**[***Supporting Information***]**

# Direct vinylogous oxidative cross-dehydrogenative coupling of 4-Nitroisoxazoles with *N*-Aryl Tetrahydroisoquinolins in water under air conditions

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**Contents**

# 1. General information

## General methods

NMR spectra were recorded on a liquid NMR spectrometer (400 MHz for $^{1}H$ and 100 MHz for $^{13}C$) using $CDCl_3$ as the solvent. The residual proton in $CDCl_3$ ($\delta$= 7.27) served as an internal standard for $^{1}H$ NMR, and the $^{13}C$-atom of $CDCl_3$ was used as an internal standard ($\delta$= 77 for $^{13}C$ NMR. Chemical shifts are reported in ppm and the coupling constants *J* are given in Hz. The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Infrared spectra were recorded on an FT-IR spectrometer, and only major peaks were reported in $cm^{-1}$. HRMS data were obtained by the ESI ionization sources. Purification of the products was performed by column chromatography on silica gel (200–300 mesh).

## Materials

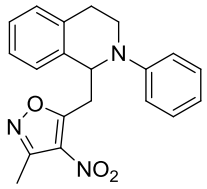
Catalysts and 3,5-dimethyl-4-nitroisoxazole are commercially available. 3,5-diethyl-4-nitroisoxazole was prepared according to the literature procedures.[1] The 2-Aryl-1,2,3,4-tetrahydro-isoquinolines were prepared according to the literature method.[2] Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification.


1. M. F. A. Adamo, S. Suresh, L. Piras, *Tetrahedron* **2009**, *65*, 5402.
2. Z. P. Li, C. J. Li, *J. Am. Chem. Soc.* **2005**, *19*, 6968.

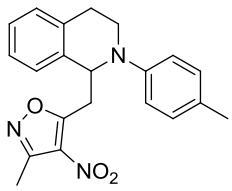
# 2 Experimental section

## 2.1 General procedure for products 3:

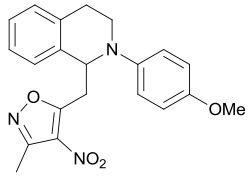
The mixture of 4-nitroisoxazoles **2** (0.2 mmol), *N*-Aryl-1,2,3,4-tetrahydro-isoquinolines **1** (0.4 mmol) and CuBr (10 mol%, 0.02 mmol) in 0.4 mL $H_2O$ were stirred at 50℃ or 80℃ for the indicated time. After the reaction was completed, the mixture was extracted with ethyl acetate. The combined organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, petroleumether/ethyl acetate = 50:1~10:1) to give the desired products **3**. It should be noted that products **3** were found to be a slightly unstable to column chromatographic purification.



**3-methyl-4-nitro-5-((2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3a):** yellow oil, 49.0 mg, 71% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.26-7.13 (m, 6H), 6.83 (d, *J* = 8.2 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 5.52 (dd, *J* = 9.3, 5.1 Hz, 1H), 3.92 (dd, *J* = 14.2, 9.4 Hz, 1H), 3.68 (dd, *J* = 8.0, 4.3 Hz, 2H), 3.49 (dd, *J* = 14.2, 5.1 Hz, 1H), 3.11 (dt, *J* = 16.1, 8.0 Hz, 1H), 2.93 (dt, *J* = 16.4, 4.2 Hz, 1H), 2.41 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 173.0 156.2 149.8 136.9 135.6 130.1 128.3 127.5 127.1 119.8 116.3 59.2 41.8 34.5 28.2 12.4. ESI-HRMS: calcd for $C_{20}H_{19}N_3O_3$+H 350.1499, found 350.1496. **IR**: ν 3440 2923 1600 1515 1417 1377 828 750 $cm^{-1}$

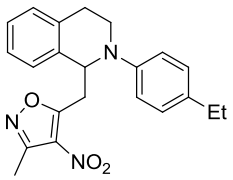


**3-methyl-4-nitro-5-((2-(p-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3b):** yellow oil, 49.1 mg, 68% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.24-7.14 (m, 4H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.76-6.73 (m, 2H), 5.47 (dd, *J* = 9.5, 4.8 Hz, 1H), 3.91 (dd, *J* = 14.3, 9.5 Hz, 1H), 3.64 (dd, *J* = 8.4, 3.9 Hz, 2H), 3.44 (dd, *J* = 14.3, 4.8 Hz, 1H), 3.09 (dt, *J* = 16.5, 8.3 Hz, 1H), 2.89 (dt, *J* = 16.4, 3.8 Hz, 1H), 2.41 (s, 3H), 2.23 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 172.3 155.4 146.9 136.2 134.7 129.7 129.1 128.7 127.4 126.8 126.2 116.3 58.8 41.1 33.6 27.7 20.3 11.5. ESI-HRMS: calcd for $C_{21}H_{21}N_3O_3$+H 364.1656, found 364.1660. **IR**: ν 3447 2922 1602 1515 1377 827 764 $cm^{-1}$

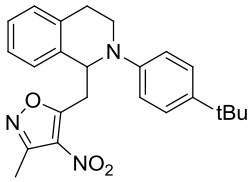


**3-methyl-4-nitro-5-((2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3c):** yellow oil, 41.4 mg, 55% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.26-7.16 (m, 4H), 6.80-6.68 (m, 4H), 5.40 (dd, *J* = 9.7, 4.3 Hz, 1H), 3.89 (dd, *J* = 14.4, 9.7 Hz, 1H), 3.74 (s, 3H), 3.61-3.53 (m, 2H), 3.38 (dd, *J* = 14.4, 4.4 Hz, 1H), 3.11-3.03 (m, 1H), 2.86 (dt, *J* = 16.5, 3.4 Hz, 1H), 2.41 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 172.5 155.4 153.6 143.4 136.3 134.6 129.2 127.3 126.8 126.2 118.8 114.5 59.6 55.5 41.7 33.5 27.3 11.5. ESI-HRMS: calcd for

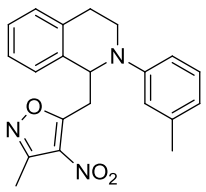
$C_{21}H_{21}N_3O_4$+H 380.1605, found 380.1607. **IR**: ν 3445 2933 1600 1511 1244 827 764 $cm^{-1}$



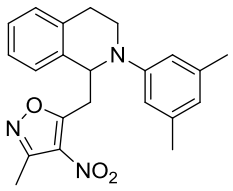
**3-methyl-4-nitro-5-((2-(4-ethylphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3d):** yellow oil, 49.5 mg, 66% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.25-7.13 (m, 4H), 6.99 (d, $J$ = 8.6 Hz, 2H), 6.77 (d, $J$ = 8.6 Hz, 2H), 5.48 (dd, $J$ = 9.4, 4.8 Hz, 1H), 3.92 (dd, $J$ = 14.3, 9.5 Hz, 1H), 3.65 (dd, $J$ = 8.2, 3.9 Hz, 2H), 3.45 (dd, $J$ = 14.3, 4.9 Hz, 1H), 3.09 (dt, $J$ = 16.4, 8.2 Hz, 1H), 2.89 (dt, $J$ = 16.3, 3.8 Hz, 1H), 2.53 (q, $J$ = 7.6 Hz, 2H), 2.40 (s, 3H), 1.18 (t, $J$ = 7.6 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 172.3 155.3 147.0 136.2 135.1 134.8 129.2 128.5 127.4 126.7 126.2 116.1 58.7 41.1 33.6 27.8 27.3 15.7 11.5. ESI-HRMS: calcd for $C_{22}H_{23}N_3O_3$+H 378.1812, found 378.1811. **IR**: ν 3446 2962 1602 1515 827 764 $cm^{-1}$



**3-methyl-4-nitro-5-((2-(4-(tert-butyl)phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3e):** yellow oil, 48.2 mg, 60% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.24-7.12 (m, 6H), 6.81-6.77 (m, 2H), 5.49 (dd, $J$ = 9.3, 5.1 Hz, 1H), 3.93 (dd, $J$ = 14.3, 9.4 Hz, 1H), 3.69-3.66 (m, 2H), 3.48 (dd, $J$ = 14.3, 5.1 Hz, 1H), 3.09 (dt, $J$ = 16.2, 8.1 Hz, 1H), 2.90 (dt, $J$ = 16.4, 4.1 Hz, 1H), 2.43 (s, 3H), 1.27 (s, 9H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 172.3 155.3 146.6 141.8 136.3 134.8 129.2 127.4 126.7 126.2 126.0 115.3 58.5 41.0 33.9 33.8 31.4 27.2 11.6. ESI-HRMS: calcd for $C_{24}H_{27}N_3O_3$+H 406.2125, found 406.2133. **IR**: ν 3443 2960 1604 1517 827 753 $cm^{-1}$

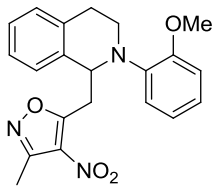


**3-methyl-4-nitro-5-((2-(m-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3f):** yellow oil, 43.9 mg, 61% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.26-7.14 (m, 4H), 7.05-7.01 (m, 1H), 6.64-6.56 (m, 3H), 5.53 (dd, $J$ = 9.3, 4.9 Hz, 1H), 3.92 (dd, $J$ = 14.2, 9.5 Hz, 1H), 3.67-3.63 (m, 2H), 3.44 (dd, $J$ = 14.3, 4.9 Hz, 1H), 3.14-3.06 (m, 1H), 2.93 (dt, $J$ = 16.3, 4.0 Hz, 1H), 2.39 (s, 3H), 2.26 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 172.2 155.3 149.1 138.9 136.2 134.8 129.1 127.4 126.7 126.2 120.0 116.4 112.9 58.6 40.8 33.6 27.6 21.6 11.5. ESI-HRMS: calcd for $C_{21}H_{21}N_3O_3$+H 364.1656, found 364.1660. **IR**: ν 3444 2923 1598 1513 1242 828 748 $cm^{-1}$

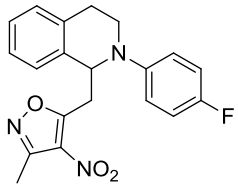


**3-methyl-4-nitro-5-((2-(3,5-dimethylphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3g):** yellow oil, 54.7 mg, 73% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.25-7.16 (m, 4H), 6.43 (s, 2H), 6.40 (s, 1H), 5.54 (dd, $J$ = 9.4, 4.5 Hz, 1H), 3.92 (dd, $J$ = 14.2, 9.6 Hz, 1H), 3.64-3.59 (m, 2H), 3.40 (dd, $J$ = 14.3, 4.6 Hz, 1H), 3.14-3.06 (m, 1H), 2.95-2.90 (m, 1H), 2.37 (s, 3H), 2.20 (s, 6H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 172.2 155.3 149.3 138.7 136.3 131.7 129.1

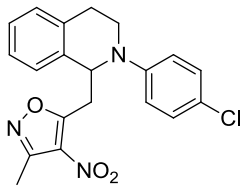
127.4 126.8 126.2 121.3 113.9 58.9 40.7 33.5 27.8 21.5 11.5. ESI-HRMS: calcd for $C_{22}H_{23}N_3O_3$+H 378.1812, found 378.1814. **IR**: ν 3444 2926 1600 1511 1244 827 764 $cm^{-1}$



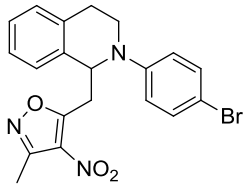

**3-methyl-4-nitro-5-((2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3h):** yellow oil, 30.0 mg, 40% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.25-7.18 (m, 4H), 6.89 (t, $J$ = 7.4 Hz, 2H), 6.70 (dd, $J$ = 15.3, 7.8 Hz, 2H), 5.73 (dd, $J$ = 10.1, 3.4 Hz, 1H), 4.02-3.94 (m, 1H), 3.79 (s, 3H), 3.64 (dt, $J$ = 12.1, 4.1 Hz, 1H), 3.51 (dd, $J$ = 12.7, 6.3 Hz, 1H), 3.24 (d, $J$ = 13.3 Hz, 1H), 3.17-3.08 (m, 1H), 2.91 (d, $J$ = 12.0 Hz, 1H), 2.35 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 172.7 155.2 152.0 139.0 136.9 134.5 129.3 127.1 127.0 125.1 123.1 120.8 120.5 111.2 57.4 55.3 42.0 33.2 28.2 11.5. ESI-HRMS: calcd for $C_{21}H_{21}N_3O_4$+H 380.1605, found 380.1614. **IR**: ν 3446 2923 1598 1514 1242 828 748 $cm^{-1}$




**3-methyl-4-nitro-5-((2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3i):** yellow oil, 40.7 mg, 56% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.25-7.15 (m, 4H), 6.87-6.79 (m, 4H), 5.40 (dd, $J$ = 9.6, 4.7 Hz, 1H), 3.89 (dd, $J$ = 14.3, 9.6 Hz, 1H), 3.68-3.55 (m, 2H), 3.44 (dd, $J$ = 14.4, 4.7 Hz, 1H), 3.11-3.02 (m, 1H), 2.88 (dt, $J$ = 16.5, 3.8 Hz, 1H), 2.43 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 172.2 156.7 (d, $^1J_{C\text{-}F}$=239 Hz) 155.4 145.7 (d, $^4J_{C\text{-}F}$=2.3 Hz ) 136.0 134.5 129.2 127.5 126.7 126.3 117.8 (d, $^3J_{C\text{-}F}$=7.6 Hz) 115.6 (d, $^2J_{C\text{-}F}$=22.2 Hz) 59.0 41.6 33.6 27.1 11.4. ESI-HRMS: calcd for $C_{20}H_{18}FN_3O_3$+H 368.1405, found 368.1415. **IR**: ν 3423 2924 1601 1509 1230 827 764 $cm^{-1}$

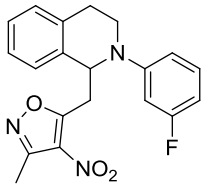



**3-methyl-4-nitro-5-((2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3j):** yellow oil, 40.2 mg, 53% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.25-7.07 (m, 6H), 6.75-6.72 (m, 2H), 5.44 (dd, $J$ = 9.4, 5.0 Hz, 1H), 3.89 (dd, $J$ = 14.3, 9.4 Hz, 1H), 3.65-3.61 (m, 2H), 3.47 (dd, $J$ = 14.3, 5.0 Hz, 1H), 3.12-3.04 (m, 1H), 2.95 (dt, $J$ = 16.4, 4.2 Hz, 1H), 2.43 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 171.9 155.5 147.6 135.7 134.5 129.2 129.0 127.6 126.7 126.4 123.9 116.7 58.4 41.2 33.6 27.3 11.5. ESI-HRMS: calcd for $C_{20}H_{18}ClN_3O_3$+H 384.1110, found 384.1119. **IR**: ν 3443 2923 1600 1516 828 752 $cm^{-1}$

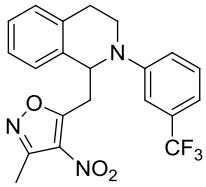



**3-methyl-4-nitro-5-((2-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3k):** yellow oil, 53.4 mg, 63% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.25-7.12 (m, 6H), 6.69-6.67 (m, 2H), 5.44 (dd, $J$ = 9.4, 5.0 Hz, 1H), 3.90 (dd, $J$ = 14.3, 9.4 Hz, 1H), 3.65-3.61 (m, 2H), 3.47 (dd, $J$ = 14.3, 5.0 Hz, 1H), 3.12-3.04 (m, 1H), 2.94 (dt, $J$ = 16.4, 4.3 Hz, 1H), 2.44 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 171.8 155.5 148.0 135.7 134.5 132.0 129.1 127.7 126.7 126.4

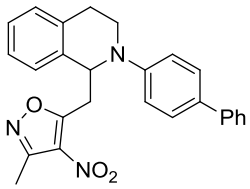
117.0 111.0 58.3 41.1 33.6 27.3 11.5. ESI-HRMS: calcd for $C_{20}H_{18}BrN_3O_3$+H 428.0604, found 428.0600 and 430.0672. **IR**: ν 3444 2922 1602 1516 1493 827 $cm^{-1}$



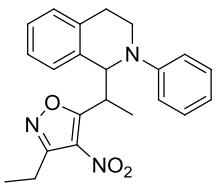
**3-methyl-4-nitro-5-((2-(3-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3l):** yellow oil, 37.1 mg, 51% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.25-7.08 (m, 5H), 6.60-6.41 (m, 3H), 5.43 (dd, *J* = 8.9, 5.7 Hz, 1H), 3.89 (dd, *J* = 14.2, 9.0 Hz, 1H), 3.71-3.61 (m, 2H), 3.55 (dd, *J* = 14.2, 5.7 Hz, 1H), 3.12-3.06 (m, 1H), 3.01-2.92 (m, 1H), 2.45 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 171.7 163.9 (d, $^1J_{C\text{-}F}$ = 244) 155.5 150.5 (d, $^3J_{C\text{-}F}$ = 10) 135.6 134.7 130.3 (d, $^3J_{C\text{-}F}$ = 10) 129.0 127.7 126.6 126.4 110.0 (d, $^4J_{C\text{-}F}$ = 2.4) 105.0 (d, $^2J_{C\text{-}F}$ = 22) 101.6 (d, $^2J_{C\text{-}F}$ = 26) 59.2 41.8 34.5 28.2 12.4. ESI-HRMS: calcd for $C_{20}H_{18}FN_3O_3$+H 368.1405, found 368.1418. **IR**: ν 3444 2924 1610 1517 1494 828 756 $cm^{-1}$



**3-methyl-4-nitro-5-((2-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3m):** yellow oil, 58.8 mg, 71% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.26-7.14 (m, 5H), 6.98 (d, *J* = 7.4 Hz, 3H), 5.51 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.89 (dd, *J* = 14.2, 9.3 Hz, 1H), 3.74-3.70 (m, 2H), 3.56 (dd, *J* = 14.2, 5.2 Hz, 1H), 3.15-2.96 (m, 2H), 2.42 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 171.6 155.4 148.9 135.6 134.5 129.8 129.1 127.8 126.6 125.5 117.5 114.9 110.8 57.9 41.1 33.8 27.3 11.4. ESI-HRMS: calcd for $C_{21}H_{18}F_3N_3O_3$+H 418.1373, found 418.1367. **IR**: ν 3450 2924 1607 1511 1122 828 $cm^{-1}$

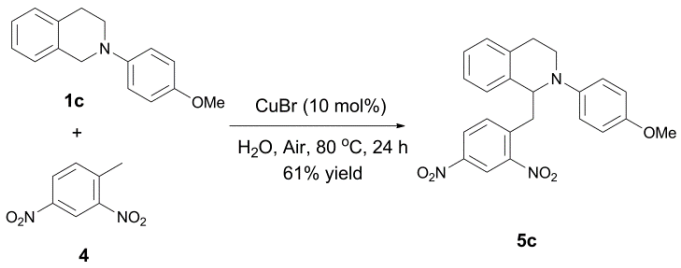


**3-methyl-4-nitro-5-((2-([1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoxazole (3n):** yellow oil, 36.1 mg, 43% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.54-7.51 (m, 2H), 7.42-7.40 (m, 4H), 7.31-7.18 (m, 5H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.59 (dd, *J* = 9.4, 4.9 Hz, 1H), 3.96 (dd, *J* = 14.3, 9.5 Hz, 1H), 3.74-3.70 (m, 2H), 3.49 (dd, *J* = 14.3, 4.9 Hz, 1H), 3.13 (dd, *J* = 16.2, 7.4 Hz, 1H), 3.00-2.95 (m, 1H), 2.55 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 172.0 155.4 148.3 140.6 136.0 134.6 131.7 129.1 128.7 127.8 127.5 126.7 125.5 125.4 125.3 115.7 58.5 40.9 33.7 27.5 11.4. ESI-HRMS: calcd for $C_{26}H_{23}N_3O_3$+H 426.1812, found 426.1815. **IR**: ν 3449 2963 1603 1509 1261 1095 802 $cm^{-1}$



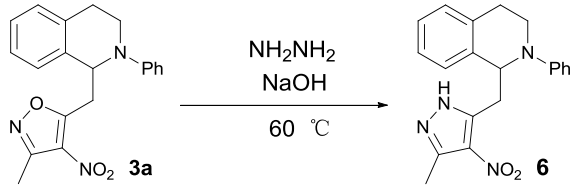
**3-ethyl-4-nitro-5-(1-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl)isoxazole (3o):** yellow oil, 30.8 mg, 41% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.30-7.22 (m, 4H), 7.12-7.08 (m, 2H), 7.01-6.91 (m, 1H), 6.67-6.48 (m, 2H), 5.19-5.03 (m, 1H), 4.46-4.25 (m, 1H), 3.88-3.63 (m, 1H), 3.33-3.23 (m, 1H), 3.10-2.74 (m, 4H), 1.39-1.09 (m, 6H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 176.1 176.0 160.2 160.0 149.8 148.3 135.5 135.4 135.2 135.1 129.3 129.1 128.8 128.6 118.4 117.7 114.7 112.9 62.6 61.8 43.3 43.0 39.7 38.2 26.9 26.6 19.6 19.5 15.6 15.3 11.5 11.2. ESI-HRMS: calcd for $C_{22}H_{23}N_3O_3$+H 378.1812, found 378.1807. **IR**: ν 3443 2977 2924 1594 1512 1454 1363 1127 829 $cm^{-1}$

**2.2 Synthesis of compound 5c:**




The mixture of 2,4-dinitro-toluene **4** (36.4 mg, 0.2 mmol), *N*-Aryl-1,2,3,4-tetrahydro-isoquinolines **1c** (0.4 mmol) and CuBr (10 mol%, 0.02 mmol) in 0.4 mL $H_2O$ were stirred at 80℃ for 24 h. After the reaction was completed, the mixture was extracted with ethyl acetate. The combined organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, petroleumether/ethyl acetate = 20:1~10:1) to give **1-(2,4-dinitrobenzyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline** (**5c) :** red oil;51.1 mg, 61% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 8.69 (s, 1H), 8.27 (s, 1H), 7.53 (s, 1H), 7.22 (s, 3H), 7.14 (s, 1H), 6.66 (d, *J* = 15.8 Hz, 4H), 4.88 (d, *J* = 4 Hz, 1H), 3.70 (s, 3H), 3.59-3.48 (m, 4H), 2.98-2.93 (m, 1H), 2.63 (d, *J* = 15.9 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 153.6 150.0 145.3 143.8 141.7 136.7 135.2 134.8 129.1 127.2 127.1 126.3 126.1 119.8 118.6 114.5 61.1 55.5 43.0 29.4 25.6. ESI-HRMS: calcd for $C_{23}H_{21}N_3O_5$+H 420.1554, found 420.1549.

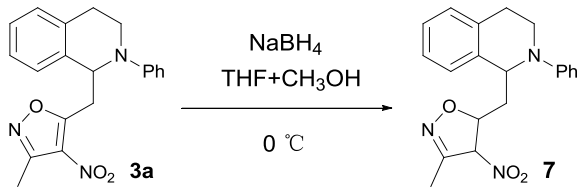
**2.3 Synthesis of compound 6:**




**3a** (0.16 mmol) and NaOH (0.16 mmol) were disolved in 0.1 mL hydrazine hydrate. The resulted mixture was stirred at 60℃ for 8 h. It was then transferred into a large beaker, diluted with water and cooled with an ice-bath. The pH was adjusted to 7.0 by addition of 3N HCl, and then extracted with ethyl acetate (5×2 mL). The combined organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was puried by column chromatography (silica gel, petroleumether/ethyl acetate = 2:1) to give a white solid of **1-((3-methyl-4-nitro-1H-pyrazol-5-yl)methyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (6):** white solid; 36.1 mg, 65% yield; mp: 154-155℃; **$^1$H NMR** (400 MHz, DMSO) $\delta$ (ppm) 7.19-7.13 (m, 6H), 6.88-6.78 (m, 3H), 5.22 (t, *J* = 6.6 Hz, 1H), 3.68 (d, *J* = 4.3 Hz, 2H), 3.58 (d, *J* = 6.9 Hz, 2H), 3.05-2.97 (m, 1H), 2.80 (d, *J* = 16.4 Hz, 1H), 2.50 (s, 3H); **$^{13}$C NMR** (100 MHz, DMSO) $\delta$ (ppm) 149.1 136.6 134.7 131.1 129.4 129.0 127.1 126.4 119.7 116.4 58.3 42.6 32.6 26.3 13.4. HRMS (ESI) calcd for $C_{20}H_{20}N_4O_2$+H 349.1659, found 349.1673. **IR**: ν 3247 2927 1588 1501 1358 1164

998 831 764 698 $cm^{-1}$

**2.3 Synthesis of compound 7:**

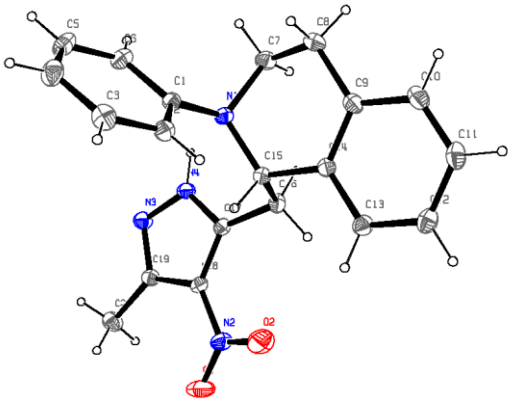



**3a** (0.25 mmol) was disolved in THF (1 mL) and MeOH (1 mL), the resulted mixture was cooled to 0 ℃ and treated with a solution of $NaBH_4$ (28.5 mg, 0.75 mmol) in MeOH (0.5 mL). The solution of the reducent was added drop wise in a 5 minutes period. The reaction mixture was then stirred for additional 60 minutes, then quenched with water (3 mL). The pH was adjusted to 7.0 by addition of 3N HCl, and then extract with ethyl acetate (5×2 mL). The combined organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was puried by column chromatography (silica gel, petroleumether/ethyl acetate = 10:1) to give compound **3-methyl-4-nitro-5-((2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-4,5-dih ydroisoxazole (7):** 80% yield.

The upper dot in TLC plate **(7a):** yellow oil; 35.9 mg, 41% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.28-7.20 (m, 5H), 7.15 (d, $J$ = 6.8 Hz, 1H), 6.97 (t, $J$ = 7.1 Hz, 2H), 6.85 (t, $J$ = 7.3 Hz, 1H), 5.79 (d, $J$ = 4.2 Hz, 1H), 5.20 (dd, $J$ = 10.4, 4.8 Hz, 1H), 4.92 (t, $J$ = 6.7 Hz, 1H), 3.63 (t, $J$ = 5.9 Hz, 2H), 2.97-2.89 (m, 1H), 2.81-2.75 (m, 1H), 2.49-2.41 (m, 1H), 2.17-2.11 (m, 1H), 1.87 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 149.3 135.0 129.6 129.5 128.9 127.5 127.2 126.6 116.1 96.2 82.3 53.9 43.9 39.0 26.3 11.3. HRMS (ESI) calcd for $C_{20}H_{21}N_3O_3$+H 352.1656, found 352.1654. **IR**: ν 3449 2924 1598 1560 1493 752 $cm^{-1}$

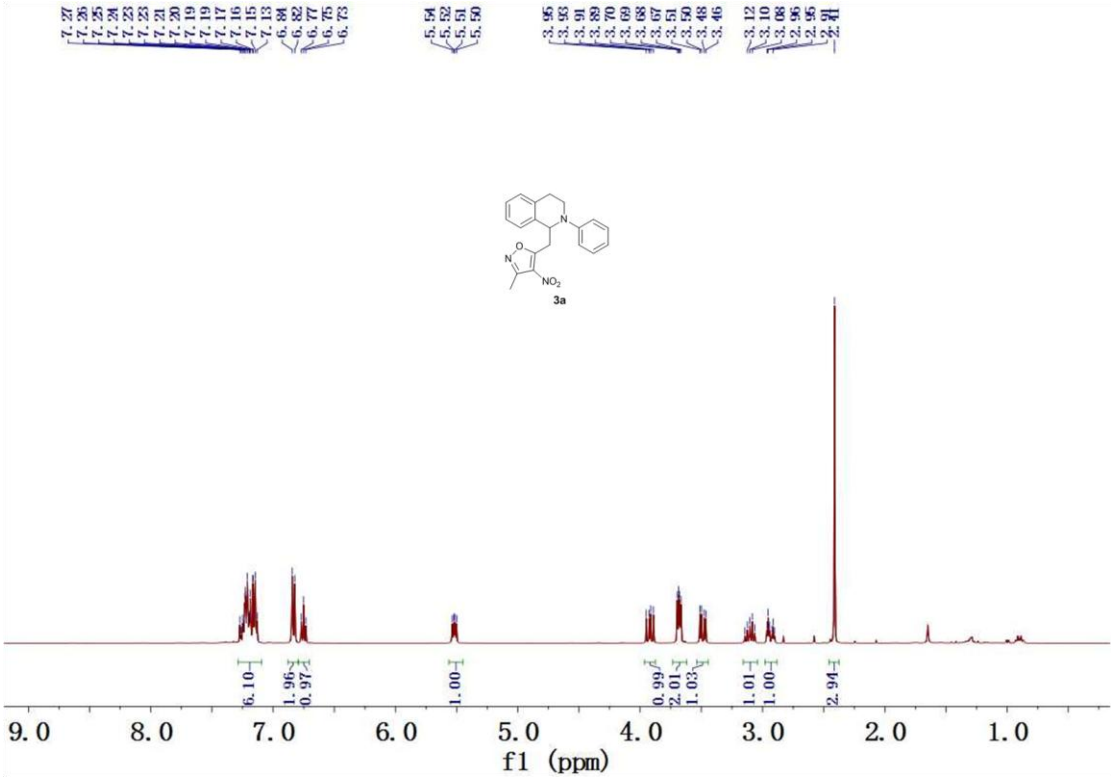
The lower dot in TLC plate **(7b):** yellow oil; 34.1 mg, 39% yield; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.25-6.81 (m, 8H), 6.83 (d, $J$ = 7.3 Hz, 1H), 5.45-5.3 (m, 2H), 5.04 (dd, $J$ = 10.7, 3.5 Hz, 1H), 3.85 (dd, $J$ = 14.2, 4.9 Hz, 1H), 3.57-3.49 (m, 1H), 3.12-3.03 (m, 1H), 2.64-2.60 (m, 1H), 2.28-2.14 (m, 5H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 149.0, 134.9, 129.5, 129.4, 129.3, 127.0, 126.8, 126.3, 119.4, 116.2, 97.0, 82.4, 56.3, 40.4, 35.1, 25.0, 11.6. HRMS (ESI) calcd for $C_{20}H_{21}N_3O_3$+H 352.1656, found 352.1661. **IR**: ν 3449 2922 1598 1561 1493 755 $cm^{-1}$

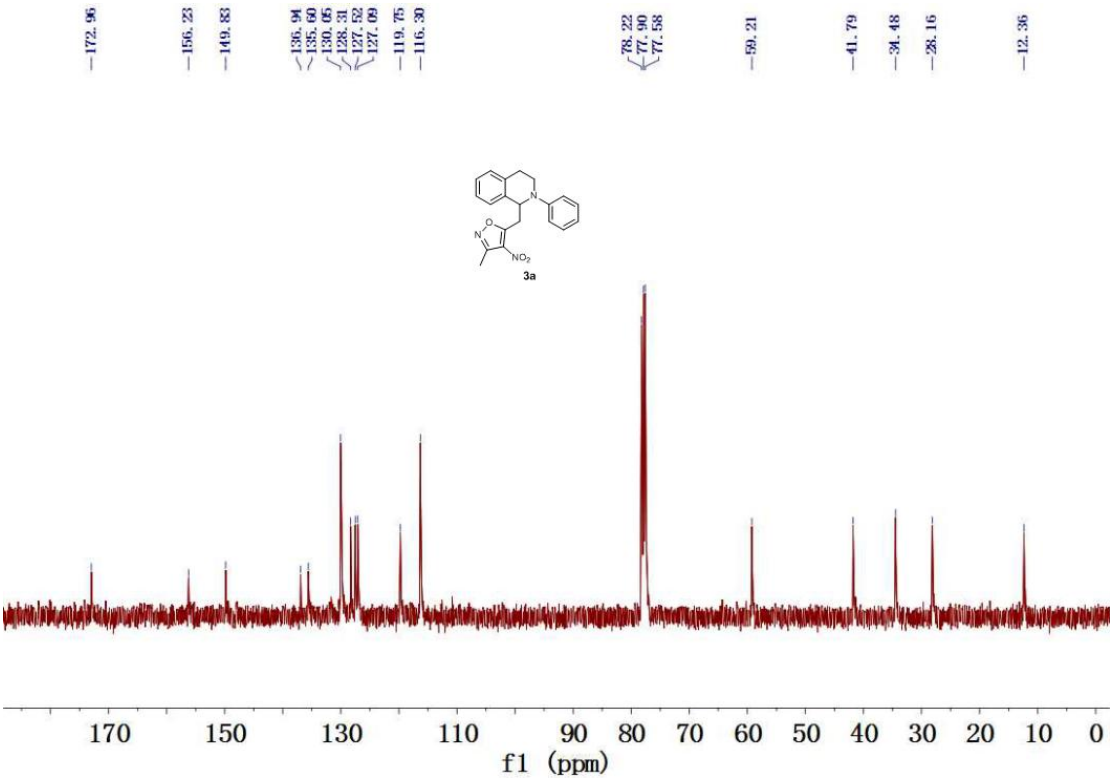
## 3. Crystal data and structure refinement for product 6

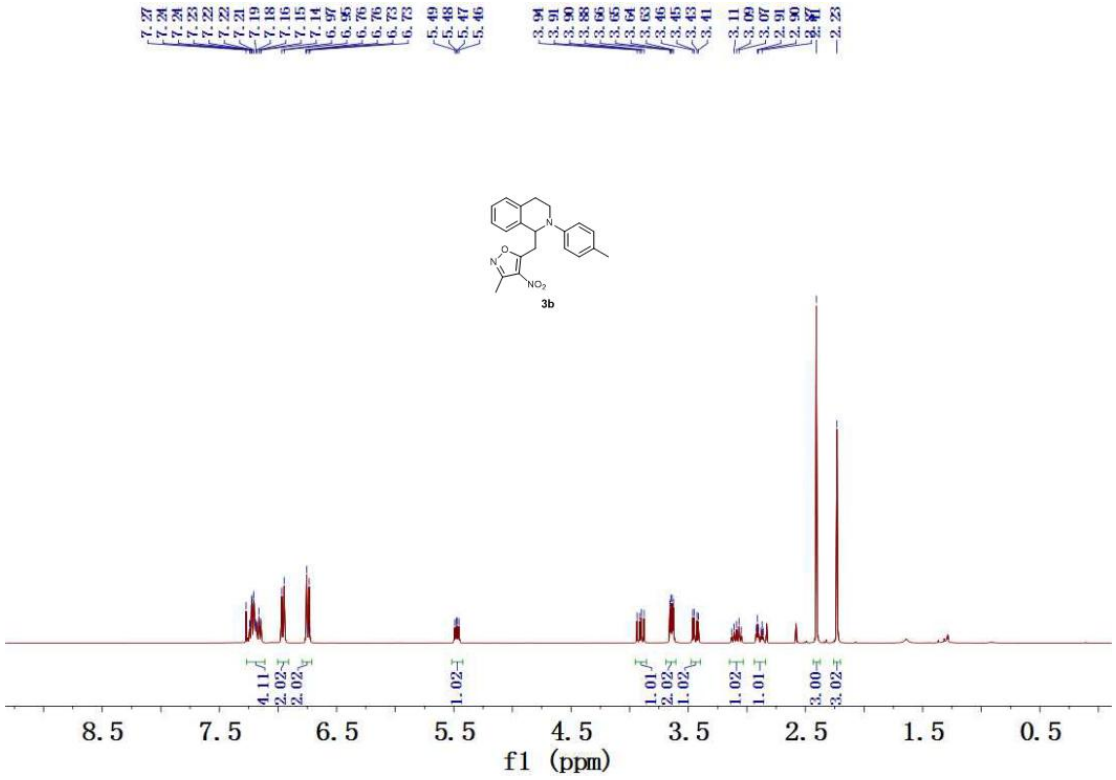


| | |
|---|---|
| **Identification code** | zy-2 |
| **Empirical formula** | C20H20N4O2 |
| **Formula weight** | 348. 16 |
| **Temperature** | 296 (2) K |
| **Wavelength** | 0.71073 A |
| **Crystal system, space group** | Triclinic, P- 1 |
| **Unit cell dimensions** | a = 6. 3993(3) A alpha = 106.376（5）deg. |
| | b = 11. 0228(5) A beta = 98.689（5）deg. |
| | c = 13. 8844(9) A gamma = 106. 505（3） deg. |
| **Volume** | 872.02 (8) A^3 |
| **Z, Calculated density** | 1.393Mg/m^3 |
| **Absorption coefficient** | 0. 125 mm^-1 |
| **F(000)** | 374 |
| **Crystal size** | 0.25 x 0.20 x 0.05 mm |
| **q for data collection** | 2. 05 to 27.45 deg. |
| **Limiting indices** | -8<=h<=8, -14<=k<=14, -18<=l<=16 |
| **Reflections collected/unique** | 7525 / 3928 [R(int) = 0.0215] |
| **Completeness to q = 27.49** | 98.5 % |
| **Absorption correction** | None |
| **Refinement method** | Full-matrix least-squares on F^2 |
| **Data/restraints/parameters** | 3928 / 0 / 236 |
| **Goodness-of-fit on F^2** | 0.967 |
| **Final R indices [I > 2sigma(I)]** | R1 = 0.0502, wR2 = 0.1347 |
| **R indices (all data)** | R1 = 0.0756, wR2 =0.1550 |
| **Absolute structure parameter** | 0.3(9) |
| **Largest diff. peak and hole** | 0.16 and -0.21e.A^-3 |

# 4. NMR spectra and HPLC chromatograms

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7.19
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7.16
7.15
7.14
6.97
6.95
6.76
6.76
6.73
6.73
5.49
5.48
5.47
5.46
3.94
3.91
3.90
3.88
3.66
3.65
3.64
3.63
3.46
3.45
3.43
3.41
3.11
3.09
3.07
2.91
2.90
2.87
2.23
3b
4.11
2.02
2.02
1.02
1.01
2.02
1.02
1.02
1.01
3.00
3.02
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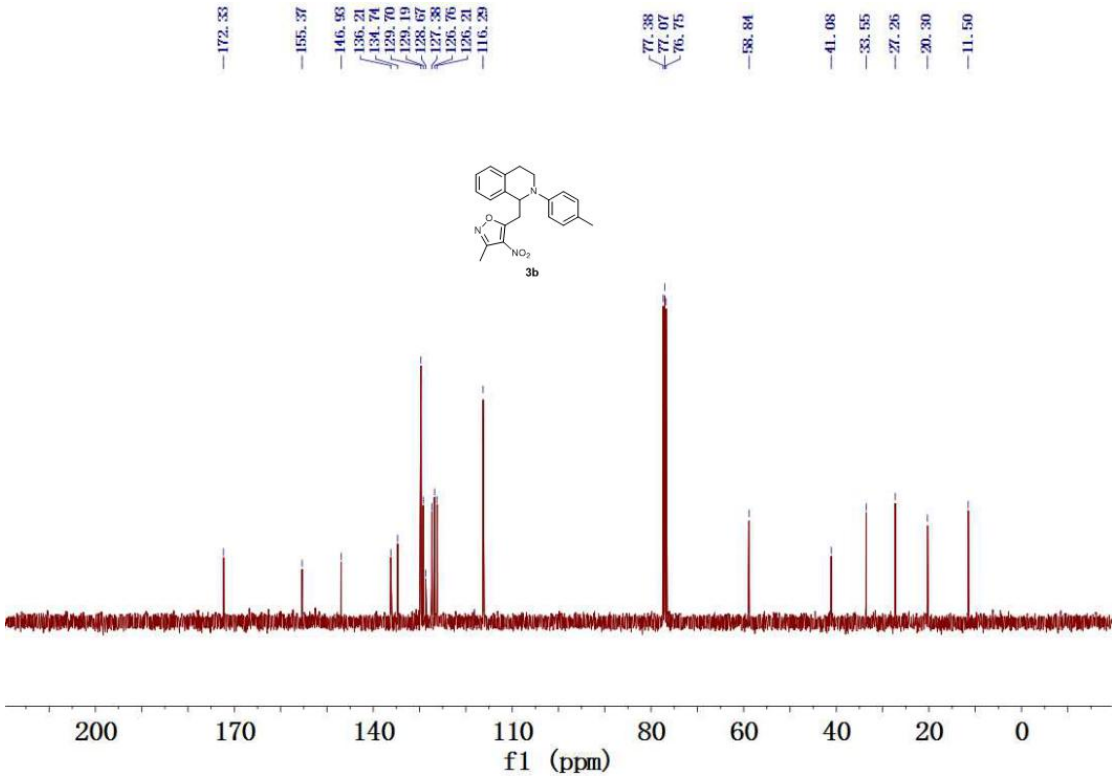
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)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128.67
127.38
126.76
126.21
116.29
77.38
77.07
76.75
58.84
41.68
33.55
27.26
20.30
11.50
3b
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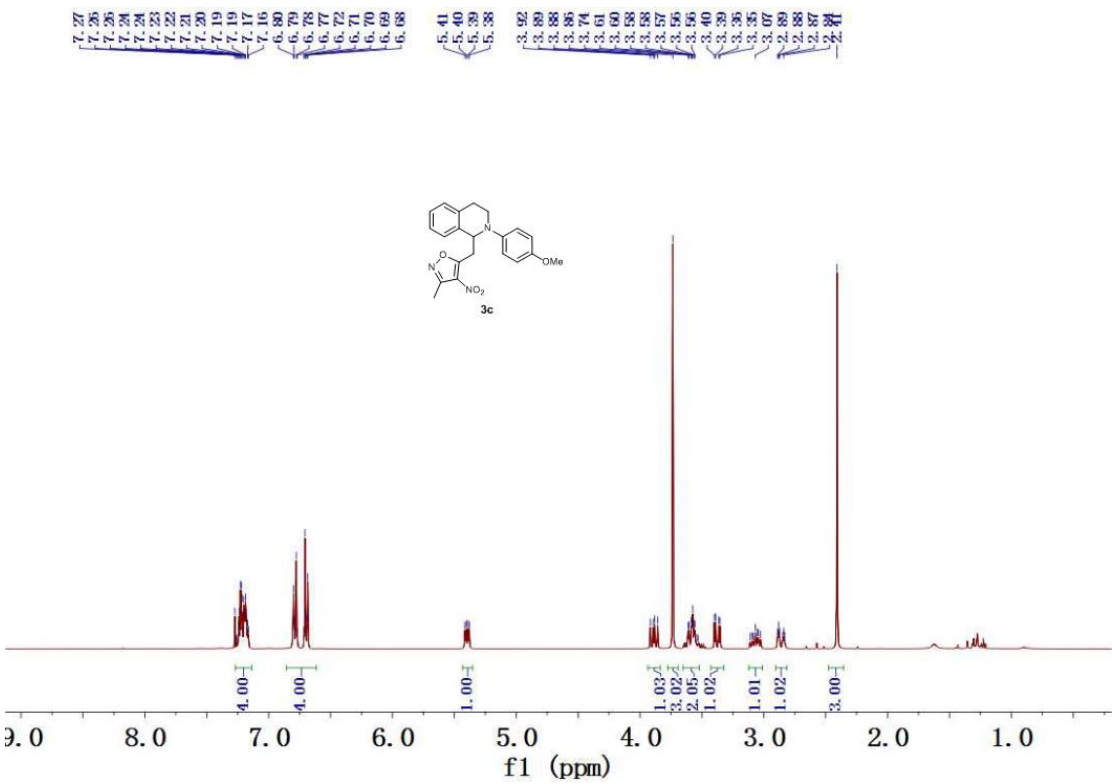
170
140
110
80
60
40
20
0
f1 (ppm)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6.69
6.68
5.41
5.40
5.39
5.38
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3.89
3.88
3.85
3.74
3.61
3.60
3.58
3.58
3.57
3.56
3.40
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3.35
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3.07
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2.88
2.87
2.81
OMe
NO2
3c
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4.00
1.00
1.03
3.02
2.05
1.02
1.01
1.02
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8.0
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6.0
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4.0
3.0
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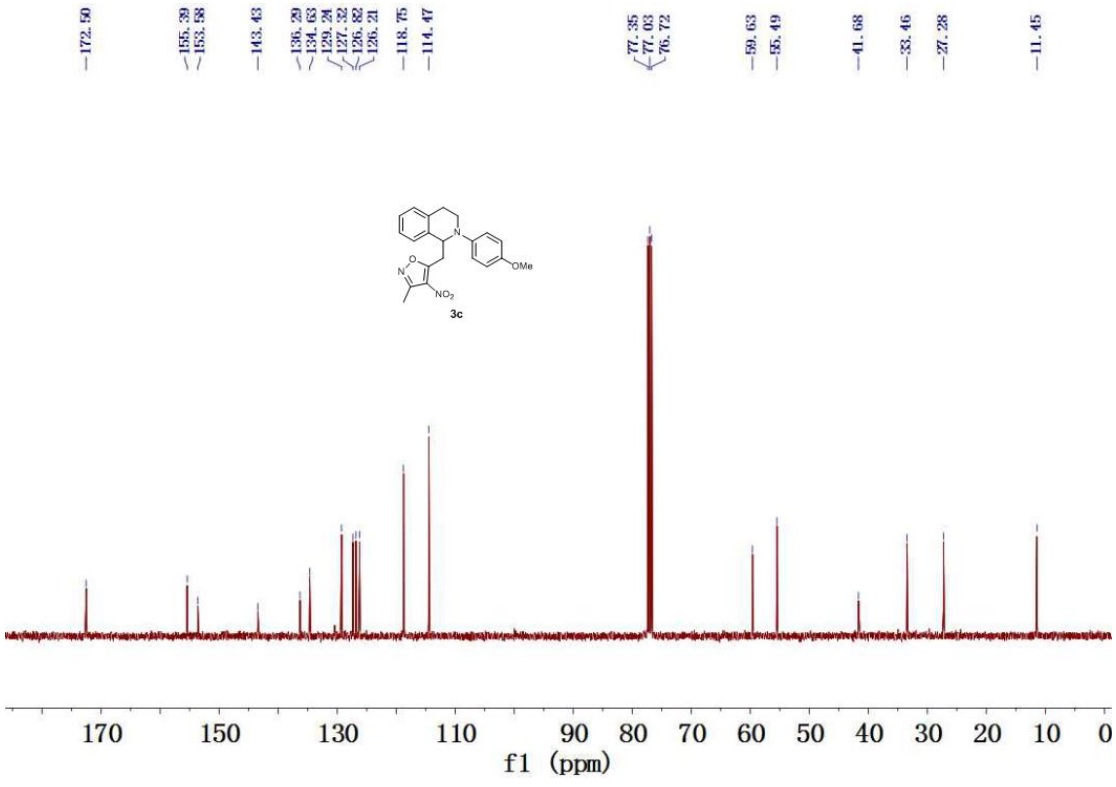
1.0
f1 (ppm)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129.24
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126.21
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114.47
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77.03
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27.28
11.45
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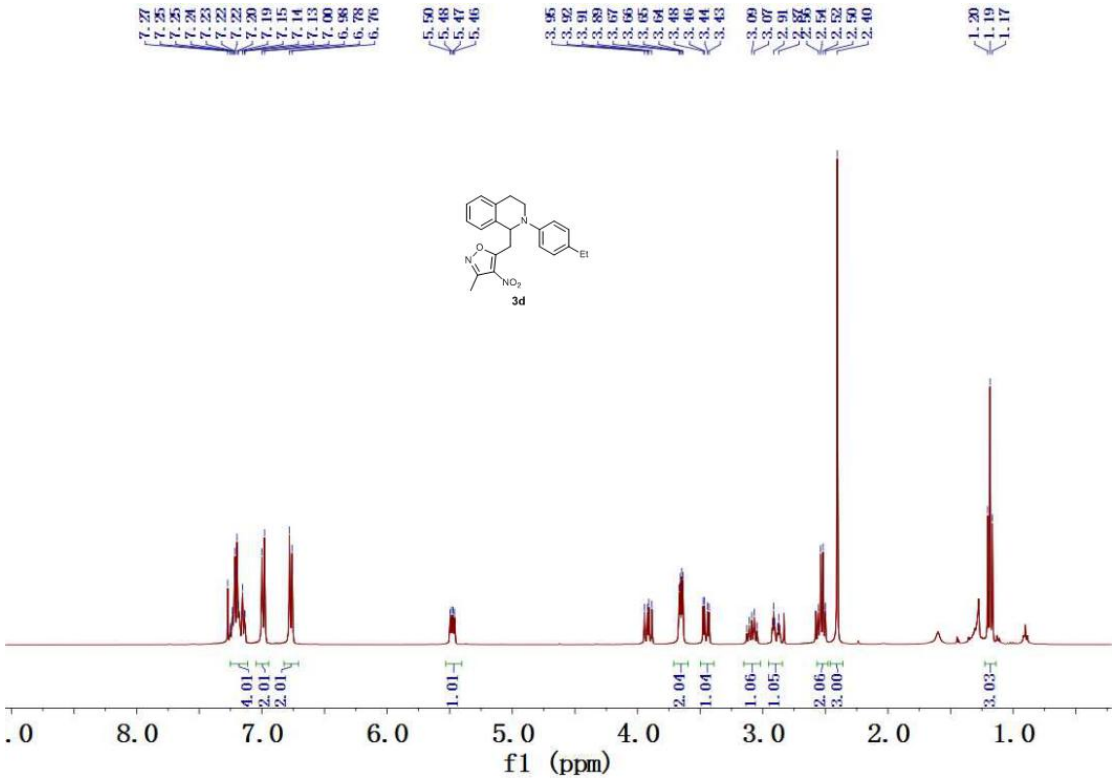
f1 (ppm)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5.47
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1.17
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1.04
1.06
1.05
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4.0
3.0
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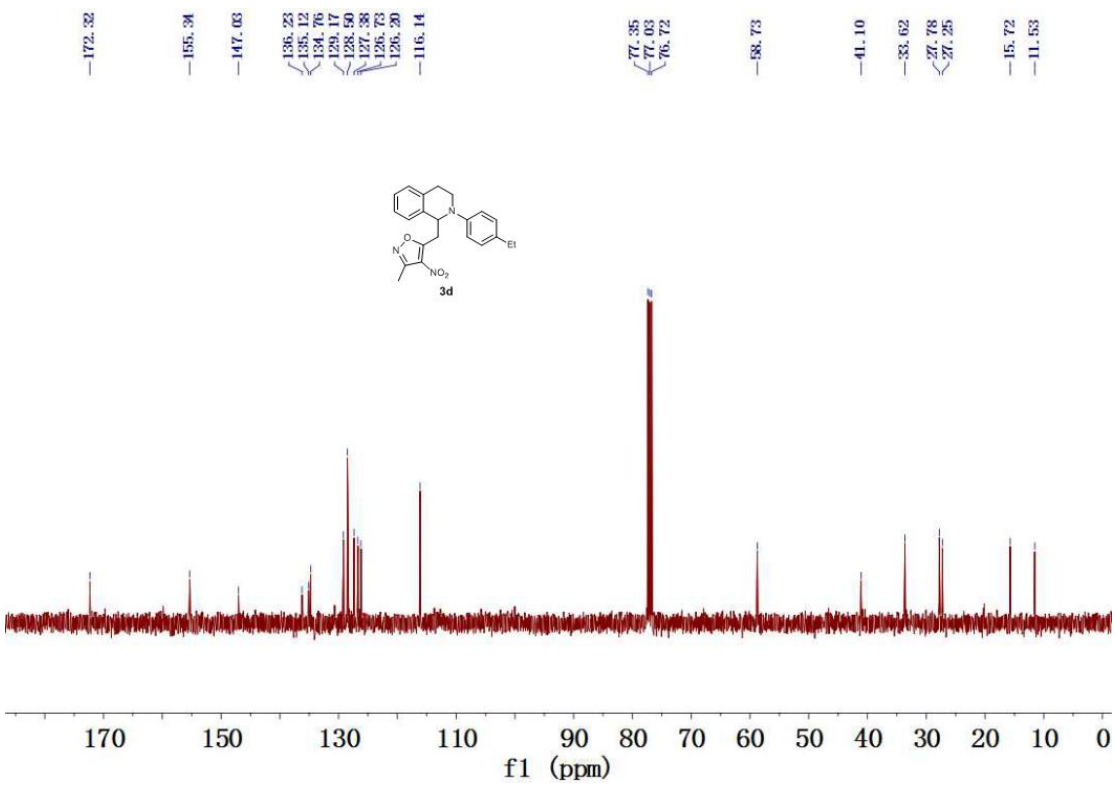
f1 (ppm)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147.03
136.23
135.12
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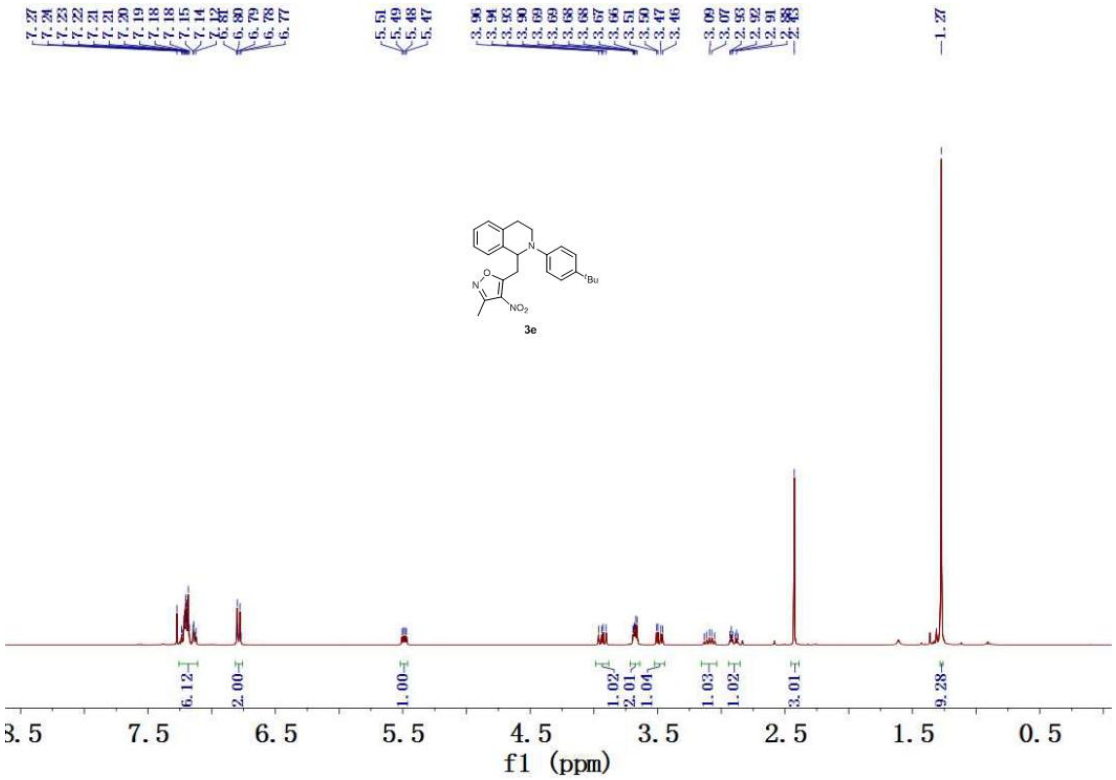
128.50
127.38
126.73
126.20
116.14
77.35
77.03
76.72
58.73
41.10
33.62
27.78
27.25
15.72
11.53
3d
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.27
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7.18
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7.14
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3.93
3.90
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3.68
3.68
3.67
3.66
3.51
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3.47
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NO2
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1.03
1.02
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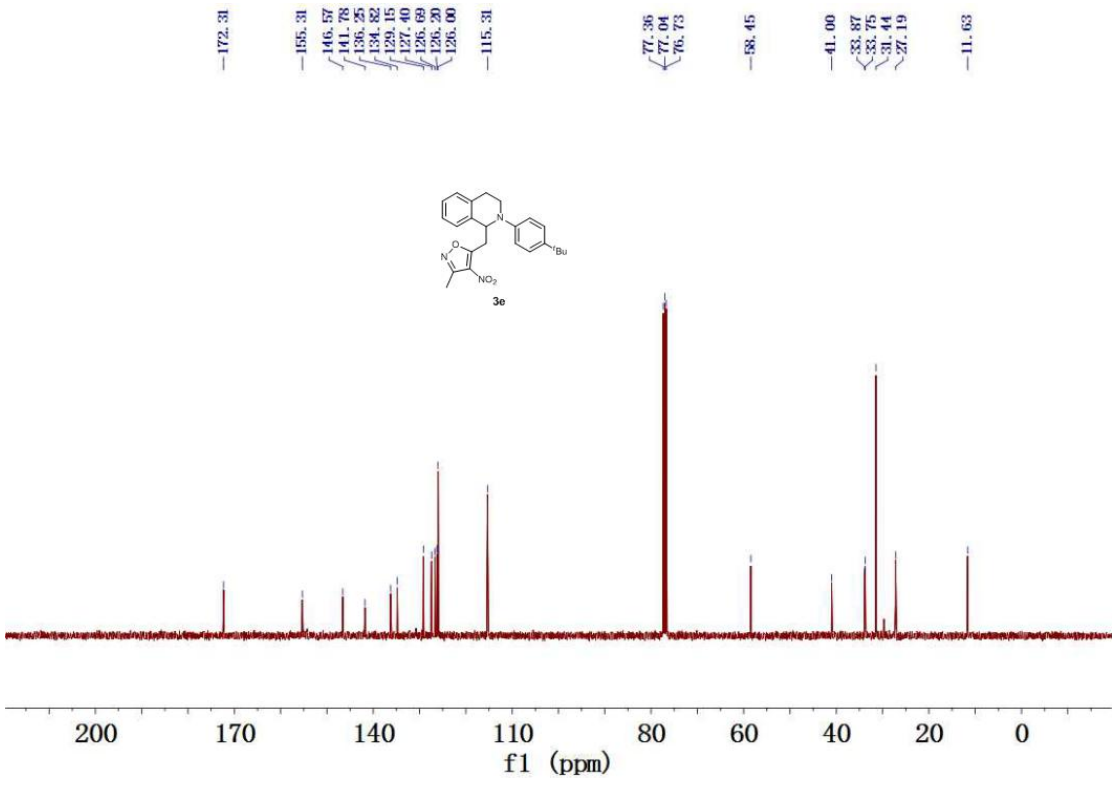
2.5
1.5
0.5
f1 (ppm)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126.00
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77.36
77.04
76.73
58.45
41.00
33.87
33.75
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27.19
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tBu
NO2
3e
200
170
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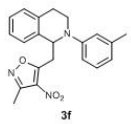
110
80
60
40
20
0
f1 (ppm)


3f


4.06
1.07
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1.04
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1.03
1.01
3.00
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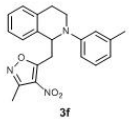
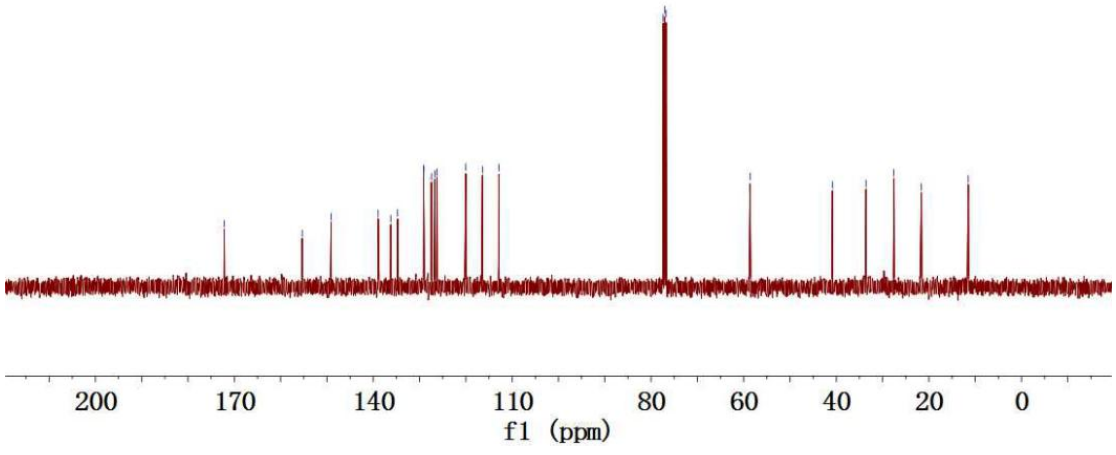
4.0
3.0
2.0
1.0
f1 (ppm)


3f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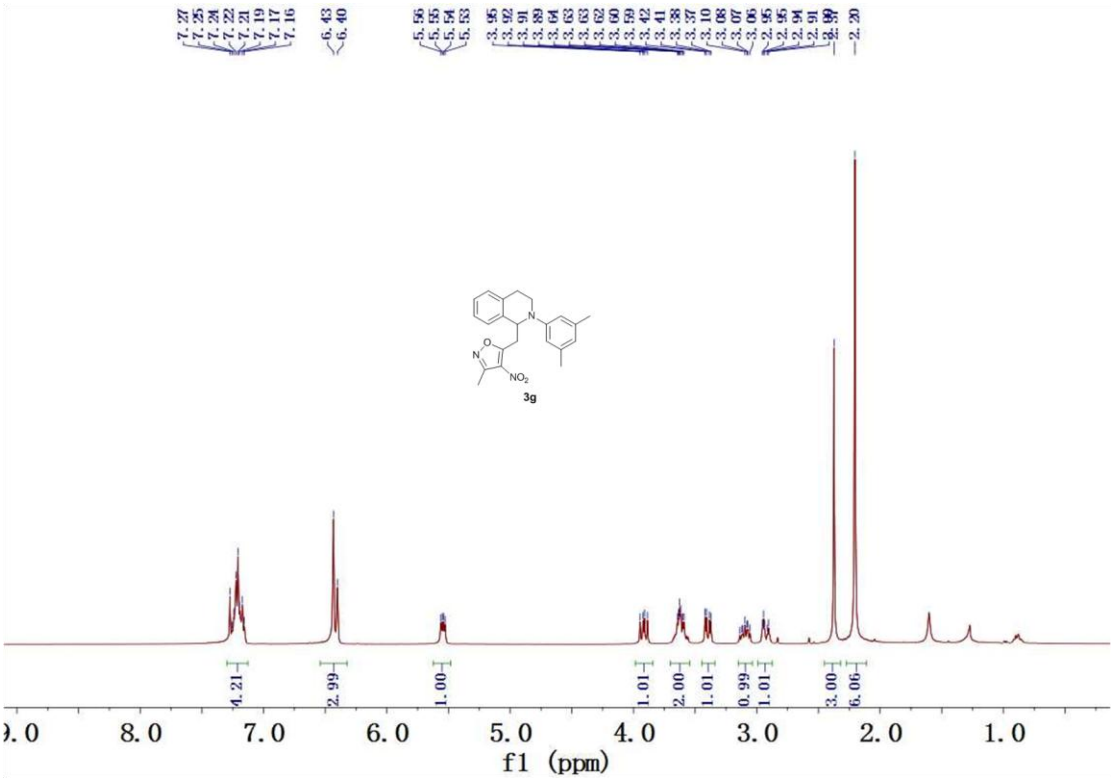
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5.54
5.53
3.95
3.92
3.91
3.89
3.64
3.63
3.62
3.60
3.59
3.42
3.41
3.38
3.37
3.10
3.08
3.07
3.06
2.95
2.95
2.94
2.91
2.20
3g
4.21
2.99
1.00
1.01
2.00
1.01
0.99
1.01
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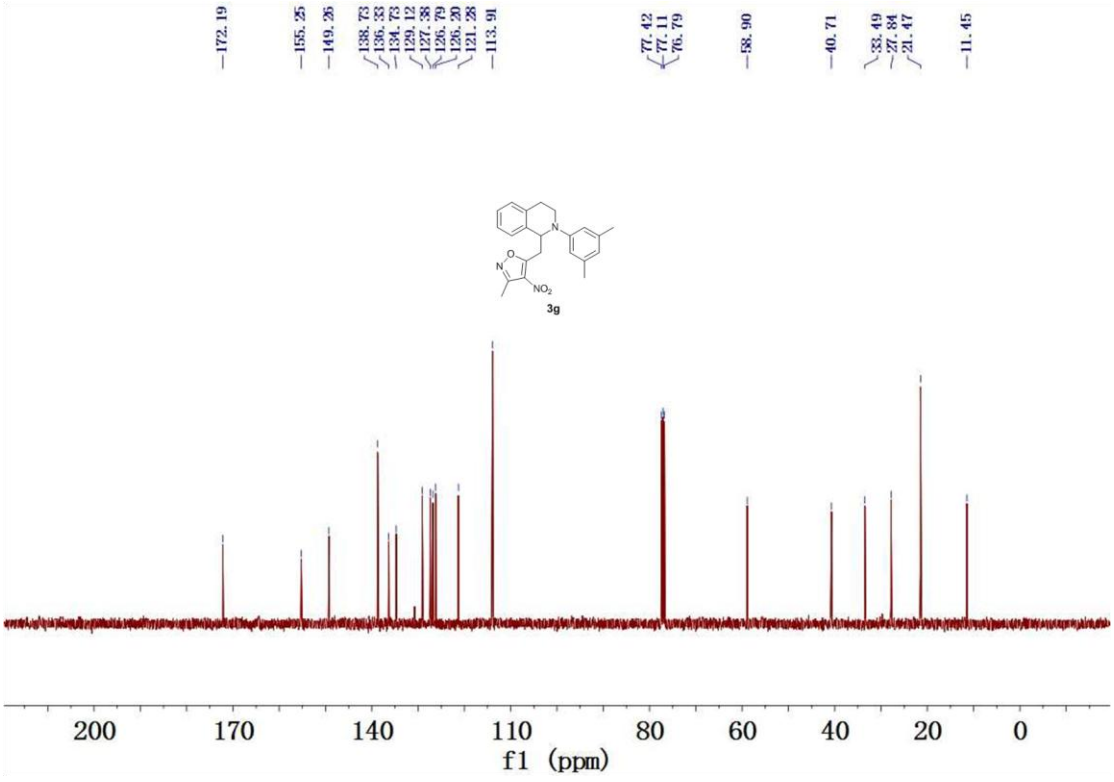
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76.79
58.90
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11.45
3g
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110
80
60
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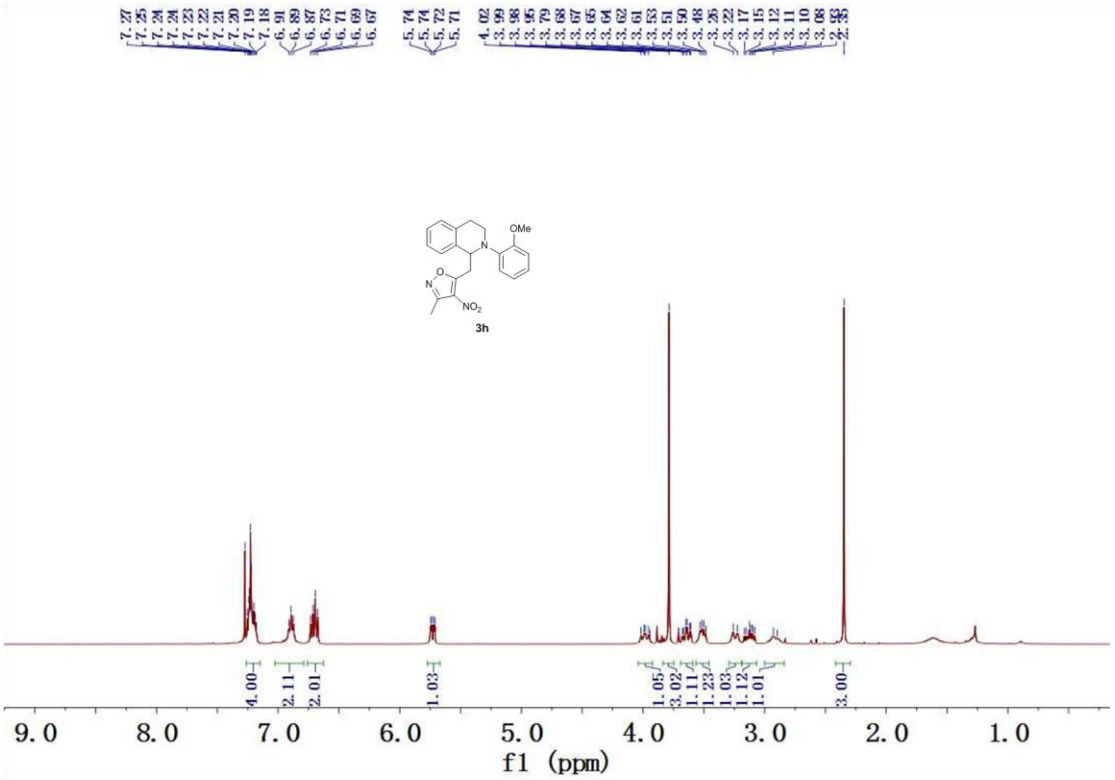
0
f1 (ppm)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6.71
6.69
6.67
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5.74
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5.71
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3.98
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3.68
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3.12
3.11
3.10
3.08
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OMe
N
O
N
NO2
3h
4.00
2.11
2.01
1.03
1.05
3.02
1.11
1.23
1.03
1.12
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6.0
5.0
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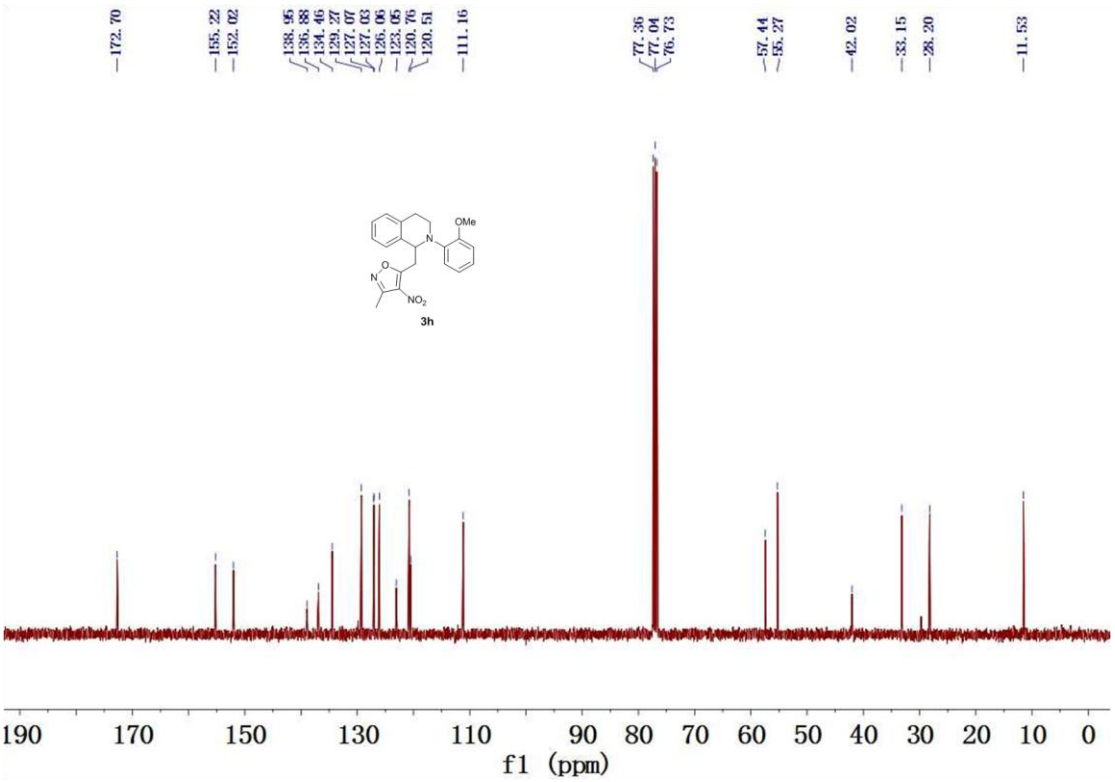
1.0
f1 (ppm)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123.05
120.76
120.51
111.16
77.36
77.04
76.73
57.44
55.27
42.02
33.15
28.20
11.53
OMe
N
O
N
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3h
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110
90
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70
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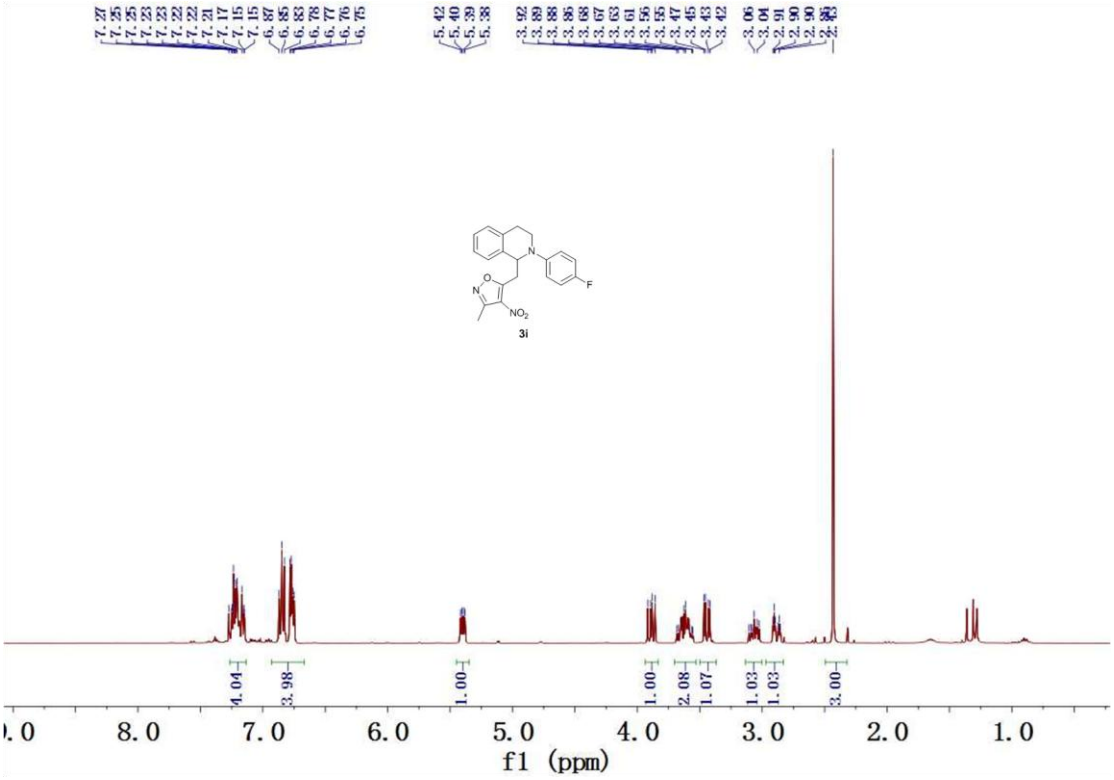
50
40
30
20
10
0
f1 (ppm)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6.78
6.77
6.76
6.75
5.42
5.40
5.39
5.38
3.92
3.89
3.88
3.86
3.68
3.67
3.63
3.61
3.56
3.55
3.47
3.45
3.43
3.42
3.06
3.04
2.91
2.90
2.90
2.83
O
N
NO2
F
3i
4.04
3.98
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1.00
2.08
1.07
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1.03
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6.0
5.0
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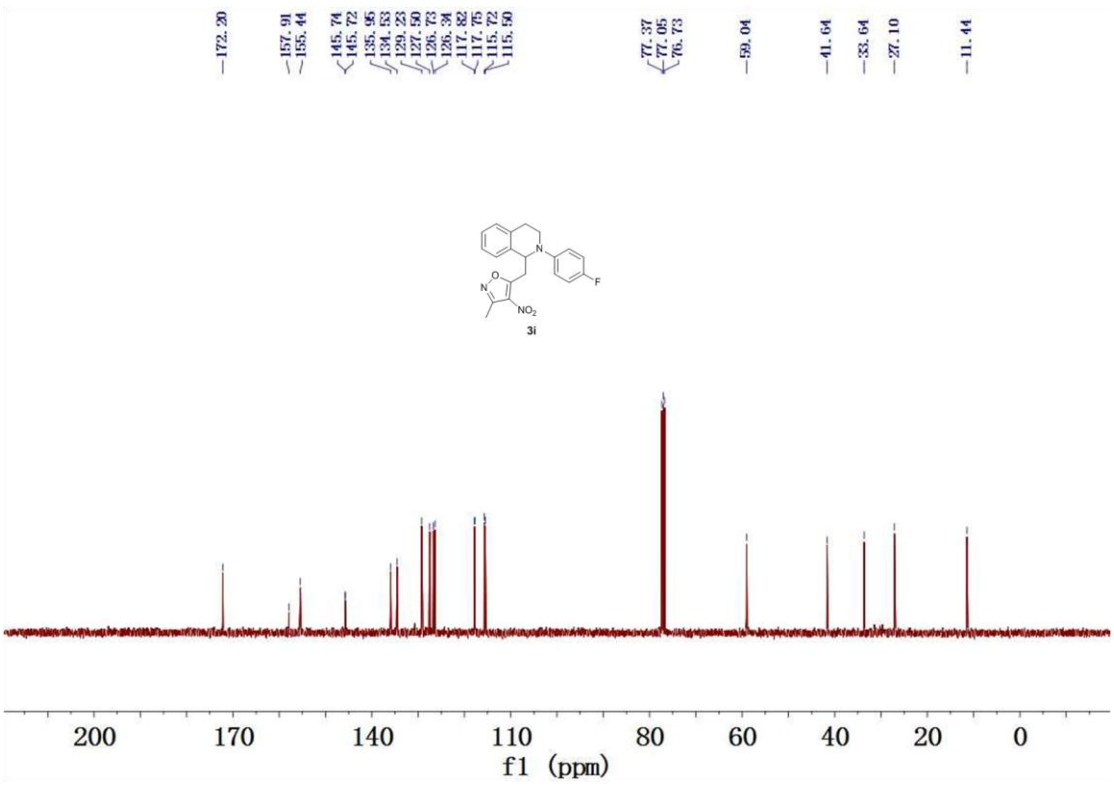
1.0
f1 (ppm)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129.23
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126.73
126.34
117.82
117.75
115.72
115.50
77.37
77.05
76.73
59.04
41.64
33.64
27.10
11.44
O
N
NO2
F
3i
200
170
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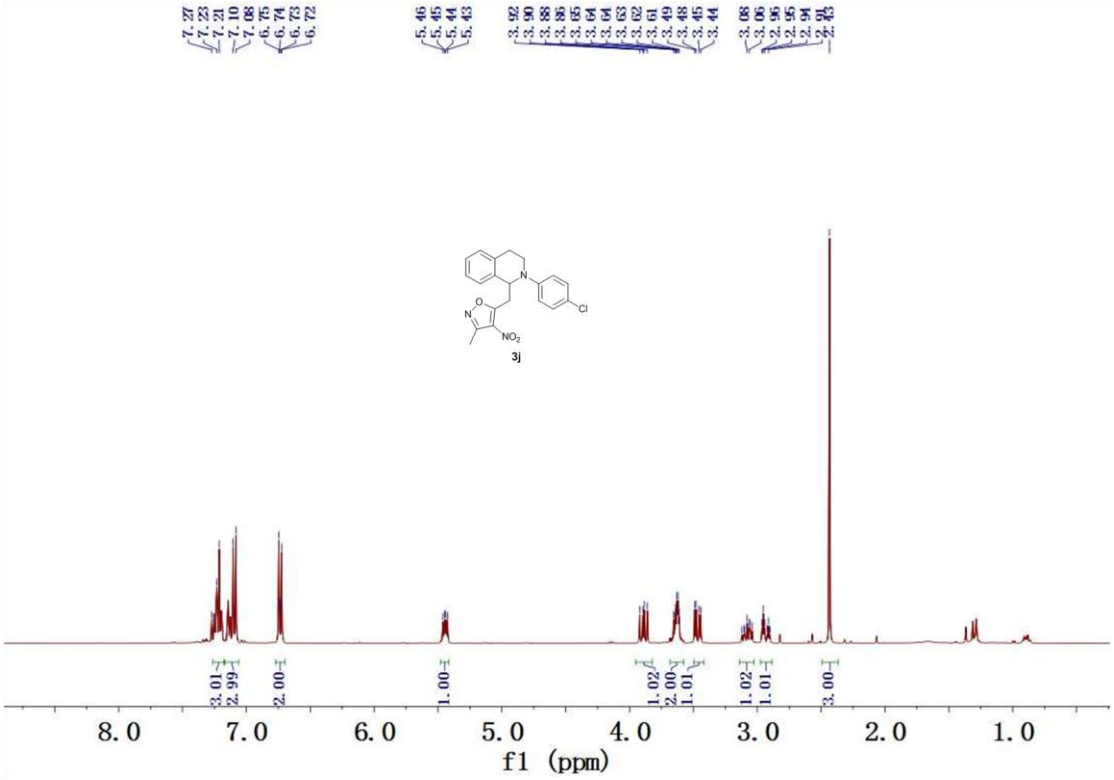
110
80
60
40
20
0
f1 (ppm)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6.72
5.46
5.45
5.44
5.43
3.92
3.90
3.88
3.86
3.85
3.64
3.63
3.62
3.61
3.49
3.48
3.45
3.44
3.08
3.06
2.95
2.91
2.43
Cl
NO2
3j
3.01
2.99
2.00
1.00
1.02
2.00
1.01
1.02
1.01
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6.0
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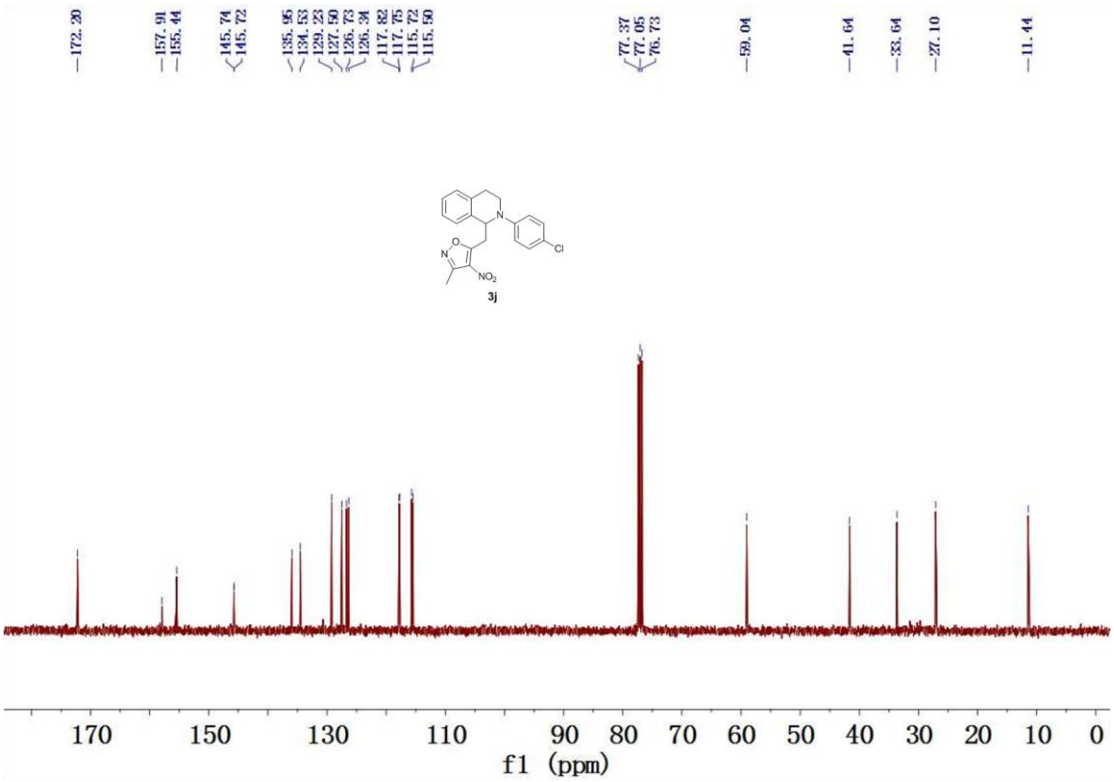
1.0
f1 (ppm)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126.34
117.82
117.75
115.72
115.50
77.37
77.05
76.73
59.04
41.64
33.64
27.10
11.44
Cl
NO2
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130
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70
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50
40
30
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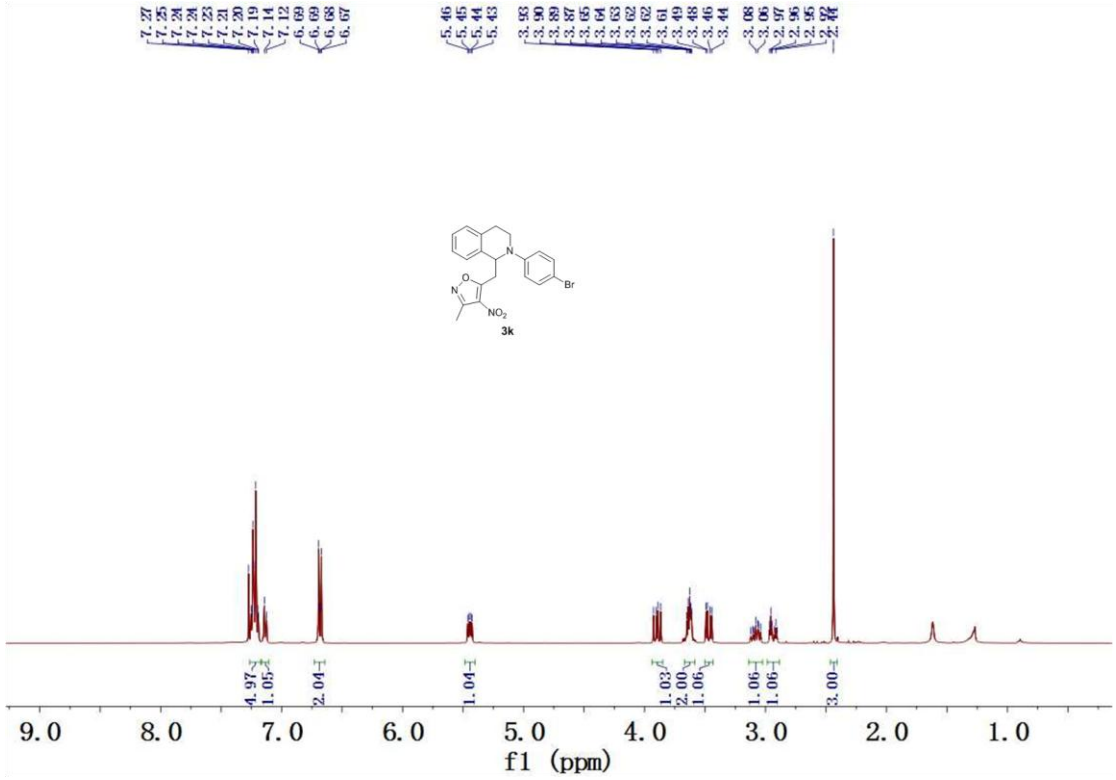
10
0
f1 (ppm)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5.46
5.45
5.44
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3.87
3.65
3.64
3.63
3.62
3.62
3.61
3.49
3.48
3.46
3.44
3.08
3.06
2.97
2.96
2.95
2.93
2.44
Br
NO2
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1.05
2.04
1.04
1.03
2.00
1.06
1.06
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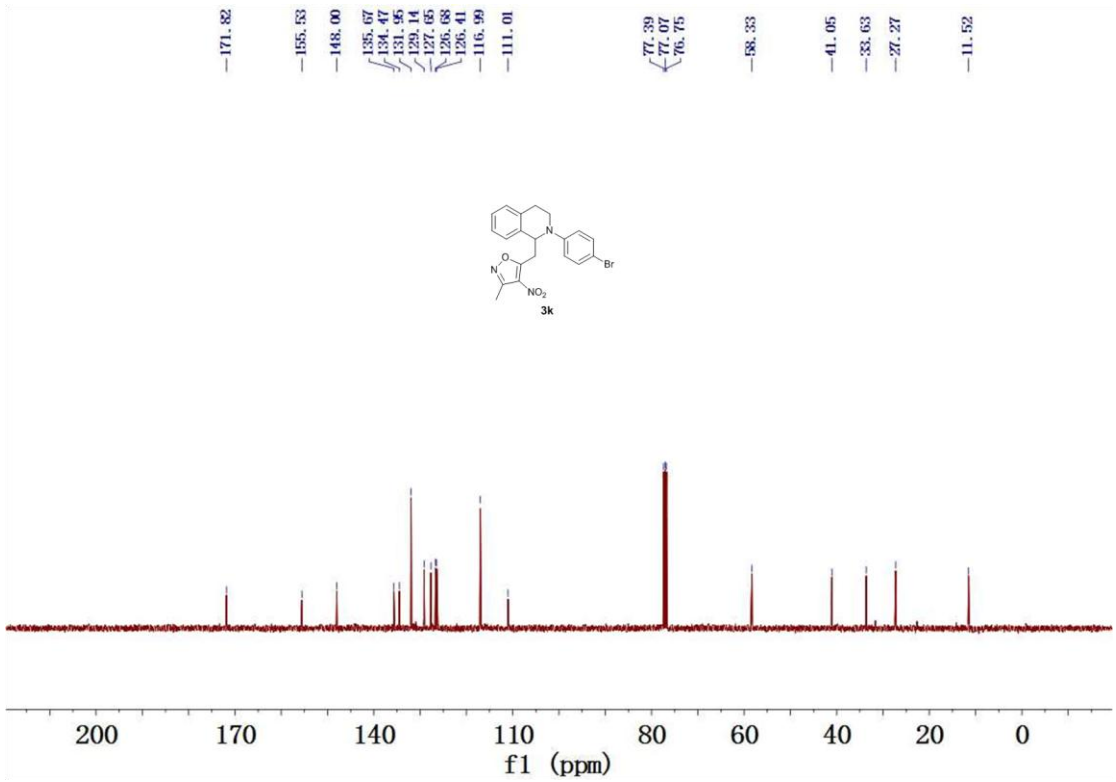
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77.39
77.07
76.75
88.33
41.05
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11.52
Br
NO2
3k
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110
80
60
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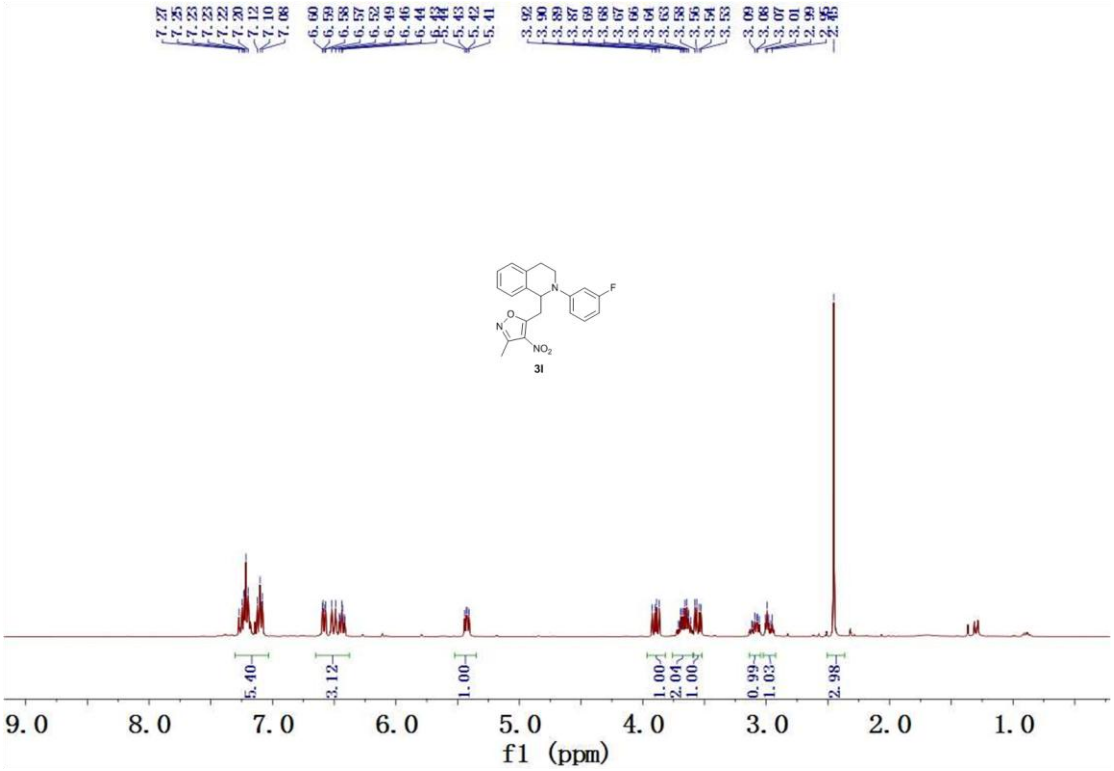
20
0
f1 (ppm)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6.57
6.52
6.49
6.46
6.44
5.43
5.42
5.41
3.92
3.90
3.89
3.67
3.69
3.68
3.67
3.66
3.64
3.63
3.58
3.56
3.54
3.53
3.09
3.06
3.07
3.01
2.99
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N
O
N
NO2
3l
5.40
3.12
1.00
1.00
2.04
1.00
0.99
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6.0
5.0
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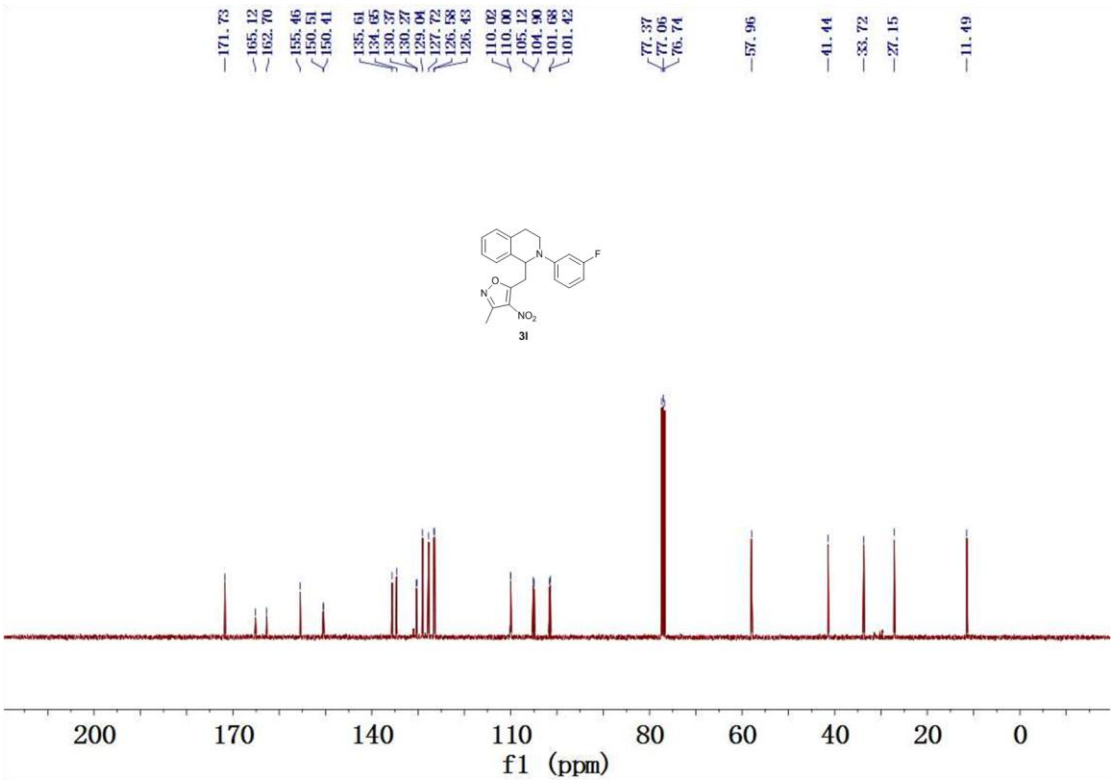
3.0
2.0
1.0
f1 (ppm)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129.04
127.72
126.58
126.43
110.02
110.00
105.12
104.90
101.68
101.42
77.37
77.06
76.74
57.96
41.44
33.72
27.15
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N
O
N
NO2
3l
200
170
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110
80
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20
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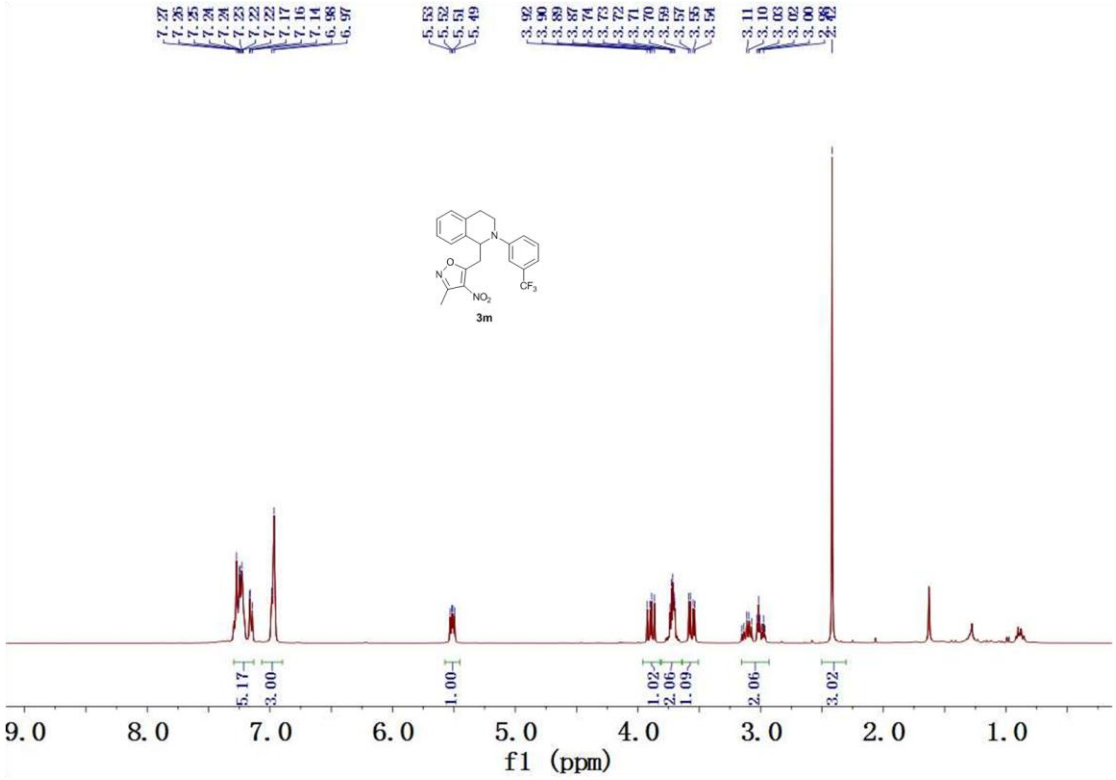
f1 (ppm)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6.97
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5.52
5.51
5.49
3.92
3.90
3.89
3.87
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3.72
3.71
3.70
3.59
3.57
3.55
3.54
3.11
3.10
3.03
3.02
3.00
2.98
2.42
3m
5.17
3.00
1.00
1.02
2.06
1.09
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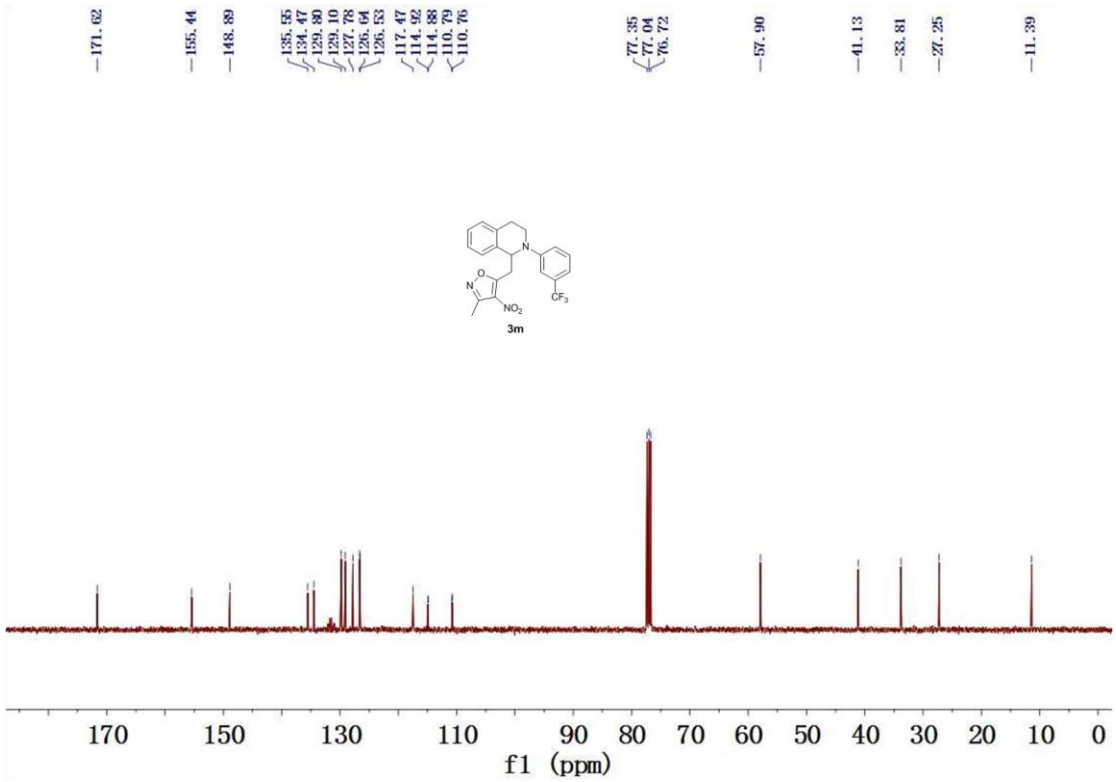
1.0
f1 (ppm)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114.88
110.79
110.76
77.35
77.04
76.72
57.90
41.13
33.81
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80
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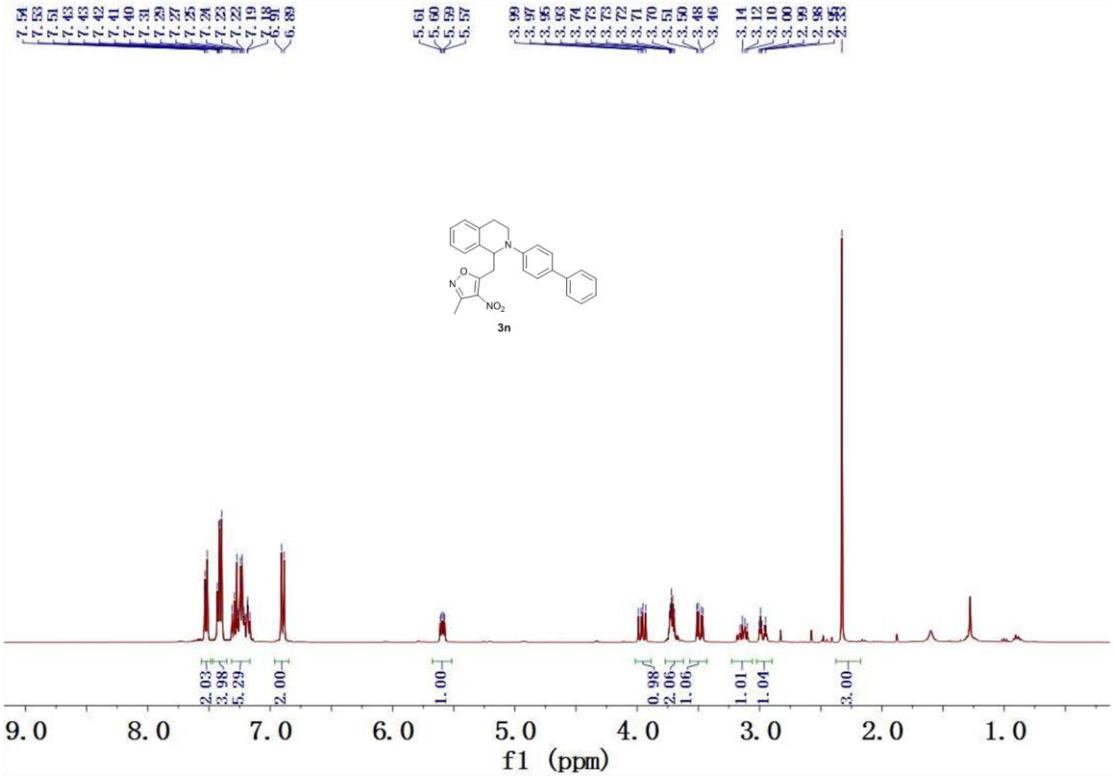
f1 (ppm)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5.57
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1.00
0.98
2.06
1.06
1.01
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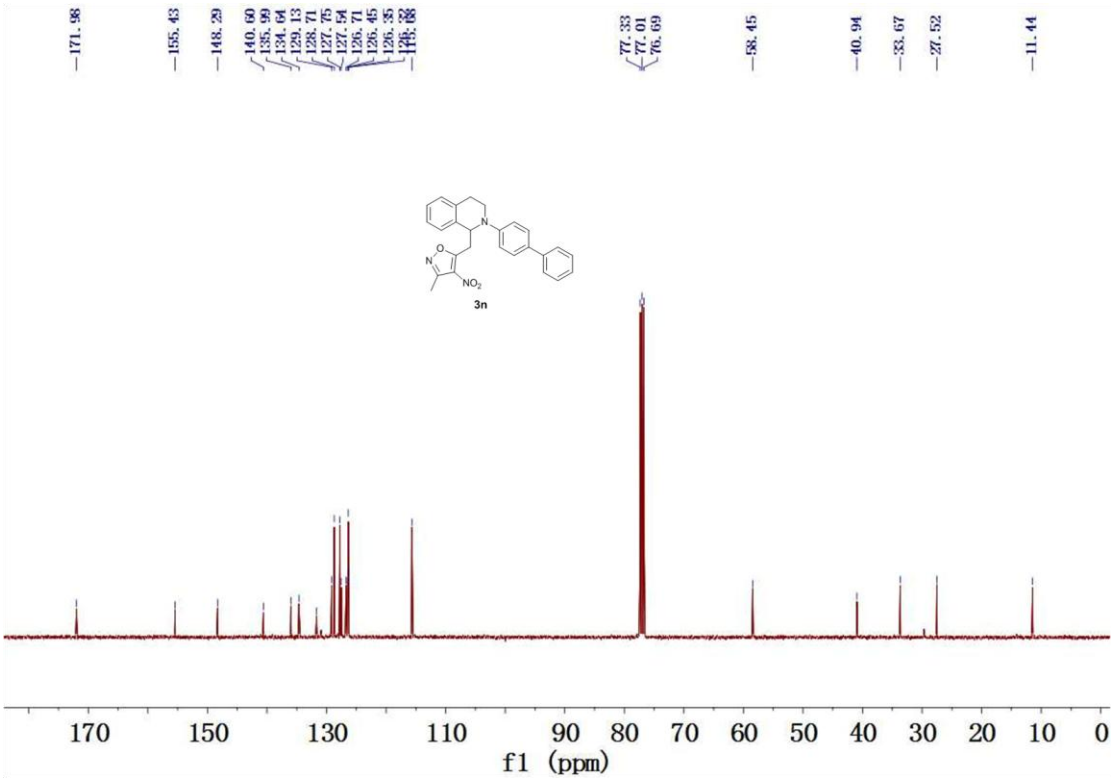
1.0
f1 (ppm)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128.71
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126.71
126.45
126.35
77.33
77.01
76.69
58.45
40.94
33.67
27.52
11.44
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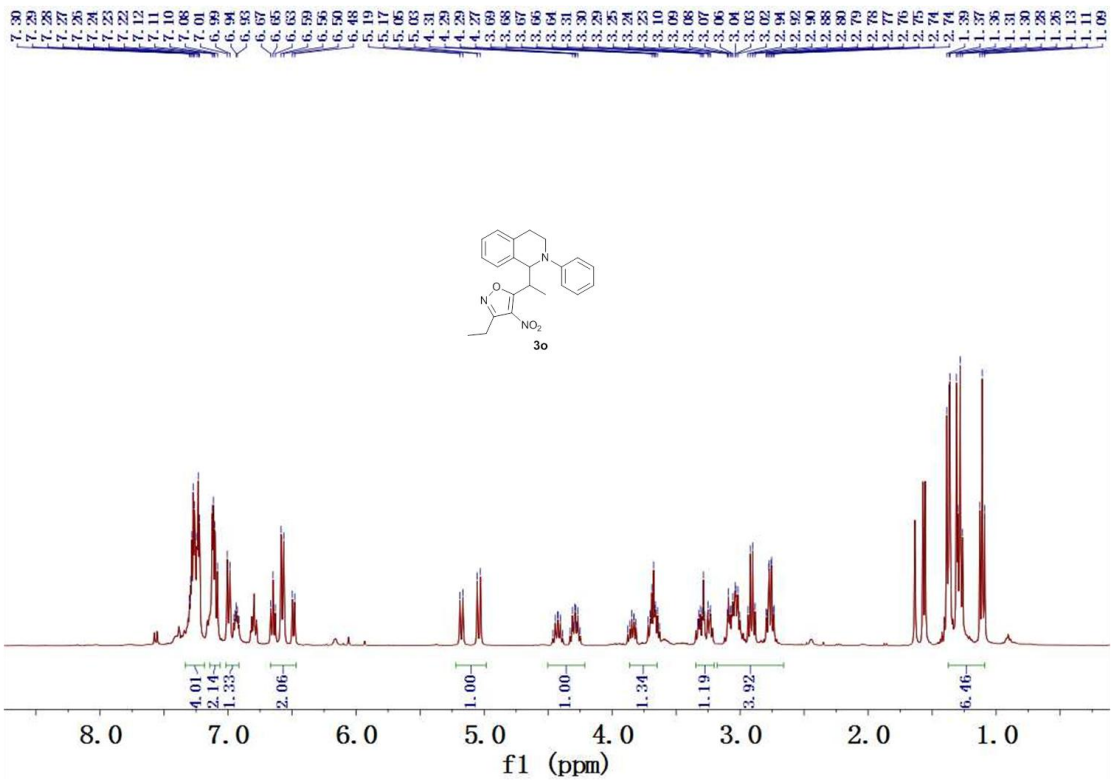
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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1.33
2.06
1.00
1.00
1.34
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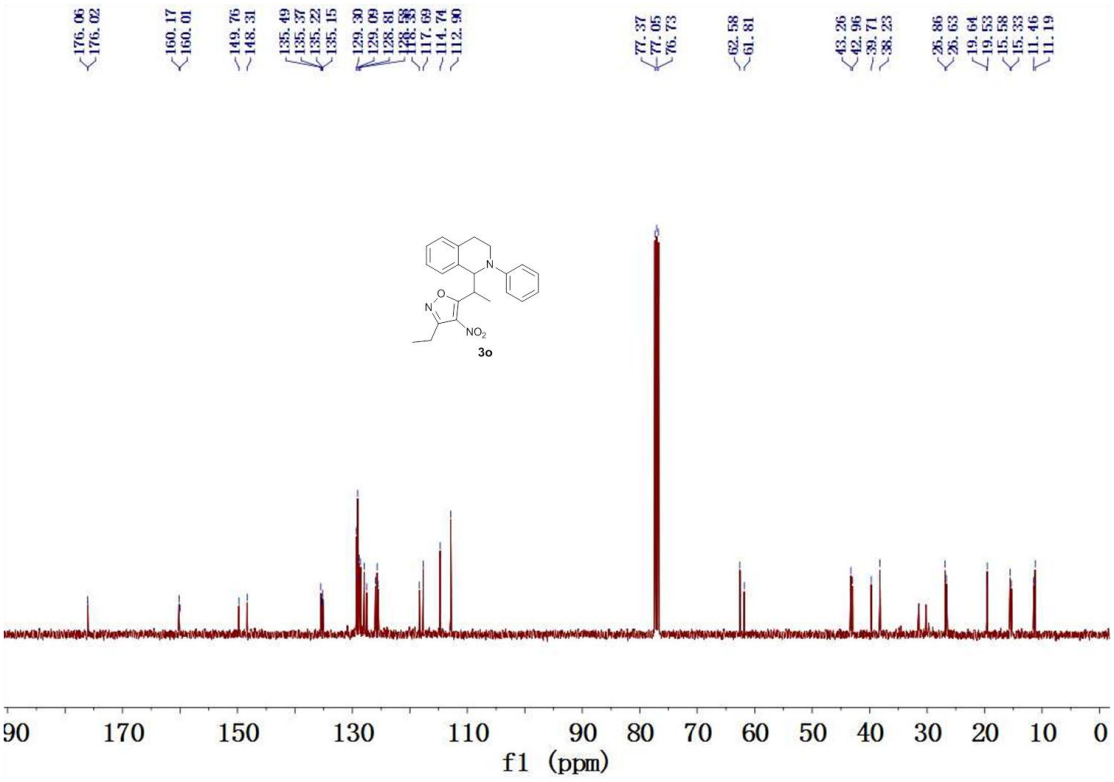
7.0
6.0
5.0
4.0
3.0
2.0
1.0
f1 (ppm)


3o
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150
130
110
90
80
70
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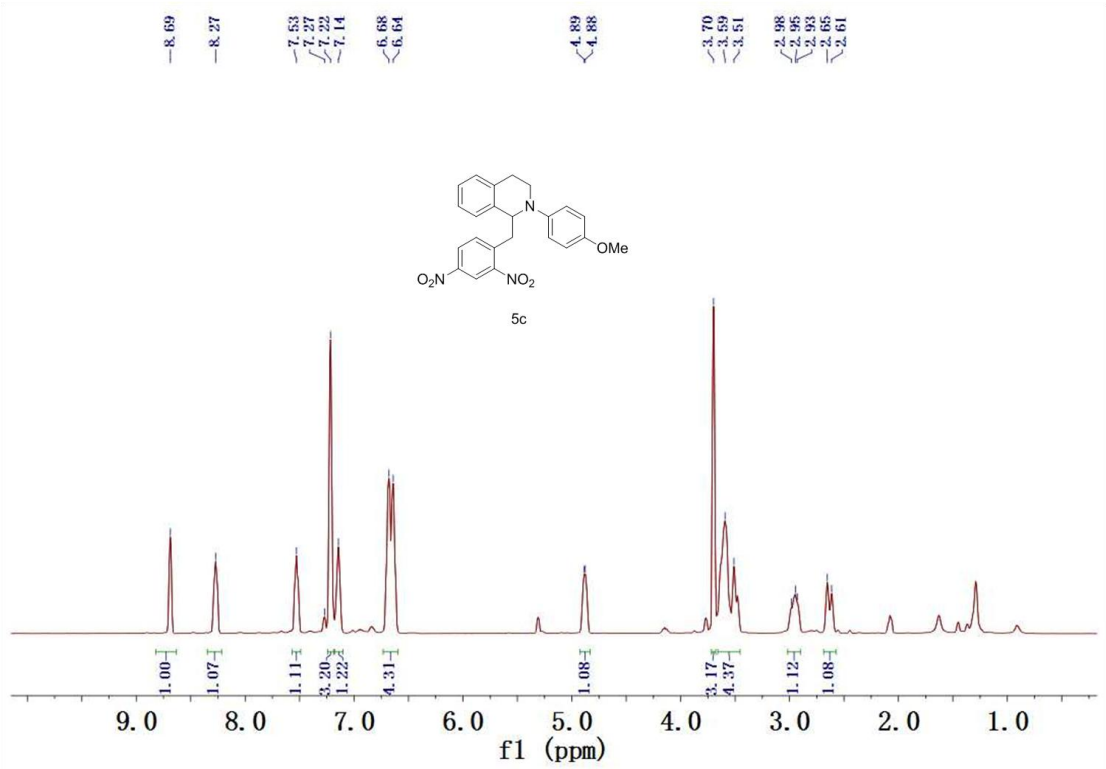
50
40
30
20
10
0
f1 (ppm)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7.22
7.14
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6.64
4.89
4.88
3.70
3.59
3.51
2.98
2.95
2.93
2.65
2.61
N
OMe
O2N
NO2
5c
1.00
1.07
1.11
3.20
1.22
4.31
1.08
3.17
4.37
1.12
1.08
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7.0
6.0
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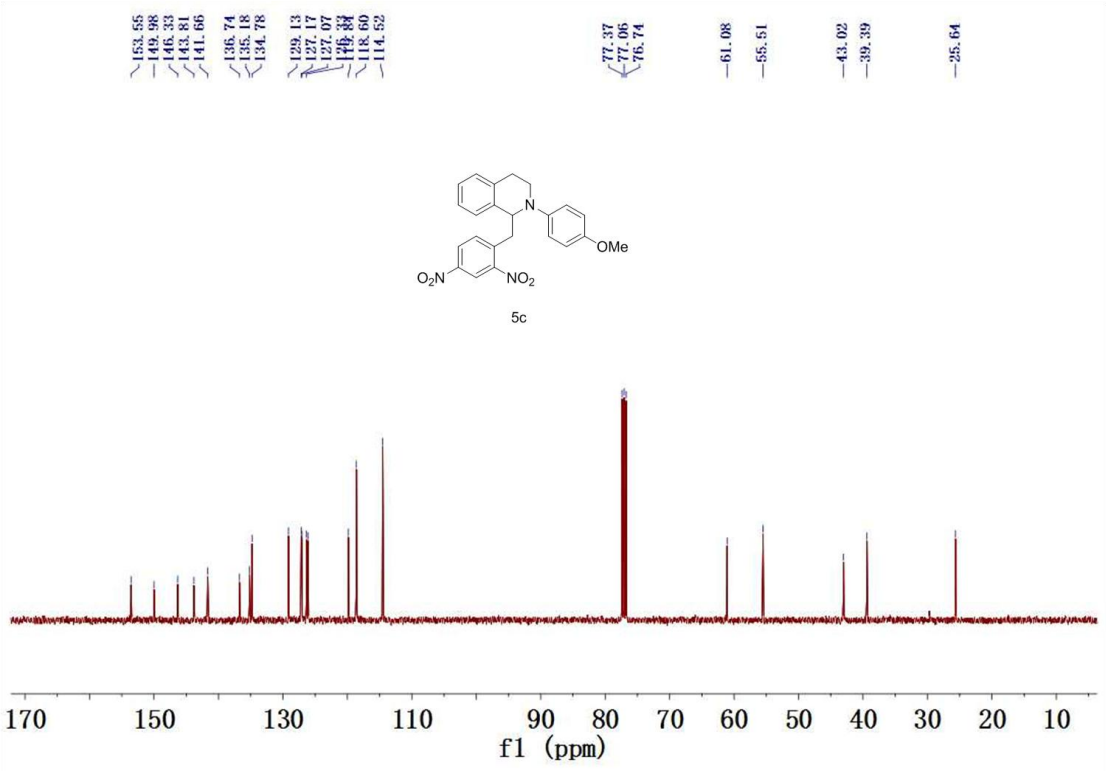
4.0
3.0
2.0
1.0
f1 (ppm)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129.13
127.17
127.07
118.60
114.52
77.37
77.06
76.74
61.08
55.51
43.02
39.39
25.64
N
OMe
O2N
NO2
5c
170
150
130
110
90
80
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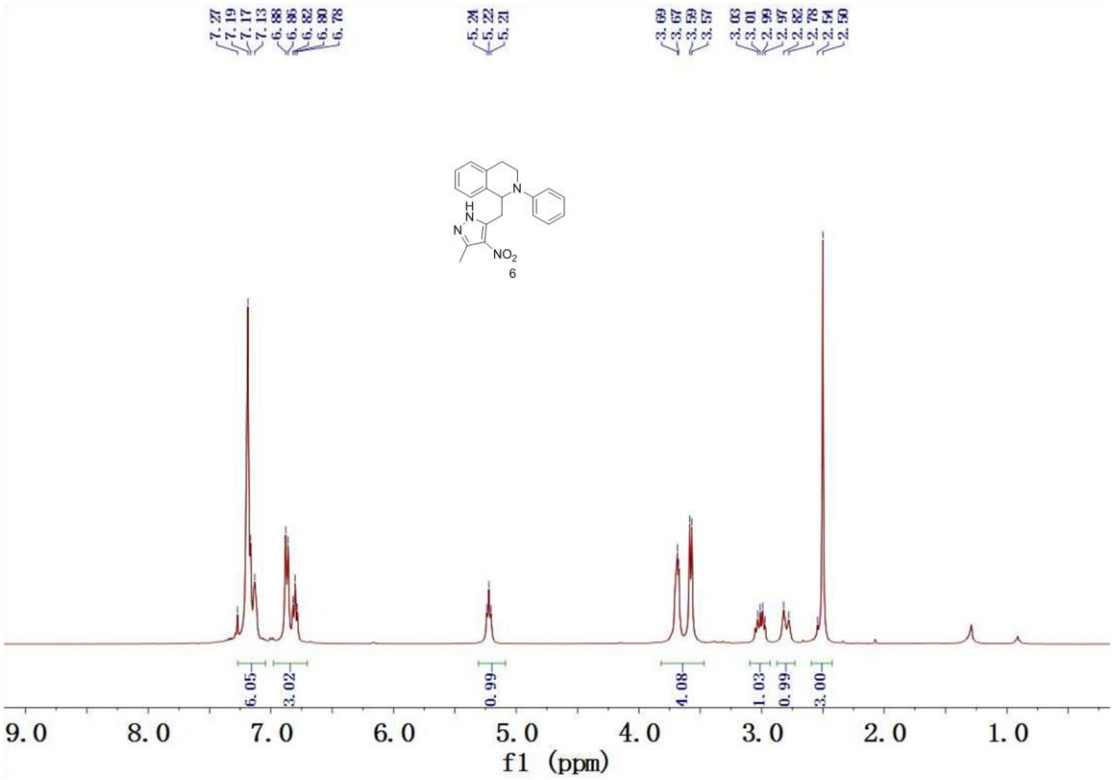
60
50
40
30
20
10
f1 (ppm)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5.22
5.21
3.69
3.67
3.59
3.57
3.03
3.01
2.99
2.97
2.82
2.78
2.54
2.50
NO2
6
6.05
3.02
0.99
4.08
1.03
0.99
3.00
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8.0
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6.0
5.0
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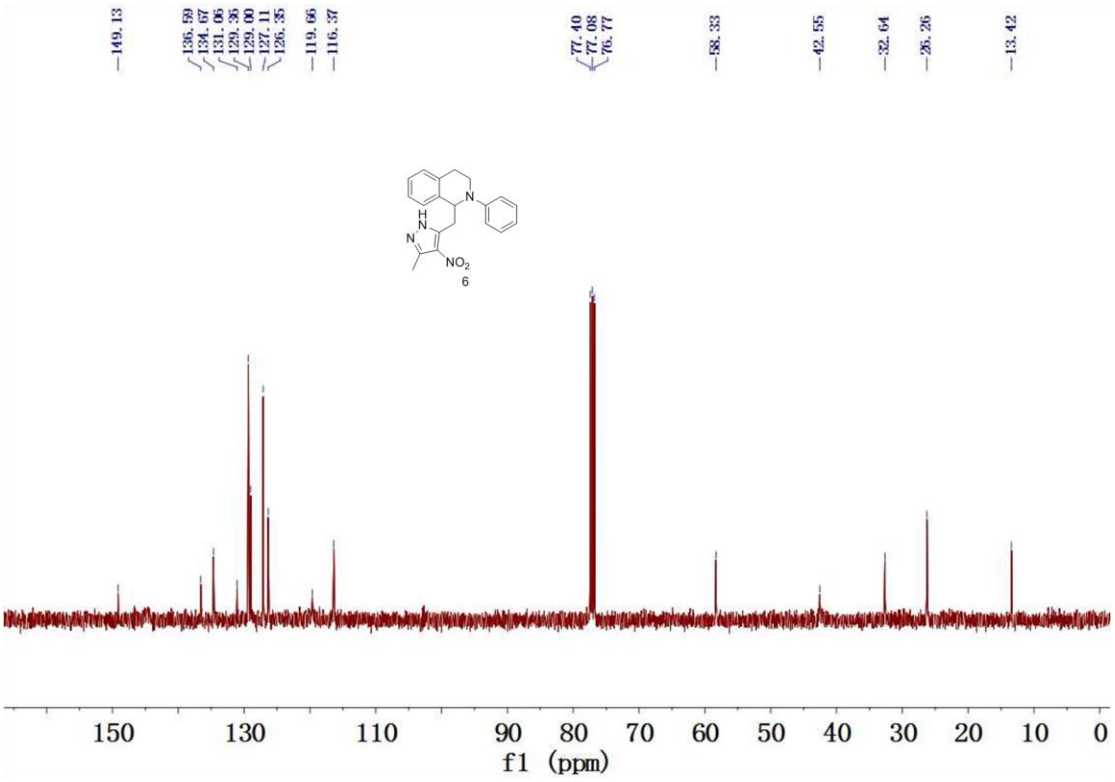
3.0
2.0
1.0
f1 (ppm)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116.37
77.40
77.08
76.77
58.33
42.55
32.64
25.26
13.42
NO2
6
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130
110
90
80
70
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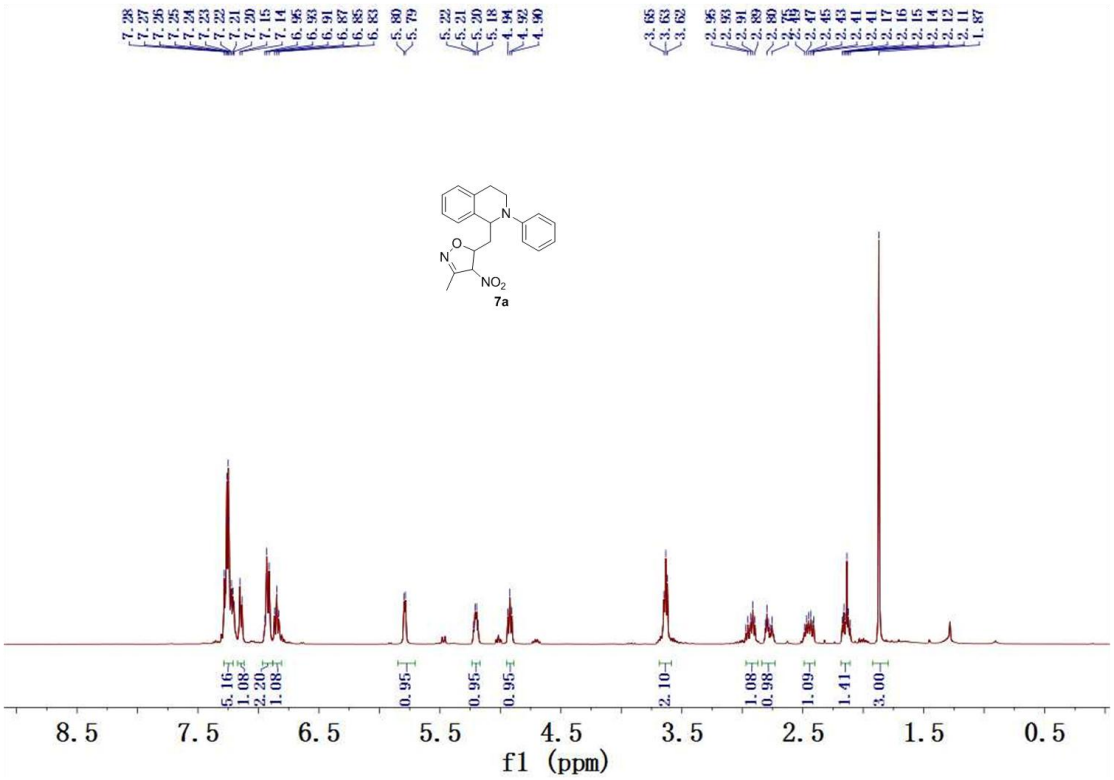
50
40
30
20
10
0
f1 (ppm)


7a
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6.5
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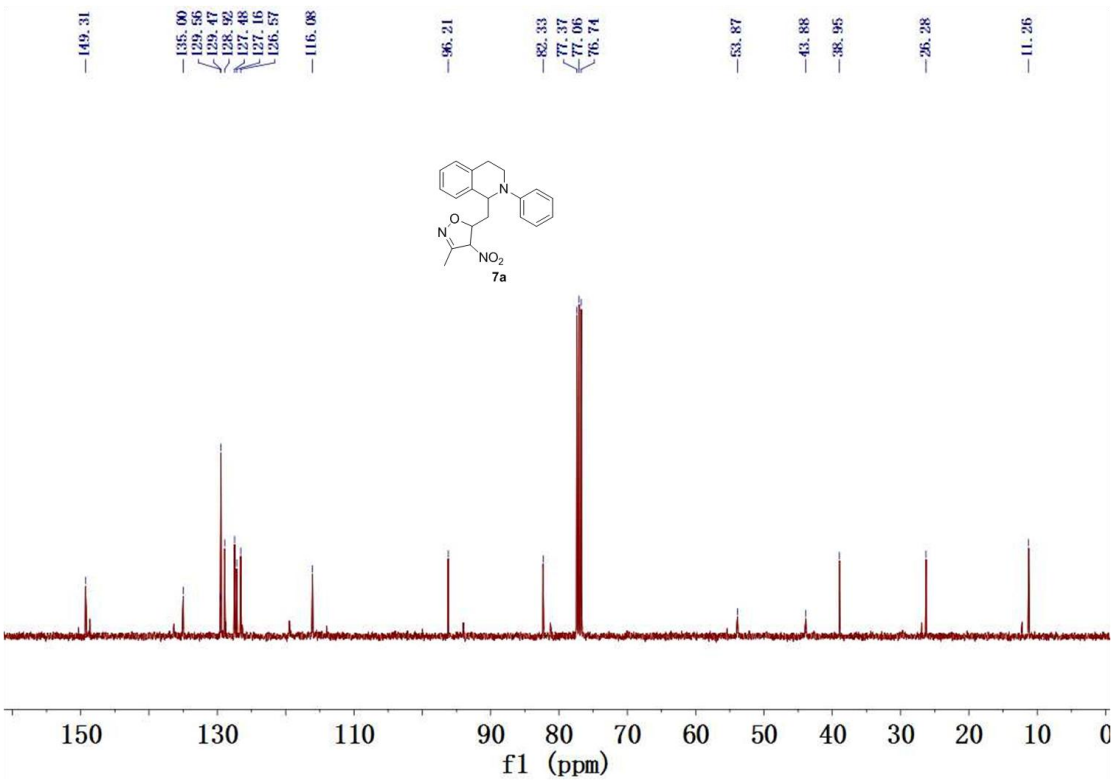
4.5
3.5
2.5
1.5
0.5
f1 (ppm)


7a
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)