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2-Amino-4-(aminomethyl)thiazole-based derivatives as potential antitumor agents: design, synthesis, cytotoxicity and apoptosis inducing activities

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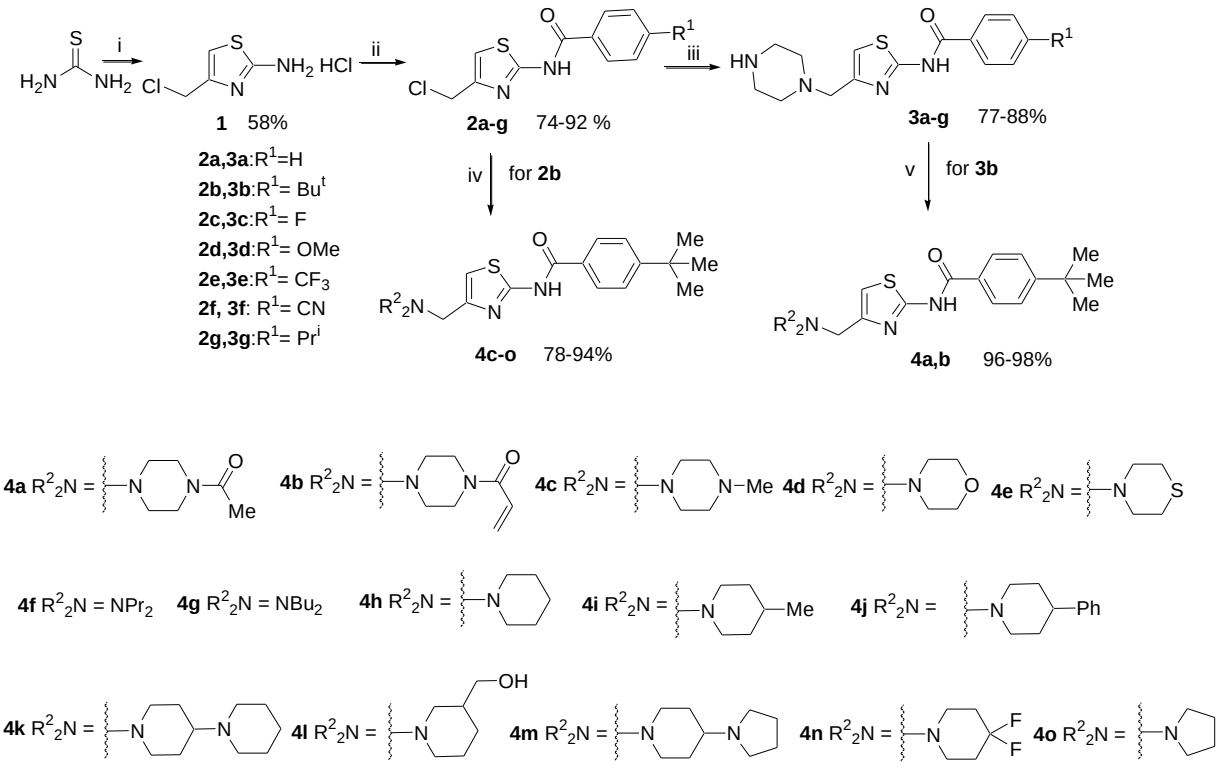
The NMR spectra were recorded on a Bruker AV-500 (or AV-600) spectrometer (Bruker, Karlsruhe, Germany) with TMS as an internal standard. HRESIMS was measured by a Shimazu LC-20AD AB SCIEX triple TOF 5600+ MS spectrometer (Shimadzu Corporation, Tokyo, Japan). Column chromatography was performed using 200-300 mesh silica gels. The solvents and reagents were dried prior as needed. Each target compound was identified and verified by ^{1}H, ^{13}C NMR, and HRESIMS.

General synthesis methods

The target N-(4-(aminomethyl)thiazol-2-yl)benzamide analogues **3a-3g** and **4a-4j** were synthesized as shown in Scheme S1. The chemical structures of title compounds **3a-3g** and **4a-4o** were confirmed by nuclear magnetic resonance (NMR) spectroscopy and high-resolution mass spectrometry (HRMS).



Scheme 1 *Reagents and conditions:* i, $ClCH_2C(O)CH_2Cl$, EtOH, room temperature, 4 h; ii, 4-$R^1C_6H_4C(O)Cl$, $NaHCO_3$, CH_2Cl_2, 0 °C, 8 h; ii, piperazine, acetonitrile, KI, reflux; iv, amine $R^2{}_2NH$, MeCN, reflux, 2 h; v acyl chloride, Et_3N, CH_2Cl_2, 0 °C, 4 h.

Synthesis of 4-(chloromethyl)thiazol-2-amine hydrochloride (1).

To a solution of thiourea (2.3 g, 30 mmol) in anhydrous EtOH (50 ml), 1,3-dichloroacetone (3.8 g, 30

mmol) in ethanol (30 ml) solution was added dropwise at 0 °C during 1 h, and then was stirred for 6 h. During this time, large amount of white solid precipitated, and the precipitate was separated by filtration and washed twice with acetone (2×50 ml), dried in vacuum to afford 3.2 g compound **1** as white solids. Yield 58%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (brs, 3H), 6.98 (s, 1H), 4.68 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.3, 136.5, 107.9, 37.6.

Synthesis of *N*-[4-(Chloromethyl)thiazol-2-yl]benzamide 2a and its analogues 2b-2g.

To a suspension of compound **1** (61.8 mg, 0.3 mmol) and sodium bicarbonate (51.6 mg, 0.6 mmol) suspended in DCM (10 ml), benzoyl chloride was added in portions, and this was stirred at 0 °C for 6 h. Then the mixture was poured into ice water, and the organic layer was washed twice with saturated NaCl solution and dried over Na_2SO_4, filtrated and concentrated. The residue was subjected to silica gel chromatography eluting with a gradient of petroleum ether-ethyl acetate (v/v=100:1) to yield **2a** (43.7 mg, 77% yield). Compounds **2b-g** were synthesized in a similar manner with the exception of replacing 4-^{tert}-butylbenzoyl chloride, 4-fluorobenzoyl chloride, 4-methoxylbenzoyl chloride, 4-(trifluoromethyl)benzoyl chloride, 4-cyanobenzoyl chloride and 4-isopropylbenzoyl chloride.

***N*-[4-(Chloromethyl)thiazol-2-yl]benzamide (2a)**: White solid; yield 86%; ^{1}H NMR (600 MHz, $CDCl_3$) δ10.91 (brs, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.62–7.50 (m, 3H), 6.96 (s, 1H), 4.38 (s, 2H).

4-(tert-Butyl)-*N*-[4-(chloromethyl)thiazol-2-yl]benzamide (2b): White solid; yield 92%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 6.97 (s, 1H), 4.56 (s, 2H), 1.29 (s, 9H).

***N*-[4-(Chloromethyl)thiazol-2-yl]-4-fluorobenzamide(2c)**: White solid; yield 87%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 – 7.94 (m, 2H), 7.21 (t, J = 8.5 Hz, 2H), 6.98 (s, 1H), 4.53 (s, 2H).

***N*-[4-(Chloromethyl)thiazol-2-yl]-4-methoxybenzamide (2d)**: White solid; yield 87%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.9 Hz, 2H), 7.01 (d, J = 8.9 Hz, 2H), 6.95 (s, 1H), 4.58 (s, 2H), 3.89 (s, 3H).

***N*-[4-(Chloromethyl)thiazol-2-yl]-4-(trifluoromethyl)benzamide(2e)**: White solid; yield 83%;^{1}H NMR (600 MHz, $CDCl_3$) δ 12.34 (brs, 1H), 8.31 (dd, J = 8.4, 7.9 Hz, 2H), 8.02 – 7.77 (m, 2H), 7.04 (s, 1H), 4.65 (s, 2H).

***N*-[4-(Chloromethyl)thiazol-2-yl]-4-cyanobenzamide (2f)**:Yellow solid; yield 83%;^{1} ^{1}H NMR (500 MHz, acetone-d_6) δ 8.32 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.28 (s, 1H), 4.69 (s, 2H).

***N*-[5-(Chloromethyl)thiazol-2-yl]-4-isopropylbenzamide (2g)**: Yellow solid; 74%; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.23 – 8.13 (m, 2H), 7.52 – 7.42 (m, 2H), 7.22 (s, 1H), 4.67 (s, 2H), 3.09 – 2.91 (m, 1H), 1.27 (d, J = 7.0 Hz, 6H).

Synthesis of *N*-[4-(piperazin-1-ylmethyl)thiazol-2-yl]benzamide 3a and its analogues 3b-g.

To a solution of piperazine (86.1 mg, 1 mmol) in anhydrous MeCN (10 ml), compound **2a** (25.2 mg, 0.1 mmol) was added and stirred at 80 °C for 6 h. After cooling to room temperature, the solvent was removed under reduced pressure, further extracted with ethyl acetate (EA) and saturated NH_4Cl solution. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on a silica gel column with dichloromethane and methanol (v/v =50:1) as the eluents to afford product **3a** as a yellow powder (27.2 g, 90% yield). Compounds **3b**-**g** were synthesized in a similar manner with the exception of replacing equivalent amount of **2b**-**g** instead of **2a** .

***N*-[4-(Piperazin-1-ylmethyl)thiazol-2-yl]benzamide (3a):** Yield 77%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 7.4 Hz, 2H), 7.58 – 7.43 (m, 3H), 6.77 (s, 1H), 3.40 (s, 2H), 2.97 – 2.81 (m, 4H), 2.51 – 2.33 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8 (C=O), 158.8, 147.5, 132.9, 132.1, 129.0, 128.9, 127.6, 127.5, 111.5, 58.5, 53.4, 45.3. HRMS *m/z* calcd for $C_{15}H_{19}N_4OS$ $(M+H)^+$ 303.1201; Found 303.1280.

4-*tert*-Butyl-*N*-[4-(piperazin-1-ylmethyl)thiazol-2-yl]benzamide (3b): Yield 88%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 6.77 (s, 1H), 3.45 (s, 2H), 2.91 (t, J = 4.8 Hz, 4H), 2.43 (s, 4H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0 (C=O), 159.1, 157.0, 148.0, 129.5, 127.7, 126.3, 111.7, 59.1, 54.2, 45.8, 35.5, 31.5. HRMS *m/z* calcd for $C_{15}H_{19}N_4OS$ $(M+H)^+$ 3303.1274; Found 303.1280.

4-Fluoro-*N*-[4-(piperazin-1-ylmethyl)thiazol-2-yl]benzamide (3c): Yield 85%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 – 7.85 (m, 3H), 7.24 – 7.14 (m, 2H), 6.80 (s, 1H), 3.51 (s, 2H), 3.13 – 3.03 (m, 4H), 2.62 (brs, 4H).^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8 (C=O), 160.61 (d, J = 178.9 Hz), 158.9, 147.1, 130.22 (d, J = 9.0 Hz), 116.36 (d, J = 22.1 Hz), 112.1, 58.3, 51.6, 44.6. HRMS *m/z* calcd for $C_{15}H_{17}FN_4OS$ $(M+H)^+$ 321.1180; Found 321.1181.

4-Methoxy-*N*-[4-(piperazin-1-ylmethyl)thiazol-2-yl]benzamide (3d): Yield 88%; ^{1}H NMR (500 MHz, Methanol-d_4) δ 9.55 (d, J = 8.9 Hz, 2H), 8.63 (d, J = 8.9 Hz, 2H), 8.58 (s, 1H), 5.45 (s, 3H), 5.27 (s, 2H), 4.83 – 4.77 (m, 4H), 4.36 (brs, 4H). ^{13}C NMR (150 MHz, DMSO) δ 164.7, 163.1, 158.9, 147.5, 130.6, 124.5, 114.3, 111.6, 57.6, 56.0, 49.4, 45.8. HRMS *m/z* calcd for $C_{16}H_{20}N_4O_2S$ $(M+H)^+$ 333.1380; Found 333.1380.

4-Trifluoromethyl-*N*-[4-(piperazin-1-ylmethyl)thiazol-2-yl]benzamide (3e): Yield 81%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H), 6.83 (s, 1H), 3.48 (s, 2H), 2.94 (q, J =

5.2, 4.7 Hz, 4H), 2.45 (brs, 4H).^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7 (C=O), 158.6, 147.8, 135.6, 134.6 ((q, J = 32.4 Hz)), 128.2, 126.2((q, J = 3.7 Hz)), 123.60 (q, J = 272.7 Hz), 111.9, 58.8, 53.9, 45.6. HRMS *m/z* calcd for $C_{16}H_{17}F_3N_4OS$ $(M+H)^+$ 371.1148; Found 371.1146.

4-Cyano-*N*-[4-(piperazin-1-ylmethyl)thiazol-2-yl]benzamide (3f): Yield 86%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 7.5 Hz, 2H), 6.72 (s, 1H), 3.37 (s, 2H), 2.80 (brs, 4H), 2.33 (brs, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5 (C=O), 160.3, 146.4, 137.0, 132.2, 128.4, 117.7 (CN), 115.4, 111.2, 58.3, 53.5, 45.9. HRMS *m/z* calcd for $C_{16}H_{17}N_5OS$ $(M+H)^+$ 328.1227; Found 328.1227.

4-Isopropyl-*N*-[4-(piperazin-1-ylmethyl)thiazol-2-yl]benzamide (3g): Yield 79%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 6.76 (s, 1H), 3.43 (s, 2H), 2.96 (p, J = 6.9 Hz, 1H), 2.89 (t, J = 4.8 Hz, 4H), 2.41 (s, 4H), 1.27 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 158.8, 154.5, 147.7, 129.7, 127.8, 127.2, 111.5, 58.8, 53.9, 45.6, 34.3, 23.8. HRMS *m/z* calcd for $C_{18}H_{24}N_4OS$ $(M+H)^+$ 345.1744; Found 345.1743.

Synthesis of *N*-{4-[(4-acetylpiperazin-1-yl)methyl]thiazol-2-yl}-4-(*tert*-butyl)benzamide (4a)：

To a solution of compound **3b** (35.8 mg, 0.1 mmol) in anhydrous pyridine (5 ml), acetyl chloride (0.15 mmol) was added and stirred at room temperature for 6 h. Then the mixture was poured into ice water and extracted with EA. The organic layer was washed twice with 0.1 M HCl solution and dried over Na_2SO_4, filtrated and concentrated. The residue was subjected to silica gel chromatography eluting with a gradient of DCM - methanol (v/v=50:1) to yield **4a** as yellow oil (38.7 mg, 96% yield).

Yellow oil; yield 96%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.81 (m, 2H), 7.58 – 7.50 (m, 2H), 6.79 (s, 1H), 3.65 – 3.59 (m, 2H), 3.50 – 3.38 (m, 4H), 2.39 (dt, J = 10.7, 5.1 Hz, 4H), 2.07 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (C=O), 164.6 (C=O), 159.0, 156.8, 147.3, 129.0, 127.4, 126.0, 111.4, 58.0, 53.1, 52.7, 46.1, 41.2, 35.2, 31.1, 21.3. calcd for $C_{22}H_{29}N_4O_2S$ $(M+H)^+$ 401.2011; Found 401.2018.

Synthesis of *N*-{4-[(4-acryloylpiperazin-1-yl)methyl]thiazol-2-yl}-4-(*tert*-butyl)benzamide (4b):

To a solution of compound **3b** (35.8 mg, 0.1 mmol) in anhydrous DCM (5 ml), triethylamine (30.0 mg, 0.2 mol) and acryloyl chloride (15.7 mg, 0.15 mmol) were added in sequence and stirred at room temperature for 4 h. Then the mixture was poured into ice water and extracted with DCM. The organic layer was washed twice with saturated NaCl solution and dried over Na_2SO_4, filtrated and concentrated. The residue was subjected to silica gel chromatography eluting with a gradient of DCM - methanol (v/v=50:1) to yield **4b** as yellow oil (40.5 mg, 98% yield).

Yellow oil; yield 98%; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.21 – 8.10 (m, 2H), 7.65 – 7.59 (m, 2H), 6.98 (s, 1H), 6.75 (dd, J = 16.7, 10.5 Hz, 1H), 6.16 (dd, J = 16.7, 2.5 Hz, 1H), 5.62 (dd, J = 10.5, 2.5 Hz, 1H), 3.61 (s, 4H), 3.57 (s, 2H), 2.48 (brs, 4H), 1.37 (s, 9H). ^{13}C NMR (150 MHz, acetone-d_6) δ 165.4 (C=O), 165.2 (C=O), 159.1, 156.9, 149.1, 130.6, 129.0, 128.7, 127.3, 126.5, 111.5, 58.7, 46.2, 35.6, 31.4. HRMS *m/z* calcd for $C_{22}H_{29}N_4O_2S$ $(M+H)^+$ 413.2011; Found 413.2015.

Synthesis of *N*-{4-[(4-acryloylpiperazin-1-yl)methyl]thiazol-2-yl}-4-(*tert*-butyl)benzamide 4c and its analogues 4c-o:

To a solution of 4-methylpiperazine (11.0 mg, 0.1 mmol) in anhydrous DMF (10 ml), compound **2b** (30.8 mg, 0.1 mmol) and KI (1.6 mg, 0.01 mmol) were added and stirred at room temperature overnight. The mixture was poured into ice water and extracted with EA. The organic layer was washed twice with saturated NH_4Cl solution and dried over Na_2SO_4, filtrated and concentrated. The residue was purified by chromatography on a silica gel column with dichloromethane and methanol (v/v =50/1) as the eluents to afford **4c** as a yellow oil (30.1 mg, 81% yield). Compounds **4d-o** were synthesized in a similar method with the exception of replacing different amines instead of 4-methylpiperazine.

4-*tert*-Butyl-*N*-{4-[(4-methylpiperazin-1-yl)methyl]thiazol-2-yl}benzamide (4c)

Yellow oil; yield 81%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 2H), 7.59 – 7.41 (m, 2H), 6.78 (s, 1H), 3.47 (s, 2H), 2.59 – 2.33 (m, 8H), 2.26 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4 (C=O), 158.4, 156.7, 148.0, 129.1, 127.3, 126.0, 111.3, 58.3, 54.8, 53.1, 46.0, 35.1, 31.1. HRMS *m/z* calcd for $C_{20}H_{29}N_4OS$ $(M+H)^+$ 373.2062; Found 373.2055

4-*tert*-Butyl-*N*-[4-(morpholinomethyl)thiazol-2-yl]benzamide (4d)

Yellow oil; yield 86%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 6.78 (s, 1H), 3.78 – 3.56 (m, 4H), 3.39 (s, 2H), 2.36 (s, 4H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7 (C=O), 158.8, 156.8, 147.7, 129.2, 127.4, 126.1, 111.4, 77.4, 77.2, 76.9, 66.9, 58.7, 53.6, 35.2, 31.2. HRMS *m/z* calcd for $C_{19}H_{26}N_3O_2S$ $(M+H)^+$ 360.1746 ; Found 360.1753

4-*tert*-Butyl-*N*-[4-(thiomorpholinomethyl)thiazol-2-yl]benzamide (4e)

White solid; mp: 189–190 °C; yield 94%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 6.78 (s, 1H), 3.48 (s, 2H), 2.68 (brs, 8H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

164.2 (C=O), 158.3, 156.7, 147.7, 128.9, 127.1, 125.9, 111.3, 59.0, 54.8, 35.0, 31.0, 27.7. HRMS *m/z* calcd for $C_{19}H_{26}N_3OS_2$ $(M+H)^+$ 376.1517 ; Found 376.1524

4-(tert-Butyl)-*N*-{5-[(dipropylamino)methyl]thiazol-2-yl}benzamide (4f)

Yellow oil; yield 86%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 6.77 (s, 1H), 3.28 (s, 2H), 2.25 (dd, J = 8.6, 6.6 Hz, 4H), 1.38 – 1.28 (m, 4H), 1.31 (s, 9H), 0.76 (t, J = 7.4 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0 (C=O), 158.8, 156.3, 149.6, 129.4, 127.6, 127.5, 125.7, 125.6, 109.9, 55.7, 54.0, 34.9, 31.0, 19.9, 11.8. HRMS *m/z* calcd for $C_{21}H_{32}N_3OS$ $(M+H)^+$ 374.2266; Found 374.2270

4-*tert*-Butyl-*N*-{5-[(dibutylamino)methyl]thiazol-2-yl}benzamide (4g)

Yellow oil; yield 91%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 6.83 (s, 1H), 3.63 (s, 2H), 2.71 – 2.31 (m, 4H), 1.56 – 1.43 (m, 4H), 1.35 (s, 9H), 1.32 – 1.23 (m, 4H), 0.89 (t, J = 7.4 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ164.3 (C=O), 156.6, 147.2, 141.7, 129.0, 127.2, 125.9, 109.3, 53.5, 35.0, 31.0, 28.5, 20.5, 13.9. HRMS *m/z* calcd for $C_{23}H_{36}N_3OS$ $(M+H)^+$ 402.2579; Found 402.2582

4-*tert*-Butyl-*N*-[4-(piperidin-1-ylmethyl)thiazol-2-yl]benzamide (4h)

Brown oil; yield 93%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 6.77 (s, 1H), 3.42 (s, 2H), 2.36 (brs, 4H), 1.56 (p, J = 5.5 Hz, 4H), 1.40 (brs, 2H), 1.34 (d, J = 3.3 Hz, 9H).^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6 (C=O), 158.6, 156.6, 147.99, 129.2, 127.4, 125.9, 111.1, 58.8, 54.4, 35.1, 31.28, 3.11, 25.6, 24.2. HRMS *m/z* calcd for $C_{20}H_{28}N_3OS$ $(M+H)^+$ 358.1953; Found 358.1956

4-*tert*-Butyl-*N*-{4-[(4-methylpiperidin-1-yl)methyl]thiazol-2-yl}benzamide (4i)

Yellow oil; yield 87%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 – 7.79 (m, 2H), 7.63 – 7.41 (m, 2H), 6.79 (s, 1H), 3.46 (s, 2H), 2.84 (d, J = 11.5 Hz, 2H), 1.97 (t, J = 10.7 Hz, 2H), 1.57 (d, J = 11.8 Hz, 2H), 1.48 – 1.42 (m, 1H), 1.35 (s, 9H), 1.31 – 1.24 (m, 2H), 0.90 (d, J = 6.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7 (C=O), 158.7, 156.7, 148.0, 129.3, 127.5, 126.0, 111.3, 58.5, 53.9, 35.2, 34.0, 31.3, 31.2, 30.7, 21.9. HRMS *m/z* calcd for $C_{21}H_{30}N_3OS$ $(M+H)^+$ 372.2110; Found 372.2113

4-*tert*-Butyl-*N*-{5-[(4-phenylpiperidin-1-yl)methyl]thiazol-2-yl}benzamide (4j)

Yellow oil; yield 91%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.24 – 7.14 (m, 3H), 6.80 (s, 1H), 3.50 (s, 2H), 2.98 (d, J = 11.5 Hz, 2H), 2.53 – 2.41 (m, 1H), 2.06 (td, J = 11.5, 2.6 Hz, 2H), 1.90 – 1.73 (m, 4H), 1.36 (s, 9H). ^{13}C NMR (125 MHz,

$CDCl_3$) δ 164.5 (C=O), 158.5, 156.8, 148.6, 146.6, 129.3, 128.5, 127.4, 127.0, 126.2, 126.2, 111.2, 58.9, 54.5, 42.8, 35.3, 33.4, 31.2. HRMS *m/z* calcd for $C_{26}H_{32}N_3OS$ $(M+H)^+$ 434.2266 ; Found 434.270.

4-*tert*-Butyl-*N*-{4-[(4-piperidinopiperidin-1-yl)methyl]thiazol-2-yl}benzamide (4k)

Yellow solid; mp: 64-65 °C; yield 90%; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.20 – 8.08 (m, 2H), 7.63 – 7.57 (m, 2H), 6.90 (s, 1H), 3.41 (s, 2H), 2.86 (d, *J* = 11.7 Hz, 3H), 2.52 – 2.38 (m, 8H), 2.17 (ddt, *J* = 11.5, 7.4, 3.8 Hz, 2H), 1.94 (td, *J* = 11.8, 2.1 Hz, 3H), 1.67 (d, *J* = 12.2 Hz, 3H), 1.55 – 1.47 (m, 12H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, acetone-d_6) δ 164.6 (C=O), 158.3, 156.0, 149.1, 129.8, 127.8, 125.6, 110.0, 62.5, 58.1, 53.2, 50.1, 34.8, 30.6, 30.5, 27.9, 26.4, 26.4, 24.8. HRMS *m/z* calcd for $C_{25}H_{37}N_4OS$ $(M+H)^+$ 441.2688 ; Found 441.2690 .

4-*tert*-Butyl-*N*-(5-{[3-(hydroxymethyl)piperidin-1-yl]methyl}thiazol-2-yl)benzamide (4l)

Yellow solid; mp: 160–161 °C; yield 78%; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.19 – 8.06 (m, 2H), 7.66 – 7.47 (m, 2H), 6.95 (s, 1H), 3.51 (s, 2H), 3.42 (dd, *J* = 10.6, 5.5 Hz, 1H), 3.34 (dd, *J* = 10.5, 7.1 Hz, 1H), 2.97 (d, *J* = 9.7 Hz, 1H), 2.79 (d, *J* = 11.0 Hz, 1H), 1.87 (t, *J* = 10.4 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.70 – 1.60 (m, 2H), 1.60 – 1.52 (m, 1H), 1.35 (s, 9H), 1.33 – 1.32 (m, 2H), 0.97 (tt, *J* = 11.2, 6.1 Hz, 1H). ^{13}C NMR (150 MHz, acetone-d_6) δ 165.5 (C=O), 159.1, 156.8, 149.0, 130.6, 128.7, 126.4, 111.5, 65.9, 59.3, 57.9, 54.8, 39.6, 35.6, 31.3, 27.8, 25.4. HRMS *m/z* calcd for $C_{21}H_{30}N_3OS$ $(M+H)^+$ 372.2110; Found 372.2104.

4-*tert*-Butyl-*N*-(4-{[4-(pyrrolidin-1-yl)piperidin-1-yl]methyl}thiazol-2-yl)benzamide (4m)

Yellow oil; yield 87%; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.15 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 6.91 (s, 1H), 3.45 (s, 2H), 2.84 (d, *J* = 11.8 Hz, 2H), 2.52 (d, *J* = 10.5 Hz, 4H), 2.11 – 1.99 (m, 3H), 1.89 – 1.79 (m, 2H), 1.70 (p, *J* = 3.1 Hz, 4H), 1.61 – 1.45 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, acetone-d_6) δ 165.5 (C=O), 159.1, 156.9, 150.0, 130.7, 128.7, 126.5, 110.9, 62.5, 59.2, 53.0, 51.9, 47.0, 35.6, 32.2, 31.4, 24.0. HRMS *m/z* calcd for $C_{24}H_{35}N_4OS$ $(M+H)^+$ 427.2532; Found 427.2537.

4-*tert*-Butyl-*N*-(4-[(4,4-difluoropiperidin-1-yl)methyl]thiazol-2-yl)benzamide(4n)

Yellow solid; mp: 154–155 °C; yield 86%;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.50 (dd, *J* = 8.4, 1.6 Hz, 2H), 6.77 (s, 1H), 3.48 – 3.26 (m, 2H), 2.42 (brs, 4H), 1.99 – 1.68 (m, 4H), 1.34 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6 (C=O), 158.8, 156.7, 147.8, 129.1, 127.3, 127.2, 125.9, 125.8, 121.80 (t, *J* = 240.6 Hz, $\underline{C}F_2$), 110.9, 57.3, 49.8, 35.1, 33.69 (t, *J* = 23.1 Hz), 31.0. HRMS *m/z* calcd for $C_{20}H_{26}N_3OF_2S$ $(M+H)^+$ 394.1765 ; Found 394.1768.

4-*tert*-Butyl-*N*-[4-(pyrrolidin-1-ylmethyl)thiazol-2-yl]benzamide(4o)

Yellow solid; mp: 66-68 °C; yield 93%; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.15 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H), 6.91 (s, 1H), 3.62 (s, 2H), 2.52 (t, J = 6.5 Hz, 4H), 1.73 (p, J = 3.1 Hz, 4H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, acetone-d_6) δ 164.5 (C=O), 157.9, 156.0, 149.9, 129.8, 127.8, 125.6, 109.4, 55.5, 53.6, 34.7, 30.5, 23.4. HRMS *m/z* calcd for $C_{19}H_{26}N_3OS$ $(M+H)^+$ 344.1797; Found 344.1795.

2.2 Bioactivities assay

2.2.1 Reagents

The title compounds were dissolved in DMSO (Sigma-Aldrich, St. Louis, MO, USA). The Cell Counting Kit-8 was obtained from Dojindo Laboratories (Kumamoto, Japan); Phosphate Buffered Saline (1×) obtained from HyClone (Los Angeles, State of California, USA); RPMI Medium 1640 basic (1×) and DMEM basic (1×) was purchased from Grand Island Biological Company (Grand Island, New York, USA); FBS was obtained from Grand Island Biological Company (Grand Island, New York, USA); Penicillin-streptomycin was purchased from Grand Island Biological Company (Grand Island, New York, USA); Rabbit monoclonal antibodies against GAPDH, cleaved-PARP, PARP, AKT, Phosphorylated-AKT were purchased from Cell Signaling Technology (Beverly, MA, USA).

2.2.2 Cell lines and cell culture

The cancer cell lines, human esophageal cancer (KYSE30), human non-small cell lung cancer (A549), human gastric cancer (BGC-823), human acute promyelocytic leukemia cell (HL-60), and human liver cancer (HePG2), were cultured in RPMI medium 1640 or DMEM containing 10% FBS and 1% penicillin-streptomycin, and incubated at 37 °C in an atmosphere of 5% CO_2.

2.2.3 Cytotoxicity assay

The cytotoxic effects of the chemicals were determined by monitoring the growth and proliferation of untreated and treated cells using the CCK-8 assay after 48 h incubation. For the experiments, KYSE30, A549, BGC-823, HL-60 and HePG2 were plated onto 96-well microplates at the following densities: 2.6 x 103 pcs/well, 4.5 x 103 pcs/well, 5 x 103 pcs/well, 2.5 x 104 pcs/well and 4.5 x 103 pcs/well. After incubation, the culture medium was removed and the cells were washed with phosphate-buffered saline and exposed to 90 μL RPMI medium 1640 or DMEM culture medium without phenol red. At designated time points, 10 μL of CCK-8 were added to each well and the microplates were incubated for 30-90 min at 37 °C. Absorbance was read spectrophotometrically in a Microplate reader at a wavelength of 450 nm. The experiments were performed in triplicate.

2.2.4 Western blot analysis

Total protein of esophageal cancer cell KYSE30 was harvested with RIPA buffer (P0013B; Beyotime) as well as Phosphatase Inhibitor Cocktail 1 (K1015-A, APE X BIO), protease inhibitors cocktail 2 (K1015-B, APE X BIO), and 100 mM PMSF (ST506-2, Beyotime) after 24 h chemical action. Equal amounts of each sample proteins were separated by sodium dodecyl sulfate polyacrylamid gel electrophoresis and transplanted to nitrocellulose filter membranes, then blocking with 5% bovine serum albumin (122019; Sigma) for 1 h. After that the membrane was incubated with anti-GAPDH (1:1000, #5174; CST), anti-PARP (1:1000, #9532; CST), anti-Cleved-PARP (1:1000, #9532; CST), anti-AKT (1:1000, #4691; CST), anti-phospho-AKT (1:2000, #4060; CST), antibodies, respectively, at 4°C overnight and then incubated with secondary antibodies (1:1000, #7074; CST) for 1 h at room temperature. Immune blot bands were visualized with an ECL solution (34094; Thermo Fisher Scientific) and detected by using a Protein Imager (734BR4132, BIO-RAD). The gray value of Western blot was measured by the ImageJ software for Microsoft Windows (National Institute of Health, Bethesda, MD).

2.2.5 TUNEL/DAPI double stains experiments

KYSE-30 cells were seeded into 6-well plates, and then treated with 12.5 μM **4k** and cultured at 37°C for 24 h, washed, fixed and stained as per the manufacturer's instructions. DNA double-strand breaks occur late in the apoptotic pathway and were assessed using the TUNEL Apoptosis Detection Kit (Beyotime, Shanghai, China) for 0.5 h, then stained with 1 g/mL DAPI (Beyotime, Shanghai, China) for 5 min and observed by fluorescence microscopy.

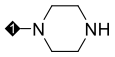
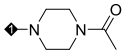
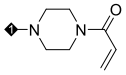
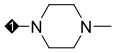
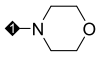
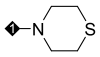
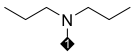
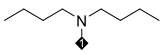
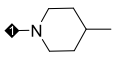
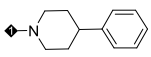
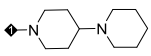
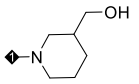
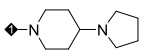
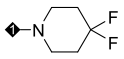
2.3 Statistical analysis

The mean ± SD values presented in the Fig.s and tables were calculated from three or more independent experiments. Comparisons between groups were evaluated using GraphPad Prism version 7.0 software. $P < 0.05$ was considered statistically significant.

Table S1. Inhibition rates (%) of compounds **3a-g** against human tumor cells.

Comp.	R^1	Inhibition rates (%) of compounds at 40 μM				
		A549	BGC-823	HePG2	KYSE30	HL-60
3a	H	9.7±0.3	1.6±1.8	13.1±1.2	19.9±5.8	22.1±3.4
3b	Bu^t	**58.1±6.3**	**73.1±2.1**	**49.1±4.6**	**70.6±1.2**	**45.6±2.1**
3c	F	1.1±0.1	4.2±3.3	17.5±3.1	10.6±4.8	5.5±4.4
3d	OMe	8.4±3.7	19.5±2.0	16.1±0.7	12.2±2.5	27.7±0.9
3e	CF_3	0.6±3.5	12.2±6.6	4.3±0.6	15.6±0.9	22.1±0.2
3f	CN	6.2±0.5	13.0±0.7	35.9±0.1	-0.3±0.6	24.7±0.5
3g	Pr^i	13.8±2.4	9.1±0.9	4.4±0.7	32.4±2.9	34.3±8.3
5-Fluorouracil		45.3±1.1	50.0±3.1	67.2±4.3	47.0±0.2	68.7±0.9
Cisplatin		76.4±2.1	90.5±1.4	87.1±3,1	72.1±0.3	73.1±0.2

Table S2. IC50 (μM) of 3b and 4a-4o against human tumor cells

Compd.	NR^2_2	IC_{50}(μM)					
		A549	BGC-823	HePG2	KYSE-30	HL-60	MCF-10A
3b		**38.1±2.1**	**38.8±0.4**	**44.4±1.6**	**34.6±0.8**	**39.0±1.3**	>100
4a		>100	>100	>100	>100	>100	>100
4b		>100	>100	>100	>100	>100	>100
4c		44.4±0.7	43.0±0.3	65.3±2.4	51.0±0.3	63.6±2.4	96.5±2.6
4d		>100	>100	>100	>100	>100	>100
4e		>100	>100	>100	>100	>100	>100
4f		>100	>100	>100	>100	>100	>100
4g		39.29±1.7	55.7±3.2	78.1±1.6	56.1±4.2	60.3±2.5	>100
4h		>100	>100	>100	>100	>100	>100
4i		47.3±0.8	83.3±0.3	103.6±2.1	65.5±1.6	**4.0±0.3**	>100
4j		83.3±0.4	84.9±3.2	47.0±1.3	46.0±0.5	92.2±2.3	>100
4k		**55.0±2.6**	**37.0±0.0**	**43.7±2.2**	**25.6±1.1**	**39.9±3.1**	51.7±1.0
4l		84.9±0.6	>100	25.5±1.8	77.4±2.4	66.7±1.0	>100
4m		80.1±0.3	73.3±1.84	46.9±1.0	50.8±2.1	67.7±0.8	>100
4n		88.3±0.3	>100	>100	85.7±2.4	>100	>100
4o		90.3±1.3	>100	29.7±1.7	66.5±1.8	63.90±2.7	90.7±3.7
5-Fluorouracil		62.4±4.1	43.8±0.7	62.9±3.3	16.8±1.1	13.7±0.6	39.7±1.1
Cisplatin		14.3±2.1	4.1±3.7	11.6±1.6	6.6±0.7	14.1±0.7	5.1±1.4

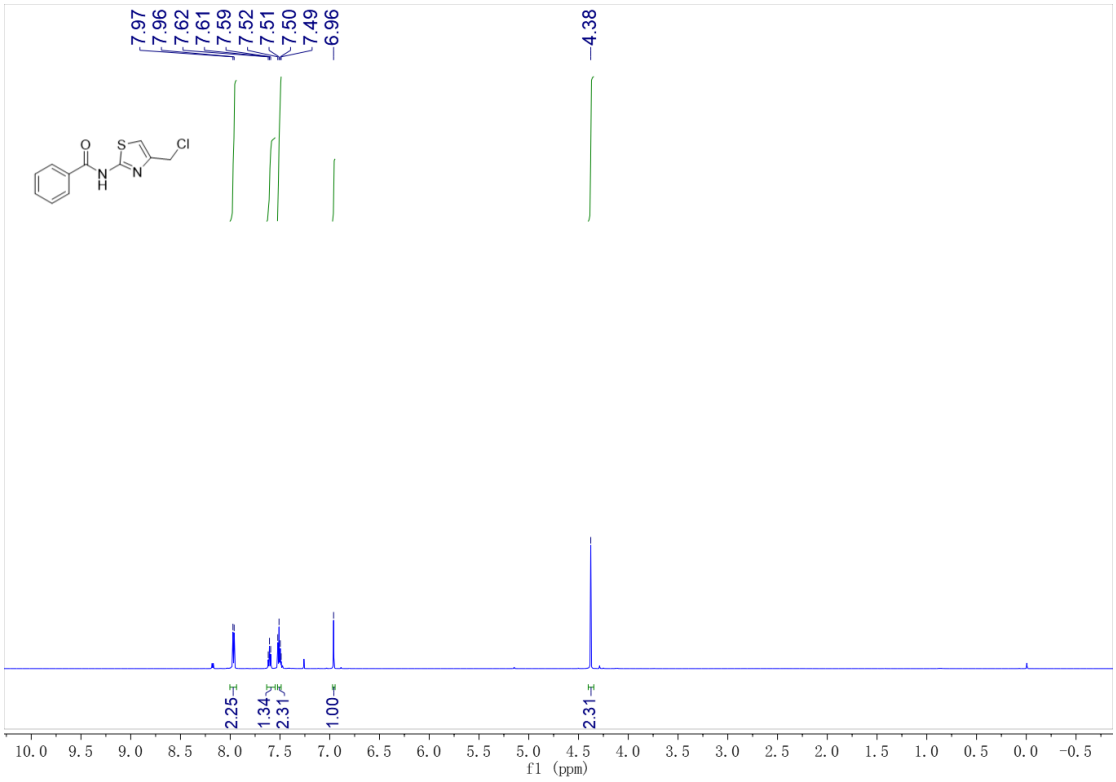


Fig. S1 ^{1}H NMR spectrum of **2a**

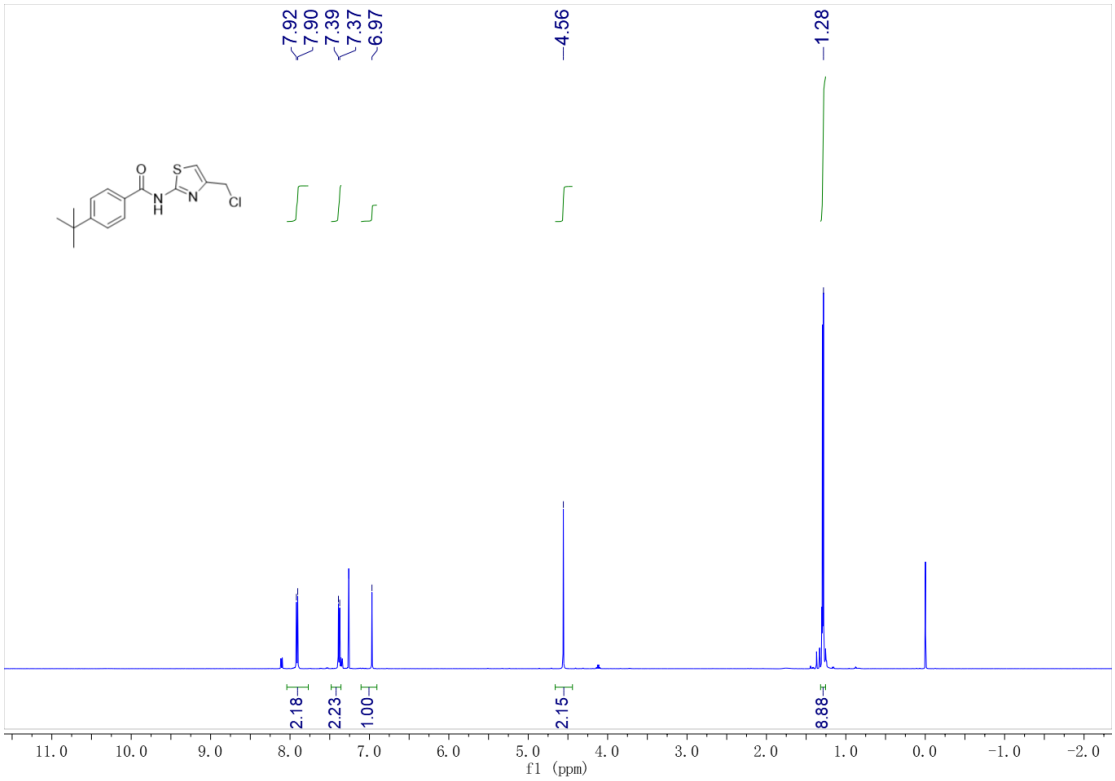


Fig. S2 ^{1}H NMR spectrum of **2b**

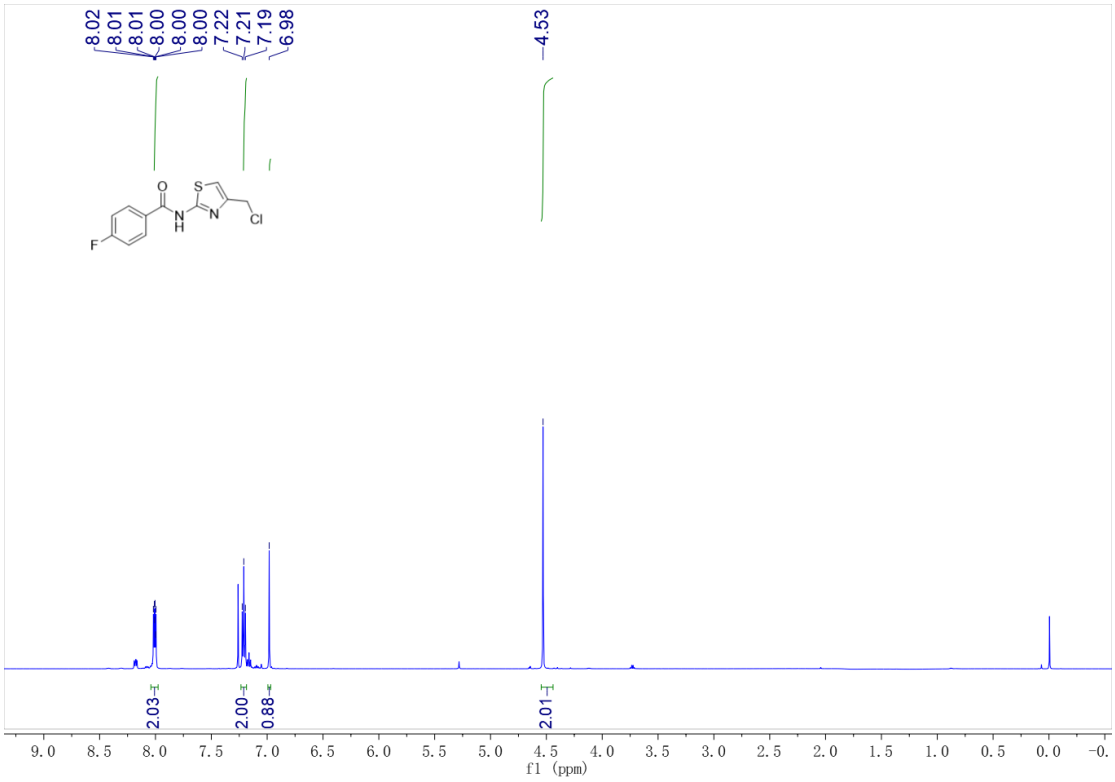


Fig. S3 ^{1}H NMR spectrum of **2c**

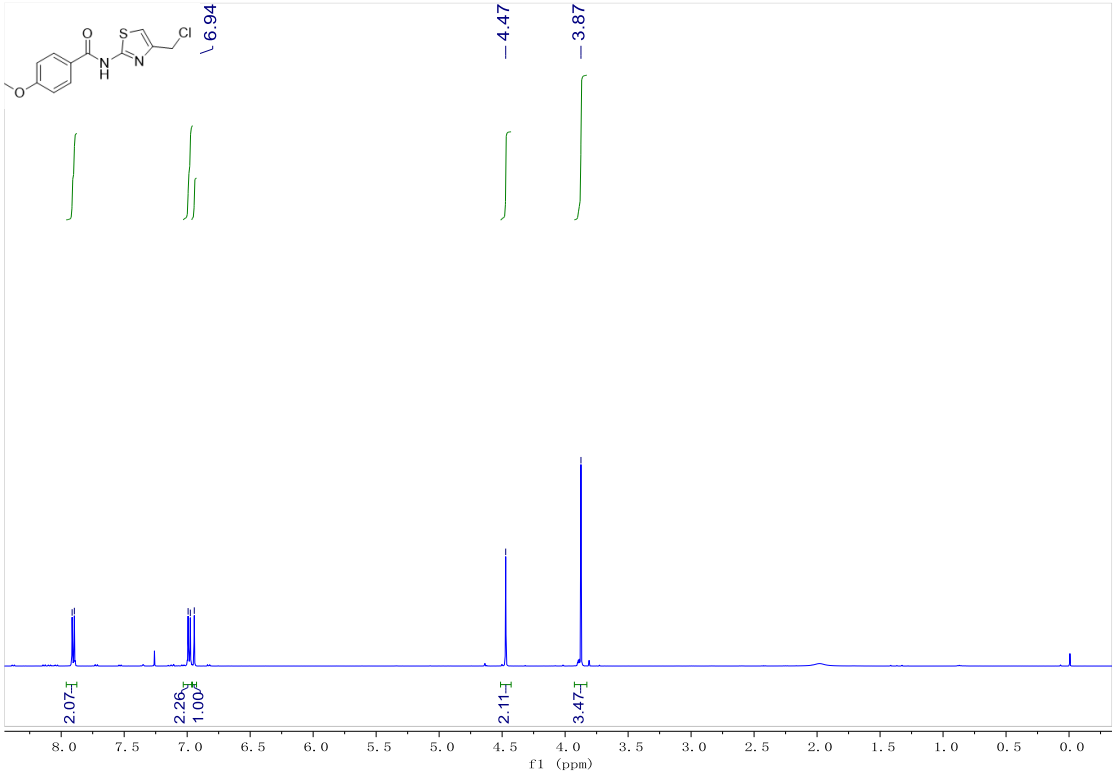


Fig. S4 ^{1}H NMR spectrum of **2d**

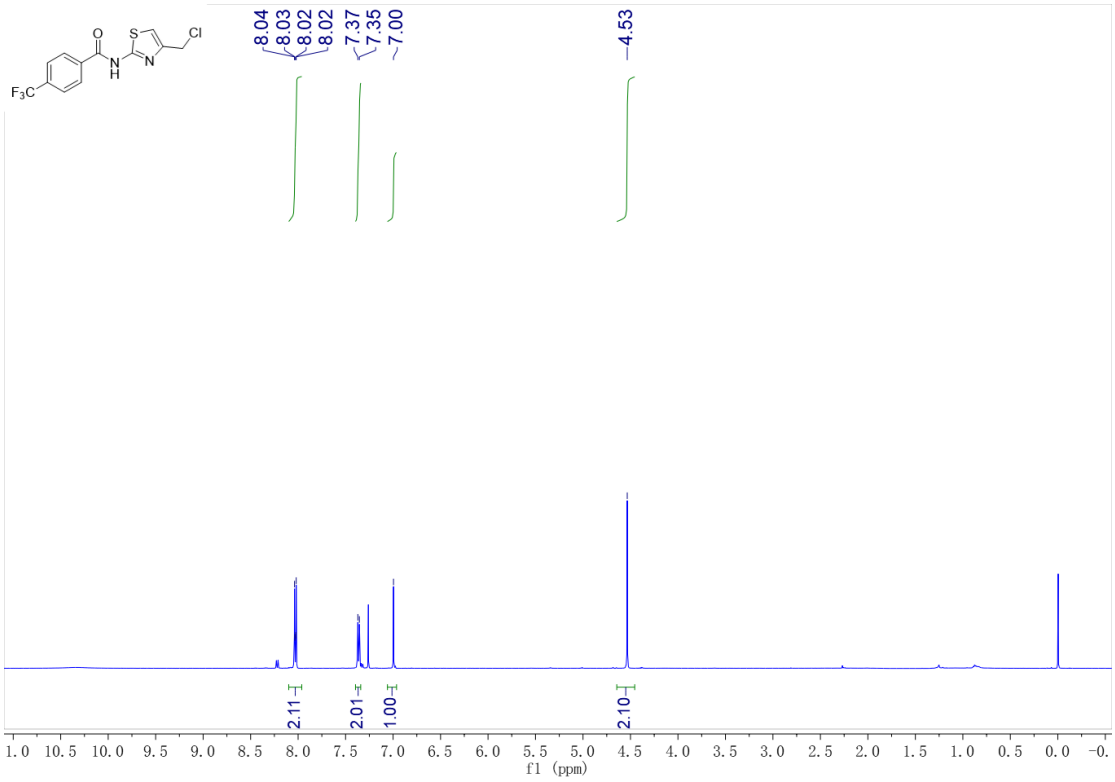


Fig. S5 ^{1}H NMR spectrum of **2e**

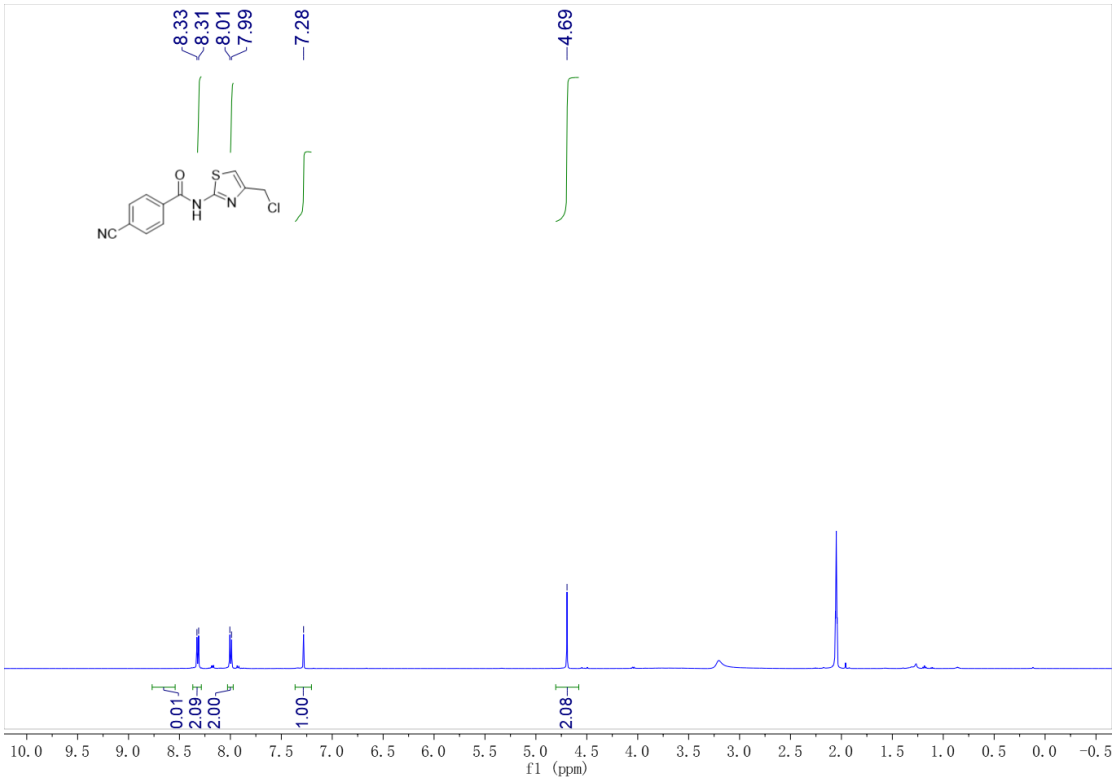


Fig. S6 ^{1}H NMR spectrum of **2f**

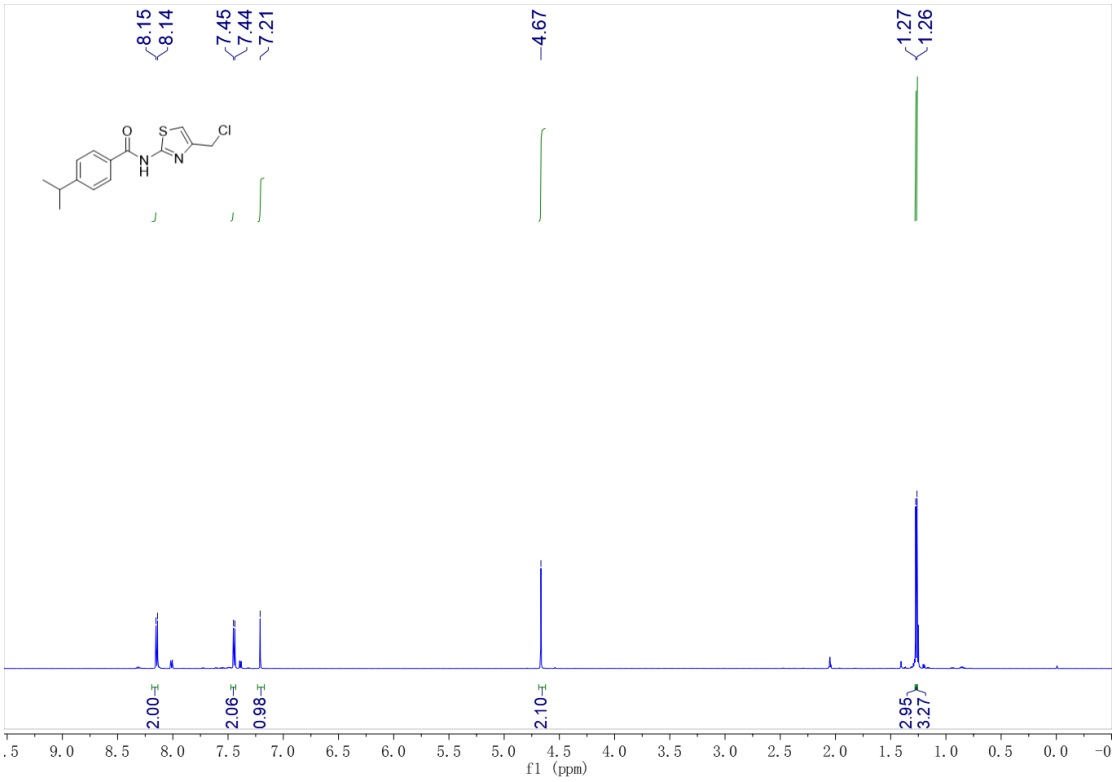


Fig. S7 ^{1}H NMR spectrum of **2g**

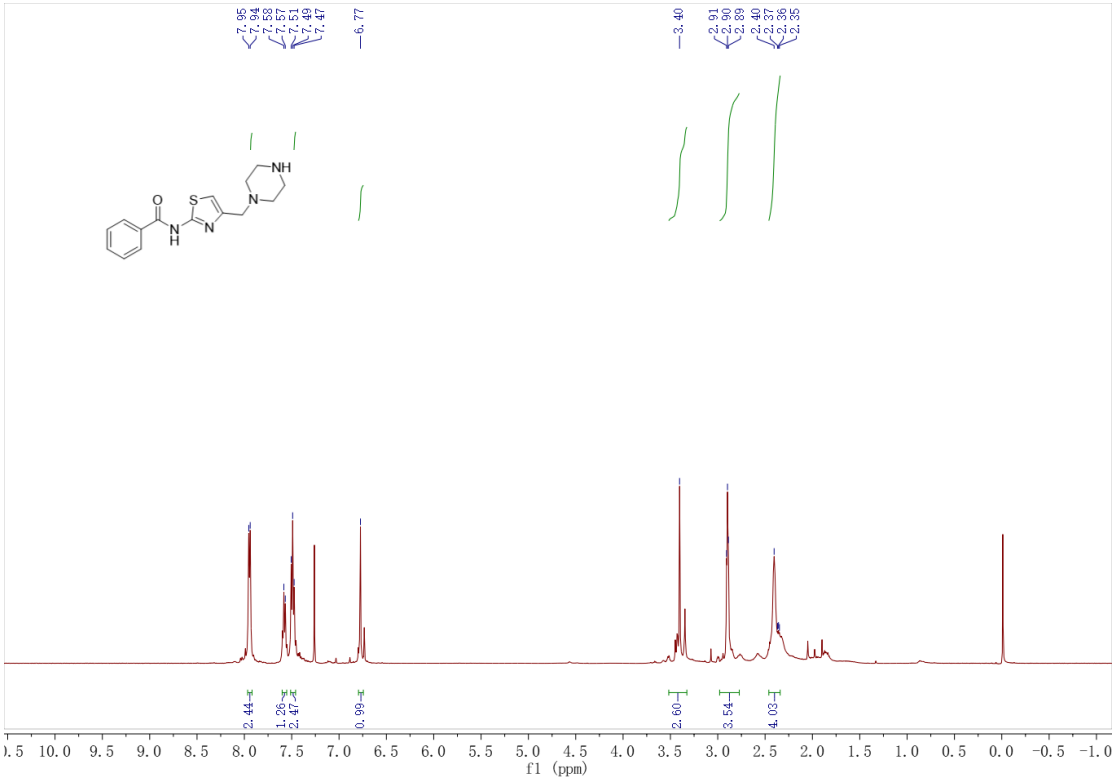


Fig. S8 ^{1}H NMR spectrum of **3a**

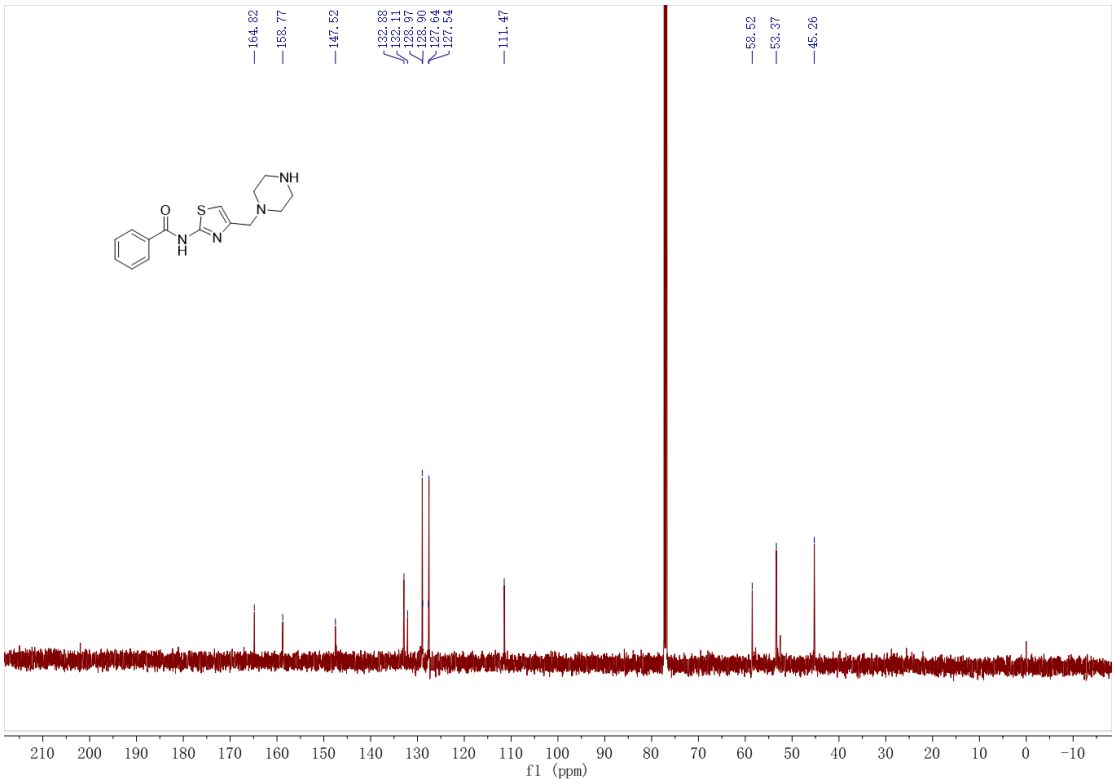
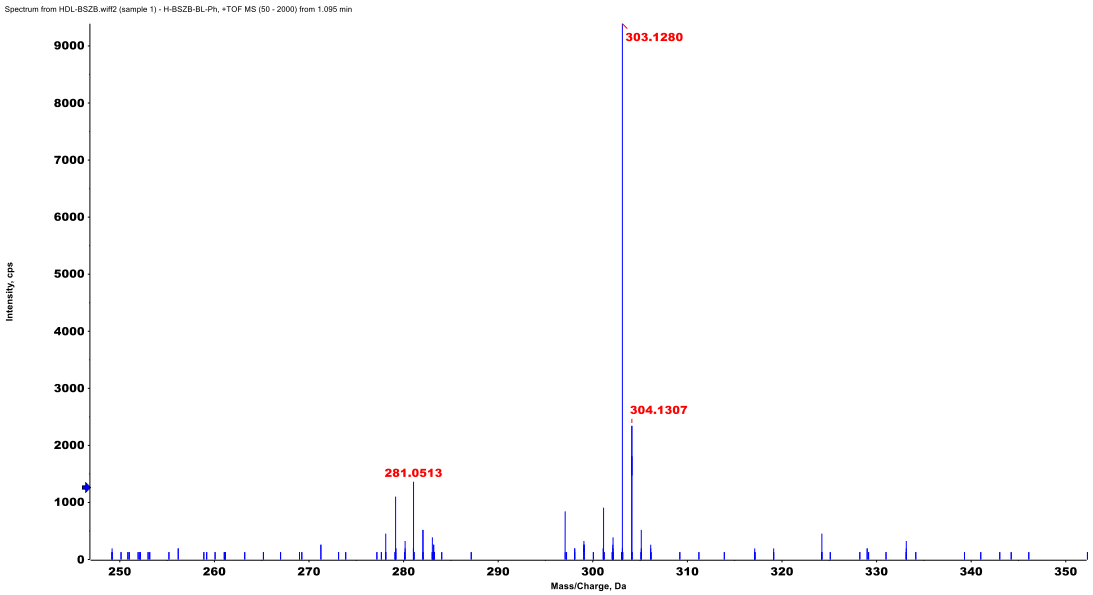


Fig. S9 ^{13}C NMR spectrum of **3a**



$[M+H]^+$ 303.1280

Hit	Formula	m/z	RDB	ppm	MS Rank
1	C15H18N4OS	303.1274	9.0	2.0	2

Fig. S10. HRESIMS of **3a**

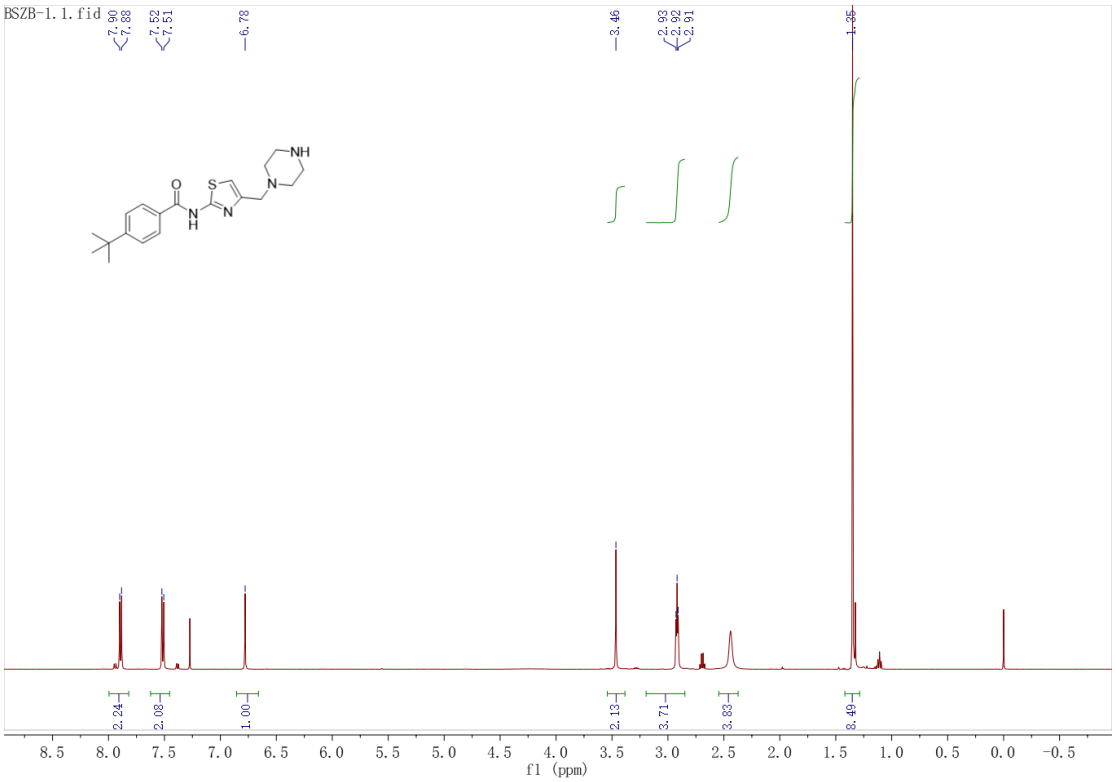


Fig. S11[1]H NMR spectrum of **3b**

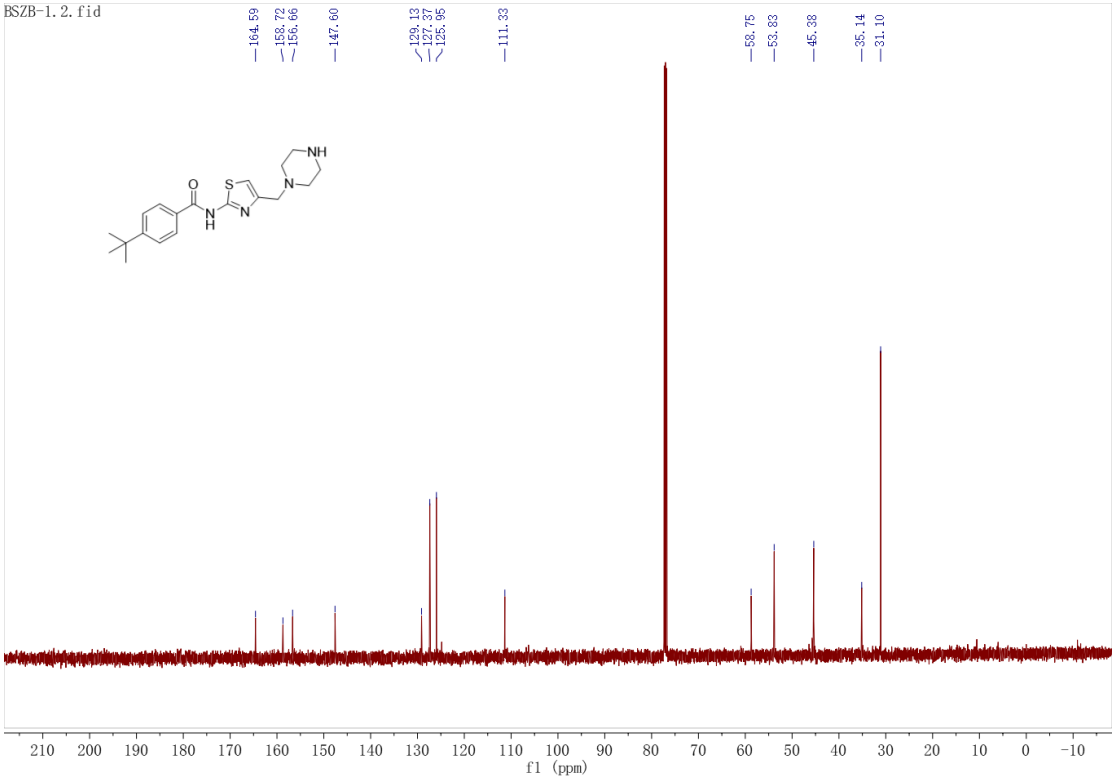
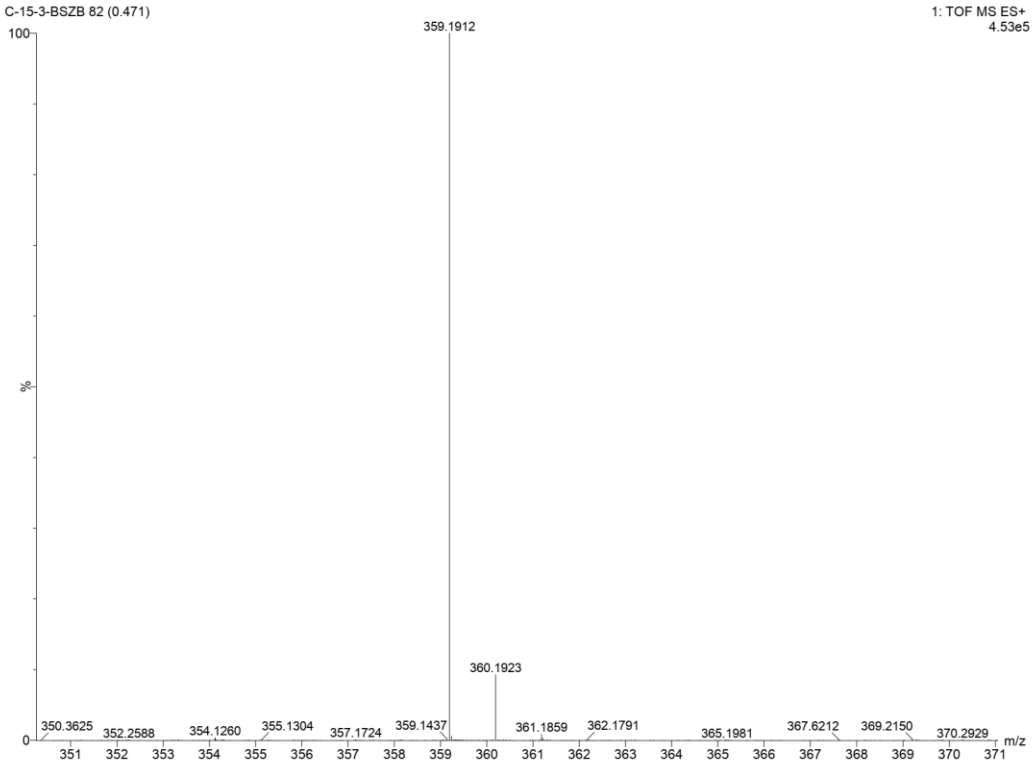


Fig. S12 [13]C NMR spectrum of **3b**



$[M+H]^+$ 359.1912

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
359.1912	359.1906	0.6	1.7	8.5	517.9	n/a	n/a	C19 H27 N4 O S

Fig. S13 HRESIMS of **3b**

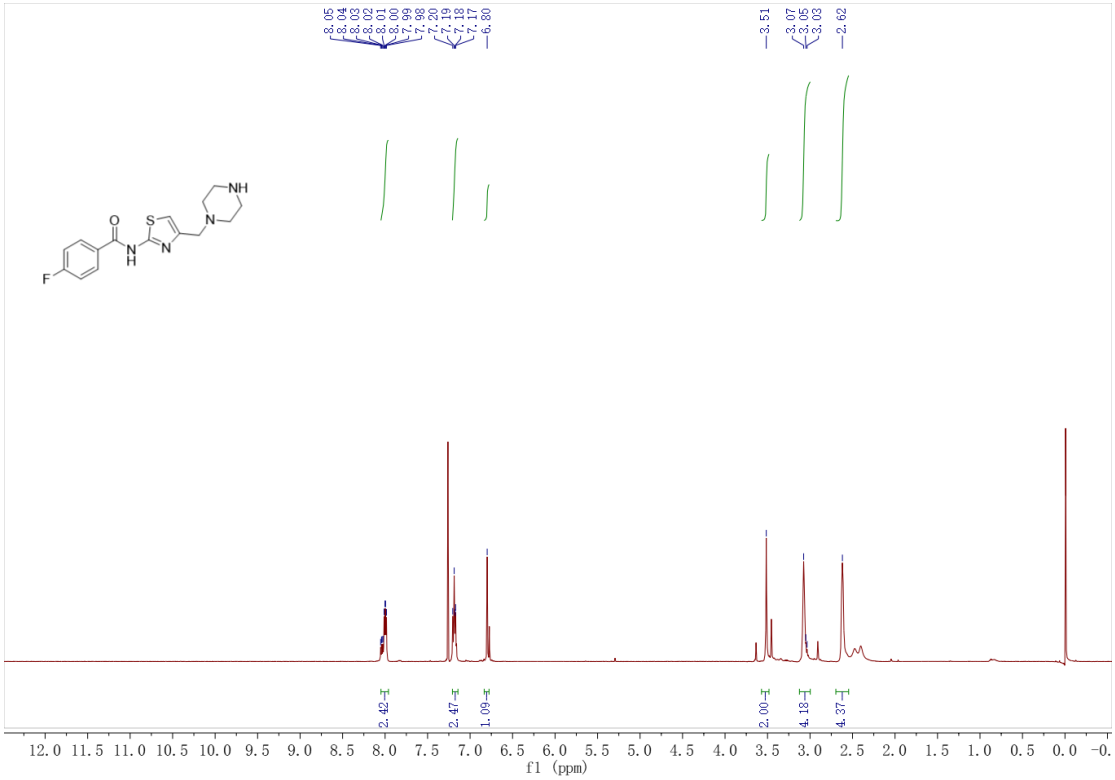


Fig. S14 ^{1}H NMR spectrum of **3c**

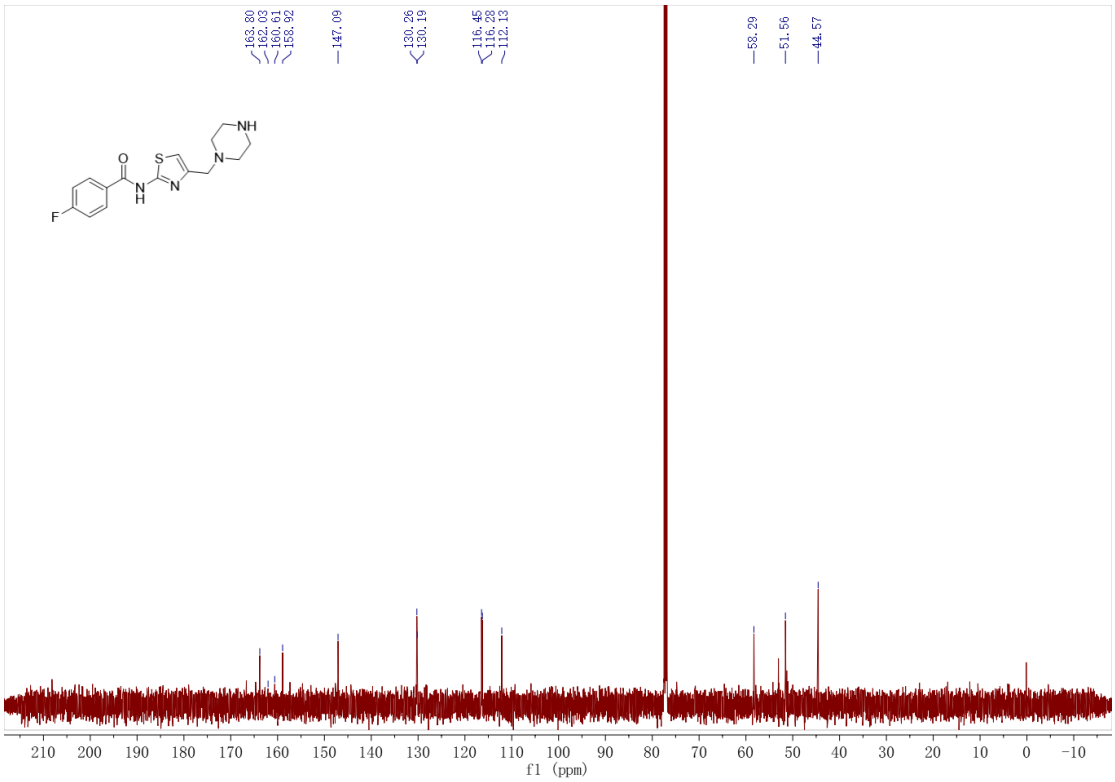
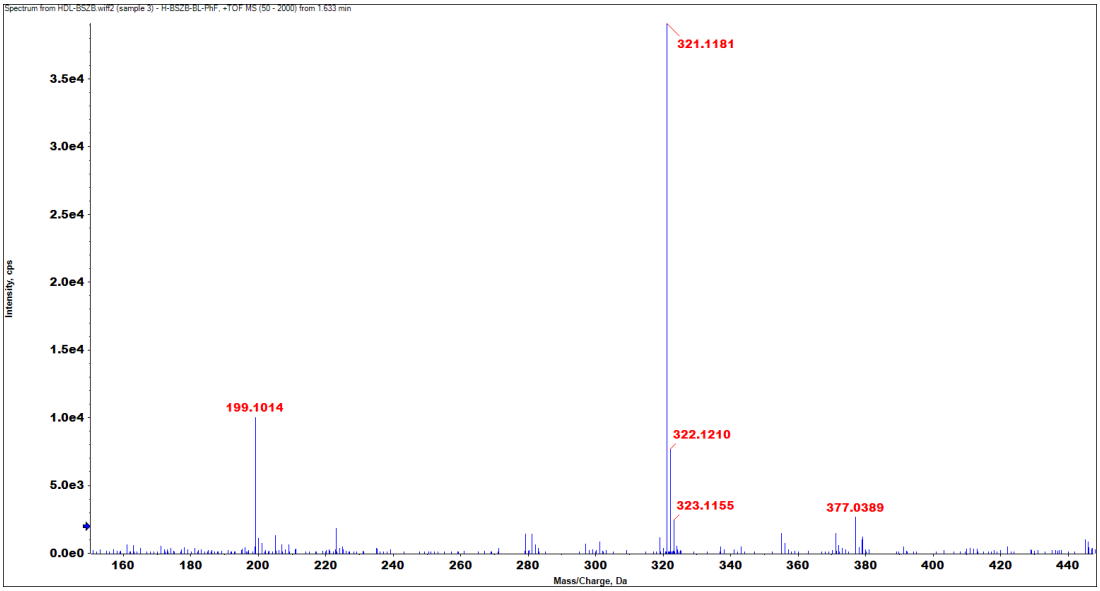


Fig. S15 ^{13}C NMR spectrum of **3c**



$[M+H]^+$ 321.1181

Hit	Formula	m/z	RDB	ppm	MS Rank
2	C15H17FN4OS	321.1180	9.0	0.4	2

Fig. S16 HRESIMS of **3c**

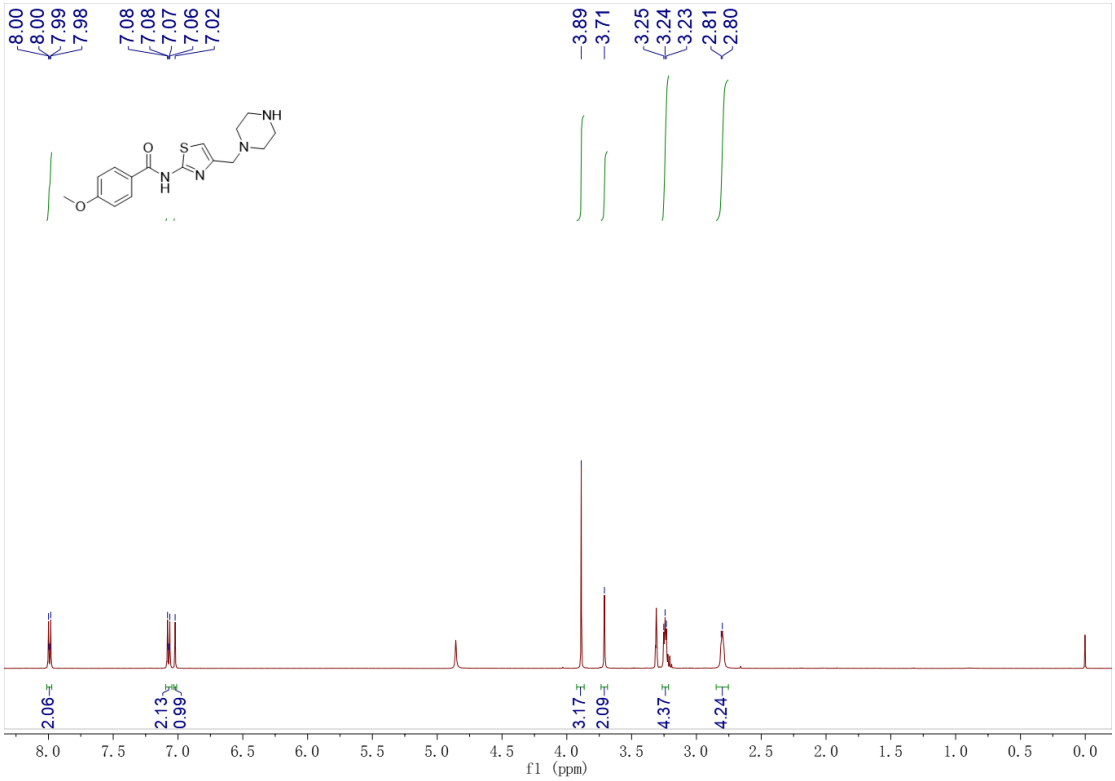


Fig. S17 ^{1}H NMR spectrum of **3d**

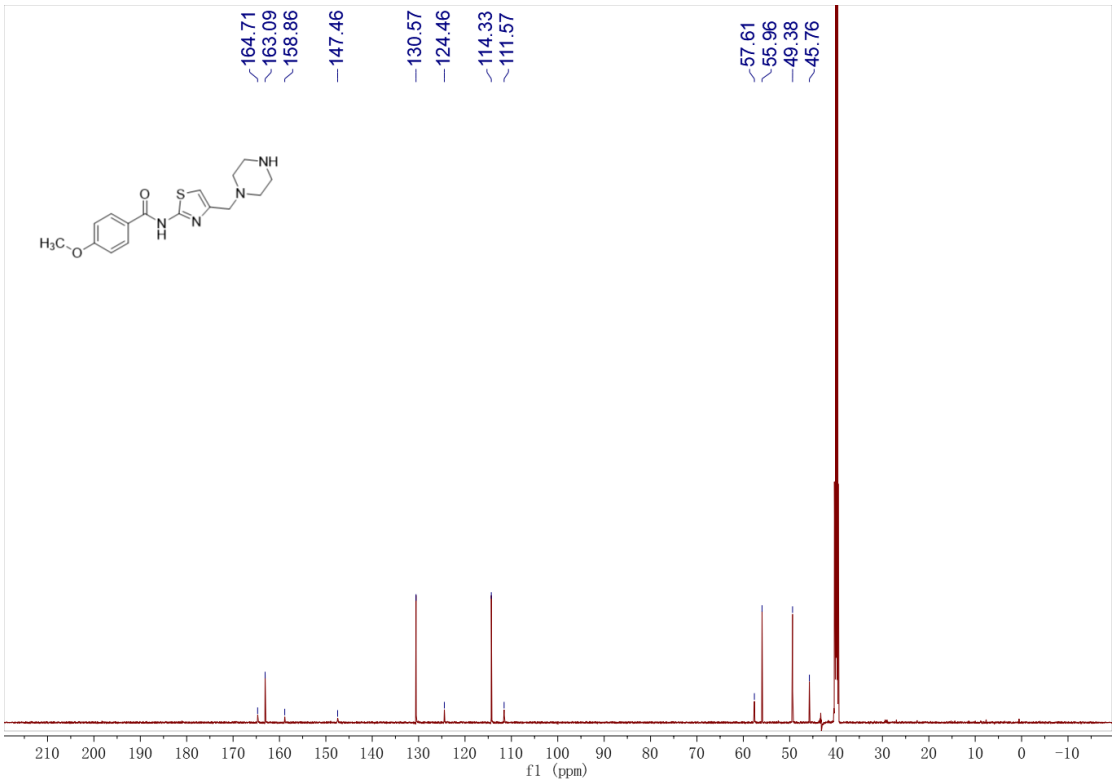
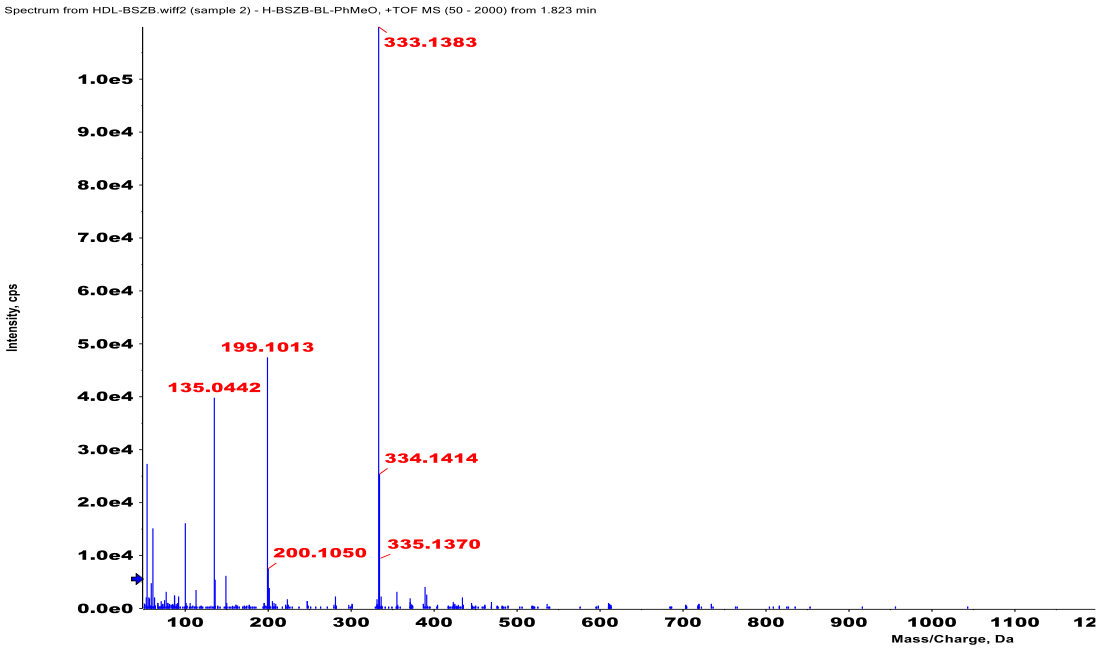


Fig. S18 ^{13}C NMR spectrum of **3d**



$[M+H]^+$ 333.1380

Hit	Formula	m/z	RDB	ppm	MS Rank
1	C16H20N4O2S	333.1380	9.0	1.0	1

Fig. S19 HRESIMS of **3d**

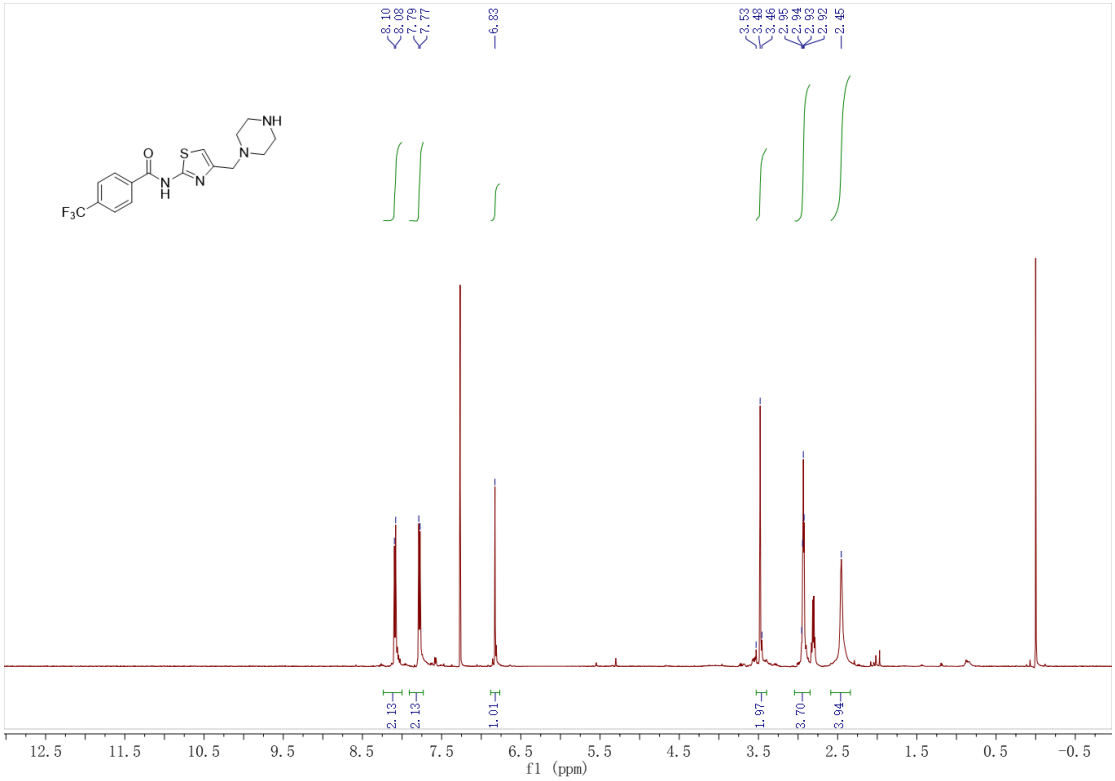


Fig. S20 ^{1}H NMR spectrum of **3e**

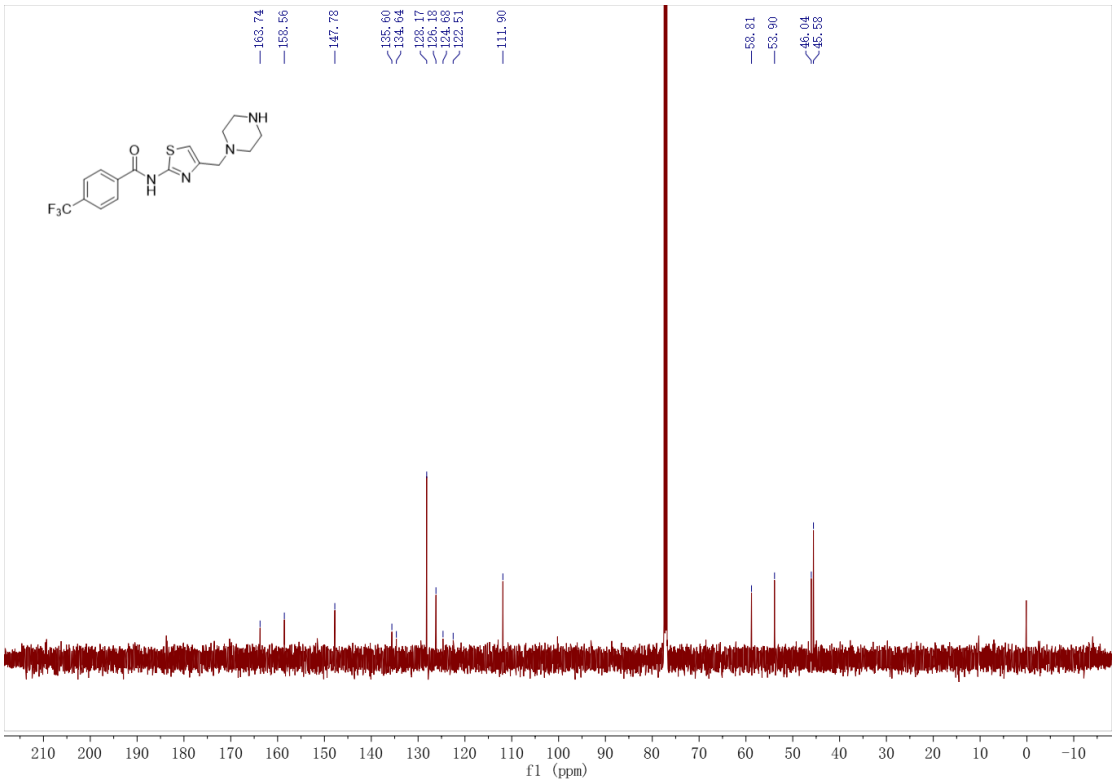
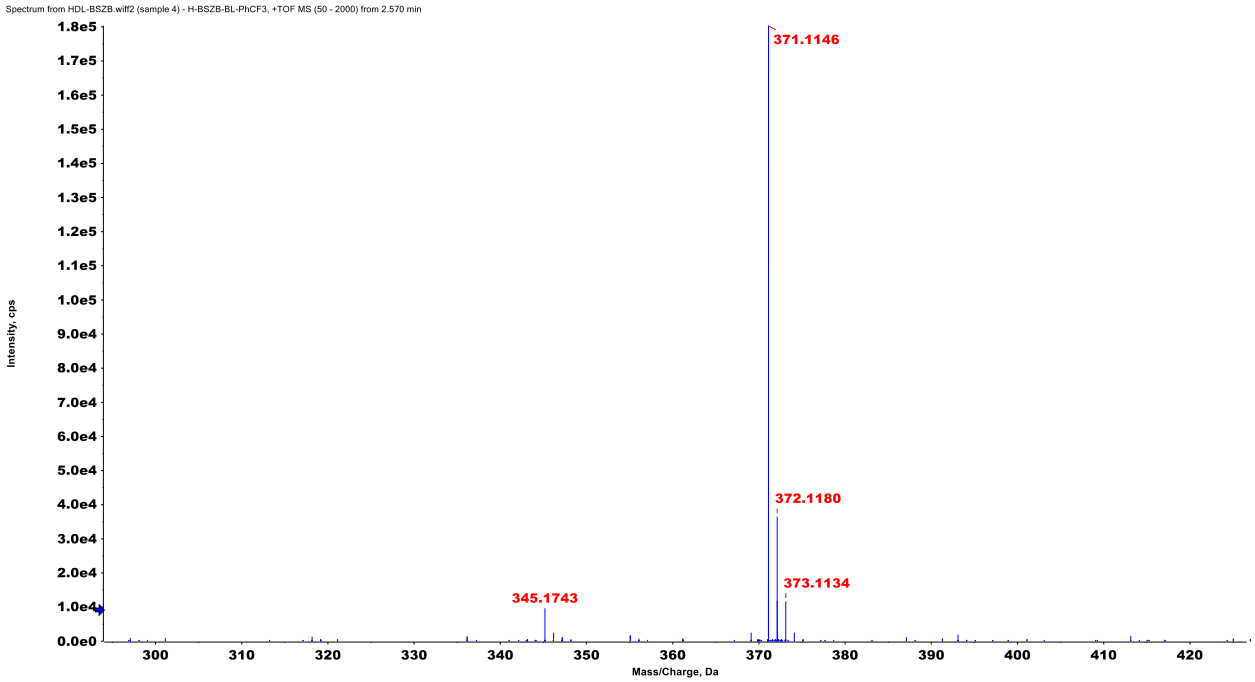


Fig. S21 ^{13}C NMR spectrum of **3e**



$[M+H]^+$ 371.1146

Hit	Formula	m/z	RDB	ppm	MS Rank
1	C16H17F3N4OS	371.1148	9.0	-0.5	4

Fig. S22 HRESIMS of **3e**

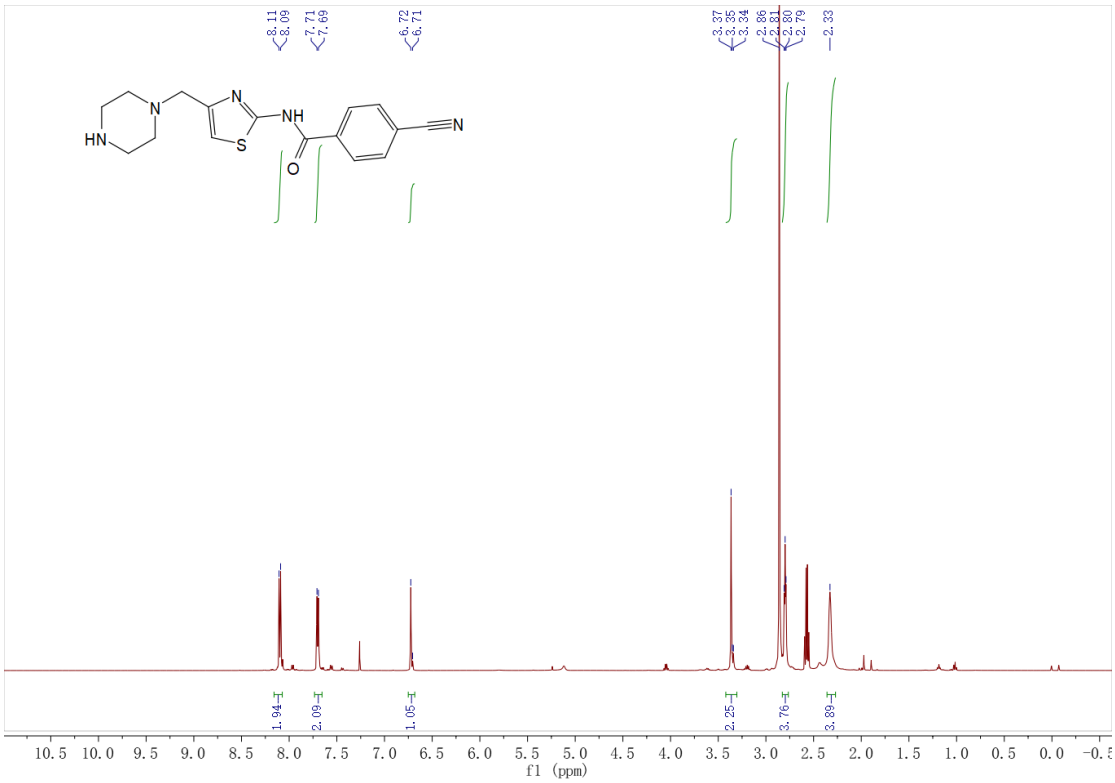


Fig. S23 ^{1}H NMR spectrum of **3f**

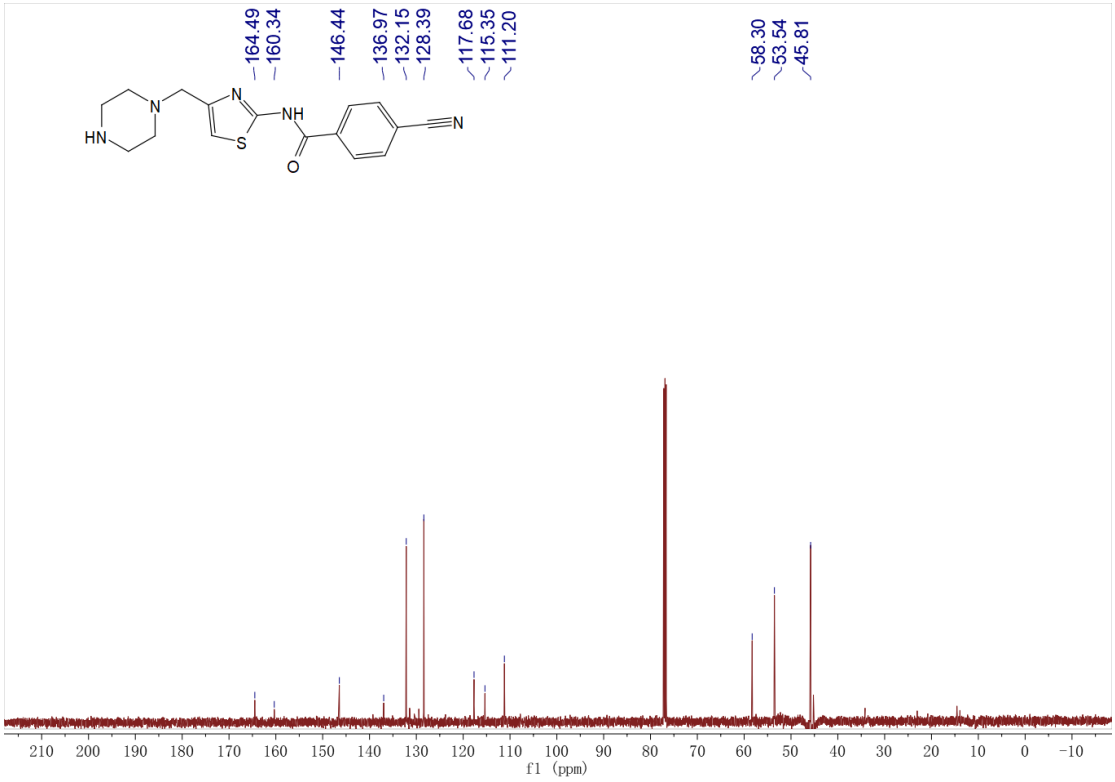
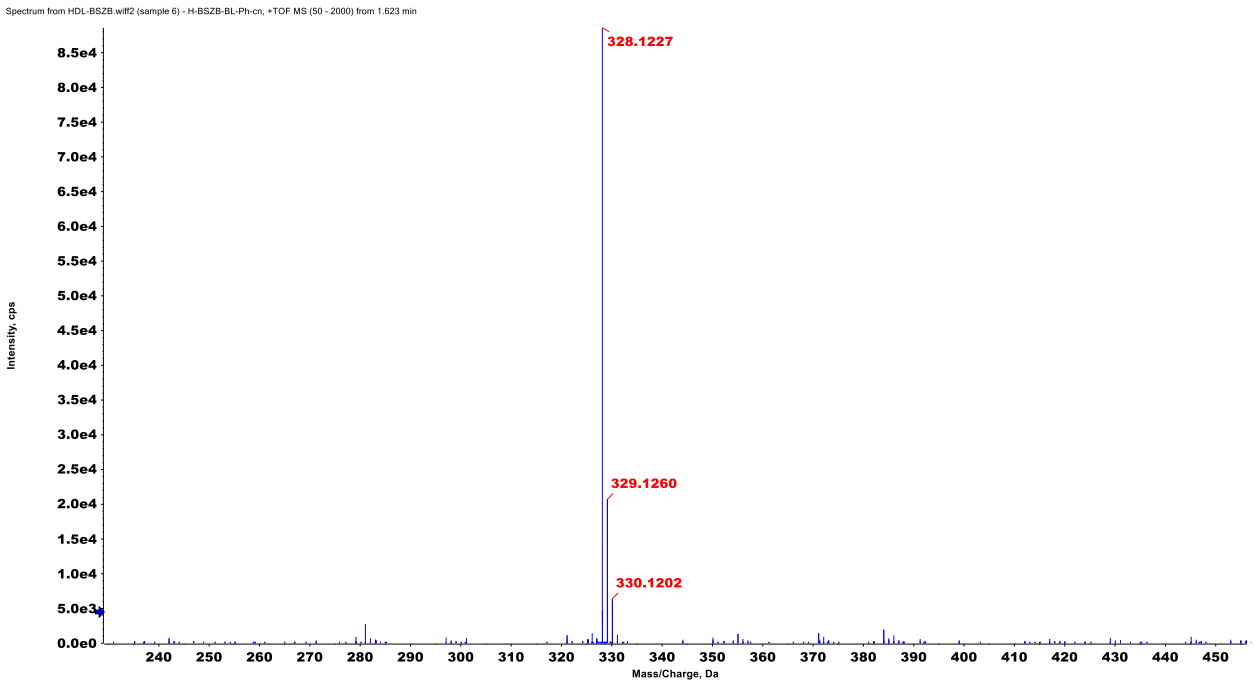


Fig. S24 ^{13}C NMR spectrum of **3f**



$[M+H]^+$ 328.1227

Hit	Formula	m/z	RDB	ppm	MS Rank
1	C16H17N5OS	328.1227	11.0	0.1	1

Fig. S25 HRESIMS of **3f**

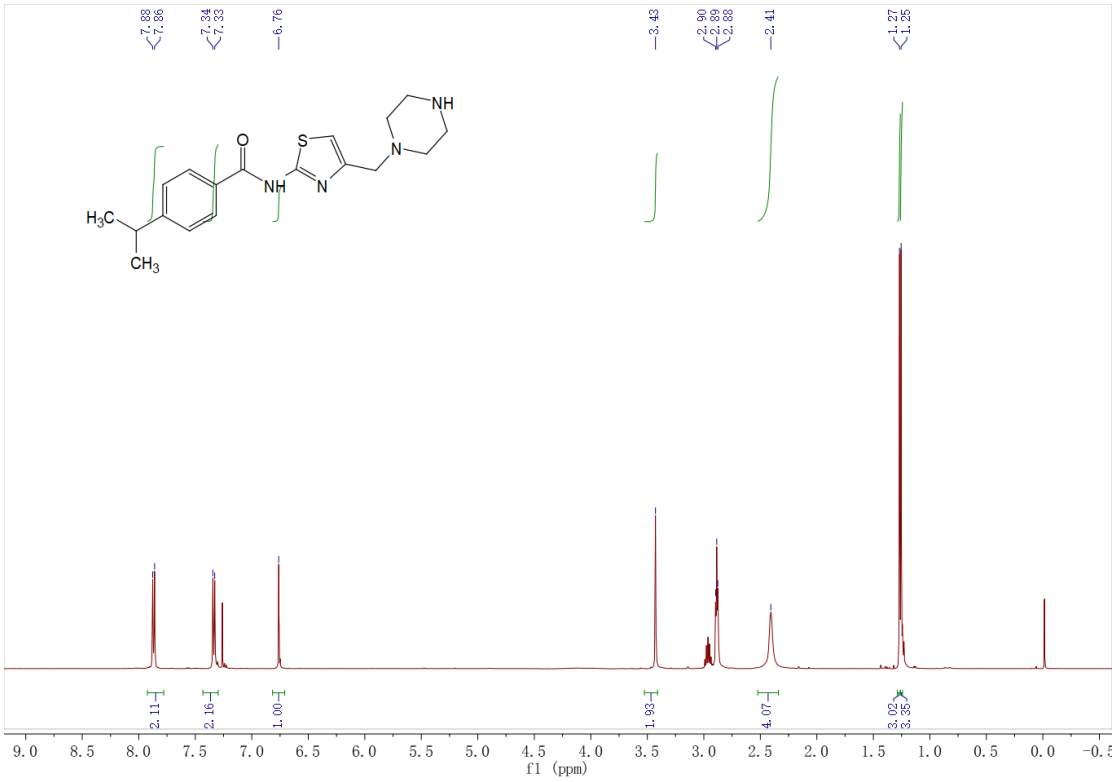


Fig. S26 ^{1}H NMR spectrum of **3g**

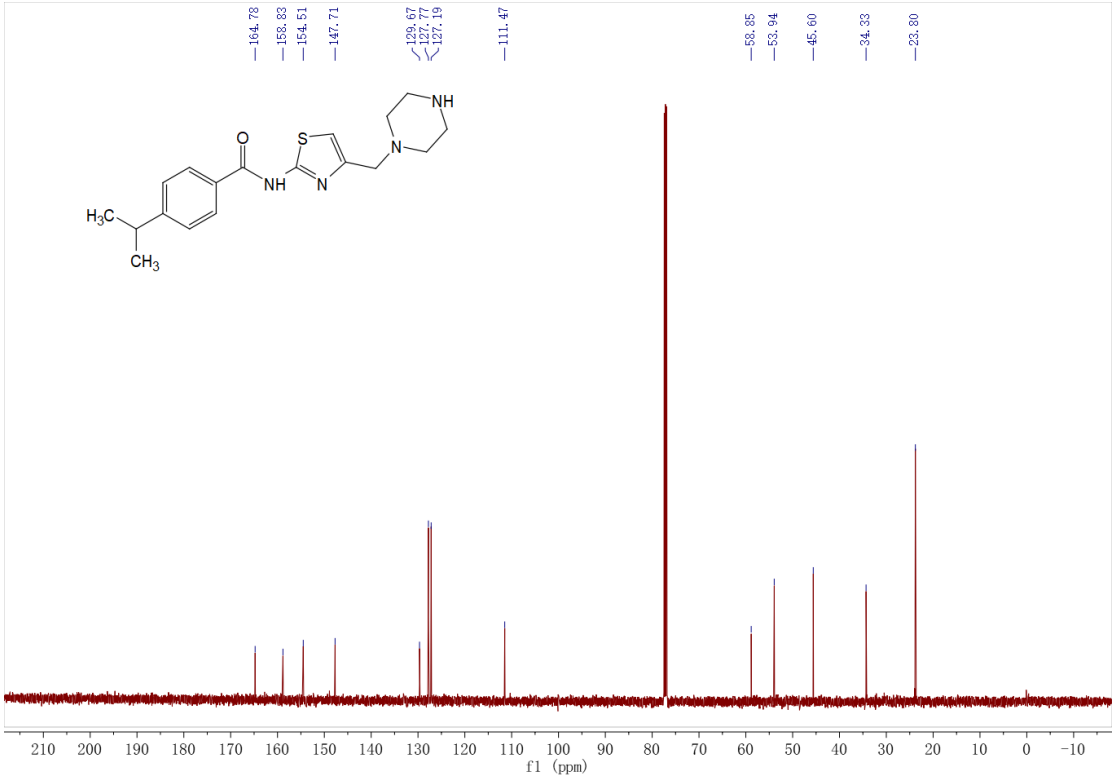
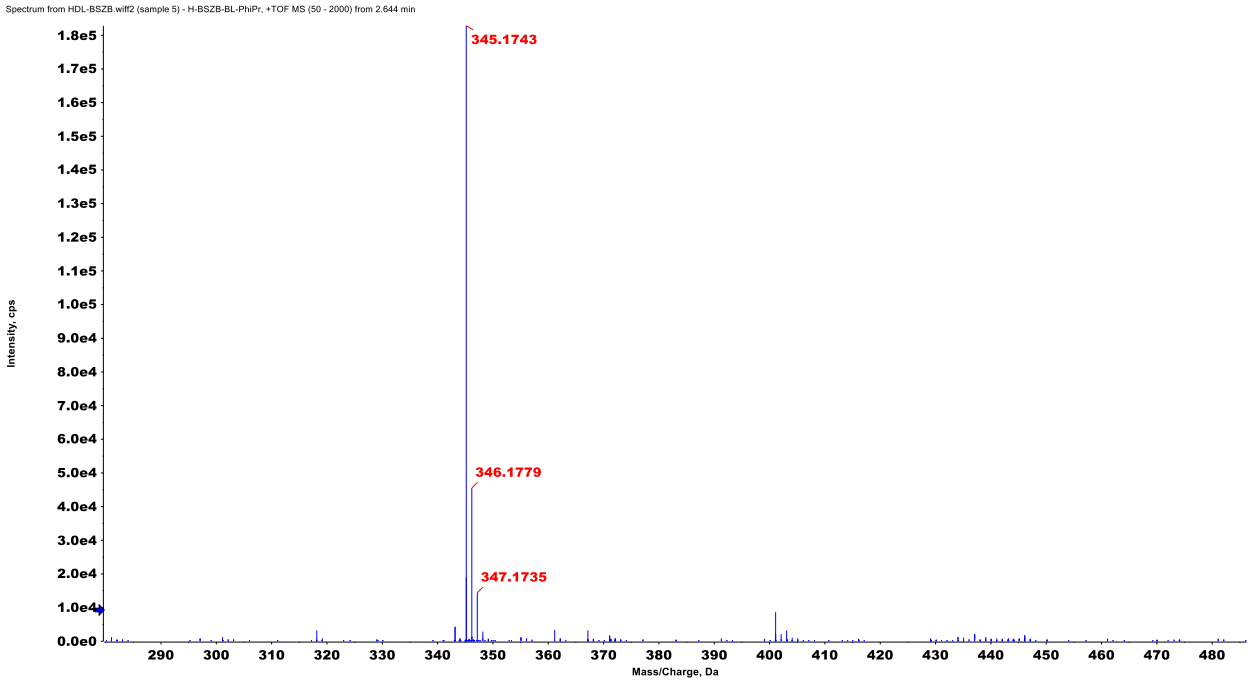


Fig. S27 ^{13}C NMR spectrum of **3g**



$[M+H]^+$ 345.1743

Hit	Formula	m/z	RDB	ppm	MS Rank
1	C18H24N4OS	345.1744	9.0	-0.2	1

Fig. S28 HRESIMS of **3g**

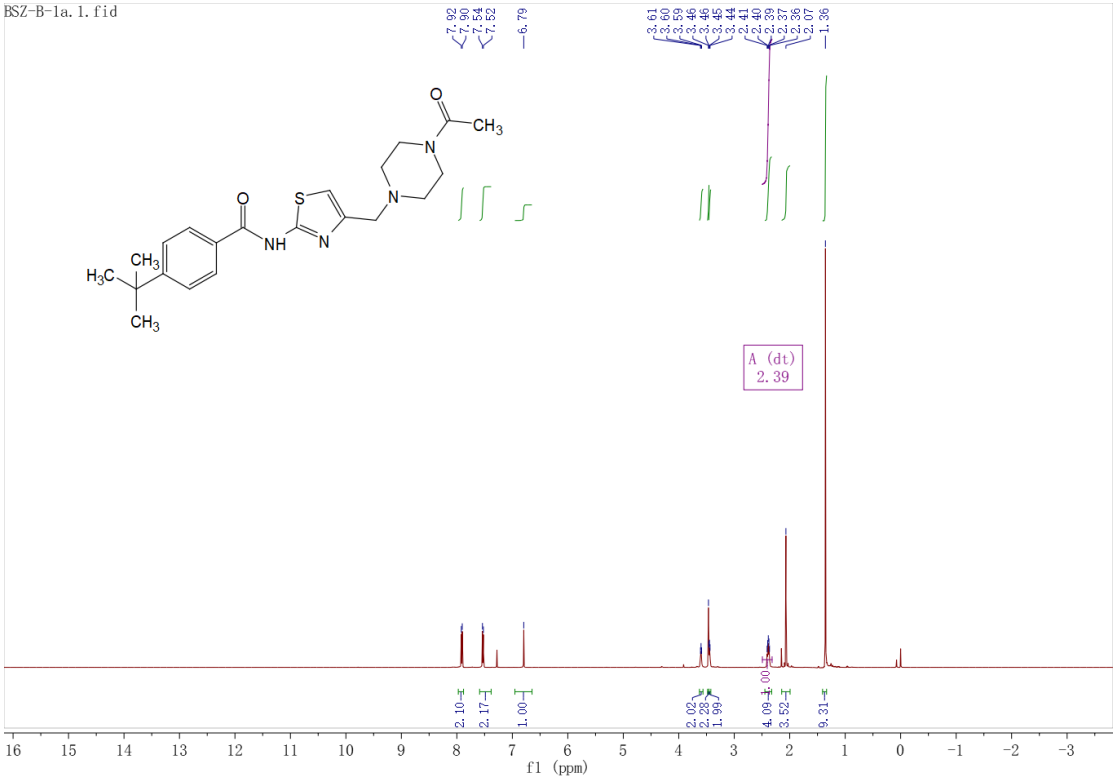


Fig. S29 ^{1}H NMR spectrum of **4a**

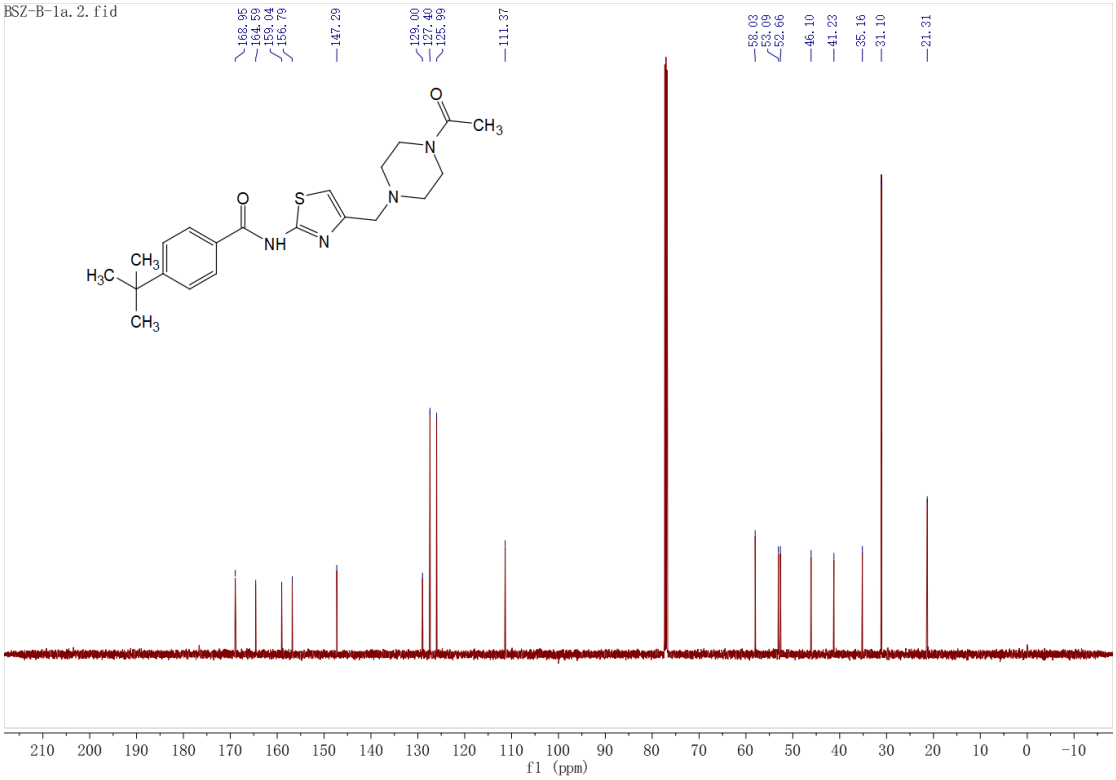
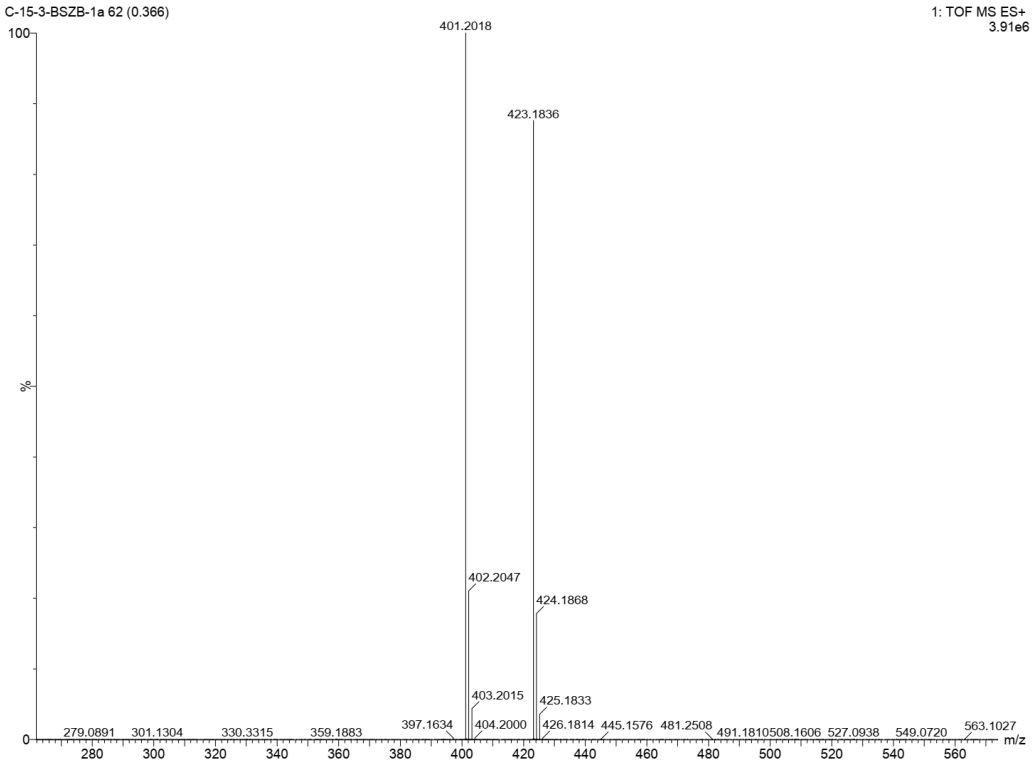


Fig. S30 ^{13}C NMR spectrum of **4a**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
401.2018	401.2011	0.7	1.7	9.5	838.7	n/a	n/a	C21 H29 N4 O2 S

Fig. S31 HRESIMS of **4a**

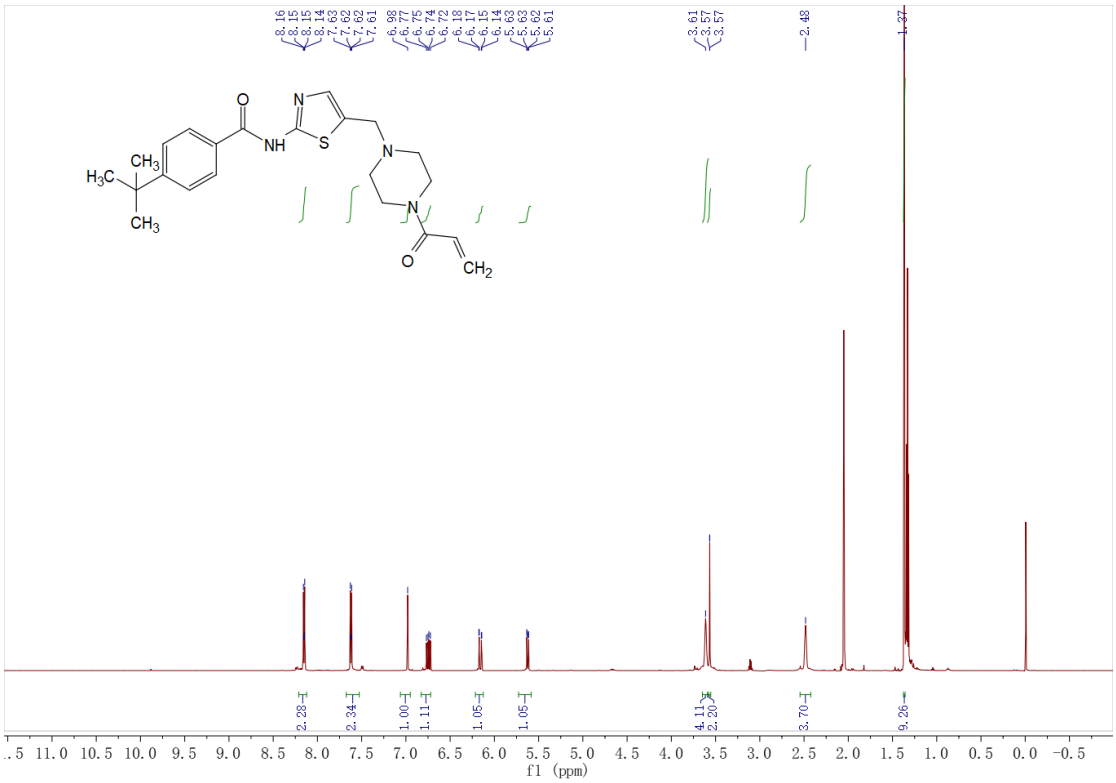


Fig. S32 ^{1}H NMR spectrum of **4b**

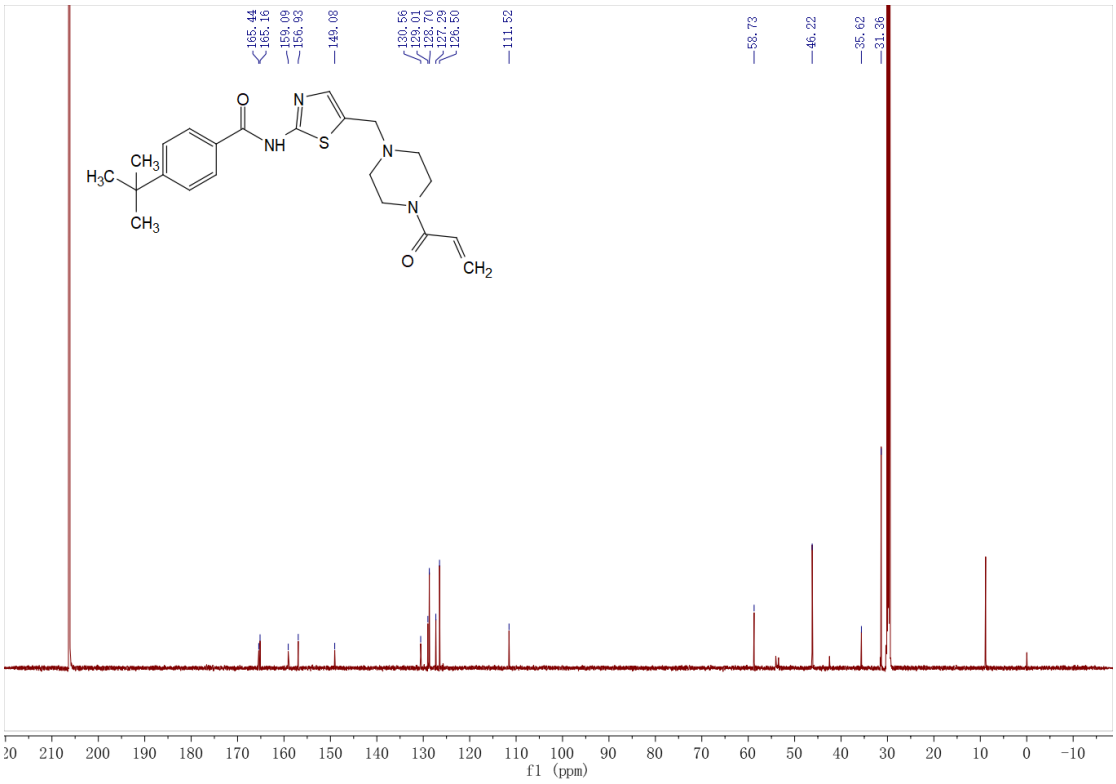
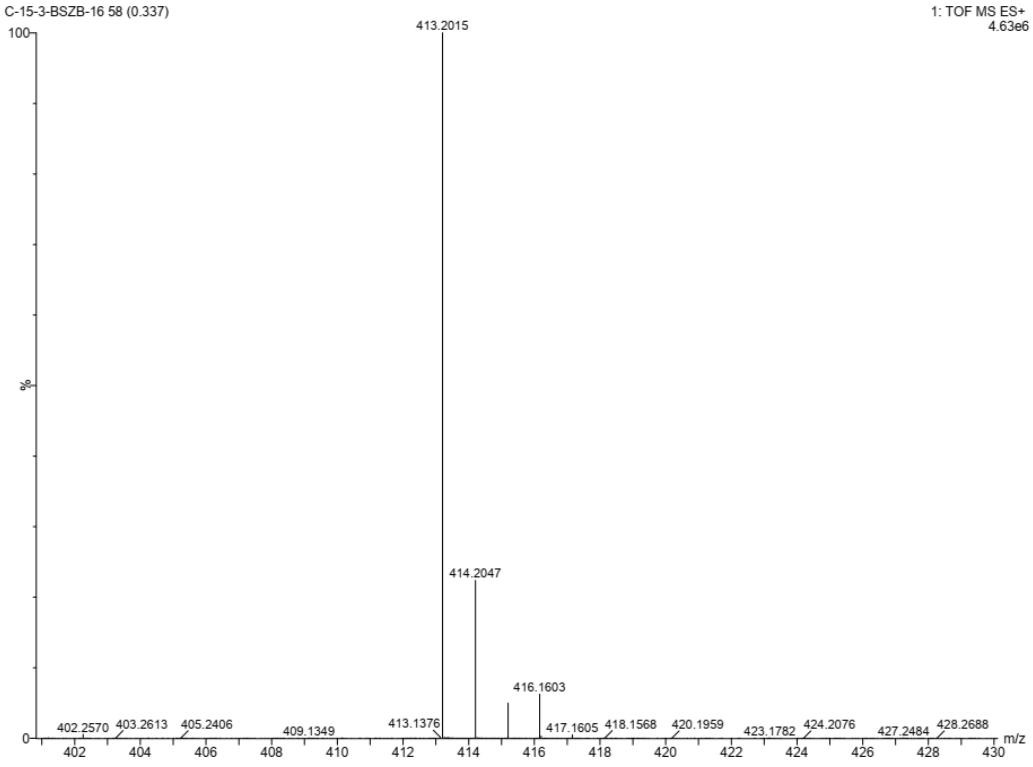


Fig. S33 ^{13}C NMR spectrum of **4b**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
413.2015	413.2011	0.4	1.0	10.5	893.1	n/a	n/a	C22 H29 N4 02 S

Fig. S34 HRESIMS of **4b**

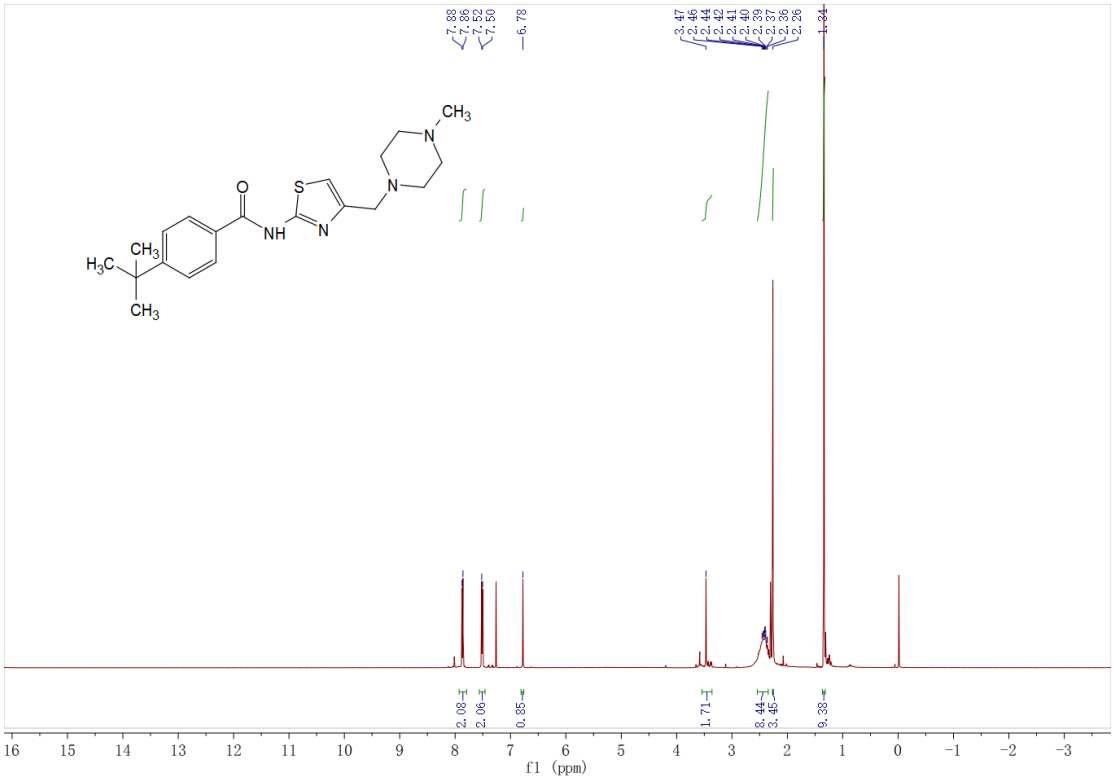


Fig. S35 ^{1}H NMR spectrum of **4c**

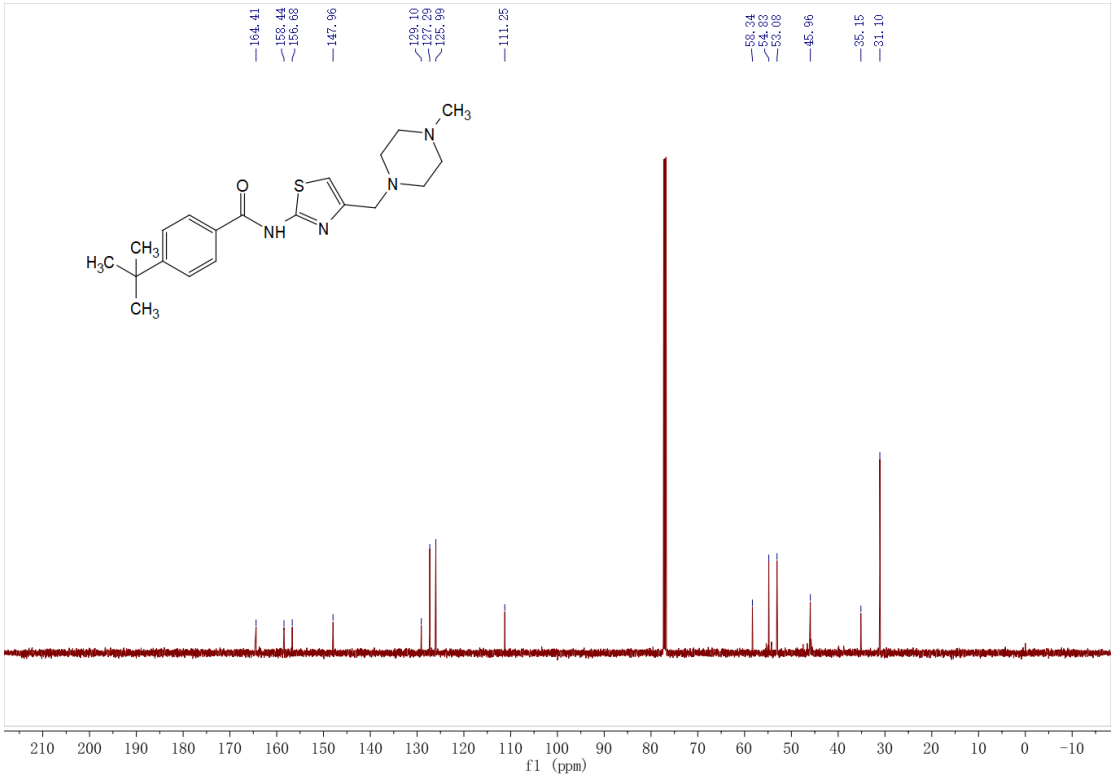
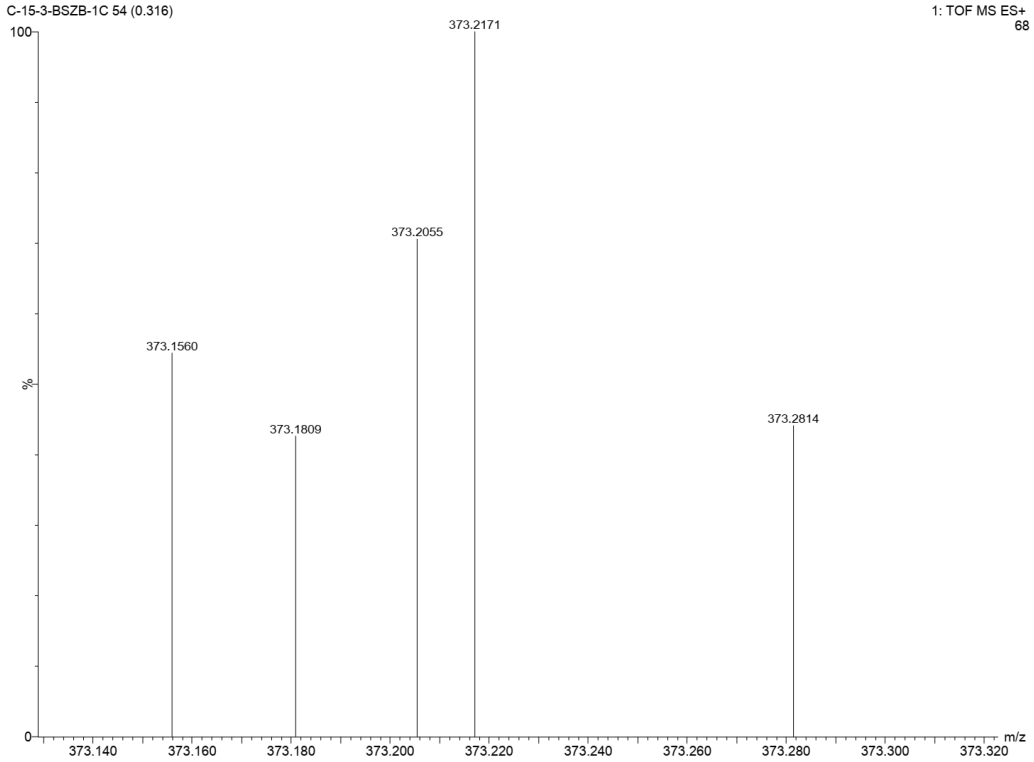


Fig. S36 ^{13}C NMR spectrum of **4c**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
373.2055	373.2062	-0.7	-1.9	8.5	31.2	n/a	n/a	C20 H29 N4 O S

Fig. S37 HRESIMS of **4c**

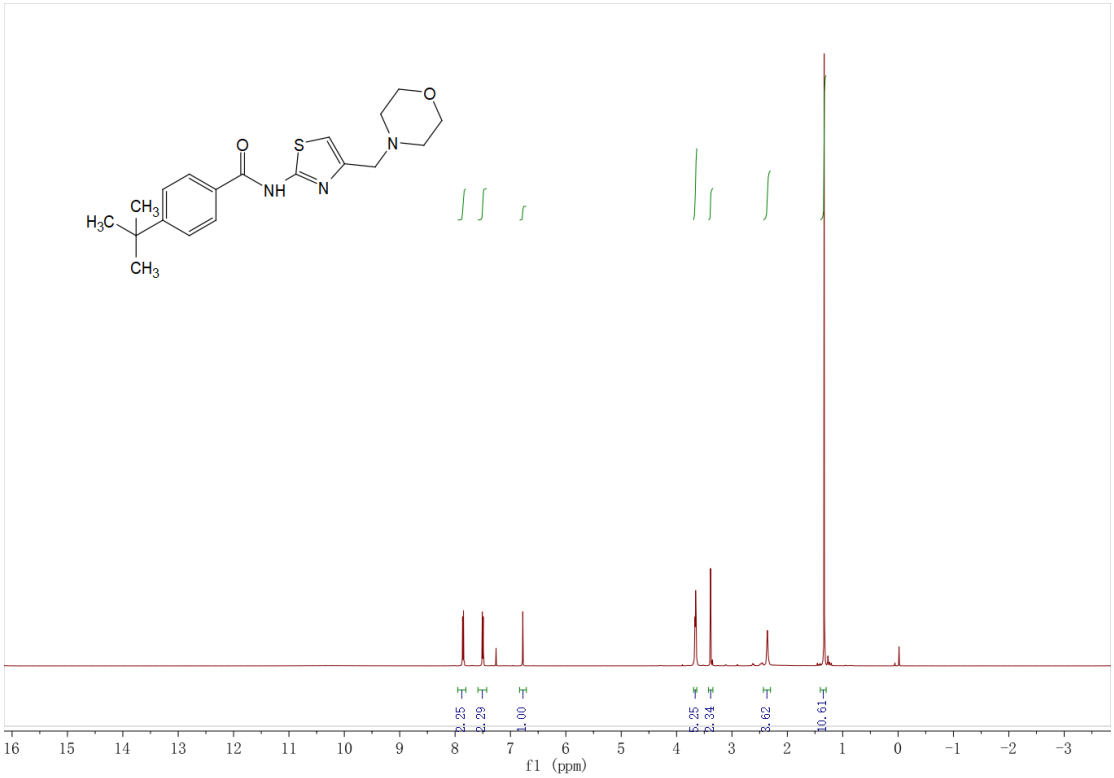


Fig. S38 ^{1}H NMR spectrum of **4d**

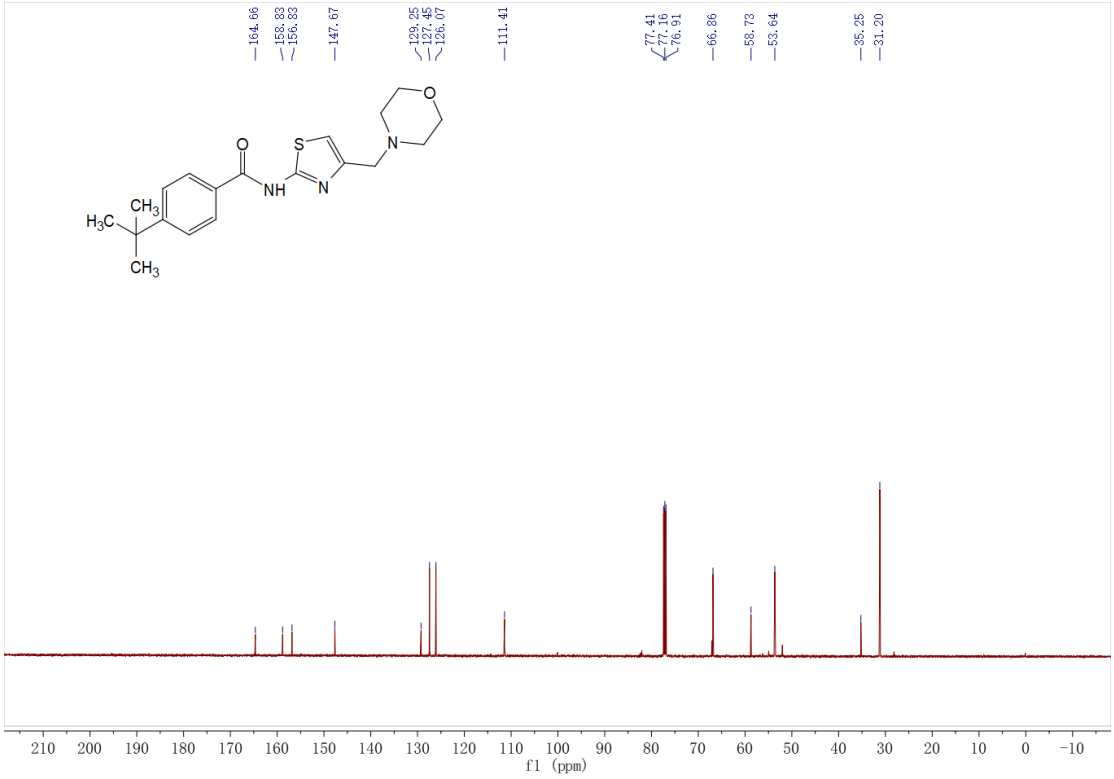
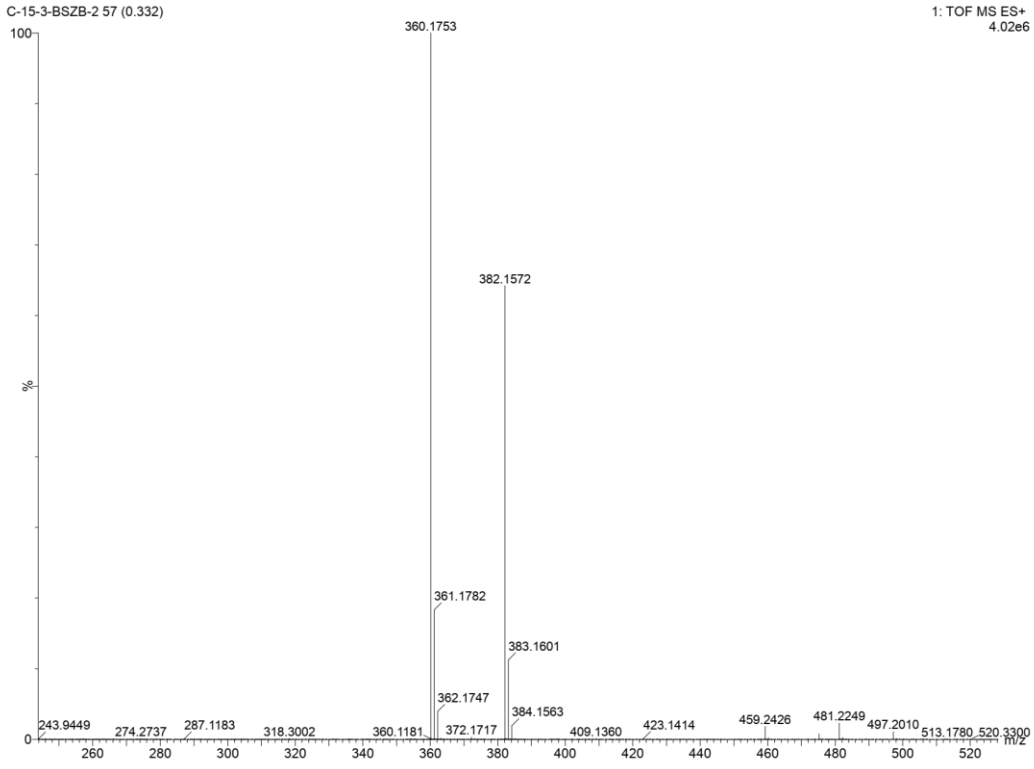


Fig. S39 ^{13}C NMR spectrum of **4d**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
360.1753	360.1746	0.7	1.9	8.5	889.4	n/a	n/a	C19 H26 N3 O2 S

Fig. S40 HRESIMS of **4d**

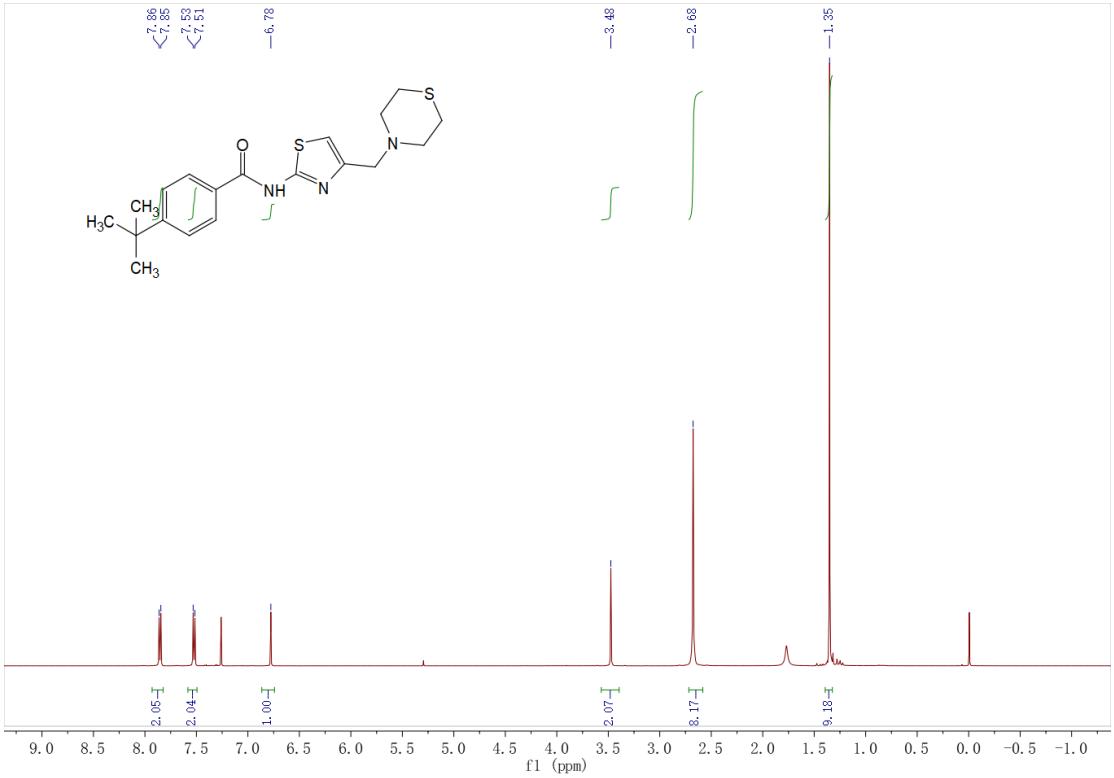


Fig. S41 ^{1}H NMR spectrum of **4e**

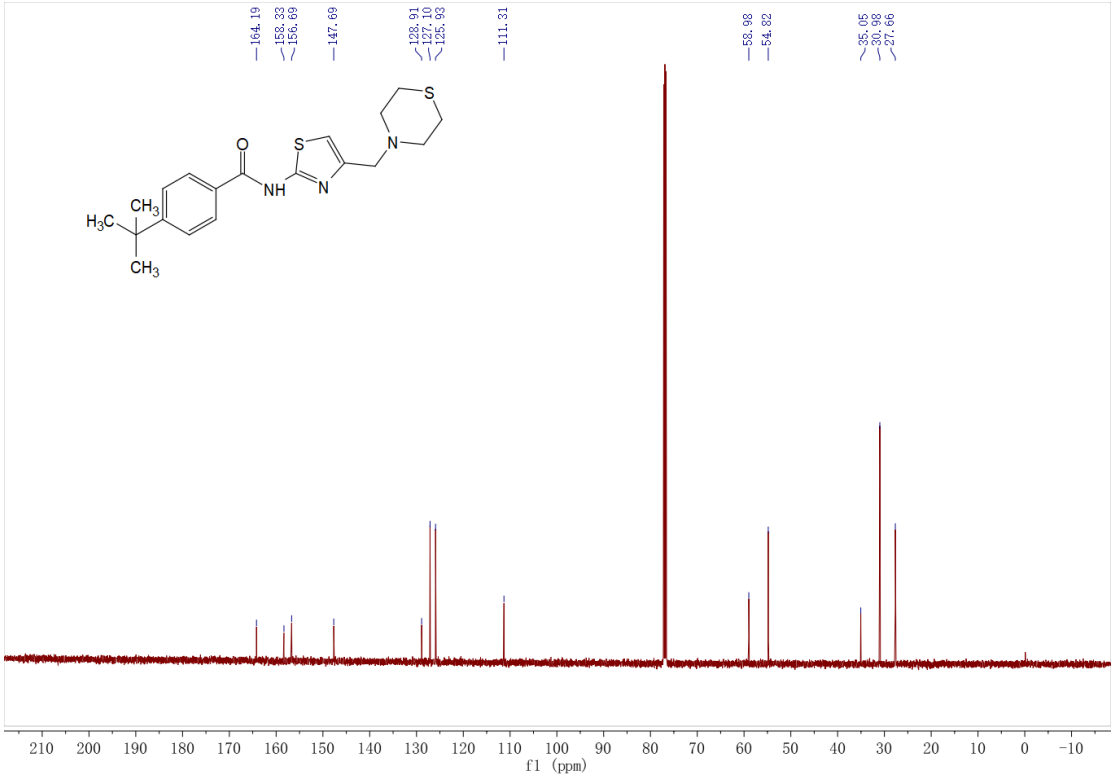
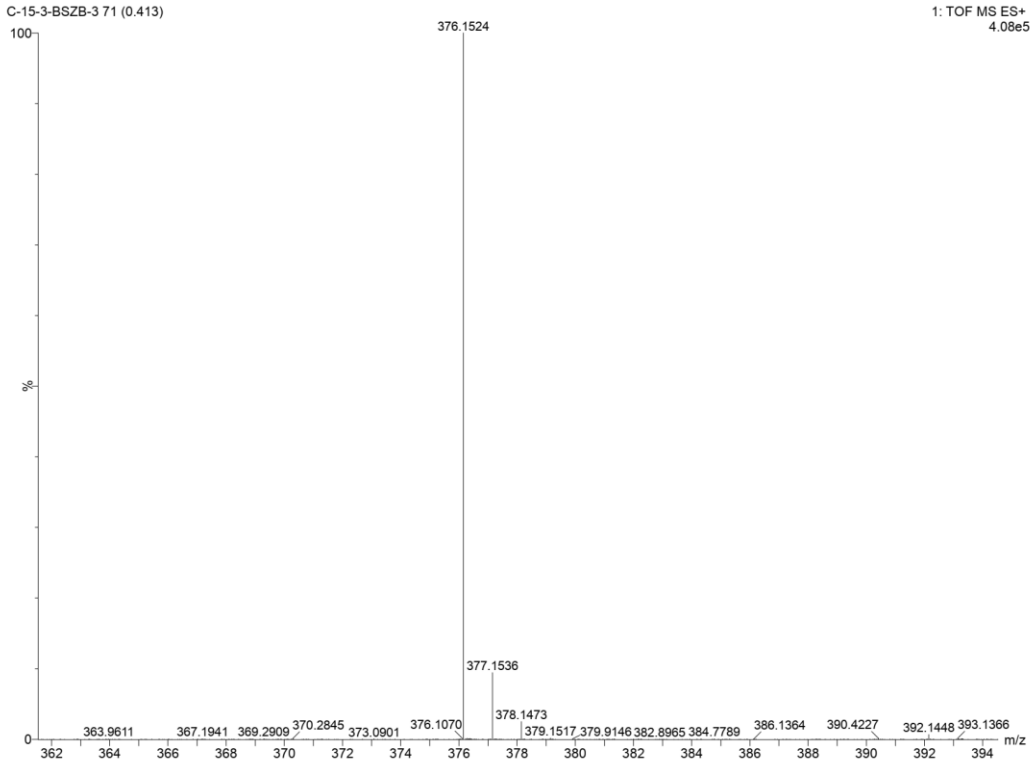


Fig. S42 ^{13}C NMR spectrum of **4e**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
376.1524	376.1517	0.7	1.9	8.5	458.6	n/a	n/a	C19 H26 N3 O S2

Fig. S43 HRESIMS of **4e**

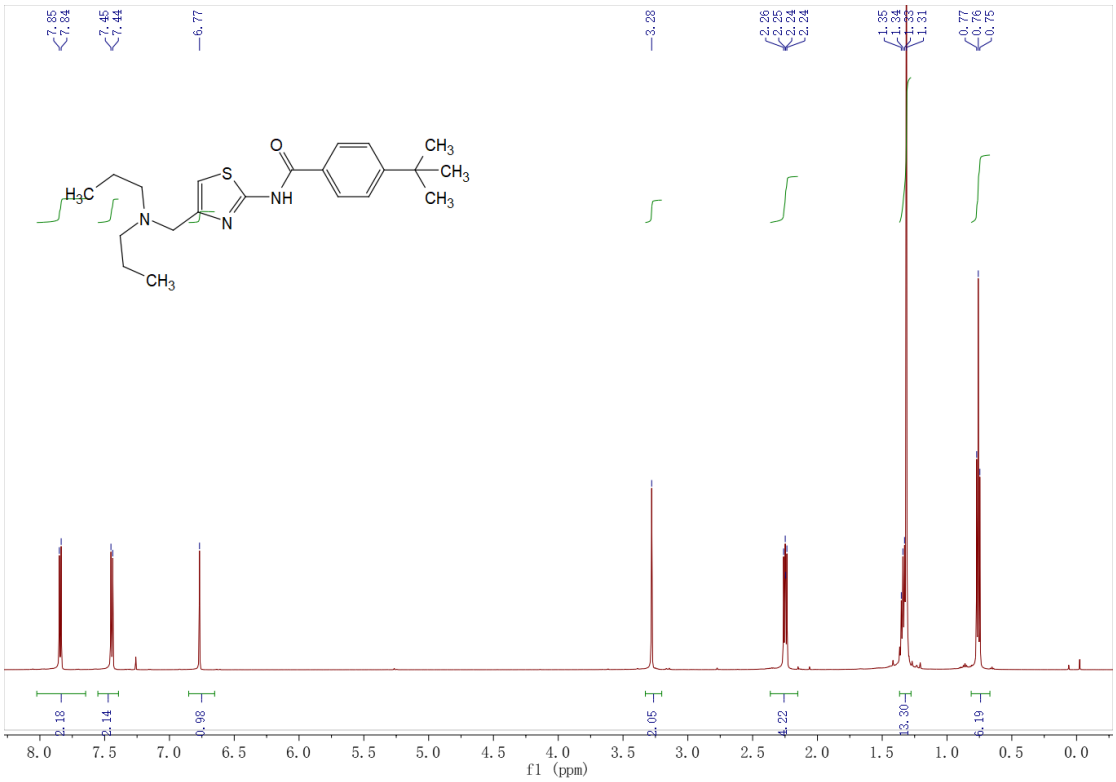


Fig. S44 ^{1}H NMR spectrum of **4f**

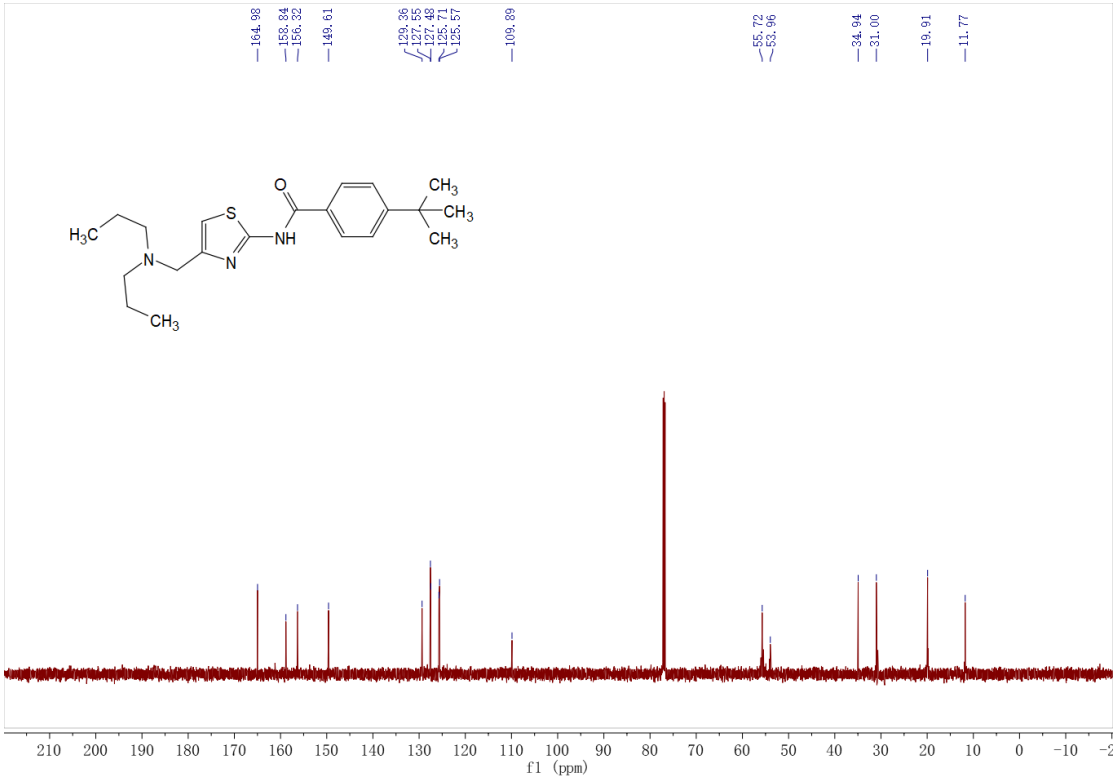
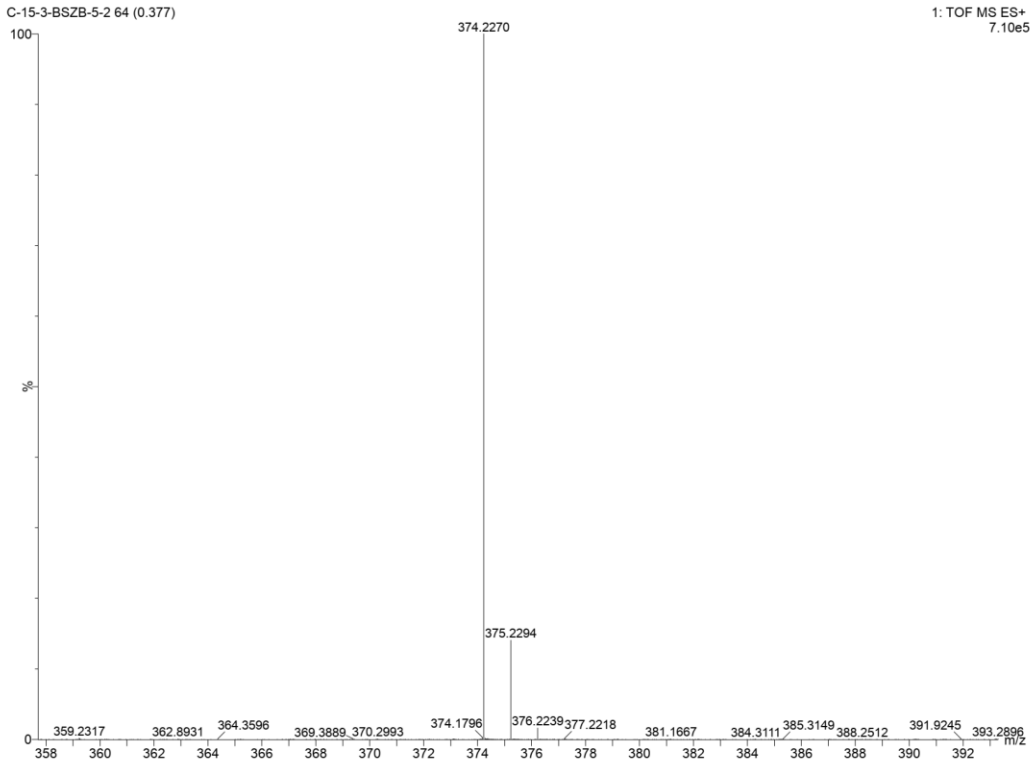


Fig. S45 ^{13}C NMR spectrum of **4f**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
374.2270	374.2266	0.4	1.1	7.5	604.3	n/a	n/a	C21 H32 N3 O S

Fig. S46 HRESIMS of **4f**

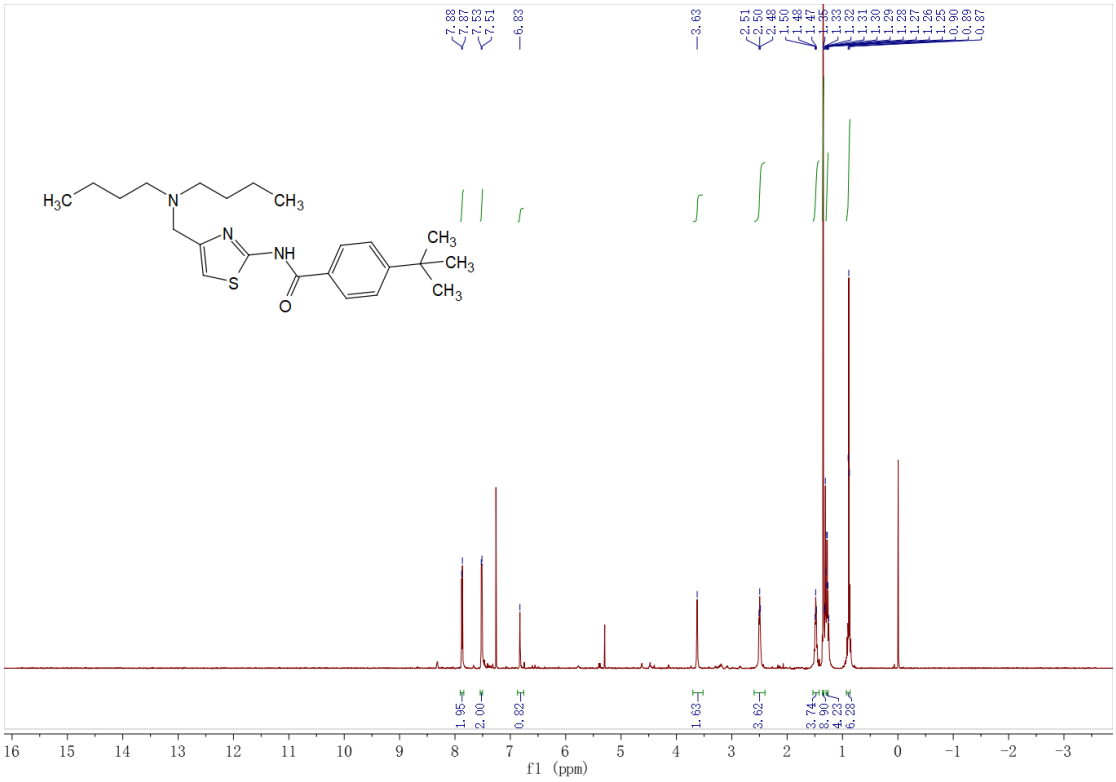


Fig. S47 ^{1}H NMR spectrum of **4g**

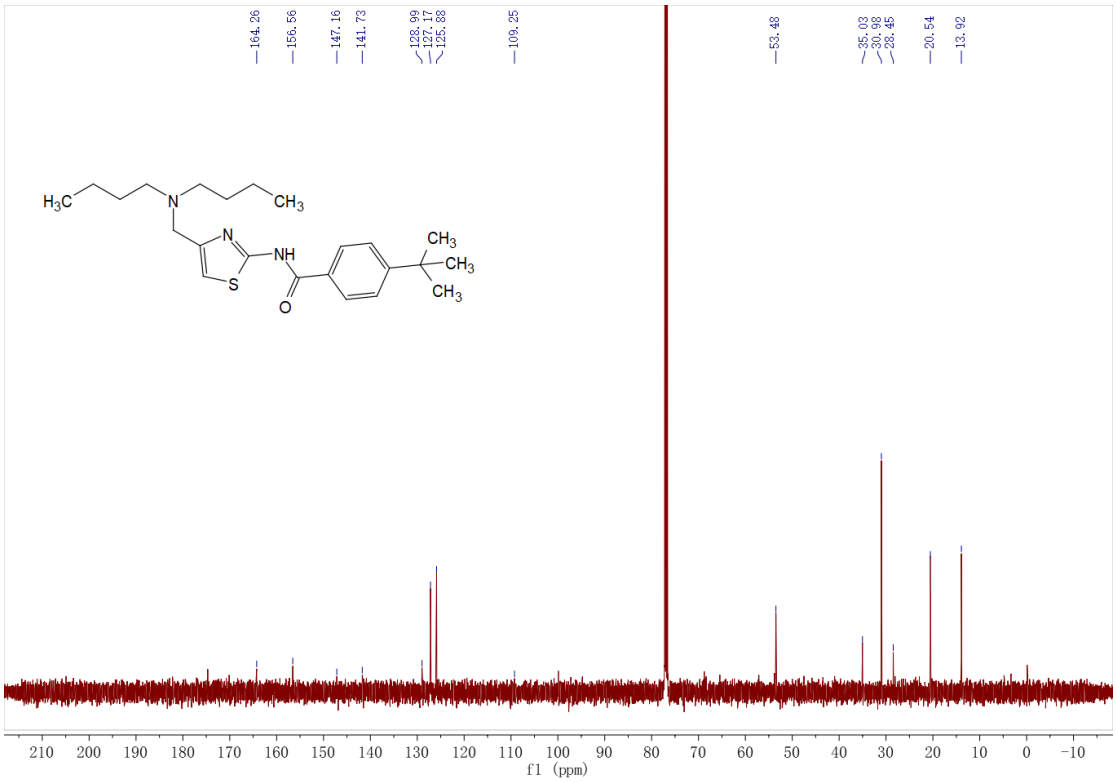
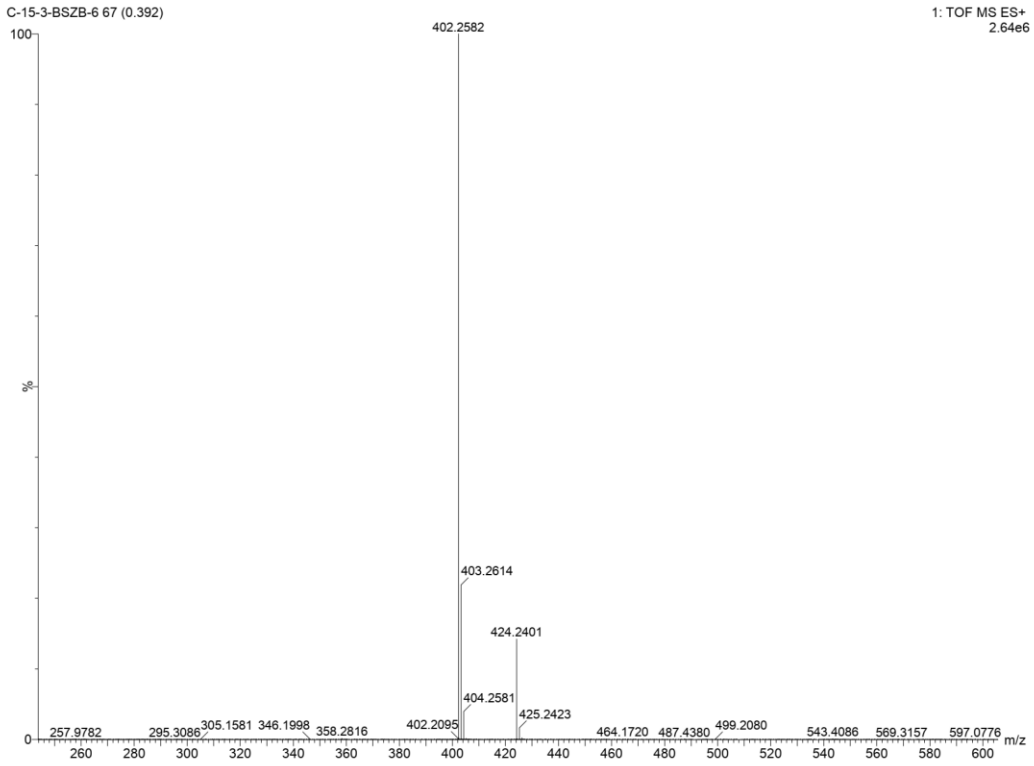


Fig. S48 ^{13}C NMR spectrum of **4g**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
402.2582	402.2579	0.3	0.7	7.5	781.9	n/a	n/a	C23 H36 N3 O S

Fig. S49 HRESIMS of **4g**

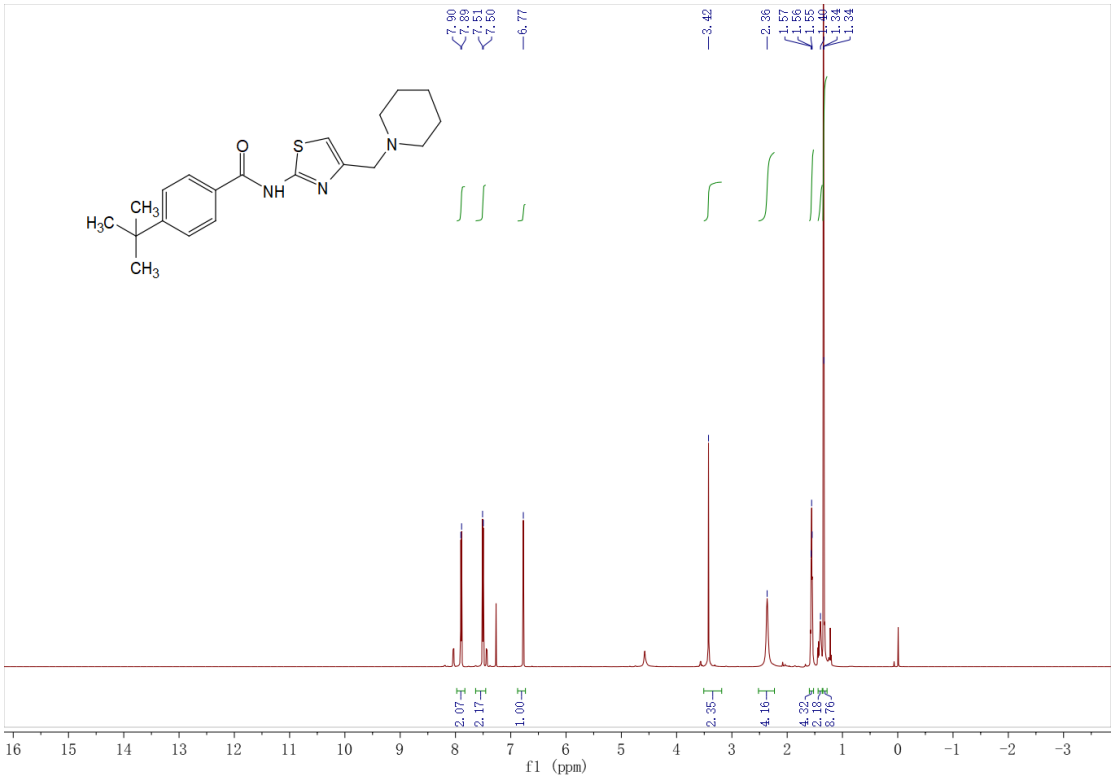


Fig. S50 ^{1}H NMR spectrum of **4h**

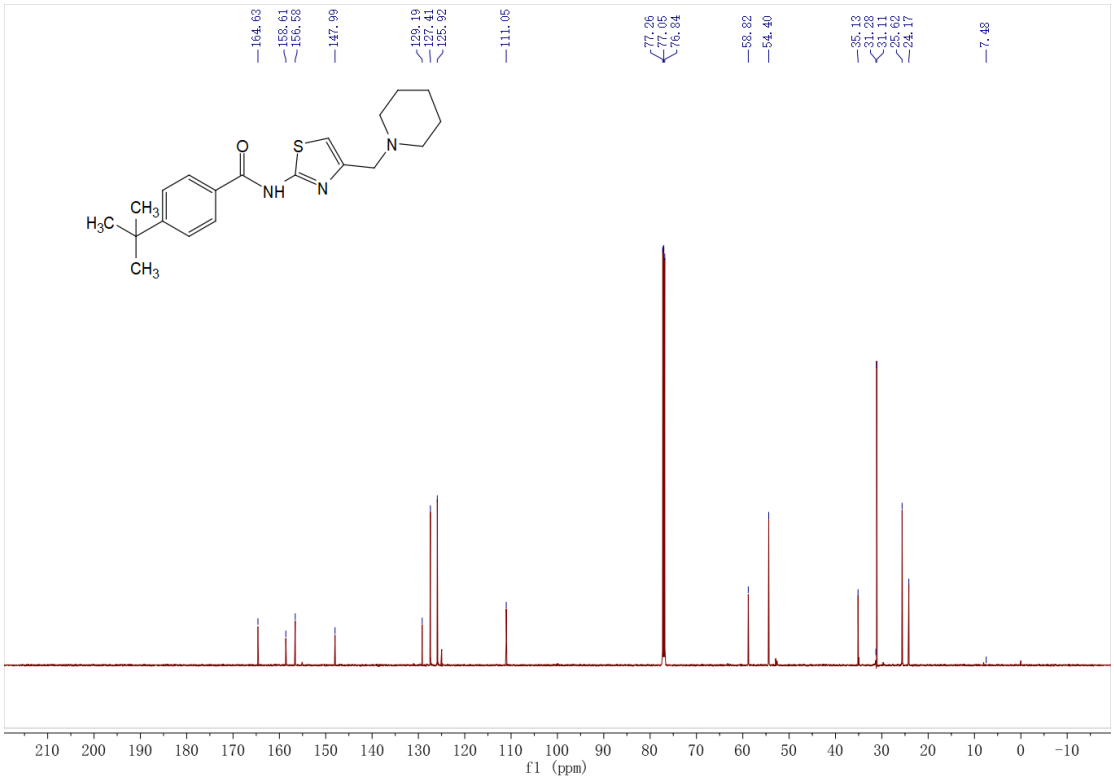
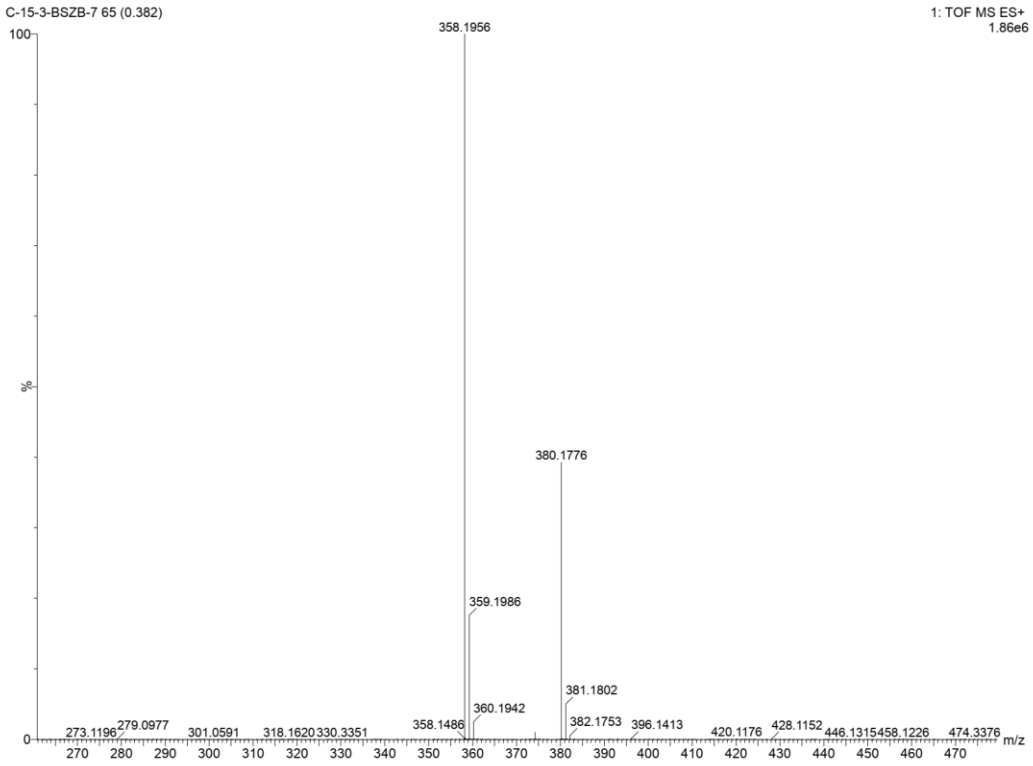


Fig. S51 ^{13}C NMR spectrum of **4h**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
358.1956	358.1953	0.3	0.8	8.5	755.1	n/a	n/a	C20 H28 N3 O S

Fig. S52 HRESIMS of **4h**

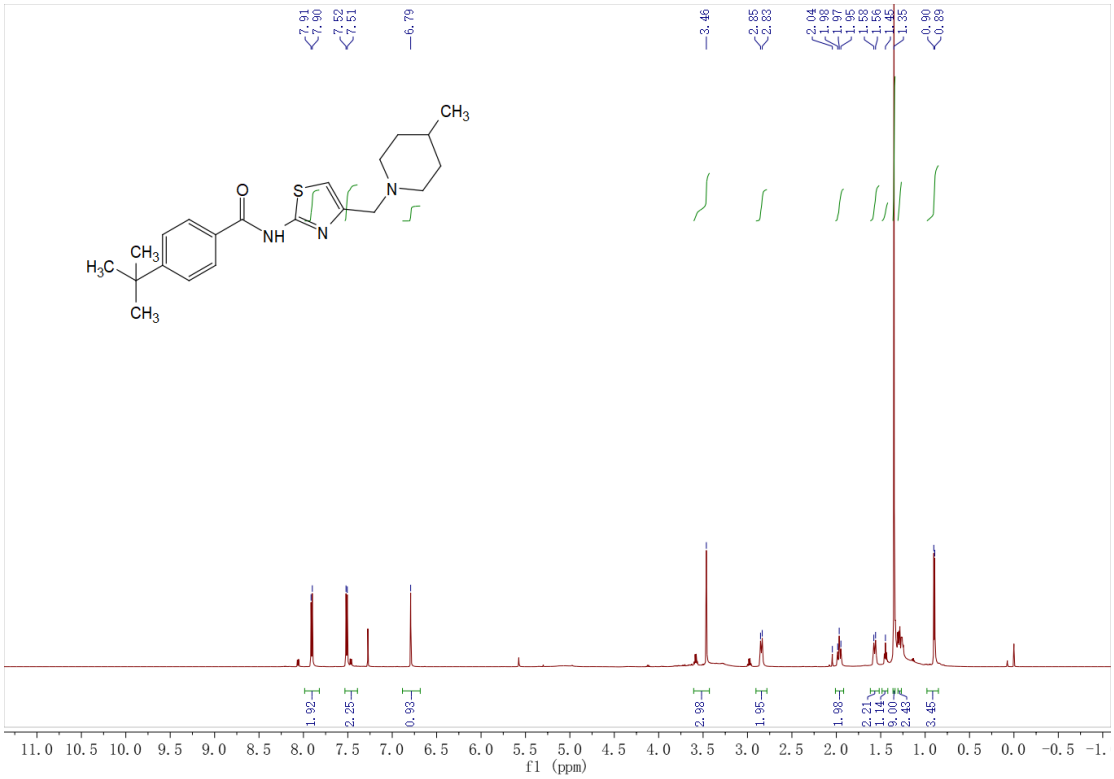


Fig. S53 ^{1}H NMR spectrum of **4i**

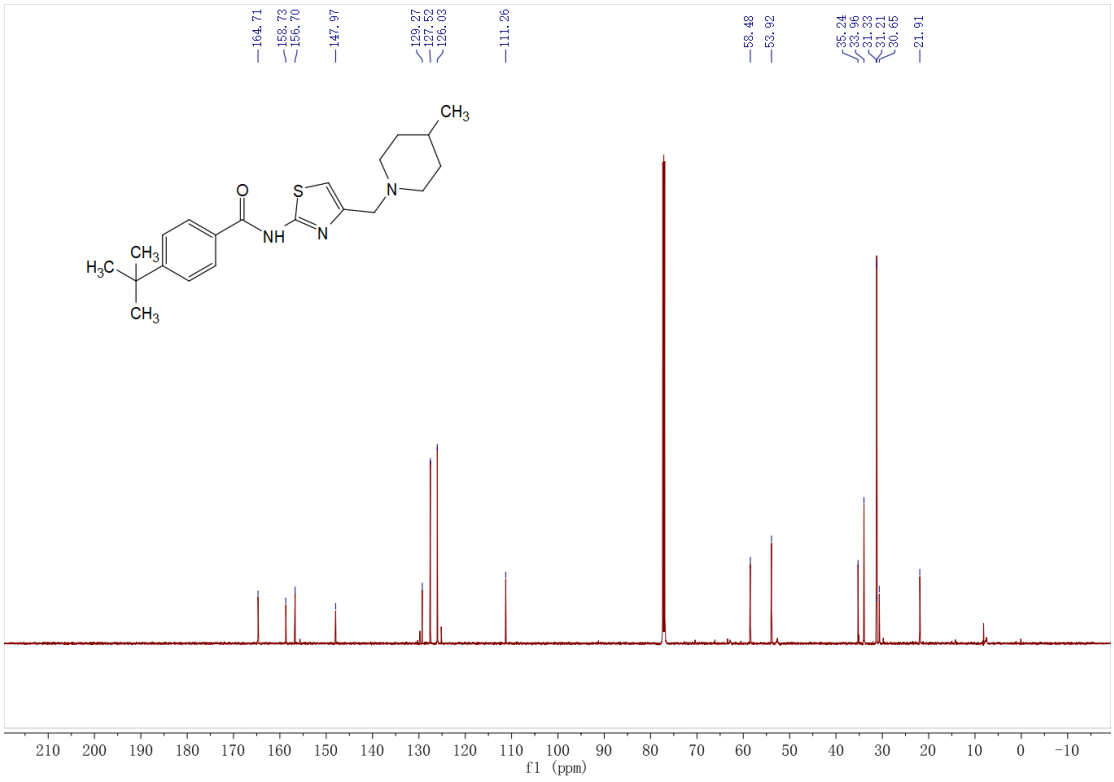
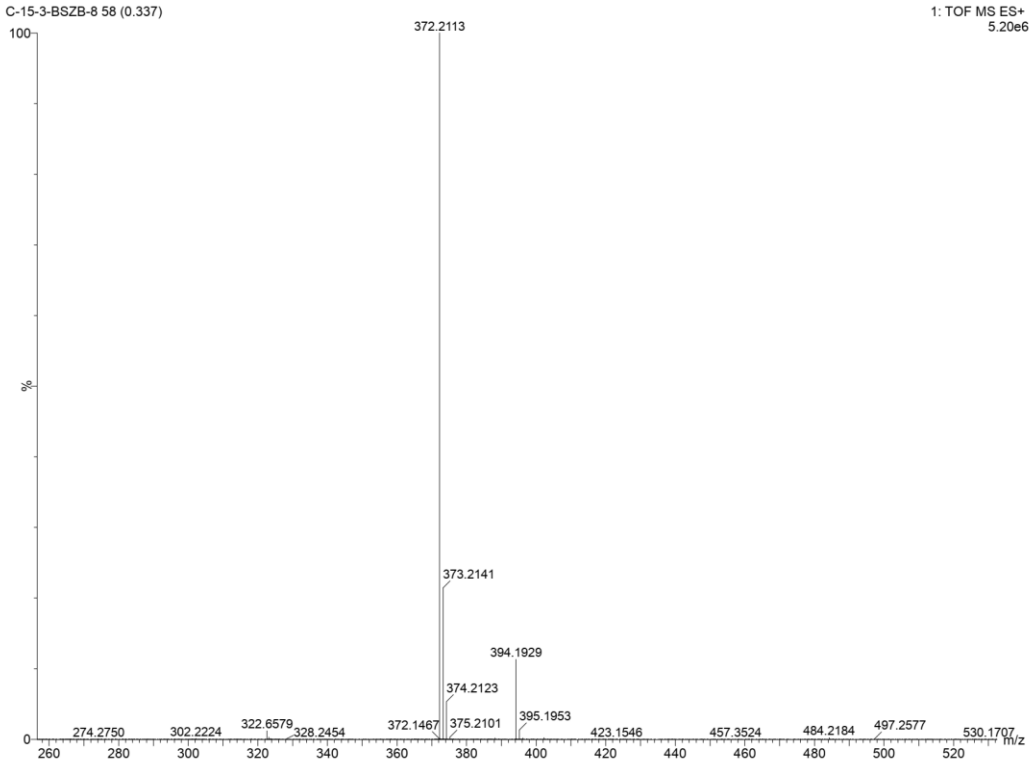


Fig. S54 ^{13}C NMR spectrum of **4i**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
372.2113	372.2110	0.3	0.8	8.5	993.3	n/a	n/a	C21 H30 N3 O S

Fig. S55 HRESIMS of **4i**

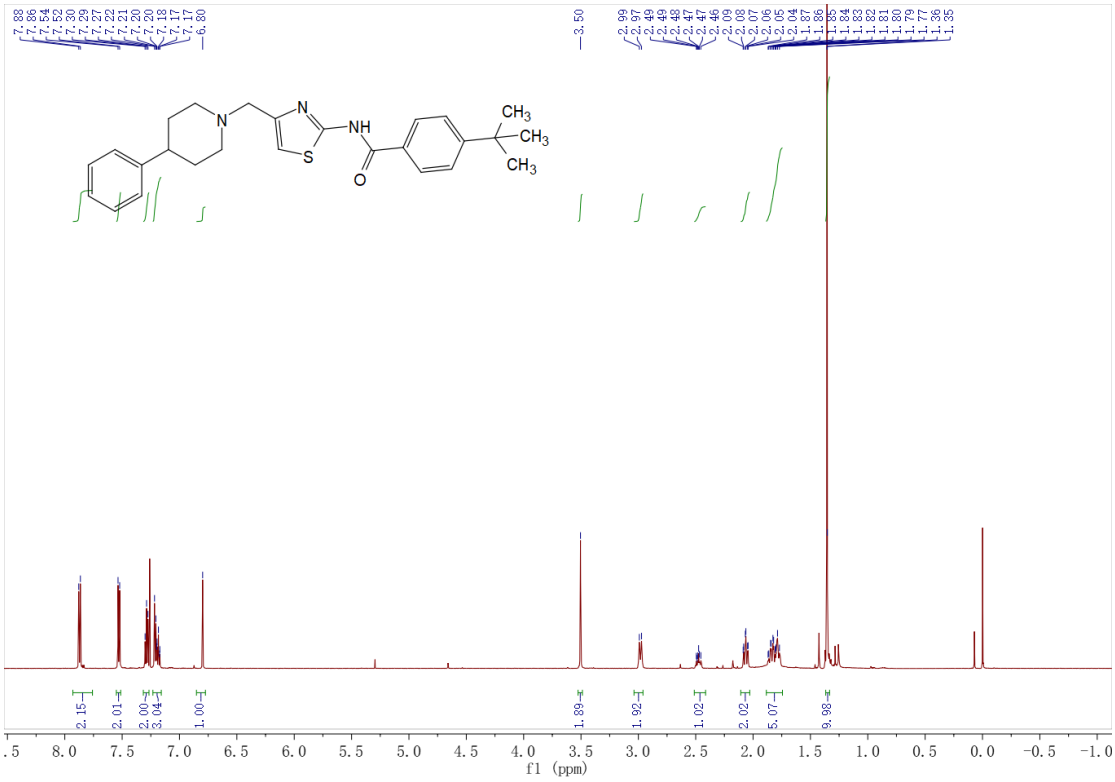


Fig. S56 ^{13}C NMR spectrum of **4j**

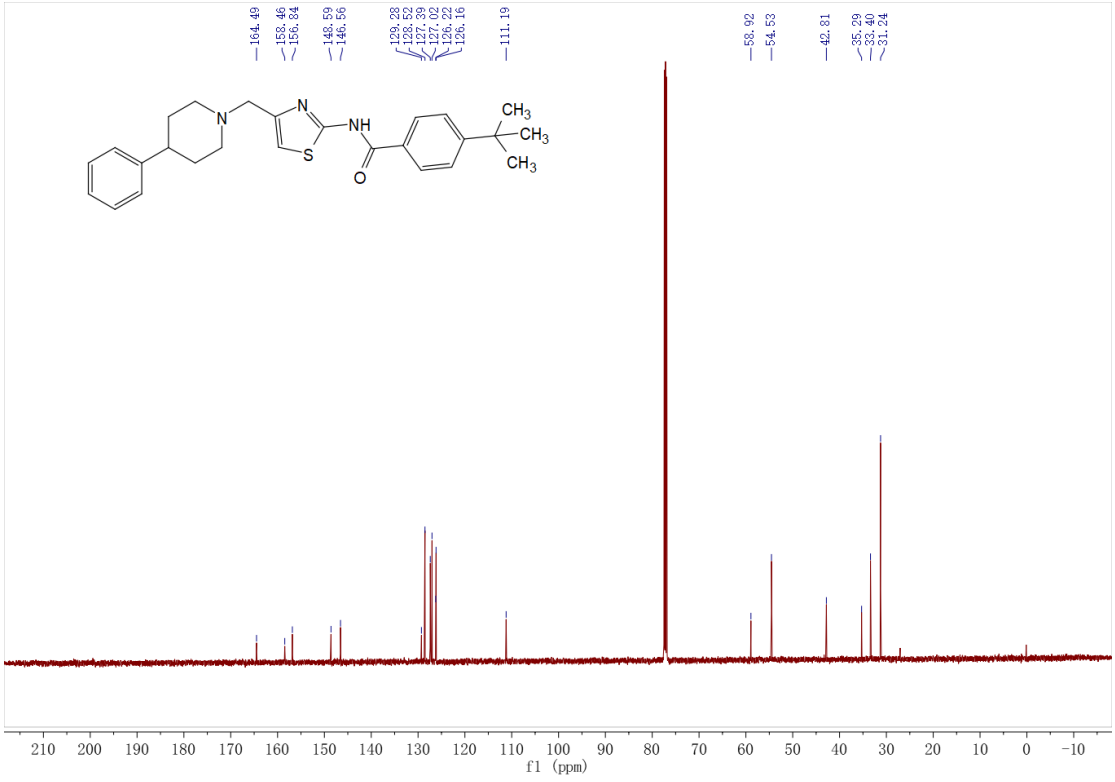
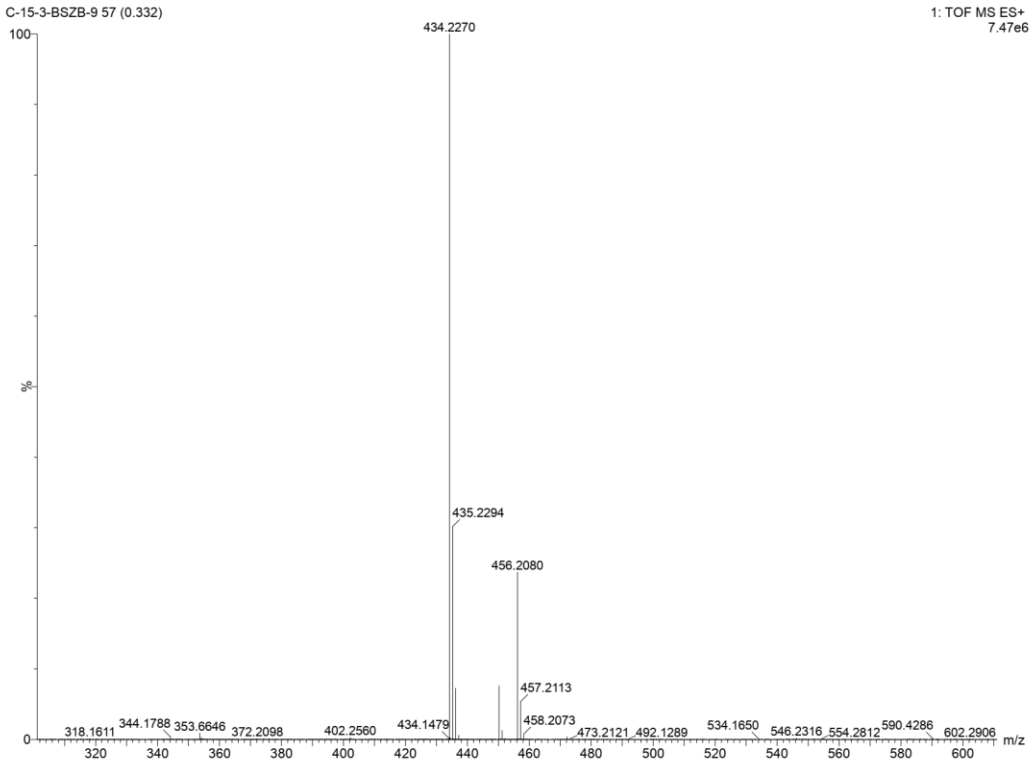


Fig. S57 ^{13}C NMR spectrum of **4j**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
434.2270	434.2266	0.4	0.9	12.5	952.4	n/a	n/a	C26 H32 N3 O S

Fig. S58 HRESIMS of **4j**

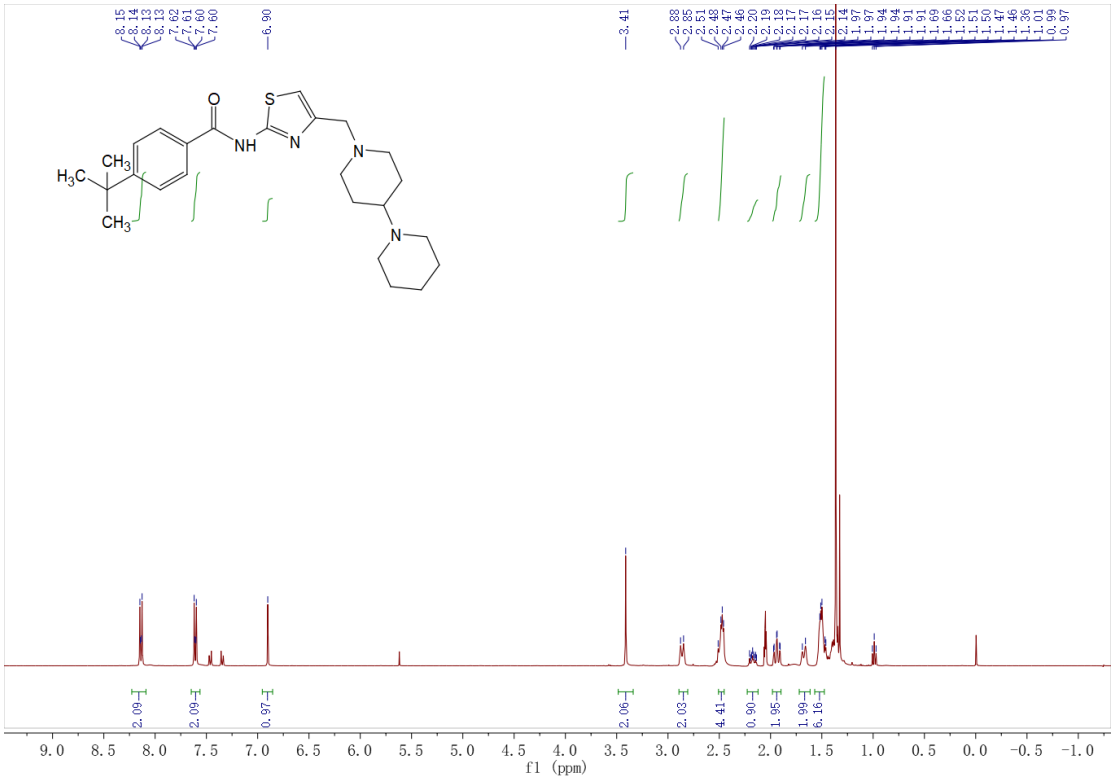


Fig. S59 ^{1}H NMR spectrum of **4k**

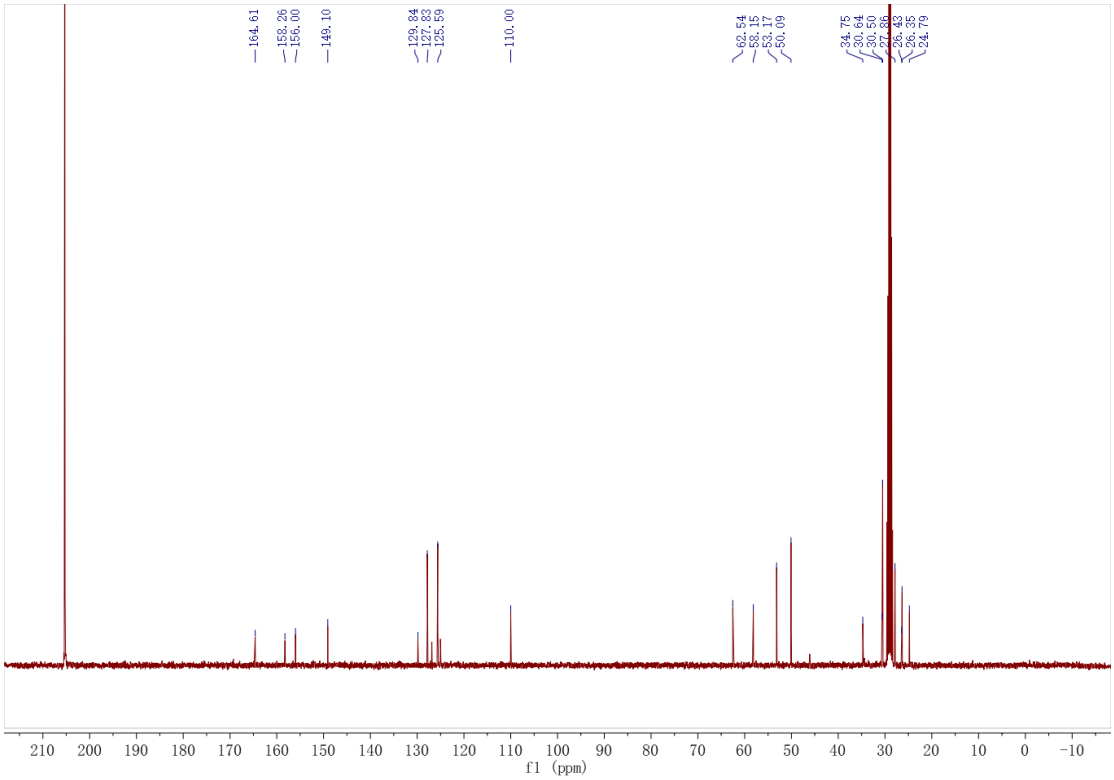
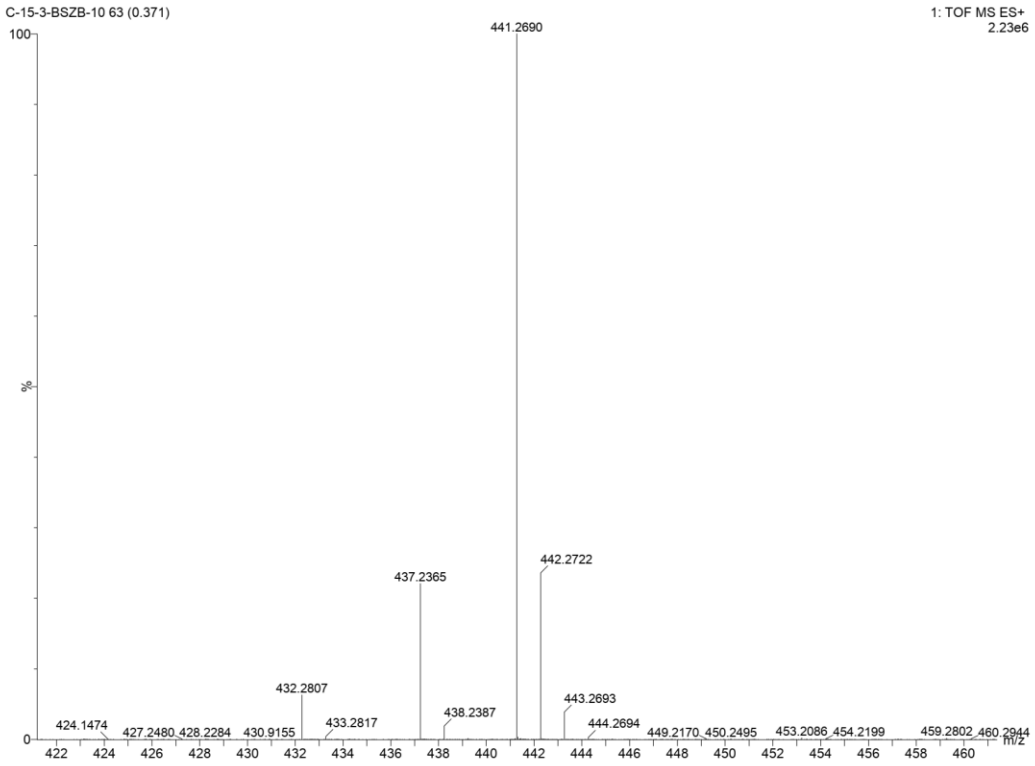


Fig. S60 ^{13}C NMR spectrum of **4k**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
441.2690	441.2688	0.2	0.5	9.5	727.3	n/a	n/a	C25 H37 N4 O S

Fig. S61 HRESIMS of **4k**

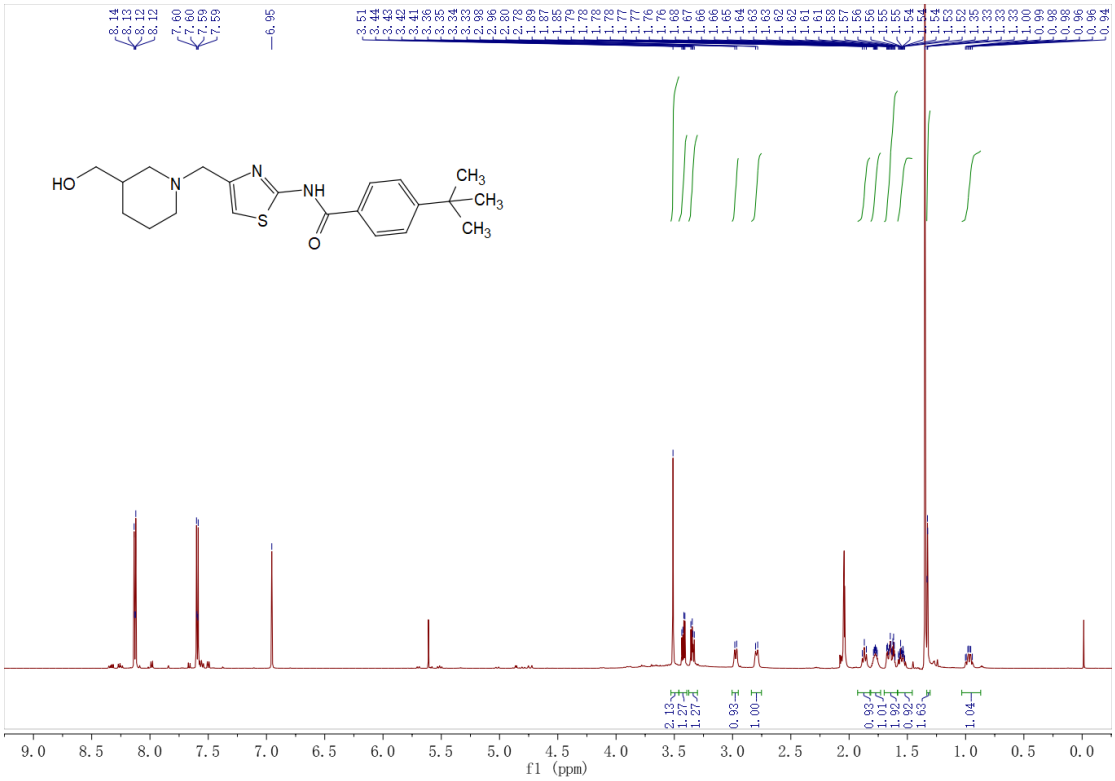


Fig. S62 ^{1}H NMR spectrum of **4l**

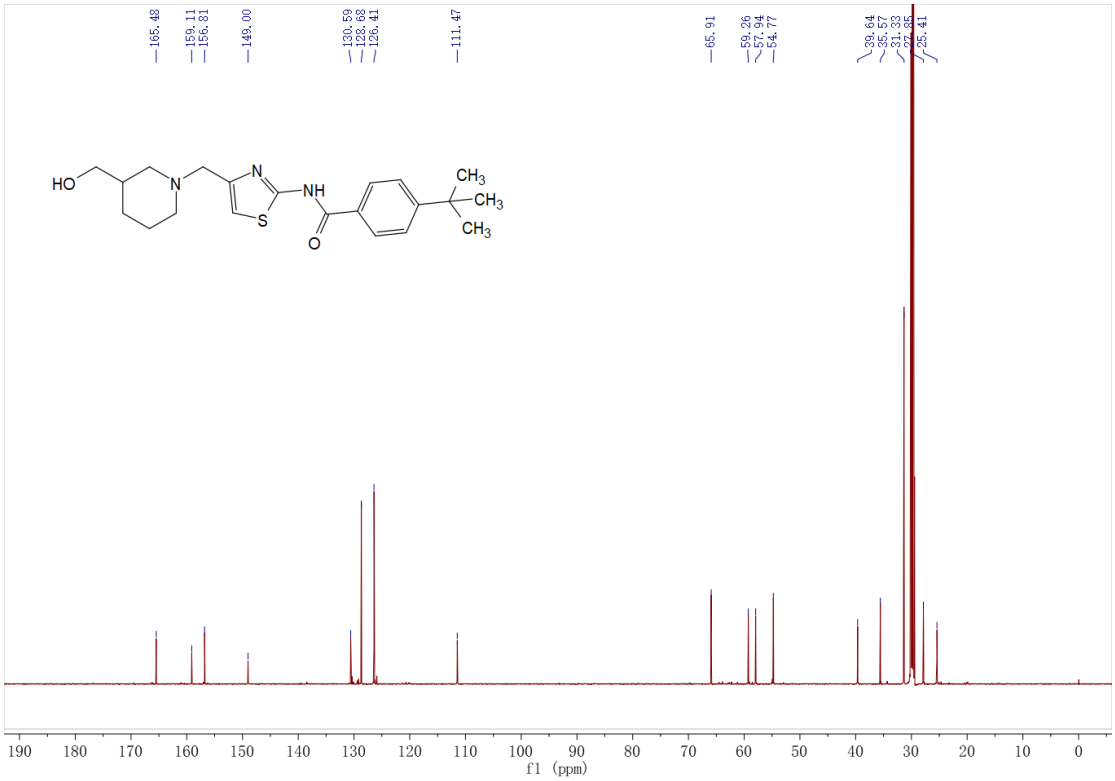
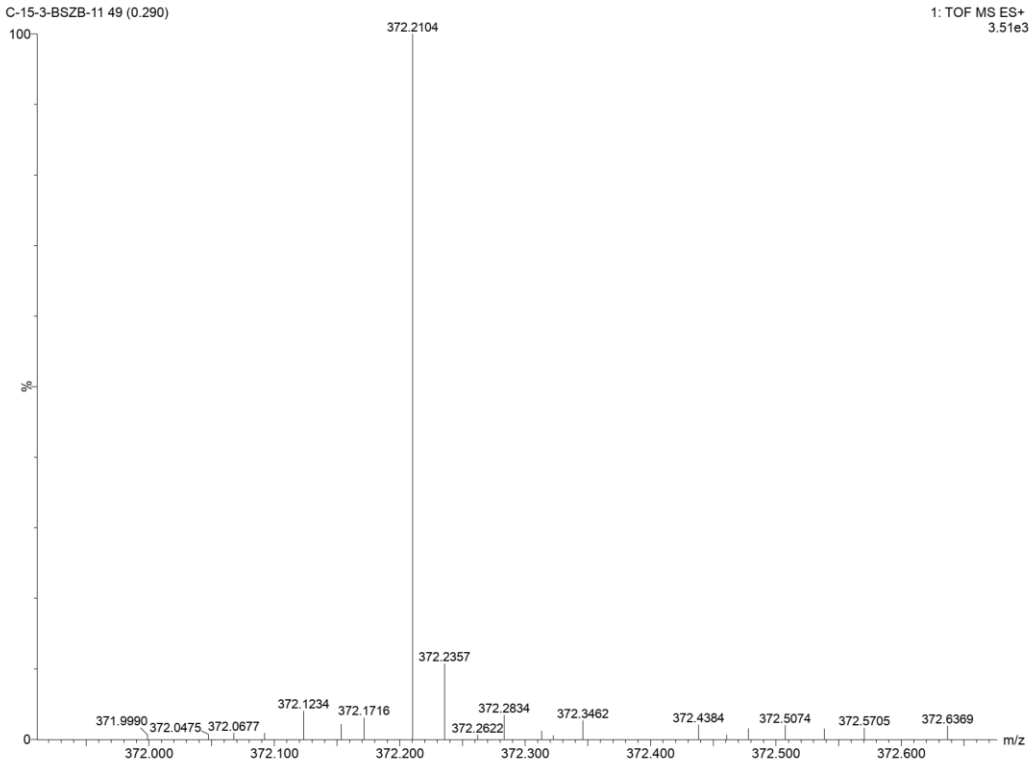


Fig. S63 ^{13}C NMR spectrum of **4l**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
372.2104	372.2110	-0.6	-1.6	8.5	133.0	n/a	n/a	C21 H30 N3 O S

Fig. S64 HRESIMS of **4l**

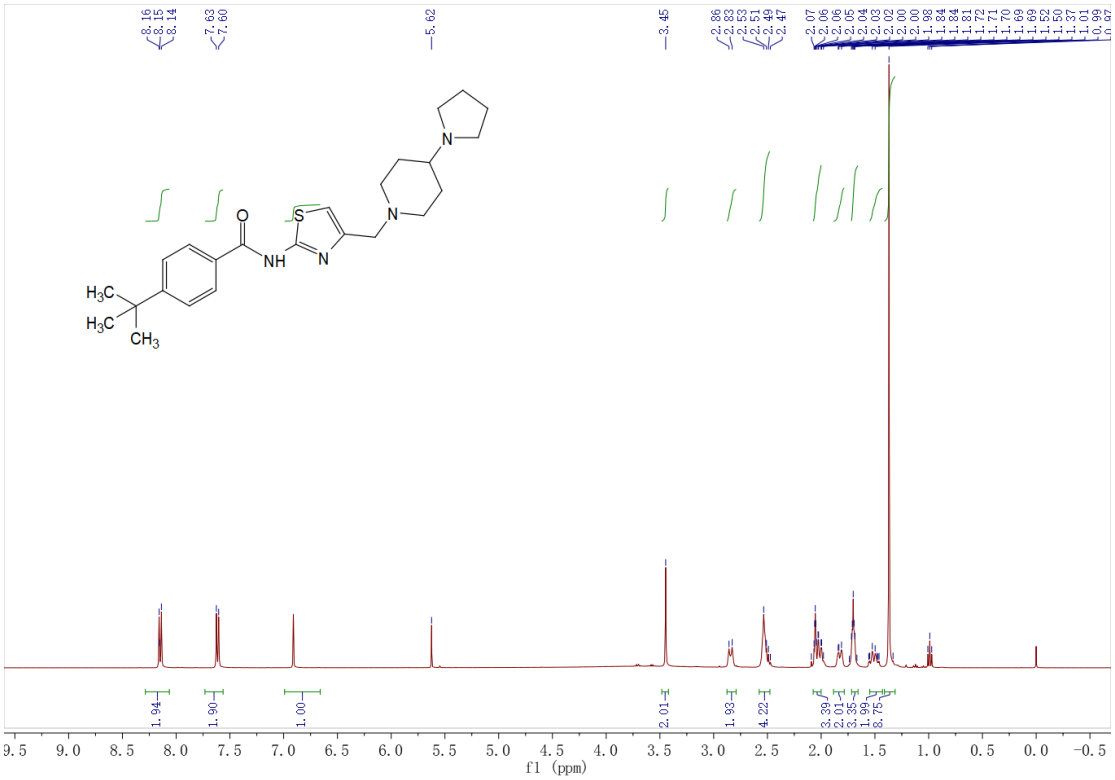


Fig. S65 ^{1}H NMR spectrum of **4m**

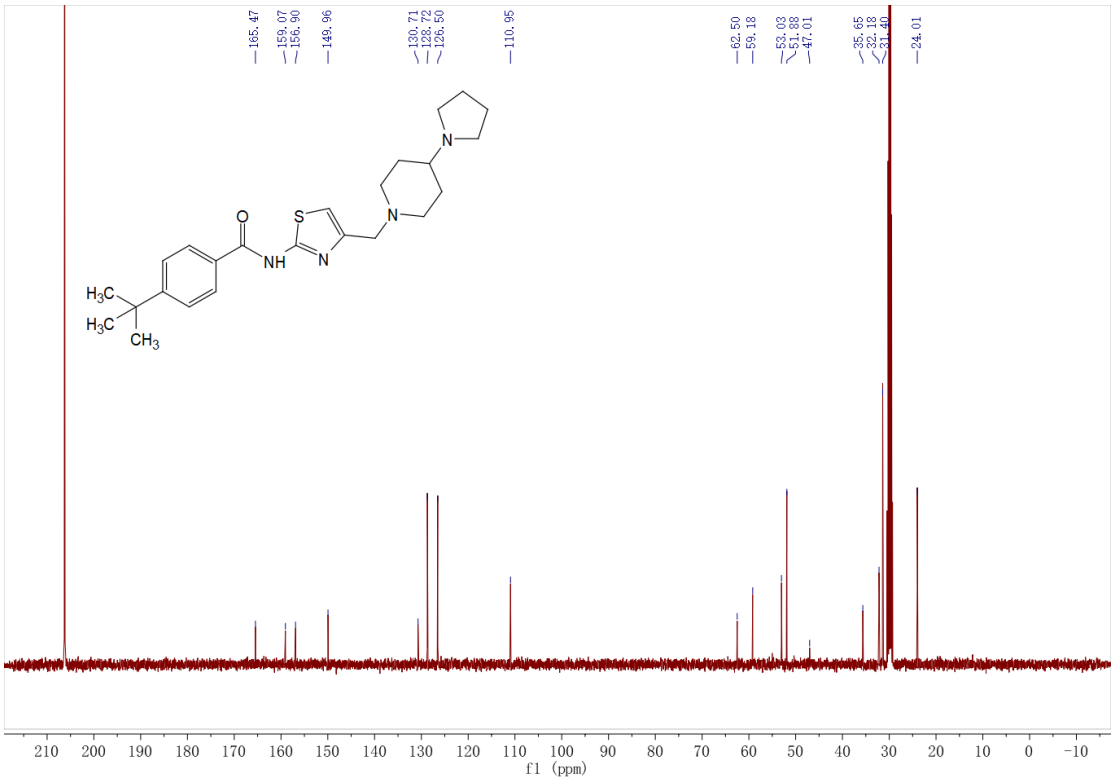
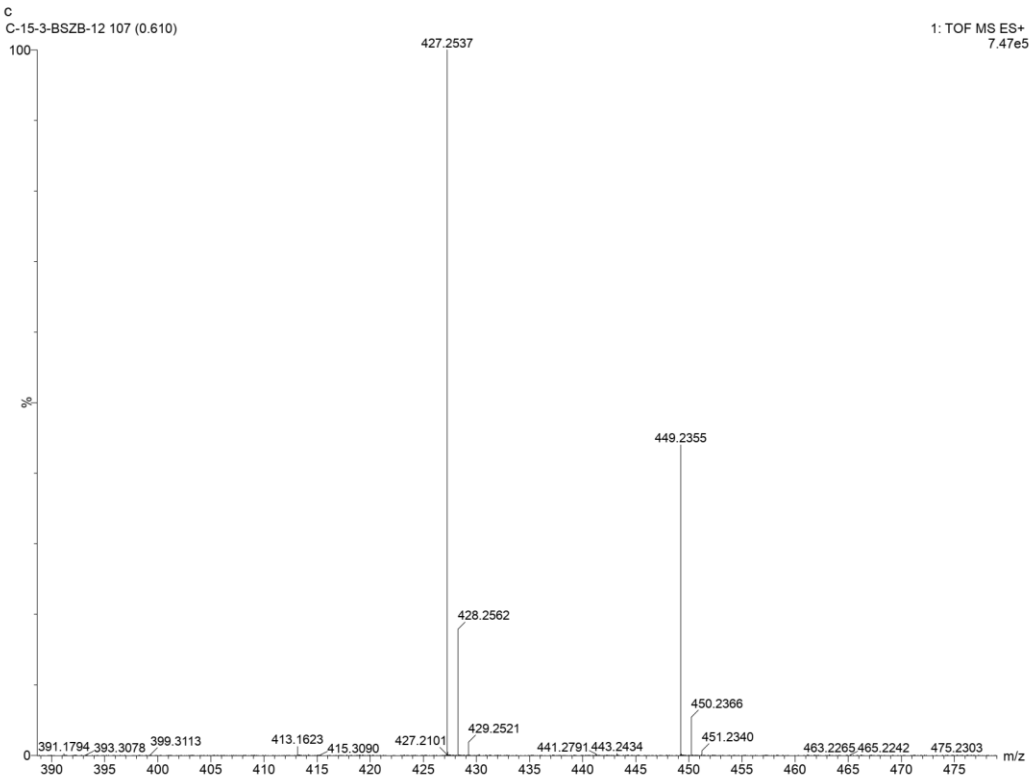


Fig. S66 ^{13}C NMR spectrum of **4m**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
427.2537	427.2532	0.5	1.2	9.5	551.6	n/a	n/a	C24 H35 N4 O S

Fig. S67 HRESIMS of **4m**

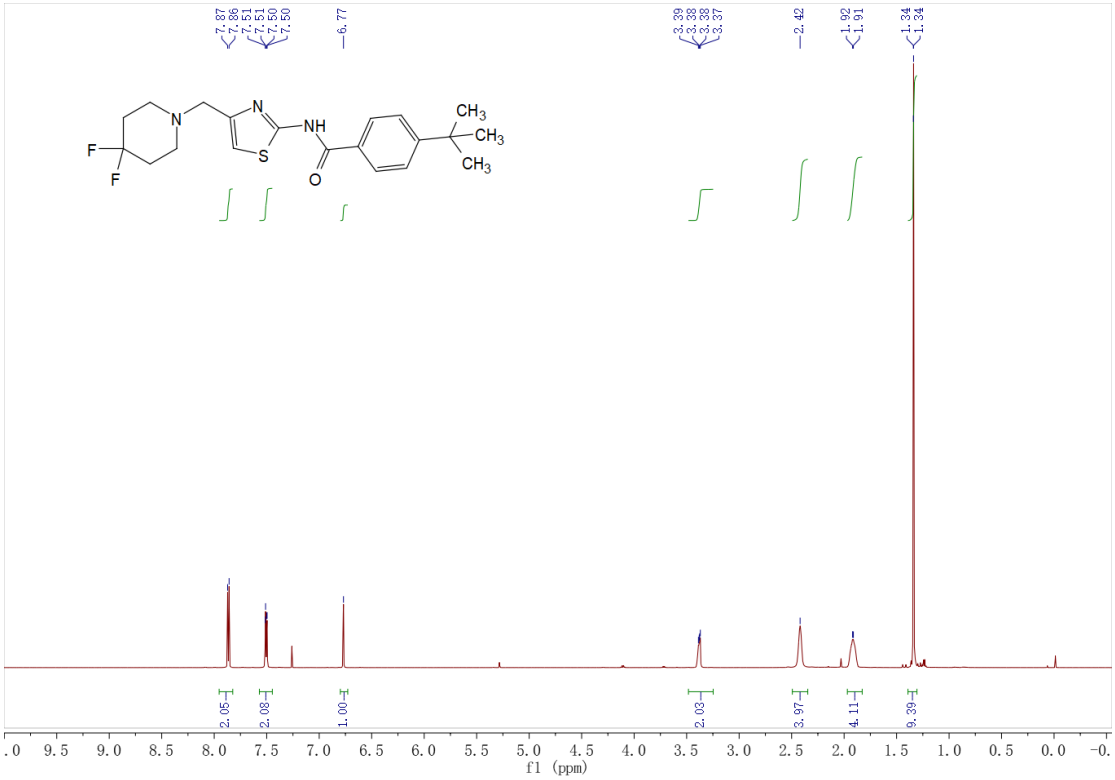


Fig. S68 ^{1}H NMR spectrum of **4n**

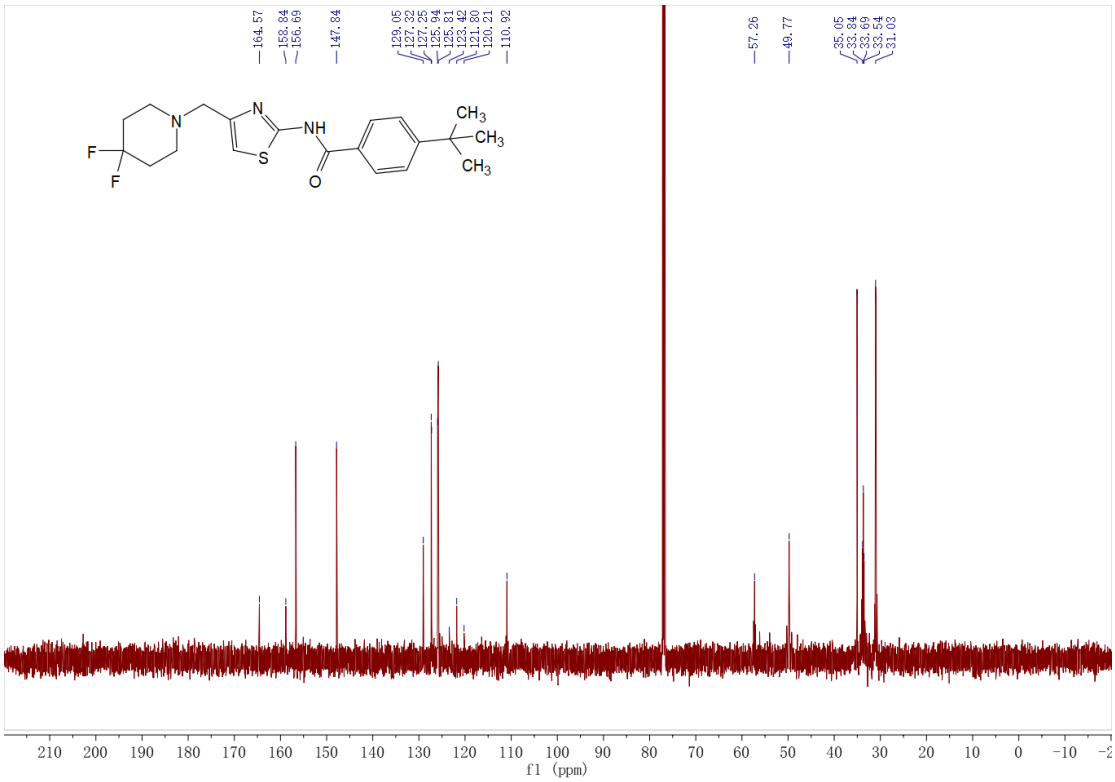
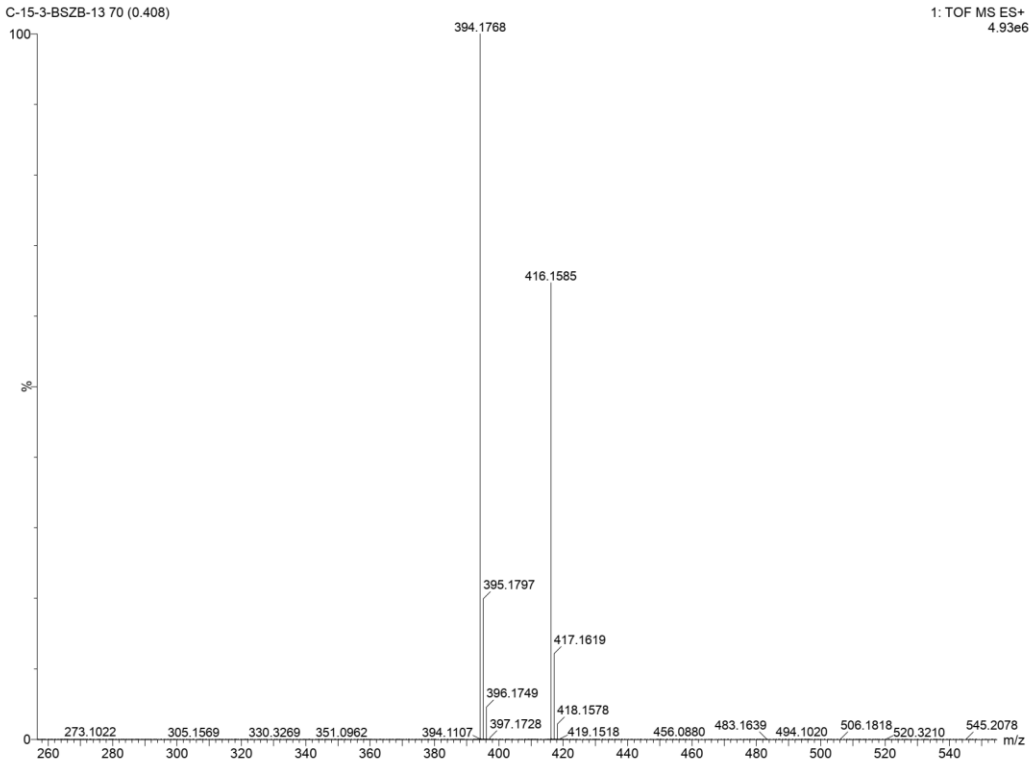


Fig. S69 ^{13}C NMR spectrum of **4n**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
394.1768	394.1765	0.3	0.8	8.5	877.8	n/a	n/a	C20 H26 N3 O F2 S

Fig. S70 HRESIMS of **4n**

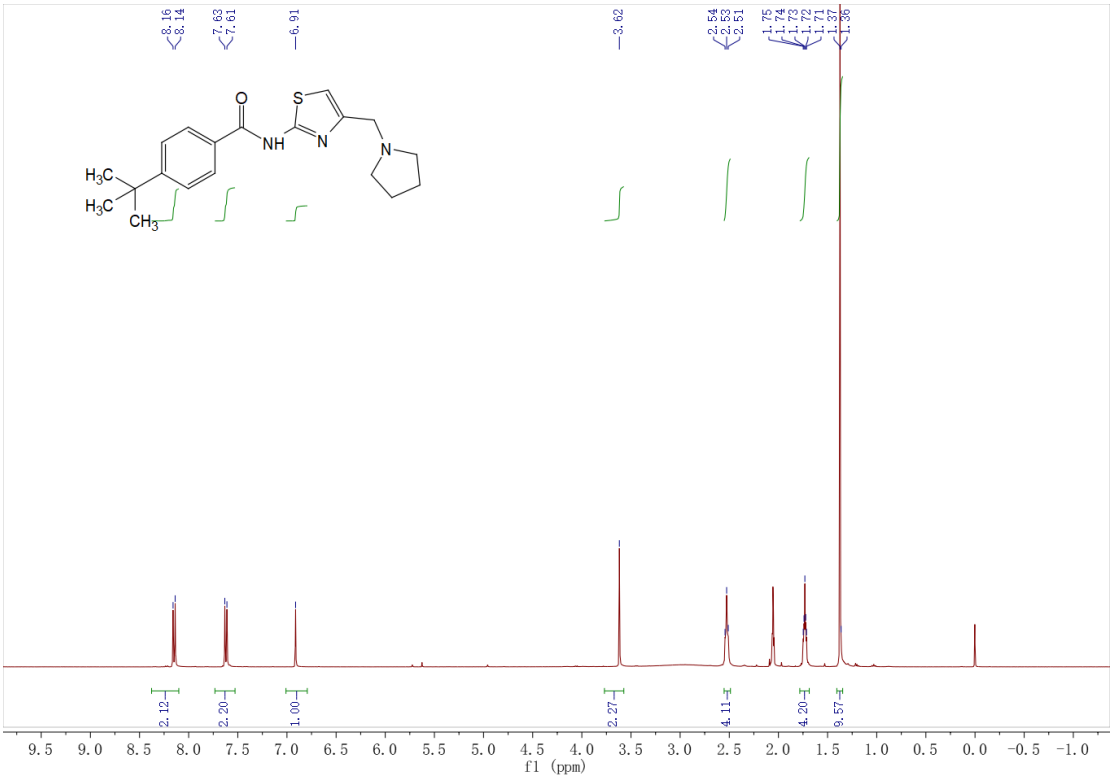


Fig. S71 ^{1}H NMR spectrum of **4o**

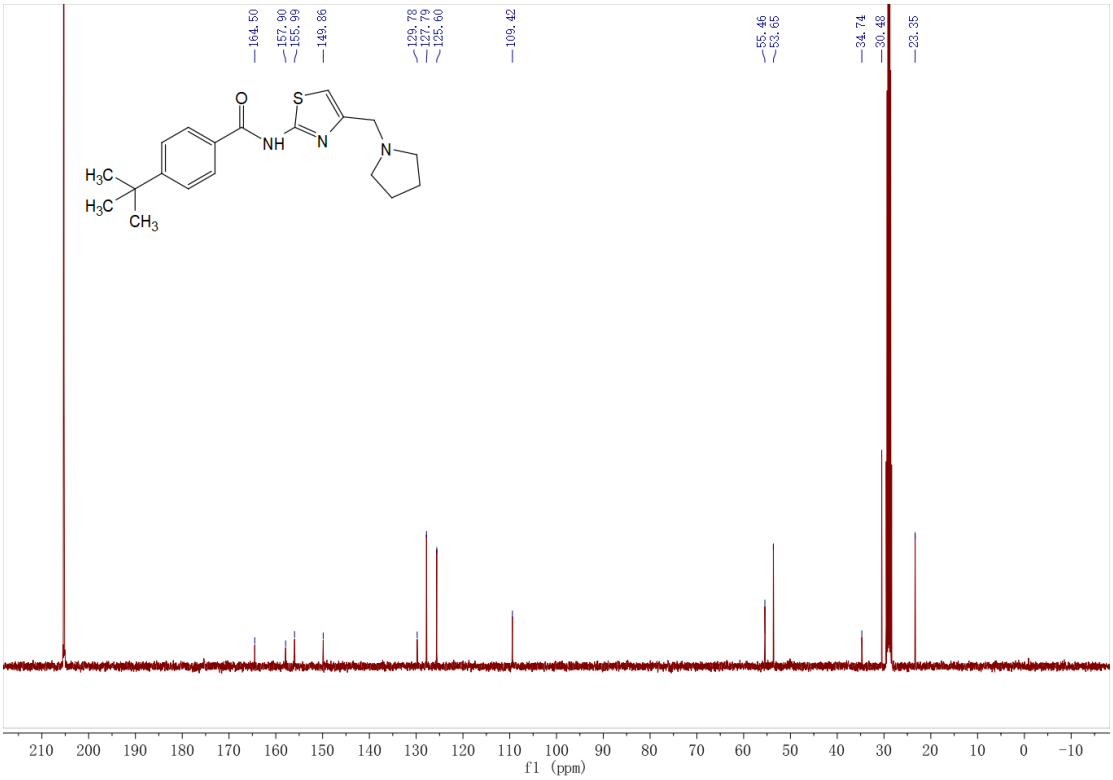
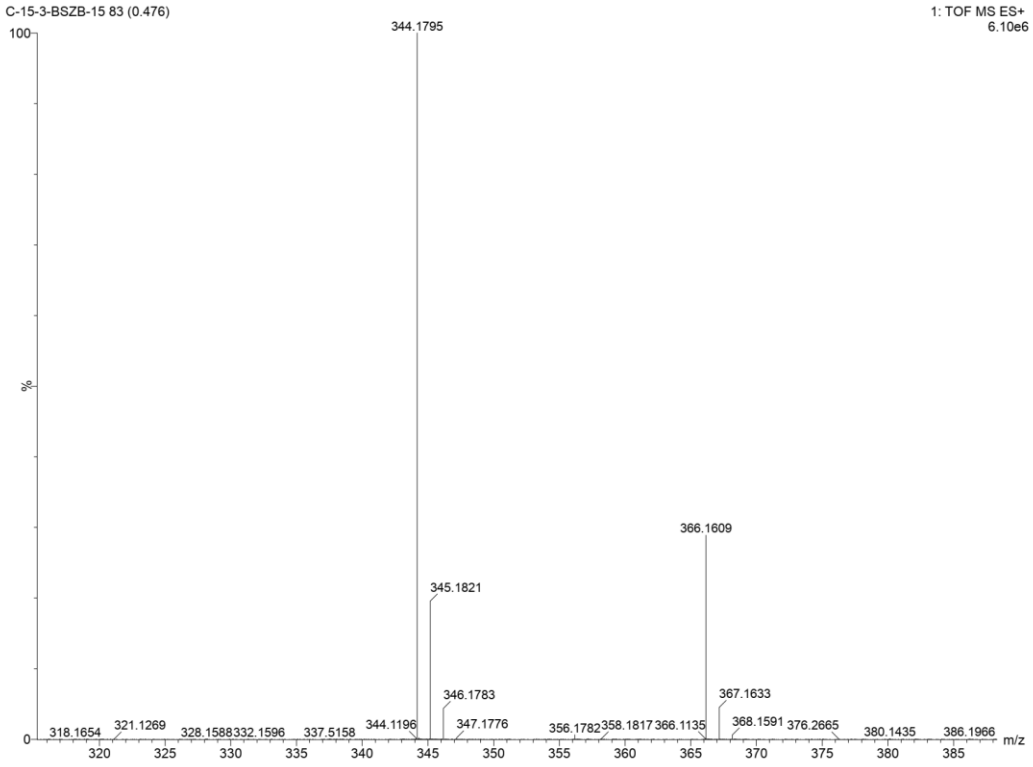


Fig. S72 ^{13}C NMR spectrum of **4o**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
344.1795	344.1797	-0.2	-0.6	8.5	936.0	n/a	n/a	C19 H26 N3 O S

Fig. S73 HRESIMS of **4o**