[Supporting Information]

Pd(II)-catalyzed C(sp^3)-H arylation of amino acid derivatives with click-triazoles as removable directing group

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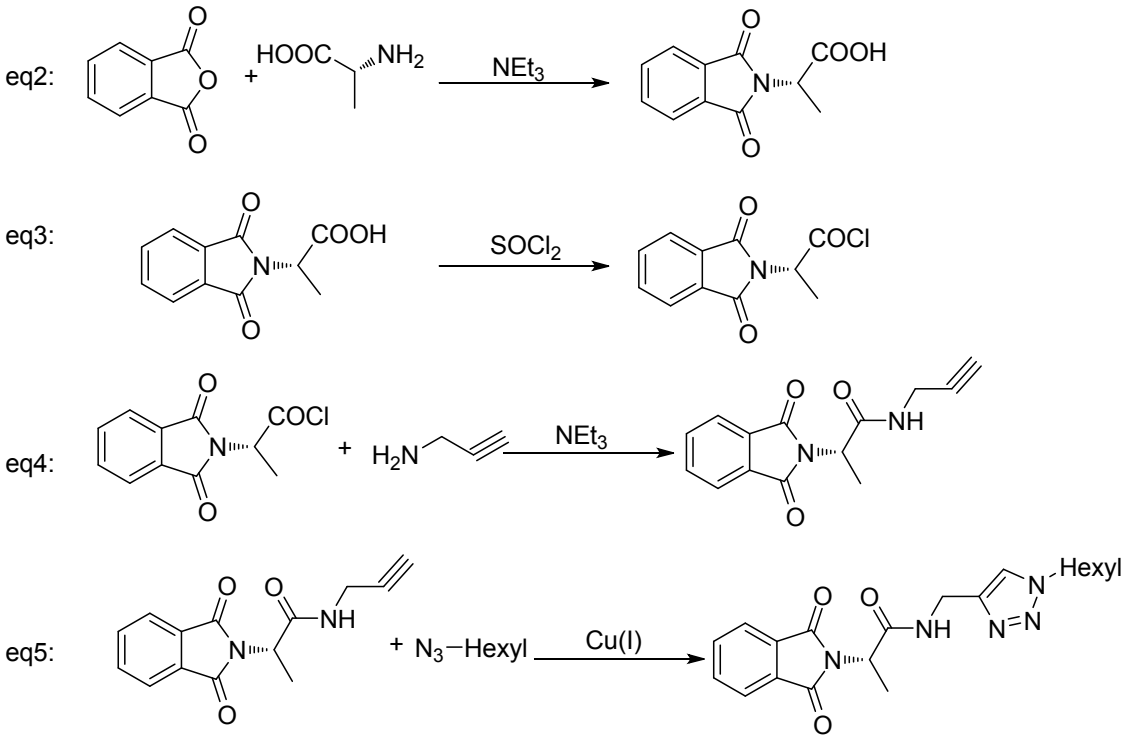
General Experimental

Unless otherwise noted all commercial materials were used without further purification. Solvents were used after purification directed by *Purification of Laboratory Chemicals, 6th Ed*. Column chromatography was performed with silica gel (300-400 mesh) produced by Qingdao Marine Chemical Factory, Qingdao (China). NMR spectra were recorded on Bruker AVANCE III 500MHz instrument with TMS as internal standard. Coupling constants were reported in Hertz (Hz).

Experimental Sections

General Procedure for Preparation of Amino Acid Derivatives

eq1: Hexyl—Br + NaN_3 ⟶ N_3—Hexyl



eq1: NaN_3(110.0 mol, 7.15 g) and 1-Bromohexane(100.0 mol, 16.51 g) were added in DMSO(200 mL) at room temperature and the reaction solutions were stirred overnight. When the reaction was finished, H_2O(50 mL) was added in the solution and extracted with methyl tertiary butyl ether(3×200 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the 1-azidohexane as a colorless oil(70%, 8.90 g).

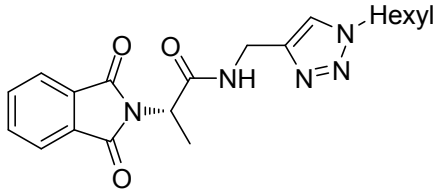
eq2: Amino acid (20.0 mmol), finely ground phthalic anhydride(20 mmol), toluene (45 mL), and Et_3N (2.0 mmol, 0.28 mL) were added to a 100 mL round bottom flask. After refluxing the reaction mixture overnight, concentrated hydrochloric acid (0.4 mL) and water (50 mL) were added in the solution. The crude product was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The organic solvent was removed and recrystallized by MeOH/H_2O to give the N-phthalimido-protected amino acid.

eq3: N-Phthalimido-protected amino acid (10.0 mmol), thionyl chloride (30.0 mmol) and four drops of DMF were added in toluene at 82 °C for 4 h. After the reaction, the excess of thionyl chloride and toluene was removed in vacuo, and the crude acyl chloride dissolved in dry CH_2Cl_2 (15 mL) used for next reaction.

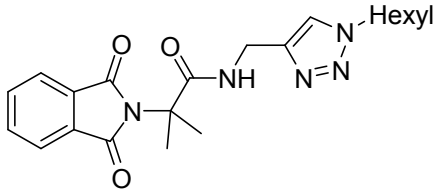
eq4: To a vigorously stirring solution of 2-propynylamine (10.0 mmol) and triethylamine(12.0 mmol) in CH_2Cl_2 (30 mL) at 0 °C, the crude acyl chloride in CH_2Cl_2 was added dropwise slowly. Then the reaction mixture was stirred for 5 h at rt. The reaction was quenched with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel(*n*-hexane/ethyl acetate (v/v 1:1)).

eq5: The alkyne amide compound(10.0 mmol), 1-azidohexane(20.0 mmol), $CuSO_4$(0.5 mmol), sodium ascorbate (1.0 mmol) were added in 30 mL acetone/H_2O(v/v 1:1) solution at N_2 atmosphere. The reaction mixture was stirred overnight at rt. After the reaction, ammonia hydroxide(10 mL) was added in the solution and extracted with ethyl acetate. The organic extracts was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel(*n*-hexane/ethyl acetate (v/v 1:2)).

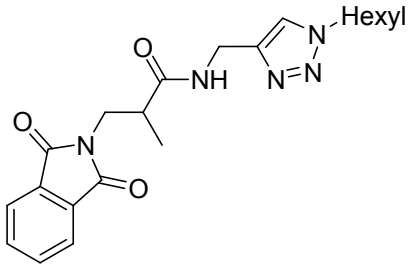
Characterization Data for Amino Acid Derivatives



1a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88(t, *J* = 6.5 Hz, 3H), 1.18(d, *J* = 3.0 Hz, 3H), 1.30(s, 6H), 1.85(t, *J* = 6.5 Hz, 2H), 4.25(t, *J* = 7.0 Hz, 2H), 4.44(d, *J* = 3.0 Hz, 2H), 4.92(q, *J* = 7.0 Hz, 1H), 7.47 (s, 1H), 7.59(s, 1H), 7.69-7.72(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H), 7.78-7.81(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 15.2, 22.4, 26.1, 30.1, 31.1, 35.1, 49.0, 50.5, 123.4, 132.0, 134.1, 167.7, 169.4. HRMS (ESI) m/z calcd for $C_{20}H_{25}N_5O_3$ $[M]^+$ 383.2030; found 383.2032.



2a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88(t, *J* = 6.8 Hz, 3H), 1.31 (s, 6H), 1.83(d, *J* = 5.0 Hz, 6H), 1.86(t, *J* = 6.7 Hz, 2H), 4.27(t, *J* = 7.3 Hz, 2H), 4.44(d, *J* = 6.0 Hz, 2H), 7.31 (d, *J* = 5.5 Hz, 1H), 7.64(s, 1H), 7.66-7.68(m, 2H), 7.71-7.72(m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 24.8, 26.1, 30.1, 31.1, 35.1, 50.5, 61.4, 122.7, 122.9, 132.0, 133.9, 144.5, 168.5, 173.3. HRMS (ESI) m/z calcd for $C_{21}H_{27}N_5O_3$ $[M]^+$ 397.2187; found 397.2174.



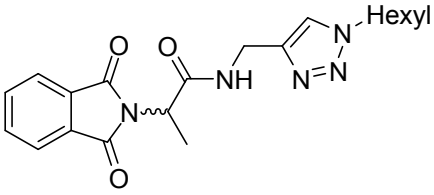
3a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.32(d, *J* = 7.0 Hz, 6H), 1.90(t, *J* = 7.0 Hz, 2H), 2.84(q, *J* = 7.0 Hz, 1H), 3.73(q, *J* = 7.0 Hz, 1H), 3.93(dd, J_1 = 13.5 Hz, J_2 = 7.5 Hz, 1H), 4.31 (t, *J* = 7.5 Hz, 2H), 4.41-4.50(m, 2H), 6.49(s, 1H). 7.55(s, 1H), 7.72(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H), 7.82(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.3, 15.6, 21.9, 25.8, 29.9, 30.8, 34.4, 39.4, 41.0, 50.2, 122.2, 123.3, 131.6, 134.3, 144.6, 168.4, 174.0. HRMS (ESI) m/z calcd for $C_{21}H_{27}N_5O_3$ $[M]^+$ 397.2187; found 397.2178.

Chiral HPLC Data

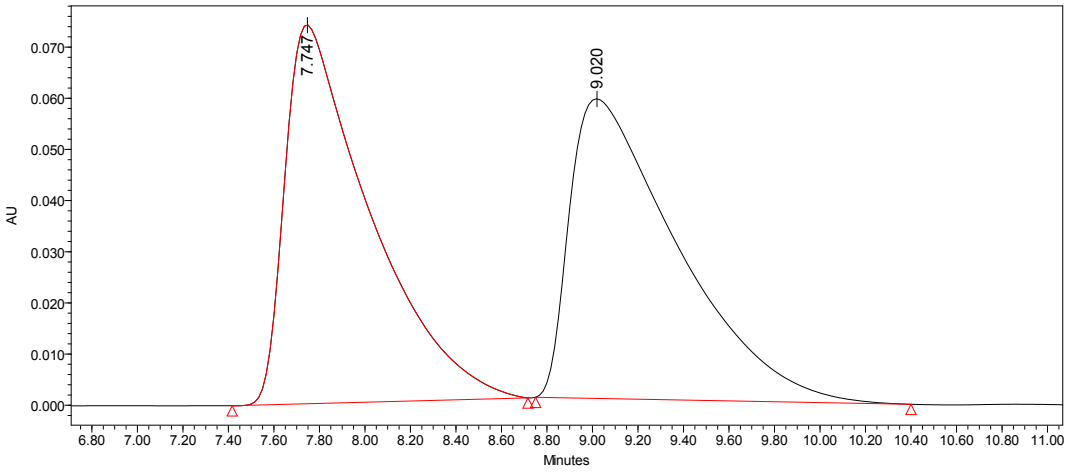
HPLC Conditions:

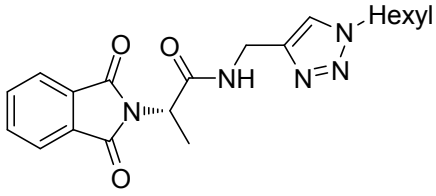
Chiral stationary phase: HPLC Chiralpack® AD-Hcolumn (*n*-hexane/isopropanol = 55:45,

0.70 mL/min) Wavelength = 254 nm tr = 8.973 min (major), >93%ee.

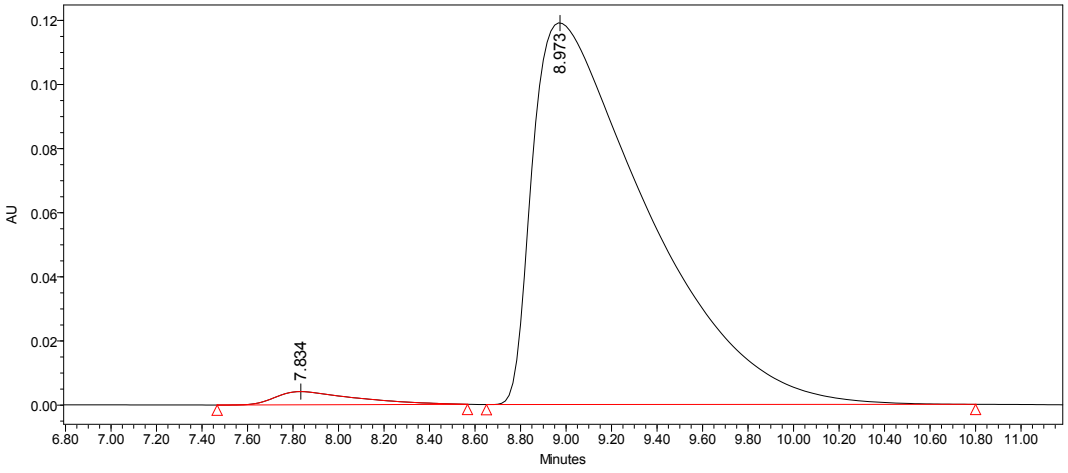


DL-1a





L-1a



Area% report for 1a:

	Retention Time	Area	% Area	Height	% Height
1	7.834	100234	2.34	4110	3.33
2	8.973	4175524	97.66	119134	96.67

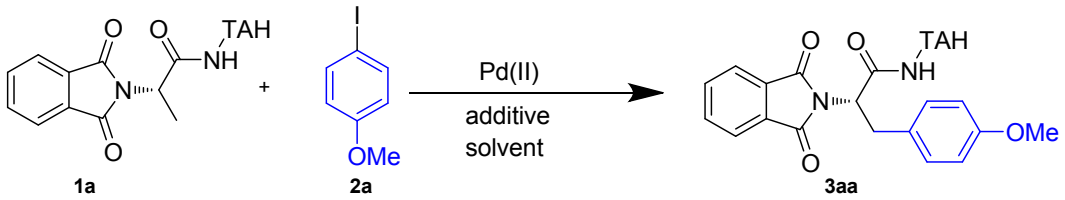
References

(1) Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997,** 413

(2) He, J.; Li, S. H.; Deng, Y. Q.; Fu, H. Y.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J. Q. *Science* **2014**, *343*, 1216.

(3) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed*. **2012,** *51*, 5188.

Optimization of Reaction Conditions



1a 2a 3aa

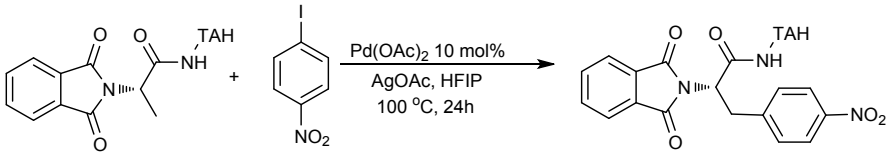
entry	catalyst	additive	solvent	temp.(°C)	time(h)	yield[b](%)
1	$Pd(OAc)_2$(10mol%)	AgOAc(0.3mol)	DCE	100	5	39
2	$Pd(OAc)_2$(10mol%)	AgOAc(0.3mol)	DMF	100	5	trace
3	$Pd(OAc)_2$(10mol%)	AgOAc(0.3mol)	*o*-xylene	100	5	ND[c]
4	$Pd(OAc)_2$(10mol%)	AgOAc(0.3mol)	toluene	100	5	ND
5	$Pd(OAc)_2$(10mol%)	AgOAc(0.3mol)	THF	100	5	ND
6	$Pd(OAc)_2$(10mol%)	AgOAc(0.3mol)	*t*-BuOH	100	5	24
7	$Pd(OAc)_2$(10mol%)	AgOAc(0.3mol)	*t*-AmylOH	100	5	31
8	**$Pd(OAc)_2$(10mol%)**	**AgOAc(0.3mol)**	**HFIP**	**100**	**5**	**93**
9	$Pd(TFA)_2$(10mol%)	AgOAc(0.3mol)	HFIP	100	5	50
10	$PdCl_2$(10mol%)	AgOAc(0.3mol)	HFIP	100	5	57
11	$Pd(PPh_3)_4$(10mol%)	AgOAc(0.3mol)	HFIP	100	5	trace
12	$Pd(OAc)_2$(10mol%)	Ag_2CO_3(0.3mol)	HFIP	100	5	27
13	$Pd(OAc)_2$(10mol%)	$AgNO_3$(0.3mol)	HFIP	100	5	15
14	$Pd(OAc)_2$(10mol%)	$AgSbF_6$(0.3mol)	HFIP	100	5	ND
15	$Pd(OAc)_2$(10mol%)	Ag_2O(0.3mol)	HFIP	100	5	ND
16	$Pd(OAc)_2$(5mol%)	AgOAc(0.3mol)	HFIP	100	24	56
17	$Pd(OAc)_2$(10mol%)	AgOAc(0.2mol)	HFIP	100	24	68
18	$Pd(OAc)_2$(10mol%)	AgOAc(0.3mol)	HFIP	100	24	76[d]
19	$Pd(OAc)_2$(10mol%)	AgOAc(0.3mol)	HFIP	80	24	42
20	$Pd(OAc)_2$(10mol%)	AgOAc(0.3mol)	HFIP	100	3	70

[a]The reactions were conducted with 0.20 mmol of **1a**, 10.0 mol% $Pd(OAc)_2$, 0.30 mmol of **2a**, 0.30 mmol of additive, 1.0 ml of solvent and stirred for 5h unless other noted. [b]Determined by **^{1}H NMR** spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c]ND= Not Detected. [d]0.2 mmol of **2a**.

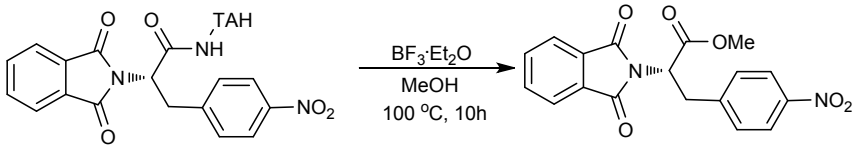
General Procedure for Pd(II)-Catalyzed C(sp^3)-H Arylation of Amino Acid Derivatives.

$Pd(OAc)_2$(0.04 mmol), AgOAc (0.60 mmol), alkyl iodine (0.60 mmol), **1** (0.40 mol), HFIP(2 mL) were introduced into a 15 mL seal tube equipped with a magnetic stirrer in air. The mixture was fiercely stirred at 100 °C for 5 h. After cooling to room temperature, the reaction was diluted with ethyl acetate (15 mL) and then filtered through a pad of Celite and washed by ethyl acetate (50 mL). The organic solvent was evaporated under vacuum and the crude product was purified by column chromatograph using silica gel with *n*-hexane/ethyl acetate (v/v 1:2) as eluent.

Gram-Scale Synthesis and Removal of the TAH group

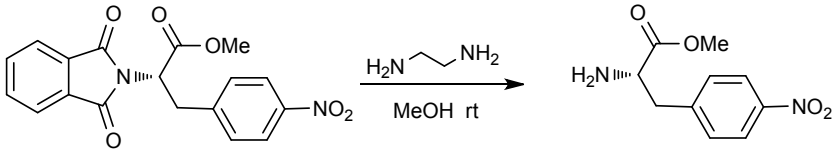


$Pd(OAc)_2$(0.30 mmol, 67.4mg), AgOAc(4.50 mmol, 0.75g), 1-iodo-4-nitrobenzene **2i**(4.50 mmol, 1.12g), **1a**(3.0 mol, 1.15g), HFIP(15 mL) were introduced into a 100 mL seal tube equipped with a magnetic stirrer in air. The mixture was fiercely stirred at 100 °C for 24 h. After cooling to room temperature, the reaction was diluted with ethyl acetate (40 mL) and then filtered through a pad of Celite and washed by ethyl acetate (100 mL). The organic solvent was evaporated under vacuum and the crude product was purified by column chromatograph using silica gel with *n*-hexane/ethyl acetate (v/v 1:2) as eluent, and **3ai** was obtained in 93% yield(1.41 g).

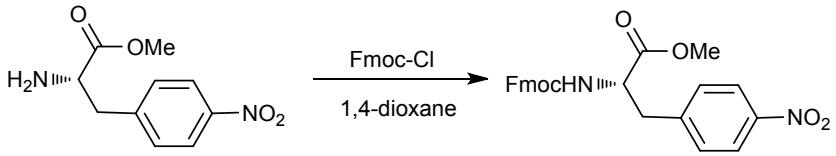


Substrate **3ai**(2.79 mmol, 1.41g), $BF_3{\cdot}Et_2O$ (20.30 mmol, 2.50 mL) were added in dry methanol(30 mL), and the solution was fiercely stirred at 100 °C for 10 h. After cooling to room temperature, Et_3N (30.10 mmol, 4.20 mL) was added dropwise to the reaction solution with stirring. The organic solvent was evaporated under vacuum and the crude product was purified by column chromatograph using silica gel with *n*-hexane/ethyl acetate (v/v 20:1 to 2:1) as eluent. The organic solvent was evaporated

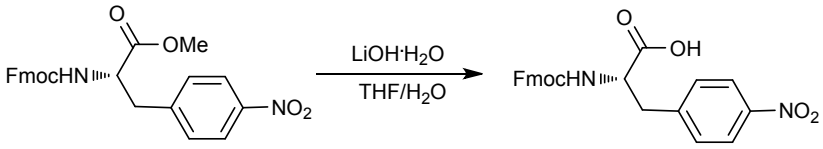
under vacuum and the product **4ai** was obtained of a colorless oil (86% yield, 0.86g).



Substrate **3ai** (2.43 mmol, 0.86 g) was dissolved in MeOH (44 mL), then 80% Ethylenediamine (10.0 mmol, 0.60g) was added. The reaction was stirred at room temperature for 20 h and the solvent was removed in vacuo. Saturated aqueous $NaHCO_3$ was added, and the solution extracted with ethyl acetate(3 × 50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated.

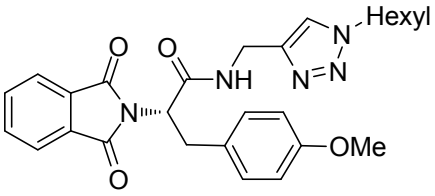


The residue was was dissolved in 1,4-dioxane(15 mL), and 10% aq. $NaHCO_3$(10 mL) was added. The mixture was cooled to 0 °C and Fmoc–Cl (2.52mmol, 0.65g) was added into the solution. After 1.5 h at 0 °C and 10 h at room temperature, H_2O and EtOAc was added to the reaction mixture. The aqueous layer was then extracted with EtOAc twice and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. the crude product was purify by column chromatography with *n*-hexane/ethyl acetate (v/v 3:1 to 2:1) as eluent.

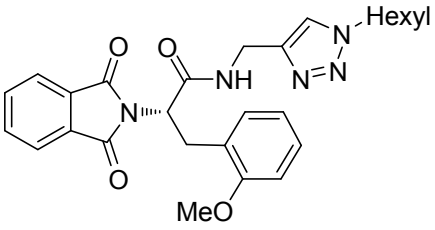


The substrate was dissolved in THF (10 mL). The solution was cooled to 0 °C, and a cold solution of $LiOH{\cdot}H_2O$ (3.0 mmol, 0.126g) in H_2O (10 mL) were added. The reaction was maintained at 0 °C for 1 hour. Then the reaction was acidified with HCl (1 N) and extracted with ethyl acetate(4 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using CH_2Cl_2/MeOH (10:1) as the eluent to afford the desired product **5ai** (49% for three steps, 0.51 g).

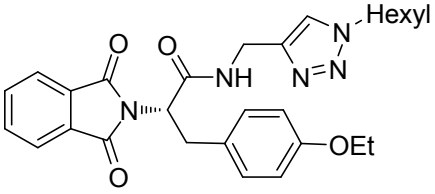
Characterization Data for Products



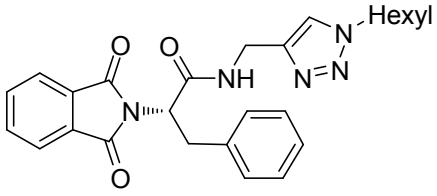
3aa (Table 2, entry 1): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(s, 3H), 1.32(s, 6H), 1.91(s, 2H), 3.43(t, J = 11.0 Hz, 1H), 3.53(d, J = 10.5 Hz, 1H), 3.68(s, 3H). 4.34(s, 2H), 4.57(s, 2H), 5.06(s, 1H), 6.67(d, J = 7.5 Hz, 2H), 7.03(d, J = 7.5 Hz, 2H), 7.66(s, 2H), 7.72(s, 2H), 7.79(s, 1H), 7.91(s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.3, 26.0, 29.8, 31.0, 33.7, 34.2, 51.5, 55.1, 55.2, 113.9, 123.4, 124.0, 128.6, 129.9, 131.6, 134.1, 158.3, 167.8, 169.1; HRMS (ESI) m/z calcd for $C_{27}H_{31}N_5O_4$ $[M]^+$ 489.2449; found 489.2467.



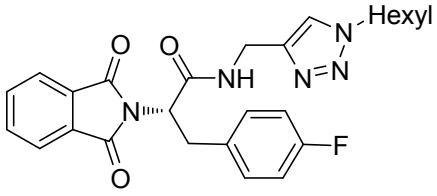
3ab (Table 2, entry 2): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, J = 6.5 Hz, 3H), 1.33(s, 6H), 1.92(s, 2H), 3.41(dd, J_1 = 13.5 Hz, J_2 = 10.5 Hz, 1H), 3.60(dd, J_1 = 13.5 Hz, J_2 = 4.5 Hz, 1H), 3.74(s, 3H), 4.35(t, J = 7.5 Hz, 2H), 4.61(s, 2H), 5.26(dd, J_1 = 10.5 Hz, J_2 = 5.5 Hz, 1H), 6.69(t, J = 7.0 Hz, 1H), 6.75(d, J = 7.5 Hz, 1H), 6.98(d, J = 6.0 Hz, 1H), 7.12(t, J = 8.0 Hz, 2H), 7.68(dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 3H), 7.75(t, J = 5.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 30.0, 30.4, 31.1, 34.8, 51.0, 52.4, 55.2, 110.2, 120.5, 123.3, 125.0, 128.5, 130.9, 131.7, 134.0, 157.5, 167.8, 169.2; HRMS (ESI) m/z calcd for $C_{27}H_{31}N_5O_4$ $[M]^+$ 489.2449; found 489.2459.



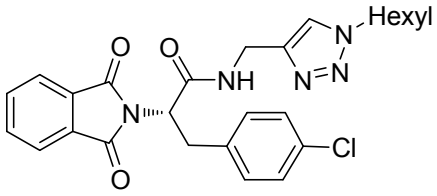
3ac (Table 2, entry 3): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, J = 7.0 Hz, 3H), 1.30-1.35(m, 9H), 1.88(t, J = 7.0 Hz, 2H), 3.43-3.54(m, 2H), 3.88-3.93(m, 2H), 4.30(t, J = 7.5 Hz, 2H), 4.47-4.56(m, 2H), 5.08(dd, J_1 = 11.0 Hz, J_2 = 6.0 Hz, 1H), 6.68(d, J = 8.5 Hz, 2H). 7.03(d, J = 8.5 Hz, 2H), 7.13(t, J = 5.5 Hz, 1H), 7.56(s, 1H), 7.68(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H), 7.75(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 14.7, 22.4, 26.1, 30.1, 31.1, 33.9, 35.1, 50.6, 55.5, 63.3, 114.6, 122.6, 123.5, 128.4, 129.9, 131.5, 134.2, 144.2, 157.8, 167.9, 168.8; HRMS (ESI) m/z calcd for $C_{28}H_{33}N_5O_4$ $[M]^+$ 503.2605; found 503.2627.



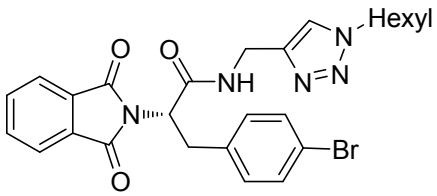
3ad (Table 2, entry 4): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, J = 6.5 Hz, 3H), 1.31(s, 6H), 1.86(dd, J_1 = 13.5 Hz, J_2 = 7.0 Hz, 2H), 3.49-3.62(m, 2H), 4.27(t, J = 7.5 Hz, 2H), 4.50(s, 2H). 5.12(q, J = 5.5 Hz, 1H), 7.10-7.16(m, 5H), 7.25(s, 1H), 7.58(s, 1H), 7.66(dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz, 2H), 7.73(dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 30.0, 31.1, 34.6, 51.0, 52.3, 123.4, 126.8, 128.5, 128.9, 131.6, 134.1, 136.8, 167.8, 168.9; HRMS (ESI) m/z calcd for $C_{26}H_{29}N_5O_3$ $[M]^+$ 459.2343; found 459.2320.



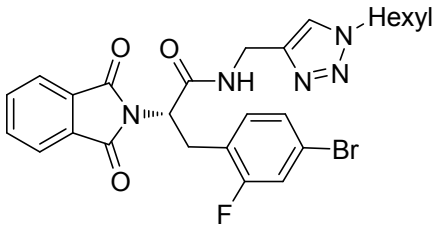
3ae (Table 2, entry 5): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, J = 5.5 Hz, 3H), 1.33(s, 6H), 1.90(s, 2H), 3.47-3.59(m, 2H), 4.32(t, J = 7.0 Hz, 2H), 4.54(s, 2H). 5.09(dd, J_1 = 11.5 Hz, J_2 = 5.0 Hz, 1H), 6.84(t, J = 8.0 Hz, 2H), 7.10(dd, J_1 = 8.5 Hz, J_2 = 6.0 Hz, 2H), 7.60(s, 1H), 7.70(t, J = 4.0 Hz, 2H), 7.75(t, J = 5.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.3, 26.1, 30.2, 31.1, 34.1, 35.3, 50.4, 55.2, 120.9, 122.2, 123.6, 130.6, 131.4, 131.8, 134.3, 135.9, 144.2, 167.8, 168.3. ^{19}F NMR (376 MHz, DMSO-d_6): δ -115.75; HRMS (ESI) m/z calcd for $C_{26}H_{28}FN_5O_3$ $[M]^+$ 477.2249; found 477.2267.



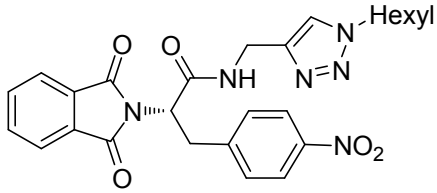
3af (Table 2, entry 6): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, J = 6.5 Hz, 3H), 1.33(s, 6H), 1.92(t, J = 7.0 Hz, 2H), 3.47-3.60(m, 2H), 4.35(t, J = 7.0 Hz, 2H), 4.52-4.62(m, 2H). 5.09(dd, J_1 = 11.5 Hz, J_2 = 5.0 Hz, 1H), 7.08(d, J = 8.5 Hz, 2H), 7.12(t, J = 8.5 Hz, 2H), 7.54(s, 1H), 7.67(s, 1H), 7.70(dd, J_1 = 6.0 Hz, J_2 = 3.5 Hz, 2H), 7.76(dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 29.9, 31.0, 33.9, 34.6, 51.2, 55.0, 123.3, 123.6, 128.7, 130.3, 131.5, 132.7, 134.4, 135.2, 143.6, 167.7, 168.6; HRMS (ESI) m/z calcd for $C_{26}H_{28}ClN_5O_3$ $[M]^+$ 493.1953; found 493.1939.



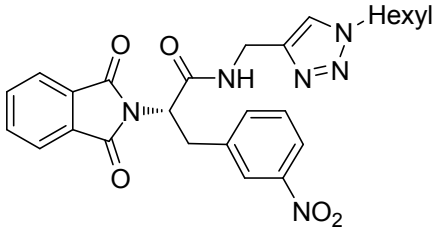
3ag (Table 2, entry 7): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, J = 6.0 Hz, 3H), 1.31(s, 6H), 1.86(s, 2H), 3.48-3.58(m, 2H), 4.27(t, J = 6.5 Hz, 2H), 4.47(s, 2H). 5.09(dd, J_1 = 11.5 Hz, J_2 = 5.0 Hz, 1H), 7.01(d, J = 8.5 Hz, 2H), 7.26(s, 1H), 7.52(s, 1H), 7.56(s, 1H), 7.68(t, J = 3.0 Hz, 2H), 7.73(t, J = 6.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.3, 26.1, 30.1, 31.1, 34.1, 35.1, 50.5, 55.0, 120.8, 123.5, 130.6, 131.4, 131.6, 134.2, 135.8, 167.7, 168.4; HRMS (ESI) m/z calcd for $C_{26}H_{28}BrN_5O_3$ $[M]^+$ 537.1448; found 537.1451.



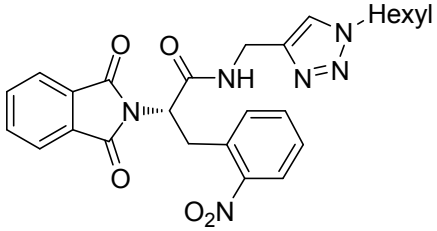
3ah (Table 2, entry 8): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, J = 5.5 Hz, 3H), 1.32(s, 6H), 1.87(s, 2H), 3.50-3.61(m, 2H), 4.28(t, J = 7.0 Hz, 2H), 4.50(dd, J_1 = 6.0 Hz, J_2 = 1.5 Hz, 2H). 5.12(dd, J_1 = 11.5 Hz, J_2 = 6.0 Hz, 1H), 6.98(t, J = 8.0 Hz, 2H), 7.06(dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.12(dd, J_1 = 9.0 Hz, J_2 = 1.5 Hz, 1H), 7.53(s, 1H), 7.71(dd, J_1 = 5.5 Hz, J_2 = 2.0 Hz, 2H), 7.78(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.2, 28.4, 30.2, 31.2, 35.3, 50.5, 53.6, 119.0, 119.3, 122.3, 123.6, 127.5, 131.5, 132.3, 132.4, 134.4, 167.6, 168.0. ^{19}F NMR (376 MHz, DMSO-d_6): δ -114.56; HRMS (ESI) m/z calcd for $C_{26}H_{27}BrFN_5O_3$ $[M]^+$ 555.1354; found 555.1365.



3ai (Table 2, entry 9): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, J = 6.0 Hz, 3H), 1.32(s, 6H), 1.86(s, 2H), 3.65-3.74(m, 2H), 4.26(t, J = 7.0 Hz, 2H), 4.48(s, 2H). 5.16(d, J = 7.5 Hz, 1H), 7.33(d, J = 8.5 Hz, 2H), 7.56(s, 2H), 7.70(s, 2H), 7.73(s, 2H), 8.02(d, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.5, 26.1, 30.2, 31.2, 34.6, 35.2, 50.7, 54.7, 123.7, 123.8, 129.9, 131.4, 134.6, 144.8, 147.1, 167.7, 168.0; HRMS (ESI) m/z calcd for $C_{26}H_{28}N_6O_5$ $[M]^+$ 504.2194; found 504.2186.

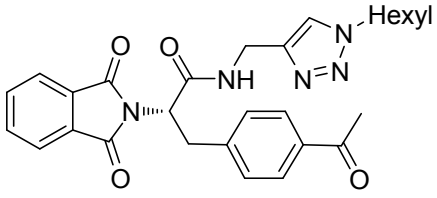


3aj (Table 2, entry 10): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88(t, J = 7.5 Hz, 3H), 1.29(s, 6H), 1.83(t, J = 6.5 Hz, 2H), 3.63-3.78(m, 2H), 4.24(t, J = 7.0 Hz, 2H), 4.43(t, J = 5.0 Hz, 2H). 5.15(q, J = 5.5 Hz, 1H), 7.34(t, J = 7.5 Hz, 1H), 7.50(d, J = 7.0 Hz, 1H), 7.51(s, 1H), 7.66(dd, J_1 = 6.0 Hz, J_2 = 3.5 Hz, 2H), 7.71(dd, J_1 = 6.0 Hz, J_2 = 3.5 Hz, 2H), 7.97(dd, J_1 = 9.0 Hz, J_2 = 1.5 Hz, 1H), 8.02(s, 1H), 8.05(s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 30.1, 31.1, 34.3, 34.8, 50.7, 54.7, 122.0, 123.5, 123.9, 129.5, 131.4, 134.3, 135.2, 139.3, 148.2, 167.7, 168.1; HRMS (ESI) m/z calcd for $C_{26}H_{28}N_6O_5$ $[M]^+$ 504.2194; found 504.2217.

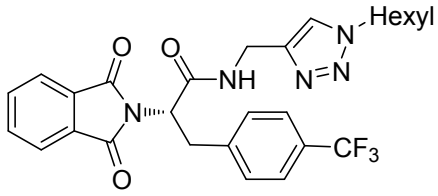


3ak (Table 2, entry 11): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, J = 6.5 Hz, 3H), 1.32(s, 6H), 1.89(t, J = 5.5 Hz, 2H), 3.67-3.73(m, 1H), 4.05(dd, J_1 =

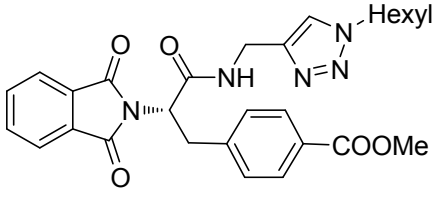
14.5 Hz, J_2 = 4.5 Hz, 1H), 4.30(t, J = 7.5 Hz, 2H), 4.54(d, J = 5.5 Hz, 2H), 5.31(dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz, 1H), 6.90(s, 1H), 7.21(dd, J_1 = 7.5 Hz, J_2 = 2.5 Hz, 1H), 7.33-7.35(m, 2H), 7.57(s, 1H), 7.71(dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 2H), 7.77(dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 2H), 8.00 (dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, , 22.4, 26.1, 30.1, 31.1, 32.6, 35.2, 50.53, 53.5, 122.6, 123.4, 125.4, 128.3, 131.5, 132.8, 132.9, 133.3, 134.2, 149.0, 167.7, 168.0; HRMS (ESI) m/z calcd for $C_{26}H_{28}N_6O_5$ $[M]^+$ 504.2194; found 504.2170.



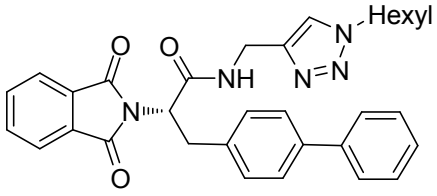
3al (Table 2, entry 12): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, J = 6.5 Hz, 3H), 1.30(s, 6H), 1.85(s, 2H), 2.49(s, 3H), 3.59-3.68(m, 2H), 4.25(t, J = 7.5 Hz, 2H), 4.46(t, J = 15.0 Hz, 2H), 5.15(q, J = 5.5 Hz, 1H), 7.23(d, J = 7.5 Hz, 2H), 7.55(s, 2H), 7.66(dd, J_1 = 6.0 Hz, J_2 = 3.5 Hz, 2H), 7.71(dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz, 2H), 7.74(d, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 26.5, 30.1, 31.1, 34.6, 35.1, 50.4, 54.8, 123.5, 128.6, 129.1, 131.4, 134.2, 135.8, 142.6, 167.8, 168.3, 197.7; HRMS (ESI) m/z calcd for $C_{28}H_{31}N_5O_4$ $[M]^+$ 501.2449; found 501.2465.



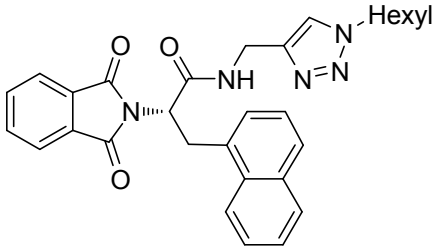
3am (Table 2, entry 13): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, J = 6.5 Hz, 3H), 1.32(s, 6H), 1.87(t, J = 7.0 Hz, 2H), 3.59-3.69(m, 2H), 4.27(t, J = 7.0 Hz, 2H), 4.49(t, J = 5.0 Hz, 2H), 5.15(q, J = 5.5 Hz, 1H), 7.26(s, 1H), 7.32(s, 1H), 7.42(d, J = 8.0 Hz, 2H), 7.54(s, 1H), 7.69(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H), 7.75(dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 30.1, 31.1, 34.4, 35.1, 50.4, 54.9, 123.5, 123.7, 128.2, 128.5, 129.2, 131.4, 134.3, 134.5, 167.8, 168.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ -62.99; HRMS (ESI) m/z calcd for $C_{27}H_{28}F_3N_5O_3$ $[M]^+$ 527.2217; found 527.2234.



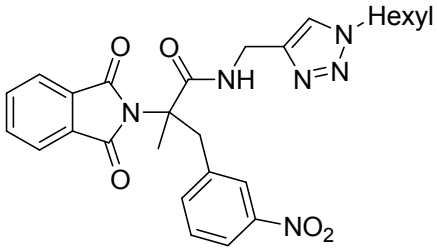
3an (Table 2, entry 14): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87(t, J = 6.5 Hz, 3H), 1.27(s, 6H), 1.80(s, 2H), 3.56-3.68(m, 2H), 3.80(s, 3H), 4.18(t, J = 7.5 Hz, 2H), 4.38(s, 2H), 5.13(dd, J_1 = 11.0 Hz, J_2 = 5.0 Hz, 1H), 7.17(d, J = 8.5 Hz, 2H), 7.54(s, 1H), 7.60(t, J = 4.0 Hz, 2H), 7.65(t, J = 4.0 Hz, 2H), 7.78(d, J = 8.0 Hz, 2H), 8.07(s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 22.3, 26.1, 30.0, 31.1, 34.6, 35.0, 50.4, 51.9, 54.8, 122.7, 123.3, 128.7, 128.9, 129.7, 131.5, 134.0, 142.5, 144.4, 166.7, 167.7, 168.3; HRMS (ESI) m/z calcd for $C_{28}H_{31}N_5O_5$ $[M]^+$ 517.2398; found 517.2399.



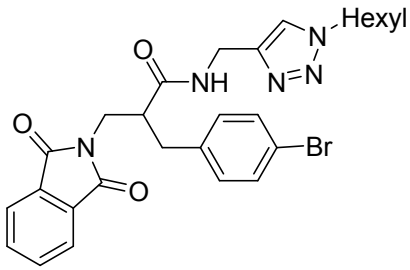
3ao (Table 2, entry 15): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91(t, J = 6.5 Hz, 3H), 1.35(s, 6H), 1.99(s, 2H), 3.52(t, J = 11.0 Hz, 1H), 3.70(dd, J_1 = 13.0 Hz, J_2 = 4.5 Hz, 1H), 4.46(d, J = 6.0 Hz, 2H), 4.69(d, J = 13.0 Hz, 1H), 4.79(d, J = 13.0 Hz, 1H), 5.20(dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz, 1H), 7.22(d, J = 8.0 Hz, 2H), 7.30(t, J = 7.5 Hz, 1H), 7.36-7.40(m, 4H), 7.48(d, J = 7.5 Hz, 2H), 7.66(dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 2H), 7.75(dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 2H), 8.03(s, 1H), 8.38(s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.2, 30.1, 31.1, 34.3, 35.1, 50.6, 55.3, 122.7, 123.5, 126.9, 127.2, 128.7, 129.3, 131.5, 134.2, 135.8, 139.6, 140.5, 144.2, 167.8, 168.7; HRMS (ESI) m/z calcd for $C_{32}H_{33}N_5O_3$ $[M]^+$ 535.2656; found 535.2663.



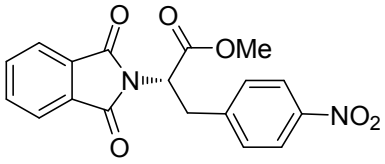
3ap (Table 2, entry 16): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(t, J = 6.5 Hz, 3H), 1.30(s, 6H), 1.83(t, J = 7.5 Hz, 2H), 3.84(dd, J_1 = 15.0 Hz, J_2 = 11.0 Hz, 1H), 4.18-4.24(m, 2H), 4.40-4.50(m, 2H). 5.30(dd, J_1 = 10.5 Hz, J_2 = 5.0 Hz, 1H), 7.15(t, J = 3.0 Hz, 2H), 7.43-7.53(m, 4H), 7.61-7.67(m, 5H), 7.78(d, J = 7.5 Hz, 1H), 8.09(d, J = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 25.9, 29.6, 30.0, 31.7, 33.5, 52.5, 54.1, 123.2, 123.4, 125.1, 125.8, 126.4, 127.3, 127.8, 128.9, 131.6, 132.9, 133.8, 134.1, 167.7, 169.3; HRMS (ESI) m/z calcd for $C_{30}H_{31}N_5O_3$ $[M]^+$ 509.2500; found 509.2510.



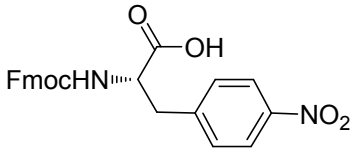
3bj: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89(dd, J_1 = 10.0 Hz, J_2 = 6.5 Hz, 3H), 1.30(d, J = 10.0 Hz, 6H), 1.83(s, 3H), 1.86(d, J = 9.0 Hz, 2H), 3.40-3.64(m, 1H), 3.89-4.03(m, 1H), 4.12-4.28(m, 3H), 4.35-4.42(m, 1H), 7.30-7.37(m, 1H), 7.54-7.61(m, 3H), 7.65-7.68(m, 3H), 7.69-7.86(m, 1H), 8.00-8.04(m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 24.8, 26.1, 30.1, 31.2, 34.9, 39.7, 40.5, 50.4, 122.3, 123.0, 123.1, 125.6, 129.0, 131.4, 134.0, 134.3, 136.9, 148.0, 168.5, 168.9; HRMS (ESI) m/z calcd for $C_{27}H_{30}N_6O_5$ $[M]^+$ 518.2350; found 518.2363.



3cg: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90(t, J = 7.0 Hz, 3H), 1.34(t, J = 5.5 Hz, 6H), 1.90(s, 2H), 2.83(dd, J_1 = 13.0 Hz, J_2 = 4.0 Hz, 1H), 3.02(dd, J_1 = 14.0 Hz, J_2 = 10.0 Hz, 1H), 3.11(s, 1H), 3.83(dd, J_1 = 14.0 Hz, J_2 = 5.0 Hz, 1H), 3.96(dd, J_1 = 14.0 Hz, J_2 = 7.5 Hz, 1H), 4.44(d, J = 6.5 Hz, 4H), 7.10(d, J = 7.5 Hz, 2H), 7.31(d, J = 8.5 Hz, 2H), 7.69(q, J = 3.0 Hz, 3H), 7.75(dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.3, 25.9, 29.5, 31.0, 32.3, 35.6, 40.0, 47.0, 53.3, 120.2, 123.3, 130.9, 131.4, 131.9, 134.1, 137.3, 168.4, 173.1; HRMS (ESI) m/z calcd for $C_{27}H_{30}BrN_5O_3$ $[M]^+$ 551.1604; found 551.1608.



4ai: ^{1}H NMR (500 MHz, $CDCl_3$): 3.64-3.73(m, 2H), 3.80(s, 3H). 5.19(dd, J_1 = 11.0 Hz, J_2 = 6.0 Hz, 1H), 7.36(d, J = 8.5 Hz, 2H), 7.73(q, J = 2.5 Hz, 2H), 7.80(q, J = 2.5 Hz, 2H), 8.07(d, J = 9.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.7, 51.5, 53.0, 123.7, 123.9, 129.9, 131.4, 134.4, 144.5, 147.1, 167.3, 168.7.



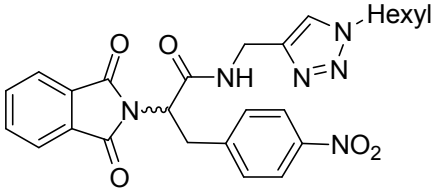
5ai: ^{1}H NMR (500 MHz, DMSO-d_6): 3.02(dd, J_1 = 14.0 Hz, J_2 = 11.0 Hz, 1H), 3.25(dd, J_1 = 14.5 Hz, J_2 = 4.5 Hz, 1H), 4.15-4.30(m, 4H), 7.26-7.31(m, 2H), 7.40(t, J = 8.0 Hz, 2H), 7.55(d, J = 9.0 Hz, 2H), 7.62(dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 2H), 7.82(d, J = 8.5 Hz, 1H), 7.88(d, J = 7.5 Hz, 2H), 8.15(d, J = 8.5 Hz, 2H), 12.9(s, 1H).. ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.2, 45.6, 54.7, 65.6, 120.0, 123.2, 125.1, 127.0, 127.5, 130.4, 140.7, 143.6, 143.7, 146.2, 146.3, 155.9, 172.7.

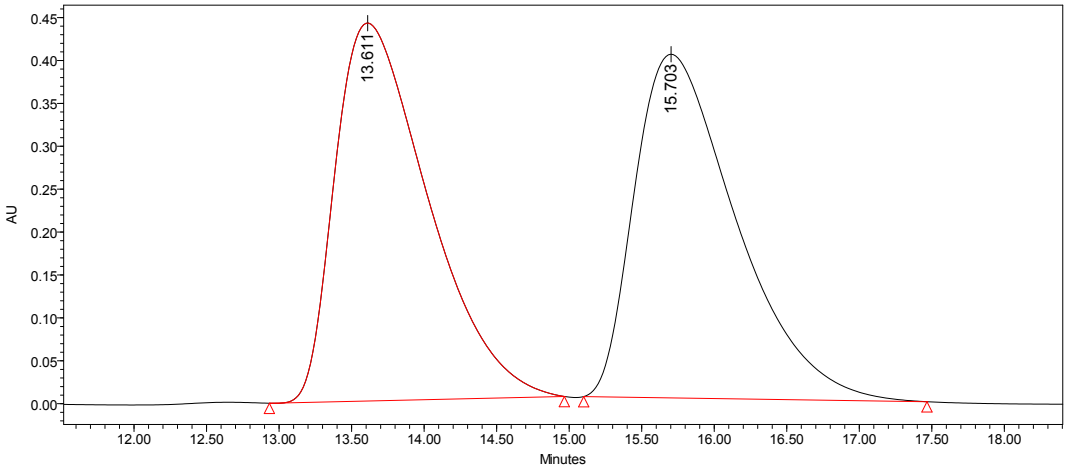
Chiral HPLC Data

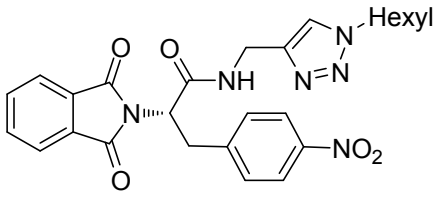
HPLC Conditions:

Chiral stationary phase: HPLC Chiralpack® AD-Hcolumn (*n*-hexane/isopropanol = 55:45, 0.70 mL/min) Wavelength = 254 nm tr = 13.649 min (major), >96% ee.

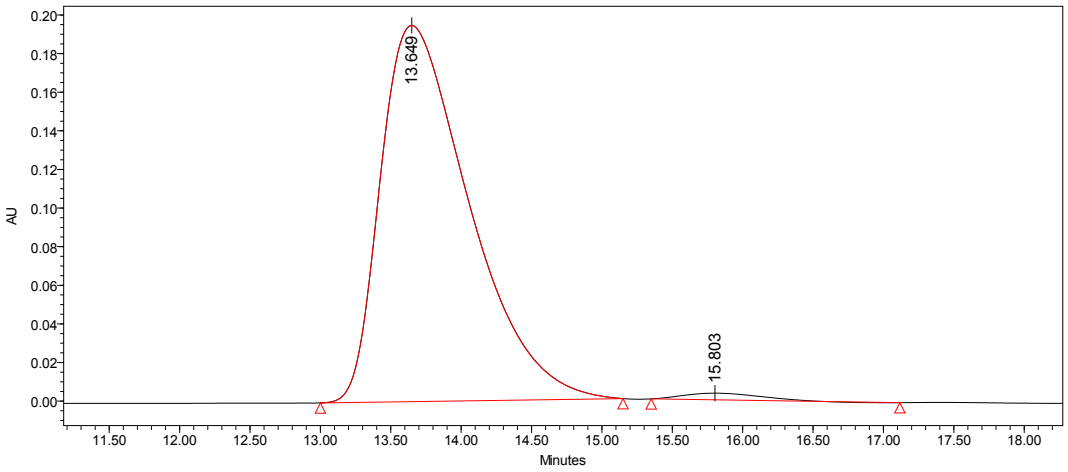
DL-3ai







L-3ai

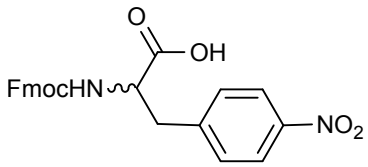


Area% report for **3ai**:

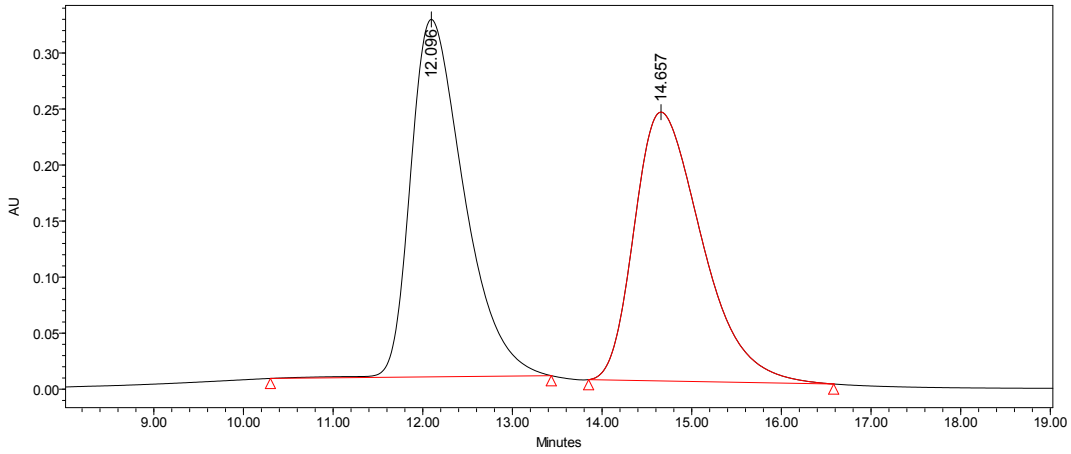
	Retention Time	Area	% Area	Height	% Height
1	13.649	8539415	98.41	194855	98.25
2	15.803	138383	1.59	3462	1.75

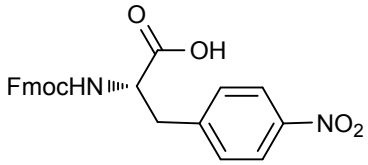
HPLC Conditions:

Chiral stationary phase: HPLC Chiralpack® AD-Hcolumn (*n*-hexane/isopropanol = 50:50, 0.60 mL/min) Wavelength = 254 nm tr = 13.649 min (major), >93% ee.

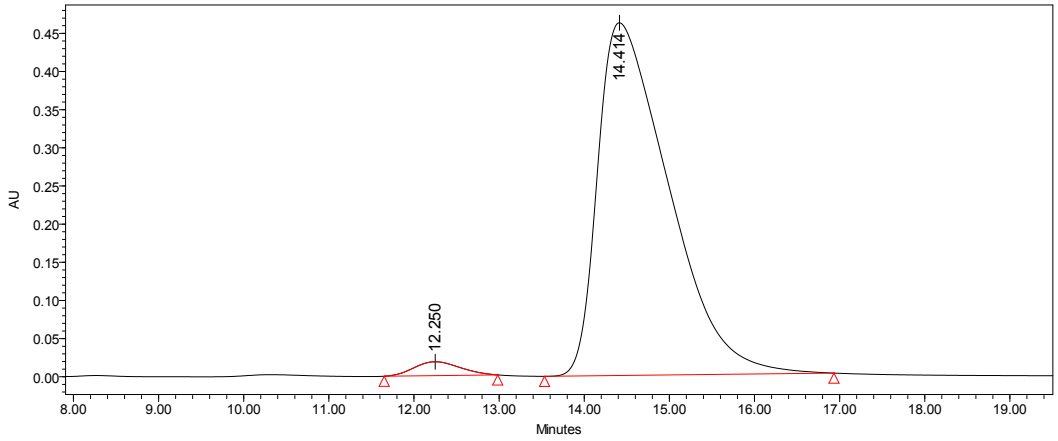


DL-5ai





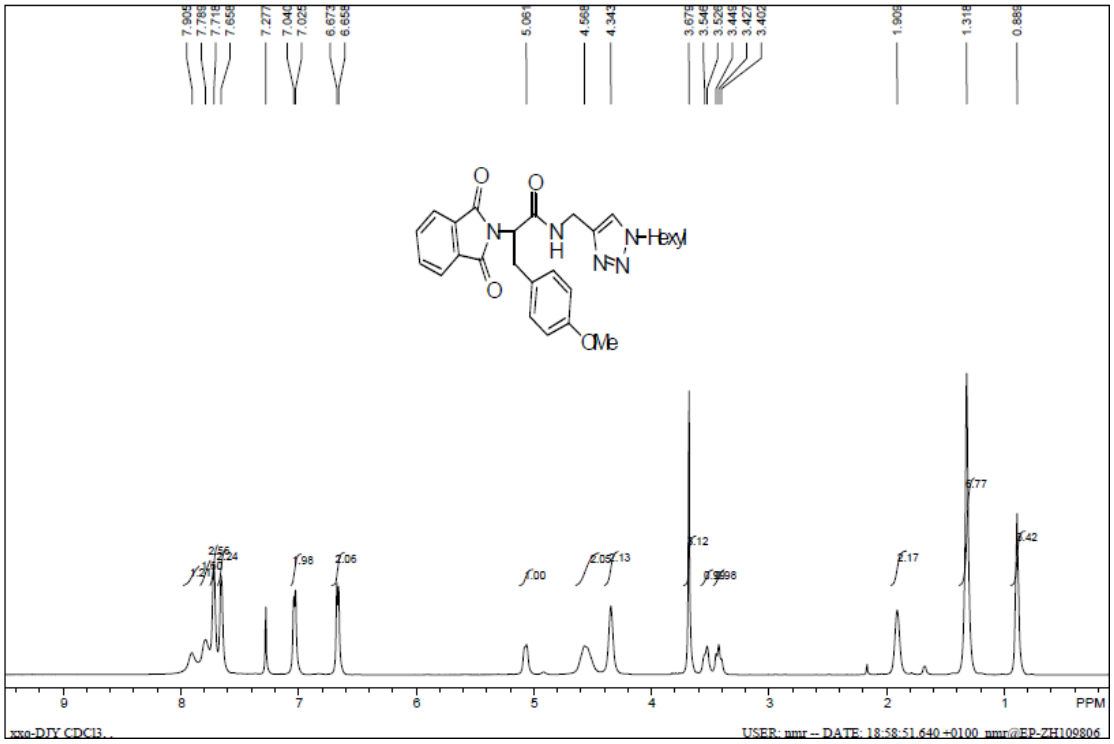
L-5ai



Area% report for **5ai**:

	Retention Time	Area	% Area	Height	% Height
1	12.250	684089	2.49	16770	3.49
2	14.414	26801076	97.51	463730	96.51

Figure 1. ^{1}H NMR and ^{13}C NMR spectra of 3aa



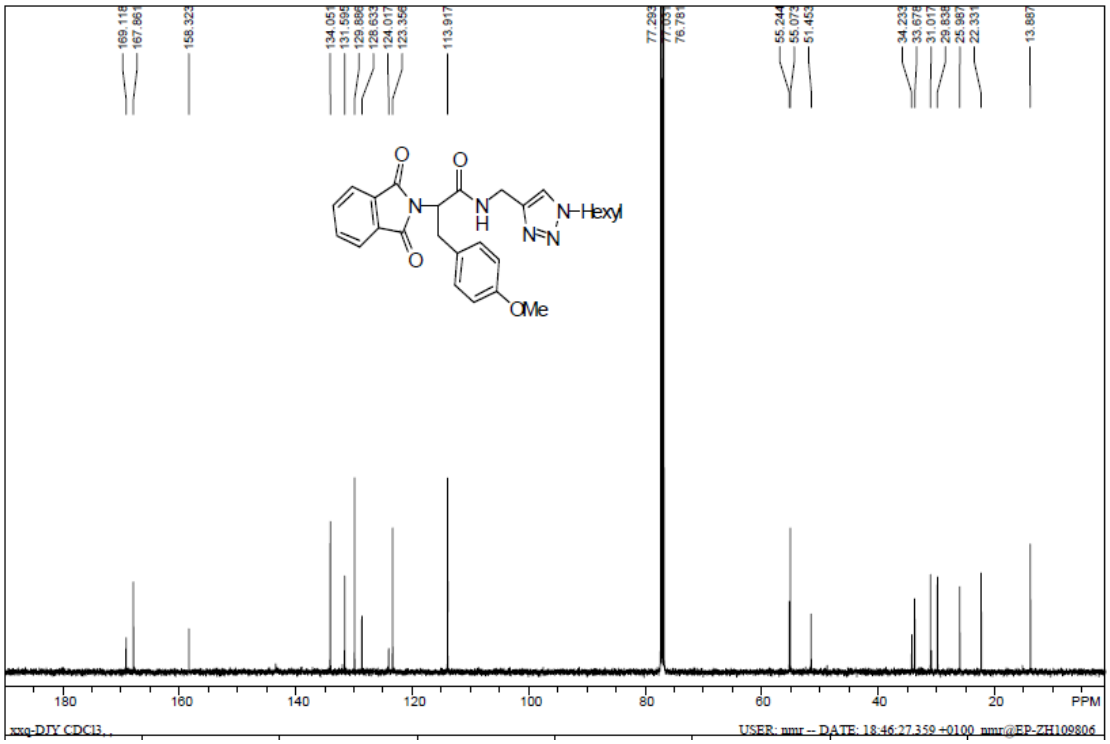
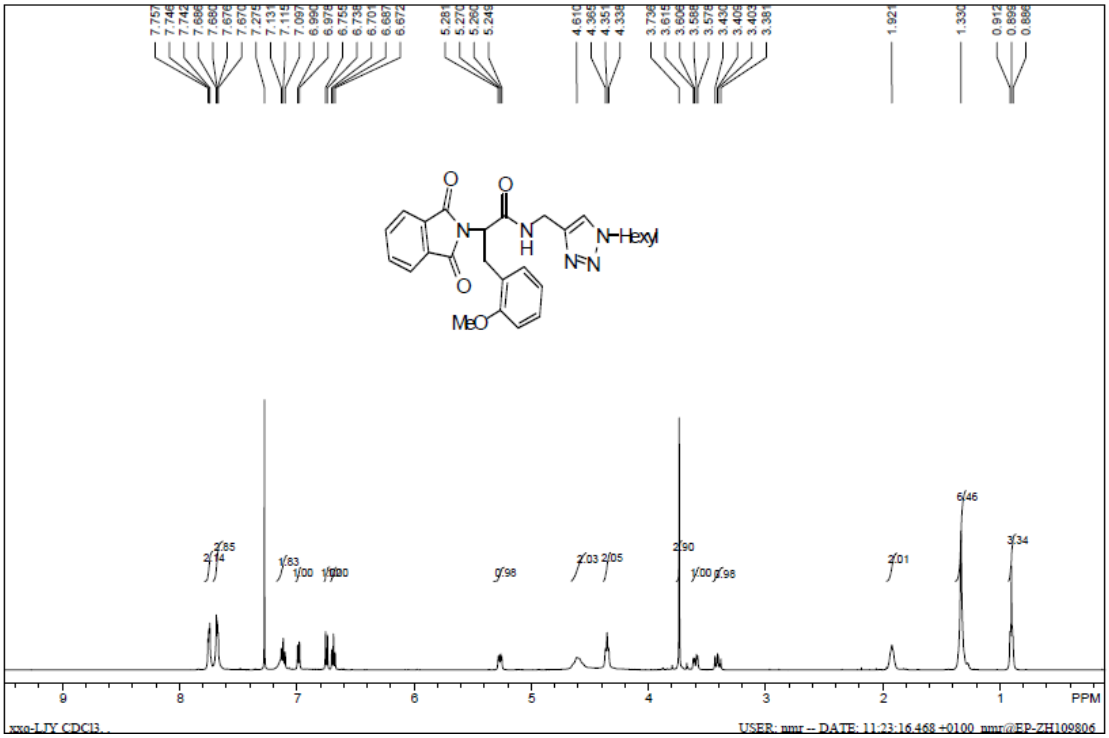


Figure 2. ^{1}H NMR and ^{13}C NMR spectra of 3ab



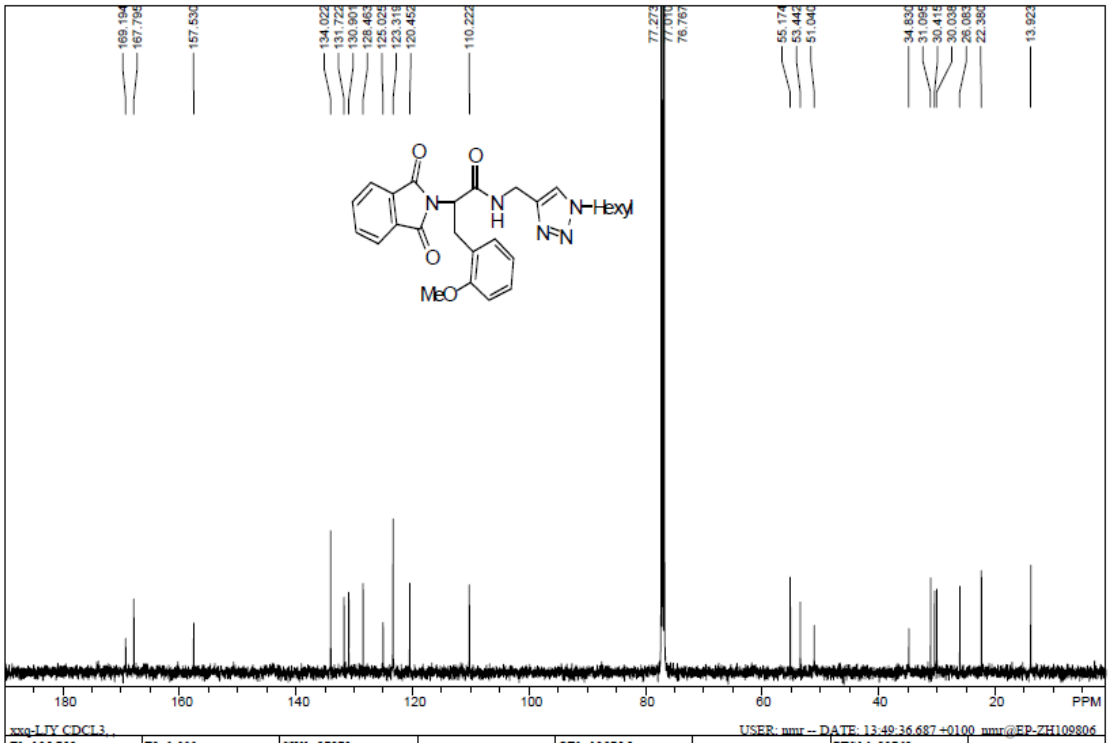
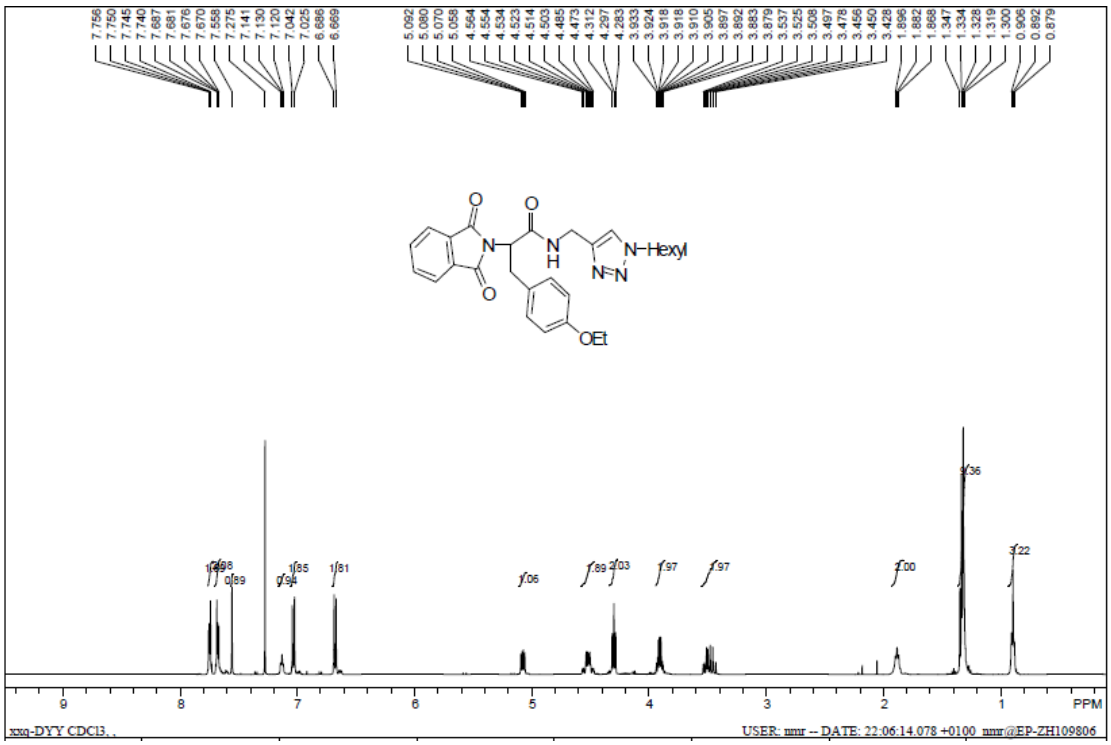


Figure 3. ^{1}H NMR and ^{13}C NMR spectra of 3ac



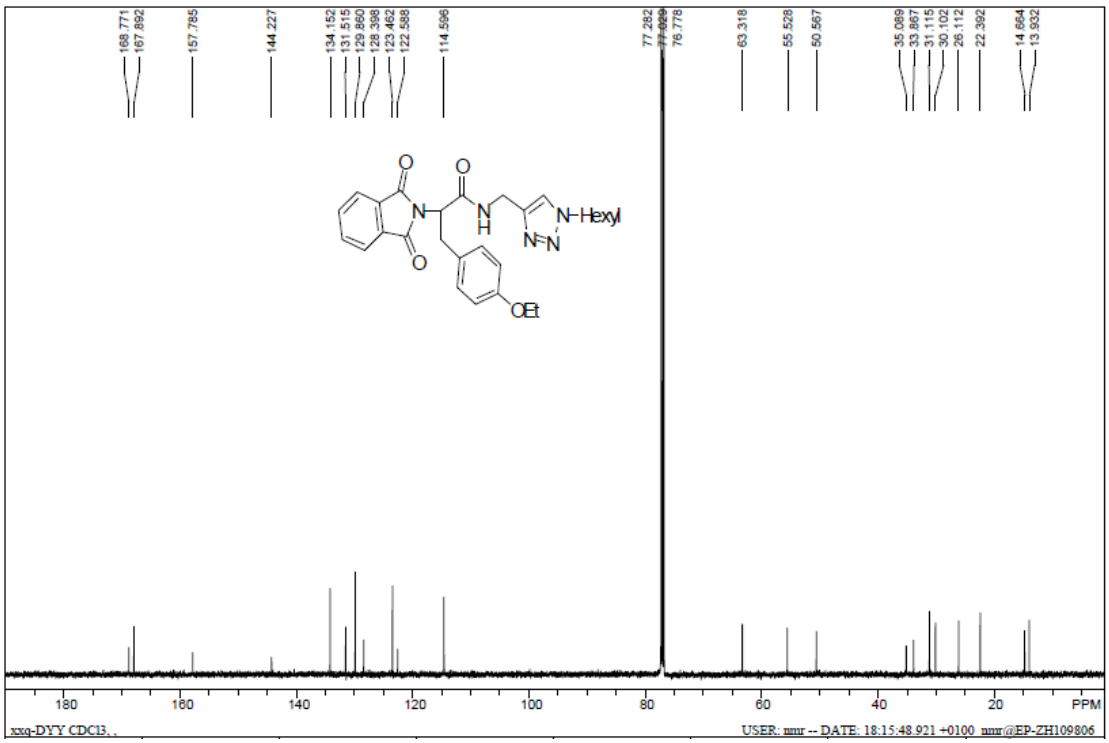
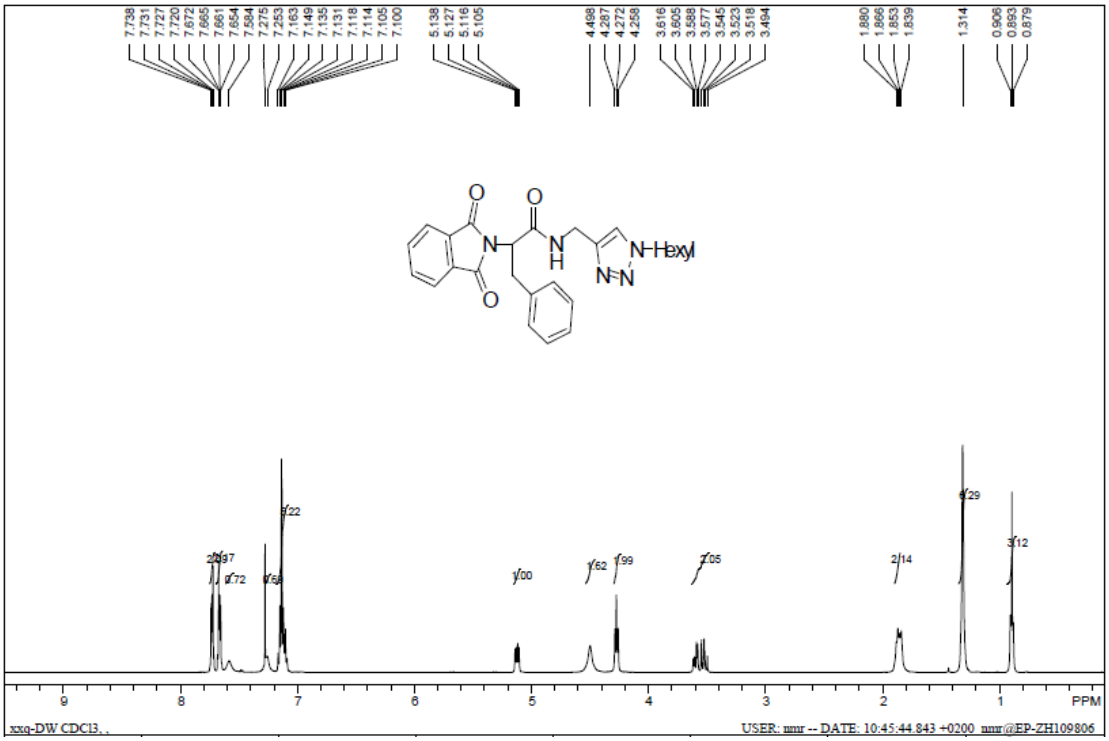


Figure 4. ^{1}H NMR and ^{13}C NMR spectra of 3ad



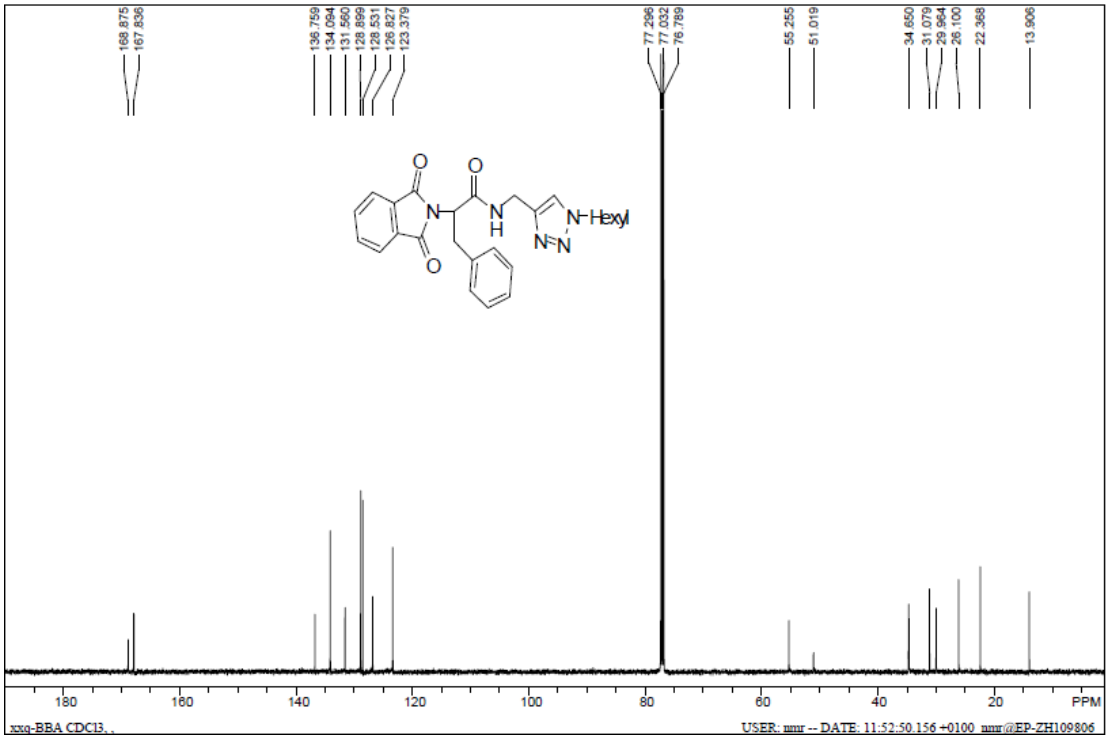
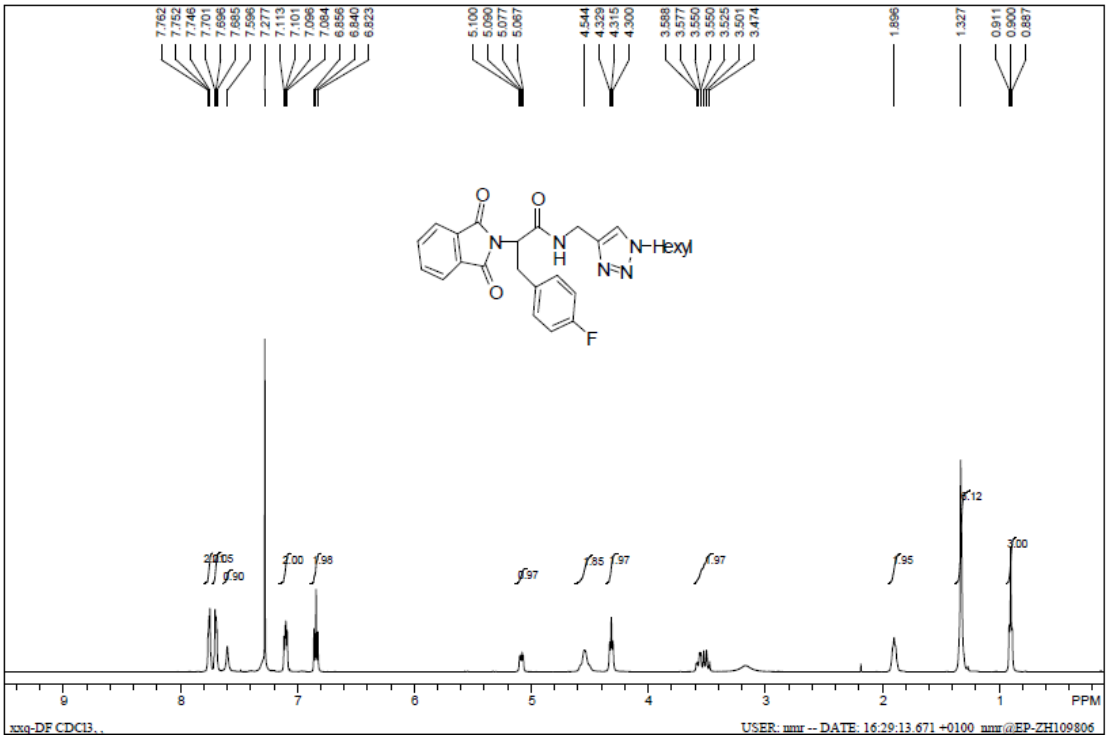
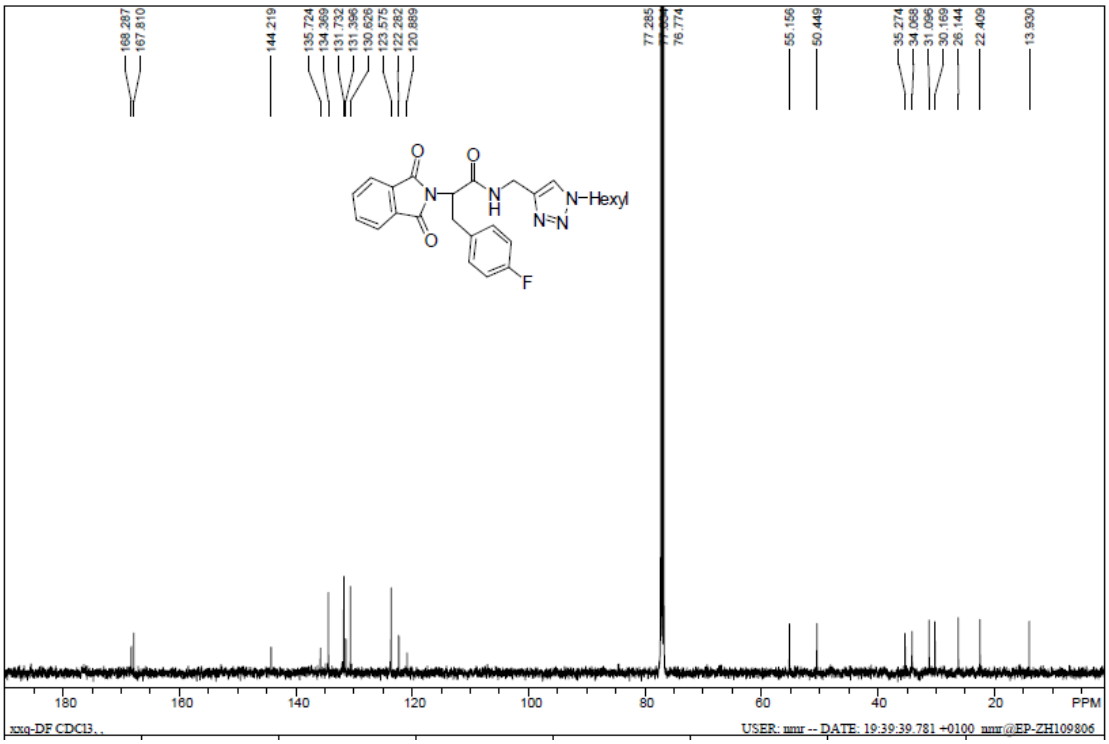


Figure 5. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra of 3ae





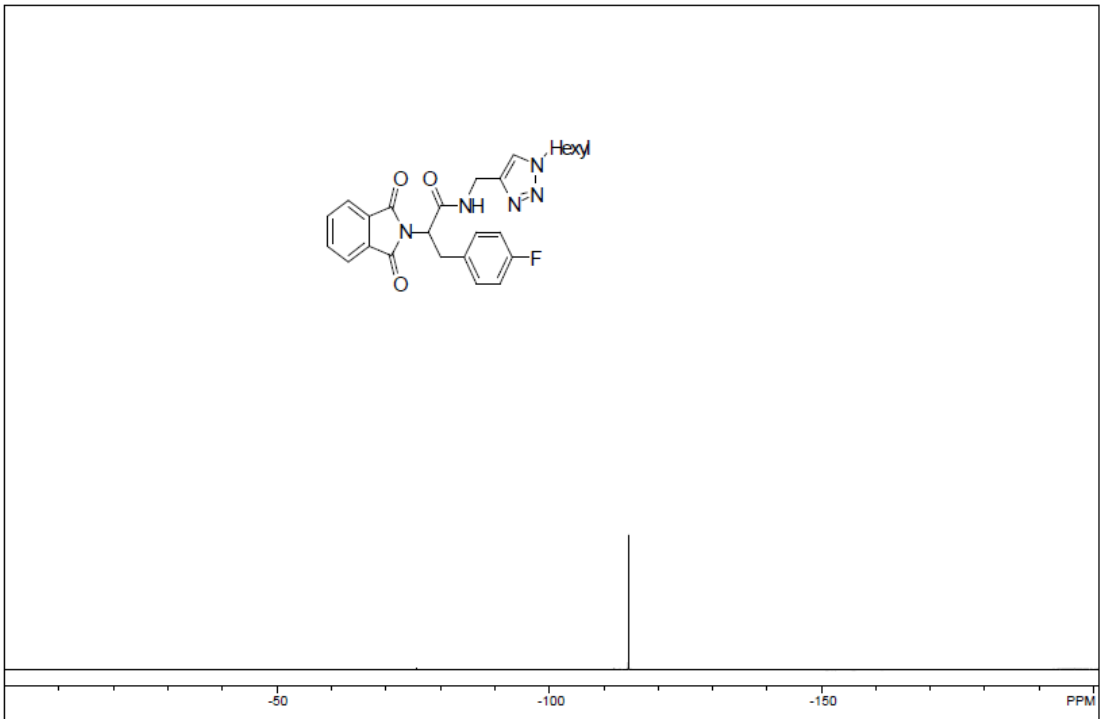
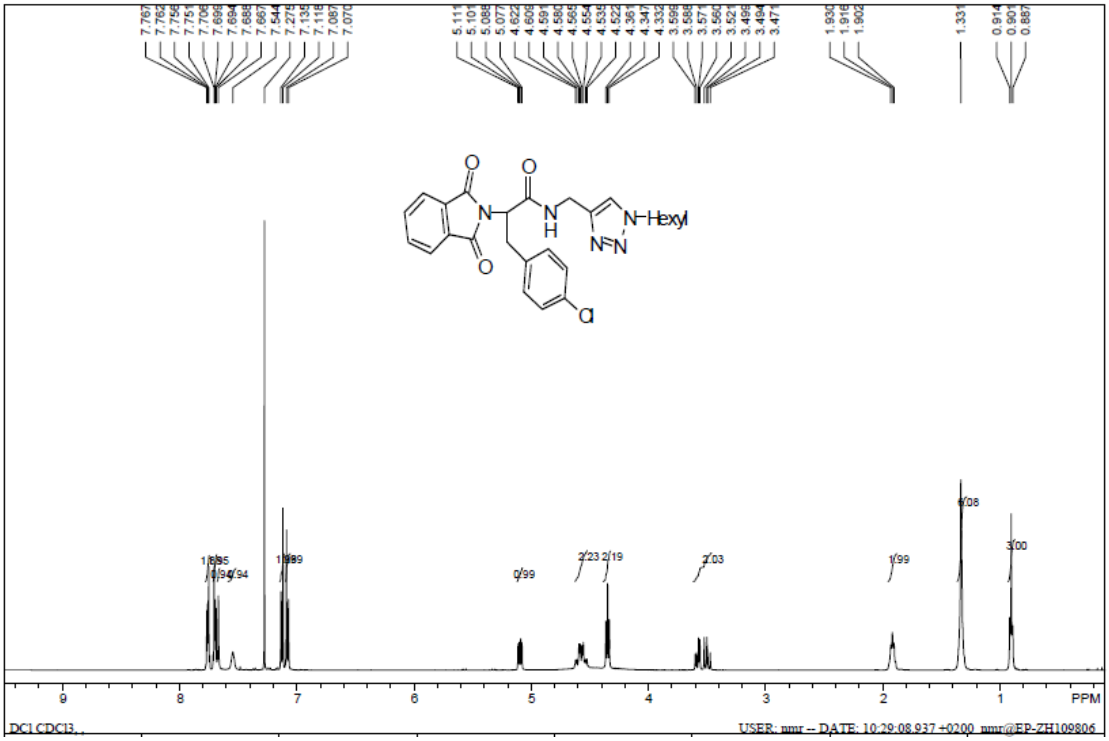

Hexyl
N
N
N
O
O
NH
N
O
F
-50
-100
-150
PPM

Figure 6. ^{1}H NMR and ^{13}C NMR spectra of 3af



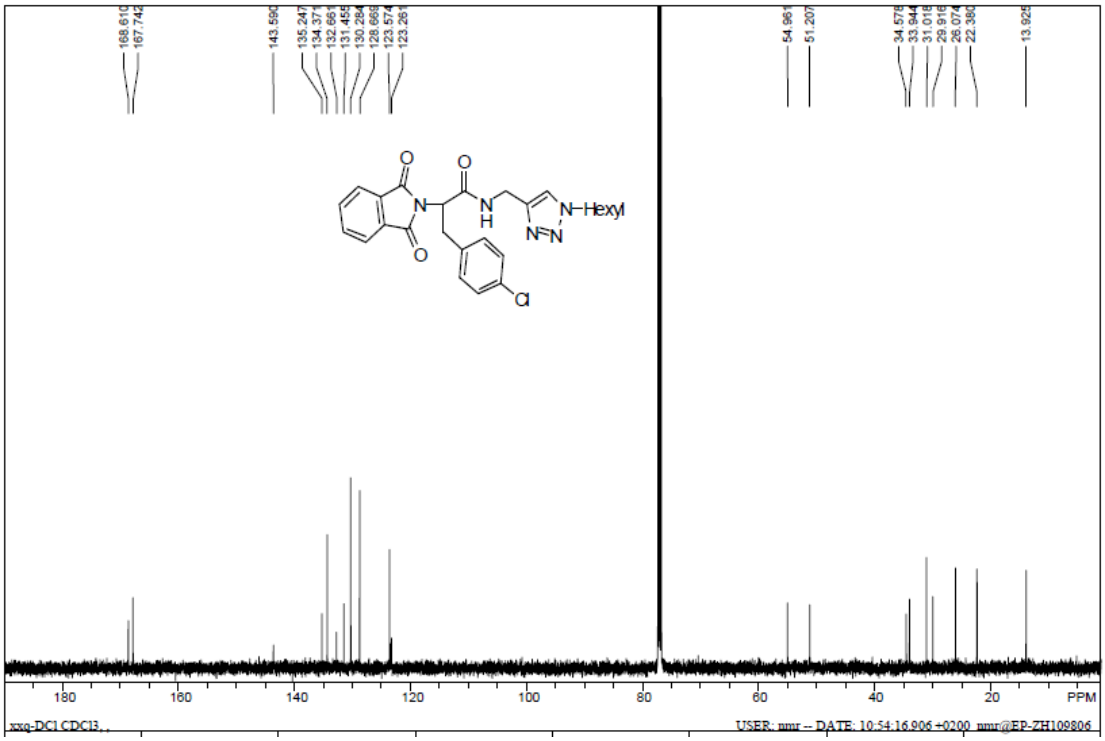
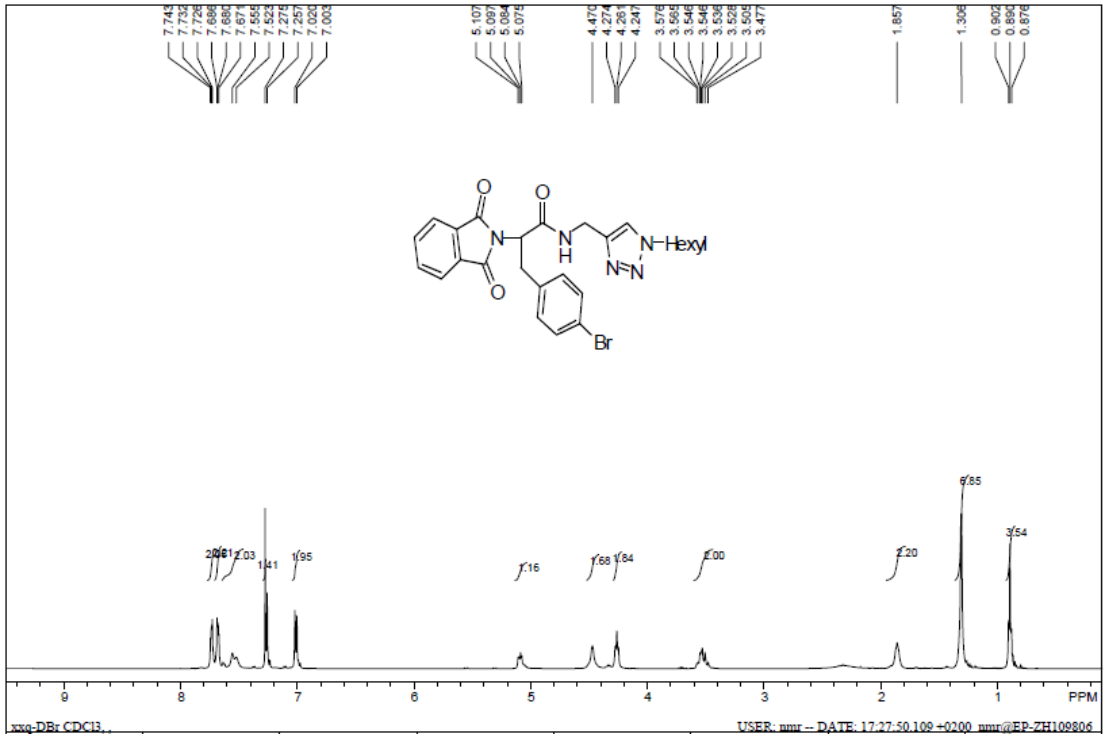


Figure 7. ^{1}H NMR and ^{13}C NMR spectra of 3ag



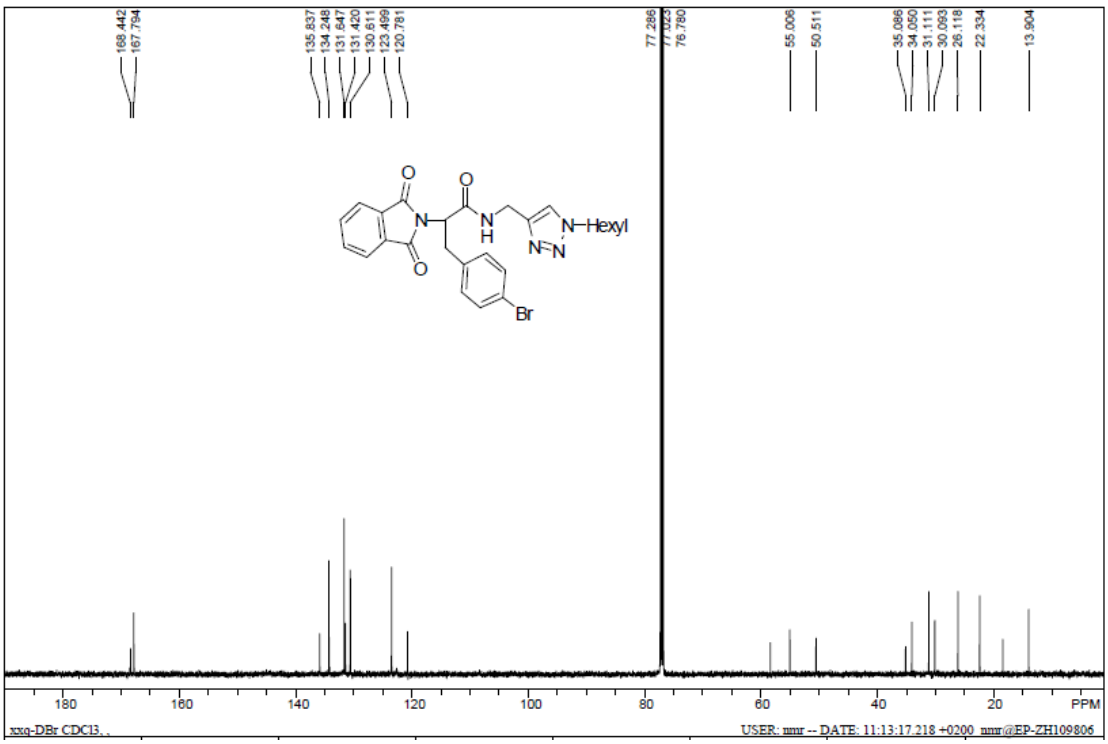
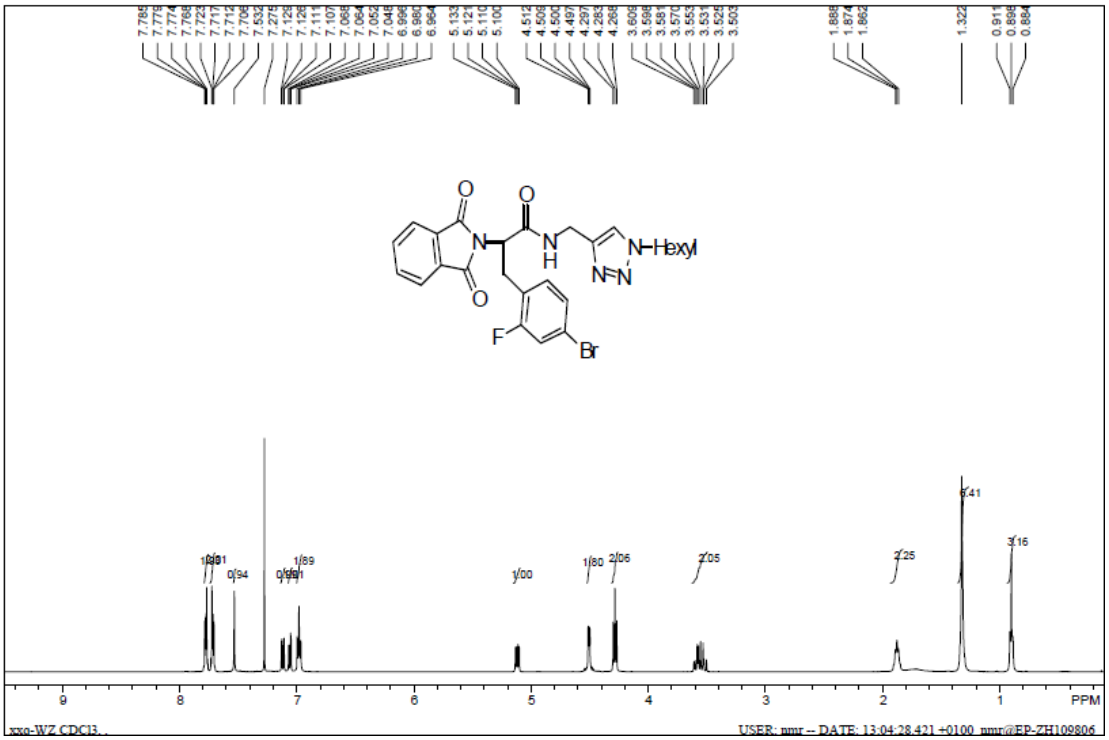
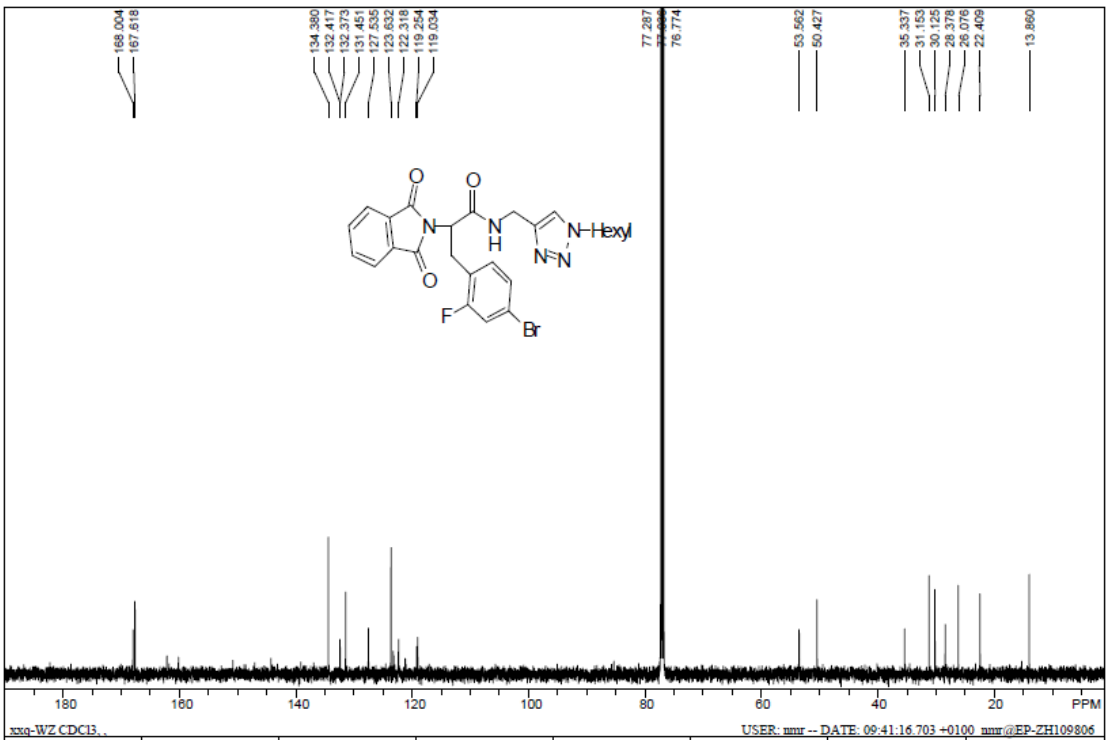


Figure 8. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra of 3ah





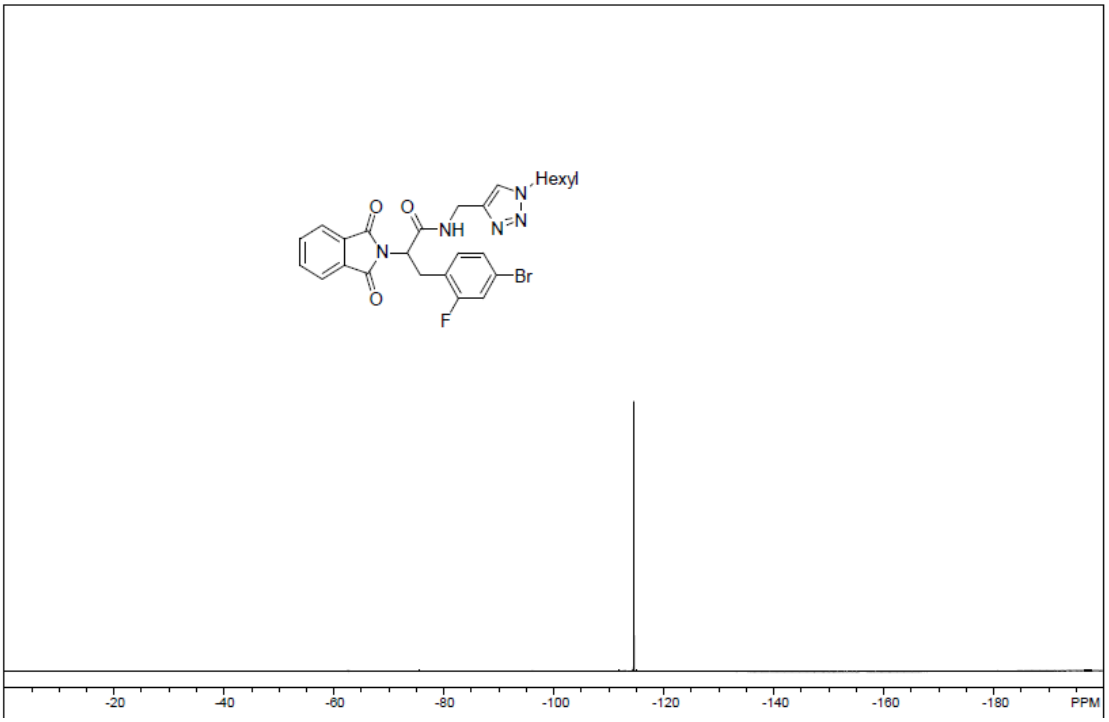
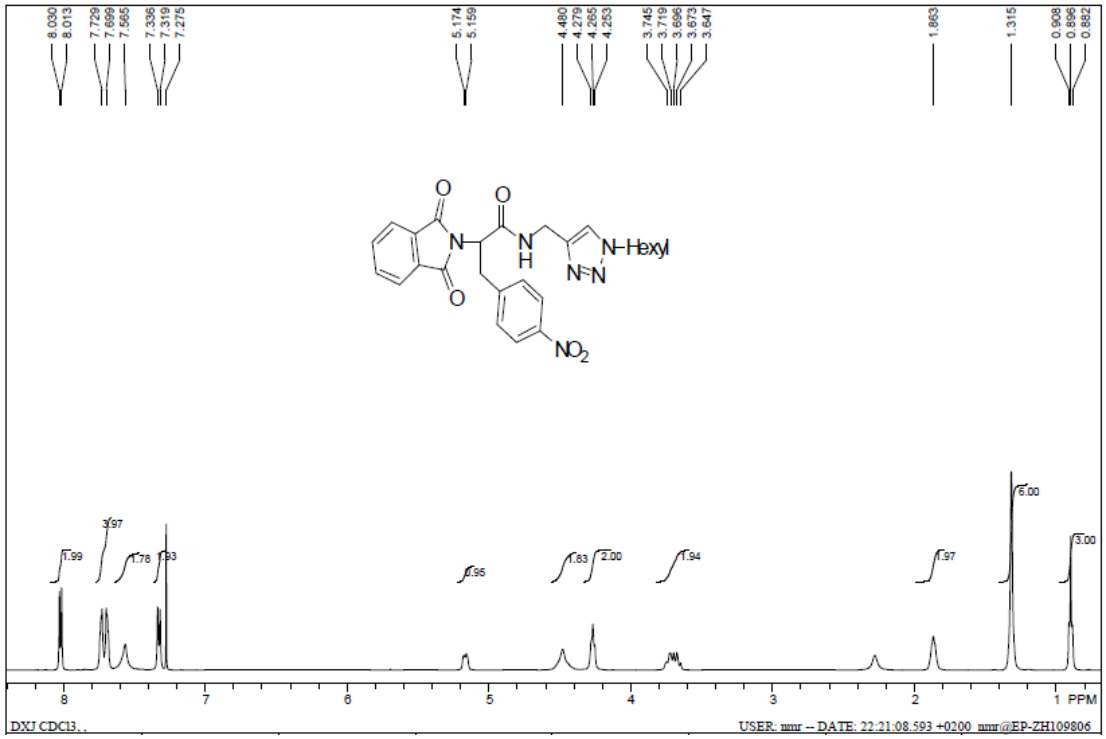

Hexyl
N
N
N
O
O
NH
N
O
Br
F
-20
-40
-60
-80
-100
-120
-140
-160
-180
PPM

Figure 9. ^{1}H NMR and ^{13}C NMR spectra of 3ai



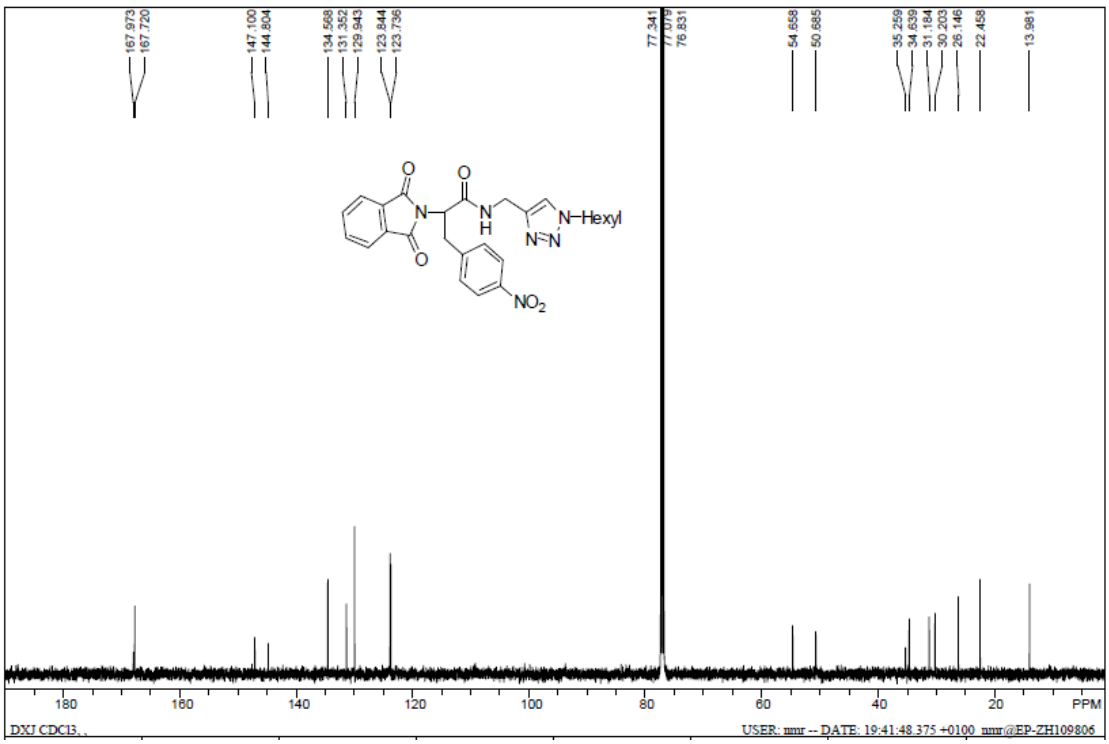
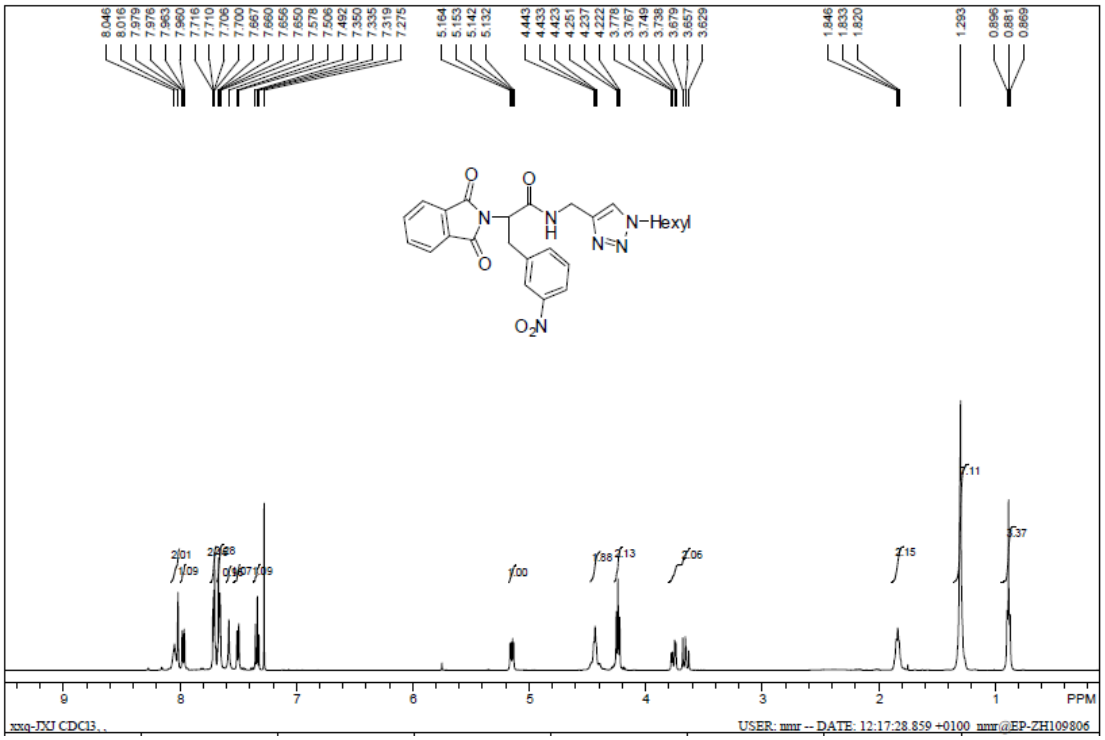


Figure 10. ^{1}H NMR and ^{13}C NMR spectra of 3aj



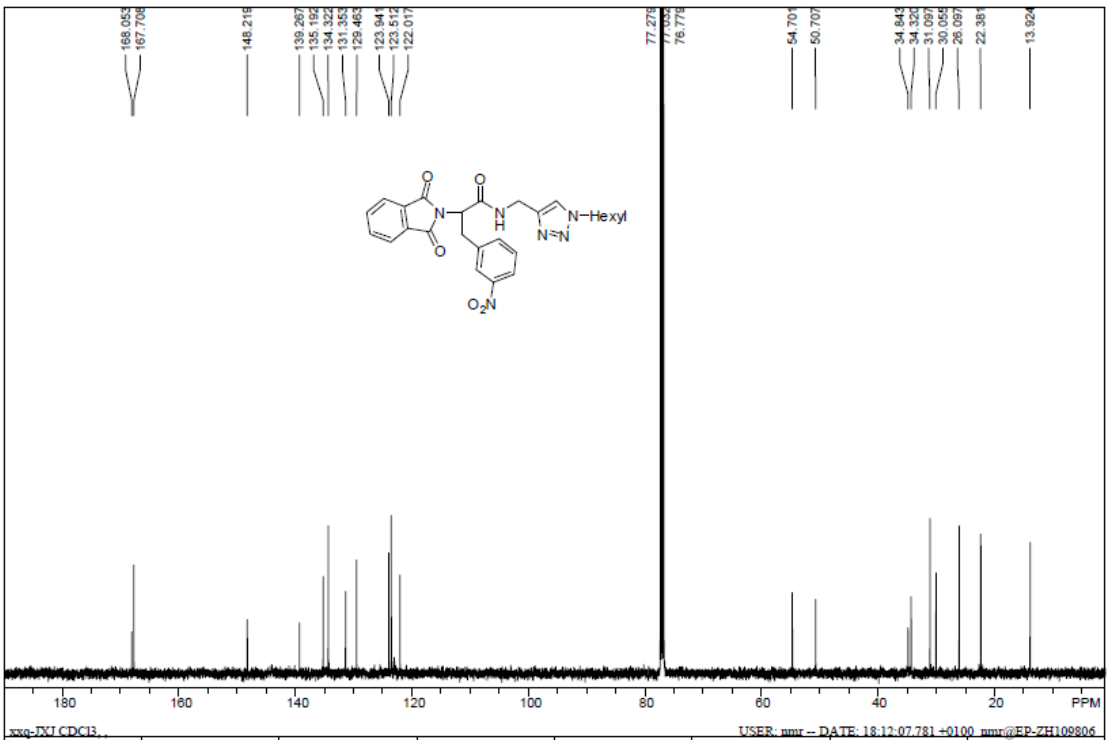
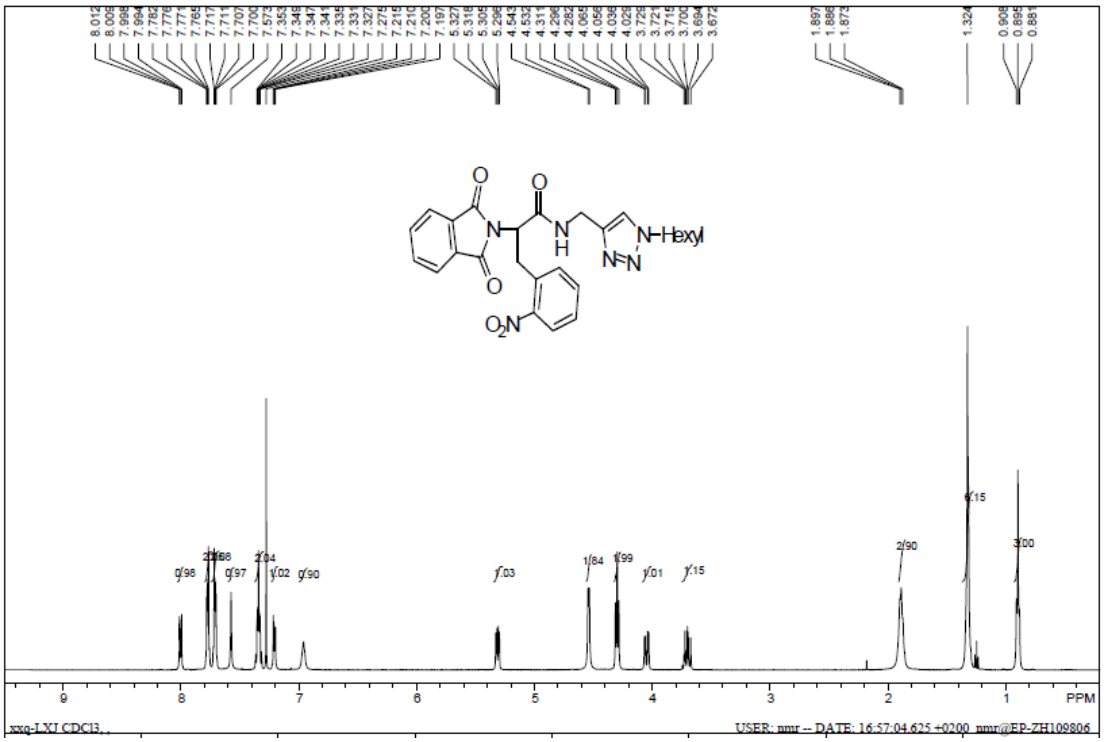


Figure 11. ^{1}H NMR and ^{13}C NMR spectra of 3ak



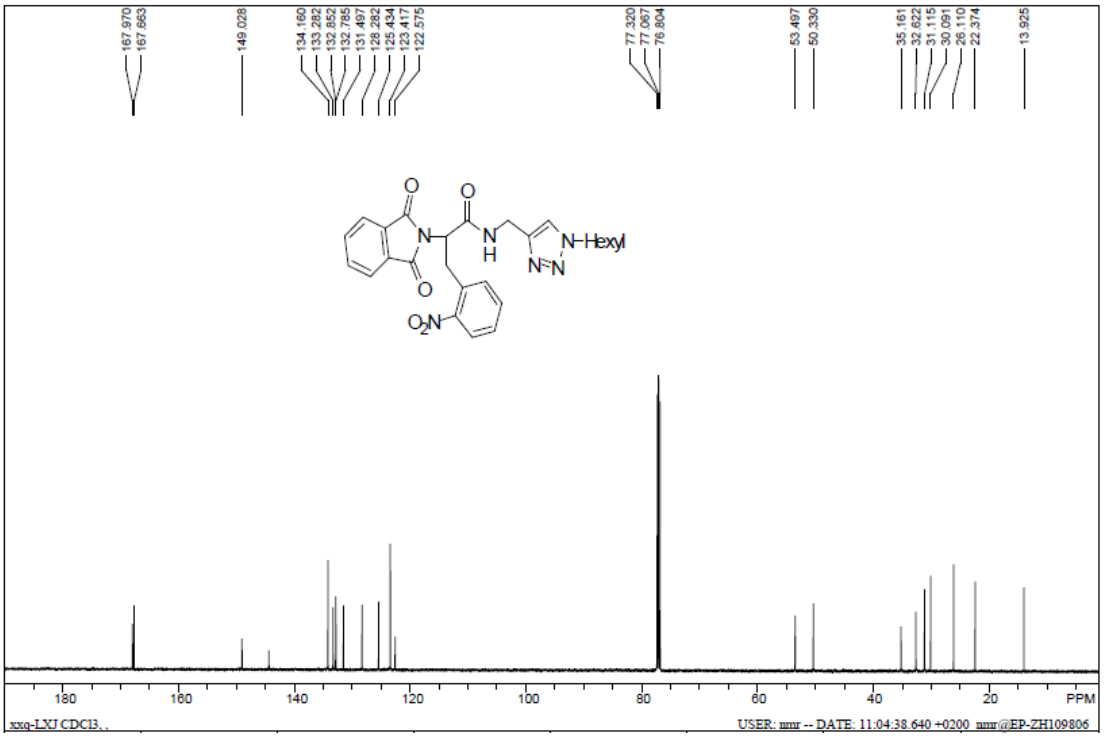
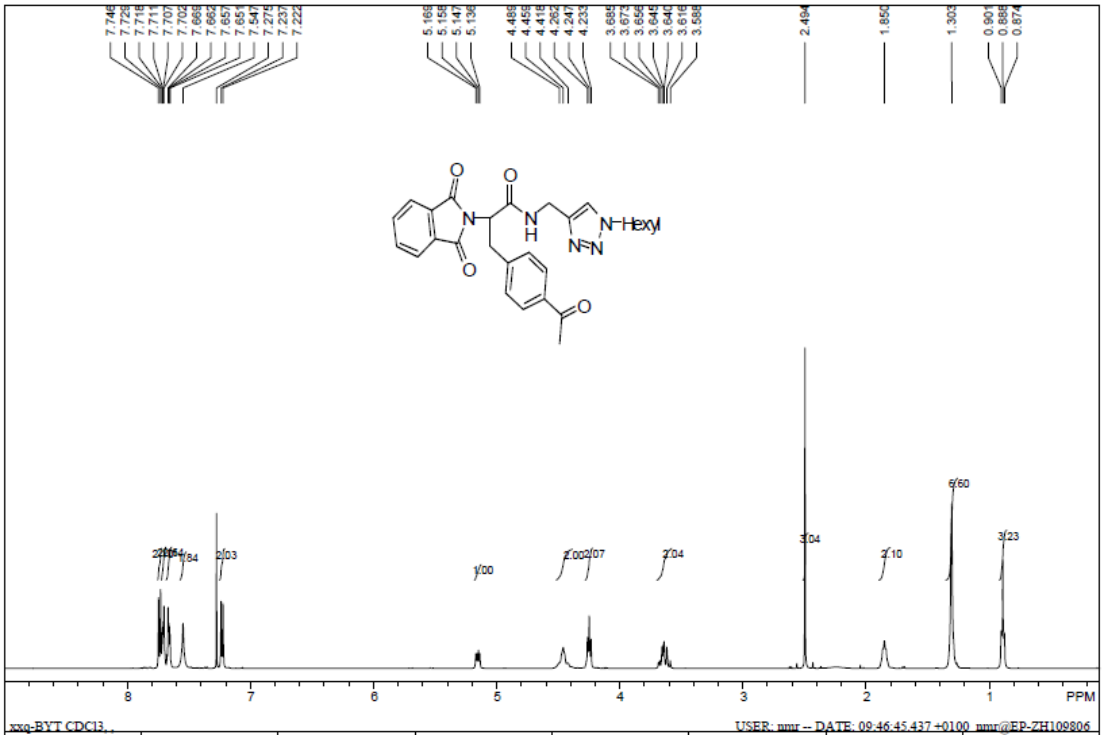


Figure 12. ^{1}H NMR and ^{13}C NMR spectra of 3al



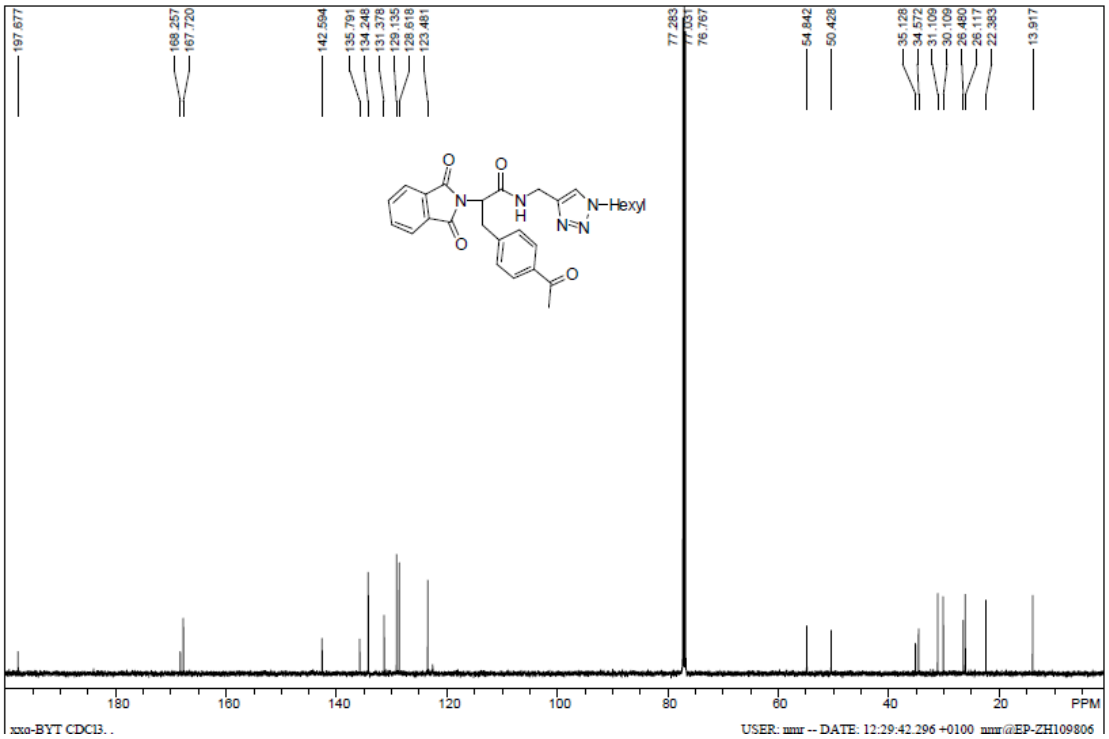
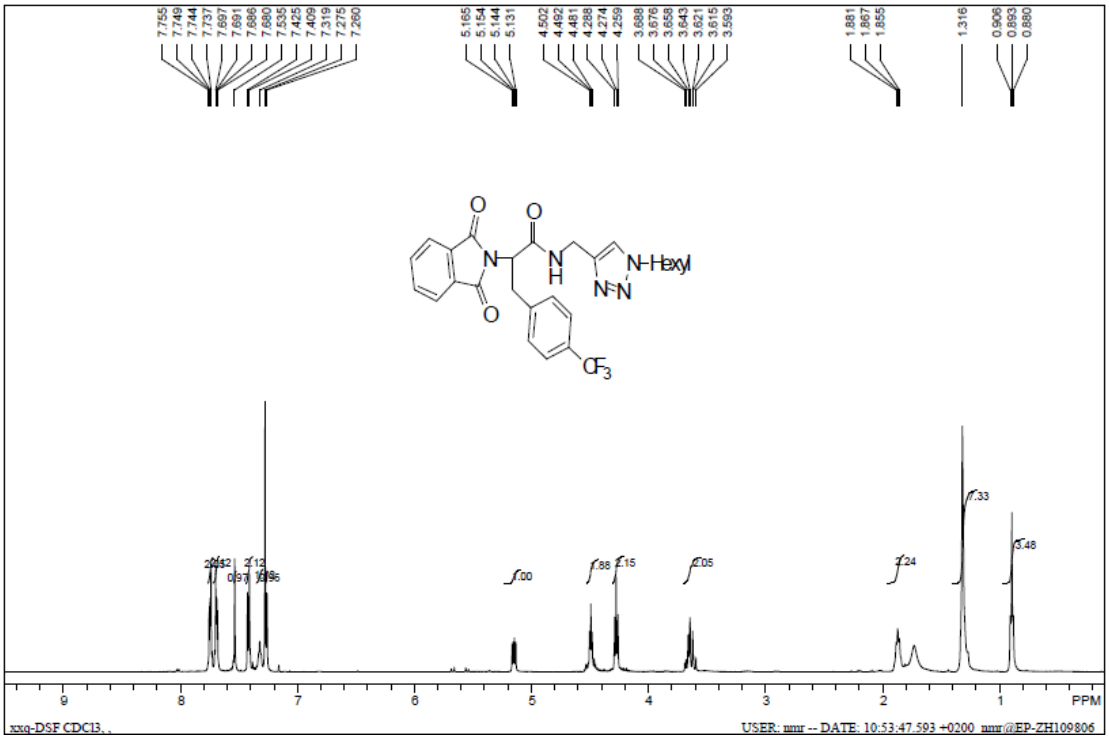
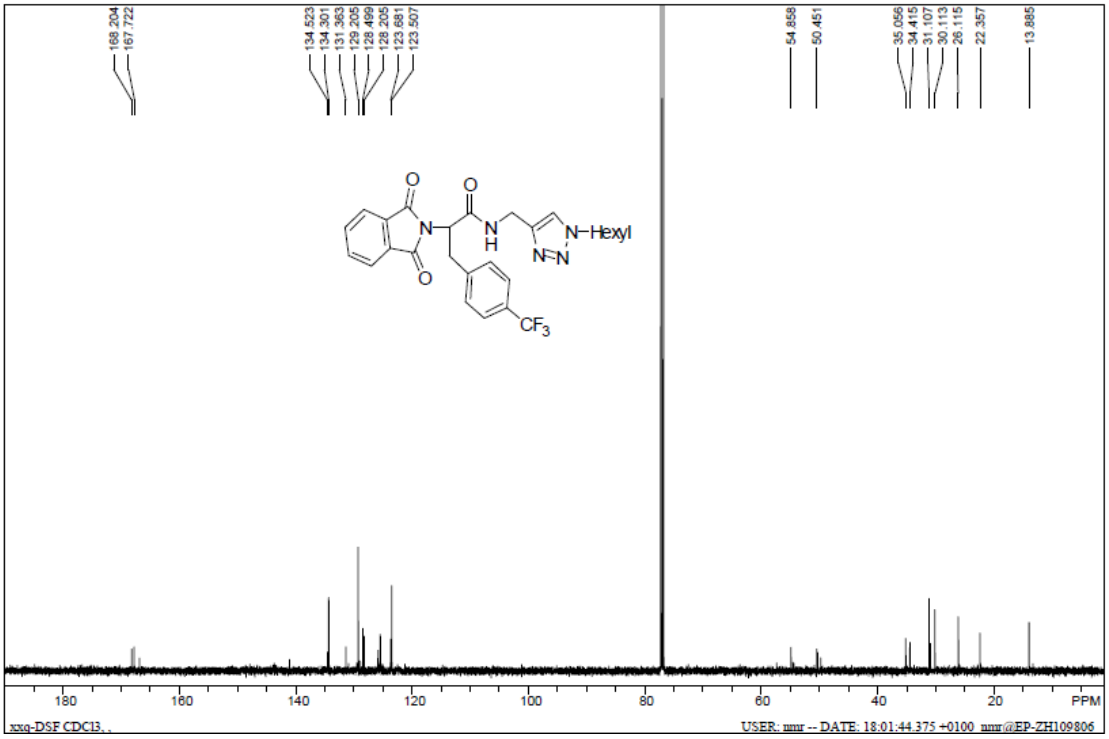


Figure 13. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra of 3am





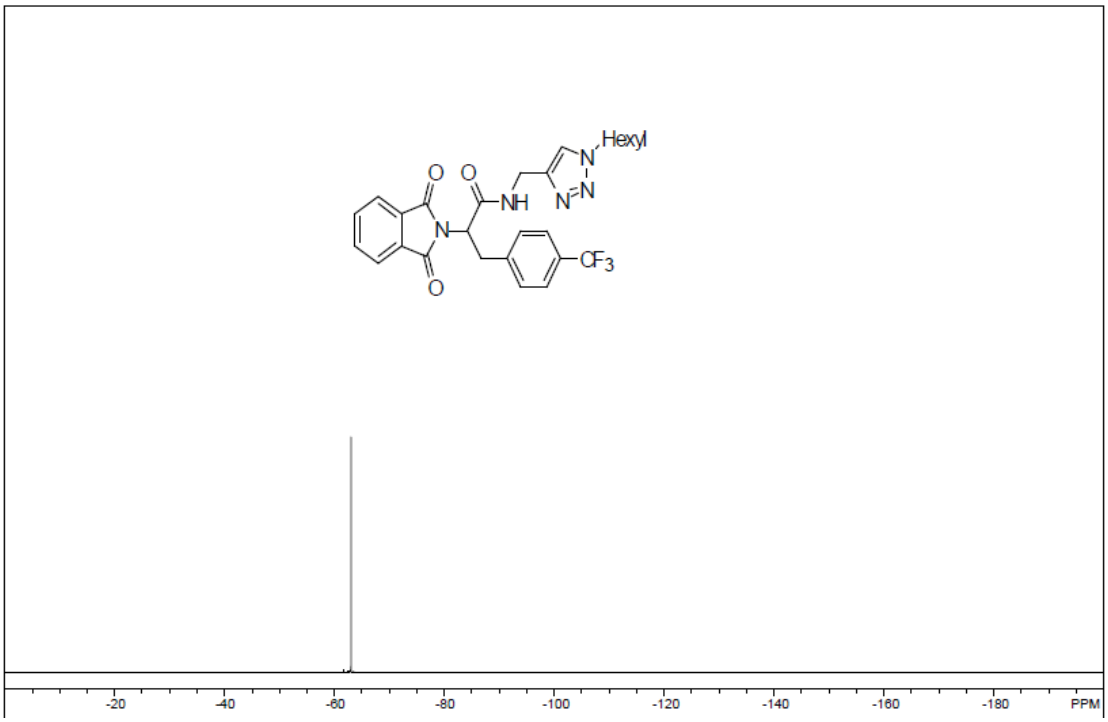
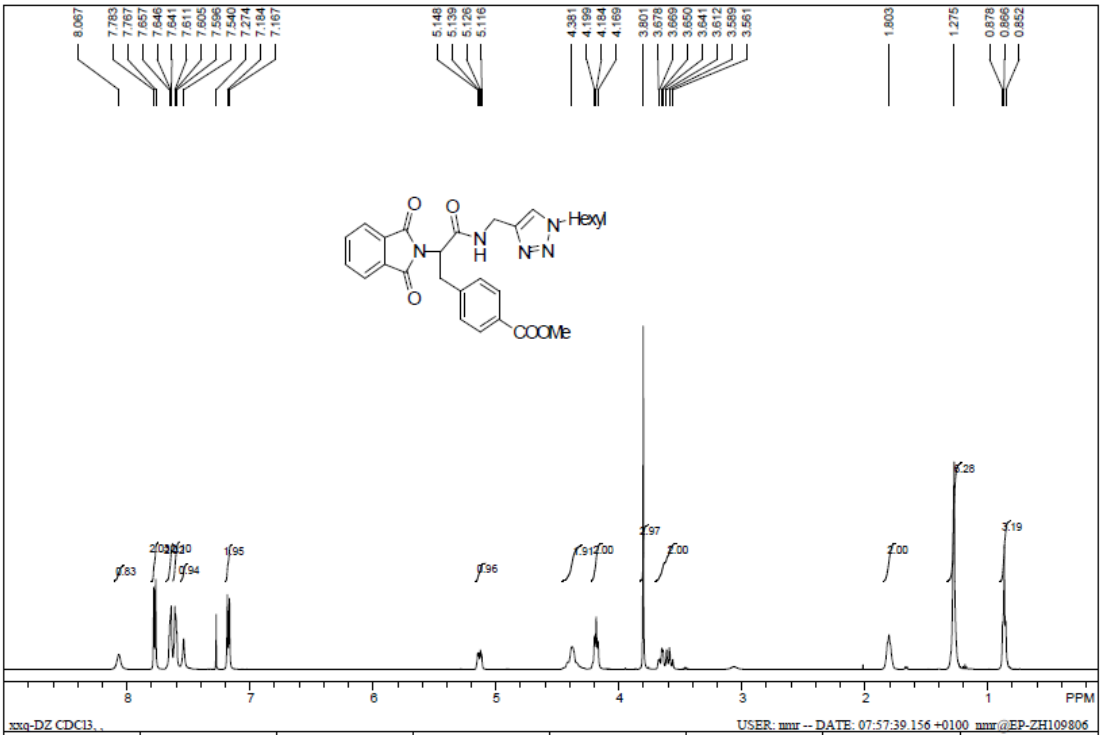

Hexyl
O
O
NH
N
N
N
O
CF3
-20
-40
-60
-80
-100
-120
-140
-160
-180
PPM

Figure 14. ^{1}H NMR and ^{13}C NMR spectra of 3an



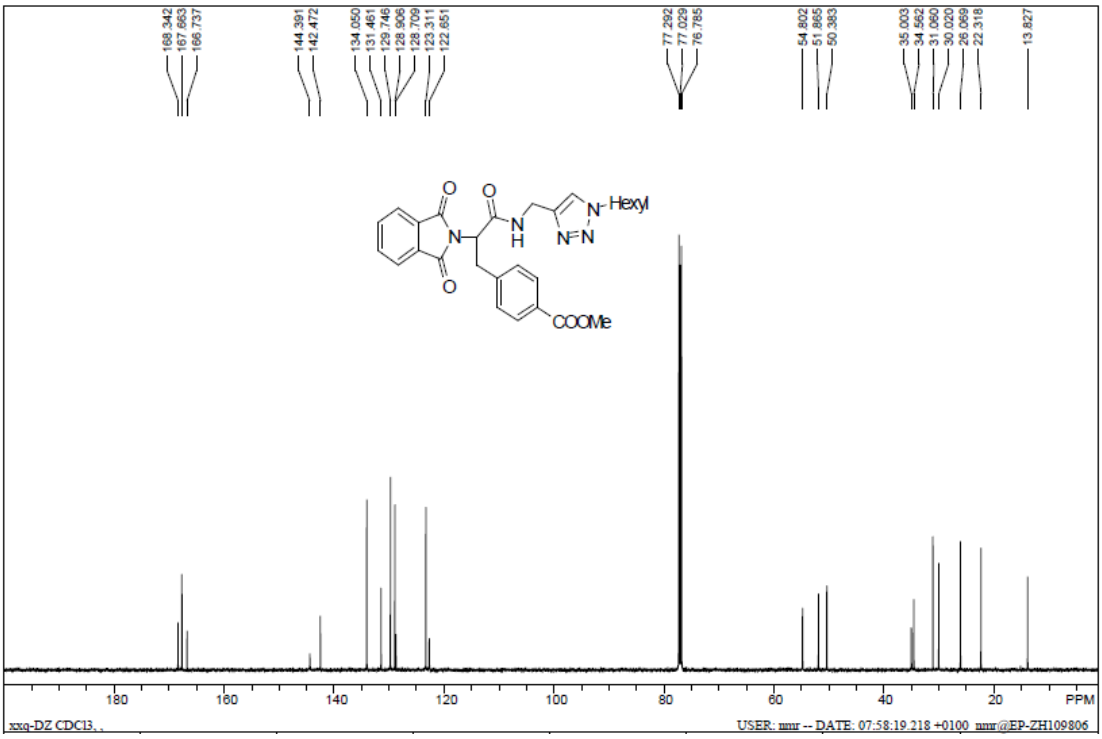
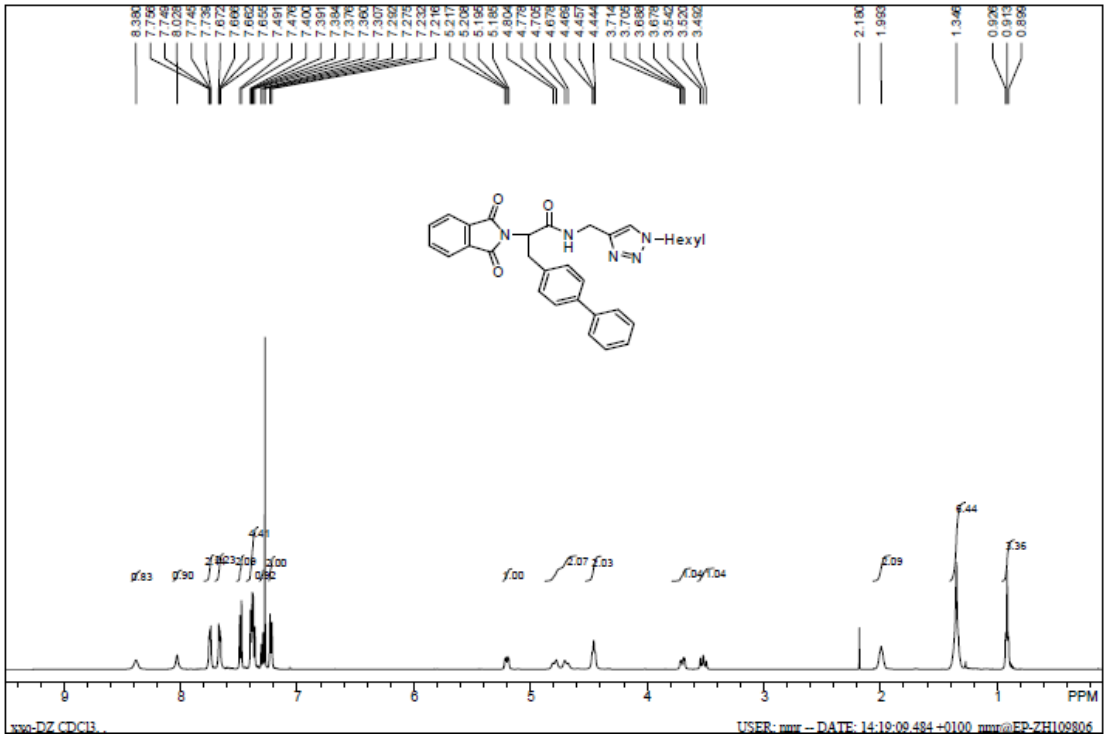


Figure 15. ^{1}H NMR and ^{13}C NMR spectra of 3ao



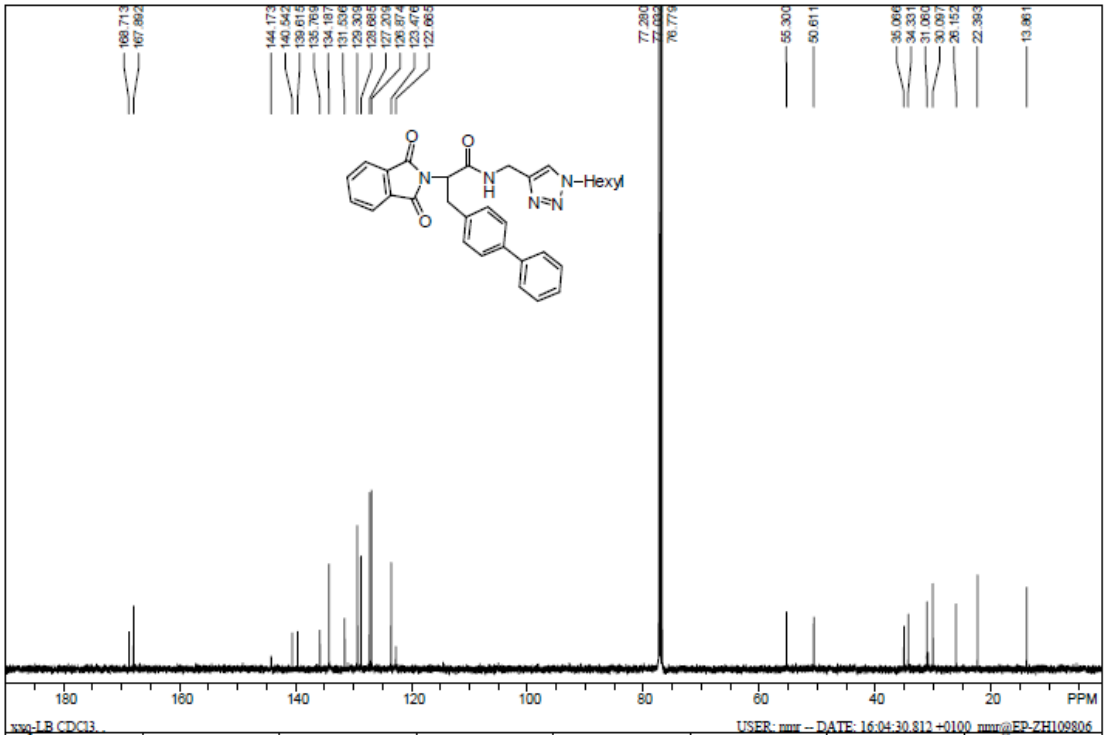
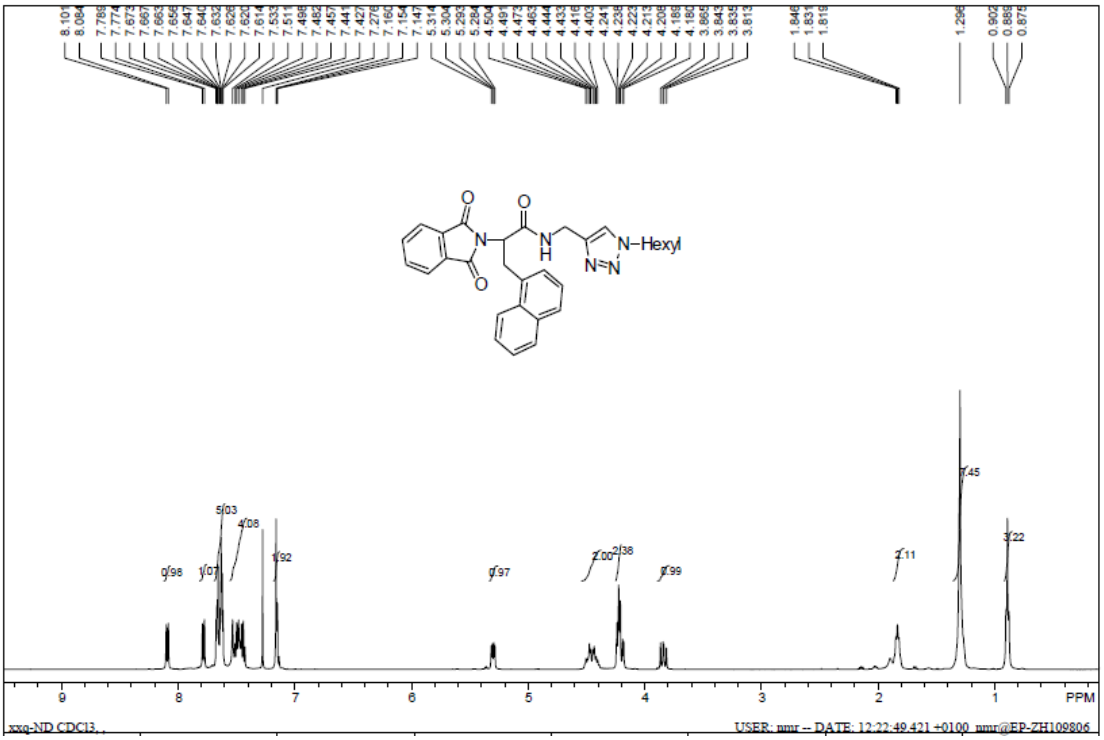


Figure 16. ^{1}H NMR and ^{13}C NMR spectra of 3ap



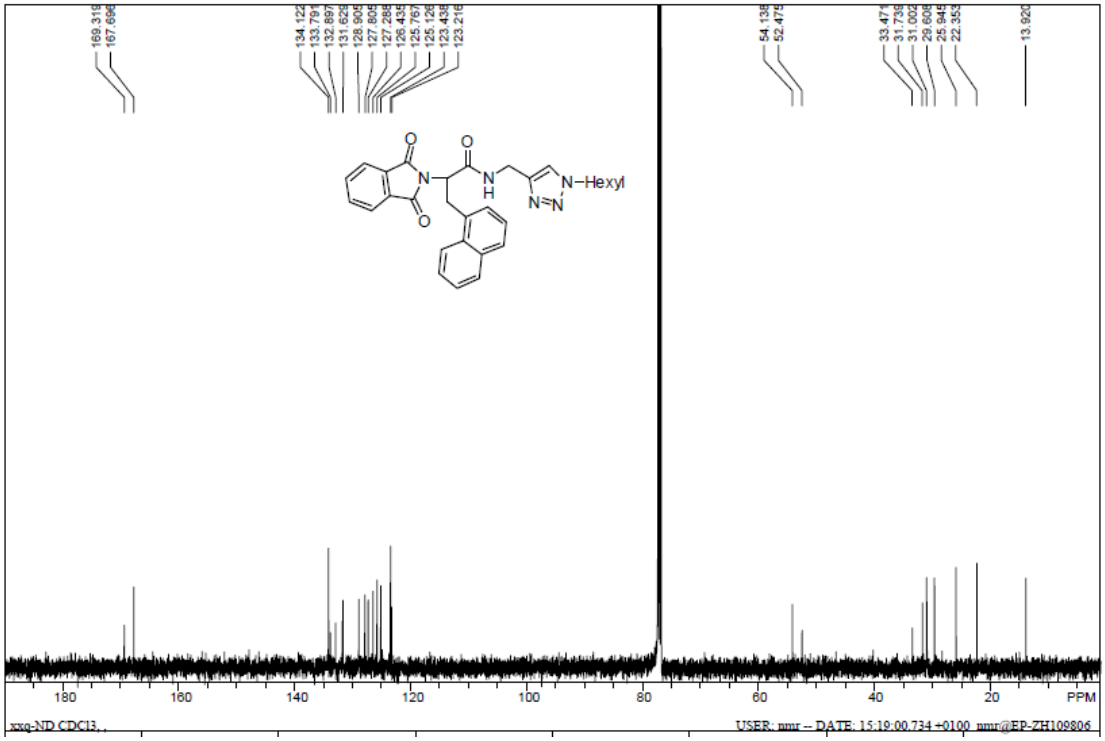
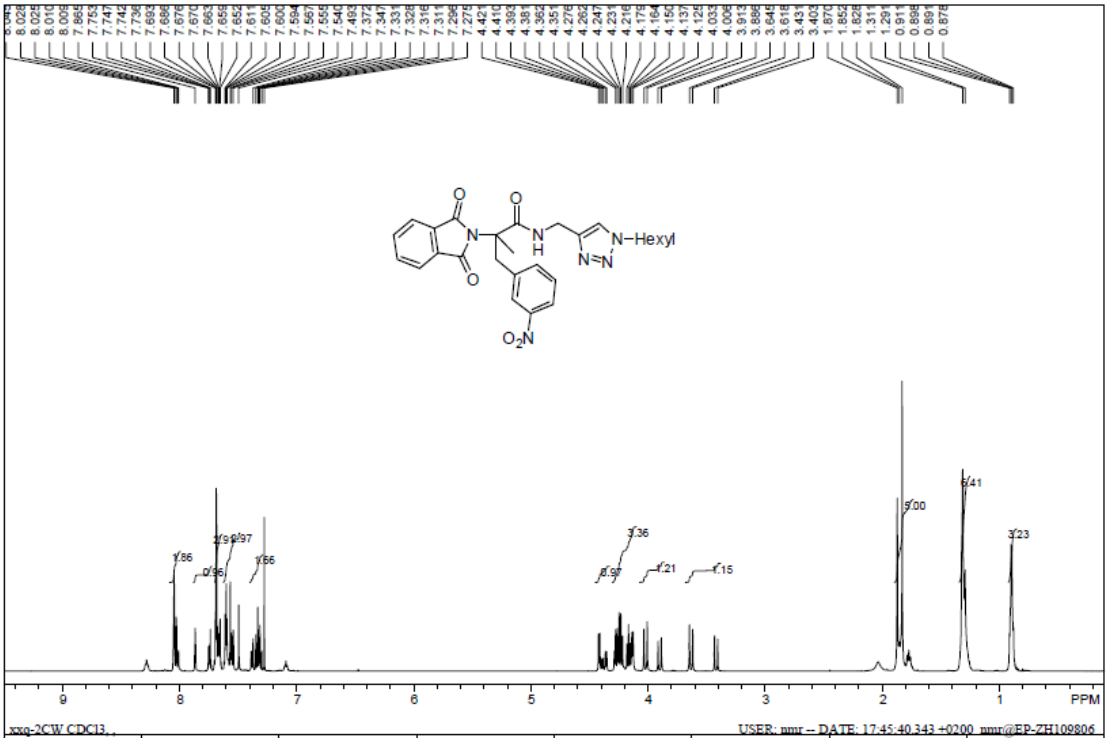


Figure 17. ^{1}H NMR and ^{13}C NMR spectra of 3bj



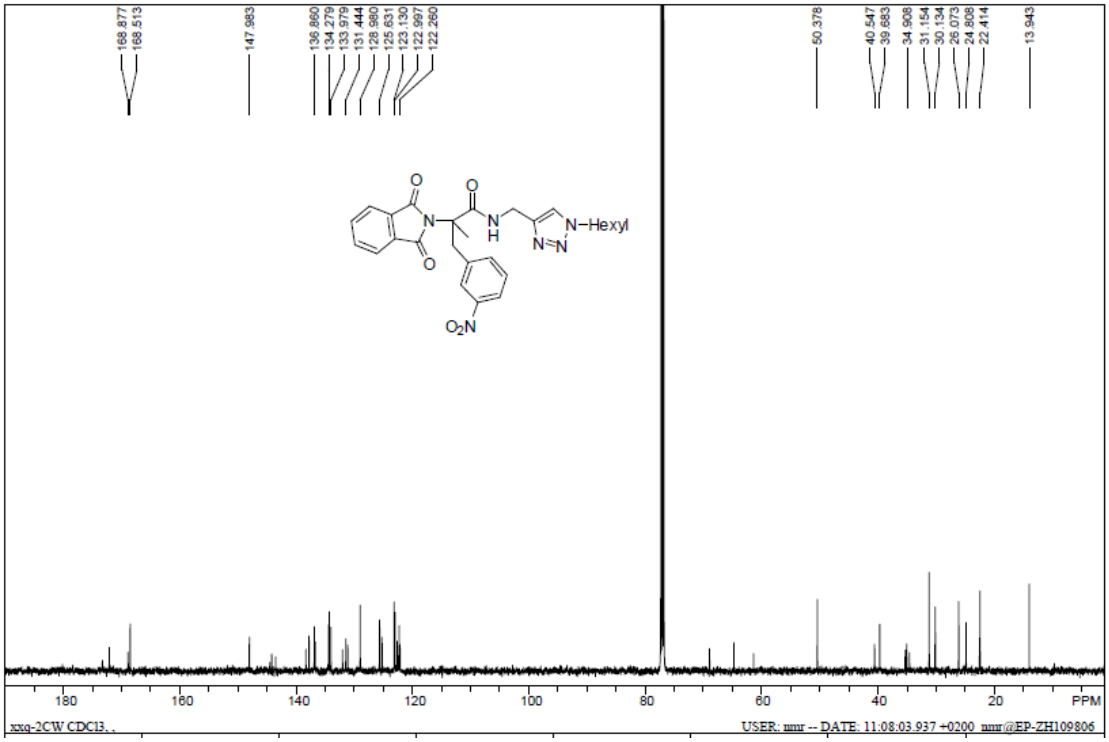
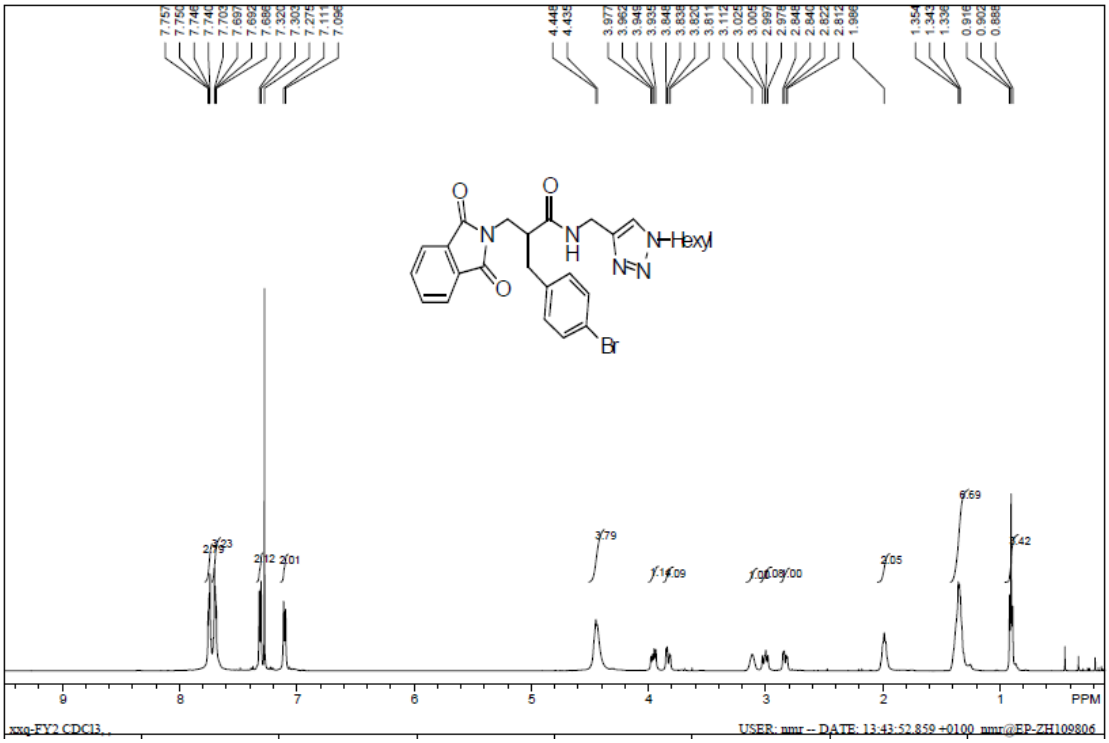


Figure 18. ^{1}H NMR and ^{13}C NMR spectra of 3cg



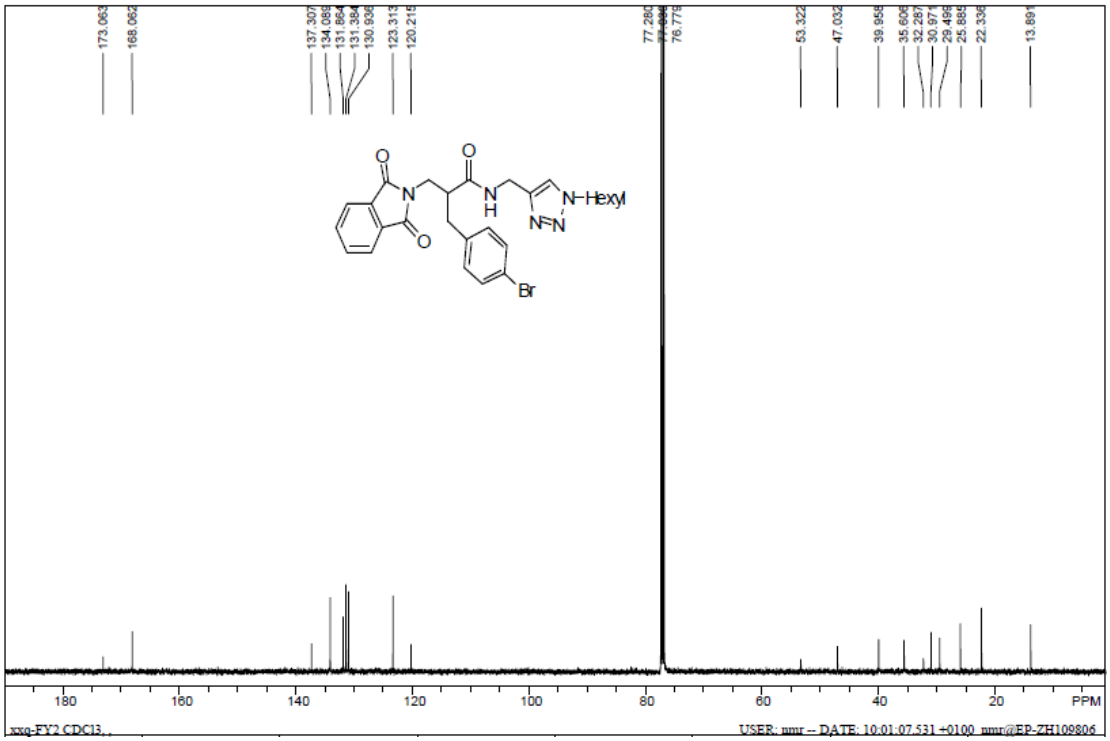
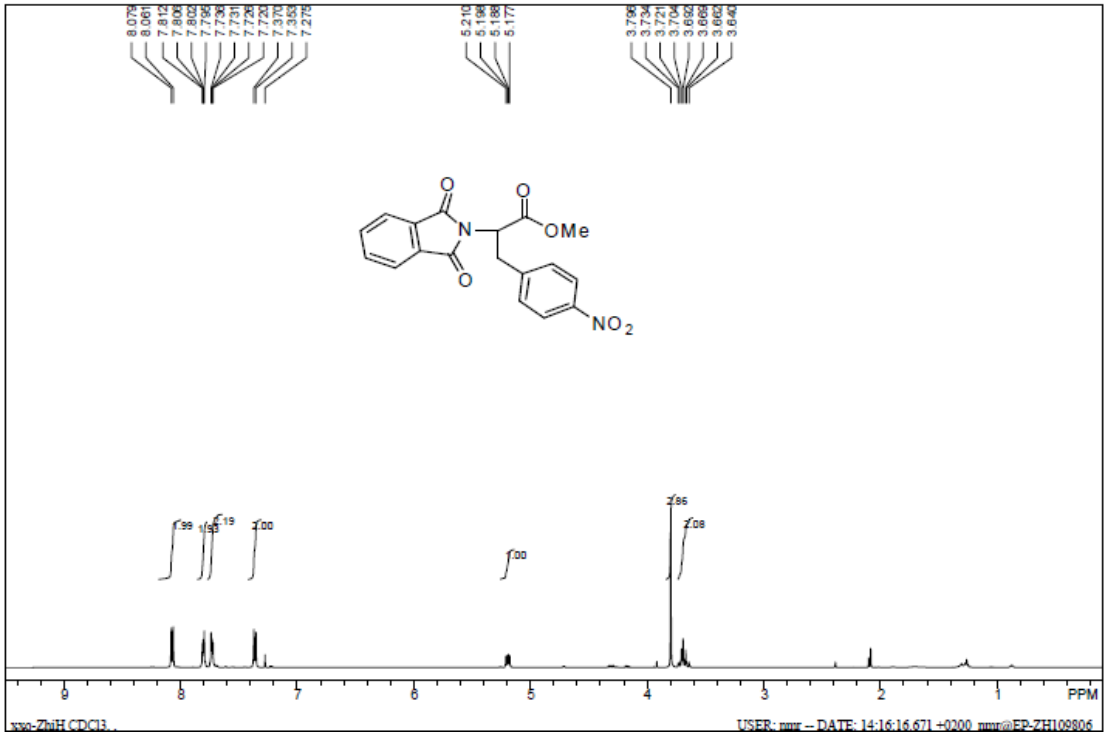


Figure 19. ^{1}H NMR and ^{13}C NMR spectra of 4ai



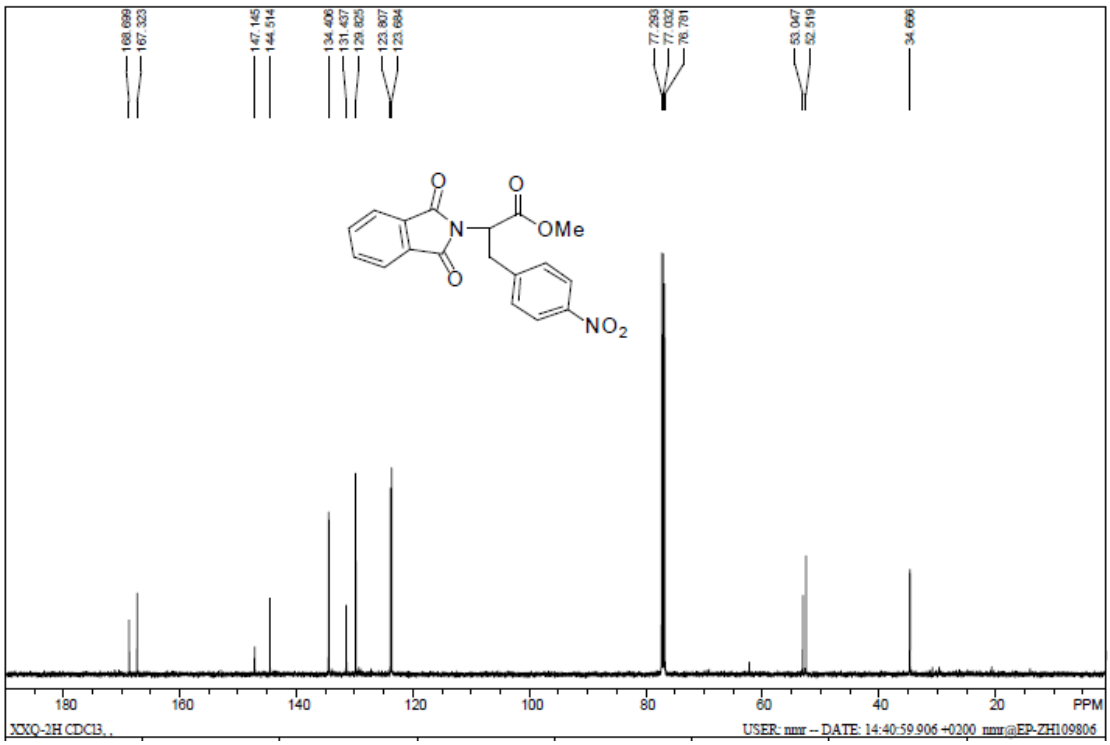


Figure 20. ^{1}H NMR and ^{13}C NMR spectra of 5ai