SUPPORTING INFORMATION

A Chiral Fluorescent Ir(III) Complex that Targets the GPX4 and ErbB Pathways to Induce Cellular Ferroptosis

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Experimental Procedures

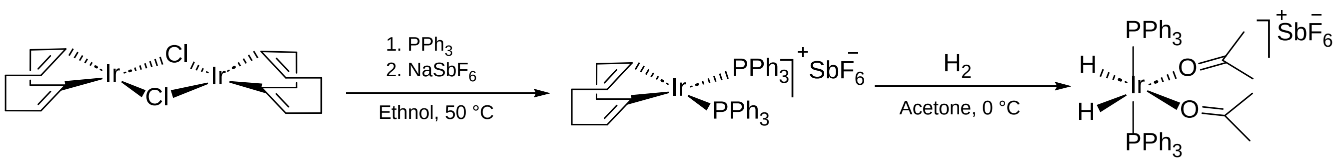
General information

All anhydrous solvents were bought from J&K Scientific and all reactants and reagents were obtained from Bide Pharm, Energy Chemical, Laajoo and Adamas and used as received unless otherwise specified. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were obtained on Bruker nuclear resonance (400 MHz) spectrometer. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane (TMS). The residual solvent signals were used as references and the chemical shifts converted to TMS scale. High resolution mass spectra (HRMS) were obtained by ESI on a quadrupole-orbitrap mass spectrometer (QExactive, ThermoFisher Scienctific). Fluorescence spectra were conducted on a Shimadzu RF-6000 spectrofluorophotometer. High performance liquid chromatography (HPLC) analysis was performed on a Shimadzu SPD-20A. UV-Vis spectra were conducted on a Shimadzu UV-1800 spectraophotometer. Circular dichroism (CD) spectra were conducted on a Jasco J-810 spectropolarimeter.
Human fibrosarcoma cells (HT-1080), human pancreatic cancer (PANC-1), human lung fibroblasts (HLFs), and human embryonic kidney 293T (HEK-293T) cells were purchased from American Type Culture Collection (Manassas, VA). All the cell lines were authenticated by using STR typing and confirmed to be mycoplasma-free by KeyGEN BioTECH Co., Ltd. (Nanjing, China). All cells were cultured in DMEM (Gibco) containing 10% FBS (Gibco), 100 units/ml penicillin, and 50 units/ml streptomycin at 37 °C in a CO_2 incubator (95% relative humidity, 5% CO_2). Female BALB/c mice (6−8 weeks) were obtained from the Model Animal Research Center of Nanjing University and maintained under protocols approved by Nanjing University Laboratory Animal Center. All animal studies were performed in accordance with the Guidelines for the Care and Use of Laboratory Animals of the Chinese Animal Welfare Committee and approved by The Institutional Animal Care and Use Committee (Nanjing University, IACUC-2109009).

Synthetic procedures

Synthesis of Ir(III) intermediate ($[IrH_2(PPh_3)_2(C_3H_6O)_2]SbF_6$):

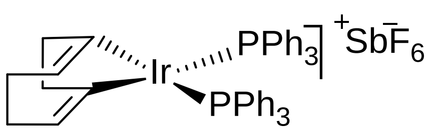
The method for preparing $[IrH_2(PPh_3)_2(C_3H_6O)_2]SbF_6$ reported by Zhao et al. was slightly modified (Scheme S1).[1]



Scheme S1. Synthetic route of $[IrH_2(PPh_3)_2(C_3H_6O)_2]SbF_6$.

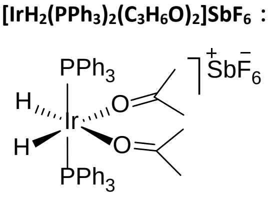
Chloro(1,5-cyclooctadiene)iridium(I) dimer (671.7 mg, 1.0 mmol 1.0 equiv) and triphenylphosphine (786.9 mg, 3.0 mmol 3.0 equiv) were dissolved in anhydrous ethanol (100 mL) under nitrogen atmosphere in a glovebox. The resulting solution was heated to 50 ℃, and sodium hexafluoroantimonate (776.2 mg, 3.0 mmol 3.0 equiv) was added when all solids were dissolved. A bright red precipitate was formed in a few minutes. The suspension was stirred for another 2h, then the solid was collected by filtration, dissolved in acetone (20 ml). The resulting white solid sodium chloride was removed by filtration. The supernatant was removed by filtration, and the resulting dark red crystals were washed with hexane (3 x 10 mL) and dried under vacuum. Dark red crystal $[Ir(COD)(PPh_3)_2]SbF_6$ (1.86g, 88%) was obtained.
$[IrCOD(PPh_3)_2]SbF_6$ (976.9 mg, 1 mmol) was dissolved in acetone (5 mL) at 0 ℃ and allowed to cool for 15 min. Hydrogen was then blowed into the solution until it turns pale yellow. Diethyl ether (20 mL) was added to afford $[IrH_2(PPh_3)_2(C_3H_6O)_2]SbF_6$ (white powder, 696 mg, 66%). All data are consistent with the reference.

$[IrCOD(PPh_3)_2]SbF_6$:



^{1}H NMR (400 MHz, Chloroform-d) δ 7.45 – 7.27 (m, 30H), 4.20 (s, 3H), 2.40 – 2.33 (m, 3H), 1.95 (q, J = 7.6 Hz, 4H).
^{13}C NMR (101 MHz, Chloroform-d) δ 134.5, 134.4, 134.3, 134.3, 131.3, 130.0, 130.0, 129.7, 129.5, 129.4, 128.9, 128.7, 128.7, 128.6, 87.2, 87.1, 87.1, 77.4, 77.0, 76.7, 31.0.
^{31}P NMR (162 MHz, Chloroform-d) δ 17.2.
HRMS (ESI, CH_3CN, m/z, relative intensity): 825.2364 (calcd for $[C_{44}H_{42}IrP_2]$ +: 825.2391), 604.1720 (calcd for $[C_{28}H_{30}IrNP]$ +: 825.2391).

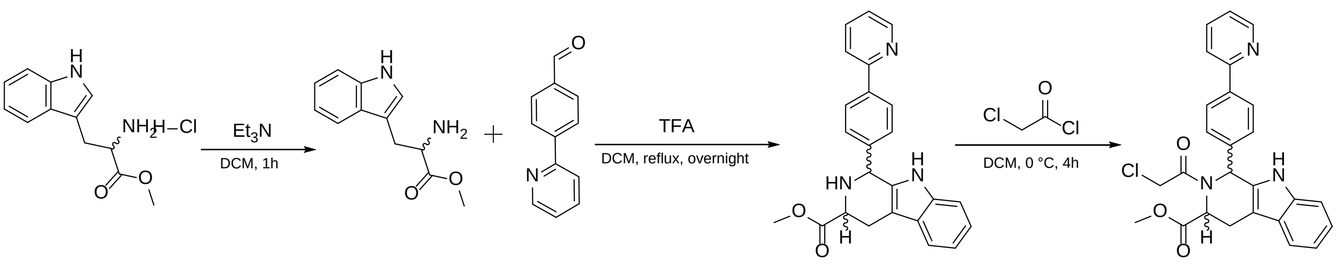
[IrH$_2$(PPh$_3$)$_2$(C$_3$H$_6$O)$_2$]SbF$_6$:



^{1}H NMR (400 MHz, Acetone-d$_6$) δ 7.53 (tdd, J = 7.6, 5.2, 3.0 Hz, 30H), -27.68 (t, J = 15.9 Hz, 2H).
^{13}C NMR (101 MHz, Acetone-d$_6$) δ 205.3, 133.8, 133.8, 133.7, 130.9, 128.8, 128.8, 128.7, 29.7, 29.6, 29.4, 29.2, 29.0, 28.8, 28.6, 28.4, 26.6.
^{31}P NMR (162 MHz, Acetone-d$_6$) δ 27.4, 27.3, 27.2, 27.2, 27.1.
HRMS (ESI, CH$_3$CN, m/z, relative intensity): 717.1513 (calcd for [C$_{36}$H$_{30}$IrP$_2$] 3+: 717.1452), 760.1833 (calcd for [C$_{38}$H$_{35}$IrNP$_2$] +: 760.1874), 801.2110 (calcd for [C$_{40}$H$_{38}$IrN$_2$P$_2$] +: 801.2139).

*Synthesis of **L1** and **L2**:*

The synthesis of ligands is based on the method reported by Stockwell et al. with a slight modification (Scheme S2).[2]



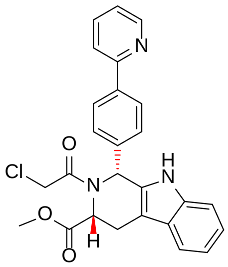
Scheme S2. General synthetic route of the ligands.

D-Tryptophan methyl ester hydrochloride (2.5 g, 10.0 mmol 1.0 equiv) in dichloromethane (50 mL) was added triethylamine (1.6 mL, 11.0 mmol 1.1 equiv) at room temperature for 1 h. The mixture was then filtered and the filtrate was concentrated under reduced pressure to afford a colorless oil. After drying under vacuum for 30 min, the oil was dissolved in anhydrous dichloromethane (50 mL), 4-(2-pyridinyl)benzaldehyde (1.8 g, 10.0 mmol 1.0 equiv) and trifluoroacetic acid (2.2 mL, 30.0 mmol 3.0 equiv) were added and the reaction was refluxed overnight. The mixture was cooled to room temperature and quenched with saturated aqueous sodium bicarbonate. The organic phase was separated, washed with brine, dried over sodium sulfate and then concentrated under reduced pressure to give the crude product. The crude product and triethylamine (2.1 mL, 15.0 mmol 1.5 equiv) were dissolved in anhydrous dichloromethane (50 mL) at 0 ℃ and allowed to cool for 15 min. Chloroacetyl chloride (955.0 µL, 12.0 mmol 1.2 equiv) was then added dropwise and the reaction mixture was allowed to stir at room temperature for 4 h. The mixture was filtered and the filter residue was dried over vacuum to afford **L2** (light yellow powder, 2.66 g, 58%). The filtrate was washed with water and brine, dried with sodium sulfate and concentrated. **L1** (yellow powder, 1.42 g, 31%) was afforded by silica gel chromatography (dichloromethane: ethyl acetate = 5: 1).

*Synthesis of **L3** and **L4**:*

L4 (pale yellow powder, 2.80 g, 61%) and **L3** (yellow powder, 1.33 g, 29%) were afforded by the same method described above with L-tryptophan methyl ester hydrochloride as the starting reagent.

Ligand (1*R*,3*R*) (L2):

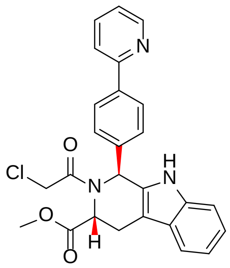


^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.65 (dd, J = 4.8, 1.8 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.86 (td, J = 7.7, 1.9 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.20 (d, J = 8.0 Hz, 1H), 7.16 – 7.08 (m, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.94 (s, 1H), 5.25 (d, J = 6.7 Hz, 1H), 4.88 (d, J = 13.9 Hz, 1H), 4.49 (d, J = 13.9 Hz, 1H), 3.51 (d, J = 15.9 Hz, 1H), 3.14 (dd, J = 16.0, 7.2 Hz, 1H), 3.06 (td, J = 7.3, 4.4 Hz, 1H), 2.89 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 170.7, 167.3, 156.1, 150.0, 140.8, 138.7, 137.7, 136.9, 130.2, 129.7, 126.5, 126.4, 123.1, 122.1, 120.7, 119.2, 118.6, 111.8, 106.8, 55.4, 52.9, 52.0, 51.7, 46.0, 43.7, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4, 21.6, 9.0.

HRMS (ESI, CH_3CN, m/z, relative intensity): 460.1388 (calcd for [$C_{26}H_{22}ClN_3O_3$ + H] +: 460.1428), 482.1220 (calcd for [$C_{26}H_{22}ClN_3O_3$ + Na] +: 482.1247).

Ligand (1*S*,3*R*) (L1):

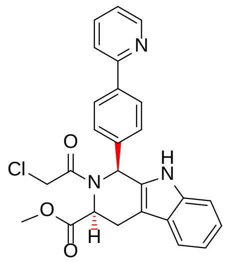


^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.63 (s, 1H), 8.09 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.85 (dt, J = 15.4, 8.2 Hz, 2H), 7.67 – 7.59 (m, 1H), 7.51 (dd, J = 15.7, 7.8 Hz, 2H), 7.27 (d, J = 30.5 Hz, 2H), 6.99 (q, J = 11.2 Hz, 2H), 6.06 (s, 1H), 5.42 (s, 1H), 4.75 (d, J = 14.0 Hz, 1H), 4.43 (d, J = 14.0 Hz, 1H), 3.54 (d, J = 9.4 Hz, 4H), 3.40 (d, J = 18.7 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 168.2, 150.0, 145.1, 137.6, 136.9, 127.6, 127.0, 126.8, 126.3, 122.9, 121.8, 120.6, 119.3, 118.5, 111.8, 104.0, 60.2, 57.1, 56.5, 53.2, 43.8, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4, 24.0, 21.2, 14.6.

HRMS (ESI, CH_3CN, m/z, relative intensity): 460.1399 (calcd for [$C_{26}H_{22}ClN_3O_3$ + H] +: 460.1428), 482.1221 (calcd for [$C_{26}H_{22}ClN_3O_3$ + Na] +: 482.1247).

Ligand (1*S*,3*S*) (L4):

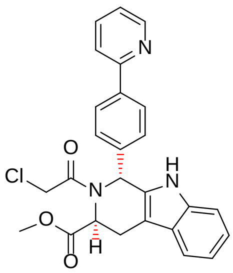


^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.63 (s, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.85 (dt, J = 15.5, 8.1 Hz, 2H), 7.63 (s, 1H), 7.51 (dd, J = 15.6, 7.8 Hz, 2H), 7.31 (s, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.00 (dt, J = 21.9, 7.6 Hz, 2H), 6.06 (s, 1H), 5.42 (s, 1H), 4.75 (d, J = 14.0 Hz, 1H), 4.43 (d, J = 14.0 Hz, 1H), 3.54 (d, J = 9.4 Hz, 4H), 3.44 – 3.35 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 168.2, 150.0, 145.1, 137.6, 136.9, 134.7, 127.6, 127.0, 126.3, 122.9, 121.8, 120.6, 119.3, 118.5, 111.8, 60.2, 57.1, 56.5, 53.2, 43.8, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4, 24.0, 21.2, 14.6.

HRMS (ESI, CH_3CN, m/z, relative intensity): 460.1397 (calcd for [$C_{26}H_{22}ClN_3O_3$ + H] +: 460.1428), 482.1221 (calcd for [$C_{26}H_{22}ClN_3O_3$ + Na] +: 482.1247).

Ligand (1*R*,3*S*) (L3):



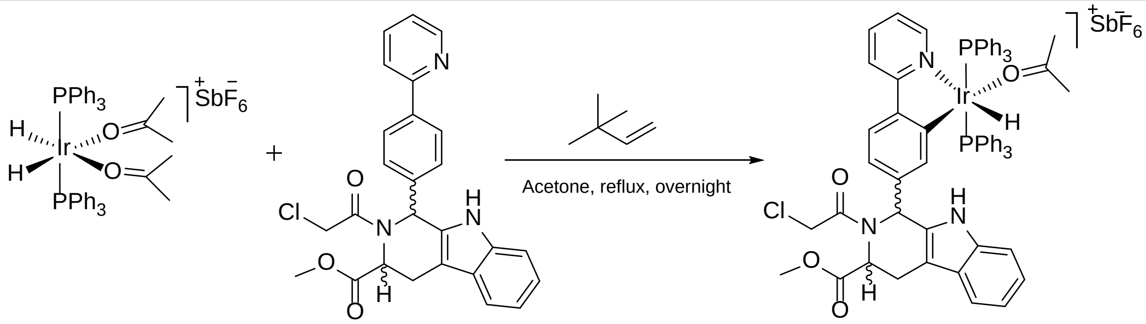
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.65 (dd, J = 4.8, 1.8 Hz, 1H), 8.01 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.86 (td, J = 7.7, 1.8 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.20 (d, J = 8.0 Hz, 1H), 7.16 – 7.08 (m, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.94 (s, 1H), 5.25 (d, J = 6.8 Hz, 1H), 4.87 (d, J = 13.8 Hz, 1H), 4.49 (d, J = 13.9 Hz, 1H), 3.51 (d, J = 15.9 Hz, 1H), 3.14 (dd, J = 16.1, 7.1 Hz, 2H), 2.89 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 170.7, 167.3, 156.1, 150.0, 140.8, 138.7, 137.7, 136.9, 130.2, 129.7, 126.5, 126.4, 123.1, 122.1, 120.7, 119.2, 118.6, 111.8, 106.8, 52.9, 52.0, 51.7, 43.7, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4, 21.6.

HRMS (ESI, CH_3CN, m/z, relative intensity): 460.1397 (calcd for [$C_{26}H_{22}ClN_3O_3$ + H] +: 460.1428), 482.1221 (calcd for [$C_{26}H_{22}ClN_3O_3$ + Na] +: 482.1247).

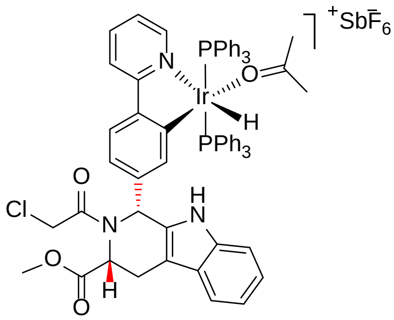
General method for synthesizing Ir-Py-RSL:

[$IrH_2(PPh_3)_2(C_3H_6O)_2$]$SbF_6$ (100.0 mg, 0.9 mmol 1.0 equiv), ligand (47.3 mg, 1.0 mmol 1.1 equiv), and 3,3-dimethyl-1-butene (50.0 µL, 3.7 mmol 4.0 equiv) were dissolved in acetone (3 mL) in a 15 mL pressure tube under nitrogen atmosphere. The mixture was stirred under reflux overnight. After cooling to room temperature, diethyl ether (10 mL) was added to the mixture and the tube was placed in the refrigerator at -4 ℃ for 10 h. The reaction mixture was filtered and dried under vacuum for 2 h to afford Ir-Py-RSL (Scheme S3).



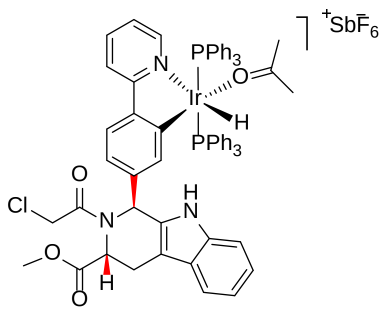
Scheme S3. General synthetic route of Ir-RSL complexes.

Ir-Py-RSL (1*R*,3*R*) (Ir2) (yellow powder, 91 mg, 66%):



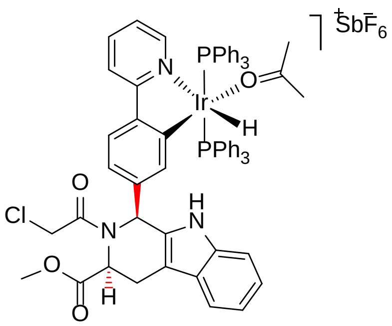
^{1}H NMR (400 MHz, Acetone-d_6) δ 9.44 (d, J = 5.4 Hz, 1H), 8.16 (s, 1H), 7.64 – 7.57 (m, 1H), 7.46 – 7.38 (m, 6H), 7.27 (dt, J = 19.6, 8.8 Hz, 20H), 7.12 – 7.03 (m, 12H), 6.20 (s, 1H), 4.35 (s, 1H), 4.09 (d, J = 31.2 Hz, 4H), 3.00 (d, J = 64.8 Hz, 3H), 2.09 (s, 6H), -15.72 (s, 1H).
^{13}C NMR (101 MHz, Acetone-d_6) δ 205.2, 163.6, 147.8, 137.3, 136.6, 136.4, 133.8, 133.7, 133.7, 133.7, 130.5, 130.3, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 127.9, 122.3, 121.7, 120.1, 119.3, 118.0, 65.2, 51.9, 31.4, 29.7, 29.5, 29.3, 29.1, 28.9, 28.8, 28.6, 28.4, 22.2, 14.7.
^{31}P NMR (162 MHz, Acetone-d_6) δ 15.4.
HRMS (ESI, CH_3CN, m/z, relative intensity): 1176.2798 (calcd for $[C_{62}H_{52}ClIrN_3O_3P_2]^+$: 1176.2802), 1217.3004 (calcd for $[C_{64}H_{55}ClIrN_4O_3P_2]^+$: 1217.3067).

Ir-Py-RSL (1*S*,3*R*) (Ir1) (yellow powder, 95 mg, 69%):



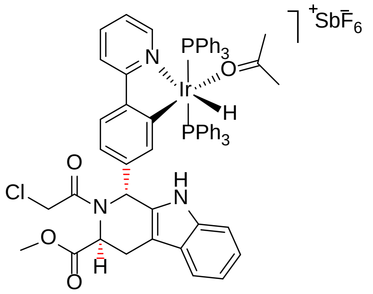
^{1}H NMR (400 MHz, Acetone-d_6) δ 9.50 (s, 1H), 7.66 – 7.60 (m, 1H), 7.55 (dd, J = 7.8, 4.8 Hz, 1H), 7.49 (td, J = 5.7, 2.8 Hz, 2H), 7.42 (t, J = 7.3 Hz, 4H), 7.37 (d, J = 7.2 Hz, 2H), 7.34 (s, 2H), 7.30 (s, 2H), 7.24 – 7.13 (m, 19H), 7.11 – 7.08 (m, 3H), 7.02 (d, J = 8.5 Hz, 4H), 6.08 (s, 1H), 4.36 (s, 1H), 4.19 (d, J = 13.6 Hz, 1H), 3.56 (s, 4H), 3.20 (dd, J = 16.0, 6.1 Hz, 1H), 2.83 (s, 1H), 2.09 (s, 6H), -15.81 (t, J = 15.1 Hz, 1H).
^{13}C NMR (101 MHz, Acetone-d_6) δ 205.2, 167.1, 147.7, 137.4, 136.8, 133.6, 133.4, 130.7, 130.5, 128.4, 128.4, 128.3, 128.3, 128.2, 127.8, 127.7, 125.6, 122.6, 121.6, 120.9, 120.2, 119.0, 118.5, 111.3, 65.2, 57.4, 54.5, 42.0, 29.7, 29.5, 29.3, 29.1, 28.9, 28.8, 28.6, 28.4, 22.4, 14.7.
^{31}P NMR (162 MHz, Acetone-d_6) δ 16.4, 15.9.
HRMS (ESI, CH_3CN, m/z, relative intensity): 1176.2774 (calcd for $[C_{62}H_{52}ClIrN_3O_3P_2]^+$: 1176.2802), 1217.3001 (calcd for $[C_{64}H_{55}ClIrN_4O_3P_2]^+$: 1217.3067).

Ir—Py-RSL (1*S*,3*S*) (Ir4) (yellow powder, 102 mg, 73%):



^{1}H NMR (400 MHz, Acetone-d_6) δ 9.51 (d, J = 5.3 Hz, 1H), 7.62 (d, J = 7.1 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.49 (ddd, J = 7.2, 5.6, 1.4 Hz, 2H), 7.42 (t, J = 7.4 Hz, 4H), 7.37 (d, J = 7.6 Hz, 2H), 7.33 (s, 2H), 7.30 (d, J = 5.5 Hz, 3H), 7.24 – 7.14 (m, 19H), 7.10 – 7.08 (m, 3H), 7.03 (s, 4H), 6.08 (s, 1H), 4.36 (s, 1H), 4.19 (d, J = 13.6 Hz, 1H), 3.55 (d, J = 6.4 Hz, 3H), 3.20 (dd, J = 15.9, 6.4 Hz, 1H), 2.83 (s, 1H), 2.09 (s, 6H), -15.81 (t, J = 15.1 Hz, 1H).
^{13}C NMR (101 MHz, Acetone-d_6) δ 205.3, 167.1, 147.7, 137.4, 136.8, 136.7, 133.5, 133.3, 131.8, 130.7, 130.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 127.8, 127.7, 127.1, 125.6, 122.6, 121.6, 120.2, 119.1, 118.5, 111.3, 65.2, 57.4, 54.5, 42.0, 31.4, 29.7, 29.5, 29.3, 29.1, 29.0, 28.8, 28.6, 28.4, 22.4, 14.7.
^{31}P NMR (162 MHz, Acetone-d_6) δ 16.4, 15.9.
HRMS (ESI, CH_3CN, m/z, relative intensity): 1176.2790 (calcd for $[C_{62}H_{52}ClIrN_3O_3P_2]^+$: 1176.2802), 1217.3006 (calcd for $[C_{64}H_{55}ClIrN_4O_3P_2]^+$: 1217.3067).

Ir-Py-RSL (1*R*,3*S*) (Ir3) (yellow powder, 88 mg, 64%):



^{1}H NMR (400 MHz, Acetone-d$_6$) δ 9.44 (d, J = 5.1 Hz, 1H), 8.16 (s, 1H), 7.63 – 7.58 (m, 1H), 7.39 (dd, J = 8.0, 3.0 Hz, 7H), 7.27 (dt, J = 20.6, 10.5 Hz, 20H), 7.10 – 7.03 (m, 11H), 6.20 (s, 1H), 4.35 (s, 1H), 4.09 (d, J = 31.0 Hz, 4H), 3.08 (s, 3H), 2.09 (s, 6H), -15.72 (s, 1H).
^{13}C NMR (101 MHz, Acetone-d$_6$) δ 205.2, 163.6, 147.8, 137.3, 136.6, 136.4, 133.8, 133.7, 133.7, 133.7, 133.6, 133.5, 130.5, 130.3, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 122.3, 121.7, 120.1, 119.3, 118.0, 111.3, 65.2, 51.9, 29.7, 29.5, 29.3, 29.1, 28.9, 28.8, 28.6, 28.4, 22.2, 14.7, 13.4.
^{31}P NMR (162 MHz, Acetone-d$_6$) δ 15.4.
HRMS (ESI, CH_3CN, m/z, relative intensity): 1176.2759 (calcd for [$C_{62}H_{52}ClIrN_3O_3P_2$] +: 1176.2802), 1217.2985 (calcd for [$C_{64}H_{55}ClIrN_4O_3P_2$] +: 1217.3067).

High performance liquid chromatography (HPLC)

HPLC analysis was performed on Shimadzu SPD-20A using Daicel Chiralpak IG-3 Column (particle size: 3 µm; dimensions: 4.6 mmI. D. x 250 mmL). Mobile phase is 95% islpropanol: 5% n-hexane, flow rate is 0.5 mL/min.

Circular dichroism (CD) spectra detection

All complexes were dissolved in tetrahydrofuran and the concentration was 10 µM. CD spectra were conducted on a Jasco J-810 spectropolarimeter. The spectra were made by Origin 2018.

Partition Coefficient, log $P_{o/w}$

Octanol-saturated water (OSW) and water-saturated octanol (WSO) were prepared by mixing analytical grade octanol and 1x PBS solution. Aliquots of stock solutions of the Ir complexes in OSW were added to equal volumes of WSO and shaken overnight. The aqueous and octanol layers were carefully separated into test tubes and analysed by UV-Vis spectroscopy. Partition coefficients were calculated using the equation:

$$\log P_{o/w} = \log([\mathrm{Ir}]_{\mathrm{WSO}}/[\mathrm{Ir}]_{\mathrm{OSW}})$$

Cellular uptake measurement

HT1080 cells were seeded onto 6-well plates (10^6 cells/well) for 24 h. 10 µM **Ir1** was added followed by incubation for 10 min, 20 min, 30 min, 60 min, and 120 min. Three repetitions were performed for each concentration. Then the medium was removed and washed 3 times with PBS. Cells were then collected for the detection of Ir content by ICP-MS.

Cytotoxicity and cell viability

The cytotoxicity of ligands, corresponding Ir(III) complexes, and cisplatin towards HT1080, PANC-1, HEK-293T, and HLF were determined using cell counting kit-8 (CCK-8) assay.
Cells were seeded in 96-well tissue culture plates (5000 cells per well) for 24 h and then incubated with different concentrations of complexes for 48 h. Subsequently, 10 µL of CCK8 was added per well and incubated for 4 h. Afterwards, the optical density (OD) was measured under 450 nm using a microplate reader (Tecan Infinite M1000 PRO). Half maximal inhibitory concentration (IC50) value was calculated using Graphpad prism analysis. All experiments were conducted three times to ensure the reproducibility of the results.

Cell death pattern

HT1080 cells were seeded in 96-well tissue culture plates (5000 cells per well) for 24 h and then 1 µM ligands and 10 µM Ir(III) complexes were added, respectively. Subsequently, 20 µM Z-VAD, 2 µM Fer-1, 40 µM DFO, and 25 µM Nec-1 were added separately and incubated for 48 h. Each group was repeated three times to ensure the reproducibility of the results. Cell viability was tested by the same procedure described above and calculated using the following formula:

$$\textbf{\textit{Cell viability}}\ (\%) = \frac{\textbf{\textit{OD Sample}} - \textbf{\textit{OD Blank}}}{\textbf{\textit{OD Control}} - \textbf{\textit{OD Blank}}} * \mathbf{100}$$

Cellular ROS and lipid peroxidation

Cellular ROS were detected using a Reactive Oxygen Species Assay Kit (KeyGEN BioTECH Co., Ltd., China) by the manufacturer's protocol. Briefly, HT1080 cells were seeded onto 6-well plates for 24 h and then treated with 10 and 20 μM solutions of **L1** and **Ir1** for 3 h, respectively. PBS was used as the control group. Three repetitions were performed for each group. Cells were then washed three times with serum-free Dulbecco's modified eagle medium (DMEM), probed with 10 μM DCFH-DA, and incubated in 5% CO_2 at 37 °C for 30 min. Cells were washed with PBS three times before being collected, and fluorescence detection was performed by the FL-1H channel on a flow cytometer (BD FACSCalibur). The lipid peroxidation level was determined using 5 μM BODIPY-C11 dye (Invitrogen, USA) by the same procedure as described above with 10 μM **L1** and **Ir1**, compared with 10 μM **L3**, **Ir3**, and PBS as the control.

Quantitative RT-PCR

HT1080 cells were seeded in 6-well tissue culture plates for 24 h. Then, 10 μM **Ir1** and PBS (control) were incubated with the cells for another 24 h. Cells were then washed once with PBS and collected by centrifugation. The total RNA was purified using RNA Extraction Kits (OMEGA, USA) according to the manufacturer's instructions, which was then used in a reverse transcription reaction using the Fastking RT Kit with gDNA (TIANGEN, China). Primers for qPCR were designed with Primer Express. Quantitative PCR was performed on triplicate samples in 96-well format using Power SYBR Green Master Mix (Takara, China) on an Applied Biosystems Cycler set to absolute quantification. The change in expression of a gene between the experimental and control conditions was computed using the ΔΔt method with actin as an internal reference gene.

Western Blot experiments

HT1080 cells were seeded in a 25 cm^2 cell culture flask for 24 h. 10 μM **Ir1** and 1 μM **L1** were added and incubated for 12 h, respectively. PBS-treated HT1080 cells were used as the control. The cells were washed three times with PBS before collecting. Whole-cell proteins were prepared by the Whole Cell Lysis assay kit (KeyGEN Biotech Co., Ltd, Nanjing, China), and the protein concentration was determined by the Super-Bradford Protein assay kit (CW Biotech, Inc., Beijing, China). The expression levels of GPX4 and FSP1 were then determined. Briefly, the extracts were first separated by 10% SDS-PAGE and transferred to a polyvinylidene difluoride membrane (BioRad, CA, USA). The membrane was blocked with 5% BSA in PBS at 25 °C for 2 h and then incubated with antibodies at 4 °C overnight. The expression of βactin was used as the internal standard. The primary antibodies against the following proteins were used: β-actin (A1978, 1:10,000 for WB) from Sigma; GPX4 (ab125066, 1:1000 for WB) from Abcam; FSP1 (aa114-163, 1:1000 for WB) from Gonxspan.

Mitochondrial Morphology Analysis

HT1080 cells were seeded in a 25 cm_2 cell culture flask for 24 h. 10 μM **Ir1** was added and incubated for 12 h. After washing with PBS three times, cells were collected and transferred to fixative, sliced, and imagined by TEM (Hitachi HT7700).

Fluorescence detection

All complexes were dissolved in DMSO and the concentration was 10 μM. The detection was performed by Shimadzu RF-6000 spectrofluorophotometer under 488 nm excitation. The spectra were made by Origin 2018.

UV-Vis spectra detection

All complexes were dissolved in acetonitrile and the concentration was 10 μM. The spectra were conducted on a Shimadzu UV-1800 spectraophotometer. The spectra were made by Origin 2018.

Intracellular localization monitoring and organelle colocalization imaging

HT1080 cells were seeded in confocal microscopy dishes for 24 h before adding 10 μM **Ir1**. After incubating for different times, the cells were washed with PBS three times and imaged in an Axio Observer Z1 ZEISS fluorescence microscope with Apotome2 software (λ_{ex} = 488 nm).

We chose the 90 min and 150 min time points group for further organelle colocalization imaging. Briefly, the cells were incubated with 2 μM MTR (λ_{ex} = 572 nm) for 15 min and then washed with PBS three times. Subsequently, 5 μM DAPI (λ_{ex} = 375 nm) was added for another 15 min incubation before washing three times by PBS. The cells were imagined by the same microscope above.

Quantification of iridium content in organelles

HT1080 cells were seeded in a 25 cm^2 cell culture flask for 24 h. Then incubated with 10 μM **Ir1** for 12 h and washed three times with PBS. Cells were collected by centrifugation and tested by inductively coupled plasma mass spectrometry (ICP-MS) to quantify the iridium content.

Label-free quantitative proteomics profiling

HT1080 cells were seeded in a 25 cm^2 cell culture flask for 24 h and then incubated with 10 μM **Ir1** and PBS (control) for 3 h, respectively. The medium was discarded and washed with PBS three times. Subsequently, cells were collected and one volume of SDT buffer (4% SDS, 100 mM Tris-HCl, 1 mM DT, pH 7.6) was used for sample lysis and protein extraction. The solution was boiled for 15 min and centrifuged at 14,000 g for 20 min. Protein digestion (200 μg for each sample) was performed according to the FASP procedure described by Mann et al. Briefly, the detergent, DTT, and other low-molecular-weight components were removed by using 200 μL of UA buffer (8 M urea, 150 mM Tris-HCl, pH 8.0) for repeated ultrafiltration (Microcon units, 10 kD). 100 μL of iodoacetamide (100 mM in UA buffer) was added to block reduced cysteine residues, and the samples were incubated for 30 min in the dark. The filter was washed with 100 μL UA buffer three times, and with 100 μL of NH_4HCO_3 (25 mM) twice. Finally, the protein suspension was digested with 4 μg of trypsin (Promega, USA) in 40 μL of 25 mM NH_4HCO_3 overnight at 37 °C, and the resulting peptides were collected as a filtrate. The peptides of each sample were desalted on C18 Cartridges (Empore™ SPE Cartridges C18 (standard density), bed I.D. 7 mm, volume 3 ml, Sigma), concentrated by vacuum centrifugation and reconstituted in 40 μl of 0.1% (v/v) formic acid. The peptide content was estimated by the UV light spectral density at 280 nm by using an extinction coefficient of 1.1 for 0.1% (g/L) solution and calculated based on the frequency of tryptophan and tyrosine in vertebrate proteins.

LC-MS/MS analysis was tested on a Q Exactive mass spectrometer (Thermo Scientific, USA) coupled to Easy nLC (Proxeon Biosystems, now Thermo Fisher Scientific). The peptides were loaded onto a reverse phase trap column (Thermo Scientific Acclaim PepMap100, 100 μm*2 cm, nanoViper C18) connected to the C18-reversed-phase analytical column (Thermo Scientific Easy Column, 10 cm long, 75 μm inner diameter, 3 μm resin) in buffer A (0.1% Formic acid) and separated with a linear gradient of buffer B (84% acetonitrile and 0.1% Formic acid) at a flow rate of 300 nl/min controlled by IntelliFlow technology. The mass spectrometer was operated in positive ion mode, and the ion scanning range was 300–1,800 m/z. The primary mass spectrometer resolution was 70,000 at 200 m/z and the AGC (automatic gain control) target was 3×10^6, the maximum inject time was 10 ms, and the dynamic exclusion time was 40 s. The mass/charge ratio of the polypeptide and polypeptide fragments was collected as follows: 20 fragments were acquired after each full scan, the MS2 Activation Type was HCD, and the Isolation window was 2 m/z. The rate was 17,500 at 200 m/z, Normalized Collision Energy 30 eV, and Underfill was 0.1%. In this study, we used the label-free quantification algorithm for quantification. The raw MS data were identified and quantified by using MaxQuant 1.5.3.17 software. The GO analysis was carried out with Blast2GO. KEGG pathway annotation on the target protein set was performed with KAAS (KEGG automatic annotation server) software. Protein subcellular localization was realized by using CELLO (http://cello.life.nctu.edu.tw/). Protein clustering was performed as follows: the quantitative information of the target protein set was normalized to the interval of (-1, 1). Then Cluster 3.0 software and Java Treeview software were used to perform hierarchical clustering analysis. Enrichment analysis was applied based on the Fisher' exact test, considering the whole quantified proteins as the background dataset. And only functional categories and pathways with p-values under a threshold of 0.05 were considered as significant. Protein-protein interaction analysis was based on IntAct database (http://www.ebi.ac.uk/intact/) by their gene symbols or STRING software. The results were further analyzed by Cytoscape software 3.2.1. All experiments were repeated three times to ensure the reproducibility of the results.

Toxicity tests *in vivo*

Balb/c mice (4-6 weeks old) were i.v. injected with **Ir1** (5 mg/kg) and ligand (1S, 3R) (5 mg/kg) separately via the tail vein. The mice were randomly divided into 3 groups and subjected to variable conditions. The blood of the mouse was collected at 7 d after injection for hematology analysis and serum biochemistry assay. Hematology analysis was measured on a Photoelectric MEK-8222K automatic five-class blood cell analyzer instrument. Serum biochemistry assays were performed using Urea Assay Kit, Aspartate aminotransferase Assay Kit, Alanine aminotransferase Assay Kit, and Lactate dehydrogenase assay kit (Nanjing Jiancheng Bioengineering Institute, China). The major organs (liver, spleen, kidney, heart, and lung) were harvested, fixed in 10% neutral buffered formalin, processed routinely into paraffin, sectioned at 8 mm, stained with hematoxylin and eosin, and examined by digital microscopy. The mice were weighed for 7 days.

Anti-tumor experiments *in vivo*

BALB/c female mice (6-8 weeks old) were injected HT1080 cells suspension in PBS (5 x 10^6 per mouse) subcutaneously into the armpit. After the HT1080 tumor model establishment, mice were divided into 3 groups. **Ir1** (5 mg/kg), **L1** (5 mg/kg), and PBS were respectively administered to the mice of each group intravenously via tail vein at 1 d, 4 d, and 7d. Tumor growth was monitored by measuring the perpendicular diameter of the tumor using a vernier caliper every three days and calculated according to the formula: Tumor volume (mm^3) = 0.5 × width^2 × length. The animals were sacrificed at 15 d after the first treatment then tumors were excised.

Supporting Figures and Tables

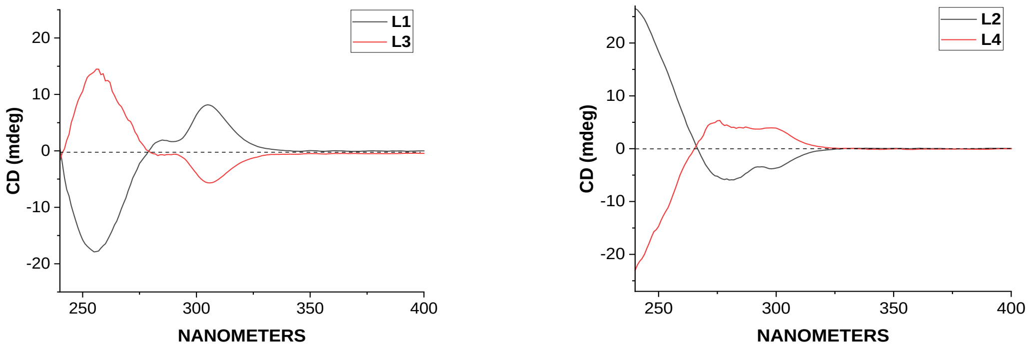


Figure S1. CD spectra of **L1**-**4**.

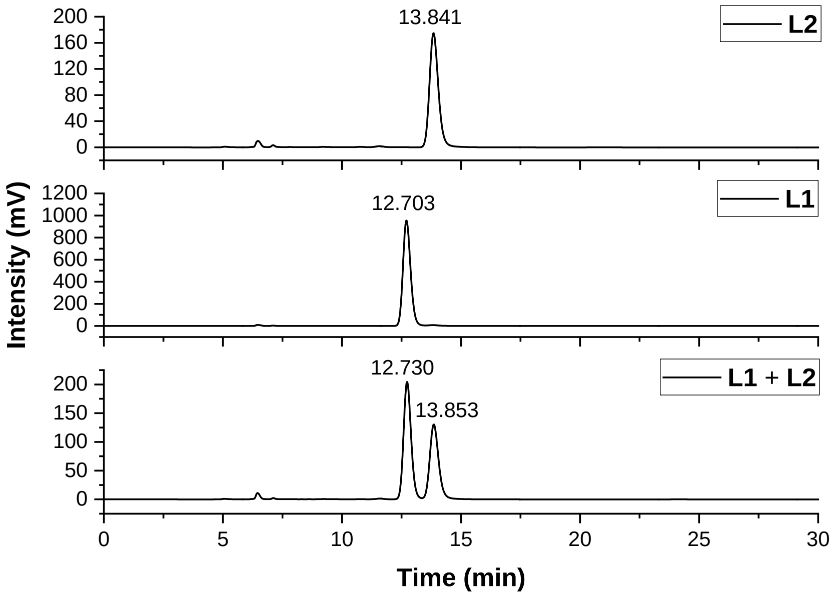


Figure S2. HPLC analysis of **L1** and **L2**.

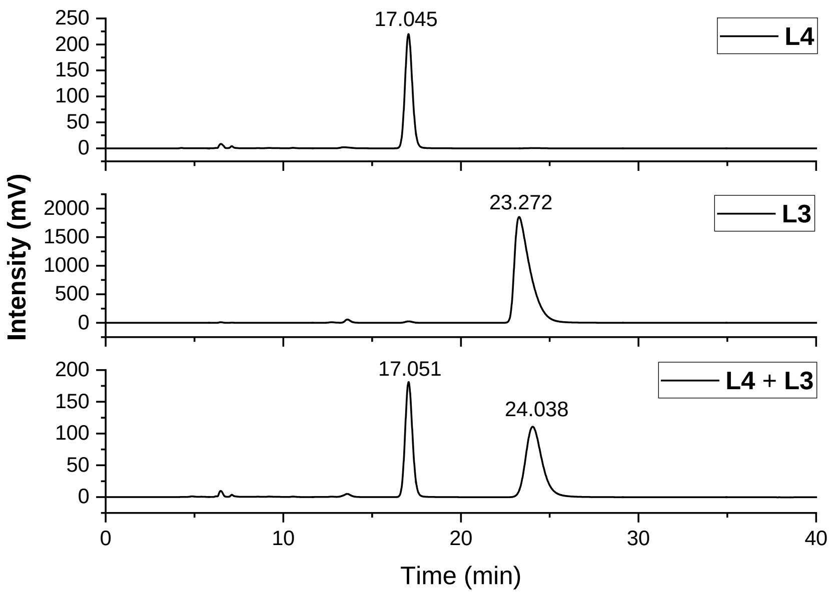


Figure S3. HPLC analysis of **L3** and **L4**.

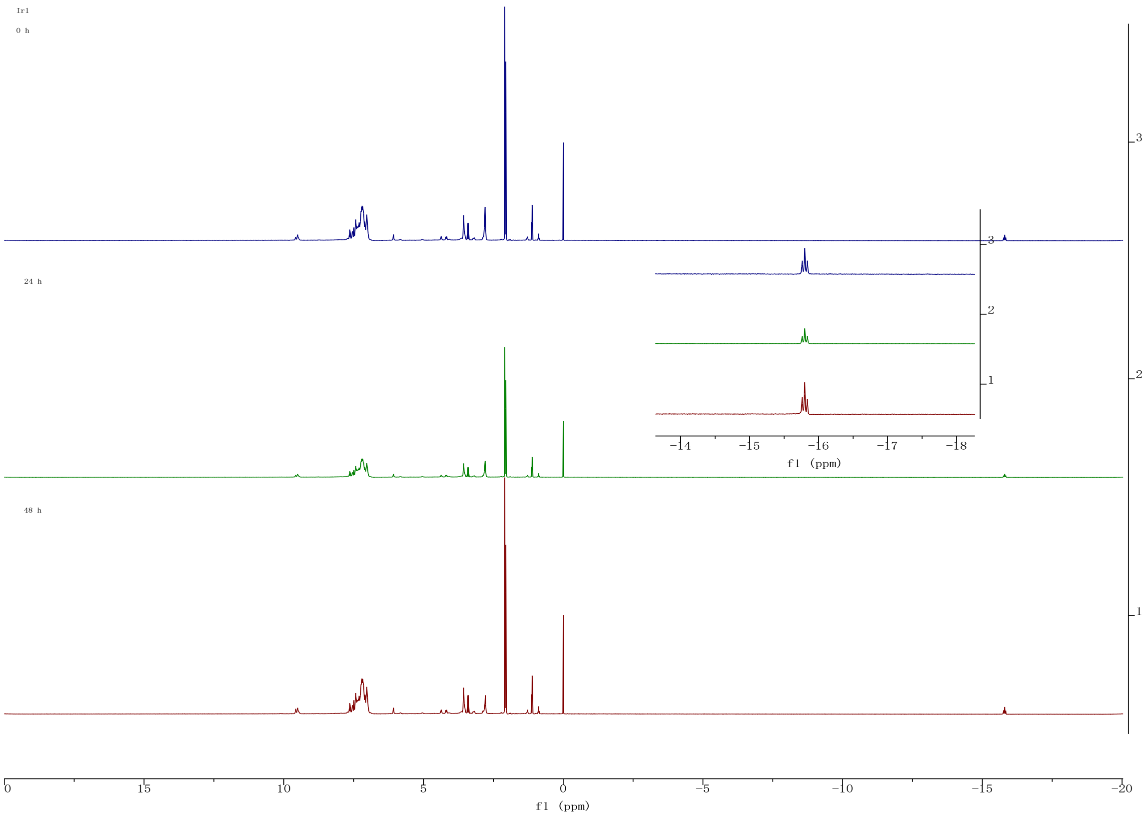


Figure S4. NMR spectra of **Ir1** in 0 h, 24 h, and 48 h at 37°C.

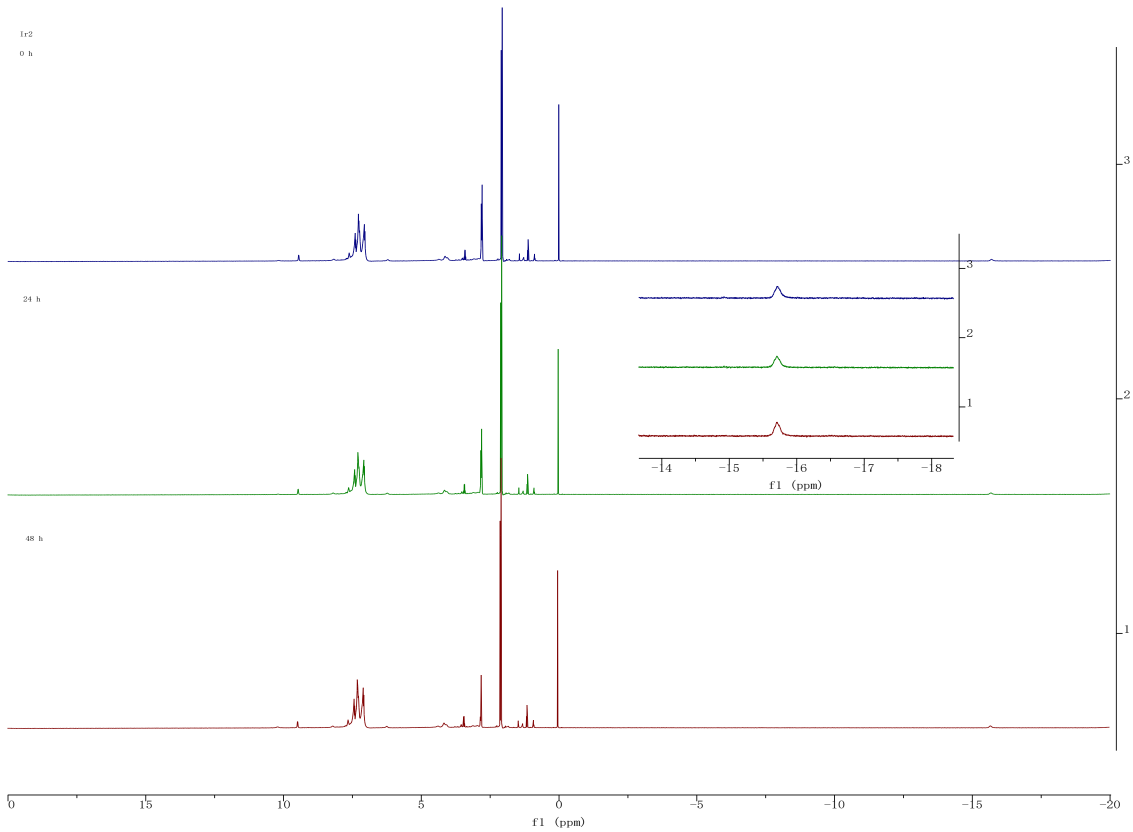


Figure S5. NMR spectra of **Ir2** in 0 h, 24 h, and 48 h at 37°C.

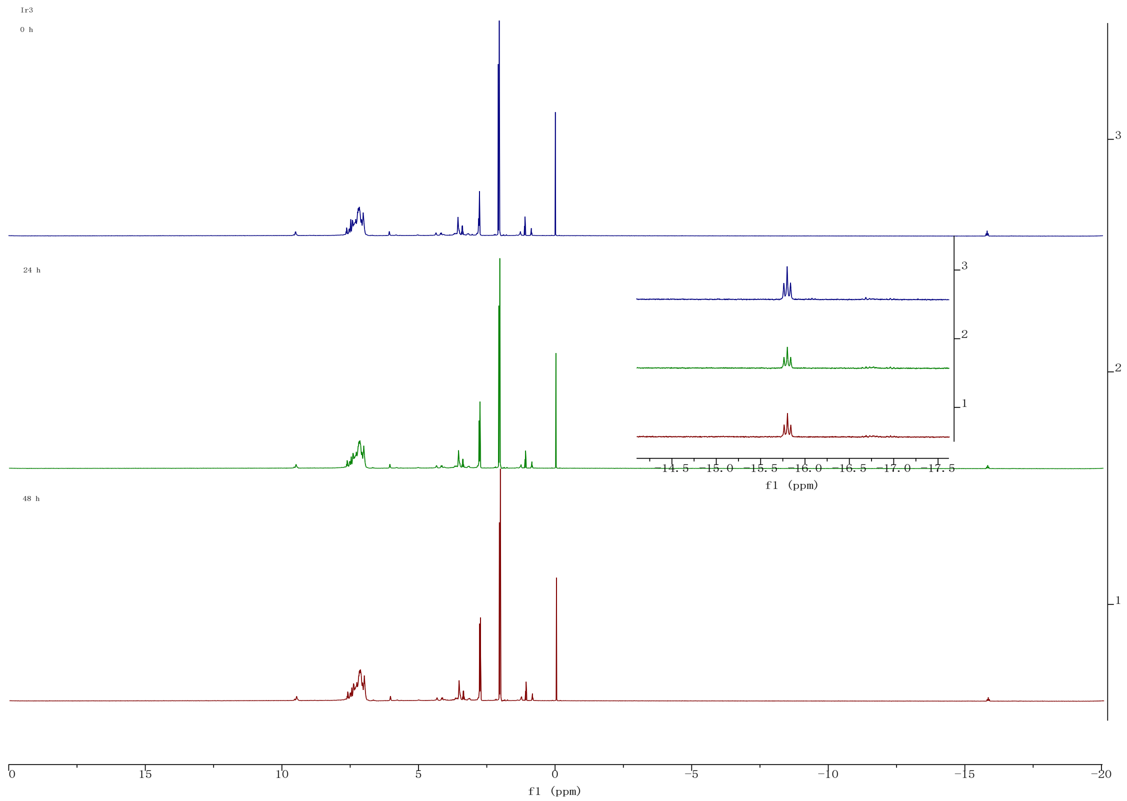


Figure S6. NMR spectra of **Ir3** in 0 h, 24 h, and 48 h at 37°C.

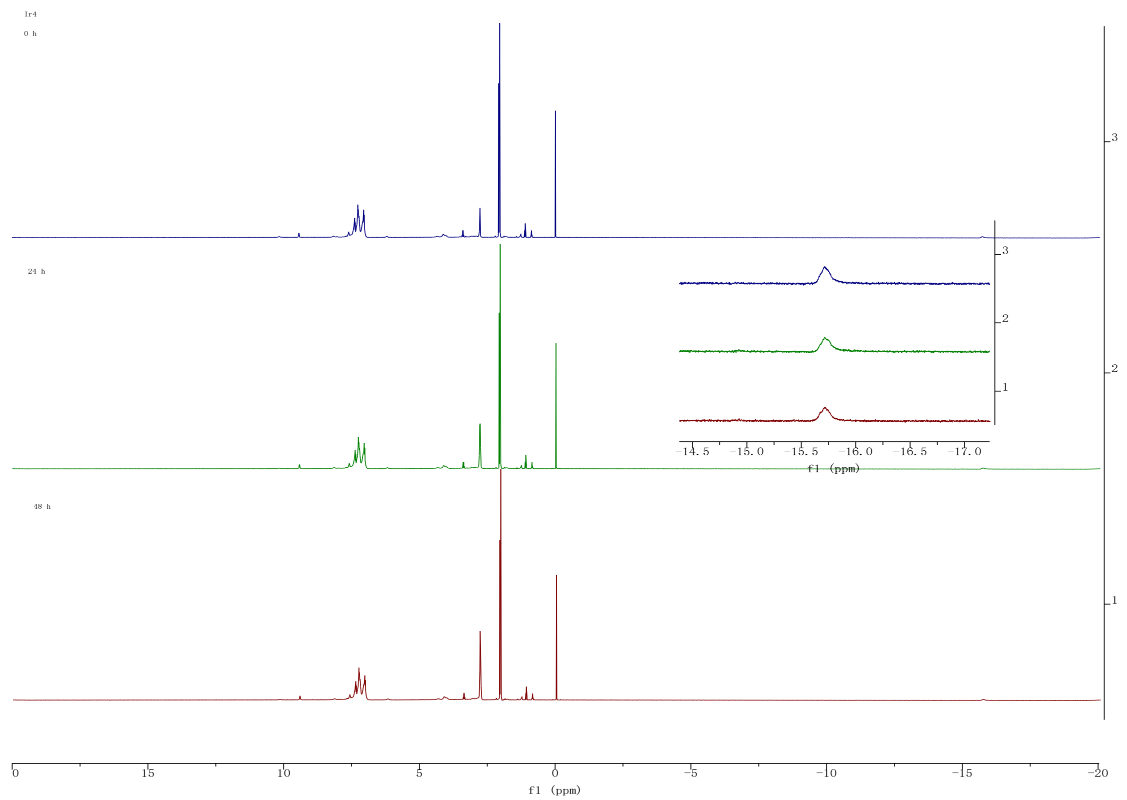


Figure S7. NMR spectra of **Ir4** in 0 h, 24 h, and 48 h at 37°C.

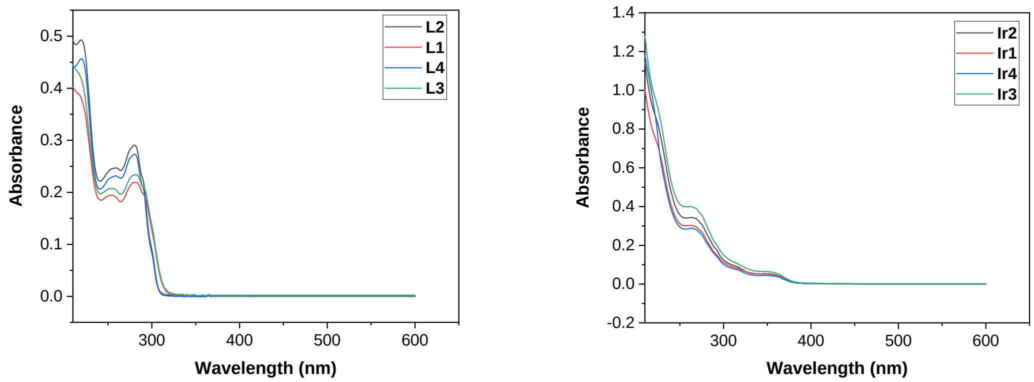


Figure S8. UV-Vis spectra of **L1-4** and **Ir1-4**.

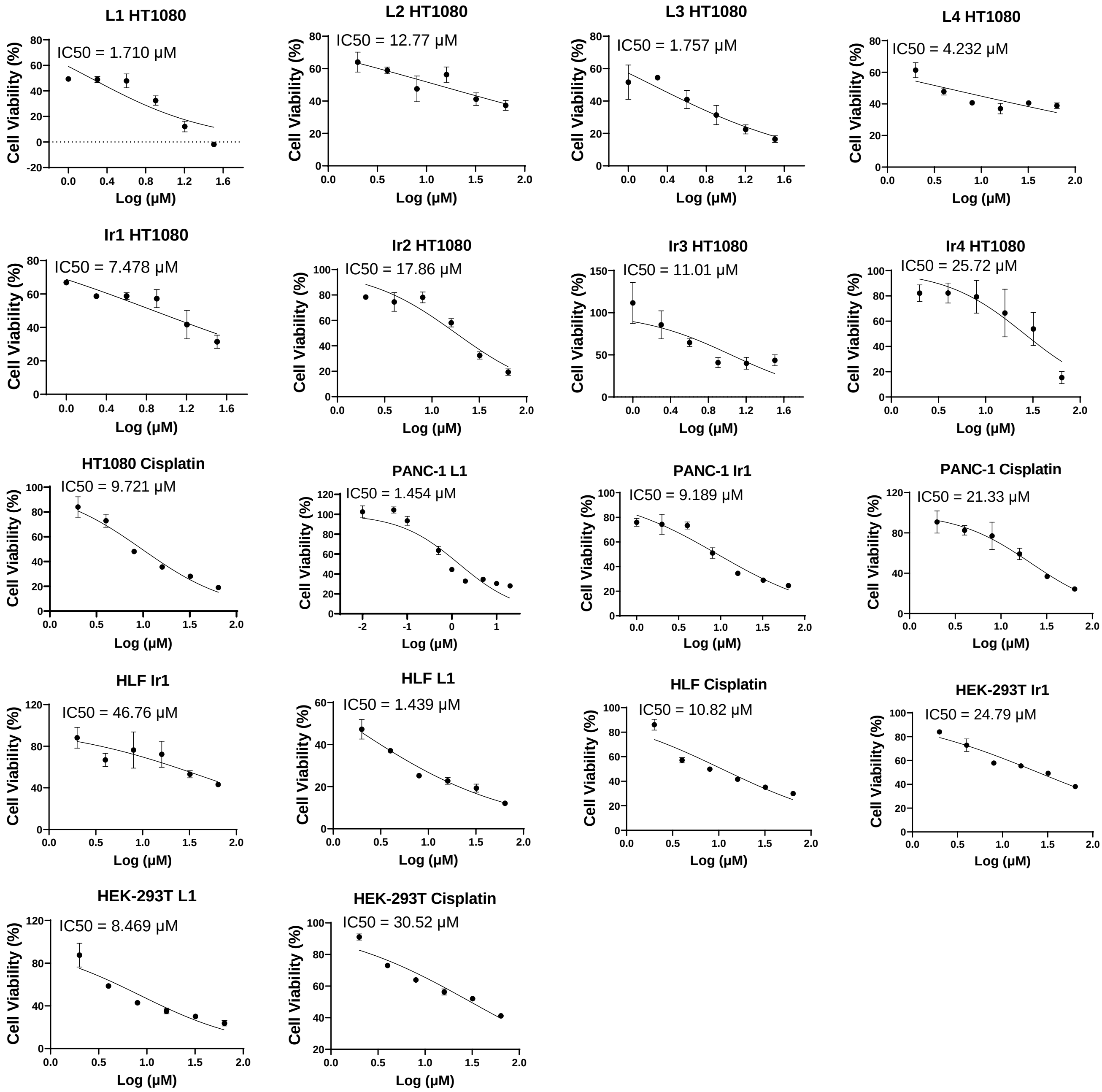


Figure S9. Dose response curves of all tested cellular toxicity.

Table S1. IC50 (µM) value of ligands and Ir(III) complexes towards HT1080 cells.

	IC50 (µM)	
L2	**L3**	**L4**
12.77	1.76	4.23
Ir2	**Ir3**	**Ir4**
17.86	11.01	25.72

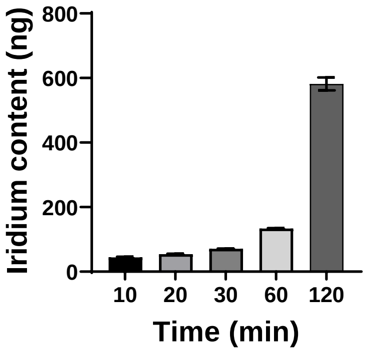


Figure S10. Cellular uptake of Ir1 during 120 min, the iridium content was count per 5 x 10^7 cells.

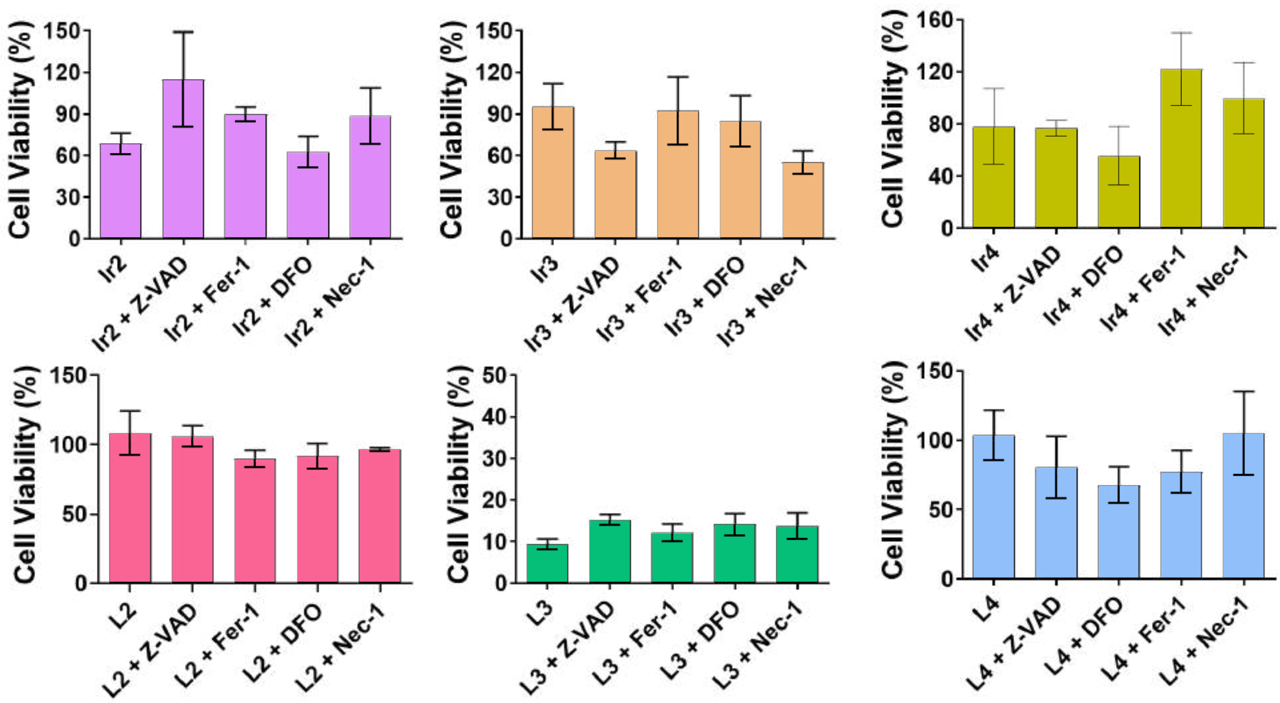


Figure S11. Viability of HT1080 cells treated with 10 µM Ir-Py-RSL/1 µM ligand, 10 µM Ir-RSL/1 µM ligand + 20 µM Z-VAD, 10 µM Ir-RSL/1 µM ligand + 2 µM Fer-1, 10 µM Ir-Py-RSL/1 µM ligand + 40 µM DFO, and 10 µM Ir-Py-RSL/1 µM ligand + 25 µM Nec-1 for 48 h. Values are expressed as the mean ± SD (n = 3).

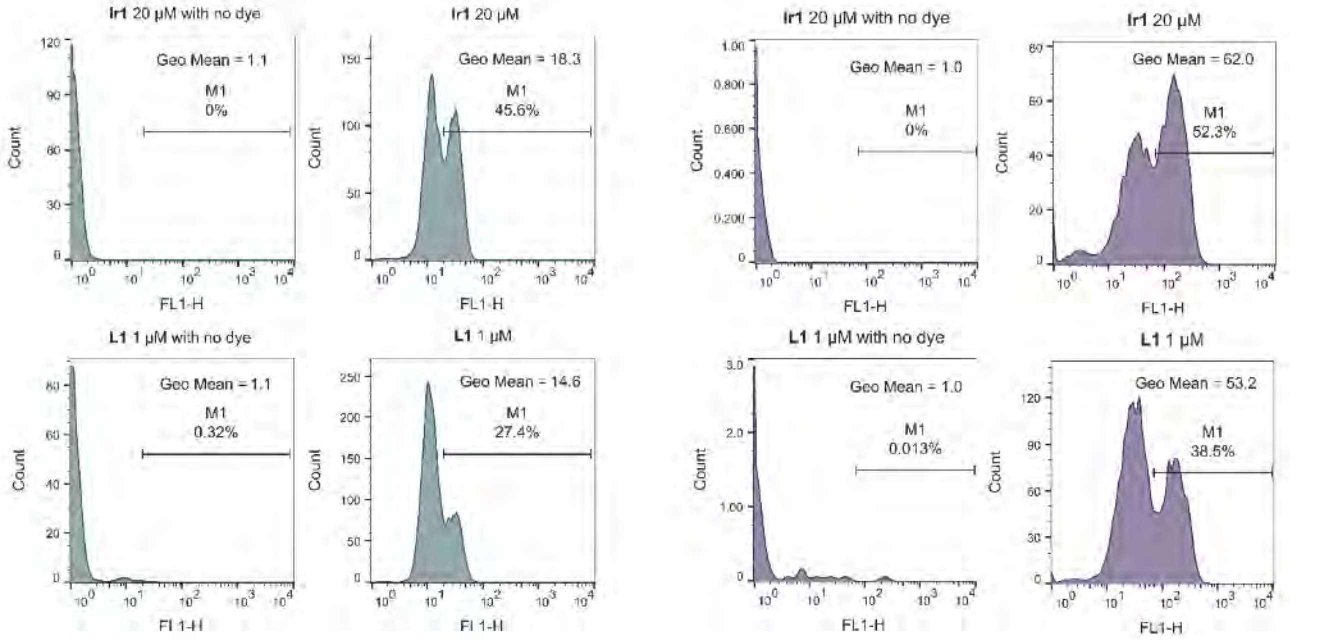


Figure S12. (Left) 1 µM **L1** and 20 µM **Ir1** with no dye, and lipid peroxidation in HT1080 cells treated with 1 µM **L1** and 20 µM **Ir1**, determined by BODIPY-C11 staining via flow cytometry after 3 h incubation. (right) 1 µM **L1** and 20 µM **Ir1** with no dye, and ROS production in HT1080 cells treated with 1 µM **L1** and 20 µM **Ir1**, determined by DCFH-DA staining after 3 h incubation.

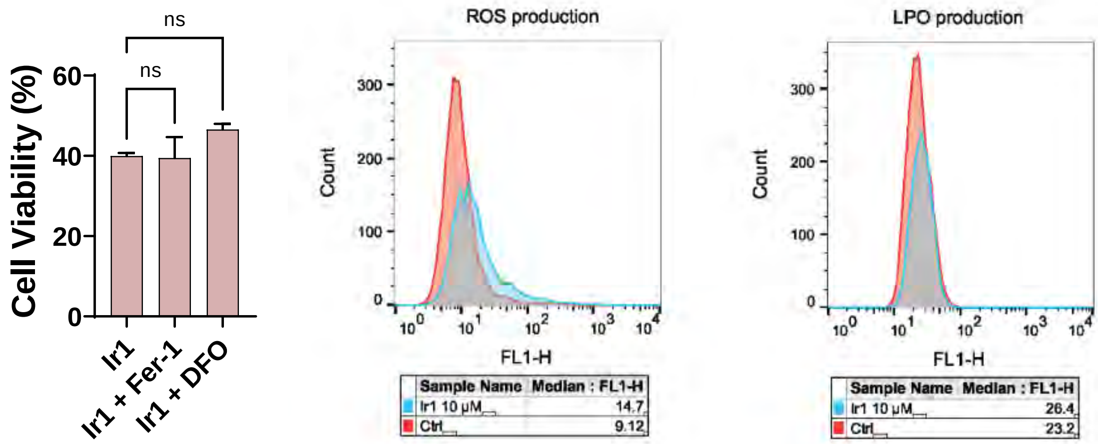


Figure S13. (Left) Viability of HLF cells treated with 10 µM **Ir1**, 10 µM **Ir1** + 2 µM Fer-1, 10 µM **Ir1** + 40 µM DFO for 48 h. (right) ROS and LPO production in HLF cells treated with 10 µM Ir1, determined by DCFH-DA and BODIPY-C11 staining respectively after 3 h incubation.

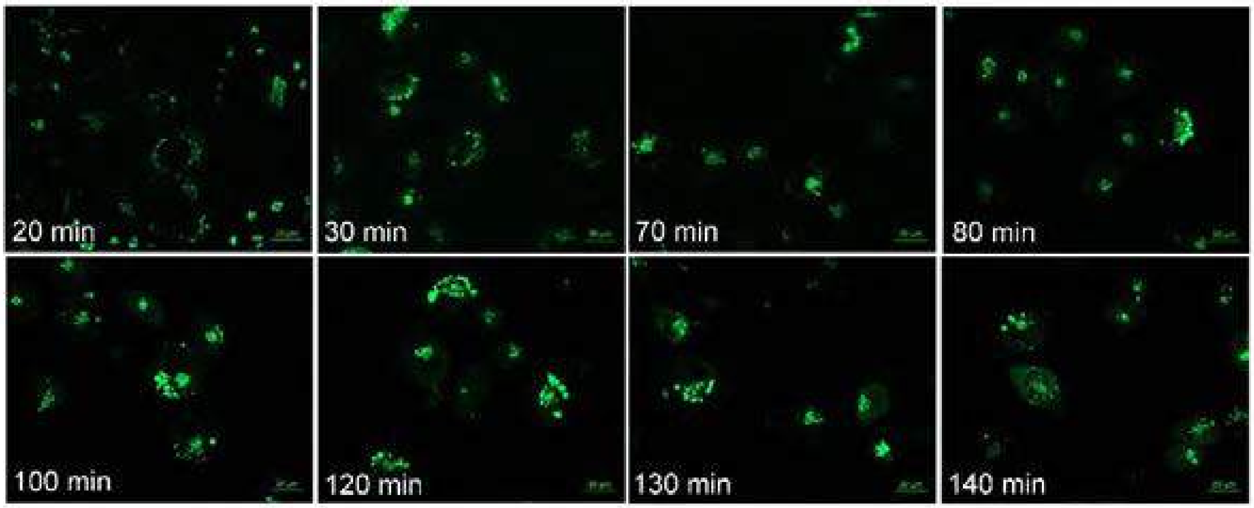


Figure S14. Microscope images of HT1080 cells at different time points after incubating with 10 µM **Ir1** ($\lambda_{ex/em}$ = 488/510 ± 20 nm); scale bar: 20 µm.

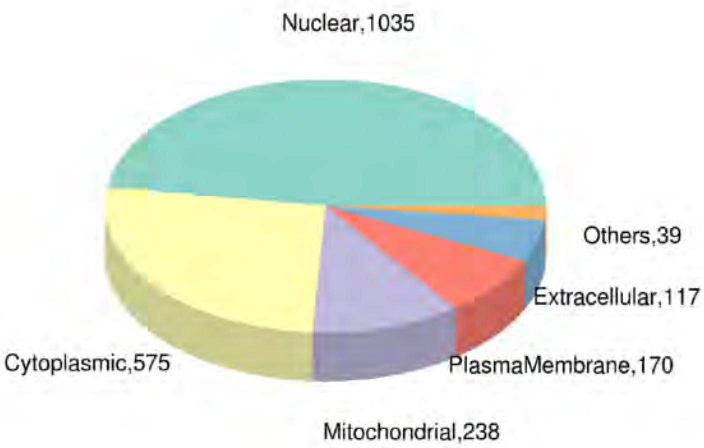


Figure S15. Subcellular localization of differentially expressed proteins of **Ir1**-treated HT1080 cells compared with PBS treated cells.

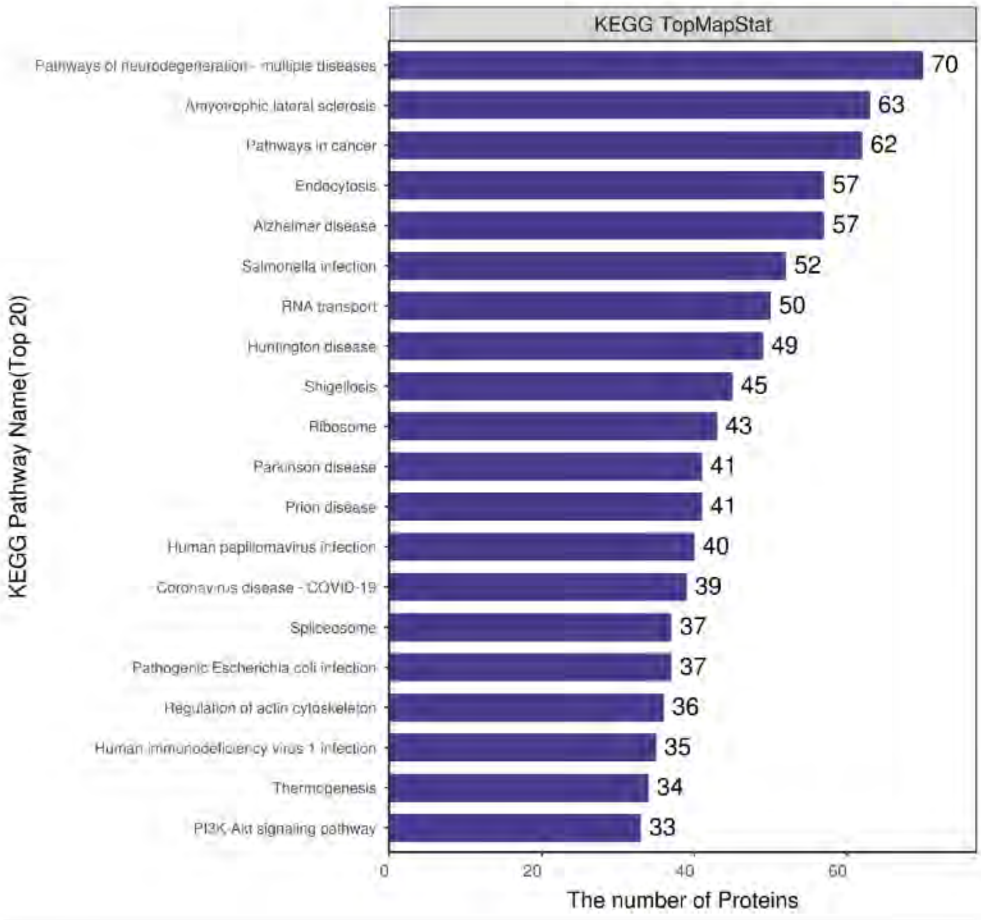


Figure S16. KEGG pathway annotation map of differentially expressed proteins (Top20) of **Ir1**-treated HT1080 cells compared with PBS treated cells.

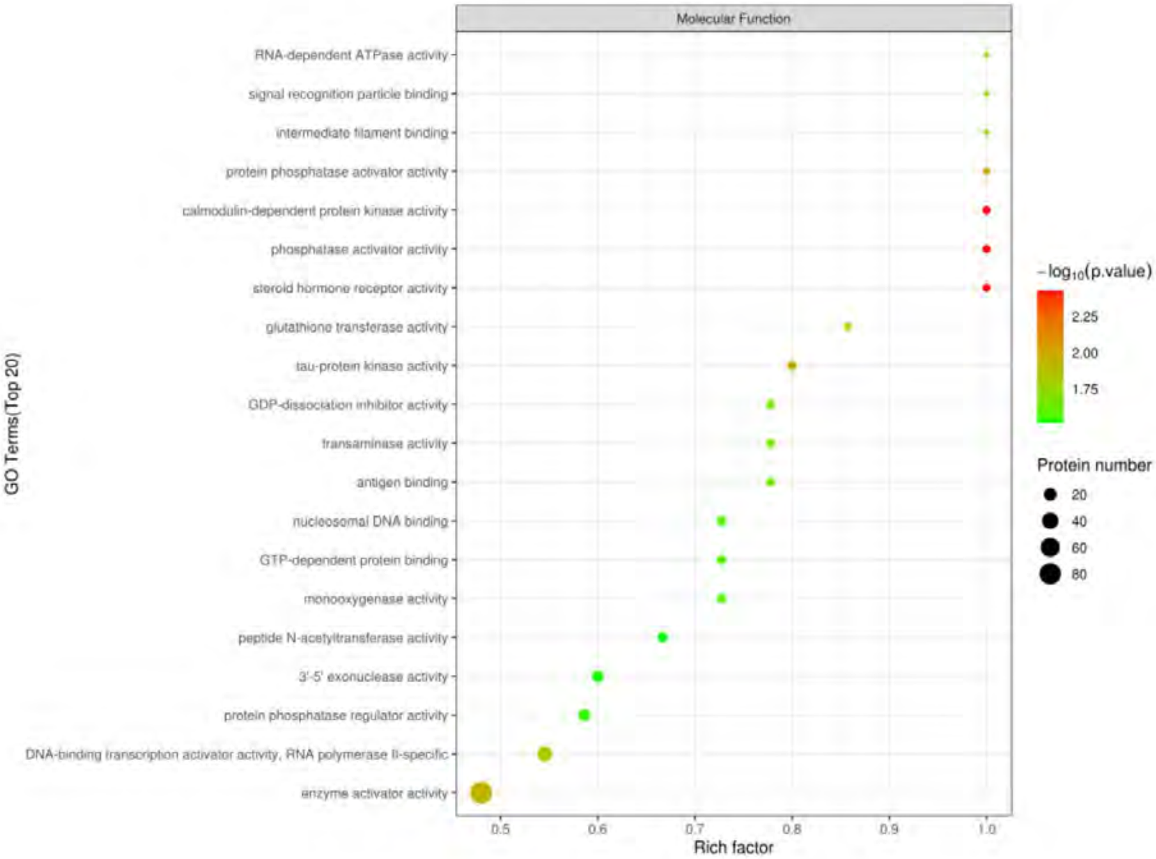


Figure S17. Group domain enrichment analysis diagram of molecular function between Ir1-treated HT1080 cells and PBS treated cells.

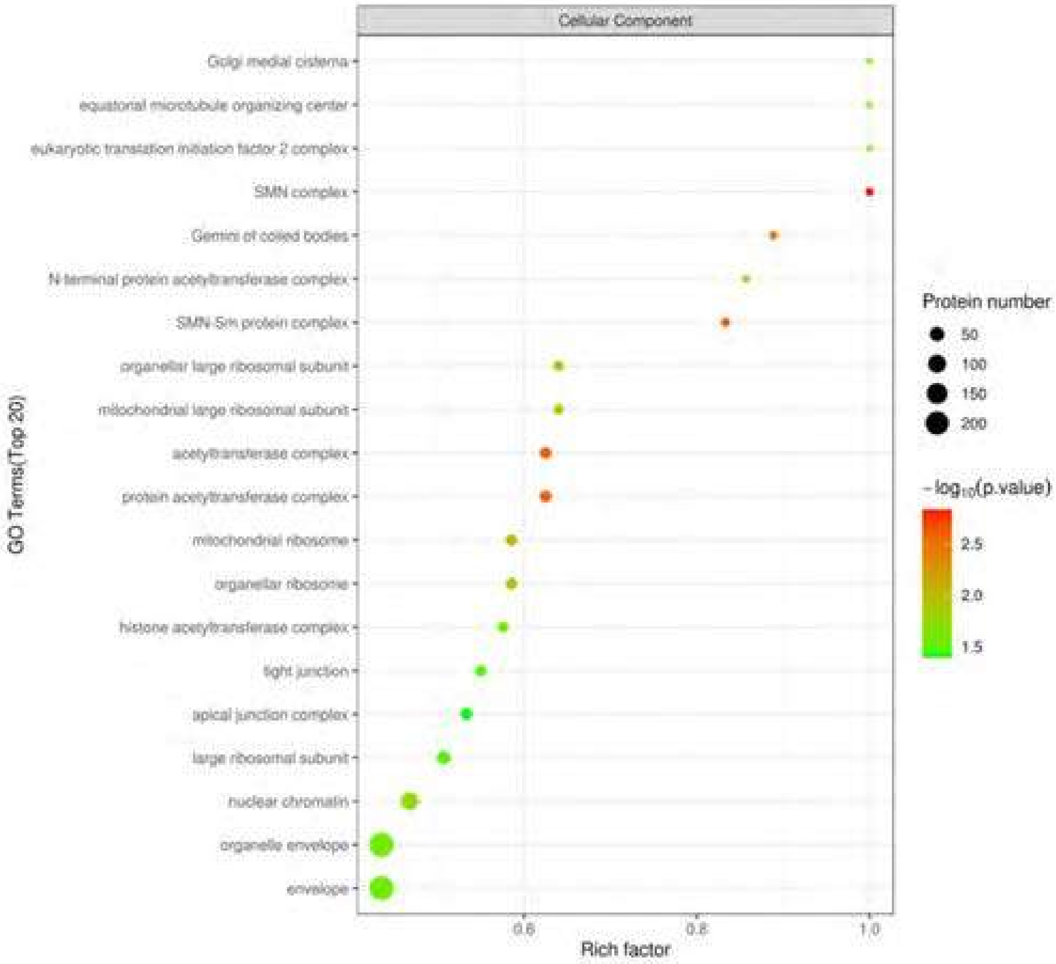


Figure S18. Group domain enrichment analysis diagram of cellular component between Ir1-treated HT1080 cells and PBS treated cells.

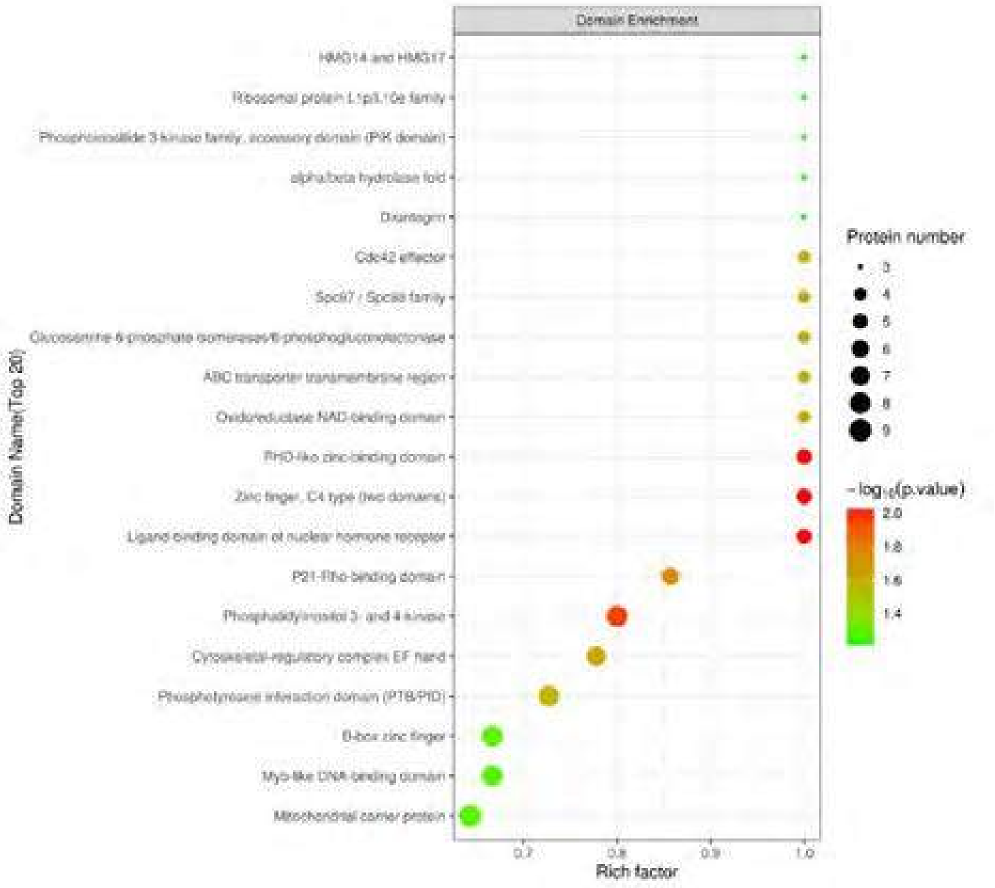


Figure S19. Group domain enrichment analysis diagram of protein domain between Ir1-treated HT1080 cells and PBS treated cells.

SUPPORTING INFORMATION

Table S2. List of destroyed proteins in **Ir1**-treated HT1080 cells compared with PBS treated cells by lable-free Quantitative proteomics analysis.

Protein name														
DOPD	RGPD3	MYO9A	RBG10	WASH6	CK098	AIP	STXB3	SMAP	RB27B	PSMD9	TAF4	HIP1	RPOM	EF2K
RTCA	P3C2A	EXOC5	PSDE	ZN593	BIN1	SDCB1	PIR	MA2B1	ACOD	TRAD1	UBFD1	BORG1	AP3D1	DVL2
GOSR2	ADA10	APAF	TR10B	TNPO2	GEMI2	CSKP	HGS	AURKA	ZN609	SYNJ2	ANR28	ARC1B	ARPC3	TIF1A
PGRC2	ACOX3	RER1	OGT1	HMGB3	IPO8	PINL	RPA34	NUP42	TTI1	RFOX2	ZW10	TGFI1	CTIF	VIP2
PRPF3	ERI3	IF4G3	HTRA2	MS18B	MED7	DENR	TPPC3	PRC1	NDUB3	BUB1	MAAI	SGTA	LANC1	STRN
U3IP2	IDH3B	KIF1C	ORC4	PEX1	ZN292	SI1L3	TBCD4	GSDME	VINEX	EXOC3	IMA7	TPST2	CCD22	PQBP1
OPHN1	ABCB7	CAPON	N4BP1	OBSL1	T22D2	ZN217	SH3L1	TRIM3	SPAG7	KATL1	PAGE1	EED	PRKRA	KS6A5
ERAL1	SPB7	SURF6	CRTAP	RENR	RNH2A	CD123	CBR3	ATRN	STAM2	PIAS2	SPF27	SPF30	CBPD	GFPT2
LTN1	MYO1D	TOX4	UFL1	FRYL	HAUS5	RHBT3	SOGA1	WDR47	AP2A2	YIF1A	MFN2	SPN1	NDUA7	ZRAB2
SNX4	KI20A	GOSR1	CCDB1	NDUAA	6PGL	ATG7	TACC2	ARI2	PSMG1	G6PE	SC24A	SC24B	PPR3D	HERC2
TTC4	BAG3	TRUB2	BCL10	NDUBA	PAK4	NB5R3	UROK	TPA	RASN	LDLR	TGFB1	RAF1	GLCM	OAT
ARLY	PCCA	IF4E	TPM3	CENPB	MCR	NFIC	STS	TPM1	TFPT	JMJD7	ERPG3	TBA3C	ARAF	MGST1
GTR1	GTR3	EPB41	BCR	ACADM	ERR1	HEM2	CCNB1	PO2F1	QCR7	PVR	UCHL3	NDKA	GNS	TIMP2
CBR1	BGAL	FER	NAGAB	PTN2	NELFE	LFA3	NDUV2	RO52	TFE3	CSK22	CCNA2	IMDH1	RASA1	SDHB
FBRL	CBL	MAOM	PTPRG	DGKA	CCND1	COT2	PPAC	MYL9	CDK2	BRD2	TNR6	TYY1	MK03	MARK3
P85A	PSB8	LYOX	TEAD1	RXRB	ERCC5	GRN	T2EA	SHC1	3MG	BLVRB	2AAB	PURA2	UFO	AMRP
GDIA	RIR2	ZEP2	AKT2	ELF1	MRP1	RFA3	RFC1	GDE	ARL2	HEM6	TGFR1	GPX4	NUP62	ZEB1
SMBP2	TXLNA	PBX2	CETN2	IPP2	KPCI	ACTY	STAT6	MTOR	PI4KA	RBM34	CDN2C	ECE1	SATT	SSRA
RANG	NAMPT	ACDSB	MK09	IF2M	GSTM5	GNPI1	LIMS1	PI42A	PSMD8	KC1D	DHYS	UB2R1	SRP09	PCY1A
PPM1F	PRI1	NUMB	HINT1	GSK3B	TAF6	MTHFS	GNAQ	ERF	MAP2	KNTC1	LRBA	PAPOA	RT29	DUS3
SMCA2	GALK1	SSRD	AL3A2	SPHM	VAMP7	MAT1	GDS1	VAV2	RBM5	HXK2	CRIP2	TXTP	ARFP2	NUBP1
MOT1	DPOG1	BLM	UBP14	HSP72	IF5	S12A2	LAMB2	SCOT1	BID	ATP5I	PEX3	GEMI4	NU107	ARPC4
RAB5B	RAP2B	MAX	PSME3	MGN	RHOA	NAA20	STXB1	SUMO2	UFM1	AP1S1	PP1A	SELT	TBPL1	RS30
GNAI1	DYLT1	CSK2B	TBA4A	SHPS1	CP4F2	RPP38	ADA17	NUCB2	RT34	RT09	COG7	DAB2	VLDLR	XIAP
EFNB1	TF2B	CDK5	CDK17	BORG5	FOXK2	GALK2	MEF2A	PYRD	PLOD1	TOP2B	KMT2A	CENPC	TAP1	CEBPZ
TLE3	CSTF1	FAK1	CTSL2	P2R3A	GFPT1	EXOS9	SUH	GABPA	TISB	S20A2	NCBP1	EP300	CPSF1	TEF
WASC5	AKP13	CDC20	STX4	TRAP1	TRAF2	PP1R8	ABR	CDC16	CAF1B	LIPA1	PRDX4	DDX10	SRSF6	G3BP1
IFIT5	MTA1	CTBP1	PHLP	RM49	ORC2	ADAM9	FKBP5	MTX1	ASAH1	ATR	KCC2D	CUL4A	FCL	RAB32
FHL1	FHL3	LAMC2	TBB2A	IDI1	PEBB	NFYC	KGP1	CDK13	KCC1A	SCRB2	DSG2	SEPT6	MORC3	ARHG7
MLEC	TFDP1	NPAT	EI2BA	ITPR1	ESPL1	MDC1	2A5D	MEF2D	ZN638	CUL7	SLMAP	NAA25	PSMD6	MO4L2
CND1	SUZ12	SYLM	SNX17	RB3GP	DPOD3	PCM1	PTPA	PWP2	RABE1	RBP1	L2GL1	TTF1	ELOC	DHC24
PUM3	KS6A1	PP1R7	SKIV2	TRADD	TRIP6	NAB2	MSMO1	ITSN1	VPS72	ETFD	PKN2	2A5E	MK14	RM23
SYPL1	KCC4	RBBP7	TAF9	MEA1	CEGT	KAT1	CAH9	NDUA9	RTN1	PCKGM	DGUOK	CL16A	AAK1	TYSD1
CTU2	DB115	TRM5	EMAL3	GRDN	GLYR1	VP26B	NAKD2	TB10B	FA98B	FND3B	GPAT3	NCBP3	SNUT2	P5CR3
BOREA	COBL1	ACTBL	DCAF6	YIF1B	HERC4	PP6R3	MTX3	EMC4	WDR44	PCID2	HABP4	NU188	FKB15	HECD3
CAMP1	ACBD5	WLS	INT11	CODA1	AHDC1	PR14L	RPRD2	MYOME	BROX	FOCAD	NAA35	CARL1	ZMYM4	KANK2
LPCT4	TBC9B	ARID2	HAUS3	SLN13	C19L1	CYTSA	ATLA3	IQEC1	ZFAN6	CNDH2	LRC8E	RETST	RINT1	NEPRO
ZCHC8	M18BP	ERAP2	S27A4	TATD1	EDC4	SCYL2	RHGBA	NFRKB	FAHD1	RL22L	PDXD1	INT5	S27A1	PSRC1
TTC37	TMM65	IN80C	TRI65	CC137	S2547	F111B	NHS	MIC27	PACS1	HACD2	KAT3	YJ005	S31E1	CCD9B
TM1L2	VP13C	RAPH1	MOB2	RS27L	INT8	MARK2	MEPCE	SYPM	MAEA	TAOK1	3BP5L	KDM3B	MICA3	DYM
RM21	VP35L	POGZ	MON2	DHX29	LRP10	HDGR2	RAI1	CCD91	SEN54	KHDC4	TMED4	CENPV	T179B	TBCD1
SETD3	NOP9	MTA70	PB1	YRDC	SAPC2	GP180	COMD7	CHD1L	NR2CA	CCD25	PRSR2	AROS	ANKL2	DDX42
C2CD5	HPS6	RIOX2	CCD71	ERI1	FMNL3	FABD	MGAP	GCC2	PHF6	LRC8A	SKA3	RM41	RB12B	RPAP2
PLPL6	CKP2L	EXOC8	TRI22	P20D2	KATL2	MICU2	AN13A	PHAR4	TRM2A	RUSD2	ABI1	TTC5	RPTOR	PORIM
NDUF2	DOCK4	INT1	ABD12	GPD1L	MILK1	VPS8	MPP5	ZCHC9	ARFG2	KTAP2	EFNMT	GPT11	RM43	ASCC1
BANP	ZBT38	AVL9	XXLT1	SUMF2	PGLT1	UBAC2	DHB11	ATAD1	SCPDL	NOA1	NECP1	FA98A	SEN2	PDPR
Z280C	EHBP1	PHC3	NGDN	DP13B	NAV1	PPHLN	SYNE1	UBP32	ARI1B	NUP37	NEDD1	SNIP1	FBX30	PUM2
GOGA5	UBA3	RDH11	LRC20	TRPM4	DMXL2	GNPI2	LRC8C	RBCC1	MICA1	GEMI5	PARD3	PP4R1	UBS3B	ZC3HF

TF3C2	TB22A	RAB2B	CHPT1	F172A	CHUR	TM263	CO040	CTF18	LEO1	DCAKD	PHIP	ATRIP	PSPC1	SYNE2
TITIN	TM158	LZIC	IRGQ	PSMF1	SNX19	TM9S4	PRP16	RT31	AKAP1	AN32B	NECT2	PGTA	PRCC	ARC1A
STAM1	DPF3	SYMPK	GGH	COR2A	CELF1	UFD1	SMRD2	GCDH	TNPO1	UBP13	KPBB	SCAM4	HPS3	SMCE1
YIPF5	PIGT	ZN622	WBP2	LFG3	CCD47	SYAP1	SO4A1	SKA1	OTUL	ZN775	ATG2B	FBXL8	ACSF2	GCC1
FXRD1	GCP3	OTUB2	SNR40	ATG4C	SPDLY	SIR1	YIPF6	SEH1	RM53	RNF31	MITOK	SGF29	DNJA3	MB12A
MMAB	CYFP2	CDCA5	DYL2	OTUB1	HMCES	CKLF7	DUS3L	LTV1	AURKB	TOE1	A7L3B	MTNB	ZCCHL	PRR11
GRM2B	SAHH3	GMPPA	SC22A	ATPMD	MET2A	ITCH	KIRR1	WNK4	CK5P3	VPS39	VPS50	VCIP1	ELMO2	TMX3
ZFP91	CLMN	BT3L4	DNJC1	EHMT2	EP400	NSUN5	ARAP1	TPPC9	SMG1	TM237	KI20B	UIF	MAGI1	SPAG5
NACC1	VP13A	EFGM	ERBIN	MTL26	PRPK	WRIP1	RANB9	PKHF1	SMC6	TM209	CP2S1	IWS1	SIN3A	RSF1
RBM15	MINT	CYH2	PCY2	NEUR1	SORT	DNJC2	SCAFB	TTC1	RGPD5	DOK1	PI51A	S29A1	FOXC2	GDF15
ARP5L	CMS1	MEP50	APOL2	NUD12	BUD13	RM45	CG050	CAB45	PDD2L	PYM1	MIC25	RIOK1	LLPH	SLD5
NTPCR	GCP2	UBAC1	EFC4B	CHCH5	CNPY3	MTG1	PSMG3	FSD1	TBCD	THTPA	ISCA1	PDC10	EFHD1	DDX23
BDH2	MTND	RN126	CP250	PBDC1	TMED9	SPA5L	RIOK2	TMUB1	NUP85	HIRP3	YJU2	NUDT9	REPI1	RPAP1
SF3B5	PAPOG	NADAP	RFIP5	B2L13	HDHD5	MAK16	CADM1	RM13	RM04	RM01	NEUL	SETD2	ASPC1	OSBL8
OSBL6	RAB34	WDR11	EDEM3	TRIM5	ZDHC5	UBE2O	WDR33	YIPF3	REXO4	CTDS1	IF5A2	MFF	UBA5	T126A
SP130	CSTFT	CYRIA	MAGT1	SMG9	ING2	TMX4	ASCC2	ISCU	ATG5	VPS16	VPS11	PPIL3	PDCL3	TAOK3
ADNP	RM46	BACD3	TCAL2	NELFA	BORG4	OSGP2	DEFI6	TRABD	SENP3	CC134	CCD86	MYH16	DHX33	YTDC2
ES8L2	RPAP3	ALG9	LDAH	RANB3	PEAK1	AAMDC	DOCK5	TDRD3	AT133	SFR19	GEMI7	MINY3	JUPI2	GHC1
SPE39	COG4	CSN7B	KT3K	SYCM	UBTD1	MYG1	RISC	ZFYV1	TENS1	S38AA	TM165	EPG5	MSL2	PLXA4
SYF1	PREB	SSU72	SYSM	MYNN	EXOS4	UBE2T	CHSTB	OSGEP	DMAP1	DCP1A	LZTL1	TIGAR	CYLD	RPR1B
MYO5C	SAS10	DBLOH	AAAS	ABCBA	BAZ1A	METL5	UBQL4	PLCC	LANC2	F207A	BMP2K	ABHDA	T106B	ABCF3
CC50A	PARVA	TBC13	INT13	WDR70	PHAG1	PK1IP	OXSM	RM22	CZIB	HPF1	TM160	NHP2	OCAD1	MARH5
IMPA3	SIR5	NSMA3	NDE1	QPCTL	DJB12	ALKB4	NSE4A	TE2IP	RM39	TMOD3	MS18A	GTSE1	ERAP1	ARP10
USE1	TLS1	SMAL1	SPG21	PTTG2	MTCH1	ITSN2	NOP53	EHD3	ARHGC	CNOT2	MPP6	CHMP5	CRIPT	HACD3
PDP1	SENP1	SH3B4	SEP10	RELCH	UBP36	STK26	ARMX1	ZNFX1	CPSF2	ANFY1	HOP2	MBD2	NCDN	TFP11
MTRR	SPAST	GRHPR	CATZ	MO4L1	ZMYM2	DIC	MALT1	CFDP1	ADDG	ABCF2	AAKG2	GCP4	SYWM	DPOLL
Z3H7B	TCF20	NDRG3	ARMX3	SUN2	TBK1	PCYOX	DDX20	SHPK	BAP29	NB5R1	S30BP	PRAF1	TAGL3	BAZ2A
PSIX4	PLXA1	NGAP	CMC2	DDX41	APC7	APC4	GGA1	TASOR	PTBP2	CPSF3	BORG2	TF3C4	NUP50	CNO11
DSE	BAG5	DNPEP	NWD2	YETS2	ISY1	KMT2B	SYNRG	PCDGG	CHIP	MINP1	S12A4	EXOC7	ZC3H4	FOXJ3
HPS5	NEUR3	SCML2	ZN148	MTMR6	GLCNE	PIN4	PSF2	CNPY2	OFUT2	DLGP4	SAC2	WDR37	RRP44	LRCH1
RCL1	GSTK1	RT07	PDIP2	COG6	TMX2	LSM2	PHOCN	RM11	CIA2B	PTH2	STA13	T22D4	ZN330	RL36
TRRAP	C170B	ARI1	RN114	PPME1	RBM7	TIM22	PAXB1	CERT	TF3C3	RBM8A	SNX11	TRUA	NCOR2	ALG5
FKBP7	GMEB1	SPCS1	MTCH2	BIG2	MD1L1	TAF6L	NEMO	S4A7	NCOA3	NUMBL	M3K4	DDX49	MORC2	S23IP

Table S3. The significant difference proteins (fold change > 2.0, P value<0.05) in **Ir1**-treated HT1080 cells compared with PBS treated cells by lable-free Quantitative proteomics analysis. Statistical significance was assessed using Student's *t*-test.

Protein	Gene Name	Unique Peptides	Ir-RSL/Ctrl	t test p value
Q16777	H2AC20	1	16.62540833	0.027167133
O95391	SLU7	5	14.67911937	0.005294149
Q96MX6	WDR92	2	13.10224283	0.000353459
Q96BR5	COA7	3	11.43761384	0.008945779
P35580	MYH10	14	10.40871386	0.023072019
Q92922	SMARCC1	3	9.929590717	0.000149806
Q9ULX6	AKAP8L	3	9.918802532	0.000309694
P43304	GPD2	7	9.104018798	0.000095509
Q8TDX7	NEK7	2	8.032643892	0.012957685
Q9Y5L4	TIMM13	1	7.797441984	0.003116738
Q641Q2	WASHC2A	7	7.240243523	0.029744064
Q2TAY7	SMU1	9	7.21591588	0.015295377
Q9BUJ2	HNRNPUL1	10	7.136205867	0.007828943
P84103	SRSF3	4	7.122423833	0.036619981
O96008	TOMM40	3	7.037985941	0.000927857
Q13555	CAMK2G	1	6.866203513	0.014373597
P49840	GSK3A	1	6.680996127	0.023505224
P05387	RPLP2	7	6.645033717	0.006435894
Q14699	RFTN1	5	6.542045413	0.001209736
O75691	UTP20	10	6.353161118	0.003055572
O60573	EIF4E2	1	6.236239708	0.005862549
O14907	TAX1BP3	3	6.235929303	0.000081558
Q9H1E3	NUCKS1	3	6.176145827	0.002463717
Q9NX63	CHCHD3	8	6.113241934	0.005857611
Q9UJM3	ERRFI1	1	6.065053482	0.024537848
Q08945	SSRP1	6	6.028221816	0.000638651
P78318	IGBP1	5	6.008981112	0.03240828
Q9UL25	RAB21	2	5.933701388	0.008741182
P49207	RPL34	5	5.784685539	0.000967468
Q3MHD2	LSM12	2	5.511713237	0.028423949
P62304	SNRPE	1	5.346643016	2.421109823
P61006	RAB8A	3	5.164647116	0.001561588
Q13011	ECH1	3	5.114015685	0.004935692
P05120	SERPINB2	5	5.110852999	0.007929302
Q9UKY7	CDV3	8	5.005933977	0.038353935
Q8TAT6	NPLOC4	7	4.959348776	0.010131656
P09132	SRP19	3	4.953895324	0.028924156
P61981	YWHAG	9	4.914045012	0.005633992
Q15813	TBCE	4	4.882023374	0.001928653
P08621	SNRNP70	8	4.856826774	0.000177945
P35269	GTF2F1	8	4.852224129	0.015621569
O75844	ZMPSTE24	3	4.810259838	0.003366096
O95816	BAG2	7	4.748127062	0.000186467
Q9Y5J1	UTP18	4	4.744172308	0.049915657
Q5BJE1	CCDC178	2	4.517137796	0.000102712
Q6SPF0	SAMD1	4	4.475980522	0.049435603
Q5VTU8	ATP5F1EP2	2	4.460077063	0.000206171
Q9NPL8	TIMMDC1	2	4.43575671	0.0065032
Q86U42	PABPN1	6	4.385992674	0.014255112
P27824	CANX	15	4.384086504	0.012327278
Q9H330	TMEM245	1	4.342399228	0.024326705
Q14696	MESD	3	4.25716511	0.002302258
O76021	RSL1D1	20	4.221954878	0.002058074
P41227	NAA10	4	4.214555279	0.000778229
P05386	RPLP1	1	4.196495903	0.001924115
Q16637	SMN1	2	4.189617819	0.000058047
Q68EM7	ARHGAP17	5	4.189420652	0.003161216
Q96I59	NARS2	1	4.136109157	0.001910123
P51148	RAB5C	3	4.102296382	0.002948386

Q15428	SF3A2	3	4.095785009	0.015766272
P10109	FDX1	1	4.085991357	0.000356373
P23588	EIF4B	21	4.055036366	0.001554749
Q99623	PHB2	12	4.049809249	0.021721839
P30084	ECHS1	5	4.025743805	0.041875977
Q96AG4	LRRC59	7	4.010878285	0.015344837
P00441	SOD1	5	3.980683984	0.02327747
P60709	ACTB	1	3.963858026	0.003738997
P45880	VDAC2	8	3.942400114	0.015722572
A1L0T0	ILVBL	3	3.898243886	0.00923444
Q92769	HDAC2	4	3.880935792	0.003114828
Q9UMY1	NOL7	1	3.873440379	0.004886284
P61106	RAB14	6	3.861018234	0.006145315
Q9UI10	EIF2B4	7	3.858971028	0.006189137
Q9BYG3	NIFK	6	3.807547544	0.027056012
P11233	RALA	4	3.801051039	0.000189935
Q14011	CIRBP	2	3.790512178	0.005103725
Q15291	RBBP5	3	3.773812261	0.000447535
Q06323	PSME1	6	3.765708135	0.012566361
P26196	DDX6	5	3.744091014	0.026699706
Q16698	DECR1	4	3.732471546	0.000874143
P54709	ATP1B3	5	3.670885545	0.014617354
Q92804	TAF15	5	3.653500227	0.008635344
P18887	XRCC1	6	3.635476652	0.011828403
Q9NQT5	EXOSC3	1	3.633107562	0.000023843
P63220	RPS21	3	3.580544897	0.008474961
Q9BQ52	ELAC2	3	3.558224533	0.02758849
Q96N66	MBOAT7	4	3.549474905	0.005524467
P51159	RAB27A	4	3.53303708	0.002373524
Q9Y3B2	EXOSC1	2	3.518504815	0.019830164
P05114	HMGN1	5	3.508359592	0.01039766
Q9Y5Y2	NUBP2	1	3.493325794	0.000303214
P62820	RAB1A	3	3.49088243	0.005168472
O60341	KDM1A	6	3.465199515	0.024381544
O00541	PES1	9	3.423289757	0.030688582
Q9BZK7	TBL1XR1	6	3.411364915	0.029951966
Q9NZL4	HSPBP1	4	3.399524975	0.009119014
Q02218	OGDH	9	3.39606616	0.044592702
P33316	DUT	6	3.390159323	0.002899408
Q15286	RAB35	3	3.384742259	0.010824102
Q9NQT4	EXOSC5	2	3.377476483	0.000013401
P08579	SNRPB2	3	3.370441748	0.000835779
Q9Y5Q8	GTF3C5	2	3.342121174	0.011847329
Q9UI09	NDUFA12	2	3.337334682	0.022593136
O00148	DDX39A	3	3.319533363	0.003689435
Q9HAV0	GNB4	2	3.317022242	0.00308352
Q9UKV3	ACIN1	21	3.304002419	0.037411338
Q9P121	NTM	4	3.288097013	0.026691039
P36957	DLST	10	3.273095144	0.009031258
P07305	H1-0	7	3.269579555	0.000065335
Q92522	H1-10	5	3.256488003	0.000135097
P08559	PDHA1	6	3.253652015	0.002052639
P20645	M6PR	4	3.235379955	0.00144049
Q16836	HADH	4	3.235178971	0.000151679
Q16643	DBN1	12	3.229570579	0.000907126
Q9C0D9	SELENOI	1	3.18370573	0.000057449
P55327	TPD52	4	3.178208227	0.00736893
Q9NQ55	PPAN	6	3.176586049	0.006049841
Q12797	ASPH	12	3.166477942	0.020358318
P0DP25	CALM3	10	3.158111393	0.009403645
P80723	BASP1	8	3.141962252	0.002280066
Q96GX5	MASTL	2	3.131990764	0.019966798
P50454	SERPINH1	4	3.131236142	0.029035571

P06756	ITGAV	6	3.097270847	0.003733708
Q14146	URB2	4	3.084550454	0.00313124
P07910	HNRNPC	16	3.043287748	0.002583225
P26599	PTBP1	9	3.036238587	0.038670014
P05204	HMGN2	7	3.023422479	0.000503962
O43164	PJA2	5	3.022274345	0.006291585
Q9H0D6	XRN2	8	3.009336014	0.002398702
Q9Y266	NUDC	15	2.991826182	0.004065602
O00139	KIF2A	3	2.982874774	0.022974373
Q10471	GALNT2	6	2.975032306	0.031072744
Q07666	KHDRBS1	5	2.967468479	0.009006735
Q0VDF9	HSPA14	4	2.961967292	0.000265416
Q8N1G2	CMTR1	4	2.960819582	0.000879877
Q9H0U4	RAB1B	3	2.949965827	0.031781907
Q9Y3L3	SH3BP1	6	2.945997016	0.017329923
Q8IVL6	P3H3	5	2.929936975	0.002767323
P04183	TK1	3	2.913901642	0.004343424
P60660	MYL6	7	2.902991504	0.000729672
Q9BWD1	ACAT2	4	2.902366165	0.001772982
Q96FQ6	S100A16	1	2.896526632	0.048674009
Q71UI9	H2AZ2	2	2.886507339	0.015215503
Q9BWM7	SFXN3	5	2.885568554	0.000724473
P13010	XRCC5	15	2.869164765	0.000442202
Q9Y5V0	ZNF706	1	2.833020179	0.049211942
Q9NR12	PDLIM7	7	2.830574376	0.027299805
P31946	YWHAB	7	2.828184979	0.027199421
Q13263	TRIM28	21	2.823978727	0.000213448
Q9Y6I3	EPN1	3	2.822677248	0.001568929
P56182	RRP1	6	2.80669766	0.028420138
P17812	CTPS1	8	2.805873158	0.009412645
P20962	PTMS	2	2.804129802	0.003393856
Q9Y3E0	GOLT1B	2	2.796450018	0.000193894
O95747	OXSR1	5	2.789489646	0.007534983
Q7Z2K6	ERMP1	3	2.781322477	0.034376662
Q13185	CBX3	6	2.774047877	0.025674214
P49406	MRPL19	2	2.769395341	0.00047136
P07237	P4HB	22	2.746697642	0.000104834
Q9HCG8	CWC22	5	2.744892106	0.021433546
P38159	RBMX	4	2.734684142	0.002478576
Q05682	CALD1	19	2.732917458	0.016635522
P11387	TOP1	11	2.729258581	0.022392219
P37235	HPCAL1	3	2.723829894	0.010683153
P84085	ARF5	3	2.719484549	0.015059521
Q6NYC8	PPP1R18	14	2.675032906	7.064832660
O43615	TIMM44	9	2.666419124	0.015563331
Q15645	TRIP13	4	2.651944355	0.000059392
Q13428	TCOF1	30	2.646198773	0.001756493
Q6NUK1	SLC25A24	9	2.64000566	0.004205347
O00629	KPNA4	3	2.62179136	0.009022506
Q9NR45	NANS	3	2.618834991	0.00518211
O15231	ZNF185	18	2.617757449	0.0040696
P08237	PFKM	6	2.601930087	0.000806017
P86791	CCZ1	2	2.596870332	0.044992425
Q14978	NOLC1	17	2.595096195	0.000214781
Q9Y4Y9	LSM5	1	2.58665792	0.010223688
Q92508	PIEZO1	2	2.586383075	0.032473804
O95373	IPO7	8	2.578266307	0.006182445
P04439	HLA-A	2	2.576774966	0.000341951
Q5JRA6	MIA3	11	2.564721534	0.003768135
Q16186	ADRM1	7	2.558461254	0.000290825
P84090	ERH	4	2.554626985	0.004557449
O76094	SRP72	11	2.551884152	0.005282451
P35232	PHB	12	2.549259385	0.012607106

P49588	AARS1	23	2.549061181	0.000147837
O00399	DCTN6	1	2.54501237	0.004726329
Q9H9A6	LRRC40	4	2.528424004	0.004432753
Q14254	FLOT2	7	2.527303995	0.000559936
Q15642	TRIP10	6	2.525576708	0.046365557
O14530	TXNDC9	3	2.523521293	0.034120852
Q6IN85	PPP4R3A	9	2.520075179	0.005128009
Q99575	POP1	8	2.517362897	0.000922472
P07741	APRT	5	2.516665733	0.021581103
O95470	SGPL1	5	2.510249684	0.003693409
P30419	NMT1	5	2.507717628	0.026686888
Q9UNN5	FAF1	6	2.506761447	0.009034306
O00472	ELL2	1	2.49365019	0.018239957
Q13045	FLII	15	2.492100557	0.003398022
Q66K74	MAP1S	7	2.491209408	0.018099248
Q9GZZ1	NAA50	6	2.490710188	0.031143334
P20290	BTF3	6	2.488992027	0.009107492
Q16706	MAN2A1	4	2.46706497	0.001156625
O00425	IGF2BP3	12	2.432097158	0.038636203
P18621	RPL17	5	2.431315203	0.027364059
Q96D71	REPS1	6	2.418433314	0.012048006
Q9UKK9	NUDT5	5	2.417056043	0.001994837
Q9UHB6	LIMA1	26	2.416996734	0.025215409
P31943	HNRNPH1	4	2.414068325	0.002393629
Q8IY18	SMC5	6	2.407764342	0.004724566
O00571	DDX3X	14	2.402448633	0.001312445
Q5JTV8	TOR1AIP1	8	2.40030681	0.028445893
P52594	AGFG1	5	2.397284808	0.000773148
Q9NZQ3	NCKIPSD	3	2.391161347	0.013909239
P78358	CTAG1A	2	2.385901799	0.010446516
Q9P0J7	KCMF1	2	2.384676414	0.002584149
O60506	SYNCRIP	10	2.379955206	0.001684493
P49755	TMED10	3	2.372514432	0.029571194
P62879	GNB2	2	2.36467867	0.01144188
P55081	MFAP1	3	2.359353575	0.002785137
Q3LXA3	TKFC	3	2.351126572	0.012553793
Q9HCC0	MCCC2	6	2.348782651	0.00946697
Q8ND24	RNF214	6	2.345389635	0.034757077
P12270	TPR	44	2.345135863	0.00065694
Q05519	SRSF11	3	2.340228309	0.023218187
Q92945	KHSRP	21	2.338725812	0.039049015
P17844	DDX5	11	2.329846355	0.000335192
P56945	BCAR1	4	2.308922844	0.014679676
Q8IZL8	PELP1	8	2.30506144	0.014051267
P35611	ADD1	11	2.302314022	0.010424711
P62195	PSMC5	10	2.302211138	0.001603302
P33993	MCM7	15	2.294774476	0.000386053
P01889	HLA-B	1	2.282181118	0.000508921
Q14677	CLINT1	8	2.277499459	0.036348804
Q9UBC2	EPS15L1	11	2.277042985	0.030800253
Q9NVZ3	NECAP2	4	2.275963663	0.005003128
O60927	PPP1R11	2	2.268254165	0.032203913
P61964	WDR5	5	2.266274741	0.001379837
Q8TCJ2	STT3B	6	2.26329082	0.003670055
Q15599	SLC9A3R2	5	2.258479368	0.03566484
Q7L0Y3	TRMT10C	5	2.257456802	0.000015858
Q13107	USP4	2	2.252090185	0.02120145
Q8WXA9	SREK1	3	2.244169679	0.003544745
Q13838	DDX39B	3	2.233809851	0.001903542
P23786	CPT2	7	2.230518661	0.022873287
Q08379	GOLGA2	5	2.225769117	0.011823814
Q9UHD9	UBQLN2	2	2.224406027	0.00282144
Q9UI26	IPO11	3	2.216866908	0.013999519

Q9HCN4	GPN1	3	2.216253866	0.023703068
Q13123	IK	7	2.21238389	0.016742937
Q8NFH3	NUP43	3	2.204043972	0.025570266
P61916	NPC2	4	2.195887109	0.001182574
P07737	PFN1	9	2.19160925	0.005097988
Q16891	IMMT	24	2.177727101	0.002921041
P33992	MCM5	10	2.175465127	0.031736855
Q9H0H5	RACGAP1	8	2.163122214	0.030528966
Q8NEB9	PIK3C3	7	2.149071167	0.013563735
O00429	DNM1L	7	2.14790087	0.000509782
Q9P2E9	RRBP1	45	2.133244472	0.000075602
P54886	ALDH18A1	12	2.129937752	0.010718842
P62333	PSMC6	6	2.125759304	0.00047056
P26641	EEF1G	17	2.110429987	0.000838768
P62277	RPS13	7	2.107011395	0.002585098
O94826	TOMM70	12	2.100675074	0.041985278
Q15434	RBMS2	4	2.100434807	0.002380404
P55884	EIF3B	12	2.096428216	0.00101644
Q9Y2W1	THRAP3	14	2.086145162	0.012635246
Q9H0S4	DDX47	4	2.086078072	0.001244591
P52926	HMGA2	4	2.080686873	0.048401427
O75746	SLC25A12	3	2.066501987	0.030309843
Q9Y399	MRPS2	3	2.058259994	0.03211717
Q99832	CCT7	19	2.053641052	0.006534338
Q9Y2U8	LEMD3	5	2.036895189	0.009030198
P50991	CCT4	18	2.025807066	0.01358645
P42566	EPS15	6	2.022344448	0.00875958
P41252	IARS1	16	2.016395281	0.008949474
P22234	PAICS	11	2.016136784	0.001052458
O95831	AIFM1	10	2.014189227	0.046338011
Q5C9Z4	NOM1	7	2.010677268	0.028054039
Q9Y314	NOSIP	3	2.00438904	0.002663226

Table S4. The significant difference proteins (fold change < 0.5, P value < 0.05) in **Ir1**-treated HT1080 cells compared with PBS treated cells by lable-free Quantitative proteomics analysis. Statistical significance was assessed using Student's *t*-test.

Protein	Gene Name	Unique Peptides	Ir-RSL/Ctrl	t test p value
P35249	RFC4	7	0.495181882	0.01413393
P20042	EIF2S2	9	0.493958392	0.003358787
Q06830	PRDX1	11	0.493460294	0.031846812
Q07157	TJP1	14	0.492129097	0.034457051
Q6IBS0	TWF2	4	0.490352645	0.001785583
Q8WUD4	CCDC12	2	0.486669423	0.043524791
P00338	LDHA	12	0.486357683	0.008677597
P62316	SNRPD2	5	0.483533988	0.01620608
P13861	PRKAR2A	7	0.478616584	0.003543698
Q9P0K7	RAI14	17	0.474372124	0.00054637
O95202	LETM1	9	0.472631525	0.014237424
Q13242	SRSF9	5	0.470805397	0.016742836
Q9P2B4	CTTNBP2NL	6	0.464161591	0.01086049
Q04837	SSBP1	4	0.463821105	0.046989151
O15067	PFAS	10	0.463597058	0.00155677
P04150	NR3C1	7	0.459868336	0.010625226
P23528	CFL1	9	0.456296929	0.011276392
O75874	IDH1	7	0.447058574	0.020746053
P17655	CAPN2	8	0.443566353	0.032785802
P61604	HSPE1	10	0.442834284	0.014946407
P05198	EIF2S1	13	0.437902874	0.000466785
Q9UPN3	MACF1	77	0.437273047	0.027928887
P10599	TXN	5	0.436236987	0.0305643
Q12792	TWF1	3	0.433882701	0.000704597
Q9BY77	POLDIP3	8	0.428820453	0.014062021
P31942	HNRNPH3	3	0.428302919	0.001477171
Q9NTJ5	SACM1L	8	0.421338156	0.004434408
O00592	PODXL	6	0.418898614	0.013061073
P40429	RPL13A	9	0.413185955	0.035397537
P09874	PARP1	21	0.40952248	0.031660041
P12081	HARS1	7	0.406737197	0.027483038
Q9UJU6	DBNL	8	0.406100303	0.001740486
P08670	VIM	41	0.403542032	0.009619732
Q15075	EEA1	39	0.398856692	0.022049042
Q9BZQ8	NIBAN1	11	0.398536598	0.033419948
P07355	ANXA2	24	0.397761682	0.031225851
O43148	RNMT	7	0.39631924	0.012031178
O75116	ROCK2	17	0.394335715	0.004569365
O95573	ACSL3	9	0.392944935	0.014996354
Q8WUF5	PPP1R13L	18	0.392010309	0.024276439
Q15404	RSU1	4	0.390556682	0.025973029
P05455	SSB	11	0.388822908	0.003730139
Q9Y5S1	TRPV2	10	0.386929017	0.031343506
P09104	ENO2	5	0.381070132	0.018614024
Q9NZB2	FAM120A	16	0.377144782	0.013351865
Q07955	SRSF1	12	0.376695542	0.011481507
Q9NQC3	RTN4	10	0.375015953	0.01154907
Q9UHB9	SRP68	11	0.37207289	0.005420118

Q9NZL9	MAT2B	3	0.369679706	0.014998095
Q9HDC9	APMAP	10	0.368770572	0.049600588
P35221	CTNNA1	10	0.368680917	0.005535825
P42224	STAT1	7	0.367038944	0.041720374
O95757	HSPA4L	7	0.366735849	0.010410276
O95785	WIZ	8	0.363654275	0.002411034
P62269	RPS18	9	0.363260142	0.015190464
P54707	ATP12A	1	0.360356537	0.001390528
O94760	DDAH1	7	0.357942626	0.002233804
P24928	POLR2A	16	0.356450052	0.037878378
P35998	PSMC2	16	0.356439691	0.031396547
Q8N1S5	SLC39A11	2	0.356201738	0.003983184
O75439	PMPCB	8	0.35379273	0.000906658
P54136	RARS1	14	0.353588365	0.00357736
P50995	ANXA11	6	0.352621618	0.042504803
P20337	RAB3B	4	0.351835238	0.032784581
O15355	PPM1G	9	0.349279727	0.024184343
P08240	SRPRA	8	0.343356856	0.041876283
P62249	RPS16	6	0.342927979	0.010022002
O75489	NDUFS3	3	0.342747356	0.007015261
Q99613	EIF3C	13	0.342458594	0.005564978
Q15070	OXA1L	2	0.342256532	0.009843658
O60763	USO1	11	0.342250106	0.019131095
P18077	RPL35A	5	0.33794187	0.012928402
Q86SQ0	PHLDB2	8	0.332087905	0.049319198
Q9NR56	MBNL1	3	0.331741602	0.003321092
Q9Y265	RUVBL1	11	0.329583348	0.000886113
Q96G03	PGM2	15	0.3271806	0.018320219
P09960	LTA4H	14	0.326583185	0.000725319
P31040	SDHA	8	0.324519949	0.022413026
Q15056	EIF4H	9	0.323660574	0.025459498
P46776	RPL27A	3	0.322185333	0.004980515
P51659	HSD17B4	7	0.317034508	0.003412429
P62877	RBX1	3	0.316372139	0.024721944
O94925	GLS	8	0.315209254	0.004829547
Q14103	HNRNPD	10	0.314680649	0.002804104
P09972	ALDOC	12	0.310604191	0.019590882
P07311	ACYP1	3	0.309299616	0.022596953
P63272	SUPT4H1	2	0.309197132	0.008517345
P27708	CAD	23	0.305078537	0.002249869
P62424	RPL7A	14	0.302698588	0.000395079
Q9Y3I0	RTCB	11	0.301171611	0.004049246
Q9UQ35	SRRM2	23	0.299875258	0.016201674
P23229	ITGA6	17	0.298862498	0.002761548
P17980	PSMC3	10	0.294944497	0.044139368
P07339	CTSD	6	0.293932848	0.002242392
P16989	YBX3	8	0.293413307	0.032662503
Q9UNH7	SNX6	9	0.290400124	0.003307383
P52566	ARHGDIB	6	0.289322777	0.019548445
Q9BXJ9	NAA15	12	0.288365632	0.003466522

P49790	NUP153	19	0.279420941	0.006817937
Q9BZZ5	API5	8	0.277075851	0.004344254
Q8TCS8	PNPT1	12	0.27372702	0.019001709
P28066	PSMA5	3	0.273260857	0.005971481
Q16527	CSRP2	2	0.269092566	0.01870586
P53611	RABGGTB	3	0.268251032	0.04490728
Q9P265	DIP2B	14	0.268001013	0.014936949
P23526	AHCY	10	0.264690583	0.000509907
P13489	RNH1	11	0.260587888	0.006753044
Q9UHX1	PUF60	9	0.258128843	0.043092124
P30050	RPL12	8	0.256555422	0.001272411
Q2NL82	TSR1	9	0.255237723	0.003158844
P07195	LDHB	12	0.25214815	0.008013915
P35250	RFC2	7	0.248029842	0.003120976
Q13177	PAK2	8	0.245626618	0.00489267
P16435	POR	1	0.242950566	0.018515326
P62263	RPS14	7	0.24196571	0.00064839
Q9H832	UBE2Z	2	0.239414653	0.028550121
Q9BZE1	MRPL37	4	0.236943058	0.006264515
Q16222	UAP1	10	0.235234337	0.000344113
P52209	PGD	8	0.235032934	0.003867398
Q32P28	P3H1	7	0.229967492	0.002001048
P14618	PKM	34	0.22714781	0.008586504
Q13765	NACA	3	0.22612885	0.019618674
Q14974	KPNB1	12	0.225019299	0.005402087
O43852	CALU	5	0.222185676	0.036710053
P42766	RPL35	3	0.221105983	0.006270245
P62280	RPS11	9	0.217975112	0.000127799
P35606	COPB2	21	0.208131538	0.001445029
P17301	ITGA2	15	0.207345357	0.006722017
P18754	RCC1	9	0.206442874	0.015346137
Q92841	DDX17	9	0.205712627	0.010237152
P84077	ARF1	2	0.202592688	0.000332031
P78417	GSTO1	7	0.2025213	0.006898259
P60900	PSMA6	8	0.197167372	0.009637365
Q9Y285	FARSA	7	0.196185865	0.00175319
P56537	EIF6	5	0.195402738	0.005563324
P08865	RPSA	8	0.195337504	0.006934493
Q6PJG2	MIDEAS	4	0.192151872	0.014457905
P50395	GDI2	11	0.188236583	0.005300852
P04083	ANXA1	15	0.186411111	0.016095617
P11766	ADH5	6	0.181635449	0.024014118
Q00653	NFKB2	6	0.181293766	0.004270469
P13073	COX4I1	4	0.179728163	0.000999726
Q15942	ZYX	14	0.179650826	0.001877821
Q93034	CUL5	8	0.179614693	0.011658142
P62306	SNRPF	2	0.179391513	0.001550923
P41091	EIF2S3	11	0.175305995	0.005579744
P17174	GOT1	6	0.174358251	0.039031384
Q02878	RPL6	11	0.171795205	0.006804704

P22392	NME2	4	0.169438817	0.007098654
Q13347	EIF3I	8	0.166523811	0.014034541
P39687	ANP32A	4	0.165022743	0.018024196
P62913	RPL11	6	0.162939967	0.000399692
P61313	RPL15	3	0.162902963	0.009749921
Q08211	DHX9	20	0.162675465	0.001615362
Q9H4A3	WNK1	11	0.162414595	0.04319889
P62753	RPS6	9	0.161438588	0.002294783
P29590	PML	11	0.155671061	0.014840471
Q12906	ILF3	15	0.144574199	0.001319819
P55060	CSE1L	18	0.142626704	0.003922667
P12814	ACTN1	16	0.138219773	0.001409309
Q96TA1	NIBAN2	7	0.137223802	0.006762723
Q13509	TUBB3	0	0.131287109	0.002839179
Q9HAV4	XPO5	12	0.12649864	0.006152721
Q93052	LPP	13	0.125415466	0.000014361
P37802	TAGLN2	9	0.125280322	0.000782839
P22061	PCMT1	6	0.124909199	0.018708607
O43143	DHX15	12	0.124087905	0.000043767
P61019	RAB2A	4	0.12331596	0.039408111
Q6NUQ4	TMEM214	6	0.122068966	0.000094330
P00505	GOT2	10	0.120781859	0.000393318
P43034	PAFAH1B1	8	0.114961324	0.001700737
P22314	UBA1	25	0.114546774	0.000105663
P61158	ACTR3	8	0.110252042	0.000823616
Q15287	RNPS1	2	0.109066821	0.000391204
O60216	RAD21	5	0.104223715	0.002636733
Q07020	RPL18	5	0.104010893	0.011928423
Q71DI3	H3C15	2	0.098202778	0.008935176
P18124	RPL7	8	0.093556154	0.000541303
O60749	SNX2	12	0.093277336	0.00018863
Q9Y3F4	STRAP	11	0.092659023	0.000561724
P08243	ASNS	5	0.091726739	0.004509179
P60842	EIF4A1	5	0.091142228	0.002580845
P29692	EEF1D	9	0.086387004	0.000046127
P11279	LAMP1	3	0.078276397	0.024449158
Q96PK6	RBM14	16	0.069617064	0.000073202
Q9Y394	DHRS7	1	0.064733533	0.024352773
P39656	DDOST	3	0.063623859	0.007301312
P62906	RPL10A	3	0.06307188	0.000002503
Q14195	DPYSL3	7	0.06212347	0.000023339
P55854	SUMO3	1	0.056192082	0.000128172
P62917	RPL8	10	0.049631294	0.002221598
P34897	SHMT2	9	0.044578592	0.000038168
P54819	AK2	6	0.044085069	0.000011212
P51149	RAB7A	9	0.042035662	0.000356734
P61353	RPL27	3	0.040354049	0.006067716
P29317	EPHA2	13	0.037668921	0.000145984
P62854	RPS26	2	0.035208754	0.00016819
P42166	TMPO	12	0.01811705	0.000994191
Q9BY44	EIF2A	16	0.012045171	0.000001075

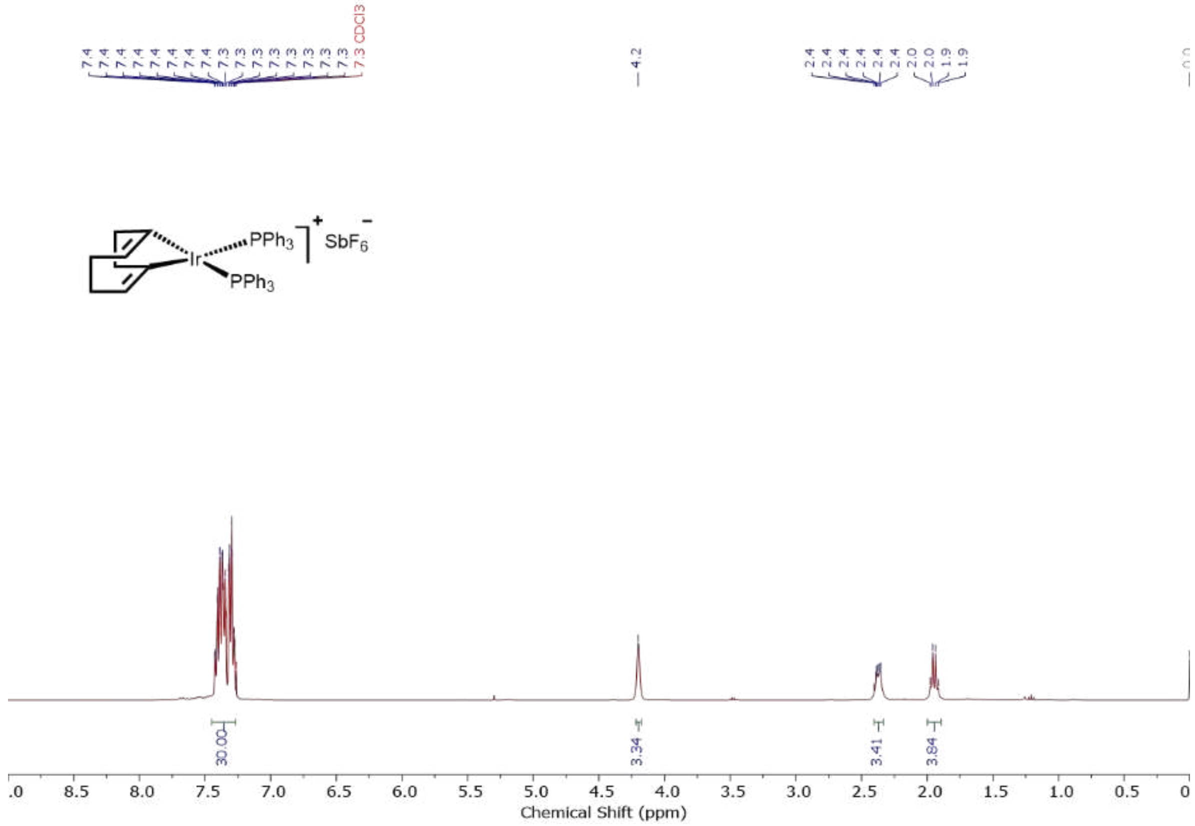


Figure S20. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of $[IrCOD(PPh_3)_2]SbF_6$.

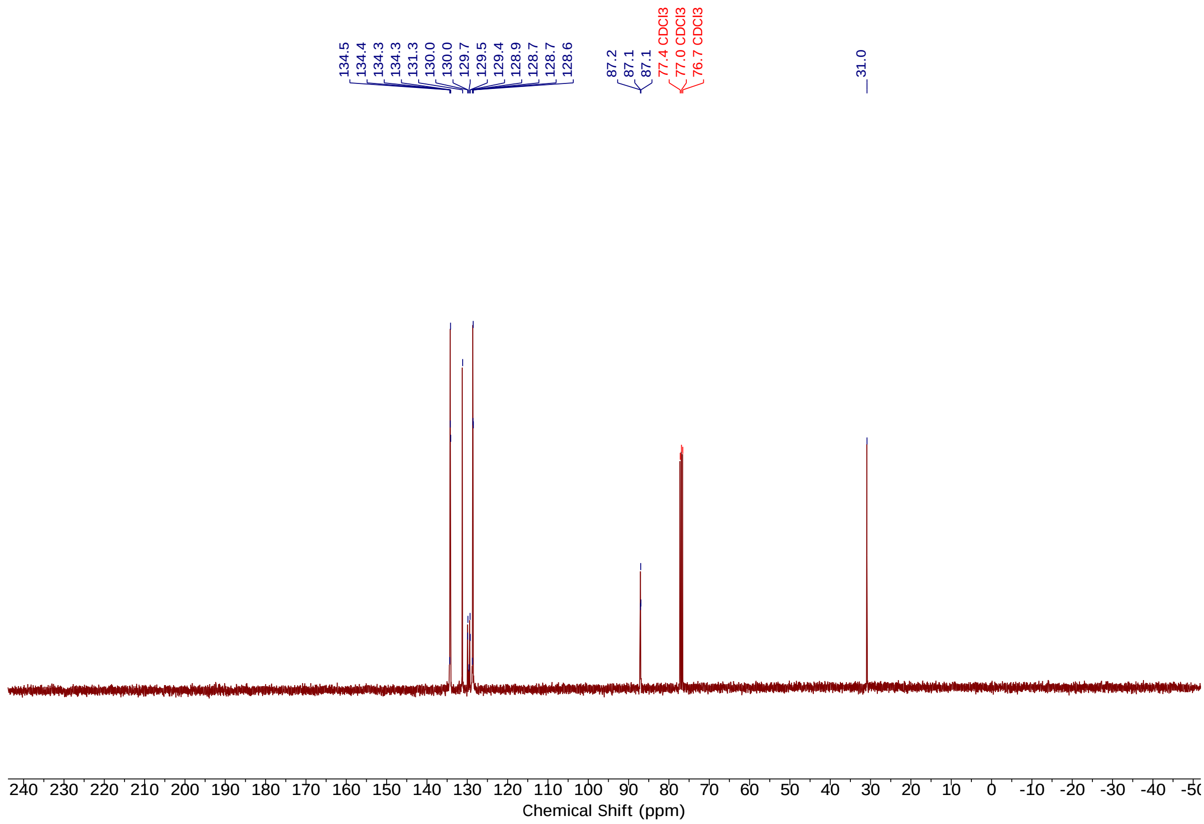


Figure S21. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of $[IrCOD(PPh_3)_2]SbF_6$.

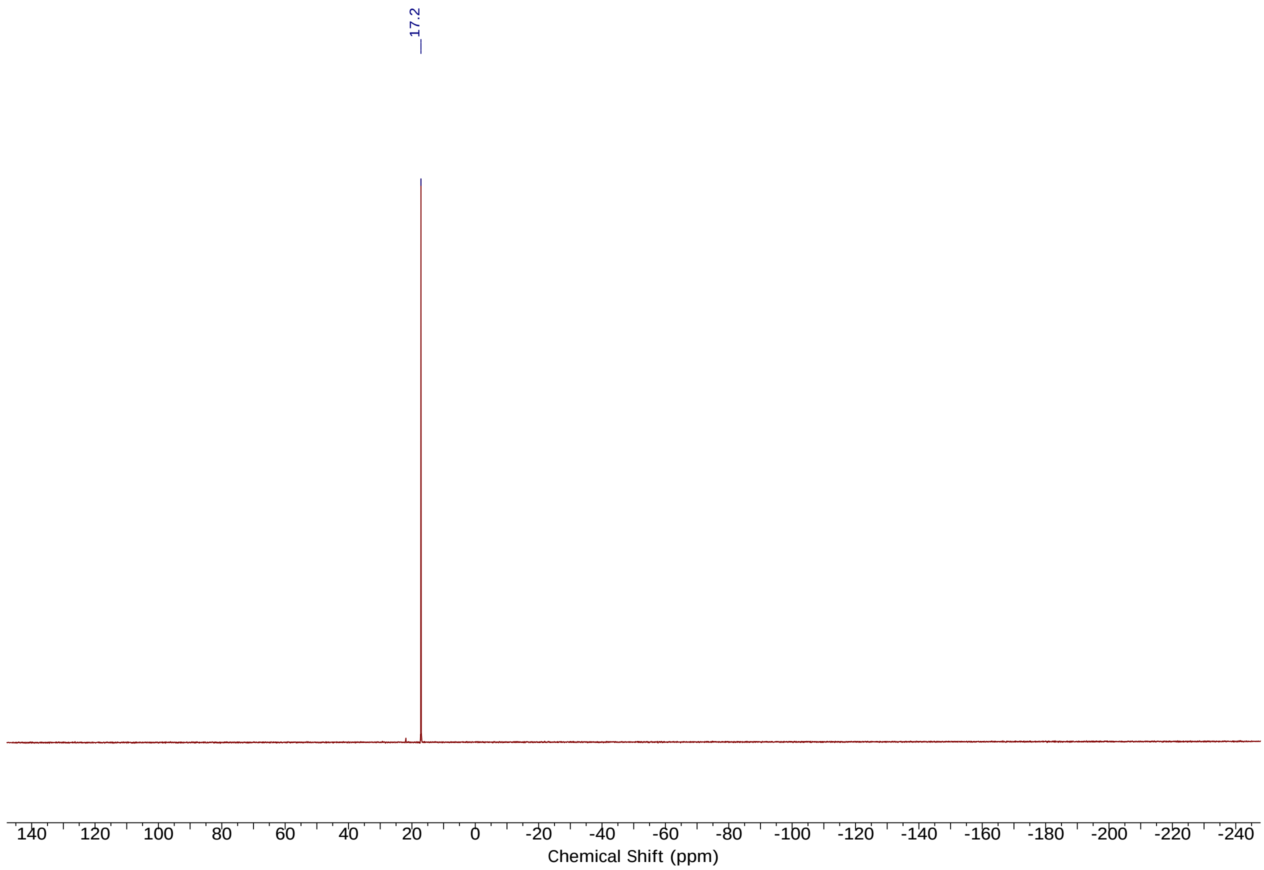


Figure S22. ^{31}P NMR spectrum (162 MHz, $CDCl_3$) of $[IrCOD(PPh_3)_2]SbF_6$.

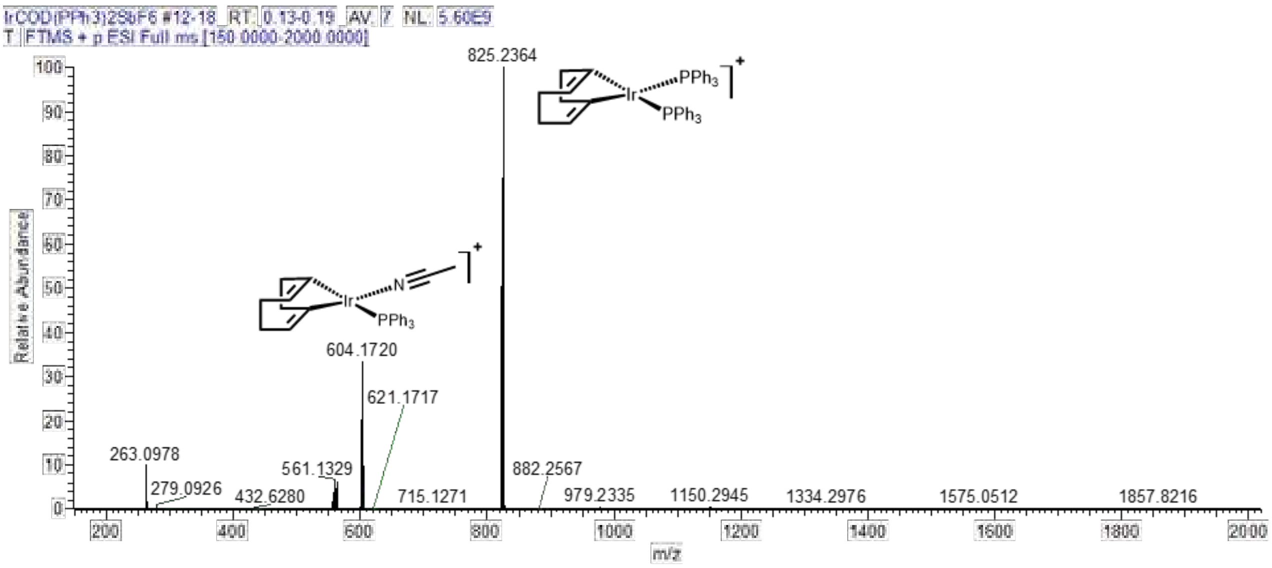


Figure S23. HRMS (solvent: MeCN) spectrum of $[IrCOD(PPh_3)_2]SbF_6$.

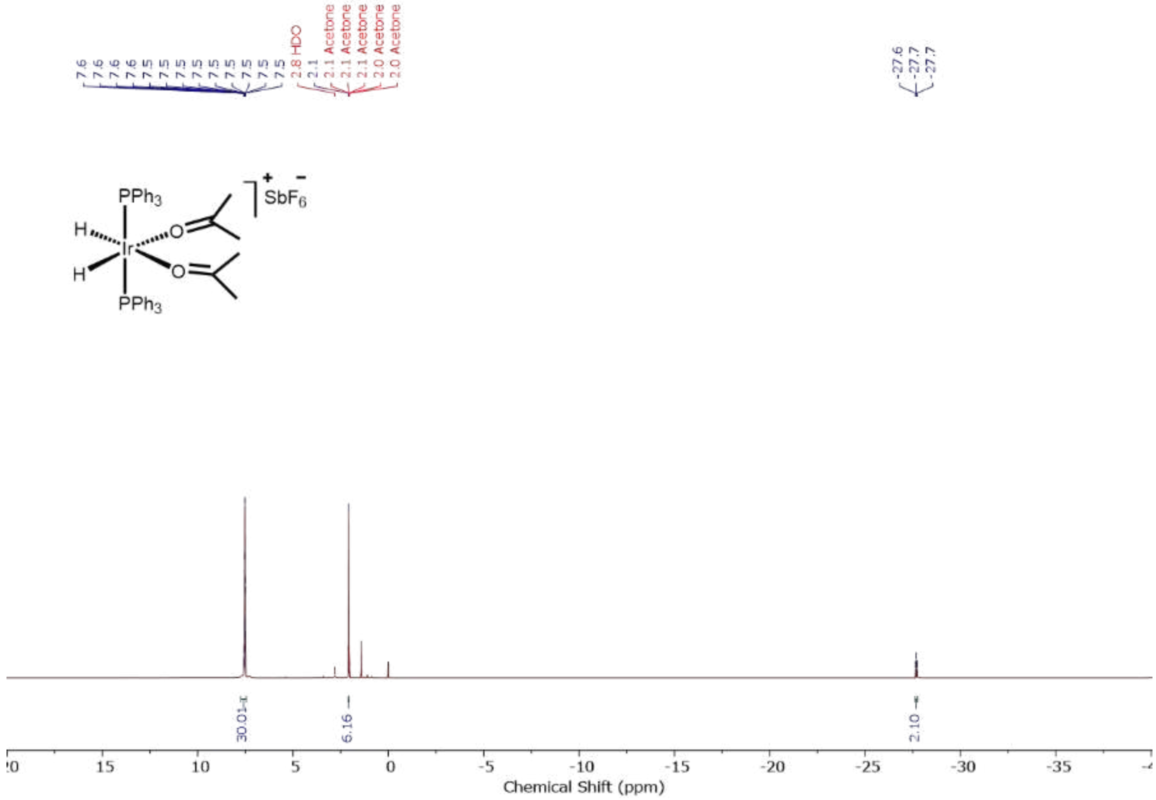


Figure S24. ^{1}H NMR spectrum (400 MHz, Acetone-d$_6$) of $[IrH_2(PPh_3)_2(C_3H_6O)_2]SbF_6$.

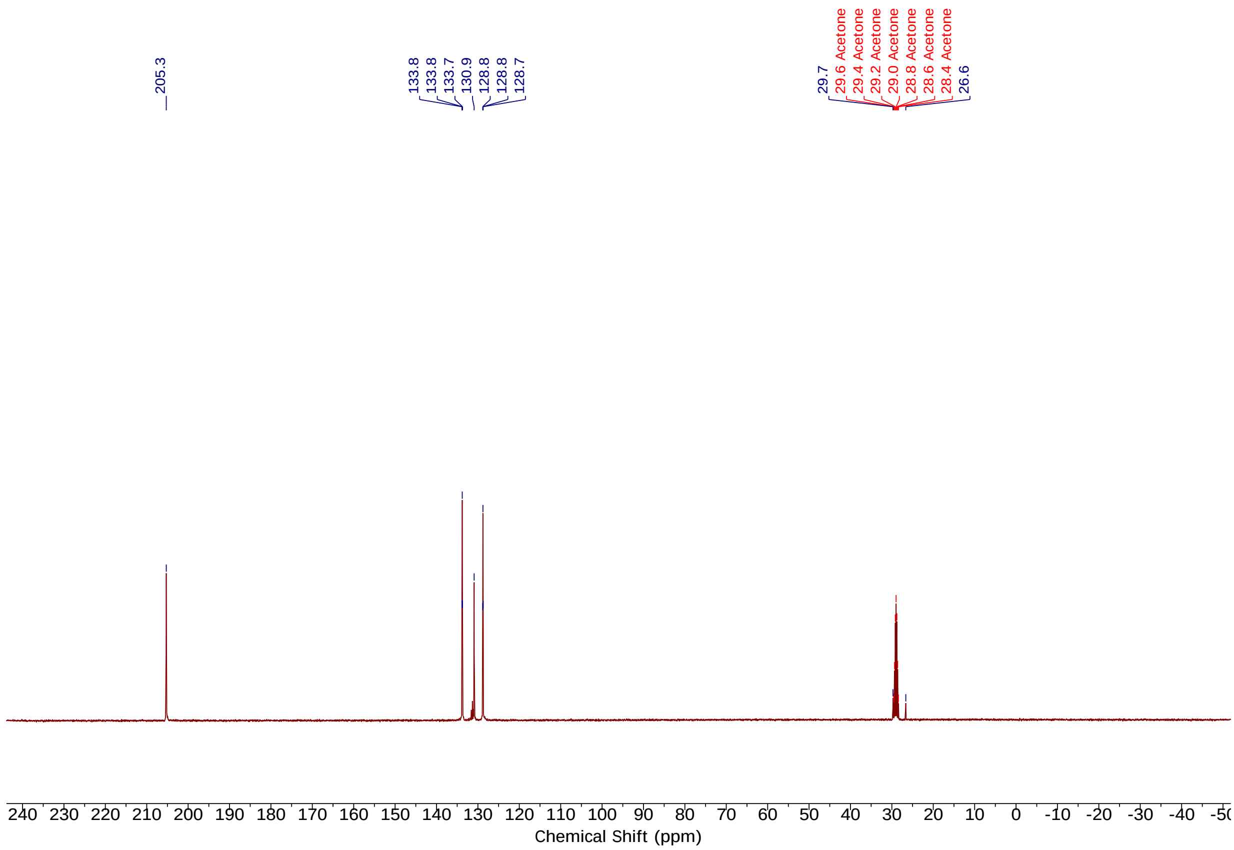


Figure S25. ^{13}C NMR spectrum (101 MHz, Acetone-d$_6$) of $[IrH_2(PPh_3)_2(C_3H_6O)_2]SbF_6$.

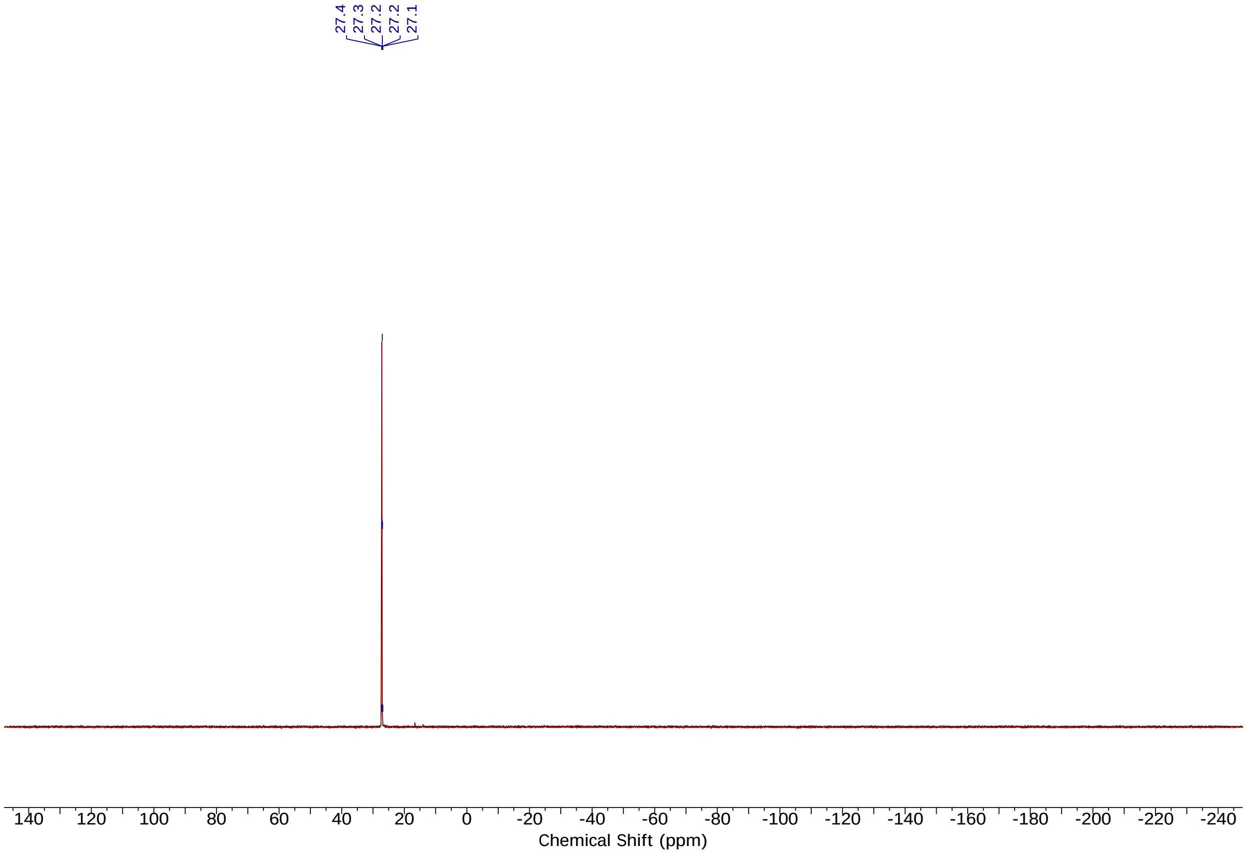


Figure S26. ^{31}P NMR spectrum (162 MHz, Acetone-d_6) of $[IrH_2(PPh_3)_2(C_3H_6O)_2]SbF_6$.

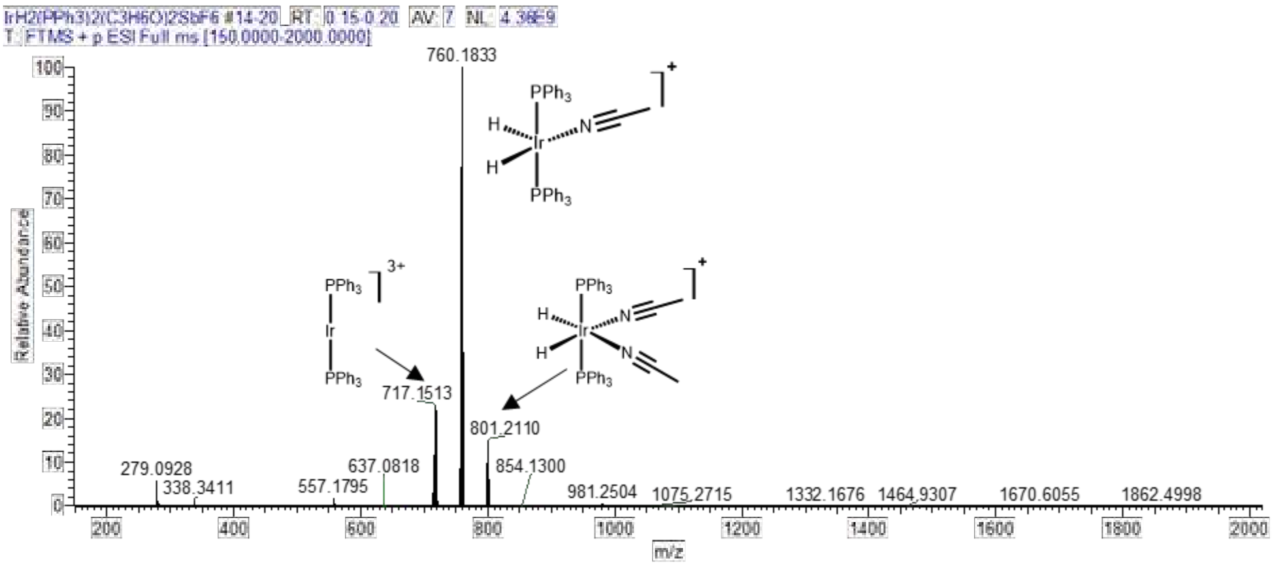


Figure S27. HRMS (solvent: MeCN) spectrum of $[IrH_2(PPh_3)_2(C_3H_6O)_2]SbF_6$.

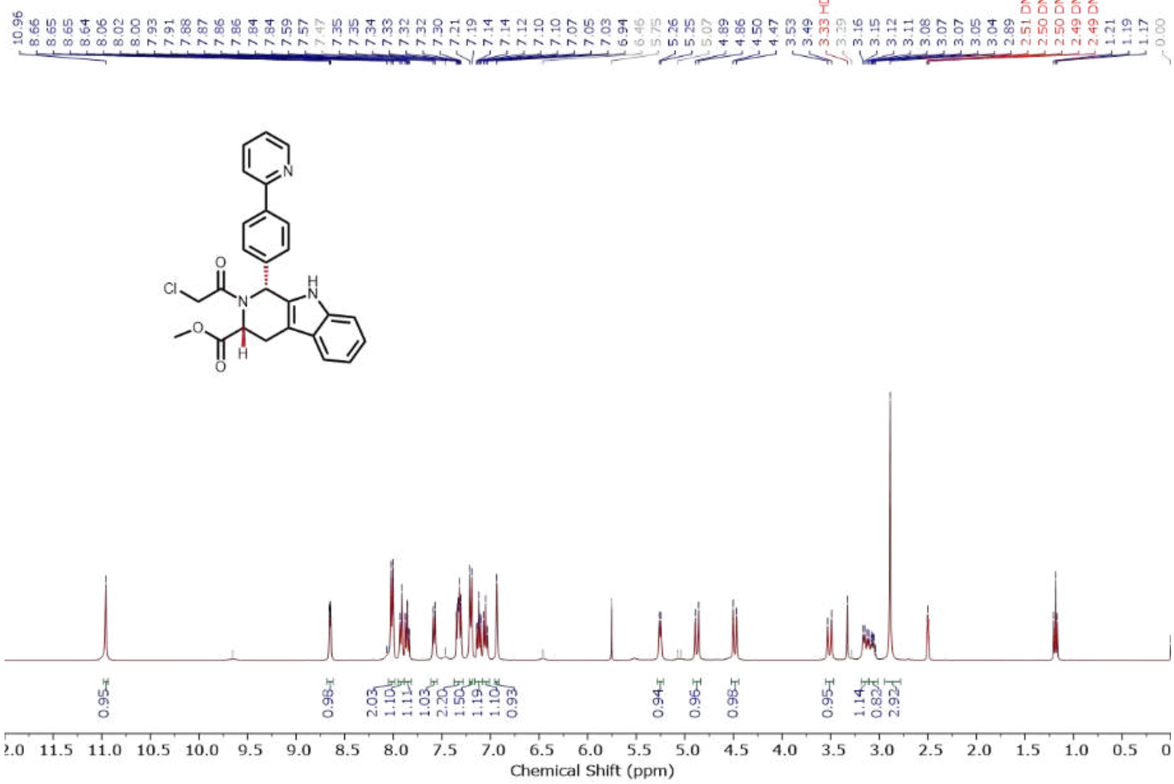


Figure S28. ^{1}H NMR spectrum (400 MHz, DMSO-d$_6$) of **L2**.

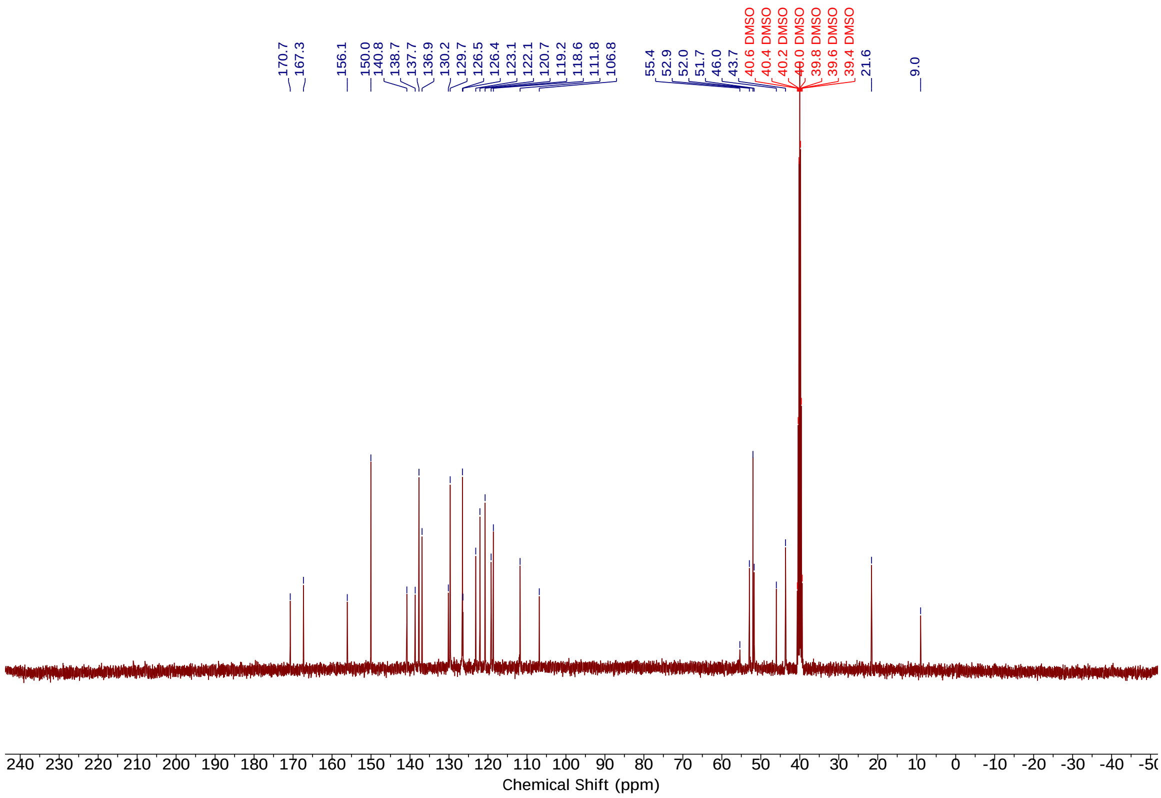


Figure S29. ^{13}C NMR spectrum (101 MHz, DMSO-d$_6$) of **L2**.

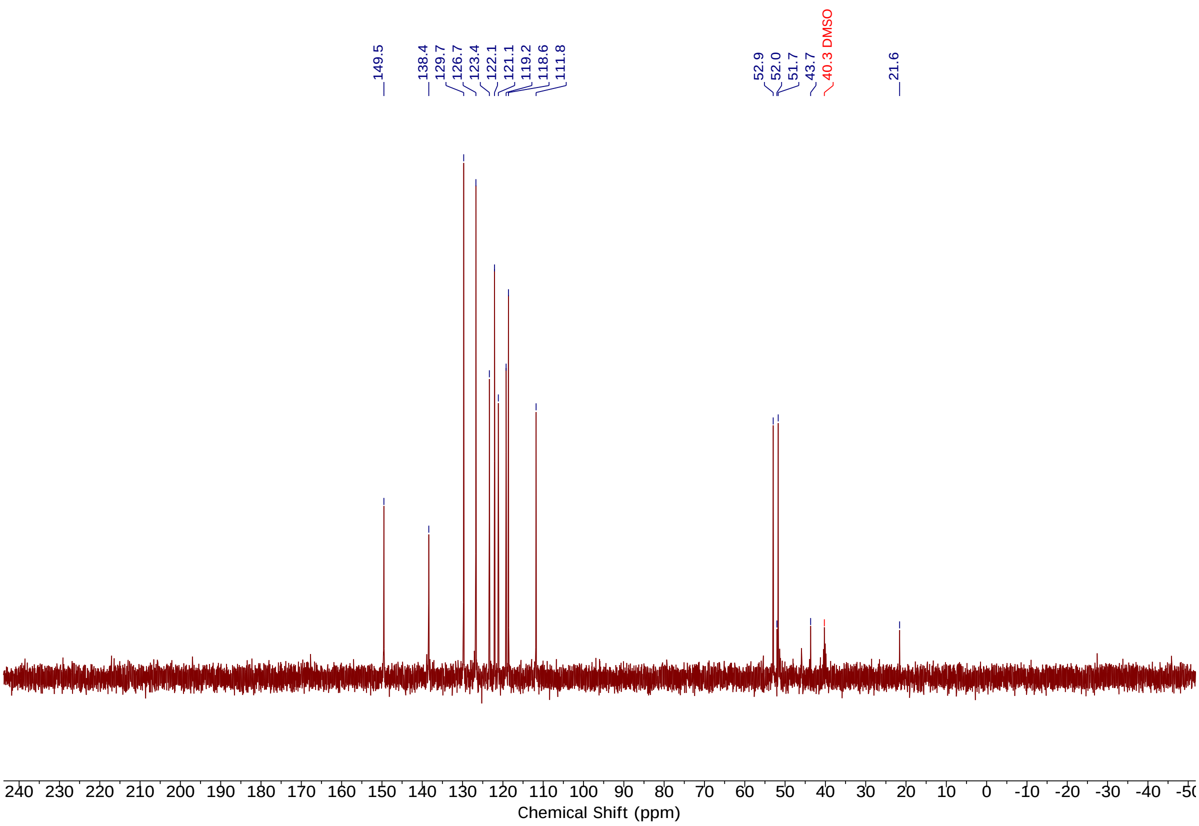


Figure S30. DEPT-90 spectrum (101 MHz, DMSO-d$_6$) of **L2**.

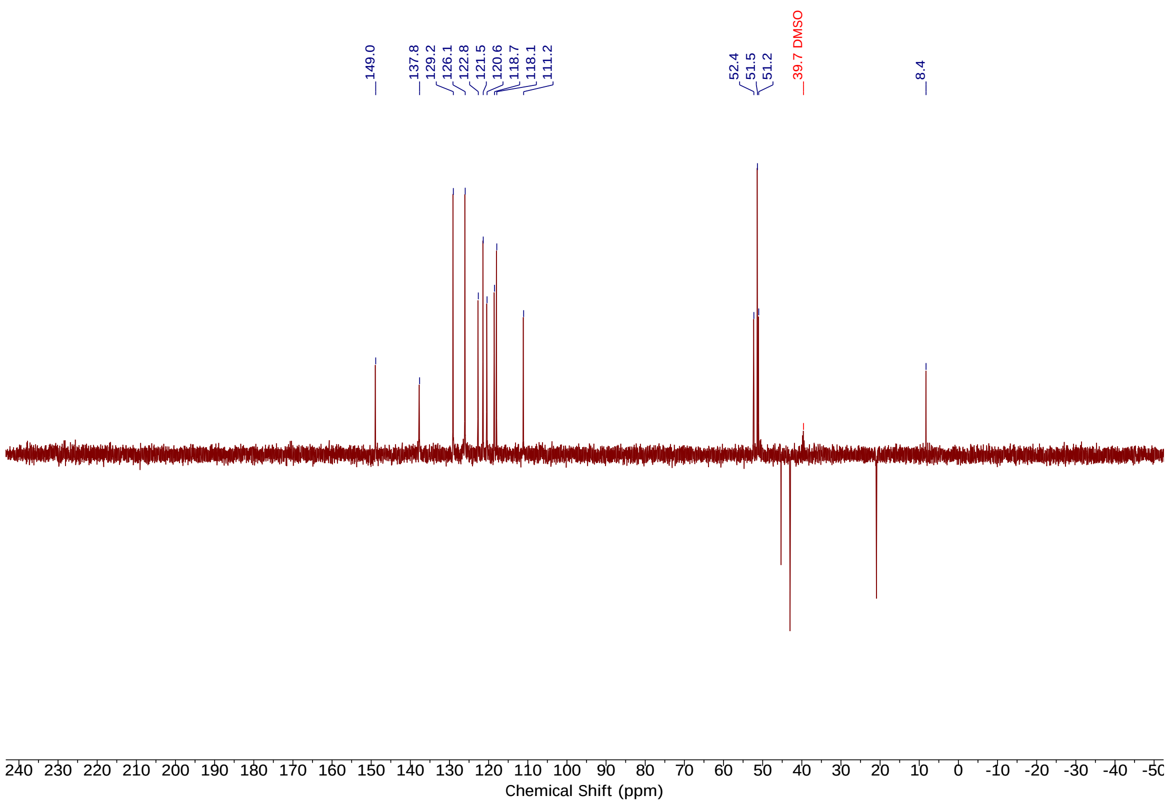


Figure S31. DEPT-135 spectrum (101 MHz, DMSO-d$_6$) of **L2**.

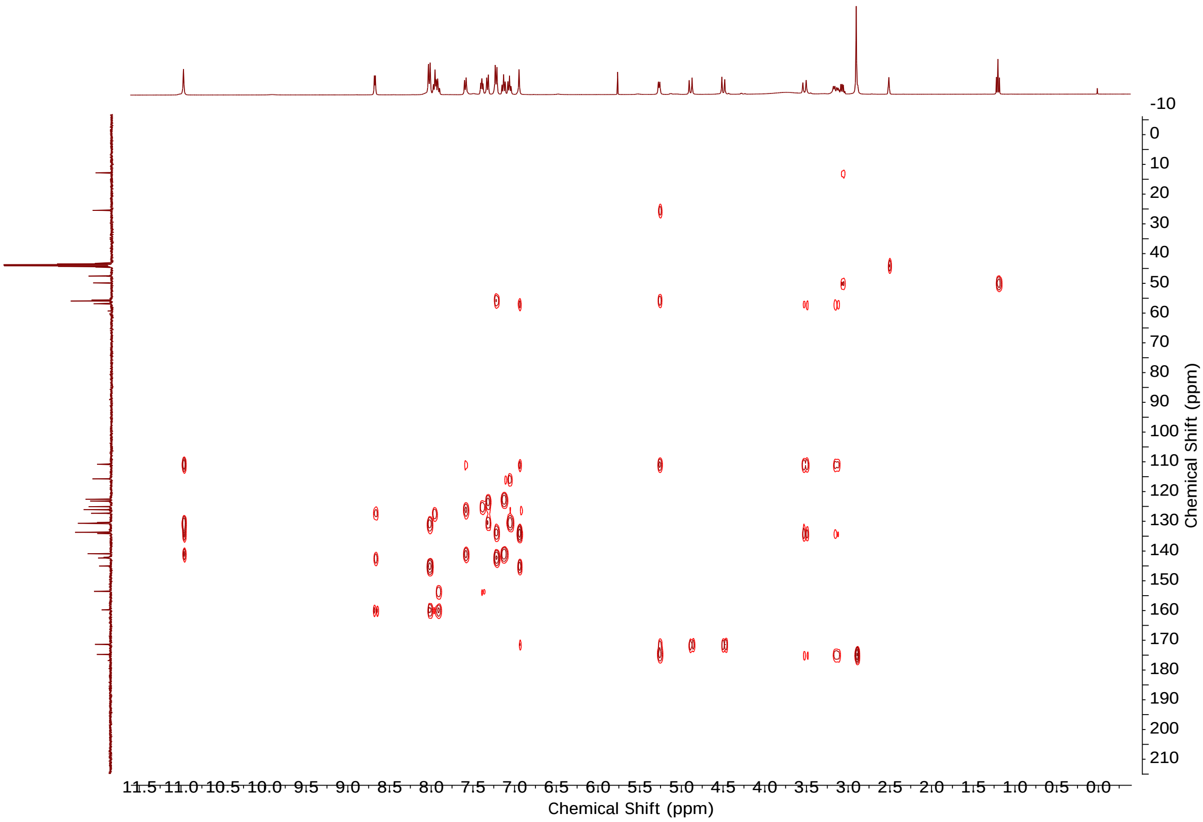


Figure S32. HMBC spectrum (400 MHz, DMSO-d$_6$) of **L2**.

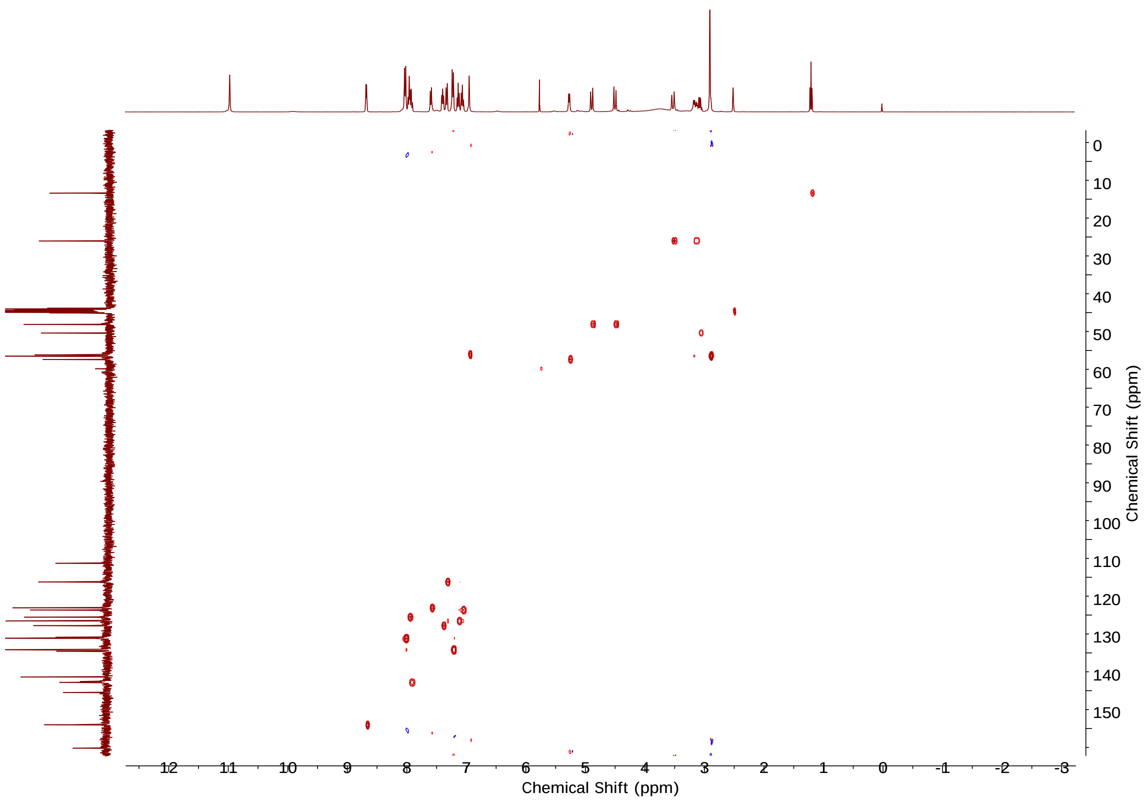
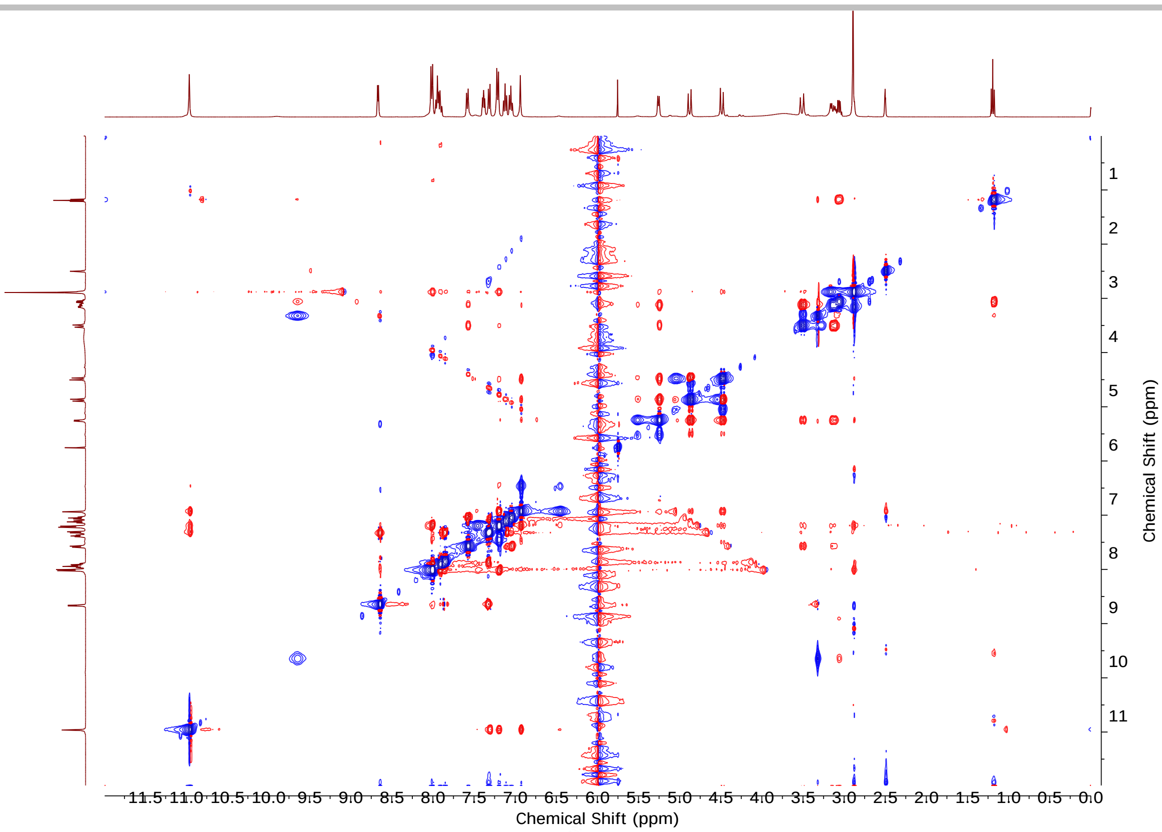


Figure S33. HSQC spectrum (400 MHz, DMSO-d$_6$) of **L2**.



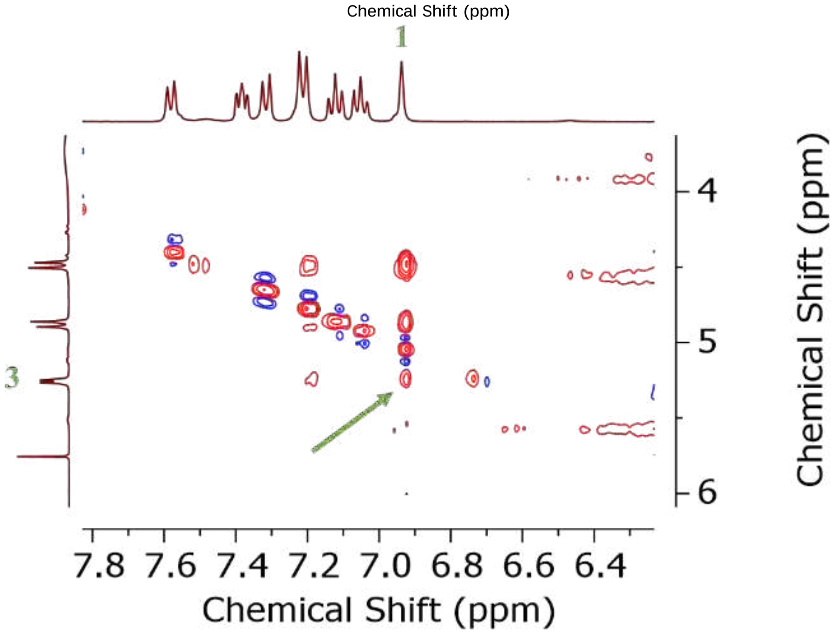


Figure S34. NOESY spectrum (400 MHz, DMSO-d_6) of **L2**.

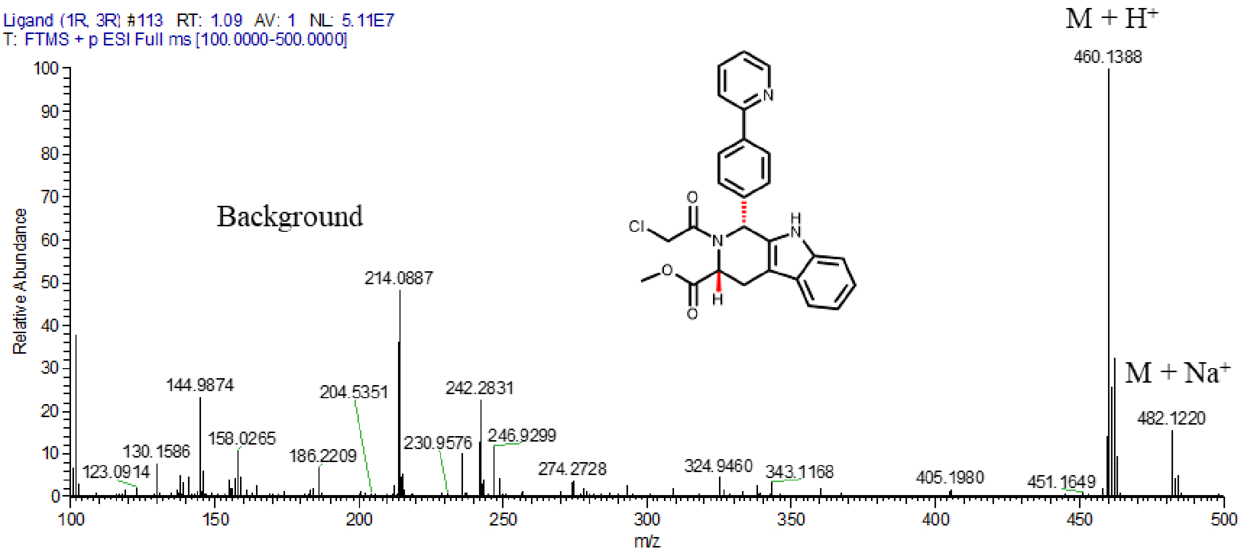


Figure S35. HRMS (solvent: MeCN) spectrum of **L2**.

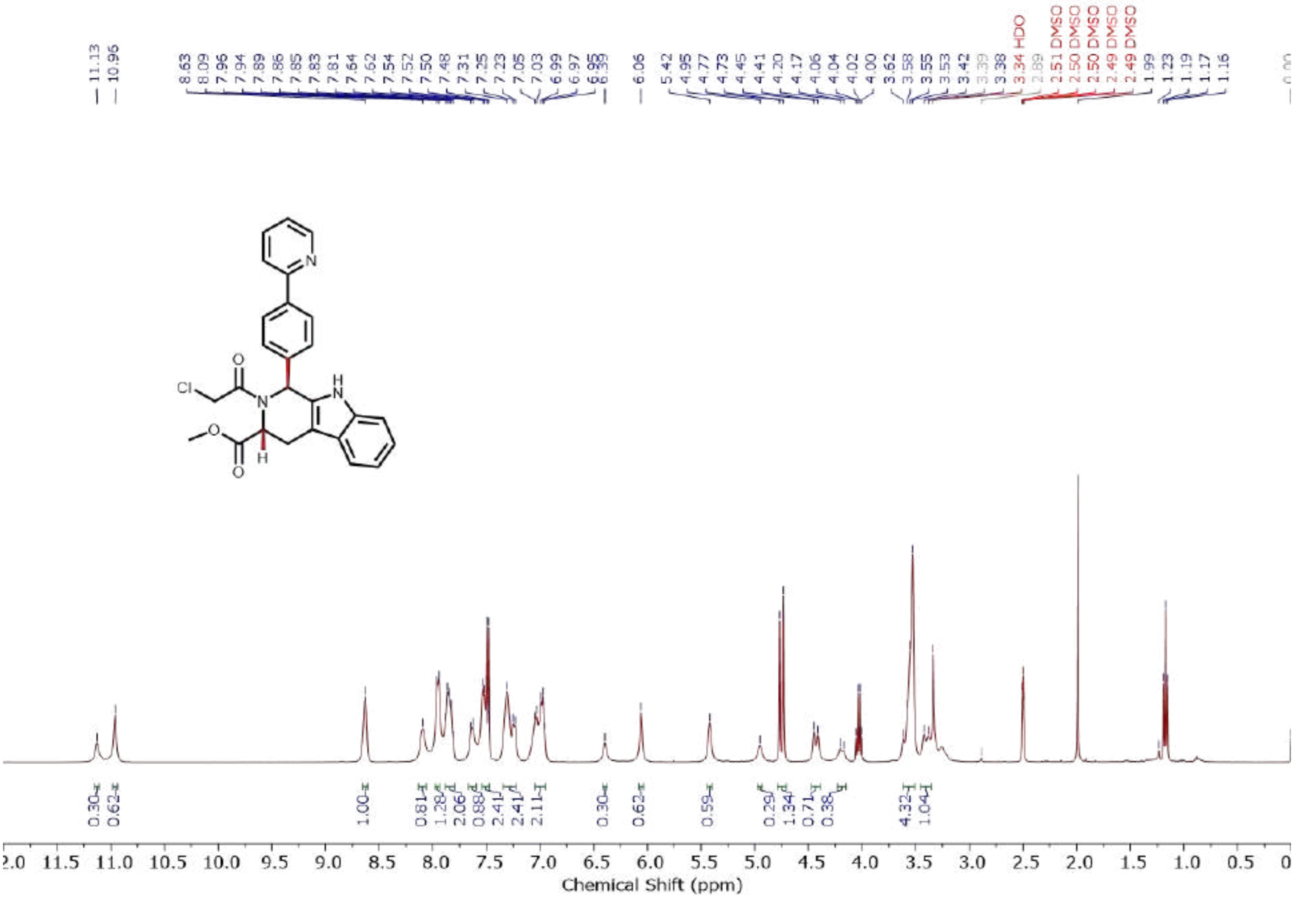


Figure S36. [1]H NMR spectrum (400 MHz, DMSO-d_6) of **L1**.

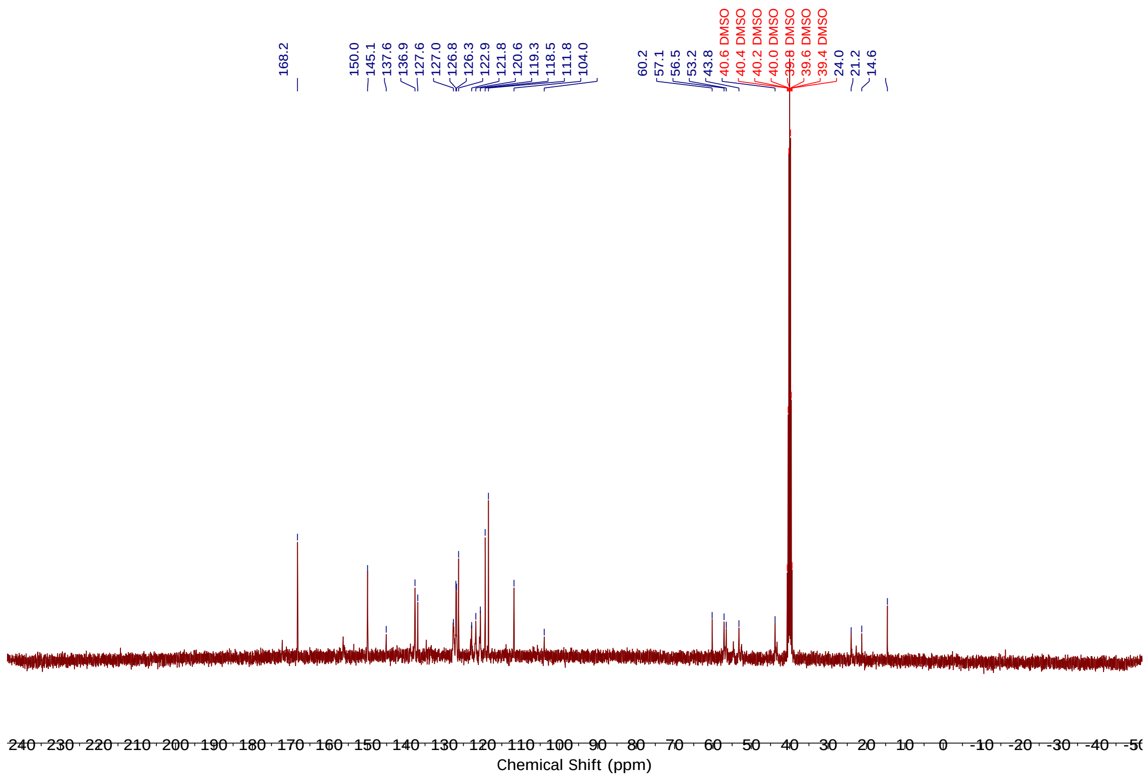


Figure S37. ^{13}C NMR spectrum (101 MHz, DMSO-d_6) of **L1**.

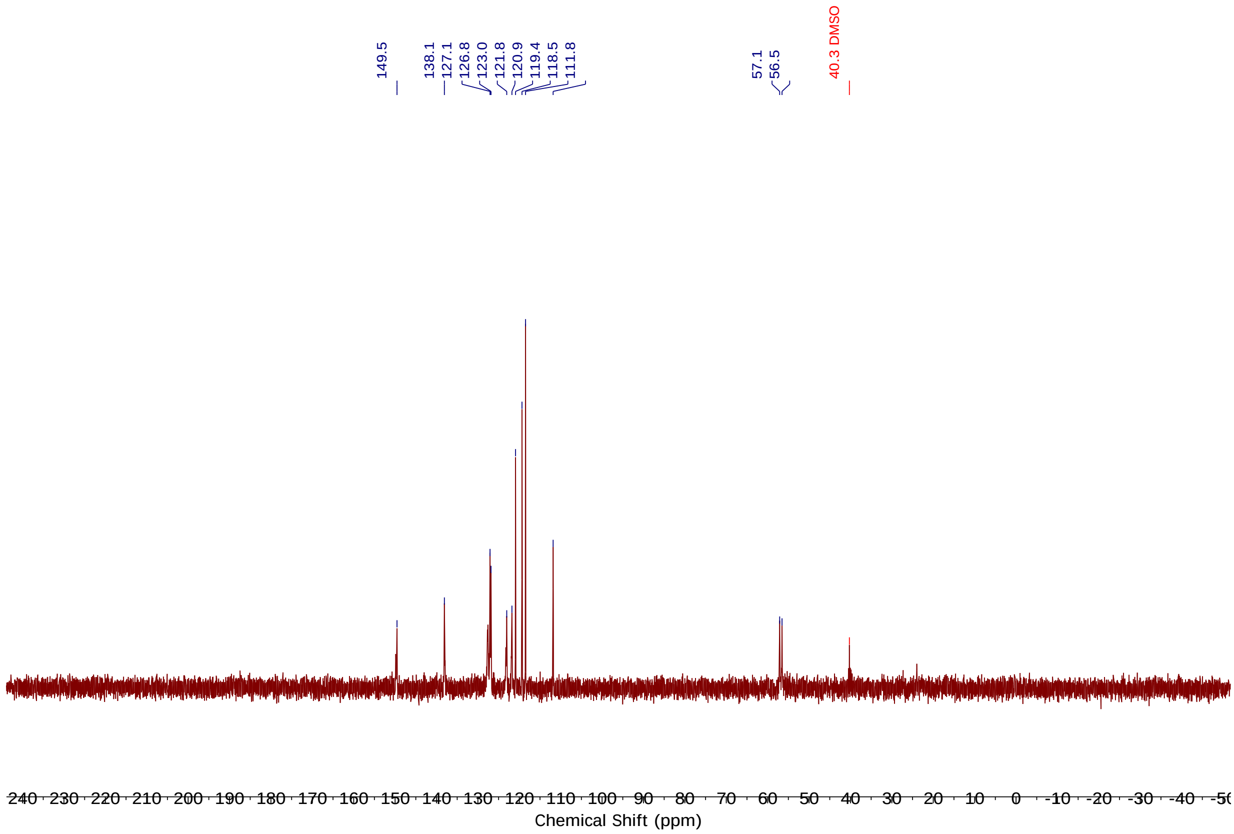


Figure S38. DEPT-90 spectrum (101 MHz, DMSO-d_6) of **L1**.

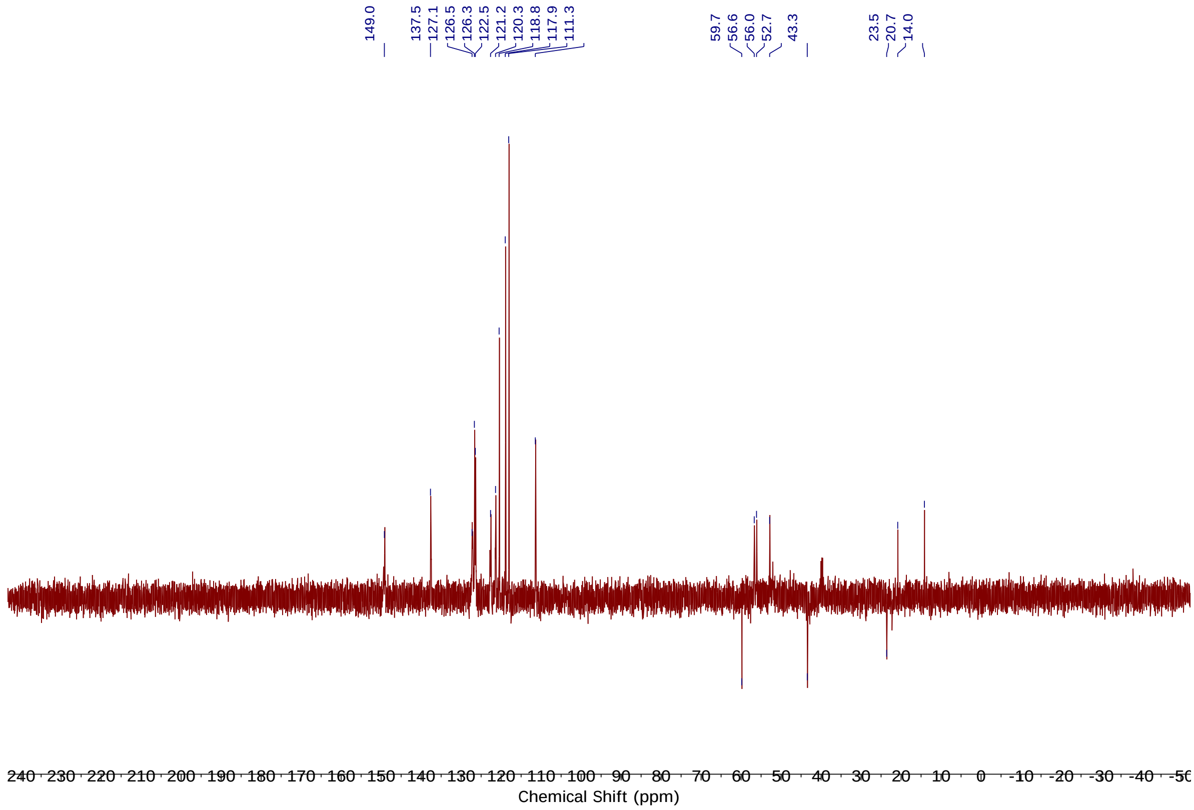


Figure S39. DEPT-135 spectrum (101 MHz, DMSO-d$_6$) of **L1**.

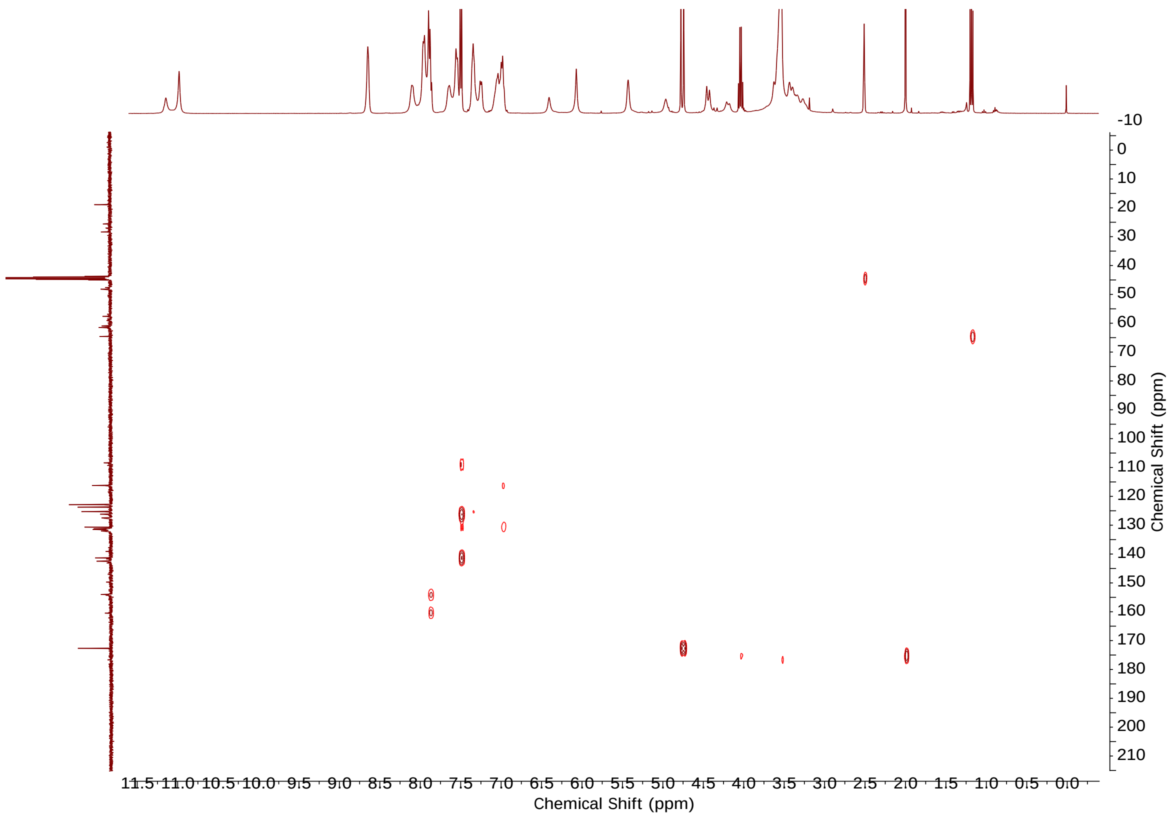


Figure S40. HMBC spectrum (400 MHz, DMSO-d$_6$) of **L1**.

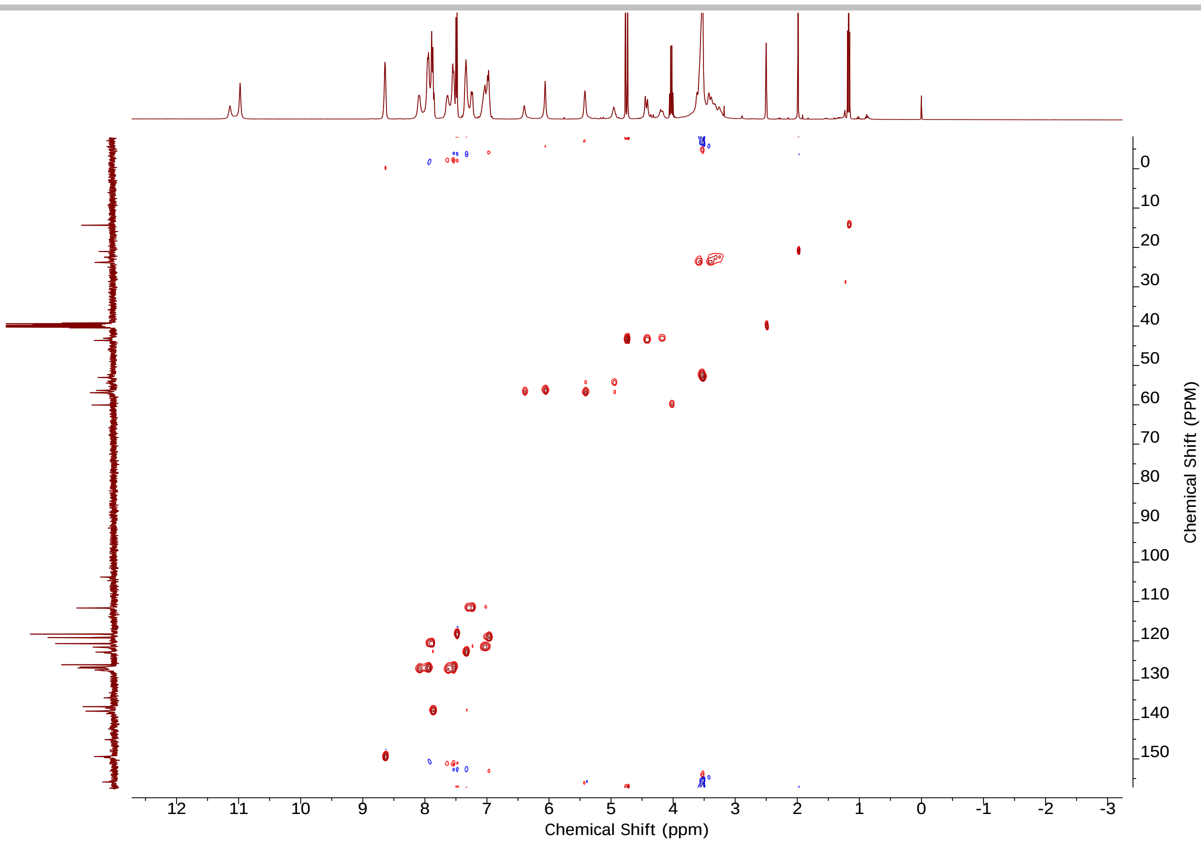


Figure S41. HSQC spectrum (400 MHz, DMSO-d$_6$) of **L1**.

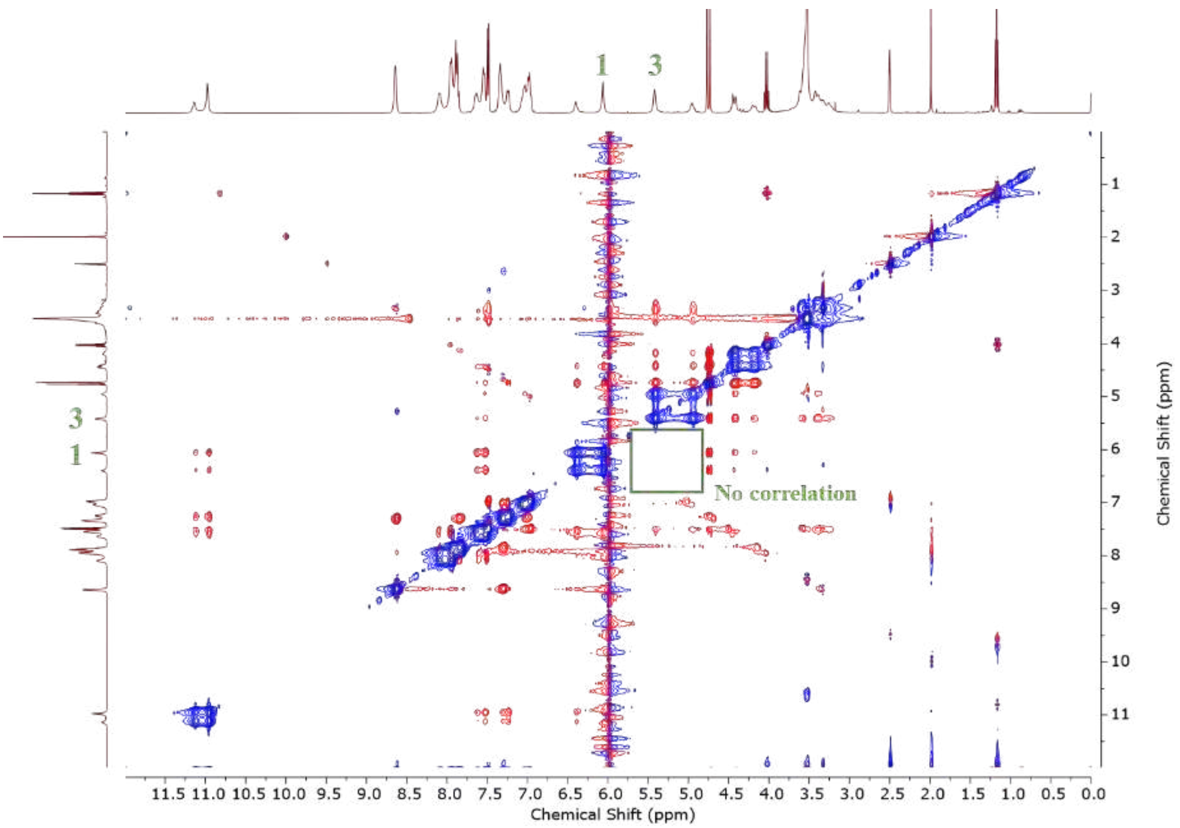


Figure S42. NOESY spectrum (400 MHz, DMSO-d$_6$) of **L1**.

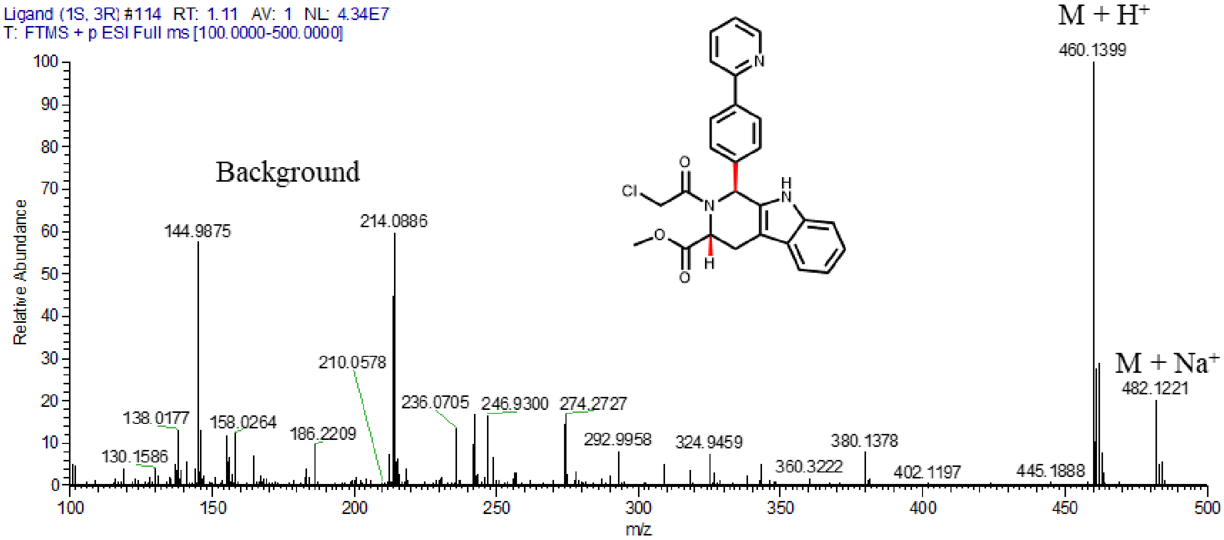


Figure S43. HRMS spectrum of **L1**.

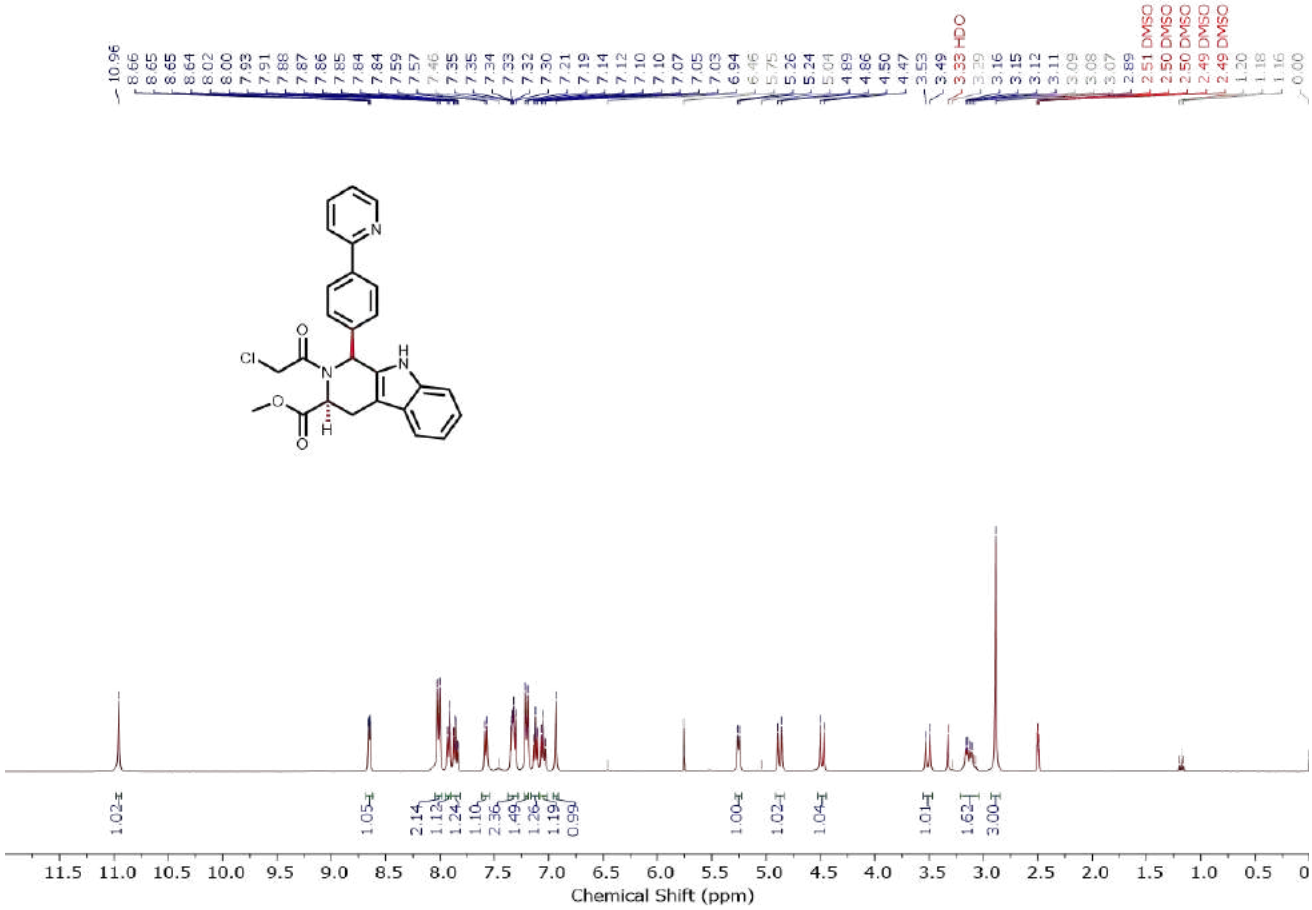


Figure S44. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **L4**.

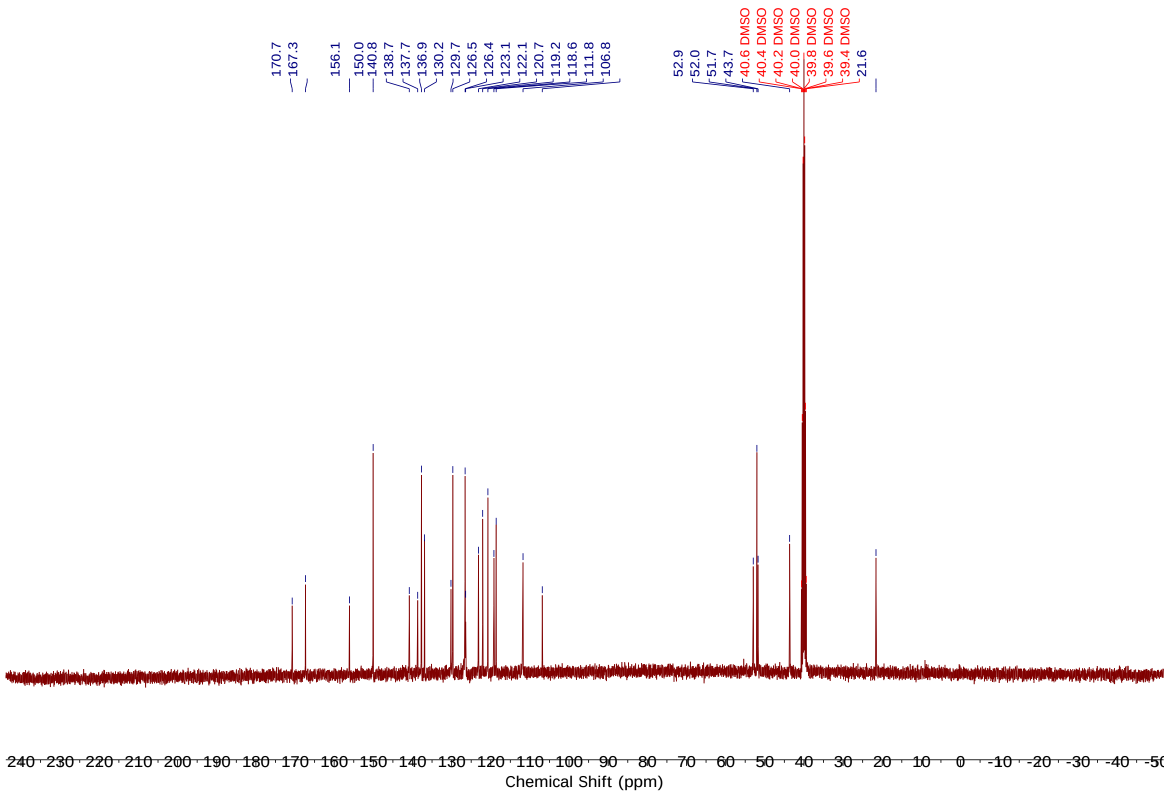


Figure S45. ^{13}C NMR spectrum (101 MHz, DMSO-d_6) of **L4**.

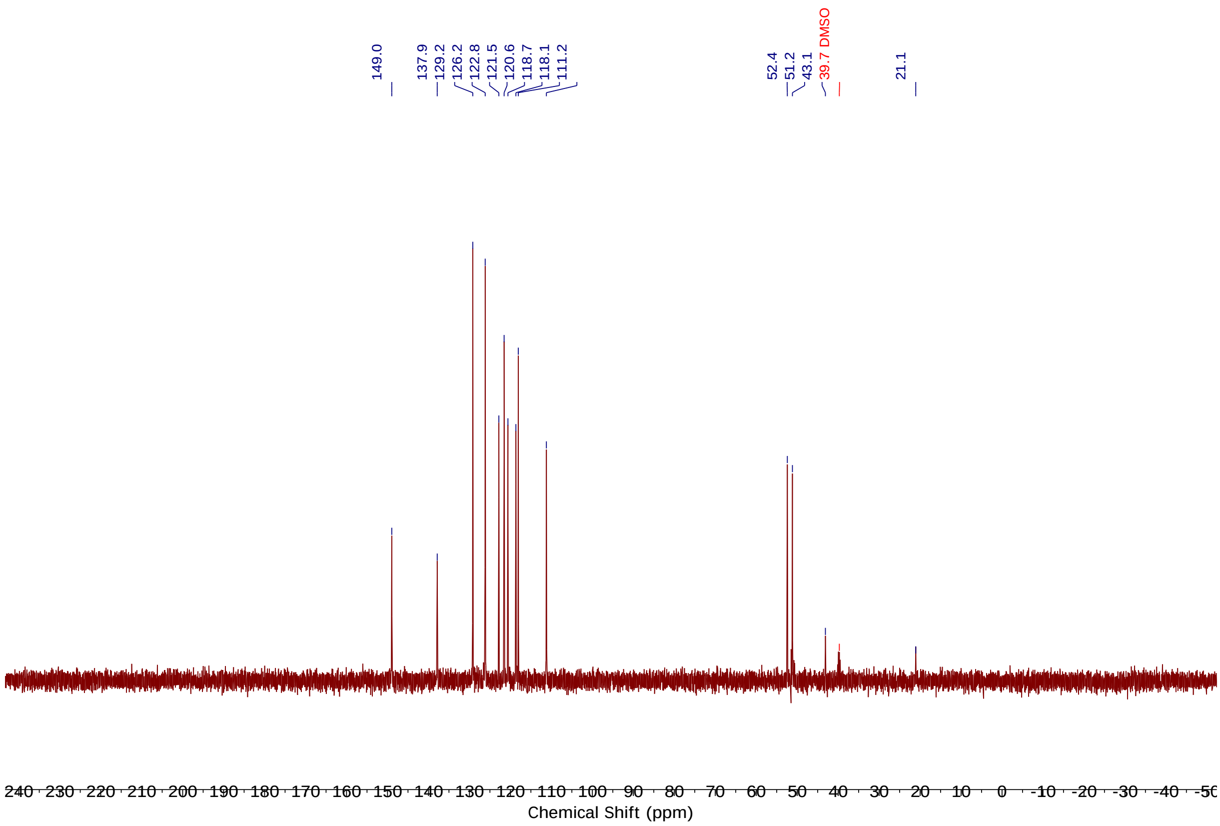


Figure S46. DEPT-90 NMR spectrum (101 MHz, DMSO-d_6) of **L4**.

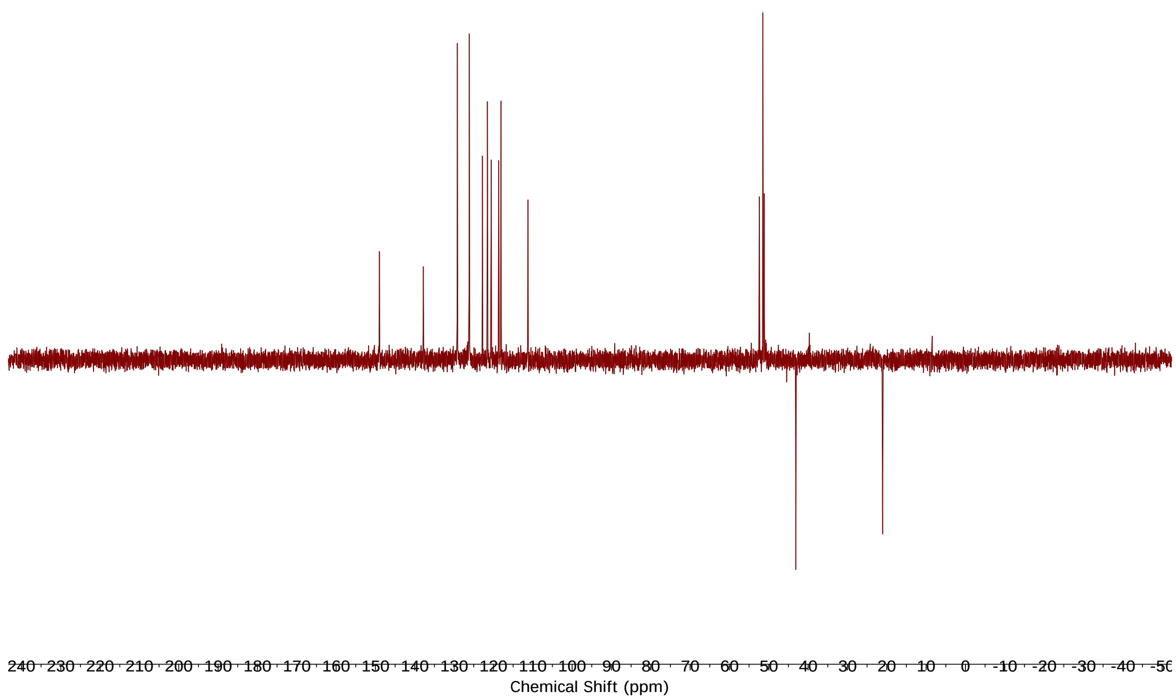


Figure S47. DEPT-135 NMR spectrum (101 MHz, DMSO-d_6) of **L4**.

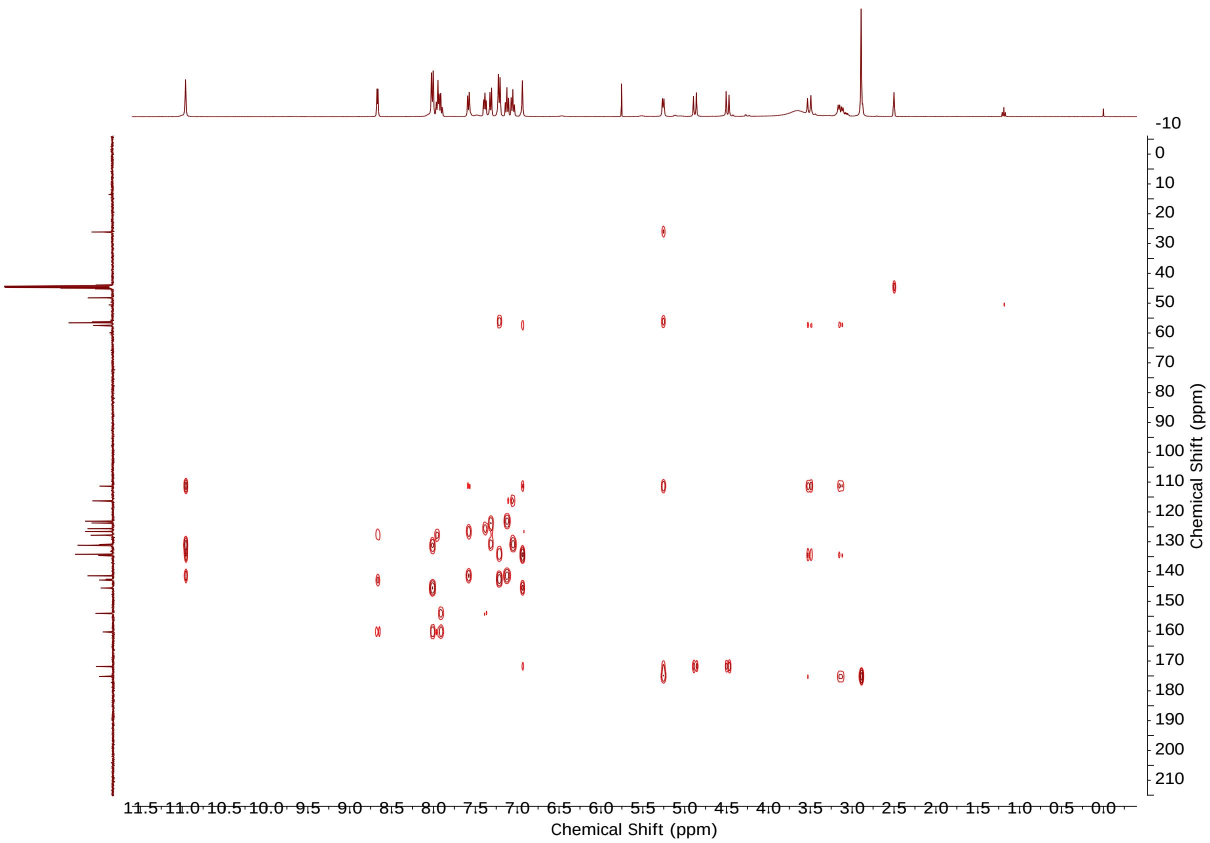


Figure S48. HMBC NMR spectrum (400 MHz, DMSO-d_6) of **L4**.

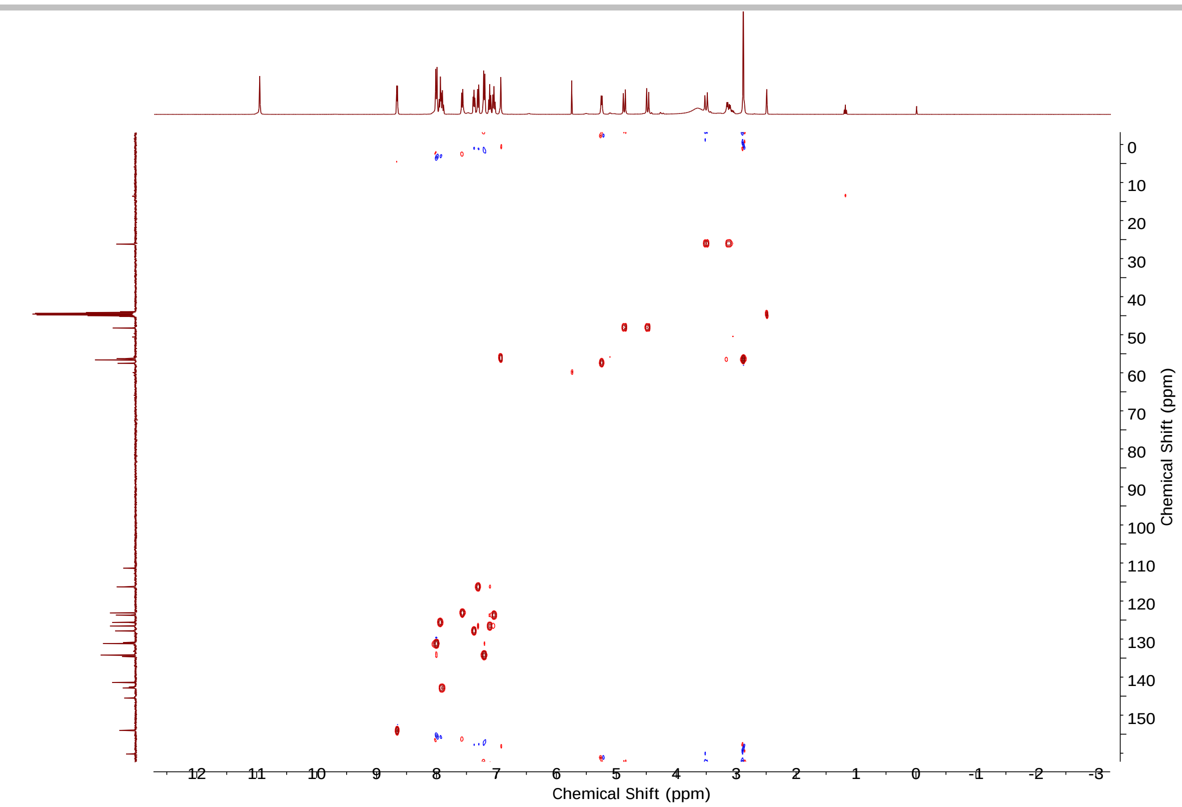
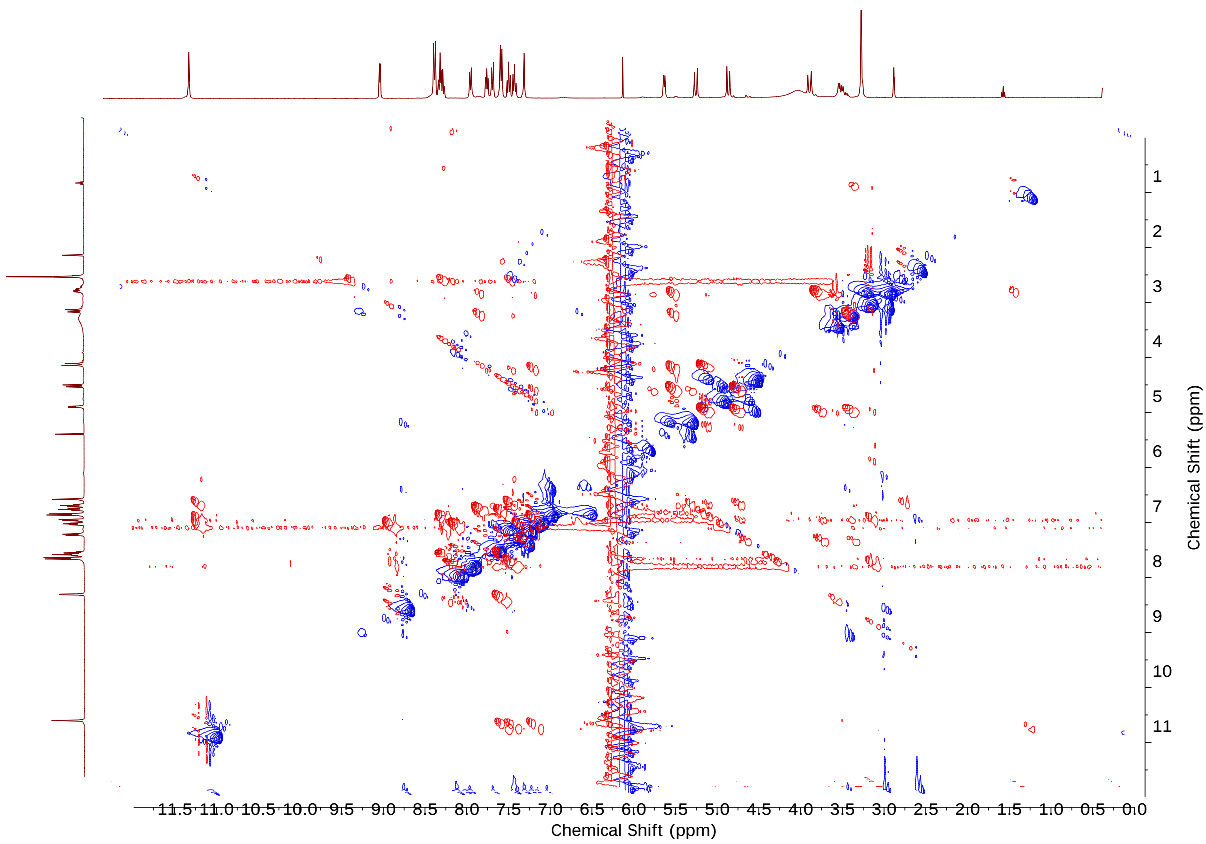


Figure S49. HSQC NMR spectrum (400 MHz, DMSO-d$_6$) of **L4**.



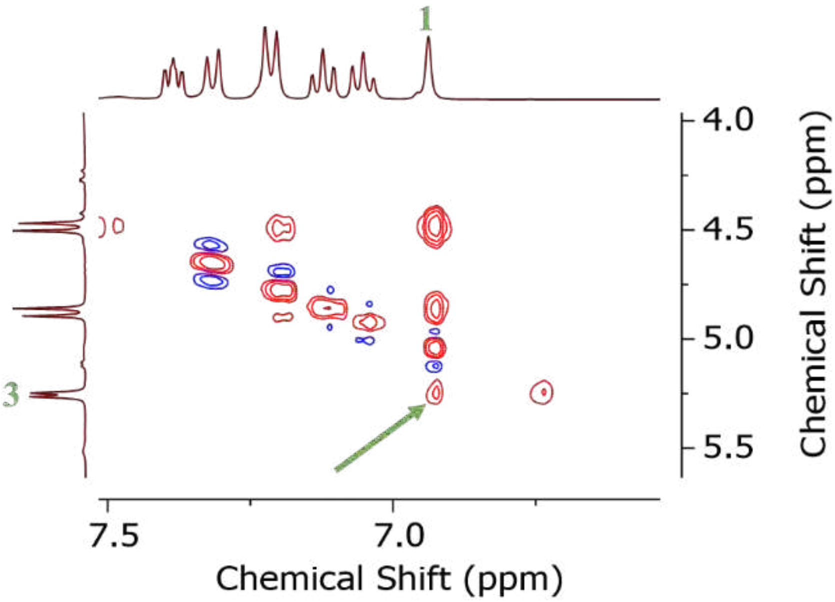


Figure S50. NOESY NMR spectrum (400 MHz, DMSO-d_6) of **L4**.

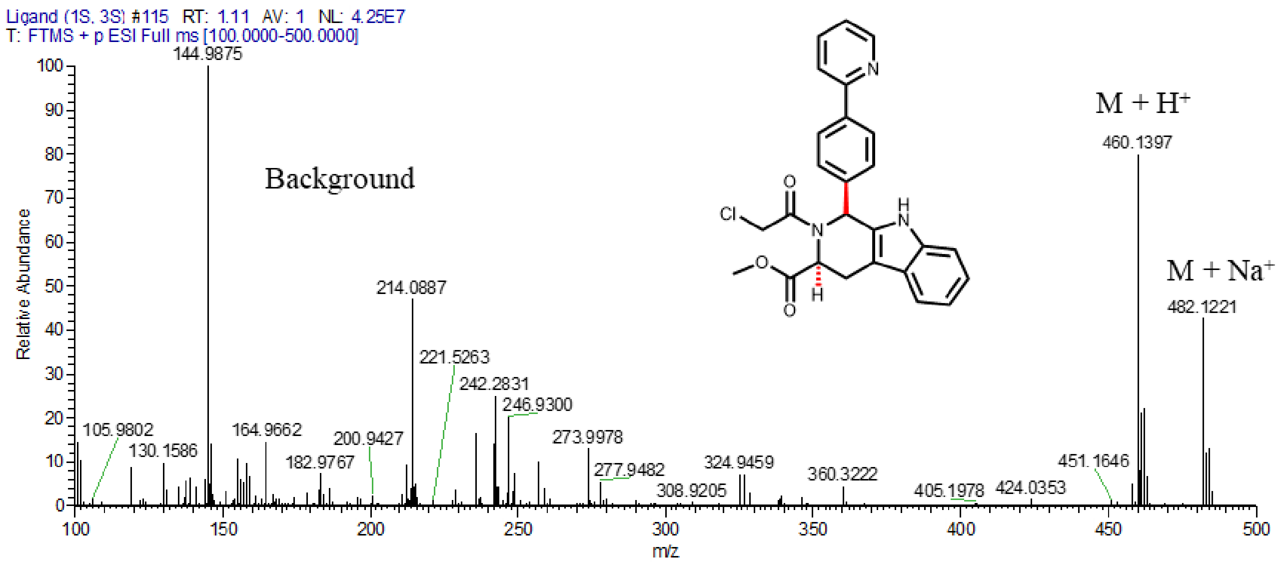


Figure S51. HRMS (solvent: MeCN) spectrum of **L4**.

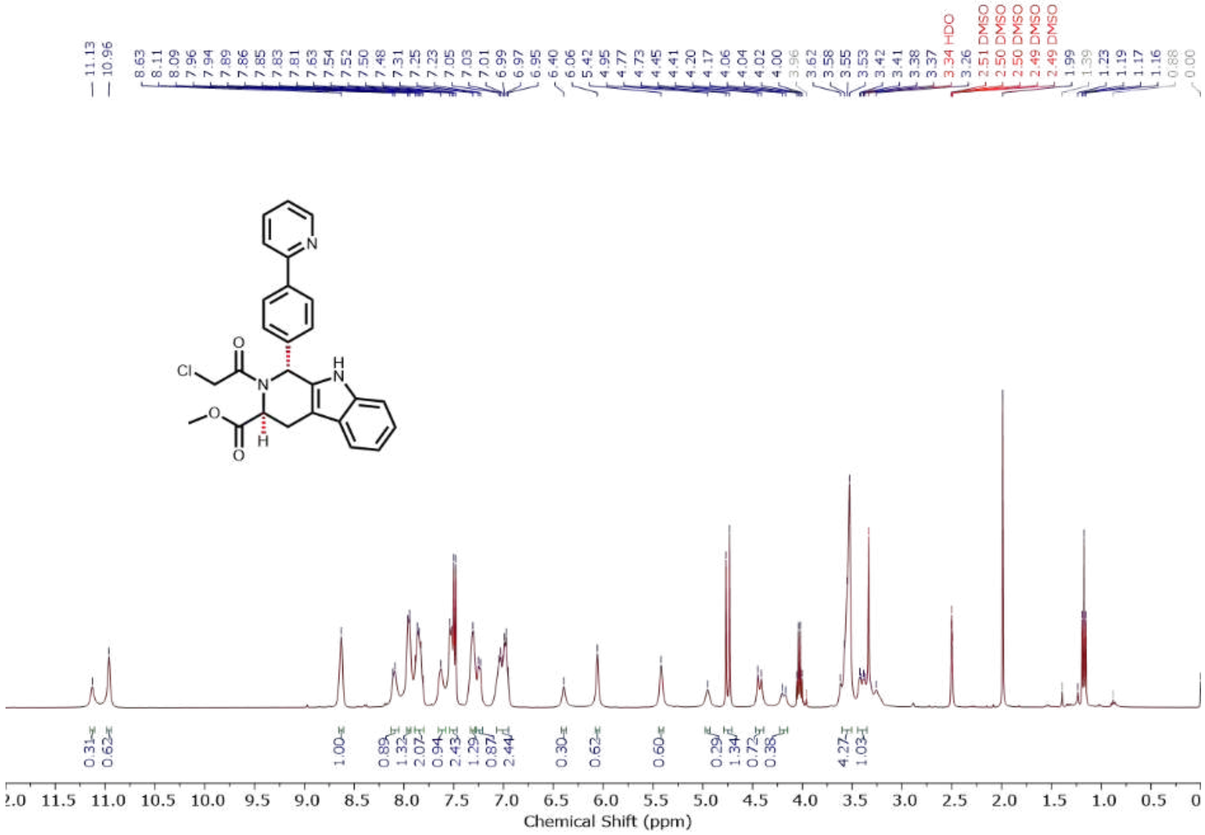


Figure S52. ^{1}H NMR spectrum (400 MHz, DMSO-d$_6$) of **L3**.

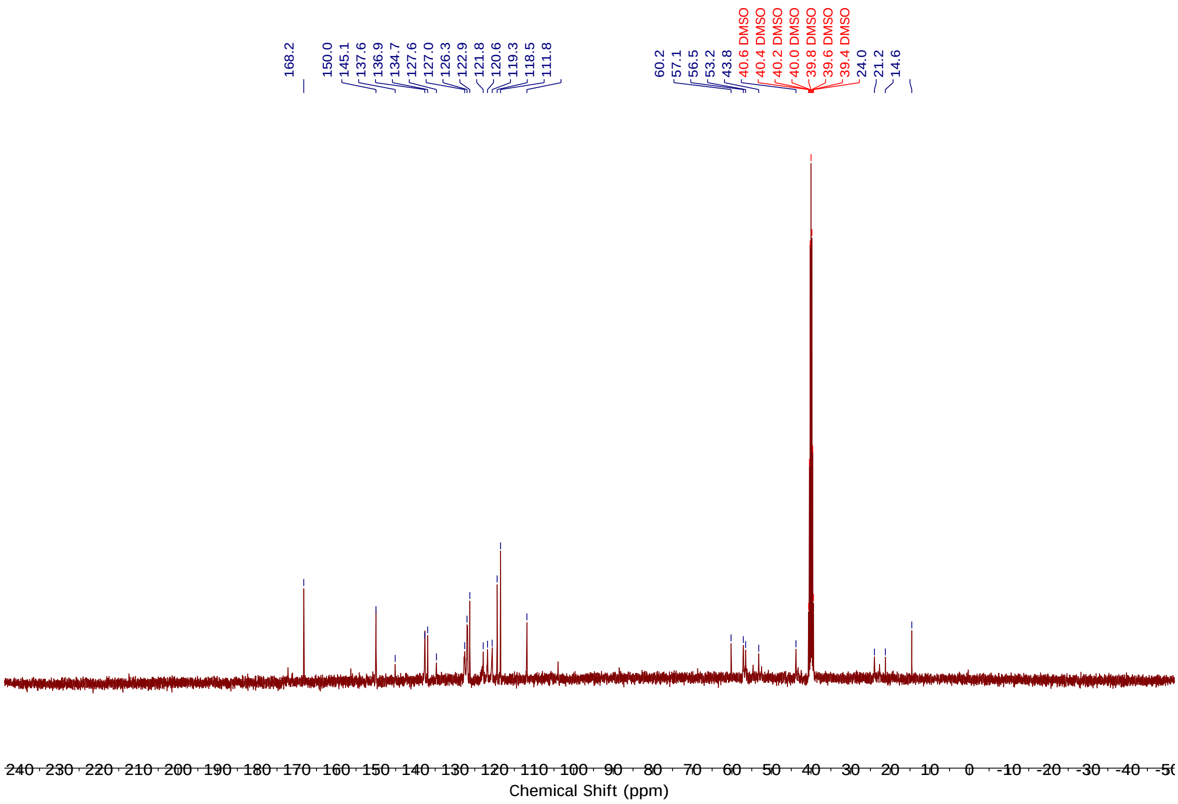


Figure S53. ^{13}C NMR spectrum (101 MHz, DMSO-d$_6$) of **L3**.

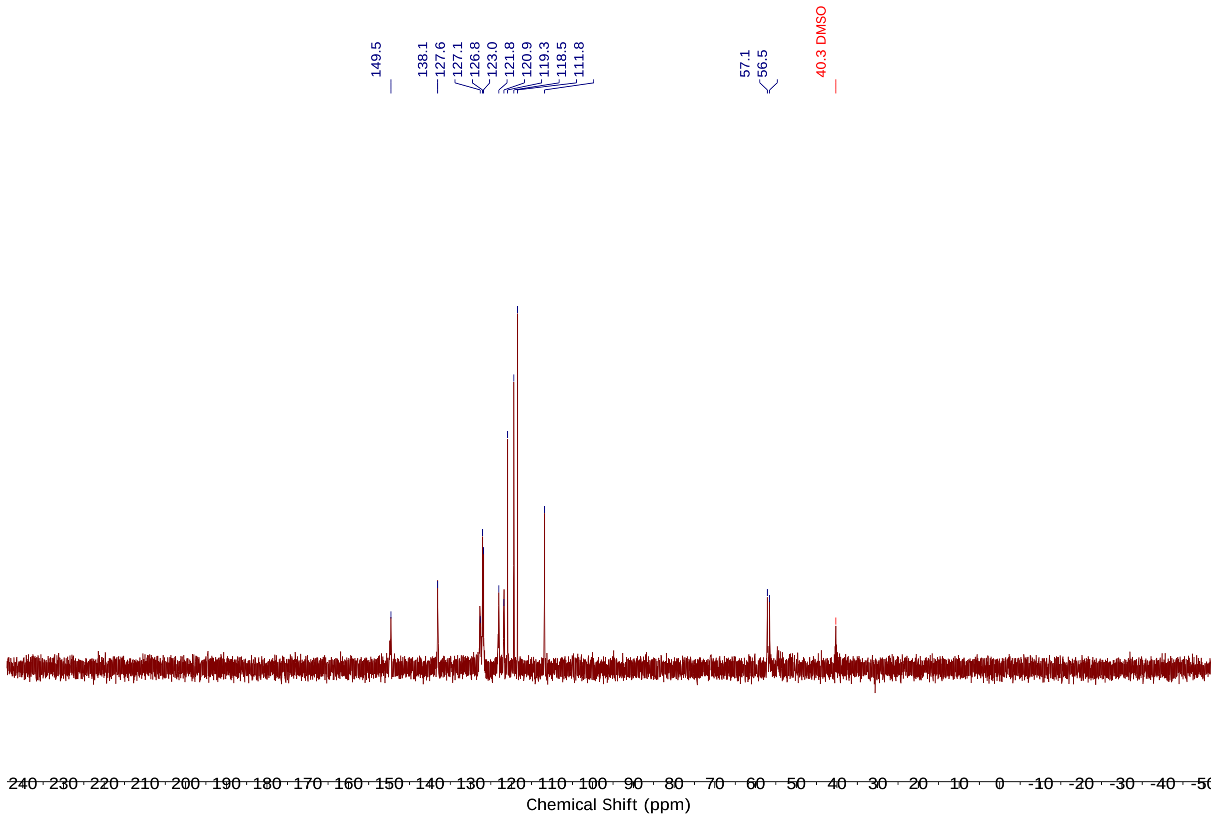


Figure S54. DEPT-90 NMR spectrum (101 MHz, DMSO-d_6) of **L3**.

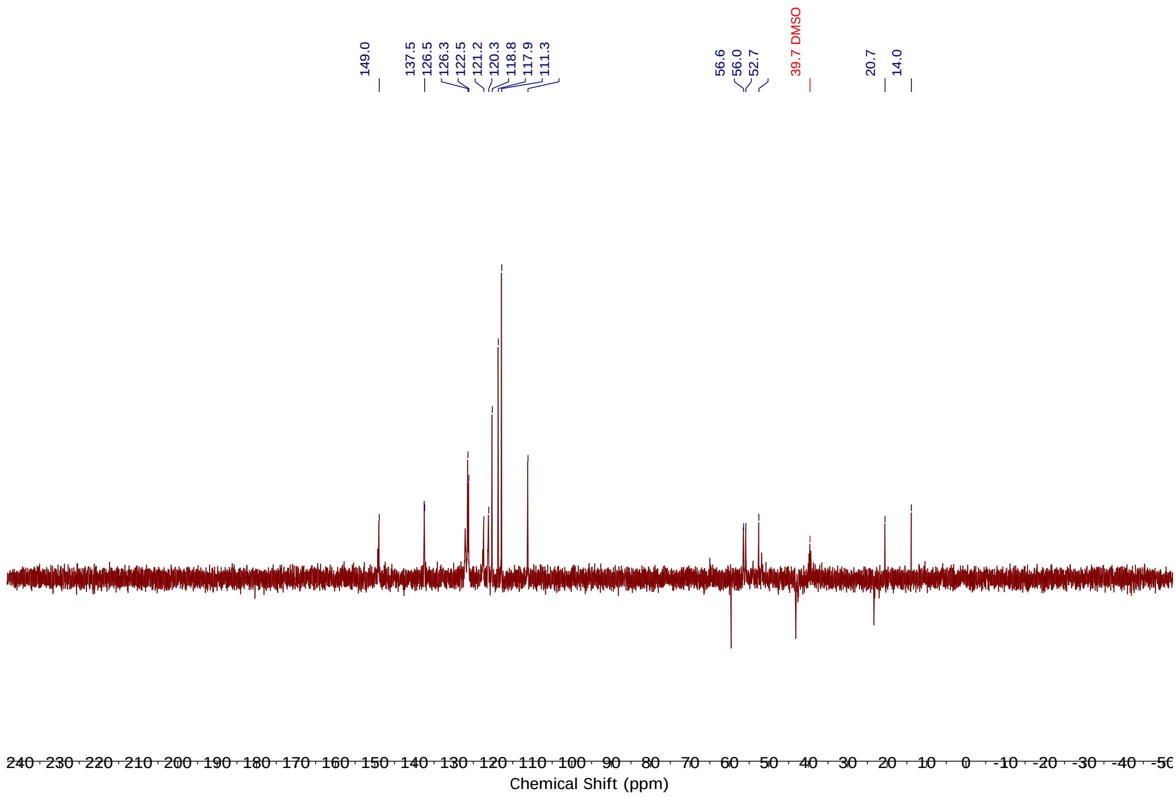


Figure S55. DEPT-135 NMR spectrum (101 MHz, DMSO-d_6) of **L3**.

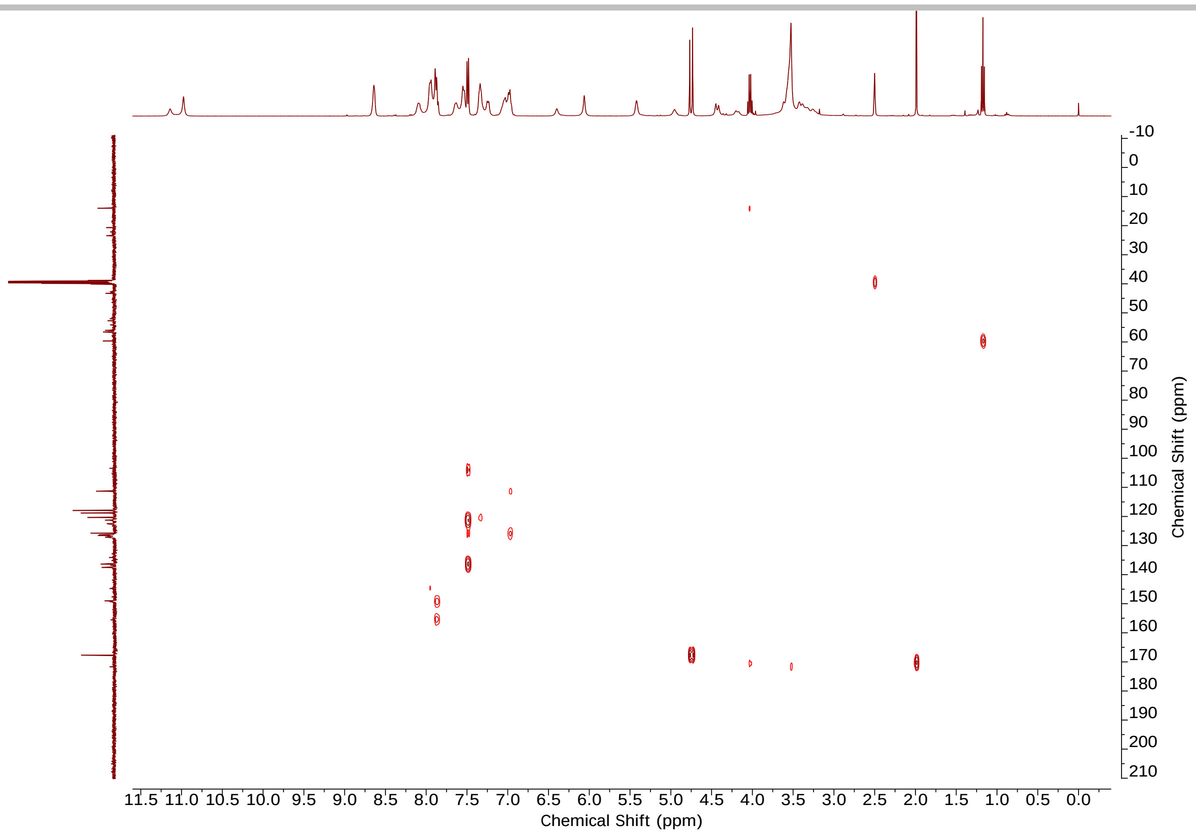


Figure S56. HMBC NMR spectrum (400 MHz, DMSO-d_6) of **L3**.

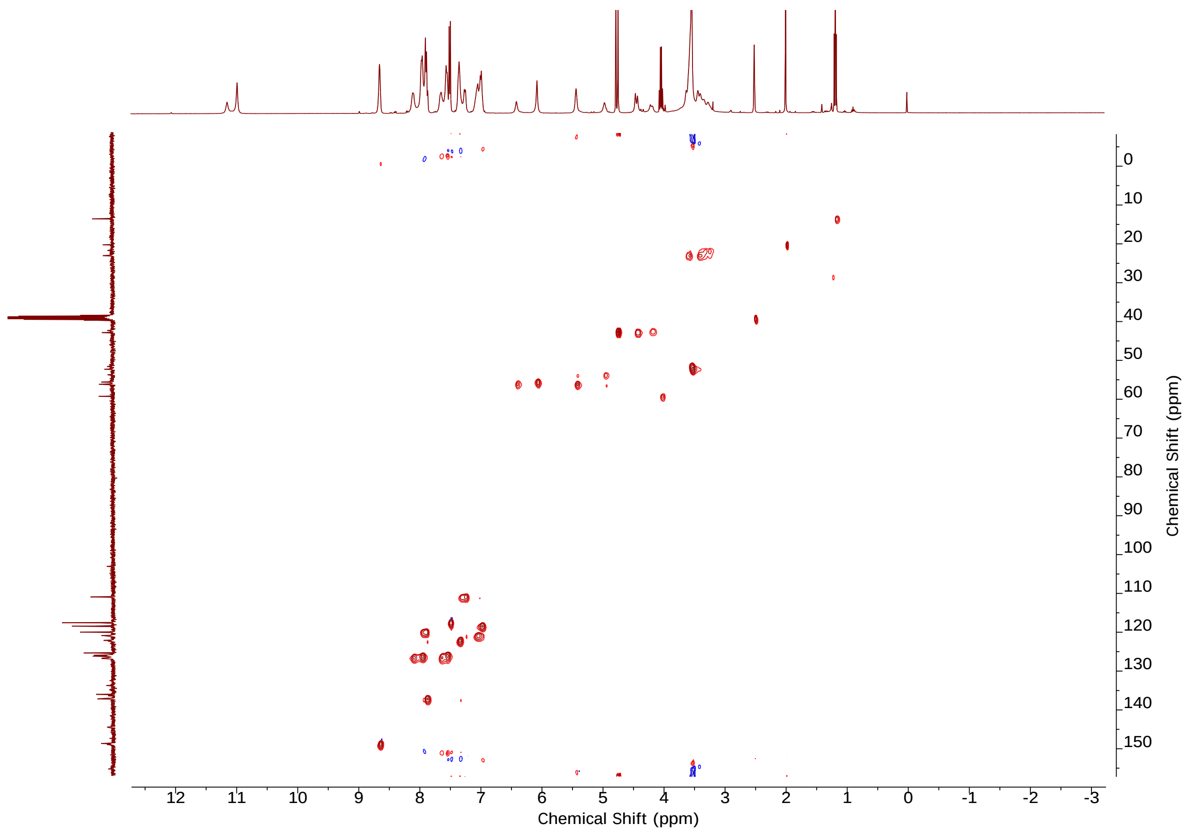


Figure S57. HSQC NMR spectrum (400 MHz, DMSO-d_6) of **L3**.

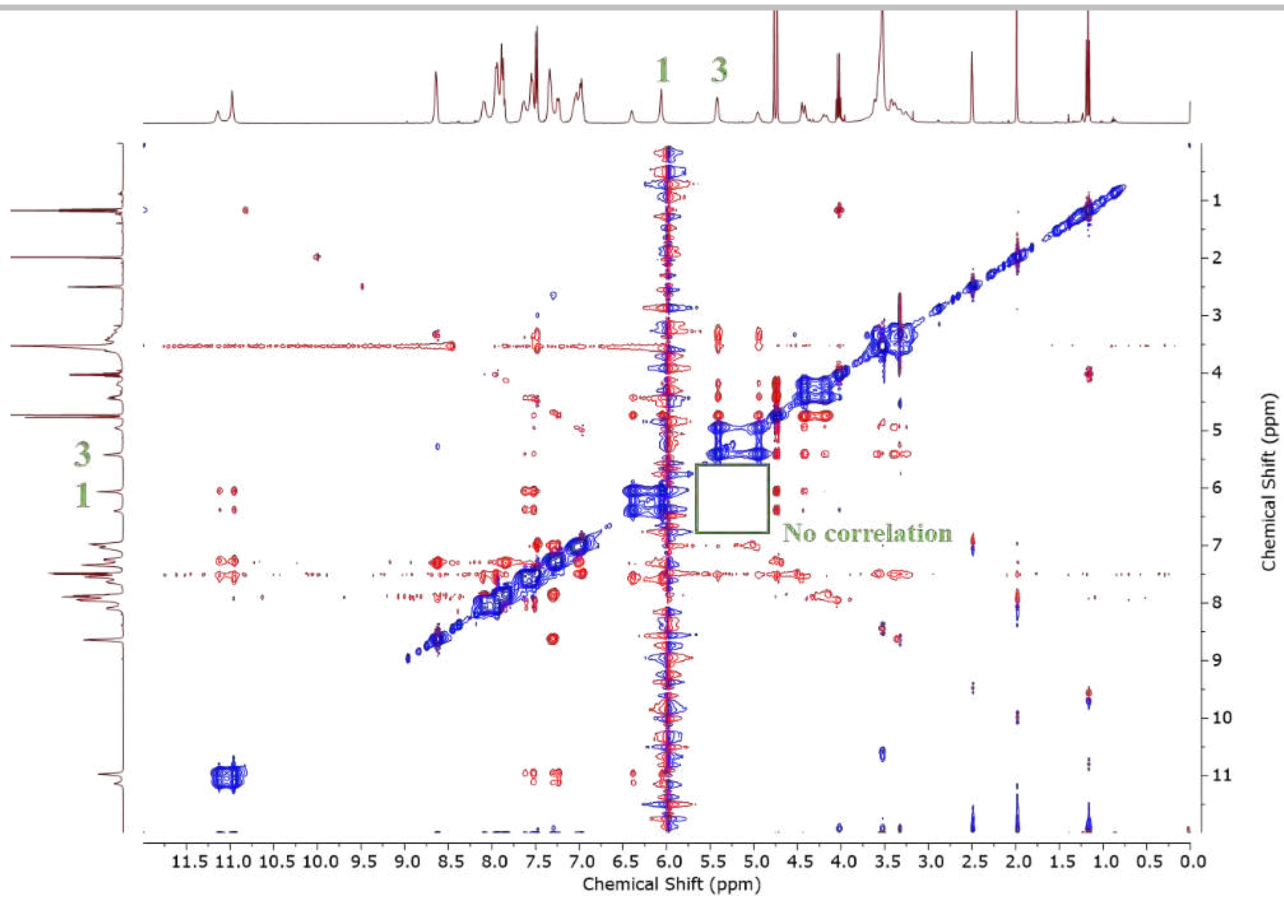


Figure S58. NOESY NMR spectrum (400 MHz, DMSO-d_6) of **L3**.

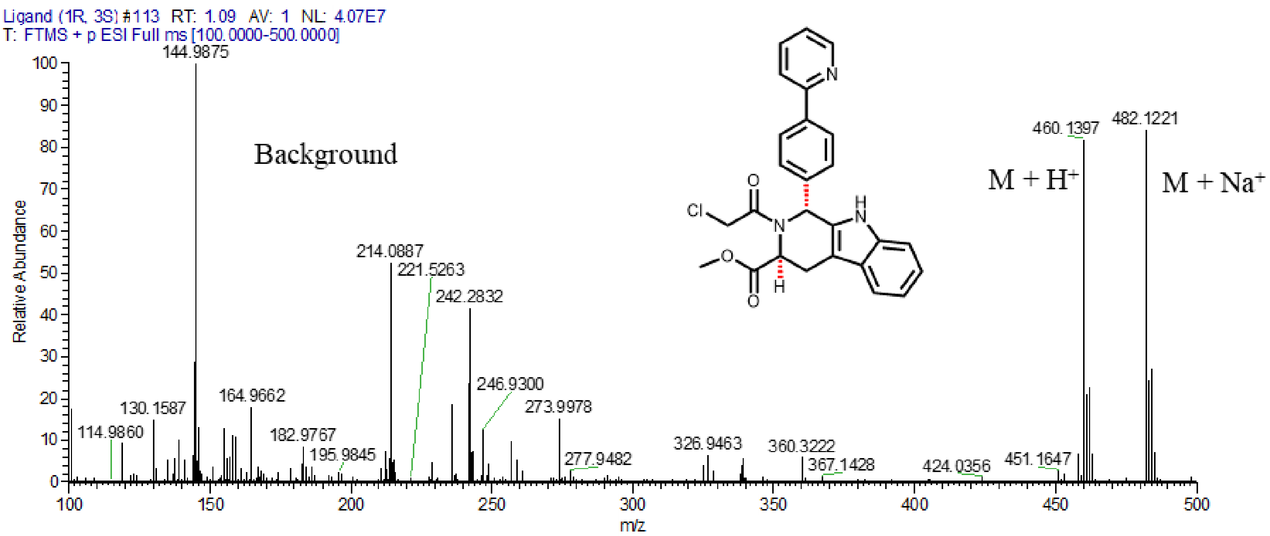


Figure S59. HRMS (solvent: MeCN) spectrum of **L3**.

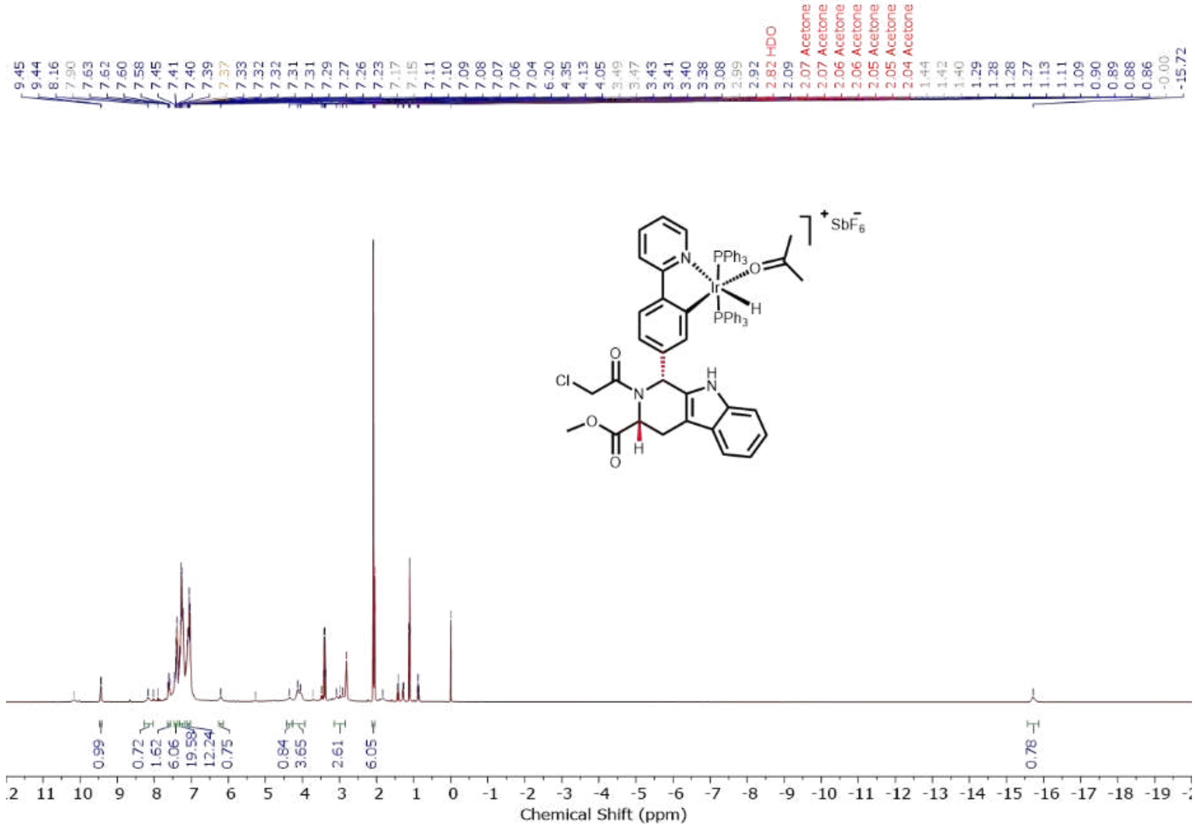


Figure S60. ^{1}H NMR spectrum (400 MHz, Acetone-d_6) of **Ir2**.

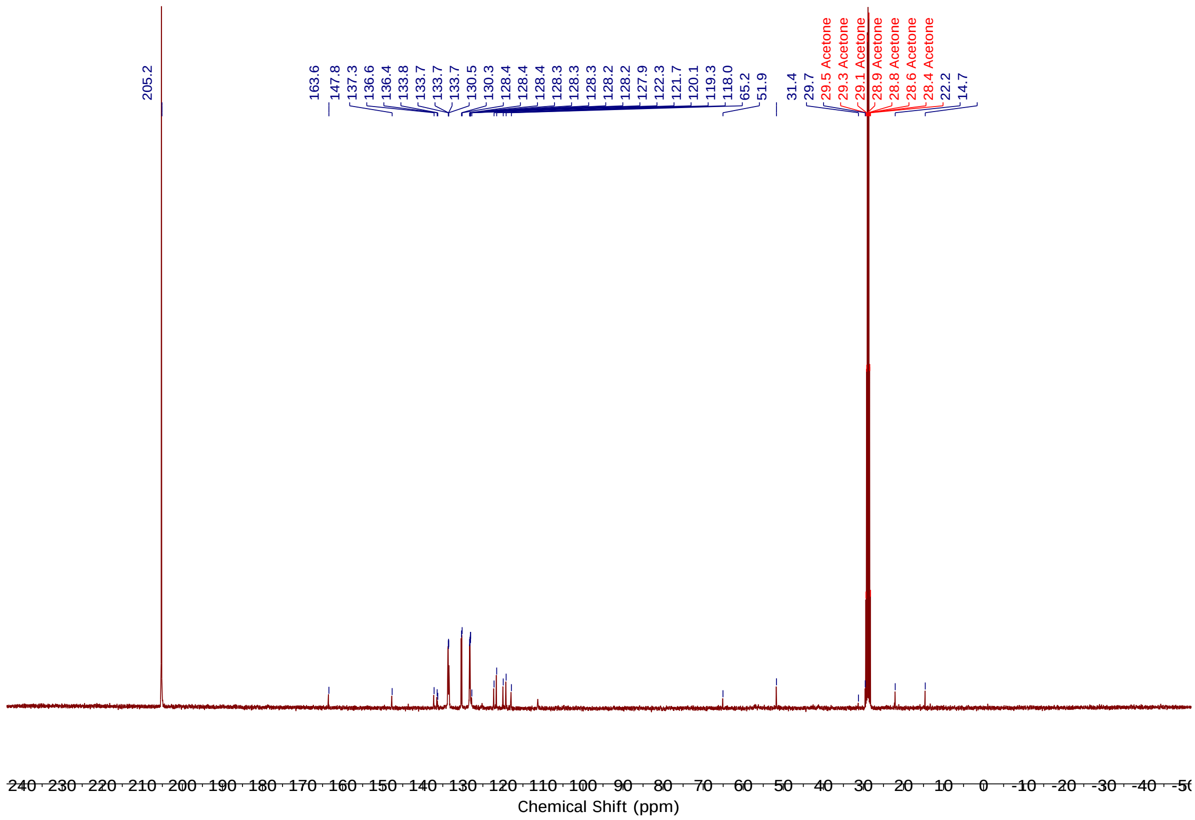


Figure S61. ^{13}C NMR spectrum (101 MHz, Acetone-d_6) of **Ir2**.

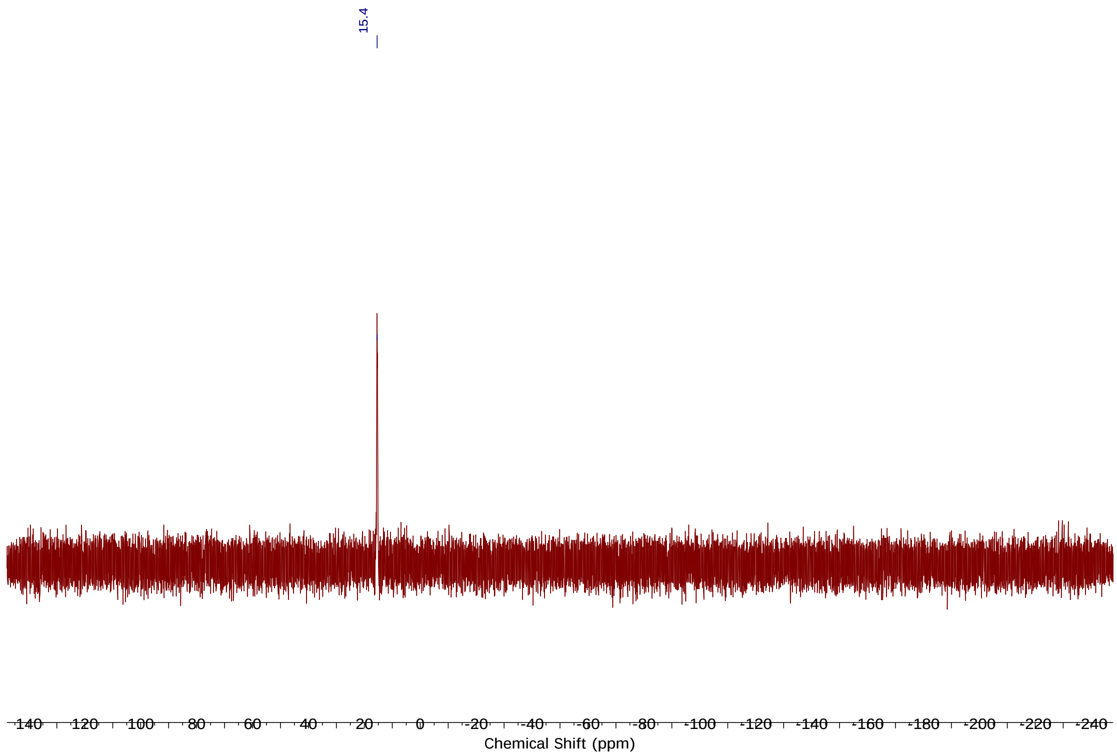


Figure S62. ^{31}P NMR spectrum (162 MHz, Acetone-d_6) of **Ir2**.

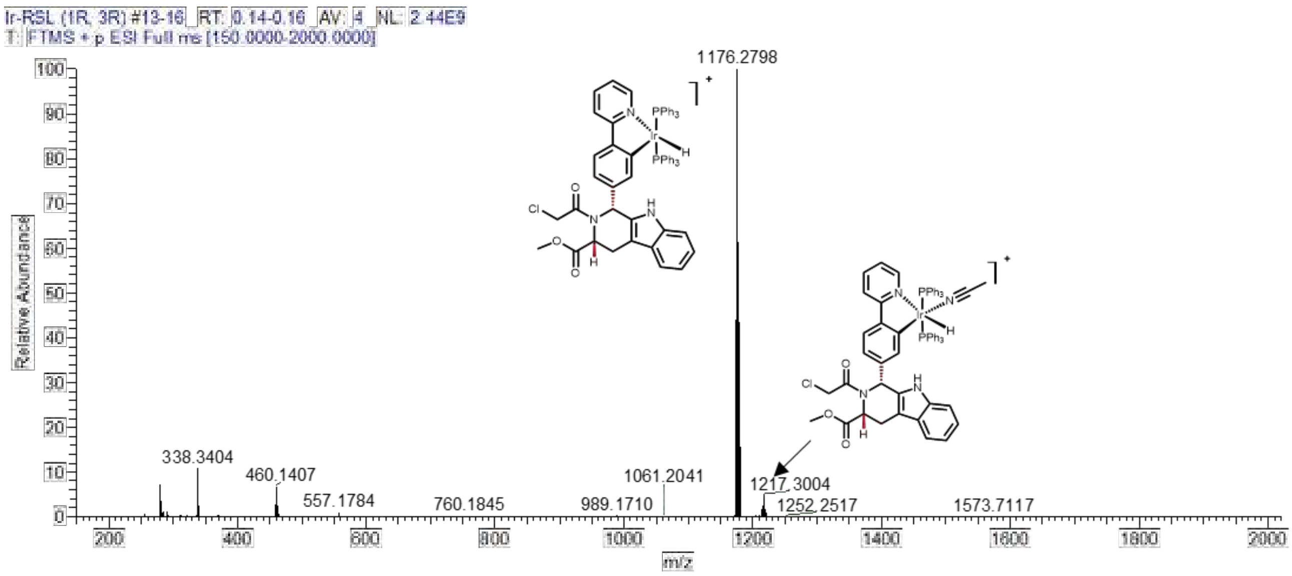


Figure S63. HRMS (solvent: MeCN) spectrum of **Ir2**.

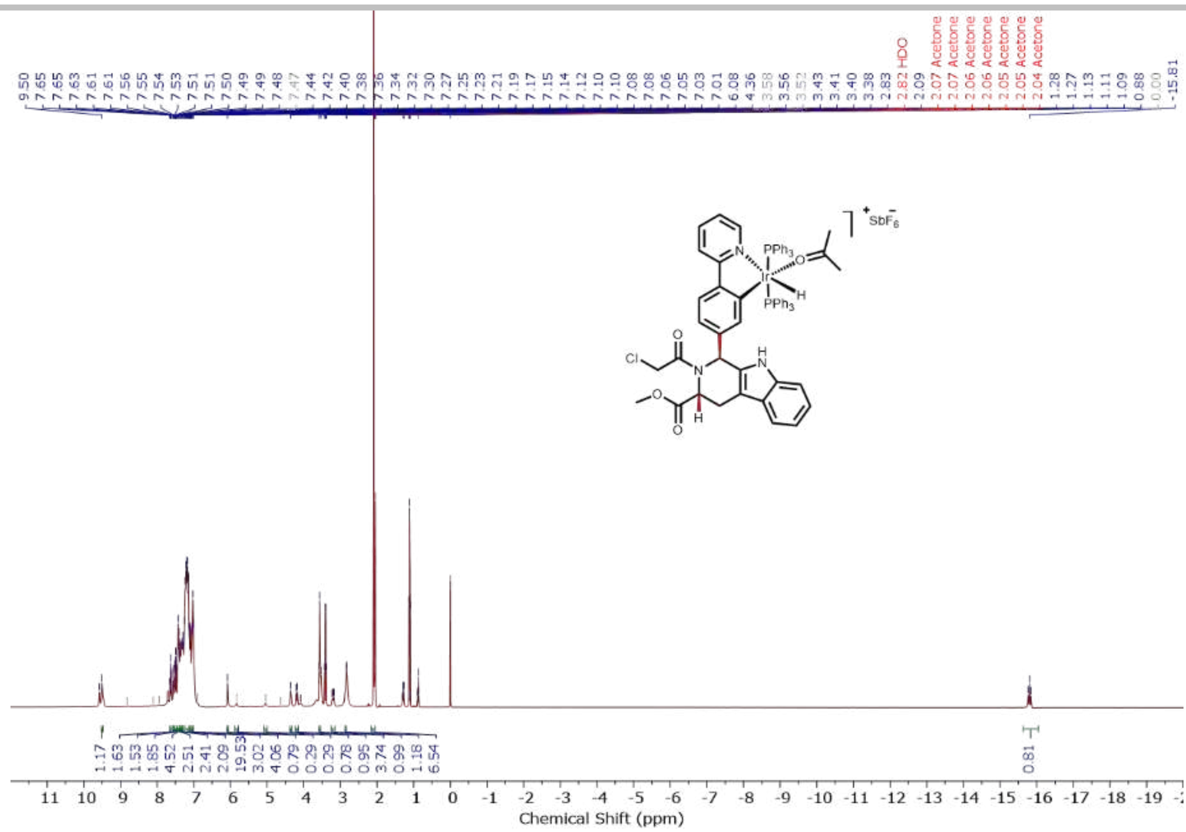


Figure S64. ^{1}H NMR spectrum (400 MHz, Acetone-d_6) of **Ir1**.

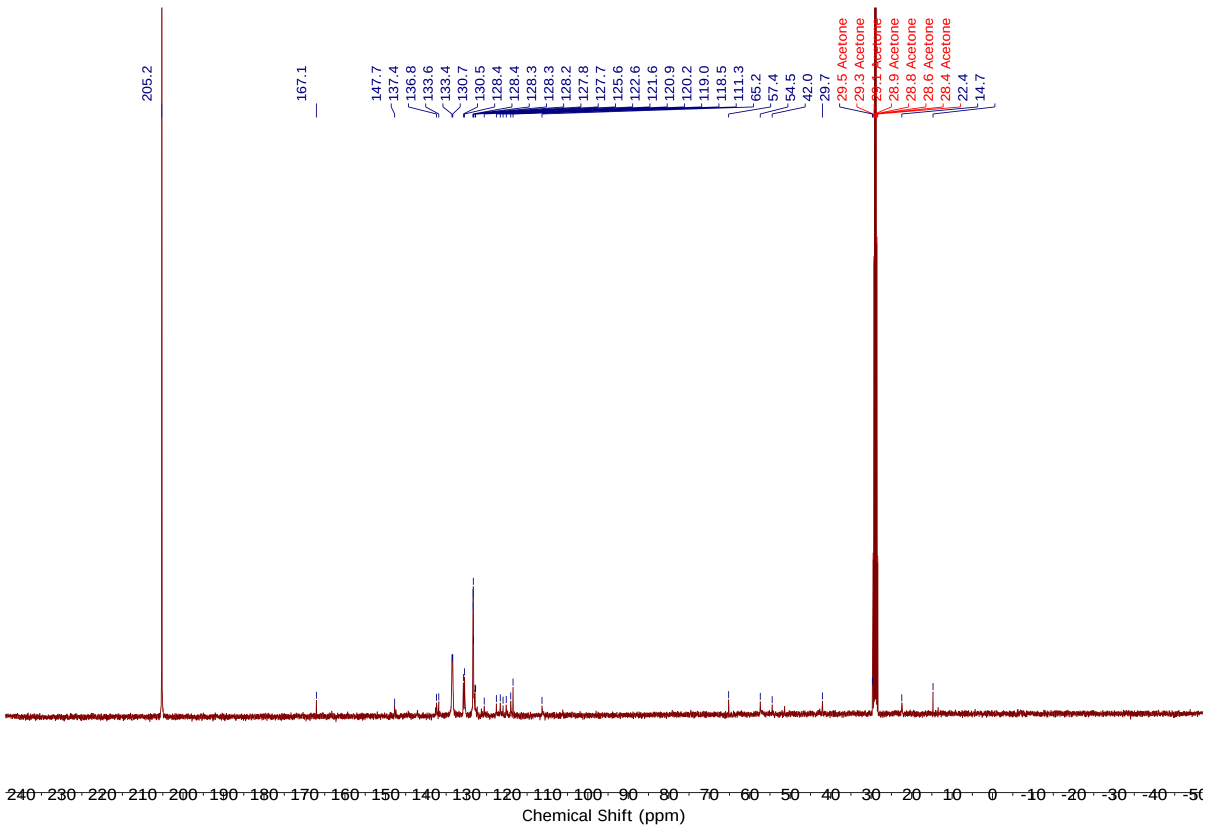


Figure S65. ^{13}C NMR spectrum (101 MHz, Acetone-d_6) of **Ir1**.

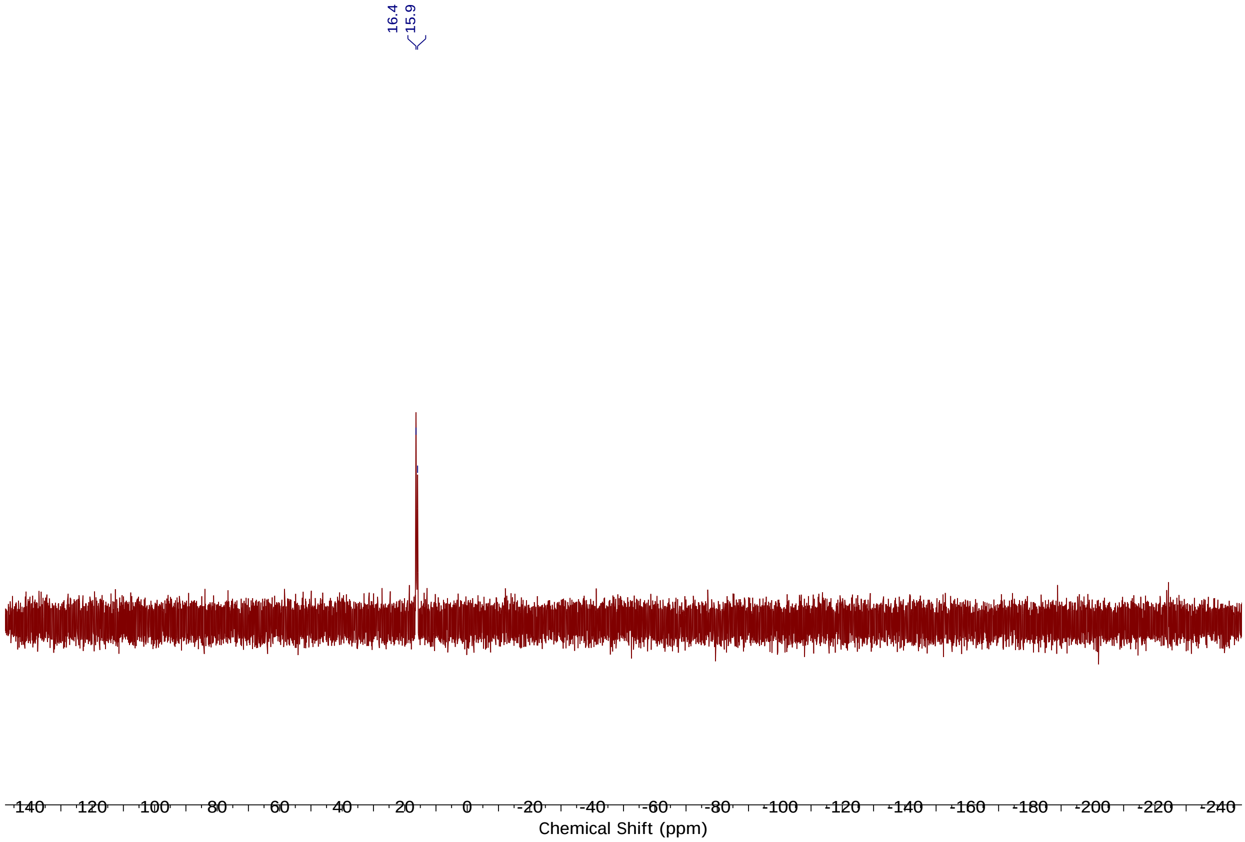


Figure S66. ^{31}P NMR spectrum (162 MHz, Acetone-d_6) of **Ir1**.

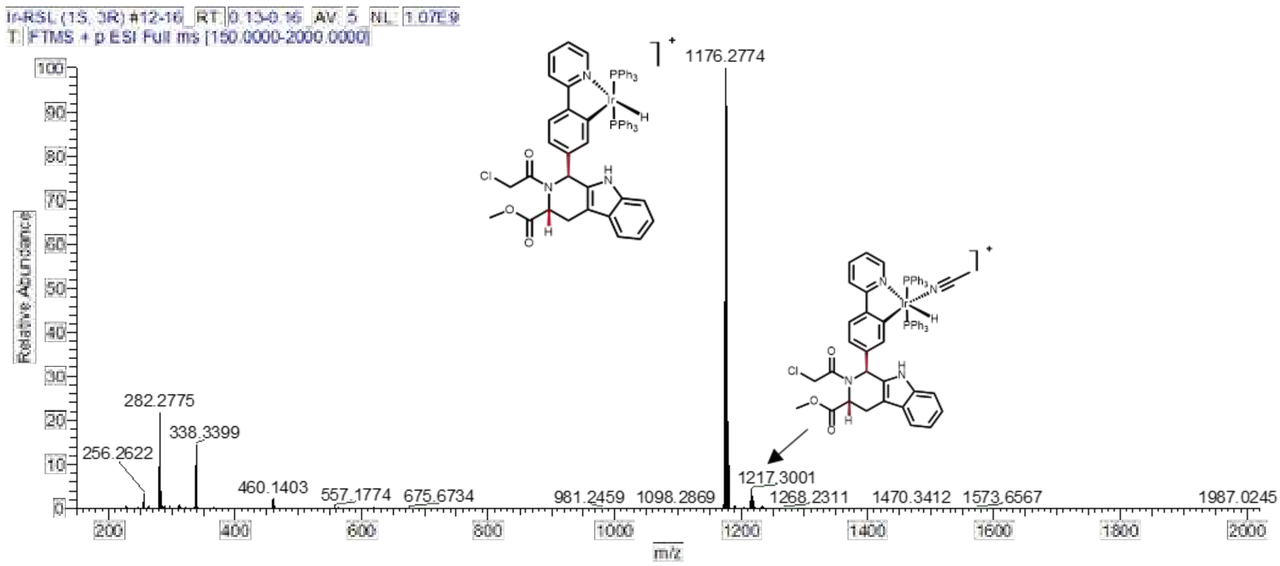


Figure S67. HRMS (solvent: MeCN) spectrum of **Ir1**.

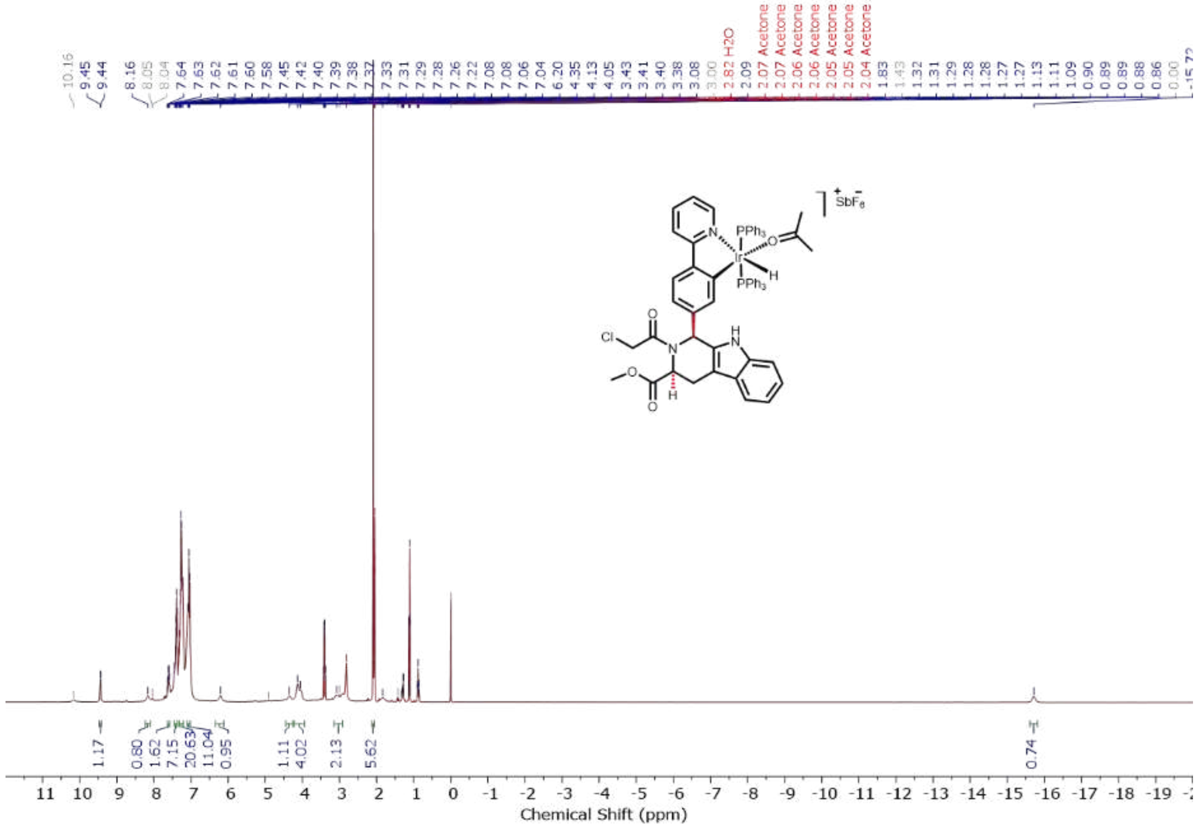


Figure S68. ^{1}H NMR spectrum (400 MHz, Acetone-d_6) of **Ir4**.

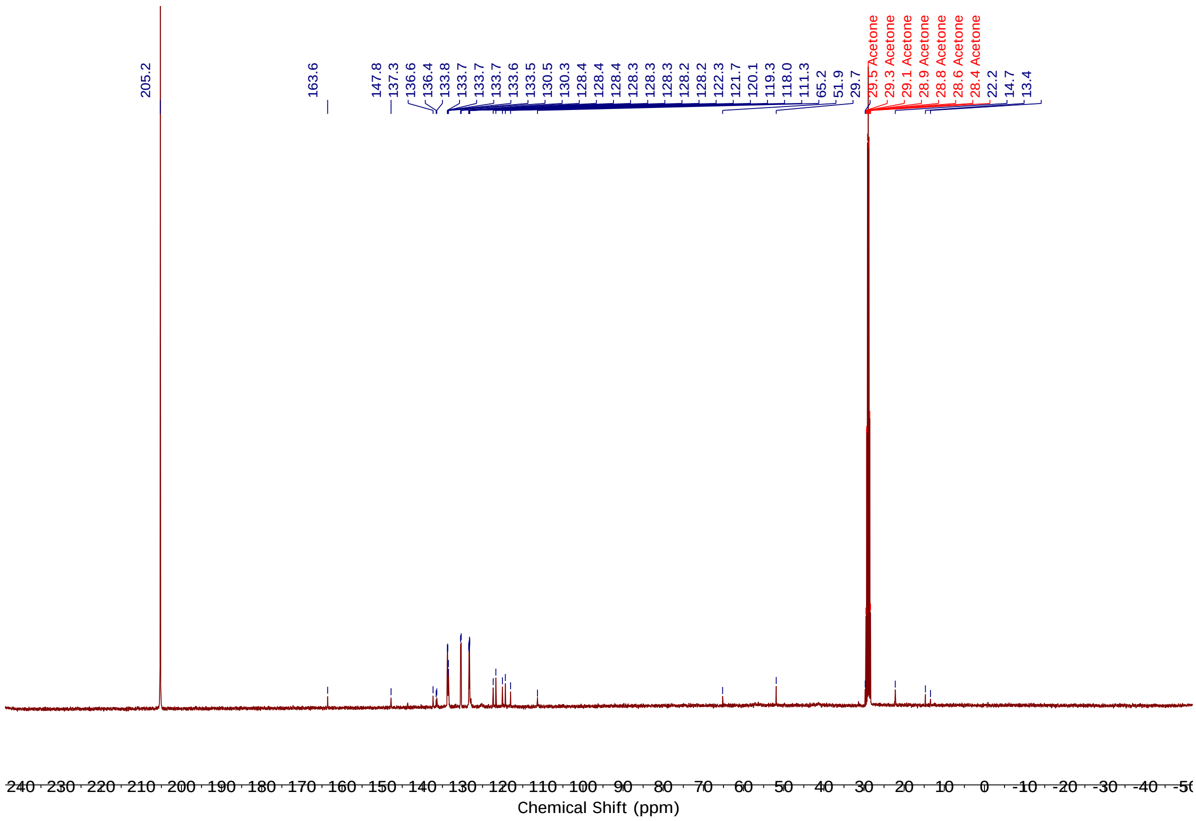


Figure S69. ^{13}C NMR spectrum (101 MHz, Acetone-d_6) of **Ir4**.

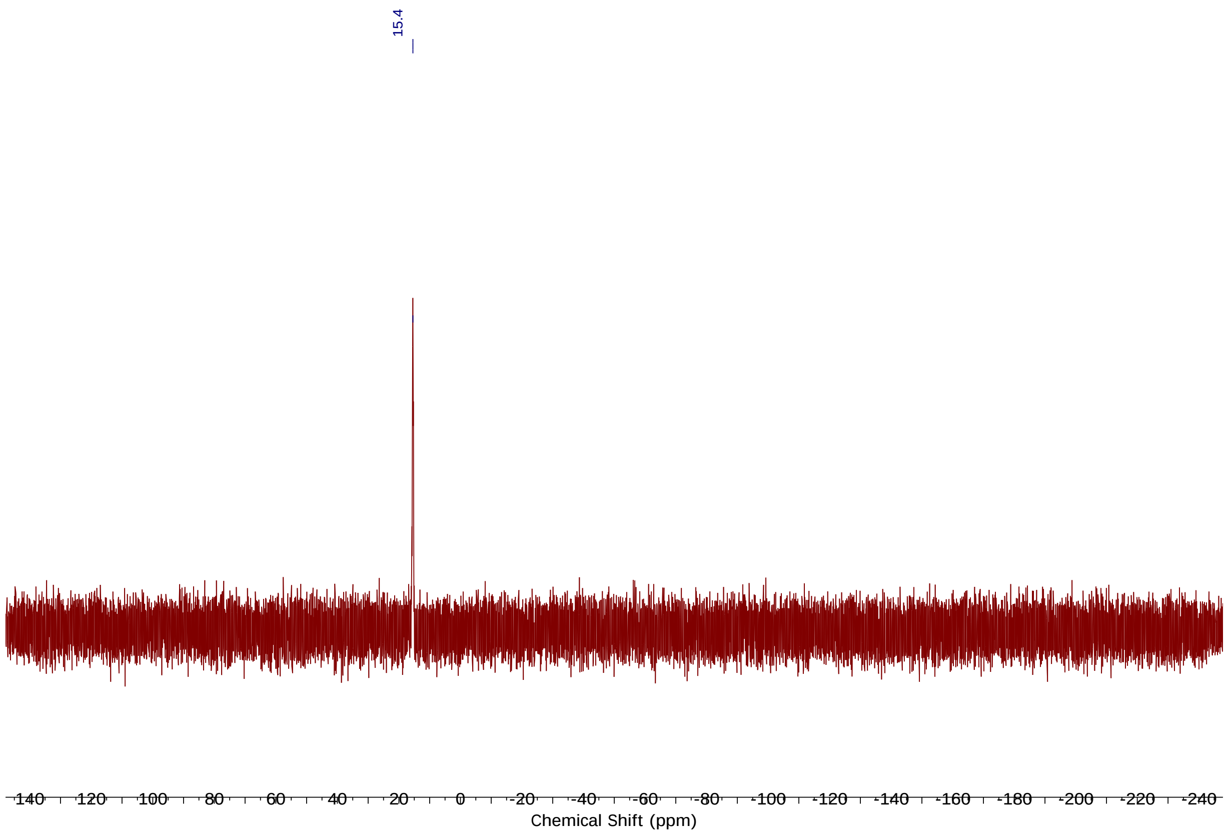


Figure S70. ^{31}P NMR spectrum (162 MHz, Acetone-d_6) of **Ir4**.

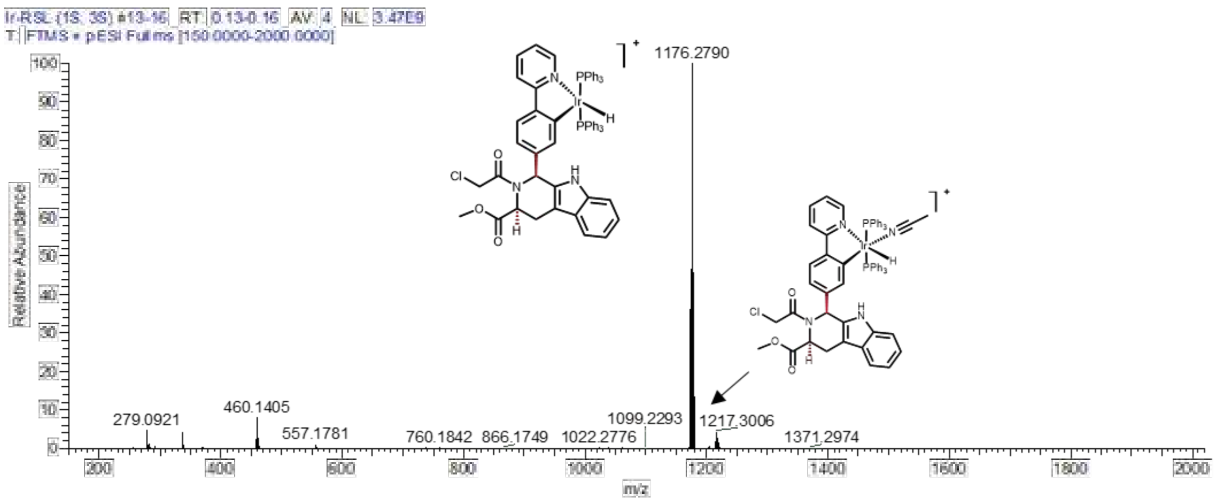


Figure S71. HRMS (solvent: MeCN) spectrum of **Ir4**.

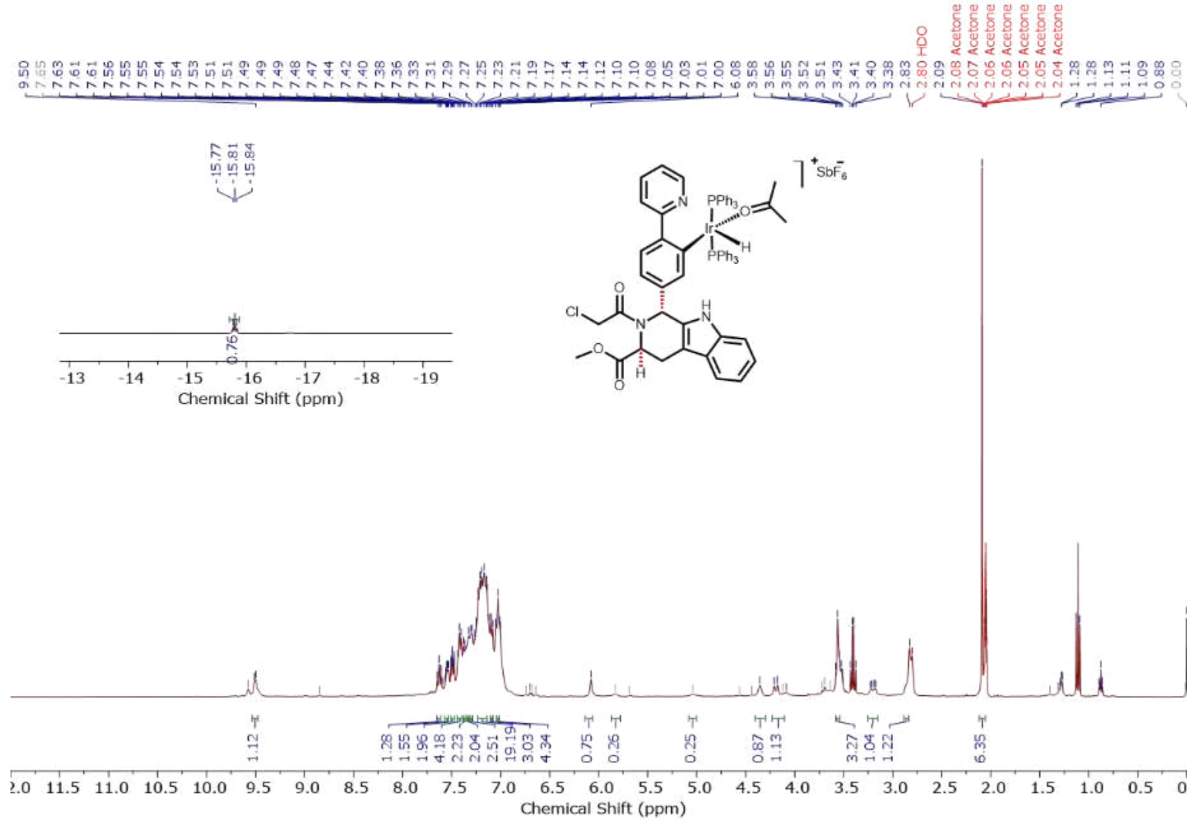


Figure S72. ^{1}H NMR spectrum (400 MHz, Acetone-d_6) of **Ir3**.

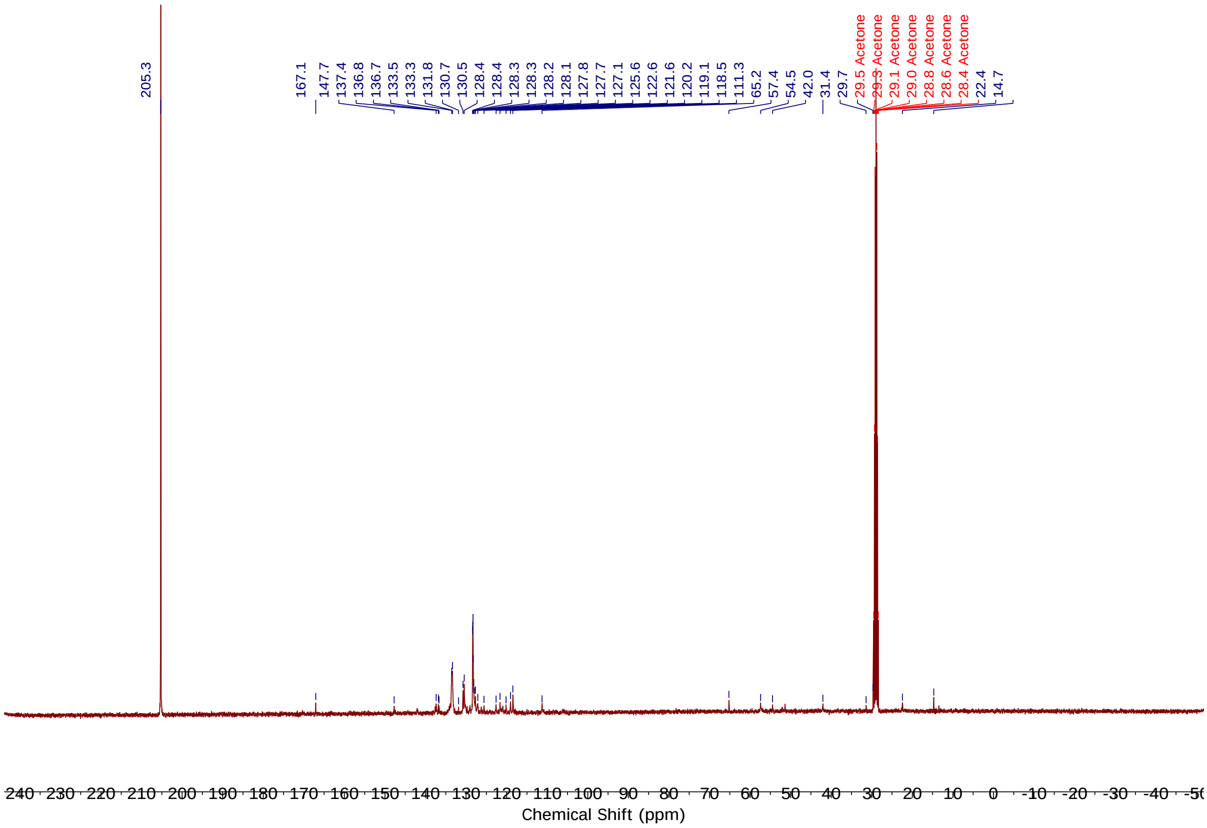


Figure S73. ^{13}C NMR spectrum (101 MHz, Acetone-d_6) of **Ir3**.

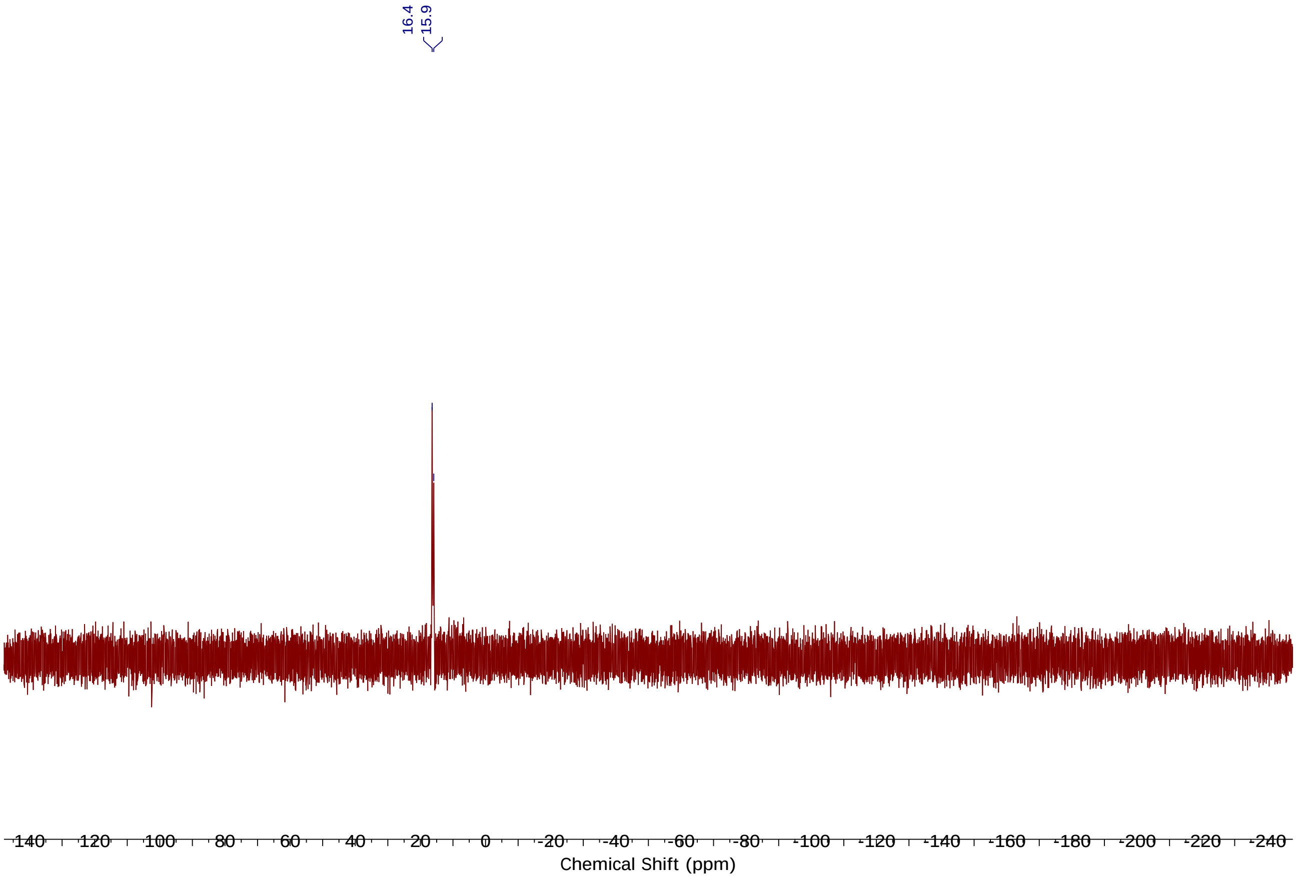


Figure S72. ^{31}P NMR spectrum (162 MHz, Acetone-d_6) of **Ir3**.

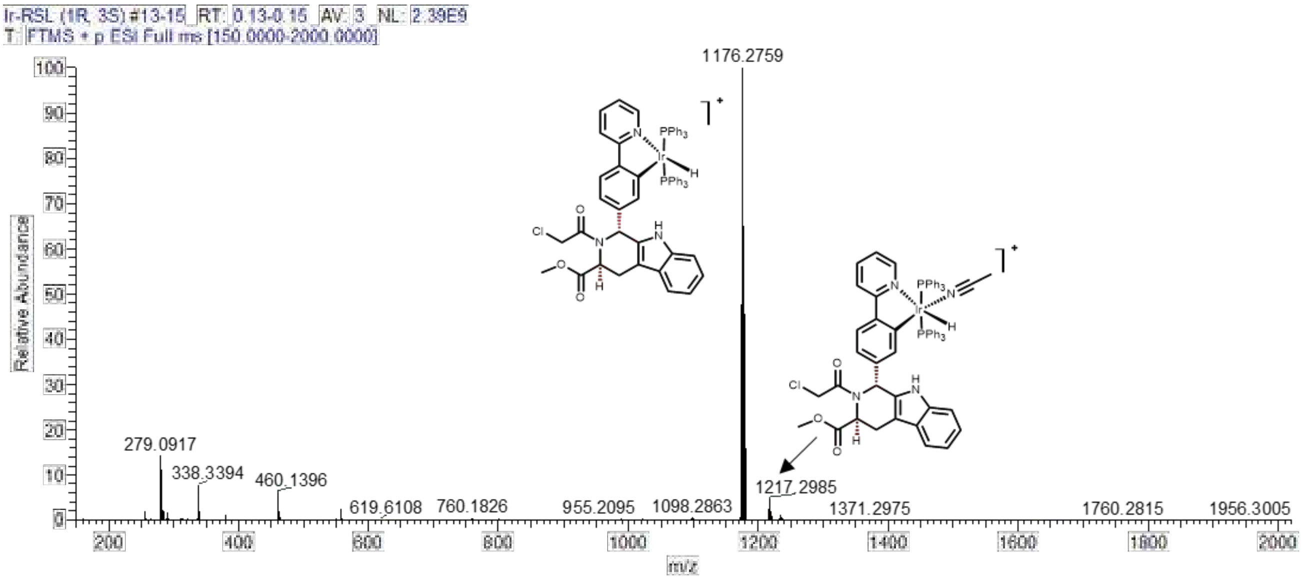


Figure S74. HRMS (solvent: MeCN) spectrum of **Ir3**.

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[1] X. Song, Y. Qian, R. Ben, X. Lu, H.-L. Zhu, H. Chao, J. Zhao, *J. Med. Chem.* **2013**, *56*, 6531-6535.
[2] W. S. Yang, R. SriRamaratnam, M. E. Welsch, K. Shimada, R. Skouta, V. S. Viswanathan, J. H. Cheah, P. A. Clemons, A. F. Shamji, C. B. Clish, L. M. Brown, A. W. Girotti, V. W. Cornish, S. L. Schreiber, B. R. Stockwell, *Cell* **2014**, *156*, 317-331.