

Supporting Information for:

Quinoline and quinazoline derivatives inhibit viral RNA synthesis by SARS-CoV-2 RdRp

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S2 Structure-activity relationship analysis

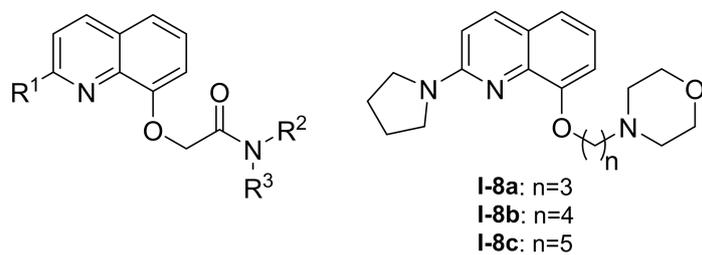
S9 Chemical synthesis of compounds and the NMR spectra data

S179 Gluc plasmid mRNA level

S179 The stability of I-13e

The Supporting Information contains 179 pages including one table (TableS1) and two figures (Figure S1, Figure S2).

TableS1 Structure-activity relationship analysis of 101 quinoline and quinazoline on anti-SARS-CoV-2 RdRp

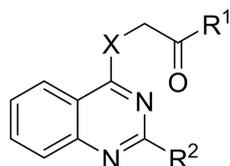


Comps.	R ¹	R ²	R ³	Inhibition of SARS-CoV-2 RdRp activity (10μM, %)
I-6a			H	9.64±4.08
I-6b			H	NA
I-6c			H	24.63±3.82
I-6d			H	21.83±4.16
I-6e			H	2.43±0.71
I-6f			H	15.62±7.35
I-6g			H	34.07±1.16
I-6h			H	29.20±7.05
I-6i			H	NA
I-6j			H	24.52±5.53
I-6k			H	NA
I-6l			H	24.05±1.49

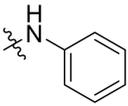
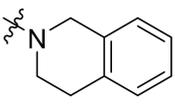
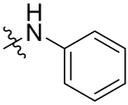
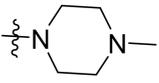
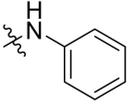
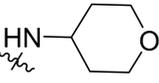
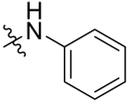
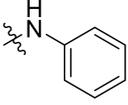
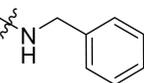
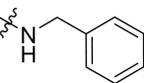
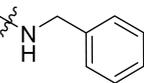
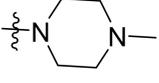
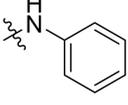
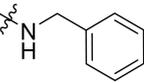
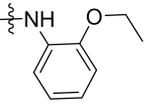
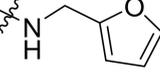
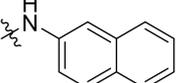
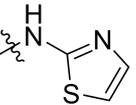
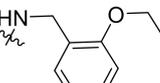
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I-6o			H	15.20±8.50
I-6p			H	NA
I-6q			H	36.44±2.74
I-6r			H	28.98±7.05
I-6s		CH ₂ CH ₂ O	CH ₂ CH ₂	31.33±4.81
I-6t			H	52.61±5.05
I-6u			H	49.57±3.27
I-13a			H	NA
I-13b			H	21.28±6.34
I-13c			H	11.27±6.79
I-13d			H	24.99±3.99
I-13e			H	<u>95.03±0.03</u>
I-13f			H	58.26±2.22
I-13g			H	37.51±3.32
I-13h			H	<u>92.85±0.62</u>
I-13i			H	<u>74.94±4.06</u>
I-8a	-	-	-	29.69±8.79

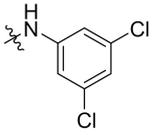
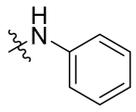
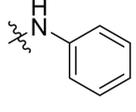
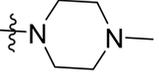
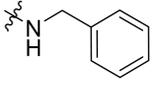
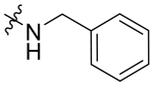
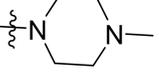
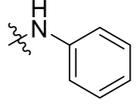
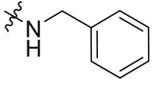
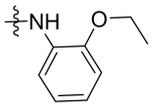
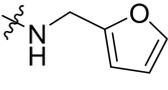
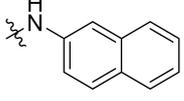
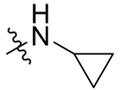
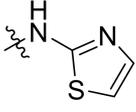
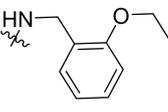
I-8b	-	-	26.23±6.66
I-8c	-	-	26.12±6.82
Remdesivir			85.69±2.68

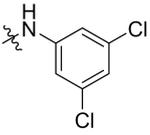
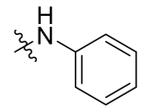
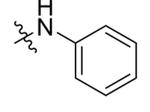
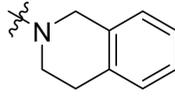
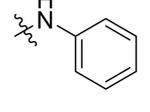
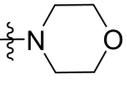
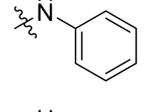
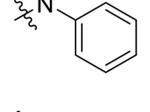
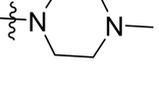
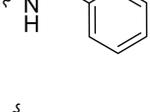
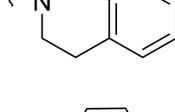
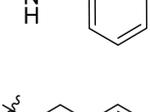
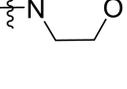
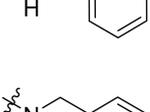
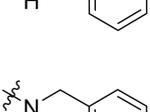
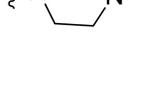
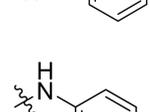
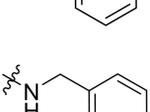
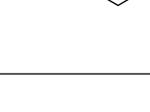
NA=No activity.



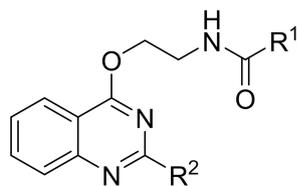
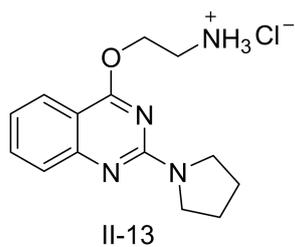
Comps.	R ¹	R ²	X	Inhibition of SARS-CoV-2 RdRp activity (10μM, %)
II-5a	OCH ₂ CH ₃		O	15.67±8.22
II-6a	OH		O	29.50±5.23
II-7a1			O	NA
II-7a2			O	NA
II-7a4			O	19.36±6.63
II-7a5			O	25.88±3.63
II-7a6			O	16.42±2.36
II-7a7			O	33.69±4.86
II-7a8			O	33.69±5.44
II-7a9			O	24.65±3.74
II-7a10			O	NA

II-10a1			O	33.25±0.53
II-10a2			O	33.28±6.65
II-10a3			O	36.57±2.87
II-10a4			O	17.60±4.97
II-10a5			O	33.88±8.91
II-9a2		Cl	O	57.82±1.84
II-10a7			O	42.13±2.96
II-10a8			O	51.70±8.68
II-7b1			S	53.88±2.81
II-7b2			S	49.03±2.58
II-7b3			S	47.32±1.27
II-7b4			S	49.78±1.38
II-7b5			S	NA
II-7b7			S	41.82±3.16
II-7b8			S	NA

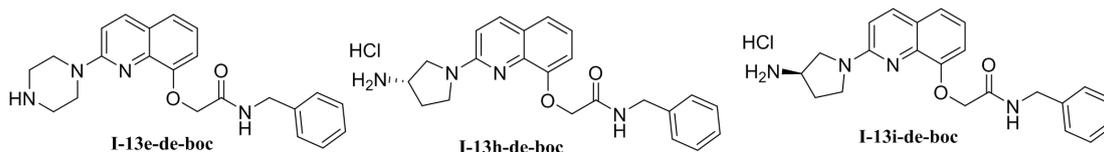
II-7b9			S	NA
II-10b2			S	NA
II-10b3			S	54.43±0.51
II-10b5			S	45.35±5.62
II-10b6			S	49.32±2.08
SS	CH ₃ CH ₂ O	SCH ₂ COOCH ₂ CH ₃	S	58.43±0.29
II-3-3	OCH ₂ CH ₃		NH	43.19±6.70
II-23a			NH	49.95±1.86
II-23b			NH	43.99±4.57
II-23c			NH	39.33±6.09
II-23d			NH	52.08±5.49
II-23e			NH	NA
II-23f			NH	47.00±1.92
II-23g			NH	46.35±1.81
II-23h			NH	52.44±2.32

II-23i			NH	41.67±0.63
II-22a		Cl	NH	56.08±0.72
II-23j			NH	58.83±3.12
II-23k			NH	55.54±1.42
II-23l			NH	49.46±1.59
II-23m			NH	41.71±0.83
II-23n			NH	26.32±0.48
II-23o			NH	52.61±0.75
II-23p			NH	55.05±2.08
II-23q			NH	56.06±0.64
C1-23		Cl	O	56.20±0.86
C2-17		Cl	S	NA
C2-21		Cl	S	44.92±4.19
Remdesivir				85.69±2.68

NA=No activity.



Compds.	R ¹	R ²	Inhibition of SARS-CoV-2 RdRp activity (10μM, %)
II-13	-	-	57.59±0.80
II-14a			48.70±3.15
II-14b			41.52±2.93
II-14c			55.44±1.41
II-14d			37.46±2.16
II-14e			44.77±0.12
II-14f			24.61±2.52
II-14g			40.28±2.36
II-14i			48.70±0.18
II-14k			51.58±0.79
II-14l			41.46±1.24
II-17b			25.67±1.39
II-17c			38.72±0.94
C4-19		Cl	49.51±0.37
Remdesivir			85.69±2.68

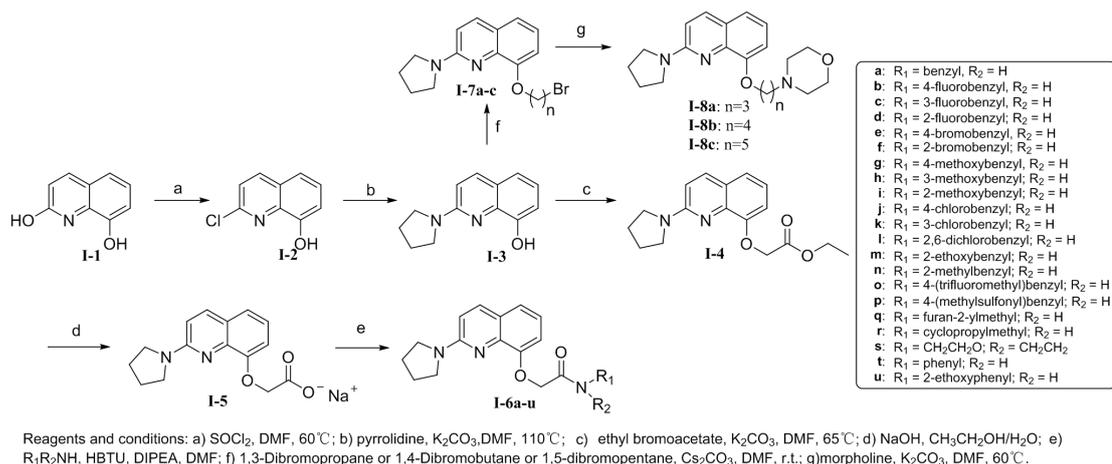


Compds.	Inhibition of SARS-CoV-2 RdRp activity (10 μ M, %)
I-13e-de-boc	<u>12.90\pm3.21</u>
I-13h-de-boc	<u>11.57\pm4.28</u>
I-13i-de-boc	<u>11.39\pm5.14</u>
Remdesivir	87.98 \pm 1.20

2. Experimental and the NMR spectra data

2.1 Synthesis

2.1.1 General procedure for the synthesis of compounds I-6



Scheme 1. Synthesis of quinoline compounds **I-6** and **I-8**.

To a suspension of 2,8-dihydroxyquinoline (**I-1**) (10.0 g, 62 mmol) in 50 mL of anhydrous N,N-dimethylformamide (DMF) was added thionyl chloride (17.8 mL, 248 mol) at -5 °C and the reaction mixture was heated at 50 °C for 12 h. After cooling to room temperature, the mixture was poured into ice water and extracted with ethyl acetate (50 mL \times 3). The combined extracts were washed with water, saturated brine, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure to give crude product 2-chloro-8-hydroxyquinoline (**I-2**) (7.5 g, 68% from **2**) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.69 (brs, 1H), 7.46 (t, *J* = 7.0 Hz, 1H), 7.38 (t, *J* = 7.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 7.0 Hz, 1H).

To a solution of **I-2** (6.0 g, 33.4 mmol) and potassium carbonate (9.2 g, 66.8 mmol) dissolved in DMF (30 mL) was added pyrrolidine (4.7 g, 66.8 mmol) and stirred for 3 h at 110°C. After cooling to room temperature, the mixture was poured into ice water (150 mL) and extracted with ethyl acetate (80 mL × 3). The combined extracts were dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (10:1, v / v) to get the title compound **I-3** (6.6 g, 92% from **I-2**) as white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.38 (s, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 3.56 (t, *J* = 6.0 Hz, 4H), 2.03 – 1.88 (m, 4H). LC-MS (ESI), *m/z*: 215[M+H]⁺, 237[M+Na]⁺.

To a solution of **I-3** (3.0 g, 14.2 mmol) and potassium carbonate (3.9 g, 24.4 mmol) dissolved in DMF (20 mL) was added ethyl bromoacetate (3.6 g, 21.2 mmol) dropwise and stirred for 5 h at 65°C and then poured into water (100 mL), extracted with ethyl acetate (80 mL × 3). The combined extracts were dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (10:1, v / v) to get compound **I-4** (4.2 g, 98% from **I-3**) as yellow oil. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.96 (d, *J* = 9.0 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.10 – 6.93 (m, 2H), 6.85 (d, *J* = 9.0 Hz, 1H), 5.03 (s, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.52 (d, *J* = 6.0 Hz, 4H), 1.97 (q, *J* = 6.0 Hz, 4H), 1.20 (t, *J* = 7.0 Hz, 3H). LC-MS (ESI), *m/z*: 301[M+H]⁺, 323[M+Na]⁺.

To a solution of **I-4** (4.3g, 14.4 mmol) in alcohol (30 mL) was added sodium hydroxide (1.2 g, 28.7 mmol) in 30 mL water at 0°C. The reaction mixture was stirred for 3 h at room temperature. The resulting solid was collected by filtration and washed successively with methanol (10 mL), and dried in vacuo to give the title compound **I-5** (3.2 g, 77%) as white solid. ¹H NMR (500 MHz, CD₃OD) δ 7.98 (d, *J* = 9.0 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 4.68 (s, 2H), 3.63 (t, *J* = 6.0 Hz, 4H), 2.09 (m, 4H). LC-MS (ESI), *m/z*: 273[M+H]⁺.

A solution of compound **I-5** (96.2 mg, 0.32 mmol), O-Benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluorophosphate (HBTU) (136.5 mg, 0.36 mmol) in DMF (2 mL) was stirred at room temperature under the atmosphere of nitrogen for 5 min.

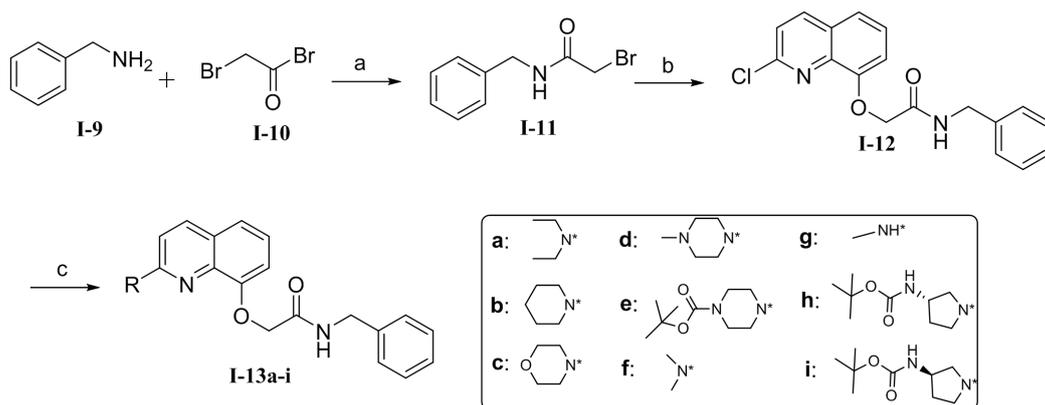
The substituted amines (0.36 mmol) and N,N-diisopropylethylamine (DIPEA) (0.36 mmol) was added to the mixture and stirred for 3 h at room temperature. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed by saturated brine, dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel) eluting with hexanes/EtOAc (1:1, v / v) to give the target compounds **I-6a–v** as white or off-white solids.

2.1.2 General procedure for the synthesis of compounds I-8

A mixture of **I-3** (138.2 mg, 0.64 mmol), cesium carbonate (417.0 mg, 1.28 mmol) and DMF (4 mL) was stirred for 10 min at room temperature and 1,3-dibromopropane (156.3 mg, 0.77 mmol) (1,4-dibromobutane or 1,5-dibromopentane) was added, and then stirred overnight at the same temperature. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed by saturated brine, dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure to give the crude compounds **I-7a–c** as yellow oils.

A mixture of **I-7a–c** (116.2 mg, 0.35 mmol), morpholine (45.3 mg, 0.52 mmol) and potassium carbonate (96.7 mg, 0.70 mmol) in DMF (2 mL) was stirred for 20 h at 50 °C under an atmosphere of nitrogen. The mixture was diluted with water and extracted with ethyl acetate (20 mL × 3). The combined extracts were washed by saturated brine, dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (1:2, v / v) to get compound **I-8a–c** as off-white solids or yellow oil.

2.1.3 General procedure for the synthesis of compounds I-13



Reagents and conditions: a) triethylamine, DCM, -5°C; b) **3**, K₂CO₃, DMF, 60°C; c) RH, K₂CO₃, DMF, 110°C.

Scheme 2. Synthesis of quinoline compounds **I-13**.

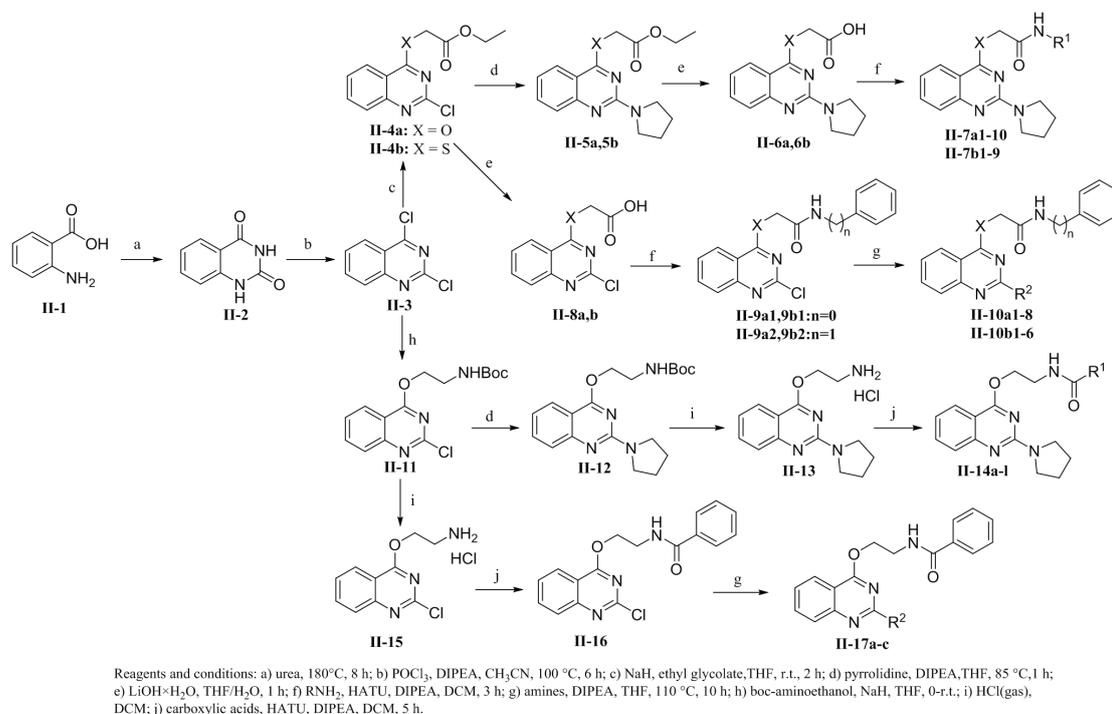
To a solution of benzylamine (**I-9**) (1.3g, 12.1 mmol) and triethylamine (1.5 g, 14.5 mmol) dissolved in dichloromethane (8 mL) was added bromoacetyl bromide (**I-10**, 2.7 g, 13.3 mmol) dropwise at -10°C and then stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure and purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (8:1, v / v) to get compound **I-11** (0.97 g, 35%) as off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.78 (t, *J* = 6.0 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.22 (m, 3H), 4.30 (d, *J* = 5.9 Hz, 2H), 3.91 (s, 2H). LC-MS (ESI), *m/z*: 228[M+H]⁺.

To a solution of **I-2** (0.69 g, 3.86 mmol) and potassium carbonate (1.07 g, 7.72 mmol) dissolved in DMF (5 mL) was added **I-11** (0.97 g, 4.24 mmol) and stirred for 2 h at 65°C and then poured into water (50 mL), extracted with ethyl acetate (40 mL × 2). The combined extracts were dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (1:1, v / v) to get compound **I-12** (1.24 g, 98% from **I-2**) as white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.69 (t, *J* = 6.0 Hz, 1H), 8.43 (d, *J* = 8.5 Hz, 1H), 7.62 (t, *J* = 9.0 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.27 – 7.21 (m, 4H), 4.84 (s, 2H), 4.36 (d, *J* = 6.0 Hz, 2H). LC-MS (ESI), *m/z*: 327 [M+H]⁺.

To a solution of **I-12** (134.2 mg, 0.41mmol) and potassium carbonate (113.3 mg, 0.82 mmol) dissolved in DMF (3 mL) was added secondary amines (0.82 mmol) and stirred for 8 h at 110°C. After cooling to room temperature, the mixture was poured into water (30 mL) and extracted with ethyl acetate (15 mL×2). The combined extracts were dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced

pressure. The residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (1:1, v / v) to get the target compound **I-13a-i**.

2.1.4 General procedure for the synthesis of compounds **II-7**



Scheme 3. Synthesis of quinazoline compounds **II-7**, **10**, **14** and **17**.

Quinazoline-2,4(1H,3H)-dione (**II-2**) and 2,4-diichloroquinazoline (**II-3**) were synthesized according to previously reported methods.

NaH (0.5 g, 12 mmol) was slowly added to the solution of ethyl glycolate (1.0 g, 10 mmol) in absolute THF (20 mL) under N₂ at 0°C. After the solution was stirred for 20 min, **II-3** (2.0 g, 10 mmol) was added to the mixture and stirred overnight. The reaction mixture was quenched with methanol and concentrated under reduced pressure and purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (15:1, v / v) to get the title compound **II-4** (2.0 g, 75% from **II-3**) as off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.26 – 8.15 (m, 1H), 8.10 – 7.98 (m, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.4 Hz, 1H), 5.24 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H).

Pyrrolidine (0.5 g, 7.2 mmol) was added to the solution of **II-4** (3.6 mmol) and *N,N*-diisopropylethylamine (DIPEA) (0.9 g, 7.2 mmol) in THF (15 mL) and then the

system was heated to 85°C for 1 h. The solvent was removed by evaporation and the residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (10:1-4:1, v / v) to get the title compound **II-5** (0.97 g, 90% from **II-4**) as off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.90 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 5.07 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.49 (s, 4H), 1.91 (d, *J* = 6.1 Hz, 4H), 1.19 (t, *J* = 7.1 Hz, 3H). The solid was then dissolved in THF (10 mL) and LiOH · H₂O (0.26 g, 6.2 mmol) in water (10 mL) was added. The reaction mixture was stirred for 1 h at room temperature and evaporated under vacuum. The residue in water (20 mL) was adjusted to pH 2 with 1 N HCl and the precipitated solid was filtered, washed with distilled water (20 mL) to give compound **II-6** as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 5.01 (s, 2H), 3.52 (d, *J* = 6.5 Hz, 4H), 1.95 – 1.88 (m, 4H).

A solution of compound **II-6** (0.32 mmol), 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (144.2 mg, 0.38 mmol) in DCM (2 mL) was stirred at room temperature under the atmosphere of nitrogen for 5 min. The substituted amines (0.38 mmol) and DIPEA (81.7 mg, 0.63 mmol) was added to the mixture and stirred for 3 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel) eluting with hexanes/EtOAc 10:1–2:1 to give the target compounds **II-7**.

2.1.5 General procedure for the synthesis of compounds **II-10**

To a solution of **II-4** (4.1 mmol) in THF (10 mL) was added LiOH · H₂O (0.35 g, 8.3 mmol) in 10 mL water and stirred for 1 h at room temperature. The solvent was removed by evaporation, and then the residue was re-dissolved in water (10 mL) and adjusted to pH 2 with 1 N HCl. The precipitated solid was filtered, washed with distilled water (10 mL) to give compound **II-8** as a white solid .

A solution of compound **II-8** (1.9 mmol), HATU (0.86 g, 2.2 mmol) in DCM (10 mL) was stirred at room temperature under the atmosphere of nitrogen for 5 min.

Aniline or benzylamine (2.2 mmol) and DIPEA (3.8 mmol) was added to the mixture and stirred for 3 h at the same temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel) eluting with hexanes/EtOAc 10:1–2:1 to give a white solid **II-9a** and an off-white solid **II-9b**. **9a1**: ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.36 (s, 1H), 8.31 (d, *J* = 8.2 Hz, 1H), 8.07 (t, *J* = 7.7 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 5.31 (s, 2H). LC-MS (ESI), *m/z*: 314[M+H]⁺. **9b1**: ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.86 – 8.80 (m, 1H), 8.33 (d, *J* = 8.2 Hz, 1H), 8.06 (t, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.39 – 7.29 (m, 4H), 7.29 – 7.24 (m, 1H), 5.15 (s, 2H), 4.39 (d, *J* = 6.0 Hz, 2H). LC-MS (ESI), *m/z*: 328[M+H]⁺.

Secondary amines (0.5 mmol) was added to the suspension of **II-9** (0.25 mmol) and DIPEA (0.75 mmol) in THF (5 mL) and then the system was heated to 110°C for 8–12 h. The mixture was concentrated under reduced pressure and then re-dissolved in ethyl acetate, washed by water, saturated brine and dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel) eluting with hexanes/EtOAc 10:1–2:1 to give the target compounds **II-10**.

2.1.6 General procedure for the synthesis of compounds II-14

NaH (0.6 g, 15.6 mmol) was slowly added to the solution of tert-butyl *N*-(2-hydroxyethyl)carbamate (2.1 g, 13.0 mmol) in absolute THF (20 mL) under N₂ at 0 °C. After the solution was stirred for 20 min, **II-3** (2.6 g, 13.0 mmol) was added to the mixture and stirred for 4 h at r.t.. The reaction mixture was quenched with methanol and concentrated under reduced pressure and purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (20:1–2:1, v / v) to get the title compound **II-11** (3.2 g, 76% from **II-3**) as off-white solid.

Pyrrolidine (0.5 g, 7.0 mmol) was added to the solution of **II-11** (1.1 g, 3.5 mmol) and DIPEA (0.9 g, 7.0 mmol) in THF (10 mL) and then the system was heated to 80°C for 1 h. The solvent was removed by evaporation and the residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (5:1–1:1, v / v) to get the title compound **II-12** (1.1 g, 92% from **II-11**) as off-white

solid. LCMS(ESI): 358[M+H]⁺. Compound **II-12** was deprotected of N-Boc by hydrogen chloride gas to give hydrochloride **II-13**.

A solution of various carboxylic acid (0.2 mmol), HATU (99 mg, 0.26 mmol) in DCM (2 mL) was stirred at room temperature under the atmosphere of nitrogen for 5 min. **13** (60 mg, 0.2 mmol) and DIPEA (78 mg, 0.6 mmol) was added to the mixture and stirred for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel) eluting with hexanes/EtOAc 10:1–2:1 to give the target compounds **II-14a-l**.

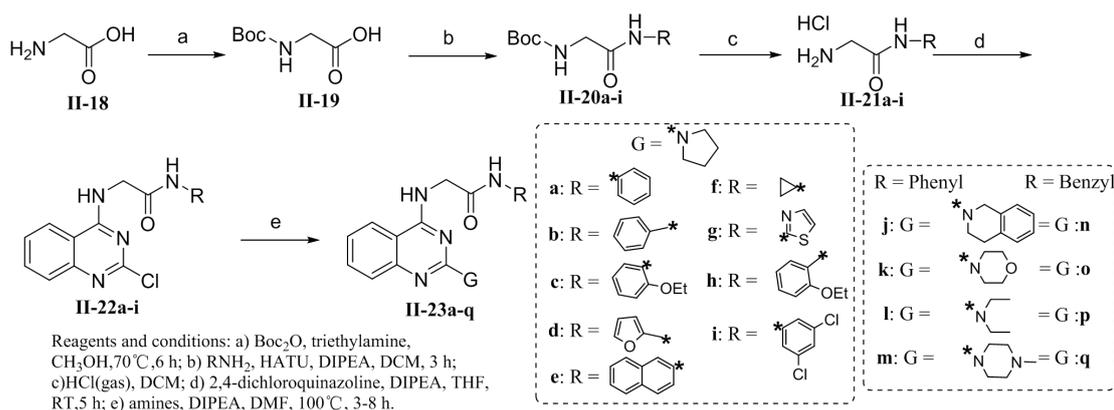
2.1.7 General procedure for the synthesis of compounds II-17

Hydrogen chloride gas was introduced to a stirred solution of **II-12** (1.2 g, 3.8 mmol) in DCM(10 mL) for 0.5 h and then the mixture was stirred for 0.5 h at r.t.. The solvent was removed by evaporation and the residue was recrystallized from ethyl acetate to give hydrochloride **II-15**.

A solution of benzoic Acid (0.24 g, 2.0 mmol), HATU (0.89 g, 2.3 mmol) in DCM (10 mL) was stirred at room temperature under the atmosphere of nitrogen for 5 min. **II-15** (0.51 g, 2.0 mmol) and DIPEA (0.52g, 4.0 mmol) was added to the mixture and stirred for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel) eluting with hexanes/EtOAc 10:1–1:1 to give compound **II-16** (0.40g, 61%).

Secondary amines (0.5 mmol) was added to the suspension of **II-16** (0.25 mmol) and DIPEA (0.75 mmol) in THF (5 mL) and then the system was heated to 110°C for 8–12 h. The mixture was concentrated under reduced pressure and then re-dissolved in ethyl acetate, washed by water, saturated brine and dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel) eluting with hexanes/EtOAc 2:1 to give the target compounds **II-17a-c**.

2.1.8 General procedure for the synthesis of compounds II-23



Scheme 4. Synthesis of quinazoline compounds **II-23**.

Glycine (**II-18**, 30.84 g, 0.41 mol) was dissolved in methanol (200 mL) and triethylamine (180 mL). Di-tert-butyl dicarbonate (179.11 g, 0.82 mol) was added and the mixture was stirred at 70°C for 5 h. The solvent was evaporated and water (100 mL) and EtOAc (150 mL) were added to the residue. The two-phase mixture was transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (2 X 80 mL). The organic phases were combined, dried over MgSO_4 , filtered and the solvent was removed by rotary evaporation to yield **II-19** as a light yellow solid.

HATU(1.2 eq.) was added to a solution of **II-19** and DIPEA(2.0 eq.) in DCM (20 mL), and various primary amines (1.2 eq.) followed by stirring for 3 hours at room temperature. The mixture was washed with brine (two times for each), and the organic layer was dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure obtaining the crude amide **II-20a-i**. The obtained amide compound was deprotected of N-Boc by hydrogen chloride gas to give **II-21a-i**.

To a solution of **II-3** (0.5 g, 2.5 mmol) and DIPEA (0.97 g, 7.5 mmol) dissolved in THF (5 mL) was added **II-21a-i** (1 eq.) and stirred for 3-5 h at room temperature. The mixture was concentrated under reduced pressure and then dissolved in ethyl acetate (20 mL), washed by water, saturated brine and dried over Na_2SO_4 . After filtration, the solvent was removed under reduced pressure to obtain the target compounds **II-22a-i**.

To a solution of **II-22a-i** (1 e.q.) and DIPEA (3 e.q.) dissolved in DMF (4 mL) was added secondary amines (2 e.q.) and stirred for 3-8 h at 100°C . After cooling to room temperature, the mixture was diluted with ethyl acetate (20 mL), washed by water, saturated brine and dried over Na_2SO_4 , and concentrated under reduced

pressure. The residue was recrystallized from ethyl acetate to get the target compound **II-23a–q**.

2.2 The NMR spectra data

N-benzyl-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6a**, a white solid, mp: 151 – 152 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.95 (t, *J* = 6.0 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.19 (m, 4H), 7.15 – 7.05 (m, 3H), 6.83 (d, *J* = 9.0 Hz, 1H), 4.79 (s, 2H), 4.38 (d, *J* = 6.0 Hz, 2H), 3.36 (s, 4H), 1.85 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.27, 155.12, 152.22, 140.62, 139.22, 137.54, 128.70, 127.54, 127.31, 123.89, 122.37, 121.25, 116.00, 111.52, 70.97, 46.80, 42.31, 25.37. LC-MS (ESI), *m/z*: 362[M+H]⁺, 384[M+Na]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₂H₂₄N₃O₂ (M+H)⁺: 362.1863; Found: 362.1851.

N-(4-fluorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6b**, a white solid, mp: 140 – 142 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.18 – 7.13 (m, 2H), 7.12 – 7.02 (m, 3H), 6.83 (d, *J* = 9.0 Hz, 1H), 4.78 (s, 2H), 4.35 (t, *J* = 6.0 Hz, 2H), 3.37 (s, 4H), 1.87 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.28, 155.09, 152.18, 140.61, 137.57, 135.46, 129.61, 123.90, 122.41, 121.25, 116.08, 115.49, 115.35, 111.49, 70.97, 46.80, 41.62, 25.37. LC-MS (ESI), *m/z*: 380[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₂H₂₃FN₃O₂ (M+H)⁺: 380.1769; Found: 380.1773.

N-(3-fluorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6c**, a white solid, mp: 132 – 133 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.05 (t, *J* = 6.0 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.09 (t, *J* = 8.0 Hz, 1H), 7.06 – 7.01 (m, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 10.0 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 4.81 (s, 2H), 4.39 (t, *J* = 6.0 Hz, 2H), 3.43 – 3.34 (m, 4H), 1.91 – 1.80 (m, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.46, 162.59, 155.10, 152.21, 142.32, 140.63, 137.59, 130.62, 123.94, 123.54, 122.49, 121.27, 116.29, 114.12, 111.50, 71.09, 46.82, 41.80, 25.36. LC-MS (ESI), *m/z*: 380[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₂H₂₃FN₃O₂ (M+H)⁺: 380.1769; Found: 380.1762.

N-(2-fluorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6d**, a white solid, mp: 136 – 137°C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.88 (t, *J* = 6.0 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.12 – 7.05 (m, 4H), 6.84 (d, *J* = 9.0 Hz, 1H), 4.80 (s, 2H), 4.42 (d, *J* = 5.5 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 4H), 1.93 – 1.86 (m, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.37, 160.49, 155.10, 152.11, 140.59, 137.55, 129.88, 129.53, 125.77, 124.70, 123.88, 122.37, 121.23, 115.89, 115.52, 111.49, 70.79, 46.79, 36.21, 25.39. LC-MS (ESI), *m/z*: 380[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₂H₂₃FN₃O₂ (M+H)⁺: 380.1769; Found: 380.1759.

N-(4-bromobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6e**, a white solid, mp: 163 – 165°C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.97 (t, *J* = 6.0 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.12 – 7.02 (m, 3H), 6.83 (d, *J* = 9.0 Hz, 1H), 4.79 (s, 2H), 4.34 (d, *J* = 6.0 Hz, 2H), 3.40 – 3.33 (m, 4H), 1.85 – 1.88 (m, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.39, 155.07, 152.17, 140.62, 138.70, 137.56, 131.55, 129.85, 123.91, 122.47, 121.27, 120.39, 116.20, 111.50, 71.04, 46.80, 41.76, 25.37. LC-MS (ESI), *m/z*: 440, 442[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₂H₂₃BrN₃O₂ (M+H)⁺: 440.0968; Found: 440.0975, 442.0954.

N-(2-bromobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6f**, a white solid, mp: 148 – 150°C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.95 (t, *J* = 6.0 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.16 – 7.06 (m, 2H), 6.82 (d, *J* = 9.0 Hz, 1H), 4.83 (s, 2H), 4.40 (d, *J* = 6.0 Hz, 2H), 3.38 (t, *J* = 6.5 Hz, 4H), 1.90 – 1.83 (m, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.52, 155.09, 152.17, 140.66, 137.57, 137.55, 132.85, 129.50, 129.33, 128.07, 123.95, 122.84, 122.45, 121.27, 116.08, 111.51, 70.92, 46.82, 42.81, 25.38. LC-MS (ESI), *m/z*: 440, 442[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₂H₂₃BrN₃O₂ (M+H)⁺: 440.0968; Found: 440.0980, 442.0945.

N-(4-methoxybenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6g**, a white solid, mp: 139 – 141°C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.80 (t, *J* = 6.0 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.13 –

7.00 (m, 3H), 6.88 – 6.73 (m, 3H), 4.76 (s, 2H), 4.29 (d, $J = 6.0$ Hz, 2H), 3.72 (s, 4H), 3.35 (s, 3H), 1.86 (s, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.06, 158.72, 155.10, 152.16, 140.58, 137.51, 131.01, 128.99, 123.85, 122.30, 121.22, 115.77, 114.11, 111.51, 70.83, 55.53, 46.78, 41.86, 25.37. LC-MS (ESI), m/z : 392[M+H] $^+$. HRMS-ESI (m/z): Calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_3$ (M+H) $^+$: 392.1969; Found: 392.1954.

N-(3-methoxybenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6h**, a white solid, mp: 98 – 100°C. ^1H NMR (500 MHz, DMSO- d_6) δ 8.99 (t, $J = 6.0$ Hz, 1H), 7.96 (d, $J = 9.0$ Hz, 1H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.25 (d, $J = 7.5$ Hz, 1H), 7.14 (t, $J = 8.0$ Hz, 1H), 7.09 (t, $J = 7.5$ Hz, 1H), 6.82 (d, $J = 9.0$ Hz, 1H), 6.77 (dd, $J = 8.0, 3.0$ Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.65 (s, 1H), 4.80 (s, 2H), 4.35 (d, $J = 6.0$ Hz, 2H), 3.62 (s, 3H), 3.37 (t, $J = 6.5$ Hz, 4H), 1.87 – 1.85 (m, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.28, 159.71, 155.10, 152.26, 140.78, 140.63, 137.52, 129.73, 123.90, 122.40, 121.24, 119.74, 116.09, 113.06, 112.84, 111.51, 71.06, 55.31, 46.80, 42.31, 25.36. LC-MS (ESI), m/z : 392[M+H] $^+$. HRMS-ESI (m/z): Calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_3$ (M+H) $^+$: 392.1969; Found: 392.1955.

N-(2-methoxybenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6i**, a white solid, mp: 103 – 105°C. ^1H NMR (500 MHz, DMSO- d_6) δ 8.70 (t, $J = 6.0$ Hz, 1H), 7.97 (d, $J = 9.0$ Hz, 1H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.26 – 7.18 (m, 2H), 7.09 (t, $J = 8.0$ Hz, 1H), 7.03 – 6.98 (m, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.83 – 6.77 (m, 2H), 4.78 (s, 2H), 4.33 (d, $J = 6.0$ Hz, 2H), 3.64 (s, 3H), 3.37 (t, $J = 6.5$ Hz, 4H), 1.86 (s, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.21, 157.14, 155.10, 152.20, 140.62, 137.49, 128.72, 128.32, 126.35, 123.86, 122.27, 121.22, 120.45, 115.71, 111.50, 110.91, 70.81, 55.62, 46.75, 37.74, 25.38. LC-MS (ESI), m/z : 392[M+H] $^+$. HRMS-ESI (m/z): Calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_3$ (M+H) $^+$: 392.1969; Found: 392.1956.

N-(4-chlorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6j**, a white solid, mp: 151 – 153°C. ^1H NMR (500 MHz, DMSO- d_6) δ 8.97 (s, 1H), 7.98 (d, $J = 9.0$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.29 – 7.24 (m, 3H), 7.15 – 7.06 (m, 3H), 6.83 (d, $J = 9.0$ Hz, 1H), 4.79 (s, 2H), 4.35 (d, $J = 6.0$ Hz, 2H), 3.36 (t, $J = 6.5$ Hz, 4H), 1.90 – 1.84 (m, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.39, 155.08, 152.17,

140.62, 138.30, 137.57, 131.91, 129.49, 128.64, 123.91, 122.46, 121.27, 116.19, 111.50, 71.03, 46.80, 41.69, 25.36. LC-MS (ESI), m/z : 396[M+H]⁺. HRMS-ESI (m/z): Calcd. for C₂₂H₂₃ClN₃O₂ (M+H)⁺: 396.1474; Found: 396.1469, 398.1441.

N-(3-chlorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6k**, a white solid, mp: 107 – 109°C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.10 (t, J = 6.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.28 – 7.23 (m, 3H), 7.15 – 7.05 (m, 3H), 6.83 (d, J = 9.0 Hz, 1H), 4.81 (s, 2H), 4.38 (d, J = 6.0 Hz, 2H), 3.39 (t, J = 6.5 Hz, 4H), 1.89 – 1.85 (m, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.50, 155.09, 152.21, 141.91, 140.62, 137.62, 133.42, 130.54, 127.35, 127.27, 126.24, 123.95, 122.55, 121.27, 116.38, 111.51, 71.16, 46.83, 41.73, 25.38. LC-MS (ESI), m/z : 396[M+H]⁺. HRMS-ESI (m/z): Calcd. for C₂₂H₂₃ClN₃O₂ (M+H)⁺: 396.1474; Found: 396.1482, 398.1443.

N-(2,6-dichlorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6l**, a white solid, mp: 108 – 110°C. ¹H NMR (500 MHz, CDCl₃) δ 8.20 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.5 Hz, 1H), 7.09 – 7.07 (m, 2H), 6.58 (d, J = 9.0 Hz, 1H), 4.82 (s, 2H), 4.77 (d, J = 5.0 Hz, 2H), 3.40 (t, J = 5.0 Hz, 4H), 1.98 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.00, 154.92, 151.75, 140.64, 137.35, 135.78, 132.73, 130.77, 129.02, 123.82, 122.15, 121.12, 115.03, 111.36, 70.09, 46.64, 39.04, 25.34. LC-MS (ESI), m/z : 430[M+H]⁺. HRMS-ESI (m/z): Calcd. for C₂₂H₂₂Cl₂N₃O₂ (M+H)⁺: 430.1084; Found: 430.1104, 432.1084.

N-(2-ethoxybenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6m**, a white solid, mp: 83 – 84°C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.68 (t, J = 6.0 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.0 Hz, 2H), 7.09 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.82 – 6.76 (m, 2H), 4.78 (s, 2H), 4.32 (d, J = 6.0 Hz, 2H), 3.82 (q, J = 7.0 Hz, 2H), 3.35 (t, J = 6.5 Hz, 4H), 1.88 – 1.81 (m, 4H), 1.15 (t, J = 7.0 Hz, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.14, 156.51, 155.04, 152.23, 140.67, 137.44, 128.70, 128.43, 126.36, 123.86, 122.31, 121.19, 120.30, 115.83, 111.76, 111.48, 70.93, 63.52, 46.72, 38.03, 25.35, 14.98. LC-MS (ESI), m/z : 406[M+H]⁺. HRMS-ESI (m/z): Calcd. for

C₂₄H₂₈N₃O₃ (M+H)⁺: 406.2125; Found: 406.2115.

N-(2-methylbenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6n**, a white solid, mp: 125 – 126 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.72 (s, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.17 – 7.01 (m, 5H), 6.78 (d, *J* = 9.0 Hz, 1H), 4.80 (s, 2H), 4.32 (s, 2H), 3.32 (s, 4H), 1.99 (s, 3H), 1.85 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.99, 155.04, 152.09, 140.62, 137.43, 136.50, 136.16, 130.36, 128.15, 127.48, 126.05, 122.28, 121.19, 115.64, 111.49, 70.71, 46.73, 40.74, 25.34, 18.75. LC-MS (ESI), *m/z*: 406[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₃H₂₆N₃O₂ (M+H)⁺: 376.2020; Found: 406.2016.

N-(4-(trifluoromethyl)benzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6o**, a white solid, mp: 176 – 178 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.12 (t, *J* = 6.0 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 4.82 (s, 2H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.36 (t, *J* = 6.5 Hz, 4H), 1.87 – 1.82 (m, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.58, 155.06, 152.20, 144.23, 140.64, 137.60, 128.22, 125.67, 125.53, 123.95, 122.55, 121.30, 116.43, 111.47, 71.16, 46.79, 41.90, 25.32. LC-MS (ESI), *m/z*: 430[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₃H₂₃F₃N₃O₂ (M+H)⁺: 430.1737; Found: 430.1721.

N-(4-(methylsulfonyl)benzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6p**, a white solid, mp: 189 – 191 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.55 (s, 1H), 7.87 – 7.82 (m, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.21 – 7.12 (m, 4H), 6.85 – 6.47 (m, 1H), 4.88 (s, 2H), 4.57 (d, *J* = 6.0 Hz, 2H), 3.39 (s, 4H), 3.00 (s, 3H), 1.90 (s, 4H). LC-MS (ESI), *m/z* : 440[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₃H₂₆N₃O₄S (M+H)⁺: 440.1639; Found: 440.1646.

N-(furan-2-ylmethyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6q**, a white solid, mp: 148 – 150 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.83 (t, *J* = 6.0 Hz, 1H),

7.98 (d, $J = 9.0$ Hz, 1H), 7.49 (s, 1H), 7.36 (d, $J = 8.0$ Hz, 1H), 7.21 (d, $J = 7.5$ Hz, 1H), 7.08 (t, $J = 7.5$ Hz, 1H), 6.87 (d, $J = 9.0$ Hz, 1H), 6.35 (s, 1H), 6.14 (s, 1H), 4.75 (s, 2H), 4.37 (d, $J = 5.5$ Hz, 2H), 3.48 – 3.45 (m, 4H), 1.96 – 1.93 (m, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.10, 155.16, 152.10, 142.76, 140.59, 137.53, 123.82, 122.32, 121.21, 115.80, 111.53, 110.81, 107.49, 70.74, 46.87, 35.65, 25.46. LC-MS (ESI), m/z : 352[M+H] $^+$. HRMS-ESI (m/z): Calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_3\text{O}_3$ (M+H) $^+$: 352.1656; Found: 352.1646.

N-(cyclopropylmethyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6r**, a white solid, mp: 147 – 149°C. ^1H NMR (500 MHz, DMSO- d_6) δ 8.33 (t, $J = 6.0$ Hz, 1H), 8.00 (d, $J = 9.0$ Hz, 1H), 7.36 (d, $J = 8.0$ Hz, 1H), 7.19 (d, $J = 7.5$ Hz, 1H), 7.08 (t, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 9.0$ Hz, 1H), 4.68 (s, 2H), 3.56 (s, 4H), 3.05 (t, $J = 6.5$ Hz, 2H), 1.98 (s, 4H), 0.90 – 0.80 (m, 1H), 0.34 (d, $J = 7.5$ Hz, 2H), 0.10 (d, $J = 5.0$ Hz, 2H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 168.84, 155.22, 152.03, 140.54, 137.60, 123.84, 122.14, 121.24, 115.25, 111.43, 70.32, 46.96, 43.08, 25.47, 11.24, 3.51. LC-MS (ESI), m/z : 326[M+H] $^+$. HRMS-ESI (m/z): Calcd. for $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_2$ (M+H) $^+$: 326.1863; Found: 326.1855.

1-morpholino-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)ethan-1-one **I-6s**, an off-white solid, mp: 70 – 72°C. ^1H NMR (500 MHz, DMSO- d_6) δ 7.97 (d, $J = 9.5$ Hz, 1H), 7.31 (d, $J = 7.5$ Hz, 1H), 7.06 – 7.01 (m, 2H), 6.87 (d, $J = 9.0$ Hz, 1H), 4.98 (s, 2H), 3.69 – 3.43 (m, 12H), 1.99 – 1.97 (m, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 170.82, 155.01, 151.83, 140.46, 137.46, 123.83, 121.60, 121.07, 113.86, 111.13, 68.85, 66.69, 47.01, 45.86, 25.50. LC-MS (ESI), m/z : 342[M+H] $^+$. HRMS-ESI (m/z): Calcd. for $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_3$ (M+H) $^+$: 342.1812; Found: 342.1817.

N-phenyl-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6t**, an off-white solid, mp: 130 – 132°C. ^1H NMR (500 MHz, DMSO- d_6) δ 10.25 (s, 1H), 8.02 (d, $J = 9.0$ Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.31 (t, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 7.5$ Hz, 1H), 7.13 – 7.06 (m, 2H), 6.94 (d, $J = 8.5$ Hz, 1H), 4.92 (s, 2H), 3.59 –

3.49 (m, 4H), 1.93 – (m, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.10, 155.24, 152.05, 140.64, 138.53, 137.76, 129.24, 124.36, 124.01, 122.51, 121.31, 120.25, 116.15, 111.55, 70.82, 47.06, 25.44. LC-MS (ESI), *m/z*: 348[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₁H₂₂N₃O₂ (M+H)⁺: 348.1707; Found: 348.1698.

N-(2-ethoxyphenyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **I-6u**, a faint yellow solid, mp: 110 – 112 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.51 (s, 1H), 8.06 (d, *J* = 8.0 Hz, H), 8.01 (d, *J* = 7.5 Hz, H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.96 – 6.89 (m, 2H), 4.91 (s, 2H), 3.99 (q, *J* = 7.0 Hz, 2H), 3.48 (s, 4H), 1.88 (s, 4H), 1.10 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 167.67, 155.15, 151.60, 148.60, 137.55, 127.09, 125.05, 124.01, 122.67, 121.07, 120.90, 115.59, 112.57, 111.46, 70.49, 64.40, 46.84, 25.40, 14.64. LC-MS (ESI), *m/z*: 392[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₃H₂₆N₃O₃ (M+H)⁺: 392.1969; Found: 392.1960.

4-(3-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)propyl)morpholine **I-8a**, a white solid, mp: 84 – 86 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.81 (d, *J* = 9.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 1H), 4.24 (t, *J* = 6.5 Hz, 2H), 3.74 (t, *J* = 5.0 Hz, 4H), 3.64 (s, 4H), 2.69 (t, *J* = 8.0 Hz, 2H), 2.53 (s, 4H), 2.17 (t, *J* = 7.0 Hz, 2H), 2.04 (t, *J* = 6.0 Hz, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 154.91, 152.92, 140.67, 137.34, 123.74, 121.22, 120.74, 113.13, 110.85, 67.71, 66.58, 55.59, 53.84, 46.88, 37.95, 25.49. LC-MS (ESI), *m/z*: 342[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₀H₂₈N₃O₂ (M+H)⁺: 342.2176; Found: 342.2164.

4-(4-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)butyl)morpholine **I-8b**, a white solid, mp: 94 – 96 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.81 (d, *J* = 9.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 1H), 4.20 (t, *J* = 6.5 Hz, 2H), 3.75 (s, 4H), 3.64 (s, 4H), 2.54 (s, 6H), 2.06 – 1.96 (m, 6H), 1.89 – 1.81 (m, 2H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 154.91, 152.94, 140.54, 137.34, 123.70, 121.23, 120.53, 112.57, 110.84, 68.99, 53.48, 46.88, 37.94, 27.29, 25.49.

LC-MS (ESI), m/z : 356[M+H]⁺. HRMS-ESI (m/z): Calcd. for C₂₁H₃₀N₃O₂ (M+H)⁺: 356.2333; Found: 356.2334.

4-(5-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)pentyl)morpholine I-8c, yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.81 (d, J = 9.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.71 (d, J = 9.0 Hz, 1H), 4.17 (t, J = 6.5 Hz, 2H), 3.72 (t, J = 5.0 Hz, 4H), 3.63 (s, 4H), 2.46 (s, 4H), 2.39 (t, J = 7.0 Hz, 2H), 2.04 (s, 4H), 1.99 (t, J = 7.0 Hz, 2H), 1.62 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 154.90, 153.03, 140.62, 137.33, 123.72, 121.22, 120.55, 112.74, 110.81, 69.30, 66.47, 58.68, 53.71, 46.86, 37.94, 29.38, 25.50, 24.11. LC-MS (ESI), m/z : 370[M+H]⁺. HRMS-ESI (m/z): Calcd. for C₂₂H₃₂N₃O₂ (M+H)⁺: 370.2489; Found: 370.2484.

N-benzyl-2-((2-(diethylamino)quinolin-8-yl)oxy)acetamide I-13a, an off-white solid, mp: 107 – 108°C. ¹H NMR (500 MHz, CDCl₃) δ 8.28 (s, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.25 – 7.17 (m, 6H), 7.12 – 7.01 (m, 2H), 6.80 (d, J = 9.0 Hz, 1H), 4.80 (s, 2H), 4.55 (d, J = 6.0 Hz, 2H), 3.48 (q, J = 7.0 Hz, 4H), 1.10 (t, J = 7.0 Hz, 6H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 172.87, 156.01, 144.04, 138.56, 138.06, 134.38, 130.03, 128.63, 128.60, 128.52, 127.38, 123.68, 120.81, 110.53, 60.44, 52.26, 42.73, 13.53. LC-MS (ESI), m/z : 364[M+H]⁺. HRMS-ESI (m/z): Calcd. for C₂₂H₂₆N₃O₂ (M+H)⁺: 364.2020; Found: 364.2016.

N-benzyl-2-((2-(piperidin-1-yl)quinolin-8-yl)oxy)acetamide I-13b, a white solid, mp: 167 – 169°C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.74 (d, J = 5.0 Hz, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 6.5 Hz, 1H), 7.29 – 7.08 (m, 9H), 4.77 (s, 2H), 4.38 (d, J = 5.0 Hz, 2H), 3.58 (d, J = 4.5 Hz, 4H), 1.62 – 1.53 (m, 2H), 1.52 – 1.41 (m, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.09, 156.96, 152.20, 139.97, 139.40, 137.94, 128.72, 127.45, 127.28, 124.08, 121.98, 121.91, 115.28, 111.08, 70.53, 45.92, 42.22, 25.67, 24.72. LC-MS (ESI), m/z : 376[M+H]⁺. HRMS-ESI (m/z): Calcd. for C₂₃H₂₆N₃O₂ (M+H)⁺: 376.2020; Found: 376.2027.

N-benzyl-2-((2-morpholinoquinolin-8-yl)oxy)acetamide **I-13c**, a white solid, mp: 153 – 155°C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.68 (t, *J* = 6.0 Hz, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.29 – 7.20 (m, 5H), 7.19 – 7.14 (m, 3H), 4.78 (s, 2H), 4.39 (d, *J* = 6.5 Hz, 2H), 3.60 (t, *J* = 5.0 Hz, 4H), 3.52 (t, *J* = 5.0 Hz, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 172.79, 157.61, 143.33, 138.46, 138.38, 135.00, 130.12, 128.68, 128.53, 127.61, 127.37, 124.44, 122.14, 110.95, 66.43, 60.47, 52.35, 45.26. LC-MS (ESI), *m/z*: 378[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₂H₂₄N₃O₃ (M+H)⁺: 378.1812; Found: 378.1821.

N-benzyl-2-((2-(4-methylpiperazin-1-yl)quinolin-8-yl)oxy)acetamide **I-13d**, a white solid, mp: 154 – 156°C. ¹H NMR (500 MHz, CDCl₃) δ 8.44 (s, 1H), 7.87 (d, *J* = 9.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 2H), 7.20 – 7.13 (m, 3H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 4.82 (s, 2H), 4.54 (d, *J* = 6.0 Hz, 2H), 3.60 (s, 4H), 2.38 (s, 4H), 2.32 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.00, 156.89, 152.30, 139.67, 139.41, 138.12, 128.74, 127.46, 127.31, 124.38, 122.42, 121.84, 115.01, 110.98, 70.34, 54.64, 45.89, 44.62, 42.20. LC-MS (ESI), *m/z*: 391[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₃H₂₇N₄O₂ (M+H)⁺: 391.2129; Found: 391.2125.

tert-butyl 4-(8-(2-(benzylamino)-2-oxoethoxy)quinolin-2-yl)piperazine-1- carboxylate **I-13e**, a white solid, mp: 152 – 154°C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.63 (d, *J* = 6.0 Hz, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.39 (dd, *J* = 6.5, 1.0 Hz, 1H), 7.30 – 7.13 (m, 8H), 4.77 (s, 2H), 4.40 (d, *J* = 5.0 Hz, 2H), 3.60 – 3.54 (m, 4H), 3.39 – 3.33 (m, 4H), 1.44 (s, 9H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.90, 156.80, 154.38, 152.25, 139.56, 139.44, 138.21, 128.74, 127.49, 127.33, 124.46, 122.55, 121.80, 114.89, 111.05, 79.52, 70.21, 44.71, 42.20, 40.45, 28.57. LC-MS (ESI), *m/z*: 477[M+H]⁺. HRMS-ESI (*m/z*): Calcd. for C₂₇H₃₃N₄O₄ (M+H)⁺: 477.2497; Found: 477.2508.

N-benzyl-2-((2-(dimethylamino)quinolin-8-yl)oxy)acetamide **I-13f**, a white solid, mp: 112 – 114°C. ¹H NMR (500 MHz, CDCl₃) δ 8.73 (s, 1H), 7.89 (s, 1H), 7.35 (d, *J* = 8.0

Hz, 1H), 7.25 (d, $J = 5.0$ Hz, 4H), 7.17 (s, 3H), 6.88 (s, 1H), 4.87 (s, 2H), 4.56 (d, $J = 6.0$ Hz, 2H), 3.04 (s, 6H). ^{13}C NMR (151 MHz, $\text{DMSO-}d_6$) δ 169.10, 157.13, 152.17, 140.13, 139.30, 137.77, 128.71, 127.60, 127.31, 123.73, 122.09, 121.58, 115.55, 110.38, 70.65, 42.35, 37.96. LC-MS (ESI), m/z : 336[M+H] $^+$. HRMS-ESI (m/z): Calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_3\text{O}_2$ (M+H) $^+$: 336.1707; Found: 336.1704.

N-benzyl-2-((2-(methylamino)quinolin-8-yl)oxy)acetamide **I-13g**, an off-white solid, mp: 113 – 114°C. ^1H NMR (600 MHz, $\text{DMSO-}d_6$) δ 9.04 (d, $J = 5.0$ Hz, 1H), 7.83 (d, $J = 7.5$ Hz, 1H), 7.32 (d, $J = 6.5$ Hz, 1H), 7.27 – 7.18 (m, 4H), 7.17 – 7.14 (m, 2H), 7.08 (t, $J = 6.5$ Hz, 2H), 6.74 (d, $J = 7.5$ Hz, 1H), 4.78 (s, 2H), 4.38 (d, $J = 5.0$ Hz, 2H), 2.76 (d, $J = 4.0$ Hz, 3H). ^{13}C NMR (151 MHz, $\text{DMSO-}d_6$) δ 169.31, 157.47, 152.31, 140.38, 139.44, 136.85, 128.71, 127.47, 127.28, 124.37, 122.29, 121.43, 115.93, 113.87, 70.98, 42.25, 27.83. LC-MS (ESI), m/z : 322[M+H] $^+$. HRMS-ESI (m/z): Calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_3\text{O}_2$ (M+H) $^+$: 322.1550; Found: 322.1554.

tert-butyl (S)-(1-(8-(2-(benzylamino)-2-oxoethoxy)quinolin-2-yl)pyrrolidine-3-yl)carbamate **I-13h**, an off-white solid, mp: 111 – 112°C. ^1H NMR (500 MHz, CDCl_3) δ 8.80 (s, 1H), 7.88 (d, $J = 9.0$ Hz, 1H), 7.35 (d, $J = 7.0$ Hz, 1H), 7.30 (s, 1H), 7.28 – 7.24 (m, 2H), 7.17 (s, 4H), 6.67 (d, $J = 9.0$ Hz, 1H), 4.87 (s, 2H), 4.59 – 4.51 (m, 2H), 4.25 (s, 1H), 3.62 (s, 1H), 3.42 (s, 2H), 3.23 (s, 1H), 2.13 (s, 1H), 1.90 – 1.70 (m, 2H), 1.51 (s, 9H). ^{13}C NMR (151 MHz, $\text{DMSO-}d_6$) δ 167.43, 155.75, 155.08, 152.24, 140.51, 139.30, 137.60, 131.98, 129.13, 128.68, 127.62, 127.27, 122.37, 115.98, 111.33, 78.34, 70.93, 52.45, 50.24, 45.18, 42.32, 30.49, 28.72. LC-MS (ESI), m/z : 477[M+H] $^+$. HRMS-ESI (m/z): Calcd. for $\text{C}_{27}\text{H}_{33}\text{N}_4\text{O}_4$ (M+H) $^+$: 477.2497; Found: 477.2516.

tert-butyl (R)-(1-(8-(2-(benzylamino)-2-oxoethoxy)quinoline-2-yl)pyrrolidine-3-yl)carbamate **I-13i**, an off-white solid, mp: 112 – 113°C. ^1H NMR (500 MHz, CDCl_3) δ 8.80 (s, 1H), 7.88 (d, $J = 9.0$ Hz, 1H), 7.35 (d, $J = 7.0$ Hz, 1H), 7.30 (s, 1H), 7.28 –

7.23 (m, 2H), 7.17 (s, 4H), 6.67 (d, $J = 9.0$ Hz, 1H), 4.87 (s, 2H), 4.61 – 4.48 (m, 2H), 4.24 (s, 1H), 3.62 (d, $J = 10.5$ Hz, 1H), 3.42 (s, 2H), 3.23 (s, 1H), 2.13 (s, 1H), 1.90 – 1.66 (m, 2H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 167.43, 155.75, 155.08, 152.25, 140.51, 139.30, 137.60, 131.97, 129.13, 128.67, 127.62, 127.26, 122.37, 115.99, 111.33, 78.34, 70.94, 52.46, 50.24, 45.18, 42.33, 30.49, 28.72. LC-MS (ESI), m/z : 477[M+H] $^+$. HRMS-ESI (m/z): Calcd. for $\text{C}_{27}\text{H}_{33}\text{N}_4\text{O}_4$ (M+H) $^+$: 477.2497; Found: 477.2495.

N-phenyl-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)acetamide **II-7a1**, a white solid, mp: 168–169°C. ^1H NMR (500 MHz, Chloroform- d) δ 8.17 (s, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.63 (t, $J = 7.7$ Hz, 1H), 7.58 (t, $J = 8.6$ Hz, 3H), 7.34 (t, $J = 7.7$ Hz, 2H), 7.15 (q, $J = 7.4$ Hz, 2H), 5.12 (s, 2H), 3.63 (s, 4H), 1.98 (d, $J = 6.1$ Hz, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 166.48, 165.86, 156.69, 153.83, 139.08, 134.36, 129.23, 124.82, 124.08, 123.94, 121.70, 119.91, 110.58, 65.45, 46.79, 25.33. HRMS-ESI (m/z): Calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_4\text{O}_2$ (M+H) $^+$: 349.1659; Found: 349.1670.

N-benzyl-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)acetamide **II-7a2**, an off-white solid, mp: 157–159°C. ^1H NMR (500 MHz, Chloroform- d) δ 7.85 (d, $J = 8.0$ Hz, 1H), 7.59 (q, $J = 11.0, 9.3$ Hz, 2H), 7.30 (d, $J = 7.2$ Hz, 2H), 7.25 (d, $J = 8.7$ Hz, 3H), 7.10 (t, $J = 7.4$ Hz, 1H), 6.67 (s, 1H), 5.08 (s, 2H), 4.54 (d, $J = 6.0$ Hz, 2H), 3.62 (s, 4H), 1.97 (d, $J = 6.4$ Hz, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 167.69, 165.89, 156.69, 139.80, 134.32, 128.62, 127.68, 127.22, 124.68, 124.39, 121.57, 110.70, 65.19, 46.82, 42.33, 25.41. HRMS-ESI (m/z): Calcd. for $\text{C}_{21}\text{H}_{23}\text{N}_4\text{O}_2$ (M+H) $^+$: 363.1816; Found: 363.1828.

N-(3,5-dichlorophenyl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)acetamide **II-7a4**, a gray solid, mp: 230–231°C. ^1H NMR (500 MHz, DMSO- d_6) δ 10.65 (s, 1H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 3H), 7.46 (d, $J = 8.5$ Hz, 1H), 7.33 (s, 1H), 7.21 (t, $J = 7.7$ Hz, 1H), 5.14 (s, 2H), 3.49 (s, 4H), 1.89 (s, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 167.38, 165.74, 156.69, 154.06, 141.38, 134.62, 134.42, 124.97, 124.02,

123.24, 121.73, 117.94, 110.47, 65.38, 46.77, 25.32. HRMS-ESI (m/z): Calcd. for $C_{20}H_{19}Cl_2N_4O_2$ ($M+H$)⁺: 417.0880; Found: 417.0890.

N-(furan-2-ylmethyl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)acetamide **II-7a5**, an off-white solid, mp: 166–168°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.87 (d, J = 8.0 Hz, 1H), 7.59 (m, 2H), 7.32 (s, 1H), 7.13 (d, J = 7.5 Hz, 1H), 6.70 (s, 1H), 6.30 (s, 1H), 6.22 (s, 1H), 5.04 (s, 2H), 4.53 (d, J = 5.8 Hz, 2H), 3.61 (s, 4H), 1.98 (d, J = 5.8 Hz, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 167.51, 165.82, 156.62, 152.58, 142.54, 134.33, 124.62, 124.31, 121.60, 110.87, 110.63, 107.42, 65.06, 46.80, 35.71, 25.43. HRMS-ESI (m/z): Calcd. for $C_{19}H_{21}N_4O_3$ ($M+H$)⁺: 353.1608; Found: 353.1630.

N-(naphthalen-2-yl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)acetamide **II-7a6**, a light yellow solid, mp: 163–165°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.41 (s, 1H), 8.25 (s, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.79 (t, J = 8.6 Hz, 3H), 7.65 (d, J = 4.1 Hz, 2H), 7.53 (d, J = 8.7 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.19 (m, 1H), 5.18 (s, 2H), 3.64 (s, 4H), 1.97 (d, J = 6.0 Hz, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 166.82, 165.93, 136.89, 134.43, 133.87, 130.28, 128.78, 127.94, 127.71, 126.88, 125.08, 124.10, 121.80, 120.54, 115.91, 110.57, 65.61, 46.87, 25.31. HRMS-ESI (m/z): Calcd. for $C_{24}H_{23}N_4O_2$ ($M+H$)⁺: 399.1816; Found: 399.1832.

N-cyclopropyl-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)acetamide **II-7a7**, an off-white solid, mp: 202–204°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.85 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.42 (s, 1H), 4.99 (s, 2H), 3.64 (s, 4H), 2.91 – 2.67 (m, 1H), 1.99 (d, J = 6.2 Hz, 4H), 0.82 (d, J = 7.0 Hz, 2H), 0.55 (d, J = 4.3 Hz, 2H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.59, 165.87, 156.74, 153.73, 134.27, 124.74, 124.24, 121.58, 110.66, 65.05, 46.82, 25.40, 22.56, 6.04. HRMS-ESI (m/z): Calcd. for $C_{17}H_{21}N_4O_2$ ($M+H$)⁺: 313.1659; Found: 313.1675.

N-(thiazol-2-yl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)acetamide **II-7a8**, a light yellow solid, mp: 218–220°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.95 (d, J = 8.1

Hz, 1H), 7.66 (t, $J = 7.7$ Hz, 1H), 7.46 (d, $J = 3.7$ Hz, 1H), 7.26 (s, 1H), 7.19 (s, 1H), 7.02 (s, 1H), 5.25 (s, 2H), 3.67 (s, 4H), 1.98 (s, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 166.90, 165.68, 158.06, 156.63, 154.07, 138.20, 134.44, 124.97, 123.98, 121.74, 114.12, 110.43, 64.70, 46.71, 25.31. HRMS-ESI (m/z): Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_5\text{O}_2\text{S}$ ($\text{M}+\text{H}$) $^+$: 356.1176; Found: 356.1198.

N-(2-ethoxybenzyl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)acetamide **II-7a9**, a off-white solid, mp: 157–159°C. ^1H NMR (500 MHz, Chloroform- d) δ 7.90 (d, $J = 8.0$ Hz, 1H), 7.60 (d, $J = 7.3$ Hz, 1H), 7.56 (s, 1H), 7.20 (t, $J = 7.9$ Hz, 1H), 7.11 (t, $J = 7.6$ Hz, 1H), 6.92 (s, 1H), 6.86 (t, $J = 7.4$ Hz, 1H), 6.71 (d, $J = 8.2$ Hz, 1H), 4.96 (s, 2H), 4.47 (d, $J = 6.2$ Hz, 2H), 3.71 (q, $J = 7.0$ Hz, 2H), 3.41 (s, 4H), 1.89 (s, 4H), 1.06 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 167.71, 165.89, 156.75, 156.34, 134.30, 128.44, 128.09, 127.21, 124.77, 124.31, 121.53, 120.28, 111.80, 110.70, 65.21, 63.69, 46.79, 37.53, 25.41, 15.10. HRMS-ESI (m/z): Calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_4\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 407.2078; Found: 407.2095.

N-(adamantan-1-yl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)acetamide **II-7a10**, a white solid, 87% yield, mp: 170–172°C. ^1H NMR (500 MHz, DMSO- d_6) δ 7.88 (d, $J = 8.0$ Hz, 1H), 7.66 (s, 1H), 7.62 (t, $J = 7.9$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.14 (t, $J = 7.7$ Hz, 1H), 4.85 (s, 2H), 3.55 (s, 5H), 2.00 (s, 3H), 1.93 (s, 10H), 1.60 (s, 6H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 166.37, 165.91, 156.97, 153.96, 134.16, 124.88, 123.99, 121.52, 110.73, 64.96, 51.40, 46.81, 41.59, 36.47, 29.28, 25.41. HRMS-ESI (m/z): Calcd. for $\text{C}_{24}\text{H}_{31}\text{N}_4\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 407.2442; Found: 407.2450.

N-phenyl-2-((2-(3,4-dihydroisoquinolin-2(1H)-yl)quinazolin-4-yl)oxy)acetamide **II-10a1**, a yellow solid, mp: 161–163°C. ^1H NMR (500 MHz, DMSO- d_6) δ 10.46 (s, 1H), 8.03 (d, $J = 8.1$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 2H), 7.67 (d, $J = 7.9$ Hz, 2H), 7.53 (d, $J = 8.5$ Hz, 1H), 7.36 (t, $J = 7.9$ Hz, 2H), 7.31 – 7.21 (m, 1H), 7.19 – 7.05 (m, 4H), 5.17 (s, 2H), 4.87 (s, 2H), 4.02 (t, $J = 6.0$ Hz, 2H), 2.78 (s, 2H). HRMS-ESI (m/z): Calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 411.1816; Found: 411.1824.

N-phenyl-2-((2-(4-methylpiperazin-1-yl)quinazolin-4-yl)oxy)acetamide **II-10a2**, an off-white solid, mp: 216–217°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.01 – 7.93 (m, 2H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.1 Hz, 3H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 5.11 (s, 2H), 3.93 (t, *J* = 5.1 Hz, 4H), 2.48 (t, *J* = 5.0 Hz, 4H), 2.34 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 166.44, 166.22, 157.87, 153.67, 139.13, 134.52, 129.16, 125.17, 123.99, 123.90, 122.42, 119.85, 110.88, 65.69, 54.77, 46.11, 43.95. HRMS-ESI (*m/z*): Calcd. for C₂₁H₂₄N₅O₂ (M+H)⁺: 378.1925; Found: 378.1924.

N-phenyl-2-((2-((tetrahydro-2H-pyran-4-yl)amino)quinazolin-4-yl)oxy)acetamide **II-10a3**, an off-white solid, mp: 116–118°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.1 Hz, 1H), 7.96 (s, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.60 – 7.50 (m, 3H), 7.34 (t, *J* = 7.8 Hz, 3H), 7.15 (t, *J* = 7.6 Hz, 1H), 5.11 (s, 2H), 4.24 (s, 1H), 4.15 (s, 1H), 3.97 (d, *J* = 11.6 Hz, 2H), 3.55 (t, *J* = 11.7 Hz, 2H), 2.04 (t, *J* = 8.6 Hz, 2H), 1.57 (dt, *J* = 12.1, 5.5 Hz, 2H). HRMS-ESI (*m/z*): Calcd. for C₂₁H₂₃N₄O₃ (M+H)⁺: 379.1765; Found: 379.1774.

N-phenyl-2-((2-(diethylamino)quinazolin-4-yl)oxy)acetamide **II-10a4**, an off-white solid, mp: 193–194°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 3H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.16 (q, *J* = 8.0, 7.5 Hz, 2H), 5.11 (s, 2H), 3.69 (q, *J* = 7.2, 6.6 Hz, 4H), 1.21 (t, *J* = 6.9 Hz, 6H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 166.48, 166.03, 157.43, 154.05, 139.39, 134.27, 129.12, 124.99, 123.95, 123.71, 121.66, 119.66, 110.51, 65.34, 41.88, 13.74. HRMS-ESI (*m/z*): Calcd. for C₂₀H₂₃N₄O₂ (M+H)⁺: 351.1816; Found: 351.1827.

N-phenyl-2-((2-(dimethylamino)quinazolin-4-yl)oxy)acetamide **II-10a5**, an off-white solid, mp: 178–180°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 6.4 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.7 Hz,

2H), 7.17 (dt, $J = 18.9, 7.4$ Hz, 2H), 5.13 (s, 2H), 3.24 (s, 6H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 166.38, 165.97, 157.43, 154.05, 139.04, 134.54, 129.24, 124.08, 123.97, 122.10, 119.93, 110.38, 65.56, 37.13. HRMS-ESI (m/z): Calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 323.1503; Found: 323.1506.

N-benzyl-2-((2-(diethylamino)quinazolin-4-yl)oxy)acetamide **II-10a7**, an off-white solid, mp: 174–176°C. ^1H NMR (500 MHz, Chloroform- d) δ 7.83 (d, $J = 8.1$ Hz, 1H), 7.58 (t, $J = 7.9$ Hz, 1H), 7.49 (d, $J = 8.7$ Hz, 1H), 7.31 (q, $J = 10.8, 9.5$ Hz, 3H), 7.08 (t, $J = 7.5$ Hz, 1H), 6.62 (s, 1H), 5.06 (s, 2H), 4.55 (d, $J = 5.9$ Hz, 2H), 3.68 (q, $J = 7.4$ Hz, 4H), 1.21 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 167.70, 166.03, 157.48, 154.10, 139.73, 134.22, 128.66, 127.69, 127.24, 124.96, 124.26, 121.50, 110.63, 65.02, 42.37, 41.81, 13.76. HRMS-ESI (m/z): Calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 365.1972; Found: 365.2000.

N-benzyl-2-((2-(4-methylpiperazin-1-yl)quinazolin-4-yl)oxy)acetamide **II-10a8**, a gray solid, mp: 182–184°C. ^1H NMR (500 MHz, Chloroform- d) δ 7.86 (d, $J = 8.1$ Hz, 1H), 7.62 (t, $J = 7.7$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.35 – 7.28 (m, 2H), 7.30 – 7.21 (m, 2H), 7.15 (t, $J = 7.5$ Hz, 1H), 6.58 (s, 1H), 5.06 (s, 2H), 4.55 (d, $J = 6.0$ Hz, 2H), 3.94 (s, 4H), 2.51 (t, $J = 5.2$ Hz, 4H), 2.37 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 167.64, 166.30, 157.90, 153.61, 139.74, 134.50, 128.70, 127.59, 127.25, 125.11, 124.33, 122.34, 111.03, 65.33, 54.71, 46.02, 43.81, 42.31. HRMS-ESI (m/z): Calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_5\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 392.2081; Found: 392.2098.

N-phenyl-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)thio)acetamide **II-7b1**, a light yellow solid, mp: 227–229°C. ^1H NMR (500 MHz, Chloroform- d) δ 9.10 (s, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.63 (p, $J = 9.0, 8.3$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.32 – 7.23 (m, 2H), 7.16 (t, $J = 7.5$ Hz, 1H), 7.07 (t, $J = 7.5$ Hz, 1H), 4.08 (s, 2H), 3.73 (d, $J = 6.0$ Hz, 4H), 2.00 (d, $J = 6.0$ Hz, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.95, 166.28, 156.17, 151.09, 139.57, 134.51, 129.24, 125.99, 124.18, 123.76, 122.13, 119.48,

117.69, 46.88, 34.65, 25.36. HRMS-ESI (m/z): Calcd. for $C_{20}H_{21}N_4OS(M+H)^+$: 365.1431, Found: 365.1428.

N-benzyl-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)thio)acetamide **II-7b2**, a yellow solid, mp: 190–192°C. 1H NMR (500 MHz, $DMSO-d_6$) δ 8.67 – 8.57 (m, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.66 (t, $J = 7.0$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.31 – 7.09 (m, 5H), 4.29 (d, $J = 6.0$ Hz, 2H), 4.07 (d, $J = 4.0$ Hz, 2H), 3.52 (t, $J = 6.0$ Hz, 4H), 1.87 (s, 4H). ^{13}C NMR (151 MHz, $DMSO-d_6$) δ 169.77, 167.49, 156.15, 139.66, 134.48, 128.63, 127.74, 127.24, 125.97, 124.26, 122.04, 117.80, 46.83, 43.13, 33.32, 25.43. HRMS-ESI (m/z): Calcd. for $C_{21}H_{23}N_4OS (M+H)^+$: 379.1587, Found: 379.1593.

N-(2-ethoxyphenyl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)thio)acetamide **II-7b3**, a yellow solid, mp: 176–178°C. 1H NMR (500 MHz, $DMSO-d_6$) δ 9.27 (s, 1H), 8.08 (d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.74 – 7.62 (m, 1H), 7.47 (d, $J = 8.5$ Hz, 1H), 7.28 – 7.17 (m, 1H), 7.07 – 6.94 (m, 2H), 6.93 – 6.84 (m, 1H), 4.26 (s, 2H), 3.95 (d, $J = 7.5$ Hz, 2H), 3.57 (d, $J = 6.5$ Hz, 5H), 1.87 (s, 5H), 1.12 – 1.03 (m, 3H). ^{13}C NMR (151 MHz, $DMSO-d_6$) δ 169.31, 166.58, 156.12, 151.30, 148.10, 134.76, 127.84, 126.05, 124.53, 124.18, 122.27, 120.81, 120.58, 117.66, 112.36, 64.27, 46.85, 34.09, 25.39, 14.58. HRMS-ESI (m/z): Calcd. for $C_{22}H_{25}N_4O_2S (M+H)^+$: 409.1693, Found: 409.1702.

N-(furan-2-ylmethyl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)thio)acetamide **II-7b4**, a yellow solid, mp: 178–180°C. 1H NMR (500 MHz, $DMSO-d_6$) δ 8.61 (t, $J = 6.0$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.65 (t, $J = 8.0$ Hz, 1H), 7.56 (s, 1H), 7.44 (d, $J = 8.5$ Hz, 1H), 7.17 (t, $J = 7.5$ Hz, 1H), 6.38 (s, 1H), 6.21 (d, $J = 3.5$ Hz, 1H), 4.29 (d, $J = 5.5$ Hz, 2H), 4.04 (s, 2H), 3.53 (d, $J = 6.0$ Hz, 4H), 1.91 (s, 4H). ^{13}C NMR (151 MHz, $DMSO-d_6$) δ 169.80, 167.35, 156.10, 152.42, 151.12, 142.62, 134.46, 125.94, 124.19, 122.04, 117.73, 110.88, 107.52, 46.82, 36.47, 33.30, 25.47. HRMS-ESI (m/z): Calcd. for $C_{19}H_{21}N_4O_2S (M+H)^+$: 369.1380, Found: 369.1382.

N-(naphthalen-2-yl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)thio)acetamide **II-7b5**, an off-white solid, mp: 236–238°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 9.35 (s, 1H), 8.15 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.72 (m, 3H), 7.67 (s, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.20 (s, 1H), 4.15 (s, 2H), 3.76 (s, 4H), 1.98 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.99, 166.57, 156.14, 151.06, 137.15, 134.55, 133.90, 130.23, 128.90, 127.94, 127.74, 126.93, 125.96, 125.10, 124.20, 122.18, 120.22, 117.68, 115.60, 46.88, 34.73, 25.32. HRMS-ESI (*m/z*): Calcd. for C₂₄H₂₃N₄OS (M+H)⁺: 415.1587, Found: 415.1619.

N-(thiazol-2-yl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)thio)acetamide **II-7b7**, a brown solid, mp: 234–236°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 11.02 – 10.71 (m, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 6.0 Hz, 2H), 7.39 (d, *J* = 4.0 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 4.0 Hz, 1H), 4.15 (s, 2H), 3.76 (t, *J* = 6.0 Hz, 4H), 2.01 (d, *J* = 6.0 Hz, 4H). HRMS-ESI (*m/z*): Calcd. for C₁₇H₁₈N₅OS₂ (M+H)⁺: 372.0948, Found: 372.0932.

N-(2-ethoxybenzyl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)thio)acetamide **II-7b8**, a light yellow solid, mp: 169–171°C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.29 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.82 – 6.76 (m, 1H), 4.25 (d, *J* = 6.0 Hz, 2H), 4.06 (s, 2H), 3.90 (q, *J* = 7.0 Hz, 2H), 3.49 (s, 4H), 1.94 – 1.77 (m, 4H), 1.22 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.60, 167.46, 156.43, 156.09, 151.23, 134.50, 128.58, 128.43, 125.98, 124.23, 122.04, 120.28, 117.78, 111.76, 63.60, 46.77, 38.52, 33.23, 25.40, 15.05. HRMS-ESI (*m/z*): Calcd. for C₂₃H₂₇N₄O₂S (M+H)⁺: 423.1849, Found: 423.1866.

N-(3,5-dichlorophenyl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)thio)acetamide **II-7b9**, a pink solid, mp: 240–241°C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.67 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 3H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.29 (s, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 4.23 (s, 2H), 3.52 – 3.43 (m, 4H), 1.82 (s, 4H). ¹³C NMR (151 MHz,

DMSO-*d*₆) δ 169.72, 167.17, 156.15, 151.09, 141.81, 134.62 (d, $J = 7.1$ Hz), 126.02, 124.15, 123.04, 122.21, 117.63, 46.90, 34.64, 25.31. HRMS-ESI (m/z): Calcd. for C₂₀H₁₉Cl₂N₄OS (M+H)⁺: 433.0651, Found: 433.0675.

N-phenyl-2-((2-(diethylamino)quinazolin-4-yl)thio)acetamide **II-10b2**, an off-white solid, mp: 180–181 °C. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.63 (t, $J = 7.5$ Hz, 1H), 7.57 (s, 1H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.08 (t, $J = 7.5$ Hz, 1H), 4.08 (s, 2H), 3.74 (q, $J = 7.0$ Hz, 4H), 1.20 (t, $J = 7.0$ Hz, 6H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.94, 166.01, 156.78, 151.16, 139.66, 134.47, 129.21, 126.09, 124.08, 123.71, 122.16, 119.42, 117.64, 41.74, 34.40, 13.71. HRMS-ESI (m/z): Calcd. for C₂₀H₂₃N₄OS (M+H)⁺: 367.1587, Found: 367.1597.

N-phenyl-2-((2-(4-methylpiperazin-1-yl)quinazolin-4-yl)thio)acetamide **II-10b3**, an off-white solid, mp: 228–230 °C. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.66 (t, $J = 8.0$ Hz, 1H), 7.55 (d, $J = 8.5$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.08 (t, $J = 7.5$ Hz, 1H), 4.04 (s, 2H), 3.98 (t, $J = 5.0$ Hz, 4H), 2.48 (t, $J = 5.0$ Hz, 4H), 2.32 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 170.58, 166.07, 157.26, 150.63, 139.55, 134.73, 129.23, 126.21, 124.13, 123.78, 122.95, 119.41, 118.01, 54.79, 46.04, 43.84, 34.67. HRMS-ESI (m/z): Calcd. for C₂₁H₂₄N₅OS (M+H)⁺: 394.1696, Found: 394.1704.

N-benzyl-2-((2-(diethylamino)quinazolin-4-yl)thio)acetamide **II-10b5**, an off-white solid, mp: 189–191 °C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.78 (d, $J = 8.1$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 7.0$ Hz, 3H), 7.12 (d, $J = 7.0$ Hz, 3H), 6.97 (s, 1H), 4.43 (d, $J = 6.0$ Hz, 2H), 4.00 (s, 2H), 3.67 (q, $J = 7.0$ Hz, 4H), 1.19 (t, $J = 7.0$ Hz, 6H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.79, 167.34, 156.76, 151.26, 139.66, 134.42, 128.67, 127.74, 127.25, 126.09, 124.13, 122.08, 117.73, 43.13, 41.80, 33.16, 13.74. HRMS-ESI (m/z): Calcd. for C₂₁H₂₅N₄OS (M+H)⁺: 381.1744, Found: 381.1739.

N-benzyl-2-((2-(4-methylpiperazin-1-yl)quinazolin-4-yl)thio)acetamide **II-10b6**, an off-white solid, 38% yield. mp: 180–181 °C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.23 – 7.15 (m, 4H), 7.10 – 7.05 (m, 2H), 7.01 (d, *J* = 6.0 Hz, 1H), 4.42 (d, *J* = 6.0 Hz, 2H), 3.97 (s, 2H), 3.92 (s, 4H), 2.44 (s, 4H), 2.32 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 170.44, 167.40, 157.21, 150.71, 139.66, 134.70, 128.69, 127.65, 127.25, 126.20, 124.19, 122.89, 118.09, 54.74, 46.01, 43.77, 43.06, 33.48. HRMS-ESI (*m/z*): Calcd. for C₂₂H₂₆N₅OS (M+H)⁺: 408.1853, Found: 408.1841.

N-(2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)ethyl) cyclopropanecarboxamide **II-14a**, an off-white solid, mp: 183–185 °C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.32 (s, 1H), 4.60 (t, *J* = 5.0 Hz, 2H), 3.78 (q, *J* = 5.3 Hz, 2H), 3.64 (d, *J* = 6.2 Hz, 4H), 1.99 (d, *J* = 6.1 Hz, 4H), 1.38 (dt, *J* = 8.0, 3.7 Hz, 1H), 0.99 (p, *J* = 4.1 Hz, 2H), 0.74 (dq, *J* = 7.2, 4.0 Hz, 2H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 173.37, 166.41, 157.17, 153.88, 134.09, 124.88, 124.17, 121.37, 110.90, 65.57, 46.85, 38.37, 25.44, 14.04, 6.71. HRMS-ESI (*m/z*): Calcd. for C₁₈H₂₂N₄O₂Na (M+Na)⁺: 349.1641; Found: 349.1657.

N-(2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)ethyl)-4-methoxy benzamide **II-14b**, an off-white solid, mp: 159–160 °C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 4.5 Hz, 2H), 7.10 (dt, *J* = 8.1, 3.9 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 3H), 4.74 (t, *J* = 5.1 Hz, 2H), 3.94 (q, *J* = 5.3 Hz, 2H), 3.82 (s, 3H), 3.62 (t, *J* = 6.6 Hz, 4H), 1.94 (d, *J* = 6.1 Hz, 4H). HRMS-ESI (*m/z*): Calcd. for C₂₂H₂₄N₄O₃Na (M+Na)⁺: 415.1746; Found: 415.1743.

N-(2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)ethyl)-4-(trifluoromethyl)benzamide **II-14c**, an off-white solid, mp: 202–204 °C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.89

(d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 7.9$ Hz, 2H), 7.66 (d, $J = 8.0$ Hz, 2H), 7.59 (t, $J = 7.7$ Hz, 1H), 7.53 (d, $J = 8.6$ Hz, 1H), 7.14 – 7.06 (m, 2H), 4.77 (t, $J = 5.0$ Hz, 2H), 3.97 (q, $J = 5.2$ Hz, 2H), 3.57 (s, 4H), 1.92 (d, $J = 6.0$ Hz, 4H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 166.46, 165.95, 157.14, 153.89, 138.64, 134.11, 128.58, 125.81, 125.79, 124.89, 124.11, 121.43, 110.92, 65.04, 46.82, 39.19, 25.42. HRMS-ESI (m/z): Calcd. for $\text{C}_{22}\text{H}_{22}\text{F}_3\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 431.1690; Found: 431.1688.

N-(2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)ethyl)cyclohexanecarboxamide **II-14d**, an off-white solid, mp: 192–194 °C. ^1H NMR (500 MHz, Chloroform- d) δ 7.88 (d, $J = 8.0$ Hz, 1H), 7.58 (t, $J = 7.7$ Hz, 1H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 5.99 (s, 1H), 4.61 (t, $J = 5.0$ Hz, 2H), 3.75 (q, $J = 5.3$ Hz, 2H), 3.66 (d, $J = 6.2$ Hz, 4H), 2.08 (td, $J = 11.6, 5.8$ Hz, 1H), 1.99 (d, $J = 6.1$ Hz, 4H), 1.83 (d, $J = 13.0$ Hz, 2H), 1.76 (d, $J = 11.0$ Hz, 2H), 1.65 (d, $J = 9.8$ Hz, 1H), 1.42 (q, $J = 12.4$ Hz, 2H), 1.23 (t, $J = 12.1$ Hz, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 175.94, 166.44, 157.16, 153.86, 134.09, 124.86, 124.16, 121.36, 110.91, 65.37, 46.85, 44.39, 38.03, 29.65, 25.93, 25.72, 25.46. HRMS-ESI (m/z): Calcd. for $\text{C}_{21}\text{H}_{28}\text{N}_4\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 391.2110; Found: 391.2108.

N-(2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)ethyl)thiophene-2-carboxamide **II-14e**, an off-white solid, mp: 227–229 °C. ^1H NMR (500 MHz, Chloroform- d) δ 7.88 (d, $J = 8.0$ Hz, 1H), 7.57 (t, $J = 7.7$ Hz, 1H), 7.52 (s, 1H), 7.50 (d, $J = 4.4$ Hz, 1H), 7.45 (d, $J = 4.9$ Hz, 1H), 7.08 (t, $J = 7.5$ Hz, 1H), 7.03 (t, $J = 4.3$ Hz, 1H), 6.90 (s, 1H), 4.72 (t, $J = 5.1$ Hz, 2H), 3.92 (q, $J = 5.3$ Hz, 2H), 3.60 (s, 4H), 1.95 (d, $J = 6.1$ Hz, 4H), 1.85 (s, 2H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 166.41, 161.97, 157.14, 153.89, 140.29, 134.07, 131.20, 128.62, 128.30, 124.88, 124.10, 121.38, 110.90, 65.18, 46.83, 38.90, 25.43. HRMS-ESI (m/z): Calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_4\text{O}_2\text{S}$ ($\text{M}+\text{H}$) $^+$: 391.1205; Found: 391.1192.

2-(4-methoxyphenoxy)-N-(2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)ethyl)acetamide II-14f, an off-white solid, mp: 161–162 °C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.1 Hz, 2H), 7.14 (s, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.79 – 6.70 (m, 4H), 4.68 (t, *J* = 5.2 Hz, 2H), 4.45 (s, 2H), 3.84 (q, *J* = 5.4 Hz, 2H), 3.71 (s, 3H), 3.66 (s, 4H), 1.97 (d, *J* = 6.1 Hz, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.83, 166.41, 157.14, 154.28, 153.88, 152.21, 134.11, 124.86, 124.13, 121.40, 116.20, 114.93, 110.89, 68.38, 65.13, 55.75, 46.85, 38.07, 25.44. HRMS-ESI (*m/z*): Calcd. for C₂₃H₂₆N₄O₄Na (M+Na)⁺: 445.1852; Found: 445.1860.

2-(naphthalen-2-yl)-N-(2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)ethyl)acetamide II-14g, an off-white solid, mp: 173–175 °C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 1H), 7.33 – 7.21 (m, 6H), 6.95 (t, *J* = 7.5 Hz, 1H), 4.40 (t, *J* = 5.5 Hz, 2H), 3.99 (s, 2H), 3.62 – 3.49 (m, 6H), 1.94 (d, *J* = 6.0 Hz, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 170.89, 166.38, 157.13, 153.88, 134.10, 133.78, 133.17, 132.40, 128.80, 128.13, 127.50, 126.28, 126.01, 125.88, 124.86, 124.51, 124.17, 121.35, 110.90, 65.19, 46.83, 40.34, 38.47, 25.42. HRMS-ESI (*m/z*): Calcd. for C₂₆H₂₆N₄O₂Na (M+Na)⁺: 449.1954; Found: 449.1954.

N-(2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)ethyl)-4-sulfamoylbenzamide II-14i, an off-white solid, mp: 234–235 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.91 (s, 1H), 7.97 (d, *J* = 7.9 Hz, 2H), 7.92 – 7.86 (m, 3H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 2H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 2H), 3.82 – 3.74 (m, 2H), 3.54 (s, 4H), 1.90 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 166.45, 166.13, 157.15, 153.89, 146.84, 137.73, 134.11, 128.32, 126.08, 124.88, 124.11, 121.43, 110.92, 65.05, 46.84, 39.17, 25.42. HRMS-ESI (*m/z*): Calcd. for C₂₁H₂₄N₅O₄S (M+H)⁺: 442.1544; Found: 442.1561.

N-(2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)ethyl)benzamide **II-14k**, an off-white solid, mp: 161–162°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.94 (s, 1H), 4.76 (t, *J* = 5.1 Hz, 2H), 3.96 (q, *J* = 5.3 Hz, 2H), 3.61 (s, 4H), 1.94 (d, *J* = 5.8 Hz, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 167.11, 166.47, 157.16, 153.88, 134.93, 134.06, 131.63, 128.72, 127.65, 124.87, 124.12, 121.39, 110.94, 65.19, 46.83, 39.04, 25.42. HRMS-ESI (*m/z*): Calcd. for C₂₁H₂₂N₄O₂Na (M+Na)⁺: 385.1641; Found: 385.1652.

4-nitro-*N*-(2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)oxy)ethyl)benzamide **II-14l**, a yellow solid, mp: 193–195°C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.07 (s, 1H), 8.30 (d, *J* = 8.0 Hz, 2H), 8.05 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 4.65 (t, *J* = 5.0 Hz, 2H), 3.86 – 3.75 (m, 2H), 3.54 (s, 4H), 1.90 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 166.43, 165.50, 157.13, 153.88, 149.50, 140.48, 134.11, 129.17, 124.88, 124.09, 124.00, 121.43, 110.90, 65.00, 46.83, 39.25, 25.42. HRMS-ESI (*m/z*): Calcd. for C₂₁H₂₂N₅O₄ (M+H)⁺: 408.1667; Found: 408.1687.

N-(2-((2-(diethylamino)quinazolin-4-yl)oxy)ethyl)benzamide **II-17b**, an off-white solid, mp: 124–125°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.61 – 7.53 (m, 1H), 7.52 – 7.45 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.13 – 7.04 (m, 1H), 6.66 (s, 1H), 4.72 (t, *J* = 5.1 Hz, 2H), 3.98 (q, *J* = 5.3 Hz, 2H), 3.69 (q, *J* = 7.1 Hz, 4H), 1.22 (t, *J* = 6.9 Hz, 6H). HRMS-ESI (*m/z*): Calcd. for C₂₁H₂₄N₄O₂Na (M+Na)⁺: 387.1797; Found: 387.1812.

N-(2-((2-(4-methylpiperazin-1-yl)quinazolin-4-yl)oxy)ethyl)benzamide **II-17c**, a brown solid, mp: 171–173°C. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.45 – 7.38 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.69 (s, 1H), 4.74 (t, *J* = 5.1 Hz, 2H), 3.97 (q, *J* = 5.4 Hz, 2H), 3.95 – 3.89 (m, 4H), 2.51 – 2.44 (m, 4H), 2.34 (s, 3H). ¹³C NMR (151

MHz, DMSO-*d*₆) δ 167.11, 166.88, 158.20, 153.46, 134.90, 134.30, 131.65, 128.73, 127.66, 125.11, 124.10, 122.22, 111.23, 65.34, 54.87, 46.17, 43.94, 39.00.

HRMS-ESI (*m/z*): Calcd. for C₂₂H₂₆N₅O₂ (M+H)⁺: 392.2081; Found: 392.2110.

N-phenyl-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)acetamide **II-23a**, an off-white solid, mp: 250–252 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.24 – 10.20 (m, 1H), 8.42 (q, *J* = 5.5 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.32 – 7.23 (m, 3H), 7.03 (q, *J* = 8.0 Hz, 2H), 4.19 (d, *J* = 5.5 Hz, 2H), 3.49 – 3.40 (m, 4H), 1.79 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.05, 160.18, 157.79, 152.63, 139.69, 132.71, 129.09, 125.21, 123.52, 123.47, 120.19, 119.65, 110.85, 46.51, 45.33, 25.43. HRMS-ESI (*m/z*): Calcd. for C₂₀H₂₂N₅O (M+H)⁺: 348.1819, Found: 348.1846.

N-benzyl-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)acetamide **II-23b**, a light yellow solid, mp: 161–162 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.44 (t, *J* = 6.0 Hz, 1H), 8.37 – 8.29 (m, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.33 – 7.16 (m, 5H), 7.03 (t, *J* = 7.5 Hz, 1H), 4.29 (d, *J* = 6.0 Hz, 2H), 4.07 (d, *J* = 6.0 Hz, 2H), 3.47 (t, *J* = 6.0 Hz, 4H), 1.85 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 170.11, 160.25, 157.84, 152.66, 140.13, 132.65, 128.50, 127.54, 127.05, 125.18, 123.62, 120.07, 111.00, 46.53, 44.73, 42.42, 25.53. HRMS-ESI (*m/z*): Calcd. for C₂₁H₂₄N₅O (M+H)⁺: 362.1976, Found: 362.1997.

N-(2-ethoxyphenyl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)acetamide **II-23c**, a white solid, mp: 147–148 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.03 (s, 1H), 8.59 (t, *J* = 6.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.02 – 6.96 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 4.25 (d, *J* = 6.0 Hz, 2H), 3.88 (q, *J* = 7.0 Hz, 2H), 3.54 – 3.40 (m, 4H), 1.83 (d, *J* = 6.0 Hz, 4H), 0.95 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.48, 160.05, 150.35, 148.01 (d, *J* = 18.3 Hz), 140.72, 133.53,

133.14, 127.75, 124.34, 124.17, 123.48, 120.34, 112.34, 110.41, 64.29, 46.80, 45.96, 25.36, 17.55, 14.48. HRMS-ESI (m/z): Calcd. for $C_{22}H_{26}N_5O_2$ (M+H)⁺: 392.2081, Found: 392.2104.

N-(furan-2-ylmethyl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)acetamide **II-23d**, a light yellow solid, mp: 199–201 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.69 (s, 1H), 8.46 (t, $J = 6.0$ Hz, 1H), 8.06 (d, $J = 8.0$ Hz, 1H), 7.55 (d, $J = 7.0$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.12 (t, $J = 8.0$ Hz, 1H), 6.37 (s, 1H), 6.19 (d, $J = 3.0$ Hz, 1H), 4.27 (d, $J = 6.0$ Hz, 2H), 4.05 (d, $J = 6.0$ Hz, 2H), 3.47 (s, 4H), 1.88 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.44, 160.05, 152.85, 142.46, 133.40, 123.86, 123.13, 121.36, 110.82, 110.65, 107.26, 46.89, 44.64, 35.92, 25.42. HRMS-ESI (m/z): Calcd. for $C_{19}H_{22}N_5O_2$ (M+H)⁺: 352.1768, Found: 352.1795.

N-(naphthalen-2-yl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)acetamide **II-23e**, a white solid, mp: 169–171 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.32 (s, 1H), 8.40 (t, $J = 6.0$ Hz, 1H), 8.28 (d, $J = 2.0$ Hz, 1H), 8.03 (d, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 9.0$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.63 (dd, $J = 9.0, 2.1$ Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 1H), 7.45 (t, $J = 7.5$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.06 (t, $J = 7.5$ Hz, 1H), 4.25 (d, $J = 5.5$ Hz, 2H), 3.50 – 3.40 (m, 4H), 1.76 (s, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.35, 160.23, 157.78, 152.66, 137.23, 133.92, 132.75, 130.16, 128.75, 127.92, 127.67, 126.85, 125.27, 124.96, 123.44, 120.52, 120.25, 115.67, 110.85, 46.51, 45.48, 25.40. HRMS-ESI (m/z): Calcd. for $C_{24}H_{24}N_5O$ (M+H)⁺: 398.1976, Found: 398.2012.

N-cyclopropyl-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)acetamide **II-23f**, an off-white solid, mp: 210–212 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.14 (t, $J = 6.0$ Hz, 1H), 8.00 (d, $J = 4.0$ Hz, 1H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.51 – 7.42 (m, 1H), 7.26 (d, $J = 8.5$ Hz, 1H), 7.02 (t, $J = 7.5$ Hz, 1H), 3.93 (d, $J = 6.0$ Hz, 2H), 3.56 – 3.44 (m, 4H), 2.63 (m, 1H), 1.88 (d, $J = 6.0$ Hz, 4H), 0.60 (dt, $J = 7.0, 3.4$ Hz, 2H), 0.45 – 0.31 (m,

2H). ^{13}C NMR (151 MHz, $\text{DMSO-}d_6$) δ 170.94, 160.13, 157.61, 152.23, 132.71, 124.98, 123.47, 120.25, 110.87, 46.57, 44.45, 25.48, 22.73, 6.03. HRMS-ESI (m/z): Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_5\text{O}$ ($\text{M}+\text{H}$) $^+$: 312.1819, Found: 312.1828.

N-(thiazol-2-yl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)acetamide **II-23g**, a light yellow solid, mp: 155–157°C. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 12.31 (s, 1H), 8.51 (q, $J = 6.0$ Hz, 1H), 8.03 (dd, $J = 8.0, 3.5$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 1H), 7.46 (d, $J = 3.5$ Hz, 1H), 7.27 (d, $J = 8.0$ Hz, 1H), 7.17 (d, $J = 3.5$ Hz, 1H), 7.04 (t, $J = 7.5$ Hz, 1H), 4.28 (d, $J = 5.5$ Hz, 2H), 3.43 – 3.37 (m, 4H), 1.77 (d, $J = 6.5$ Hz, 4H). ^{13}C NMR (151 MHz, $\text{DMSO-}d_6$) δ 169.30, 160.08, 158.58, 157.63, 152.61, 138.09, 132.81, 125.21, 123.55, 120.26, 113.69, 110.75, 46.44, 44.52, 25.40. HRMS-ESI (m/z): Calcd. for $\text{C}_{17}\text{H}_{19}\text{N}_6\text{OS}$ ($\text{M}+\text{H}$) $^+$: 355.1336, Found: 355.1360.

N-(2-ethoxybenzyl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)acetamide **II-23h**, an off-white solid, mp: 170–172°C. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 8.32 (t, $J = 6.0$ Hz, 1H), 8.11 (t, $J = 6.0$ Hz, 1H), 8.03 – 7.93 (m, 1H), 7.52 – 7.44 (m, 1H), 7.28 (d, $J = 8.0$ Hz, 1H), 7.20 – 7.15 (m, 1H), 7.14 – 7.11 (m, 1H), 7.03 (t, $J = 7.5$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.78 (t, $J = 7.5$ Hz, 1H), 4.24 (d, $J = 6.0$ Hz, 2H), 4.07 (d, $J = 6.0$ Hz, 2H), 3.94 (q, $J = 7.0$ Hz, 2H), 3.45 (s, 4H), 1.84 (s, 4H), 1.23 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (151 MHz, $\text{DMSO-}d_6$) δ 170.09, 160.22, 157.79, 156.32, 152.70, 132.71, 128.29, 128.01, 127.47, 125.22, 123.53, 120.18, 120.11, 111.61, 110.93, 63.58, 46.49, 44.86, 37.78, 25.50, 15.05. HRMS-ESI (m/z): Calcd. for $\text{C}_{23}\text{H}_{28}\text{N}_5\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 406.2238, Found: 406.2249.

N-(3,5-dichlorophenyl)-2-((2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)acetamide **II-23i**, an off-white solid, mp: 185–187°C. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 10.44 (s, 1H), 8.44 (t, $J = 5.5$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 2.0$ Hz, 2H), 7.50 (t, $J = 8.0$ Hz, 1H), 7.36 – 7.22 (m, 2H), 7.06 (t, $J = 7.5$ Hz, 1H), 4.16 (d, $J = 5.5$ Hz, 2H), 3.41 (t, $J = 6.0$ Hz, 4H), 1.79 (s, 4H). ^{13}C NMR (151 MHz, $\text{DMSO-}d_6$) δ 169.90,

160.13, 157.52, 152.37, 141.92, 134.53, 132.87, 125.12, 123.44, 122.78, 120.40, 117.72, 110.73, 46.55, 45.59, 25.38. HRMS-ESI (m/z): Calcd. for $C_{20}H_{19}Cl_2N_5O$ ($M+H$)⁺: 416.1040, Found: 416.1063.

N-phenyl-2-((2-(3,4-dihydroisoquinolin-2(1H)-yl)quinazolin-4-yl)amino)acetamide

II-23j, an off-white solid, mp: 151–153 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.26 (s, 1H), 8.53 (t, J = 5.4 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 8.0 Hz, 1H), 7.37 – 7.26 (m, 3H), 7.15 – 6.97 (m, 6H), 4.84 (s, 2H), 4.21 (d, J = 5.5 Hz, 2H), 3.96 (t, J = 6.0 Hz, 2H), 2.69 (s, 2H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.97, 160.46, 158.65, 152.24, 139.74, 135.43, 135.17, 132.96, 129.17, 128.88, 126.78, 126.39, 126.16, 125.48, 123.55, 123.43, 121.00, 119.59, 111.06, 46.24, 45.57, 41.51, 28.60. HRMS-ESI (m/z): Calcd. for $C_{25}H_{24}N_5O$ ($M+H$)⁺: 410.1976, Found: 410.1984.

N-phenyl-2-((2-morpholinoquinazolin-4-yl)amino)acetamide **II-23k**, a light yellow

solid, mp: 228–230 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.24 (t, J = 7.7 Hz, 1H), 8.56 (q, J = 5.5 Hz, 1H), 8.07 (dd, J = 8.0, 3.2 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.53 (t, J = 8.0 Hz, 1H), 7.29 (t, J = 7.5 Hz, 3H), 7.12 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 4.16 (d, J = 5.5 Hz, 2H), 3.66 (t, J = 5.0 Hz, 4H), 3.47 (t, J = 5.0 Hz, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.90, 160.46, 158.78, 152.09, 139.59, 132.98, 129.13, 125.54, 123.56, 123.49, 121.23, 119.61, 111.22, 66.57, 45.50, 44.55. HRMS-ESI (m/z): Calcd. for $C_{20}H_{22}N_5O_2$ ($M+H$)⁺: 364.1768, Found: 364.1779.

N-phenyl-2-((2-(diethylamino)quinazolin-4-yl)amino)acetamide **II-23l**, a light yellow

solid, mp: 142–144 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.07 (s, 1H), 8.32 (t, J = 6.0 Hz, 1H), 8.06 – 7.92 (m, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.53 – 7.44 (m, 1H), 7.27 (q, J = 8.0 Hz, 3H), 7.03 (dt, J = 12.5, 8.0 Hz, 2H), 4.16 (d, J = 6.0 Hz, 2H), 3.54 (q, J = 7.0 Hz, 4H), 1.00 (s, 6H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.91, 160.33, 158.20, 152.67, 139.75, 132.69, 129.09, 125.33, 123.45, 123.32, 120.21, 119.54,

110.72, 45.25, 41.32, 13.99. HRMS-ESI (m/z): Calcd. for $C_{20}H_{24}N_5O$ ($M+H$)⁺: 350.1976, Found: 350.1999.

N-phenyl-2-((2-(4-methylpiperazin-1-yl)quinazolin-4-yl)amino)acetamide **II-23m**, an off-white solid, mp: 189–191 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.21 (d, J = 6.0 Hz, 1H), 8.50 (q, J = 5.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.52 (t, J = 8.0 Hz, 1H), 7.33 – 7.23 (m, 3H), 7.09 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 4.16 (d, J = 5.5 Hz, 2H), 3.68 (t, J = 5.0 Hz, 4H), 2.17 (t, J = 5.0 Hz, 4H), 2.09 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.87, 160.43, 158.71, 152.17, 139.57, 132.94, 129.11, 125.48, 123.57, 123.39, 121.06, 119.65, 111.07, 54.94, 46.15, 45.48, 43.72. HRMS-ESI (m/z): Calcd. for $C_{21}H_{25}N_6O$ ($M+H$)⁺: 377.2085, Found: 377.2090.

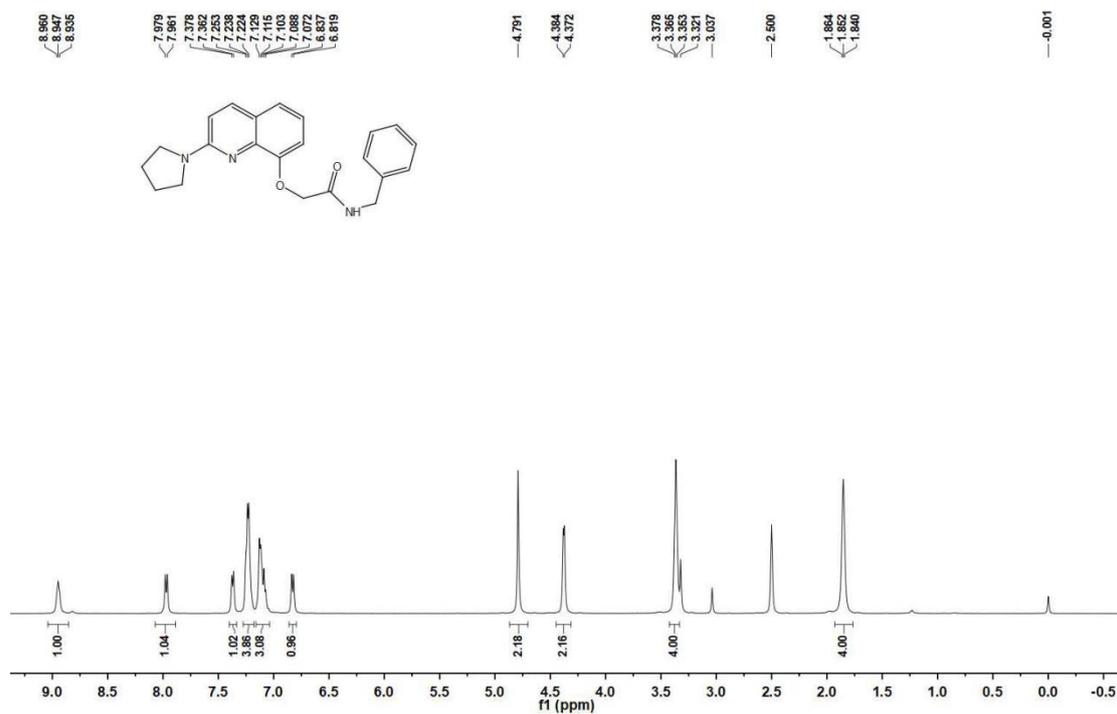
N-benzyl-2-((2-(3,4-dihydroisoquinolin-2(1H)-yl)quinazolin-4-yl)amino)acetamide **II-23n**, a yellow solid, mp: 102–104 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.52 (t, J = 6.0 Hz, 1H), 8.42 (t, J = 6.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.57 – 7.50 (m, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.27 – 7.13 (m, 9H), 7.09 (t, J = 7.5 Hz, 1H), 4.90 (s, 2H), 4.31 (d, J = 6.0 Hz, 2H), 4.11 (d, J = 6.0 Hz, 2H), 4.00 (t, J = 6.0 Hz, 2H), 2.81 (t, J = 6.0 Hz, 2H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 170.07, 160.51, 158.64, 152.21, 140.02, 135.51, 135.22, 132.93, 129.04, 128.57, 127.53, 127.07, 126.87, 126.49, 126.32, 125.39, 123.57, 120.90, 111.20, 46.25, 44.86, 42.52, 41.52, 28.74. HRMS-ESI (m/z): Calcd. for $C_{26}H_{26}N_5O$ ($M+H$)⁺: 424.2132, Found: 424.2129.

N-benzyl-2-((2-morpholinoquinazolin-4-yl)amino)acetamide **II-23o**, a pink solid, mp: 224–225 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.47 (q, J = 6.0 Hz, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.58 – 7.45 (m, 1H), 7.33 – 7.29 (m, 1H), 7.27 (d, J = 7.0 Hz, 2H), 7.24 – 7.19 (m, 3H), 7.11 (t, J = 7.5 Hz, 1H), 4.29 (d, J = 6.0 Hz, 2H), 4.06 (d, J = 6.0 Hz, 2H), 3.69 (t, J = 5.0 Hz, 4H), 3.60 (t, J = 5.0 Hz, 4H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.95, 160.54, 158.89, 152.08, 140.08, 132.92, 128.61, 127.49, 127.09, 125.52,

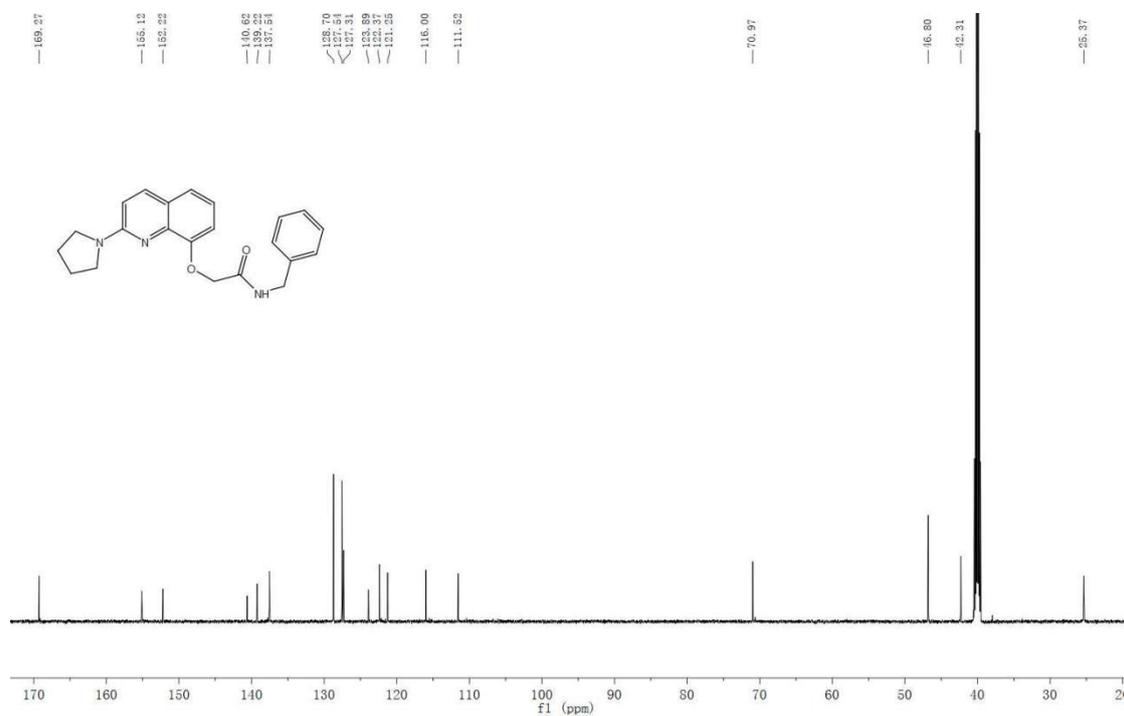
123.60, 121.12, 111.38, 66.65, 44.82, 44.58, 42.42. HRMS-ESI (m/z): Calcd. for $C_{21}H_{24}N_5O_2$ ($M+H$)⁺: 378.1925, Found: 378.1939.

N-benzyl-2-((2-(diethylamino)quinazolin-4-yl)amino)acetamide **II-23p**, an off-white solid, mp: 222–224 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.13 (s, 1H), 9.90 (s, 1H), 8.74 – 8.66 (m, 1H), 8.38 – 8.30 (m, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.29 – 7.24 (m, 3H), 4.32 (d, J = 5.5 Hz, 2H), 4.21 (d, J = 5.5 Hz, 2H), 3.70 (s, 4H), 1.18 (s, 6H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 168.34, 159.97, 139.77, 135.10, 128.66, 128.62, 127.75, 127.68, 127.26, 127.23, 124.56, 110.09, 44.89, 42.66, 38.16, 13.35. HRMS-ESI (m/z): Calcd. for $C_{21}H_{26}N_5O$ ($M+H$)⁺: 364.2132, Found: 364.2162.

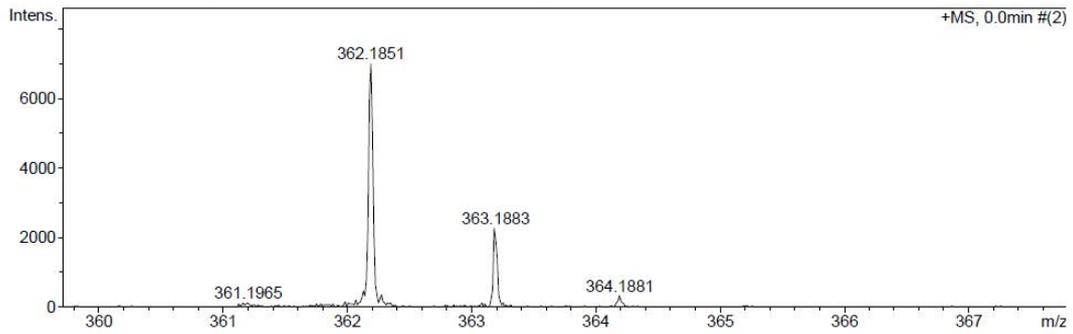
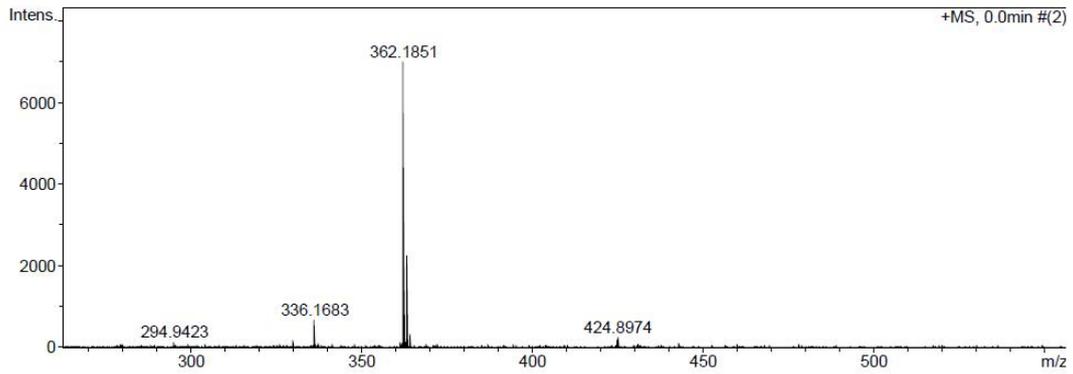
N-benzyl-2-((2-(4-methylpiperazin-1-yl)quinazolin-4-yl)amino)acetamide **II-23q**, light yellow solid, mp: 129–131 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.46 (t, J = 6.0 Hz, 1H), 8.38 (t, J = 6.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.27 (dd, J = 11.0, 8.0 Hz, 3H), 7.21 (d, J = 8.0 Hz, 3H), 7.08 (t, J = 7.5 Hz, 1H), 4.29 (d, J = 6.0 Hz, 2H), 4.05 (d, J = 6.0 Hz, 2H), 3.73 (t, J = 5.0 Hz, 4H), 2.31 (t, J = 5.0 Hz, 4H), 2.20 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 170.03, 160.48, 158.82, 152.21, 140.04, 132.88, 128.62, 127.46, 127.09, 125.44, 123.53, 120.91, 111.20, 55.11, 46.36, 44.79, 43.81, 42.43. HRMS-ESI (m/z): Calcd. for $C_{22}H_{27}N_6O$ ($M+H$)⁺: 391.2241, Found: 391.2229.



The ¹H NMR spectra of compound I-6a



The ¹³C NMR spectra of compound I-6a

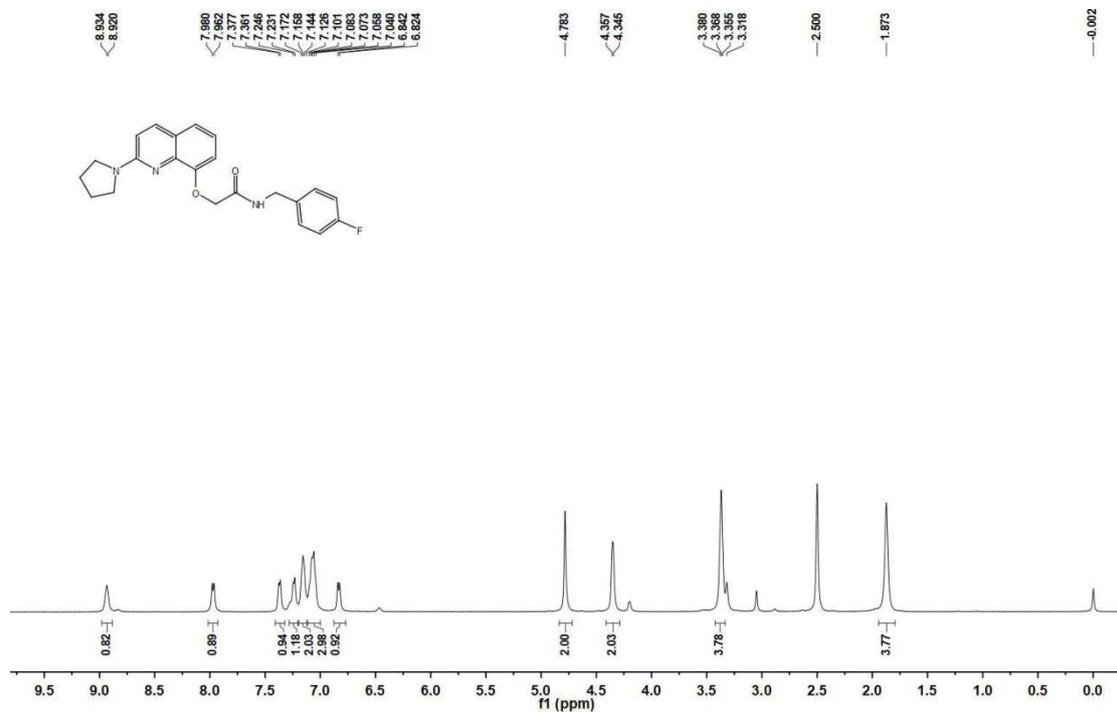


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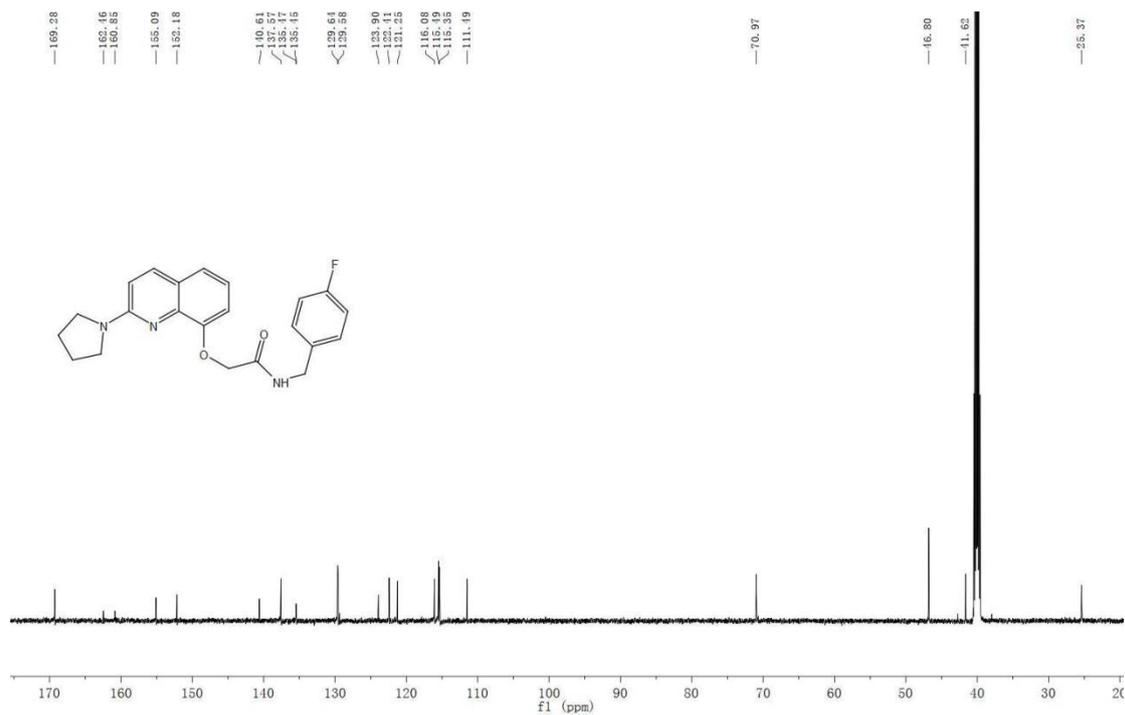
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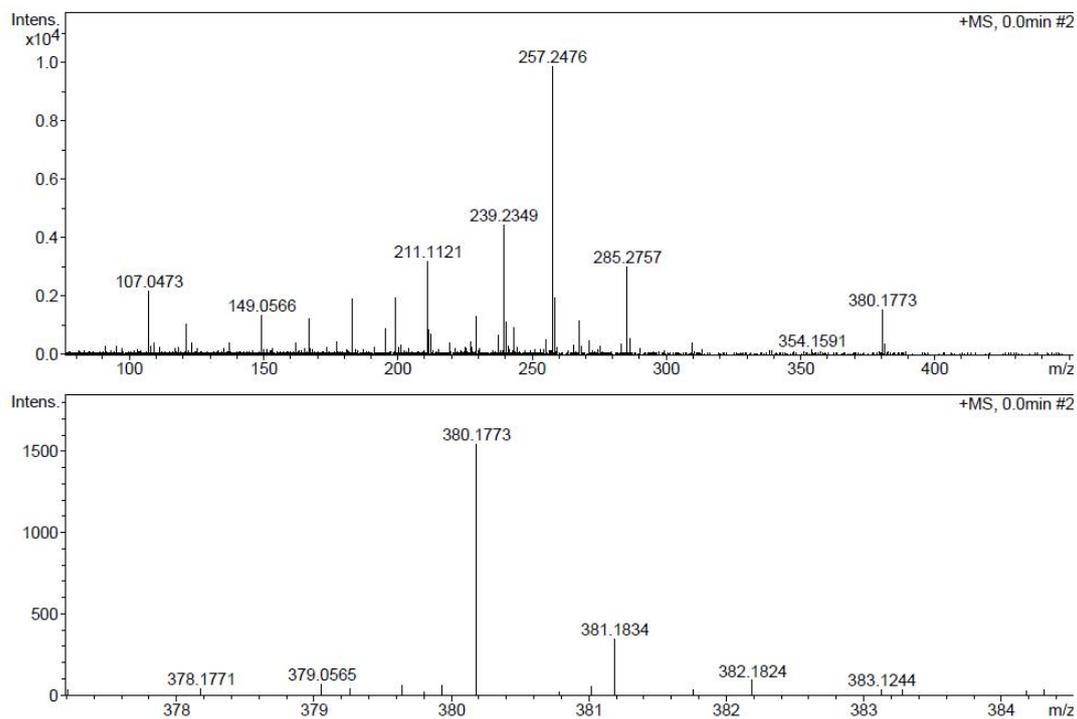
The HR-MS spectra of compound I-6a



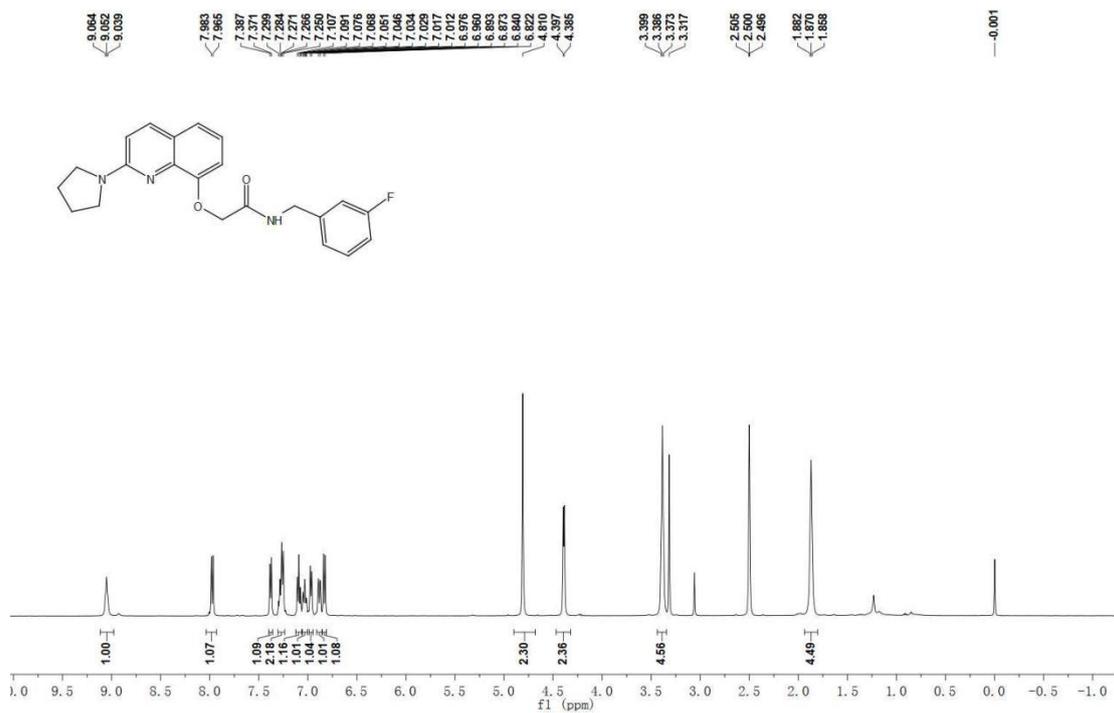
The ¹H NMR spectra of compound I-6b



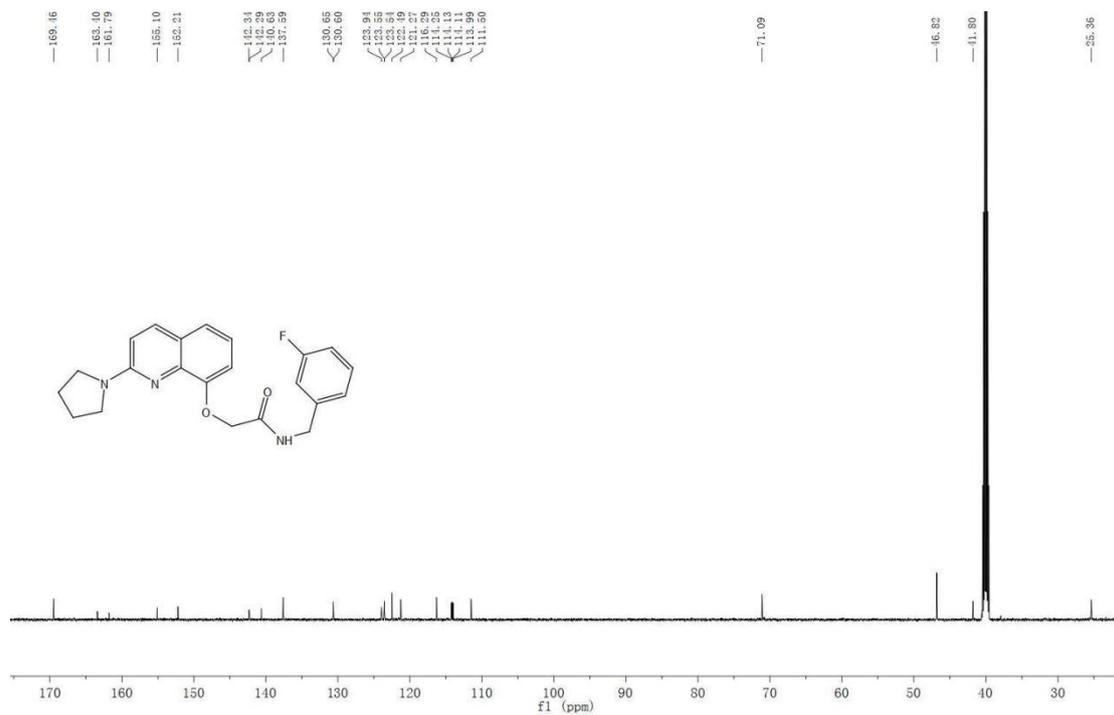
The ¹³C NMR spectra of compound I-6b



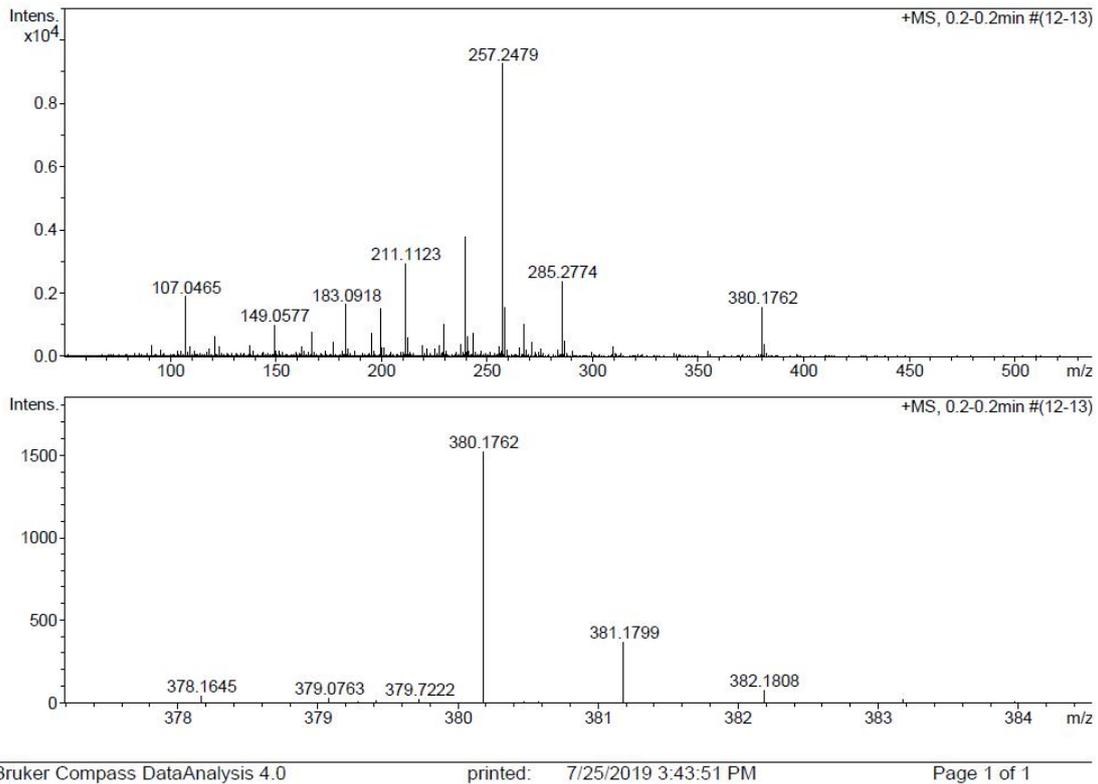
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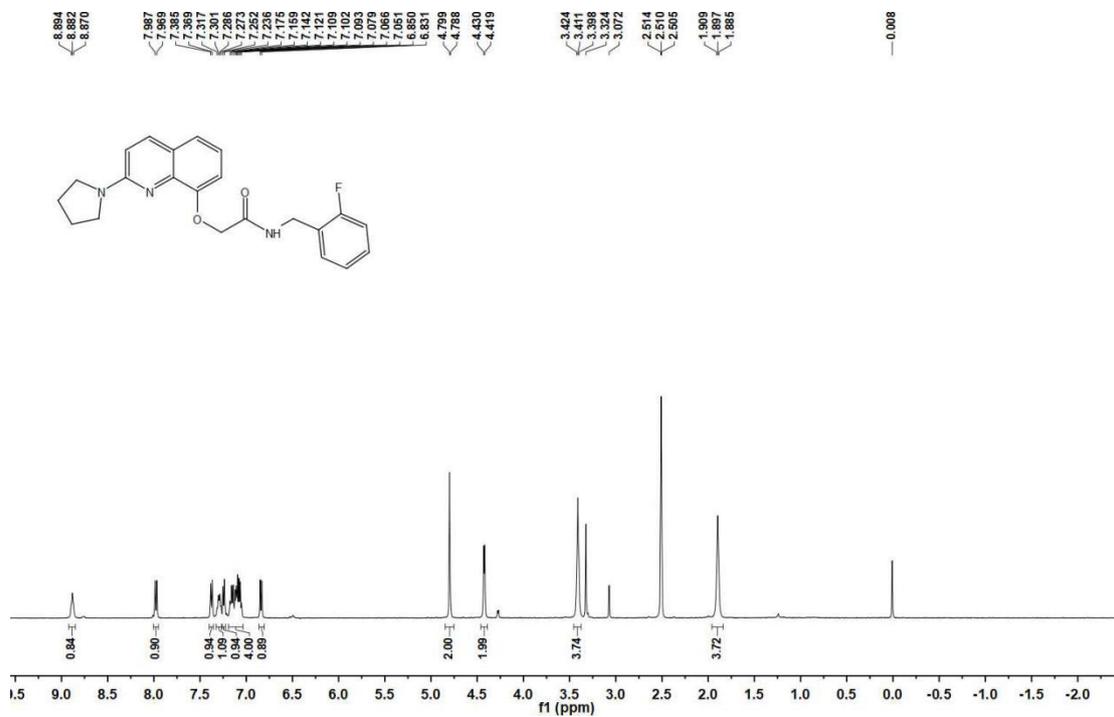
The ¹H NMR spectra of compound I-6c



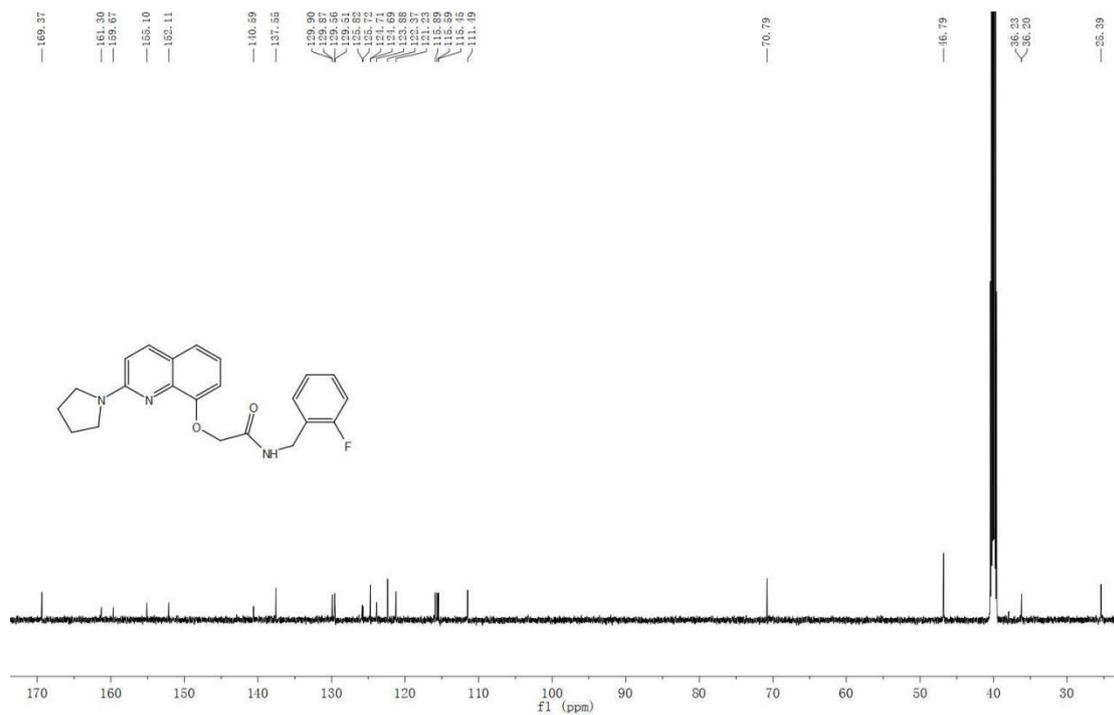
The ¹³C NMR spectra of compound I-6c



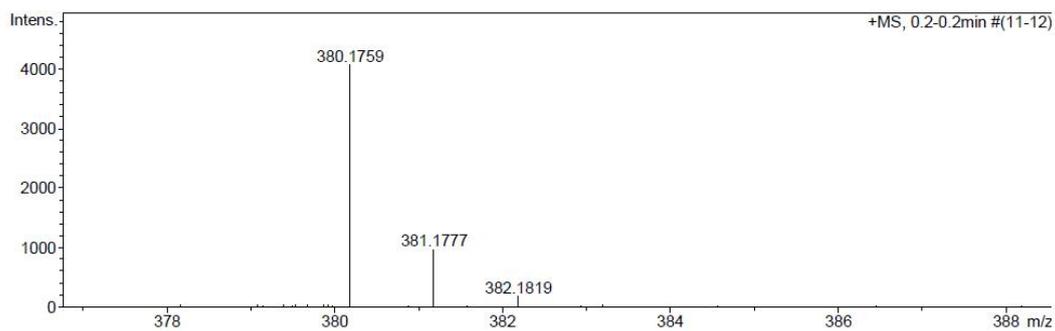
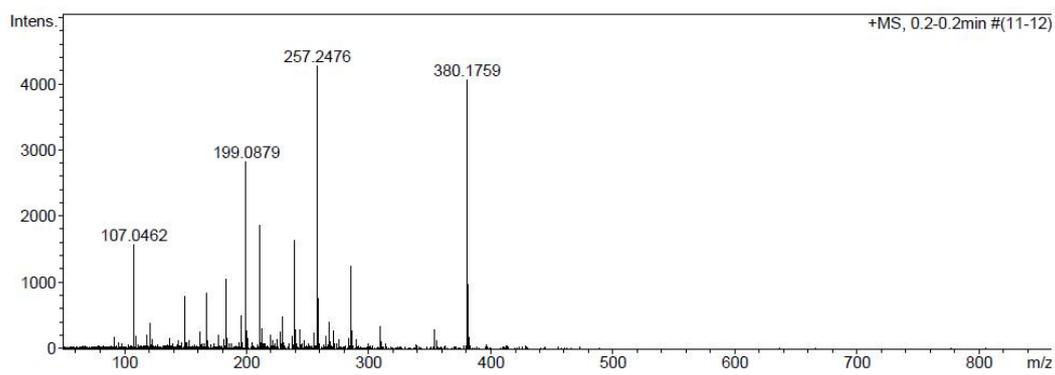
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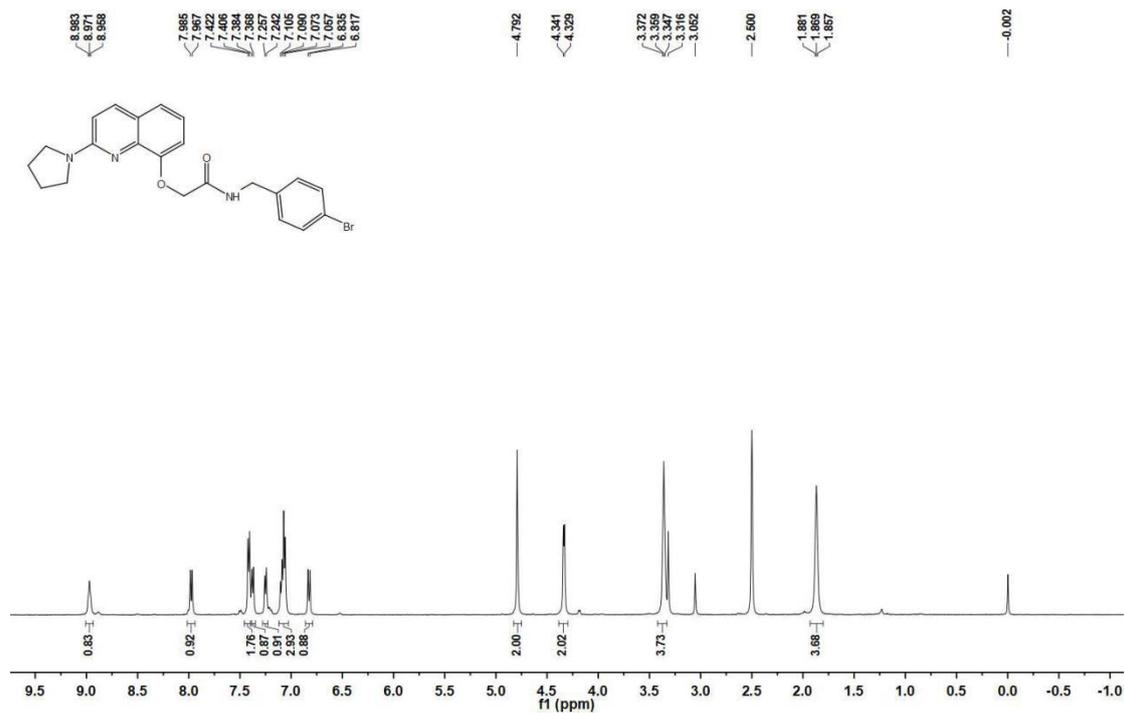
The ¹H NMR spectra of compound I-6d



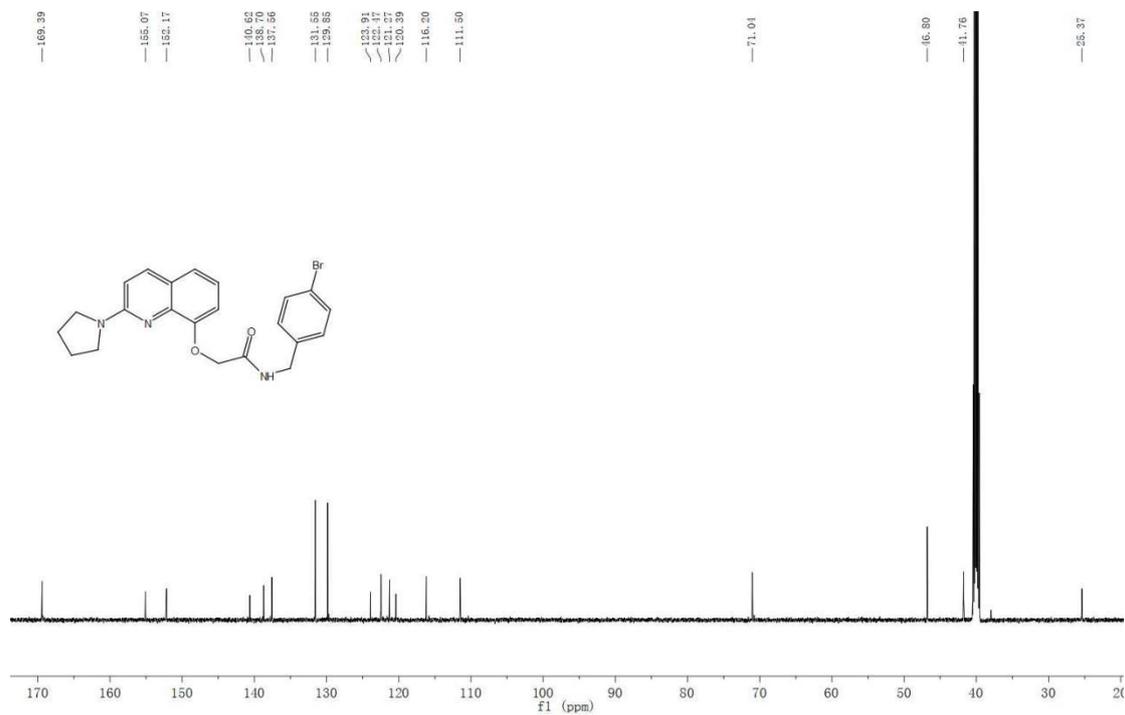
The ¹³C NMR spectra of compound I-6d



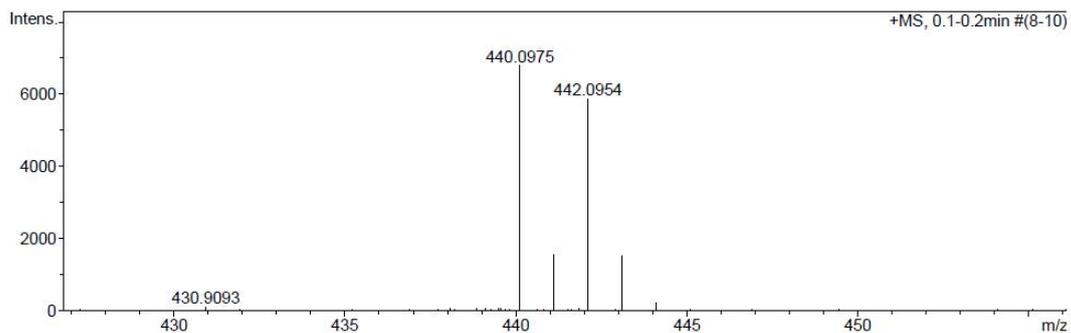
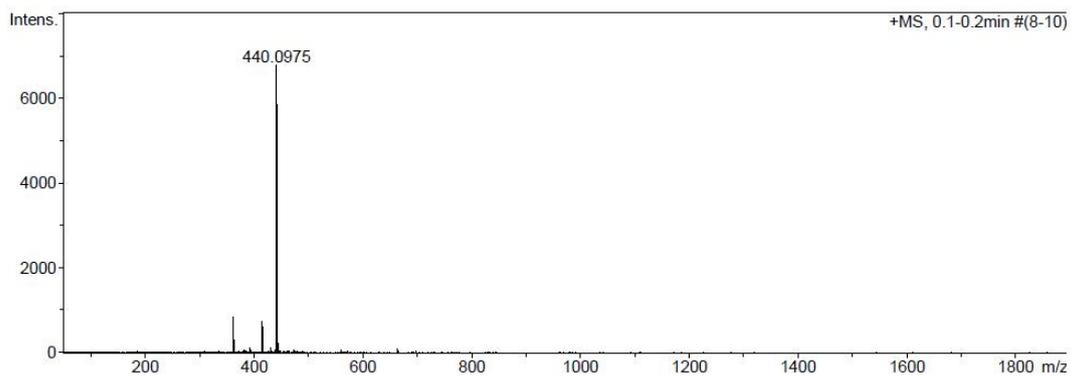
The HR-MS spectra of compound I-6d



The ¹H NMR spectra of compound I-6e



The ¹³C NMR spectra of compound I-6e

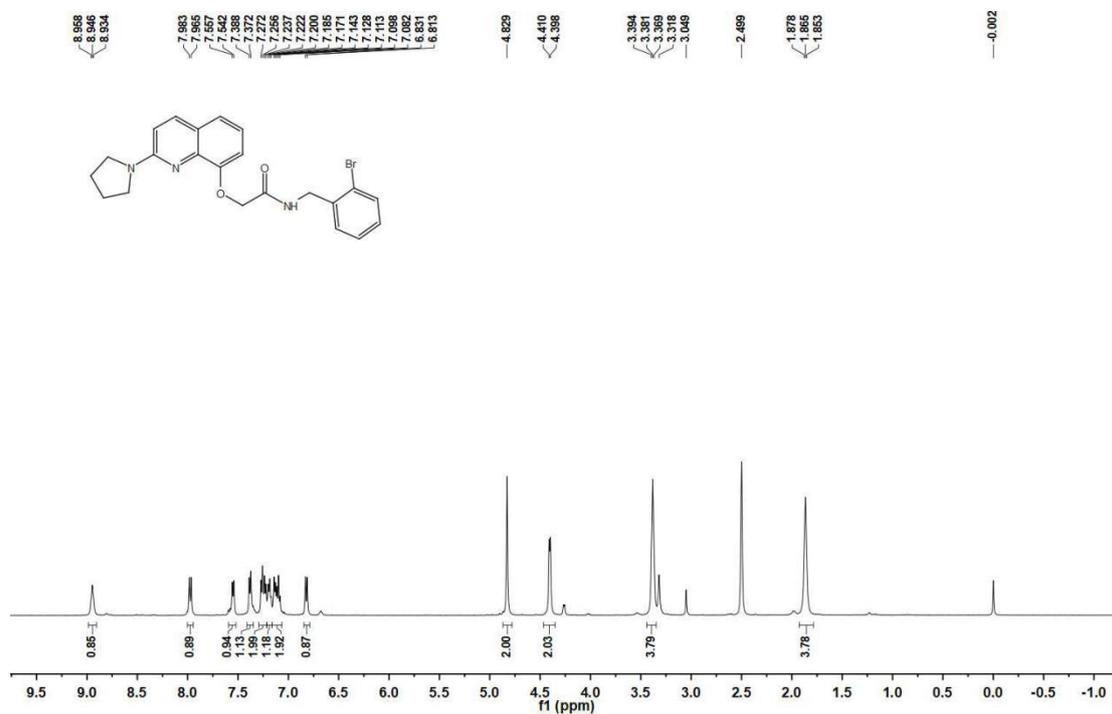


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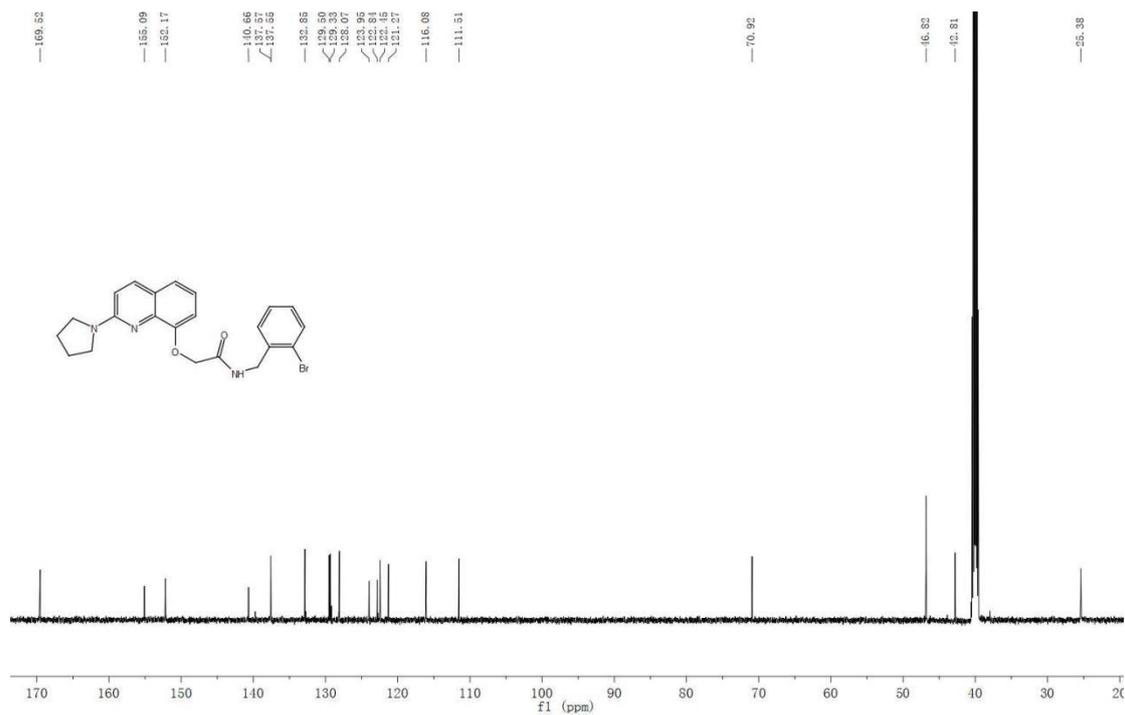
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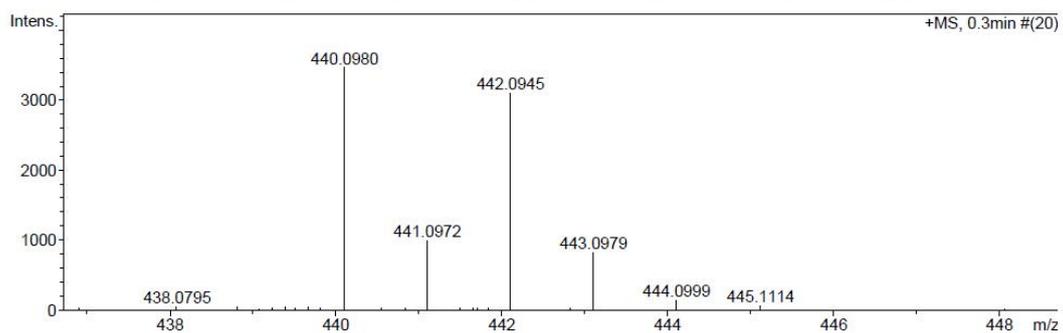
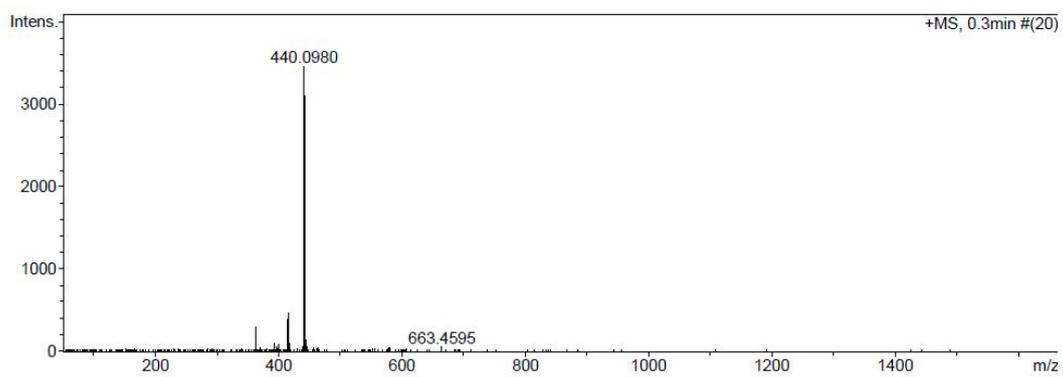
The HR-MS spectra of compound I-6



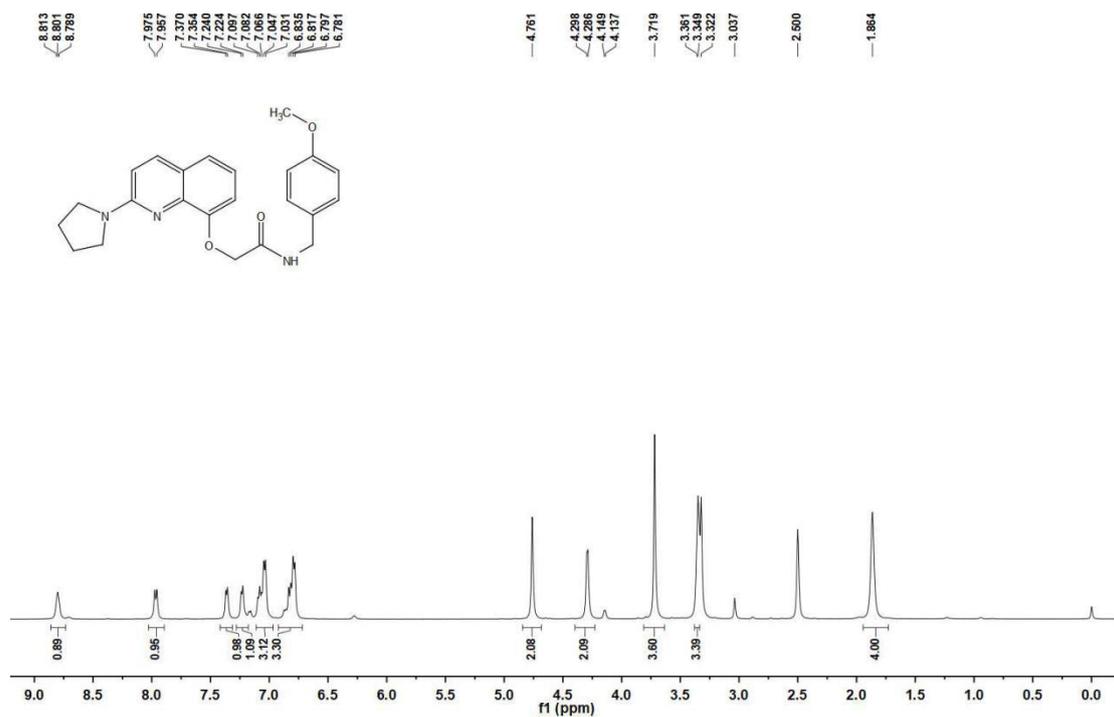
The ¹H NMR spectra of compound I-6f



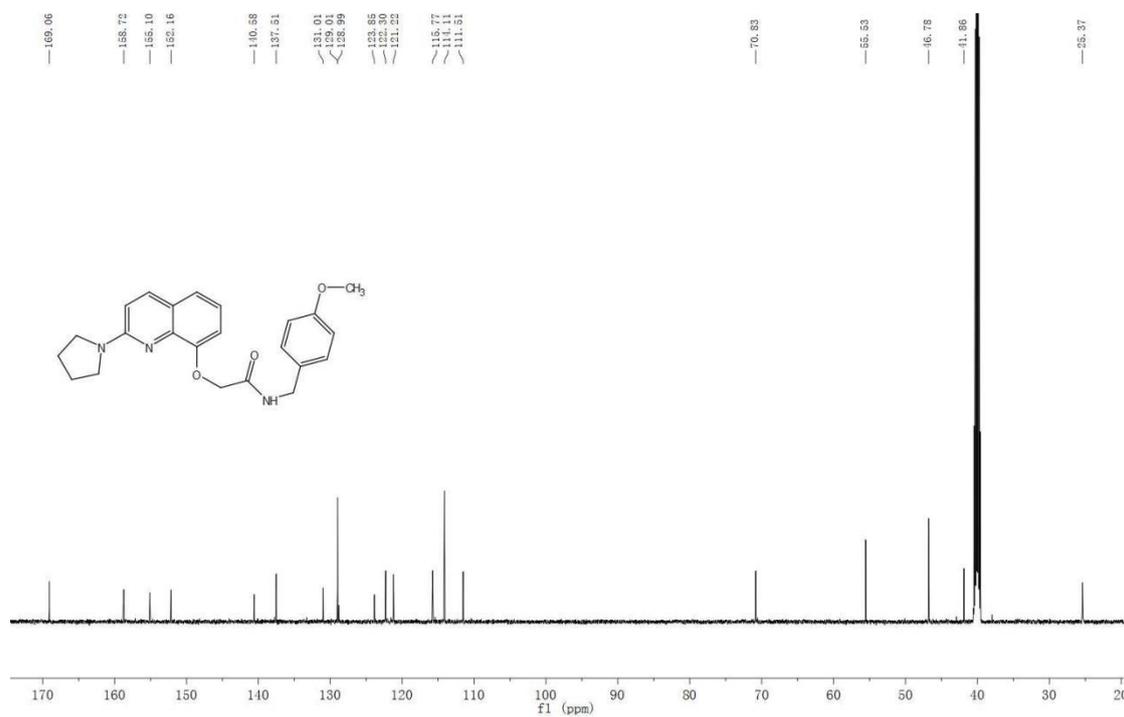
The ¹³C NMR spectra of compound I-6f



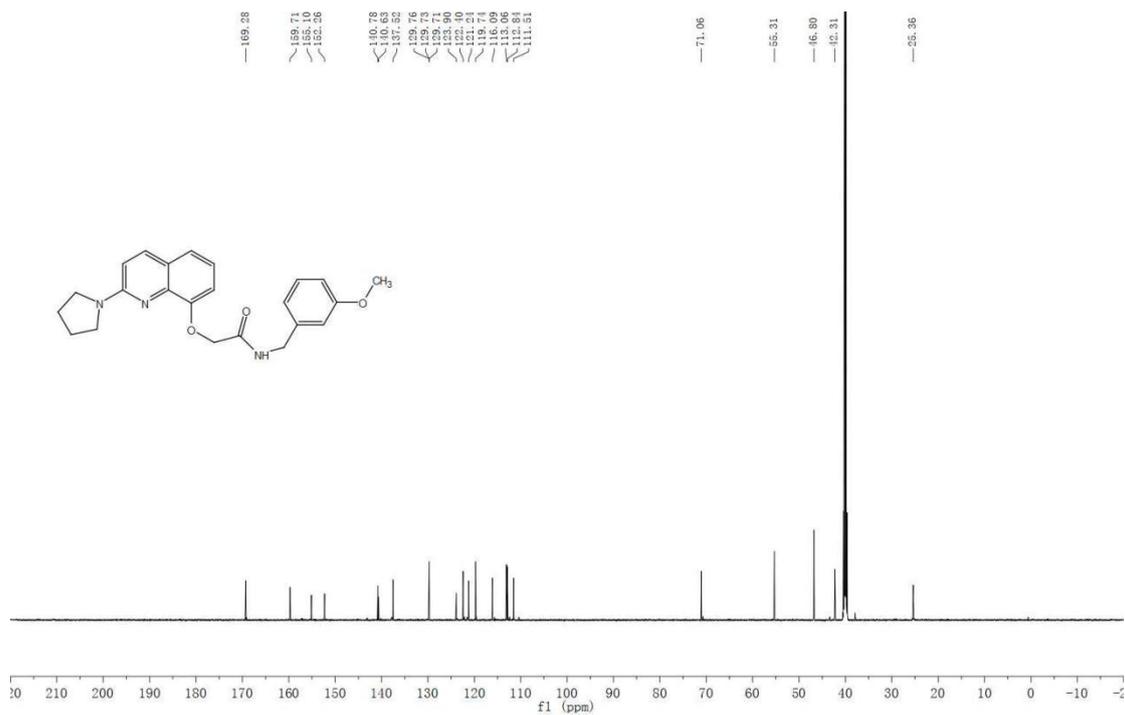
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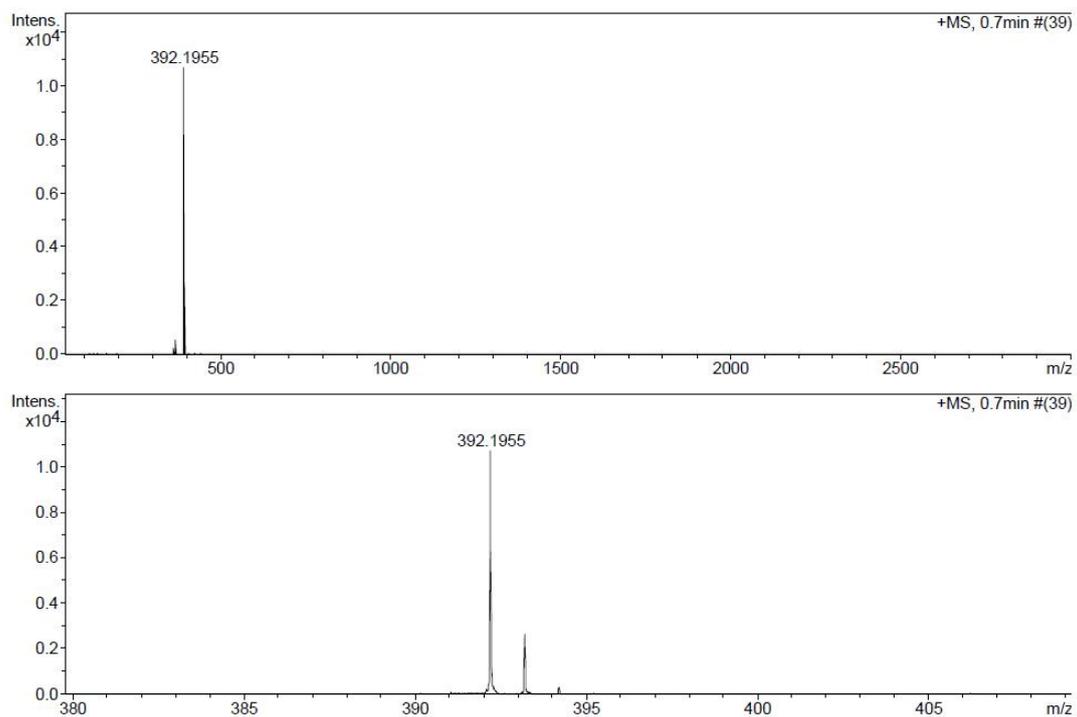
The ¹H NMR spectra of compound I-6g



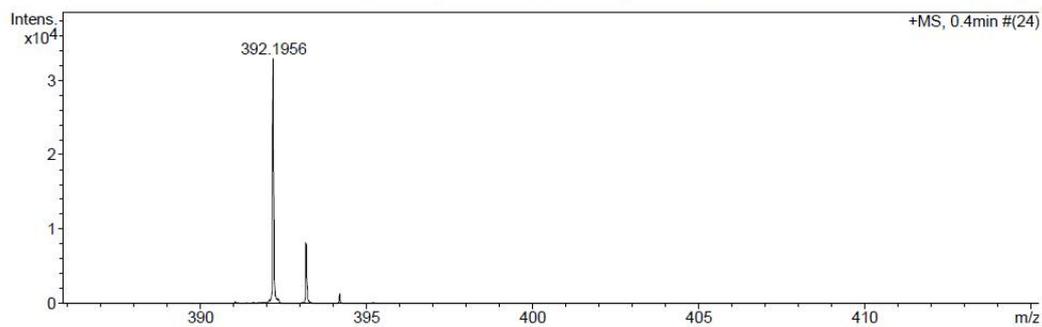
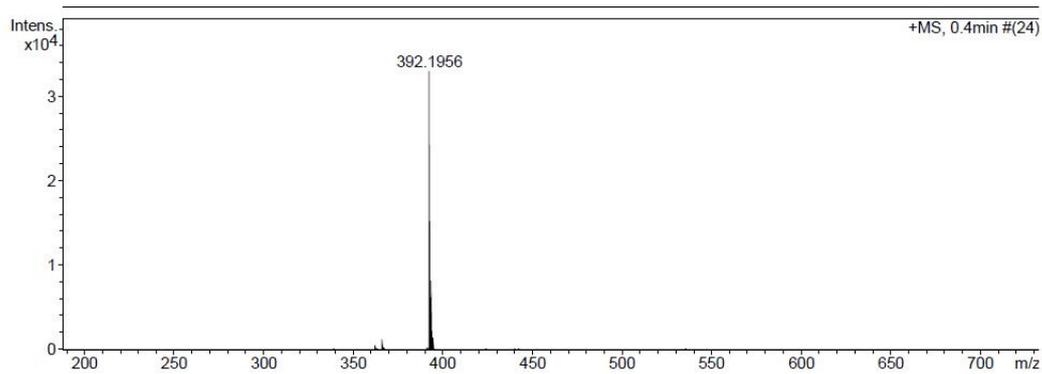
The ¹³C NMR spectra of compound I-6g



The ¹³C NMR spectra of compound I-6h



The HR-MS spectra of compound I-6h



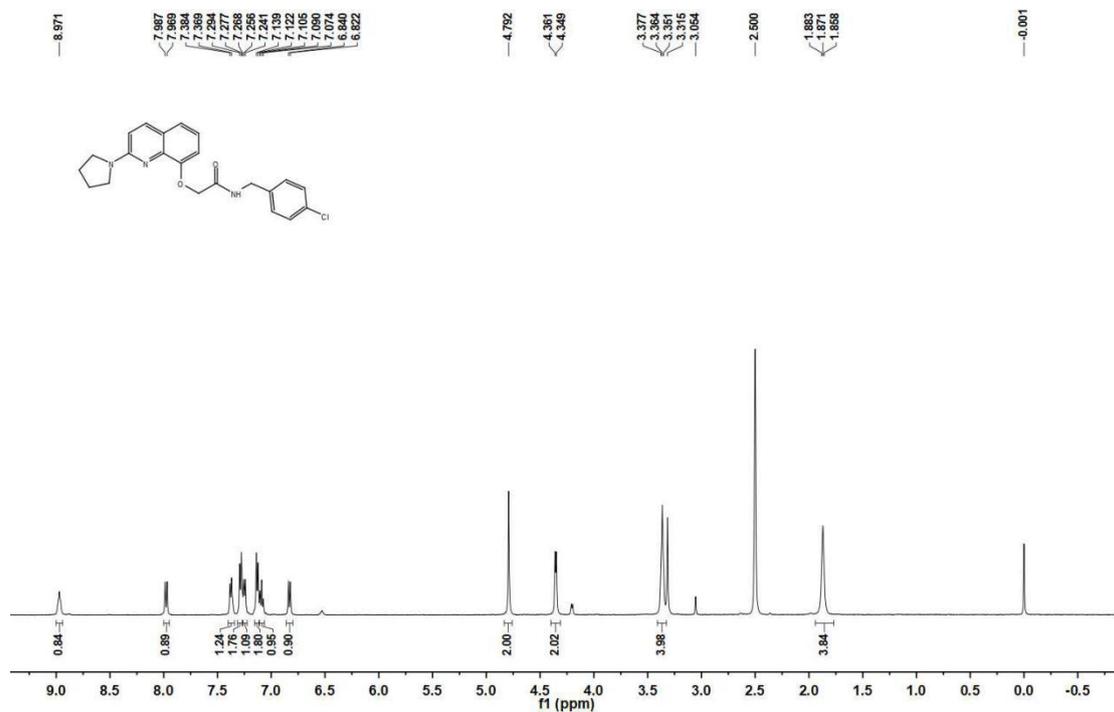
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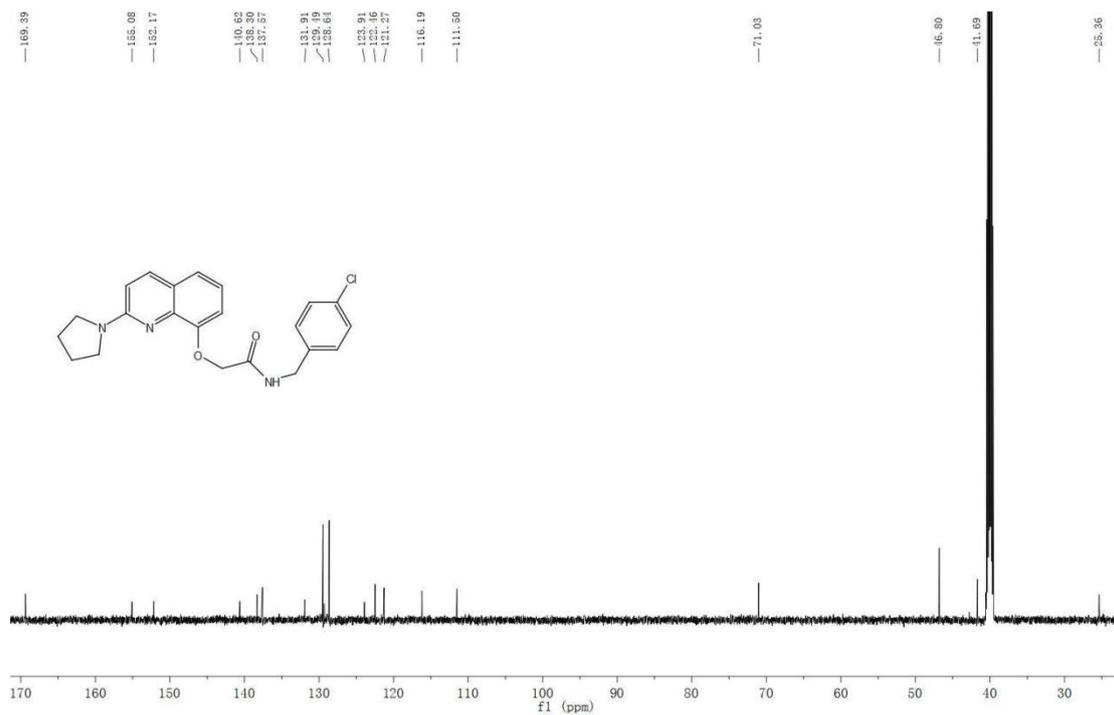
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The HR-MS spectra of compound

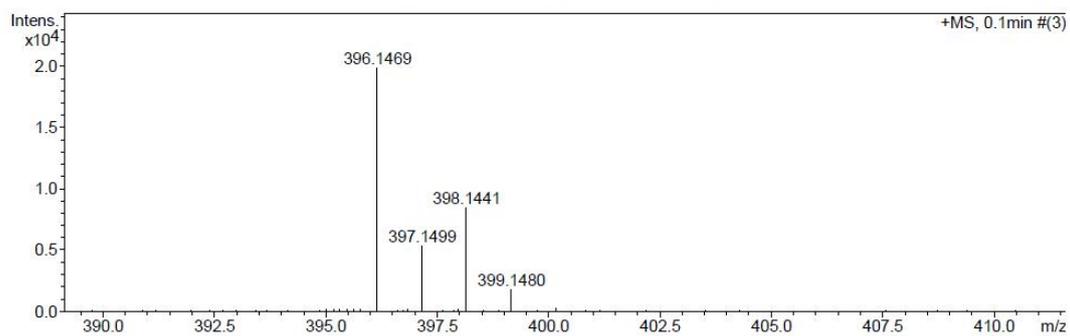
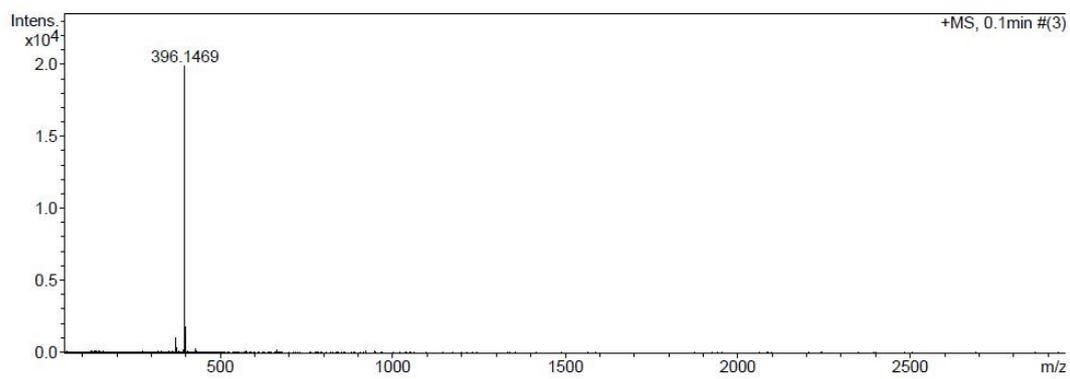
I-6i



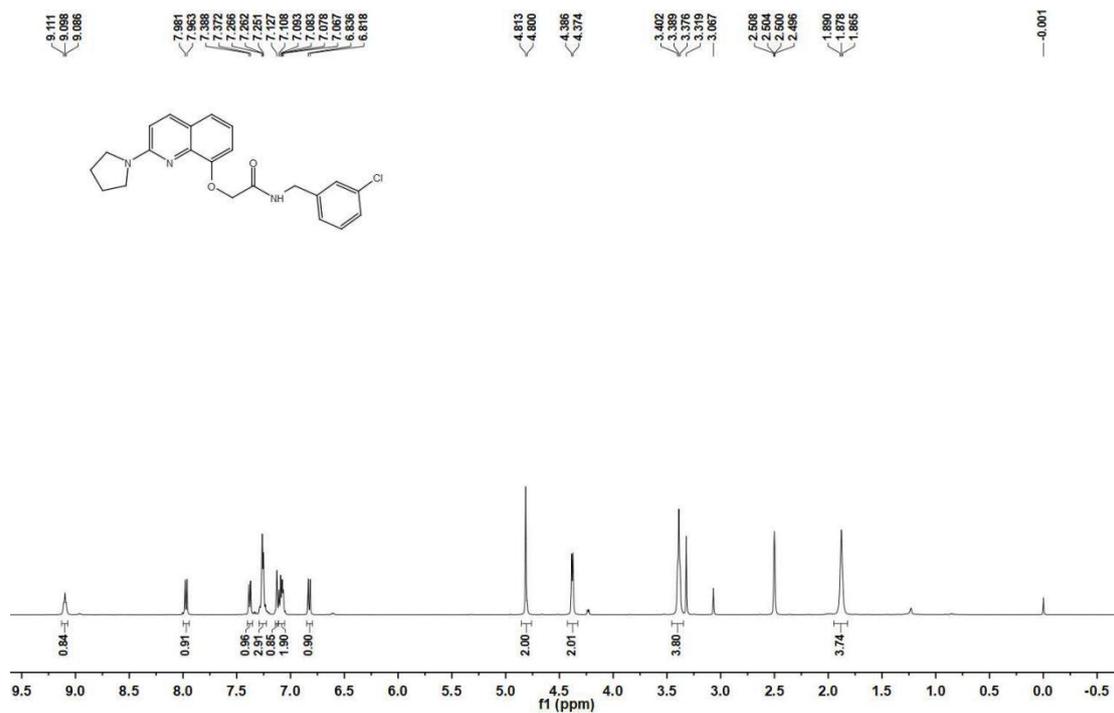
The ¹H NMR spectra of compound I-6j



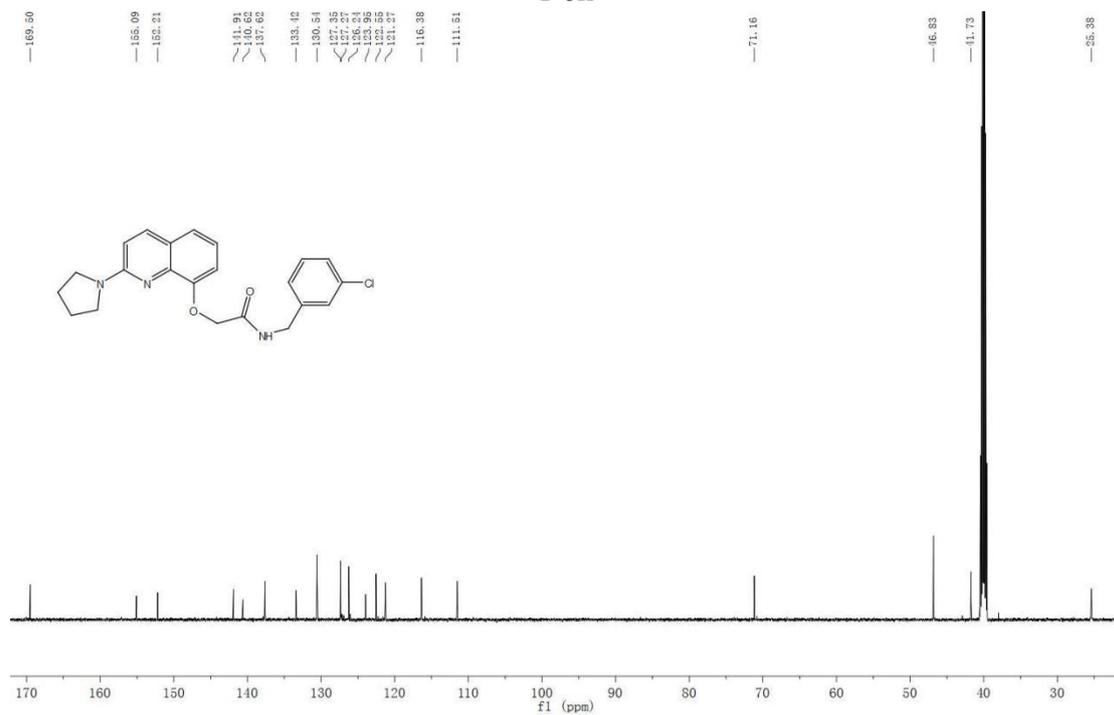
The ¹³C NMR spectra of compound I-6j



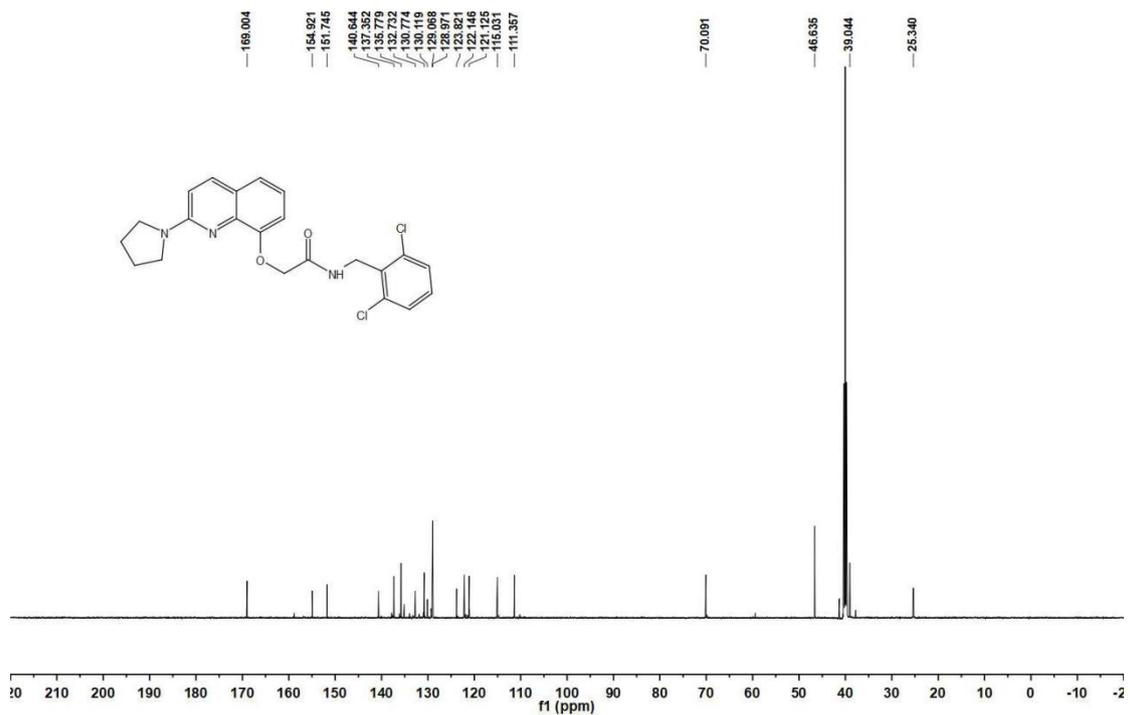
The HR-MS spectra of compound I-6j



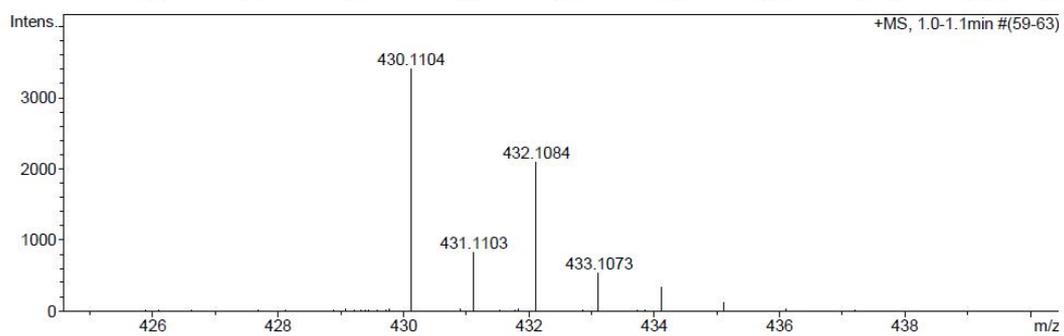
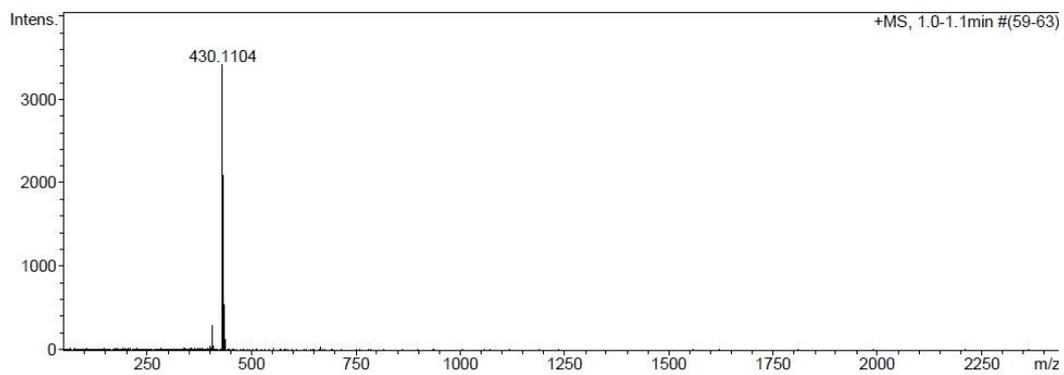
The ¹H NMR spectra of compound I-6k



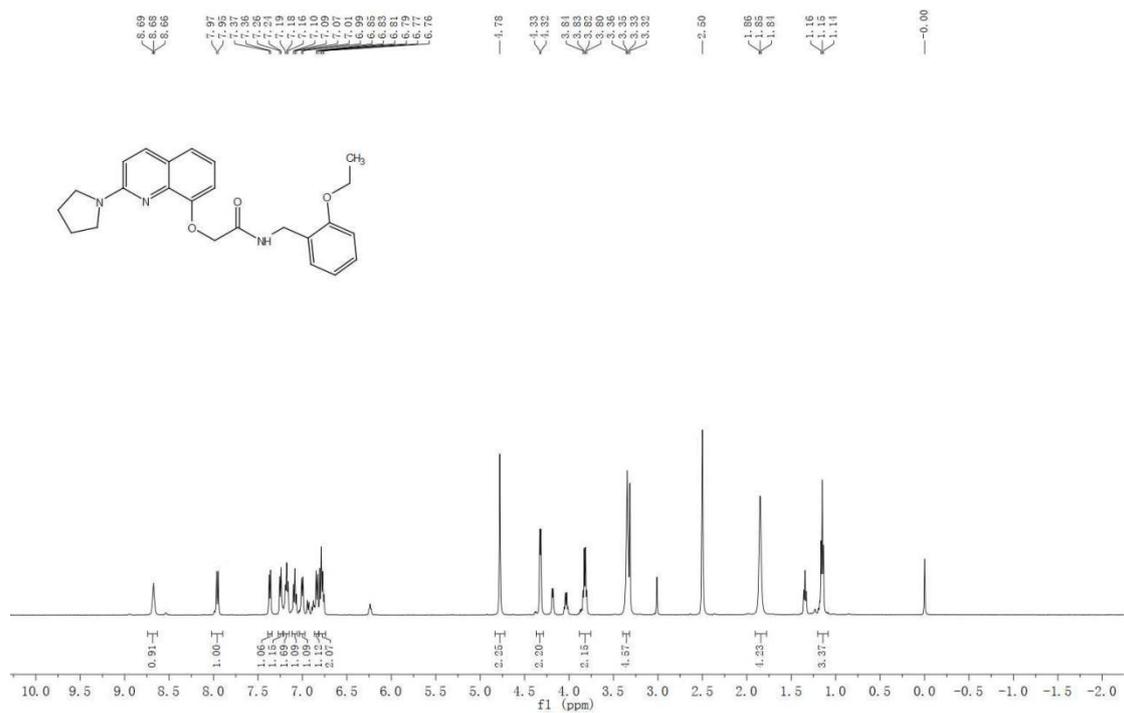
The ¹³C NMR spectra of compound I-6k



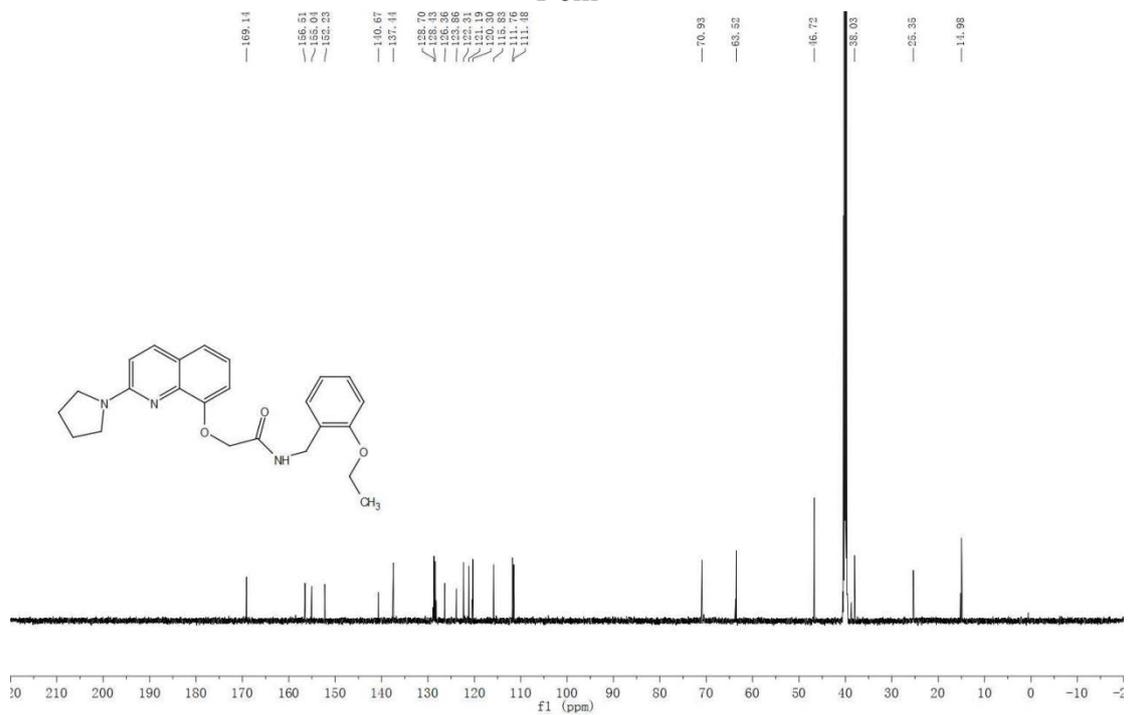
The ^{13}C NMR spectra of compound I-61



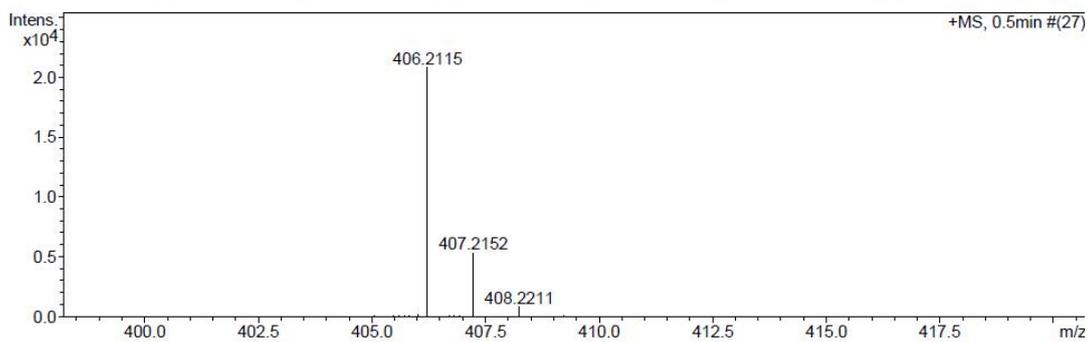
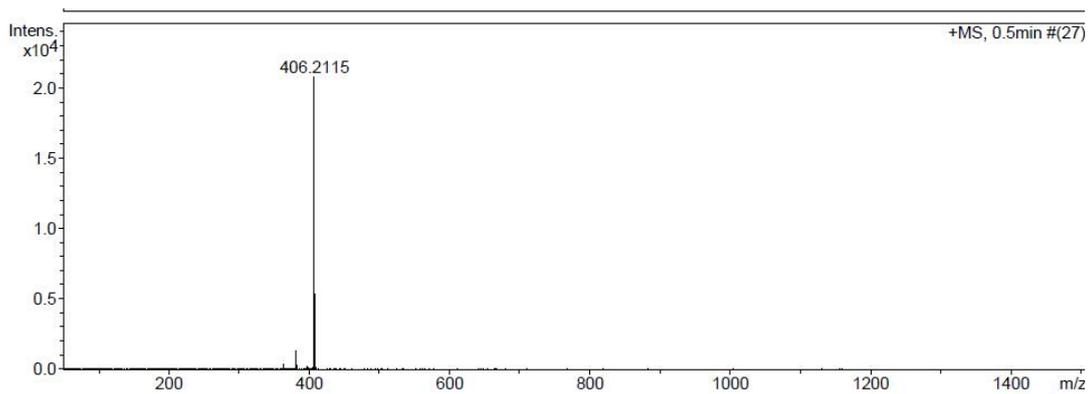
The HR-MS spectra of compound I-61



The ¹H NMR spectra of compound I-6m



The ¹³C NMR spectra of compound I-6m



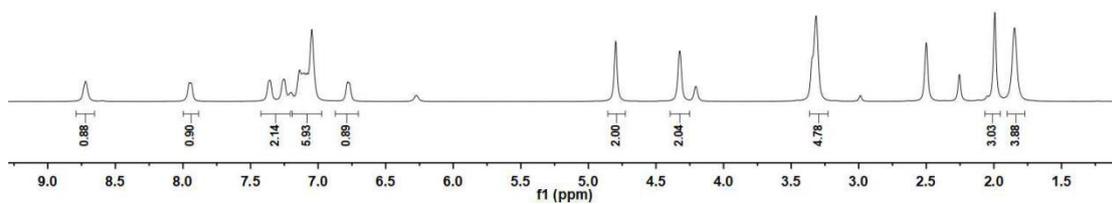
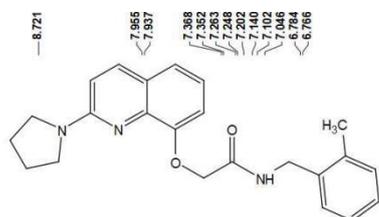
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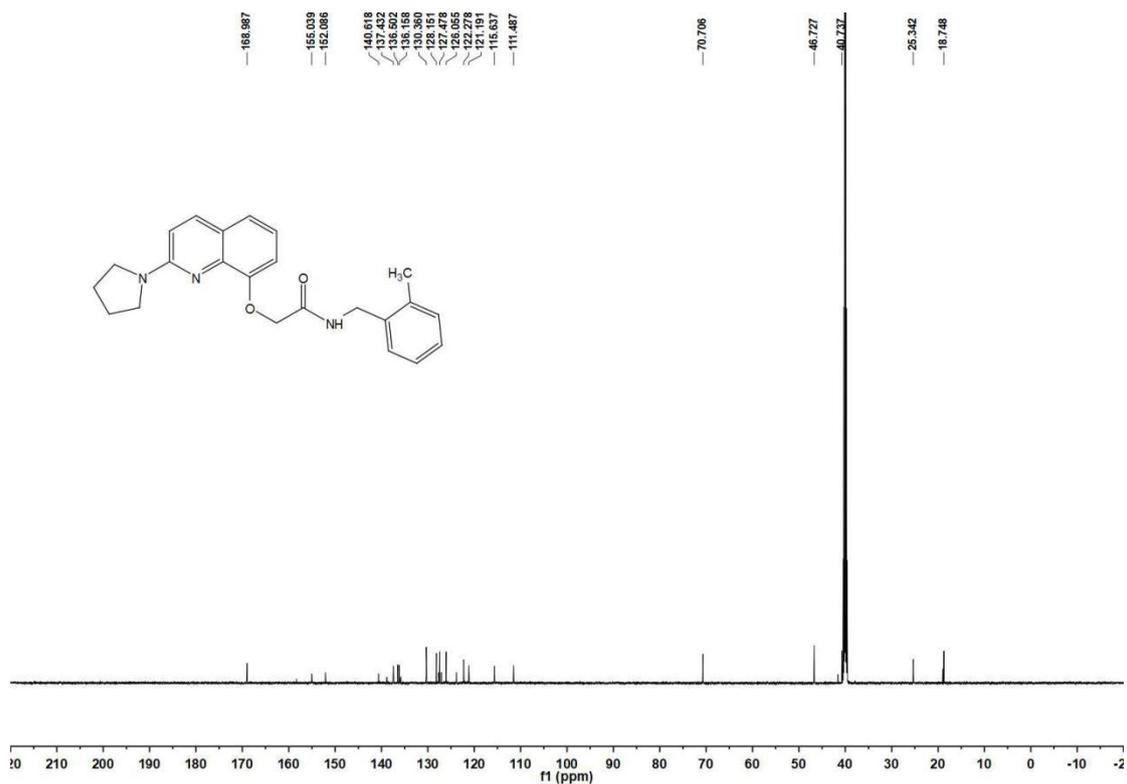
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The HR-MS spectra of compound

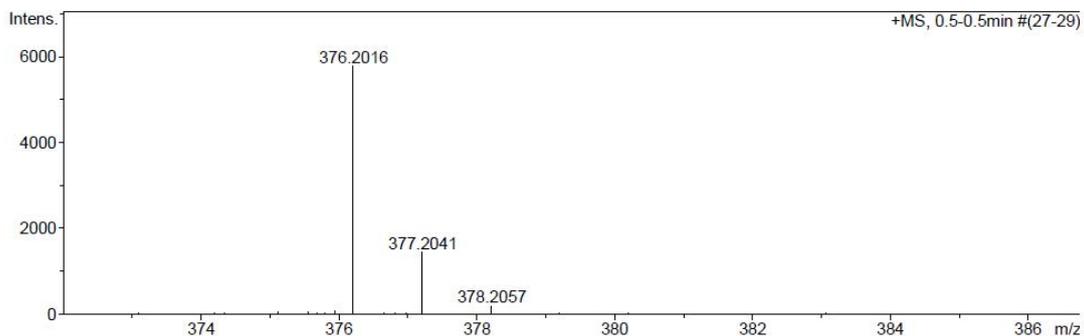
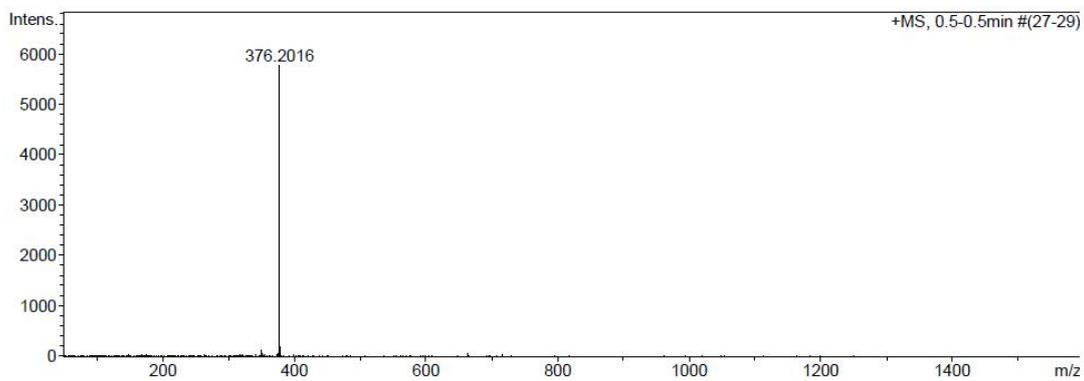
I-6n



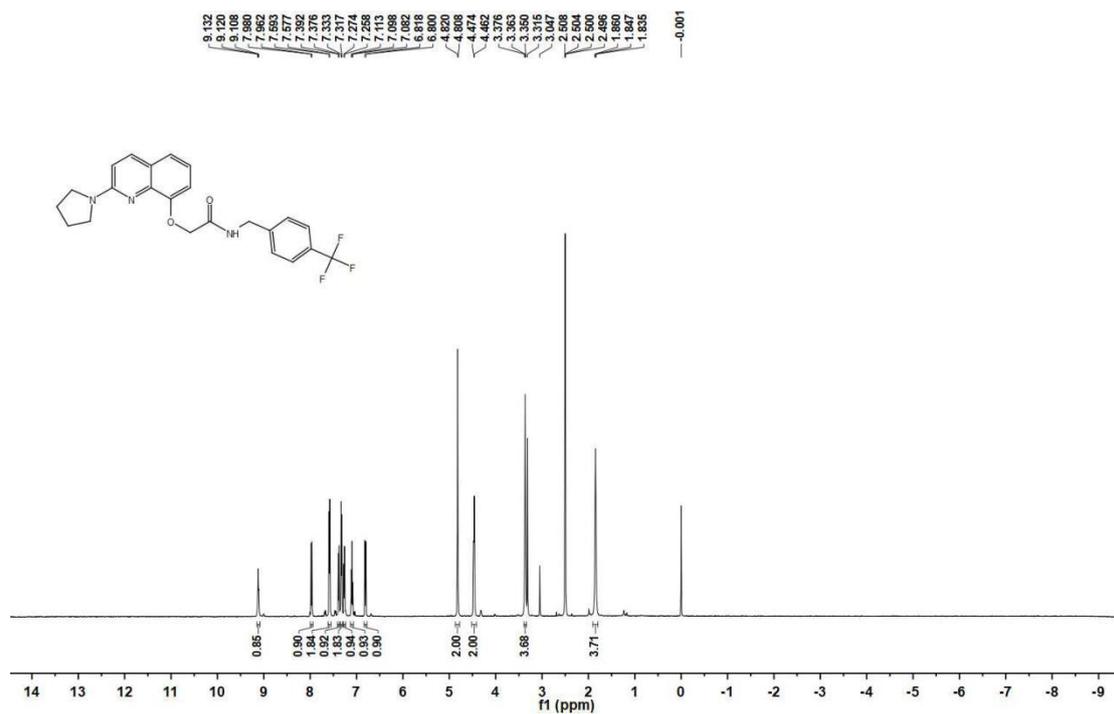
The ¹H NMR spectra of compound I-6n



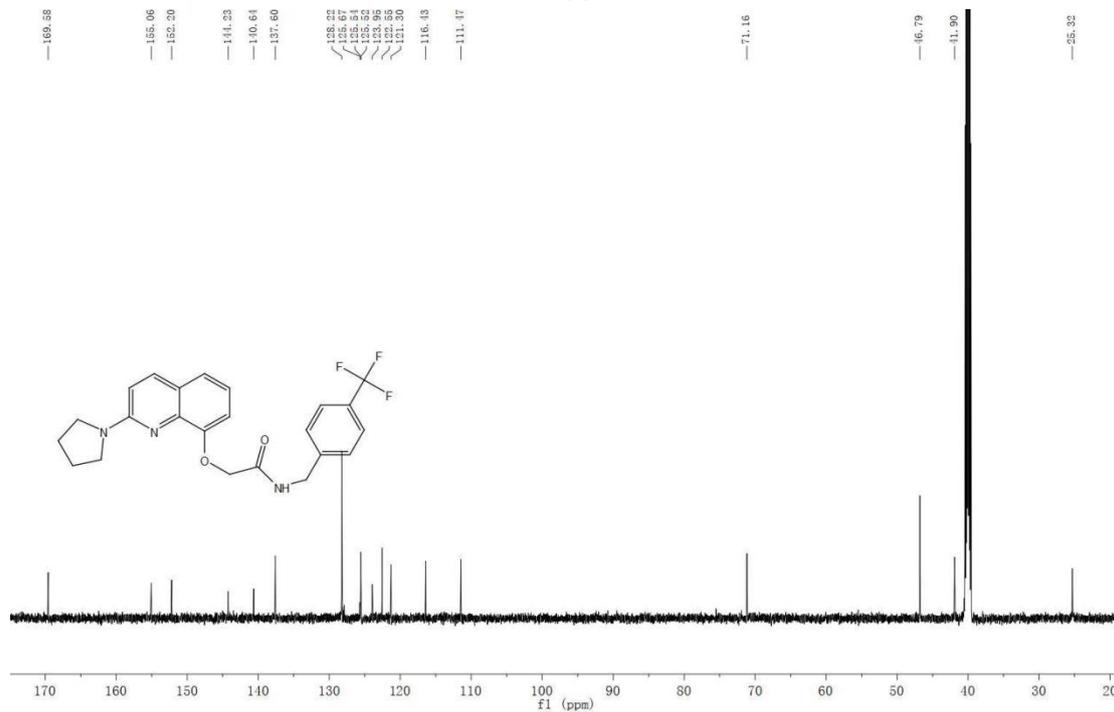
The ^{13}C NMR spectra of compound I-6n



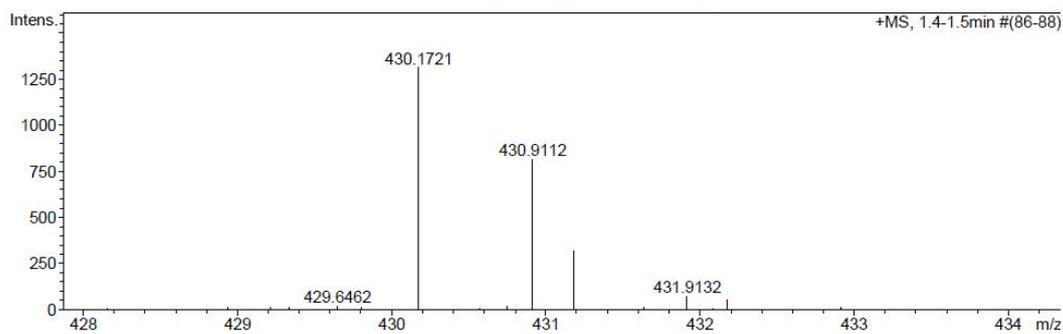
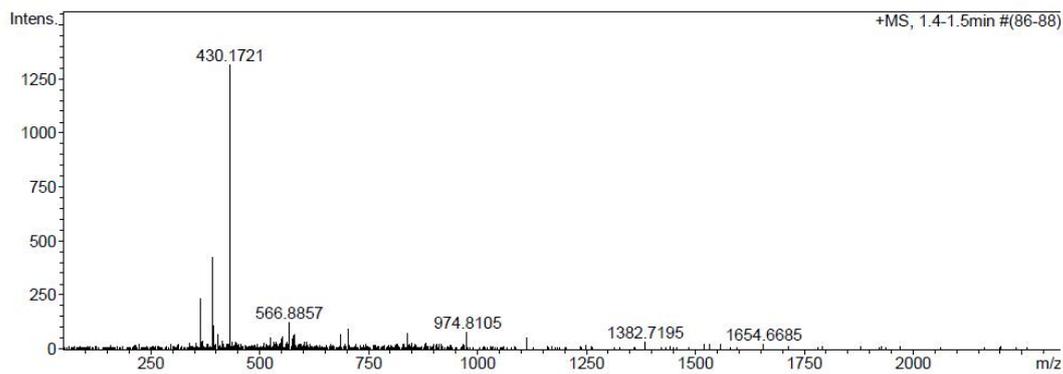
The HR-MS spectra of compound I-6n



The ¹H NMR spectra of compound I-60



The ¹³C NMR spectra of compound I-60

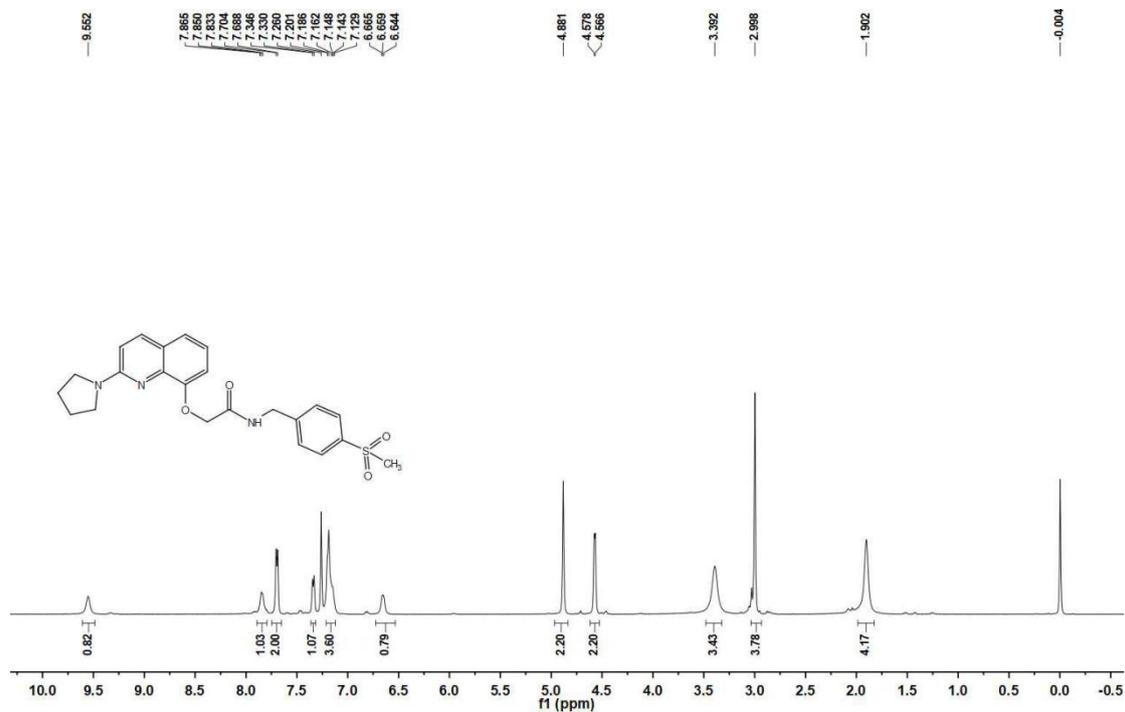


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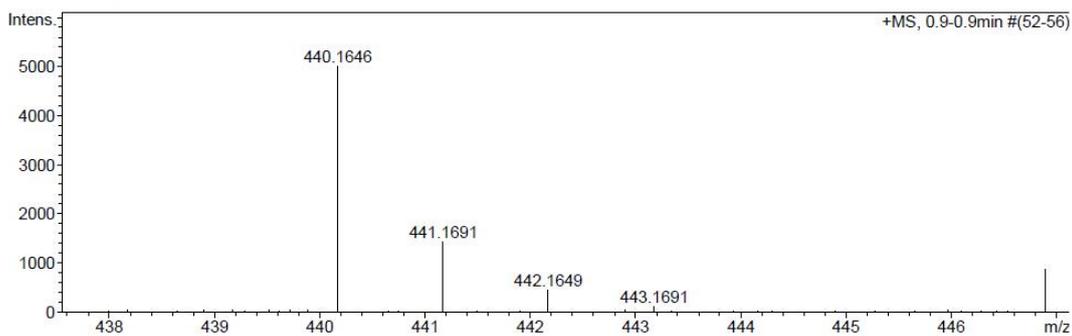
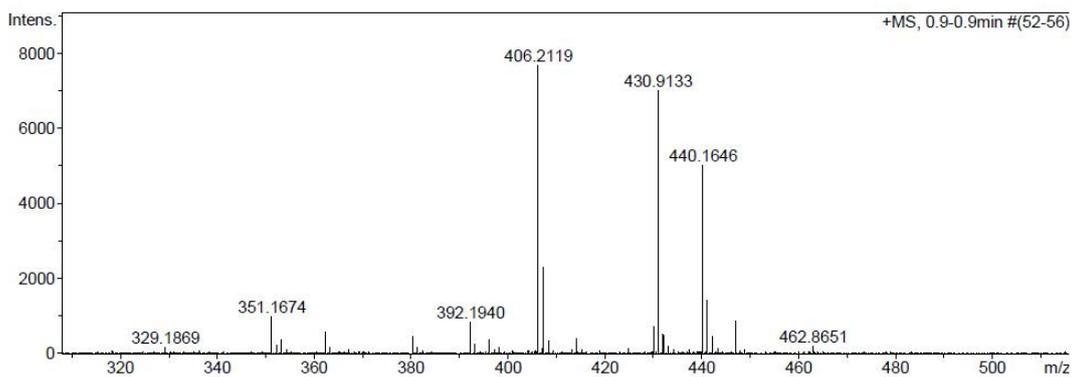
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The HR-MS spectra of compound I-6o



The ¹H NMR spectra of compound I-6p



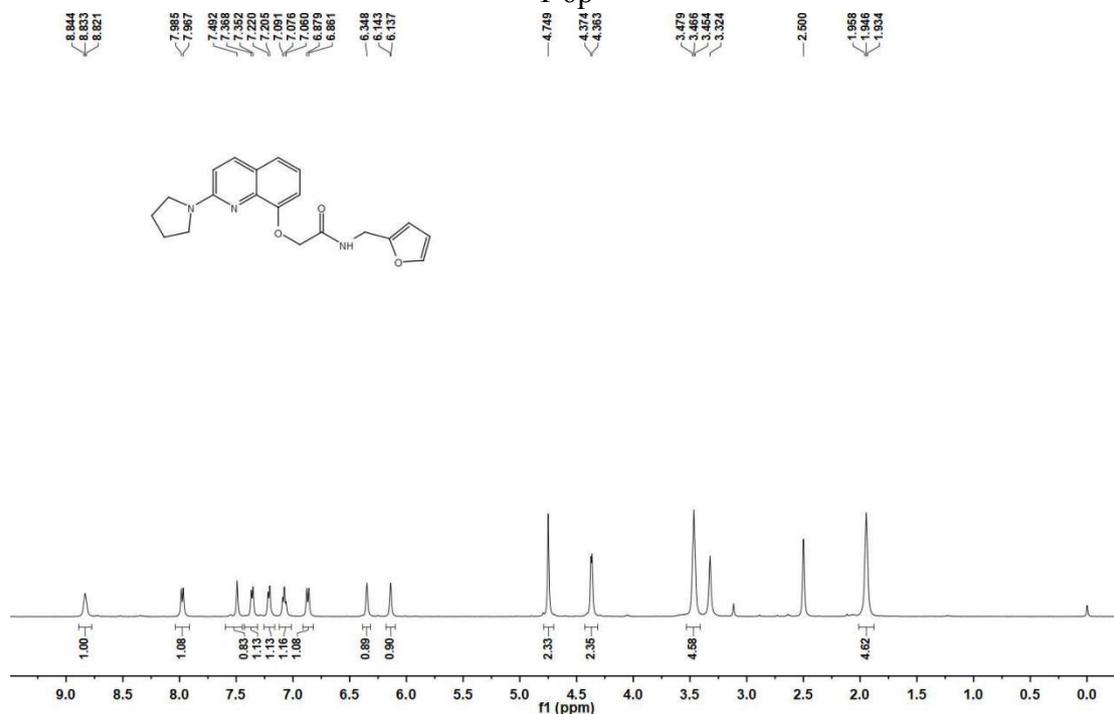
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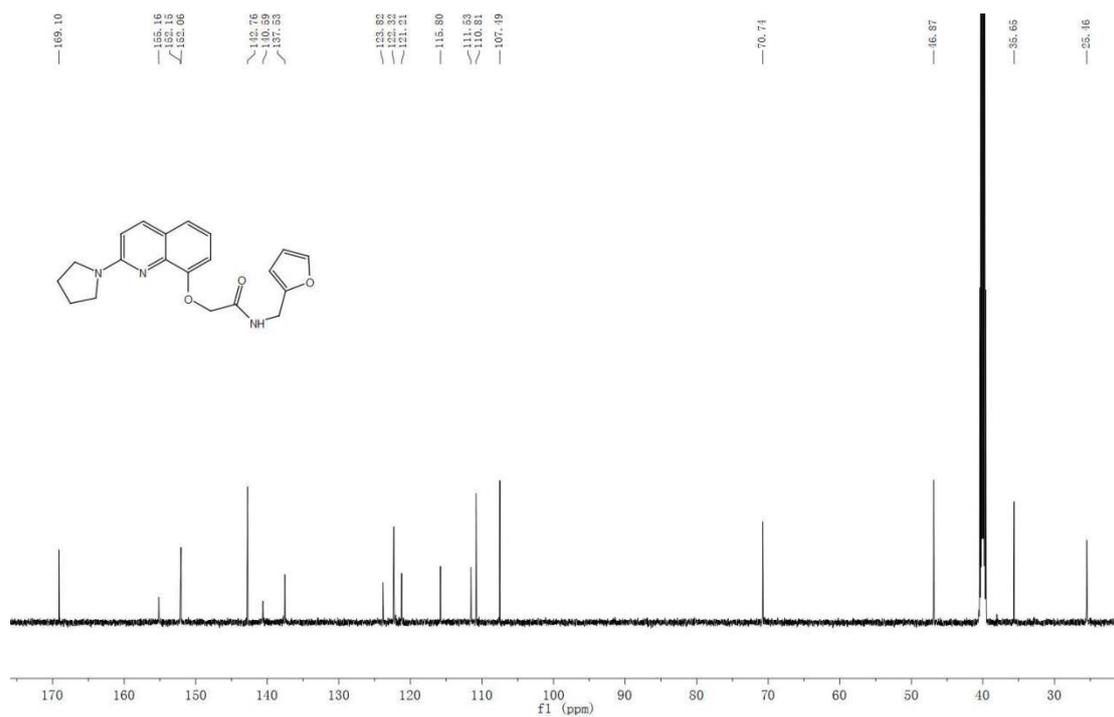
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The HR-MS spectra of compound

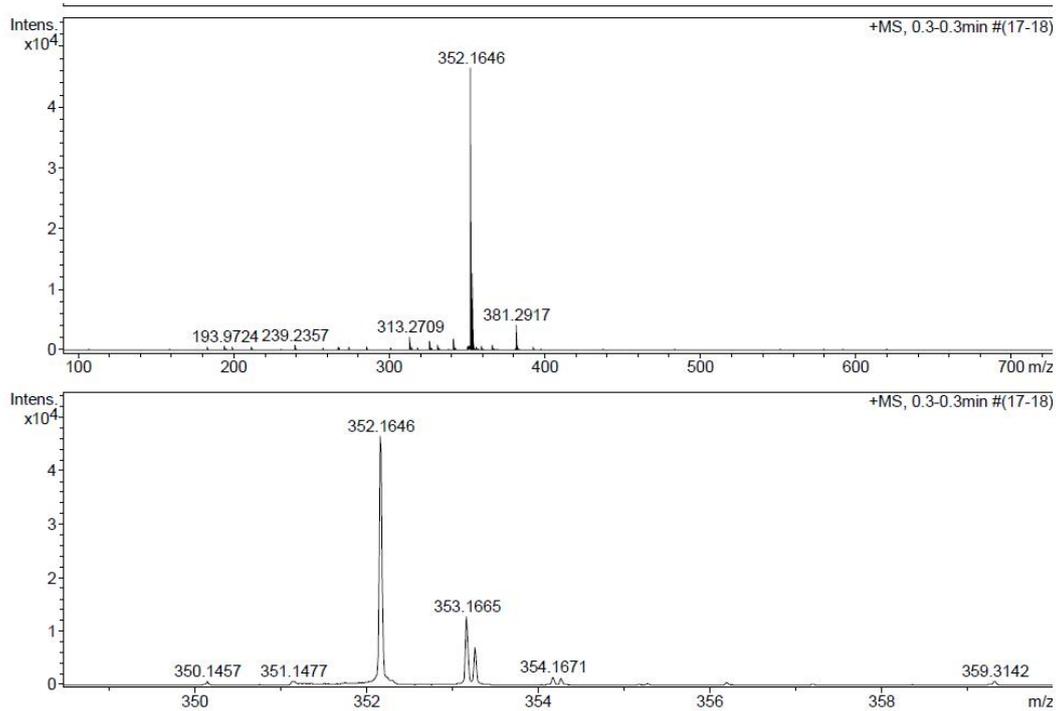
I-6p



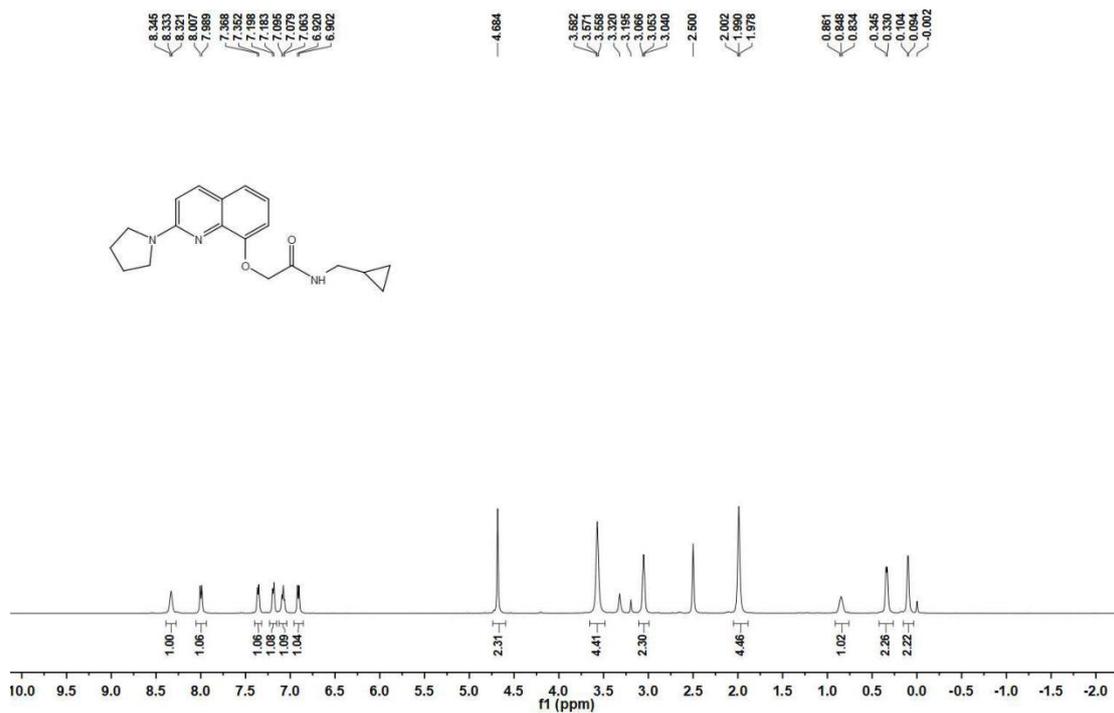
The ¹H NMR spectra of compound I-6q



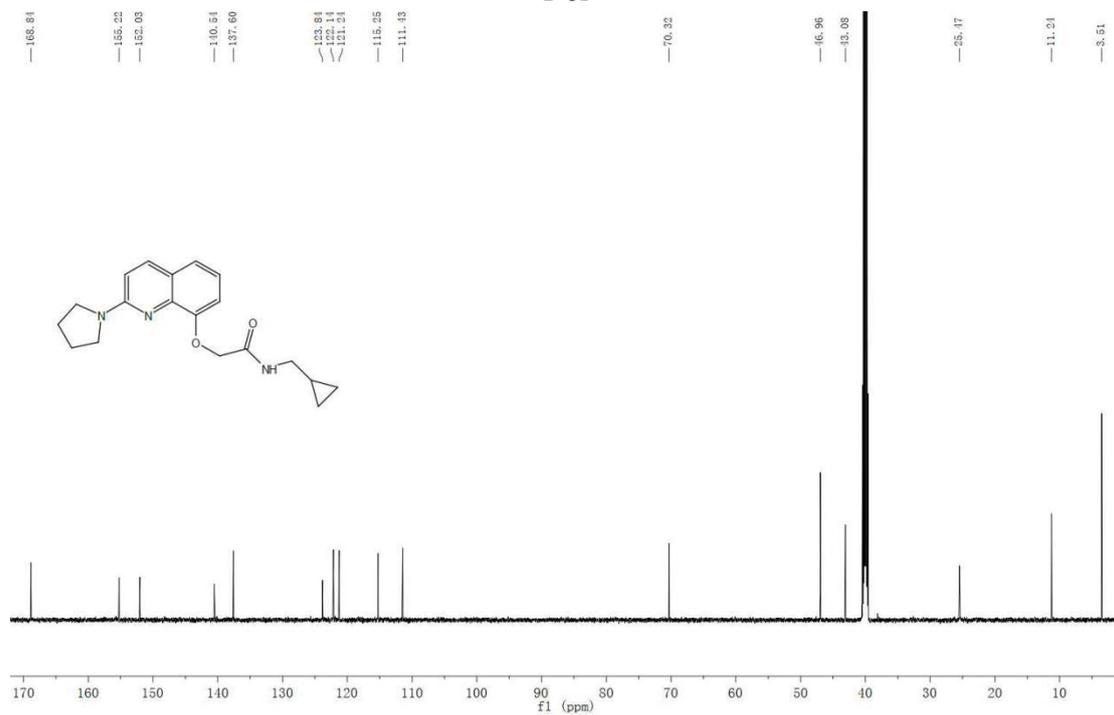
The ¹³C NMR spectra of compound I-6q



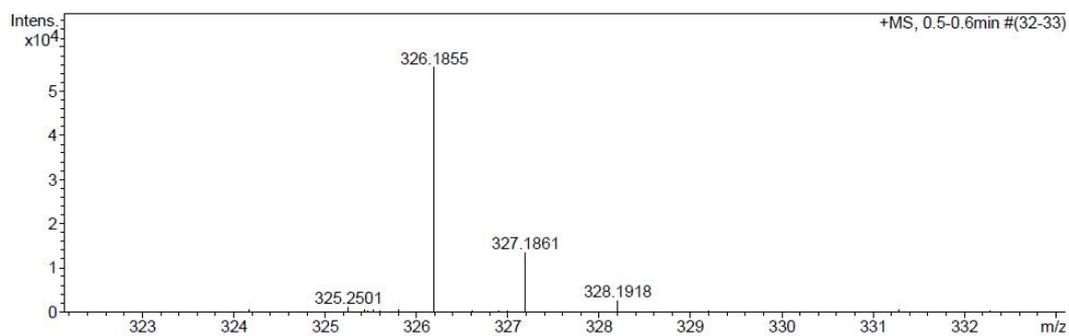
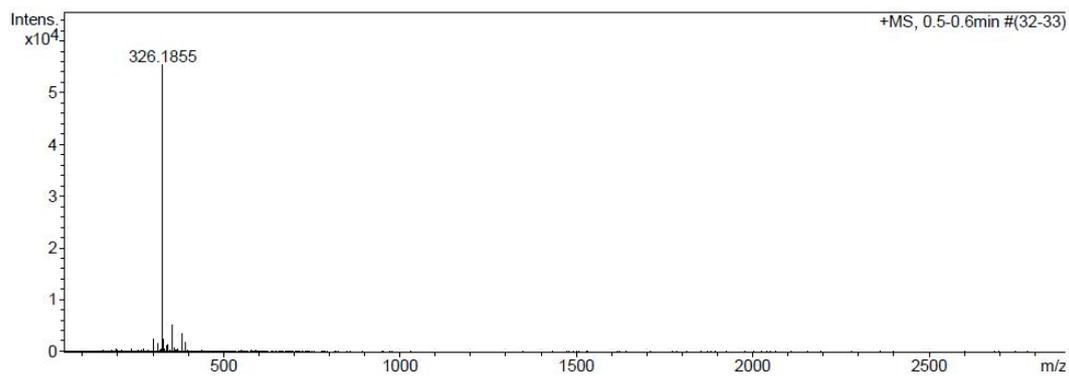
The HR-MS spectra of compound I-6q



The ^1H NMR spectra of compound I-6r



The ^{13}C NMR spectra of compound I-6r



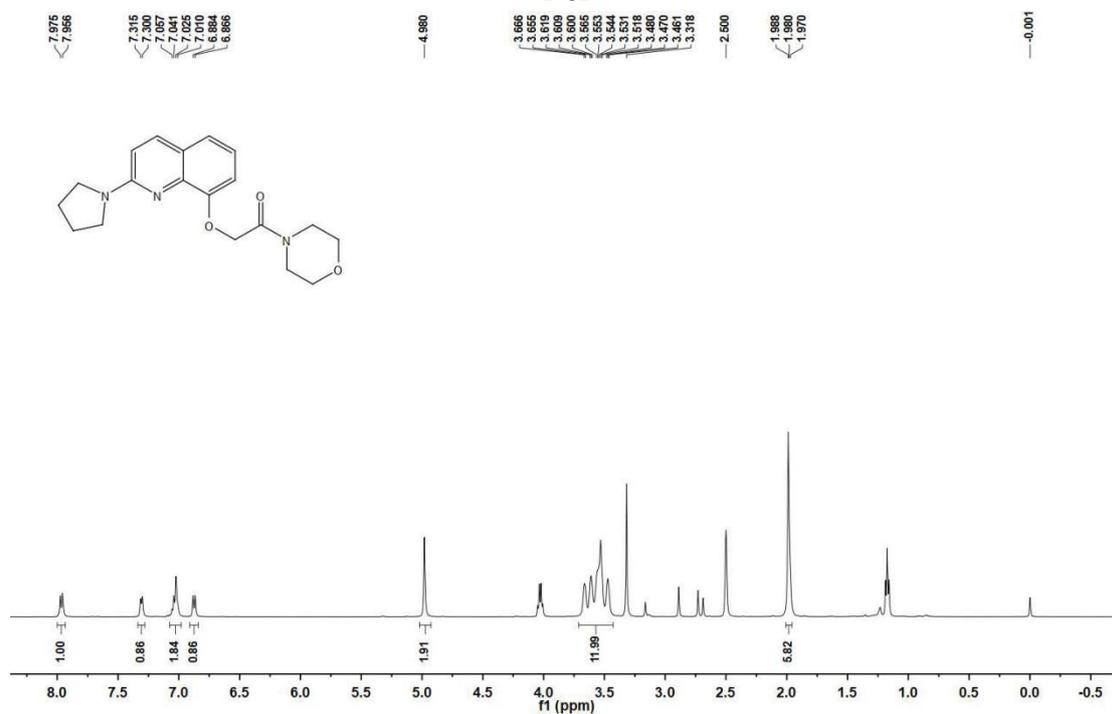
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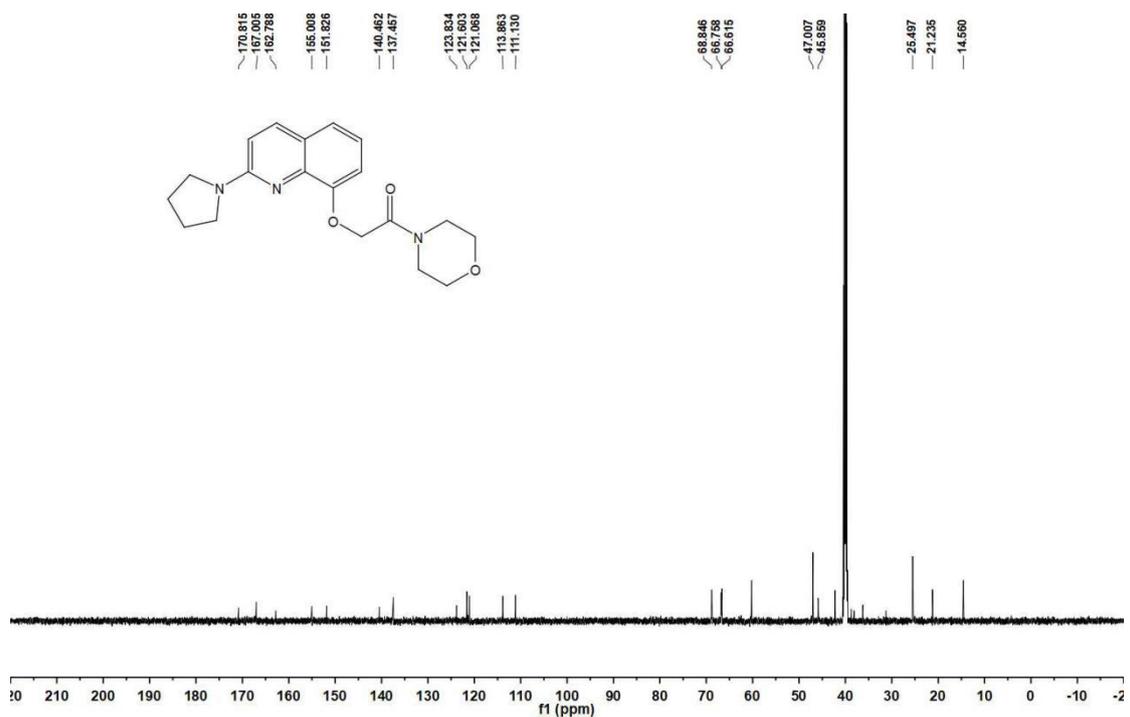
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The HR-MS spectra of compound

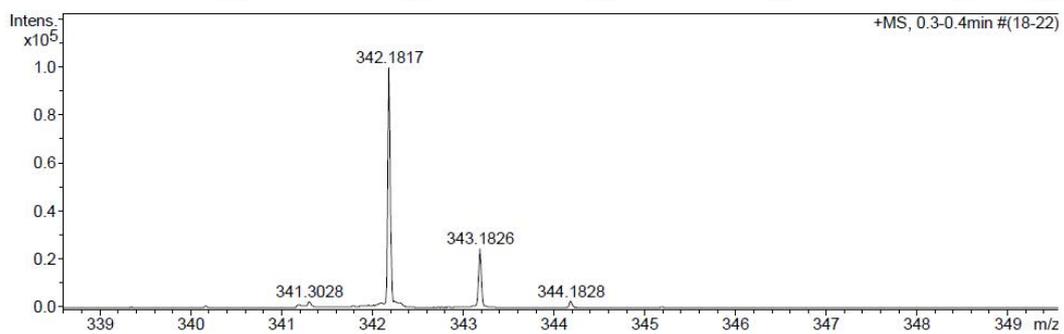
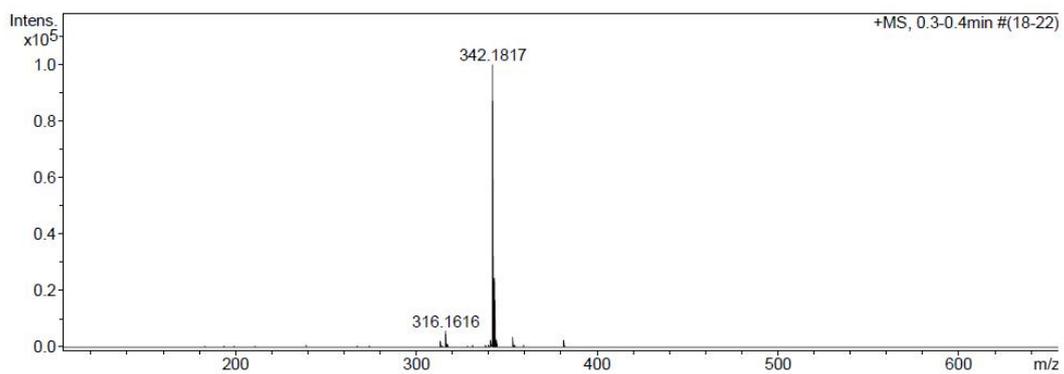
I-6r



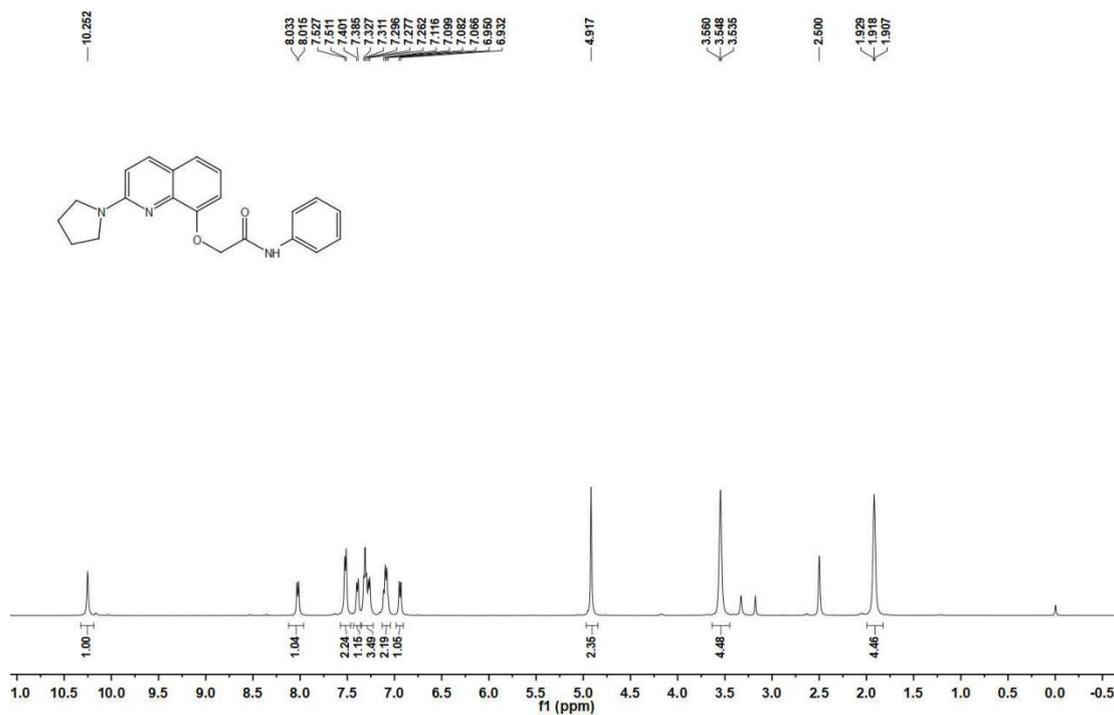
The ¹H NMR spectra of compound I-6s



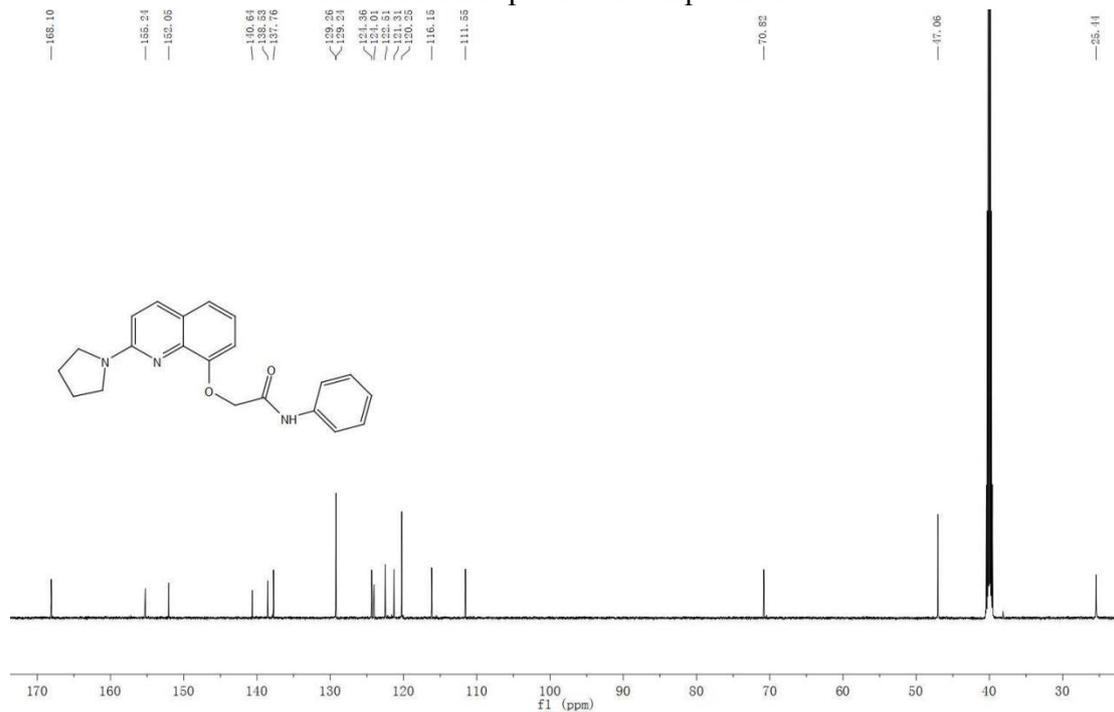
The ¹³C NMR spectra of compound I-6s



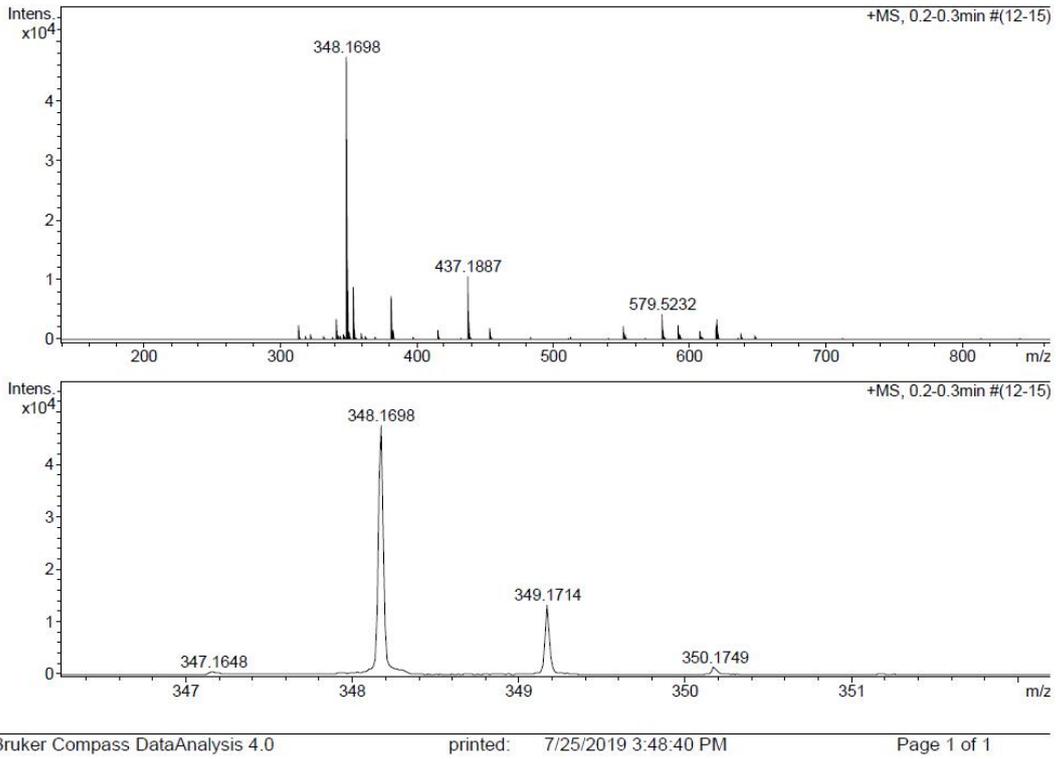
The HR-MS spectra of compound I-6s



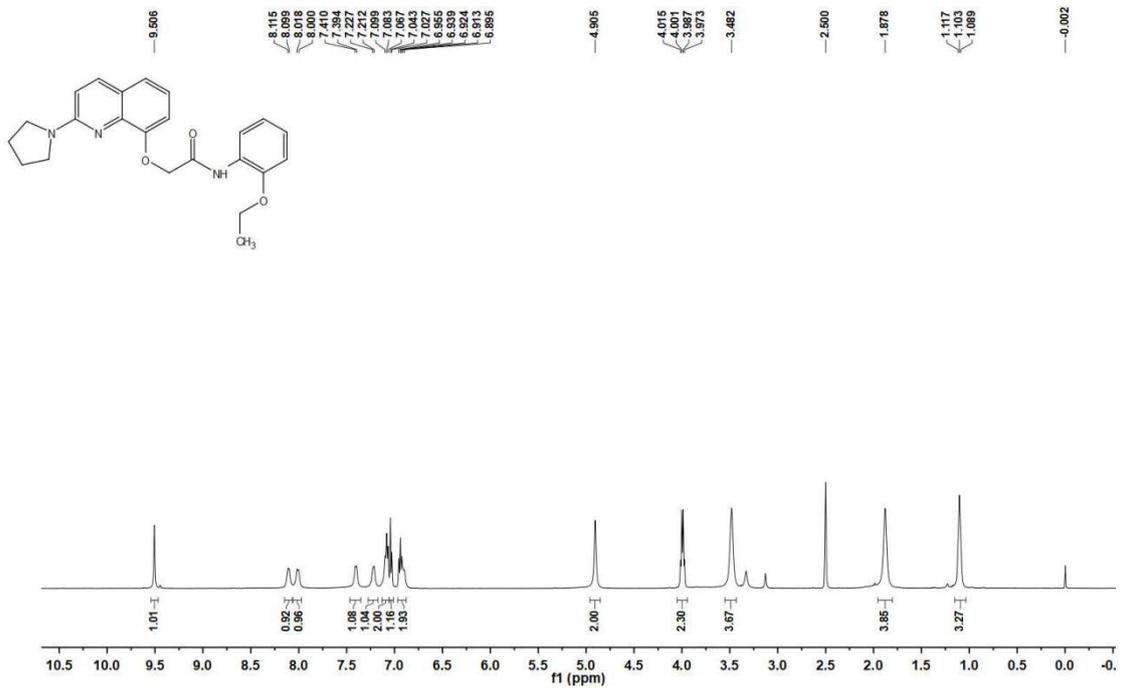
The ¹H NMR spectra of compound I-6t



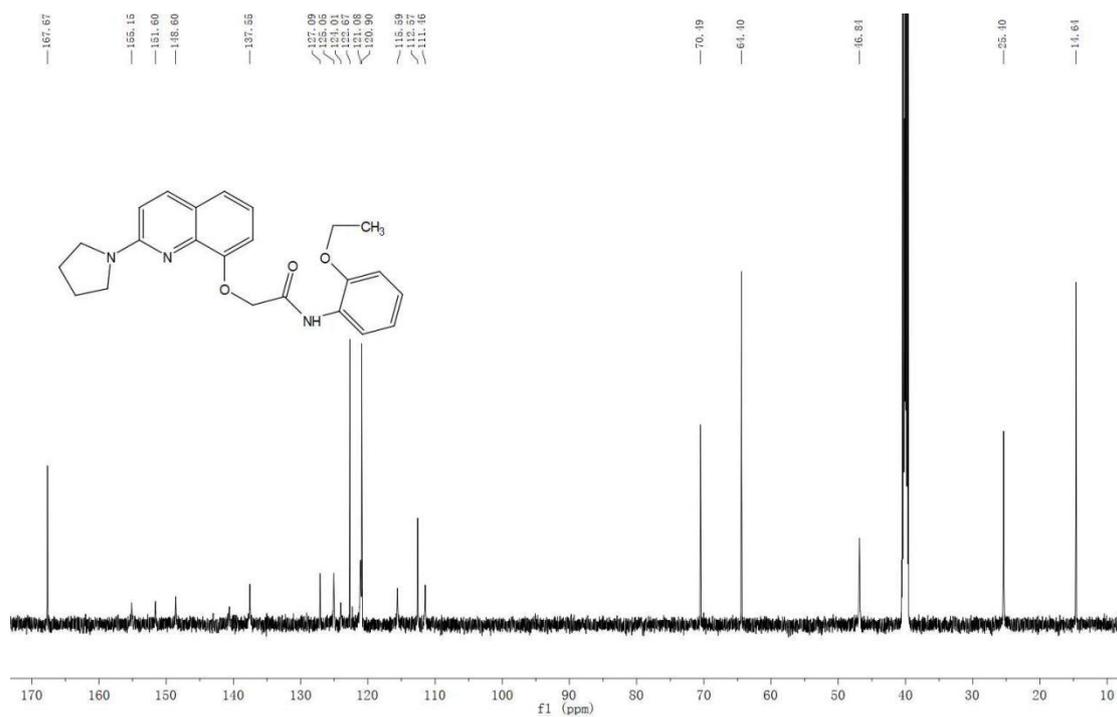
The ¹³C NMR spectra of compound I-6t



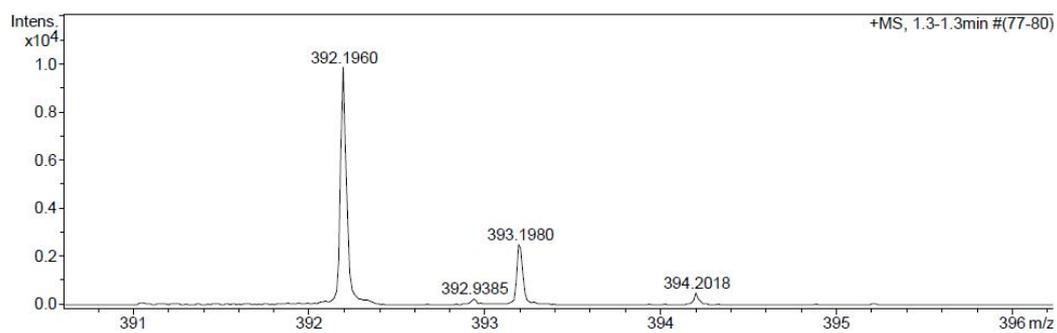
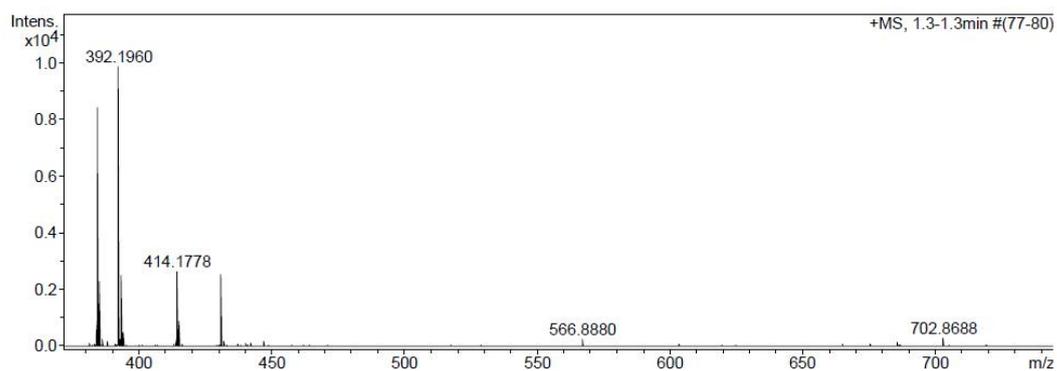
The HR-MS spectra of compound I-6t



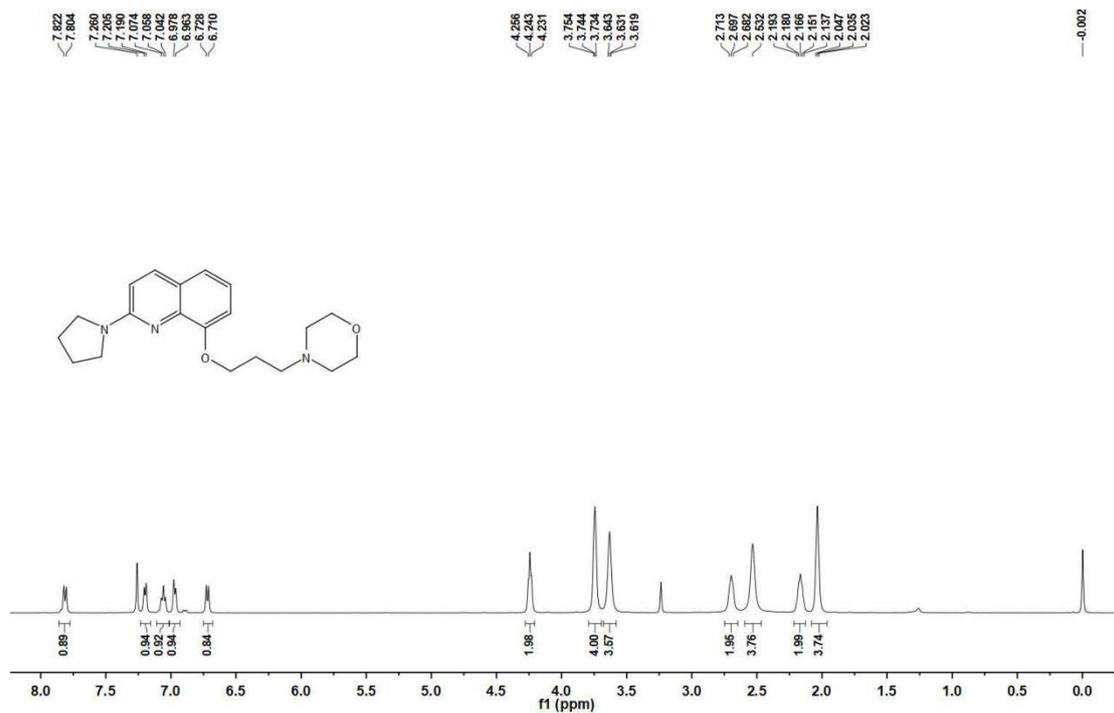
The ¹H NMR spectra of compound I-6u



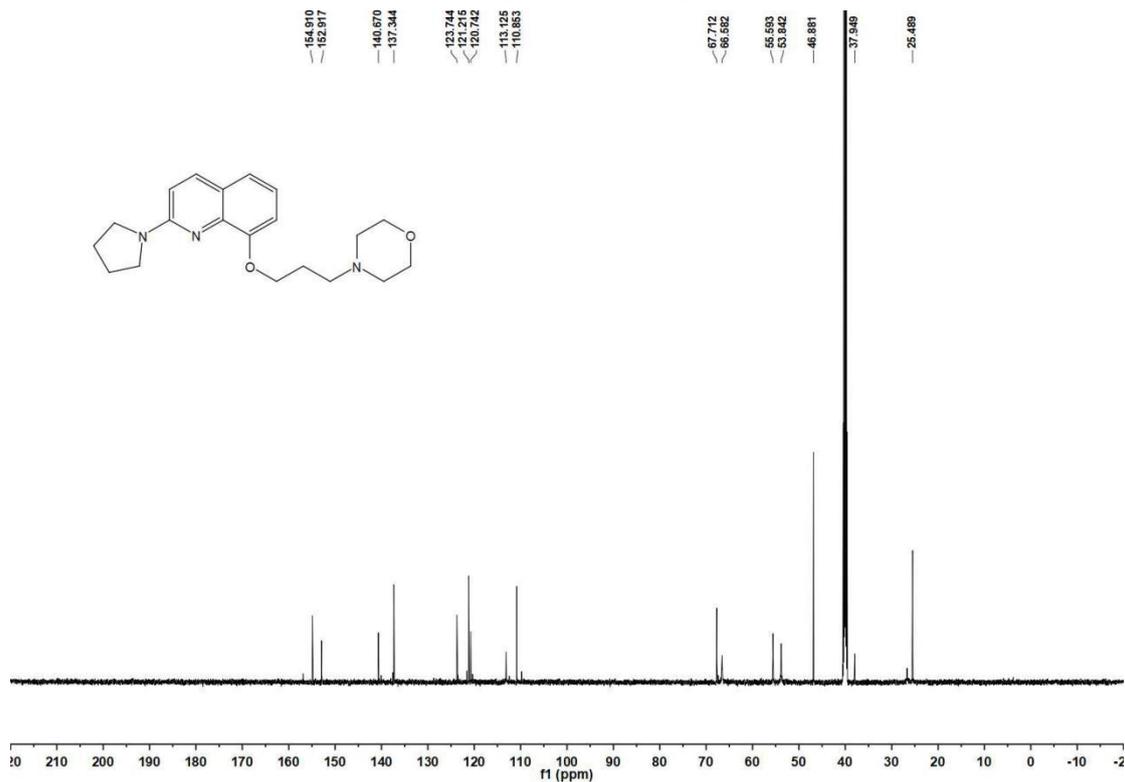
The ^{13}C NMR spectra of compound I-6u



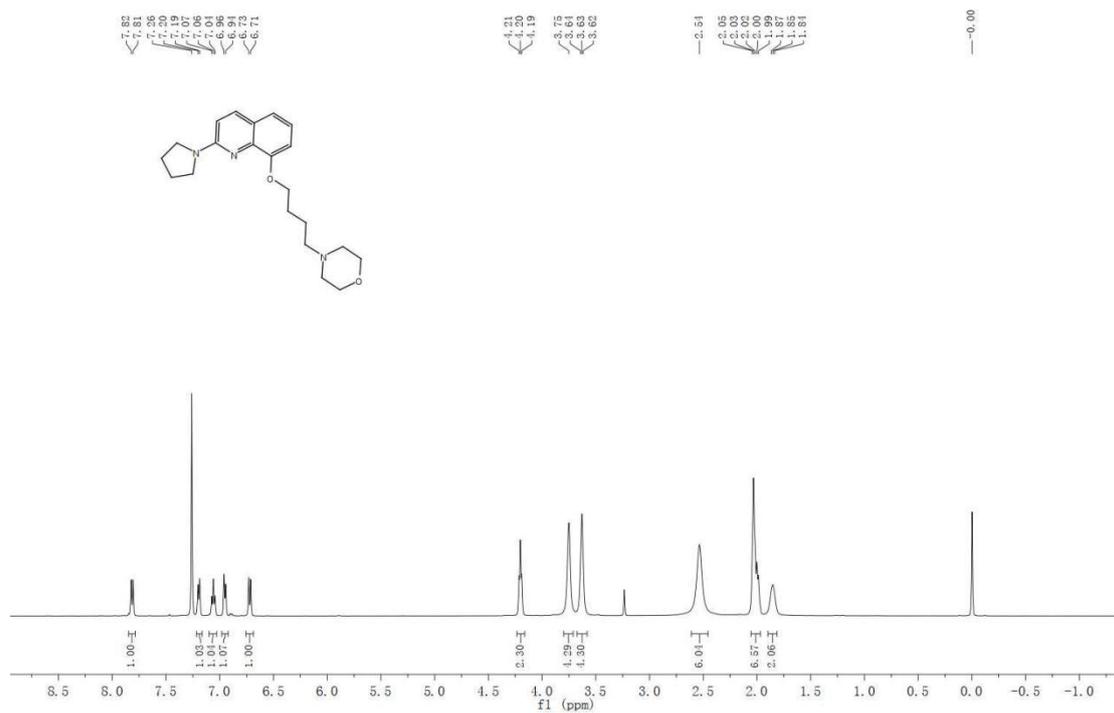
The HR-MS spectra of compound I-6u



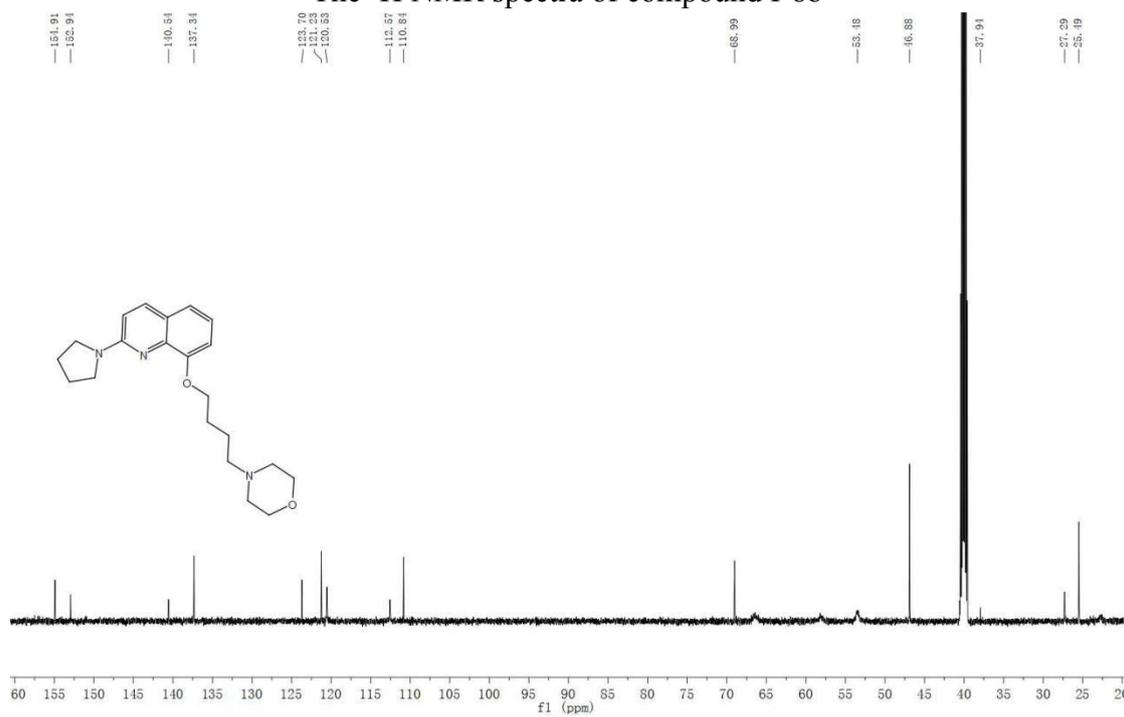
The ¹H NMR spectra of compound I-8a



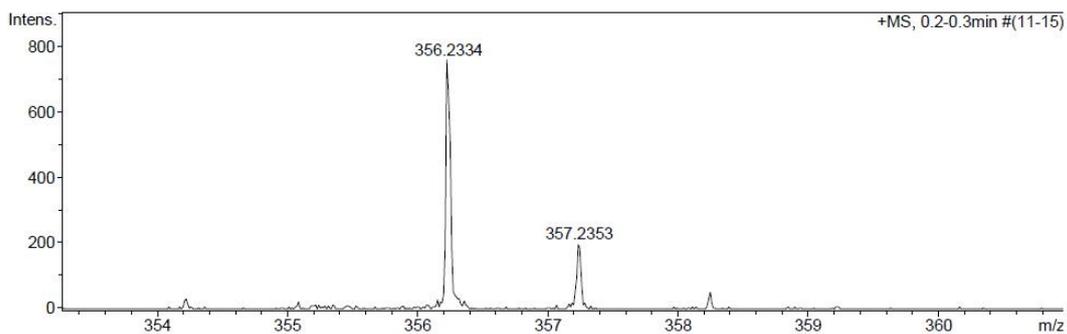
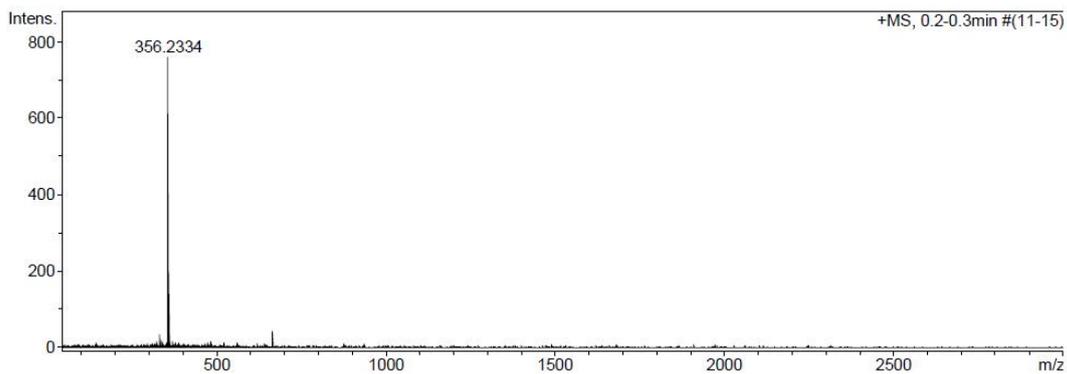
The ¹³C NMR spectra of compound I-8a



The ¹H NMR spectra of compound I-8b



The ¹³C NMR spectra of compound I-8b



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The HR-MS spectra of compound I-8b

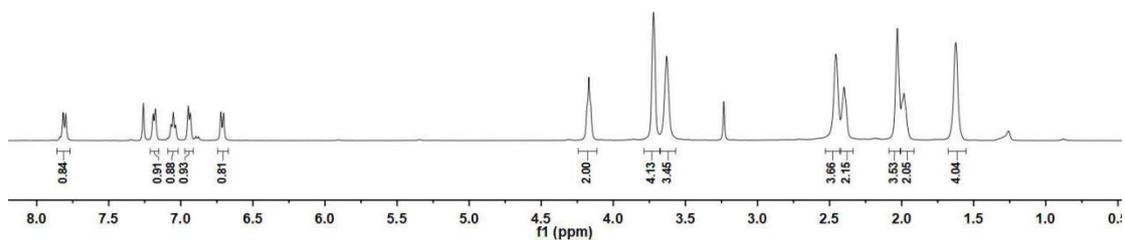
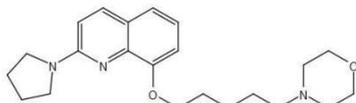
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7.798

7.260
7.192
7.176
7.068
7.052
7.036
6.949
6.933
6.772
6.704

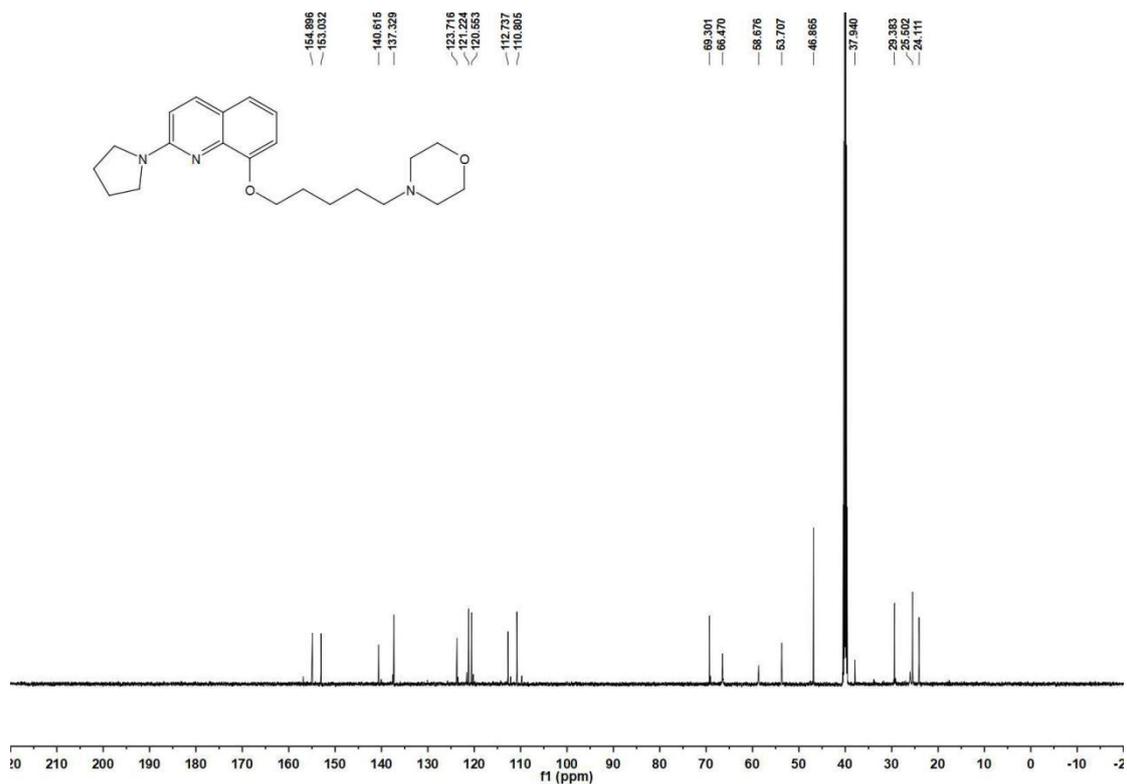
4.183
4.170
4.156

3.720
3.721
3.711
3.630

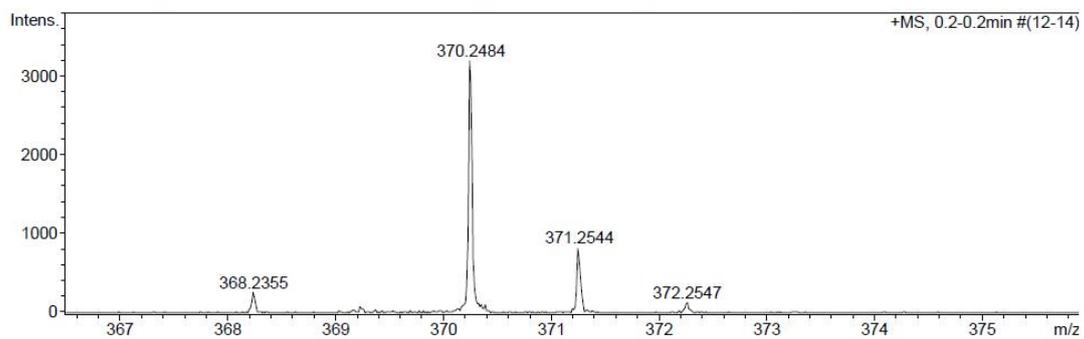
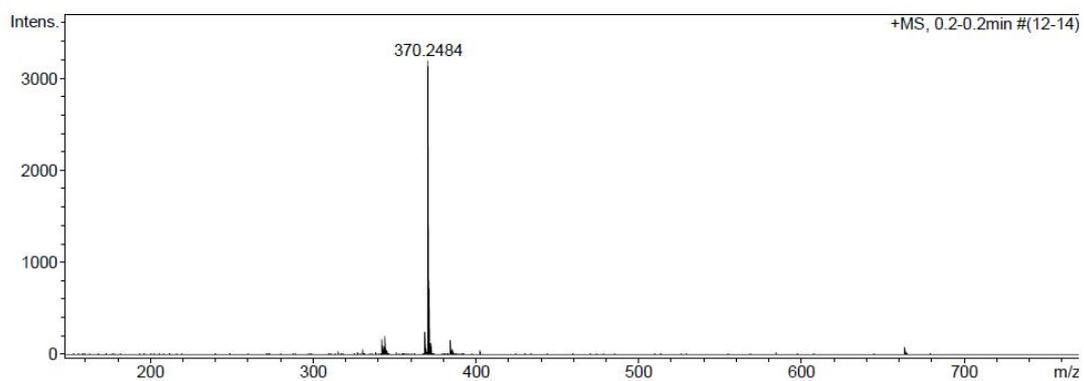
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2.411
2.398
2.384
2.042
2.030
2.017
1.988
1.970
1.629
1.616



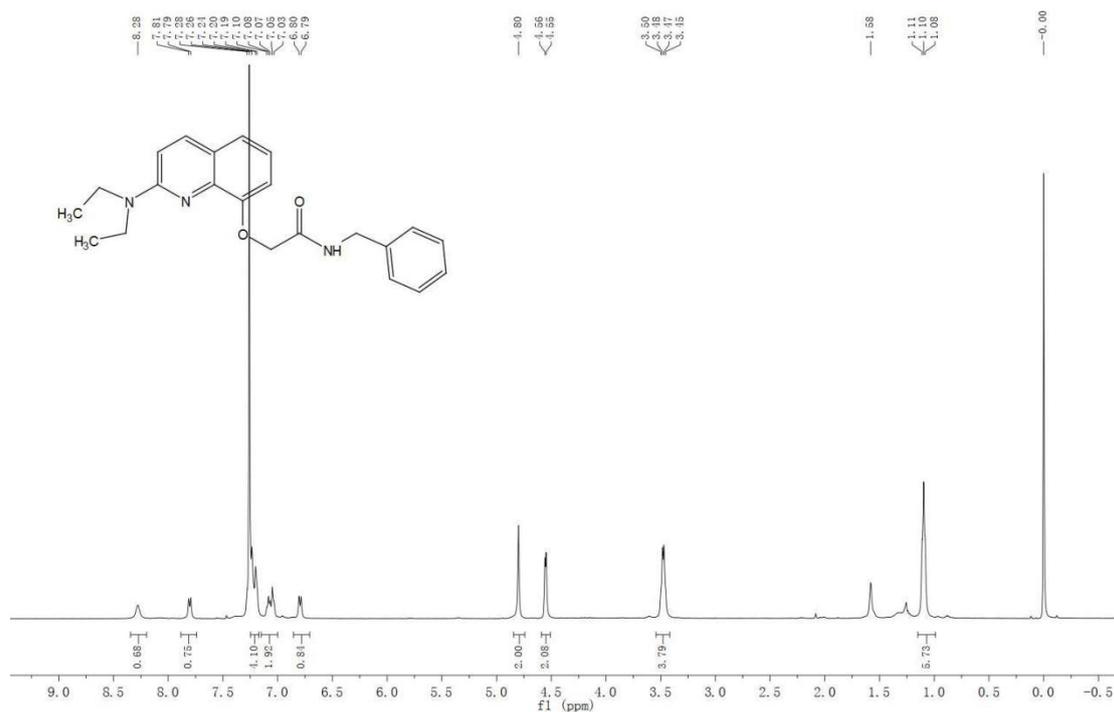
The ¹H NMR spectra of compound I-8c



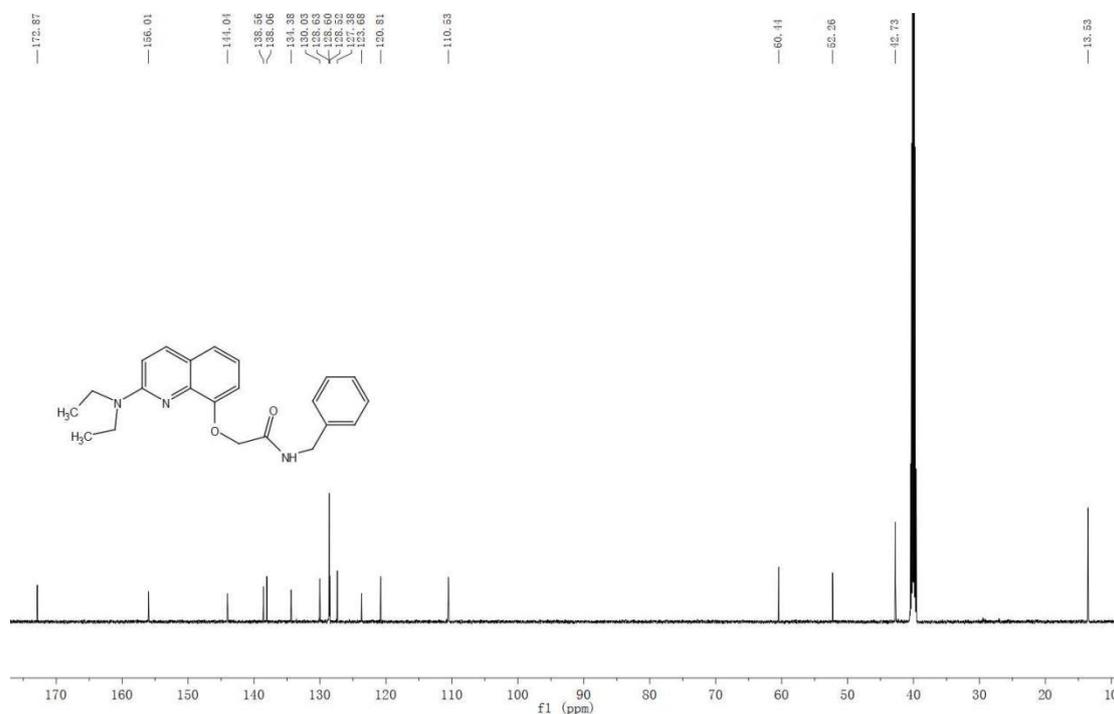
The ^{13}C NMR spectra of compound I-8c



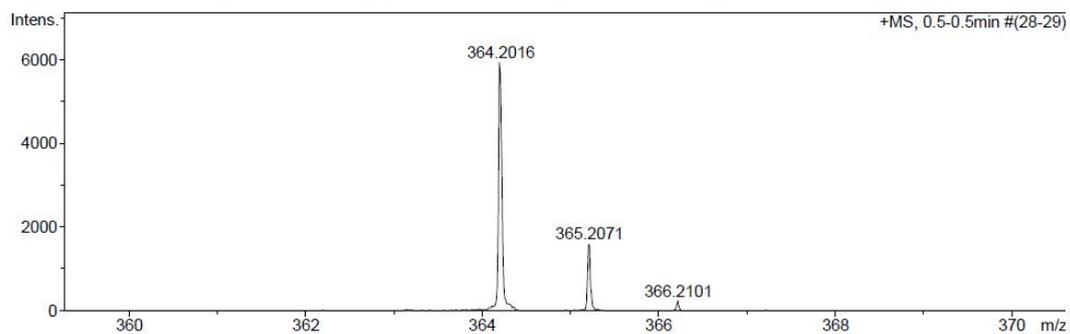
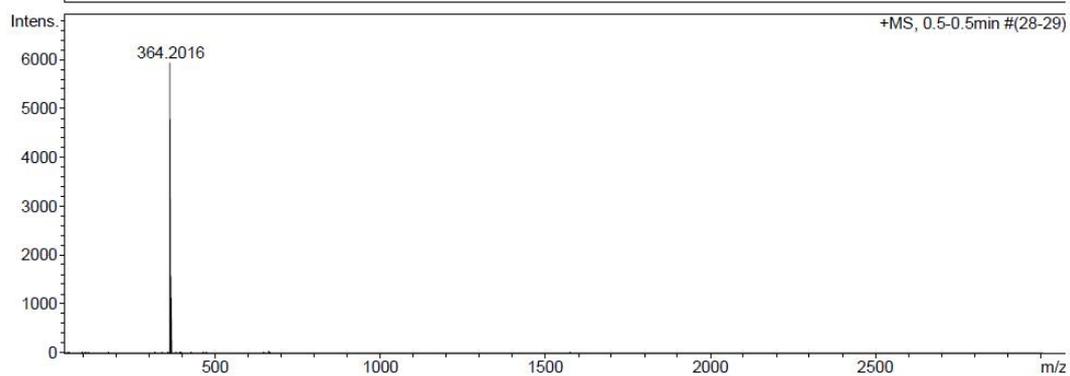
The HR-MS spectra of compound I-8c



The ¹H NMR spectra of compound I-13a



The ¹³C NMR spectra of compound I-13a

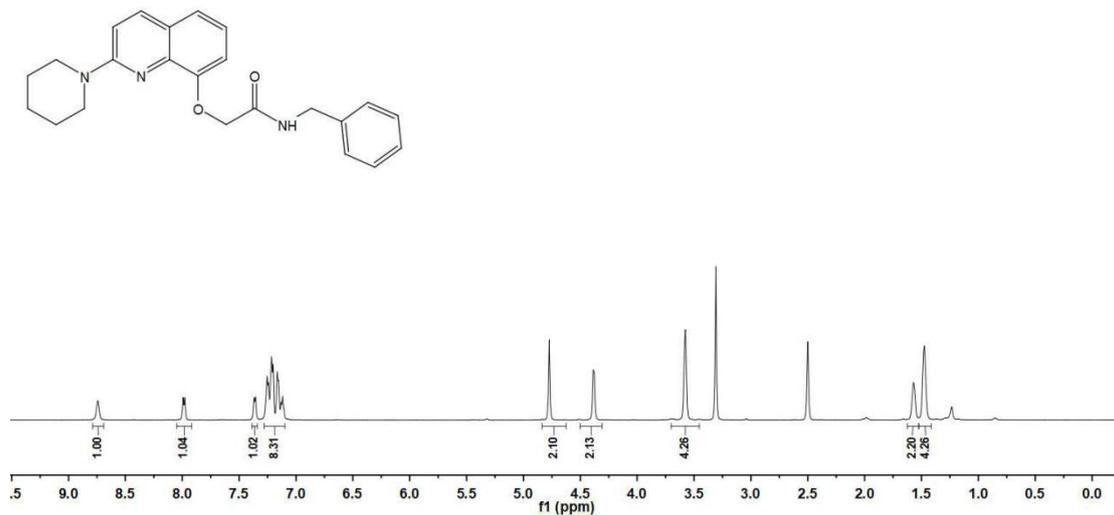
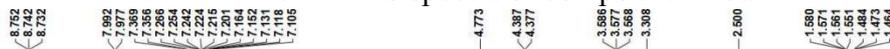


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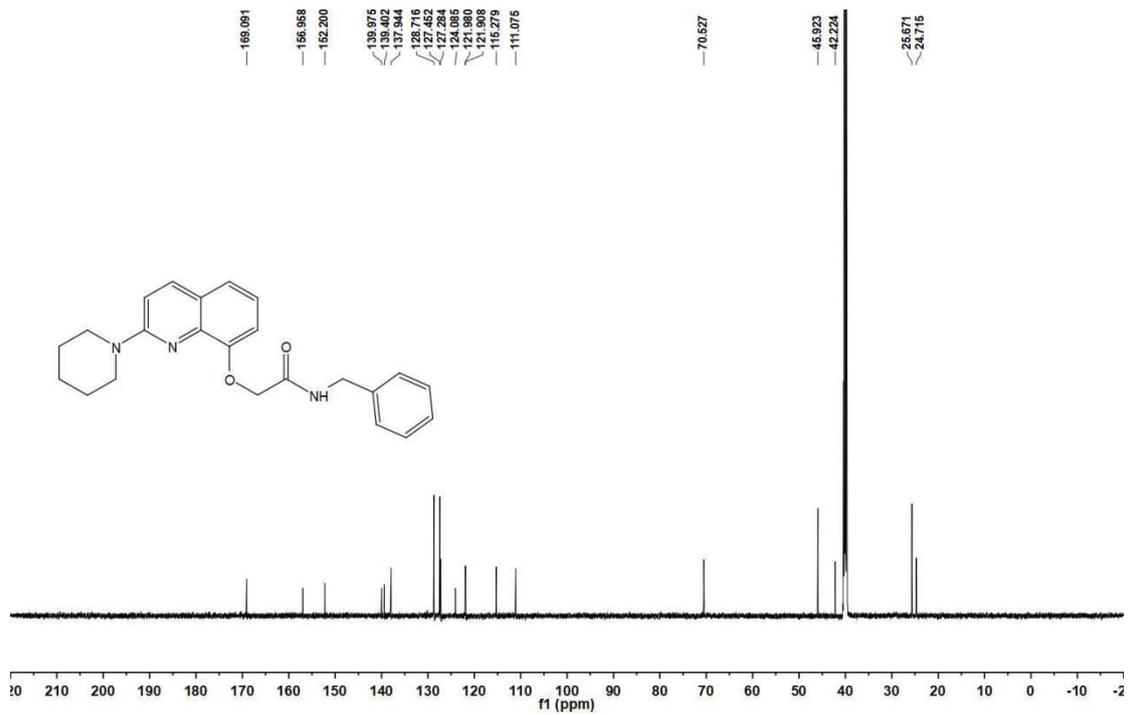
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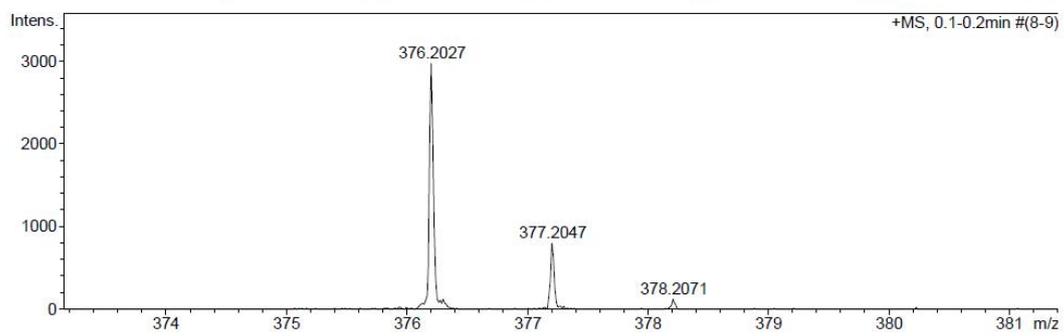
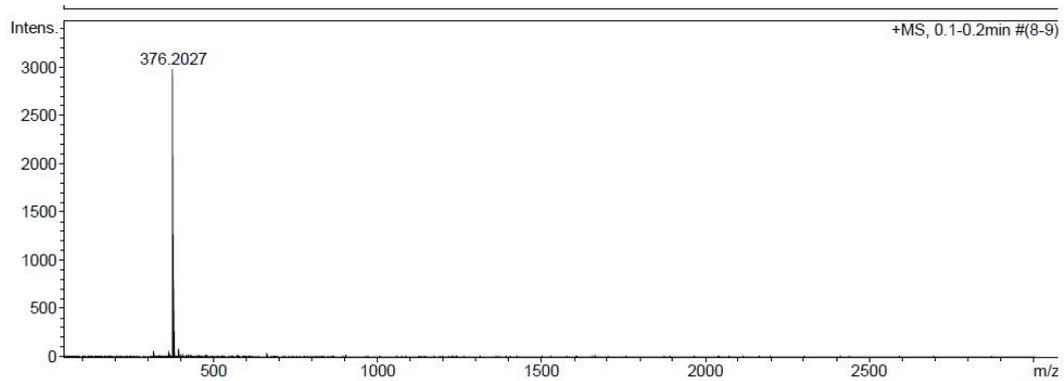
The HR-MS spectra of compound I-13a



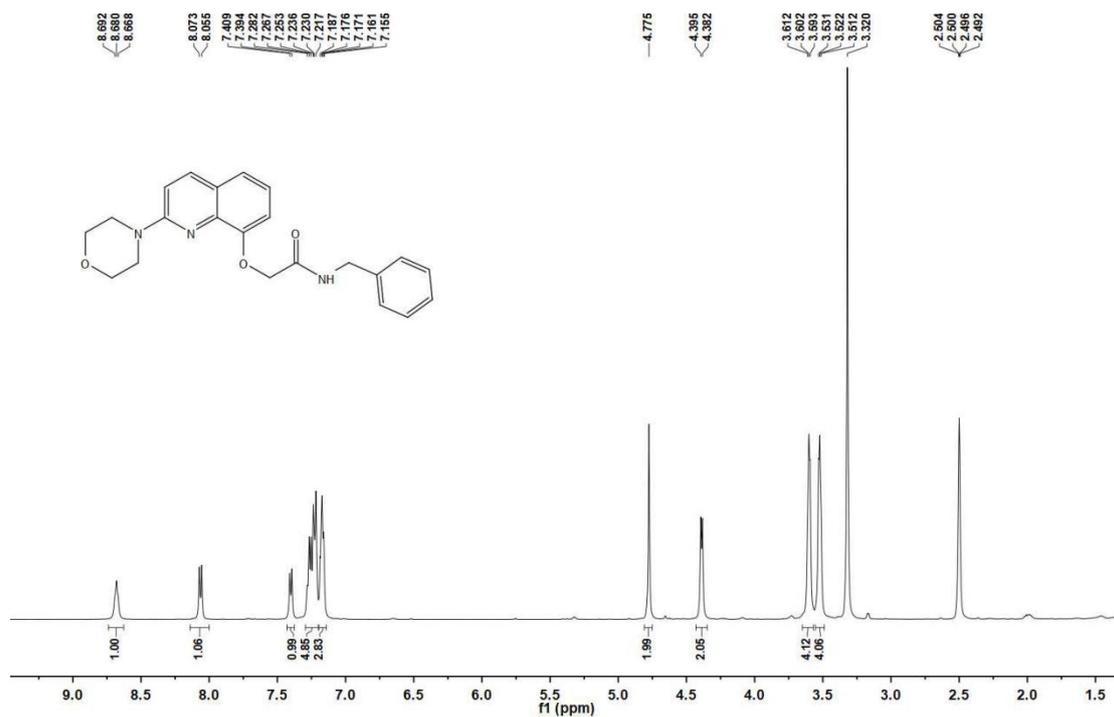
The ¹H NMR spectra of compound I-13b



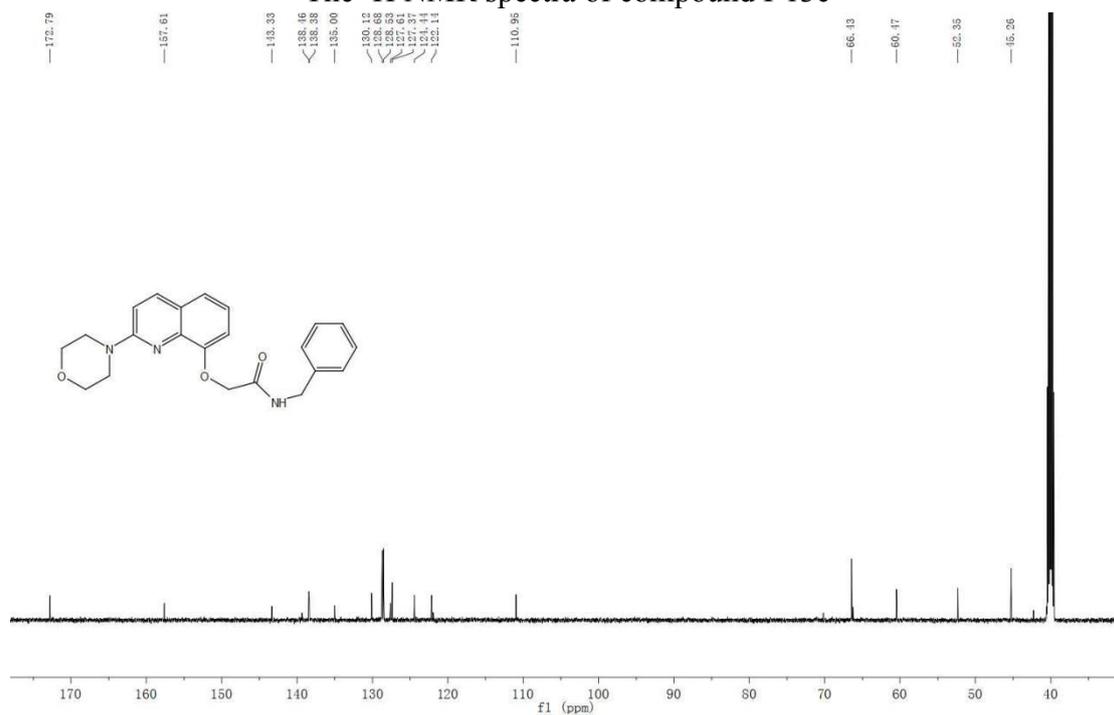
The ^{13}C NMR spectra of compound I-13b



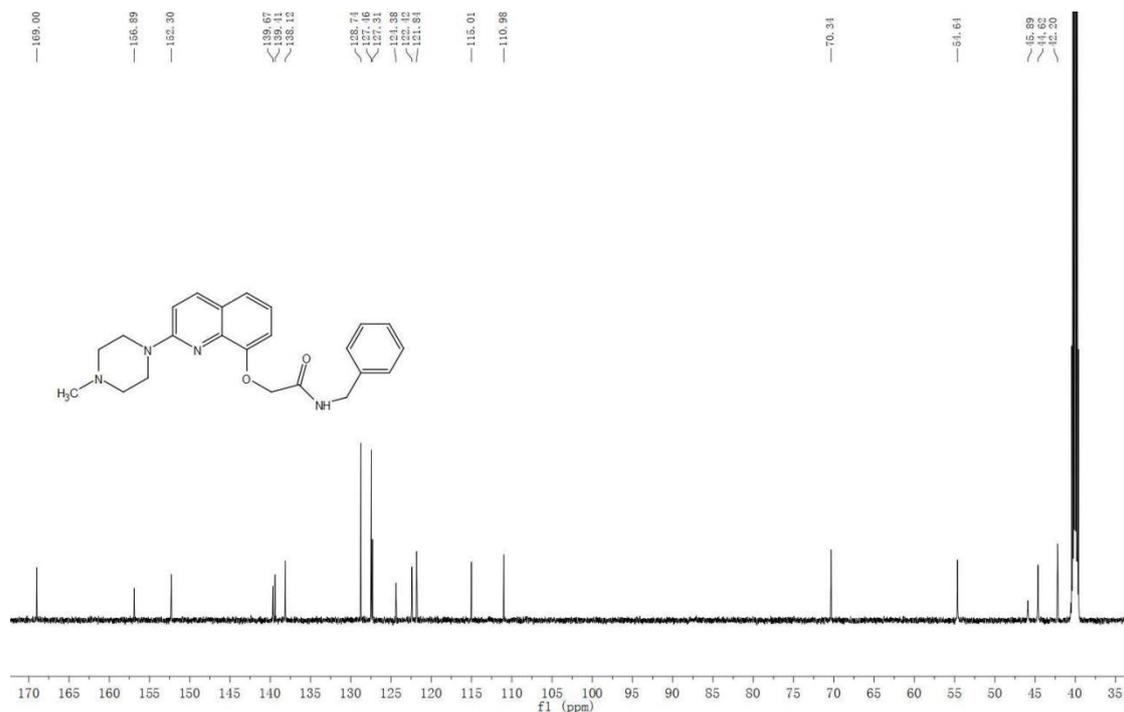
The HR-MS spectra of compound I-13b



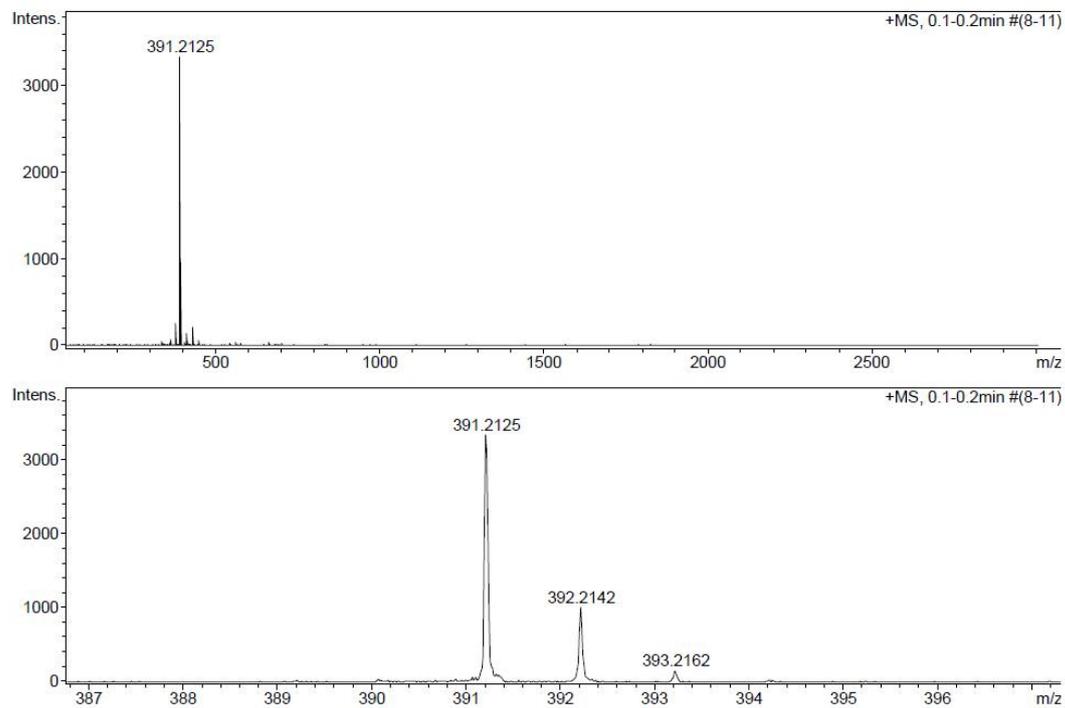
The ¹H NMR spectra of compound I-13c



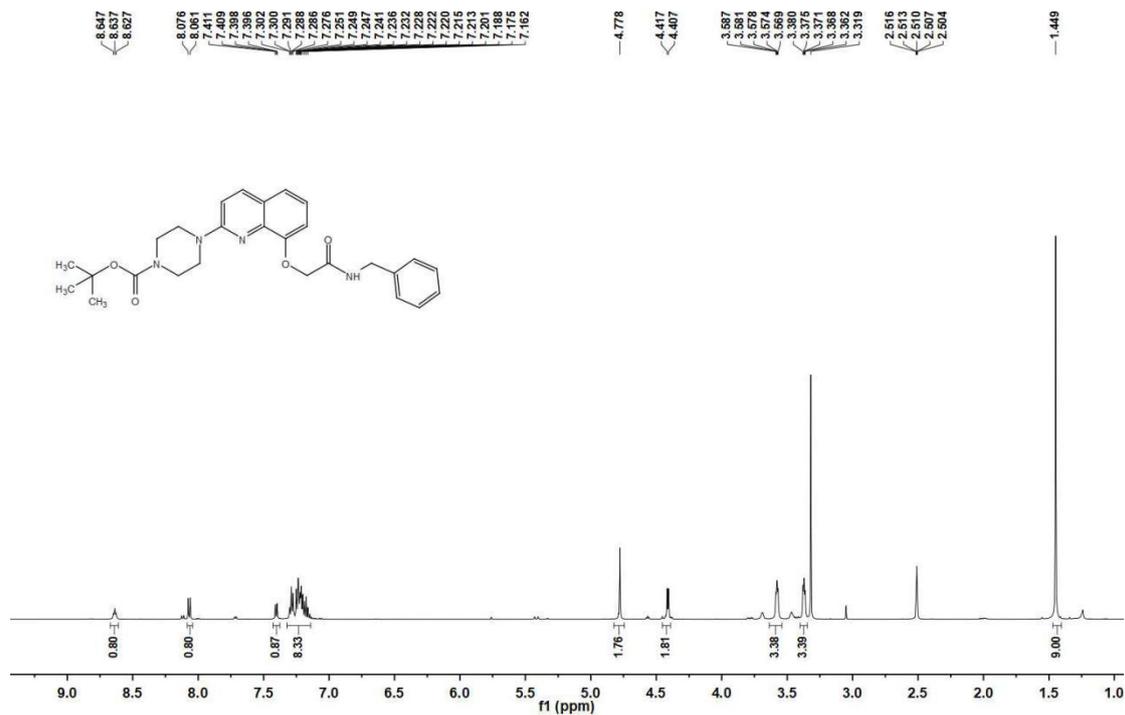
The ¹³C NMR spectra of compound I-13c



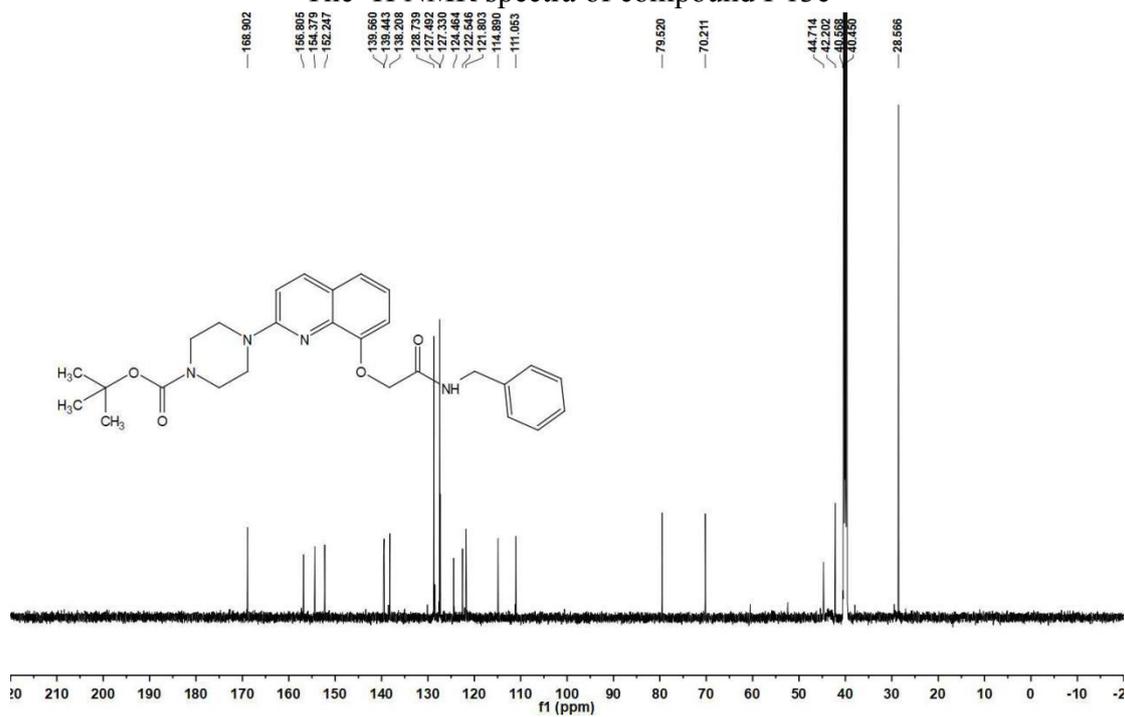
The ¹³C NMR spectra of compound I-13d



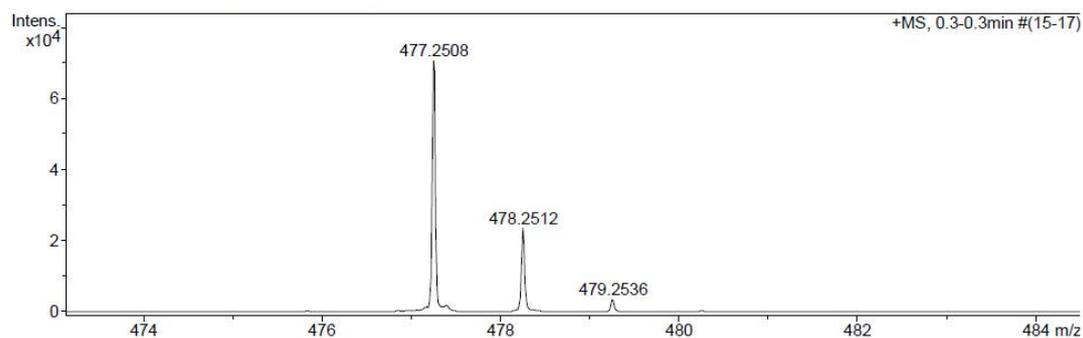
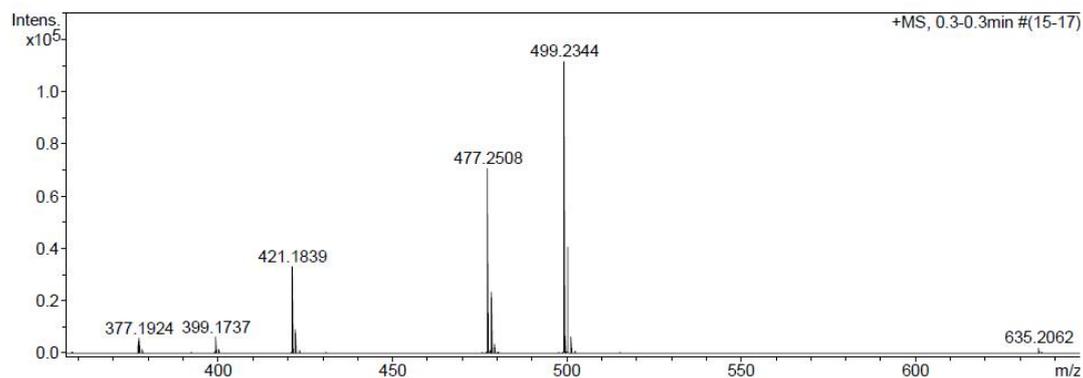
The HR-MS spectra of compound I-13d



The ¹H NMR spectra of compound I-13e



The ¹³C NMR spectra of compound I-13e

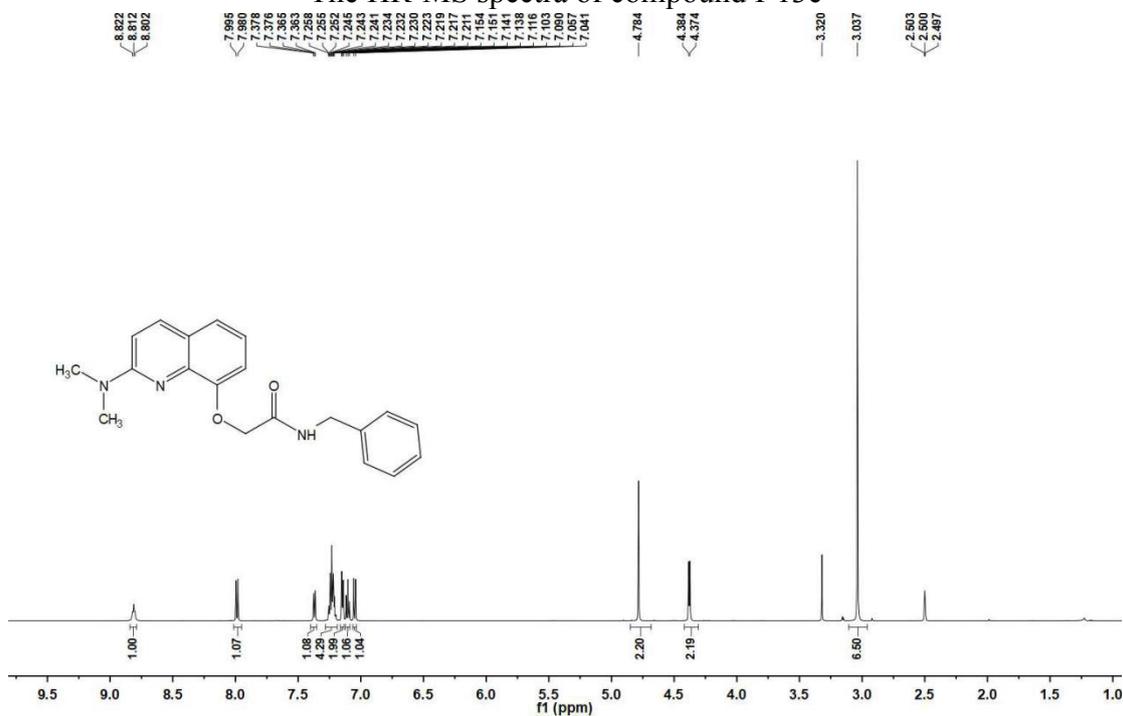


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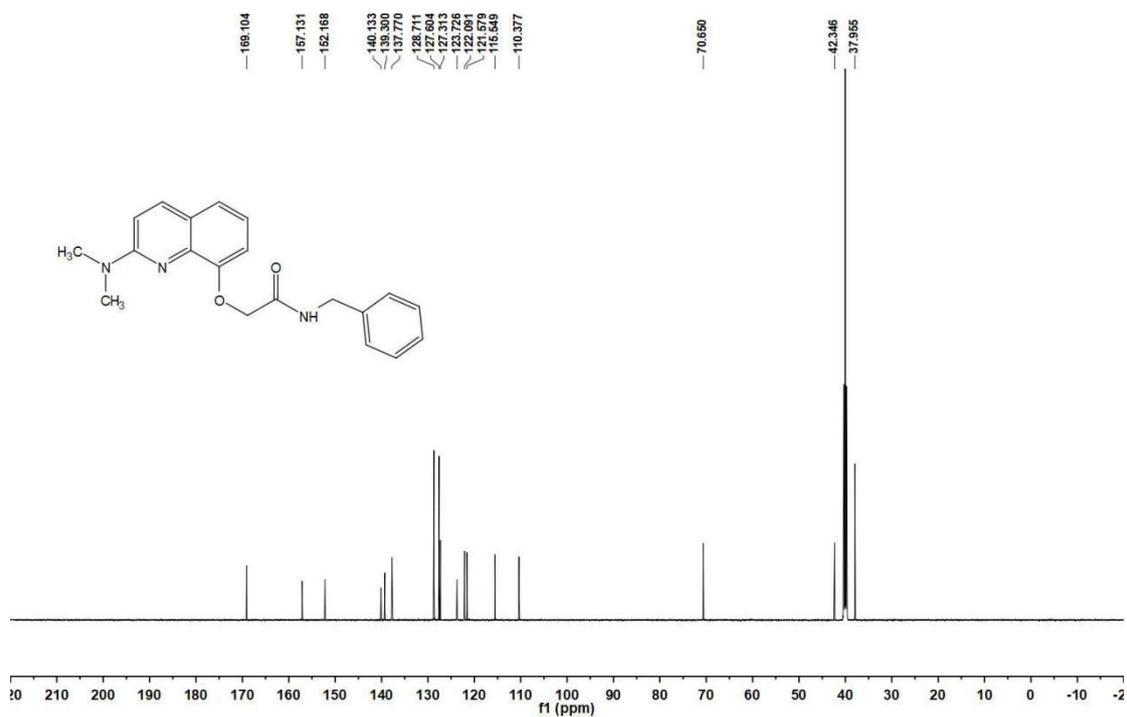
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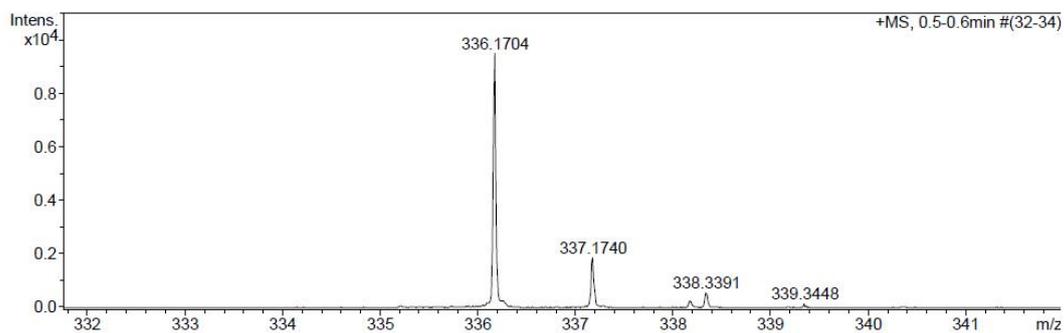
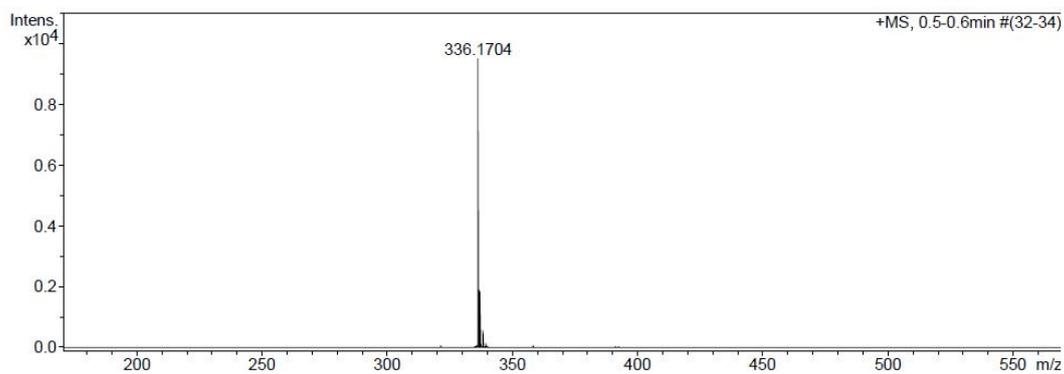
The HR-MS spectra of compound I-13e



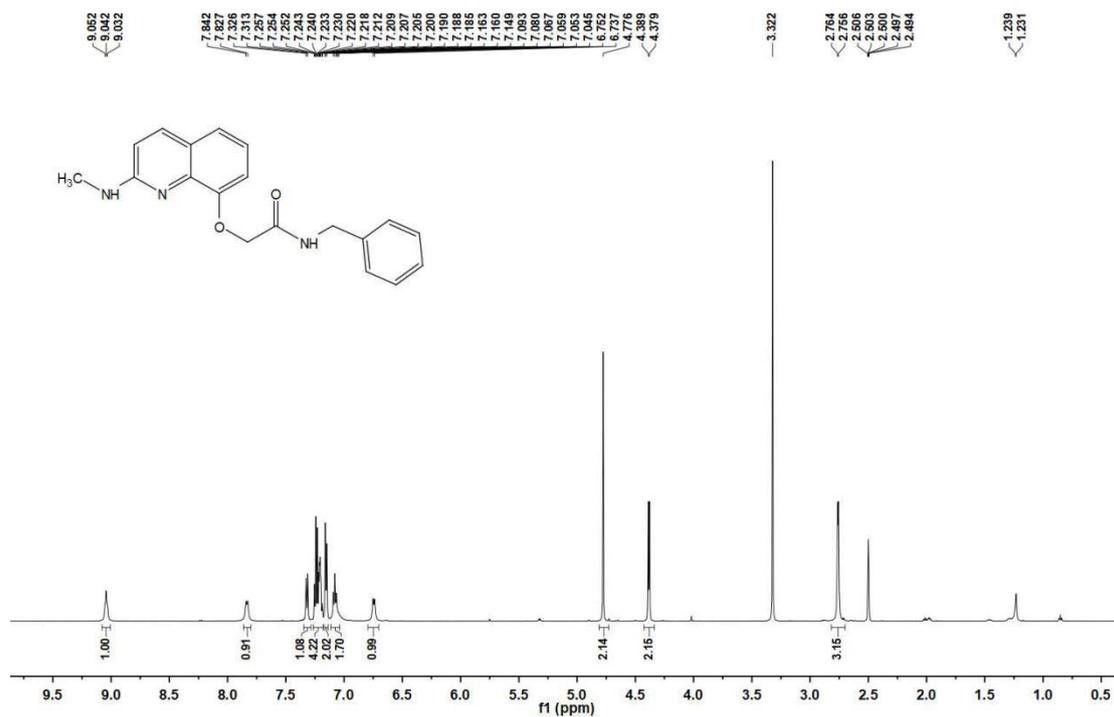
The ¹H NMR spectra of compound I-13f



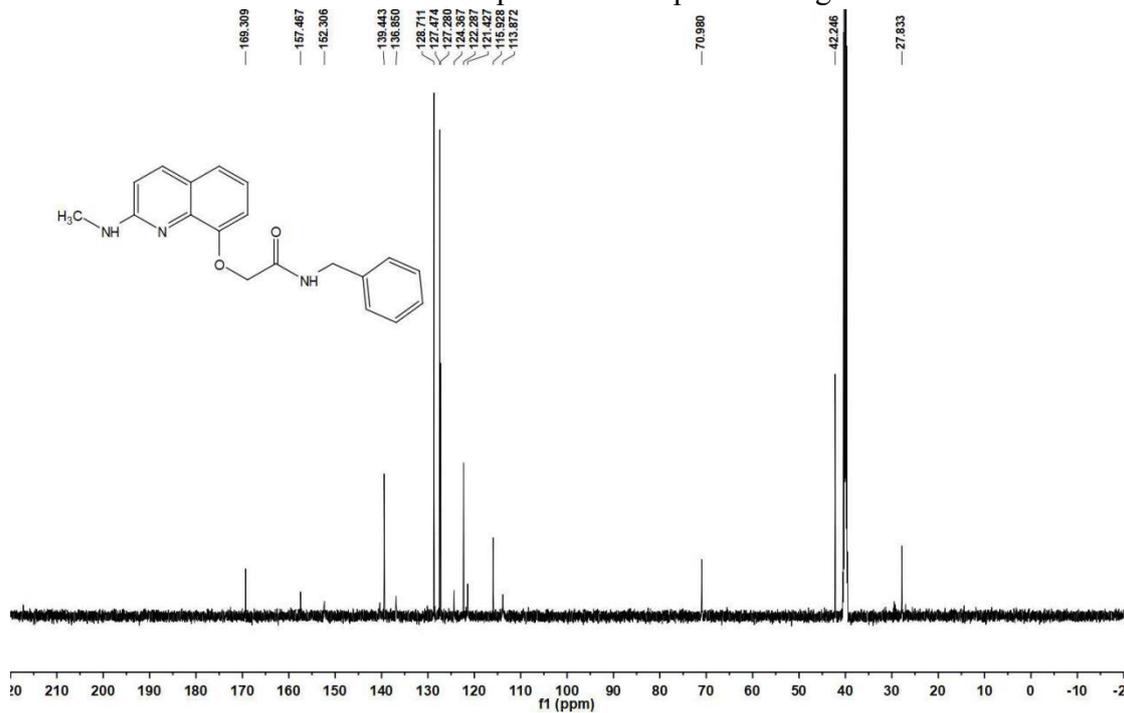
The ¹³C NMR spectra of compound I-13f



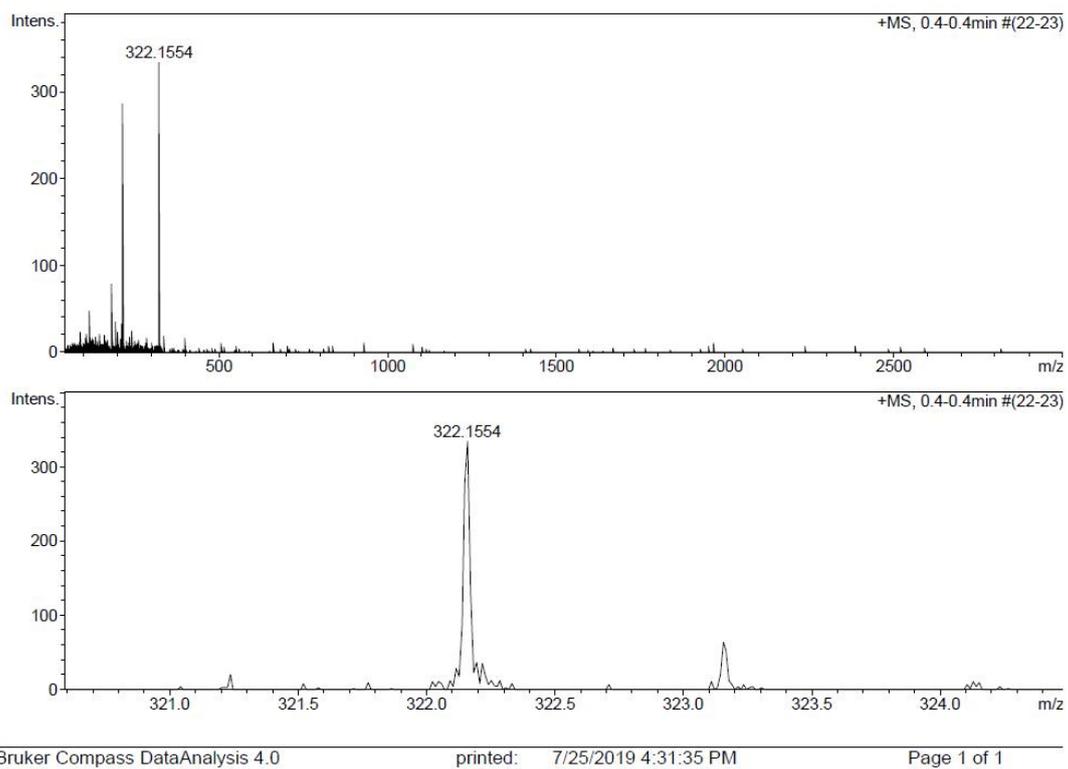
The HR-MS spectra of compound I-13f



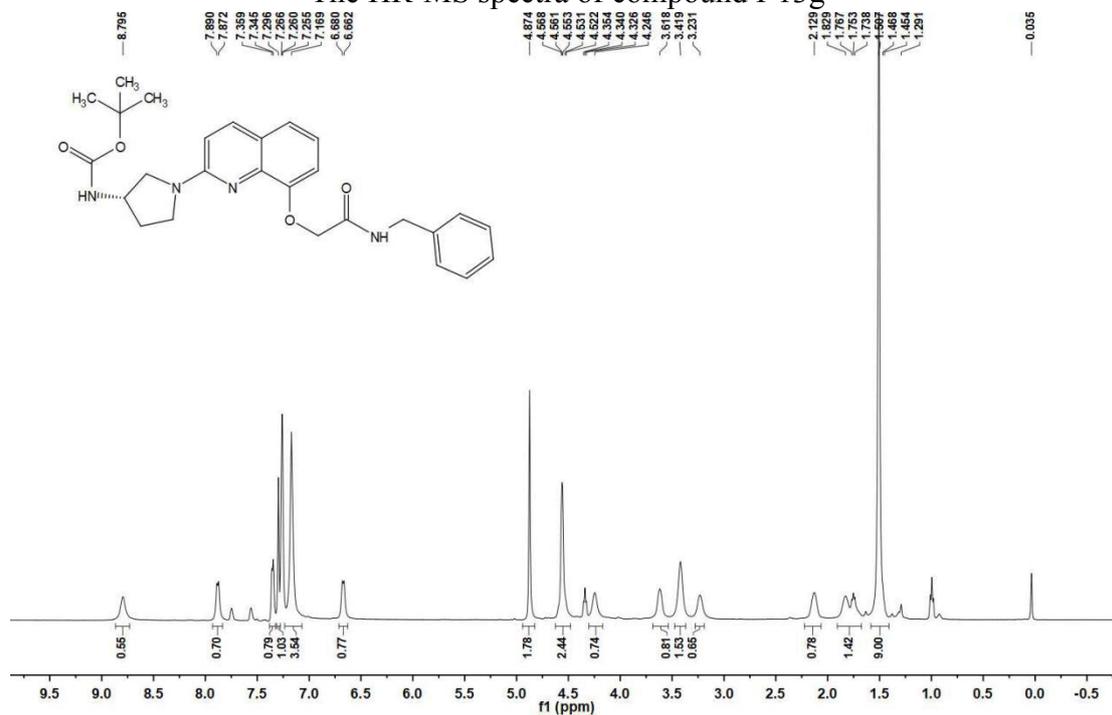
The ^1H NMR spectra of compound I-13g



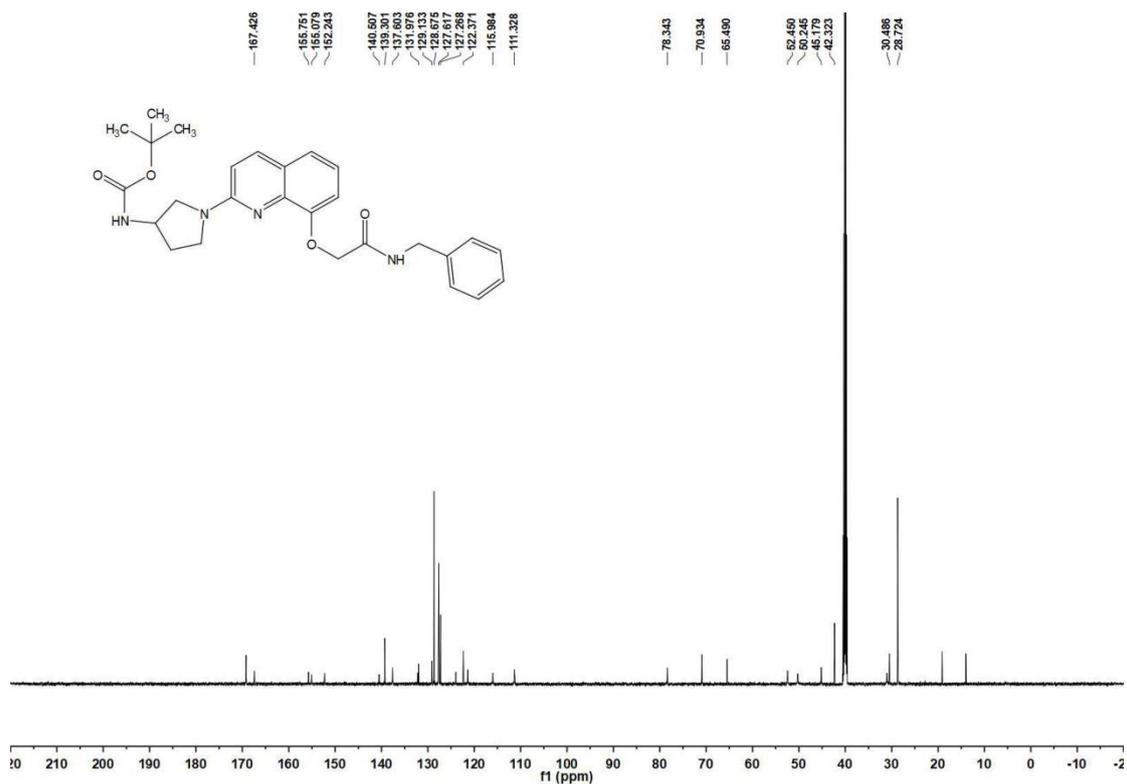
The ^{13}C NMR spectra of compound I-13g



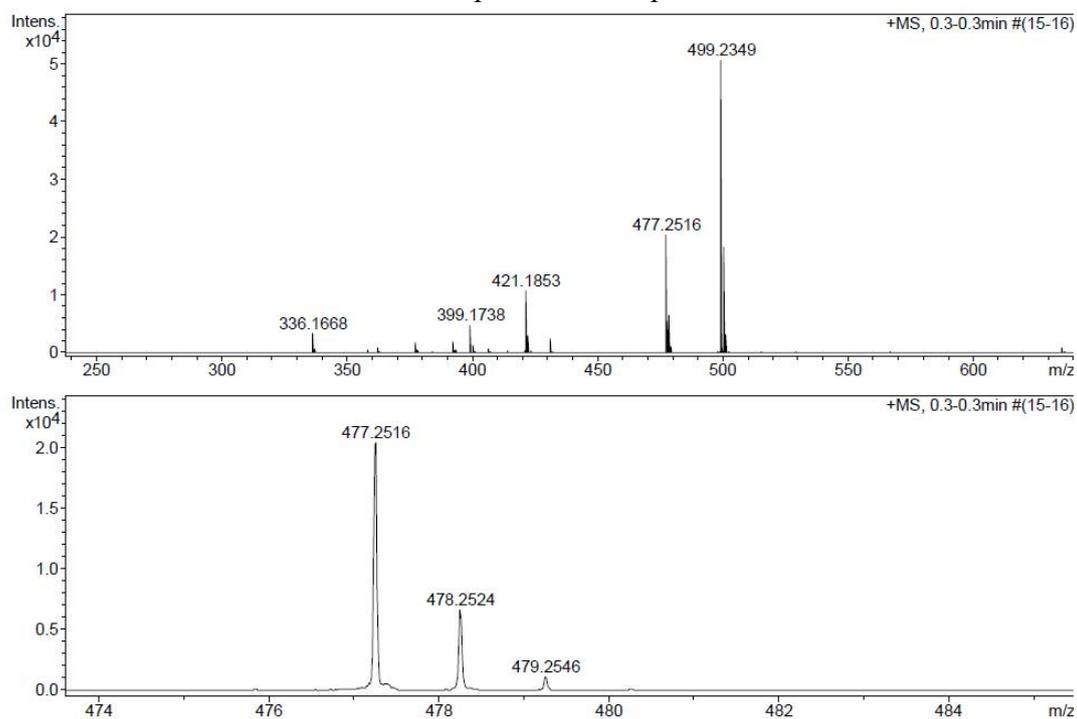
The HR-MS spectra of compound I-13g



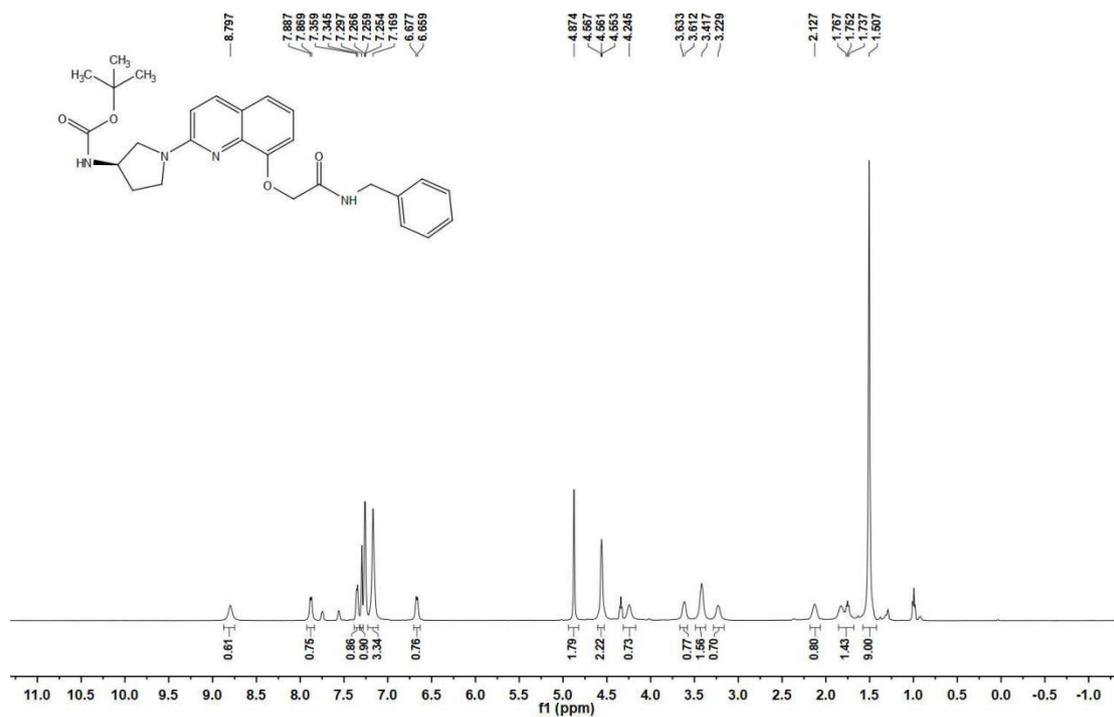
The ¹H NMR spectra of compound I-13h



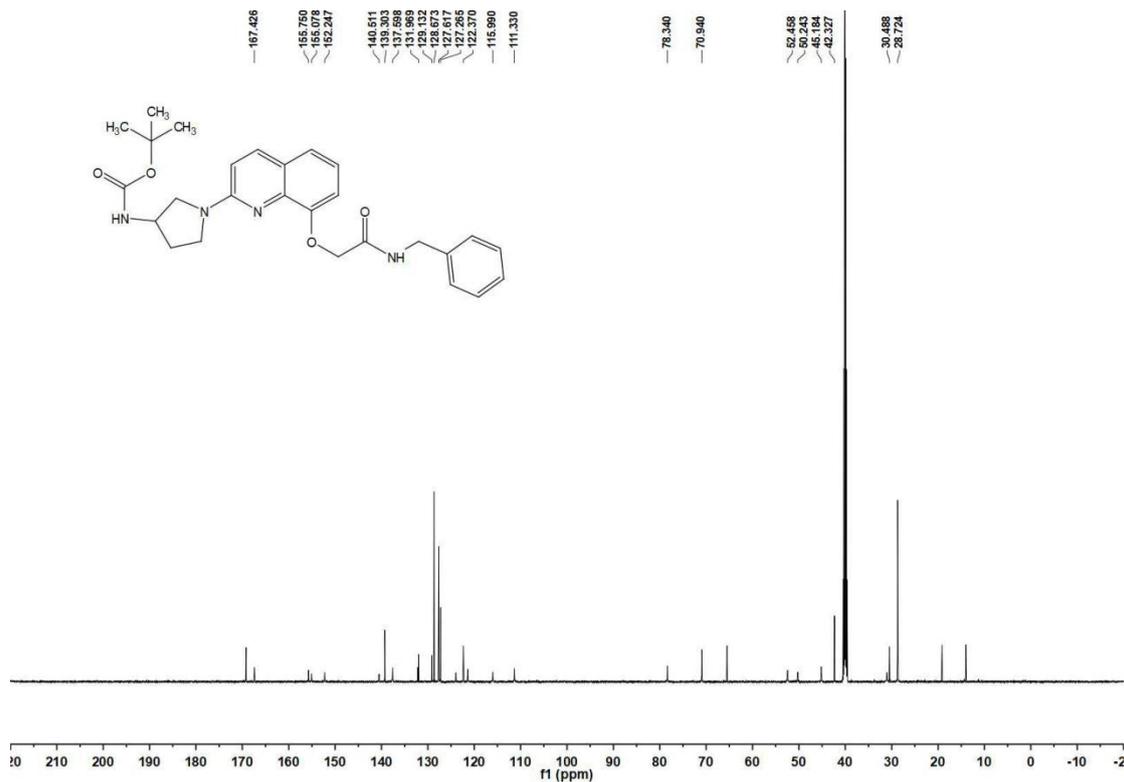
The ¹³C NMR spectra of compound I-13h



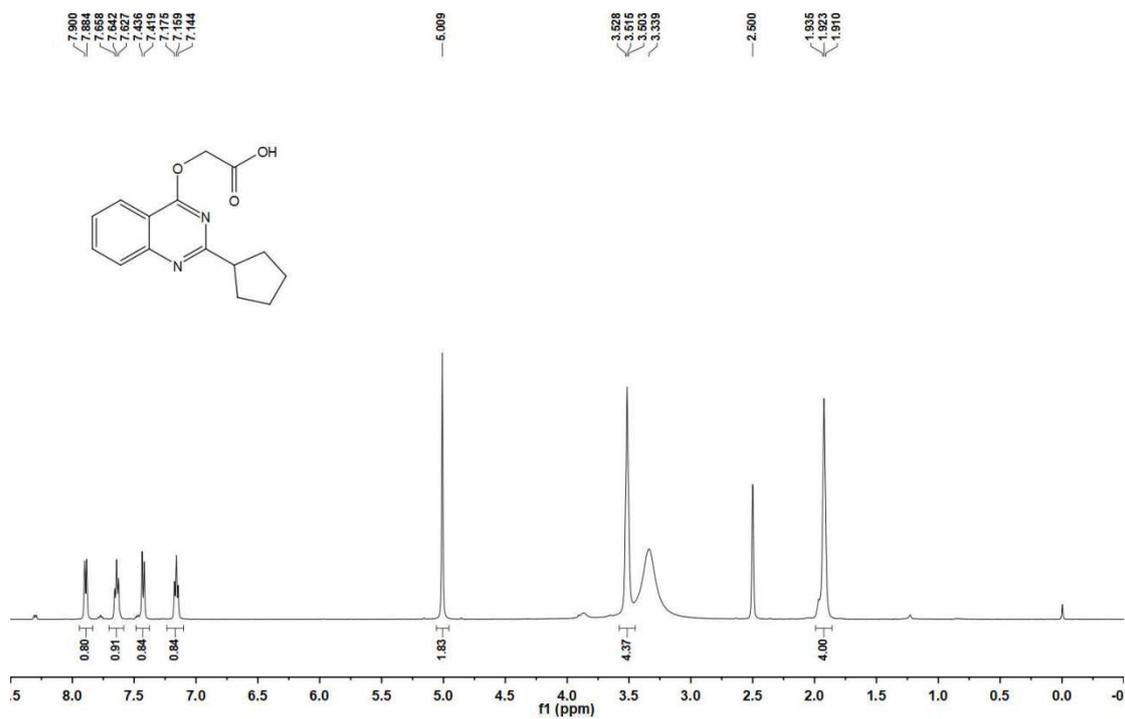
The HR-MS spectra of compound I-13h



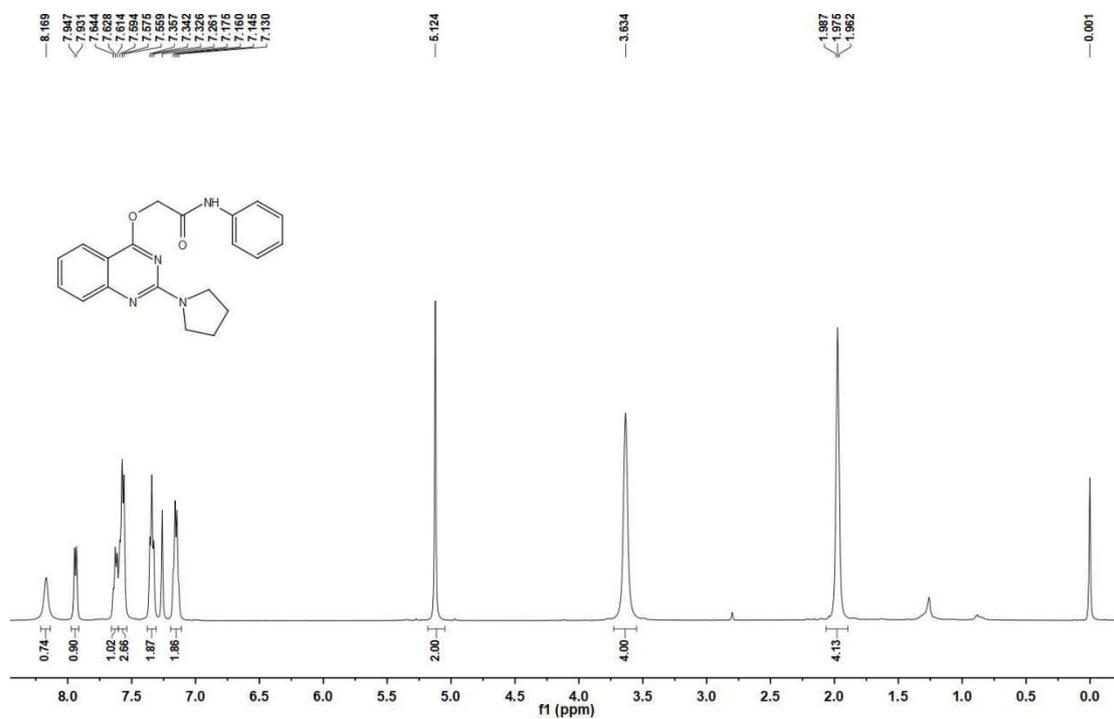
The ¹H NMR spectra of compound I-13i



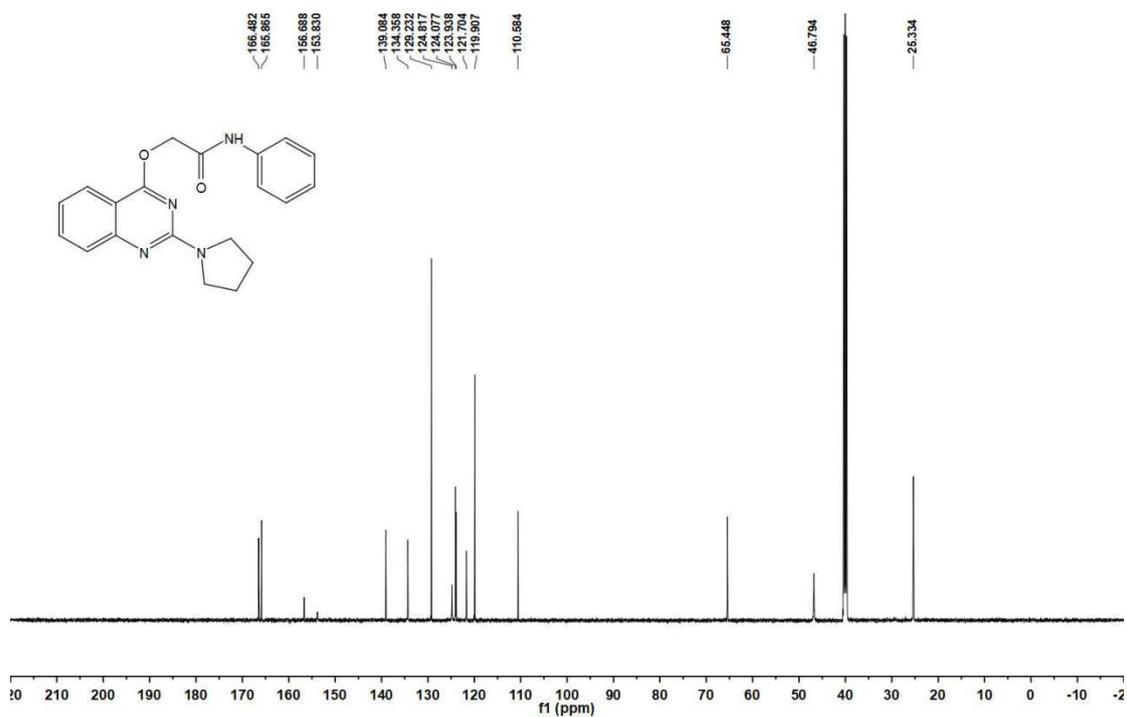
The ¹³C NMR spectra of compound I-13i



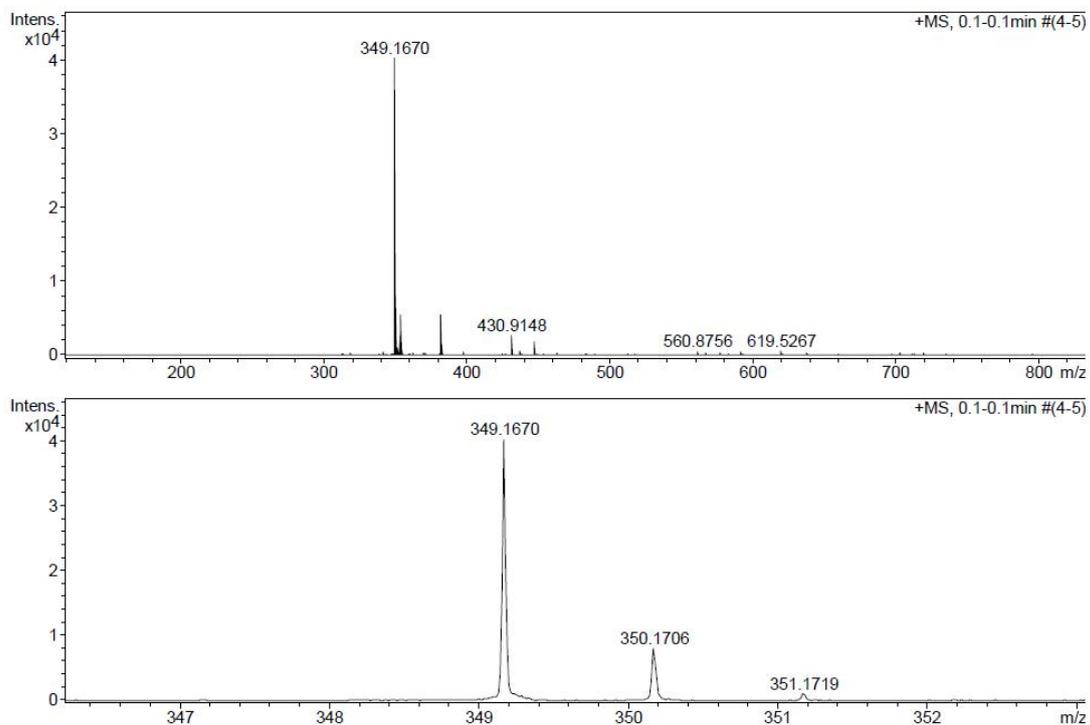
The ¹H NMR spectra of compound II-6a



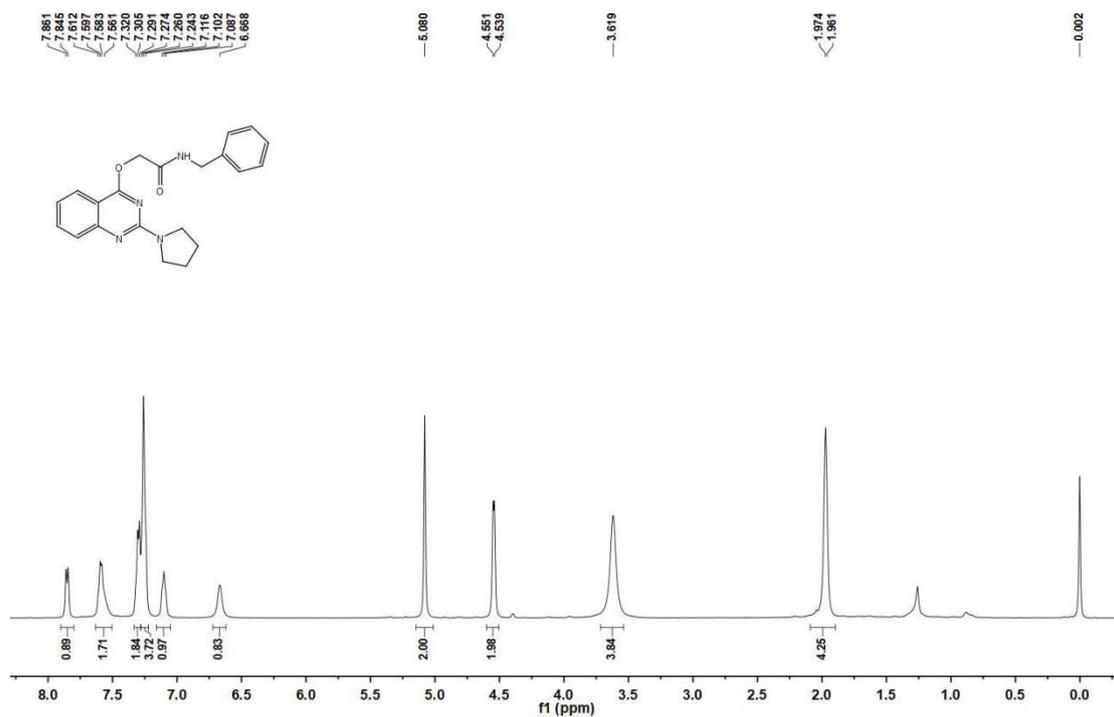
The ¹H NMR spectra of compound II-7a1



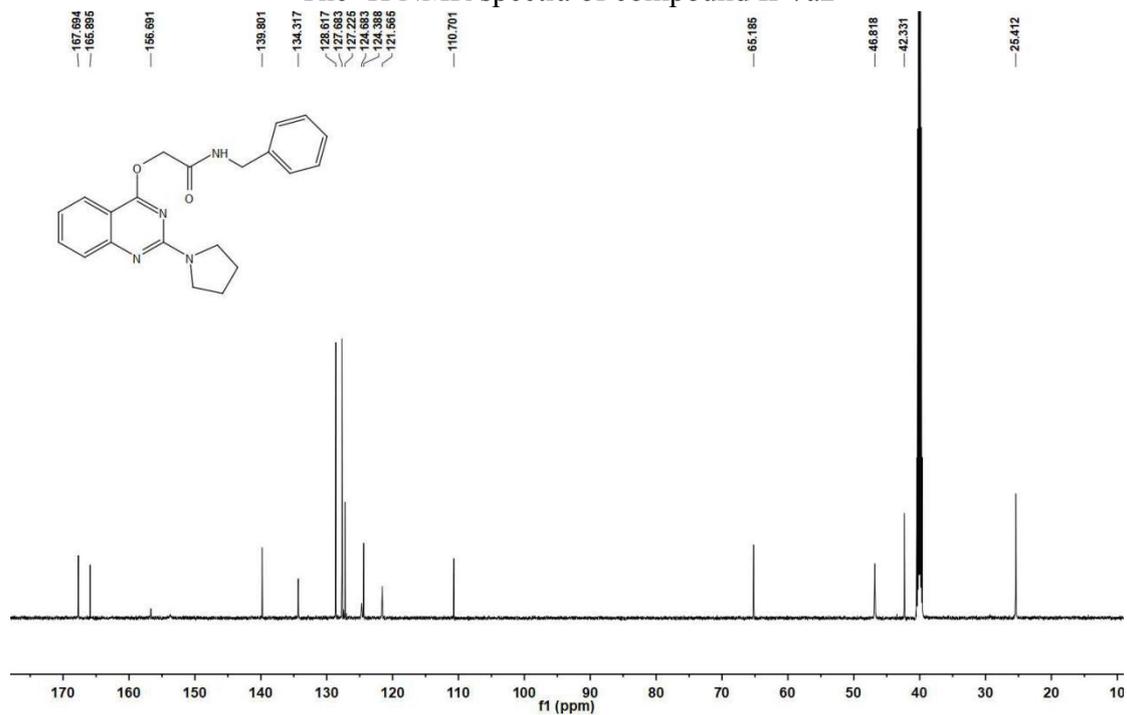
The ^{13}C NMR spectra of compound II-7a1



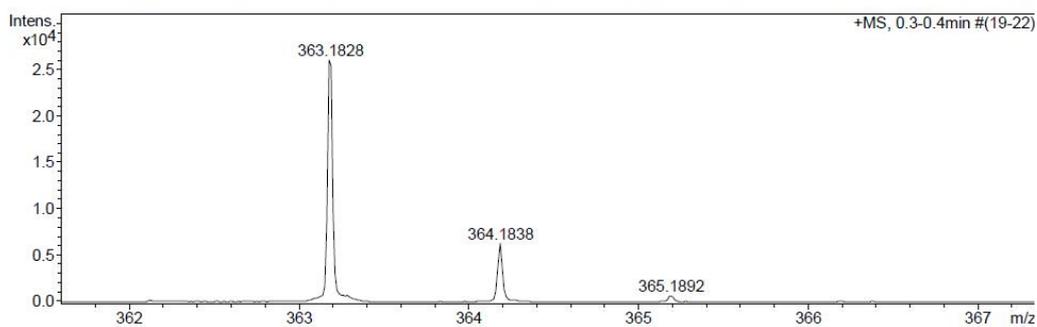
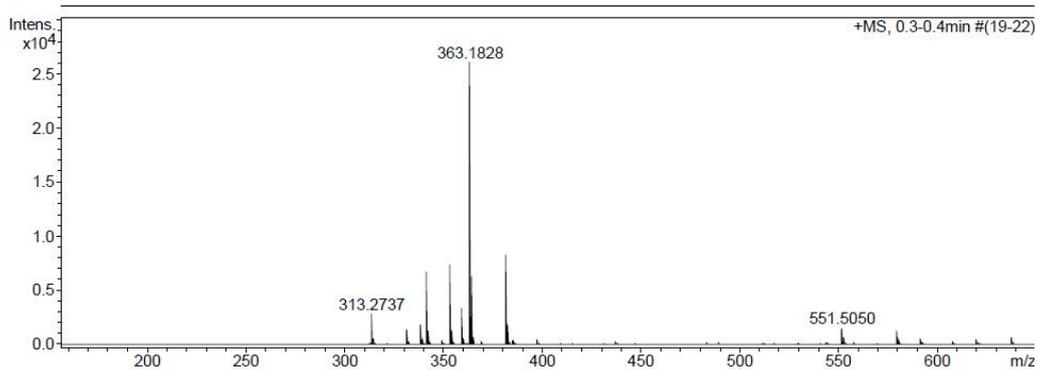
The HR-MS spectra of compound II-7a1



The ¹H NMR spectra of compound II-7a2



The ¹³C NMR spectra of compound II-7a2

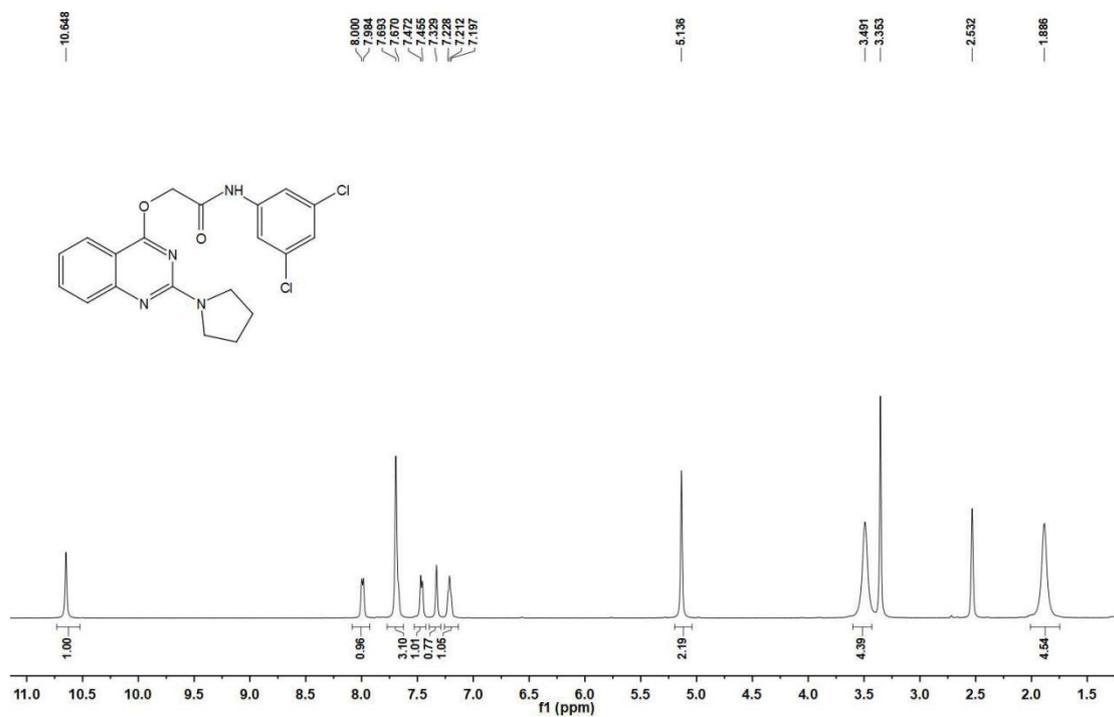


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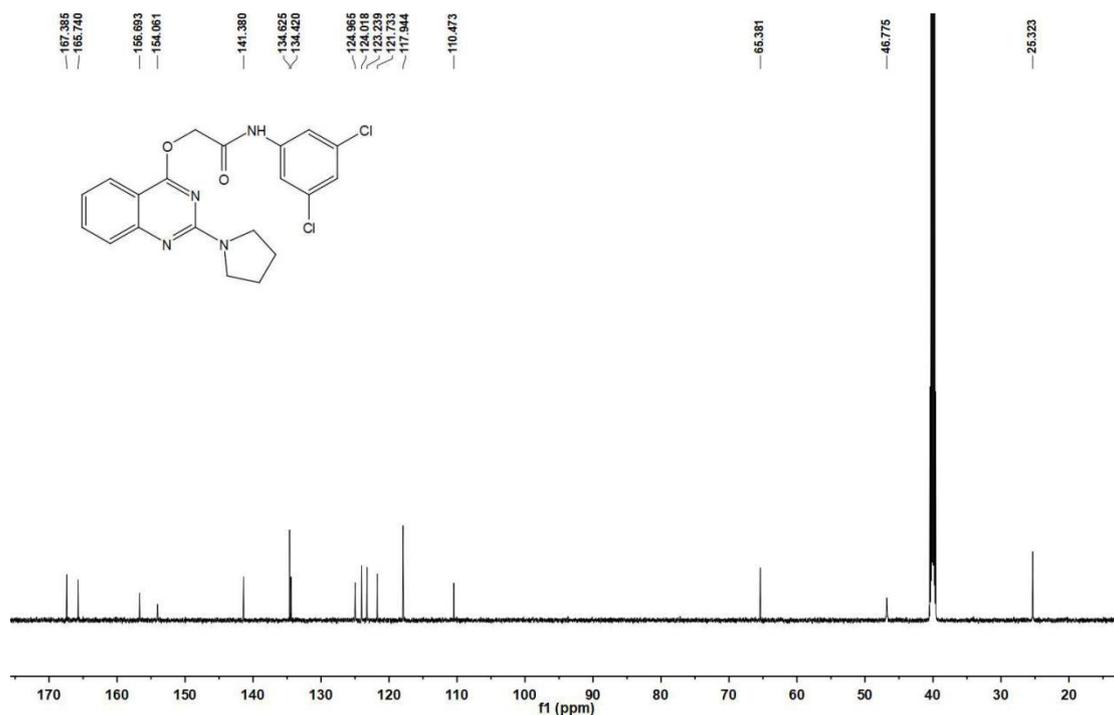
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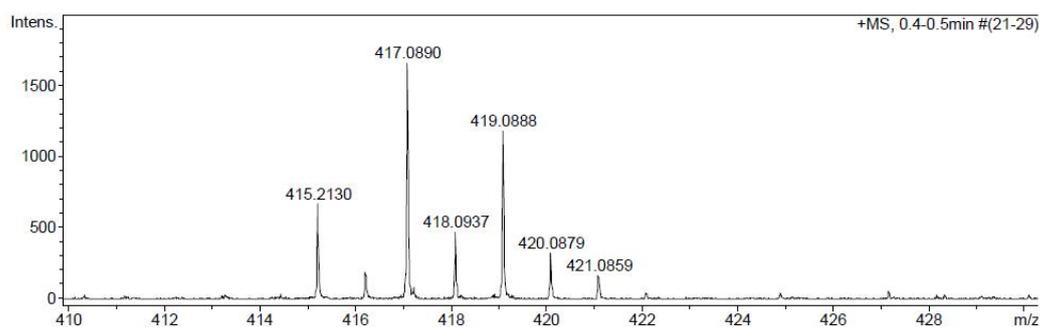
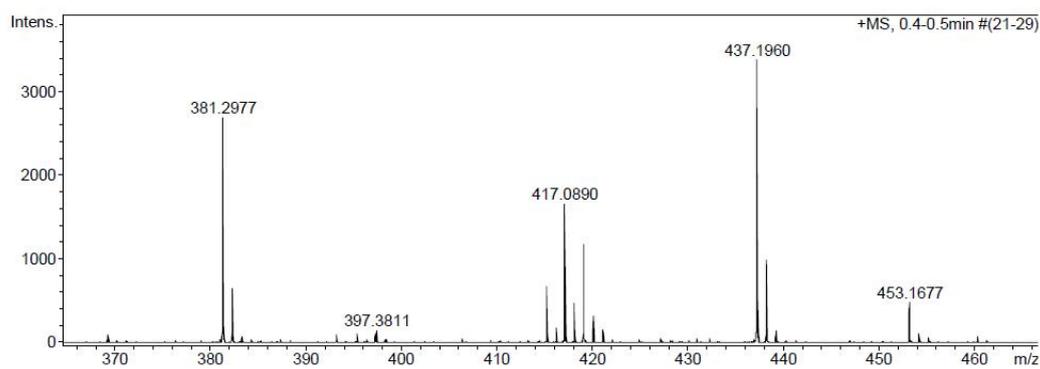
The HR-MS spectra of compound II-7a2



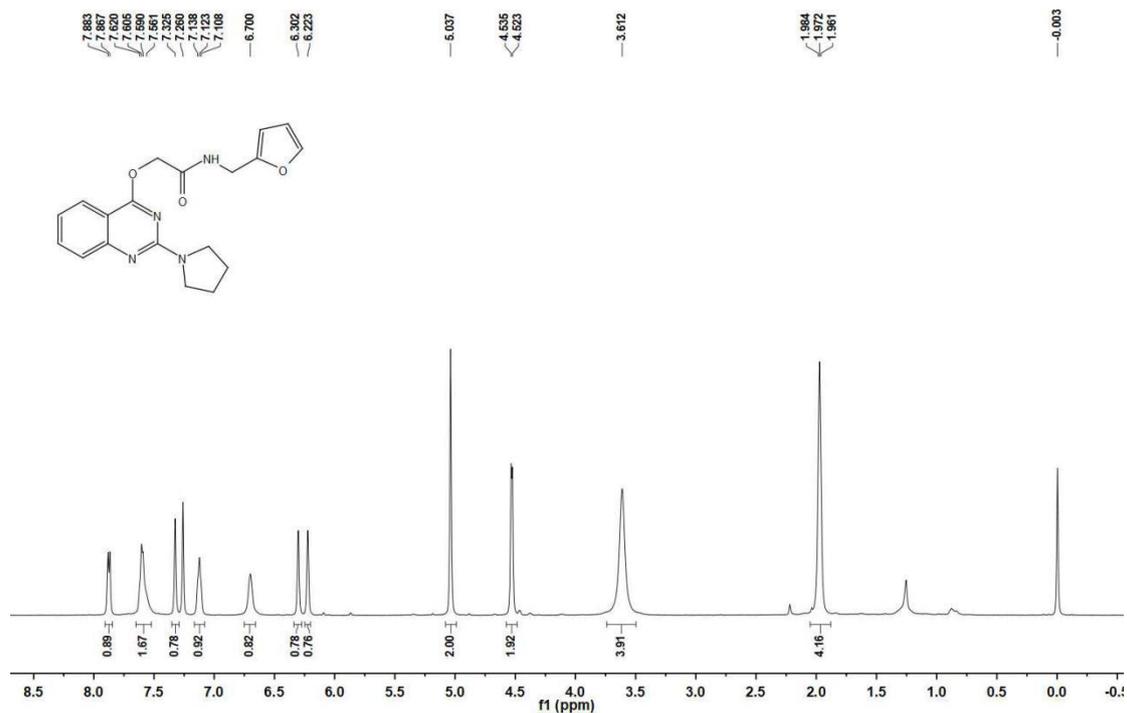
The ¹H NMR spectra of compound II-7a4



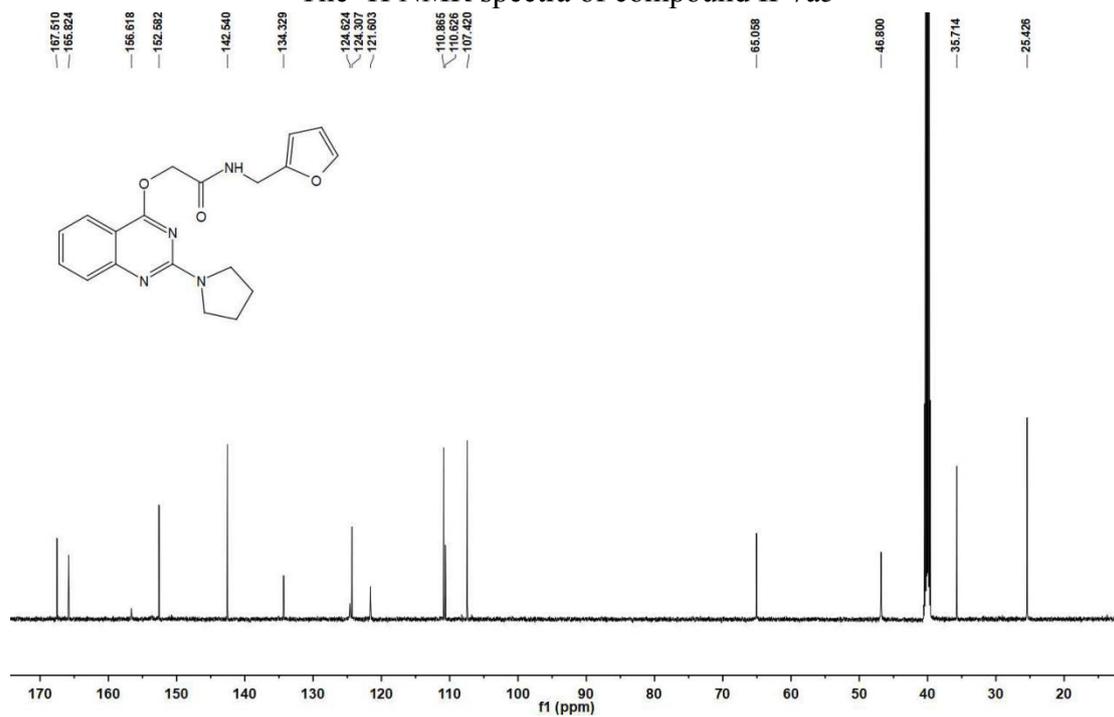
The ¹³C NMR spectra of compound II-7a4



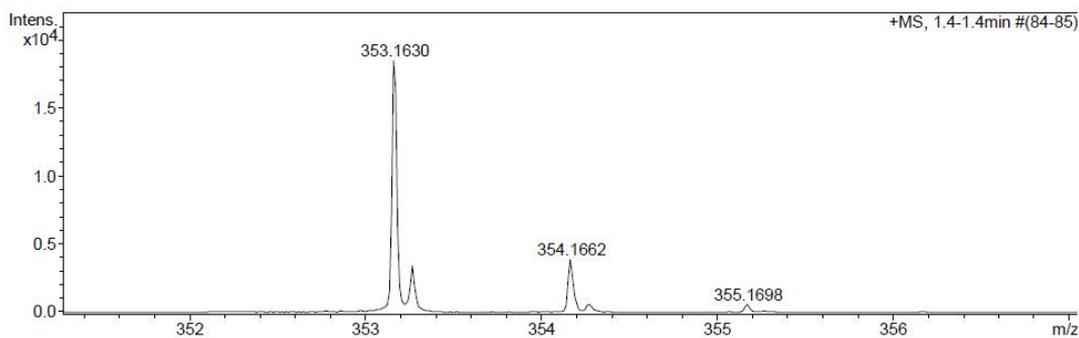
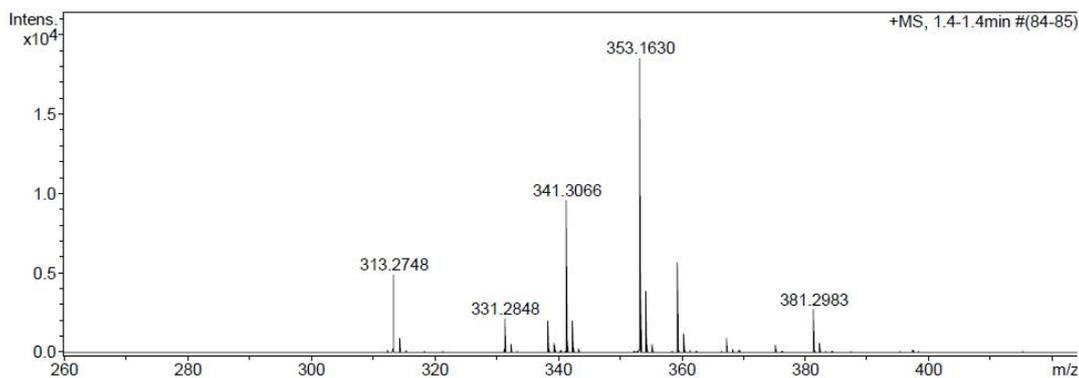
The HR-MS spectra of compound II-7a4



The ¹H NMR spectra of compound II-7a5



The ¹³C NMR spectra of compound II-7a5

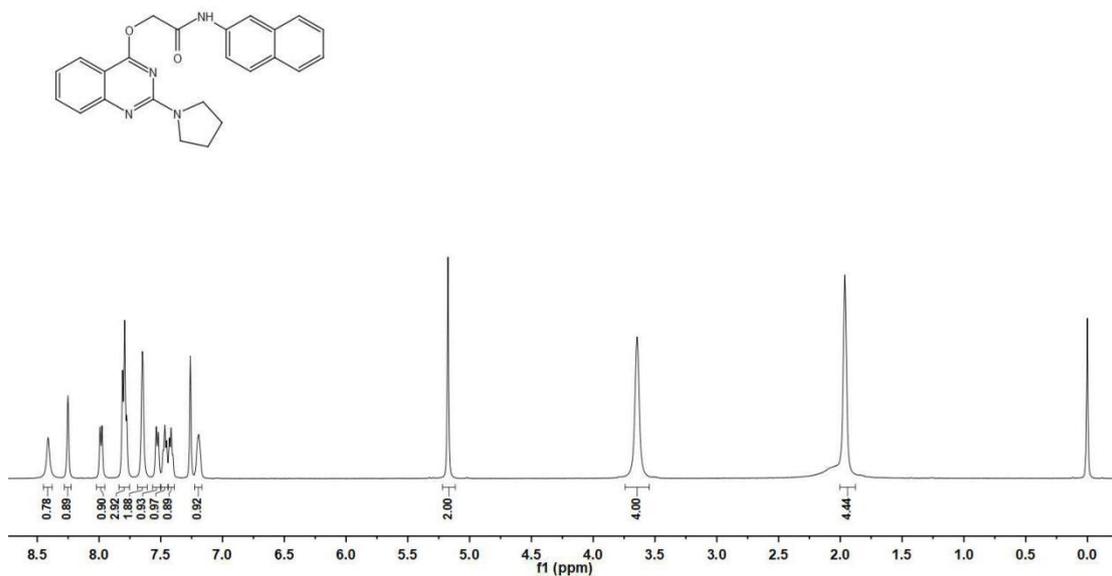


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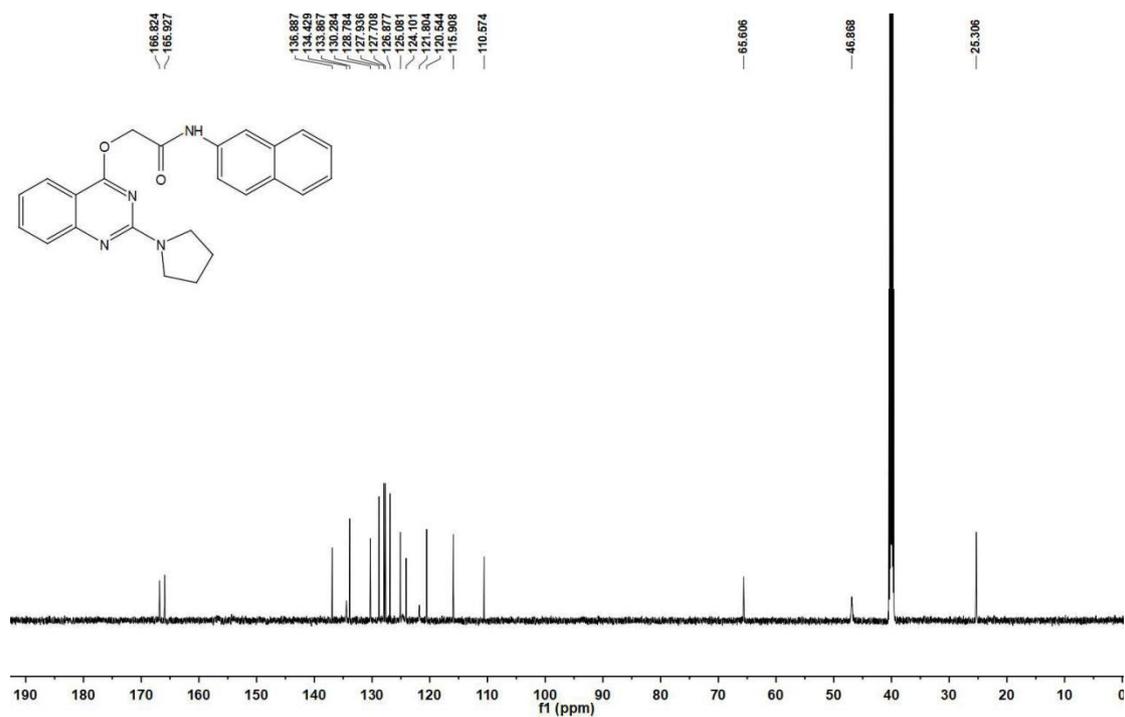
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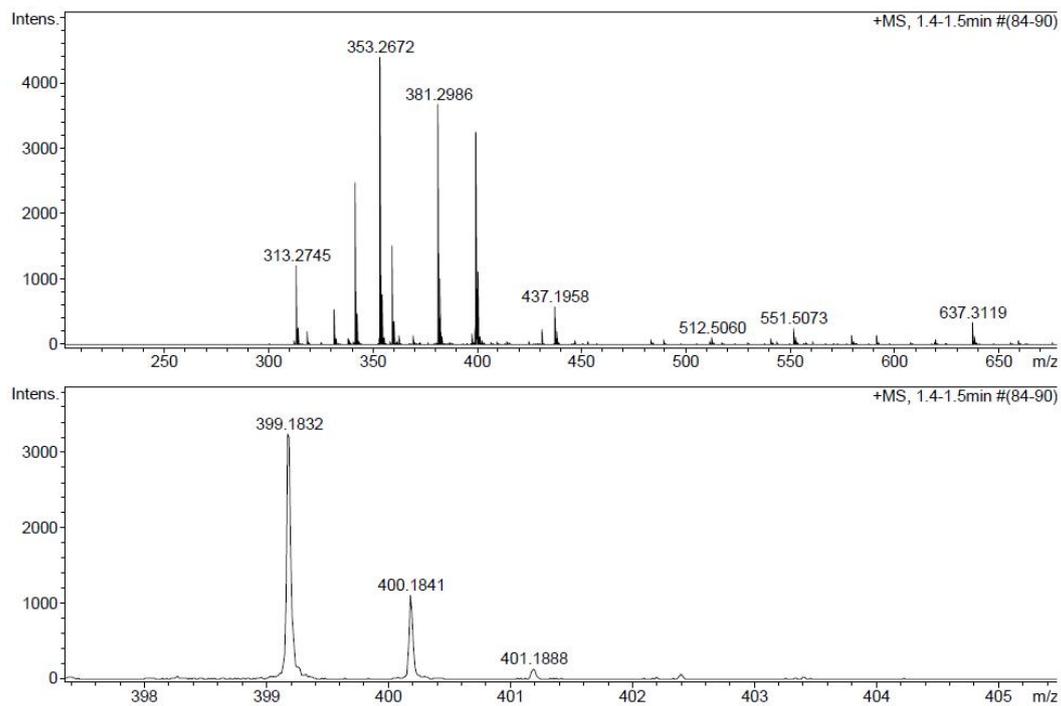
The HR-MS spectra of compound II-7a5



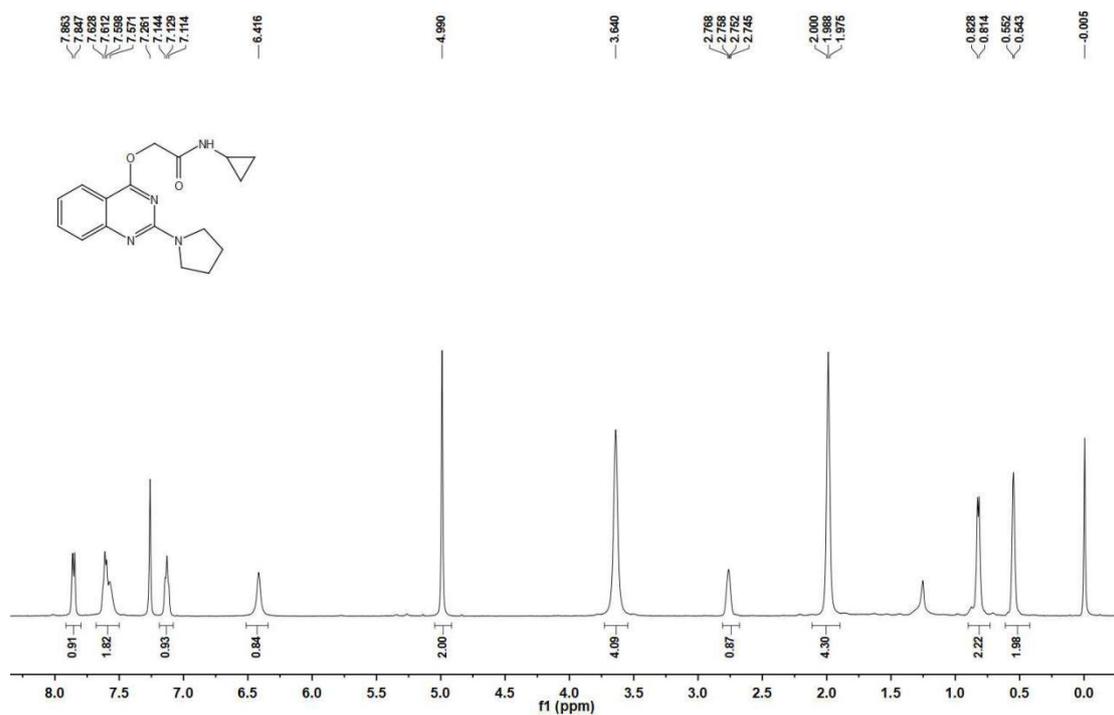
The ¹H NMR spectra of compound II-7a6



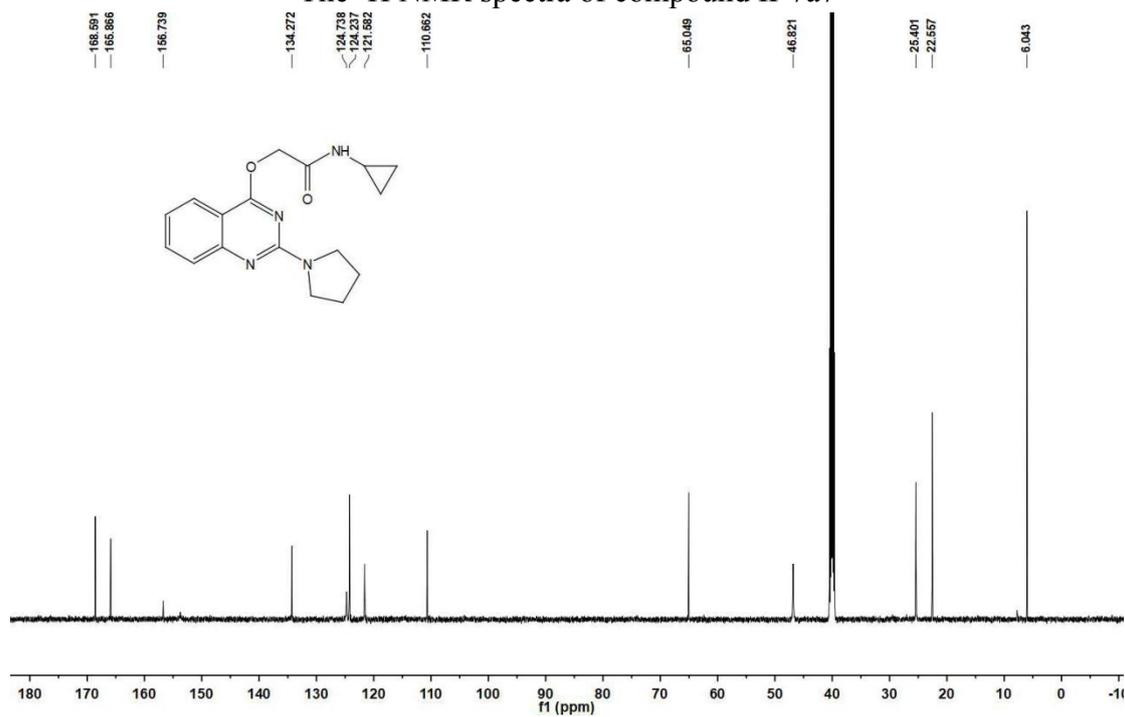
The ¹³C NMR spectra of compound II-7a6



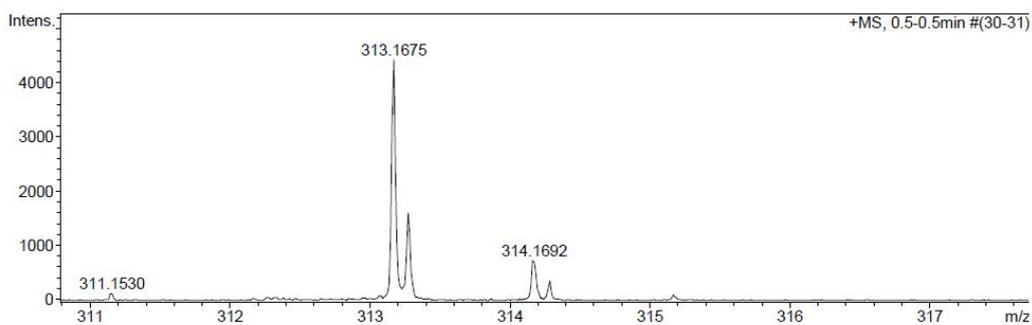
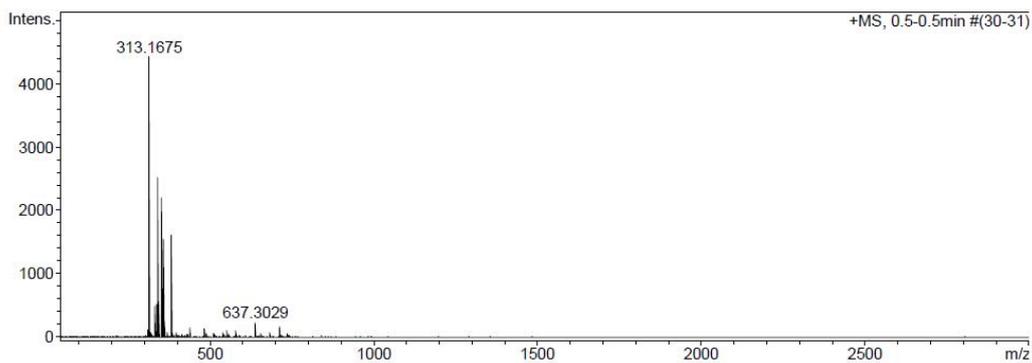
The HR-MS spectra of compound II-7a6



The ¹H NMR spectra of compound II-7a7



The ¹³C NMR spectra of compound II-7a7

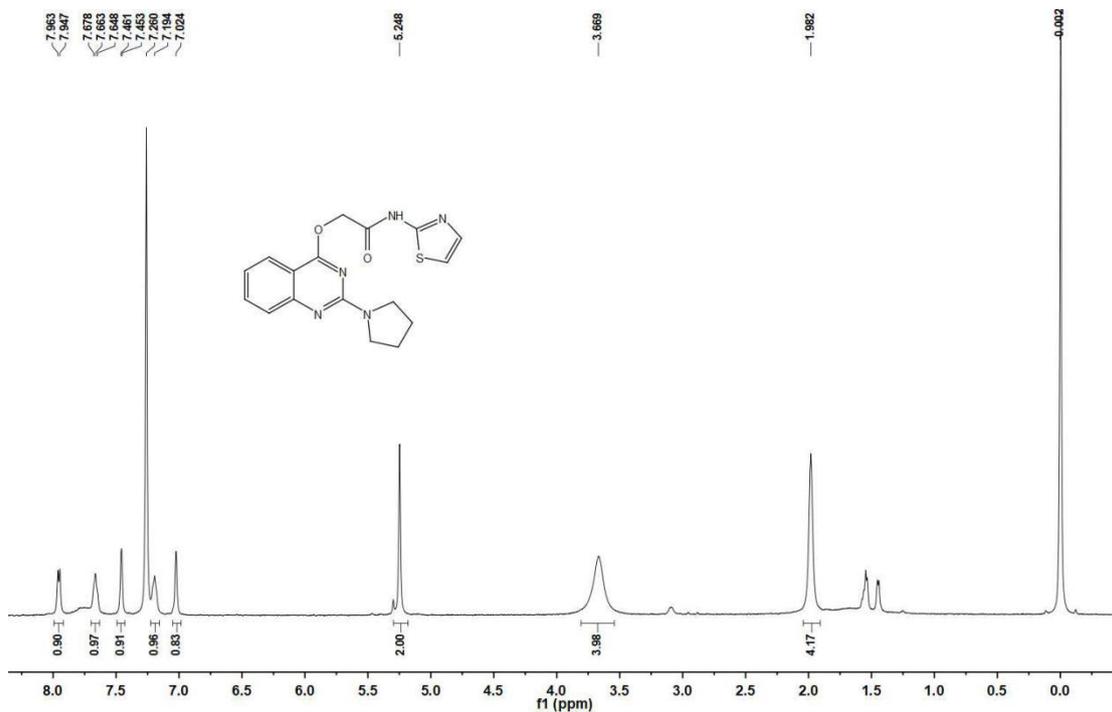


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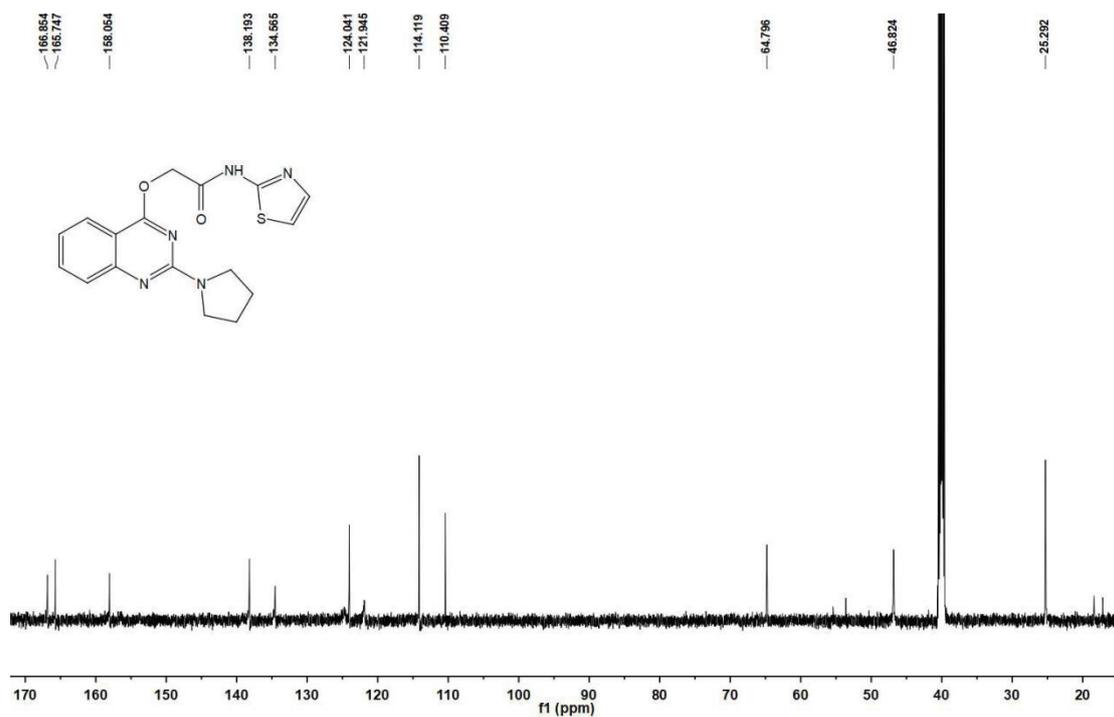
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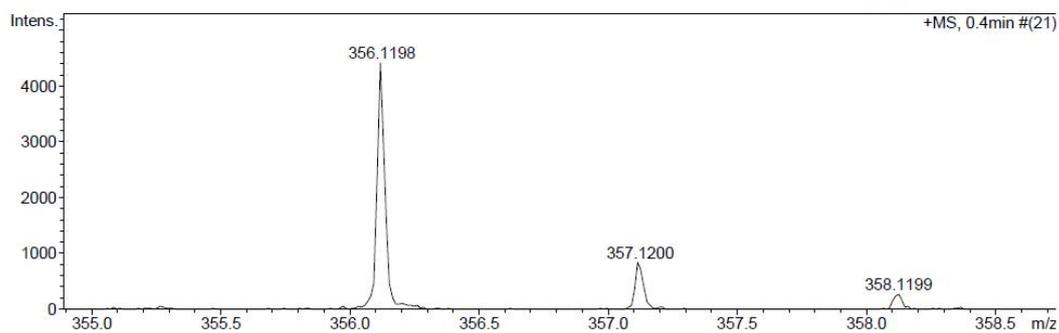
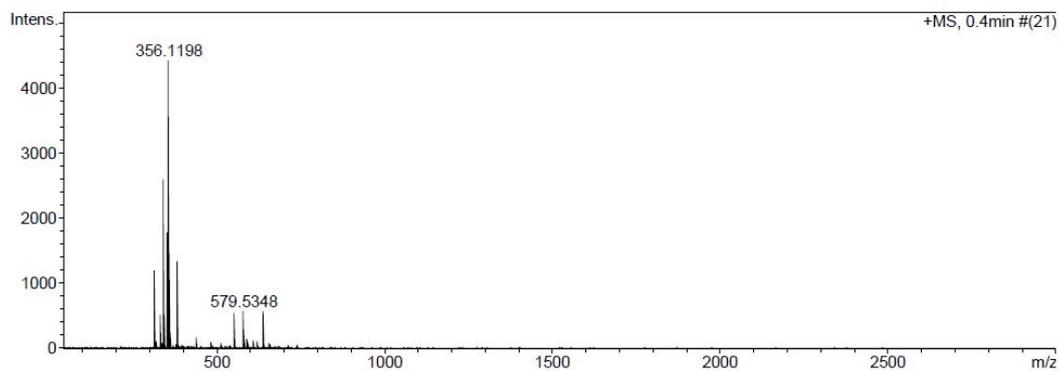
The HR-MS spectra of compound II-7a7



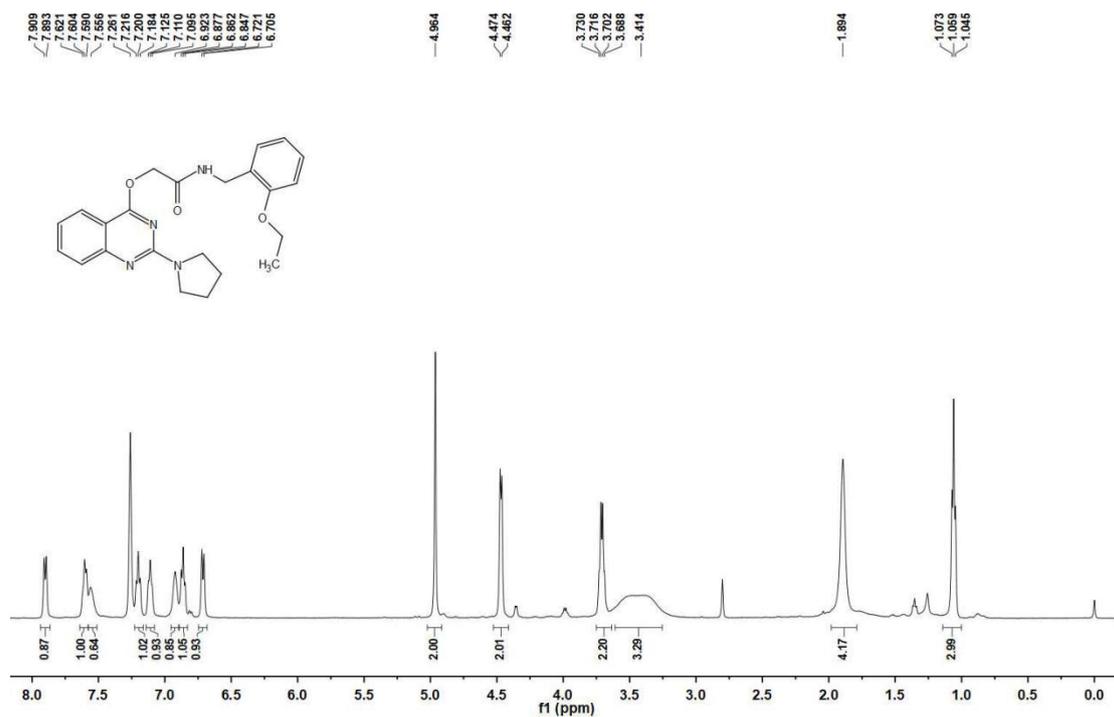
The ¹H NMR spectra of compound II-7a8



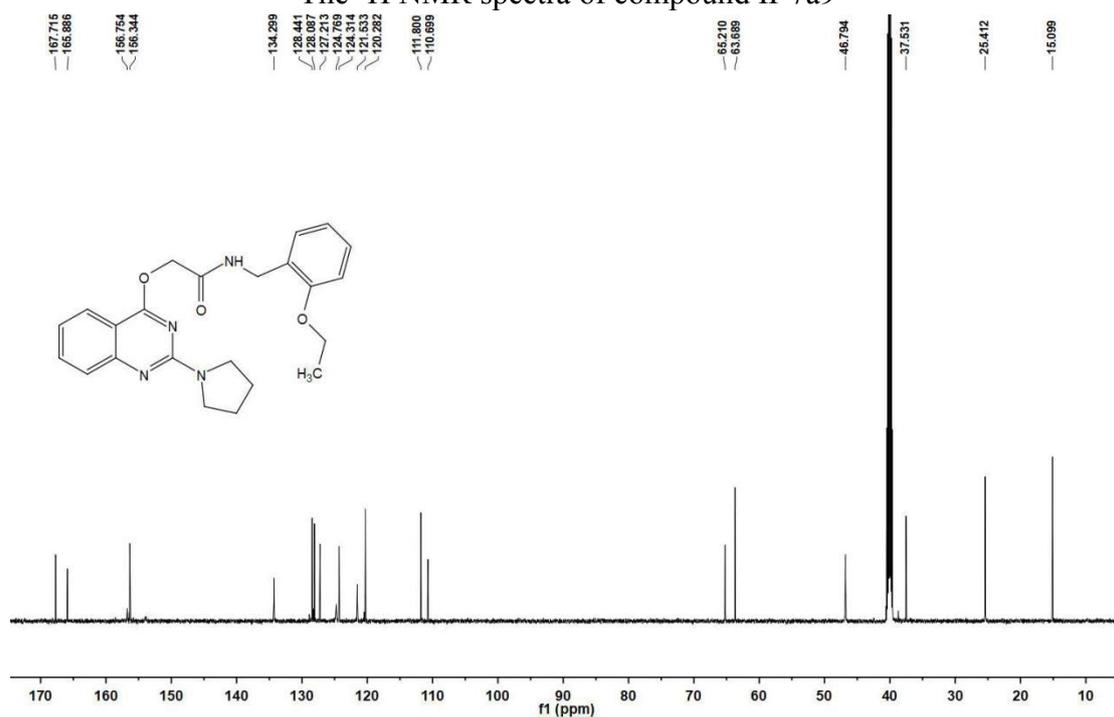
The ¹³C NMR spectra of compound II-7a8



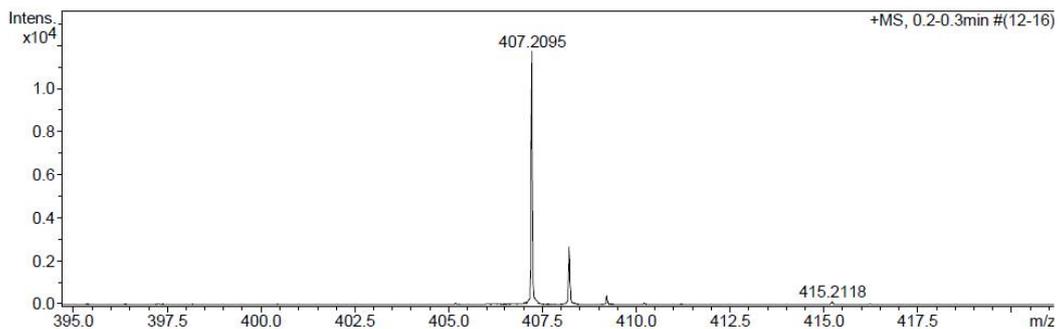
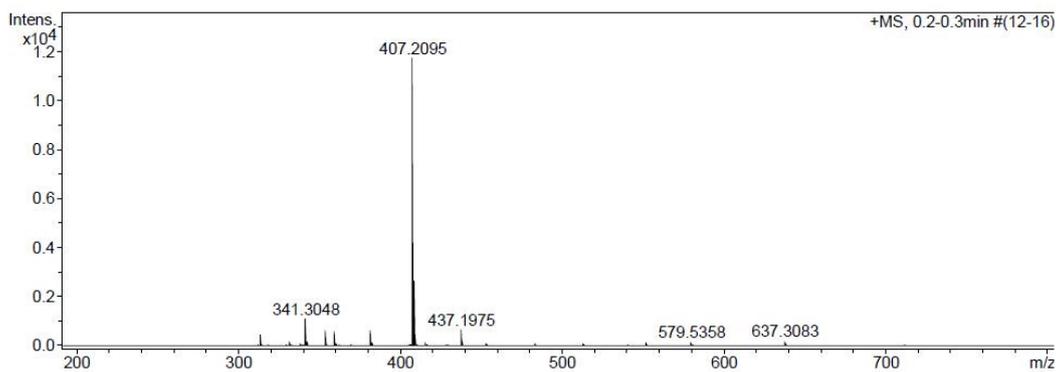
The HR-MS spectra of compound II-7a8



The ¹H NMR spectra of compound II-7a9



The ¹³C NMR spectra of compound II-7a9

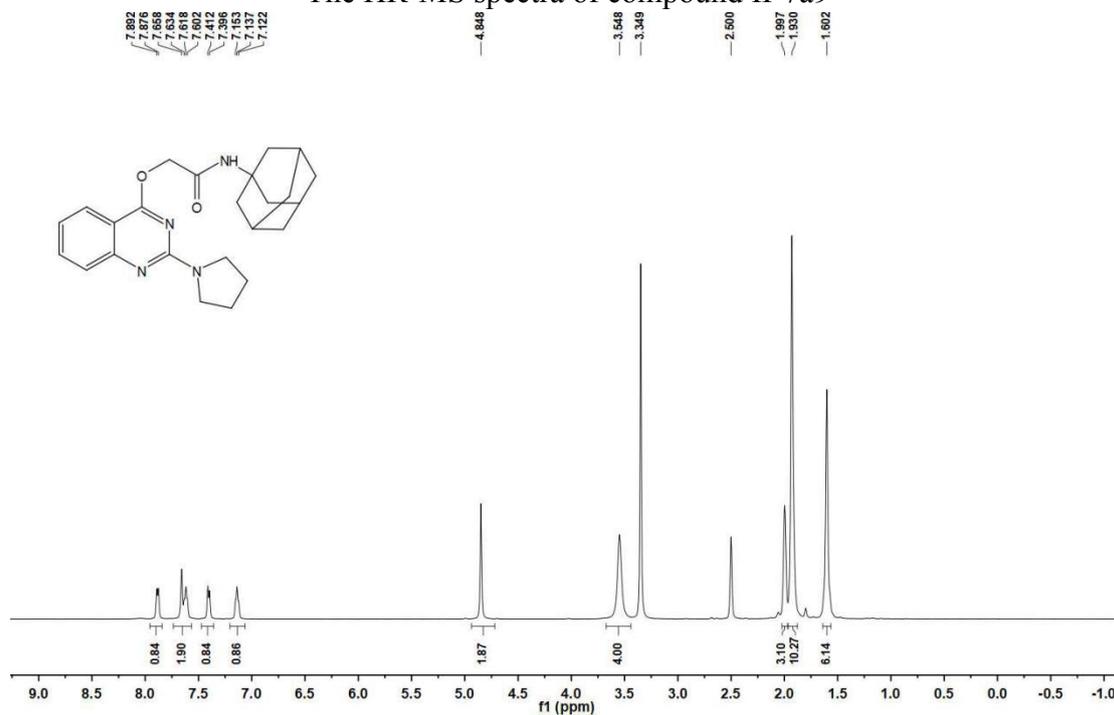


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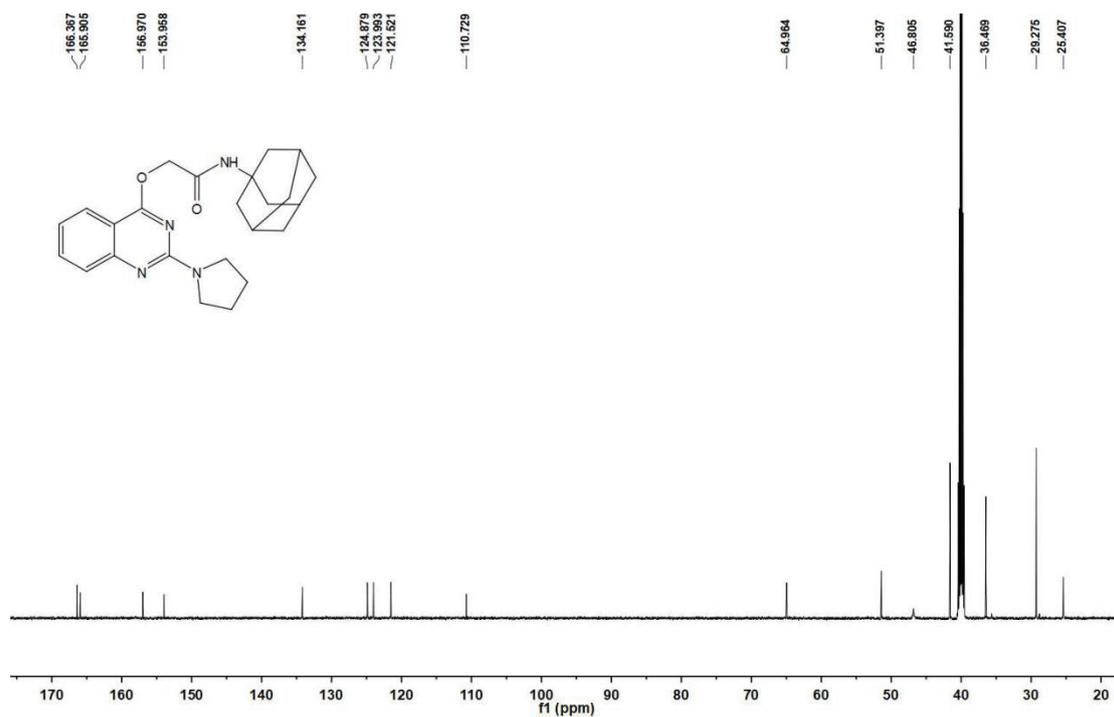
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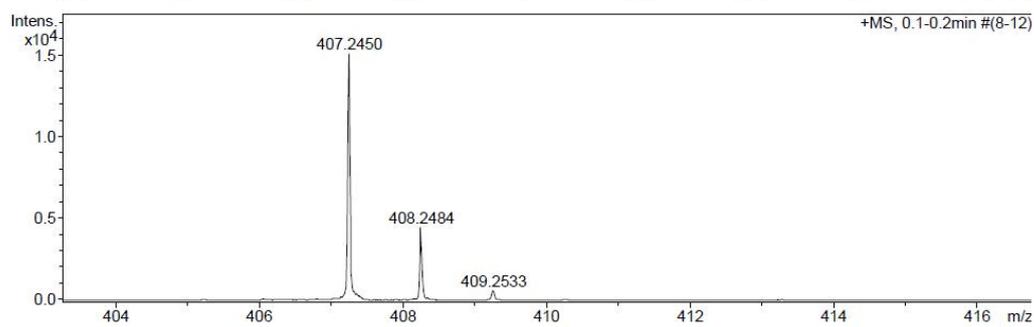
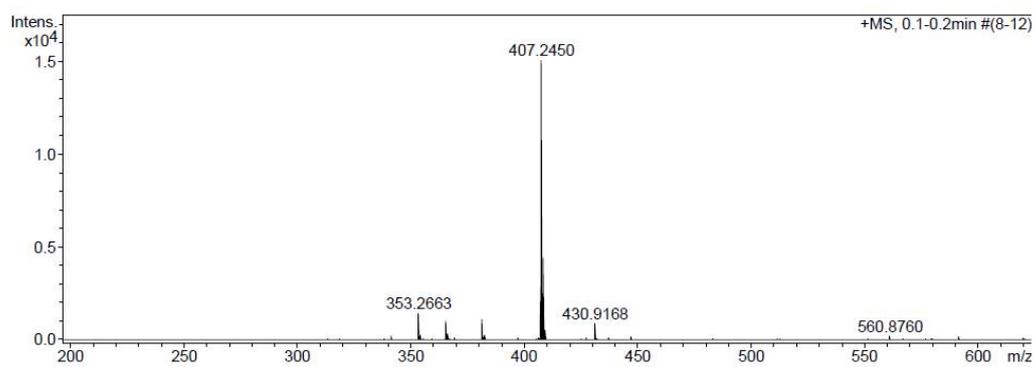
The HR-MS spectra of compound II-7a9



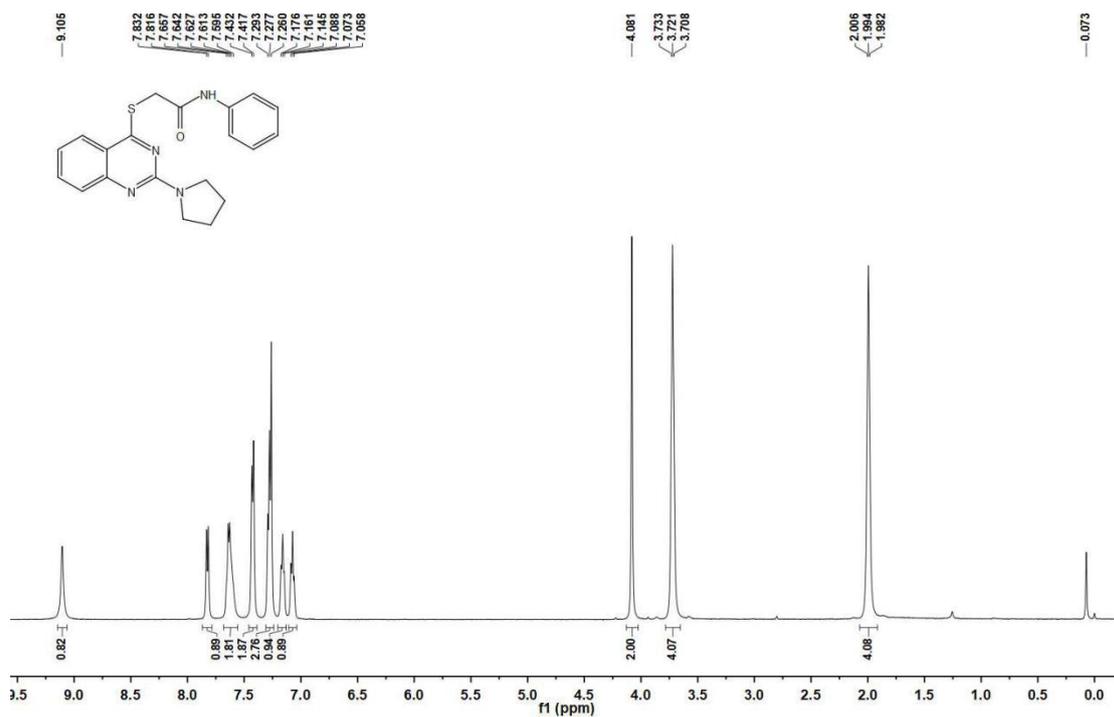
The ¹H NMR spectra of compound II-7a10



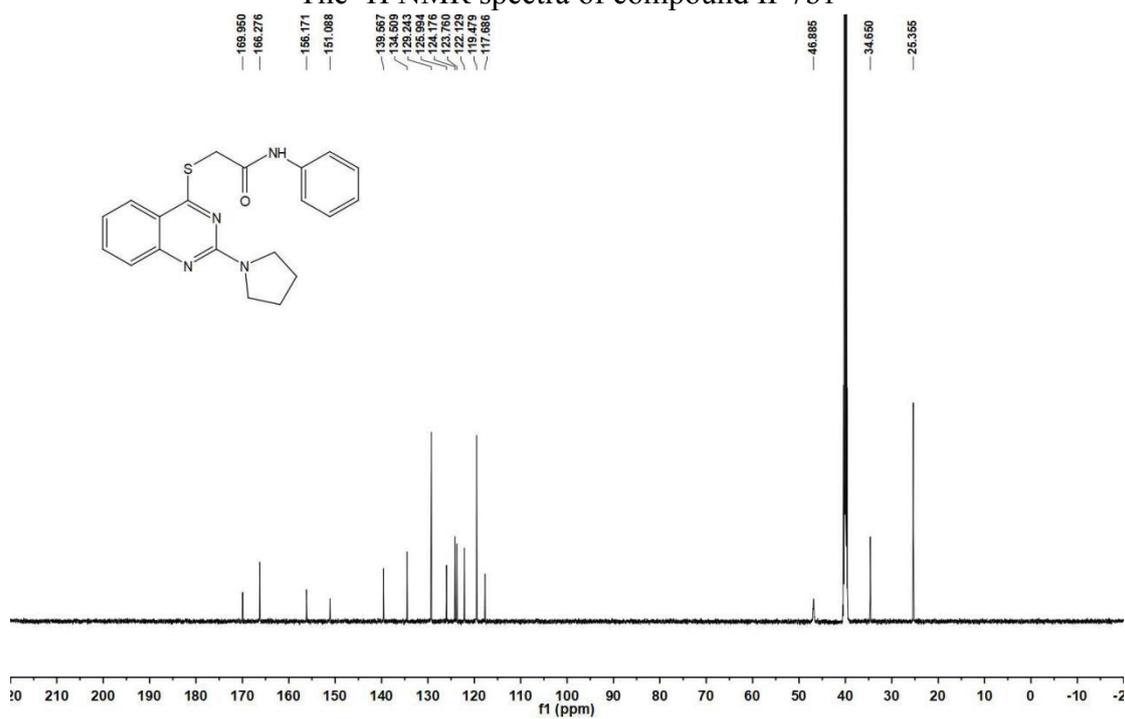
The ^{13}C NMR spectra of compound II-7a10



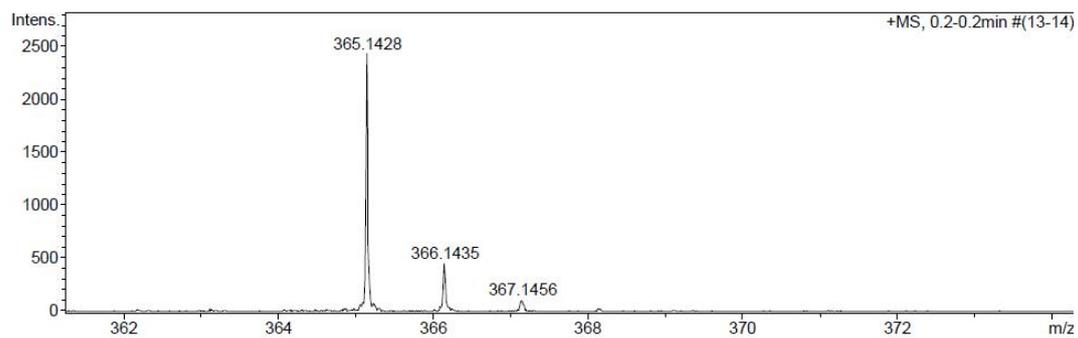
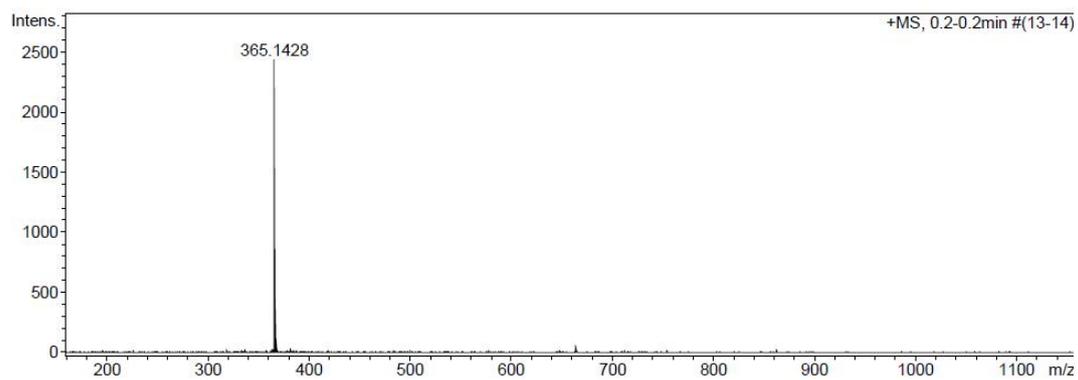
The HR-MS spectra of compound II-7a10



The ^1H NMR spectra of compound II-7b1



The ^{13}C NMR spectra of compound II-7b1

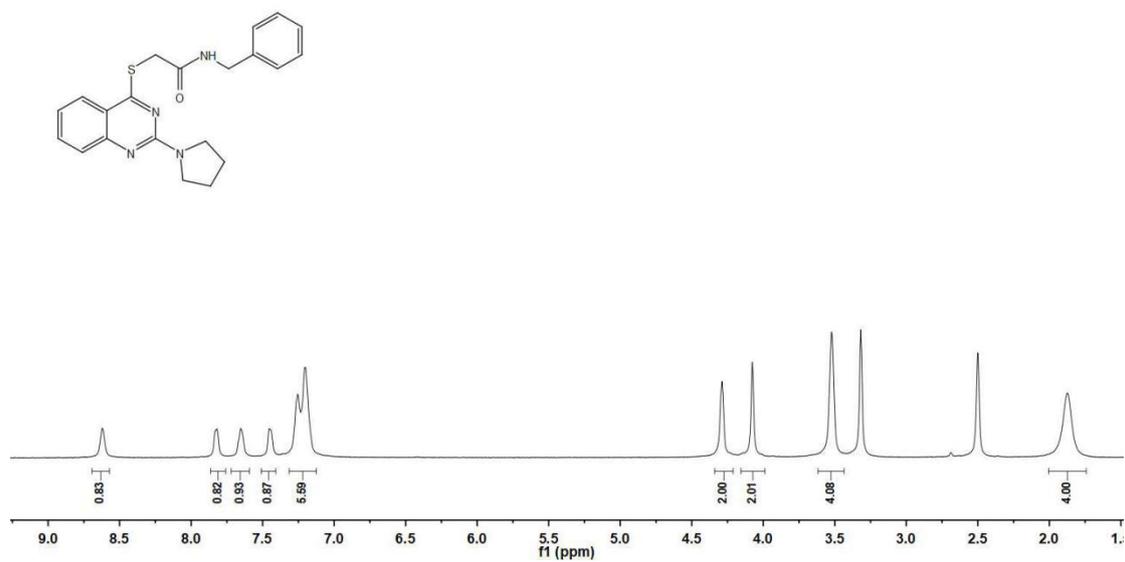
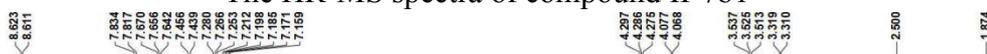


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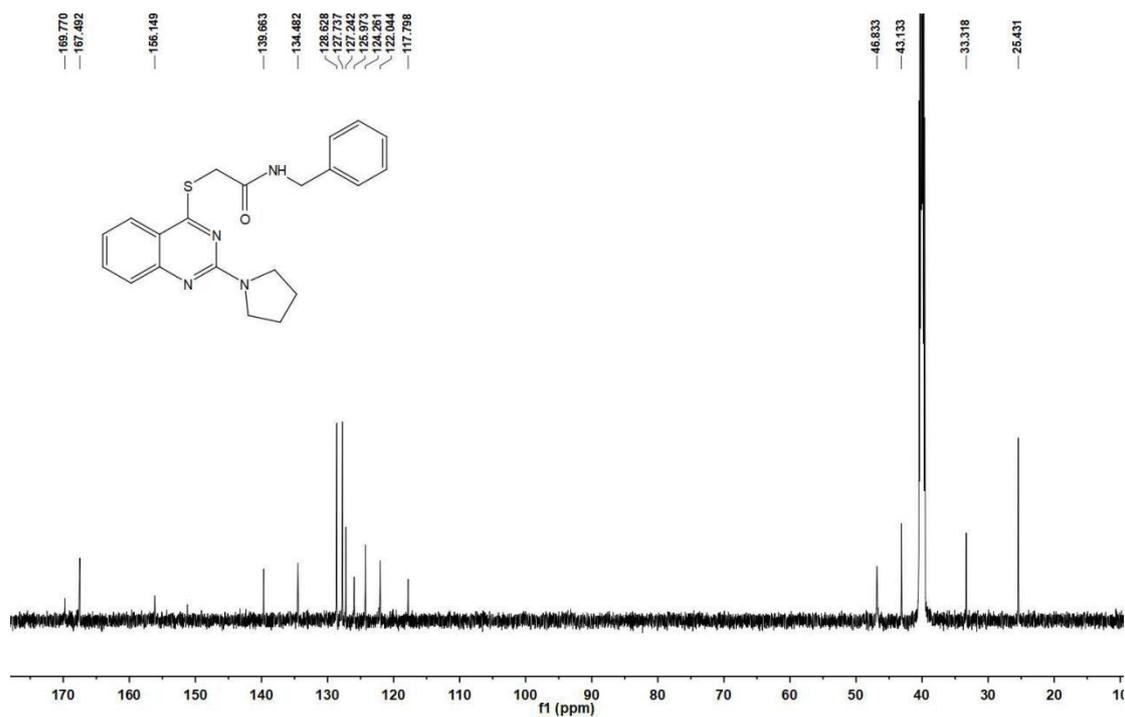
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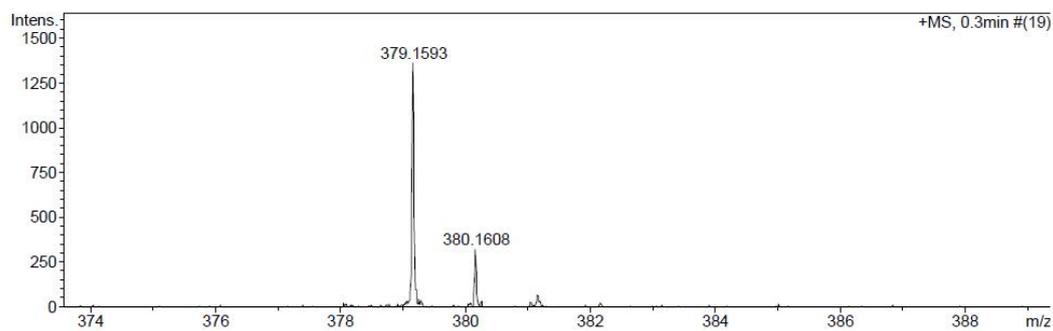
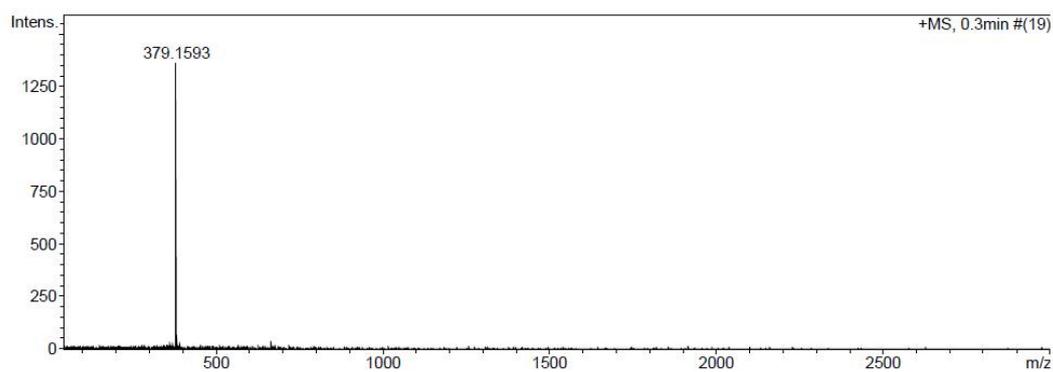
The HR-MS spectra of compound II-7b1



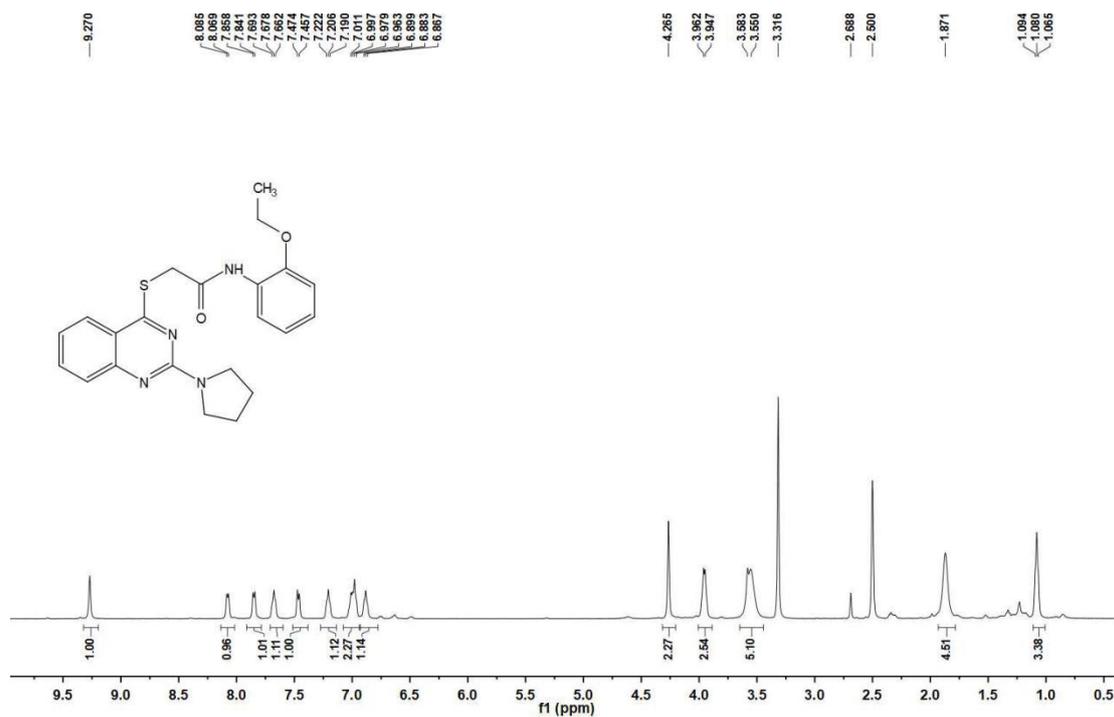
The ¹H NMR spectra of compound II-7b2



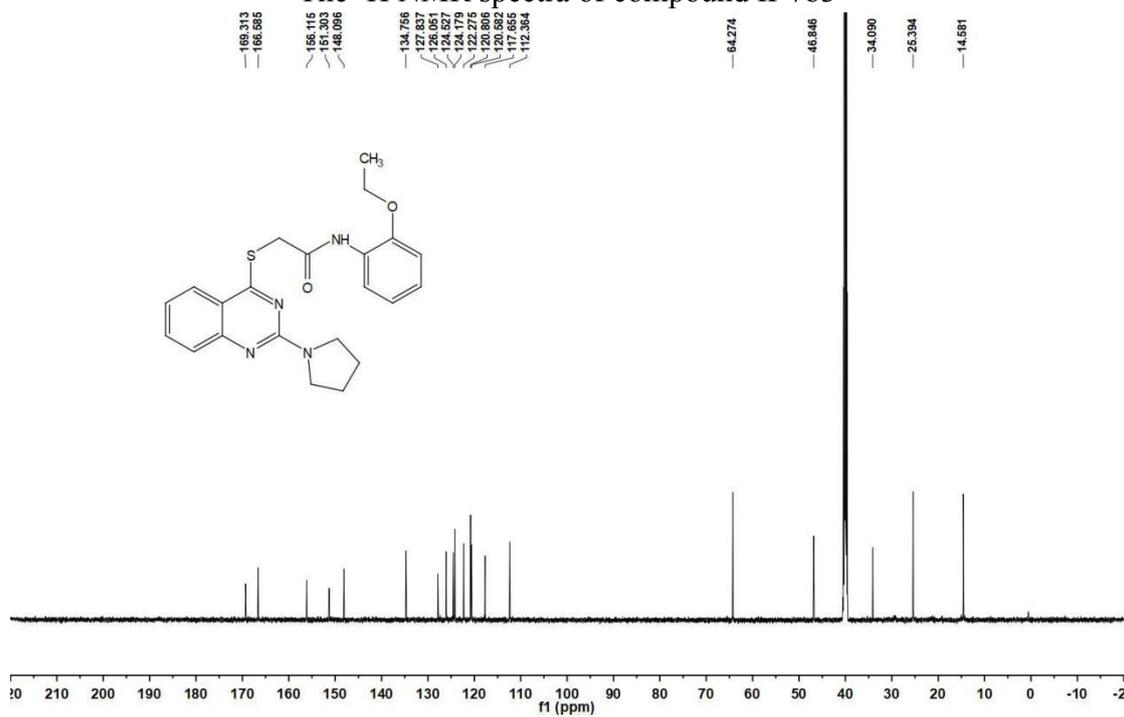
The ¹³C NMR spectra of compound II-7b2



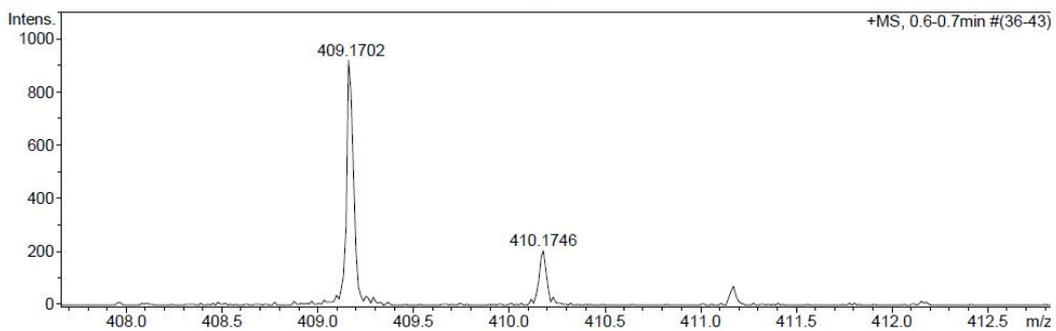
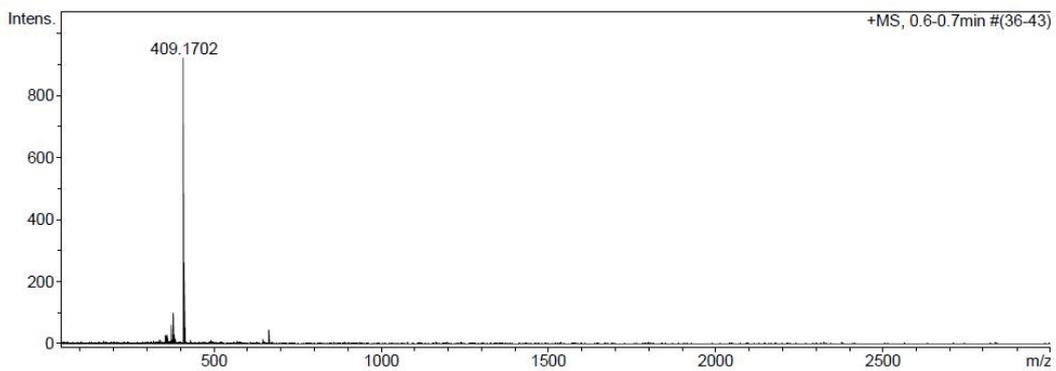
The HR-MS spectra of compound II-7b2



The ¹H NMR spectra of compound II-7b3



The ¹³C NMR spectra of compound II-7b3

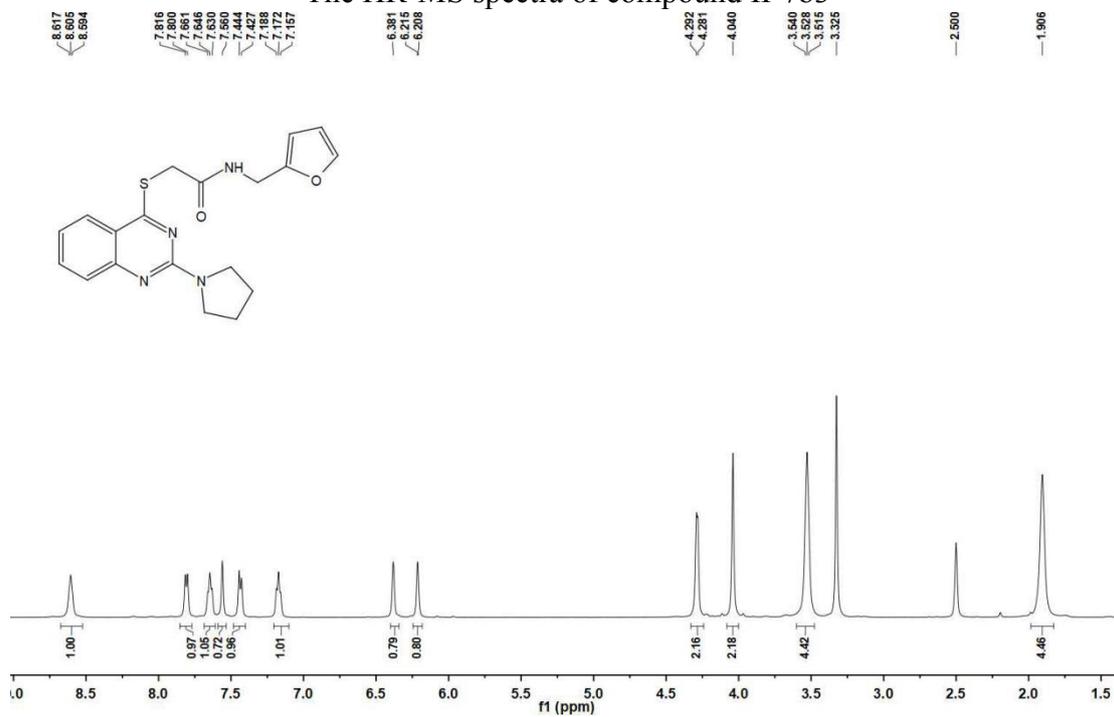


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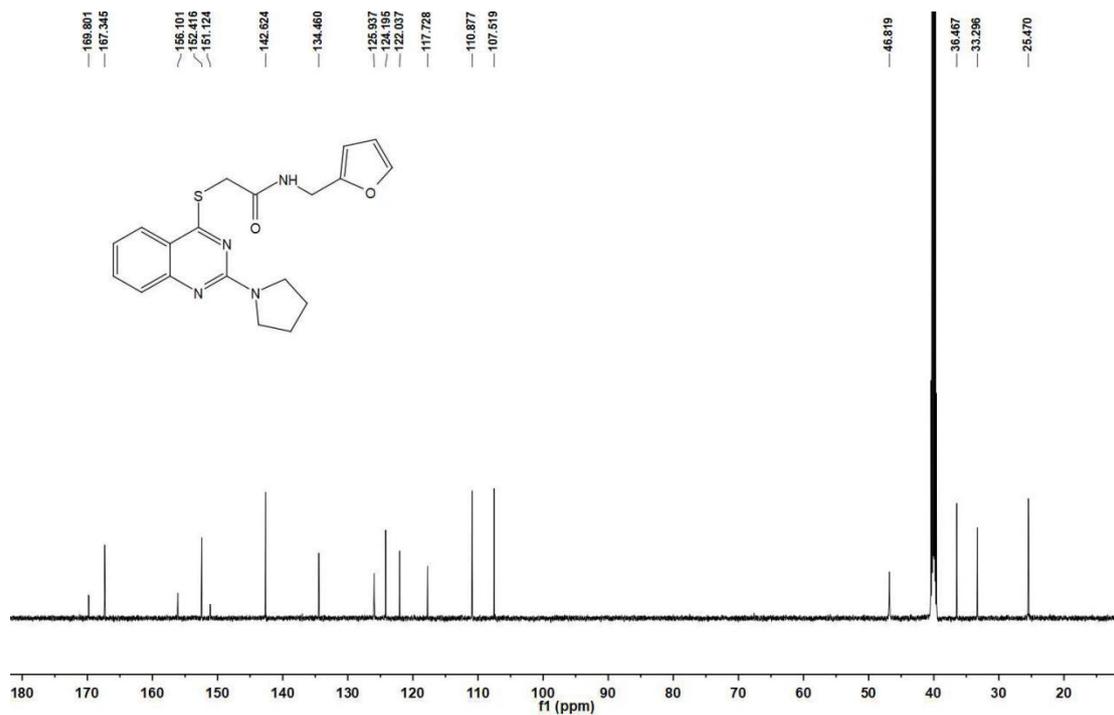
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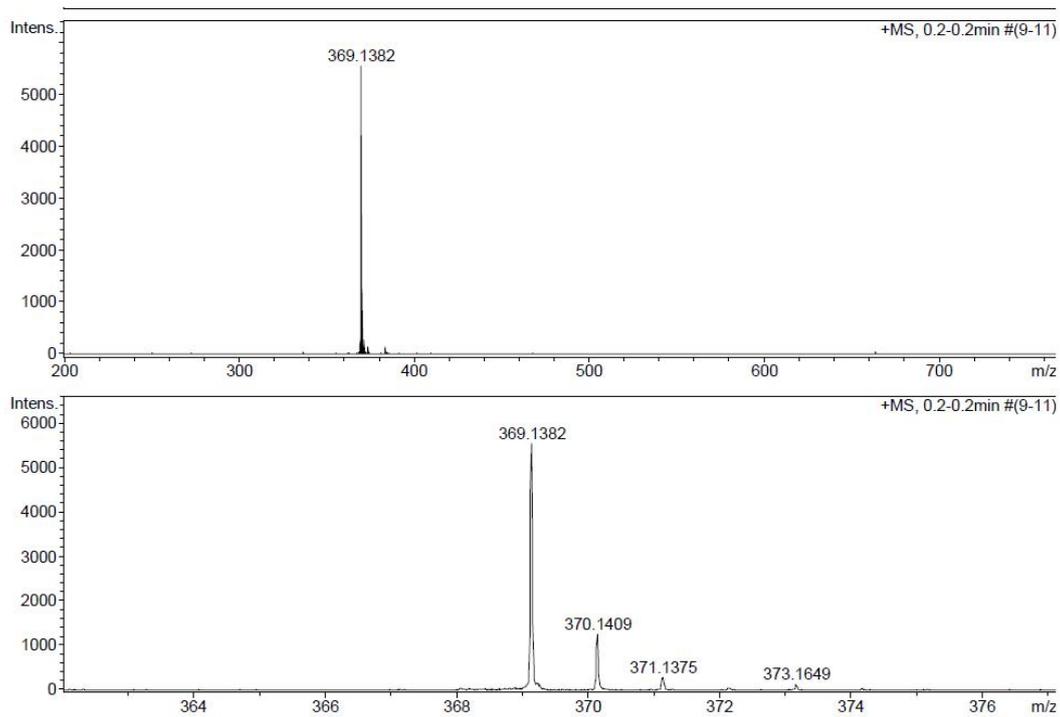
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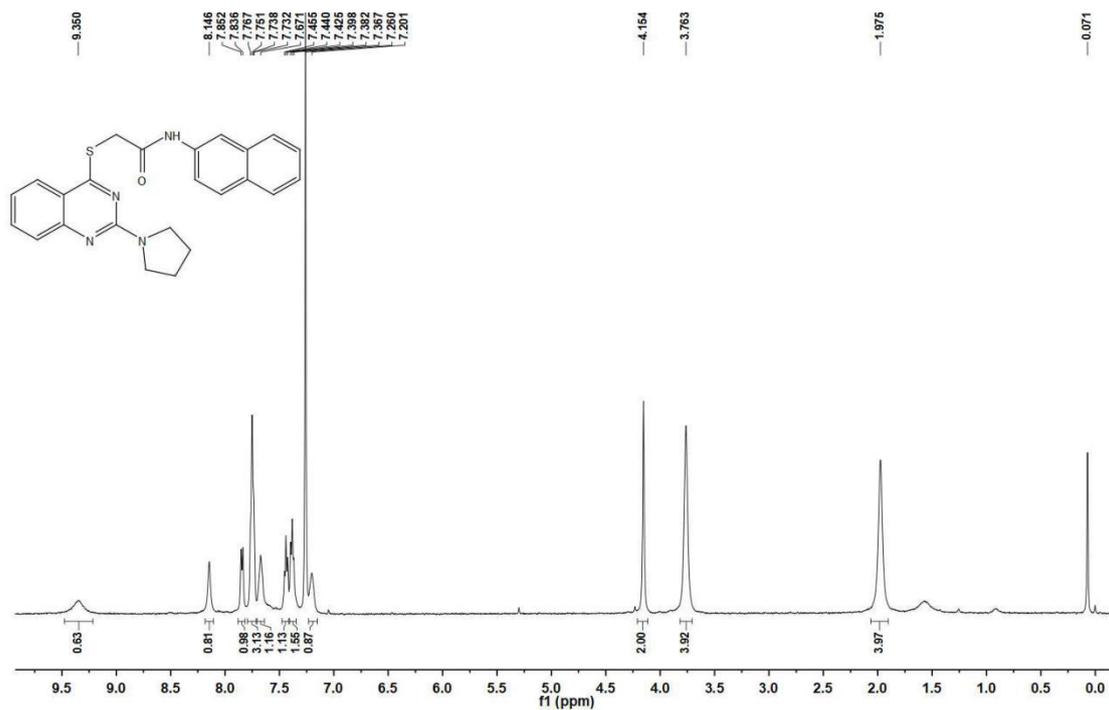
The ¹H NMR spectra of compound II-7b4



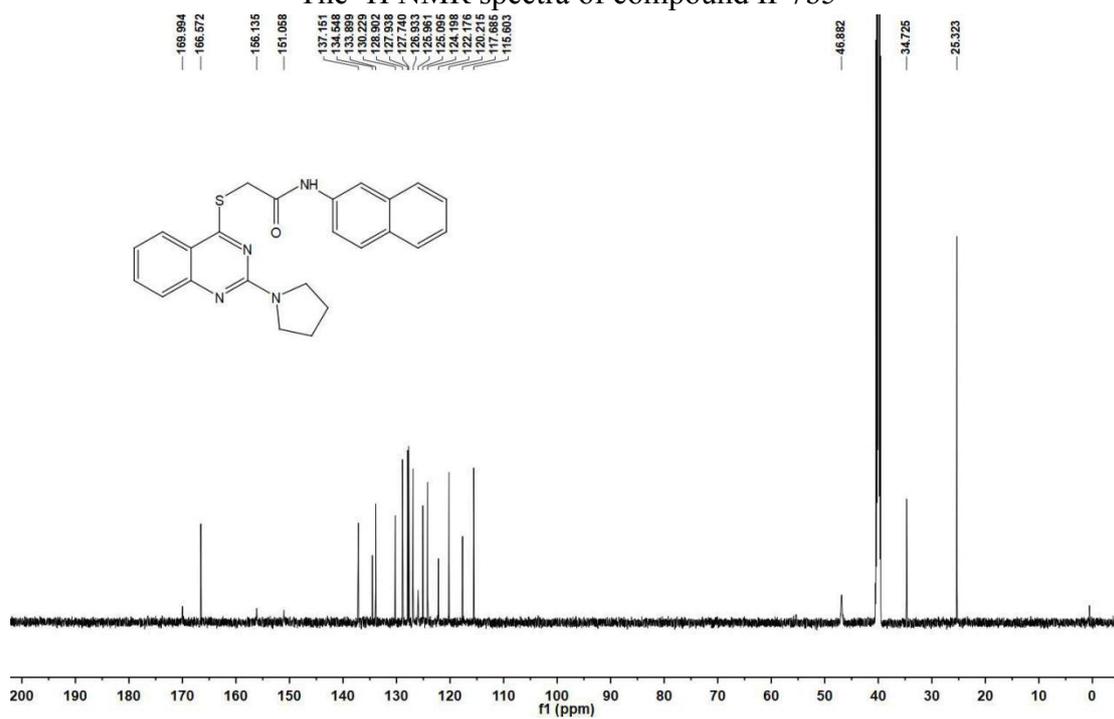
The ¹³C NMR spectra of compound II-7b4



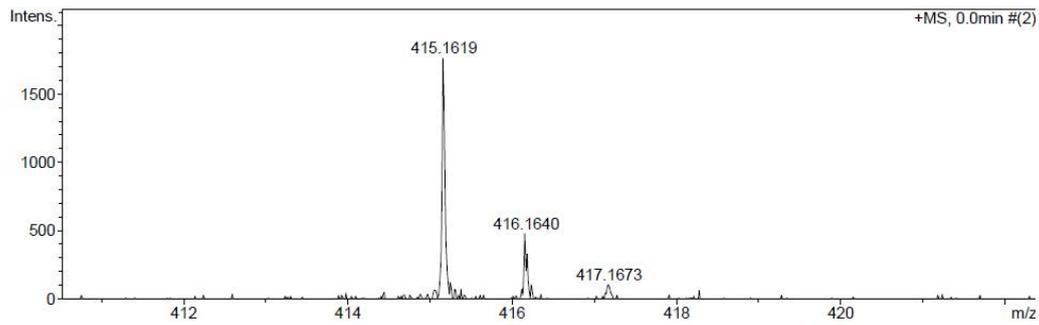
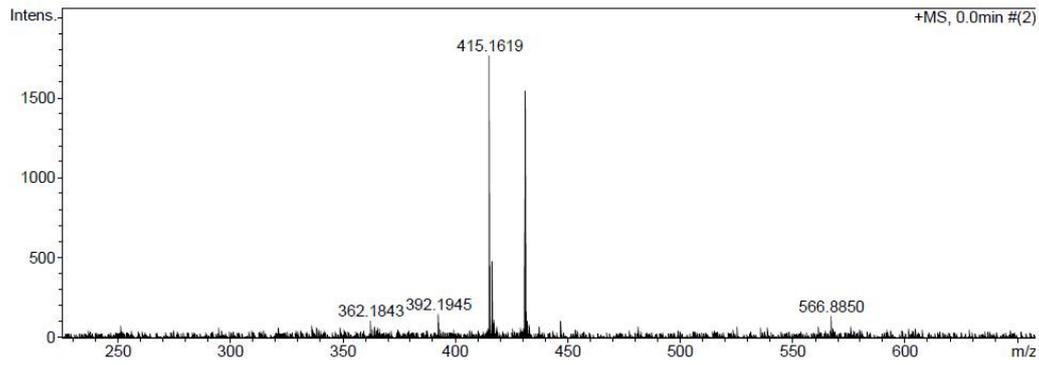
The HR-MS spectra of compound II-7b4



The ¹H NMR spectra of compound II-7b5



The ¹³C NMR spectra of compound II-7b5

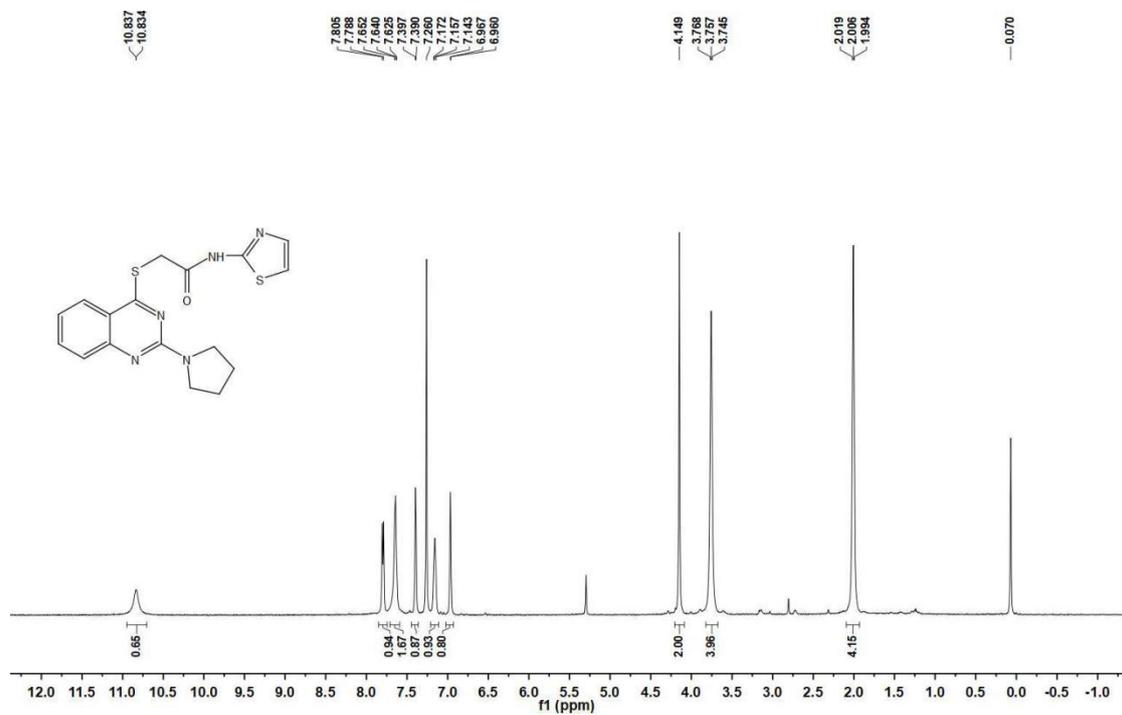


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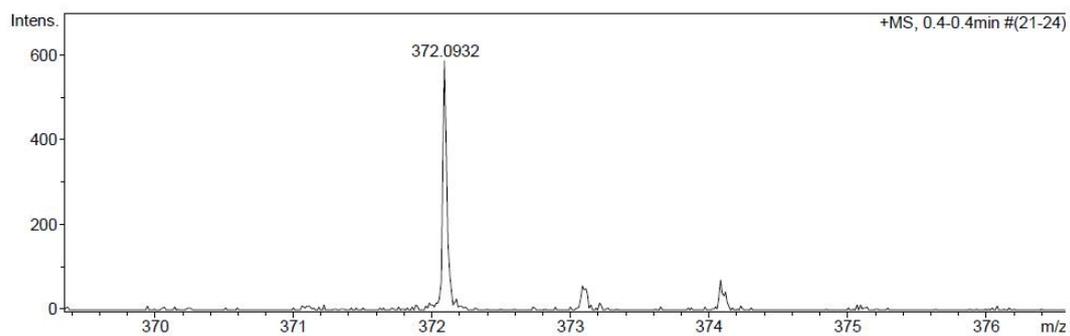
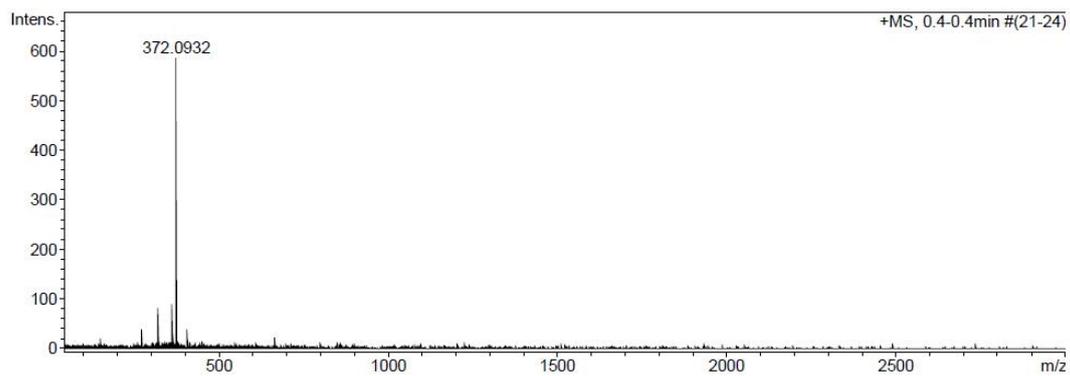
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The HR-MS spectra of compound II-7b5



The ¹H NMR spectra of compound II-7b7

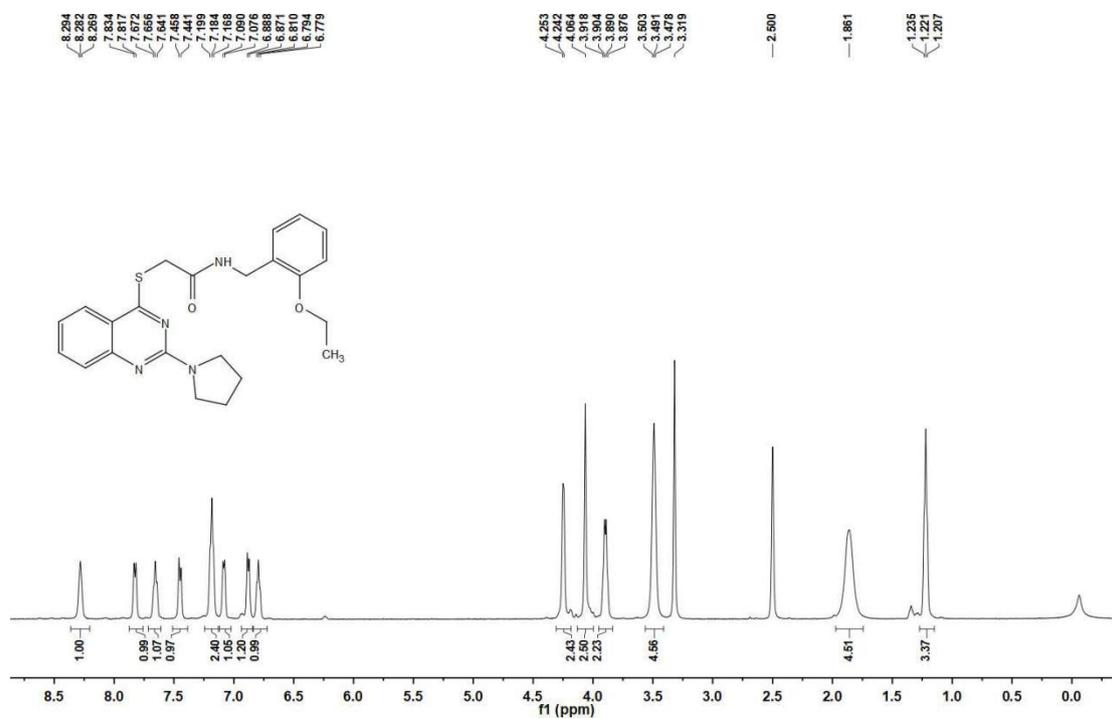


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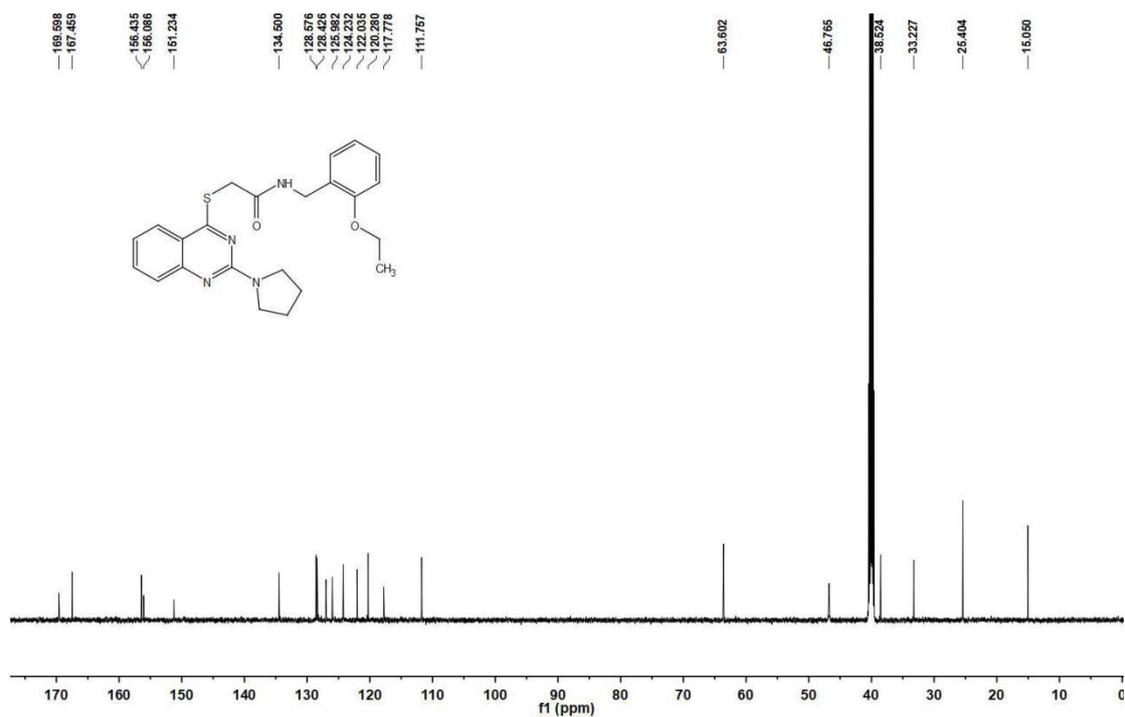
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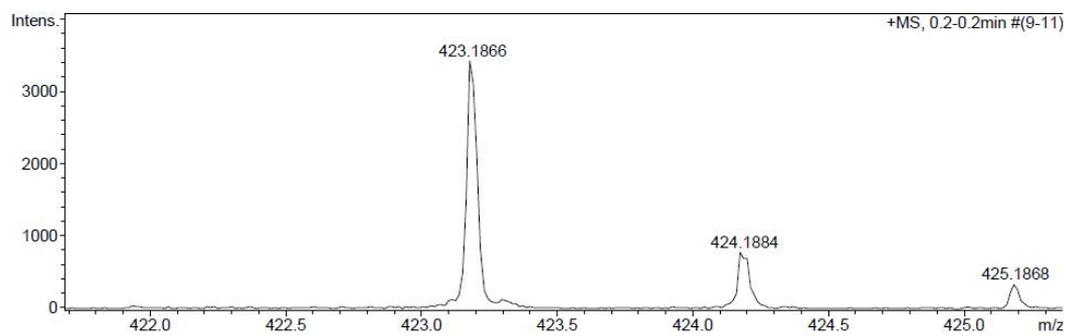
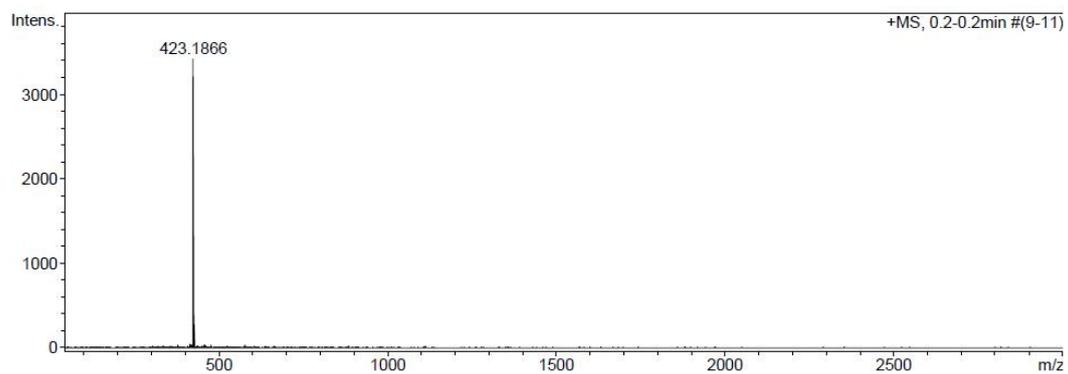
The HR-MS spectra of compound II-7b7



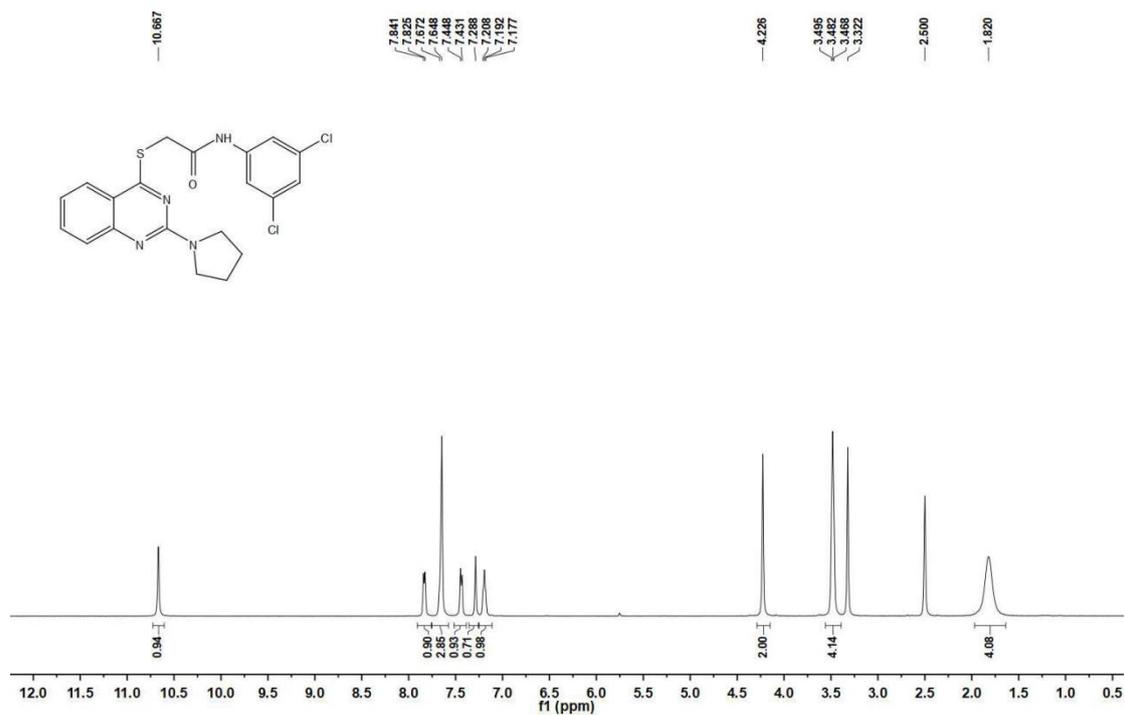
The ¹H NMR spectra of compound II-7b8



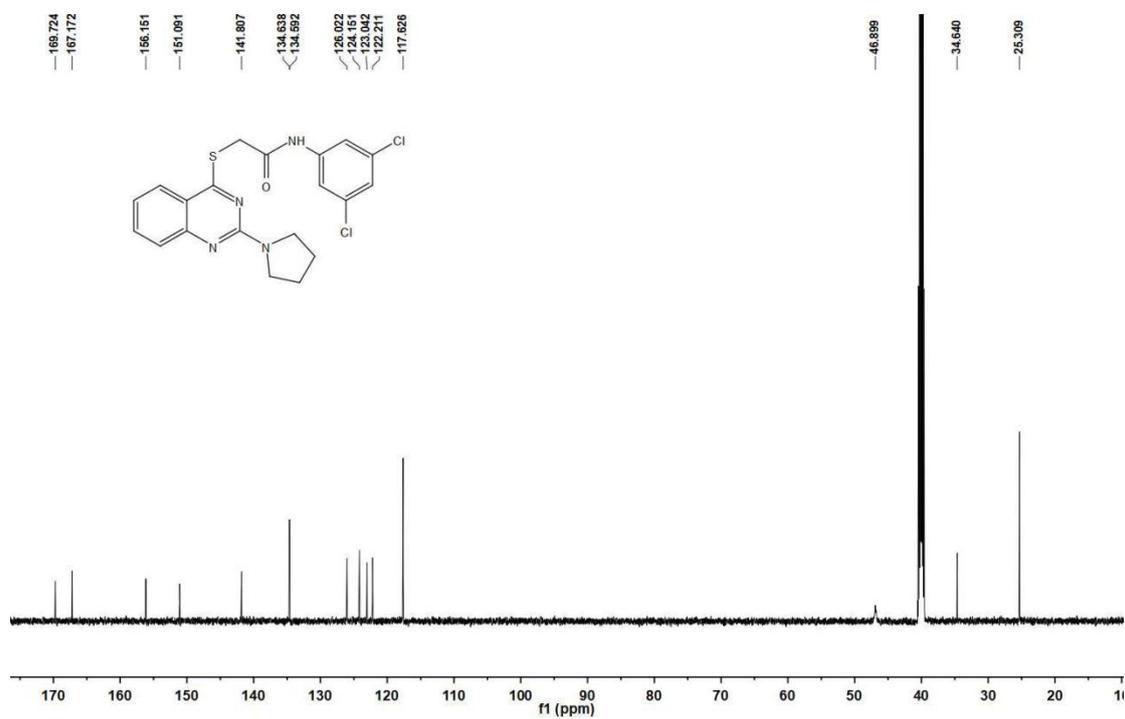
The ¹³C NMR spectra of compound II-7b8



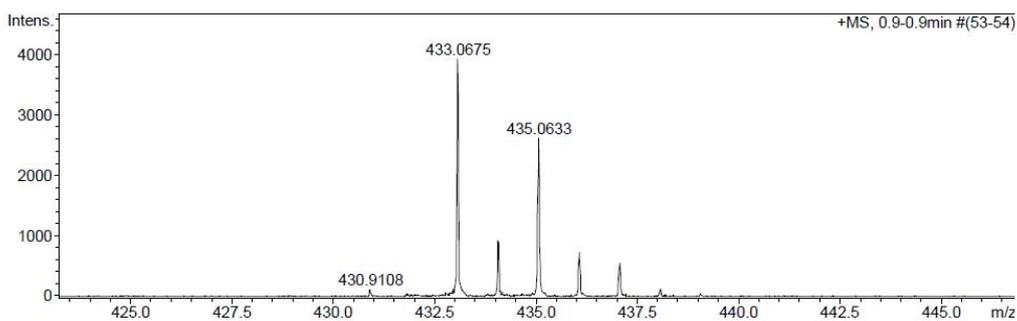
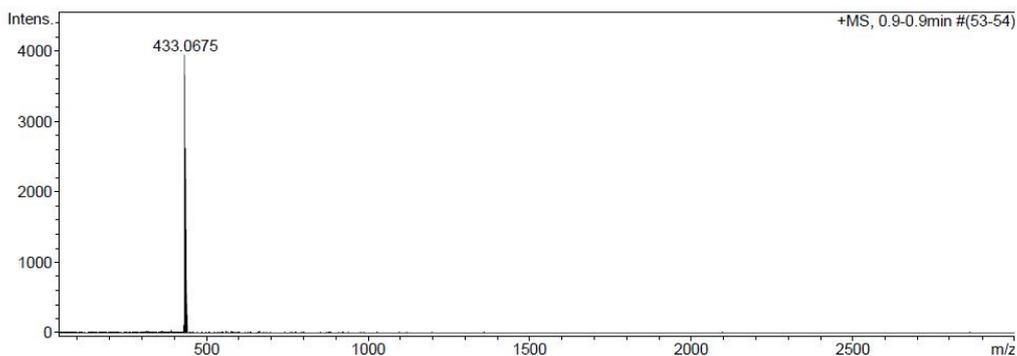
The HR-MS spectra of compound II-7b8



The ¹H NMR spectra of compound II-7b9



The ¹³C NMR spectra of compound II-7b9

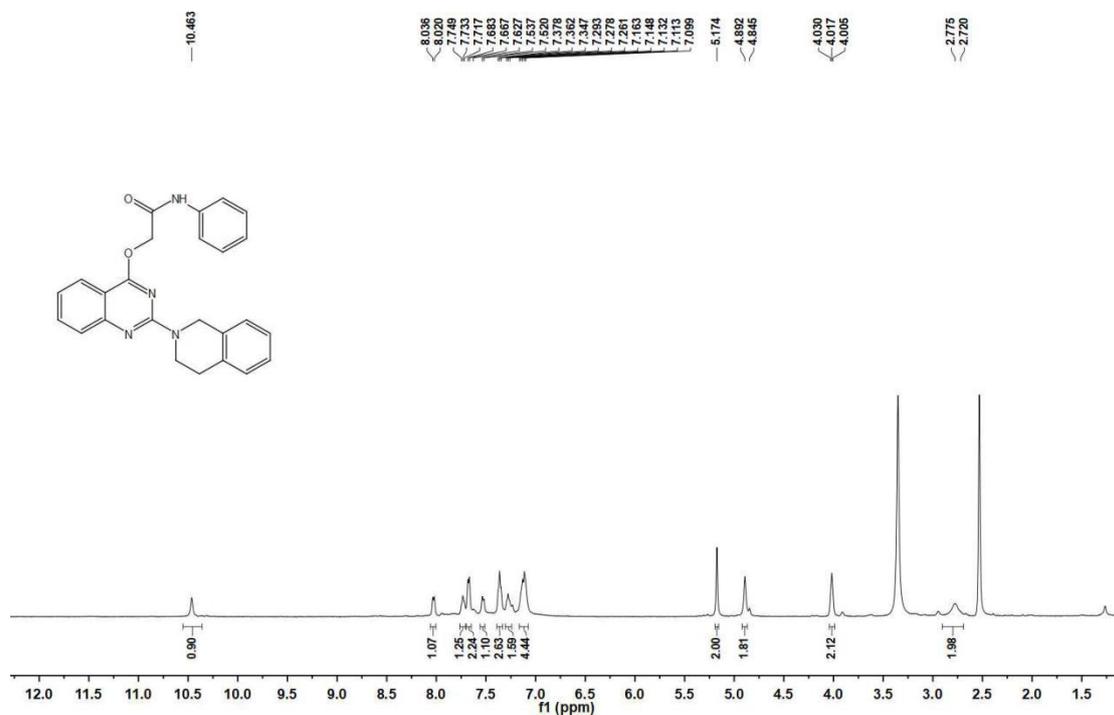


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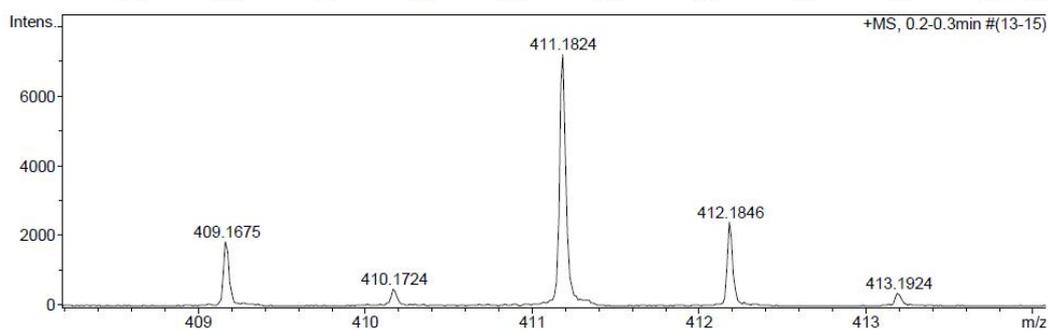
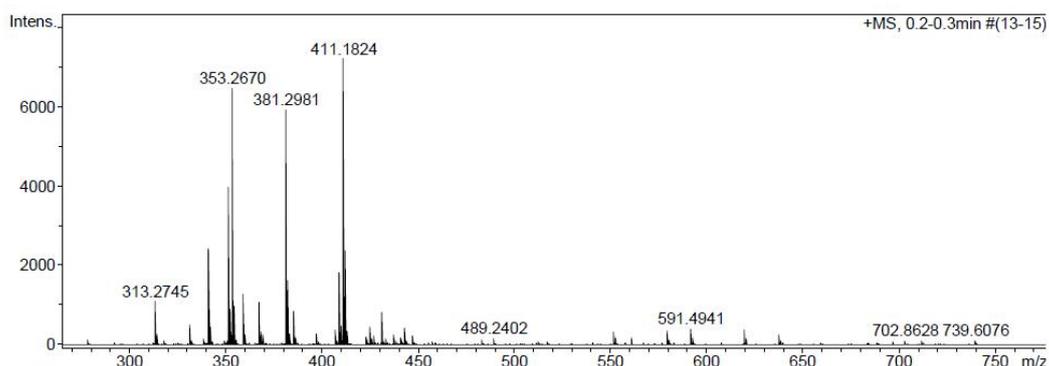
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The HR-MS spectra of compound II-7b9



The ¹H NMR spectra of compound II-10a1

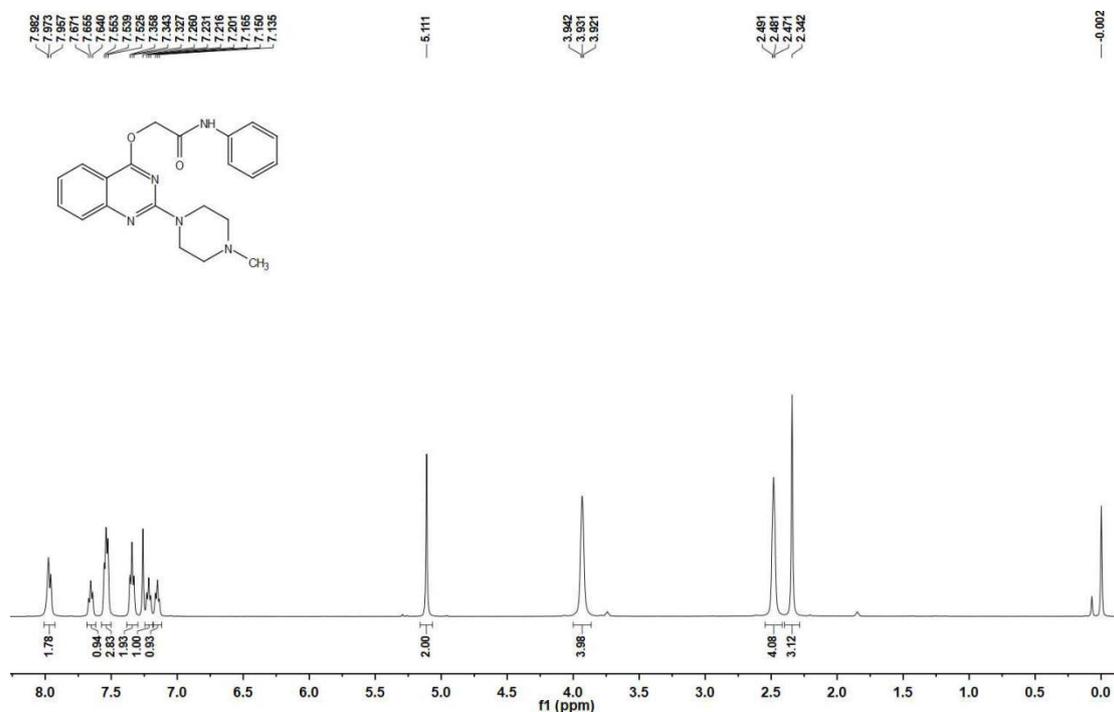


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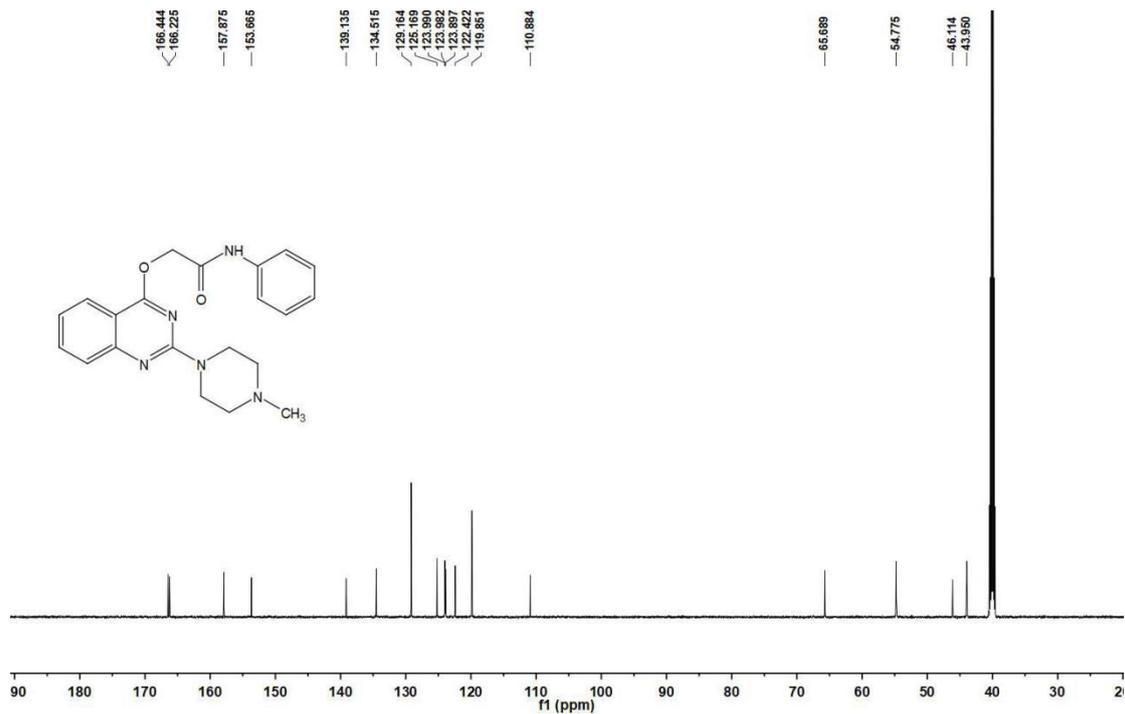
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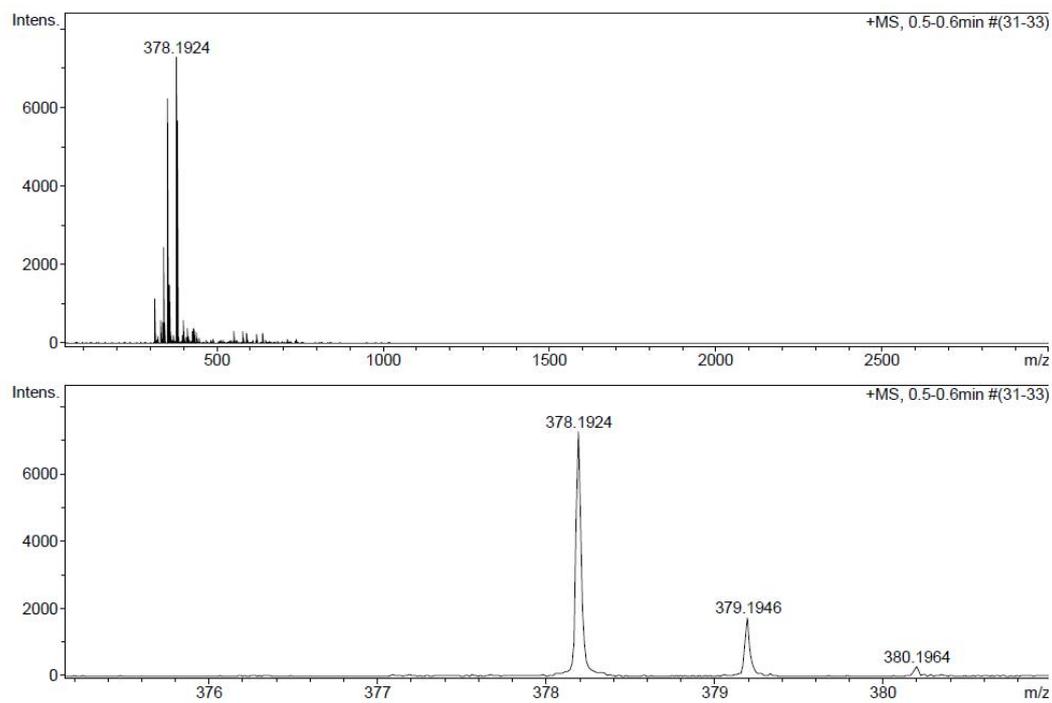
The HR-MS spectra of compound II-10a1



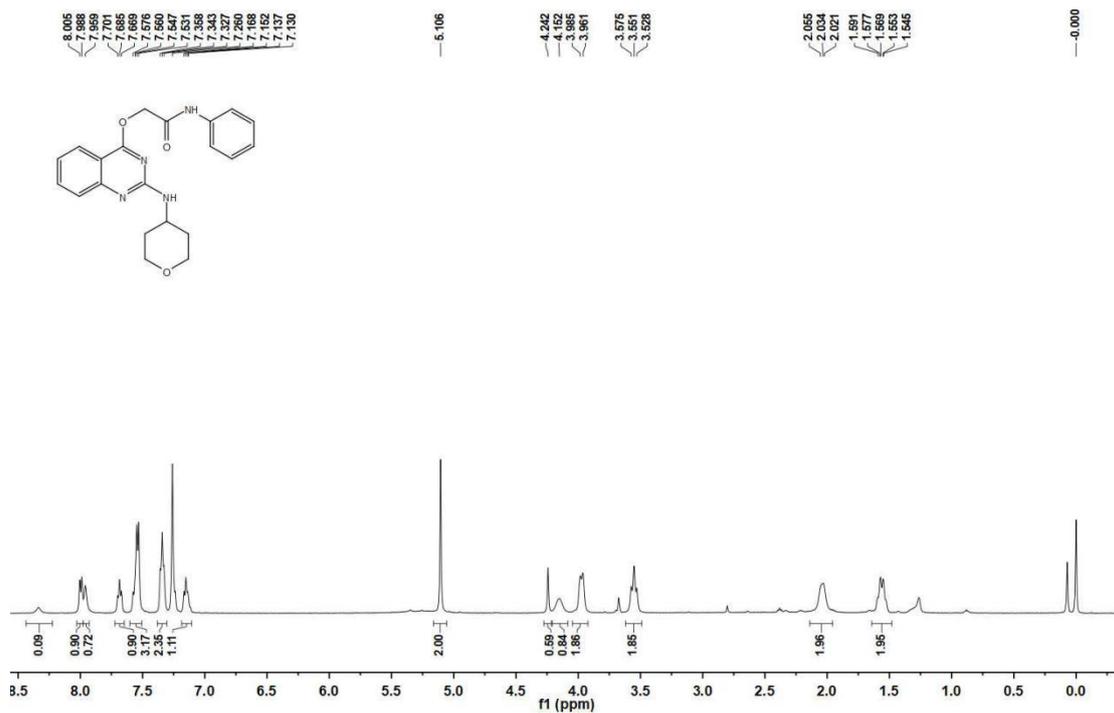
The ¹H NMR spectra of compound II-10a2



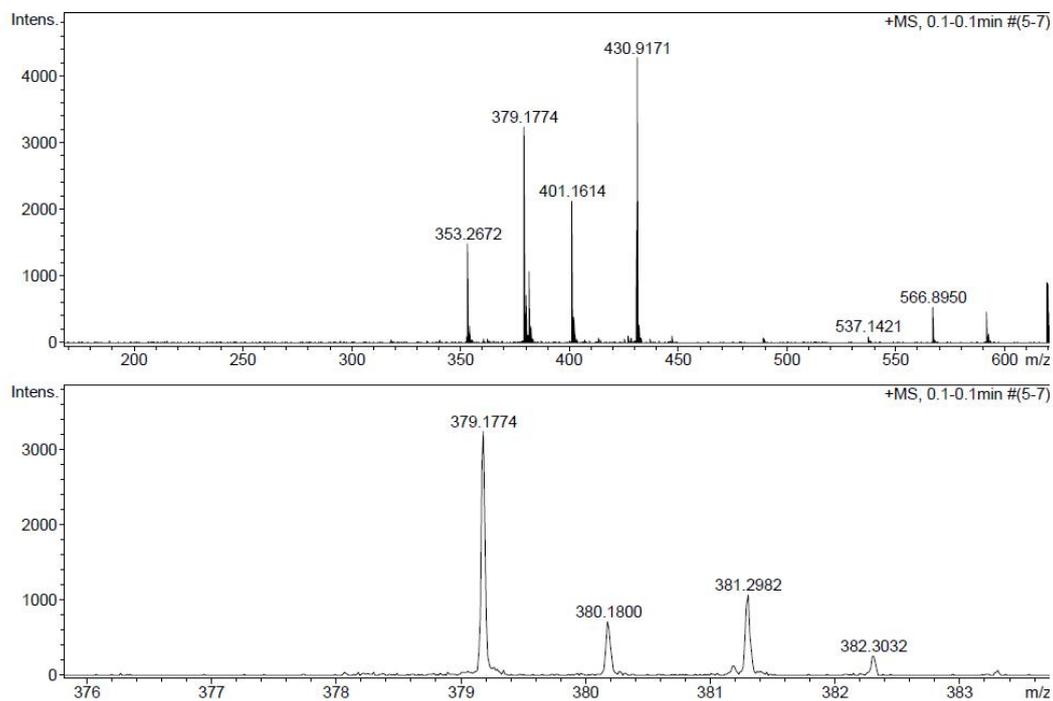
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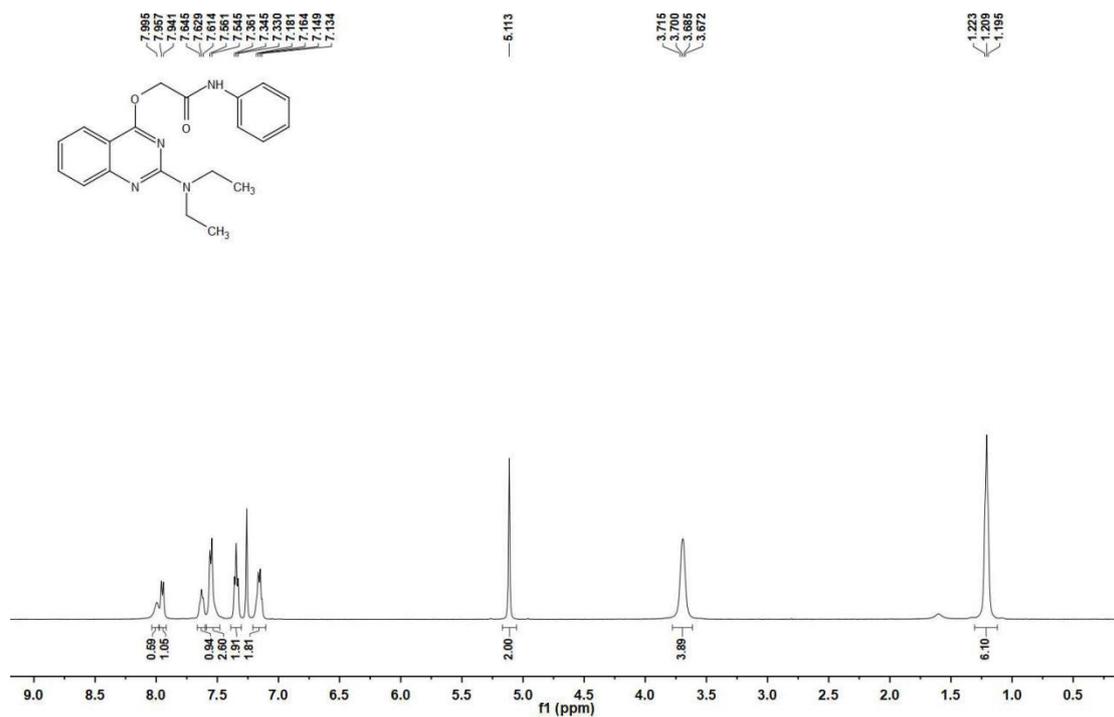
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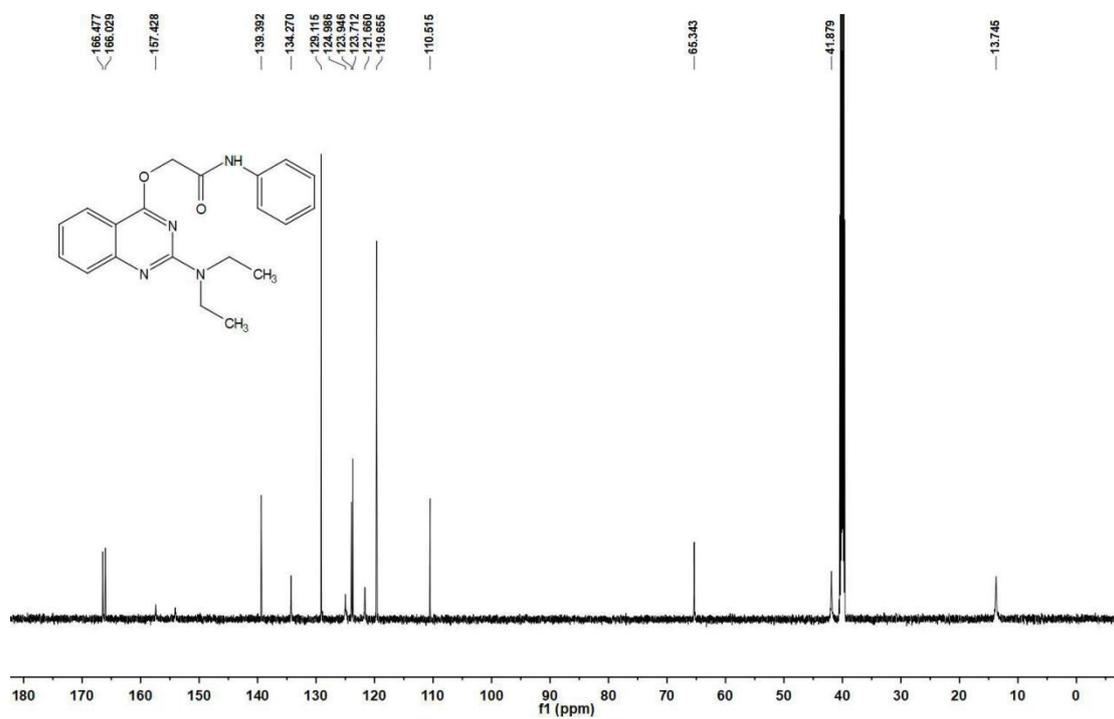
The ¹H NMR spectra of compound II-10a3



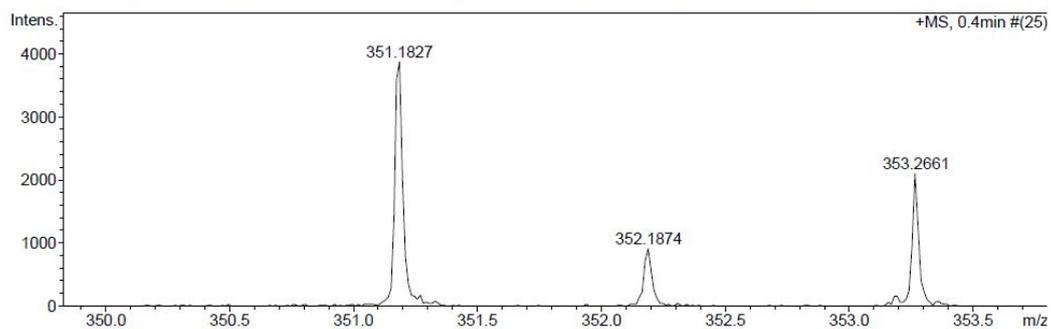
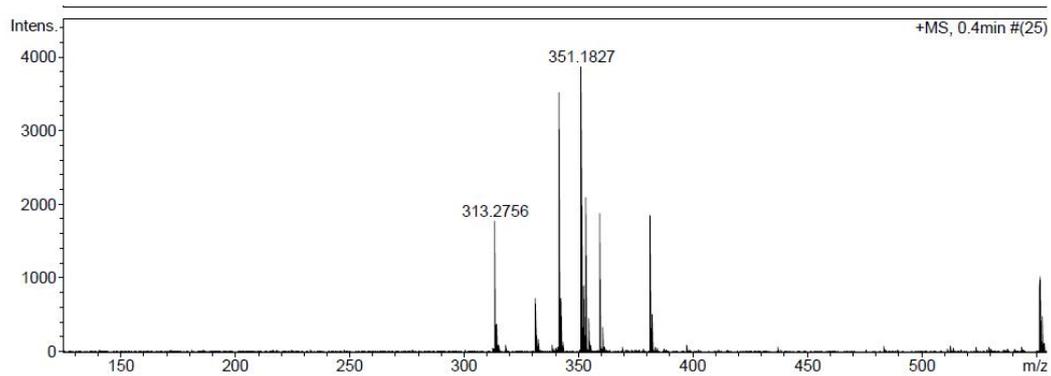
The HR-MS spectra of compound II-10a3



The ¹H NMR spectra of compound II-10a4



The ¹³C NMR spectra of compound II-10a4

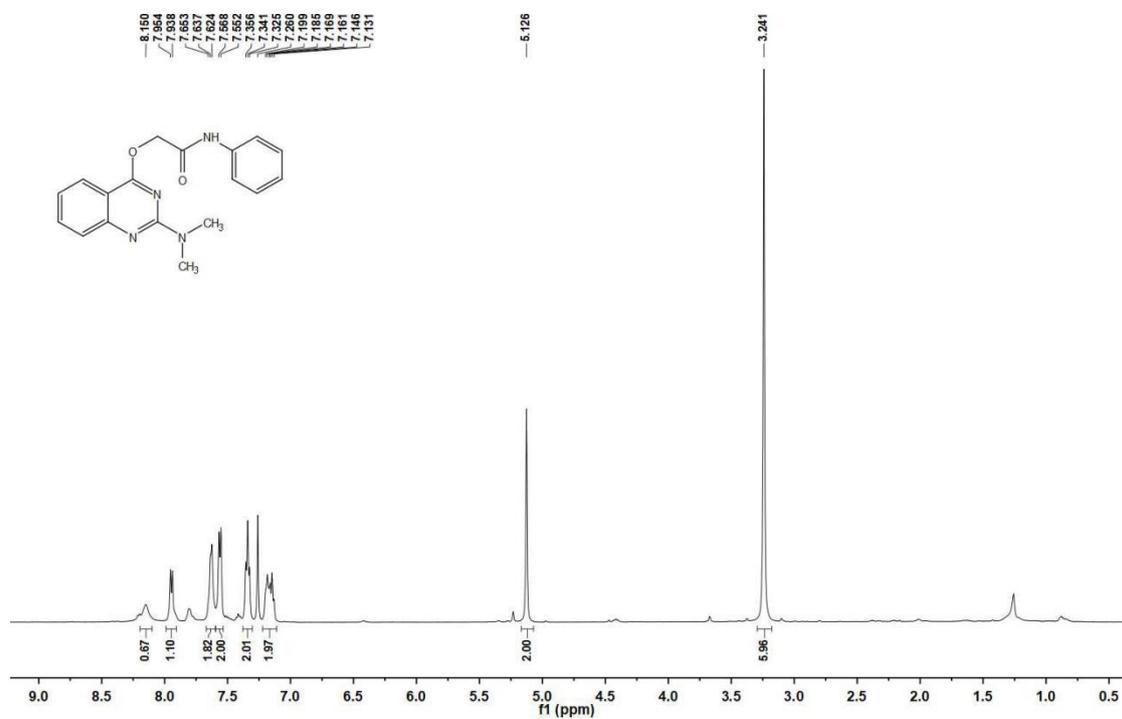


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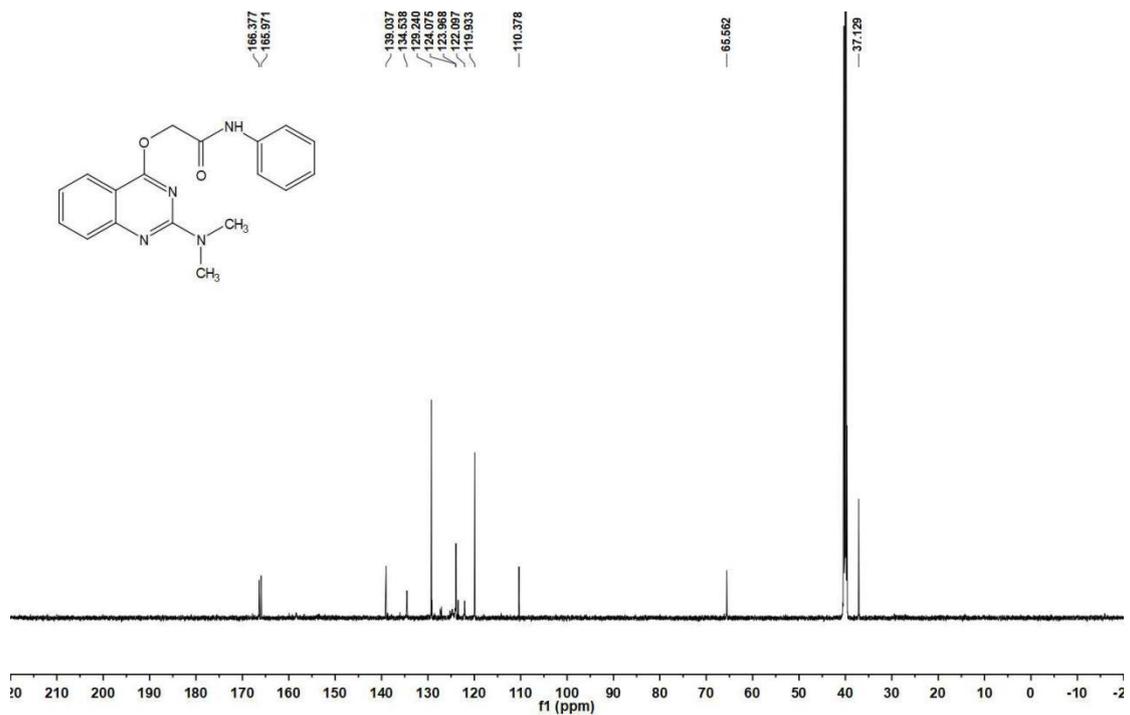
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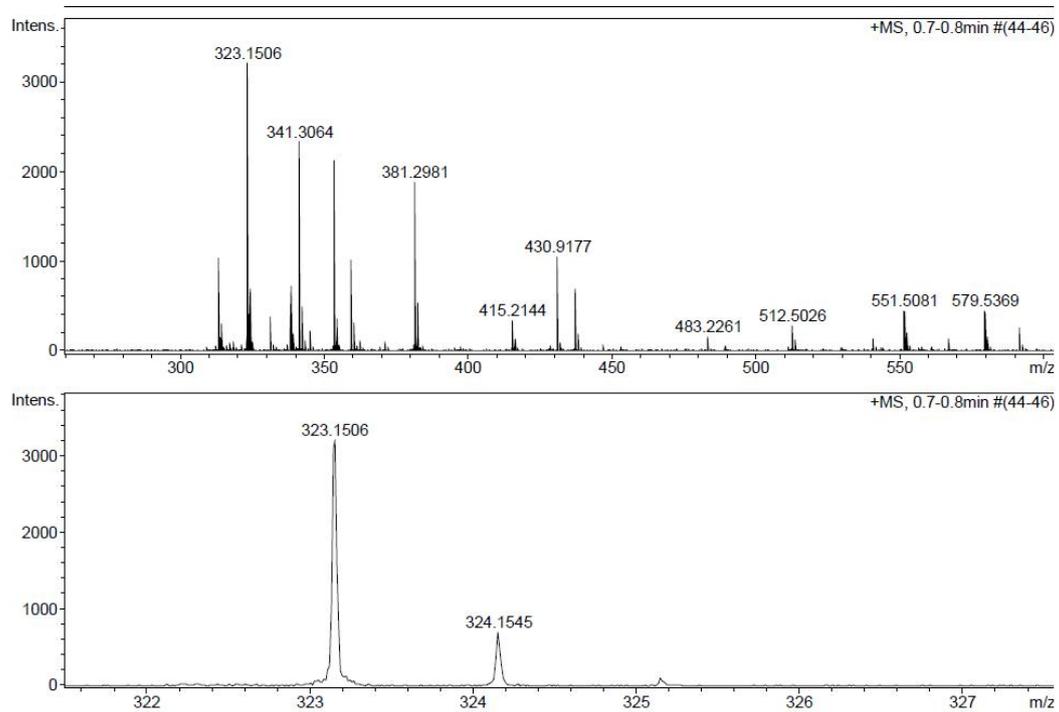
The HR-MS spectra of compound II-10a4



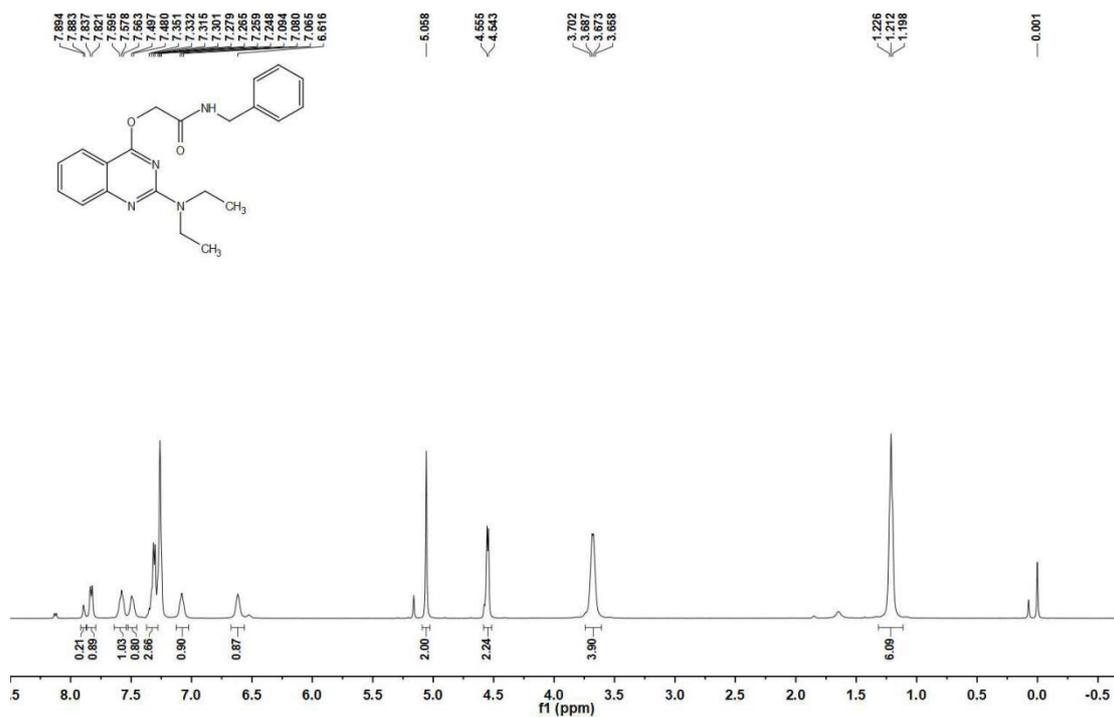
The ¹H NMR spectra of compound II-10a5



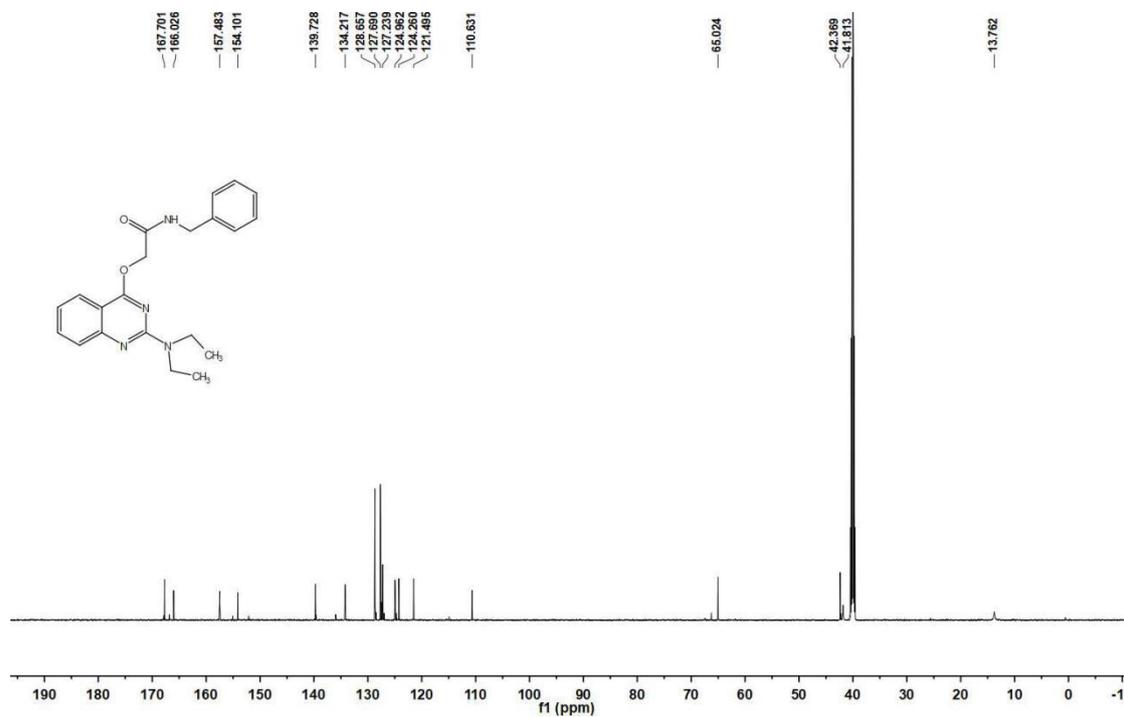
The ¹³C NMR spectra of compound II-10a5



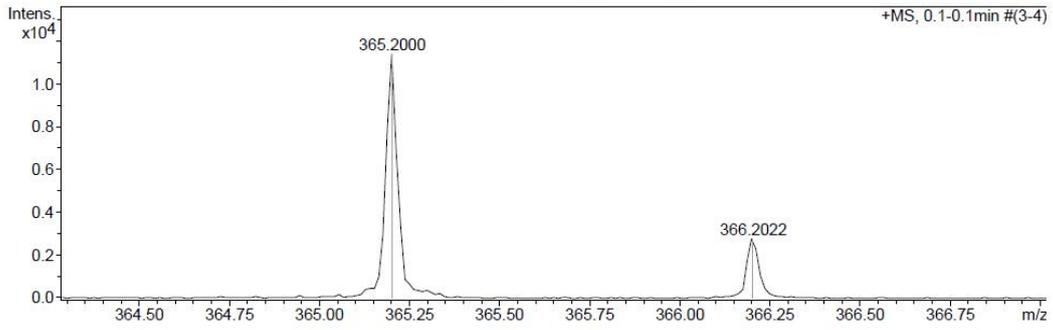
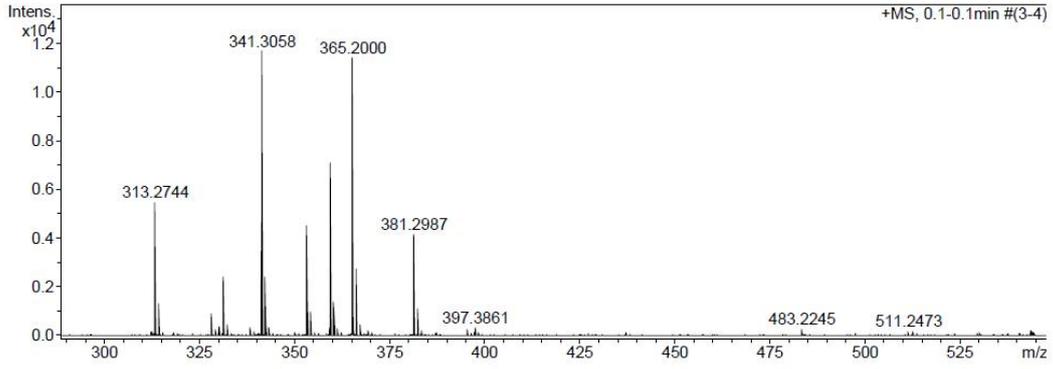
The HR-MS spectra of compound II-10a5



The ¹H NMR spectra of compound II-10a7



The ¹³C NMR spectra of compound II-10a7

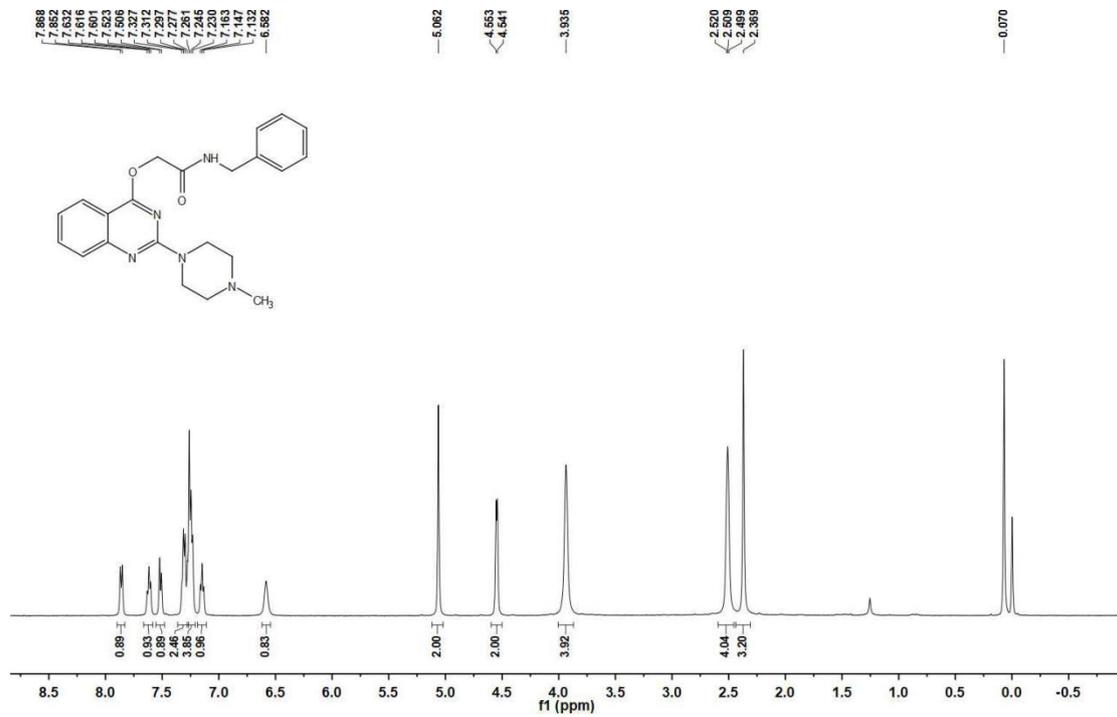


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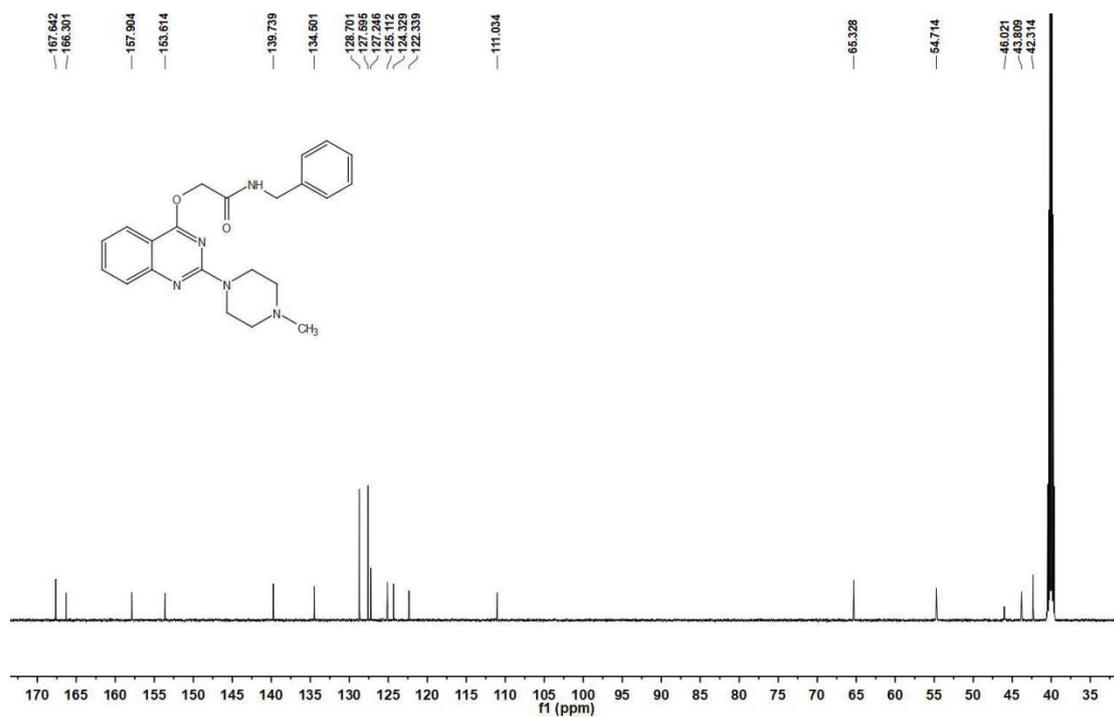
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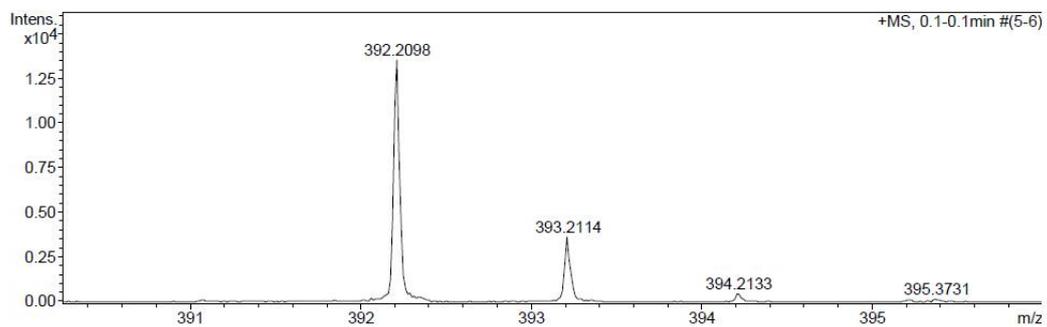
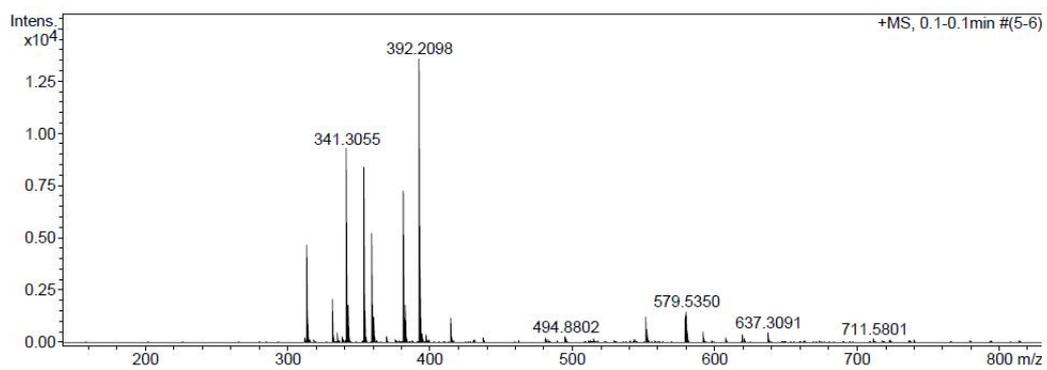
The HR-MS spectra of compound II-10a7



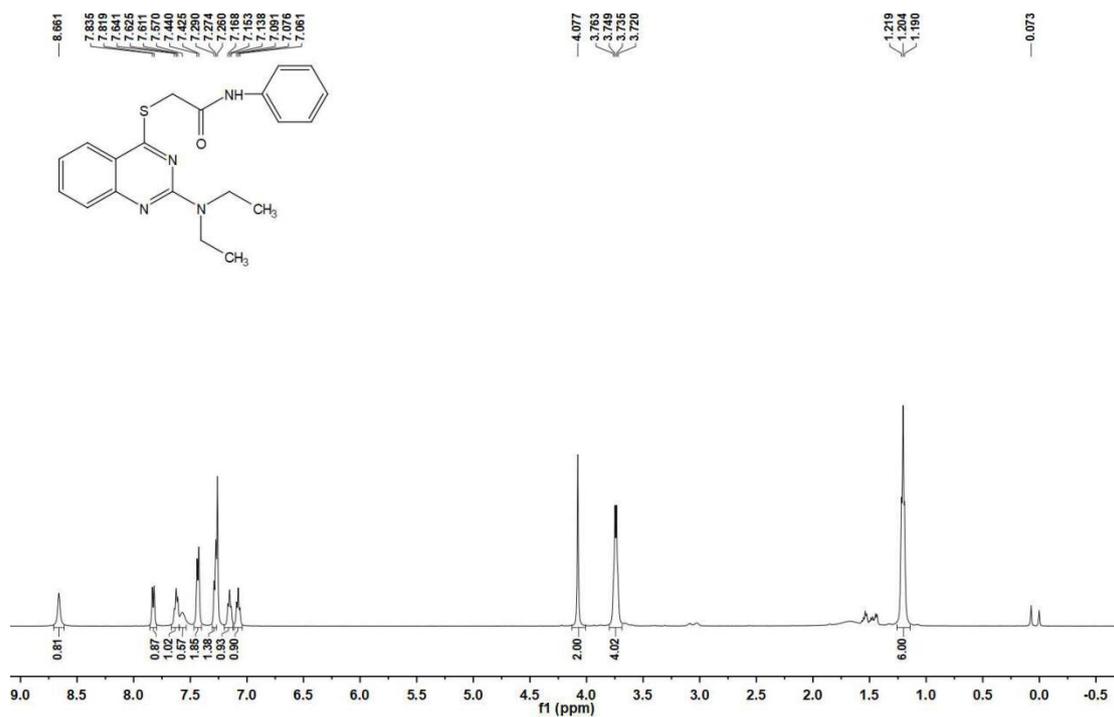
The ¹H NMR spectra of compound II-10a8



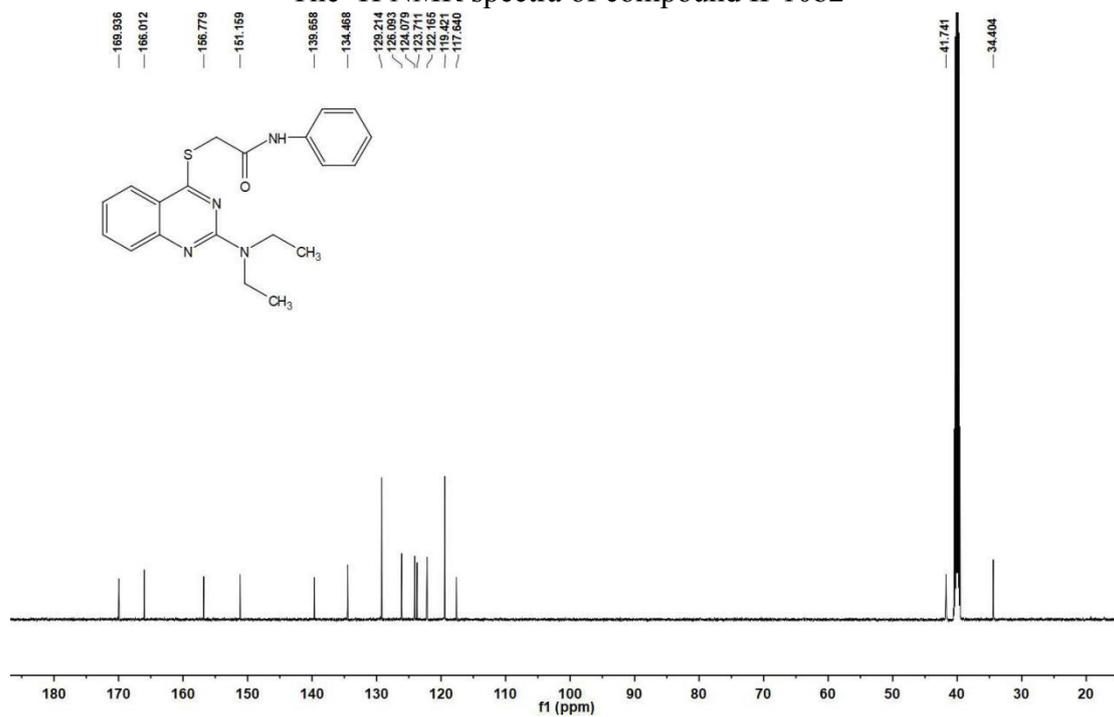
The ^{13}C NMR spectra of compound II-10a8



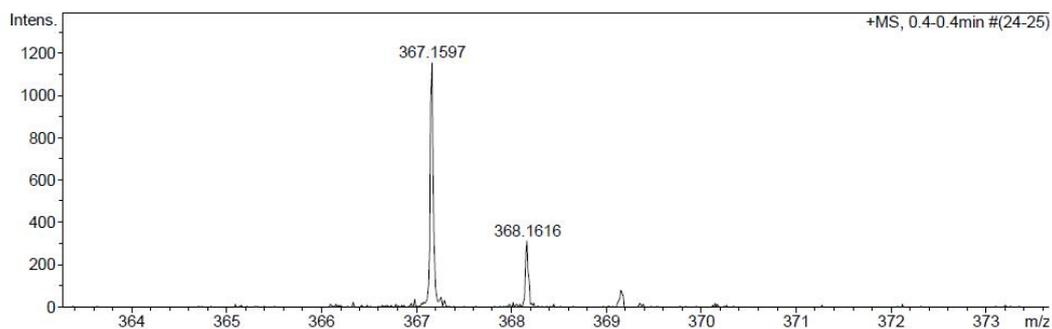
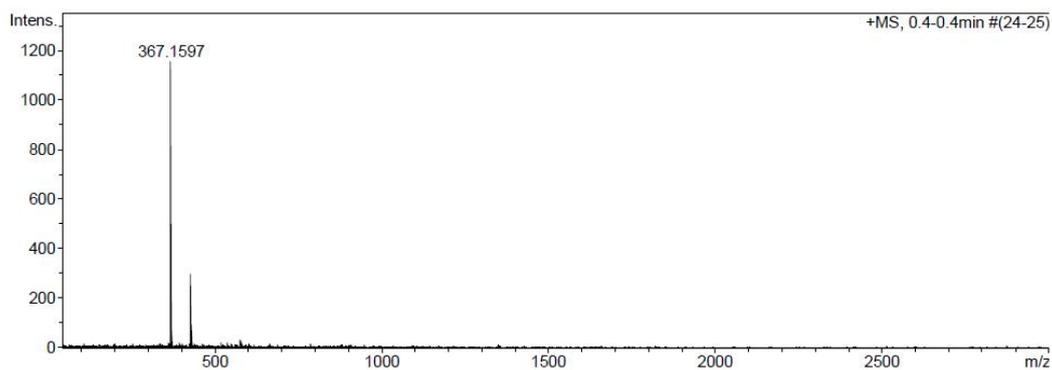
The HR-MS spectra of compound II-10a8



The ^1H NMR spectra of compound II-10b2



The ^{13}C NMR spectra of compound II-10b2

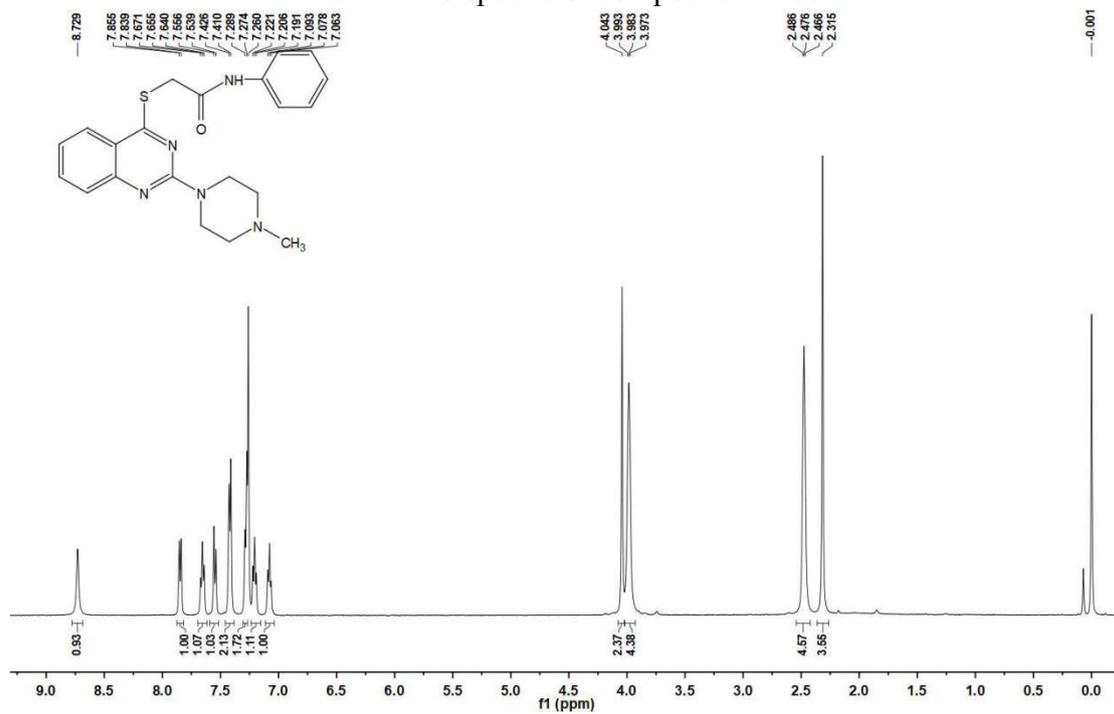


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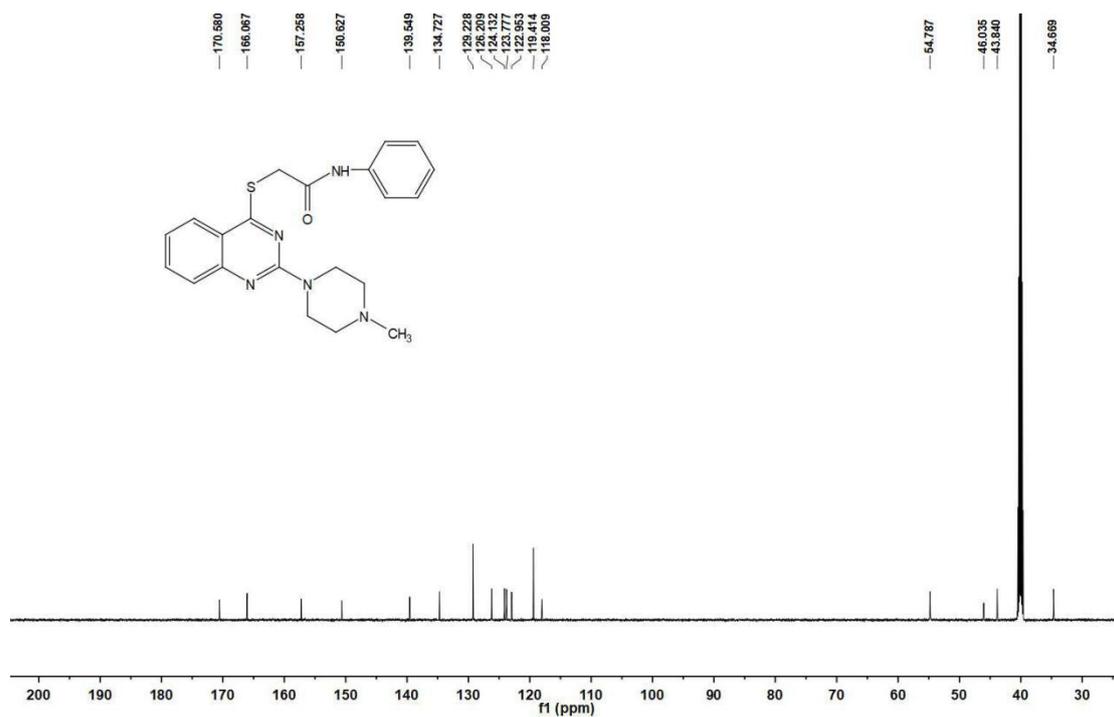
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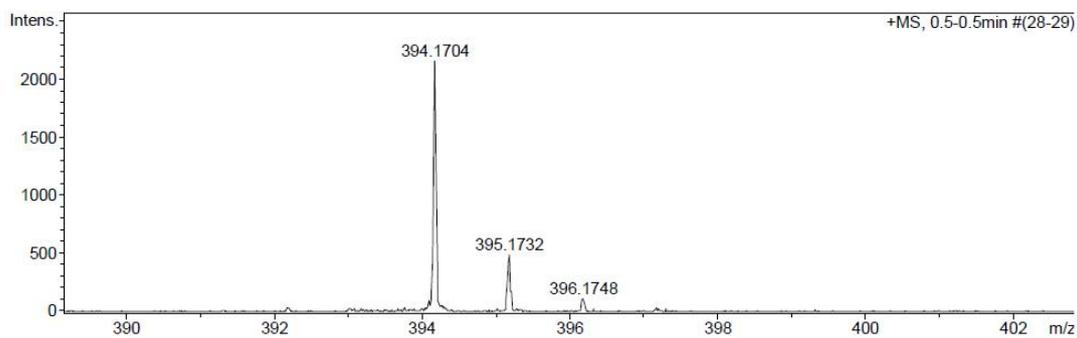
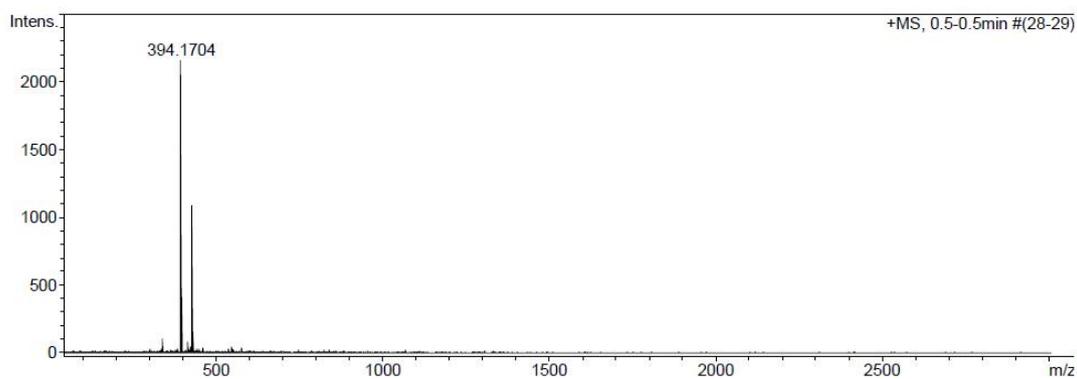
The HR-MS spectra of compound II-10b2



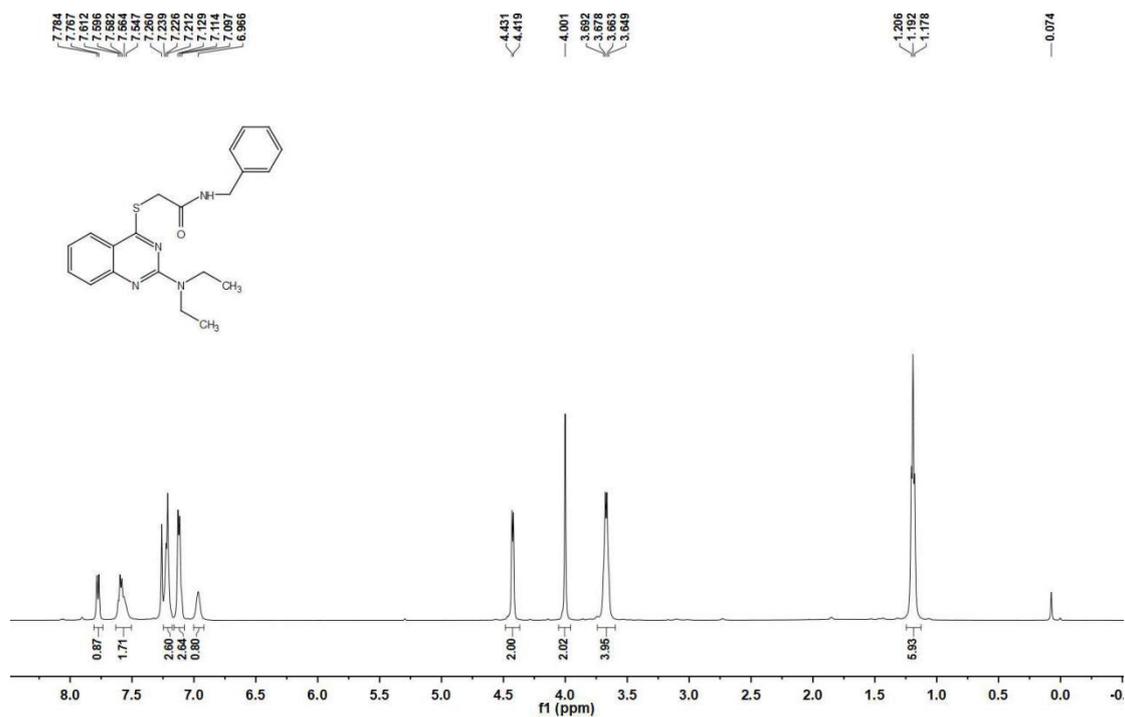
The ¹H NMR spectra of compound II-10b3



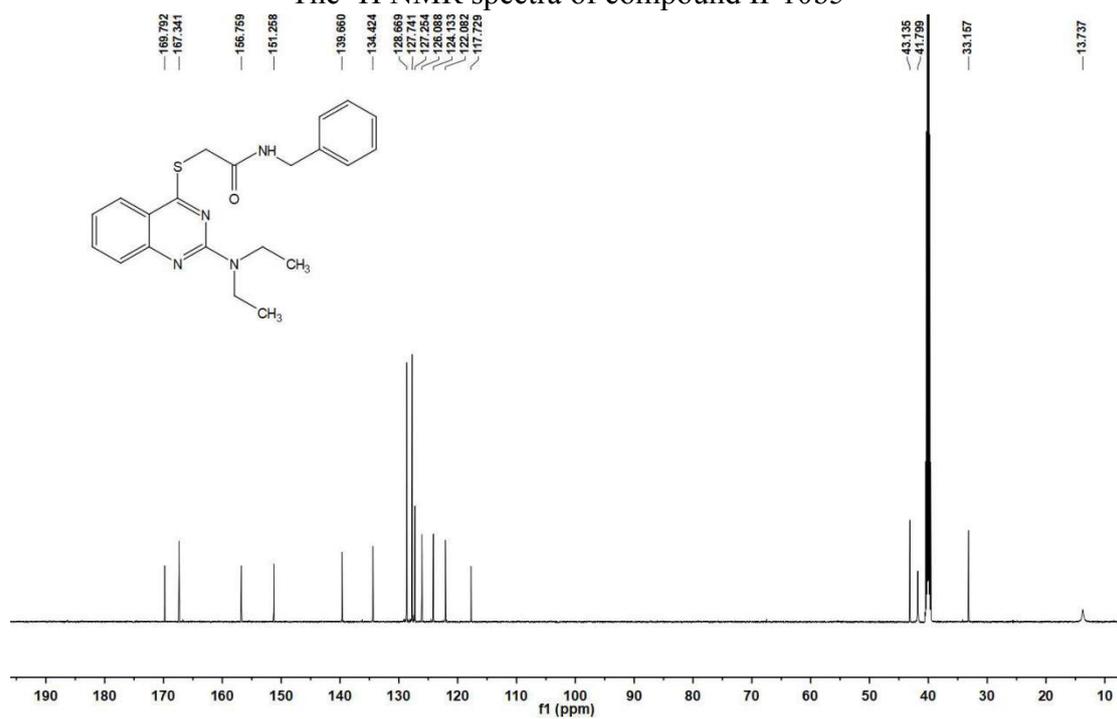
The ¹³C NMR spectra of compound II-10b3



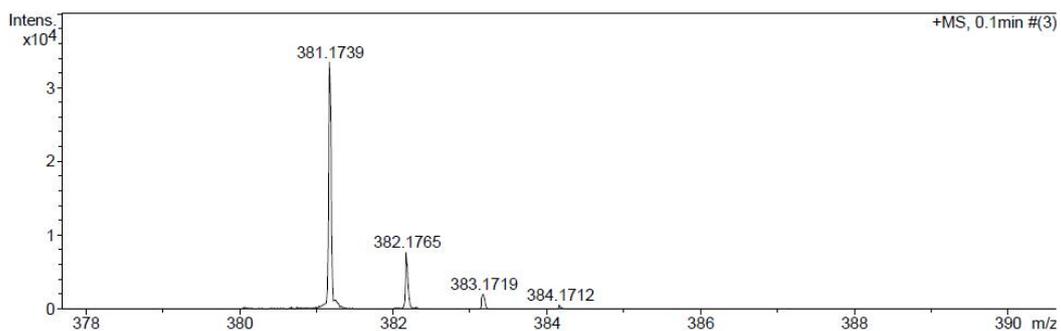
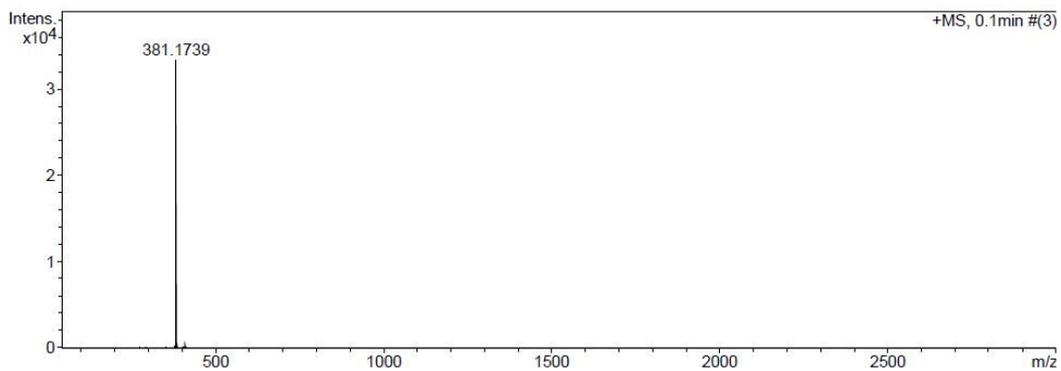
The HR-MS spectra of compound II-10b3



The ¹H NMR spectra of compound II-10b5



The ¹³C NMR spectra of compound II-10b5

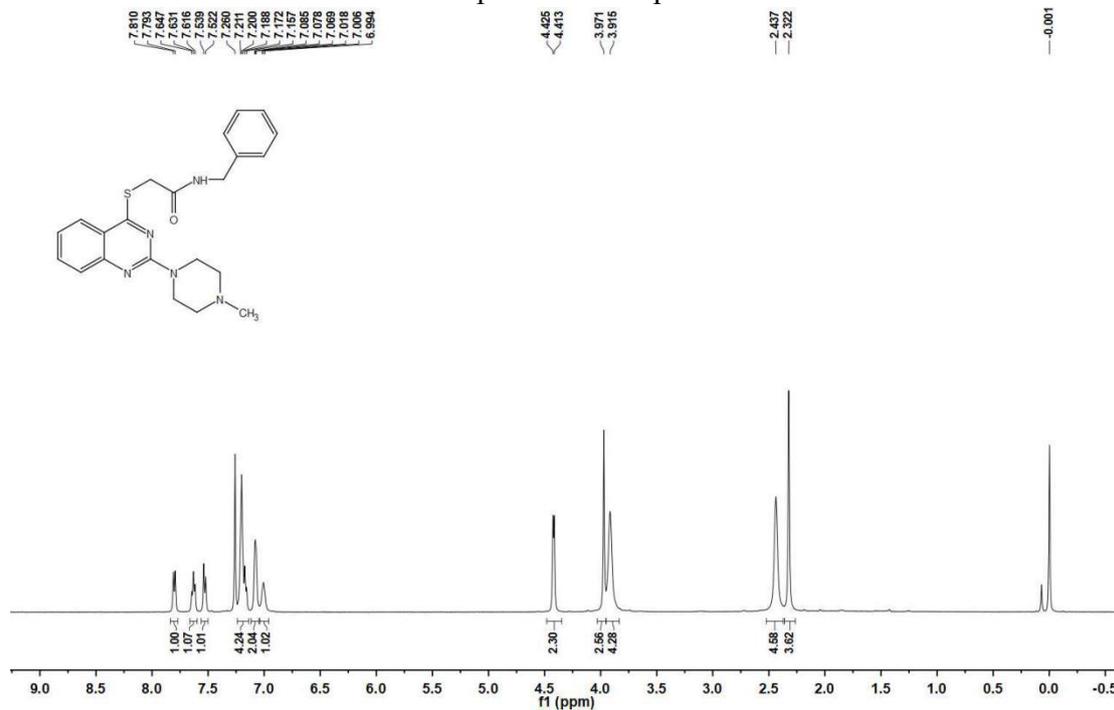


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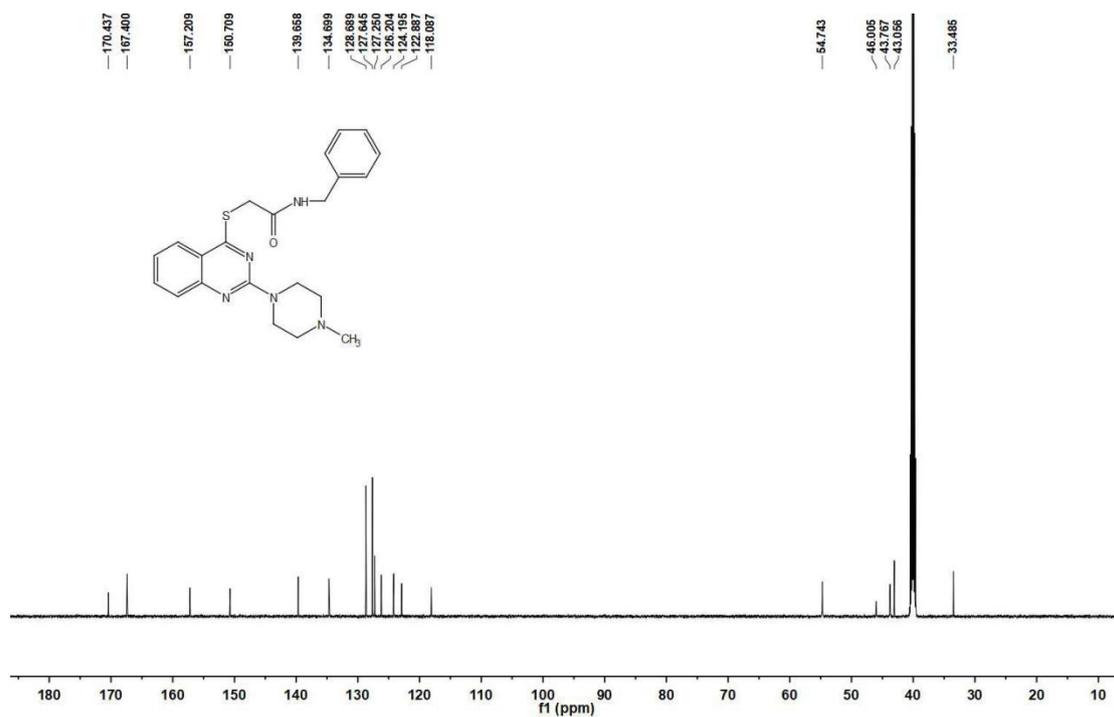
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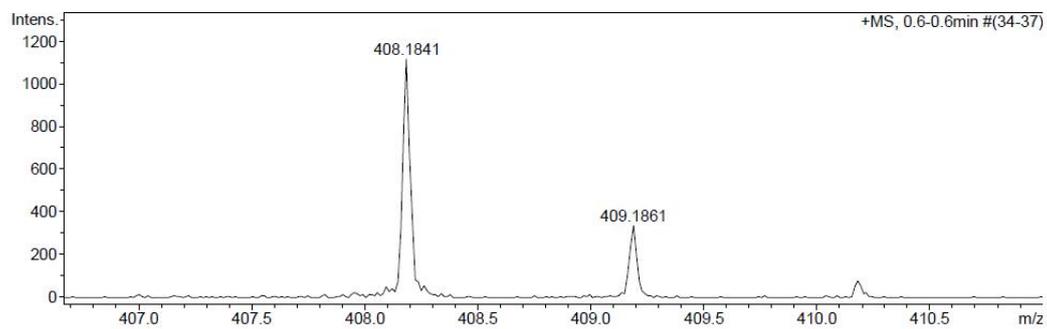
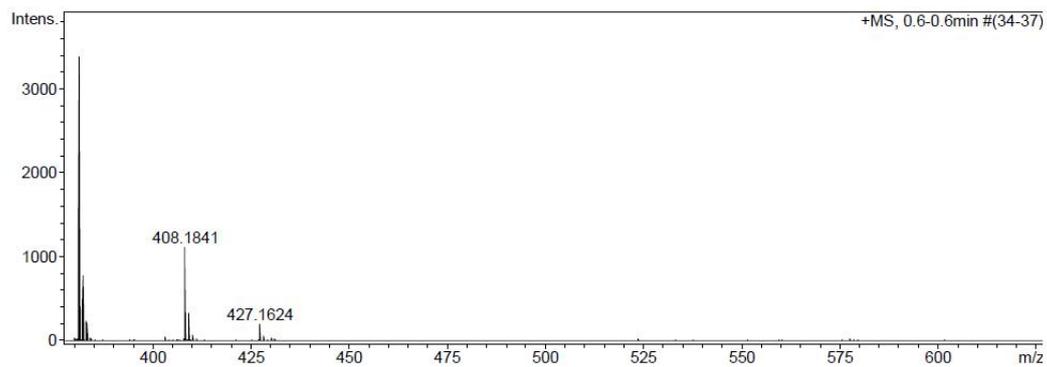
The HR-MS spectra of compound II-10b5



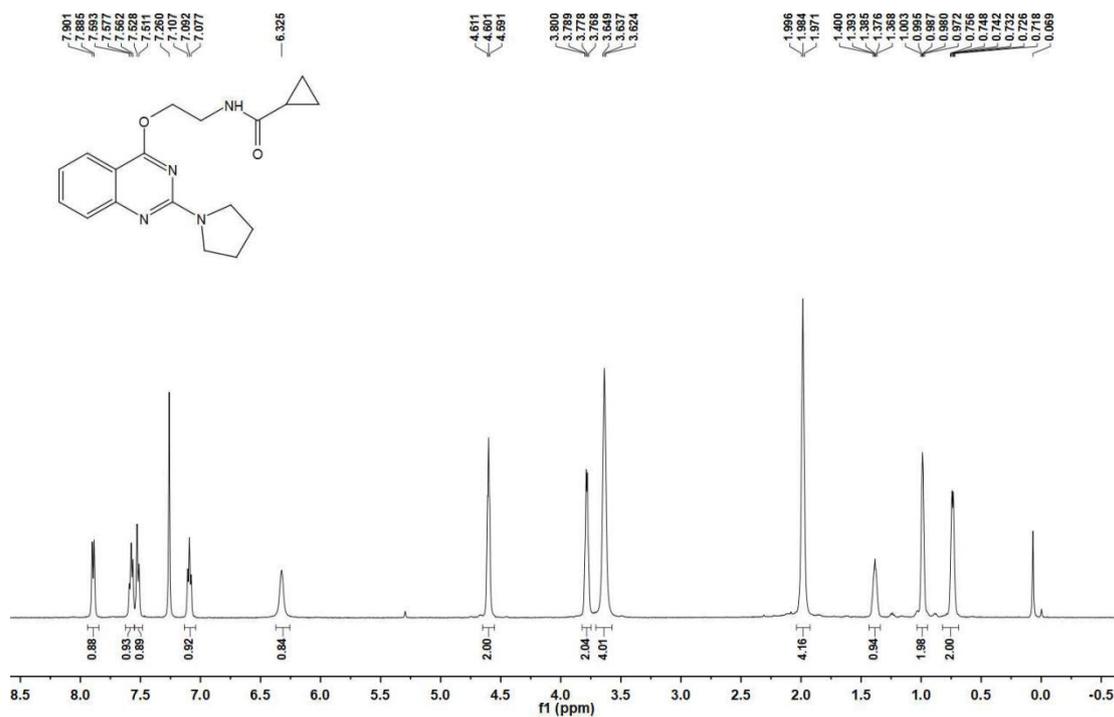
The ¹H NMR spectra of compound II-10b6



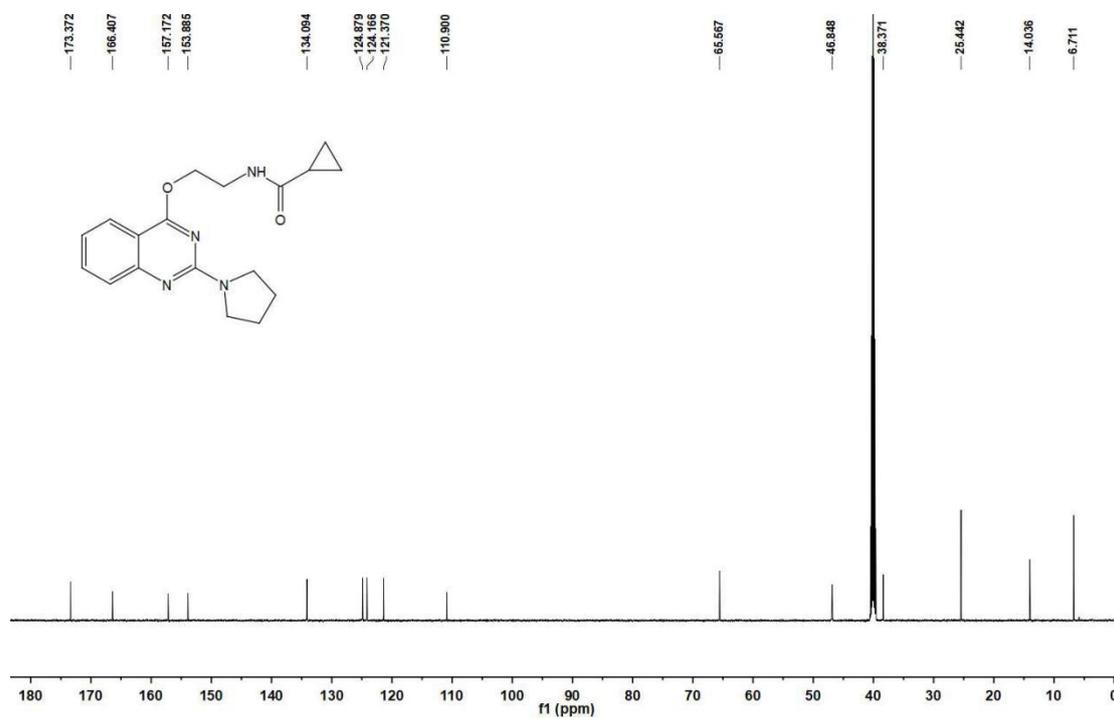
The ¹³C NMR spectra of compound II-10b6



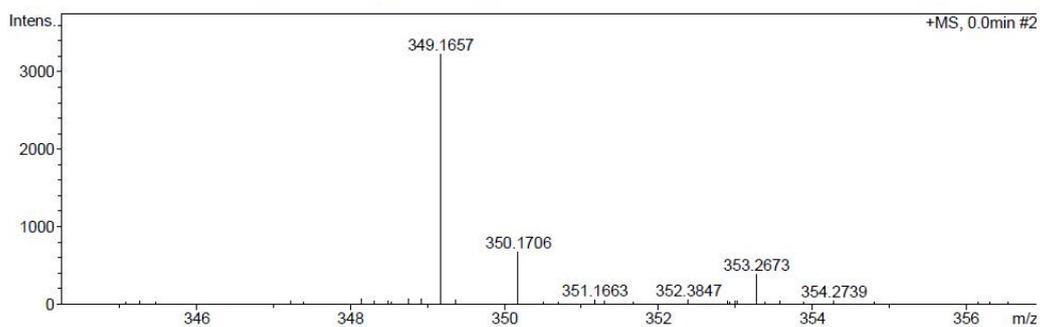
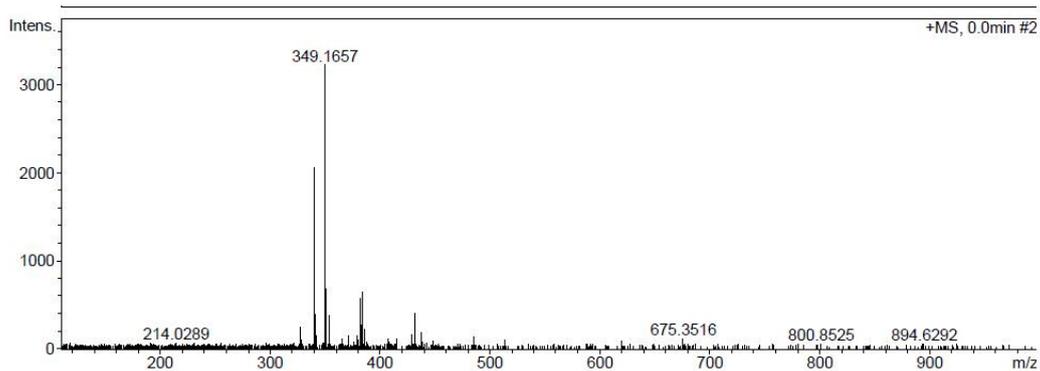
The HR-MS spectra of compound II-10b6



The ¹H NMR spectra of compound II-14a



The ¹³C NMR spectra of compound II-14a



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The HR-MS spectra of compound II-14a

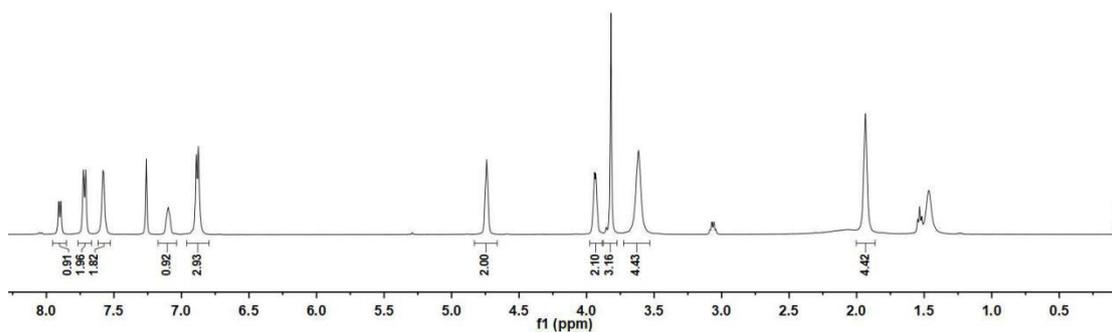
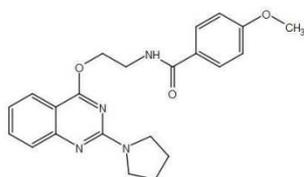
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7.893
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7.574
7.280
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7.105
7.088
7.081
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6.874

4.750
4.730

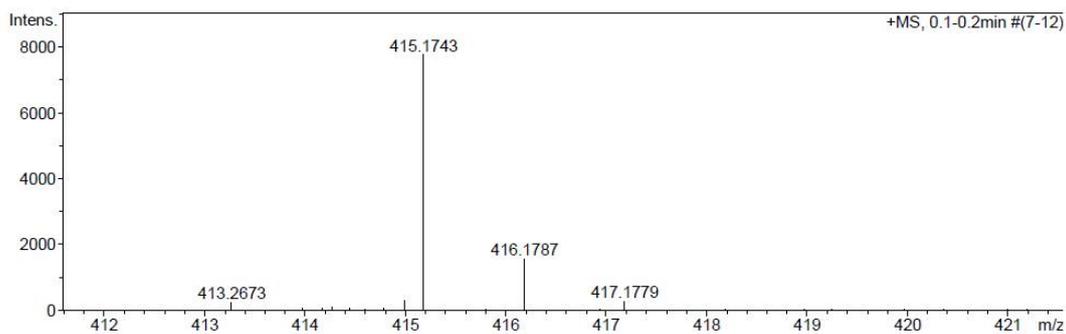
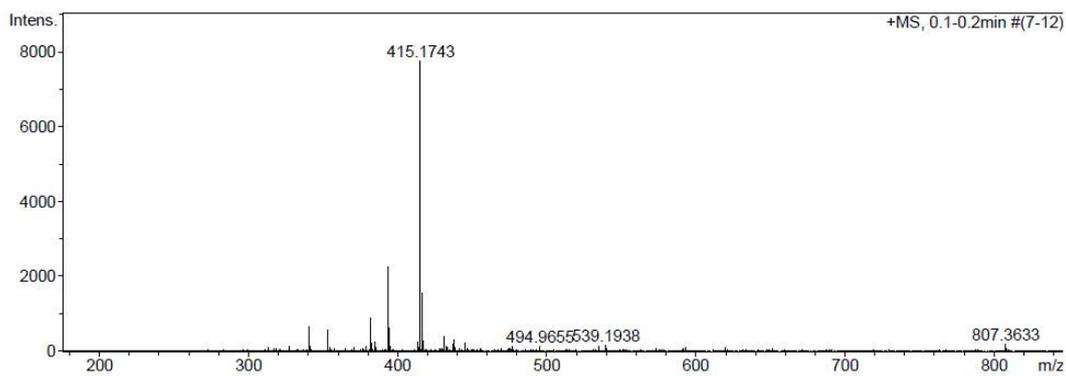
3.952
3.941
3.931
3.920
3.820
3.830
3.617
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1.947
1.935
1.923

1.466



The ¹H NMR spectra of compound II-14b

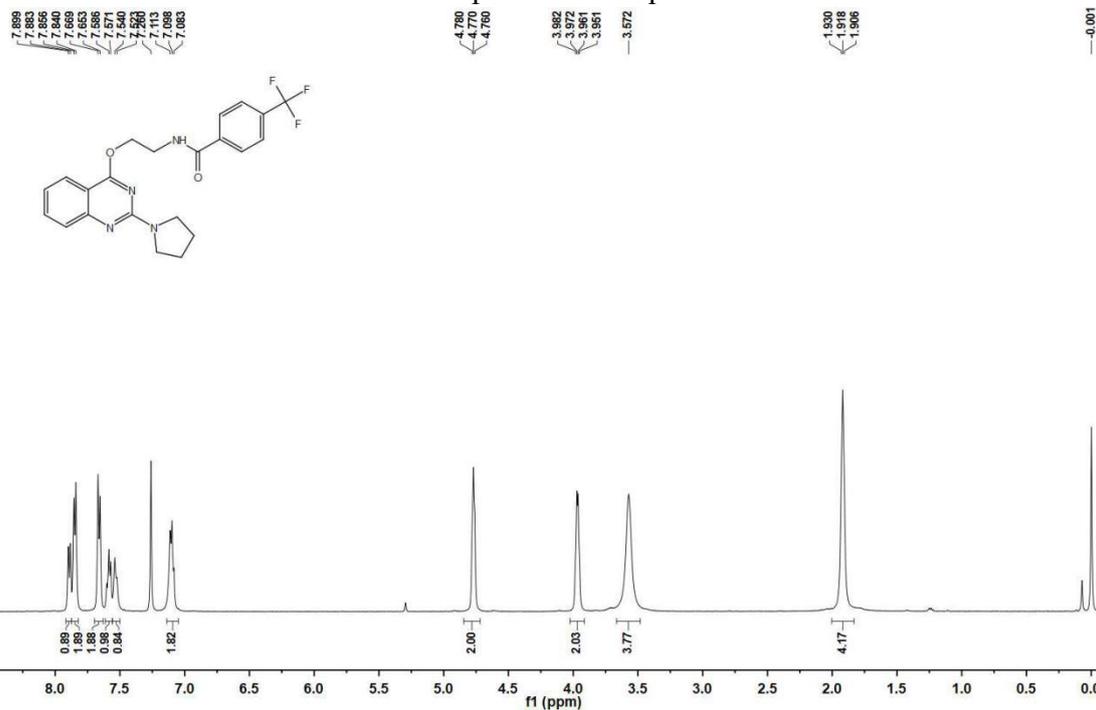


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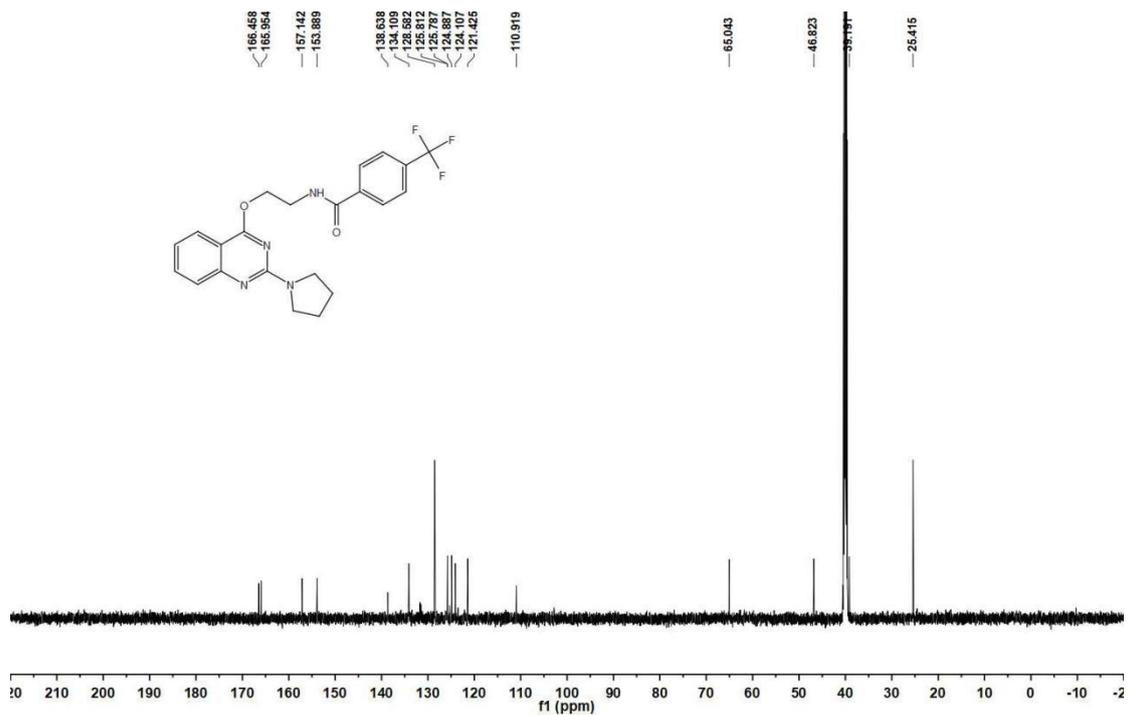
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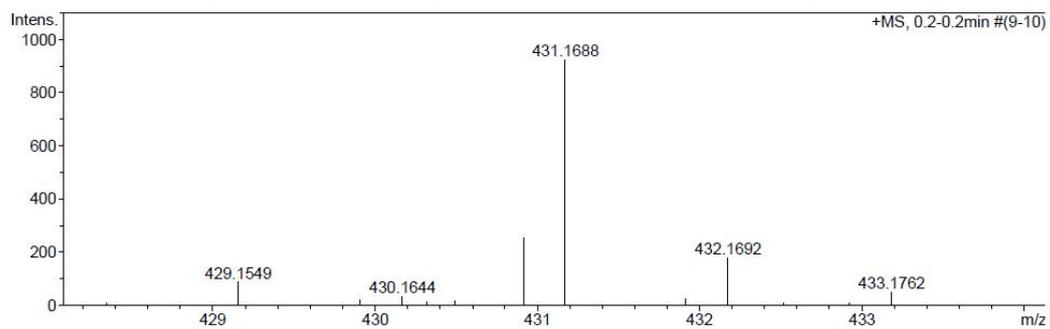
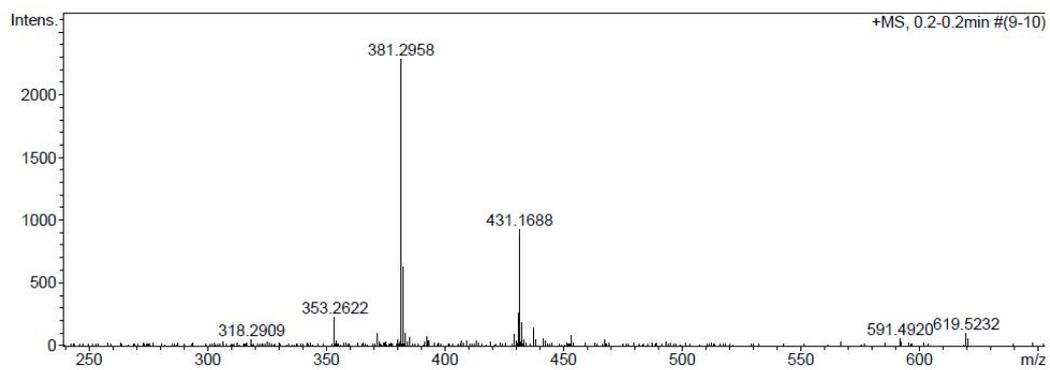
The HR-MS spectra of compound II-14b



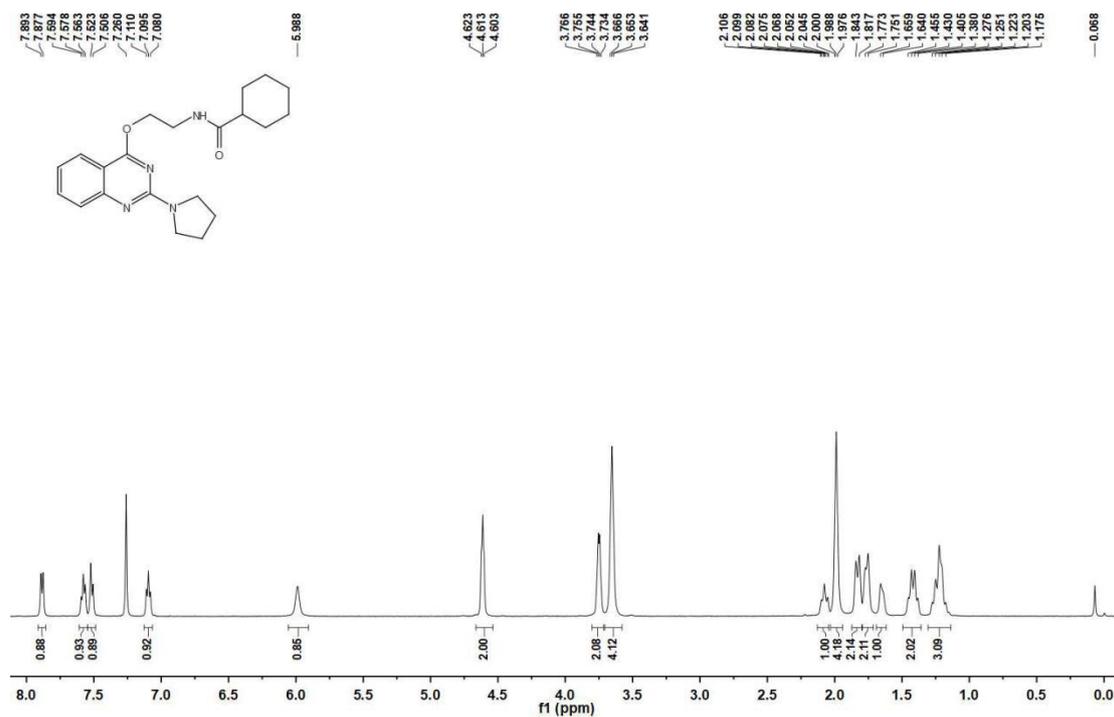
The ¹H NMR spectra of compound II-14c



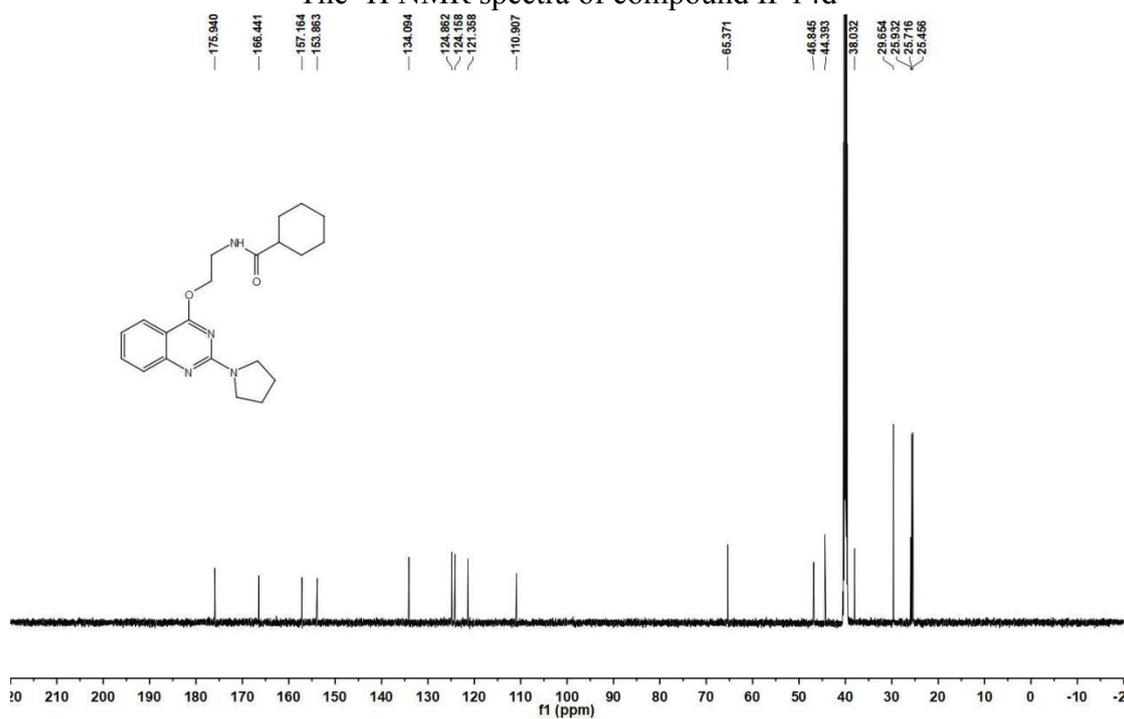
The ¹³C NMR spectra of compound II-14c



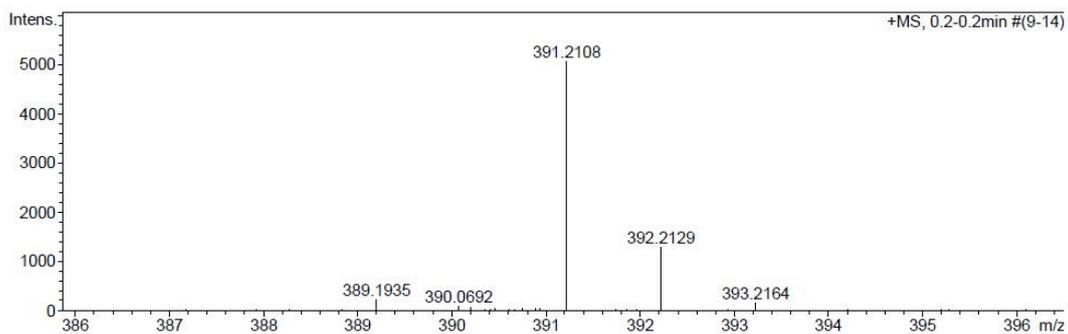
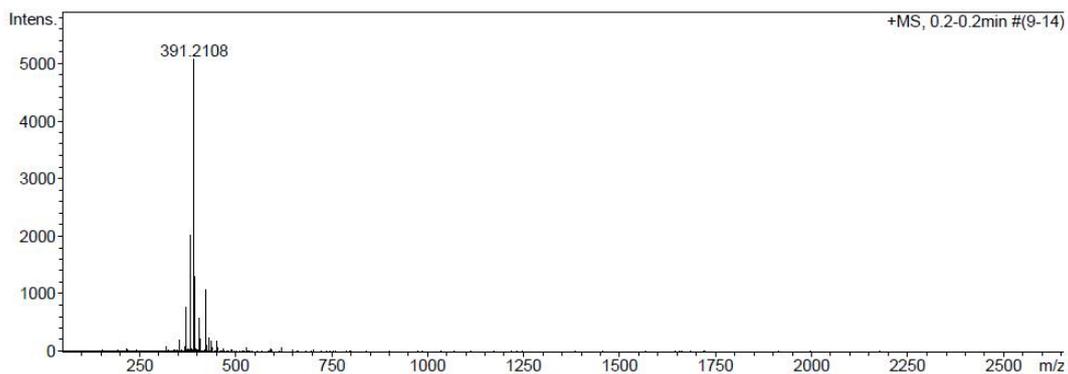
The HR-MS spectra of compound II-14c



The ¹H NMR spectra of compound II-14d



The ¹³C NMR spectra of compound II-14d

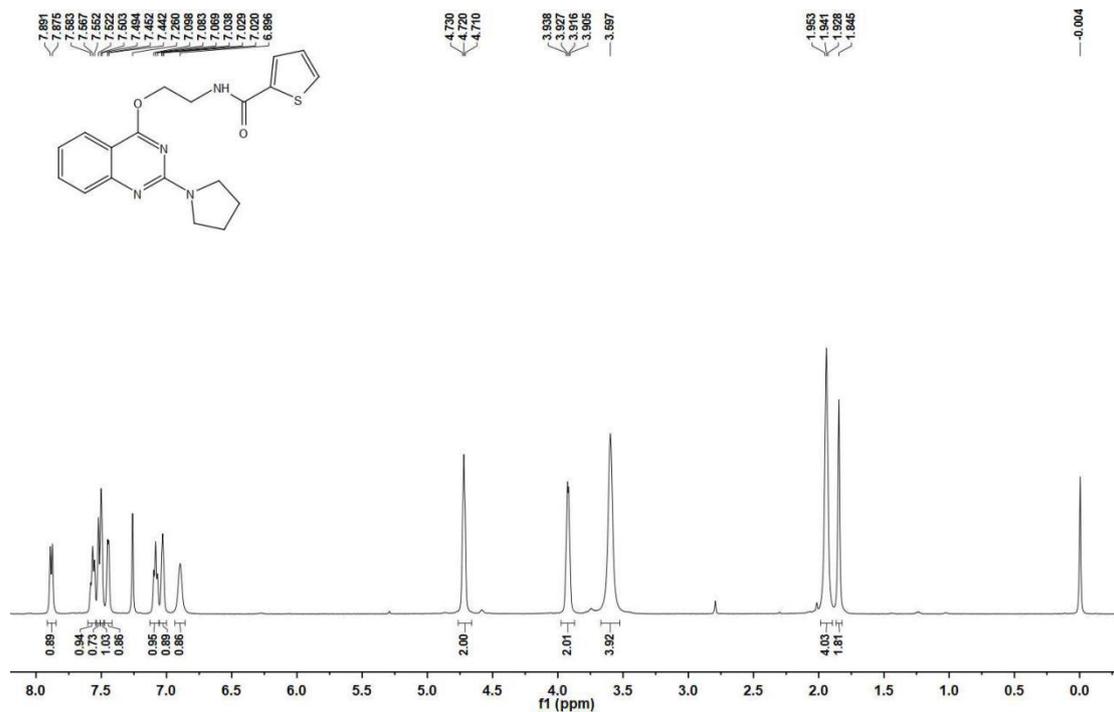


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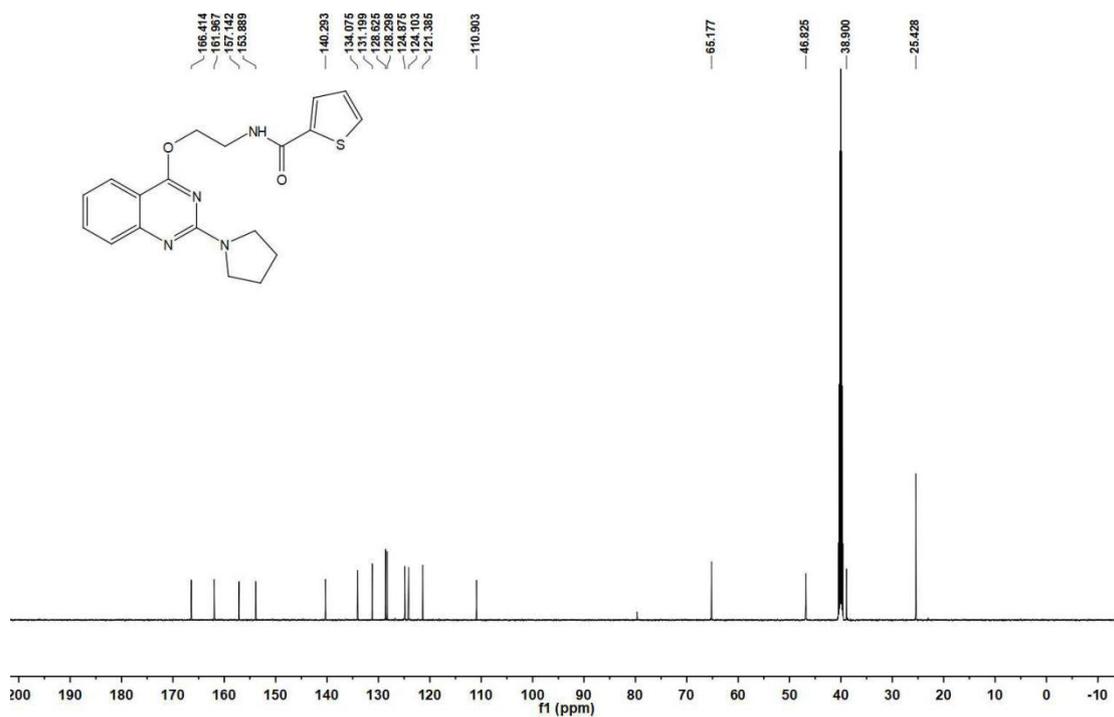
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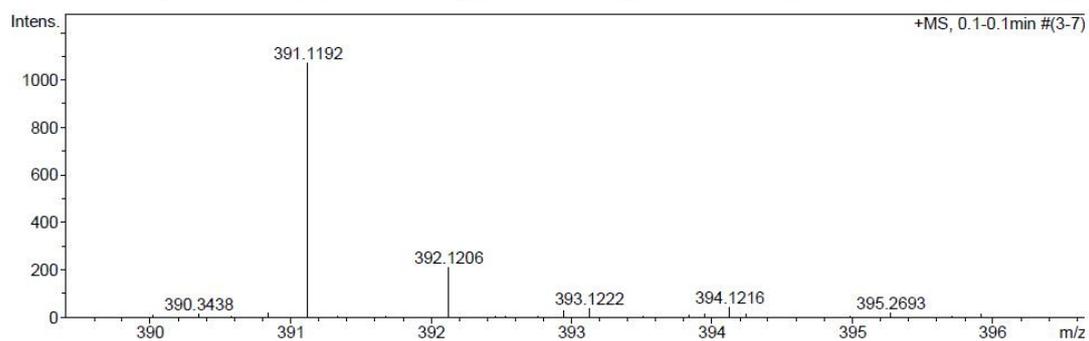
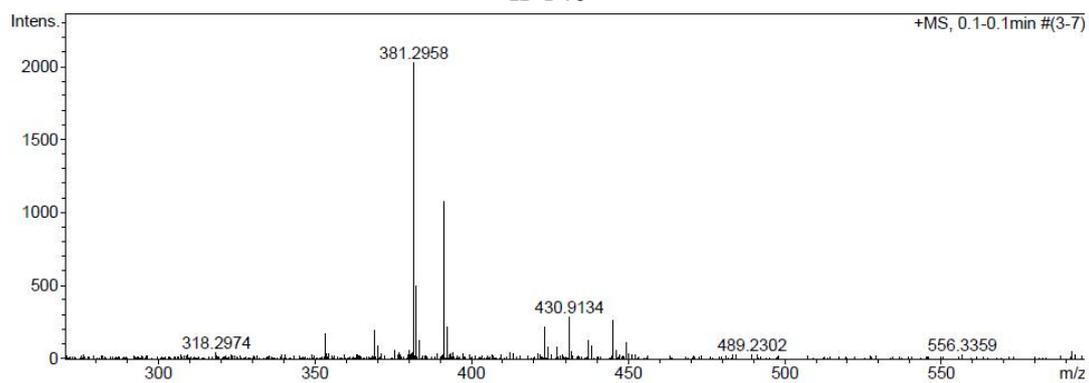
The HR-MS spectra of compound II-14d



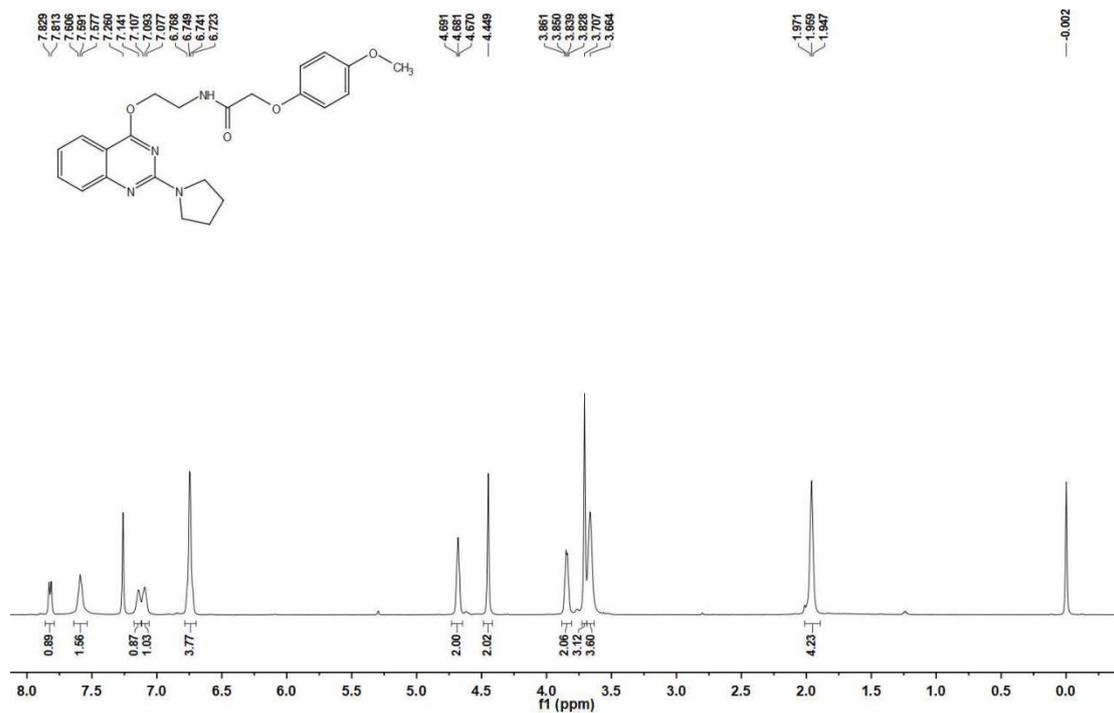
The ¹H NMR spectra of compound II-14e



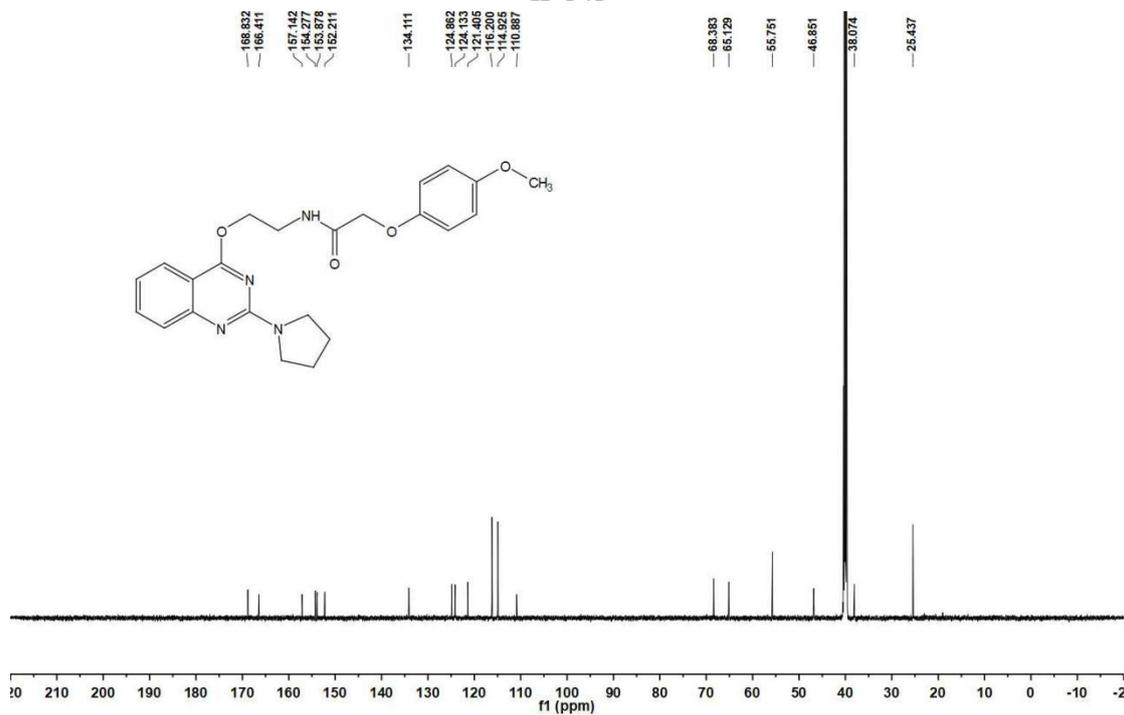
The ¹³C NMR spectra of compound II-14e



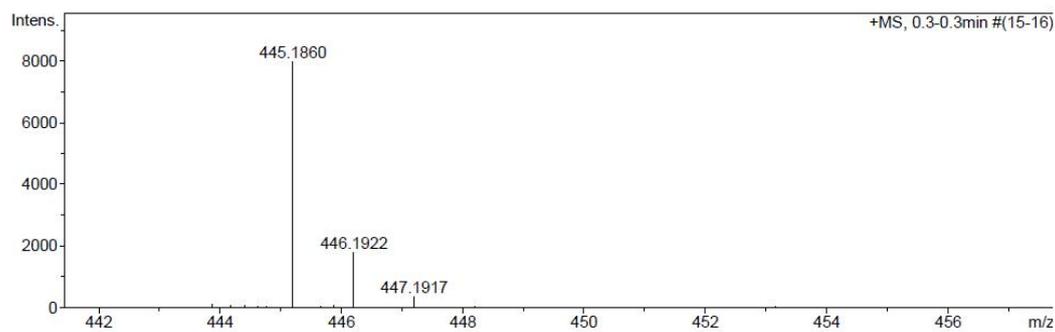
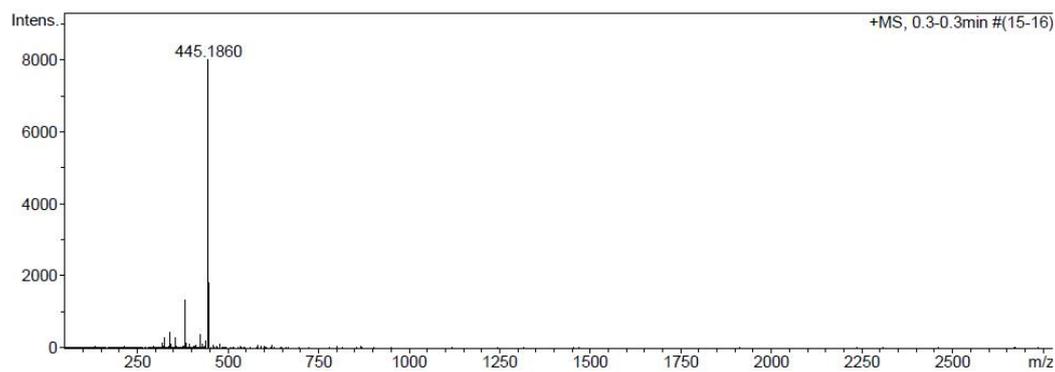
The HR-MS spectra of compound II-14e



The ¹H NMR spectra of compound II-14f



The ¹³C NMR spectra of compound II-14f

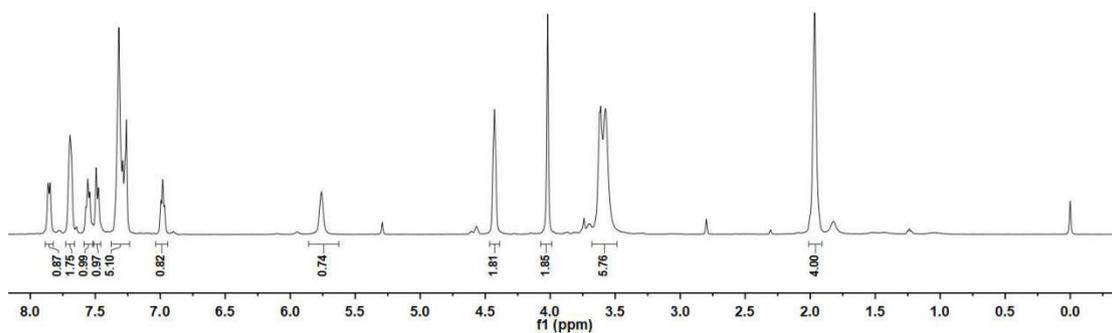
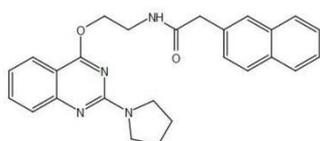


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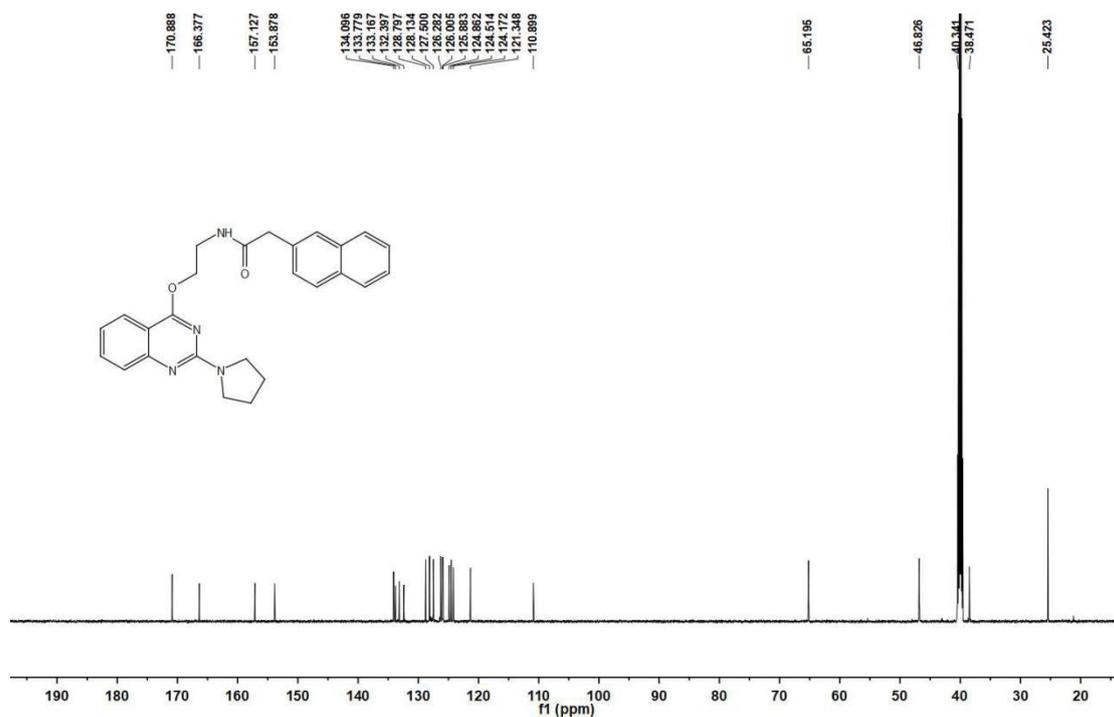
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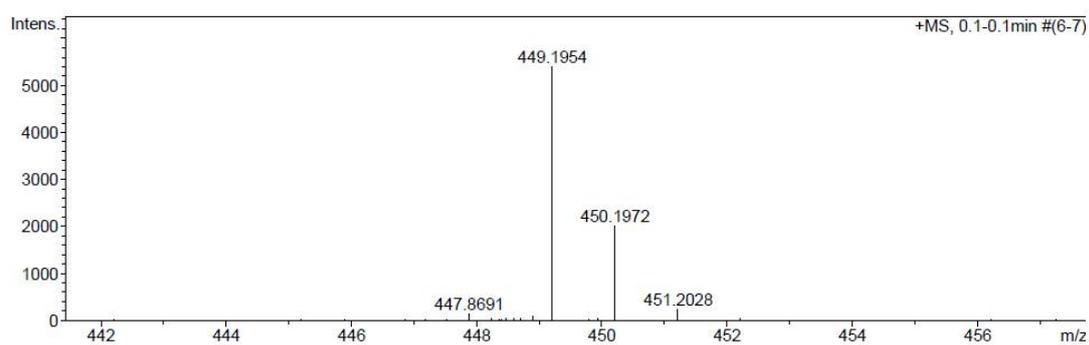
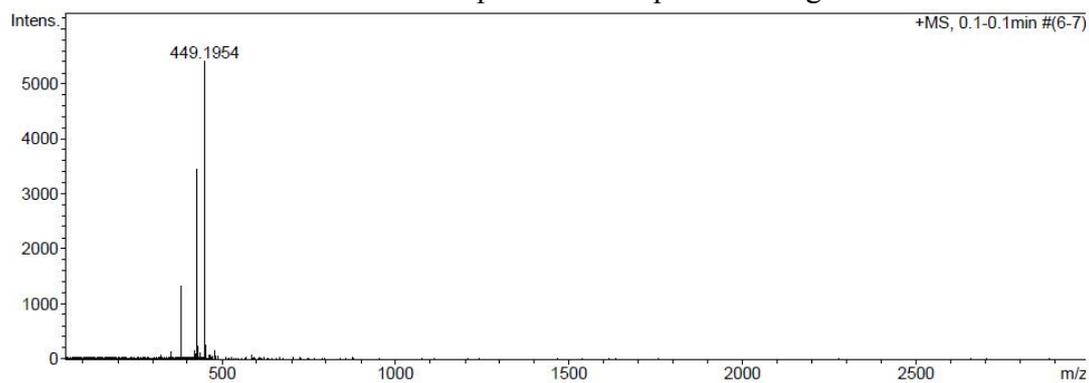
The HR-MS spectra of compound II-14f



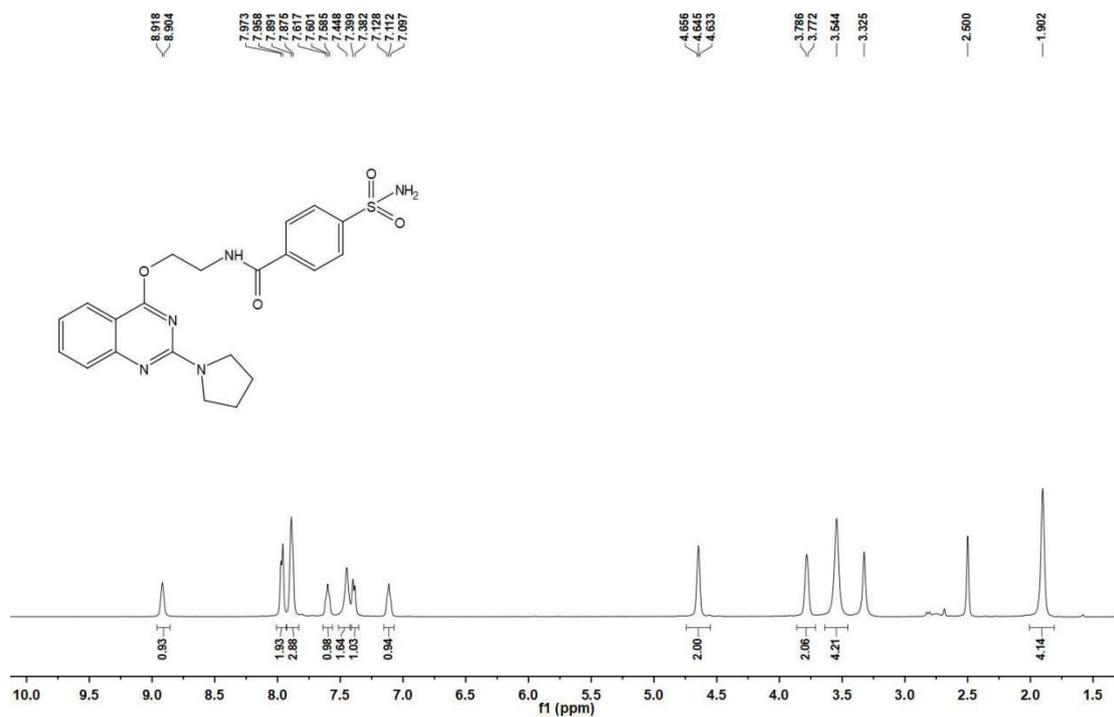
The ¹H NMR spectra of compound II-14g



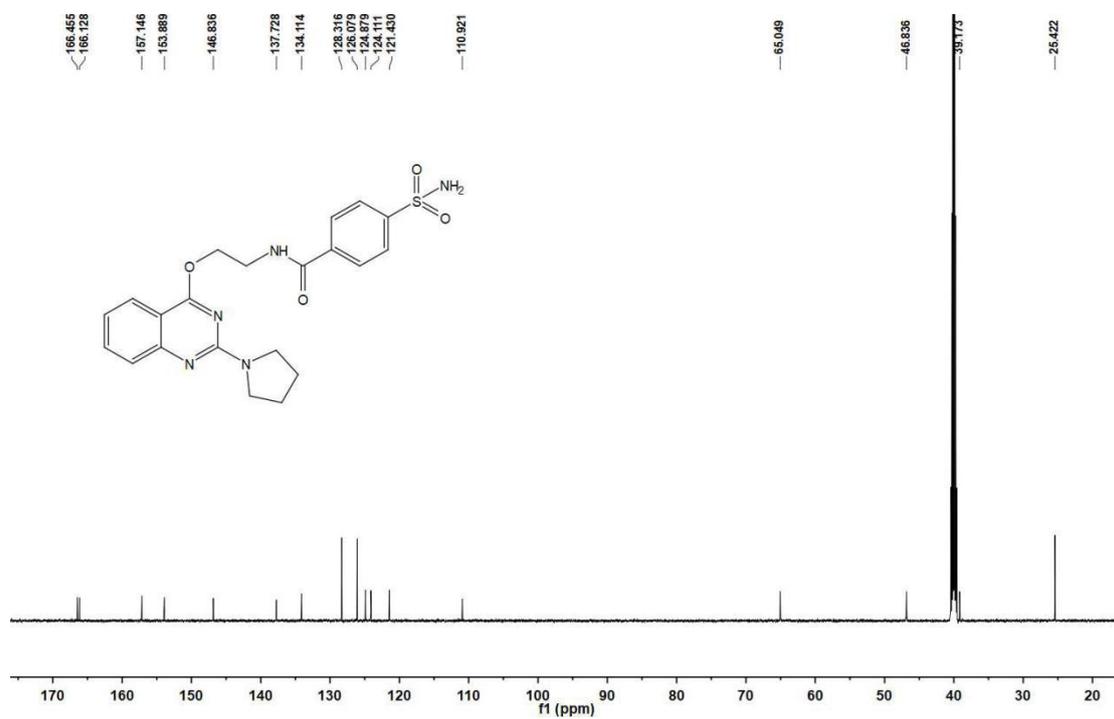
The ¹³C NMR spectra of compound II-14g



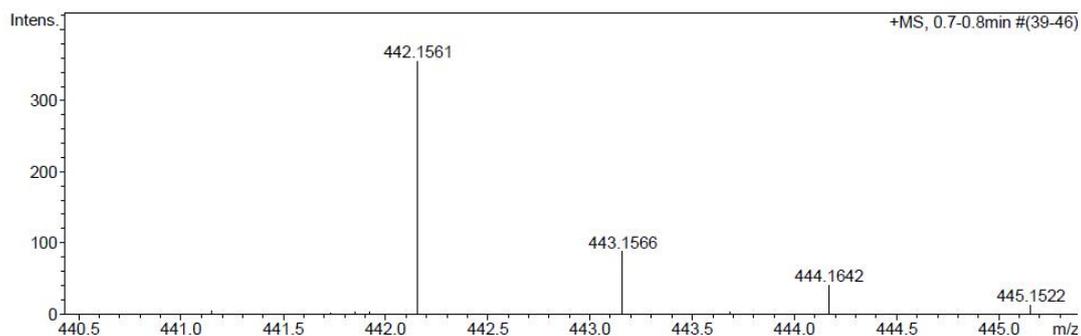
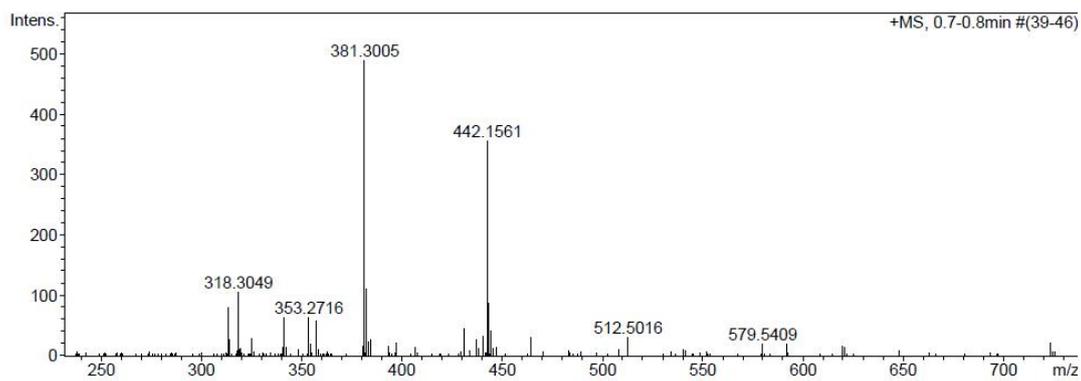
The HR-MS spectra of compound II-14g



The ¹H NMR spectra of compound II-14i



The ¹³C NMR spectra of compound II-14i

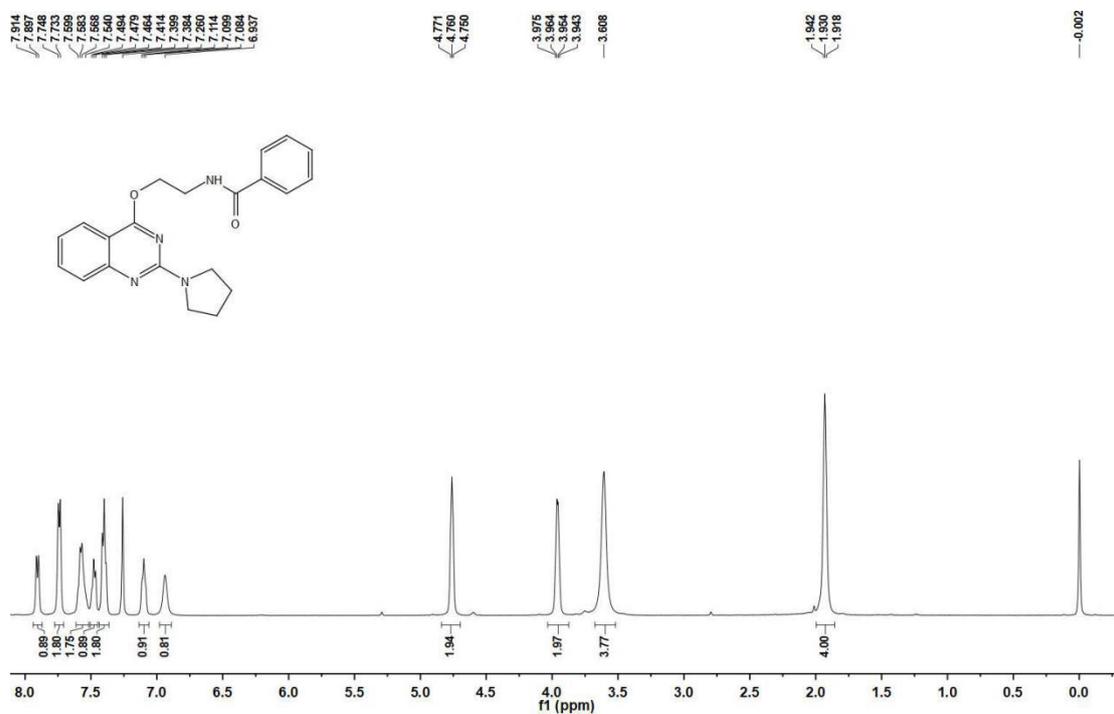


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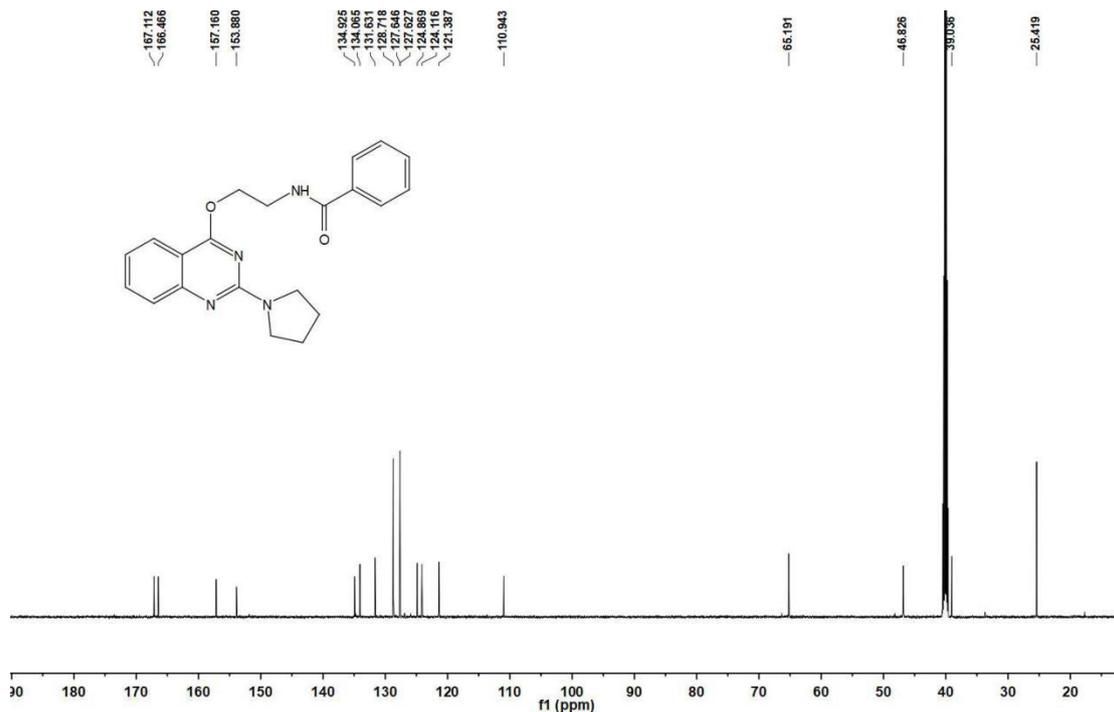
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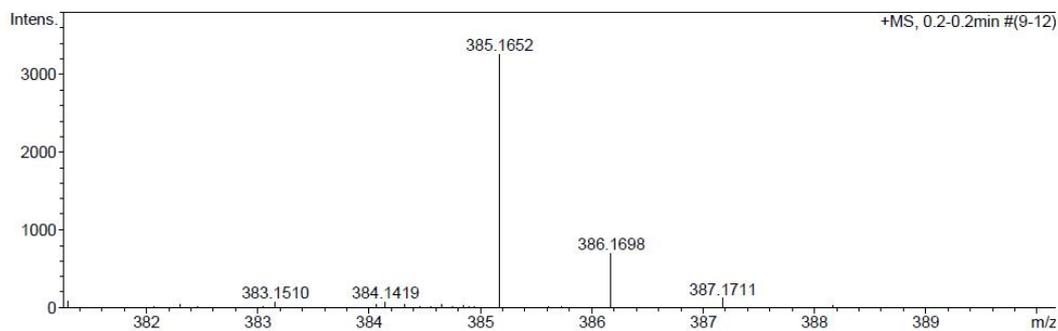
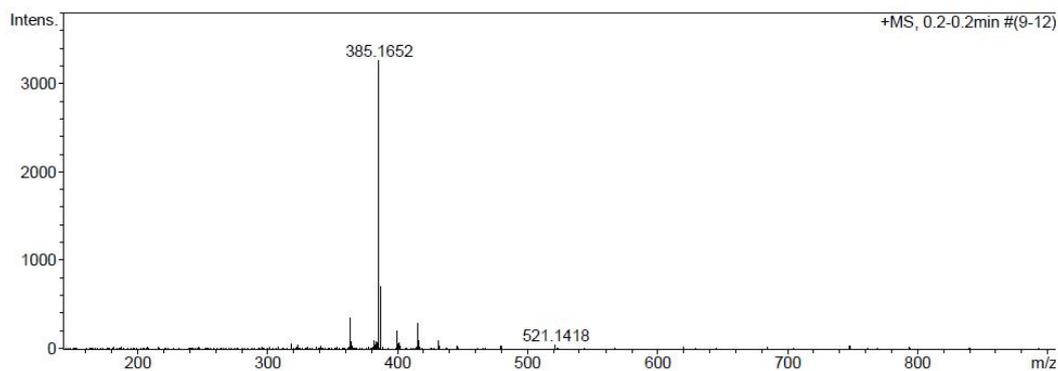
The HR-MS spectra of compound II-14i



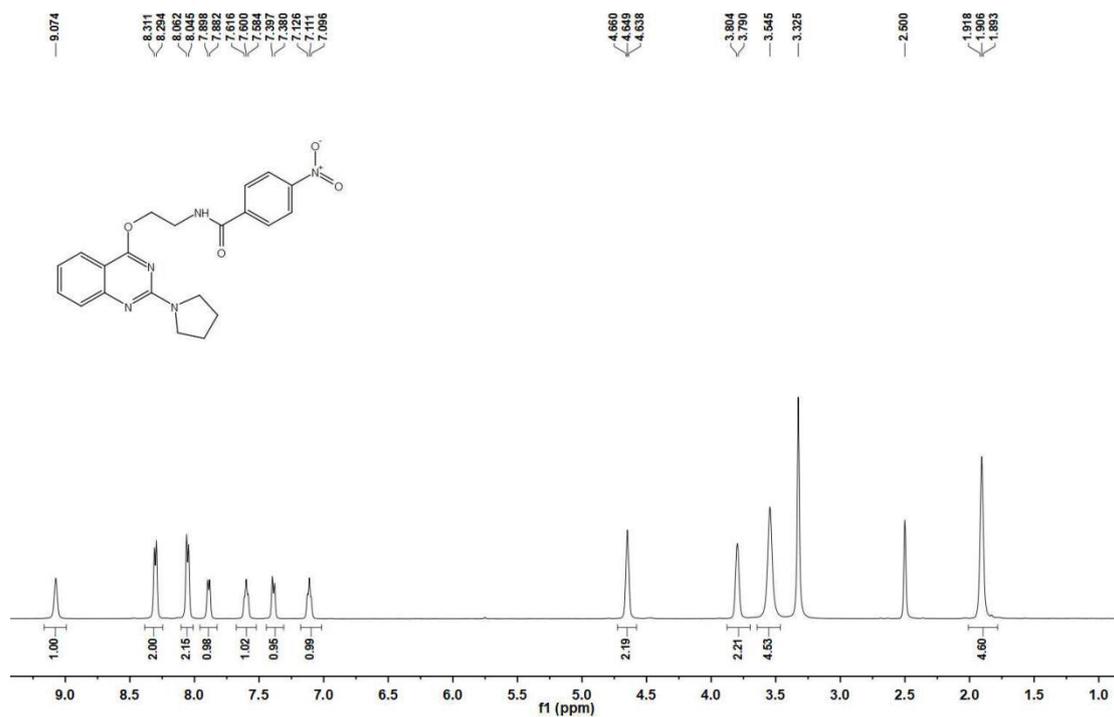
The ¹H NMR spectra of compound II-14k



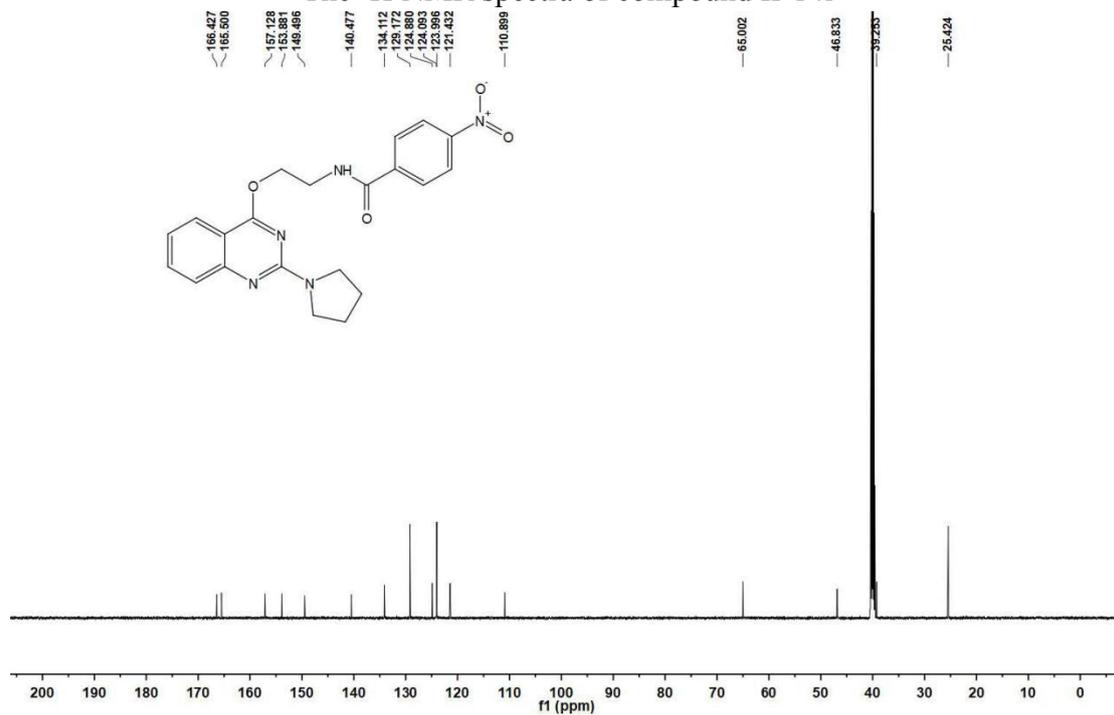
The ¹³C NMR spectra of compound II-14k



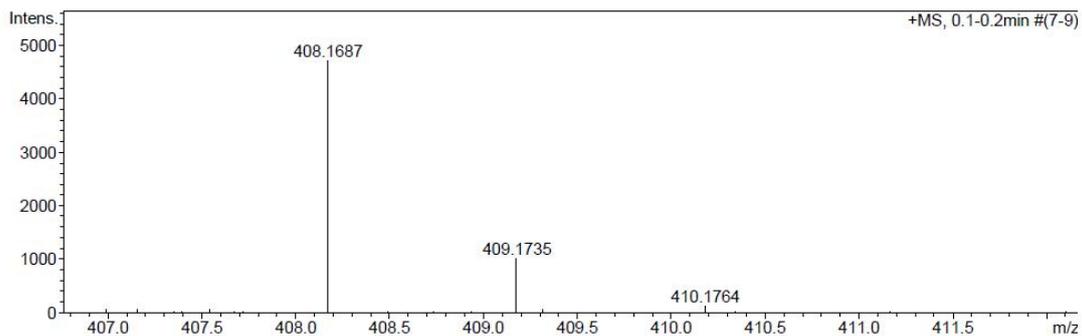
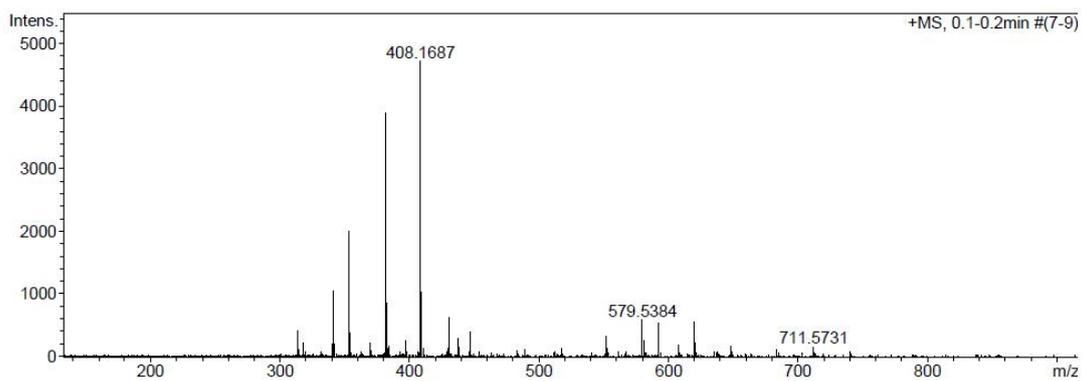
The HR-MS spectra of compound II-14k



The ^1H NMR spectra of compound II-141



The ^{13}C NMR spectra of compound II-141

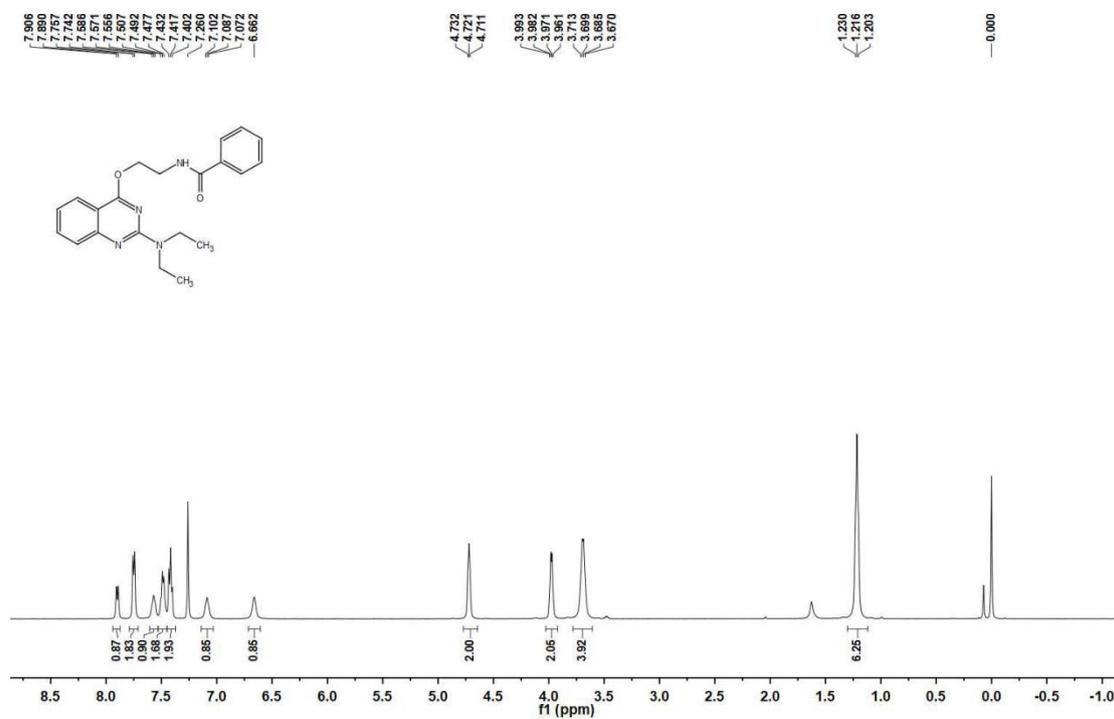


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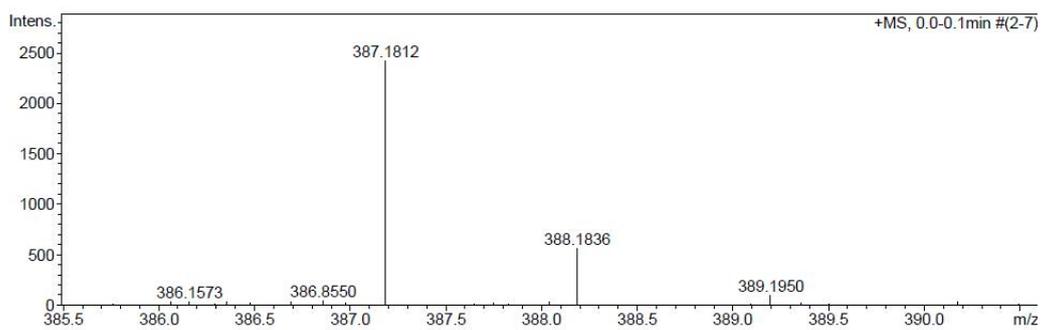
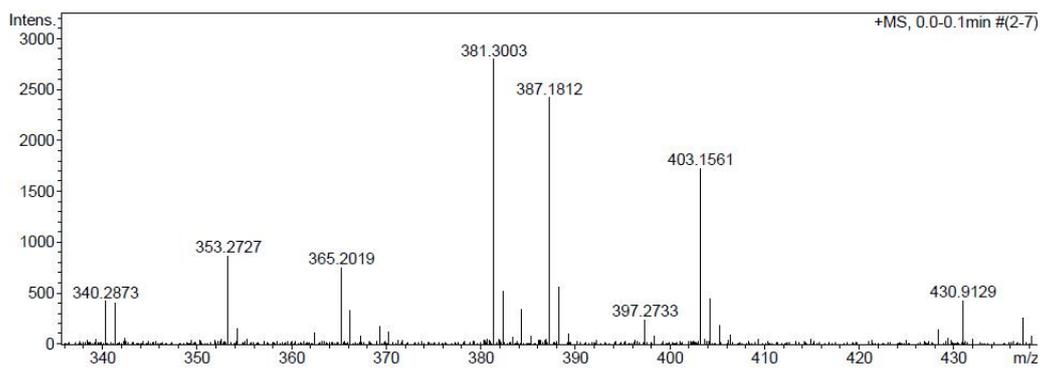
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The HR-MS spectra of compound II-141



The ¹H NMR spectra of compound II-17b

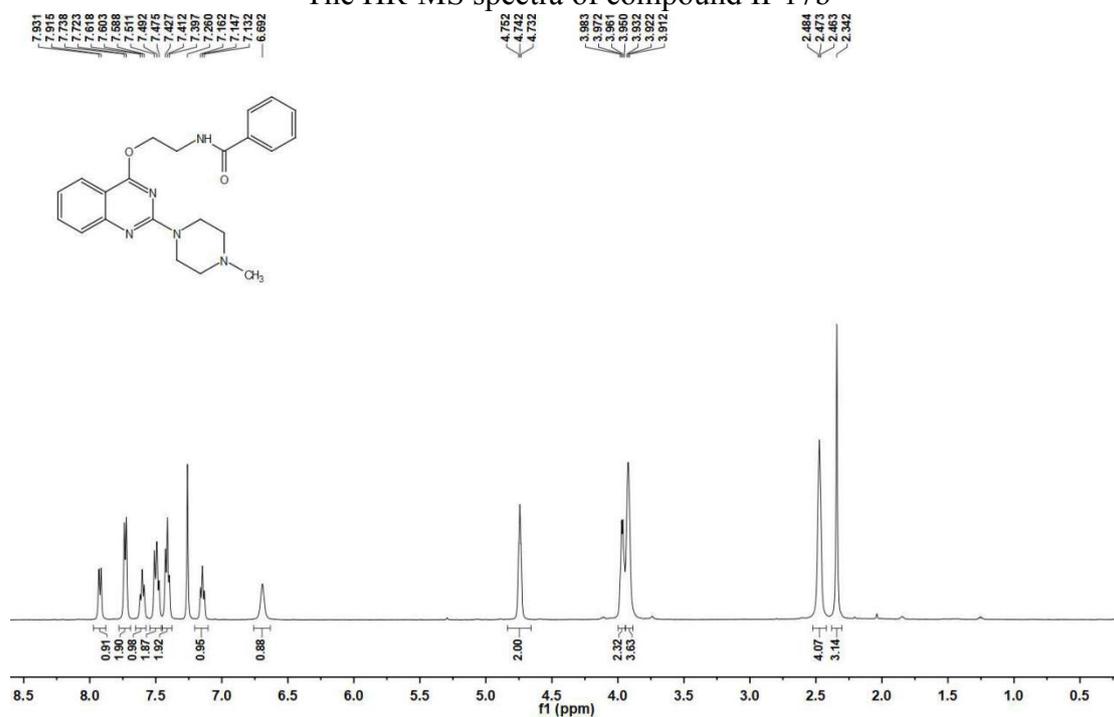


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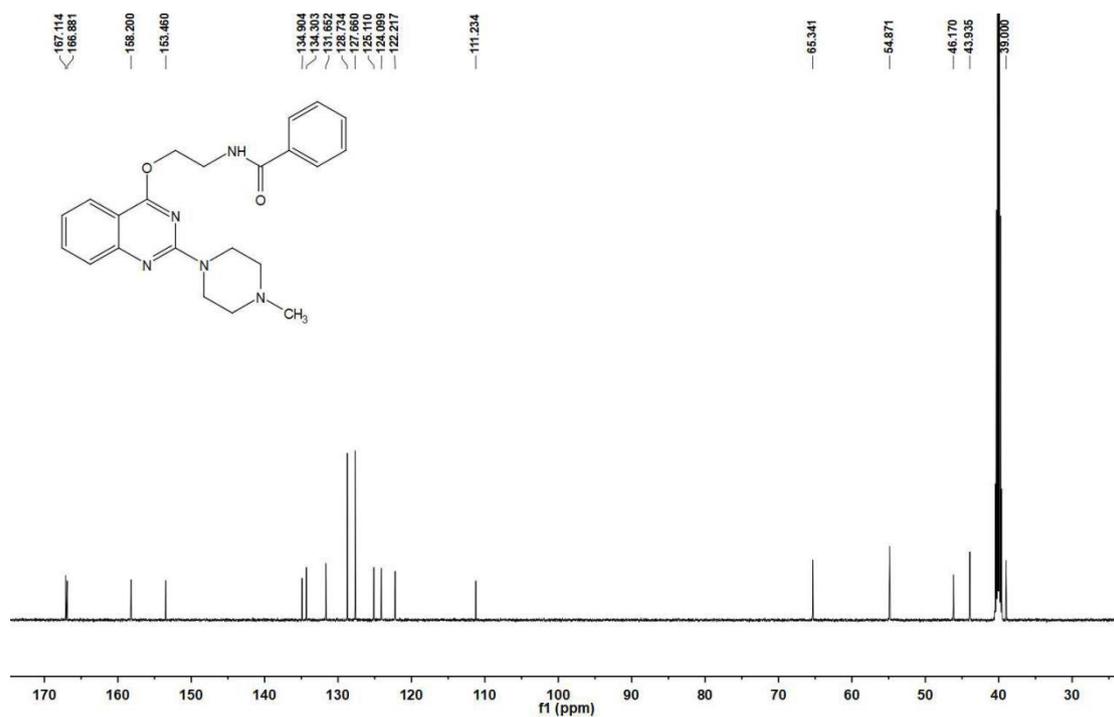
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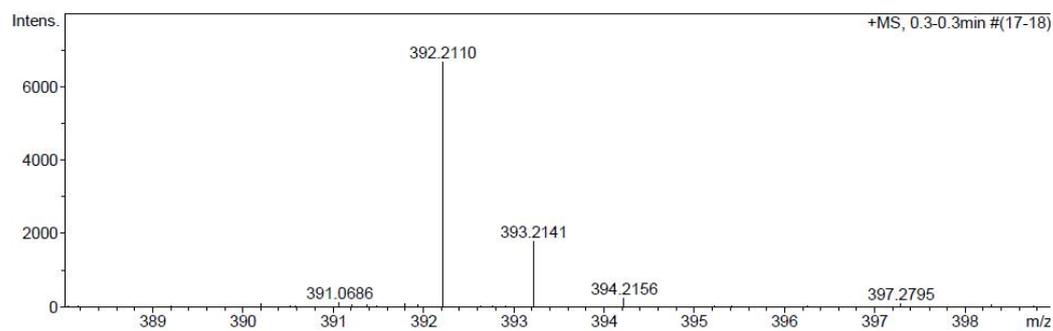
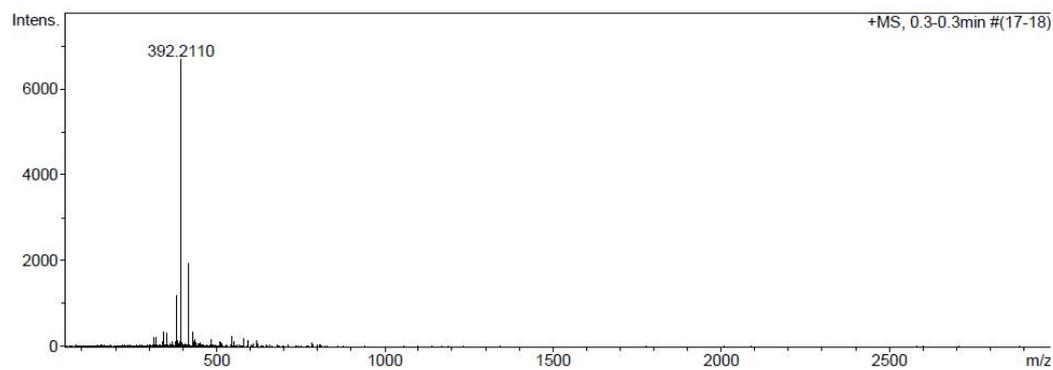
The HR-MS spectra of compound II-17b



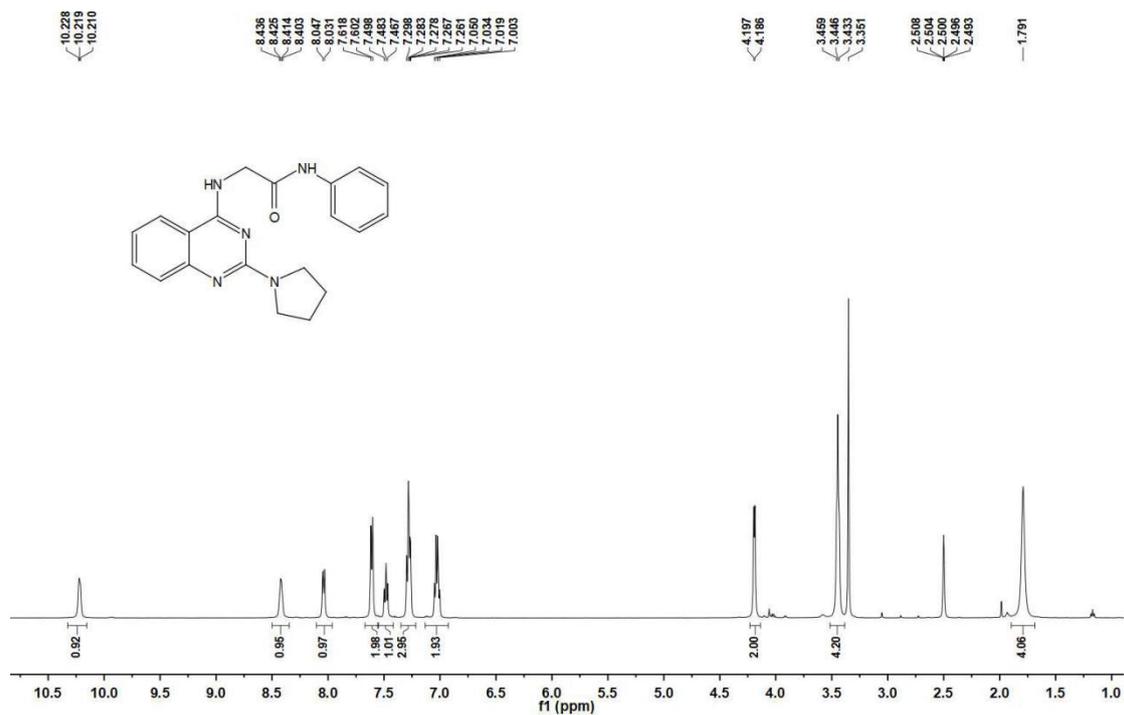
The ¹H NMR spectra of compound II-17c



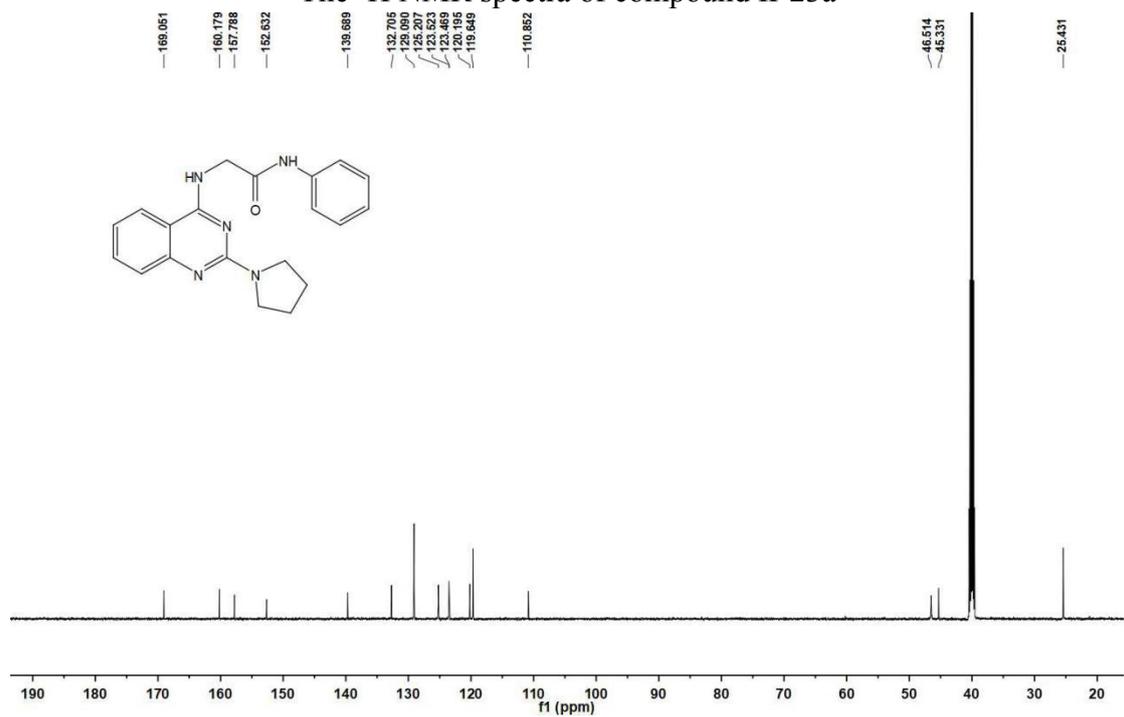
The ¹³C NMR spectra of compound II-17c



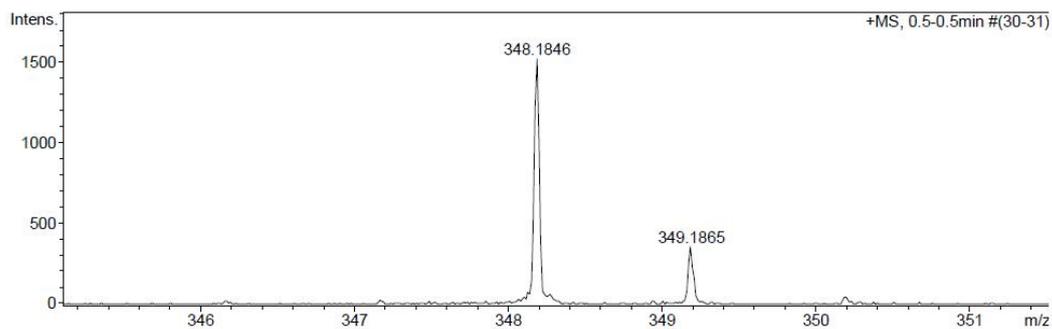
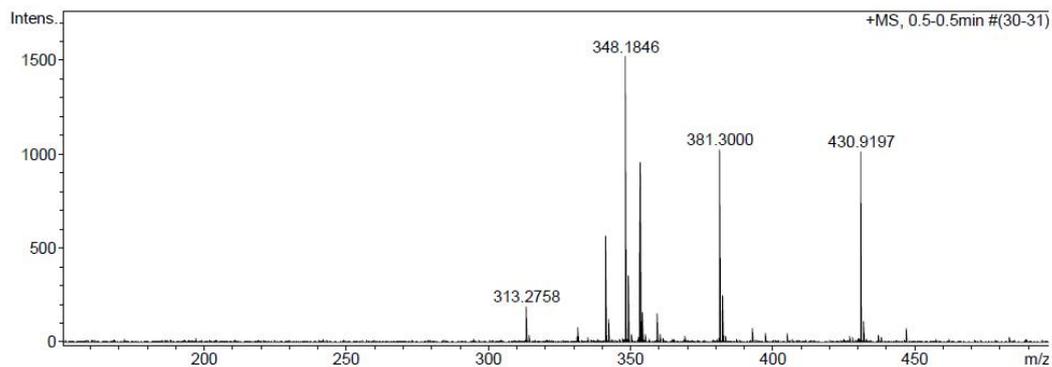
The HR-MS spectra of compound II-17c



The ^1H NMR spectra of compound II-23a



The ^{13}C NMR spectra of compound II-23a



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The HR-MS spectra of compound II-23a

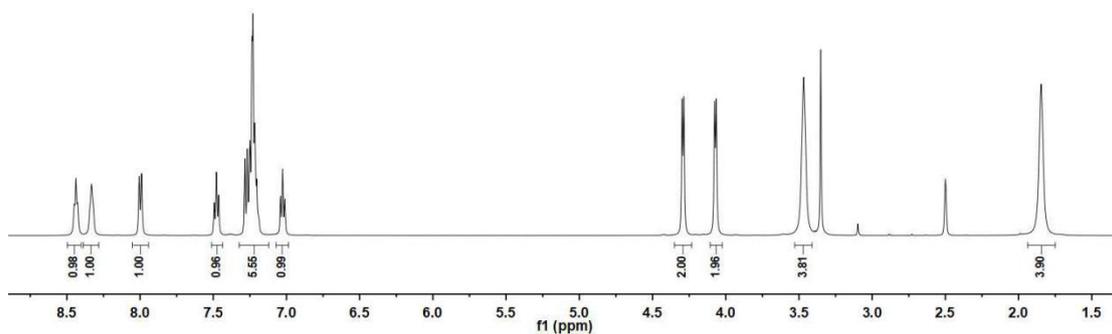
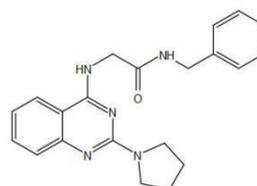
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8.326
8.344
8.333
8.327
8.315
8.016
7.989
7.484
7.478
7.463
7.451
7.267
7.250
7.236
7.229
7.216
7.194
7.189
7.185
7.041
7.026
7.011

4.298
4.286
4.076
4.065

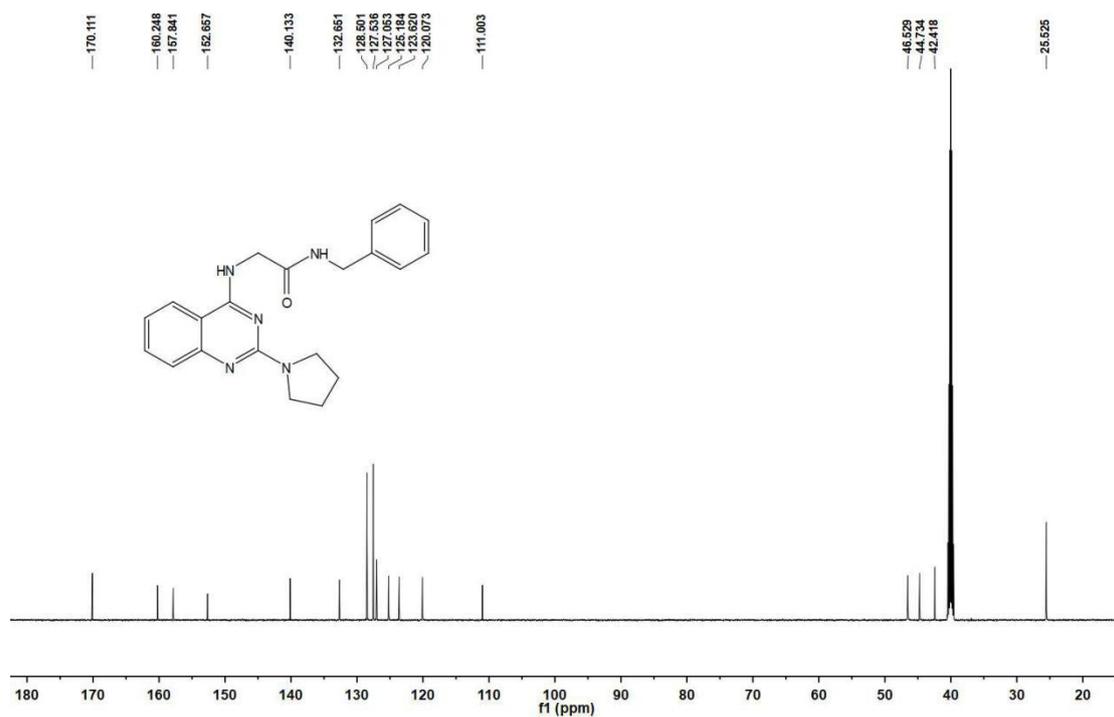
3.480
3.468
3.456
3.351

2.504
2.500
2.495

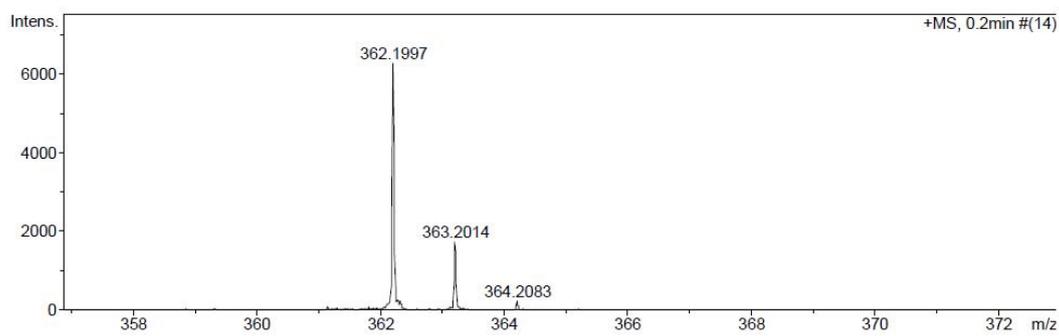
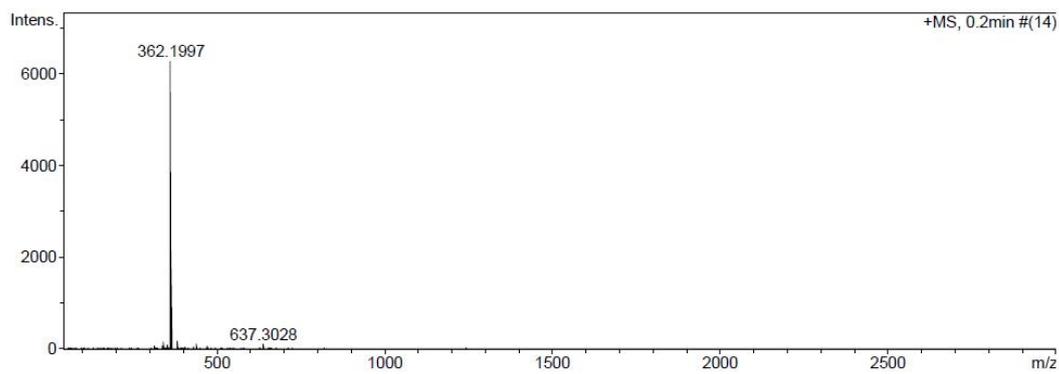
1.846



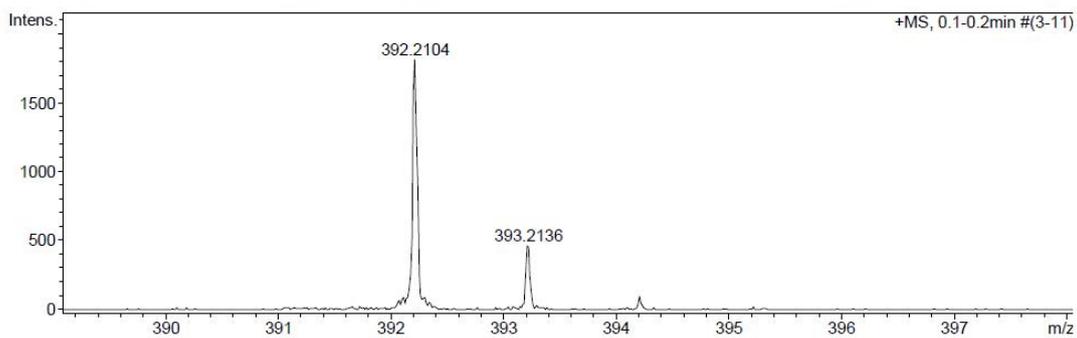
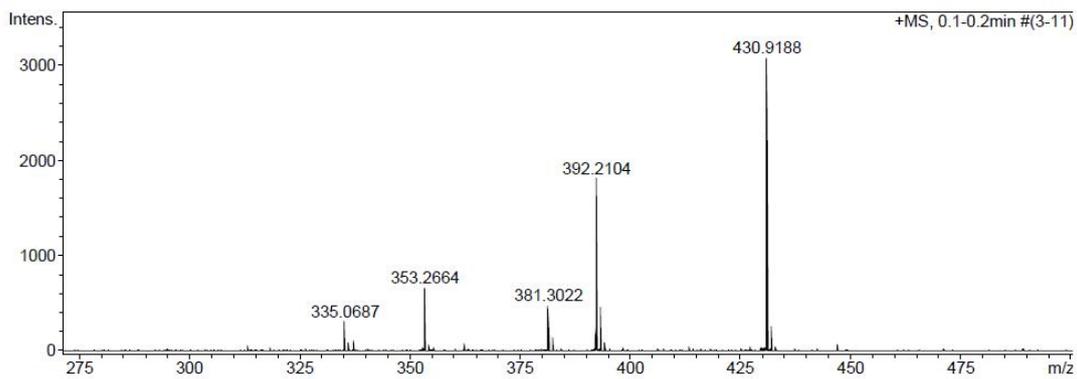
The ¹H NMR spectra of compound II-23b



The ¹³C NMR spectra of compound II-23b



The HR-MS spectra of compound II-23b



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The HR-MS spectra of compound II-23c

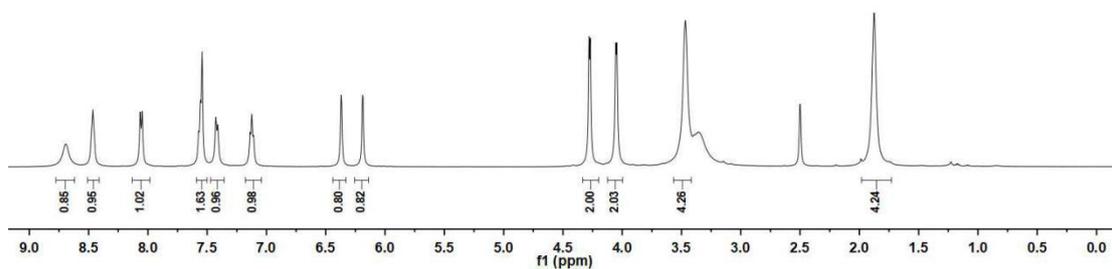
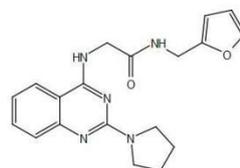
8.693
8.476
8.453
8.065
8.048
7.572
7.557
7.493
7.470
7.139
7.124
7.108

6.369
6.191
6.185

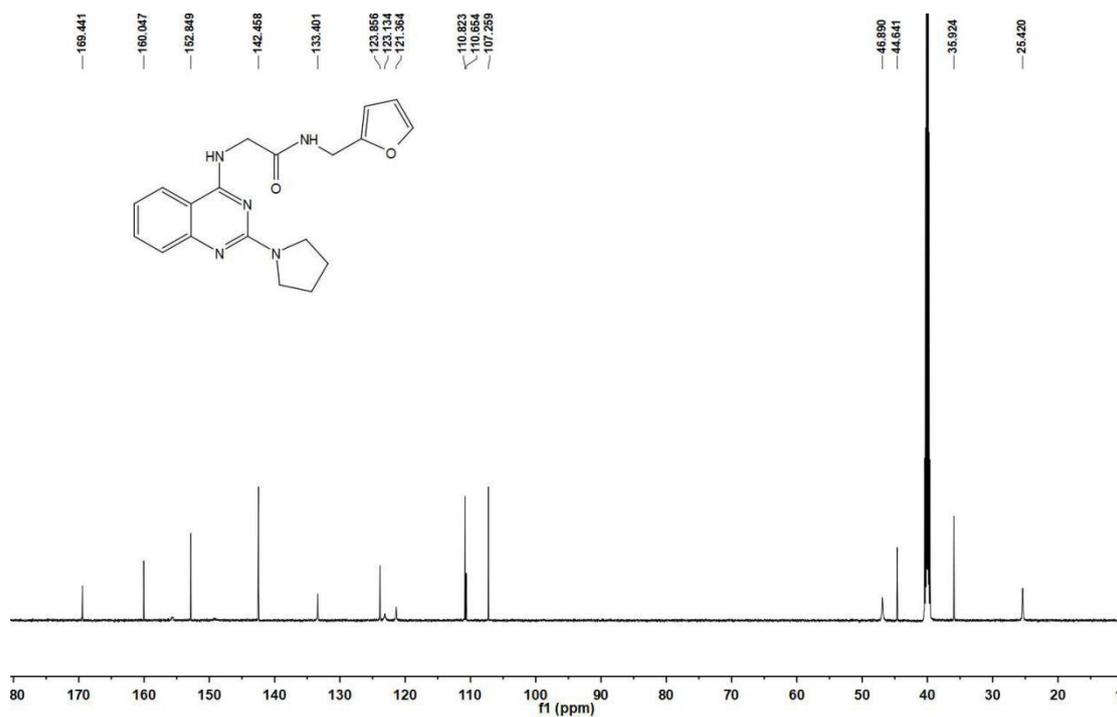
4.280
4.268
4.055
4.044

3.468

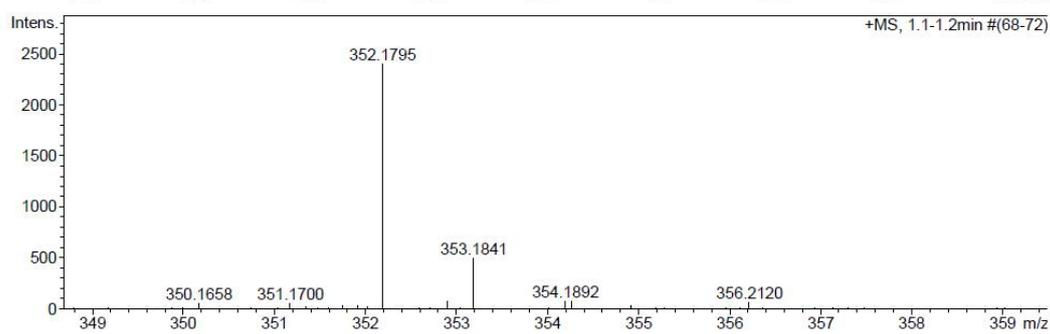
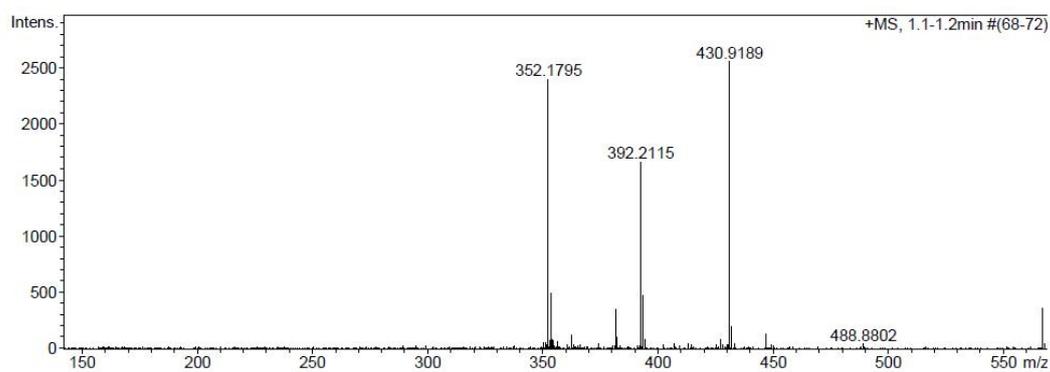
1.875



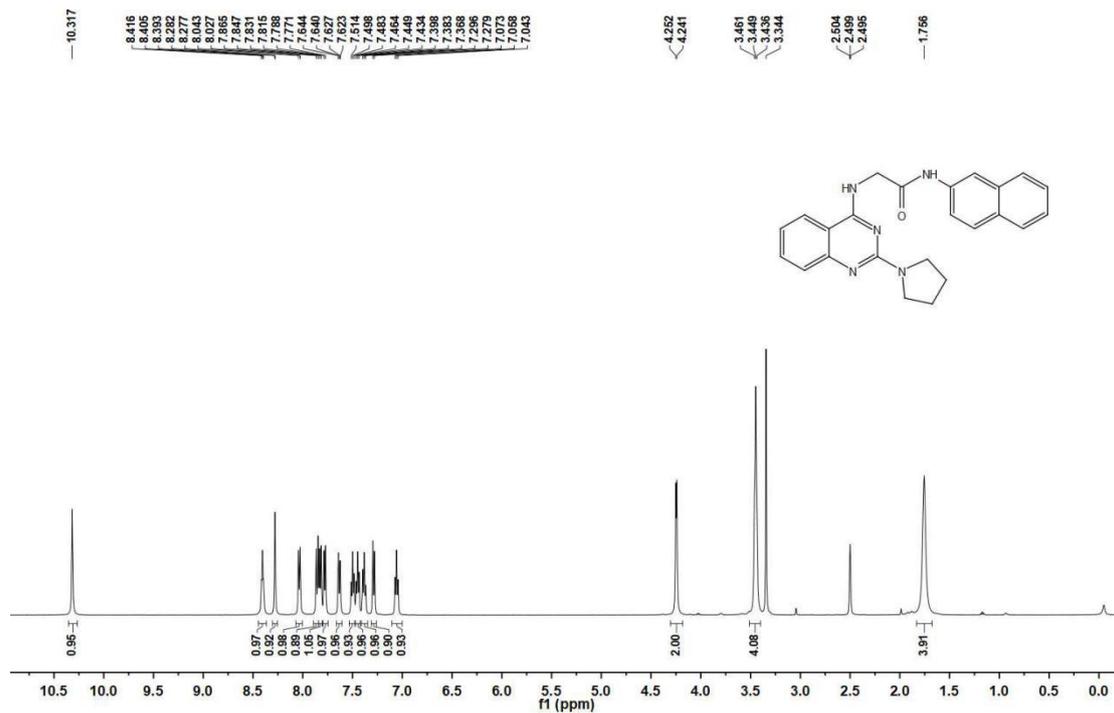
The ¹H NMR spectra of compound II-23d



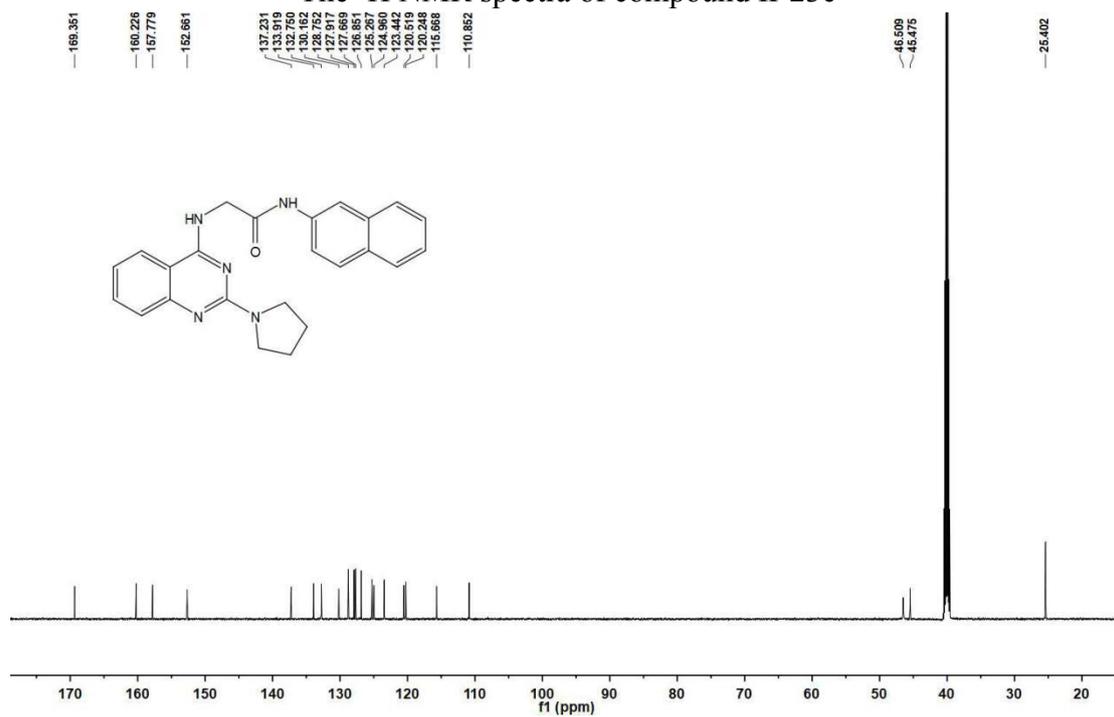
The ^{13}C NMR spectra of compound II-23d



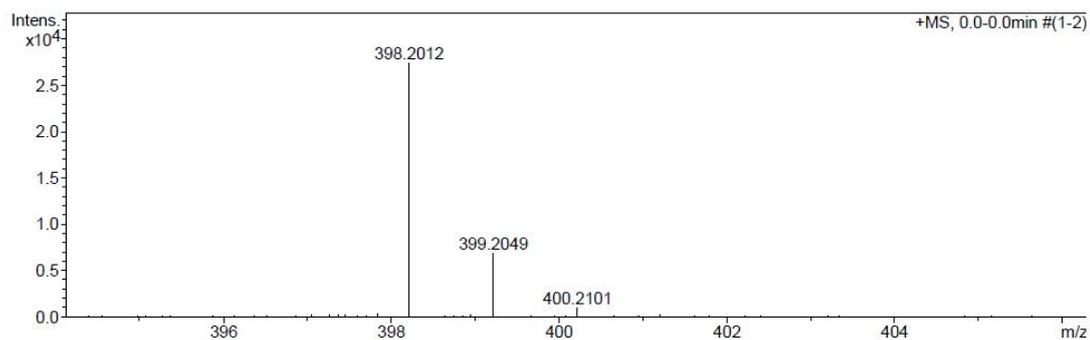
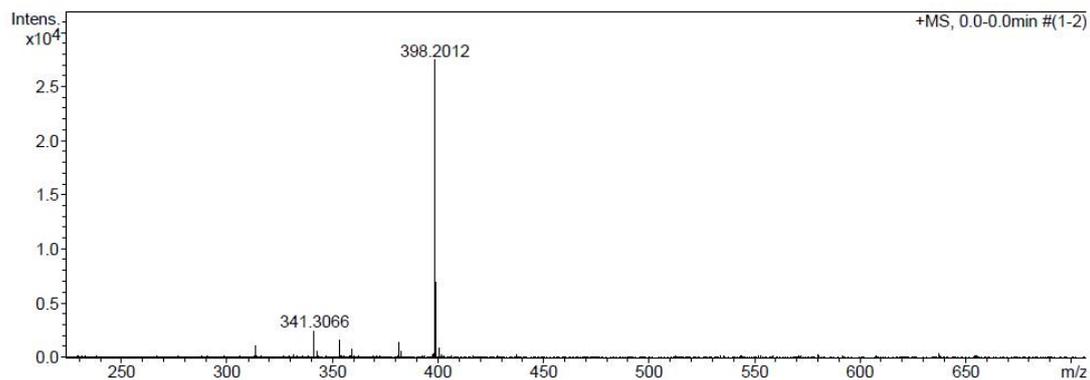
The HR-MS spectra of compound II-23d



The ¹H NMR spectra of compound II-23e



The ¹³C NMR spectra of compound II-23e

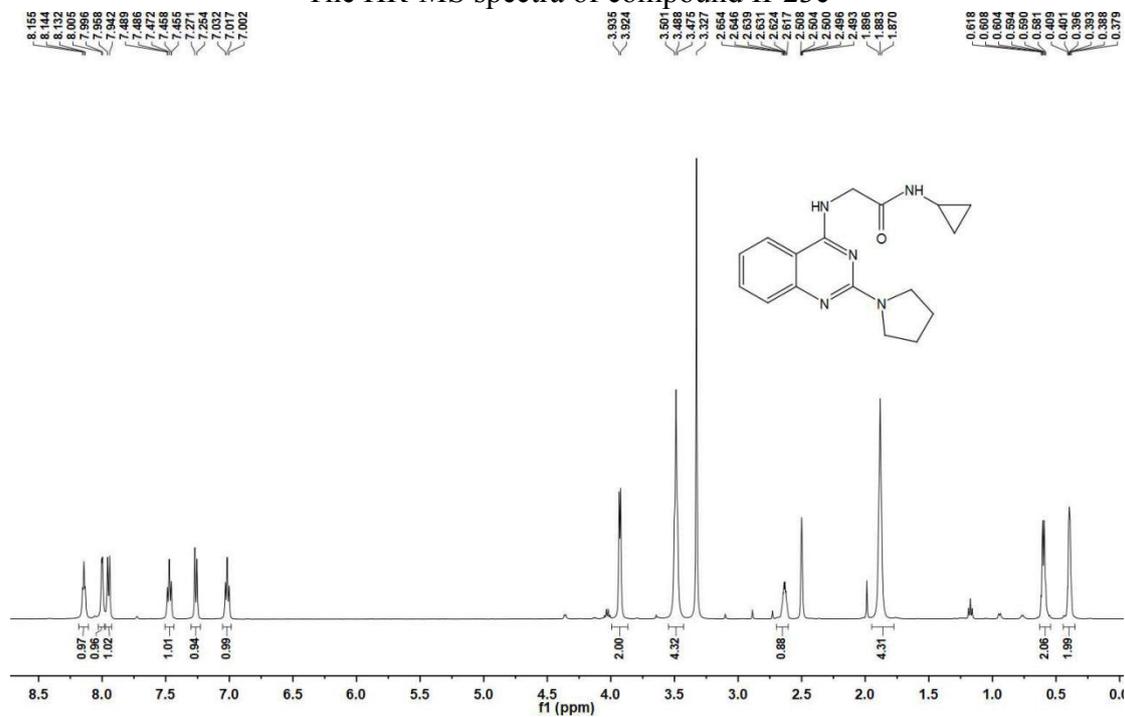


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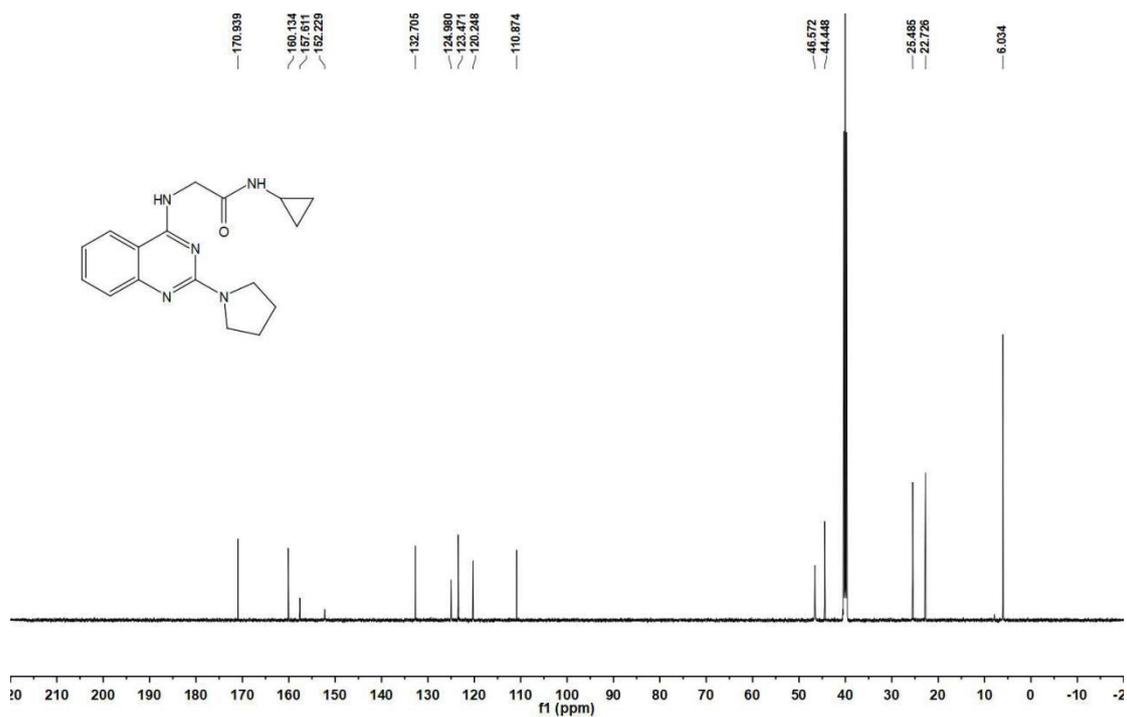
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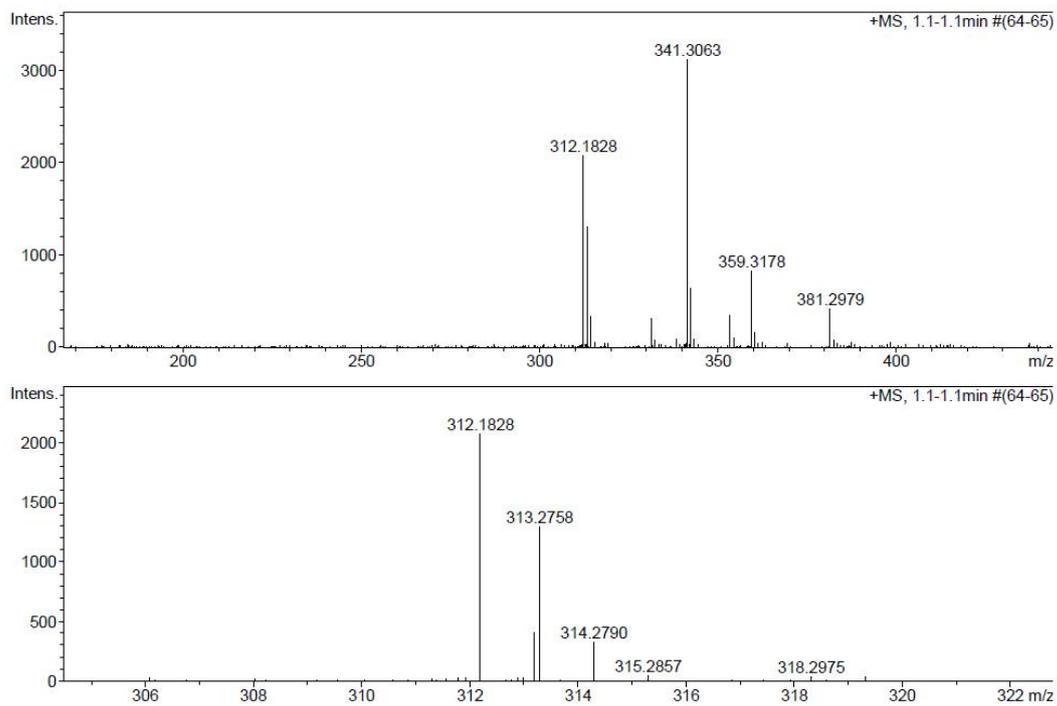
The HR-MS spectra of compound II-23e



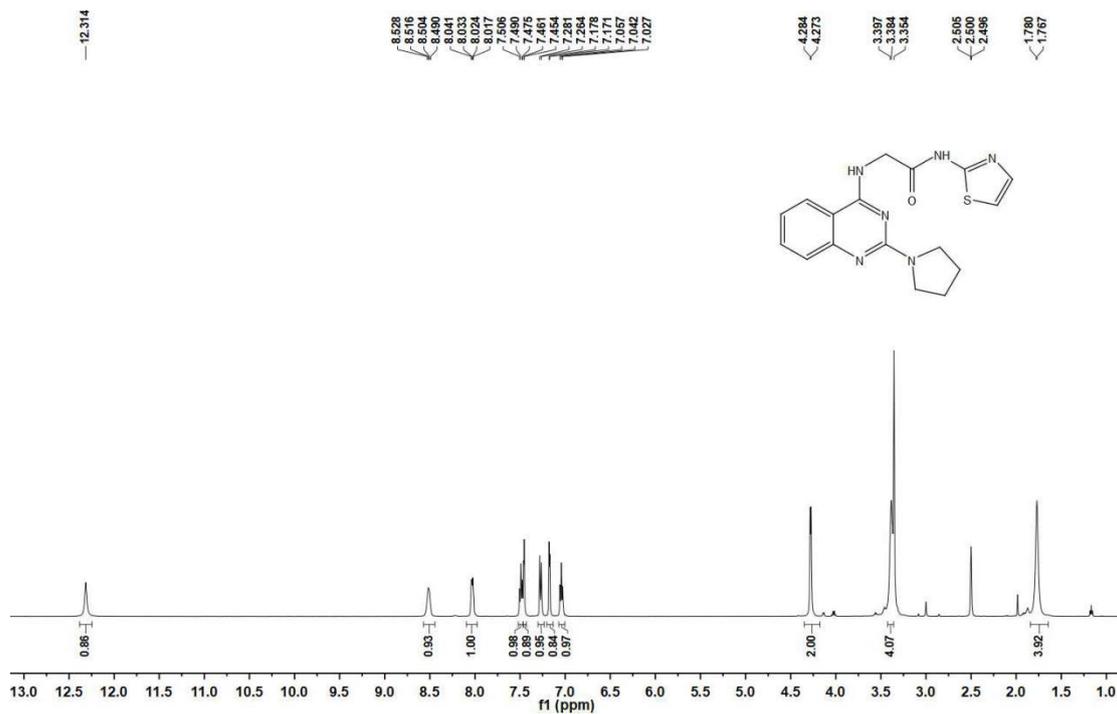
The ¹H NMR spectra of compound II-23f



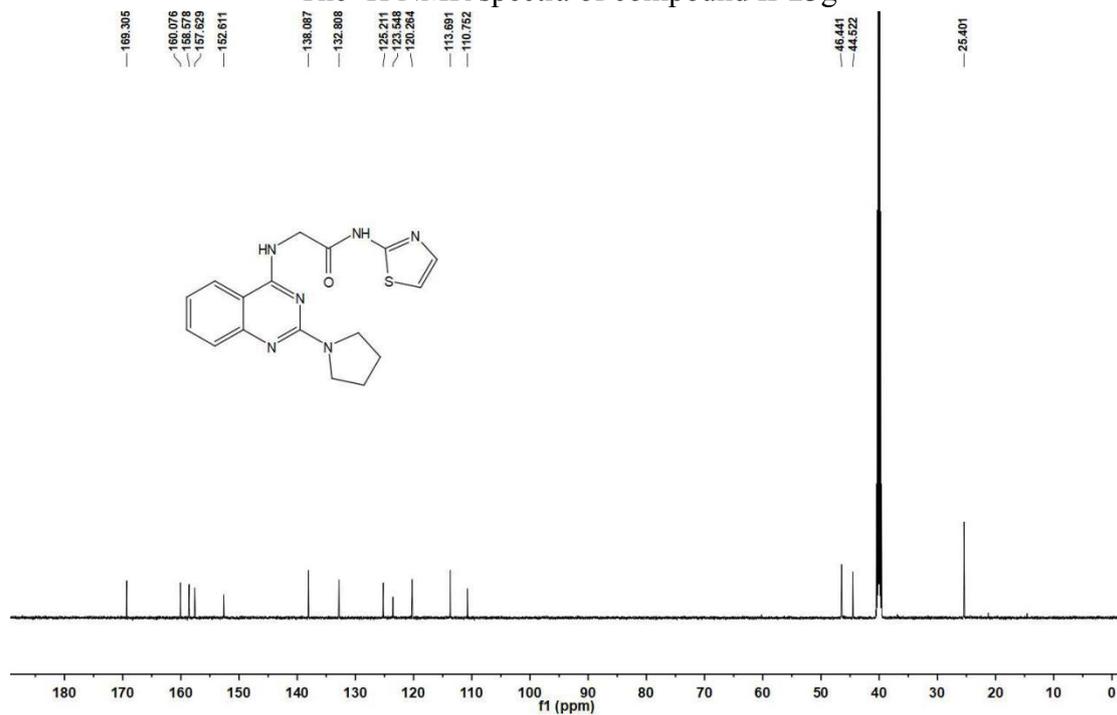
The ¹³C NMR spectra of compound II-23f



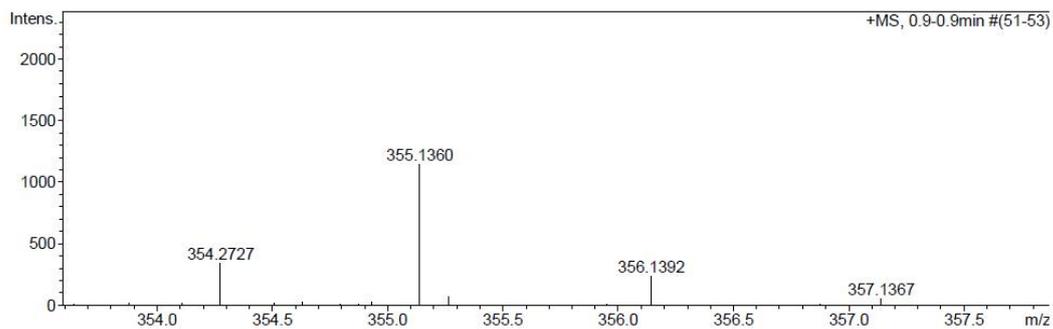
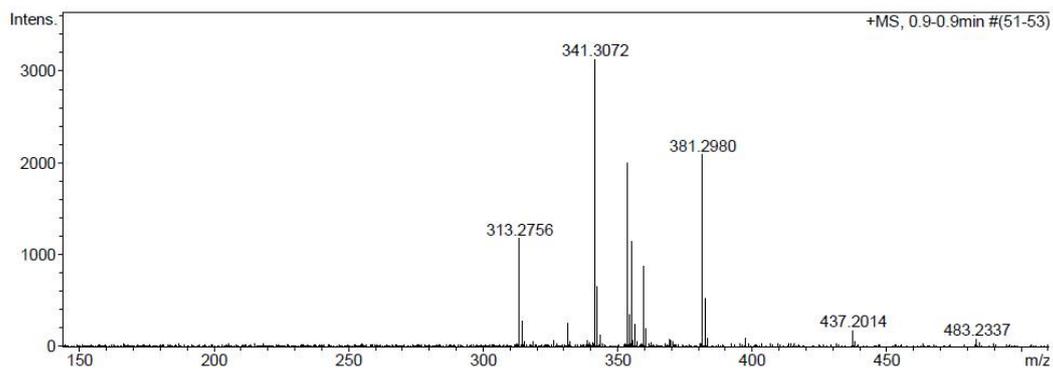
The HR-MS spectra of compound II-23f



The ^1H NMR spectra of compound II-23g



The ^{13}C NMR spectra of compound II-23g

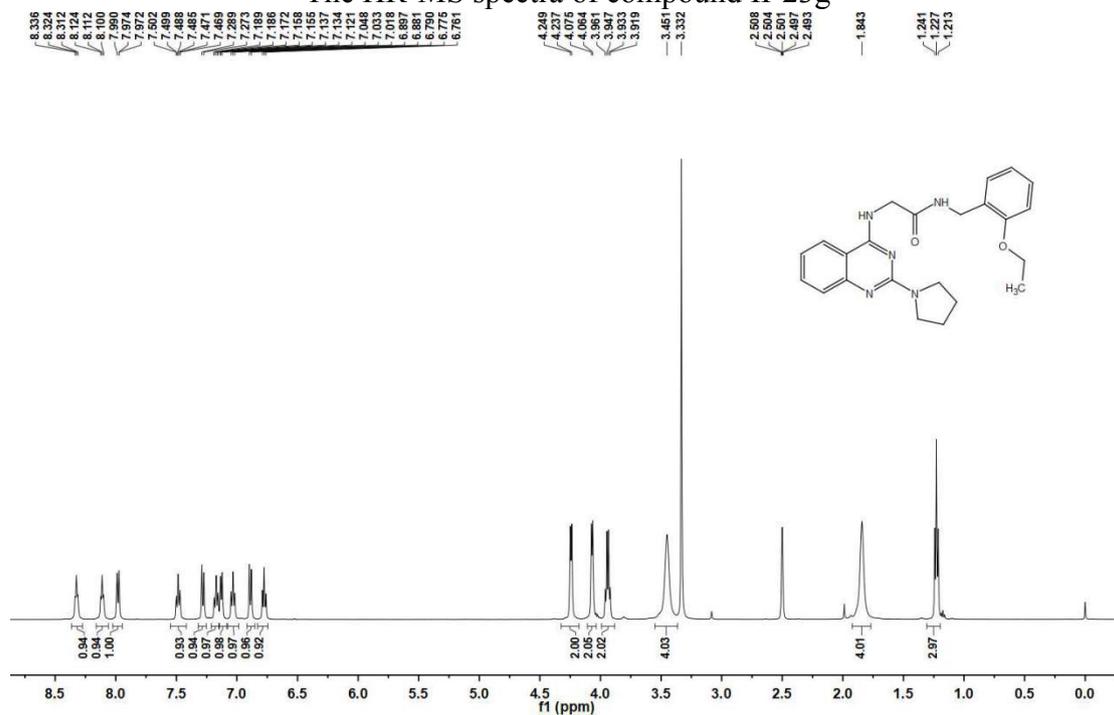


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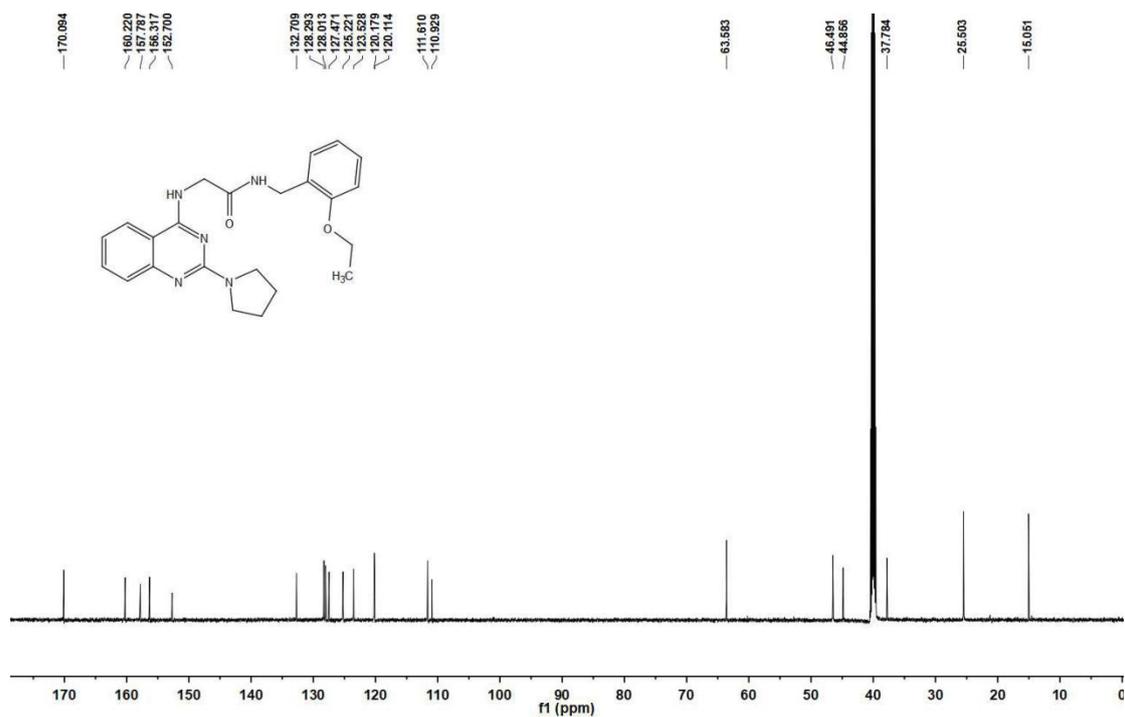
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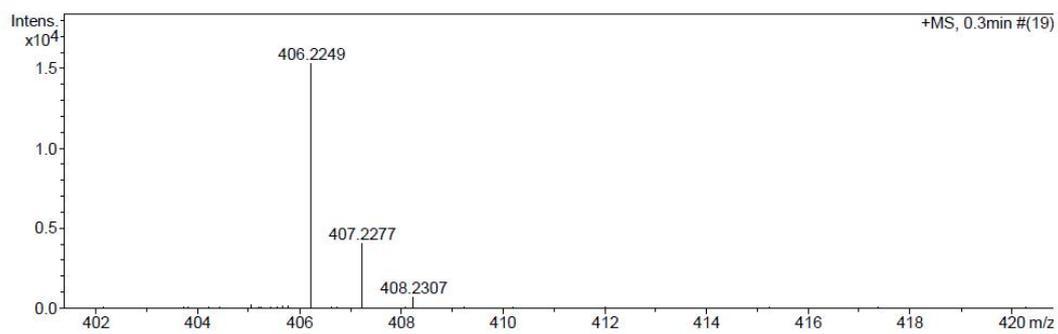
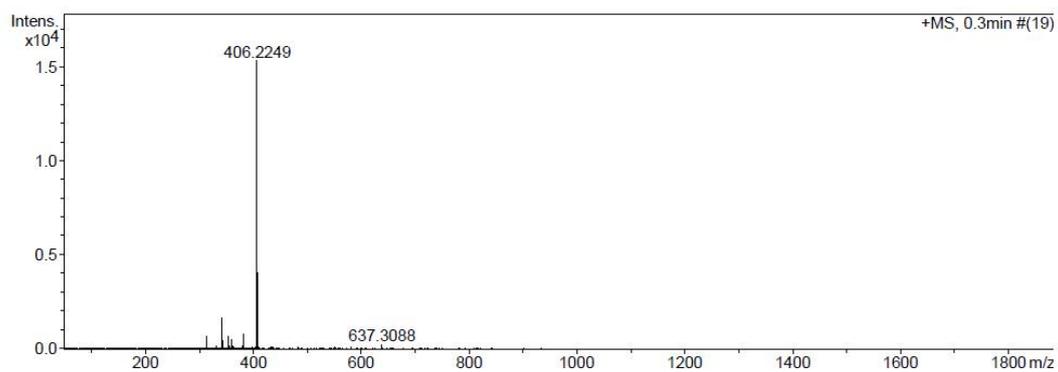
The HR-MS spectra of compound II-23g



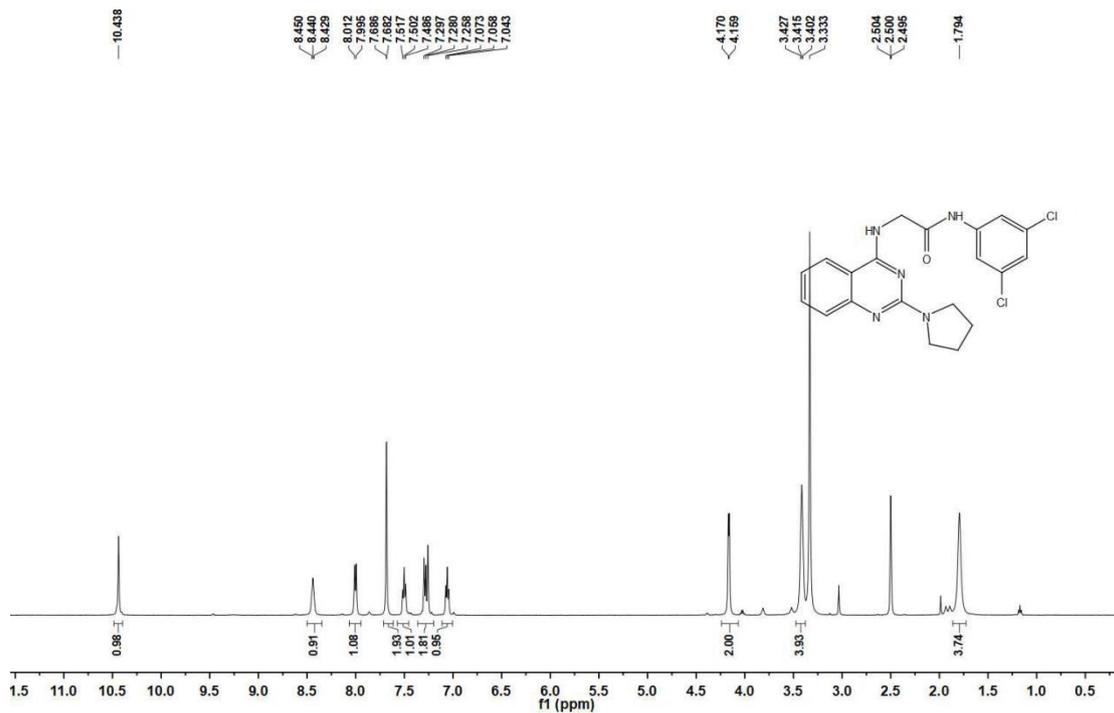
The ¹H NMR spectra of compound II-23h



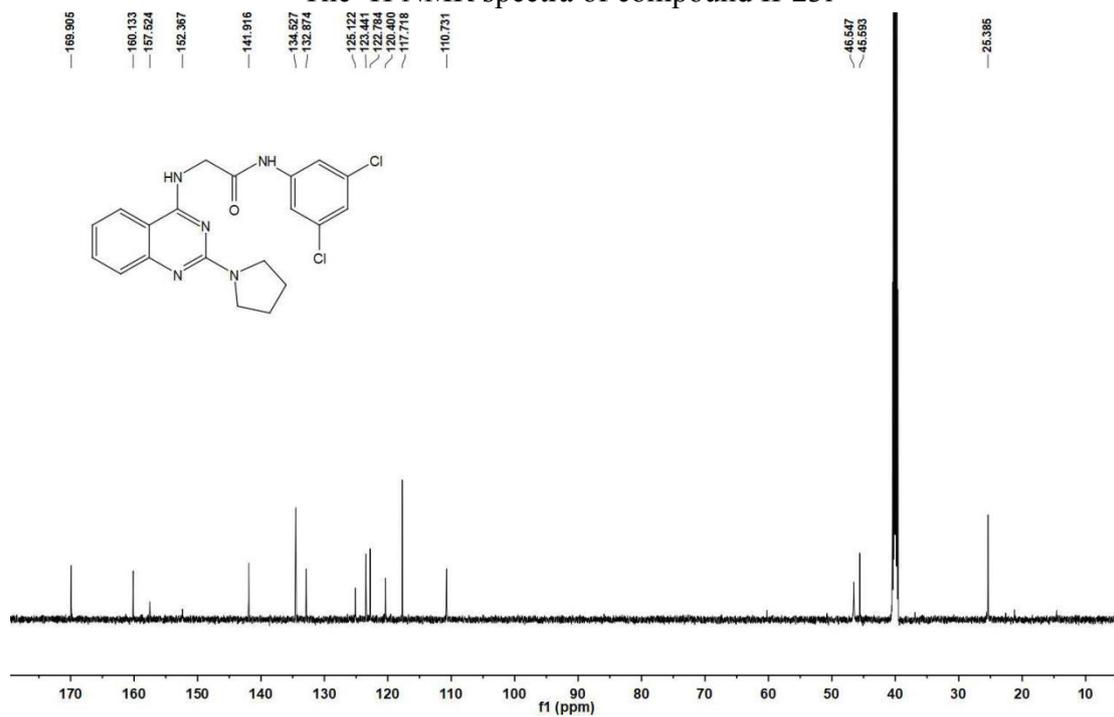
The ¹³C NMR spectra of compound II-23h



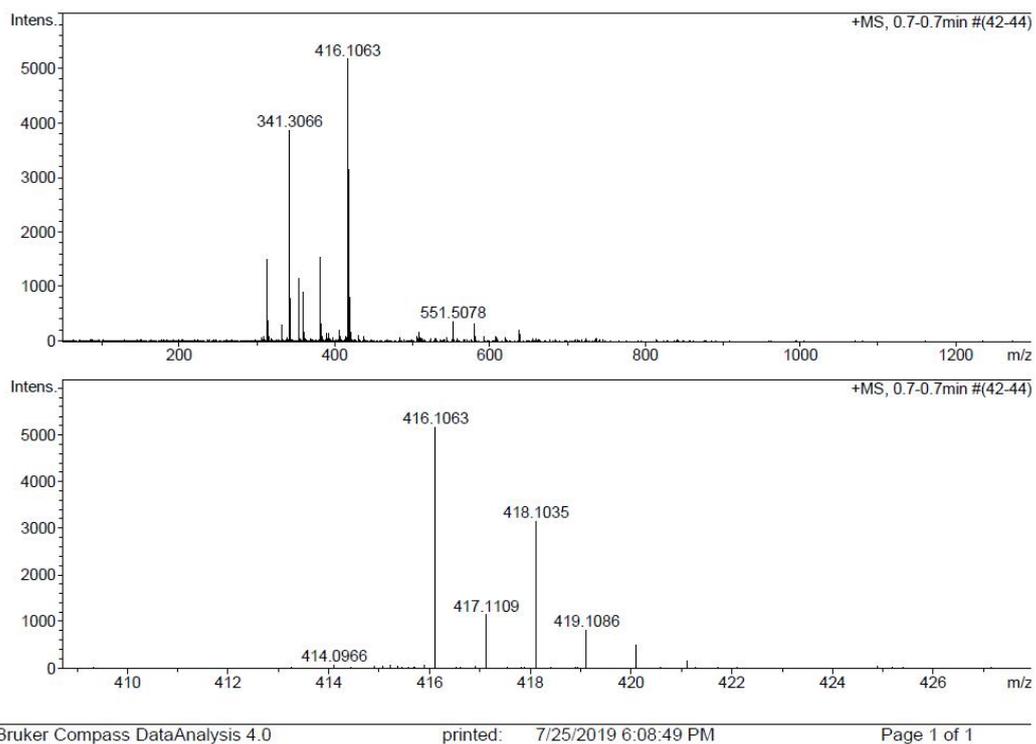
The HR-MS spectra of compound II-23h



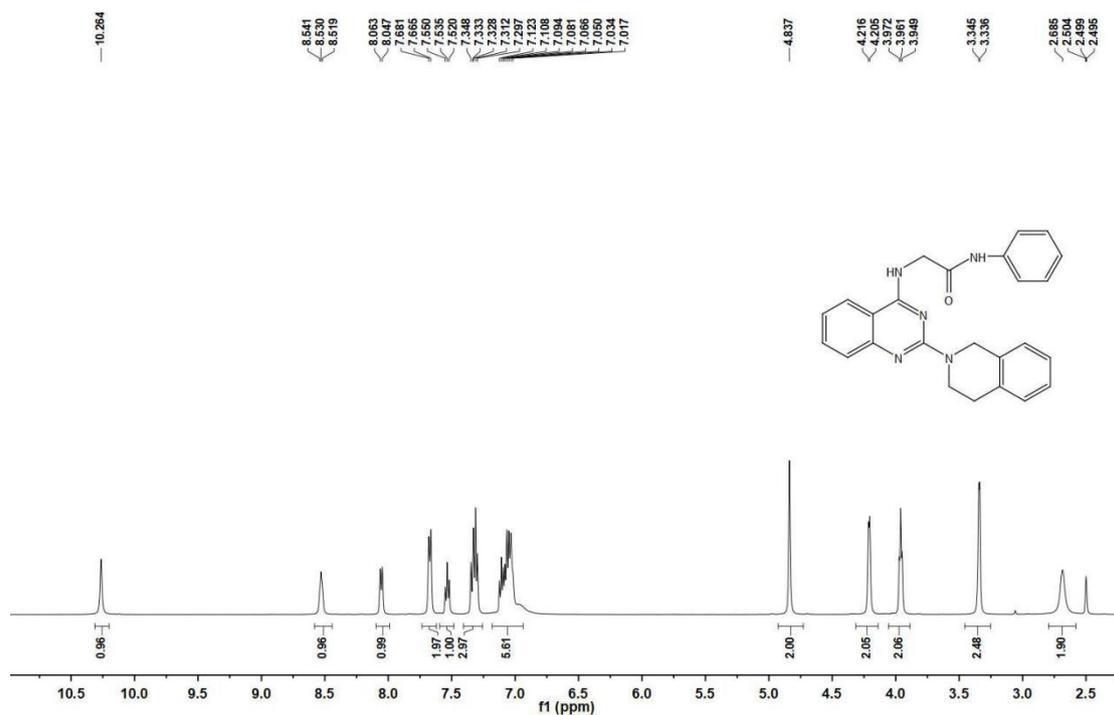
The ¹H NMR spectra of compound II-23i



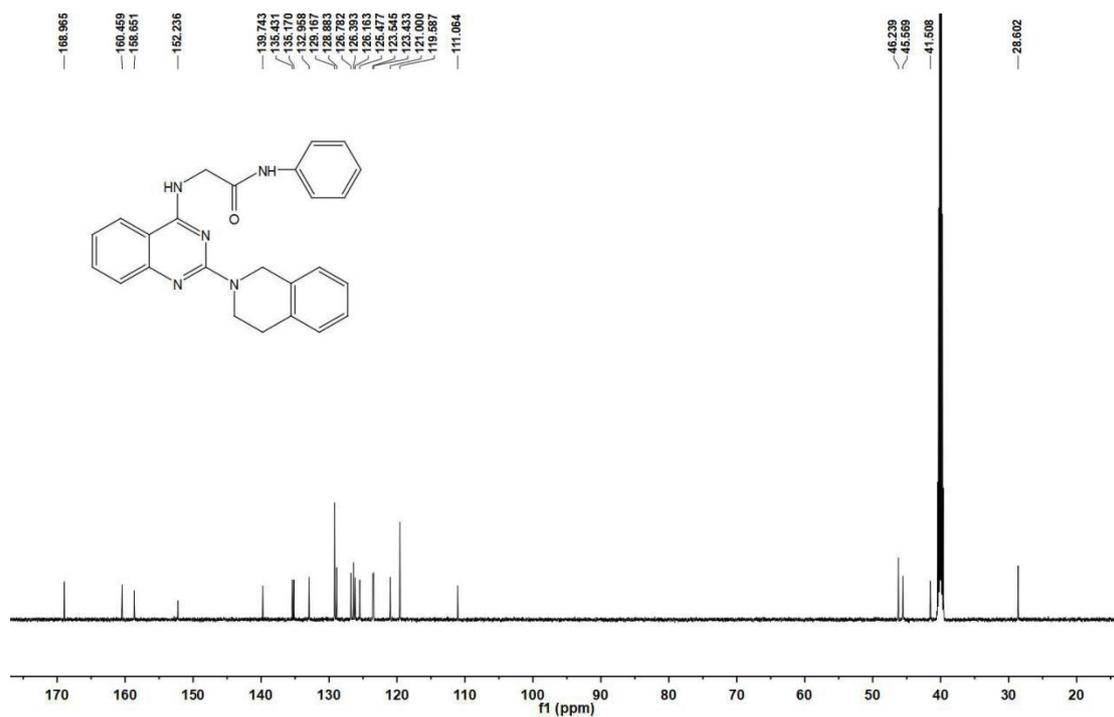
The ¹³C NMR spectra of compound II-23i



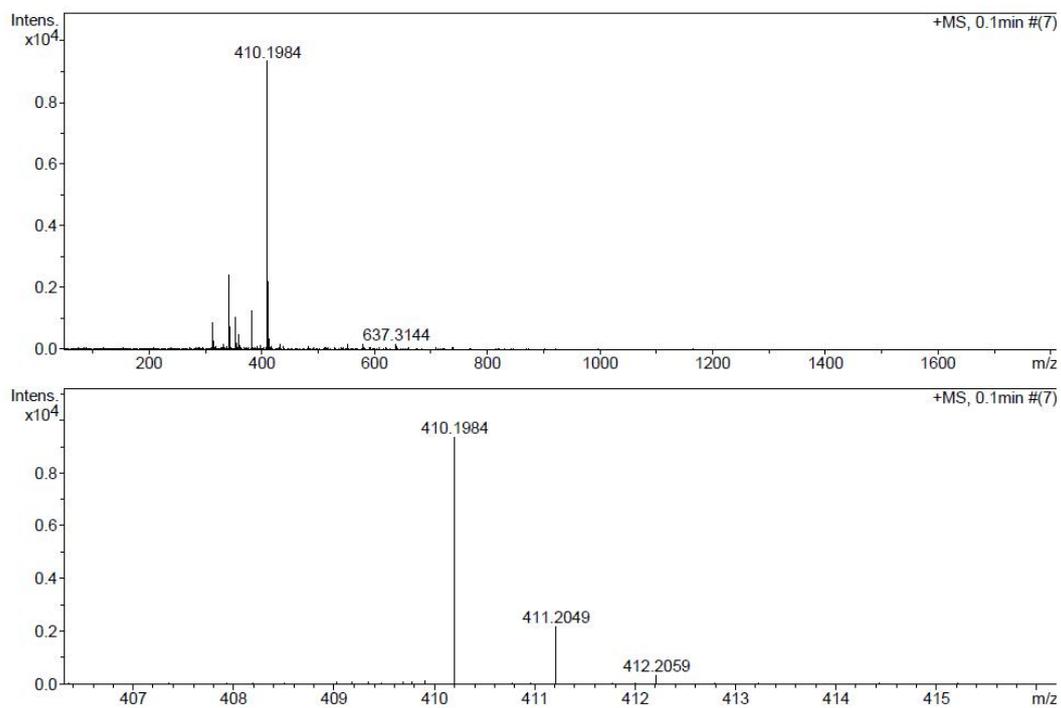
The HR-MS spectra of compound II-23i



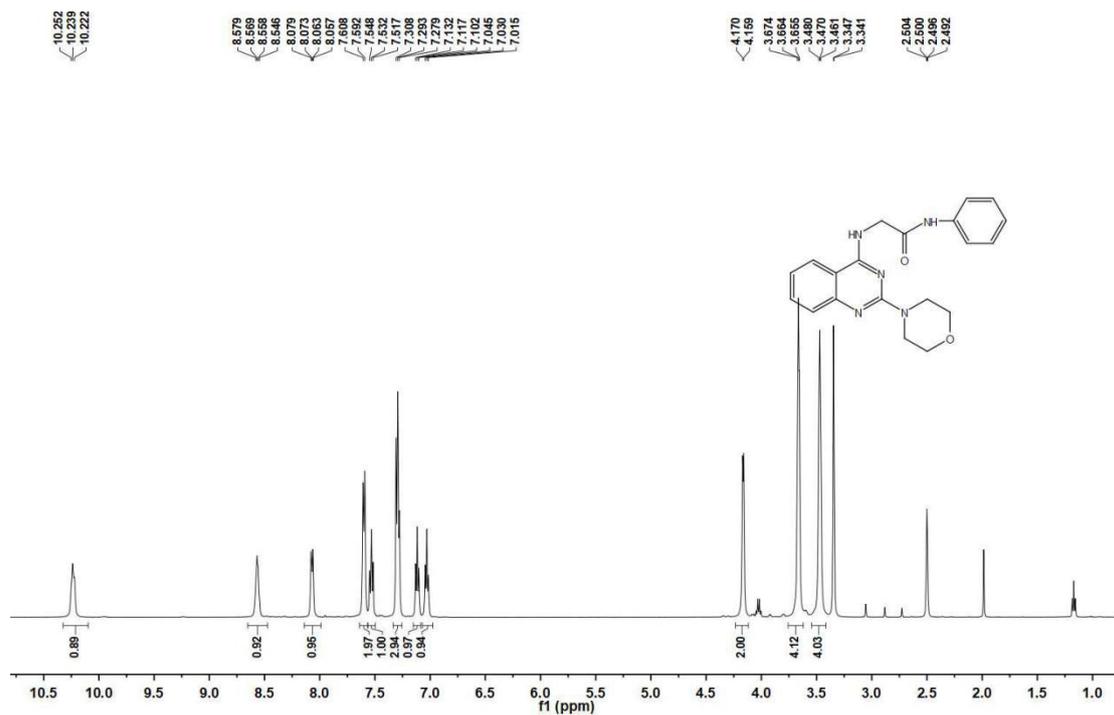
The ^1H NMR spectra of compound II-23j



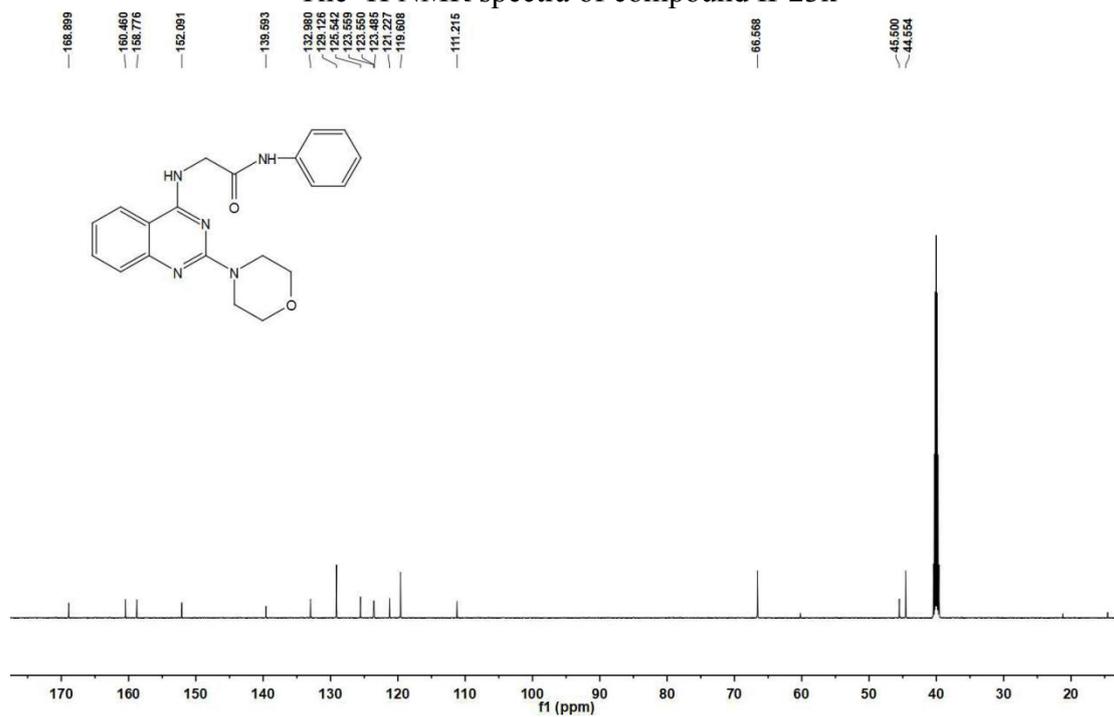
The ¹³C NMR spectra of compound II-23j



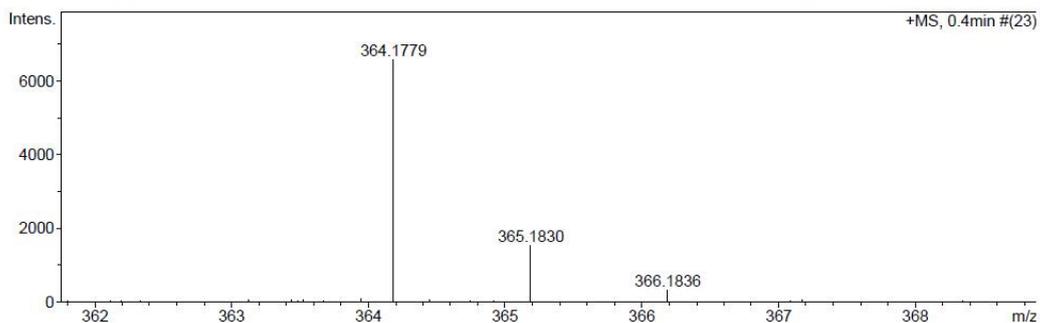
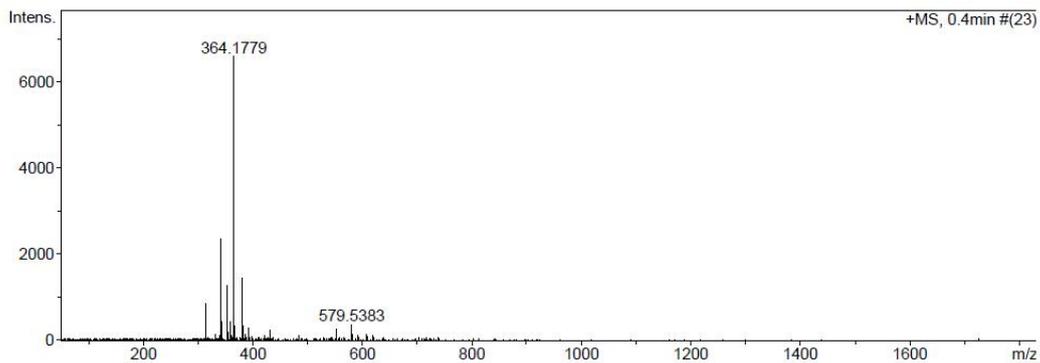
The HR-MS spectra of compound II-23j



The ^1H NMR spectra of compound II-23k



The ^{13}C NMR spectra of compound II-23k

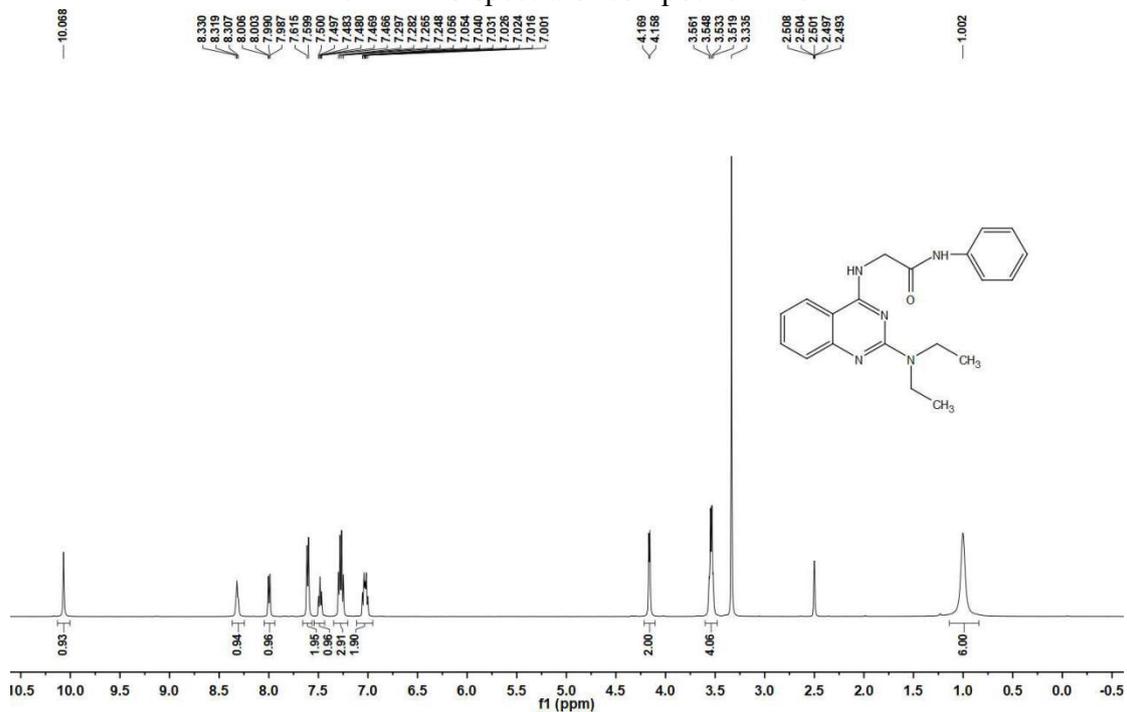


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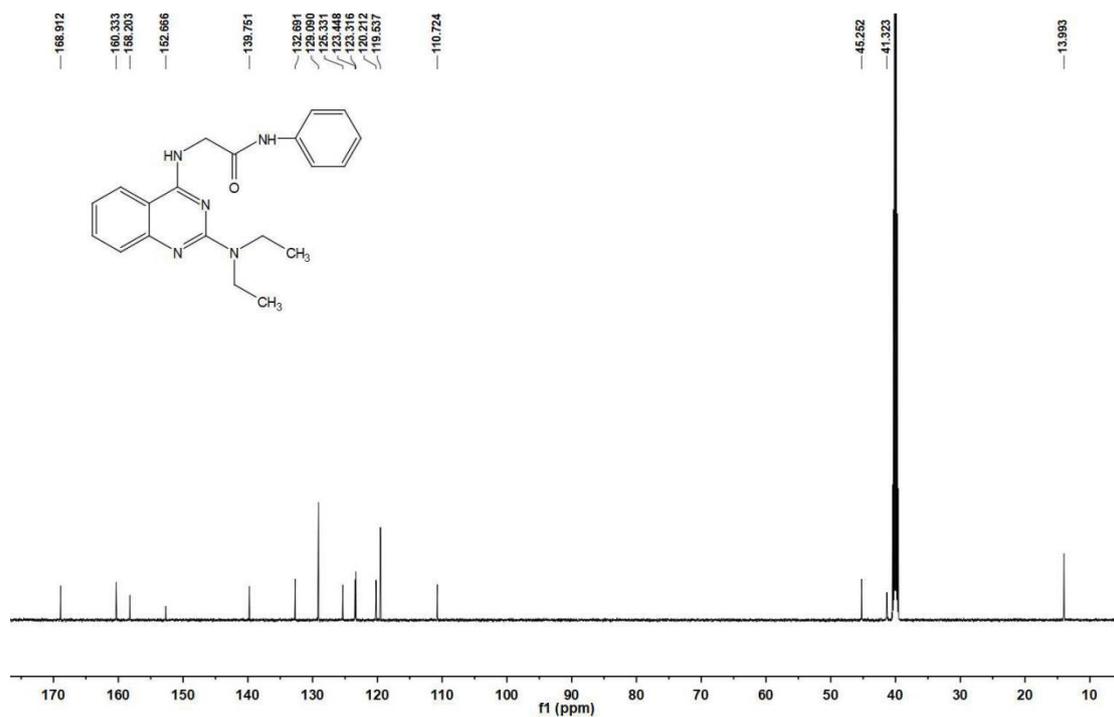
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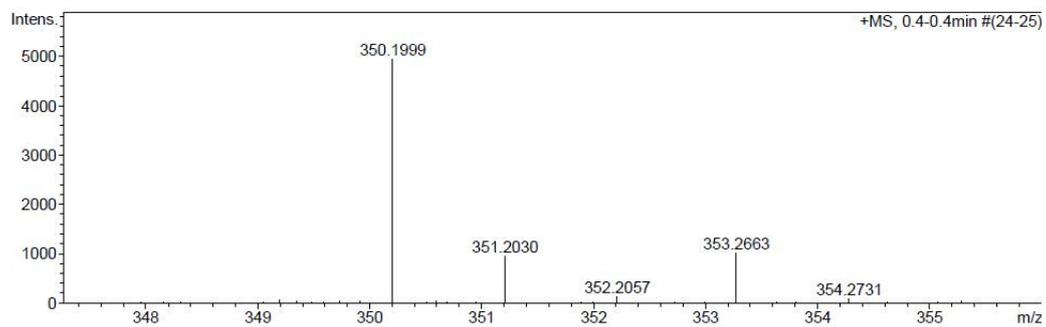
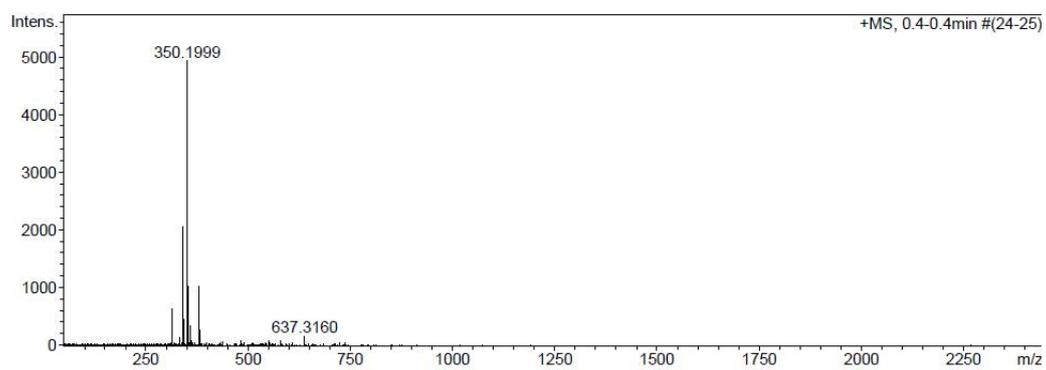
The HR-MS spectra of compound II-23k



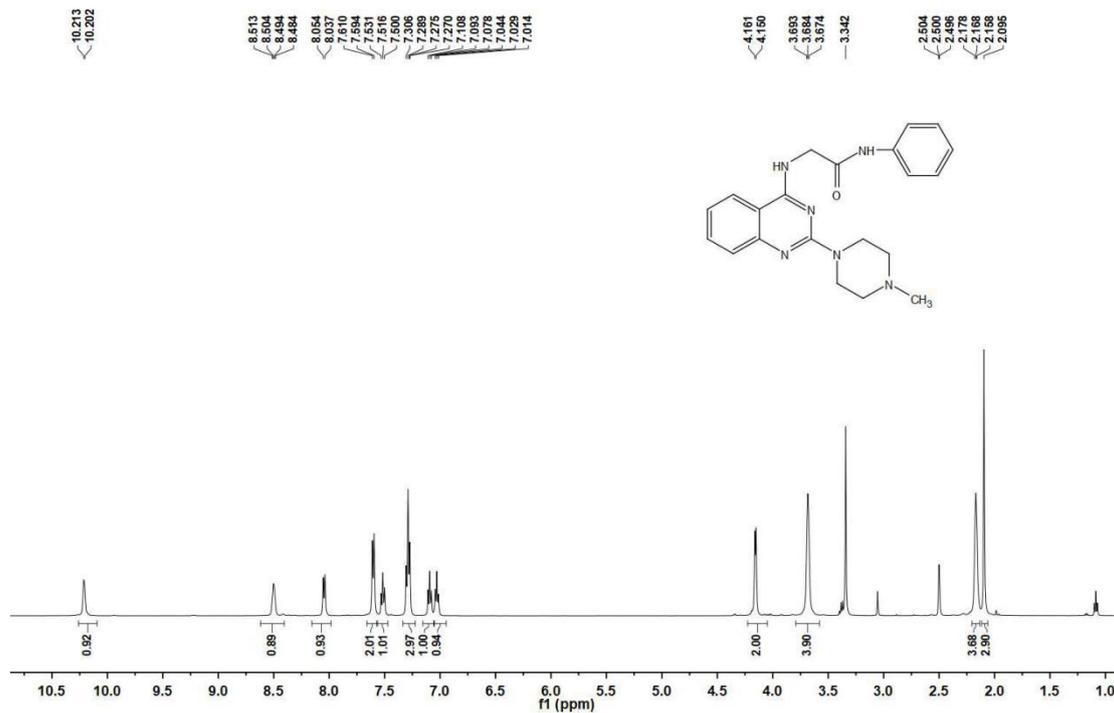
The ¹H NMR spectra of compound II-23l



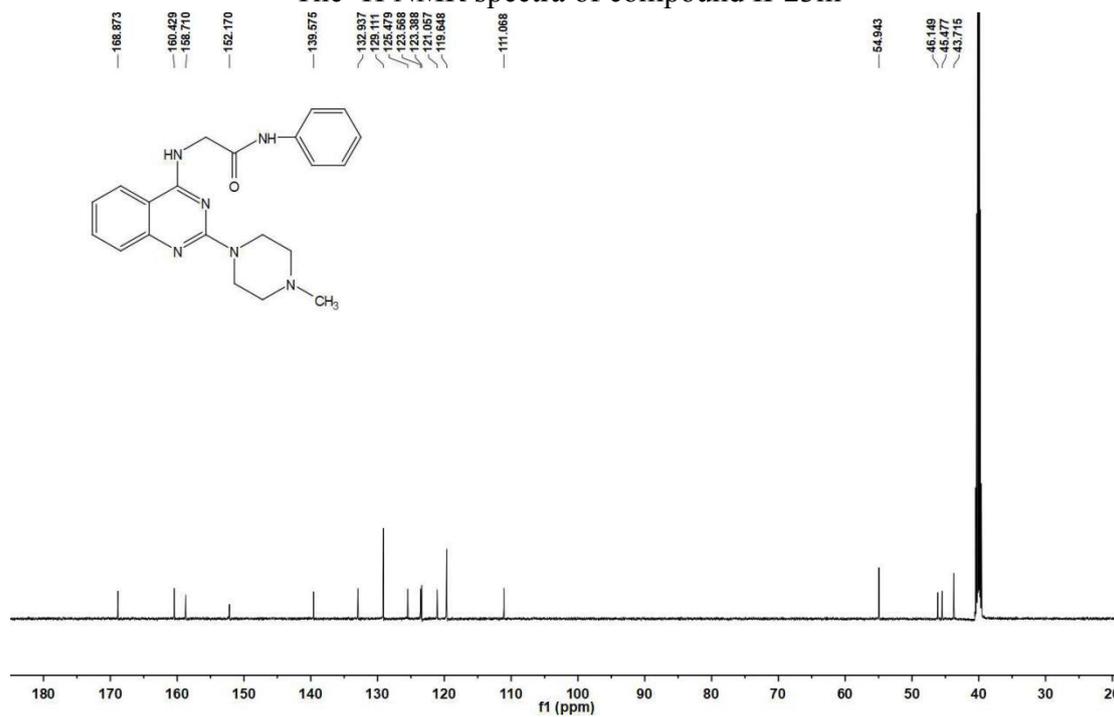
The ¹³C NMR spectra of compound II-231



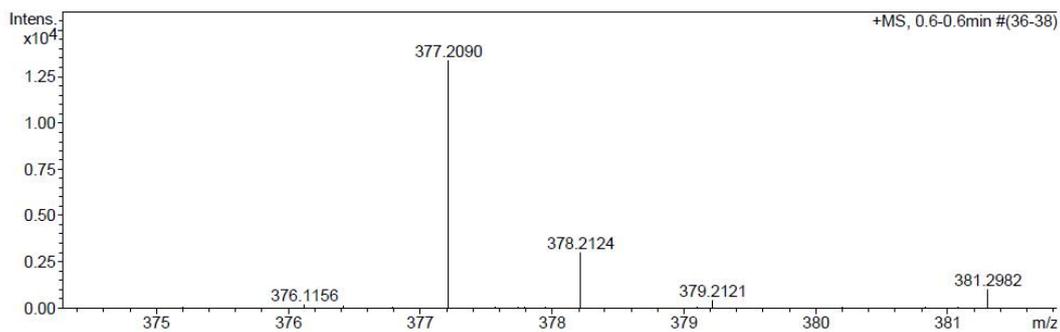
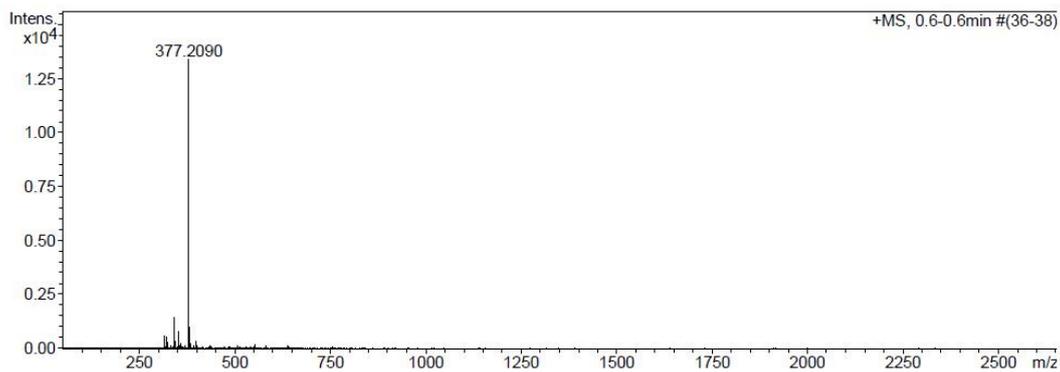
The HR-MS spectra of compound II-231



The ¹H NMR spectra of compound II-23m



The ¹³C NMR spectra of compound II-23m

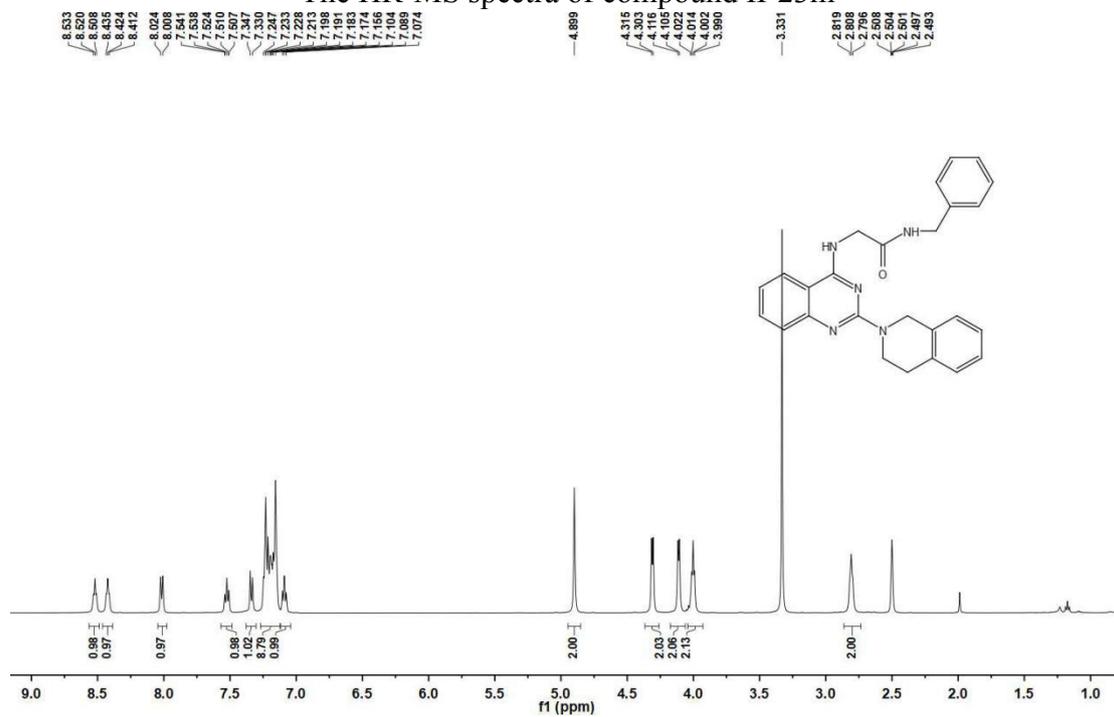


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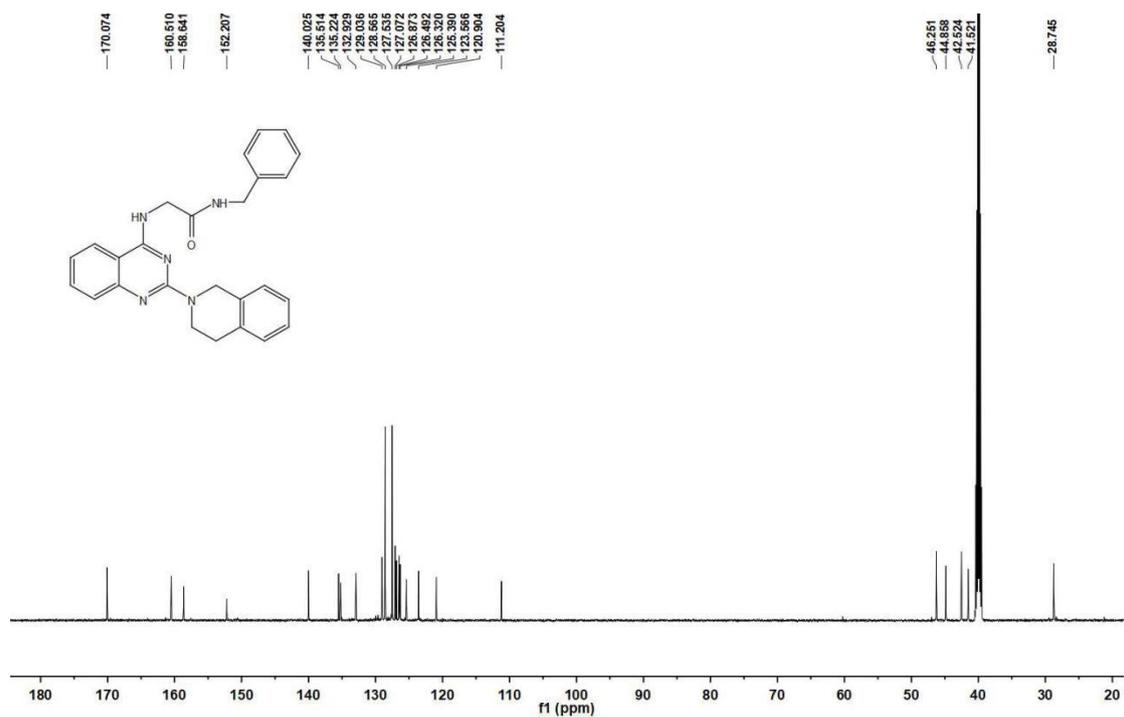
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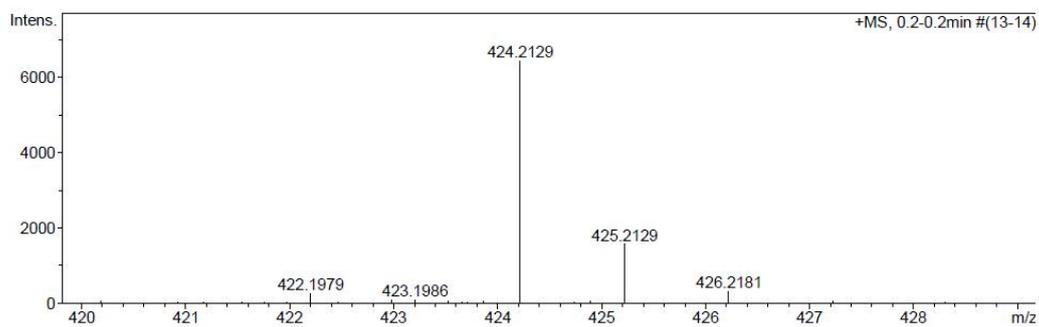
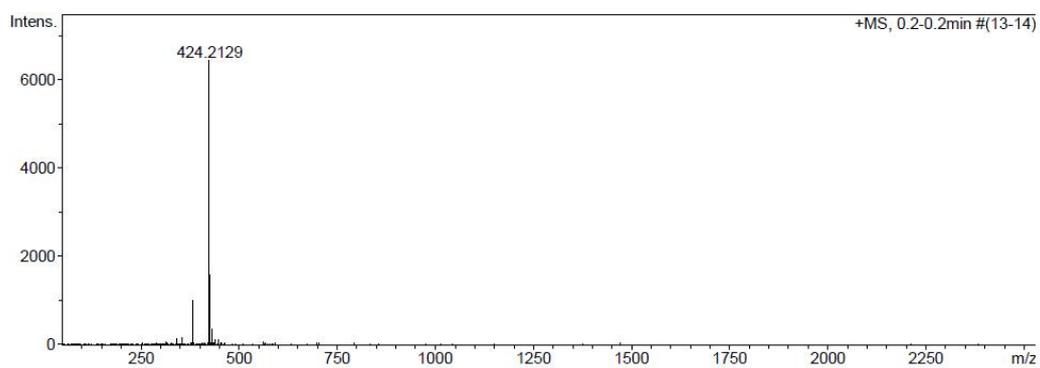
The HR-MS spectra of compound II-23m



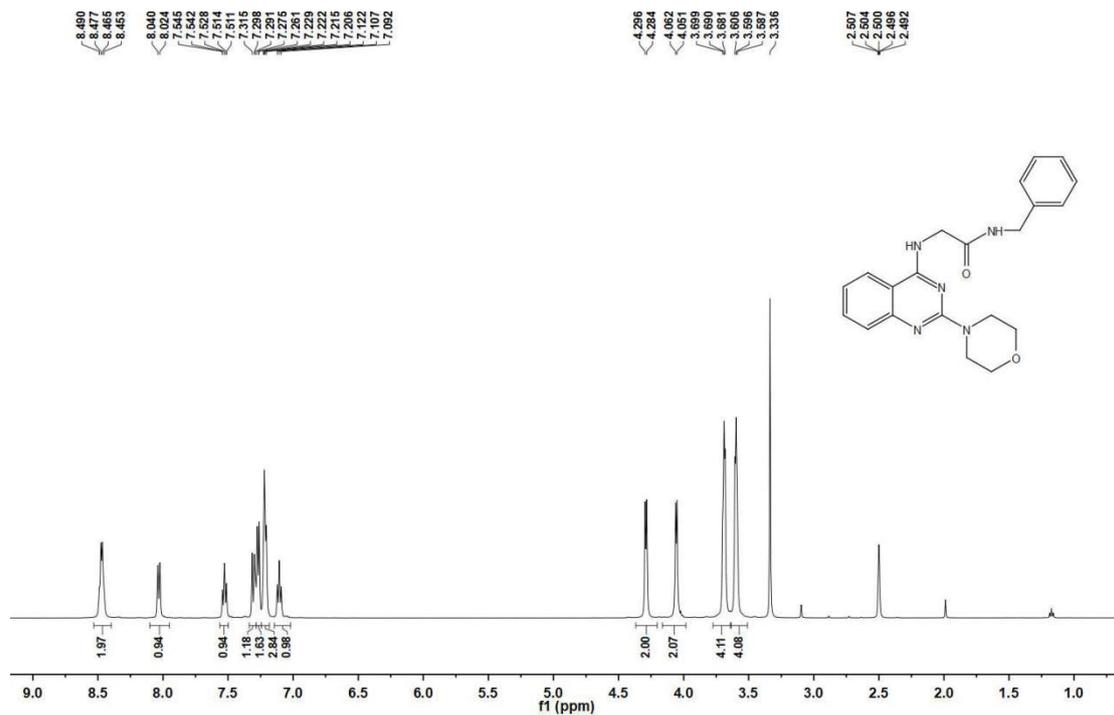
The ¹H NMR spectra of compound II-23n



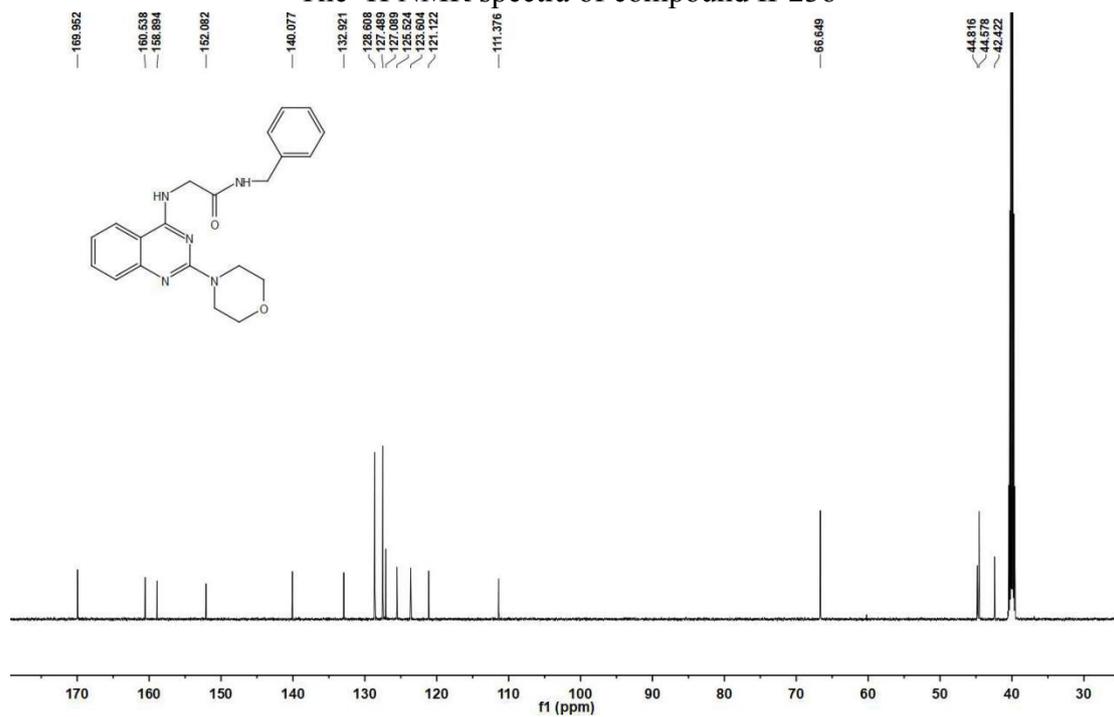
The ^{13}C NMR spectra of compound II-23n



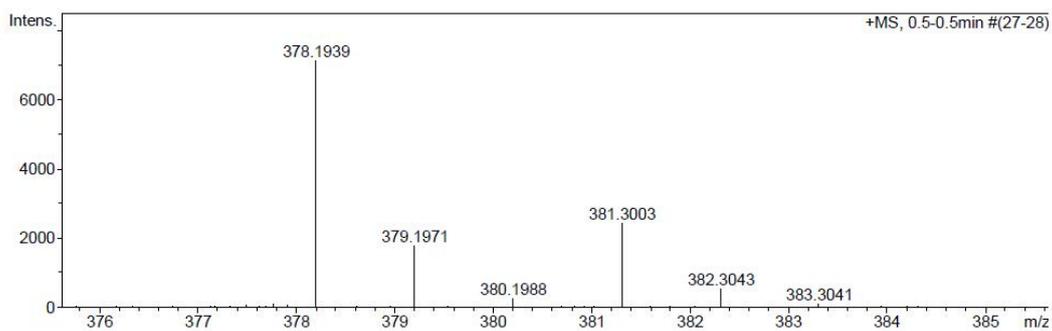
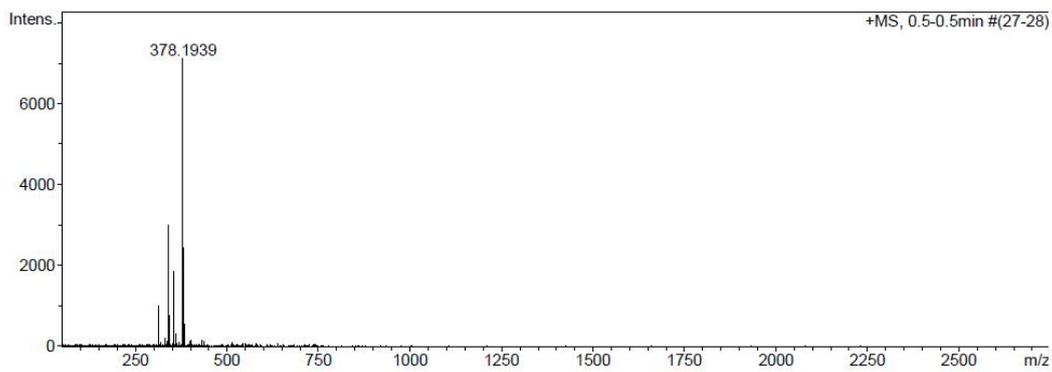
The HR-MS spectra of compound II-23n



The ^1H NMR spectra of compound II-23o



The ^{13}C NMR spectra of compound II-23o

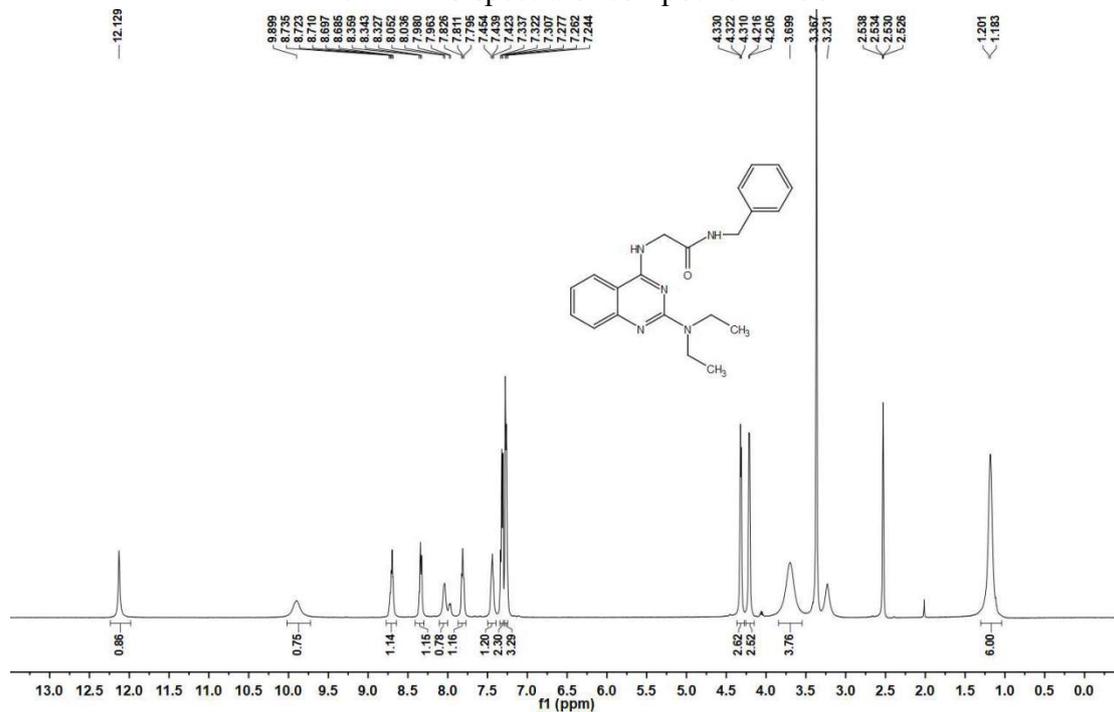


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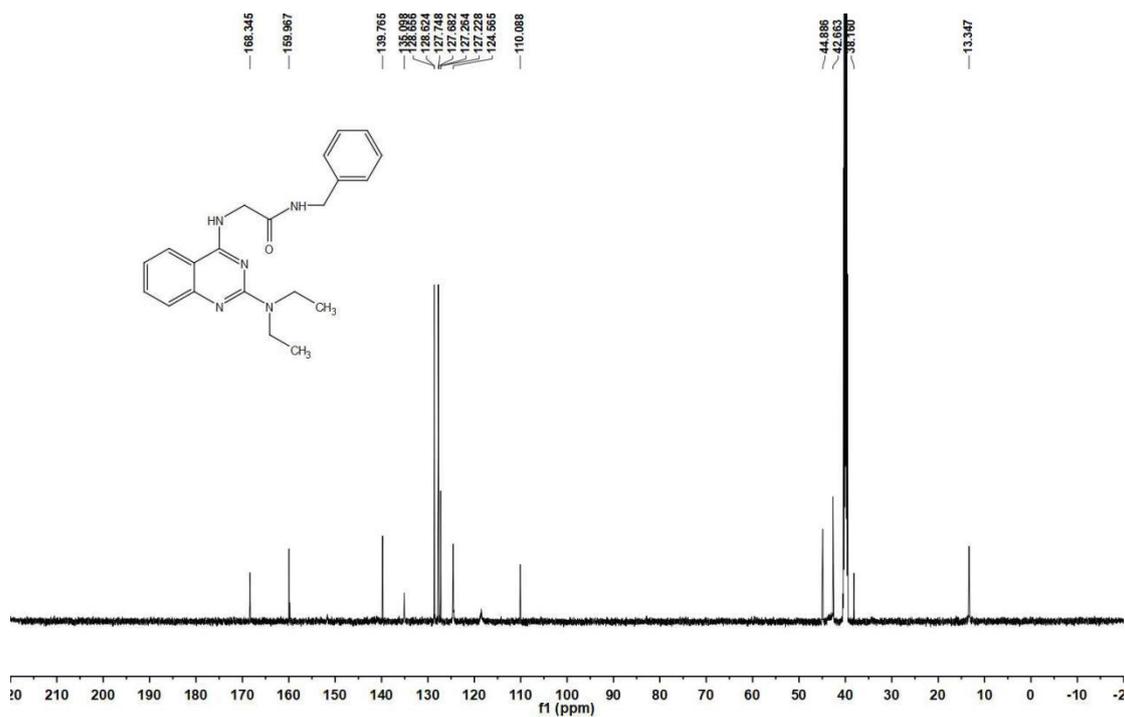
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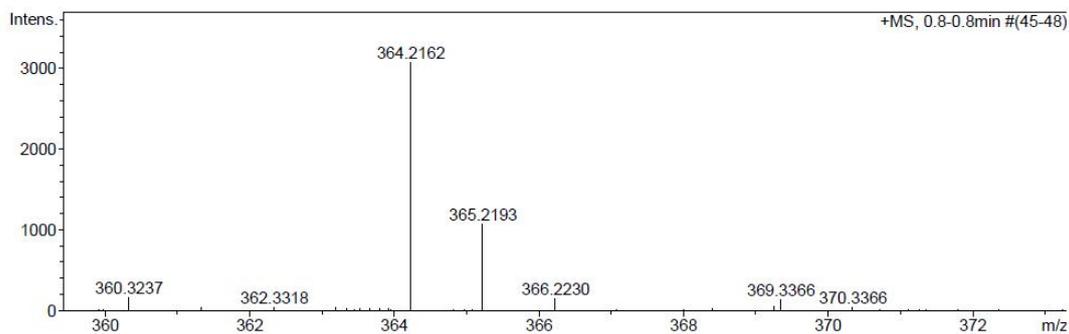
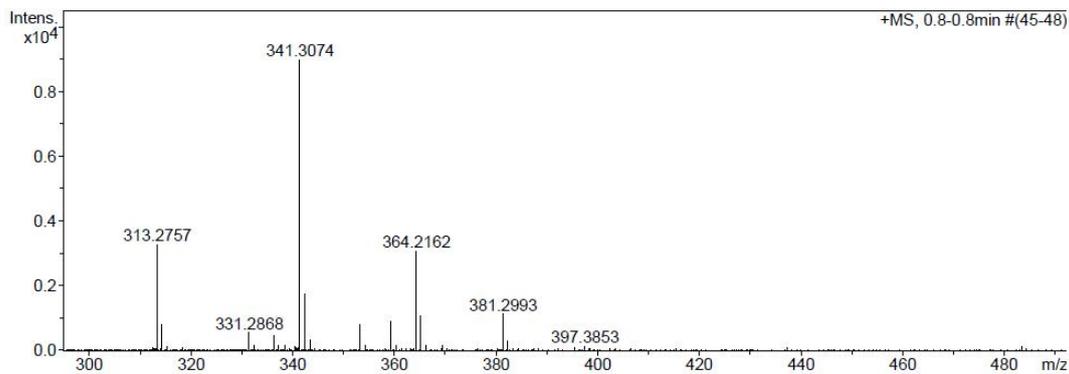
The HR-MS spectra of compound II-23o



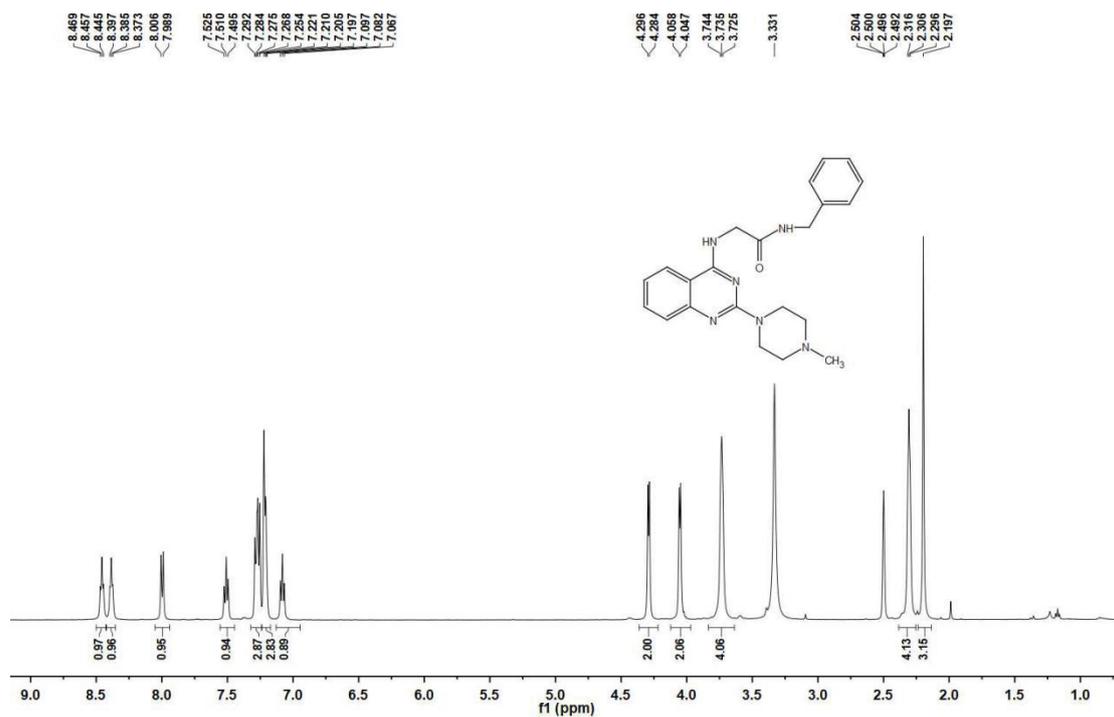
The ¹H NMR spectra of compound II-23p



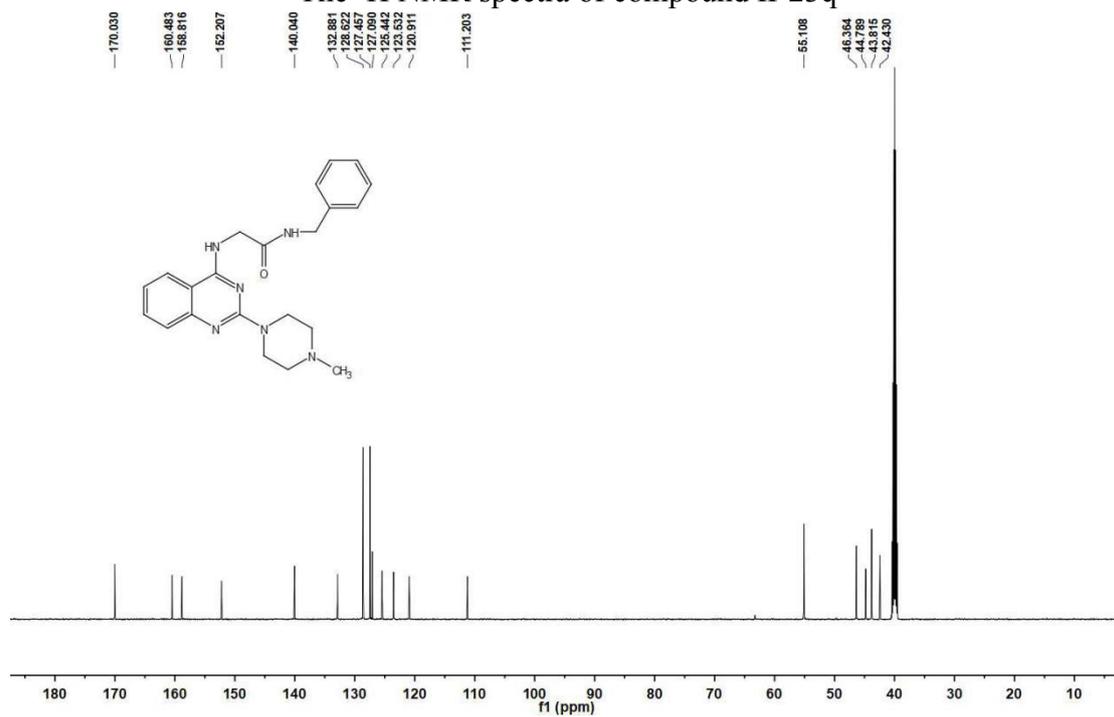
The ¹³C NMR spectra of compound II-23p



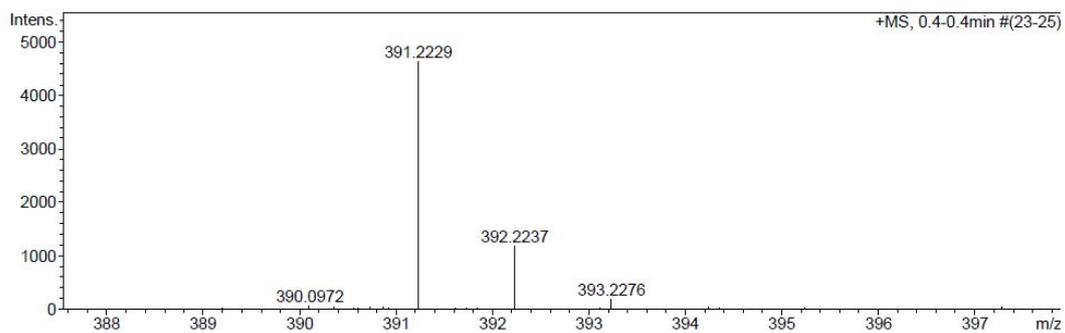
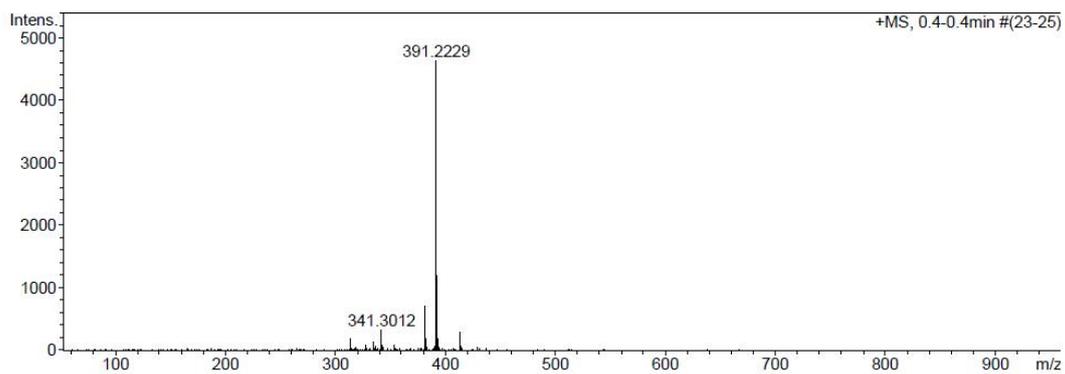
The HR-MS spectra of compound II-23p



The ¹H NMR spectra of compound II-23q



The ¹³C NMR spectra of compound II-23q



The HR-MS spectra of compound II-23q

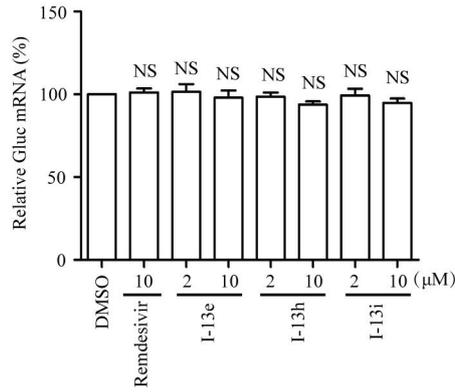


Figure S1 Effects of compound I-13e, I-13h and I-13i on Gluc plasmid mRNA level. HEK293T cells were seeded in 6 wells and transfected with pCoV-Gluc (10 ng/wells). Six hours post-transfection, supernatants were replaced with fresh medium containing I-13e, I-13h, I-13i and Remdesivir, respectively. Cells were cultured for another 24 hours, total cellular RNA was extracted, levels of Gluc were determined by real-time RT-PCR. Results shown are the average of three independent experiments. Error bars indicate SD and NS represents not significant.

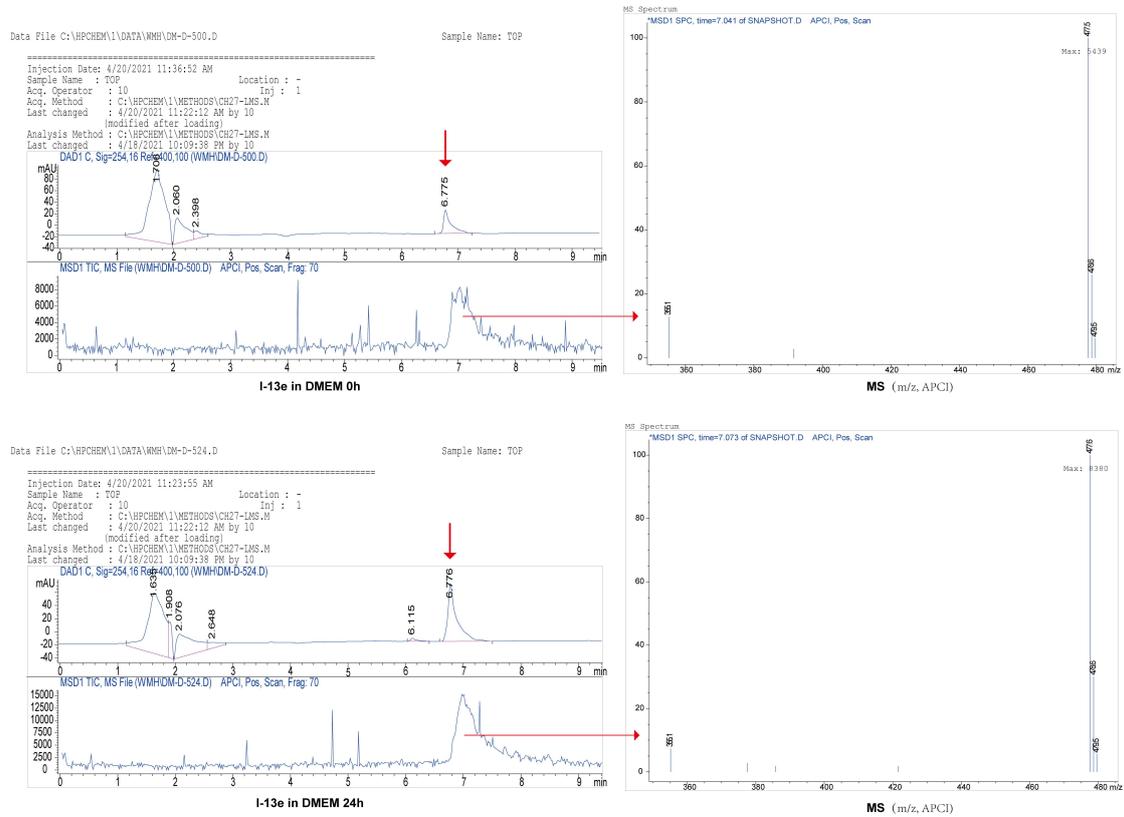


Figure S2 The HPLC-MS spectra of compound I-13e in DMEM at 37°C for 24 hour time.