Electronic Supplementary Information

Iron-Catalyzed Cascade Cyanoalkylation/Radical Dearomatization of *N*-phenylcinnamamides: Access to Cyanoalkylated 1-Azaspiro[4.5]decanes

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Table of Contents

1. General Information

All regents were commercial available and used without further purification. All reactions were conducted under argon atmosphere. The reaction was detected using Thin Layer Chromatography (TLC). The products were separated using TLC. ^{1}H, ^{19}F and ^{13}C NMR spectra were conducted by 400 MHz spectrometer at room temperature, using $CDCl_3$ as solvent with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are determined in ppm downfield from tetramethylsilane. Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; m, multiplet. HRMS data were recorded by a TOF LC/MS. Substrates were prepared according to reported literatures.[1, 2]

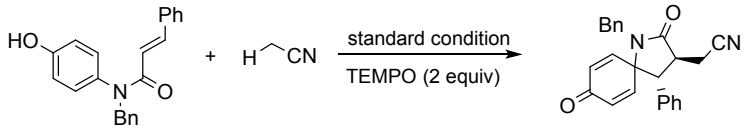
2. Experment procedure

N-(4-hydroxyphenyl)-*N*-alkyl-cinnamamides (**1**, 0.2 mmol), $Fe(acac)_2$ (0.04 mmol, 20 mol%), DTBP (0.4 mmol, 2.0 equiv.), nitriles (2 mL) and a stir bar were added into a sealed tube. The sealed tube was degassed by freeze-thaw-pump for three times. Then the sealed tube was heated at 120 °C for 12 h as the TLC showed that the reaction was finished. The mixture was cooled to room temperature and concentrated in vacuum. The residue was purified using TLC on silica gel (GF254) to give the corresponding products (**3**).

3. Research on the Mechanism

3.1 Free Radical Capture Experiments

N-(4-hydroxyphenyl)-*N*-benzyl-cinnamamides (**1d**, 0.2 mmol), $Fe(acac)_2$ (0.020 mmol, 20 mol%), DTBP (0.4 mmol, 2.0 equiv.), MeCN (2 mL), 2,2,6,6-tetramethylpiperidine oxide (TEMPO) (0.4 mmol, 2.0 equiv.) and a stir bar were added into a sealed tube. The sealed tube was degassed by freeze-thaw-pump for three times. Then the sealed tube was heated at 120 °C for 12 h as the TLC showed that the reaction was finished. The mixture was cooled to room temperature and concentrated in vacuum. The residue was separated using preparative TLC on silica gel (GF254).



1d **3d:** not detected

3.2 The KIE Studies

The KIE studies on solvent (competition reaction)

N-(4-hydroxyphenyl)-*N*-benzyl-cinnamamide (**1d**, 0.2 mmol), $Fe(acac)_2$ (0.025 mmol, 20 mol%), DTBP (0.4 mmol, 2.0 equiv), CH_3CN (1 mL), CD_3CN (1 mL) and a stir bar were added into a sealed tube. The sealed tube was degassed by freeze-thaw-pump for three times. Then the sealed tube was heated at 120 ℃ for 12 h. And the mixture was concentrated in vacuum and the residue was purified using preparative TLC on silica gel (GF254) to give the corresponding product **3d** and **[D_2]-3d**. On the ^{1}H NMR spectra, the signal of H at δ 3.10-3.01 belongs to the *α*-C-H of cyan group. The integral of C-H at δ 3.10-3.01 is 1.0 for **3d** and it is 0.86 for the mixture of **3d** and **[D_2]-3d**. The KIE value can be calculated as $k_H/k_D = 0.86/(1-0.86) \approx 6.1$ (Figure S1).[3]

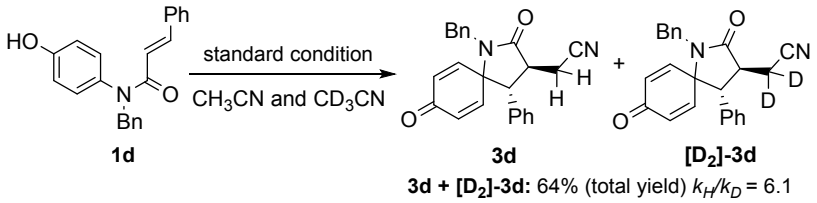
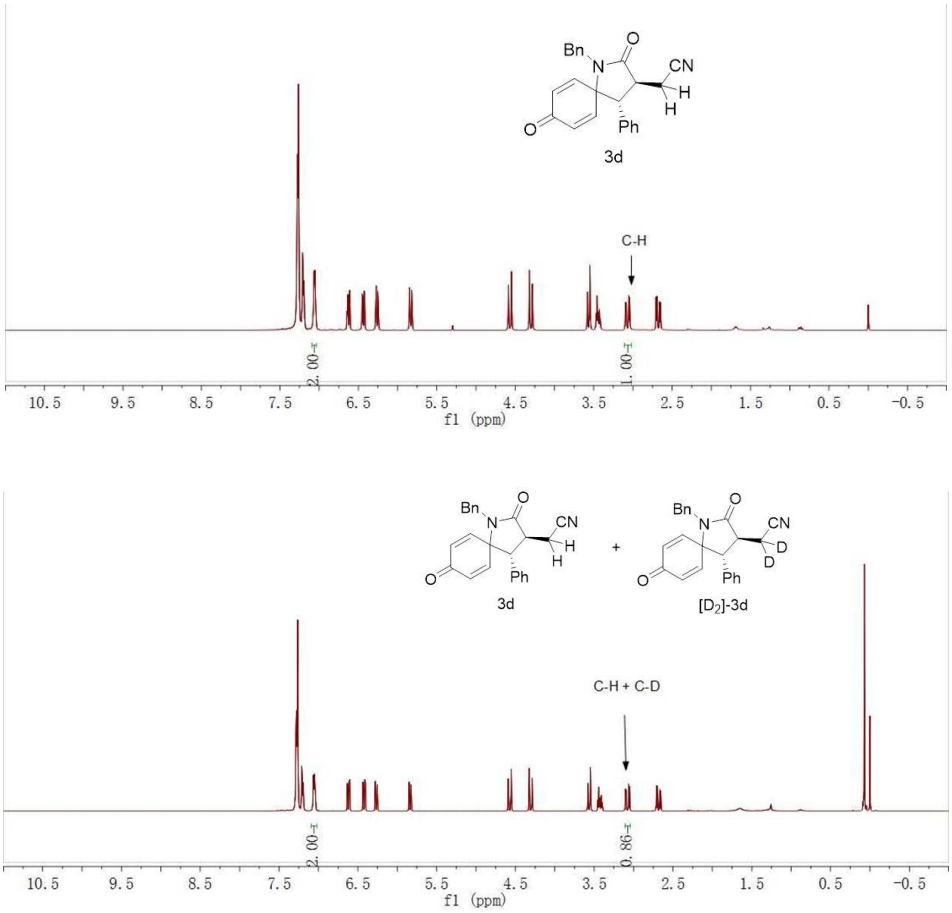
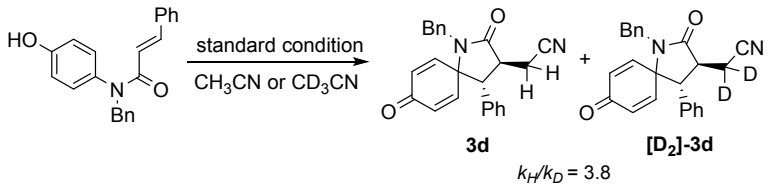


Figure S1. The ^{1}H NMR spectrum of the KIE results.

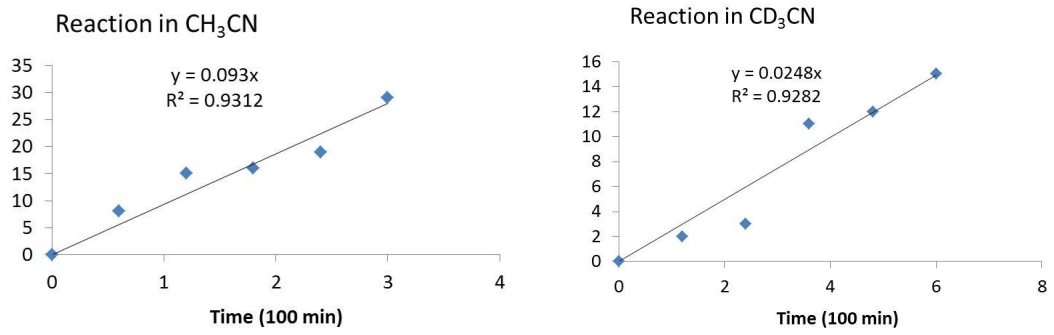


The Kinetic Isotopic Effect Studies on Solvent (parallel reaction)

In ten parallel sealed tubes, *N*-(4-hydroxyphenyl)-*N*-benzyl-cinnamamide (**1d**, 0.2 mmol) was treated by standard condition in CH_3CN or D_3-CH_3CN (five experiments for each). Then the reactions was quenched by cooling to room temperature in specified time. The mixture was analyzed by ^{1}H NMR with CH_2Br_2 as inert standard to record the yield of products **3d** or **[D$_2$]-3d**. A significant intermolecular kinetic isotope effect (k_H/k_D = 3.8) was observed.[4] The results were listed below:



^{1}H NMR of **[D_2]-3d** (400 MHz, $CDCl_3$): δ 7.28-7.23 (m, 6H), 7.21 – 7.19 (m, 1H), 7.03 (dd, *J* = 6.5, 3.0 Hz, 2H), 6.59 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.44 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.25 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.79 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.51 (d, *J* = 14.9 Hz, 1H), 4.27 (d, *J* = 14.9 Hz, 1H), 3.23 – 3.14 (m, 2H).



4. Reference

(1) G. F. Han, Q. Wang, Y. X. Liu and Q. M. Wang, *Org. Lett.* 2014, **16**, 5914.

(2) O. Lozano, G. Blessley, T. M. Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman and V. Gouverneur. *Angew. Chem. Int. Ed.* 2011, **50**, 8105.

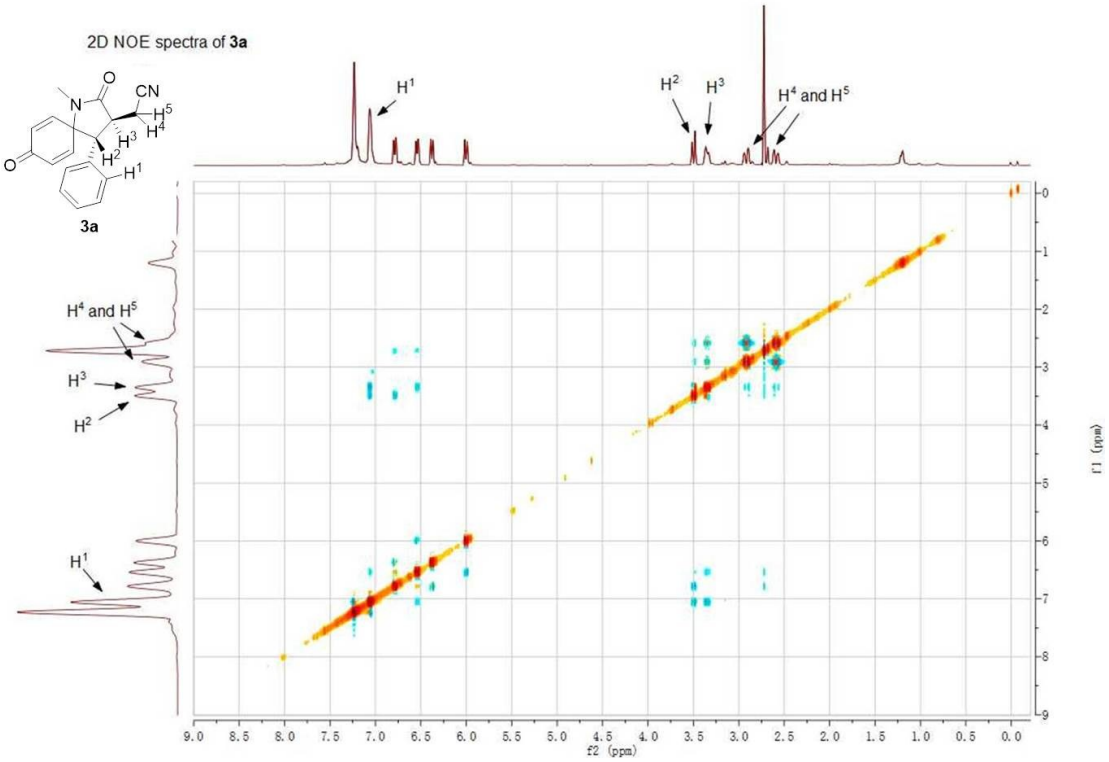
(3) Z. J. Li, Y. X. Xiao and Z.-Q. Liu, *Chem. Commun.* 2015, **51**, 9969.

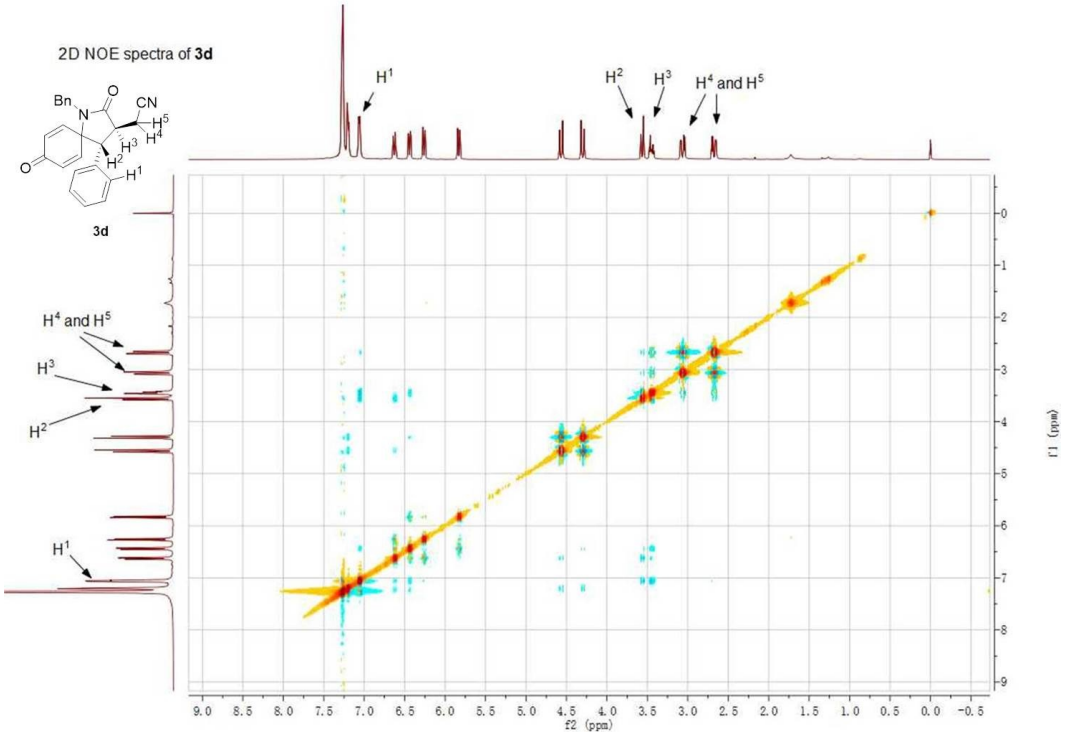
(4) C. D. Pan, H. L. Zhang and C. J. Zhu, *Org. Biomol. Chem.* 2015, **13**, 361.

5. Characterization for the Products

5.1 2D NOE spectra of **3a** and **3d**

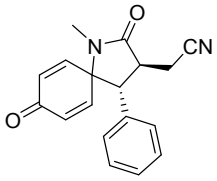
Figure S2. 2D NOE spectra of **3a** and **3d**





5.2 Characterization Data for the Products

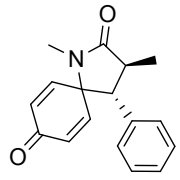
2-(1-methyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3a)



3a

67%, 19.4 mg, white solid, m.p.: 52.0-54.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.29 (m, 3H), 7.16-7.11 (m, 2H), 6.86 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.61 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.45 (dd, *J* = 10.1, 1.9 Hz, 1H), 6.07 (dd, *J* = 10.2, 1.9 Hz, 1H), 3.57 (d, *J* = 12.5 Hz, 1H), 3.46-3.39 (m, 1H), 2.99 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.79 (s, 3H), 2.66 (dd, *J* = 17.1, 5.1 Hz, 1H). ^{13}C NMR (100MHz, $CDCl_3$): δ 184.0, 171.7, 148.0, 145.1, 133.0, 132.2, 131.7, 129.0, 129.0, 128.0, 116.7, 65.0, 53.7, 40.5, 27.4, 17.6. HRMS (ESI) calcd. for $C_{18}H_{17}N_2O_2^+$ ($M+H^+$) : 293.1285, found: 293.1283.

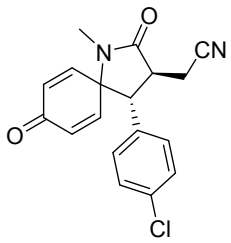
1,3-dimethyl-4-phenyl-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (3a')



3a'

30%, 8.2 mg, white solid, m.p.: 136.2-138.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 3H), 7.11 – 7.08 (m, 2H), 6.78 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.57 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.42 (dd, *J* = 10.1, 2.0 Hz, 1H), 6.04 (dd, *J* = 10.2, 2.0 Hz, 1H), 3.22 (d, *J* = 12.2 Hz, 1H), 3.12 (dd, *J* = 12.4, 6.5 Hz, 1H), 2.76 (d, *J* = 0.5 Hz, 3H), 1.29 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 176.0, 149.1, 146.0, 132.6, 131.8, 128.7, 128.3, 127.9, 57.1, 38.8, 28.8, 27.1, 14.6. HRMS (ESI) calcd. for $C_{17}H_{17}NNaO_2^+$ ($M+Na^+$) : 290.1151, found: 290.1149.

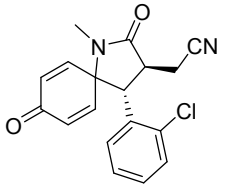
2-(4-(4-chlorophenyl)-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3b)



3b

58%, 18.7 mg, white solid, m.p.: 136.2-138.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.81 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.53 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.47 (dd, *J* = 10.1, 1.9 Hz, 1H), 6.13 (dd, *J* = 10.2, 1.9 Hz, 1H), 3.54 (d, *J* = 12.5 Hz, 1H), 3.34 – 3.25 (m, 1H), 3.00 (dd, *J* = 17.1, 5.1 Hz, 1H), 2.81 (s, 3H), 2.69 (dd, *J* = 17.1, 4.8 Hz, 1H). ^{13}C NMR (100MHz, $CDCl_3$): δ 183.6, 171.1, 147.5, 144.4, 135.2, 133.3, 132.6, 130.2, 129.3, 129.3, 116.3, 64.8, 53.3, 40.6, 27.4, 17.7. HRMS (ESI) calcd. for $C_{18}H_{15}ClN_2NaO_2^+$(M+Na$^+$): 349.0714, found: 349.0711.

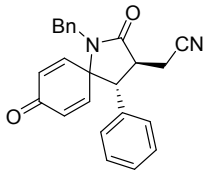
2-(4-(2-chlorophenyl)-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3c)



3c

52%, 16.8 mg, white solid, m.p.: 158.2-160.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.37 (m, 1H), 7.31 – 7.19 (m, 3H), 6.94 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.69 (dd, *J* = 10.2, 2.8 Hz, 1H), 6.39 (dd, *J* = 10.1, 1.9 Hz, 1H), 6.19 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.33 (d, *J* = 12.3 Hz, 1H), 3.32 (s, 1H), 2.88 (dd, *J* = 16.9, 5.6 Hz, 1H), 2.80 (s, 3H), 2.70 (dd, *J* = 17.1, 4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.9, 171.2, 148.2, 144.4, 135.8, 132.57, 131.0, 130.2, 129.9, 128.7, 127.1, 116.2, 64.8, 50.0, 42.2, 27.2, 17.9. HRMS (ESI) calcd. for $C_{18}H_{15}ClN_2NaO_{18}^+$(M+Na$^+$): 349.0714, found: 349.0710.

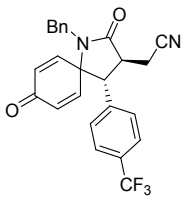
2-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3d)



3d

71%, 26.0 mg, white solid, m.p.: 84.7-86.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.24 (m, 1H), 7.23-7.15 (m, 1H), 7.10-7.03 (m, 1H), 6.63 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.44 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.26 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.83 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.57 (d, *J* = 15.0 Hz, 1H), 4.30 (d, *J* = 15.0 Hz, 1H), 3.56 (d, *J* = 12.6 Hz, 1H), 3.45 (dt, *J* = 12.6, 4.8 Hz, 1H), 3.07 (dd, *J* = 17.0, 4.7 Hz, 1H), 2.68 (dd, *J* = 17.0, 4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.1, 171.8, 147.7, 145.3, 136.9, 132.2, 131.3, 131.2, 129.1, 128.9, 128.7, 128.6, 128.1, 128.1, 116.5, 65.2, 54.2, 45.7, 40.5, 28.8, 17.7. HRMS (ESI) calcd. for $C_{24}H_{21}N_2O_2^+$(M+H$^+$): 369.1598, found: 369.1585.

2-(1-benzyl-2,8-dioxo-4-(4-(trifluoromethyl)phenyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3e)

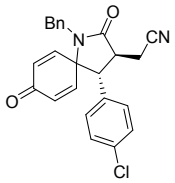


3e

66%, 28.6 mg, white solid, m.p.: 183.6-185.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.24 (m, 4H), 7.20 (dd, *J* = 11.2, 4.7 Hz, 4H), 6.64 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.42 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.30 (dd, *J* = 10.1, 1.9 Hz, 1H), 5.87 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.57 (d, *J* = 15.0 Hz, 1H), 4.32 (d, *J* = 15.0

Hz, 1H), 3.62 (d, *J* = 12.6 Hz, 1H), 3.45 (dt, *J* = 12.5, 4.8 Hz, 1H), 3.08 (dd, *J* = 17.1, 4.9 Hz, 1H), 2.70 (dd, *J* = 17.1, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.6, 171.2, 147.2, 144.5, 136.7, 135.6, 132.5, 131.5, 128.8, 128.6, 128.6, 128.5, 128.2, 126.0, 126.0, 123.5 (d, *J* = 270.8 Hz), 116.2, 64.9, 53.9, 45.8, 40.6, 17.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.64. HRMS (ESI) calcd. for $C_{25}H_{20}F_3N_2O_2^+$(M+H$^+$): 437.1471, found: 437.1468.

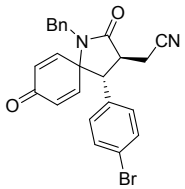
2-(1-benzyl-4-(4-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3f)



3f

53%, 21.2 mg, white solid, m.p.: 181.7-183.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.23 (m, 4H), 7.20 – 7.16 (m, 2H), 7.06 (d, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.66 – 6.58 (m, 1H), 6.48 – 6.40 (m, 1H), 6.32 – 6.21 (m, 1H), 5.91 – 5.79 (m, 1H), 4.61-4.51 (m, 1H), 4.35 – 4.25 (m, 1H), 3.53 (dd, *J* = 12.6, 2.5 Hz, 1H), 3.46 – 3.35 (m, 1H), 3.09-2.98 (m, 1H), 2.73-2.61 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.3, 171.9, 147.5, 145.5, 138.9, 136.9, 135.0, 132.1, 131.4, 130.0, 129.6, 129.2, 128.8, 128.6, 128.2, 128.0, 116.6, 65.3, 53.9, 45.7, 40.6, 21.1, 17.7. HRMS (ESI) calcd. for $C_{24}H_{20}ClN_2O_2^+$(M+H$^+$): 403.1208, found: 403.1204.

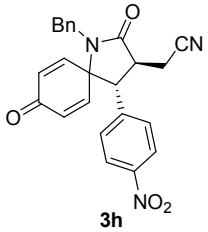
2-(1-benzyl-4-(4-bromophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3g)



3g

51%, 22.6 mg, white solid, m.p.: 221.5-223.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.29 – 7.25 (m, 3H), 7.23 – 7.15 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.60 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.39 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.28 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.88 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.56 (d, *J* = 15.0 Hz, 1H), 4.32 (d, *J* = 15.0 Hz, 1H), 3.51 (d, 12.4Hz, 1H), 3.41-3.08 (dt, *J* = 12.6, 4.9 Hz, 1H), 3.06 (dd, *J* = 17.1, 4.9 Hz, 1H), 2.69 (dd, *J* = 17.1, 4.8 Hz, 1H). ^{13}C NMR (100MHz, $CDCl_3$): δ 183.8, 171.3, 147.4, 144.8, 136.7, 132.4, 132.2, 131.5, 130.4, 129.7, 128.8, 128.6, 128.2, 123.3, 116.3, 77.4, 77.3, 77.0, 76.7, 65.0, 53.7, 45.8, 40.6, 17.7. HRMS (ESI) calcd. for $C_{24}H_{19}BrN_2NaO_2^+$(M+Na$^+$): 469.0522, found: 469.0517.

2-(1-benzyl-4-(4-nitrophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3h)

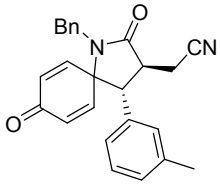


3h

46%, 18.8 mg, white solid, m.p.: 249.3-251.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.7 Hz, 2H), 7.28 (dd, *J* = 6.3, 2.1 Hz, 4H), 7.19 (dd, *J* = 6.5, 2.8 Hz, 2H), 6.64 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.41 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.32 (dd, *J* = 10.1, 1.9 Hz, 1H), 5.87 (dd, *J* = 10.2, 1.9 Hz, 1H), 3.66 (d, *J* = 12.5 Hz, 1H), 3.46 (dt, *J* = 12.4, 5.0 Hz, 1H), 3.06 (dd, *J* = 17.2, 5.5 Hz, 1H), 2.77 (dd, *J* = 17.2, 4.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.4, 170.8, 146.9, 144.3, 138.8, 136.5, 132.7, 131.7, 129.2, 128.9, 128.6, 128.3,

124.1, 116.1, 64.9, 54.0, 45.9, 40.6, 17.9. HRMS (ESI) calcd. for $C_{24}H_{20}N_3O_4^+$(M+H$^+$): 414.1448, found: 414.1443.

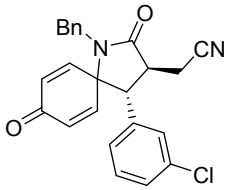
2-(1-benzyl-2,8-dioxo-4-(m-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3i)



3i

68%, 25.8 mg, white solid, m.p.: 132.4-135.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 3H), 7.24-7.19 (m, 2H), 7.16 – 7.09 (m, 3H), 7.08 – 7.03 (m, 1H), 6.67-6.59 m, 2H), 6.18 (dd, *J* = 9.9, 1.7 Hz, 1H), 5.95 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.58 (d, *J* = 15.0 Hz, 1H), 4.29 (d, *J* = 15.0 Hz, 1H), 3.99 (d, *J* = 12.4 Hz, 1H), 3.36 (dt, *J* = 12.3, 4.7 Hz, 1H), 3.07 (dd, *J* = 17.0, 4.3 Hz, 1H), 2.55 (dd, *J* = 17.0, 5.1 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.2, 171.8, 147.8, 145.4, 138.6, 136.9, 132.1, 131.3, 131.1, 129.8, 128.9, 128.8, 128.7, 128.6, 128.0, 125.0, 116.5, 65.2, 54.1, 45.7, 40.6, 21.4, 17.6. HRMS (ESI) calcd. for $C_{25}H_{22}N_2NaO_2^+$(M+Na$^+$): 405.1573, found:405.1570.

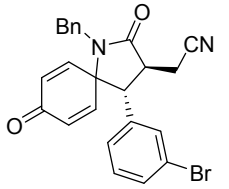
2-(1-benzyl-4-(3-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3j)



3j

54%, 21.6 mg, white solid, m.p.: 153.2-155.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 1H), 7.24 – 7.18 (m, 3H), 7.18 – 7.07 (m, 5H), 6.65 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.48 (dd, *J* = 10.2, 2.7 Hz, 1H), 6.13 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.87 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.48 (d, *J* = 14.9 Hz, 1H), 4.34 – 4.17 (m, 2H), 3.43-3.20 (br, 1H), 2.85 (dd, *J* = 17.1, 5.6 Hz, 1H), 2.63 (dd, *J* = 17.1, 4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.0, 170.4, 147.1, 143.9, 135.8, 130.7, 130.4, 129.9, 129.1, 128.6, 127.7, 127.6, 127.1, 125.9, 115.3, 64.1, 59.4, 44.6, 41.1, 16.8. HRMS (ESI) calcd. for $C_{24}H_{20}ClN_2O_2^+$(M+H$^+$): 403.1208, found: 403.1204.

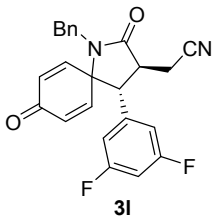
2-(1-benzyl-4-(3-bromophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3k)



3k

64%, 28.4 mg, white solid, m.p.: 175.4-177.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.31 – 7.25 (m, 4H), 7.24 – 7.12 (m, 4H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.61 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.41 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.30 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.88 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.54 (d, *J* = 15.0 Hz, 1H), 4.34 (d, *J* = 15.0 Hz, 1H), 3.52 (d, *J* = 12.6 Hz, 1H), 3.37 (dt, *J* = 12.6, 4.8 Hz, 1H), 3.09 (dd, *J* = 17.1, 4.7 Hz, 1H), 2.69 (dd, *J* = 17.1, 4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.8, 171.2, 147.3, 144.7, 136.7, 133.8, 132.5, 132.3, 131.4, 130.9, 130.5, 128.8, 128.6, 128.2, 127.1, 123.0, 116.2, 65.0, 53.7, 45.7, 40.5, 17.7. HRMS (ESI) calcd. for $C_{24}H_{20}BrN_2O_2^+$(M+H$^+$): 447.0703, found: 447.0706.

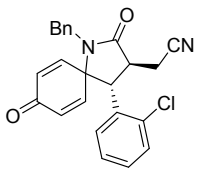
2-(1-benzyl-4-(3,5-difluorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3l)



3l

52%, 20.9 mg, white solid, m.p.: 171.2-173.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.26 (m, 3H), 7.18 (dd, *J* = 6.7, 2.8 Hz, 2H), 6.81-6.72 (m, 1H), 6.68 – 6.55 (m, 3H), 6.38 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.32 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.91 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.54 (d, *J* = 15.0 Hz, 1H), 4.34 (d, *J* = 15.0 Hz, 1H), 3.53 (d, *J* = 12.5 Hz, 1H), 3.31 (dt, *J* = 12.5, 4.9 Hz, 1H), 3.08 (dd, *J* = 17.1, 5.0 Hz, 1H), 2.72 (dd, *J* = 17.1, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.6, 170.9, 163.03 (dd, *J* = 251.2, 13.1 Hz), 147.0, 144.4, 136.6, 132.7, 131.5, 128.8, 128.6, 128.2, 111.5, 111.3, 111.2, 104.9, 64.7, 53.7, 45.8, 40.6, 17.7. HRMS (ESI) calcd. for $C_{24}H_{19}F_2N_2O_2^+$(M+H$^+$): 405.1409, found: 405.1405.

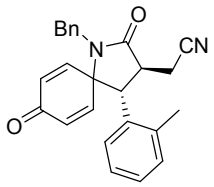
2-(1-benzyl-4-(2-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3m)



3m

45%, 18.1 mg, white solid, m.p.: 165.3-167.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 1H), 7.30 – 7.26 (m, 3H), 7.25 – 7.14 (m, 5H), 6.73 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.56 (dd, *J* = 10.1, 2.6 Hz, 1H), 6.21 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.94 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.60 – 4.52 (m, 1H), 4.39 – 4.26 (m, 2H), 3.39 (s, 1H), 2.92 (dd, *J* = 17.1, 5.6 Hz, 1H), 2.70 (dd, *J* = 17.1, 4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.1, 171.5, 148.2, 144.9, 136.8, 131.74, 131.5, 130.9, 130.2, 129.6, 128.8, 128.6, 128.1, 127.0, 116.3, 65.1, 50.4, 45.6, 42.2, 17.9. HRMS (ESI) calcd. for $C_{24}H_{19}ClN_2NaO_2^+$(M+Na$^+$): 425.1027, found: 425.1024.

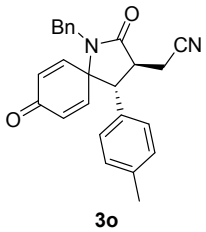
2-(1-benzyl-2,8-dioxo-4-(o-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3n)



3n

47%, 17.8 mg, white solid, m.p.: 114.3-116.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.18 (m, 3H), 7.16 – 7.12 (m, 2H), 7.09 – 7.03 (m, 3H), 7.02 – 6.95 (m, 1H), 6.63-6.51 (m, 2H), 6.10 (dd, *J* = 9.9, 2.0 Hz, 1H), 5.87 (dt, *J* = 7.0, 3.6 Hz, 1H), 4.51 (d, *J* = 15.0 Hz, 1H), 4.22 (d, *J* = 15.0 Hz, 1H), 3.92 (d, *J* = 12.4 Hz, 1H), 3.29 (dt, *J* = 12.4, 4.7 Hz, 1H), 2.99 (dd, *J* = 17.0, 4.4 Hz, 1H), 2.47 (dd, *J* = 17.0, 5.1 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.1, 170.8, 147.3, 144.8, 137.1, 135.9, 130.7, 130.6, 130.1, 129.0, 127.7, 127.6, 127.5, 127.0, 126.4, 125.1, 115.5, 64.4, 59.4, 44.6, 41.9, 19.3, 16.5. HRMS (ESI) calcd. for $C_{25}H_{22}N_2NaO_2^+$(M+Na$^+$): 405.1573, found: 405.1576.

2-(1-benzyl-2,8-dioxo-4-(p-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3o)

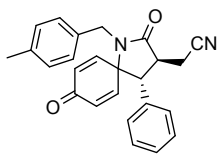


3o

51%, 19.4 mg, white solid, m.p.: 151.3-153.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 3H), 7.24 – 7.16 (m, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 6.60 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.42 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.25 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.84 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.56 (d, *J* = 15.0 Hz,

1H), 4.30 (d, *J* = 15.0 Hz, 1H), 3.52 (d, *J* = 12.6 Hz, 1H), 3.39 (dt, *J* = 12.6, 4.8 Hz, 1H), 3.06 (dd, *J* = 17.0, 4.7 Hz, 1H), 2.67 (dd, *J* = 17.0, 4.9 Hz, 1H), 2.28 (s, 3H). HRMS (ESI) calcd. for $C_{25}H_{23}N_2O_2$+(M+H$^+$): 383.1754, found: 383.1753.

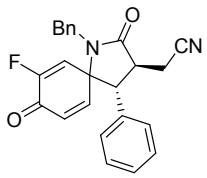
2-(1-(4-methylbenzyl)-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3p)



3p

68%, 25.8 mg, white solid, m.p.: 73.6-76.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 3H), 7.11 – 7.02 (m, 6H), 6.63 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.44 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.26 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.83 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.51 (d, *J* = 14.9 Hz, 1H), 4.26 (d, *J* = 14.9 Hz, 1H), 3.55 (d, *J* = 12.6 Hz, 1H), 3.44 (dt, *J* = 12.6, 4.8 Hz, 1H), 3.05 (dd, *J* = 17.0, 4.7 Hz, 1H), 2.67 (dd, *J* = 17.0, 4.9 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.2, 171.7, 147.9, 145.4, 137.8, 133.8, 132.1, 131.3, 131.1, 129.3, 129.0, 128.9, 128.5, 128.1, 116.5, 65.2, 54.1, 45.4, 40.5, 21.1, 17.6. HRMS (ESI) calcd. for $C_{25}H_{22}N_2NaO_2^+$(M+Na$^+$): 405.1573, found: 405.1576.

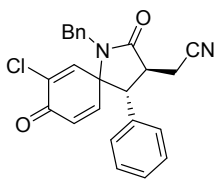
2-(1-benzyl-7-fluoro-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3q)



3q

55%, 21.1 mg, white solid, m.p.: 105.0-107.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.30 (m, 3H), 7.28 – 7.25 (m, 3H), 7.25 – 7.21 (m, 2H), 7.10 – 7.05 (m, 3H), 6.46 (dd, *J* = 10.1, 2.8 Hz, 1H), 6.21 (dd, *J* = 11.7, 2.8 Hz, 1H), 5.86 (dd, *J* = 10.1, 7.1 Hz, 1H), 4.51 (d, *J* = 15.1 Hz, 1H), 4.33 (d, *J* = 15.1 Hz, 1H), 3.61 (d, *J* = 12.6 Hz, 1H), 3.49-3.43 (m, 1H), 3.07 (dd, *J* = 17.1, 4.7 Hz, 1H), 2.70 (dd, *J* = 17.1, 4.9 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 176.7, 171.5, 154.9 (d, *J* = 272.4 Hz), 146.1, 138.6, 134.9, 130.7, 130.2, 130.0, 130.0, 129.4, 129.2, 128.5, 128.5, 127.9, 126.6, 123.4, 123.2, 116.3, 66.8, 66.7, 54.7, 45.1, 40.4, 17.6. HRMS (ESI) calcd. for $C_{24}H_{20}FN_2O_2^+$(M+H$^+$): 387.1503, found: 387.1507.

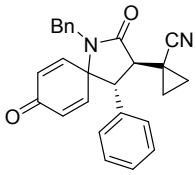
2-(1-benzyl-7-chloro-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3r)



3r

54%, 21.6 mg, white solid, m.p.: 125.6-128.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.28 (m, 6H), 7.22 – 7.16 (m, 2H), 7.08-7.01 (m, 2H), 6.72 (d, *J* = 2.9 Hz, 1H), 6.45 (dd, *J* = 10.1, 2.9 Hz, 1H), 5.91 (d, *J* = 10.1 Hz, 1H), 4.65 (d, *J* = 14.8 Hz, 1H), 4.24 (d, *J* = 14.8 Hz, 1H), 3.58 (d, *J* = 12.6 Hz, 1H), 3.47-3.40 (m, 1H), 3.07 (dd, *J* = 17.0, 4.7 Hz, 1H), 2.69 (dd, *J* = 17.0, 4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 171.3, 145.6, 143.8, 136.7, 135.4, 130.9, 130.0, 129.3, 129.2, 128.9, 128.7, 128.3, 127.9, 116.3, 66.9, 54.3, 45.9, 40.4, 17.7. HRMS (ESI) calcd. for $C_{24}H_{19}ClN_2NaO_2^+$(M+Na$^+$): 425.1027, found: 425.1029.

1-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)cyclopropane-1-carbonitrile (3s)

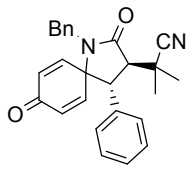


3s

53%, 20.7 mg, white solid, m.p.: 104.3-106.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.22 (m, 6H), 7.22 – 7.18 (m, 2H), 7.03 (dd, *J* = 6.5, 3.1 Hz, 2H), 6.59 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.44 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.25 (dd, *J* = 5.5Hz, 1H), 5.79 (dd, *J* = 5.5Hz, 1H), 4.52 (d, *J* = 14.9 Hz, 1H), 4.27 (d, *J* = 14.9 Hz, 1H), 3.25 – 3.13 (m, 2H), 1.39 – 1.26 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.5, 176.1, 149.0, 146.3, 137.7, 133.1, 131.8, 130.7, 128.7, 128.6, 128.6, 128.4, 128.0, 127.8, 65.4, 57.5, 45.4, 38.7, 14.6. HRMS (ESI) calcd. for $C_{26}H_{23}N_2O_2^+$(M+H$^+$): 395.1754, found: 395.1752.

2-(-1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)-2-methylpropanenitrile (3t)

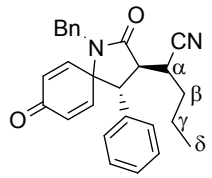
(d.r.= 1.0: 0.4)



3t

34%, 13.2 mg, white solid, m.p.: 85.7-87.1. °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.10 (m, 9H), 7.08 – 6.99 (m, 1H), 6.62 – 6.53 (m, 1H), 6.46-6.33 (m, 3.0 Hz, 1H), 6.28 – 6.16 (m, 1H), 5.80 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.61 (dd, *J* = 78.1, 15.0 Hz, 1H), 4.18 (dd, *J* = 69.0, 15.0 Hz, 1H), 3.54 (d, *J* = 11.4 Hz, 1H), 3.21 (dd, *J* = 22.2, 9.1 Hz, 1H), 1.67 (d, *J* = 73.3 Hz, 3H), 1.23 (d, *J* = 18.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.2, 171.8, 149.0, 148.2, 146.6, 137.1, 134.2, 131.8, 131.5, 130.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.0, 127.9, 123.0, 64.5, 57.5, 52.6, 50.5, 45.5, 38.7, 35.9, 26.5, 25.6, 14.6. HRMS (ESI) calcd. for $C_{26}H_{25}N_2O_2^+$(M+H$^+$): 397.1911, found: 397.1914.

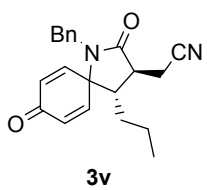
2-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)pentanenitrile (3u)



3u

37%, 14.5 mg, white solid, m.p.: 94.3-95.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.16 (m, 8H), 7.12 – 7.01 (m, 2H), 6.65 – 6.52 (m, 1H), 6.51 – 6.38 (m, 1H), 6.27-6.17 (m, 2.0 Hz, 1H), 5.85 – 5.76 (m, 1H), 4.68 – 4.48 (m, 1H), 4.30-4.11 (m, 1H), 3.69 – 3.53 (m, 1H), 3.39 – 3.16 (m, 1H), 1.55-1.41 (m, 1H), 1.36 – 1.17 (m, 5H), 1.01 – 0.86 (m, 1H), 0.79 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 184.2, 176.1, 172.1, 149.0, 148.1, 146.3, 146.2, 137.72, 136.9, 133.1, 131.8, 131.7, 130.9, 130.7, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.3, 128.2, 128.0, 128.0, 127.8, 119.4, 65.4, 65.2, 57.5, 52.8, 45.7, 45.7, 45.4, 38.7, 33.9, 32.6, 29.7, 20.8, 14.6, 13.1. HRMS (ESI) calcd. for $C_{27}H_{27}N_2O_2^+$(M+H$^+$): 411.2067, found: 411.2070.

2-(-1-benzyl-2,8-dioxo-4-propyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3v)



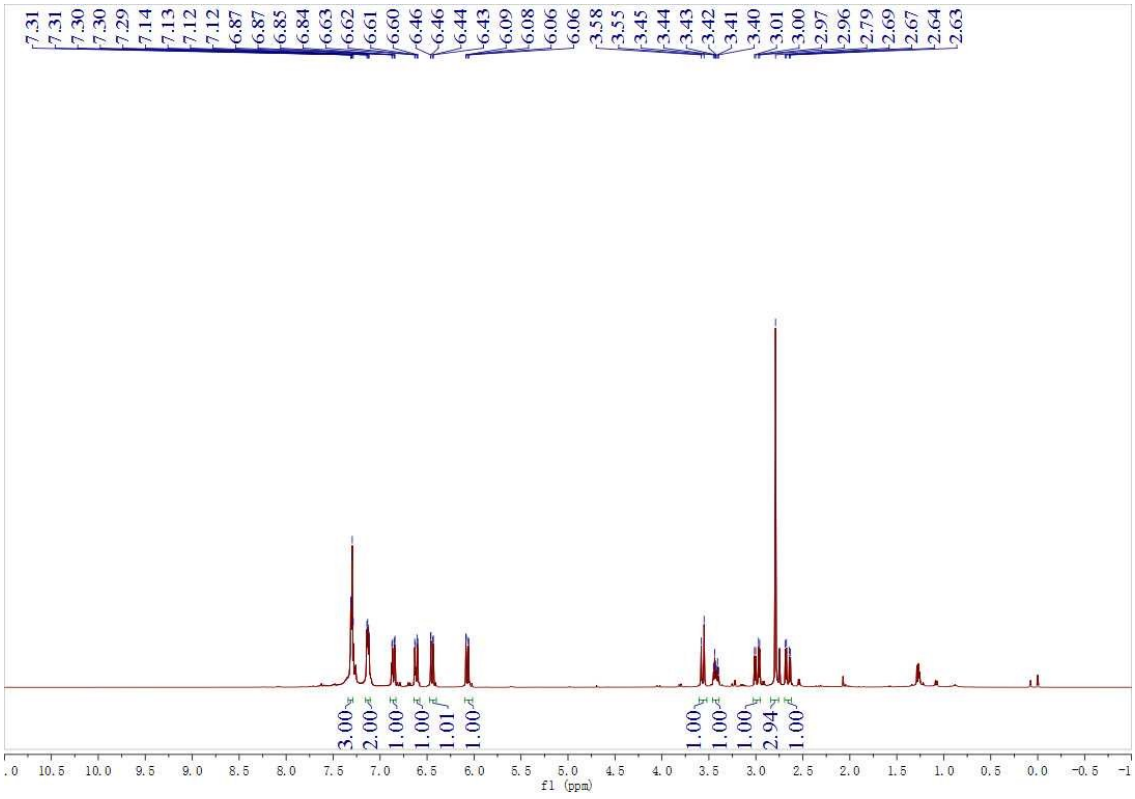
3v

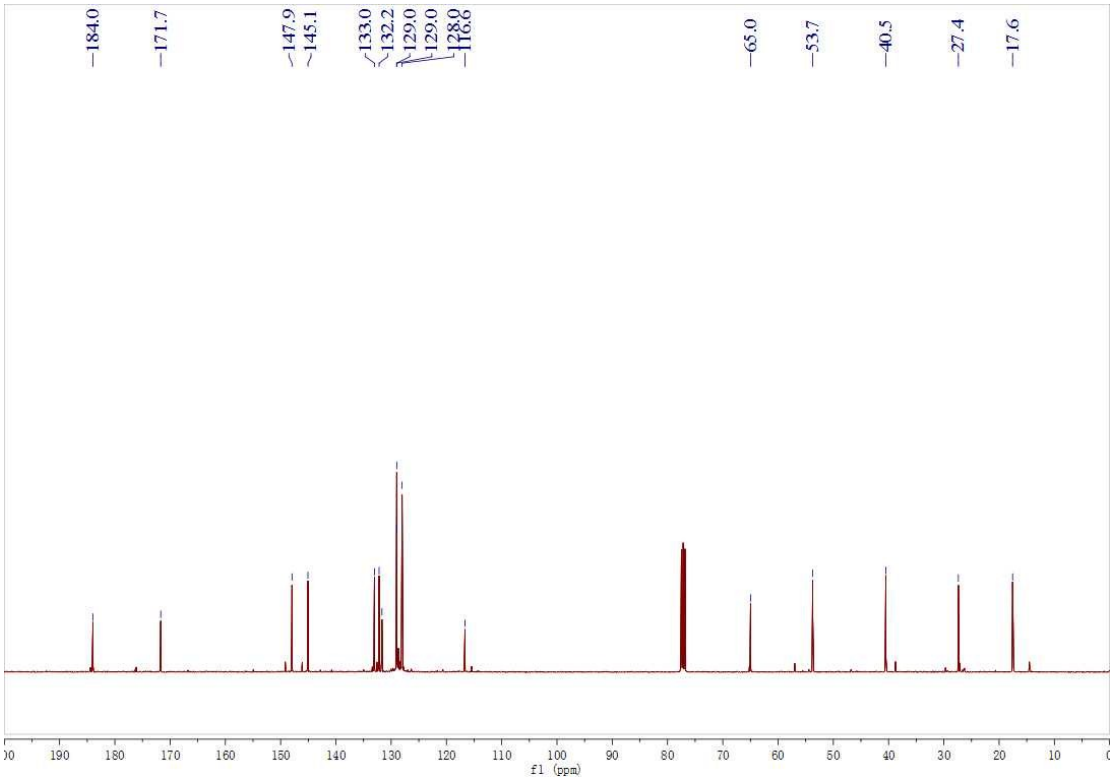
32%, 11.2 mg, white solid, m.p.: 73.4-75.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.25 (d, *J* = 1.5 Hz, 4H), 7.15 (dd, *J* = 7.2, 2.3 Hz, 2H), 6.51-6.43 (m, 2H), 6.30-6.23 (m, 2H), 4.54 (d, *J* = 15.0 Hz, 1H), 4.16 (d, *J* = 15.0 Hz, 1H), 3.11 (dd, *J* = 17.1, 4.5 Hz, 1H), 2.84 – 2.76 (m, 1H), 2.62 (dt, *J* = 11.3, 4.7 Hz, 1H), 2.39 – 2.32 (m, 1H), 2.26 – 2.17 (m, 1H), 1.38 – 1.31 (m, 3H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 172.4, 149.1, 145.3, 137.0, 131.7, 131.6, 128.7, 128.4, 127.9, 116.8, 64.1, 47.2, 45.3, 43.3, 31.7, 21.2, 18.9, 14.1. HRMS (ESI) calcd. for $C_{21}H_{22}N_2NaO_2^+$(M+Na$^+$): 357.1573, found: 357.1571.

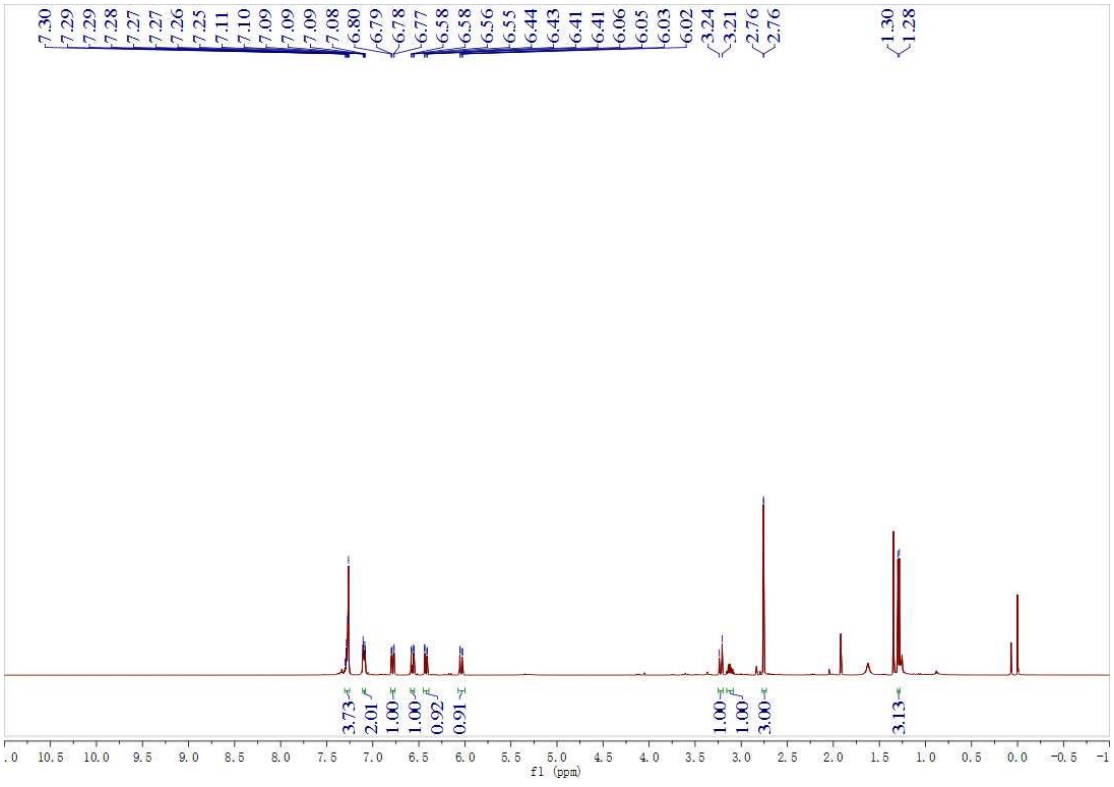
5. Copies of ^{1}H, ^{19}F and ^{13}C NMR spectra

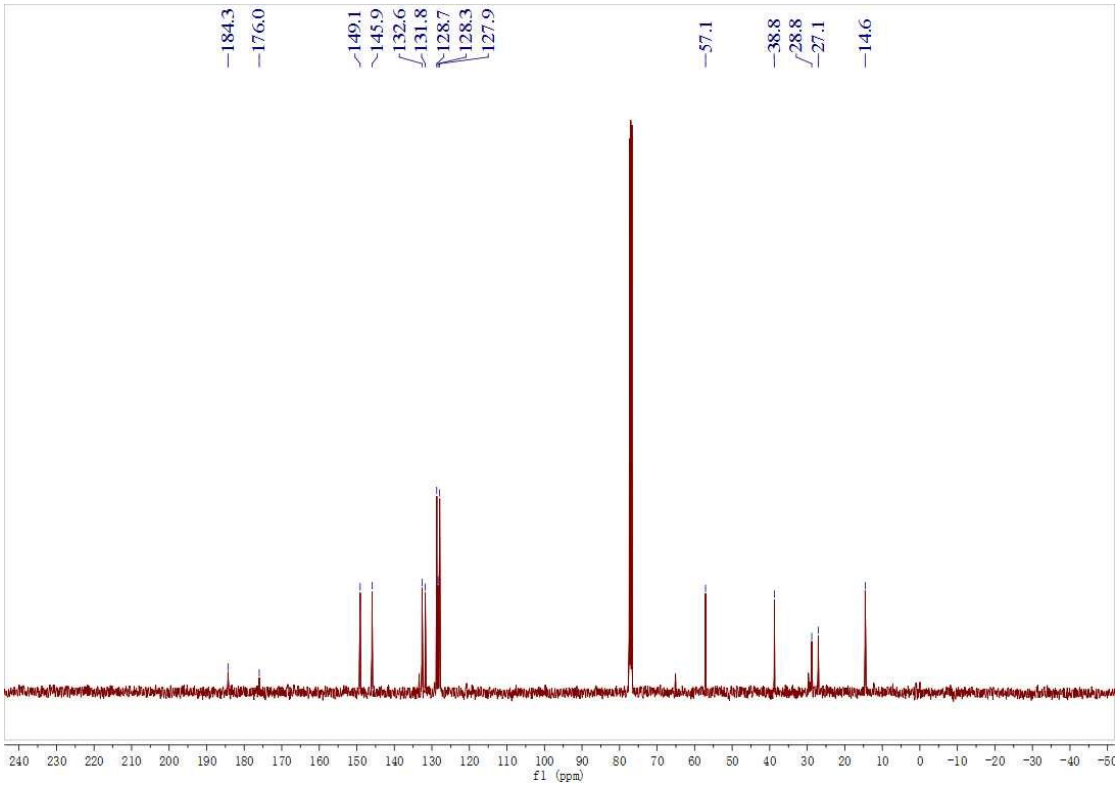
2-(1-methyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3a)



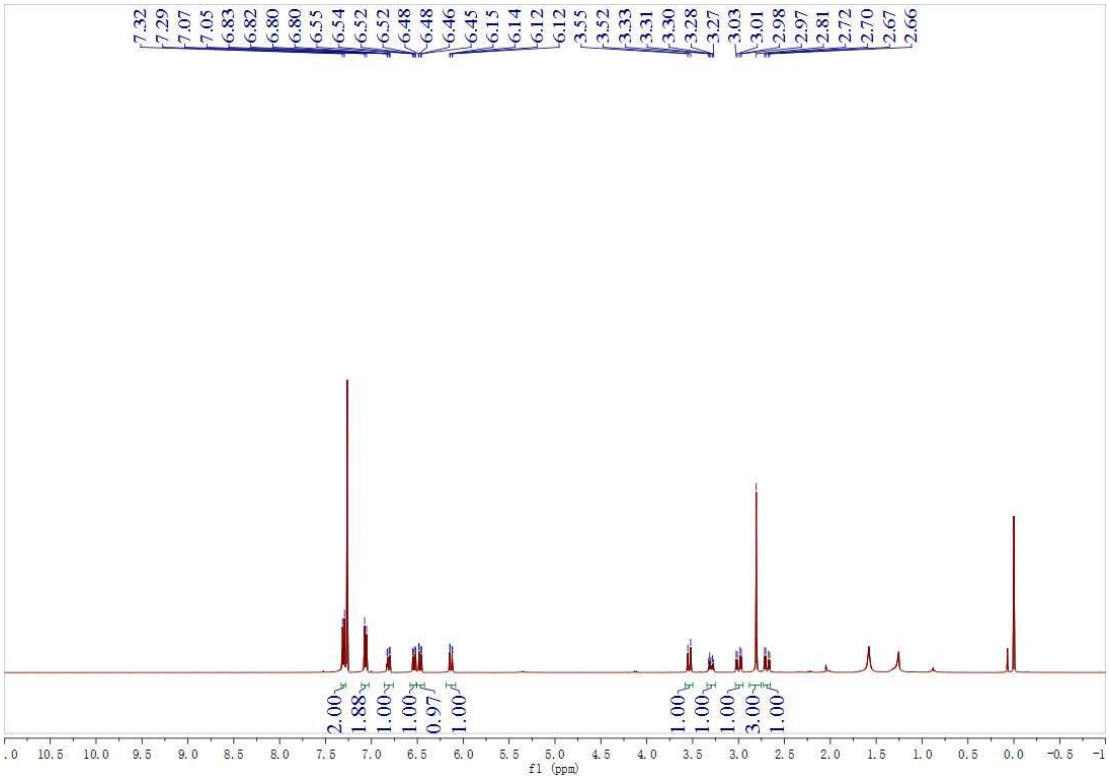


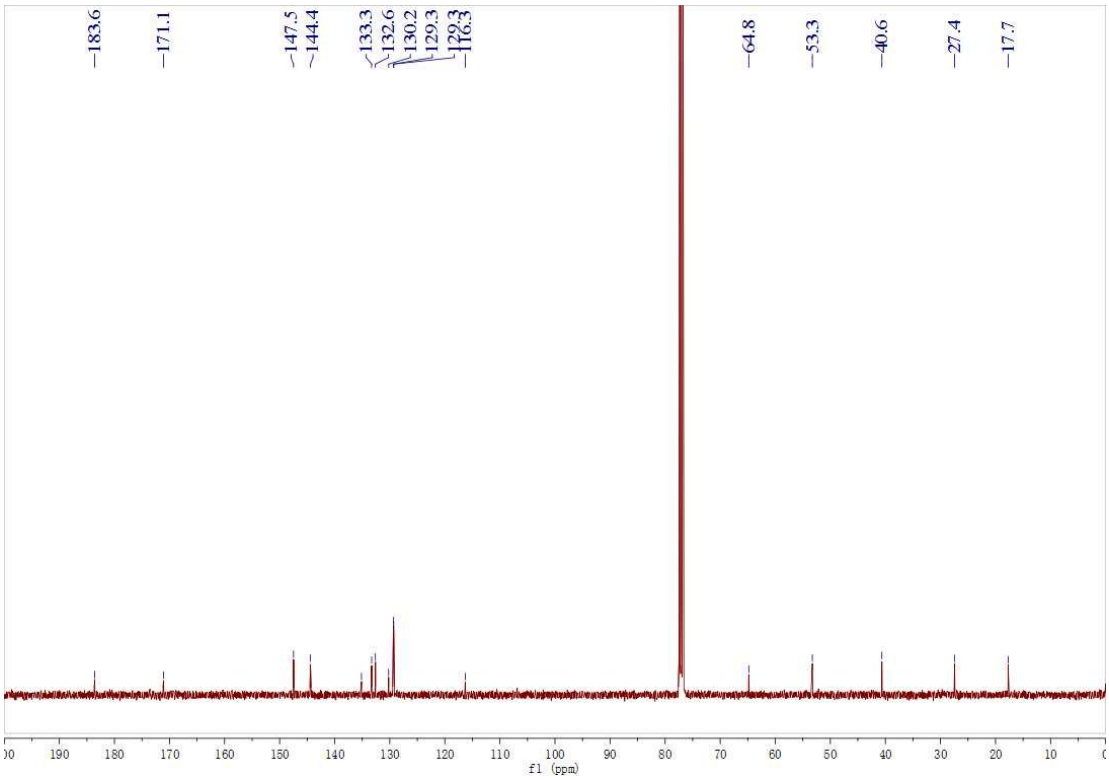
1,3-dimethyl-4-phenyl-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (3a')



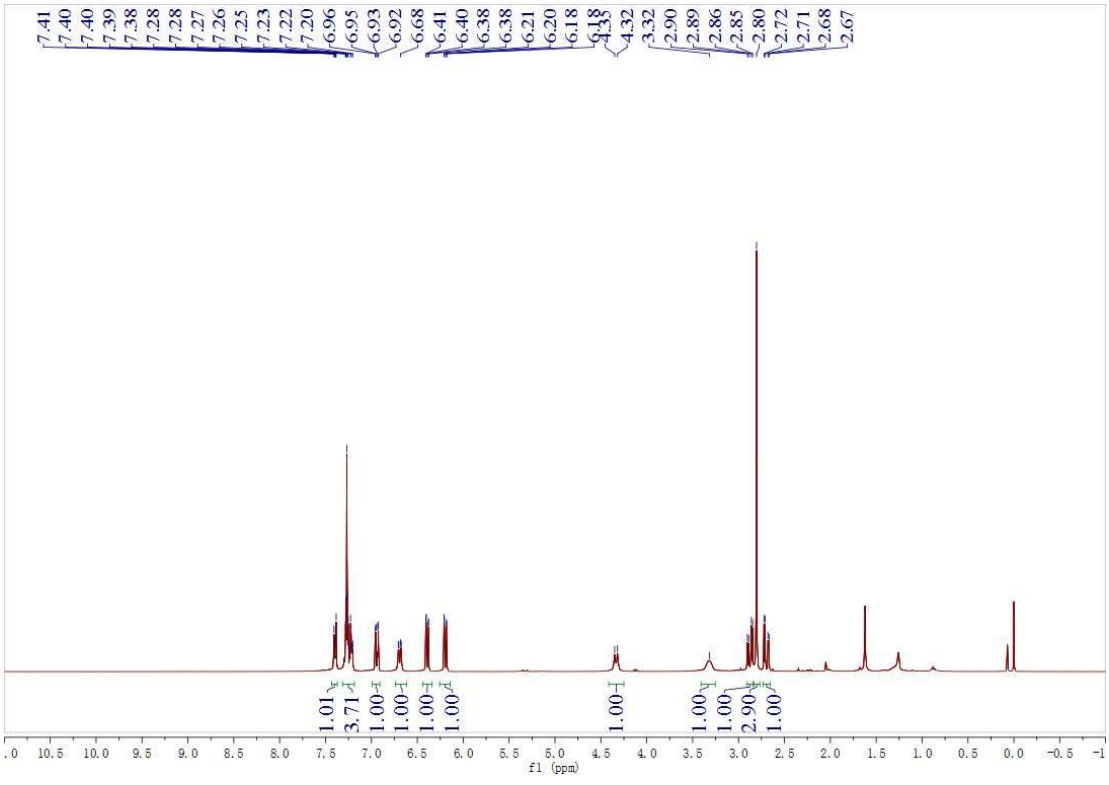


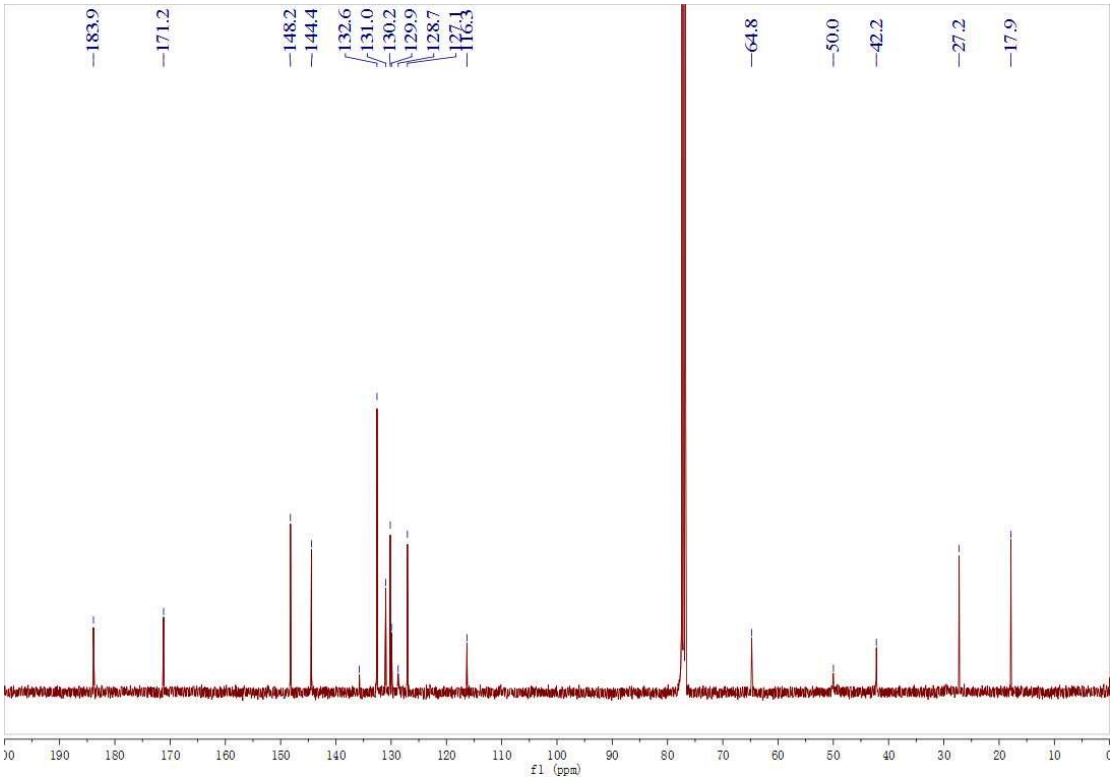
2-(4-(4-chlorophenyl)-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3b)



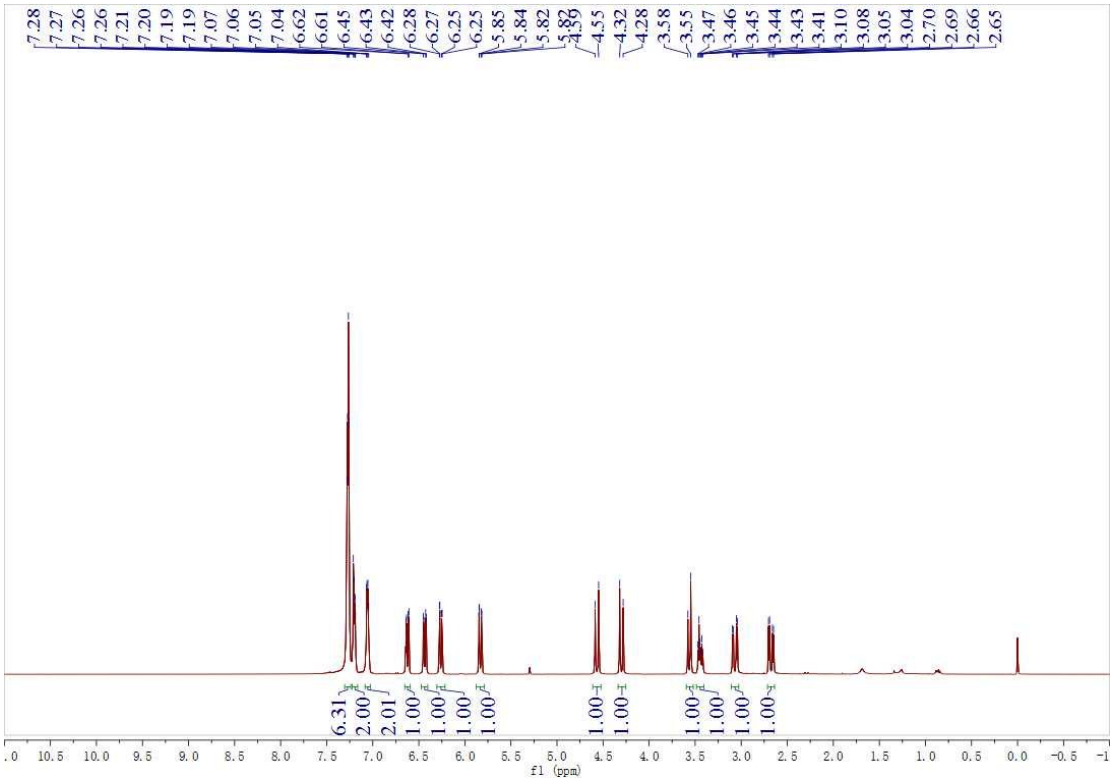


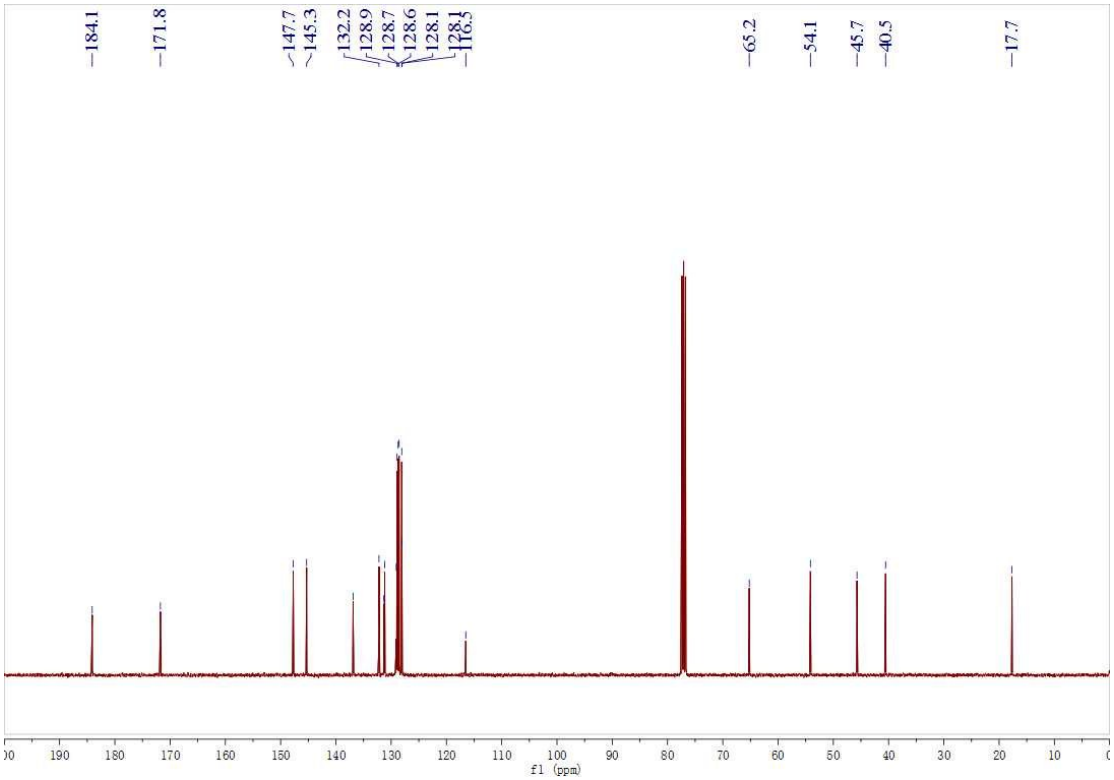
2-(4-(2-chlorophenyl)-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3c)



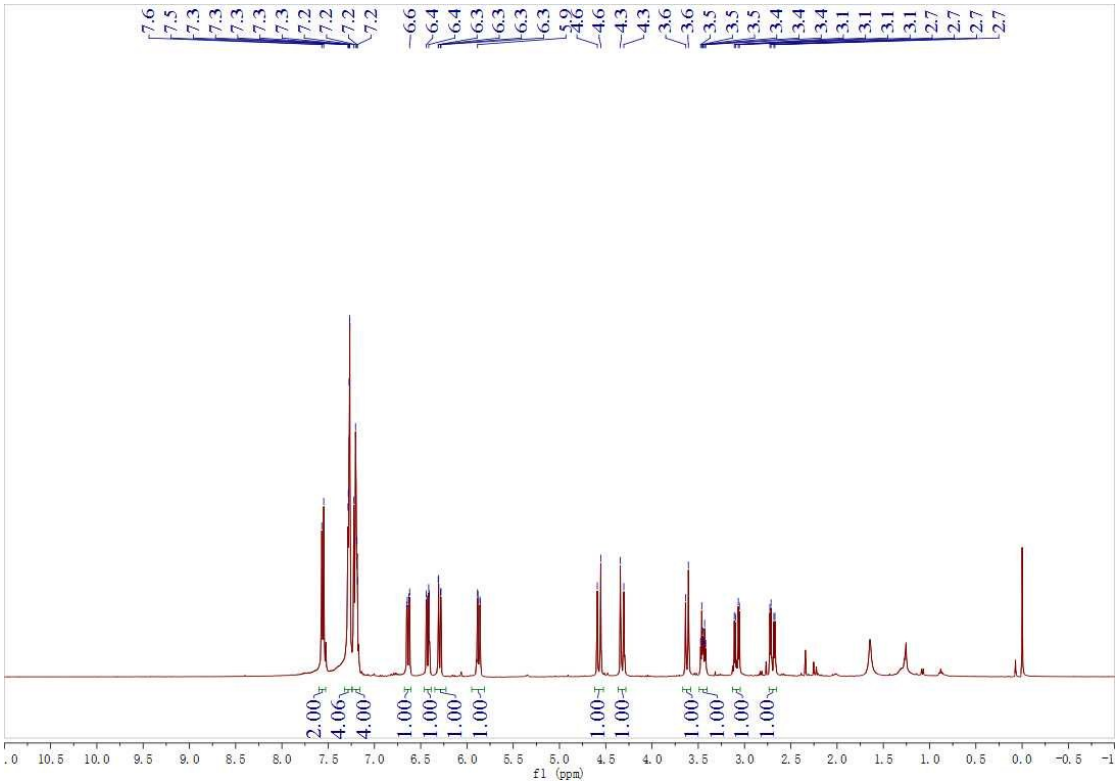


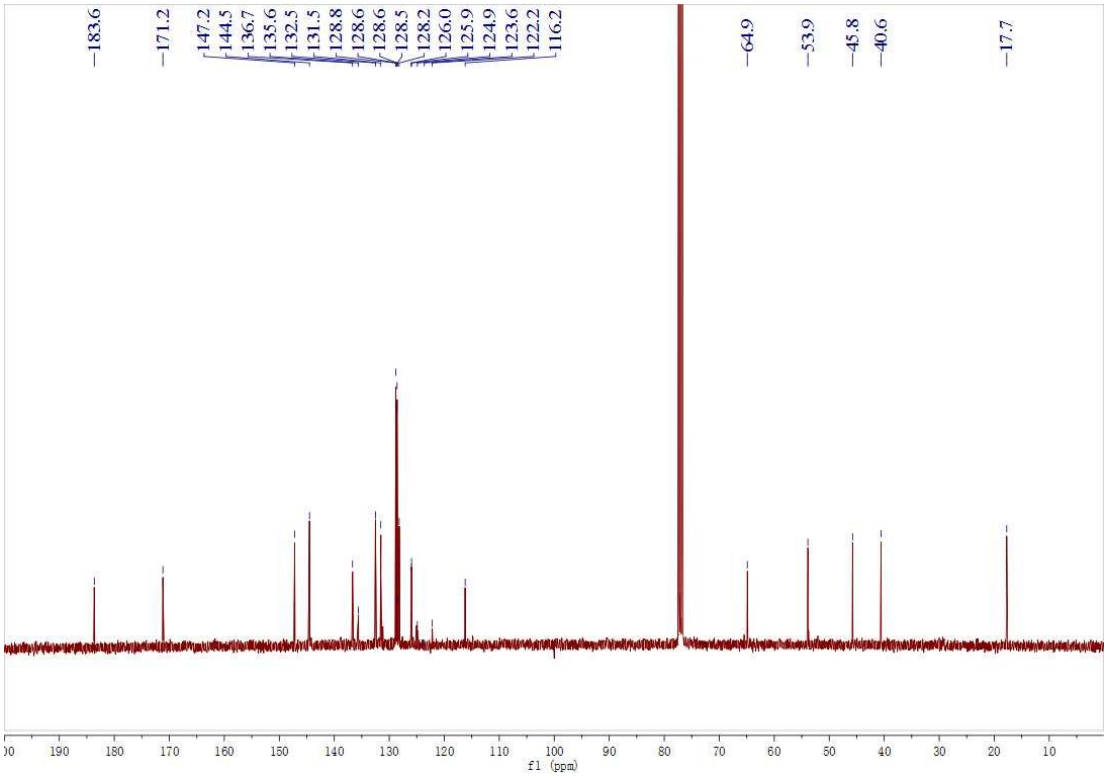
2-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3d)

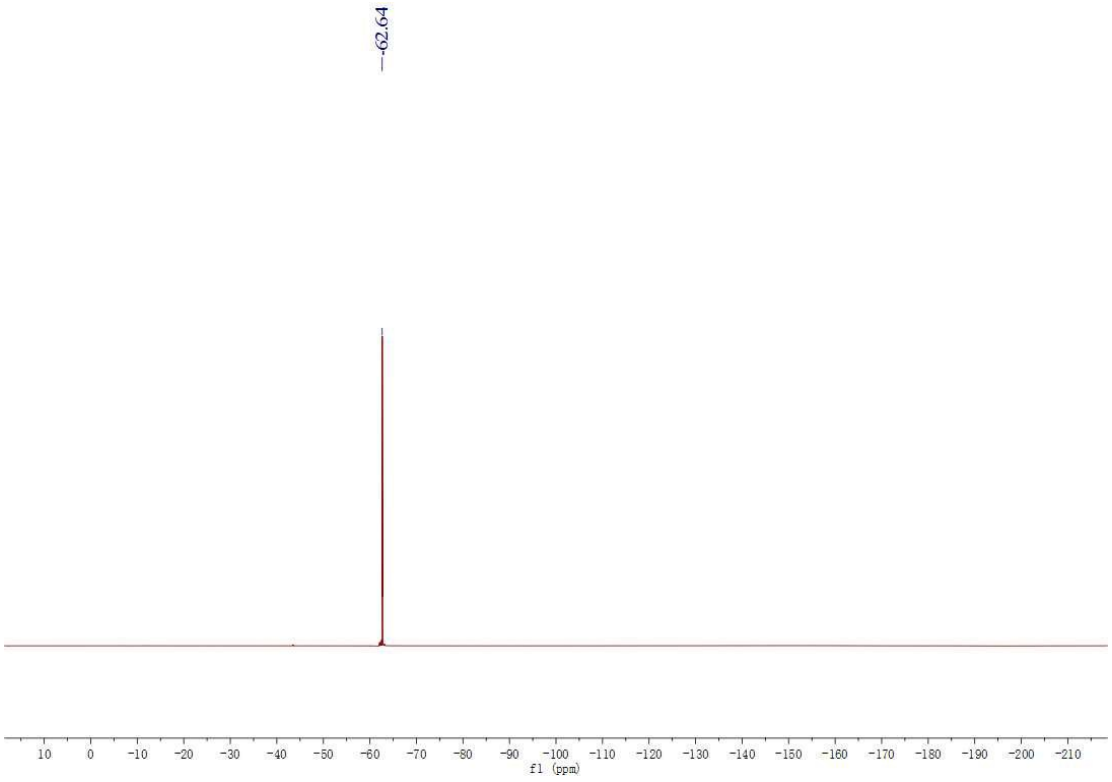




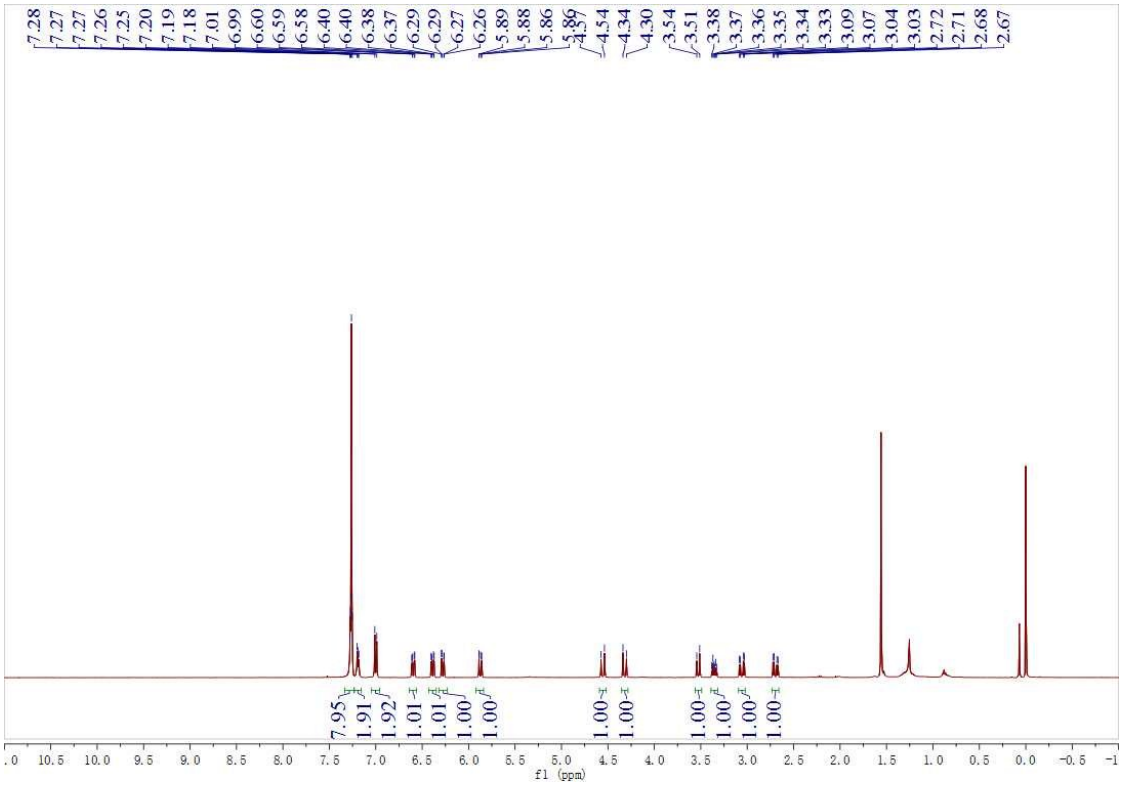
2-(1-benzyl-2,8-dioxo-4-(4-(trifluoromethyl)phenyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3e)

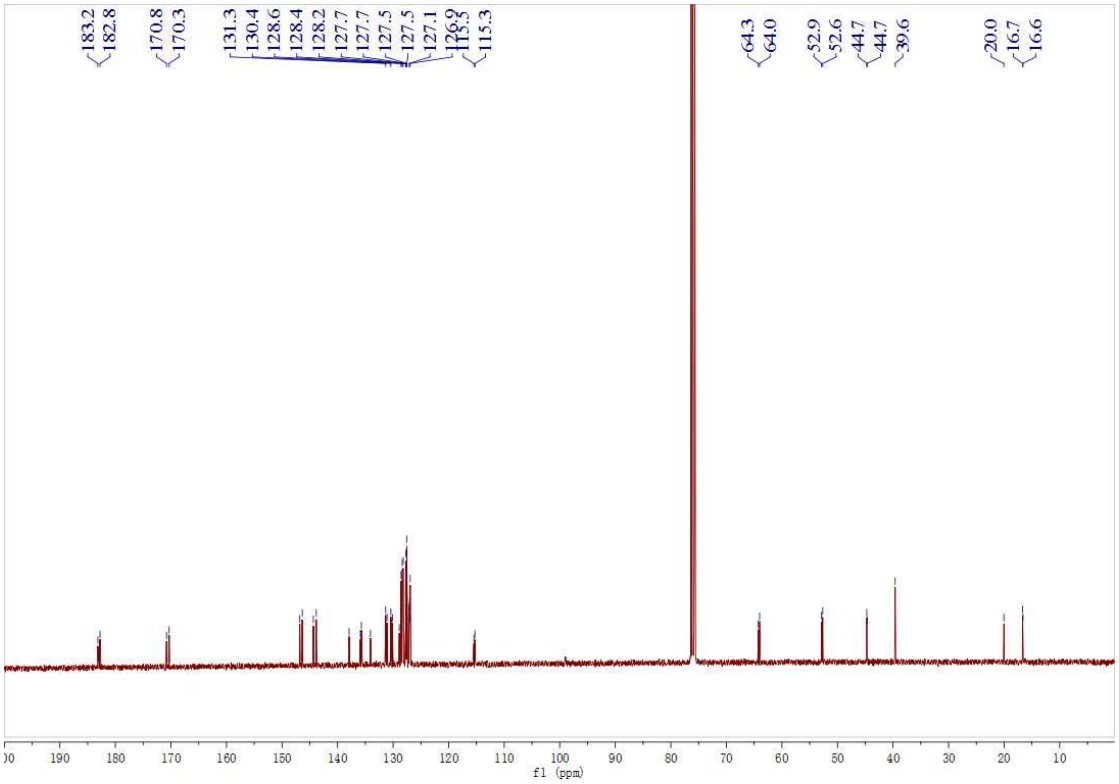



183.6
171.2
147.2
144.5
136.7
135.6
132.5
131.5
128.8
128.6
128.6
128.5
128.2
126.0
125.9
124.9
123.6
122.2
116.2
64.9
53.9
45.8
40.6
17.7
f1 (ppm)

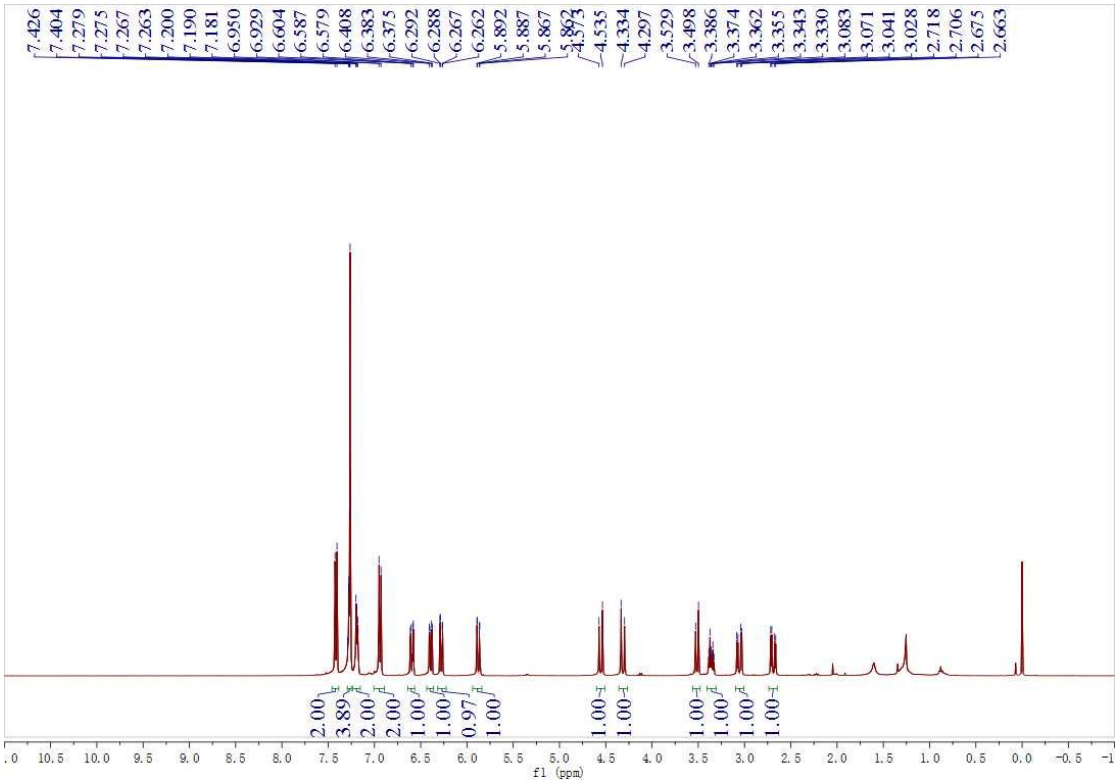

-62.64
f1 (ppm)

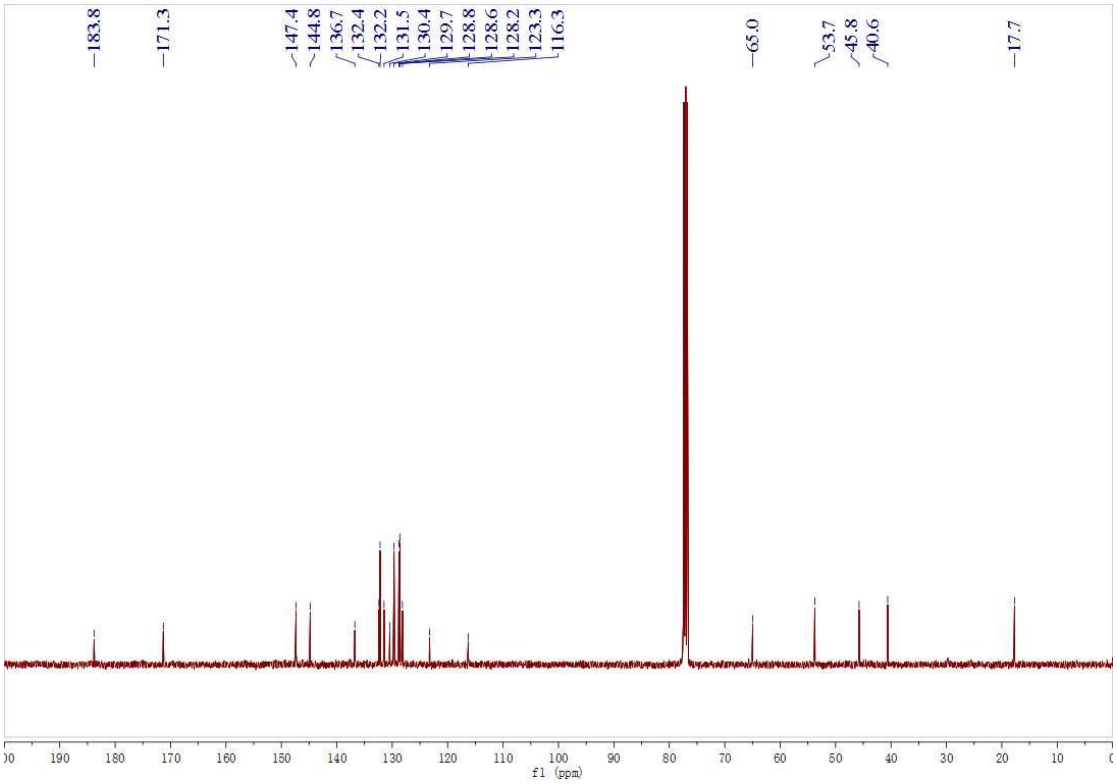
2-(1-benzyl-4-(4-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3f)



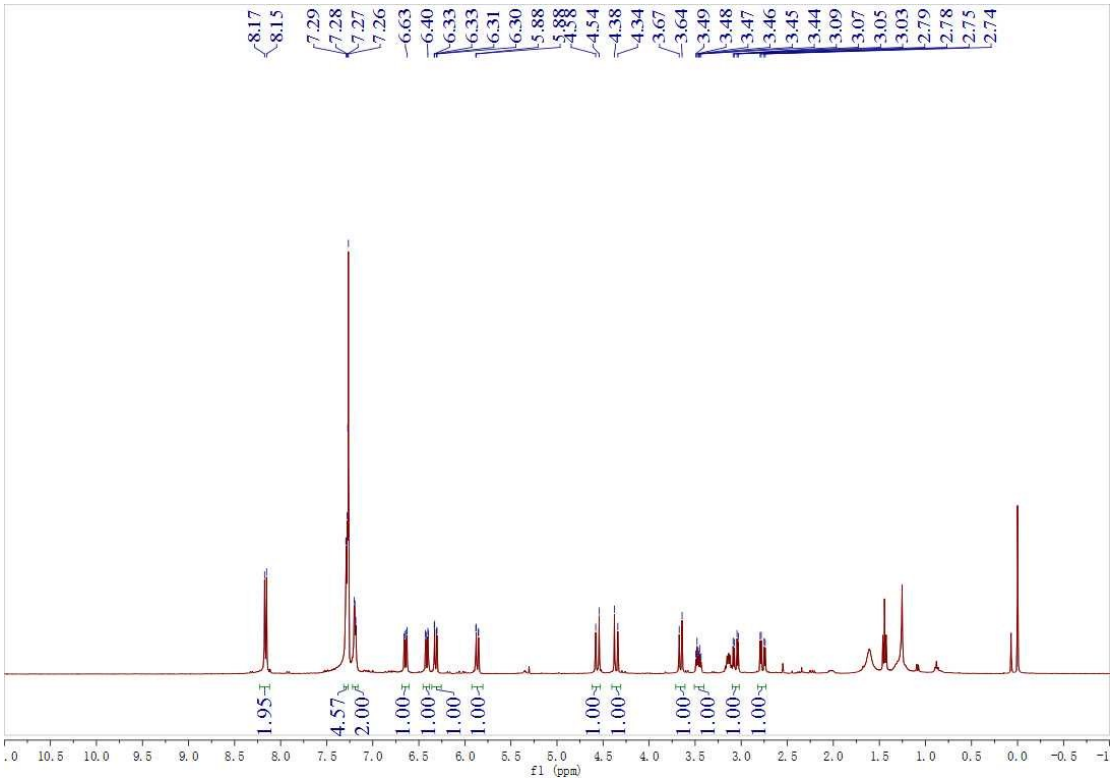


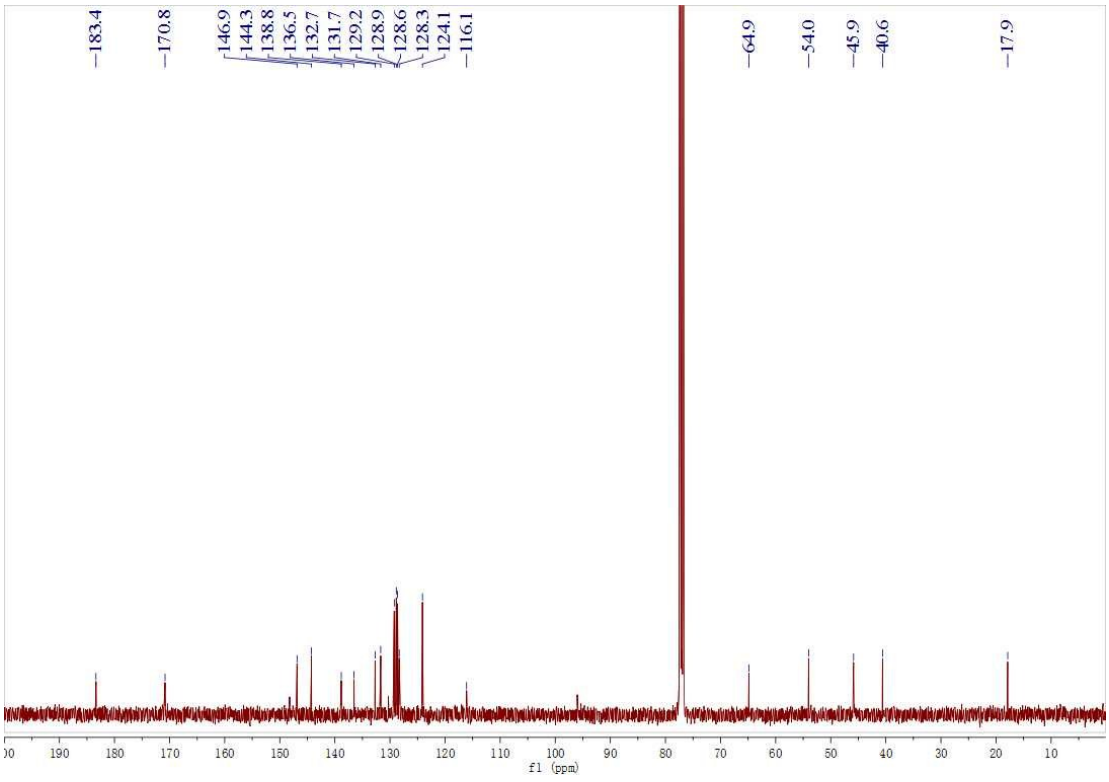
2-(1-benzyl-4-(4-bromophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3g)



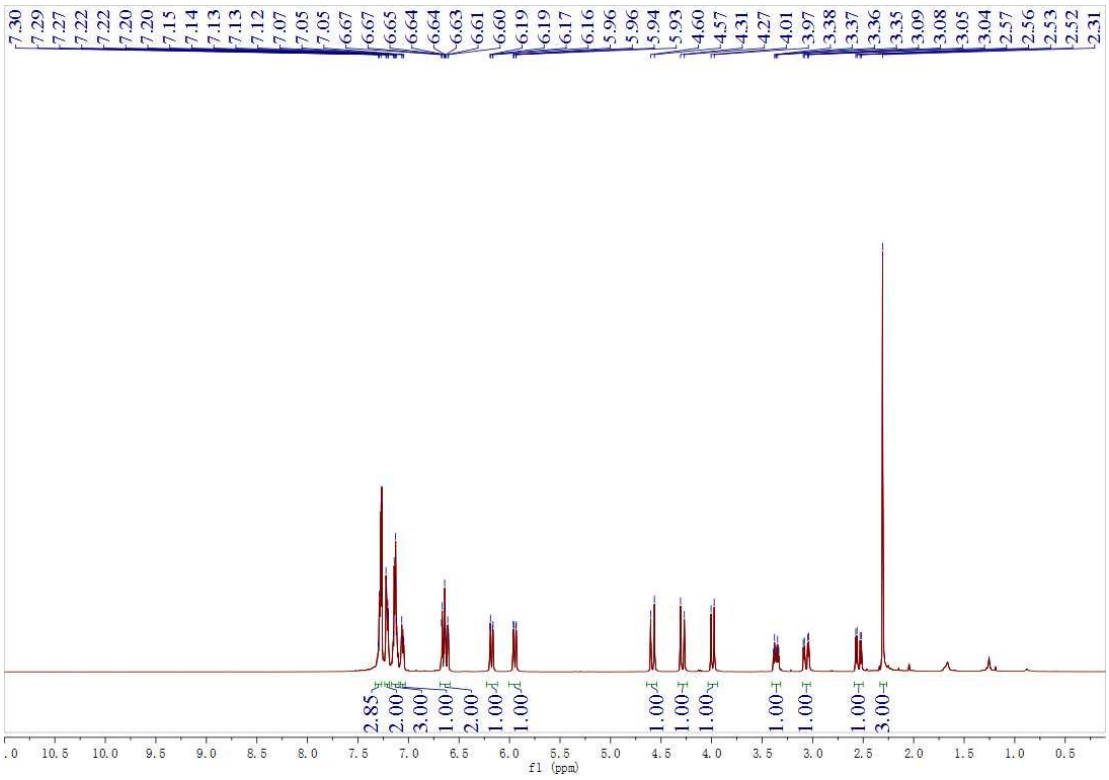


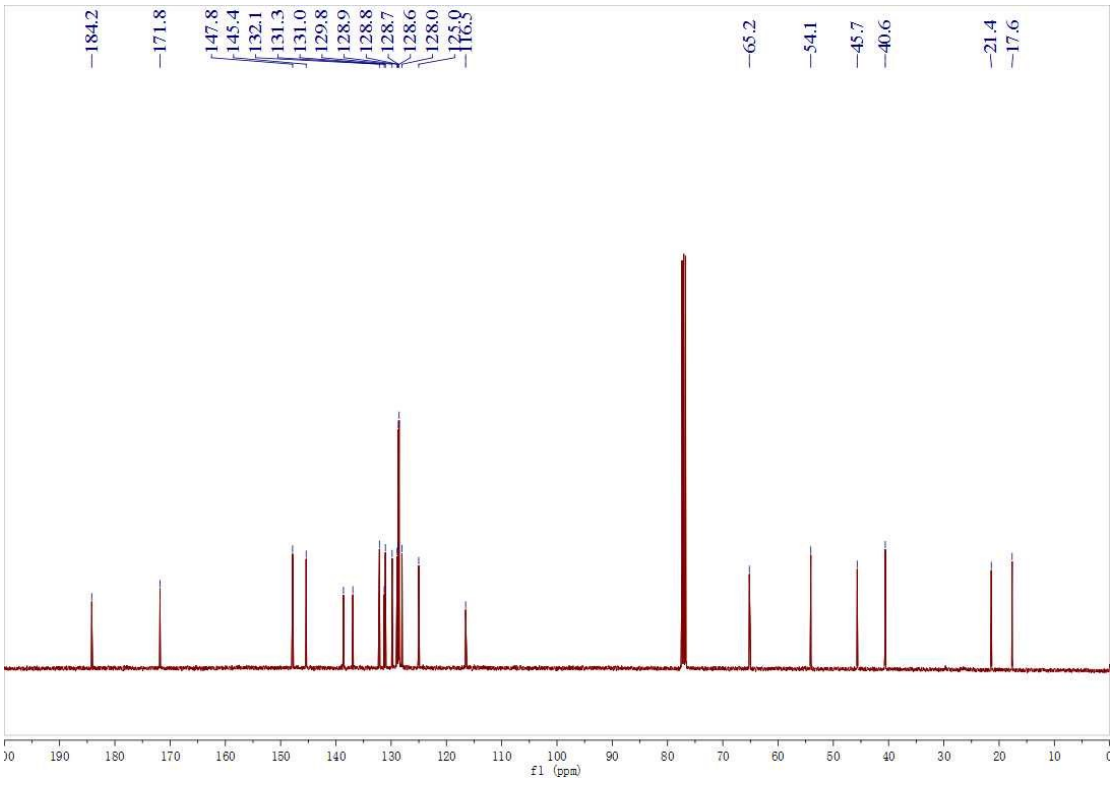
2-(1-benzyl-4-(4-nitrophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3h)



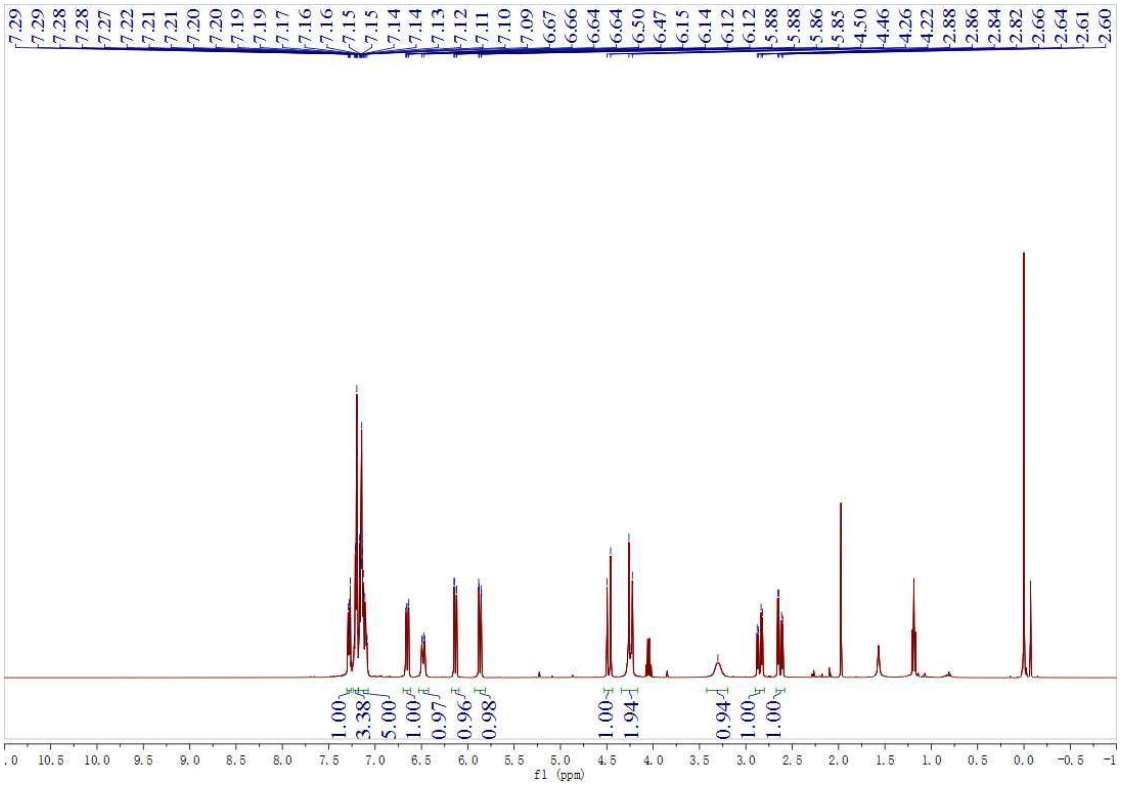


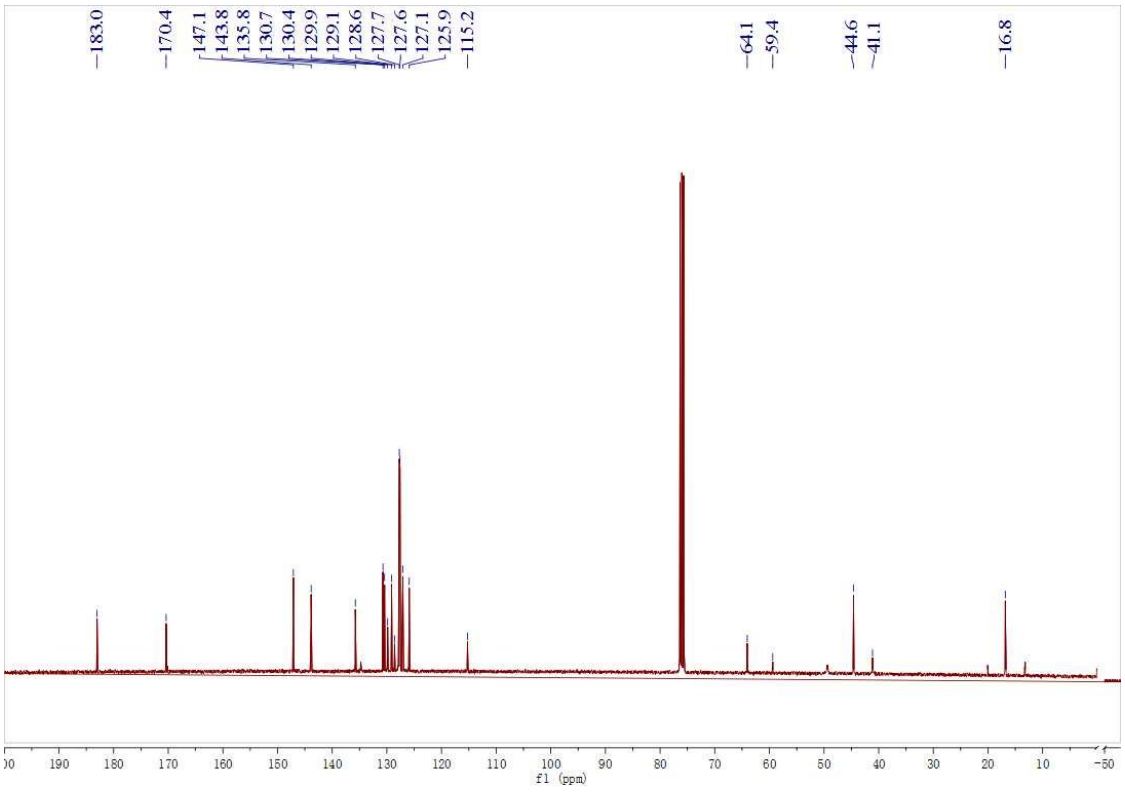
2-(1-benzyl-2,8-dioxo-4-(m-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3i)



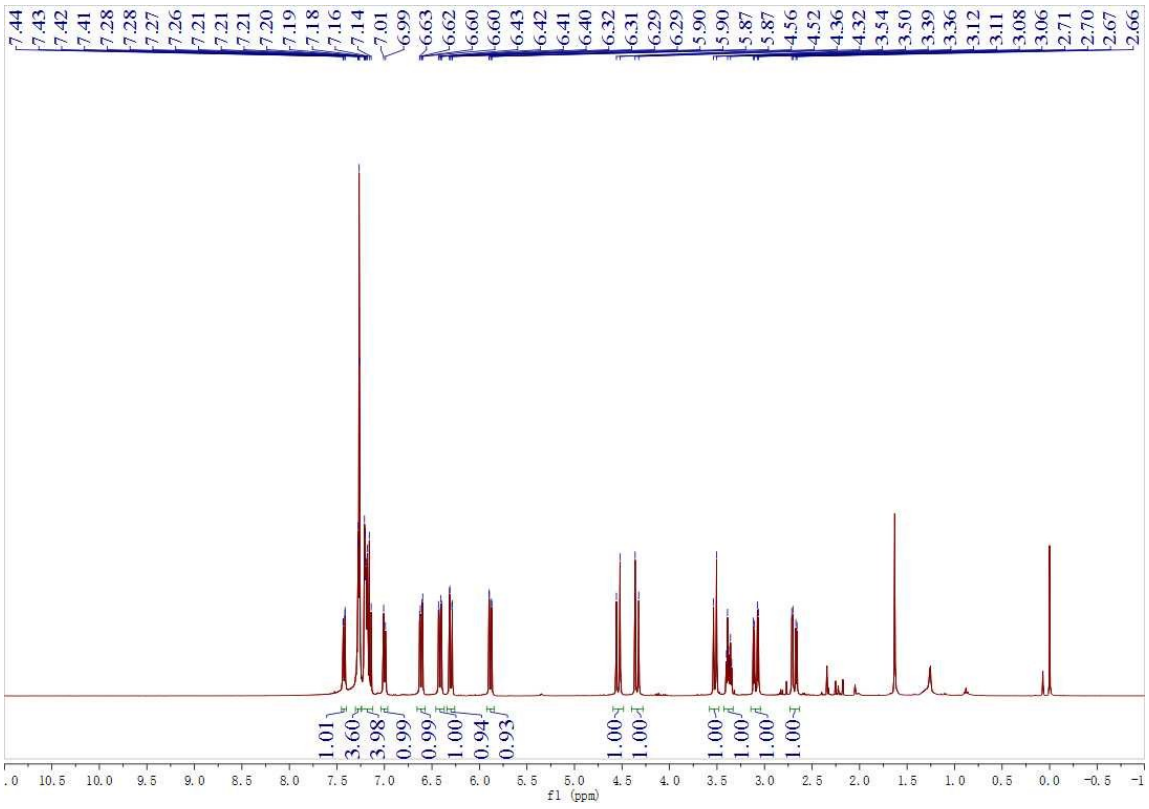


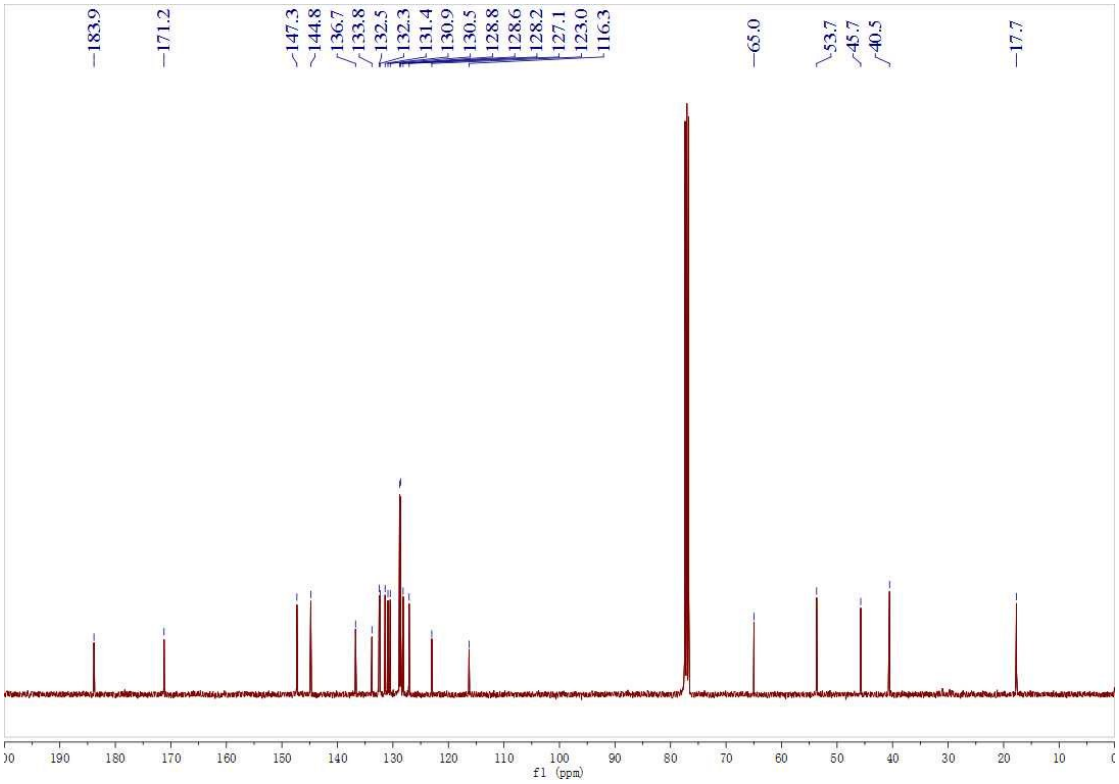
2-(1-benzyl-4-(3-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3j)



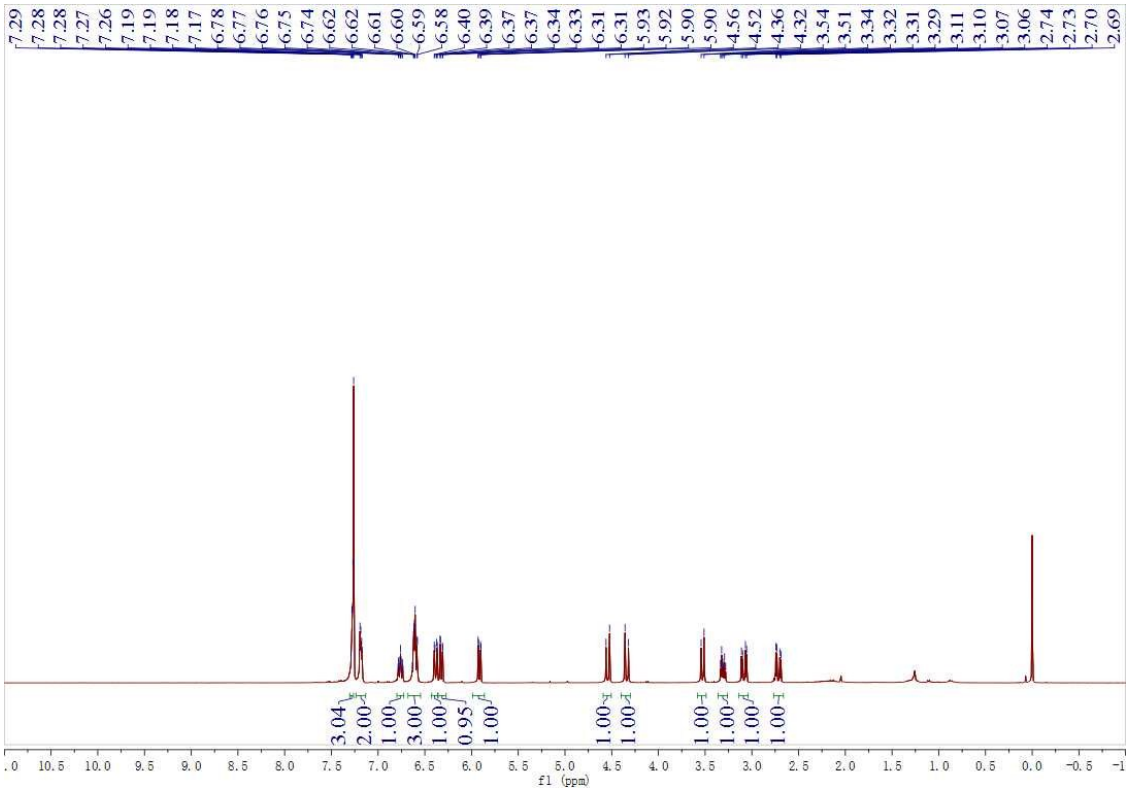


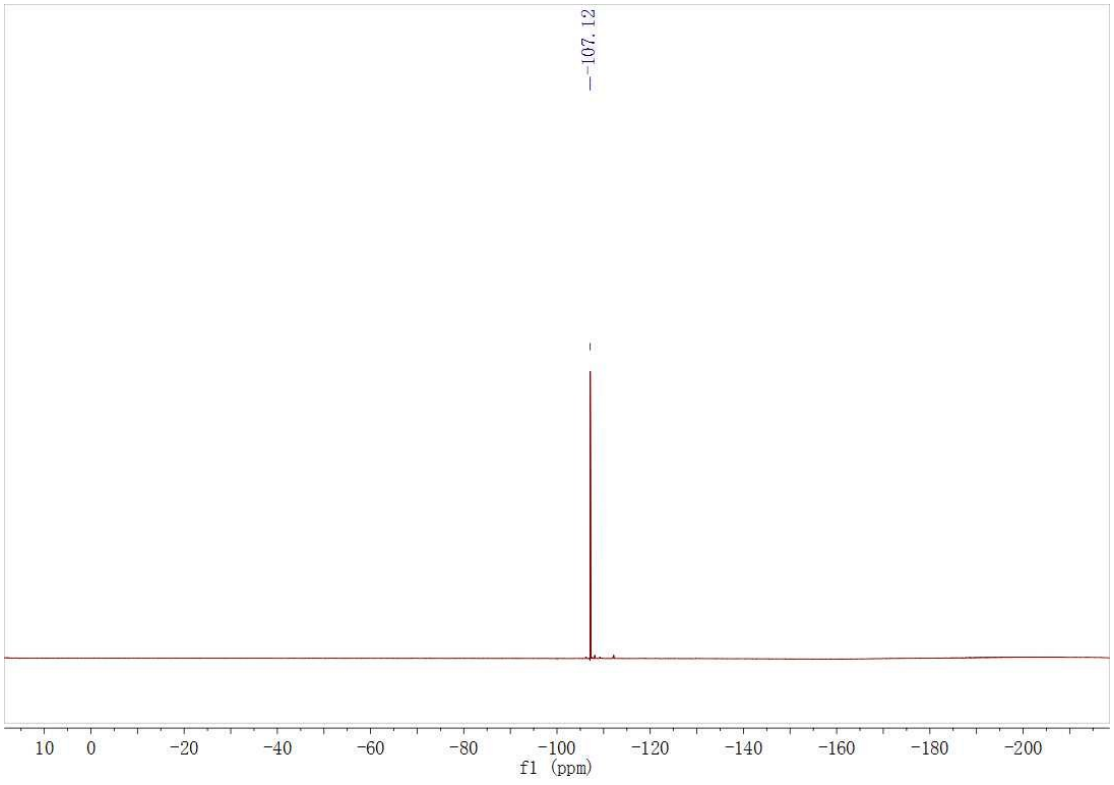
2-(1-benzyl-4-(3-bromophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3k)

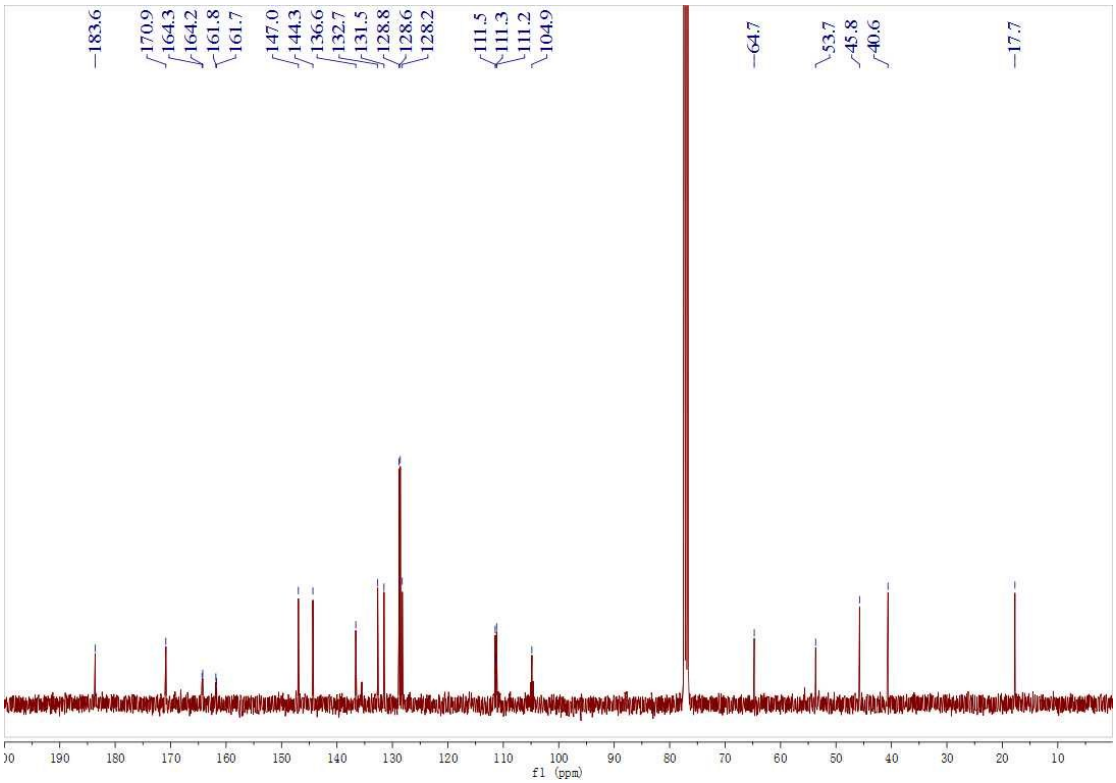




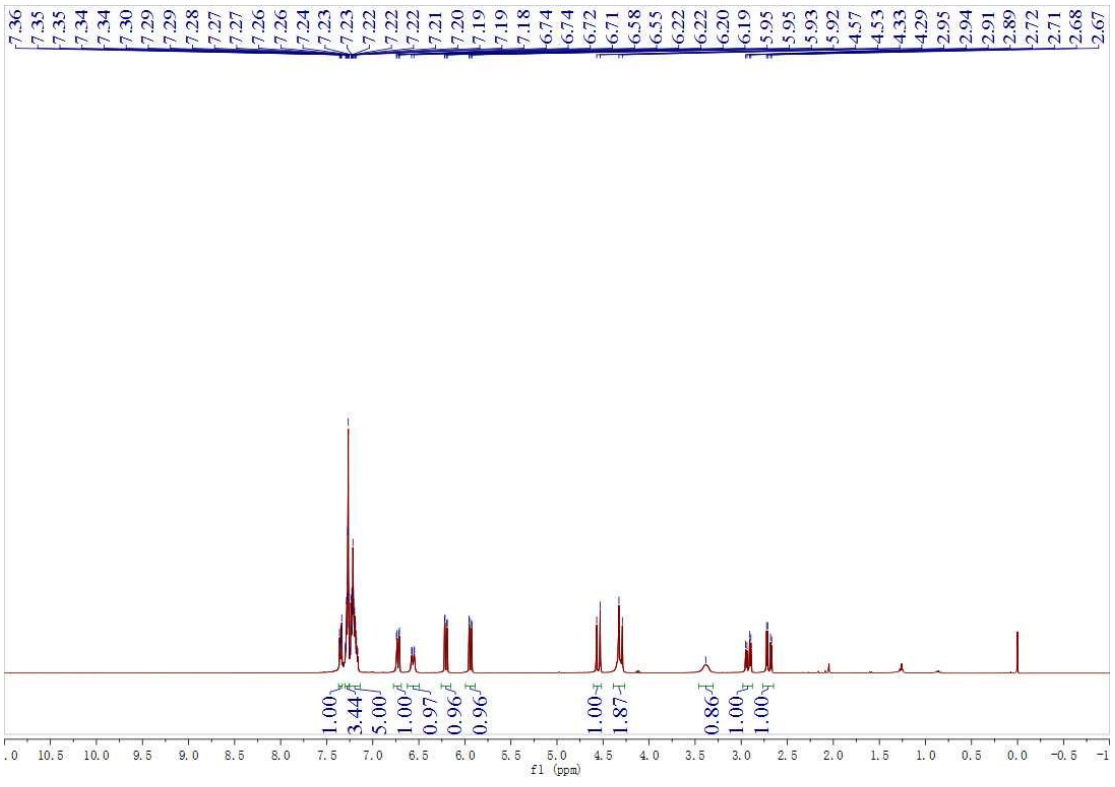
2-(1-benzyl-4-(3,5-difluorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3l)

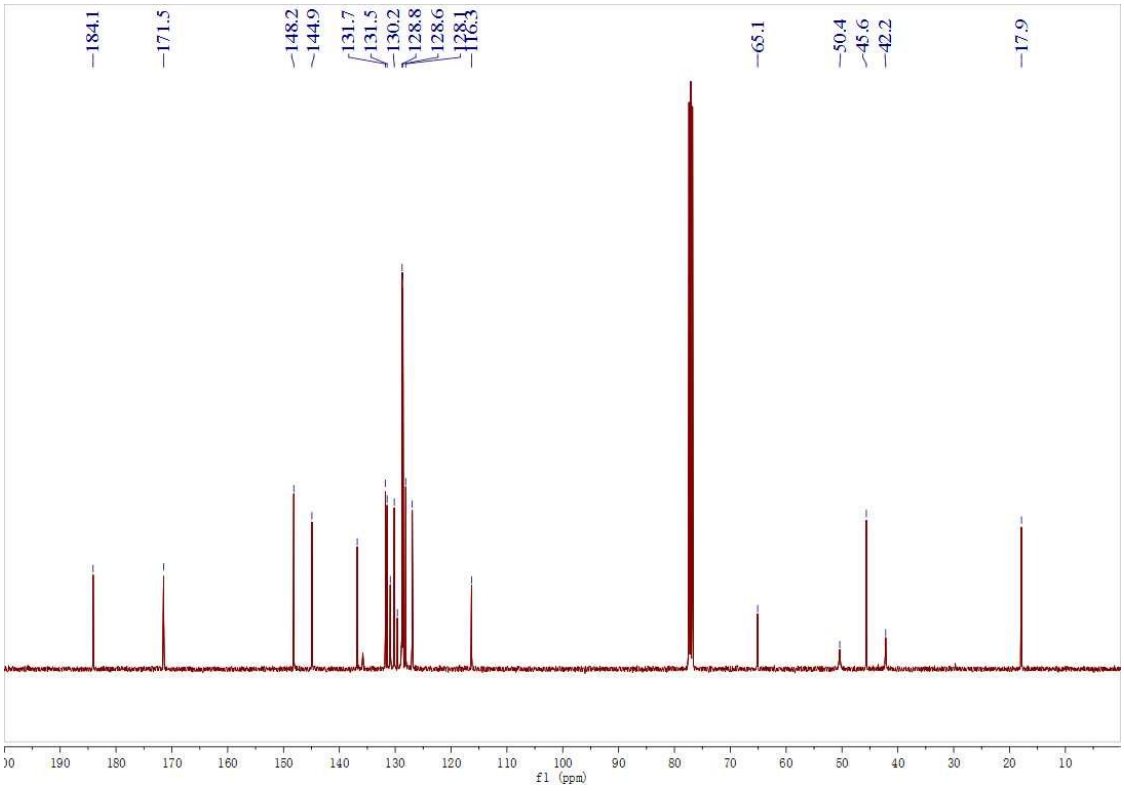




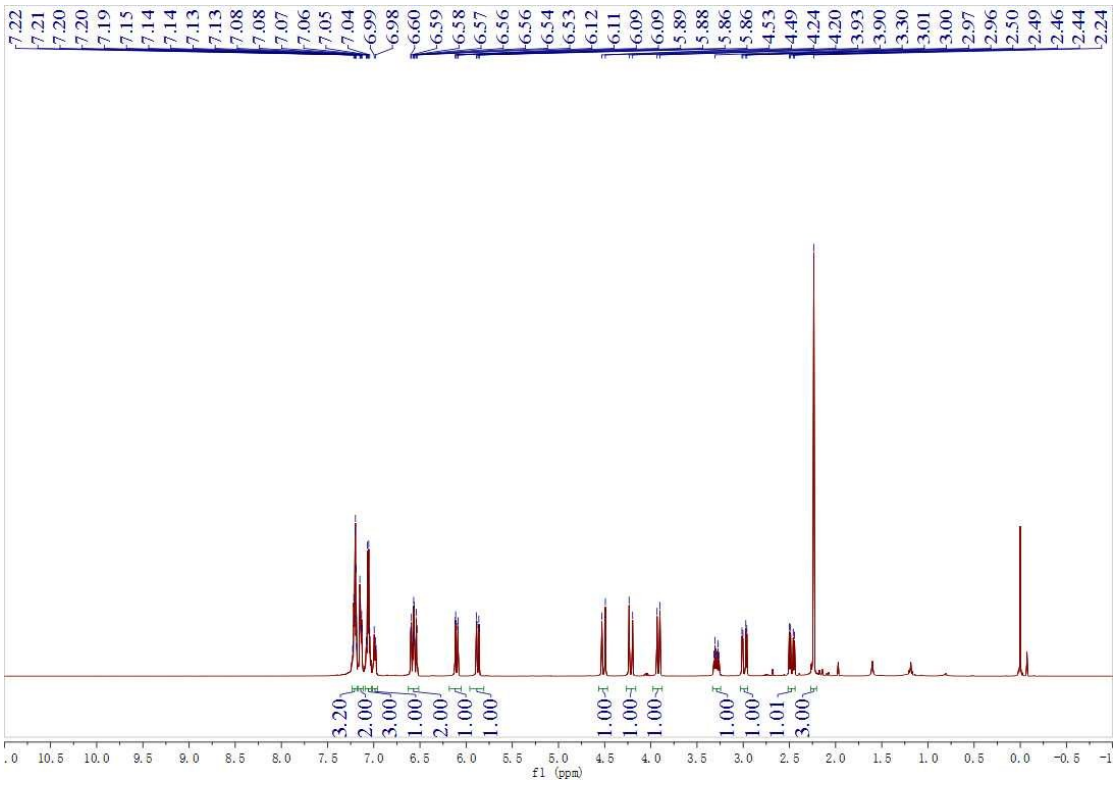


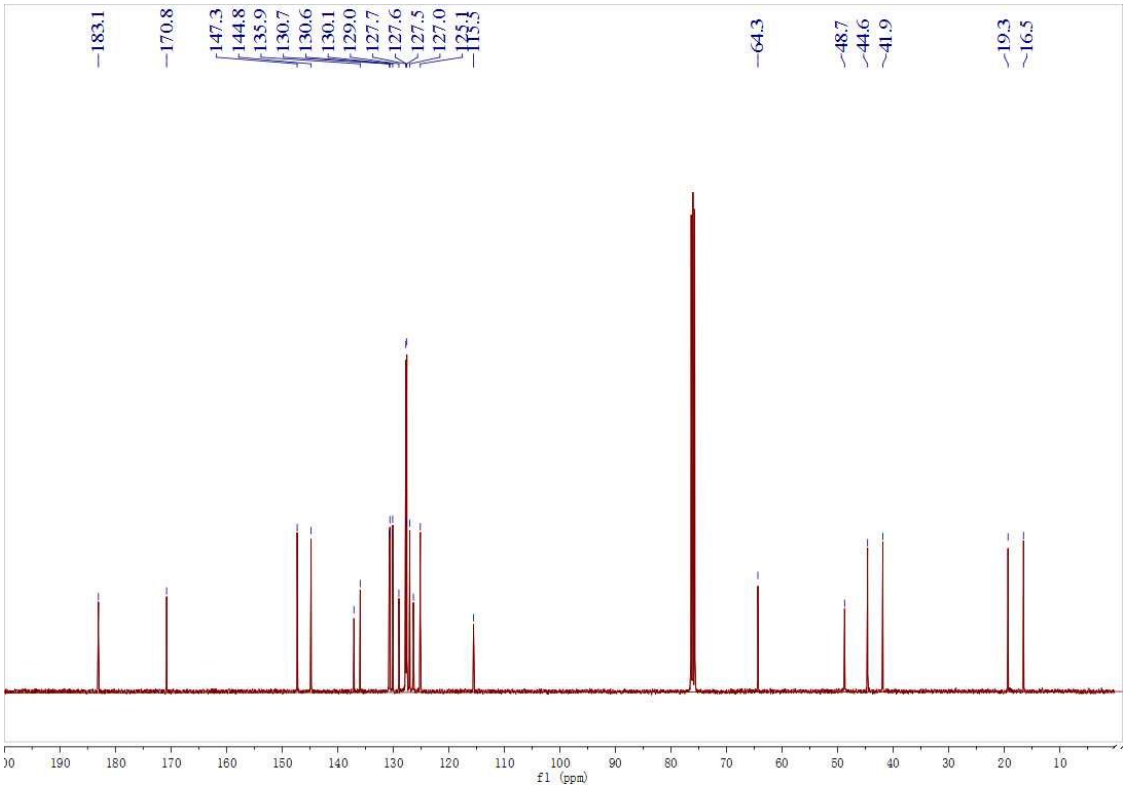
2-(1-benzyl-4-(2-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3m)



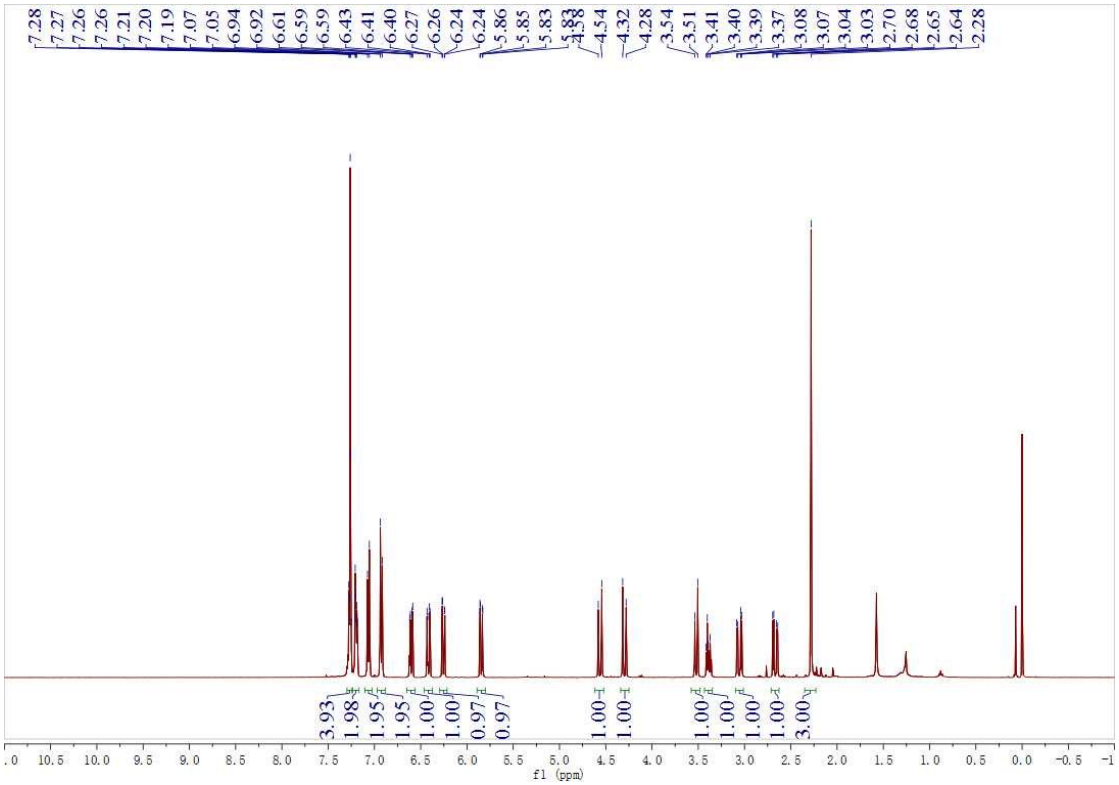


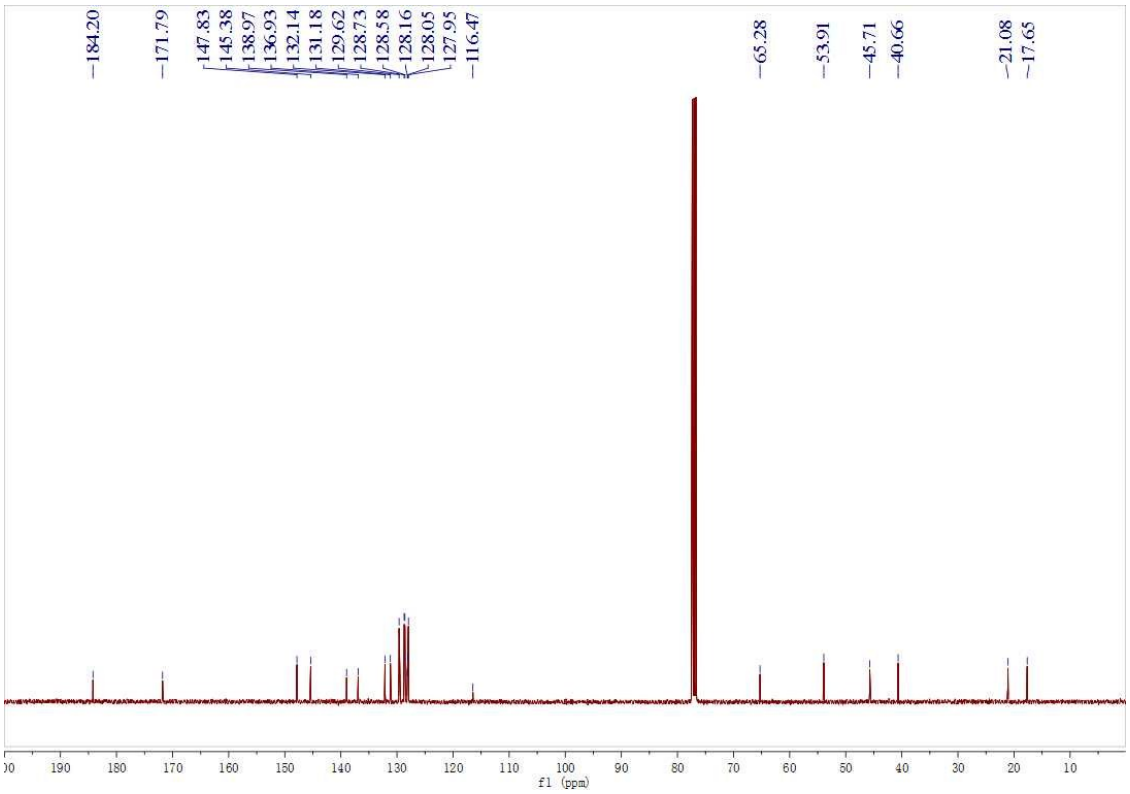
2-(1-benzyl-2,8-dioxo-4-(o-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3n)



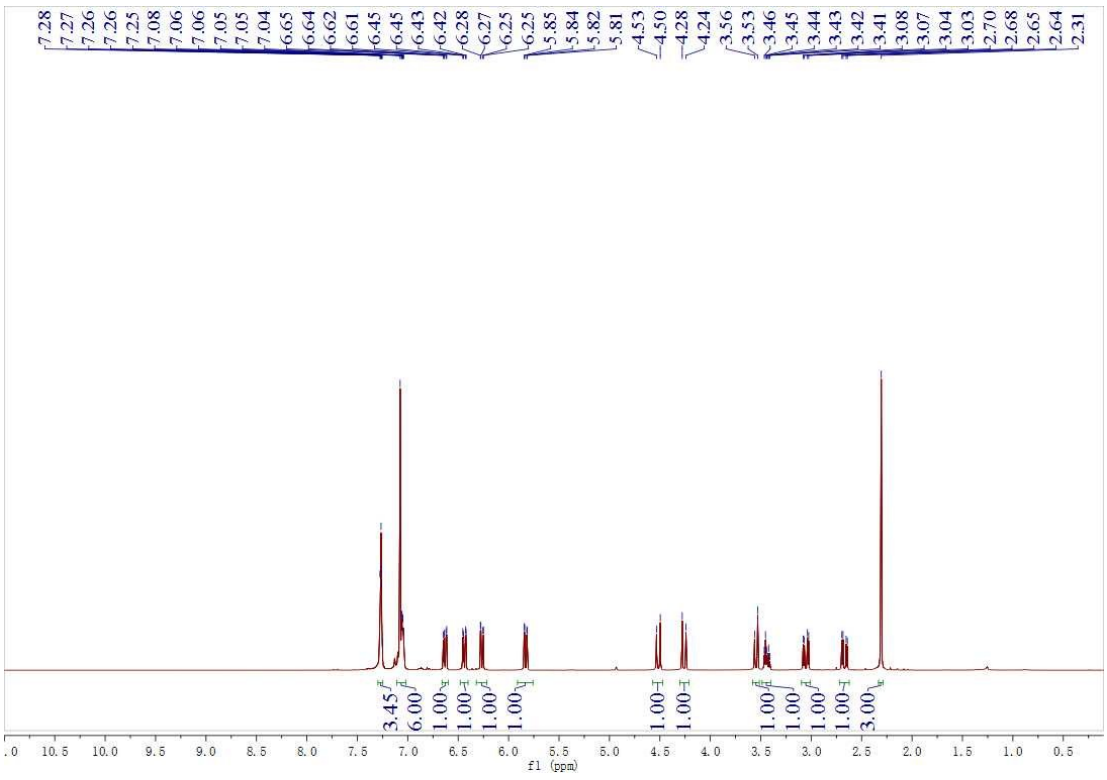


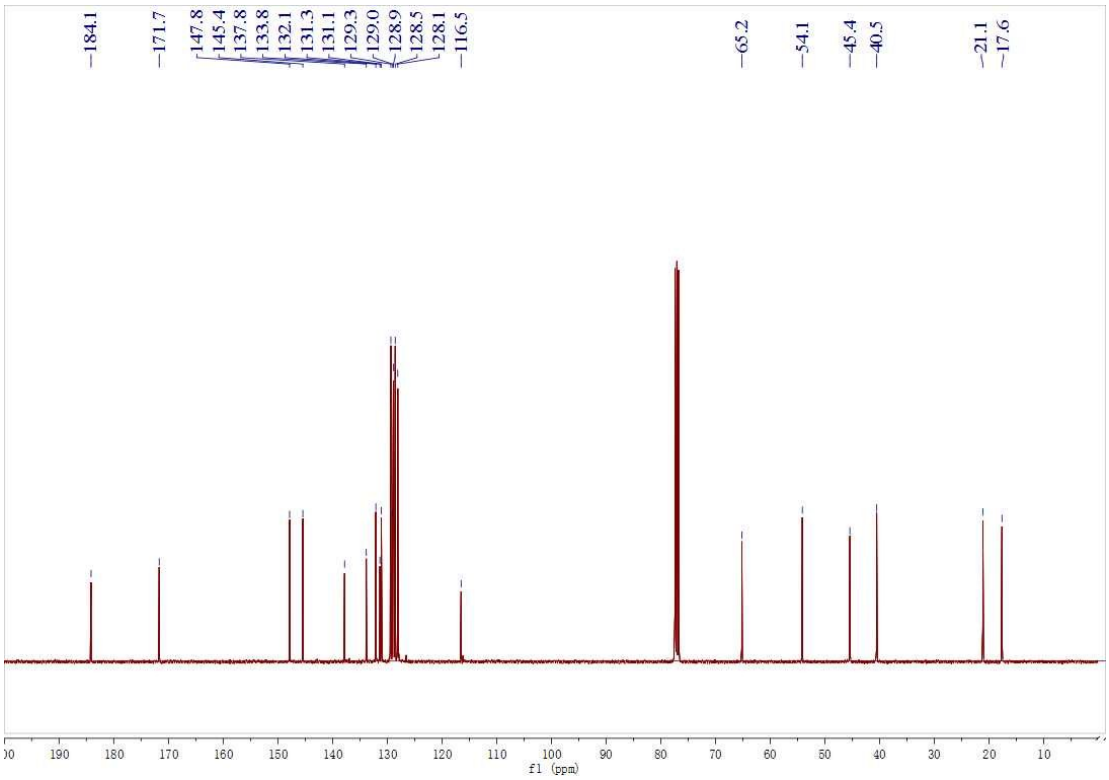
2-(1-benzyl-2,8-dioxo-4-(p-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3o)



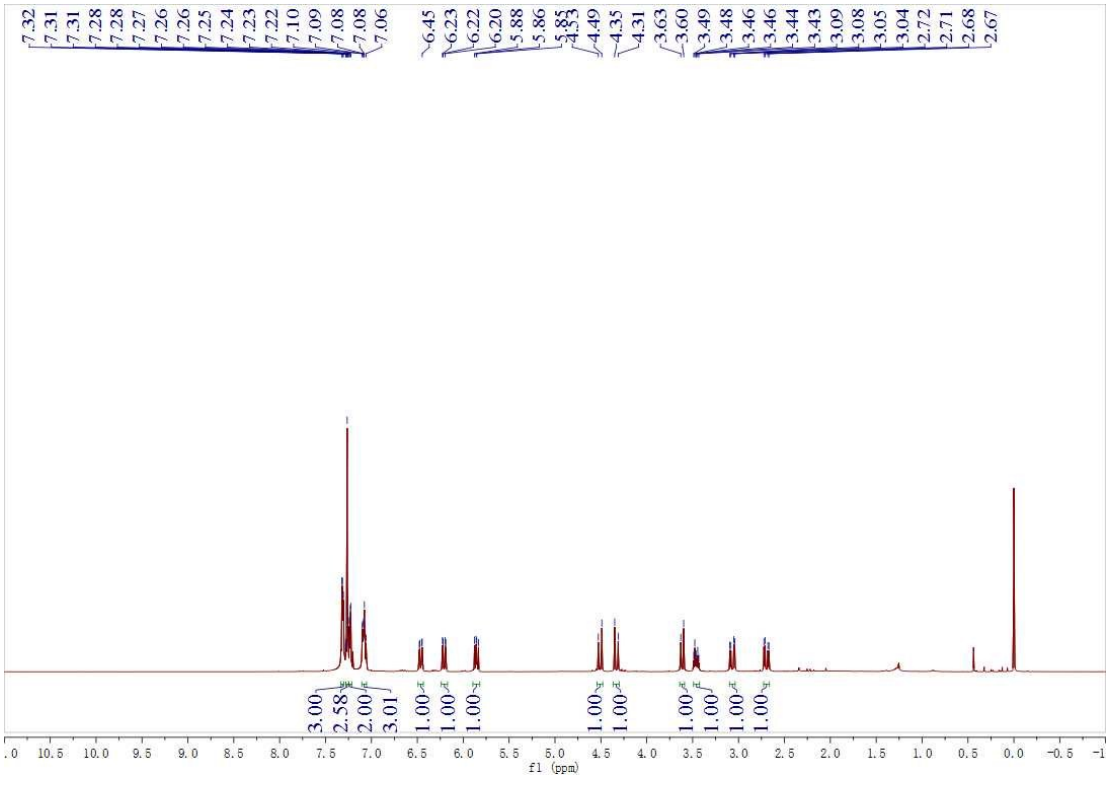


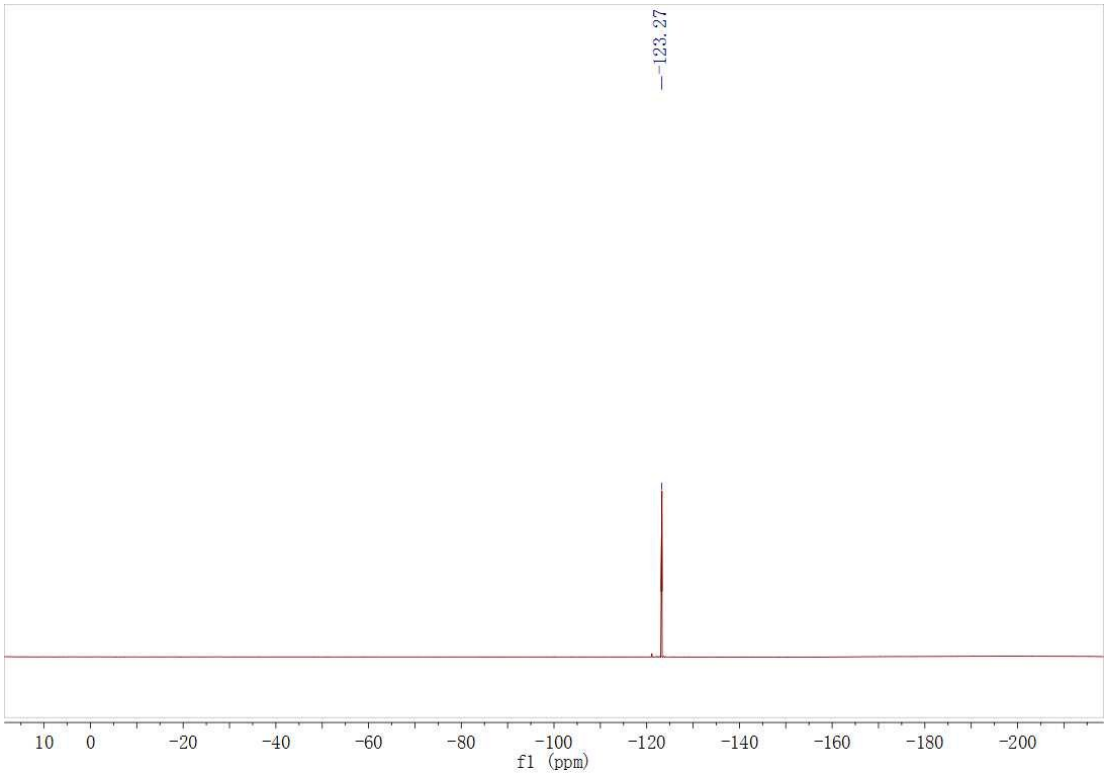
2-(1-(4-methylbenzyl)-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3p)

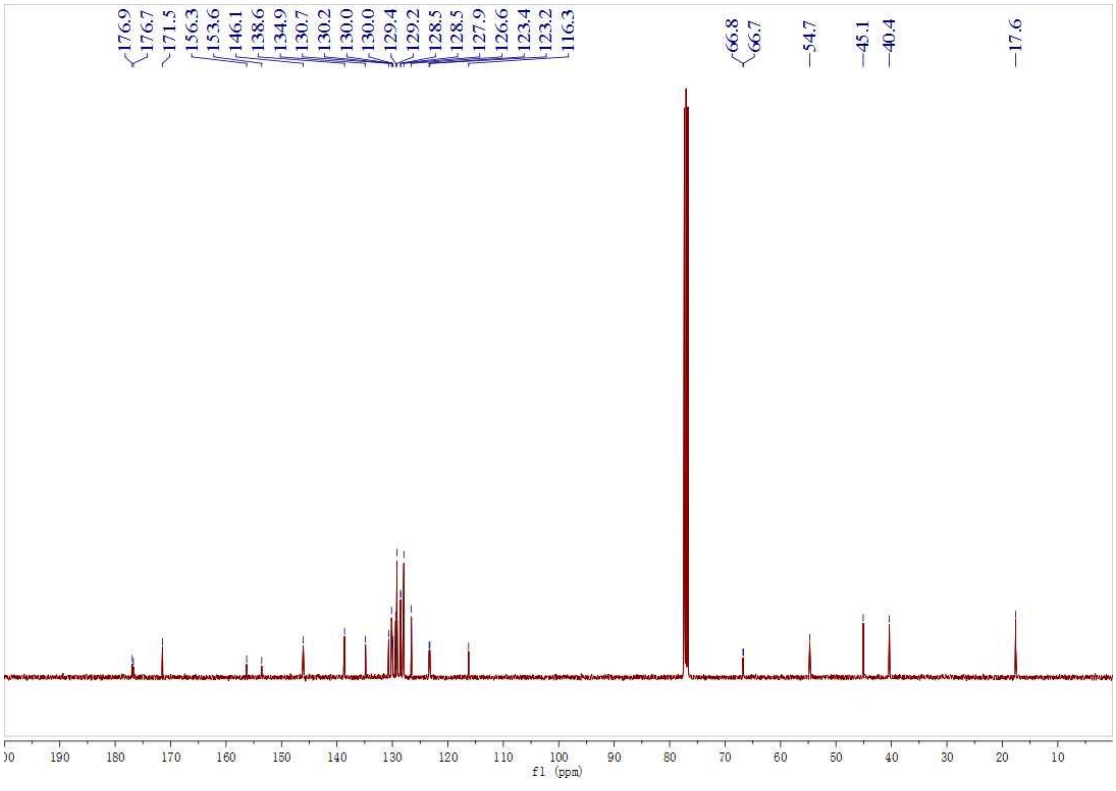




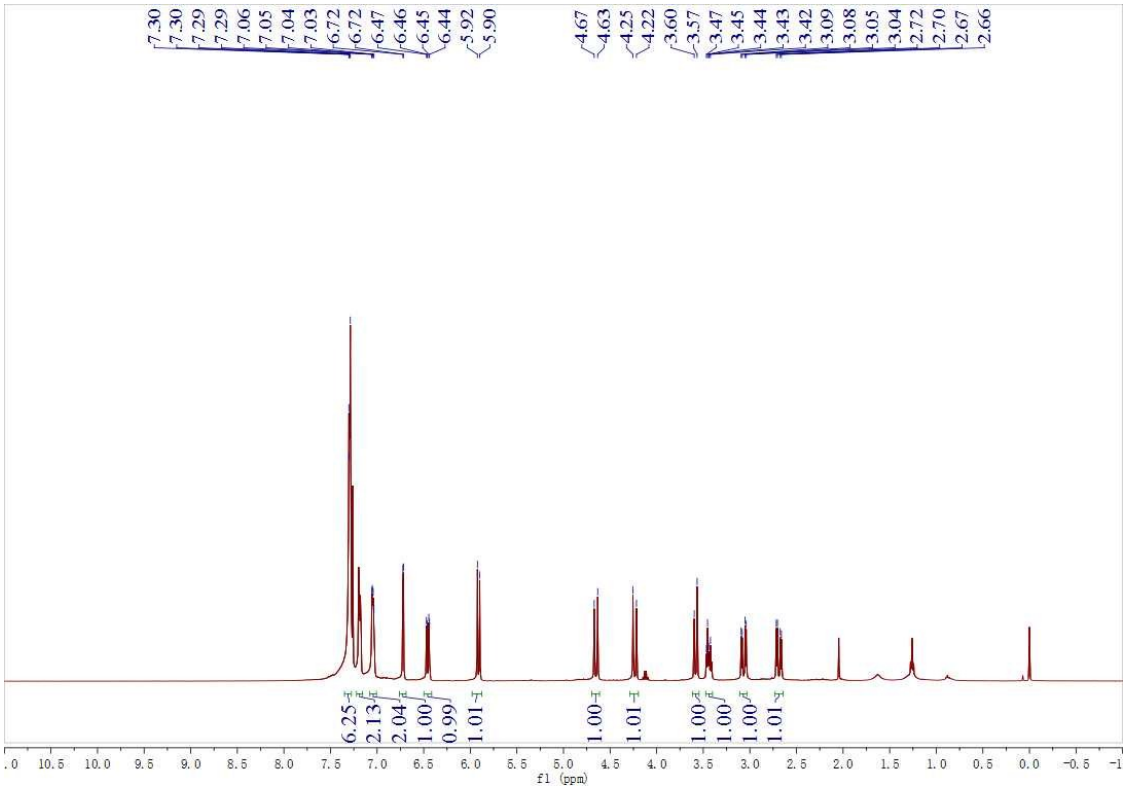
2-(1-benzyl-7-fluoro-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3q)

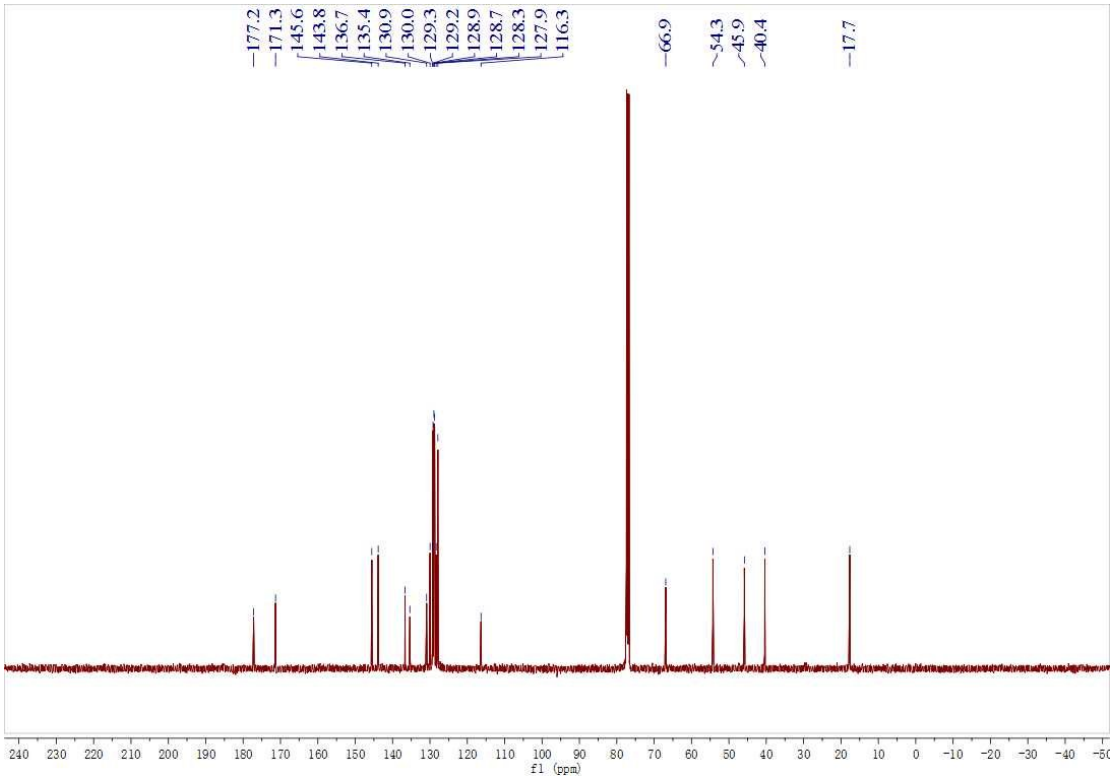



-123.27
10 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200
f1 (ppm)

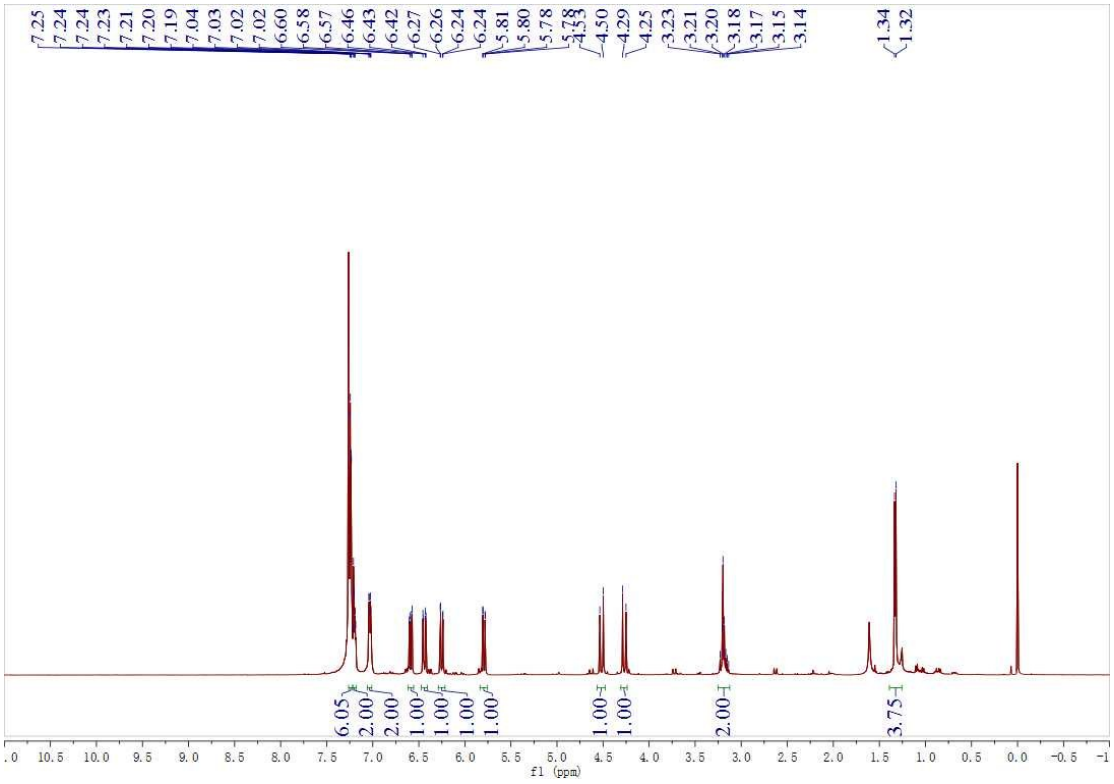

176.9
176.7
171.5
156.3
153.6
146.1
138.6
134.9
130.7
130.2
130.0
130.0
129.4
129.2
128.5
128.5
127.9
126.6
123.4
123.2
116.3
66.8
66.7
54.7
45.1
40.4
17.6
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

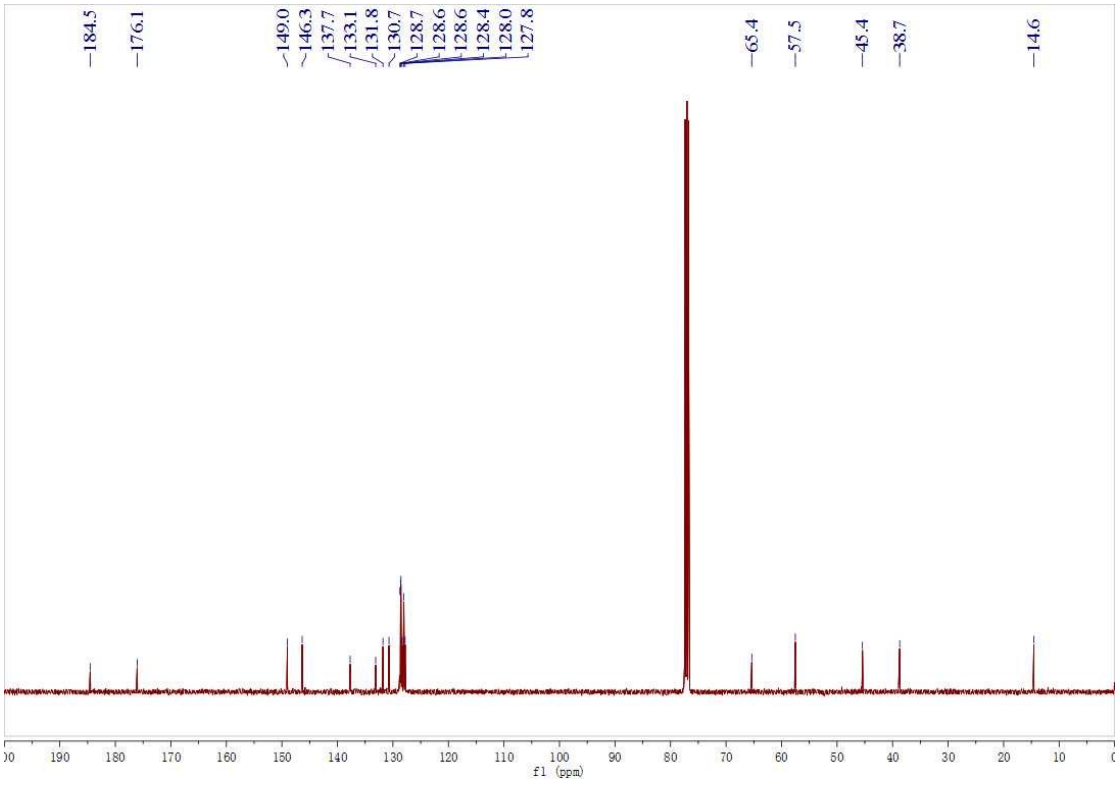
2-(1-benzyl-7-chloro-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3r)



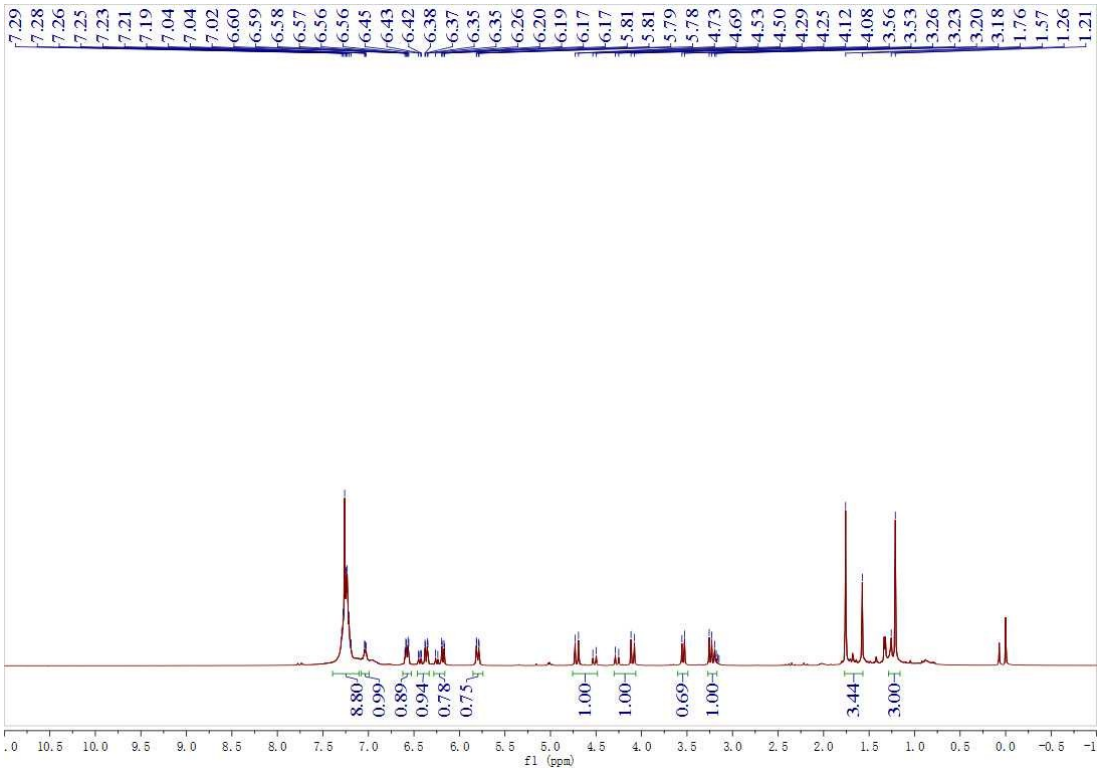


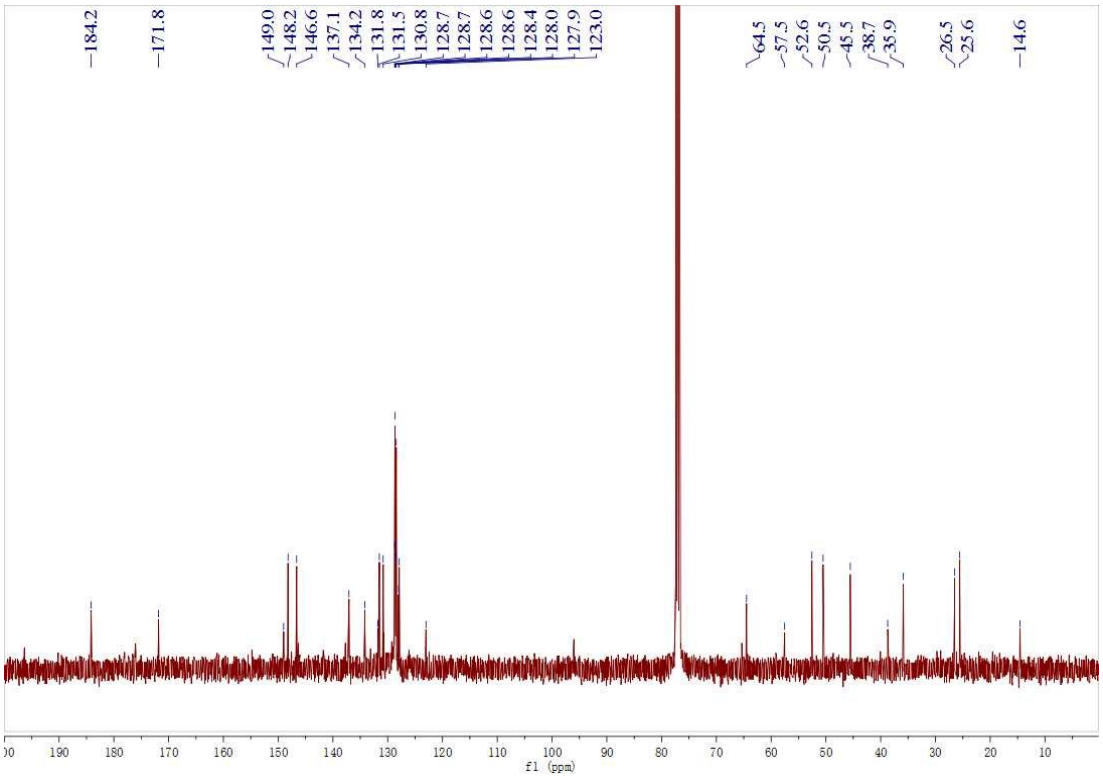
1-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)cyclopropane-1-carbonitrile (3s)



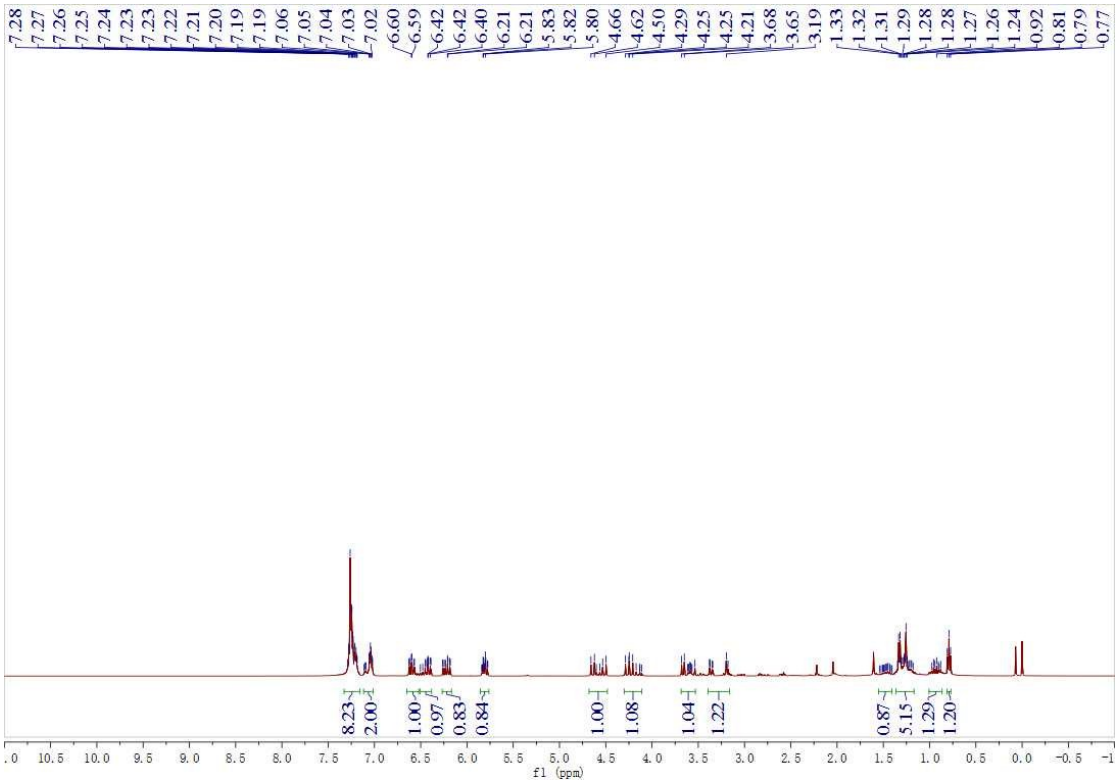


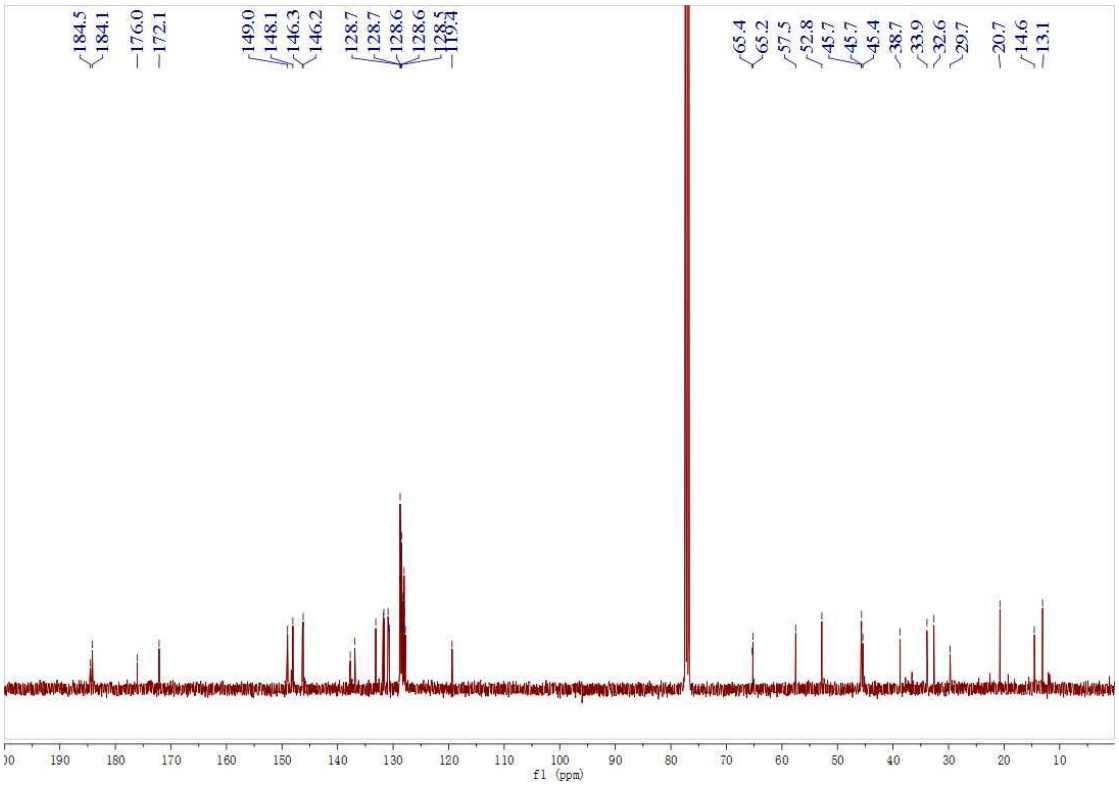
2-(-1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)-2-methylpropanenitrile (3t)



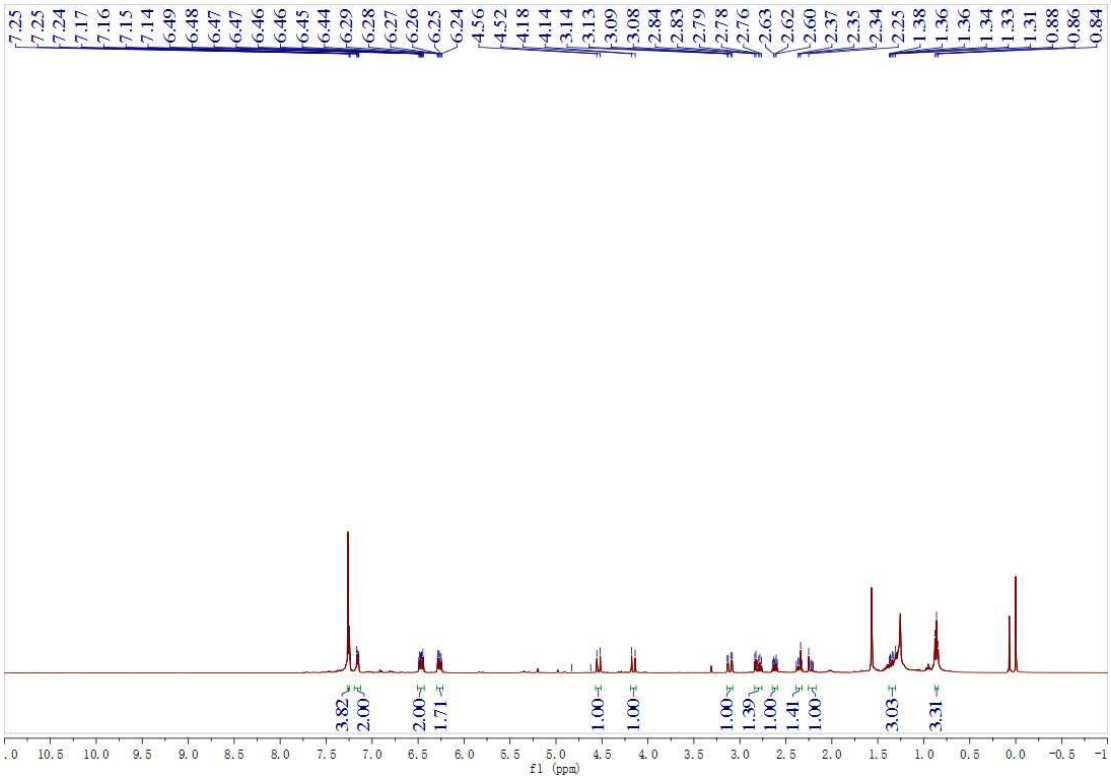


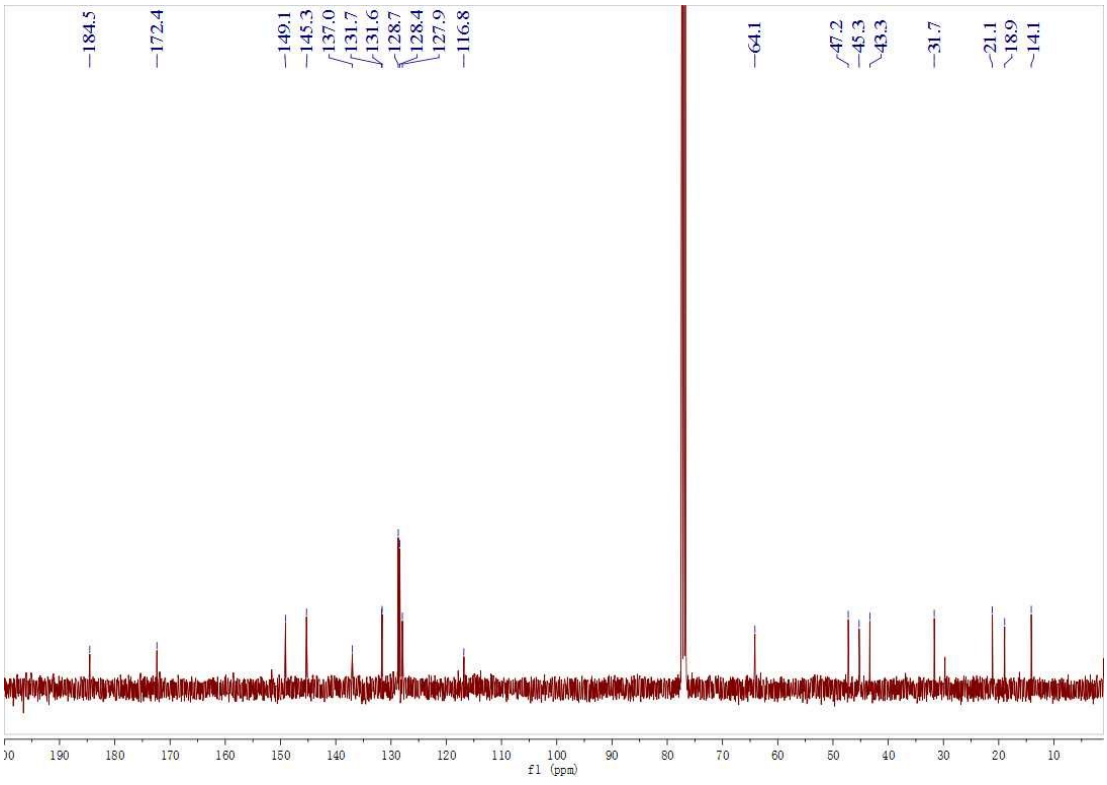
2-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)pentanenitrile (3u)





2-(-1-benzyl-2,8-dioxo-4-propyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3v)





2-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile ([D_2]-3d)