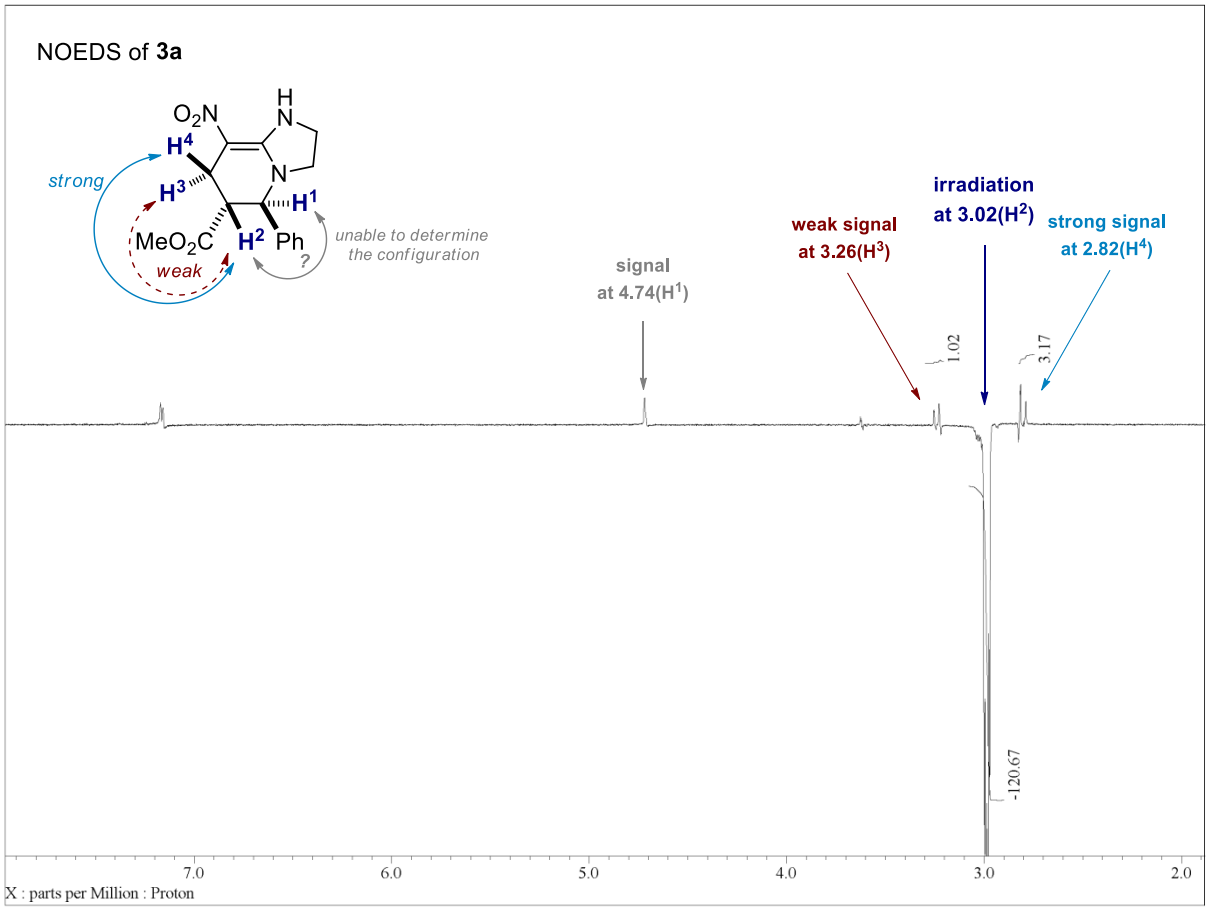
3 X. Li, J. Su, Z. Liu, Y. Zhu, Z. Dong, S. Qiu, J. Wang, L. Lin, Z. Shen, W. Yan, K. Wang and R. Wang, *Org. Lett.* 2016, **18**, 956.

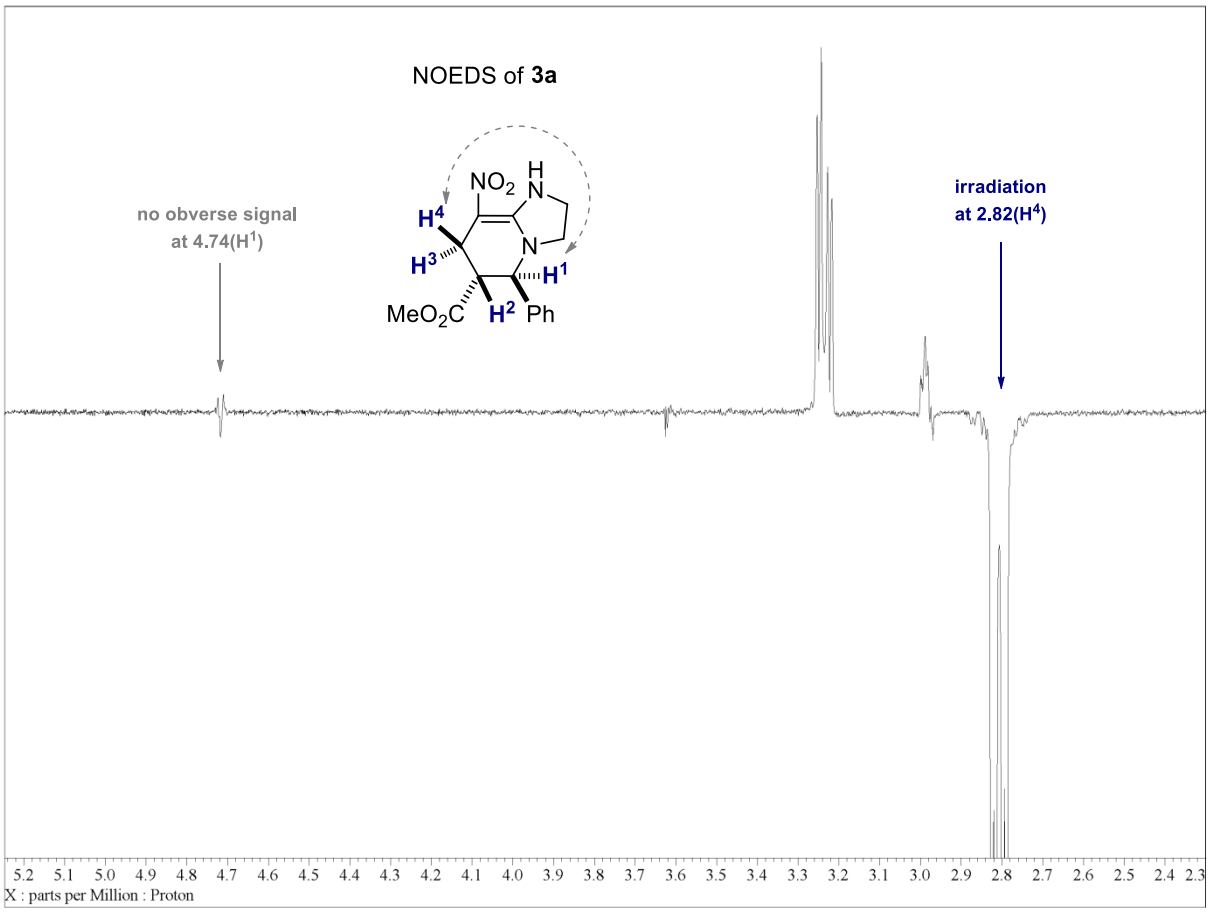
7. NMR Spectra

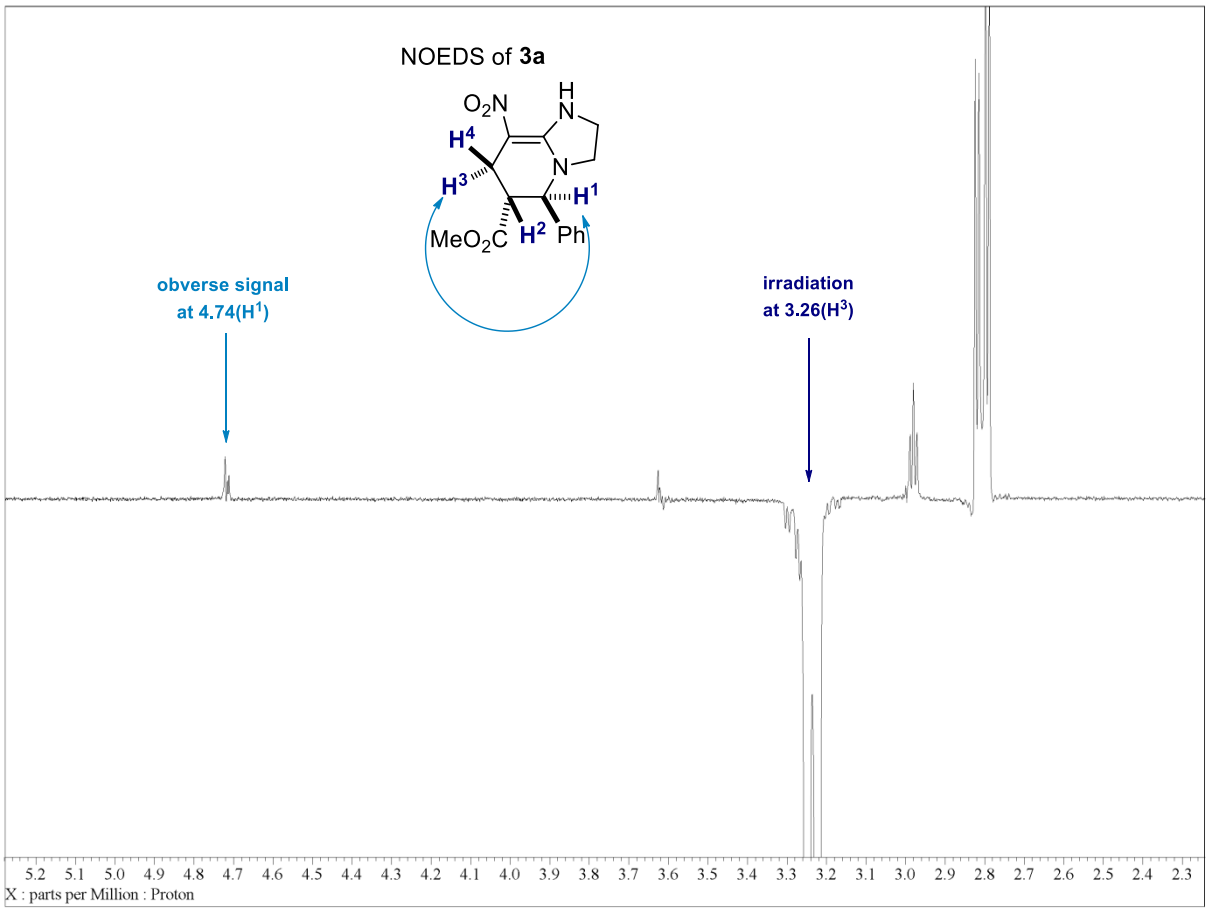


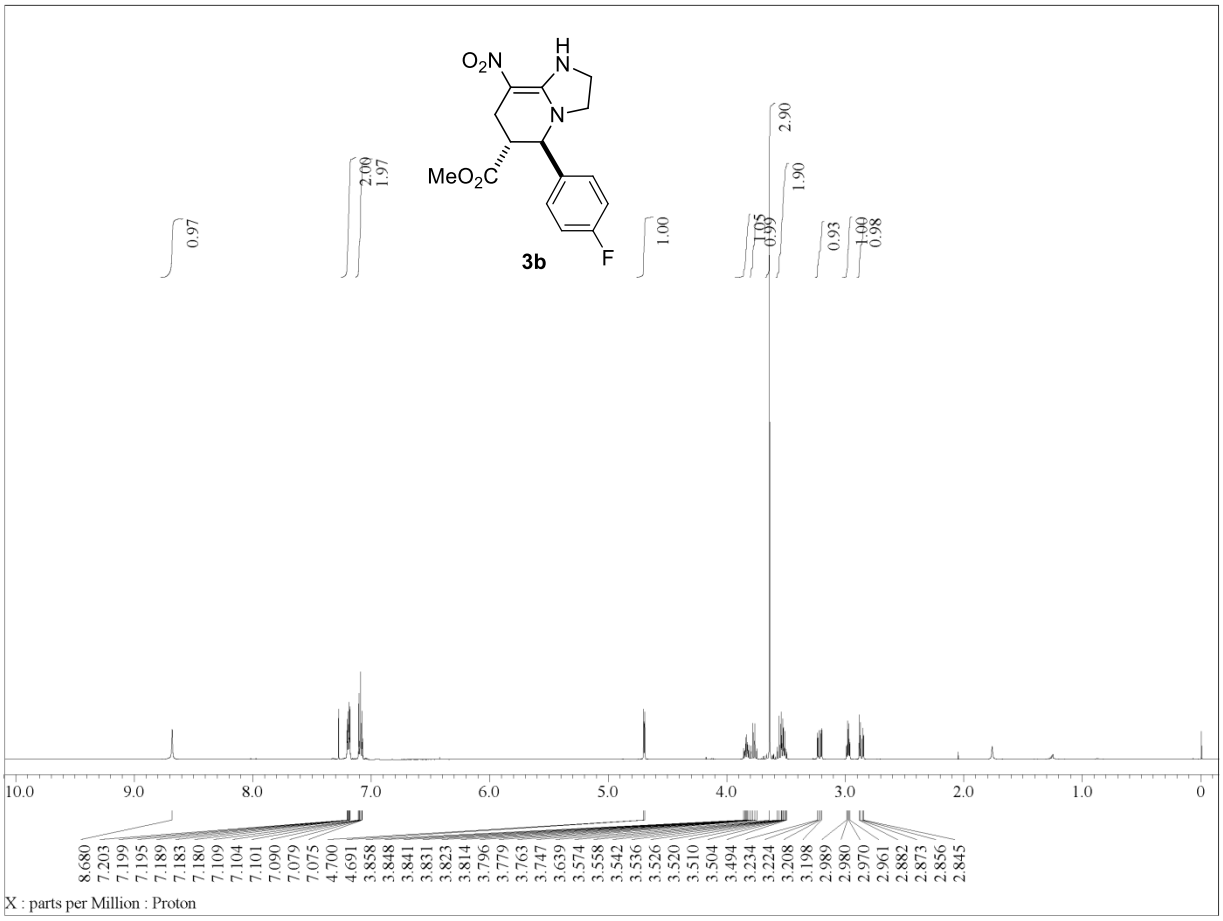


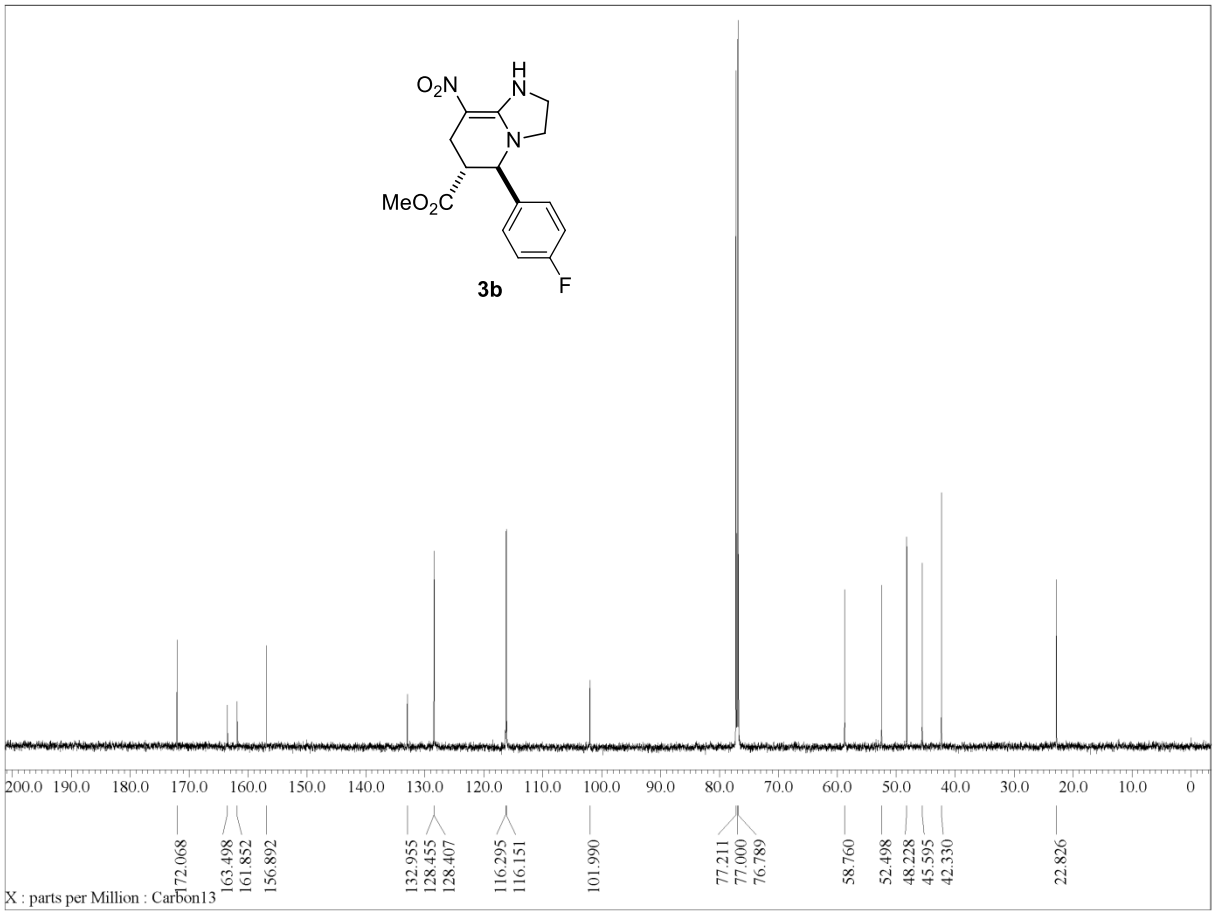

H1
H3
H2
H4
abundance
X : 2.79084[ppm]
Y : 22.74883[ppm]
I : 0.18194[mabn]
O2N
H4
H3
MeO2C
H2
Ph
N
H
H1
HMQC of 3a
Y : parts per Million : Carbon13
X : parts per Million : Proton
(thousandths)

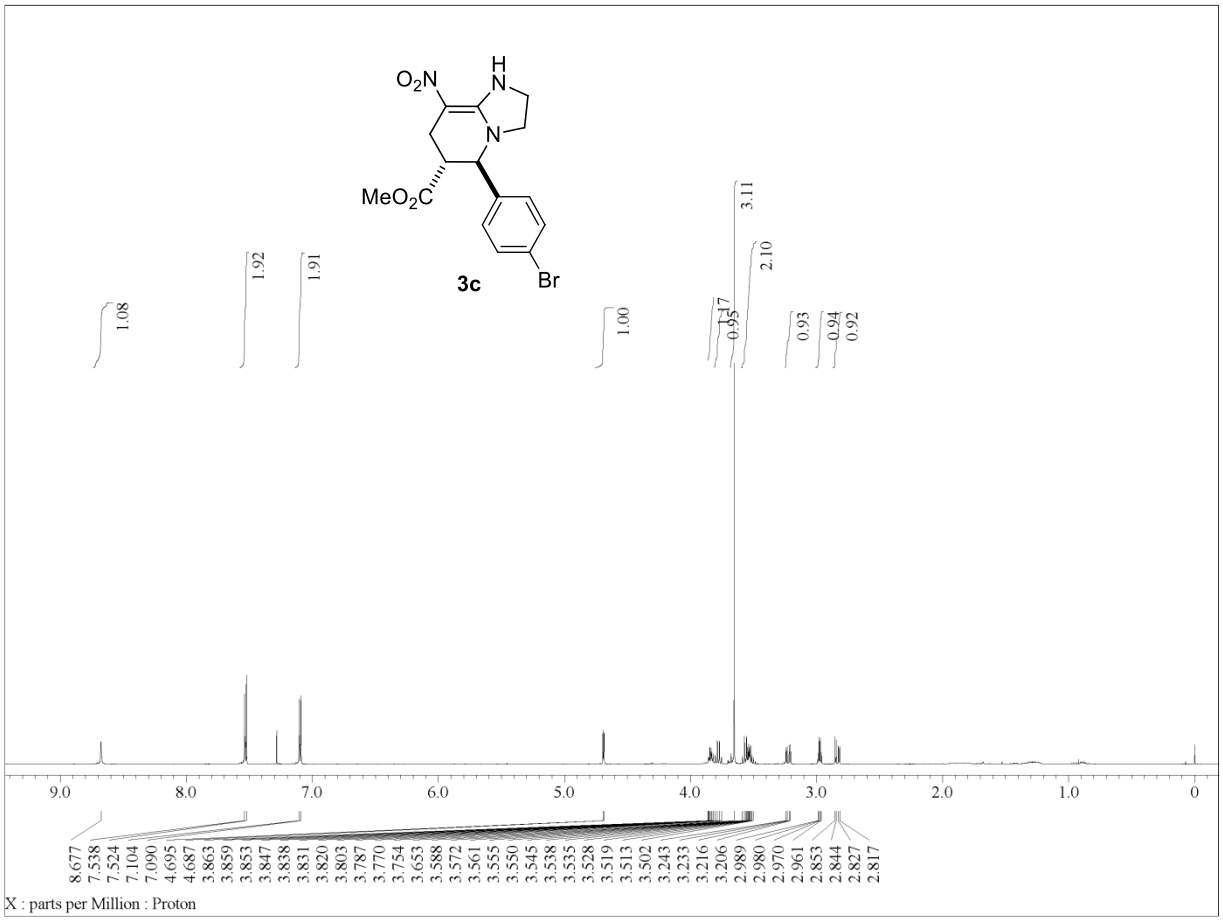

NOEDS of 3a
strong
weak
unable to determine
the configuration
signal
at 4.74(H1)
weak signal
at 3.26(H3)
irradiation
at 3.02(H2)
strong signal
at 2.82(H4)
1.02
3.17
-120.67
X : parts per Million : Proton


NOEDS of 3a
no obverse signal
at 4.74(H1)
irradiation
at 2.82(H4)
NO2
H
N
N
H4
H3
H1
MeO2C
H2
Ph
5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3
X : parts per Million : Proton


NOEDS of 3a
O2N
H
N
N
H4
H3
H1
MeO2C
H2
Ph
obverse signal
at 4.74(H1)
irradiation
at 3.26(H3)
5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3
X : parts per Million : Proton


O2N
H
N
N
MeO2C
F
3b
0.97
2.00
1.97
1.00
2.90
1.90
1.05
0.99
0.93
1.00
0.98
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.680
7.203
7.199
7.195
7.189
7.183
7.180
7.109
7.104
7.101
7.090
7.079
7.075
4.700
4.691
3.858
3.848
3.841
3.831
3.823
3.814
3.796
3.779
3.763
3.747
3.639
3.574
3.558
3.542
3.536
3.526
3.520
3.510
3.504
3.494
3.234
3.224
3.208
3.198
2.989
2.980
2.970
2.961
2.882
2.873
2.856
2.845
X : parts per Million : Proton


O2N
H
N
N
MeO2C
F
3b
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
172.068
163.498
161.852
156.892
132.955
128.455
128.407
116.295
116.151
101.990
77.211
77.000
76.789
58.760
52.498
48.228
45.595
42.330
22.826
X : parts per Million : Carbon13


O2N
H
N
N
MeO2C
Br
3c
1.08
1.92
1.91
1.00
0.95
1.17
3.11
2.10
0.93
0.94
0.92
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.677
7.538
7.524
7.104
7.090
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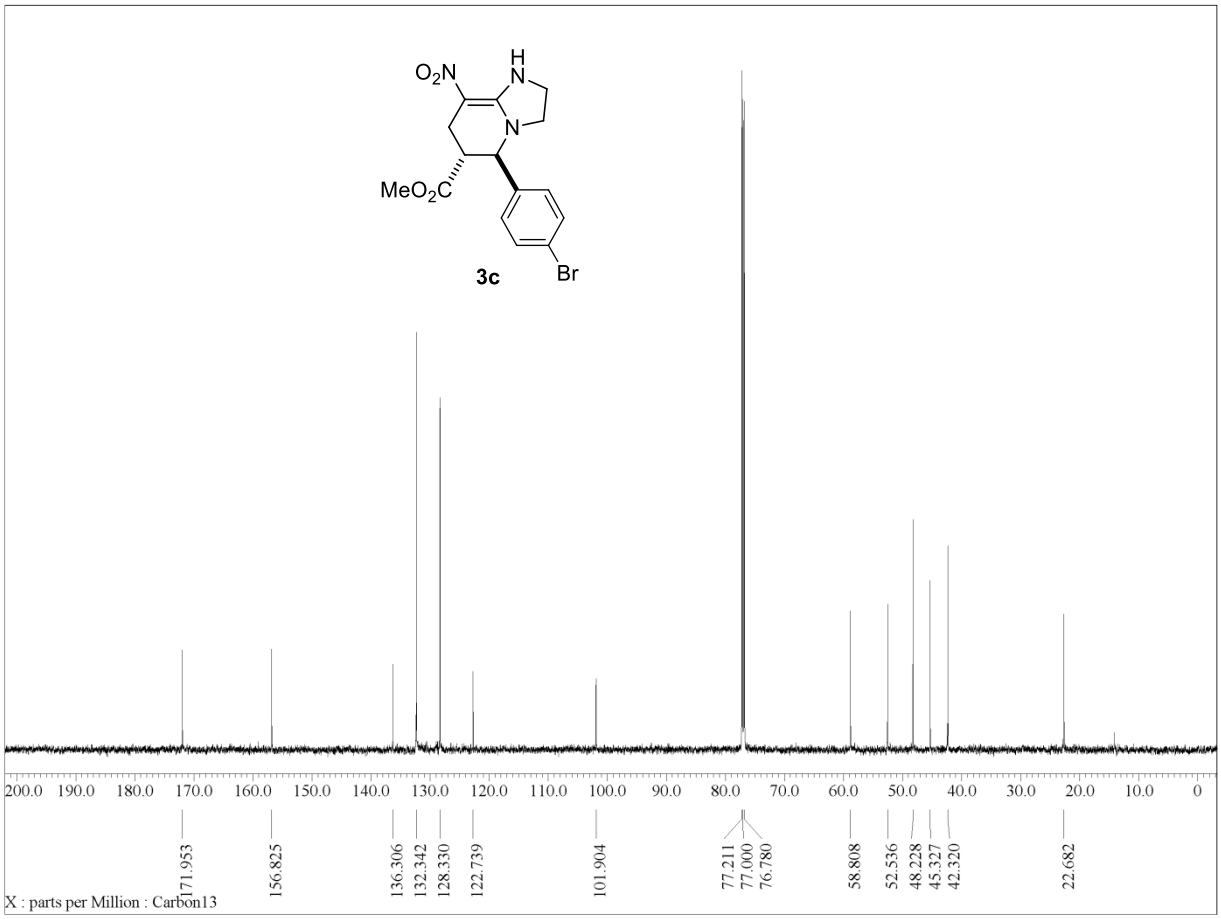
4.687
3.863
3.859
3.853
3.847
3.838
3.831
3.820
3.803
3.787
3.770
3.754
3.653
3.588
3.572
3.561
3.555
3.550
3.545
3.538
3.535
3.528
3.519
3.513
3.502
3.243
3.233
3.216
3.206
2.989
2.980
2.970
2.961
2.853
2.844
2.827
2.817
X : parts per Million : Proton


O2N
H
N
N
MeO2C
Br
3c
200.0
190.0
180.0
170.0
160.0
150.0
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130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
171.953
156.825
136.306
132.342
128.330
122.739
101.904
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77.000
76.780
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45.327
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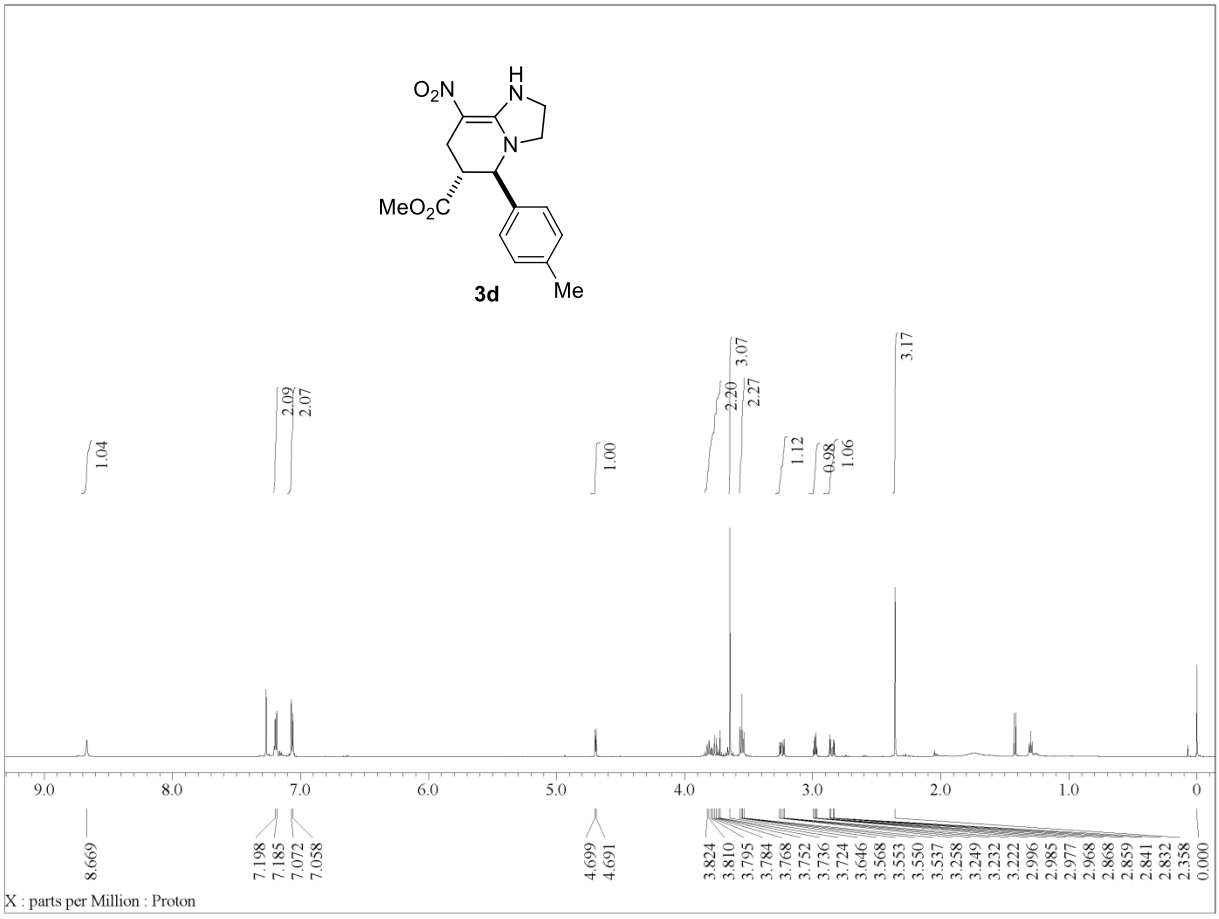
22.682
X : parts per Million : Carbon13


O2N
H
N
N
MeO2C
3d
Me
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2.09
2.07
1.00
3.07
2.20
2.27
1.12
0.98
1.06
3.17
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.669
7.198
7.185
7.072
7.058
4.699
4.691
3.824
3.810
3.795
3.784
3.768
3.752
3.736
3.724
3.646
3.568
3.553
3.550
3.537
3.258
3.249
3.232
3.222
2.996
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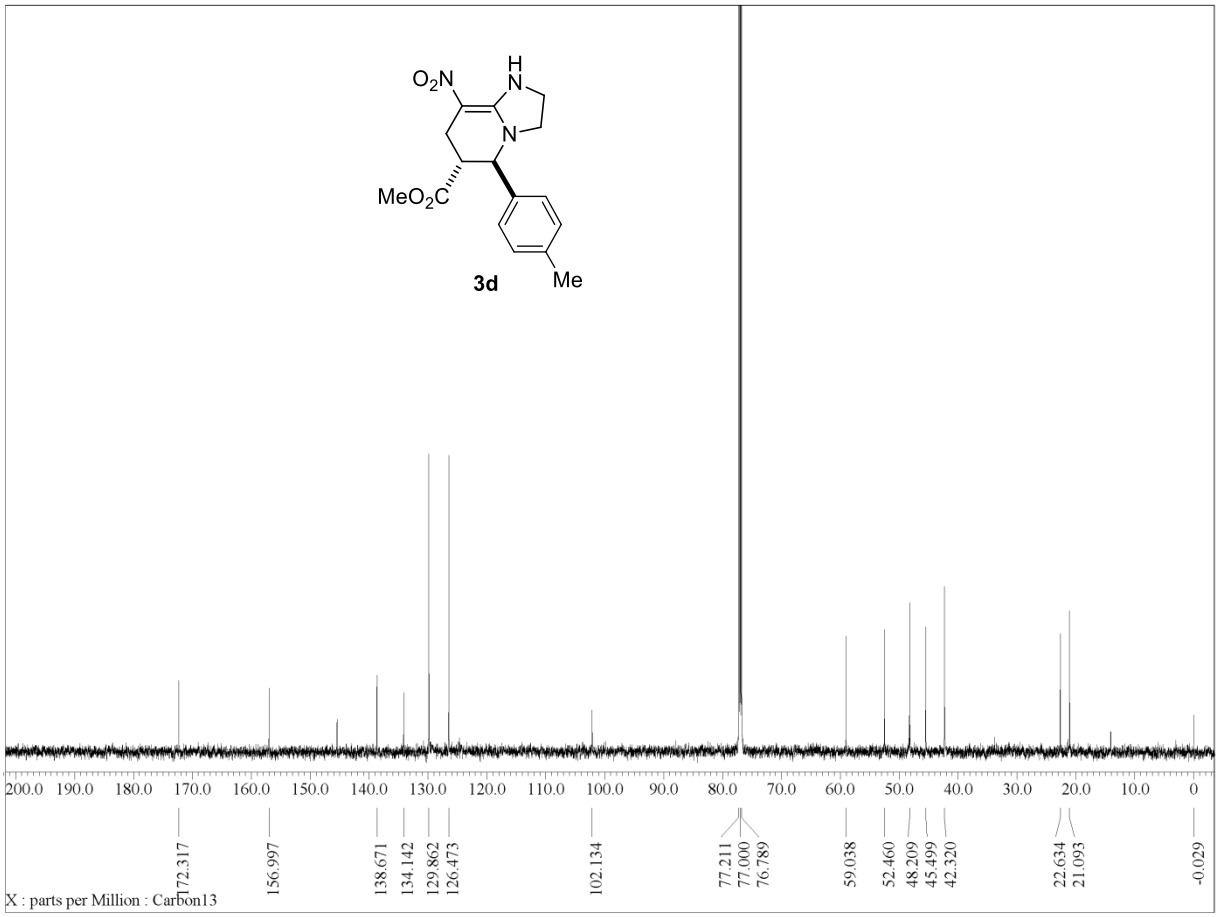
X : parts per Million : Proton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H
N
N
MeO2C
3d
Me
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
172.317
156.997
138.671
134.142
129.862
126.473
102.134
77.211
77.000
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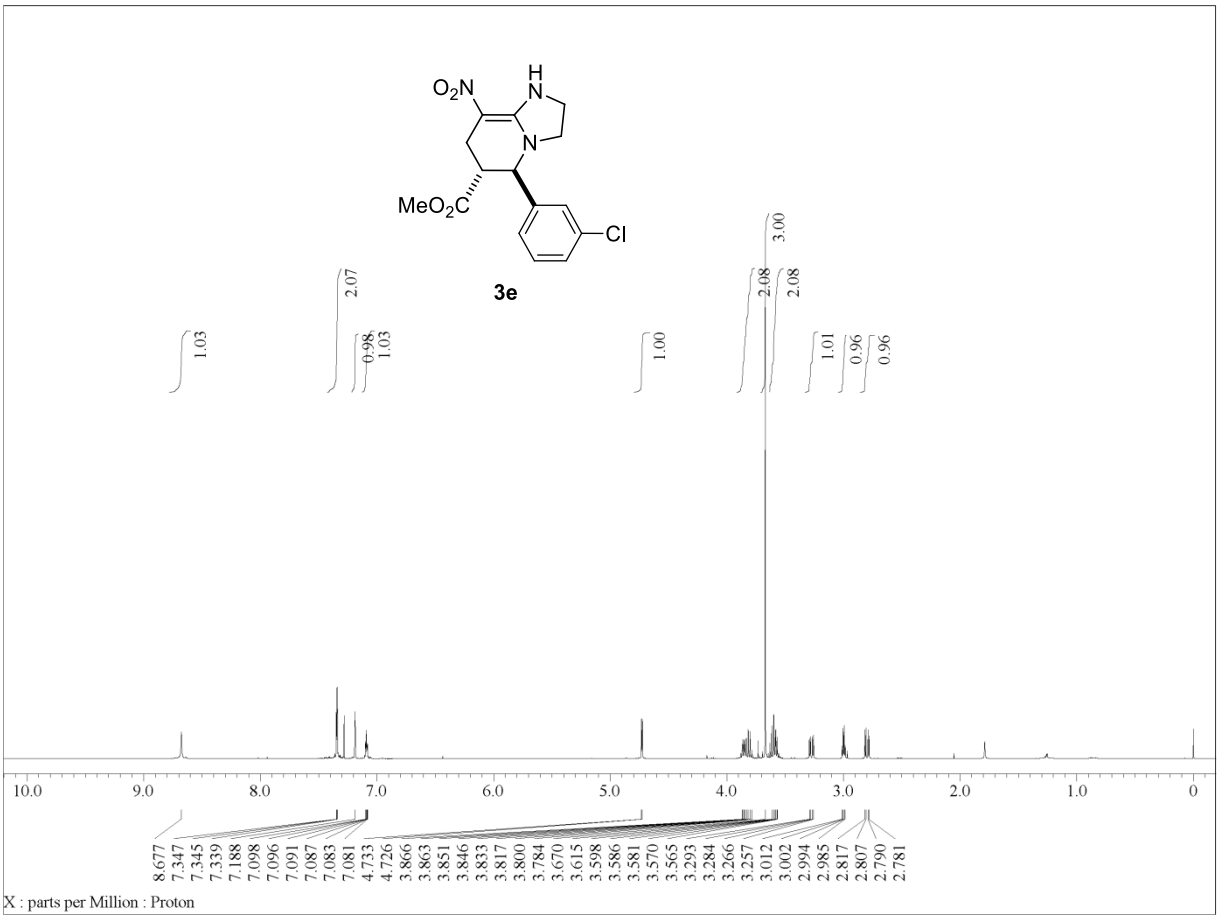
22.634
21.093
-0.029
X : parts per Million : Carbon13


O2N
H
N
N
MeO2C
Cl
3e
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2.07
0.98
1.03
1.00
3.00
2.08
2.08
1.01
0.96
0.96
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.677
7.347
7.345
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7.096
7.091
7.087
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7.081
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4.726
3.866
3.863
3.851
3.846
3.833
3.817
3.800
3.784
3.670
3.615
3.598
3.586
3.581
3.570
3.565
3.293
3.284
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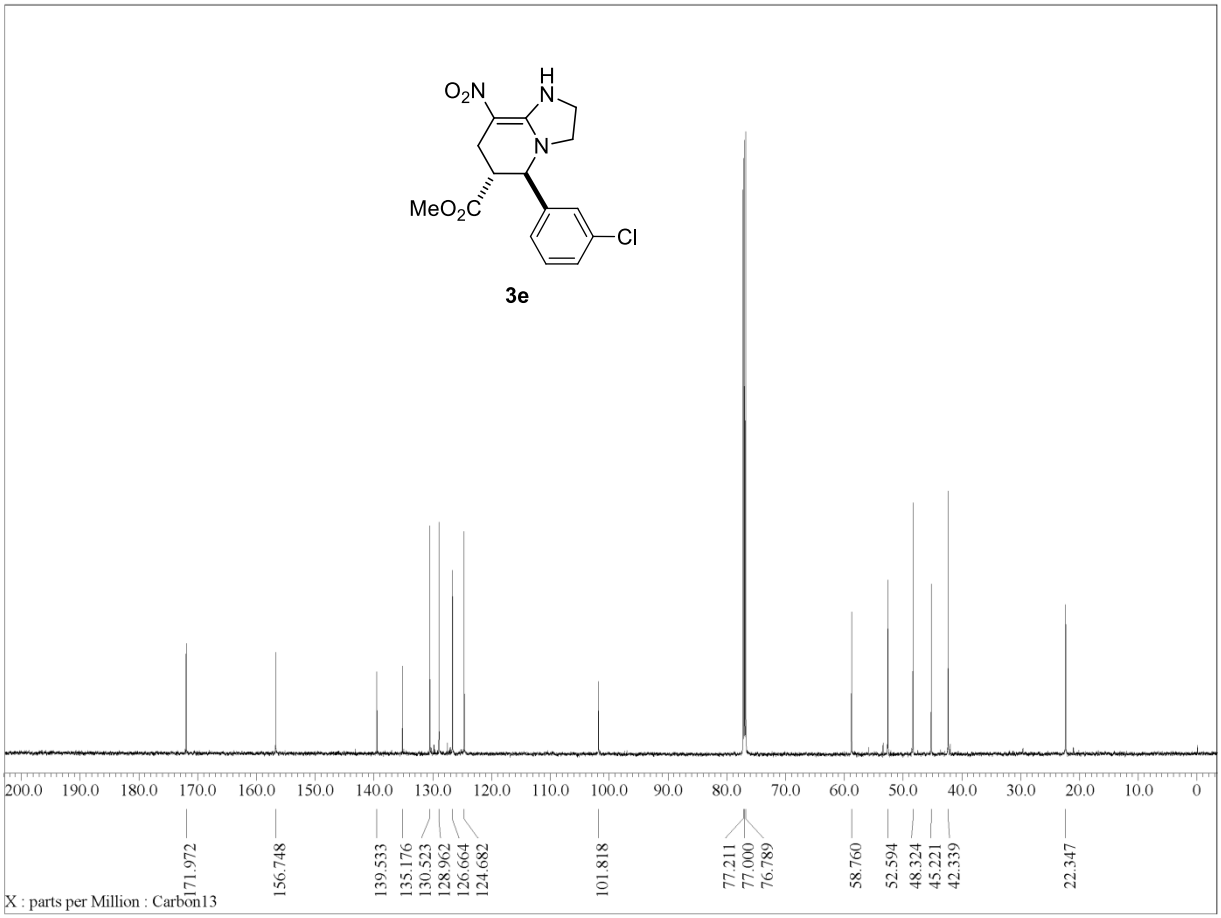
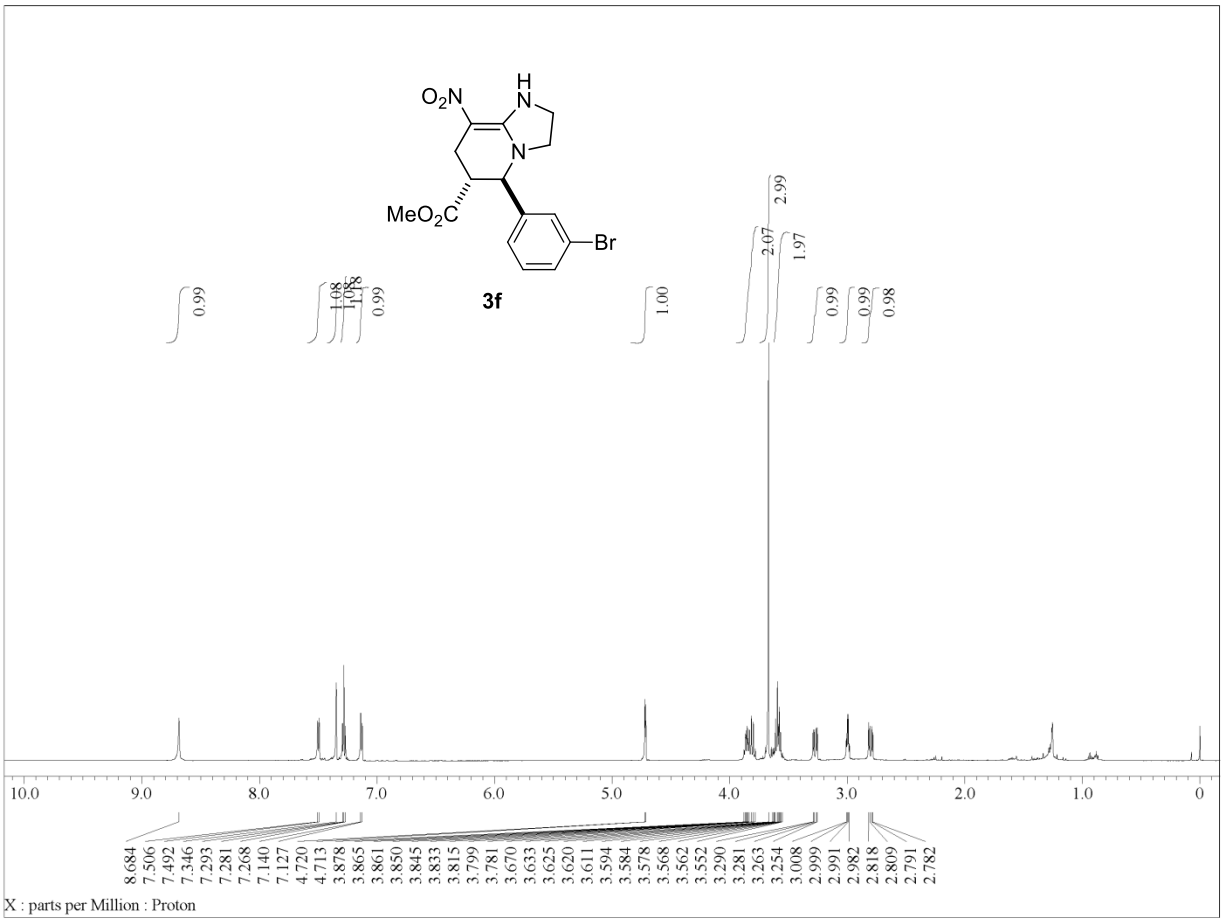
X : parts per Million : Proton


O2N
H
N
N
MeO2C
Cl
3e
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
171.972
156.748
139.533
135.176
130.523
128.962
126.664
124.682
101.818
77.211
77.000
76.789
58.760
52.594
48.324
45.221
42.339
22.347
X : parts per Million : Carbon13


O2N
H
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N
MeO2C
Br
3f
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1.08
1.08
0.99
1.00
2.99
2.07
1.97
0.99
0.99
0.98
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.684
7.506
7.492
7.346
7.293
7.281
7.268
7.140
7.127
4.720
4.713
3.878
3.865
3.861
3.850
3.845
3.833
3.815
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3.633
3.625
3.620
3.611
3.594
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3.281
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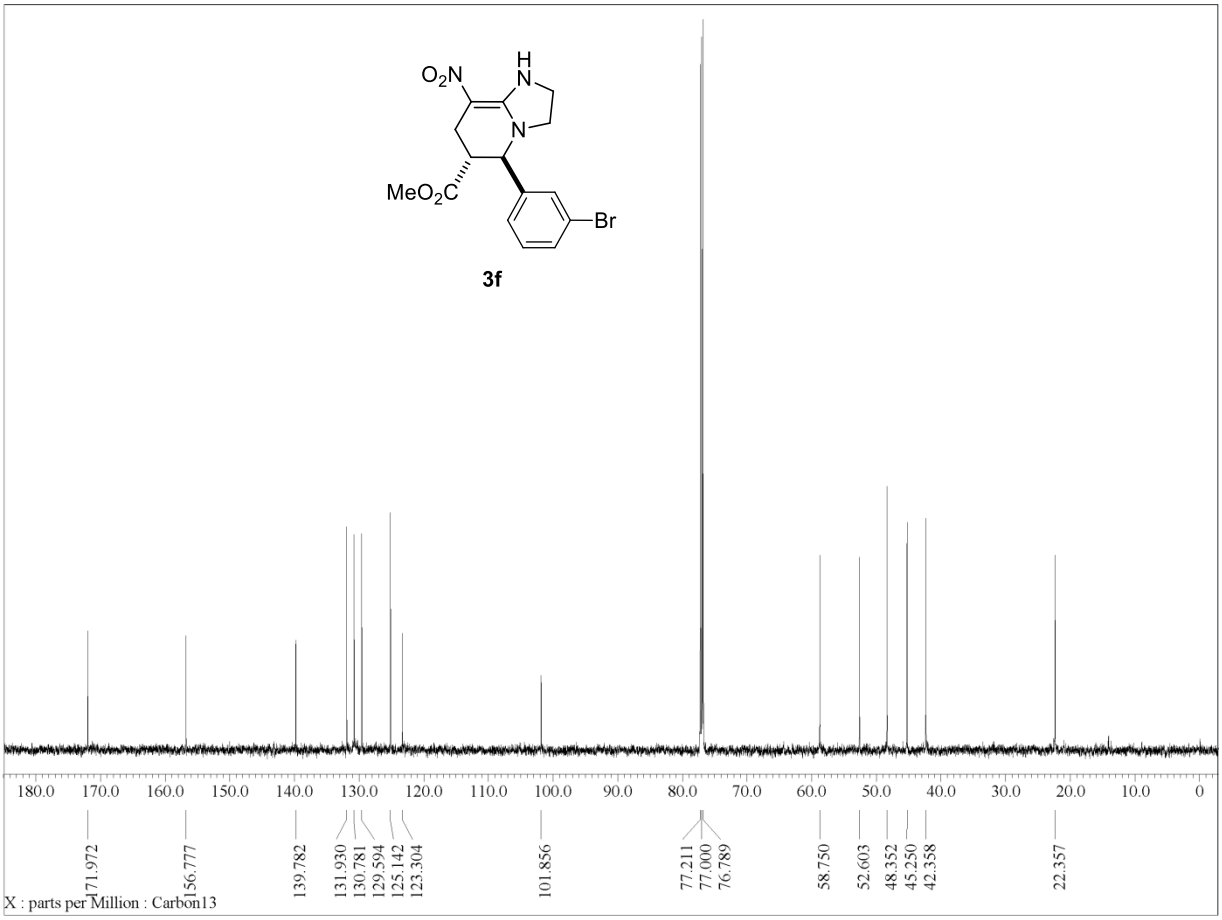
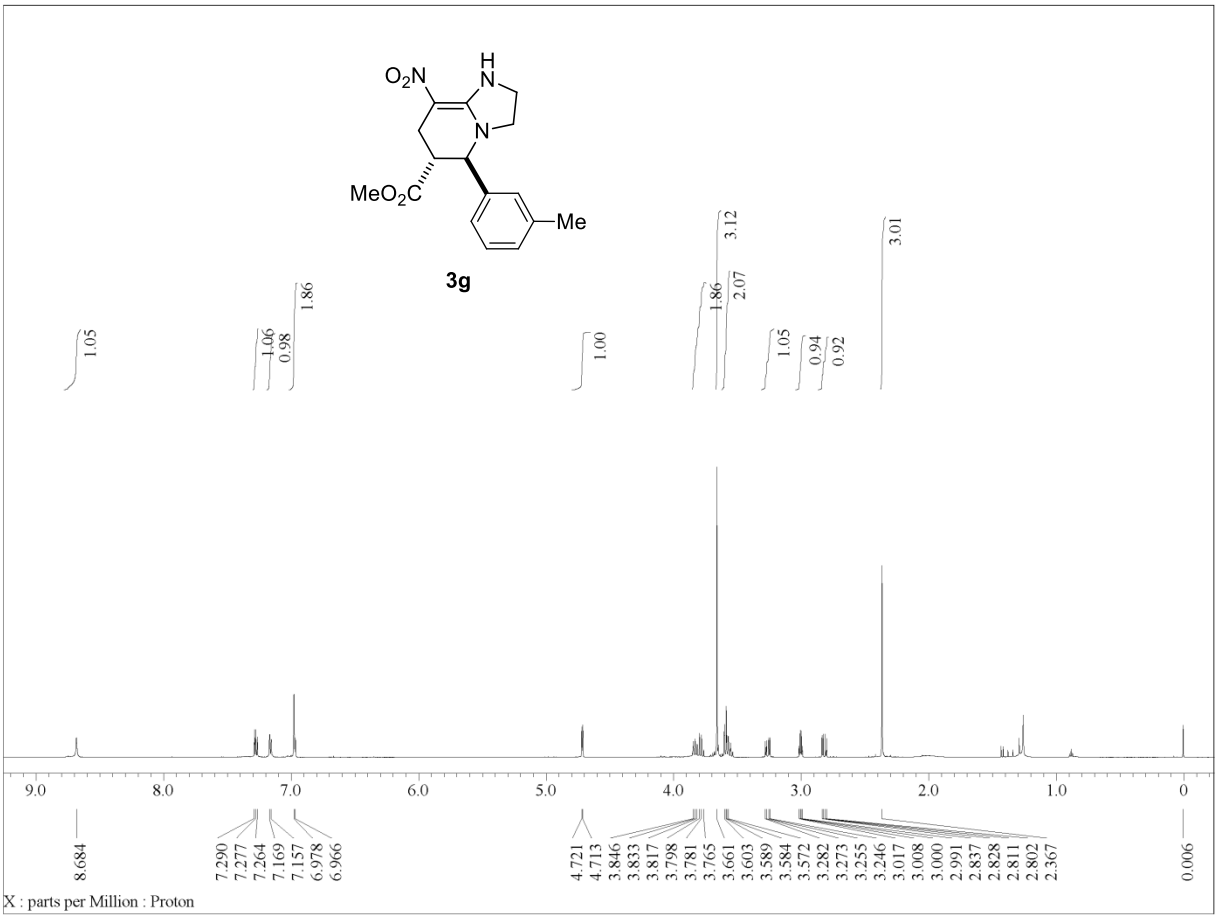
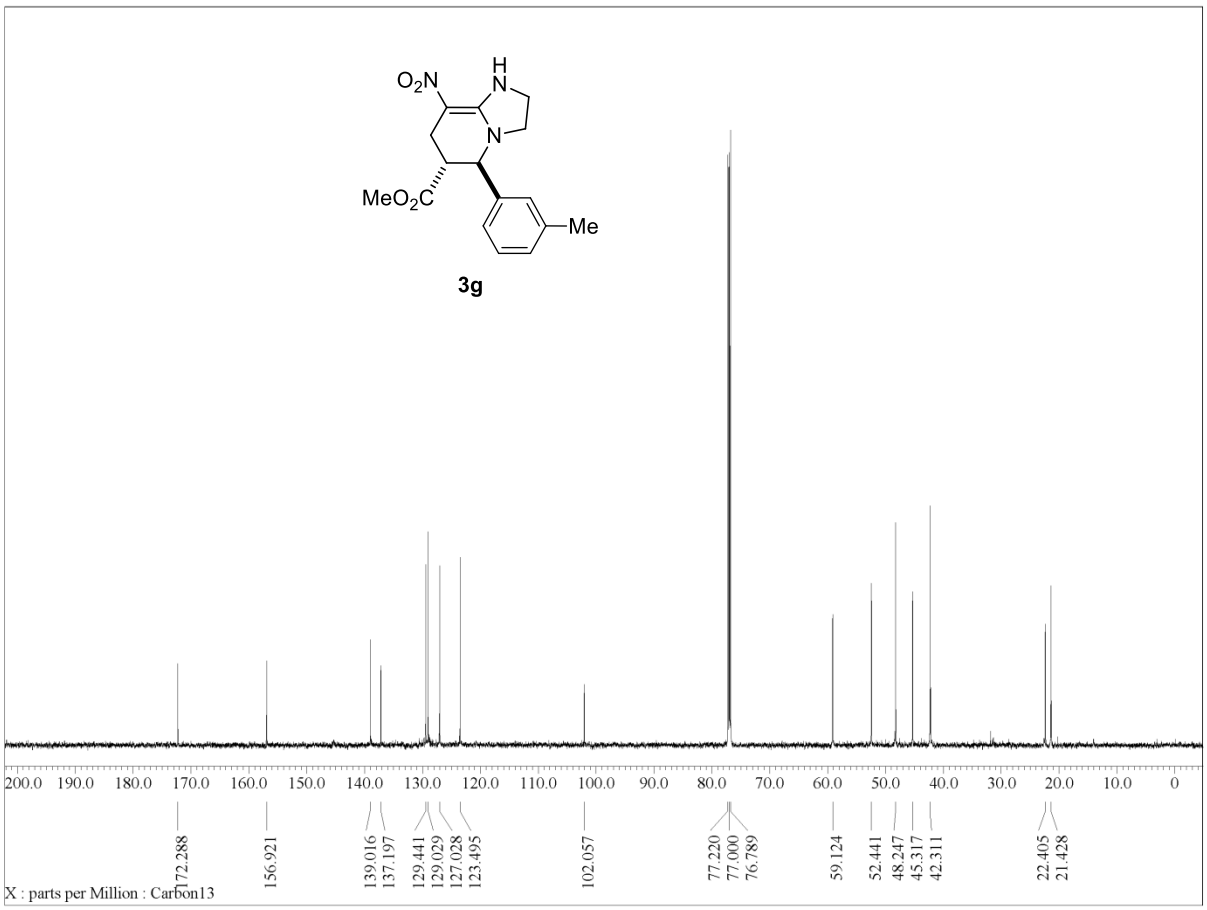
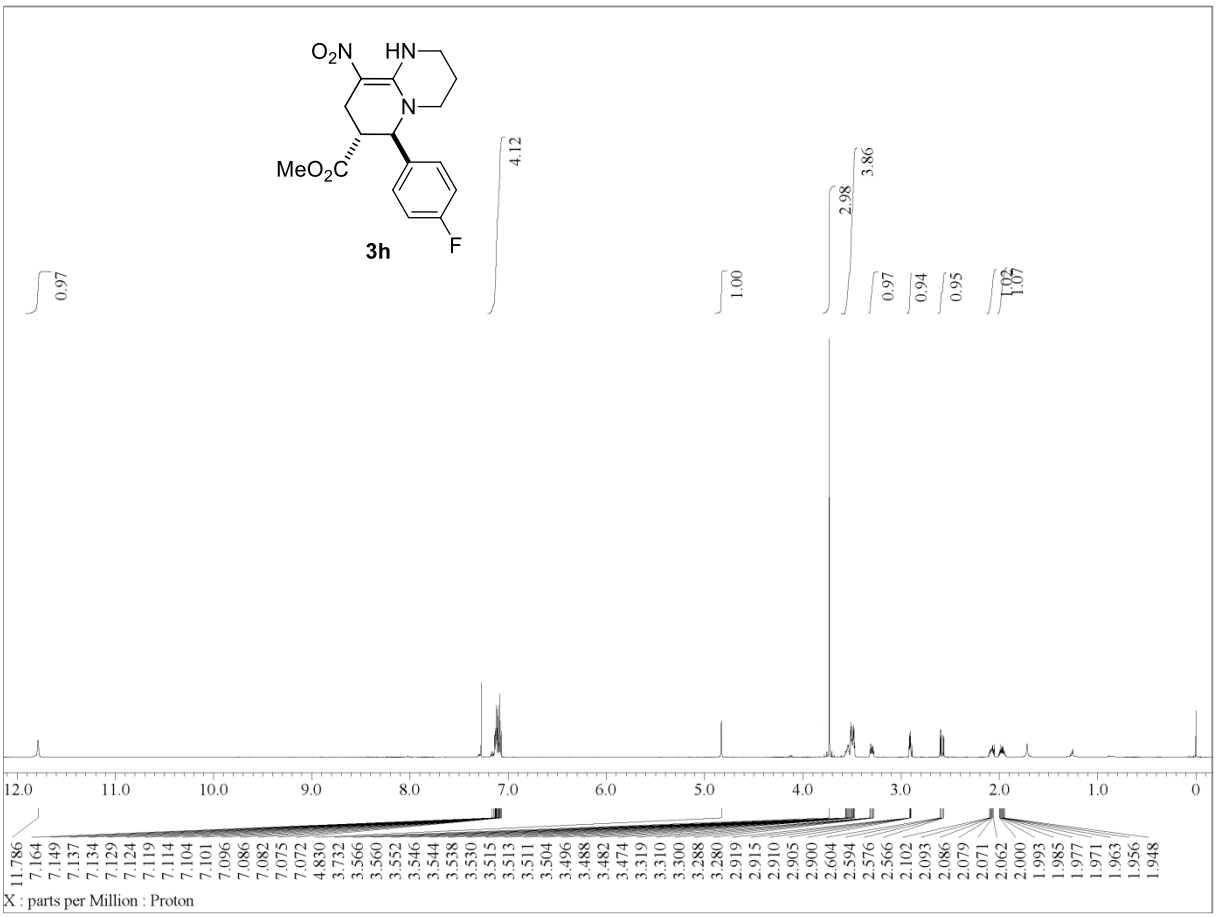
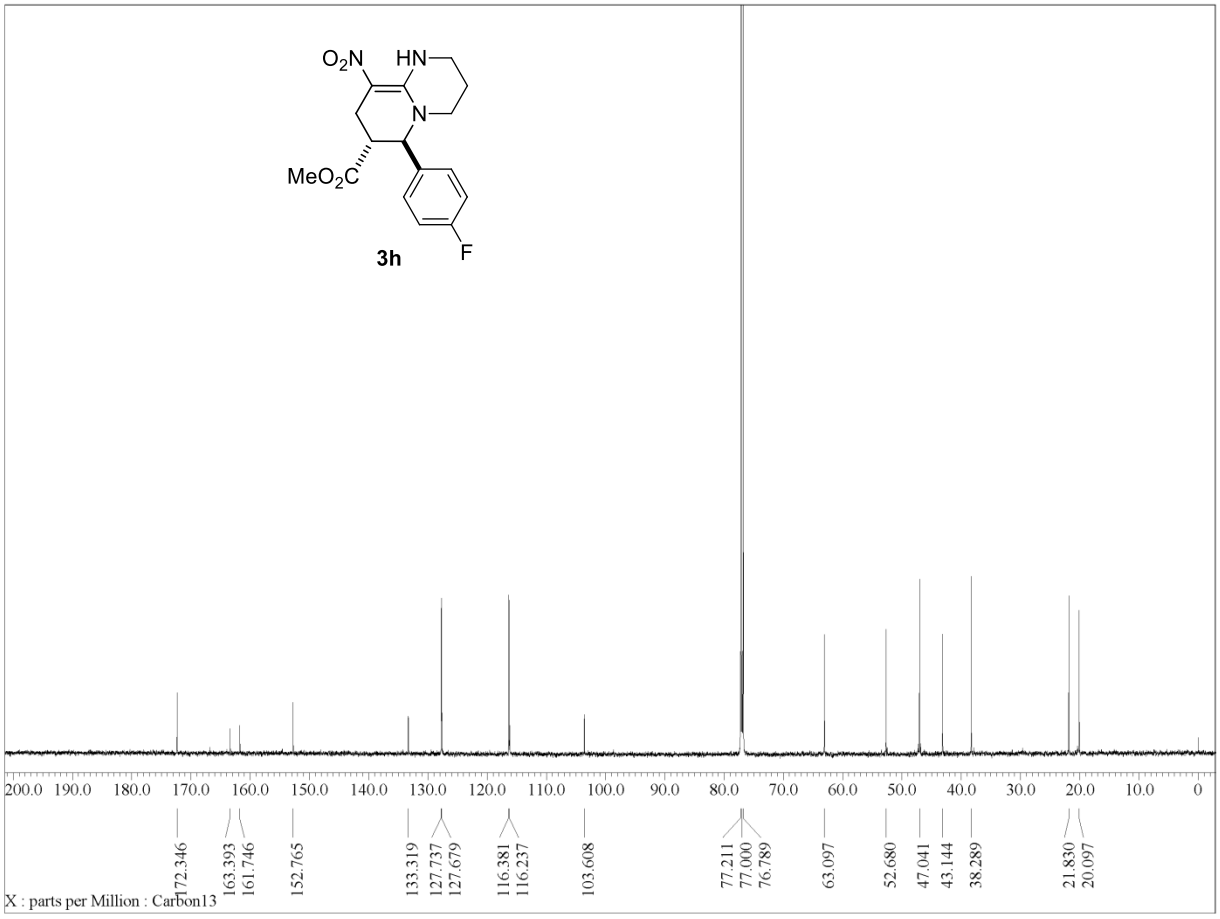
2.782
X : parts per Million : Proton

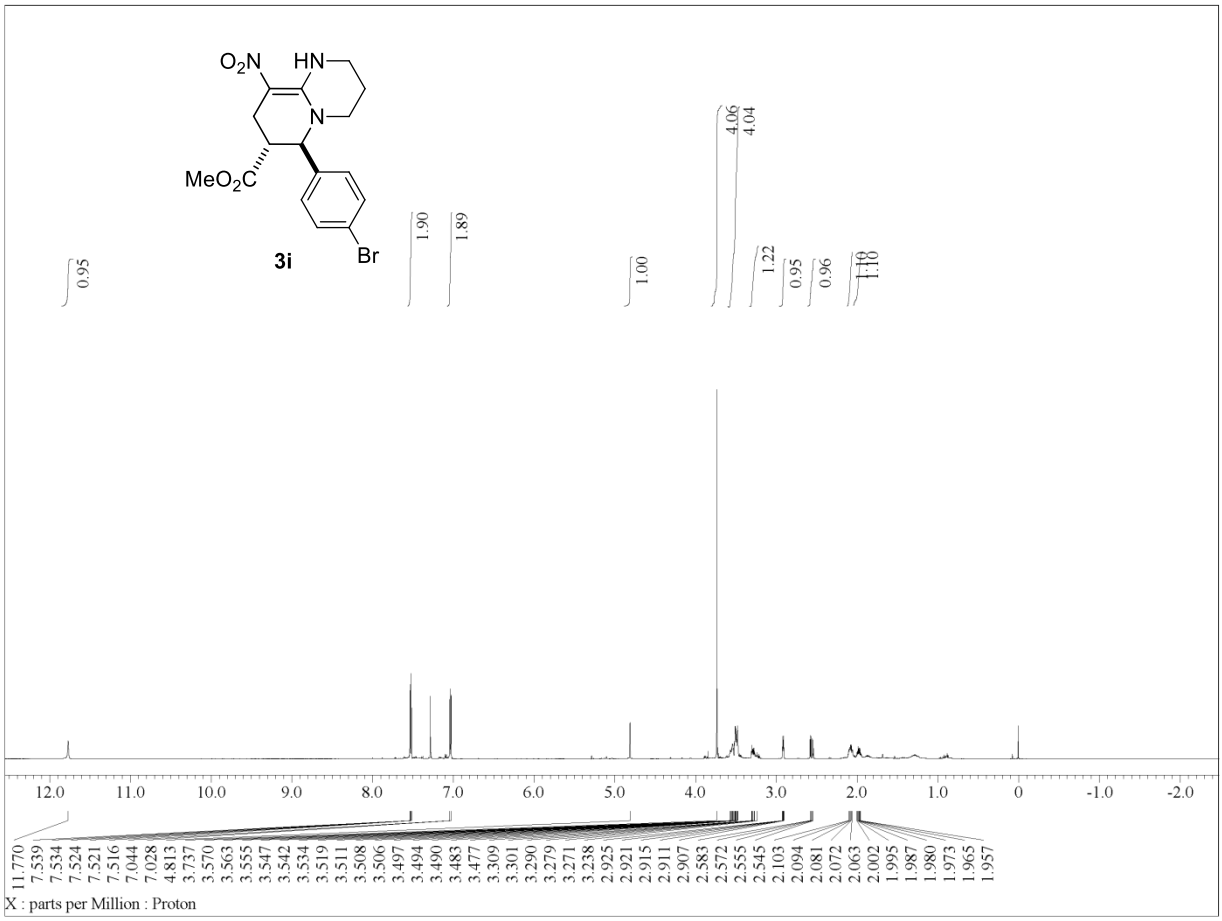

O2N
H
N
N
MeO2C
Br
3f
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
171.972
156.777
139.782
131.930
130.781
129.594
125.142
123.304
101.856
77.211
77.000
76.789
58.750
52.603
48.352
45.250
42.358
22.357
X : parts per Million : Carbon13

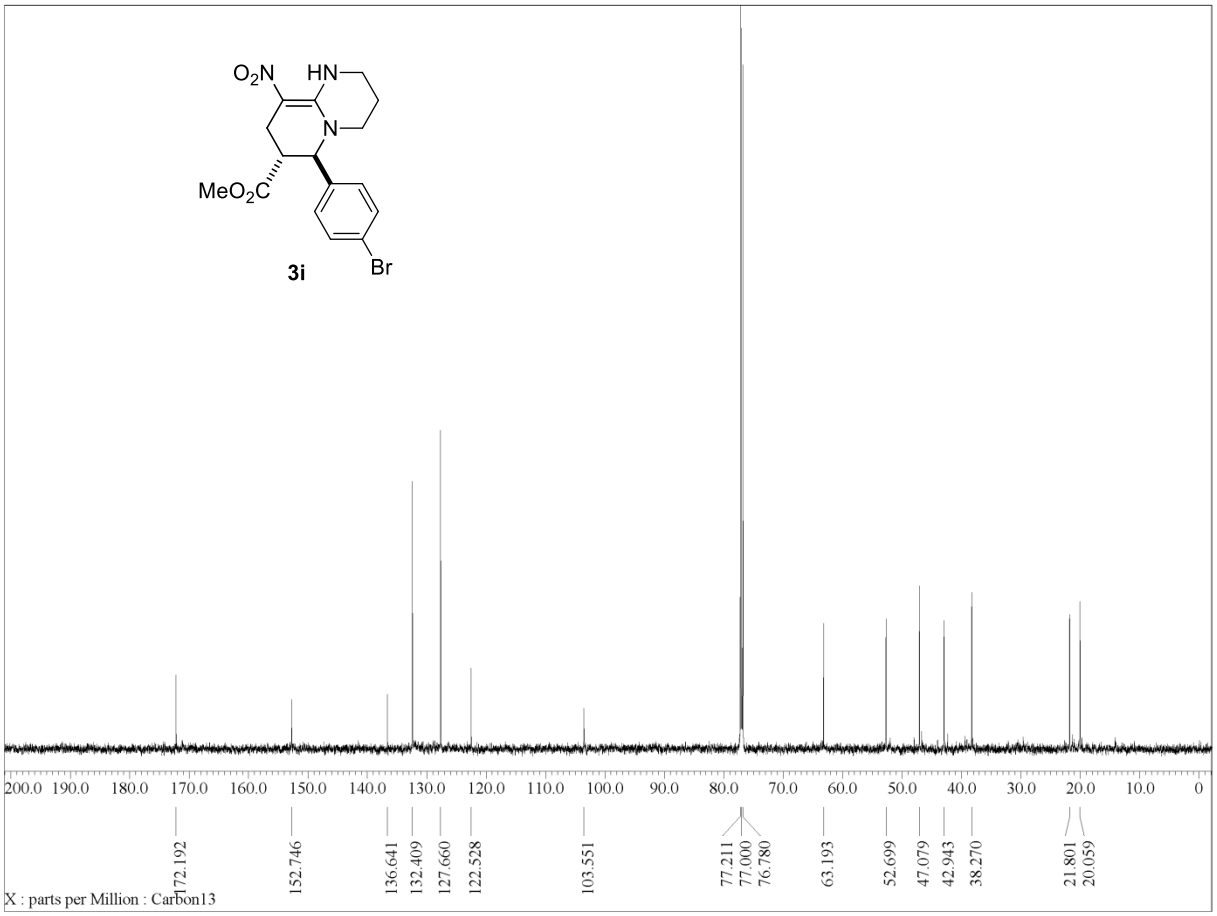

O_2N
H
N
N
MeO_2C
Me
3g
1.05
1.06
0.98
1.86
1.00
1.86
2.07
3.12
1.05
0.94
0.92
3.01
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.684
7.290
7.277
7.264
7.169
7.157
6.978
6.966
4.721
4.713
3.846
3.833
3.817
3.798
3.781
3.765
3.661
3.603
3.589
3.584
3.572
3.282
3.273
3.255
3.246
3.017
3.008
3.000
2.991
2.837
2.828
2.811
2.802
2.367
0.006
X : parts per Million : Proton

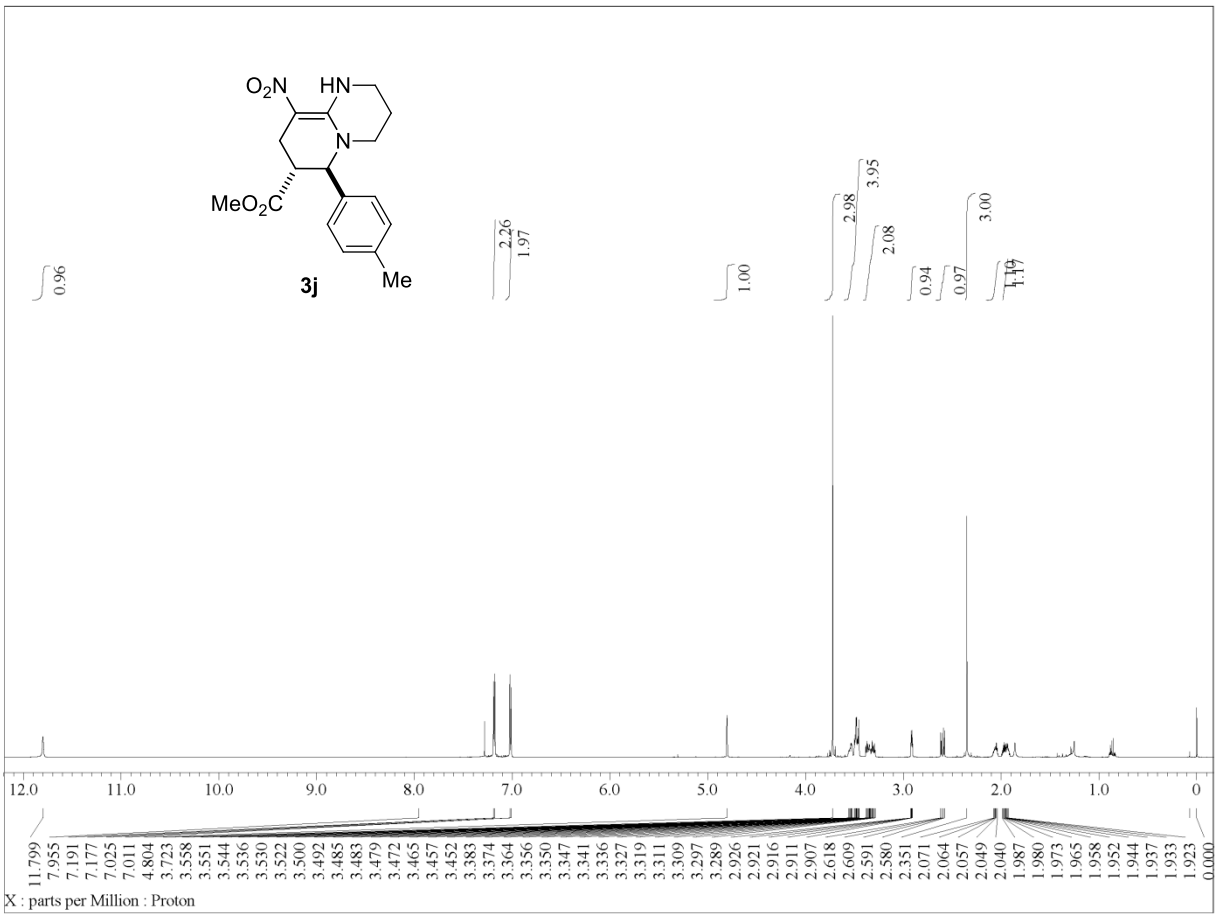

O_2N
H
N
N
MeO_2C
Me
3g
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
172.288
156.921
139.016
137.197
129.441
129.029
127.028
123.495
102.057
77.220
77.000
76.789
59.124
52.441
48.247
45.317
42.311
22.405
21.428
X : parts per Million : Carbon13

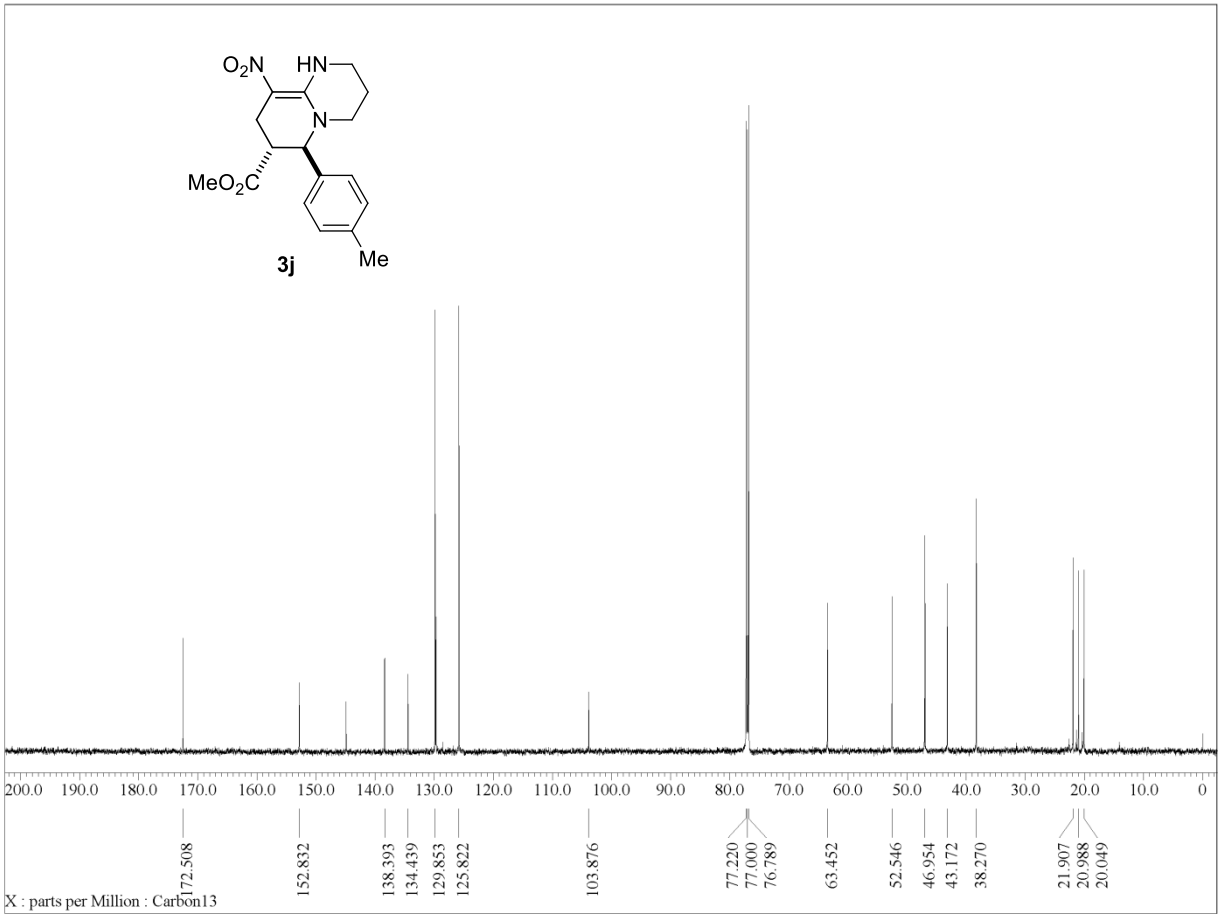

O2N
HN
N
MeO2C
F
3h
0.97
4.12
1.00
2.98
3.86
0.97
0.94
0.95
1.02
1.07
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
11.786
7.164
7.149
7.137
7.134
7.129
7.124
7.119
7.114
7.104
7.101
7.096
7.086
7.082
7.075
7.072
4.830
3.732
3.566
3.560
3.552
3.546
3.544
3.538
3.530
3.515
3.513
3.511
3.504
3.496
3.488
3.482
3.474
3.319
3.310
3.300
3.288
3.280
2.919
2.915
2.910
2.905
2.900
2.604
2.594
2.576
2.566
2.102
2.093
2.086
2.079
2.071
2.062
2.000
1.993
1.985
1.977
1.971
1.963
1.956
1.948
X : parts per Million : Proton

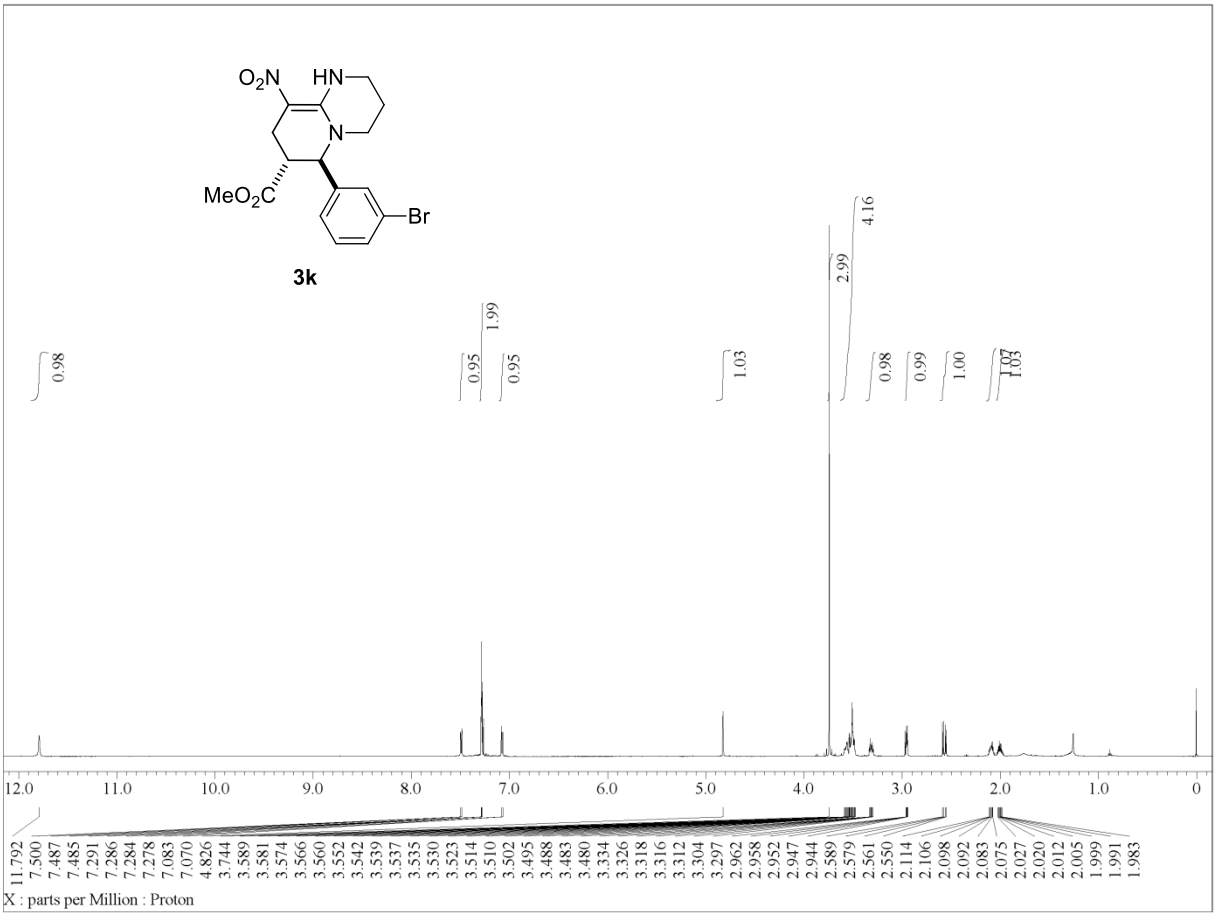

O2N
HN
N
MeO2C
F
3h
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
172.346
163.393
161.746
152.765
133.319
127.737
127.679
116.381
116.237
103.608
77.211
77.000
76.789
63.097
52.680
47.041
43.144
38.289
21.830
20.097
X : parts per Million : Carbon13

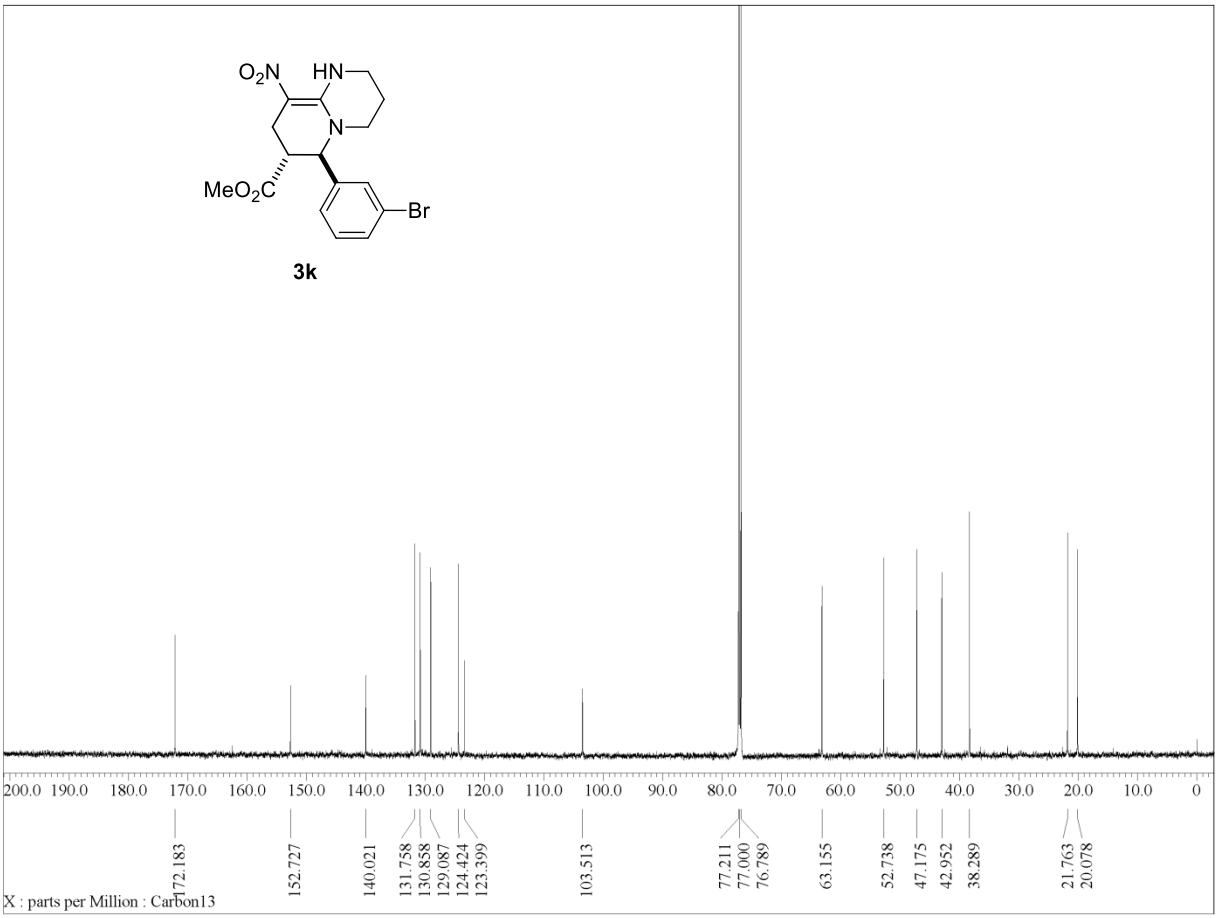

O2N
HN
N
MeO2C
Br
3i
0.95
1.90
1.89
1.00
4.06
4.04
1.22
0.95
0.96
1.10
1.10
12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0 -1.0 -2.0
11.770 7.539 7.534 7.524 7.521 7.516 7.044 7.028 4.813 3.737 3.570 3.563 3.555 3.547 3.542 3.534 3.519 3.511 3.508 3.506 3.497 3.494 3.490 3.483 3.477 3.309 3.301 3.290 3.279 3.271 3.238 2.925 2.921 2.915 2.911 2.907 2.583 2.572 2.555 2.545 2.103 2.094 2.081 2.072 2.063 2.002 1.995 1.987 1.980 1.973 1.965 1.957
X : parts per Million : Proton

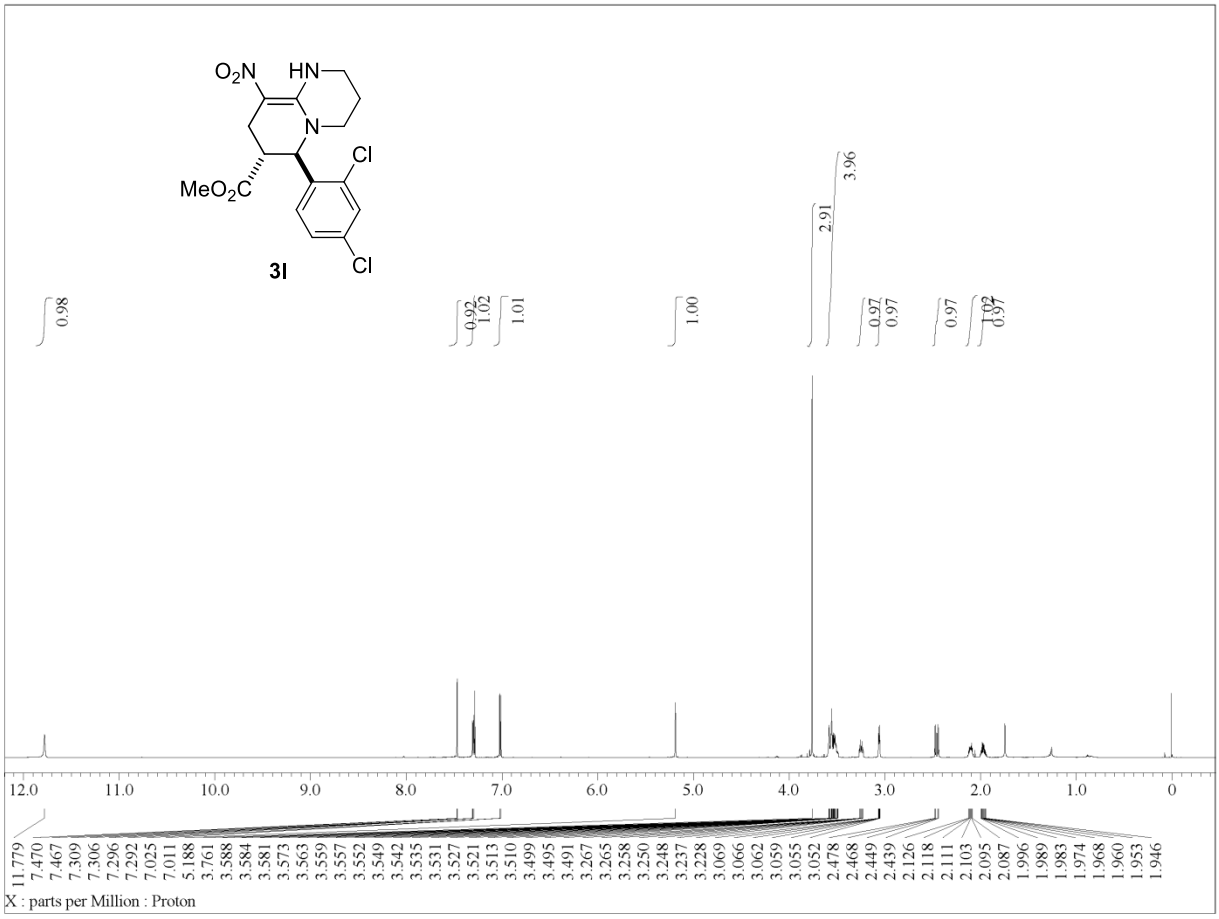

O2N
HN
N
MeO2C
Br
3i
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
172.192 152.746 136.641 132.409 127.660 122.528 103.551 77.211 77.000 76.780 63.193 52.699 47.079 42.943 38.270 21.801 20.059
X : parts per Million : Carbon13

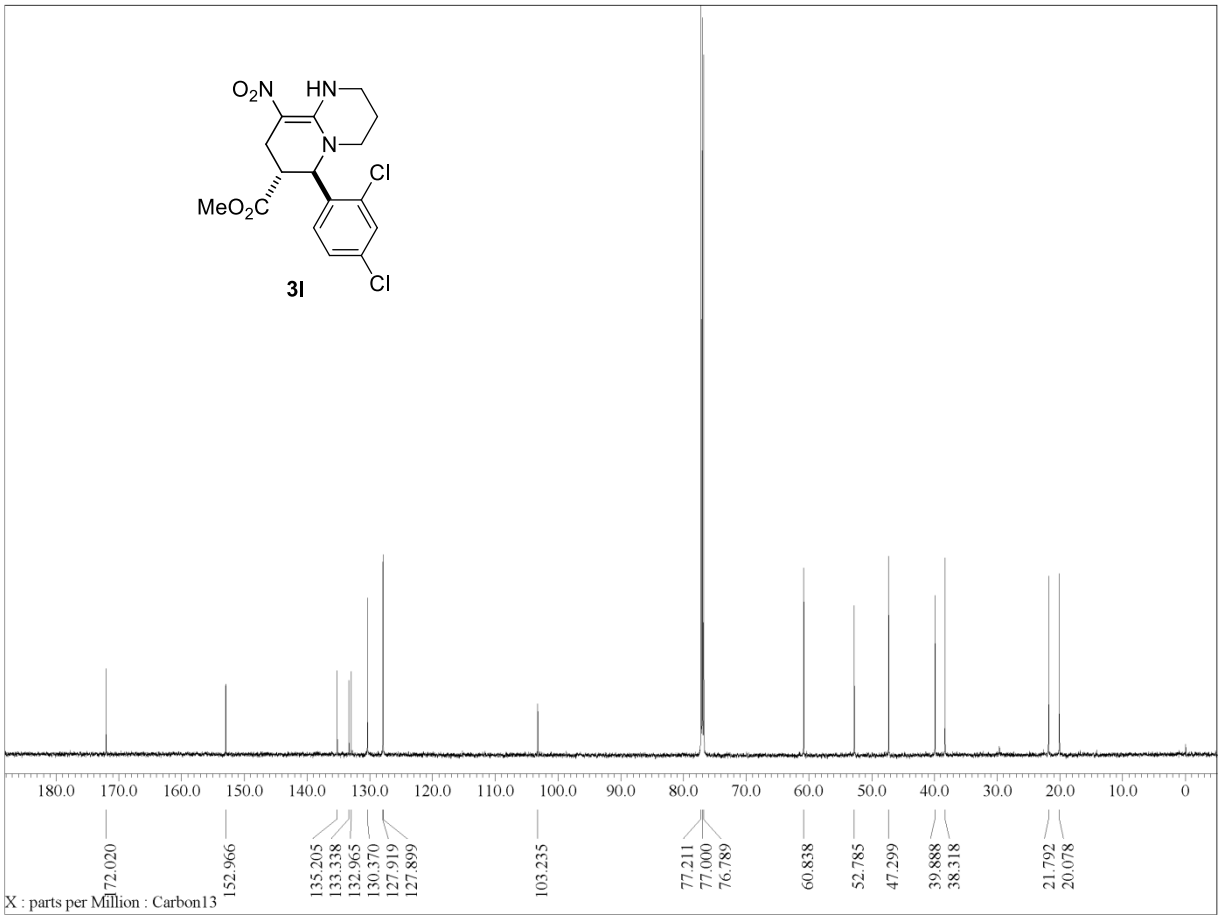

O2N
HN
N
MeO2C
Me
3j
0.96
2.26
1.97
1.00
2.98
3.95
2.08
0.94
0.97
3.00
1.19
1.17
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
11.799
7.955
7.191
7.177
7.025
7.011
4.804
3.723
3.558
3.551
3.544
3.536
3.530
3.522
3.500
3.492
3.485
3.483
3.479
3.472
3.465
3.457
3.452
3.383
3.374
3.364
3.356
3.350
3.347
3.341
3.336
3.327
3.319
3.311
3.309
3.297
3.289
2.926
2.921
2.916
2.911
2.907
2.618
2.609
2.591
2.580
2.351
2.071
2.064
2.057
2.049
2.040
1.987
1.980
1.973
1.965
1.958
1.952
1.944
1.937
1.933
1.923
0.000
X : parts per Million : Proton

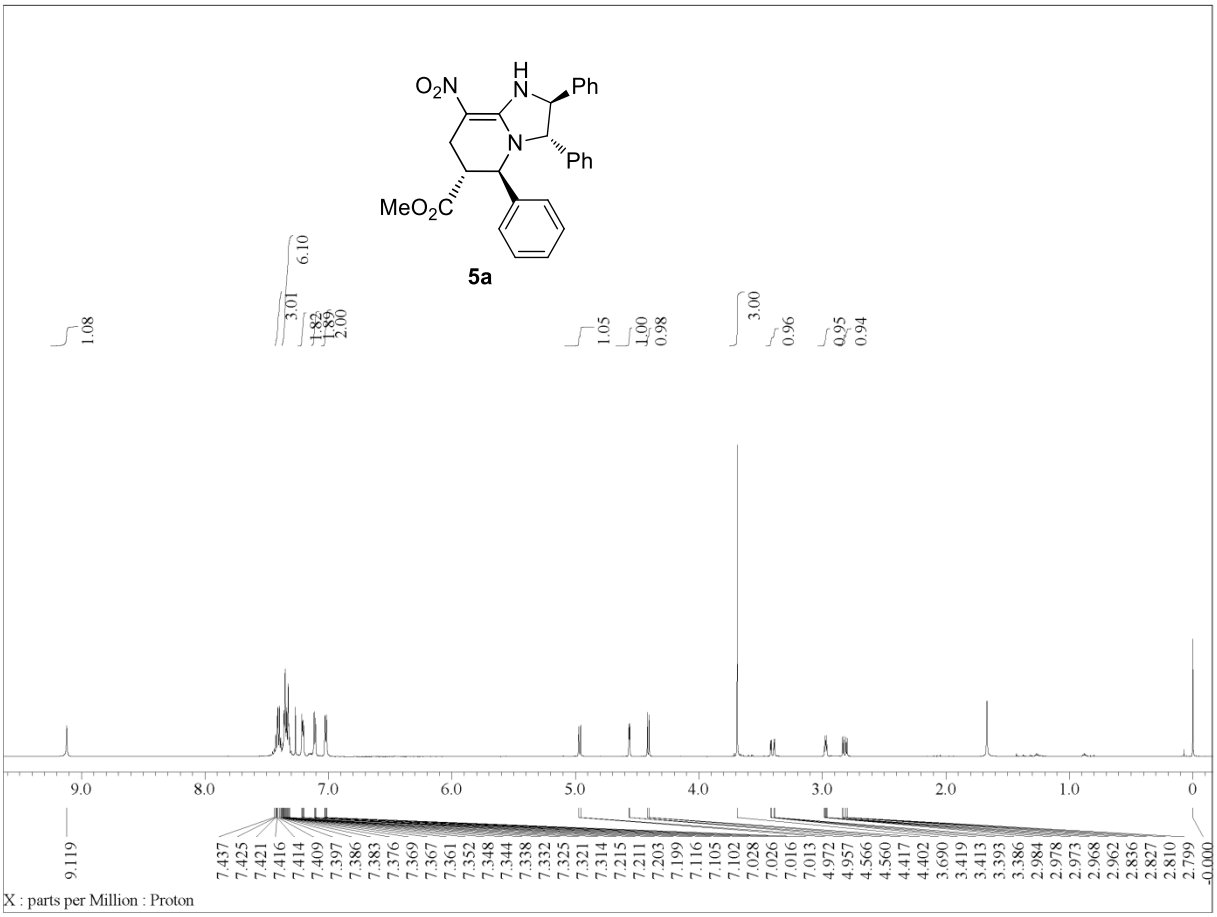

O2N
HN
N
MeO2C
Me
3j
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
172.508
152.832
138.393
134.439
129.853
125.822
103.876
77.220
77.000
76.789
63.452
52.546
46.954
43.172
38.270
21.907
20.988
20.049
X : parts per Million : Carbon13

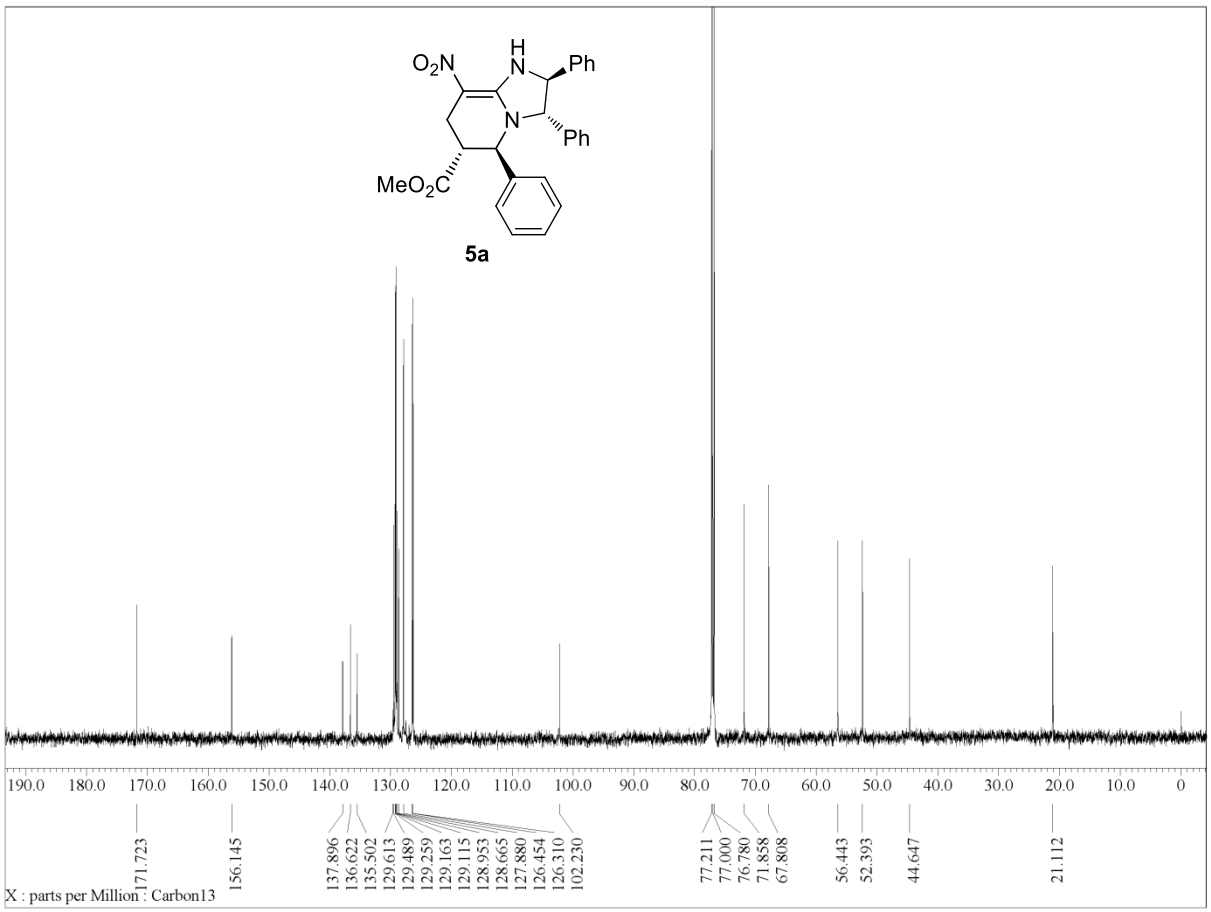

O2N
HN
N
MeO2C
Br
3k
0.98
0.95
1.99
0.95
1.03
2.99
4.16
0.98
0.99
1.00
1.07
1.03
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
11.792
7.500
7.487
7.485
7.291
7.286
7.284
7.278
7.083
7.070
4.826
3.744
3.589
3.581
3.574
3.566
3.560
3.552
3.542
3.539
3.537
3.535
3.530
3.523
3.514
3.510
3.502
3.495
3.488
3.483
3.480
3.334
3.326
3.318
3.316
3.312
3.304
3.297
2.962
2.958
2.952
2.947
2.944
2.589
2.579
2.561
2.550
2.114
2.106
2.098
2.092
2.083
2.075
2.027
2.020
2.012
2.005
1.999
1.991
1.983
X : parts per Million : Proton

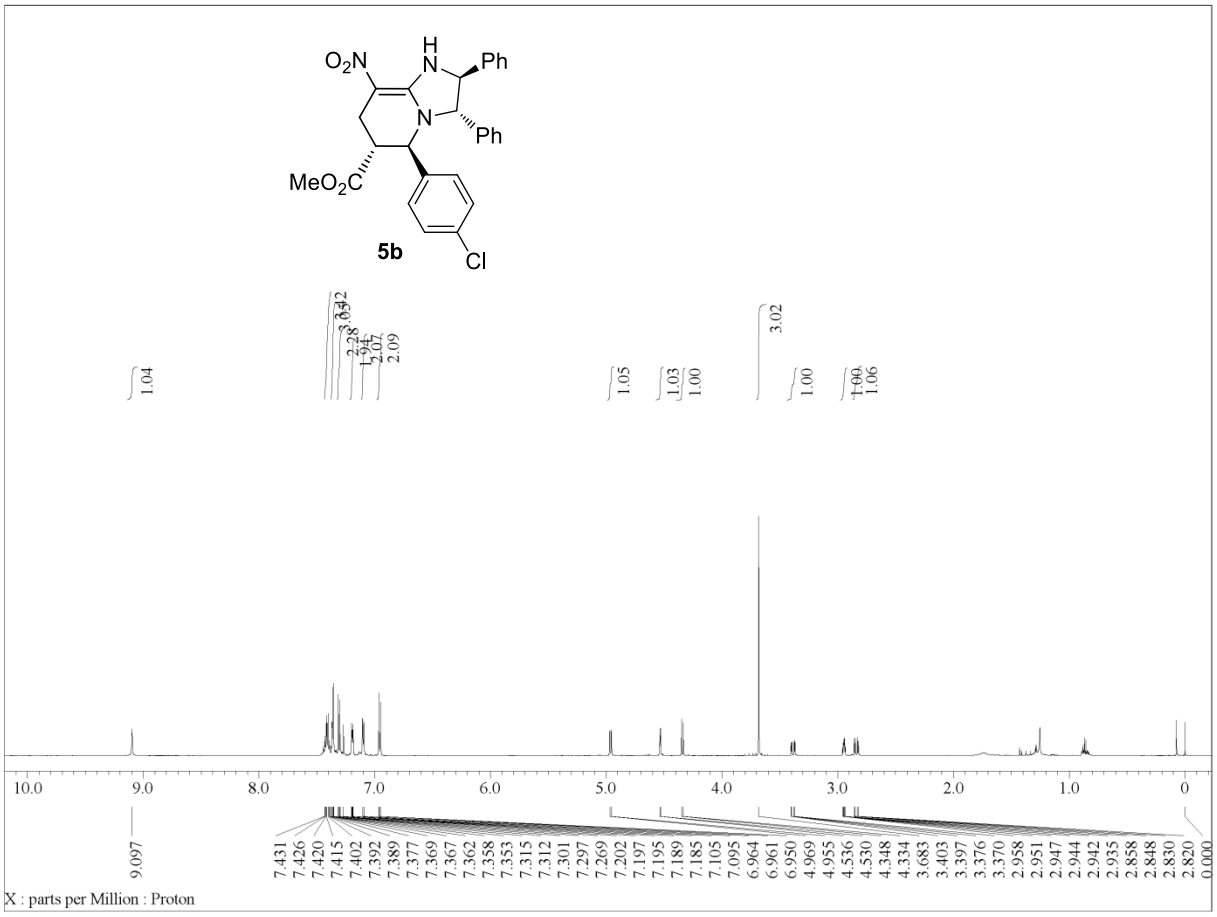

O2N
HN
N
MeO2C
Br
3k
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
172.183
152.727
140.021
131.758
130.858
129.087
124.424
123.399
103.513
77.211
77.000
76.789
63.155
52.738
47.175
42.952
38.289
21.763
20.078
X : parts per Million : Carbon13

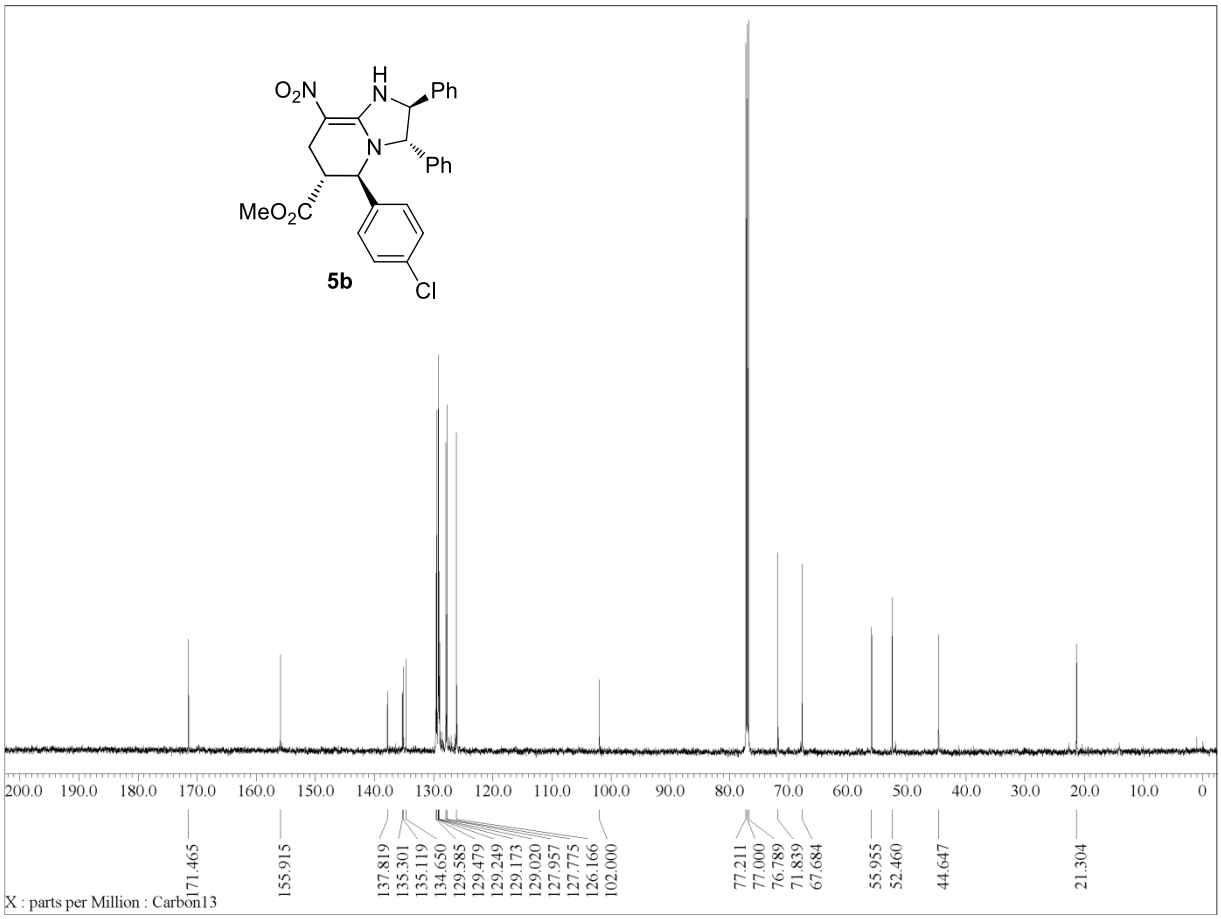

O2N
HN
N
Cl
MeO2C
Cl
3l
0.98
0.92
1.02
1.01
1.00
2.91
3.96
0.97
0.97
0.97
1.02
0.97
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
11.779
7.470
7.467
7.309
7.306
7.296
7.292
7.025
7.011
5.188
3.761
3.588
3.584
3.581
3.573
3.563
3.559
3.557
3.552
3.549
3.542
3.535
3.531
3.527
3.521
3.513
3.510
3.499
3.495
3.491
3.267
3.265
3.258
3.250
3.248
3.237
3.228
3.069
3.066
3.062
3.059
3.055
3.052
2.478
2.468
2.449
2.439
2.126
2.118
2.111
2.103
2.095
2.087
1.996
1.989
1.983
1.974
1.968
1.960
1.953
1.946
X : parts per Million : Proton

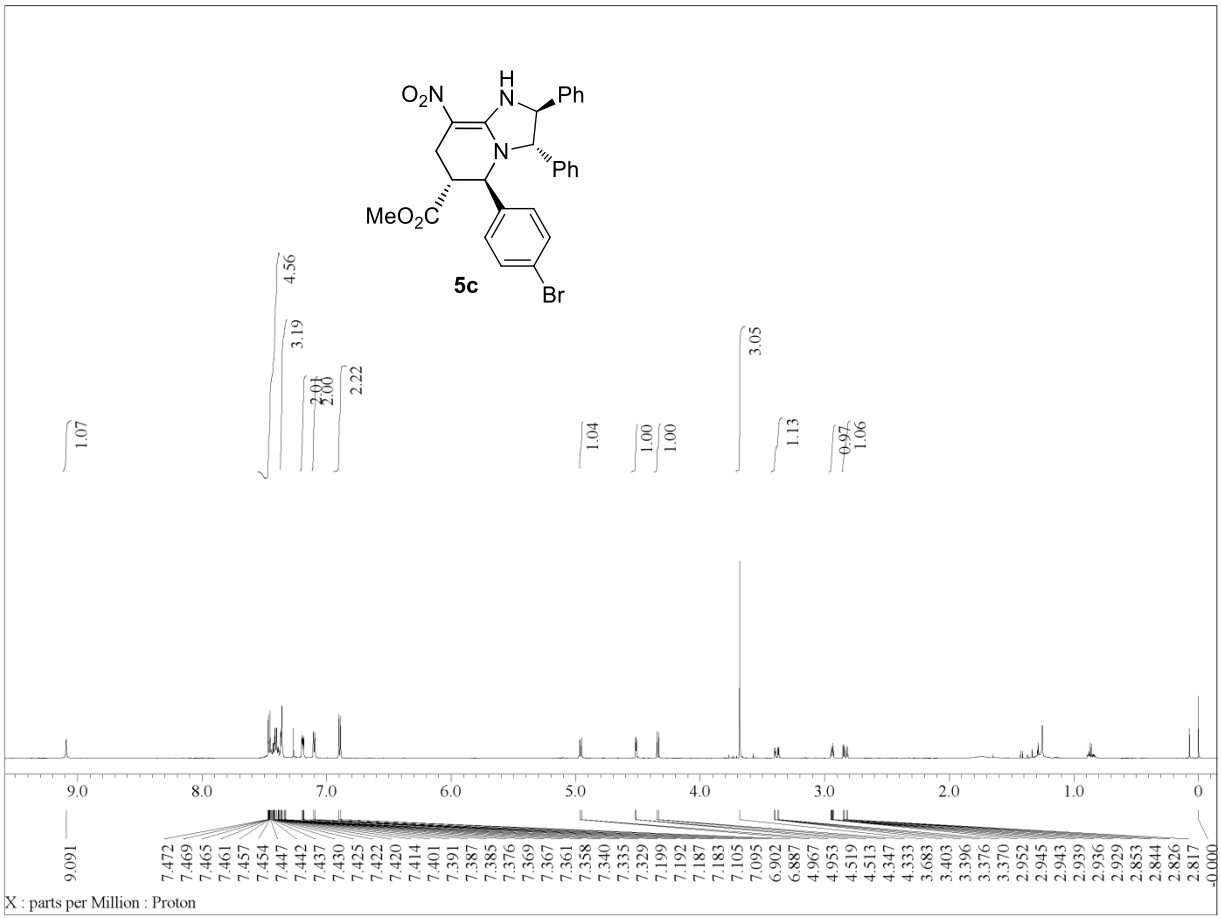

O2N
HN
N
Cl
MeO2C
Cl
3l
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
172.020
152.966
135.205
133.338
132.965
130.370
127.919
127.899
103.235
77.211
77.000
76.789
60.838
52.785
47.299
39.888
38.318
21.792
20.078
X : parts per Million : Carbon13

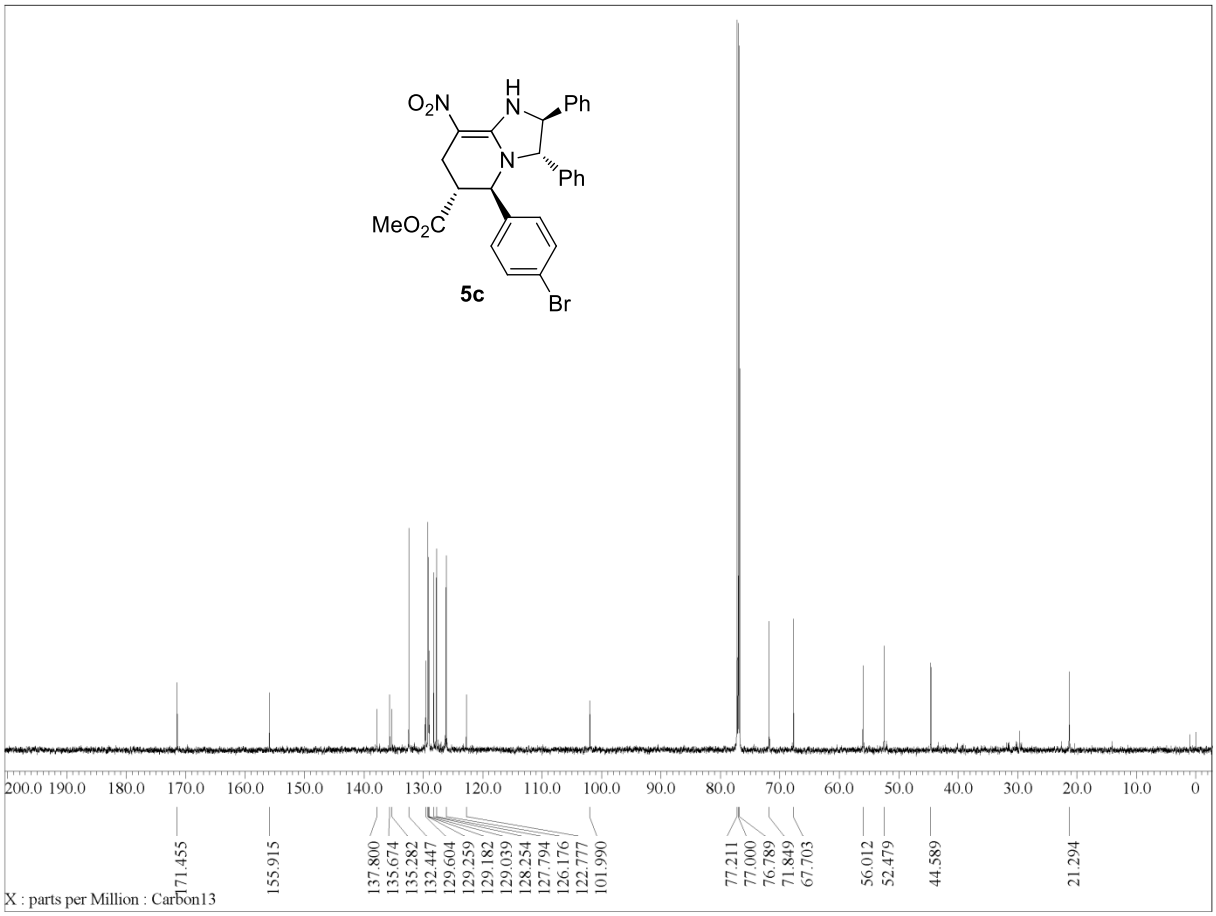

O2N
H
N
Ph
N
Ph
MeO2C
5a
1.08
3.01
6.10
1.82
1.85
2.00
1.05
1.00
0.98
3.00
0.96
0.95
0.94
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.119
7.437
7.425
7.421
7.416
7.414
7.409
7.397
7.386
7.383
7.376
7.369
7.367
7.361
7.352
7.348
7.344
7.338
7.332
7.325
7.321
7.314
7.215
7.211
7.203
7.199
7.116
7.105
7.102
7.028
7.026
7.016
7.013
4.972
4.957
4.566
4.560
4.417
4.402
3.690
3.419
3.413
3.393
3.386
2.984
2.978
2.973
2.968
2.962
2.836
2.827
2.810
2.799
-0.000
X : parts per Million : Proton

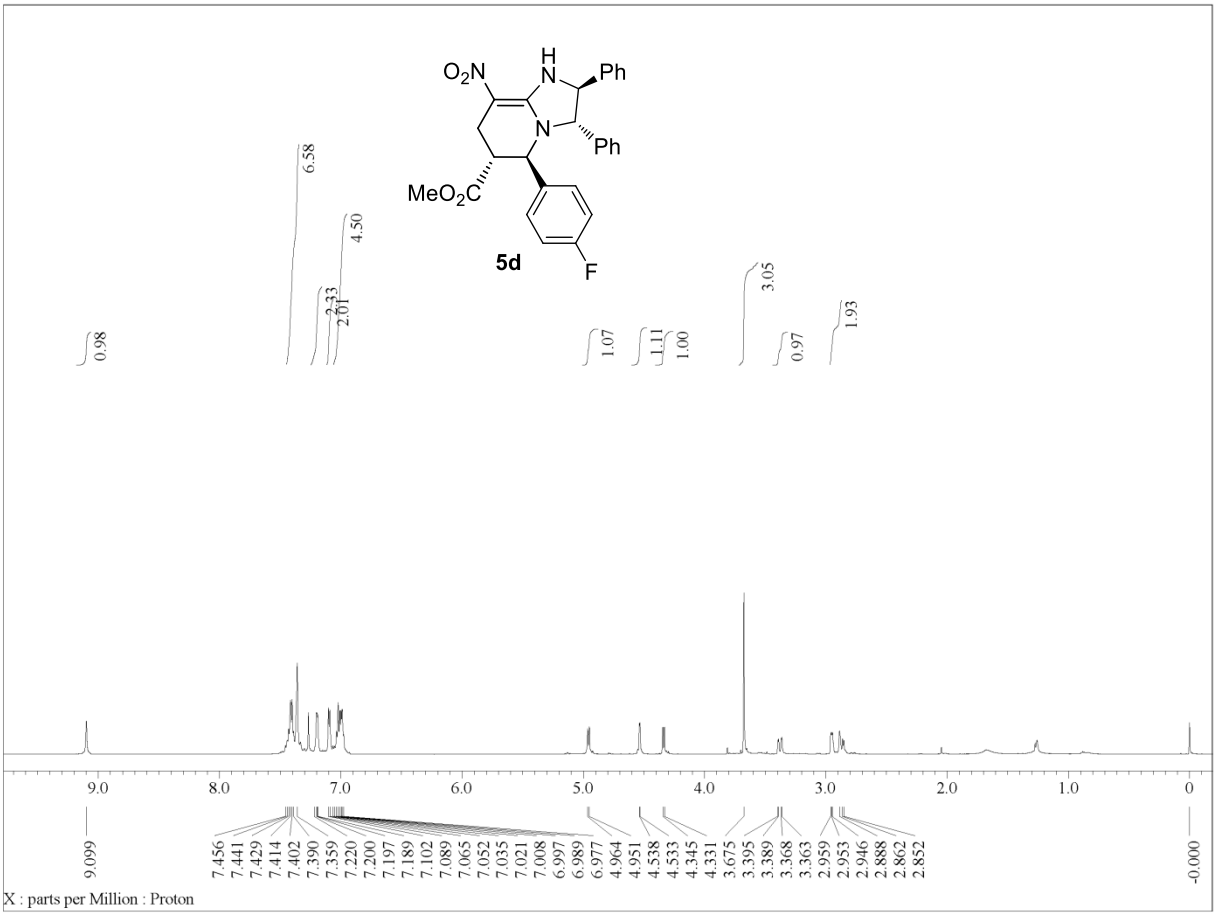

O2N
H
N
Ph
N
Ph
MeO2C
5a
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
171.723
156.145
137.896
136.622
135.502
129.613
129.489
129.259
129.163
129.115
128.953
128.665
127.880
126.454
126.310
102.230
77.211
77.000
76.780
71.858
67.808
56.443
52.393
44.647
21.112
X : parts per Million : Carbon13


5b
1.04
2.09
1.05
1.03
1.00
3.02
1.00
1.06
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.097
X : parts per Million : Proton


5b
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
171.465
155.915
137.819
135.301
135.119
134.650
129.585
129.479
129.249
129.173
129.020
127.957
127.775
126.166
102.000
77.211
77.000
76.789
71.839
67.684
55.955
52.460
44.647
21.304
X : parts per Million : Carbon13


O2N
H
N
Ph
N
Ph
MeO2C
5c
Br
4.56
3.19
2.01
2.00
2.22
1.07
1.04
1.00
1.00
3.05
1.13
0.97
1.06
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.091
7.472
7.469
7.465
7.461
7.457
7.454
7.447
7.442
7.437
7.430
7.425
7.422
7.420
7.414
7.401
7.391
7.387
7.385
7.376
7.369
7.367
7.361
7.358
7.340
7.335
7.329
7.199
7.192
7.187
7.183
7.105
7.095
6.902
6.887
4.967
4.953
4.519
4.513
4.347
4.333
3.683
3.403
3.396
3.376
3.370
2.952
2.945
2.943
2.939
2.936
2.929
2.853
2.844
2.826
2.817
-0.000
X : parts per Million : Proton


O2N
H
N
Ph
N
Ph
MeO2C
5c
Br
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
171.455
155.915
137.800
135.674
135.282
132.447
129.604
129.259
129.182
129.039
128.254
127.794
126.176
122.777
101.990
77.211
77.000
76.789
71.849
67.703
56.012
52.479
44.589
21.294
X : parts per Million : Carbon13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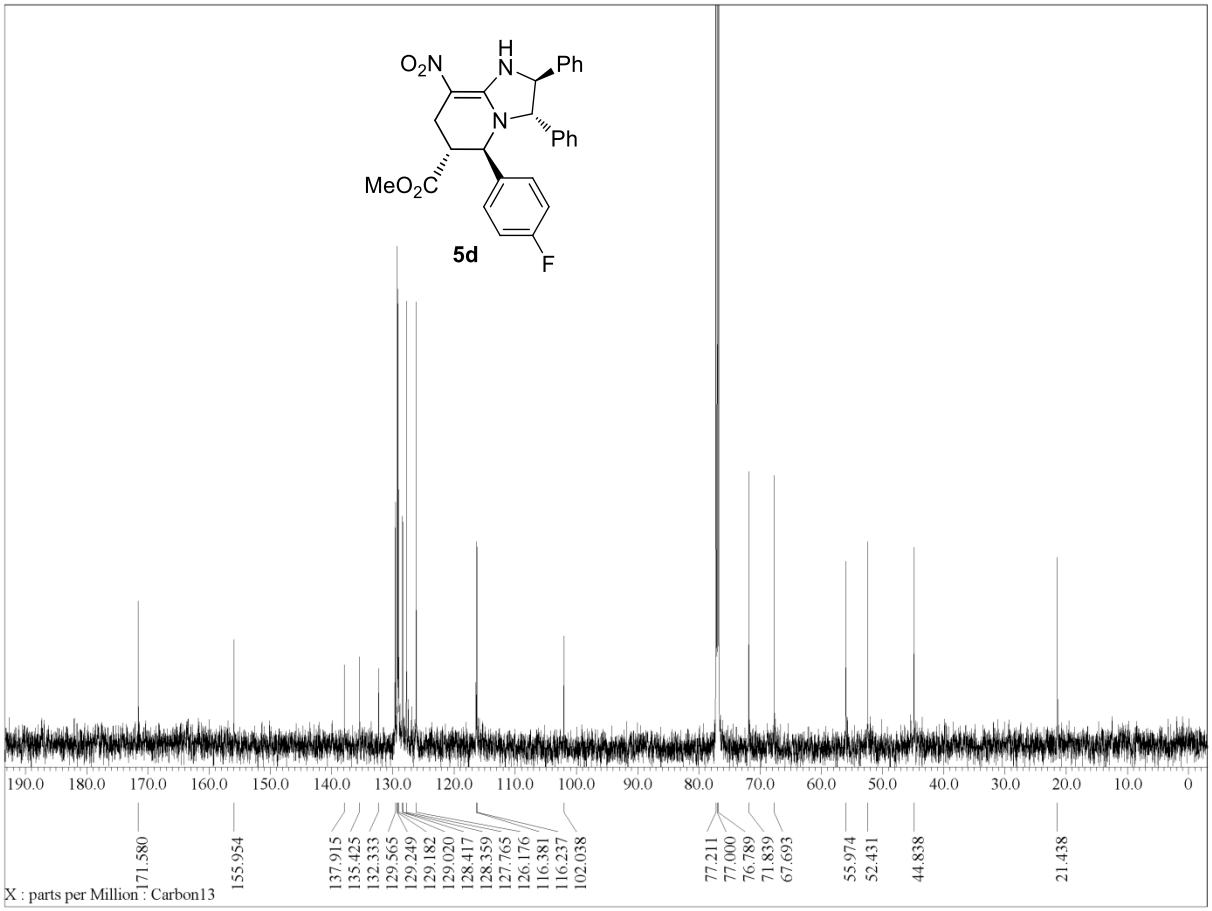
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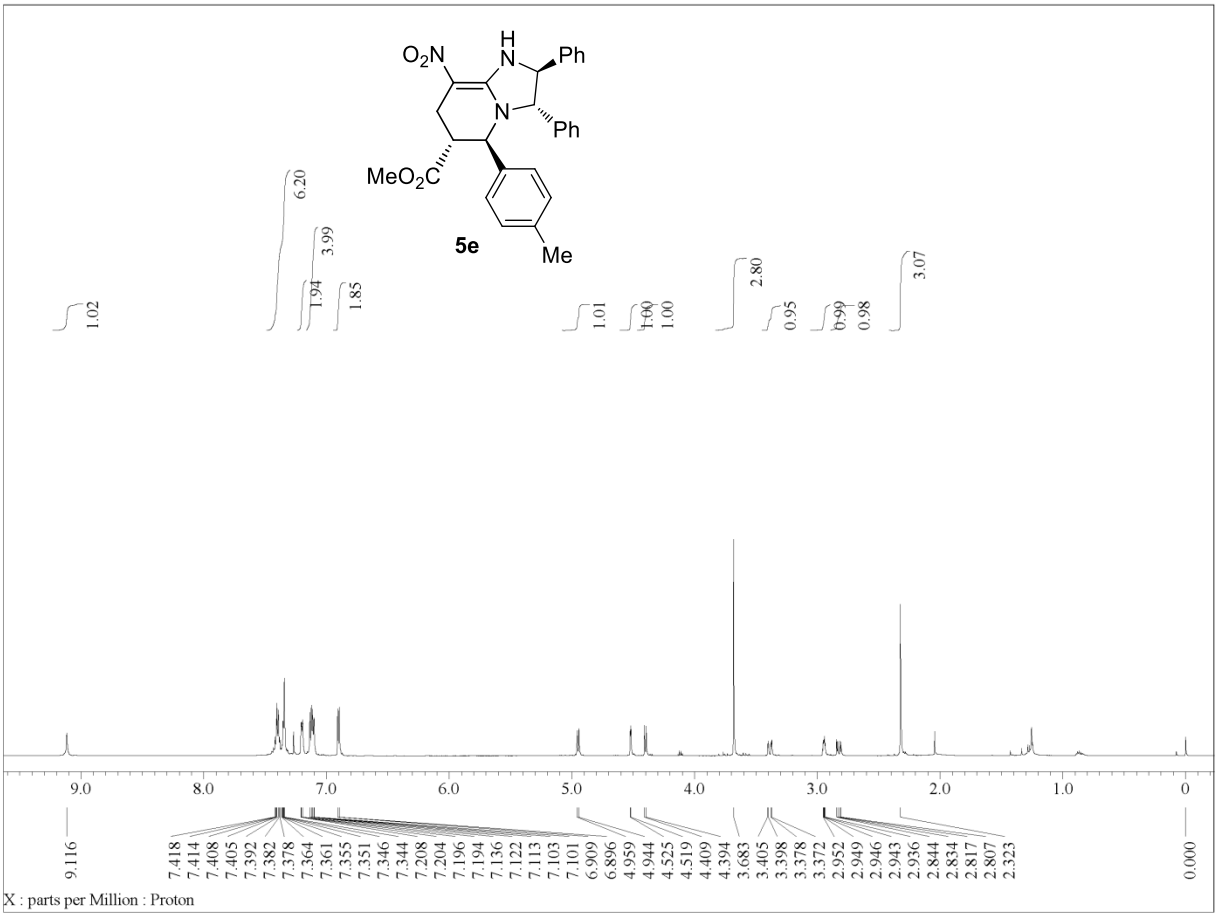
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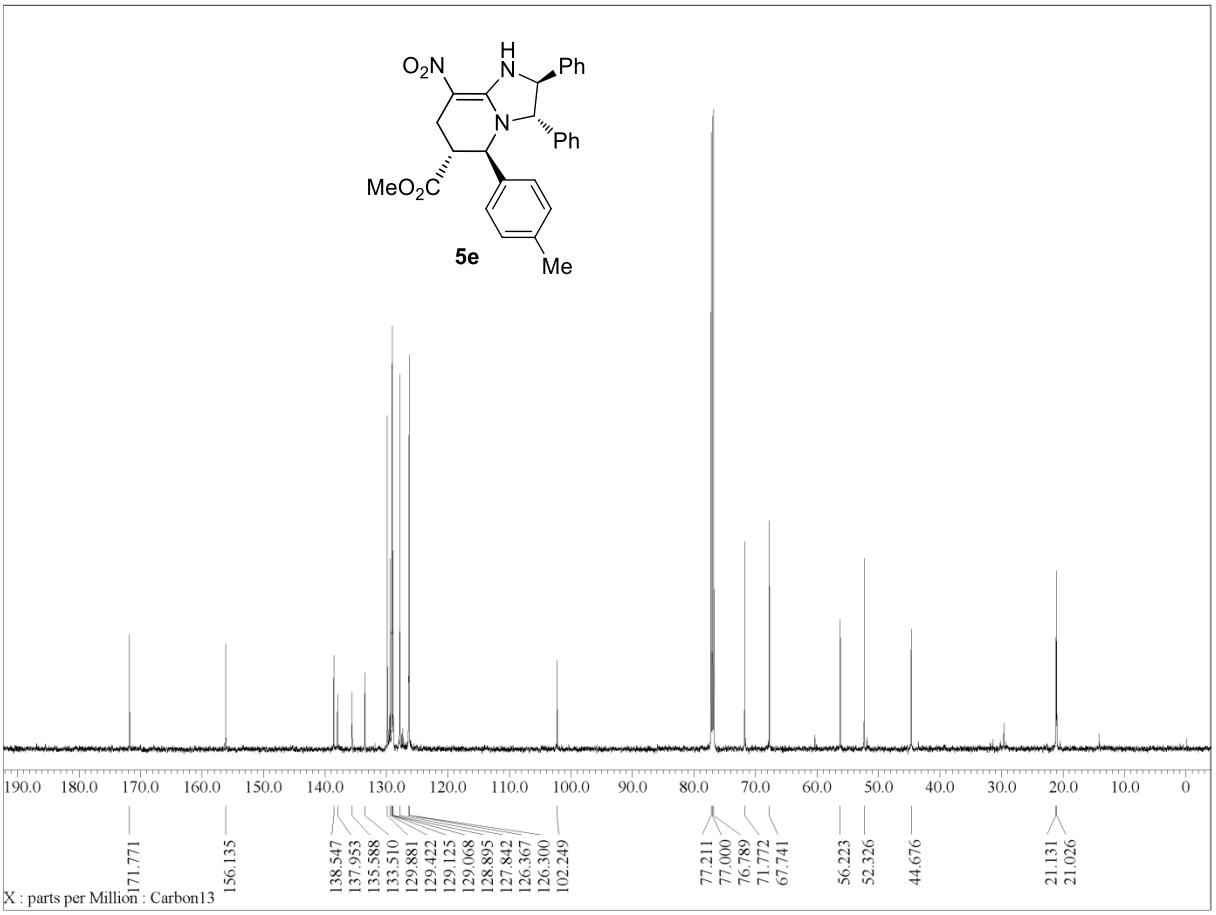
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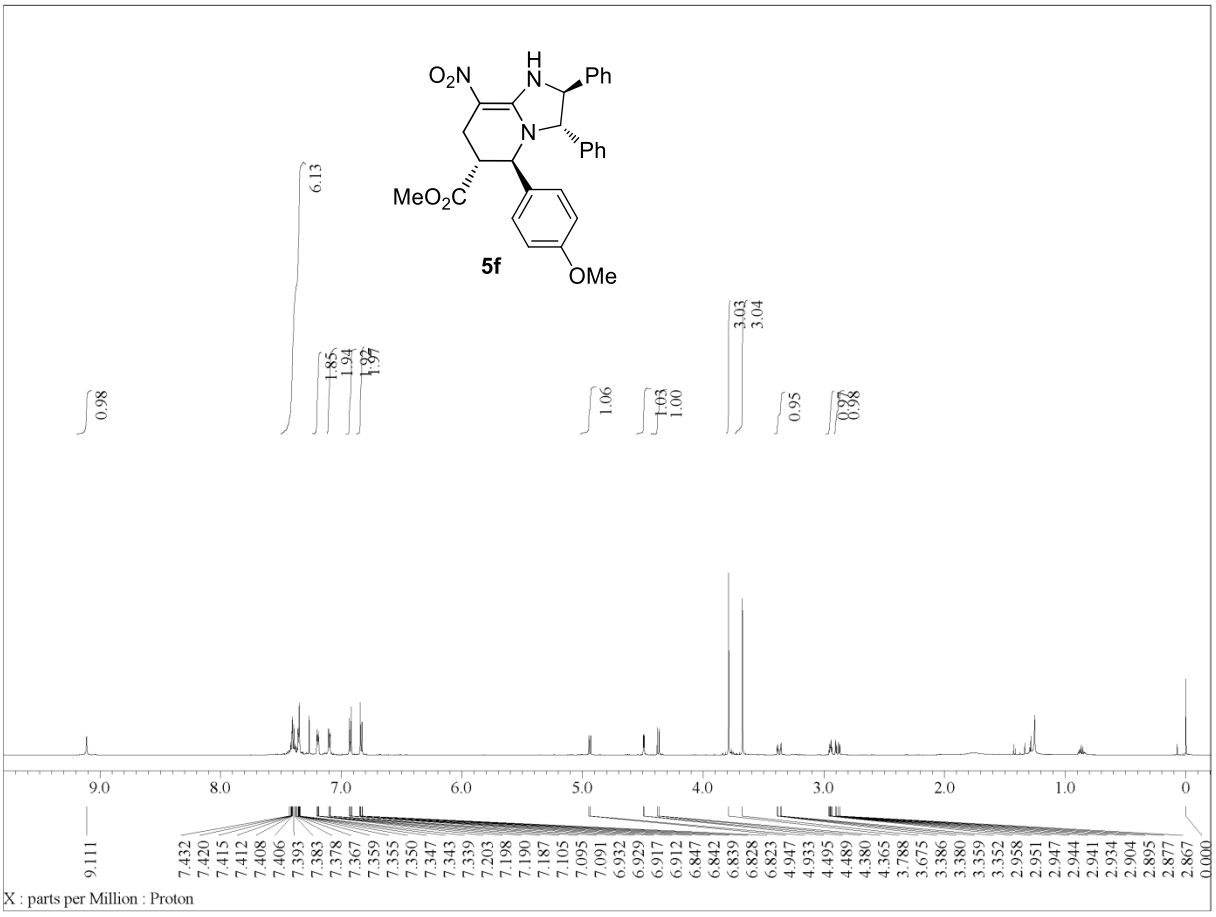
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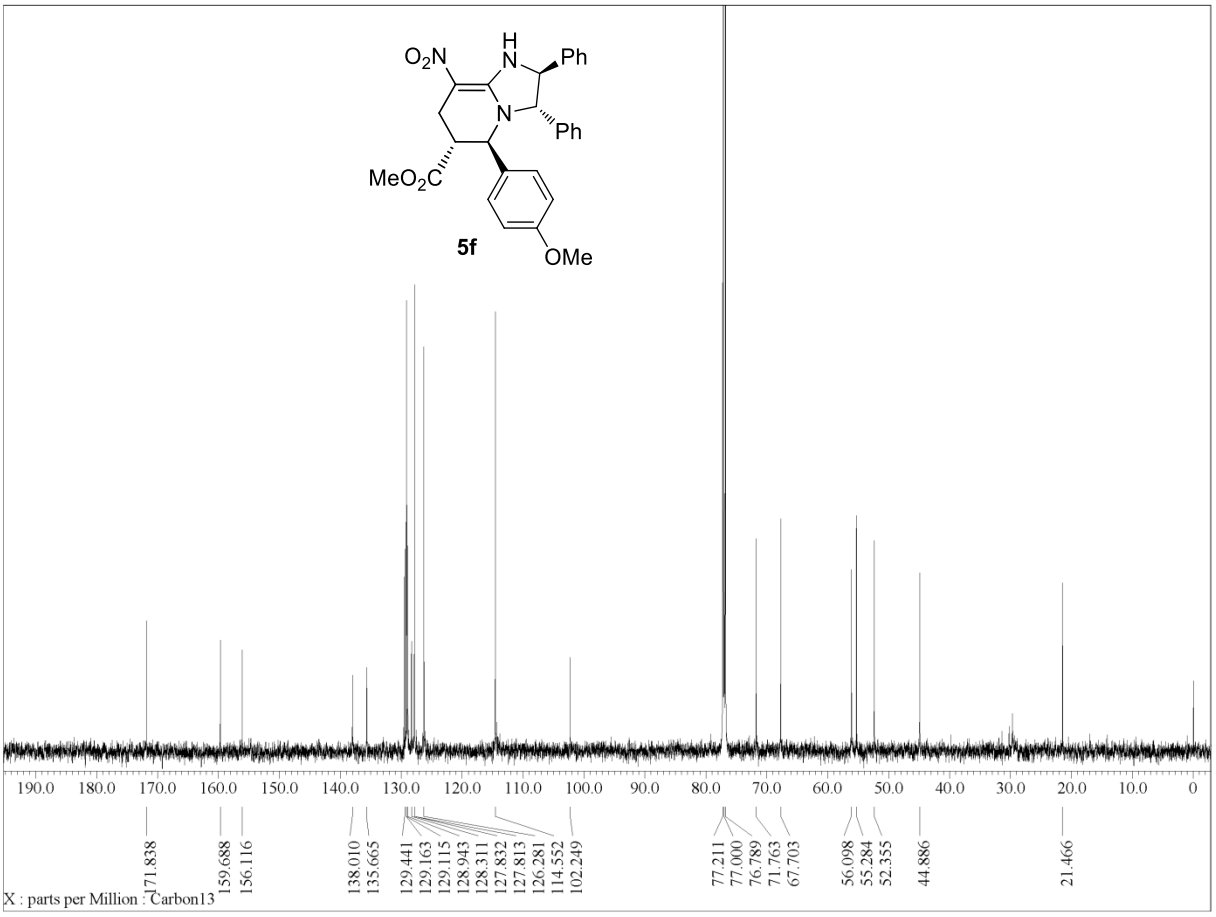
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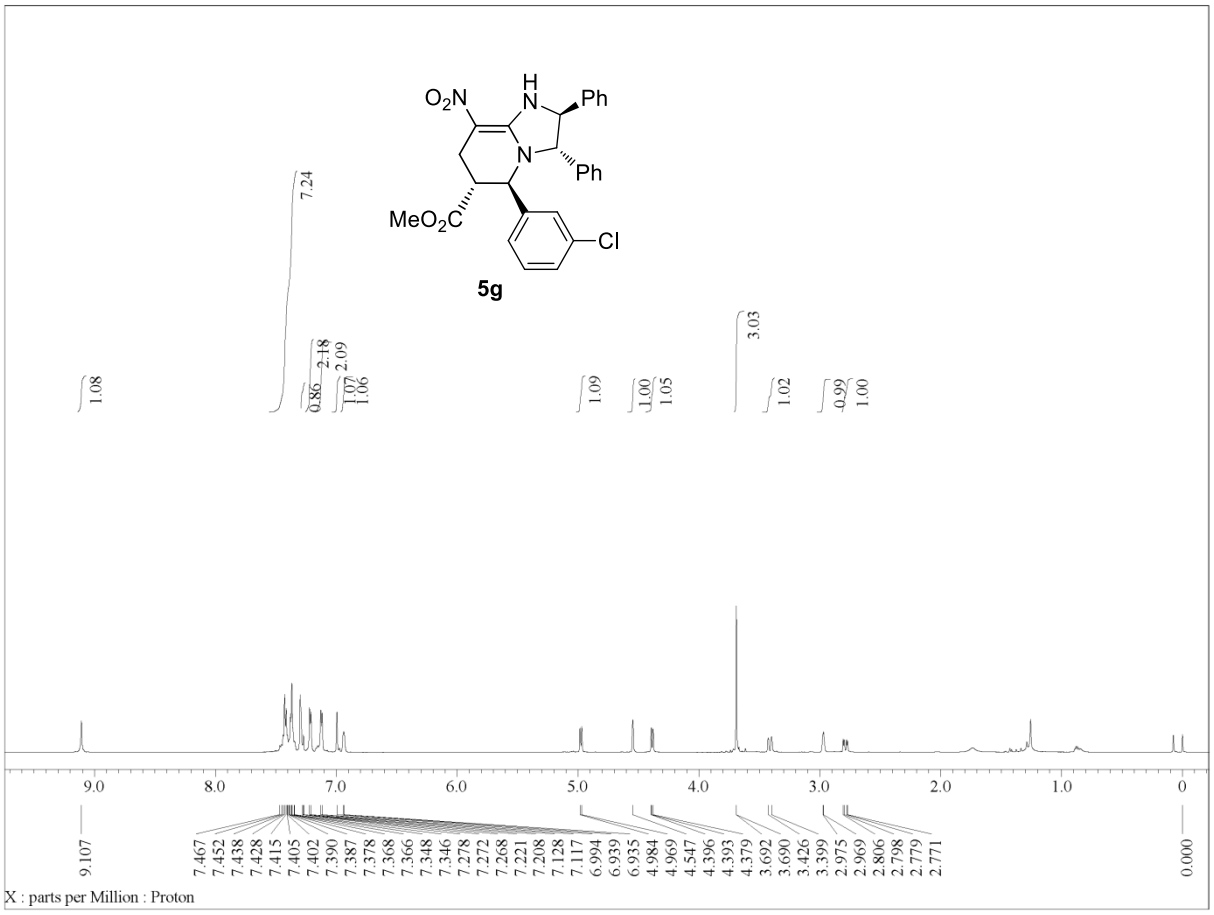
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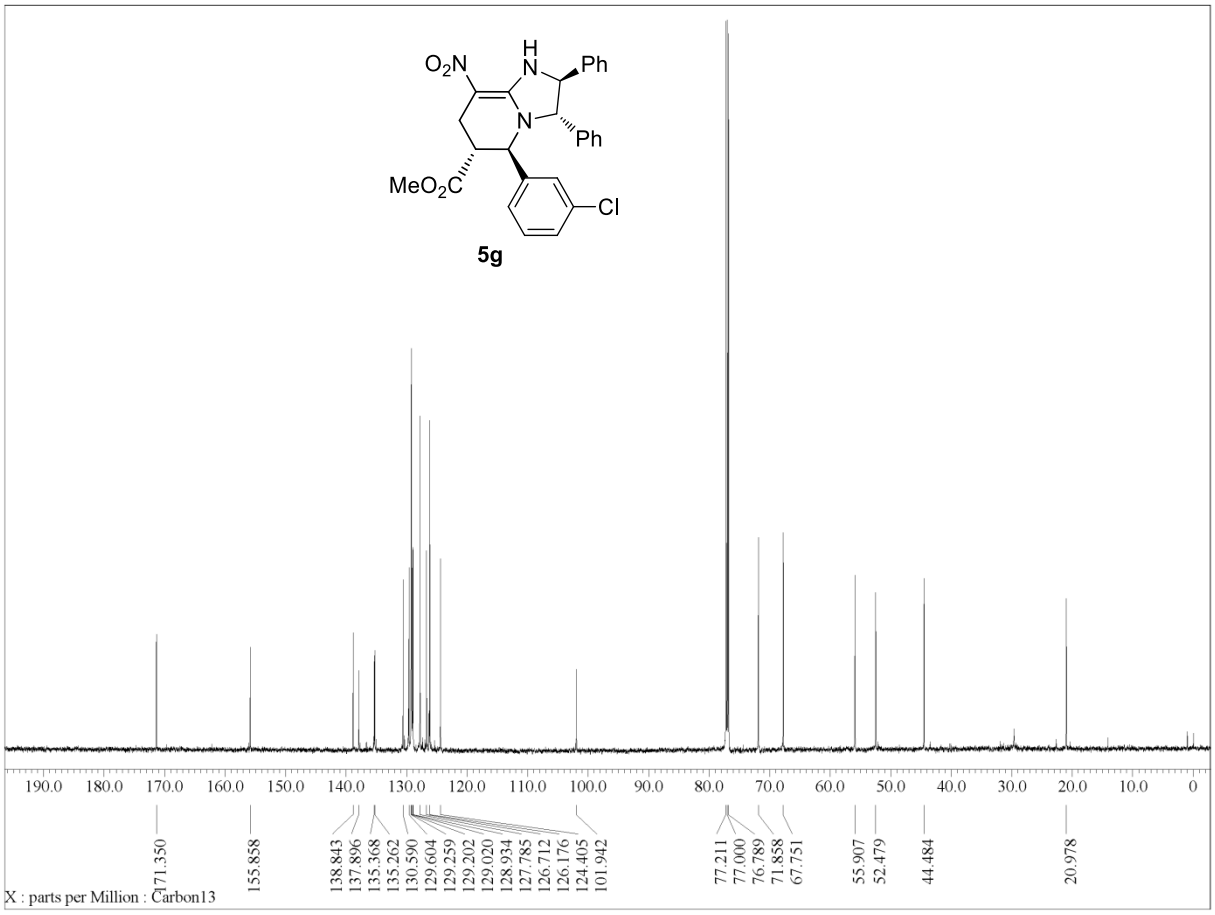
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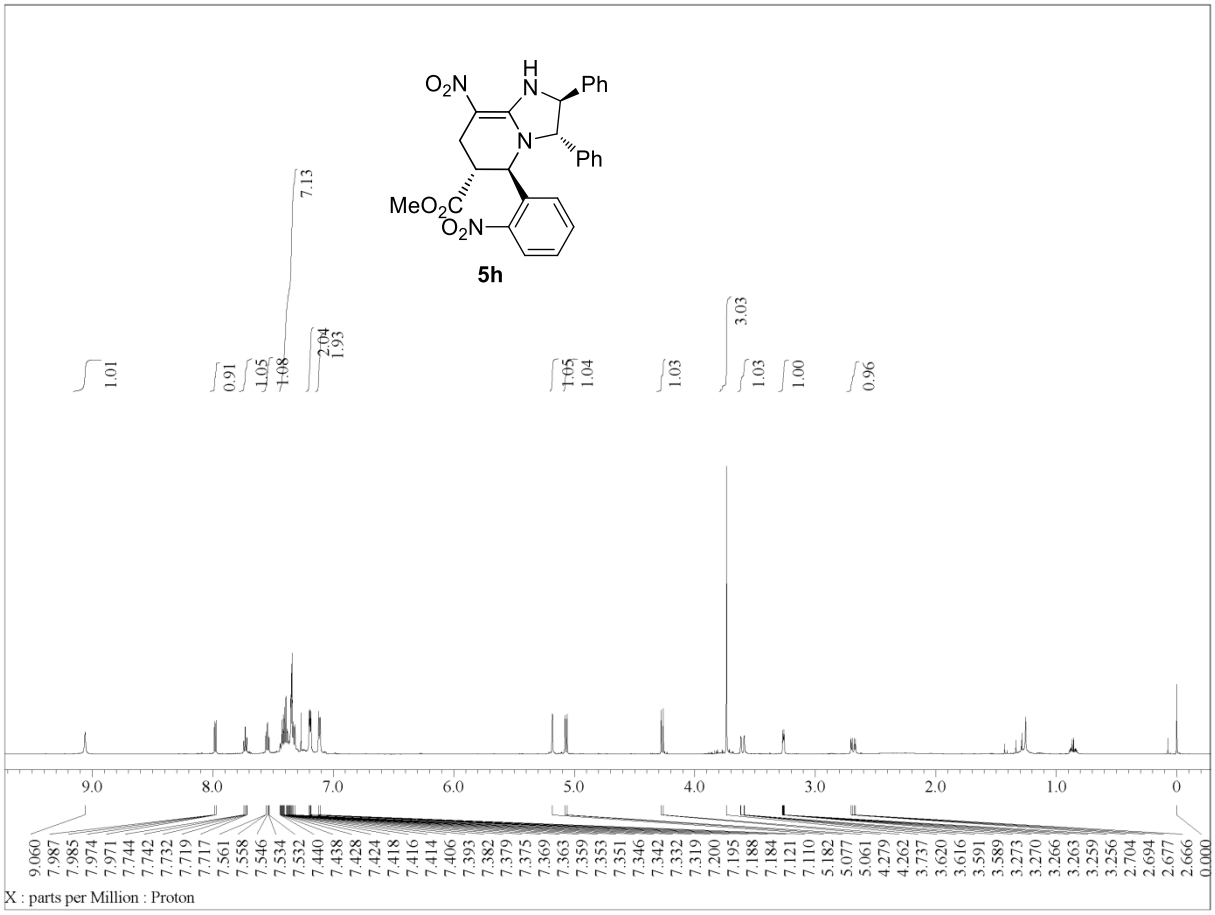
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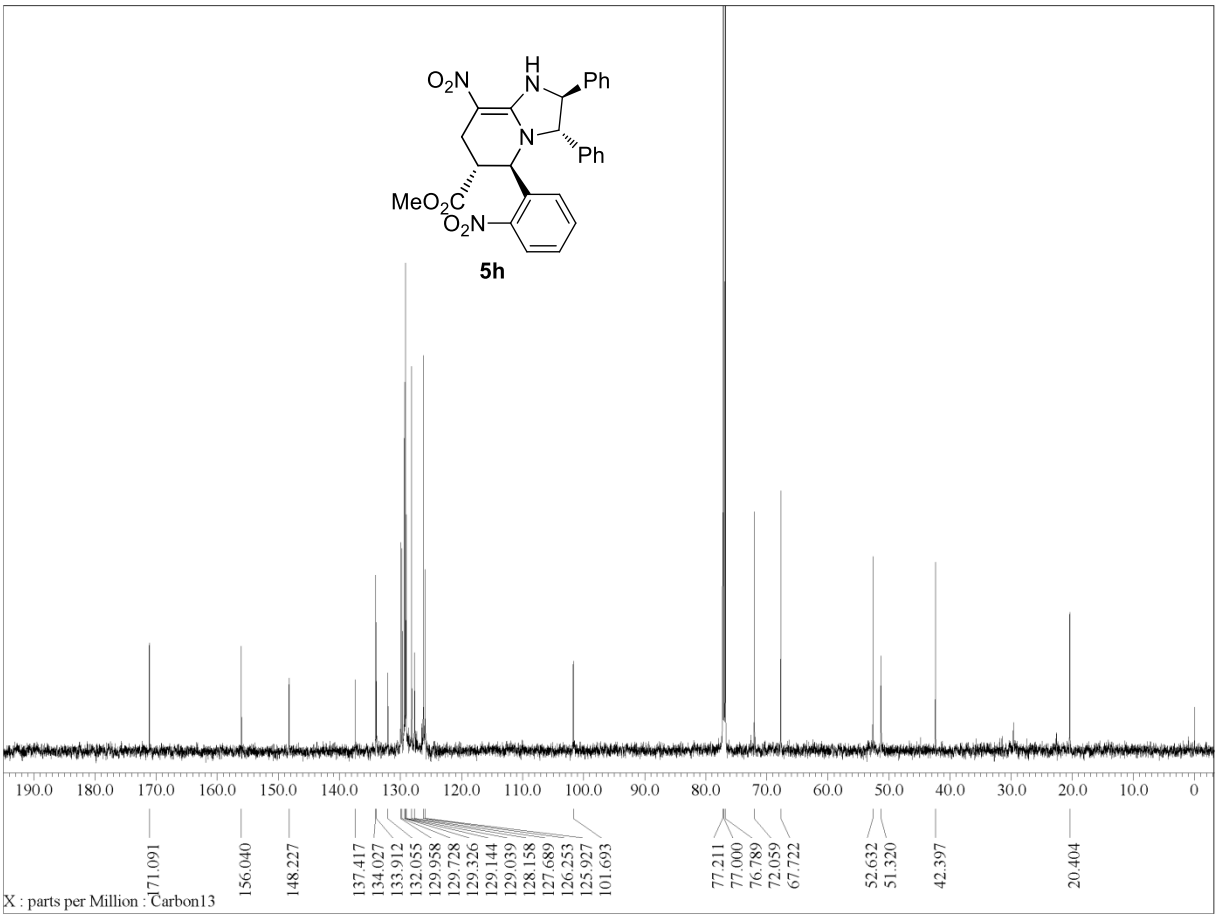
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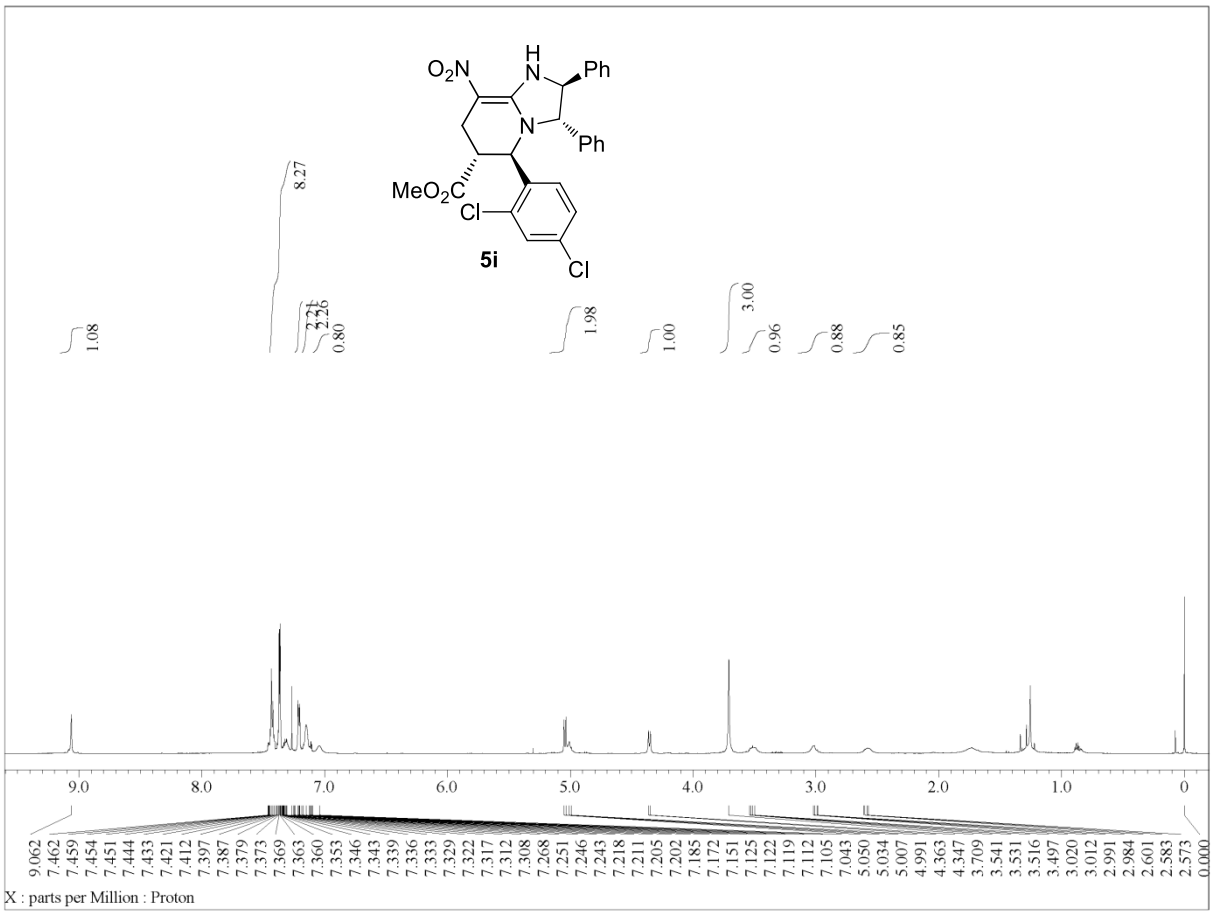
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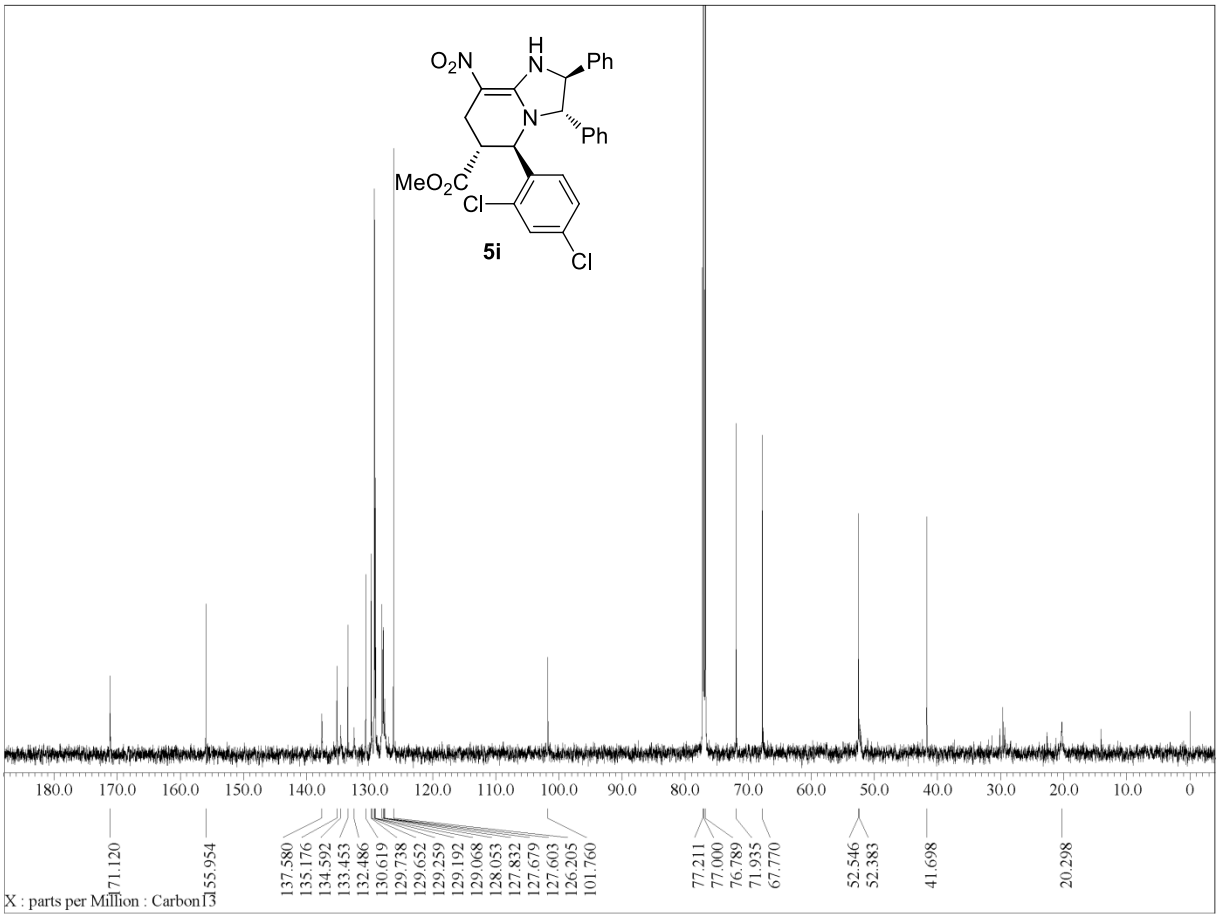
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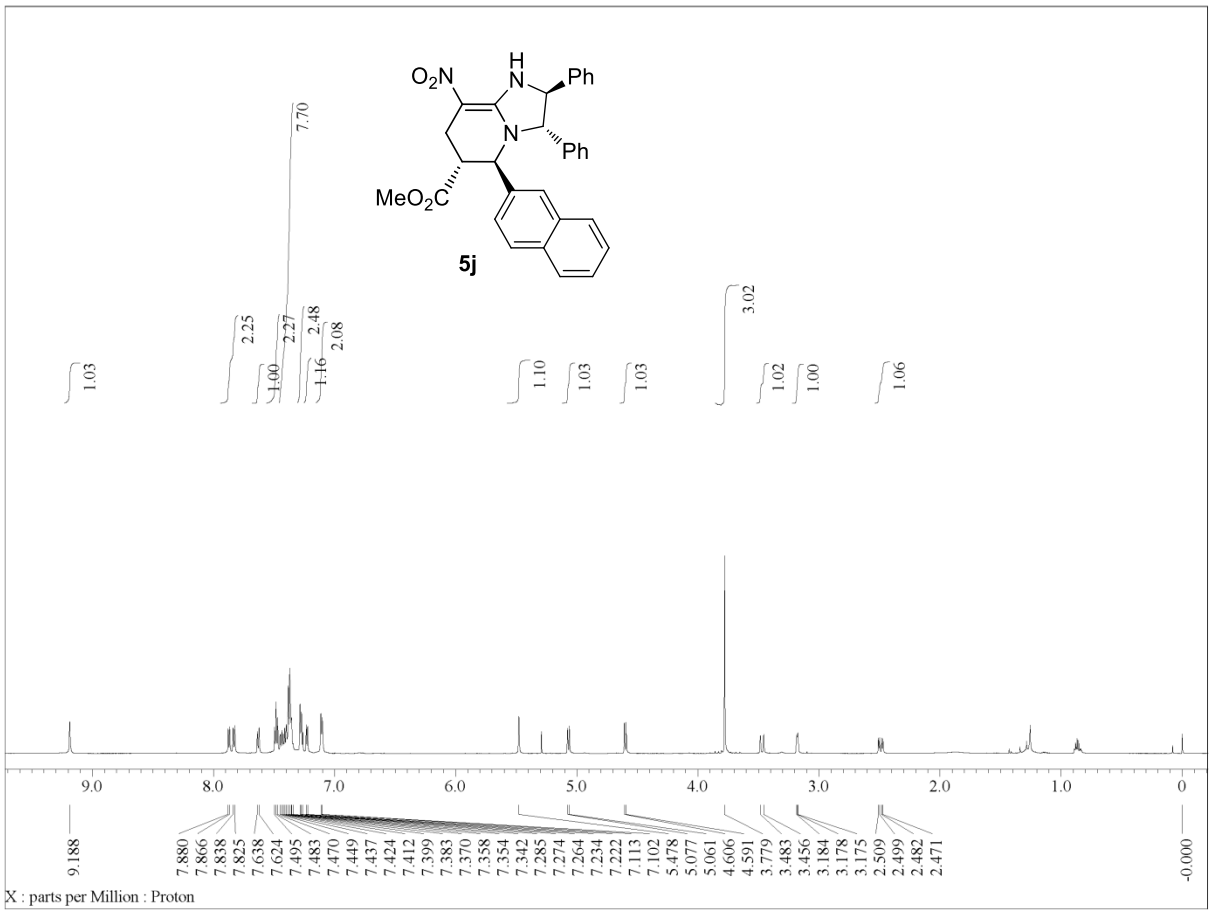
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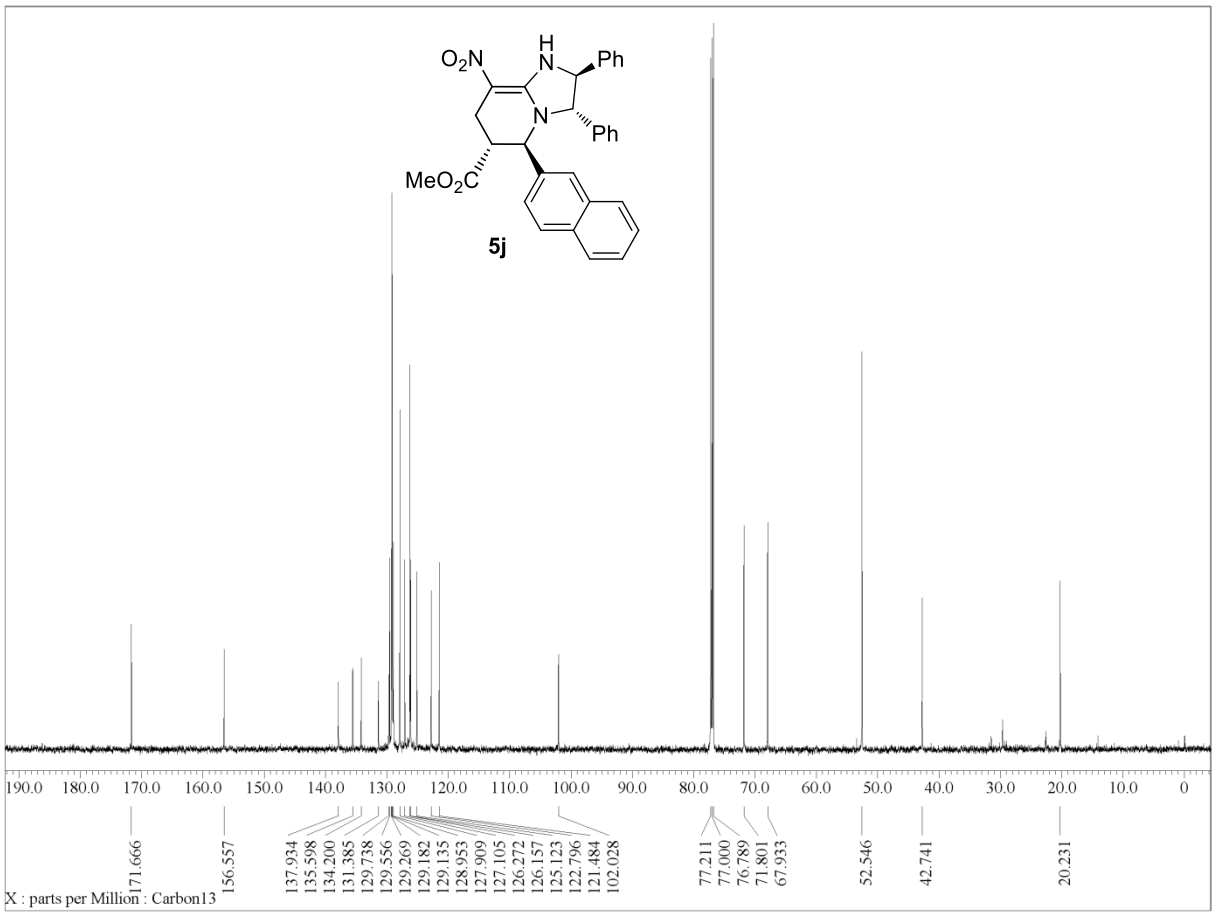
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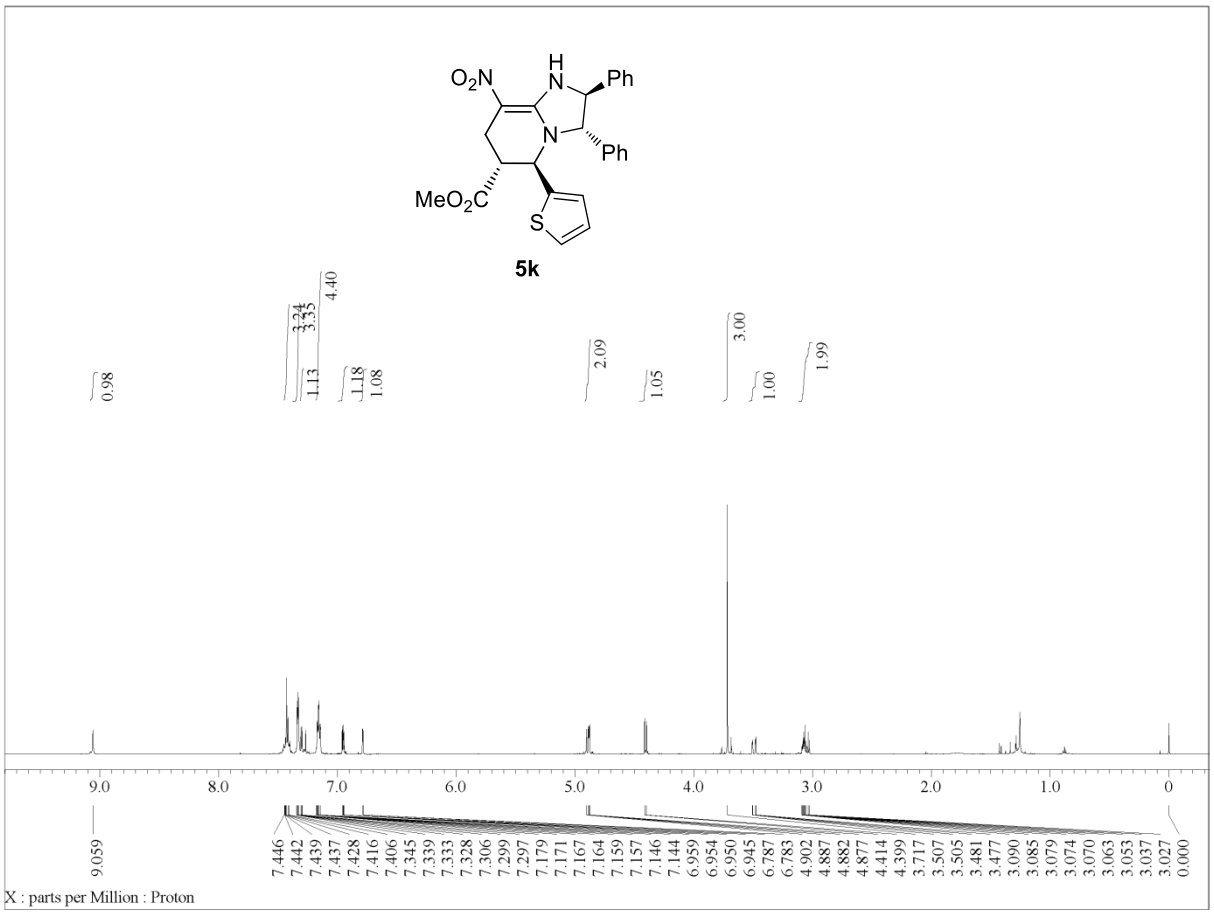
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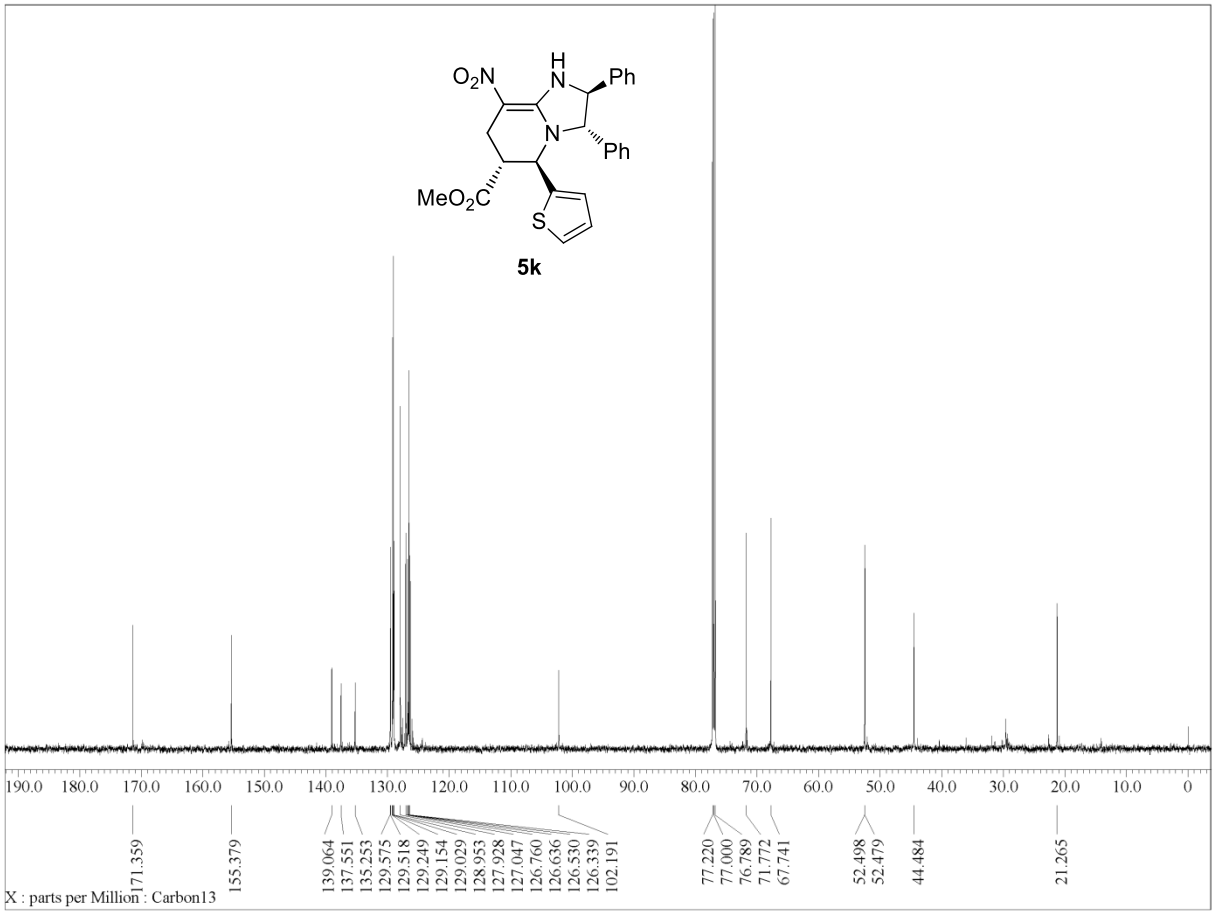
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52.479
44.484
21.265
X : parts per Million : Carbon13

8. Cell culture and cellular proliferation assay

The human breast cancer cell line MDA-MB-231 and human colorectal carcinoma cell HCT116 were obtained from American Type Culture Collection (ATCC), the cells were incubated under sterile conditions at 37℃ and were maintained in a humidified atmosphere 5% (v/v) CO_2 with RPMI-1640 or DMEM medium containing 10% fetal bovine serum (GIBCO, Waltham, MA, USA). MTT assay was performed to evaluate the cellular proliferation inhibitory activities of test compounds by cancer cells. In general, cells were seeded into 96-well plates and treated with a series of concentration of test drugs for 24 h. The MTT reagent (5 mg/ml) was added per well for 3 h at 37℃. After that, the MTT was removed and 150 μl DMSO was added to dissolve the formazan crystals. Then, optical density (OD) was measured at 570 nm of the solution. The control group consisted of untreated cells. The percentage of cell viability averaged from three individual experiments.

9. HTRF based MDM2-p53 interaction assay

The enzymatic assay of test compounds was using the HTRF based method provided by Cisbio Co. Ltd., in brief, the HTRF assay used a GST-tagged kinase domain of the MDM2, and then the biotinylated substrate peptide of p53 and two HTRF detection reagent are added. The HTRF signal is proportional to the amount of interactions between GST-tagged MDM2 protein and the biotinylated substrate p53 peptide, the detailed experimental procedures are according to the manufacturer's protocols and were reported in previous articles by us and other groups.[ref] These experiments involve the transfer of energy from europium pyridine-bis-bipyridine cryptate (Eu-PBBP) as donor fluorophore to Alexa 647 as acceptor fluorophore. We used the ligand labeled with Eu-PBBP and the monoclonal anti-MDM2 antibody labeled with Alexa 647 provided by Cisbio international research group. Cells or membranes were incubated with 2 nM Eu-PBBP labeled p53 substrate peptide, 3 nM Alexa 647-labeled anti-MDM2 antibody, and increasing concentrations (10 pM to 10 μM) of test compounds. As a negative control, cells or membranes were incubated only with the donor fluorophore-labeled antibody. Competition experiments in a 384-well plate were performed in a final volume of 50 μL. After an incubation of 16h at 4 °C, preparations were excited at 337 nm and fluorescence emissions were measured on 620 nm and 665 nm, wavelengths which correspond to the total europium cryptate emission and to the FRET signal, respectively. The specific signal was calculated using the following equation: DeltaF = (R − Rneg)/(Rneg) where R is the ratio (fluorescence 665 nm/fluorescence 620 nm) calculated for each assay and Rneg is the same ratio for the negative control.

References:

[1] M.-C. Yang, C. Peng, H. Huang, L. Yang, X.-H. He, W. Huang, H.-L. Cui, G. He and B. Han, *Org. Lett.* 2017, **19**, 6752.

[2] L. Albizu, G. Teppaz, R. Seyer, H. Bazin, H. Ansanay, M. Manning, B. Mouillac and T. Durroux, *J. Med. Chem.* 2007, **50**, 4976.

[3] M. Gicquel, C. Gomez, M. C. G. Alvarez, O. Pamlard, V. Guérineau, E. Jacquet, J. Bignon, A. Voituriez and A. Marinetti, *J. Med. Chem.* 2018, **61**, 9386.

10. Molecular docking

The CDOCKER module in Discovery Studio 3.5 were employed for molecular docking in the current study. The crystal structure of MDM2 complexed with RG7112 (PDB ID: 4IPF) was chosen as the reference structure since it has the highest resolution (1.7 Å) among all the imidazole-based MDM2 inhibitors co-crystal structures. We adjusted the docking parameters until the docked pose is as close as possible to the original crystallized structure in the p53 substrate binding site of MDM2. The docking parameters of CDOCKER used default settings, unless for special statements.

11. Western blot analysis

HCT116 Cells were treated with 0.5, 2.0 μM of compound **5c** or 2.0 μM of RG7112 as described above, collected and washed twice with ice-cold PBS, then lysed in RIPA buffer (20 mM Tris-HCl, 150 mM NaCl, 0.5% sodium deoxycholate, 5 mM EDTA, 1% Nonidet P-40, 0.1% SDS) supplemented with protease and phosphatase inhibitor cocktails (Sigma-Aldrich, MA, USA). Protein concentration was measured using the bicinchoninic acid assay (Keygen, Nanjing, China). Total protein (approximately 50 μg) was fractionated on a 10-15% sodium dodecyl sulfate polyacrylamide gel, then electrophoretically transferred to a polyvinylidene difluoride membrane (Millipore, CA, USA). Membranes were incubated at 4 °C overnight with primary antibodies against MDM2, p53, p21 and GAPDH. Membranes were then incubated with alkaline phosphatase-conjugated secondary antibody, antibody binding was visualized using enhanced chemiluminescence, and bands were quantitated using an imaging system.

12. Immunofluorescence assay

The HCT116 cells were seeded and cultured in 6-well dishes, HCT116 cells were treated with 2.0 μM of compound **5c** or RG7112 for 24 hours, then washed and fixed by 10% formalin. The fixed samples were treated by TritonX-100, incubated overnight at 4 °C with the anti-p53 primary antibodies, followed by incubation with the secondary antibody for 1 h in the dark, and observed using fluorescence microscopy (Axio Observer A1, Zeiss, Germany).

13. Superposition of compound 5c binding conformers and p53 substrate peptide (Figure S1).

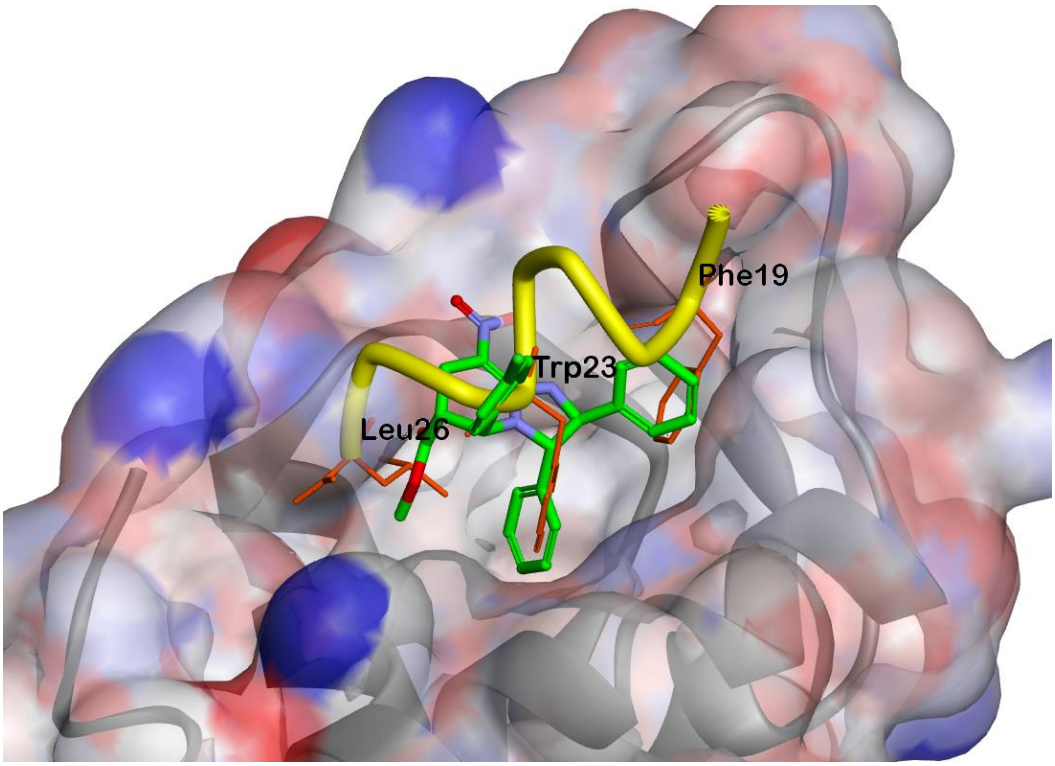

Figure **S1**. Comparison of compound **5c** to p53 substrate peptide, green: compound **5c**, yellow: main chain of p53 substrate peptide, orange: the interaction residues of p53 substrate peptide to MDM2, Phe19, Trp23 and Leu26.

14. Inhibition of MDM2 activity and of proliferation of HCT116 and MDA-MB231 cells by synthetic imidazoline derivatives (Table S3).

Compound	MDM2		HCT116		MDA-MB-231	
	Mean	SD	Mean	SD	Mean	SD
3a	7.79	0.51	16.24	1.46	21.82	1.22
3b	8.78	0.83	18.37	1.69	28.90	2.75
3c	4.34	0.41	21.98	2.31	12.60	0.84
3d	15.54	1.43	18.65	1.42	16.93	1.35
3e	5.78	0.53	25.02	1.73	26.34	2.55
3f	16.43	1.71	29.31	1.67	17.70	1.56
3g	13.91	1.86	12.05	1.42	13.21	1.57
3h	2.04	0.20	24.81	2.65	29.78	2.00
3i	11.12	1.42	28.79	3.60	17.61	0.99
3j	8.97	1.18	28.5	1.69	29.84	2.28
3k	14.51	1.19	23.54	2.14	28.26	1.42
3l	11.21	0.95	28.52	2.07	23.66	2.38
5a	72.57	9.83	68.46	9.17	76.93	6.17
5b	76.43	4.74	85.32	9.73	77.69	6.29
5c	80.99	7.87	91.99	6.91	89.28	4.35
5d	61.25	6.37	86.59	11.50	75.77	4.39
5e	72.17	6.64	86.35	4.49	82.06	7.83
5f	79.66	5.02	82.71	10.67	81.96	6.88
5g	71.29	4.78	79.23	6.51	84.75	10.42
5h	62.92	4.98	61.25	3.92	57.12	5.43
5i	65.06	6.63	63.69	5.99	62.86	6.13
5j	69.65	6.11	73.21	5.22	64.25	6.94
5k	72.31	6.94	84.51	12.47	85.21	4.86
RG7112	85.42	3.08	83.66	6.31	80.83	4.59