Supporting Information

Methods

MTT assay

Stock solutions (10mM) of the ligands and Sn complexes were prepared by dissolving the complexes in DMSO, and diluted to various concentrations with PBS. The MTT assay was employed to investigate cell toxicity. Briefly, all cells were seeded in 96-well plates (2×10^5 cells/mL). After incubation for 24 h, the complexes were added to the culture medium at various concentrations and the cells were incubated for 48 h. MTT solution (10 mL) was added to each well and incubated for 4 h. One-hundred microliters of DMSO was added to each well after the culture medium was removed. The absorbance was measured by an enzyme-labelling instrument and IC_{50} values were calculated.

X-ray crystallography

To obtain X-ray crystal data, the single crystals of five Sn(II) compounds were analyzed using Bruker Apex-II CCD diffractometer. Olex2 software was used to analyze the structure of the compound. Crystal data for Sn(II) compounds are listed in Table 1, while selected bond lengths and angles are shown in Tables S1 and S2.

Cellular uptake

To investigate the underlying mechanisms of the enhanced activity of the modified complexes, ICP-MS was performed to detect distribution of

the complexes in cancer cells. Briefly, the selected cells were treated with the five complexes at the same dose (1 mM) for 24 h, the mitochondria isolation kit and nuclei isolation kit were used to separate and extract the mitochondrial membrane fraction, nuclear fraction, and cytoplasm. Meanwhile, Sn content in the control cells was also measured.

3D tumor spheroid model

Hela cells with good digestion and logarithmic growth were cultured in Corning 96-well 3D spherical plate for 24 h with a certain amount of cell suspension. After the cells spontaneously formed 3D cell spheres, a certain concentration of C5 was added, and 3 multiple pores were set at each concentration. The morphology of the cells was observed with an inverted microscope for 8 days.

5×10^4 Hela cells were placed in specially treated 96-well plates and cultured for 2-3 days until the cells aggregated into dense 3D tumor spheres [1]. The selected compounds at a concentration of 8 μM were added to 96 well plates and incubated for 12 h. Then, the samples were removed from the medium and stained for 0.5 h with a mixed solution: 1 μl Calcein-AM (20 nM) and 3 μl PI (15 nM) in 1×Assay Buffer. The final results were observed by an inverted fluorescence microscope.

Wound healing assay

Scratch wound healing assay was performed in Hela cell lines to investigate the effect of complexes on cancer cell migration. In short,

2×10^5 Hela cells were cultured in a six-well plate, and the cell population increased to 90 %. The sterile toothpick was then used to draw a straight line. After washing with cold PBS three times, serum-free medium was incubated with C5 (1μM, 2μM) Photographs were taken at different time points (0,12 hours) using a open-field inverted microscope.

Invasion assays

Briefly, 75 μL matrigel solution (1 mg/mL) was placed into each well and allowed to solidify for 60 min, and 5×10^4 Hela cells with or without treatment were added in the upper chamber, whereas 600 μL of medium was placed to the lower well. After incubation in a constant temperature incubator for 24 h, the underlying cells were immobilized with methanol and stained with crystal violet.

Cell apoptosis assay

After treatment of Hela cells with C5, apoptosis in Hela cells was determined by double staining (Annexin-V and PI). The Hela cells were cultured, treated with C5 (1 μM and 2 μM) and collected by centrifugation. The cells were incubated in 200 μl of Annexin v binding buffer, and 5μl of Annexin-V was added to each cell's tube, excepting PI control. The cells were then incubated at 37 °C for 20 mints in the dark. After 20 mints, 300μl of 1x-Annexin-V binding buffer was added to each tube, followed by 4 μl of PI to each cell's tube, except the Annexin-V control and 20 minutes of incubation in dark at 37 °C. The cells were then

analyzed for apoptosis using flow cytometry.

Measurement of the Δψm

A flow cytometer employing JC-1 probe was used to detect changes in Δψm in Hela cells. The cells in 6-well plates were exposed to C5 (1 or 2 μM) for 24 h, harvested, and washed twice with cool PBS solution. JC-1 stock solution was added to the cells and incubated for 30 min. A flow cytometer was used to detect the fluorescence of separated cells.

UV spectroscopy determination DNA binding with C5

calf thymus DNA (CT DNA) drops gradually to the C5 buffer solution containing concentration for 20 μM (including 5 mM Tris HCl, 50 mM NaCl than dishes of color, 5 min at room temperature after each drop and balance, under the condition of wavelength is 200-800 nm, and then use the UV-vis spectrum measurement, get a series of corresponding absorbance values, with the Origin drawing can be UV curve.

Fluorescence spectroscopy determination DNA binding with C5

EB was used as the control to measure the binding ability of the drug and DNA. The Tris HCl buffer solution pH=7.2 was added to the colorimetric dish with light transmission on both sides, and then EB was mixed and then CT DNA was added. As a control, C5 was added continuously and incubated for 5 min at room temperature. The fluorescence curves were measured with a fluorescence spectrometer at the excitation wavelength scanning interval of 540-750 nm.

DNA cleavage studies

Briefly, supercoiled plasmid pBR322 DNA, Tris-HCl buffer and different concentrations of C5 (1, 2 mM) were mixed and incubated in a tube at 37 C for 3 h. Subsequently, the loading buffer was added into the mixture. The mixture was loaded onto 1% agarose gel containing 1% (v/v) gold View II, and analysis by gel electrophoresis in 1X TBE buffer at 80 V.

Topoisomerase II inhibition assay [2]

The human DNA topoisomerase II (Topo II) inhibitory activity by C5 was determined by measuring the relaxation of supercoiled plasmid DNA pBR322. Each reaction mixture contained 35 mM Tris-HCl (pH 8.0), 0.1% BSA, 72 mM KCl, 5 mM dithiothreitol, 5 mM $MgCl_2$, 5 mM spermidine, 0.25 μg plasmid DNA pBR322, 1 Unit Topo II and C5 at a specified concentration. These samples were incubated at 37 °C for 30 min, and the reaction was terminated by addition of 2 μL of 5×loading buffer (0.25% bromophenol blue, 4.5% SDS and 45% glycerol). The samples were analyzed on 1% agarose containing 0.02% (v/v) goldview at 8 V/cm for 1 h with 1 × TBE as the running buffer.

References

[1] Z. Deng, N. Wang, Y. Liu, Z. Xu, Z. Wang, T.C. Lau, G. Zhu, A Photocaged, Water-Oxidizing, and Nucleolus-Targeted Pt (IV) Complex with a Distinct Anticancer Mechanism, J. Am. Chem. Soc. 142 (2020)

7803-7812.

[2] M.R Webb, S.E. Ebeler, A gel electrophoresis assay for the simultaneous determination of topoisomerase I inhibition and DNA intercalation, Anal. Biochem. 2003, 321, 22-30.

Table S1 C1-C5 configurations and their Log P values

Symbol	Label	Shape	Symmetry	CShM	Log P values
C1	SS-4	Seesaw or sawhorse‡ (cis-divacant octahedron)	C_{2v}	4.30495	1.38
C2	SS-4	Seesaw or sawhorse‡ (cis-divacant octahedron)	C_{2v}	4.37917	2.61
C3	SS-4	Seesaw or sawhorse‡ (cis-divacant octahedron)	C_{2v}	4.36143	3.05
C4	SS-4	Seesaw or sawhorse‡ (cis-divacant octahedron)	C_{2v}	5.64367	3.91
C5	SS-4	Seesaw or sawhorse‡ (cis-divacant octahedron)	C_{2v}	4.68217	4.29

Table S2 Bond lengths of C1-C5

Identification	**C1**	**C2**	**C3**	**C4**	**C5**
Sn1-N1	2.489(4)	2.465(5)	2.476(3)	2.465(3)	2.488(4)
Sn1-N2	2.321(4)	2.345(4)	2.328(2)	2.337(2)	2.327(3)
Sn1-S1	2.6455(14)	2.6530(16)	2.6468(9)	2.6647(10)	2.6731(12)
Sn1-Cl1	2.4849(14)	2.480(2)	2.4893(10)	2.4968(9)	2.4903(11)

Table S3 Bond Angles of C1-C5

Identification	C1	C2	C3	C4	C5
N2-Sn1-S1	73.64(9)	72.08(11)	72.44(6)	72.00(7)	71.68(7)
N2-Sn1-Cl1	87.71(9)	90.26(12)	89.20(6)	95.78(6)	89.51(7)
N2-Sn1-N1	68.29(13)	68.41(15)	68.45(9)	68.49(9)	68.84(11)
N1-Sn1-S1	141.36(10)	140.38(11)	140.76(7)	138.32(6)	139.94(9)
Cl1-Sn1-N1	81.61(10)	86.89(12)	85.21(7)	82.25(6)	82.77(9)
Cl1-Sn1-S1	90.69(5)	90.57(7)	91.17(3)	89.05(3)	90.47(4)

Table S4 Acute toxicity of C5 (alive/total)

	15 μmol/kg	20 μmol/kg	25 μmol/kg	30 μmol/kg	35 μmol/kg
C5	10/10	2/10	3/10	5/10	8/10

Table S5 Serological analysis of mice injected NaCl, cisplatin, C5 complex

Complex	CK (U/L)	BUN (mmol/L)	ALT(U/L)	AST(U/L)
NaCl	306 ± 13	7.6 ± 1.4	43.7 ± 5.9	95.7 ± 12
C5	324 ± 15	10.2 ± 1.8	51.3 ± 6.3	119 ± 15
cisplatin	342 ± 18	17.8 ± 2.5	66.9 ± 8.1	142 ± 18

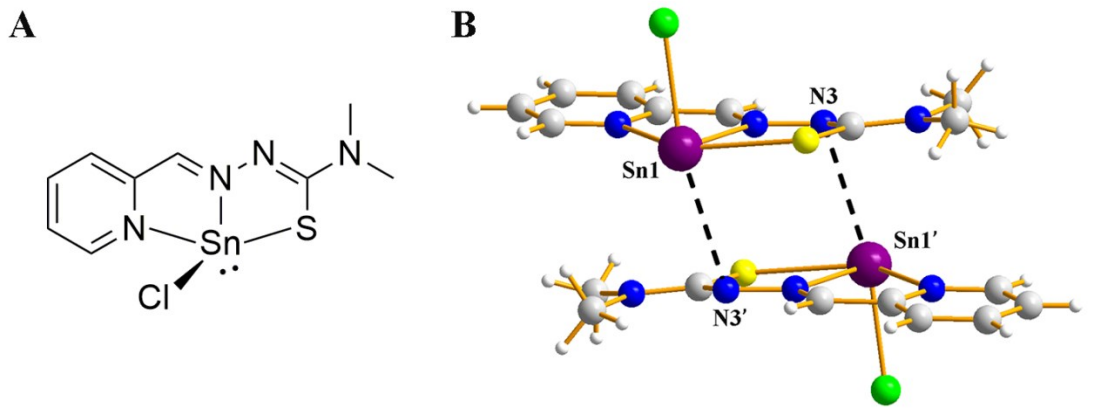

Fig S1 Spatial configuration and stacking pattern of Sn complex

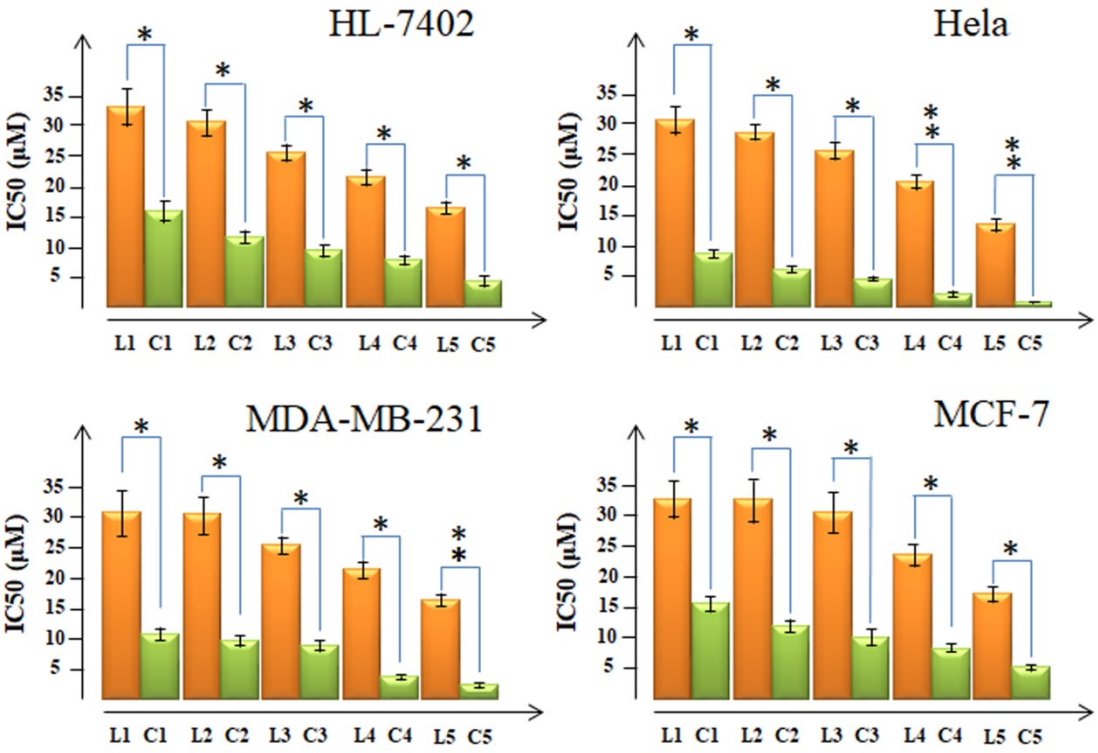

Fig S2 Comparison of IC_{50} between ligands L1-L5 and Sn(II) complexes C1-C5 in four tumor cell lines (*P < 0.05).

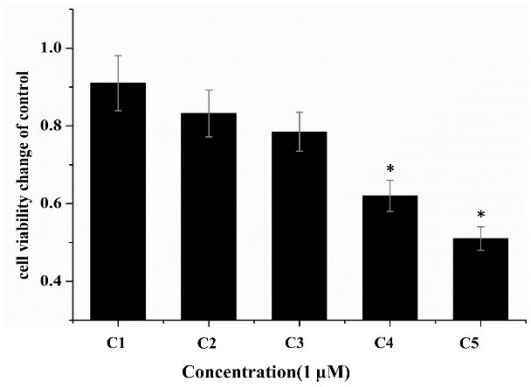

Fig S3 The survival rate of Hela cells treated with C1-C5 relative to blank cells (*P < 0.05)

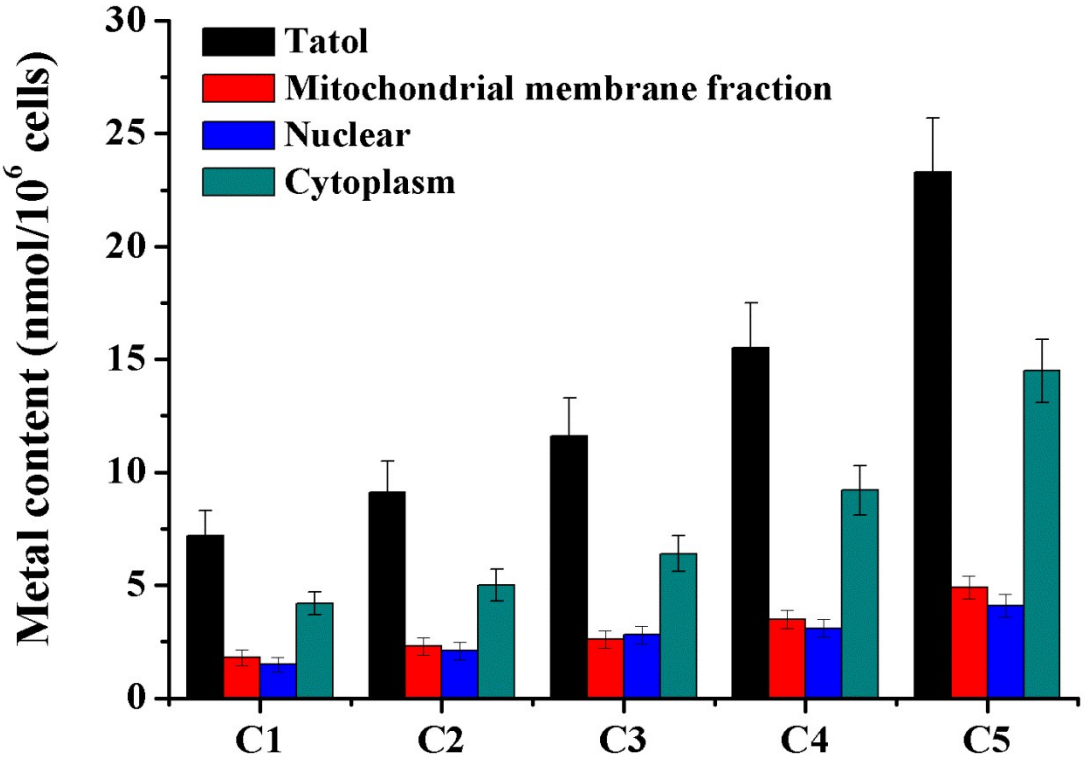

Fig S4 The uptake of five Sn(II) compounds by HeLa cells

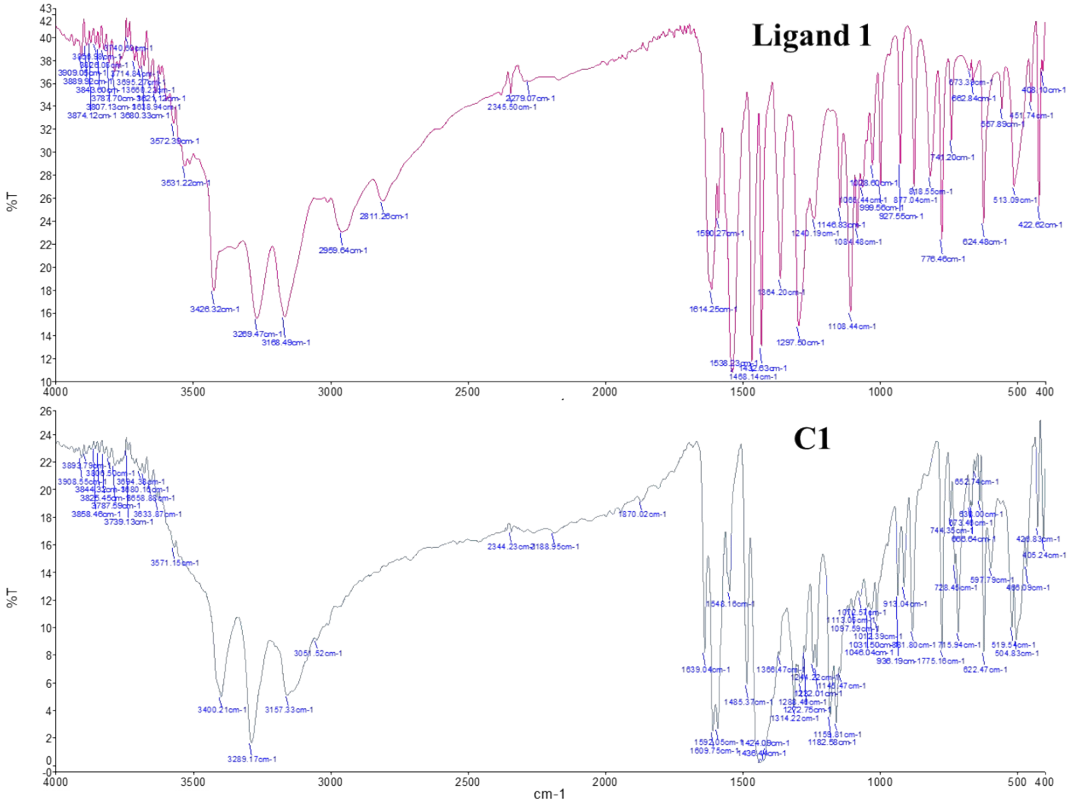

Fig S5 IR spectrum of L1 and C1

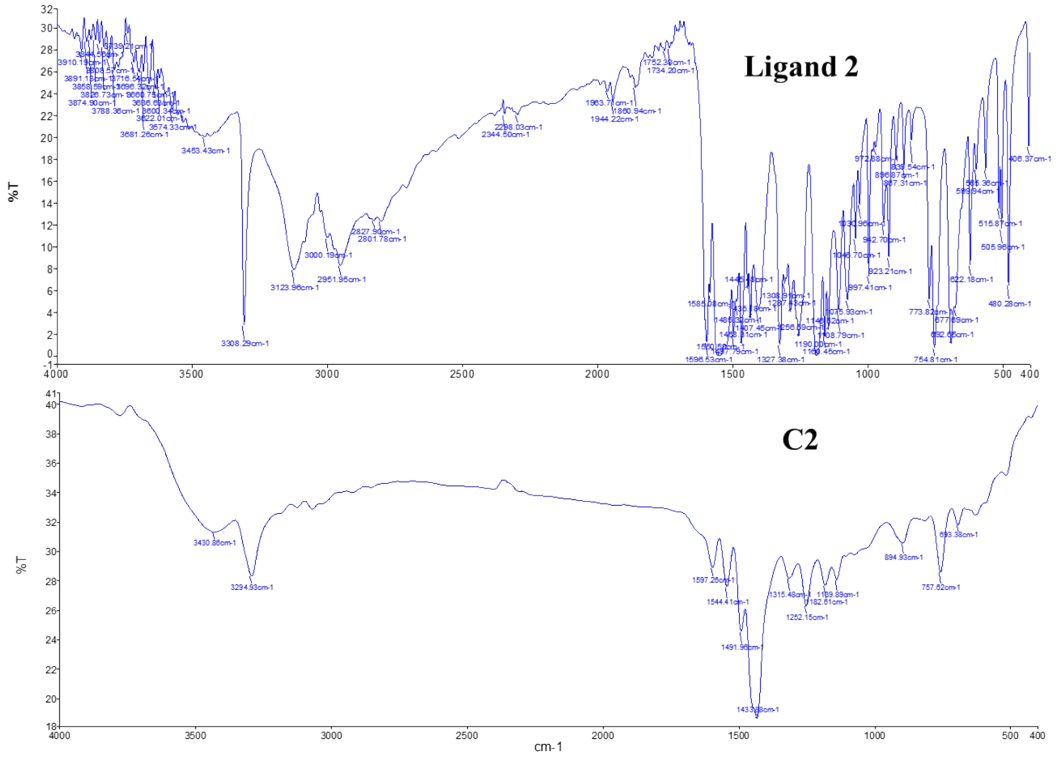

Fig S6 IR spectrum of L2 and C2

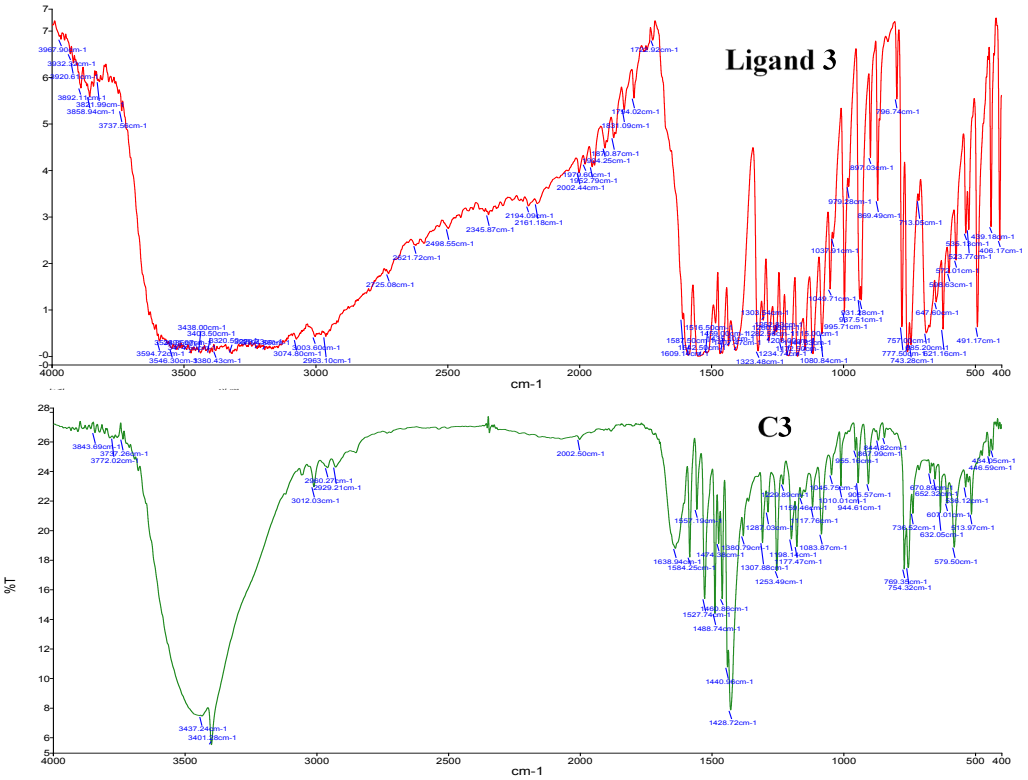

Fig S7 IR spectrum of L3 and C3

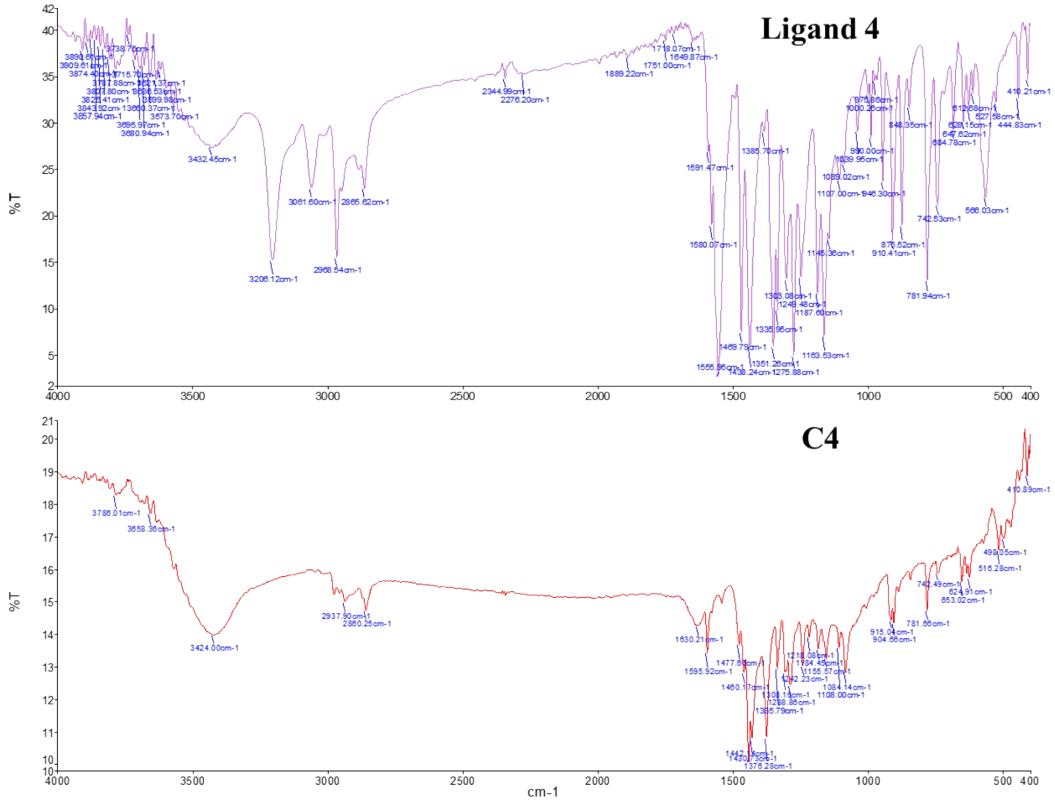

Fig S8 IR spectrum of L4 and C4

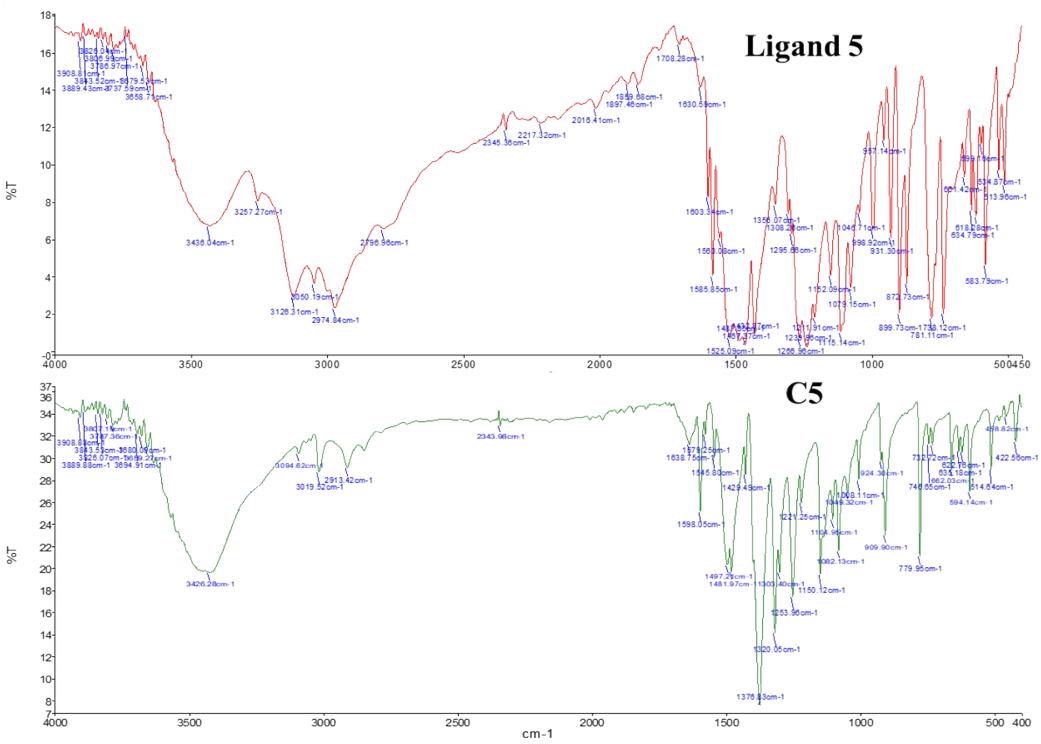

Fig S9 IR spectrum of L5 and C5

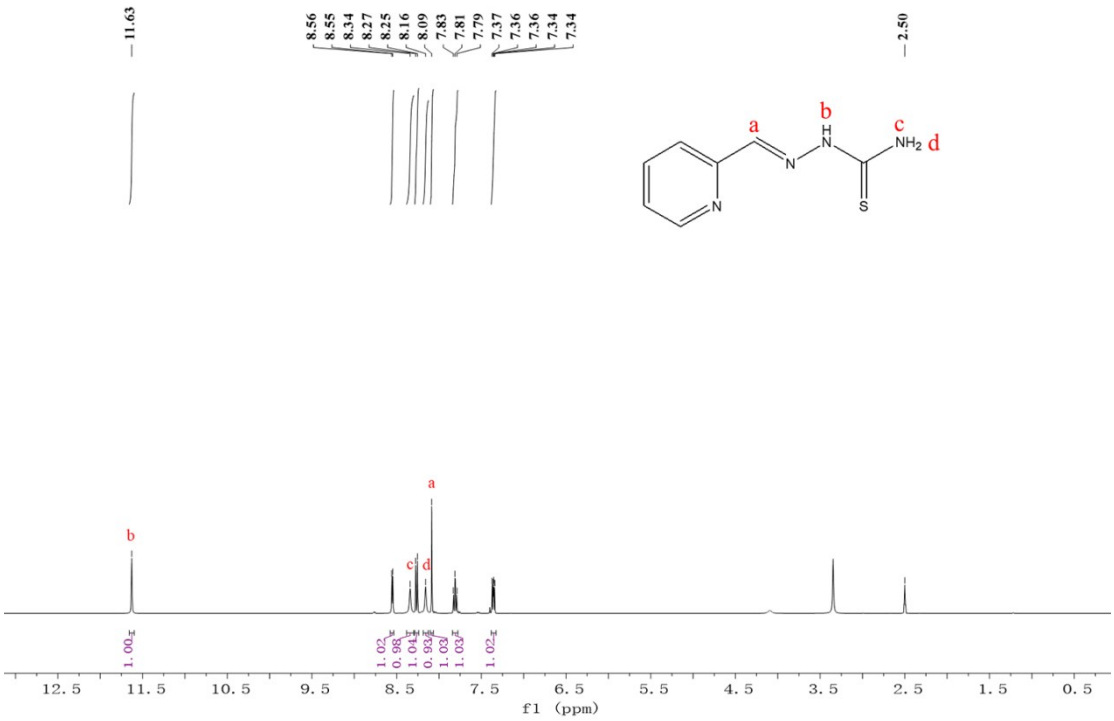

Fig S10 ^{1}H-NMR spectrum of L1

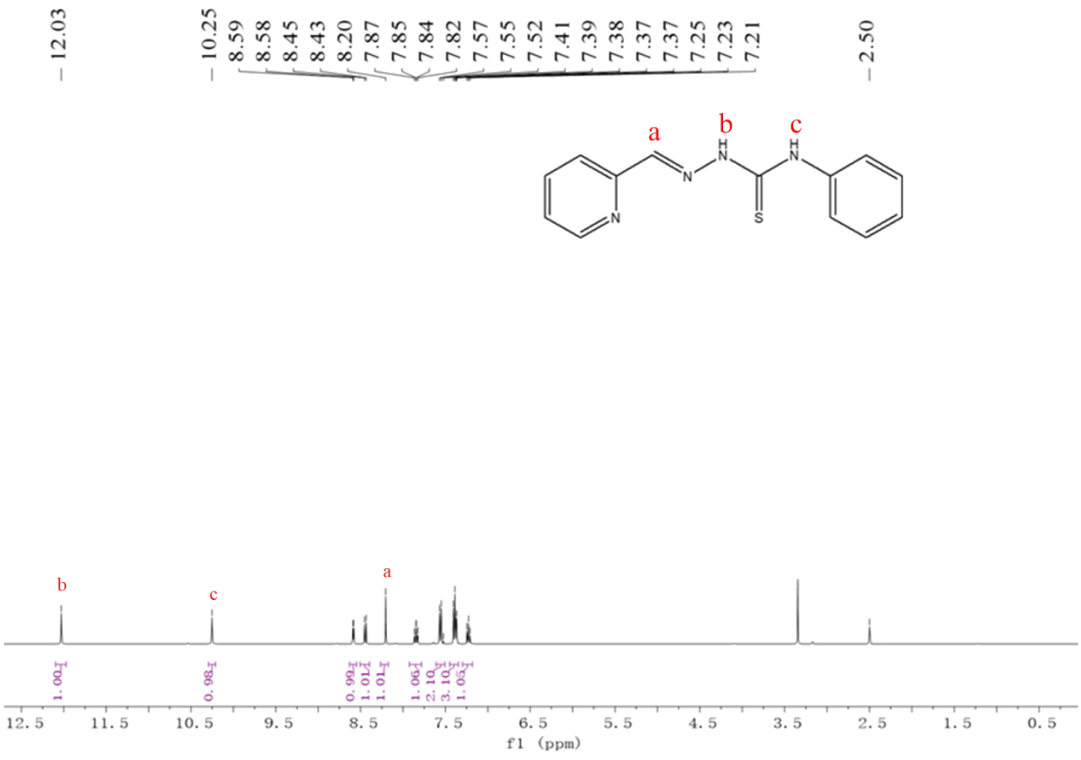

Fig S11 ^{1}H-NMR spectrum of L2

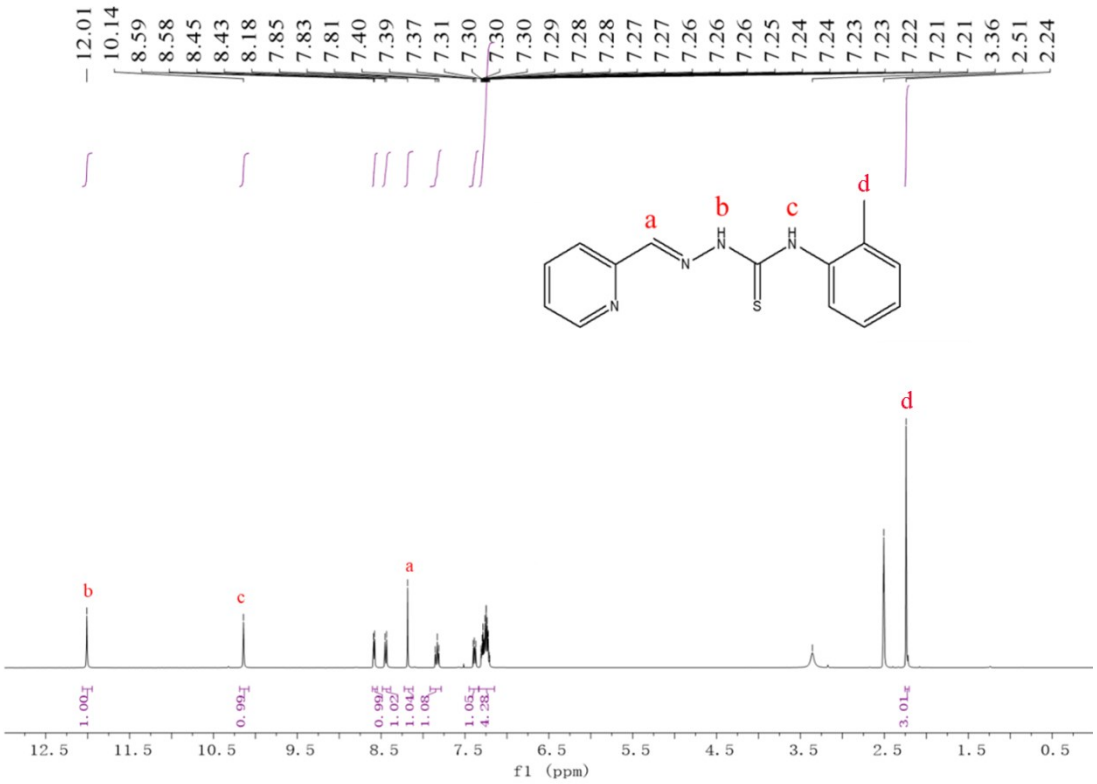

Fig S12 [1]H-NMR spectrum of L3

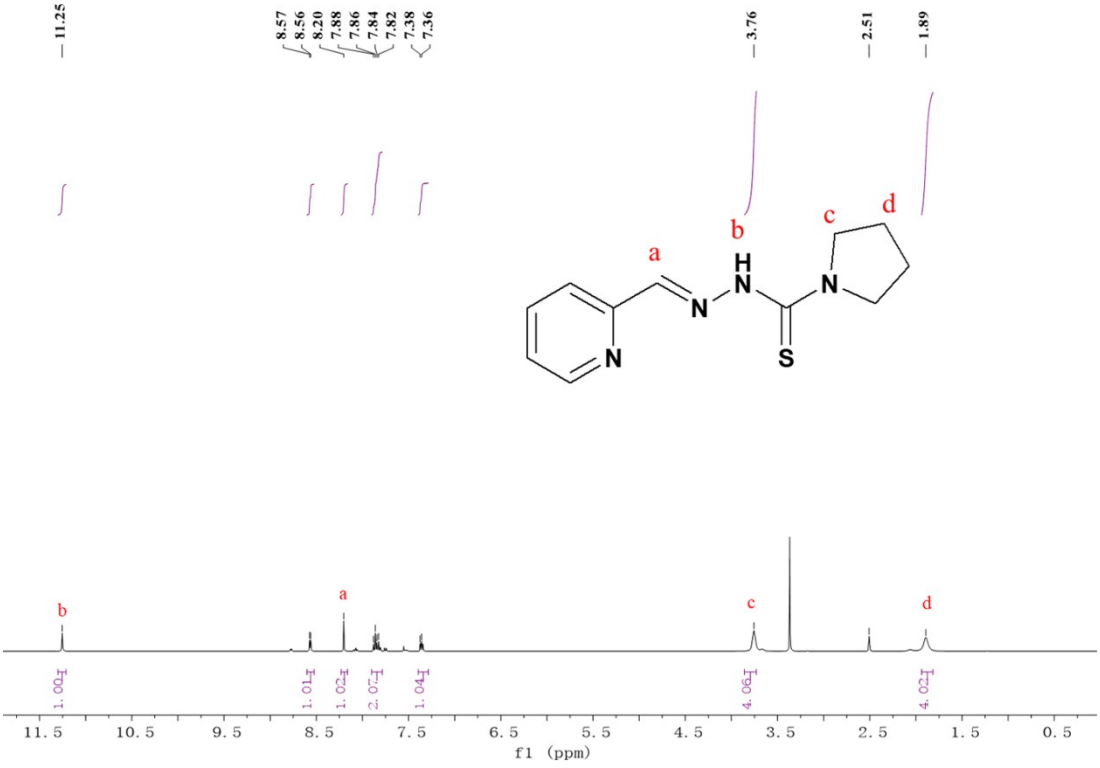

Fig S13 [1]H-NMR spectrum of L4

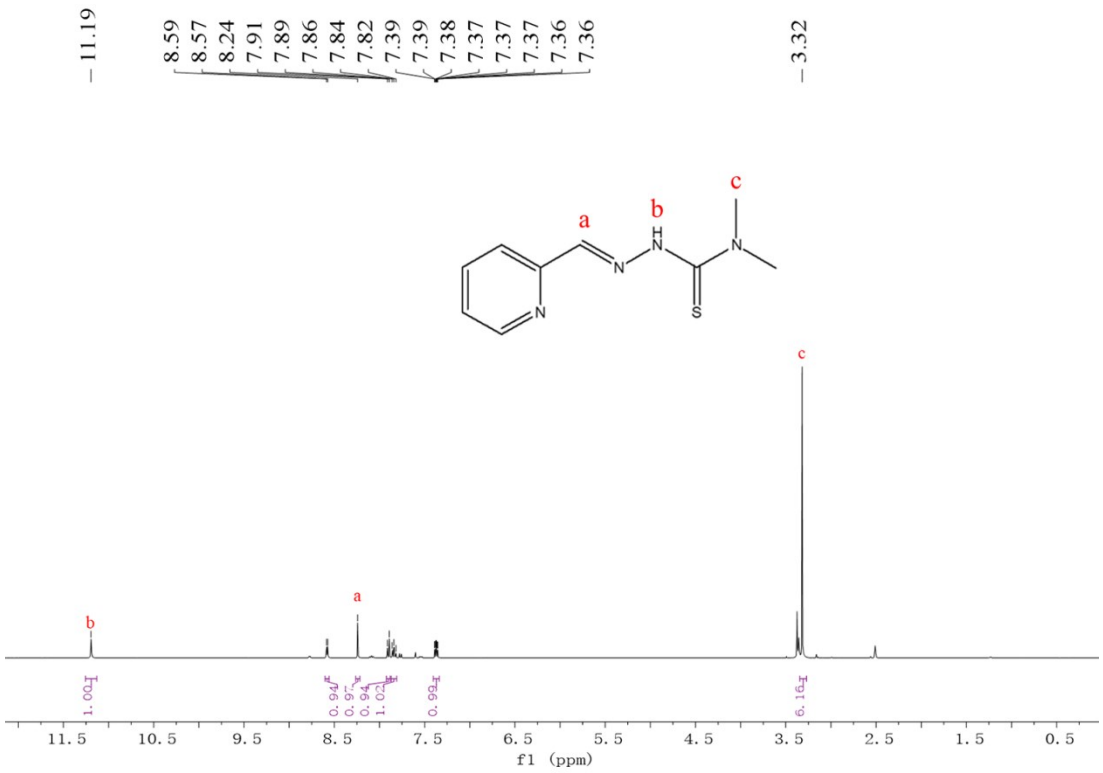

Fig S14 [1]H-NMR spectrum of L5

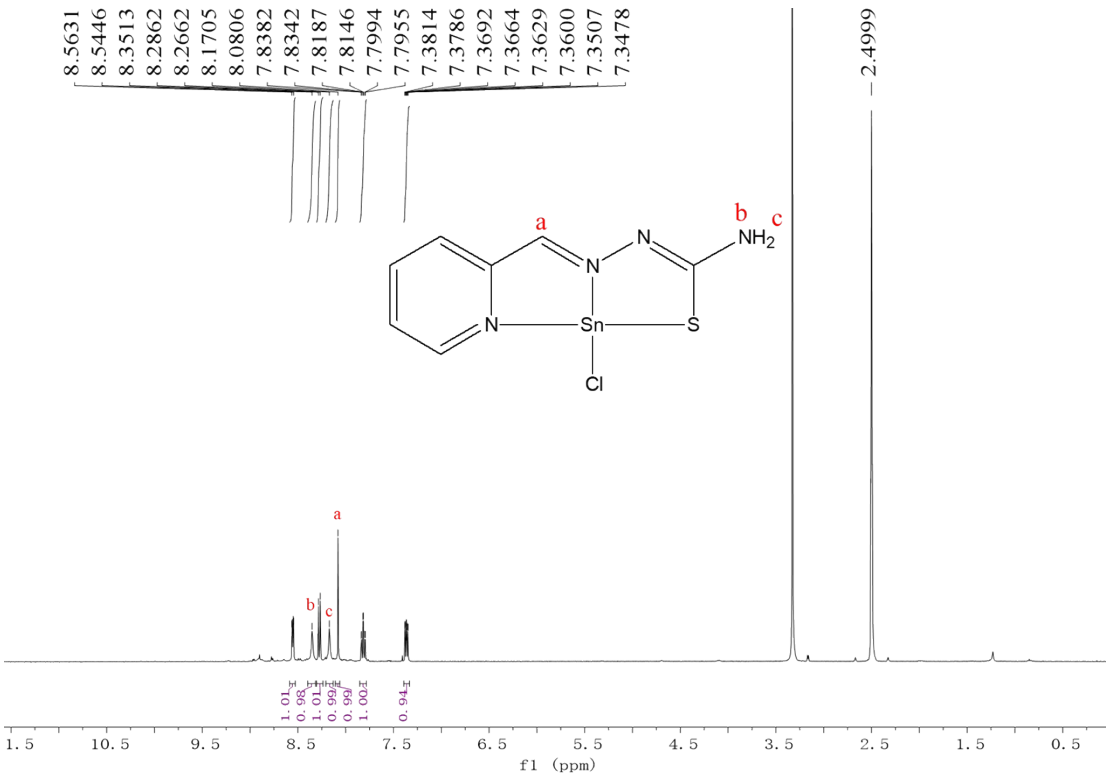

Fig S15 [1]H-NMR spectrum of C1

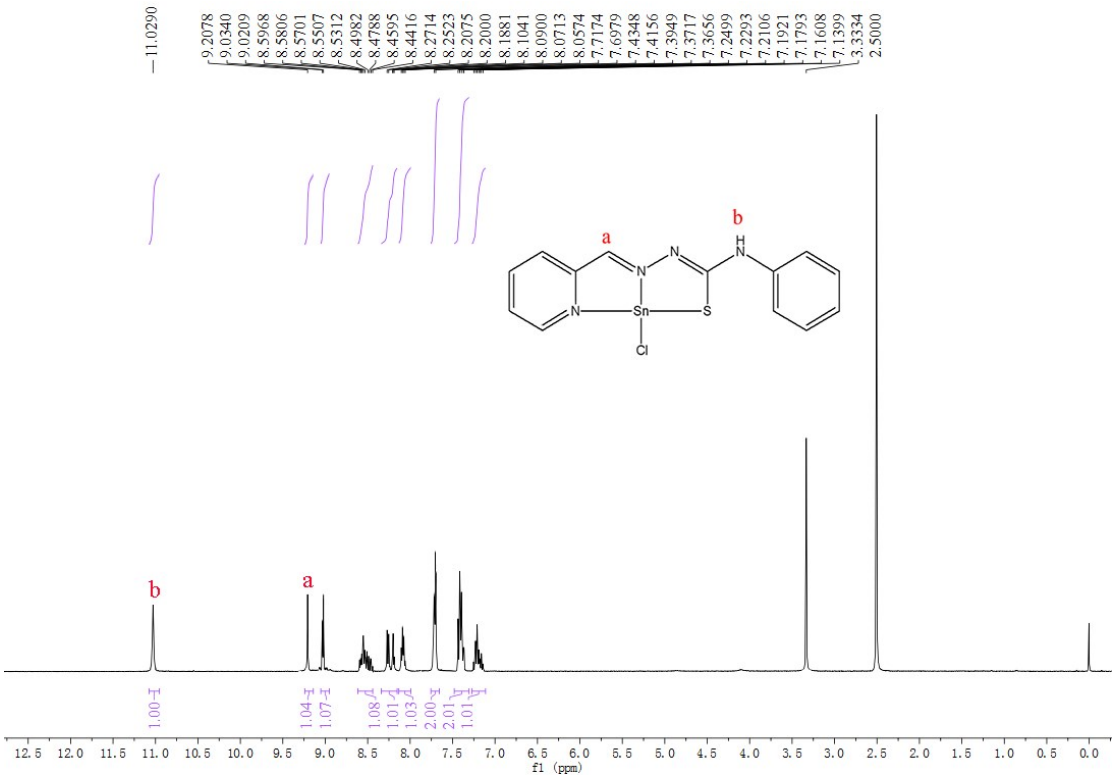

Fig S16 [1]H-NMR spectrum of C2

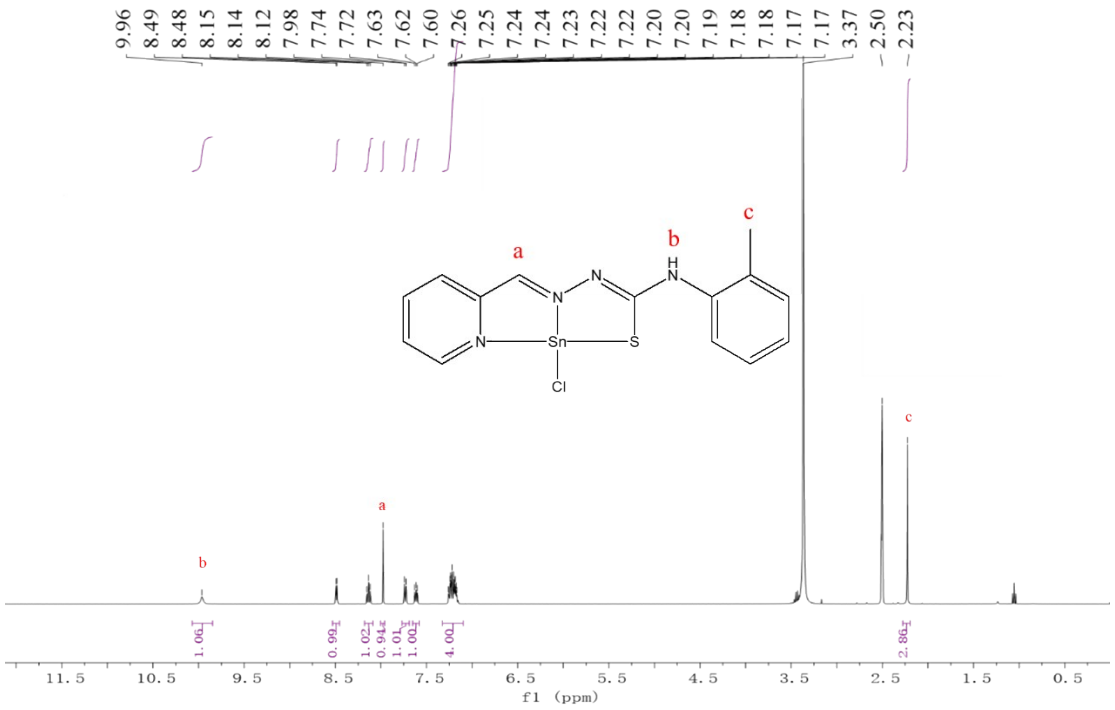

Fig S17 [1]H-NMR spectrum of C3

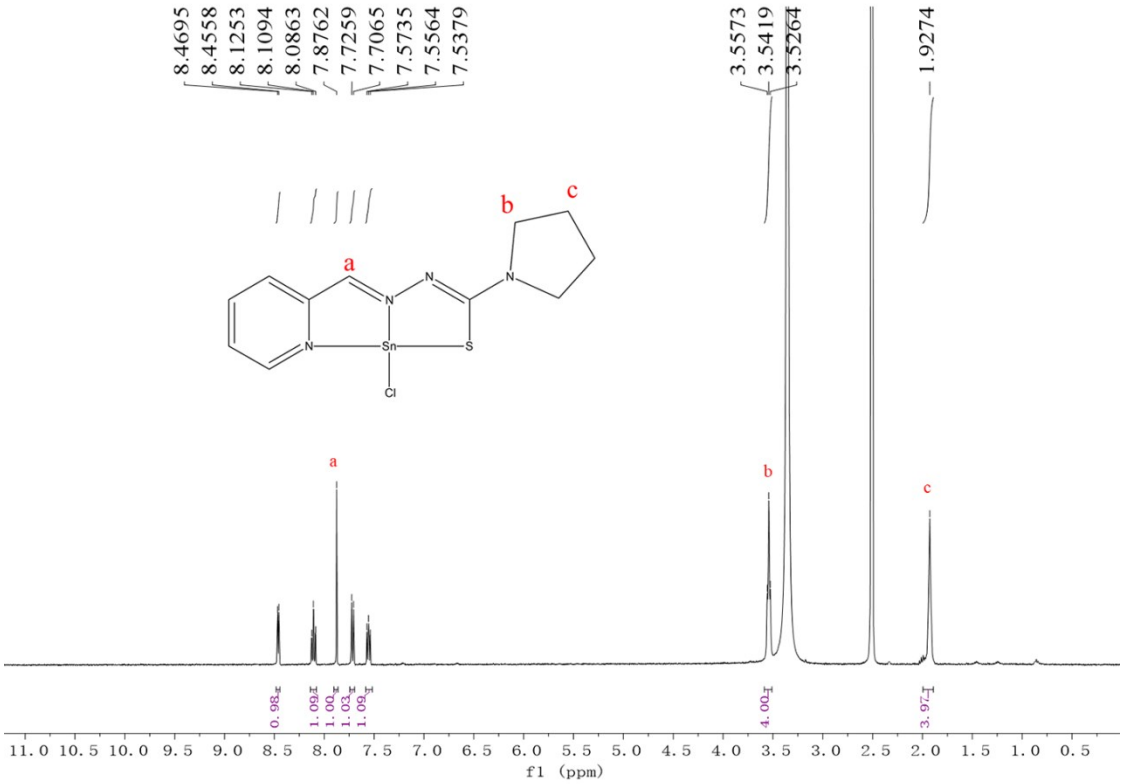

Fig S18 ^{1}H-NMR spectrum of C4

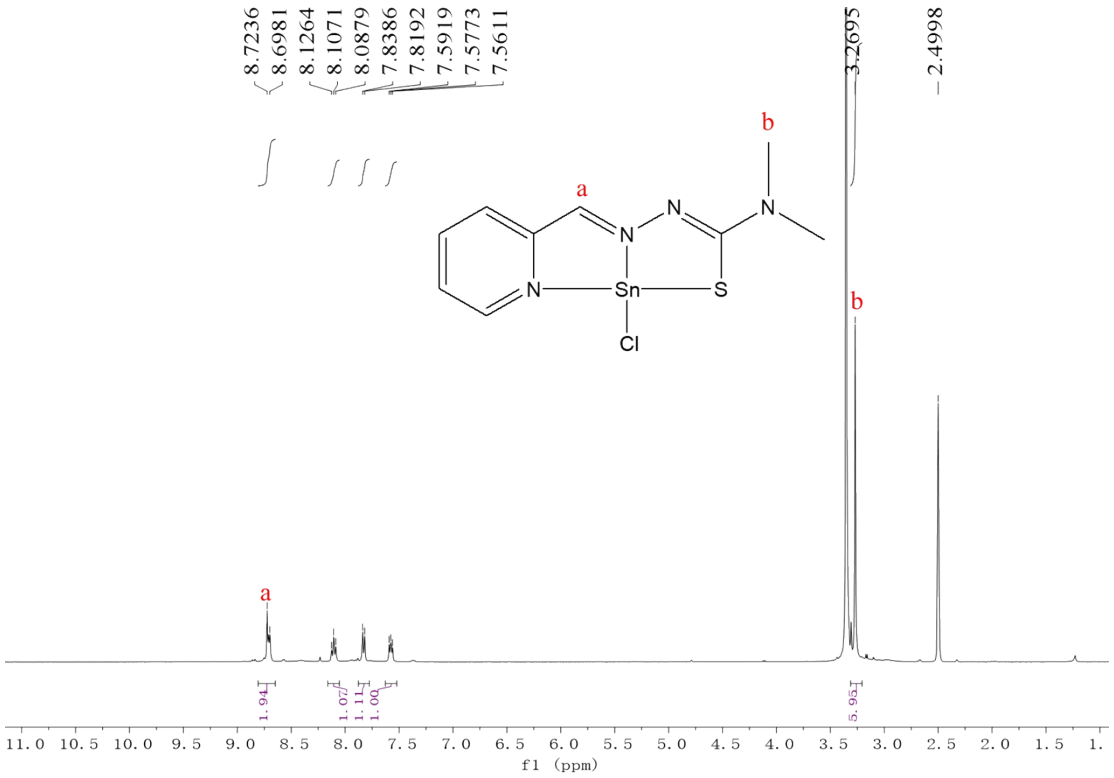

Fig S19 ^{1}H-NMR spectrum of C5

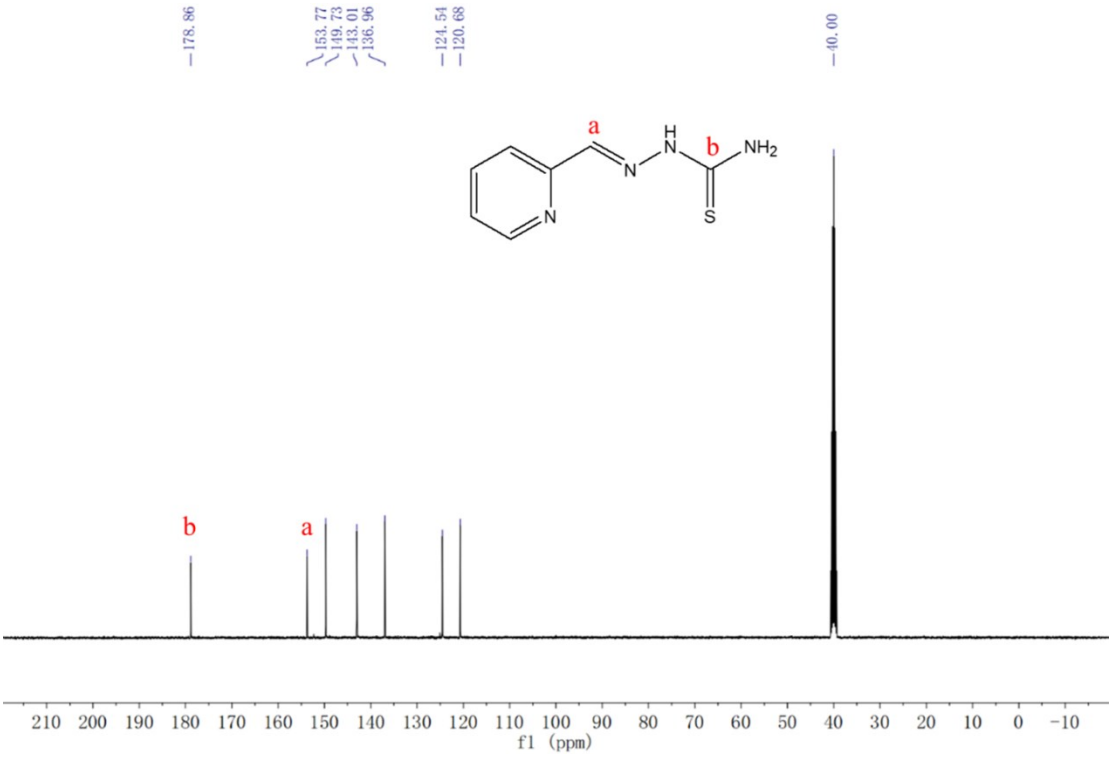

Fig S20 ^{13}C-NMR spectrum of L1

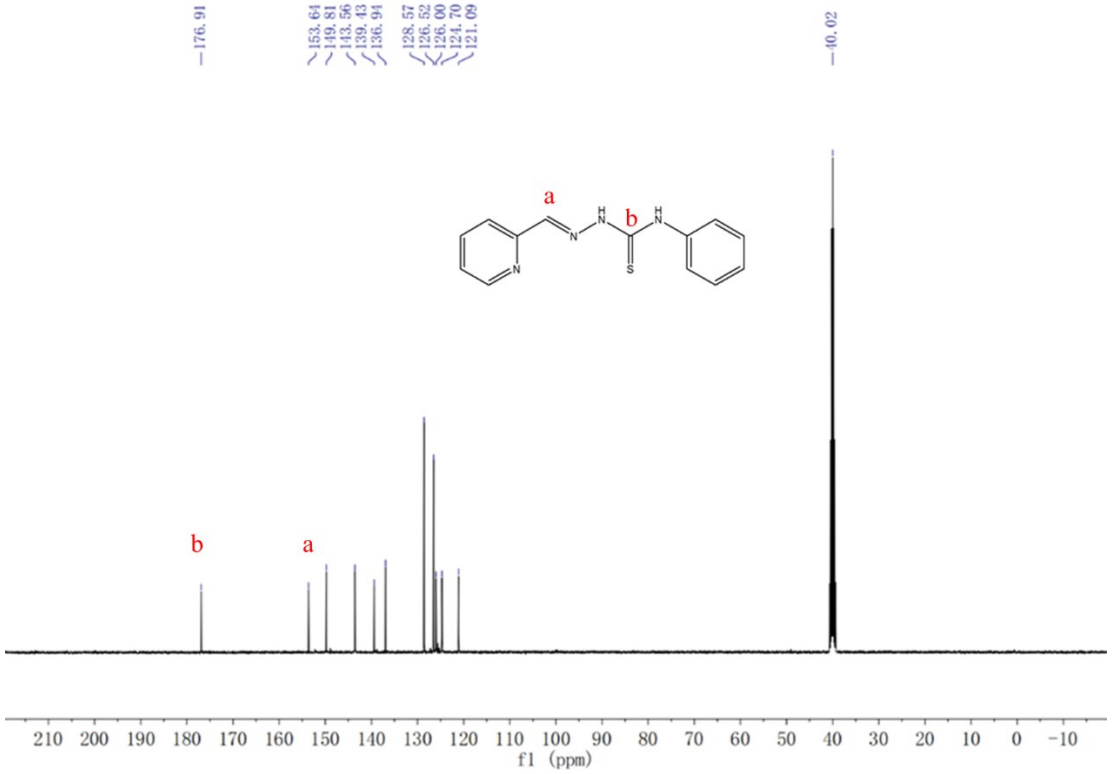

Fig S21 ^{13}C-NMR spectrum of L2

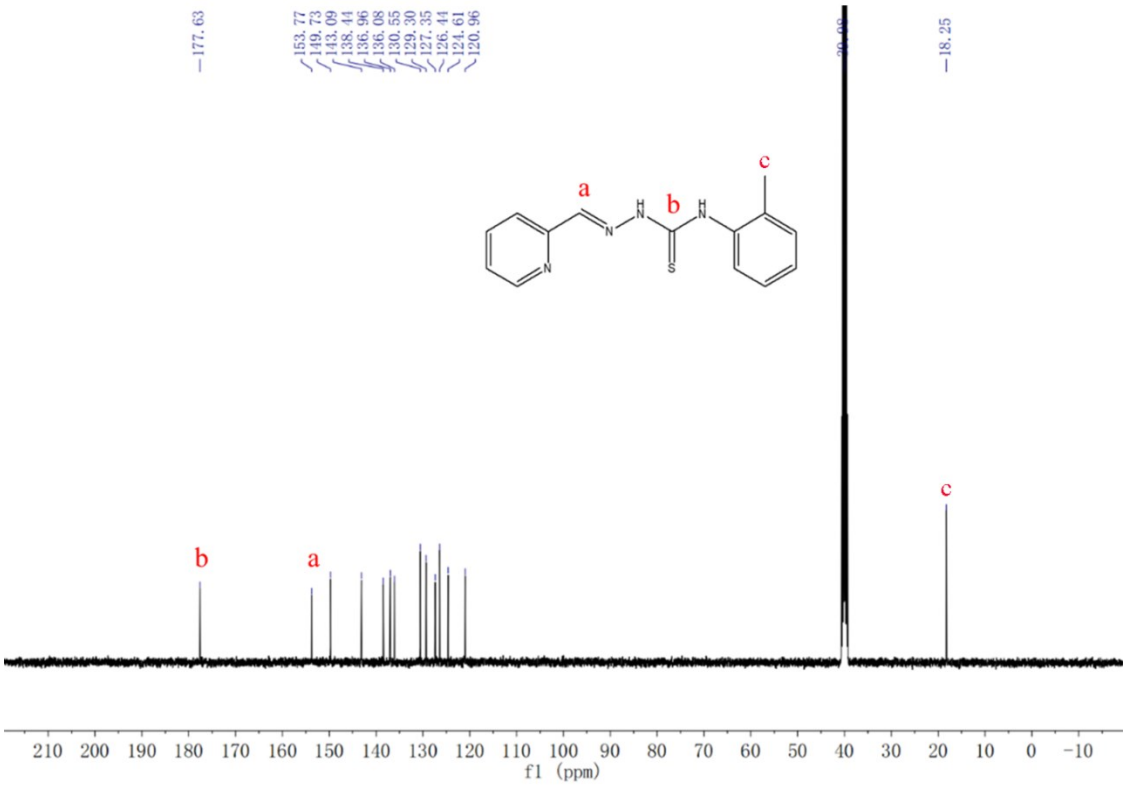

Fig S22 ^{13}C-NMR spectrum of L3

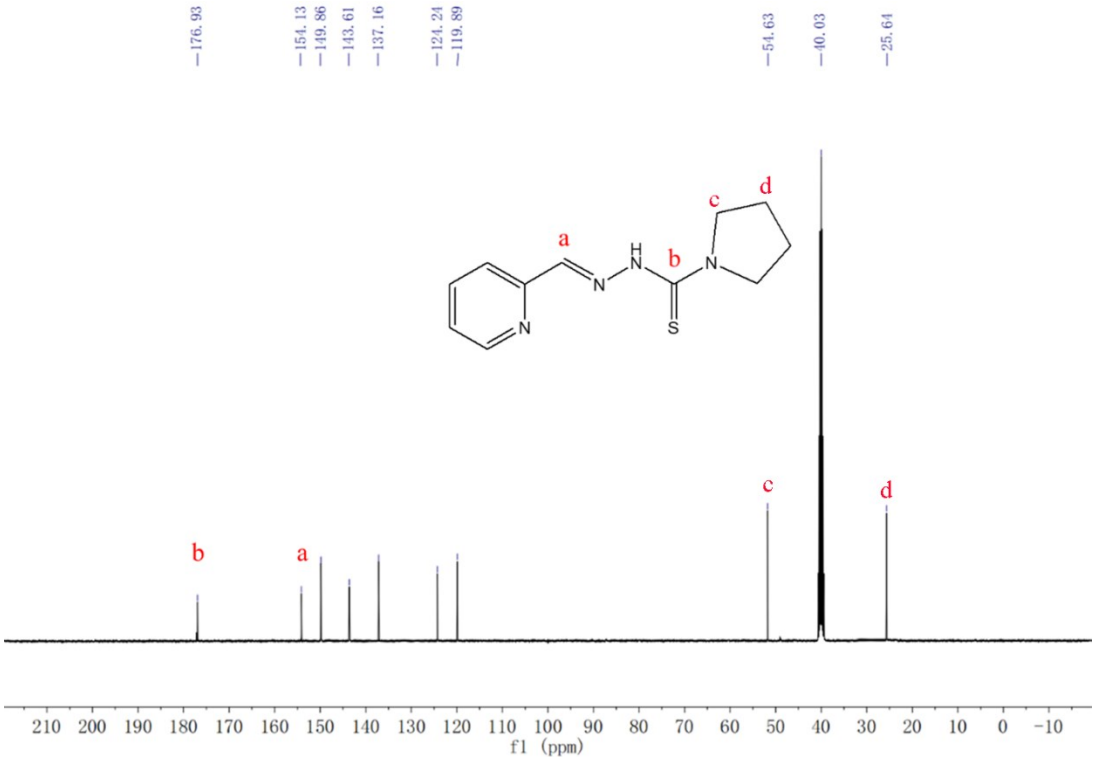

Fig S23 ^{13}C-NMR spectrum of L4

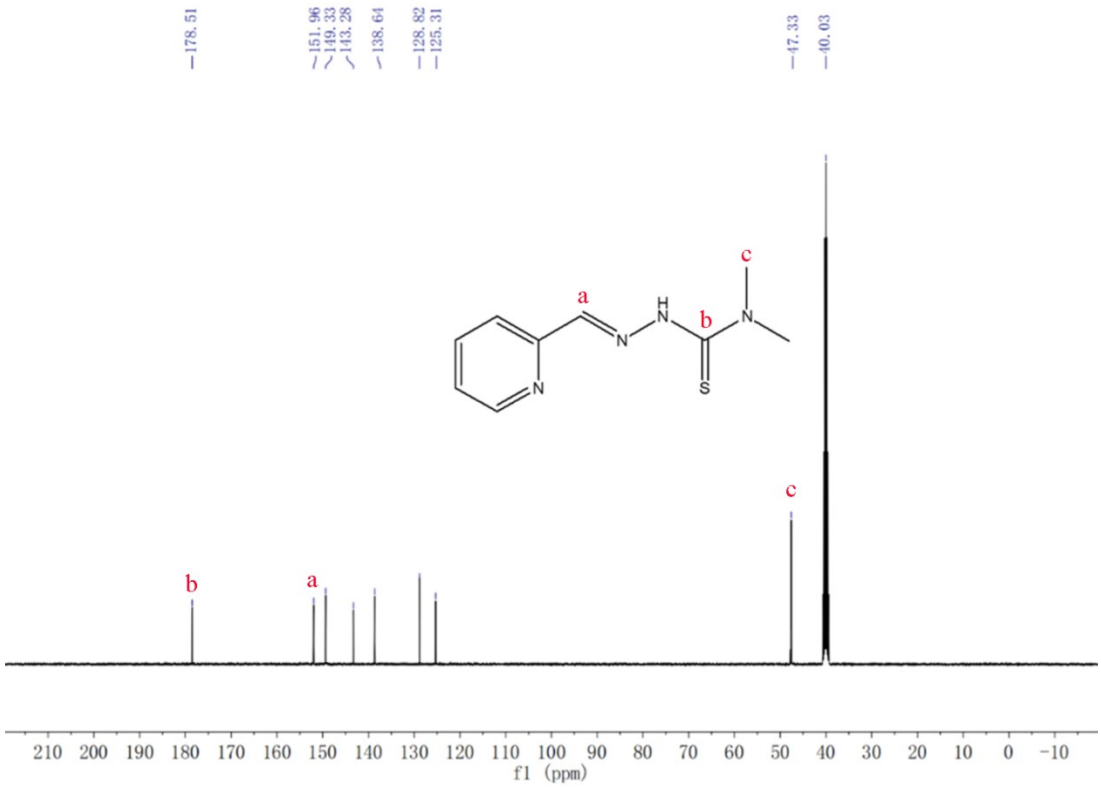

Fig S24 ^{13}C-NMR spectrum of L5

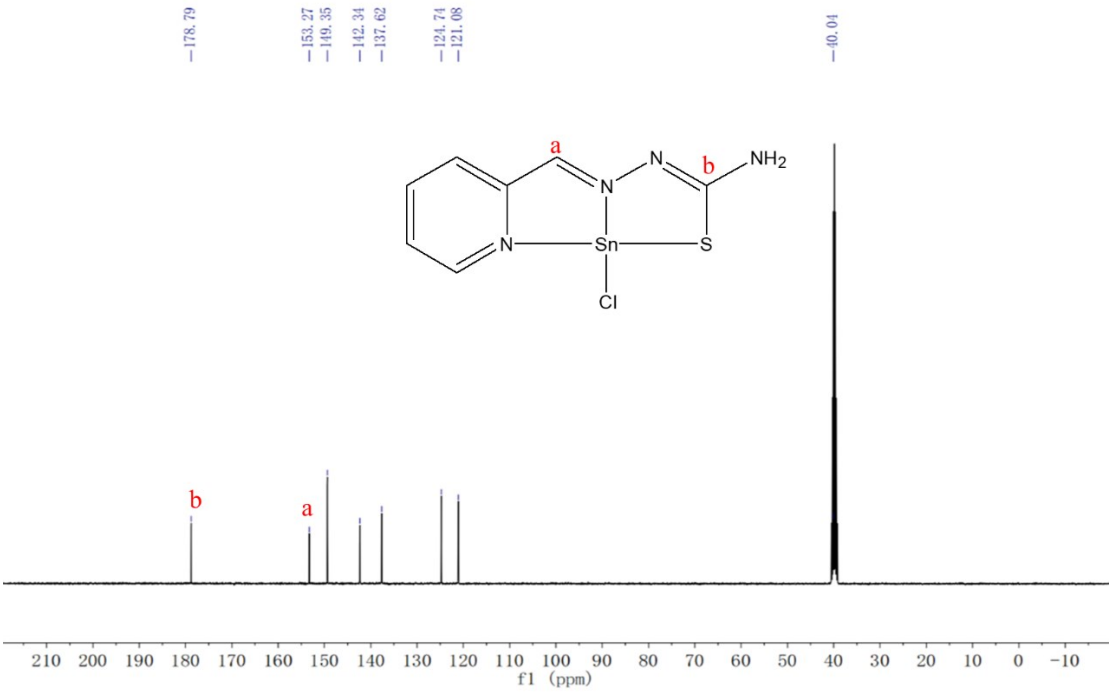

Fig S25 ^{13}C-NMR spectrum of C1

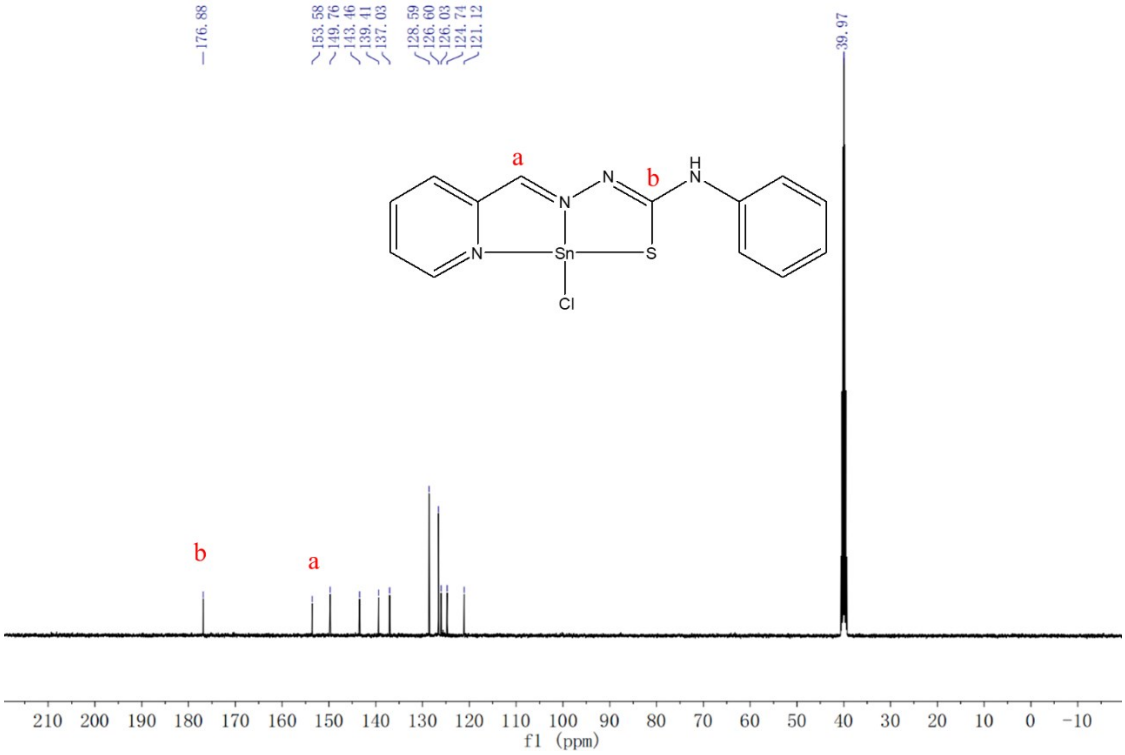

Fig S26 ^{13}C-NMR spectrum of C2

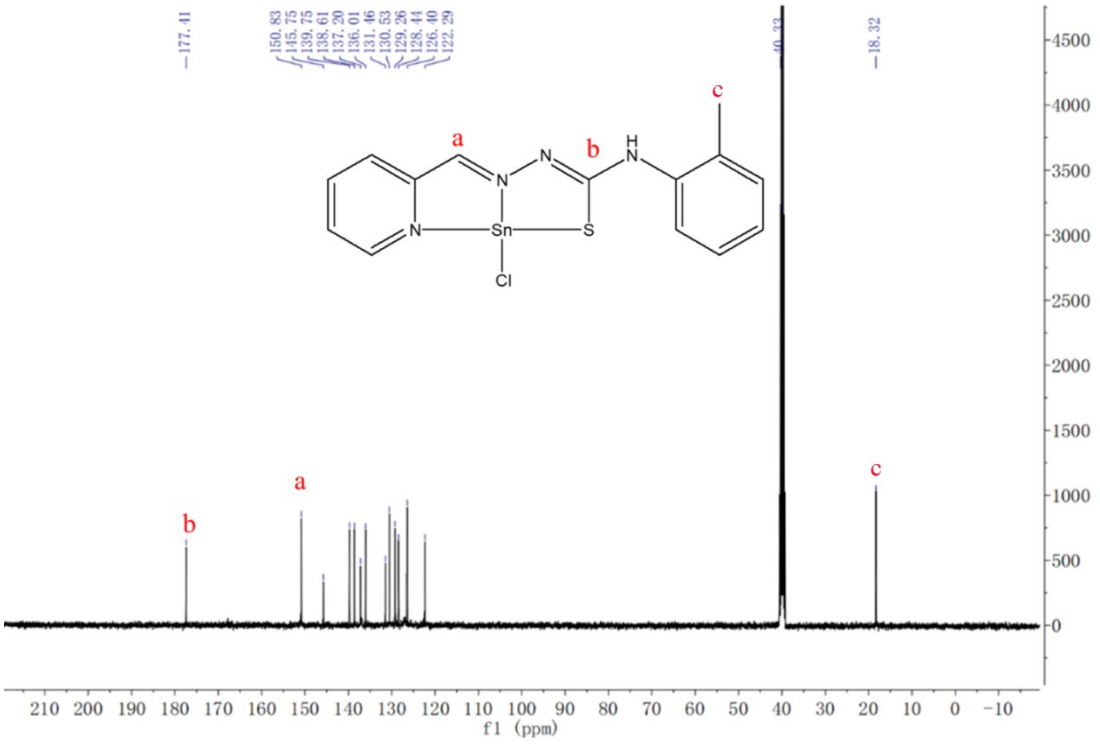

Fig S27 ^{13}C-NMR spectrum of C3

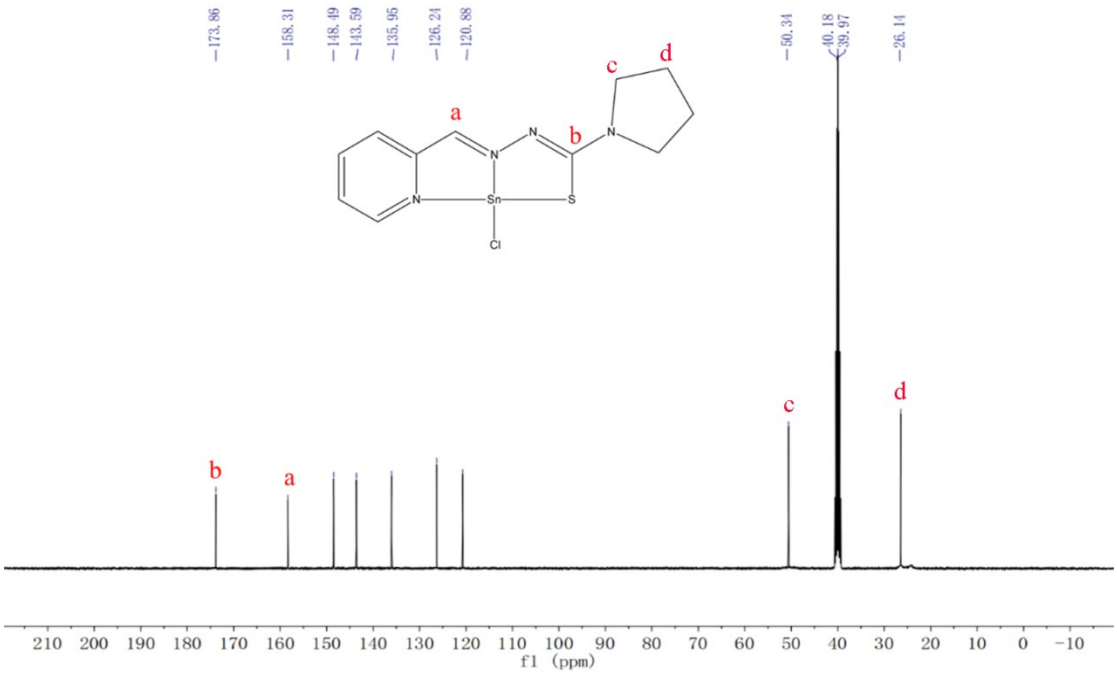

Fig S28 ^{13}C-NMR spectrum of C4

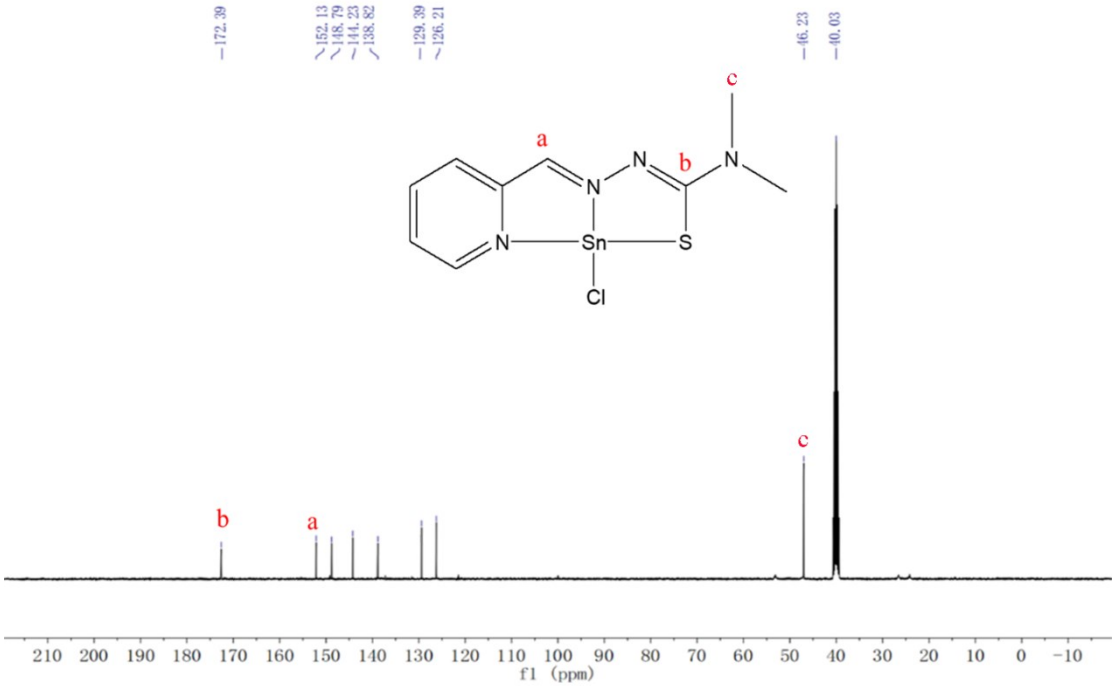

Fig S29 ^{13}C-NMR spectrum of C5

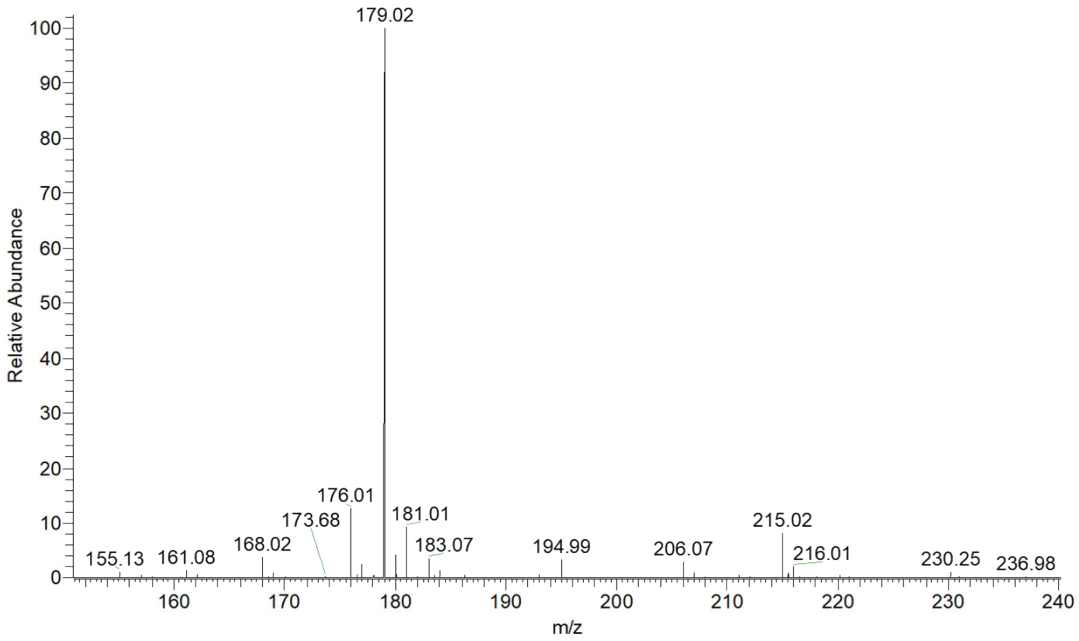

Fig S30 ESI-mass spectrum of the L1 showing an intense signal at m/z =179.02 for $[C_7H_8N_4S\text{-}H]^-$

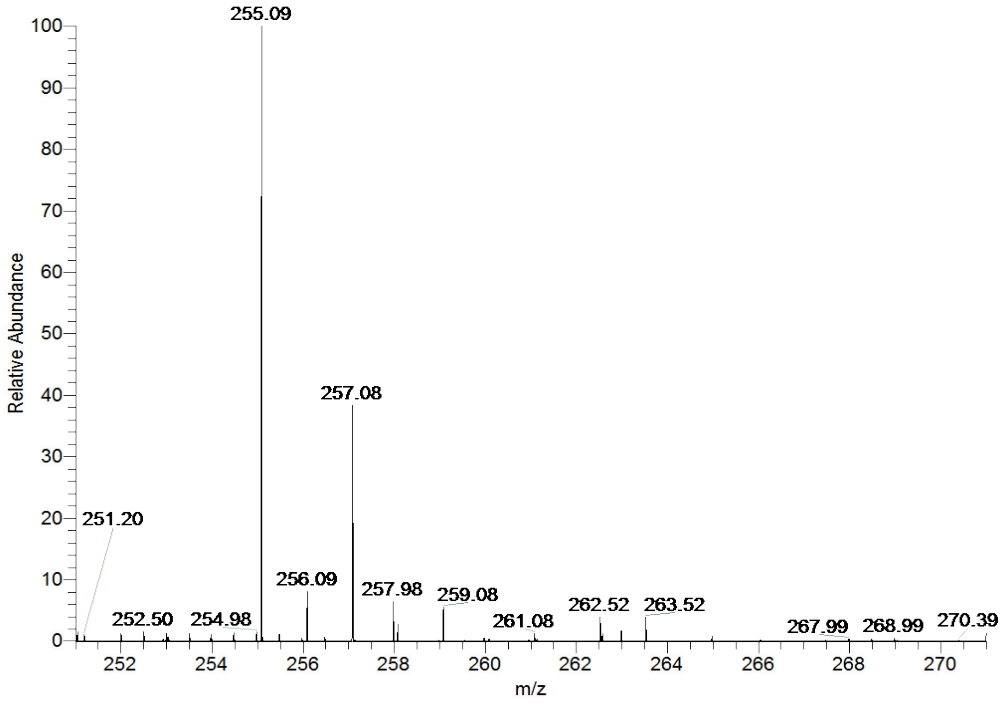

Fig S31 ESI-mass spectrum of the L2 showing an intense signal at m/z =255.09 for $[C_{13}H_{12}N_4S\text{-}H]^-$

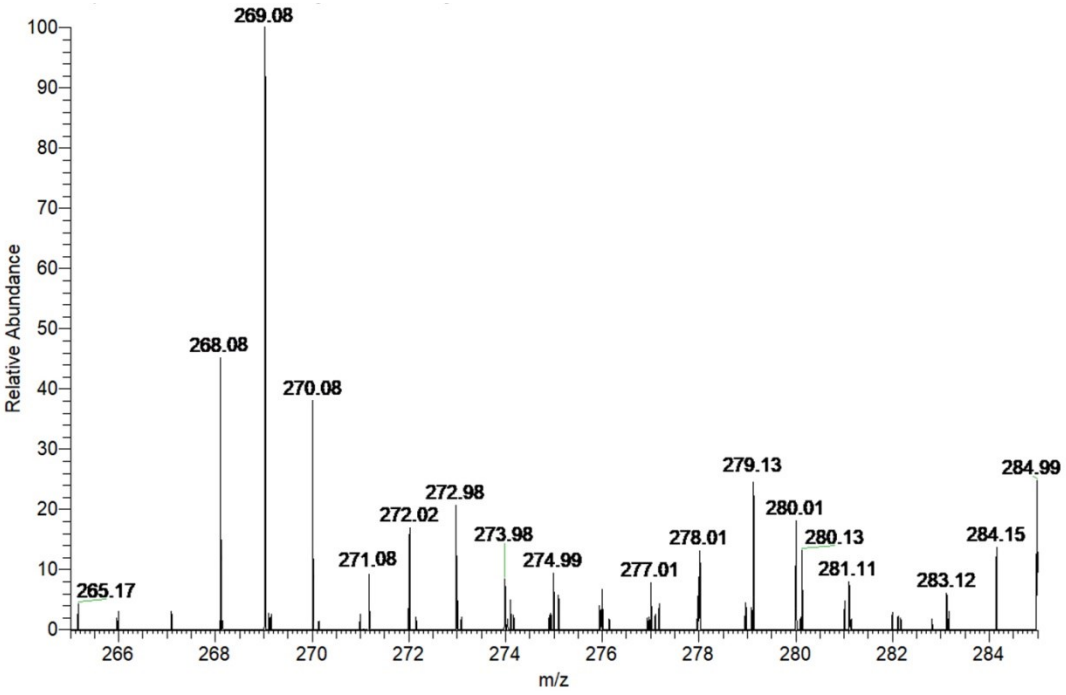

Fig S32 ESI-mass spectrum of the L3 showing an intense signal at m/z =269.08 for $[C_{13}H_{12}N_4S\text{-}H]^-$

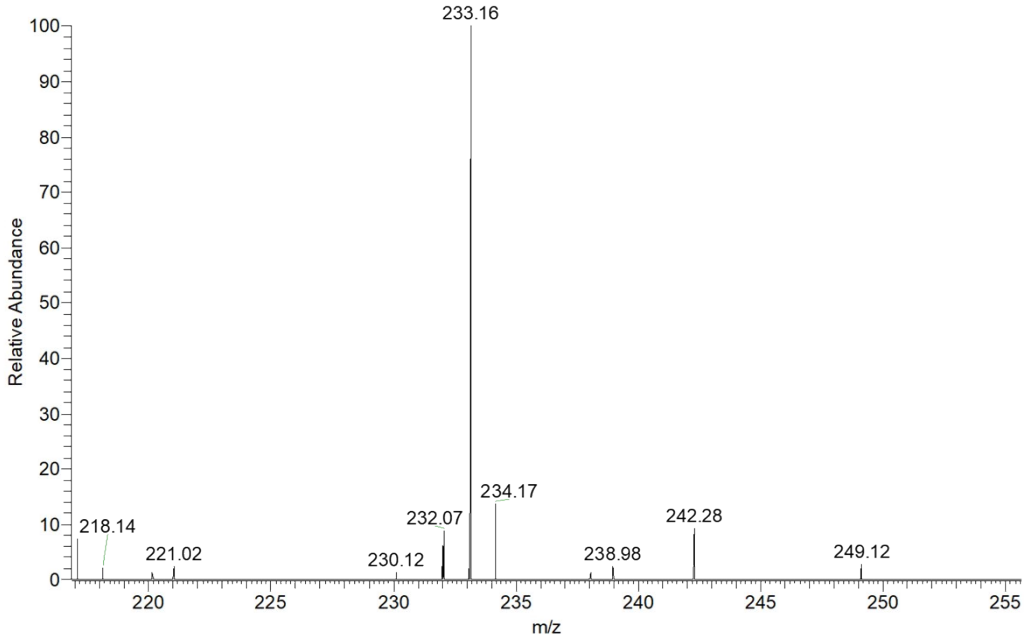

Fig S33 ESI-mass spectrum of the L4 showing an intense signal at m/z =233.16 for $[C_{11}H_{14}N_4S\text{-}H]^-$

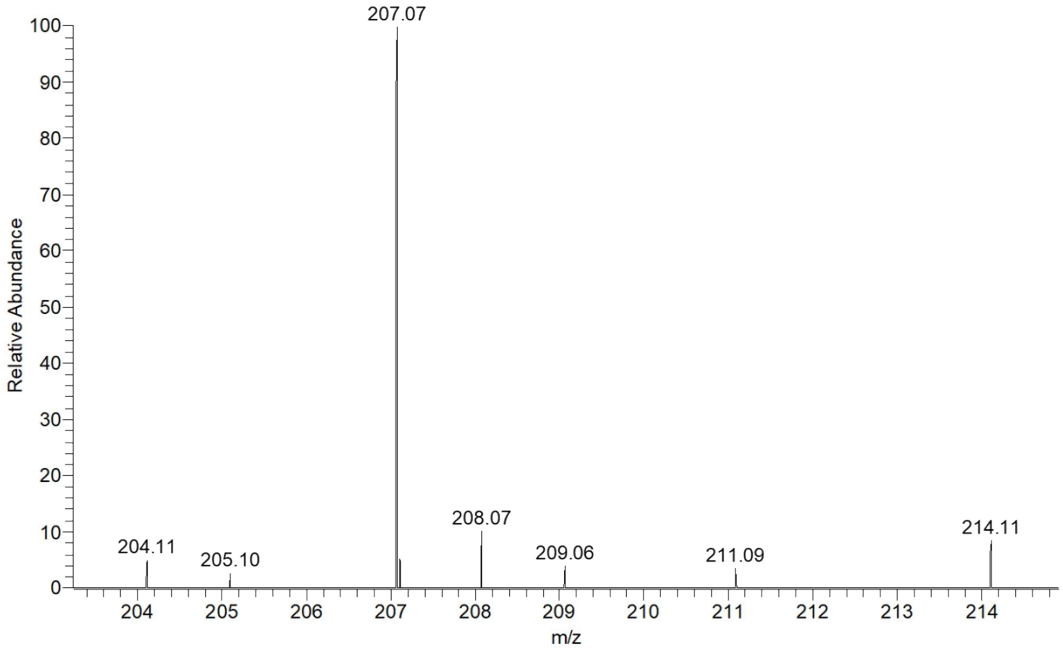

Fig S34 ESI-mass spectrum of the L5 showing an intense signal at m/z =207.07 for $[C_9H_{12}N_4S\text{-}H]^-$

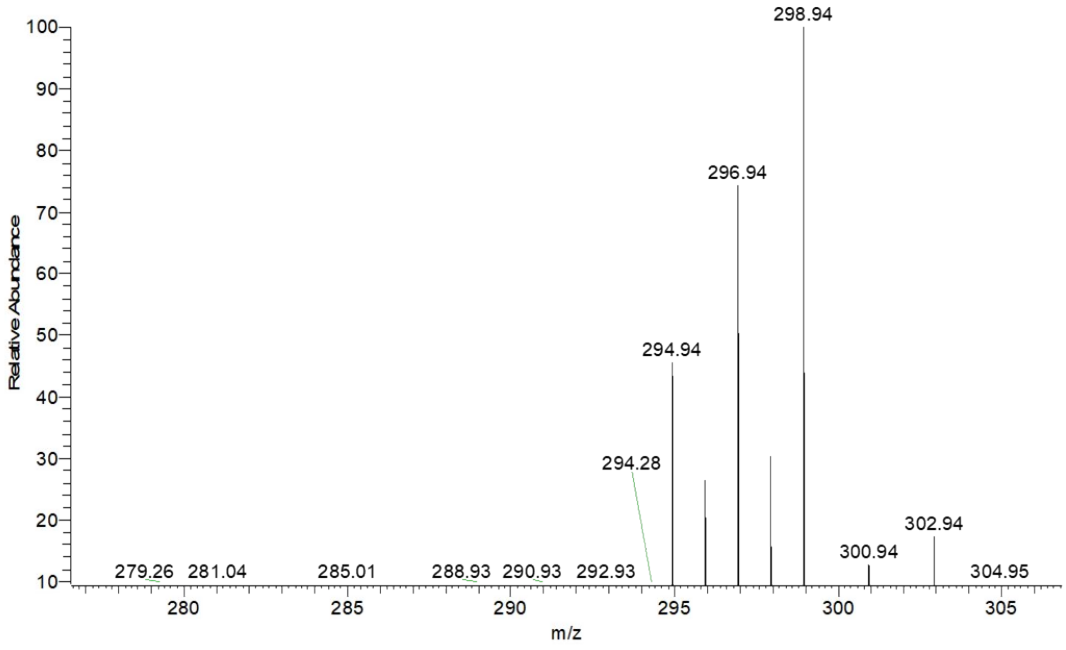

Fig S35 ESI-mass spectrum of the C1 showing an intense signal at m/z: 298.94 for $[C_7H_7ClN_4SSn\text{-}Cl]^+$

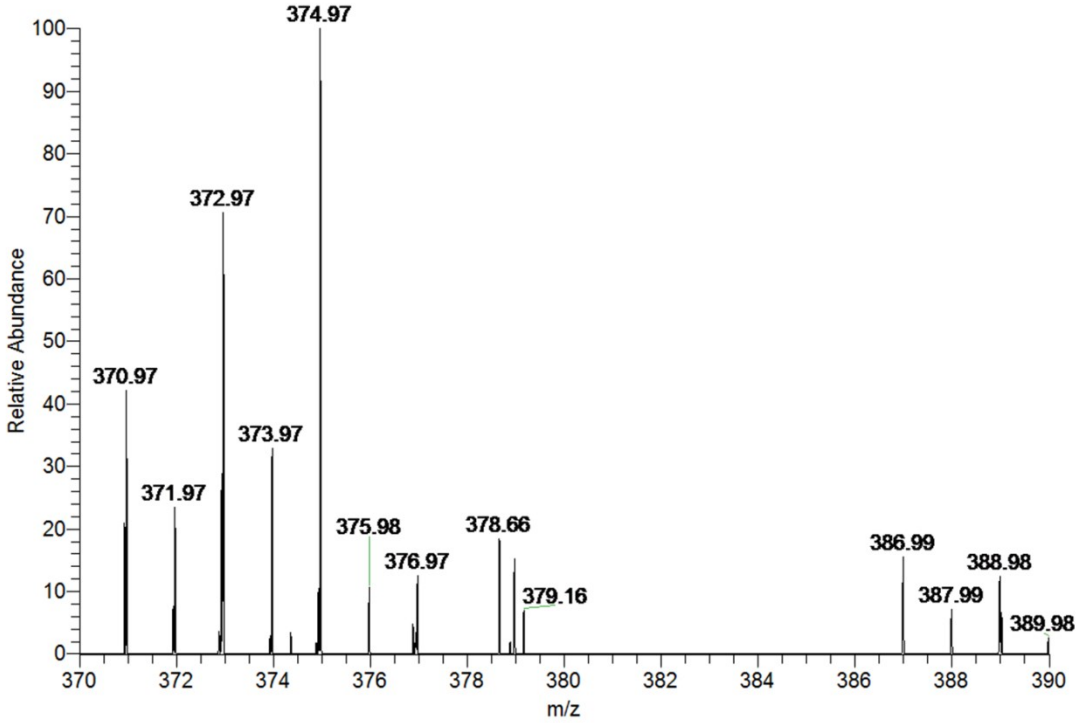

Fig S36 ESI-mass spectrum of the C2 showing an intense signal at m/z: 374.97 for $[C_{13}H_{11}ClN_4SSn\text{-}Cl]^+$

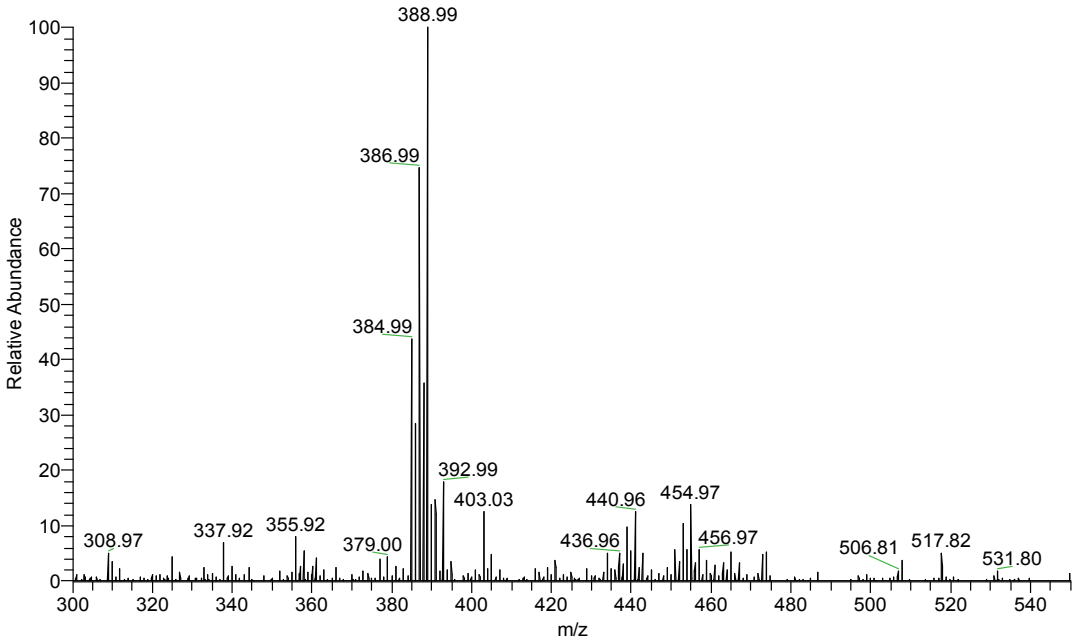

Fig S37 ESI-mass spectrum of the C3 showing an intense signal at m/z: 388.99 for $[C_{14}H_{13}ClN_4SSn\text{-}Cl]^+$

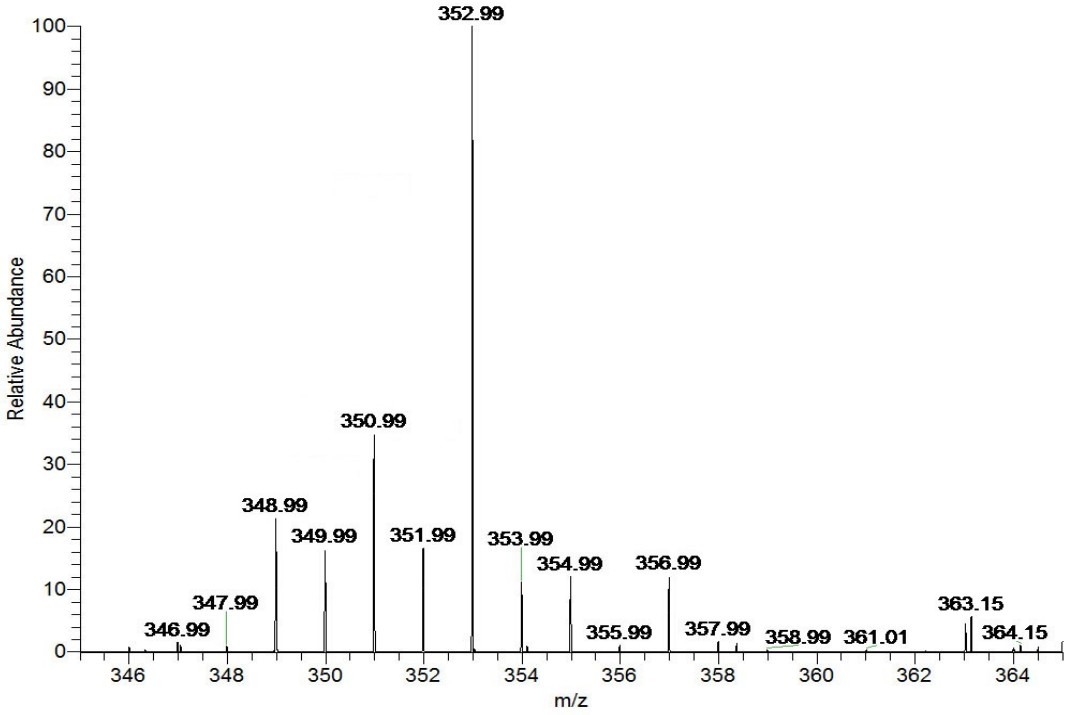

Fig S38 ESI-mass spectrum of the C4 showing an intense signal at m/z: 352.99 for $[C_{11}H_{13}ClN_4SSn\text{-}Cl]^+$

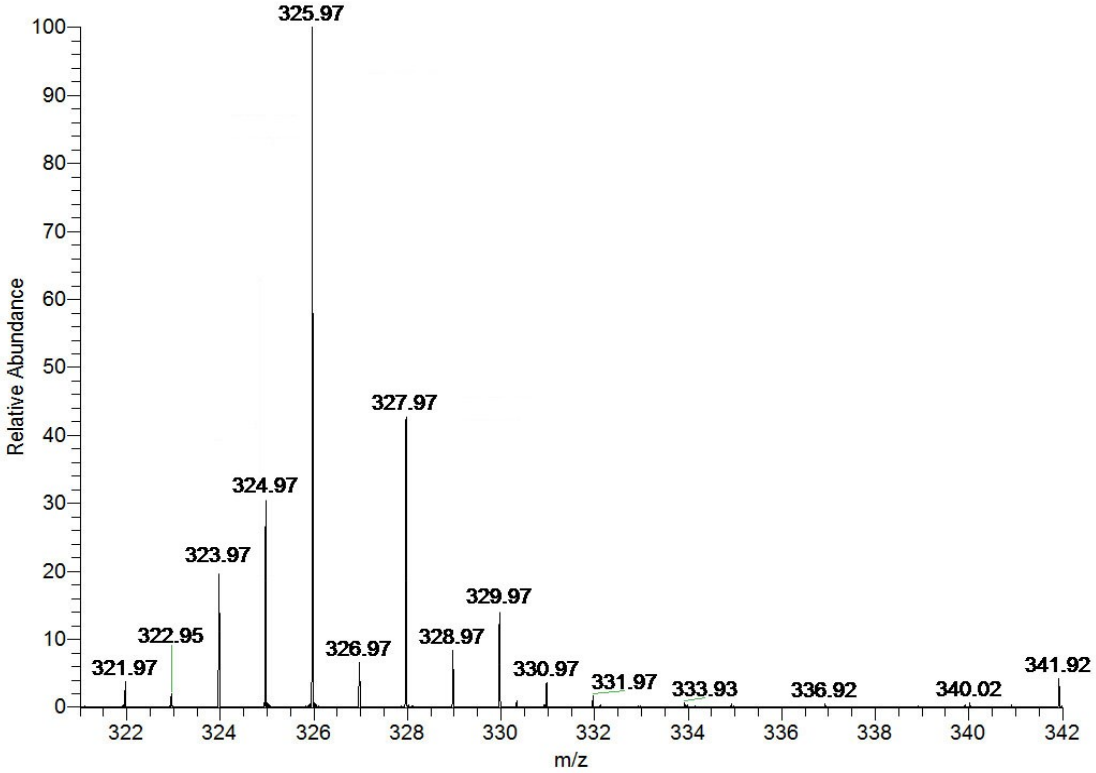

Fig S39 ESI-mass spectrum of the C5 showing an intense signal at m/z:

325.97 for $[C_9H_{11}ClN_4SSn\text{-}Cl]^+$

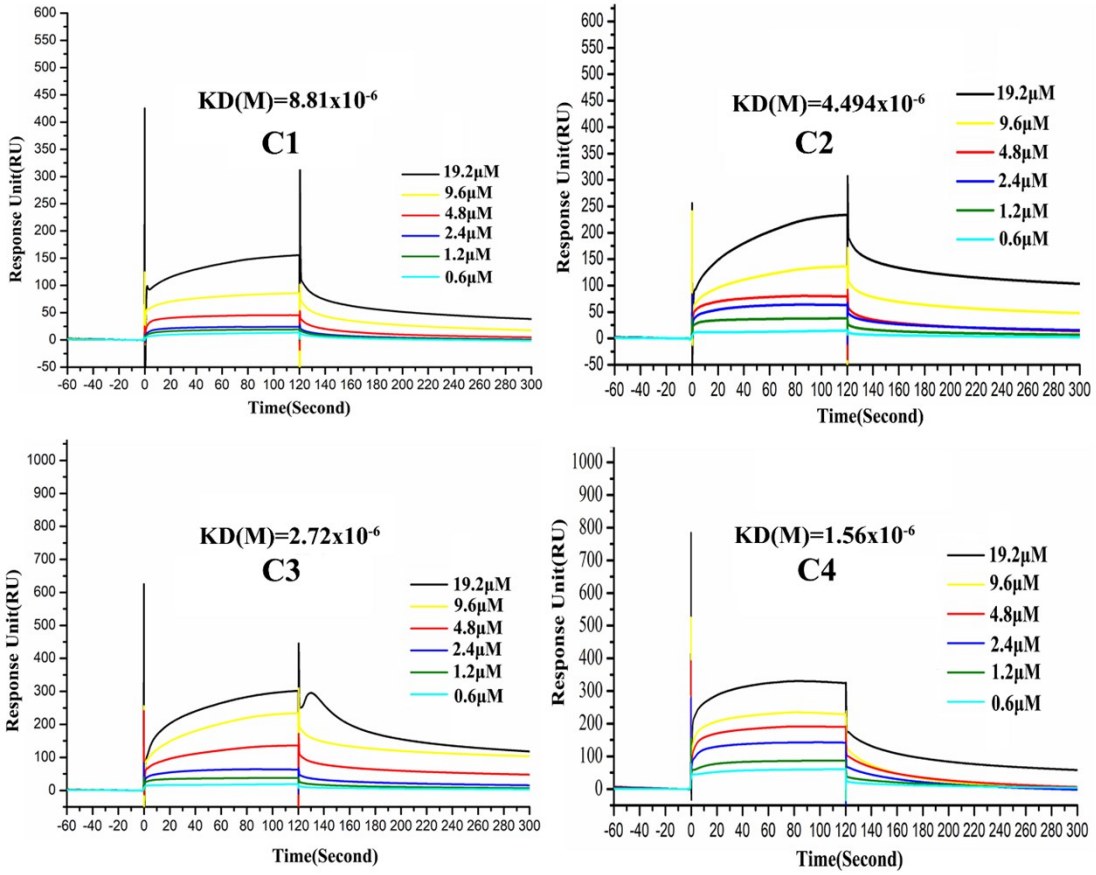

Fig S40 The response curve of the interaction between C1-C4 and Bcl-xL immobilized on a CM5 sensor chip by SPR.

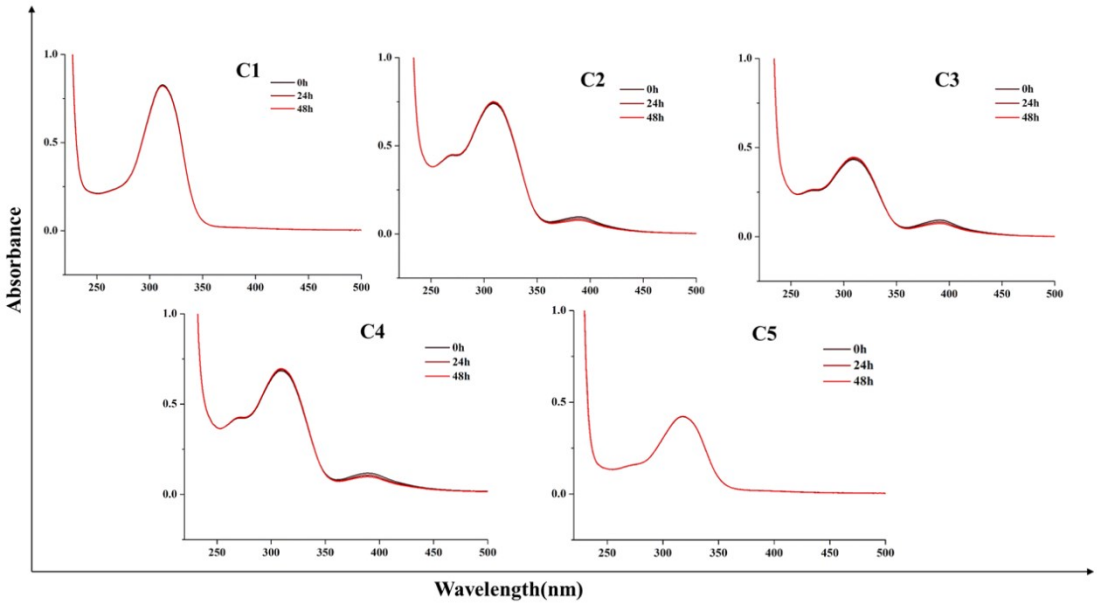

Fig S41 UV-Vis spectra of Sn(II) complexes

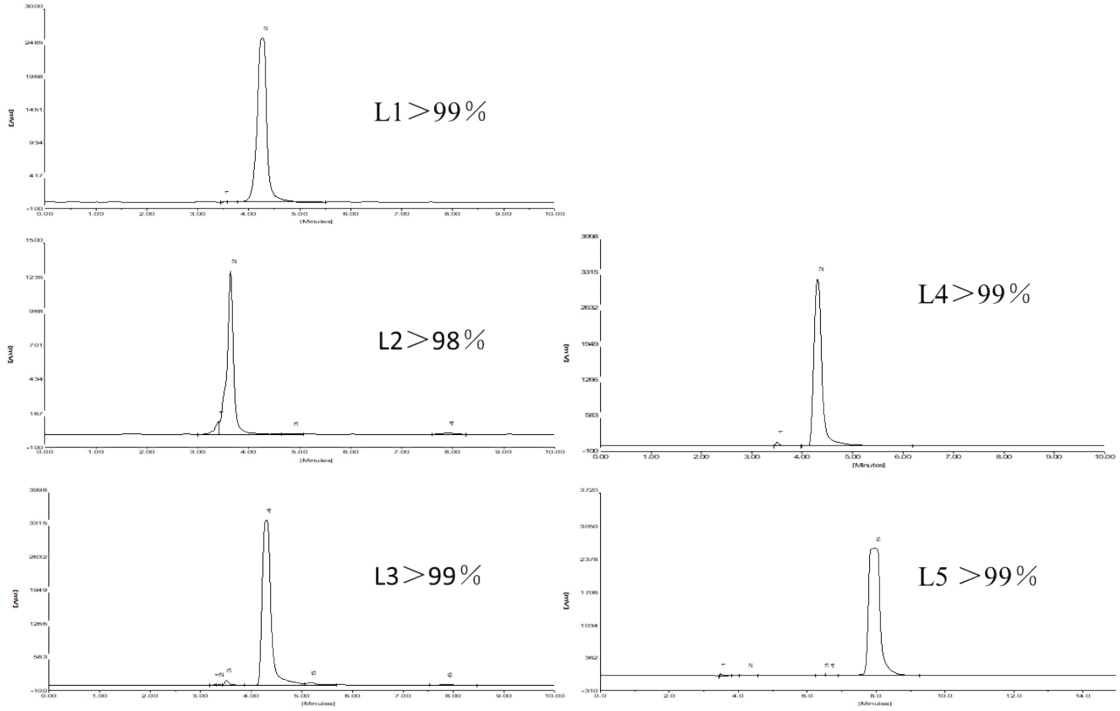

Fig S42 The purity of L1-L5 were determined by HPLC

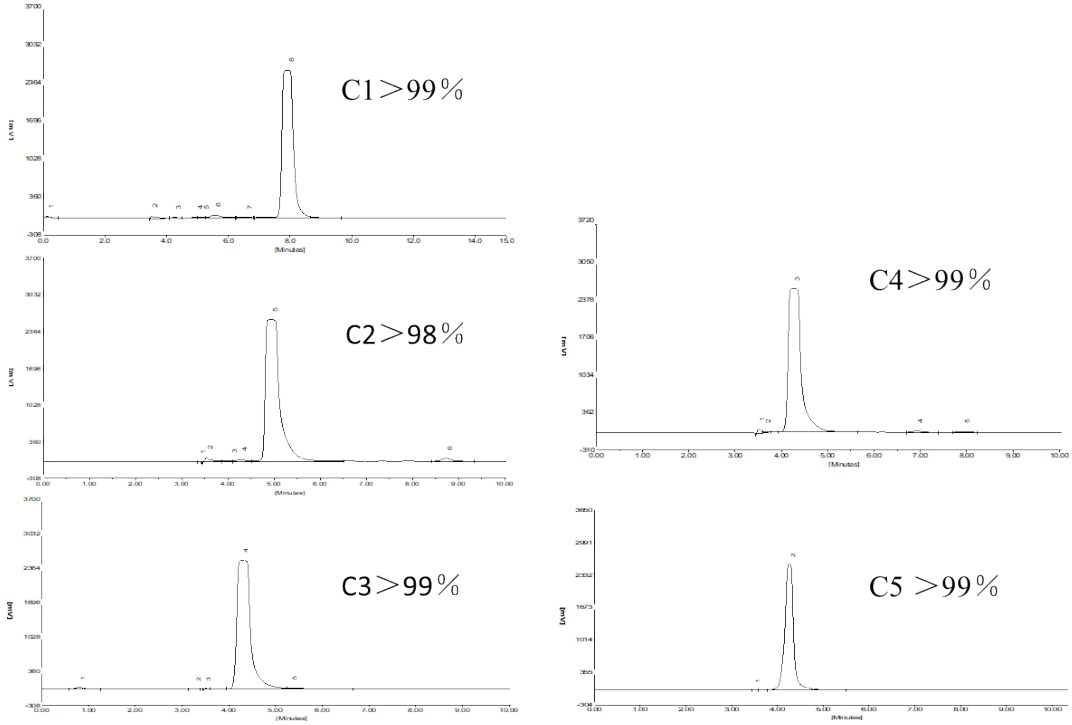

Fig S43 The purity of C1-C5 were determined by HPLC