Supporting Information for

Original article

Novel phthalimides regulating PD-1/PD-L1 interaction as potential immunotherapy agents

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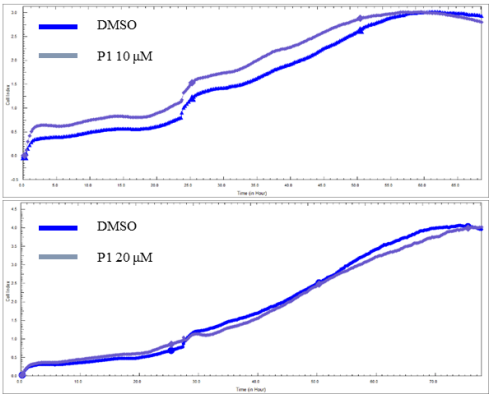
A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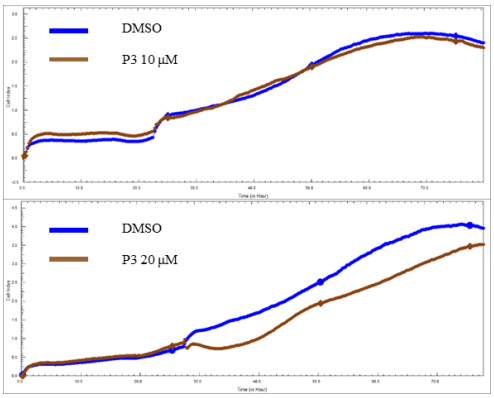
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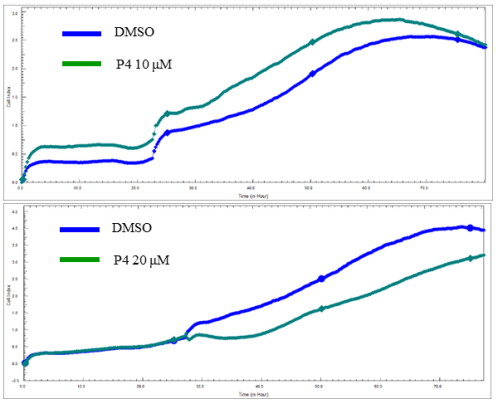
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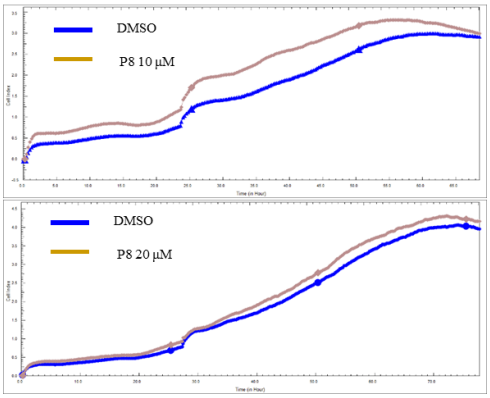
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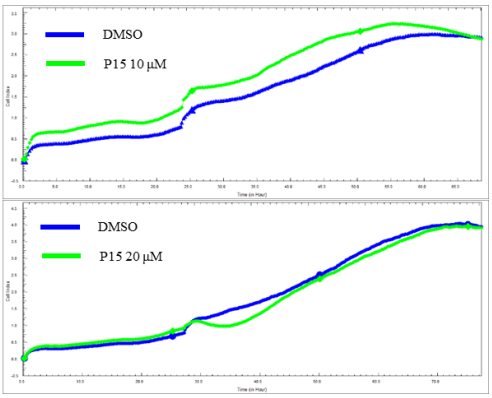
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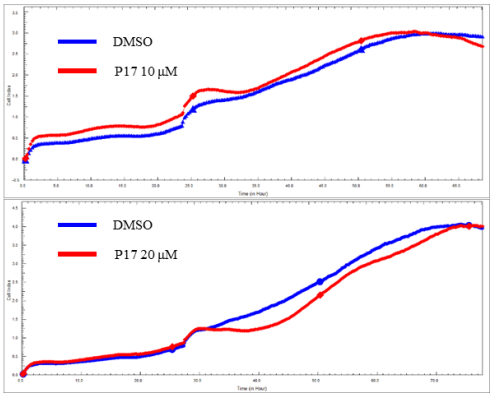
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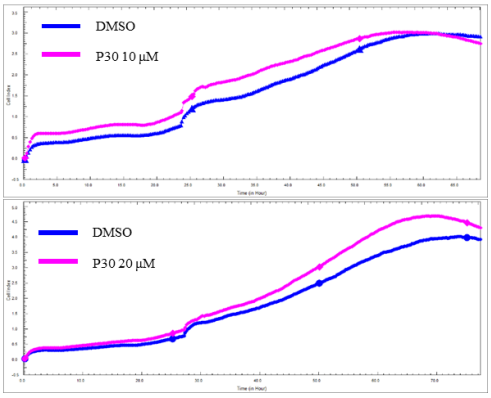
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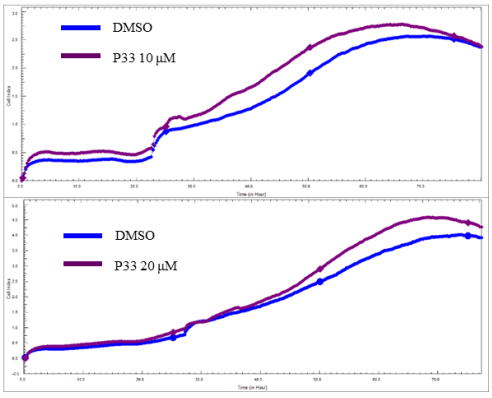
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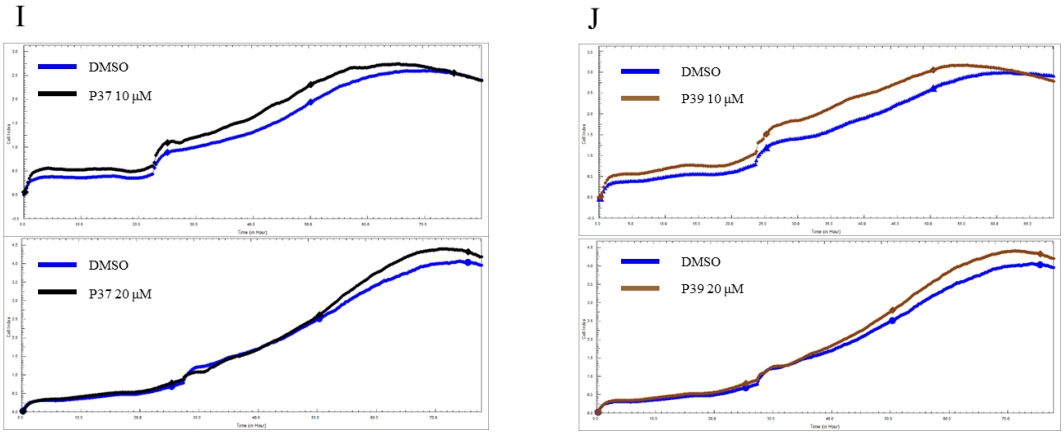


Figure S1 The cytotoxicity effect of ten compounds on tumor cells. A375 cells were treated with indicated concentrations of compounds for 72 h, cell viability in A375 cells was measured simultaneously by xCELLigence system (Agilent) with RTCA Software. (A) Compound **P1.** (B) Compound **P3.** (C) Compound **P4.** (D) Compound **P8.** (E) Compound **P15.** (F) Compound **P17.** (G) Compound **P30.** (H) Compound **P33.** (I) Compound **P37.** (J) Compound **P39**

Table S1 Data collection and refinement statistics for PD-L1/P39 complex

	PD-L1 with P39
Wavelength	0.97853
Resolution range	48.93 - 2.701 (2.798 - 2.701)
Space group	P 21 21 21
Unit cell	84.033 97.864 136.31 90 90 90
Total reflections	415781 (41117)
Unique reflections	31442 (3048)
Multiplicity	13.2 (13.5)
Completeness (%)	99.76 (98.01)
Mean I/sigma(I)	19.68 (4.83)
Wilson B-factor	38.94
R-merge	0.1504 (0.6753)
R-meas	0.1564 (0.7016)
R-pim	0.04265 (0.1882)
CC1/2	0.998 (0.944)
CC*	0.999 (0.986)
Reflections used in refinement	31439 (3048)
Reflections used for *R*-free	1999 (194)

R-work	0.2346 (0.2758)
R-free	0.2884 (0.3258)
CC (work)	0.913 (0.829)
CC (free)	0.892 (0.699)
Number of non-hydrogen	8143
Atoms	
Macromolecules	8099
Solvent	44
Protein residues	1001
RMS (bonds)	0.006
RMS (angles)	0.78
Ramachandran favored (%)	92.59
Ramachandran allowed (%)	7.31
Ramachandran outliers (%)	0.10
Rotamer outliers (%)	0.00
Clashscore	8.96
Average B-factor	50.98
macromolecules	51.12
solvent	24.38

Statistics for the highest-resolution shell are shown in parentheses.

Table S2 PK parameters of **P39**

PK Parameter	iv (5 mg/kg)	*po* (50 mg/kg)
$t_{1/2}$ (h)	6.44±0.98	4.33±2.87
T_{MAX} (h)	0.08	0.53±0.46
C_{MAX}(ng/mL)	4353.33±1196.93	26.04±29.58
AUC_{0-t} (h·ng/mL)	3238.17±1341.60	75.05±19.80
$AUC_{0-\infty}$ (h·ng/mL)	3259.45±1355.38	100.26±2.90
CL (mL/h/kg)	339.69±119.98	
F (%)		0.31±0.00

AUC, area under the curve; $t_{1/2}$, half-life; T_{MAX}, time of maximum plasma concentration; C_{MAX}, maximum plasma concentration; CL, plasma clearance; *F*, oral bioavailability. n = 3, mean ± SD.

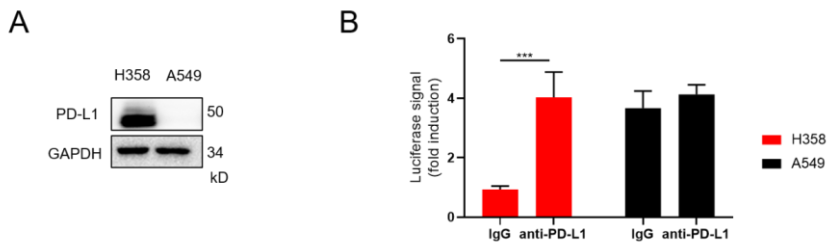


Figure S2 (A) PD-L1 levels in H358 or A549 cells were determined by immunoblotting. (B) Interaction of PD-1/PD-L1 between Jurkat NFAT-luciferase reporter cells and IgG or anti-PD-L1 treated A549 or H358 cells were measured with luciferase reporter assay. A549 cells which has undetectable PD-L1 level (as negative control) and H358 cells which has high constitutive PD-L1 level (as positive control) were used in our PD-1/PD-L1 blocking assay (Fig. S2A). The interaction of PD-1/PD-L1 between Jurkat NFAT-luciferase reporter cells and PD-L1 antibody-treated A549 or H358 cells has been validated (Fig. S2B).

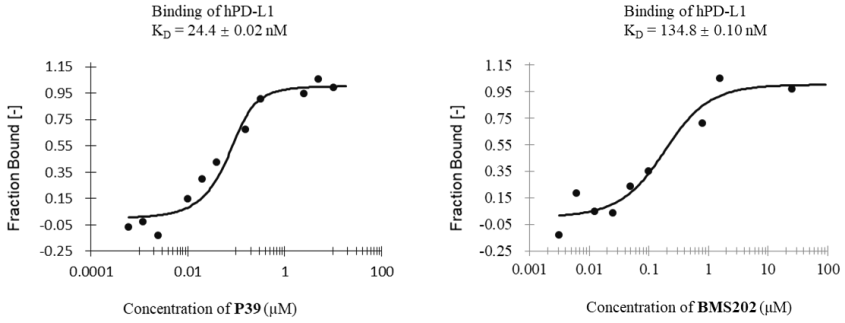


Figure S3 Interaction of hPD-L1with compound **P39** and BMS202 were tested through Microscale Thermophoresis (MST).

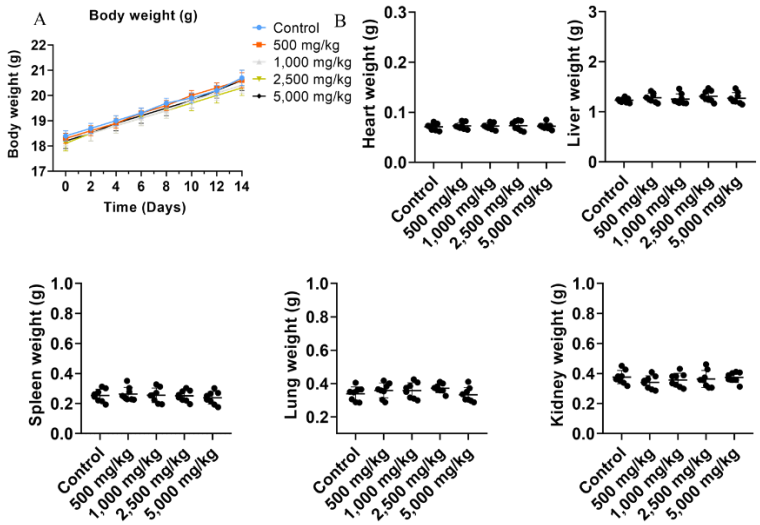


Figure S4 ICR mice (n = 8) were *po* treated with water or **P39** (500 mg/k, 1,000 mg/kg, 2500 mg/kg or 5000 mg/kg). The Body weight (A) was monitored for 14 days, and organ weights including heart, lung, spleen, liver, and kidney (B) were measured after the mice were sacrificed

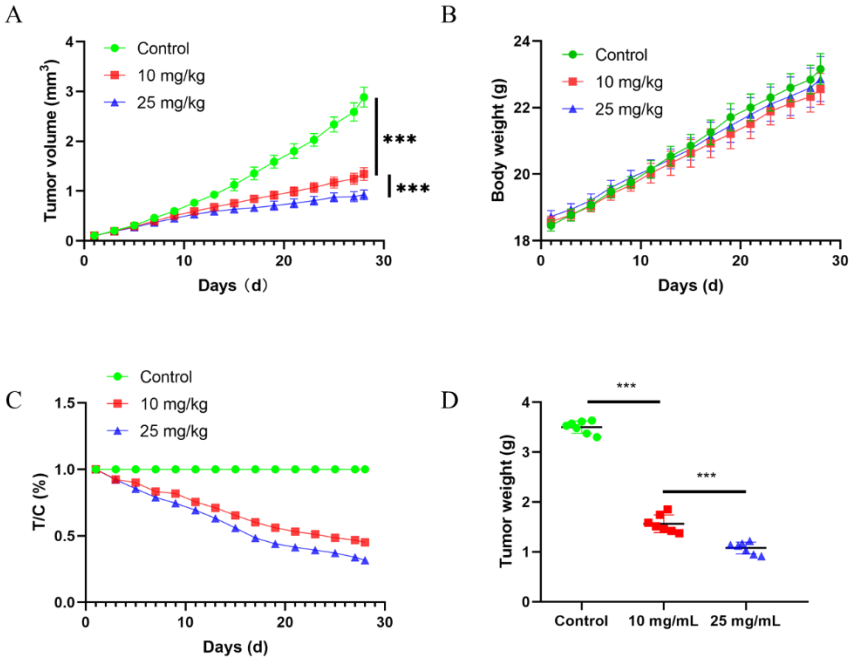


Figure S5. *In vivo* antitumor activity of **P39**. C57BL/6 mice (n = 7) were implanted subcutaneously with MC38 tumor cells and i.p. treated with PBS or **P39** (10 mg/kg or 25 mg/kg), the tumor volume (A), Body weight (B), inhibit rate of tumor (C) and tumor weight (D) were recorded for 28 days. All data are displayed as the mean ± SEM (7 female mice in each group). ***P< 0.001.

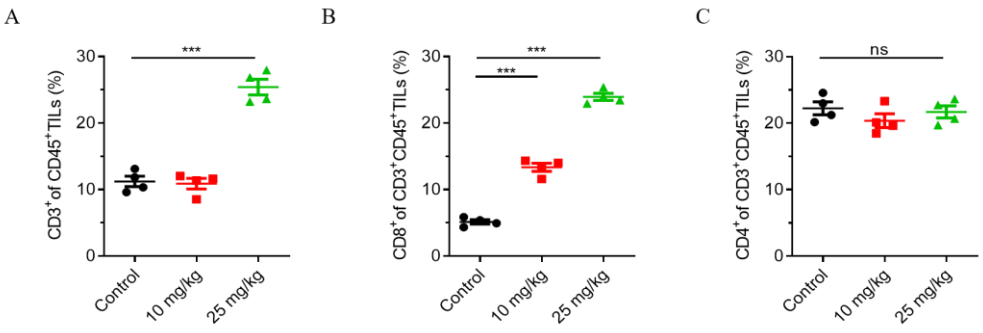


Figure S6. P39 enhanced antitumor immunity on a MC38 mouse model. (A) C57BL/6 mice with MC38 tumor were treated with PBS or **P39**. The population of $CD3^+$ in $CD45^+$ TILs were analyzed by flow cytometry. (B) Population of $CD8^+$ in $CD3^+CD45^+$

TILs were analyzed by flow cytometry. (C) Population of $CD4^+$ in $CD3^+CD45^+$ TILs were analyzed by flow cytometry. All results in A to C were shown as mean ± SD, n = 4. ***P< 0.001.

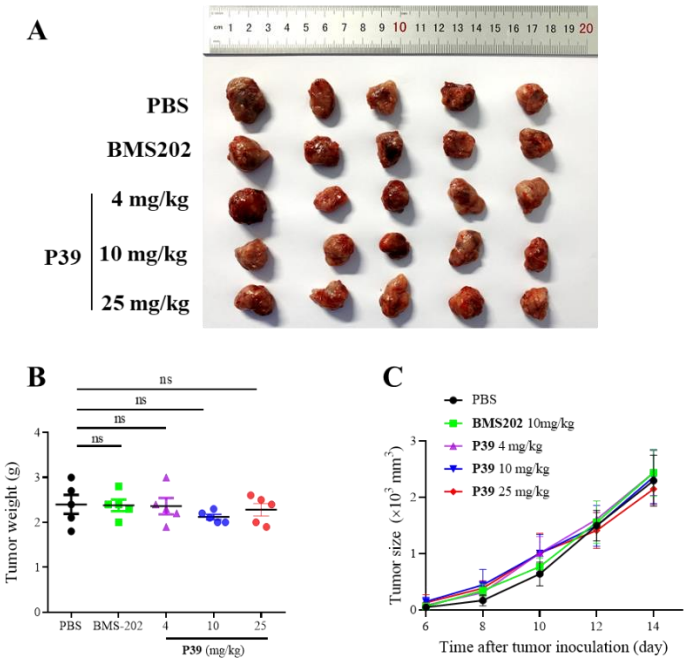


Figure S7. *In vivo* antitumor activity of **P39** on Balb/c-nude mice. Balb/c-nude mice bearing Lewis lung carcinoma (LLC) cells overexpressing hPD-L1 (LLC-hPD-L1) were treated with PBS, BMS202 (10 mg/kg) and **P39** (4, 10 and 25 mg/kg). The tumor growth was monitored (n = 5). (A) *Ex vivo* observation of the tumors from the treated mice. (B) Comparison of the weight of the tumors from the mice treated with PBS, BMS202 or **P39**. (C) Tumor volume was measured every 2 days. Data shown are mean value ± standard error of mean (SEM). $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, ns, no significant.

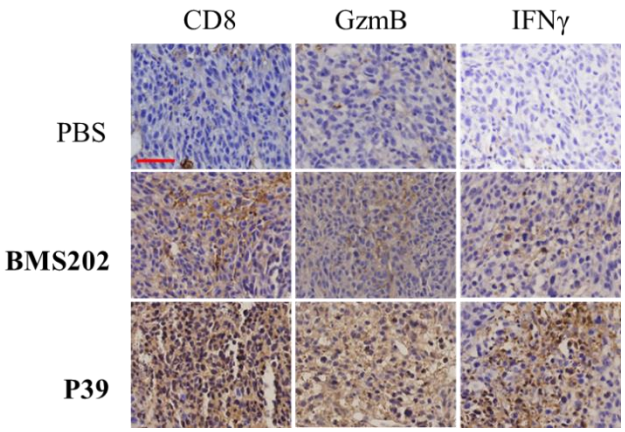


Figure S8. Immunohistochemical staining of tumor tissues in BMS202 (10 mg/kg) or **P39** (10 mg/kg) treated hPD-1-knockin C57BL/6 mice. Representative images of CD8, GzmB, and IFN-*γ* staining of paraffin section of tumors were shown (Scale bar = 50 μm).

General synthesis information：

Commercially available reagents and solvents were purchased and used directly without subsequent purification. TLC was used to monitor all reactions using GF254 plates. Purification was accomplished using a silica gel. Setting TMS as an internal standard, the ^{1}H and ^{13}C NMR spectra were acquired on a BRUKER spectrometer (AV-300, AV-400, or AV-500). HRMS measurements were performed on Agilent QTOF 6520 mass spectrometer, with an electron spray ionization as the ion source. Silica gel was used for chromatography. The purity of all final compounds was analyzed with a Shimadzu 2020 series HPLC system using an Inertsil ODS-3 column (4.6 mm × 100 mm, 5 μm) with H_2O containing 1‰ trifluoroacetic acid (mobile phase A) and MeOH (mobile phase B), and the purity of target compounds was determined to be > 95%.

4.2. Synthesis

General Synthesis Procedure of Compounds **8a-8d and 14**

Dissolve phenylboronic acid/1,4-benzodioxane-6-boronic acid (1.05 equiv), **7a-7d** (1 equiv), K_2CO_3 (2.5 equiv), and palladium acetate (0.06 equiv) in the solution of ethanol/H_2O (1:1). After degasified with argon 3 times, the mixture was reacted at rt for 14 h. Extracted with EA three times and the combined EA phase was concentrated. A silica gel column was used to purify and obtain compounds **8a-8d** and **14**.

2-Methyl-[1,1'-biphenyl]-3-amine ***(8a).*** Colorless oil, yield 82%. ^{1}H NMR (300 MHz, chloroform-*d*) *δ* 7.48–7.23 (m, 5H), 7.06 (m, 1H), 6.70 (d, *J* = 7.7 Hz, 2H), 3.69 (s, 2H), 2.05 (s, 3H). MS(ESI): *m/z* 184.3 $[M+H]^+$.

3-Amino-[1,1'-biphenyl]-2-carbonitrile ***(8b).*** Colorless oil, yield 79%. ^{1}H NMR (300 MHz, DMSO-d_6) *δ* 7.53–7.38 (m, 5H), 7.34 (m, 1H), 6.81 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.61 (dd, *J* = 7.4, 0.9 Hz, 1H), 6.11 (s, 2H). MS(ESI): *m/z* 195.2 $[M+H]^+$.

2-Fluoro-[1,1'-biphenyl]-3-amine ***(8c).*** Colorless oil, yield 81%. ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 7.57–7.33 (m, 5H), 6.94 (m, 1H), 6.78 (m, 1H), 6.60 (m, 1H), 5.20 (s, 2H). MS(ESI): *m/z* 188.2 $[M+H]^+$.

2-Chloro-[1,1'-biphenyl]-3-amine ***(8d).*** Colorless oil, yield 80%. ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 7.49–7.30 (m, 5H), 7.07 (m, 1H), 6.82 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.52 (dd,

J = 7.4, 1.6 Hz, 1H), 5.46 (s, 2H). MS(ESI): *m/z* 204.1 $[M+H]^+$.

General Synthesis Procedure of Compounds **9a-9d**.

Compound **8a-8d** (1.0 equiv) and 4-hydroxyphthalic acid (1.2 equiv) were dissolved in acetic acid and reacted at 120 ℃ for 7 h. Added ice water to precipitate the target product. After filtered, the white solid was purified using a silica gel column (DCM:MeOH = 10:1) to obtain target intermedia **9a-9d**.

5-Hydroxy-2-(2-methyl-[1,1'-biphenyl]-3-yl)isoindoline-1,3-dione ***(9a).*** White solid, yield 83%. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.82 (d, *J* = 8.2 Hz, 1H), 7.43–7.31 (m, 8H), 7.18 (m, 2H), 2.06 (s, 3H). MS(ESI): *m/z* 330.2 $[M+H]^+$.

3-(5-Hydroxy-1,3-dioxoisoindolin-2-yl)-[1,1'-biphenyl]-2-carbonitrile ***(9b).*** White solid, yield 79%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.22 (s, 1H), 8.03–7.82 (m, 2H), 7.81–7.68 (m, 2H), 7.59 (m, 5H), 7.33–7.17 (m, 2H). MS(ESI): *m/z* 341.2 $[M+H]^+$.

2-(2-Fluoro-[1,1'-biphenyl]-3-yl)-5-hydroxyisoindoline-1,3-dione ***(9c).*** White solid, yield 81%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.70–7.62 (m, 1H), 7.59–7.42 (m, 7H), 7.30–7.20 (m, 2H). MS(ESI): *m/z* 334.2 $[M+H]^+$.

2-(2-Chloro-[1,1'-biphenyl]-3-yl)-5-hydroxyisoindoline-1,3-dione ***(9d).*** White solid, yield 80%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.66–7.55 (m, 3H), 7.53–7.41 (m, 5H), 7.29–7.19 (m, 2H). MS(ESI): *m/z* 350.2 $[M+H]^+$.

General Synthesis Procedure of Compounds **10a-10d**

Compound **9a-9d** (1.0 equiv) and hexamethylenetetramine (2.5 equiv) were dissolved in TFA (compound **9a-9d**: TFA = 1 mmol: 2 mL) at 0 ℃ and heated to 120 ℃ for 10 h. Cooling to rt, the solution was refluxed for 2 h after 2.5 times the volume of HCl (1M) was slowly added. Extracted with EA three times and the combined EA phase was concentrated. A silica gel column was used to purify and obtain compound **10a-10d.**

6-Hydroxy-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindoline-5-carbaldehyde ***(10a).*** White solid, yield 35%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 10.41 (s, 1H), 8.11 (s, 1H), 7.51–7.33 (m, 9H), 1.98 (s, 3H). MS(ESI): *m/z* 358.4 $[M+H]^+$.

3-(5-Formyl-6-hydroxy-1,3-dioxoisoindolin-2-yl)-[1,1'-biphenyl]-2-carbonitrile ***(10b).*** White solid, yield 30%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (s, 1H), 10.42 (s, 1H), 8.19 (s, 1H), 8.00 (m, 1H), 7.78 (m, 2H), 7.65–7.53 (m, 6H). MS(ESI): *m/z* 369.3 $[M+H]^+$.

2-(2-Fluoro-[1,1'-biphenyl]-3-yl)-6-hydroxy-1,3-dioxoisoindoline-5-carbaldehyde ***(10c).*** White solid, yield 32%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.14 (s, 1H), 7.68–7.54 (m, 3H), 7.53–7.38 (m, 6H). MS(ESI): *m/z* 362.3 $[M+H]^+$.

2-(2-Chloro-[1,1'-biphenyl]-3-yl)-6-hydroxy-1,3-dioxoisoindoline-5-carbaldehyde ***(10d).*** White solid, yield 30%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.13 (s, 1H), 7.68 (m, 1H), 7.61–7.37 (m, 8H). MS(ESI): *m/z* 378.3 $[M+H]^+$.

General Synthesis Procedure of Compounds **11a-11h**

Compound **10a-10d** (1 equiv) was dissolved in DMF, then Cs_2CO_3 (2 equiv) and 3-cyanobenzyl bromide/2-cyanobenzyl bromide/4-cyanobenzyl bromide/benzyl bromide or 4-isopropyl benzyl bromide (2 equiv) were added and reacted at 80 ℃ for 2 h. After five times the volume of water was added, the reaction solution was extracted with EA three times. The combined EA phase was concentrated and the target intermedia **11a-11f** was purified using a silica gel column**.**

3-(((6-Formyl-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(11a).*** White solid, yield 80%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 8.18 (s, 1H), 8.11 (m, 1H), 7.94 (m, 2H), 7.87 (m, 1H), 7.68 (m, 1H), 7.52–7.35 (m, 8H), 5.65 (s, 2H), 2.00 (s, 3H). MS(ESI): *m/z* 473.3 $[M+H]^+$.

2-(((6-Formyl-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(11b).*** White solid, yield 76%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.17 (s, 1H), 8.06 (s, 1H), 7.98 (m, 1H), 7.90 (m, 1H), 7.82 (m, 1H), 7.64 (m, 1H), 7.52–7.36 (m, 8H), 5.76 (m, 2H), 2.01 (s, 3H). MS(ESI): *m/z* 473.5 $[M+H]^+$.

4-(((6-Formyl-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(11c).*** White solid, yield 77%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.18 (s, 1H), 7.95–7.90 (m, 3H), 7.81–7.77 (m, 2H), 7.50–7.46 (m, 2H), 7.42 (m, 3H), 7.38–7.35 (m, 3H), 5.69 (s, 2H), 1.99 (s, 3H). MS(ESI): *m/z* 495.4 $[M + Na]^+$.

6-(Benzyloxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindoline-5-carbaldehyde ***(11d).*** White solid, yield 80%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.14 (s, 1H), 7.94 (s, 1H), 7.58 (m, 2H), 7.40 (m, 11H), 5.58 (s, 2H), 1.99 (s, 3H). MS(ESI): *m/z* 448.4 $[M+H]^+$.

6-((4-Isopropylbenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindoline-5-carbaldehyde ***(11e).*** White solid, yield 77%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.14 (s, 1H), 7.95 (s, 1H), 7.57–7.45 (m, 3H), 7.45–7.35 (m, 6H), 7.34–7.28 (m, 2H), 7.25–7.16 (m, 1H), 5.54 (s, 2H), 2.90 (m, 1H), 2.00 (s, 3H), 1.23–1.20 (m, 6H). MS(ESI): *m/z* 512.5 $[M + Na]^+$.

3-(5-Formyl-6-hydroxy-1,3-dioxoisoindolin-2-yl)-[1,1'-biphenyl]-2-carbonitrile ***(11f).***

White solid, yield 79%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.24 (s, 1H), 8.10 (s, 1H), 8.03–7.77 (m, 6H), 7.70–7.52 (m, 6H), 5.66 (s, 2H). MS(ESI): *m/z* 484.4 $[M+H]^+$.

2-(2-Fluoro-[1,1'-biphenyl]-3-yl)-6-hydroxy-1,3-dioxoisoindoline-5-carbaldehyde ***(11g).*** White solid, yield 77%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.20 (s, 1H), 8.10 (m, 1H), 8.00–7.91 (m, 2H), 7.86 (m, 1H), 7.74–7.64 (m, 2H), 7.62–7.44 (m, 7H), 5.65 (s, 2H). MS(ESI): *m/z* 499.4 $[M + Na]^+$.

2-(2-Chloro-[1,1'-biphenyl]-3-yl)-6-hydroxy-1,3-dioxoisoindoline-5-carbaldehyde ***(11h).*** White solid, yield 78%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.21 (s, 1H), 8.10 (m, 1H), 7.99–7.92 (m, 2H), 7.87 (m, 1H), 7.70–7.59 (m, 4H), 7.53–7.44 (m, 5H), 5.65 (s, 2H). MS(ESI): *m/z* 515.3 $[M + Na]^+$.

General Synthesis Procedure of Compounds **P1-P8, P11-P16, P18-29, P31-P32, P34, P36, P38, P40.**

Compound **10a, 11a-11h** (1 equiv) and various amines (3 equiv) were dissolved in DCM, and $NaBH(OAc)_3$ (4 equiv) was added 2 h later. Continued the reaction for 10 h at room temperature. NH_4Cl solution was added and mixed well. The DCM phase was concentrated and the crude product was purified using a silica gel column to obtain compounds **P1-P8, P11-P16, P18-29, P31-P32, P34, P36, P38, P40**.

3-(((6-(((2-Hydroxyethyl)amino)methyl)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(P1).*** White solid, yield 30%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03–7.96 (m, 2H), 7.86 (m, 2H), 7.71–7.60 (m, 2H), 7.48 (m, 2H), 7.43–7.32 (m, 6H), 5.48 (s, 2H), 3.92 (s, 2H), 3.51 (t, J = 5.7 Hz, 2H), 2.64 (t, J = 5.7 Hz, 2H), 1.98 (s, 3H). HRMS (ESI): for $C_{32}H_{27}N_3O_4$ $[M+H]^+$ calcd, 518.2074, found 518.2072. Purity, 98.37%.

5-Hydroxy-6-(((2-hydroxyethyl)amino)methyl)-2-(2-methyl-[1,1'-biphenyl]-3-yl)isoindoline-1,3-dione ***(P2)*** White solid, yield 24%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (s, 1H), 7.50–7.44 (m, 2H), 7.41–7.27 (m, 6H), 6.84 (s, 1H), 4.05 (s, 2H), 3.58 (t, J = 5.4 Hz, 2H), 2.79 (t, J = 5.4 Hz, 2H), 1.95 (s, 3H). HRMS (ESI): for $C_{24}H_{22}N_2O_4$ $[M+H]^+$ calcd, 403.1652, found 403.1652. Purity, 99.33%.

2-(((6-(((2-Hydroxyethyl)amino)methyl)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(P3).*** White solid, yield 23%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.84–7.79 (m, 2H), 7.75 (s, 1H), 7.62 (m, 1H), 7.48 (m, 2H), 7.43–7.34 (m, 6H), 5.56 (s, 2H), 3.94 (s, 2H), 3.50 (m, 2H), 2.65 (s, 2H), 1.99 (s, 3H). HRMS (ESI): for $C_{32}H_{27}N_3O_4$ $[M+H]^+$ calcd,

518.2074, found 518.2075. Purity, 97.134%.

4-(((6-(((2-Hydroxyethyl)amino)methyl)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(P4).*** White solid, yield 22%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.94–7.86 (m, 2H), 7.71 (m, 2H), 7.61 (s, 1H), 7.52–7.29 (m, 8H), 5.53 (s, 2H), 4.57 (m, 1H), 3.92 (s, 2H), 3.51 (m, 2H), 2.64 (t, J = 5.7 Hz, 2H), 1.97 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.05, 166.93, 160.67, 142.79, 142.12, 140.53, 136.63, 133.76, 132.55, 132.55, 132.23, 131.77, 130.40, 129.06, 129.06, 128.48, 128.35, 128.35, 127.77, 127.77, 127.26, 126.34, 123.74, 123.66, 118.68, 110.68, 106.58, 69.19, 60.49, 51.20, 47.33, 15.34. HRMS (ESI): for $C_{32}H_{27}N_3O_4$ $[M+H]^+$ calcd, 518.2074, found 518.2077. Purity, 95.49%.

5-(Benzyloxy)-6-(((2-hydroxyethyl)amino)methyl)-2-(2-methyl-[1,1'-biphenyl]-3-yl)isoindoline-1,3-dione ***(P5).*** White solid, yield 26%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.63 (s, 1H), 7.54–7.35 (m, 13H), 5.42 (s, 2H), 4.56 (s, 1H), 3.90 (s, 2H), 3.51 (m, 2H), 2.63 (t, J = 5.7 Hz, 2H), 1.98 (s, 3H). HRMS (ESI): for $C_{31}H_{28}N_2O_4$ $[M+H]^+$ calcd, 493.2122, found 493.2123. Purity, 96.89%.

5-(((2-Hydroxyethyl)amino)methyl)-6-((4-isopropylbenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)isoindoline-1,3-dione ***(P6).*** White solid, yield 21%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.67 (s, 1H), 7.51–7.42 (m, 5H), 7.41–7.35 (m, 5H), 7.32–7.29 (m, 2H), 5.39 (s, 2H), 4.03 (s, 2H), 3.57 (m, 2H), 2.90 (m, 1H), 2.76 (t, J = 5.6 Hz, 2H), 1.98 (s, 3H), 1.22 (d, J = 6.9 Hz, 6H). HRMS (ESI): for $C_{34}H_{34}N_2O_4$ $[M+H]^+$ calcd, 535.2591, found 535.2593. Purity, 95.76%.

3-(((2-(2-Methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxo-6-(((tetrahydro-2H-pyran-4-yl)amino)methyl)isoindolin-5-yl)oxy)methyl)benzonitrile ***(P7).*** White solid, yield 42%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 1H), 8.06 (s, 1H), 8.00 (m, 1H), 7.86 (m, 2H), 7.70–7.63 (m, 2H), 7.50–7.34 (m, 8H), 5.48 (s, 2H), 3.99 (s, 2H), 3.83 (m, 2H), 3.26 (m, 2H), 2.76 (m, 1H), 1.97 (s, 3H), 1.90–1.77 (m, 2H), 1.44–1.29 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.91, 166.82, 160.96, 142.81, 140.52, 137.97, 134.34, 133.73, 132.88, 132.39, 131.92, 131.72, 131.01, 130.44, 129.87, 129.07, 129.07, 128.47, 128.37, 128.37, 127.27, 126.37, 124.95, 123.53, 118.60, 111.56, 106.77, 69.20, 65.63, 65.63, 53.13, 43.31, 32.08, 32.05, 15.34. HRMS (ESI): for $C_{35}H_{31}N_3O_4$ $[M+H]^+$ calcd, 558.2387, found 558.2385. Purity, 98.52%.

((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)-L-proline ***(P8).*** White solid, yield 40%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (m, 1H), 8.02 (m, 1H), 7.92–7.82 (m, 2H), 7.67 (m, 2H), 7.49 (m, 2H), 7.45–7.31

(m, 6H), 5.49 (m, 2H), 4.14–3.95 (m, 2H), 3.43 (m, 1H), 3.08 (m, 1H), 2.57 (m, 1H), 2.13 (m, 1H), 1.99 (s, 3H), 1.91 (m, 1H), 1.82 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 173.90, 166.91, 166.80, 160.92, 142.80, 140.54, 138.00, 133.78, 133.45, 132.93, 132.23, 131.86, 131.75, 130.92, 130.43, 129.86, 129.07, 128.46, 128.36, 127.26, 126.36, 125.38, 123.68, 118.62, 111.57, 106.97, 69.14, 65.61, 53.17, 51.88, 28.78, 23.13, 15.36. HRMS (ESI): for $C_{35}H_{29}N_3O_5$ $[M+H]^+$ calcd, 572.2180, found 572.2181. Purity, 97.32%.

5-Hydroxy-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindoline-4-carbaldehyde ***(12).*** Compound **9a** (9.87 g, 30 mmol) and hexamethylenetetramine (10.5 g, 75 mmol) were dissolved in 60 mL TFA at 0 ℃ and heated to 120 ℃ for 10 h. The solution was refluxed for 2 h after 150 mL HCl (1M) was slowly added. Extracted with EA three times and the combined EA phase was concentrated. A silica gel column (PE/DCM/EA = 3:1:0.1) was used to obtain compound **12** (1.07 g, yield 10%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 10.82 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.52–7.33 (m, 9H), 2.02 (s, 3H). MS(ESI): *m/z* 358.2 $[M+H]^+$.

3-(((4-Formyl-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(13).*** Compound **12** (714 mg, 2 mmol) was dissolved in 10 mL DMF, then cesium carbonate (1.30 mg, 4 mmol) and 3-cyanobenzyl bromide (784 mg, 4 mmol) were added and reacted at 80 ℃ for 2 h. After 50 mL water was added, the reaction solution was extracted with EA three times. The combined EA phase was concentrated. A silica gel column (PE/EA = 1:1) was used to purify and obtain compound **13** (708 mg, yield 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.22 (d, J = 8.5 Hz, 1H), 8.03 (s, 1H), 7.92–7.82 (m, 2H), 7.69 (m, 2H), 7.51–7.35 (m, 8H), 5.50 (s, 2H), 2.03 (s, 3H). MS(ESI): *m/z* 473.4 $[M+H]^+$.

3-(((2-(2-Methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxo-4-(((tetrahydro-2H-pyran-4-yl)amino)methyl)isoindolin-5-yl)oxy)methyl)benzonitrile ***(P9).*** Compound **13** (236 mg, 0.5 mmol) and 4-aminotetrahydropyran (152 mg, 1.5 mmol) were dissolved in 2.5 mL DCM, and $NaBH(OAc)_3$ (422 mg, 2 mmol) was added 2 h later. Continued the reaction for 10 h at room temperature. NH_4Cl solution was added and mixed well. The DCM phase was concentrated and the crude product was purified using a silica gel column (DCM/MeOH = 10:1) to obtain compound **P9** (153 mg, yield 55%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (m, 1H), 7.93–7.82 (m, 3H), 7.66 (m, 1H), 7.54–7.34 (m, 9H), 5.43 (s, 2H), 4.22 (s, 2H), 3.76 (m, 2H), 3.21 (m, 2H), 2.64 (m, 1H), 1.99 (s, 3H), 1.75 (m, 2H), 1.23 (m, 2H). HRMS (ESI): for $C_{35}H_{31}N_3O_4$ $[M+H]^+$ calcd,

558.2387, found 558.2386. Purity, 95.64%.

((5-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-4-yl)methyl)-L-proline ***(P10).*** Compound **P10** (white solid) was prepared from the compound **13** (236 mg, 0.5 mmol) and L-Proline (173 mg, 1.5 mmol) according to the preparation procedure of compound **P9**, 114 mg, yield 40%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (m, 1H), 7.97–7.90 (m, 2H), 7.83 (m, 1H), 7.64 (m, 1H), 7.53–7.34 (m, 9H), 5.51–5.36 (m, 2H), 4.53–4.33 (m, 2H), 3.42 (m, 1H), 3.16 (m, 1H), 2.83–2.69 (m, 1H), 2.13–2.04 (m, 1H), 2.00 (s, 3H), 1.79 (m, 3H). HRMS (ESI): for $C_{35}H_{29}N_3O_5$ $[M+H]^+$ calcd, 572.2180, found 572.2181. Purity, 95.96%.

(S)-1-((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)piperidine-2-carboxylic acid ***(P11).*** White solid, yield 40%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 4.1 Hz, 1H), 7.97 (m, 1H), 7.85 (m, 2H), 7.71–7.59 (m, 2H), 7.52–7.33 (m, 8H), 5.48 (s, 2H), 3.87 (t, J = 14.8 Hz, 1H), 3.73 (m, 1H), 3.24 (brs, 1H), 2.90 (m, 1H), 2.28 (m, 1H), 1.99 (s, 3H), 1.81 (m, 2H), 1.46 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.86, 167.53, 167.35, 161.41, 143.27, 141.03, 138.59, 135.08, 134.29, 133.02, 132.64, 132.36, 132.28, 131.25, 130.90, 130.36, 129.56, 129.55, 128.95, 128.86, 128.86, 127.75, 126.85, 125.11, 124.20, 119.09, 112.06, 107.35, 69.44, 63.96, 54.13, 49.92, 29.43, 25.45, 22.18, 15.85. HRMS (ESI): for $C_{36}H_{31}N_3O_5$ $[M+H]^+$ calcd, 586.2336, found 586.2335. Purity, 98.94%.

(S)-1-((2-(2-Cyano-[1,1'-biphenyl]-3-yl)-6-((3-cyanobenzyl)oxy)-1,3-dioxoisoindolin-5-yl)methyl)piperidine-2-carboxylic acid ***(P12).*** White solid, yield 34%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (m, 1H), 8.02–7.94 (m, 2H), 7.86 (m, 2H), 7.78 (m, 2H), 7.71–7.54 (m, 7H), 5.51 (s, 2H), 3.92–3.76 (m, 2H), 3.15 (m, 1H), 2.97–2.87 (m, 1H), 2.32 (m, 1H), 1.82 (brs, 2H), 1.49 (m, 4H). HRMS (ESI): for $C_{36}H_{28}N_4O_5$ $[M+H]^+$ calcd, 597.2132, found 597.2136. Purity, 96.64%.

3-(((2-(2-Chloro-[1,1'-biphenyl]-3-yl)-1,3-dioxo-6-(((tetrahydro-2H-pyran-4-yl)amino)methyl)isoindolin-5-yl)oxy)methyl)benzonitrile ***(P13).*** White solid, yield 46%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 8.00 (m, 1H), 7.90–7.83 (m, 2H), 7.70–7.64 (m, 3H), 7.64–7.55 (m, 2H), 7.53–7.41 (m, 5H), 5.49 (s, 2H), 4.00 (s, 2H), 3.83 (m, 2H), 3.26 (m, 2H), 2.78 (m, 1H), 1.91–1.76 (m, 2H), 1.43–1.26 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.28, 166.22, 161.09, 141.30, 138.18, 137.93, 134.79, 132.67, 132.38, 132.33, 131.94, 131.00, 130.79, 130.57, 129.87, 129.20, 129.20, 128.36, 128.36, 128.06, 127.84, 125.02, 125.02, 123.36, 118.60, 111.57, 106.95, 69.24,

65.63, 65.63, 53.14, 43.35, 32.14, 32.14. HRMS (ESI): for $C_{34}H_{28}ClN_3O_4$ $[M+H]^+$ calcd, 578.1841, found 578.1841. Purity, 98.71%.

((2-(2-Chloro-[1,1'-biphenyl]-3-yl)-6-((3-cyanobenzyl)oxy)-1,3-dioxoisoindolin-5-yl)methyl)-L-proline ***(P14).*** Compound **P14** White solid, yield 42%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (m, 1H), 8.02 (m, 1H), 7.87 (m, 2H), 7.73–7.55 (m, 5H), 7.55–7.39 (m, 5H), 5.55–5.40 (m, 2H), 4.10 (m, 1H), 3.97 (m, 1H), 3.43 (m, 1H), 3.07 (m, 1H), 2.60–2.53 (m, 1H), 2.13 (m, 1H), 1.86 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.93, 166.28, 166.18, 161.09, 141.30, 138.19, 137.95, 133.87, 132.74, 132.31, 132.25, 131.88, 130.94, 130.82, 130.58, 129.86, 129.21, 129.21, 128.36, 128.36, 128.06, 127.83, 125.51, 125.41, 123.48, 118.62, 111.58, 107.15, 69.20, 65.65, 53.21, 51.90, 28.81, 23.17. HRMS (ESI): for $C_{34}H_{26}ClN_3O_5$ $[M+H]^+$ calcd, 592.1634, found 592.1631. Purity, 98.21%.

3-(((2-(2-Fluoro-[1,1'-biphenyl]-3-yl)-1,3-dioxo-6-(((tetrahydro-2H-pyran-4-yl)amino)methyl)isoindolin-5-yl)oxy)methyl)benzonitrile ***(P15).*** White solid, yield 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 8.02 (m, 1H), 7.88 (m, 2H), 7.74–7.64 (m, 3H), 7.61–7.43 (m, 7H), 5.50 (s, 2H), 4.03 (s, 2H), 3.84 (m, 2H), 3.28 (m, 2H), 2.80 (m, 1H), 1.89–1.79 (m, 2H), 1.38 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.11, 166.07, 161.07, 155.43, 153.43, 137.91, 134.81, 134.18, 132.70, 132.40, 131.93, 131.42, 131.02, 129.86, 129.86, 129.38, 129.28, 128.84, 128.82, 128.75, 128.75, 128.26, 125.01, 124.96, 123.39, 120.19, 120.07, 118.59, 111.56, 106.91, 69.22, 65.64, 65.64, 53.13, 43.37, 32.15, 32.15. HRMS (ESI): for $C_{34}H_{28}FN_3O_4$ $[M+H]^+$ calcd, 562.2137, found 562.2135. Purity, 97.34%.

((6-((3-Cyanobenzyl)oxy)-2-(2-fluoro-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)-L-proline ***(P16).*** White solid, yield 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 8.03 (s, 1H), 7.87 (m, 2H), 7.75–7.37 (m, 10H), 5.59–5.41 (m, 2H), 4.10 (m, 1H), 3.98 (m, 1H), 3.43 (m, 1H), 3.07 (m, 1H), 2.57 (m, 1H), 2.13 (m, 1H), 1.86 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.90, 166.11, 166.04, 161.08, 155.46, 153.46, 137.94, 134.20, 133.76, 132.79, 132.25, 131.87, 131.43, 130.94, 129.88, 129.85, 129.38, 129.28, 128.84, 128.82, 128.75, 128.75, 128.26, 125.50, 124.96, 123.51, 120.21, 120.09, 118.62, 111.58, 107.15, 69.19, 65.59, 53.21, 51.91, 28.82, 23.15. HRMS (ESI): for $C_{34}H_{26}FN_3O_5$ $[M+H]^+$ calcd, 576.1929, found 576.1930. Purity, 96.19%.

3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-methylaniline ***(14).*** Colorless oil, yield 84%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.88 (m, 2H), 6.73–6.65 (m, 2H), 6.60 (d, J =

7.6 Hz, 1H), 6.37 (d, *J* = 7.3 Hz, 1H), 4.86 (s, 2H), 4.26 (s, 4H), 1.92 (s, 3H). MS(ESI): *m/z* 242.2 $[M+H]^+$.

2-(3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-methylphenyl)-6-hydroxy-1,3-dioxoisoindoline-5-carboxylic acid ***(15).*** Compound **14** (3.62 g, 15 mmol) and 5-hydroxybenzene-1,2,4-tricarboxylic acid (4.07 mg, 18 mmol) were dissolved in 75 mL acetic acid and reacted at 120 ℃ for 7 h. Added 375 mL ice water to precipitate the target product. After filtered, a silica gel column (DCM:MeOH = 10:1) was used to obtain compound **15** as a white solid (4.65 g, yield 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.56–7.23 (m, 4H), 6.97–6.73 (m, 3H), 4.28 (s, 4H), 1.99 (s, 3H). MS(ESI): *m/z* 432.3 $[M+H]^+$.

2-(3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-methylphenyl)-5-hydroxy-6-(hydroxymethyl)isoindoline-1,3-dione ***(16).*** Compound **15** (4.32 g, 10 mmol) was dissolved in 25 mL THF. Then, in an ice bath, 25 mL BH_3·THF (1 mmol/mL) was slowly added in drop by drop. After stirring at rt for 12 h, 10 mL methanol was slowly added in ice bath. The solution was concentrated at a reduced pressure. A silica gel column (PE/EA = 1:1) was used to obtain compound 16 (2.93 g, yield 70%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 7.88 (s, 1H), 7.45–7.22 (m, 4H), 6.99–6.75 (m, 3H), 4.59 (s, 2H), 4.29 (s, 4H), 1.98 (s, 3H). MS(ESI): *m/z* 418.3 $[M+H]^+$.

2-(3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-methylphenyl)-6-hydroxy-1,3-dioxoisoindoline-5-carbaldehyde ***(17).*** Dissolved compound **16** (2.5 g, 6 mmol) in 30 mL DCM, then MnO_2 (15.66 g, 180 mmol) was added. Reacted for 24 h at rt, and the solvent was removed at a reduced pressure. A silica gel column (PE/EA = 2:1) was used to obtain compound **17** (1.87 g, yield 75%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.11 (s, 1H), 7.48 (s, 1H), 7.39–7.31 (m, 3H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.85–6.79 (m, 2H), 4.29 (s, 4H), 1.99 (s, 3H). MS(ESI): *m/z* 416.4 $[M+H]^+$.

3-(((2-(3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-methylphenyl)-6-formyl-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(18).*** Dissolved compound **17** (1.66 g, 4 mmol) in 20 mL DMF, then cesium carbonate (2.6 g, 8 mmol) and 3-cyanobenzyl bromide (1.57 g, 8 mmol) were added and reacted at 80 ℃ for 2 hours. Mixed the reaction solution with 100 mL water and extracted with EA three times. EA was removed at a reduced pressure. A silica gel column (PE/EA = 1:1) was used to obtain compound **18** (1.7 g, yield 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 8.17 (s, 1H), 8.10 (m, 1H), 7.97–7.91 (m, 2H), 7.87 (m, 1H), 7.68 (m, 1H), 7.43–7.36 (m,

2H), 7.33 (m, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.86–6.77 (m, 2H), 5.64 (s, 2H), 4.29 (s, 4H), 2.01 (s, 3H). MS(ESI): *m/z* 531.4 $[M+H]^+$.

3-(((2-(3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-methylphenyl)-1,3-dioxo-6-(((tetrahydro-2H-pyran-4-yl)amino)methyl)isoindolin-5-yl)oxy)methyl)benzonitrile ***(P17).*** Compound **18** (265 mg, 0.5 mmol) and 4-aminotetrahydropyran (152 mg, 1.5 mmol) were dissolved in 2.5 mL DCM and $NaBH(OAc)_3$ (422 mg, 2 mmol) was added 2 h later. Continued the reaction for 10 h at room temperature. NH_4Cl solution was added and mixed well. The DCM phase was concentrated. A silica gel column (DCM/MeOH = 10:1) was used to obtain compound **P17** (160 mg, yield 52%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 8.02 (m, 1H), 7.87 (m, 2H), 7.70–7.62 (m, 2H), 7.40–7.30 (m, 3H), 6.94 (d, J = 8.2 Hz, 1H), 6.84–6.76 (m, 2H), 5.49 (s, 2H), 4.28 (s, 4H), 4.08 (s, 2H), 3.84 (m, 2H), 3.27 (m, 2H), 2.89 (m, 1H), 1.98 (s, 3H), 1.86 (m, 2H), 1.41 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.86, 166.78, 161.03, 143.05, 142.76, 142.28, 137.93, 133.79, 133.60, 133.06, 132.43, 131.94, 131.64, 131.07, 130.46, 129.86, 128.21, 126.28, 125.21, 123.49, 122.05, 118.61, 117.62, 116.92, 111.56, 106.83, 69.25, 65.58, 65.58, 64.10, 64.10, 53.22, 43.13, 31.73, 31.73, 15.36. HRMS (ESI): for $C_{37}H_{33}N_3O_6$ $[M+H]^+$ calcd, 616.2442, found 616.2434. Purity, 98.50%.

N-(2-(((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)amino)ethyl)acetamide ***(P18).*** White solid, yield 23%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04–7.97 (m, 2H), 7.87 (m, 3H), 7.67 (m, 1H), 7.63 (s, 1H), 7.51–7.33 (m, 8H), 5.48 (s, 2H), 3.89 (s, 2H), 3.18 (m, 2H), 2.61 (t, J = 6.4 Hz, 2H), 1.98 (s, 3H), 1.80 (s, 3H). HRMS (ESI): for $C_{34}H_{30}N_4O_4$ $[M+H]^+$ calcd, 559.2340, found 559.2342. Purity, 95.13%.

3-(((6-(((2-Hydroxyethyl)(methyl)amino)methyl)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(P19).*** White solid, yield 21%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07–7.97 (m, 2H), 7.86 (m, 2H), 7.69–7.62 (m, 2H), 7.50–7.34 (m, 8H), 5.48 (s, 2H), 3.73 (brs, 2H), 3.55 (brs, 2H), 2.64–2.52 (m, 2H), 2.28 (s, 3H), 1.98 (s, 3H). HRMS (ESI): for $C_{33}H_{29}N_3O_4$ $[M+H]^+$ calcd, 532.2231, found 532.2234. Purity, 97.05%.

Tert-butyl (2-(((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)amino)ethyl)carbamate ***(P20).*** White solid, yield 33%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.98 (m, 1H), 7.86 (m, 2H), 7.66 (m, 1H), 7.61 (s, 1H), 7.51–7.33 (m, 8H), 6.80 (m, 1H), 5.47 (s, 2H), 3.87 (s, 2H), 3.06 (m, 2H),

2.60 (t, J = 6.5 Hz, 2H), 1.97 (s, 3H), 1.36 (s, 9H). HRMS (ESI): for $C_{37}H_{36}N_4O_5$ $[M+H]^+$ calcd, 617.2758, found 617.2755. Purity, 96.6%.

3-(((6-(((2-(Dimethylamino)ethyl)amino)methyl)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(P21).*** White solid, yield 24%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 8.00 (m, 1H), 7.87 (m, 2H), 7.71–7.63 (m, 2H), 7.51–7.34 (m, 8H), 5.48 (s, 2H), 3.96 (s, 2H), 2.83–2.67 (m, 4H), 2.39 (s, 6H), 1.98 (s, 3H). HRMS (ESI): for $C_{34}H_{32}N_4O_3$ $[M+H]^+$ calcd, 545.2547, found 545.2546. Purity, 97.16%.

(S)-3-(((6-((2-(Hydroxymethyl)pyrrolidin-1-yl)methyl)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(P22).*** White solid, yield 25%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (s, 1H), 8.06–7.98 (m, 2H), 7.92–7.80 (m, 2H), 7.70–7.61 (m, 2H), 7.52–7.33 (m, 8H), 5.50 (s, 2H), 4.28 (m, 1H), 3.81 (m, 1H), 3.49 (m, 1H), 3.40 (m, 1H), 2.98 (m, 1H), 2.87 (m, 1H), 2.42 (m, 1H), 1.98 (s, 3H), 1.96–1.83 (m, 1H), 1.68 (m, 3H). HRMS (ESI): for $C_{35}H_{31}N_3O_4$ $[M+H]^+$ calcd, 558.2387, found 558.2387. Purity, 97.53%.

(R)-3-(((6-((3-Hydroxypyrrolidin-1-yl)methyl)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(P23).*** White solid, yield 28%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (m, 1H), 7.94 (s, 1H), 7.86 (m, 2H), 7.70–7.61 (m, 2H), 7.54–7.32 (m, 8H), 5.48 (s, 2H), 4.76 (d, J = 4.5 Hz, 1H), 4.24 (m, 1H), 3.86–3.69 (m, 2H), 2.82–2.68 (m, 2H), 2.44 (m, 1H), 2.04 (m, 1H), 1.98 (s, 3H), 1.60 (m, 1H). HRMS (ESI): for $C_{34}H_{29}N_3O_4$ $[M+H]^+$ calcd, 544.2231, found 544.2232. Purity, 96.07%.

3-(((2-(2-Methyl-[1,1'-biphenyl]-3-yl)-6-(morpholinomethyl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(P24).*** White solid, yield 26%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.93 (s, 1H), 7.86 (m, 2H), 7.71–7.62 (m, 2H), 7.48 (m, 2H), 7.44–7.32 (m, 6H), 5.49 (s, 2H), 3.67 (brd, 2H), 3.62 (m, 4H), 2.46 (m, 4H), 1.98 (s, 3H). HRMS (ESI): for $C_{34}H_{29}N_3O_4$ $[M+H]^+$ calcd, 544.2231, found 544.2232. Purity, 98.52%.

3-(((6-((3-Hydroxyazetidin-1-yl)methyl)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)methyl)benzonitrile ***(P25).*** White solid, yield 35%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.92–7.82 (m, 3H), 7.70–7.63 (m, 2H), 7.51–7.45 (m, 2H), 7.42–7.34 (m, 6H), 5.49 (s, 2H), 4.31 (m, 1H), 3.89 (brs, 2H), 3.73 (brs, 2H), 3.37 (brs, 2H), 3.06 (brs, 1H), 1.98 (s, 3H). HRMS (ESI): for $C_{33}H_{27}N_3O_4$ $[M+H]^+$ calcd, 530.2074, found 530.2077. Purity, 96.97%.

(S)-1-((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)pyrrolidine-2-carboxamide ***(P26).*** White solid, yield 32%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 5.2 Hz, 1H), 7.97 (s, 1H), 7.85 (m, 2H), 7.69–7.62 (m, 2H), 7.48 (m, 2H), 7.42–7.34 (m, 6H), 7.31 (m, 1H), 6.98 (m, 1H), 5.49 (s, 2H), 3.93 (m, 1H), 3.76 (m, 1H), 3.08 (m, 1H), 3.00 (m, 1H), 2.33 (m, 1H), 2.09 (m, 1H), 1.98 (s, 3H), 1.76 (m, 3H). HRMS (ESI): for $C_{35}H_{30}N_4O_4$ $[M+H]^+$ calcd, 571.2340, found 571.2340. Purity, 98.22%.

1-((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)azetidine-3-carboxylic acid ***(P27).*** White solid, yield 34%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (m, 1H), 7.92–7.81 (m, 3H), 7.67 (m, 1H), 7.62 (s, 1H), 7.51–7.44 (m, 2H), 7.42–7.30 (m, 6H), 5.48 (m, 2H), 3.77 (m, 2H), 3.51 (m, 2H), 3.36–3.22 (m, 3H), 1.97 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.34, 166.92, 166.84, 160.69, 142.80, 140.55, 138.09, 133.79, 132.65, 132.14, 131.85, 131.76, 130.86, 130.78, 130.43, 129.91, 129.07, 129.07, 128.48, 128.38, 128.37, 127.27, 126.36, 123.75, 118.66, 111.58, 106.79, 69.00, 56.84, 56.84, 56.51, 33.78, 15.37. HRMS (ESI): for $C_{34}H_{27}N_3O_5$ $[M+H]^+$ calcd, 558.2023, found 558.2024. Purity, 98.88%.

Ethyl ((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)-L-serinate ***(P28)*** White solid, yield 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 4.3 Hz, 1H), 7.98 (m, 1H), 7.86 (m, 2H), 7.66 (m, 2H), 7.52–7.34 (m, 8H), 5.48 (s, 2H), 4.91 (m, 1H), 4.05 (m, 2H), 3.99 (m, 1H), 3.86 (m, 1H), 3.63 (m, 2H), 1.98 (s, 3H), 1.15 (m, 3H). HRMS (ESI): for $C_{35}H_{31}N_3O_6$ $[M+H]^+$ calcd, 590.2286, found 590.2284. Purity, 97.06%.

Tert-butyl ((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)-L-serinate ***(P29).*** White solid, yield 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.97 (m, 1H), 7.85 (m, 2H), 7.68–7.60 (m, 2H), 7.50–7.34 (m, 8H), 5.47 (s, 2H), 3.97 (m, 1H), 3.84 (m, 1H), 3.59 (m, 2H), 3.22 (m, 1H), 1.97 (s, 3H), 1.35 (d, J = 8.7 Hz, 9H). HRMS (ESI): for $C_{37}H_{35}N_3O_6$ $[M+H]^+$ calcd, 618.2599, found 618.2601. Purity, 98.21%.

General Synthesis Procedure of Compounds **P30**, **P33**, **P35**, **P37**, **P39**, and **P41.**

Trifluoroacetic acid was slowly added into the solution of compounds **P29, P32, P34, P36, P38, P40** in DCM. After stirring for 12 h and detected with TLC. The solution was concentrated and a silica gel column was used to obtain compounds **P30**, **P33**, **P35**, **P37**, **P39**, and **P41**.

((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)-L-serine ***(P30).*** White solid, yield 89%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.09 (s, 1H), 8.00 (s, 1H), 7.88 (m, 2H), 7.71–7.60 (m, 2H), 7.52–7.34 (m, 8H), 5.49 (s, 2H), 4.04 (m, 2H), 3.66 (m, 2H), 3.22 (m, 1H), 1.99 (s, 3H). HRMS (ESI): for $C_{33}H_{27}N_3O_6$ $[M+H]^+$ calcd, 562.1973, found 562.1977. Purity, 98.17%.

Methyl ((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)glycinate ***(P31).*** White solid, yield 54 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04–7.98 (m, 2H), 7.86 (m, 2H), 7.67 (m, 2H), 7.51–7.35 (m, 8H), 5.48 (s, 2H), 3.97 (s, 2H), 3.48 (s, 2H), 3.34 (s, 3H), 1.98 (s, 3H). HRMS (ESI): for $C_{33}H_{27}N_3O_5$ $[M+H]^+$ calcd, 546.2023, found 546.2023. Purity, 97.72%.

Tert-butyl ((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)glycinate ***(P32).*** White solid, yield 65%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01–7.96 (m, 2H), 7.85 (m, 2H), 7.67–7.61 (m, 2H), 7.50–7.34 (m, 8H), 5.47 (s, 2H), 3.91 (s, 2H), 3.29 (s, 2H), 1.98 (s, 3H), 1.37 (s, 9H). HRMS (ESI): for $C_{36}H_{33}N_3O_5$ $[M+H]^+$ calcd, 588.2493, found 588.2492. Purity, 98.91%.

((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)glycine ***(P33).*** White solid, yield 89%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 8.05 (s, 1H), 7.89 (m, 2H), 7.74 (s, 1H), 7.67 (m, 1H), 7.50–7.35 (m, 8H), 5.53 (s, 2H), 4.44 (s, 2H), 3.95 (s, 2H), 1.98 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.86, 166.79, 160.97, 142.80, 140.53, 137.94, 133.76, 133.16, 133.06, 132.19, 131.88, 131.72, 130.78, 130.43, 129.88, 129.07, 129.06, 128.46, 128.36, 128.36, 127.27, 126.36, 124.74, 123.61, 118.63, 111.58, 106.81, 69.19, 49.73, 46.14, 15.35. HRMS (ESI): for $C_{32}H_{25}N_3O_5$ $[M+H]^+$ calcd, 532.1867, found 532.1866. Purity, 95.95%.

Tert-butyl N-((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)-N-methylglycinate ***(P34).*** White solid, yield 68%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 2H), 7.86 (m, 2H), 7.68–7.62 (m, 2H), 7.50–7.34 (m, 8H), 5.47 (s, 2H), 3.85 (s, 2H), 3.30 (m, 2H), 2.35 (s, 3H), 1.98 (s, 3H), 1.41 (s, 9H). HRMS (ESI): for $C_{37}H_{35}N_3O_5$ $[M+H]^+$ calcd, 602.2649, found 602.2647. Purity, 97.21%.

N-((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)-N-methylglycine ***(P35).*** White solid, yield 91%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 8.02 (m, 1H), 7.88 (m, 2H), 7.73 (s, 1H), 7.67 (m, 1H), 7.52–7.34 (m, 8H), 5.51 (s, 2H), 4.23 (s, 2H), 3.73 (s, 2H), 2.59 (s, 3H), 1.99 (s, 3H). ^{13}C

NMR (126 MHz, DMSO-d_6) δ 171.45, 166.86, 166.76, 161.28, 142.81, 140.53, 137.95, 133.76, 133.20, 132.25, 131.90, 131.72, 130.89, 130.45, 129.88, 129.07, 129.07, 128.45, 128.37, 128.37, 127.28, 126.38, 125.66, 123.68, 118.63, 111.59, 107.15, 69.19, 57.22, 53.96, 41.65, 15.37. HRMS (ESI): for $C_{33}H_{27}N_3O_5$ $[M+H]^+$ calcd, 546.2023, found 546.2018. Purity, 99.21%.

Tert-butyl ((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)-L-alaninate ***(P36).*** White solid, yield 66%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 8.02 (d, J = 7.4 Hz, 1H), 7.98 (m, 1H), 7.86 (m, 2H), 7.69–7.62 (m, 2H), 7.52–7.32 (m, 8H), 5.48 (s, 2H), 3.97–3.78 (m, 2H), 3.25 (m, 1H), 1.98 (s, 3H), 1.37 (d, J = 6.8 Hz, 9H), 1.22 (m, 3H). HRMS (ESI): for $C_{37}H_{35}N_3O_5$ $[M+H]^+$ calcd, 602.2649, found 602.2647. Purity, 97.66%.

((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)-L-alanine ***(P37).*** White solid, yield 87%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (s, 1H), 8.06 (m, 1H), 7.95–7.84 (m, 2H), 7.74 (s, 1H), 7.66 (m, 1H), 7.54–7.32 (m, 8H), 5.52 (s, 2H), 4.42 (s, 2H), 4.08 (m, 1H), 1.98 (s, 3H), 1.48 (d, J = 7.0 Hz, 3H). HRMS (ESI): for $C_{33}H_{27}N_3O_5$ $[M+H]^+$ calcd, 546.2023, found 546.2023. Purity, 97.75%.

Tert-butyl (2S)-2-(((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)amino)-3-hydroxybutanoate ***(P38).*** White solid, yield 61%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.10 (m, 1H), 8.00 (m, 1H), 7.89 (m, 2H), 7.72–7.65 (m, 2H), 7.54–7.48 (m, 2H), 7.46–7.38 (m, 6H), 5.51 (s, 2H), 4.01 (m, 1H), 3.85 (m, 2H), 3.03 (s, 1H), 2.01 (s, 3H), 1.37 (d, J = 7.1 Hz, 9H), 1.17 (d, J = 6.2 Hz, 3H). HRMS (ESI): for $C_{38}H_{37}N_3O_6$ $[M+H]^+$ calcd, 632.2755, found 632.2754. Purity, 97.93%.

(2S)-2-(((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)amino)-3-hydroxybutanoic acid ***(P39).*** White solid, yield 88%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (m, 1H), 7.99 (m, 1H), 7.87 (m, 2H), 7.69–7.61 (m, 2H), 7.52–7.34 (m, 8H), 5.48 (s, 2H), 4.07 (m, 1H), 3.91 (m, 2H), 3.06 (m, 1H), 1.99 (s, 3H), 1.18 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ167.00, 166.90, 160.87, 142.82, 140.55, 137.97, 135.69, 133.78, 132.54, 132.23, 131.89, 131.76, 130.82, 130.44, 129.92, 129.08, 129.08, 128.46, 128.38, 128.38, 127.29, 126.38, 124.18, 123.60, 118.61, 111.57, 106.60, 69.13, 67.26, 66.79, 46.44, 20.06, 15.36. HRMS (ESI): for $C_{34}H_{29}N_3O_6$ $[M+H]^+$ calcd, 576.2129, found 576.2130. Purity, 95.18%.

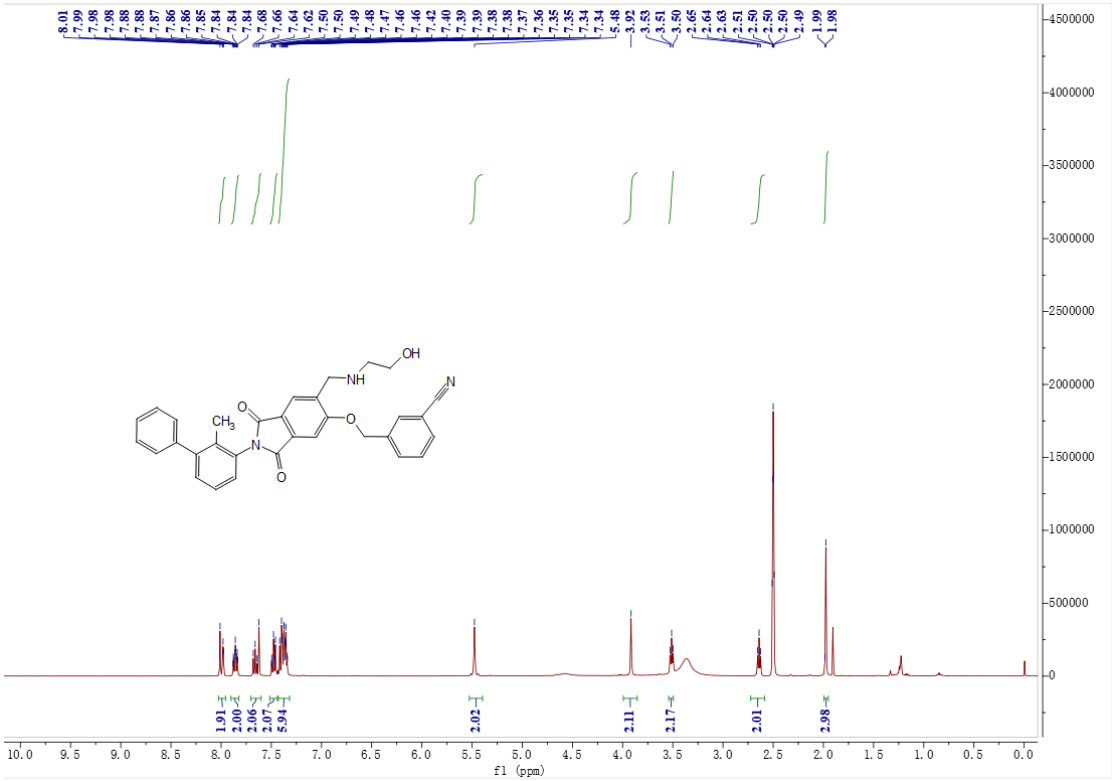
Tert-butyl ((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-

dioxoisoindolin-5-yl)methyl)-L-phenylalaninate ***(P40).*** White solid, yield 69%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (m, 2H), 7.84 (m, 2H), 7.68–7.60 (m, 2H), 7.51–7.34 (m, 8H), 7.27–7.17 (m, 5H), 5.44 (s, 2H), 3.95–3.74 (m, 2H), 3.39 (m, 1H), 2.94–2.79 (m, 2H), 1.97 (s, 3H), 1.21 (d, J = 10.0 Hz, 9H). HRMS (ESI): for $C_{43}H_{39}N_3O_5$ $[M+H]^+$ calcd, 678.2962, found 678.2961. Purity, 96.33%.

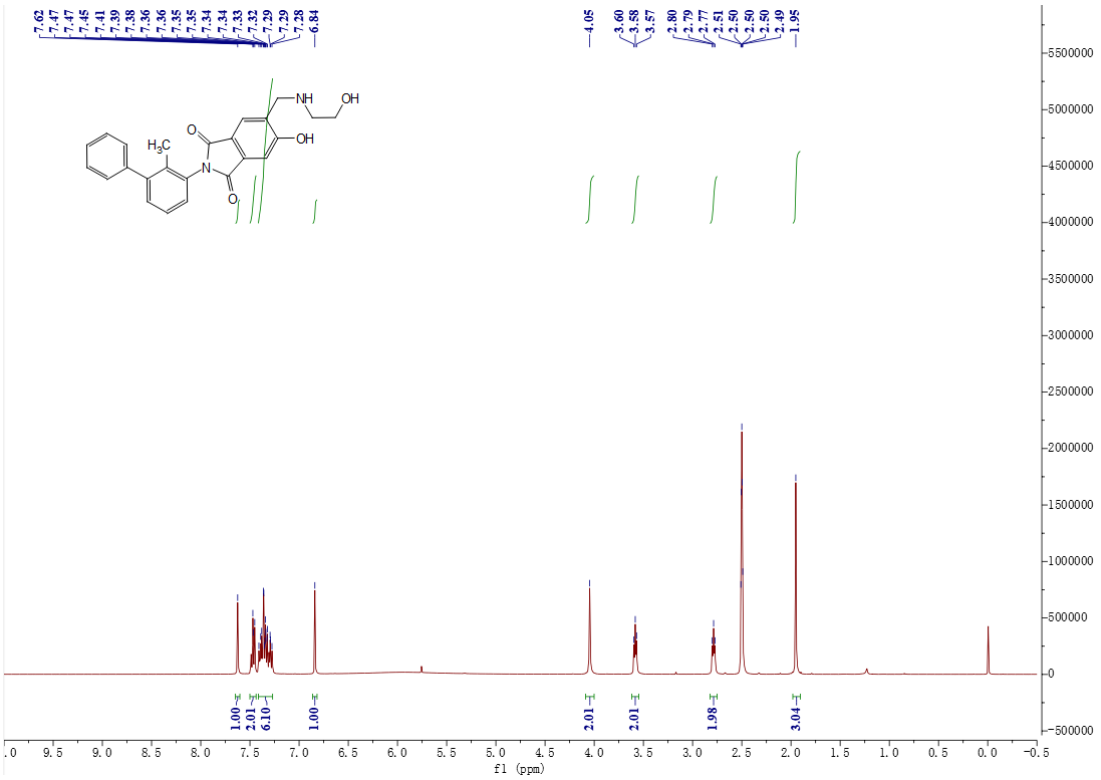
((6-((3-Cyanobenzyl)oxy)-2-(2-methyl-[1,1'-biphenyl]-3-yl)-1,3-dioxoisoindolin-5-yl)methyl)-L-phenylalanine ***(P41).*** White solid, yield 92%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (m, 1H), 8.06 (m, 1H), 7.97–7.82 (m, 2H), 7.75 (s, 1H), 7.66 (m, 1H), 7.54–7.19 (m, 13H), 5.53 (s, 2H), 4.56–4.38 (m, 2H), 4.27 (m, 1H), 3.31 (m, 1H), 3.09 (m, 1H), 1.99 (s, 3H). HRMS (ESI): for $C_{39}H_{31}N_3O_5$ $[M+H]^+$ calcd, 622.2336, found 622.2335. Purity, 95.97%.

Spectra of Target Compounds P1-P41

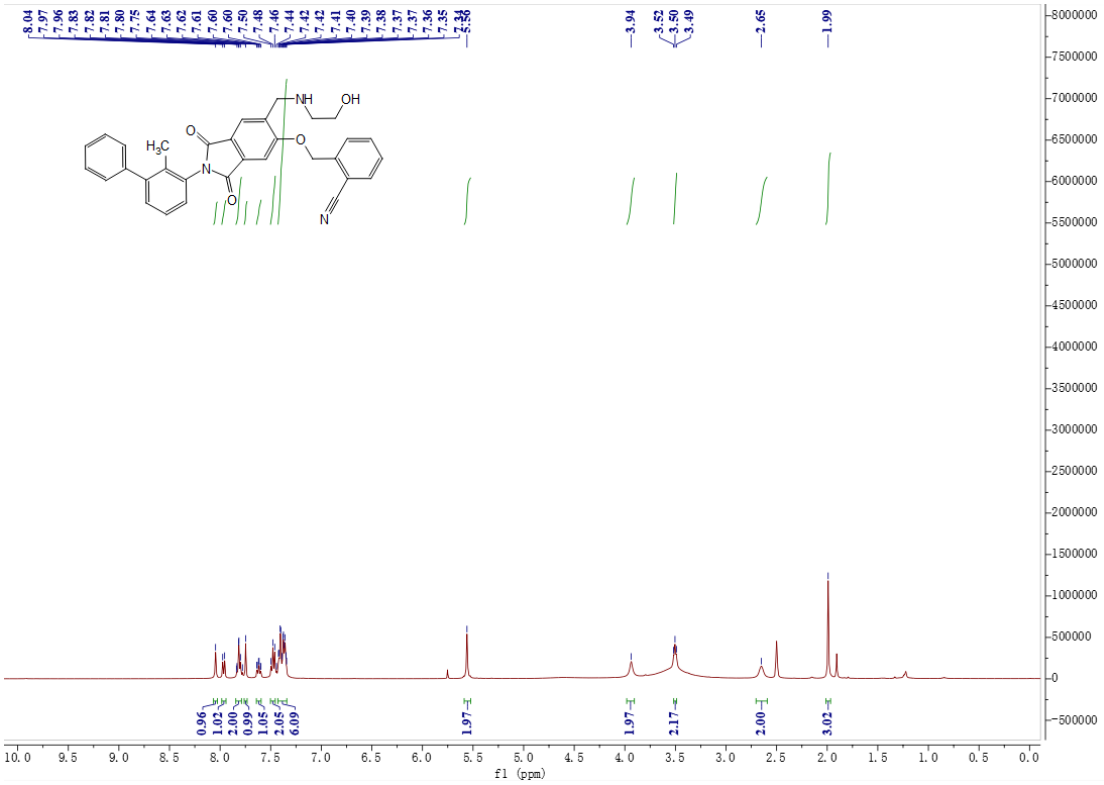
^{1}H NMR spectrum of **P1**



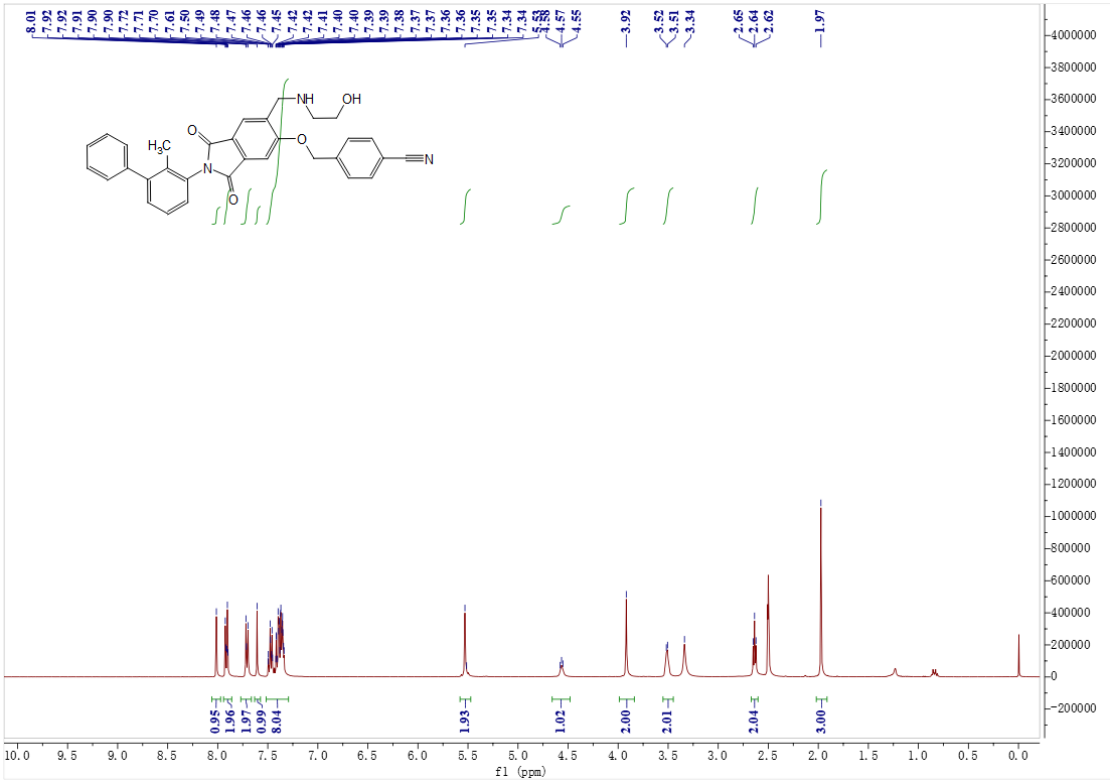
^{1}H NMR spectrum of **P2**



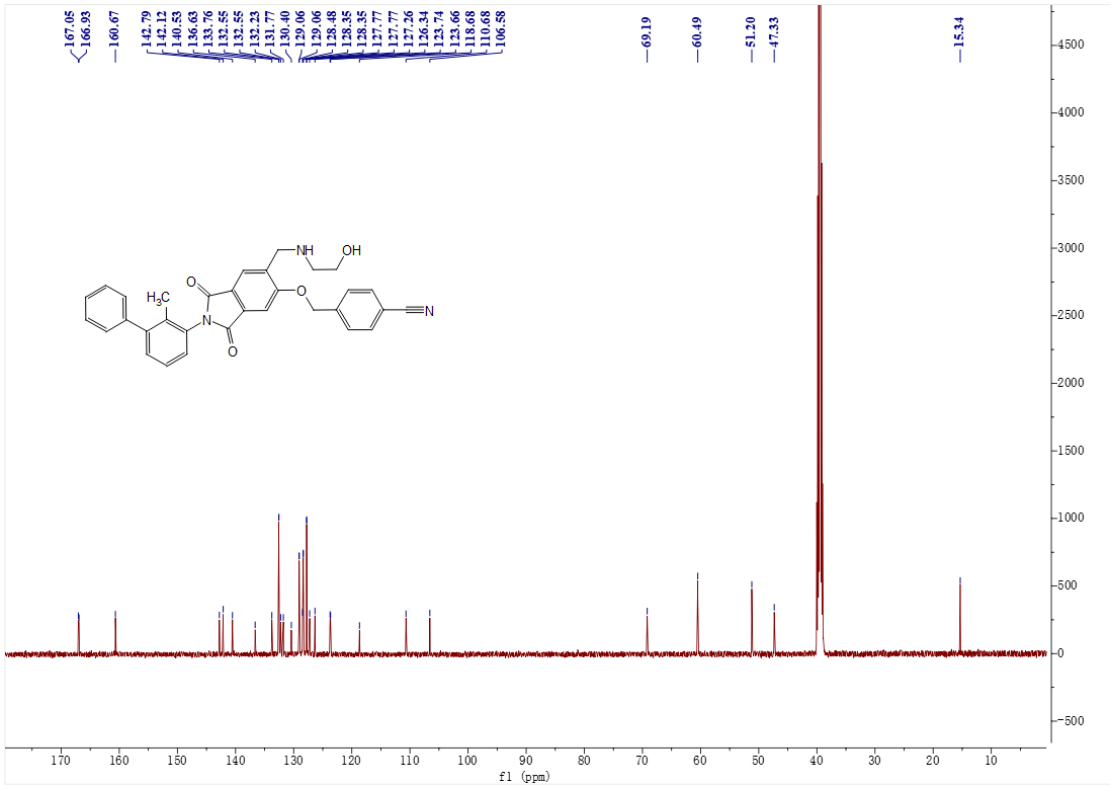
^{1}H NMR spectrum of **P3**



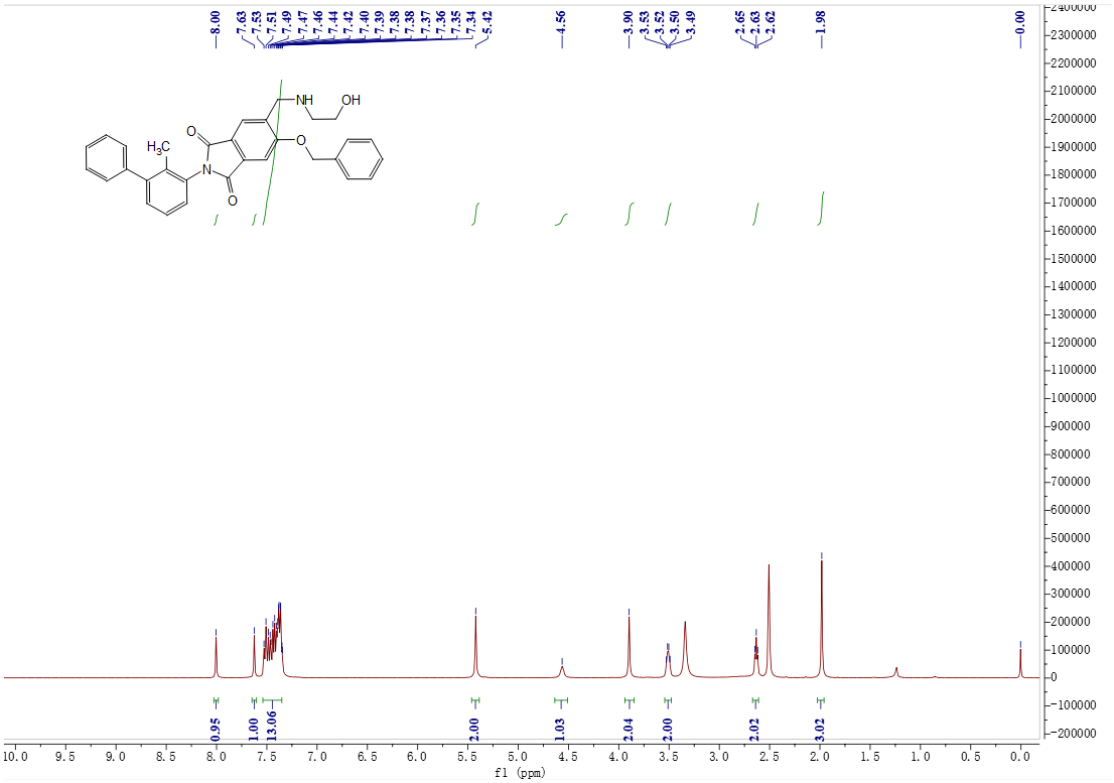
^{1}H NMR spectrum of **P4**



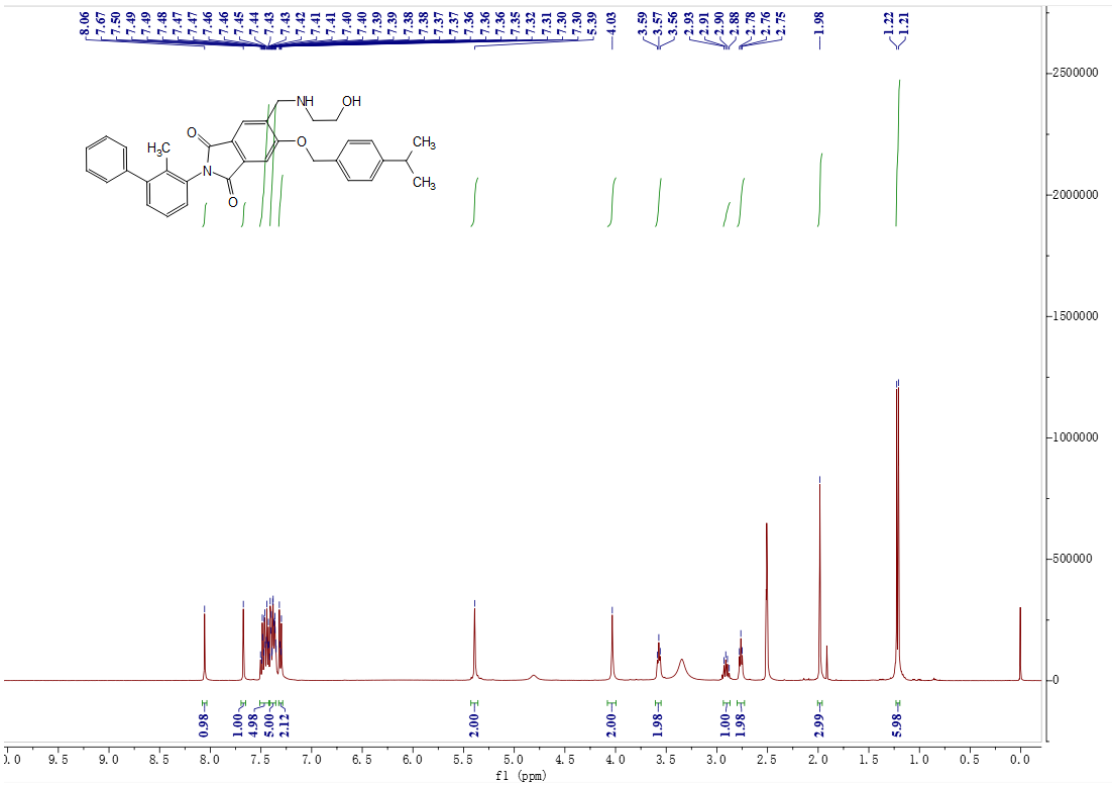
^{13}C NMR spectrum of **P4**



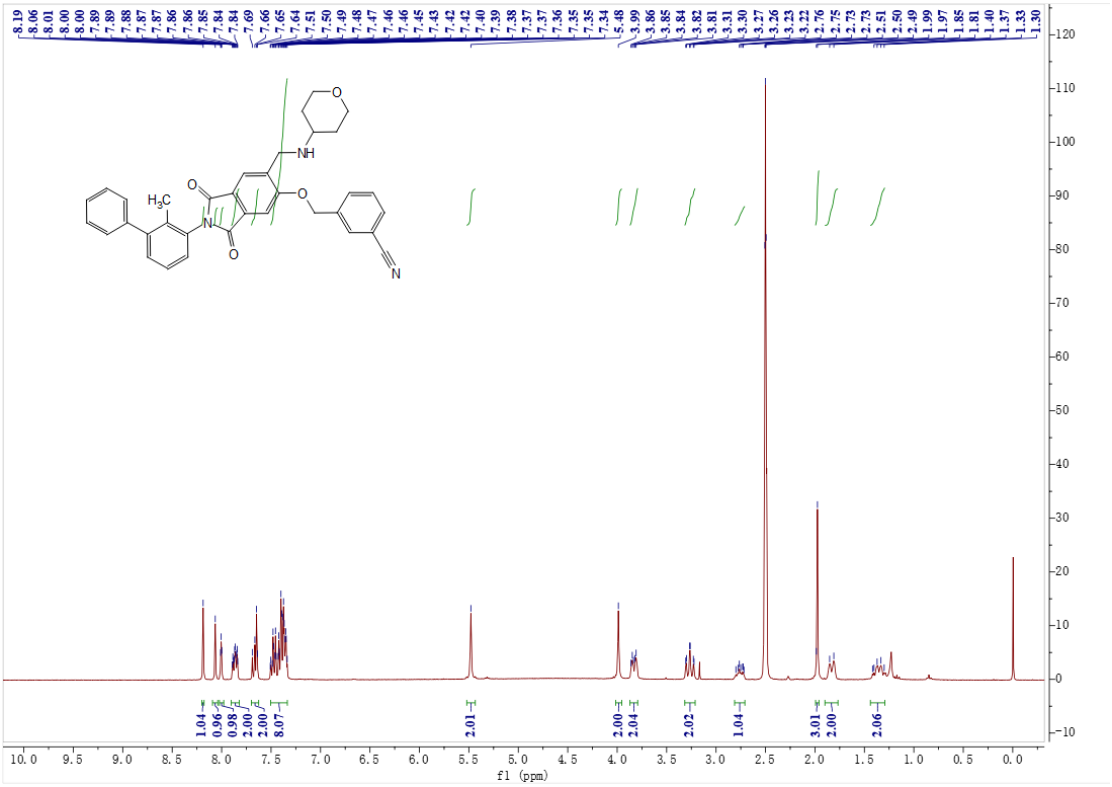
^{1}H NMR spectrum of **P5**



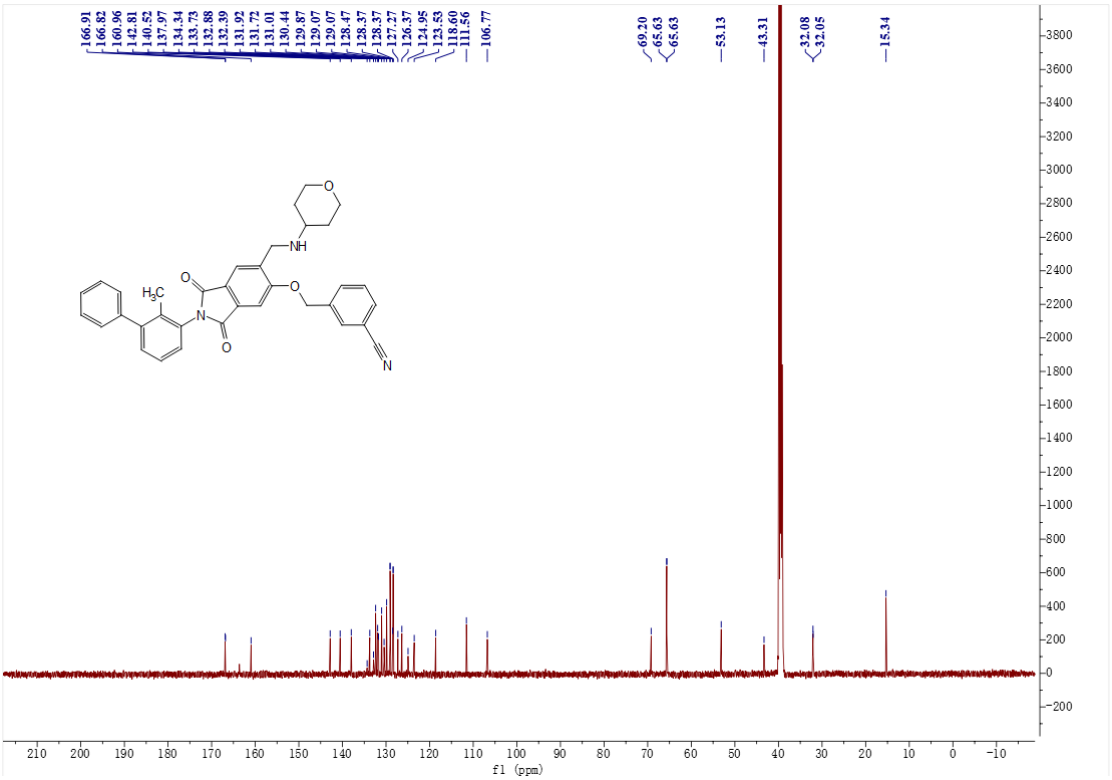
^{1}H NMR spectrum of **P6**



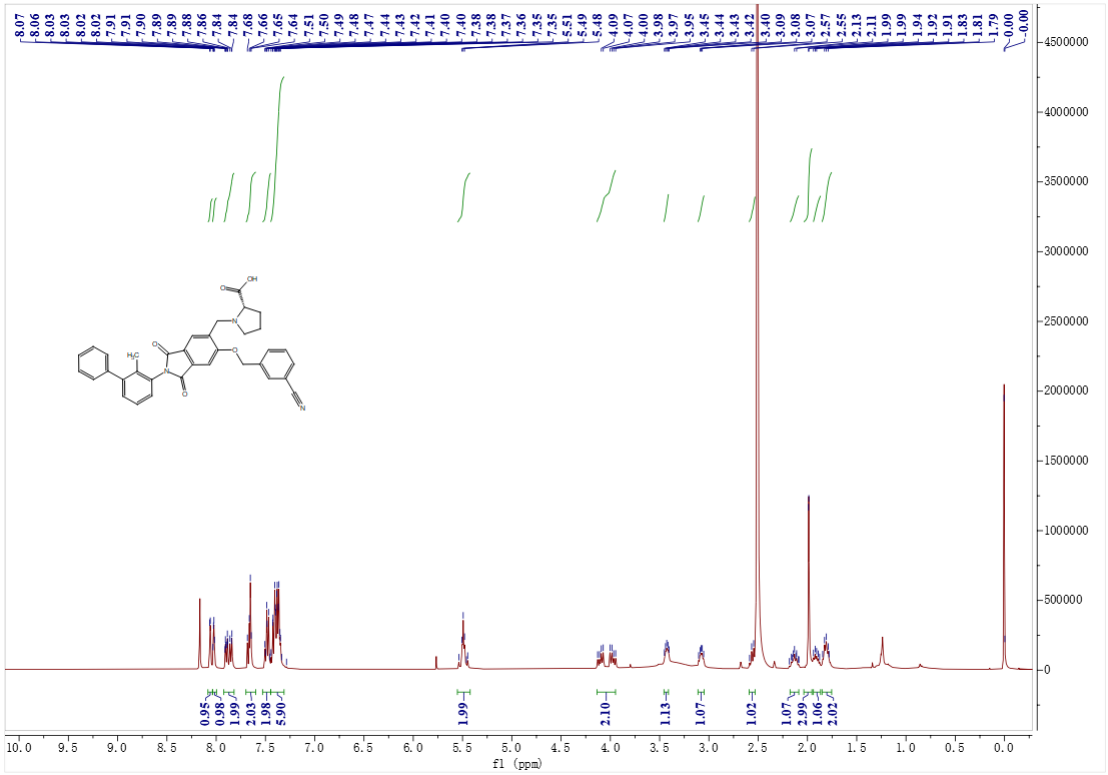
^{1}H NMR spectrum of **P7**



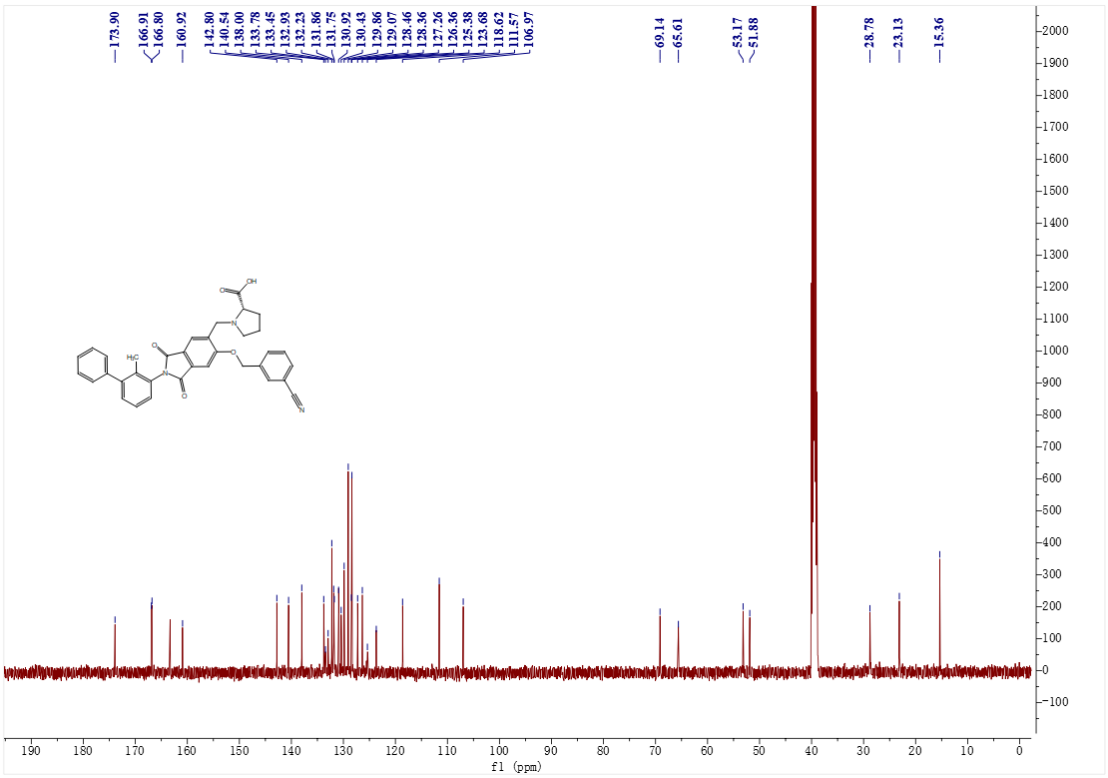
^{13}C NMR spectrum of **P7**



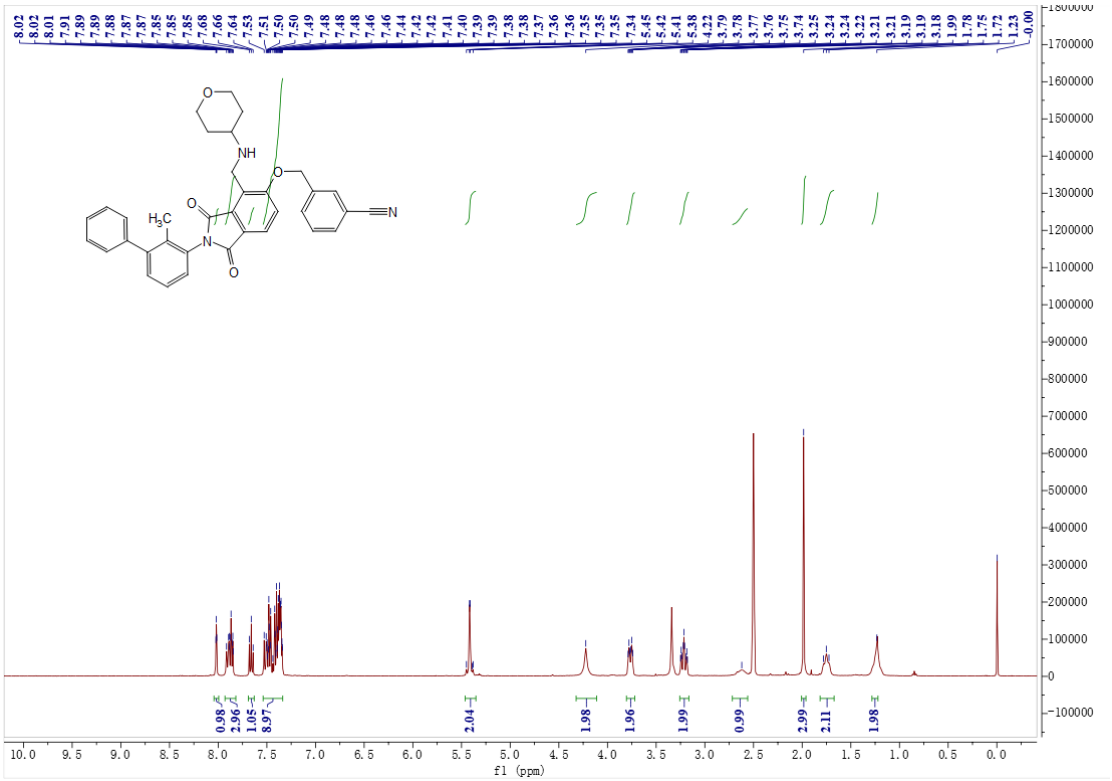
^{1}H NMR spectrum of **P8**



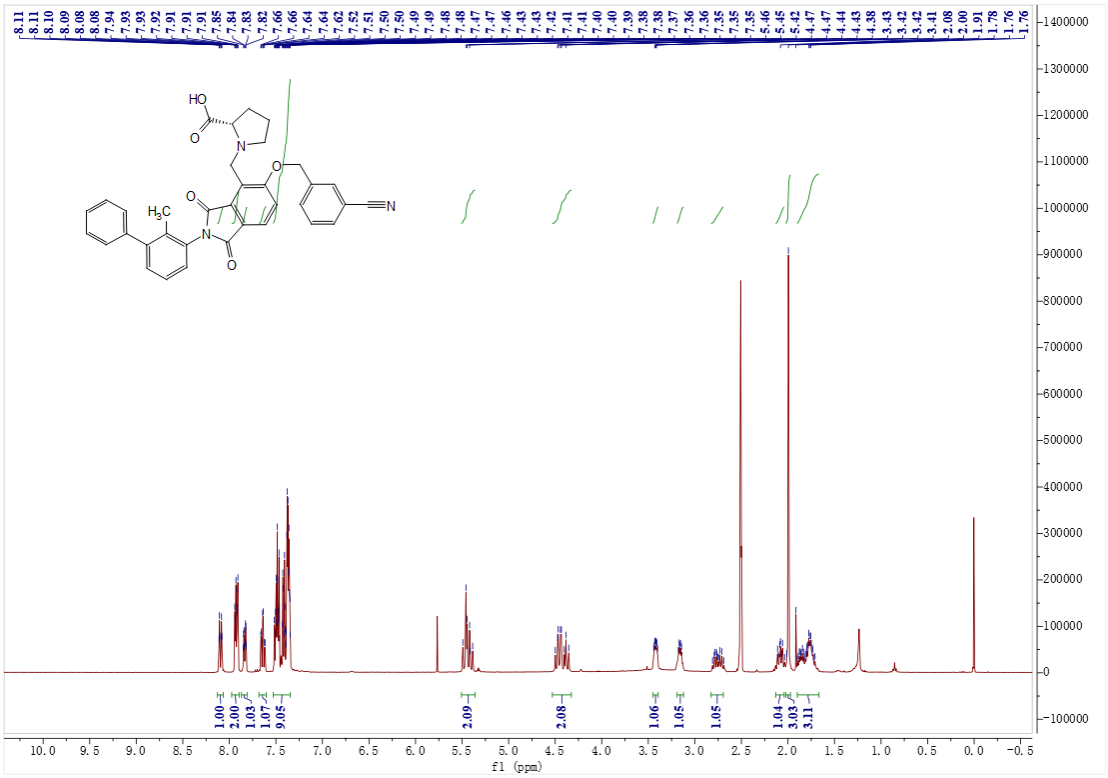
^{13}C NMR spectrum of **P8**



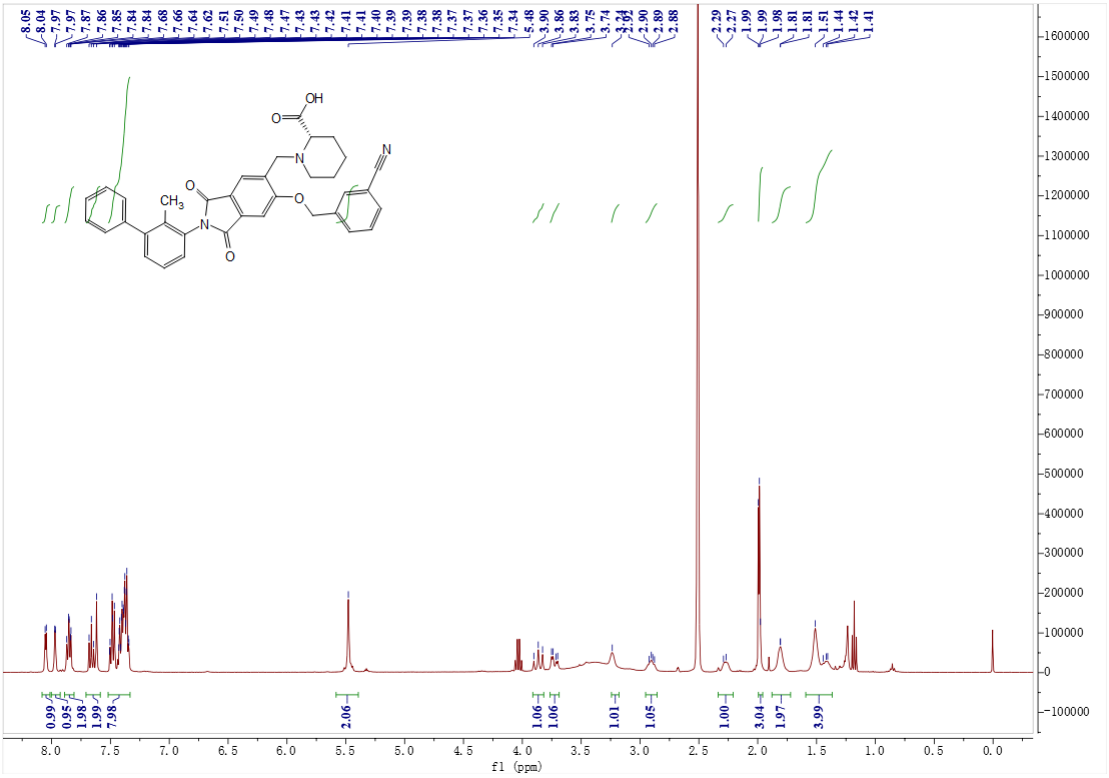
^{1}H NMR spectrum of **P9**



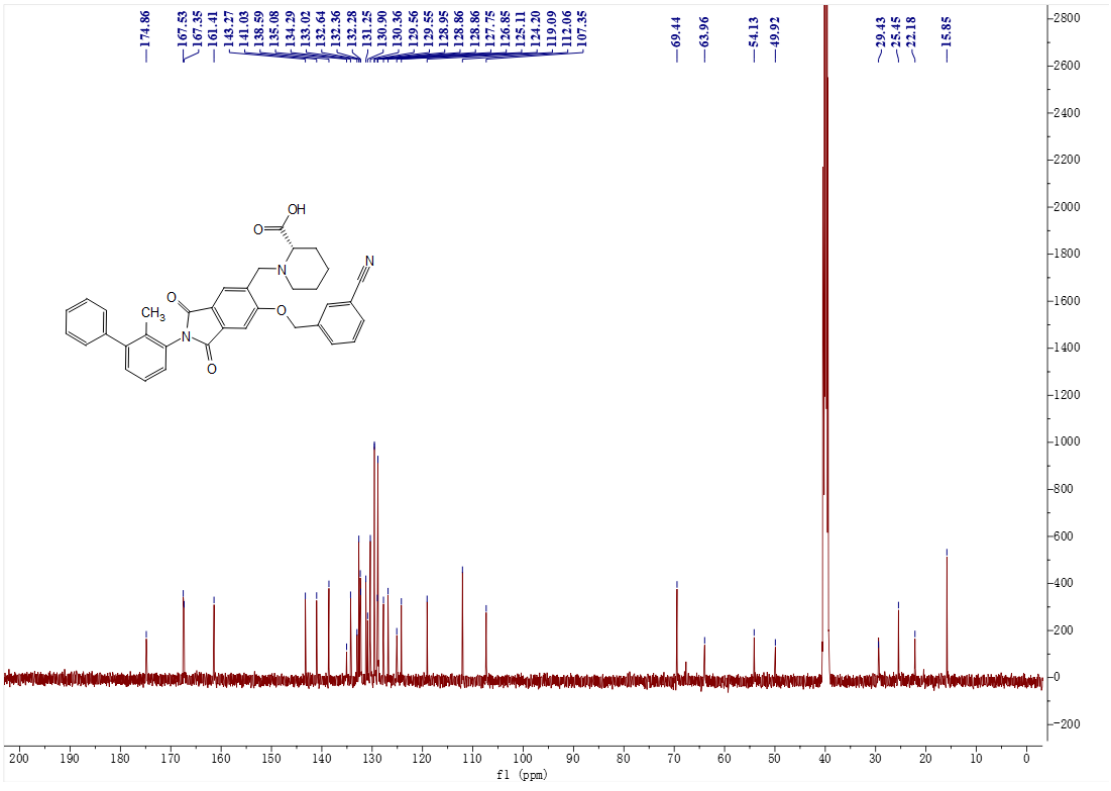
^{1}H NMR spectrum of **P10**



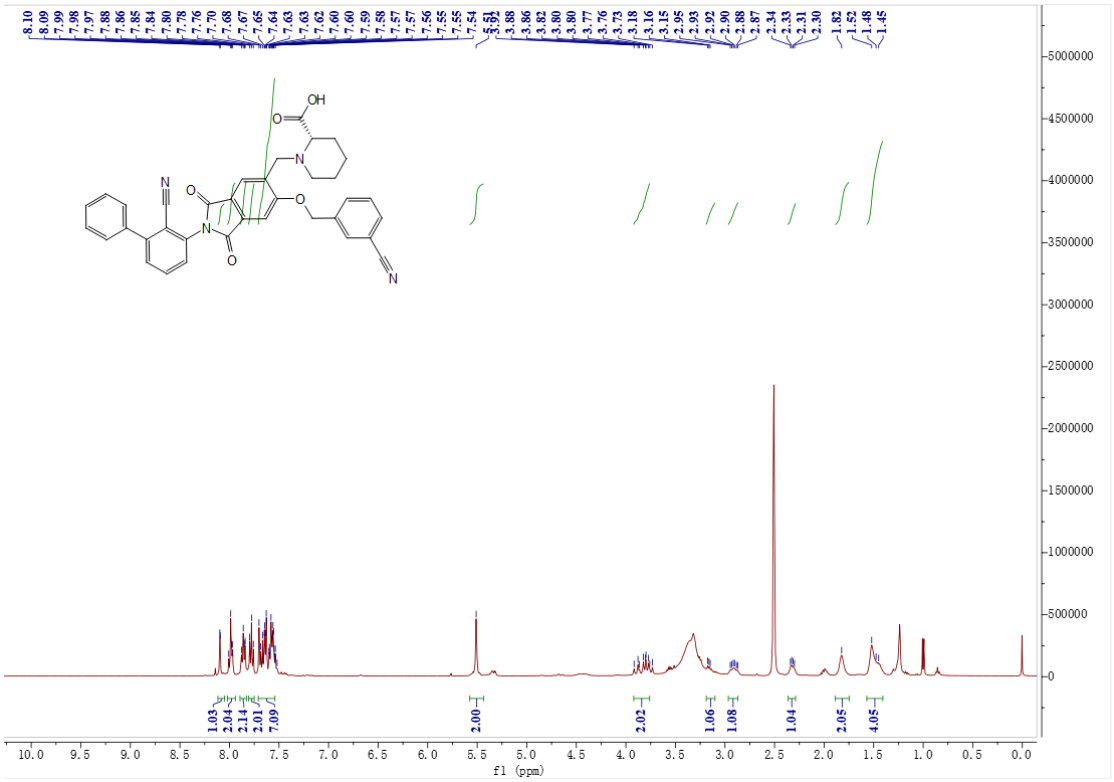
^{1}H NMR spectrum of **P11**



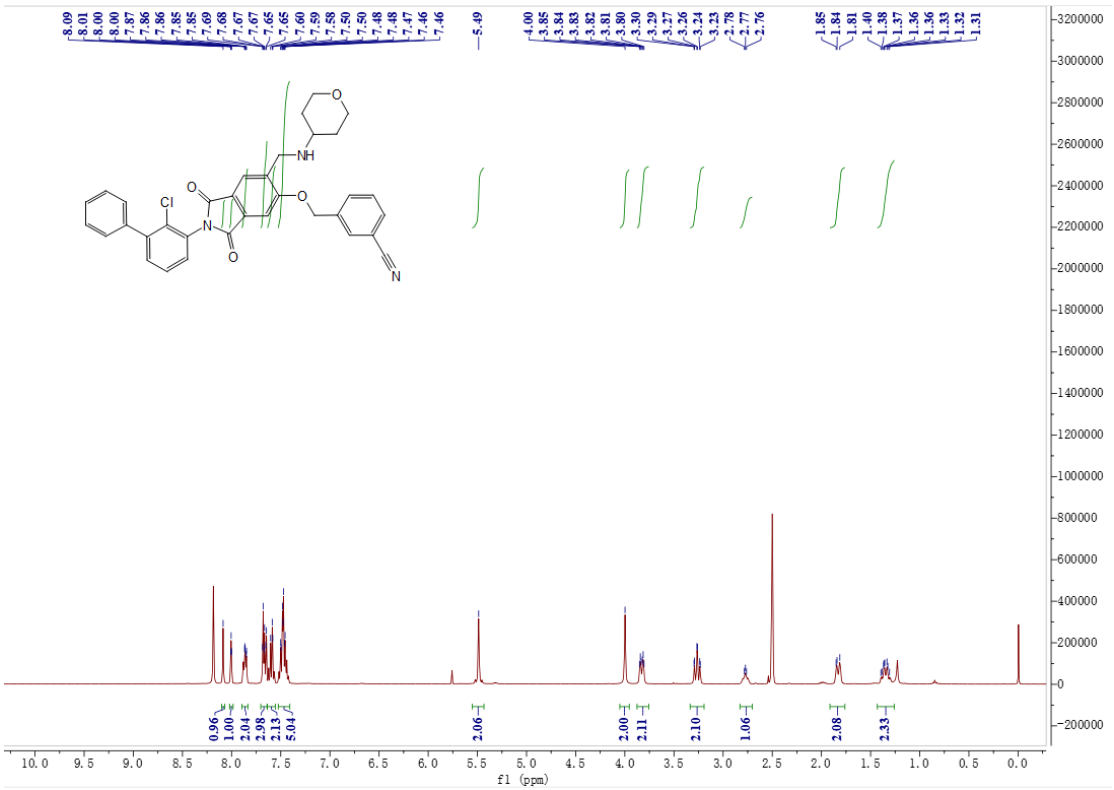
^{13}C NMR spectrum of **P11**



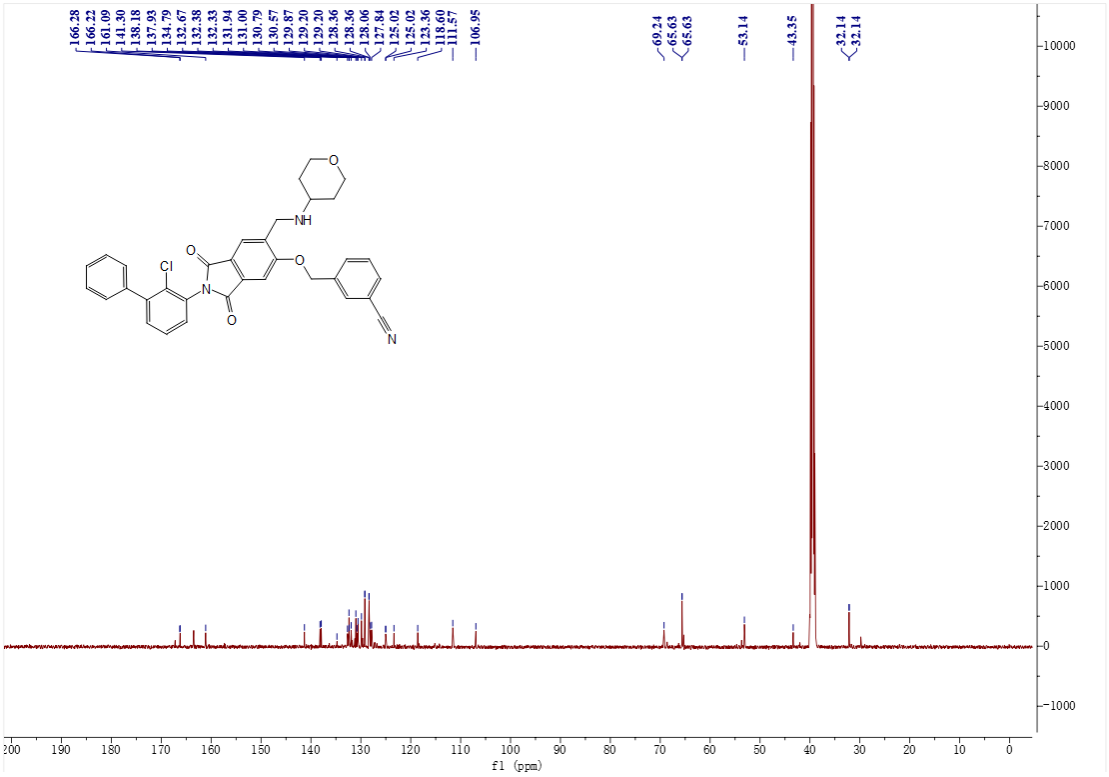
^{1}H NMR spectrum of **P12**



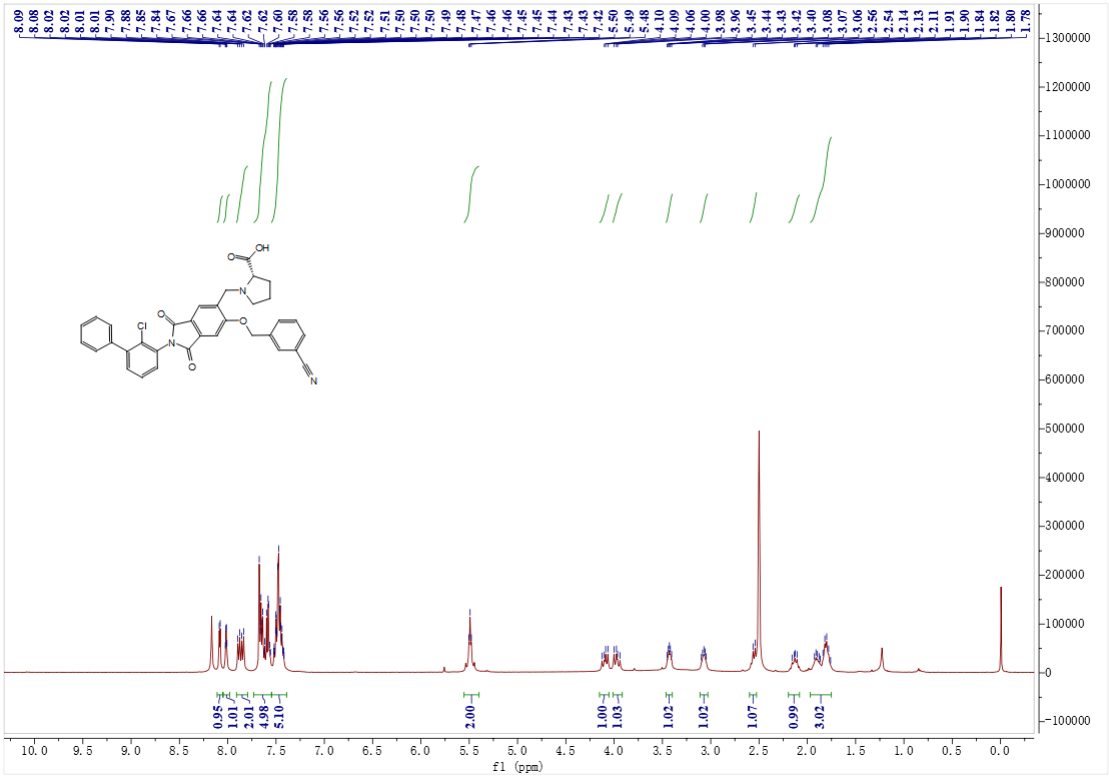
^{1}H NMR spectrum of **P13**



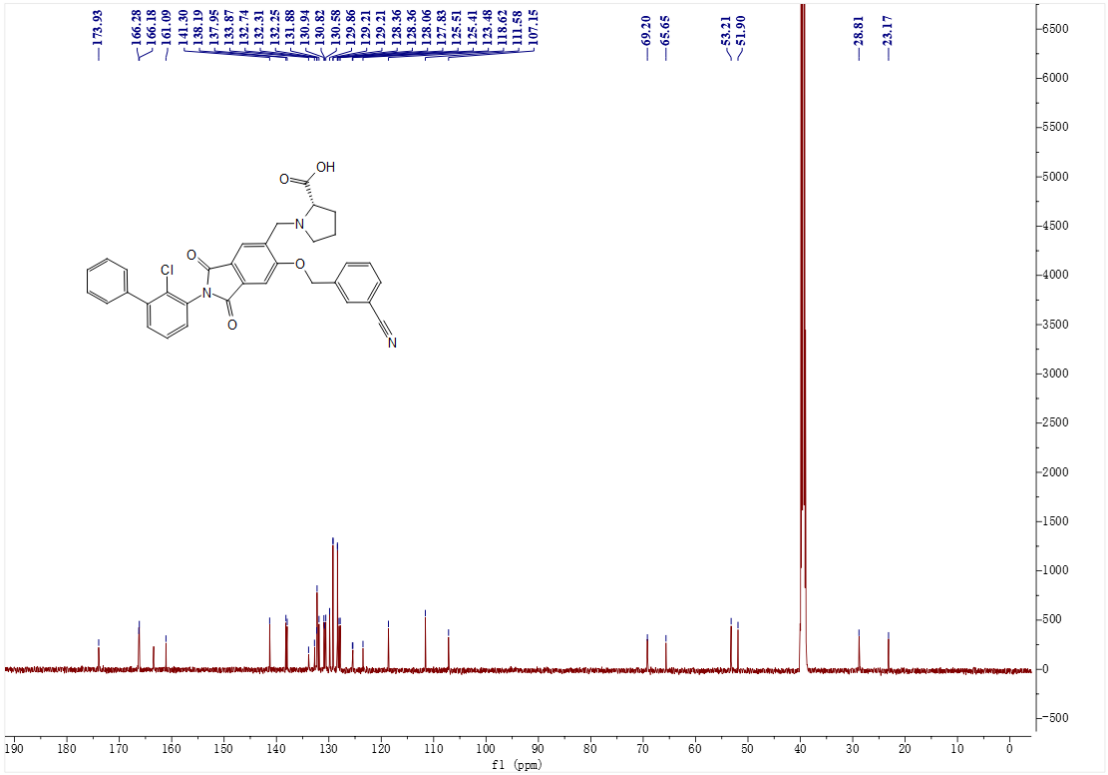
^{13}C NMR spectrum of **P13**



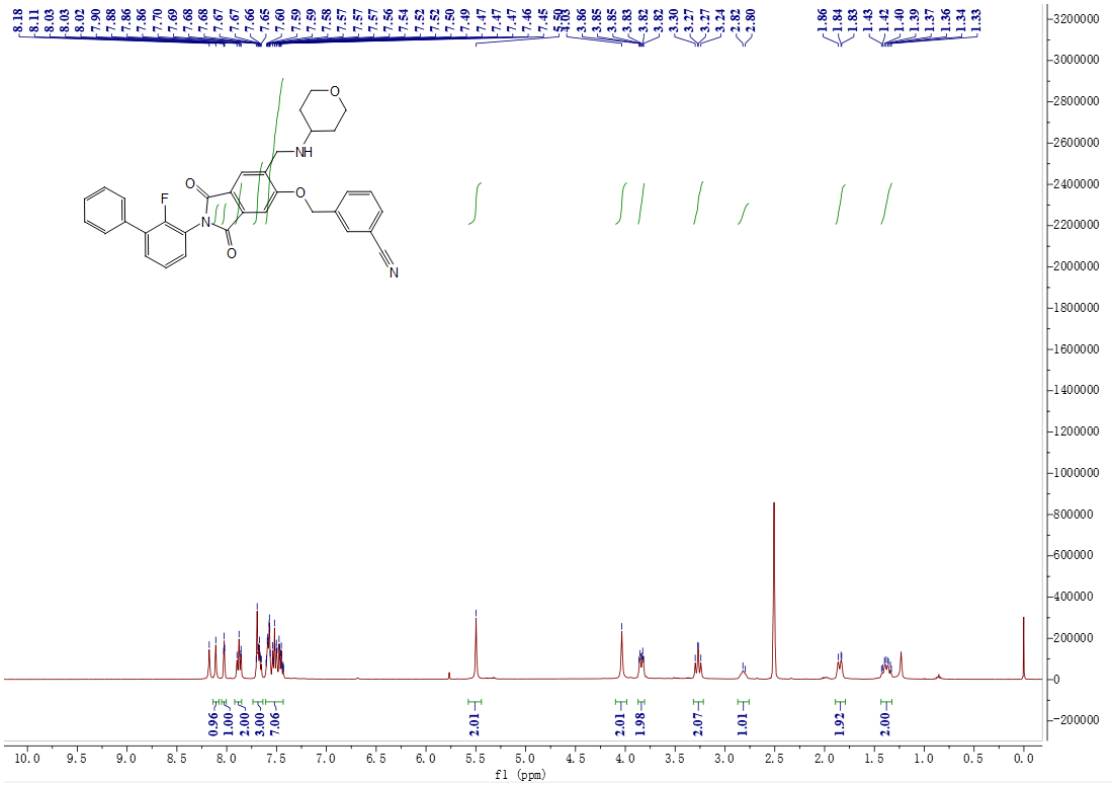
^{1}H NMR spectrum of **P14**



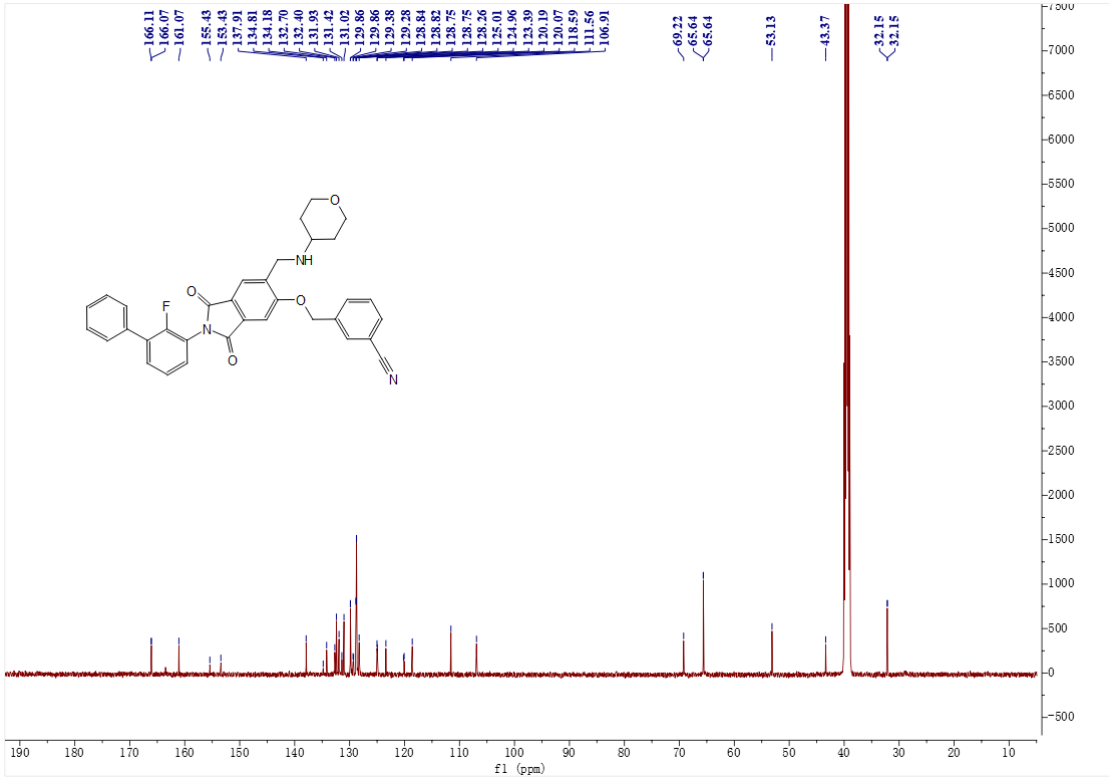
^{13}C NMR spectrum of **P14**



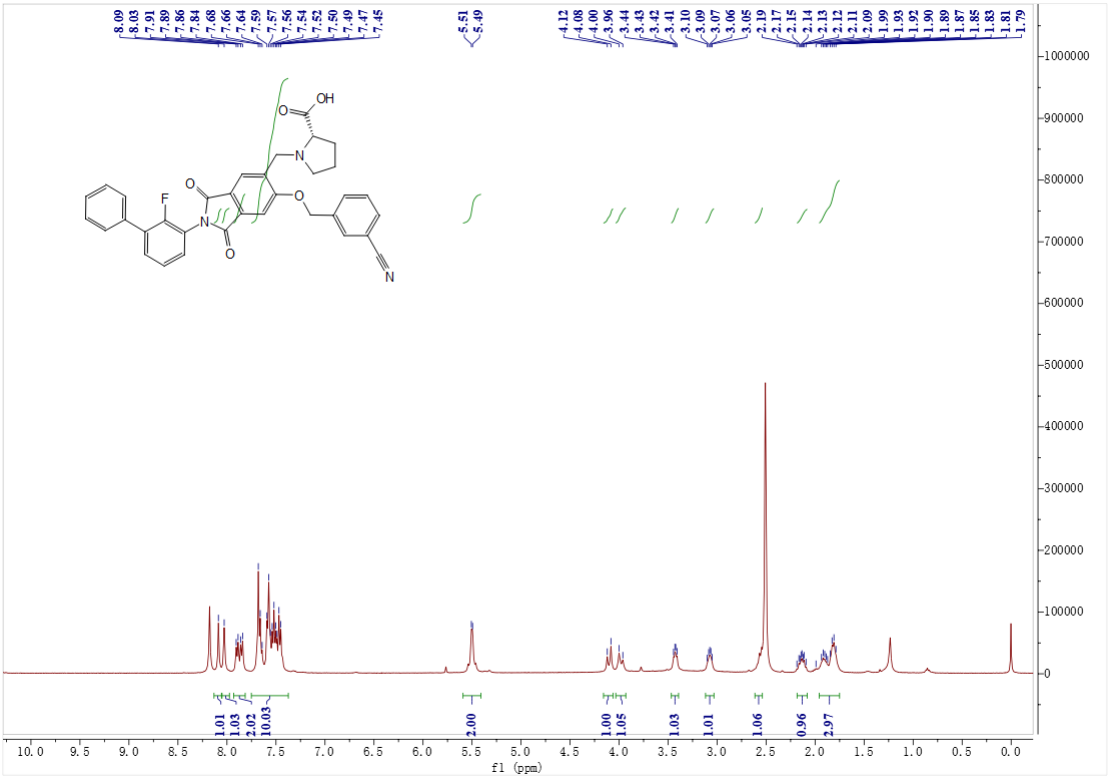
^{1}H NMR spectrum of **P15**



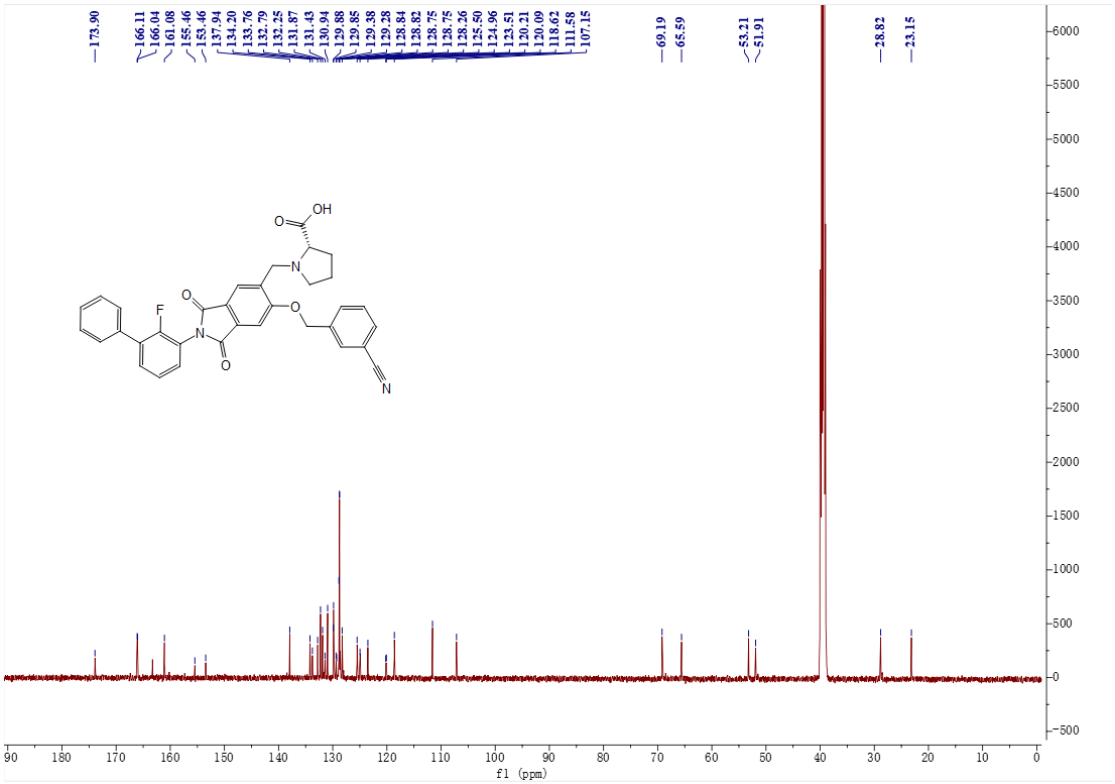
^{13}C NMR spectrum of **P15**



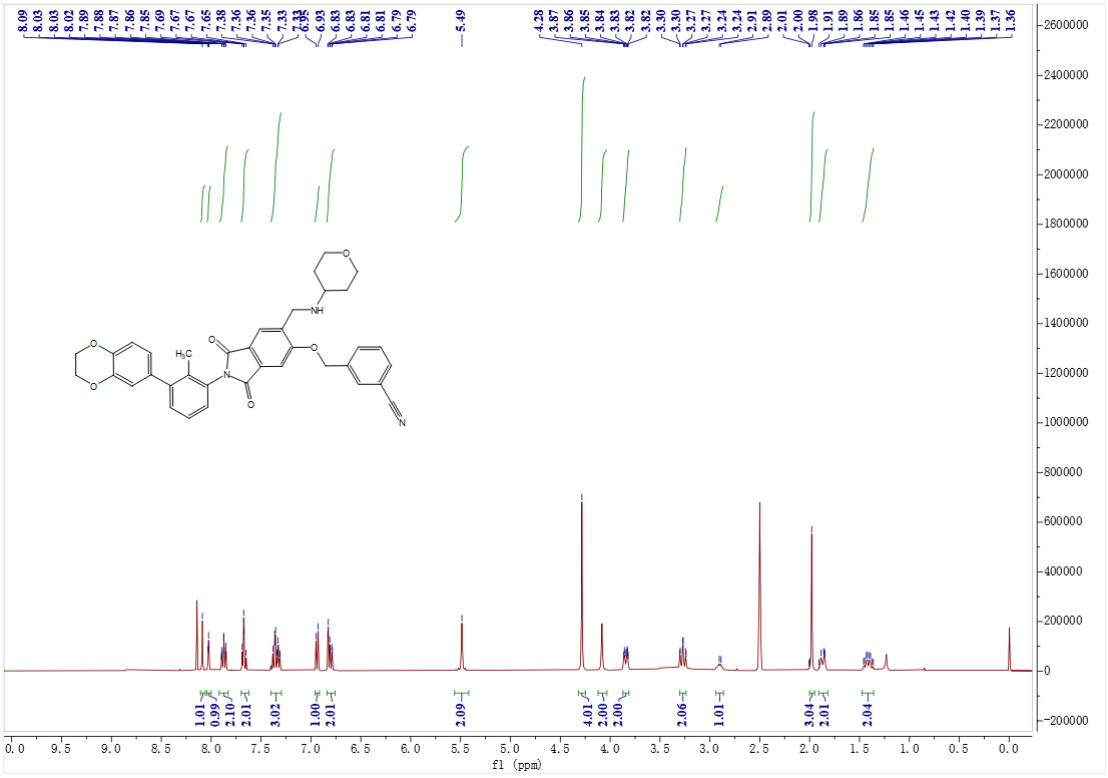
^{1}H NMR spectrum of **P16**



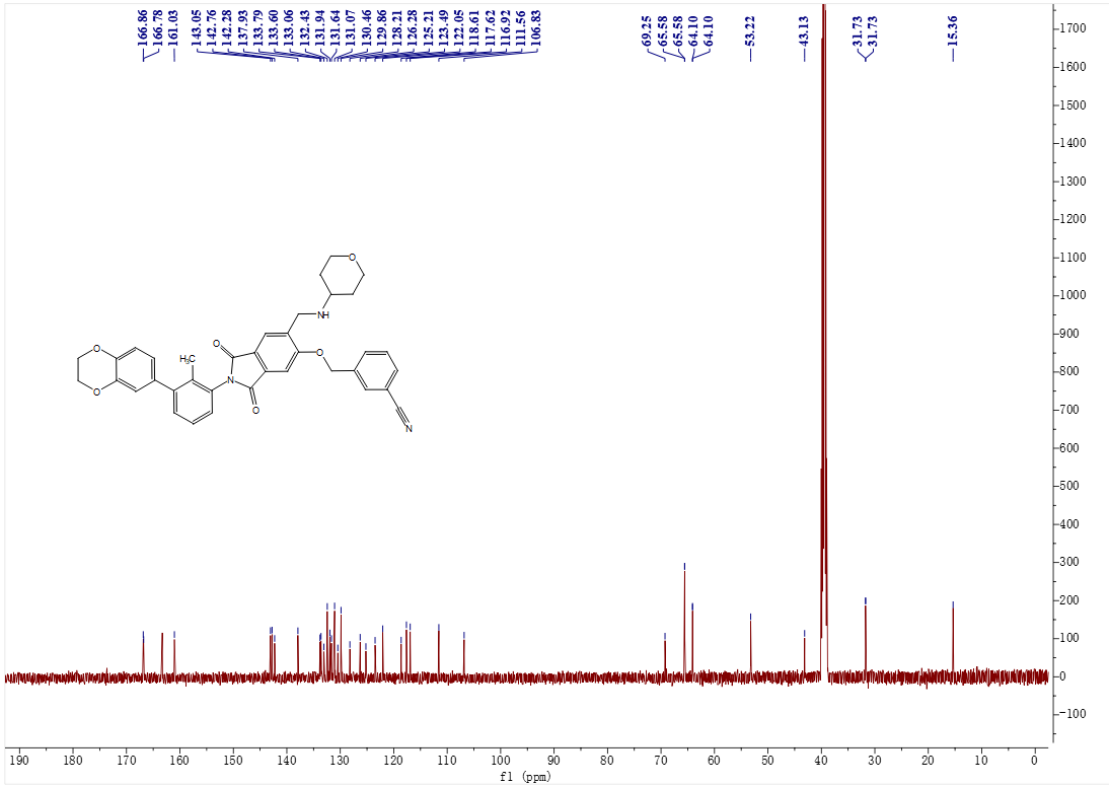
^{13}C NMR spectrum of **P16**



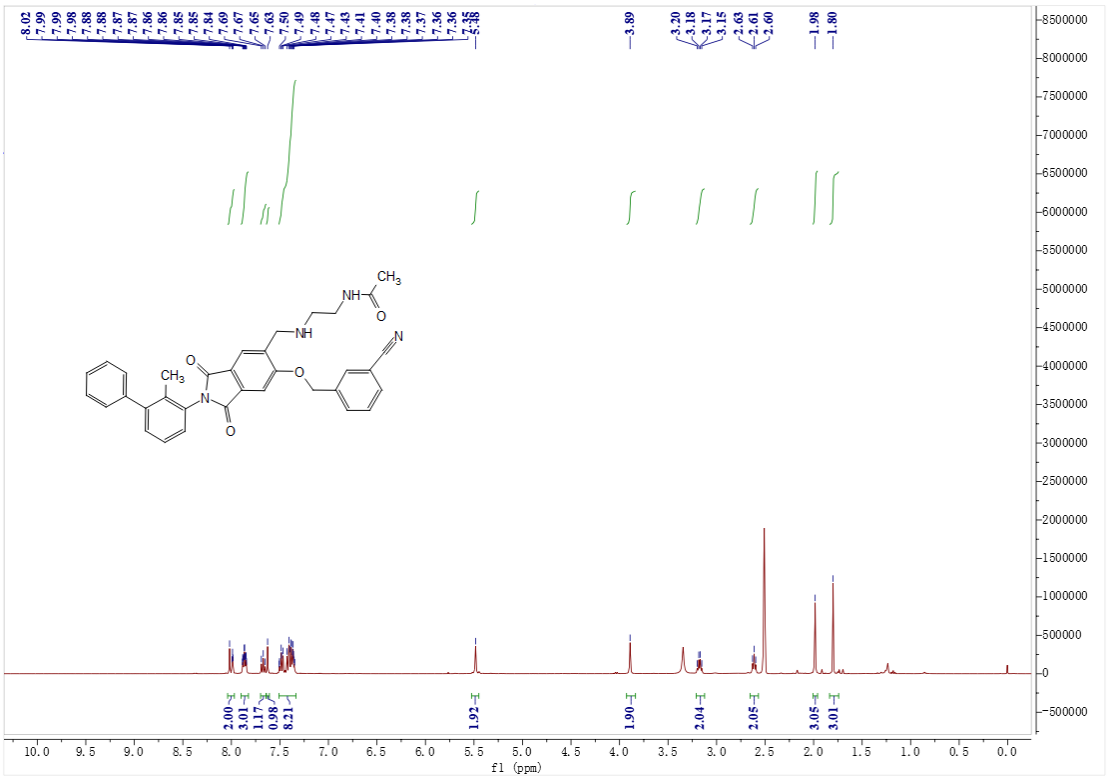
^{1}H NMR spectrum of **P17**



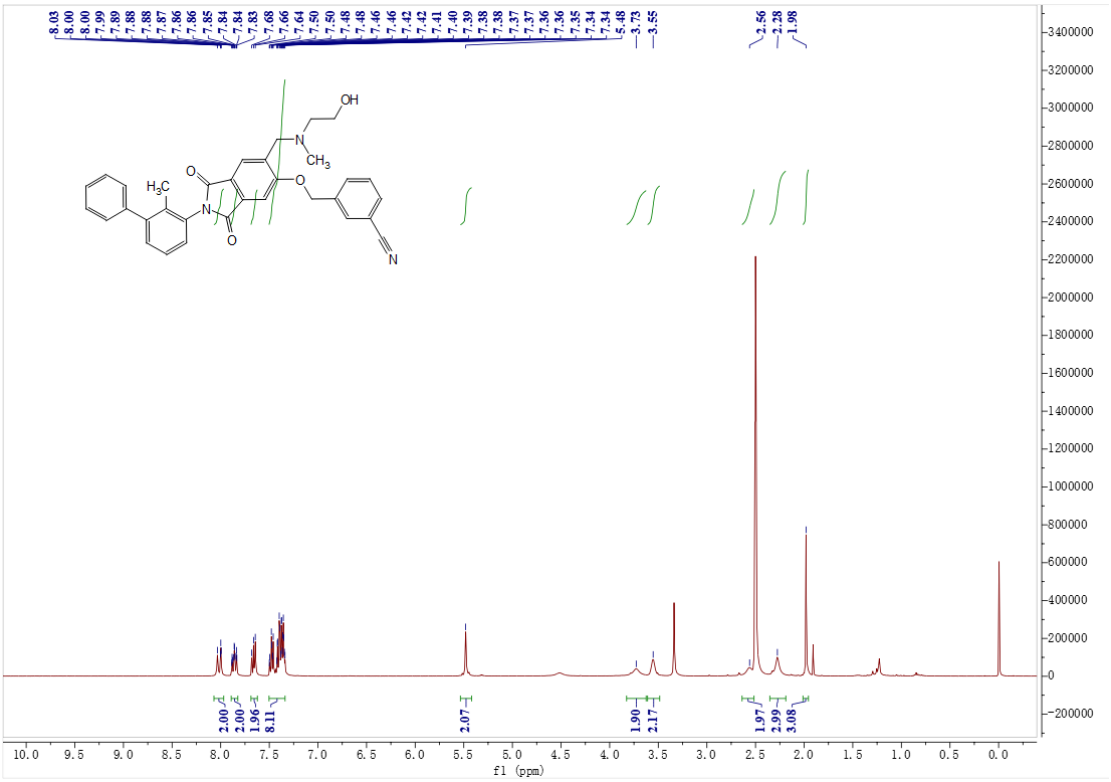
^{13}C NMR spectrum of **P17**



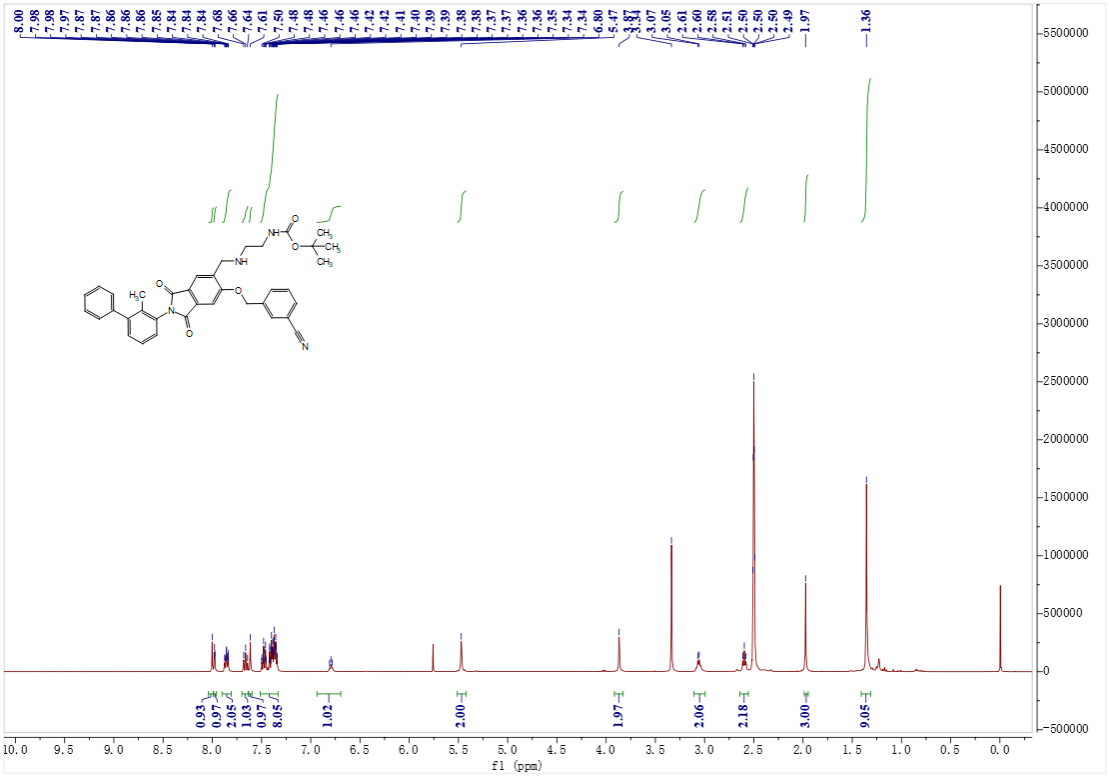
^{1}H NMR spectrum of **P18**



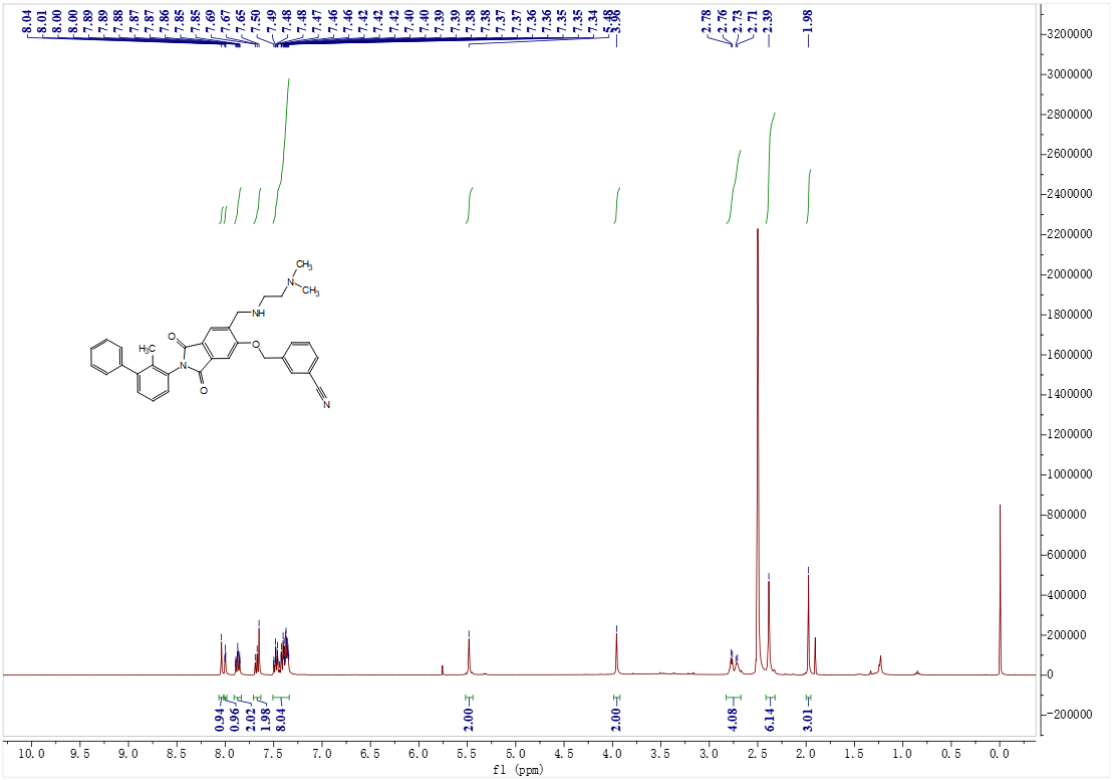
^{1}H NMR spectrum of **P19**



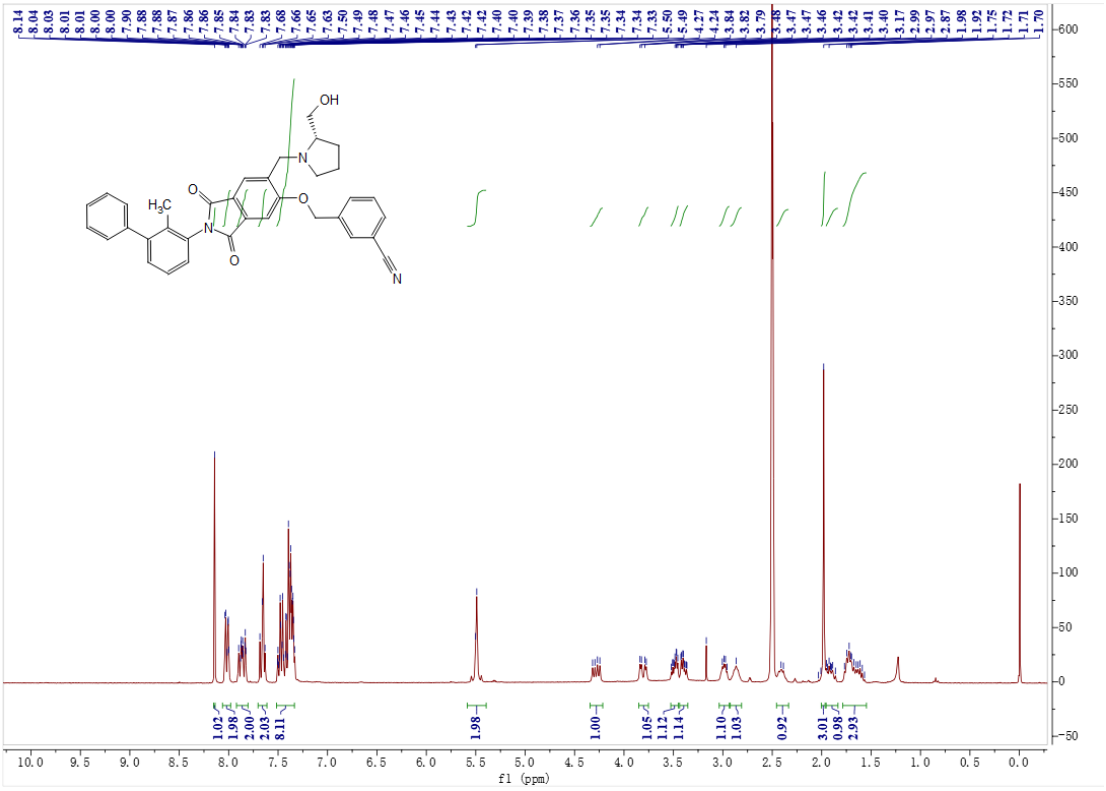
^{1}H NMR spectrum of **P20**



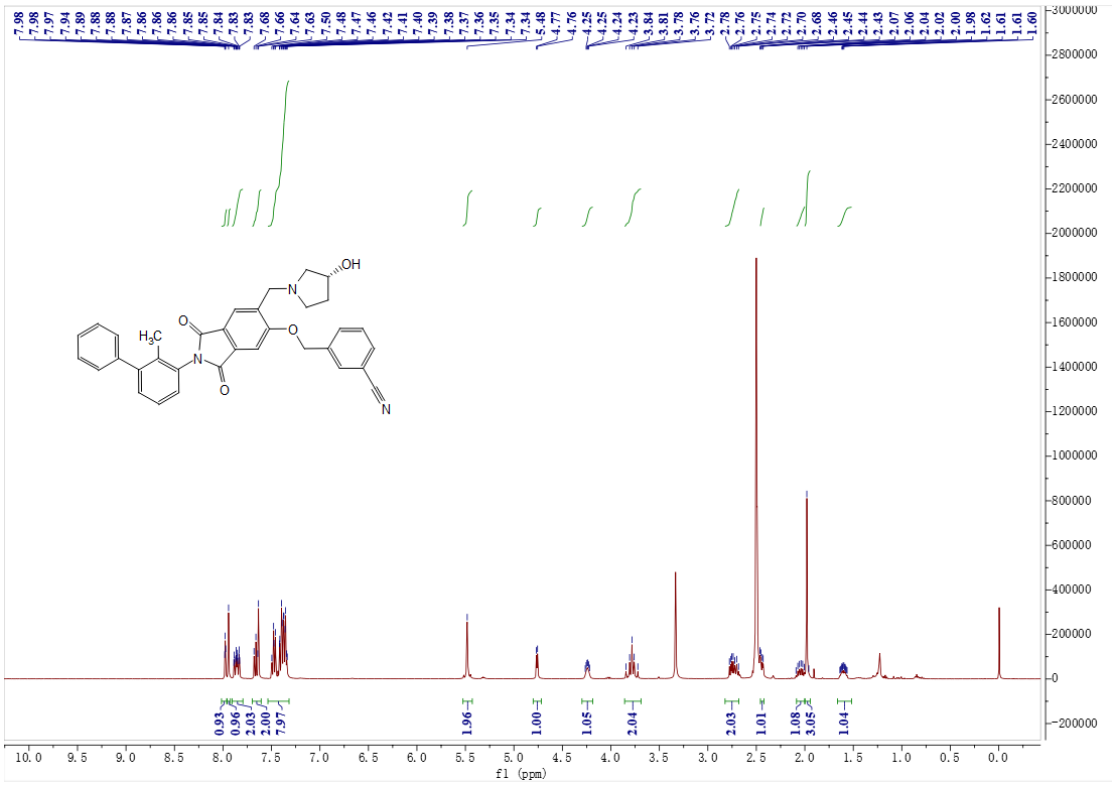
^{1}H NMR spectrum of **P21**



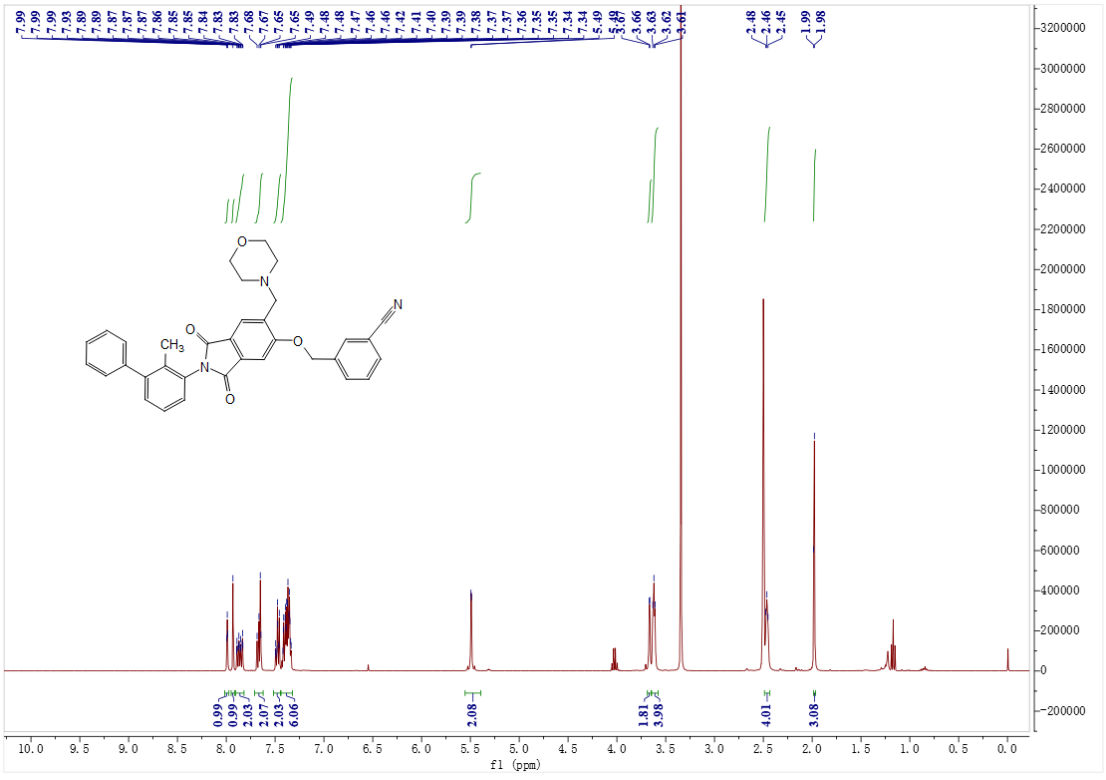
^{1}H NMR spectrum of **P22**



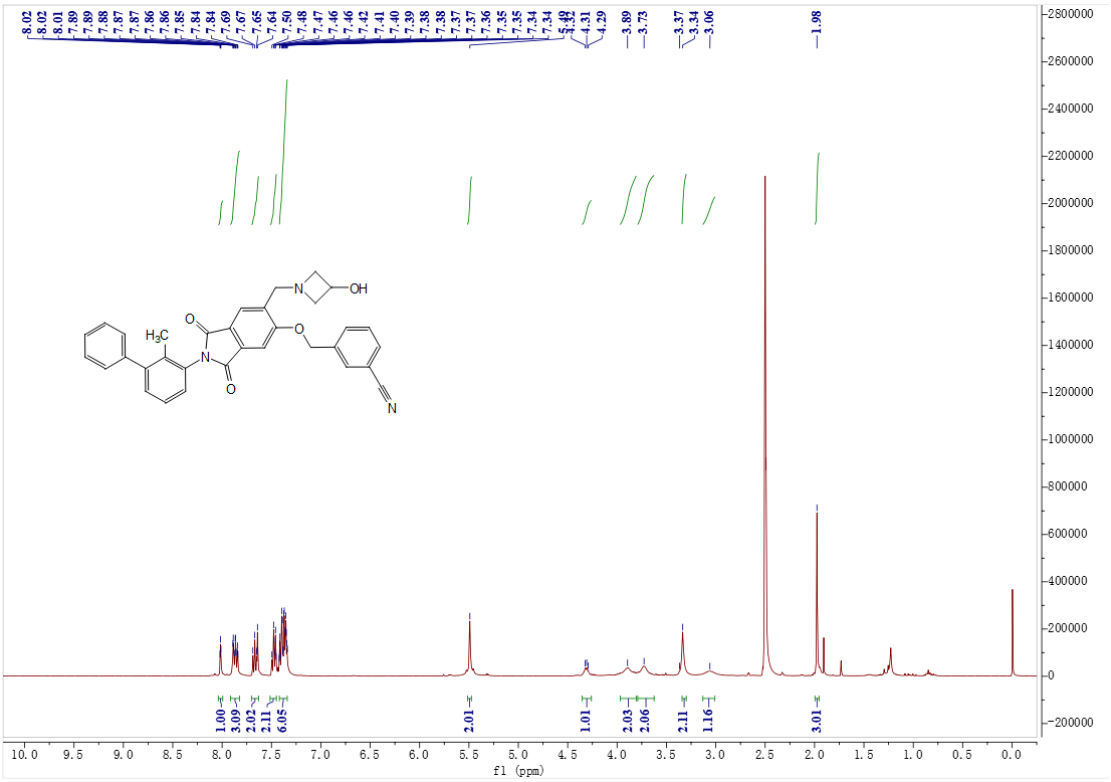
^{1}H NMR spectrum of **P23**



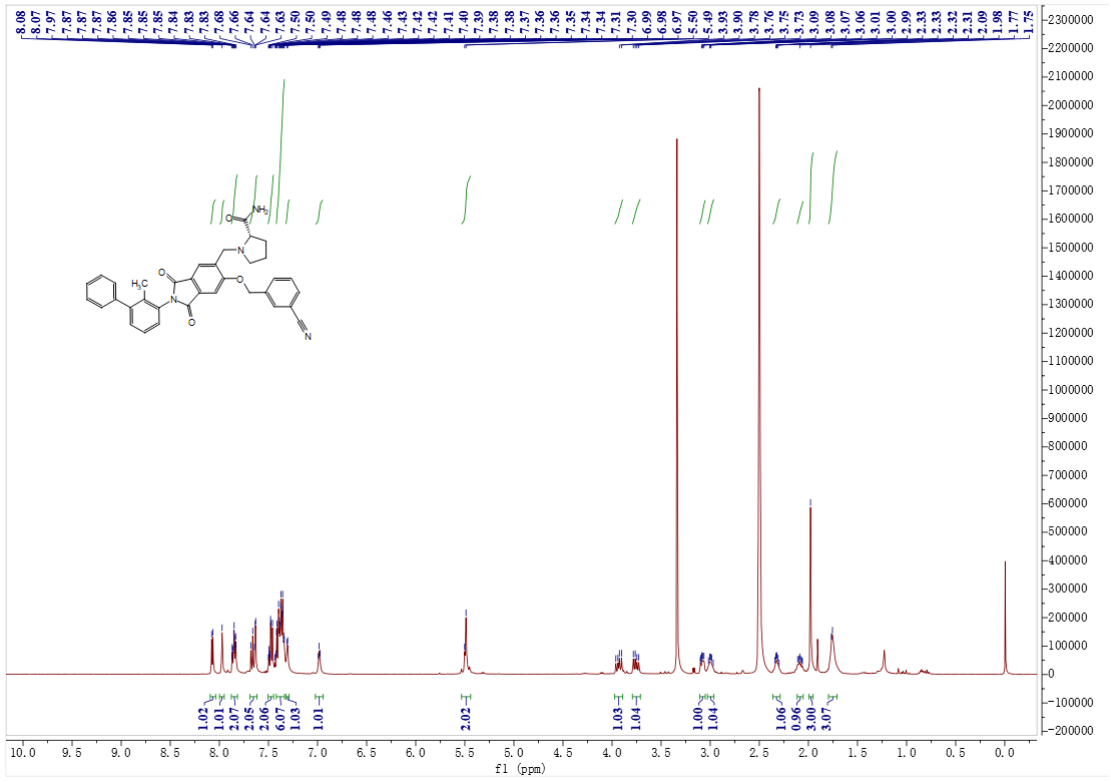
^{1}H NMR spectrum of **P24**



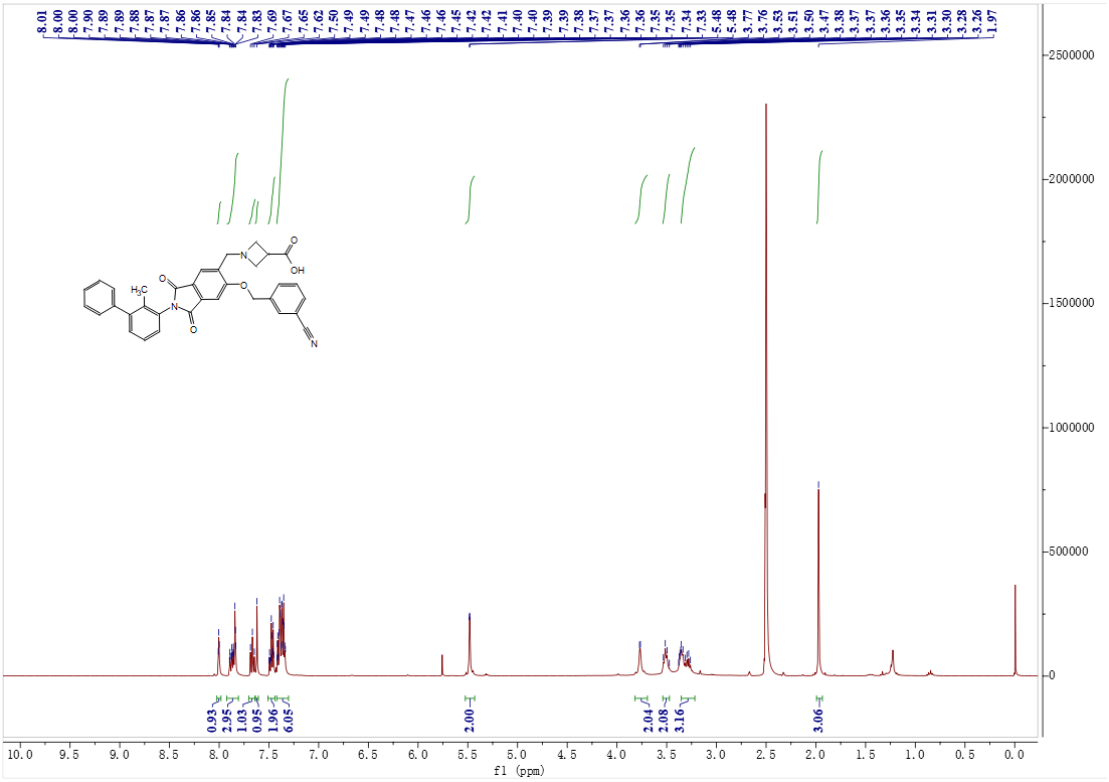
^{1}H NMR spectrum of **P25**



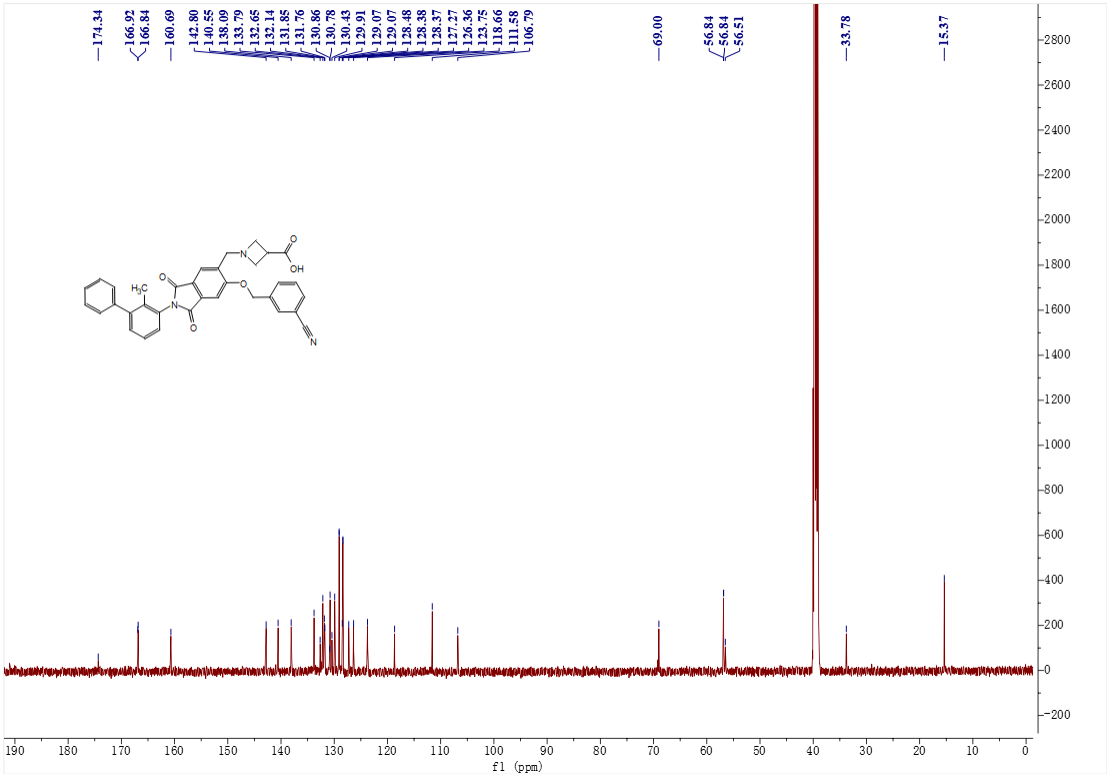
^{1}H NMR spectrum of **P26**



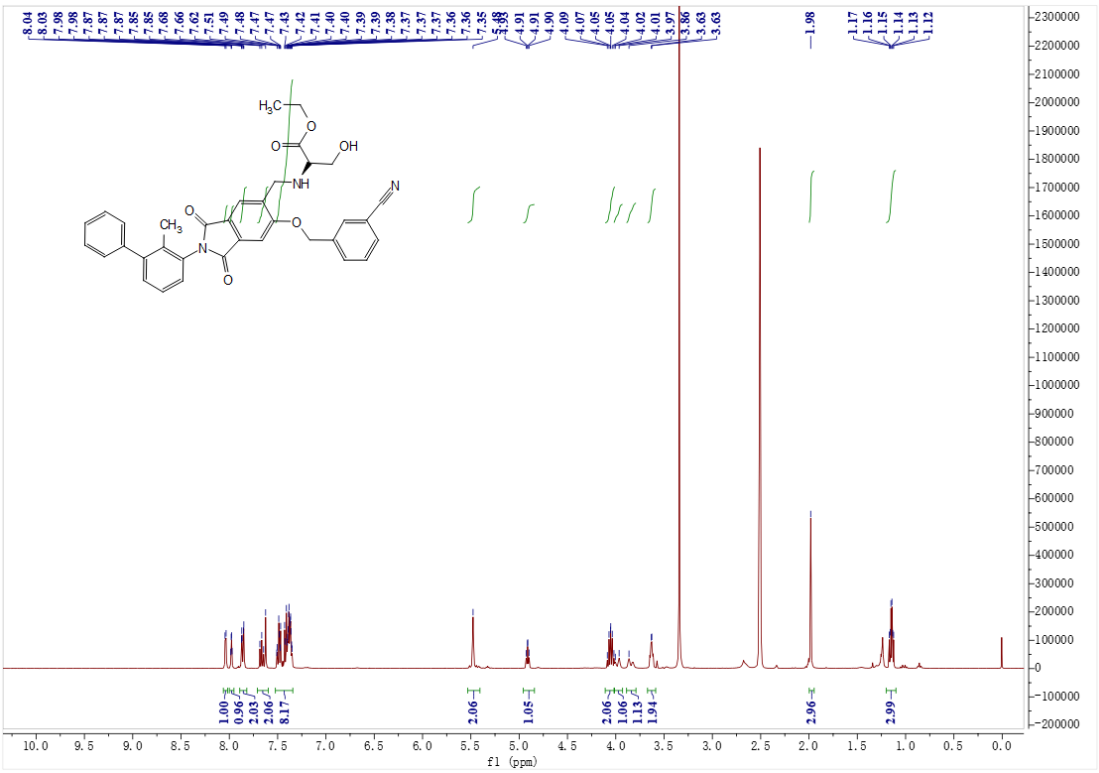
^{1}H NMR spectrum of **P27**



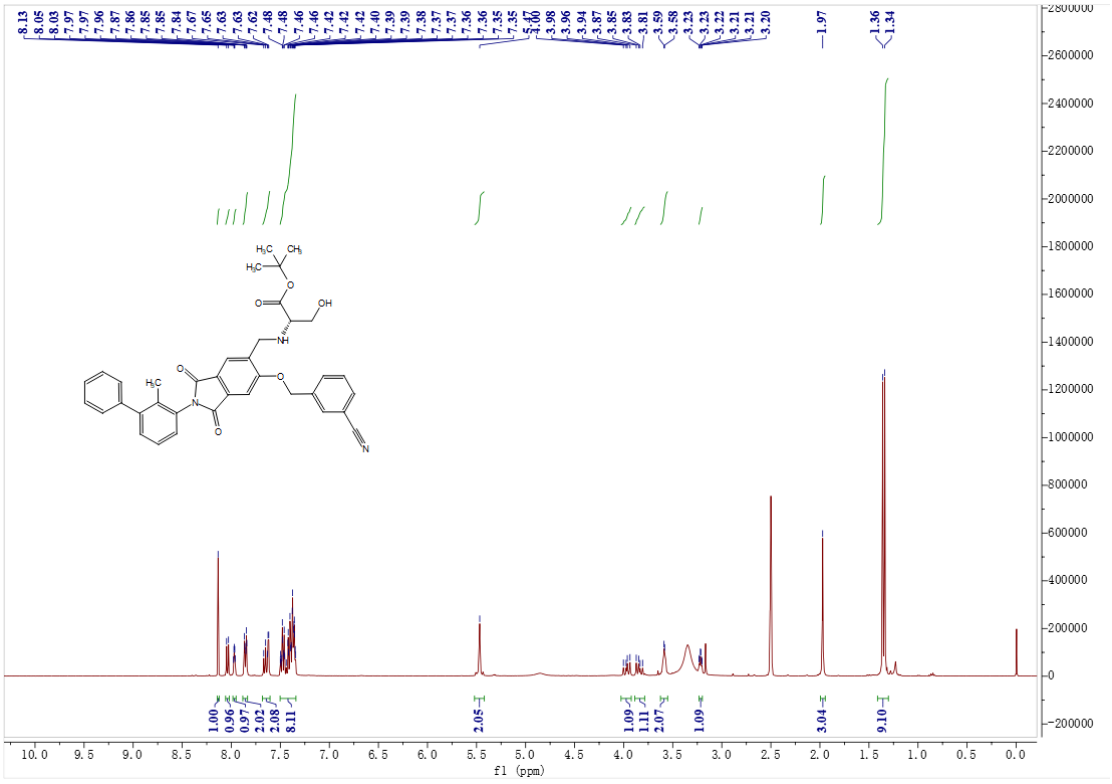
^{13}C NMR spectrum of **P27**



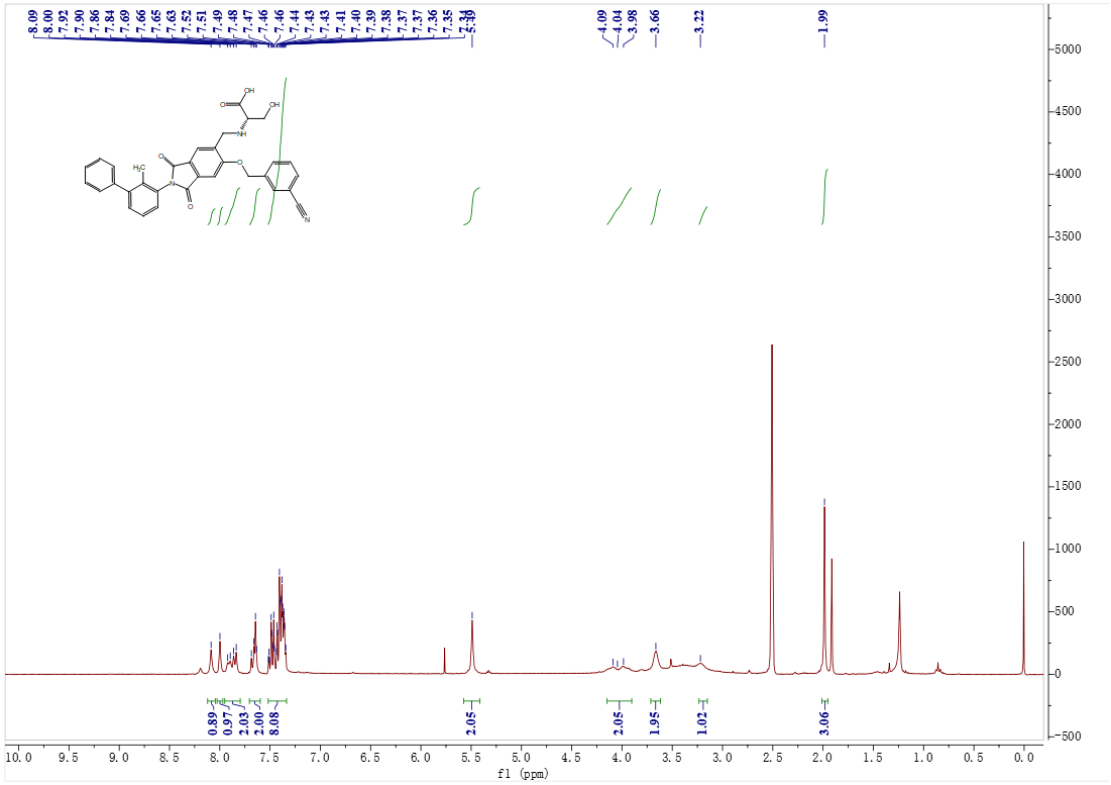
^{1}H NMR spectrum of **P28**



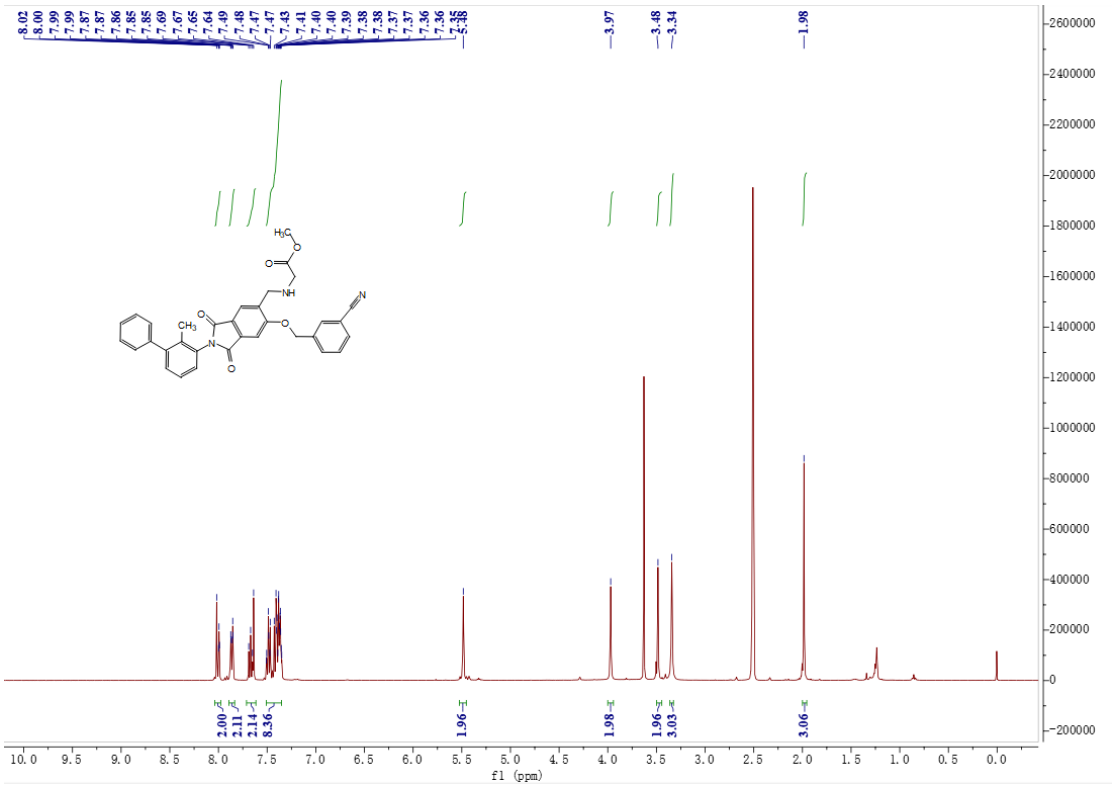
^{1}H NMR spectrum of **P29**



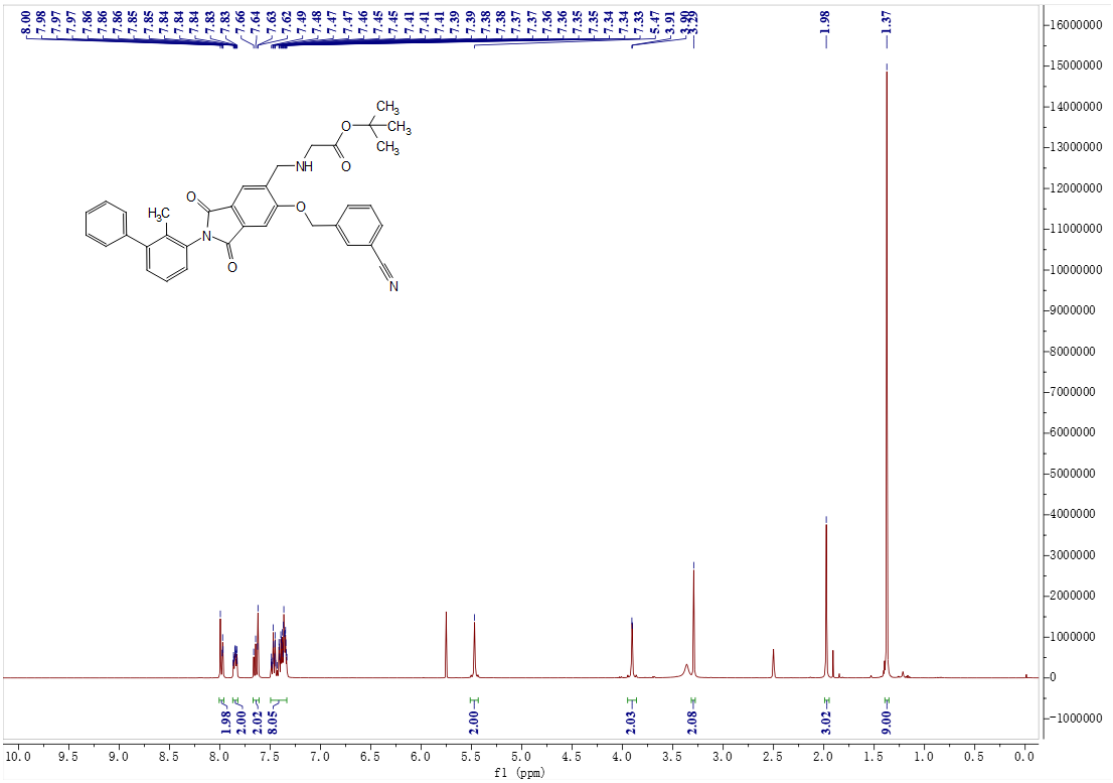
^{1}H NMR spectrum of **P30**



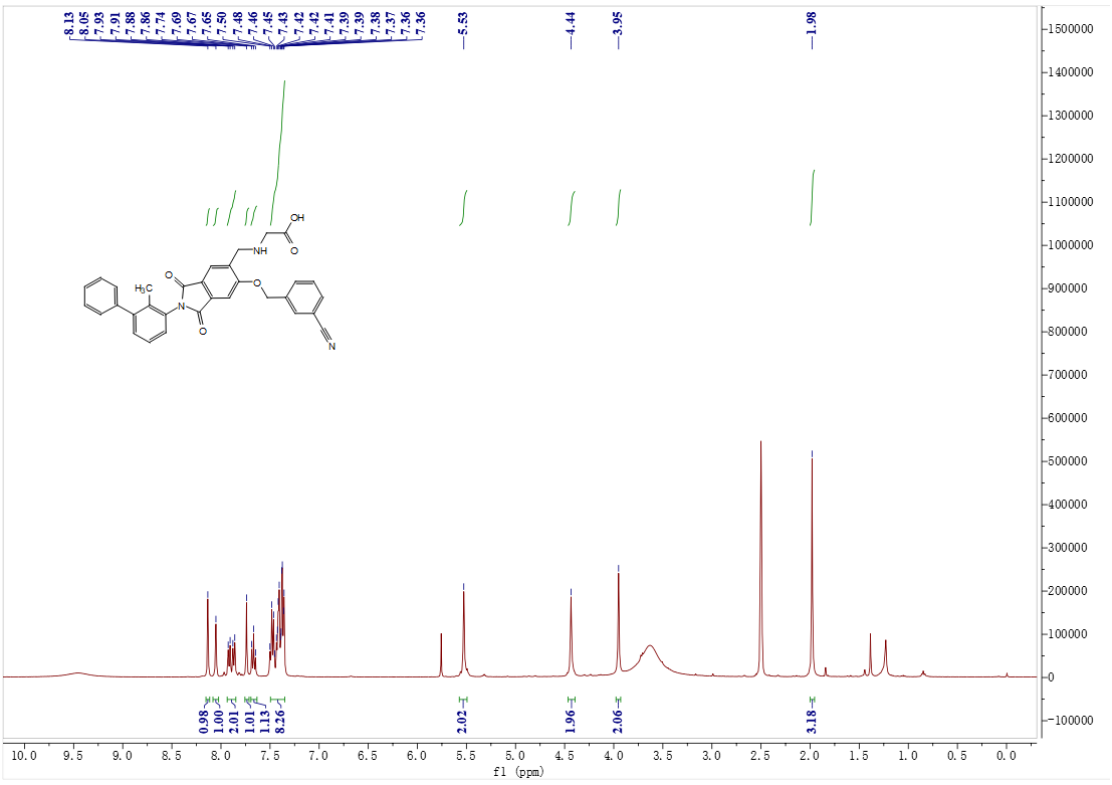
^{1}H NMR spectrum of **P31**



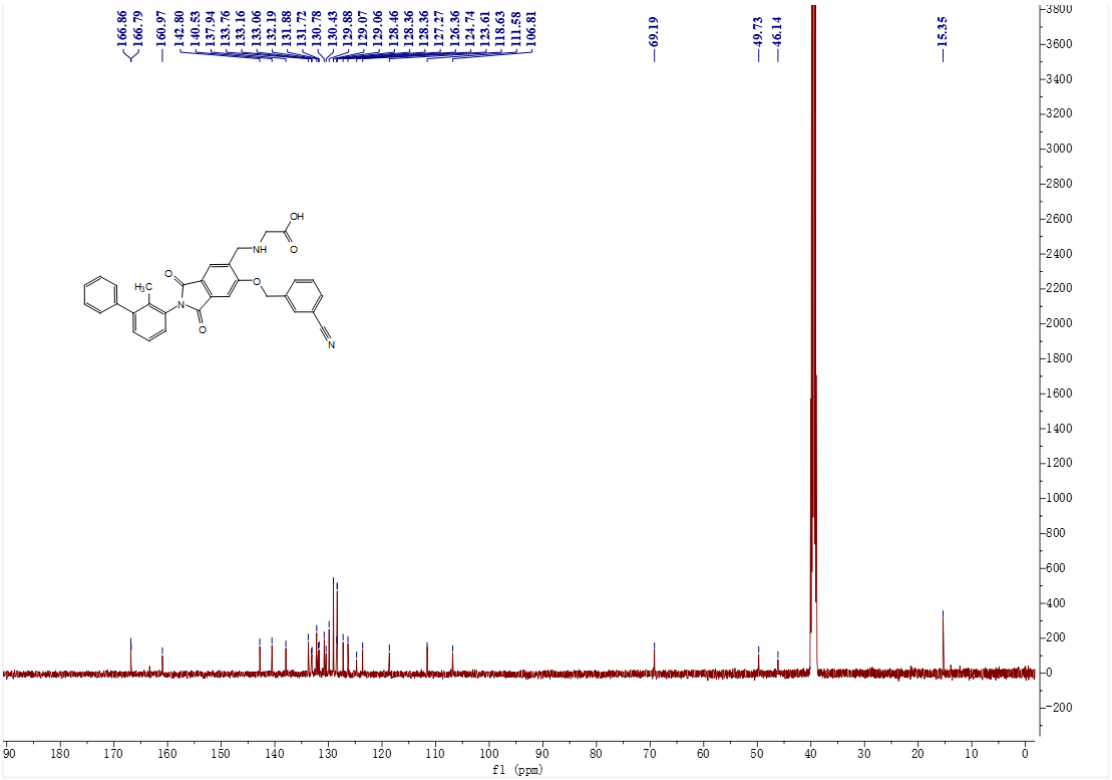
^{1}H NMR spectrum of **P32**



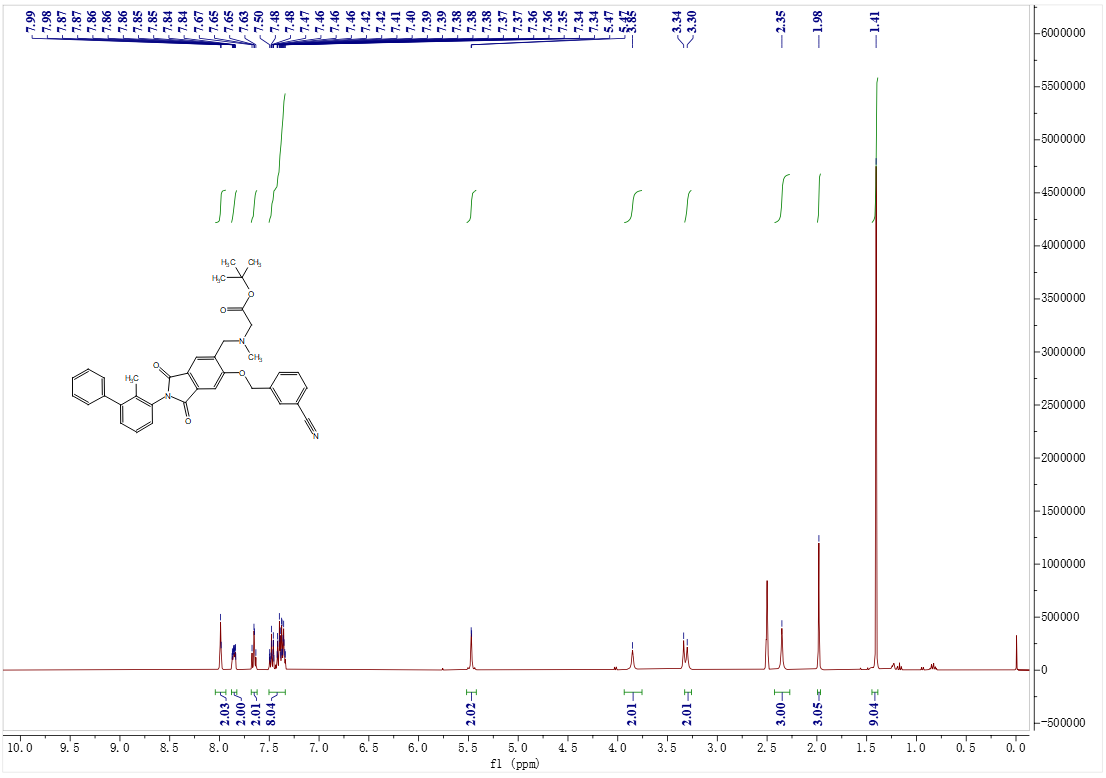
^{1}H NMR spectrum of **P33**



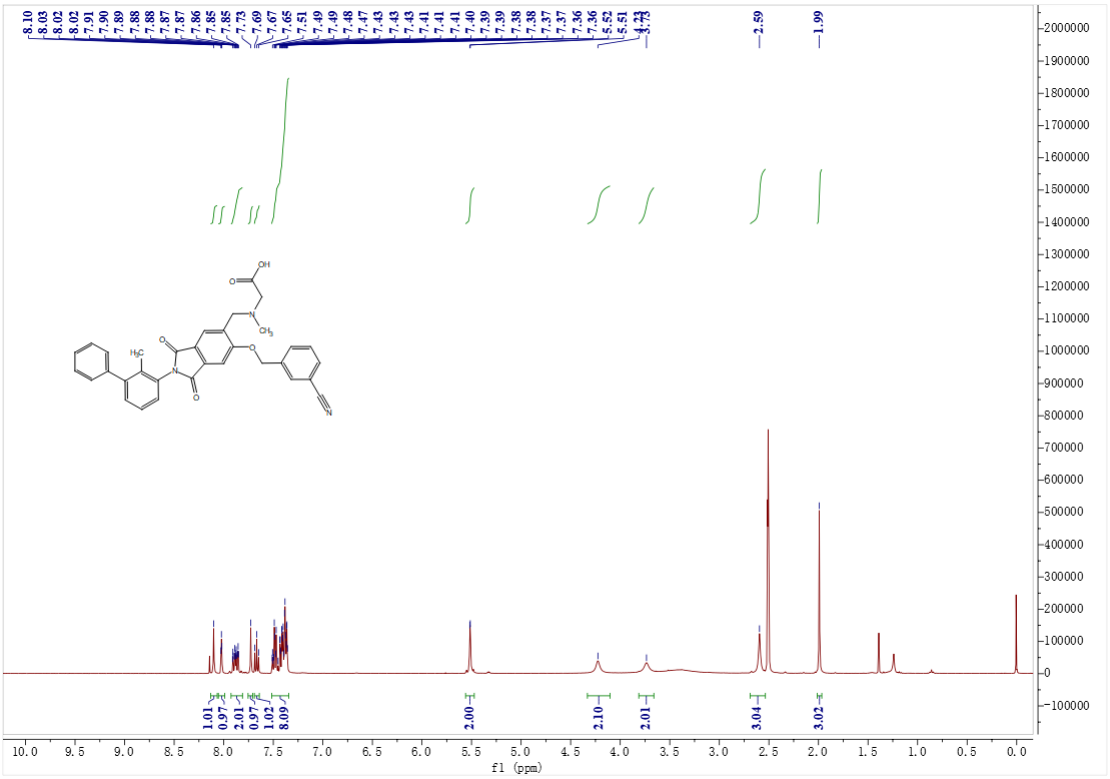
^{13}C NMR spectrum of **P33**



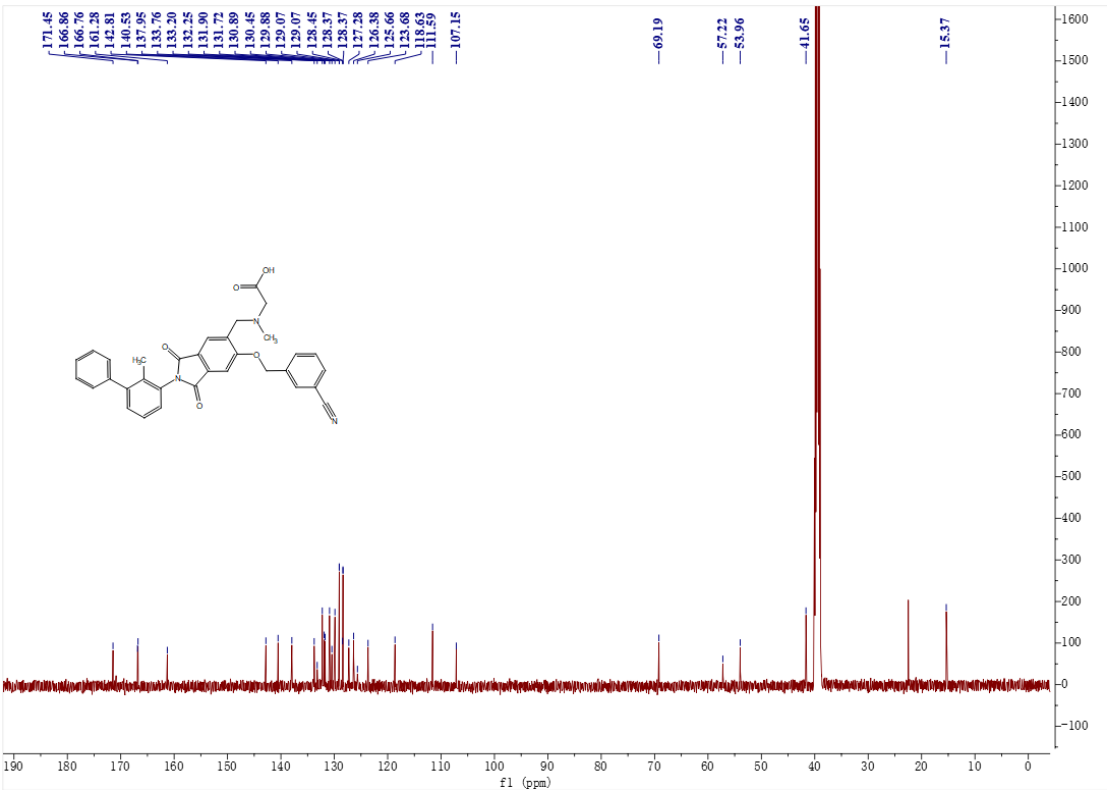
^{1}H NMR spectrum of **P34**



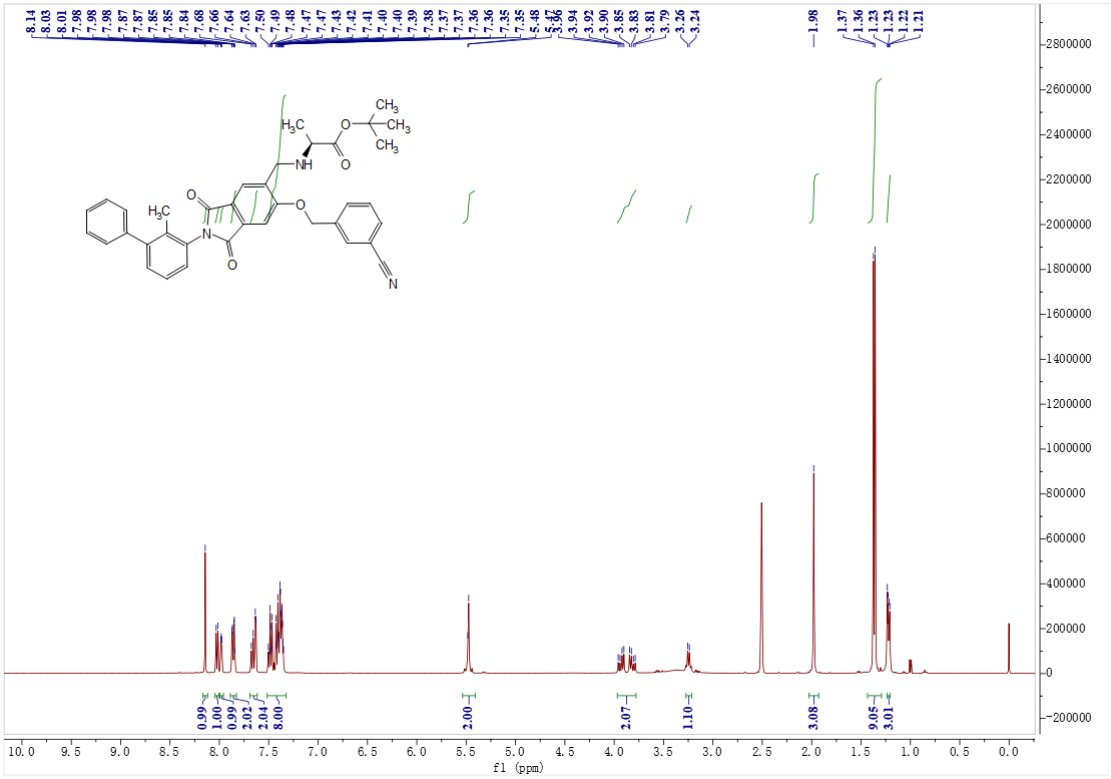
^{1}H NMR spectrum of **P35**



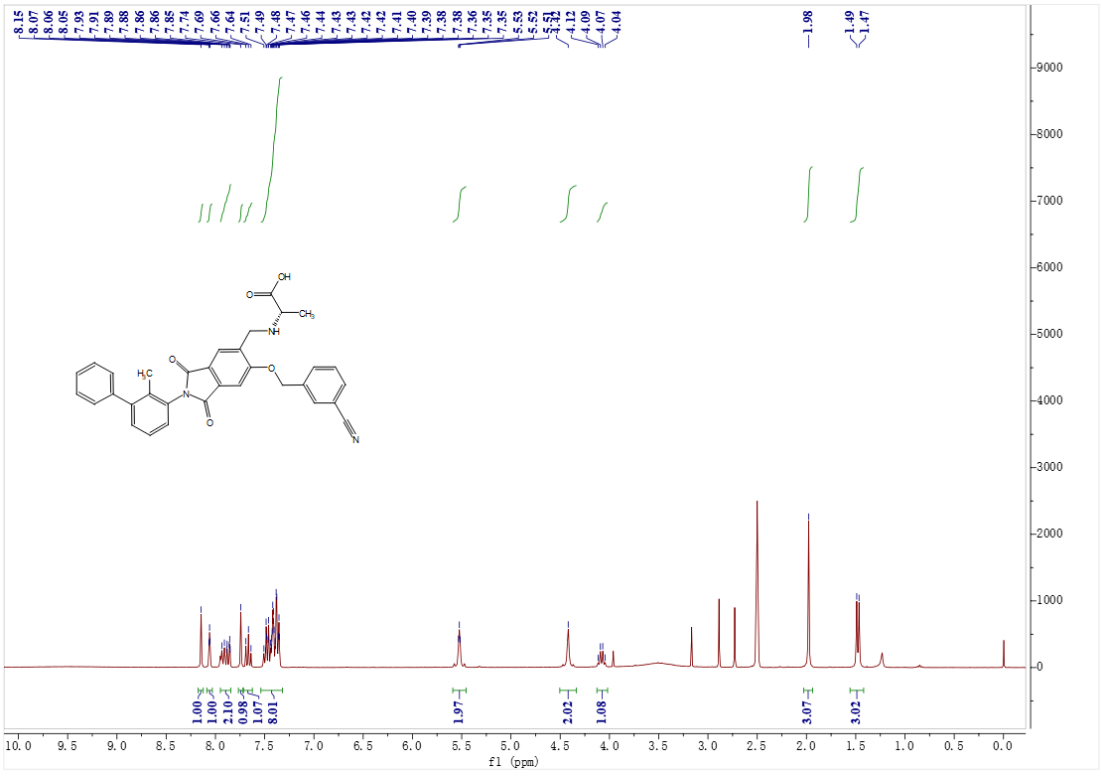
^{13}C NMR spectrum of **P36**



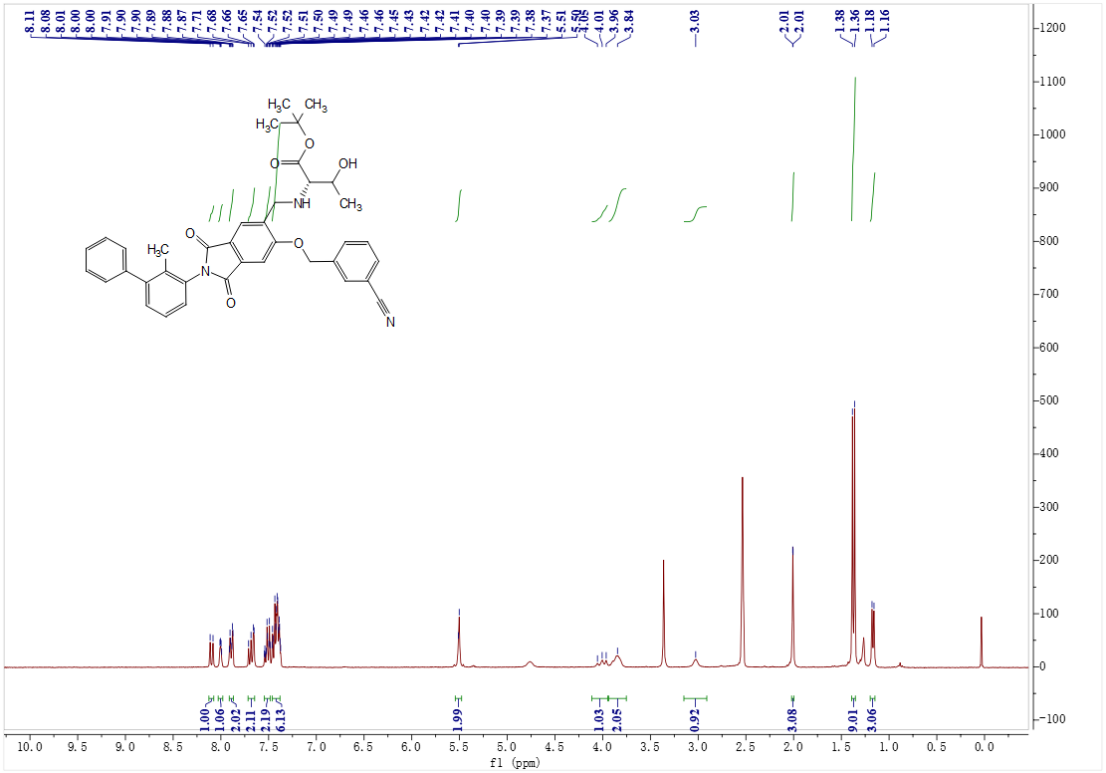
^{1}H NMR spectrum of **P36**



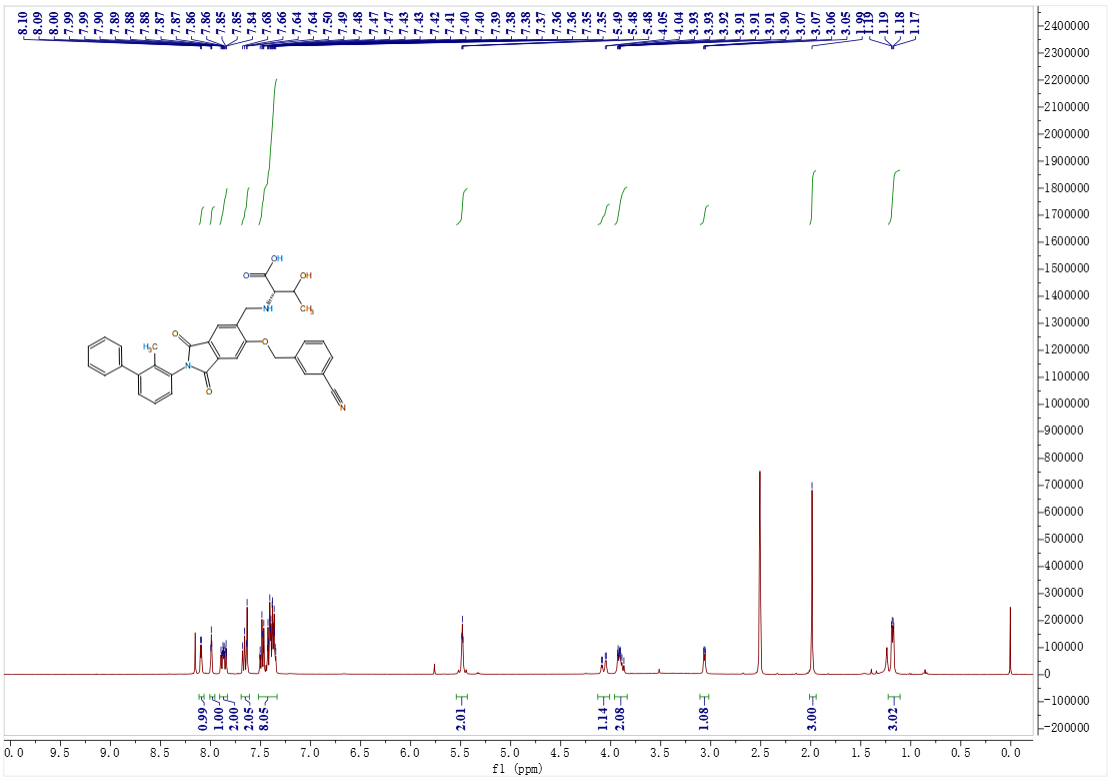
^{1}H NMR spectrum of **P37**



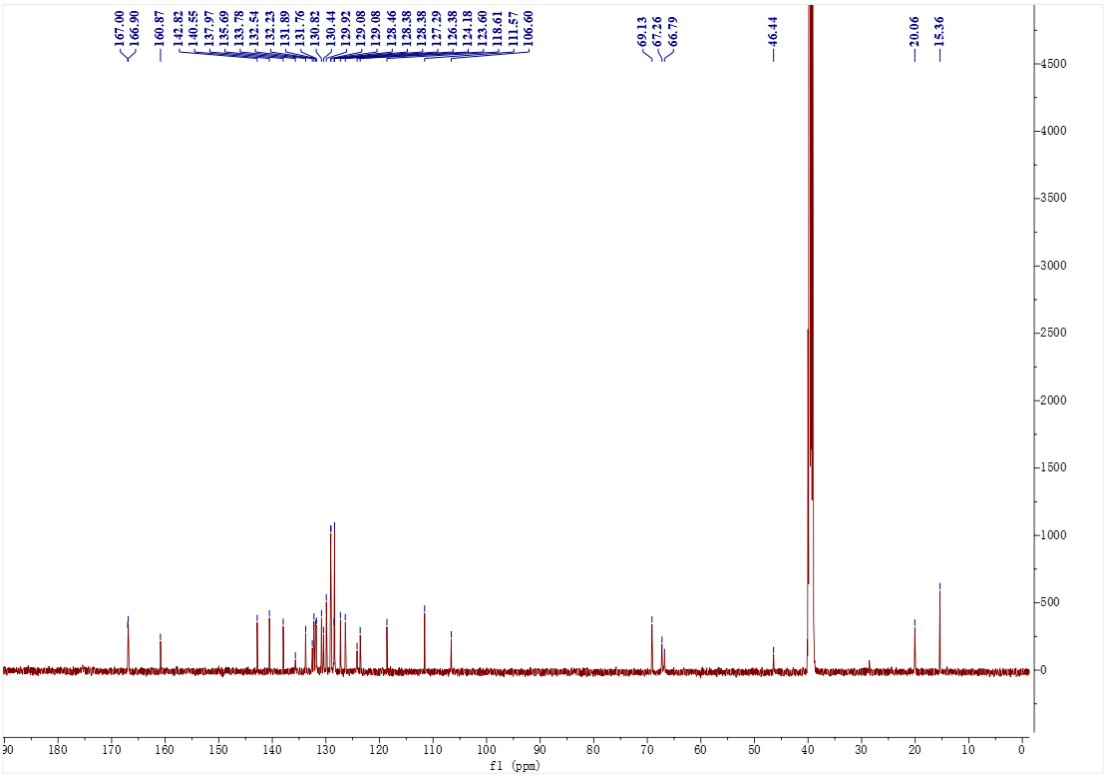
^{1}H NMR spectrum of **P38**



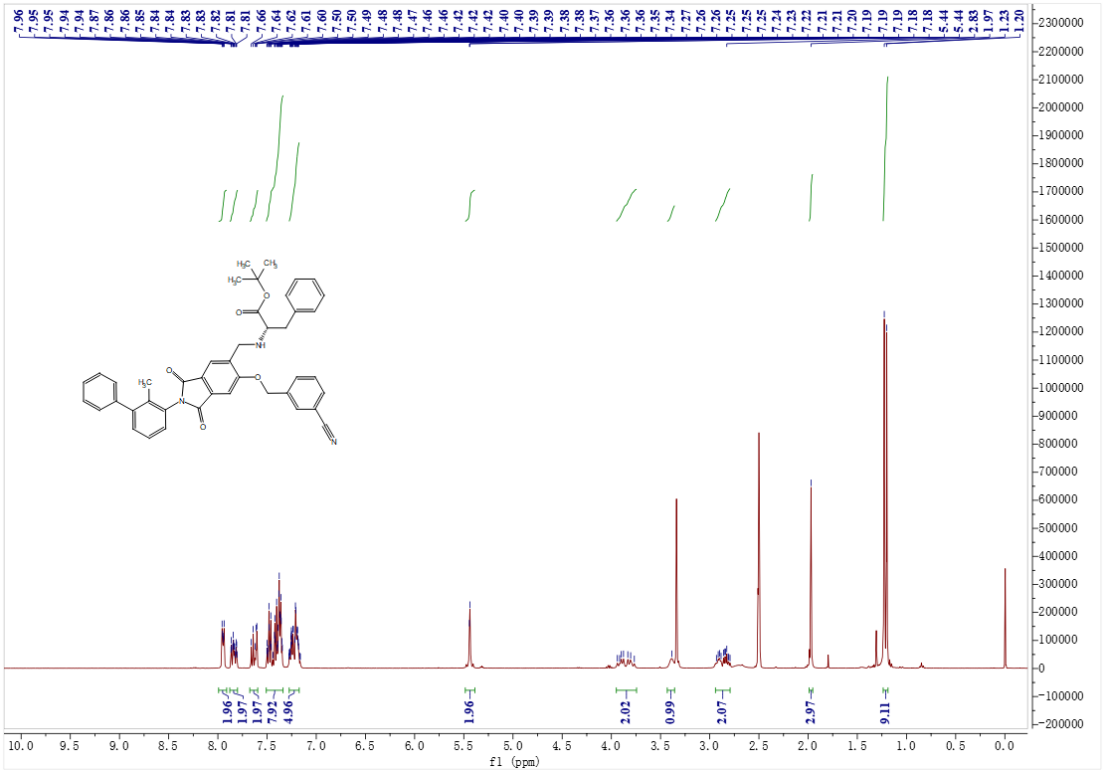
^{1}H NMR spectrum of **P39**



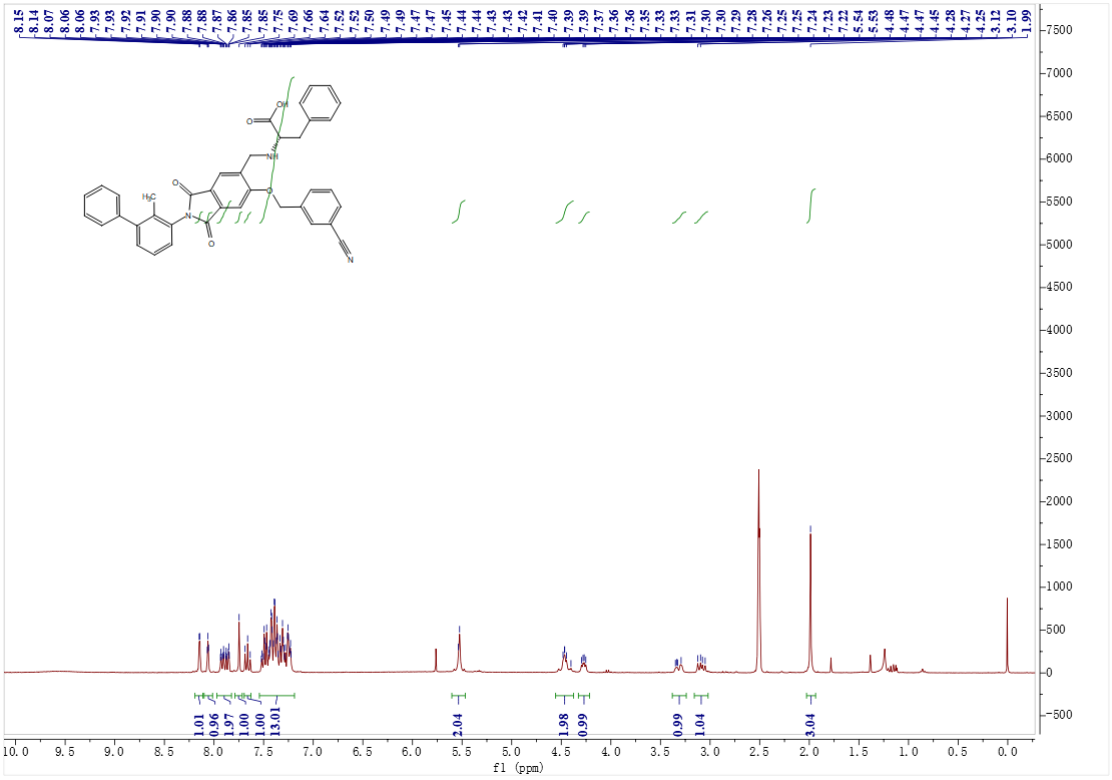
^{13}C NMR spectrum of **P39**



^{1}H NMR spectrum of **P40**

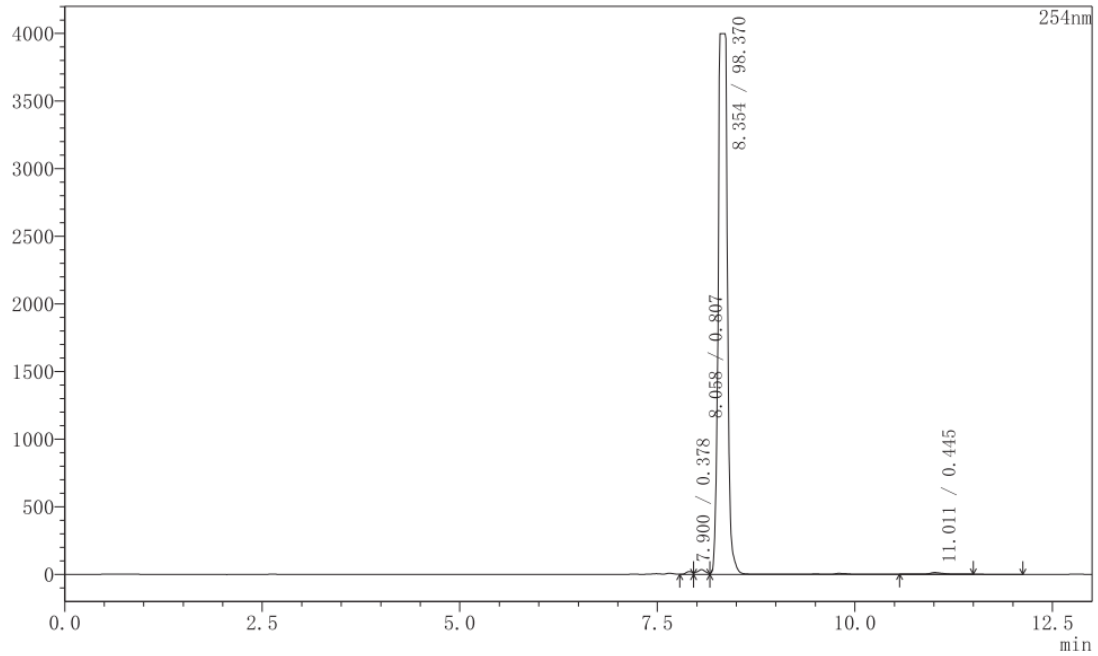


^{1}H NMR spectrum of **P41**

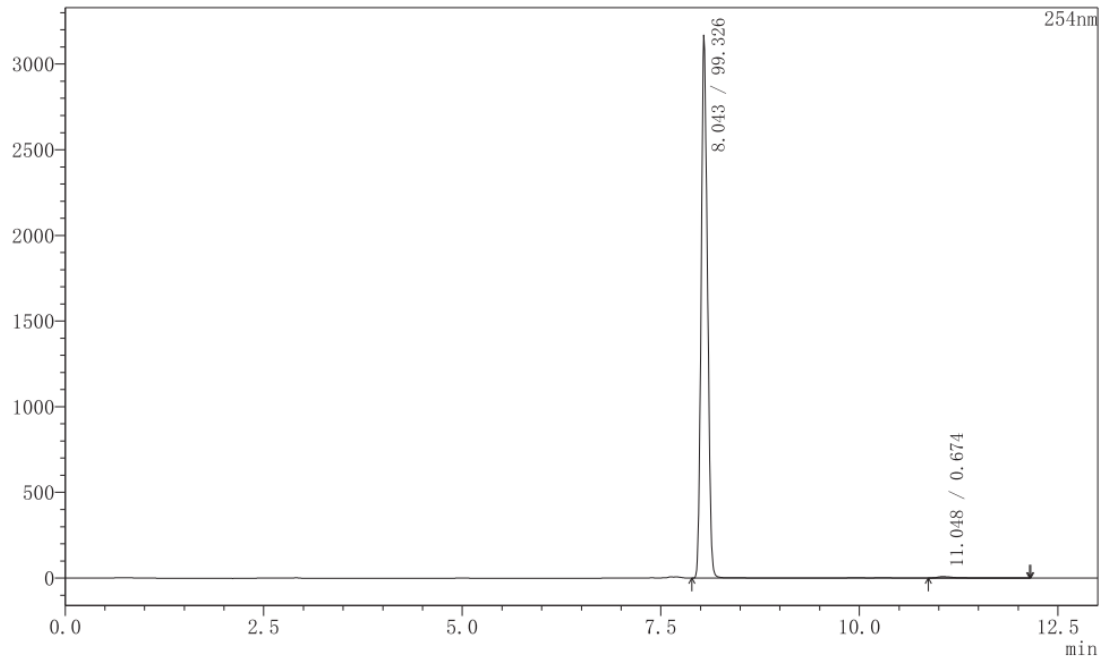


HPLC Data of Compounds P1-P41

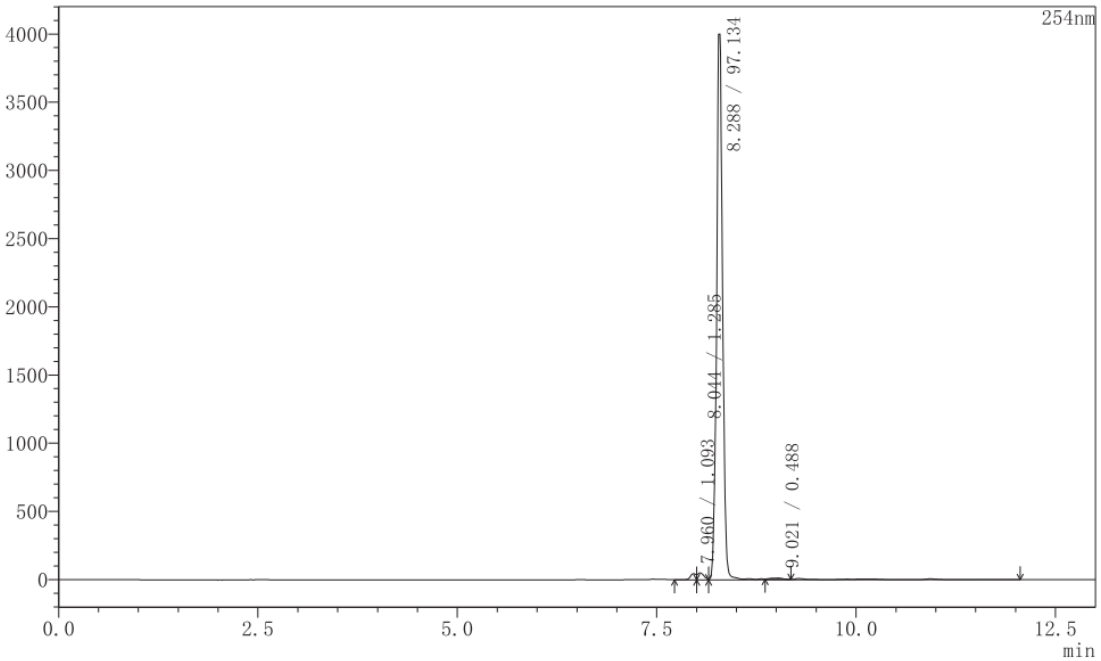
HPLC spectra of Compound **P1**



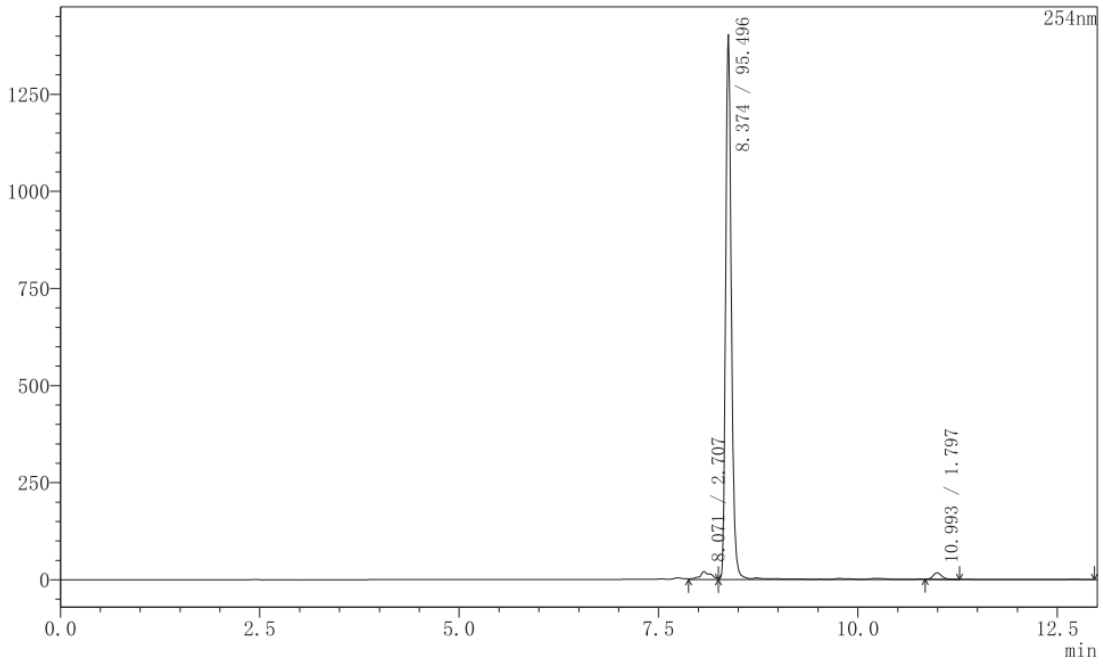
HPLC spectra of Compound **P2**



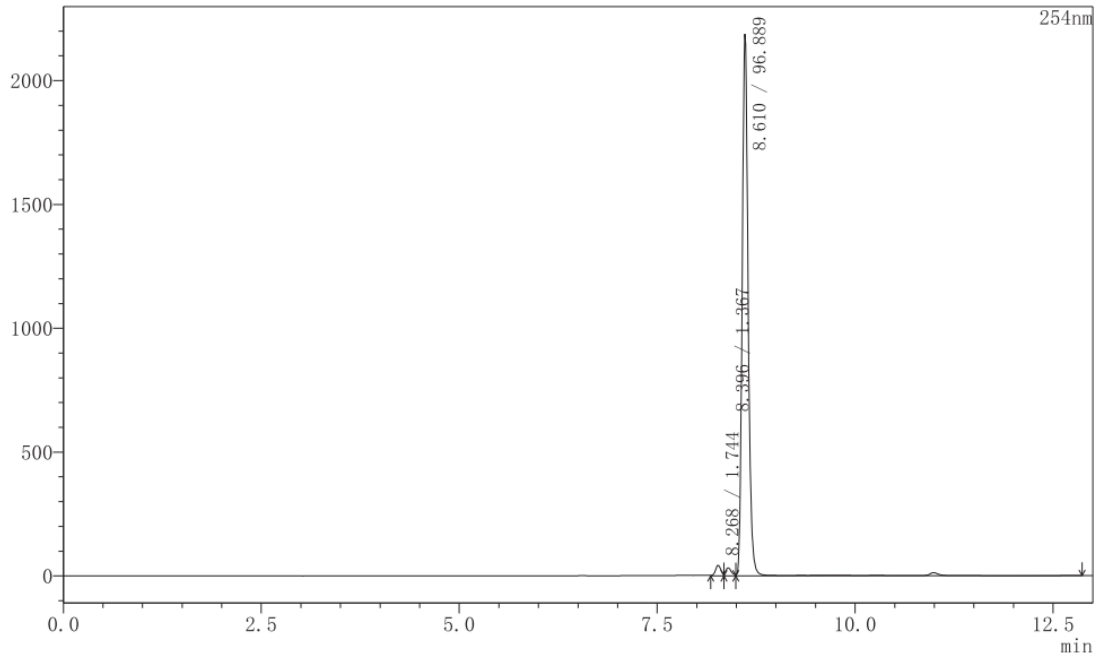
HPLC spectra of Compound **P3**



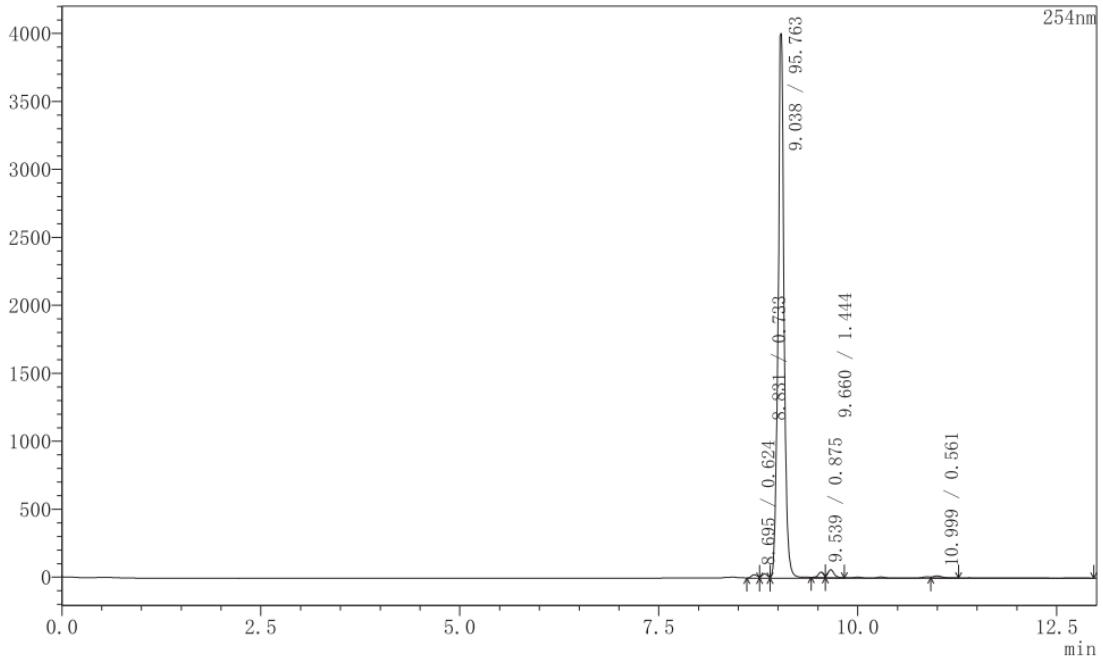
HPLC spectra of Compound **P4**



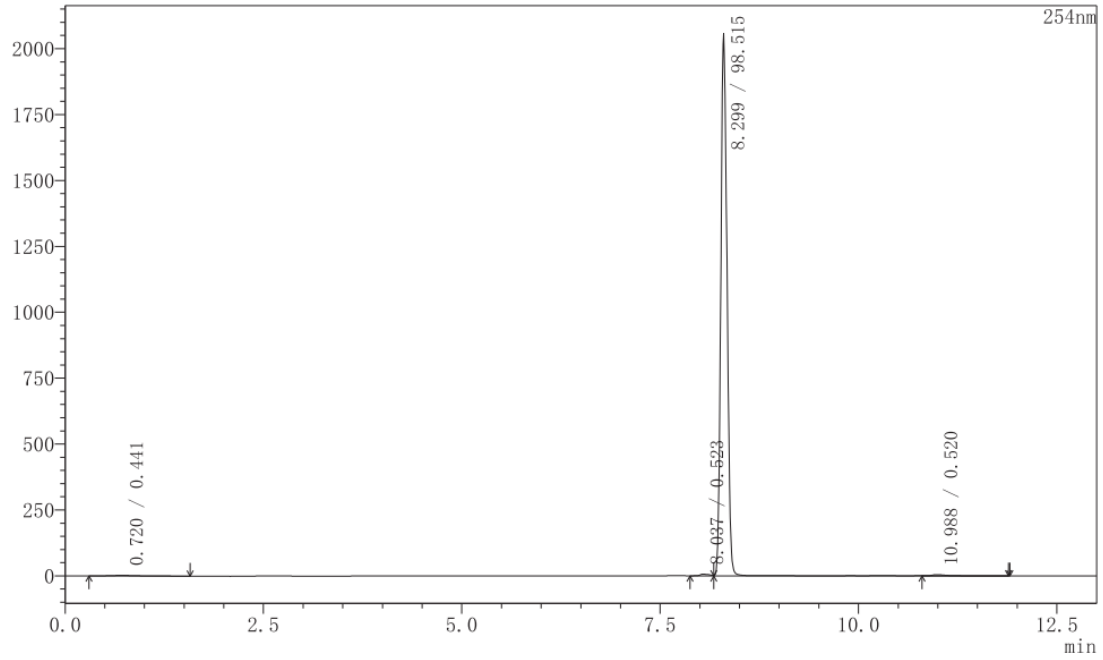
HPLC spectra of Compound **P5**



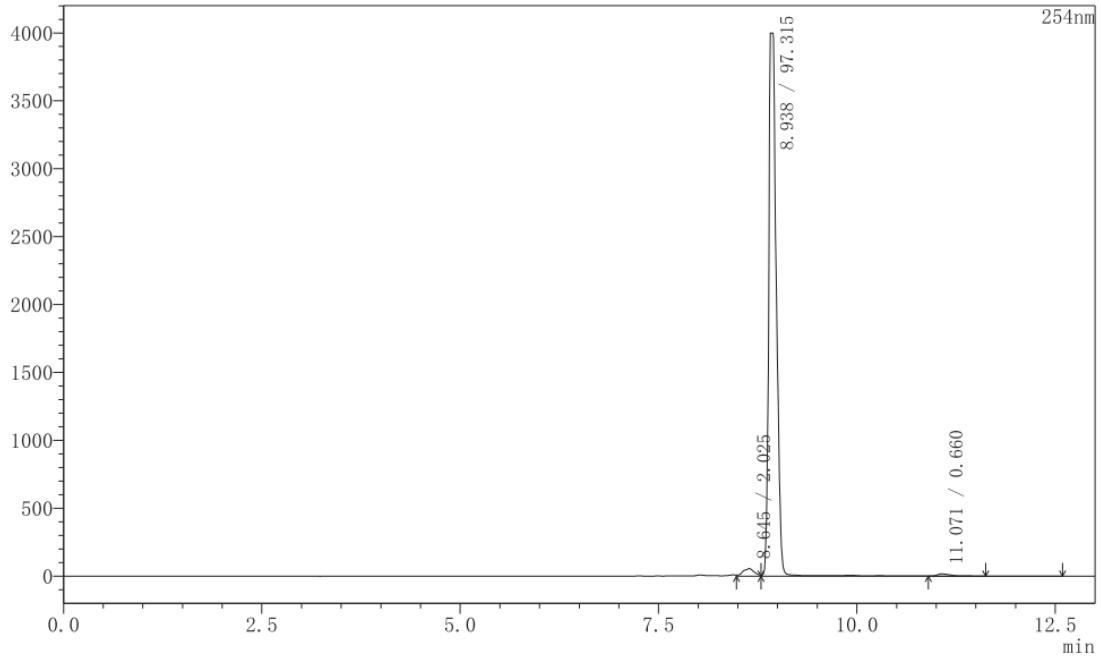
HPLC spectra of Compound **P6**



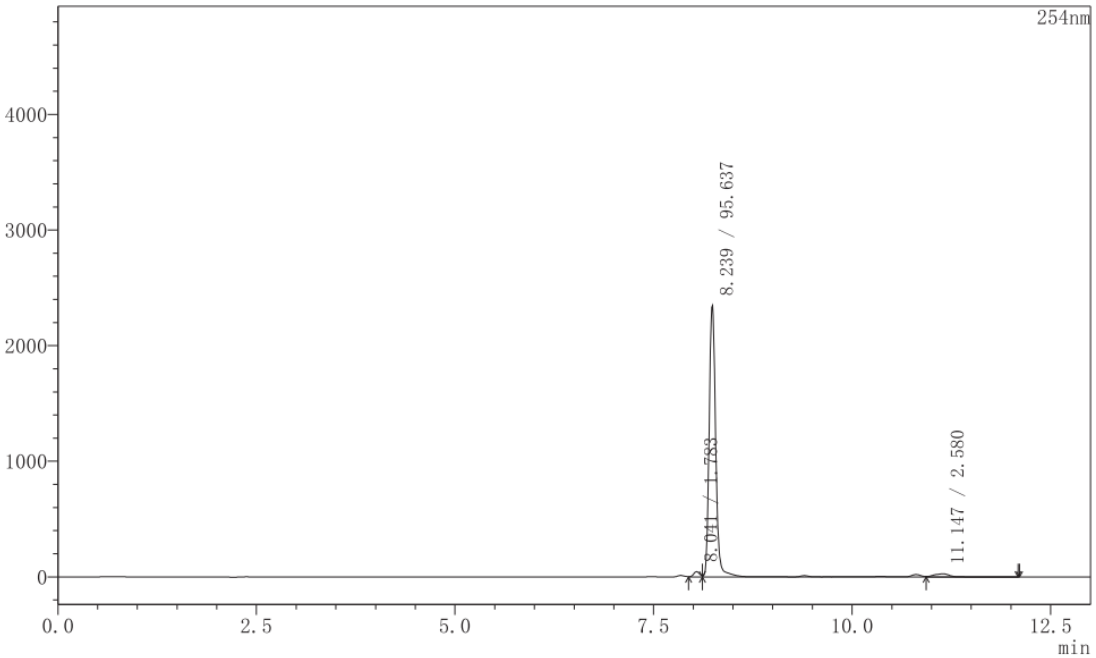
HPLC spectra of Compound **P7**



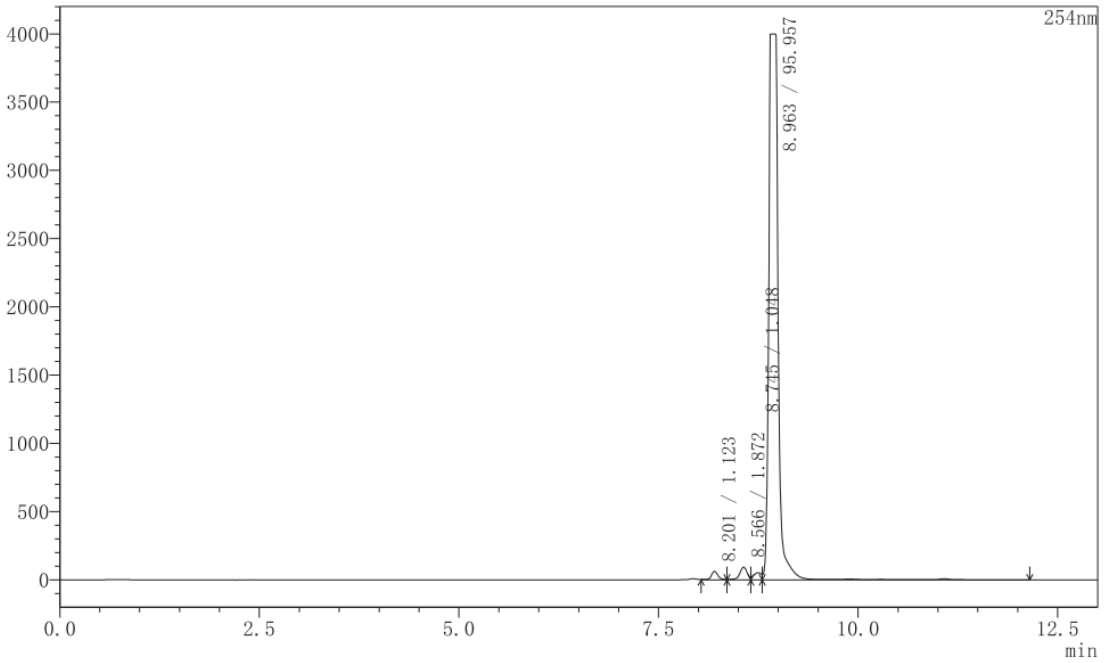
HPLC spectra of Compound **P8**



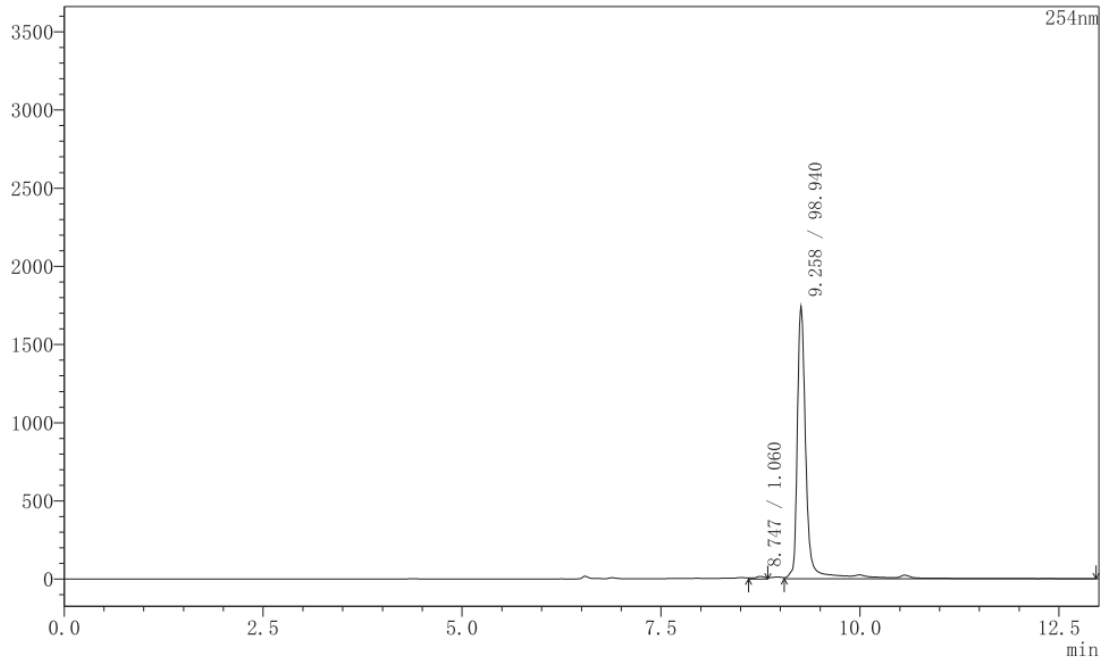
HPLC spectra of Compound **P9**



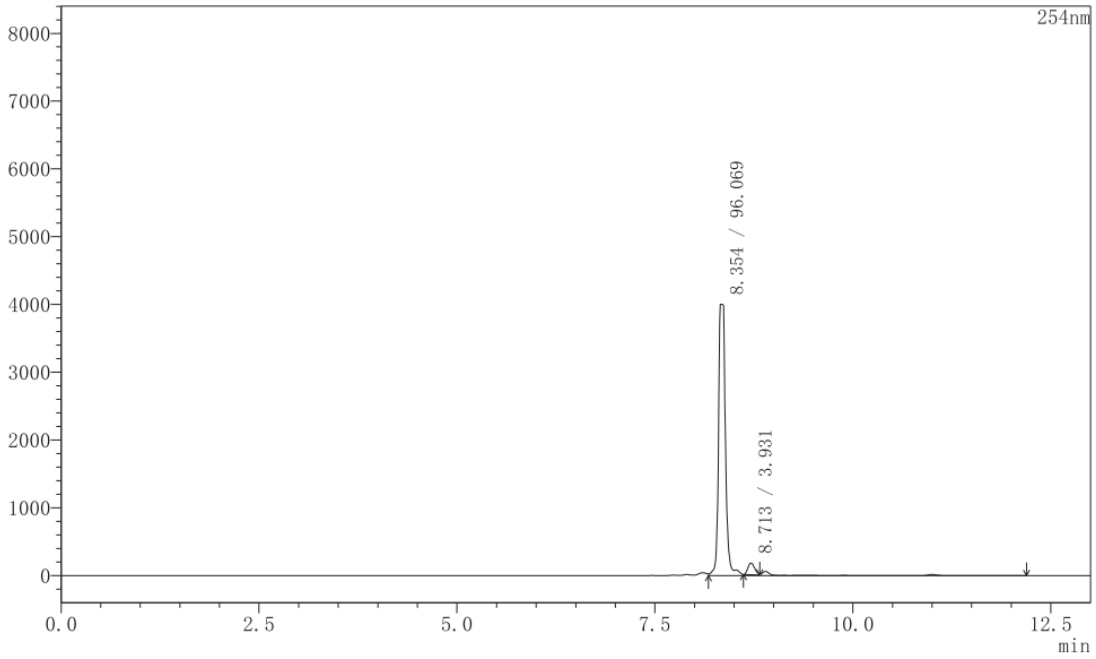
HPLC spectra of Compound **P10**



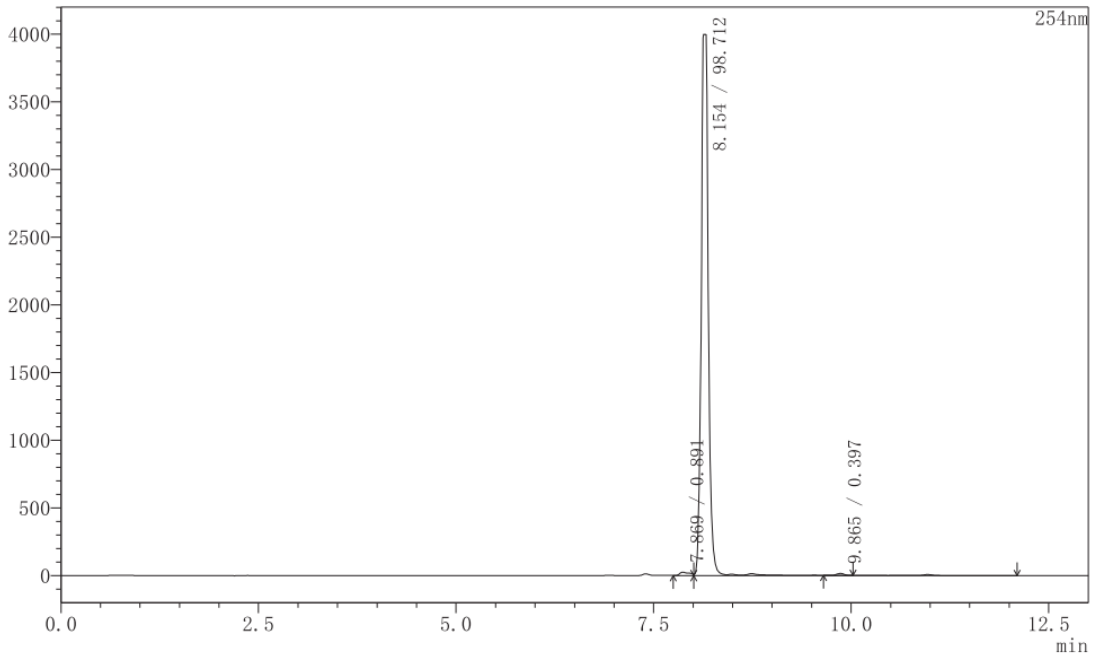
HPLC spectra of Compound **P11**



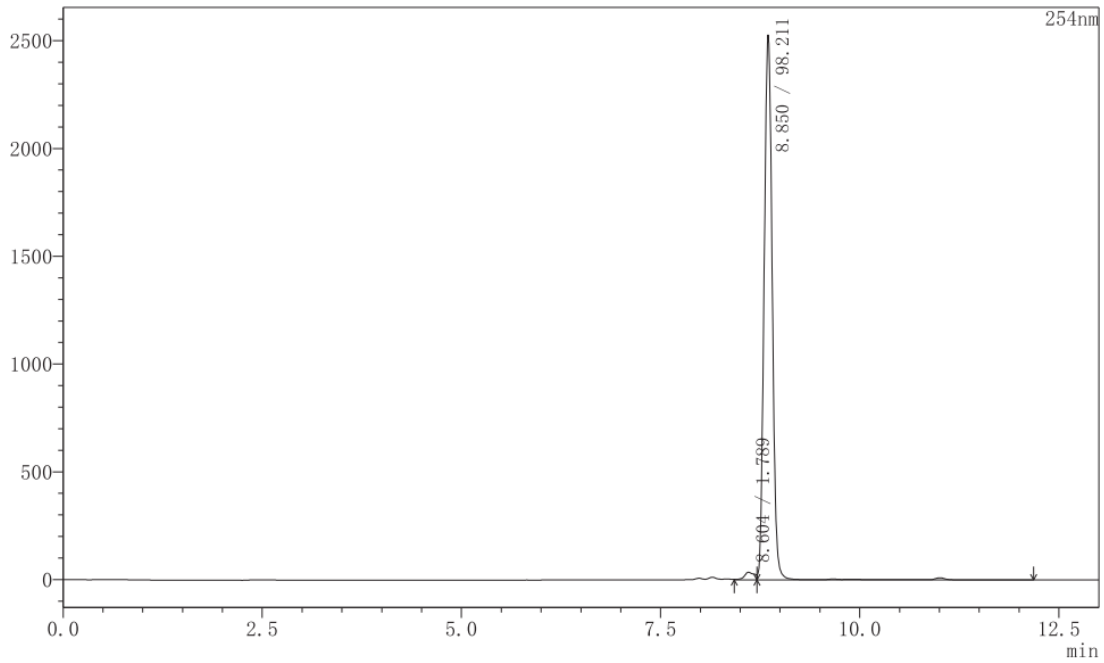
HPLC spectra of Compound **P12**



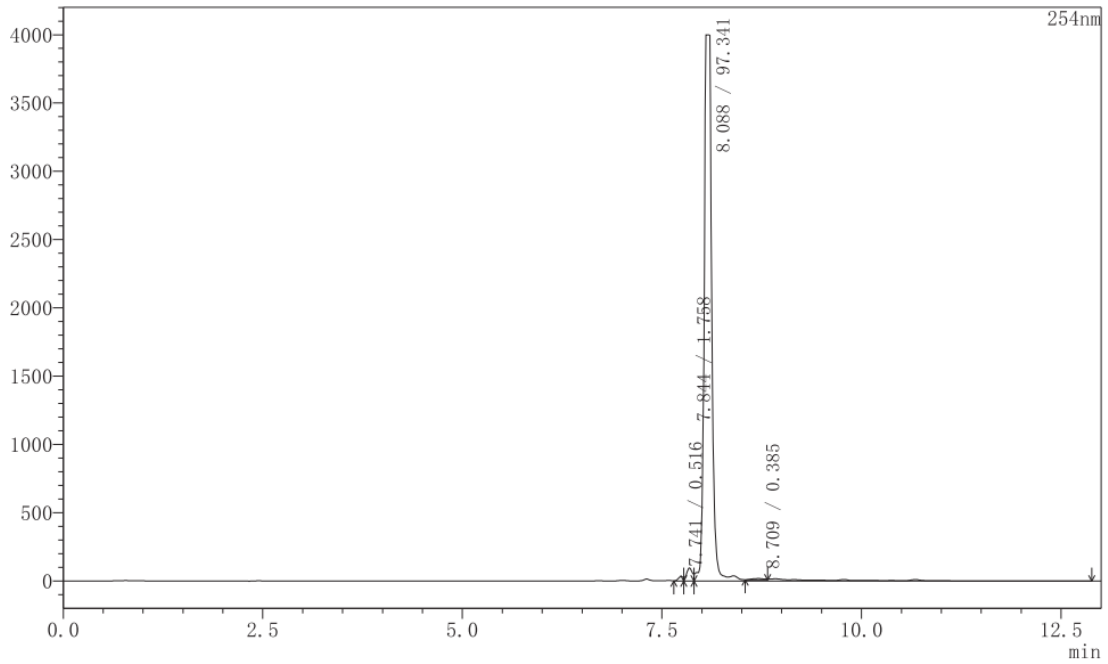
HPLC spectra of Compound **P13**



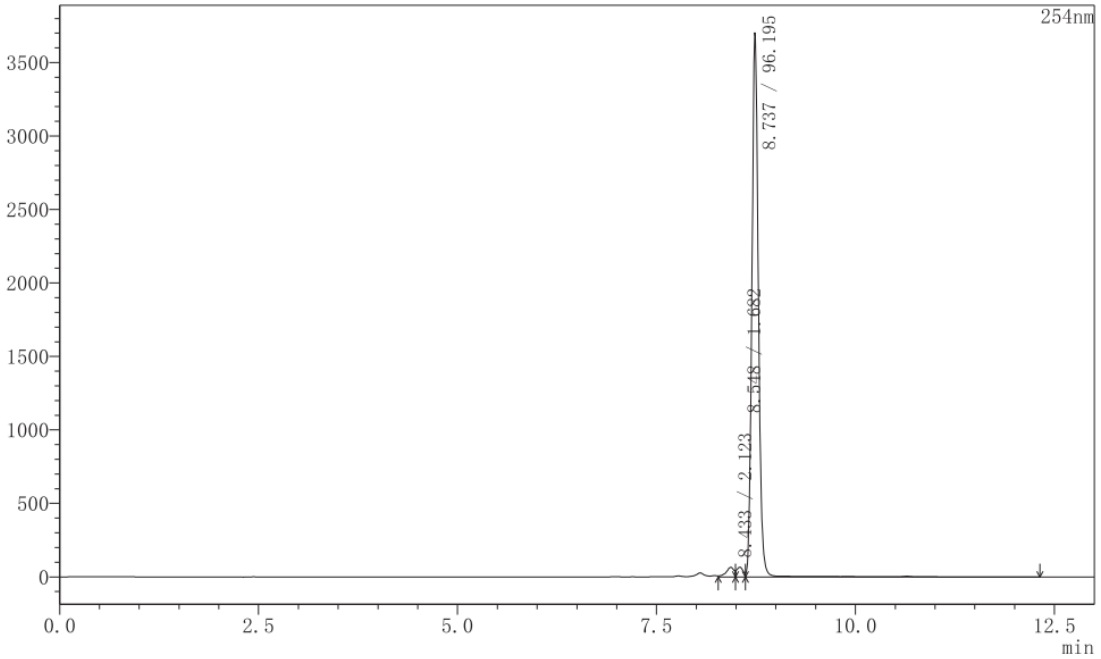
HPLC spectra of Compound **P14**



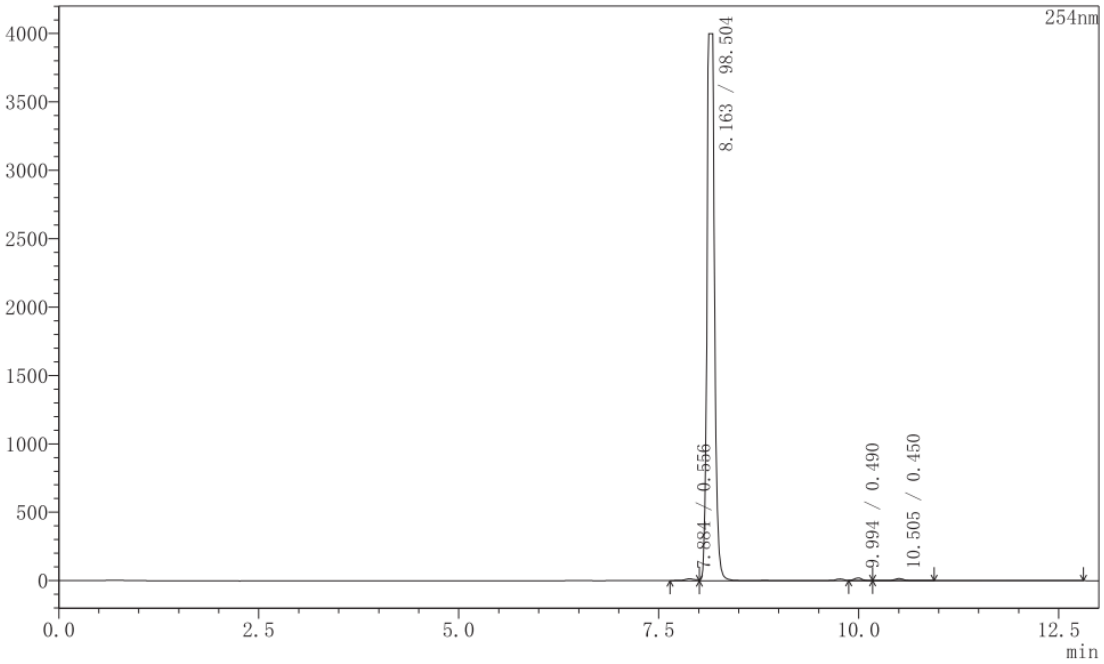
HPLC spectra of Compound **P15**



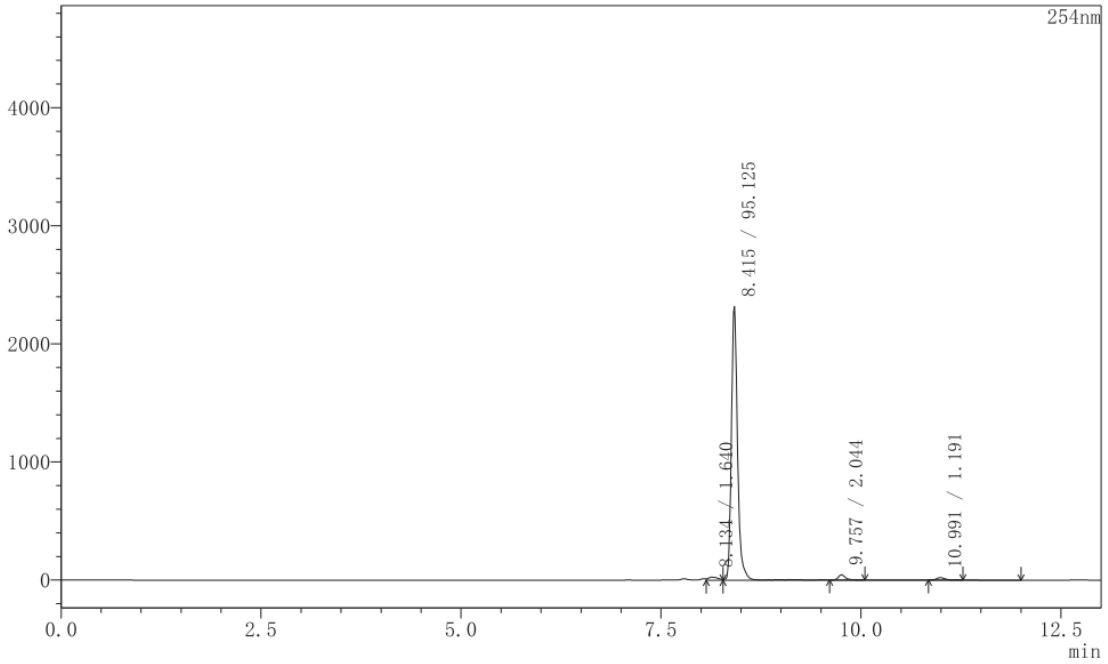
HPLC spectra of Compound **P16**



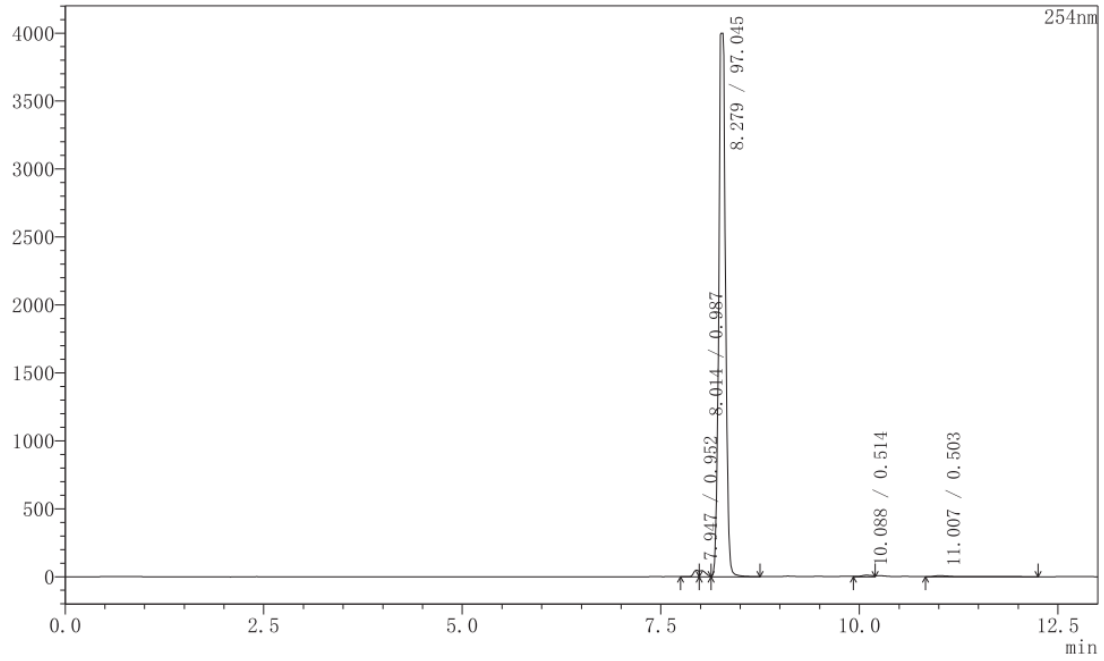
HPLC spectra of Compound **P17**



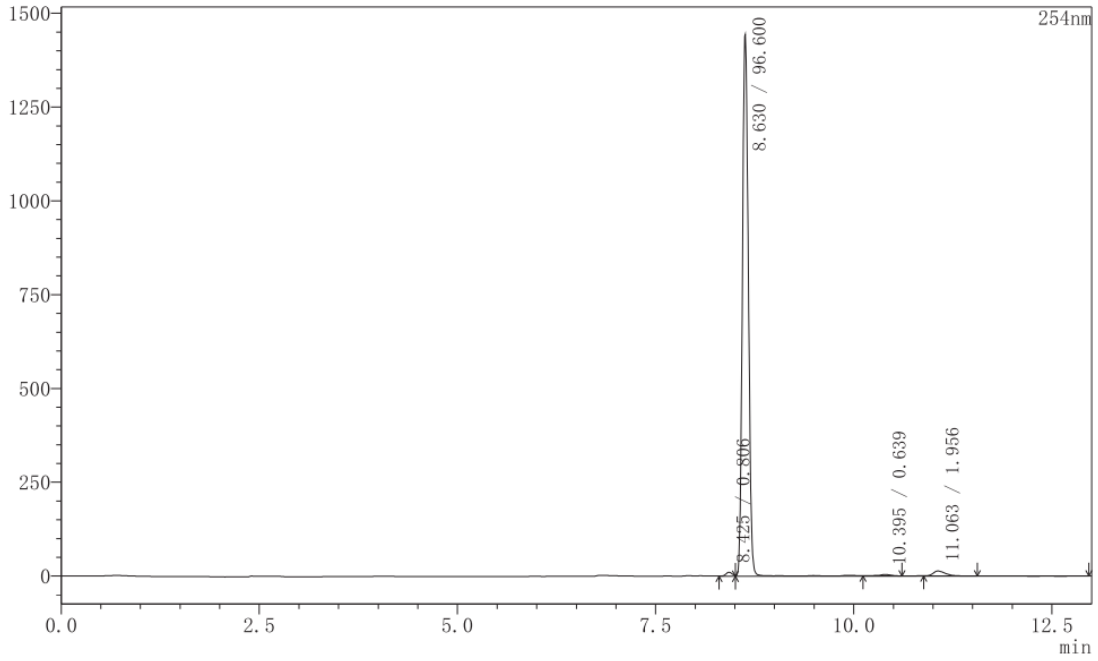
HPLC spectra of Compound **P18**



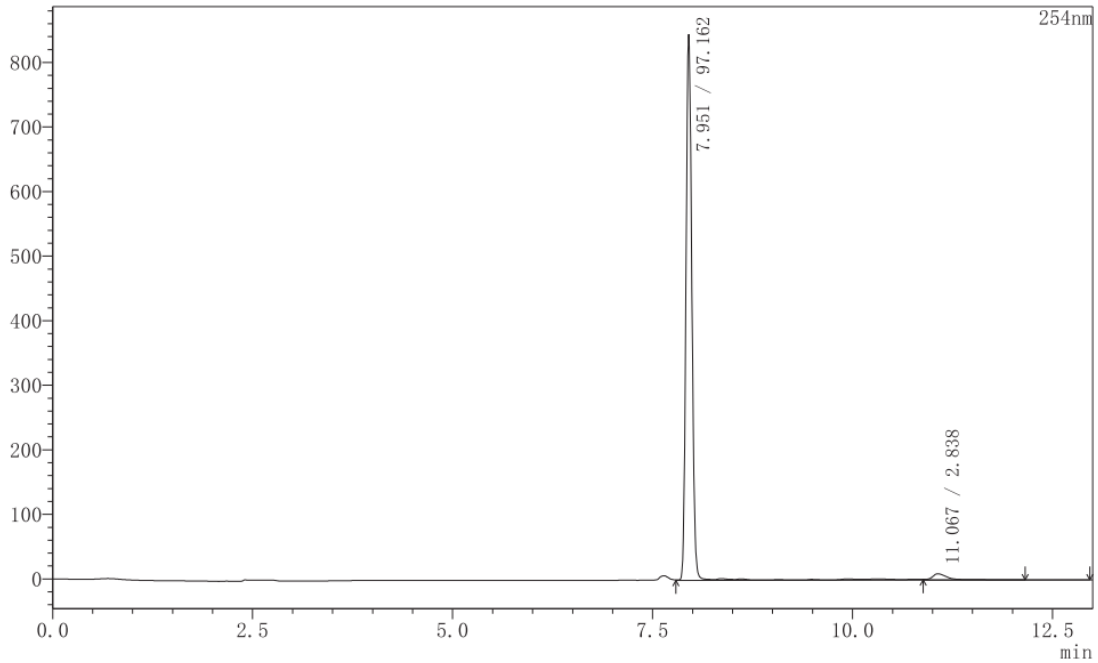
HPLC spectra of Compound **P19**



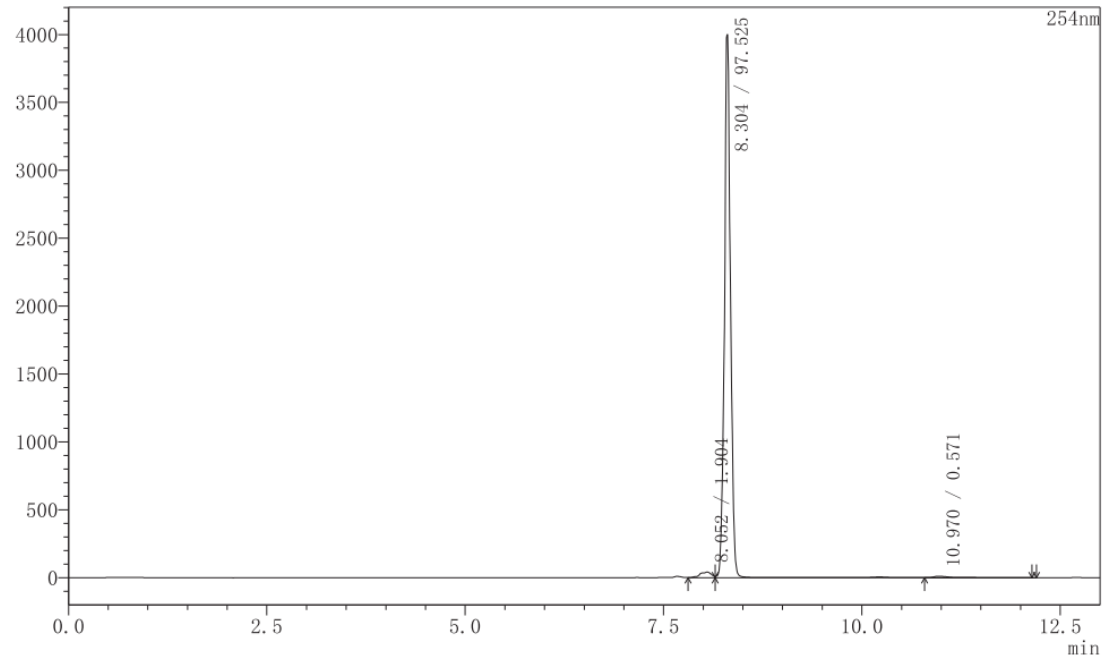
HPLC spectra of Compound **P20**



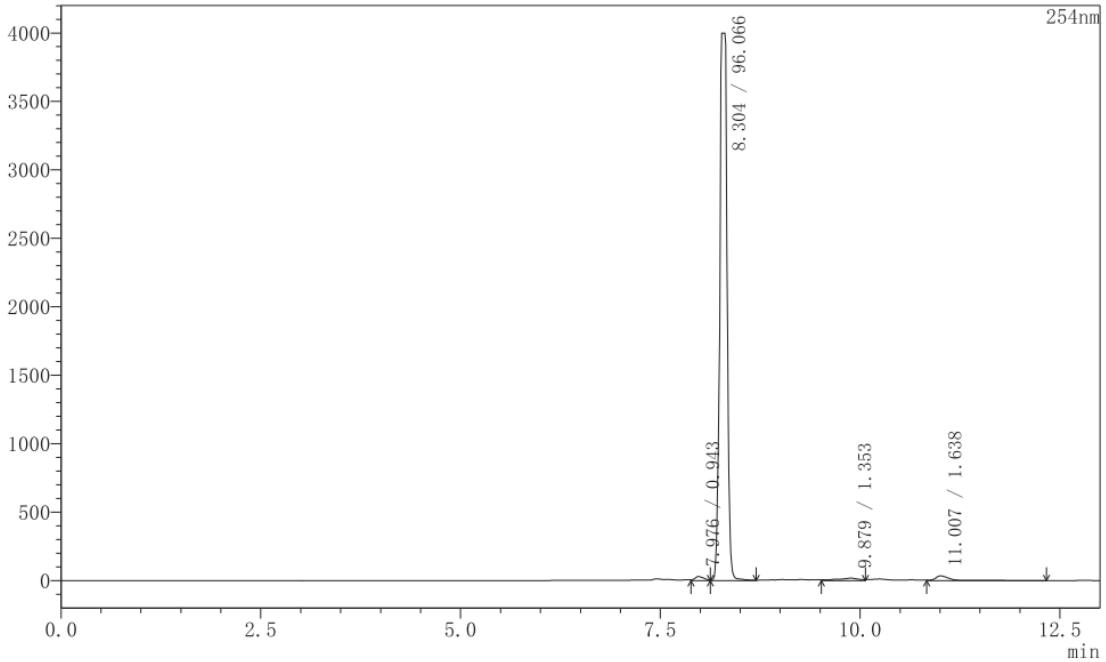
HPLC spectra of Compound **P21**



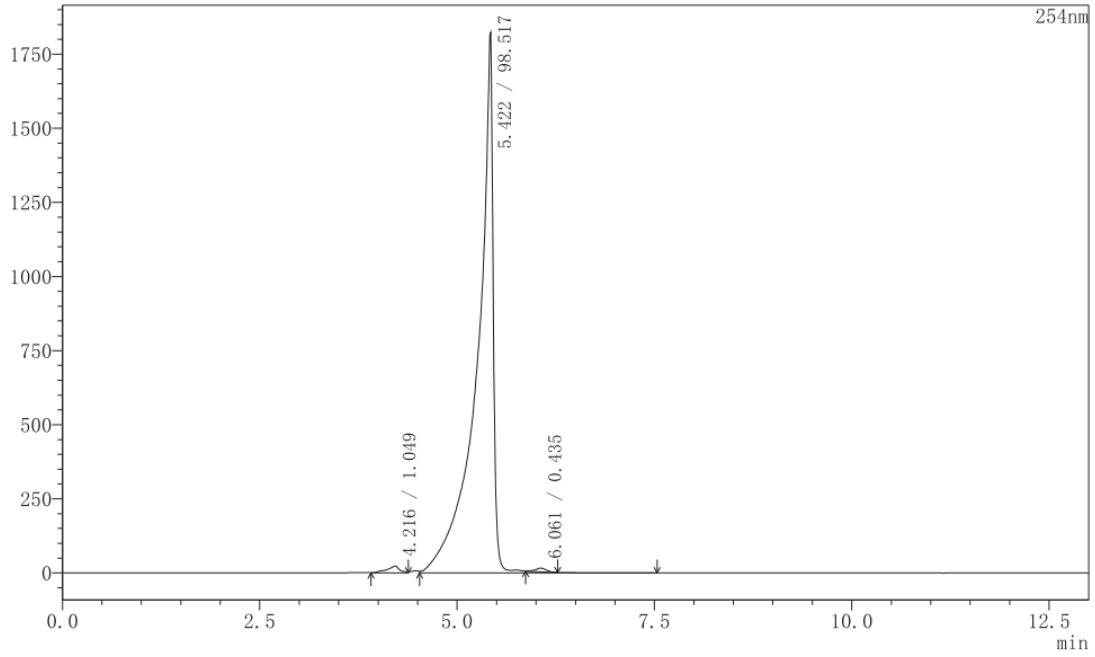
HPLC spectra of Compound **P22**



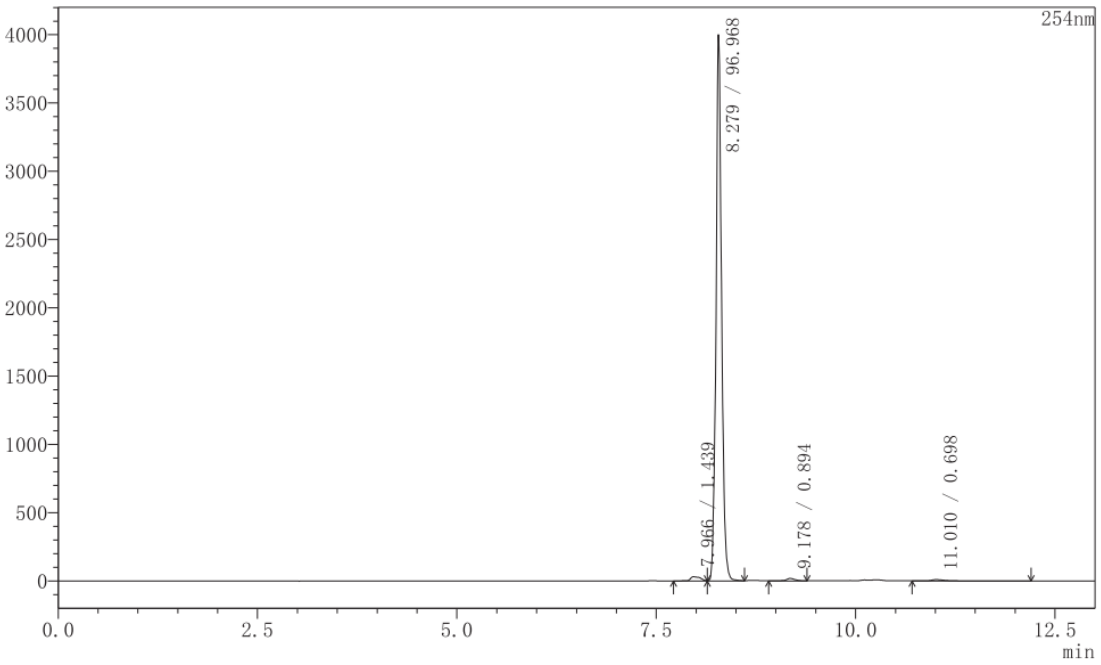
HPLC spectra of Compound **P23**



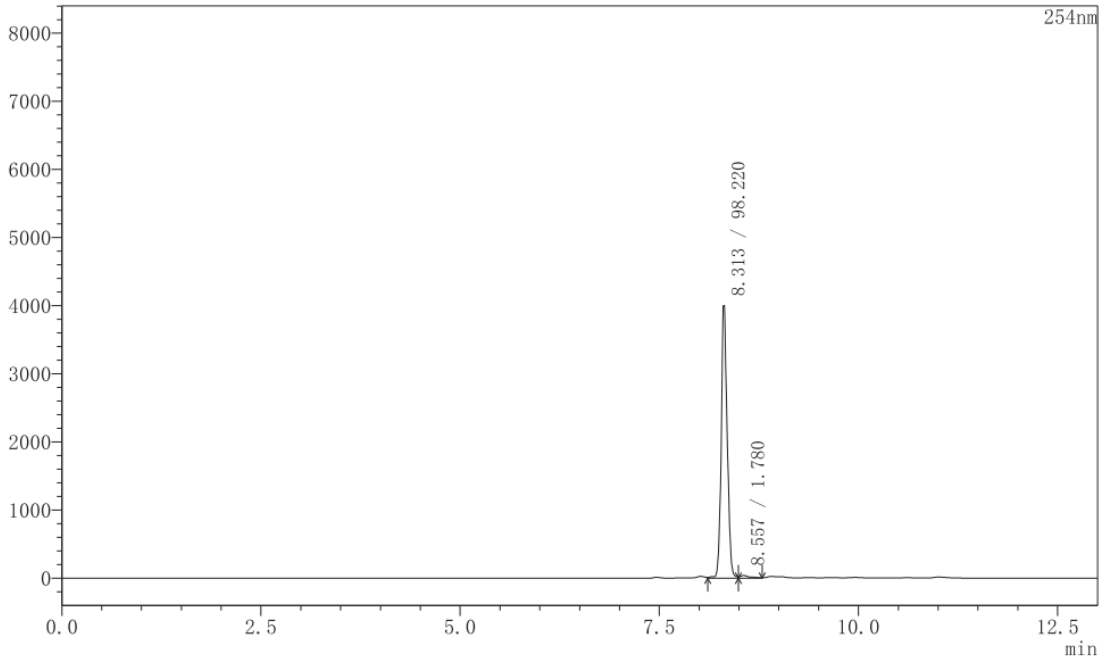
HPLC spectra of Compound **P24**



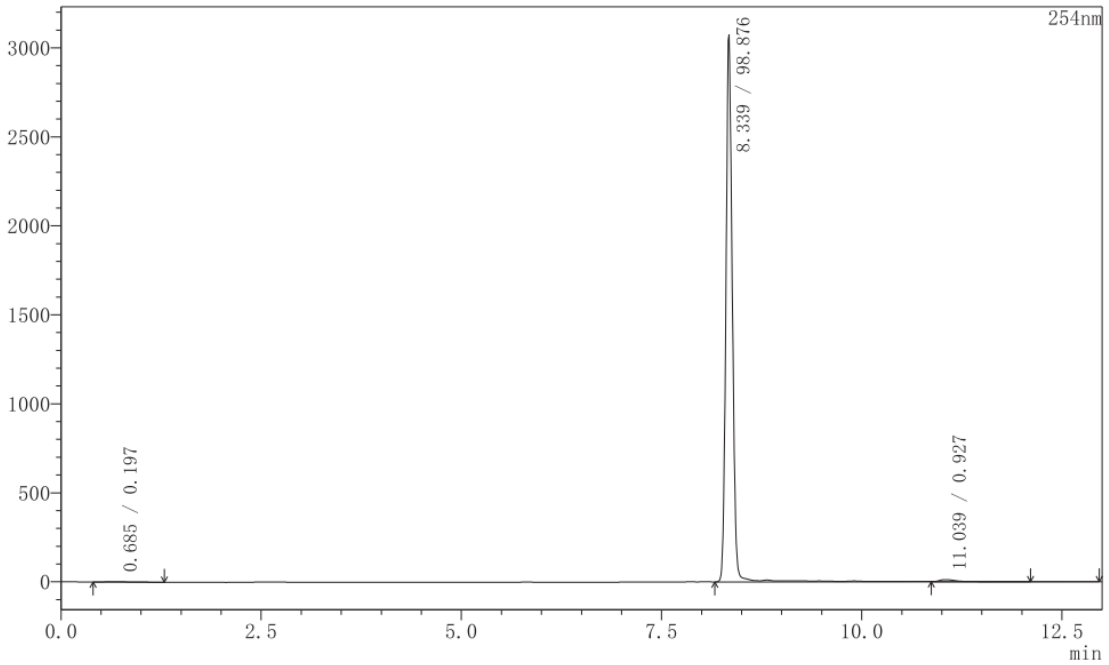
HPLC spectra of Compound **P25**



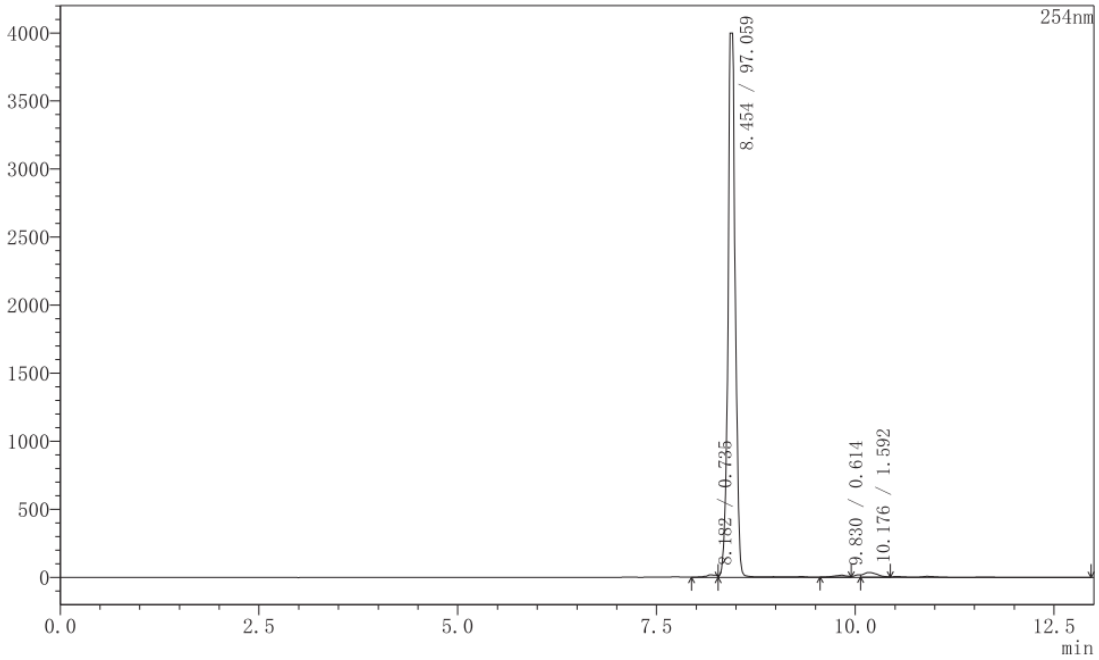
HPLC spectra of Compound **P26**



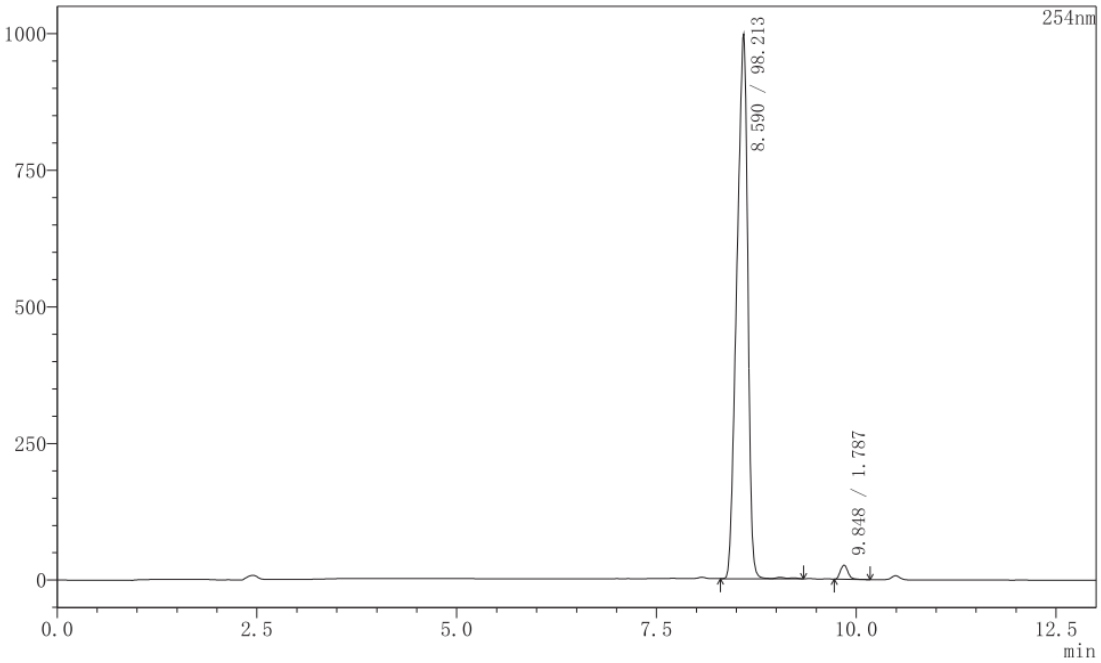
HPLC spectra of Compound **P27**



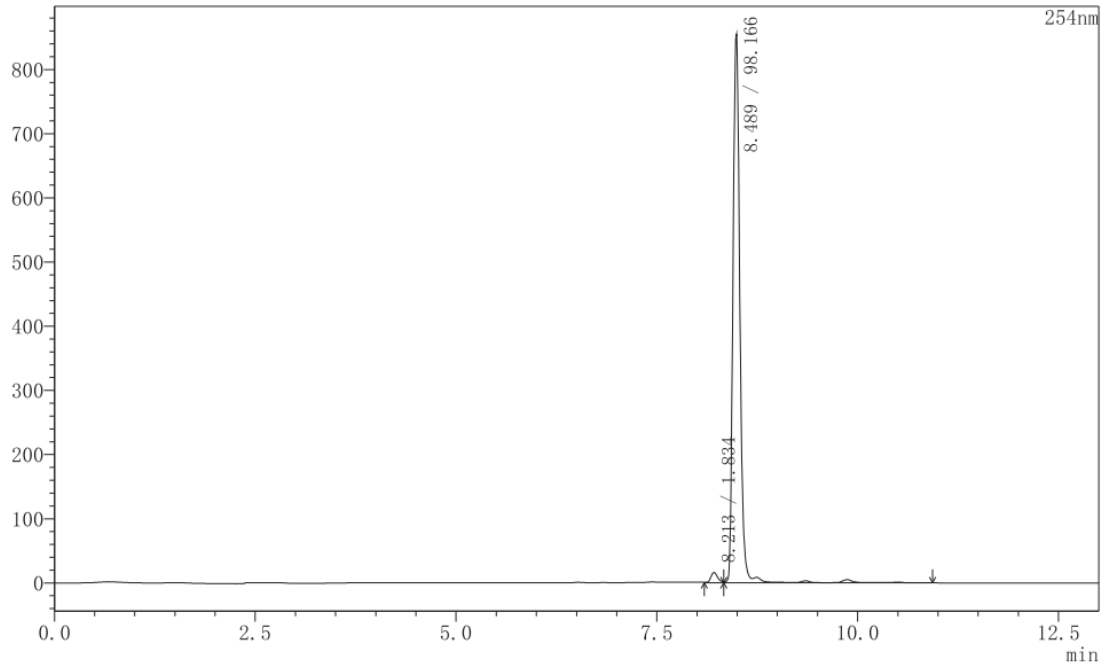
HPLC spectra of Compound **P28**



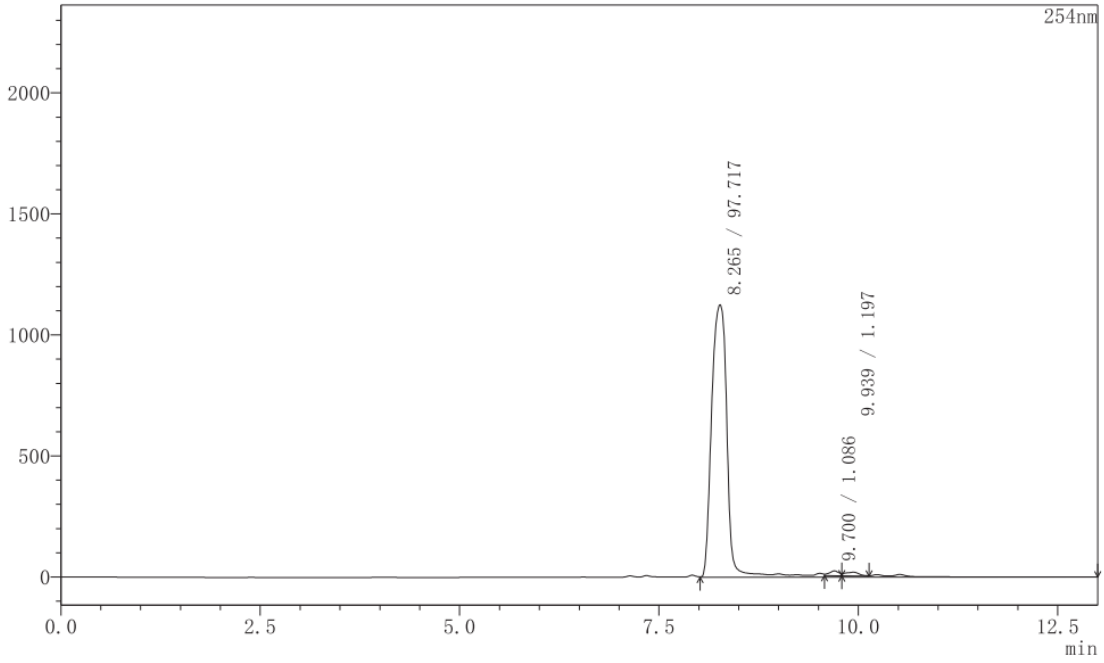
HPLC spectra of Compound **P29**



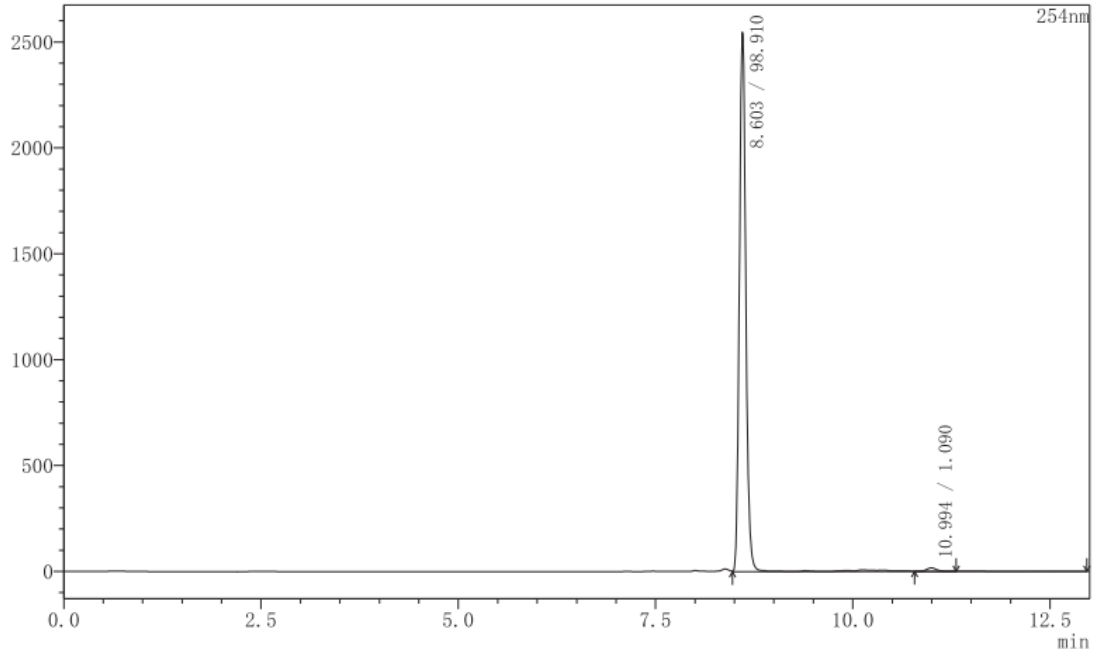
HPLC spectra of Compound **P30**



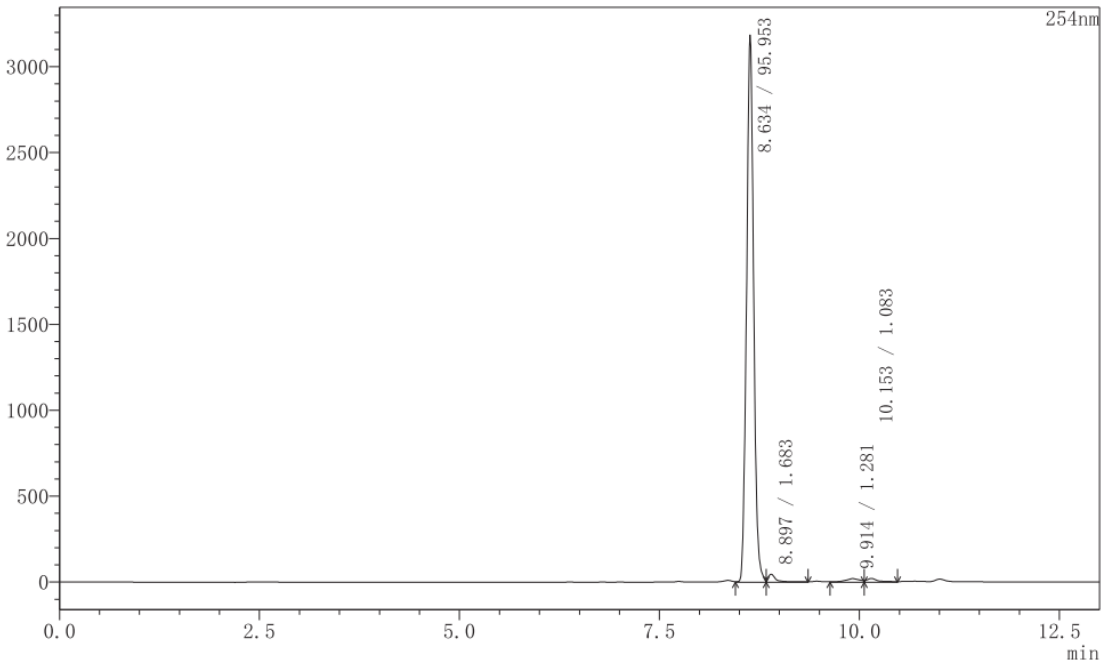
HPLC spectra of Compound **P31**



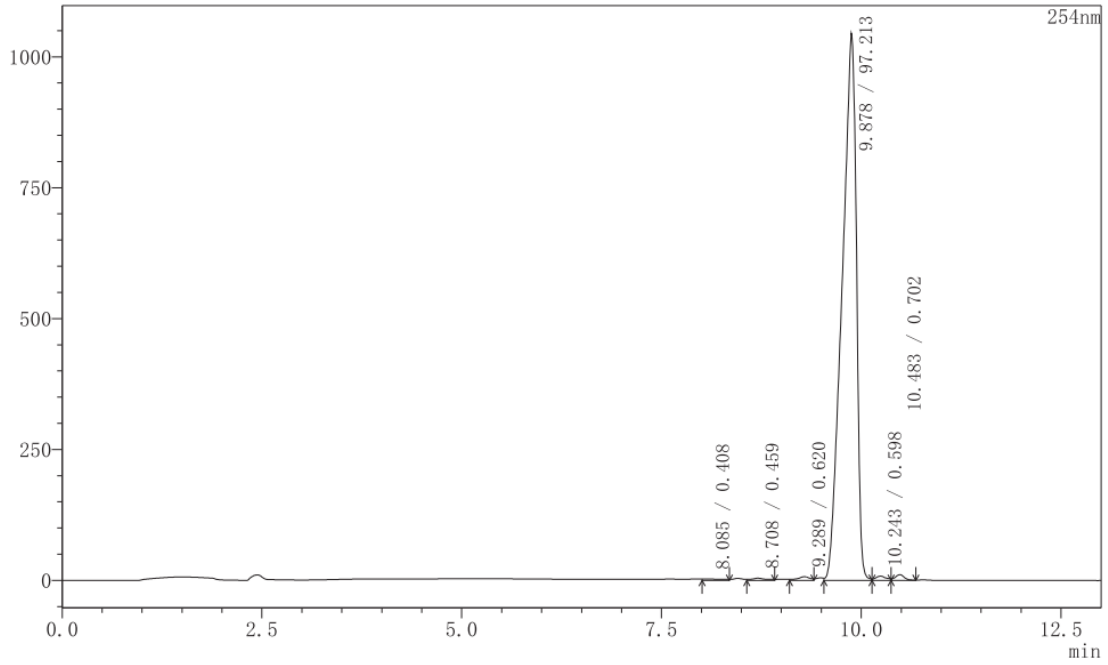
HPLC spectra of Compound **P32**



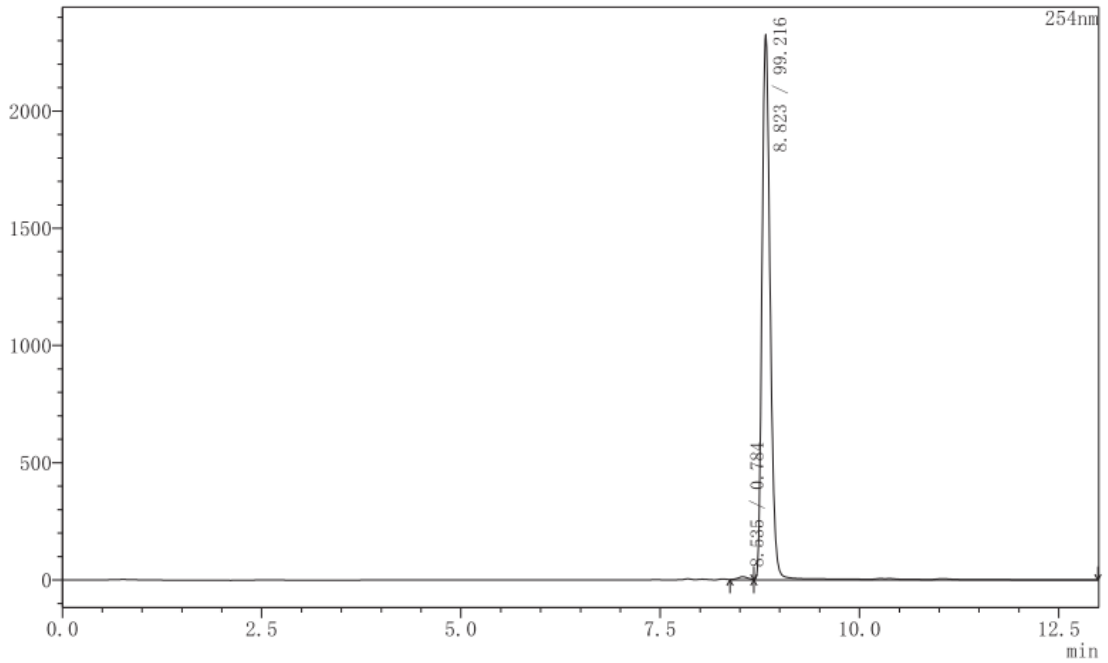
HPLC spectra of Compound **P33**



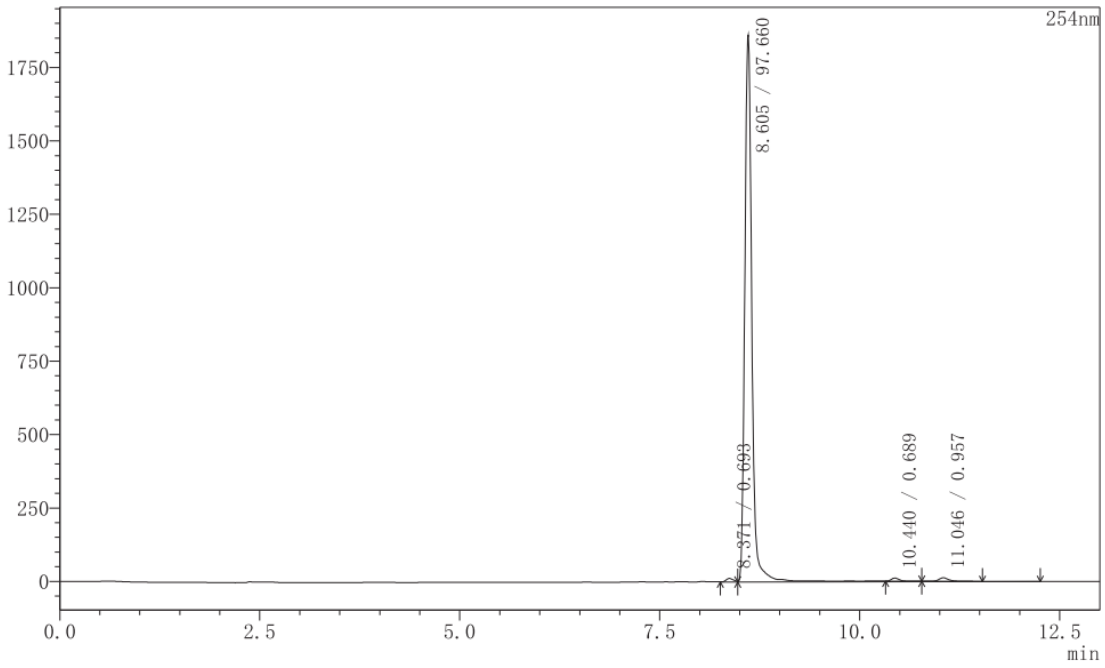
HPLC spectra of Compound **P34**



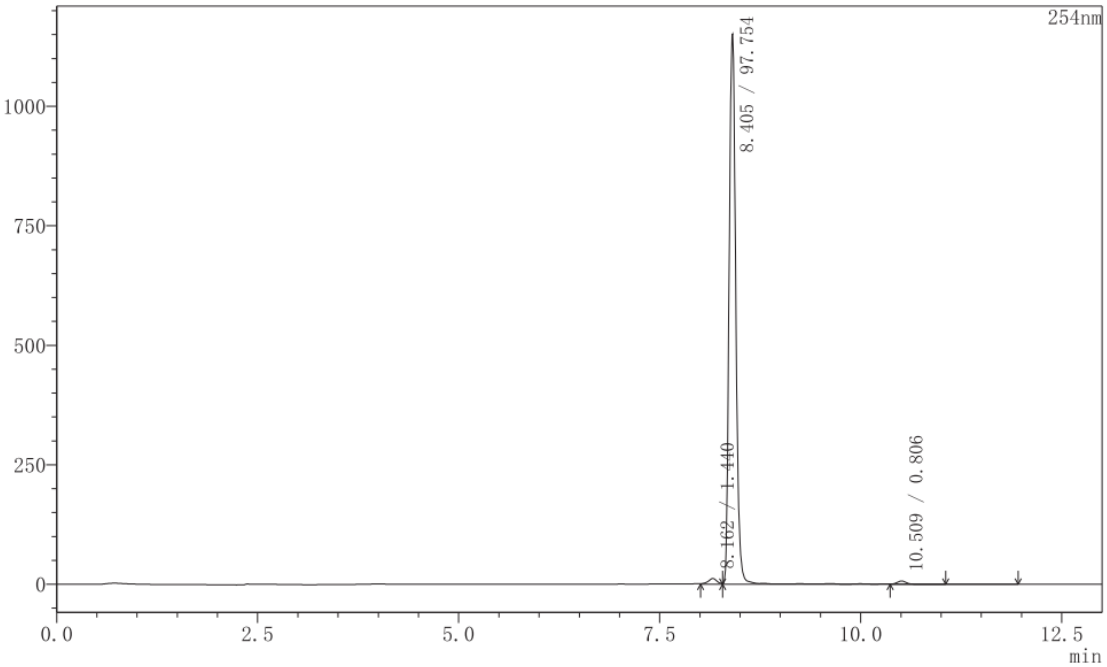
HPLC spectra of Compound **P35**



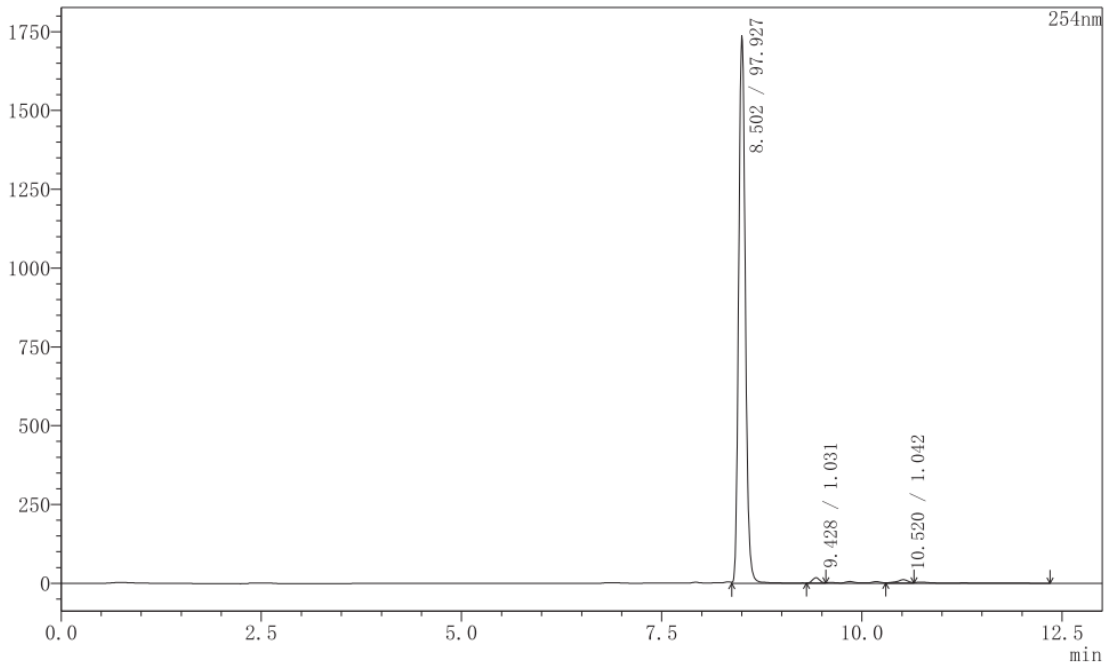
HPLC spectra of Compound **P36**



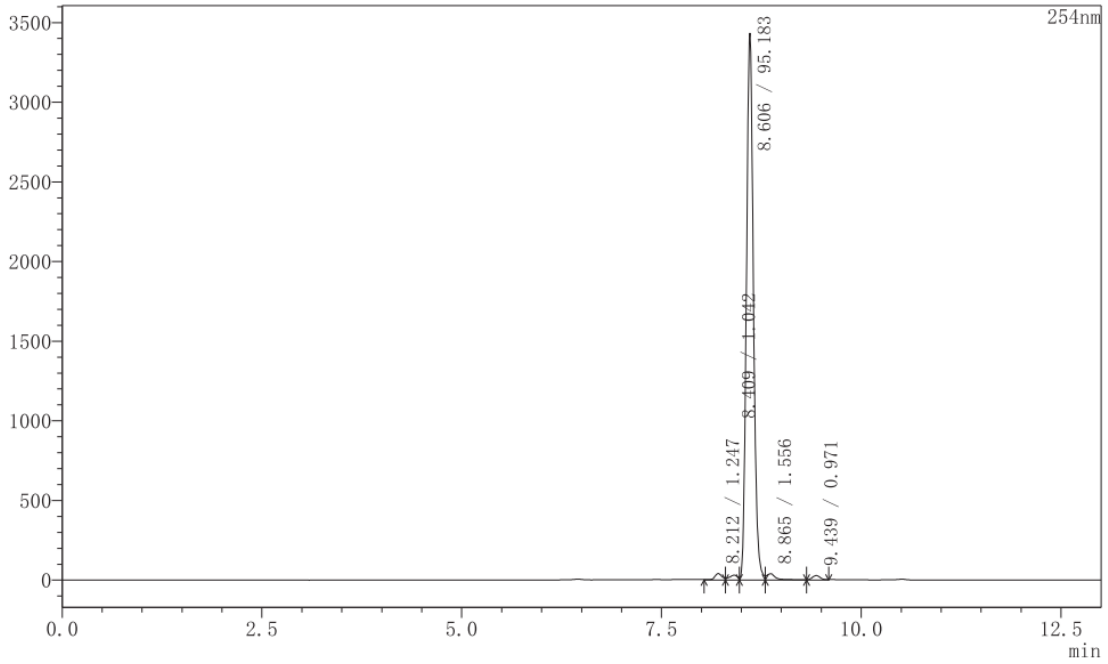
HPLC spectra of Compound **P37**



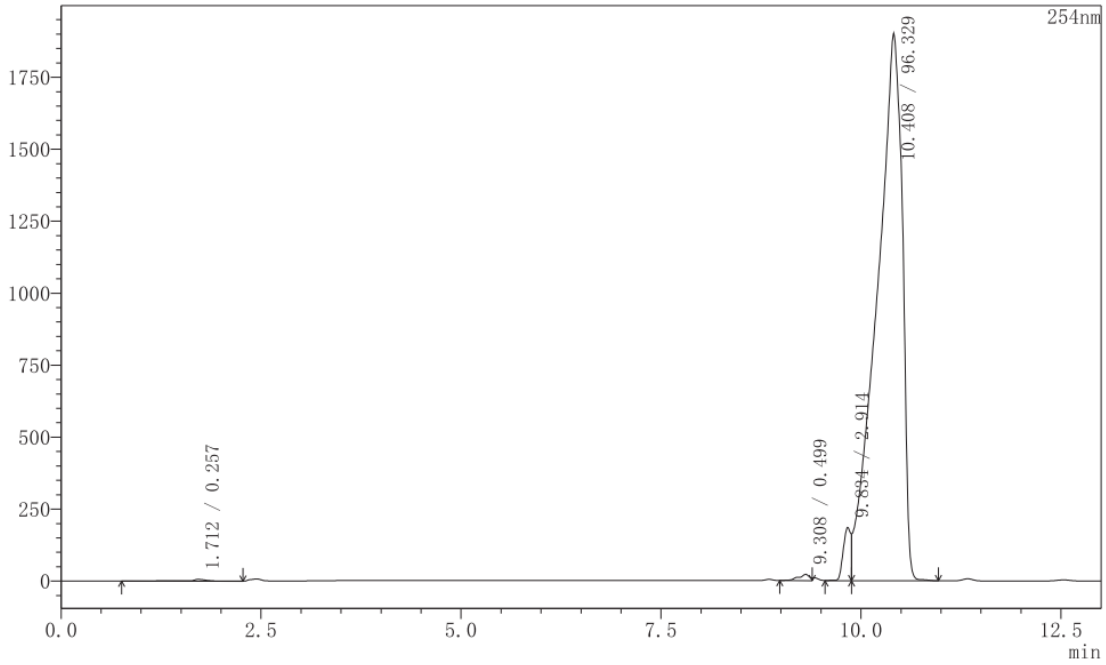
HPLC spectra of Compound **P38**



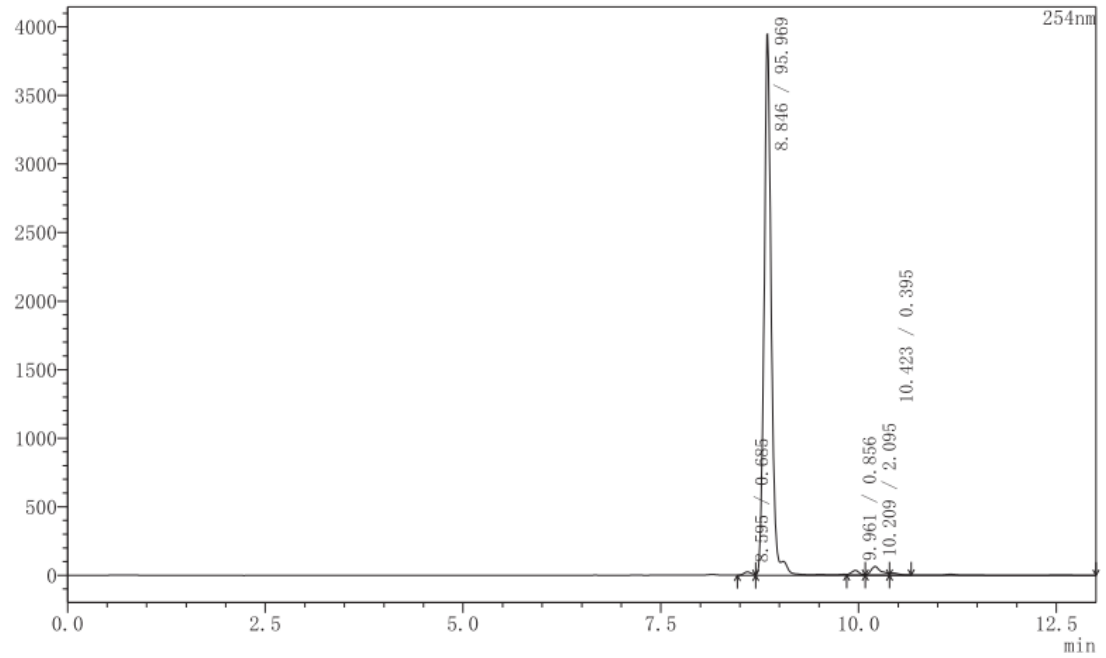
HPLC spectra of Compound **P39**



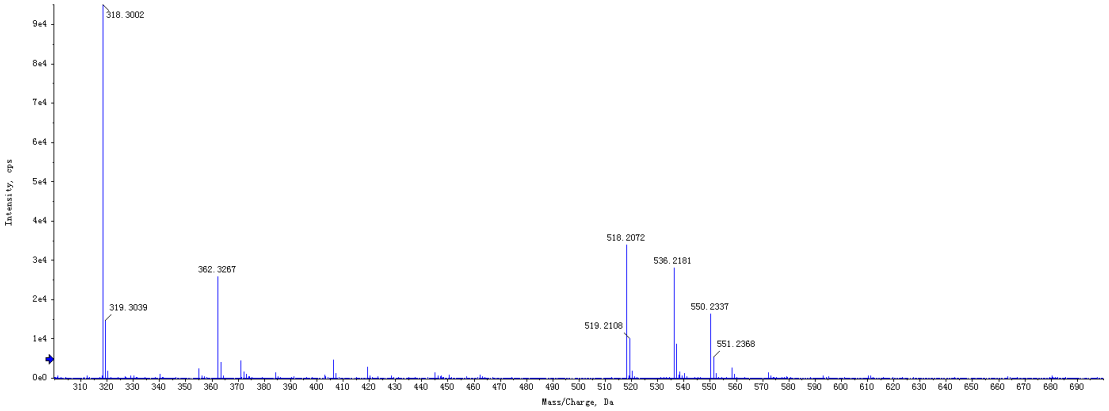
HPLC spectra of Compound **P40**



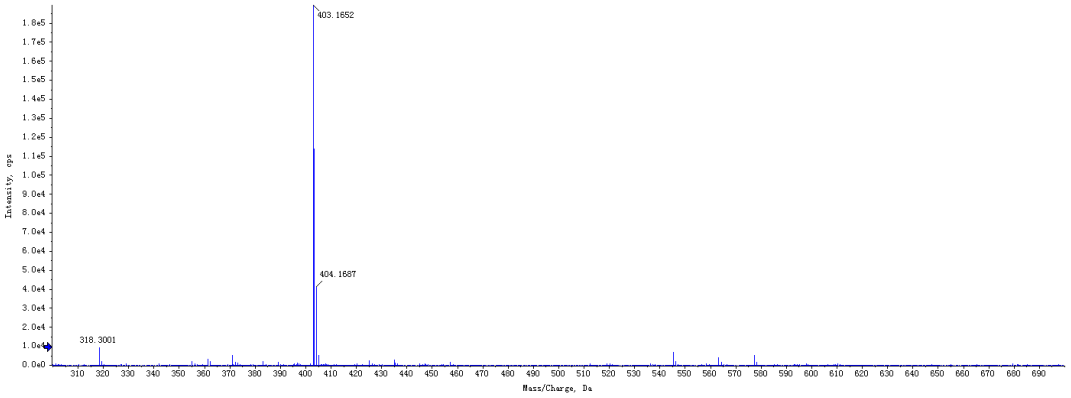
HPLC spectra of Compound **P41**



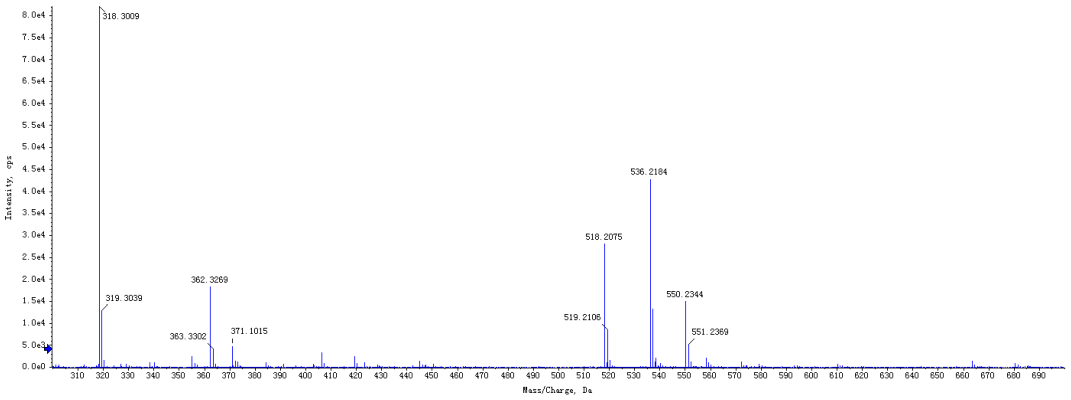
HRMS spectra of Compound **P1**



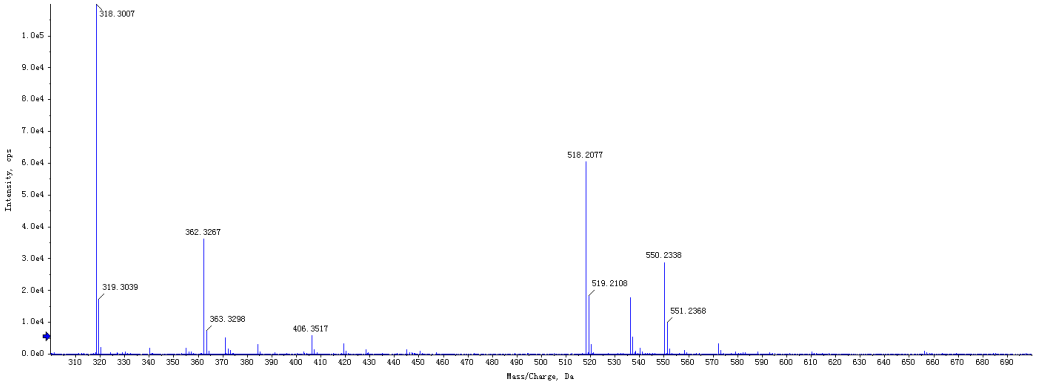
HRMS spectra of Compound **P2**



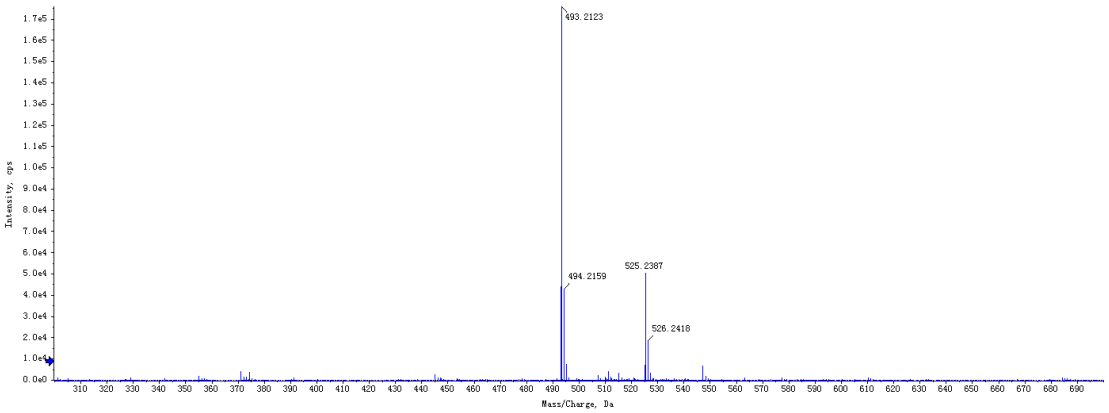
HRMS spectra of Compound **P3**



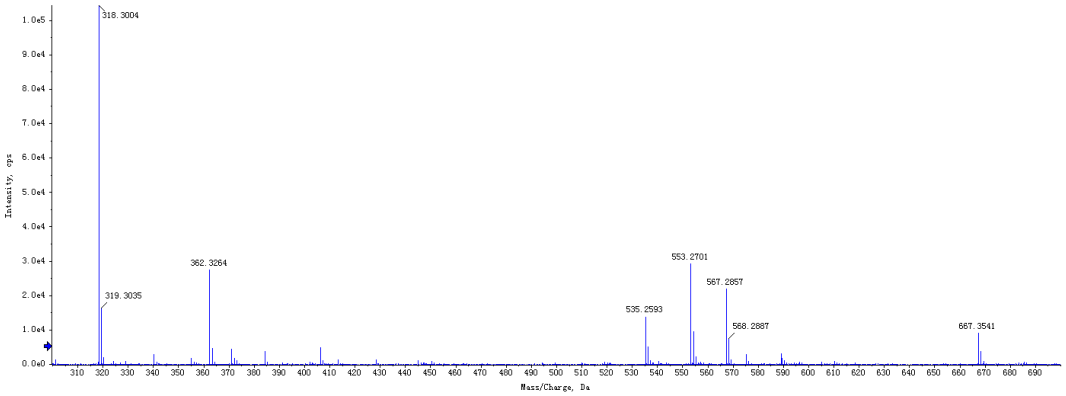
HRMS spectra of Compound **P4**



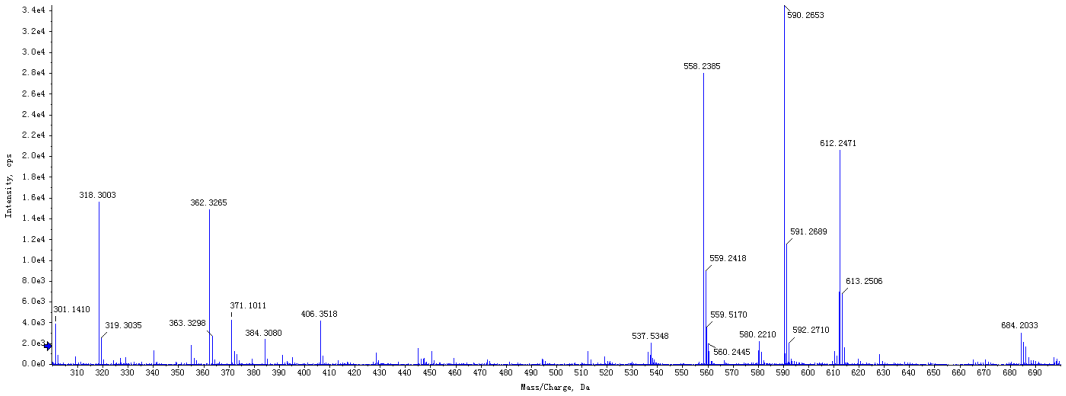
HRMS spectra of Compound **P5**



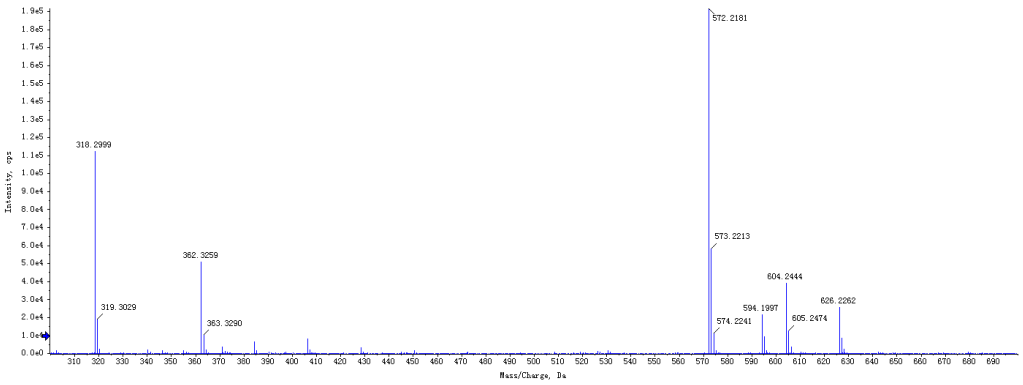
HRMS spectra of Compound **P6**



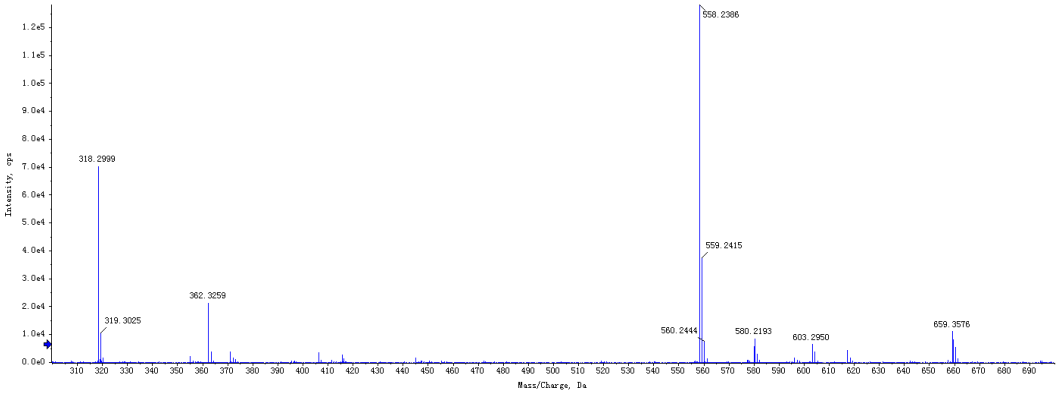
HRMS spectra of Compound **P7**



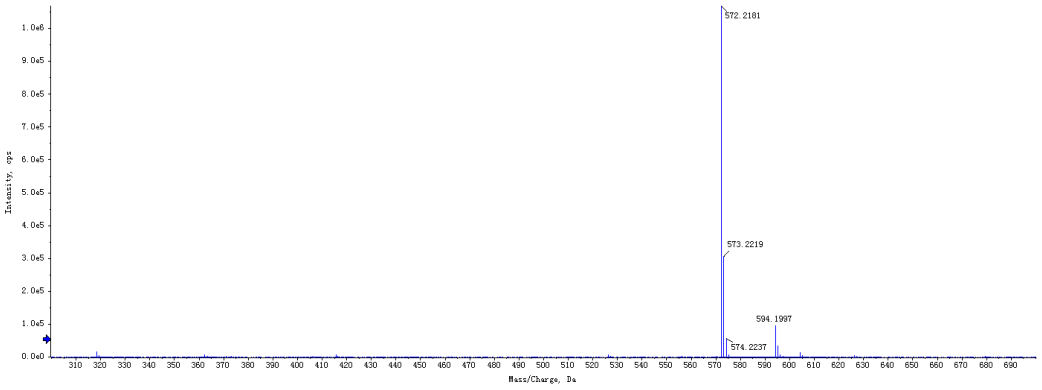
HRMS spectra of Compound **P8**



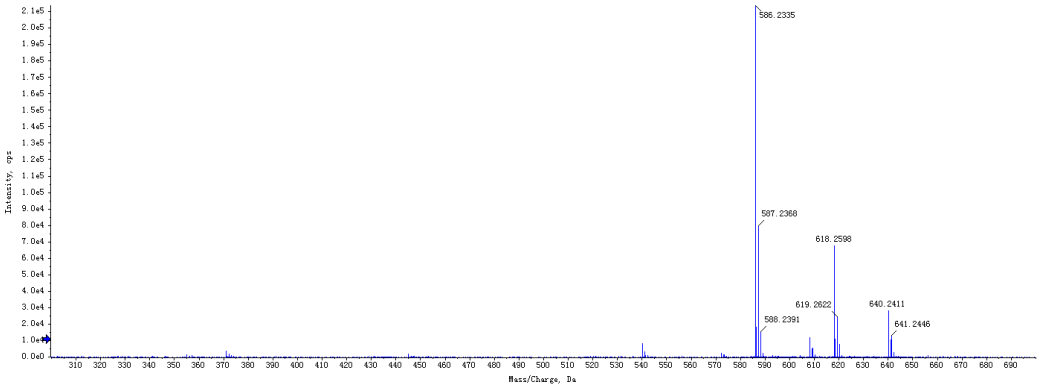
HRMS spectra of Compound **P9**



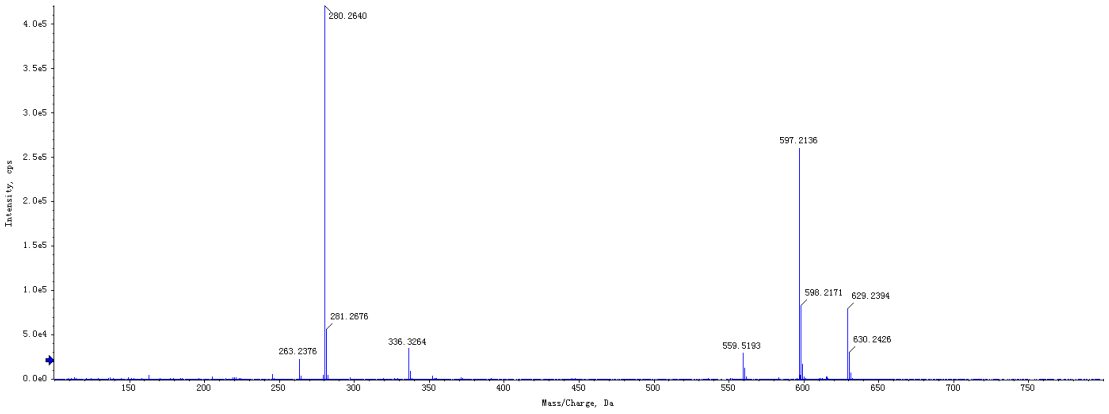
HRMS spectra of Compound **P10**



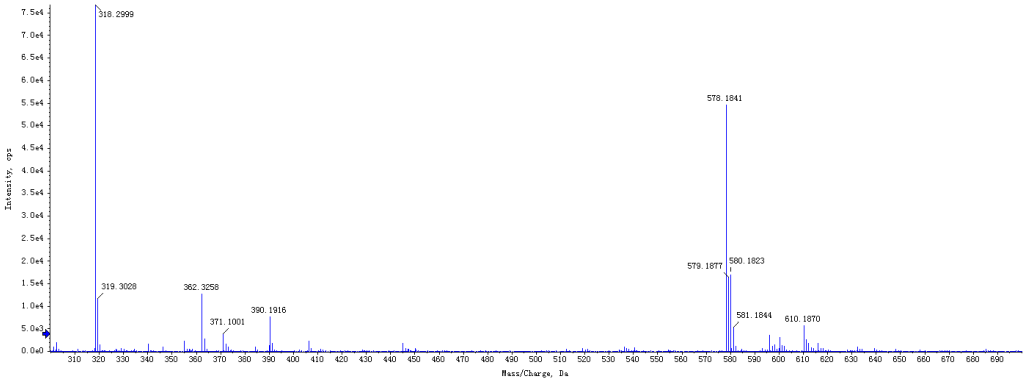
HRMS spectra of Compound **P11**



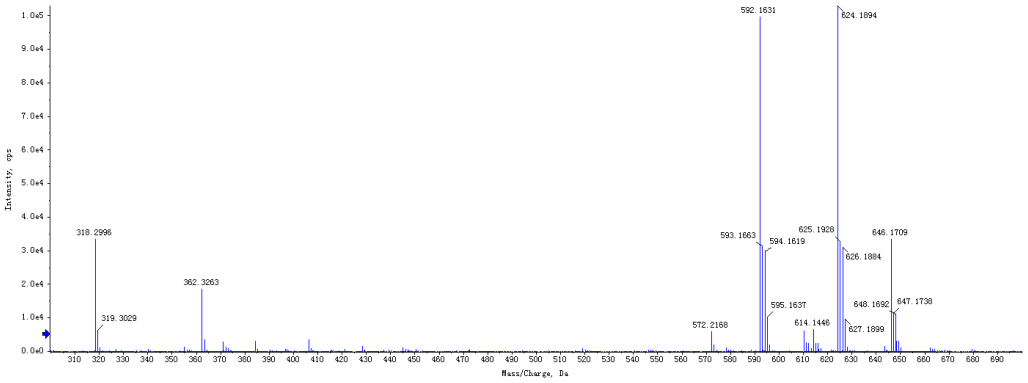
HRMS spectra of Compound **P12**



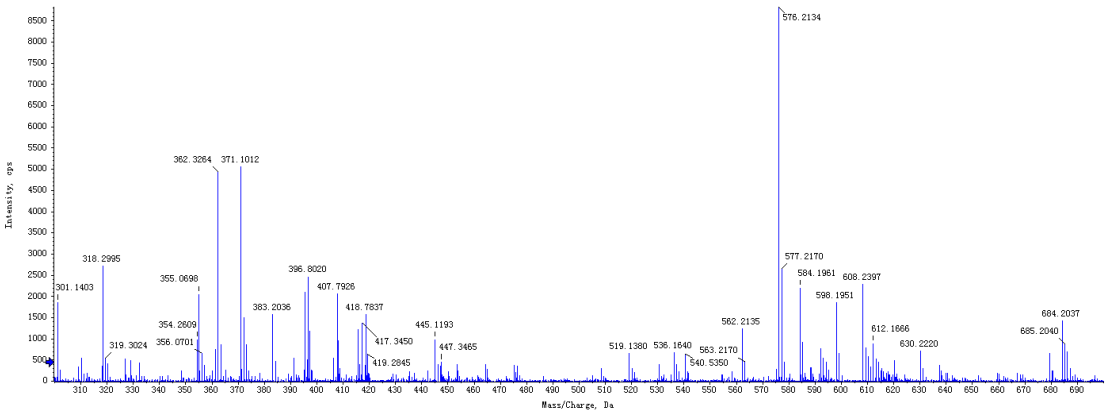
HRMS spectra of Compound **P13**



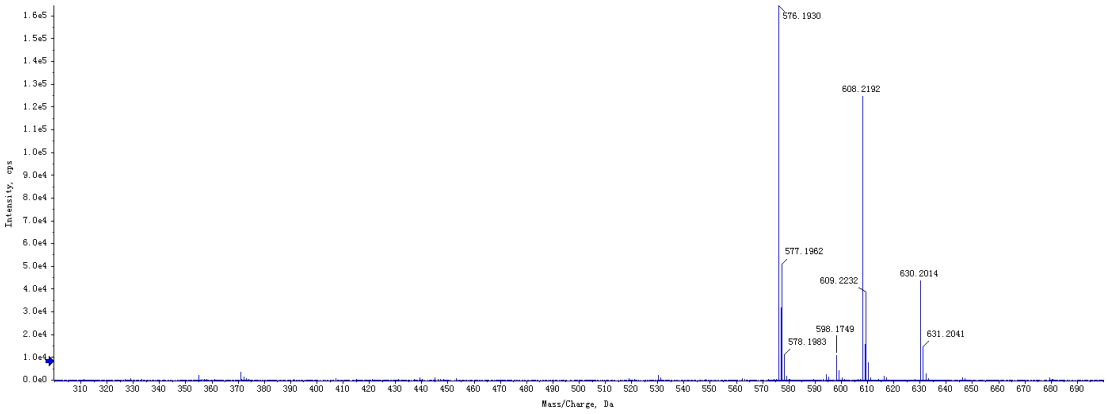
HRMS spectra of Compound **P14**



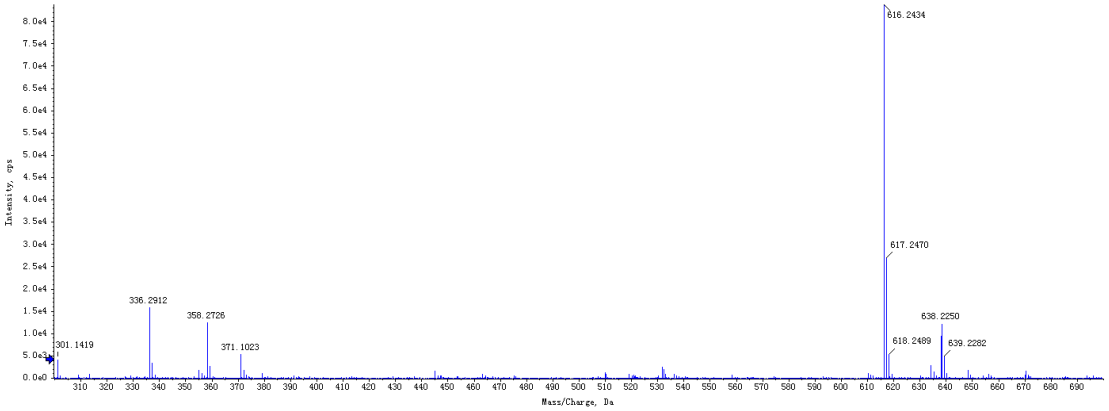
HRMS spectra of Compound **P15**



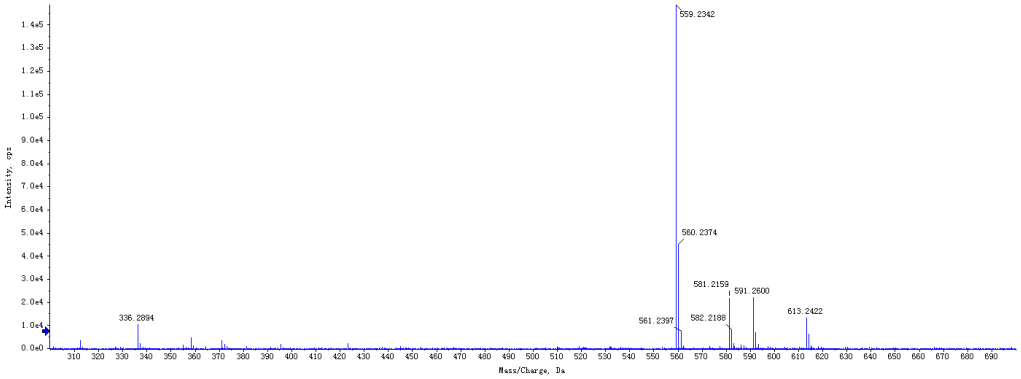
HRMS spectra of Compound **P16**



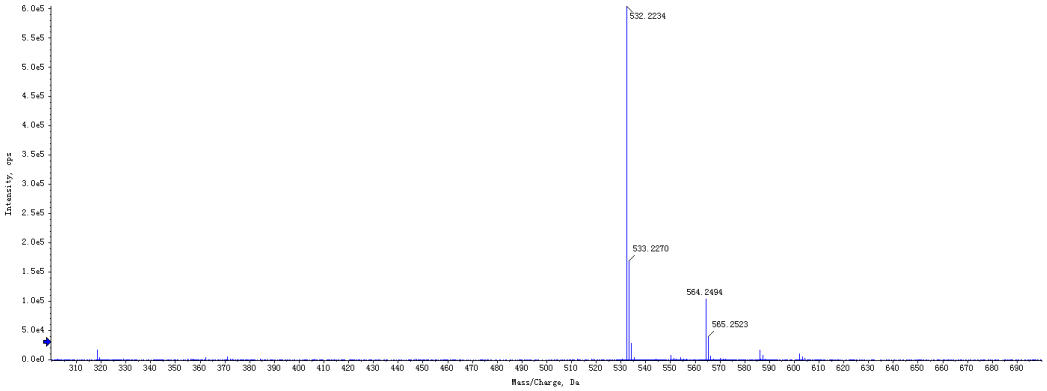
HRMS spectra of Compound **P17**



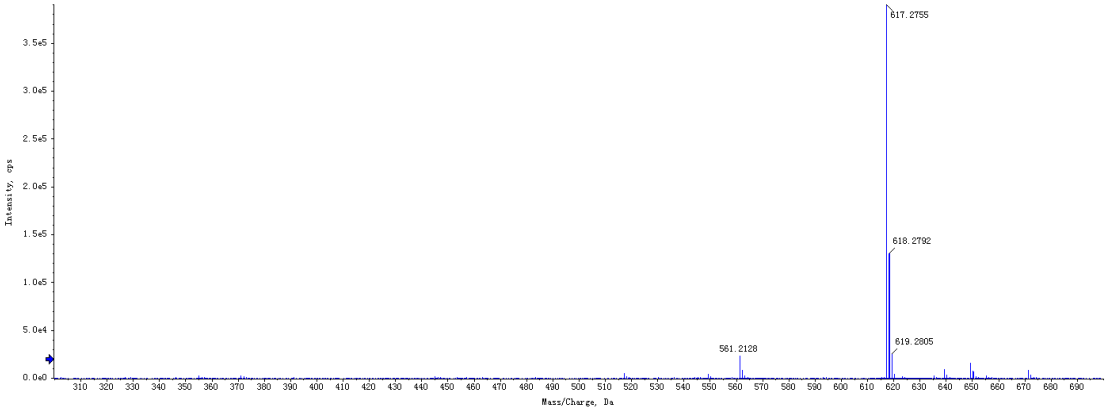
HRMS spectra of Compound **P18**



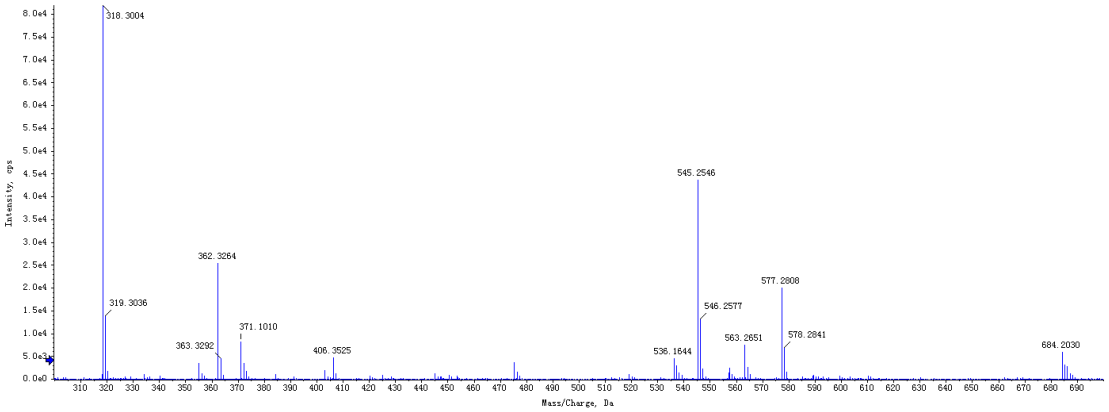
HRMS spectra of Compound **P19**



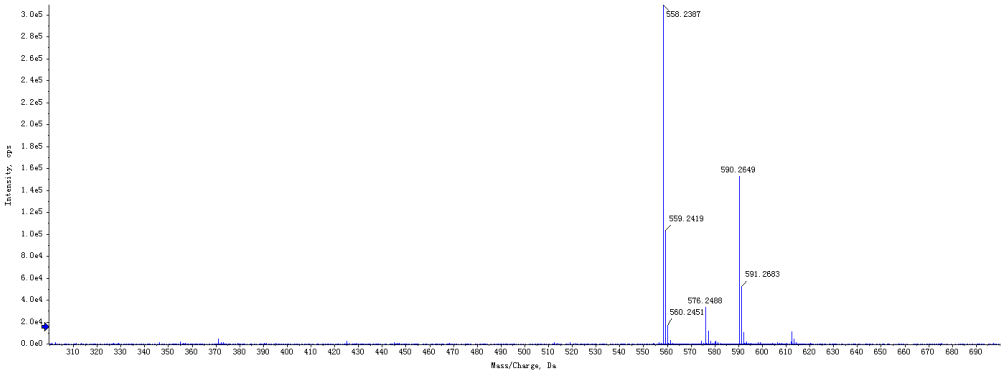
HRMS spectra of Compound **P20**



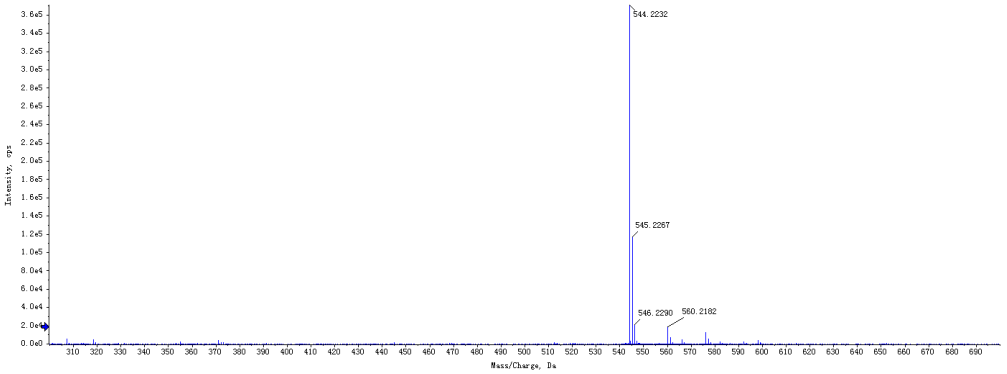
HRMS spectra of Compound **P21**



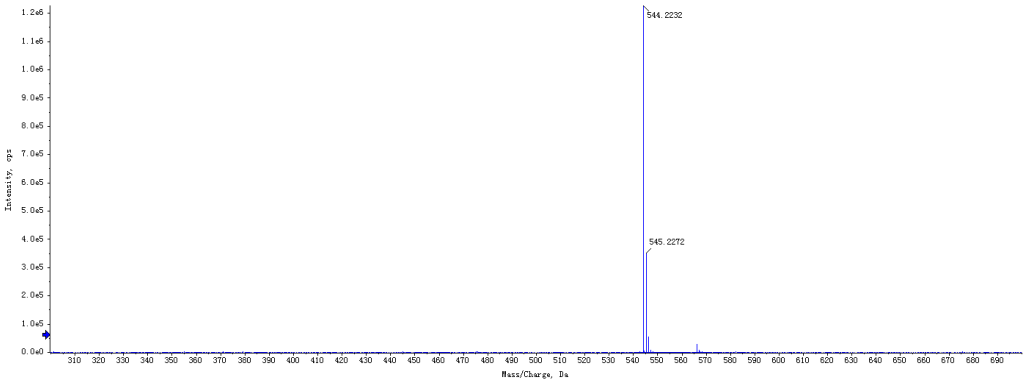
HRMS spectra of Compound **P22**



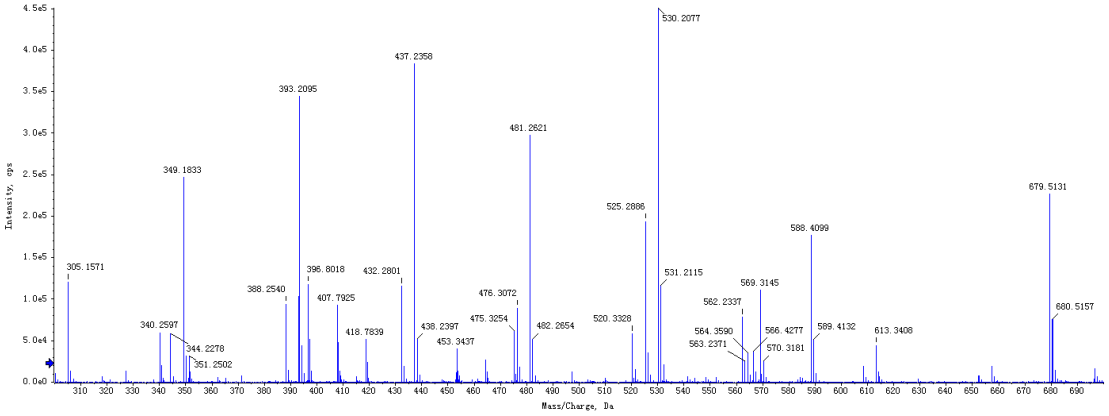
HRMS spectra of Compound **P23**



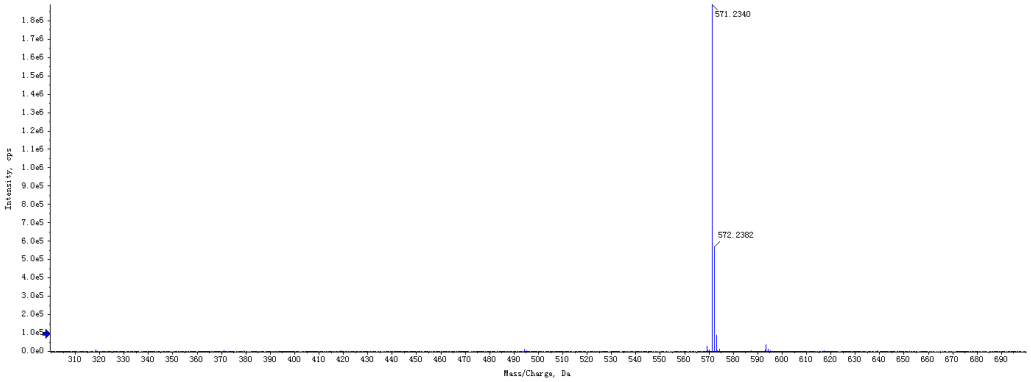
HRMS spectra of Compound **P24**



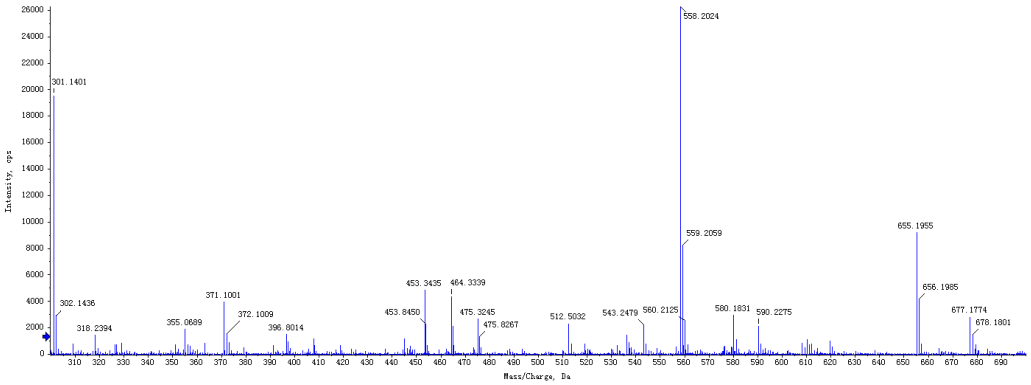
HRMS spectra of Compound **P25**



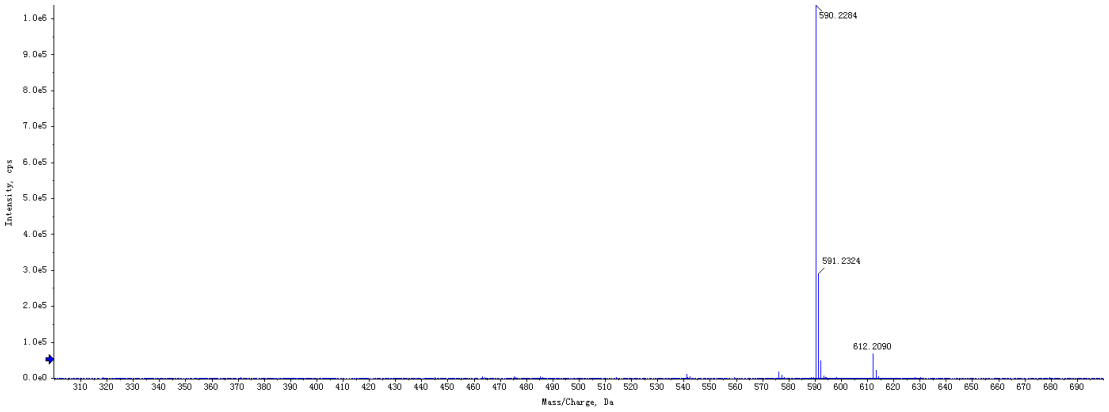
HRMS spectra of Compound **P26**



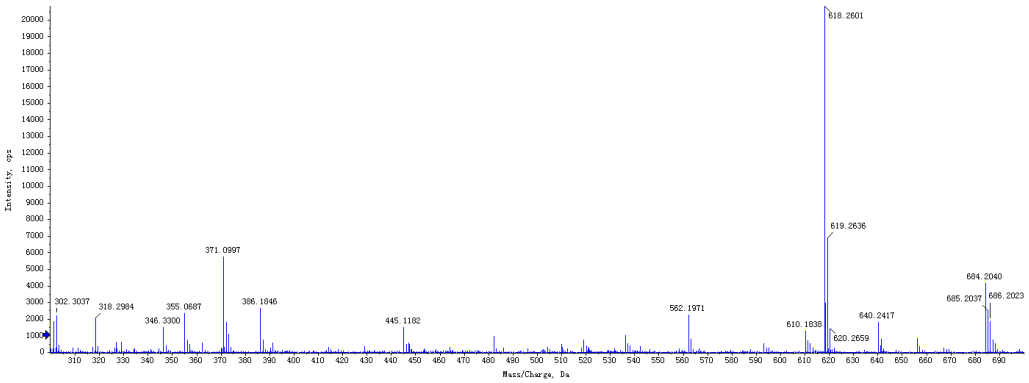
HRMS spectra of Compound **P27**



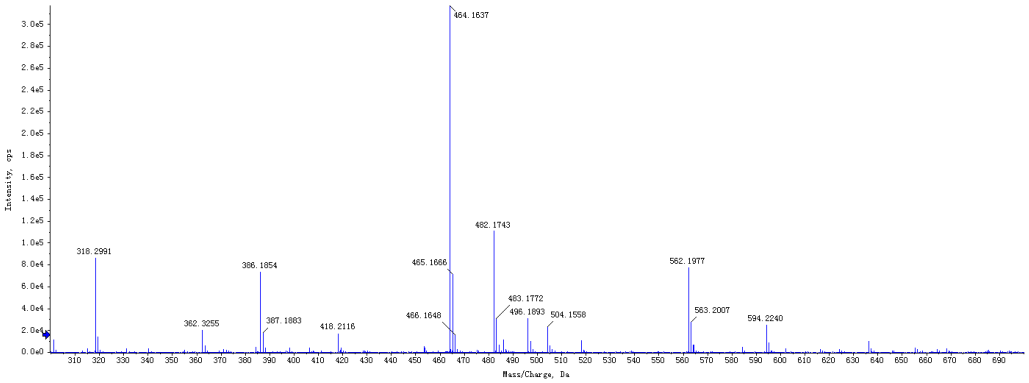
HRMS spectra of Compound **P28**



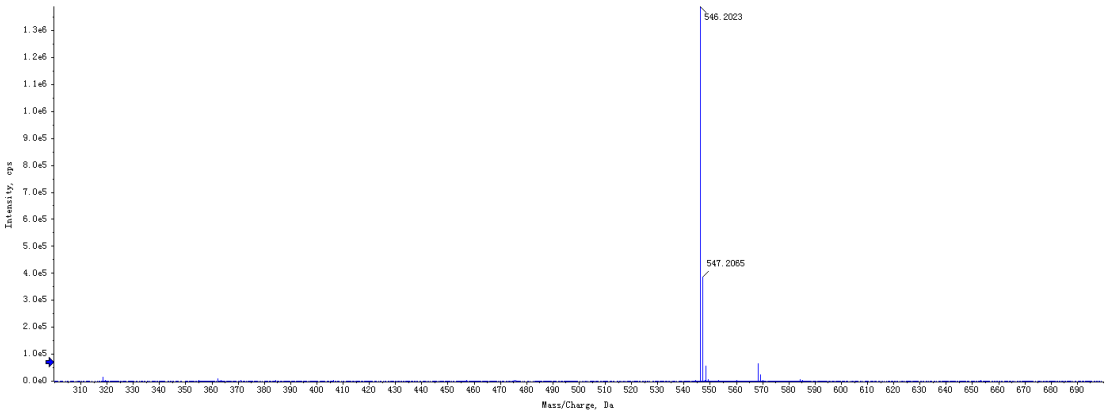
HRMS spectra of Compound **P29**



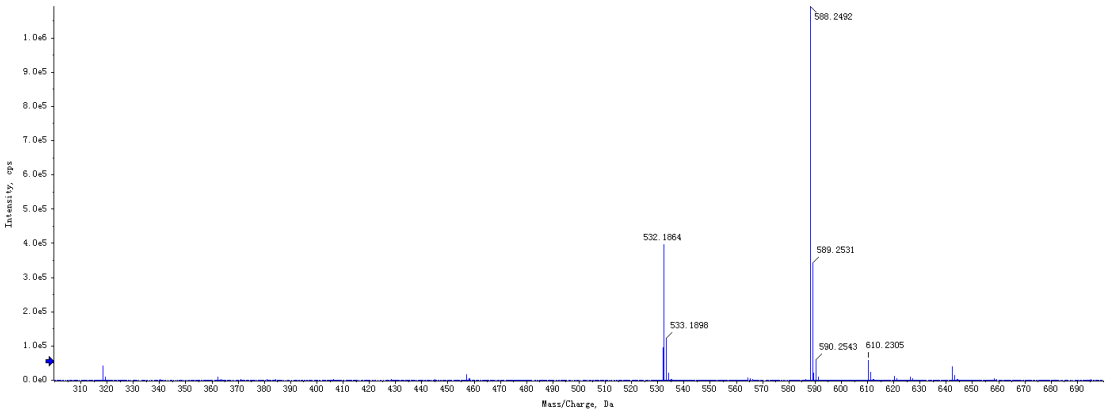
HRMS spectra of Compound **P30**



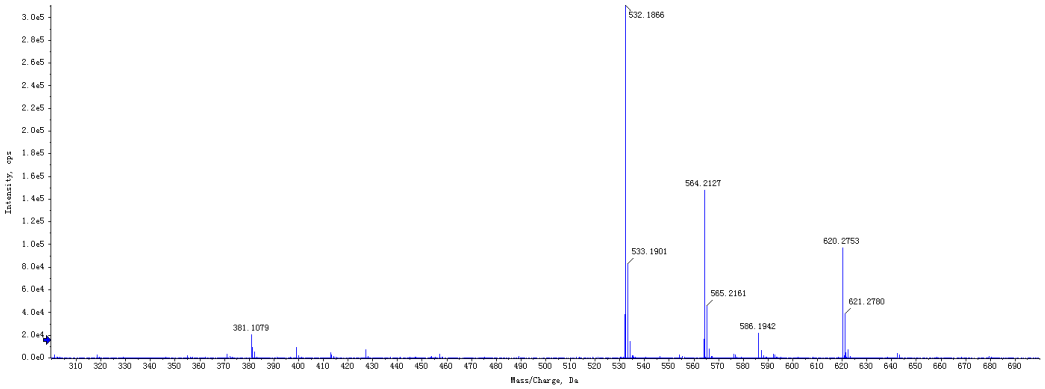
HRMS spectra of Compound **P31**



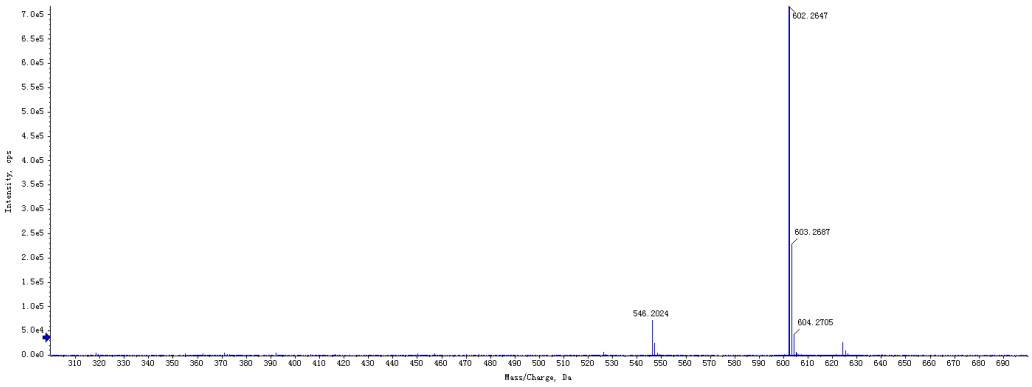
HRMS spectra of Compound **P32**



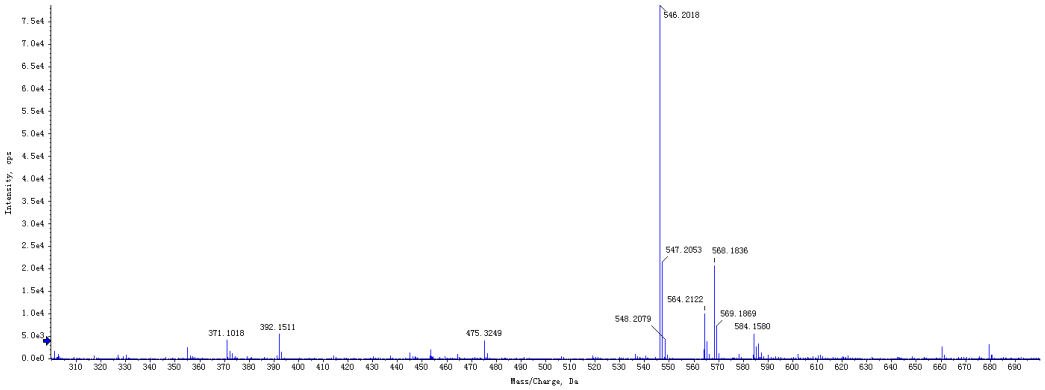
HRMS spectra of Compound **P33**



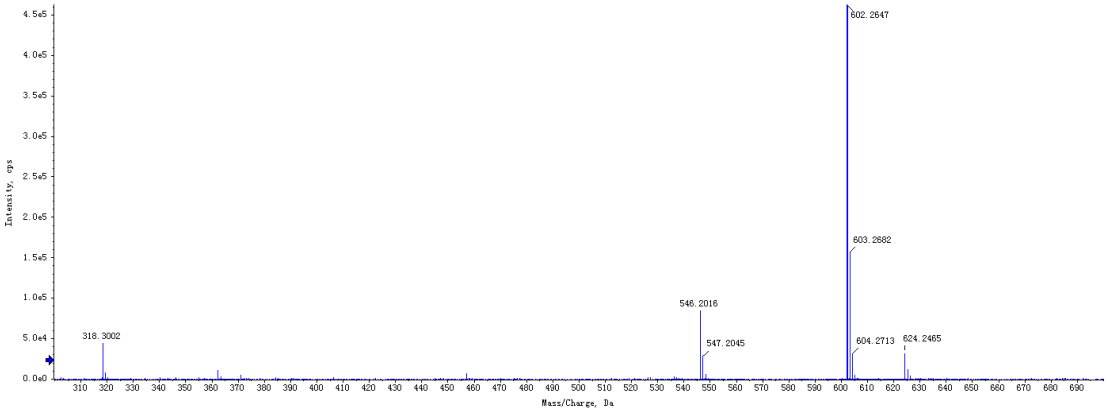
HRMS spectra of Compound **P34**



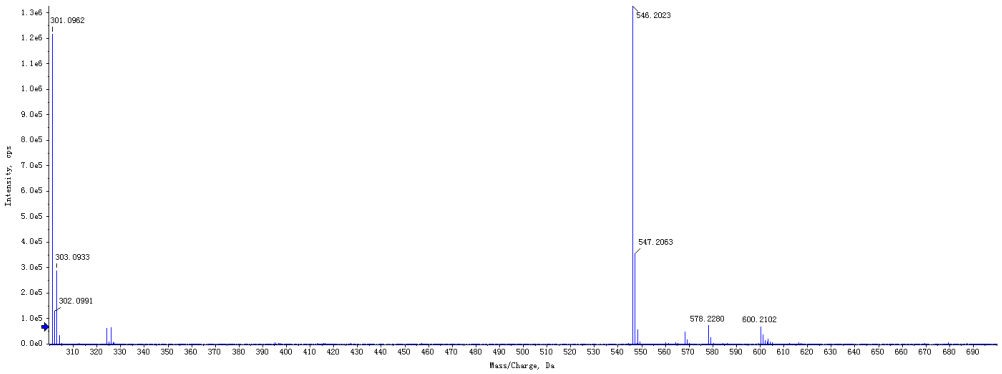
HRMS spectra of Compound **P35**



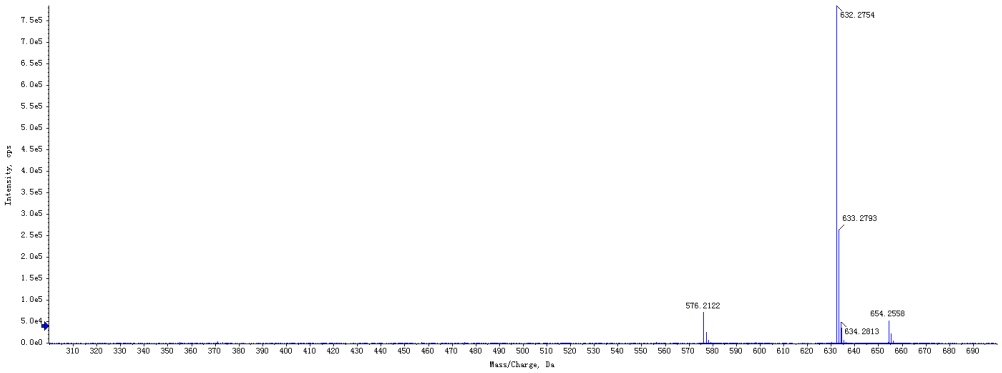
HRMS spectra of Compound **P36**



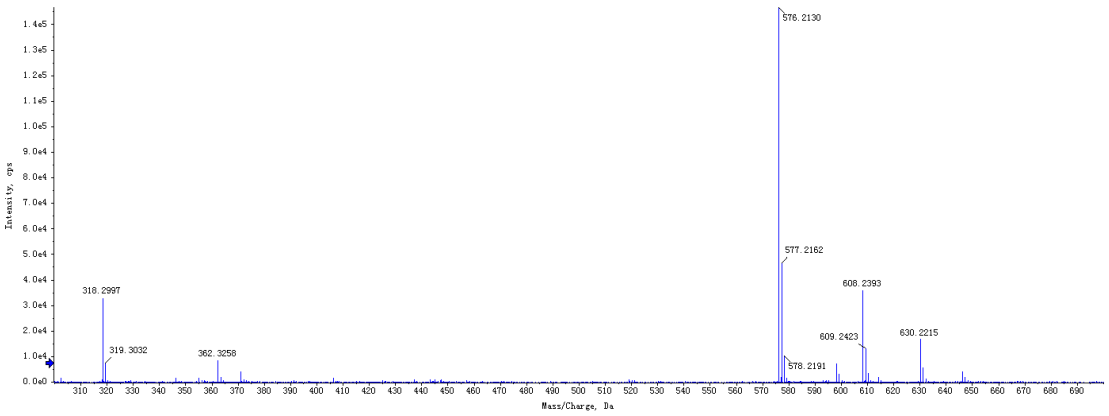
HRMS spectra of Compound **P37**



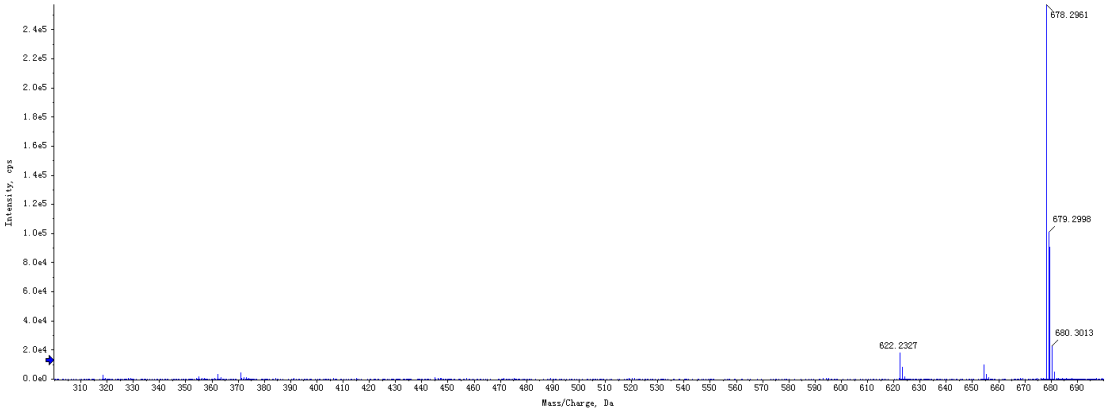
HRMS spectra of Compound **P38**



HRMS spectra of Compound **P39**



HRMS spectra of Compound **P40**



HRMS spectra of Compound **P41**