Supporting Information

Design, Synthesis and Fungicidal Activity of Isothiazole-thiazole Derivatives

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Table of Contents for the Supporting Information

1. Crystal data

Table S1: Crystal data and structure refinement for compound **6j**.

Compd.	6j
Empirical formula	C22 H15 Br Cl2 F3 N5 O S2
Formula weight	637.32
Temperature	133(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 19.530(2) A alpha = 90 deg. b = 6.0340(5) A beta = 105.189(2) deg. c = 21.523(2) A gamma = 90 deg.
Volume	2447.7(4) A^3
Z, Calculated density	4, 1.729 Mg/m^3
Absorption coefficient	2.119 mm^-1
F (000)	1272
Crystal size	0.20 x 0.18 x 0.12 mm
Theta range for data collection	3.13 to 27.57 deg.
Limiting indices	-25<=h<=25, -7<=k<=7, -27<=l<=27
Reflections collected / unique	29802 / 5627 [R(int) = 0.0406]
Completeness to theta	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7851 and 0.6766
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5627 / 0 / 325
Goodness-of-fit on F^2	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0309, wR2 = 0.0820
R indices (all data)	R1 = 0.0397, wR2 = 0.0845
Largest diff. peak and hole	1.073 and -0.631 e.A^-3

2. Tables for Bioassay

Table S2: In vitro antifungal activities of compounds **6a-6u** at 50 mg/L

Compd.	Inhibition rate (%) ± SD							
	A. S[a]	*B. C*	*C. A*	*G. Z*	*P. P*	*P. S*	*R. C*	*S. S*
6a	53±2	41±1	45±0	72±2	28±0	28±1	22±2	50±2
6b	16±0	30±2	17±1	4±0	30±1	28±1	0	100
6c	19±1	60±3	40±2	33±0	21±2	51±2	4±1	73±1
6d	6±0	60±2	2±0	-21±2	28±2	25±1	1±0	60±0
6e	7±0	41±0	49±1	2±0	15±0	14±2	6±0	28±2
6f	53±3	62±3	64±3	76±3	44±0	41±2	46±2	33±0
6g	43±2	35±1	38±2	60±1	24±2	15±0	28±2	50±1
6h	50±2	46±2	62±1	-4±0	57±3	22±0	50±2	50±2
6i	38±0	30±0	63±0	67±3	65±3	48±2	69±3	8±1
6j	65±1	54±2	60±2	58±2	65±2	17±1	53±0	50±3
6k	13±0	10±1	17±1	28±1	23±0	26±0	4±0	58±2
6l	6±1	63±2	30±2	5±1	25±0	26±1	11±2	70±4
6m	1±1	67±3	25±1	9±0	25±2	11±1	34±1	43±0
6n	7±0	57±1	21±2	0	21±1	25±0	7±0	48±2
6o	73±3	35±0	32±1	72±4	65±3	61±2	62±3	42±1
6p	16±2	23±0	25±1	4±1	24±0	0	13±1	65±2
6q	13±0	33±1	33±1	14±2	11±0	11±1	3±0	21±1
6r	29±0	30±1	13±0	7±1	34±1	28±1	18±1	70±3
6s	74±4	69±3	67±0	68±3	59±2	53±2	46±2	67±3
6t	65±2	47±1	63±2	64±2	62±3	56±2	39±2	66±2
6u	51±1	50±2	56±1	68±2	30±1	40±1	66±0	65±2
Oxathiapiprolin	10±1	56±2	32±2	100	16±0	25±1	20±1	90±3
Isotianil	23±1	7±1	17±1	21±1	24±1	22±0	16±1	45±2
Azoxystrobin	44±2	79±3	68±1	100	65±2	84±2	100	100

[a] *A. S*: *Alternaria solani, B. C*: *Botrytis cinereal, C. A*: *Cercospora arachidicola, G. Z*: *Gibberella zeae, P. P*: *Physalospora piricola*, *P. S*: *Pellicularia sasakii, R. C*: *Rhizoctonia cerealis* and *S. S*: *Sclerotinia sclerotiorum*

Table S3: In vivo antifungal activities of compounds **6a-6u** at 10 mg/L, 1 mg/L and 0.1 mg/L against *P. cubensis* and *P. infestans*.

Compd.	Inhibition rate (%) ± SD					
	P. cubensis			*P. infestans*		
	10 mg/L	1 mg/L	0.1 mg/L	10 mg/L	1 mg/L	0.1 mg/L
6a	//	//	//	//	//	//
6b	95±3	80±2	//	95±3	40±2	15±1
6c	40±1	10±1	//	40±2	10±1	0
6d	35±2	10	//	10±0	0	0
6e	10±1	0	//	10±1	0	0
6f	//	//	//	//	//	//
6g	//	//	//	//	//	//
6h	10±0	0	//	//	//	//
6i	//	//	//	35±0	10±0	0
6j	//	//	//	//	//	//
6k	80±0	50±1	//	80±3	35±3	10±1
6l	70±3	40±1	//	60±2	20±1	0
6m	95±2	70±3	//	90±3	50±2	20±2
6n	85±3	50±2	//	85±2	45±2	15±0
6o	10±1	0	//	//	//	//
6p	100	98±1	15±1	100	45±1	20±2
6q	10±0	0	//	//	//	//
6r	50±1	20±1	//	35±1	10±0	0
6s	98±3	20±	//	100	35±0	10±0
6t	//	//	//	70±2	15±1	10±1
6u	100	100	30±1	100	85±2	35±2
Oxathiapiprolin	100	98±2	100	100	98±2	95±4
Isotianil	100	70±1	0	98±2	45±0	15±0

Table S4: In vivo antifungal activities of compounds **6p** and **6u** at 0.01 mg/L and 0.001 mg/L against *P. cubensis* and *P. infestans*.

Compd.	Inhibition rate (%) ± SD	
	0.01 mg/L	0.001 mg/L
6p	10±1	0
6u	10±0	0
Oxathiapiprolin	70±3	15±1
Isotianil	0	0

3. Physico-Chemical Data of the Compounds Synthesized

*2-Bromo-1-(3,4-dichloroisothiazol-5-yl)ethanone (**2**)*: White solid, m.p. 52-53 °C, yield 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (d, *J* = 2.9 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.30 (s), 156.43 (s), 150.49 (s), 123.25 (s), 32.26 (s). HRMS (ESI) $[M-H]^-$ calcd for $C_5H_2BrCl_2NOS$ $(M-H)^-$: 271.8418, found: 271.8344.

*tert-Butyl 4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidine-1-carboxylate (**4**)*: White crystal, m.p. 153-155 °C, yield 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 4.21 (t, *J* = 10.7 Hz, 2H), 3.19 (m, 1H), 2.93 (t, *J* = 12.1 Hz, 2H), 2.13 (m, 2H), 1.77 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.31 (s), 155.10 (s), 154.66 (s), 148.73 (s), 143.35 (s), 116.74 (s), 79.75 (s), 43.40 (s), 40.38 (s), 32.19 (s), 28.44 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{16}H_{19}Cl_2N_3O_2S_2$ $[M+H]^+$: 420.0296, found: 420.0345.

*3,4-Dichloro-5-(2-(piperidin-4-yl)thiazol-4-yl)isothiazole (**5**)*: White solid, m.p. 97-99 °C, yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 5.31 (s, 1H), 3.22 (t, *J* = 11.6 Hz, 2H), 3.17 (s, 1H), 2.78 (t, *J* = 11.7 Hz, 2H), 2.14 (m, 2H), 1.76 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.51 (s), 155.26 (s), 148.73 (s), 143.20 (s), 116.66 (s), 46.25 (s), 40.86 (s), 33.66 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_{11}Cl_2N_3S_2$ $[M+H]^+$: 319.9771, found: 319.9850.

*1-(4-(4-(3,4-Dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)ethanone (**6a**)*: White solid, m.p. >200 °C, yield 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 6.35 (s, 1H), 5.01 (s, 2H), 4.58 (d, *J* = 13.3 Hz, 1H), 4.08 (d, *J* = 12.5 Hz, 1H), 3.33 (s, 2H), 2.93 (m, 1H), 2.34 (s, 3H), 2.22 (m, 2H), 1.91 – 1.68 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 175.78 (s), 164.20 (s), 155.15 (s), 147.85 (s), 142.28 (s), 141.62 (s), 131.49 (s), 128.63 (s), 119.28 (s), 103.47 (s), 64.99 (s), 51.08 (s), 43.86 (s), 41.15 (s), 31.96 (s), 31.62 (s), 10.60 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{16}Cl_2F_3N_5OS_2$ $[M+H]^+$: 510.0125, found: 510.0203.

*1-(4-(4-(3,4-Dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)-2-phenylethanone (**6b**)*: White solid, m.p. 135-136 °C, yield 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.26 (dd, *J* = 21.2, 6.6 Hz, 5H), 4.64 (d, *J* = 13.1 Hz, 1H), 3.93 (d, *J* = 13.4 Hz, 1H), 3.75 (s, 2H), 3.25 – 3.06 (m, 2H), 2.81 m, 1H), 2.05 (m, 2H), 1.76 – 1.63 (m, 1H), 1.46 (m,

1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.61 (s), 169.55 (s), 155.01 (s), 148.73 (s), 143.29 (s), 134.99 (s), 128.81 (s), 128.59 (s), 126.89 (s), 116.91 (s), 45.77 (s), 41.52 (s), 41.19 (s), 40.03 (s), 32.21 (s), 31.88 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{17}Cl_2N_3OS_2$ $[M+H]^+$: 438.0190, found: 438.0261.

*(4-(4-(3,4-Dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)(5-(difluoromethyl)-1-phenyl-1H-pyrazol-4-yl)methanone (**6c**)*: White solid, m.p. 125-127 °C, yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.78 (s, 1H), 7.54 (s, 5H), 6.93 (t, *J* = 53.0 Hz, 1H), 4.76 (s, 1H), 4.24 (d, *J* = 64.7 Hz, 1H), 3.38 (s, 2H), 3.14 (s, 1H), 2.27 (m, 2H), 1.91 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.36 (s), 162.42 (s), 154.96 (s), 148.85 (s), 143.49 (s), 138.90 (s), 138.50 (s), 134.74 (s), 129.47 (s), 129.33 (s), 125.45 (s), 118.64 (s), 116.94 (s), 107.97 (t, *J* = 237.2 Hz), 47.24 (s), 41.75 (s), 40.15 (s), 32.18 (s), 30.58 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{17}Cl_2F_2N_5OS_2$ $[M+H]^+$: 540.0220, found: 540.0299.

*(4-(4-(3,4-Dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)(5-(difluoromethyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)methanone (**6d**)*: White crystal, m.p. 139-141 °C, yield 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.77 (s, 1H), 7.49 (dd, *J* = 14.2, 8.0 Hz, 1H), 7.35 (dd, *J* = 19.4, 8.6 Hz, 2H), 7.21 (t, *J* = 8.2 Hz, 1H), 6.98 (t, *J* = 52.8 Hz, 1H), 4.74 (s, 1H), 4.27 (dd, *J* = 35.7, 29.1 Hz, 1H), 3.37 (t, *J* = 12.8, 9.3 Hz, 2H), 3.13 (m, 1H), 2.28 (m, 2H), 1.99 – 1.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.95 (s), 164.49 (s), 162.84 (s), 162.02 (s), 155.63 (s), 149.56 (s), 144.21 (s), 140.87 (d, *J* = 10.0 Hz), 139.46 (s), 131.25 s), 121.74 (s), 119.90 (s), 117.63 (s), 117.21 (s), 113.90 (s), 108.45 (t, *J* = 237.5 Hz), 47.89 (s), 42.54 (s), 40.80 (s), 32.91 (s), 32.09 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{16}Cl_2F_3N_5OS_2$ $[M+H]^+$: 558.0125, found: 558.0197.

*(1-(4-Chlorophenyl)-5-(difluoromethyl)-1H-pyrazol-4-yl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6e**)*: White solid, m.p. 153-155 °C, yield 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.77 (s, 1H), 7.50 (s, 4H), 6.99 (t, *J* = 52.8 Hz, 1H), 4.73 (s, 1H), 4.27 – 4.00 (m, 1H), 3.38 (t, *J* = 10.9 Hz, 2H), 3.12 (m, 1H), 2.28 (m, 2H), 1.91 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.24 (s), 162.17 (s), 154.93 (s), 148.86 (s), 143.50 (s), 138.70 (s), 137.55 (s), 135.43 (s), 130.93 (s), 129.48 (s), 126.70 (s), 119.10 (s), 116.95 (s), 107.75 (t, *J* = 237.4 Hz) , 47.08 (s), 41.87 (s), 40.10 (s), 32.06 (s), 30.57 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{16}Cl_3F_2N_5OS_2$ $[M+H]^+$:

573.9830, found: 573.9901.

*(1-(4-Bromophenyl)-5-(difluoromethyl)-1H-pyrazol-4-yl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6f**)*: White solid, m.p. 163-164 °C, yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.77 (s, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 6.98 (t, *J* = 52.8 Hz, 1H), 4.73 (s, 1H), 4.28 – 4.04 (m, 1H), 3.38 (t, *J* = 10.8 Hz, 2H), 3.12 (m, 1H), 2.28 (m, 2H), 1.91 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.20 (s), 161.14 (s), 153.89 (s), 147.81 (s), 142.45 (s), 137.70 (s), 137.02 (s), 134.07 (s), 131.43 (s), 125.90 (s), 122.43 (s), 118.10 (s), 115.93 (s), 106.71 (t, *J* = 237.4 Hz), 46.19 (s), 40.87 (s), 39.05 (s), 31.23 (s), 30.89 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{16}BrCl_2F_2N_5OS_2$ $[M+H]^+$: 617.9325, found: 617.9505.

*(4-(4-(3,4-Dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)(1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)methanone (**6g**)*: White solid, m.p. 181-183 °C, yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.76 (s, 1H), 7.50 (d, *J* = 8.2 Hz, 5H), 4.79 (d, *J* = 12.8 Hz, 1H), 3.91 (d, *J* = 12.7 Hz, 1H), 3.34 (t, *J* = 14.6 Hz, 2H), 3.10 (m, 1H), 2.26 (m, 2H), 1.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.24 (s), 161.65 (s), 154.94 (s), 148.86 (s), 143.48 (s), 138.68 (s), 138.10 (s), 129.88 (s), 129.27 (s), 125.80 (s), 120.85 (s), 119.52 (s), 118.16 (s), 116.97 (s), 46.97 (s), 41.49 (s), 40.03 (s), 32.30 (s), 31.74 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{16}Cl_2F_3N_5OS_2$ $[M+H]^+$: 558.0125, found: 558.0190.

*(4-(4-(3,4-Dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)(1-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)methanone (**6h**)*: White powder, m.p. 187-189 °C, yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.68 (s, 1H), 7.40 (dd, *J* = 8.6, 4.6 Hz, 2H), 7.13 (t, *J* = 8.4 Hz, 2H), 4.71 (d, *J* = 13.4 Hz, 1H), 3.81 (d, *J* = 13.4 Hz, 1H), 3.28 (d, *J* = 3.4 Hz, 1H), 3.25 (s, 1H), 3.02 (m, 1H), 2.18 (m, 2H), 1.89 – 1.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.13 (s), 163.30 (s), 160.81 (s), 160.44 (s), 153.87 (s), 147.84 (s), 142.45 (s), 137.16 (s), 133.65 (s), 126.84 (d, *J* = 9.0 Hz), 119.72 (s), 118.55 (s), 117.03 (s), 115.63 (dd, *J* = 67.0, 15.0 Hz), 45.92 (s), 40.46 (s), 38.95 (s), 31.24 (s), 30.68 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{15}Cl_2F_4N_5OS_2$ $[M+H]^+$: 576.0031, found: 576.0100.

(1-(4-Chlorophenyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)(4-(4-(3,4-dichloroisothiazol-

*5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6i**)*: White solid, m.p. 133-135 °C, yield 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.77 (s, 1H), 7.54 – 7.48 (m, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 4.79 (d, *J* = 13.5 Hz, 1H), 3.90 (d, *J* = 13.6 Hz, 1H), 3.42 – 3.28 (m, 2H), 3.11 (m, 1H), 2.27 (m, 2H), 1.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.15 (s), 161.39 (s), 154.91 (s), 148.87 (s), 143.52 (s), 138.40 (s), 137.15 (s), 135.96 (s), 129.52 (s), 127.05 (s), 120.77 (s), 119.88 (s), 118.08 (s), 116.94 (s), 46.94 (s), 41.49 (s), 39.99 (s), 32.28 (s), 31.71 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{15}Cl_3F_3N_5OS_2$ $[M+H]^+$: 591.9736, found: 591.9806.

*(1-(4-Bromophenyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6j**)*: White solid, m.p. 166-168 °C, yield 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 5.2 Hz, 1H), 7.77 (d, *J* = 4.5 Hz, 1H), 7.63 (s, 2H), 7.36 (s, 2H), 4.75 (s, 1H), 3.87 (s, 1H), 3.32 (s, 2H), 3.09 (s, 1H), 2.23 (m, 2H), 1.84 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.11 (s), 160.27 (s), 153.87 (s), 147.68 (s), 142.32 (s), 137.39 (s), 136.61 (s), 131.43 (s), 126.22 (s), 122.89 (s), 119.71 (s), 118.91 (s), 117.02 (s), 115.96 (s), 45.88 (s), 40.42 (s), 38.87 (s), 31.33 (s), 30.91 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{15}BrCl_2F_3N_5OS_2$ $[M+H]^+$: 635.9231, found: 635.9305.

*(5-Chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6k**)*: White solid, m.p. 167-169 °C, yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 74.7 Hz, 1H), 7.50 – 7.04 (m, 5H), 4.60 (s, 1H), 3.59 (d, *J* = 64.5 Hz, 1H), 3.12 (t, *J* = 64.9 Hz, 2H), 2.99 – 2.75 (m, 1H), 2.12 (m, 2H), 1.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.17 (s), 159.72 (s), 154.92 (s), 148.88 (s), 143.49 (s), 136.79 (s), 129.85 (s), 129.45 (s), 125.30 (s), 121.60 (s), 121.60 (s), 118.92 (s), 116.99 (s), 114.77 (s), 46.80 (s), 41.68 (s), 40.01 (s), 32.60 (m), 31.80 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{15}Cl_3F_3N_5OS_2$ $[M+H]^+$: 591.9736, found: 591.9812.

*(5-Chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6l**)*: White solid, m.p. 145-147 °C, yield 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.49 (dd, *J* = 8.7, 4.6 Hz, 2H), 7.17 (dd, *J* = 14.8, 6.4 Hz, 2H), 4.68 (s, 1H), 3.74 (d, *J* = 13.1 Hz, 1H), 3.28 (t, *J* = 10.8 Hz, 2H), 3.09 (s, 1H), 2.19 m, 2H), 1.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.07 (s), 163.21 (s), 160.71 (s), 158.54 (s), 153.88 (s), 147.84 (s), 142.46 (s), 131.81

(s), 126.40 (s), 126.31 (s), 120.49 (s), 117.80 (s), 115.96 (s), 115.63 (s), 115.39 (s), 113.80 (s), 45.72 (s), 40.55 (s), 38.92 (s), 31.52 (s), 30.73 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{14}Cl_3F_4N_5OS_2$ $[M+H]^+$: 609.9641, found: 609.9711.

*(5-Chloro-1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6m**)*: White solid, m.p. 171-173 °C, yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.45 (s, 4H), 4.68 (s, 1H), 3.73 (d, *J* = 13.2 Hz, 1H), 3.28 (t, *J* = 10.7 Hz, 2H), 3.09 (s, 1H), 2.35 – 2.09 (m, 2H), 1.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.77 (s), 160.19 (s), 155.60 (s), 149.59 (s), 144.22 (s), 136.62 (s), 135.95 (s), 131.62 (s), 130.37 (s), 127.16 (s), 122.19 (s), 119.50 (s), 117.67 (s), 115.76 (s), 47.42 (s), 42.29 (s), 40.62 (s), 33.25 (s), 33.25 (s), 32.45 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{14}Cl_4F_3N_5OS_2$ $[M+H]^+$: 625.9346, found: 625.9415.

*(1-(4-Bromophenyl)-5-chloro-3-(trifluoromethyl)-1H-pyrazol-4-yl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6n**)*: White powder, m.p. 176-178 °C, yield 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.56 – 7.34 (m, 4H), 4.66 (s, 1H), 3.73 (d, *J* = 13.1 Hz, 1H), 3.27 (t, *J* = 10.7 Hz, 2H), 3.07 (s, 1H), 2.18 (m, 2H), 1.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.04 (s), 158.44 (s), 153.87 (s), 147.78 (s), 142.40 (s), 134.84 (s), 134.18 (s), 131.61 (s), 129.91 (s), 128.63 (s), 127.80 (s), 125.42 (s), 120.45 (s), 117.76 (s), 115.98 (s), 114.01 (s), 45.76 (s), 40.59 (s), 38.92 (s), 31.56 (s), 30.70 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{14}BrCl_3F_3N_5OS_2$ $[M+H]^+$: 669.8841, found: 669.8881.

*(3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6o**)*: White powder, m.p. >200 °C, yield 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.5 Hz, 1H), 8.09 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.36 (dd, *J* = 8.0, 4.7 Hz, 1H), 6.57 (s, 1H), 4.59 (s, 1H), 4.24 (s, 1H), 3.34 (s, 2H), 2.97 (m, 1H), 2.17 (m, 2H), 1.92 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.20 (s), 159.37 (s), 154.93 (s), 148.90 (s), 147.64 (s), 146.48 (s), 143.52 (s), 140.13 (s), 139.47 (s), 127.73 (s), 127.17 (s), 125.21 (s), 116.91 (s), 109.98 (s), 47.16 (s), 41.89 (s), 40.06 (s), 32.15 (s), 31.70 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{20}H_{14}BrCl_3N_6OS_2$ $[M+H]^+$: 602.8919, found: 602.8979.

*(4-(4-(3,4-Dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)(phenyl)methanone (**6p**)*:

White crystal, m.p. 163-164 °C, yield 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.33 (s, 5H), 4.68 (s, 1H), 3.81 (s, 1H), 3.23 (m, 1H), 3.04 (t, *J* = 55.1 Hz, 2H), 2.10 (m, 2H), 1.74 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.60 (s), 170.57 (s), 155.00 (s), 148.72 (s), 143.31 (s), 135.78 (s), 129.81 (s), 128.57 (s), 126.94 (s), 117.00 (s), 47.40 (s), 41.07 (d, *J* = 166.2 Hz), 32.35 (d, *J* = 46.9 Hz). HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{15}Cl_2N_3OS_2$ $[M+H]^+$: 424.0034, found: 424.0109.

*(4-(4-(3,4-Dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)(4-fluorophenyl)methanone (**6q**): White crystal, m.p. 164-165 °C, yield 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ* 8.08 (s, 1H), 7.50 – 7.39 (m, 2H), 7.12 (t, *J* = 8.3 Hz, 2H), 4.74 (s, 1H), 3.92 (s, 1H), 3.34 (t, *J* = 11.3 Hz, 1H), 3.14 (s, 2H), 2.22 (s, 2H), 1.86 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.46 (s), 169.61 (s), 164.67 (s), 162.18 (s), 154.96 (s), 148.76 (s), 143.38 (s), 131.81 (s), 129.29 (s), 116.95 (s), 115.74 (s), 115.53 (s), 47.37 (s), 40.21 (s), 32.33 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{14}Cl_2FN_3OS_2$ $[M+H]^+$: 441.9939, found: 442.0008.

*(4-Chlorophenyl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6r**)*: White solid, m.p. 179-181 °C, yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.50 – 7.32 (m, 4H), 4.74 (s, 1H), 3.88 (s, 1H), 3.39 – 3.28 (m, 1H), 3.14 (t, *J* = 42.4 Hz, 2H), 2.20 (m, 2H), 1.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.40 (s), 169.50 (s), 154.94 (s), 148.87 (s), 143.49 (s), 135.93 (s), 134.14 (s), 128.87 (s), 128.53 (s), 116.92 (s), 47.47 (s), 40.23 (s), 32.17 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{14}Cl_3N_3OS_2$ $[M+H]^+$: 457.9644, found: 457.9711.

*(3-Chlorophenyl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6s**)*: White solid, m.p. 116-118 °C, yield 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.47 – 7.30 (m, 4H), 4.76 (s, 1H), 3.88 (s, 1H), 3.35 (m, 1H), 3.16 (t, *J* = 51.4 Hz, 2H), 2.23 (m, 2H), 1.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.33 (s), 167.94 (s), 153.91 (s), 147.84 (s), 142.48 (s), 136.50 (s), 133.68 (s), 132.29 (s), 128.94 (s), 126.13 (s), 123.98 (s), 115.88 (s), 46.34 (s), 40.85 (s), 39.17 (s), 31.43 (s), 30.99 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{14}Cl_3N_3OS_2$ $[M+H]^+$: 457.9644, found: 457.9715.

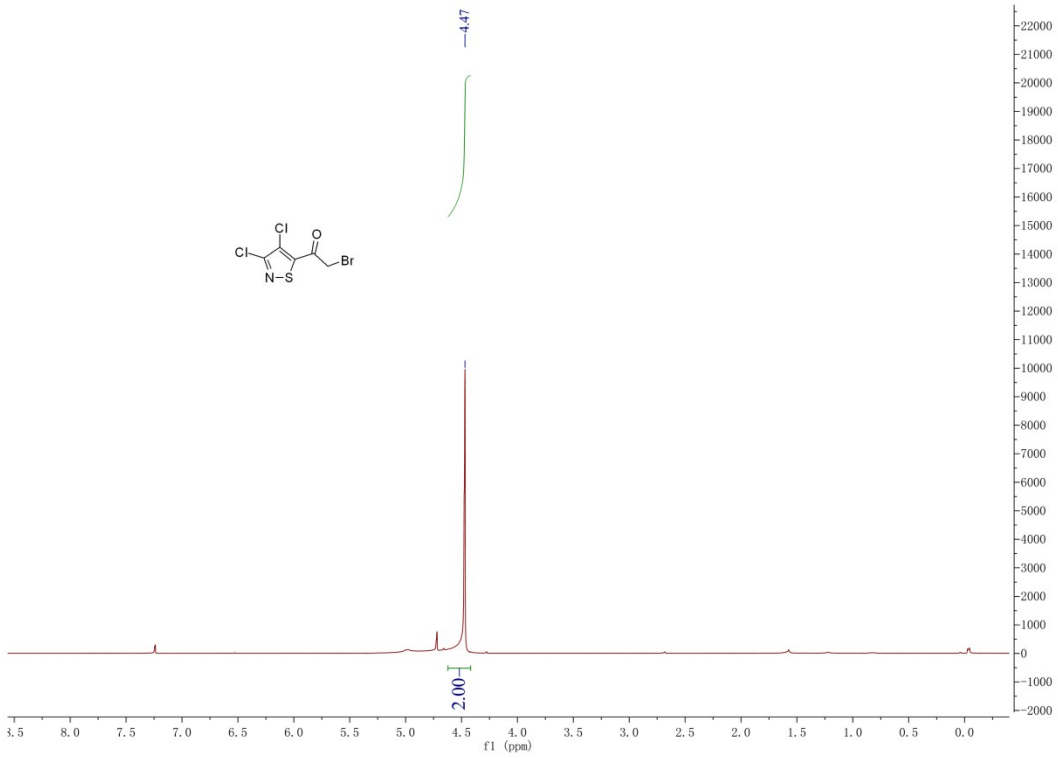
*(4-Bromophenyl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6t**)*: White crystal, m.p. 187-189 °C, yield 60%. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.10 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 4.76 (s, 1H), 3.89 (s, 1H), 3.36 (s, 1H), 3.16 (t, *J* = 45.6 Hz, 2H), 2.27 (m, 2H), 1.88 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.37 (s), 169.56 (s), 154.94 (s), 148.88 (s), 143.49 (s), 134.57 (s), 131.83 (s), 128.71 (s), 124.18 (s), 116.92 (s), 40.21 (s), 30.58 (s), 29.71 (s). HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{14}BrCl_2N_3OS_2$ $[M+H]^+$: 501.9139, found: 501.9209.

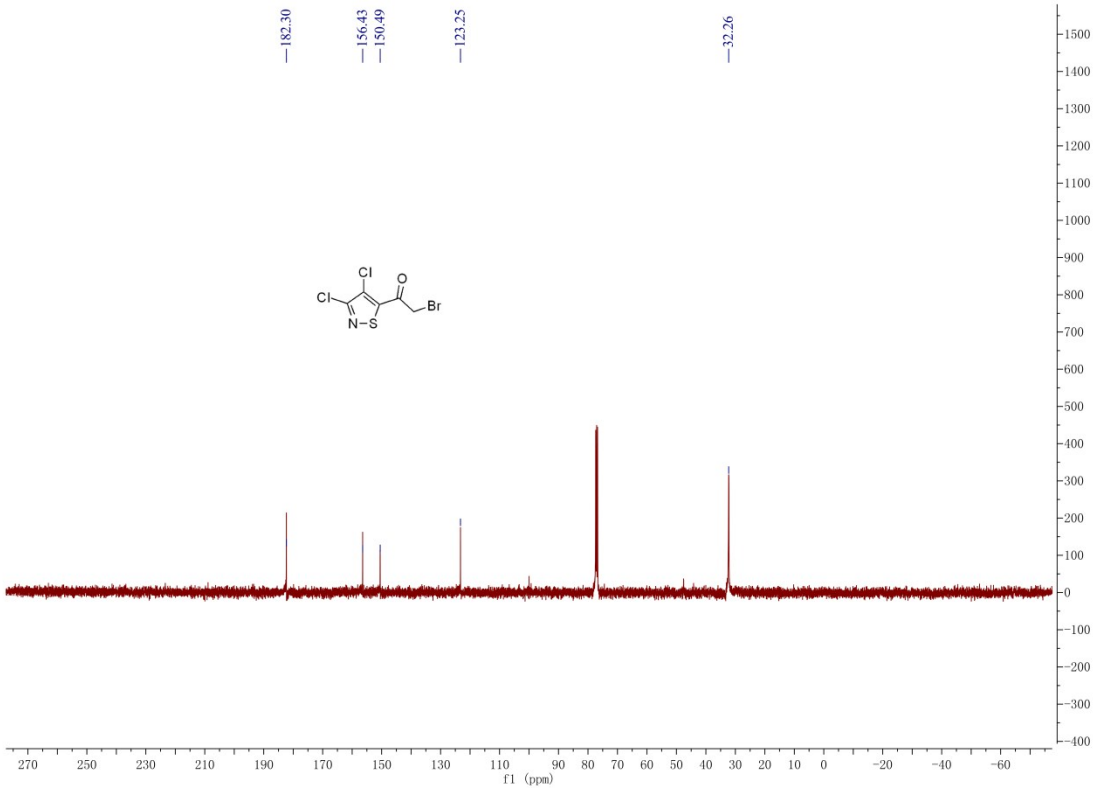
*(3-Bromophenyl)(4-(4-(3,4-dichloroisothiazol-5-yl)thiazol-2-yl)piperidin-1-yl)methanone (**6u**)*: White solid, m.p. 117-119 °C, yield 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.49 (d, *J* = 11.8 Hz, 2H), 7.34 – 7.18 (m, 2H), 4.66 (s, 1H), 3.78 (s, 1H), 3.25 (m, 1H), 3.07 (t, *J* = 66.6 Hz, 2H), 2.13 (m, 2H), 1.77 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.34 (s), 168.83 (s), 154.94 (s), 148.81 (s), 143.40 (s), 137.69 (s), 132.89 (s), 130.23 (s), 130.00 (s), 125.46 (s), 122.75 (s), 116.99 (s), 47.36 (s), 41.88 (s), 40.14 (s), 32.63 (s), 31.99(s). HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{14}BrCl_2N_3OS_2$ $[M+H]^+$: 501.9139, found: 501.9216.

4. NMR-Spectra

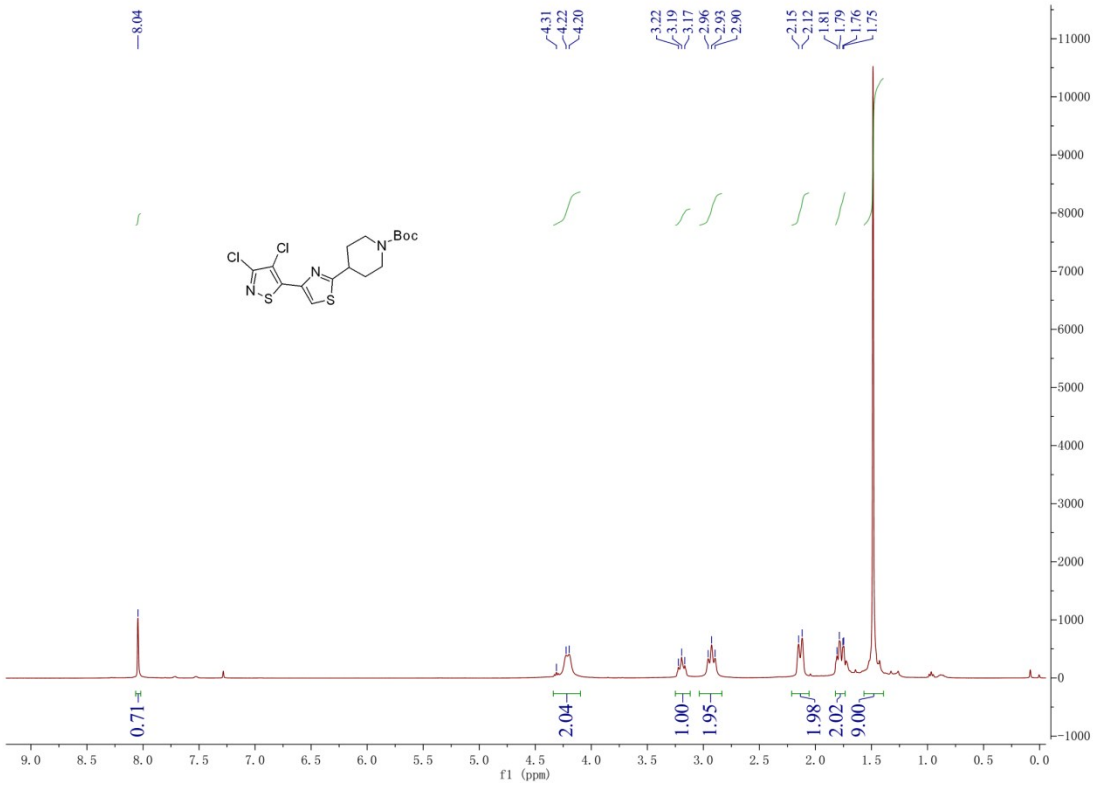
^{1}H NMR (400 MHz, $CDCl_3$) of compound **2**



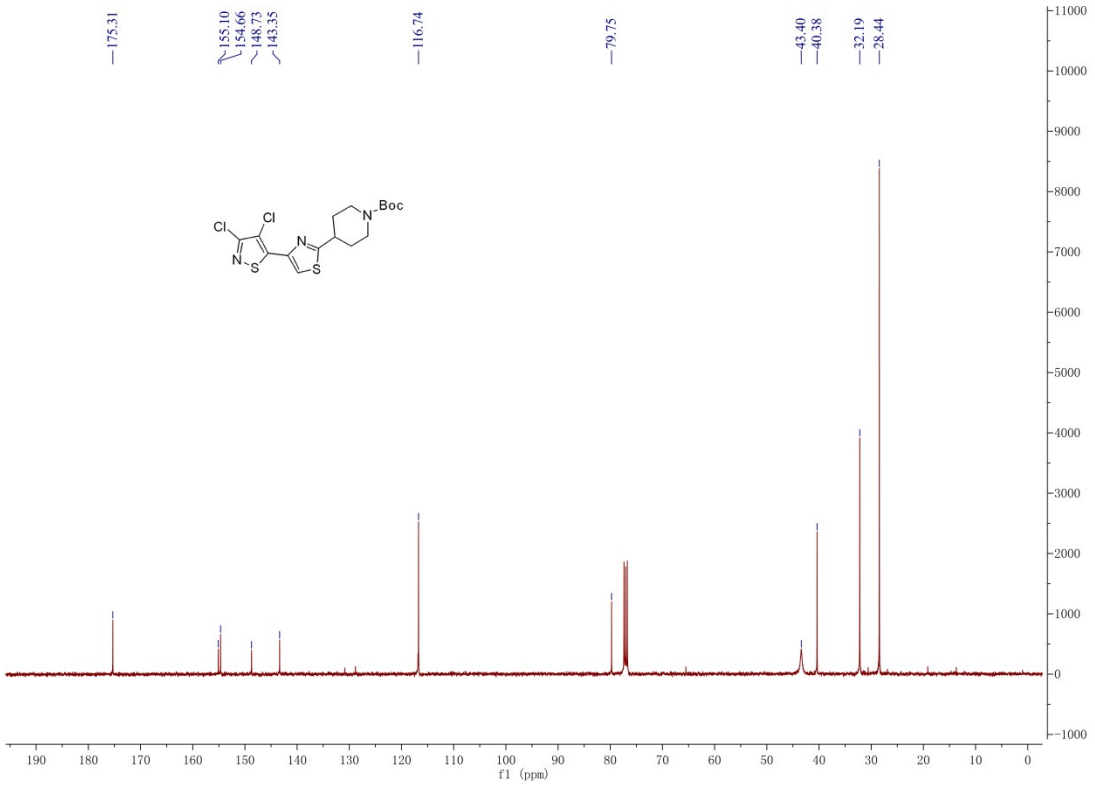
^{13}C NMR (101 MHz, $CDCl_3$) of compound **2**



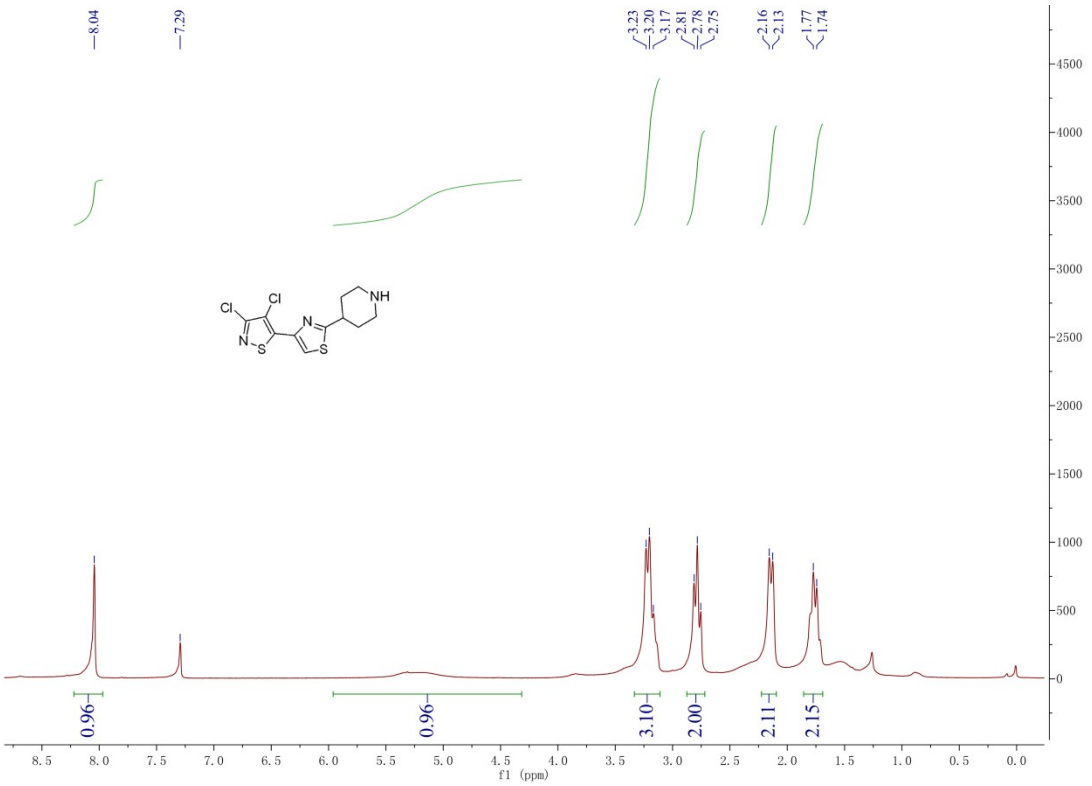
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4**



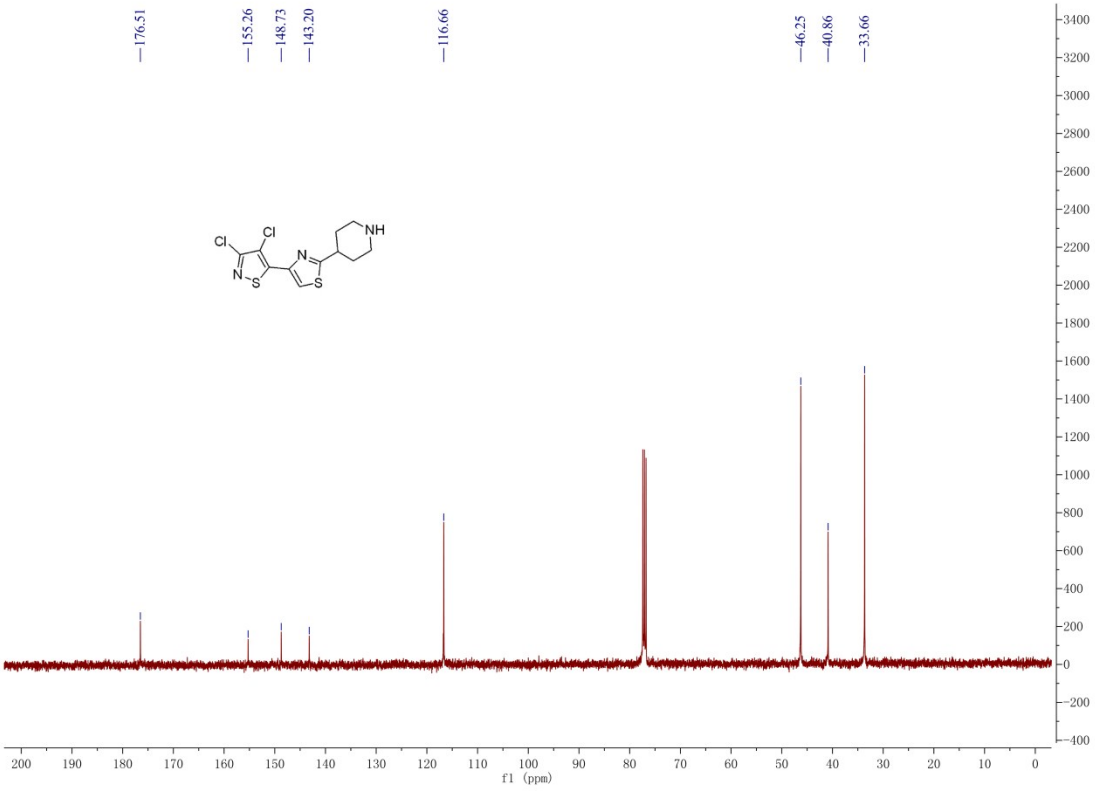
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4**



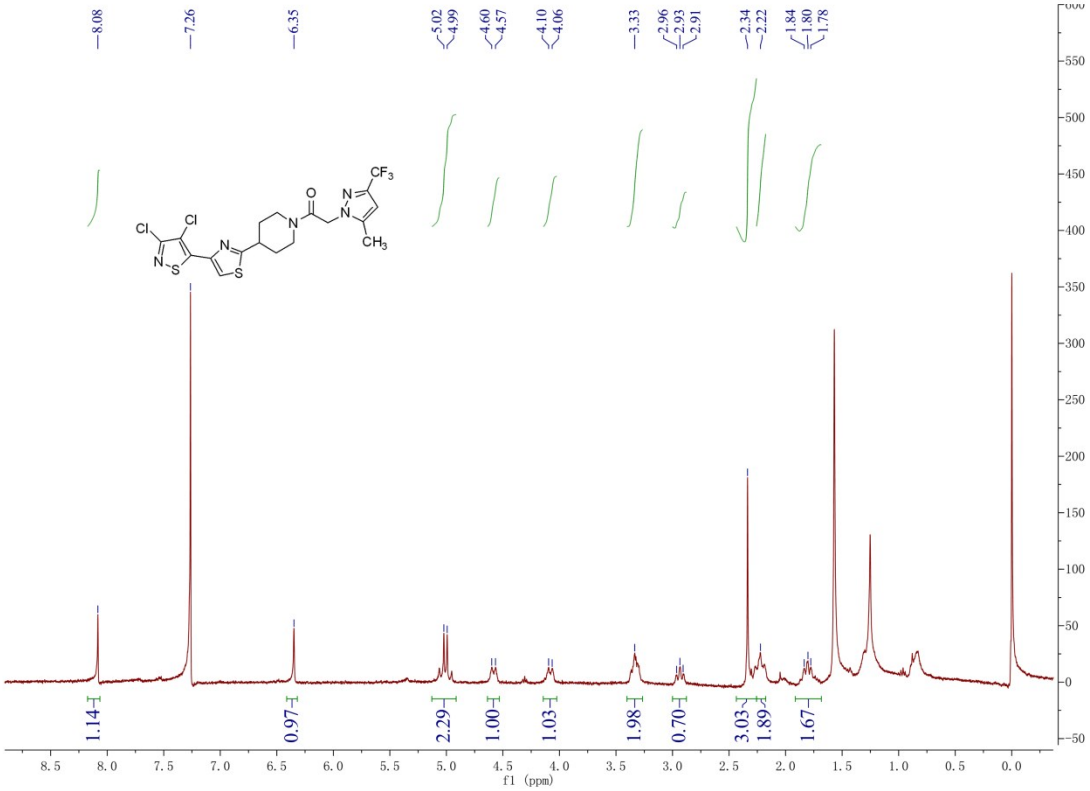
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5**



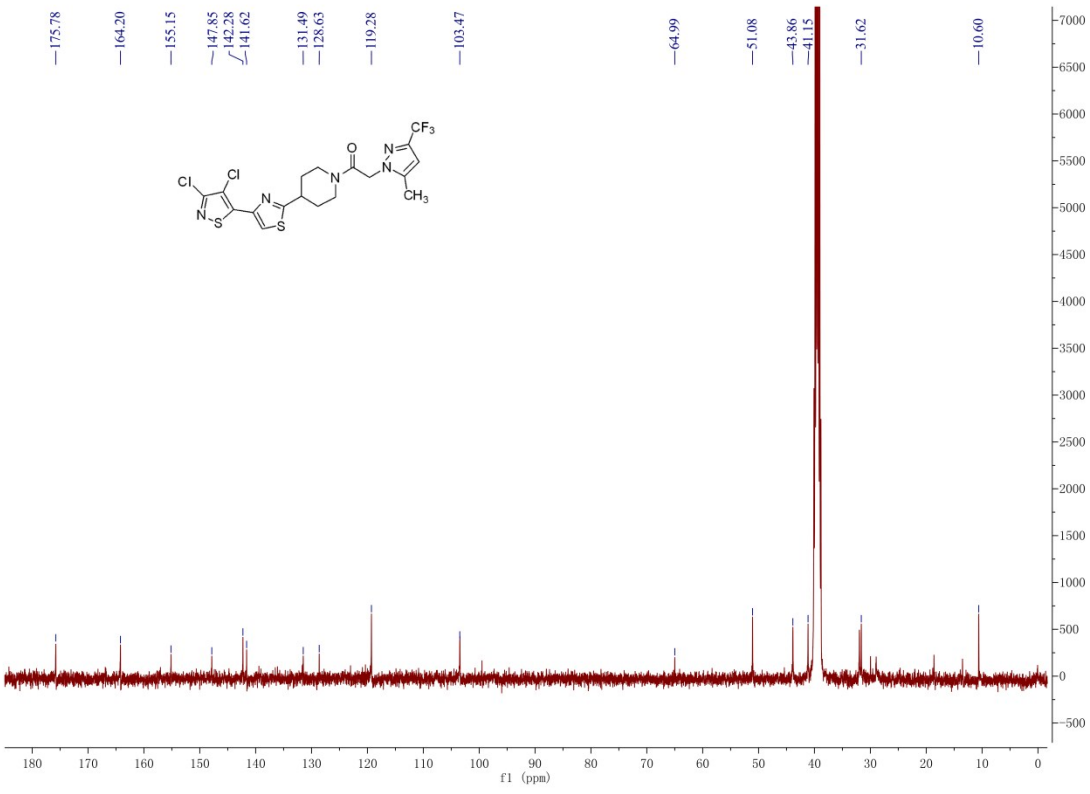
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5**



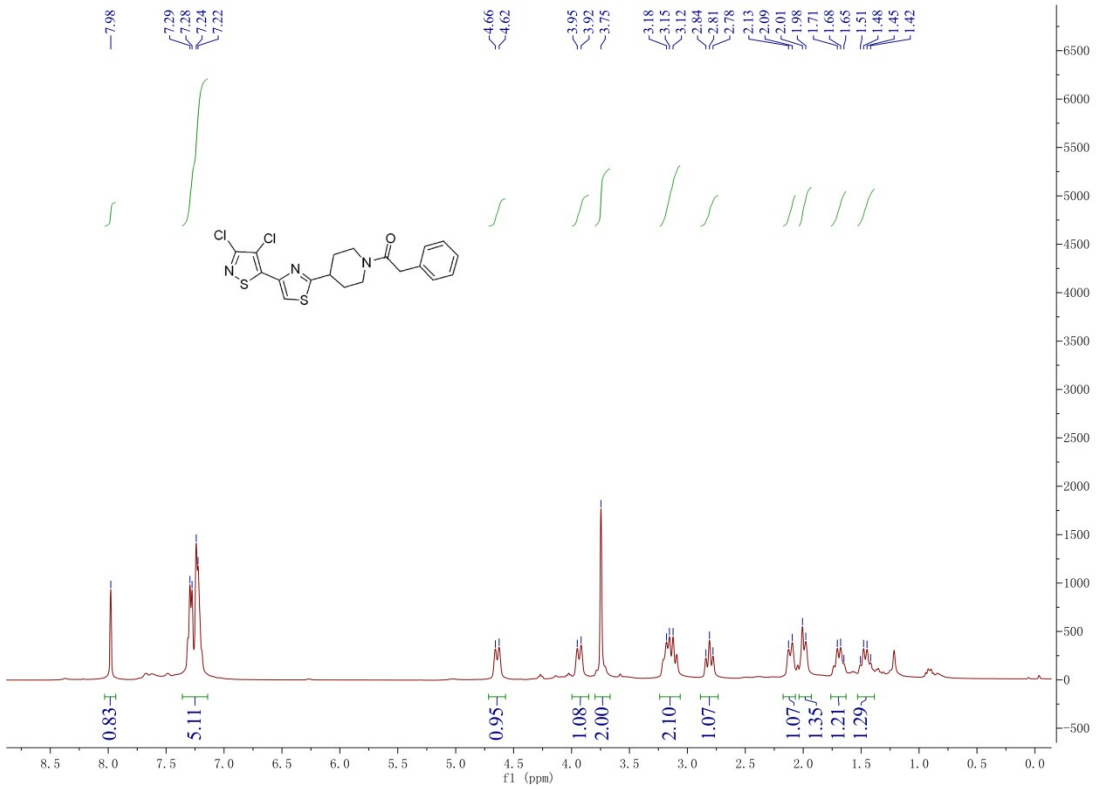
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6a**



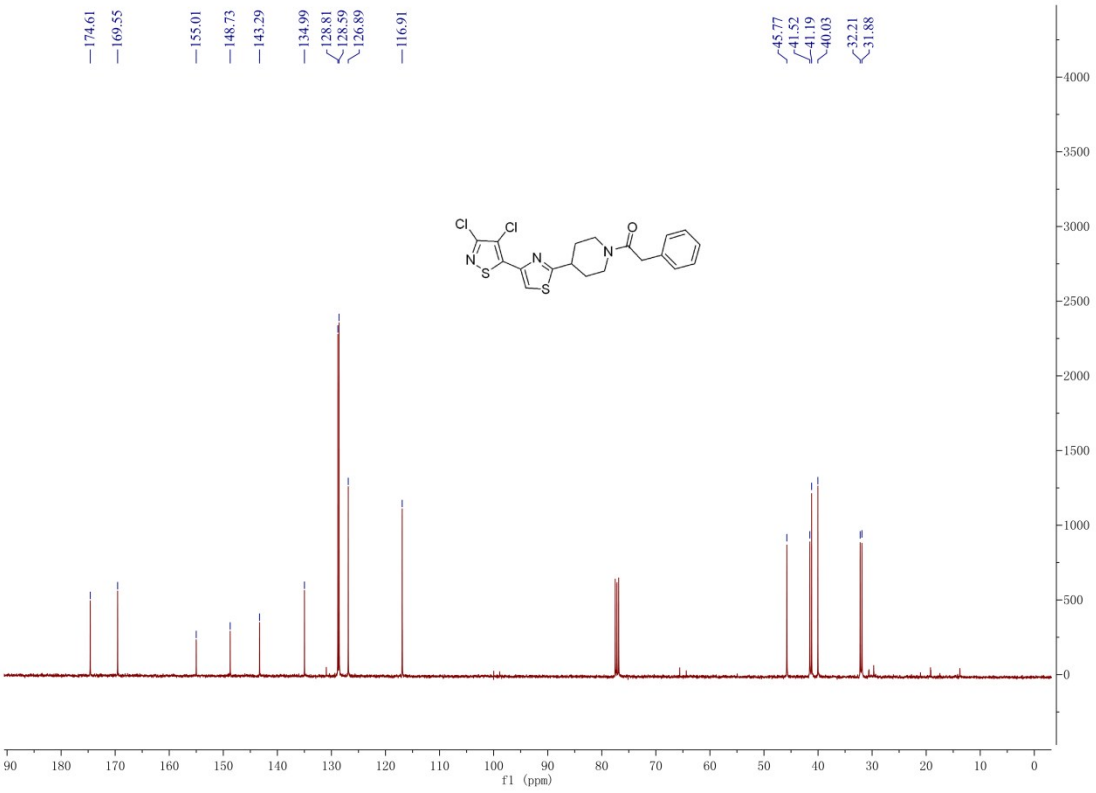
^{13}C NMR (101 MHz, DMSO) of compound **6a**



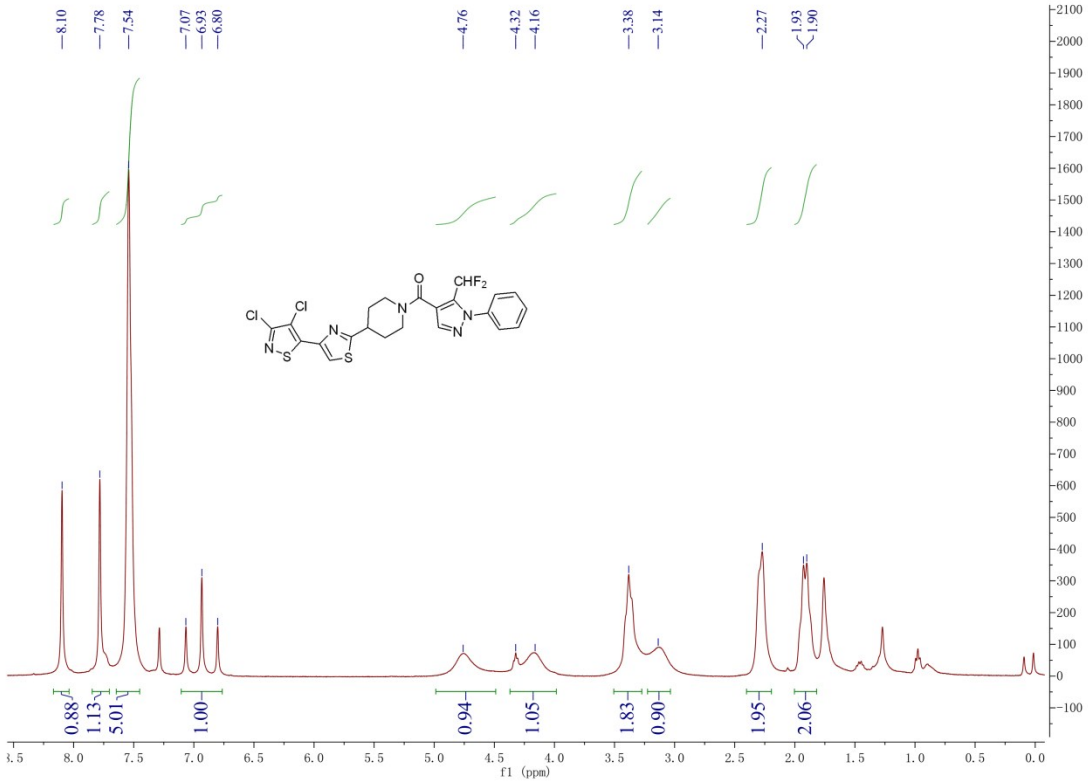
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6b**



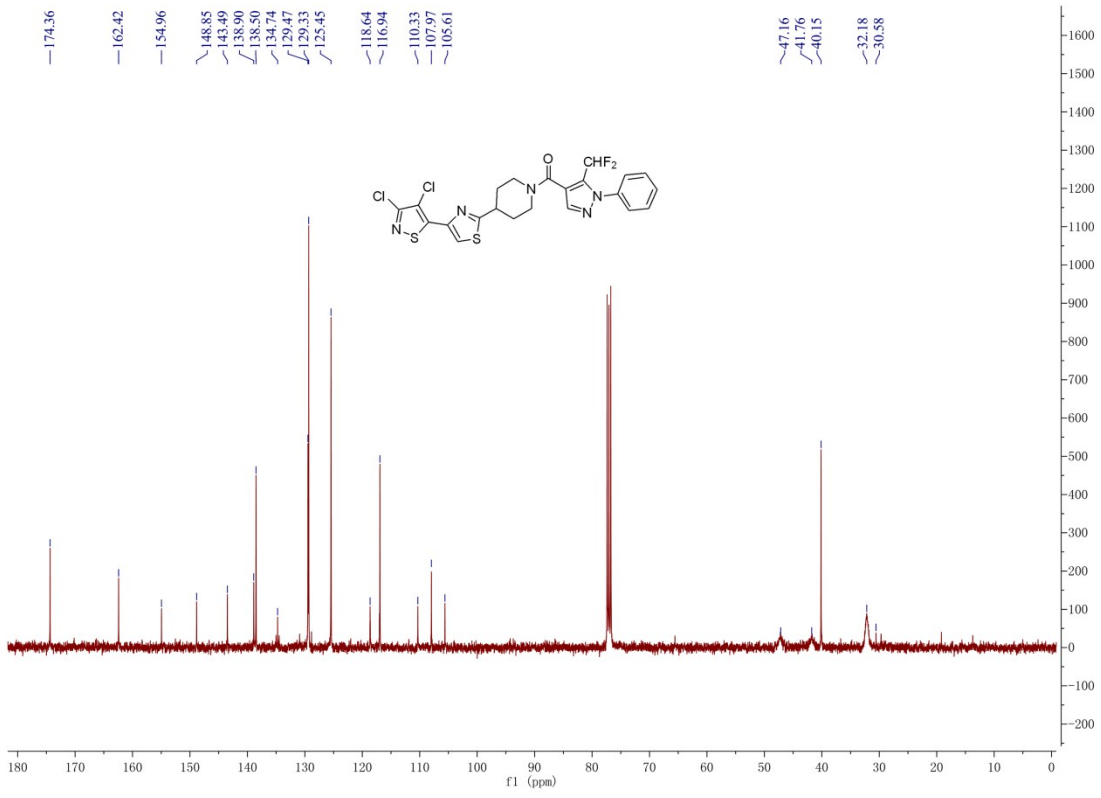
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6b**



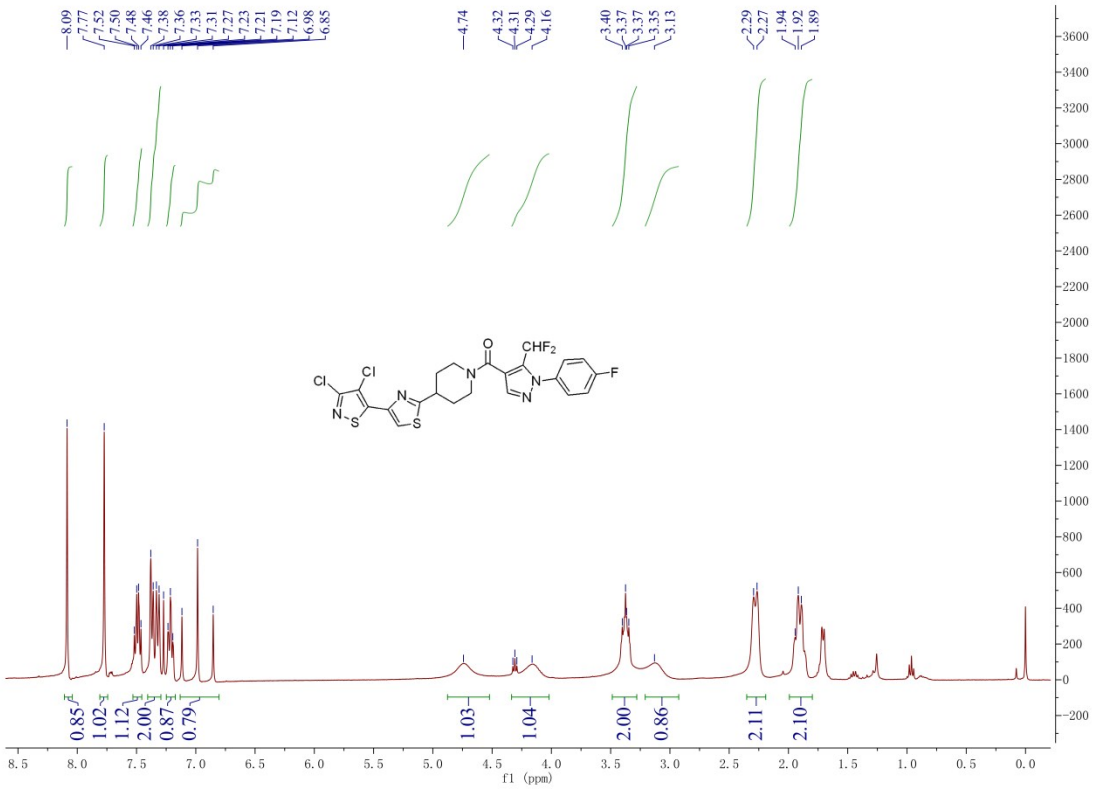
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6c**



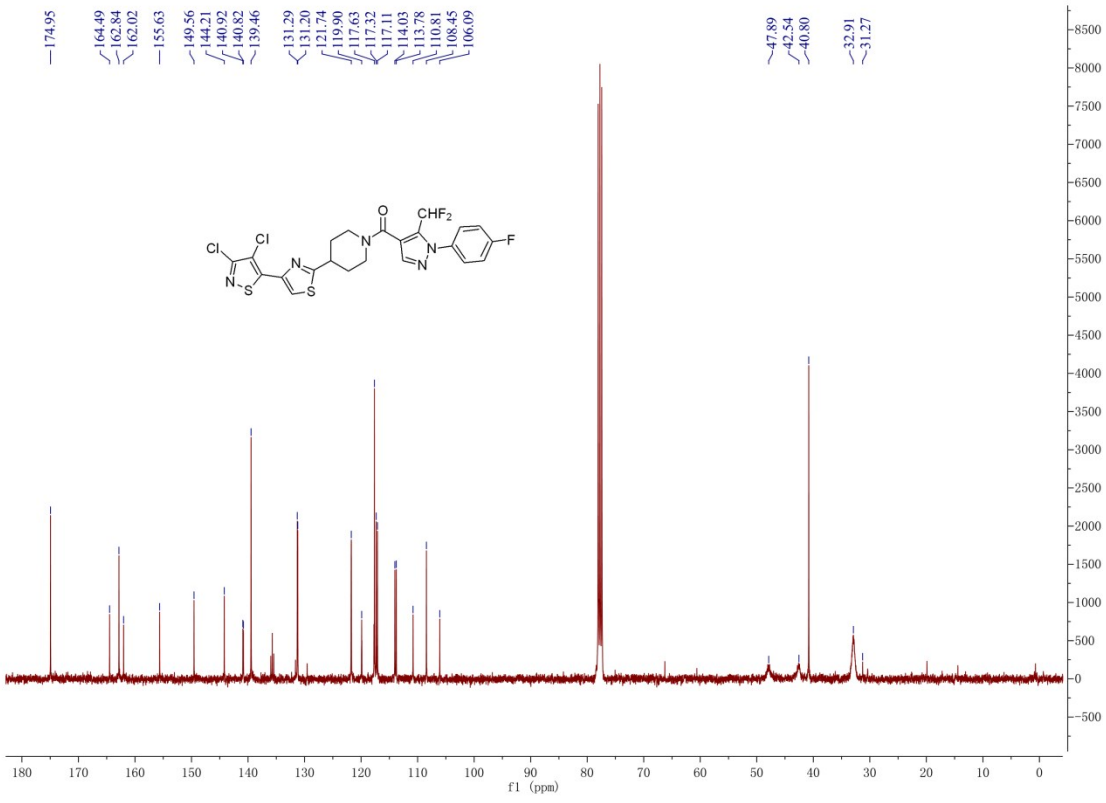
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6c**



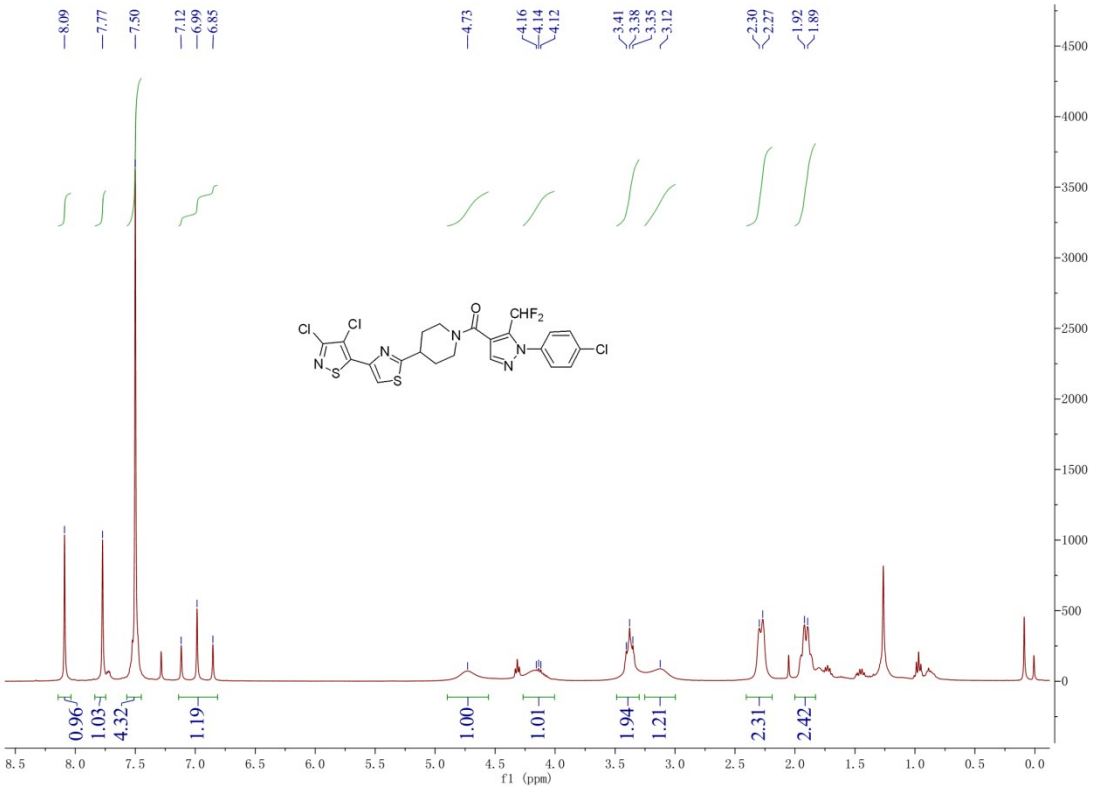
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6d**



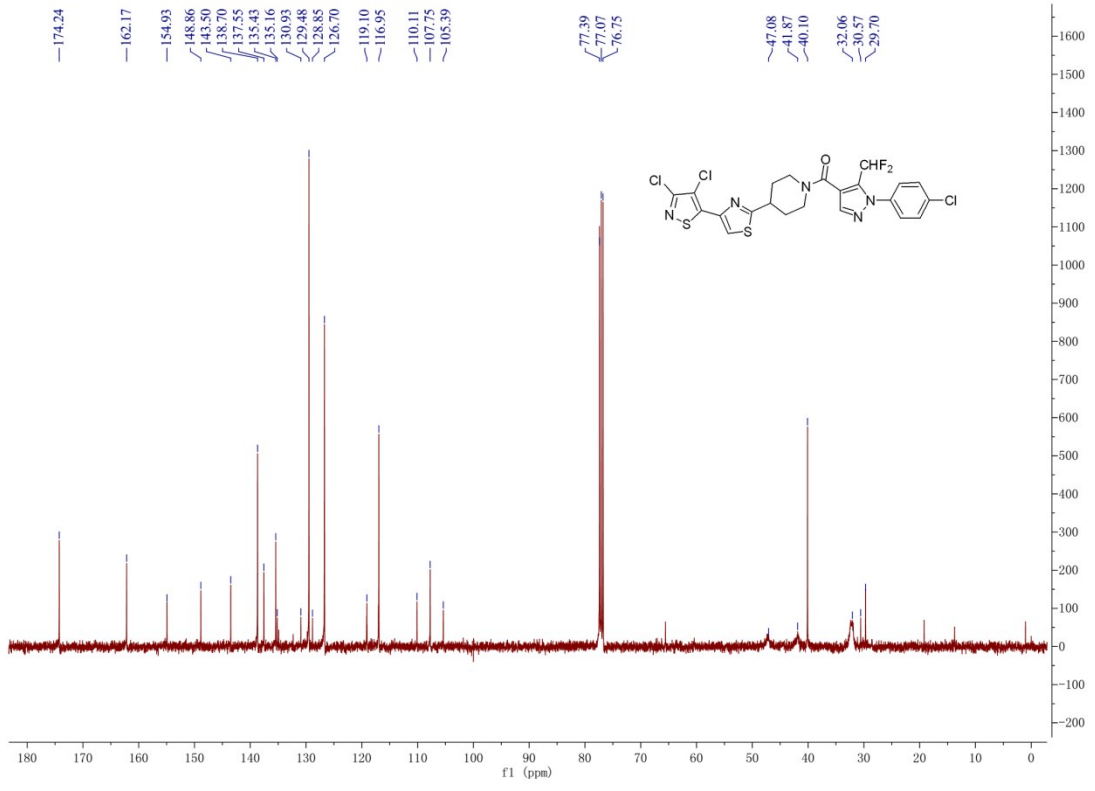
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6d**



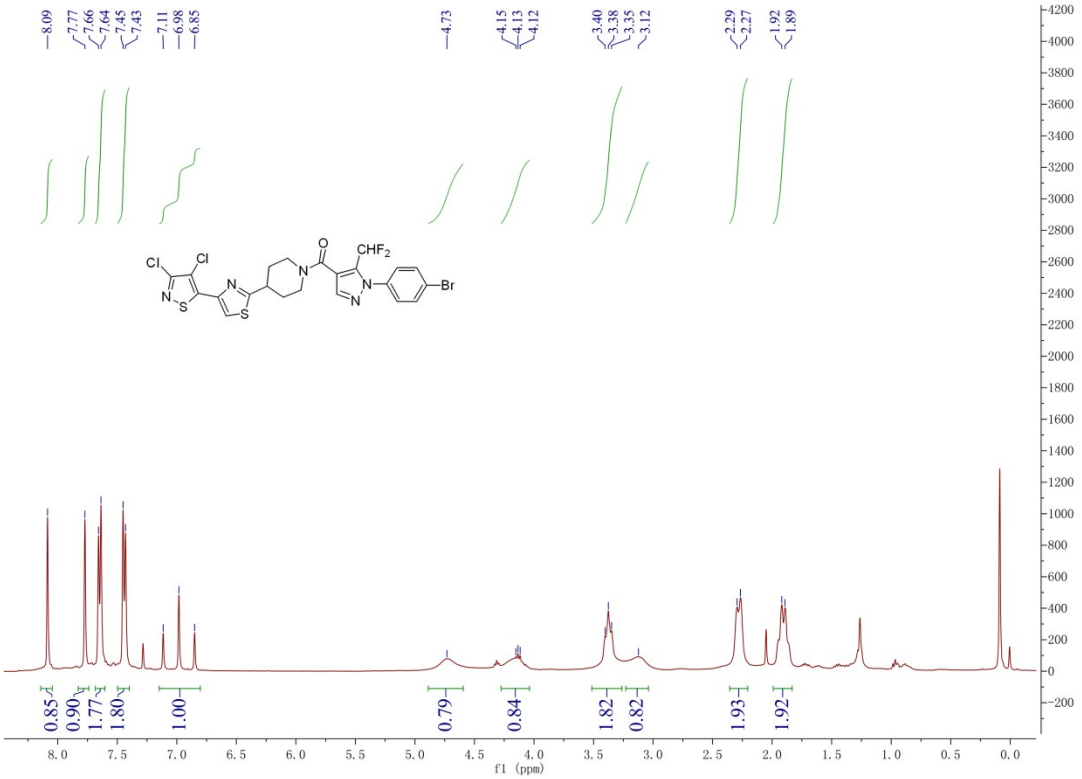
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6e**



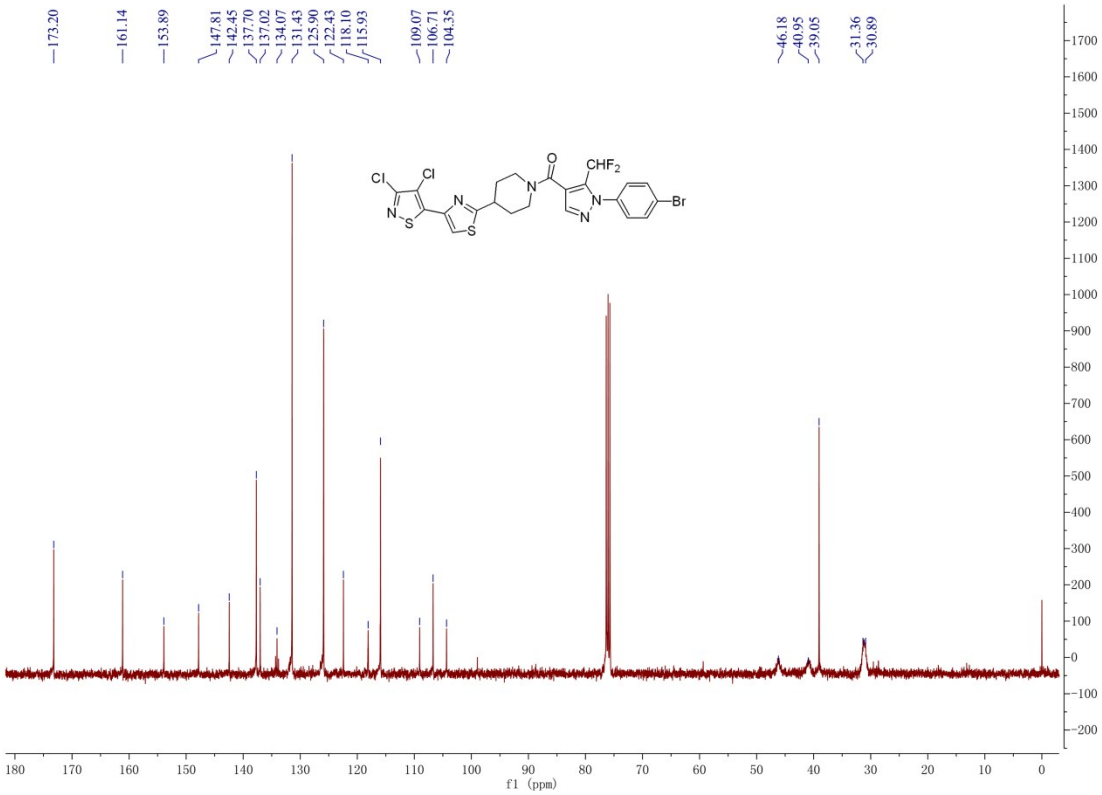
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6e**



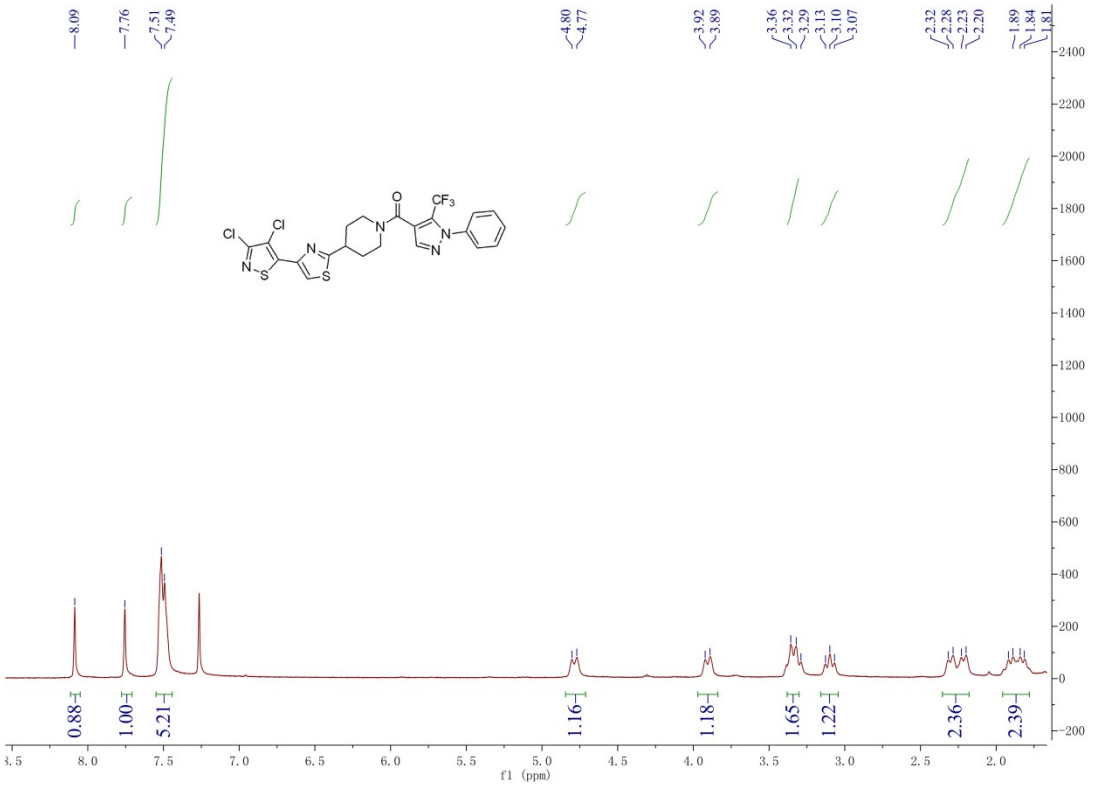
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6f**



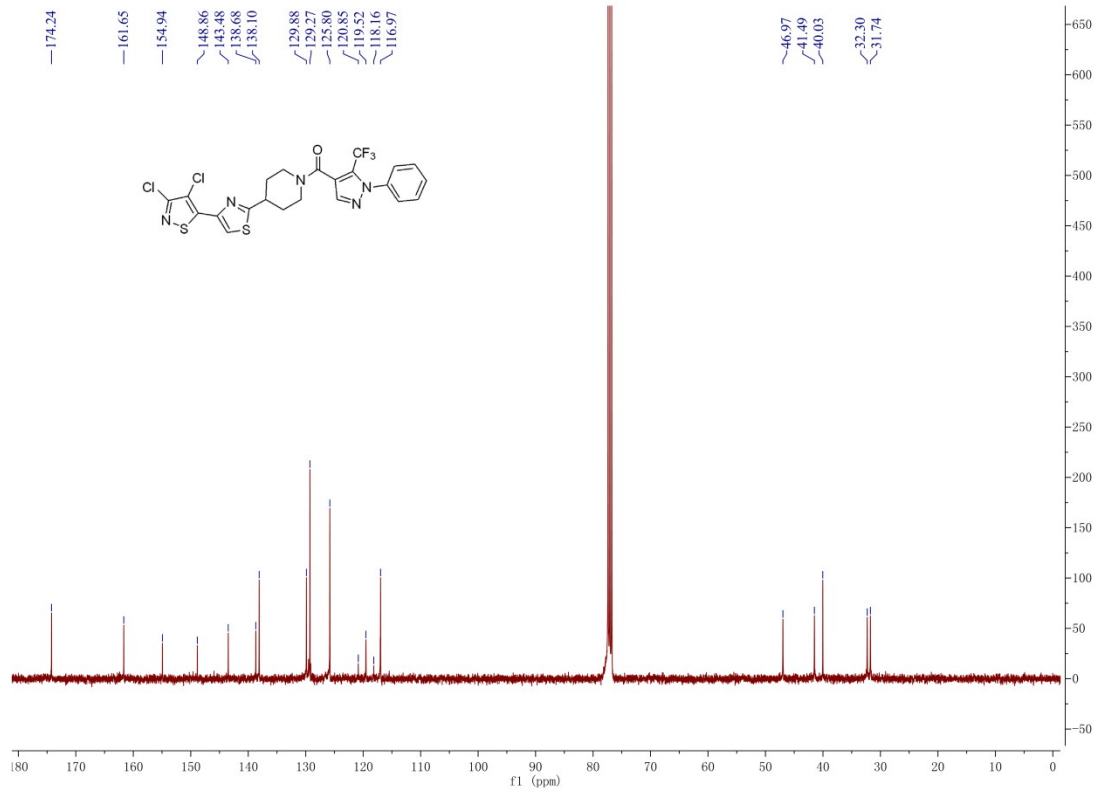
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6f**



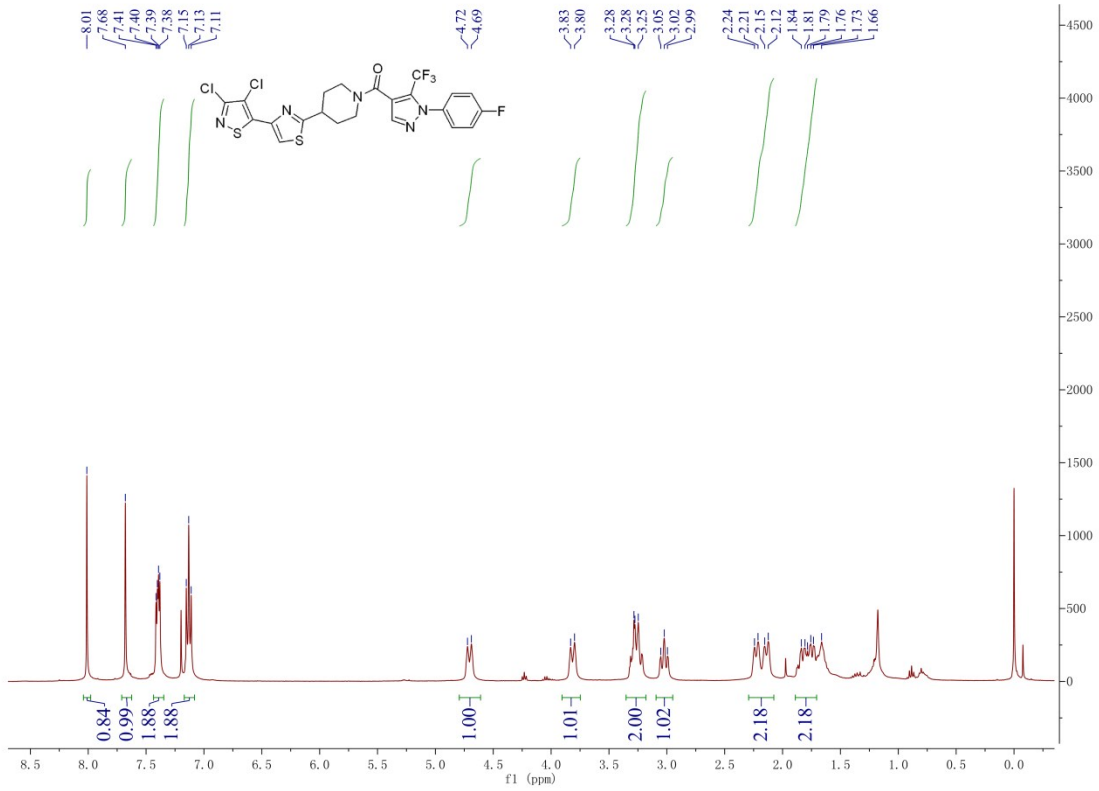
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6g**



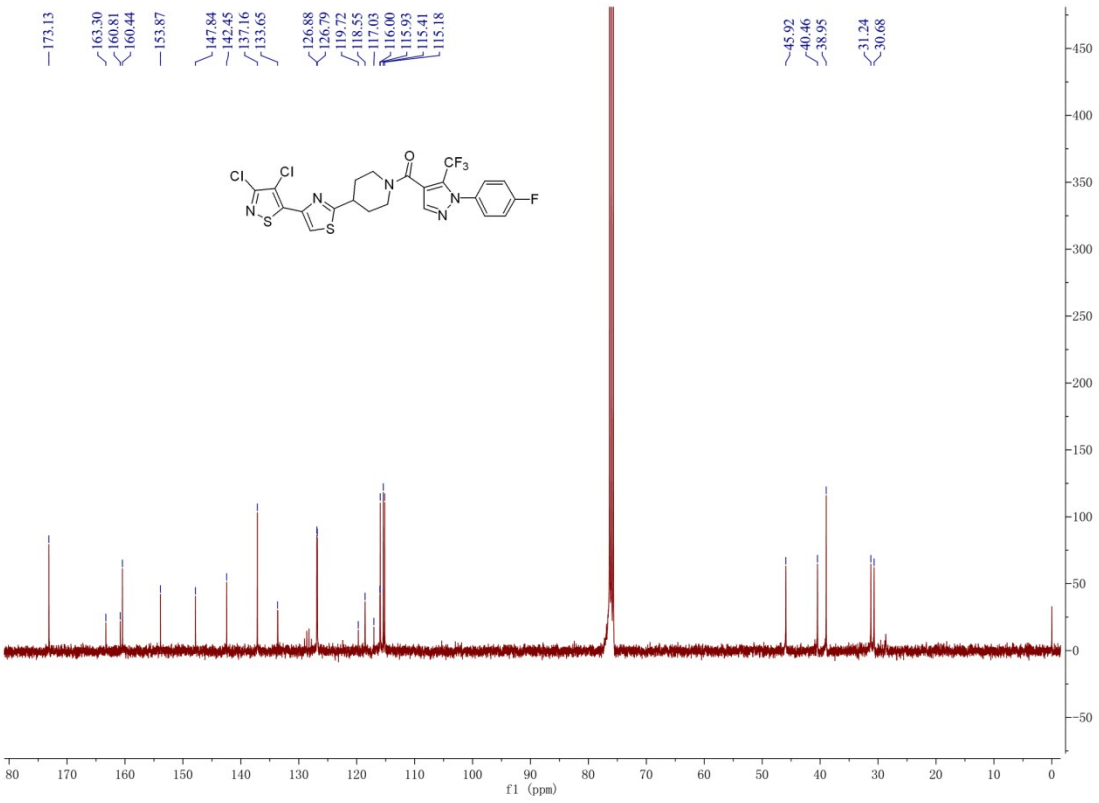
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6g**



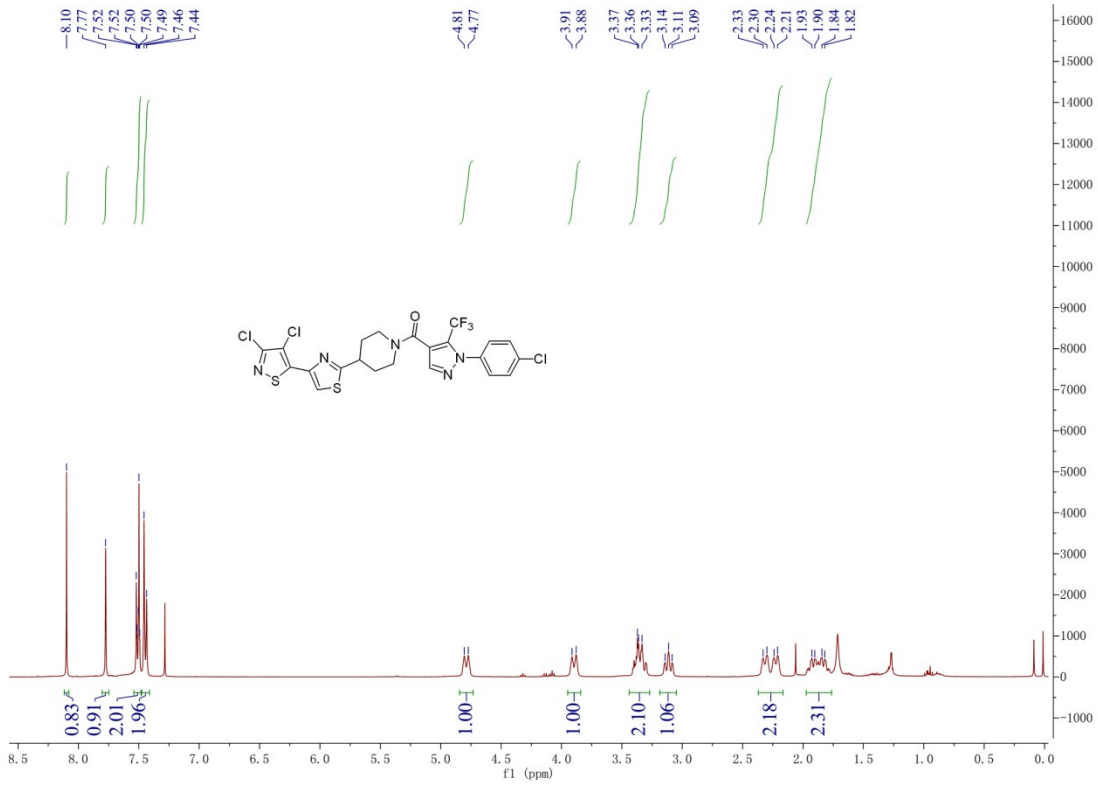
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6h**



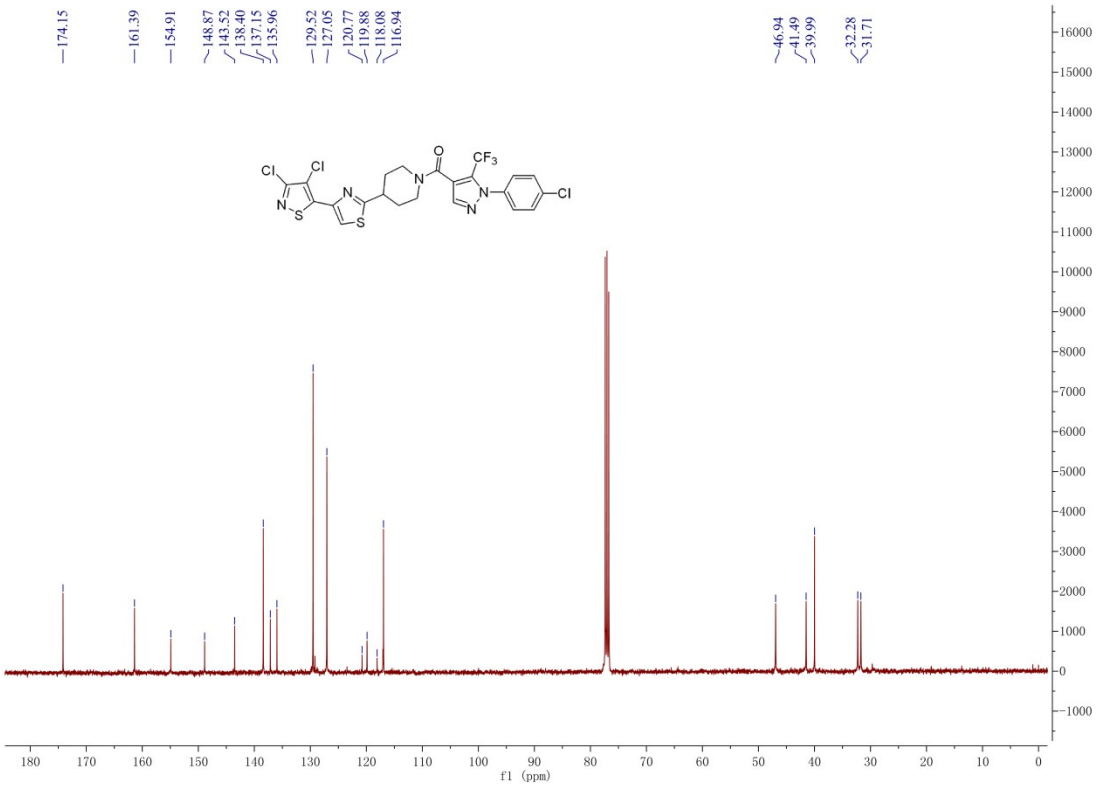
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6h**



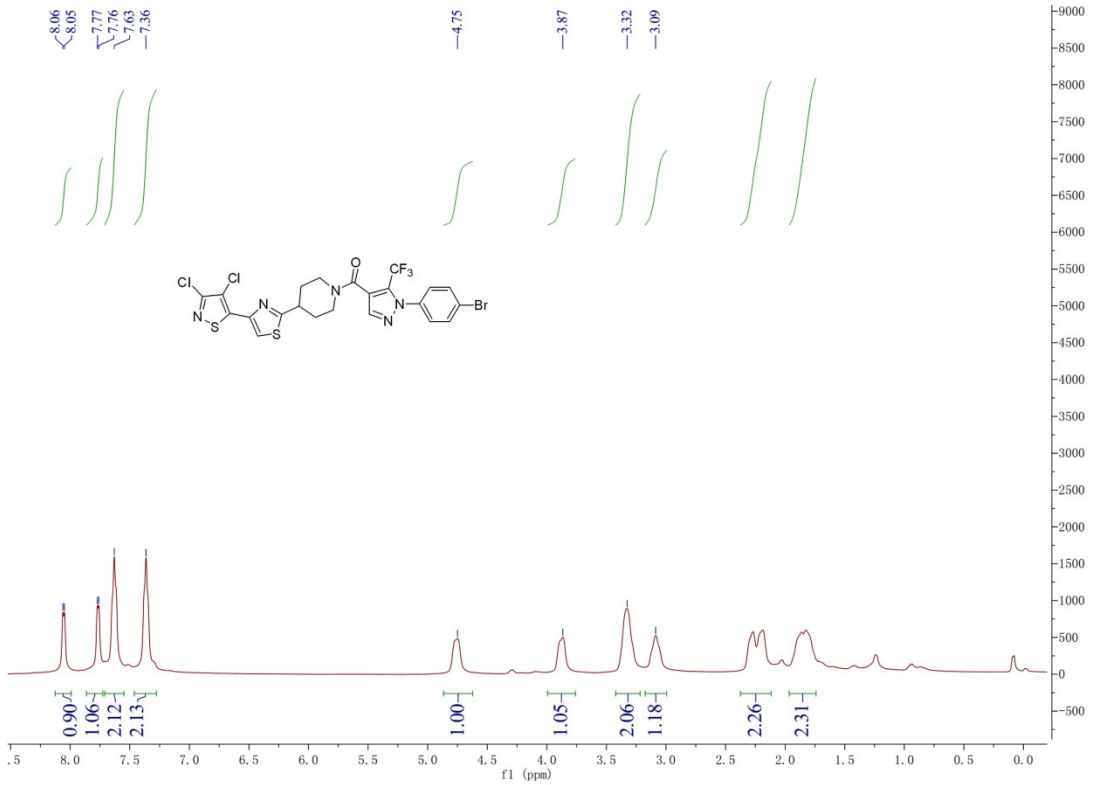
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6i**



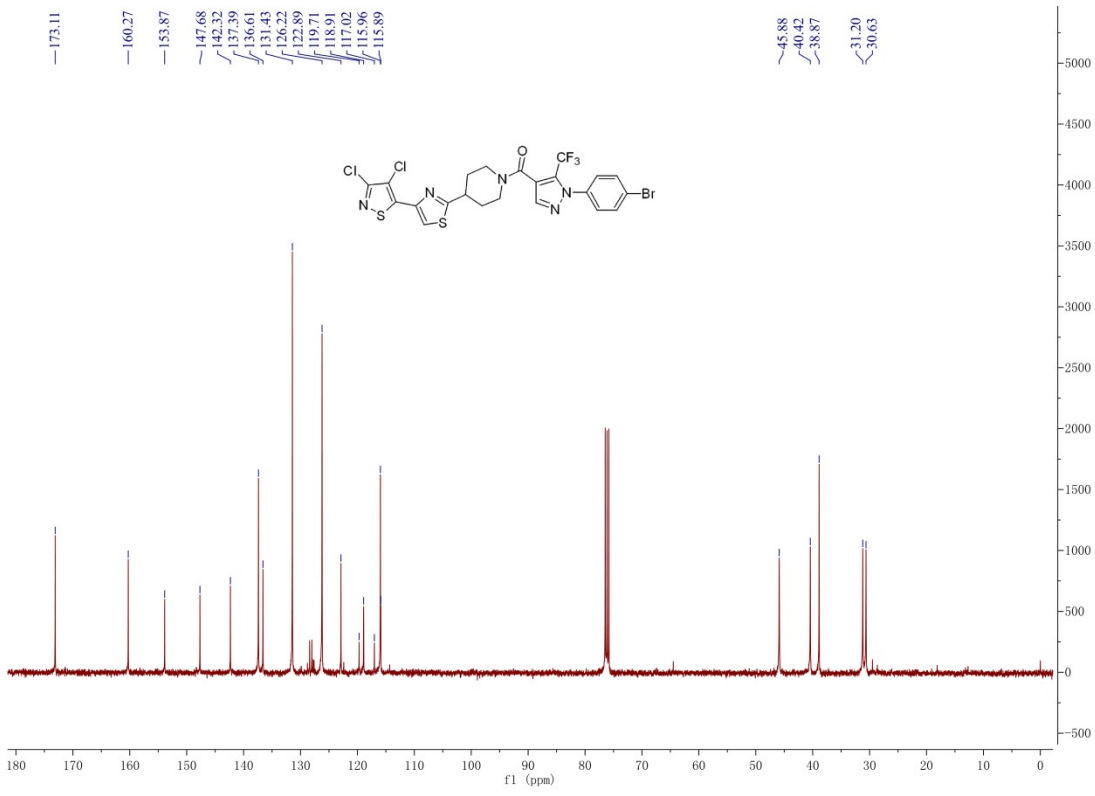
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6i**



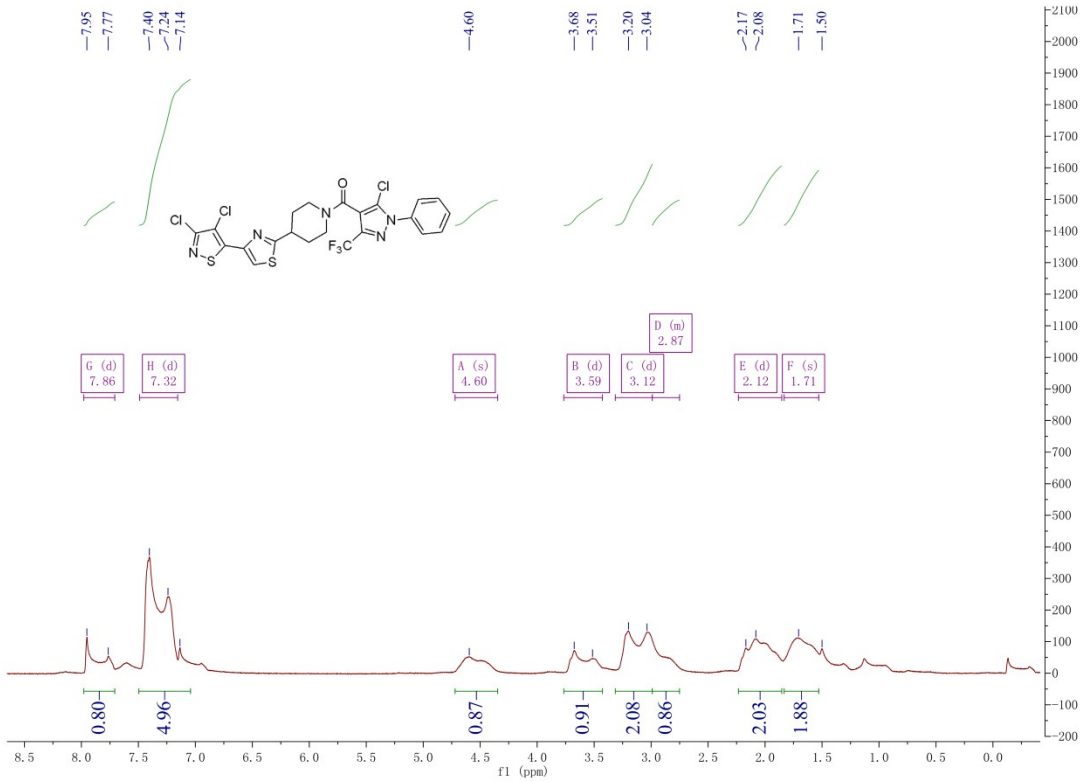
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6j**



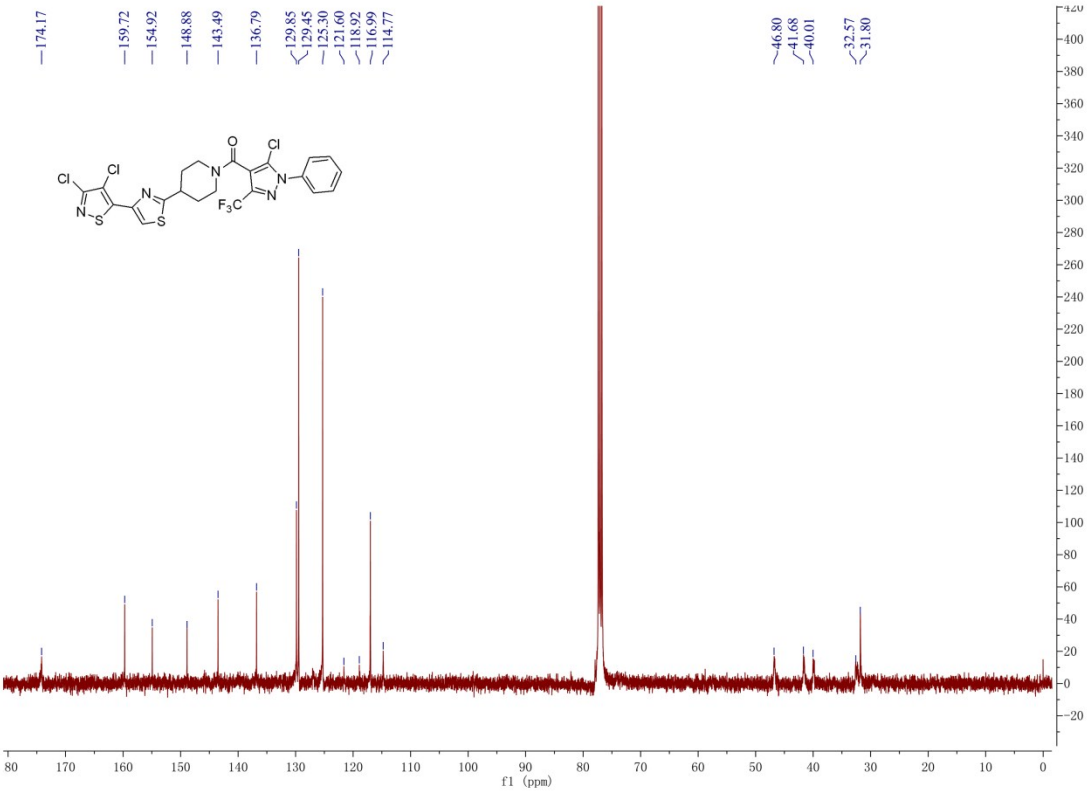
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6j**



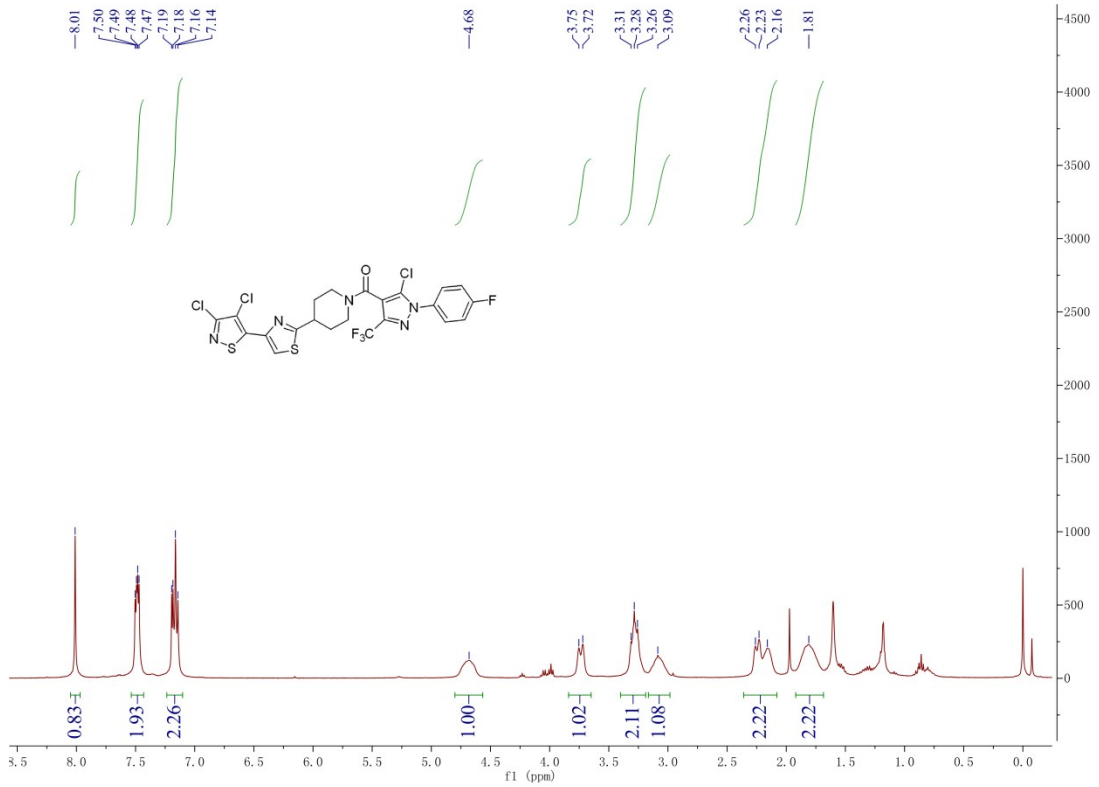
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6k**



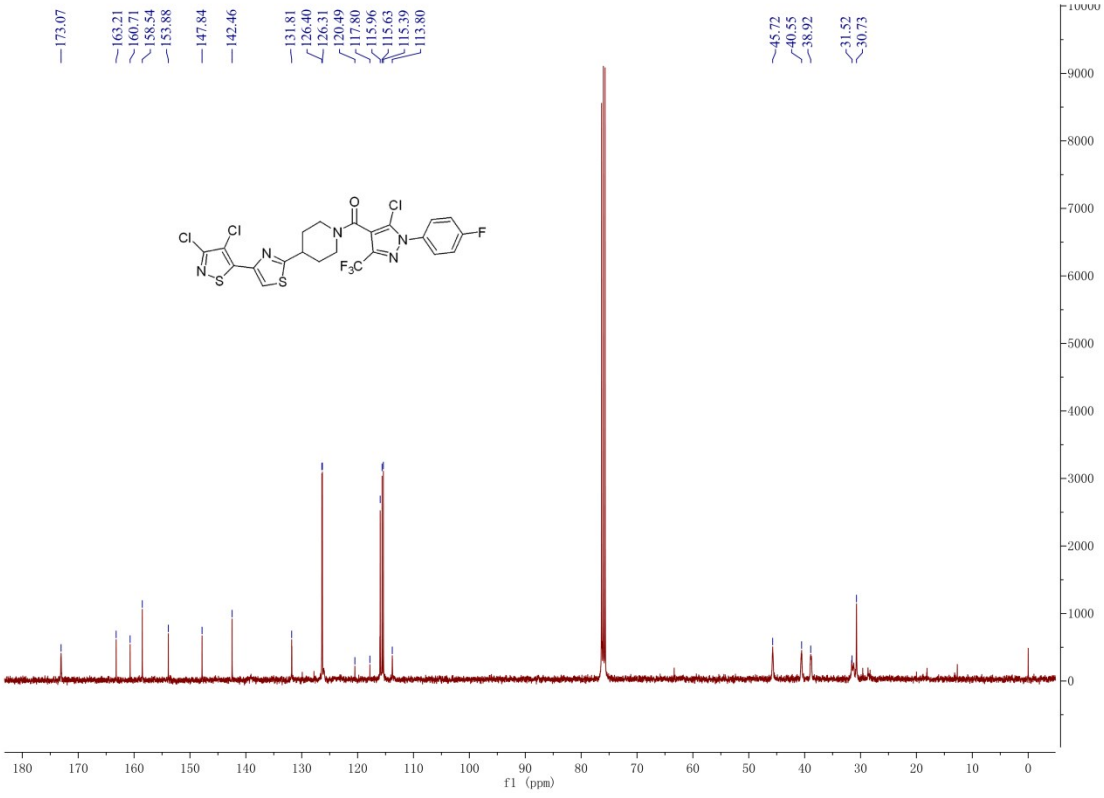
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6k**



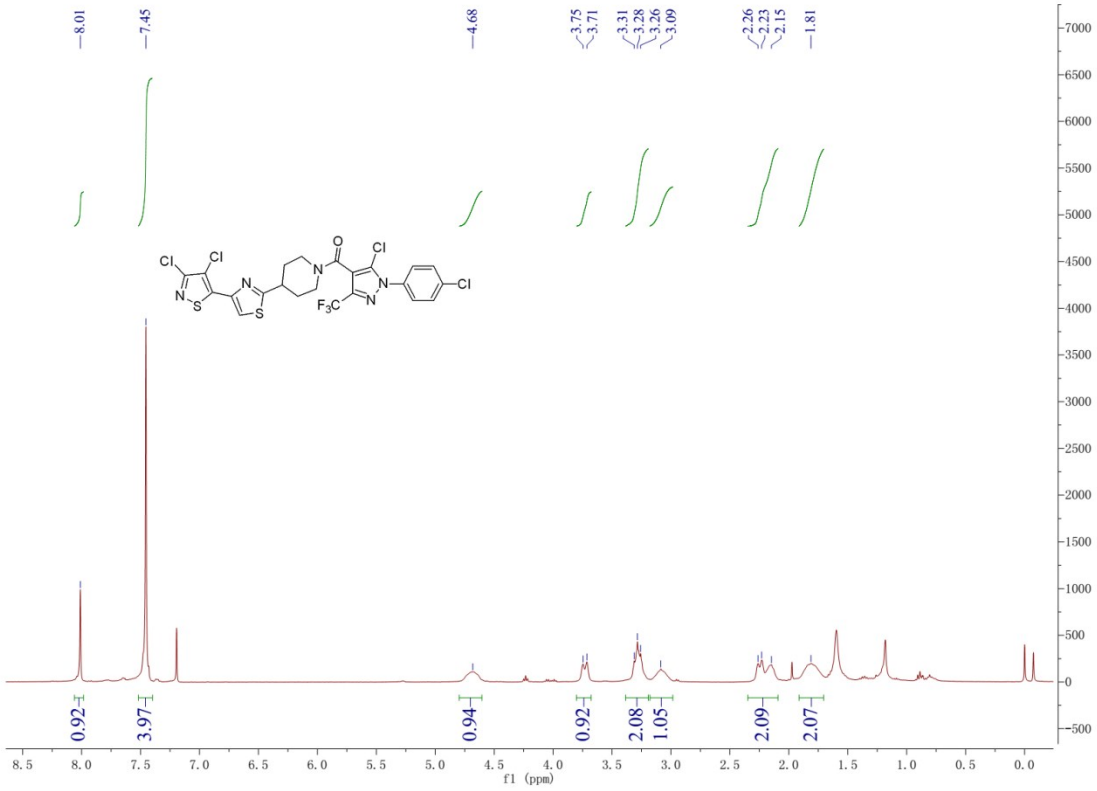
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6l**



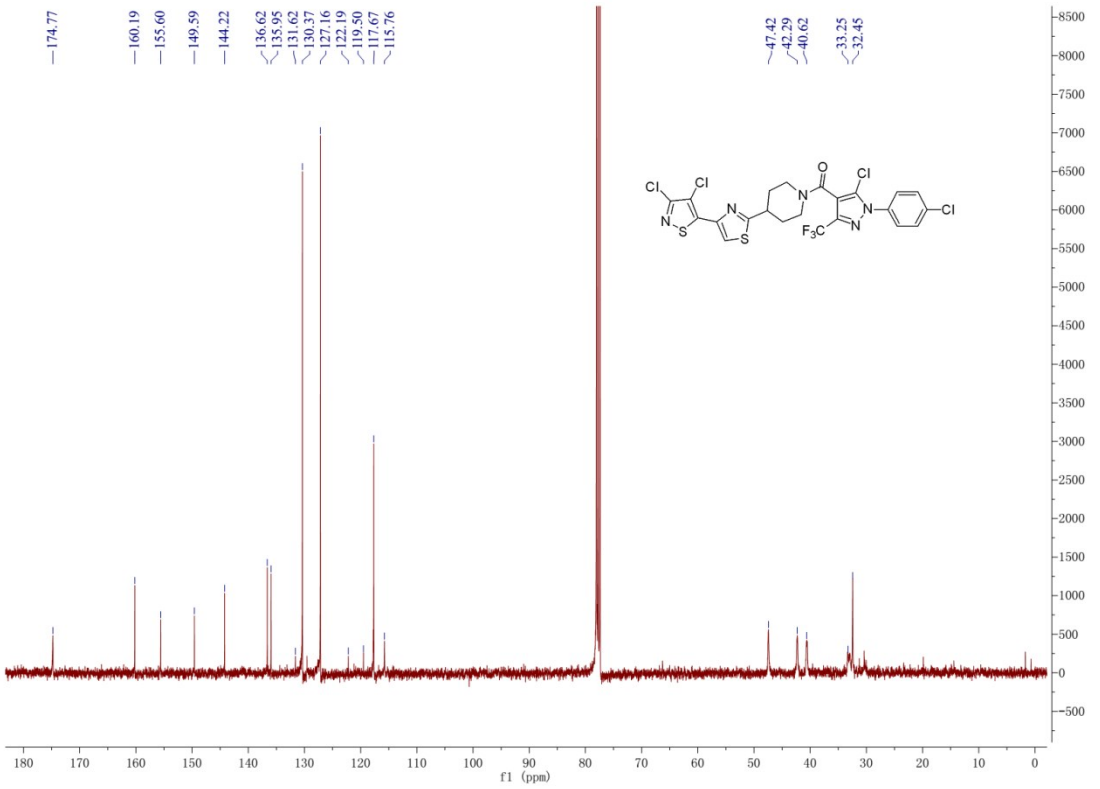
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6l**



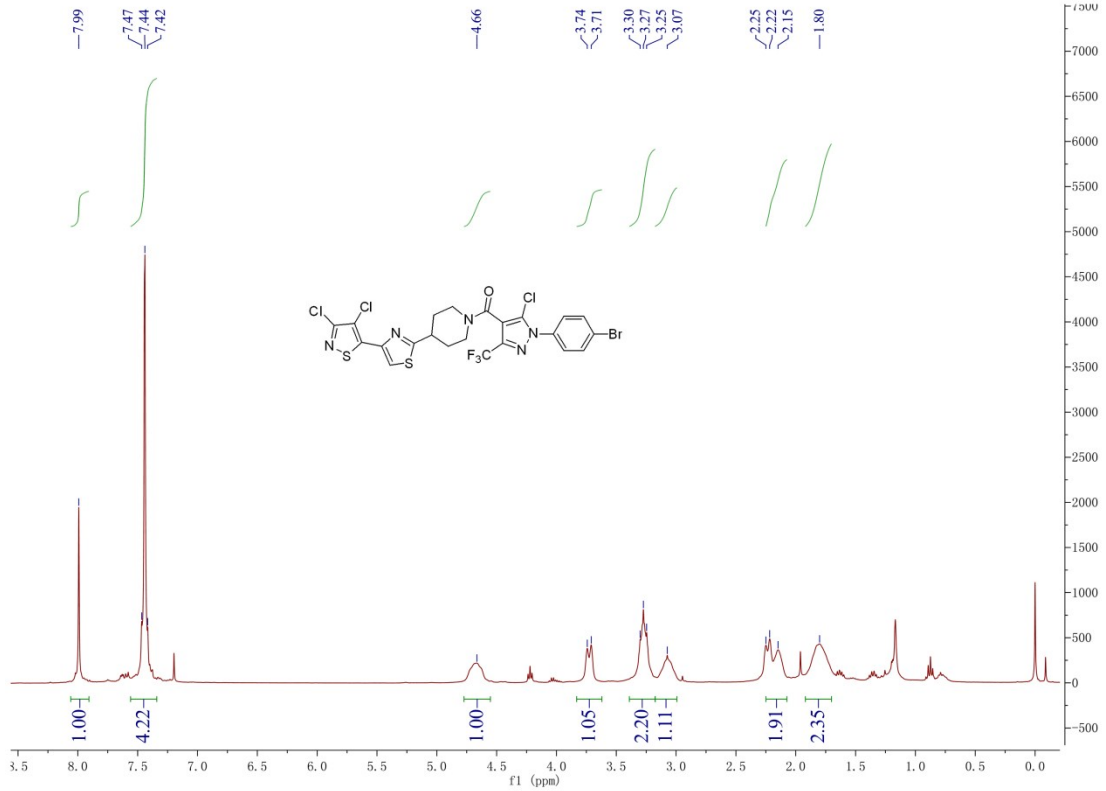
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6m**



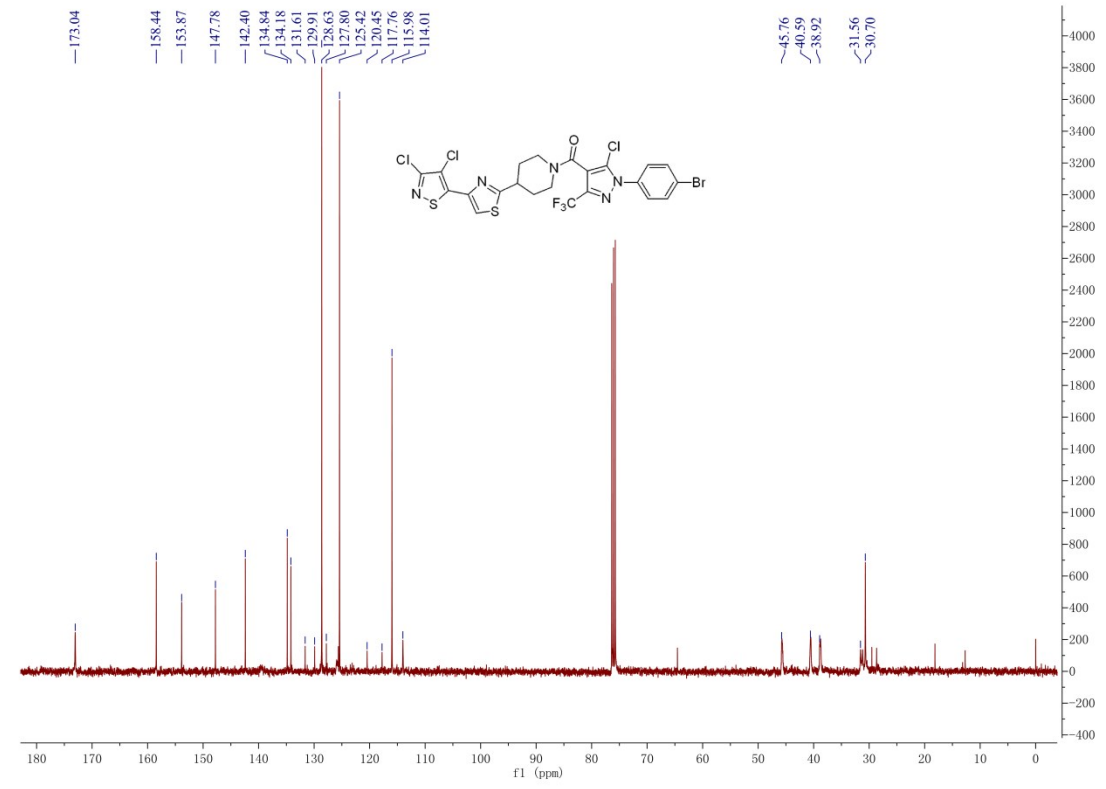
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6m**



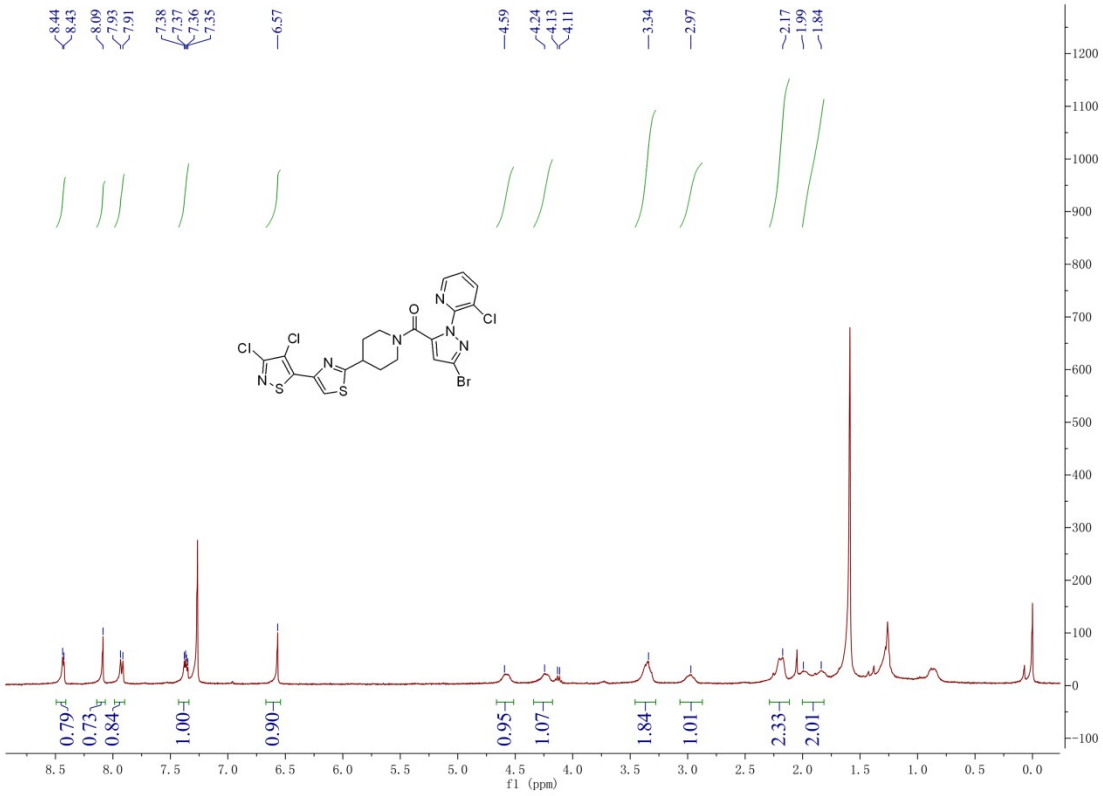
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6n**



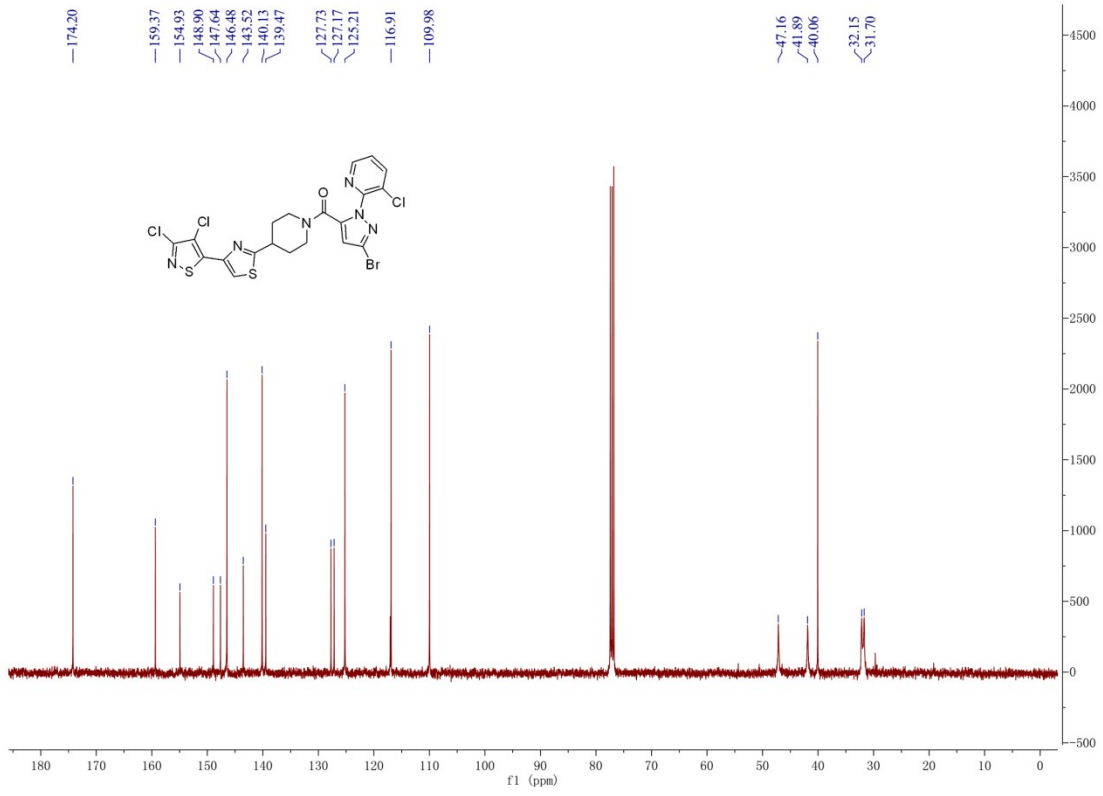
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6n**



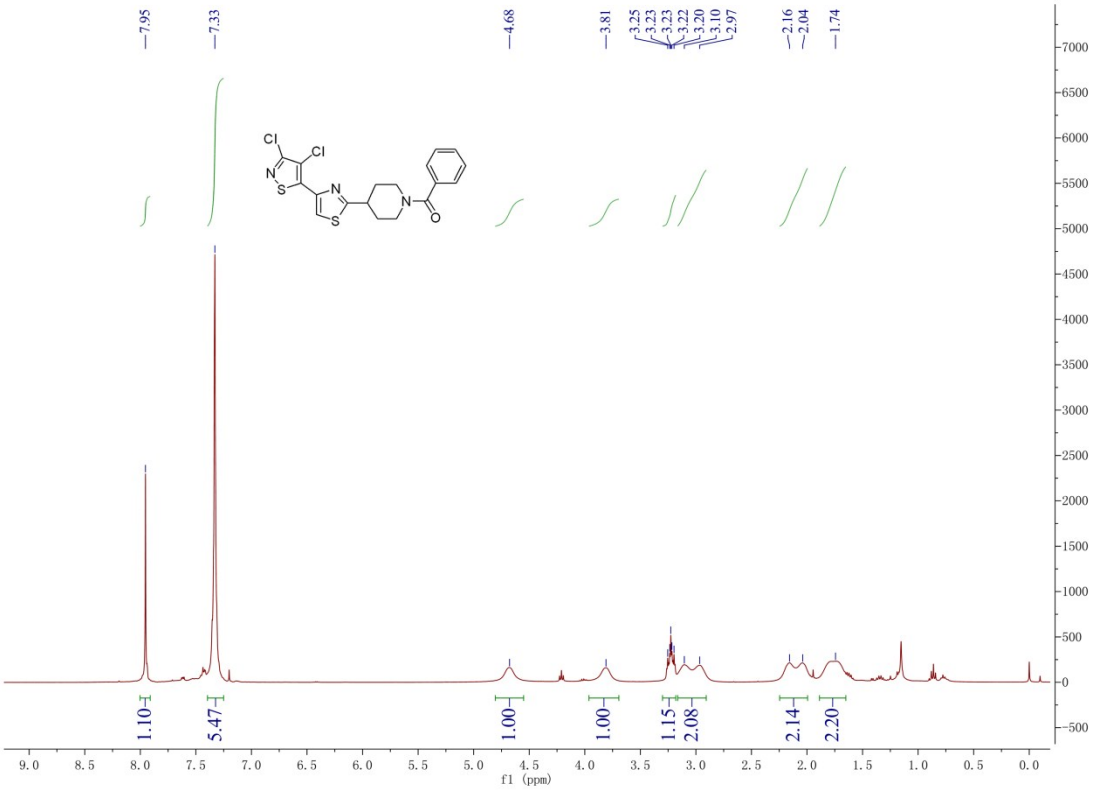
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6o**



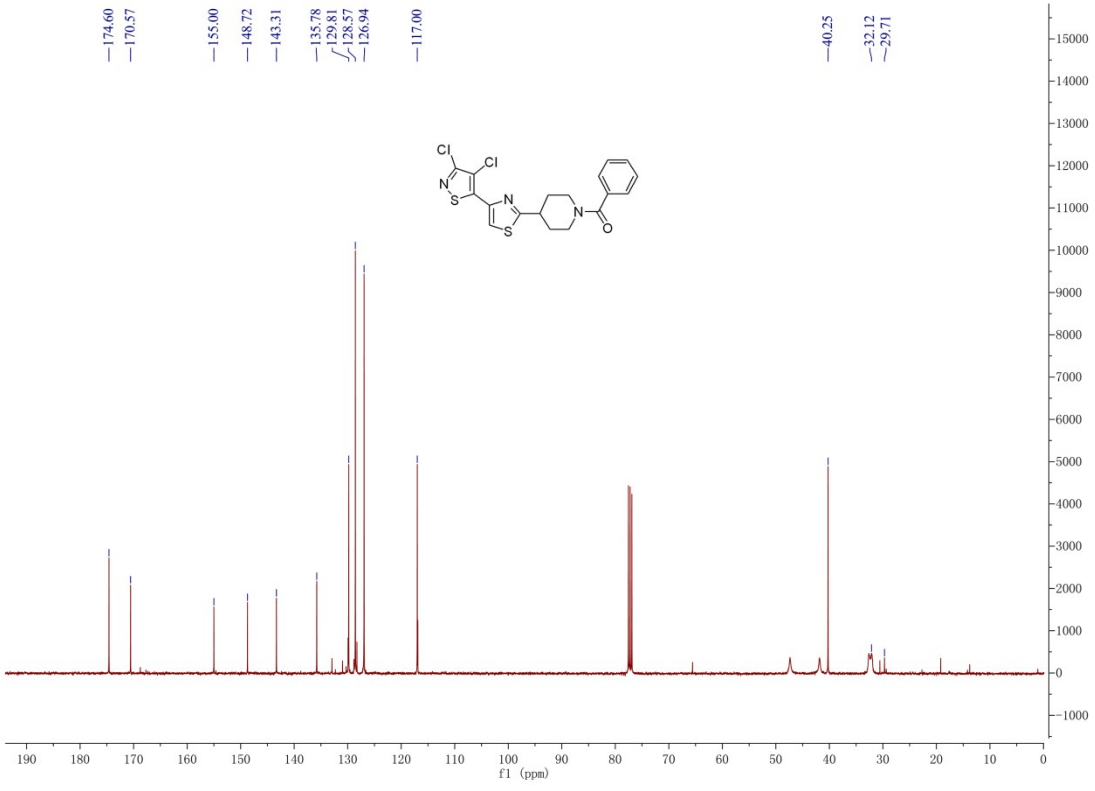
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6o**



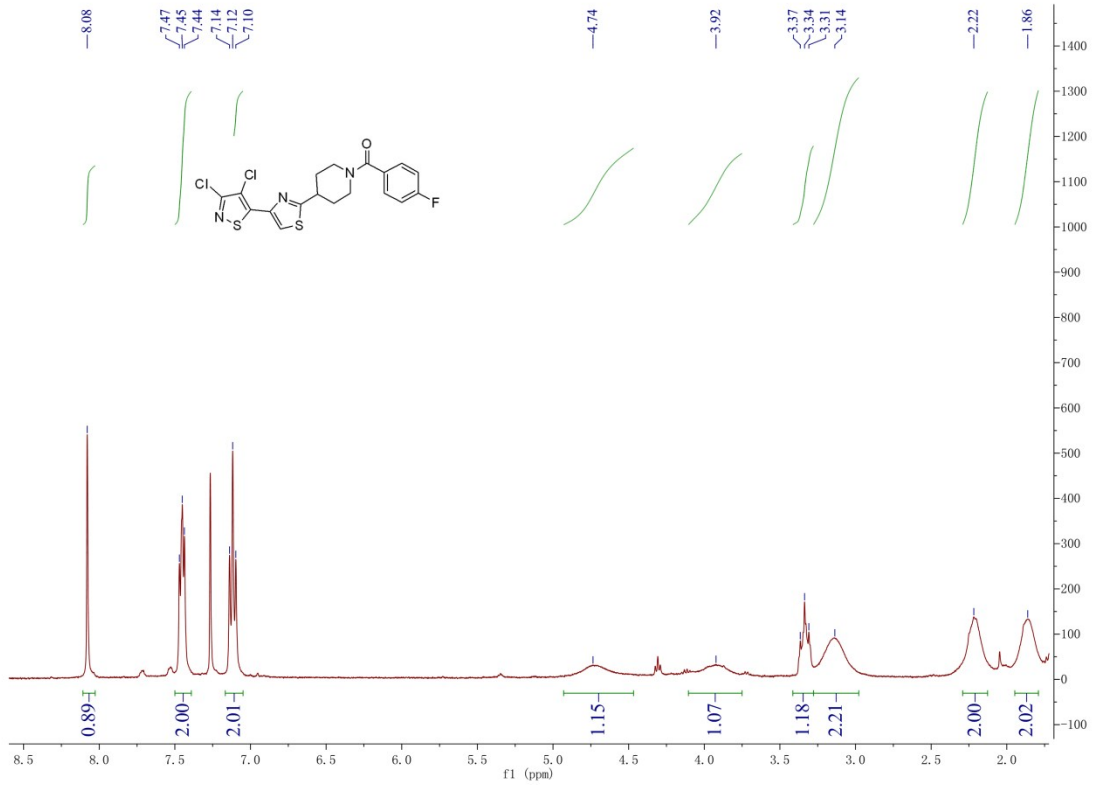
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6p**



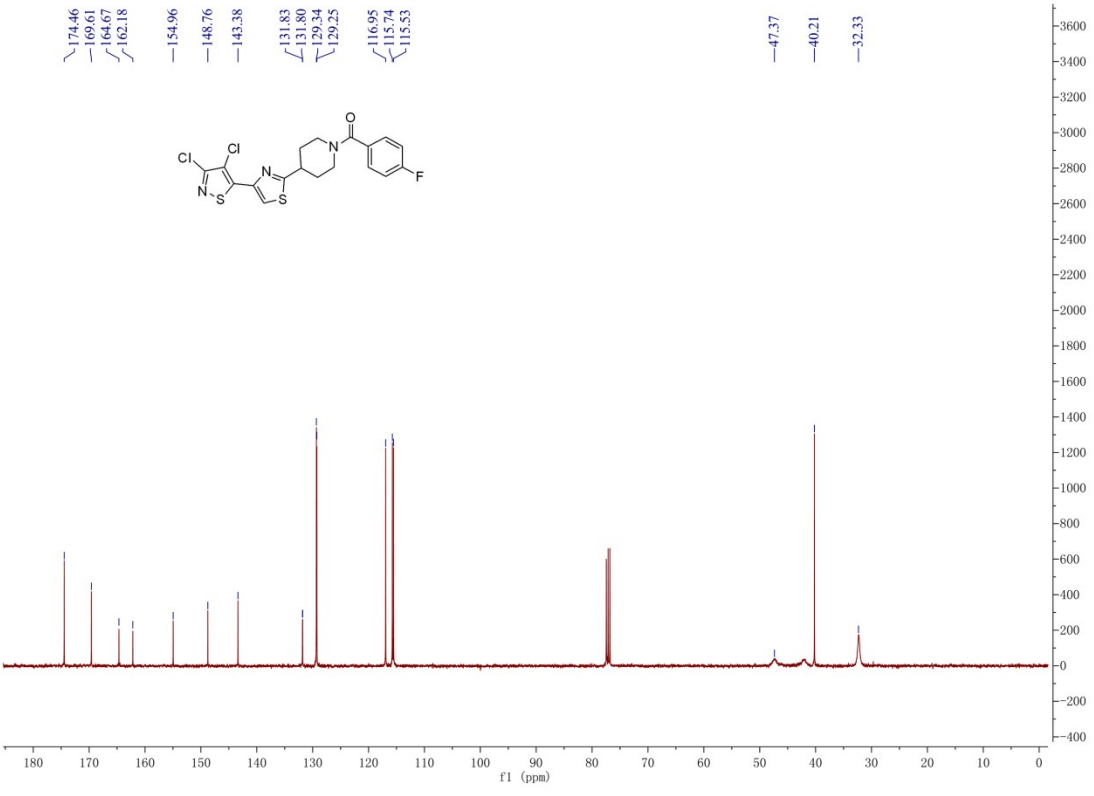
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6p**



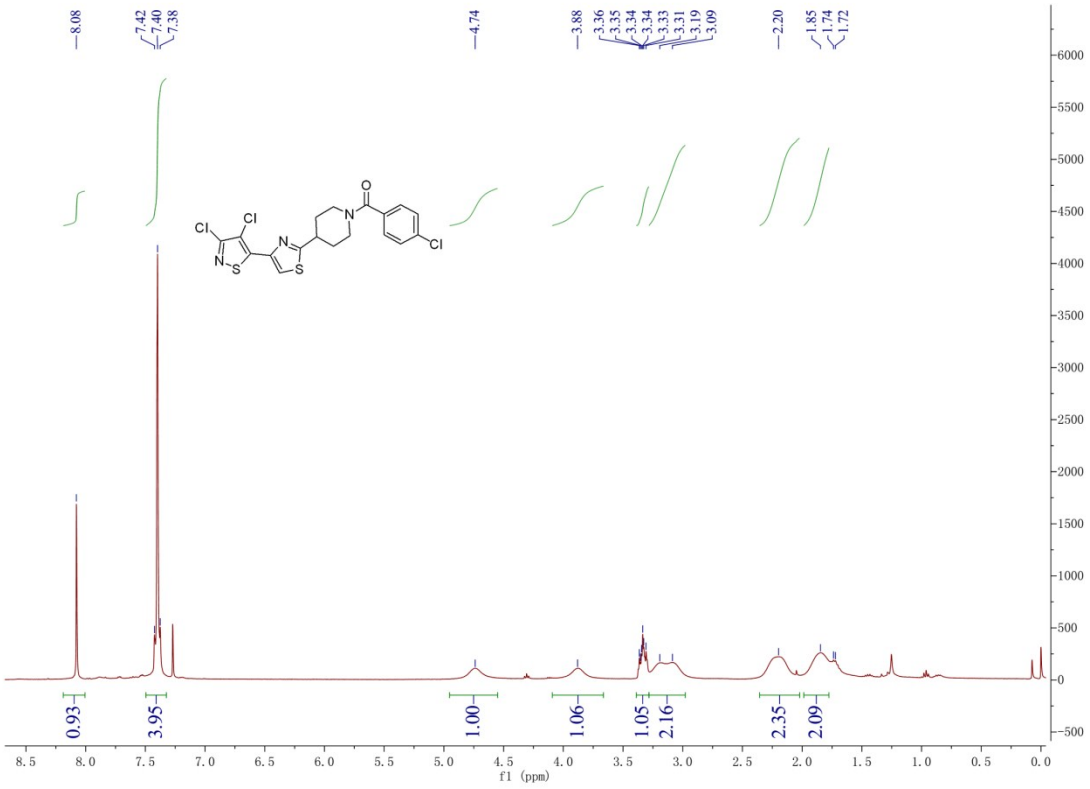
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6q**



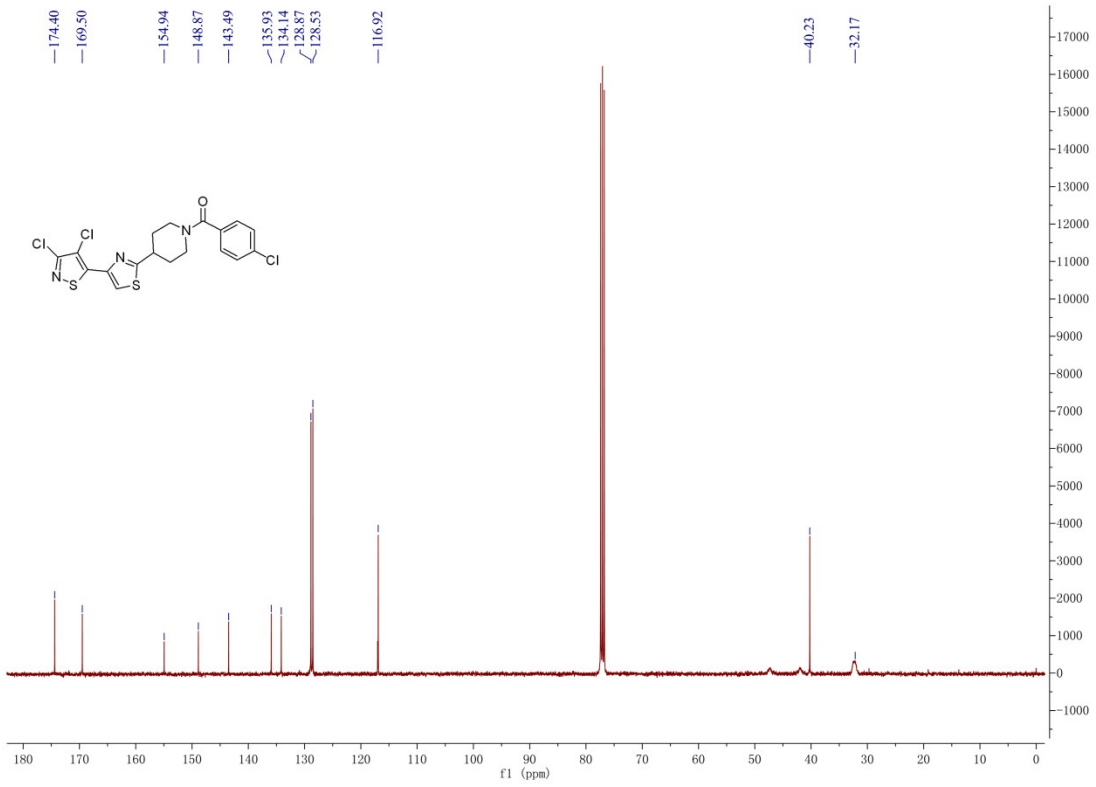
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6q**



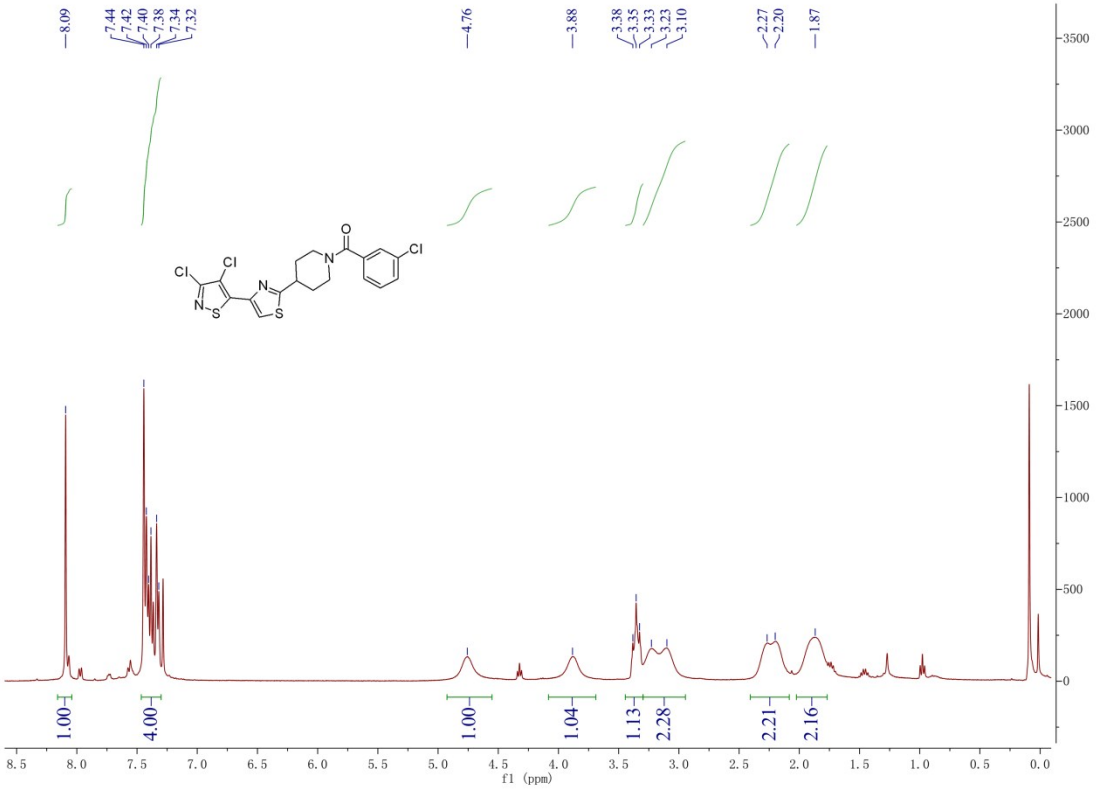
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6r**



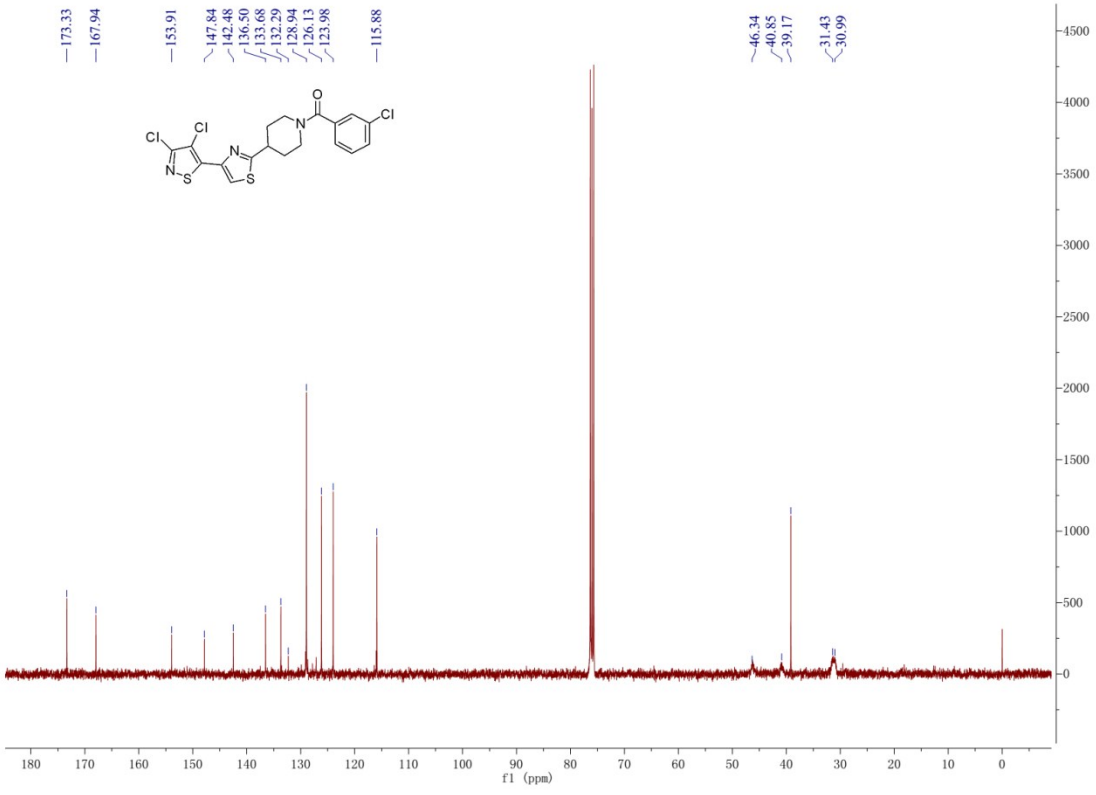
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6r**



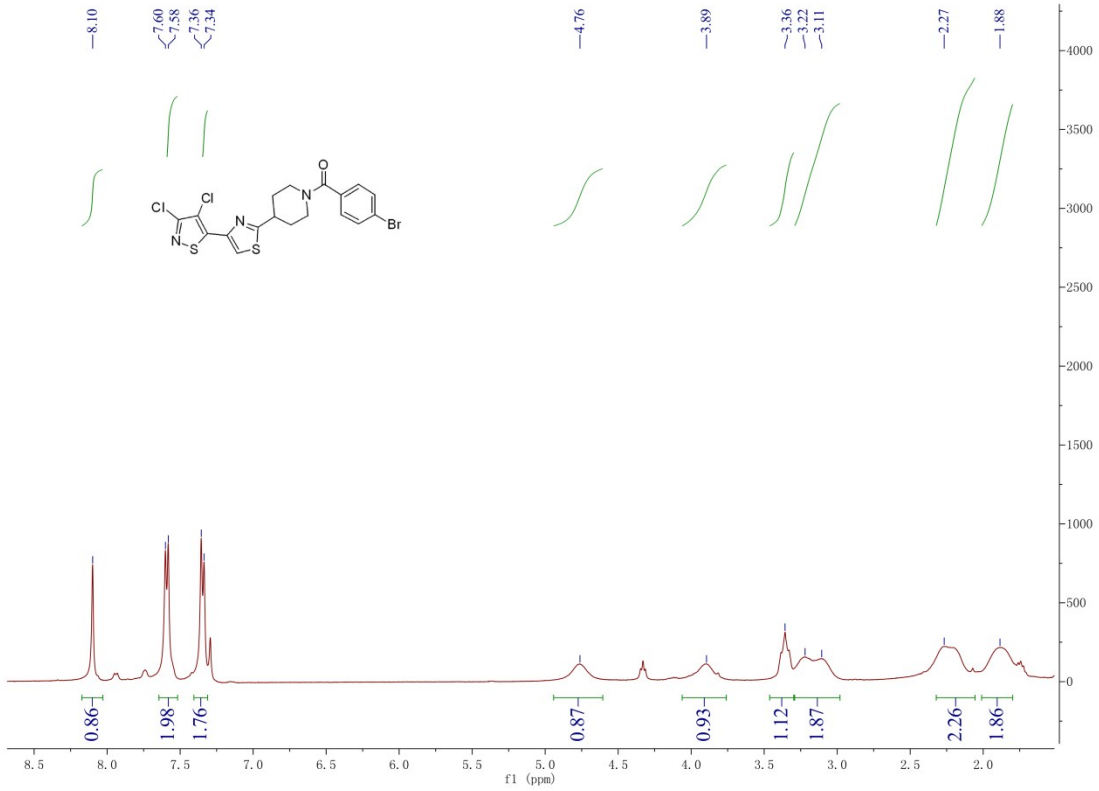
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6s**



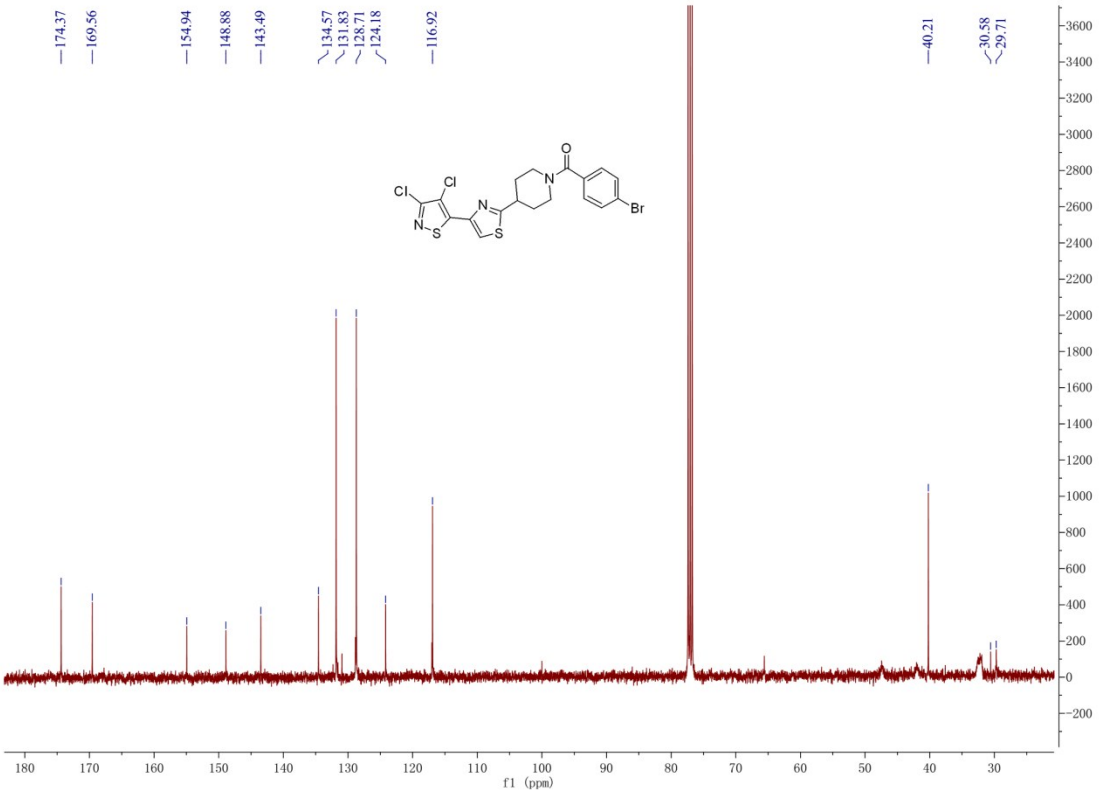
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6s**



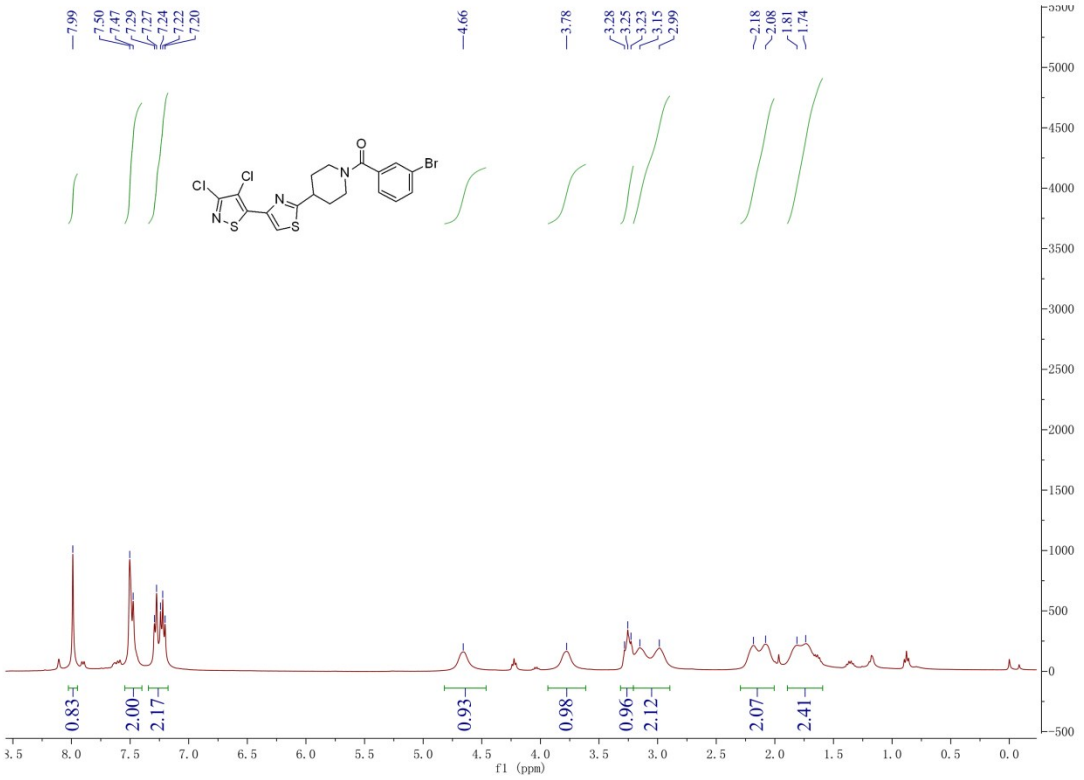
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6t**



^{13}C NMR (101 MHz, $CDCl_3$) of compound **6t**



^{1}H NMR (400 MHz, $CDCl_3$) of compound **6u**



^{13}C NMR (101 MHz, $CDCl_3$) of compound **6u**