Supplementary Information

Rh(III)-Catalyzed Directed C-H Carbenoid Coupling Reveals Aromatic Bisphosphonates Inhibiting Metallo- and Serine-β-Lactamases

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Contents

Supplementary Experimental Section 2
SE. 1. Chemical Synthesis. 2
1.1 General Information 2
1.2 Preparation of Substrates 2
1.3 Experimental Procedures and Characterizations 7
1.4 Mechanistic studies 27
SE. 2. Computational Studies. 33
SE. 3. Protein Production. 33
SE. 4. Inhibition, Competitive, Reversibility, and Cellular Assays. 34
SE. 5. ITC Analyses. 36
Supplementary Tables 37
Supplementary Figures 51
^{1}H NMR, ^{13}C NMR, ^{31}P NMR of Compounds 62
Reference 139

Supplementary Experimental Section

SE. 1. Chemical Synthesis.

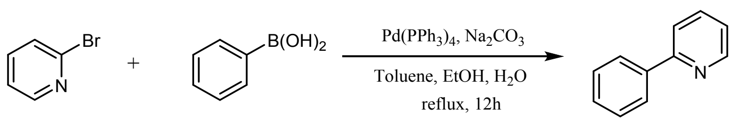
1.1 General Information

Unless otherwise noted, all reactions were carried out in reaction vessels in sealed tubes. Reactions were carried out without any precautions to extrude moisture or air unless otherwise noted. Solvents used were of analytical purity. All reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light. Product purification was done using silica gel column chromatography. Thin layer chromatography (TLC) characterization was performed with precoated silica gel GF254 (0.2mm), while column chromatography characterization was performed with silica gel (100-200mesh). ^{1}H and ^{13}C spectra were recorded with tetramethylsilane as the internal standard. ^{13}C and ^{31}P spectra were recorded with broadband ^{1}H decoupling model. ^{1}H NMR spectra were recorded at 400 or 600 MHz, ^{13}C NMR spectra were recorded at 100 or 150 MHz and ^{31}P NMR spectra were recorded at 162 MHz. Chemical shifts (δ) were reported as parts per million (ppm) downfield from tetramethylsilane and the following abbreviations were used to identify the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and all combinations thereof can be explained by their integral parts. HRMS spectra were recorded on a Waters Q-TOF Premier. Commercial reagents were from Best-reagent (Homepage: http://www.best-reagent.com) or Astatech Chemical Technology Co, Ltd. (Homepage: http://www.astabio-chem.com). All reagents were used without further purification.

1.2 Preparation of Substrates

2-Arylpyridine derivatives **1a**-**1r** were prepared via Suzuki coupling of the corresponding boronic acids and 2-bromopyridine using a reported procedure [S1]. 2-phenylpyrimidine derivatives **1q**, **1u**-**1y** and 3-phenylisoquinoline derivatives **1t**, **1z** were prepared according to reported procedures [S2-S4]. Substrate **1p** was commercially available and used without further purification. All substrates are shown in Scheme S1.

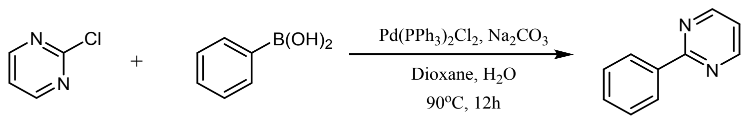
Preparation of 2-phenylpyridine [S1]



To a solution of 2-bromopyridine (0.32 g, 2.0 mmol) in toluene (7 mL), ethanol (3.5

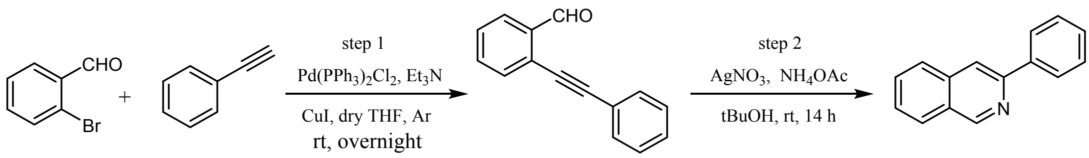
mL), and H_2O (7 mL) was added Na_2CO_3 (1.6 g, 15 mmol) followed by $Pd(PPh_3)_4$ (0.069 g, 0.060 mmol) and arylboronic acid (2.6 mmol) under argon in a 50 mL two-necked flask. The reaction mixture was refluxed for 5 h, then cooled to room temperature. To the reaction mixture was added aqueous NH_4Cl (15 mL); the mixture was then extracted with EtOAc three times; the organic extracts were dried over $MgSO_4$, then evaporated in vacup to afford the crude product, which was purified by flash chromatography on silica gel to provide the desired products.

Preparation of 2-phenylpyrimidine [S2]



To a 50 ml Schlenk tube was added $Pd(PPh_3)_2Cl_2$ (84 mg, 3.0 mol%), Na_2CO_3 (6.36 g, 60 mmol), phenylboronic acid (1.76 g, 14.4 mmol), 2-chloropyrimidine (1.36 g, 12 mmol), toluene (7 mL), ethanol (3.5 mL), and H_2O (7 mL). The reaction was heated to 105 ℃ and stirred for 5 h. After completion, the solvent was removed under reduced pressure and ethyl acetate was added which was washed with water and brine respectively. The combined organic layer was dried over anhydrous sodium sulfate and purified by silica gel column chromatography to afford the desired product.

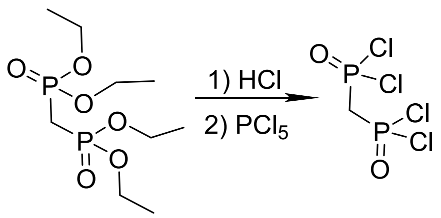
Preparation of 3-phenylisoquinoline



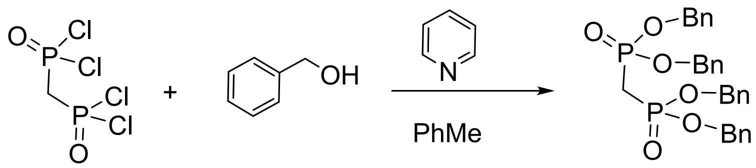
Step 1: To a mixture of $Pd(PPh_3)_2Cl_2$ (379 mg, 5 mol %) and 2-bromobenzaldehyde (2.0 g, 10.8 mmol) in THF (77 ml) was added triethylamine (4.5 ml, 32.4 mmol). After being stirred for 10 min at room temperature, phenylacetylene (1.7 g, 16.2 mmol) and copper iodide (5 mol %) were added to the reaction mixture. The mixture was stirred at room temperature for 12h under argon. The reaction mixture was quenched with saturated aq. NH_4Cl, extracted with EtOAc three times, and washed with brine. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. The crude mixture was purified by silica-gel column chromatography to provide the desired products [S3-S4].

Step 2: *t*-BuOH (47 ml) was added to a mixture of $AgNO_3$ (0.57 mmol, 0.1 equiv.), ammonium acetate (8.55 mmol, 1.5 equiv.) and 2-(phenylethynyl)-benzaldehyde (5.70 mmol, 1 equiv.) under argon atmosphere. The resulting mixture was stirred at room temperature; the reaction was monitored by TLC. After completion, the reaction was quenched by the addition of $NaHCO_3$ (0.48 mmol, 4 equiv.) at room temperature and stirring was continued for additional 4 h. The mixture was then filtered through a cotton plug, washed with EtOAc (5–10 mL), then dried over anhydrous Na_2SO_4. The filtrate was evaporated under reduced pressure and the residue was purified through silica gel column chromatography to obtain the pure isoquinoline derivative [S5].

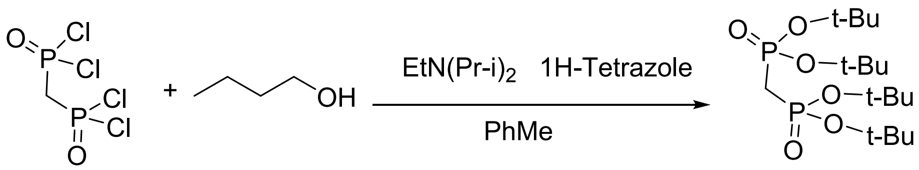
Preparation of diazo-diphosphonates 2



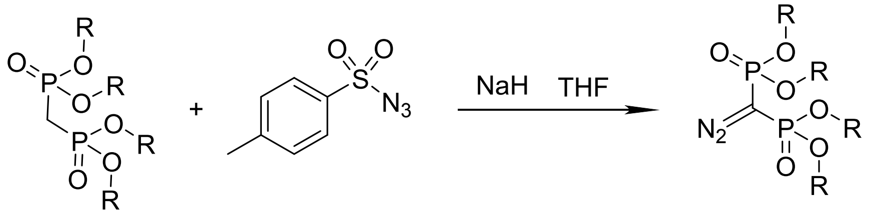
Step 1: A mixture of 17.6g (0.1 mol) of bis-(dihydroxyphosphiny)-1-methane, and 40.0 g. (0.1 mol) of methane-diphosphonic acid tetraethyl ester was strongly heated to effect dissolution. PCl_5 (166 g, 0.8 mole) was added, with stirring, over a period of about half an hour to a cooled solution of the acid. During most of the addition of the PCl_5 in an ice-bath was employed. The mixture was heated several minutes to dissolve the last traces of PCl_5, then transferred to a larger vessel; 400 ml. of petroleum ether was added and crystallization was induced. The product was cooled in an ice-bath, filtered, and washed with 200 ml. of petroleum ether [S6].



Step 2[1]: A suspension of methylene bis-(phosphonic dichloride) (5.00 g, 20.0 mmol) was stirred rapidly in dry toluene (20 mL) at 0 °C. A mixture of dry benzyl alcohol (8.66 mL, 83.0 mmol) and dry pyridine (6.15 mL, 76.1 mmol) was added dropwise via an addition funnel over a 2-hour period, while the temperature was maintained at 0 °C. After the addition was complete, the reaction was allowed to reach 20 °C and stirred for a further 3 h. The solids were removed by filtration and washed twice with toluene (2 × 20 mL). The filtrate was washed twice with 2 M NaOH (2 × 15 mL) and water (15 mL), dried ($MgSO_4$), and concentrated in vacuo. Removal of benzyl alcohol impurity by distillation (120 °C, 1 mmHg) gave product as a colorless oil [S7].

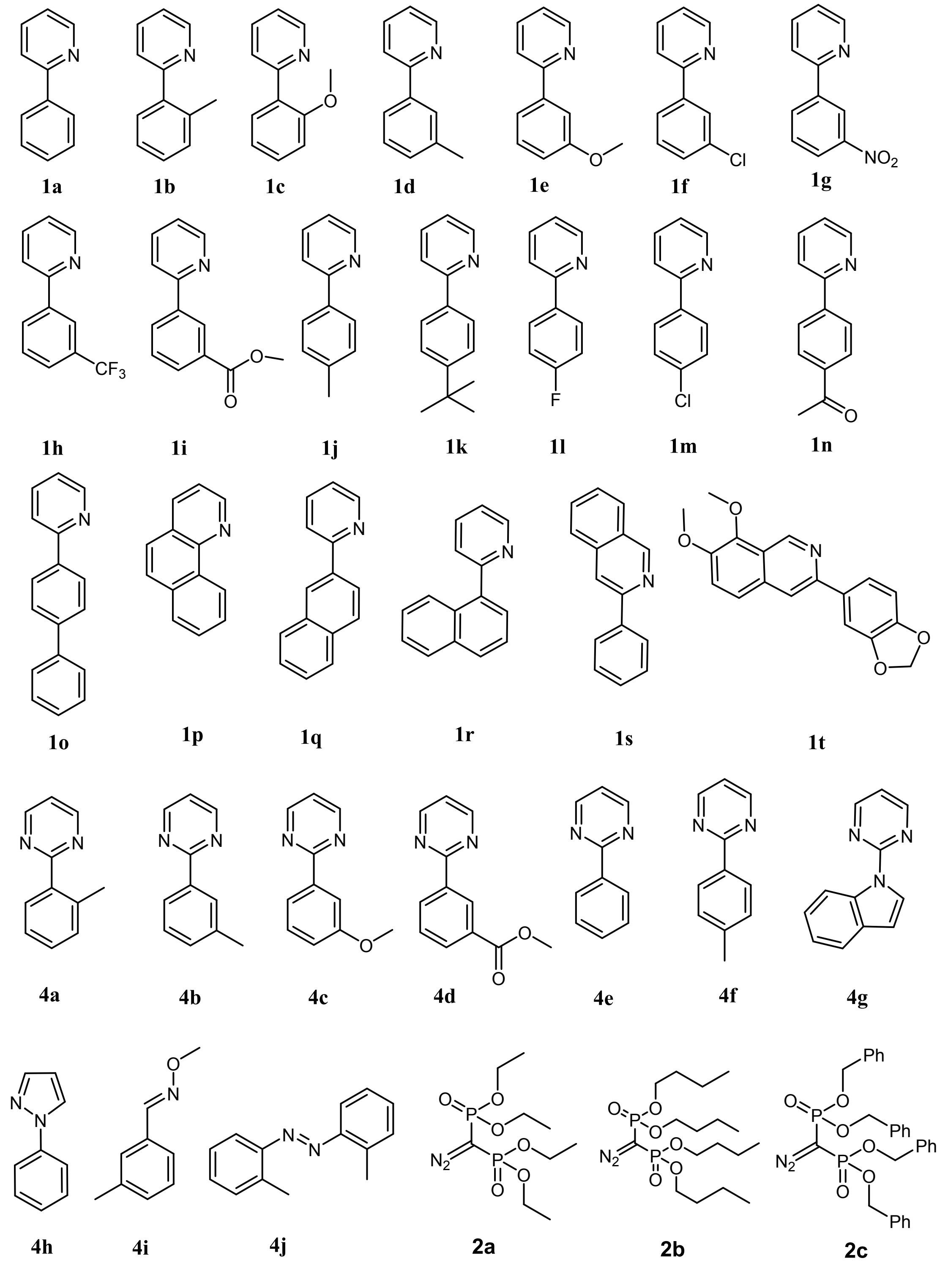


Step 2[2]**:** Methylene bis-(phosphonic dichloride) (5.00 g, 20.0 mmol) and 1H-tetrazole (0.2 g, 3.5 mmol) were dissolved in 20 mL dry toluene, with vigorous stirring (under nitrogen). When the dissolution was complete, a solution of the alcohol (64.0 mmol) and diisopropylethylamine (6.12 mL, 70.4 mmol) in 20 mL of toluene was added dropwise through an addition funnel over a 2 hour period. After stirring the reaction overnight (about 16-18 hours) at room temperature under a nitrogen atmosphere, the solvent was removed in vacuo. The resulting residue was dissolved in hexane and the diisopropylammonium and tetrazonium salts were removed by filtration using a Hirsch funnel. The solution was concentrated in vacuo and the resulting crude product, a light yellow oil, was purified by flash chromatography (10:90 v/v acetone/hexane; first band) [S8].



R=Et, Bu-n, Bn

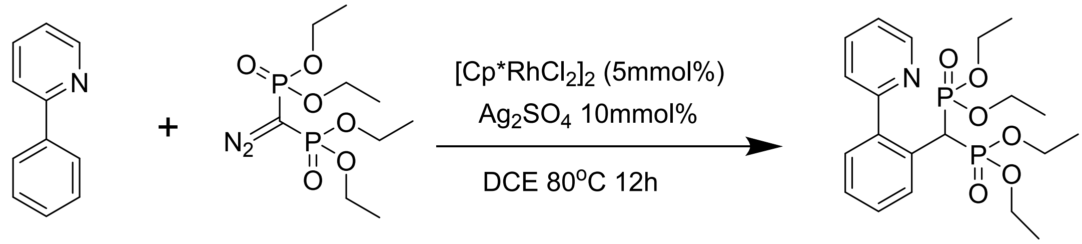
Step 3: To a stirred solution of 60% NaH (1.8g, 4.5 mmol) in 100 ml dry THF was added methanediphosphonic acid tetra-ester (10.0g, 3.5 mmol) dropwise at 0℃ under N_2. After 10 min stirring, Ts-N_3 (6.8 g, 3.5 mmol) was added dropwise. The resulting mixture was stirred at rt for 30 min. The reaction was quenched with water (10 mL), and the product was extracted with EtOAc (100 mL x 3). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude compound was purified by column chromatography to get 6.0 g product as pale yellow oil [S9].



Scheme S1. Substrate Scope.

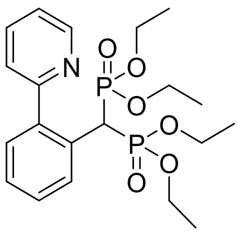
1.3 Experimental Procedures and Characterizations

1.3.1 General procedure for the synthesis of 3 (taking 3a as an example):

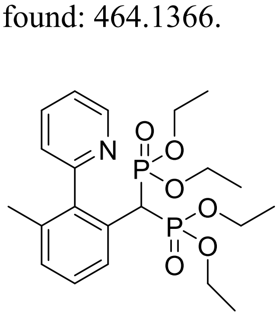


To a 15 ml tube was added **1a** (0.3 mmol, 46.56 mg), **2a** (0.36 mmol, 113.1 mg), $[Cp^{*}RhCl_2]_2$ (9.20 mg 5mol%), Ag_2SO_4(10.14 mg 10 mol%) in DCE (3.0 mL). The tube was sealed and stirred at 80℃ for 12 h. After completion, the reaction mixture was concentrated in vacuo and purified by silica gel column chromatography(80:1 DCM/MeOH) to provide the product **3aa** (pale brown oil) in 93% yield.

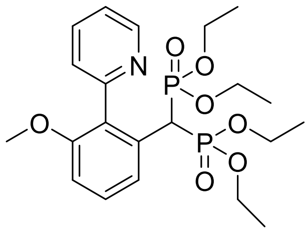
1.3.2 Characterizations



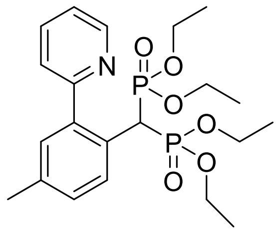
Tetraethyl ((2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3aa). Yield 93%, pale brown oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.77 (td, J = 7.6, 1.4 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.48 – 7.34 (m, 3H), 7.32 – 7.20 (m, 1H), 5.09 (t, J = 25.6 Hz, 1H), 4.29 – 3.87 (m, 8H), 1.21 (t, J = 7.2 Hz, 6H), 1.15 (t, J = 7.2 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.09, 149.10, 140.62, 136.57, 131.20, 130.36, 128.31, 128.07, 127.66, 124.55, 121.94, 63.31, 63.26, 62.74, 62.69, 39.78 (t, J=130.5Hz), 16.25, 16.21, 16.17, 16.13; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.45; HRMS (ESI): m/z calculated for $C_{20}H_{29}NO_6P_2$ [M+Na^{+}]: 464.1362, found: 464.1366.



Tetraethyl ((3-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ba).
Yield 72%, pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.4 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.21 (d, *J* = 7.6 Hz, 1H), 4.10 – 3.94, (m, 8H), 3.72 (t, *J* = 25.2 Hz, 1H), 2.02 (s, 3H), 1.24 (t, *J* = 6.8 Hz, 6H), 1.18 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.25, 149.60, 136.73, 136.12, 129.48, 127.83, 127.77, 127.74, 125.57, 122.14, 112.47, 63.38, 63.30, 62.79, 62.74, 41.45 (t, *J* = 130.5 Hz), 20.77, 16.30, 16.26, 16.24, 16.20; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.12 18.79; HRMS (ESI): *m/z* calculated for $C_{21}H_{31}NO_6P_2$ [M+Na$^+$]: 478.1519, found: 478.1513.

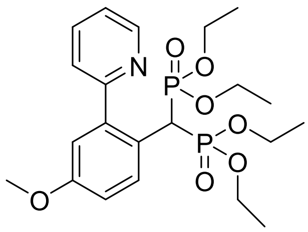


Tetraethyl ((3-methoxy-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ca).
Yield 68%, pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, *J* = 4.4 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.44 – 7.31 (m, 4H), 7.08 (d, *J* = 7.6 Hz, 1H), 3.99 – 3.74 (m, 9H), 3.67 (s, 3H), 1.12 (t, *J* = 6.8 Hz, 6H), 1.02 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCL_3$) δ 157.40, 149.08, 136.03, 129.78, 129.70, 128.99, 126.72, 126.15, 122.17, 119.23, 110.29, 63.39, 62.78, 55.76, 40.89 (t, *J* = 137.0 Hz), 16.32; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.69; HRMS (ESI): *m/z* calculated for $C_{21}H_{31}NO_7P_2$ [M+Na$^+$]: 494.1468, found: 494.1463.

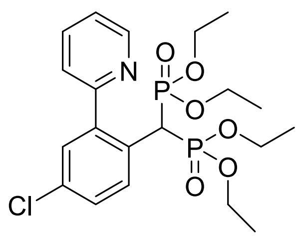


Tetraethyl ((4-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3da).
Yield 96%, pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.4 Hz, 1H), 7.82 (s, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.24 (dd, *J* = 7.6, 5.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 5.14 (t, *J* = 26.0 Hz, 1H), 4.15 – 3.97 (m, 8H), 2.42 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 6H), 1.15 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.16, 148.92, 138.07, 137.66, 136.56, 131.83, 130.24, 128.49, 127.79, 124.58, 121.70, 63.21, 63.17, 62.67, 62.63, 39.57 (t, *J* =

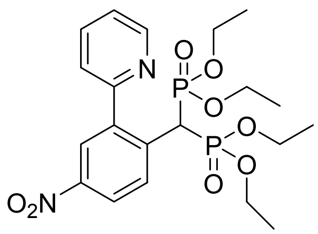
130.5 Hz), 21.36, 16.27, 16.23, 16.15, 16.11; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.58; HRMS (ESI): *m/z* calculated for $C_{21}H_{31}NO_6P_2$ [M+Na$^+$]: 478.1519, found: 478.1513.



Tetraethyl ((4-methoxy-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ea). Yield 83%, yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.4 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.77 (td, *J* = 8.0, 1.3 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.267 (d, *J* = 8.0 Hz, 1H), 7.00 – 6.95 (m, 2H), 4.89 (t, *J* = 26.0 Hz, 1H), 4.16 – 3.93 (m, 8H), 3.84 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 6H), 1.17 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCL_3$) δ 158.90, 158.74, 149.12, 141.88, 136.58, 132.38, 124.47, 122.05, 119.82, 115.73, 113.99, 63.19, 62.62, 55.29, 39.06 (t, *J* = 130.5 Hz), 16.24; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.73; HRMS (ESI): *m/z* calculated for $C_{21}H_{31}NO_7P_2$ [M+Na$^+$]: 494.1468, found: 494.1462.

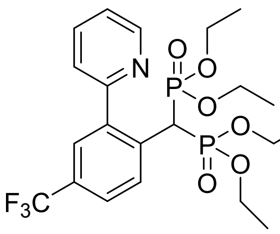


Tetraethyl ((4-chloro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3fa). Yield 78%, yellow oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.69 (d, *J* = 4.4 Hz, 1H), 7.97 (t, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.54 (s, 1H), 7.48 – 7.42 (m, 1H), 5.21 (t, *J* = 25.2 Hz, 1H), 3.98 – 3.82 (m, 8H), 1.11 (t, *J* = 7.2 Hz, 6H), 1.01 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.72, 149.18, 142.03, 136.71, 133.49, 132.52, 130.16, 128.24, 126.96, 124.39, 122.34, 63.21, 62.71, 39.35 (t, *J* = 130.0 Hz), 16.14; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.75; HRMS (ESI): *m/z* calculated for $C_{20}H_{28}ClNO_6P_2$ [M+Na$^+$]: 498.0973, found: 498.0976.

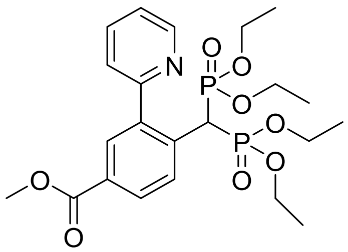


Tetraethyl ((4-nitro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ga). Yield

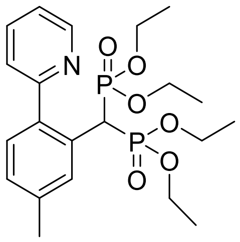
78%, yellow oil,^{1}H NMR (600 MHz, DMSO-d_6) δ 8.74 (d, *J* = 4.4 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.27 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.04 (t, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.55 – 7.48 (m, 1H), 5.40 (t, *J* = 24.6 Hz, 1H), 4.14 – 3.70 (m, 8H), 1.12 (t, *J* = 7.2 Hz, 6H), 1.02 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.01, 149.39, 147.00, 141.68, 137.22, 136.47, 132.50, 125.14, 124.61, 122.95, 122.73, 63.45, 63.41, 63.16, 63.12, 40.29 (t, *J* = 130.5 Hz), 16.27, 16.23, 16.22, 16.18; ^{31}P NMR (162 MHz, DMSO-d_6) δ 17.85; HRMS (ESI): *m/z* calculated for $C_{20}H_{28}NO_8P_2$ [M+Na$^+$]: 509.1213, found: 509.1217.



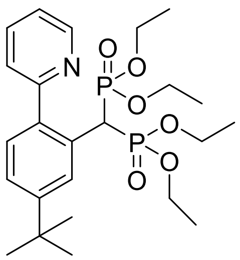
Tetraethyl ((2-(pyridin-2-yl)-4-(trifluoromethyl)phenyl)methylene)bis(phosphonate) (3ha). Yield 56%, yellow oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.72 (d, *J* = 4.4 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 8.00 (t, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.79 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.51 – 7.45 (m, 1H), 5.30 (t, *J* = 25.2 Hz, 1H), 4.02 – 3.83 (m, 8H), 1.12 (t, *J* = 7.2 Hz, 6H), 1.00 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (150 MHz, $CDCL_3$) δ 157.78, 149.28, 141.14, 136.86, 132.73, 131.74, 129.74 (q, *J* = 32.4 Hz), 128.76, 127.08, 124.78, 124.57, 122.51, 63.32, 63.27, 62.93, 62.89, 40.02 (t, *J* = 130.5 Hz), 16.23, 16.18, 16.15, 16.11; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.36 ; HRMS (ESI): *m/z* calculated for $C_{21}H_{28}F_3NO_6P_2$ [M+Na$^+$]: 532.1236, found: 532.1233.



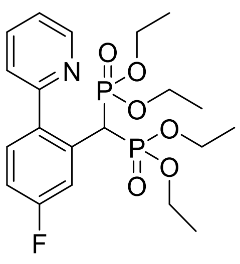
Methyl 4-(bis(diethoxyphosphoryl)methyl)-3-(pyridin-2-yl)benzoate (3ia). Yield 63%, yellow oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.71 (d, *J* = 4.4 Hz, 1H), 8.10 – 7.94 (m, 4H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.50 – 7.44 (m, 1H), 5.29 (t, *J* = 25.2 Hz, 1H), 4.10 – 3.66 (m, 11H), 1.11 (t, *J* = 7.2 Hz, 6H), 0.99 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.16, 149.02, 140.55, 136.81, 133.68, 131.37, 130.73 129.22, 128.97, 128.68, 124.57, 122.29, 63.27, 62.79, 40.04 (t, *J* = 130.2 Hz), 16.13; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.34; HRMS (ESI): *m/z* calculated for $C_{22}H_{31}NO_8P_2$ [M+Na$^+$]: 522.1417, found: 522.1412.



Tetraethyl ((5-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ja).
Yield 96%, yellow solid, mp 145-147 ℃, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.4 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.25 (s, 2H), 7.23 (s, 1H), 4.91 (t, *J* = 25.6 Hz, 1H), 4.11 – 3.96 (m, 8H), 2.38 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 6H), 1.16 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.12, 149.07, 137.37, 136.52, 136.50, 131.06, 130.99, 129.15, 124.80, 124.53, 121.88, 63.24, 62.63, 39.56 (t, *J* = 130.0 Hz), 21.06, 16.24; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.59; HRMS (ESI): *m/z* calculated for $C_{21}H_{31}NO_6P_2$ [M+Na$^+$]: 478.1519, found: 478.1513.

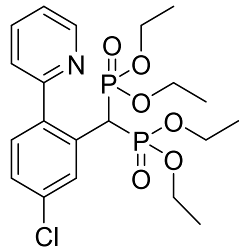


Tetraethyl ((5-(tert-butyl)-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ka).
Yield 96%, yellow oil, ^{1}H NMR (600 MHz, DMSO-*d₆*) δ 8.66 (d, *J* = 4.4 Hz, 1H), 7.98 – 7.89 (m, 2H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.40 – 7.36 (m, 1H), 5.40 (t, *J* = 25.2 Hz, 1H), 4.01 – 3.74 (m, 8H), 1.32 (s, 9H), 1.08 (t, *J* = 7.2 Hz, 6H), 0.98 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.68, 151.23, 148.57, 137.05, 130.08, 128.80, 127.52, 124.67, 124.44, 121.85, 63.24, 63.20, 62.60, 62.55, 39.95 (t, *J* = 132.0 Hz), 34.69, 31.09, 16.27, 16.23, 16.18, 16.14; ^{31}P NMR (162 MHz, DMSO-d_6) δ 19.46; HRMS (ESI): *m/z* calculated for $C_{24}H_{37}NO_6P_2$ [M+Na$^+$]: 520.1988, found: 520.1981.



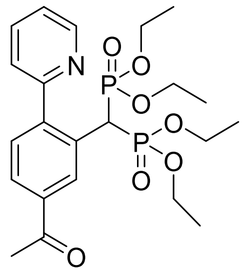
Tetraethyl ((5-fluoro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3la).

Yield 67%, yellow solid, mp 112-114 ℃, ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.66 (d, *J* = 4.4 Hz, 1H), 7.94 (t, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 10.2 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 5.31 (t, *J* = 25.2 Hz, 1H), 3.98 – 3.80 (m, 8H), 1.10 (t, *J* = 7.2 Hz, 6H), 0.99 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.06 (d, *J* = 246.0 Hz), 158.17, 149.04, 136.74, 131.88 (d, *J* = 8.0 Hz), 130.84 (dd, *J* = 16.0, 8.0 Hz), 124.53, 122.02, 118.10(d, *J* = 23.0 Hz), 114.71(d, *J* = 21.0 Hz), 63.24, 63.92, 39.93 (t, *J* = 131.0 Hz), 16.16; ^{31}P NMR (162 MHz, DMSO) δ 18.58; HRMS (ESI): *m/z* calculated for $C_{20}H_{28}FNO_6P_2$ [M+Na$^+$]: 482.1268, found: 482.1263.



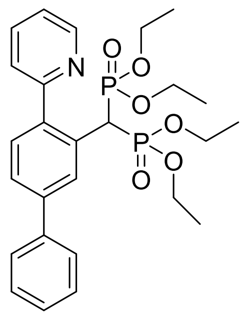
Tetraethyl ((5-chloro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ma).

Yield 87%, pale yellow solid, mp 147-148 ℃, ^{1}H NMR (600 MHz, DMSO-*d*) δ 8.67 (d, *J* = 4.4 Hz, 1H), 7.95 (t, *J* = 7.8 Hz, 1H), 7.85 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.42 (dd, *J* = 7.8, 1.8 Hz, 1H), 5.32 (t, *J* = 25.2 Hz, 1H), 4.00 – 3.81 (m, 8H), 1.11 (t, *J* = 7.2 Hz, 6H), 0.99 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.08, 149.14, 138.95, 136.74 , 134.16, 131.46, 131.12, 130.42, 127.77, 124.51, 122.17, 63.33, 63.28, 62.85,62.81, 39.79 (t, *J* = 132.0 Hz), 16.23, 16.19, 16.15, 16.11; ^{31}P NMR (162 MHz, DMSO-*d*) δ 18.55; HRMS (ESI): *m/z* calculated for $C_{20}H_{28}ClNO_6P_2$ [M+Na$^+$]: 498.0973, found: 498.0980.

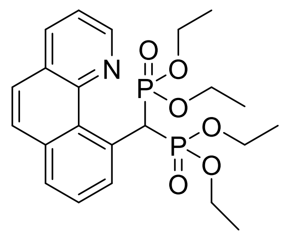


Tetraethyl ((5-acetyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3na).
Yield 84%, pale yellow oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.70 (d, *J* = 4.8 Hz, 1H), 8.44 (d, *J* = 1.8 Hz, 1H), 7.98 (t, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.45 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.33 (t, *J* = 25.2 Hz, 1H), 3.97 – 3.83 (m, 8H), 2.60 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 6H), 1.00 (t, *J* = 7.2 Hz, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.56, 158.02, 149.16, 144.61, 136.79, 136.40, 131.91, 130.66, 129.05, 126.85, 124.55, 122.50, 63.21, 62.83, 39.55 (t, *J* = 131.0 Hz), 26.66, 16.17; ^{31}P NMR (162

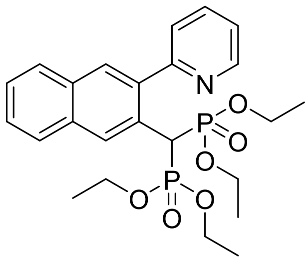
MHz, DMSO-d_6) δ 18.80; HRMS (ESI): *m/z* calculated for $C_{22}H_{31}NO_7P_2$ [M+Na^+]: 506.1468, found: 506.1468.



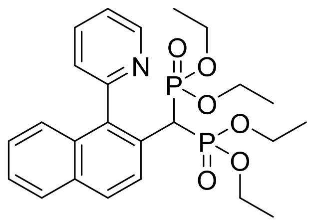
Tetraethyl ((4-(pyridin-2-yl)-[1,1'-biphenyl]-3-yl)methylene)bis(phosphonate) (3oa). Yield 96%, pale brown oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.69 (d, *J* = 4.2 Hz, 1H), 8.19 (s, 1H), 7.96 (t, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.8, 2H), 5.43 (t, *J* = 25.2 Hz, 1H), 3.99 – 3.81 (m, 8H), 1.11 (t, *J* = 7.2 Hz, 6H), 0.96 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.80, 149.07, 140.49, 139.93, 139.35, 136.52, 130.73, 129.88, 128.72, 128.64 127.49, 126.91, 125.93, 124.41, 121.85, 63.19, 62.64, 39.78 (t, *J* = 133.0 Hz), 16.14; ^{31}P NMR (162 MHz, DMSO-d_6) δ 19.27; HRMS (ESI): *m/z* calculated for $C_{26}H_{33}NO_6P_2$ [M+Na^+]: 540.1675, found: 540.1671.



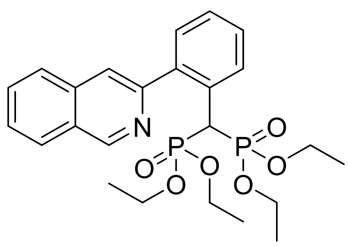
Tetraethyl (benzo[h]quinolin-10-ylmethylene)bis(phosphonate) (3pa). Yield 52%, pale brown solid, mp 88-90 ℃, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (t, *J* = 26.4 Hz, 1H), 9.01 (d, *J* = 3.2 Hz, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.78 – 7.69 (m, 2H), 4.10 – 3.96 (m, 4H), 3.82 – 3.68 (m, 4H), 1.12 (t, *J* = 7.2 Hz, 6H), 0.78 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.11, 146.29, 136.27, 135.40, 132.74, 129.83, 129.29, 128.73, 127.67, 127.26, 125.39, 121.19, 62.67, 62.51, 39.50 (t, *J* = 130.0Hz), 16.19, 16.00; ^{31}P NMR (162 MHz, DMSO-d_6) δ 20.59; HRMS (ESI): *m/z* calculated for $C_{22}H_{29}NO_6P_2$ [M+Na^+]: 488.1362, found: 488.1365.



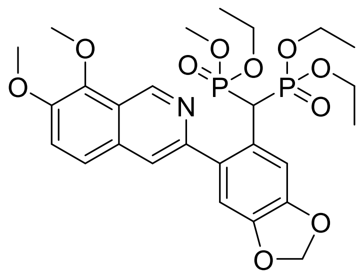
Tetraethyl ((3-(pyridin-2-yl)naphthalen-2-yl)methylene)bis(phosphonate) (3qa). Yield 91%, pale yellow oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.70 (d, J = 4.4 Hz, 1H), 8.35 (s, 1H), 8.06 (s, 1H), 7.98 (dd, J = 7.2, 1.2 Hz, 2H), 7.91 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.46 – 7.42 (m, 1H), 5.44 (t, J = 25.8 Hz, 1H), 4.00 – 3.90 (m, 4H), 3.88 – 3.78 (m, 4H), 1.11 (t, J = 7.2 Hz, 6H), 0.94 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.04, 148.81, 136.91, 132.76, 132.26, 130.92, 129.97, 128.06, 127.75, 126.71, 126.60, 125.66, 124.99, 122.03, 119.24, 63.31, 62.74, 39.53 (t, J = 129.0 Hz), 16.21; ^{31}P NMR (162 MHz, DMSO-d_6) δ 19.24 . HRMS (ESI): m/z calculated for $C_{24}H_{31}NO_6P_2$ [M+Na$^+$]: 514.1519, found: 514.1513.



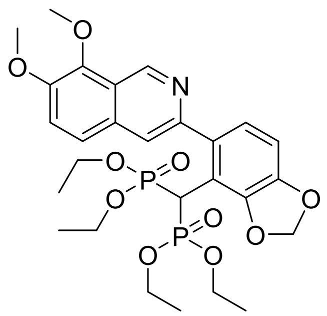
Tetraethyl ((1-(pyridin-2-yl)naphthalen-2-yl)methylene)bis(phosphonate) (3ra). Yield 90%, pale brown oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.80 (d, J = 4.2 Hz, 1H), 8.02 – 8.00 (m, 2H), 7.96 (t, J = 7.8 Hz, 2H), 7.53 – 7.51 (m, 2H), 7.44 (d, J = 7.8 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.16 (d, J = 8.4 Hz, 1H), 3.97 – 3.77 (m, 9H), 1.13 (dt, J = 14.4, 7.2 Hz, 6H), 0.98 (dt, J = 14.4, 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.27, 149.72, 138.52, 136.10, 132.67, 132.50, 128.10, 127.84, 127.27, 126.60, 126.29, 126.13, 125.87, 122.47, 63.15, 62.73, 42.04 (t, J = 132.0 Hz), 16.15; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.71, 18.15; HRMS (ESI): m/z calculated for $C_{24}H_{31}NO_6P_2$ [M+Na$^+$]: 514.1519, found: 514.1517.



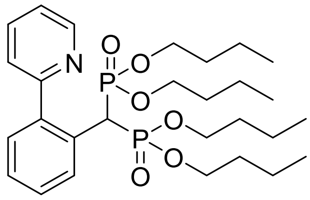
Tetraethyl ((2-(isoquinolin-3-yl)phenyl)methylene)bis(phosphonate) (3sa). Yield 90%, pale brown oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.80 (d, J = 4.2 Hz, 1H), 8.02 – 8.00 (m, 2H), 7.96 (t, J = 7.8 Hz, 2H), 7.53 – 7.51 (m, 2H), 7.44 (d, J = 7.8 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.16 (d, J = 8.4 Hz, 1H), 3.97 – 3.77 (m, 9H), 1.13 (dt, J = 14.4, 7.2 Hz, 6H), 0.98 (dt, J = 14.4, 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.27, 149.72, 138.52, 136.10, 132.67, 132.50, 128.10, 127.84, 127.27, 126.60, 126.29, 126.13, 125.87, 122.47, 63.15, 62.73, 42.04 (t, J = 132.0 Hz), 16.15; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.71, 18.15; HRMS (ESI): *m/z* calculated for $C_{24}H_{31}NO_6P_2$ [M+Na$^+$]: 491.1627, found: 491.1622.



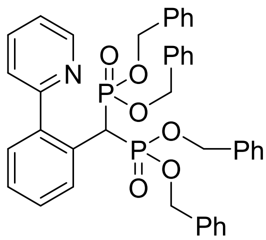
Tetraethyl ((6-(7,8-dimethoxyisoquinolin-3-yl)benzo[d][1,3]dioxol-5-yl) methylene) bis(phosphonate) (3ta). Yield 40%, yellow oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.44 (s, 1H), 7.91 (s, 1H), 7.78 (q, J = 9.0 Hz, 2H), 7.35 (s, 1H), 7.12 (s, 1H), 6.13 (s, 2H), 5.17 (t, J = 25.6 Hz, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 3.97 – 3.83(m, 8H), 1.10 (t, J = 7.2 Hz, 6H), 1.02 (t, J = 7.2 Hz, 6H); δ^{13}C NMR (100MHz, $CDCl_3$) δ 150.40, 148.87, 147.22, 147.12, 146.78, 143.79, 132.02, 122.76, 122.60, 121.60, 120.37, 120.15, 110.89, 110.59, 101.34, 63.13, 62.67, 61.60, 56.99,56.95, 39.95 (t, J = 133.0 Hz), 16.18; ^{31}P NMR (162 MHz, DMSO-d_6) δ 19.39; HRMS (ESI): *m/z* calculated for $C_{27}H_{35}NO_{10}P_2$ [M+Na$^+$]: 618.1628, found: 618.1625.



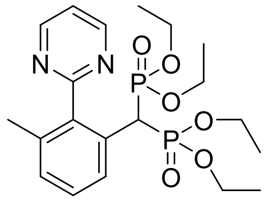
Tetraethyl((5-(7,8-dimethoxyisoquinolin-3-yl)benzo[d][1,3]dioxol-4-yl)-methylene)-bis(phosphonate) (3ta[1]). Yield 38%, pale yellow oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 7.87 (s, 1H), 7.79 (s, 2H), 7.00 (q, J =8.0 Hz, 2H), 6.08 (s, 2H), 5.47 (t, J = 27.2 Hz, 1H), 4.01 – 3.80 (m, 14H), 1.08 (t, J = 6.8 Hz, 6H), 1.02 (t, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCL_3$) δ 152.51, 150.96, 148.77, 147.47, 146.35, 132.27, 124.43, 122.65, 122.55, 120.33, 120.19, 117.15, 110.33, 107.56, 101.17, 62.99, 62.44, 61.62, 57.01, 56.96, 38.28 (t, J = 132.0 Hz), 16.21; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.87; HRMS (ESI): m/z calculated for $C_{27}H_{35}NO_{10}P_2$ [M+Na$^+$]: 618.1628, found: 618.1624.



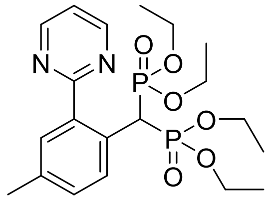
Tetrabutyl ((2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ab). Yield50% ,pale yellow oil, ^1H NMR (600 MHz, $CDCl_3$) δ 8.69 (d, J = 4.8 Hz, 1H), 8.02 (d, J = 6.6 Hz, 1H), 7.78 (t, J = 6.6 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.41 (d, J = 7.8 Hz, 1H), 7.39 (s, 1H), 5.12 (t, J = 25.8 Hz, 1H), 4.93 – 3.93 (m, 8H), 1.57 – 1.53 (m, 4H), 1.52 – 1.47 (m, 4H), 1.30 – 1.25 (m, 8H), 0.86 (dt, J = 15.0, 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.09, 148.97, 140.43, 136.48, 131.28, 130.27, 128.30, 128.17, 127.49, 124.44, 121.83, 66.70, 66.31, 39.64 (t, J = 132.0 Hz), 32.33, 18.50, 13.51; ^{31}P NMR (162 MHz, DMSO-d_6) δ 19.31; HRMS (ESI): m/z calculated for $C_{28}H_{45}NO_6P_2$ [M+Na$^+$]: 576.2614, found: 576.2617.



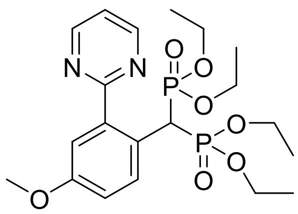
Tetrabenzyl ((2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ac). Yield 82% ,pale yellow oil, ^1H NMR (600 MHz, DMSO-d_6) δ 8.64 (d, J = 4.2 Hz, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.79 (t, J = 7.2 Hz, 1H), 7.48 – 7.43 (m, 3H), 7.37 – 7.34 (m, 1H), 7.34 – 7.21 (m, 13H), 7.18 (d, J = 7.2 Hz, 4H), 7.06 (d, J = 7.2 Hz, 4H), 5.74 (t, J = 27.0, 1H), 4.98 – 4.80 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.96, 148.78, 140.56, 136.72, 136.25, 131.60, 130.51, 128.55, 128.34, 128.30, 128.12, 128.03, 127.99, 127.85, 127.77, 124.54, 121.92, 68.39, 68.17, 40.10(t, J = 131.0 Hz); ^{31}P NMR (162 MHz, DMSO-d_6) δ 20.04. HRMS (ESI): m/z calculated for $C_{40}H_{37}NO_6P_2$ [M+Na$^+$]: 712.1988, found: 712.1984.



Tetraethyl ((3-methyl-2-(pyrimidin-2-yl)phenyl)methylene)bis(phosphonate) (5a). Yield 65%, pale yellow oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.97 (d, *J* = 4.8 Hz, 2H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 4.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 4.06 (t, *J* = 25.2 Hz, 1H), 3.95 – 3.73 (m, 8H), 2.05 (s, 3H), 1.10 (t, *J* = 6.6 Hz, 6H), 1.00 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.96, 156.93, 139.26, 136.75, 129.75, 128.38,128.27, 128.11, 118.97, 63.41, 63.37, 62.75, 62.70, 41.02 (t, *J* = 130.5 Hz), 20.81, 16.24; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.78; HRMS (ESI): *m/z* calculated for $C_{20}H_{30}N_2O_6P_2$ [M+Na$^+$]: 479.1471, found: 479.1478.

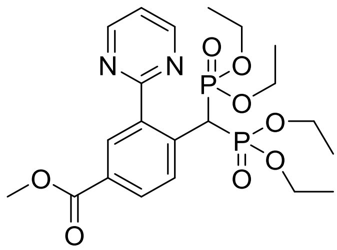


Tetraethyl ((4-methyl-2-(pyrimidin-2-yl)phenyl)methylene)bis(phosphonate) (5b). Yield93%, pale yellow oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.94 (d, *J* = 4.8 Hz, 2H), 7.81 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 4.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 6.23 (t, *J* = 25.8 Hz, 1H), 3.96 – 3.77 (m, 8H), 2.36 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 6H), 0.95 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.73, 156.90, 137.36, 137.12, 132.01, 131.71, 130.55, 126.43, 118.62, 63.09, 62.52, 38.86 (t, *J* = 130.5 Hz), 21.07, 16.17; ^{31}P NMR (162 MHz, DMSO-d_6) δ 19.63; HRMS (ESI): *m/z* calculated for $C_{20}H_{30}N_2O_6P_2$ [M+Na$^+$]: 479.1471, found: 479.1473.

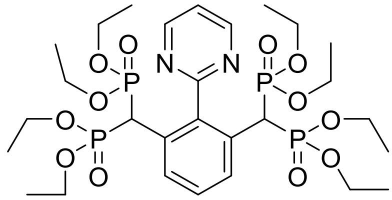


Tetraethyl ((4-methoxy-2-(pyrimidin-2-yl)phenyl)methylene)bis(phosphonate) (5c). Yield 82%, pale yellow oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (d, *J* = 4.8 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.54 (s, 1H), 7.50 (t, *J* = 4.8 Hz, 1H), 7.11 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.20 (t, *J* = 26.0 Hz, 1H), 3.96 – 3.88 (m, 4H), 3.88 – 3.76 (m, 8H), 1.10 (t, *J* = 6.8 Hz, 6H), 0.96 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.32, 158.76, 156.87, 138.38, 133.01, 121.35, 118.77, 116.32, 115.85, 63.05, 62.46, 55.28, 38.40 (t, *J* = 130.5 Hz), 16.13; ^{31}P NMR (162 MHz, DMSO-d_6) δ 19.76 ; HRMS

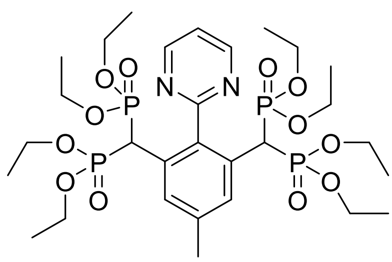
(ESI): *m/z* calculated for $C_{20}H_{30}N_2O_7P_2$ [M+Na$^+$]: 495.1420, found: 495.1423.



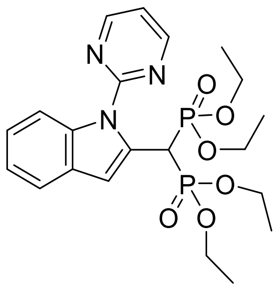
Methyl 4-(bis(diethoxyphosphoryl)methyl)-3-(pyrimidin-2-yl)benzoate (5d). Yield 91%, pale yellow oil , ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.03 (d, *J* = 4.8 Hz, 2H), 8.65 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 4.8 Hz, 1H), 6.48 (t, *J* = 25.8 Hz, 1H), 4.03 – 3.93 (m, 4H), 3.92 – 3.82 (m, 7H), 1.10 (t, *J* = 7.2 Hz, 6H), 0.97 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.46, 165.76, 157.04, 137.53, 134.96, 132.76, 132.02, 130.19, 129.41, 119.05, 63.28, 63.24, 62.76, 62.72, 52.17, 39.65 (t, *J* = 130.5 Hz), 16.15; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.58; HRMS (ESI): *m/z* calculated for $C_{21}H_{30}N_2O_8P_2$ [M+Na$^+$]: 523.1370, found: 523.1375.



Octaethyl((2-(pyrimidin-2-yl)-1,3-phenylene)bis(methanetriyl))tetrakis(phosphonate) (5e). Yield 90%, pale yellow oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (d, *J* = 4.8 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 4.8 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 4.41 (t, *J* = 25.6 Hz, 2H), 3.93 – 3.79 (m, 16H), 1.11 (t, *J* = 6.8 Hz, 12H), 1.01 (t, *J* = 6.8 Hz, 12H); 13C NMR (150 MHz, $CDCl_3$) δ 165.75, 156.93, 130.56, 129.43, 128.24, 119.18, 63.26, 62.68, 41.16 (t, *J* = 130.5 Hz), 16.21; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.70; HRMS (ESI): *m/z* calculated for $C_{28}H_{48}N_2O_{12}P_4$ [M+Na$^+$]: 751.2050, found: 751.2053.

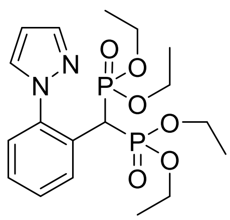


Octaethyl((5-methyl-2-(pyrimidin-2-yl)-1,3-phenylene)bis(methanetriyl))tetrakis-(phosphonate) (5f). Yield 74%, pale yellow solid, mp71-73 ℃, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (d, J = 4.8 Hz, 2H), 7.65 (s, 2H), 7.54 (t, J = 4.8 Hz, 1H), 4.48 (t, J = 25.6 Hz, 2H), 3.94 – 3.77 (m, 16H), 2.36 (s, 3H), 1.11 (t, J = 7.2 Hz, 12H), 1.01 (t, J = 7.2 Hz, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.89, 156.84, 137.98, 136.46, 131.23, 129.14, 118.96, 63.19, 62.62, 40.91 (t, J = 130.5 Hz), 21.55, 16.21; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.79; HRMS (ESI): m/z calculated for $C_{29}H_{50}N_2O_{12}P_4$ [M+Na$^+$]: 765.2206, found: 765.2203.



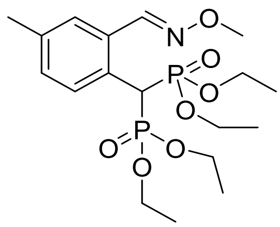
Tetraethyl ((1-(pyrimidin-2-yl)-1H-indol-2-yl)methylene)bis(phosphonate) (5g).

Yield 67%, pale yellow solid, mp167-169 ℃, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (d, J = 4.8 Hz, 2H), 8.18 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 7.2 Hz, 1H), 7.49 (t, J = 4.8 Hz, 1H), 7.22 (dt, J = 21.2, 7.2 Hz, 2H), 7.06 (s, 1H), 6.13 (t, J = 26.0 Hz, 1H), 4.02 – 3.85 (m, 8H), 1.13 (t, J = 6.8 Hz, 6H), 1.02 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCL_3$) δ 158.07, 136.79, 128.60, 128.05, 123.43, 122.06, 120.61, 119.21, 117.14, 114.40, 110.87, 63.53, 62.84, 37.27 (t, J = 131.0 Hz), 16.23; ^{31}P NMR (162 MHz, DMSO-d_6) δ 17.28; HRMS (ESI): m/z calculated for $C_{21}H_{29}N_3O_6P_2$ [M+Na$^+$]: 504.1424, found: 504.1425.

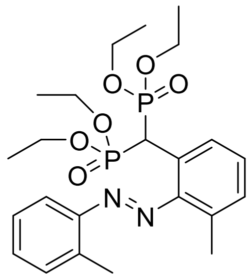


Tetraethyl ((2-(1H-pyrazol-1-yl)phenyl)methylene)bis(phosphonate) (5h). Yield 82%, pale solid, mp75-78 ℃ ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.82 (s, 1H), 7.52 – 7.45 (m, 2H), 7.41 (d, J = 7.2 Hz, 1H), 6.55 (d, J = 1.8 Hz, 1H), 4.69 (t, J = 25.2 Hz, 1H), 4.00 – 3.91 (m, 4H), 3.90 – 3.80 (m, 4H), 1.15 (t, J = 7.2 Hz, 6H), 1.01 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.91, 139.95, 131.51, 131.49, 128.32, 128.25, 126.61 126.25, 106.64, 63.33, 62.86, 38.30 (t, J = 126.0Hz), 16.23, 16.16, 16.13, 16.01; ^{31}P NMR (162 MHz, DMSO-d_6) δ

18.33; HRMS (ESI): *m/z* calculated for $C_{18}H_{28}N_2O_6P_2$ [M+Na$^+$]: 453.1315, found: 453.1317.

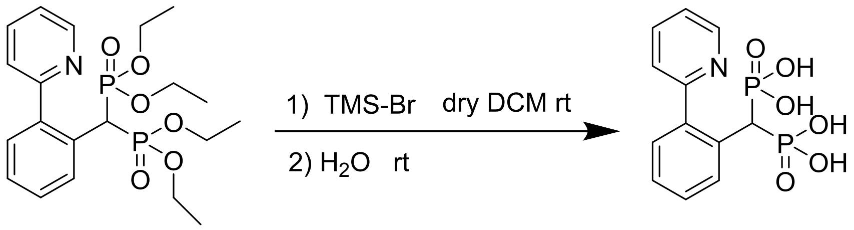


Tetraethyl ((2-((methoxyimino)methyl)-4-methylphenyl)methylene)(E)-bis(phosphonate) (5i). Yield 52%, pale yellow oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.43 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 5.13 (t, *J* = 26.0 Hz, 1H), 4.07 – 4.00 (m, 4H), 3.90 – 3.80 (m, 7H), 2.30 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 6H), 1.02 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz,CDCll_3) δ 148.59, 137.86, 131.24, 130.53, 130.36, 129.70, 125.27, 63.70, 63.23, 62.09, 39.46 (t, *J* = 132.0Hz), 20.92, 16.23, 16.19, 16.11, 16.07; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.82; HRMS (ESI): *m/z* calculated for $C_{18}H_{31}NO_7P_2$ [M+Na$^+$]: 458.1468, found: 458.1468.



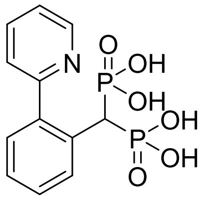
Tetraethyl ((3-methyl-2-(o-tolyldiazenyl)phenyl)methylene)(E)-bis(phosphonate) (5j). Yield 92%, pale yellow oil, ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.93 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.32 (q, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 7.2 Hz, 1H), 5.27 (t, *J* = 25.2 Hz, 1H), 4.14 – 3.99 (m, 8H), 2.71 (s, 3H), 2.43 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 6H), 1.15 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.08, 149.49, 138.31, 132.28, 132.12, 132.07, 129.46, 129.22, 127.79, 127.33, 114.70, 63.04, 63.00, 62.78, 62.76, 20.81, 17.85, 16.54, 16.50, 16.32, 16.30; ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.68; HRMS (ESI): *m/z* calculated for $C_{23}H_{34}N_2O_6P_2$ [M+Na$^+$]: 519.1784, found: 519.1788.

1.3.2 General procedure for the synthesis of acid (taking 3aa acid as an example):

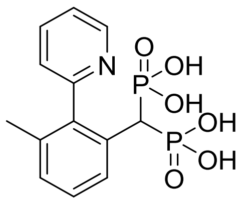


3aa **3aa acid**

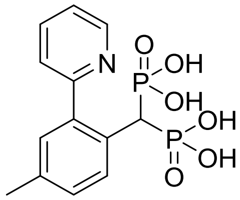
To a solution of **3aa** (30.0 mg, 0.068 mmol) in 5 mL of dry CH_2Cl_2, trimethylsilyl - bromide (62.5mg, 0.41 mmol) was added and the reaction mixture was stirred under a nitrogen flow. The reaction was monitored by TLC. After 4 h, the reaction was quenched with 10 mL of H_2O and the aqueous layer was evaporated in vacuo to obtain **3aa acid** as a microcrystalline powder in 96% yield.



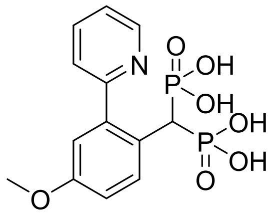
((2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3aa acid). Yield 96%, yellow powder, ^{1}H NMR (400 MHz, D_2O) δ 8.65 (d, J = 5.2 Hz, 1H), 8.51 (td, J = 8.0, 1.2 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.90 (t, J = 7.2 Hz, 2H), 7.57 – 7.48 (m, 1H), 7.44 – 7.38 (m, 2H), 3.41 (t, J = 23.6 Hz, 1H); ^{13}C NMR (150 MHz, D_2O) δ 152.15, 146.90, 141.03, 132.14, 131.41, 131.25, 130.60, 128.71, 127.77, 125.77, 112.52; ^{31}P NMR (162 MHz, D_2O) δ 16.69; HRMS (ESI): *m/z* calculated for $C_{13}H_{13}NO_6P_2$ [M+Na$^+$]: 352.0110, found: 352.0113.



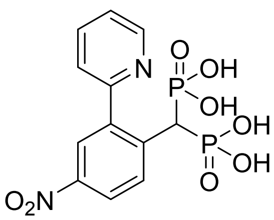
((3-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3ba acid). Yield 95%, yellow powder, ^{1}H NMR (400 MHz, D_2O) δ 8.81 (s, 1H), 8.64 (s, 1H), 8.04 (d, J = 7.2Hz, 2H), 7.75 (s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 3.11 (s, 1H), 1.99 (s, 3H); ^{13}C NMR (150 MHz, D_2O) δ 158.22, 149.65, 136.72, 136.09, 129.41, 127.88, 127.77, 127.74, 125.57, 122.14, 112.51, 20.77; ^{31}P NMR (162 MHz, D_2O) δ 14.87; HRMS (ESI): *m/z* calculated for $C_{13}H_{15}NO_6P_2$ [M+Na$^+$]: 366.0267, found: 366.0263.



((4-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3da acid). Yield 97%, yellow powder, ^{1}H NMR (400 MHz, D_2O) δ 8.63 (s, 1H), 8.49 (s, 1H), 8.02 (s, 1H), 7.88 (s, 1H), 7.70 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 3.85 (t, *J* = 23.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100MHz, D_2O) δ 152.26, 146.94, 146.89, 142.50, 141.08, 131.48, 131.21, 129.06, 128.70, 128.65, 125.62, 20.67; ^{31}P NMR (162 MHz, D_2O) δ 17.32; HRMS (ESI): *m/z* calculated for $C_{13}H_{15}NO_6P_2$ [M+Na$^+$]: 366.0267, found: 366.0261.

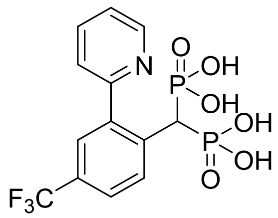


((4-methoxy-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3ea acid). Yield 96%, pale yellow powder, ^{1}H NMR (400 MHz, D_2O) δ 8.66 (s, 1H), 8.52 (t, *J* = 7.6 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.93 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.21 – 7.06 (m, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 3.73 (s, 3H), 3.37 (t, *J* = 23.2 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 158.19, 151.65, 147.05, 141.28, 133.06, 132.01, 128.73, 126.10, 123.83, 117.35, 116.41, 55.67; ^{31}P NMR (162 MHz, D_2O) δ 16.11; HRMS (ESI): *m/z* calculated for $C_{13}H_{15}NO_7P_2$ [M+Na$^+$]: 382.0216, found: 382.0217.

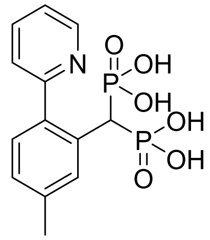


((4-nitro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3ga acid). Yield 97%, yellow powder, ^{1}H NMR (400 MHz, D_2O) δ 8.83 (d, *J* = 4.8 Hz, 1H), 8.68 (t, *J* = 7.2 Hz, 1H), 8.42 (s, 2H), 8.22 (d, *J* = 7.2 Hz, 2H), 8.10 (d, *J* = 7.2 Hz, 1H), 3.64 (t, *J* = 23.2 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 149.84, 147.39, 146.44, 141.84, 140.84, 133.12, 132.07, 129.06, 126.83, 126.33, 125.77; ^{31}P NMR (162 MHz, D_2O) δ

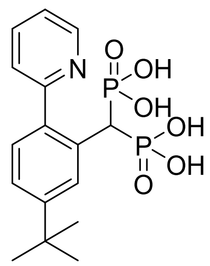
13.77; HRMS (ESI): *m/z* calculated for $C_{12}H_{12}N_2O_8P_2$ [M+Na$^+$]: 396.9961, found: 396.9964.



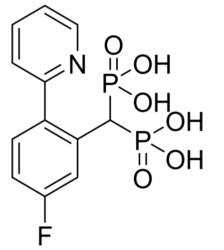
((2-(pyridin-2-yl)-4-(trifluoromethyl)phenyl)methylene)bis(phosphonic acid) (3ha acid). Yield 97%, yellow powder, ^{1}H NMR (400 MHz, D_2O) δ 8.80 (d, *J* = 4.8 Hz, 1H), 8.65 (td, *J* = 8.0, 1.5 Hz, 1H), 8.24 – 8.12 (m, 2H), 8.10 – 8.02 (m, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.87 (s, 1H), 3.58 (t, *J* = 23.6 Hz, 1H); ^{13}C NMR (150 MHz, D_2O) δ 157.78, 149.32, 141.12, 136.83, 132.79, 131.71, 129.69 (q, *J* = 54.0 Hz, 1H), 128.69, 127.08, 124.80, 124.50, 122.47; ^{31}P NMR (162 MHz, D_2O) δ 14.88; HRMS (ESI): *m/z* calculated for $C_{13}H_{12}F_3NO_6P_2$ [M+Na$^+$]: 366.0267, found: 366.0261.



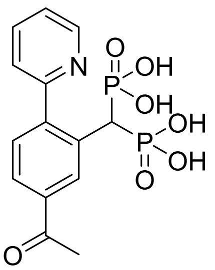
((5-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3ja acid). Yield 98%, pale yellow powder, ^{1}H NMR (400 MHz, D_2O) δ 8.64 (s, 1H), 8.50 (t, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.90 (s, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.24 (s, 1H), 3.42 (t, *J* = 24.0 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 152.19, 146.96, 141.16, 138.51, 132.24, 131.88, 131.62, 130.46, 128.66, 128.39, 125.83, 42.85 (t, *J*=123.0Hz), 19.97; ^{31}P NMR (162 MHz, D_2O) δ 15.93; HRMS (ESI): *m/z* calculated for $C_{13}H_{15}NO_6P_2$ [M+Na$^+$]: 366.0267, found: 366.0265.



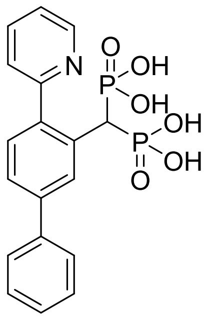
((5-(tert-butyl)-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3ka acid). Yield 97%, yellow powder, ^{1}H NMR (600 MHz, D_2O) δ 8.67 (s, 1H), 8.52 (s, 1H), 8.14 – 7.97 (m, 2H), 7.92 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 3.52 (t, *J* = 21.6 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (100MHz, D_2O) δ 157.72, 154.64, 154.59, 149.36, 143.56, 133.48, 131.14, 130.97, 128.12, 127.65, 36.95, 32.71, ^{31}P NMR (162 MHz, D_2O) δ 18.48; HRMS (ESI): *m/z* calculated for $C_{16}H_{21}NO_6P_2$ [M+Na$^+$]: 408.0736, found: 408.0733.



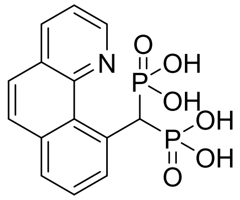
((5-fluoro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3la acid). Yield 97%, pale yellow powder, ^{1}H NMR (400 MHz, D_2O) δ 8.83 (d, *J* = 5.2 Hz, 1H), 8.69 (t, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.15 – 8.04 (m, 1H), 7.83 (d, *J* = 10.0 Hz, 1H), 7.63 (dd, *J* = 8.4, 6.0 Hz, 1H), 7.33 (t, *J* = 8.4 Hz, 1H), 3.59 (t, *J* = 22.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.00 (d, *J* = 246.0 Hz), 158.07, 149.01, 136.74, 131.88 (d, *J* = 8.4 Hz), 130.84 (dd, *J* = 16.0, 8.0 Hz), 124.71, 122.02, 118.07(d, *J* = 23.0 Hz), 114.67 (d, *J* = 21.0 Hz); ^{31}P NMR (162 MHz, D_2O) δ 15.66; HRMS (ESI): *m/z* calculated for $C_{12}H_{12}FNO_6P_2$ [M+Na$^+$]: 370.0016, found: 370.0013.



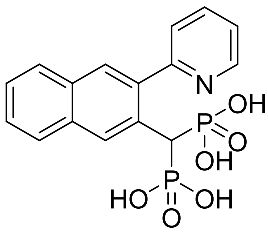
((5-acetyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3na acid). Yield 95%, pale yellow powder, ^{1}H NMR (400 MHz, D_2O) δ 8.77 (s, 1H), 8.61 (s, 1H), 8.52 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.07 – 7.94 (m, 2H), 7.61 (d, *J* = 7.8 Hz, 1H), 3.56 (t, *J* = 23.6 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, D2O) δ 202.70, 150.88, 147.17, 141.60, 138.40, 136.37, 133.14, 131.78, 130.78, 128.79, 127.19, 126.50, 43.42 (t, J=125.0Hz), 26.55; 31P NMR (162 MHz, D2O) δ 14.99; HRMS (ESI): *m/z* calculated for $C_{13}H_{15}NO_6P_2$ [M+Na$^+$]: 394.0216, found: 394.0213.



((4-(pyridin-2-yl)-[1,1'-biphenyl]-3-yl)methylene)bis(phosphonic acid) (3oa acid). Yield 98%, pale yellow powder, ^{1}H NMR (600 MHz, D_2O) δ 8.70 (d, *J* = 4.8 Hz, 1H), 8.55 (t, *J* = 7.2 Hz, 1H), 8.20 (s, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.95 (s, 1H), 7.70 (d, *J* = 7.2 Hz, 3H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.41 – 7.34 (m, 1H), 3.58 (t, *J* = 24.0 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 158.81, 149.07, 140.49, 139.93, 139.35, 136.52, 130.73, 129.88, 128.72, 128.64 127.49, 126.91, 125.93, 124.41, 121.85; ^{31}P NMR (162 MHz, D_2O) δ 15.78; HRMS (ESI): *m/z* calculated for $C_{13}H_{15}NO_6P_2$ [M+Na$^+$]: 428.0423, found: 428.0421.

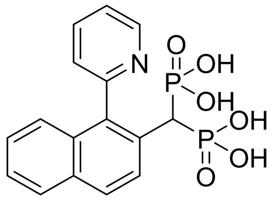


(benzo[h]quinolin-10-ylmethylene)bis(phosphonic acid) (3pa acid). Yield 95%, yellow powder, ^{1}H NMR (400 MHz, D_2O) δ 8.87 (d, *J* = 3.6 Hz, 2H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.44 (s, 1H), 7.32 – 7.00 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 159.33, 136.36, 126.64, 123.43, 122.21, 120.58, 119.17, 112.53; ^{31}P NMR (162 MHz, D_2O) δ 15.94; HRMS (ESI): *m/z* calculated for $C_{14}H_{13}NO_6P_2$ [M+Na$^+$]: 376.0110, found: 376.0112.

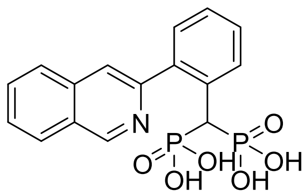


((3-(pyridin-2-yl)naphthalen-2-yl)methylene)bis(phosphonic acid) (3qa acid). Yield 96%, yellow powder, ^{1}H NMR (600 MHz, D_2O) δ 8.70 (d, *J* = 4.8 Hz, 1H), 8.55 (t, *J* = 7.2 Hz, 1H), 8.20 (s, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.95 (s, 1H), 7.70 (d, *J* = 7.2 Hz, 3H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.41 – 7.34 (m, 1H), 3.58 (t, *J*

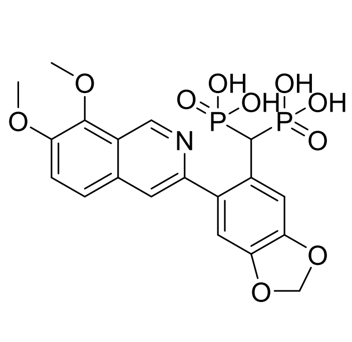
= 24.0 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 159.02, 148.81, 136.96, 132.71, 132.26, 131.00, 129.99, 128.06, 127.75, 126.75, 126.60, 125.61, 125.08, 124.99, 122.03; ^{31}P NMR (162 MHz, D_2O) δ 16.35; HRMS (ESI): *m/z* calculated for $C_{16}H_{15}NO_6P_2$ [M+Na$^+$]: 402.0267, found: 402.0263.



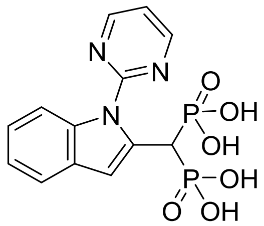
((1-(pyridin-2-yl)naphthalen-2-yl)methylene)bis(phosphonic acid) (3ra acid). Yield 96%, yellow powder, ^{1}H NMR (400 MHz, D_2O) δ 8.81 (s, 1H), 8.63 (t, *J* = 7.2 Hz, 1H), 8.05 (t, *J* = 8.4 Hz, 3H), 8.01 – 7.89 (m, 2H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 3.26 (t, *J* = 24.8 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 150.36, 147.36, 142.31, 131.96, 131.62, 131.34, 130.58, 128.44, 127.98, 126..86, 126.69, 124.22, 123.31; ^{31}P NMR (162 MHz, D_2O) δ 15.33; HRMS (ESI): *m/z* calculated for $C_{16}H_{15}NO_6P_2$ [M+Na$^+$]: 402.0267, found: 402.0265.



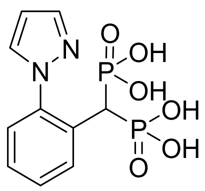
((2-(isoquinolin-3-yl)phenyl)methylene)bis(phosphonic acid) (3sa acid). Yield 96%, yellow powder, ^{1}H NMR (600 MHz, D_2O) δ 9.54 (d, *J* = 7.2 Hz, 1H), 8.42 (d, *J* = 11.4 Hz, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.11 (t, *J* = 6.6 Hz, 1H), 7.92 (d, *J* = 6.6 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 3.53 (t, *J* = 22.8 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 152.51, 151.87, 140.97, 136.18, 131.12, 130.77, 130.64, 128.13, 128.04, 127.66, 127.43, 127.37, 127.16, 126.65, 120.86; ^{31}P NMR (162 MHz, D_2O) δ 16.16 ; HRMS (ESI): *m/z* calculated for $C_{16}H_{15}NO_6P_2$ [M+Na$^+$]: 402.0267, found: 402.0265.



((6-(7,8-dimethoxyisoquinolin-3-yl)benzo[d][1,3]dioxol-5-yl)methylene)bis(phosphonic acid) (3ta acid). Yield 98%, pale yellow powder, ^{1}H NMR (600 MHz, D_2O) δ 9.54 (d, *J* = 7.2 Hz, 1H), 8.22 (d, *J* = 15.0 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.36 (s, 1H), 6.87 (s, 1H), 5.95 (s, 2H), 3.99 (s, 6H), 3.41 (t, *J* = 23.4 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 150.95, 149.47, 147.40, 144.63, 142.08, 140.21, 133.59, 126.51, 125.38, 123.34, 122.30, 112.48, 110.76, 110.38, 102.20, 61.13, 56.19; ^{31}P NMR (162 MHz, D_2O) δ 16.16; HRMS (ESI): *m/z* calculated for $C_{19}H_{19}NO_{10}P_2$ [M+Na$^+$]: 506.0376, found: 506.0371.



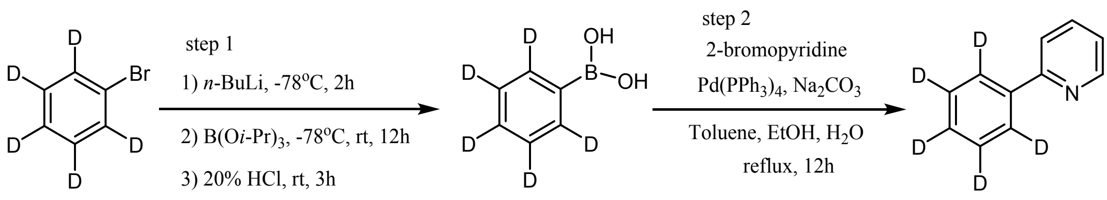
((1-(pyrimidin-2-yl)-1H-indol-2-yl)methylene)bis(phosphonic acid) (5g acid). Yield 98%, yellow powder, ^{1}H NMR (600 MHz, D_2O) δ 8.82 (d, *J* = 4.8 Hz, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 4.8 Hz, 1H), 7.25 – 7.11 (m, 2H), 7.00 (s, 1H), 5.02 (t, *J* = 25.2 Hz, 1H); ^{13}C NMR (150 MHz, D_2O) δ 159.27, 155.74, 136.38, 129.84, 128.16, 123.49, 122.21, 120.56, 119.13, 112.51, 38.15 (t, *J*=121.5Hz); ^{31}P NMR (162 MHz, D_2O) δ 18.20; HRMS (ESI): *m/z* calculated for $C_{13}H_{13}N_3O_6P_2$ [M+Na$^+$]: 392.0172, found: 392.0178.



((2-(1H-pyrazol-1-yl)phenyl)methylene)bis(phosphonic acid) (5h acid). Yield 98%, pale powder ^{1}H NMR (400 MHz, D_2O) δ 7.99 (s, 1H), 7.91 (dd, *J* = 20.4, 7.2Hz, 2H), 7.52 (d, *J* = 7.2Hz, 1H), 7.43 (t, *J* = 7.2, 1H), 7.37 (d, *J* = 7.2Hz, 1H), 6.65 (s, 1H), 3.76 (t, *J* = 23.4 Hz, 1H); 13C NMR (100 MHz, D2O) δ 139.36, 137.37, 134.17, 133.01, 130.64, 130.24, 128.54, 127.44; ^{31}P NMR (162 MHz, D2O) δ 15.91; HRMS (ESI): *m/z* calculated for $C_{10}H_{12}N_2O_6P_2$ [M+Na$^+$]: 318.0171, found: 318.0178.

1.4 Mechanistic studies

1.4.1 Synthesis of 2-(pentadeuteriophenyl)pyridine(1a-*d$_5$*)

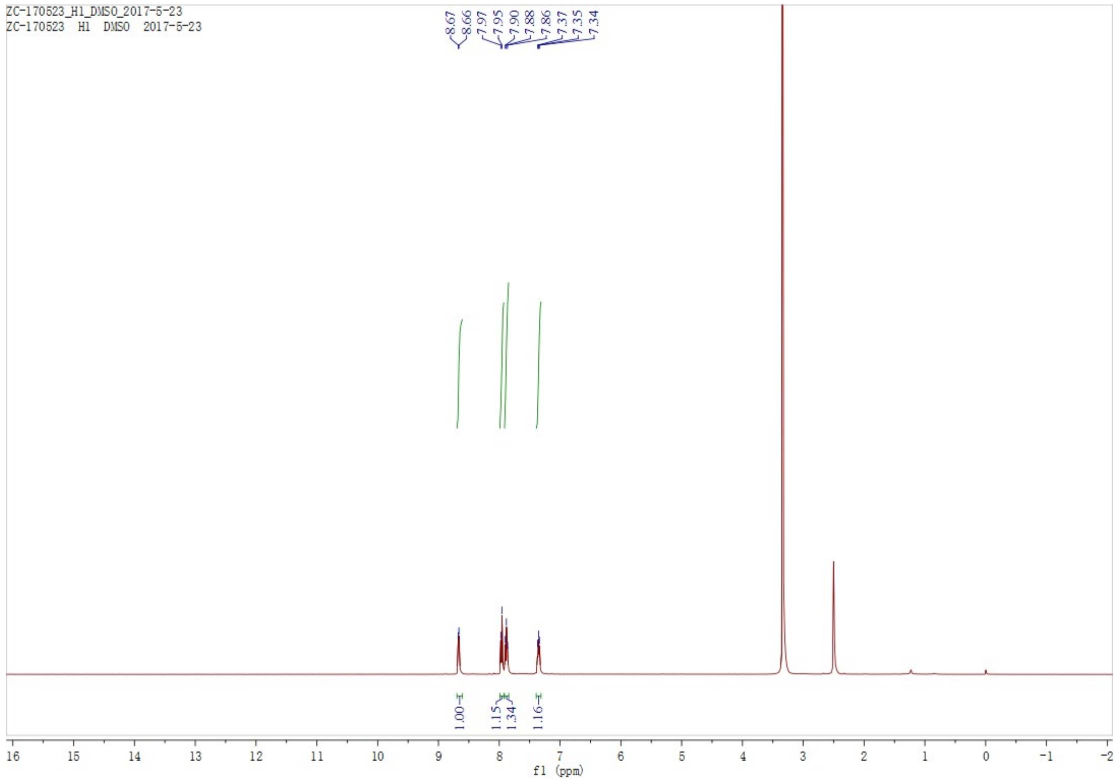


1a-*d₅*

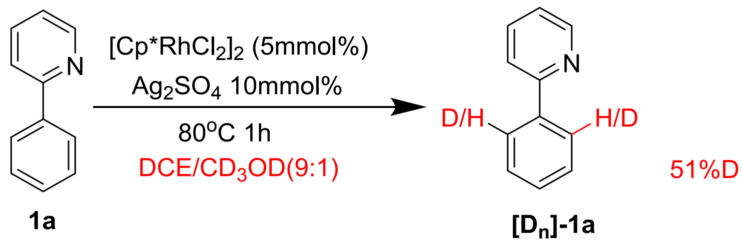
Step1: A two-neck 25 mL flask fitted with magnetic stirring bar, and low-temperature thermometer was charged with bromobenzene-D_5 (0.5 mL, 4.8 mmol) under argon atmosphere. Dry THF (12 mL) was added, and the solution was cooled to -78°C. To this solution was added *n*-butyllithium (3.6 mL, 1.6 M, 5.7 mmol) drop wise using slow addition pump over 30 minutes. The solution was stirred at -78°C for 2 h whereupon triisopropyl borate (1.3 g, 7.1 mmol) dissolved in 1.2 mL of dry THF was added drop wise to the reaction system. The solution was allowed to warm to room temperature overnight. After that the reaction was quenched with dilute HCl (20%, 8.4 mL), and the reaction mixture was stirred for 3 h at room temperature. The resulted biphasic solution was extracted with Et_2O (3 X 6 mL). The ether solution was washed twice with H_2O and concentrated by rotary evaporation. To the crude product, hexane 75 ml was added. The white (*d5*-phenyl)boronic acid solid precipitated in hexane was filtered and dried and used without further purification (409 mg, 67.8%) [S10].

Step2: To a solution of 2-bromopyridine (200 mg, 1.26 mmol) in toluene (5 mL), ethanol (2 mL), and H_2O (5 mL) was added Na_2CO_3 (1.0 g, 9.43 mmol) followed by $Pd(PPh_3)_4$ (44mg, 0.038 mmol) and (d_5-phenyl)boronic acid (209 mg, 1.65 mmol) under argon in a 25 mL two-necked flask. The reaction mixture was refluxed for 12 h, and then cooled to room temperature. To the reaction mixture was added aqueous NH_4Cl (10 mL), extracted by EtOAc for three times, dried over $MgSO_4$, and evaporated in vacuum to afford the crude product, which was purified by flash chromatography on silica gel to provide **1a-d_5** Pale yellow oil (132 mg，65.4%) [S1].

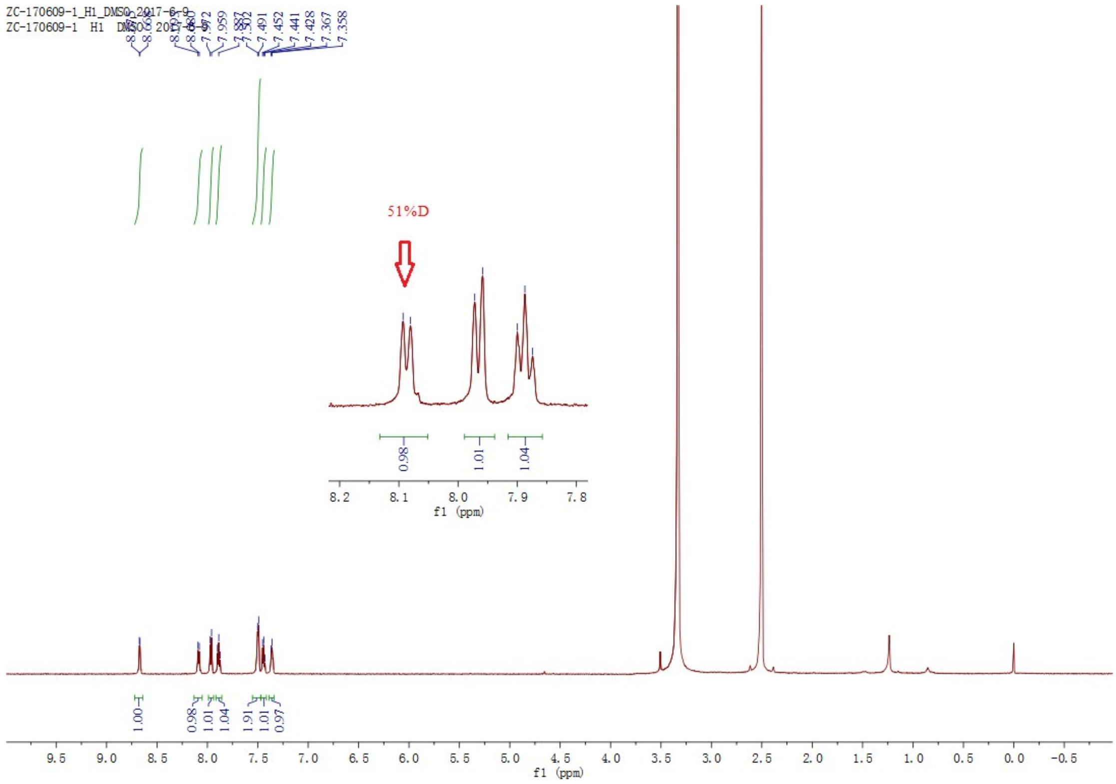
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.4 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.39 – 7.31 (m, 1H).



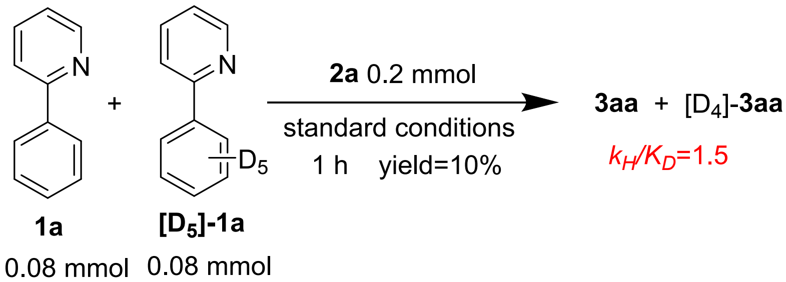
1.4.2 Reversible D/H exchange



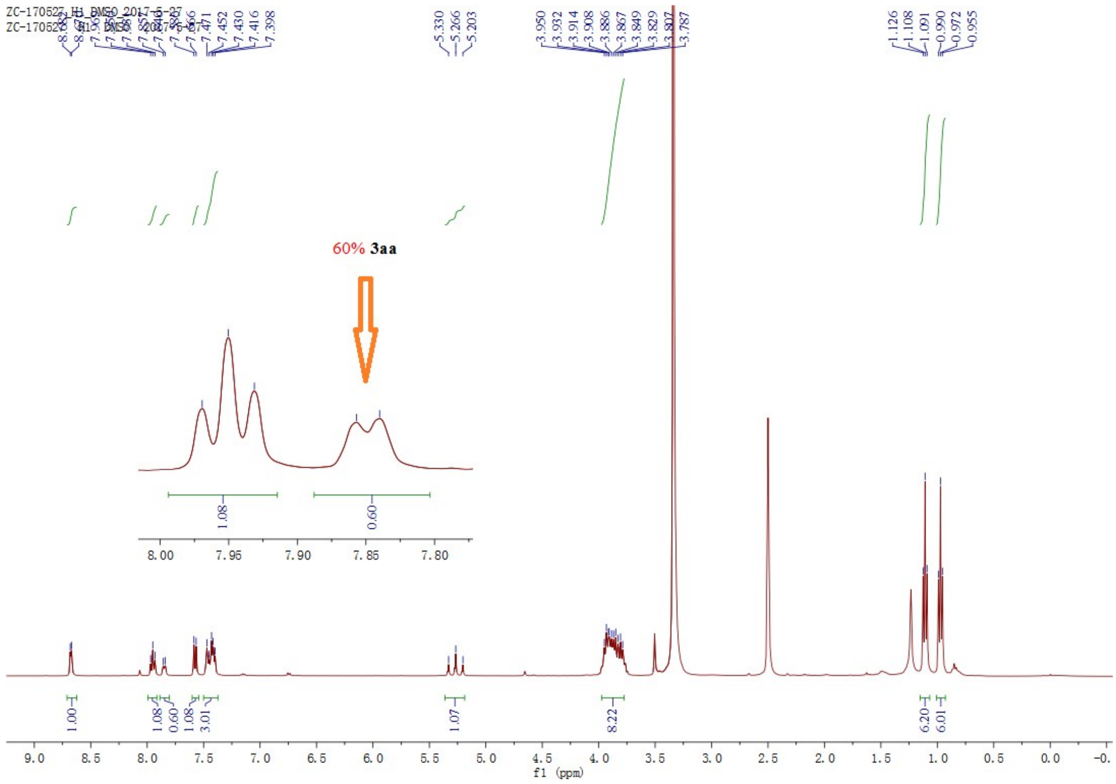
To a 15 ml oven-dried tube was added **1a** (0.19 mmol, 30.0 mg), $[Cp^*RhCl_2]_2$ (6.0 mg 5 mol%), Ag_2SO_4(6.0 mg 10 mol%) in DCE (1.8 mL):CD_3OD(0.2ml), The tube was sealed and stirred at 80 ℃ for 1h. After completion, the reaction mixture was concentrated in vacuo and purified by silica gel column chromatography (50:1 PE/EA) to provide the product**[D$_n$]-1a** (pale brown oil)., which was analyzed by ^{1}H NMR in DMSO-d_6. H/D exchange of 1a at the ortho-position was observed by ^{1}H NMR (with 51% D) in the presence of the suggesting reversible C-H activation. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.67 (d, J = 3.8 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.50 (d, J = 6.5 Hz, 2H), 7.47 – 7.41 (m, 1H), 7.36 (d, J = 5.5 Hz, 1H).



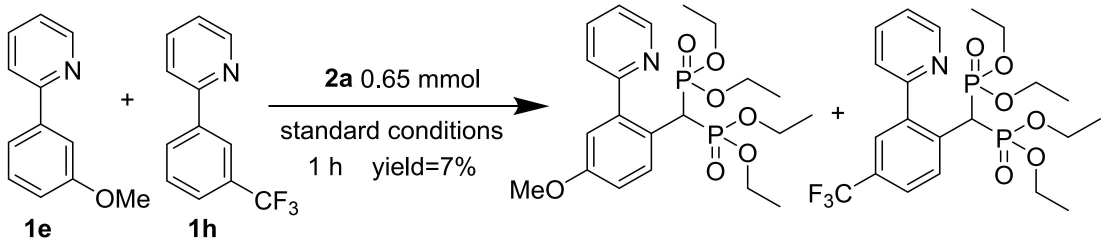
1.4.3 Determination of intermolecular kinetic isotope effect (KIE)



To a 15 ml oven-dried tube was added **1a** (0.08 mmol, 12.5 mg), **[D$_5$]-1a** (0.08 mmol, 12.7 mg), **2a** (0.20 mmol, 63.0mg), [Cp*RhCl$_2$]$_2$ (5.0 mg 5 mol%), Ag_2SO_4(5.0 mg 10 mol%) in DCE(3ml). The tube was sealed and stirred at 80 ℃ for 1h. After completion, the reaction mixture was concentrated in vacuo and purified by silica gel column chromatography to afford the mixture of **3aa** and **[D$_4$]-3aa**, which was analyzed by ^{1}H NMR in DMSO-*d6*.1H NMR spectra of the **3aa** and **[D$_4$]-3aa** determined the intramolecular KIE value equal to 1.5.

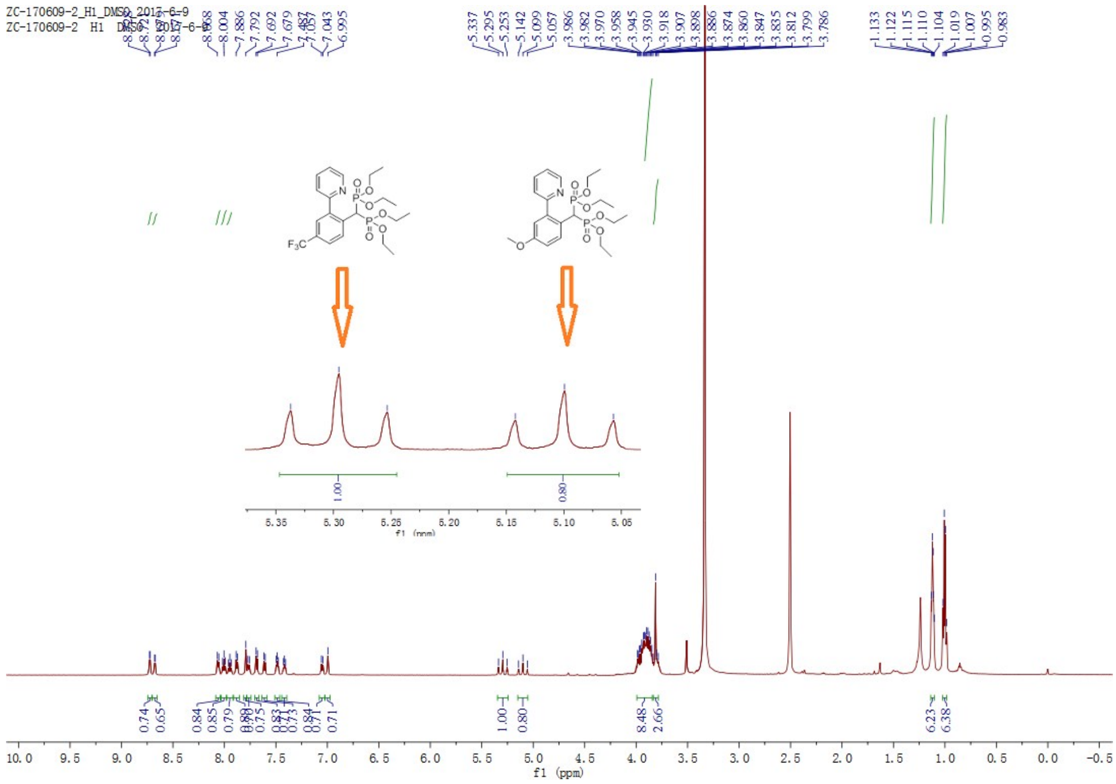


1.4.4 Competitive Reaction



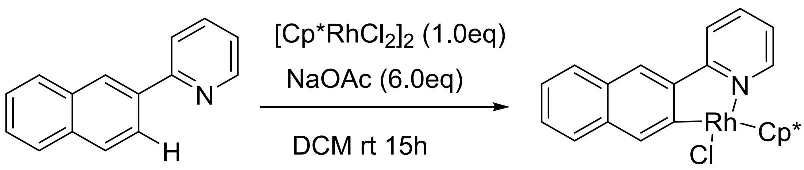
3ea/3ha = 1:1.25

To a 15 ml oven-dried tube was added **1e** (0.27 mmol, 50.0 mg), **1h** (0.27 mmol, 60.0 mg), **2a** (0.65 mmol, 204.0mg), $[Cp^*RhCl_2]_2$ (16.7 mg 5 mol%), Ag_2SO_4(16.8 mg 10 mol%) in DCE(4ml). The tube was sealed and stirred at 80 ℃ for 1h. After completion, the reaction mixture was concentrated in vacuo and purified by silica gel column chromatography to afford a mixture of **3ea** and **3ha**, which was analyzed by ^{1}H NMR in DMSO-*d6*.1H NMR spectra **3ea** and **3ha** were afforded in a ratio of 1:1.25.



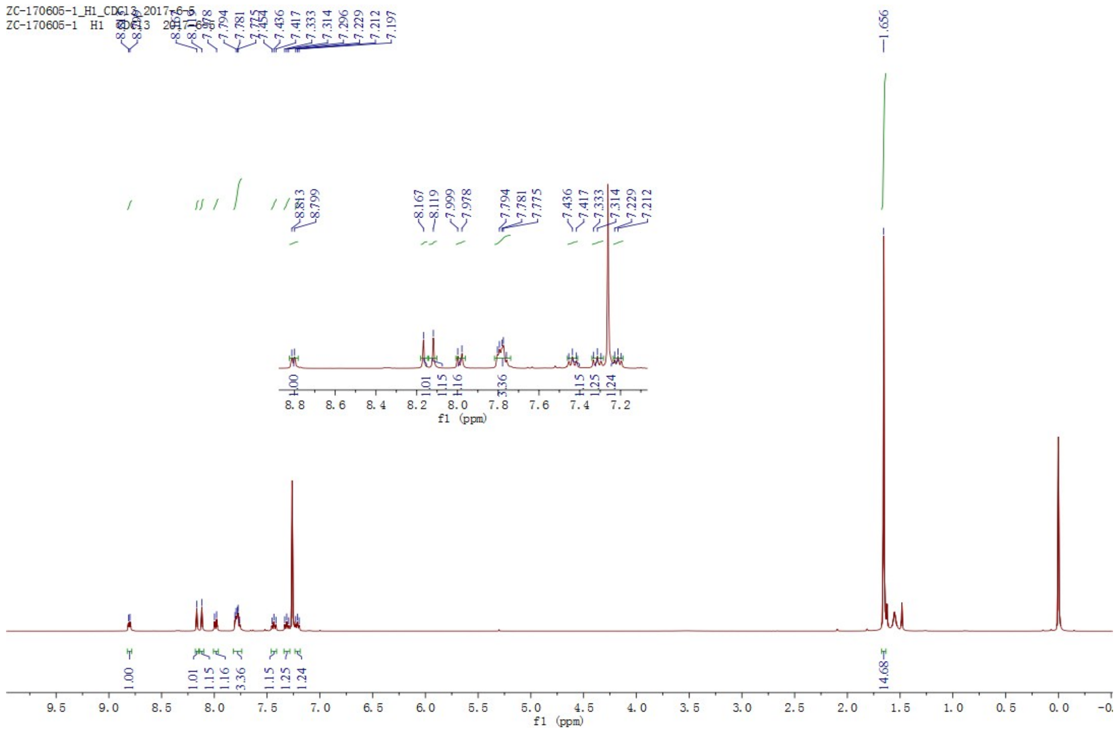
1.4.5 Cyclometalled Rh(III) Complex 6

(a) Synthesis of cyclometalled Rh(III) complex **6**

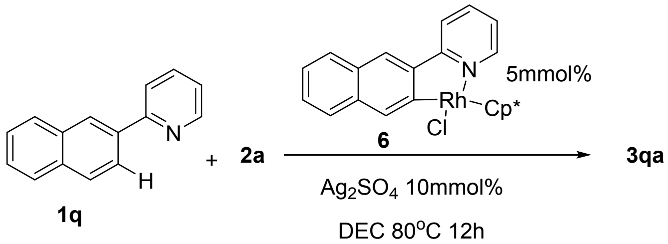


6

The cyclorhodated complex was prepared according to the literature procedure [S11]. A 50 mL Schlenk flask was charged with $[Cp^*RhCl_2]_2$ (50.0 mg, 0.081 mmol), NaOAc (29.1m g, 0.49 mmol), **1q**(41.5g, 0.20 mmol) and CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 15 h. The solution was filtered through Celite® and concentrated under reduced pressure. The product was then washed with hexane to afford a cyclometallated Rh(III) complex **6** as an orange solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.81 (d, J = 5.4 Hz, 1H), 8.17 (s, 1H), 8.12 (s, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.82 – 7.74 (m, 3H), 7.44 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.24 – 7.19 (m, 1H), 1.66 (s, 15H).

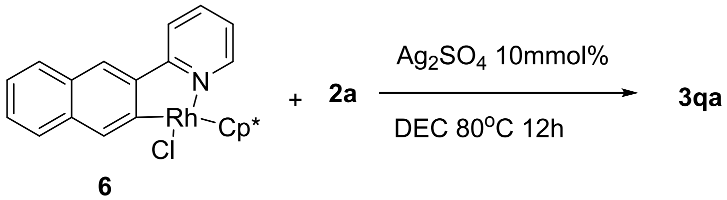


(b) Complex **6**-catalyzed coupling reaction



Complex **6** (5.0 mol %),**1q** (0.15mmol, 30 mg), Ag_2SO_4 (10mol %), **2a** (0.18 mmol, 55.2mg) and DCE (3 mL) were added to a test tube. The reaction mixture was stirred at 80 ℃ for 8 h. The solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography using DCM/MEOH (80:1) to afford the title compound **3qa** (52%).

(c) Reaction of complex **6** with **2a**



Complex **6** (0.04 mmol, 20.0 mg), Ag_2SO_4 (0.08mmol, 24.9mg), **2a** (0.048 mmol, 16.0 mg) and DCE (3 mL) were added to a test tube. The reaction mixture was stirred at 80 ℃ for 8 h. After that, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using DCM/MEOH (80:1) to afford the desired compound **3qa** in yield 61%.

SE. 2. Computational Studies.

In order to exploit the potential applications of aromatic bisphosphonates, we employed a virtual target screening system, termed IFPTarget,[S12] to predict possible binding targets for the representative aromatic bisphosphonate acid **3aa**. The 3D structure of **3aa** acid was prepared as described previously. [S12-14] Using IFPTarget, **3aa** acid was screened against an established target library, [S12] which contains 11,863 protein structures covering 2842 unique targets. The possible target hits for **3aa** acid were ranked by a comprehensive index (Cvalue), [S12] which involves the predicted docking score (Vinascore), interaction fingerprint similarity (IFPscore), and the predicted binding affinity (IDscore). [S15] The top 1% target "hits" identified by IFPTarget are given in Table S2. Predicted results were analyzed using the Discovery Studio Visualizer. The figures for the predicted binding modes were made using PyMol program.

The molecular docking analyses for **3qa** acid with NDM-1, VIM-2, and TEM-1 were carried out using AutoDock Vina. The complex structures of NDM-1: Cephalosporins (PDB ID: 4RL0), [S16] VIM-2:2-(2-chloro-6-fluorobenzyl)-3-oxoisoin doline-4-carboxylic acid (compound 16) (PDB ID: 5LE1),[S14] and TEM-1: (1*R*)-2-Phenylacetamido-2-(3-carboxyphenyl)ethyl boronic acid (PDB ID: 1ERO) [S17] were used as docking templates. All the water molecules and solvent molecules were removed. Gasteiger-Marsili charges were added to the protein model, and non-polar hydrogens were merged onto their respective heavy atoms. The grid centers were set as coordinates of [x, y, z = 3.0, 16.9, 41.6] for NDM-1, [x, y, z = 111.5, 72.1, 9.8] for VIM-2, and [x, y, z = 41.8, 37.0, 32.9] for TEM-1, and the grid size was as 23Å × 23Å × 23Å. The other parameters for Vina were set as default. The docking results were viewed using PyMol program.

SE. 3. Protein Production.

Recombinant forms of VIM-2 MBL (residues 27-266), NDM-1 MBL (residues 1-270), TEM-1 SBL (residues 24-286), and KPC-2 SBL (residues 26-289) were produced in *E. coli Transetta (DE3)* cells (Novagen) at 37 ℃ using LB medium supplemented with 50 μg/ml ampicillin and 50 μg/ml chloramphenicol. Cells were grown until the OD_{600} reached 0.6-0.7. At this point the temperature was lowered to 30 ℃ (for VIM-2), 20 ℃ (for NDM-1), 27 ℃ (for TEM-1) or 20 ℃ (for TEM-1), expression was induced with IPTG (0.5 mM final concentration) and the cells were further incubated for 18-20 hours. Cells were harvested by centrifugation (15min, 4000 rmp) and were resuspended in lysis buffer A (20 mM Tris-HCl, pH 8.0, 250 mM NaCl) supplemented with EDTA-free protease-inhibitor, and then lysed using an ultrahighpressure homogenizer (JNBIO). The cellular debris was removed by centrifugation of the lysate at 15,000 rpm for 30 min; the supernatant was then loaded onto a Ni-NTA column (Roche), followed by extensive washing using buffer B (20 mM Tris–HCl, pH 8.0, 250 mM NaCl, 5 mM imidazole) to remove nonspecifically binding proteins. The target proteins were eluted with buffer C (20 mM Tris–HCl, pH 8.0, 250 mM NaCl, 250 mM imidazole). Fractions containing the purified enzyme were concentrated using Amicon Ultra 10K (Millipore), and then desalted using a HiTrap Desalting column (GE Heaithcare) into reaction buffer (VIM-2/NDM-1: 20 mM Tris-HCl, pH 7.5, 200 mM NaCl, 0.5 mM TCEP; TEM-1/KPC-2: 50 mM Phosphate, pH 7.0) for enzyme kinetic analyses. The purified enzymes were concentrated by centrifugal ultrafiltration and stored at -80 ℃. All purification steps were identified *via* 12% SDS-PAGE, and the concentrations of the purified proteins were determined through a NanoDrop 2000 spectrophotometer (Thermo Scientic).

SE. 4. Inhibition, Competitive, Reversibility, and Cellular Assays.

Assays were performed using a Thermo microplate reader (Varioskan LUX) and were performed at room temperature (24-25 ℃). The assay buffer for VIM-2 and NDM-1 is: 50 mM HEPES-NaOH (~pH 7.2), 1 μg/mL BSA (to minimize the denaturation of the enzyme), 1 μM $ZnSO_4$, and 0.1% Triton X-100 (to large extent exclude the possibility that compounds form large colloid-like aggregates that sequester and thereby inhibit enzymes). The assay buffer for KPC-2 and TEM-1 is: 50 mM phosphate, pH 7.0, 1 μg/mL BSA, and 0.1% Triton X-100. The activities of VIM-2, NDM-1, KPC-2, and TEM-1 were determined using the fluorescent substrate FC-5 [S14, S18, S19]. Hydrolysis of FC5 was monitored by following the variation in fluorescence at excitation 380 nm and emission at 460 nm, respectively. In all tests, 96 well flat bottom black plates were used. The details are described as follows.

Inhibition Assays.

In the inhibition assays, the final concentration of the substrate FC-5 is 5 μM, and the concentrations of VIM-2, NDM-1, KPC-2, and TEM-1 are 0.2 nM, 0.2 nM, 2 nM, and 10nM, respectively. Except where noted, the compounds for inhibition assays were prepared in 100 mM DMSO stock solutions. For IC_{50} determination, compounds were 3-fold diluted from 600 μM. The IC_{50} values (concentration required to affect 50% inhibition of enzyme activity) for all aromatic bisphosphonates were determined by preincubation of the tested compound with the appropriate amount of enzymes in the assay buffer for 10 min (NDM-1 and VIM-2) or 4h (KPC-2 and TEM-1) at room temperature, prior to the initiation of the reactions by the addition of the substrates. The bisphosphonate ester compounds (**3aa-3ta** and **5a-5j**, Scheme 1-2) were initially tested against VIM-2, NDM-1, KPC-2, and TEM-1 at 100 μM; for compounds showing inhibition >50% at 100 μM, the IC_{50} values were determined. The fluorescence intensity was recorded every 60 seconds. All assays were carried out in triplicates.

Substrate Competitive Assays.

The calibration curve of fluorescence values verus product concentrations (or the FC-5 substrate [S18,S19]) was first determined. The saturated enzymes were reacted with FC-5 with different concentration (from 100 μM ~ 0.195 μM, 2-fold dilutions) for 24 h at 4 ℃ in the assay buffer to obtain the calibration curve (the fluorescence intensity was obtained every 60 seconds). Then, the catalytic abilities of NDM-1 or VIM-2 in the absence and the presence of **3qa** acid were then determined. For NDM-1, treating with different concentrations of **3qa** acid (0 μM, 3 μM, 10 μM, 30 μM, and 90 μM), the enzyme kinetic values were determined using the FC-5 substrate. Similarly, the enzyme kinetic values were determined for VIM-2 at different concentrations of **3qa** acid (0 μM, 1 μM, 3 μM, 10 μM, and 30 μM).

The Jump-Dilution Assays.

The jump-dilution method [S20] was used to determine the reversibility of MBL/SBL inhibition by **3qa** acid. *L*-captopril and EDTA were used as controls. 170 μM **3qa** acid (10-fold the IC_{50} value to NDM-1), 25 μM EDTA (10-fold the IC_{50} value to NDM-1), or 500 μM L-captopril (10-fold the IC_{50} value to NDM-1) were preincubated with 10 nM NDM-1 (100-fold the concentration of NDM-1 used in inhibition assays) for 30 min at room temperature (24-25 ℃). Similarly, 38 μM **3qa** acid (10-fold the IC_{50} value to VIM-2), 25 μM EDTA (10-fold the IC_{50} value to VIM-2), or 20 μM *L*-captopril (10-fold the IC_{50} value to VIM-2) were preincubated with 10 nM VIM-2 (100-fold the concentration of VIM-2 used in the inhibition assays). The samples are then rapidly diluted 100-fold into an assay solution, and the enzyme activities are measured.

Microdilution Broth Minimum Inhibitory Concentrations (MICs)

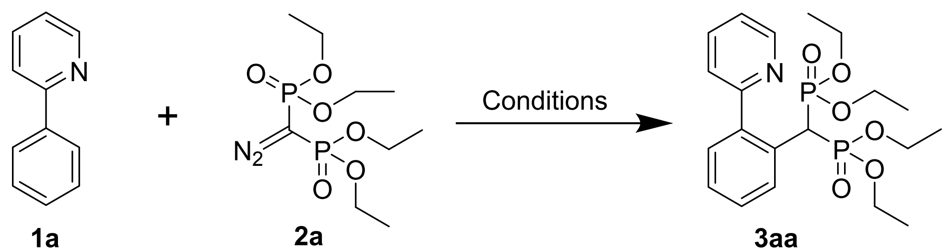
Strains of *E. coli* Transetta containing plasmids pET28-lacUV5-VIM-2 (*E. coli*-VIM-2) and pET28-lacUV5 (as control) were used to assess the cellular activities of the inhibitors. The pET28-lacUV5 and pET28-lacUV5-VIM-2 plasmids were obtained by multi-step gene cloning. Single colonies of the *E. coli*-VIM-2 strain on Mueller Hinton (MH) agar plates were transferred to 5 mL of MH liquid medium, and grown at 37 ℃ to an OD_{600} of ~0.6. The MICs of meropenem in the absence or presence of **3qa acid** and **5g acid** were determined according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The concentrations of *E. coli*-VIM-2 and *E. coli* strains were diluted to ~10^7 colony forming units (CFU) per mL in the MH medium, then transferred to the microtiter plates, and treated with meropenem (final concentrations of 64 mg/L to 0.125 mg/L in 2-fold dilution) or/and the inhibitors (final concentrations of 100 μM, 50 μM, 25 μM, and 10 μM). The microtiter plates were incubated for 16-20 h at 37 ℃ and visually evaluated for bacterial growth. Each determinate was performed in duplicate.

SE. 5. ITC Analyses.

ITC binding assays were carried out using a MicroCal ITC200 calorimeter (GE Healthcare) at 25 ℃. The **3qa** acid (500 μM or 600 μM) was titrated with NDM-1 (60 μM), VIM-2 (50 μM), or TEM-1 (50 μM), separately. In the calorimeter cell and syringe only contained <1% DMSO. The system was equilibrated until the cell temperature reached 25 ℃. All titrations were conducted using a preliminary injection of 0.2 μL **3qa** acid (500 μM or 600 μM) and then a series of 19 individual injections of 2 μL at time intervals of 150 s. The titration cell was continuously stirred at 750 rpm. The obtained curves were fitted to a single binding site model using ITC data analysis module of Origin 7.5 (OriginLab).

Supplementary Tables

Table S1. Reaction Optimization[a]

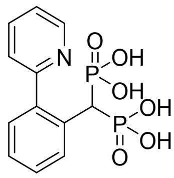


1a 2a 3aa

Entry	Catalyst	Ag Salt	Solvent	*T*[℃]	Time[h]	Yield[b]
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DCE	80	24	81%
2	$Pd(OAc)_2$	$AgSbF_6$	DCE	80	24	N.R.
3	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	DCE	80	24	N.R.
4	$Cp^*Co(CO)I_2$	$AgSbF_6$	DCE	80	24	N.R.
5	$[Cp^*Co(CH_3CN)_3][SbF_6]_2$	$AgSbF_6$	DCE	80	24	N.R
6	$[Cp^*IrCl_2]_2$	$AgSbF_6$	DCE	80	24	20%
7	$[Cp^*RhCl_2]_2$	AgOAc	DCE	80	24	N.R
8	$[Cp^*RhCl_2]_2$	Ag_2SO_4	DCE	80	24	91%
9	$[Cp^*RhCl_2]_2$	$AgNO_3$	DCE	80	24	N.R
10	$[Cp^*RhCl_2]_2$	Ag_2CO_3	DCE	80	24	N.R
11	$[Cp^*RhCl_2]_2$	Ag_2SO_4	DCE	80	12	93%
12	$[Cp^*RhCl_2]_2$	Ag_2SO_4	DCE	60	12	80%
13	$[Cp^*RhCl_2]_2$	Ag_2SO_4	DCE	40	12	56%
14	$[Cp^*RhCl_2]_2$	Ag_2SO_4	THF	80	12	45%
15	$[Cp^*RhCl_2]_2$	Ag_2SO_4	MeOH	80	12	88%
16	$[Cp^*RhCl_2]_2$	Ag_2SO_4	CH_3CN	80	12	21%
17	$[Cp^*RhCl_2]_2$	Ag_2SO_4	Dioxane	80	12	N.R

[a] Reaction conditions: 1 (0.2 mmol), 2a (0.24 mmol), $[Cp^*RhCl_2]_2$ (5mol %), $AgSO_4$ (10mol %), DCE 2ml under air; [b] Isolated yields.

Table S2. The top 1% target 'hits' identified by IFPTarget for **3aa** acid.



3aa acid

Rank	Target Name	PDB	Cvalue	IFPscore	Vinascore	IDscore	No. of IFPs
1	**Geranylgeranyl pyrophosphate synthase GGPS**	**3LDW**	**16.04**	**1.00**	**-7.40**	**7.17**	**5**
2	**Human farnesyl pyrophosphate synthase FPPS**	**2F9K**	**15.91**	**0.98**	**-8.60**	**7.09**	**8**
3	HIV-1 reverse transcriptase	1VRU	15.55	1.00	-8.30	5.32	8
4	Polyprotein	2D3Z	15.19	1.00	-6.00	5.75	5
5	Rat phosphodiesterase 10A	3LXG	15.10	1.00	-5.80	5.65	3
6	Coagulation Factor X	4BTT	15.04	1.00	-6.00	5.34	5
7	Bromodomain-containing protein 4 BRD4	4J0S	15.04	1.00	-6.60	4.98	5
8	cAMP-specific 3',5'-cyclic phosphodiesterase PDE7A	3G3N	14.97	1.00	-6.10	5.11	3
9	Bromodomain-containing protein 4 BRD4	3U5L	14.96	1.00	-6.20	5.02	4
10	Bromodomain-containing protein 4 BRD4	3MXF	14.89	1.00	-6.60	4.59	4
11	Glutaminyl cyclase	4MHZ	14.87	1.00	-5.30	5.32	4
12	Endo-1,4-beta-xylanase d	1UX7	14.82	1.00	-4.80	5.49	3
13	Bromodomain-containing protein 4 BRD4	4F3I	14.79	1.00	-6.70	4.25	4
14	Bromodomain-containing protein 4 BRD4	4QZS	14.76	1.00	-6.20	4.49	4
15	Bromodomain-containing protein 4 BRD4	4BW1	14.74	1.00	-6.20	4.43	4
16	Mycobacterium tuberculosis	4OWM	14.73	1.00	-6.10	4.47	4
17	Polymerase PA	4AWF	14.70	1.00	-5.50	4.74	4
18	Transthyretin	1E4H	14.67	1.00	-5.60	4.61	3
19	Bromodomain-containing protein 4 BRD4	4MEQ	14.66	1.00	-5.90	4.40	4
20	Mycobacterium tuberculosis	4OWO	14.63	1.00	-5.90	4.31	3

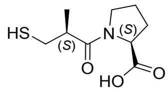
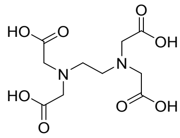
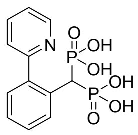
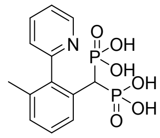
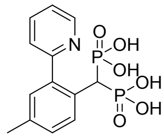
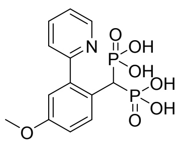
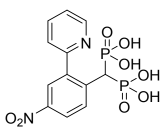
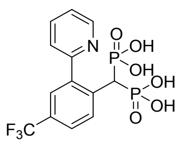
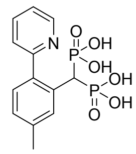
21	Bromodomain testis-specific protein	4FLP	14.62	1.00	-6.30	4.06	4
22	RNA-directed RNA polymerase	4EO6	14.53	1.00	-6.00	3.99	4
23	Integrase	4AH9	14.53	1.00	-6.00	3.98	3
24	Lactoylglutathione lyase	4KYK	14.51	1.00	-5.50	4.23	3
25	N-terminal endonuclease domain of Bunyaviridae RNA Polymerases	2XI7	14.46	0.96	-5.30	5.97	4
26	Human farnesyl pyrophosphate synthase FPPS	2F89	14.43	0.93	-6.50	6.21	10
27	L-lactate dehydrogenase A chain	4I9U	14.41	1.00	-5.40	4.03	4
28	Bromodomain-containing protein 4 BRD4	4O70	14.40	1.00	-5.40	4.00	3
29	PA-I galactophilic lectin	4A6S	14.38	1.00	-5.10	4.13	5
30	CAMP and cAMP-inhibited cGMP 3',5'-cyclic phosphodiesterase 10A, PDE10A	3WS9	14.36	1.00	-5.10	4.08	3
31	Human peroxiredoxin-5	4MMM	14.28	1.00	-5.00	3.93	6
32	Wild type human transthyretin TTR	3NEE	14.26	1.00	-5.60	3.51	4
33	Thrombin alpha	1MU8	14.25	0.93	-6.80	5.75	6
34	Vp39	1B42	14.23	0.90	-7.30	6.61	4
35	Transthyretin	1E5A	14.22	1.00	-4.90	3.83	4
36	Carbonic anhydrase 2	1H4N	14.20	0.94	-7.30	4.65	5
37	**Metallo-β-lactamase NDM-1**	**4EXS**	**14.17**	**0.91**	**-7.10**	**6.19**	**3**
38	Polymerase protein PA	4E5G	14.06	0.96	-5.40	4.86	4
39	Polymerase protein PA	4AVG	14.02	0.93	-6.30	5.45	7
40	P-30 protein (T89N/E91A)	2GMK	13.99	1.00	-4.20	3.64	4
41	Lactoylglutathione lyase	4KYH	13.98	0.94	-6.40	4.91	5
42	Serum albumin	1GNJ	13.94	0.88	-8.60	6.08	5
43	Human farnesyl pyrophosphate synthase FPPS	2F94	13.92	0.87	-8.00	6.80	9
44	Acetylcholine-binding protein	2XZ5	13.90	0.88	-7.30	6.77	3
45	Leshmaniasis major Farnesyl diphosphate synthase	4K10	13.89	0.94	-6.30	4.42	5
46	Antibody fab fragment	1CT8	13.88	0.86	-8.20	6.83	10
47	Metallo-beta-lactamase CphA	3IOG	13.87	0.95	-6.10	4.27	5
48	PDE4B	2QYL	13.84	0.90	-6.30	6.16	4
49	Transthyretin	4ABV	13.79	1.00	-4.20	3.10	3

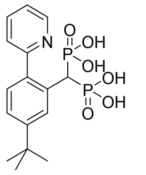
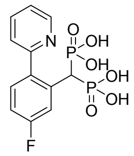
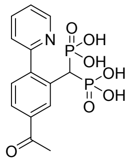
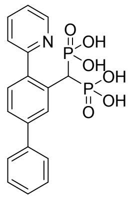
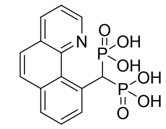
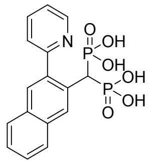
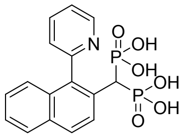
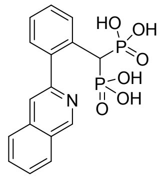
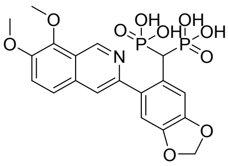
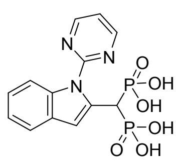
50	**Metallo-β-lactamase VIM-2**	**4PVT**	**13.71**	**0.89**	**-8.00**	**5.18**	**5**
51	Abscisic acid receptor PYL9/RCAR9	3W9R	13.70	0.92	-6.50	4.97	4
52	Beta-lactamase II	1HLK	13.68	0.90	-7.40	5.06	4
53	Dihydroorotase	2EG7	13.66	0.90	-6.70	5.27	8
54	Farnesyl pyrophosphate synthase	4DWB	13.65	0.86	-7.90	6.41	7
55	Nucleotide binding domain of the	3LLM	13.63	0.92	-5.80	5.21	8
56	PEPCK-Mn2^{+}	2RKD	13.62	0.92	-6.10	5.01	6
57	HIV-1 RNase H p15	3HYF	13.62	0.92	-5.60	5.29	6
58	Proto-oncogene tyrosine-transferase src	1O4R	13.61	0.93	-6.40	4.30	9
59	Transferase	1C8K	13.61	0.86	-7.70	6.50	5
60	Ectonucleotide pyrophosphatase/phosphodiesterase family member 2	3WAV	13.52	0.88	-6.70	6.11	3
61	HIV-1 IN core domain	3LPT	13.51	0.90	-6.70	5.05	4
62	Human nicotinamide phosphoribosyltransferase	3DKJ	13.45	0.90	-6.70	5.00	12
63	Proto-oncogene tyrosine-transferase src	1O4O	13.41	1.00	-3.60	2.45	5
64	Fatty acid binding protein, adipocyte	1TOW	13.40	0.88	-8.30	4.82	5
65	Dodecin	2CCC	13.40	0.88	-7.00	5.61	3
66	Cystic fibrosis transmembrane conductance regulator	1R0X	13.37	0.88	-6.60	5.78	7
67	Bromodomain-containing protein 4 BRD4	3P5O	13.37	0.90	-6.30	4.90	4
68	Intracellular B30.2 Domain of BTN3A1	4N7U	13.36	0.94	-5.40	3.86	4
69	HIV-1 reverse transcriptase	3LP0	13.34	0.91	-4.90	5.30	3
70	1-Deoxy-D-xylulose 5-phosphate reductoisomerase	3R0I	13.33	0.91	-5.60	4.83	5
71	Rna polymerase	2HAI	13.33	0.88	-7.30	5.23	5
72	Human BRD4	2YEL	13.32	0.90	-6.50	4.66	4
73	Genome polyprotein	4JU7	13.30	0.90	-6.70	4.49	4
74	X Secretory Phospholipase A2	4UY1	13.29	0.88	-7.60	4.94	3
75	Heparin-binding growth factor 1	3UD7	13.28	0.94	-4.90	3.94	6
76	Polymerase protein PA	4E5F	13.28	0.91	-5.30	4.89	3

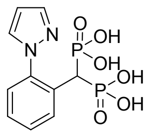
77	Hiv-1 reverse transcriptase	1RTI	13.27	0.86	-7.40	5.77	5
78	Bromodomain BRD2	4A9M	13.26	0.90	-6.60	4.44	4
79	Pseudomonas aeruginosa Madelate racemase mutant K166R	1MDL	13.25	0.90	-5.30	5.19	3
80	Interleukin-13 receptor subunit alpha-1	4HWB	13.24	0.90	-6.70	4.33	3
81	Fatty acid-binding protein	1HMT	13.24	0.90	-7.10	4.07	3
82	14-3-3 Protein sigma	4DHP	13.24	0.91	-5.50	4.65	6
83	Soluble epoxide hydrolase 2	3WKD	13.22	0.88	-7.20	5.02	3
84	Dihydroorotase	1XGE	13.22	0.89	-6.40	4.91	6
85	Farnesyl pyrophosphate synthase	4GA3	13.20	0.82	-8.00	6.86	8
86	Succinyl-CoA:acetate coenzyme A transferase	4EU3	13.20	0.92	-5.20	4.42	4
87	14-3-3 Protein sigma	3T0M	13.17	0.93	-5.20	3.83	4
88	Methionine aminopeptidase	2Q93	13.14	0.84	-5.90	6.91	5
89	Glycogen phosphorylase	1GGN	13.14	0.85	-7.20	6.02	7
90	Farnesyl pyrophosphate synthase	4DZW	13.14	0.83	-8.40	6.01	9
91	Conserved hypothetical protein	2GL0	13.13	0.83	-8.20	6.21	8
92	Bromodomain-containing protein 4 BRD4	3U5J	13.13	0.88	-7.10	4.84	3
93	Human Peroxiredoxin-5	4K7I	13.12	0.93	-5.00	3.82	6
94	AmpC β-lactamase	4OKP	13.09	0.92	-5.90	3.70	4
95	14-3-3 Protein sigma	4DHR	13.08	0.90	-5.40	4.67	5
96	Renin	4GJ8	13.06	0.86	-8.10	4.78	5
97	6-Phosphogluconate dehydrogenase	4GWK	13.05	0.92	-4.30	4.56	4
98	Geranylgeranyl pyrophosphate synthetase	2Z50	13.04	0.89	-6.70	4.24	6
99	Botulinum neurotoxin A	4ELC	13.02	0.90	-6.20	4.03	4
100	Replication protein A 70 kDa DNA-binding subunit	4LUV	13.02	0.90	-4.20	5.24	3
101	Ribonucleoside-diphosphate	3RSR	13.01	0.84	-7.20	5.75	7
102	CREB-binding protein	2L84	12.98	0.90	-6.10	4.00	3
103	Glycogen phosphorylase B	8GPB	12.97	0.85	-7.80	5.04	5
104	D-alanyl-D-alanine carboxypeptidase	2Y4A	12.97	0.88	-6.40	4.84	6
105	Human phosphodiesterase 4d	3G58	12.96	0.83	-6.40	6.55	4
106	Fucose-binding lectin PA-IIL	2JDU	12.96	0.90	-5.20	4.47	4

	(G24N)						
107	Transthyretin	3CFT	12.94	0.86	-6.00	5.75	4
108	Human MTH1 protein	4N1T	12.94	0.83	-6.20	6.62	6
109	Dengue virus ns5 RNA dependent RNA polymerase	2J7W	12.94	0.90	-5.00	4.54	6
110	Hiv-1 reverse transcriptase	1IKW	12.93	0.82	-8.30	5.95	7
111	Farnesyl pyrophosphate synthase	4E1E	12.92	0.83	-7.70	6.00	7
112	Ribonuclease 2	1HI3	12.91	0.90	-5.40	4.23	7
113	14-3-3 Protein sigma	4DHN	12.89	0.90	-5.30	4.25	5
114	14-3-3 Protein sigma	4DHO	12.89	0.89	-6.00	4.27	4
115	Integrase	4NYF	12.88	0.90	-5.90	3.85	4
116	Polymerase PA	4MK1	12.88	0.89	-5.60	4.32	5
117	PDE2a catalytic domain	4D09	12.86	0.86	-6.50	5.24	5
118	Hiv-2 protease	6UPJ	12.85	0.88	-6.20	4.64	3

Table S3. The inhibition activity of aromatic bisphosphonates against the clinically relevant β-lactamases NDM-1, VIM-2, TEM-1 and KPC-2.

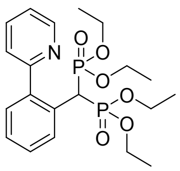
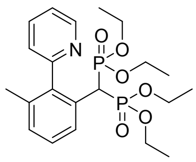
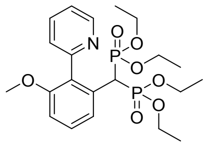
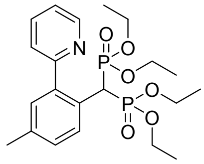
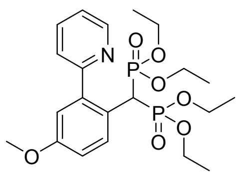
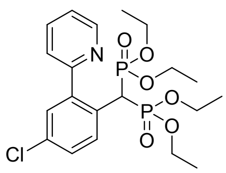
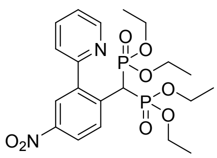
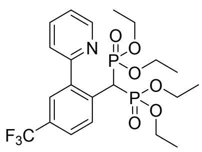
Cpd ID	Chemical structure	IC_{50} (μM) / pIC_{50} / s.e. $logIC_{50}$[a]			
		NDM-1	VIM-2	TEM-1	KPC-2
L-captopril		46.38 / 4.33 / 0.088	0.74 / 6.13 / 0.120	>400 / < 3.40 / ~	>400 / < 3.40 / ~
EDTA		2.07 / 5.68 / 0.06	2.35 / 5.63 / 0.042	>400 / < 3.40 / ~	>400 / < 3.40 / ~
3aa acid		32.04 / 4.49 / 0.025	11.07 / 4.96 / 0.029	68.39 / 4.16 / 0.040	>400 / < 3.40 / ~
3ba acid		>400 / <3.40 / ~	7.65 / 5.12 / 0.074	126.30 / 3.90 / 0.065	>400 / <3.40 / ~
3da acid		117.4 / 3.93 / 0.11	8.89 / 5.05 / 0.059	>400 / <3.40 / ~	>400 / <3.40 / ~
3ea acid		75.59 / 4.12 / 0.045	14.58 / 4.84 / 0.047	>400 / <3.40 / ~	>400 / <3.40 / ~
3ga acid		78.31 / 4.11 / 0.036	14.08 / 4.85 / 0.065	>400 / <3.40 / ~	>400 / <3.40 / ~
3ha acid		97.08 / 4.01 / 0.032	4.32 / 5.36 / 0.096	137.0 / 3.86 / 0.04	>400 / <3.40 / ~
3ja acid		91.13 / 4.04 / 0.038	8.63 / 5.06 / 0.068	>400 / <3.40 / ~	>400 / <3.40 / ~

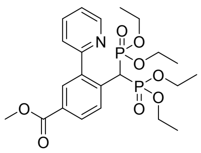
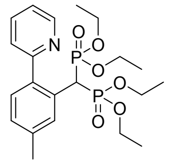
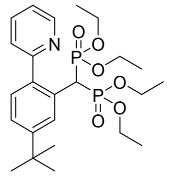
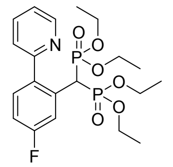
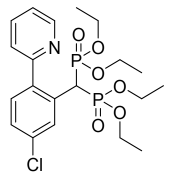
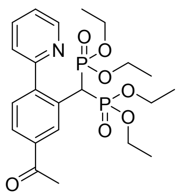
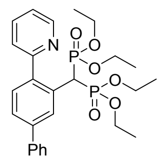
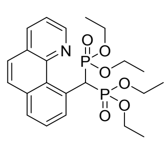
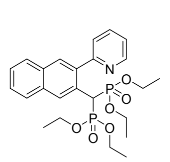
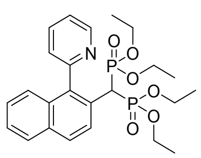
3ka acid		>400 / <3.40 / ~	7.86 / 5.10 / 0.041	>400 / <3.40 / ~	>400 / <3.40 / ~
3la acid		123.8 / 3.91 / 0.037	2.26 / 5.65 / 0.032	>400 / <3.40 / ~	>400 / <3.40 / ~
3na acid		179.8 / 3.75 / 0.087	5.10 / 5.29 / 0.036	>400 / <3.40 / ~	>400 / <3.40 / ~
3oa acid		55.64 / 4.26 / 0.021	36.53 / 7.44 / 0.062	0.93 / 6.03 / 0.056	>400 / <3.40 / ~
3pa acid		268.3 / 3.57 / 0.18	19.84 / 4.70 / 0.072	145.50 / 3.84 / 0.061	>400 / <3.40 / ~
3qa acid		17.11 / 4.77 / 0.044	3.78 / 5.42 / 0.041	1.73 / 5.76 / 0.055	>400 / <3.40 / ~
3ra acid		120.6 / 3.92 / 0.076	4.57 / 5.34 / 0.053	1.18 / 5.93 / 0.24	>400 / <3.40 / ~
3sa acid		16.24 / 4.79 / 0.036	2.47 / 5.61 / 0.077	38.9 / 4.41 / 1.46	>400 / <3.40 / ~
3ta acid		17.23 / 4.76 / 0.045	5.36 / 5.27 / 0.045	1.72 / 5.77 / 0.16	>400 / <3.40 / ~
5g acid		15.00 / 4.82 / 0.030	5.58 / 5.25 / 0.043	11.52 / 4.94 / 0.040	>400 / <3.40 / ~

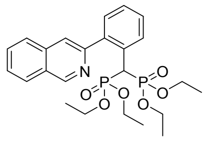
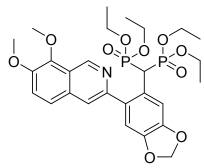
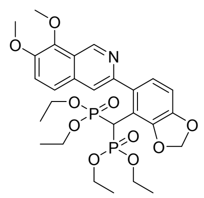
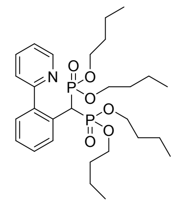
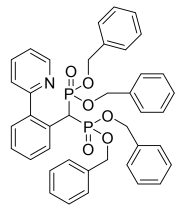
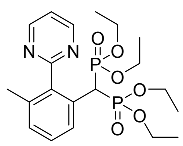
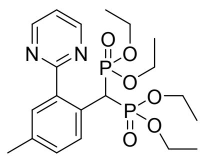
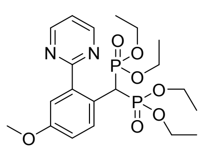
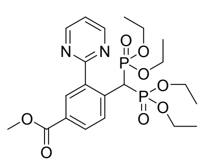
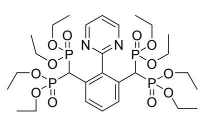
5h acid		>400 / <3.40 / ~	3.92 / 5.41 / 0.070	86.39 / 4.06 / 0.59	>400 / <3.40 / ~

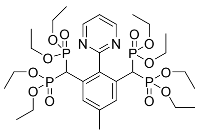
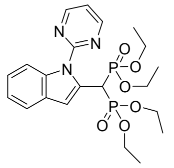
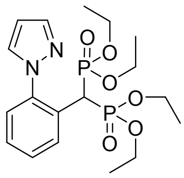
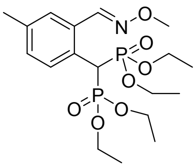
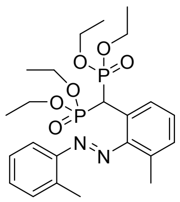
[a] The method for measuring IC_{50}/pIC_{50} (n=3) values is described in Experimental Section; IC_{50} curves are given in Fig. S5-7.

Table S4. The inhibitory activities of aromatic bisphosphonates **3aa-5ja** against NDM-1, VIM-2, TEM-1 and KPC-2.

ID	Chemical Structure	Inhibition%@100 μM (IC_{50} (μM) / pIC_{50} / s.e pIC_{50})[a]			
		NDM-1 MBL	VIM-2 MBL	TEM-1 SBL	KPC-2 SBL
3aa		30.32 ± 0.70	26.49 ± 23.69	2.23 ± 1.58	24 ± 1.60
3ba		18.78±0.04	32.05±12.05	65.22±2.89 (79.5 / 4.10 / 0.152)	30.56±6.15
3ca		53.74±1.05 (>100)	16.01±10.72	36.63±8.49	41.11±8.78
3da		25.5±1.00	44±0.39	3.65±0.15	45.47±7.16
3ea		32.18±0.29	47.6±27.67	39±9.67	48±0.06
3fa		33.65±0.14	52.16±1.48	21.37±2.30	40.77±8.30
3ga		33.88±0.73	26.5±26.54	10.72±8.90	60.11±2.80
3ha		16±2.22	41.6±0.05	9.15±11.72	29.92±7.38

3ia		46±1.58	33.53±20.67	64.41±10.60 (>100)	9.46±7.65
3ja		8.81±0.54	13.08±2.8	45.83±0.94	5.79±6.80
3ka		48.95±1.19	42.99±5.09	19.31±1.21	42.32±3.05
3la		16.05±0.79	34.48±3.06	27.36±12.62	42.07±8.60
3ma		56.04±1.95	39.33±25.8	3.40±0.07	42.48±4.99
3na		22.08±0.34	38.6±0.04	47.13±8.80	26±0.32
3oa		37.32±1.99	5.21±2.31	95.22±1.46 (133 / 3.876 / 0.209)	38.35±7.45
3pa		39.3±7.47	28.6±0.01	56.26±8.42 (>100)	49.31±1.94
3qa		19.55±6.67	7.5±9.90	45.73±6.34	47.36±2.63
3ra		33.16±5.43	47.00±0.09	27.53±1.05	15.35±2.85

3sa		47.58±3.56	60.66±3,26	47.57±12.04	45±2.65
3ta		46.6±11.10	45.25±14.41	39.87±14.02	3.5±0.89
3ta[1]		72.67 ± 0.52 (42.2 / 4.37 / 0.044)	98.02±0.31 (7.94 / 5.1 / 0.082)	96.32±2.19 (1.10 / 5.96 / 0.068)	18±0.27
3ba		39.96±4.68	25.3±23.2	76.3±4.59 (119 / 3.92 / 0.064)	15±9.38
3ca		36.93±6.04	54.17±10.37	37.7±7.51	60.61±0.07 (>100)
5a		44.14±1.75	28.16±3.13	9.6±6.08	13.36±11.92
5b		46.47±10.71	8.71±6.83	58.42±9.70	36±0.60
5c		36.87±4.19	29.6±0.01	24.21±12.27	34.5±22.00
5d		48.93±4.26	44.96±4.03	19.19±8.41	47.2±0.84
5e		52.32 ± 6.64 (>100)	78.12±3.92	30.6±14.00	15.33±5.75

5f		58 ± 3.17 (>100)	83.51±2.68 (>100)	94.92±10.43 (>100)	16.8±5.46
5g		39.92±5.01	62.3±6.49	8.68±8.66	21.4±0.66
5h		26.93±2.33	39.18±22.43	18.98±3.60	26.16±2.03
5i		85.4±0.15 (7.13 / 5.15 / 0.036)	86.49±5.98 (6.58 / 5.18 / 0.025)	96.82±6.85 (3.75 / 5.42 / 0.115)	37.57±24.84
5j		9.27±4.36	39.87±9.83	30.7±0.74	17.83±6.84

[a]The method for measuring mean ± SD (n=3) values is described in the Supplementary Methods.

Table S5. MICs of meropenem in the absence or presence of **3qa acid** and **5g acid** against VIM-2-producing *E. coli* transetta strain.

Assay No.	Inhibitor (Concentration)	Meropenem	MIC (μg/mL)	
			E. coli-VIM-2	*E. coli*
1	**-**	+	16	<0.125
2	**3qa acid** (100 μM)	**-**	>64	>64
3	**5g acid** (100 μM)	**-**	>64	>64
4	**3qa acid** (100 μM)	+	4	<0.125
5	**3qa acid** (50 μM)	+	4	<0.125
6	**3qa acid** (25 μM)	+	16	<0.125
7	**3qa acid** (10 μM)	+	16	<0.125
8	**5g acid** (100 μM)	+	4	<0.125
9	**5g acid** (50 μM)	+	4	<0.125
10	**5g acid** (25 μM)	+	16	<0.125
11	**5g acid** (10 μM)	+	16	<0.125

Supplementary Figures

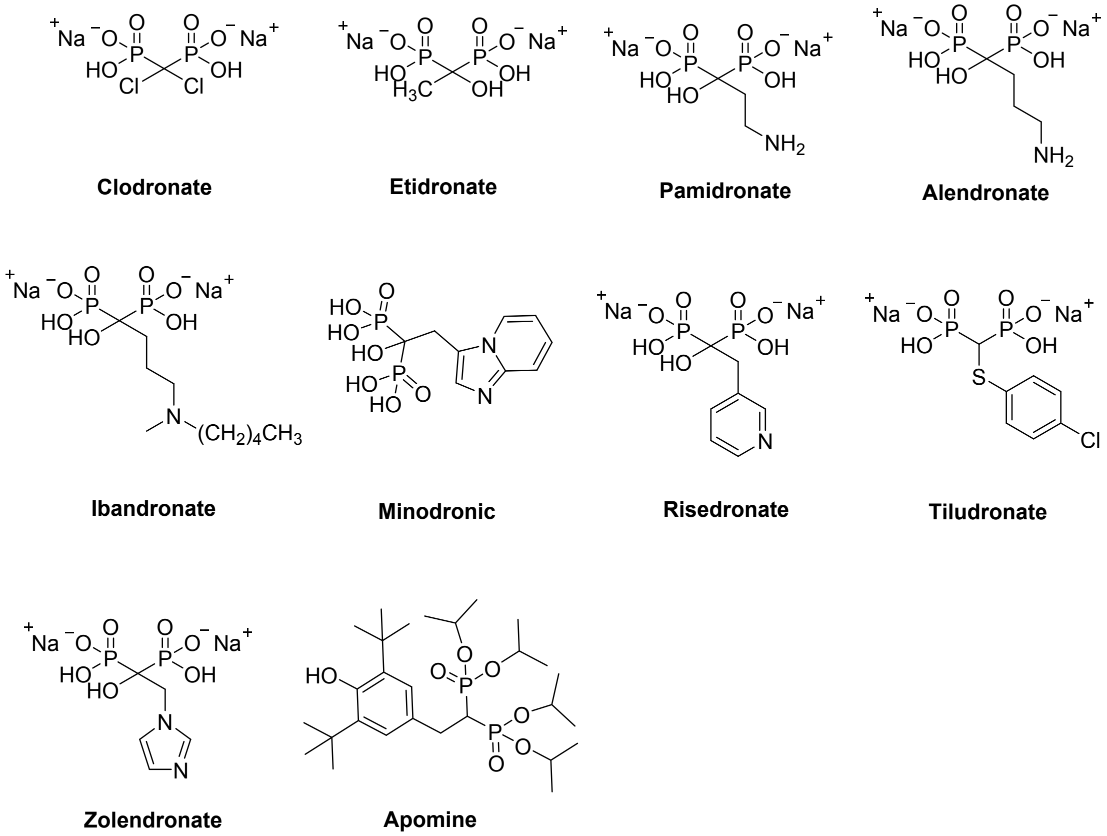


Figure S1. Chemical structures of representative clinically useful bisphosphonates.

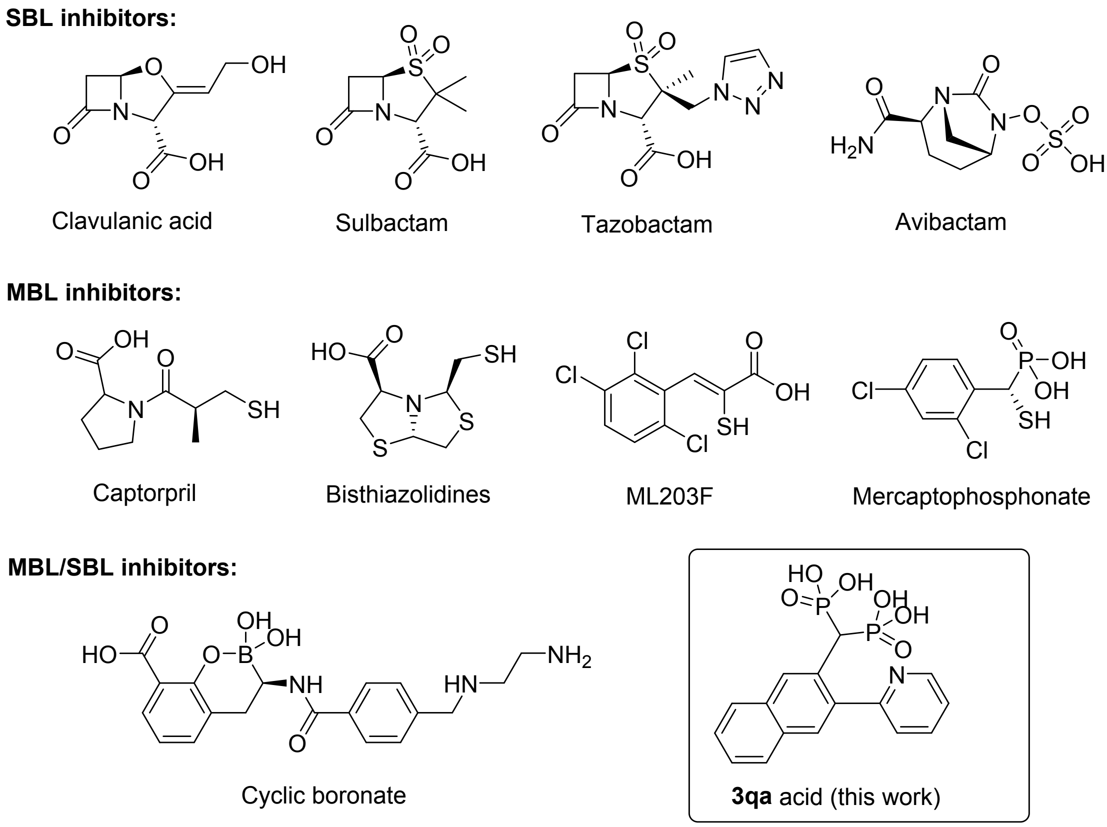


Figure S2. The clinically useful SBL inhibitors, representative MBL inhibitors and MBL/SBL dual inhibitors.

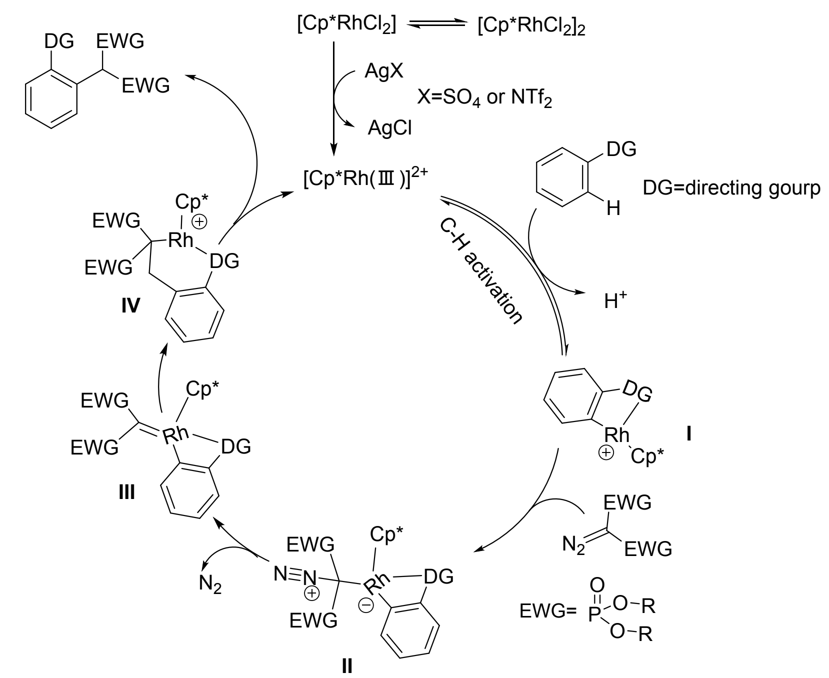


Figure S3. Proposed mechanism for the insertion reaction.

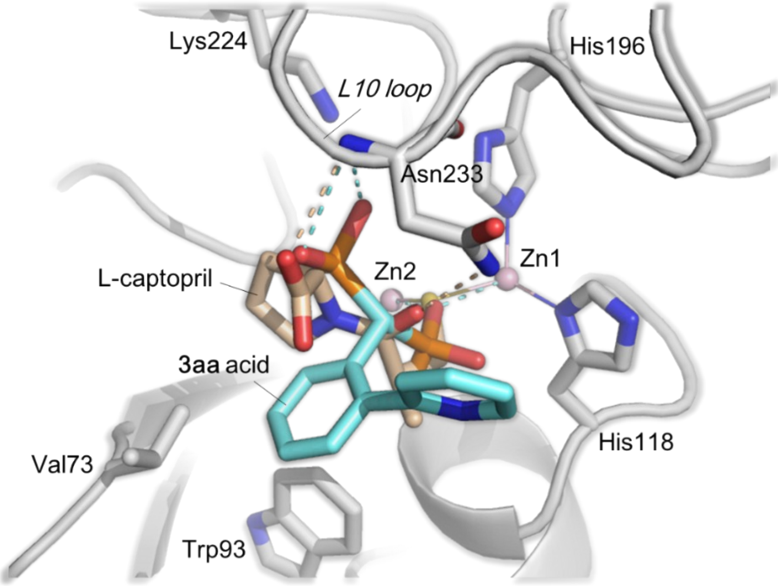


Figure S4. Comparison of the predicted binding mode of **3aa** acid based on an NDM-1:L-captopril (PDB ID: 4EXS)[S21] complex structure, revealing that **3aa** acid likely has a similar binding mode to that of L-captopril.

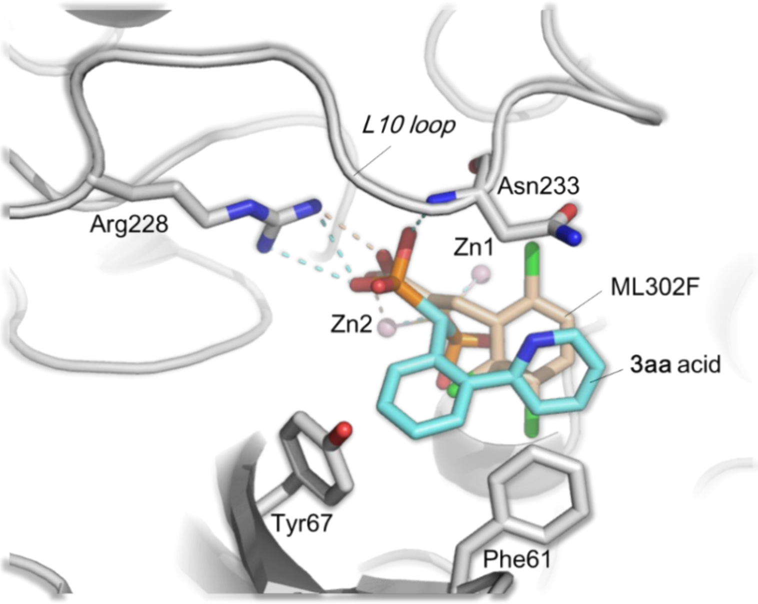


Figure S5. Comparison of the predicted binding mode of **3aa** acid based on an VIM-2:ML302F (PDB ID: 4PVT) [S22] complex structure, revealing that **3aa** acid likely has a similar binding mode to that of ML302F.

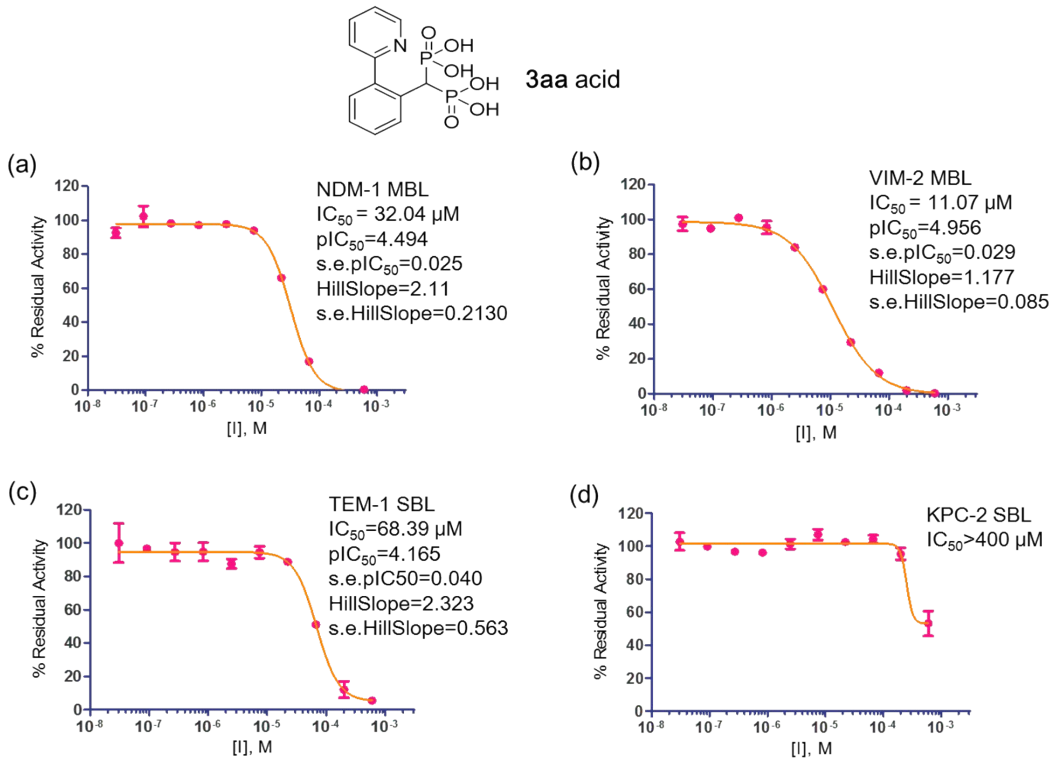


Figure S6. The IC_{50} curves of **3aa** acid with (a) NDM-1, (b) VIM-2, (c) TEM-1, and (d) KPC-2.

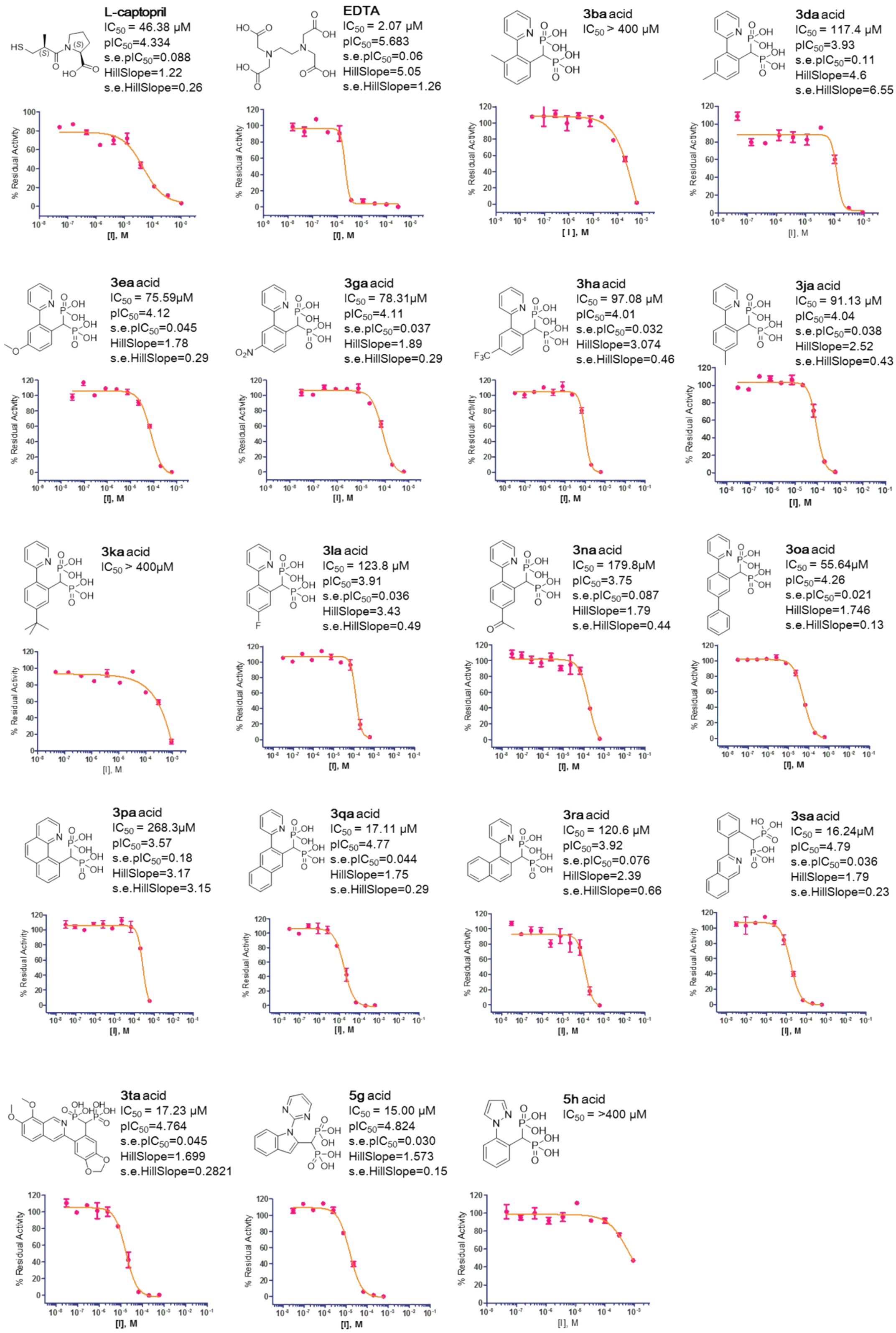


Figure S7. The IC_{50} curves of all the compounds in Table 1 with NDM-1.

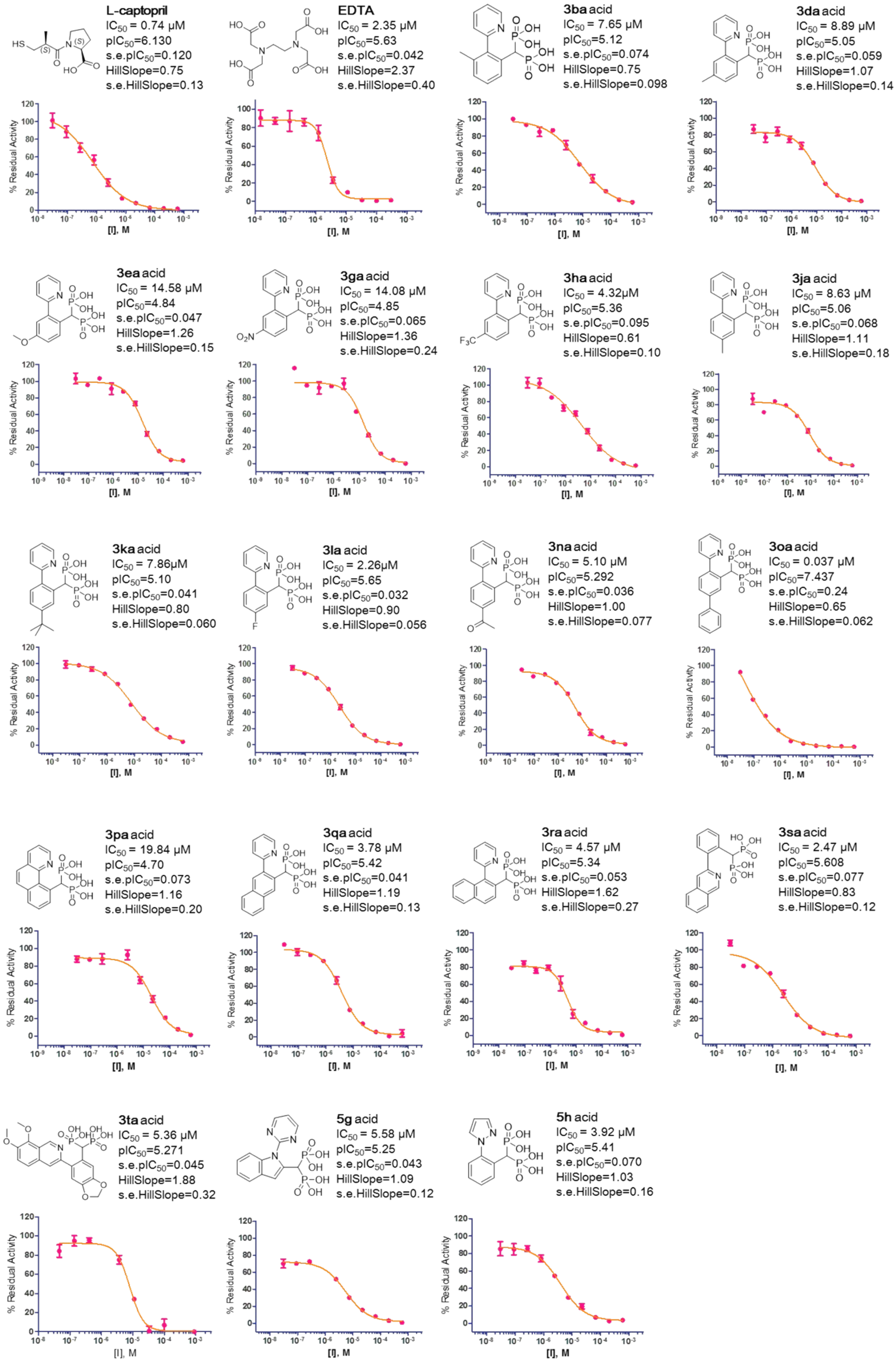


Figure S8. The IC_{50} curves of all the compounds in Table 1 with VIM-2.

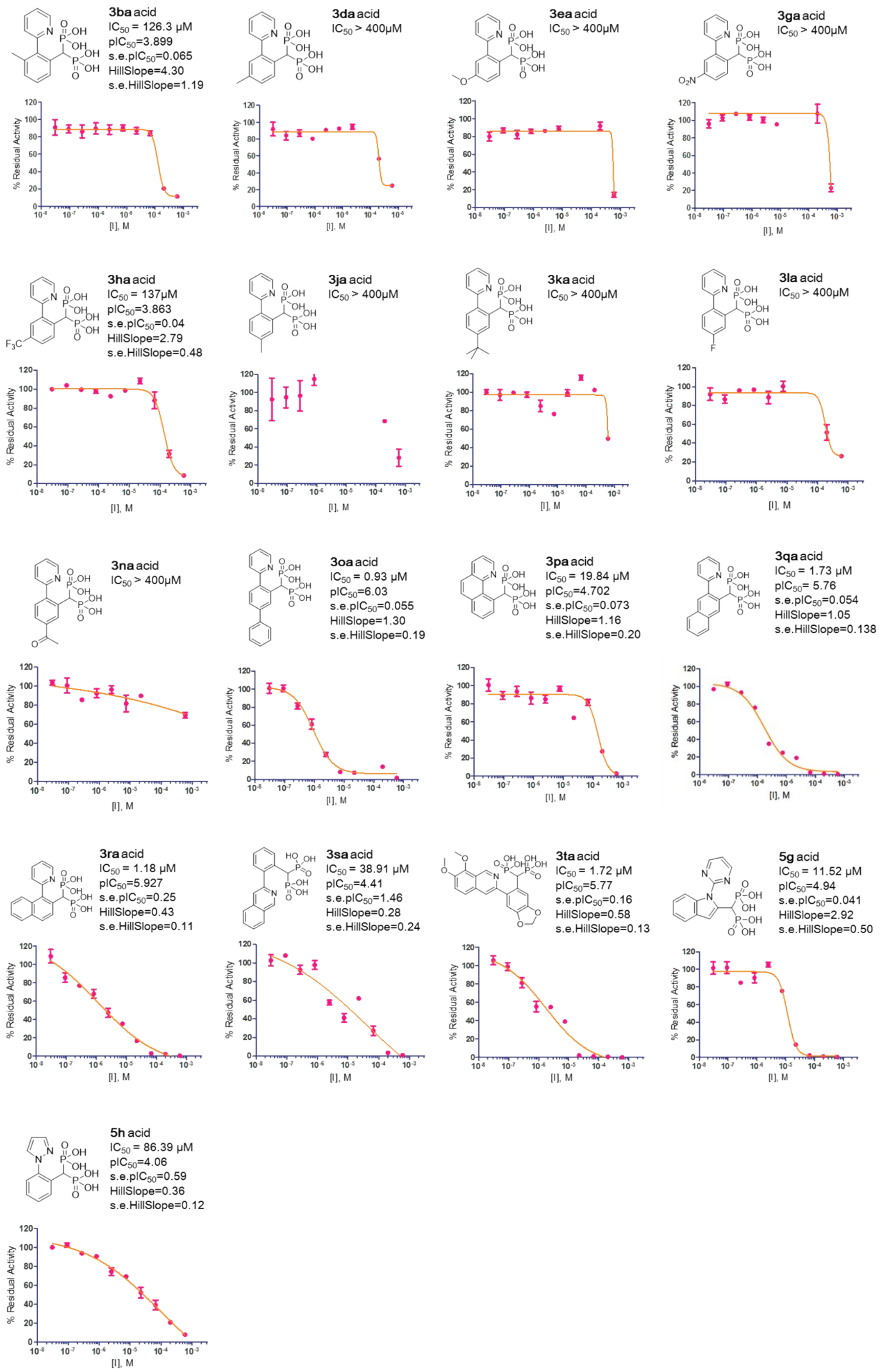


Figure S9. The IC_{50} curves of all the compounds in Table 1 with the TEM-1 SBL.

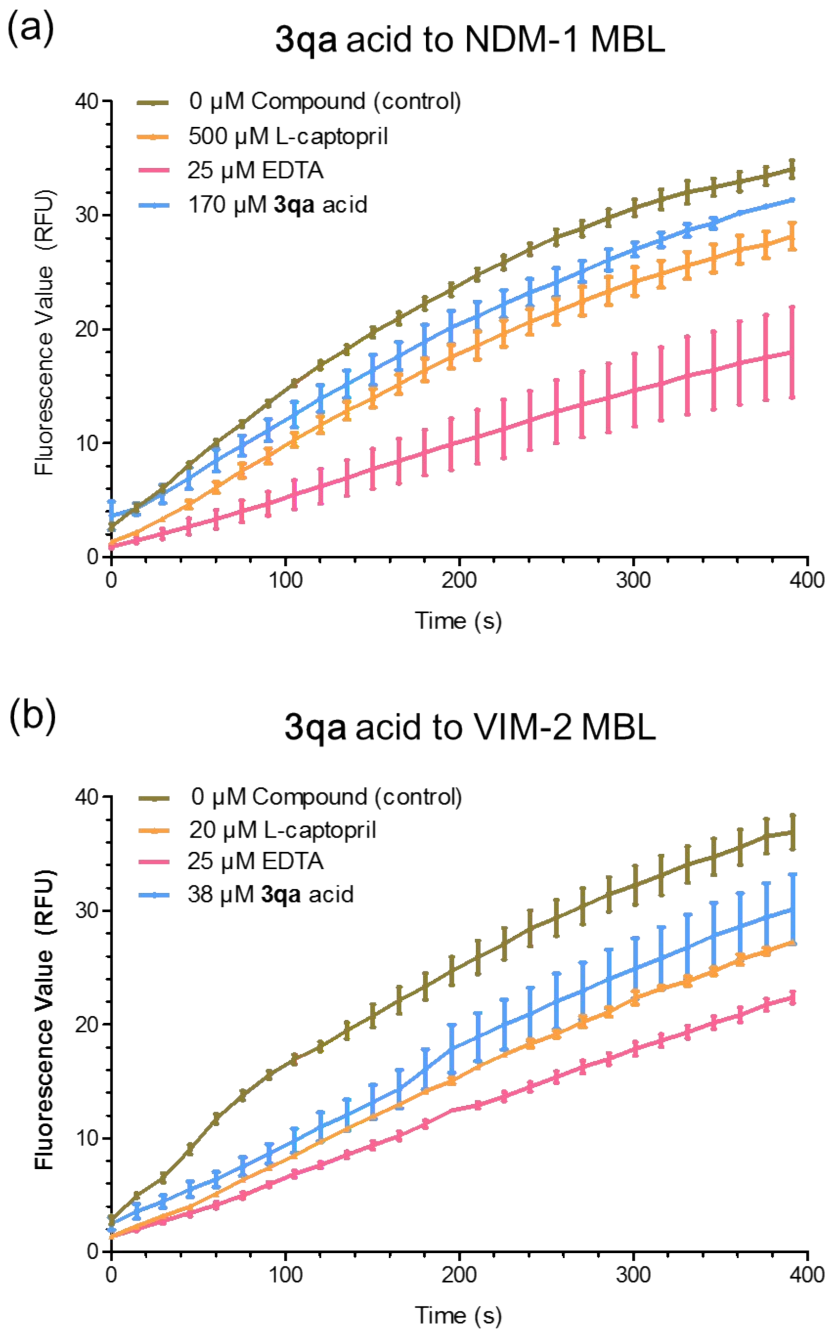


Figure S10. Testing the reversibility of **3qa** acid inhibiting (a) NDM-1 and (b) VIM-2. *L*-captopril and EDTA were used as controls (the details please see Supplementary Experimental Section SE.4). The samples of inhibitors and NDM-1/VIM-2 were preincubated for 30 min at room temperature, then rapidly diluted 100-fold into an assay solution, and finally determined the enzyme activities.

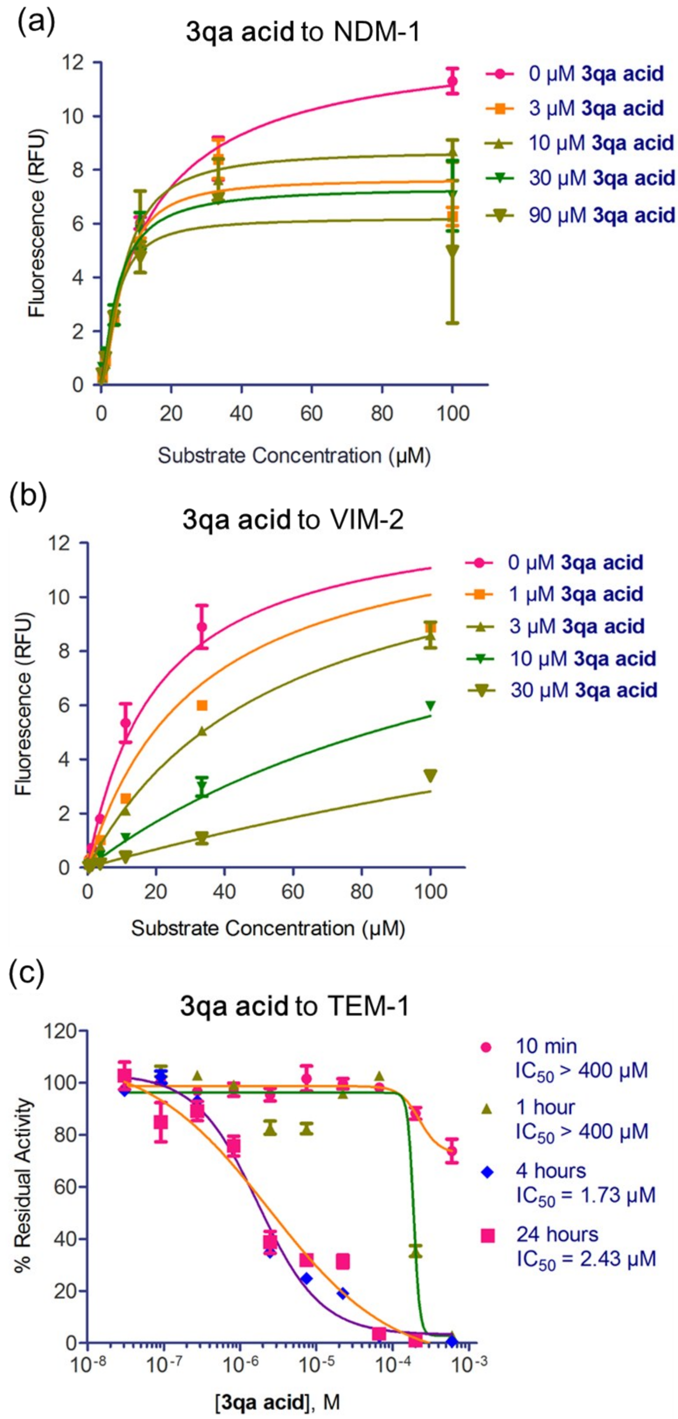


Figure S11. Testing how **3qa acid** affects the activity of NDM-1, VIM-2, and TEM-1. (a) The results reveal that **3qa acid** inhibits NDM-1 probably through the partially mixed inhibition type, but which inhibits VIM-2 probably in a substrate-competitive manner. (b) The inhibitory activities were tested after preincubation of **3qa acid** with TEM-1 for 10 min, 1 hour, 4 hours, and 24 hours, respectively. The results revealed that **3qa acid** manifests time-dependent inhibition with TEM-1.

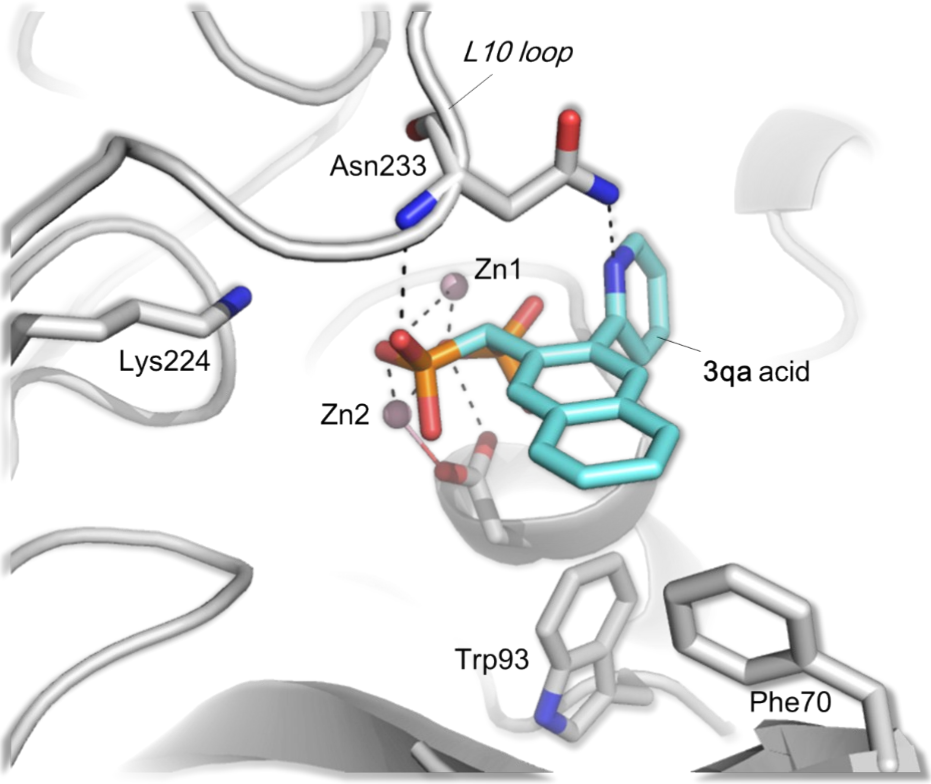


Figure S12. The predicted binding mode of **3qa** acid with NDM-1.

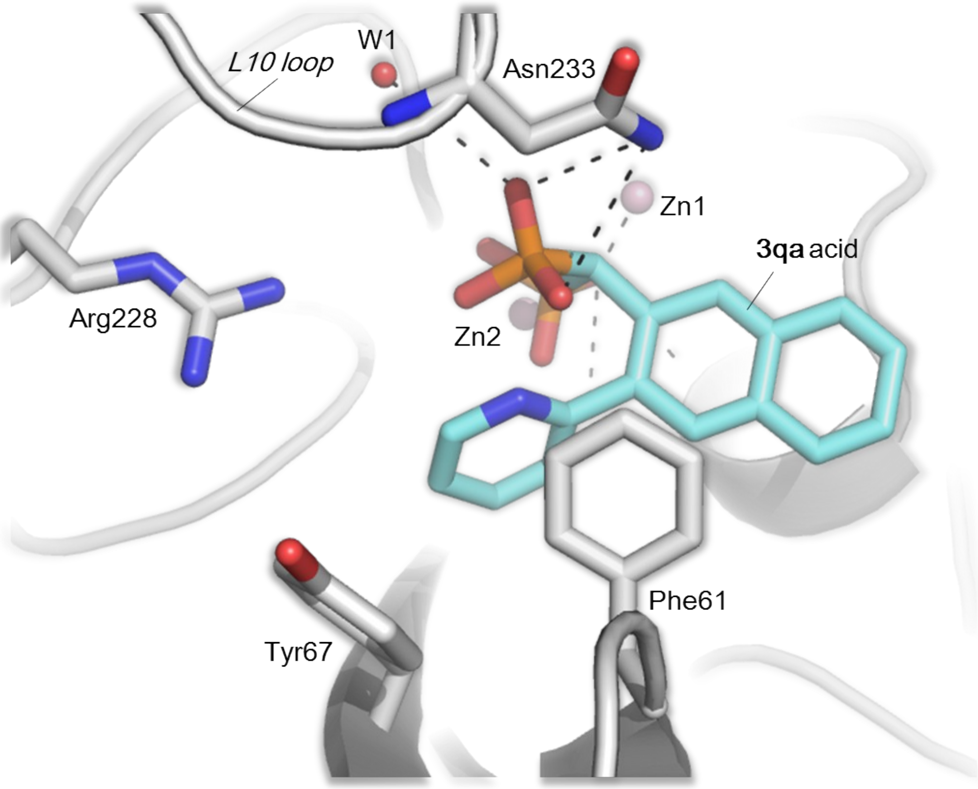


Figure S13. The predicted binding mode of **3qa** acid with VIM-2.

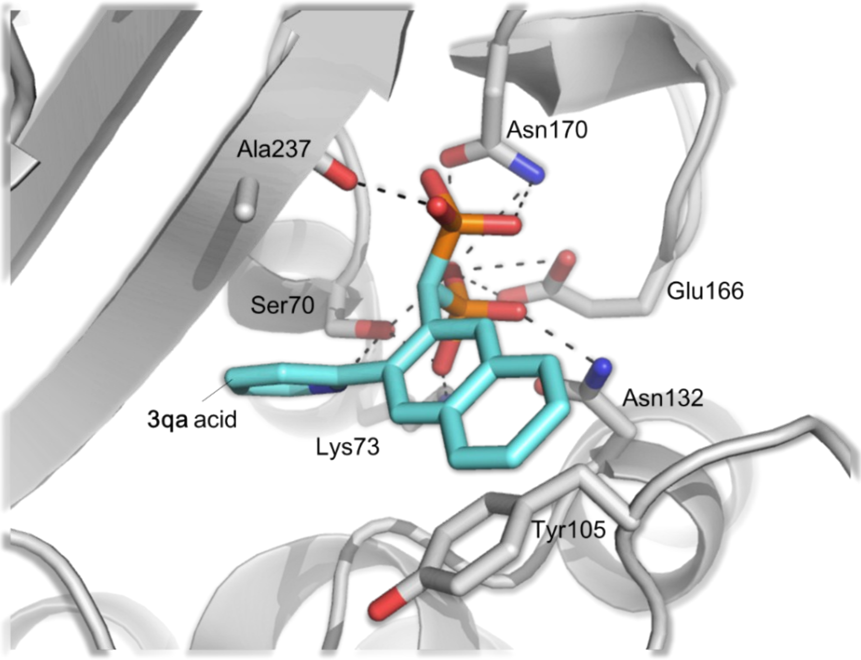
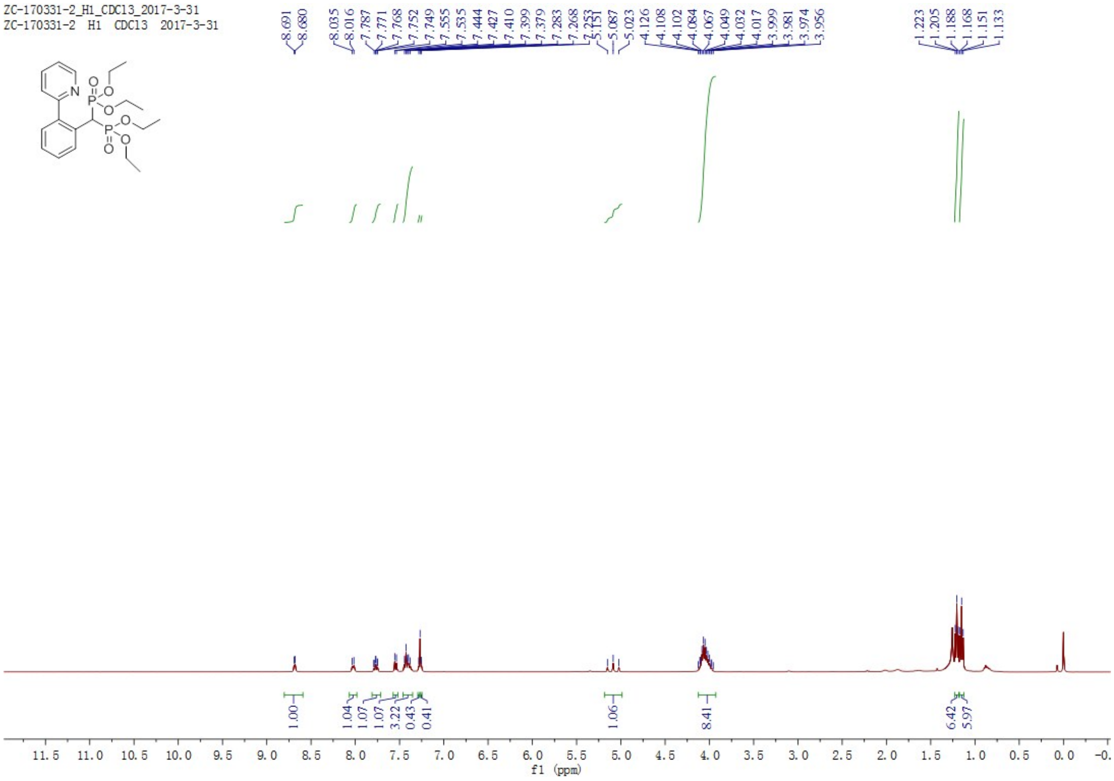
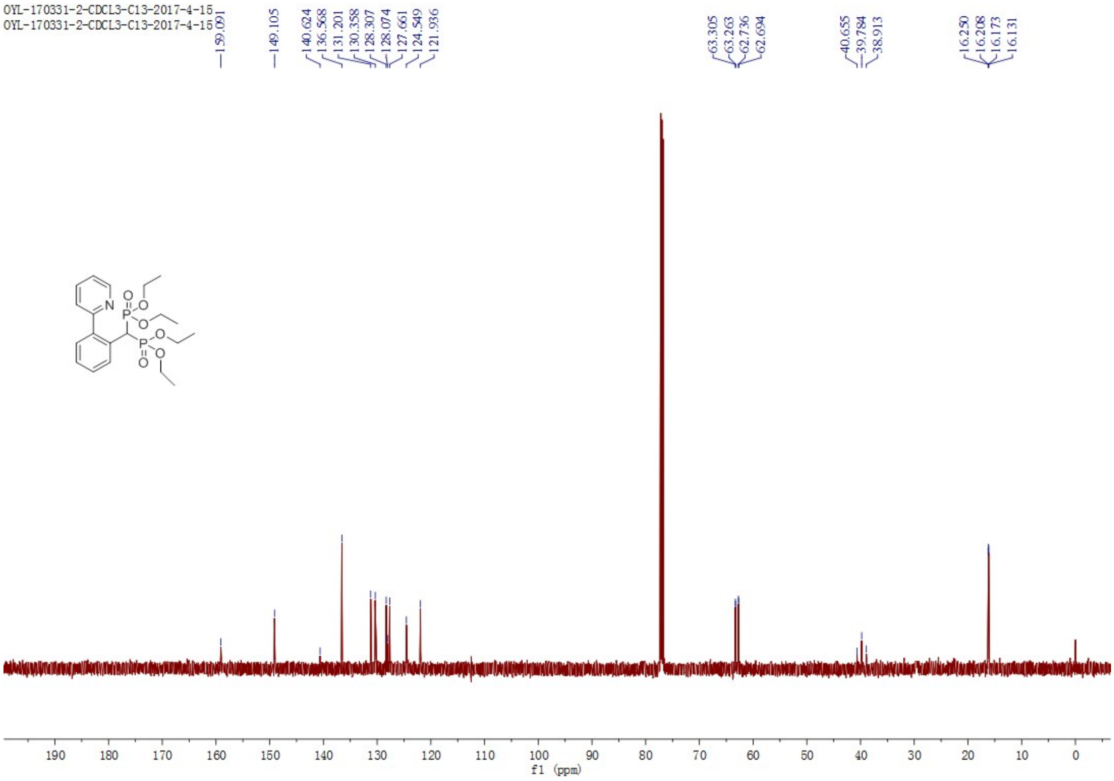


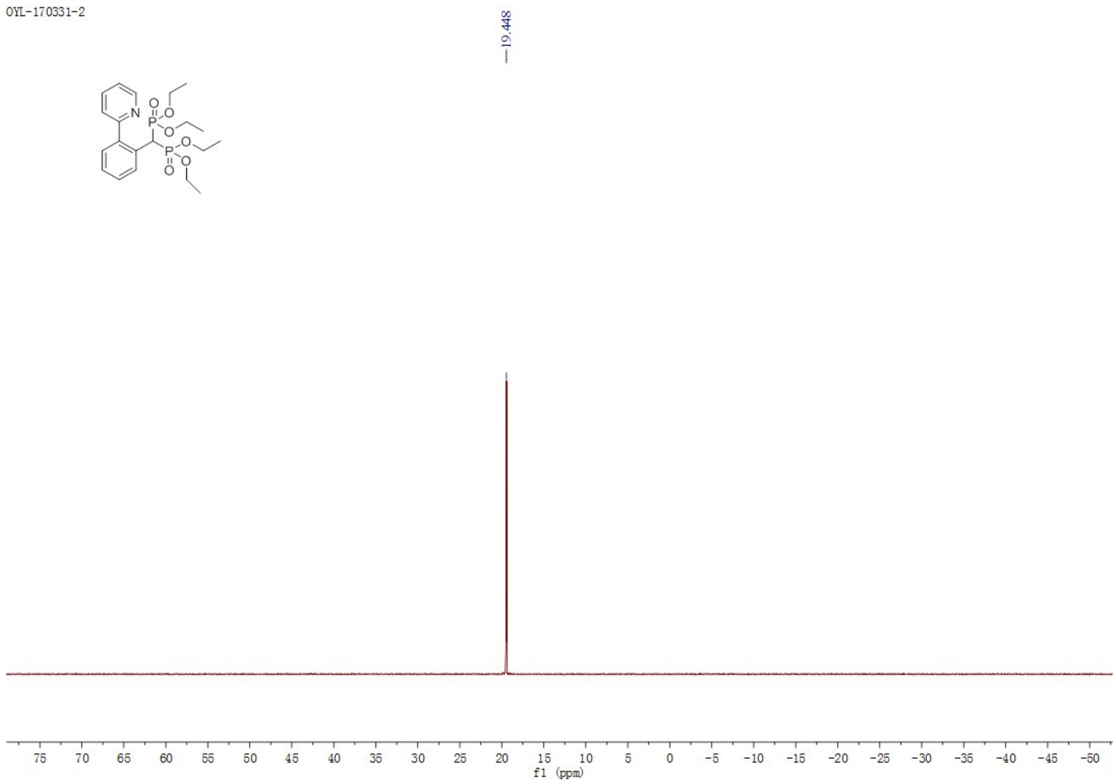
Figure S14. The predicted binding mode of **3qa** acid with TEM-1.

^{1}H NMR, ^{13}C NMR, ^{31}P NMR of Compounds

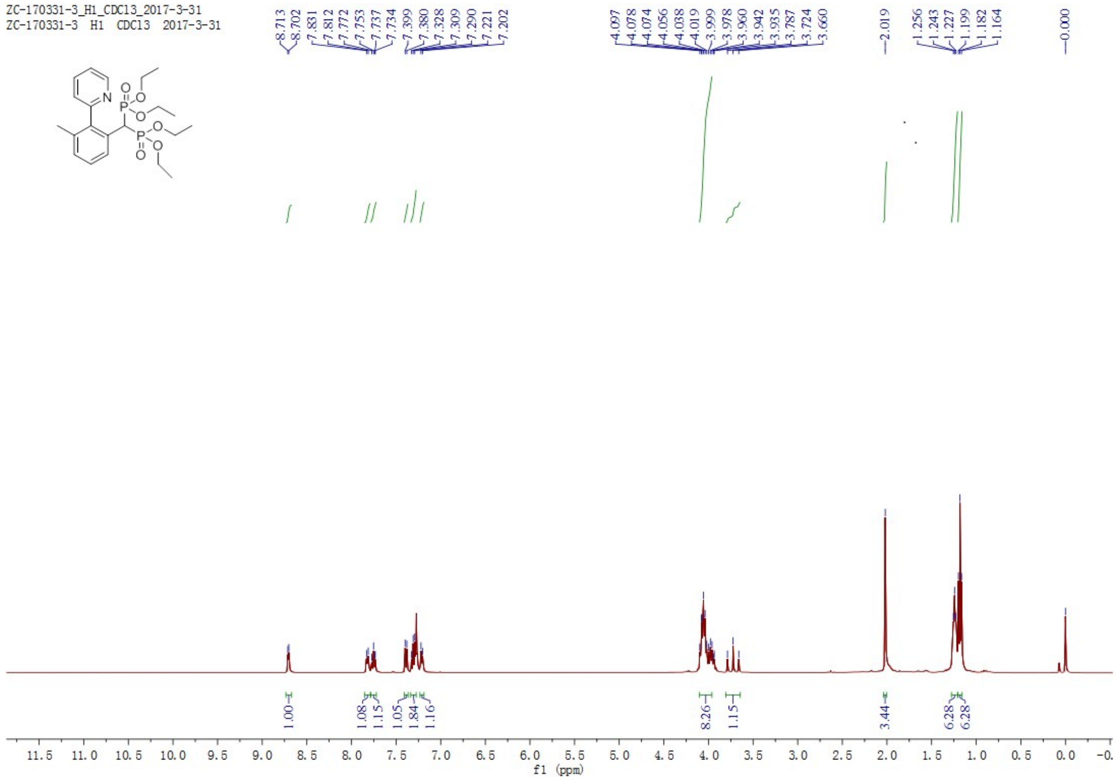
Compound **3aa**

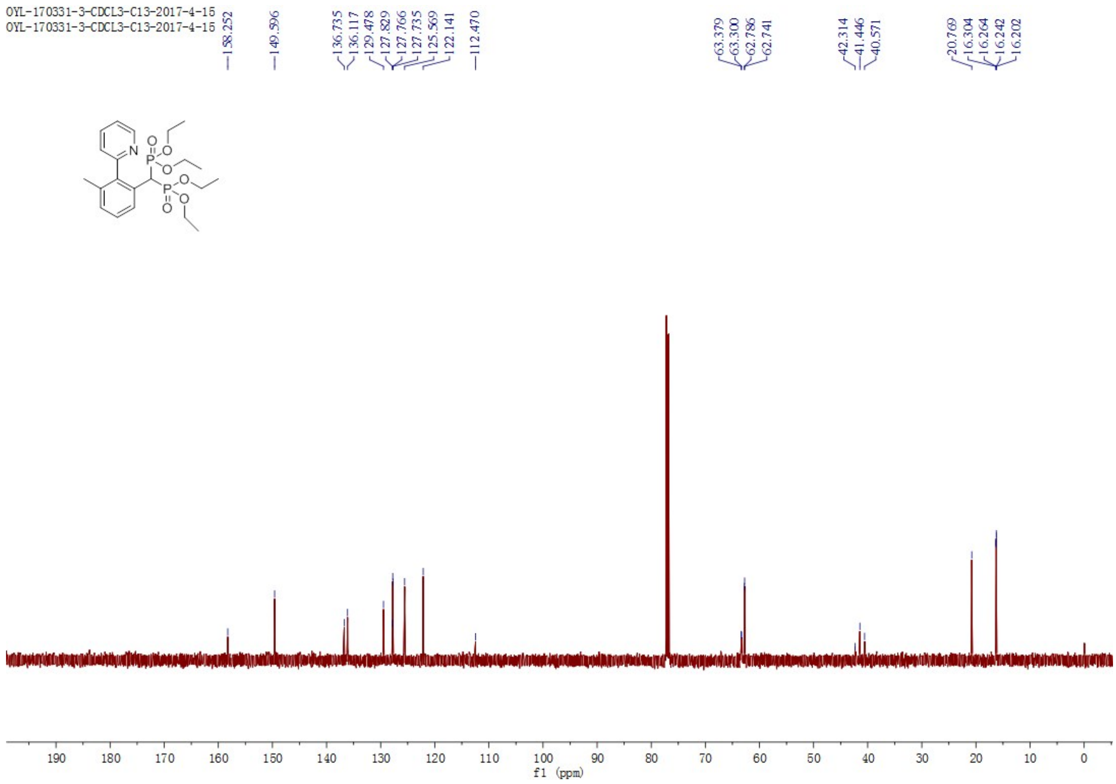






Compound **3ba**

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OYL-170331-3-CDCL3-C13-2017-4-15
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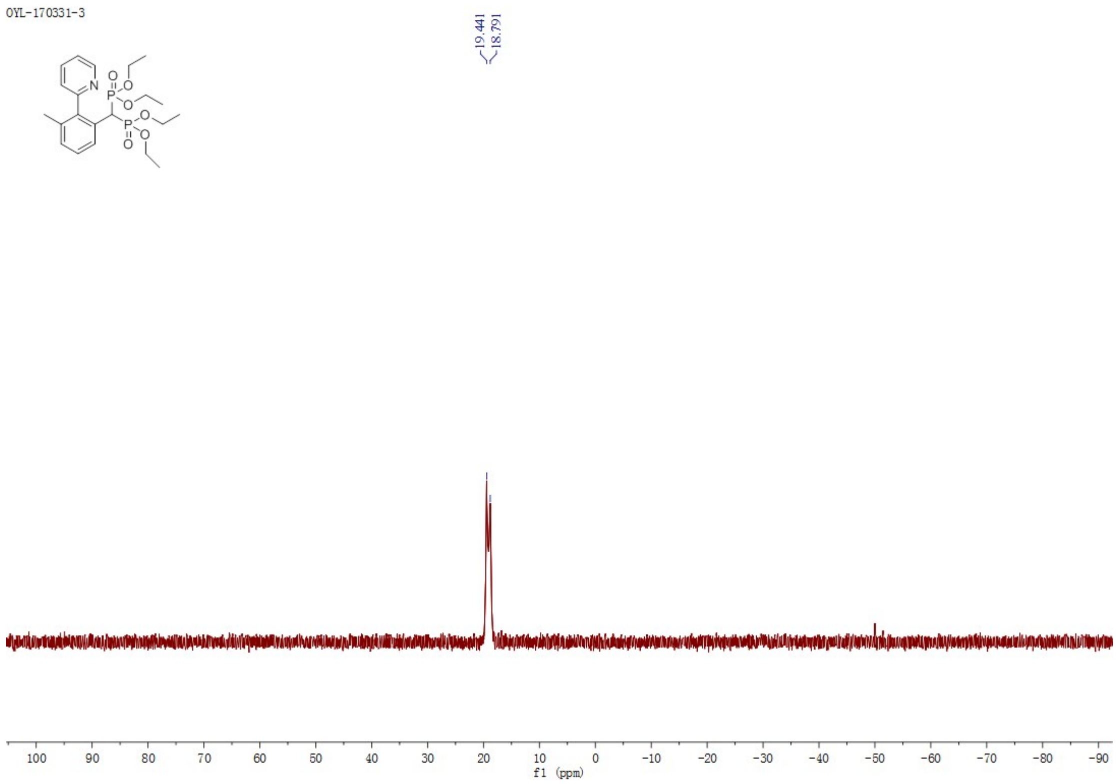
129.478
127.829
127.766
127.735
125.569
122.141
112.470
63.379
63.300
62.786
62.741
42.314
41.446
40.571
20.769
16.304
16.264
16.242
16.202
N
P
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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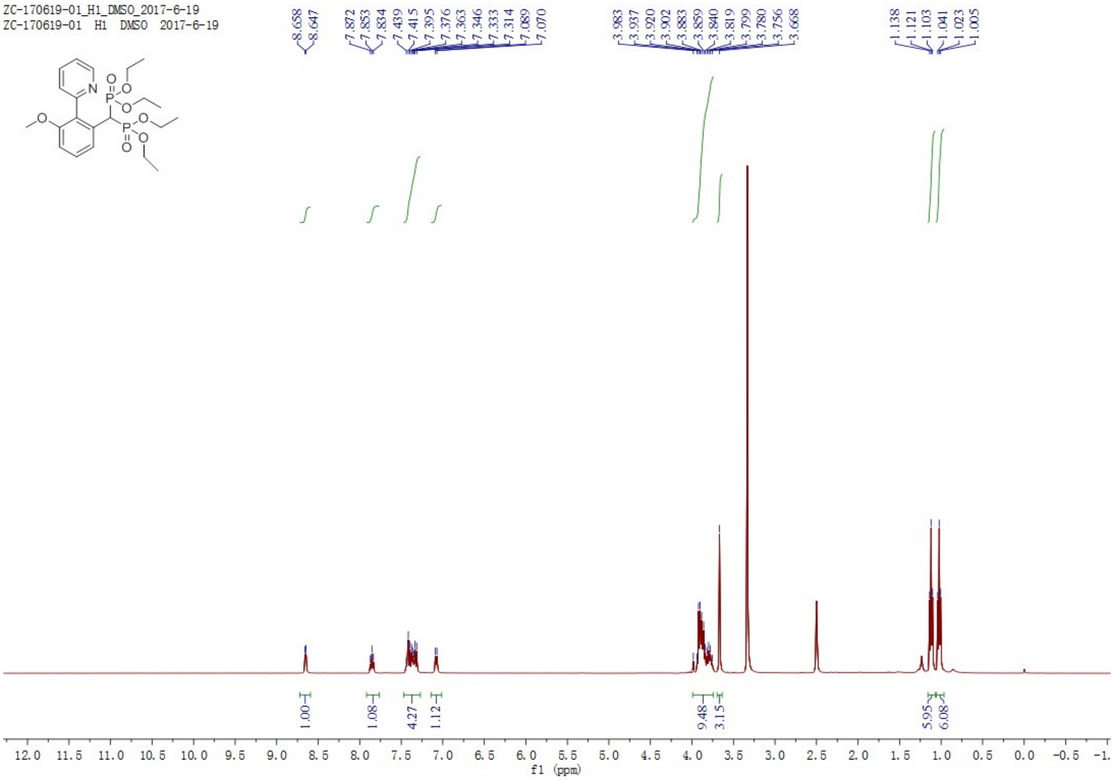
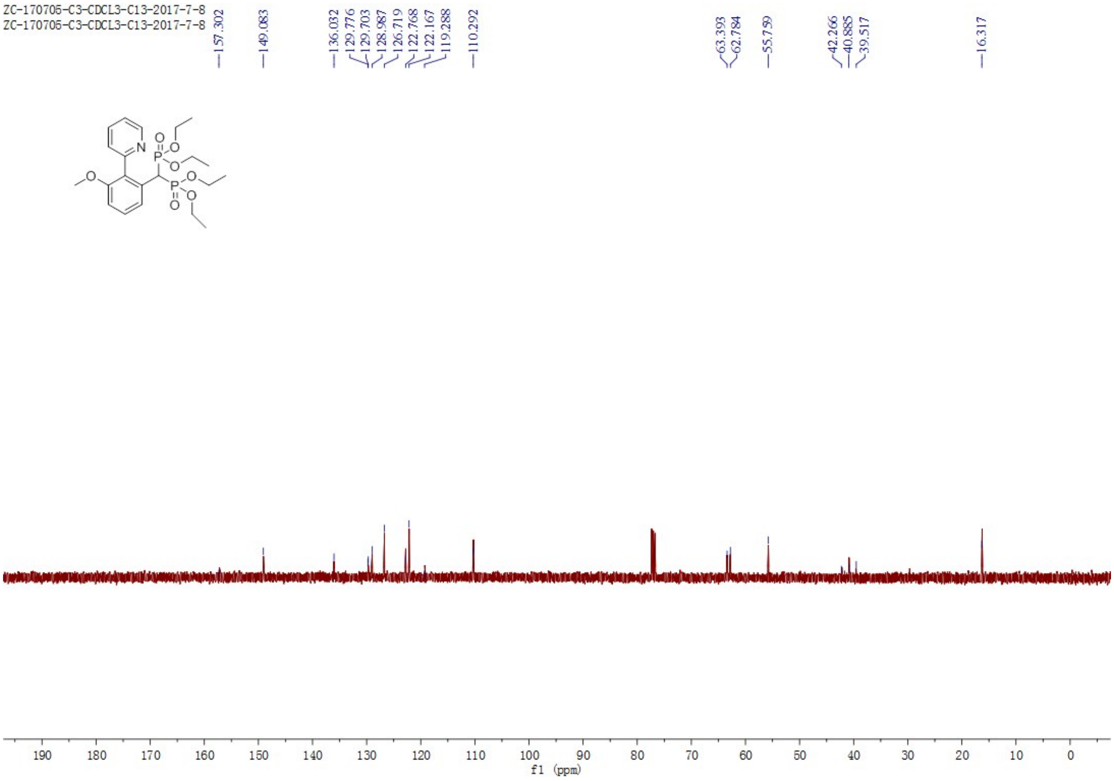
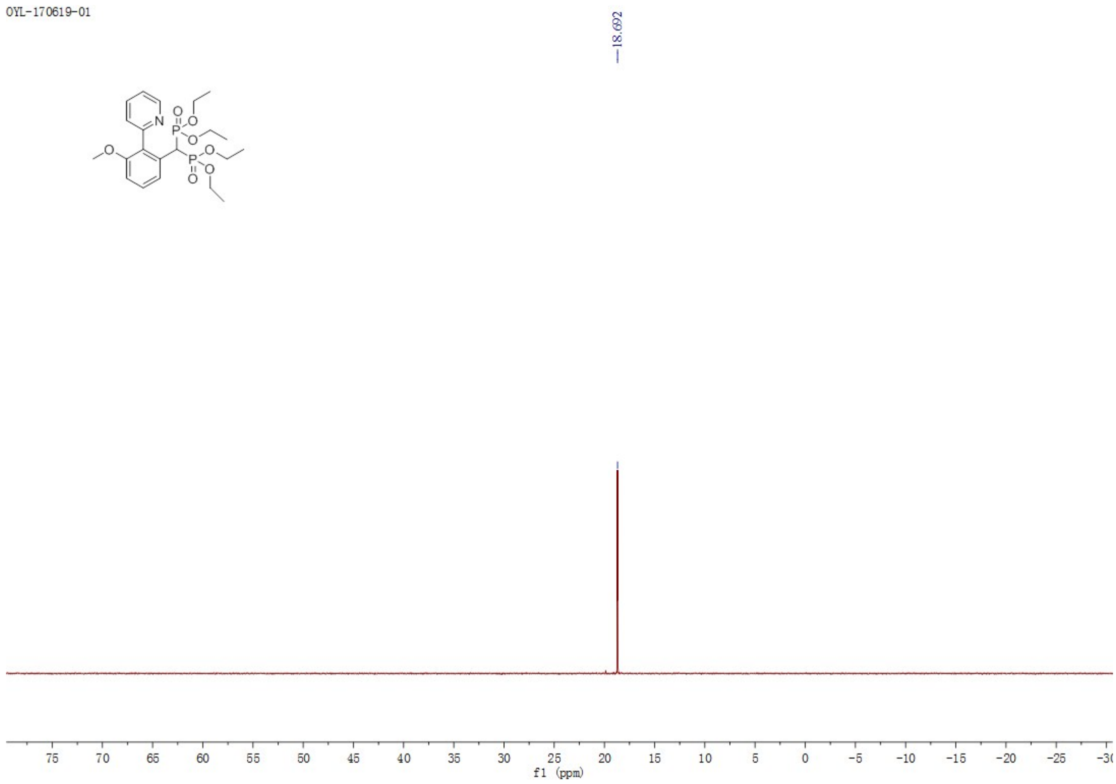
18.791
N
P
O
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)

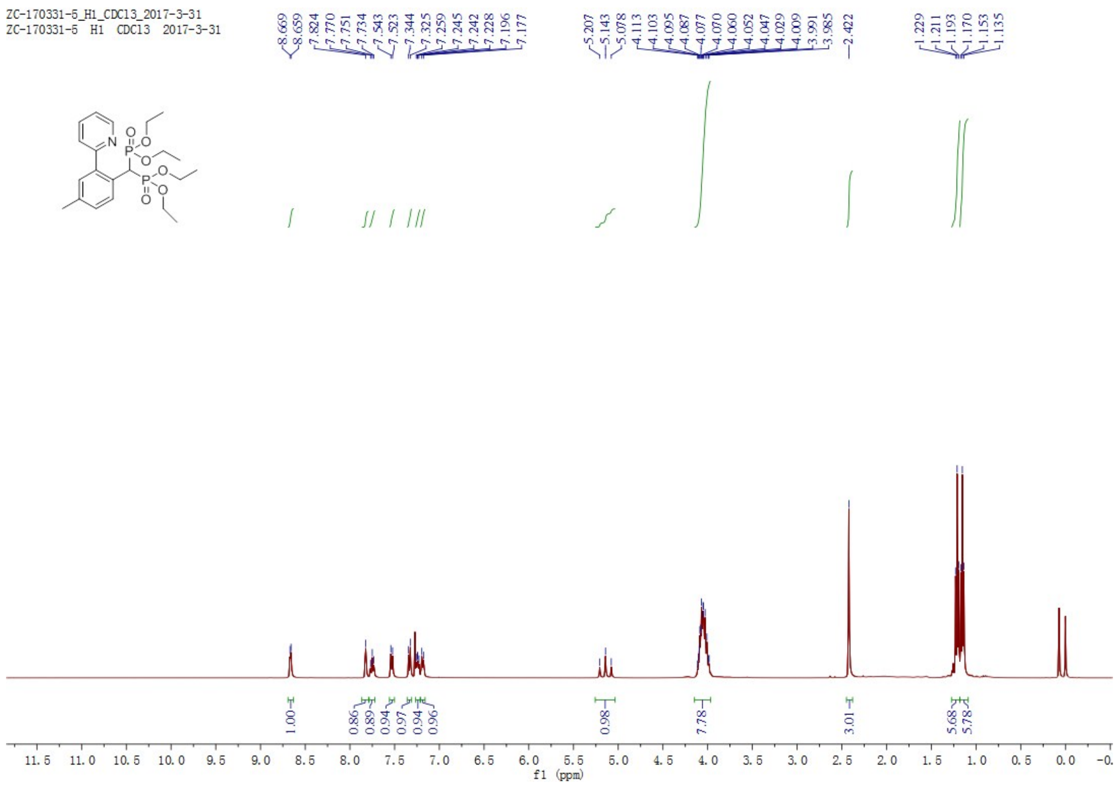
Compound **3ca**

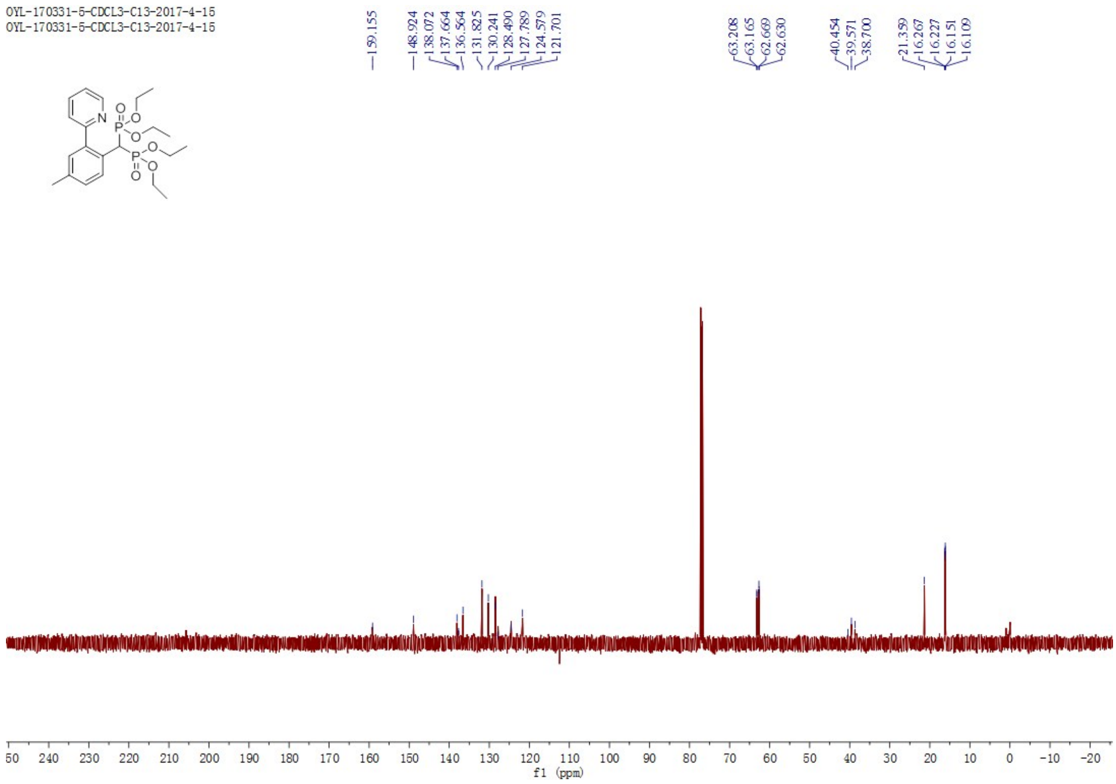


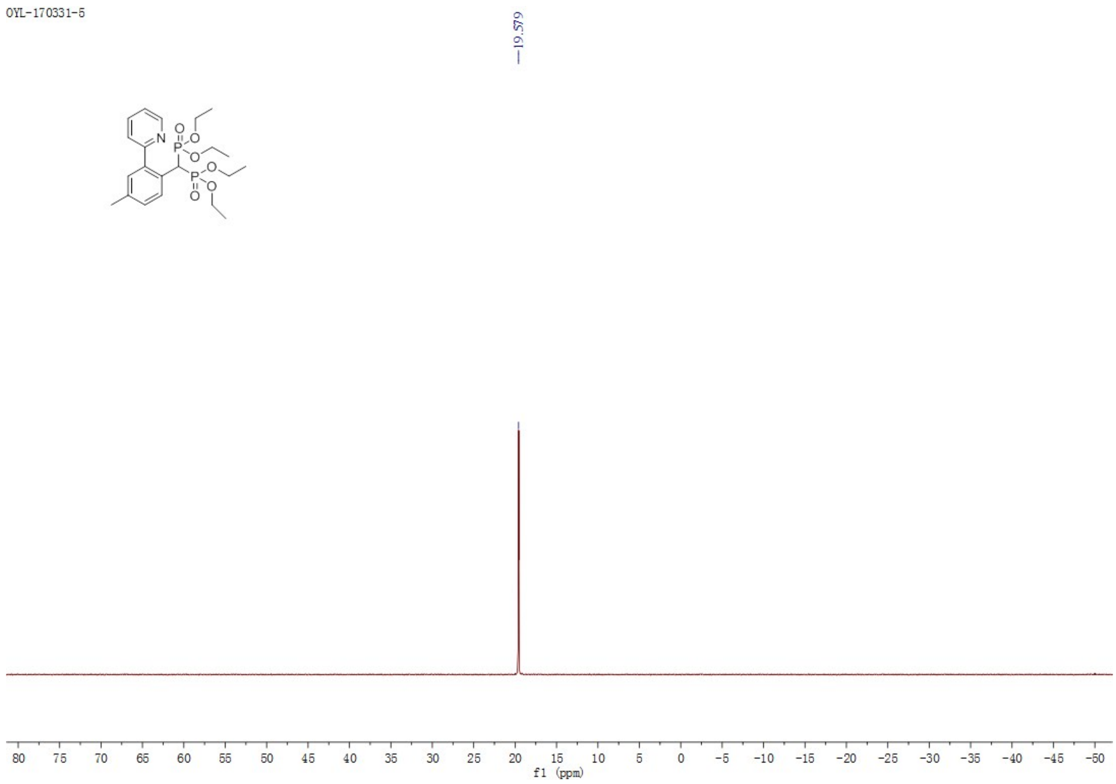




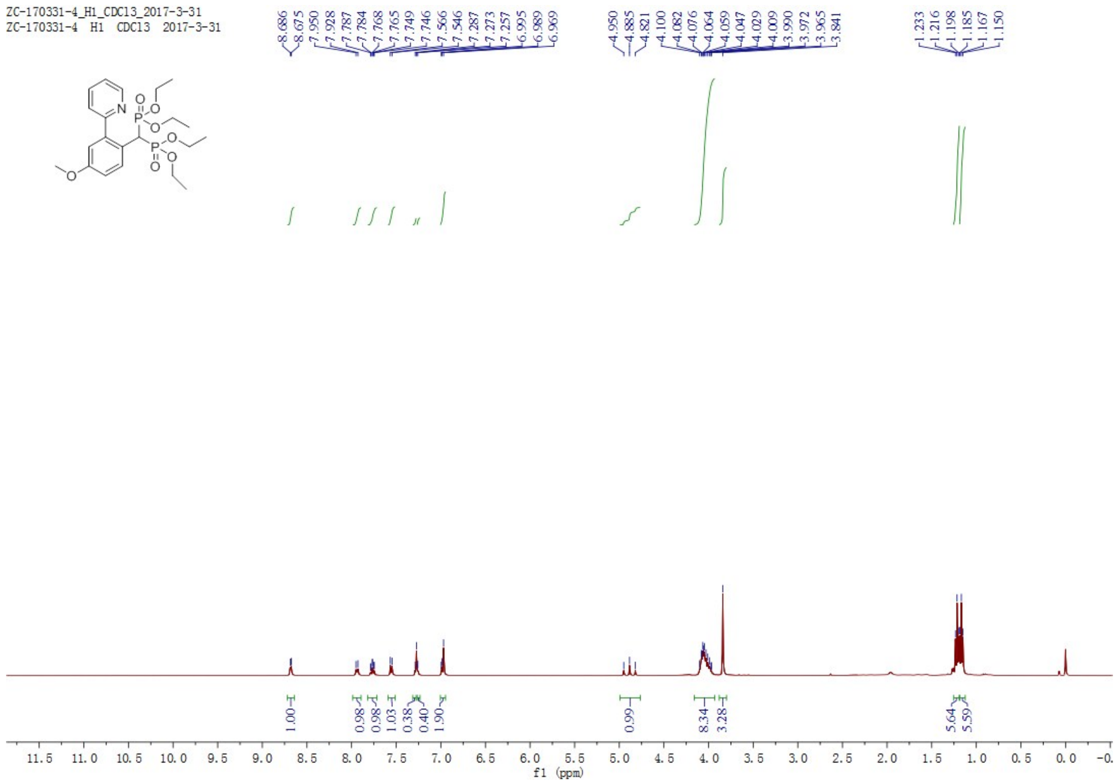
Compound **3da**







Compound **3ea**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ZC-170331-4 H1 CDCl3 2017-3-31
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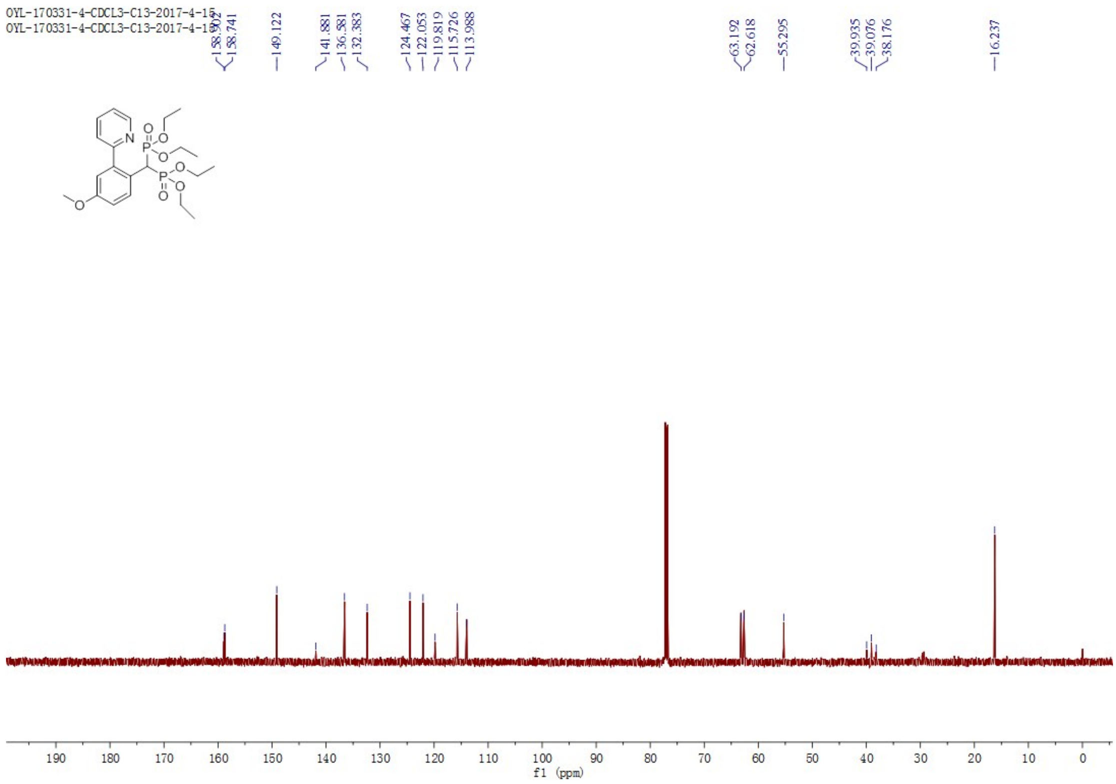
7.950
7.928
7.787
7.784
7.768
7.765
7.749
7.746
7.566
7.546
7.287
7.273
7.257
6.995
6.989
6.969
4.950
4.885
4.821
4.100
4.082
4.076
4.064
4.059
4.047
4.029
4.009
3.990
3.972
3.965
3.841
1.233
1.216
1.198
1.185
1.167
1.150
1.00
0.98
0.98
1.03
0.38
0.40
1.90
0.99
8.34
3.28
5.64
5.59
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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OYL-170331-4-CDCL3-C13-2017-4-15
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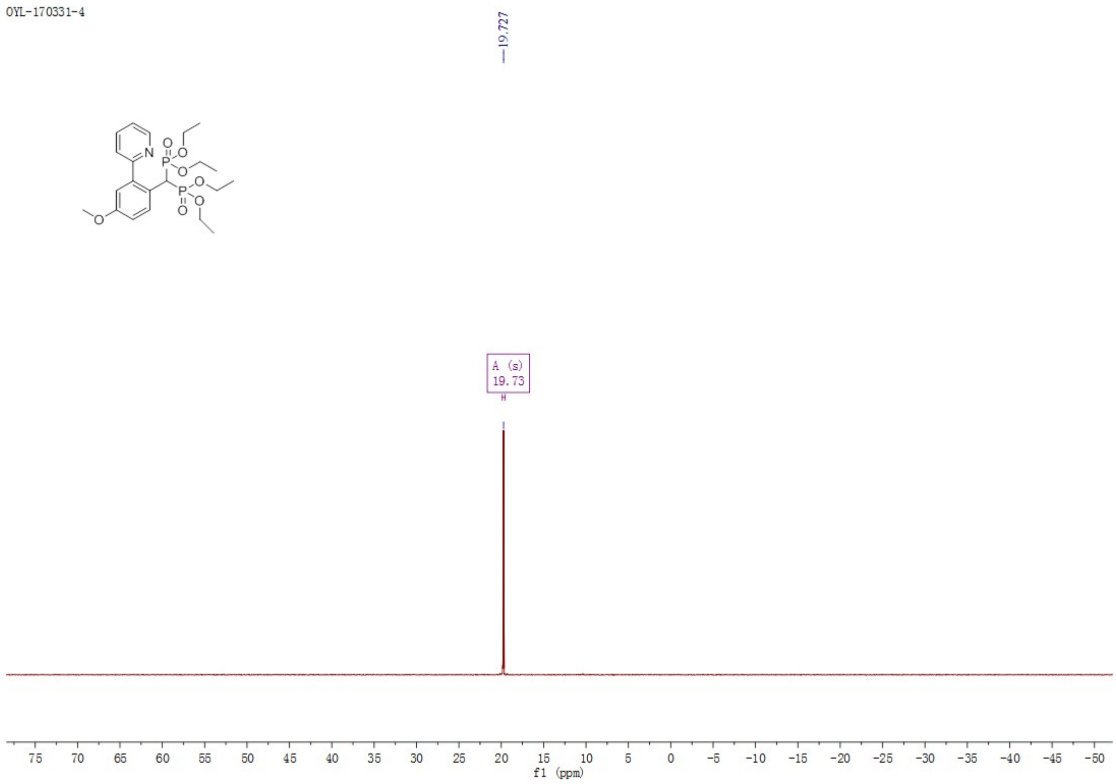
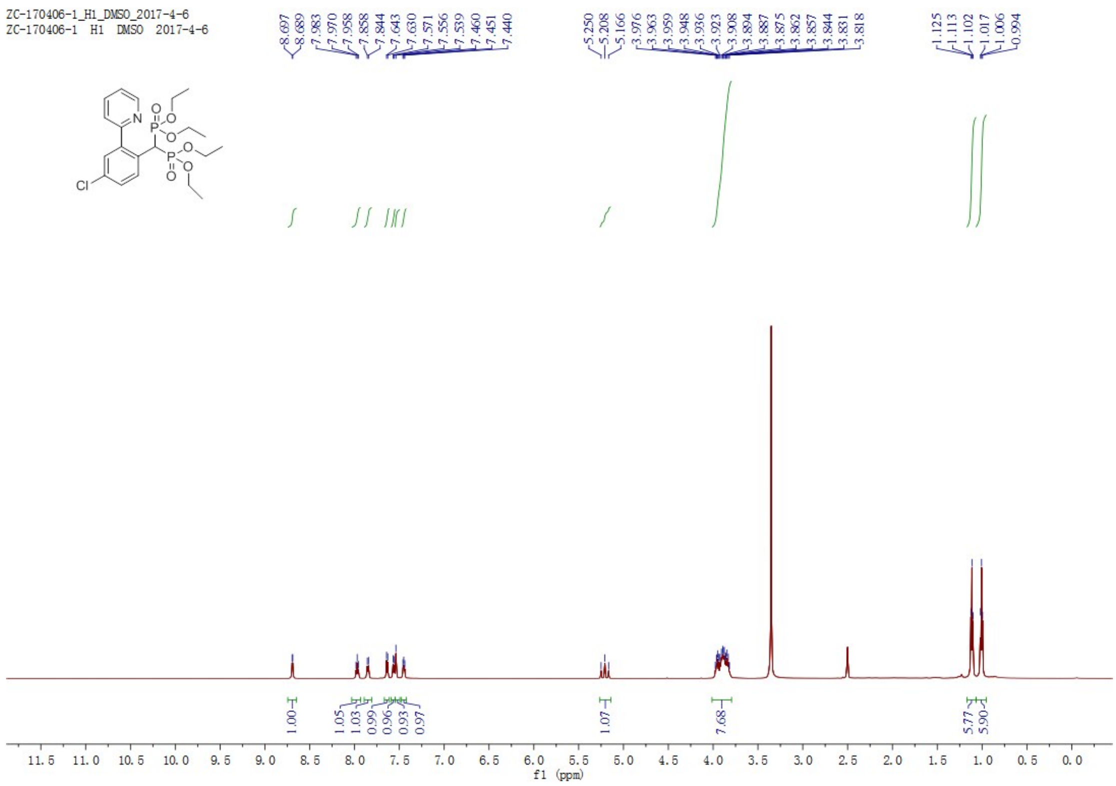
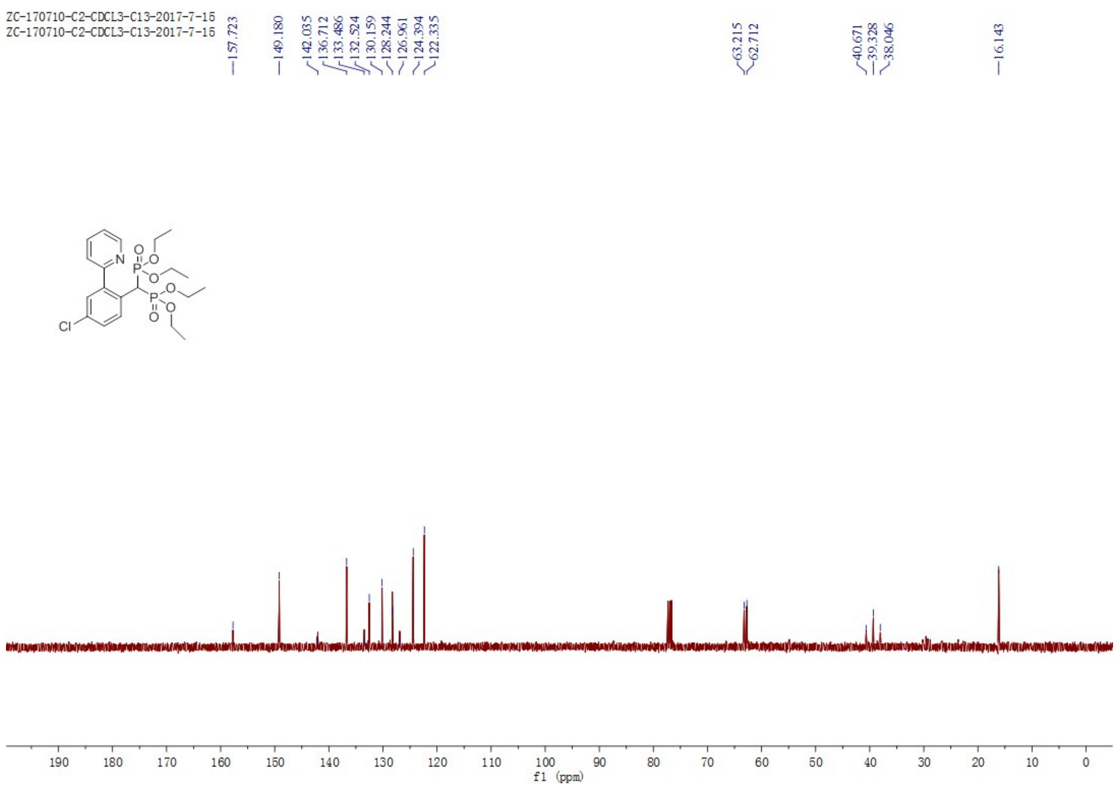
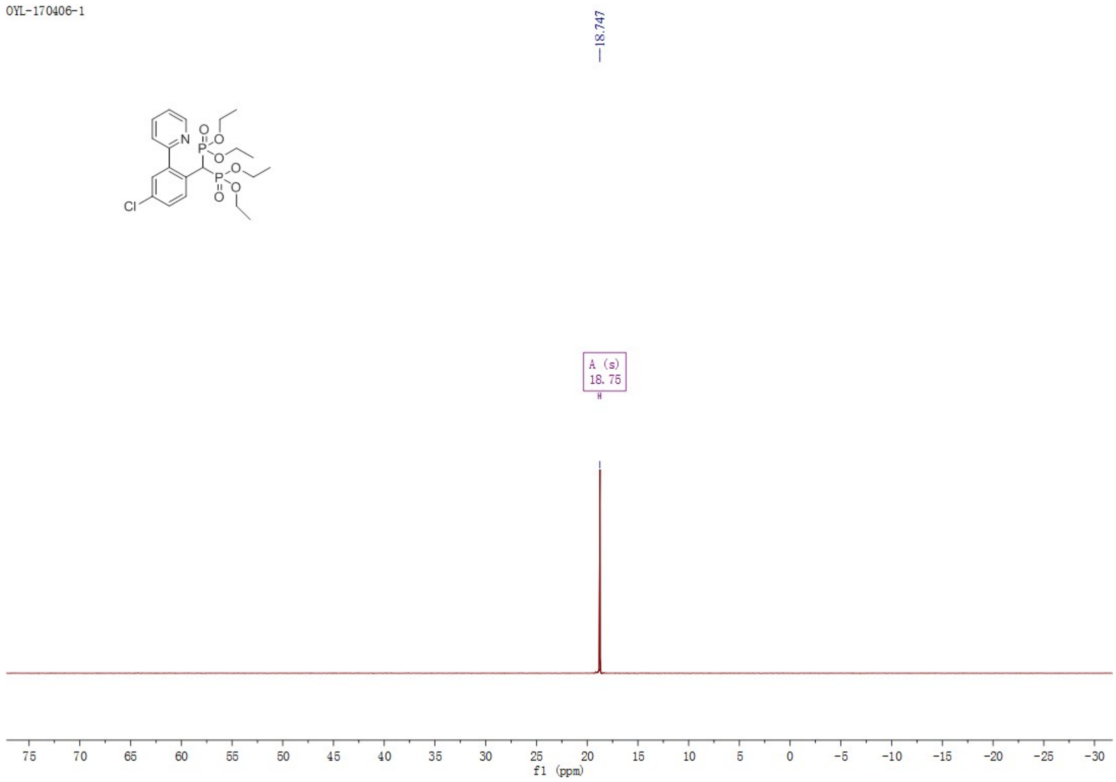
141.881
136.581
132.383
124.467
122.053
119.819
115.726
113.988
63.192
62.618
55.295
39.935
39.076
38.176
16.237
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



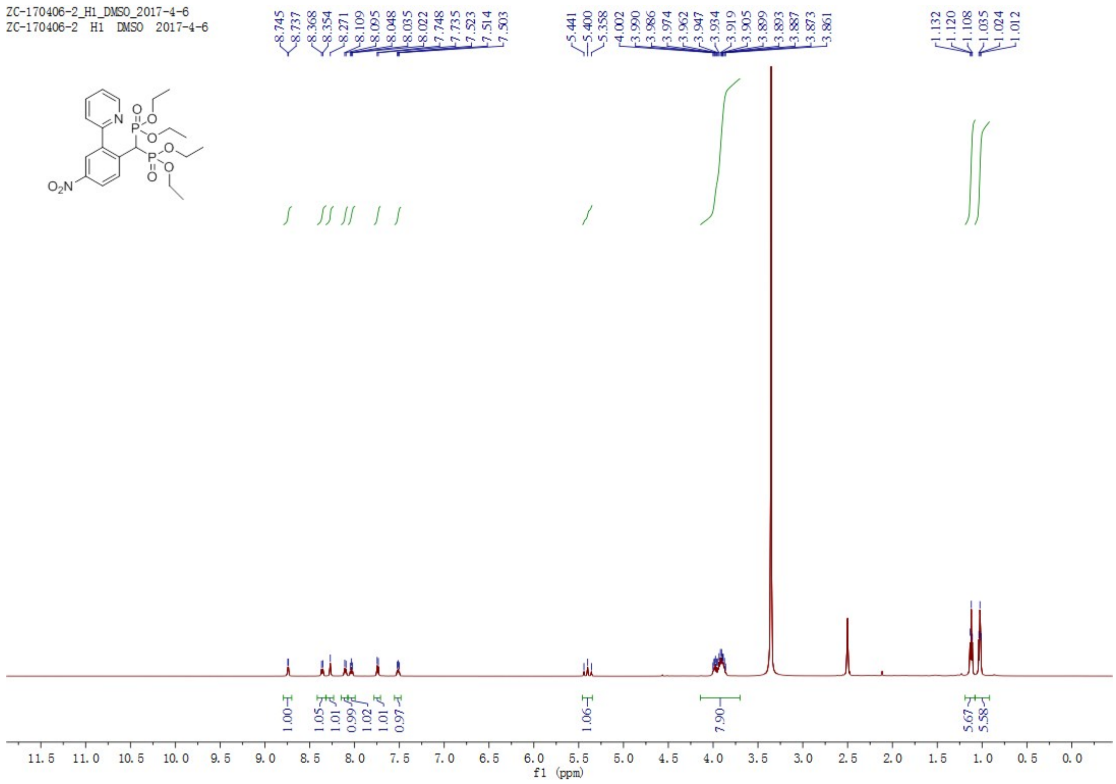
Compound **3fa**

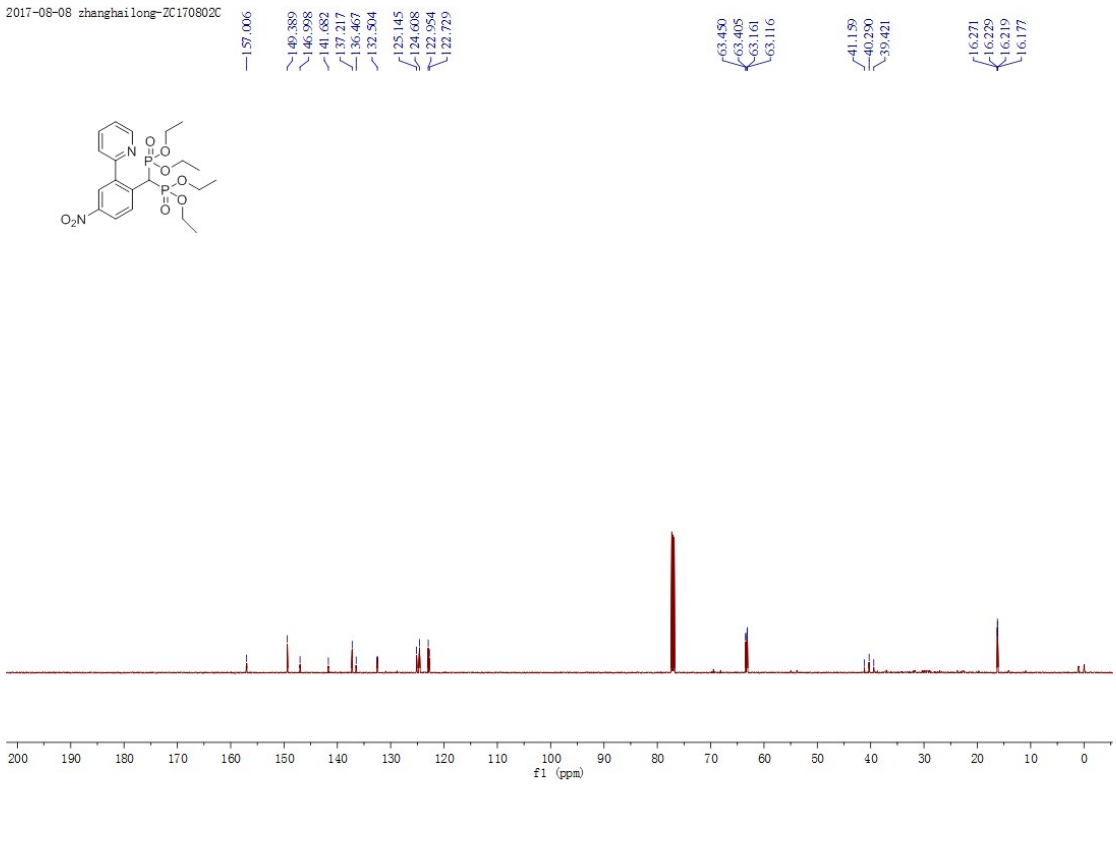


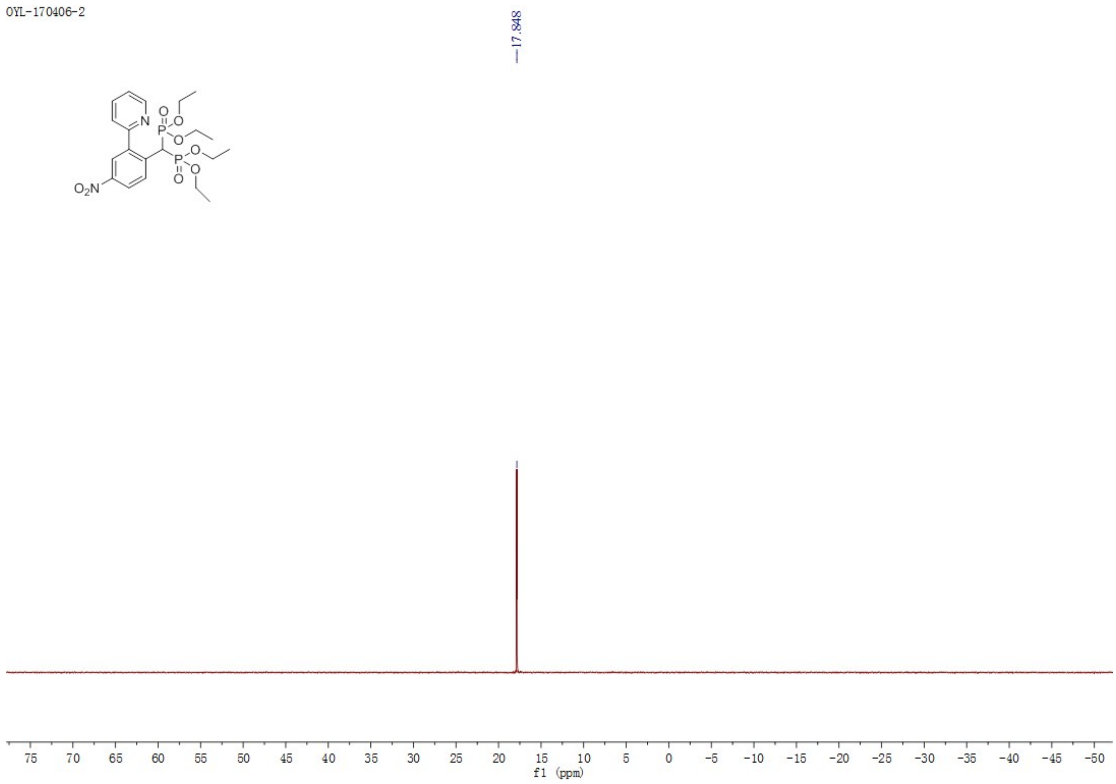




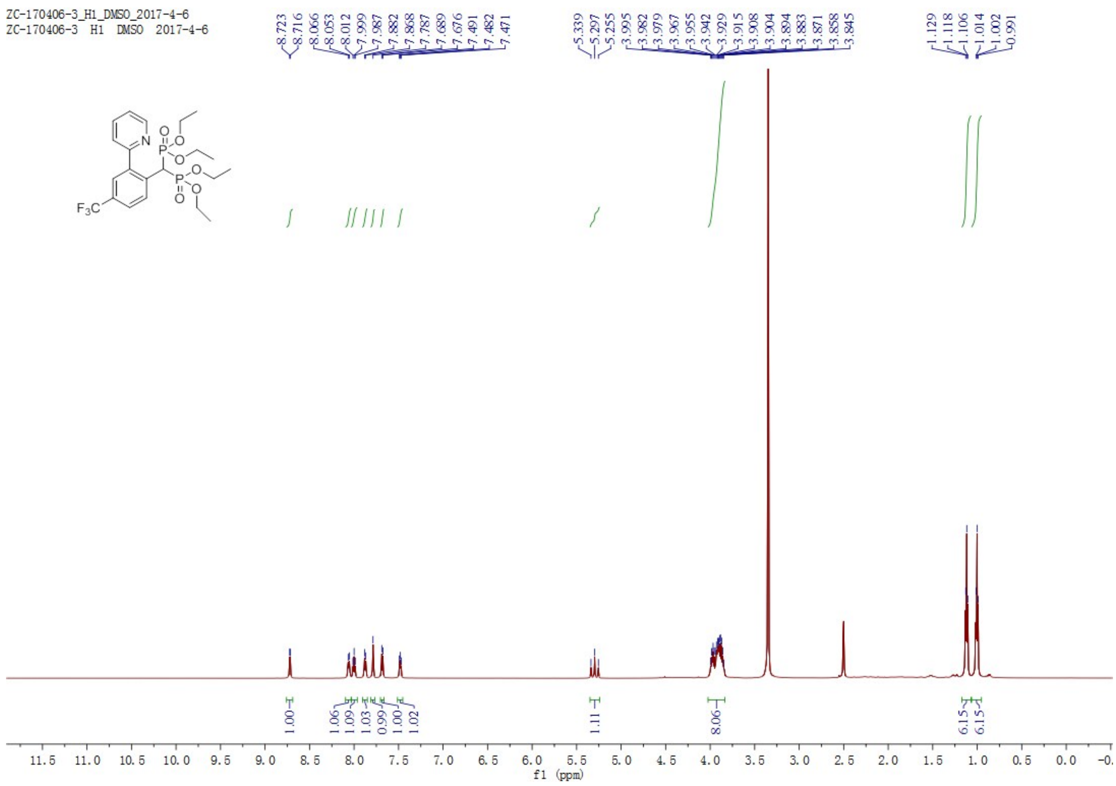
Compound **3ga**

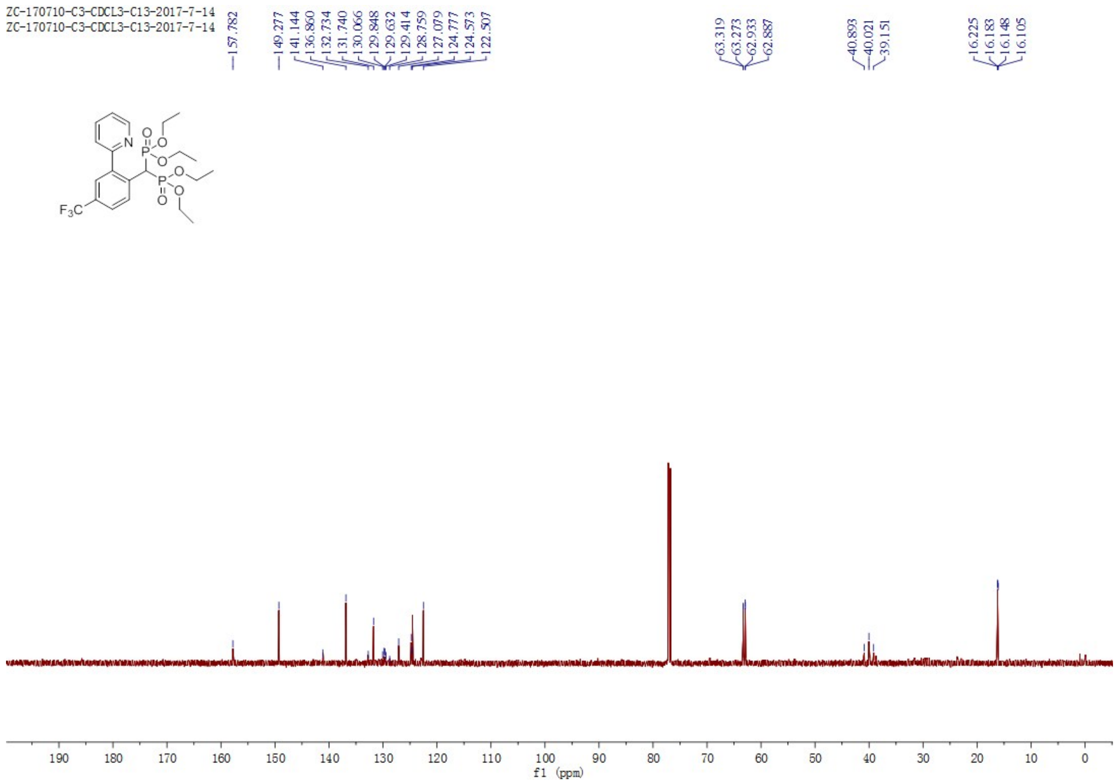


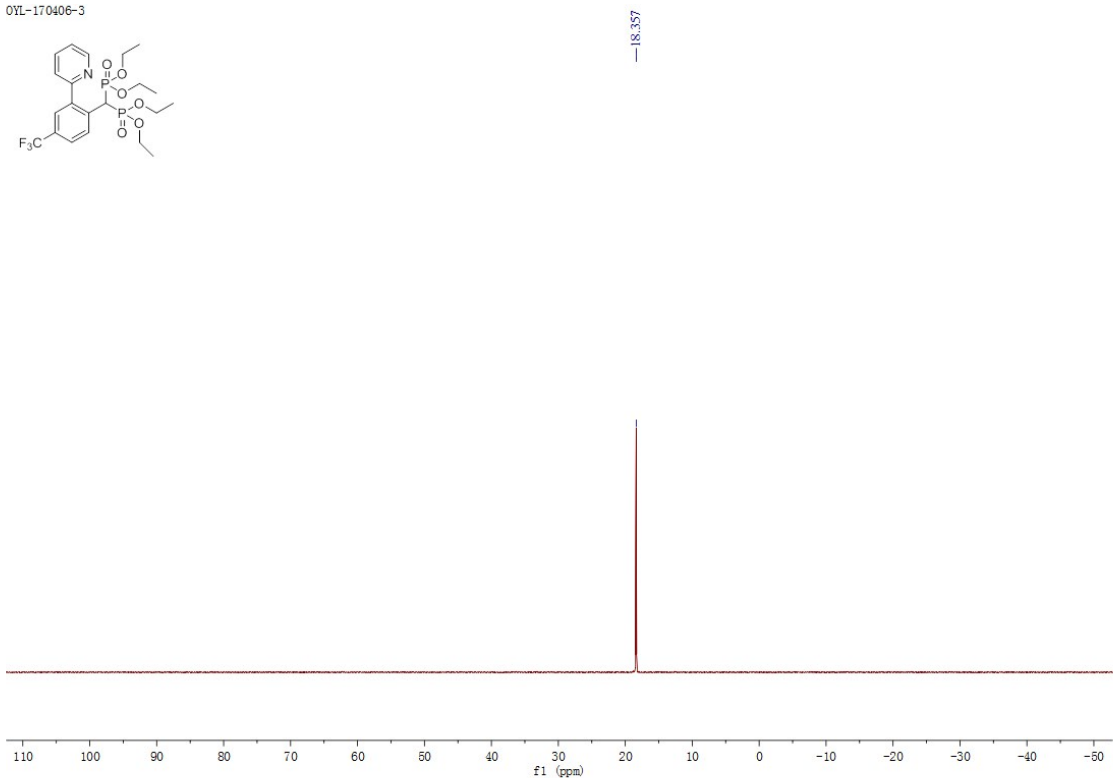




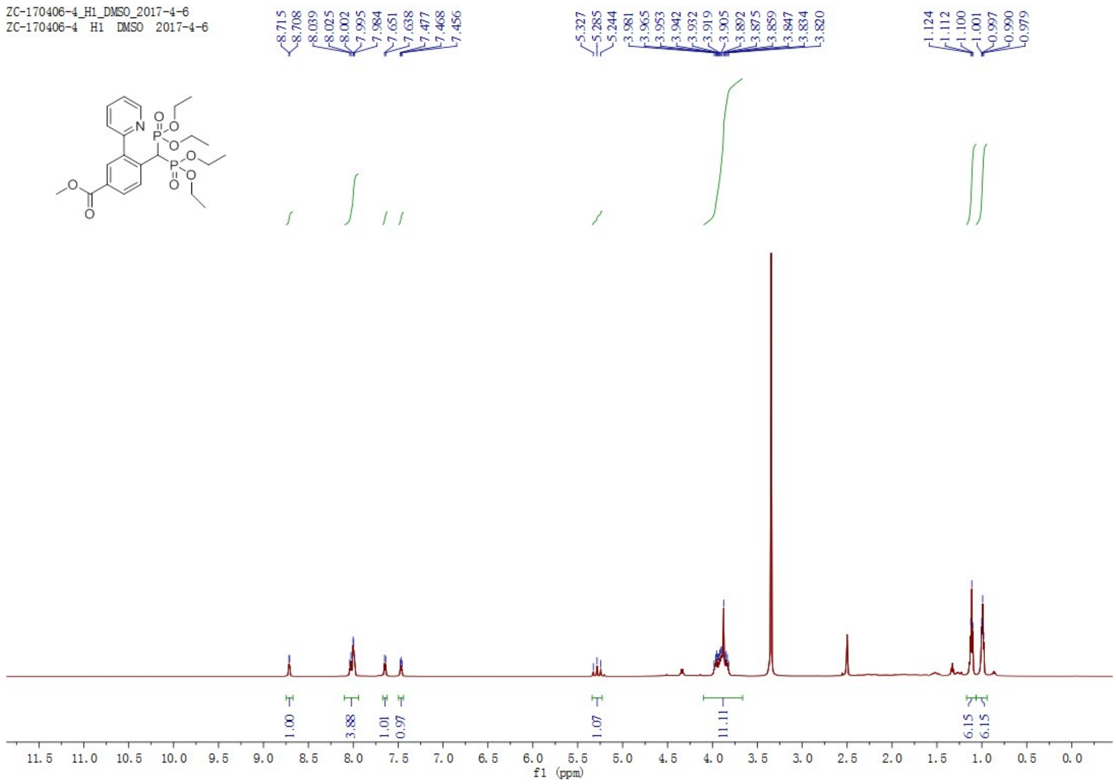
Compound **3ha**







Compound **3ia**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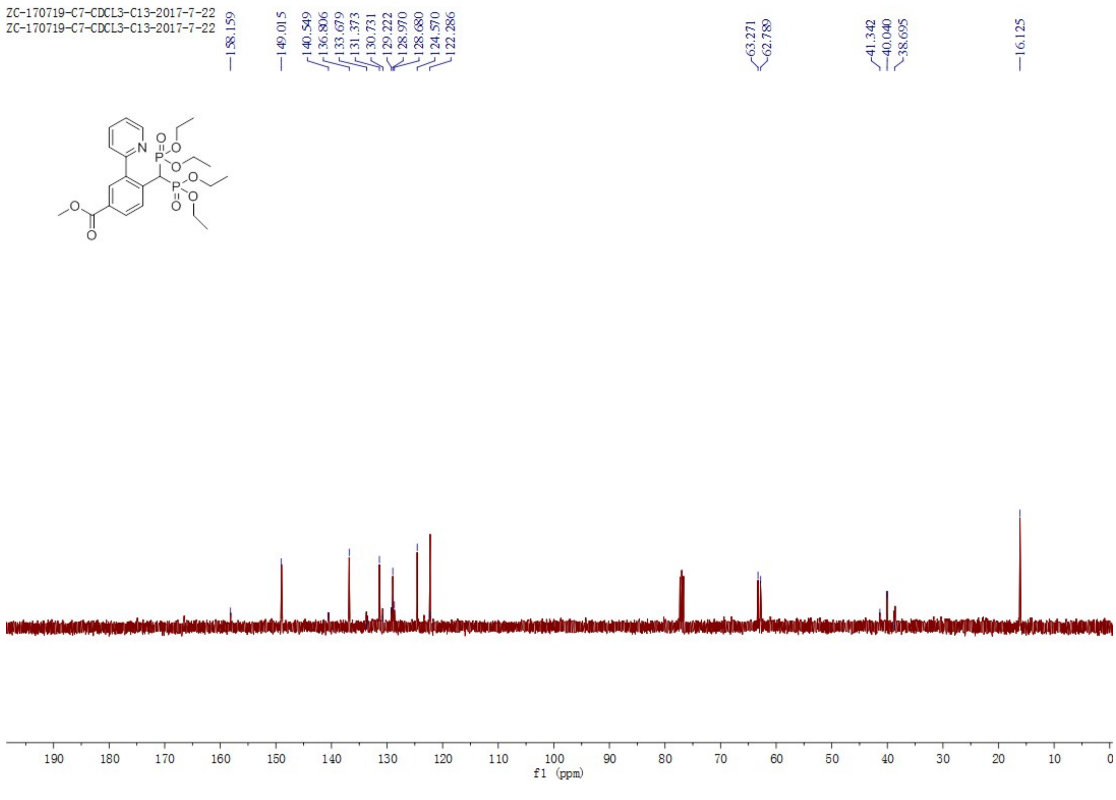
5.327 5.285 5.244 3.981 3.965 3.953 3.942 3.932 3.919 3.905 3.892 3.875 3.859 3.847 3.834 3.820
1.124 1.112 1.100 1.001 0.997 0.990 0.979
N
O
P
O
O
1.00 3.88 1.01 0.97 1.07 11.11 6.15 6.15
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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63.271 62.789
41.342 40.040 38.695
16.125
N
O
P
O
O
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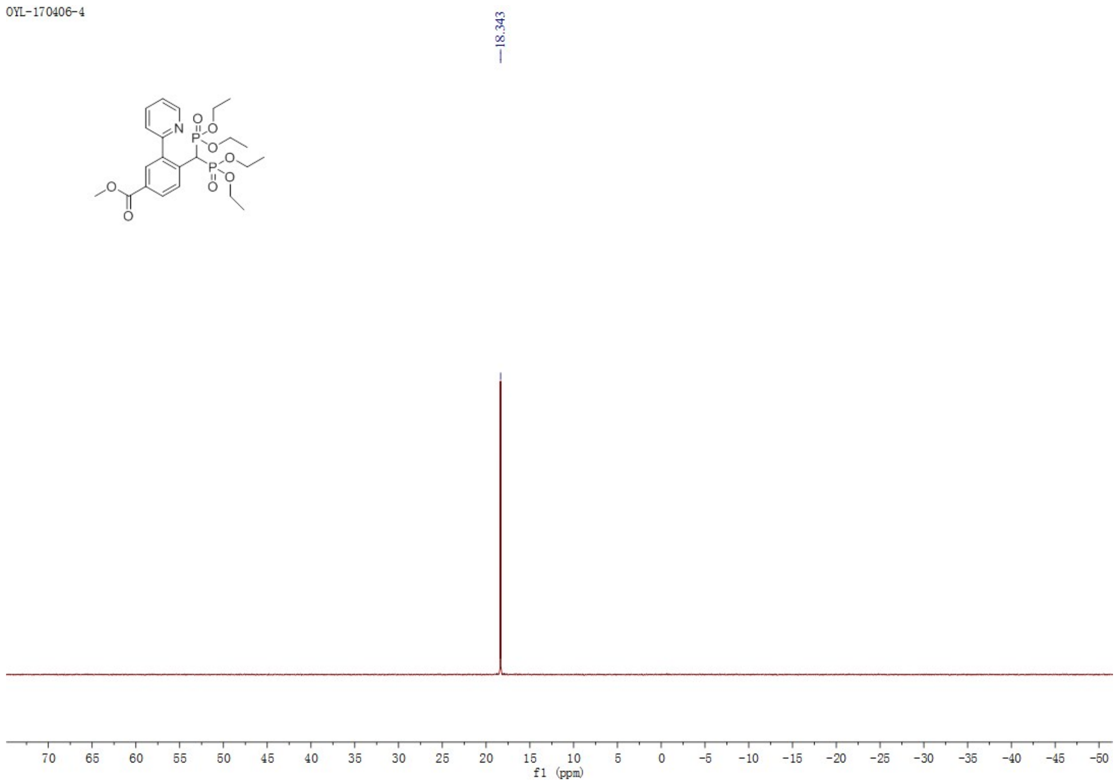
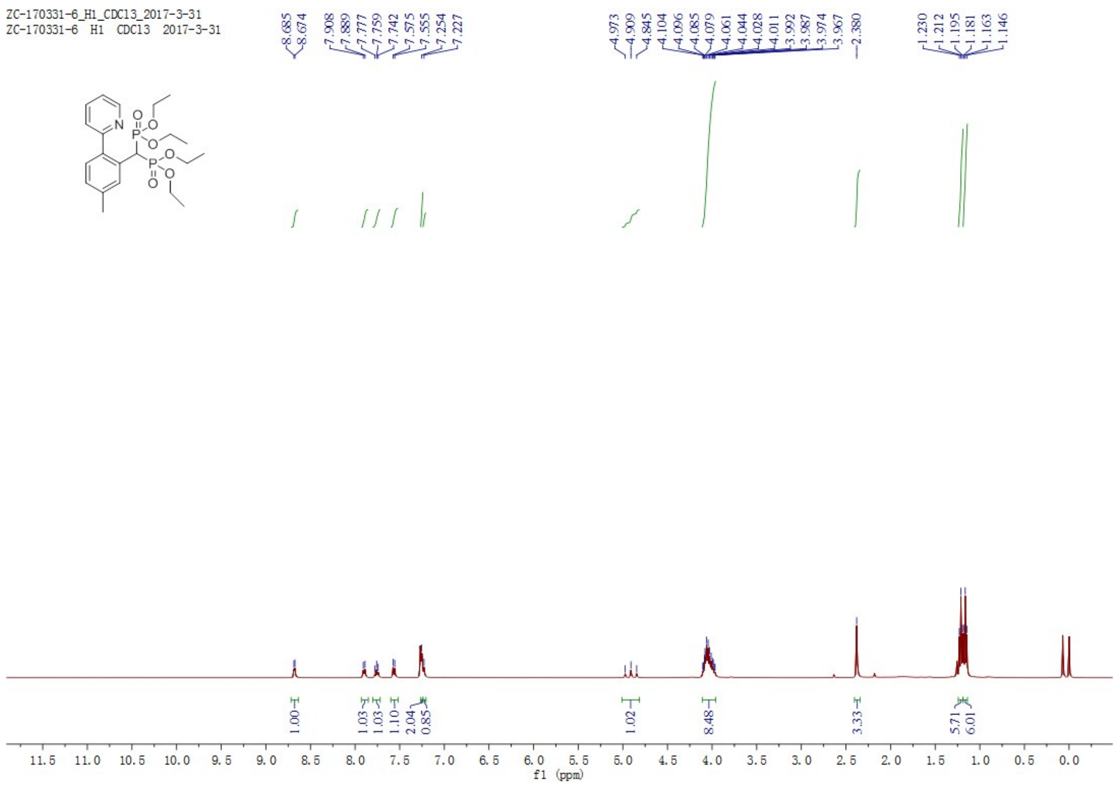
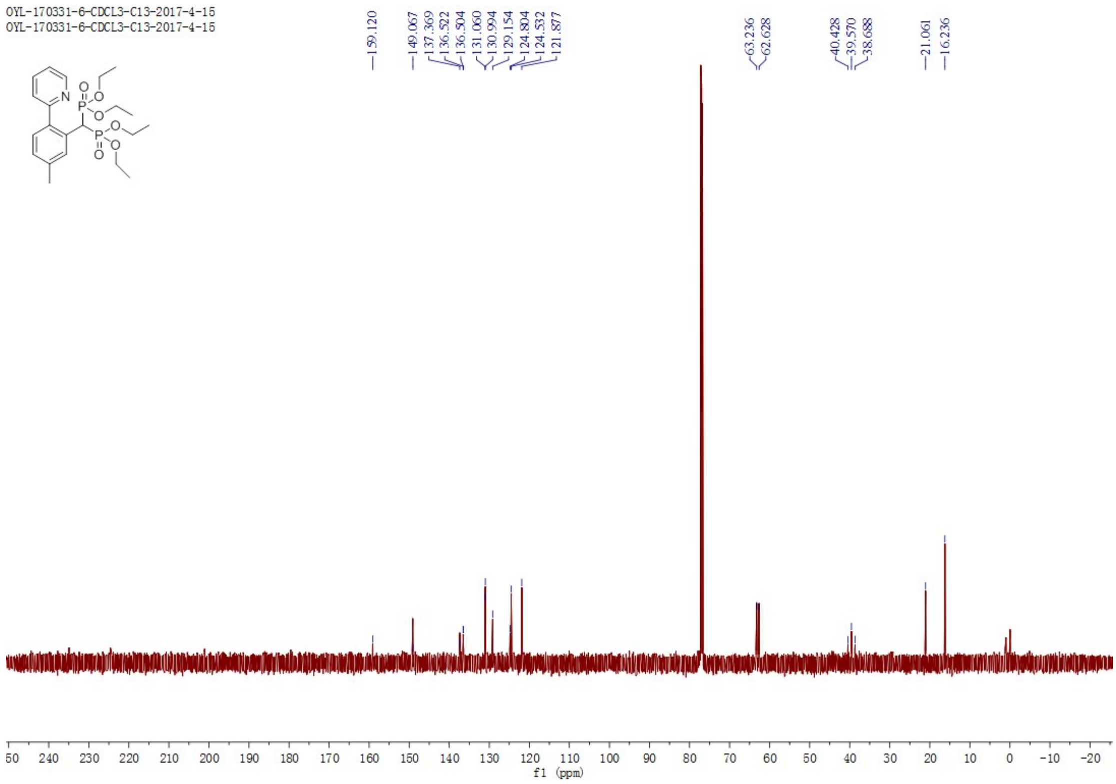
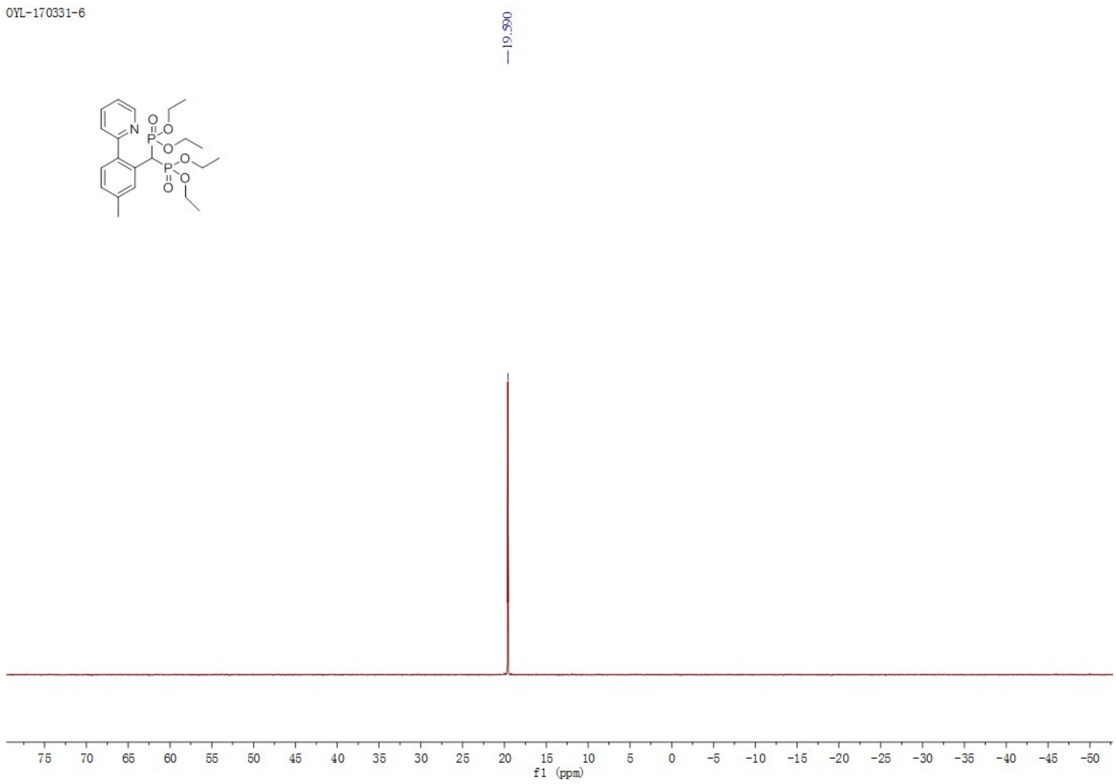
f1 (ppm)



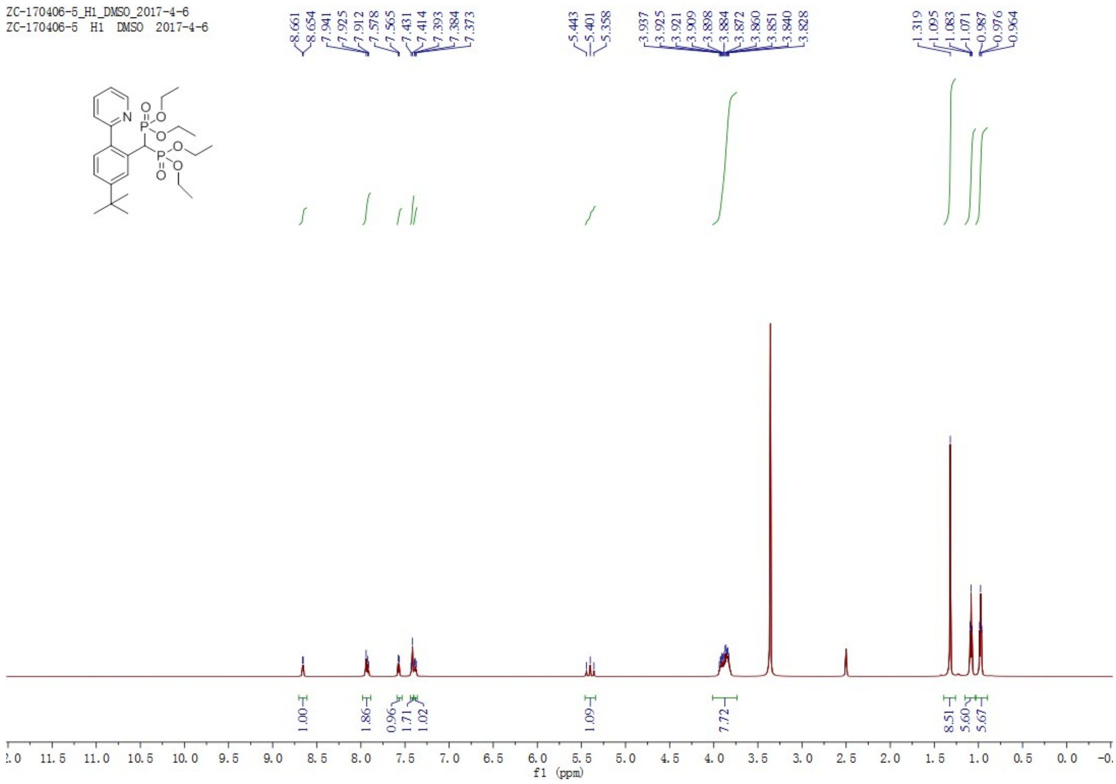
Compound **3ja**







Compound **3ka**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ZC-170406-5 H1 DMSO 2017-4-6
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5.443 5.401 5.358
3.937 3.925 3.921 3.909 3.898 3.884 3.872 3.860 3.851 3.840 3.828
1.319 1.095 1.083 1.071 0.987 0.976 0.964
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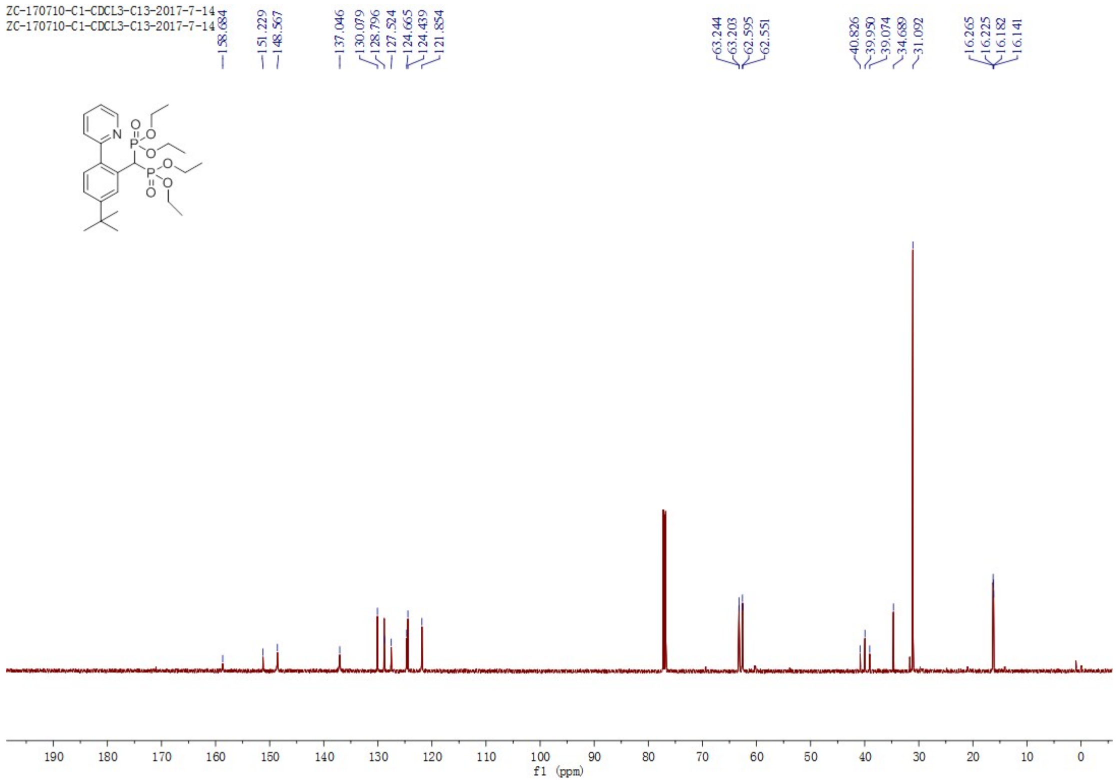
f1 (ppm)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ZC-170710-C1-CDCL3-C13-2017-7-14
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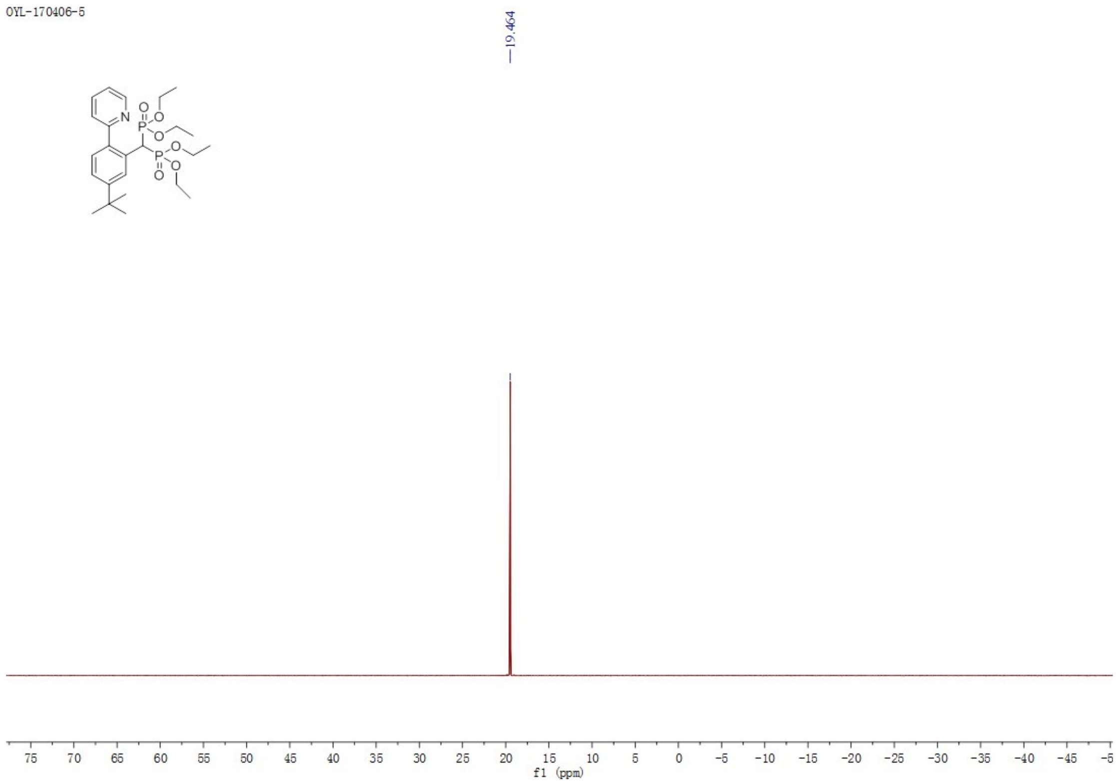
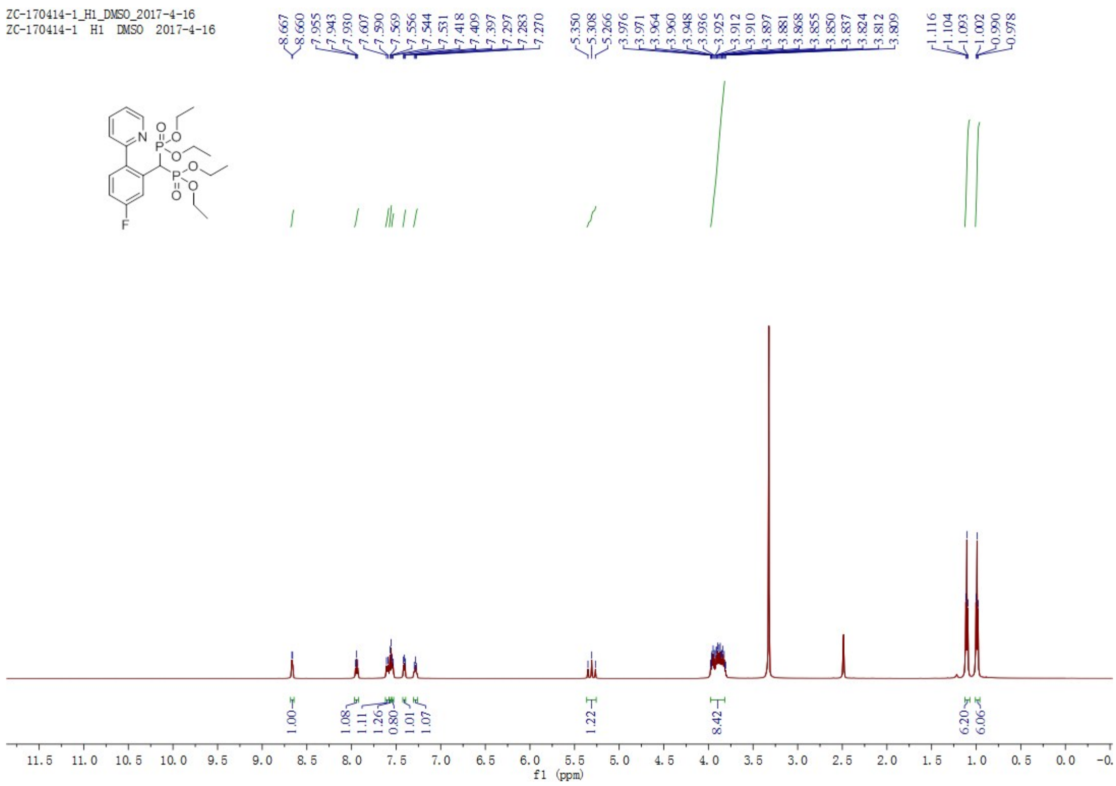
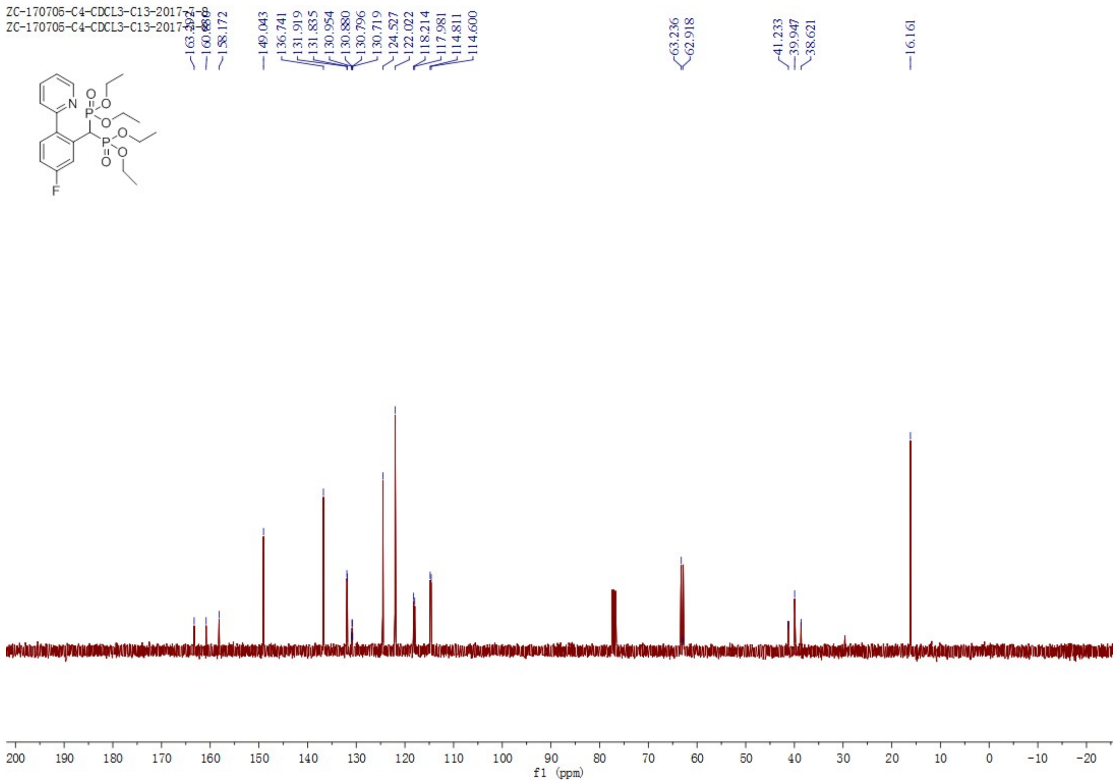
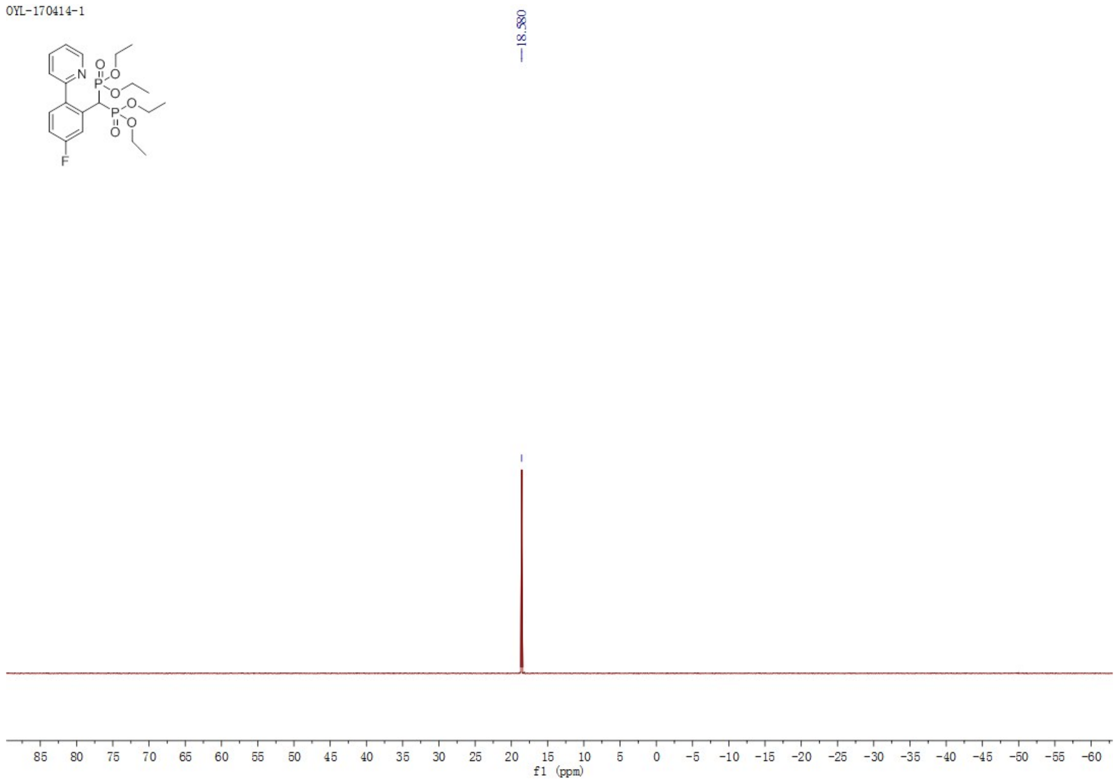
16.265 16.225 16.182 16.141
f1 (ppm)



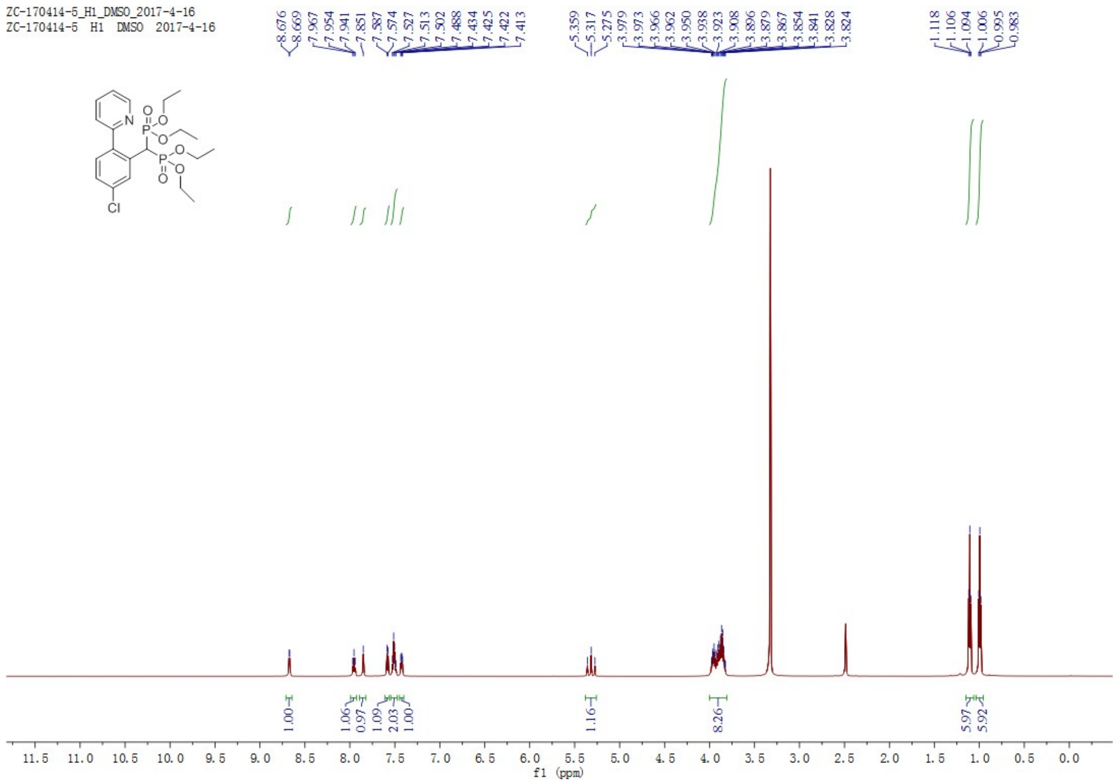
Compound **3la**







Compound **3ma**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7.941
7.851
7.587
7.574
7.527
7.513
7.502
7.488
7.434
7.425
7.422
7.413
5.359
5.317
5.275
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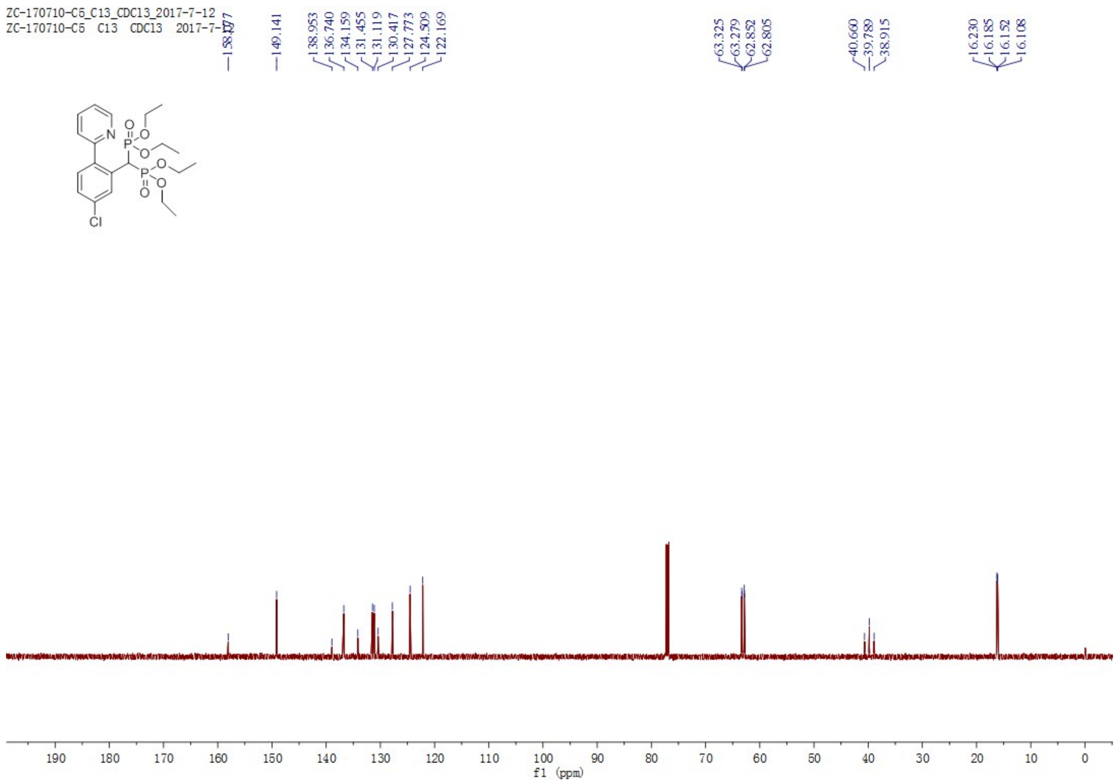
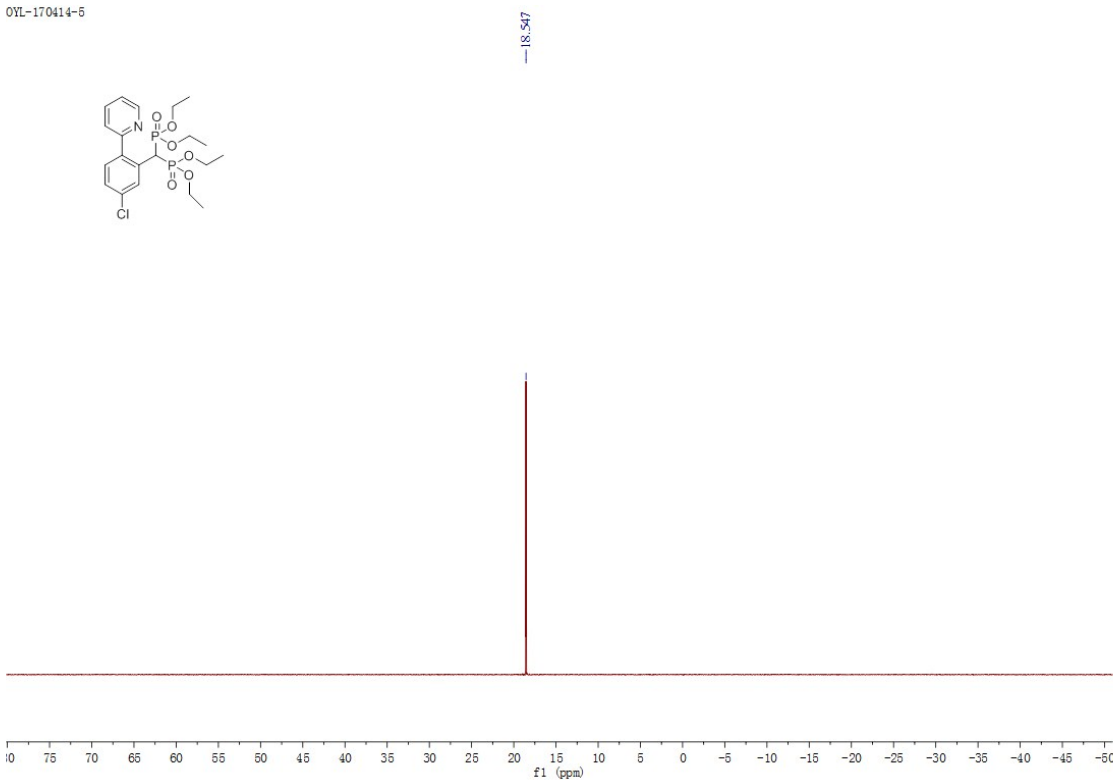
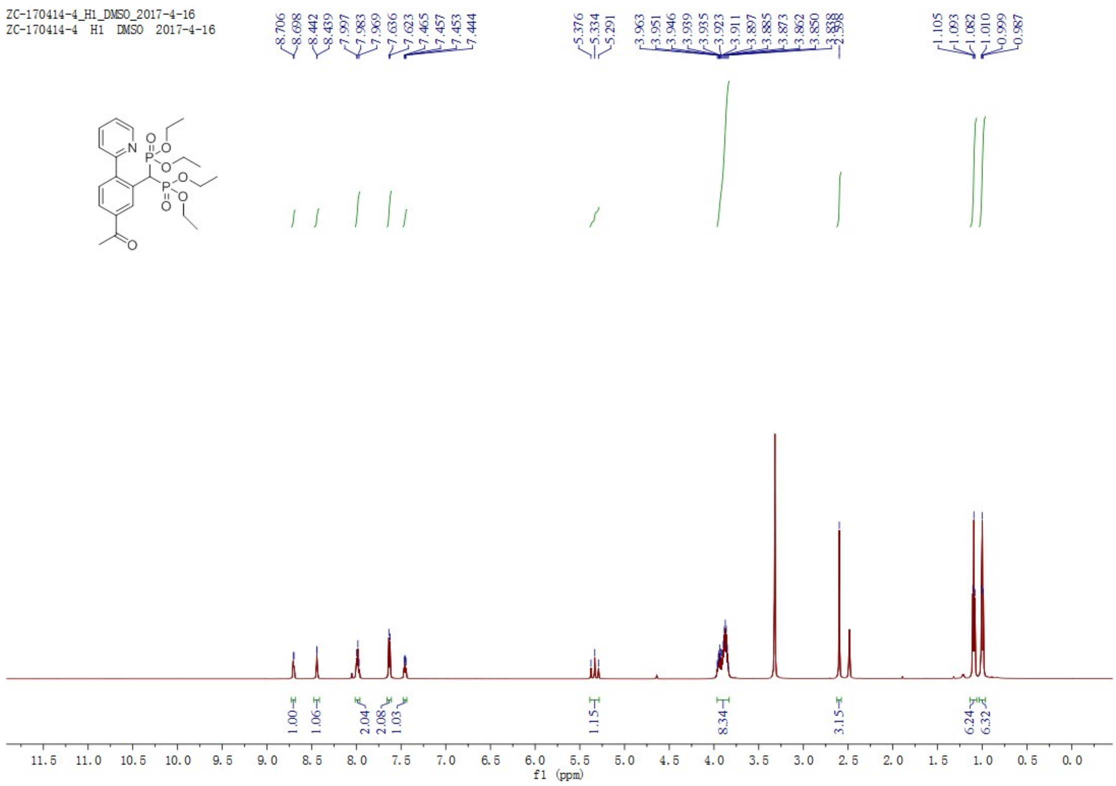
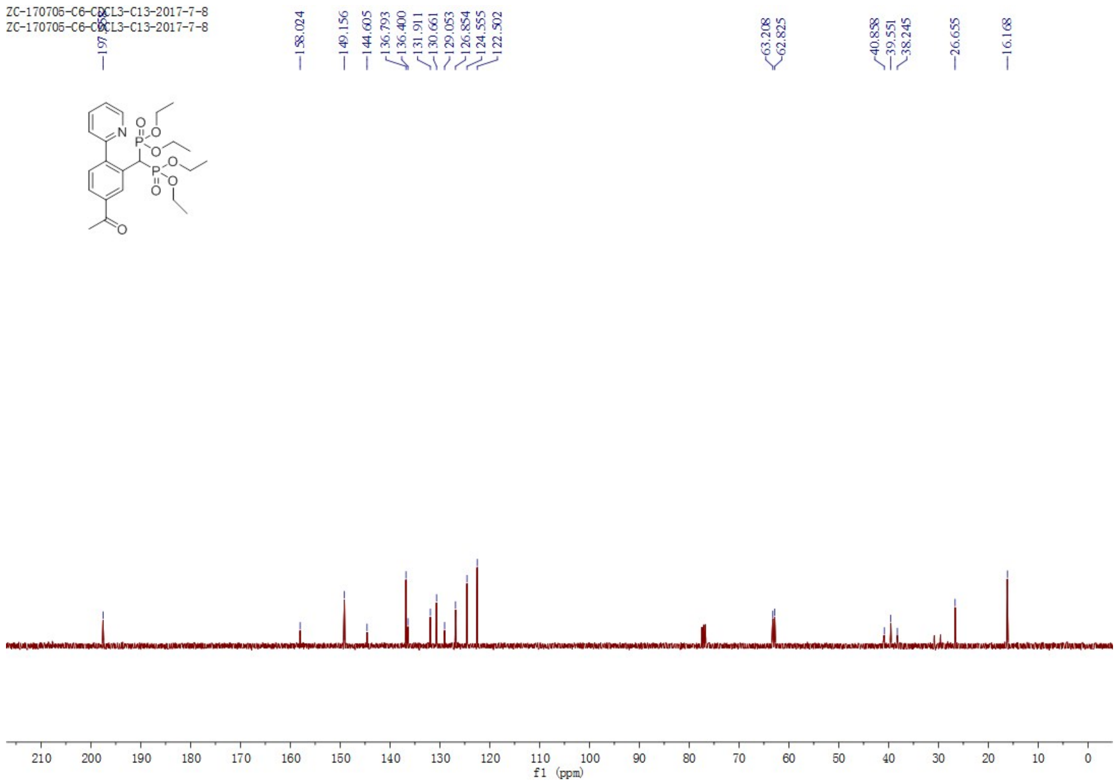
3.973
3.966
3.962
3.950
3.938
3.923
3.908
3.896
3.879
3.867
3.854
3.841
3.828
3.824
1.118
1.106
1.094
1.006
0.995
0.983
N
O
P
Cl
1.00
1.06
0.97
1.09
2.03
1.00
1.16
8.26
5.97
5.92
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

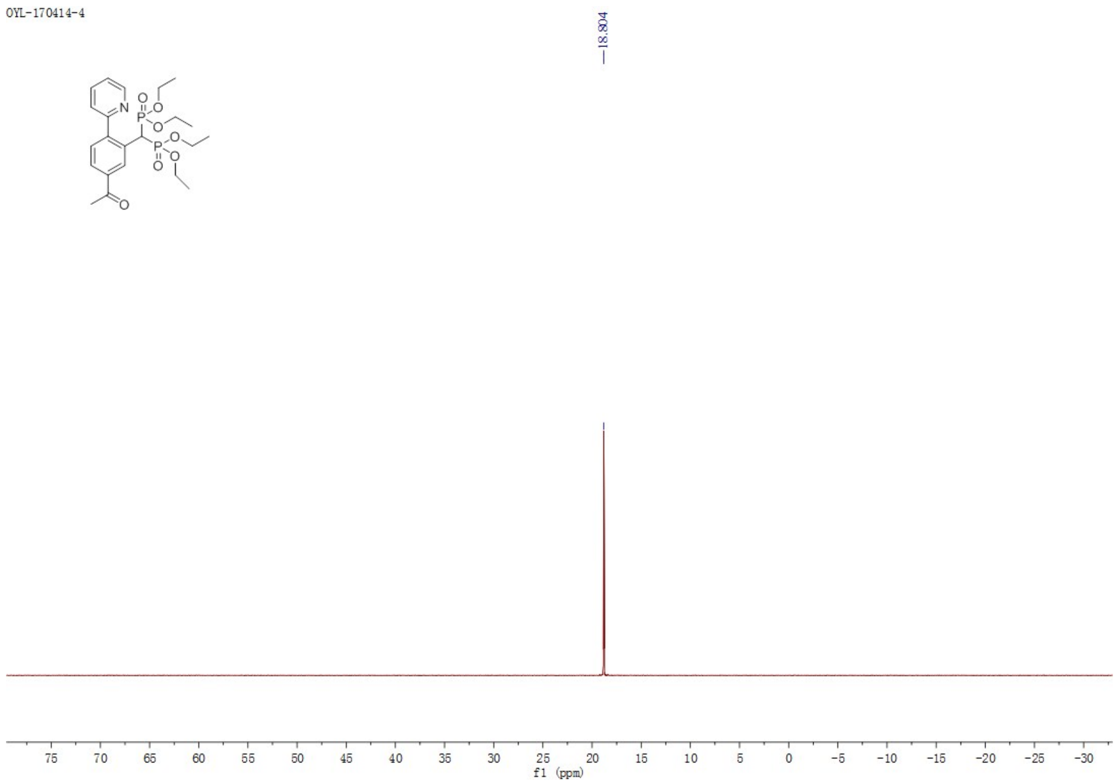

ZC-170710-C5_C13_CDCl3_2017-7-12
ZC-170710-C5 C13 CDCl3 2017-7-12
149.141
138.953
136.740
134.159
131.455
131.119
130.417
127.773
124.509
122.169
63.325
63.279
62.852
62.805
40.660
39.789
38.915
16.230
16.185
16.152
16.108
N
O
P
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



Compound **3na**

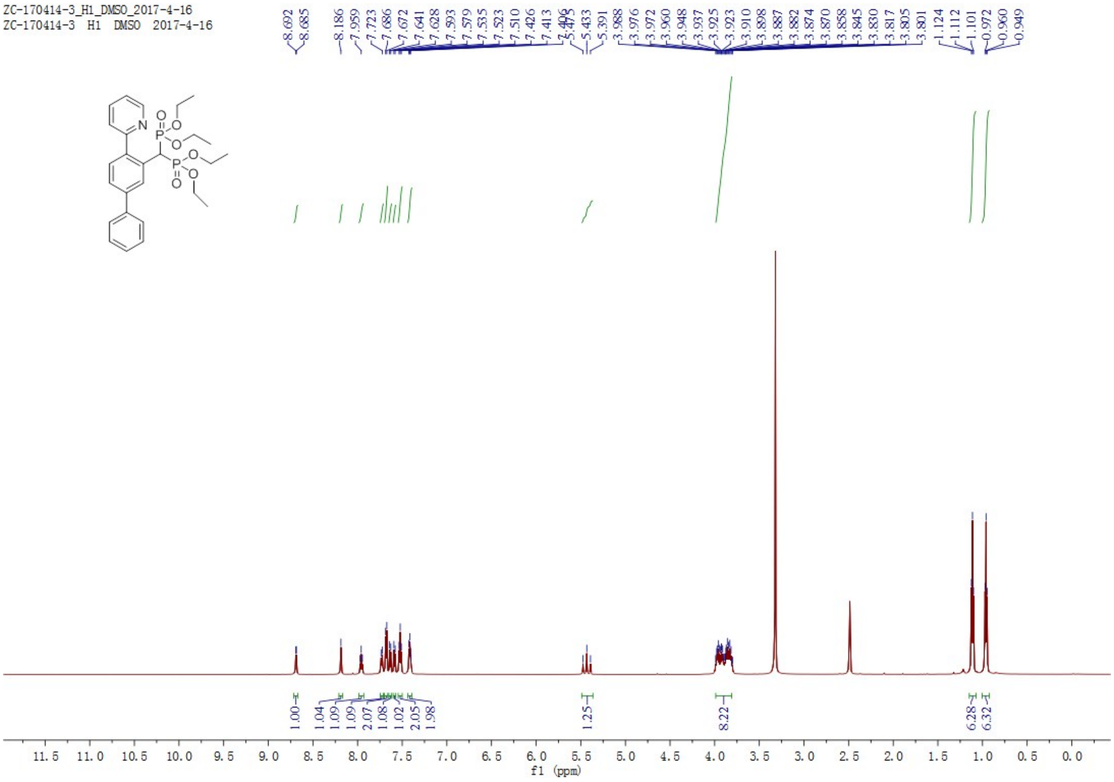




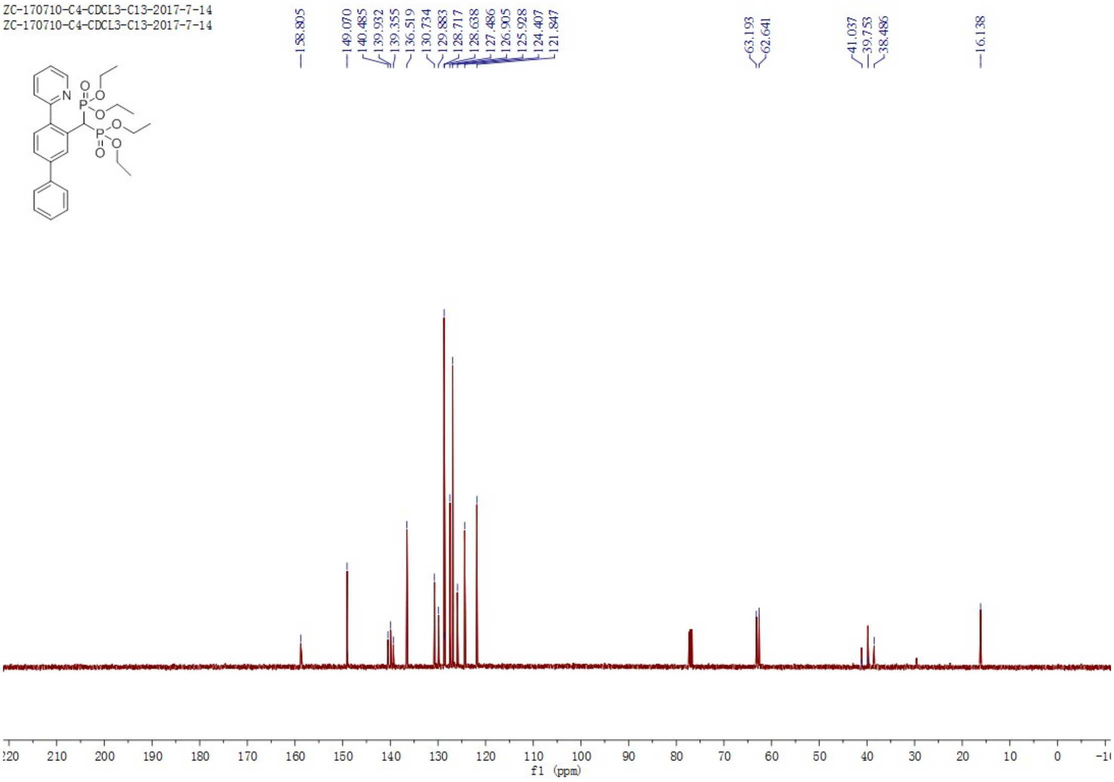


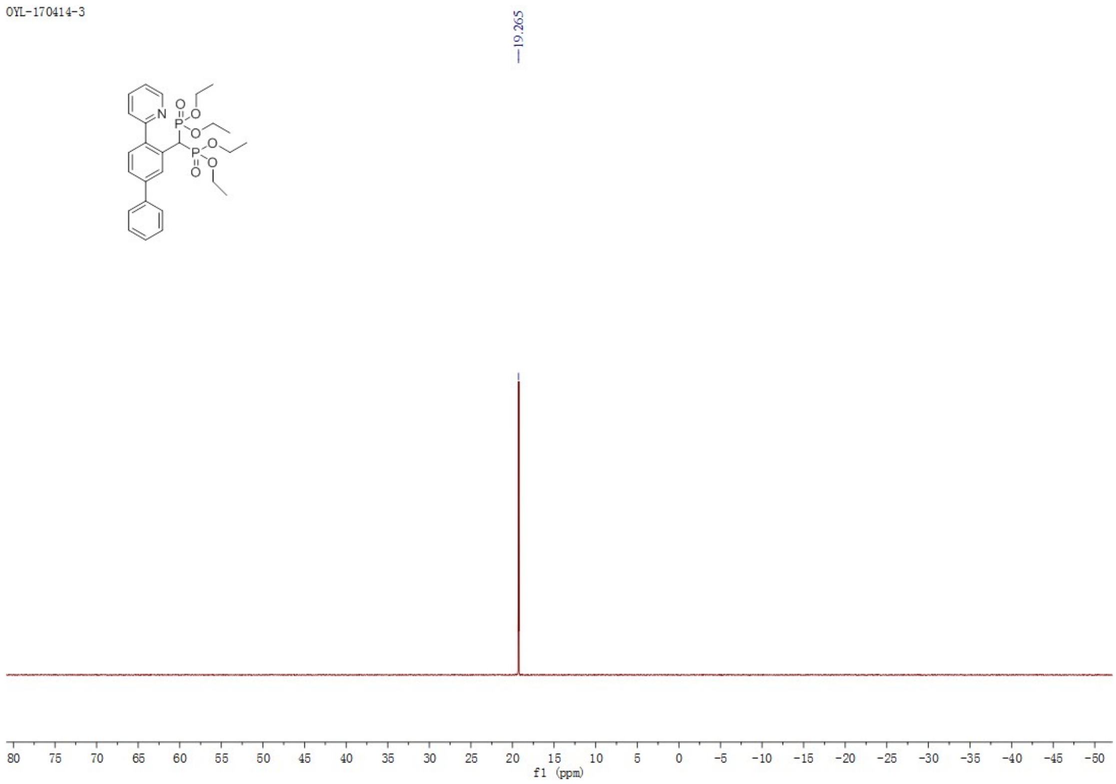
Compound **3oa**

ZC-170414-3_H1_DMSO_2017-4-16
ZC-170414-3 H1 DMSO 2017-4-16

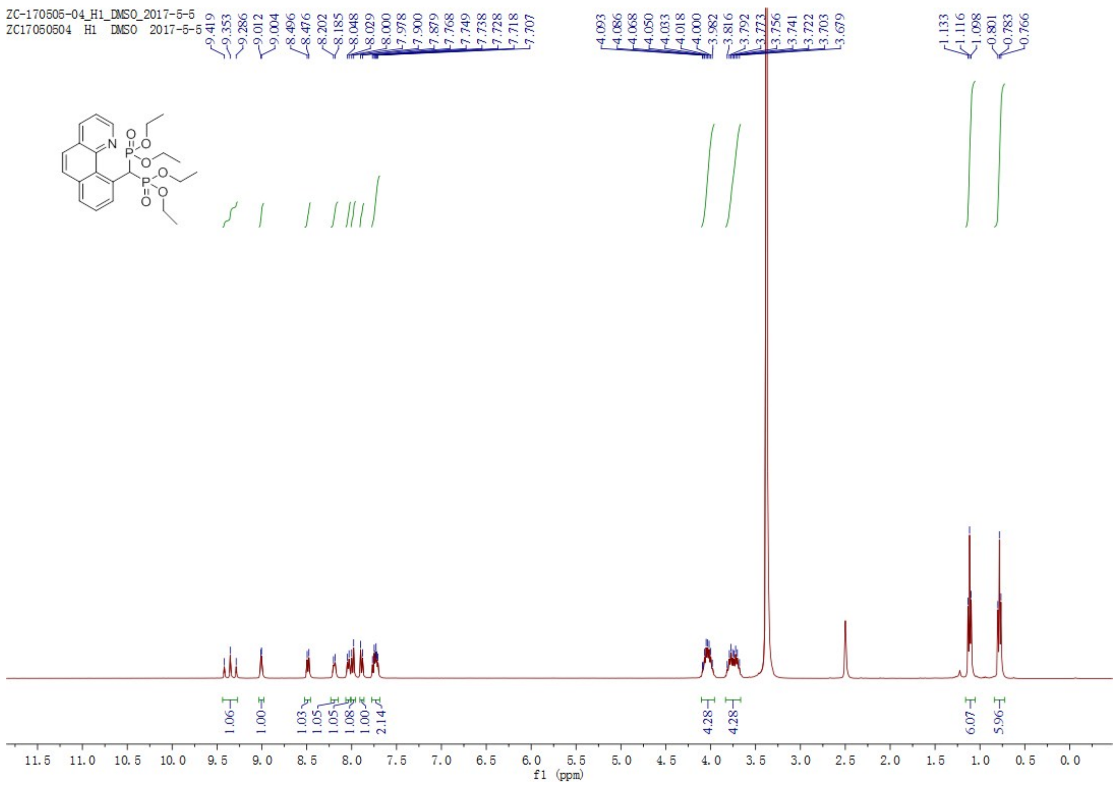


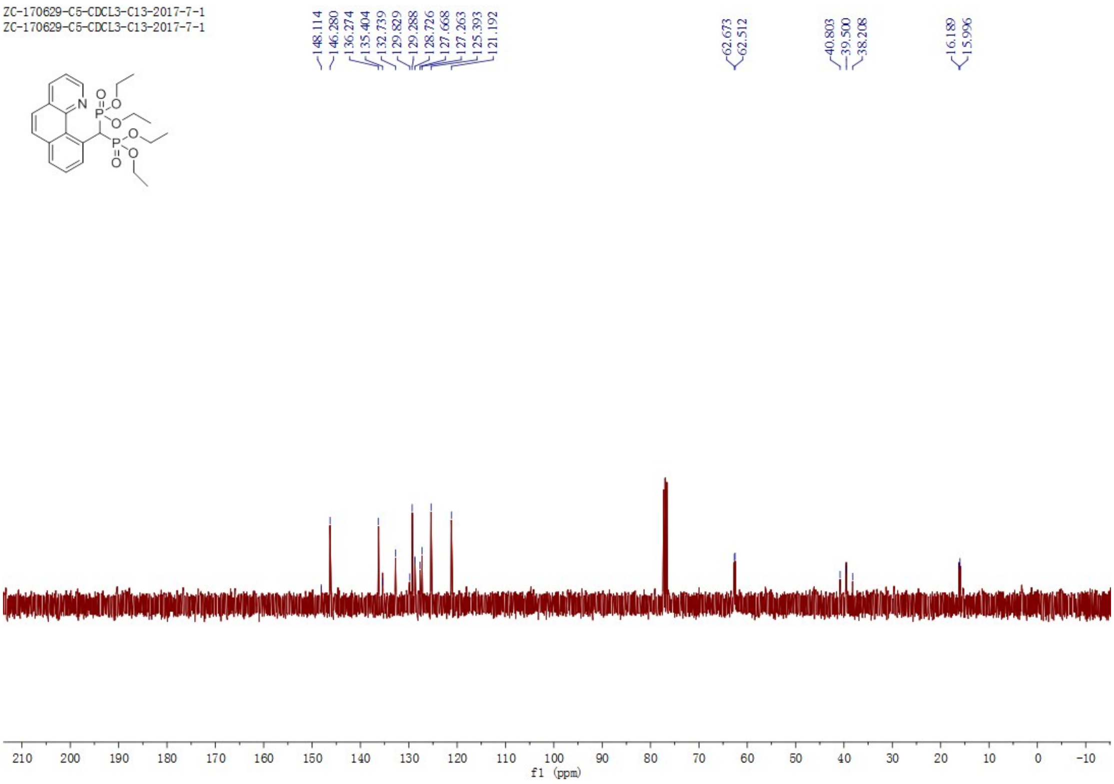
ZC-170710-C4-CDCL3-C13-2017-7-14
ZC-170710-C4-CDCL3-C13-2017-7-14

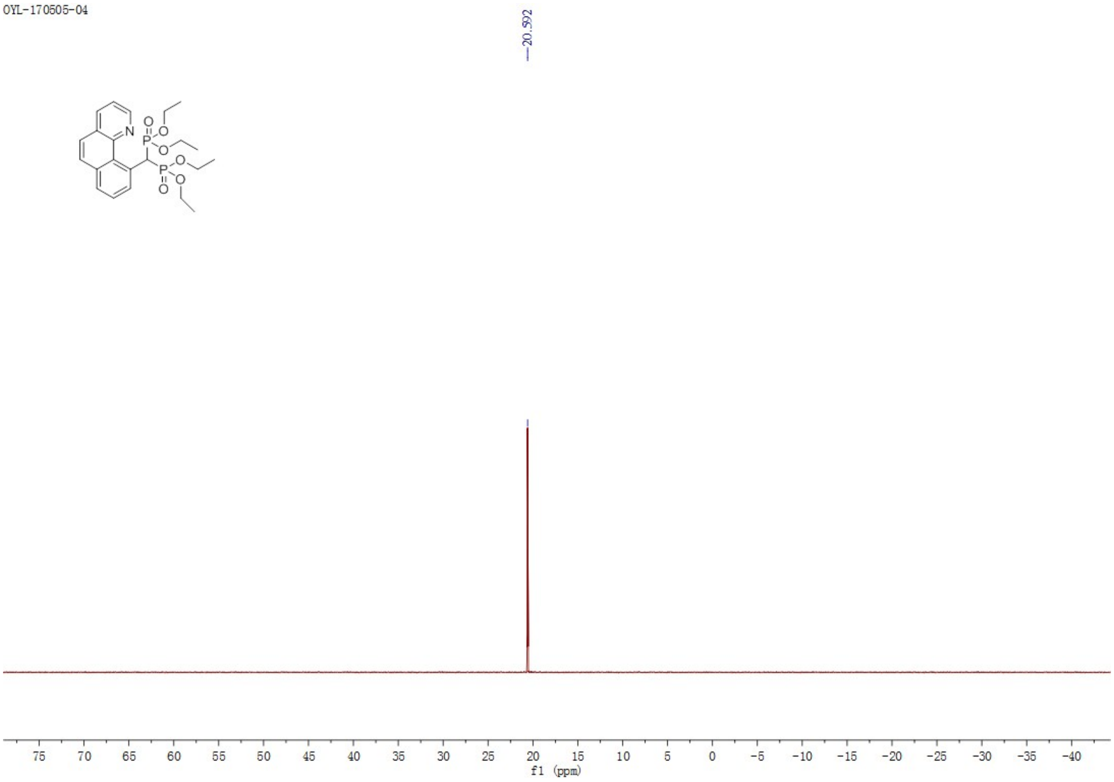




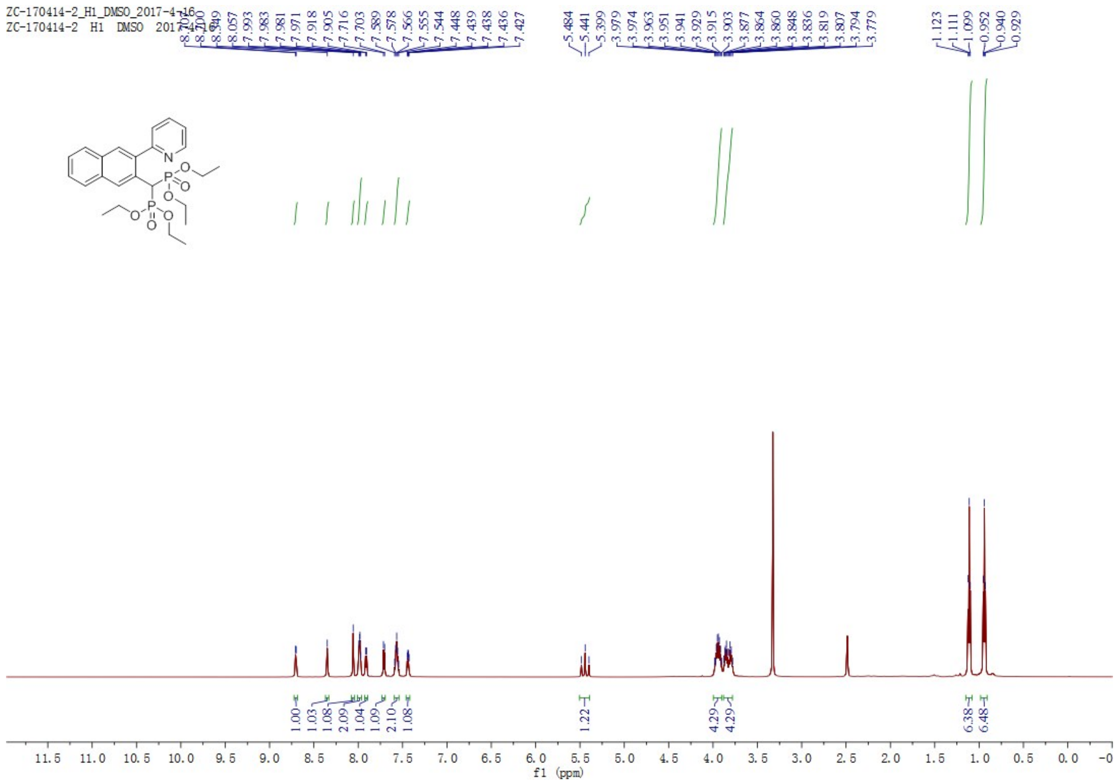
Compound **3pa**

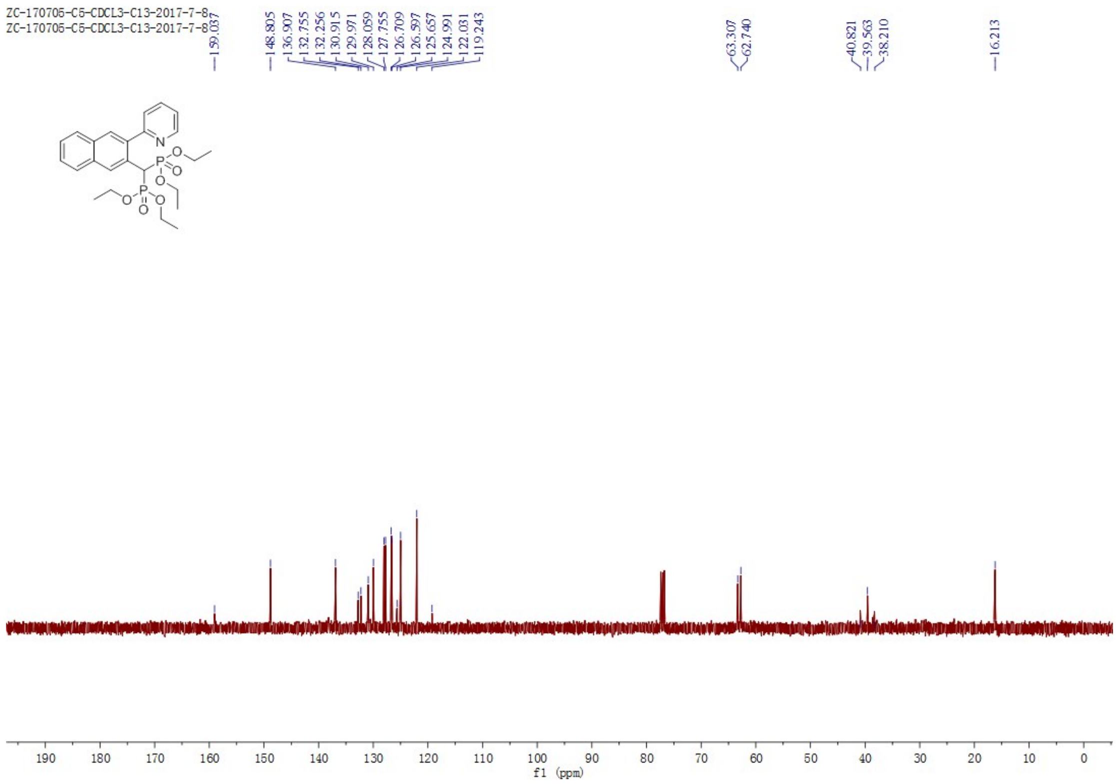


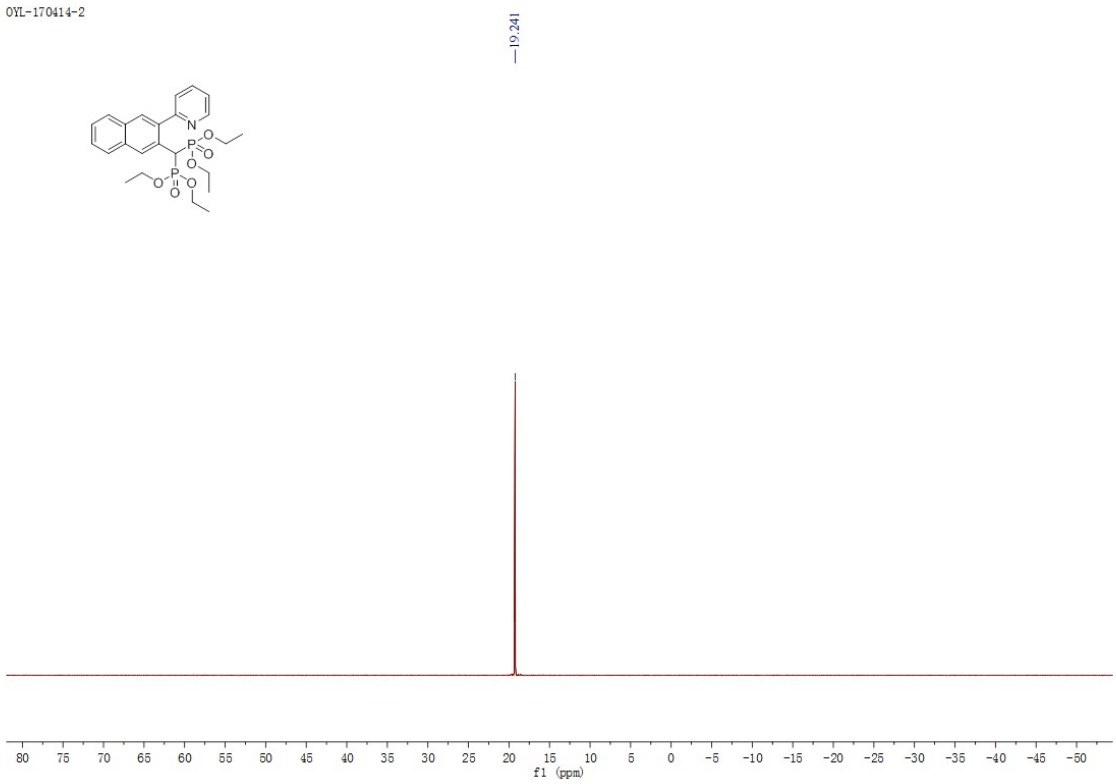




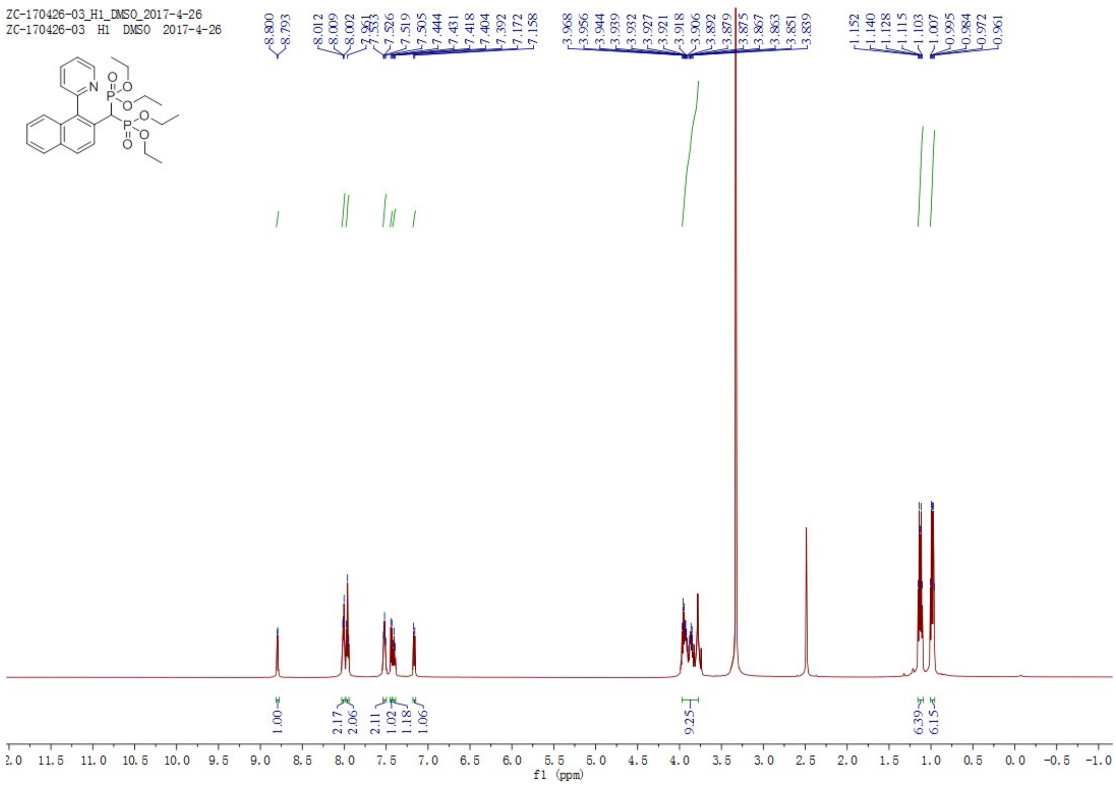
Compound **3qa**

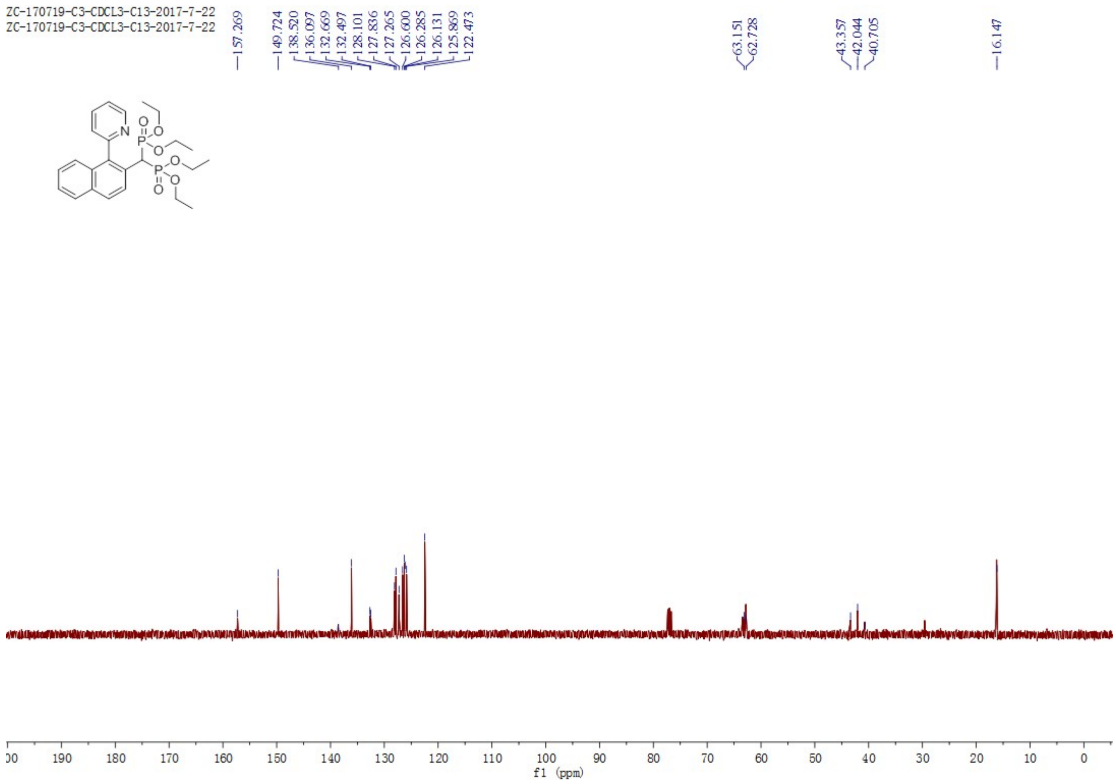

ZC-170414-2_H1_DMSO_2017-4-16
ZC-170414-2 H1 DMSO 2017-4-16
8.057 7.993 7.983 7.981 7.971 7.918 7.905 7.716 7.703 7.589 7.578 7.566 7.555 7.544 7.448 7.439 7.438 7.436 7.427
5.484 5.441 5.399
3.979 3.974 3.963 3.951 3.941 3.929 3.915 3.903 3.877 3.864 3.860 3.848 3.836 3.819 3.807 3.794 3.779
1.123 1.111 1.099 0.952 0.940 0.929
N
P
O
1.00 1.03 1.08 2.09 1.04 1.09 2.10 1.08
1.22
4.29 4.29
6.38 6.48
f1 (ppm)

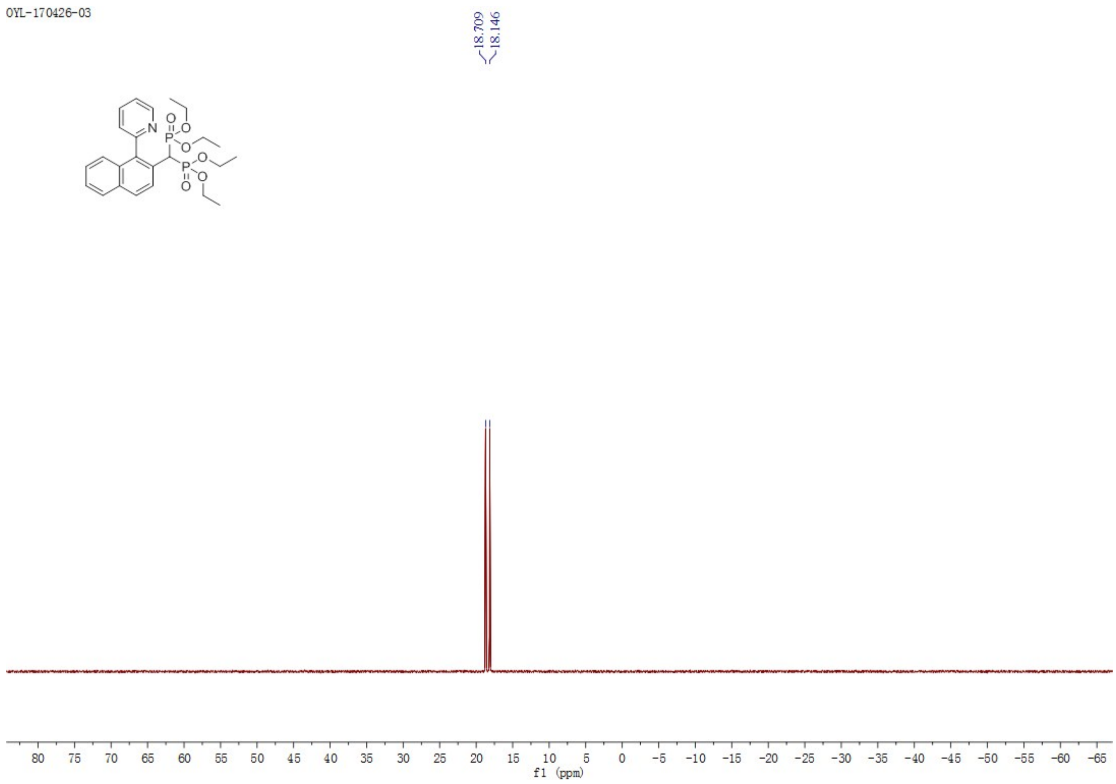

ZC-170705-C5-CDCL3-C13-2017-7-8
ZC-170705-C5-CDCL3-C13-2017-7-8
159.037
148.805 136.907 132.755 132.256 130.915 129.971 128.059 127.755 126.709 126.597 125.657 124.991 122.031 119.243
63.307 62.740
40.821 39.563 38.210
16.213
N
P
O
f1 (ppm)



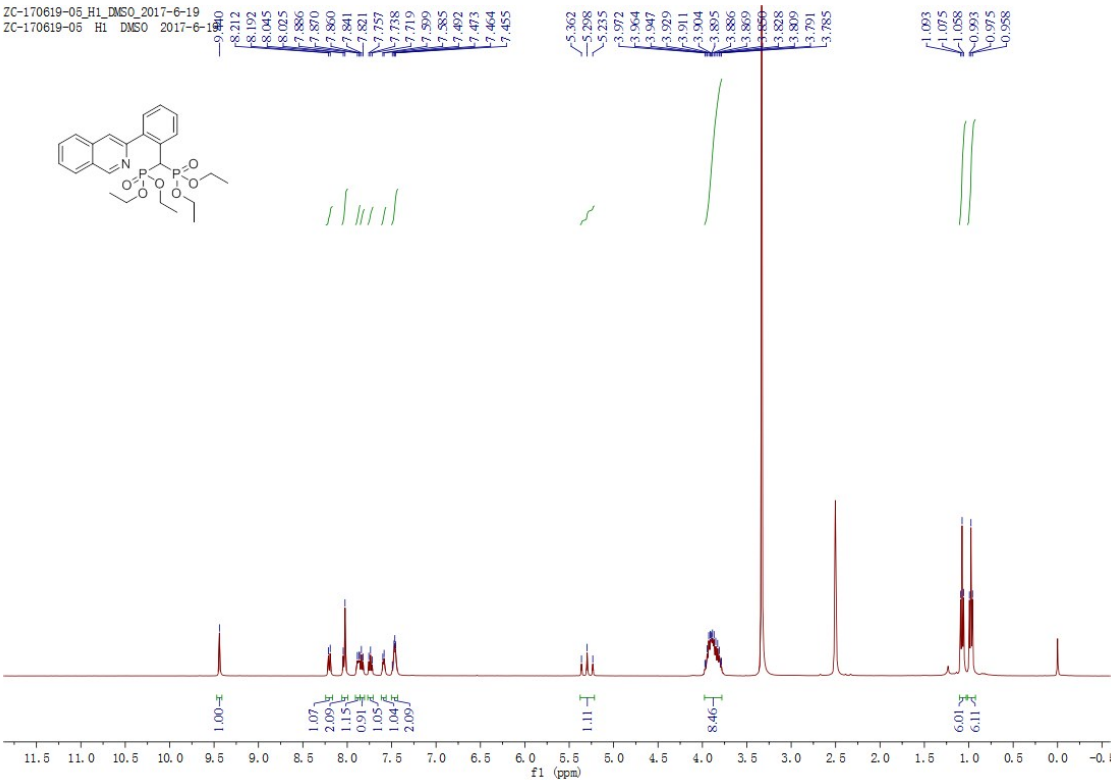
Compound **3ra**

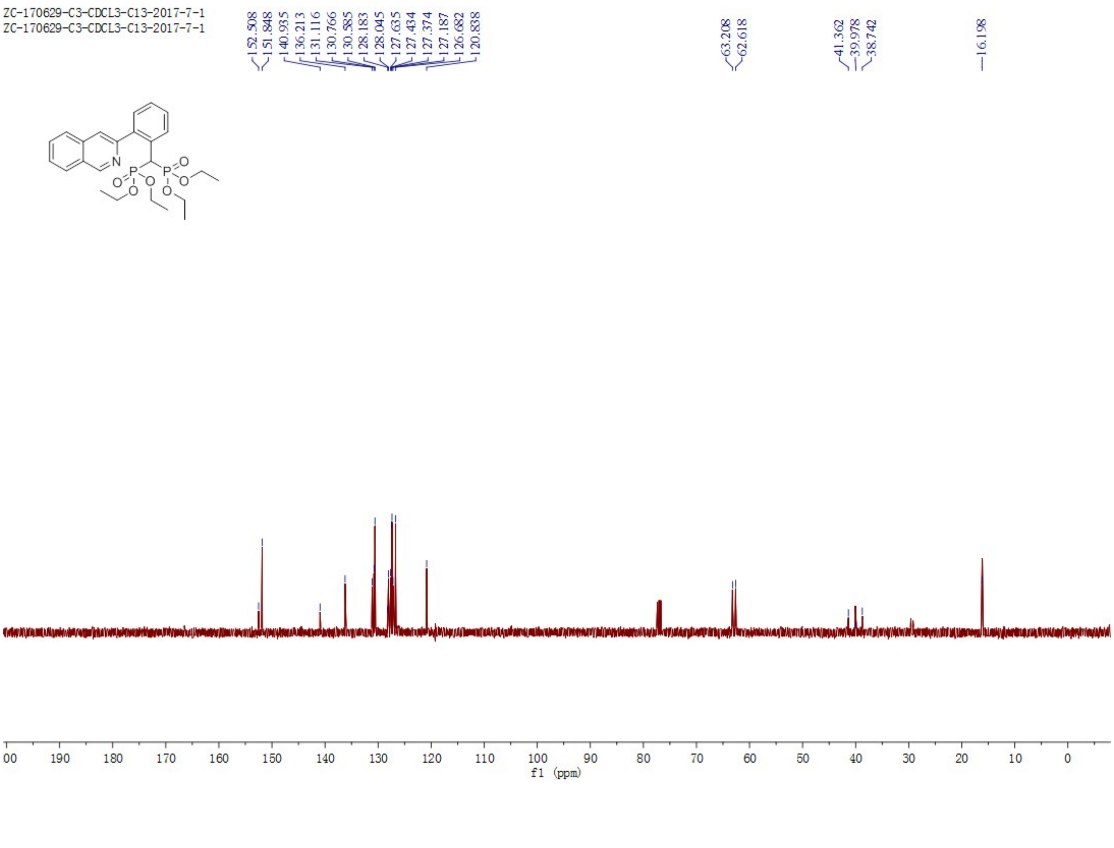


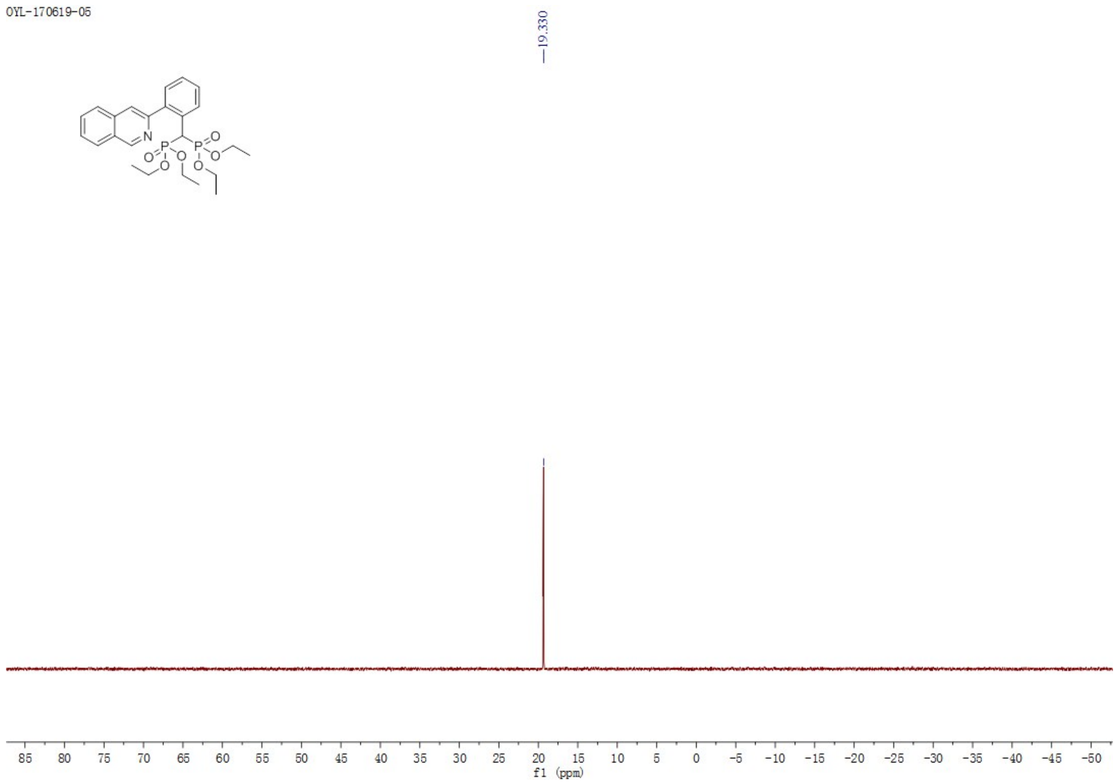




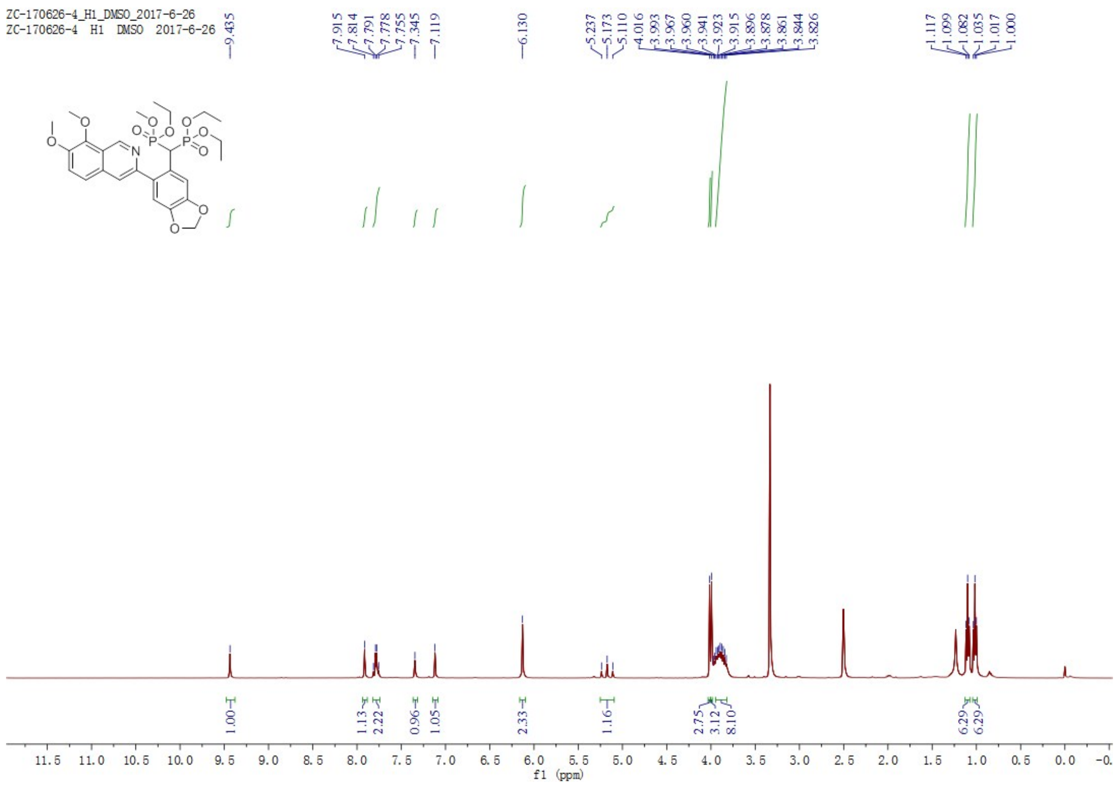
Compound **3sa**

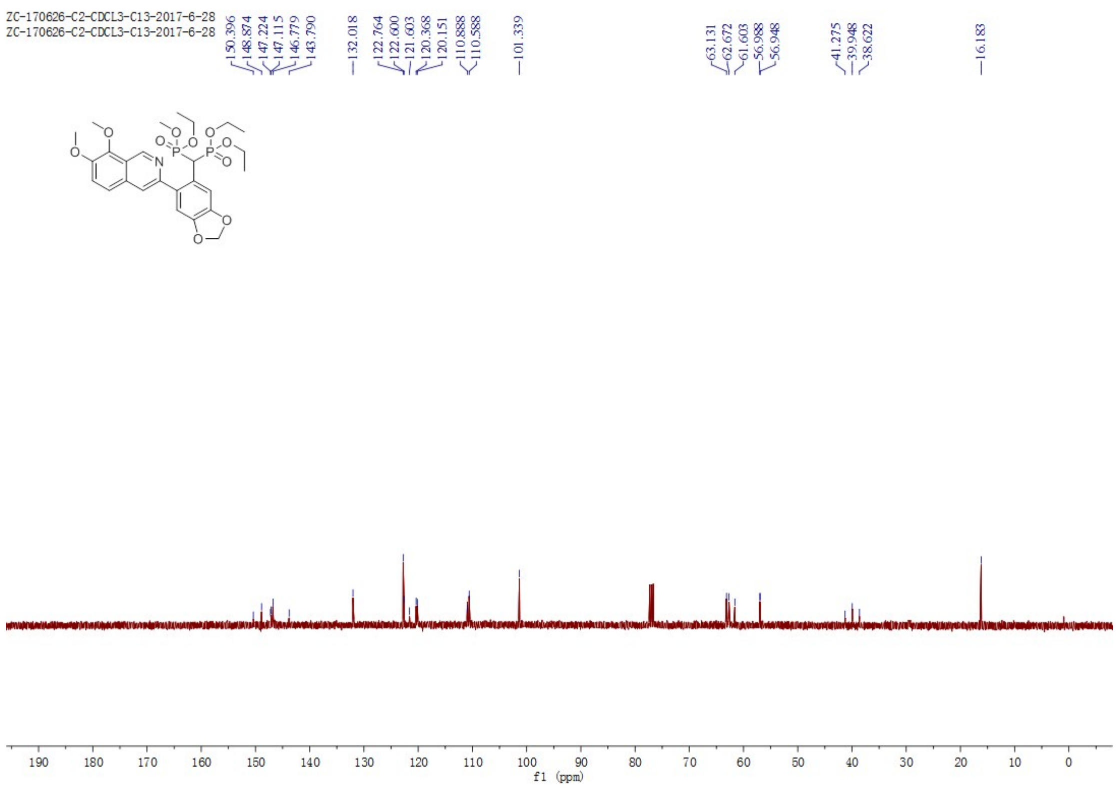

ZC-170619-05_H1_DMSO_2017-6-19
ZC-170619-05 H1 DMSO 2017-6-19
9.440
8.212
8.192
8.045
8.025
7.886
7.870
7.860
7.841
7.821
7.757
7.738
7.719
7.599
7.585
7.492
7.473
7.464
7.455
5.362
5.298
5.235
3.972
3.964
3.947
3.929
3.911
3.904
3.895
3.886
3.869
3.828
3.809
3.791
3.785
1.093
1.075
1.058
0.993
0.975
0.958
N
O
P
1.00
1.07
2.09
1.15
0.91
1.05
1.04
2.09
1.11
8.46
6.01
6.11
f1 (ppm)

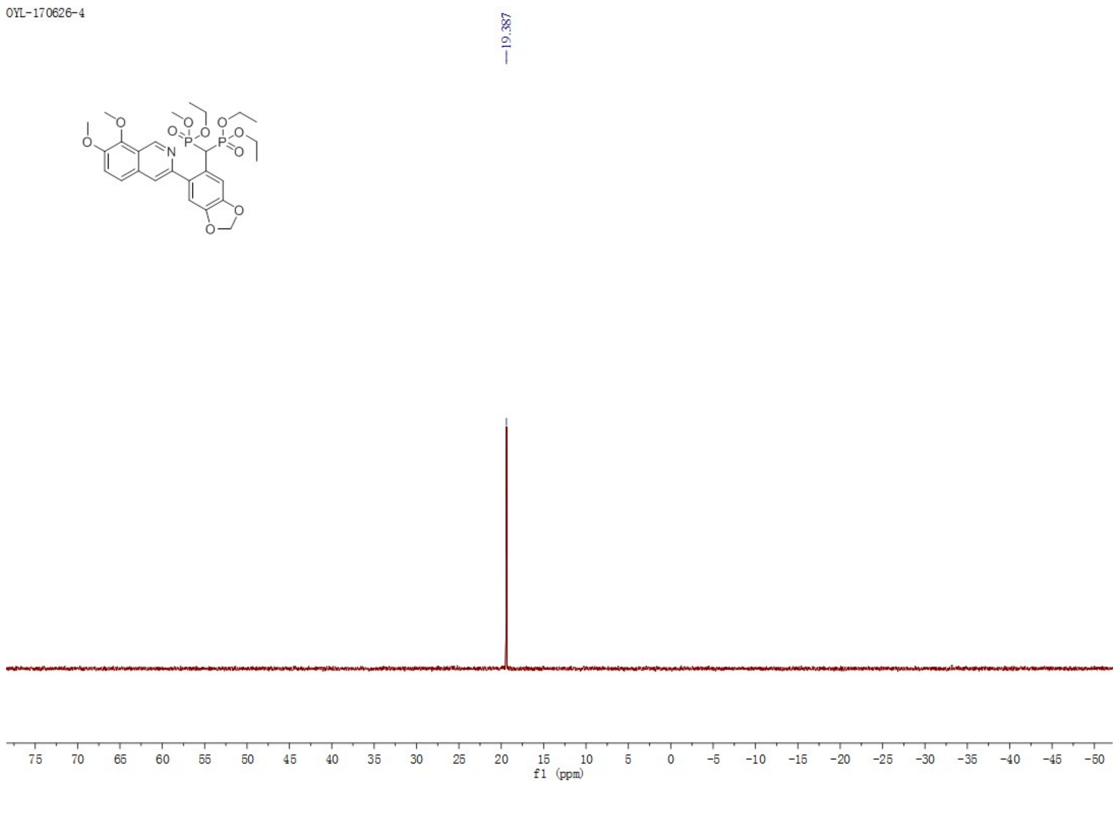

ZC-170629-C3-CDCL3-C13-2017-7-1
ZC-170629-C3-CDCL3-C13-2017-7-1
152.508
151.848
140.935
136.213
131.116
130.766
130.585
128.183
128.045
127.635
127.434
127.374
127.187
126.682
120.838
63.208
62.618
41.362
39.978
38.742
16.198
N
O
P
f1 (ppm)



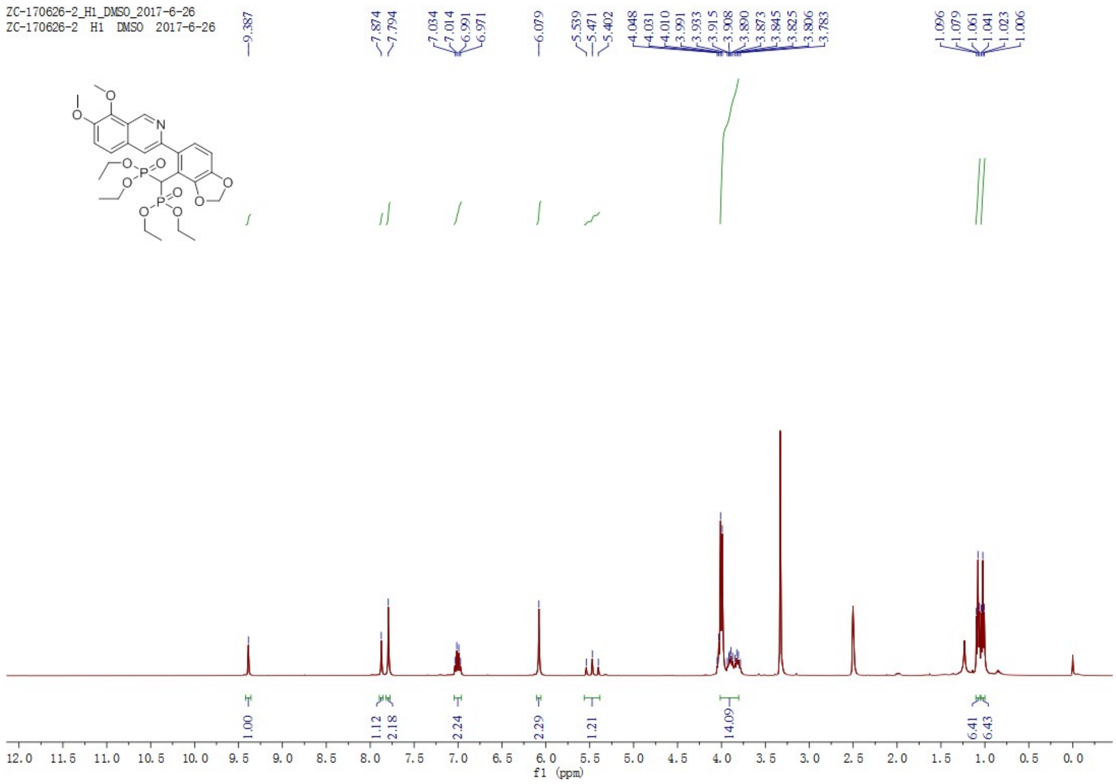
Compound **3ta**

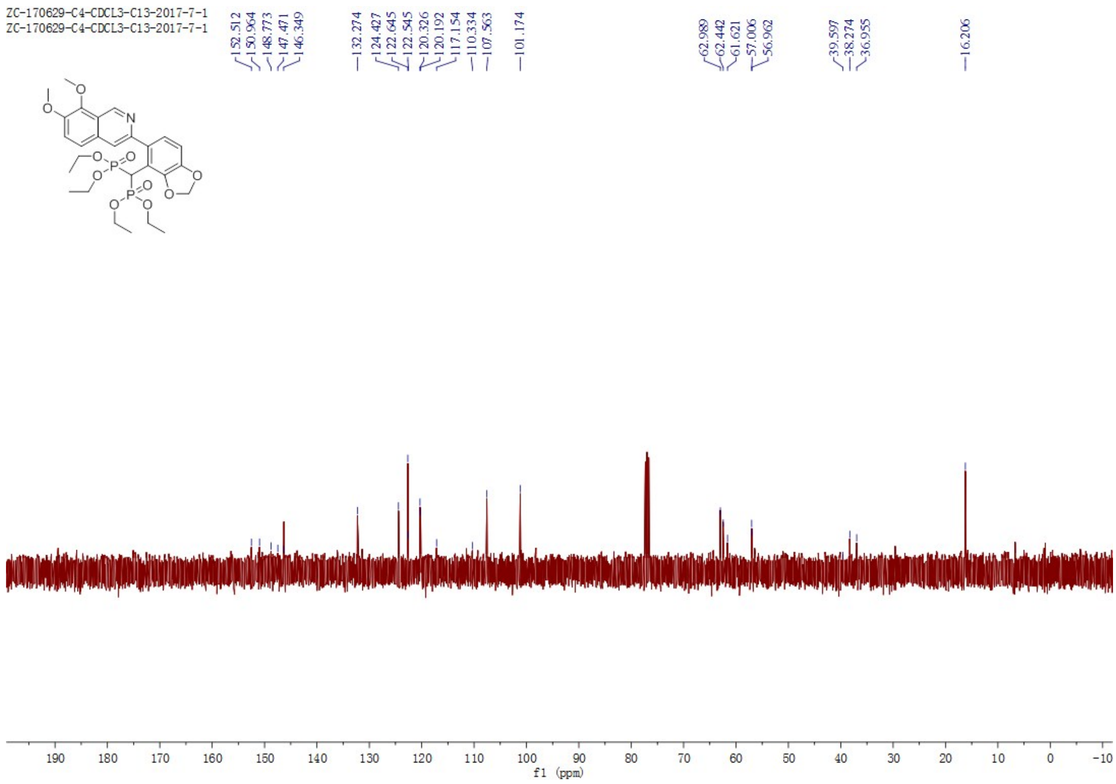


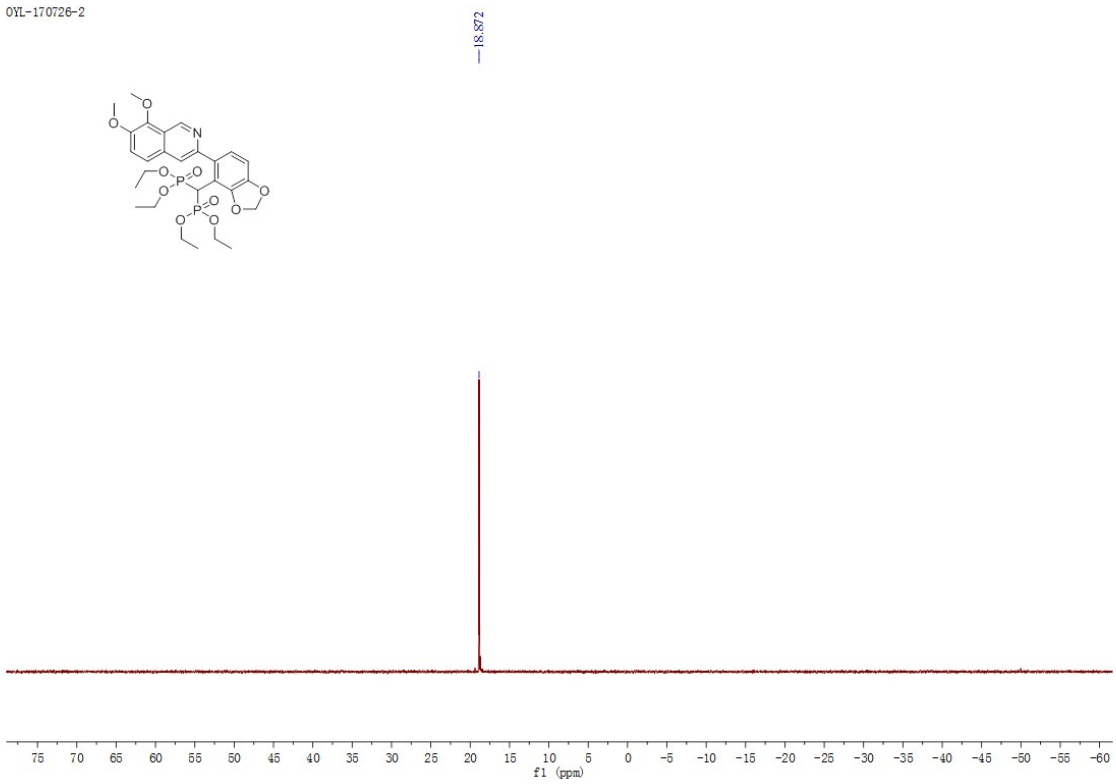




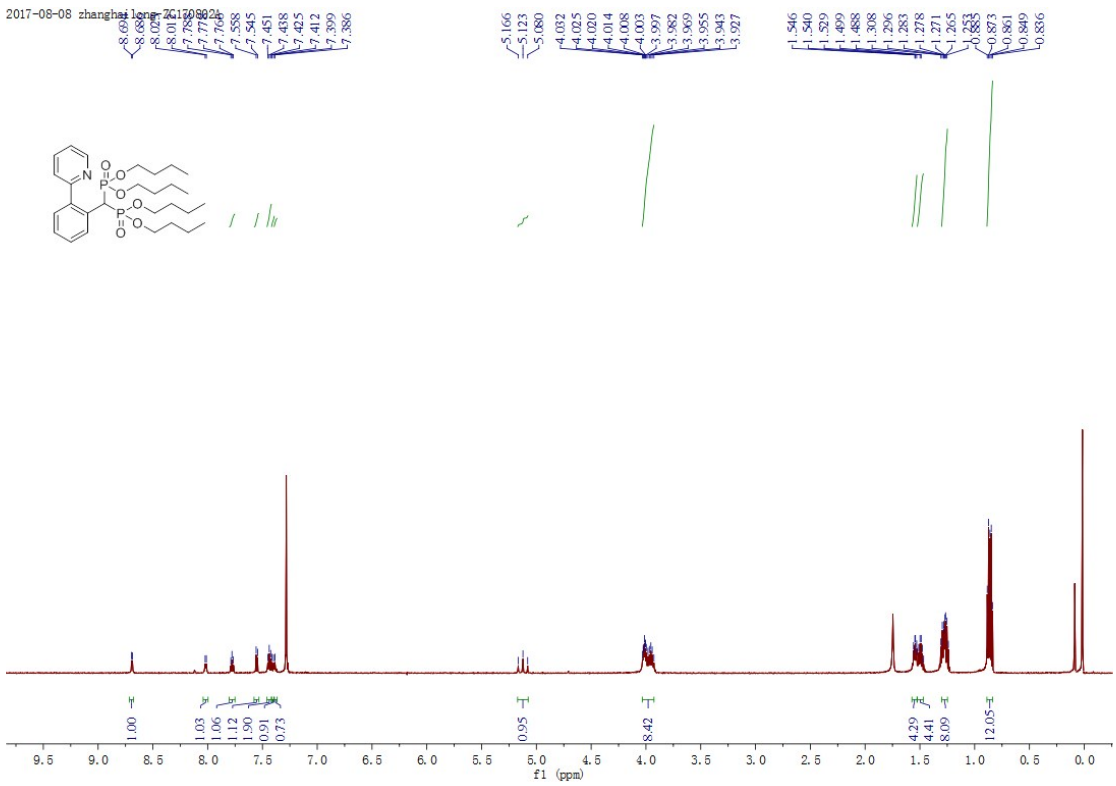
Compound **3ta**[1]

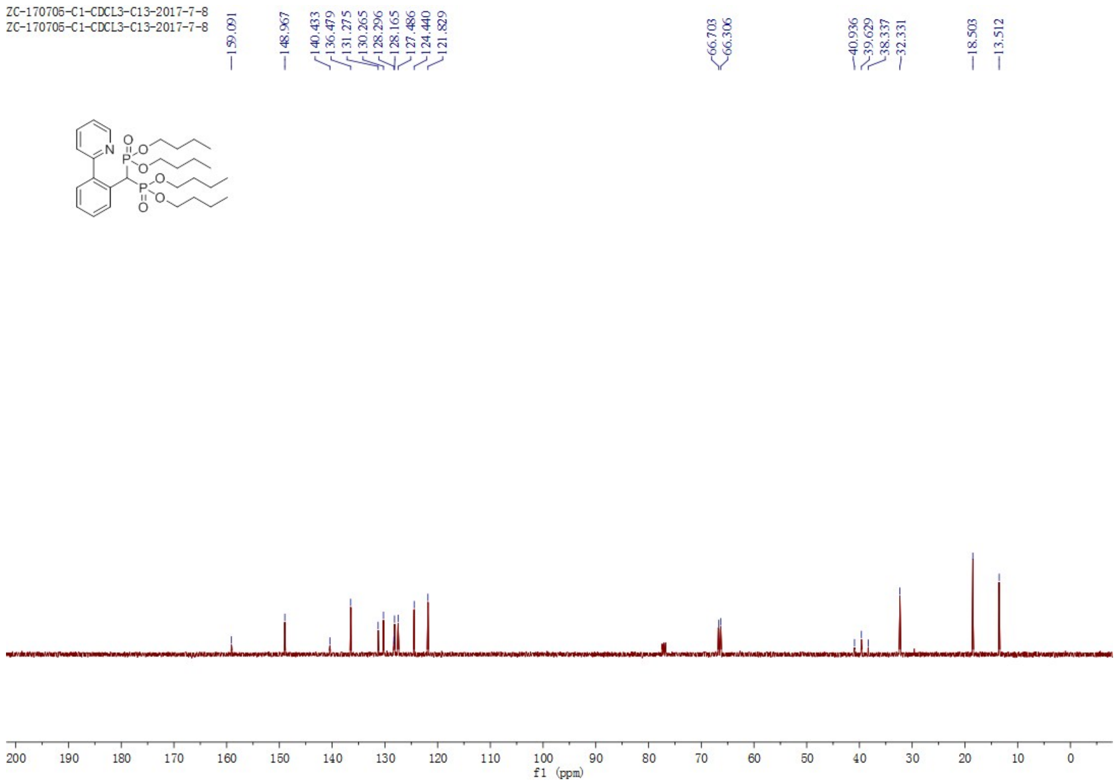

ZC-170626-2_H1_DMSO_2017-6-26
ZC-170626-2 H1 DMSO 2017-6-26
9.387
7.874
7.794
7.034
7.014
6.991
6.971
6.079
5.539
5.471
5.402
4.048
4.031
4.010
3.991
3.933
3.915
3.908
3.890
3.873
3.845
3.825
3.806
3.783
1.096
1.079
1.061
1.041
1.023
1.006
1.00
1.12
2.18
2.24
2.29
1.21
14.09
6.41
6.43
f1 (ppm)

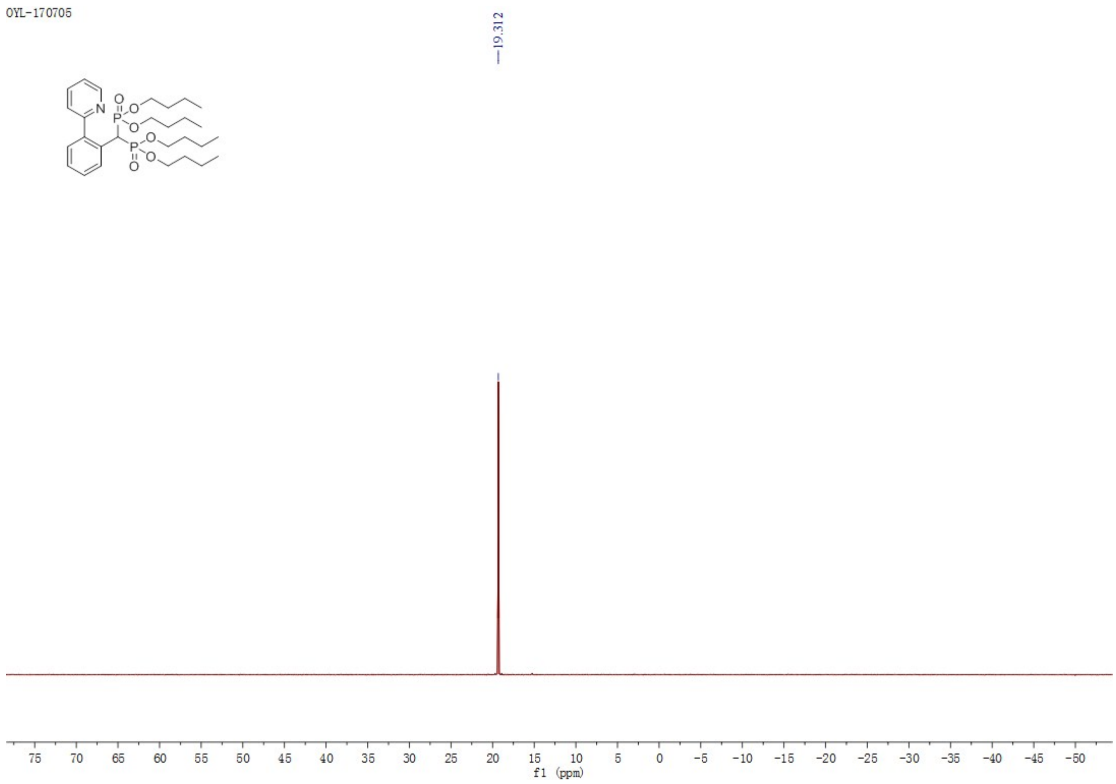

ZC-170629-C4-CDCL3-C13-2017-7-1
ZC-170629-C4-CDCL3-C13-2017-7-1
152.512
150.964
148.773
147.471
146.349
132.274
124.427
122.645
122.545
120.326
120.192
117.154
110.334
107.563
101.174
62.989
62.442
61.621
57.006
56.962
39.597
38.274
36.955
16.206
f1 (ppm)



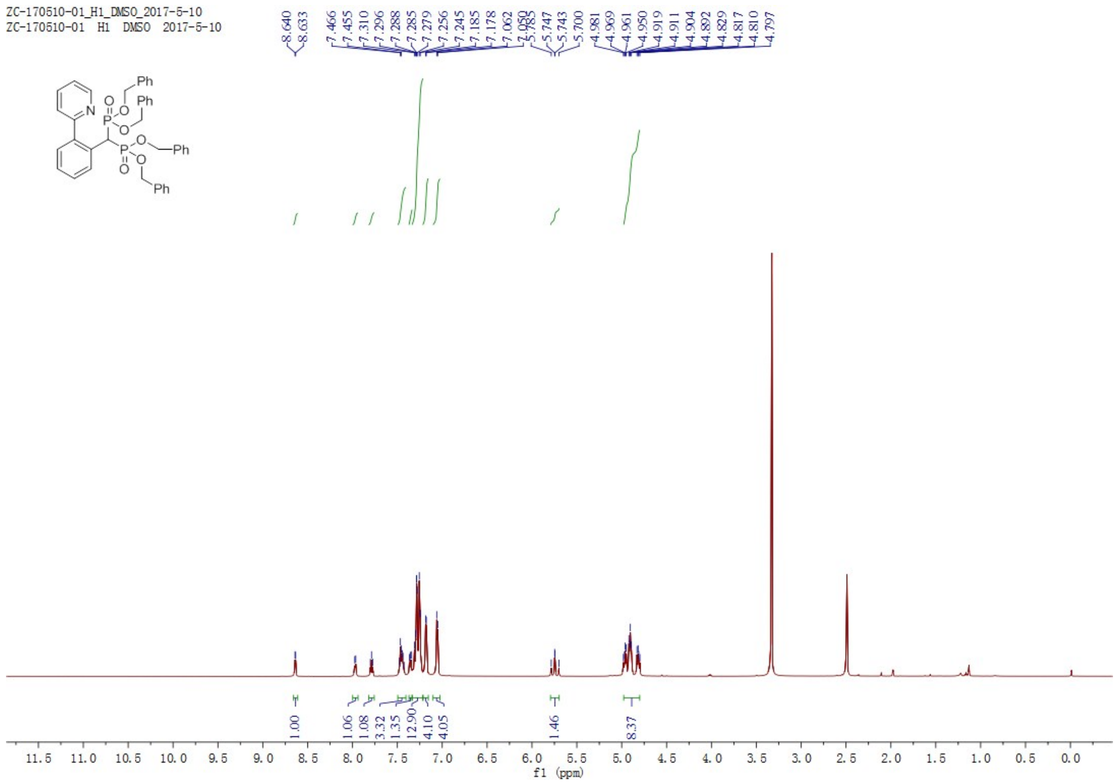
Compound **3ab**

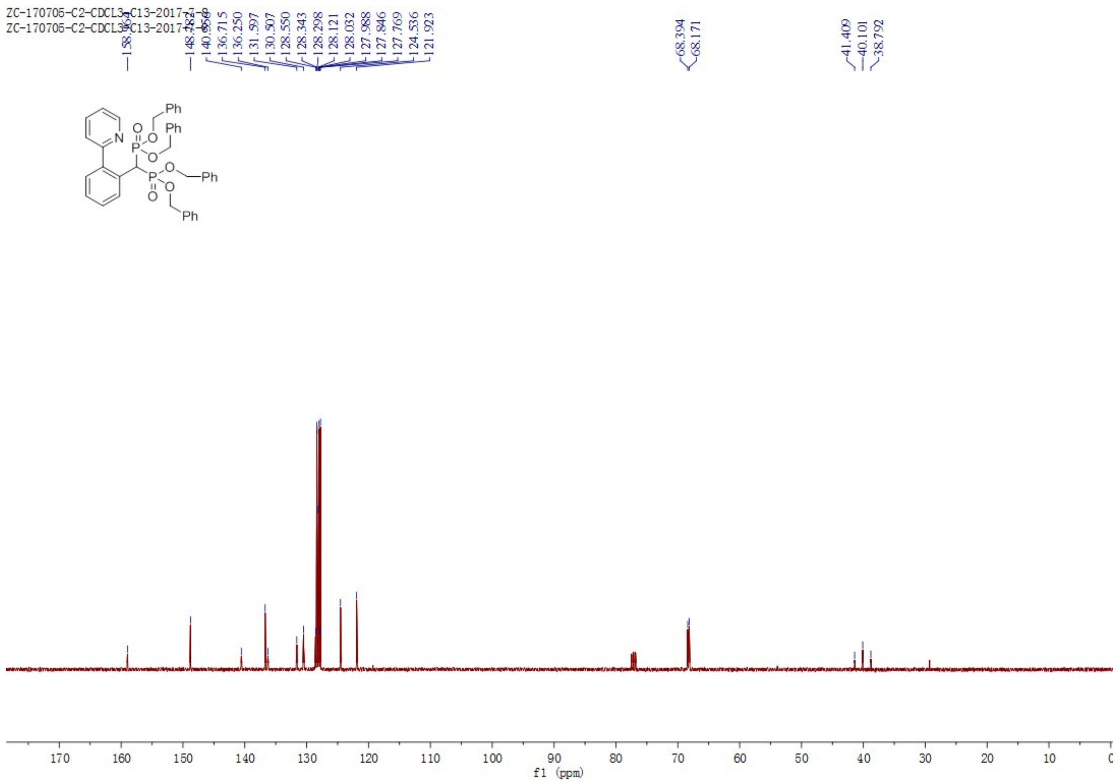


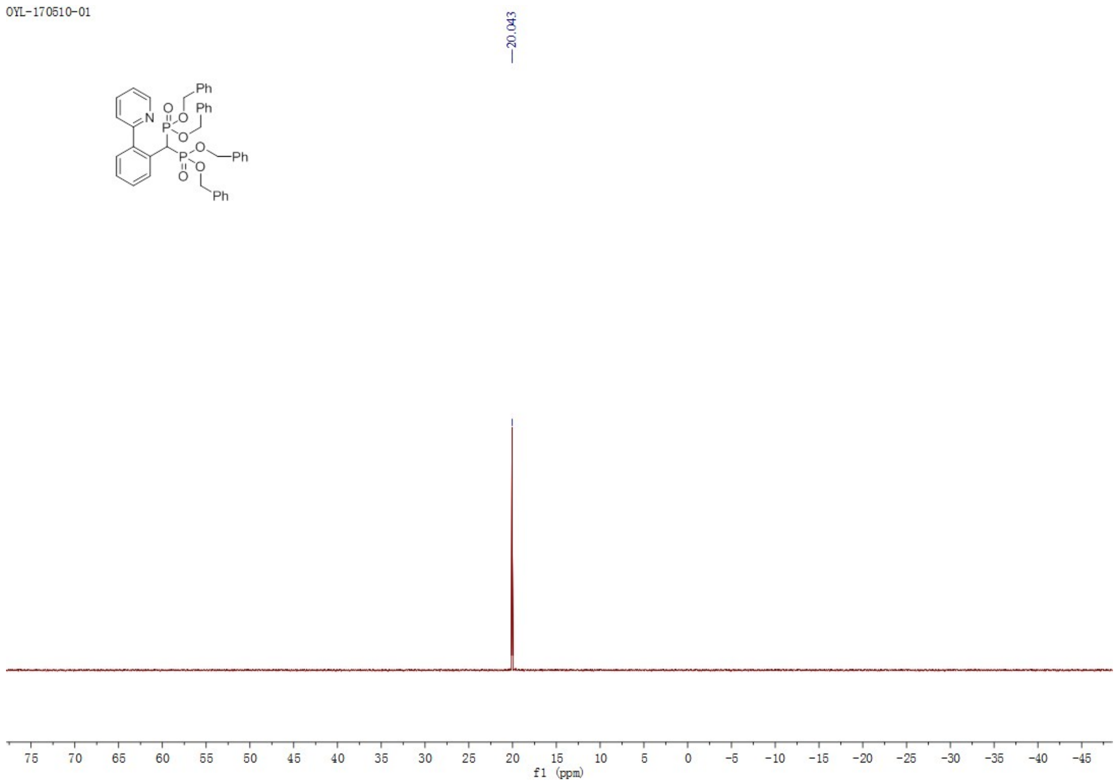




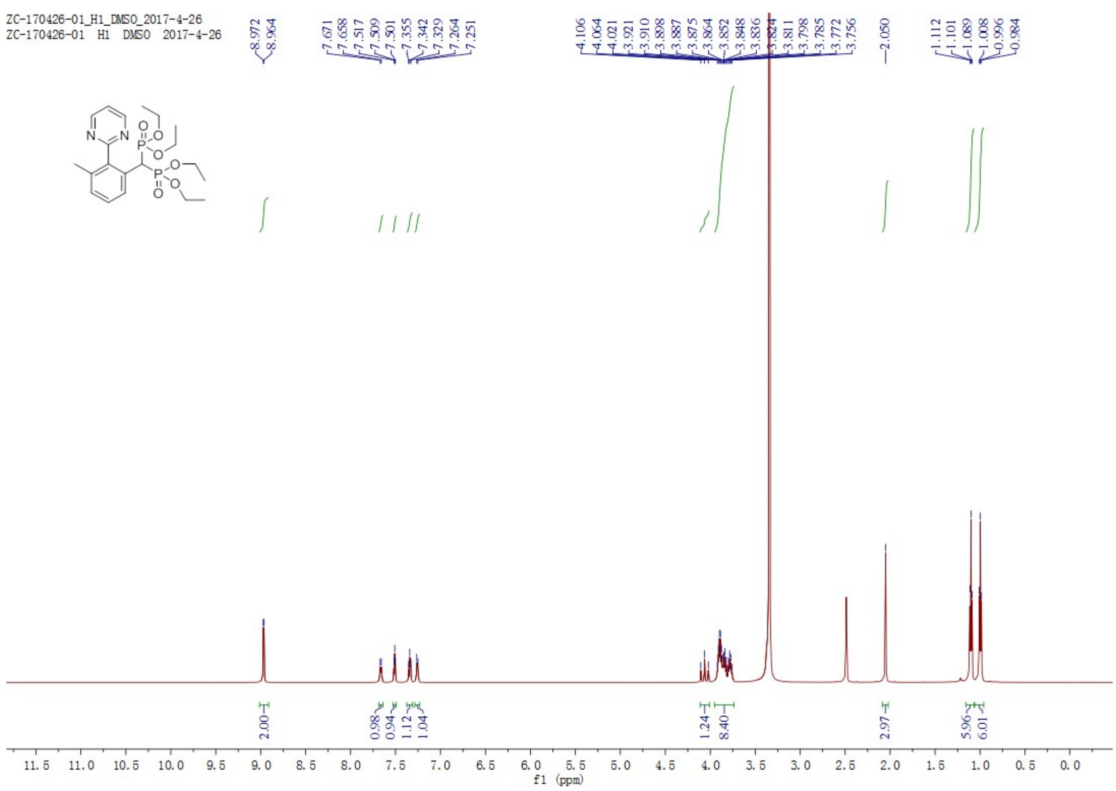
Compound **3ac**

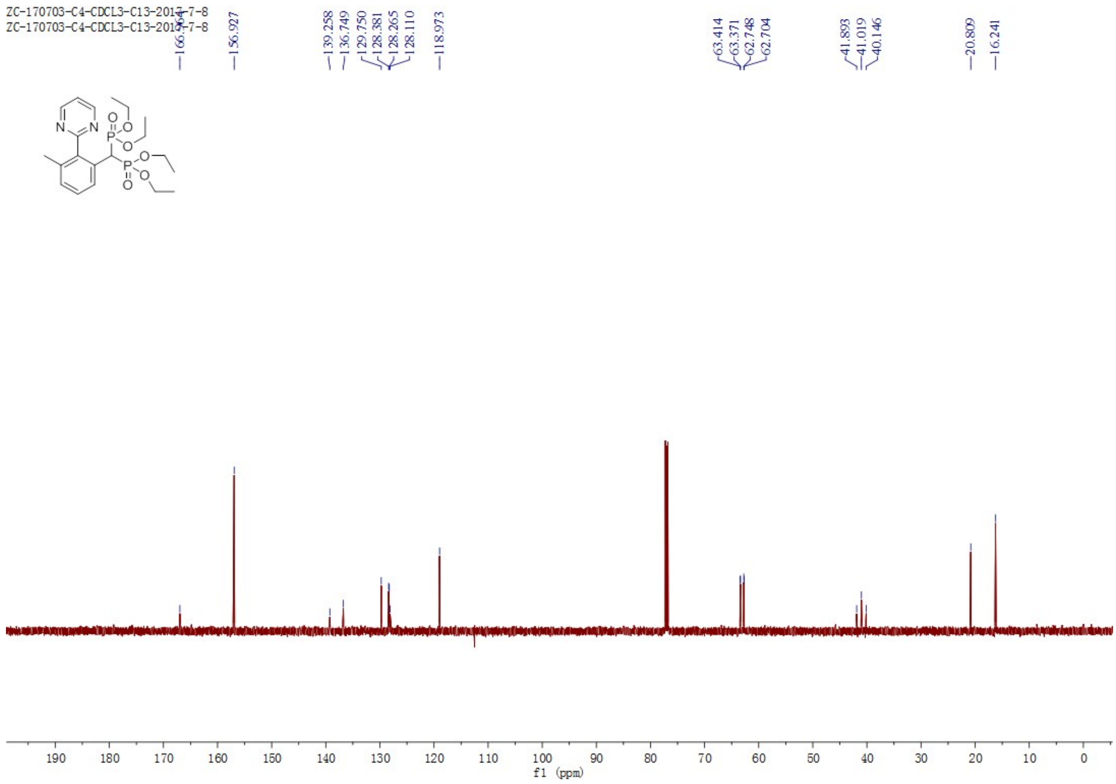

ZC-170510-01_H1_DMSO_2017-5-10
ZC-170510-01 H1 DMSO 2017-5-10
8.640
8.633
7.466
7.455
7.310
7.296
7.288
7.285
7.279
7.256
7.245
7.185
7.178
7.062
5.747
5.743
5.700
4.981
4.969
4.961
4.950
4.919
4.911
4.904
4.892
4.829
4.817
4.810
4.797
Ph
Ph
Ph
Ph
N
O
P
O
P
O
O
O
O
1.00
1.06
1.08
3.32
1.35
12.90
4.10
4.05
1.46
8.37
f1 (ppm)

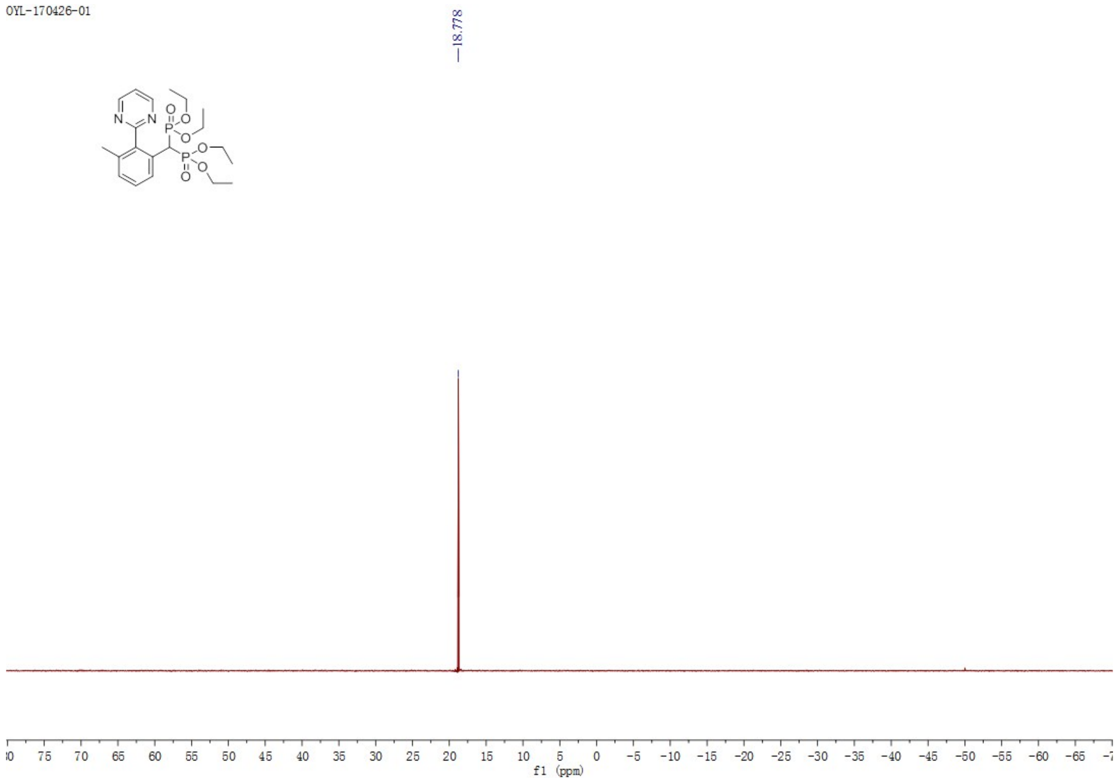

ZC-170705-C2-CDCL3-C13-2017-7-6
136.715
136.250
131.597
130.507
128.550
128.343
128.298
128.121
128.032
127.988
127.846
127.769
124.536
121.923
68.394
68.171
41.409
40.101
38.792
Ph
Ph
Ph
Ph
N
O
P
O
P
O
O
O
O
f1 (ppm)


OYL-170510-01
20.043
f1 (ppm)

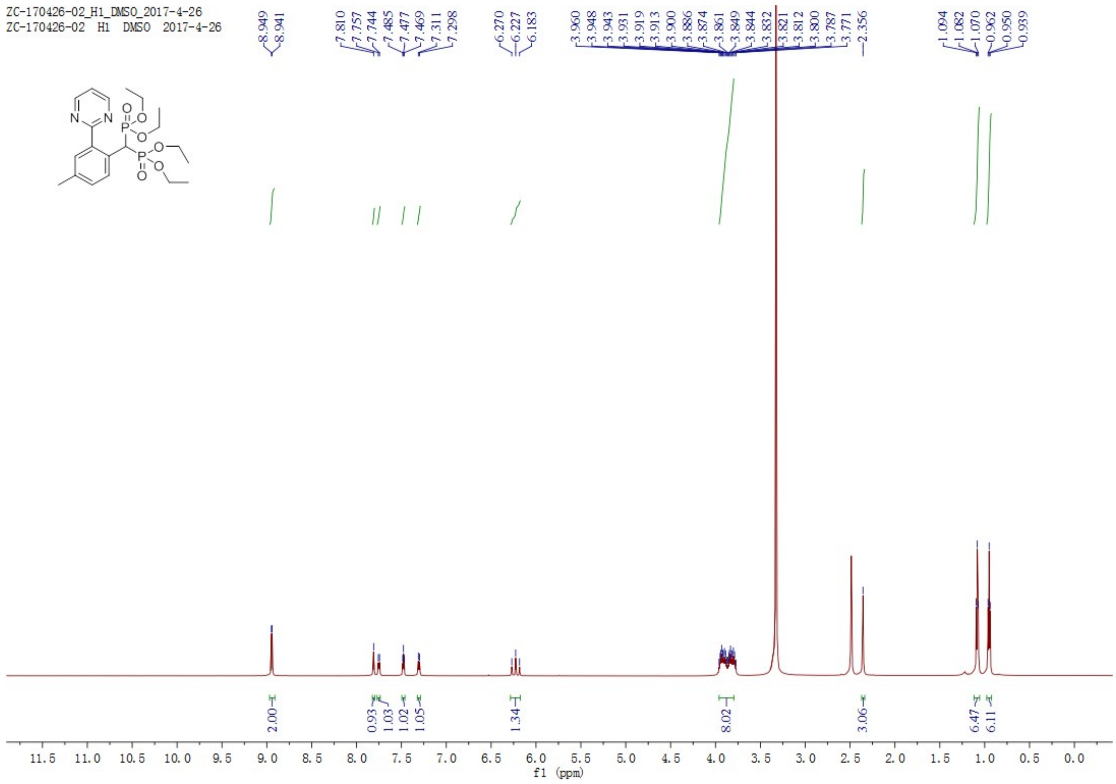
Compound **5a**

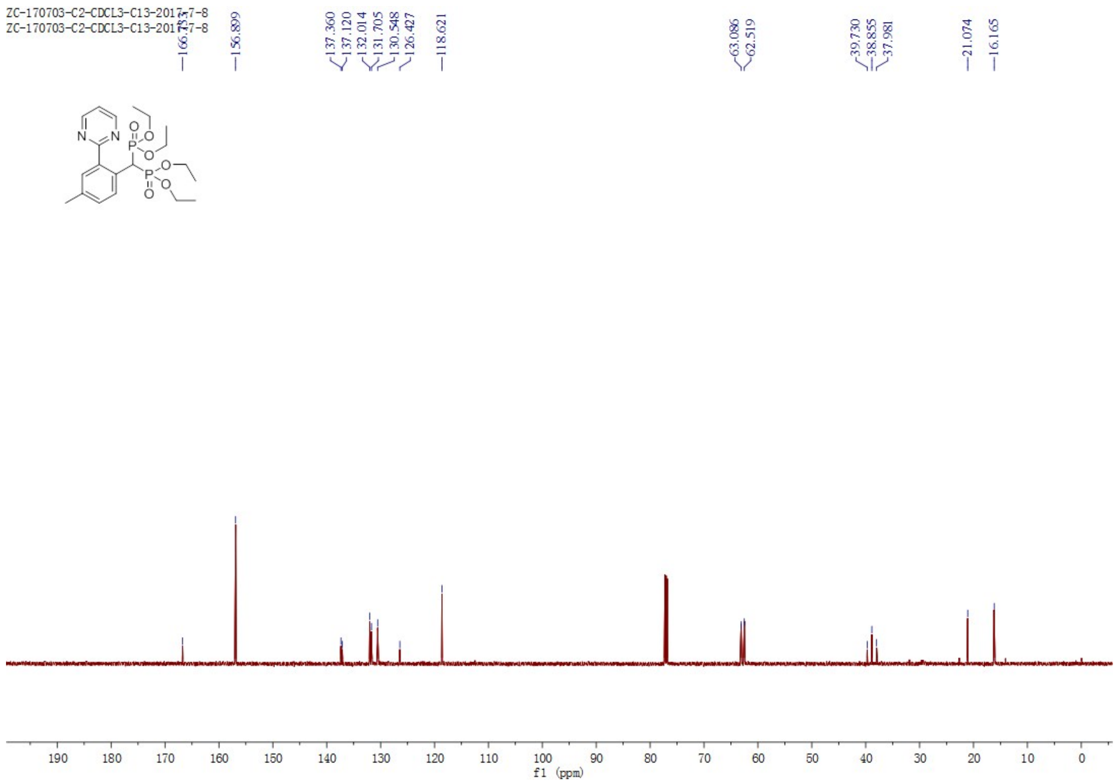

ZC-170426-01_H1_DMSO_2017-4-26
ZC-170426-01 H1 DMSO 2017-4-26
f1 (ppm)

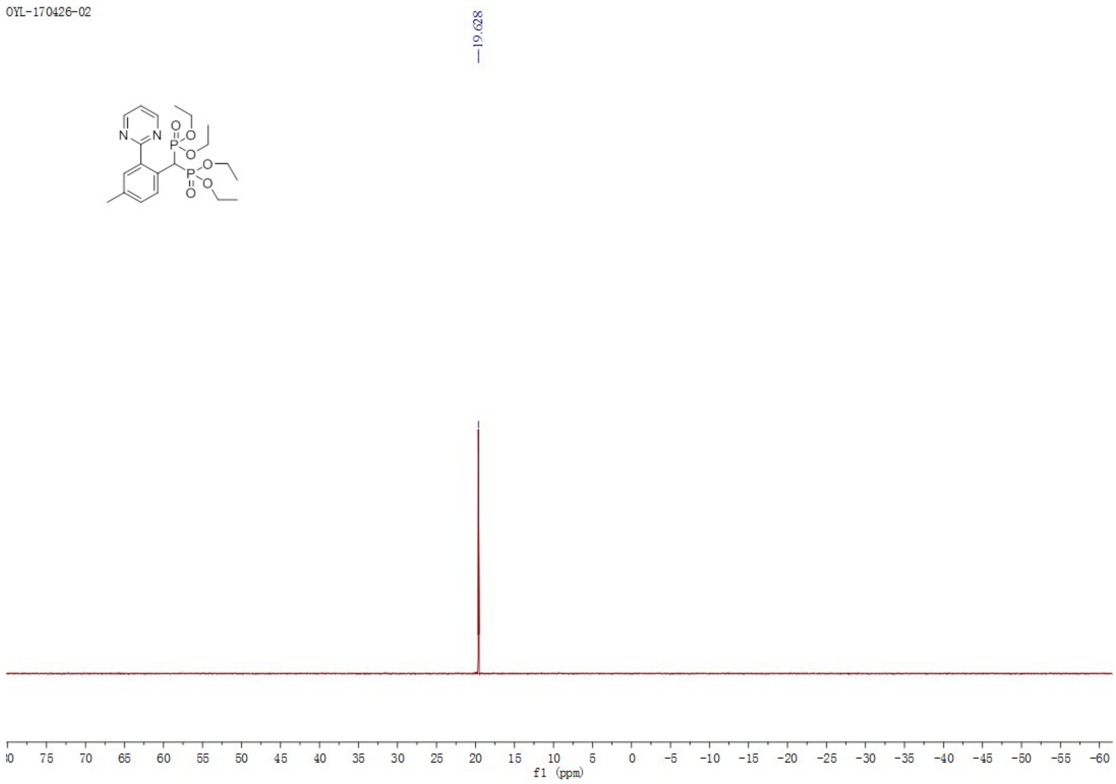

ZC-170703-C4-CDCL3-C13-2017-7-8
ZC-170703-C4-CDCL3-C13-2017-7-8
166.564
156.927
139.258
136.749
129.750
128.381
128.265
128.110
118.973
63.414
63.371
62.748
62.704
41.893
41.019
40.146
20.809
16.241
f1 (ppm)


OYL-170426-01
18.778
f1 (ppm)

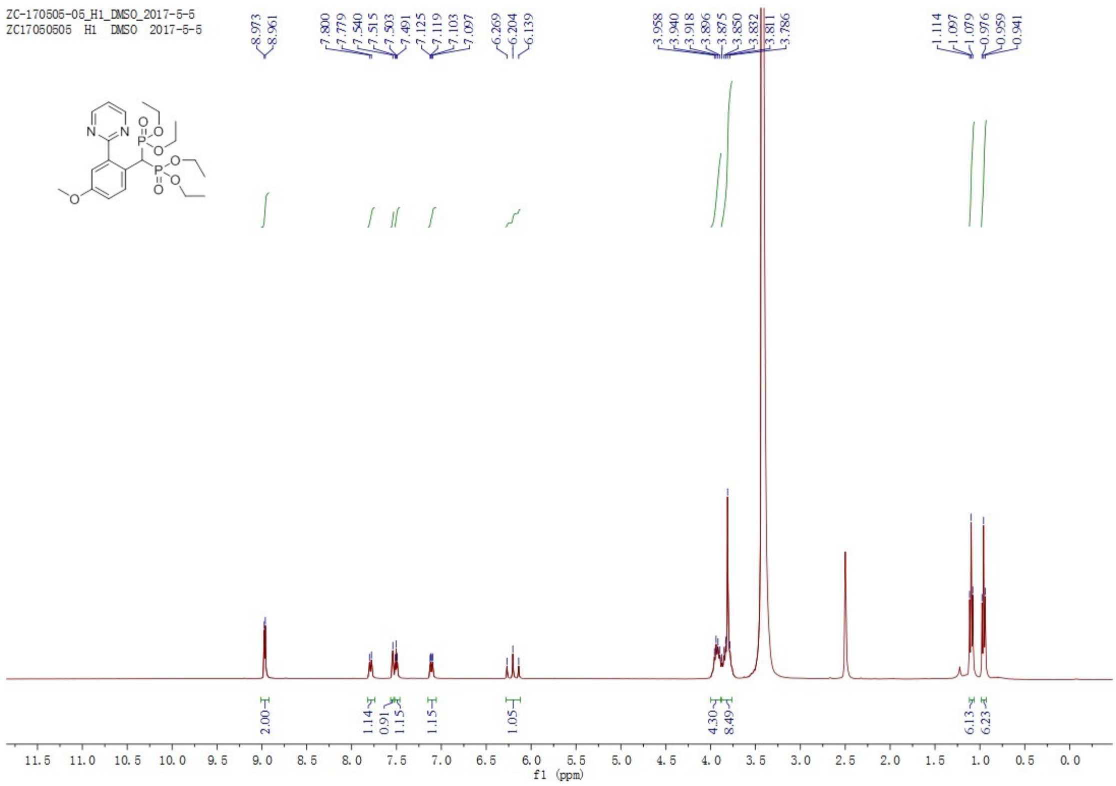
Compound **5b**

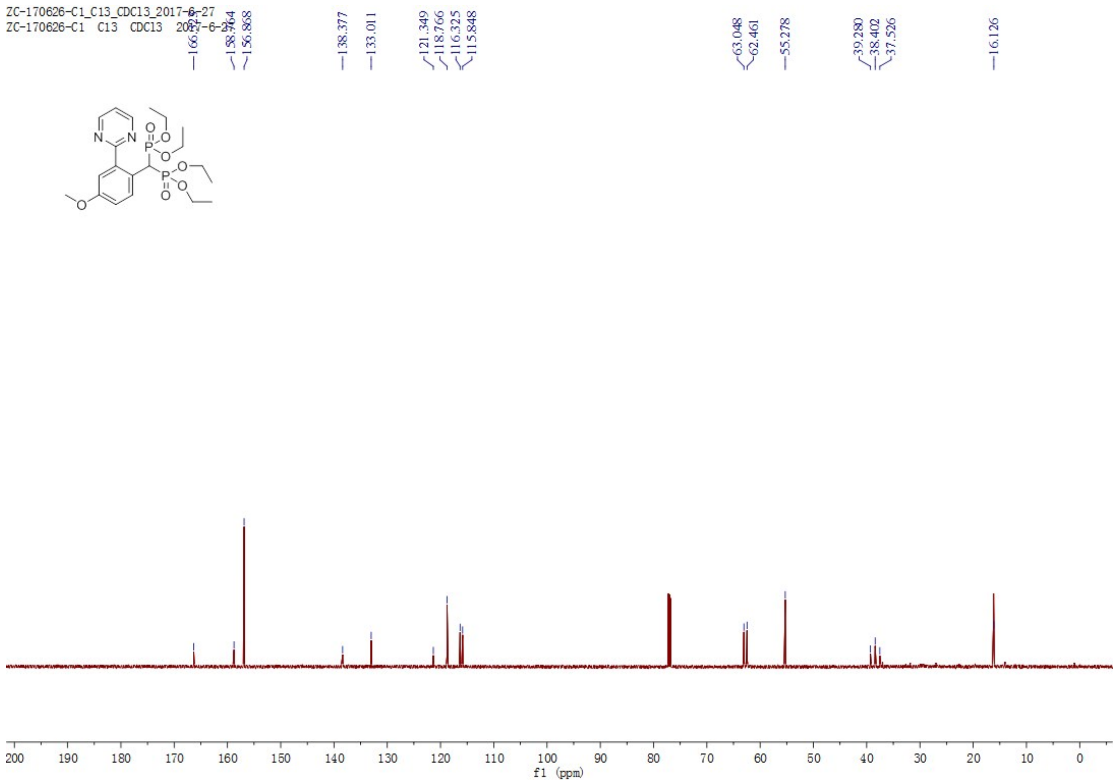

ZC-170426-02_H1_DMSO_2017-4-26
ZC-170426-02 H1 DMSO 2017-4-26
8.949
8.941
7.810
7.757
7.744
7.485
7.477
7.469
7.311
7.298
6.270
6.227
6.183
3.960
3.948
3.943
3.931
3.919
3.913
3.900
3.886
3.874
3.861
3.849
3.844
3.832
3.821
3.812
3.800
3.787
3.771
2.356
1.094
1.082
1.070
0.962
0.950
0.939
N
N
P
O
O
O
P
O
O
O
2.00
0.93
1.03
1.02
1.05
1.34
8.02
3.06
6.47
6.11
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

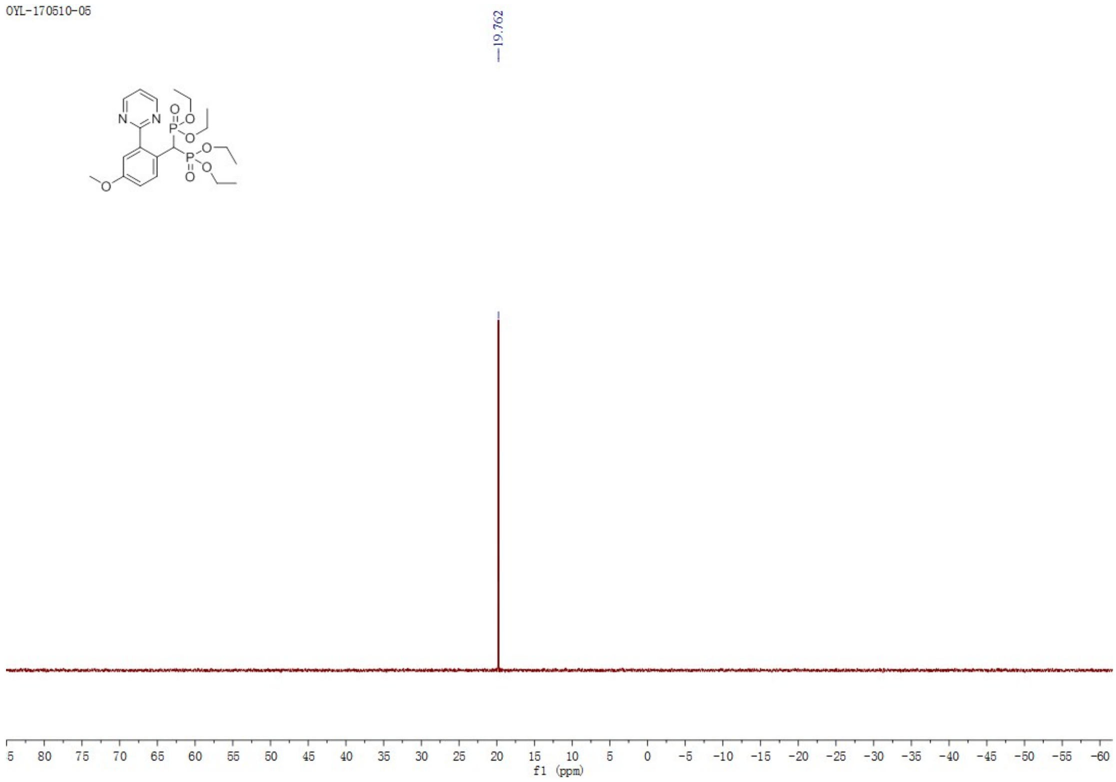

ZC-170703-C2-CDCL3-C13-2017-7-8
ZC-170703-C2-CDCL3-C13-2017-7-8
156.899
137.360
137.120
132.014
131.705
130.548
126.427
118.621
63.086
62.519
39.730
38.855
37.981
21.074
16.165
N
N
P
O
O
O
P
O
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OYL-170426-02
19.628
f1 (ppm)

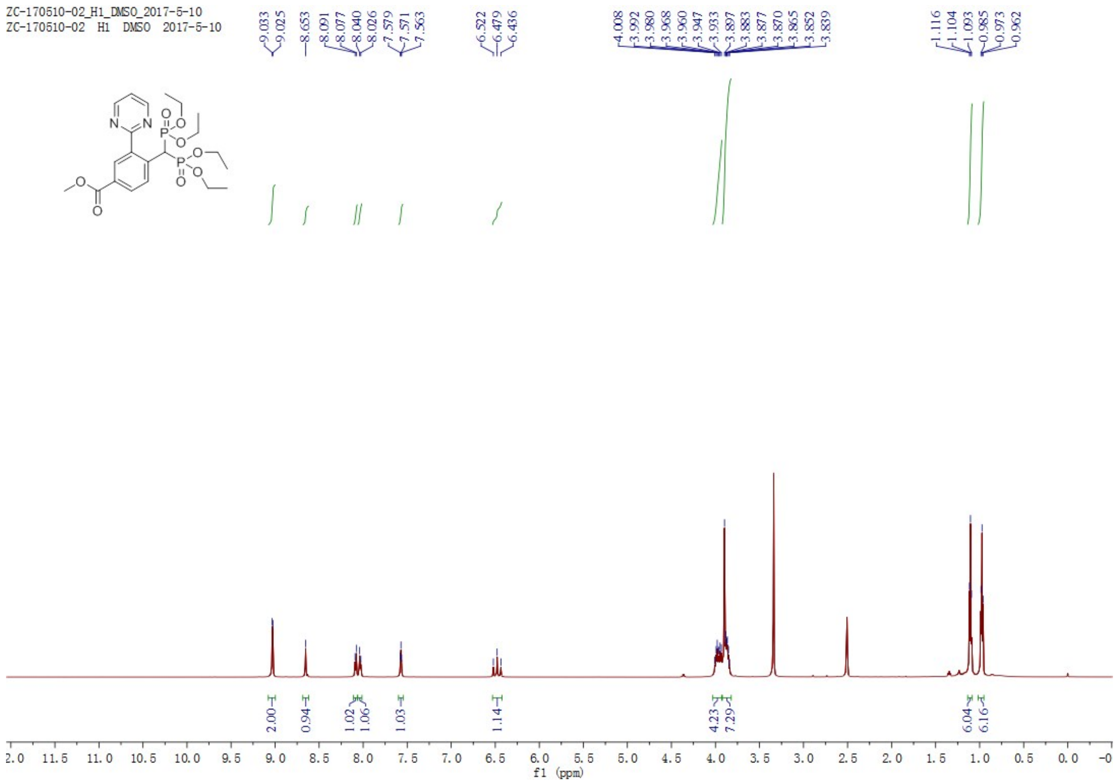
Compound **5c**

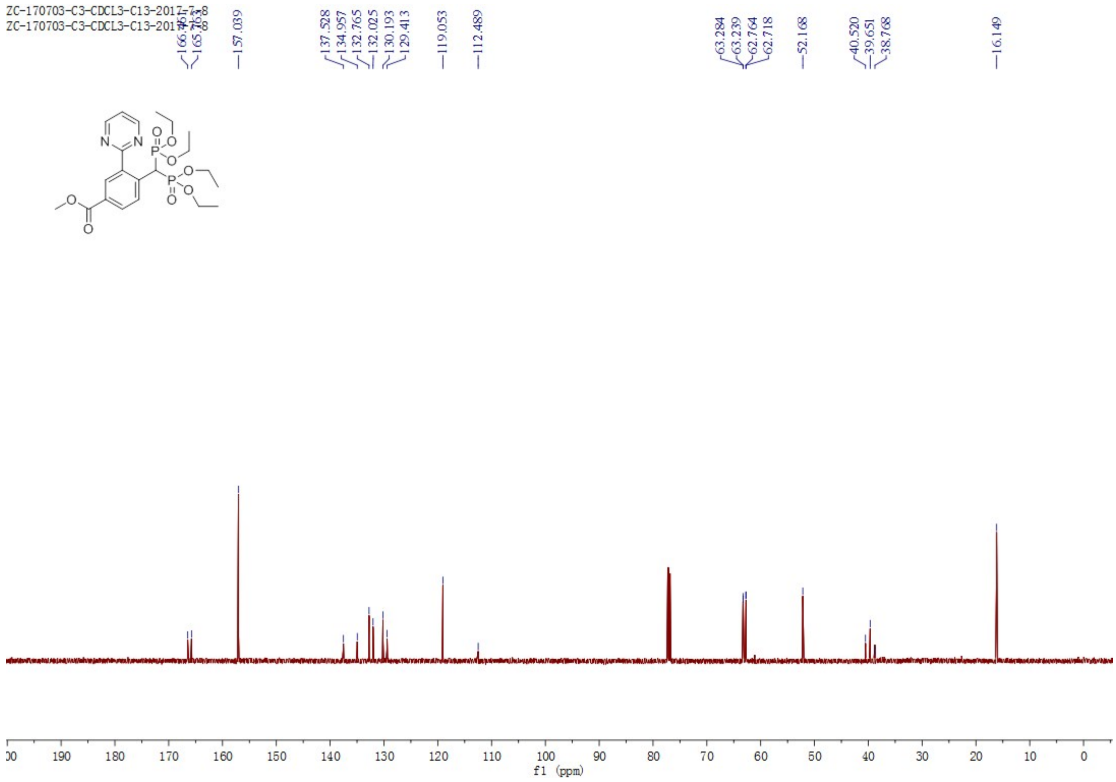

ZC-170505-05_H1_DMSO_2017-5-5
ZC17050505 H1 DMSO 2017-5-5
f1 (ppm)

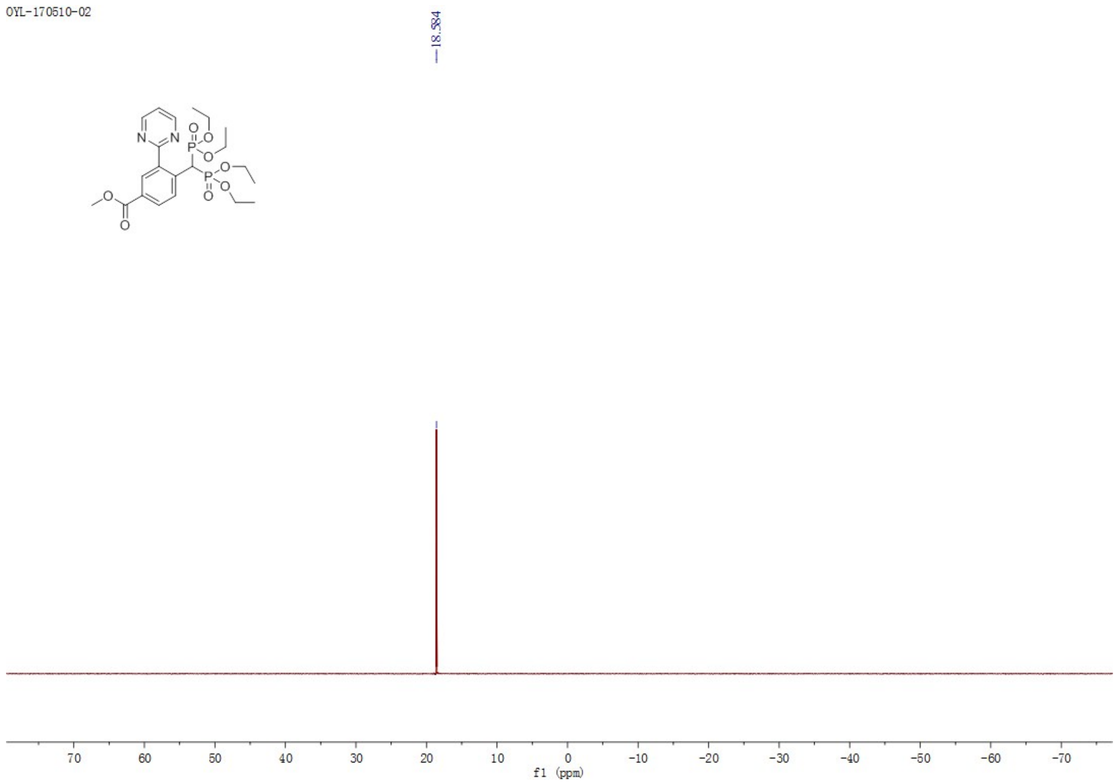

ZC-170626-C1_C13_CDCl3_2017-6-27
156.868
138.377
133.011
121.349
118.766
116.325
115.848
63.048
62.461
55.278
39.280
38.402
37.526
16.126
f1 (ppm)


OYL-170510-05
19.762
f1 (ppm)

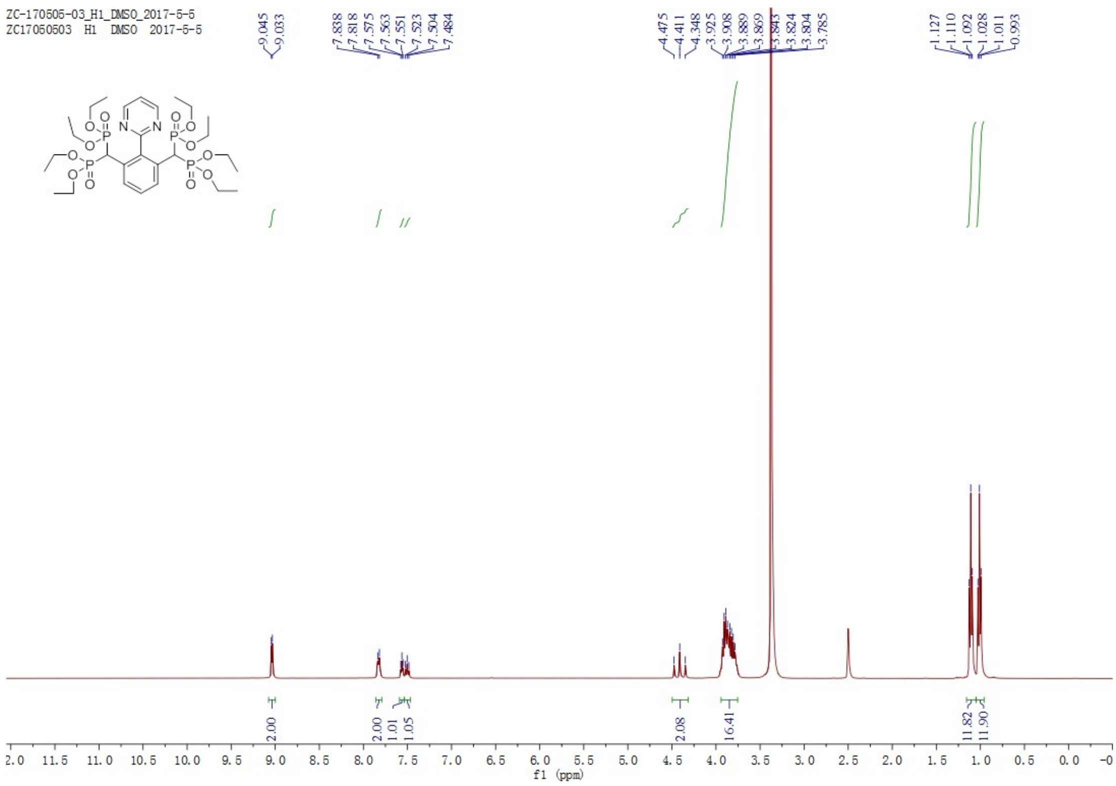
Compound **5d**

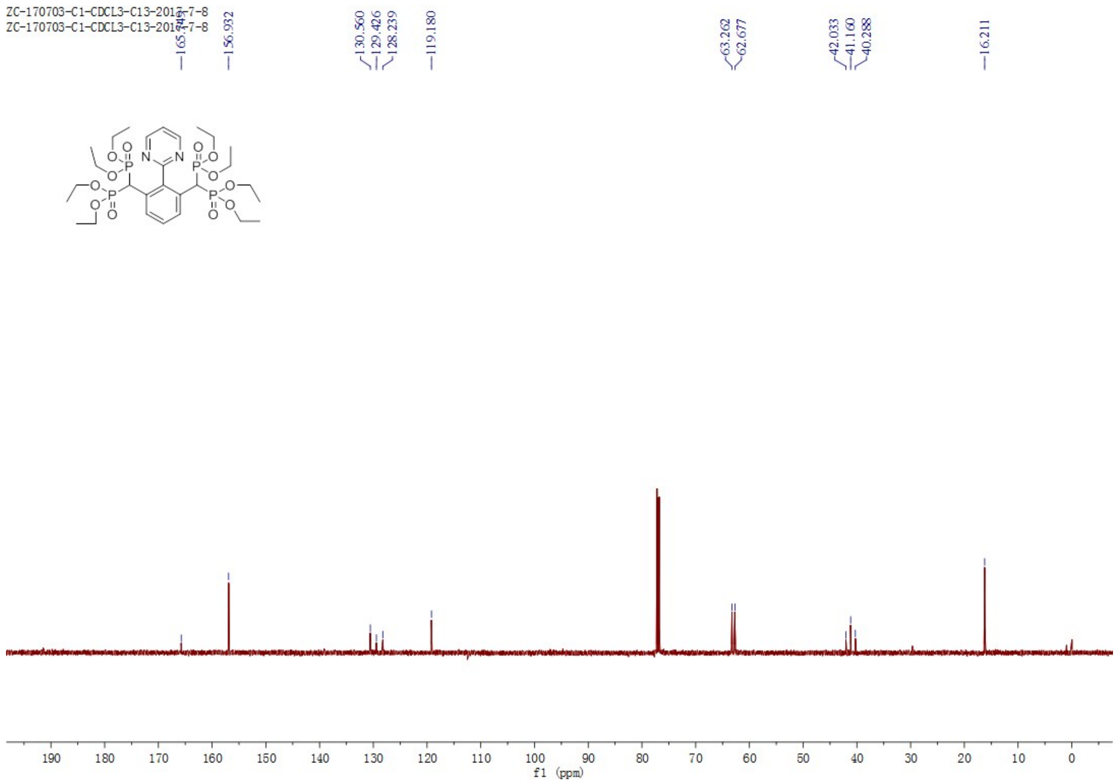

ZC-170510-02_H1_DMSO_2017-5-10
ZC-170510-02 H1 DMSO 2017-5-10
9.033
9.025
8.653
8.091
8.077
8.040
8.026
7.579
7.571
7.563
6.522
6.479
6.436
4.008
3.992
3.980
3.968
3.960
3.947
3.933
3.897
3.883
3.877
3.870
3.865
3.852
3.839
1.116
1.104
1.093
0.985
0.973
0.962
2.00
0.94
1.02
1.06
1.03
1.14
4.23
7.29
6.04
6.16
f1 (ppm)

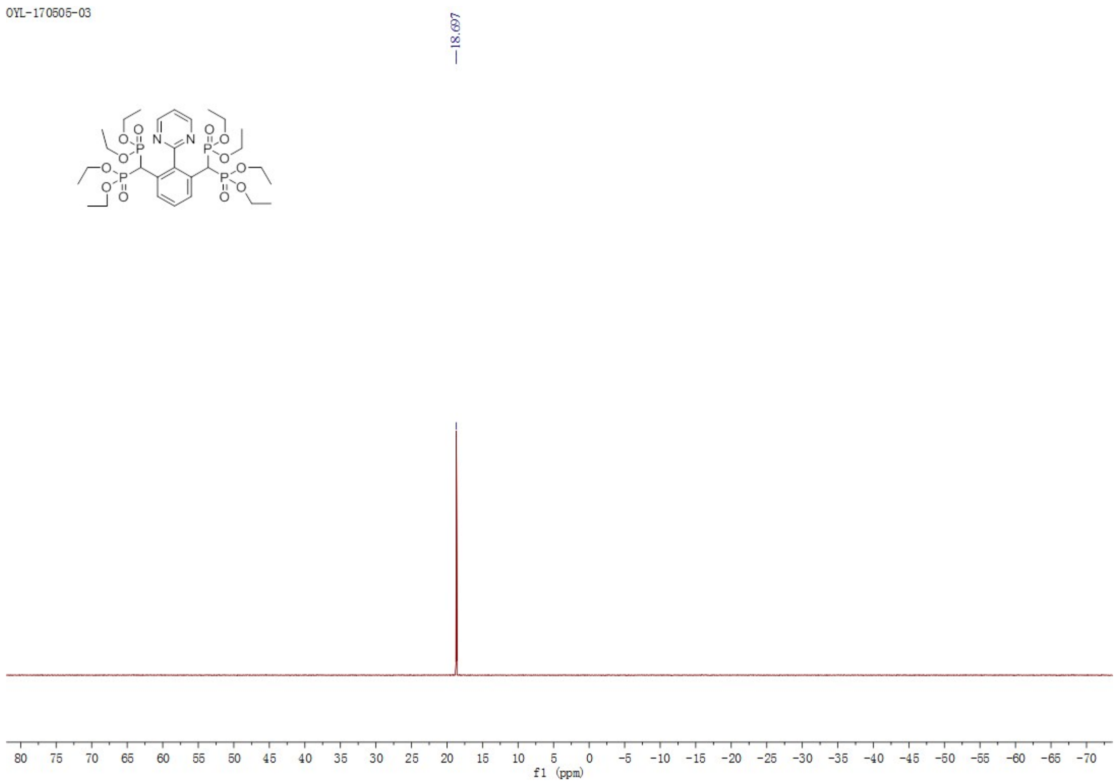

ZC-170703-C3-CDCL3-C13-2017-7-8
ZC-170703-C3-CDCL3-C13-2017-7-8
157.039
137.528
134.957
132.765
132.025
130.193
129.413
119.053
112.489
63.284
63.239
62.764
62.718
52.168
40.520
39.651
38.768
16.149
f1 (ppm)


OYL-170510-02
18.584
f1 (ppm)

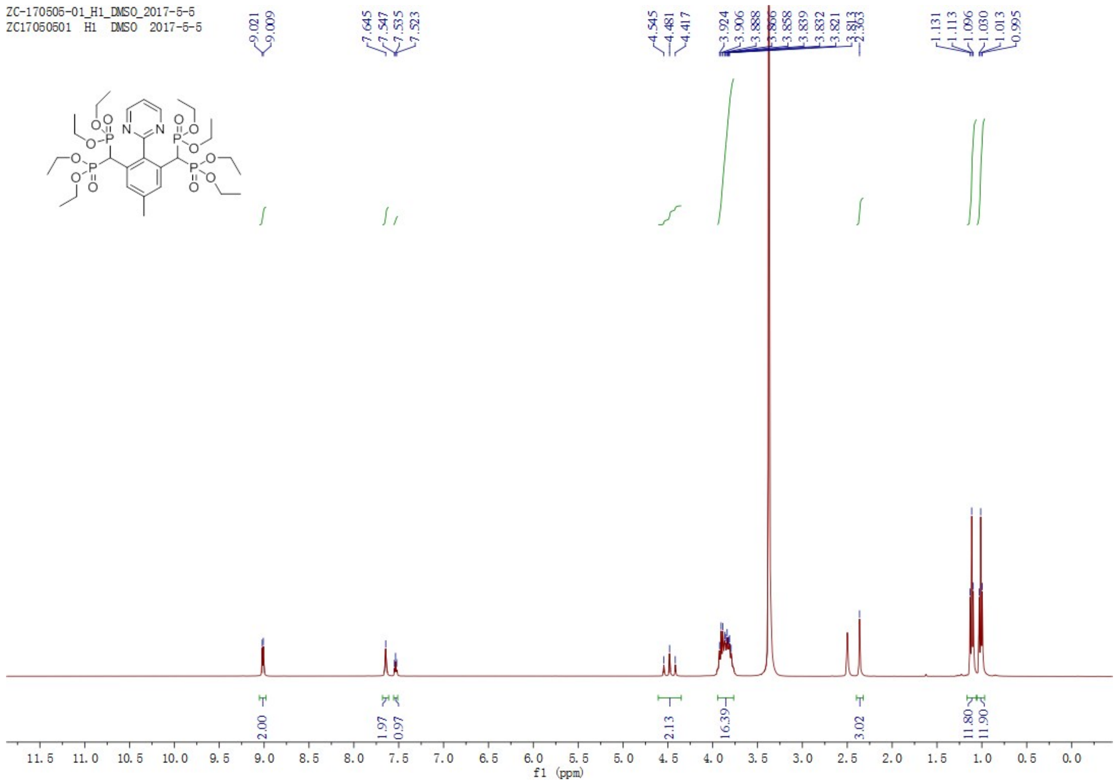
Compound **5e**

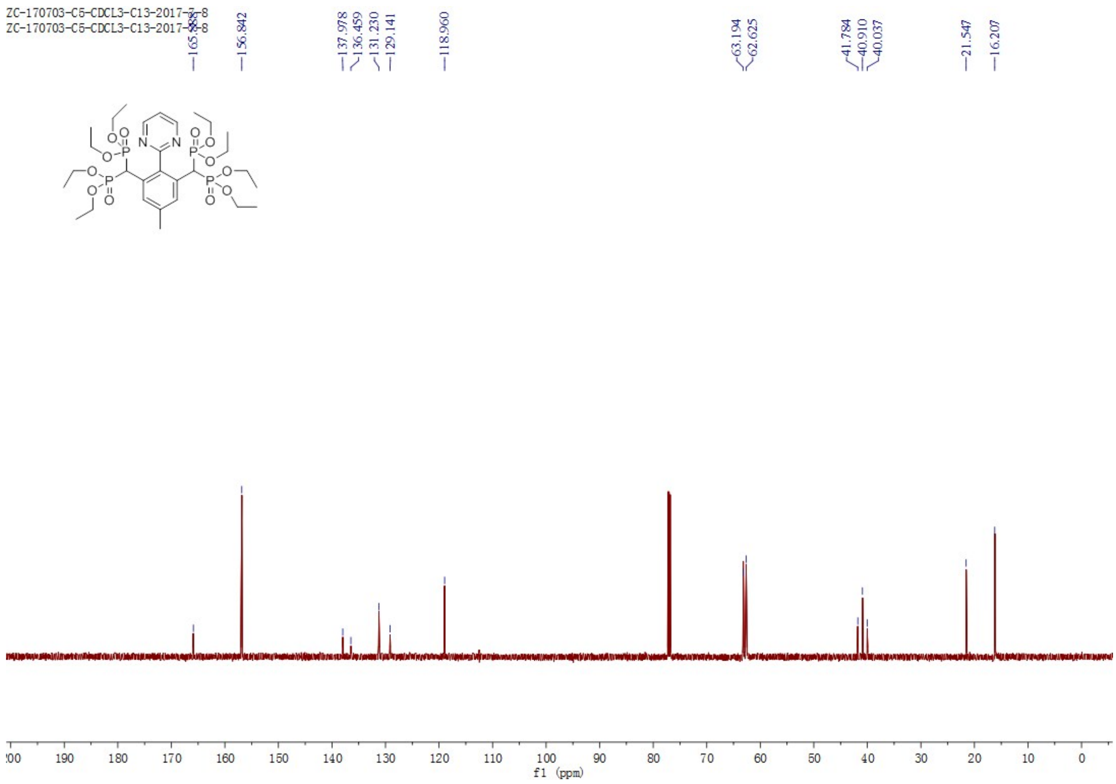

ZC-170505-03_H1_DMSO_2017-5-5
ZC17050503 H1 DMSO 2017-5-5
9.045
9.033
7.838
7.818
7.575
7.563
7.551
7.523
7.504
7.484
4.475
4.411
4.348
3.925
3.908
3.889
3.869
3.843
3.824
3.804
3.785
1.127
1.110
1.092
1.028
1.011
0.993
2.00
2.00
1.01
1.05
2.08
16.41
11.82
11.90
f1 (ppm)

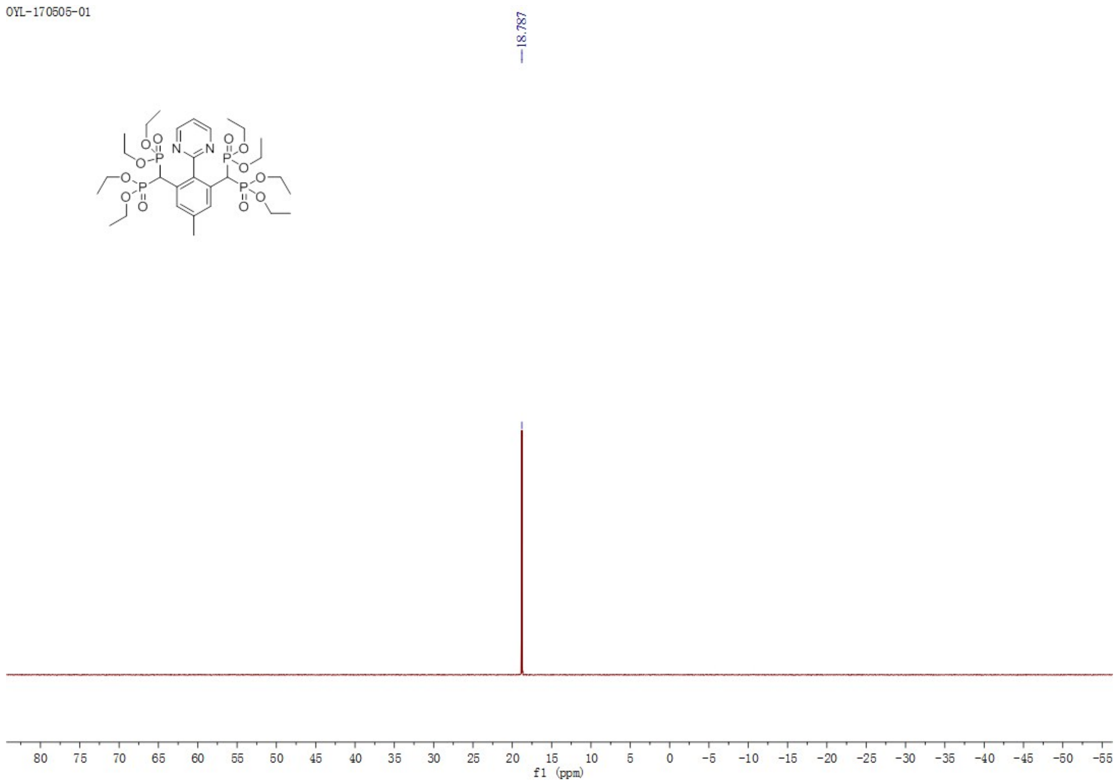

ZC-170703-C1-CDCL3-C13-2017-7-8
ZC-170703-C1-CDCL3-C13-2017-7-8
165.749
156.932
130.560
129.426
128.239
119.180
63.262
62.677
42.033
41.160
40.288
16.211
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OYL-170605-03
18.697
80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70
f1 (ppm)

Compound **5f**

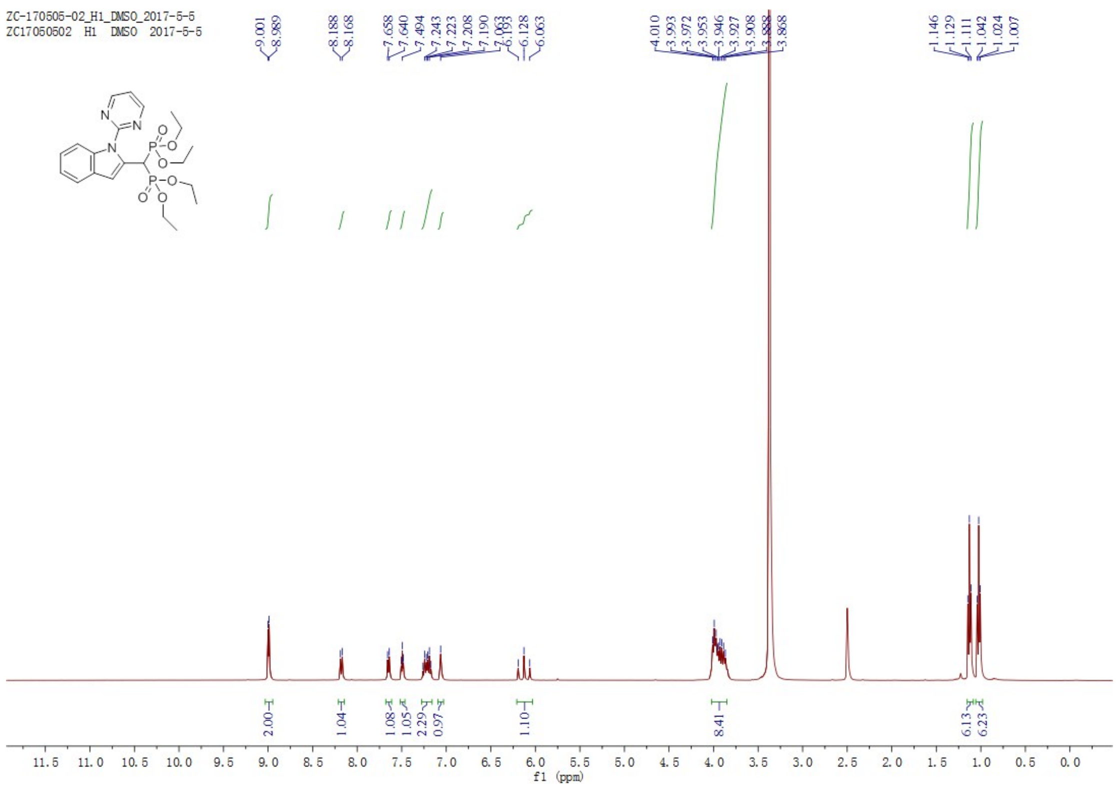

ZC-170505-01_H1_DMSO_2017-5-5
ZC17050501 H1 DMSO 2017-5-5
f1 (ppm)


ZC-170703-C5-CDCL3-C13-2017-7-8
f1 (ppm)

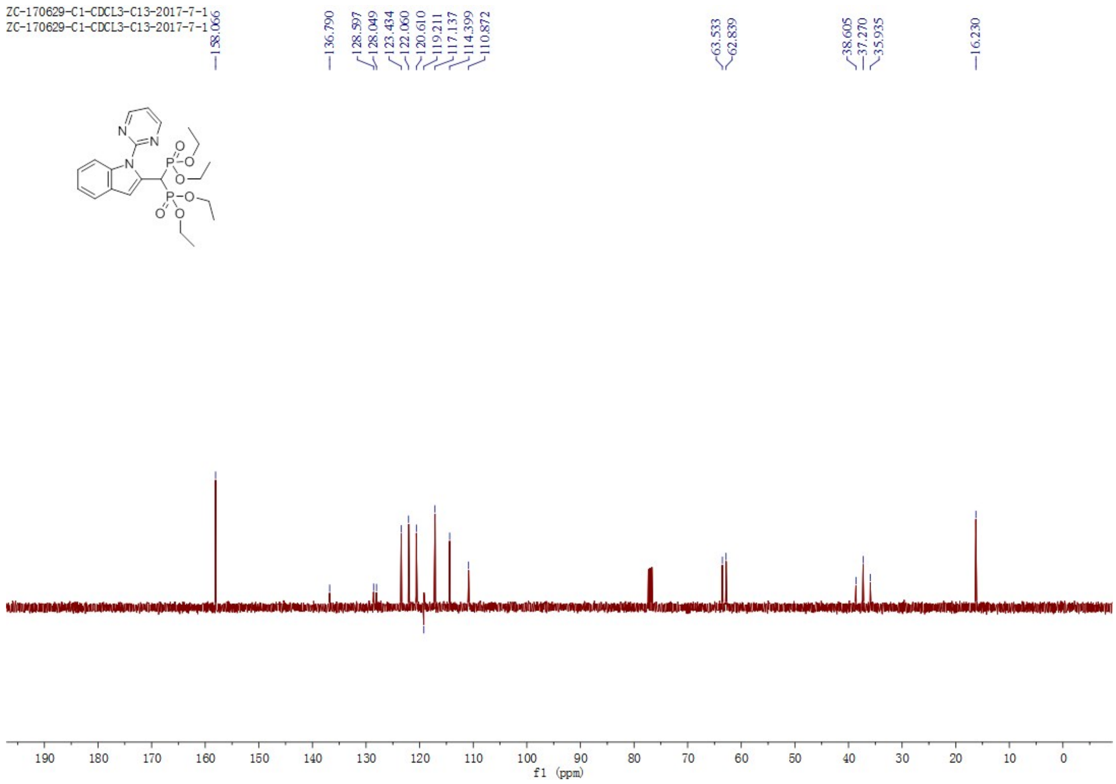


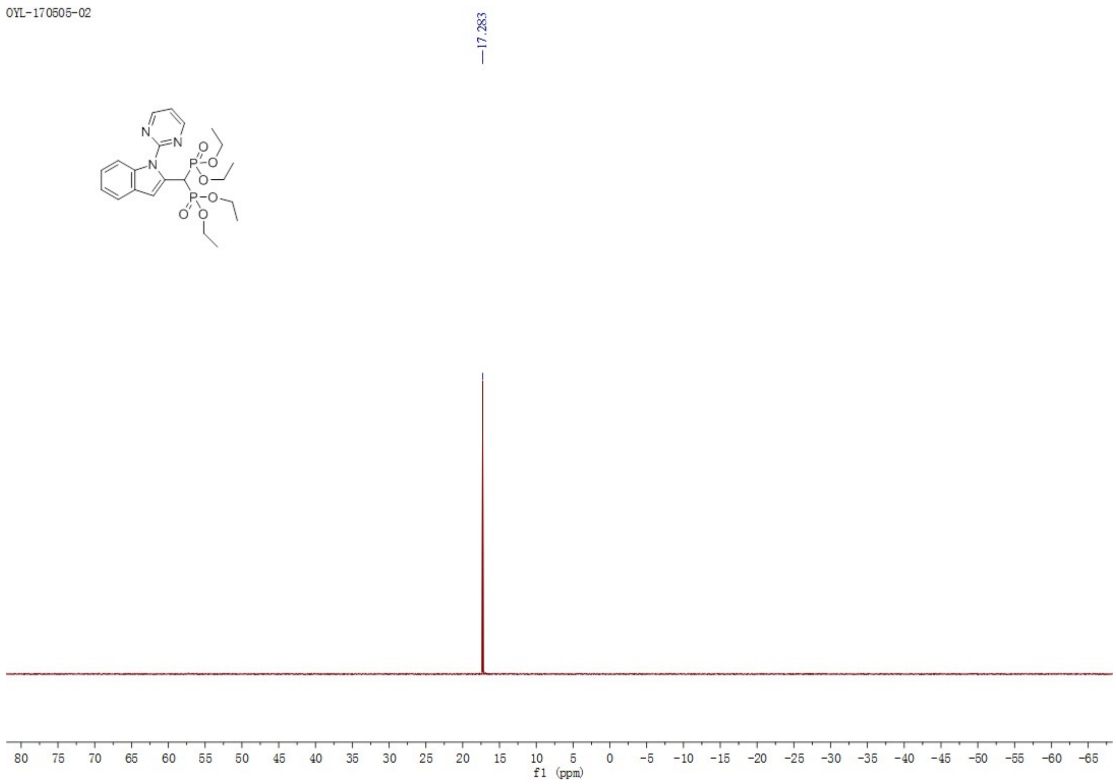
OYL-170505-01
18.787
f1 (ppm)

Compound **5g**

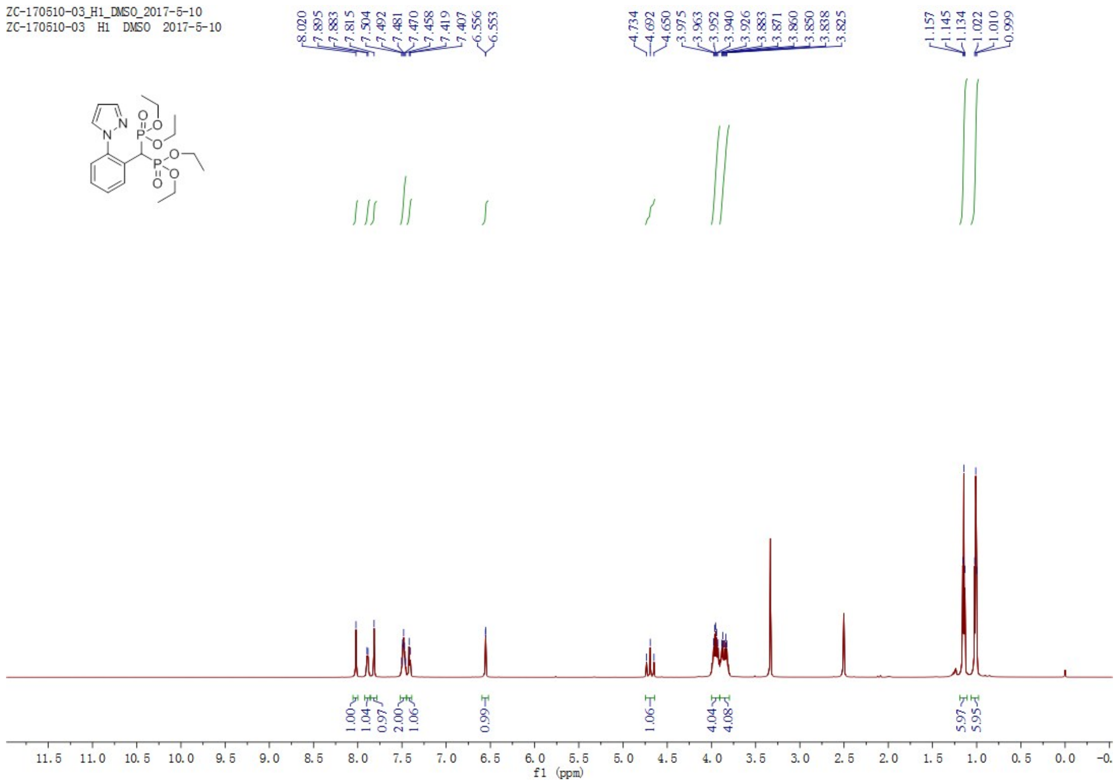


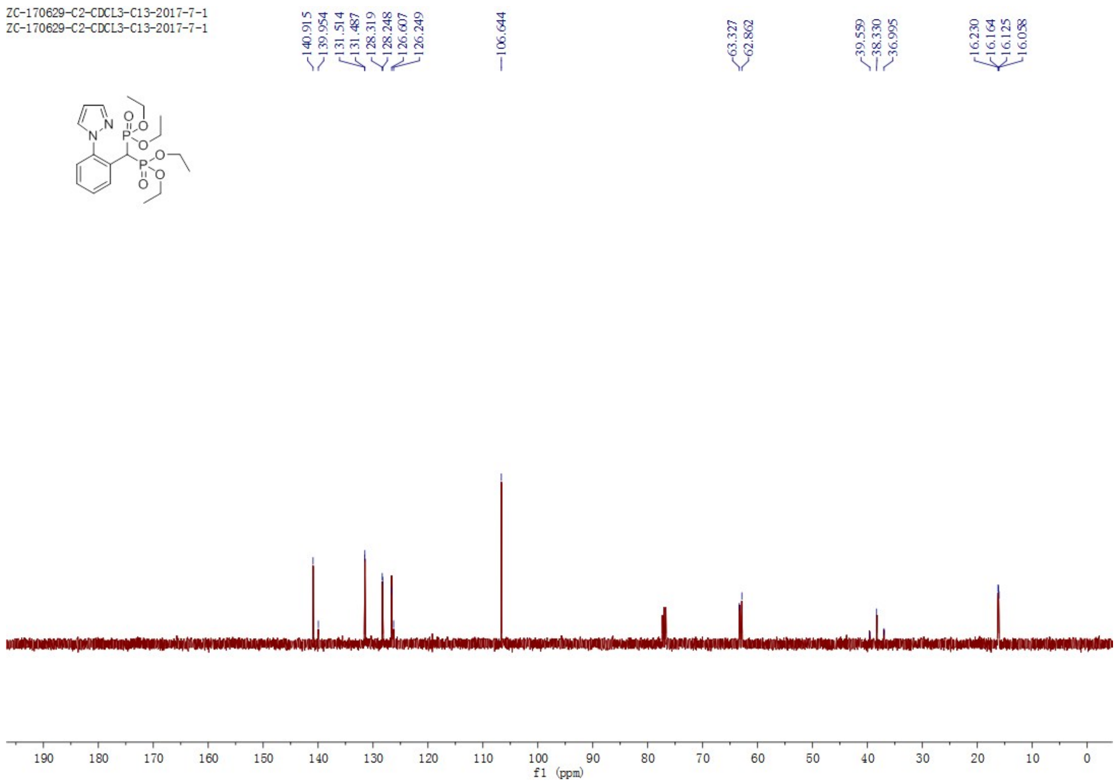
ZC-170505-02_H1_DMSO_2017-5-5
ZC17050502 H1 DMSO 2017-5-5
9.001
8.989
8.188
8.168
7.658
7.640
7.494
7.243
7.223
7.208
7.190
7.063
6.193
6.128
6.063
4.010
3.993
3.972
3.953
3.946
3.927
3.908
3.888
3.868
1.146
1.129
1.111
1.042
1.024
1.007
2.00
1.04
1.08
1.05
2.29
0.97
1.10
8.41
6.13
6.23
f1 (ppm)

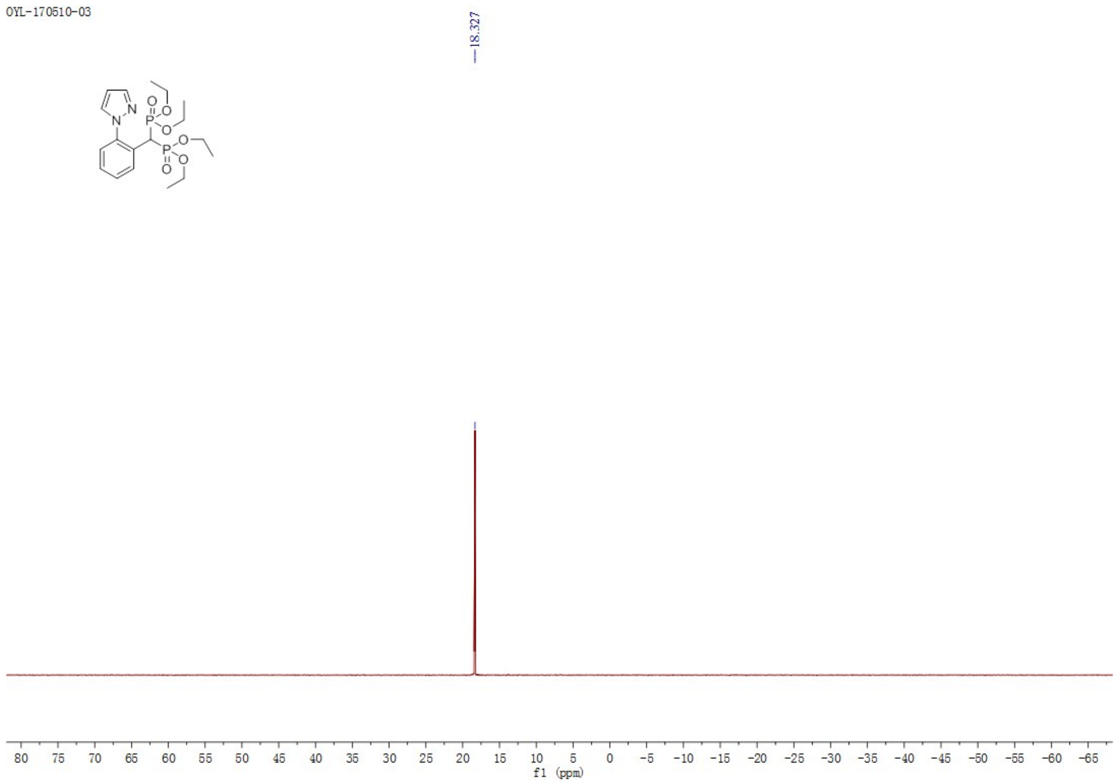

ZC-170629-C1-CDCL3-C13-2017-7-1
ZC-170629-C1-CDCL3-C13-2017-7-1
158.066
136.790
128.597
128.049
123.434
122.060
120.610
119.211
117.137
114.399
110.872
63.533
62.839
38.605
37.270
35.935
16.230
f1 (ppm)


OYL-170505-02
17.283
f1 (ppm)

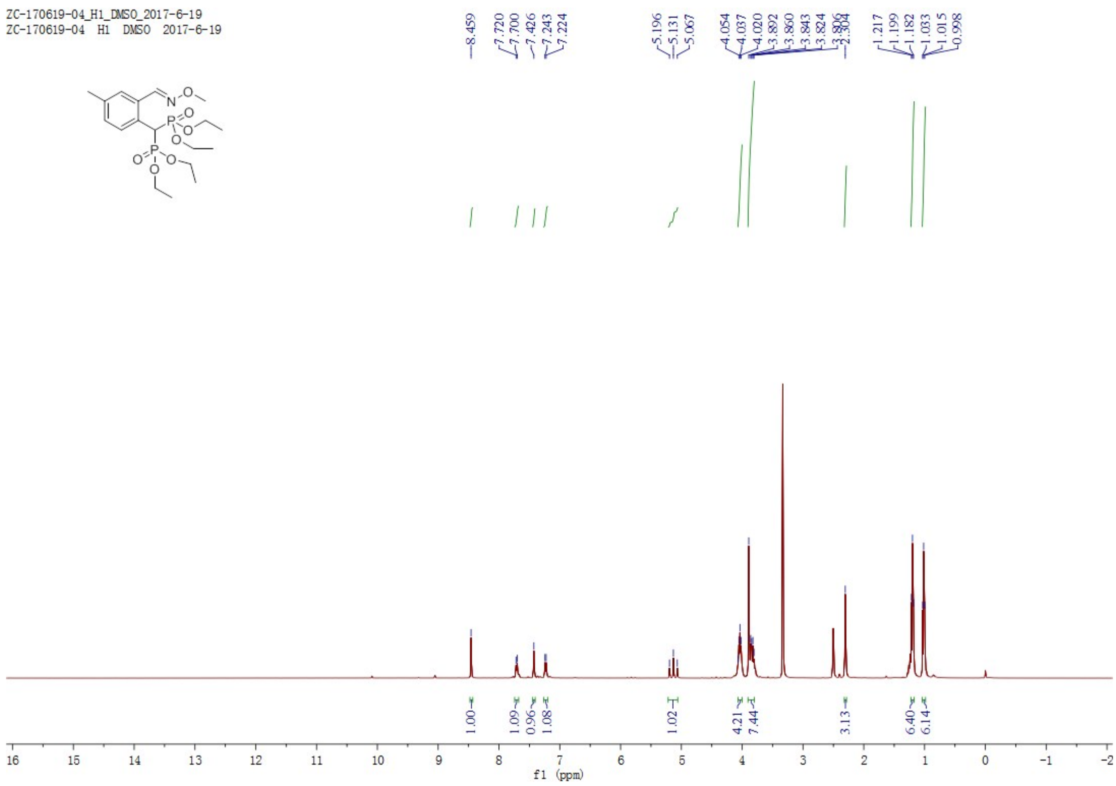
Compound **5h**

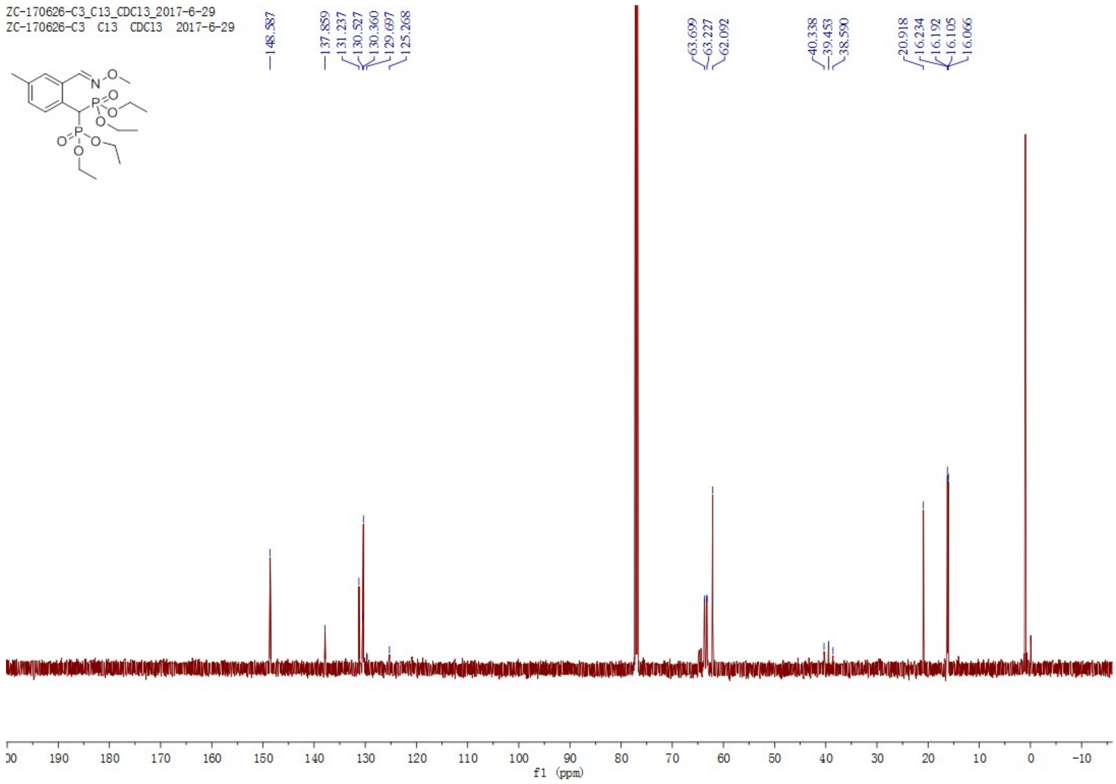

ZC-170510-03_H1_DMSO_2017-5-10
ZC-170510-03 H1 DMSO 2017-5-10
8.020 7.895 7.883 7.815 7.504 7.492 7.481 7.470 7.458 7.419 7.407 6.556 6.553
4.734 4.692 4.650 3.975 3.963 3.952 3.940 3.926 3.883 3.871 3.860 3.850 3.838 3.825
1.157 1.145 1.134 1.022 1.010 0.999
1.00 1.04 0.97 2.00 1.06 0.99 1.06 4.04 4.08 5.97 5.95
f1 (ppm)

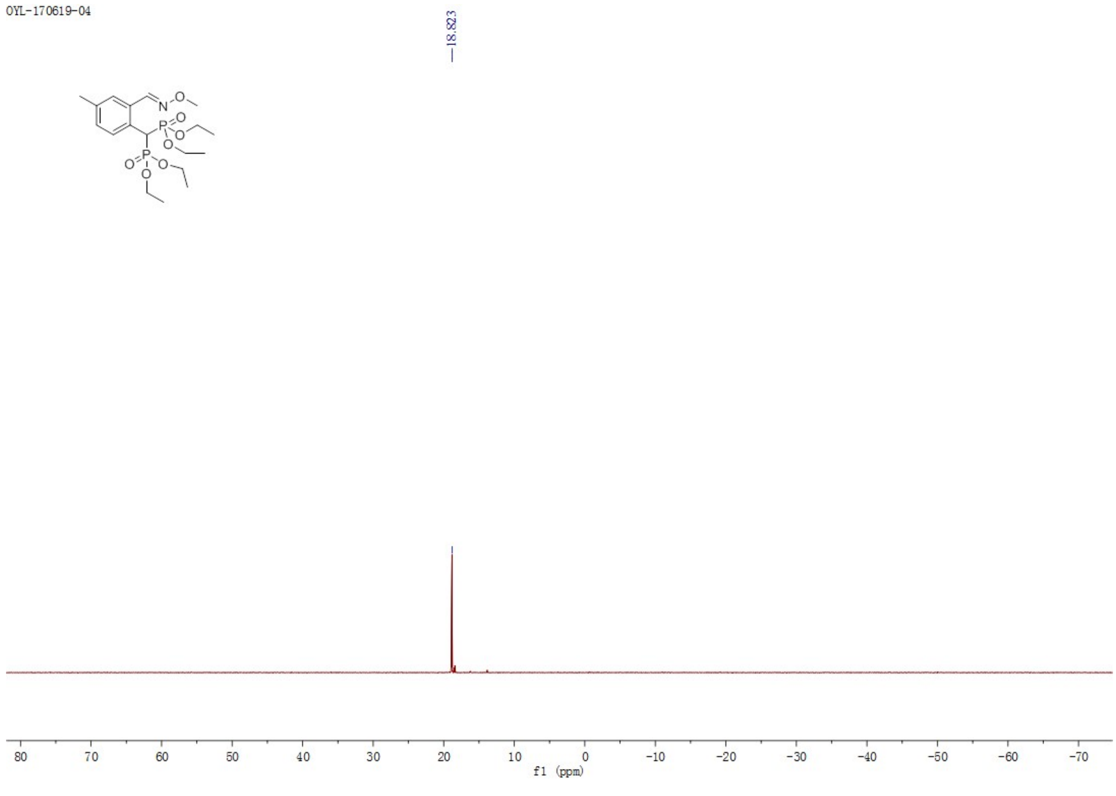

ZC-170629-C2-CDCL3-C13-2017-7-1
ZC-170629-C2-CDCL3-C13-2017-7-1
140.915 139.954 131.514 131.487 128.319 128.248 126.607 126.249
106.644
63.327 62.862
39.559 38.330 36.995
16.230 16.164 16.125 16.058
f1 (ppm)


OYL-170510-03
18.327
f1 (ppm)

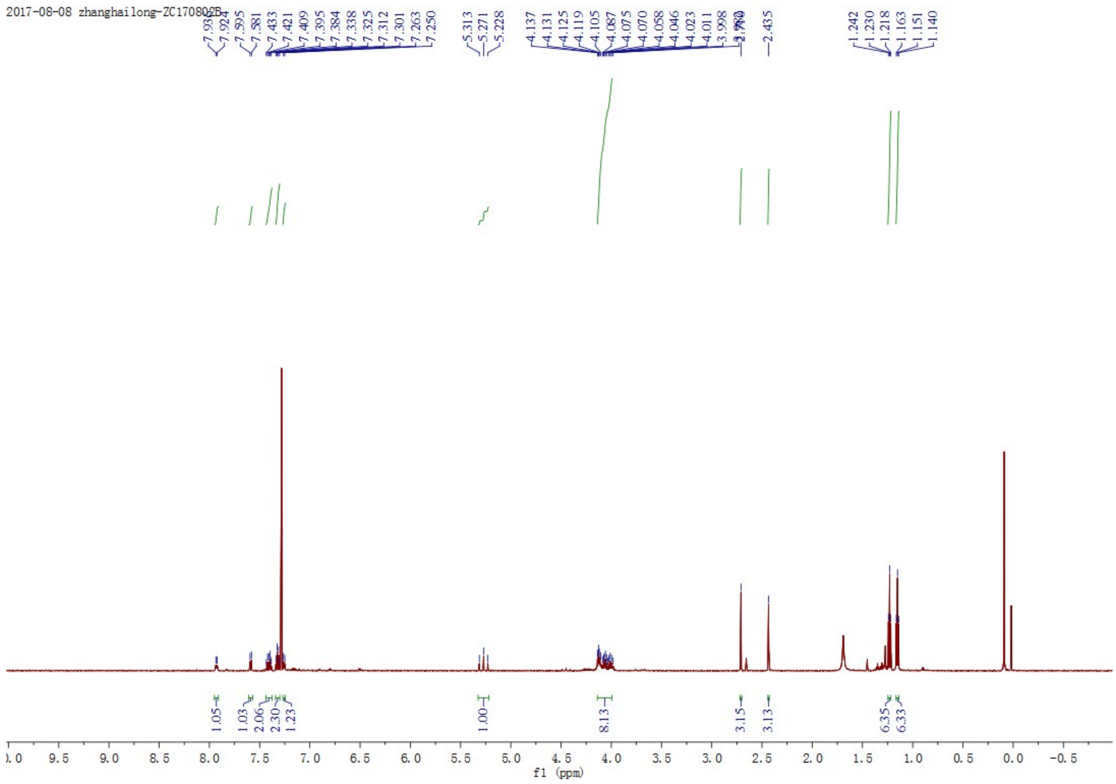
Compound **5i**


ZC-170619-04_H1_DMSO_2017-6-19
ZC-170619-04 H1 DMSO 2017-6-19
f1 (ppm)

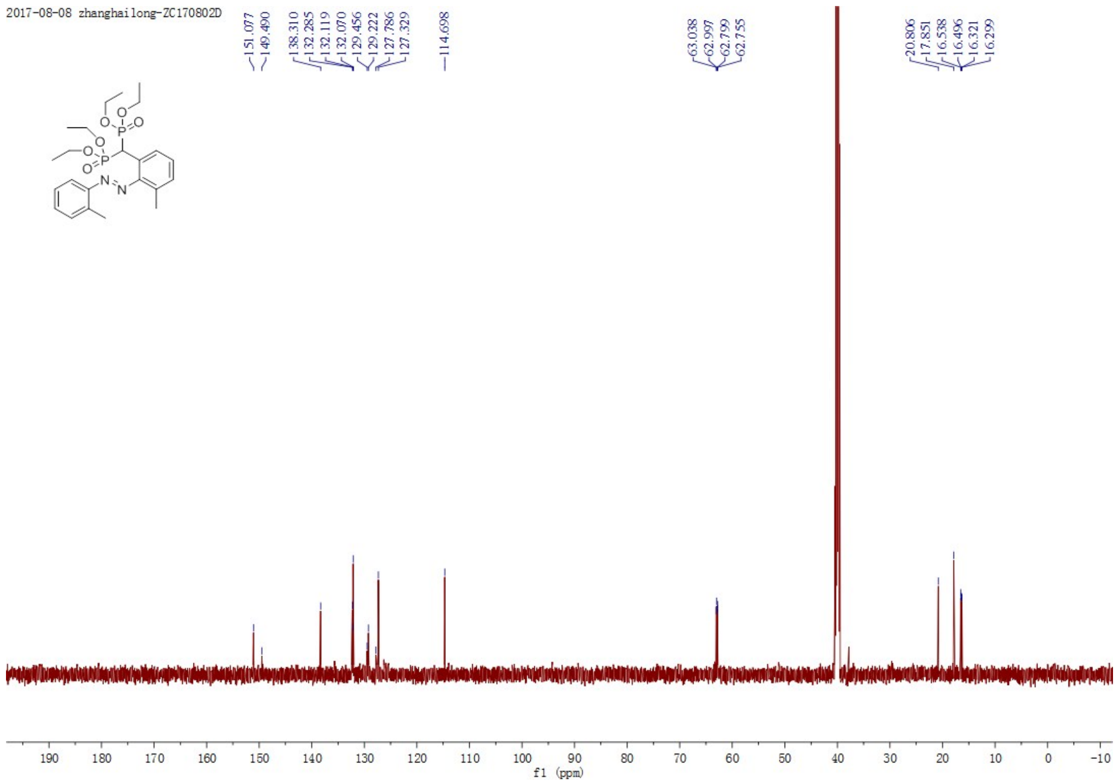

ZC-170626-C3_C13_CDCl3_2017-6-29
ZC-170626-C3 C13 CDCl3 2017-6-29
148.587
137.859
131.237
130.527
130.360
129.697
125.268
63.699
63.227
62.092
40.338
39.453
38.590
20.918
16.234
16.192
16.105
16.066
f1 (ppm)


OYL-170619-04
18.823
f1 (ppm)

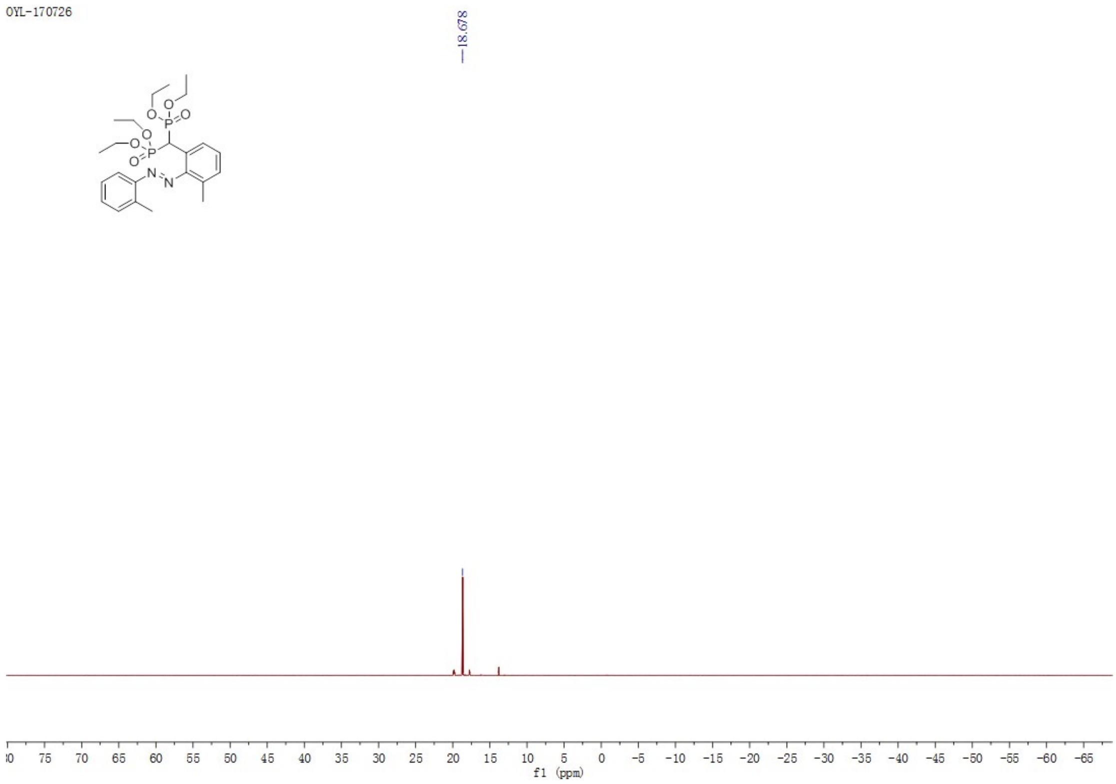
Compound **5j**



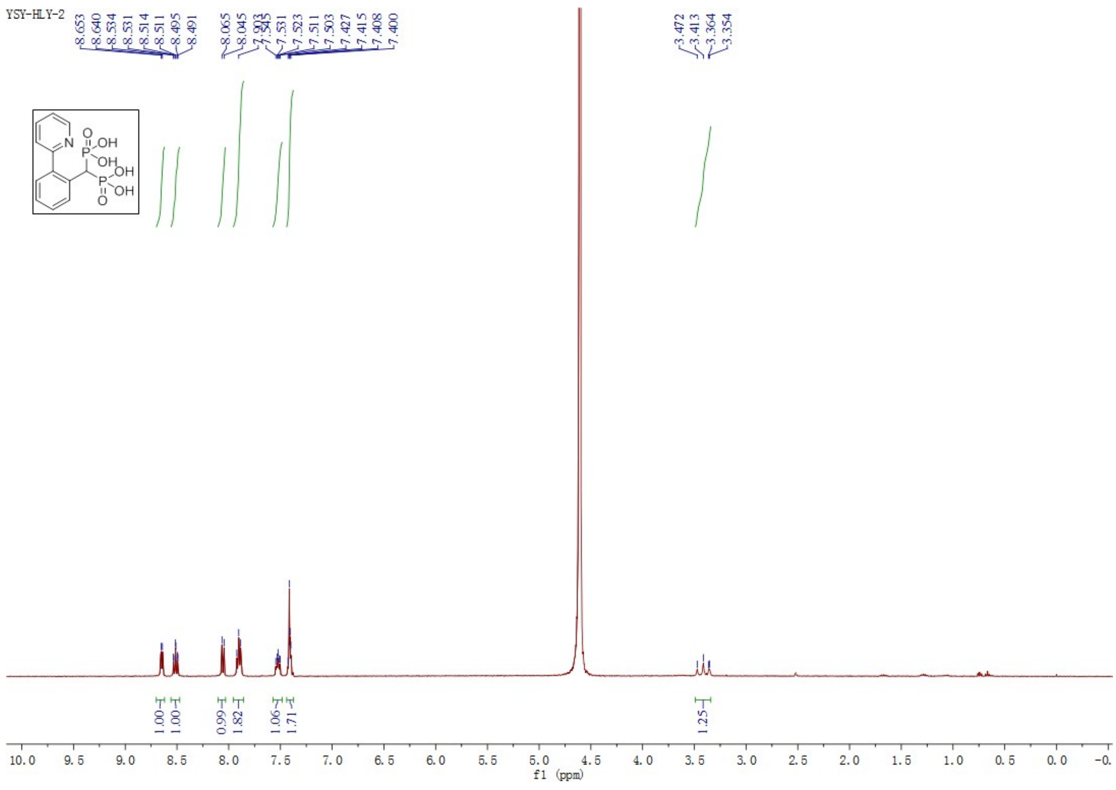
2017-08-08 zhanghailong-ZC170802B
7.595
7.581
7.433
7.421
7.409
7.395
7.384
7.338
7.325
7.312
7.301
7.263
7.250
5.313
5.271
5.228
4.137
4.131
4.125
4.119
4.105
4.087
4.075
4.070
4.058
4.046
4.023
4.011
3.998
2.435
1.242
1.230
1.218
1.163
1.151
1.140
1.05
1.03
2.06
2.30
1.23
1.00
8.13
3.15
3.13
6.35
6.33
f1 (ppm)

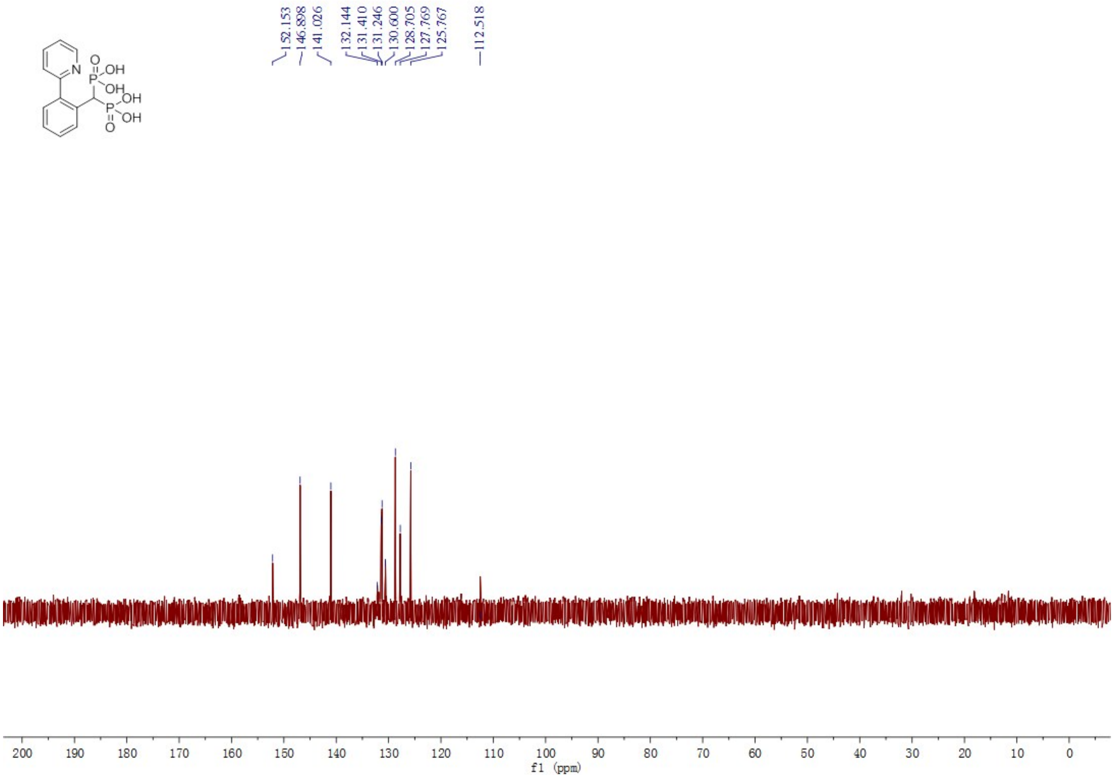


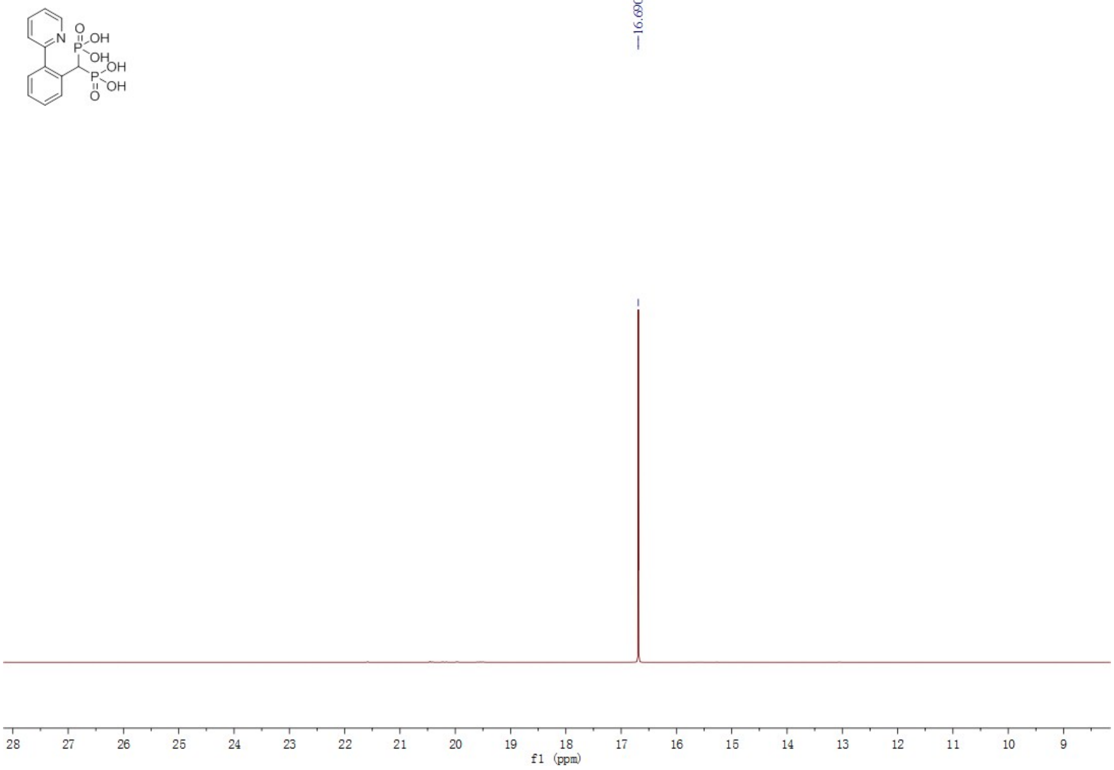
2017-08-08 zhanghailong-ZC170802D
151.077
149.490
138.310
132.285
132.119
132.070
129.456
129.222
127.786
127.329
114.698
63.038
62.997
62.799
62.755
20.806
17.851
16.538
16.496
16.321
16.299
f1 (ppm)



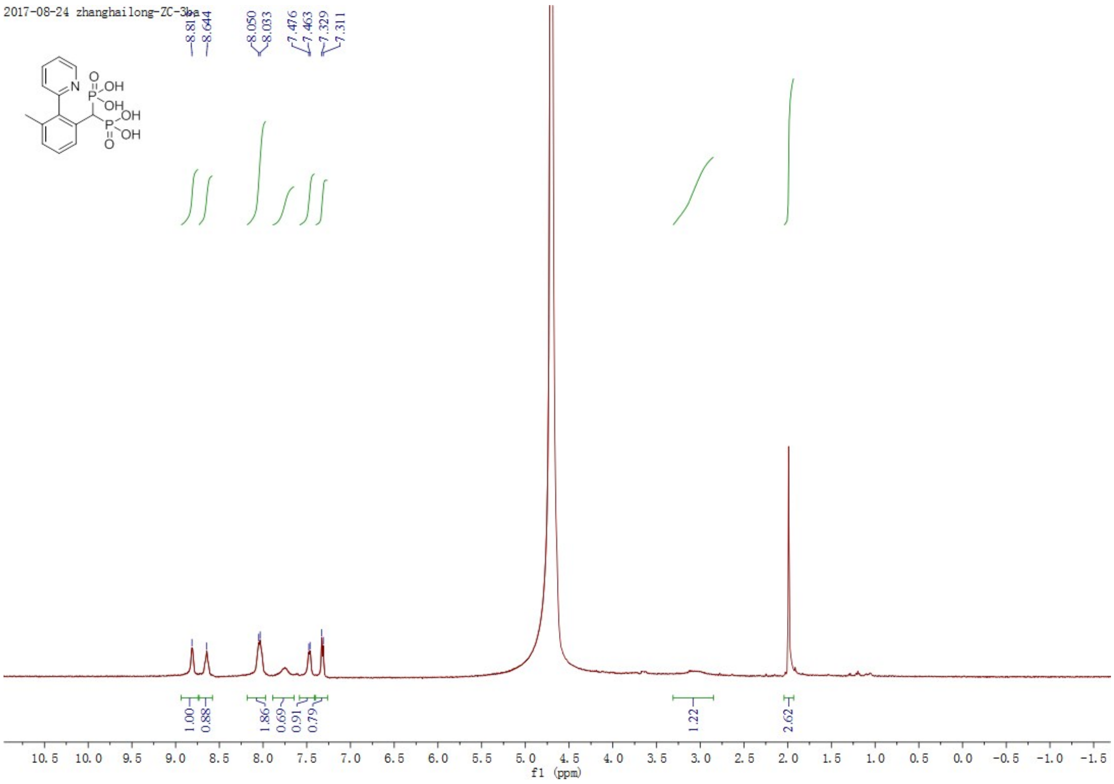
Compound **3aa acid**

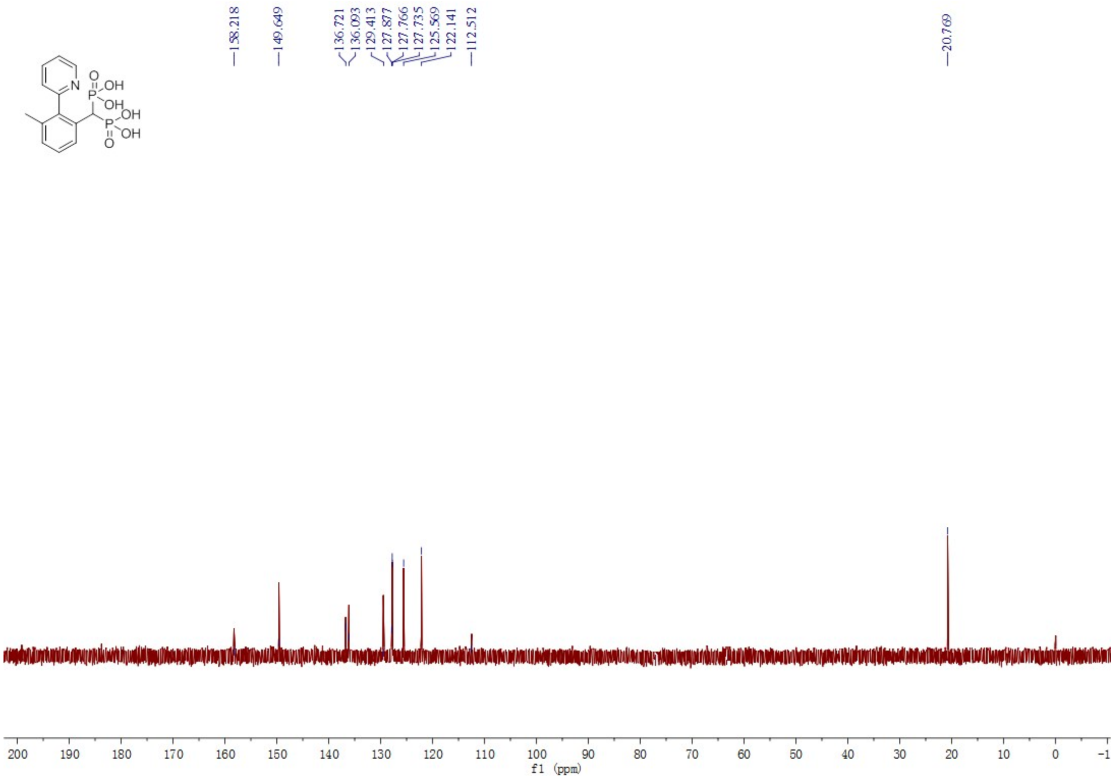


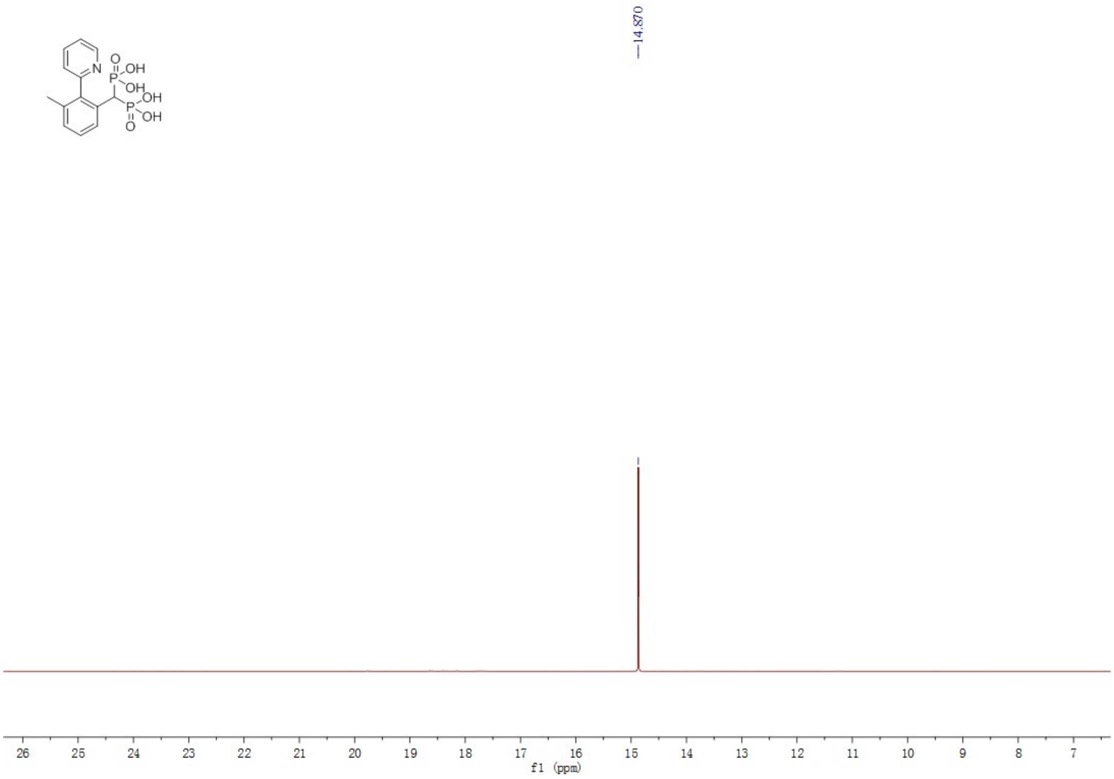




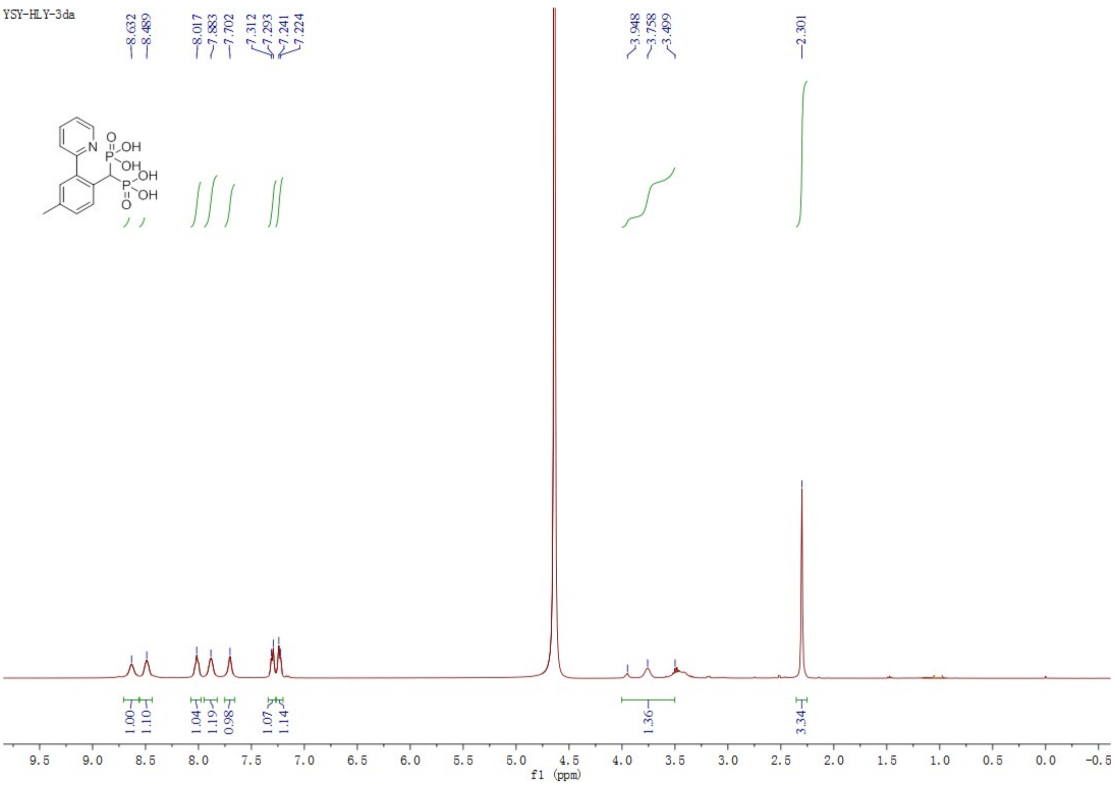
Compound **3ba acid**

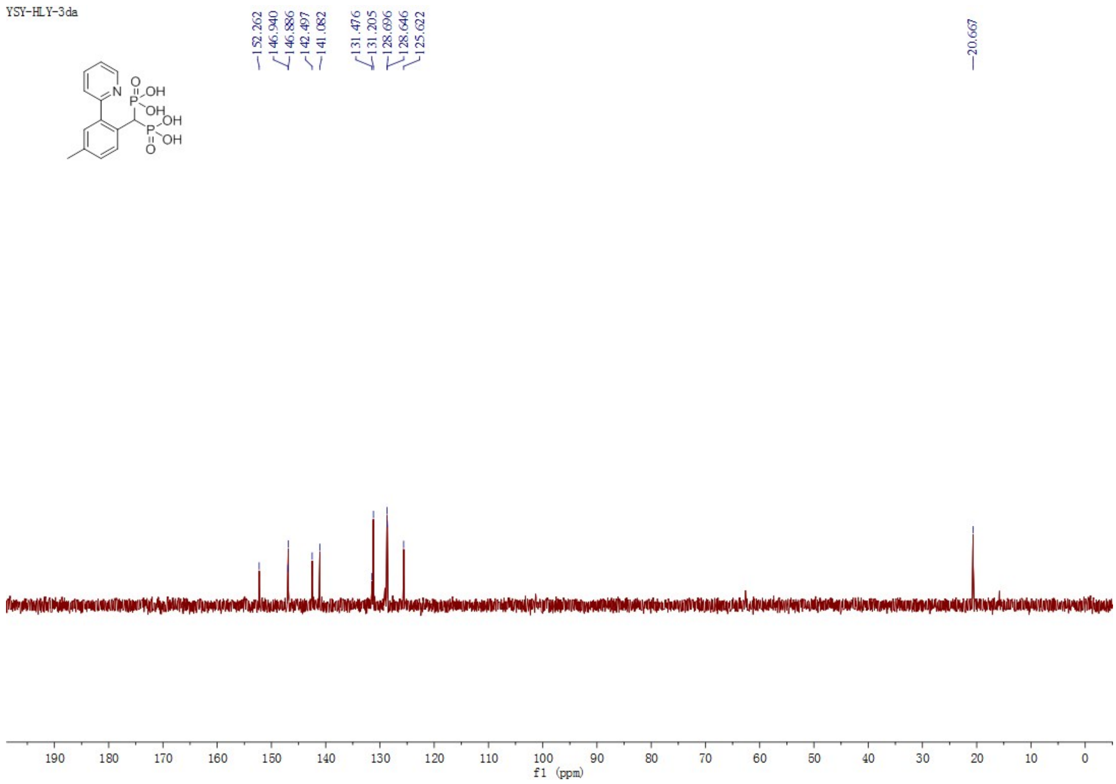

2017-08-24 zhanghailong-ZC-3ba
8.811
8.644
8.050
8.033
7.476
7.463
7.329
7.311
N
O
P
OH
OH
P
OH
OH
O
1.00
0.88
1.86
0.69
0.91
0.79
1.22
2.62
f1 (ppm)

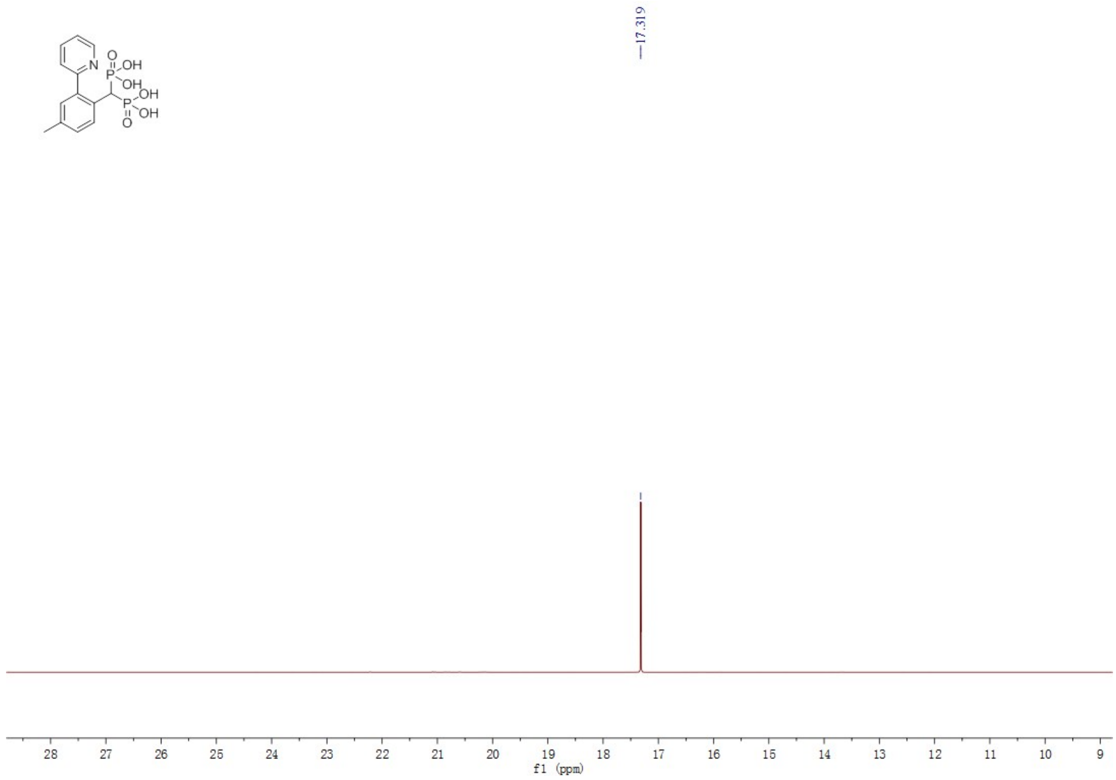

158.218
149.649
136.721
136.093
129.413
127.877
127.766
127.735
125.569
122.141
112.512
20.769
N
O
P
OH
OH
P
OH
OH
O
f1 (ppm)



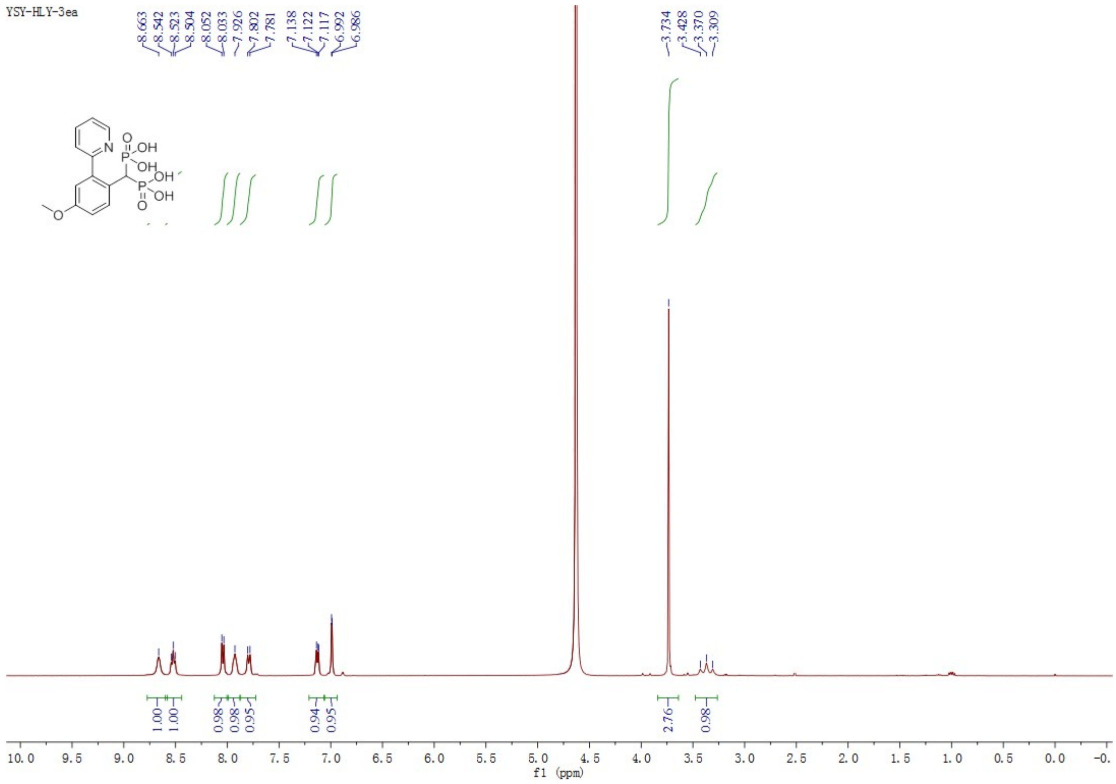
Compound **3da acid**

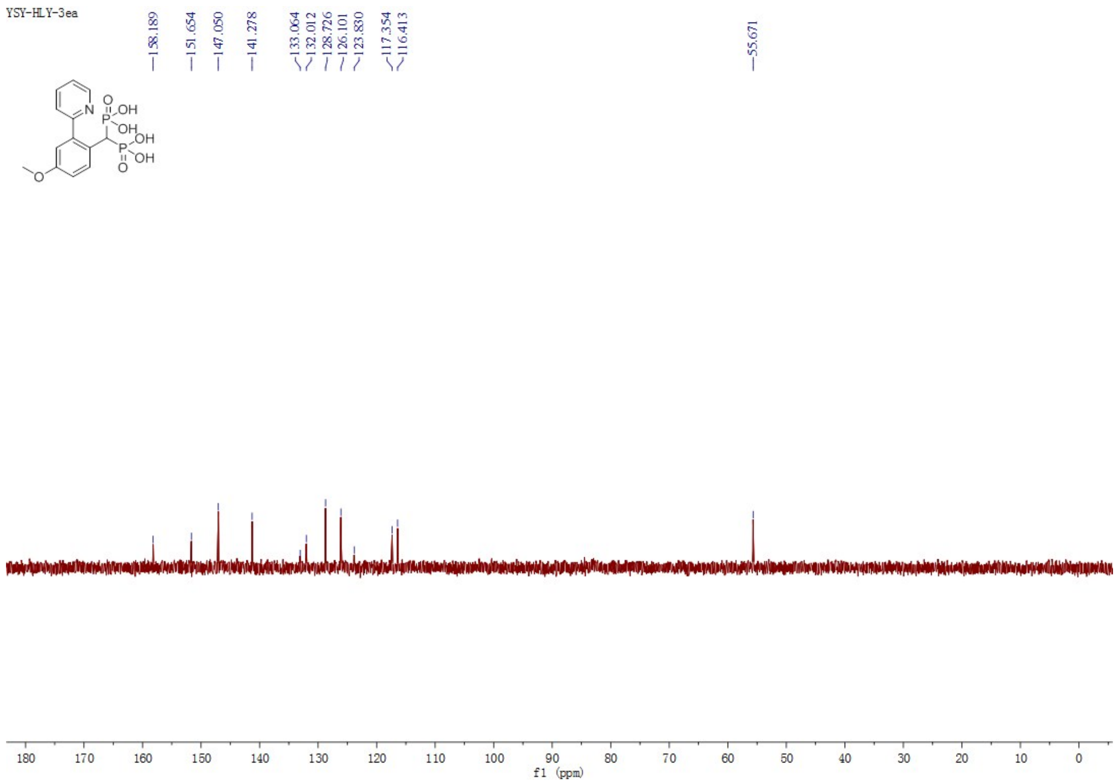


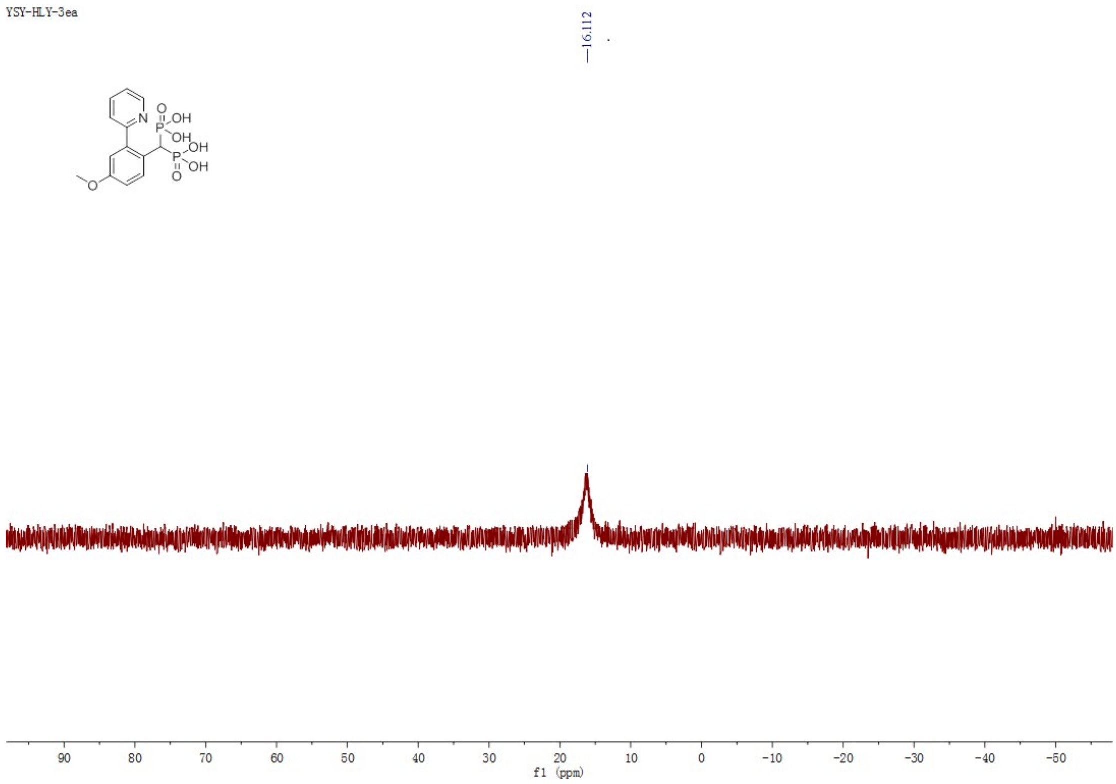




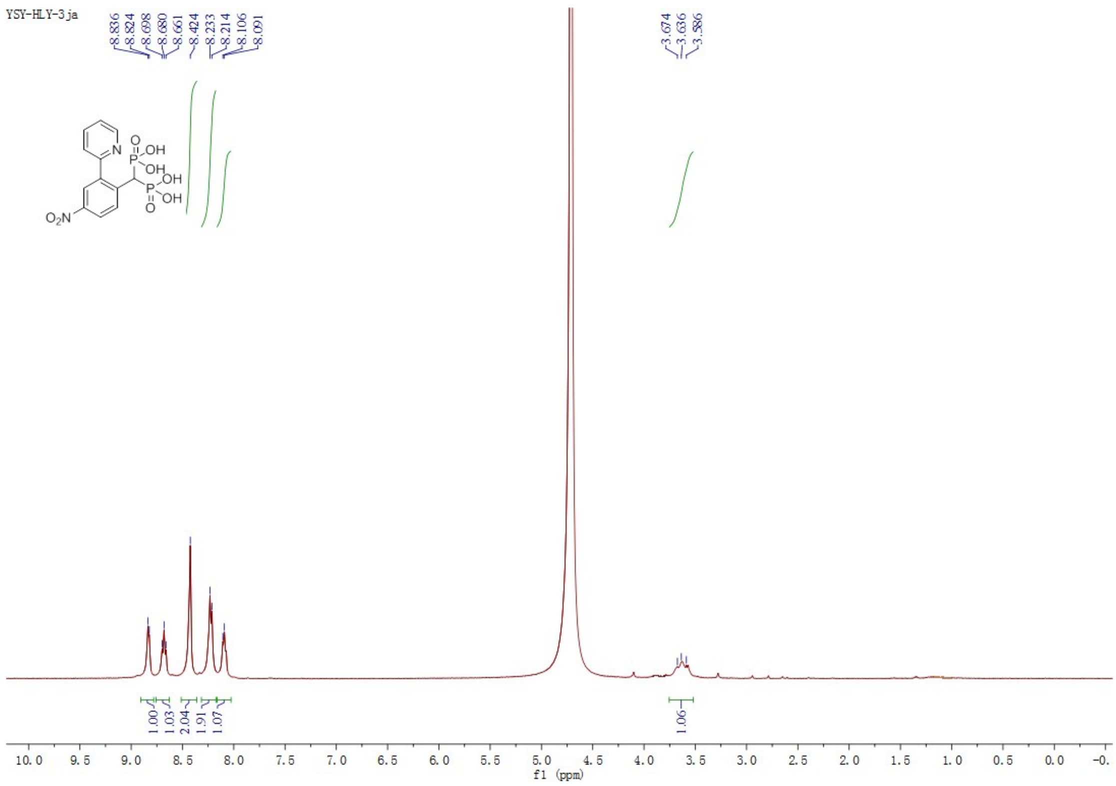
Compound **3ea acid**

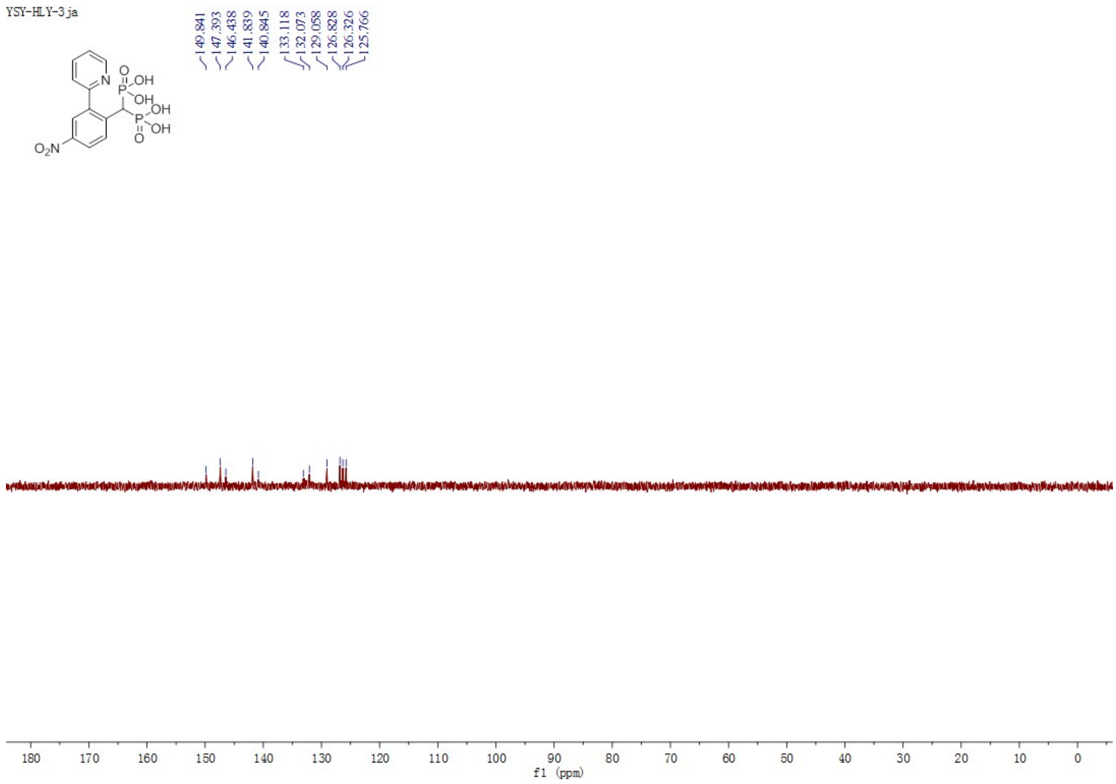

YSY-HLY-3ea
8.663
8.542
8.523
8.504
8.052
8.033
7.926
7.802
7.781
7.138
7.122
7.117
6.992
6.986
3.734
3.428
3.370
3.309
1.00
1.00
0.98
0.98
0.95
0.94
0.95
2.76
0.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

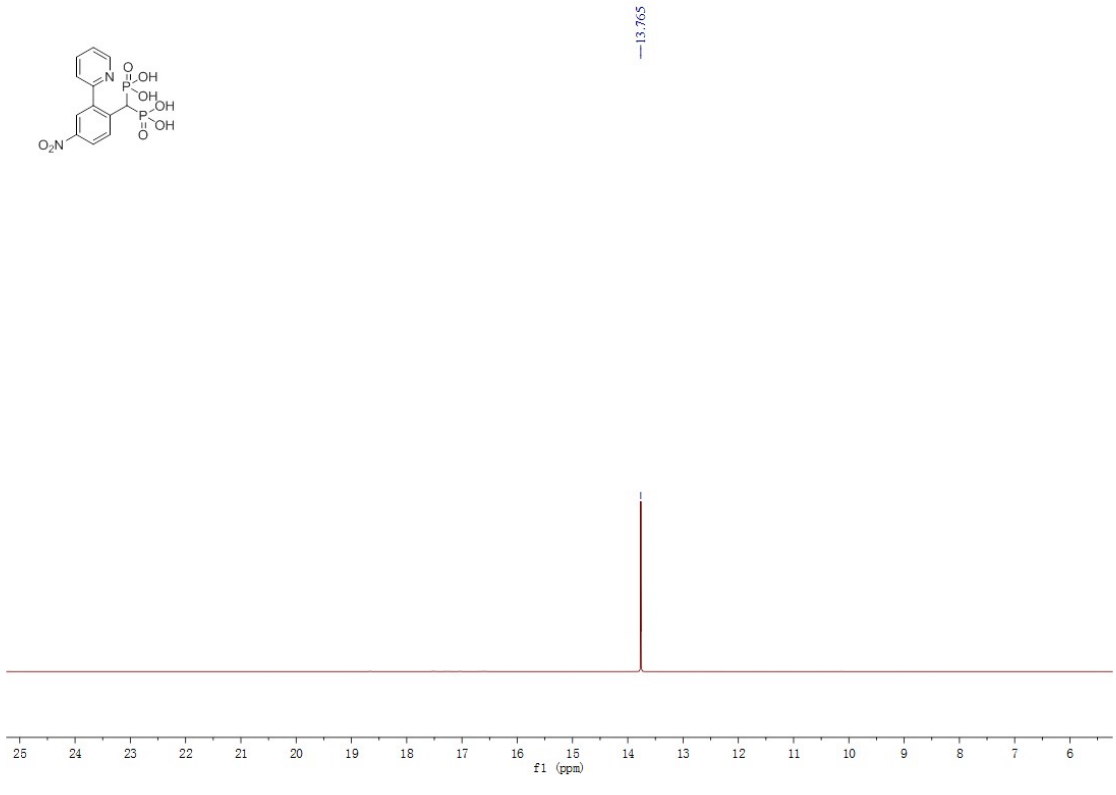

YSY-HLY-3ea
158.189
151.654
147.050
141.278
133.064
132.012
128.726
126.101
123.830
117.354
116.413
55.671
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



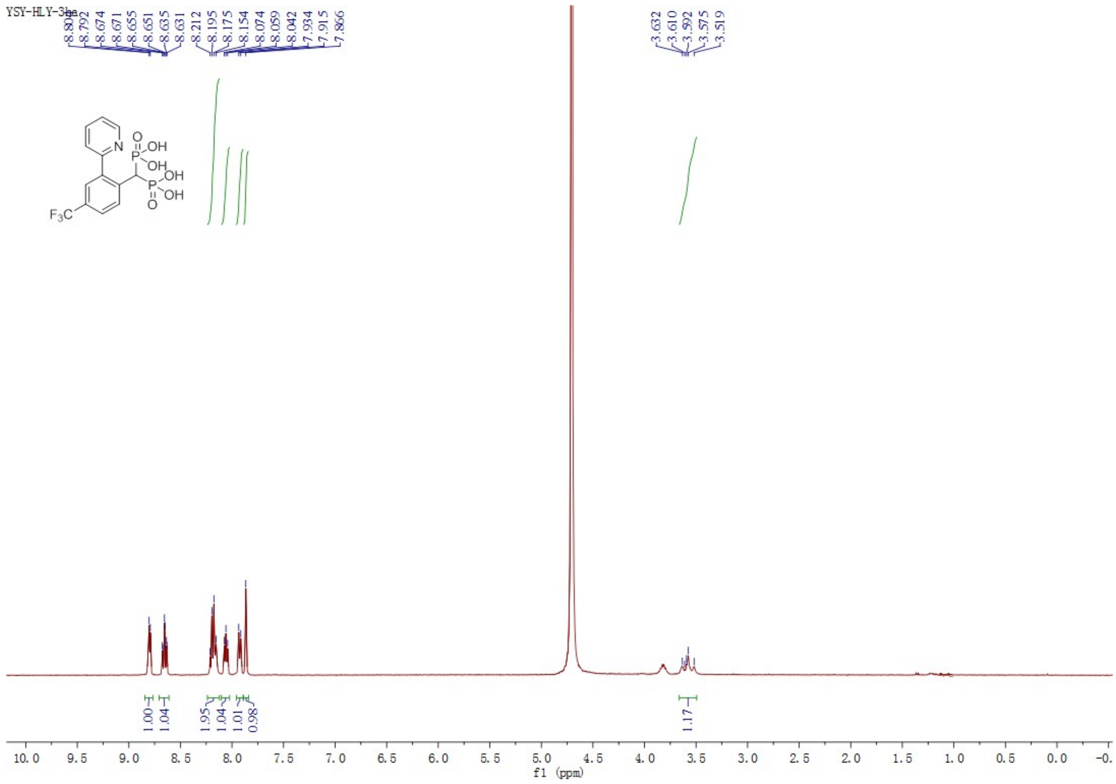
Compound **3ga acid**

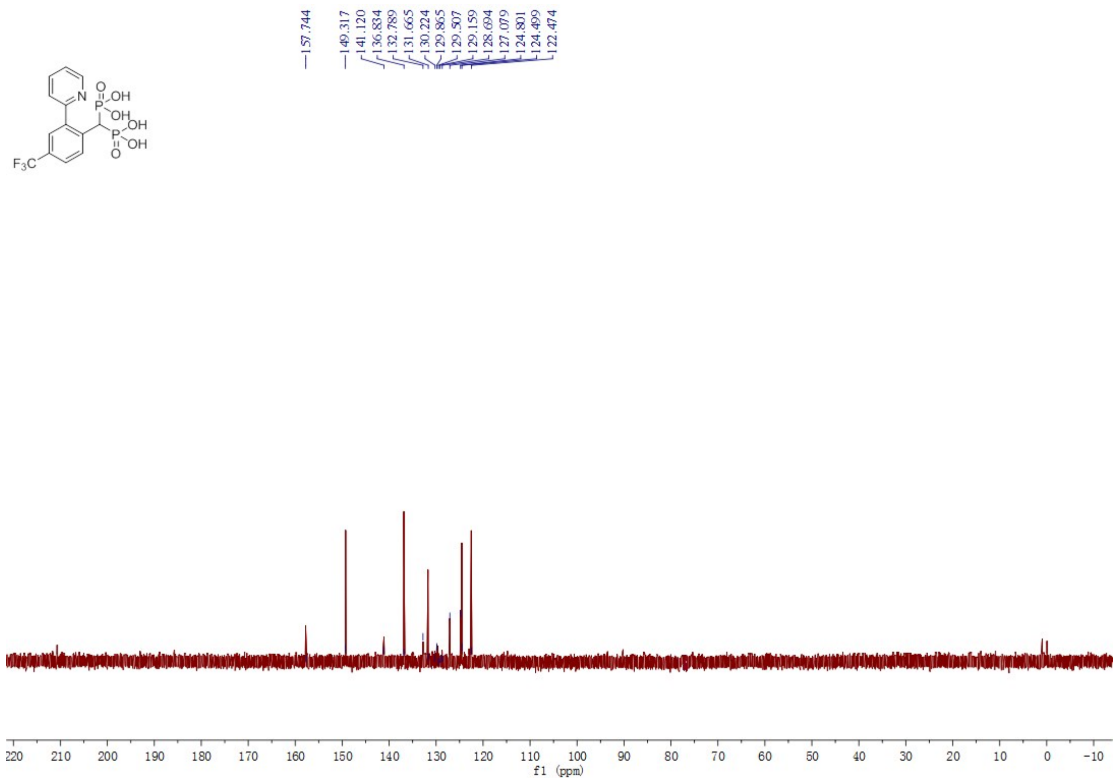


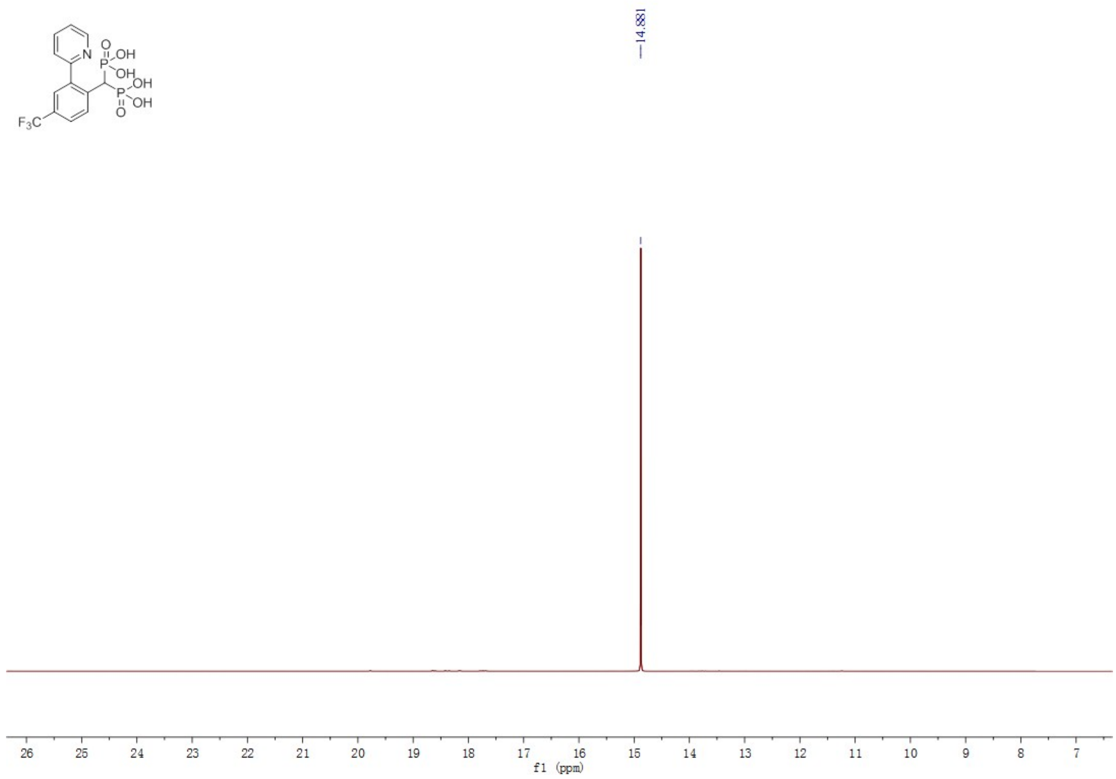




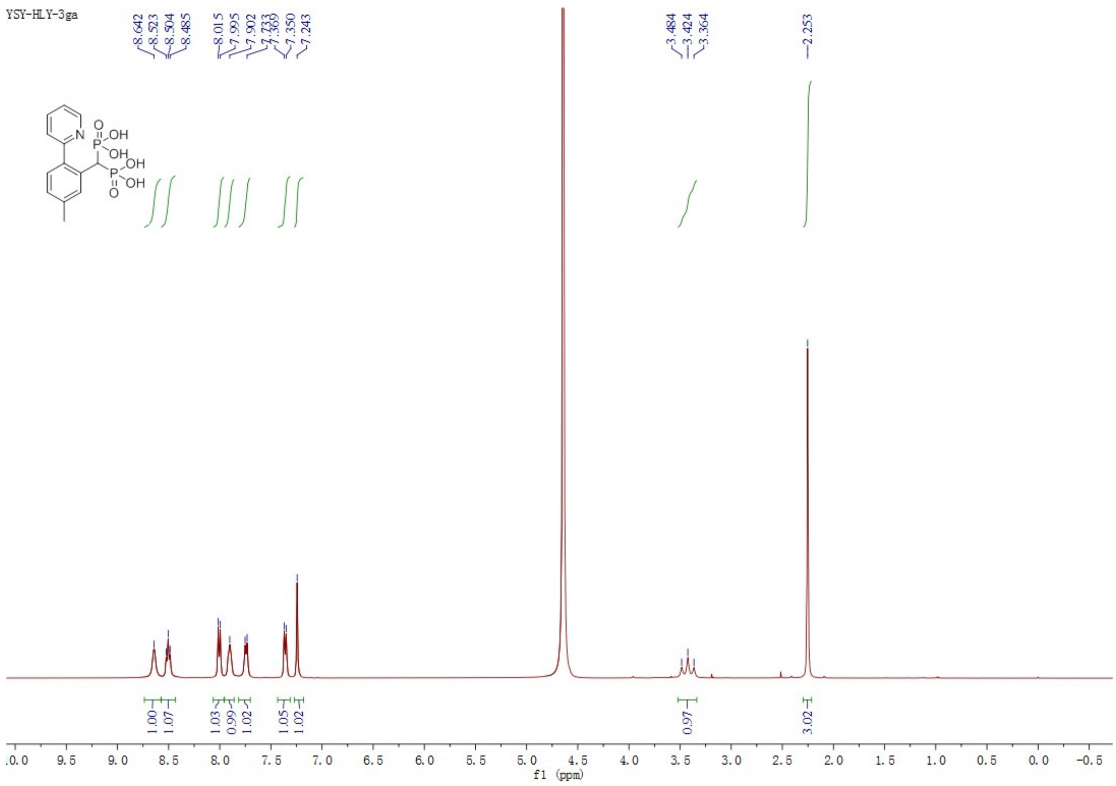
Compound **3ha acid**

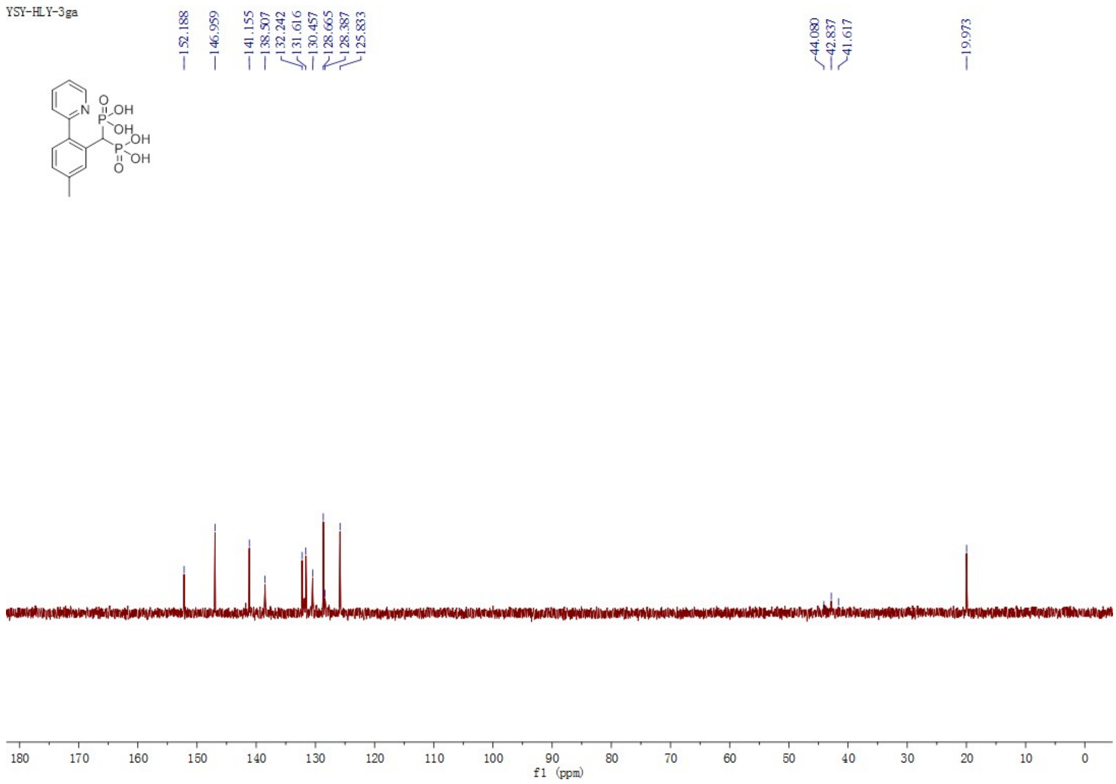

YSY-HLY-3ha
8.809 8.792 8.674 8.671 8.655 8.651 8.635 8.631 8.212 8.195 8.175 8.154 8.074 8.059 8.042 7.934 7.915 7.866
3.632 3.610 3.592 3.575 3.519
OH
OH
OH
OH
N
P
P
O
O
F3C
1.00 1.04 1.95 1.04 1.01 0.98 1.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

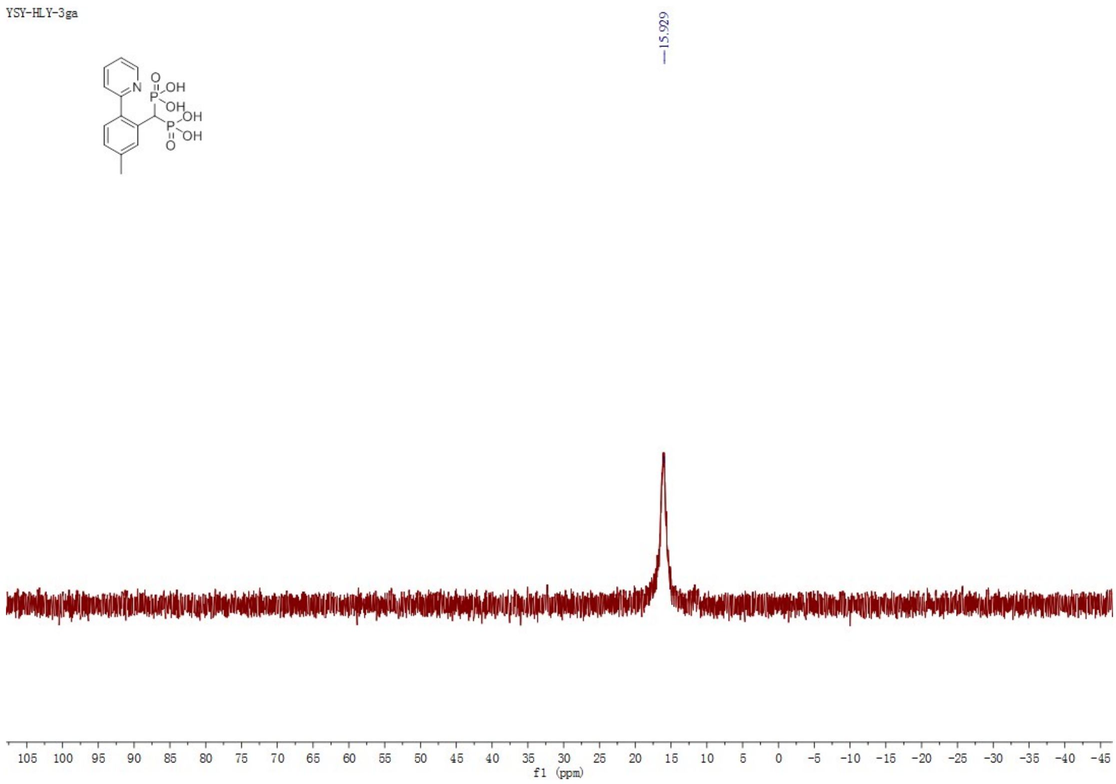

157.744
149.317 141.120 136.834 132.789 131.665 130.224 129.865 129.507 129.159 128.694 127.079 124.801 124.499 122.474
OH
OH
OH
OH
N
P
P
O
O
F3C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



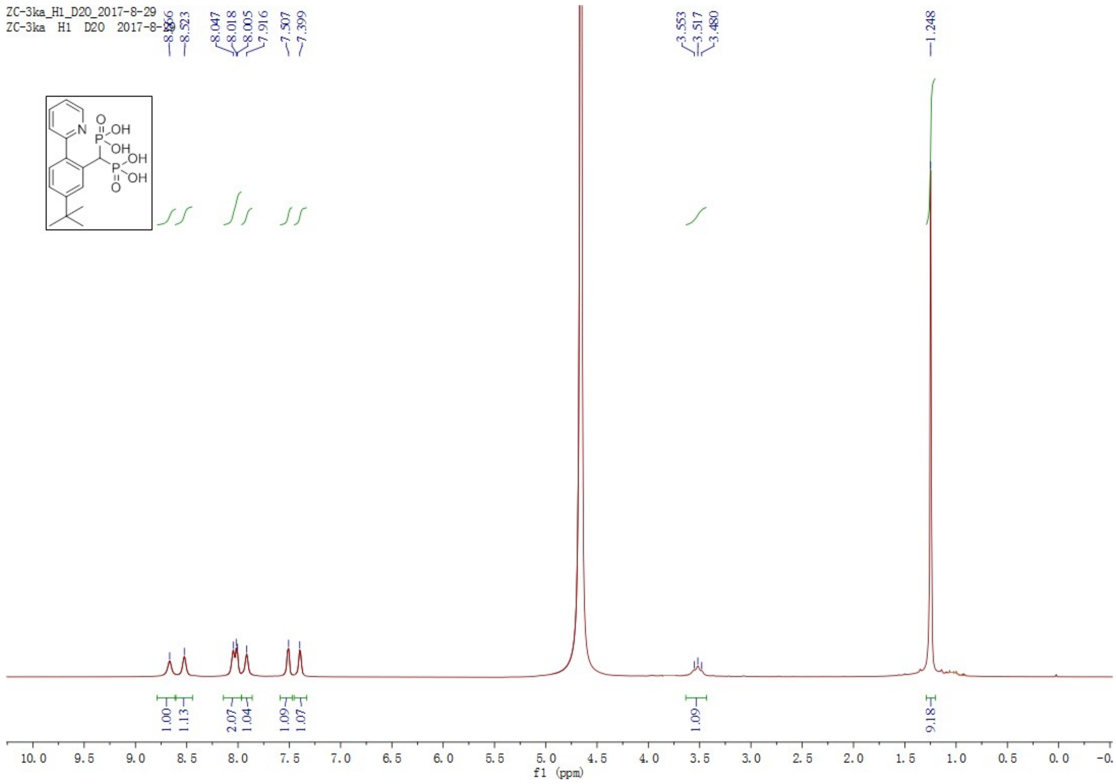
Compound **3ja acid**

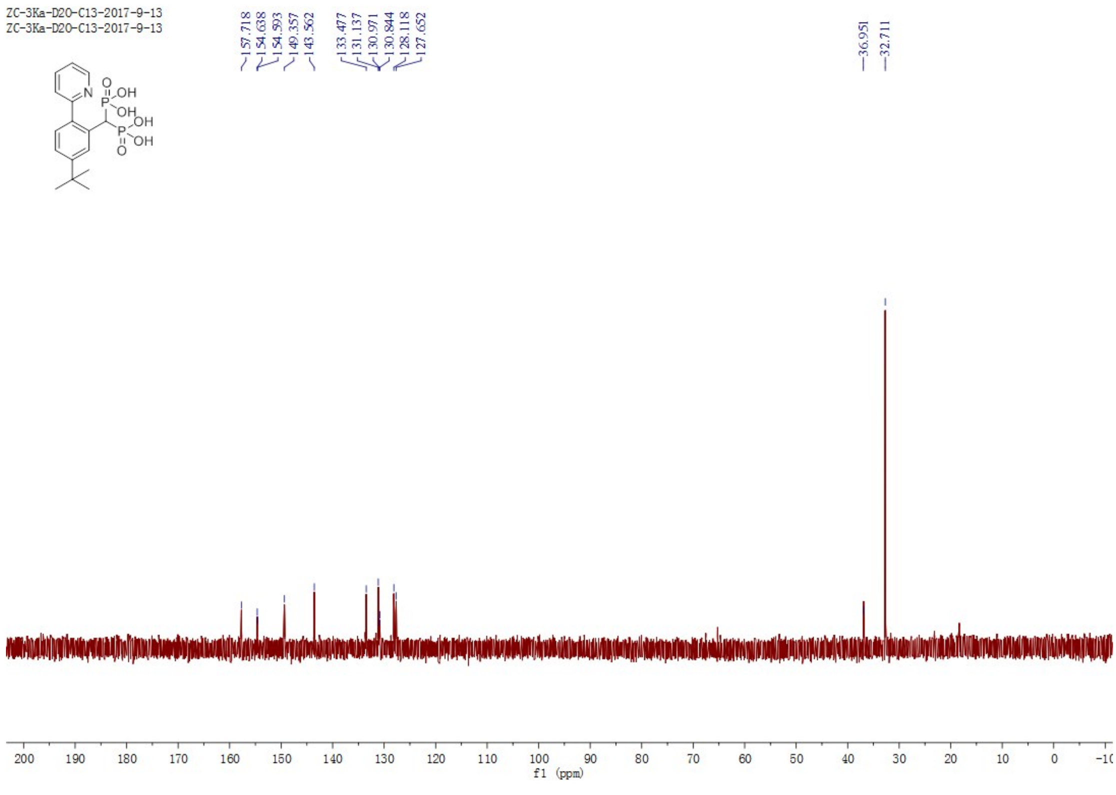


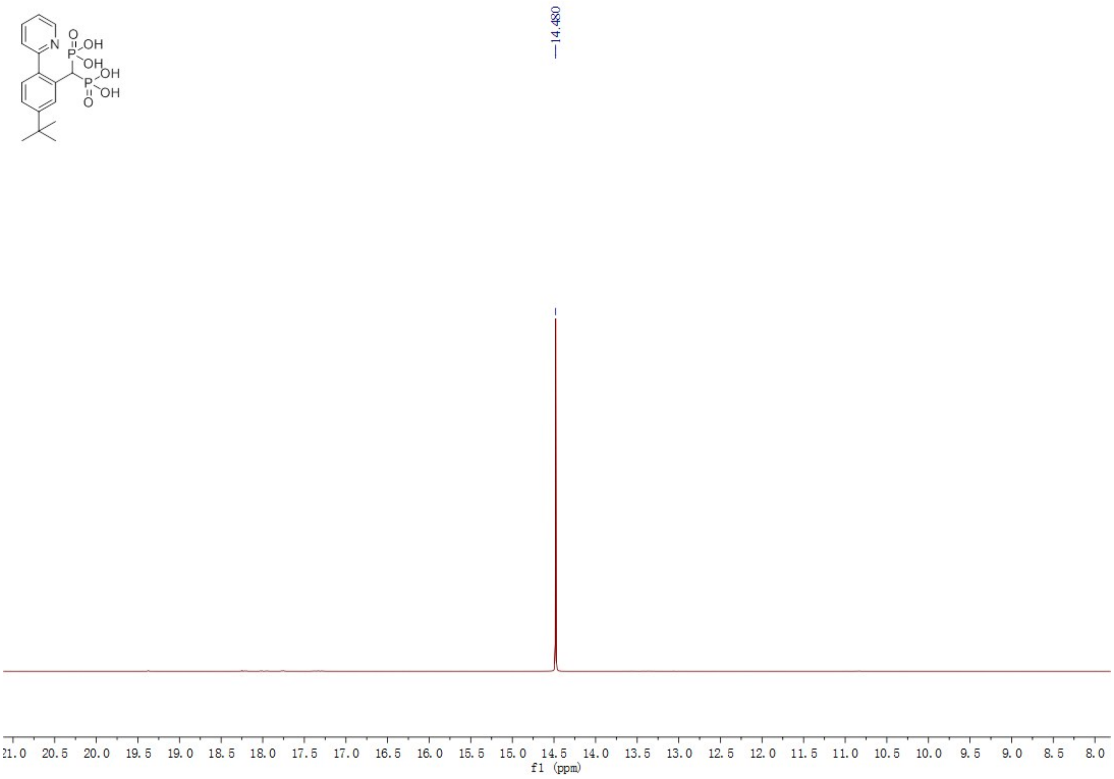




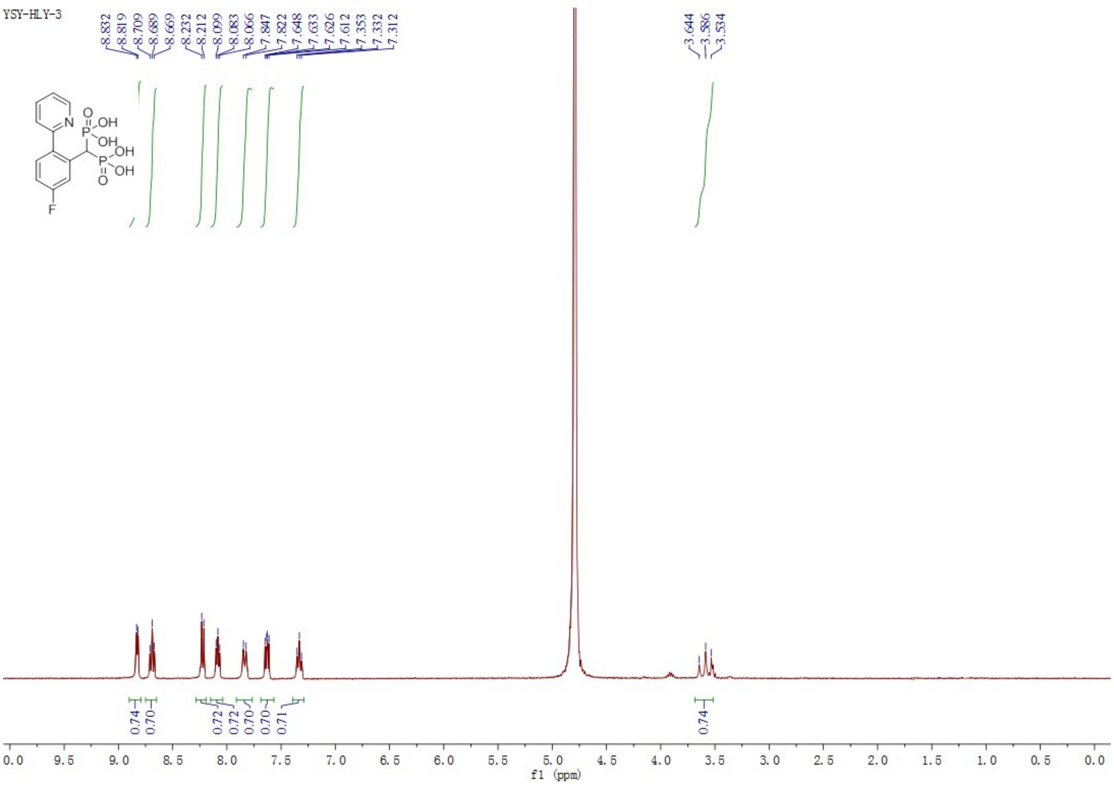
Compound **3ka acid**

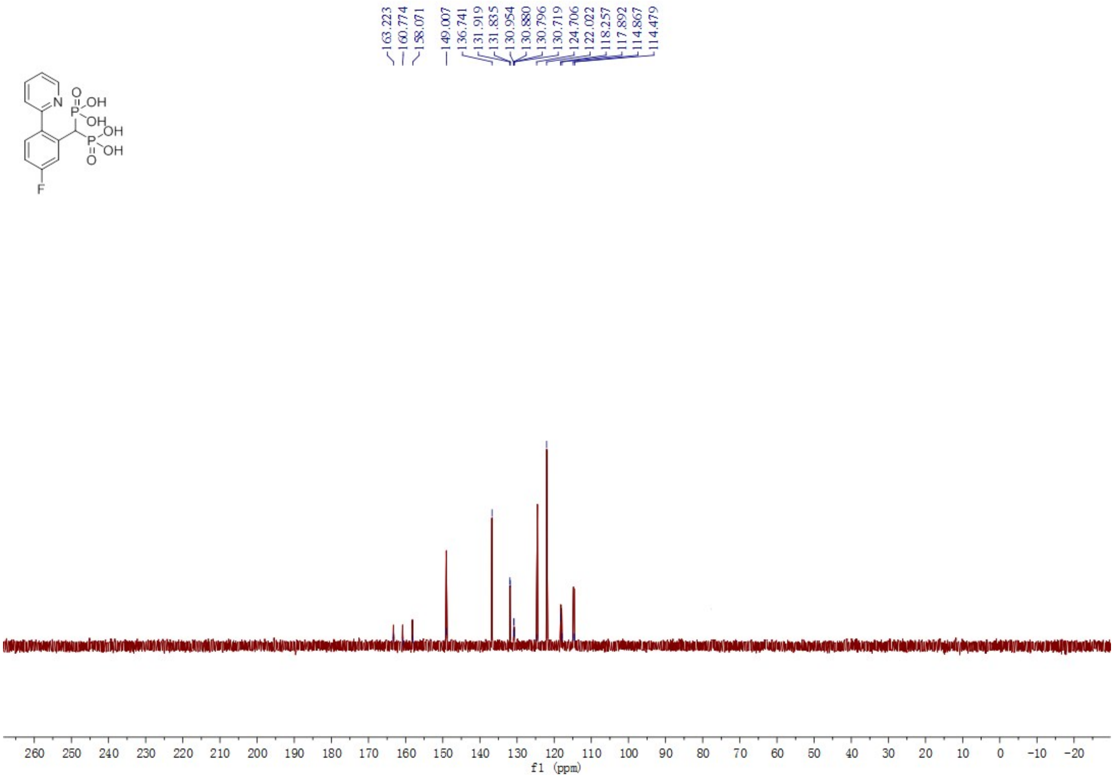

ZC-3ka_H1_D2O_2017-8-29
ZC-3ka H1 D2O 2017-8-29
8.656
8.523
8.047
8.018
8.005
7.916
7.507
7.399
3.553
3.517
3.480
1.248
1.00
1.13
2.07
1.04
1.09
1.07
1.09
9.18
f1 (ppm)

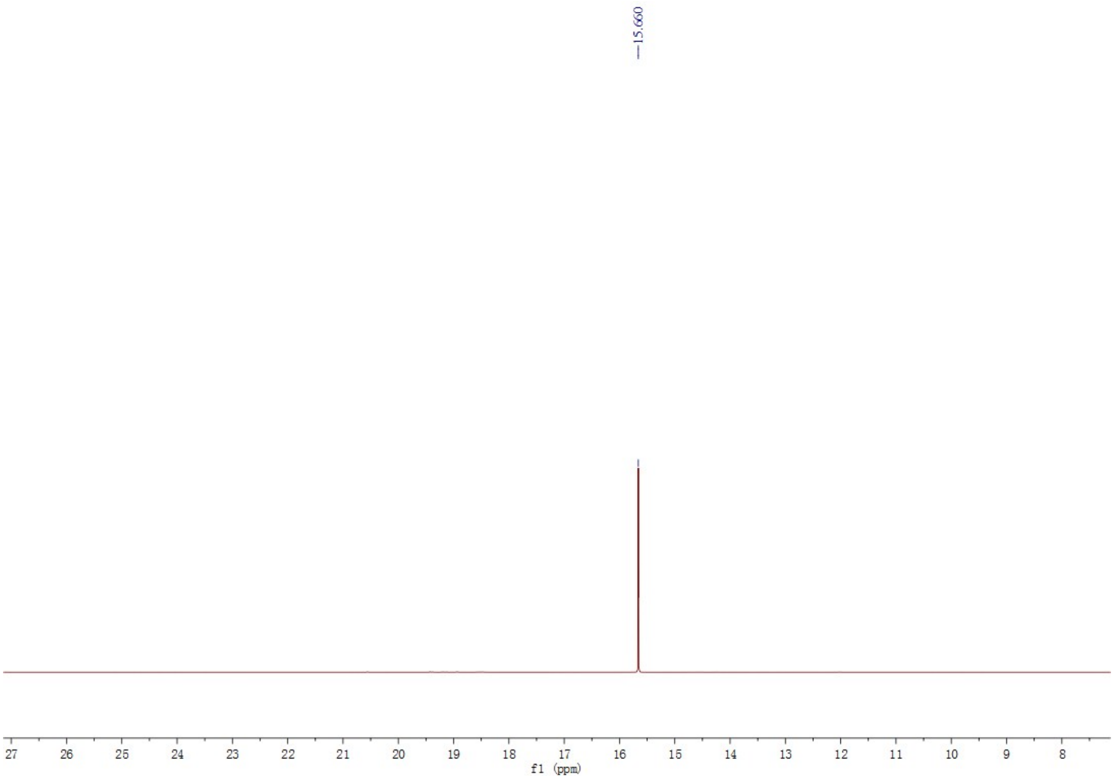

ZC-3Ka-D2O-C13-2017-9-13
ZC-3Ka-D2O-C13-2017-9-13
157.718
154.638
154.593
149.357
143.562
133.477
131.137
130.971
130.844
128.118
127.652
36.951
32.711
f1 (ppm)



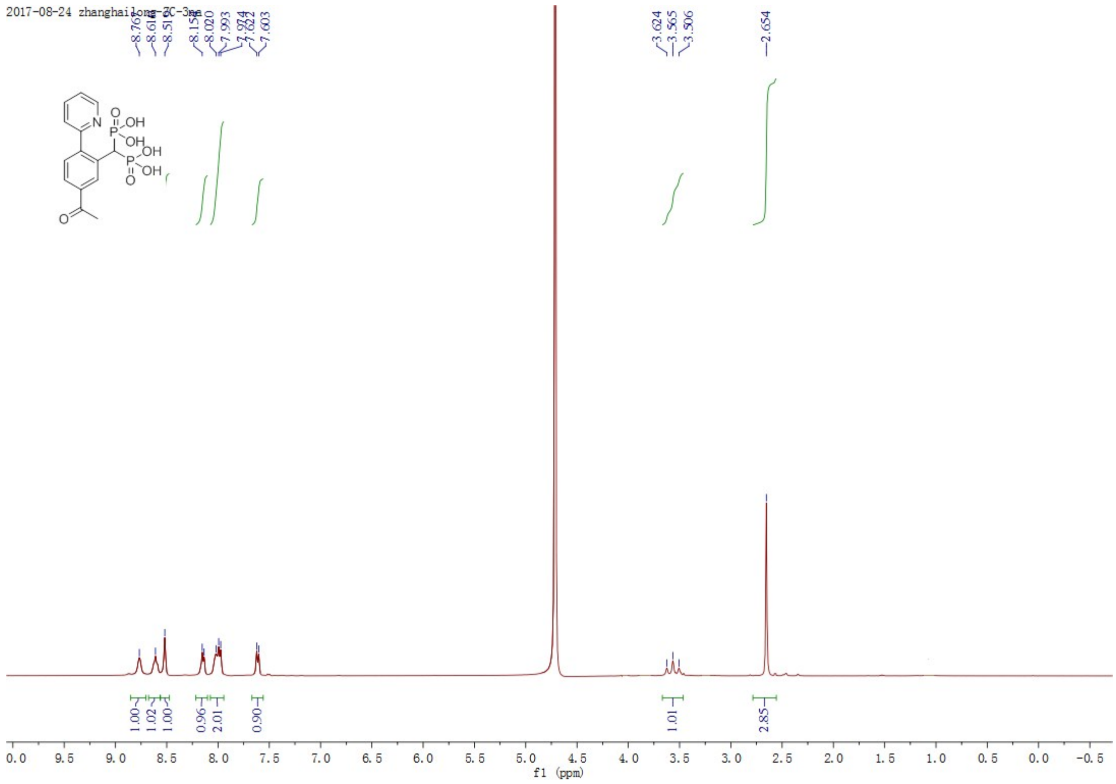
Compound **3la acid**

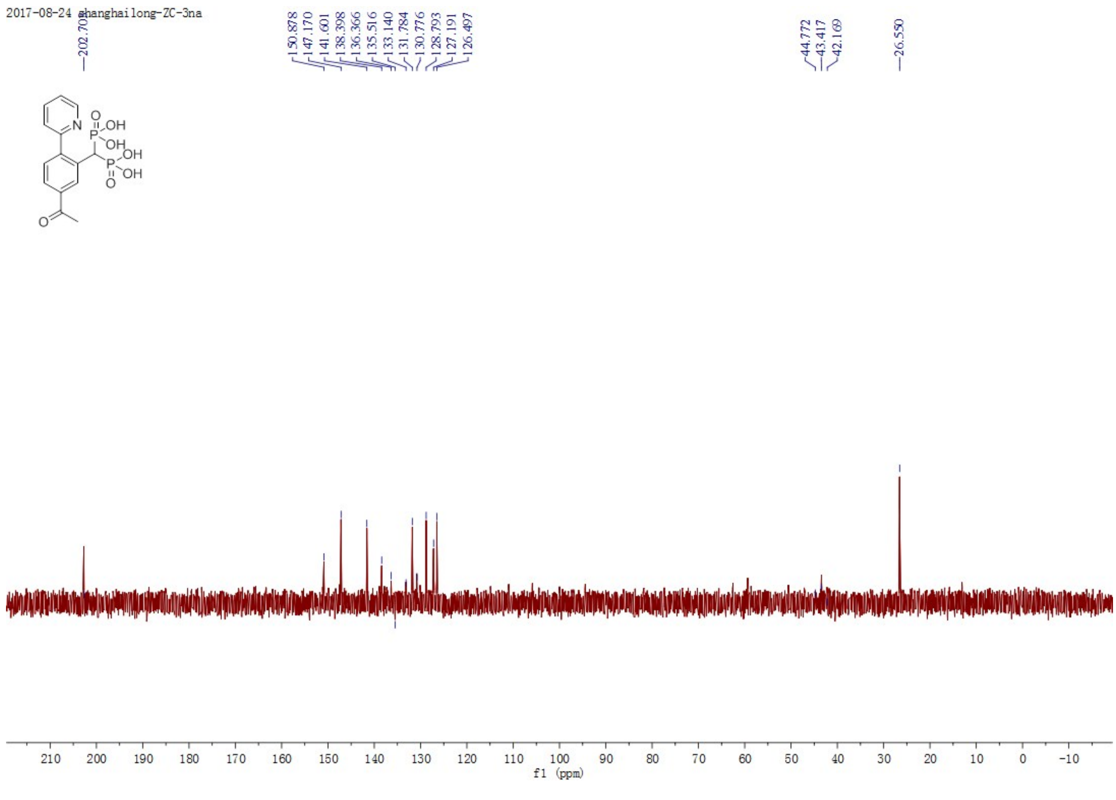


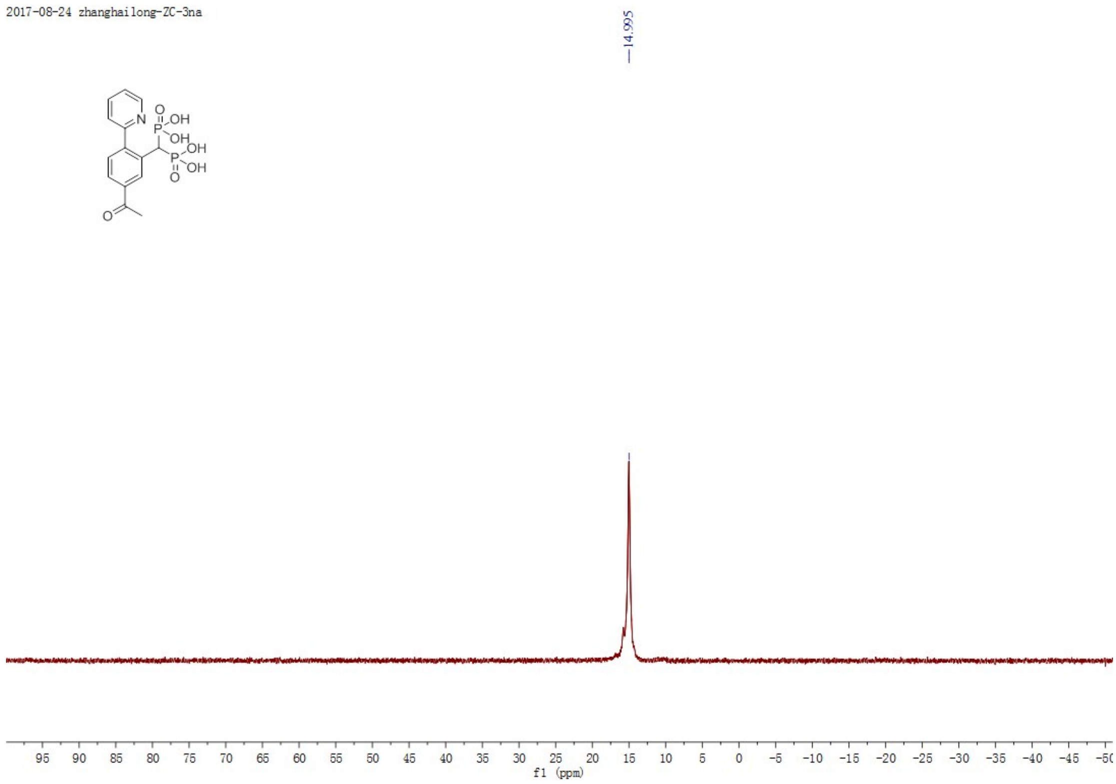




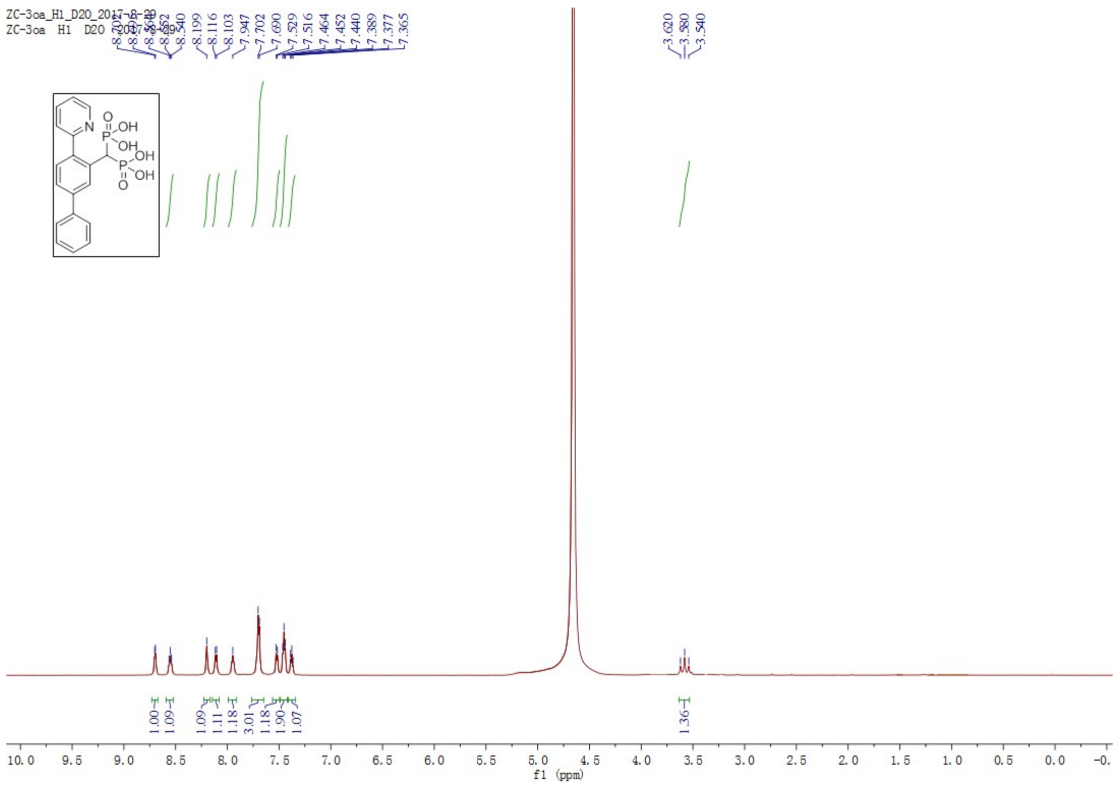
Compound **3na acid**

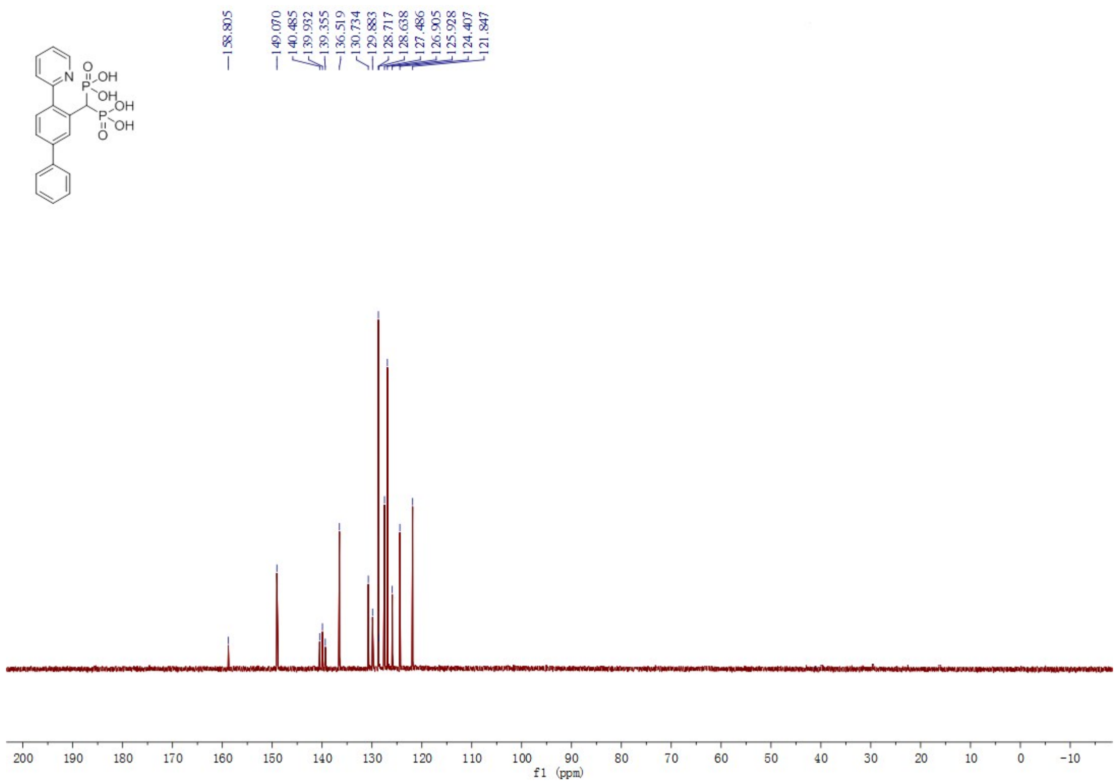

2017-08-24 zhanghailong-ZC-3na
8.76
8.61
8.51
8.15
8.020
7.993
7.974
7.622
7.603
3.624
3.565
3.506
2.654
1.00
1.02
1.00
0.96
2.01
0.90
1.01
2.85
f1 (ppm)

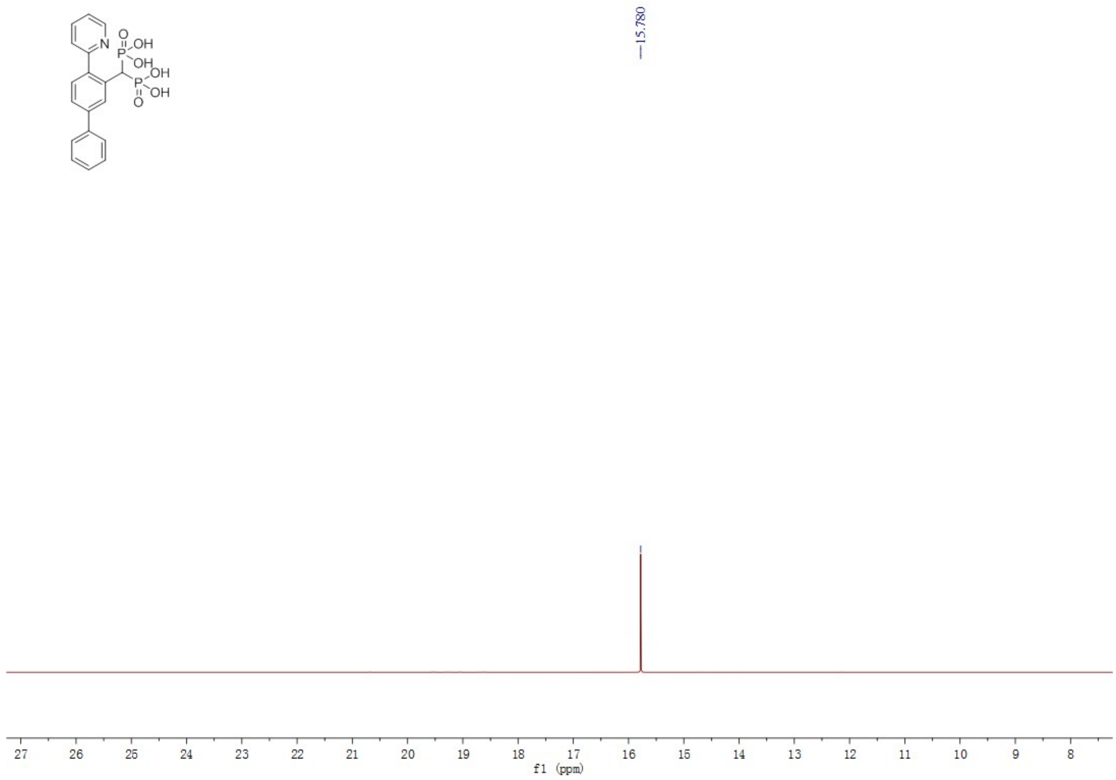

2017-08-24 zhanghailong-ZC-3na
202.70
150.878
147.170
141.601
138.398
136.366
135.516
133.140
131.784
130.776
128.793
127.191
126.497
44.772
43.417
42.169
26.550
f1 (ppm)



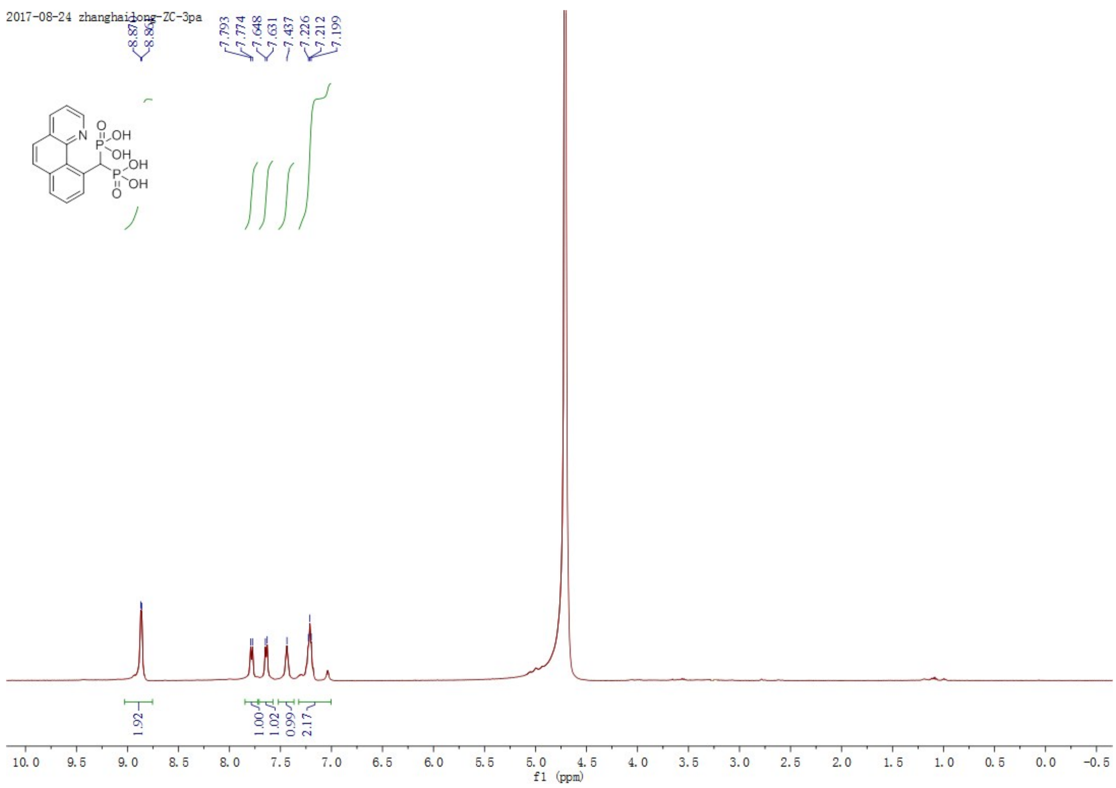
Compound **3oa acid**

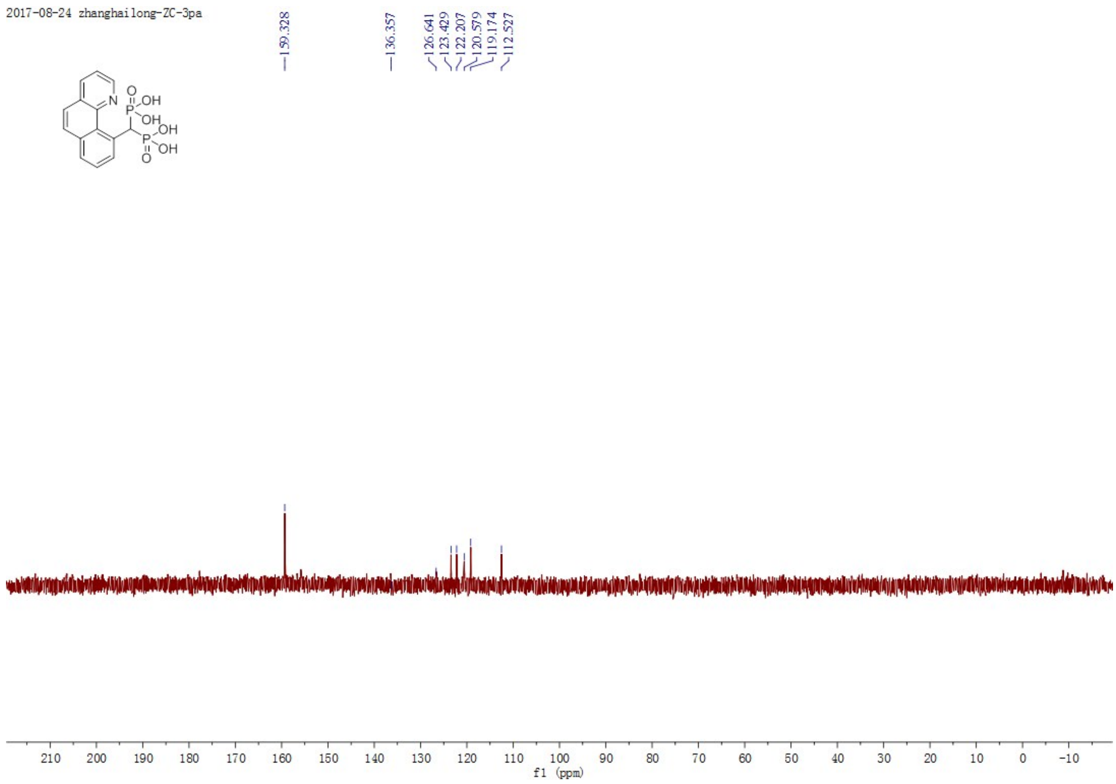


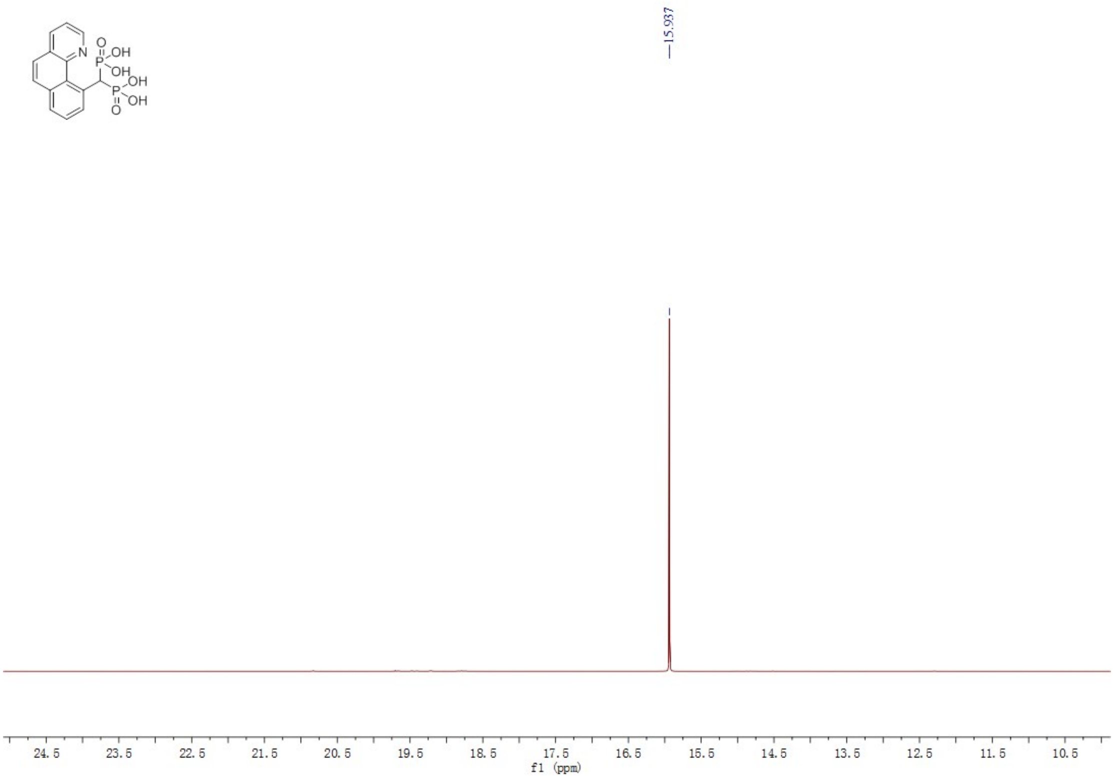




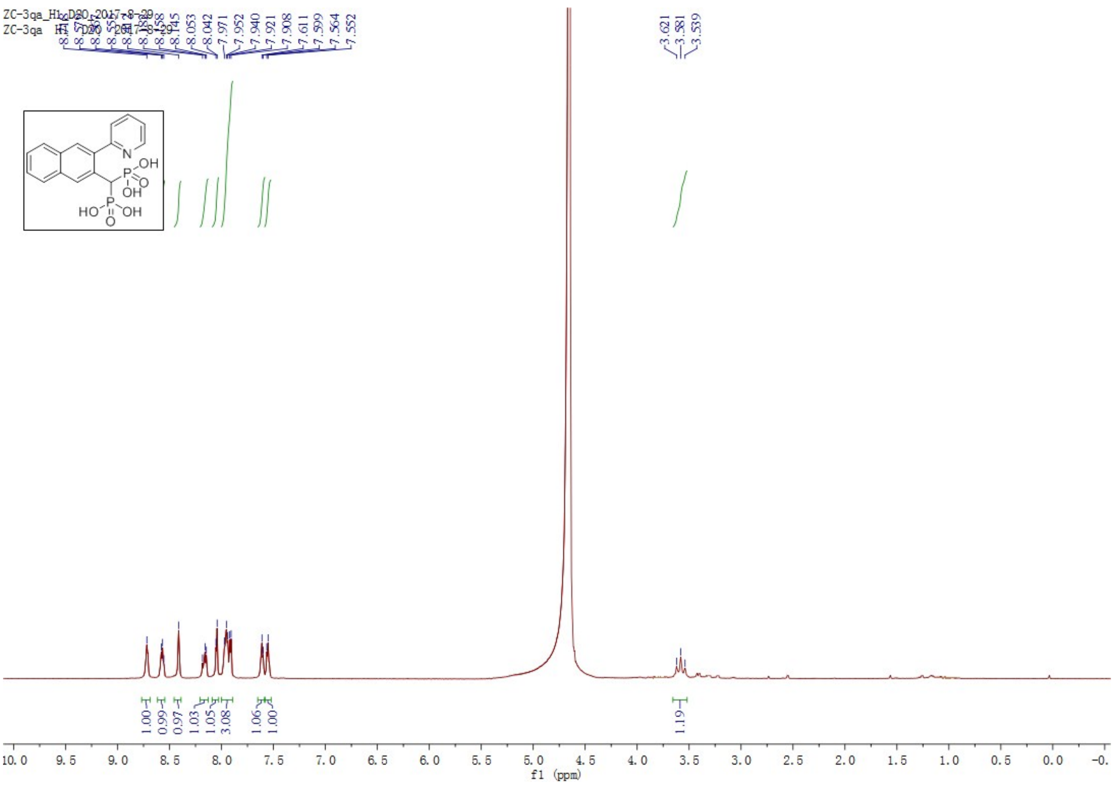
Compound **3pa acid**

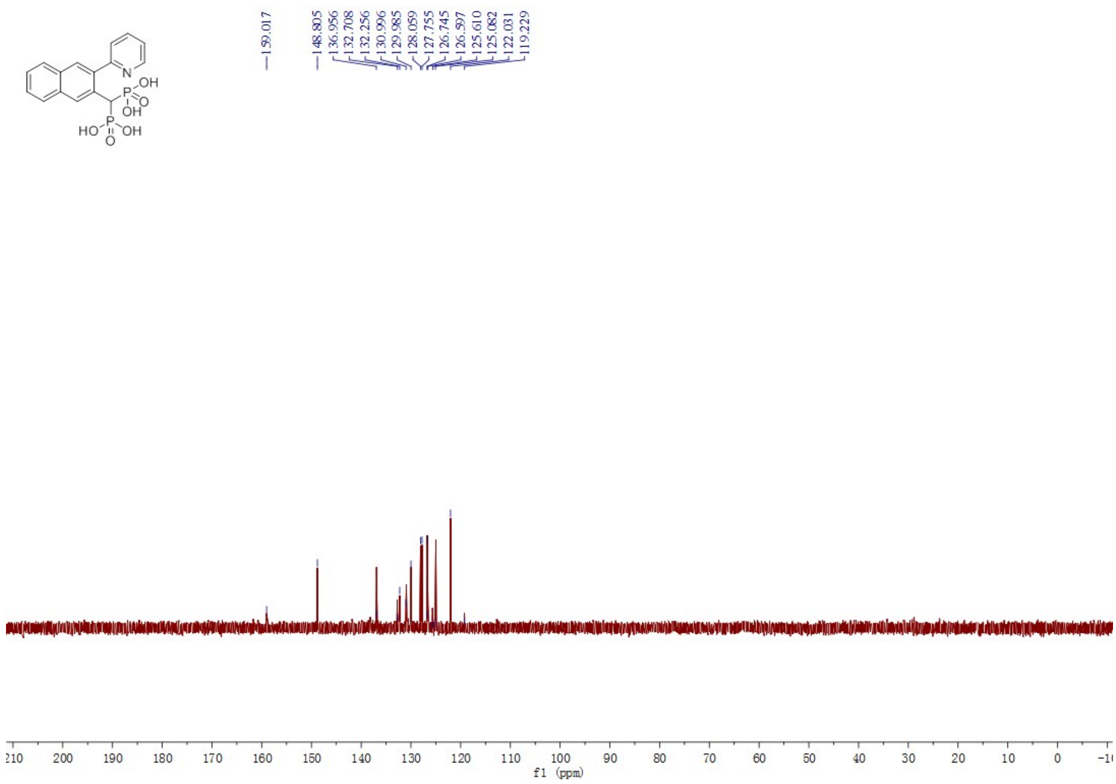

2017-08-24 zhanghailong-ZC-3pa
8.871
8.865
7.793
7.774
7.648
7.631
7.437
7.226
7.212
7.199
1.92
1.00
1.02
0.99
2.17
f1 (ppm)

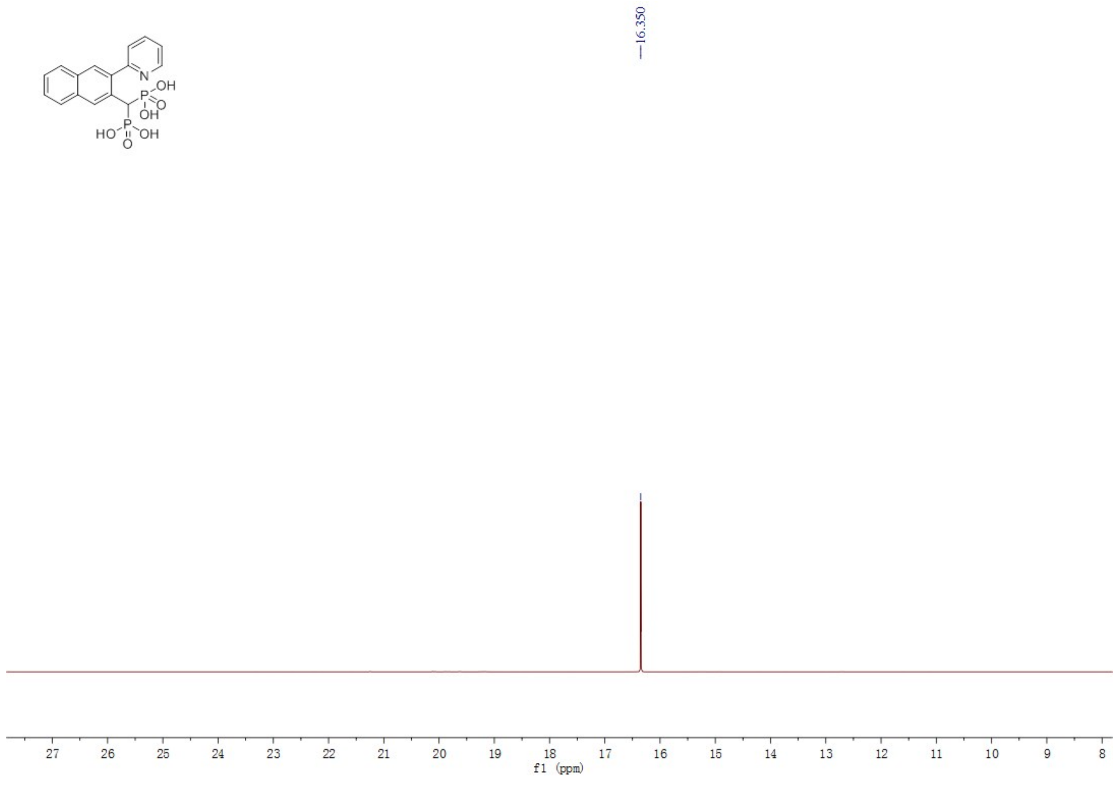

2017-08-24 zhanghailong-ZC-3pa
159.328
136.357
126.641
123.429
122.207
120.579
119.174
112.527
f1 (ppm)



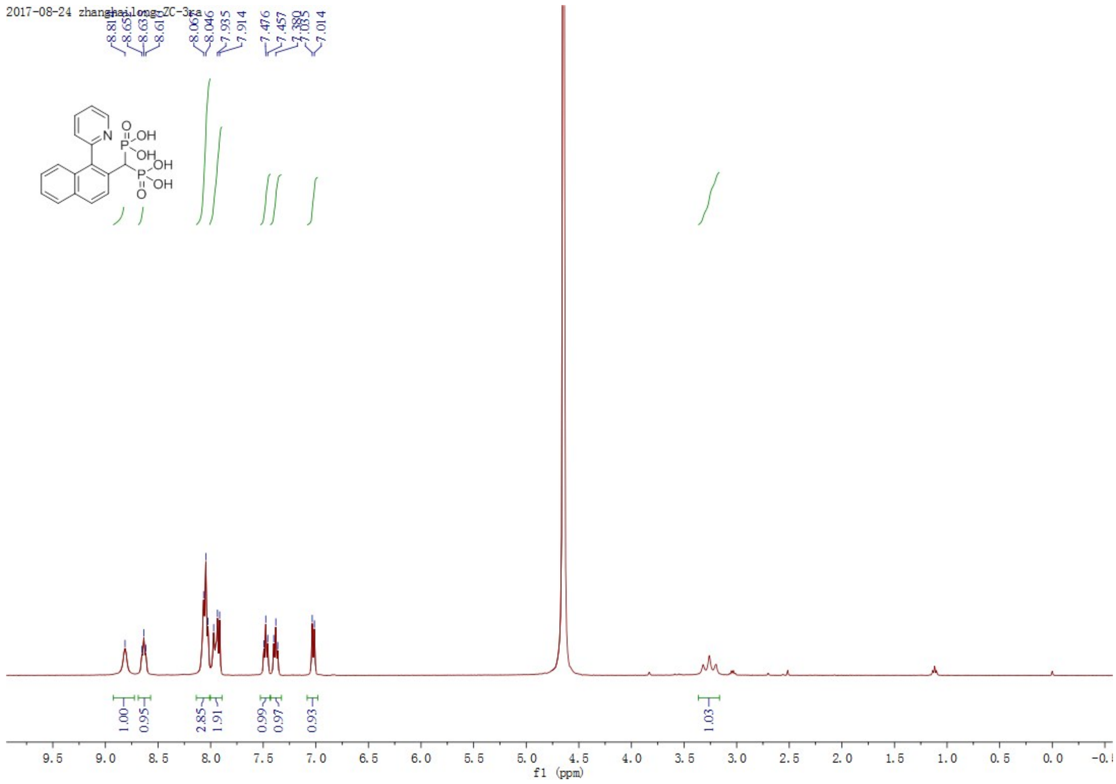
Compound **3qa acid**

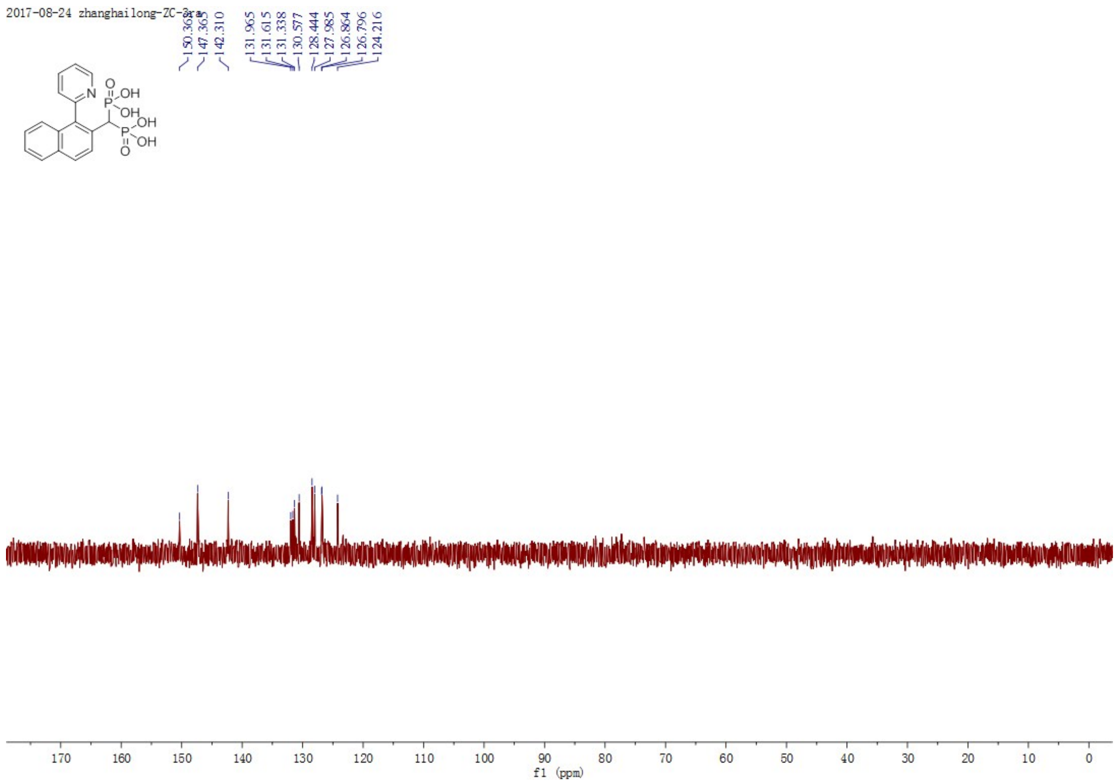


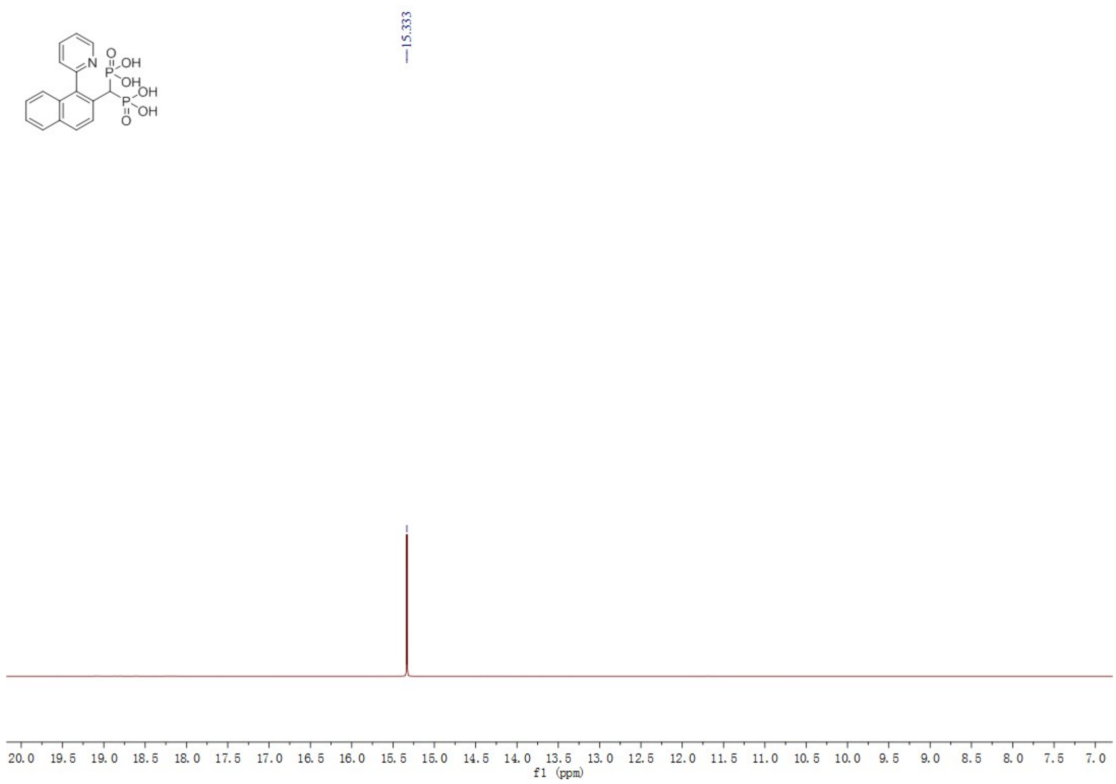




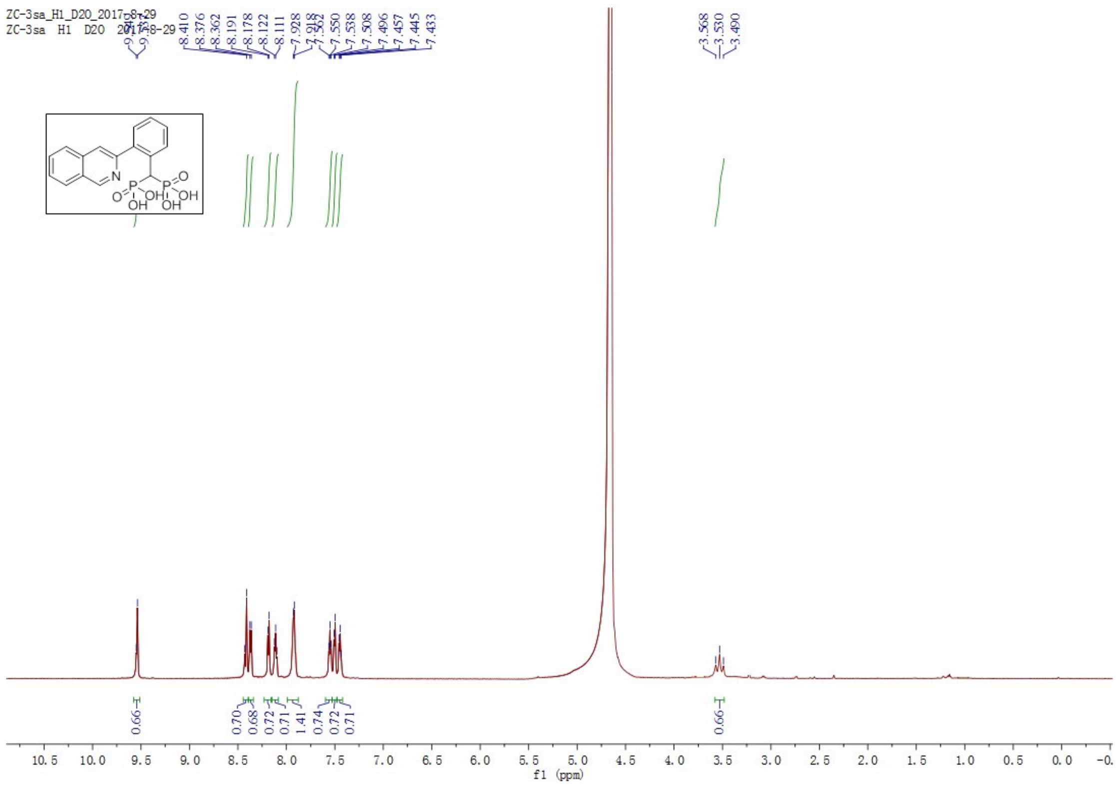
Compound **3ra acid**

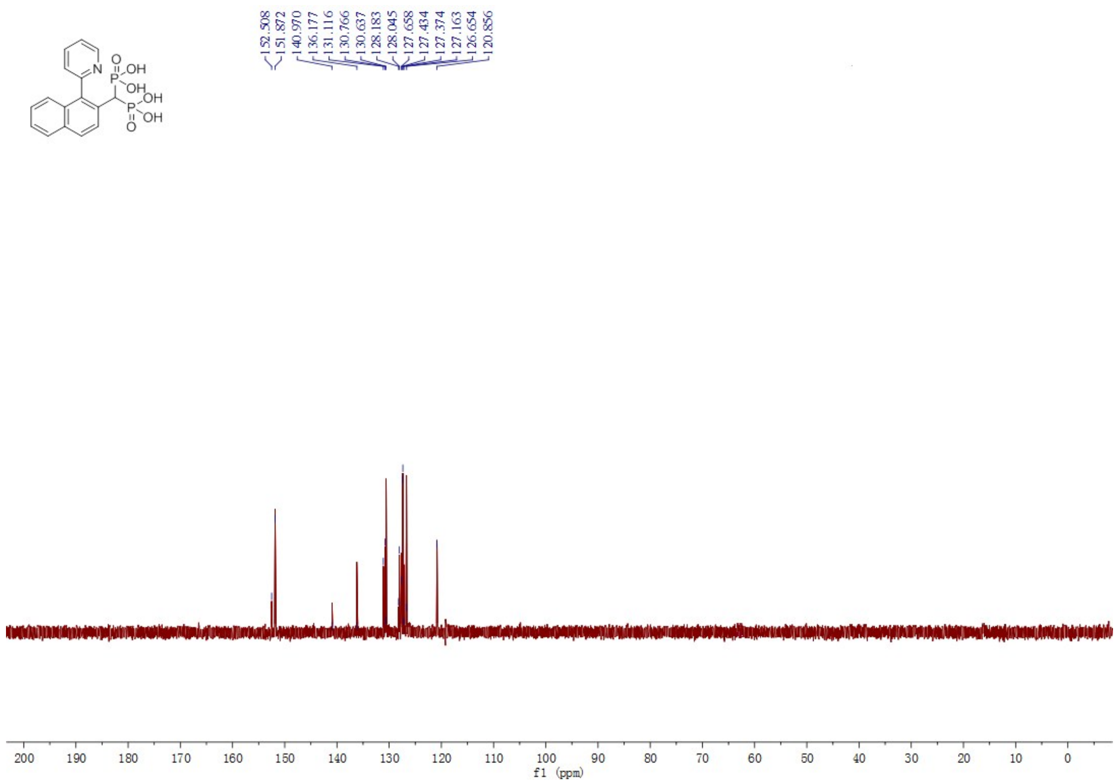

2017-08-24 zhanghailong-ZC-3ra
8.81
8.65
8.63
8.61
8.061
8.046
7.935
7.914
7.476
7.457
7.380
7.035
7.014
OH
OH
OH
OH
1.00
0.95
2.85
1.91
0.99
0.97
0.93
1.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


2017-08-24 zhanghailong-ZC-3ra
150.368
147.365
142.310
131.965
131.615
131.338
130.577
128.444
127.985
126.864
126.796
124.216
OH
OH
OH
OH
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

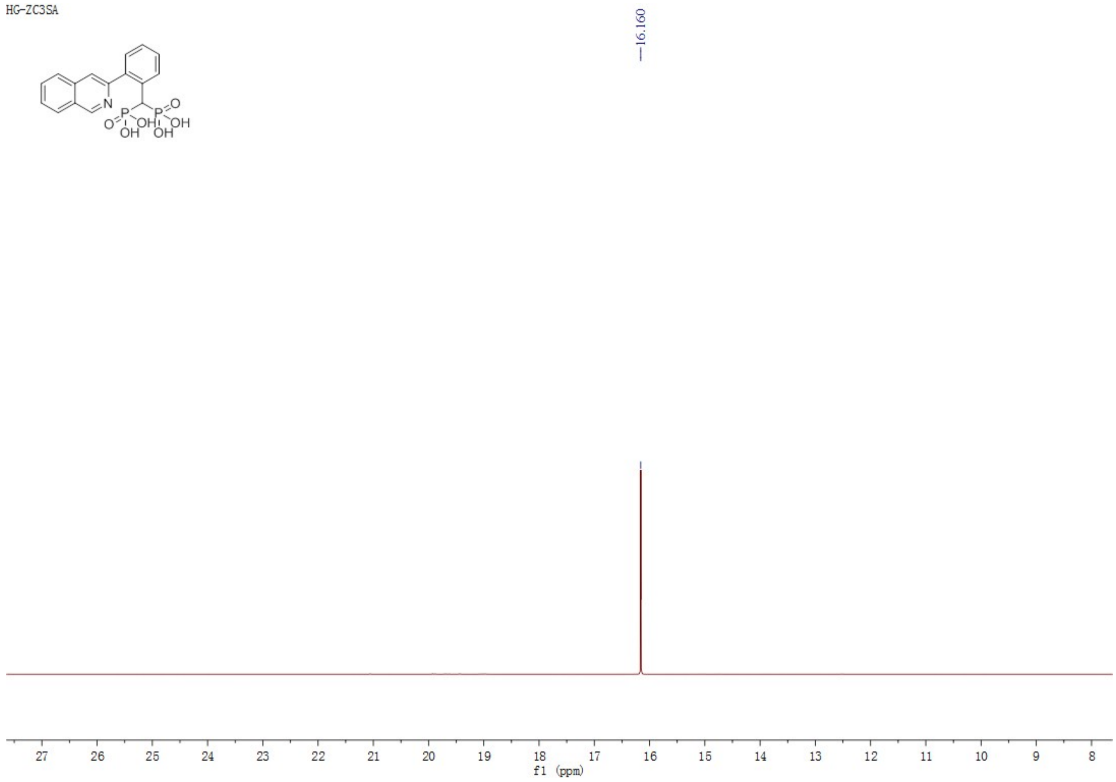


Compound **3sa acid**

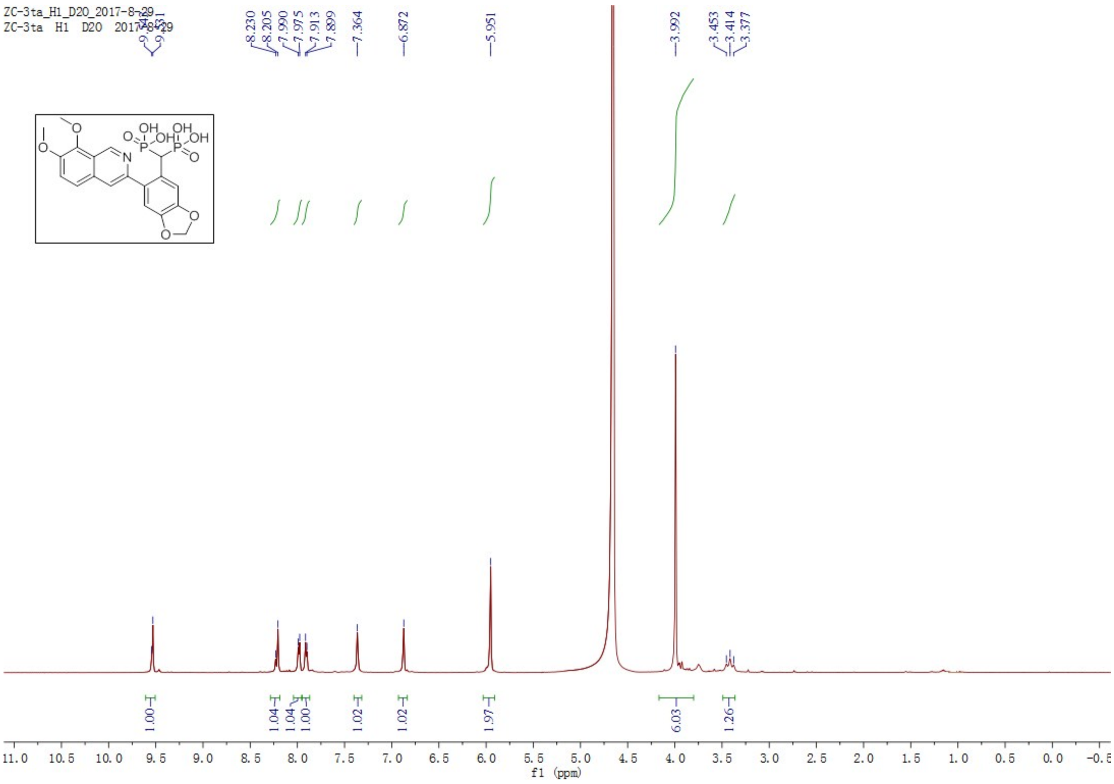


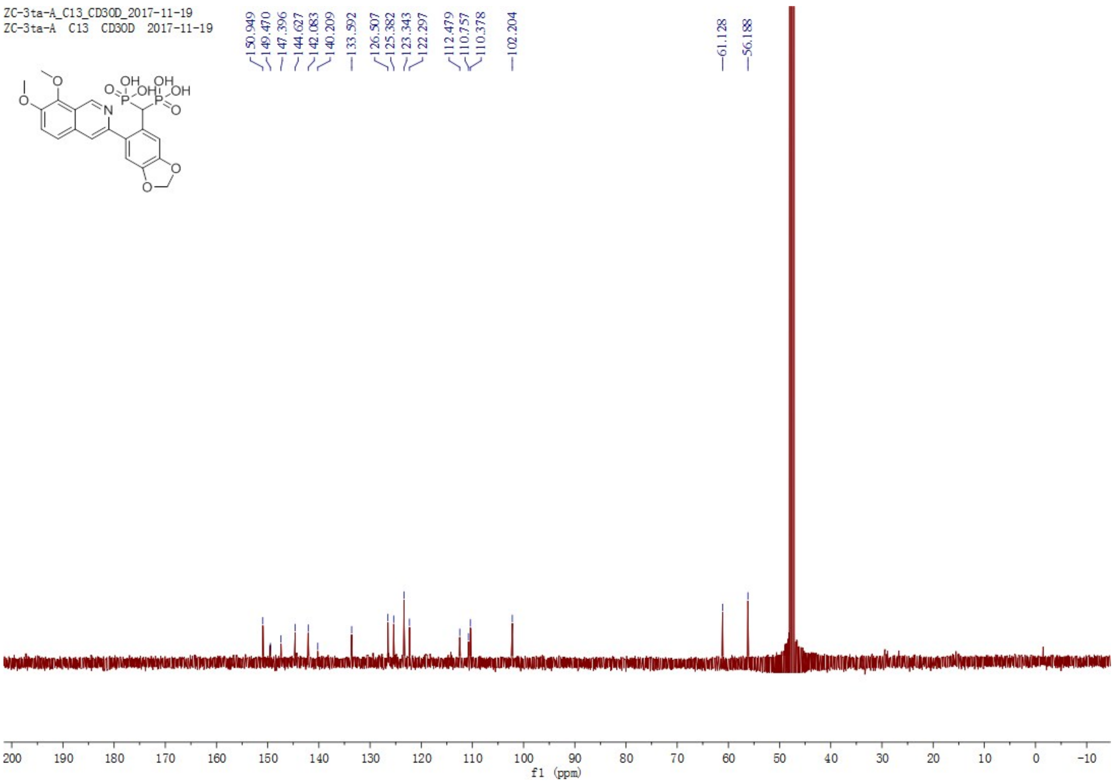


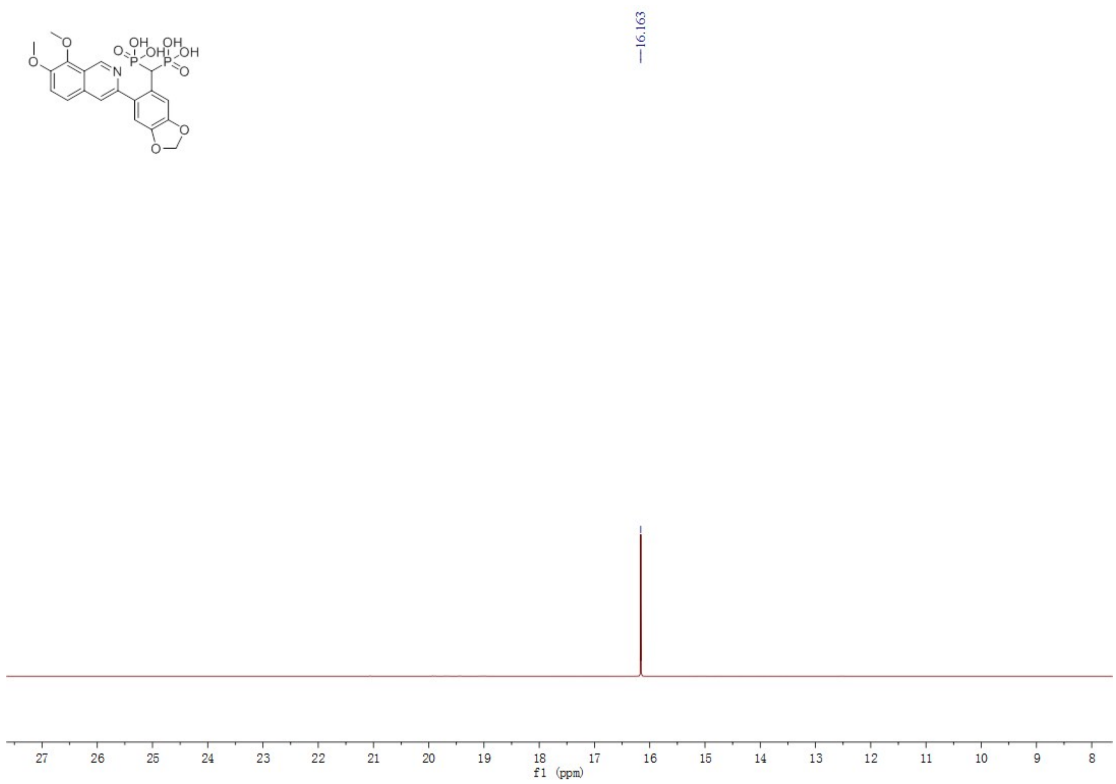
HG-ZC3SA



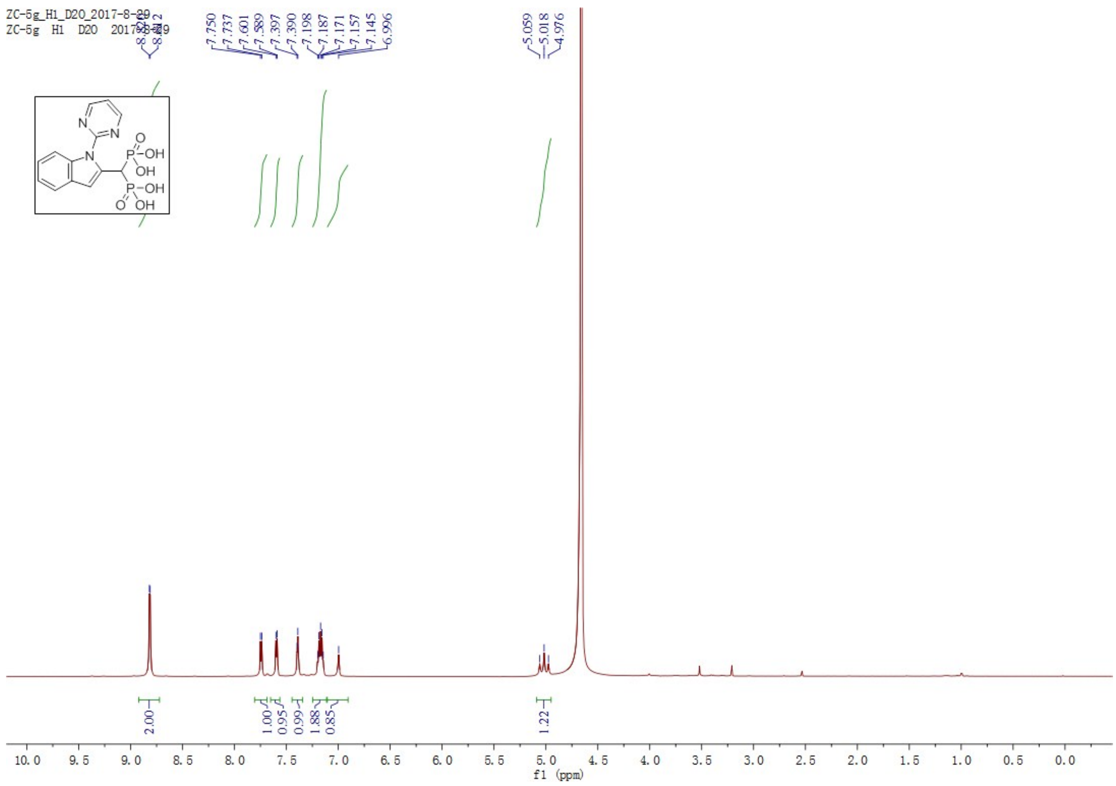
Compound **3ta acid**

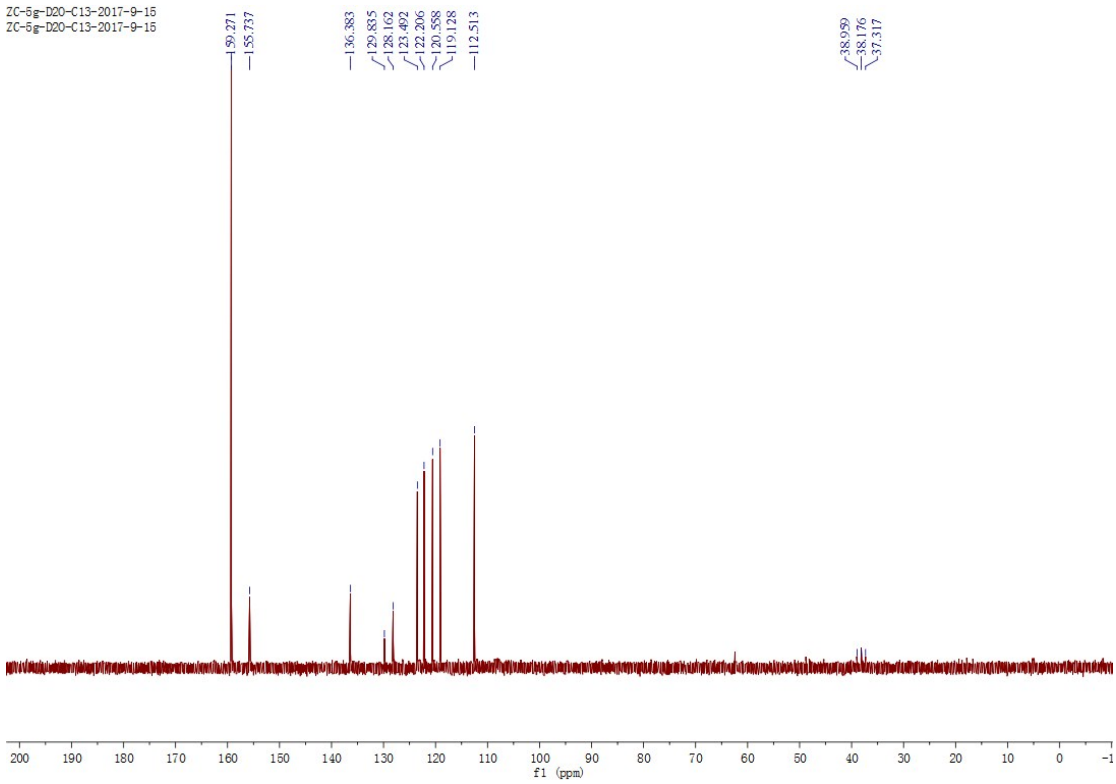

ZC-3ta_H1_D2O_2017-8-29
ZC-3ta H1 D2O 2017-8-29
8.230
8.205
7.990
7.975
7.913
7.899
7.364
6.872
5.951
3.992
3.453
3.414
3.377
1.00
1.04
1.04
1.00
1.02
1.02
1.97
6.03
1.26
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

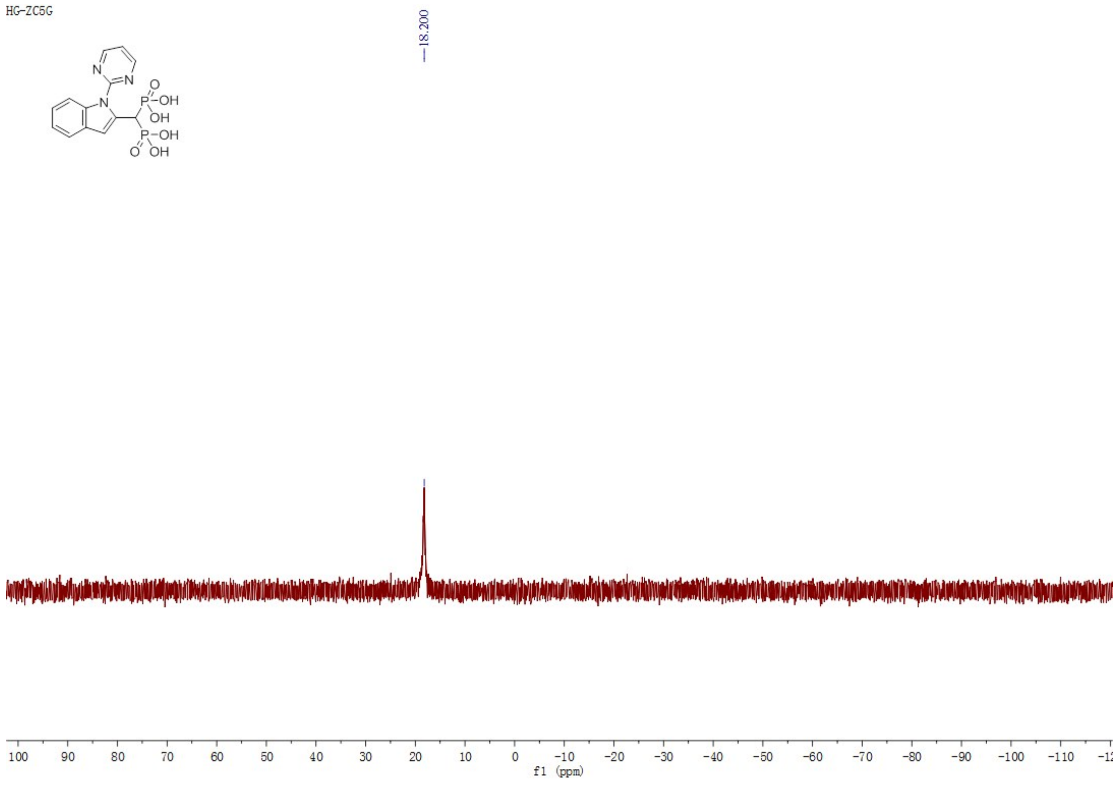

ZC-3ta-A_C13_CD3OD_2017-11-19
ZC-3ta-A C13 CD3OD 2017-11-19
150.949
149.470
147.396
144.627
142.083
140.209
133.592
126.507
125.382
123.343
122.297
112.479
110.757
110.378
102.204
61.128
56.188
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



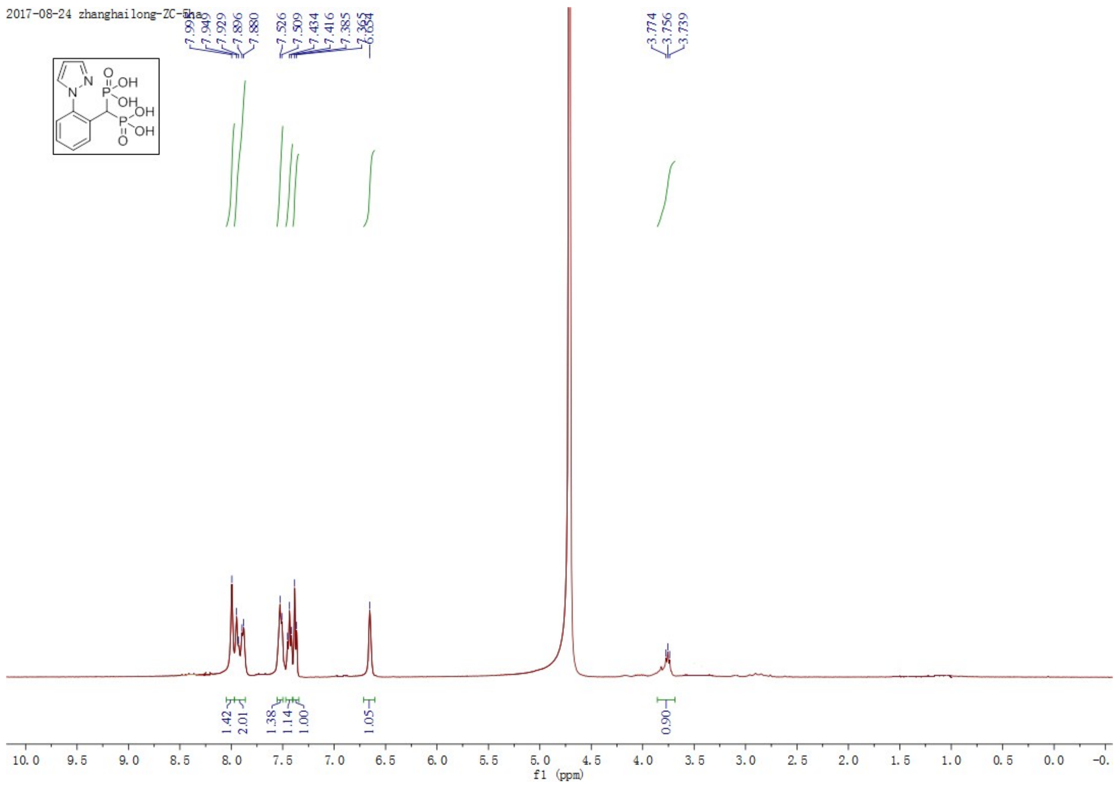
Compound **5g acid**

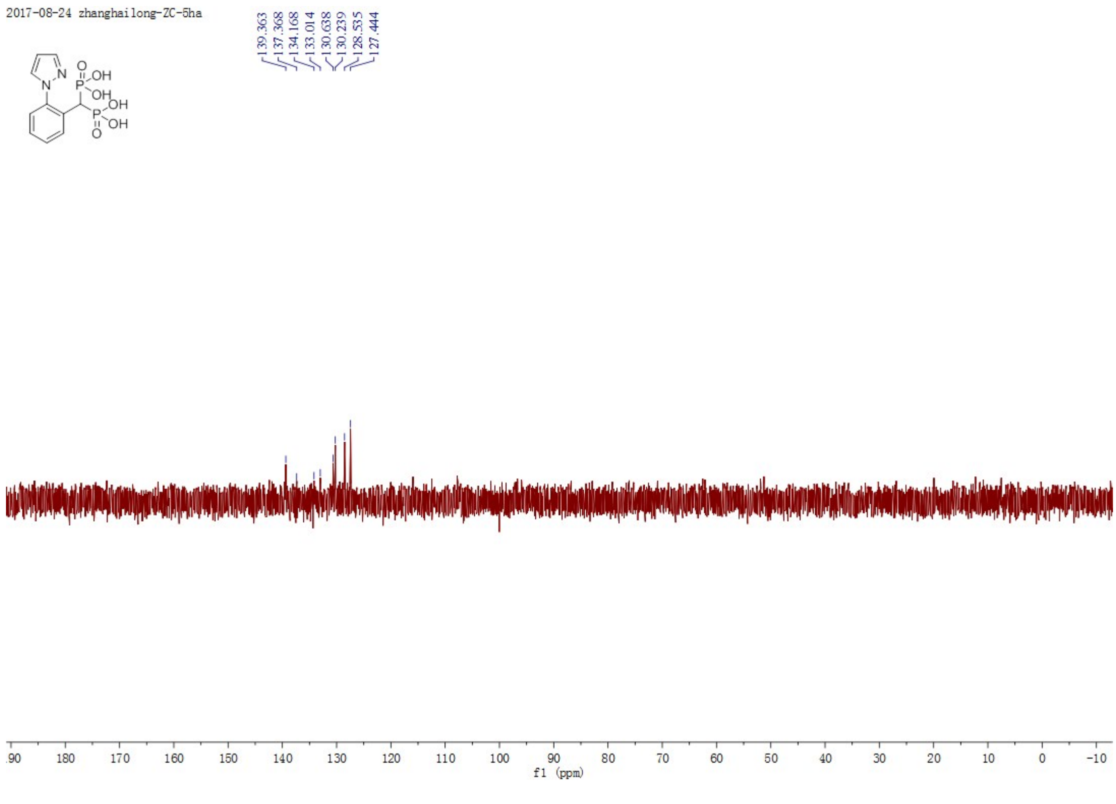




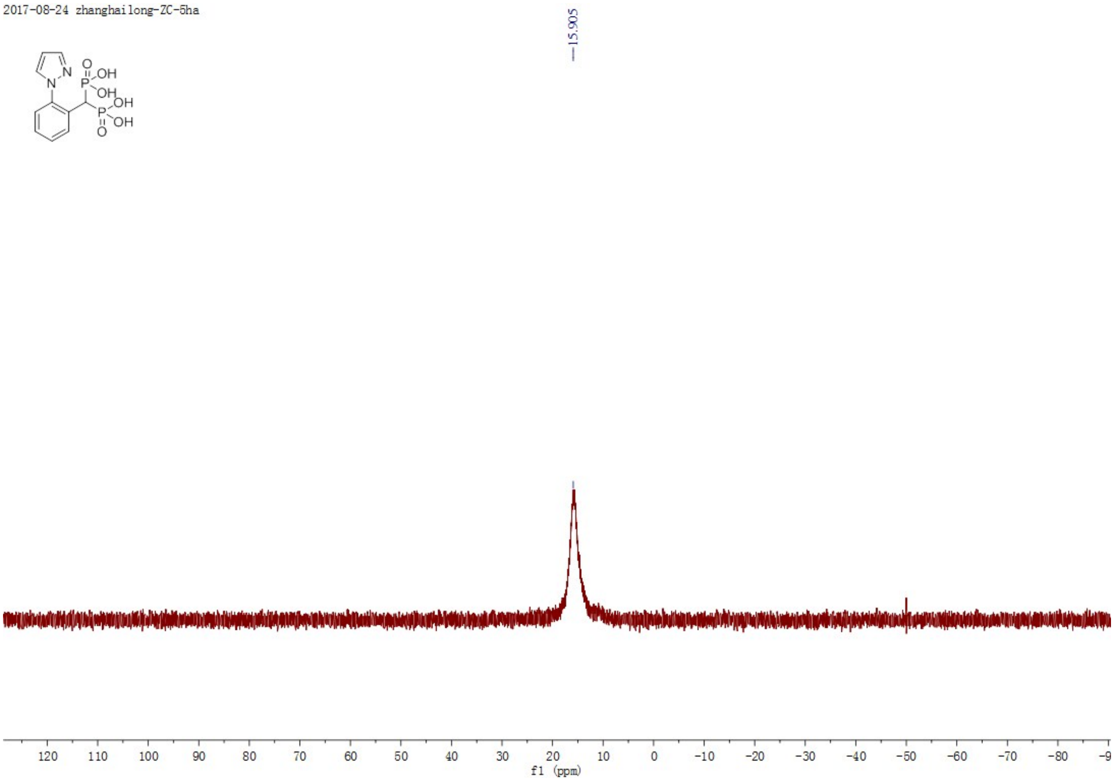


Compound **5h acid**


2017-08-24 zhanghailong-ZC-5ha
7.929
7.896
7.880
7.526
7.509
7.434
7.416
7.385
3.774
3.756
3.739
N
N
P
OH
OH
O
P
OH
OH
O
1.42
2.01
1.38
1.14
1.00
1.05
0.90
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


2017-08-24 zhanghailong-ZC-5ha
139.363
137.368
134.168
133.014
130.638
130.239
128.535
127.444
N
N
P
OH
OH
O
P
OH
OH
O
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2017-08-24 zhanghailong-ZC-5ha



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