Supporting Information for:

Synthesis and Investigation of Thieno[2,3-*b*]pyridines that Restore Activity of Topotecan

Emily K. Paulin[a], Natalie A. Haverkate[a], Petr Tomek[b], Jagdish K. Jaiswal[b,c], Emily Dobbs[a], Jumana Nahhas[a], Euphemia Leung[b,d], Xiang Gao[e], Lin-Kun An[e,f], Lisa I. Pilkington[a,g*], David Barker[a,h*]

[a] *School of Chemical Sciences, University of Auckland, Auckland 1010, New Zealand*

[b] *Auckland Cancer Society Research Centre and Department of Molecular Medicine and Pathology, University of Auckland, Grafton, Auckland 1023, New Zealand*

[c] *Maurice Wilkins Centre for Molecular Biodiscovery, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand*

[d] *Department of Molecular Medicine and Pathology, University of Auckland, Auckland 1023, New Zealand*

[e] *School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou, 510006 P. R. China*

[f] *Guangdong Provincial Key Laboratory of New Drug Design and Evaluation, Guangzhou 510006, China*

[g] *Te Pūnaha Matatini, Auckland 1142, New Zealand*

[h] *The MacDiarmid Institute for Advanced Materials and Nanotechnology, Victoria University of Wellington, Wellington 6012, New Zealand*

*Corresponding author. Tel.: +64-9-373-7599; e-mail: d.barker@auckland.ac.nz (D.B), lisa.pilkington@auckland.ac.nz (L.I.P)

Contents

General synthetic procedures

*General Procedure A: Synthesis of sodium enolates **2a-k**.*

To a mixture of sodium metal (1 equiv.) in dry diethyl ether was added a mixture of substituted cyclic ketone (1 equiv.) and ethyl formate (1 equiv.) in dry diethyl ether dropwise under an atmosphere of nitrogen. Absolute ethanol (cat.) was added and the reaction stirred at r.t. for 24 h. The crude product was filtered, washed with diethyl ether and the solvent was removed *in vacuo* to give the desired compound which was used in the next reaction without further purification.

*General Procedure B: Synthesis of carbonitriles **3a-k**.*

A mixture of sodium enolate (1 equiv.) and cyanothioacetamide (1 equiv.) in water and piperidinium acetate solution (prepared using acetic acid (20%), water (45%) and piperidine (35%)) was heated at reflux for 24 h before acidifying with glacial acetic acid. The reaction was cooled to r.t., stirred for 24 h, filtered, washed with ice water and collected to give the desired compound which was used in the next reaction without further purification.

*General Procedure C: Synthesis of N-phenylacetamides **4,5** and **8a-l**.*

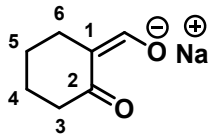
To a solution of substituted aniline (1 equiv.) and triethylamine (1.2 equiv.) in CH_2Cl_2 was added chloroacetyl chloride (1.2 equiv.) dropwise and the reaction stirred for 1 h at 0 °C, followed by 24 h at r.t.. The solution was diluted with CH_2Cl_2, washed twice with 2 M HCl, water, sat. aq. $NaHCO_3$, brine, dried with Na_2SO_4 and the solvent removed *in vacuo* to give the desired compound.

*General Procedure D: Synthesis of thieno[2,3-*b*]pyridines **6a-k**, **7a-k**, **9a-l**, and **10a-l**.*

A mixture of carbonitrile (1 equiv.), 2-chloro-*N*-phenylacetamide (1 equiv.) and anhydrous sodium carbonate (2 equiv.) in absolute ethanol was heated at reflux for 24-48 h. The mixture was cooled to r.t. and the solvent was removed *in vacuo*, to give a crude solid which was recrystallised with methanol, filtered, and washed with water to give the desired compound.

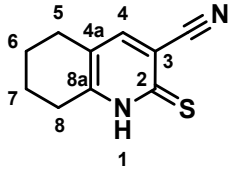
Synthetic procedures and compound characterisation data for series 1

Sodium (*E*)- and (*Z*)-(2-oxocyclohexylidene)methanolate 2a



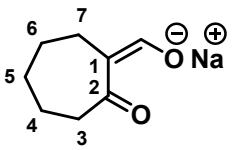
The reaction was carried out following General Procedure **A** using cyclohexanone **1a** (2.00 g, 20.4 mmol), ethyl formate (1.65 mL, 20.4 mmol), sodium metal (0.47 g, 20.4 mmol) in dry ether (110 mL) and absolute ethanol (0.01 mL) for 24 h to give the *title compound* **2a** (2.64 g, 87%) as a yellow solid. m.p. >230 °C, decomp. (lit. m.p. 253 °C.[1]). δ_H (400 MHz, D_2O) 1.57 – 1.63 (2H, m, H-5), 1.67 – 1.73 (2H, m, H-4), 2.21 (4H, q, *J* = 6.2 Hz, H-3 and H-6), 8.47 and 9.09 (1H, s, *E/Z* isomers, 1-CH). The ^{1}H NMR values were in agreement with the literature values.[2]

2-Thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile 3a



The reaction was carried out following General Procedure **B** using sodium enolate **2a** (2.00 g, 10.5 mmol), cyanothioacetamide (1.05 g, 10.5 mmol), water (13 mL), piperidinium acetate solution (1.18 mL) and glacial acetic acid (1.82 mL) for 48 h to give the *title compound* **3a** (1.88 g, 74%) as a brown solid. m.p. >230 °C, decomp. (lit m.p. 249-251 °C.[3]). δ_H (400 MHz, $(CD_3)_2SO$) 1.65-1.67 (4H, m, H-6 and H-7), 2.51 (2H, t, *J* = 6.2 Hz, H-8), 2.71 (2H, t, *J* = 6.2 Hz, H-5), 7.88 (1H, s, H-4), 13.9 (1H, br s, NH). The ^{1}H NMR values were in agreement with the literature values.[4]

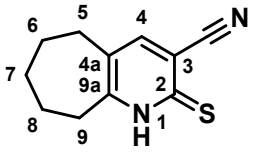
Sodium (*E*)- and (*Z*)-(2-oxocycloheptylidene)methanolate 2b



The reaction was carried out following General Procedure **A** using cycloheptanone **1b** (0.50 g, 4.46 mmol), ethyl formate (0.36 mL, 4.46 mmol), sodium metal (0.10 g, 4.46 mmol) in dry ether (24 mL) and absolute ethanol (0.01 mL) for 24 h to give the *title compound* **2b** (0.56 g, 90%) as a yellow solid.

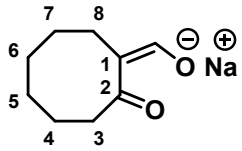
m.p. >230 °C, decomp. δ_H (400 MHz, D_2O) 1.47 (2H, p, *J* = 5.6 Hz, H-6), 1.63 (2H, p, *J* = 5.6 Hz, H-4 or H-5), 1.73 (2H, p, *J* = 5.6 Hz, H-4 or H-5), 2.34 (2H, d, *J* = 5.6 Hz, H-7), 2.49 (2H, d, *J* = 5.6 Hz, H-3), 8.48 and 8.85 (1H, s, *E/Z* isomers, 1-CH). δ_C (100 MHz, D_2O) 22.4 (C-7), 24.9 (C-4 or C-5), 29.6 (C-6), 34.3 (C-4 or C-5), 42.5 (C-3), 167.9 (*E*/*Z* isomers, 1-CH), 171.1 (C-2). ν_{max} (ATR)/cm^{-1} 2934 (C-H alkane), 1679 (C=O carbonyl), 1583 (C=C aromatic), 1444 (-C-H bending).

2-Thioxo-2,5,6,7,8,9-hexahydro-1*H*-cyclohepta[*b*]pyridine-3-carbonitrile 3b



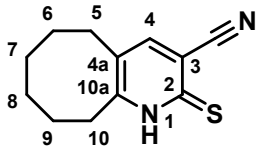
The reaction was carried out following General Procedure **B** using sodium enolate **2b** (0.50 g, 3.60 mmol), cyanothioacetamide (0.36 g, 3.60 mmol), water (3.5 mL), piperidinium acetate solution (0.32 mL) and glacial acetic acid (0.49 mL) for 48 h to give the *title compound* **3b** (0.51 g, 69%) as a brown solid. m.p. >230 °C, decomp. (lit. m.p. 247 °C.[4]). δ_H (400 MHz, $(CD_3)_2SO$) 1.51-1.58 (4H, m, H-6 and H-8), 1.75 (2H, s, H-7), 2.62 (2H, d, *J* = 5.4 Hz, H-9), 2.93 (2H, d, *J* = 5.4 Hz, H-5), 7.95 (1H, s, H-4), 13.93 (1H, br s, NH). The ^{1}H NMR data was in agreement with the literature values.[4]

Sodium (*E*)- and (*Z*)-(2-oxocyclooctylidene)methanolate 2c



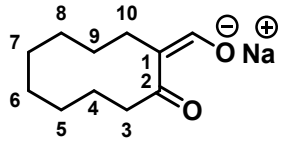
The reaction was carried out following General Procedure **A** using cyclooctanone **1c** (1.50 g, 11.9 mmol), ethyl formate (0.96 mL, 11.9 mmol), sodium metal (0.27 g, 11.9 mmol) in dry ether (63 mL) and absolute ethanol (0.02 mL) for 24 h to give the *title compound* **2c** (1.67 g, 70%) as a yellow solid. m.p. >230 °C, decomp. δ_H (400 MHz, D_2O) 1.45-1.55 (6H, m, H-5, H-6 and H-7), 1.68-1.74 (2H, m, H-4), 2.41 (2H, s, H-8), 2.52 (2H, t, *J* = 6.5 Hz, H-3), 8.48 and 8.98 (1H, s, *E*/Z isomers, 1-CH). δ_C (100 MHz, D_2O) 22.5 (C-8), 26.2 (C-6), 26.2 (C-7), 28.6 (C-5), 30.4 (C-3), 116.0 (C-1), 171.1 and 179.4 (*E*/*Z* isomers, 1-CH), 204.3 (C-2). ν_{max} (ATR)/cm^{-1} 2931 (C-H alkane), 1697 (C=O carbonyl), 1564 (C=C aromatic), 1467 (-C-H bending).

2-Thioxo-1,2,5,6,7,8,9,10-octahydrocycloocta[*b*]pyridine-3-carbonitrile 3c



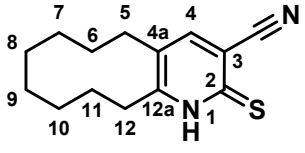
The reaction was carried out following General Procedure **B** using sodium enolate **2c** (1.50 g, 9.79 mmol), cyanothioacetamide (0.98 g, 9.79 mmol), water (9.6 mL), piperidinium acetate solution (0.86 mL), and glacial acetic acid (1.33 mL) for 48 h to give the *title compound* **3c** (1.49 g, 70%) as a brown solid. m.p. 198-200 °C. (lit. m.p. 258-260 °C).[5] δ_H (400 MHz, $(CD_3)_2SO$) 1.35 (4H, s, H-7 and H-8), 1.58 (2H, s, H-6 or H-9), 1.67 (2H, s, H-6 or H-9), 2.59 (2H, t, J = 6.1 Hz, H-5), 2.84 (2H, t, J = 6.1 Hz, H-10), 7.96 (1H, s, H-4), 13.97 (1H, br s, NH). The ^{1}H NMR values were in agreement with the literature values.[5]

Sodium (*E*)- and (*Z*)-(2-oxocyclodecylidene)methanolate 2d



The reaction was carried out following General Procedure **A** using cyclodecanone **1d** (1.00 g, 6.48 mmol), ethyl formate (0.52 mL, 6.48 mmol), sodium metal (0.15 g, 6.48 mmol) in dry ether (35 mL) and absolute ethanol (0.01 mL) for 24 h to give the *title compound* **2d** (1.07 g, 91%) as a yellow solid. m.p. >230 °C, decomp. δ_H (400 MHz, D_2O) 1.24-1.29 (4H, m, H-4 and H-9), 1.30-1.34 (8H, m, H-5, H-6, H-7 and H-8), 1.76-1.84 (2H, m, H-10), 2.35-2.40 (2H, m, H-3), 8.47 and 8.96 (1H, s, *E*/*Z* isomers, 1-CH). ν_{max} (ATR)/cm^{-1} 2922 (C-H alkane), 1698 (C=O carbonyl), 1589 (C=C aromatic), 1439 (-C-H bending).

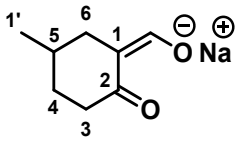
2-Thioxo-1,2,5,6,7,8,9,10,11,12-decahydrocyclodeca[*b*]pyridine-3-carbonitrile 3d



The reaction was carried out following General Procedure **B** using sodium enolate **2d** (1.00 g, 5.52 mmol), cyanothioacetamide (0.55 g, 5.52 mmol), water (5.4 mL), piperidinium acetate solution (0.49 mL) and glacial acetic acid (0.75 mL) for 48 h to give the *title compound* **3d** (1.20 g, 88%) as a brown solid. m.p. >230 °C, decomp. (lit. m.p. 250 °C).[4] δ_H (400 MHz, $(CD_3)_2SO$) 1.10-1.17 (4H, m, H-8 and

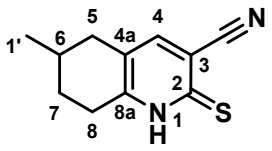
H-9), 1.42 (4H, d, J = 5.3 Hz, H-7 and H-10), 1.74-1.83 (4H, m, H-6 and H-11), 2.64 (2H, t, J = 6.5 Hz, H-5), 2.84 (2H, t, J = 6.5 Hz, H-12), 8.02 (1H, s, H-4), 13.82 (1H, br s, NH). The ^{1}H NMR values were in agreement with the literature values.[4]

Sodium (*E*)- and (*Z*)-(5-methyl-2-oxocyclohexylidene)methanolate 2e



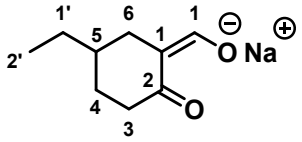
The reaction was carried out following General Procedure **A** using 4-methyl cyclohexanone **1e** (0.50 g, 4.46 mmol), ethyl formate (0.36 mL, 4.46 mmol), sodium metal (0.10 g, 4.46 mmol) in dry ether (24 mL) and absolute ethanol (0.01 mL) for 24 h to give the *title compound* **2e** (0.44 g, 73%) as a yellow solid. m.p. >230 °C, decomp. δ_H (400 MHz, (D_2O) 1.01 (3H, d, J = 6.3 Hz, H-1'), 1.32-1.40 (1H, m, H-5), 1.70-1.77 (2H, m, H-6), 1.78-1.81 (1H, m, H-3$_A$), 2.25-2.29 (2H, m, H-4), 2.40-2.45 (1H, m, H-3$_B$), 8.48 and 9.08 (1H, s, *E/Z* isomers, 1-CH). δ_C (100 MHz, D_2O) 20.9 (C-1'), 28.4 (C-5), 30.2 (C-3), 30.4 (C-6), 36.1 (C-4), 111.7 (C-1), 171.1 and 181.1 (*E*/*Z* isomers, 1-CH), 198.9 (C-2). ν_{max} (ATR)/cm^{-1} 2934 (C-H alkane), 1696 (C=O carbonyl), 1581 (C=C aromatic), 1482 (C-H bending).

6-Methyl-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile 3e



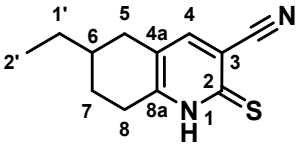
The reaction was carried out following General Procedure **B** using sodium enolate **2e** (0.40 g, 2.87 mmol), cyanothioacetamide (0.29 g, 2.87 mmol), water (2.8 mL), piperidinium acetate solution (0.25 mL), and glacial acetic acid (0.39 mL) for 48 h to give the *title compound* **3e** (0.39 g, 65%) as a brown solid. m.p. >230 °C, decomp. δ_H (400 MHz, (CD_3)$_2$SO) 0.97 (3H, d, J = 6.4 Hz, H-1'), 1.60-1.65 (2H, m, H-8), 2.60 (1H, dd, J = 12.1, 5.5 Hz, H-6), 2.75-2.78 (2H, m, H-7), 3.01 (2H, t, J = 5.5 Hz, H-5), 7.84 (1H, s, H-4), 13.88 (1H, br s, NH). δ_C (100 MHz, (CD_3)$_2$SO) 20.9 (C-1'), 26.5 (C-8), 27.3 (C-7), 33.7 (C-6), 43.8 (C-5), 113.4 (C-3), 115.9 (CN), 121.2 (C-4a), 145.7 (C-4), 156.7 (C-8a), 175.8 (C-2). ν_{max} (ATR)/cm^{-1} 3182 (N-H amine), 2924 (C-H aromatic), 2875 (C-H alkane), 2207 (C-N nitrile), 1592 (C=C aromatic), 1377 (-C-H bending), 1174 (C-N aliphatic). *m/z* (ESI$^+$): 227 (MNa$^+$, 100%). HRMS (ESI$^+$) found (MNa$^+$): 227.0615 $C_{11}H_{12}N_2NaS$ requires 227.0613.

Sodium (*E*)- and (*Z*)-(5-ethyl-2-oxocyclohexylidene)methanolate 2f



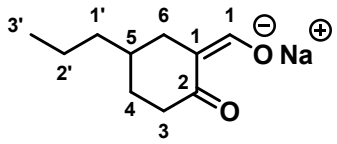
The reaction was carried out following General Procedure **A** using 4-ethylcyclohexanone **1f** (1.00 g, 7.92 mmol), ethyl formate (0.64 mL, 7.92 mmol), sodium metal (0.18 g, 7.92 mmol), dry ether (43 mL) and absolute ethanol (0.02 mL) for 24 h to give the *title compound* **2f** (1.10 g, 90%) as a yellow solid. m.p. >230 °C, decomp. δ_H (400 MHz, D_2O) 0.94 (3H, t, J = 7.2 Hz, H-2'), 1.31-1.45 (4H, m, H-1', H-5 and 4-H_A), 1.74 (1H, dd, J = 15.8, 11.0 Hz, 6-H_A), 1.83-1.88 (1H, m, 4-H_B), 2.25-2.29 (2H, m, H-3), 2.47 (1H, dd, J = 15.8, 5.1 Hz, 6-H_B), 8.48 and 9.09 (1H, s, *E*/*Z* isomers, 1-CH). δ_C (100 MHz, D_2O) 11.1 (C-2'), 27.8 (C-6), 28.1 (C-4), 28.3 (C-1'), 35.2 (C-5), 36.1 (C-3), 111.8 (C-1), 171.1 and 181.2 (*E*/*Z* isomers, 1-CH), 199.1 (C-2). ν_{max} (ATR)/cm^{-1} 2925 (C-H alkane), 1620 (C=O carbonyl), 1596 (C=C aromatic), 1488 (-C-H bending).

6-Ethyl-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile 3f



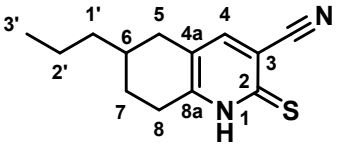
The reaction was carried out following General Procedure **B** using enolate **2f** (1.07 g, 6.07 mmol), cyanothioacetamide (0.61 g, 6.07 mmol), water (6.0 mL), piperidinium acetate solution (0.53 mL) and glacial acetic acid (0.83 mL) for 48 h to give the *title compound* **3f** (1.00 g, 75%) as a brown solid. m.p. >230 °C, decomp. δ_H (400 MHz, $(CD_3)_2SO$) 0.90 (3H, t, J = 7.4 Hz, H-2'), 1.28-1.35 (3H, m, H-1', and 7-H_A), 1.49-1.54 (1H, m, H-6), 1.84-1.88 (1H, m, 7-H_B), 2.09 (1H, dd, J = 15.8, 10.9 Hz, 5-H_A), 2.61-2.84 (3H, m, H-8 and 5-H_B), 7.87 (1H, s, H-4), 13.91 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 11.2 (C-2'), 26.3 (C-7), 26.5 (C-8), 27.8 (C-1'), 31.5 (C-5), 33.9 (C-6), 113.4 (C-3), 117.1 (CN), 121.2 (C-4a), 145.8 (C-4), 153.0 (C-8a), 175.4 (C-2). ν_{max} (ATR)/cm^{-1} 3107 (N-H amine), 2933 (C-H aromatic), 2875 (C-H alkane), 2219 (C-N nitrile), 1604 (C=C aromatic), 1459 (-C-H bending), 1171 (C-N aliphatic). *m/z* (ESI$^+$): 241 (MNa+, 100%). HRMS (ESI$^+$) found (MNa+): 241.0763 $C_{12}H_{14}N_2NaS$ requires 241.0770.

Sodium (*E*)- and (*Z*)-(2-oxo-5-propylcyclohexylidene)methanolate 2g



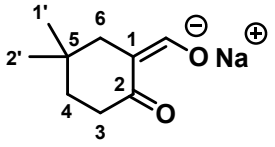
The reaction was carried out following General Procedure **A** using 4-propylcyclohexanone **1g** (0.60 g, 4.28 mmol), ethyl formate (0.35 mL, 4.28 mmol), sodium metal (0.10 g, 4.28 mmol), dry ether (19 mL) and absolute ethanol (0.01 mL) for 24 h to give the *title compound* **2g** (0.76 g, 94%) as a yellow solid. m.p. >230 °C, decomp. δ_H (400 MHz, D_2O) 0.91 (3H, t, J = 7.3 Hz, H-3'), 1.29-1.40 (5H, m, H-1', H-2' and 4-H_A), 1.51-1.58 (1H, m, H-5), 1.73 (1H, dd, J = 15.8, 11.0 Hz, 6-H_A), 1.80-1.85 (1H, m, 4-H_B), 2.24-2.28 (2H, m, H-3), 2.45 (1H, dd, J = 15.8, 5.1 Hz, 6-H_B), 8.47 and 9.08 (1H, s, *E*/*Z* isomers, 1-CH). δ_C (100 MHz, D_2O) 13.6 (C-3'), 19.7 (C-2'), 28.2 (C-6), 28.4 (C-4), 32.8 (C-5), 36.1 (C-3), 37.7 (C-1'), 111.9 (C-1), 171.1 and 181.2 (*E*/*Z* isomers, 1-CH), 199.1 (C-2). ν_{max} (ATR)/cm^{-1} 2936 (C-H alkane), 1636 (C=O carbonyl), 1597 (C=C aromatic), 1490 (-C-H bending).

6-Propyl-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile 3g



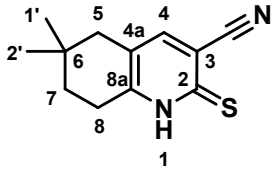
The reaction was carried out following General Procedure **B** using enolate **2g** (0.70 g, 3.68 mmol), cyanothioacetamide (0.37 g, 3.68 mmol), water (3.6 mL), piperidinium acetate solution (0.32 mL) and glacial acetic acid (0.50 mL) for 48 h to give the *title compound* **3g** (0.60 g, 70%) as a brown solid. m.p. >230 °C, decomp. δ_H (400 MHz, $(CD_3)_2SO$) 0.87 (3H, t, J = 7.3 Hz, H-3'), 1.23-1.36 (5H, m, H-1', H-2' and 7-H_A), 1.59-1.64 (1H, m, H-6), 1.84-1.86 (1H, m, 7-H_B), 2.09 (1H, dd, J = 15.8, 10.9 Hz, 5-H_A), 2.59-2.64 (1H, m, 5-H_B), 2.69-2.81 (3H, m, H-8), 7.85 (1H, s, H-4), 13.90 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 14.1 (C-3'), 19.4 (C-2'), 26.5 and 26.6 (C-7 and C-8), 31.8 and 31.9 (C-5 and C-6), 37.3 (C-1'), 113.4 (C-3), 117.1 (CN), 121.2 (C-4a), 145.7 (C-4), 152.9 (C-8a), 175.4 (C-2). ν_{max} (ATR)/cm^{-1} 3189 (N-H amine), 3120 (C-H aromatic), 2870 (C-H alkane), 2218 (C-N nitrile), 1606 (C=C aromatic), 1488 (-C-H bending), 1173 (C-N aliphatic). *m/z* (ESI$^+$): 255 (MNa+, 100%). HRMS (ESI$^+$) found (MNa+): 255.0921 $C_{13}H_{16}N_2NaS$ requires 255.0926.

Sodium (*E*)- and (*Z*)-(5,5-dimethyl-2-oxocyclohexylidene)methanolate 2h



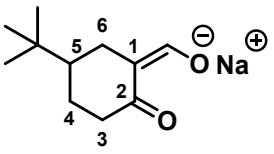
The reaction was carried out following General Procedure **A** using 4,4-dimethylcyclohexan-1-one **1h** (0.50 g, 3.96 mmol), ethyl formate (0.29 mL, 3.96 mmol), sodium metal (0.09 g, 3.96 mmol), dry ether (21 mL) and absolute ethanol (0.01 mL) for 24 h to give the *title compound* **2h** (0.52 g, 85%) as a yellow solid. m.p. >230 °C, decomp. δ_H (400 MHz, D_2O) 0.97 (6H, s, H-1' and H-2'), 1.54 (2H, t, J = 6.8 Hz, H-4), 2.04 (2H, s, H-6), 2.26 (2H, t, J = 6.8 Hz, H-3), 8.48 and 9.11 (1H, s, *E*/*Z* isomers, 1-CH). δ_C (100 MHz, D_2O) 27.1 (C-1' and C-2'), 28.1 (C-3), 33.5 (C-5), 34.8 (C-4), 35.5 (C-6), 111.4 (C-1), 171.1 and 181.6 (*E*/*Z* isomers, 1-CH), 198.5 (C-2). ν_{max} (ATR)/cm^{-1} 2953 (C-H alkane), 1661 (C=O carbonyl), 1578 (C=C aromatic), 1446 (-C-H bending).

6,6-Dimethyl-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile 3h



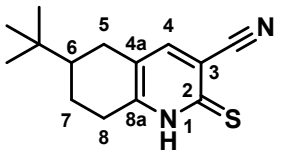
The reaction was carried out following General Procedure **B** using sodium enolate **2h** (0.50 g, 3.26 mmol), cyanothioacetamide (0.33 g, 3.26 mmol), water (3.2 mL), piperidinium acetate solution (0.29 mL) and glacial acetic acid (0.44 mL) for 48 h to give the *title compound* **3h** (0.48 g, 68%) as a brown solid. m.p. >230 °C, decomp. δ_H (400 MHz, $(CD_3)_2SO$) 0.91 (6H, s, H-1' and H-2'), 1.50 (2H, t, J = 6.7 Hz, H-7), 2.29 (2H, s, H-5), 2.71 (2H, t, J = 6.7 Hz, H-8), 7.85 (1H, s, H-4), 13.94 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 24.1 (C-8), 27.3 (C-1' and C-2'), 28.6 (C-6), 33.0 (C-7), 38.9 (C-5), 113.4 (C-3), 117.1 (CN), 120.7 (C-4a), 146.2 (C-4), 151.9 (C-8a), 175.3 (C-2). ν_{max} (ATR)/cm^{-1} 3183 (N-H amine), 2950 (C-H aromatic), 2897 (C-H alkane), 2225 (C-N nitrile), 1591 (C=C aromatic), 1505 (-C-H bending), 1178 (C-N aliphatic). *m/z* (ESI$^+$): 241 (MNa$^+$, 100%). HRMS (ESI$^+$) found (MNa$^+$): 241.0777 $C_{12}H_{14}N_2NaS$ requires 241.0770.

Sodium (*E*)- and (*Z*)-(5-(*tert*-butyl)-2-oxocyclohexylidene)methanolate 2i



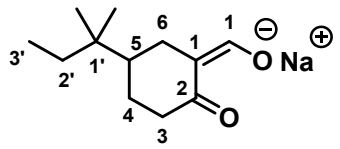
The reaction was carried out following General Procedure **A** using 4-ethylcyclohexanone **1i** (0.60 g, 3.89 mmol), ethyl formate (0.31 mL, 3.89 mmol), sodium metal (0.09 g, 3.89 mmol), dry ether (18 mL) and absolute ethanol (0.01 mL) for 24 h to give the *title compound* **2i** (0.16 g, 77%) as a yellow solid. m.p. >230 ºC, decomp. δ_H (400 MHz, D_2O) 0.91 (9H, s, 3 × *tert*-butyl CH_3), 1.20-1.34 (2H, m, 4-H_A and H-5), 1.83 (1H, dd, J = 15.8. 11.0 Hz, 6-H_A), 1.88-1.92 (1H, m, 4-H_B), 2.24-2.28 (2H, m, H-3), 2.41-2.46 (1H, m, 6-H_B), 8.47 and 9.09 (1H, s, *E*/*Z* isomers, 1-CH). δ_C (100 MHz, D_2O) 23.1 (C-6), 23.7 (C-4), 26.7 (3 × *tert*-butyl CH_3), 31.7 (*tert*-butyl quat. C), 37.5 (C-3), 44.1 (C-5), 112.2 (C-1), 171.1 and 181.3 (*E*/*Z* isomers, 1-CH), 199.0 (C-2). ν_{max} (ATR)/cm^{-1} 2938 (C-H alkane), 1626 (C=O carbonyl), 1596 (C=C aromatic), 1490 (-C-H bending).

6-(*tert*-Butyl)-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile 3i



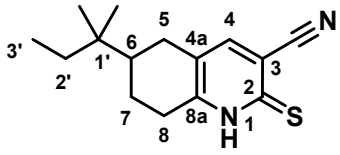
The reaction was carried out following General Procedure **B** using enolate **2i** (0.58 g, 2.84 mmol), cyanothioacetamide (0.28 g, 2.84 mmol), water (2.8 mL), piperidinium acetate solution (0.25 mL) and glacial acetic acid (0.39 mL) for 48 h to give the *title compound* **3i** (0.58 g, 83%) as a brown solid. m.p. >230 ºC, decomp. δ_H (400 MHz, $(CD_3)_2SO$) 0.89 (9H, s, 3 × *tert*-butyl CH_3), 1.23-1.39 (2H, m, 7-H_A and H-6), 1.91-1.95 (1H, m, 7-H_B), 2.23 (1H, dd, J = 15.8, 11.0 Hz, 5-H_A), 2.58-2.68 (2H, m, 8-H_A and 5-H_B), 2.83-2.90 (1H, m, 8-H_B), 7.87 (1H, s, H-4), 13.90 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 22.0 (C-7), 26.9 (3 × *tert*-butyl CH_3), 27.1 (C-5), 27.9 (C-8), 32.0 (*tert*-butyl quat. C), 42.7 (C-6), 113.3 (C-3), 117.2 (CN), 121.9 (C-4a), 146.1 (C-4), 153.0 (C-8a), 175.4 (C-2). ν_{max} (ATR)/cm^{-1} 2953 (C-H aromatic), 2869 (C-H alkane), 2223 (C-N nitrile), 1601 (C=C aromatic), 1472 (-C-H bending), 1171 (C-N aliphatic). *m/z* (ESI^+): 269 (MNa+, 100%). HRMS (ESI^+) found (MNa+): 269.1079 $C_{14}H_{18}N_2NaS$ requires 269.1083.

Sodium (*E*)- and (*Z*)-(2-oxo-5-(*tert*-pentyl)cyclohexylidene)methanolate 2j



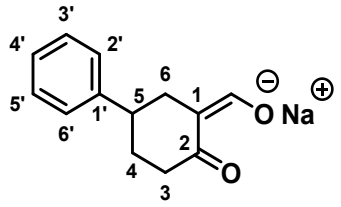
The reaction was carried out following General Procedure **A** using 4-(*tert*-pentyl)cyclohexanone **1j** (0.50 g, 2.97 mmol), ethyl formate (0.24 mL, 2.97 mmol), sodium metal (0.07 g, 2.97 mmol) in dry ether (16 mL) and absolute ethanol (0.01 mL) for 24 h to give the *title compound* **2j** (0.44 g, 77%) as a yellow solid. m.p. >230 °C, decomp. δ_H (400 MHz, D_2O) 0.83 (9H, s, H-3' and 2 × *tert*-pentyl CH_3), 1.25-1.36 (4H, m, H-2', H-5 and H-4_A), 1.78-1.84 (2H, m, H-6_A and H-4_B), 2.21-2.25 (2H, m, H-3), 2.35 (1H, dd, J = 10.9, 4.1 Hz, H-6_B) 8.44 and 9.05 (1H, s, *E*/*Z* isomers, 1-CH). δ_C (100 MHz, D_2O) 7.47 (C-3'), 22.5 (C-6), 23.2 (C-4), 23.3 and 23.4 (2 × *tert*-pentyl CH_3), 32.2 (C-2'), 33.9 (C-1'), 37.4 (C-3), 40.9 (C-5), 171.0 and 181.1 (*E*/*Z* isomers, 1-CH), 199.0 (C-2). ν_{max} (ATR)/cm^{-1} 2961 (C-H alkane), 1717 (C=O carbonyl), 1569 (C=C aromatic), 1422 (-C-H bending).

6-(*tert*-Pentyl)-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile 3j



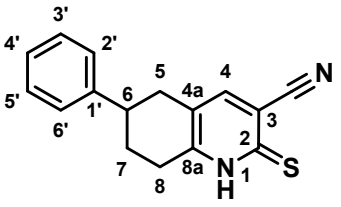
The reaction was carried out following General Procedure **B** using sodium enolate **2j** (0.40 g, 2.05 mmol), cyanothioacetamide (0.21 g, 2.05 mmol), water (2.0 mL), piperidinium acetate solution (0.18 mL) and glacial acetic acid (0.28 mL) for 48 h to give the *title compound* **3j** (0.38 g, 72%) as a brown solid. m.p. >230 °C, decomp. δ_H (400 MHz, $(CD_3)_2SO$) 0.78-0.84 (9H, m, H-3' and 2 × *tert*-pentyl CH_3), 1.22-1.34 (4H, m, H-2', H-6 and H-7_A), 1.87-1.92 (1H, m, H-7_B), 2.22-2.29 (1H, m, H-5_A), 2.54-2.57 (1H, m, H-5_B), 2.66-2.71 (1H, m, H-8_A), 2.88 (1H, dd, J = 14.8, 3.9 Hz, H-8_B) 7.90 (1H, s, H-4), 13.91 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 7.98 (C-3'), 21.6 (C-7), 23.5 and 23.6 (2 × *tert*-pentyl CH_3), 26.7 (C-5), 27.8 (C-8), 31.9 (C-2'), 34.3 (C-1'), 113.3 (C-3), 117.2 (CN), 121.9 (C-4a), 146.1 (C-4), 153.0 (C-8a), 175.3 (C-2). C-6 not observed. ν_{max} (ATR)/cm^{-1} 3185 (N-H amine), 2957 (C-H aromatic), 2872 (C-H alkane), 2223 (C-N nitrile), 1599 (C=C aromatic), 1506 (-C-H bending), 1174 (C-N aliphatic). *m/z* (ESI^+): 283 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 283.1219 $C_{15}H_{20}N_2NaS$ requires 283.1239.

Sodium (*E*)- and (*Z*)-(2-oxo-5-phenylcyclohexylidene)methanolate 2k



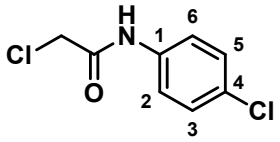
The reaction was carried out following General Procedure **A** using 4-phenyl cyclohexanone **1k** (1.00 g, 5.74 mmol), ethyl formate (0.46 mL, 5.74 mmol), sodium metal (0.13 g, 5.74 mmol) in dry ether (30 mL) and absolute ethanol (0.01 mL) for 24 h to give the *title compound* **2k** (0.97 g, 84%) as a yellow solid. m.p. >230 °C, decomp. δ_H (400 MHz, D_2O) 1.82-1.89 (2H, m, H-4), 2.19-2.26 (1H, m, 3-H_A), 2.31-2.41 (2H, m, H-6), 2.61-2.66 (1H, m, 3-H_B), 2.78-2.86 (1H, m, H-5), 7.34-7.41 (5H, m, H-2', H-3', H-4', H-5' and H-6'), 8.48 and 9.16 (1H, s, *E/Z* isomers, 1-CH). δ_C (100 MHz, D_2O) 29.2 (C-4), 29.8 (C-5), 36.2 (C-2), 39.6 (C-3), 57.4 (C-6), 111.7 (C-1), 126.3 (C-4'), 127.0 (C-2' and C-6' or C-3' and C-5'), 128.7.6 (C-2' and C-6' or C-3' and C-5'), 147.1 (C-1'), 171.1 and 181.5 (*E*/*Z* isomers, 1-CH), 197.7 (C-2). ν_{max} (ATR)/cm^{-1} 2932 (C-H alkane), 1695 (C=O carbonyl), 1581 (C=C aromatic), 1493 (-C-H bending).

6-Phenyl-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile 3k



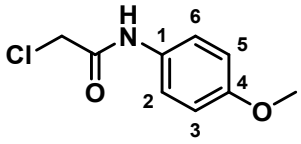
The reaction was carried out following General Procedure **B** using sodium enolate **2k** (0.90 g, 4.47 mmol), cyanothioacetamide (0.45 g, 4.47 mmol), water (4.8 mL), piperidinium acetate solution (0.39 mL), and glacial acetic acid (0.61 mL) for 48 h to give the *title compound* **3k** (1.10 g, 92%) as a brown solid. m.p. >230 °C, decomp. δ_H (400 MHz, $(CD_3)_2SO$) 1.83-2.01 (2H, m, H-8), 2.57-2.81 (2H, m, H-5), 2.85-2.89 (2H, m, H-7), 2.87-2.95 (1H, m, H-6), 7.21-7.34 (5H, m, H-2' to H-6'), 7.92 (1H, s, H-4), 13.99 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 27.2 (C-7), 27.5 (C-8), 33.3 (C-5), 38.3 (C-6), 113.5 (C-3), 117.1 (CN), 121.4 (C-4a), 126.4 (C-4'), 126.7 (C-3' and C-5' or C-2' or C-6'), 128.5 (C-3' and C-5' or C-2' or C-6'), 144.9 (C-1'), 145.7 (C-4), 152.5 (C-8a), 175.6 (C-2). ν_{max} (ATR)/cm^{-1} 3189 (N-H amine), 3025 (C-H aromatic), 2889 (C-H alkane), 2228 (C-N nitrile), 1596 (C=C aromatic), 1493 (-C-H bending), 1177 (C-N aliphatic). *m/z* (ESI^+): 289 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 289.0795 $C_{16}H_{14}N_2NaS$ requires 289.0770.

2-Chloro-*N*-(4-chlorophenyl)acetamide 4



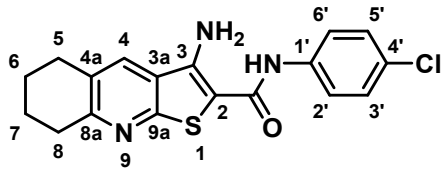
The reaction was carried out following General Procedure **C** using 4-chloroaniline (1.00 g, 7.84 mmol), chloroacetyl chloride (0.97 g, 7.62 mmol) and triethylamine (1.21 mL, 8.62 mmol) in CH_2Cl_2 (35 mL) to give the *title compound* **4** (1.16 g, 73%) as a dark green solid. m.p. 170-172 °C. (lit. m.p. 168-170 °C)[6]. δ_H (400 MHz, $CDCl_3$) 4.19 (2H, s, $COCH_2Cl$), 7.31 (2H, d, J = 8.8 Hz, H-3 and H-5), 7.51 (2H, d, J = 8.8 Hz, H-2 and H-6), 8.31 (1H, br s, NH). The ^{1}H NMR values were in agreement with the literature values.[6]

2-Chloro-*N*-(4-methoxyphenyl)acetamide 5



The reaction was carried out following General Procedure **C** using *p*-anisidine (0.50 g, 4.06 mmol), chloroacetyl chloride (0.39 mL, 4.87 mmol) and triethylamine (0.68 mL, 4.87 mmol) in CH_2Cl_2 (20.0 mL) to give the *title compound* **5** (0.84 g, quant.) as a white solid. m.p. 112- 115 °C. (lit. m.p. 117-119 °C).[7] δ_H (400 MHz, $CDCl_3$) 3.80 (3H, s, CH_2), 4.17 (2H, s, CH_2), 6.88 (2H, t, J = 9.0 Hz, H-3 and H-5), 7.44 (2H, d, J = 9.0 Hz, H-2 and H-6), 8.22 (1H, br s, NH). The ^{1}H NMR values were in agreement with the literature values.[7]

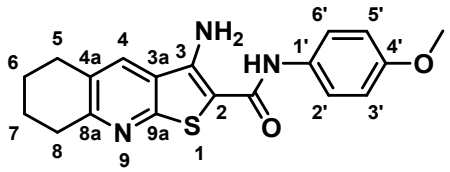
3-Amino-*N*-(4'-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 6a



The reaction was carried out following General Procedure **D** using carbonitrile **3a** (0.25 g, 1.31 mmol), 2-chloro-*N*-(4-chlorophenyl)acetamide **4** (0.27 g, 1.31 mmol) and anhydrous sodium carbonate (0.28 g, 2.62 mmol) in absolute ethanol (5.24 mL) for 48 h and then purified by flash chromatography (1:1 petroleum ether/EtOAc) to give the *title compound* **6a** (0.20 g, 43%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.85 (4H, m, H-6 and H-7), 2.89 (2H, t, J = 6.3 Hz, H-5), 2.96 (2H, t, J = 6.3 Hz, H-8), 7.35 (2H, br s, NH_2), 7.37 (2H, d, J = 8.9 Hz, H-3' and H-5'), 7.75 (2H, d, J = 8.9 Hz, H-2' and H-6'), 8.20 (1H, s, H-4), 9.48 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 22.3 (C-7), 22.4 (C-6), 28.3

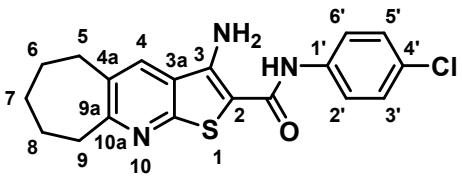
(C-5), 32.5 (C-8), 95.3 (C-2), 122.5 (C-2' and C-6'), 124.3 (C-3a), 126.9 (C-4'), 128.2 (C-3' and C-5'), 130.9 (C-4), 138.1 (C-1'), 147.2 (C-3), 156.0 (C-4a), 159.2 (C-8a), 164.1 (C-9a), 206.4 (2-CONH). ν_{max} (ATR)/cm^{-1} 3420 (N-H amide), 3315 (N-H amine), 2923 (C-H aromatic), 2895 (C-H aliphatic), 1605 (C=O amide), 1586 (C=C aromatic), 1486 (C-H bending), 1244 (C-N aromatic), 1091 (C-N aliphatic) 811 (C-Cl). *m/z* (ESI$^+$): 382 (^{37}ClMNa$^+$, 40%), 380 (^{35}ClMNa$^+$, 100%). HRMS (ESI$^+$) found (^{37}ClMNa$^+$): 382.0591 $C_{18}H_{16}{}^{37}ClN_3NaOS$ requires 382.0569. Found (^{35}ClMNa$^+$): 380.0589 $C_{18}H_{16}{}^{35}ClN_3NaOS$ requires 380.0595.

3-Amino-*N*-(4'-methoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 7a



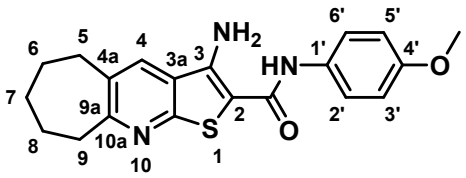
The reaction was carried out following General Procedure **D** using carbonitrile **3a** (0.25 g, 1.31 mmol), 2-chloro-*N*-(4-methoxyphenyl)acetamide **5** (0.26 g, 1.31 mmol) and anhydrous sodium carbonate (0.28 g, 2.62 mmol) in absolute ethanol (5.24 mL) for 48 h and then purified by flash chromatography (1:1 petroleum ether/EtOAc) to give the *title compound* **7a** (0.38 g, 82%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.84 (4H, m, H-6 and H-7), 2.89 (2H, t, *J* = 6.3 Hz, H-5), 2.96 (2H, t, *J* = 6.3 Hz, H-8), 3.75 (3H, s, 4'-OCH_3), 6.90 (2H, d, *J* = 9.1 Hz, H-3' and H-5'), 7.25 (2H, br s, NH_2), 7.57 (2H, d, *J* = 9.1 Hz, H-2' and H-6'), 8.17 (1H, s, H-4), 9.24 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 22.3 (C-7), 22.5 (C-6), 28.3 (C-5), 32.5 (C-8), 55.1 (4'-OCH_3), 95.9 (C-2), 113.5 (C-3' and C-5'), 122.8 (C-2' and C-6'), 124.5 (C-3a), 128.2 (C-4a), 130.7 (C-4), 131.9 (C-1'), 146.4 (C-3), 155.4 (C-4'), 155.9 (C-8a), 158.9 (C-9a), 163.9 (2-CONH). ν_{max} (ATR)/cm^{-1} 3420 (N-H amide), 3314 (N-H amine), 2944 (C-H aromatic), 2836 (C-H aliphatic), 1597 (C=O amide), 1510 (C=C aromatic), 1495 (-C-H bending), 1315 (C-N aromatic), 1106 (C-O ether), 1039 (C-N aliphatic). *m/z* (ESI$^+$): 376 (MNa$^+$, 100%). HRMS (ESI$^+$) found (MNa$^+$): 376.1091 $C_{19}H_{19}N_3NaO_2S$ requires 376.1091.

3-Amino-*N*-(4'-chlorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]thieno[3,2-*e*]pyridine-2-carboxamide 6b



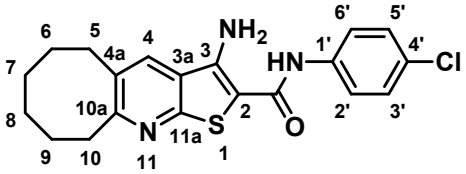
The reaction was carried out following General Procedure **D** using carbonitrile **3b** (0.25 g, 1.22 mmol), 2-chloro-*N*-(4-chlorophenyl)acetamide **4** (0.25 g, 1.22 mmol) and anhydrous sodium carbonate (0.26 g, 2.45 mmol) in absolute ethanol (4.80 mL) for 48 h to give the *title compound* **6b** (0.33 g, 74%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.67 (4H, s, H-6 and H-7), 1.86 (2H, s, H-8), 2.88 (2H, d, *J* = 9.5 Hz, H-5), 3.09 (2H, d, *J* = 9.5 Hz, H-9), 7.33 (2H, br s, NH_2), 7.37 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 7.76 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 8.21 (1H, s, H-4), 9.50 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 26.2 (C-7), 27.9 (C-6), 31.6 (C-8), 34.5 (C-5), 38.8 (C-9), 95.7 (C-2), 122.4 (C-2' and C-6'), 124.2 (C-3a), 126.8 (C-4'), 128.2 (C-3' and C-5'), 130.4 (C-4), 134.1 (C-4a), 138.1 (C-1'), 147.3 (C-3), 155.5 (C-9a), 164.0 (2-CONH), 164.9 (10a). ν_{max} (ATR)/cm^{-1} 3431 (N-H amide), 3317 (N-H amine), 2934 (C-H aromatic), 2842 (C-H aliphatic), 1603 (C=O amide), 1584 (C=C aromatic), 1487 (-C-H bending), 1234 (C-N aromatic), 1090 (C-N aliphatic) 806 (C-Cl). *m/z* (ESI^+): 396 ($^{37}ClMNa^+$, 40%), 394 ($^{35}ClMNa^+$, 100%). HRMS (ESI^+) found ($^{37}ClMNa^+$): 396.0751 $C_{19}H_{18}{}^{37}ClN_3NaOS$ requires 396.0726. Found ($^{35}ClMH^+$): 394.0751 $C_{19}H_{18}{}^{35}ClN_3NaOS$ requires 394.0751.

3-Amino-*N*-(4'-methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]thieno[3,2-*e*]pyridine-2-carboxamide 7b



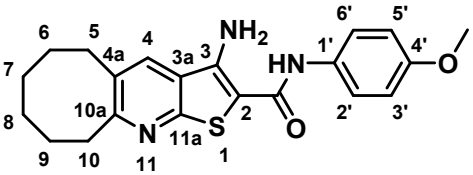
The reaction was carried out following General Procedure **D** using carbonitrile **3b** (0.22 g, 1.08 mmol), 2-chloro-*N*-(4-methoxyphenyl)acetamide **5** (0.22 g, 1.08 mmol) and anhydrous sodium carbonate (0.23 g, 2.15 mmol) in absolute ethanol (4.32 mL) for 48 h to give the *title compound* **7b** (0.30 g, 75%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.67 (4H, s, H-6 and H-7), 1.86 (2H, s, H-8), 2.88 (2H, d, *J* = 9.7 Hz, H-5), 3.09 (2H, d, *J* = 9.7 Hz, H-9), 3.75 (3H, s, 4'-OCH_3), 6.90 (2H, d, *J* = 9.0 Hz, H-3' and H-5'), 7.23 (2H, br s, NH_2), 7.58 (2H, d, *J* = 9.0 Hz, H-2' and H-6'), 8.19 (1H, s, H-4), 9.26 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 26.2 (C-7), 27.9 (C-6), 30.7 (C-8), 31.6 (C-5), 34.5 (C-9), 55.1 (4'-OCH_3), 96.3 (C-2), 113.5 (C-3' and C-5'), 122.8 (C-3' and C-5'), 124.4 (C-3a), 130.3 (C-4), 131.9 (C-1'), 134.0 (C-4a), 146.6 (C-3), 155.3 (C-4'), 155.4 (C-10a), 163.8 (2-CONH), 164.6 (9a). ν_{max} (ATR)/cm^{-1} 3434 (N-H amide), 3320 (N-H amine), 2929 (C-H aromatic), 2843 (C-H aliphatic), 1599 (C=O amide), 1508 (C=C aromatic), 1495 (-C-H bending), 1235 (C-N aromatic), 1039 (C-O ether), 1039 (C-N aliphatic). *m/z* (ESI^+): 390 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 390.1255 $C_{20}H_{21}N_3NaO_2S$ requires 390.1247.

3-Amino-*N*-(4'-chlorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]thieno[3,2-*e*]pyridine-2-carboxamide 6c



The reaction was carried out following General Procedure **D** using carbonitrile **3c** (0.25 g, 1.15 mmol), 2-chloro-*N*-(4-chlorophenyl)acetamide **4** (0.23 g, 1.15 mmol) and anhydrous sodium carbonate (0.24 g, 2.29 mmol) in absolute ethanol (4.60 mL) for 48 h and then purified by flash chromatography (1:1 petroleum ether/EtOAc) to give the *title compound* **6c** (0.85 g, 60%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.33 (4H, s, H-7 and H-8), 1.71 (4H, d, *J* = 6.3 Hz, H-6 and H-9), 2.87 (2H, t, *J* = 6.3 Hz, H-5), 3.01 (2H, t, *J* = 6.3 Hz, H-10), 7.33 (2H, br s, NH_2), 7.36 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 7.74 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 8.22 (1H, s, H-4), 9.47 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 25.4 (C-7 or C-8), 25.5 (C-7 or C-8), 30.5 (C-6 or C-9), 31.2 (C-5), 32.1 (C-6 or C-9), 34.3 (C-10), 95.6 (C-2), 122.5 (C-2' and C-6'), 124.7 (C-3a), 126.9 (C-4'), 128.2 (C-3' and C-5'), 130.8 (C-4), 132.3 (C-4a), 138.1 (C-1'), 147.2 (C-3), 156.4 (C-11a), 162.9 (C-10a), 164.1 (2-CONH). ν_{max} (ATR)/cm^{-1} 3390 (N-H amide), 3296 (N-H amine), 2923 (C-H aromatic), 2855 (C-H aliphatic), 1645 (C=O amide), 1592 (C=C aromatic), 1487 (-C-H bending), 1310 (C-N aromatic), 1089 (C-N aliphatic) 821 (C-Cl). *m/z* (ESI^+): 388 ($^{37}ClMH^+$, 40%), 386 ($^{35}ClMH^+$, 100%). HRMS (ESI^+) found ($^{37}ClMH^+$): 388.1055 $C_{20}H_{21}{}^{37}ClN_3OS$ requires 388.1064. Found ($^{35}ClMH^+$): 386.1074 $C_{20}H_{21}{}^{35}ClN_3OS$ requires 386.1088.

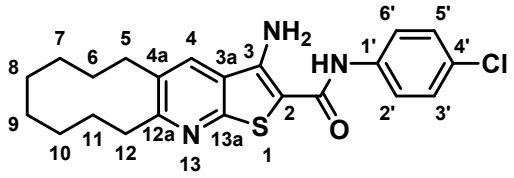
3-Amino-*N*-(4'-methoxyphenyl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]thieno[3,2-*e*]pyridine-2-carboxamide 7c



The reaction was carried out following General Procedure **D** using carbonitrile **3c** (0.25 g, 1.15 mmol), 2-chloro-*N*-(4-methoxyphenyl)acetamide **5** (0.23 g, 1.15 mmol) and anhydrous sodium carbonate (0.24 g, 2.29 mmol) in absolute ethanol (4.60 mL) for 48 h and then purified by flash chromatography (1:1 petroleum ether/EtOAc) to give the *title compound* **7c** (0.90 g, 64%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.34 (4H, s, H-7 and H-8), 1.72 (4H, s, H-6 and H-9), 2.87 (2H, t, *J* = 5.5 Hz, H-5), 3.01 (2H, t, *J* = 5.5 Hz, H-10), 3.75 (3H, s, 4'-OCH_3), 6.90 (2H, d, *J* = 8.4 Hz, H-3' and H-5'),

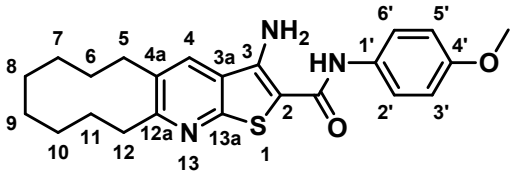
7.28 (2H, br s, NH_2), 7.59 (2H, d, J = 8.4 Hz, H-2' and H-6'), 8.25 (1H, s, H-4), 9.27 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 25.4 (C-7 or C-8), 25.5 (C-7 or C-8), 30.5 (C-6 or C-9), 31.2 (C-5), 32.1 (C-6 or C-9), 34.3 (C-10), 55.1 (4'-OCH_3), 96.2 (C-2), 113.5 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.9 (C-3a), 130.7 (C-4), 131.9 (C-4a), 132.1 (C-1'), 146.5 (C-3), 155.4 (C-4'), 156.3 (C-11a), 162.5 (C-10a), 163.8 (2-CONH). ν_{max} (ATR)/cm^{-1} 3437 (N-H amide), 3324 (N-H amine), 2962 (C-H aromatic), 2916 (C-H aliphatic), 1604 (C=O amide), 1586 (C=C aromatic), 1487 (-C-H bending), 1308 (C-N aromatic), 1243 (C-O ether), 1073 (C-N aliphatic). *m/z* (ESI^+): 382 (MH^+, 100%). HRMS (ESI^+) found (MH^+): 382.1575 $C_{21}H_{24}N_3O_2S$ requires 382.1584.

3-Amino-*N*-(4'-chlorophenyl)-5,6,7,8,9,10,11,12-octahydrocyclodeca[*b*]thieno[3,2-*e*]pyridine-2-carboxamide 6d



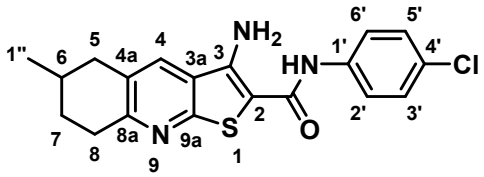
The reaction was carried out following General Procedure **D** using carbonitrile **3d** (0.40 g, 1.62 mmol), 2-chloro-*N*-(4-chlorophenyl)acetamide **4** (0.33 g, 1.62 mmol) and anhydrous sodium carbonate (0.34 g, 3.25 mmol) in absolute ethanol (6.48 mL) for 48 h and then purified by flash chromatography (1:1 petroleum ether/EtOAc) to give the *title compound* **6d** (0.06 g, 9%) as a yellow solid. m.p. 205-209 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.00-1.09 (4H, m, H-8 and H-9), 1.47 (4H, s, H-7 and H-10), 1.85 (2H, s, H-6 or H-11), 1.91 (2H, s, H-6 or H-11), 2.94 (2H, s, H-5), 3.04 (2H, s, H-12), 7.34 (2H, br s, NH_2), 7.36 (2H, d, J = 9.1 Hz, H-3' and H-5'), 7.74 (2H, d, J = 9.1 Hz, H-2' and H-6'), 8.33 (1H, s, H-4), 9.46 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 20.6 (C-8 or C-9), 20.7 (C-8 or C-9), 25.5 (C-7 or C-10), 26.1 (C-7 or C-10), 28.1 (C-6 or C-11), 28.2 (C-5), 29.1 (C-6 or C-11), 31.1 (C-12), 95.5 (C-2), 122.4 (C-2' and C-6'), 124.5 (C-3a), 126.9 (C-4'), 128.2 (C-3' and C-5'), 131.1 (C-4), 131.8 (C-4a), 138.0 (C-1'), 147.1 (C-3), 156.4 (C-13a), 162.0 (C-12a), 164.1 (2-CONH). ν_{max} (ATR)/cm^{-1} 3425 (N-H amide), 3319 (N-H amine), 2926 (C-H aromatic), 2846 (C-H aliphatic), 1726 (C=O amide), 1589 (C=C aromatic), 1485 (-C-H bending), 1310 (C-N aromatic), 1093 (C-N aliphatic), 823 (C-Cl). *m/z* (ESI^+): 416 ($^{37}ClMH^+$, 40%), 414 ($^{35}ClMH^+$, 100%). HRMS (ESI^+) found ($^{37}ClMH^+$): 416.1381 $C_{22}H_{25}{}^{37}ClN_3OS$ requires 416.1378. Found ($^{35}ClMH^+$): 414.1397 $C_{22}H_{25}{}^{35}ClN_3OS$ requires 414.1401.

3-Amino-*N*-(4'-methoxyphenyl)-5,6,7,8,9,10,11,12-octahydrocyclodeca[*b*]thieno[3,2-*e*]pyridine-2-carboxamide 7d



The reaction was carried out following General Procedure **D** using carbonitrile **3d** (0.40 g, 1.62 mmol), 2-chloro-*N*-(4-methoxyphenyl)acetamide **5** (0.32 g, 1.62 mmol) and anhydrous sodium carbonate (0.34 g, 3.25 mmol) in absolute ethanol (6.48 mL) for 48 h and then purified by flash chromatography (1:1 petroleum ether/EtOAc) to give the *title compound* **7d** (0.15 g, 23%) as a yellow solid. m.p. 180-185 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.04-1.10 (4H, m, H-8 and H-9), 1.49 (4H, s, H-7 and H-10), 1.86 (2H, t, J = 6.0 Hz, H-6 or H-11), 1.93 (2H, s, H-6 or H-11), 2.95 (2H, t, J = 6.0 Hz, H-5), 3.06 (2H, s, H-12), 3.76 (3H, s, 4'-OCH_3), 6.91 (2H, d, J = 9.1 Hz, H-3' and H-5'), 7.27 (2H, br s, NH_2), 7.58 (2H, d, J = 9.1 Hz, H-2' and H-6'), 8.31 (1H, s, H-4), 9.24 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 14.1 (C-8 or C-9), 20.6 (C-8 or C-9), 25.5 (C-7 or C-10), 26.1 (C-7 or C-10), 28.1 (C-6 or C-11), 28.2 (C-6 or C-11), 29.1 (C-5), 31.1 (C-12), 55.1 (4'-OCH_3), 96.1 (C-2), 113.5 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.7 (C-3a), 131.0 (C-4), 131.6 (C-4'), 131.9 (C-4a), 146.3 (C-3), 155.4 (C-1'), 156.3 (C-13a), 161.7 (C-12a), 163.8 (2-CONH). ν_{max} (ATR)/cm^{-1} 3431 (N-H amide), 3325 (N-H amine), 2913 (C-H aromatic), 2845 (C-H aliphatic),1718 (C=O amide), 1592 (C=C aromatic), 1493 (-C-H bending), 1248 (C-N aromatic), 1227 (C-O ether), 1030 (C-N aliphatic). *m/z* (ESI^+): 410 (MH^+, 100%). HRMS (ESI^+) found (MH^+): 410.1885 $C_{23}H_{28}N_3O_2S$ requires 410.1897.

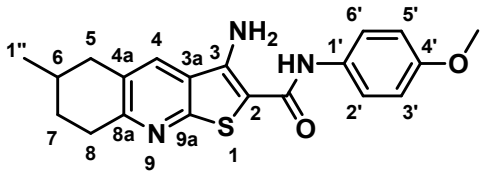
3-Amino-*N*-(4'-chlorophenyl)-6-methyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 6e



The reaction was carried out following General Procedure **D** using carbonitrile **3e** (0.20 g, 1.00 mmol), 2-chloro-*N*-(4-chlorophenyl)acetamide **4** (0.20 g, 1.00 mmol) and anhydrous sodium carbonate (0.21 g, 2.00 mmol) in absolute ethanol (4.00 mL) for 48 h and then purified by flash chromatography (1:1 petroleum ether/EtOAc) to give the *title compound* **6e** (0.06 g, 16%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.07 (3H, d, J = 6.4 Hz, H-1''), 1.21 (1H, s, H-6), 1.49-1.53 (1H, m, 7-H_A), 1.86-1.95 (1H, m, 7-H_B), 2.53 (1H, dd, J = 4.6, 11.2 Hz, 5-H_A), 2.89 (1H, dd, J = 4.6, 11.2 Hz, 5-H_B),

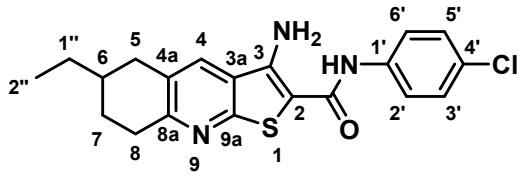
2.96-2.30 (2H, m, H-8), 7.33 (2H, br s, NH_2), 7.36 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 7.73 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 8.16 (1H, s, H-4), 9.45 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 21.3 (C-1"), 28.3 (C-6), 30.5 (C-7), 32.0 (C-8), 36.7 (C-5), 95.3 (C-2), 122.4 (C-3' and C-5'), 124.9 (C-3a), 126.8 (C-4'), 127.9 (C-4a), 128.2 (C-2' and C-6'), 130.8 (C-4), 138.1 (C-1'), 147.2 (C-3), 156.1 (C-8a), 158.9 (C-9a), 164.1 (2-CONH). ν_{max} (ATR)/cm^{-1} 3425 (N-H amide), 3319 (N-H amine), 2920 (C-H aromatic), 2853 (C-H aliphatic), 1606 (C=O amide), 1587 (C=C aromatic), 1487 (-C-H bending), 1308 (C-N aromatic), 1091 (C-N aliphatic) 819 (C-Cl). *m/z* (ESI^+): 374 ($^{37}ClMH^+$, 40%), 372 ($^{35}ClMH^+$, 100%). HRMS (ESI^+) found ($^{37}ClMH^+$): 374.0907 $C_{19}H_{19}{}^{37}ClN_3OS$ requires 374.0907. Found ($^{35}ClMH^+$): 372.0924 $C_{19}H_{19}{}^{35}ClN_3OS$ requires 372.0932.

3-Amino-*N*-(4'-methoxyphenyl)-6-methyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 7e



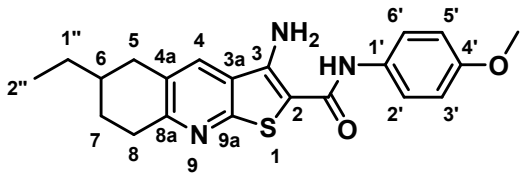
The reaction was carried out following General Procedure **D** using carbonitrile **3e** (0.20 g, 1.00 mmol), 2-chloro-*N*-(4-methoxyphenyl)acetamide **5** (0.20 g, 1.00 mmol) and anhydrous sodium carbonate (0.21 g, 2.00 mmol) in absolute ethanol (4.00 mL) for 48 h and then purified by flash chromatography (1:1 petroleum ether/EtOAc) to give the *title compound* **7e** (0.21 g, 57%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.07 (3H, d, *J* = 6.4 Hz, H-1"), 1.23 (1H, s, H-6), 1.48-1.57 (1H, m, 7-H_A), 1.88-1.97 (1H, m, 7-H_B), 2.53 (1H, dd, *J* = 11.2, 4.6 Hz, 5-H_A), 2.91 (1H, dd, *J* = 11.2, 4.6 Hz, 5-H_B), 2.99-3.01 (2H, m, H-8), 3.74 (3H, s, 4'-OCH_3), 6.89 (2H, d, *J* = 9.0 Hz, H-3' and H-5'), 7.25 (2H, br s, NH_2), 7.57 (2H, d, *J* = 9.0 Hz, H-2' and H-6'), 8.14 (1H, s, H-4), 9.24 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 21.3 (C-1"), 28.2 (C-6), 30.6 (C-7), 32.0 (C-8), 36.8 (C-5), 55.1 (4'-OCH_3), 95.9 (C-2), 113.5 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.4 (C-3a), 127.8 (C-4a), 130.6 (C-4), 131.9 (C-1'), 146.4 (C-3), 155.4 (C-4'), 156.0 (C-9a), 158.6 (C-8a), 163.8 (2-CONH). ν_{max} (ATR)/cm^{-1} 3436 (N-H amide), 3323 (N-H amine), 2923 (C-H aromatic), 2864 (C-H aliphatic), 1596 (C=O amide), 1508 (C=C aromatic), 1496 (-C-H bending), 1230 (C-N aromatic), 1107 (C-O ether), 1034 (C-N aliphatic). *m/z* (ESI^+): 390 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 390.1235 $C_{20}H_{21}N_3NaO_2S$ requires 390.1247.

3-Amino-*N*-(4'-chlorophenyl)-6-ethyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 6f



The reaction was carried out following General Procedure **D** using carbonitrile **3f** (0.30 g, 1.37 mmol), 2-chloro-*N*-(4-chlorophenyl)acetamide **4** (0.28 g, 1.37 mmol) and anhydrous sodium carbonate (0.29 g, 2.74 mmol) in absolute ethanol (5.00 mL) for 48 h and then purified by flash chromatography (1:1 petroleum ether/EtOAc) to give the *title compound* **6f** (0.33 g, 62%) as a yellow solid. m.p. >230 ºC. δ_H (400 MHz, $(CD_3)_2SO$) 0.96 (3H, t, J = 7.4 Hz, H-2''), 1.36-1.53 (3H, m, H-1'', and 7-H_A), 1.62-1.69 (1H, m, H-6), 1.98-2.03 (1H, m, 7-H_B), 2.54 (1H, dd, J = 15.8, 10.9 Hz, 5-H_A), 2.90-3.03 (3H, m, H-8 and 5-H_B), 7.34 (2H, br s, NH_2), 7.36 (2H, d, J = 9.0 Hz, H-3' and H-5'), 7.74 (2H, d, J = 9.0 Hz, H-2' and H-6'), 8.18 (1H, s, H-4), 9.46 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 11.4 (C-2''), 28.08 (C-1'' and C-7), 32.0 (C-8), 34.6 (C-5), 34.9 (C-6), 95.4 (C-2), 122.5 (C-2' and C-6'), 124.3 (C-3a), 126.9 (C-4'), 127.9 (C-4a), 128.2 (C-3' and C-5'), 130.1 (C-4), 138.1 (C-1'), 147.2 (C-3), 156.1 (C-9a), 159.2 (C-8a), 164.0 (2-CONH). ν_{max} (ATR)/cm^{-1} 3433 (N-H amide), 3323 (N-H amine), 2927 (C-H aromatic), 2892 (C-H aliphatic), 1607 (C=O amide), 1587 (C=C aromatic), 1488 (-C-H bending), 1309 (C-N aromatic), 1091 (C-N aliphatic), 818 (C-Cl). *m/z* (ESI^+): 410 ($^{37}ClMNa^+$, 40%), 408 ($^{35}ClMNa^+$, 100%). HRMS (ESI^+) found ($^{37}ClMNa^+$): 410.0915 $C_{20}H_{20}{}^{37}ClN_3NaOS$ requires 410.0883. Found ($^{35}ClMNa^+$): 408.0920 $C_{20}H_{20}{}^{35}ClN_3NaOS$ requires 408.0908.

3-Amino-6-ethyl-*N*-(4'-methoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 7f

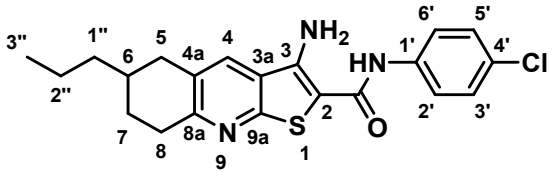


The reaction was carried out following General Procedure **D** using carbonitrile **3f** (0.30 g, 1.37 mmol), 2-chloro-*N*-(4-methoxyphenyl)acetamide **5** (0.27 g, 1.37 mmol) and anhydrous sodium carbonate (0.29 g, 2.74 mmol) in absolute ethanol (5.00 mL) for 48 h to give the *title compound* **7f** (0.31 g, 59%) as a yellow solid. m.p. >230 ºC. δ_H (400 MHz, $(CD_3)_2SO$) 0.97 (3H, t, J = 7.4 Hz, H-2''), 1.36-1.53 (3H, m, H-1'', and 7-H_A), 1.64-1.69 (1H, m, H-6), 1.98-2.03 (1H, m, 7-H_B), 2.52 (1H, dd, J = 15.8, 10.9 Hz, 5-H_A), 2.89-3.05 (3H, m, H-8 and 5-H_B), 3.74 (3H, s, 4'-OCH_3), 6.89 (2H, d, J = 9.0 Hz, H-3' and H-5'), 7.23 (2H, br s, NH_2), 7.56 (2H, d, J = 9.0 Hz, H-2' and H-6'), 8.15 (1H, s, H-4), 9.23 (1H, br s, NH). δ_C

(100 MHz, $(CD_3)_2SO$) 11.4 (C-2''), 28.08 and 28.11 (C-1'' and C-7), 32.0 (C-8), 34.6 (C-5), 35.0 (C-6), 55.1 (4'-OCH_3), 96.0 (C-2), 113.5 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.5 (C-3a), 127.8 (C-4a), 130.7 (C-4), 131.9 (C-1'), 146.4 (C-3), 155.4 (C-4'), 156.0 (C-9a), 158.9 (C-8a), 163.9 (2-CONH). ν_{max} (ATR)/cm^{-1} 3426 (N-H amide), 3314 (N-H amine), 2964 (C-H aromatic), 2922 (C-H aliphatic), 1602 (C=O amide), 1592 (C=C aromatic), 1496 (-C-H bending), 1261 (C-N aromatic), 1107 (C-O ether), 1035 (C-N aliphatic). *m/z* (ESI^+): 404 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 404.1405 $C_{21}H_{23}N_3NaO_2S$ requires 404.1403.

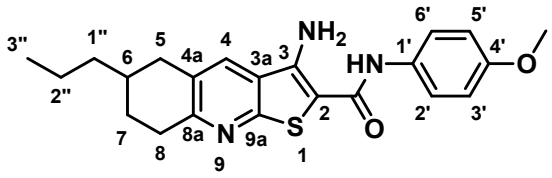
3-Amino-*N*-(4'-chlorophenyl)-6-propyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide

6g



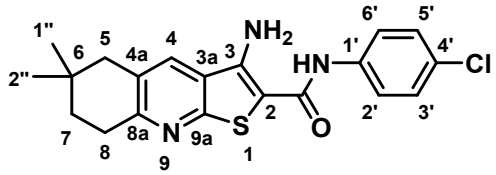
The reaction was carried out following General Procedure **D** using carbonitrile **3g** (0.20 g, 0.86 mmol), 2-chloro-*N*-(4-chlorophenyl)acetamide **4** (0.18 g, 0.86 mmol) and anhydrous sodium carbonate (0.18 g, 1.72 mmol) in absolute ethanol (4.00 mL) for 48 h to give the *title compound* **6g** (0.30 g, 88%) as a yellow solid. m.p. >230 ºC. δ_H (400 MHz, $(CD_3)_2SO$) 0.92 (3H, t, J = 7.2 Hz, H-3''), 1.34-1.51 (5H, m, H-1'', H-2'' and 7-H_A), 1.75-1.80 (1H, m, H-6), 1.97-2.00 (1H, m, 7-H_B), 2.53 (1H, dd, J = 15.8, 10.9 Hz, 5-H_A), 2.91-3.00 (3H, m, H-8 and 5-H_B), 7.32 (2H, br s, NH_2), 7.36 (2H, d, J = 9.0 Hz, H-3' and H-5'), 7.74 (2H, d, J = 9.0 Hz, H-2' and H-6'), 8.17 (1H, s, H-4), 9.46 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 14.2 (C-3''), 19.6 (C-2''), 28.5 (C-7), 32.0 (C-8), 32.9 (C-6), 34.9 (C-5), 37.6 (C-1''), 95.3 (C-2), 122.5 (C-2' and C-6'), 124.3 (C-3a), 126.9 (C-4'), 127.9 (C-4a), 128.3 (C-3' and C-5'), 130.1 (C-4), 138.1 (C-1'), 147.2 (C-3), 156.1 (C-9a), 159.2 (C-8a), 164.1 (2-CONH). ν_{max} (ATR)/cm^{-1} 3433 (N-H amide), 3327 (N-H amine), 2954 (C-H aromatic), 2855 (C-H aliphatic), 1604 (C=O amide), 1586 (C=C aromatic), 1487 (-C-H bending), 1309 (C-N aromatic), 1090 (C-N aliphatic), 816 (C-Cl). *m/z* (ESI^+): 424 ($^{37}ClMNa^+$, 40%), 422 ($^{35}ClMNa^+$, 100%). HRMS (ESI^+) found ($^{37}ClMNa^+$): 424.1052 $C_{21}H_{22}{}^{37}ClN_3NaOS$ requires 424.1040. Found ($^{35}ClMNa^+$): 422.1059 $C_{21}H_{22}{}^{35}ClN_3NaOS$ requires 422.1064.

3-Amino-*N*-(4'-methoxyphenyl)-6-propyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 7g



The reaction was carried out following General Procedure **D** using carbonitrile **3g** (0.20 g, 0.86 mmol), 2-chloro-*N*-(4-methoxyphenyl)acetamide **5** (0.17 g, 0.86 mmol) and anhydrous sodium carbonate (0.18 g, 1.72 mmol) in absolute ethanol (4.00 mL) for 48 h to give the *title compound* **7g** (0.18 g, 52%) as a yellow solid. m.p. >230 ºC. δ_H (400 MHz, $(CD_3)_2SO$) 0.94 (3H, t, J = 7.2 Hz, H-3"), 1.34-1.53 (5H, m, H-1", H-2" and 7-H_A), 1.77-1.78 (1H, m, H-6), 1.98-1.99 (1H, m, 7-H_B), 2.53 (1H, dd, J = 15.8, 10.9 Hz, 5-H_A), 2.91-2.99 (3H, m, H-8 and 5-H_B), 3.74 (3H, s, 4'-OCH_3), 6.89 (2H, d, J = 9.0 Hz, H-3' and H-5'), 7.23 (2H, br s, NH_2), 7.56 (2H, d, J = 9.0 Hz, H-2' and H-6'), 8.14 (1H, s, H-4), 9.23 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 14.2 (C-3"), 19.6 (C-2"), 28.5 (C-7), 32.0 (C-8), 32.9 (C-6), 34.9 (C-5), 37.7 (C-1"), 55.1 (4'-OCH_3), 95.9 (C-2), 113.5 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.5 (C-3a), 127.8 (C-4a), 130.7 (C-4), 131.9 (C-1'), 146.4 (C-3), 155.4 (C-4'), 156.0 (C-9a), 158.9 (C-8a), 163.9 (2-CONH). ν_{max} (ATR)/cm^{-1} 3427 (N-H amide), 3313 (N-H amine), 3176 (C-H aromatic), 2934 (C-H aliphatic), 1602 (C=O amide), 1500 (C=C aromatic), 1439 (-C-H bending), 1262 (C-N aromatic), 1170 (C-O ether), 1033 (C-N aliphatic). *m/z* (ESI^+): 418 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 418.1570 $C_{22}H_{25}N_3NaO_2S$ requires 418.1560.

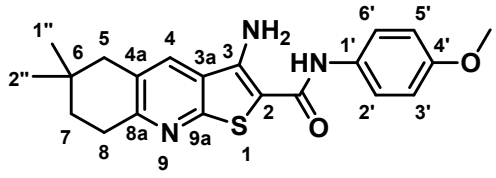
3-Amino-*N*-(4'-chlorophenyl)-6,6-dimethyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 6h



The reaction was carried out following General Procedure **D** using carbonitrile **3h** (0.20 g, 0.92 mmol), 2-chloro-*N*-(4-chlorophenyl)acetamide **4** (0.19 g, 0.92 mmol) and anhydrous sodium carbonate (0.19 g, 1.83 mmol) in absolute ethanol (3.66 mL) for 48 h to give the *title compound* **6h** (0.17 g, 49%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.00 (6H, s, H-1" and H-2"), 1.68 (2H, t, J = 6.7 Hz, H-7), 2.66 (2H, s, H-5), 2.97 (2H, t, J = 6.7 Hz, H-8), 7.34 (2H, br s, NH_2), 7.36 (2H, d, J = 8.6 Hz, H-3' and H-5'), 7.73 (2H, d, J = 8.6 Hz, H-2' and H-6'), 8.15 (1H, s, H-4), 9.48 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 27.5 (C-1" and C-2"), 29.1 (C-8), 29.5 (C-6), 35.0 (C-7), 42.3 (C-5), 95.9 (C-2),

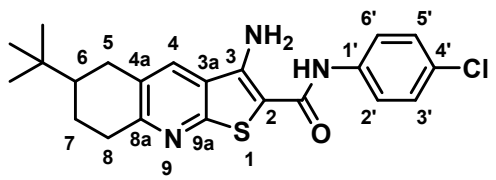
122.5 (C-2' and C-6'), 124.4 (C-3a), 126.9 (C-4'), 127.4 (C-4a), 128.2 (C-3' and C-5'), 131.2 (C-4), 138.2 (C-1'), 147.3 (C-3), 156.1 (C-8a), 158.3 (C-9a), 164.1 (2-CONH). ν_{max} (ATR)/cm^{-1} 3444 (N-H amide), 3342 (N-H amine), 2951 (C-H aromatic), 2884 (C-H aliphatic), 1605 (C=O amide), 1586 (C=C aromatic), 1488 (-C-H bending), 1392 (C-N aromatic), 1089 (C-N aliphatic), 814 (C-Cl). *m/z* (ESI$^+$): 388 (^{37}ClMH$^+$, 40%), 386 (^{35}ClMH$^+$, 100%). HRMS (ESI$^+$) found (^{37}ClMH$^+$): 388.1052 $C_{20}H_{21}{}^{37}ClN_3OS$ requires 388.1064. Found (^{35}ClMH$^+$): 386.1077 $C_{20}H_{21}{}^{35}ClN_3OS$ requires 386.1088.

3-Amino-*N*-(4'-methoxyphenyl)-6,6-dimethyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 7h



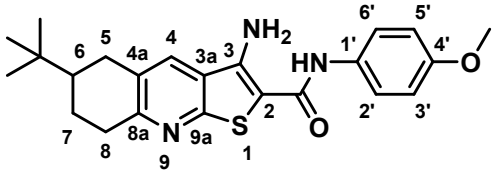
The reaction was carried out following General Procedure **D** using carbonitrile **3h** (0.20 g, 0.92 mmol), 2-chloro-*N*-(4-methoxyphenyl)acetamide **5** (0.18 g, 0.92 mmol) and anhydrous sodium carbonate (0.19 g, 1.83 mmol) in absolute ethanol (3.66 mL) for 48 h to give the *title compound* **7h** (0.15 g, 43%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 1.00 (6H, s, H-1" and H-2"), 1.68 (2H, t, *J* = 6.8 Hz, H-7), 2.66 (2H, s, H-5), 2.97 (2H, t, *J* = 6.8 Hz, H-8), 3.74 (3H, s, 4'-OCH_3), 6.89 (2H, d, *J* = 8.0 Hz, H-3' and H-5'), 7.24 (2H, br s, NH_2), 7.56 (2H, d, *J* = 8.0 Hz, H-2' and H-6'), 8.13 (1H, s, H-4), 9.24 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 27.5 (C-1" and C-2"), 29.1 (C-8), 29.5 (C-6), 35.0 (C-7), 42.3 (C-5), 55.1 (4'-OCH_3), 95.9 (C-2), 113.5 (C-3' and C-5'), 122.8 (C-2' and C-6'), 124.6 (C-3a), 127.3 (C-4a), 131.1 (C-4), 131.9 (C-4'), 146.4 (C-3), 155.4 (C-1'), 156.0 (C-9a), 158.0 (C-8a), 163.8 (2-CONH). ν_{max} (ATR)/cm^{-1} 3430 (N-H amide), 3320 (N-H amine), 2958 (C-H aromatic), 2892 (C-H aliphatic), 1602 (C=O amide), 1508 (C=C aromatic), 1496 (-C-H bending), 1235 (C-N aromatic), 1105 (C-O ether), 1035 (C-N aliphatic). *m/z* (ESI$^+$): 382 (MH$^+$, 100%). HRMS (ESI$^+$) found (MH$^+$): 382.1570 $C_{21}H_{24}N_3O_2S$ requires 382.1584.

3-Amino-6-(*tert*-butyl)-*N*-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 6i



The reaction was carried out following General Procedure **D** using carbonitrile **3i** (0.25 g, 1.01 mmol), 2-chloro-*N*-(4-chlorophenyl)acetamide **4** (0.21 g, 1.01 mmol) and anhydrous sodium carbonate (0.21 g, 2.02 mmol) in absolute ethanol (4.00 mL) for 48 h to give the *title compound* **6i** (0.34 g, 81%) as a yellow solid. m.p. >230 ºC. δ_H (400 MHz, $(CD_3)_2SO$) 0.96 (9H, s, 3 × *tert*-butyl CH_3), 1.39-1.55 (2H, m, 7-H_A and H-6), 2.03-2.07 (1H, m, 7-H_B), 2.66 (1H, dd, J = 15.8, 10.9 Hz, 5-H_A), 2.86-2.96 (2H, m, 8-H_A and 5-H_B), 3.03-3.08 (1H, m, 8-H_B), 7.31 (2H, br s, NH_2), 7.35 (2H, d, J = 9.0 Hz, H-3' and H-5'), 7.74 (2H, d, J = 9.0 Hz, H-2' and H-6'), 8.20 (1H, s, H-4), 9.47 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 23.8 (C-7), 27.1 (3 × *tert*-butyl CH_3), 29.9 (C-5), 32.2 (*tert*-butyl quat. C), 33.2 (C-8), 43.8 (C-6), 122.5 (C-2' and C-6'), 124.4 (C-3a), 126.7 (C-4'), 128.2 (C-3' and C-5'), 128.4 (C-4a), 131.0 (C-4), 138.5 (C-1'), 146.9 (C-3), 156.0 (C-9a), 159.1 (C-8a), 164.2 (2-CONH). C-2 not observed. ν_{max} (ATR)/cm^{-1} 3445 (N-H amide), 3331 (N-H amine), 2962 (C-H aromatic), 2890 (C-H aliphatic), 1607 (C=O amide), 1504 (C=C aromatic), 1489 (-C-H bending), 1242 (C-N aromatic), 1091 (C-N aliphatic), 817 (C-Cl). *m/z* (ESI^+): 438 ($^{37}ClMNa^+$, 40%), 436 ($^{35}ClMNa^+$, 100%). HRMS (ESI^+) found ($^{37}ClMNa^+$): 438.1225 $C_{22}H_{24}{}^{37}ClN_3NaOS$ requires 438.1197. Found ($^{35}ClMNa^+$): 436.1233 $C_{22}H_{24}{}^{35}ClN_3NaOS$ requires 436.1221.

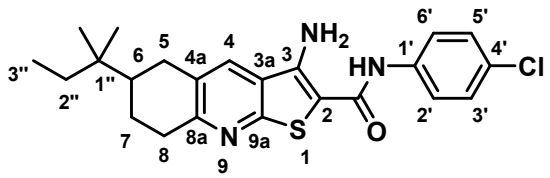
3-Amino-6-(*tert*-butyl)-*N*-(4-methoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 7i



The reaction was carried out following General Procedure **D** using carbonitrile **3i** (0.25 g, 1.01 mmol), 2-chloro-*N*-(4-methoxyphenyl)acetamide **5** (0.20 g, 1.01 mmol) and anhydrous sodium carbonate (0.21 g, 2.02 mmol) in absolute ethanol (4.00 mL) for 48 h to give the *title compound* **7i** (0.32 g, 78%) as a yellow solid. m.p. >230 ºC. δ_H (400 MHz, $(CD_3)_2SO$) 0.96 (9H, s, 3 × *tert*-butyl CH_3), 1.38-1.55 (2H, m, 7-H_A and H-6), 2.03-2.07 (1H, m, 7-H_B), 2.66 (1H, dd, J = 15.8, 10.9 Hz, 5-H_A), 2.87-2.96 (2H, m, 8-H_A and 5-H_B), 3.02-3.08 (1H, m, 8-H_B), 3.74 (3H, s, 4'-OCH_3), 6.89 (2H, d, J = 9.0 Hz, H-3' and H-5'), 7.21 (2H, br s, NH_2), 7.56 (2H, d, J = 9.0 Hz, H-2' and H-6'), 8.18 (1H, s, H-4), 9.23 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 23.9 (C-7), 27.1 (3 × *tert*-butyl CH_3), 29.9 (C-5), 32.2 (*tert*-butyl quat. C), 33.2 (C-8), 43.8 (C-6), 55.1 (4'-OCH_3), 96.0 (C-2), 113.5 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.5 (C-3a), 128.4 (C-4a), 130.9 (C-4), 131.9 (C-1'), 146.4 (C-3), 155.4 (C-4'), 155.9 (C-9a), 158.9 (C-8a), 163.9 (2-CONH). ν_{max} (ATR)/cm^{-1} 3436 (N-H amide), 3318 (N-H amine), 2961 (C-H aromatic), 2850 (C-H aliphatic), 1602 (C=O amide), 1523 (C=C aromatic), 1439 (-C-H bending), 1236 (C-N aromatic),

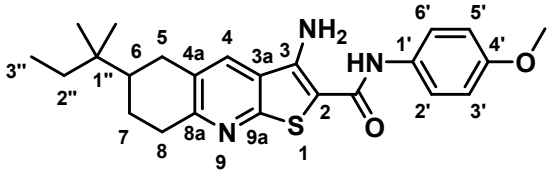
1168 (C-O ether), 1074 (C-N aliphatic). *m/z* (ESI^+): 432 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 432.1716 $C_{23}H_{27}N_3NaO_2S$ requires 432.1716.

3-Amino-*N*-(4'-chlorophenyl)-6-(*tert*-pentyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 6j



The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.20 g, 0.77 mmol), 2-chloro-*N*-(4-chlorophenyl)acetamide **4** (0.16 g, 0.77 mmol) and anhydrous sodium carbonate (0.16 g, 1.54 mmol) in absolute ethanol (3.08 mL) for 48 h to give the *title compound* **6j** (0.15 g, 45%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 0.85 (3H, t, J = 7.4 Hz, H-3"), 0.90 (6H, s, 2 × *tert*-pentyl CH_3), 1.34-1.41 (2H, m, H-2"), 1.43-1.51 (1H, m, 7-H_A), 1.57-1.65 (1H, m, H-6), 1.98-2.04 (1H, m, 7-H_B), 2.65-2.86 (2H, m, H-5), 2.91-3.09 (2H, m, H-8), 7.31 (2H, br s, NH_2), 7.36 (2H, d, J = 8.8 Hz, H-3' and H-5'), 7.74 (2H, d, J = 8.8 Hz, H-2' and H-6'), 8.21 (1H, s, H-4), 9.47 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 8.1 (C-3"), 23.4 (C-7), 23.7 (1 x *tert*-pentyl CH_3), 23.8 (1 x *tert*-pentyl CH_3), 29.5 (C-5), 32.0 (C-2"), 33.3 (C-8), 34.4 (C-1"), 41.2 (C-6), 95.8 (C-2), 122.5 (C-2' and C-6'), 124.3 (C-3a), 126.7 (C-4'), 128.2 (C-3' and C-5'), 128.5 (C-4a), 131.1 (C-4), 138.4 (C-1'), 147.0 (C-3), 156.0 (C-9a), 159.2 (C-8a), 164.1 (2-CONH). ν_{max} (ATR)/cm^{-1} 3437 (N-H amide), 3324 (N-H amine), 2963 (C-H aromatic), 2923 (C-H aliphatic), 1606 (C=O amide), 1586 (C=C aromatic), 1487 (-C-H bending), 1397 (C-N aromatic), 1089 (C-N aliphatic) 812 (C-Cl). *m/z* (ESI^+): 430 ($^{37}ClMH^+$, 40%), 428 ($^{35}ClMH^+$, 100%). HRMS (ESI^+) found ($^{37}ClMH^+$): 430.1532 $C_{23}H_{27}{}^{37}ClN_3OS$ requires 430.1535. Found ($^{35}ClMH^+$): 428.1547 $C_{23}H_{27}{}^{35}ClN_3OS$ requires 428.1558.

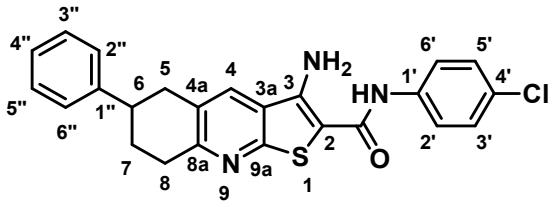
3-Amino-*N*-(4'-methoxyphenyl)-6-(*tert*-pentyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 7j



The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.20 g, 0.77 mmol), 2-chloro-*N*-(4-methoxyphenyl)acetamide **5** (0.15 g, 0.77 mmol) and anhydrous sodium carbonate (0.16 g, 1.54 mmol) in absolute ethanol (3.08 mL) for 48 h to give the *title compound* **7j** (0.12 g, 38%) as a

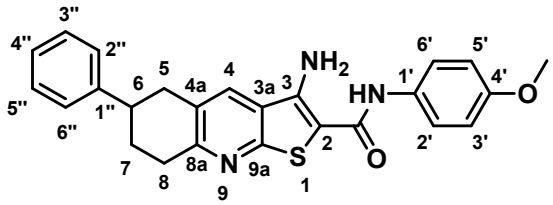
yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 0.84 (3H, *J* = 7.4 Hz, H-3''), 0.89 (6H, m, 2 × *tert*-pentyl CH_3), 1.34-1.41 (2H, m, H-2''), 1.43-1.51 (1H, m, 7-H_A), 1.57-1.65 (1H, m, H-6), 1.98-2.04 (1H, m, 7-H_B), 2.65-2.86 (2H, m, H-5), 2.91-3.09 (2H, m, H-8), 3.74 (3H, s, 4'-OCH_3), 6.89 (2H, d, *J* = 9.1 Hz, H-3' and H-5'), 7.21 (2H, br s, NH_2), 7.56 (2H, d, *J* = 9.1 Hz, H-2' and H-6'), 8.19 (1H, s, H-4), 9.23 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 8.1 (C-3''), 23.5 (C-7), 23.7 (1 × *tert*-pentyl CH_3), 23.8 (1 × *tert*-pentyl CH_3), 29.5 (C-5), 32.0 (C-2''), 33.3 (C-8), 34.4 (C-1''), 41.2 (C-6), 55.1 (4'-OCH_3), 96.0 (C-2), 113.6 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.4 (C-3a), 128.5 (C-4a), 130.9 (C-4), 131.9 (C-1'), 146.4 (C-3), 155.4 (C-4'), 155.9 (C-8a), 158.9 (C-9a) 163.8 (2-CONH). ν_{max} (ATR)/cm^{-1} 3437 (N-H amide), 3320 (N-H amine), 2962 (C-H aromatic), 2931 (C-H aliphatic), 1604 (C=O amide), 1504 (C=C aromatic), 1487 (-C-H bending), 1269 (C-N aromatic), 1168 (C-O ether), 1013 (C-N aliphatic). *m/z* (ESI^+): 424 (MH^+, 100%). HRMS (ESI^+) found (MH^+): 424.2040 $C_{24}H_{30}N_3O_2S$ requires 424.2053.

3-Amino-*N*-(4'-chlorophenyl)-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 6k



The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.50 g, 1.88 mmol), 2-chloro-*N*-(4-chlorophenyl)acetamide **4** (0.38 g, 1.88 mmol) and anhydrous sodium carbonate (0.40 g, 3.76 mmol) in absolute ethanol (7.52 mL) for 48 h and then purified by flash chromatography (1:1 petroleum ether/EtOAc) to give the *title compound* **6k** (0.50 g, 61%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 2.11 (2H, s, H-7), 3.06 (2H, s, H-5), 3.10 (3H, s, H-6 and H-7), 7.23-7.37 (9H, m, H-3', H-5', NH_2, H-1'', H-2'', H-3'', H-4'' and H-5''), 7.74 (2H, d, *J* = 8.7 Hz, H-2' and H-6'), 8.23 (1H, s, H-4), 9.50 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 29.6 (C-7), 32.6 (C-6 and C-8), 36.3 (C-5), 95.5 (C-2), 122.5 (C-2' and C-6'), 124.3 (C-3a), 126.8-128.5 (5 × aromatic-CH, C-3', C-4' and C-5'), 130.9 (C-4), 131.8 (C-4a), 138.1 (C-1'), 145.7 (C-1''), 147.2 (C-3), 156.3 (C-9a), 158.6 (C-8a), 164.1 (2-CONH). ν_{max} (ATR)/cm^{-1} 34.37 (N-H amide), 3324 (N-H amine), 2963 (C-H aromatic), 2896 (C-H aliphatic), 1606 (C=O amide), 1586 (C=C aromatic), 1487 (-C-H bending), 1309 (C-N aromatic), 1089 (C-N aliphatic) 816 (C-Cl). *m/z* (ESI^+): 436 ($^{37}ClMH^+$, 40%), 434 ($^{35}ClMH^+$, 100%). HRMS (ESI^+) found ($^{37}ClMH^+$): 436.1045 $C_{24}H_{21}{}^{37}ClN_3OS$ requires 436.1066. Found ($^{35}ClMH^+$): 434.1074 $C_{24}H_{21}{}^{35}ClN_3OS$ requires 434.1088.

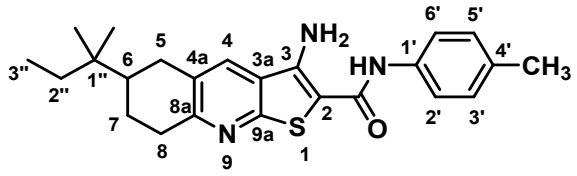
3-Amino-*N*-(4'-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 7k



The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.1 g, 0.38 mmol), 2-chloro-*N*-(4-methoxyphenyl)acetamide **5** (0.08 g, 0.38 mmol) and anhydrous sodium carbonate (0.08 g, 0.75 mmol) in absolute ethanol (1.50 mL) for 48 h and then purified by flash chromatography (1:1 petroleum ether/EtOAc) to give the *title compound* **7k** (0.41 g, 51%) as a yellow solid. m.p. >230 °C. δ_H (400 MHz, $(CD_3)_2SO$) 2.11 (2H, s, H-7), 3.07 (5H, s, H-5, H-6 and H-7), 3.74 (4'-OCH_3), 6.89 (2H, d, J = 9.0 Hz, H-3' and H-5'), 7.26 (2H, br s, NH_2), 7.31-7.37 (5H, m, H-1", H-2", H-3", H-4" and H-5"), 7.56 (2H, d, J = 9.0 Hz, H-2' and H-6'), 8.20 (1H, s, H-4), 9.25 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 29.7 (C-7), 32.6 (C-6 and C-8), 36.3 (C-5), 55.1 (4'-OCH_3), 96.0 (C-2), 113.5 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.5 (C-3a), 126.3-128.5 (C-2", C-3", C-4", C-5" and C-6"), 130.7 (C-4), 131.9 (C-4'), 132.1 (C-4a), 145.7 (C-3), 154.3 (C-1'), 155.4 (C-9a), 158.3 (C-8a), 163.8 (2-CONH). ν_{max} (ATR)/cm^{-1} 3437 (N-H amide), 3323 (N-H amine), 2925 (C-H aromatic), 2873 (C-H aliphatic), 1602 (C=O amide), 1589 (C=C aromatic), 1499 (C-H bending), 1266 (C-N aromatic), 1177 (C-O ether), 1029 (C-N aliphatic). *m/z* (ESI^+): 452 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 452.1399 $C_{25}H_{23}N_3NaO_2S$ requires 452.1403.

Synthetic procedures and compound characterisation data for series 2

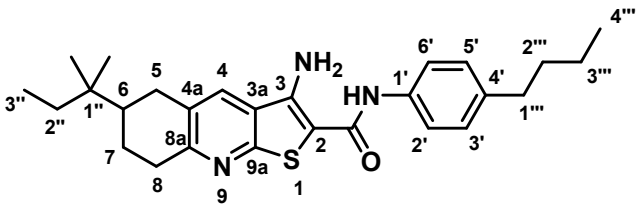
3-Amino-6-(*tert*-pentyl)-*N*-(*p*-tolyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 10a



The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.15 g, 0.609 mmol), chlorophenylacetamide **8a** (0.11 g, 0.609 mmol), sodium carbonate (0.13 g, 1.22 mmol) and ethanol (5 mL) for 24 h to give the *title compound* **10a** (0.16 g, 64%) as yellow crystals. m.p. >230 °C. δ_H (400 MHz, $((CD_3)_2SO$) 0.84 (3H, t, J = 7.5 Hz, H-3″), 0.89 (6H, s, 2 x CH_3 (*t*-pentyl)), 1.33-1.40 (2H, m, H-2″), 1.43-1.50 (1H, m, 7-H_A or 7-H_B), 1.58-1.63 (1H, m, H-6), 1.99-2.02 (1H, m, 7-H_A or 7-H_B), 2.27

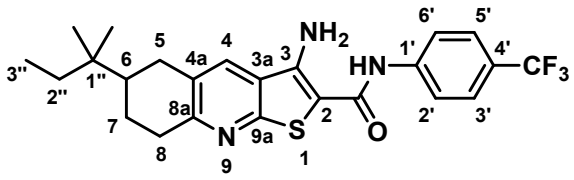
(3H, s, $ArCH_3$), 2.64-2.89 (2H, m, H-5), 2.90-3.08 (2H, m, H-8), 7.11 (2H, d, *J*= 8.4 Hz, H-3′ and H-5′), 7.24 (2H, br s, NH_2), 7.56 (2H, d, *J* = 8.4 Hz, H-2′ and H-6′), 8.19 (1H, s, H- 4), 9.26 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 8.1 (C-3″), 20.5 (4′-$\underline{C}H_3$), 23.5 (C-7), 23.7 (CH_3 (*t*-pentyl)), 23.8 (CH_3 (*t*-pentyl)), 29.5 (C-5), 32.0 (C-2″), 33.3 (C-8), 34.4 (C-1″), 41.2 (C-6), 121.1 (C-2′ and C-6′), 124.4 (3a), 128.5 (C-4a), 128.8 (C-3′ and C-5′), 131.0 (C-4), 132.2 (C-1′), 136.4 (C-4′), 146.6 (C-3), 155.9 (C-9a), 159.1 (C-8a), 164.0 (C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3432 (N-H amide), 3316 (N-H amine), 2960 (C-H aromatic), 1590 (C=O amide), 1499 (C=C aromatic), 1397 (C-H aliphatic bending), 1315 (C-N aromatic), 1074 (C-N aliphatic). *m/z* (ESI^+): 430 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 430.1934 $C_{24}H_{29}N_3NaOS$ requires 430.1924.

3-Amino-*N*-(4′-butylphenyl)-6-(*tert*-pentyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 10b



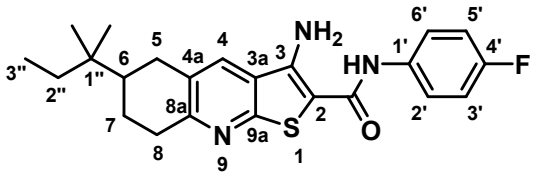
The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.15 g, 0.609 mmol), chlorophenylacetamide **8b** (0.14 g, 0.609 mmol), sodium carbonate (0.13 g, 1.22 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **10b** (0.16 g, 60%) as pale-yellow crystals. m.p. >230 °C. δ_H (400 MHz, $((CD_3)_2SO$) 0.84 (3H, t, *J*= 7.60 Hz, H-3″), 0.90 (9H, t, *J* = 7.3 Hz, 2 x CH_3 (*t*-pentyl) and H-4″), 1.23-1.31 (2H, m, H-3‴), 1.33-1.40 (2H, m, H-2″) 1.42-1.47 (1H, m, 7-H_A or 7-H_B), 1.49- 1.56 (2H, m, H-2‴), 1.58-1.63 (1H, m, H-6), 1.99-2.03 (1H, m, 7-H_A or 7-H_B), 2.54 (2H, t, *J* = 7.8 Hz, H-1‴), 2.64-2.87 (2H, m, H-5), 2.89-3.08 (2H, m, H-8), 7.11 (2H, d, *J* = 8.4 Hz, H-3′ and H-5′), 7.23 (2H, br s, NH_2), 7.56 (2H, d, *J* = 8.4 Hz, H-2′ and H-6′), 8.19 (1H, s, H-4), 9.25 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 8.1 (C-3″), 13.8 (C-4″), 21.7 (C-3‴), 23.5 (C-7), 23.7 (2 x CH_3 (*t*-pentyl)), 29.5 (C-5) 32.0 (C-2″), 33.2 (C-2‴), 33.3 (C-8), 34.2 (C-1‴), 34.4 (C-1″), 41.2 (C-6), 121.2 (C-2′ and C-6′), 124.4 (C-3a), 128.1 (C-3′ and C-5′), 128.5 (C-4a), 131.0 (C-4), 136.6 (C-1′), 137.2 (C-4′), 146.6 (C-3), 155.9 (C-9a), 159.0 (C-8a), 164.0 (C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3432 (N-H amide), 3323 (N-H amine), 2959 (C-H aromatic), 1589 (C=O amide), 1497 (C=C aromatic), 1396 (C-H aliphatic bending), 1316 (C-N aromatic), 1074 (C-N aliphatic). *m/z* (ESI^+): 472 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 472.2385 $C_{27}H_{35}N_3NaOS$ requires 472.2393.

3-Amino-6-(*tert*-pentyl)-*N*-(4'-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 10c



The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.15 g, 0.609 mmol), chlorophenylacetamide **8c** (0.14 g, 0.609 mmol), sodium carbonate (0.13 g, 1.22 mmol) and ethanol (5 mL) for 24 h to give the *title compound* **10c** (0.17 g, 60%) as yellow crystals. m.p. >230 °C. δ_H (400 MHz, ($(CD_3)_2SO$) 0.84 (3H, t, *J* = 7.6 Hz, H-3″), 0.90 (6H, d, *J* =1.4 Hz, 2 x CH_3 (*t*-pentyl)), 1.32-1.40 (2H, m, H-2″), 1.42-1.50 (1H, m, 7-H_A or 7-H_B), 1.57-1.64 (1H, m, H-6), 1.99-2.02 (1H, m, 7-H_A or 7-H_B), 2.64-2.71 (1H, m, 5-H_A or 5-H_B), 2.81-2.88 (1H, m, 5-H_A or 5-H_B), 3.02-3.08 (2H, m, H-8), 7.31 (2H, br. s, NH_2), 7.60 (2H, d, *J* =8.4 Hz, H-3′ and H-5′), 7.89 (2H, d, *J* =8.4 Hz, H-2′ and H-6′), 8.17 (1H, s, H-4), 9.66 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 8.1 (C-3″), 23.5 (C-7), 23.7 (CH_3 (*t*-pentyl)), 23.8 (CH_3 (*t*-pentyl)), 29.5 (C-5), 32.0 (C-2″), 33.3 (C-8), 34.4 (C-1″), 41.2 (C-6), 120.8 (C-2′ and C-6′), 124.3 (C-3a), 124.5 (q, $^1J_{FC}$ = 269.0 Hz, CF), 125.6 (C-3′ and C-5′), 128.4 (C-4a), 131.0 (C-4), 133.2 (C-1′), 140.3 (C-4′), 146.6 (C-3), 156.1 (C-9a), 159.4 (C-8a), 164.5 (C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3441 (N-H amide), 3326 (N-H amine), 2961 (C-H aromatic), 1602 (C=O amide), 1500 (C=C aromatic), 1313 (C-N aromatic), 1066 (C-N aliphatic), 1015 (C-F). *m/z* (ESI^+): 462 (MH^+, 100%). HRMS (ESI^+) found (MH^+): 462.1824 $C_{24}H_{27}F_3N_3OS$ requires 462.1821.

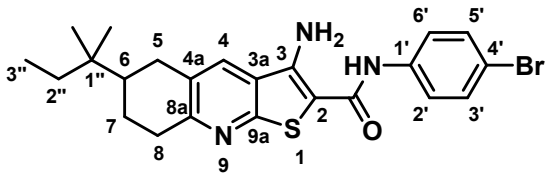
3-Amino-*N*-(4′-fluorophenyl)-6-(*tert*-pentyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 10d



The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.15 g, 0.609 mmol), chlorophenylacetamide **8d** (0.11 g, 0.609 mmol), sodium carbonate (0.13 g, 1.22 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **10d** (0.17 g, 68 %) as grey crystals. m.p. >230 °C. δ_H (400 MHz, ($(CD_3)_2SO$) 0.84 (3H, t, *J* = 7.6 Hz, H-3″), 0.90 (6H, d, *J* = 1.4 Hz, 2 x CH_3 (*t*-pentyl)), 1.30-1.40 (2H, m, H-2″), 1.41-1.50 (1H, m, 7-H_A or 7-H_B), 1.57-1.63 (1H, m, H-6), 1.99-2.03 (1H, m, 7-H_A or 7-H_B), 2.64-2.72 (1H, m, 5-H_A or 5-H_B), 2.81-2.87 (1H, m, 5-H_A or 5-H_B), 2.89-2.96 (1H, m, 8-H_A or 8-H_B), 3.03-3.08 (1H, m, 8-H_A or 8-H_B), 7.12-7.16 (2H, m, H-3′ and H-5′), 7.26 (2H, br s, NH_2), 7.67-7.70 (2H, m, H-2′ and H-6′), 8.19 (1H, s, H-4), 9.40 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 8.5 (C-3″), 23.9 (C-7), 24.2 (2 x CH_3 (*t*-pentyl)), 30.0 (C-5), 32.5 (C-2″), 33.7 (C-8), 34.9 (C-1″), 41.7 (C-6),

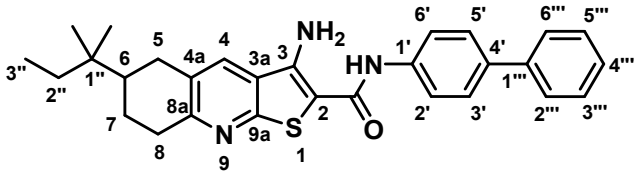
115.3 (d, $^{2}J_{FC}$= 22.2 Hz, C-3′ and C-5′), 123.4 (d, $^{3}J_{FC}$= 7.7 Hz, C-2′ and C-6′), 124.5 (C-3a), 129.0 (C-4a), 130.4 (C-1′), 131.5 (C-4), 135.8 (C-4′), 147.3 (C-3), 156.4 (C-9a), 159.6 (C-8a), 164.5 (C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3404 (N-H amide), 3302 (N-H amine), 2960 (C-H aromatic), 1595 (C=O amide), 1490 (C=C aromatic), 1394 (C-H aliphatic bending), 1331 (C-N aromatic), 1112 (C-F), 1070 (C-N aliphatic). *m/z* (ESI^{+}): 412 (MH^{+}, 100%). HRMS (ESI+) found (MNa^{+}): 412.1862 $C_{23}H_{27}FN_3OS$ requires 412.1853.

3-Amino-*N*-(4′-bromophenyl)-6-(*tert*-pentyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 10e



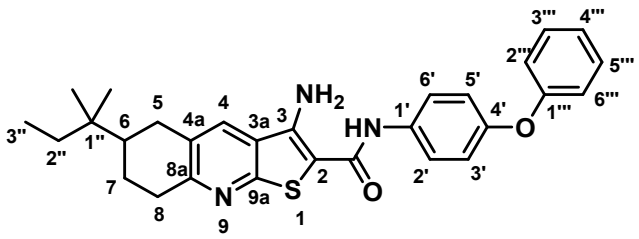
The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.15 g, 0.609 mmol), chlorophenylacetamide 8**e** (0.15 g, 0.609 mmol), sodium carbonate (0.13 g, 1.22 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **10e** (0.20 g, 70%) as yellow crystals. m.p. >230 °C. δ_H (400 MHz, (CD_3)$_2$SO) 0.84 (3H, t, *J* = 8.0 Hz, H-3″), 0.89 (6H, s, 2 x CH_3 (*t*-pentyl)), 1.33-1.38 (2H, m, H-2″), 1.42-1.50 (1H, m, 7-H_A or 7-H_B), 1.58-1.63 (1H, m, H-6), 1.99-2.02 (1H, m, 7-H_A or 7-H_B), 2.64-2.89 (2H, m, H-5), 2.90-3.08 (2H, m, H-8), 7.31 (2H, br s, NH_2), 7.49 (2H, d, *J* = 8.8 Hz, H-3′ and H-5′), 7.67 (2H, d, *J* = 8.0 Hz, H-2′ and H-6′), 8.20 (1H, s, H-4), 9.46 (1H, br s, NH). δ_C (100 MHz, (CD_3)$_2$SO) 8.1 (C-3″), 23.4 (C-7), 23.7 (2 x CH_3 (*t*-pentyl)), 29.5 (C-5) 32.0 (C-2″), 33.3 (C-8), 34.4 (C-1″), 41.2 (C-6), 122.9 (C-2′ and C-6′), 124.3 (C-3a), 128.5 (C-4a), 131.06 (C-4), 131.11 (C-3′ and C-5′), 138.1 (C-1′), 140.3 (C-4′), 147.0 (C-3), 156.0 (C-9a), 159.2 (C-8a), 164.1(C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3442 (N-H amide), 3323 (N-H amine), 2961 (C-H aromatic), 1604 (C=O amide), 1501 (C=C aromatic), 1393 (C-H aliphatic bending), 1328 (C-N aromatic), 1070 (C-N aliphatic), 884 (C-Br). *m/z* (ESI^{+}): 472 (MH^{+}, 100%). HRMS (ESI^{+}) found (MH^{+}): 472.1052 $C_{23}H_{27}BrN_3OS$ requires 472.1053.

***N*-([1′,1″-Biphenyl]-4′-yl)-3-amino-6-(*tert*-pentyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 10f**



The reaction was carried out following General Procedure **D** using carbonitrile **13** (0.15 g, 0.609 mmol), chlorophenylacetamide **8f** (0.15 g, 0.609 mmol), sodium carbonate (0.13 g, 1.22 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **10f** (0.16 g, 54%) as yellow crystals. m.p. >230 °C. δ_H (400 MHz, ($(CD_3)_2SO$) 0.82 (3H, t, J = 7.5 Hz, H-3″), 0.90 (6H, d, J = 0.9 Hz, 2 x CH_3 (*t*-pentyl)), 1.32-1.40 (2H, m, H-2″), 1.42-1.51 (1H, m, 7-H_A or 7-H_B), 1.58-1.64 (1H, m, H-6), 2.00-2.02 (1H, m, 7-H_A or 7-H_B), 2.65-2.72 (1H, m, 5-H_A or 5-H_B), 2.82-2.87 (1H, m, 5-H_A or 5-H_B), 2.90-2.97 (1H, m, 8-H_A or 8-H_B), 3.04-3.09 (1H, m, 8-H_A or 8-H_B), 7.31-7.35 (3H, m, H-4‴ and NH_2), 7.43-7.47 (2H, m, H-3′ and H-5′), 7.62-7.68 (4H, m, 4 x Ar‴-H), 7.78-7.82 (2H, d, J = 8.7 Hz, H-2′ and H-6′), 8.22 (1H, s, H-4), 9.45 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 8.1 (C-3″), 23.4 (C-7), 23.72 (CH_3 (*t*-pentyl)), 23.79 (CH_3 (*t*-pentyl)), 29.6 (C-5) 32.0 (C-2″), 33.3 (C-8), 34.4 (C-1″), 41.2 (C-6), 121.3 (C-2′ and C-6′), 124.4 (C-3a), 126.2 (C-2‴ and C-6‴ or C-3‴ and C-5‴), 126.6 (C-3‴ and C-5‴ or C-2‴ and C-6‴), 128.6 (C-4a), 128.9 (C-3′ and C-5′), 131.1 (C-4), 134.9 (C-4'), 139.8 (C-1'), 146.9 (C-3), 156.0 (C-9a), 159.8 (C-8a), 164.1 (C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3425 (N-H amide), 3311 (N-H amine), 2961 (C-H aromatic), 1590 (C=O amide), 1501 (C=C aromatic), 1396 (C-H aliphatic bending), 1319 (C-N aromatic), 1072(C-N aliphatic). *m/z* (ESI^+): 492 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 492.2068 $C_{29}H_{31}N_3NaOS$ requires 492.2080.

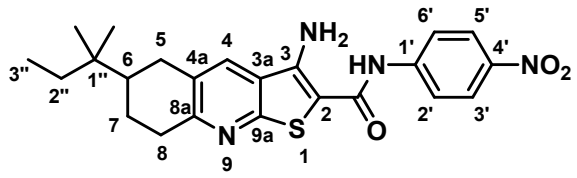
3-Amino-6-(*tert*-pentyl)-*N*-(4′-phenoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 10g



The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.15 g, 0.609 mmol), chlorophenylacetamide **8g** (0.15 g, 0.609 mmol), sodium carbonate (0.13 g, 1.22 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **19g** (0.20 g, 68%) as yellow crystals. m.p. >230 °C. δ_H (400 MHz, ($(CD_3)_2SO$) 0.84 (3H, t, J = 7.5 Hz, H-3″), 0.91 (6H, s, 2 x CH_3 (*t*-pentyl)), 1.33-1.42 (2H, m, H-2″), 1.43-1.52 (1H, m, 7-H_A or 7-H_B), 1.59-1.65 (1H, m, H-6), 2.01-2.04 (1H, m, 7-H_A or 7-H_B), 2.66-2.89 (2H, m, H-5), 2.90-3.10 (2H, m, H-8), 7.00 (4H, d, J = 8.7 Hz, H-2″, H-6″, H-3′, and H-5′), 7.12

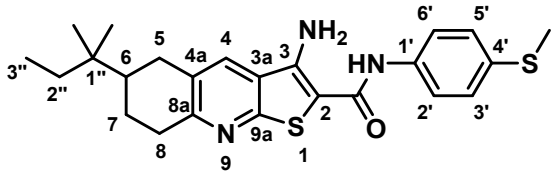
(1H, t, *J* = 7.4 Hz, H-4″), 7.27 (2H, br s, NH_2), 7.37-7.41 (2H, m, H-3″ and H-5″), 7.68-7.72 (2H, d, *J* = 9.0 Hz, H-2′ and H-6′), 8.21 (1H, s, H-4), 9.40 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 8.06 (C-3″), 23.5 (C-7), 23.7 (2 x CH_3 (*t*-pentyl)), 29.5 (C-5) 32.0 (C-2″), 33.3 (C-8), 34.4 (C-1″), 41.2 (C-6), 117.9 (C-2″ and C-6″), 119.0 (C-3′ and C-5′), 122.8 (C-2′ and C-6′), 123.0 (C-4″), 124.4 (C-3a), 128.5 (C-4a), 130.00 (C-3″ and C-5″), 129.95 (C-4), 134.9 (C-1′ or C-4′), 146.4 (C-3), 151.9 (C-4′ or C-1′), 156.0 (C-9a), 157.3 (C-1″), 159.1 (C-8a), 164.0 (C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3441 (N-H amide), 3324 (N-H amine), 2961 (C-H aromatic), 1602 (C=O amide), 1501 (C=C aromatic), 1394 (C-H aliphatic bending), 1327 (C-N aromatic), 1246 (C-O aryl ether),1069 (C-N aliphatic). *m/z* (ESI^+): 508 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 508.2019 $C_{29}H_{31}N_3NaO_2S$ requires 508.2029.

3-Amino-*N*-(4′-nitrophenyl)-6-(*tert*-pentyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 10h



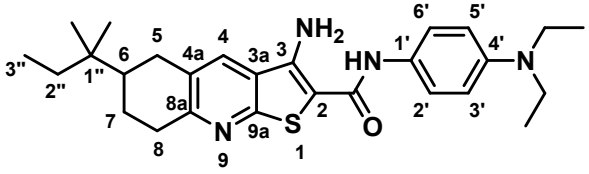
The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.15 g, 0.609 mmol), chlorophenylacetamide **8h** (0.13 g, 0.609 mmol), sodium carbonate (0.13 g, 1.22 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **10h** (0.17 g, 65 %) as pale-yellow crystals. m.p. >230 °C. δ_H (400 MHz, ((CD3)2SO) 0.84 (3H, t, *J*= 7.5 Hz, H-3″), 0.89 (6H, s, 2 x CH_3 (*t*-pentyl)), 1.31-1.40 (2H, m, H-2″), 1.42-1.50 (1H, m, 7-H_A or 7-H_B), 1.57-1.63 (1H, m, H-6), 1.99-2.02 (1H, m, 7-H_A or 7-H_B), 2.64-2.71 (1H, m, 5-H_A or 5-H_B), 2.81-2.85 (1H, m, 5-H_A or 5-H_B), 2.91-2.96 (1H, m, 8-H_A or 8-H_B), 3.02-3.08 (1H, m, 8-H_A or 8-H_B), 7.39 (2H, br s, NH_2), 7.92 (2H, d, *J* = 8.6 Hz, H-3′ and H-5′), 8.14-8.16 (2H, d, *J* =9.0 Hz, H-2′ and H-6′), 8.19 (1H, s, H-4), 9.92 (1H, br s, NH). δ_C (100 MHz, (CD3)2SO) 8.1 (C-3″), 23.5 (C-7), 23.71 (CH_3 (*t*-pentyl)), 23.78 (CH_3 (*t*-pentyl)) 29.6 (C-5) 32.0 (C-2″), 33.3 (C-8), 34.4 (C-1″), 41.2 (C-6), 120.2 (C-3′ and C-5′), 124.3 (C-3a), 124.6 (C-2′ and C-6′), 128.5 (C-4a), 131.1 (C-4), 131.3 (C-1′), 141.1 (C-4′), 147.0 (C-3), 156.3 (C-9a), 159.3 (C-8a), 165.1 (C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3439 (N-H amide), 3325 (N-H amine), 2963 (C-H aromatic), 1599 (C=O amide), 1498 (C=C aromatic), 1405 (C-H aliphatic bending), 1365 (N-O), 1308 (C-N aromatic), 1071 (C-N aliphatic). *m/z* (ESI^+): 461 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 461.1622 $C_{23}H_{26}N_4NaO_3S$ requires 461.1618.

3-Amino-*N*-(4′-(methylthio)phenyl)-6-(*tert*-pentyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2carboxamide 10i



The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.15 g, 0.609 mmol), chlorophenylacetamide **8i** (0.13 g, 0.609 mmol), sodium carbonate (0.13 g, 1.22 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **10i** (0.13 g, 49%) as pale-yellow crystals. m.p. >230 °C. δ_H (400 MHz, ($(CD_3)_2SO$) 0.84 (3H, t, *J*= 7.5 Hz, H-3″), 0.90 (6H, s, 2 x CH_3 (*t*-pentyl)), 1.34-1.40 (2H, m, H-2″), 1.43-1.50 (1H, m, 7-H_A or 7-H_B), 1.58-1.63 (1H, m, H-6), 1.99-2.03 (1H, m, 7-H_A or 7-H_B), 2.47 (3H, s, S-CH3), 2.64-2.71 (1H, m, 5-H_A or 5-H_B), 2.81-2.89 (1H, m, 5-H_A or 5-H_B), 2.91-2.96 (1H, m, 8-H_A or 8-H_B), 3.03-3.08 (1H, m, 8-H_A or 8-H_B), 7.26 (2H, br s, NH_2), 7.49 (2H, d, *J* = 8.8 Hz, H-3′ and H-5′), 7.67 (2H, d, *J* = 8.0 Hz, H-2′ and H-6′), 8.19 (1H, s, H-4), 9.35 (1H, br s, NH).
δ_C (100 MHz, $(CD_3)_2SO$) 8.1 (C-3″), 15.6 (S-CH_3), 23.5 (C-7), 23.7 (2 x CH_3 (*t*-pentyl)), 29.5 (C-5) 32.0 (C-2″), 33.3 (C-8), 34.4 (C-1″), 41.2 (C-6), 121.7 (C-2′ and C-6′), 122.8 (C-3a), 126.8 (C-3′ and C-5′), 128.5 (C-4a), 131.0 (C-4), 133.5 (C-1′), 137.5 (C-4′), 146.8 (C-3), 156.0 (C-9a), 158.6 (C-8a), 164.0 (C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3405 (N-H amide), 3312 (N-H amine), 2960 (C-H aromatic), 1606 (C=O amide), 1490 (C=C aromatic), 1396 (C-H aliphatic bending), 1327 (C-N aromatic), 1073 (C-N aliphatic). *m/z* (ESI^+): 462 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 462.1639 $C_{24}H_{29}N_3NaOS_2$ requires 462.1644.

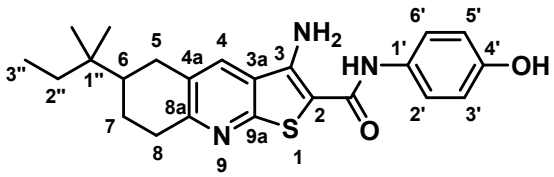
3-Amino-*N*-(4′-(diethylamino)phenyl)-6-(*tert*-pentyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 10j



The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.15 g, 0.609 mmol), chlorophenylacetamide **8j** (0.15 g, 0.609 mmol), sodium carbonate (0.13 g, 1.22 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **10j** (0.20 g, 72%) as yellow crystals. m.p. >230 °C. δ_H (400 MHz, ($(CD_3)_2SO$) 0.84 (3H, t, *J* = 7.6 Hz, H-3″), 0.90 (6H, d, *J* = 1.5 Hz, 2 x CH_3 (*t*-pentyl)), 1.08 (6H, t, *J*= 7.0 Hz, 2 x CH_3 (*tert*-amine)), 1.32 – 1.42 (2H, m, H-2″), 1.40 – 1.50 (1H, m, 7-H_A), 1.57 – 1.64 (1H, m, H-6), 1.98 – 2.03 (1H, m, H_B-7), 2.64-2.71 (1H, m, 5-H_A), 2.81-2.86 (1H, m, 5-H_B), 2.89-2.96 (1H, m, 8-H_A), 3.02-3.08 (1H, m, 8-H_B), 3.31 (1H, q, *J* = 7.6 Hz, 2 x CH_2 (*tert*-amine)), 6.62 (2H, d, *J*

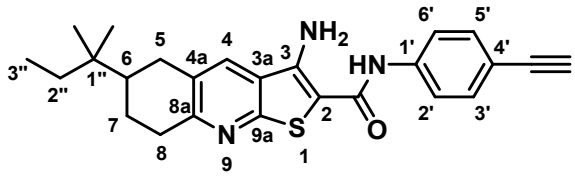
= 9.1 Hz, H-3′ and H-5′), 7.15 (1H, br s, NH_2), 7.40 (2H, d, *J* = 9.0 Hz, H-2′ and H-6′), 8.16 (1H, s, H-4), 9.05 (1H, s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 8.1 (C-3″), 12.4 (2 x CH_3 (*tert*-amine)), 23.5 (C-7), 23.7 (CH_3 (*t*-pentyl)), 23.8 (CH_3 (*t*-pentyl)), 29.5 (C-5), 32.0 (C-2″), 33.2 (C-8), 34.4 (C-1″), 41.2 (C-6), 43.7 (2 x CH_2 (*tert*-amine)), 96.4 (C-2), 111.6 (C-3′ and C-5′), 123.3 (C-2′ and C-6′), 124.5 (C-3a), 127.3 (C-1′), 128.4 (C-4a), 130.8 (C-4), 144.2 (C-4′), 145.9 (C-3), 155.8 (C-9a), 158.7 (C-8a), 163.6 (C=O). ν_{max} (ATR)/cm^{-1} 3434 (N-H amide), 3318 (N-H amine), 2967 (C-H aromatic), 1600 (C=O amide), 1513 (C=C aromatic), 1394 (C-H aliphatic bending), 1319 (C-N aromatic), 1073 (C-N aliphatic). *m/z* (ESI^+): 487 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 487.2508 $C_{27}H_{36}N_4NaOS$ requires 487.2502.

3-Amino-*N*-(4′-hydroxyphenyl)-6-(*tert*-pentyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 10k



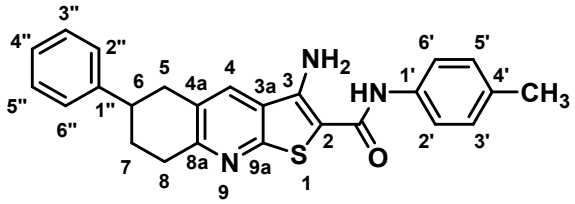
The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.15 g, 0.609 mmol), chlorophenylacetamide **8k** (0.11 g, 0.609 mmol), sodium carbonate (0.13 g, 1.22 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **10k** (0.13 g, 52%) as light brown crystals. m.p. >230 °C. δ_H (400 MHz, $((CD_3)_2SO$) 0.85 (3H, t, *J* = 8.0 Hz, H-3″), 0.91 (6H, d, *J* = 0.7 Hz, 2 x CH_3 (*t*-pentyl)), 1.31-1.41 (2H, m, H-2″), 1.43-1.51 (1H, m, 7-H_A or 7-H_B), 1.59-1.65 (1H, m, H-6), 2.01-2.04 (1H, m, 7-H_A or 7-H_B), 2.66-2.73 (1H, m, 5-H_A or 5-H_B), 2.82-2.88 (1H, m, 5-H_A or 5-H_B), 2.90-2.97 (1H, m, 8-H_A or 8-H_B), 3.04-3.09 (1H, m, 8-H_A or 8-H_B), 3.33 (1H, br s, OH), 6.71 (2H, d, *J* = 8.8 Hz, H-3′ and H-5′), 7.19 (2H, br s, NH_2), 7.40 (2H, d, *J* = 8.8 Hz, H-2′ and H-6′), 8.18 (1H, s, H-4), 9.14 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 8.1 (C-3″), 23.5 (C-7), 23.72 (CH_3 (*t*-pentyl)), 23.78 (CH_3 (*t*-pentyl)), 29.5 (C-5), 32.0 (C-2″), 33.3 (C-8), 34.4 (C-1″), 41.2 (C-6), 114.8 (C-3′ and C-5′), 123.3 (C-2′ and C-6′), 124.5 (C-3a), 128.4 (C-4a), 130.1 (C-1′), 130.9 (C-4), 137.0 (C-4′), 146.4 (C-3), 155.9 (C-9a), 158.8 (C-8a), 163.8 (C=O). ν_{max} (ATR)/cm^{-1} 3468 (O-H), 3460 (N-H amide), 3321 (N-H amine), 2961 (C-H aromatic), 1589 (C=O amide), 1493 (C=C aromatic), 1395 (C-H aliphatic bending), 1316 (C-N aromatic), 1070 (C-N aliphatic). *m/z* (ESI^+): 410 (MH^+, 100%). HRMS (ESI^+) found (MH^+): 410.1896 $C_{23}H_{28}N_3O_2S$ requires 410.1897.

3-Amino-*N*-(4′-ethynylphenyl)-6-(*tert*-pentyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 10l



The reaction was carried out following General Procedure **D** using carbonitrile **3j** (0.10 g, 0.406 mmol), chlorophenylacetamide **8l** (0.079 g, 0.406 mmol), sodium carbonate (0.086 g, 0.812 mmol) and ethanol (3 mL) for 48 h to give the *title compound* **10l** (0.15 g, 88%) as yellow crystals. m.p. >230 °C. δ_H (400 MHz, ($(CD_3)_2SO$) 0.84 (3H, t, *J* = 7.5 Hz, H-3″), 0.89 (6H, s, 2 x CH_3 (*t*-pentyl)), 1.31-1.40 (2H, m, H-2″), 1.41- (1H, m, 7-H_A or 7-H_B), 1.58-1.63 (1H, m, H-6), 1.99-2.02 (1H, m, H-7-H_A or 7-H_B), 2.64-2.89 (2H, m, H-5), 2.90-3.08 (2H, m, H-8), 7.32 (2H, s, NH2), 7.41 (2H, d, *J* = 8.7 Hz, H-3′ and H-5′), 7.74 (2H, d, *J* = 8.7 Hz, H-2′ and H-6′), 8.21 (1H, s, H-4), 9.50 (1H, s, NH). C≡C<u>H</u> is not observed. δC (100 MHz, $(CD_3)_2SO$) 8.1 (C-3″), 23.4 (C-7), 23.71 (CH_3 (*t*-pentyl)), 23.78 (CH_3 (*t*-pentyl)), 29.5 (C-5) 32.0 (C-2″), 33.3 (C-8), 34.4 (C-1″), 41.2 (C-6), 79.8 (C≡<u>C</u>H), 83.7 (<u>C</u>≡CH) 115.9 (C-4′), 120.6 (C-2′ and C-6′), 124.3 (C-3a), 128.6 (C-4a), 131.1 (C-4) 132.0 (C-3′ and C-5′), 140.2 (C-1′), 147.2 (C-3), 156.0 (C-9a), 159.4 (C-8a), 164.1 (C=O). ν_{max} (ATR)/cm^{-1} 3437 (N-H amide), 3326 (N-H amine), 2963 (C-H aromatic), 1608 (C=O amide), 1496 (C=C aromatic), 1397 (C-H aliphatic bending), 1312 (C-N aromatic), 1074 (C-N aliphatic). *m/z* (ESI^+): 418 (MH^+, 100%). HRMS (ESI^+) found (MH^+): 418.1948 $C_{25}H_{28}N_3OS$ requires 418.1948.

3-Amino-6-phenyl-*N*-(*p*-tolyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9a

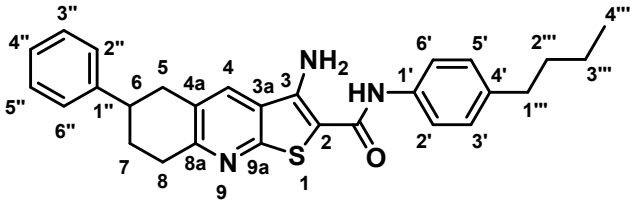


The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8a** (0.10 g, 0.563 mmol), sodium carbonate (0.12 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9a** (0.11 g, 49%) as yellow crystals. m.p.>230 °C.

δ_H (400 MHz, ($(CD_3)_2SO$) 2.06-2.13 (2H, m, H-7), 2.27 (3H, s, CH_3), 3.07-3.16 (5H, m, H-6, H-5 and H-8), 7.10-7.13 (2H, d, *J* = 8.4 Hz, H-3′ and H-5′), 7.22-7.26 (1H, m, H-4″), 7.29 (2H, br s, NH_2), 7.32-7.37 (4H, m, H-3″, H-5″, H-2″ and H-6″), 7.56-7.58 (2H, d, *J*= 8.4 Hz, H-2′ and H-6′), 8.20 (1H, s, H-4), 9.23 (1H, s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 20.5 (CH_3), 29.7 (C-7), 32.6 (C-8), 36.3 (C-5), 40.2 (C-6), 96.0 (C-2), 121.2 (C-2′ and C-6′), 124.5 (C-3a), 126.3 (C-4″), 126.8 (C-2″ and C-6″), 127.9 (C-4a), 128.5 (C-3″ and C-5″), 128.8 (C-3′ and C-5′), 130.7 (C-4), 132.2 (C-4′), 135.7 (C-1′), 145.7 (C-1″), 146.6 (C-3), 156.2 (C-9a), 158.3 (C- 8a), 163.9 (C=O). ν_{max} (ATR)/cm^{-1} 3316 (N-H amide), 2961 (C-H aromatic), 1591 (C=O amide), 1501 (C=C aromatic), 1394 (C-H aliphatic bending), 1324 (C-N

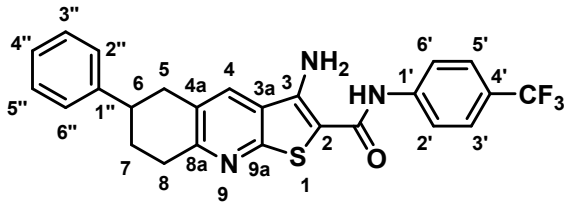
aromatic), 1070 (C-N aliphatic). *m/z* (ESI^+): 414 (MH^+, 100%). HRMS (ESI^+) found (MH^+): 414.1672 $C_{25}H_{24}N_3OS$ requires 414.1635.

3-Amino-*N*-(4′-butylphenyl)-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9b



The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8b** (0.13 g, 0.563 mmol), sodium carbonate (0.12 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9b** (0.16 g, 60%) as yellow crystals. m.p. > 230 °C. δ_H (400 MHz, $((CD_3)_2SO)$ 0.90 (3H, t, *J* = 7.4 Hz, H-4‴), 1.28-1.33 (2H, m, H-3‴), 1.51-1.58 (2H, m, H-2‴), 2.11-2.13 (2H, m, H-7), 2.54 (2H, t, *J* =7.7 Hz, H-1‴), 3.08-3.14 (5H, m, H-6, H-5 and H-8), 7.13 (2H, d, *J* = 8.5 Hz, H-3′ and H-5′), 7.24-7.26 (1H, m, H-4″), 7.28 (2H, br s, NH_2), 7.33-7.38 (4H, m, H-3″, H-5″, H-2″, and H-6″), 7.57 (2H, d, *J* = 6.87 Hz, H-2′ and H-6′), 8.20 (1H, s, H-4), 9.29 (1H, s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 13.8 (C-4‴), 21.7 (C-3‴), 29.7 (C-7), 32.6 (C-5 or C-8), 33.3 (C-2‴), 34.3 (C- 1‴), , 36.3 (C-8 or C-5), 40.5 (C-6), 106.9 (C-2), 121.2 (C-2′ and C-6′), 123.0 (C-3a), 126.3 (C-4″), 126.8 (C-3″ and C-5″), 128.1 (C-2″ and C-6″), 128.5 (C-3′ and C-5′), 131.6 (C-4), 132.0 (C-4a), 137.3 (C-1′), 137.6 (C-4′), 146.9 (C-3), 149.8 (C-1″), 157.3 (C-9a), 158.1 (C-8a), 162.8 (C=O). ν_{max} (ATR)/cm^{-1} 3437 (N-H amide), 3325 (N-H amine), 2960 (C-H aromatic), 1589 (C=O amide), 1500 (C=C aromatic), 1395 (C-H aliphatic bending), 1312 (C-N aromatic), 1069 (C-N aliphatic). *m/z* (ESI^+): 478 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 478.1920 $C_{28}H_{29}N_3NaOS$ requires 478.1924.

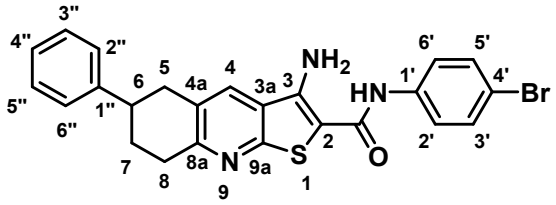
3-Amino-6-phenyl-*N*-(4′-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9c



The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8c** (0.13 g, 0.563 mmol), sodium carbonate (0.12 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9c** (0.17 g, 67%) as yellow crystals. m.p.>230 °C.

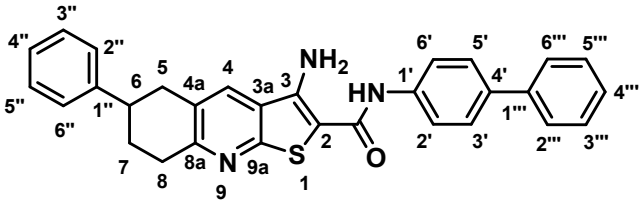
δ_H (400 MHz, ((CD$_3$)$_2$SO) 2.08-2.13 (2H, m, C-7), 3.08 (3H, s, H-6 and H-5), 3.10-3.14 (2H, m, H-8), 7.22- 7.26 (1H, m, H-4″), 7.32-7.36 (4H, m, H-3″, H-5″, H-2″, and H-6″), 7.38-7.41 (2H, m, NH$_2$), 7.65 (2H, d, J = 8.3 Hz, H-3′ and H-5′), 7.93 (2H, d, J = 8.3 Hz, H-2′ and H-6′), 8.22 (1H, s, H-4), 9.70 (1H, s, NH). δ_C (100 MHz, (CD$_3$)$_2$SO) 29.7 (C-7), 32.6 (C-8), 36.3 (C-5), 40.2 (C-6), 88.5 (C-2), 120.7 (C-2′ and C-6′), 121.6 (C-4′), 123.3 (C-3a), 124.6 (q, $^1J_{FC}$ = 269.6 Hz, C-F), 125.5 (d, $^3J_{FC}$ = 3.8 Hz, C-3′ and C-5′), 126.3 (C-4″), 126.8 (C-2″ and C-6″), 127.9 (C-4a), 128.5 (C-3″ and C-5″), 130.8 (C-4), 135.1 (C-1′), 145.7 (C-1″ and C-3), 156.4 (C-9a), 158.5 (C-8a), 164.6 (C=O). ν_{max} (ATR)/cm^{-1} 3429 (N-H amide), 3321 (N-H amine), 2961 (C-H aromatic), 1591 (C=O amide), 1498 (C=C aromatic), 1314 (C-N aromatic), 1064 (C-N aliphatic), 1016 (C-F). *m/z* (ESI$^+$): 468 (MH$^+$, 100%). HRMS (ESI$^+$) found (MH$^+$): 468.1366 $C_{25}H_{21}F_3N_3OS$ requires 468.1352.

3-Amino-*N*-(4′-bromophenyl)-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9e



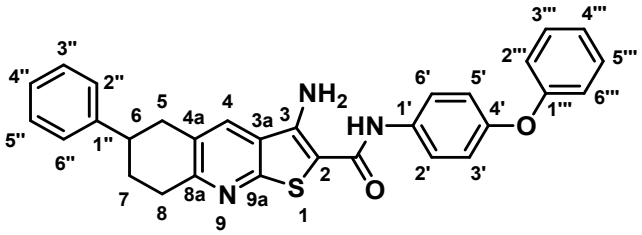
The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8e** (0.14 g, 0.563 mmol), sodium carbonate (0.12 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9e** (0.19 g, 69%) as yellow crystals. m.p. >230 °C. δ_H (400 MHz, ((CD$_3$)$_2$SO) 2.06-2.13 (2H, m, H-7), 3.07-3.13 (5H, m, H-6, H-5 and H-8), 7.22-7.26 (1H, m, H-4″), 7.32-7.37 (6H, m, H-3″, H-5″, H-2″, H-6″ and NH$_2$), 7.47 (2H, d, J = 8.9 Hz, H-3′ and H-5′), 7.68 (2H, d, J = 8.8 Hz, H-2′ and H-6′), 8.20 (1H, s, H-4), 9.50 (1H, s, NH). δ_C (100 MHz, (CD$_3$)$_2$SO) 29.7 (C-7), 32.6 (C-8), 36.0 (C-5), 40.2 (C-6), 99.1 (C-2), 115.1 (C-4′), 122.9 (C- 2′ and C-6′), 124.4 (C-3a), 126.3 (C-4″), 126.8 (C-2″ and C-6″), 127.9 (C-4a), 128.5 (C-3″ and C-5″), 130.7 (C-4), 131.1 (C-3′ and C-5′), 132.1 (C-1′), 145.7 (C-1″), 147.2 (C-3), 156.2 (C-9a), 157.9 (C-8a), 161.7 (C=O). ν_{max} (ATR)/cm^{-1} 3424 (N-H amide), 3317 (N-H amine), 2970 (C-H aromatic), 1605 (C=O amide), 1516 (C=C aromatic), 1395 (C-H aliphatic bending), 1310 (C-N aromatic), 1070 (C-N aliphatic), 869 (C-Br). *m/z* (ESI$^+$): 478 (MH$^+$, 100%). HRMS (ESI$^+$) found (MH$^+$): 478.0584 $C_{24}H_{21}BrN_3OS$ requires 478.0583.

***N*-([1,1′-Biphenyl]-4′-yl)-3-amino-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9f**



The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8f** (0.14 g, 0.563 mmol), sodium carbonate (0.12 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9f** (0.24 g, 89%) as yellow crystals. m.p. > 230 °C. δ_H (400 MHz, ($(CD_3)_2SO$) 1.99-2.12 (2H, m, H-7), 2.80-2.87 (1H, m, 5-H_A), 2.93-3.00 (3H, m, H-6 and 8-H_A, 5-H_B), 3.09-3.15 (1H, m, 8-H_B), 7.20-7.24 (1H, m, H-4″ or H-4‴), 7.28-7.37 (6H, m, NH_2, 4 x Ar-H), 7.42-7.47 (2H, m, H-3′ and H-5′), 7.62-7.65 (4H, m, 4 x Ar-H), 7.66-7.69 (2H, m, H-2′ and H-6′), 7.79-7.83 (1H, m, H-4‴ or H-4″), 8.00 (1H, s, H-4), 10.4 (1H, s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 29.2 (C-7), 32.6 (C-8), 34.75 (C-5), 39.2 (C-6), 116.7 (C-3a), 119.5 (C-2′ and C- 6′), 121.3 (C-4‴ or C-4″), 126.2 (C-1″ or C-1‴), 126.5 (C-1‴ or C-1″), 126.7 (C-4″ or C-4‴), 126.8 (2x Ar-C), 127.0 (2 x Ar-C) 127.9 (2 x Ar-C), 128.0 (C-4a), 128.4 (2 x Ar-C), 128.9 (C-3′ and C-5′), 135.0 (C- 4′), 139.8 (C-1′), 142.0 (C-4), 145.2 (C-3), 156.8 (C-9a), 161.0 (C-8a), 164.1 (C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3308 (N-H amide), 3029 (N-H amine), 2960 (C-H aromatic), 1592 (C=O amide), 1502 (C=C aromatic), 1391 (C-H aliphatic bending), 1325 (C-N aromatic), 1069 (C-N aliphatic). *m/z* (ESI^+): 498 (MNa^+, 100%). HRMS (ESI^+) found (MNa^+): 498.1608 $C_{30}H_{25}N_3NaOS$ requires 498.1611.

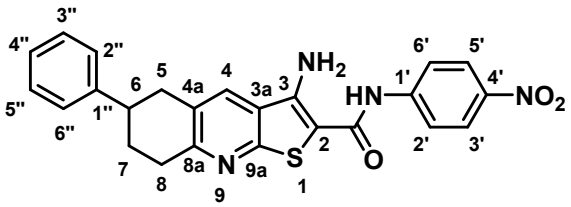
3-Amino-*N*-(4′-phenoxyphenyl)-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9g



The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8g** (0.14 g, 0.563 mmol), sodium carbonate (0.12 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9g** (0.17 g, 60%) as yellow crystals. m.p. >230 °C. δ_H (400 MHz, ($(CD_3)_2SO$) 2.08-2.13 (2H, m, H-7), 3.08 (3H, s, H-6 and H-5), 3.10-3.14 (2H, m, H-8), 6.99-7.01 (4H, d, *J* = 8.9 Hz, H-2‴, H-6‴, H-3‴, and H-5‴), 7.09-7.13 (1H, m, H-4‴), 7.22-7.26 (1H, m, H- 4″), 7.31 (2H, br s, NH_2), 7.31-7.40 (6H, m, H-2″, H-6″, H-3″, H-5″, H-3′, and H-5′), 7.67-7.72 (2H, m, H- 2′ and H-6′), 8.21 (1H, s, H-4), 9.41 (1H, s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 29.7 (C-7), 32.6 (C-8), 36.3 (C-5), 40.2 (C-6), 95.8 (C-2), 118.0 (C-2‴ and C-6‴ or C-3‴ and C-5‴), 119.0 (C-3‴ and C-

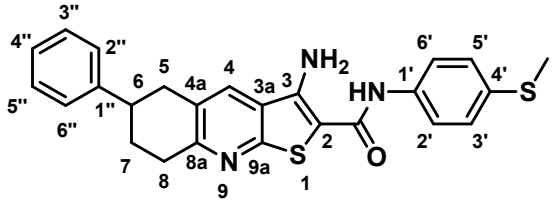
5‴ or C-2‴ and C-6‴), 121.6 (C-3a), 122.9 (C-2′ and C-6′), 123.0 (C-4‴), 126.3 (C-4″), 126.8 (C-3′ and C-5′), 127.9 (C-4a), 128.5 (C-2″ and C-6″) 130.0 (C-3″ and C-5″), 130.8 (C- 4), 133.1 (C-1′), 135.6 (C-1‴), 142.7 (C-4′), 145.7 (C-1″), 148.0 (C-3), 157.3 (C-9a), 158.4 (C-8a), 164.0 (C=O). ν_{max} (ATR)/cm^{-1} 3448 (N-H amide), 3335 (N-H amine), 3029 (C-H aromatic), 1589 (C=O amide), 1500 (C=C aromatic), 1397 (C-H aliphatic bending), 1309 (C-N aromatic), 1220 (C-O aryl ether), 1068 (C-N aliphatic). *m/z* (ESI$^+$): 492 (MH$^+$, 100%). HRMS (ESI$^+$) found (MH$^+$): 492.1740 $C_{30}H_{26}N_3O_2S$ requires 492.1740.

3-Amino-*N*-(4′-nitrophenyl)-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9h



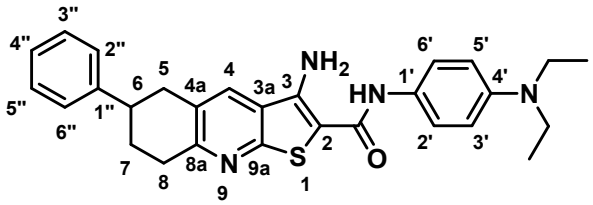
The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8h** (0.12 g, 0.563 mmol), sodium carbonate (0.12 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9h** (0.20 g, 80%) as yellow crystals. m.p. >230 °C. δ_H (400 MHz, ((CD$_3$)$_2$SO) 2.06-2.13 (2H, m, H-7), 3.07 (3H, s, H-6 and H-5), 3.09-3.13 (2H, m, H-8), 7.22-7.26 (1H, m, H-4″), 7.34-7.36 (4H, m, H-3″, H-5″, H-2″, and H-6″), 7.37-7.41 (2H, m, NH$_2$), 7.91 (2H, d, *J* = 7.7 Hz, H-3′ and H-5′), 8.14 (2H, d, *J* = 8.8 Hz, H-2′ and H-6′), 8.18 (1H, s, H-4), 9.95 (1H, s, NH). δ_C (100 MHz, (CD$_3$)$_2$SO) 29.7 (C-7), 32.6 (C-8), 36.4 (C-5), 40.2 (C-6), 120.6 (C-3′ and C-5′) 124.6 (C-2′ and C-6′), 125.2 (C-3a), 126.3 (C-4″), 126.8 (C-2″ and C-6″), 127.4 (C-4a), 128.5 (C-3″ and C-5″), 130.5 (C-4), 136.5 (C-1′), 142.3 (C-4′), 145.8 (C-1″), 152.5 (C-3), 156.6 (C-9a), 158.0 (C-8a), 164.0 (C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3437 (N-H amide), 3330 (N-H amine), 2970 (C-H aromatic), 1591 (C=O amide), 1491 (C=C aromatic), 1405 (C-H aliphatic bending), 1330 (N-O), 1304 (C-N aromatic), 1070 (C-N aliphatic). *m/z* (ESI$^+$): 445 (MH$^+$, 100%). HRMS (ESI$^+$) found (MH$^+$): 445.1329 $C_{24}H_{21}N_4O_3S$ requires 445.1329.

3-Amino-*N*-(4-(methylthio)phenyl)-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9i



The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8i** (0.12 g, 0.563 mmol), sodium carbonate (0.12 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9i** (0.20 g, 78%) as yellow crystals. m.p. > 230 °C. δ_H (400 MHz, ($(CD_3)_2SO$) 2.08-2.13 (2H, m, H-7), 2.46 (3H, s, CH_3), 3.08 (3H, s, H-5 and H-6), 3.09-3.14 (2H, m, H-8), 7.22-7.26 (3H, m, H-4″, H-3′, and H-5′), 7.33 (2H, m, NH_2), 7.35-7.38 (4H, m, H-3″, H-5″, H-2″ and H-6″), 7.64-7.68 (2H, m, H-2′ and H-6′), 8.21 (1H, s, H-4), 9.38 (1H, br s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 15.5 (CH_3), 29.7 (C-7), 32.6 (C-8), 36.3 (C-5), 40.0 (C-6), 121.7 (C-2′ and C-6′), 124.4 (C-3a), 126.3 (C-4″), 126.75 (C-3′ or C-5′), 126.81 (C-3′ or C-5′), 127.9 (C-4a), 128.5 (C-2″, C-6″, C-3″, C-5″), 130.8 (C-4), 131.8 (C-4′), 136.6 (C-1′), 145.7 (C-1″), 146.8 (C-3), 156.2 (C-9a), 158.4 (C-8a), 164.0 (C=O). C-2 not observed. ν_{max} (ATR)/cm^{-1} 3438 (N-H amide), 3326 (N-H amine), 2961 (C-H aromatic), 1604 (C=O amide), 1490 (C=C aromatic), 1396 (C-H aliphatic bending), 1326 (C-N aromatic), 1244 (C-O aryl ether), 1069 (C-N aliphatic). *m/z* (ESI^+): 446 (MH^+, 100%). HRMS (ESI^+) found (MH^+): 446.1355 $C_{25}H_{24}N_3OS_2$ requires 446.1355.

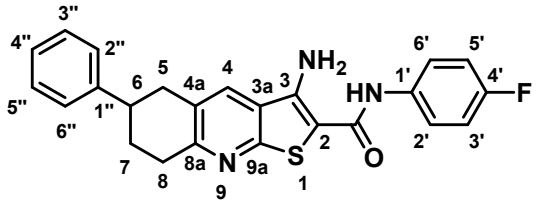
3-Amino-*N*-(4-(diethylamino)phenyl)-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9j



The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8j** (0.14 g, 0.563 mmol), sodium carbonate (0.12 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9j** (0.20 g, 76%) as yellow crystals. m.p. > 230 °C. δ_H (400 MHz, ($(CD_3)_2SO$) 1.05-1.12 (6H, m, 2 x CH_3 (*tert*-amine)), 2.00-2.14 (2H, m, H-7), 2.83-2.90 (1H, m, 8-H_A) 2.97-3.00 (3H, m, H-6 and H-5), 3.09-3.13 (1H, m, 8-H_B), 3.27-3.34 (4H, m, 2x CH_2 (*tert*-amine)), 4.11 (2H, s, NH_2), 6.63 (2H, d, *J*= 8.8 Hz, H-3′ and H-5′), 7.23-7.26 (1H, m, H-4″), 7.33-7.36 (6H, m, H-3″, H-5″, H-2″, H-6″, H-2′, and H-6′) 7.38-7.44 (2H, m, NH_2), 8.01 (1H, s, H-4), 9.94 (1H, s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 12.4 (2x CH_3), 29.0 (C-7), 32.6 (C-8), 36.4 (C-5), 39.1 (C-6), 43.7 (2 x CH_2), 103.2 (C-2), 112.0 (C-3′ and C-5′), 115.9 (sees c-4) 121.1 (C-2′ and C-6′), 124.0 (C-3a), 126.7 (C-4″), 127.7 (C-2″ and C-6″), 127.8 (C-4a), 128.2 (C-1′), 128.5 (C-3″ and C-5″), 141.7 (C-4), 144.1 (C-4′), 145.3 (C-1″), 156.4 (C-3), 157.1 (C-9a), 161.0 (C-8a), 164.9 (C=O). ν_{max} (ATR)/cm^{-1} 3325 (N-H amide), 3279 (N-H amine), 2964 (C-H aromatic), 1600 (C=O amide), 1502 (C=C aromatic), 1391

(C-H aliphatic bending), 1331 (C-N aromatic), 1070 (C-N aliphatic). *m/z* (ESI^+): 471 (MH^+, 100%). HRMS (ESI^+) found (MH^+): 471.2213 $C_{28}H_{31}N_4OS$ requires 471.2213.

3-Amino-*N*-(4-fluorophenyl)-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9d

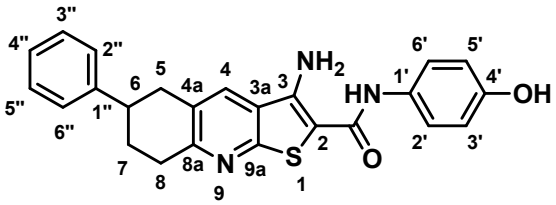


The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8d** (0.14 g, 0.563 mmol), sodium carbonate (0.12 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9d** (0.14 g, 58%) as yellow crystals. m.p. > 230 °C.

δ_H (400 MHz, $((CD_3)_2SO)$ 2.08-2.13 (2H, m, H-7), 3.07 (3H, s, H-6 and H-5), 3.09-3.14 (2H, m, H-8), 7.12-7.17 (2H, m, H-3′ and H-5′), 7.22-7.26 (1H, m, H-4″), 7.31-7.33 (2H, m, NH_2), 7.35-7.38 (4H, m, H-3″, H- 5″, H-2″, and H-6″), 7.67-7.71 (2H, m, H-2′ and H-6′), 8.21 (1H, s, H-4), 9.43 (1H, s, NH). δ_C (100 MHz, $(CD_3)_2SO$) 29.6 (C-7), 32.6 (C-8), 36.3 (C-5), 39.4 (C-6), 95.7 (C-2), 114.9 (d, $^2J_{F/C}$= 21.7 Hz, C-3′ and C-5′), 123.0 (d, $^3J_{F/C}$= 7.7 Hz, C-2′ or C-6′), 124.4 (C-3a), 126.3 (C-4″), 126.8 (C-2″ and C- 6″), 127.9 (C-4a), 128.5 (C-3″ and C-5″), 130.8 (C-4), 135.4 (C-1′), 145.7 (C-1″), 146.8 (C-3), 156.2 (C-9a), 158.4 (C-8a), 158.2 (d, $^1J_{FC}$ = 239.9 Hz, C-4′), 164.0 (C=O). ν_{max} (ATR)/cm^{-1} 3446 (N-H amide), 3334 (N-H amine), 2971 (C-H aromatic), 1607 (C=O amide), 1490 (C=C aromatic), 1405 (C-H aliphatic bending), 1310 (C-N aromatic), 1151 (C-F), 1070 (C-N aliphatic). *m/z* (ESI^+): 418 (MH^+, 100%).

HRMS (ESI^+) found (MH^+): 418.1384 $C_{24}H_{21}FN_3OS$ requires 418.1384.

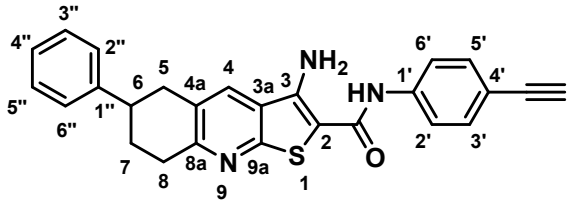
3-Amino-*N*-(4-hydroxyphenyl)-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9k



The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8k** (0.10 g, 0.563 mmol), sodium carbonate (0.12 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9k** (0.11 g, 46%) as brown crystals. m.p. > 230 °C.

δ_H (400 MHz, ((CD$_3$)$_2$SO) 2.08-2.12 (2H, m, H-7), 3.08 (3H, s, H-6 and H-5), 3.10-3.13 (2H, m, H-8), 6.70 (2H, dt, *J* = 8.8, 3.2 Hz, H-3′ and H-5′), 7.22-7.26 (3H, m, H-4″ and NH$_2$), 7.31-7.38 (4H, m, H-3″, H-5″, H-2″, and H-6″), 7.39-7.42 (3H, m, OH, H-2′ and H-6′), 8.19 (1H, s, H-4), 9.15 (1H, s, NH). δ_C (100 MHz, (CD$_3$)$_2$SO) 29.7 (C-7), 32.6 (C-8), 36.3 (C-5), 40.2 (C-6), 96.3 (C-2), 114.8 (C-3′ and C-5′), 123.3 (C-2′ and C-6′), 124.6 (C-3a), 126.8 (C-4″), 127.8 (C-2″ and C-6″), 128.5 (C-3″ and C-5″), 130.7 (C- 4), 131.1 (C-1′), 135.0 (C-4a), 145.7 (C-1″), 146.2 (C-3), 154.4 (C-4′), 154.7 (C-8a), 157.6 (C-9a), 160.0 (C=O). ν_{max} (ATR)/cm^{-1} 3470 (O-H), 3350 (N-H amide), 3307 (N-H amine), 2960 (C-H aromatic), 1590 (C=O amide), 1502 (C=C aromatic), 1390 (C-H aliphatic bending), 1323 (C-N aromatic), 1068 (C-N aliphatic). *m/z* (ESI$^+$): 416 (MH$^+$, 100%). HRMS (ESI$^+$) found (MH$^+$): 416.1427 $C_{24}H_{22}N_3O_2S$ requires 416.1427.

3-Amino-*N*-(4-ethynylphenyl)-6-phenyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide 9l



The reaction was carried out following General Procedure **D** using carbonitrile **3k** (0.15 g, 0.563 mmol), chlorophenylacetamide **8l** (0.11 g, 0.563 mmol), sodium carbonate (0.13 g, 1.13 mmol) and ethanol (5 mL) for 48 h to give the *title compound* **9l** (0.23 g, quant.) as yellow crystals. m.p. > 230 °C. δ_H (400 MHz, ((CD$_3$)$_2$SO) 2.08 (≡CH), 2.12 (2H, br s, H-7), 3.08-3.14 (5H, m, H-8, H-6, and H-5), 7.23-7.26 (1H, m, H-4″), 7.33-7.36 (6H, m, H-3″, H-5″, H-2″, H-6″ and NH$_2$), 7.41 (2H, d, *J*= 8.4 Hz, H-3′ and H-5′), 7.74 (2H, d, *J*= 8.6 Hz, H-2′ and H-6′), 8.22 (1H, s, H-4), 9.54 (1H, s, NH). δ_C (100 MHz, (CD$_3$)$_2$SO) 29.6 (C-7), 32.6 (C-8), 36.3 (C-5), 40.1 (C-6), 79.8 (≡CH), 83.7 (C≡CH), 115.9 (C-1″), 120.6 (C-2′ and C-6′), 120.9 (C-3a), 126.3 (C-4″), 126.8 (C-3″ and C-5″), 127.9 (C-4a), 128.4 (C-2″ and C-6″), 130.8 (C-4), 131.9 (C-3′ and C-5′), 140.0 (C-1′), 145.7 (C-4′), 147.2 (C-3), 156.3 (C-9a), 158.6 (C-8a), 164.1 (C=O). C-2 is not observed. ν_{max} (ATR)/cm^{-1} 3440 (N-H amide), 3322 (N-H amine), 2961 (C-H aromatic), 1592 (C=O amide), 1500 (C=C aromatic), 1395 (C-H aliphatic bending), 1313 (C-N aromatic), 1069 (C-N aliphatic). C≡CH is not observed. *m/z* (ESI$^+$):424 (MH$^+$, 100%). HRMS (ESI$^+$) found (MH$^+$): 424.1472 $C_{26}H_{22}N_3OS$ requires 424.1478.

^{1}H and ^{13}C NMR spectra of synthesised compounds

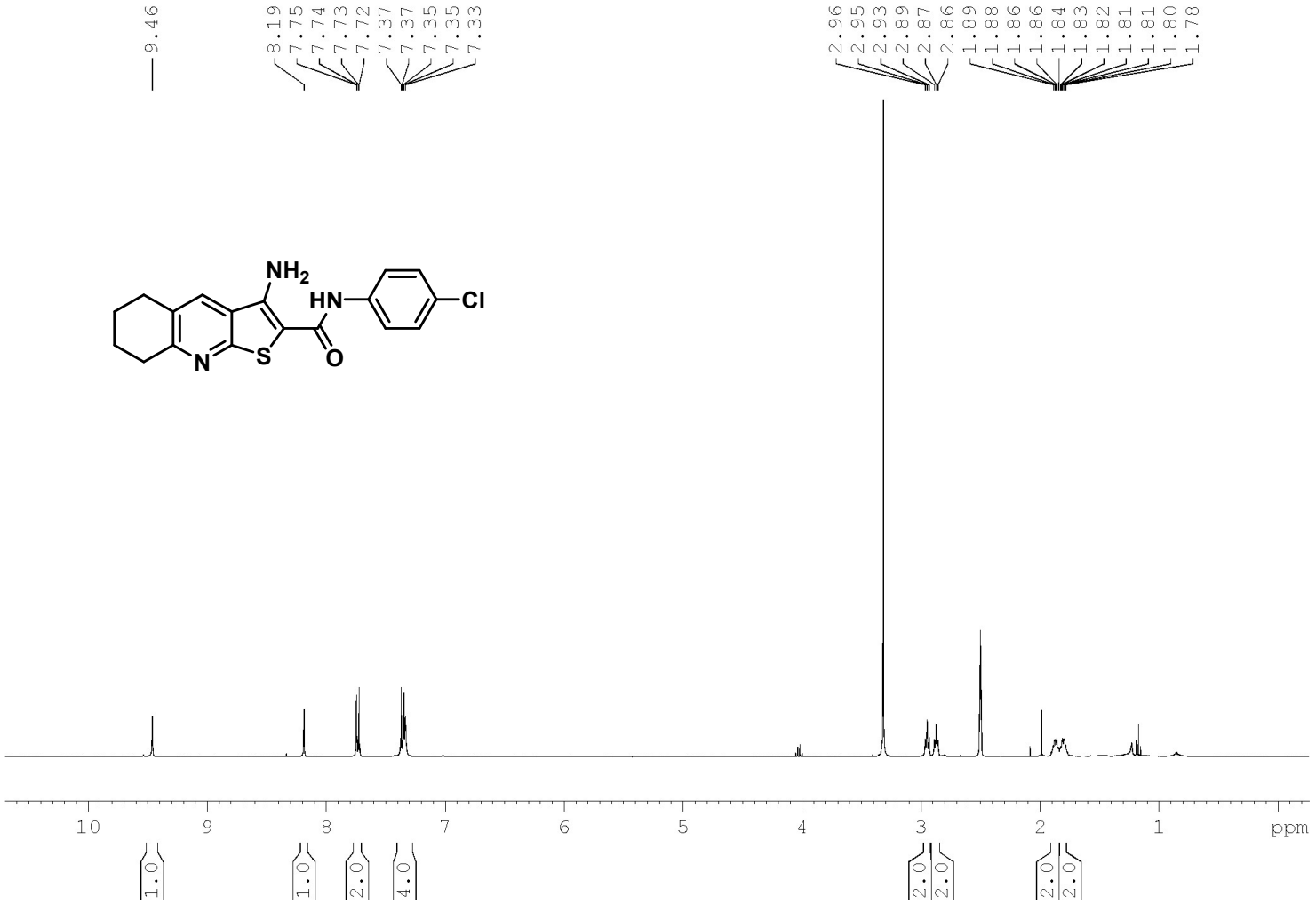


Figure S1: ^{1}H NMR spectrum of **6a** (400 MHz; DMSO-d_6).

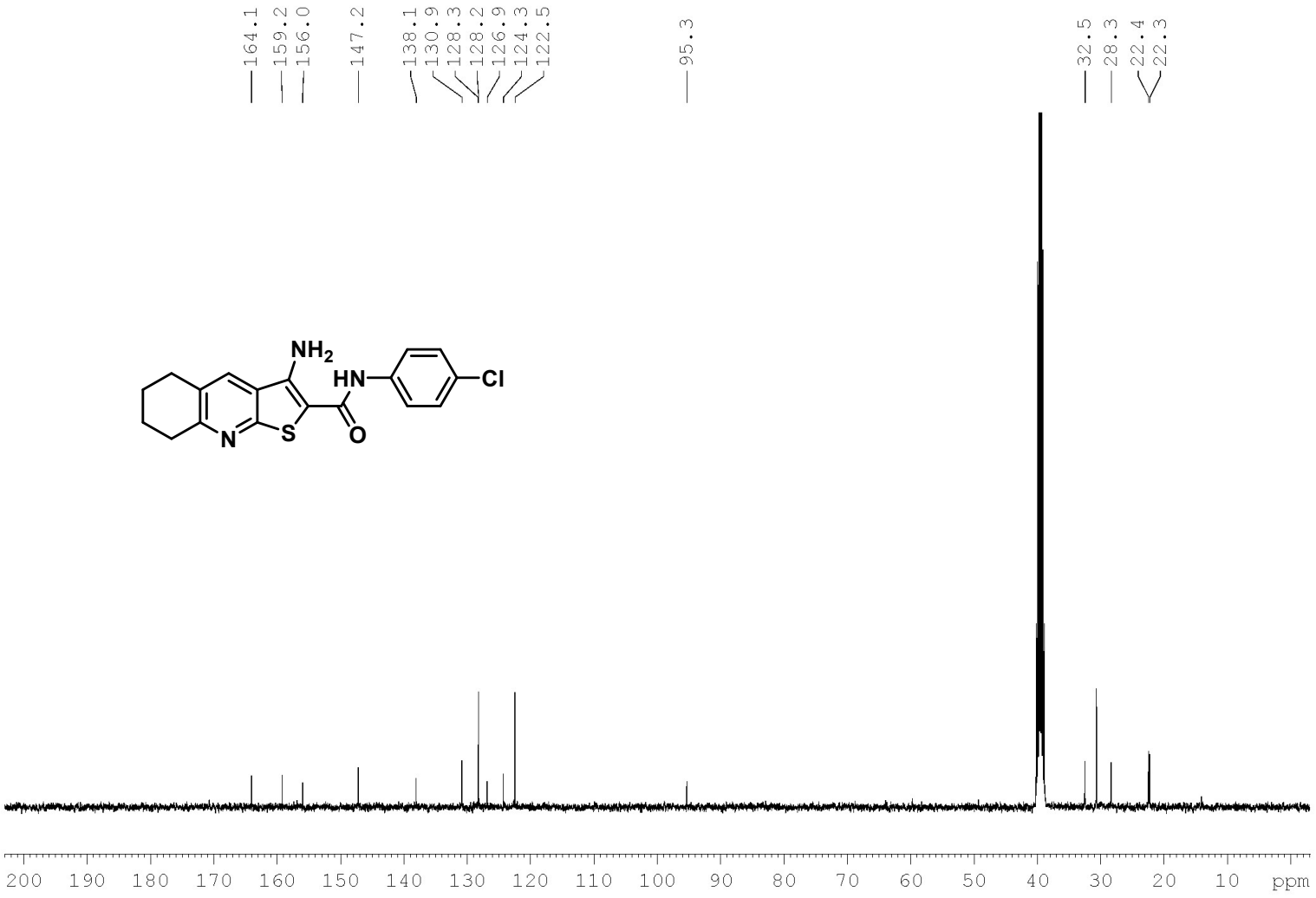


Figure S2: ^{13}C NMR spectrum of **6a** (100 MHz; DMSO-d_6).

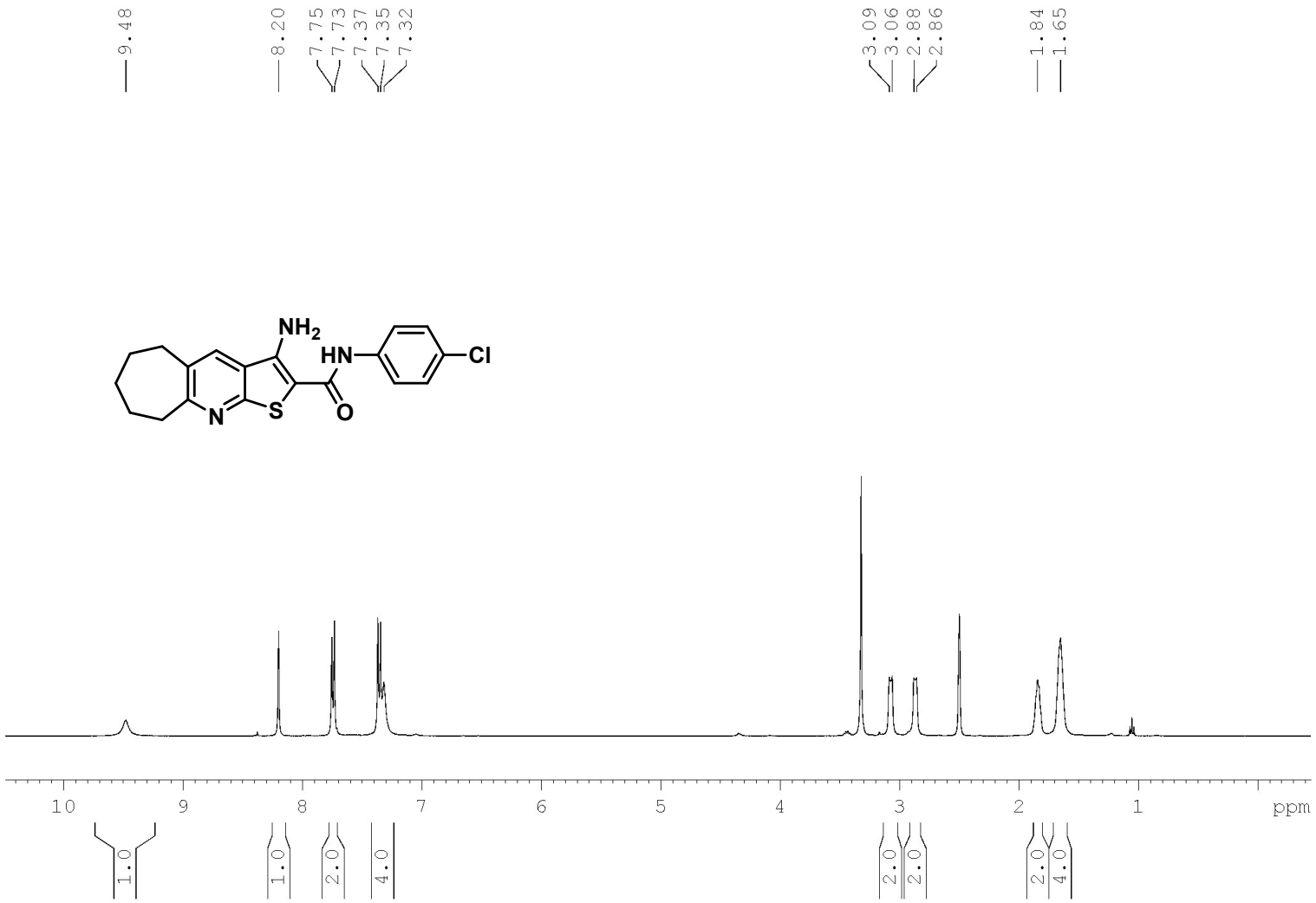


Figure S3: [1]H NMR spectrum of **6b** (400 MHz; DMSO-d_6).

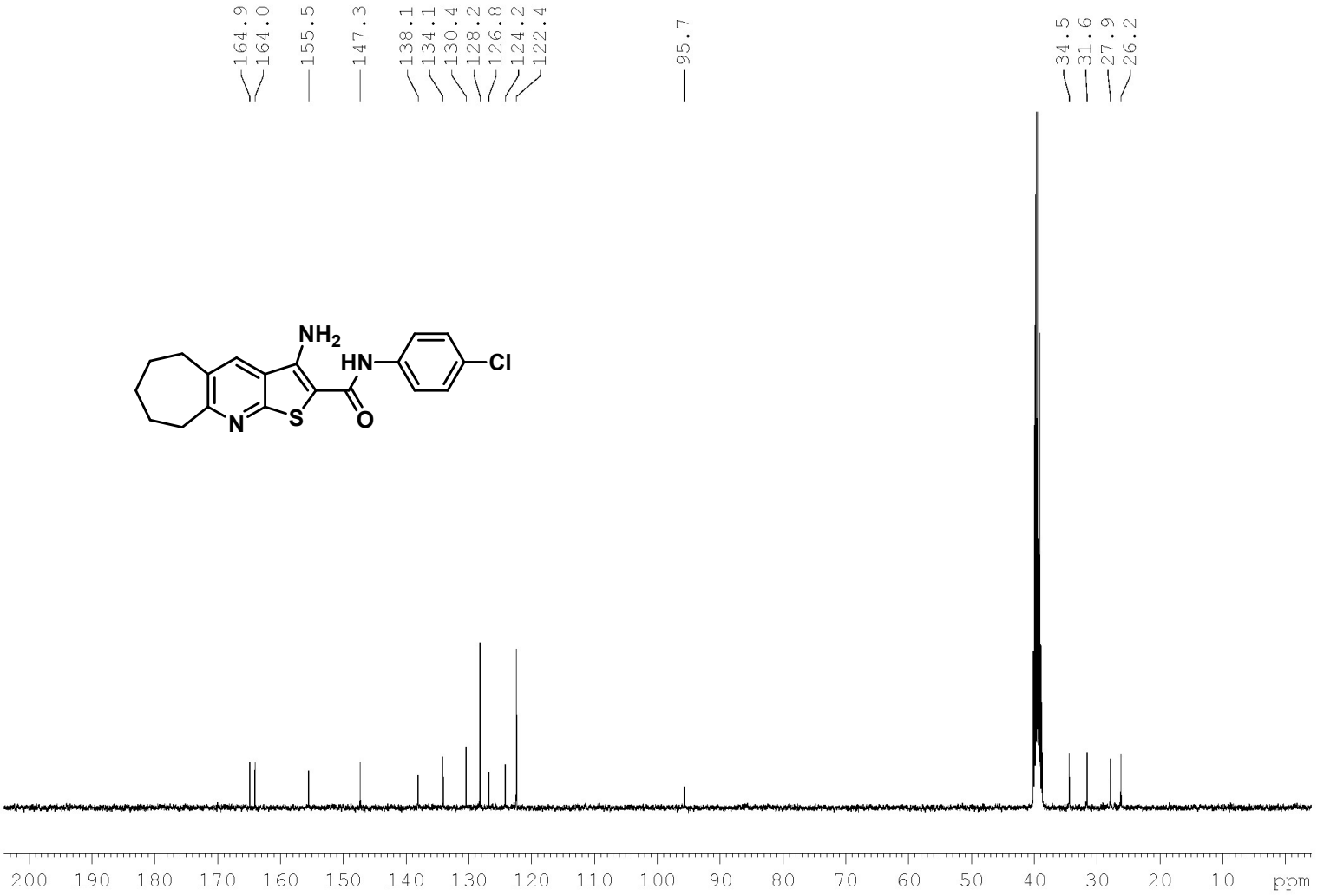


Figure S4: ^{13}C NMR spectrum of **6b** (100 MHz; DMSO-d_6).

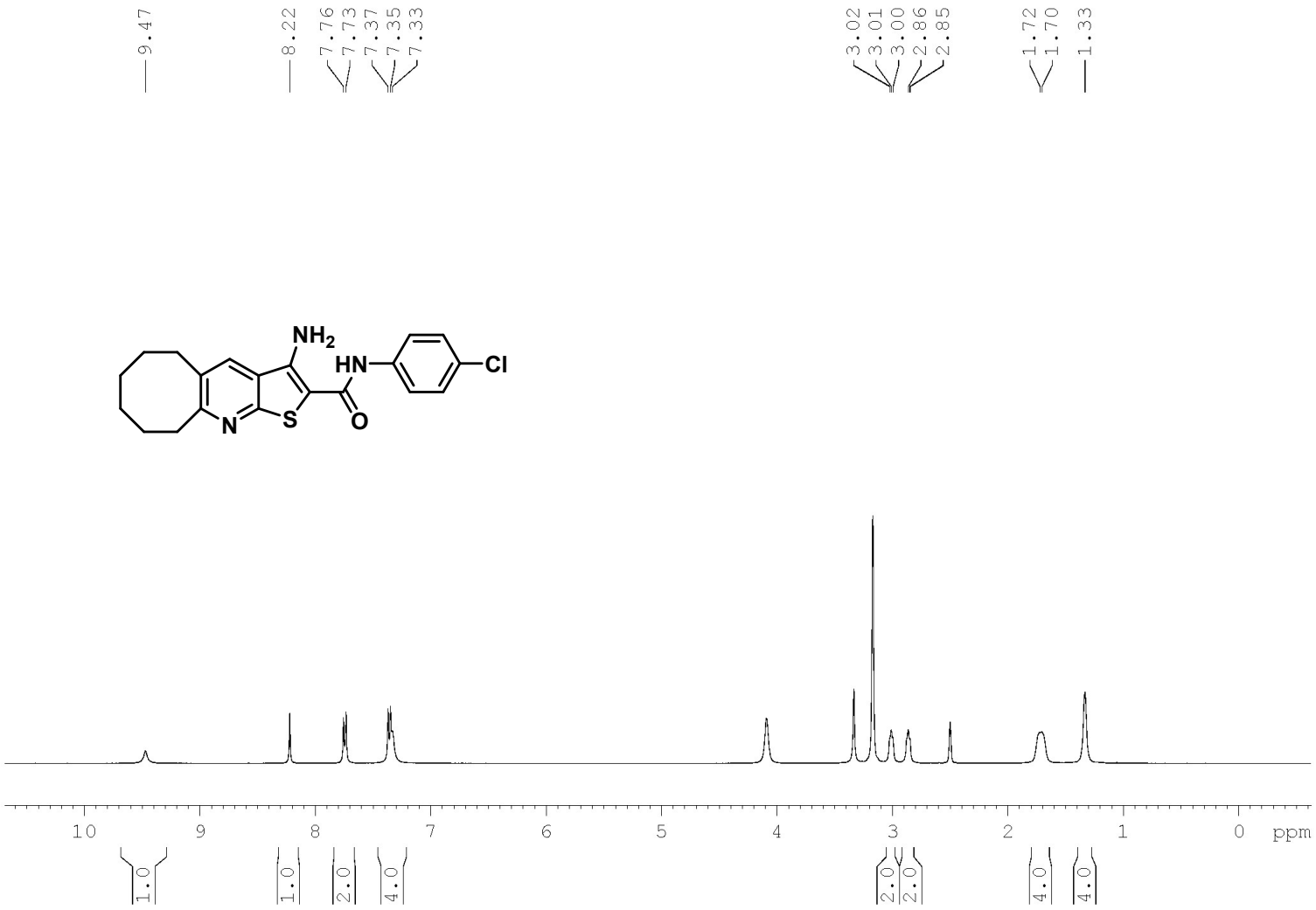


Figure S5: ^{1}H NMR spectrum of **6c** (400 MHz; DMSO-d_6).

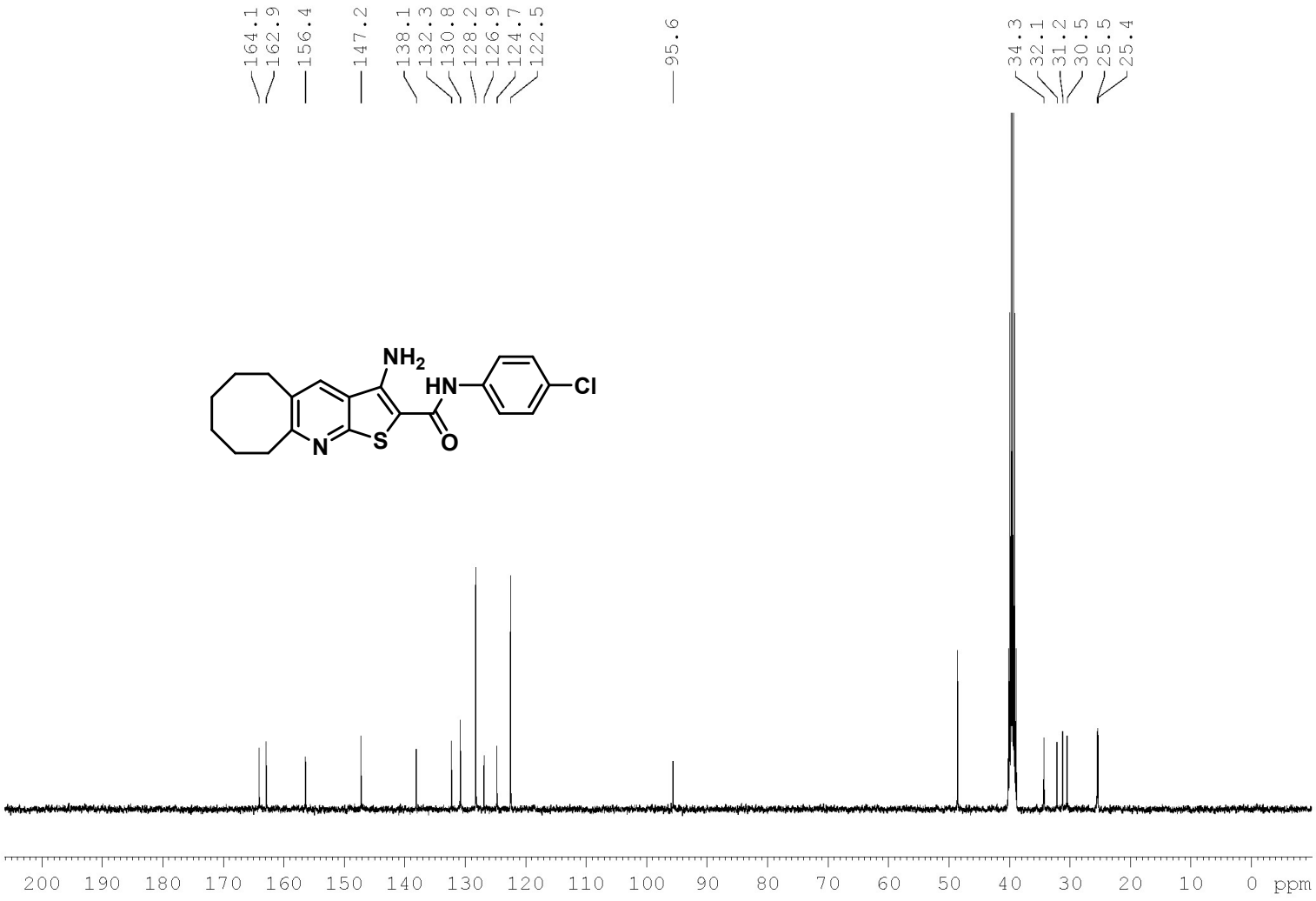


Figure S6: ^{13}C NMR spectrum of **6c** (100 MHz; DMSO-d_6).

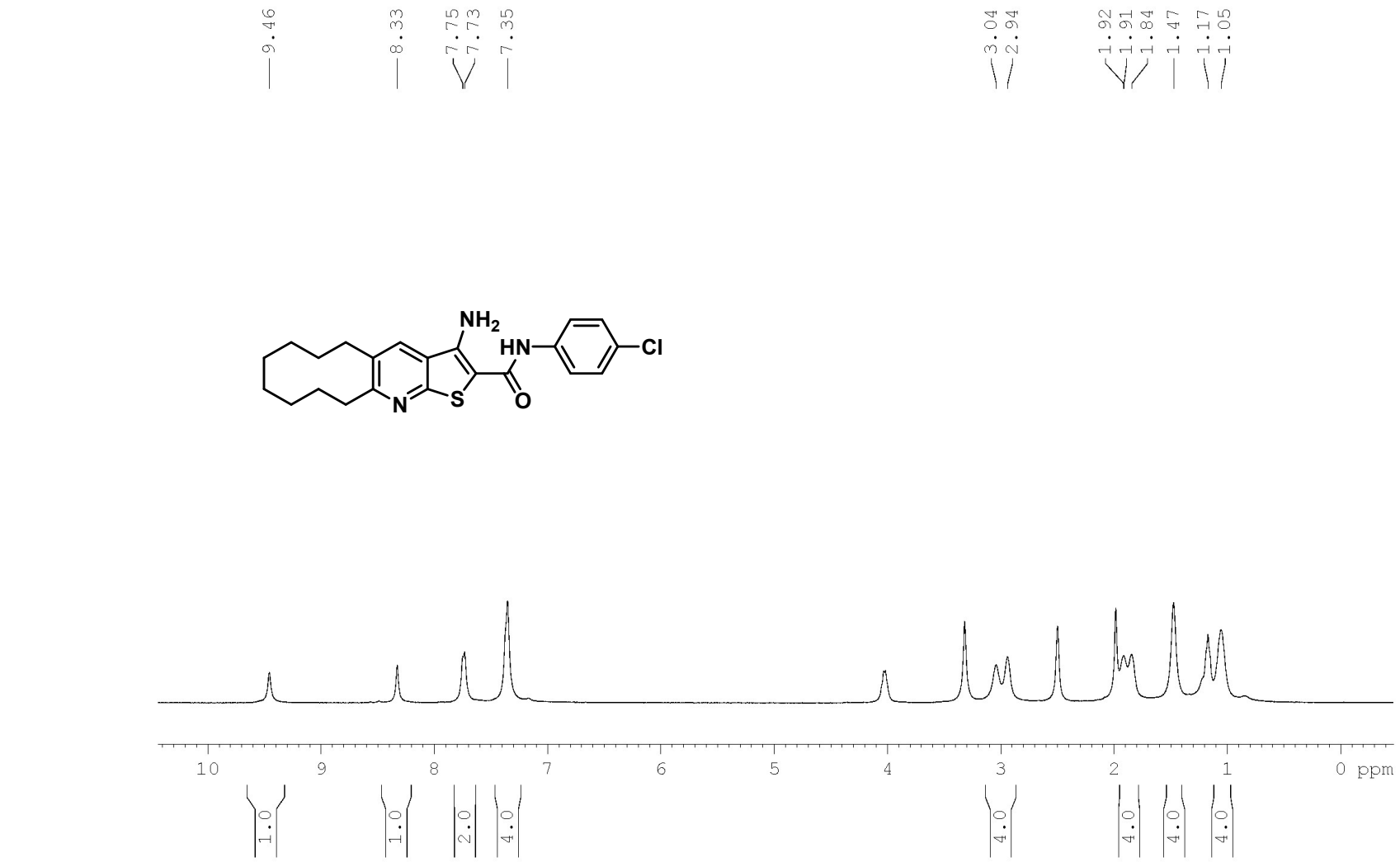


Figure S7: ^{1}H NMR spectrum of **6d** (400 MHz; DMSO-d_6).

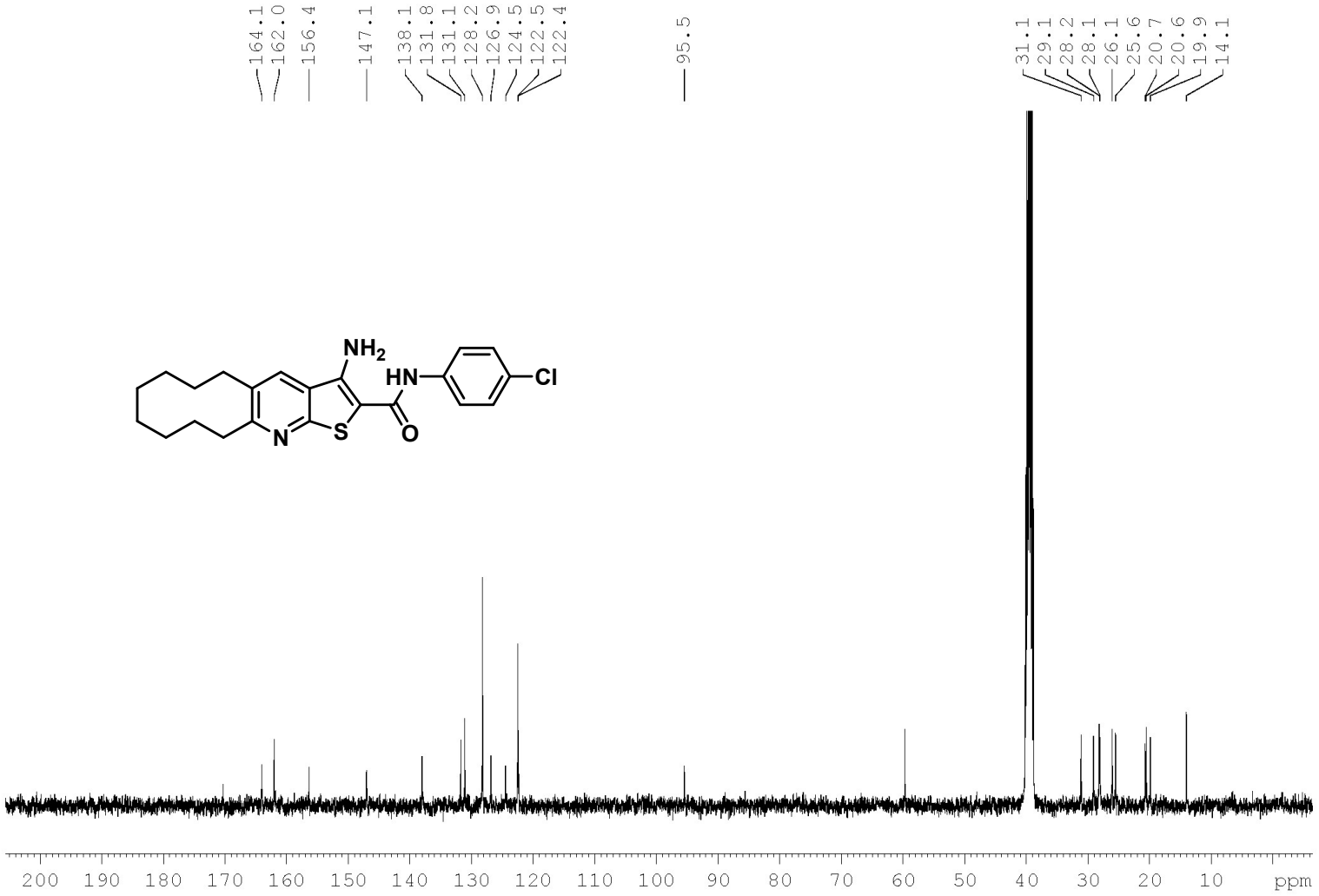


Figure S8: ^{13}C NMR spectrum of **6d** (100 MHz; DMSO-d_6).

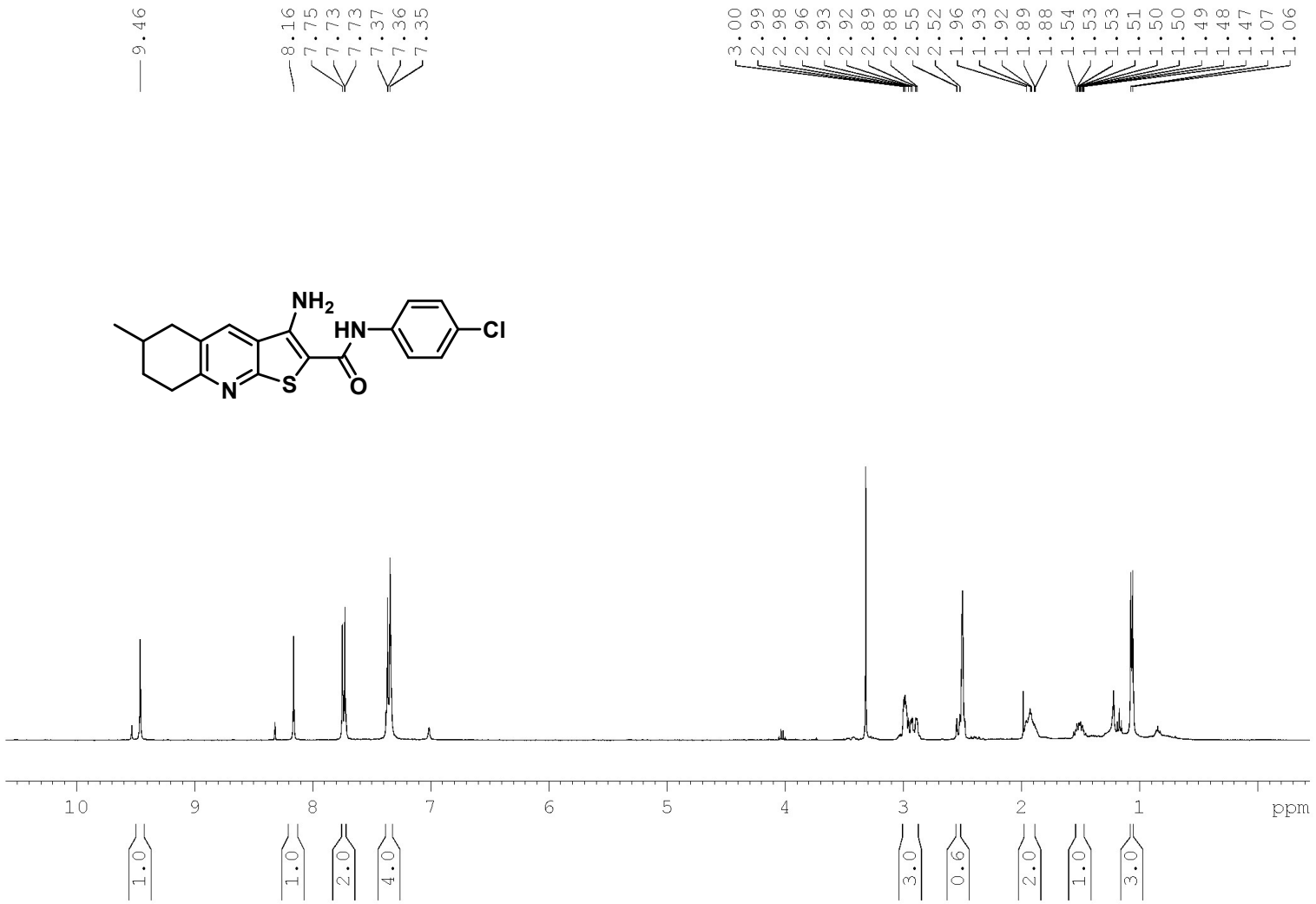


Figure S9: [1]H NMR spectrum of **6e** (400 MHz; DMSO-d_6).

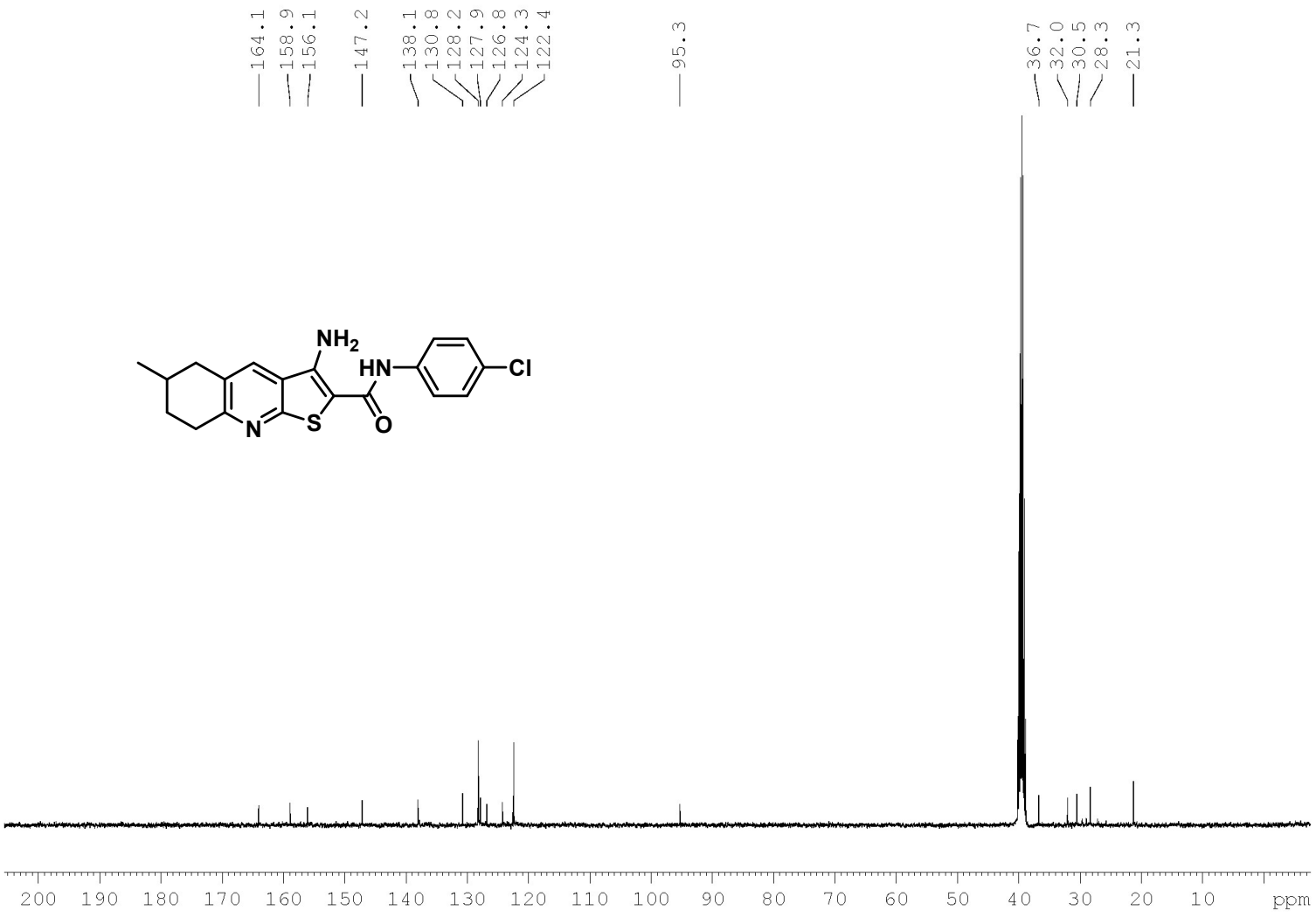


Figure S10: ^{13}C NMR spectrum of **6e** (100 MHz; DMSO-d_6).

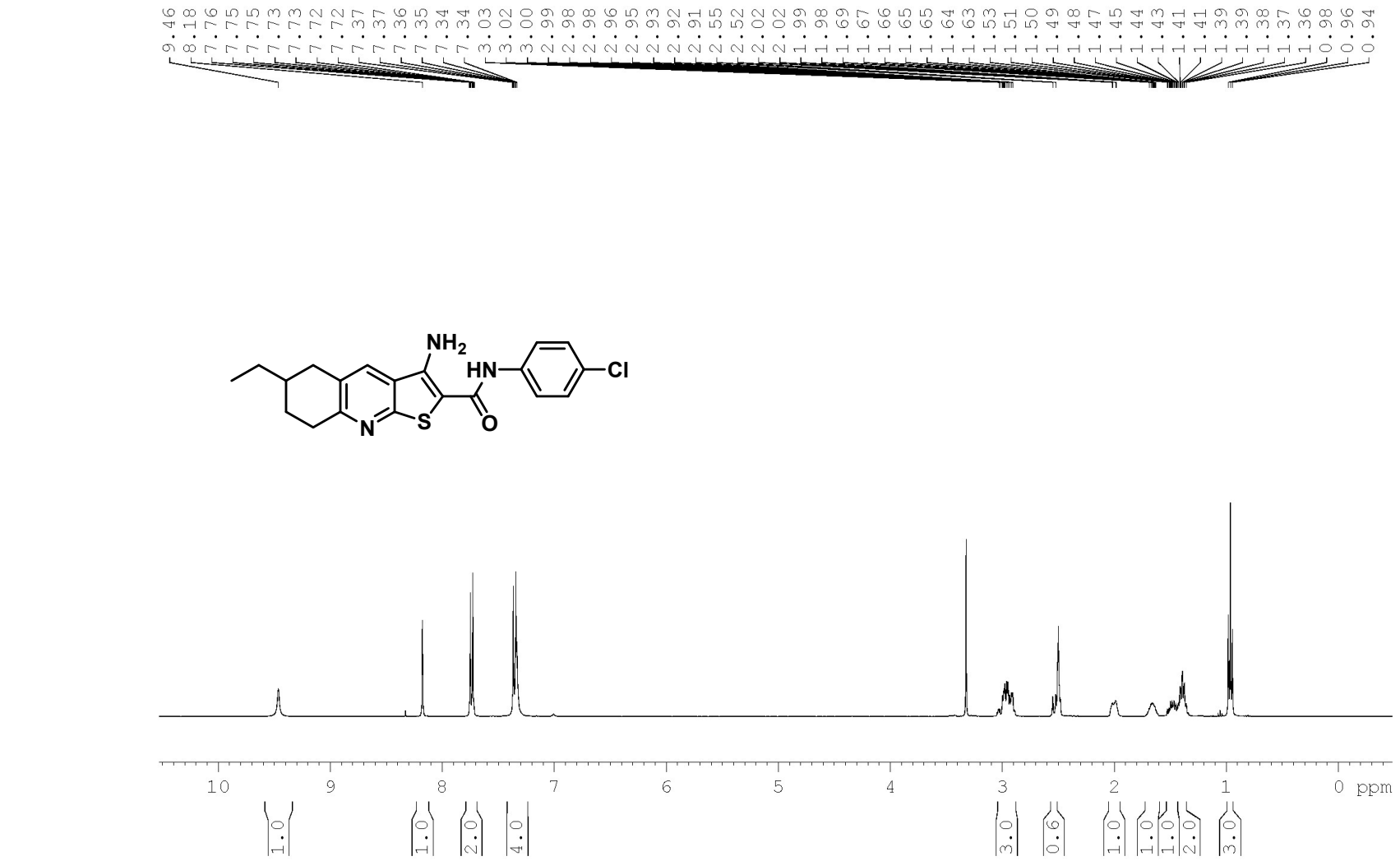


Figure S11: ^{1}H NMR spectrum of **6f** (400 MHz; DMSO-d_6).

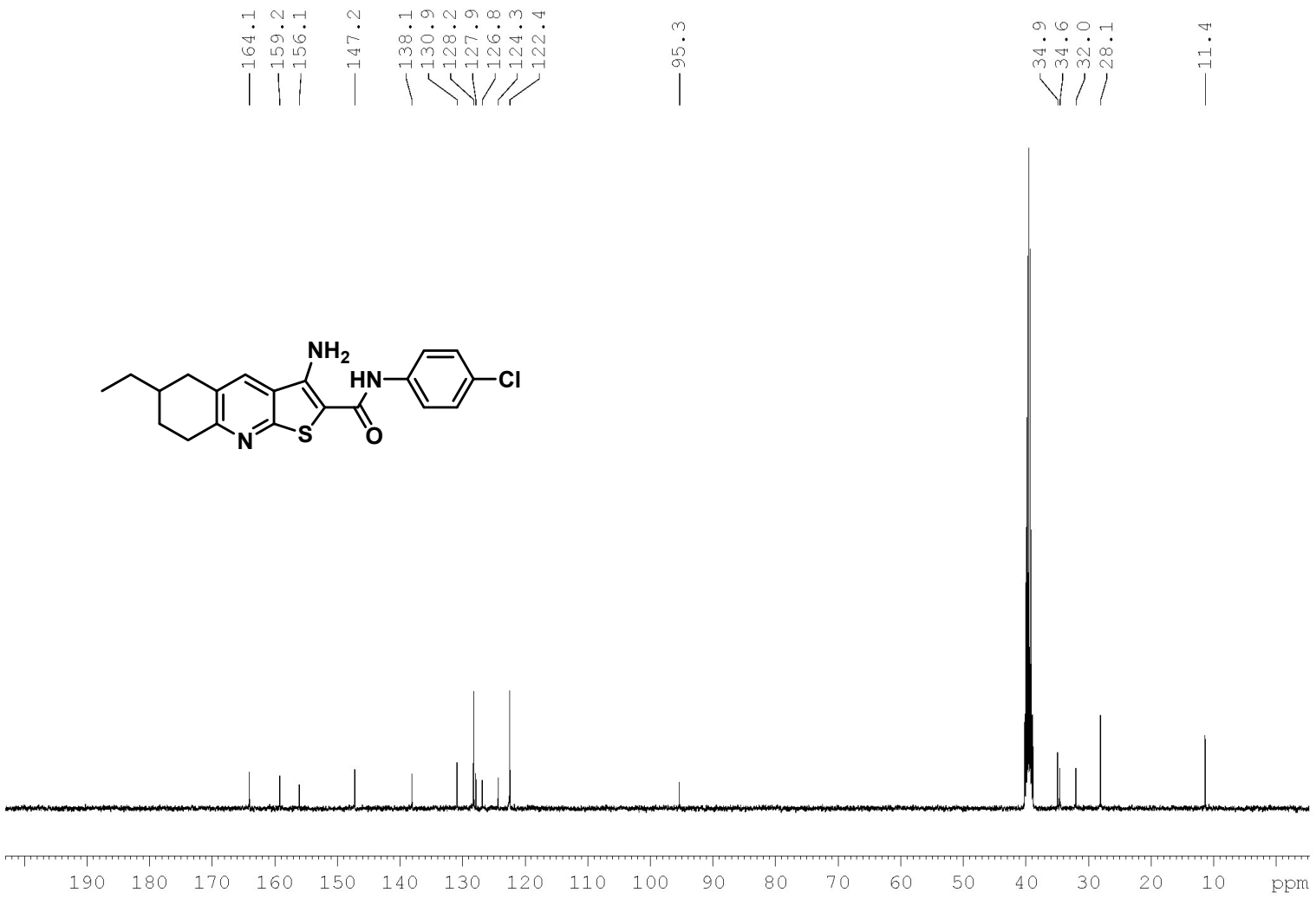


Figure S12: ^{13}C NMR spectrum of **6f** (100 MHz; DMSO-d_6).

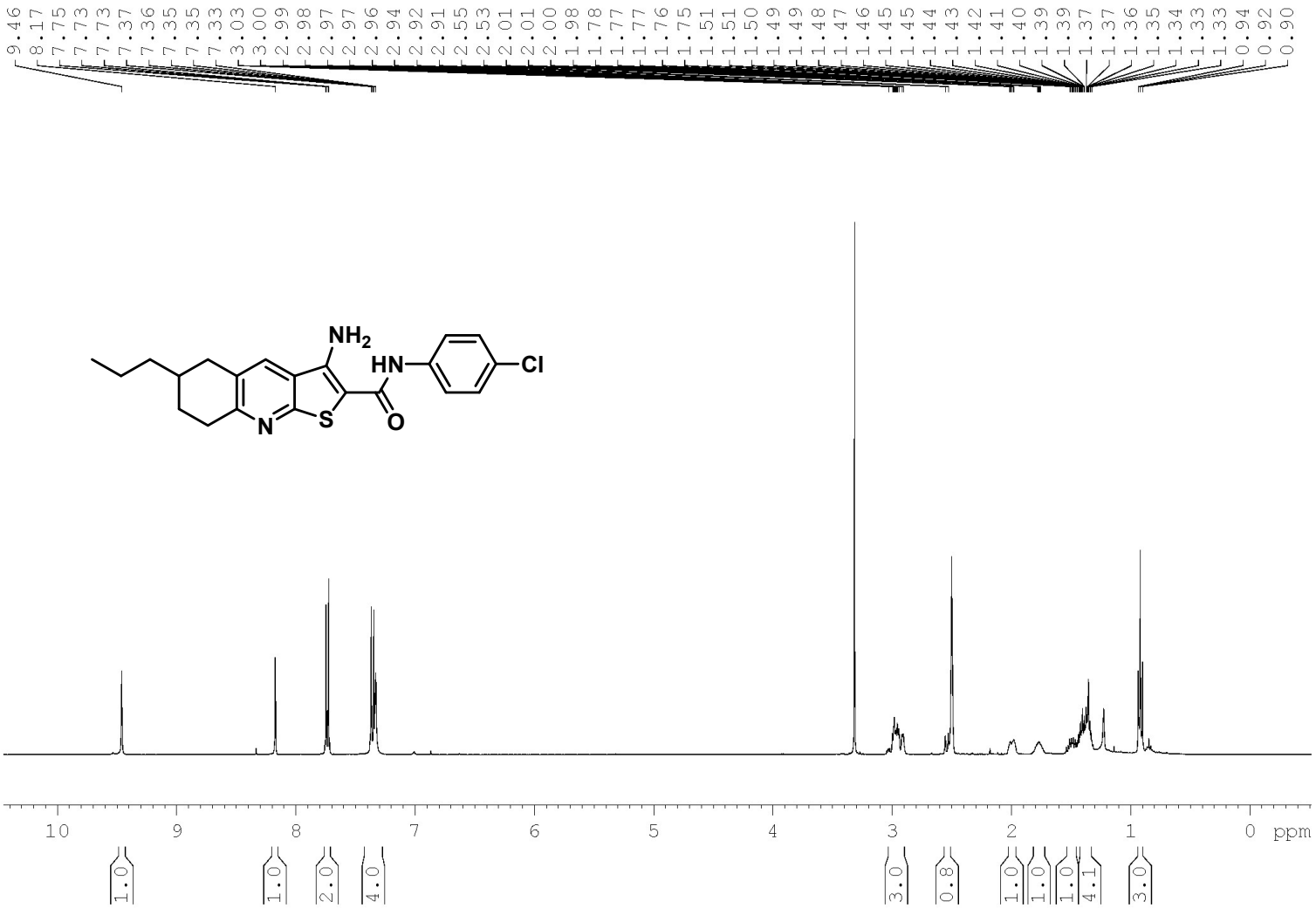


Figure S13: ^{1}H NMR spectrum of **6g** (400 MHz; DMSO-d_6).

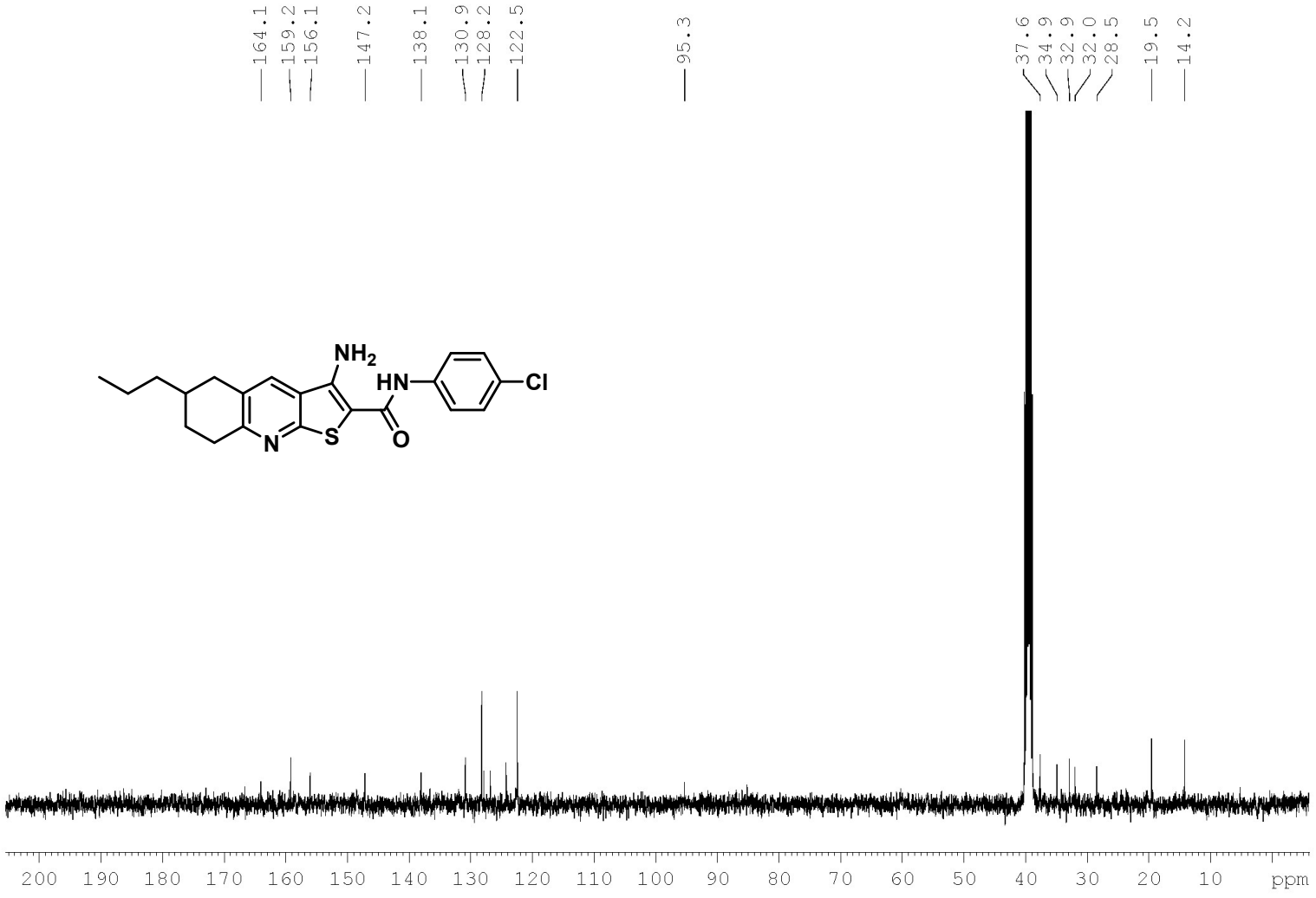


Figure S14: ^{13}C NMR spectrum of **6g** (100 MHz; DMSO-d_6).

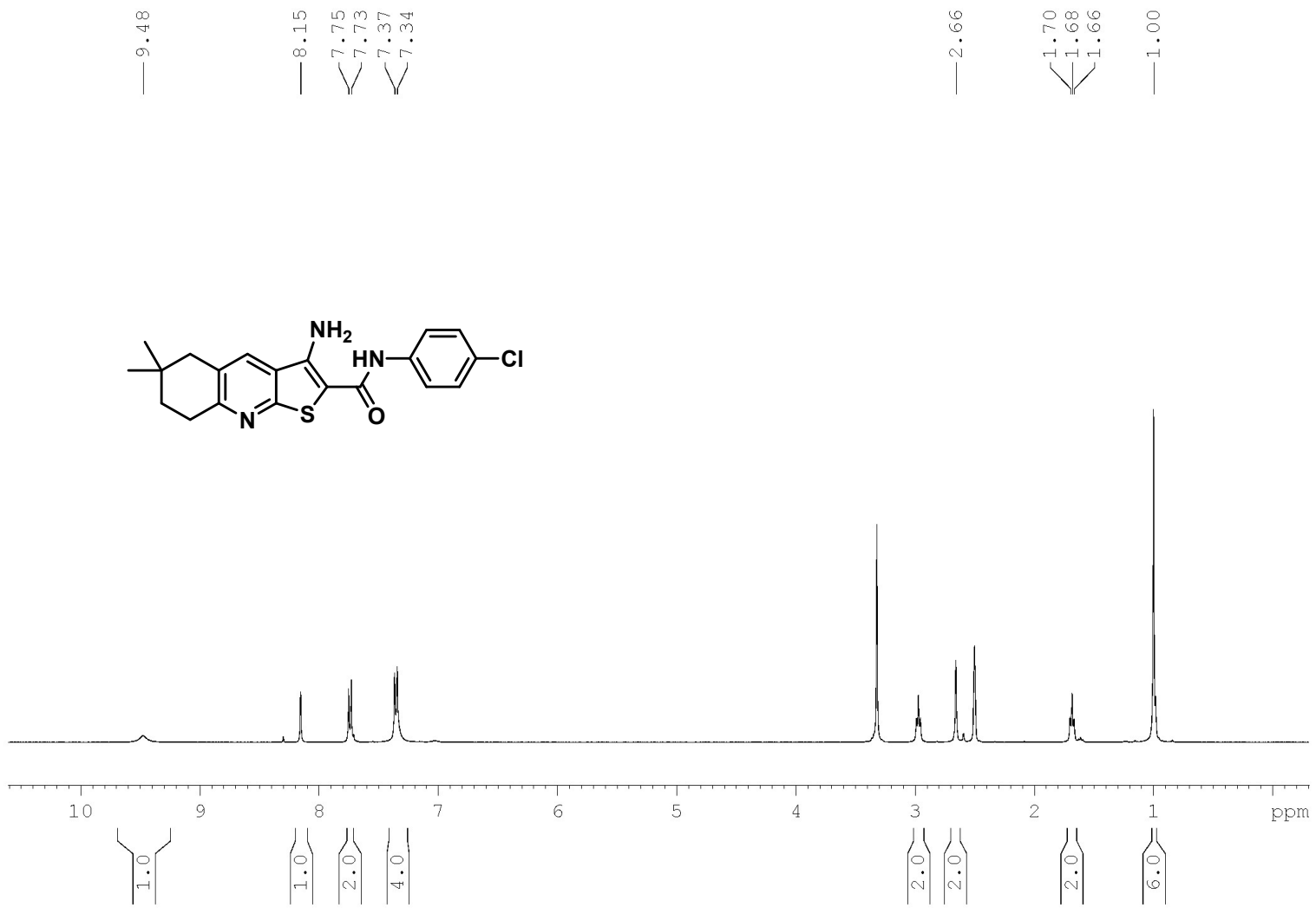


Figure S15: ^{1}H NMR spectrum of **6h** (400 MHz; DMSO-d_6).

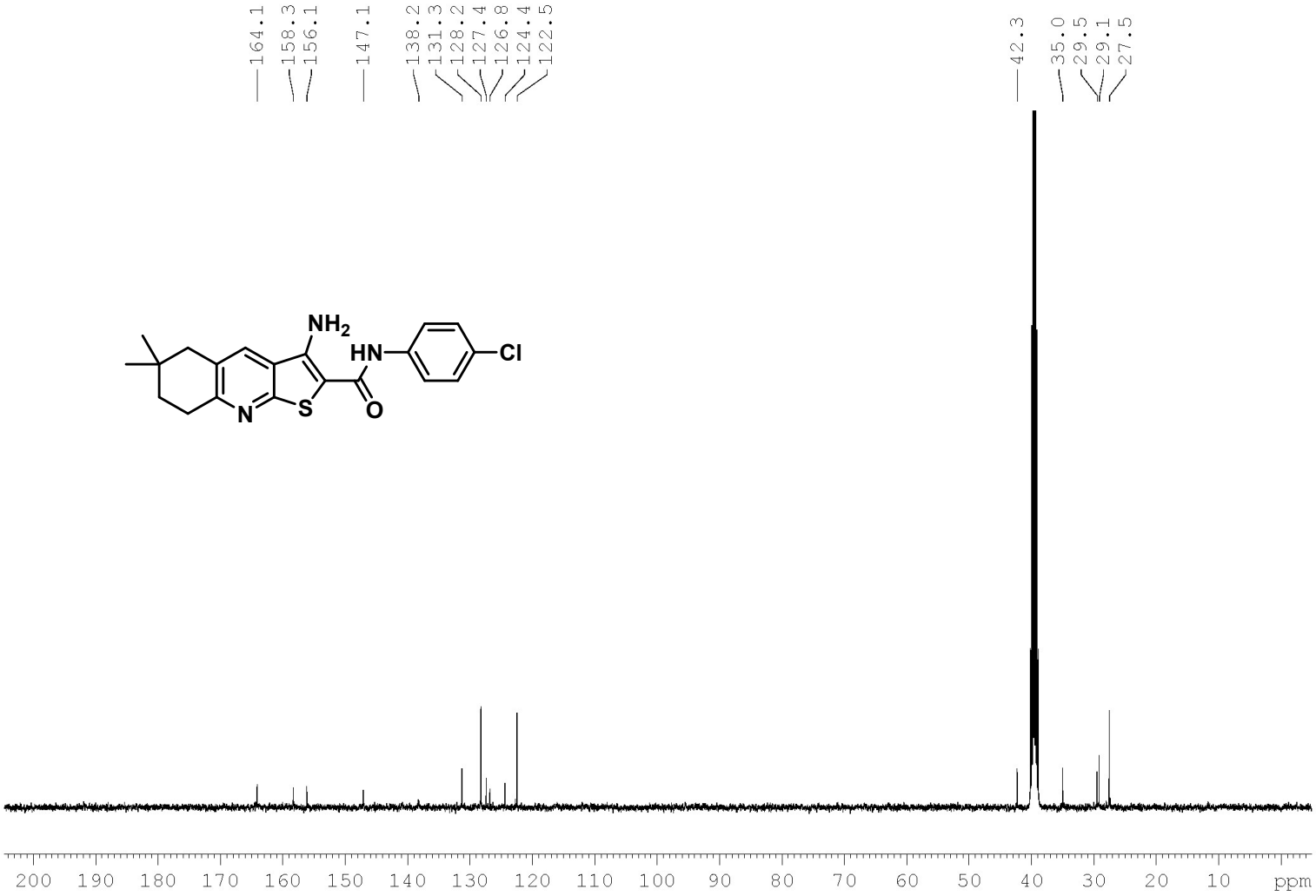


Figure S16: ^{13}C NMR spectrum of **6h** (100 MHz; DMSO-d_6).

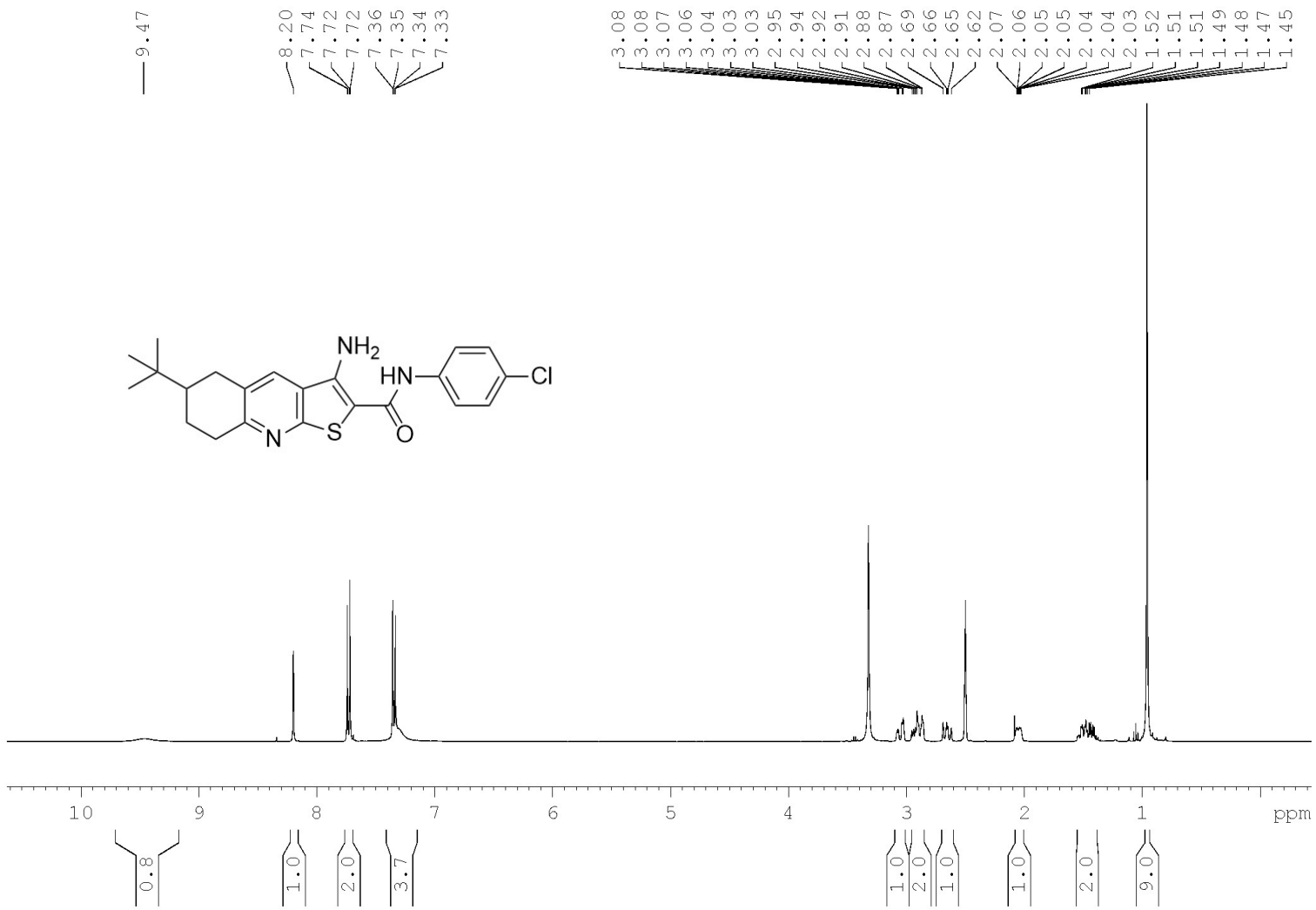


Figure S17: ^{1}H NMR spectrum of **6i** (400 MHz; DMSO-d_6).

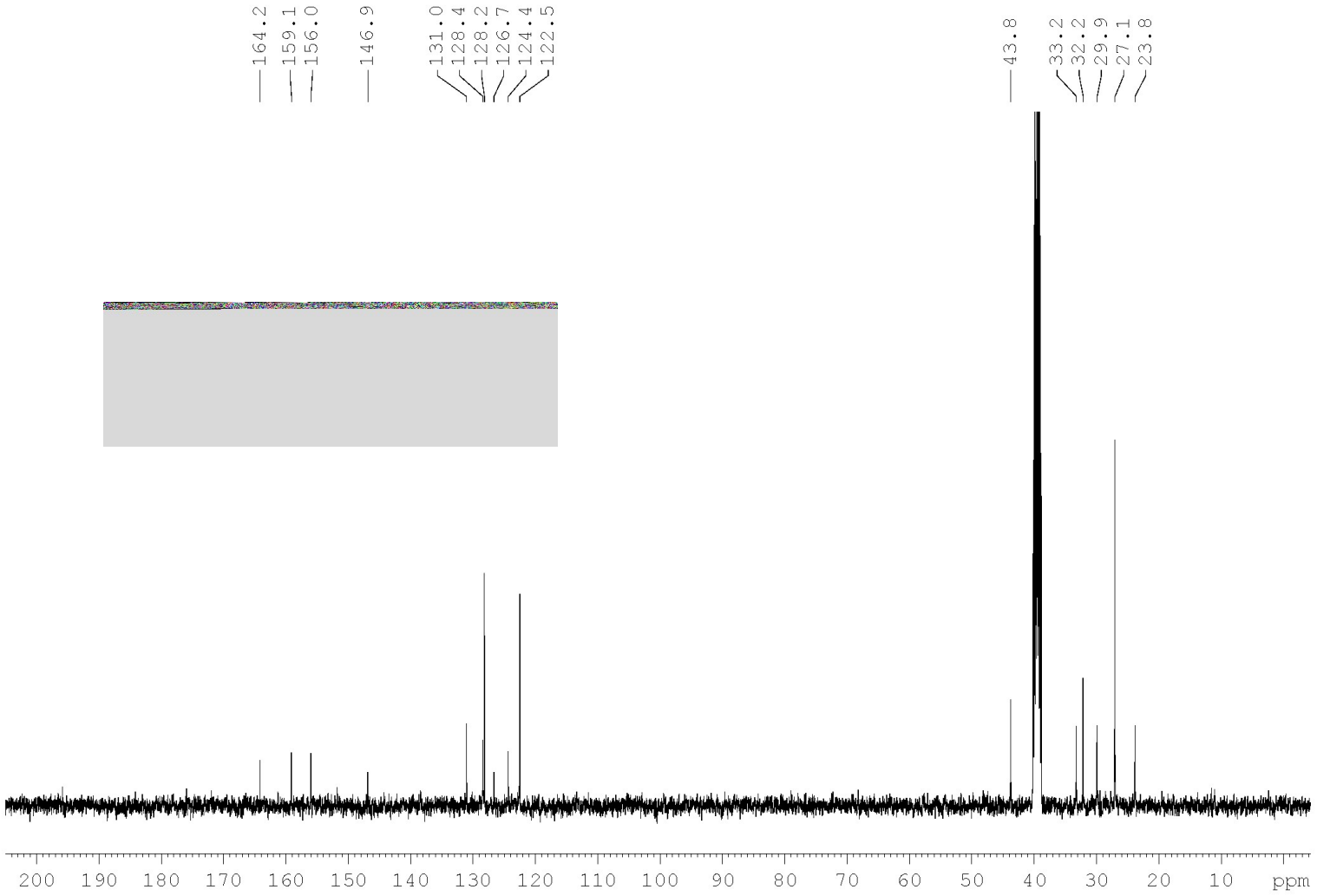


Figure S18: ^{13}C NMR spectrum of **6i** (100 MHz; DMSO-d_6).

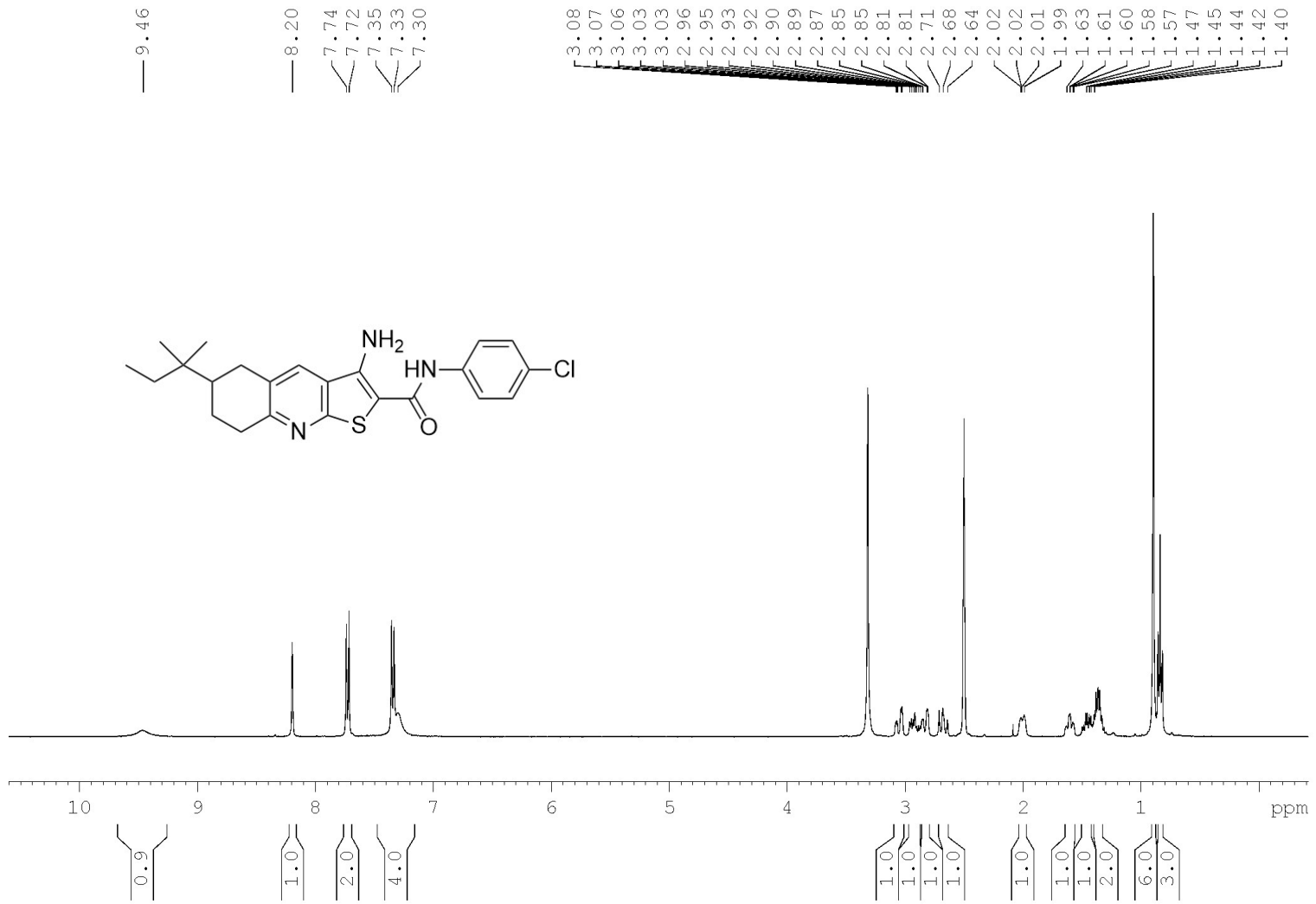


Figure S19: ^{1}H NMR spectrum of **6j** (400 MHz; DMSO-d_6).

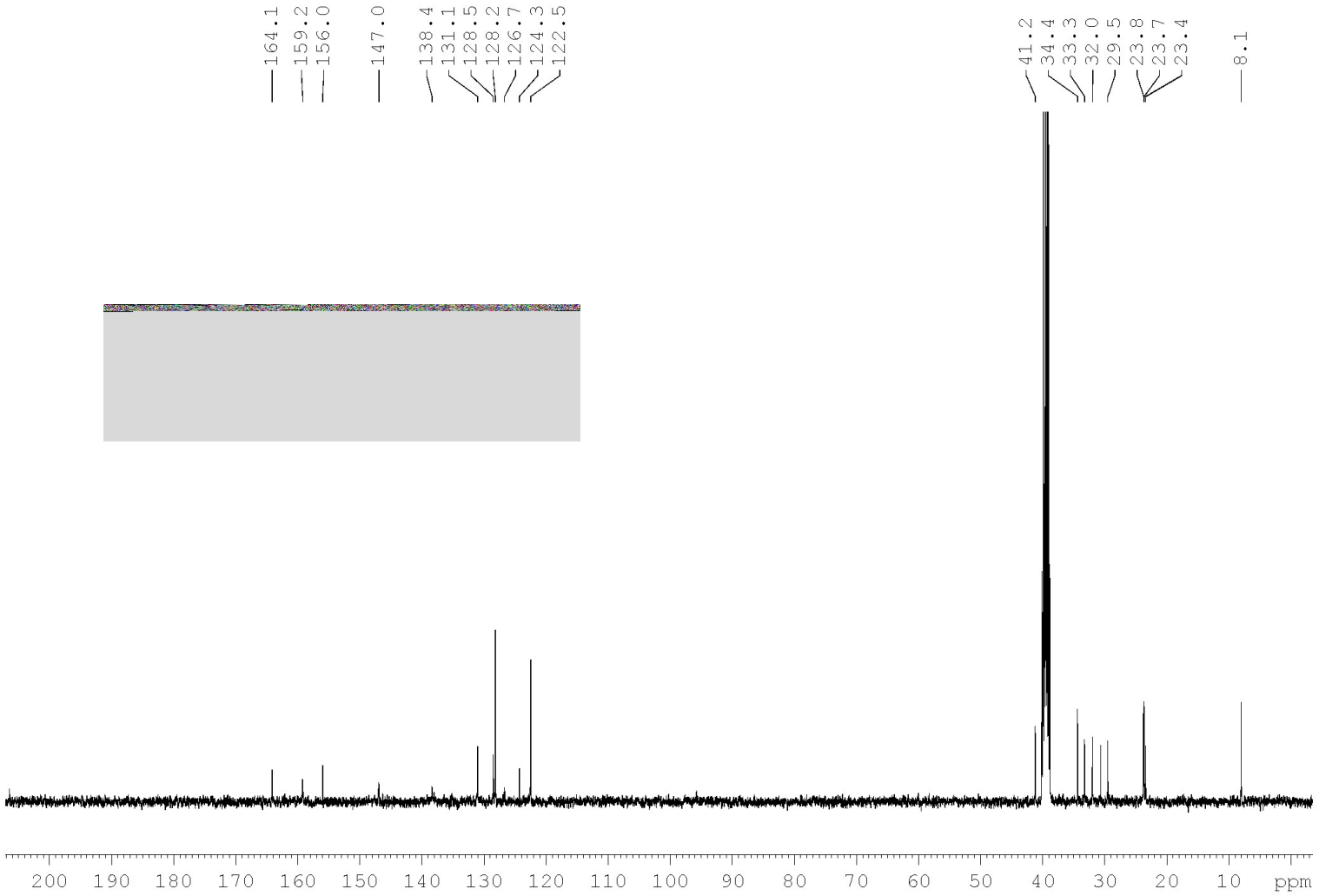


Figure S20: ^{13}C NMR spectrum of **6j** (100 MHz; DMSO-d_6).

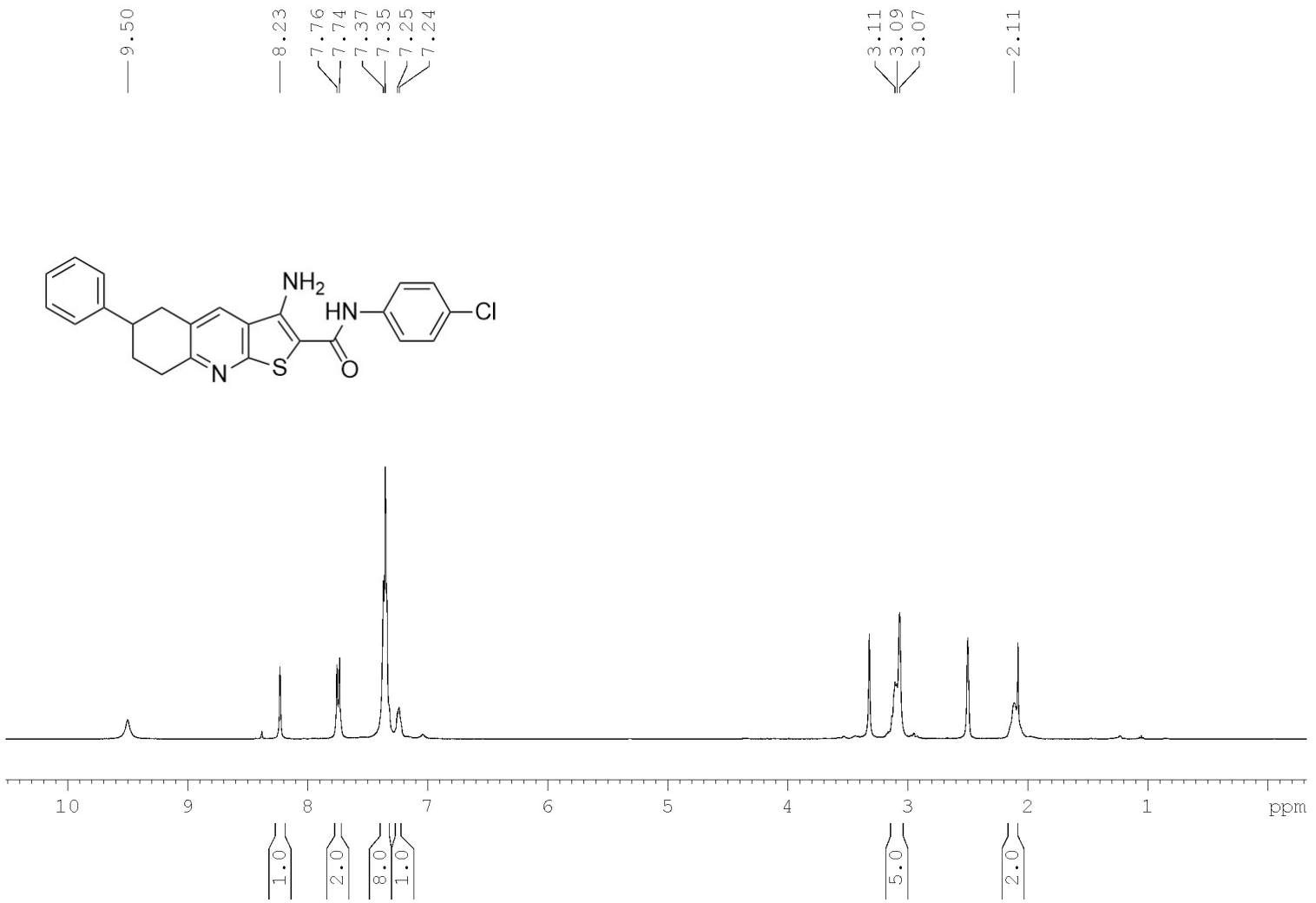


Figure S21: ^{1}H NMR spectrum of **6k** (400 MHz; DMSO-d_6).

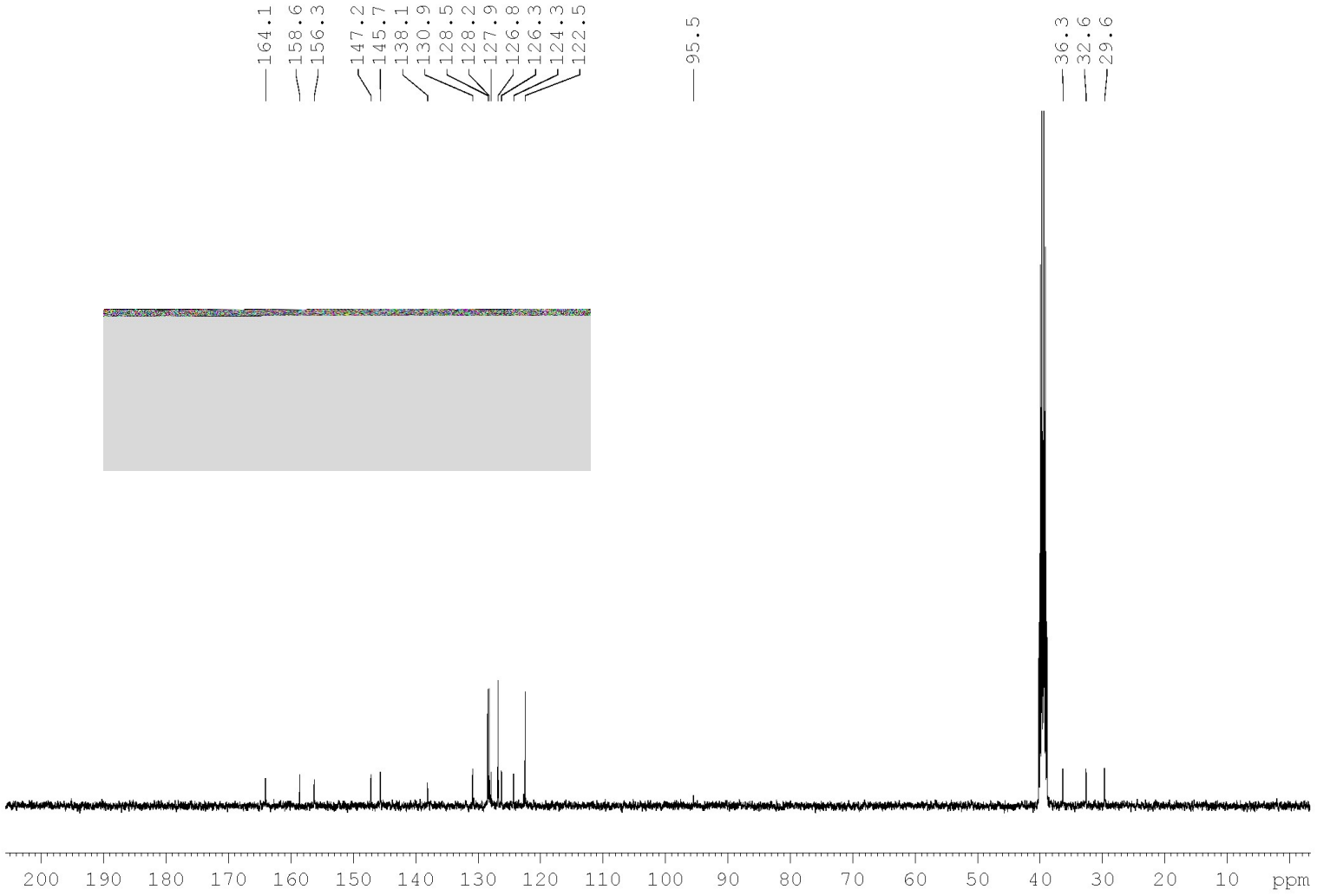


Figure S22: ^{13}C NMR spectrum of **6k** (100 MHz; DMSO-d_6).

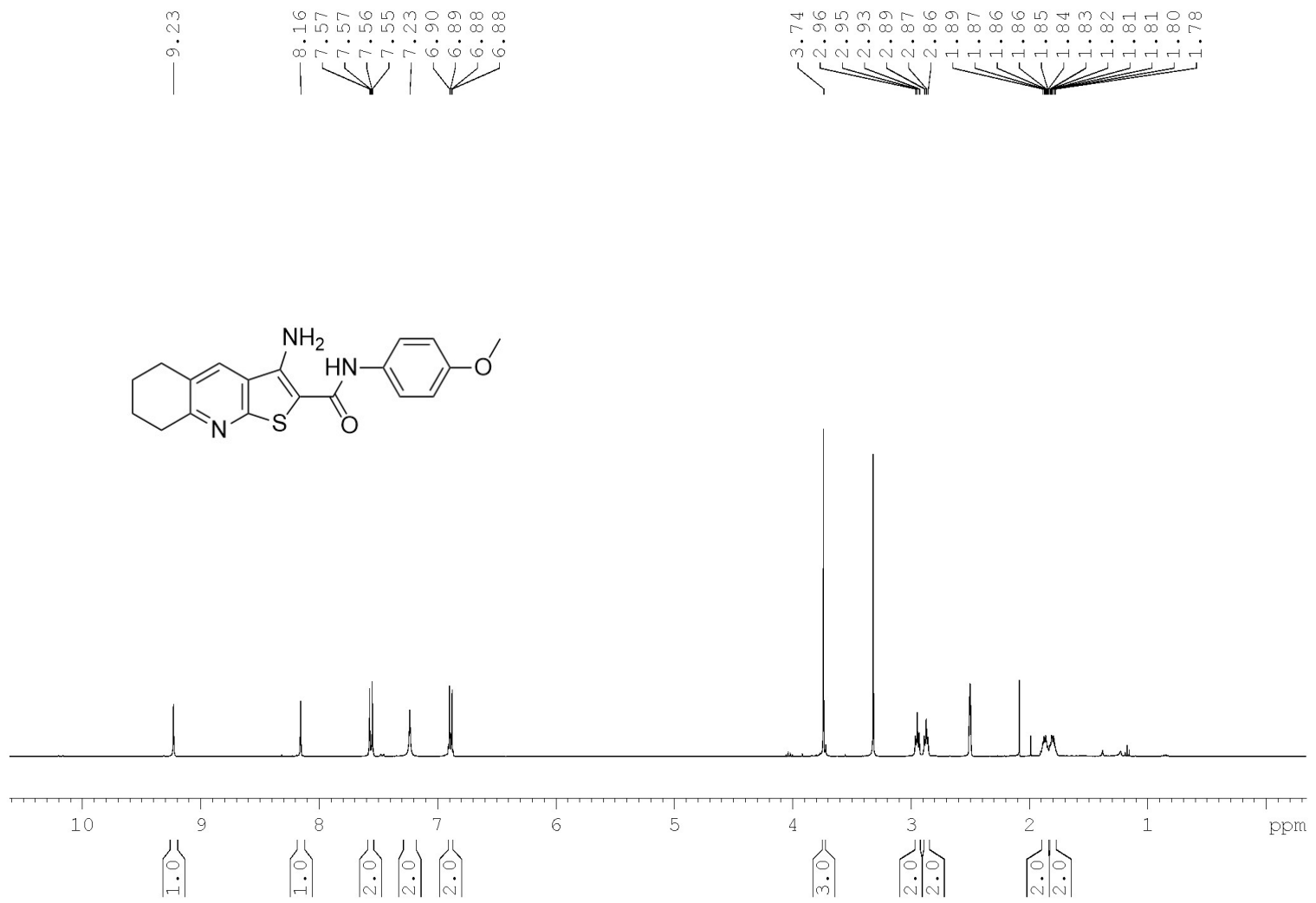


Figure S23: ^{1}H NMR spectrum of **7a** (400 MHz; DMSO-d_6).

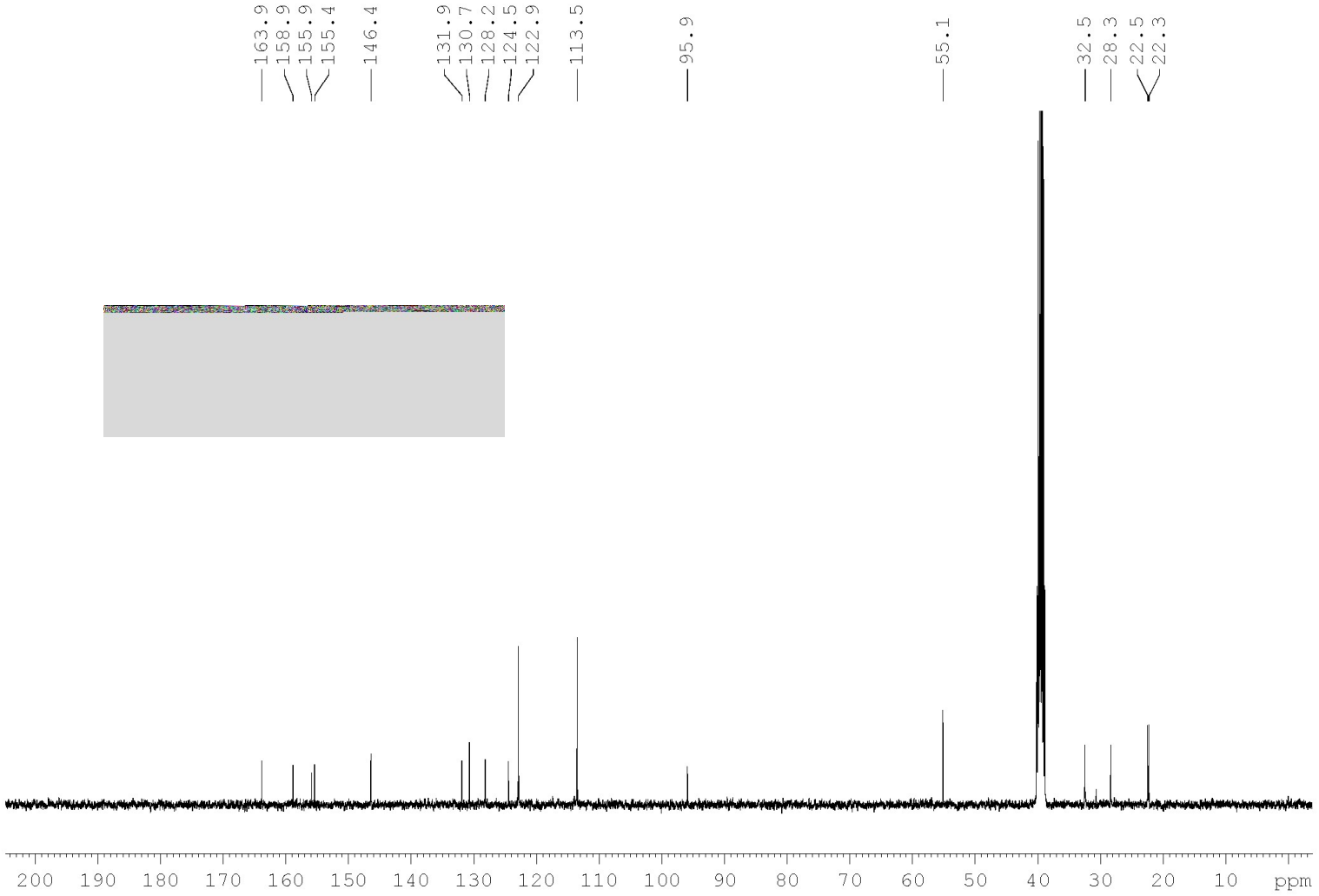


Figure S24: ^{13}C NMR spectrum of **7a** (100 MHz; DMSO-d_6).

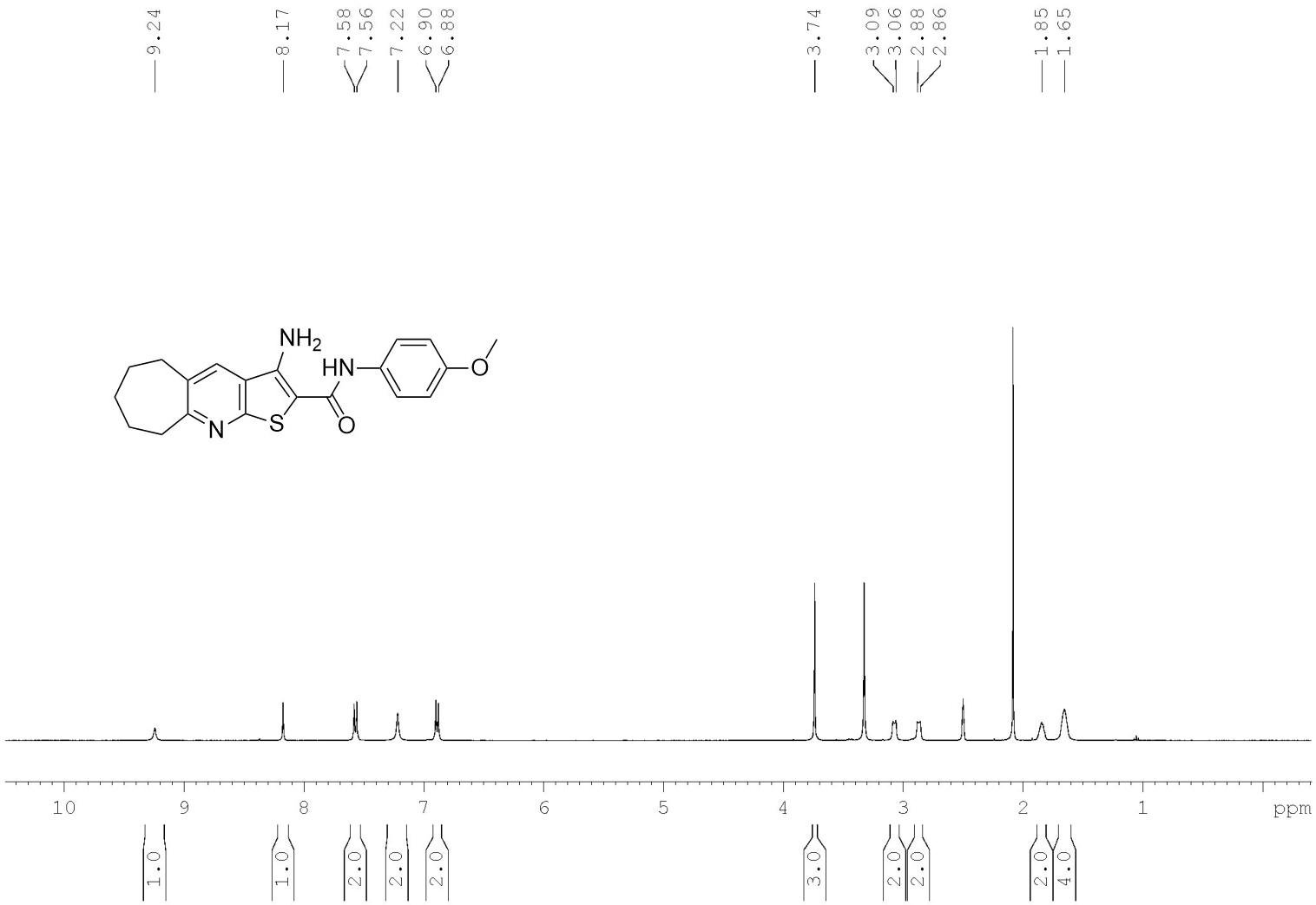


Figure S25: ^{1}H NMR spectrum of **7b** (400 MHz; DMSO-d_6).

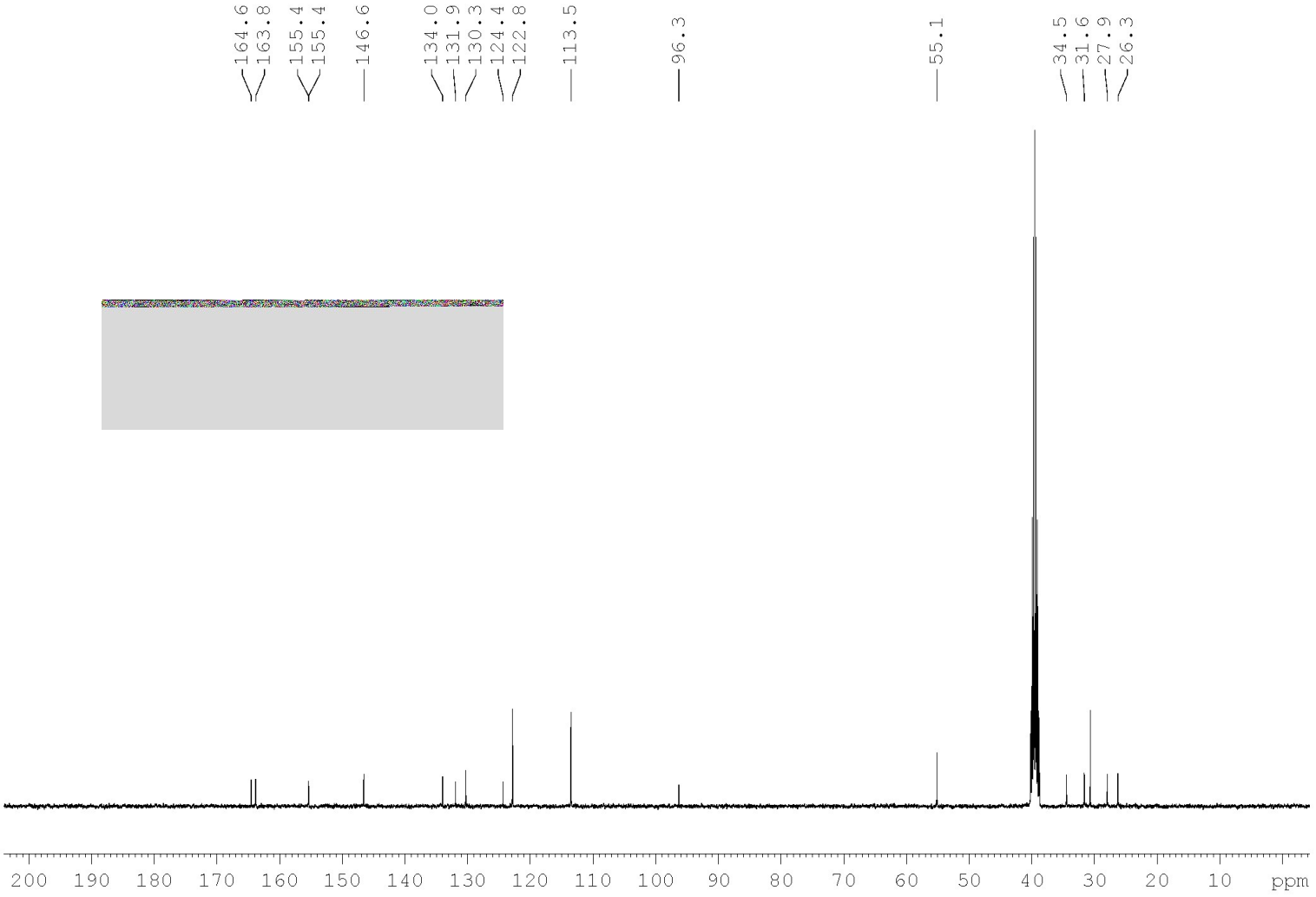


Figure S26: ^{13}C NMR spectrum of **7b** (100 MHz; DMSO-d_6).

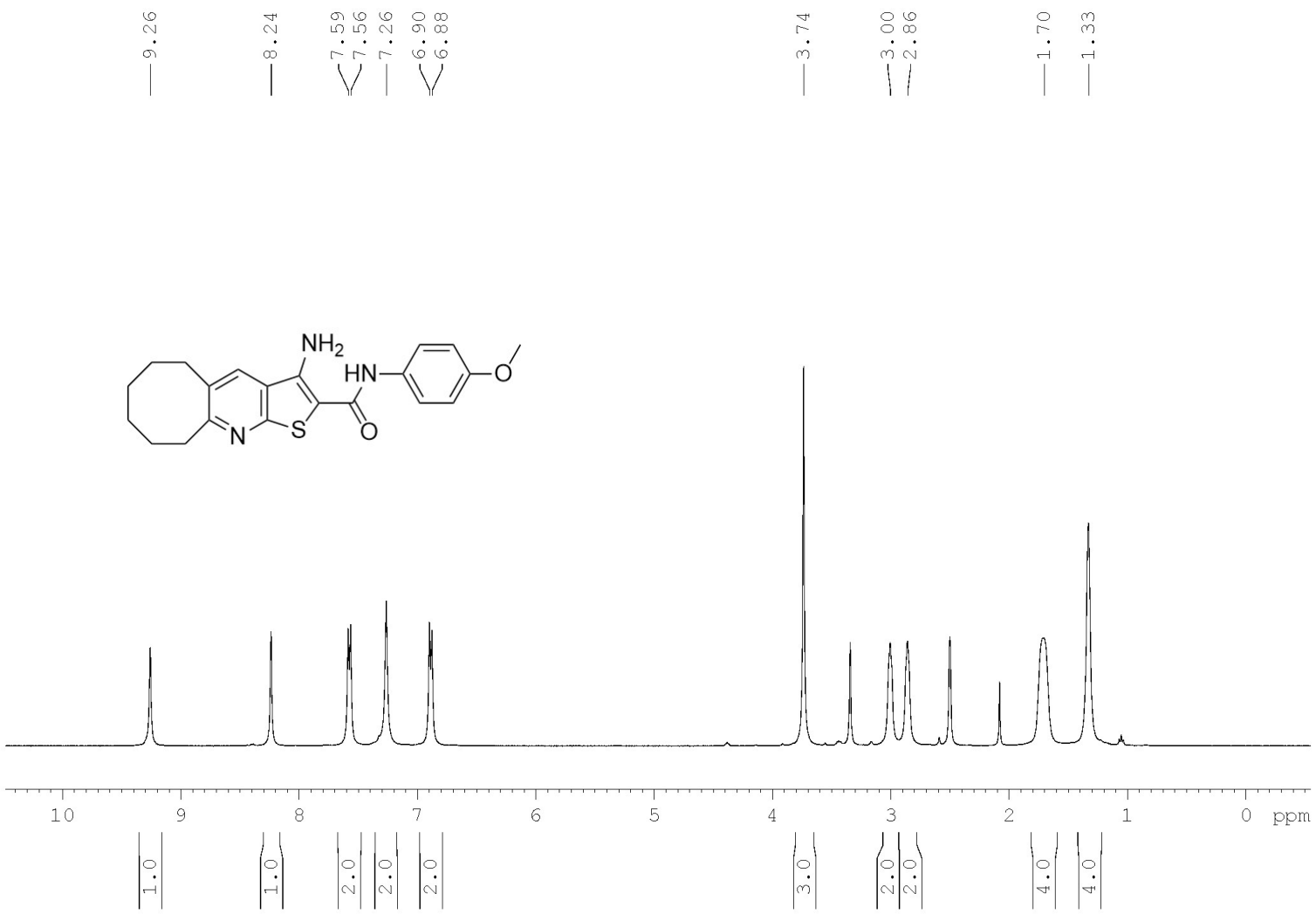


Figure S27: ^{1}H NMR spectrum of **7c** (400 MHz; DMSO-d_6).

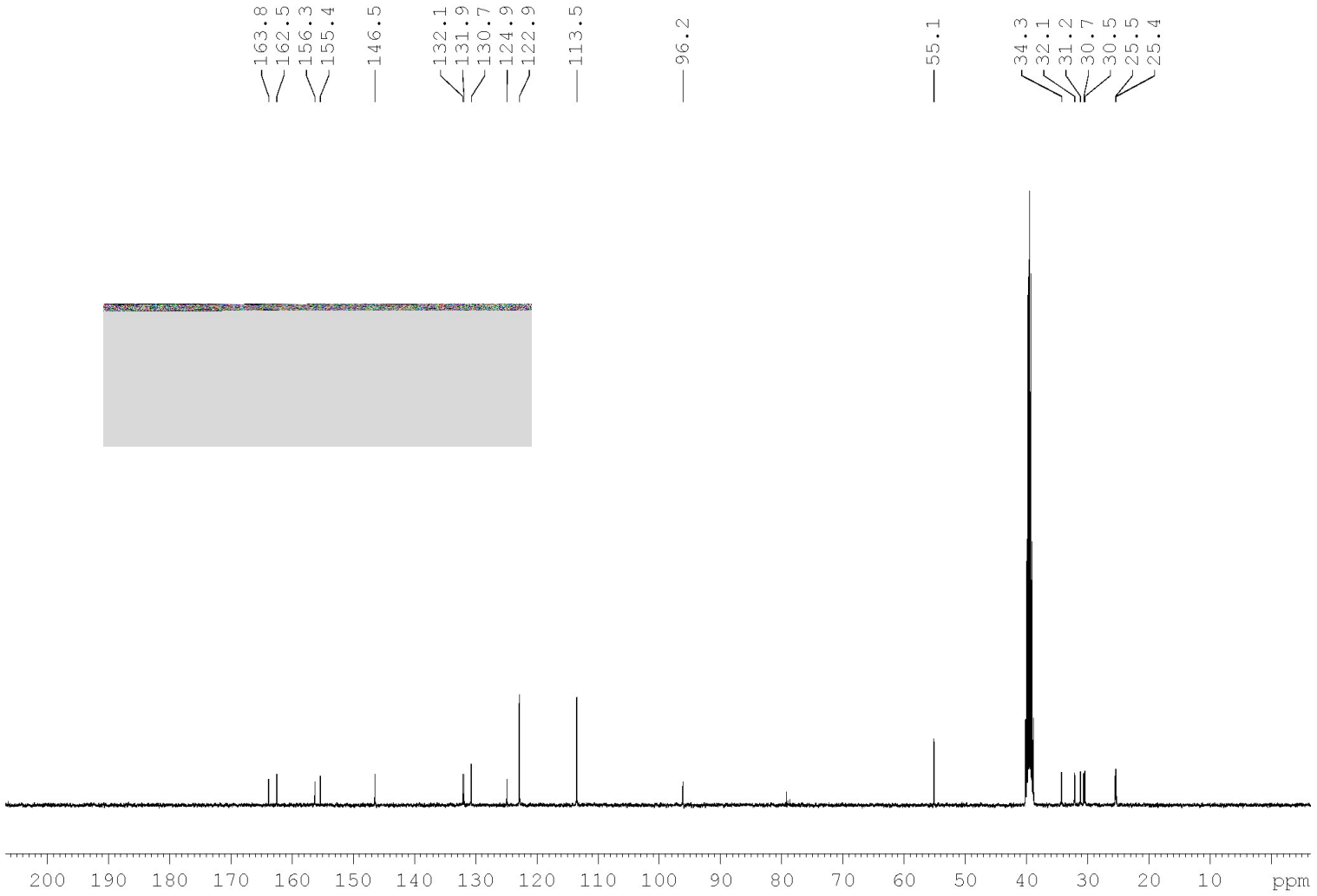


Figure S28: ^{13}C NMR spectrum of **7c** (100 MHz; DMSO-d_6).

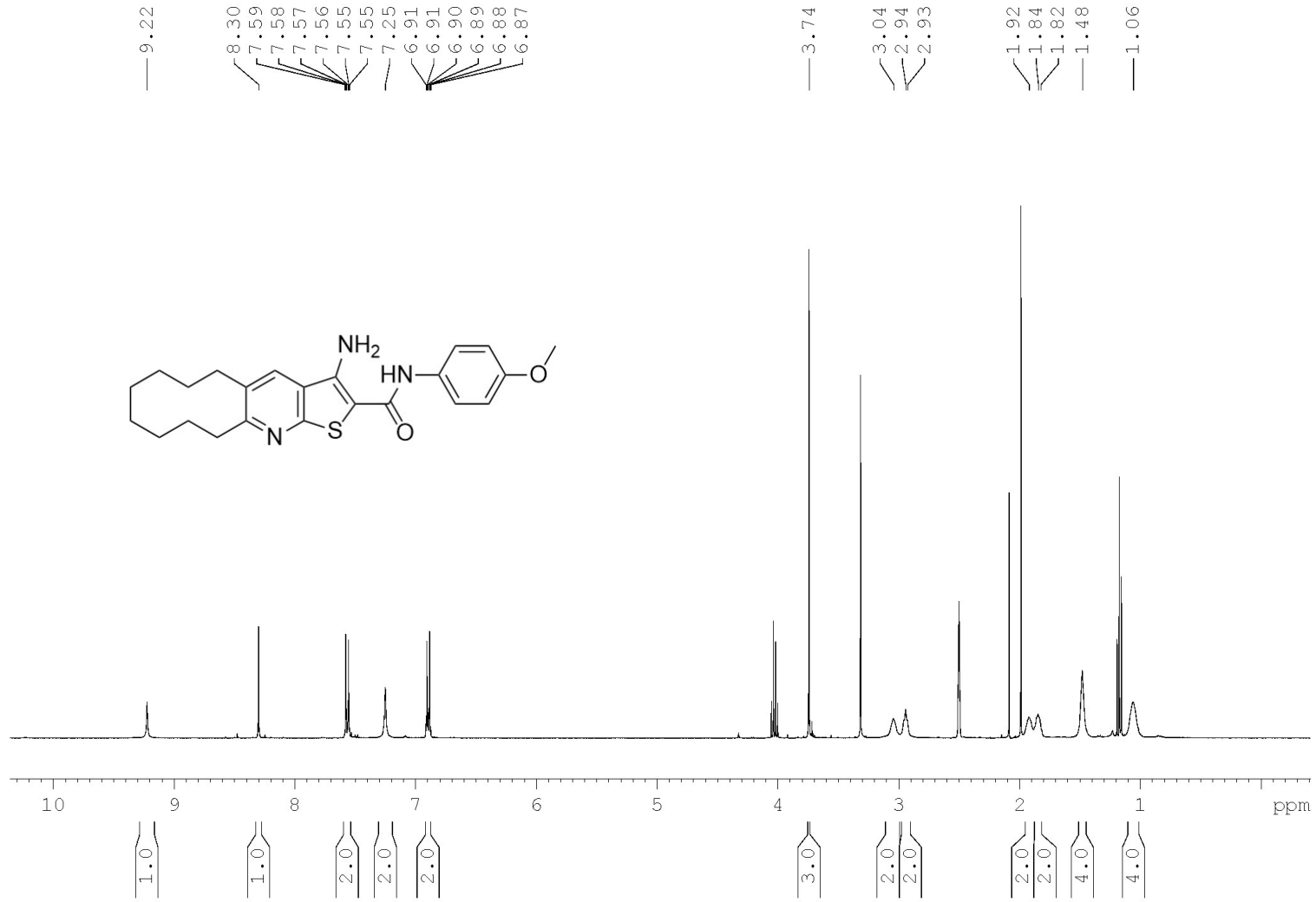


Figure S29: ^{1}H NMR spectrum of **7d** (400 MHz; DMSO-d_6).

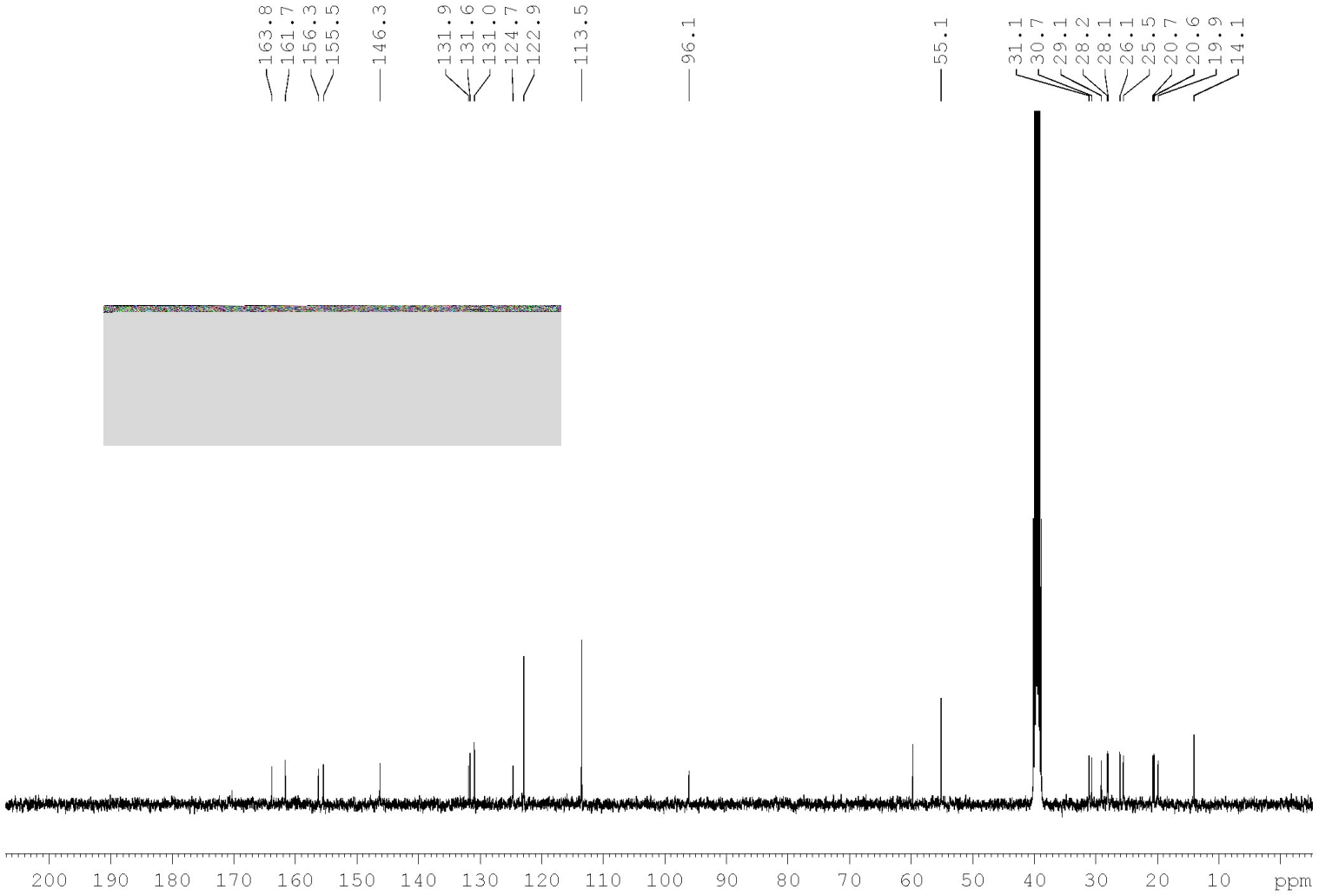


Figure S30: ^{13}C NMR spectrum of **7d** (100 MHz; DMSO-d_6).

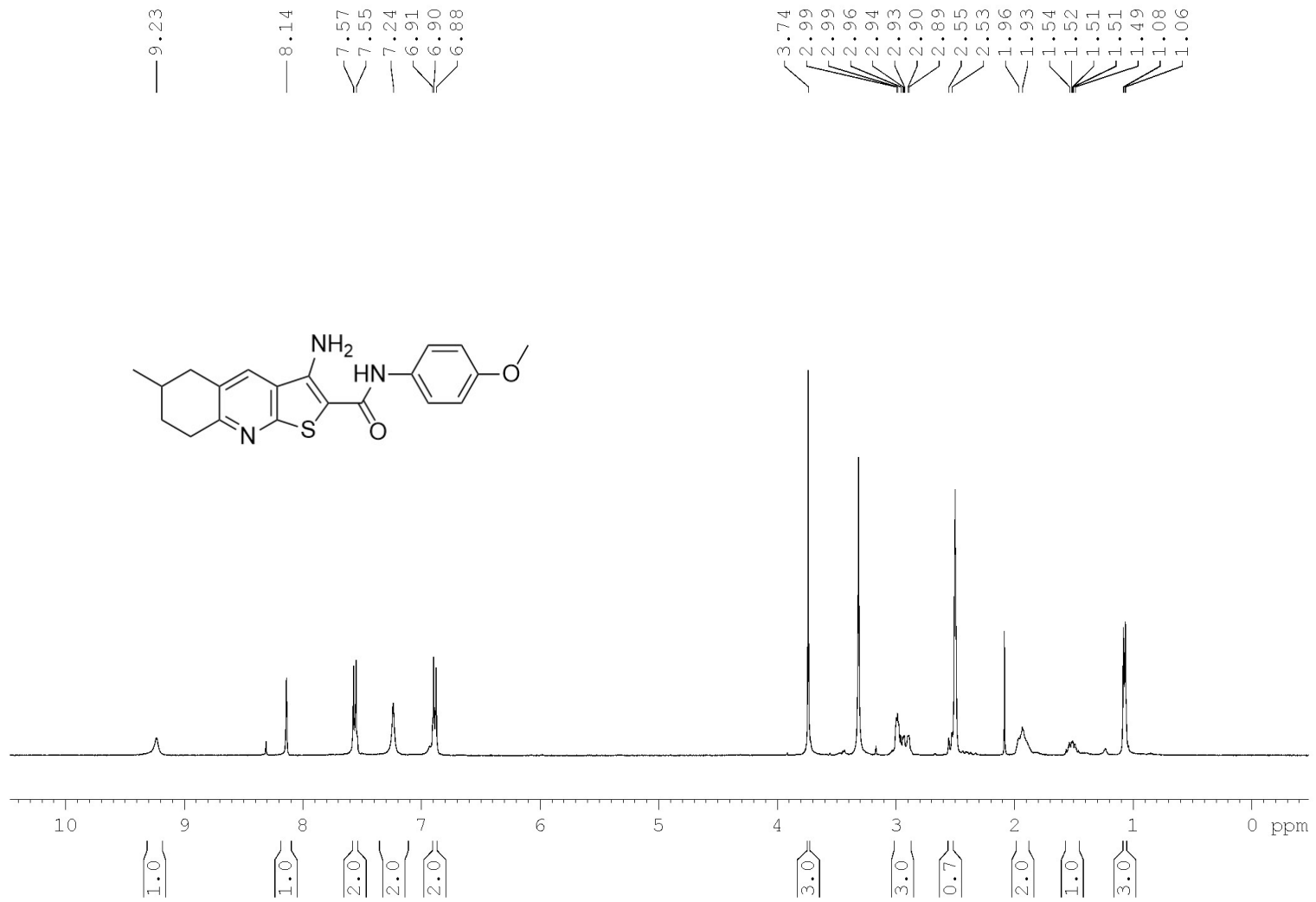


Figure S31: ^{1}H NMR spectrum of **7e** (400 MHz; DMSO-d_6).

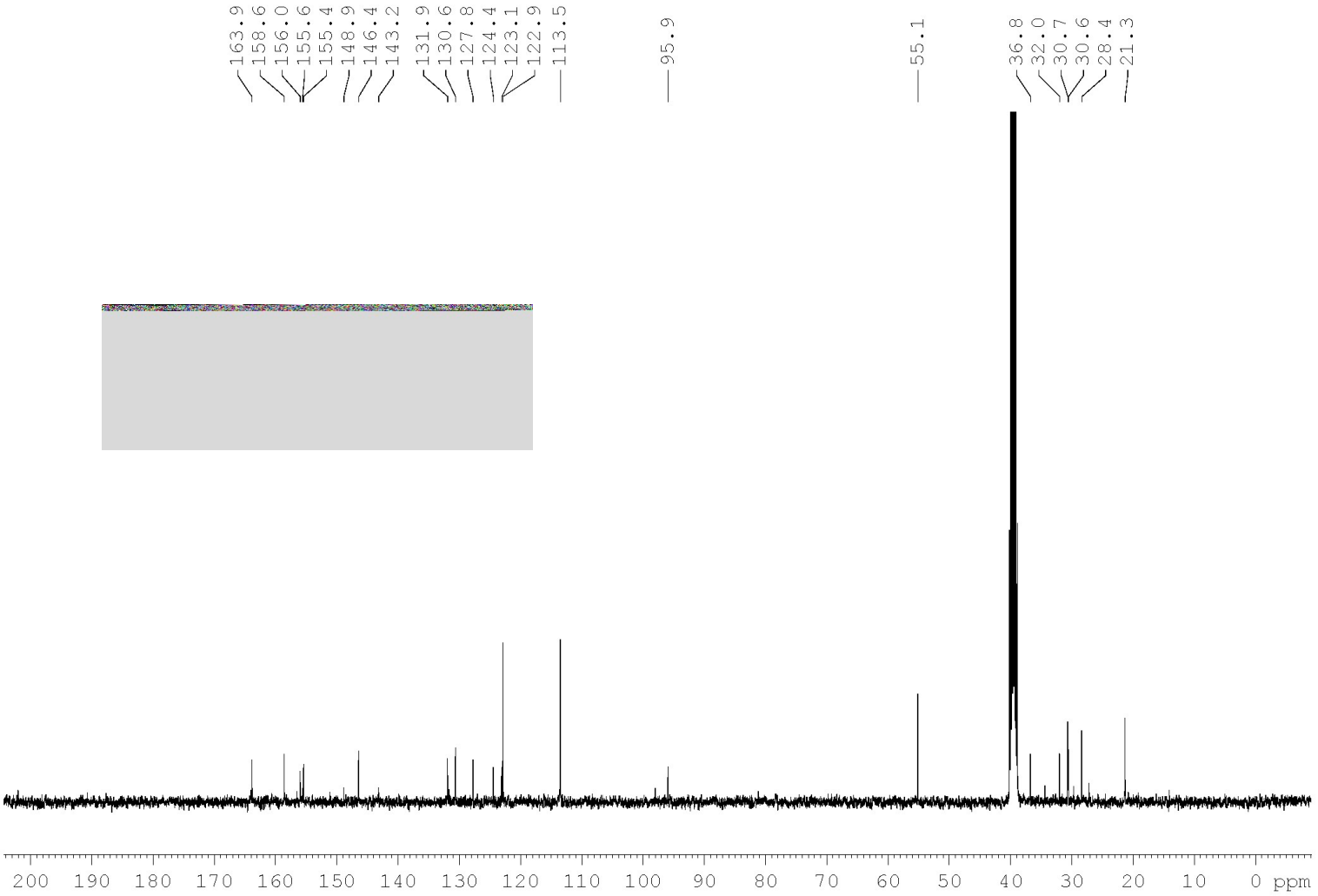


Figure S32: ^{13}C NMR spectrum of **7e** (100 MHz; DMSO-d_6).

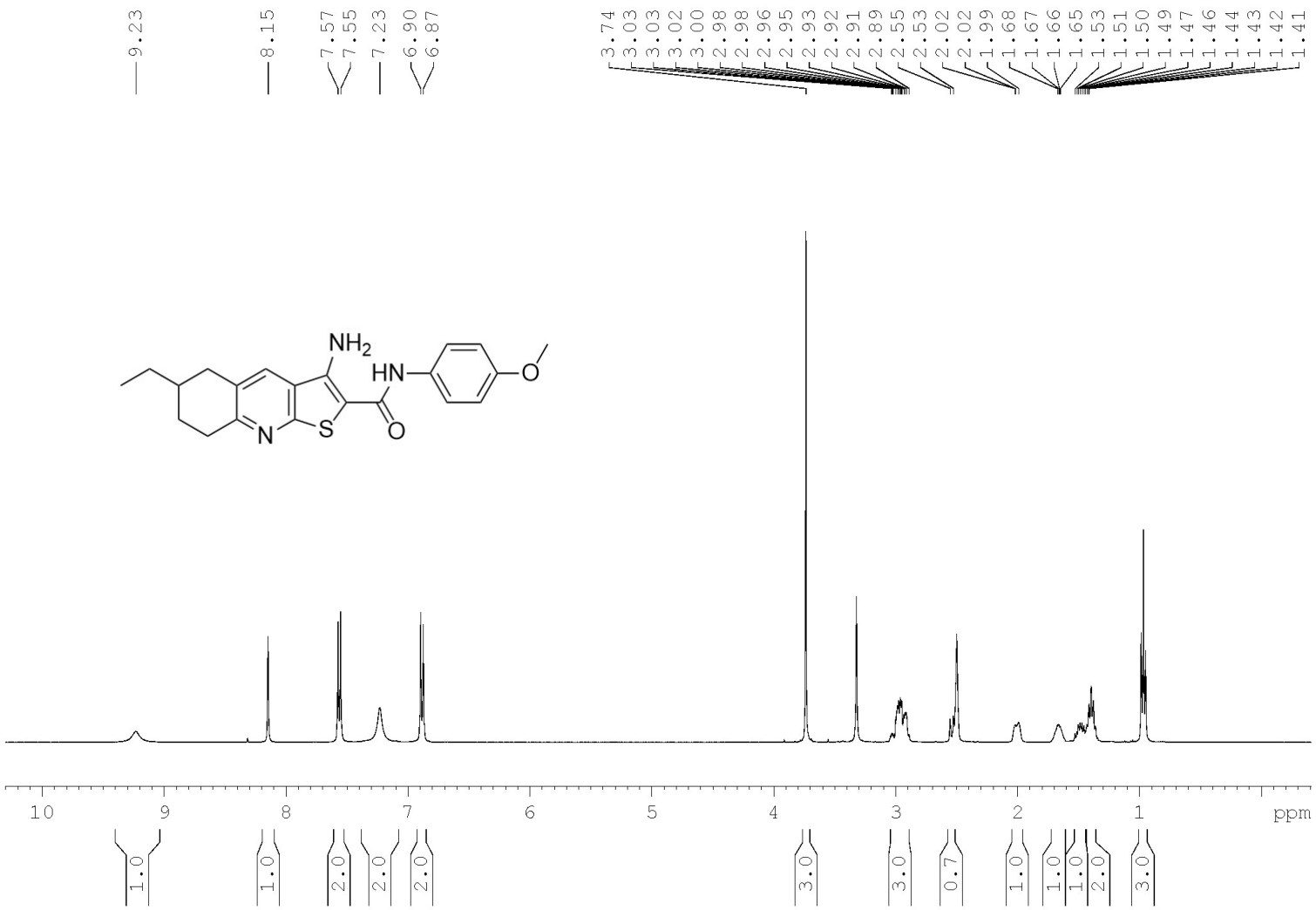


Figure S33: ^{1}H NMR spectrum of **7f** (400 MHz; DMSO-d_6).

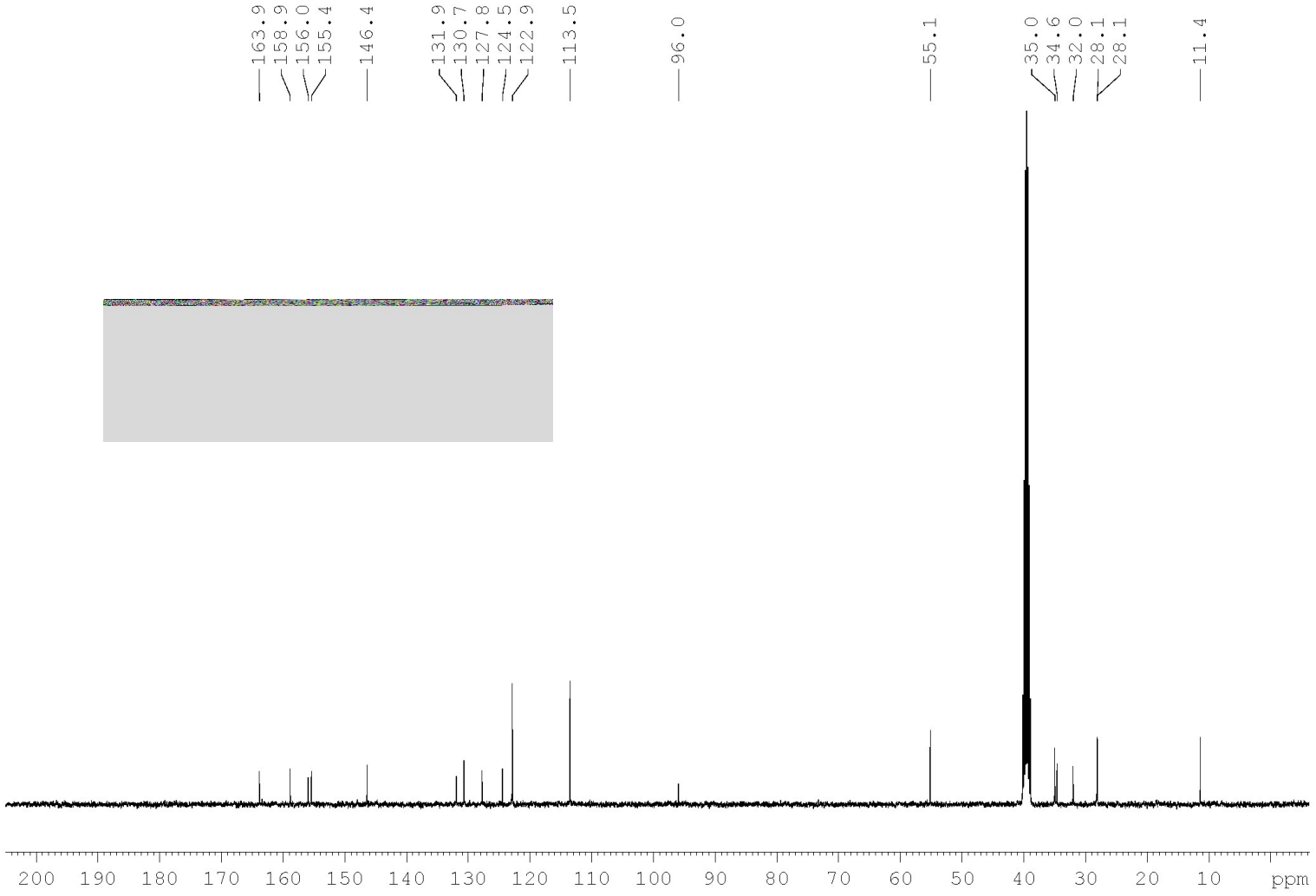


Figure S34: ^{13}C NMR spectrum of **7f** (100 MHz; DMSO-d_6).

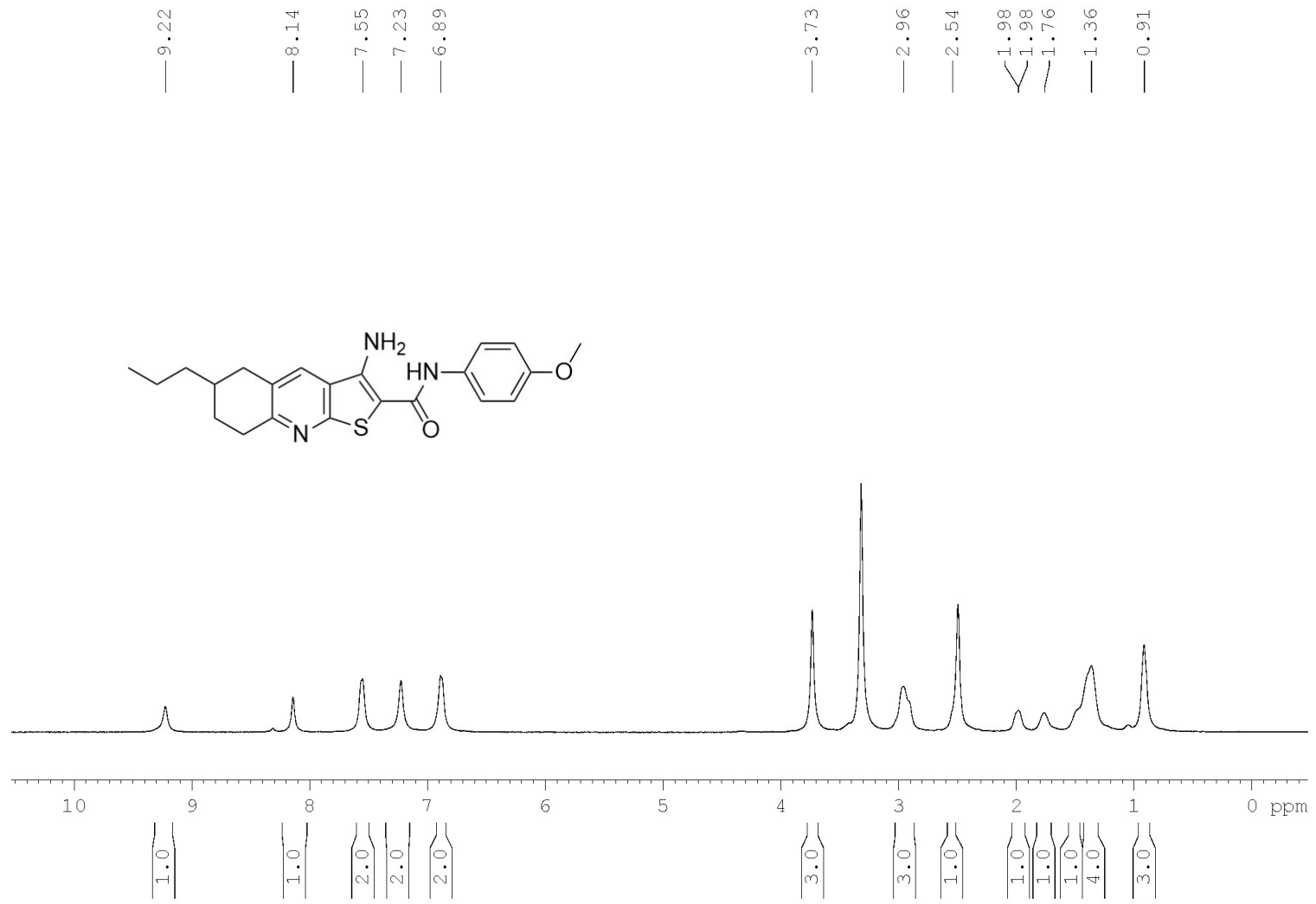


Figure S35: ^{1}H NMR spectrum of **7g** (400 MHz; DMSO-d_6).

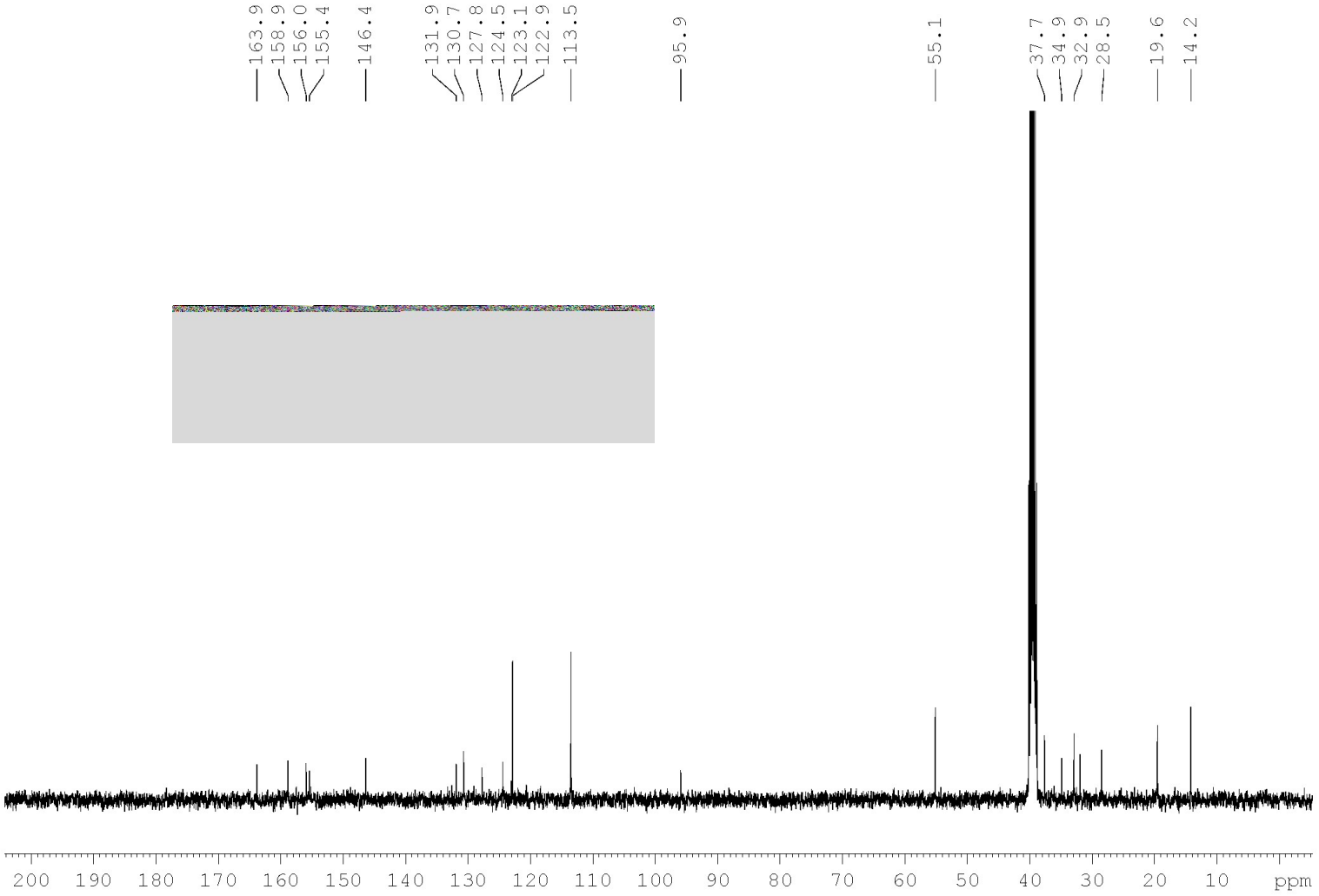


Figure S36: ^{13}C NMR spectrum of **7g** (100 MHz; DMSO-d_6).

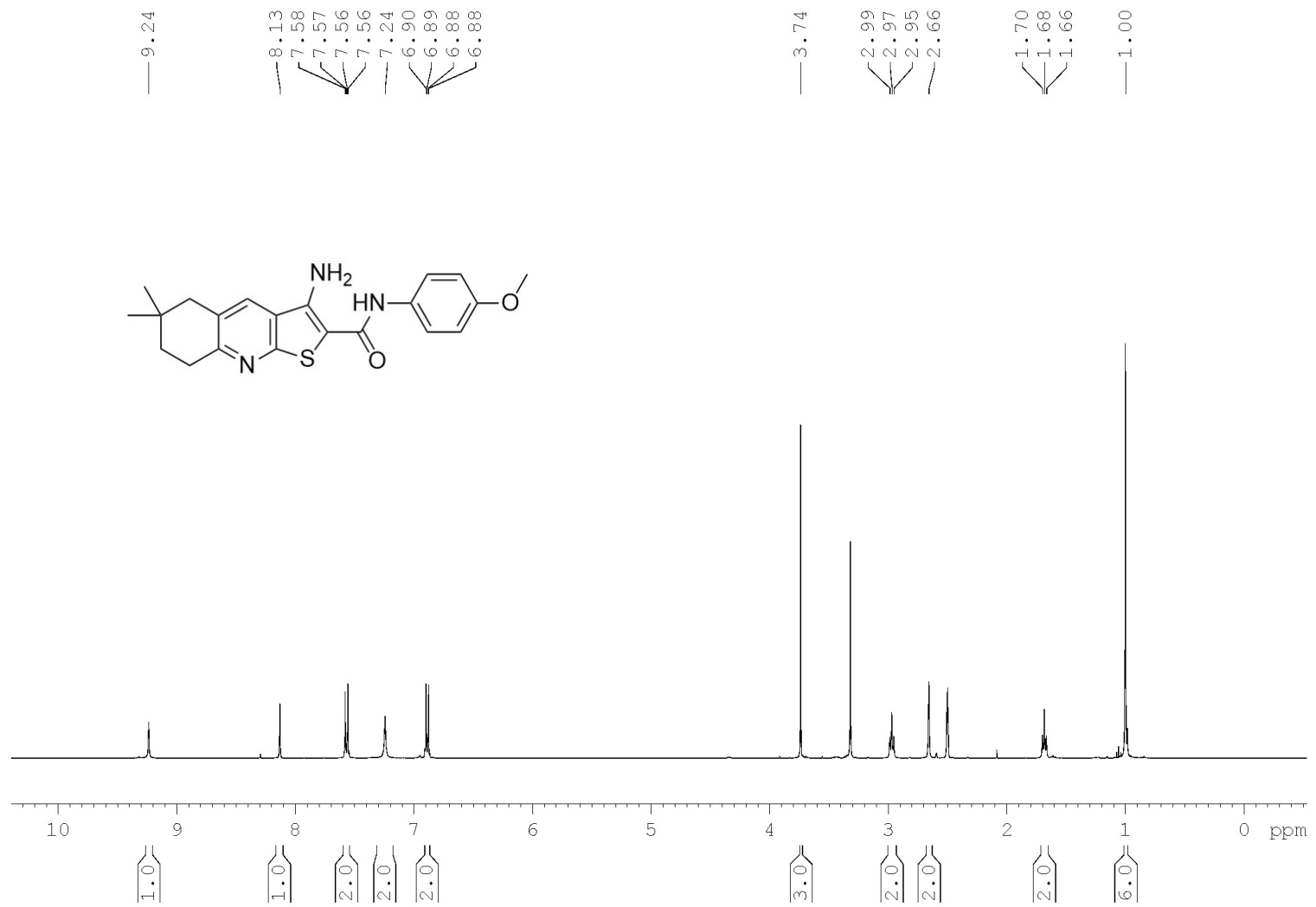


Figure S37: ^{1}H NMR spectrum of **7h** (400 MHz; DMSO-d_6).

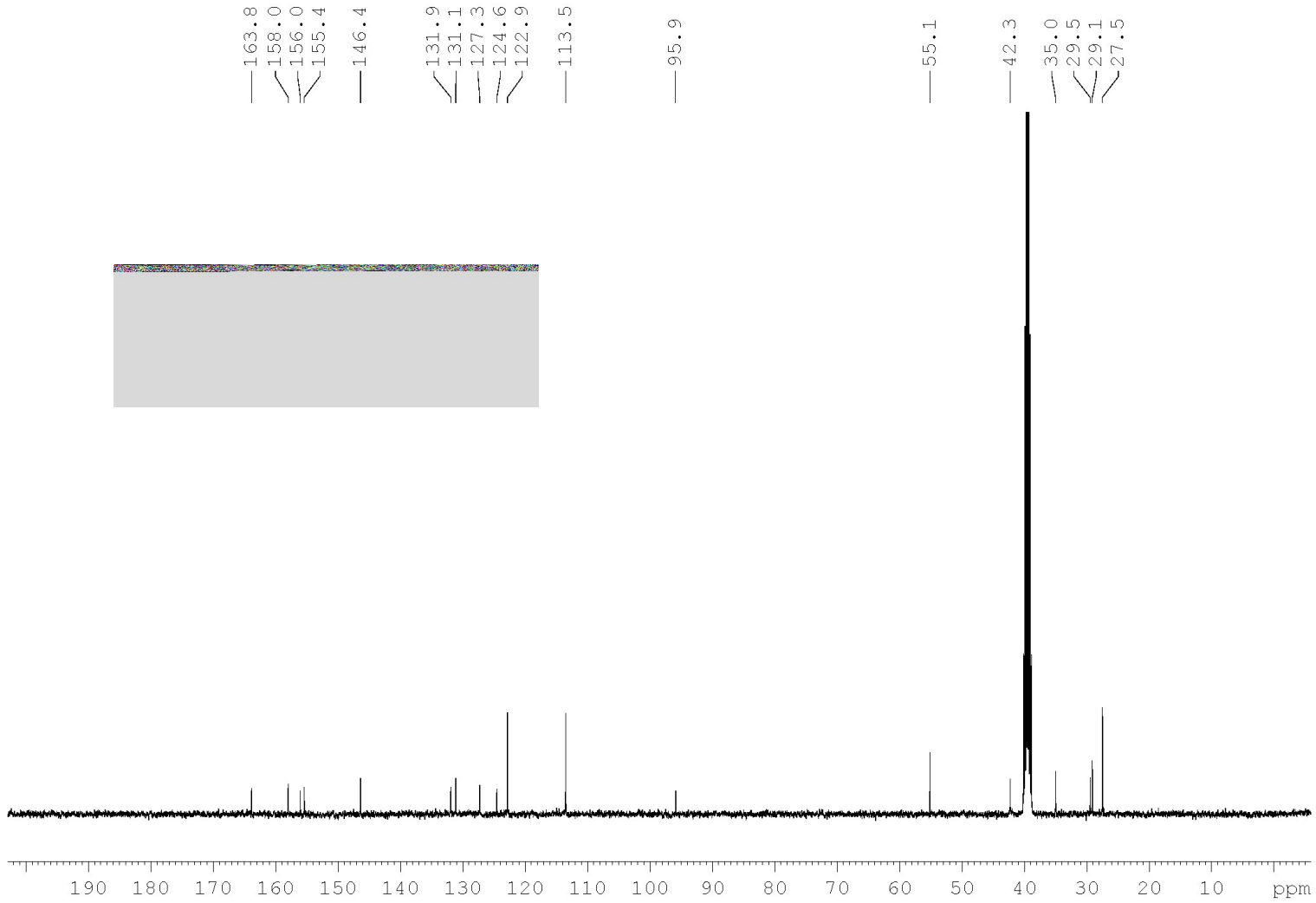


Figure S38: ^{13}C NMR spectrum of **7h** (100 MHz; DMSO-d_6).

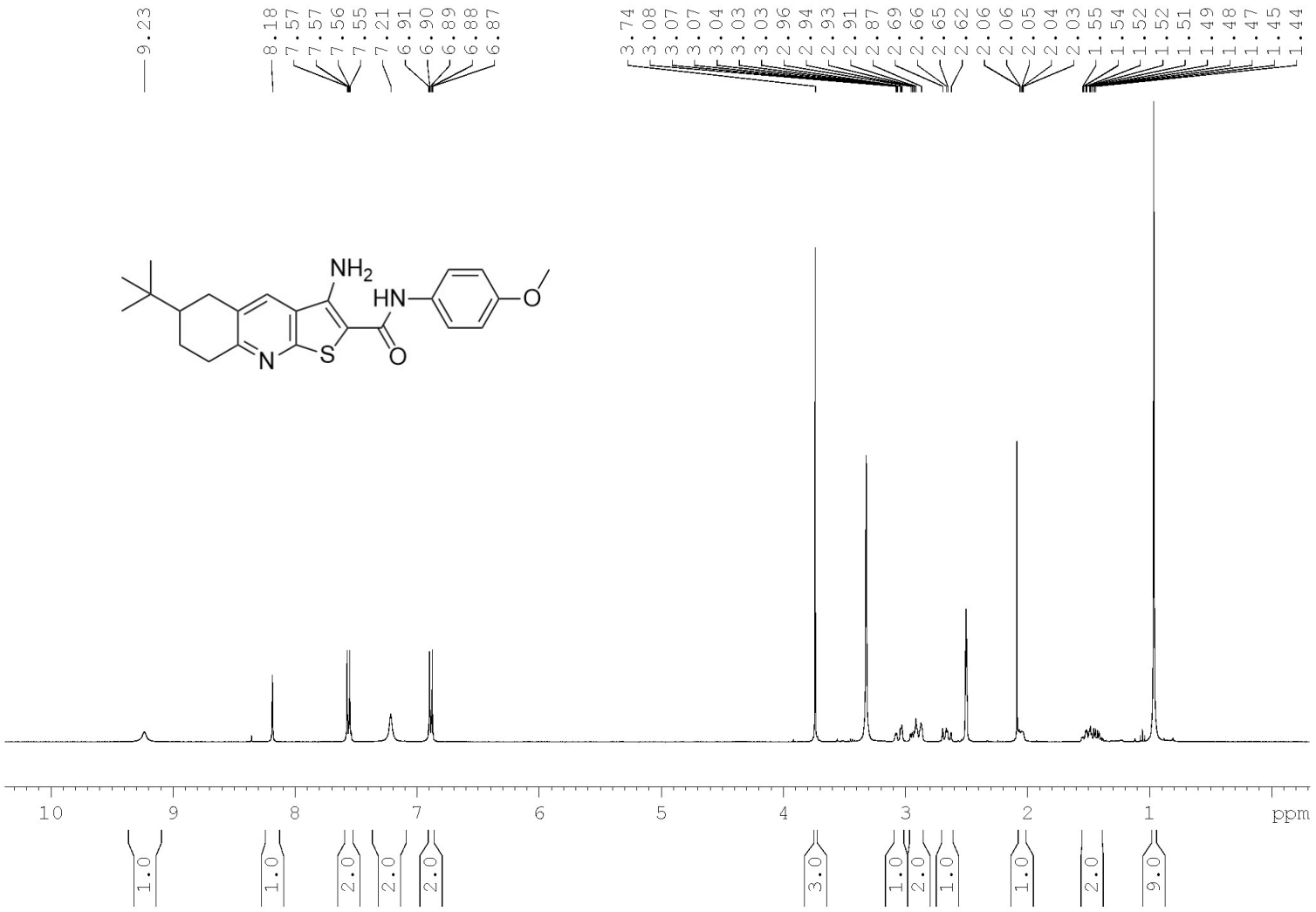


Figure S39: ^{1}H NMR spectrum of **7i** (400 MHz; DMSO-d_6).

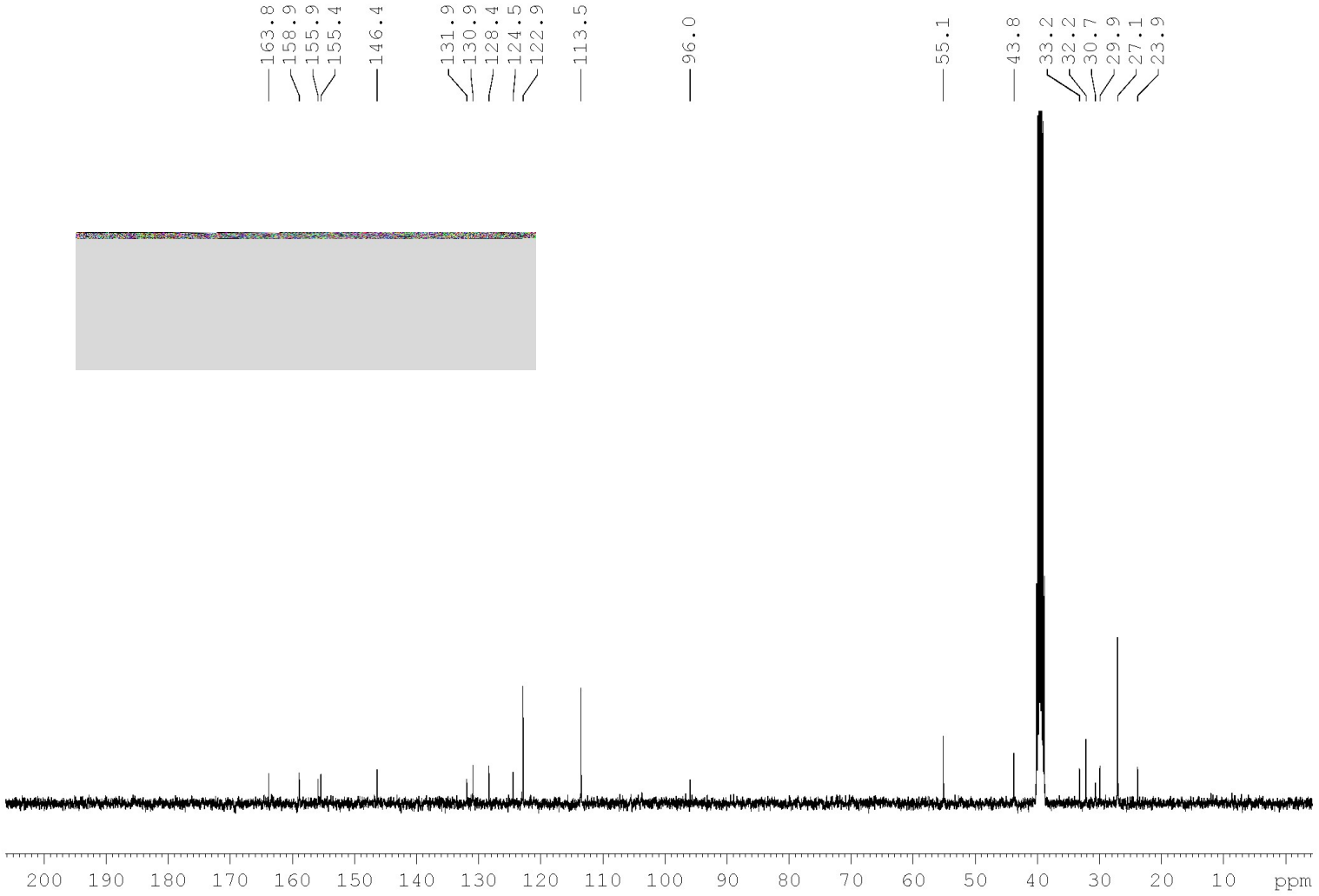


Figure S40: ^{13}C NMR spectrum of **7i** (100 MHz; DMSO-d_6).

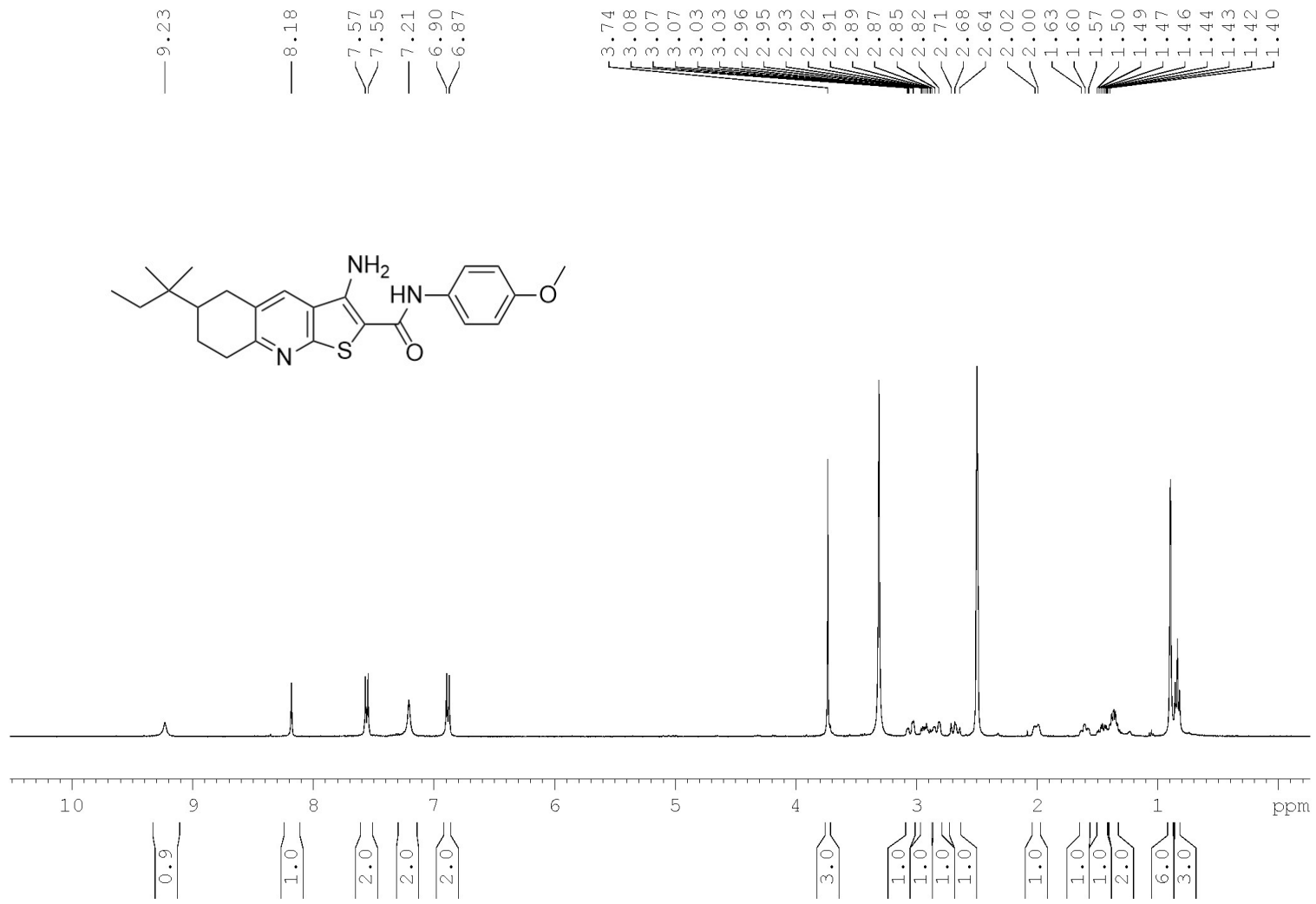


Figure S41: ^{1}H NMR spectrum of **7j** (400 MHz; DMSO-d_6).

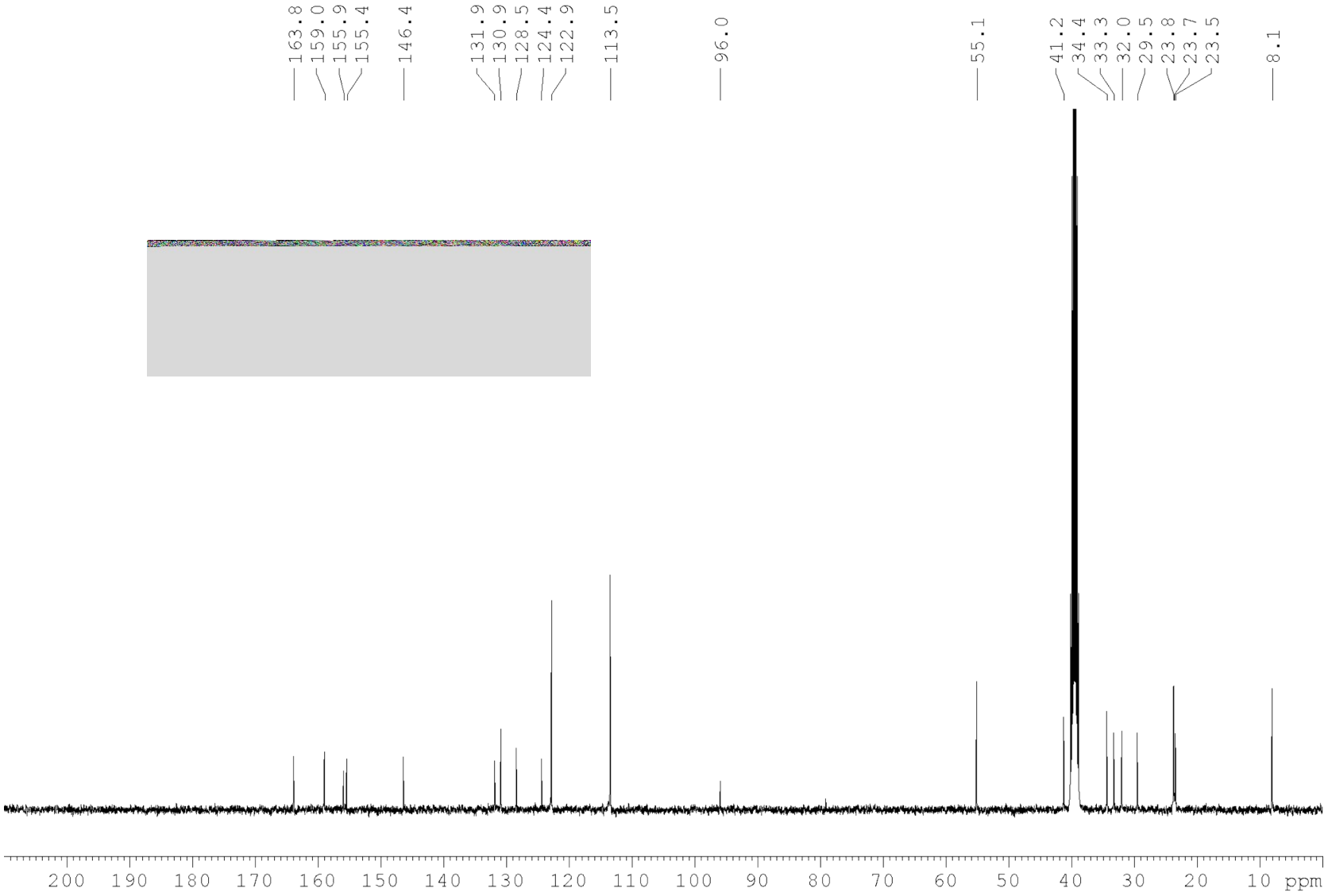


Figure S42: ^{13}C NMR spectrum of **7j** (100 MHz; DMSO-d_6).

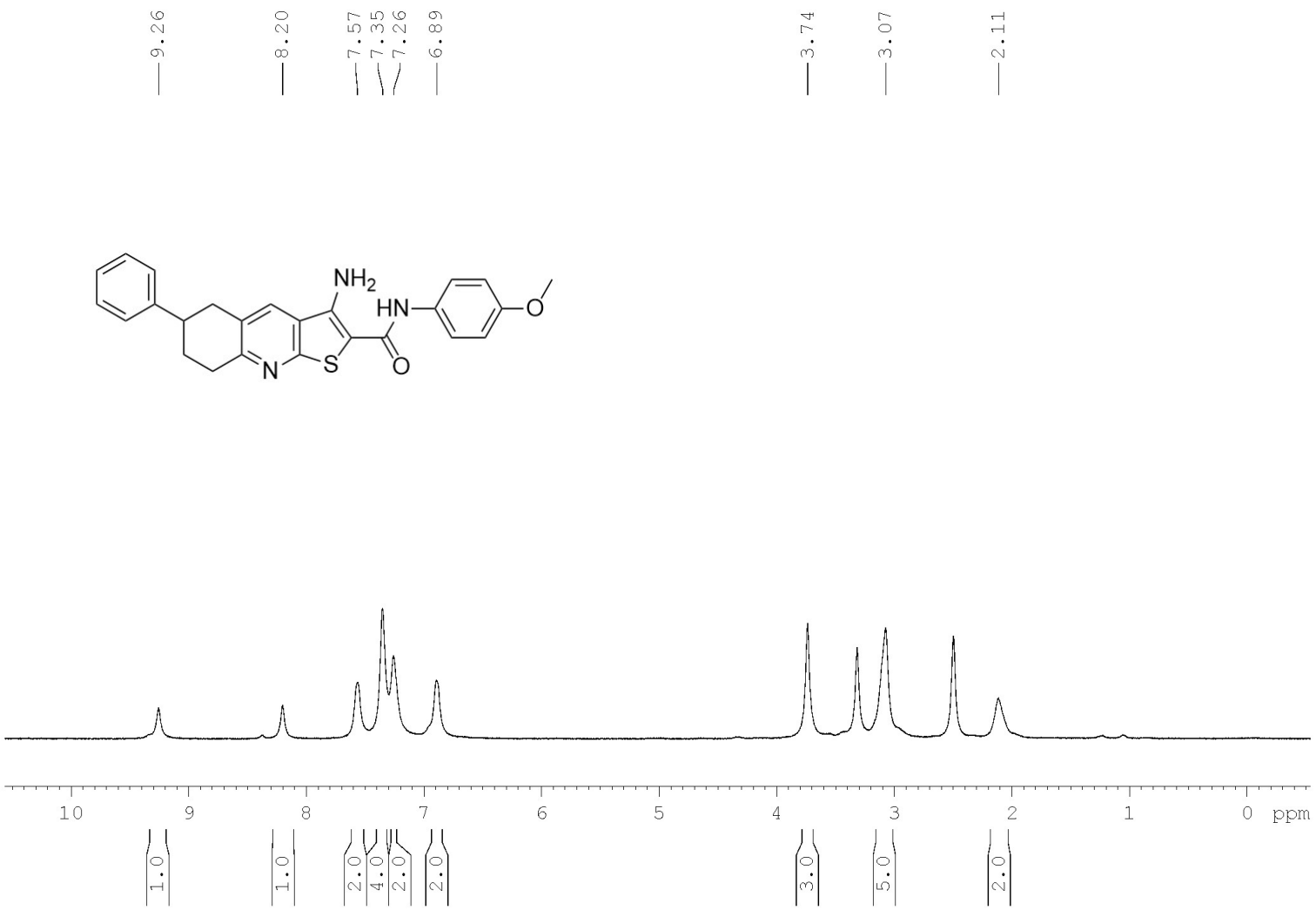


Figure S43: ^{1}H NMR spectrum of **7k** (400 MHz; DMSO-d_6).

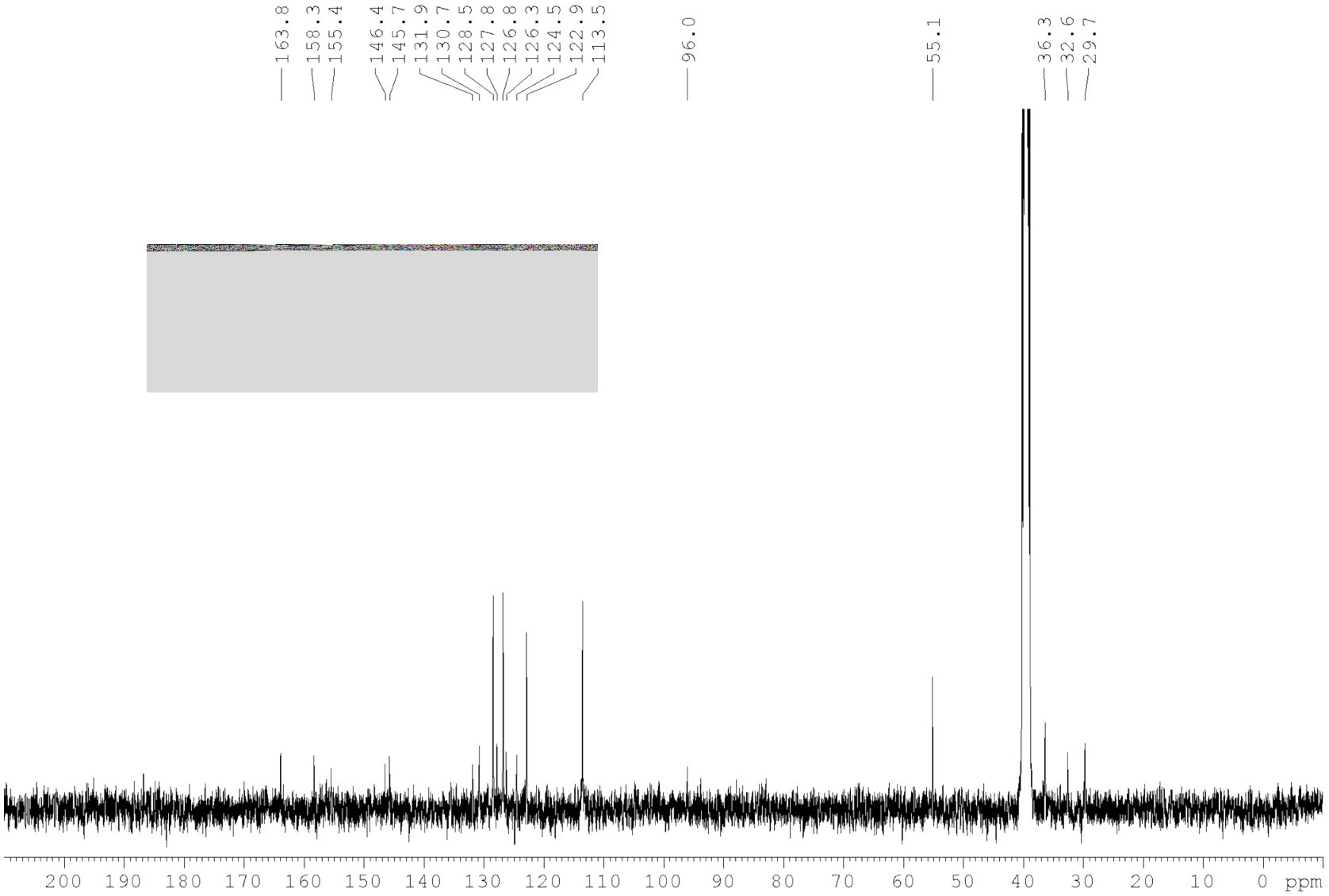


Figure S44: ^{13}C NMR spectrum of **7k** (100 MHz; DMSO-d_6).

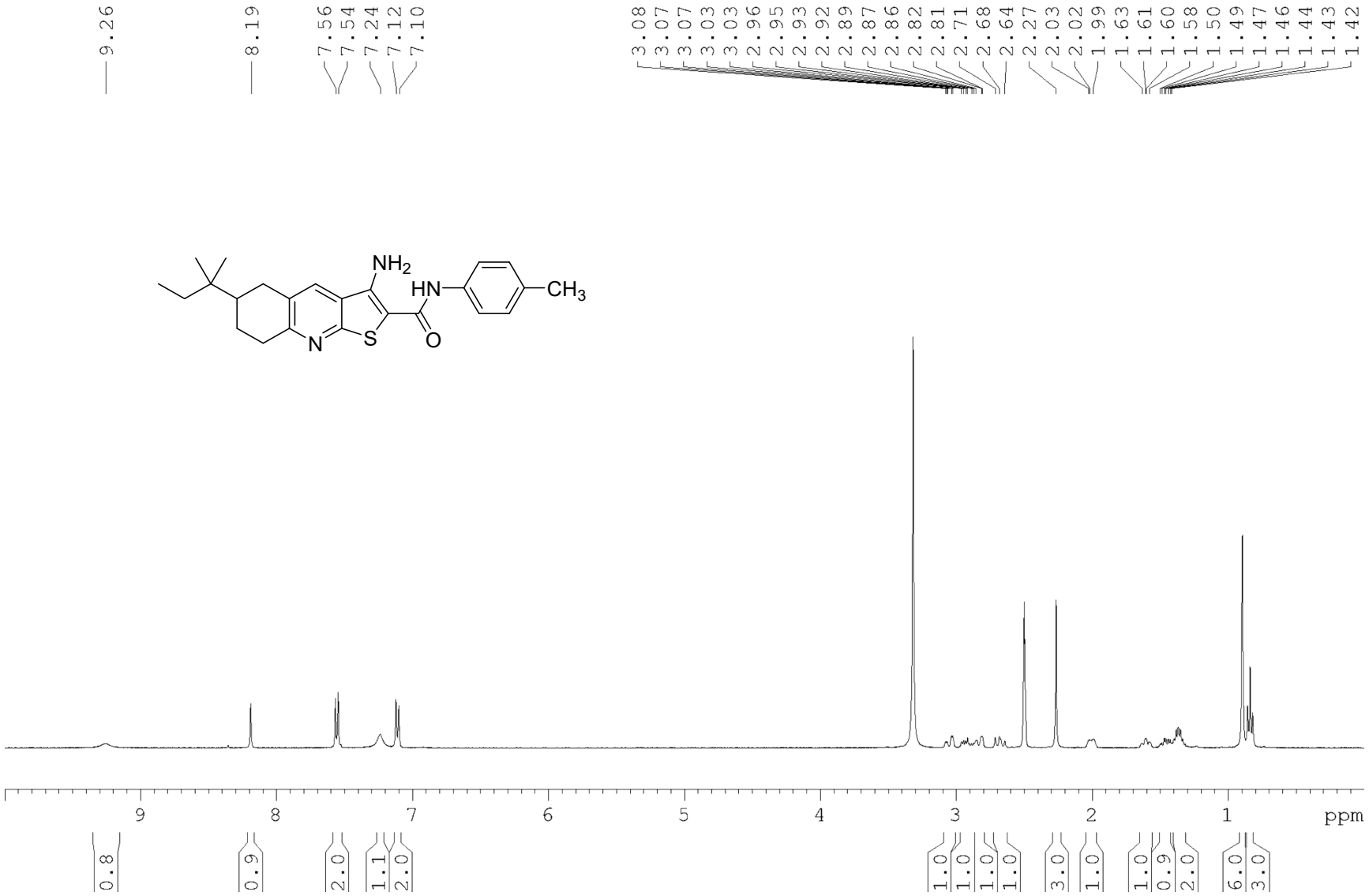


Figure S45: ^{1}H NMR spectrum of **10a** (400 MHz; DMSO-d_6).

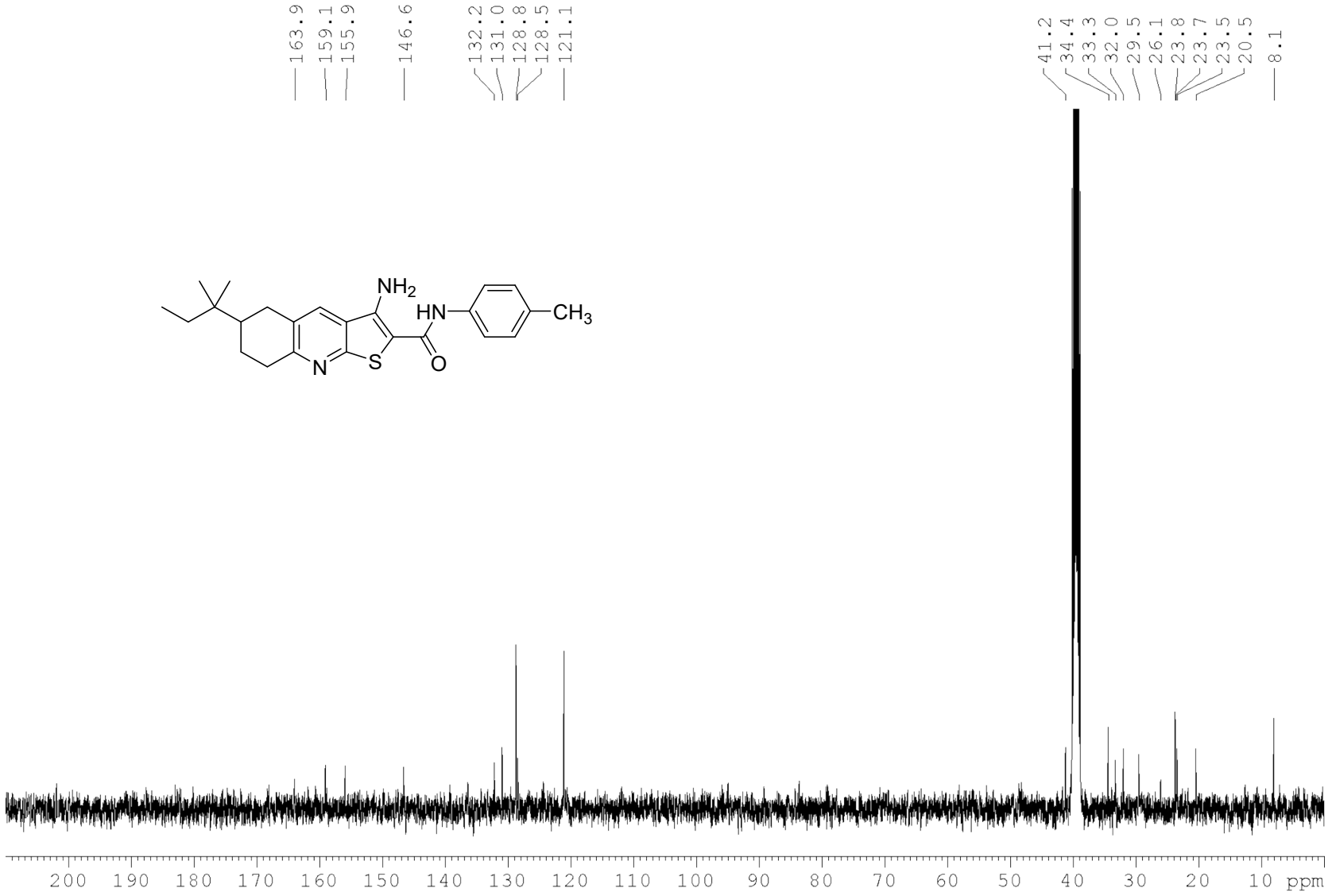


Figure S46: ^{13}C NMR spectrum of **10a** (100 MHz; DMSO-d_6).

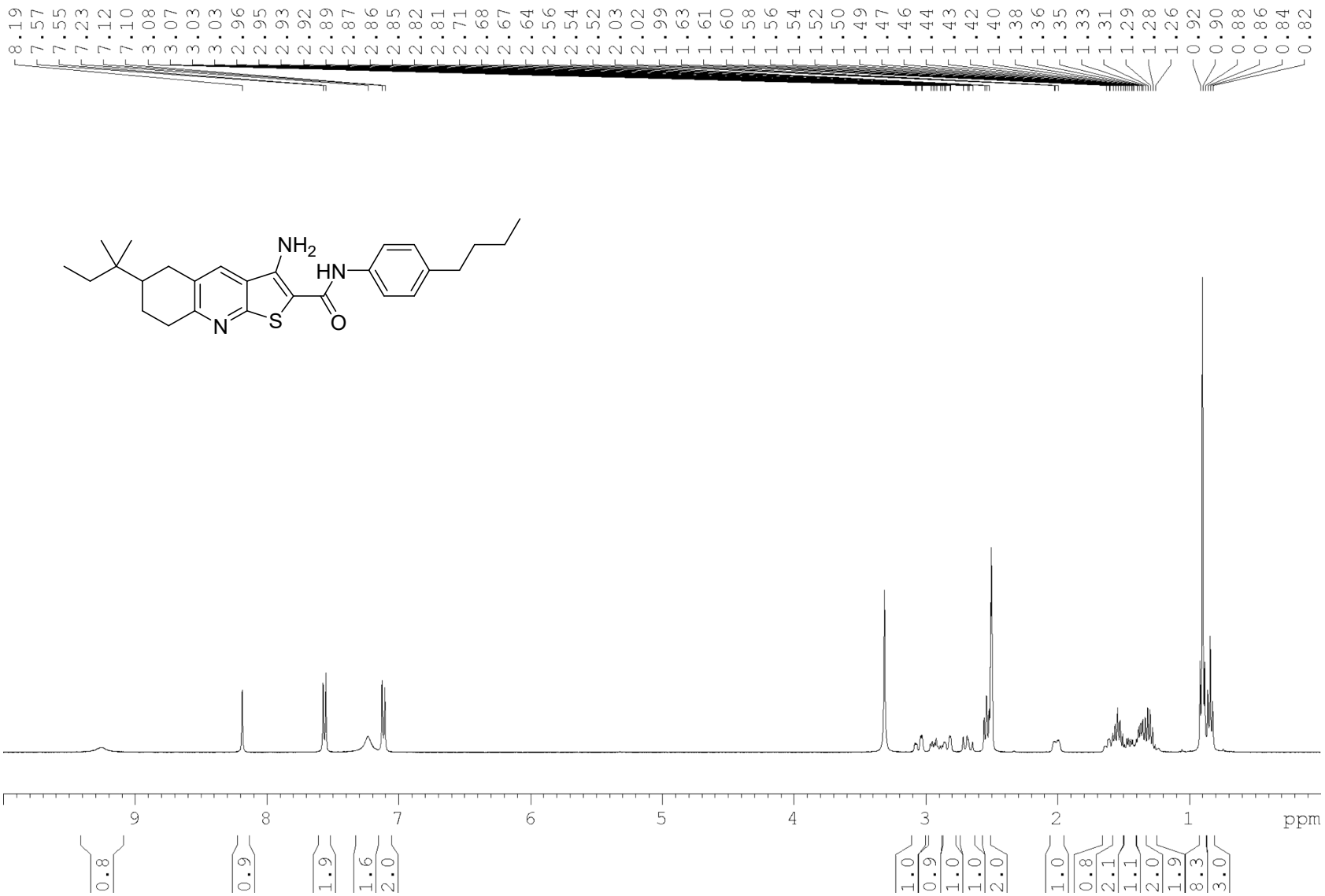


Figure S47: ^{1}H NMR spectrum of **10b** (400 MHz; DMSO-d_6).

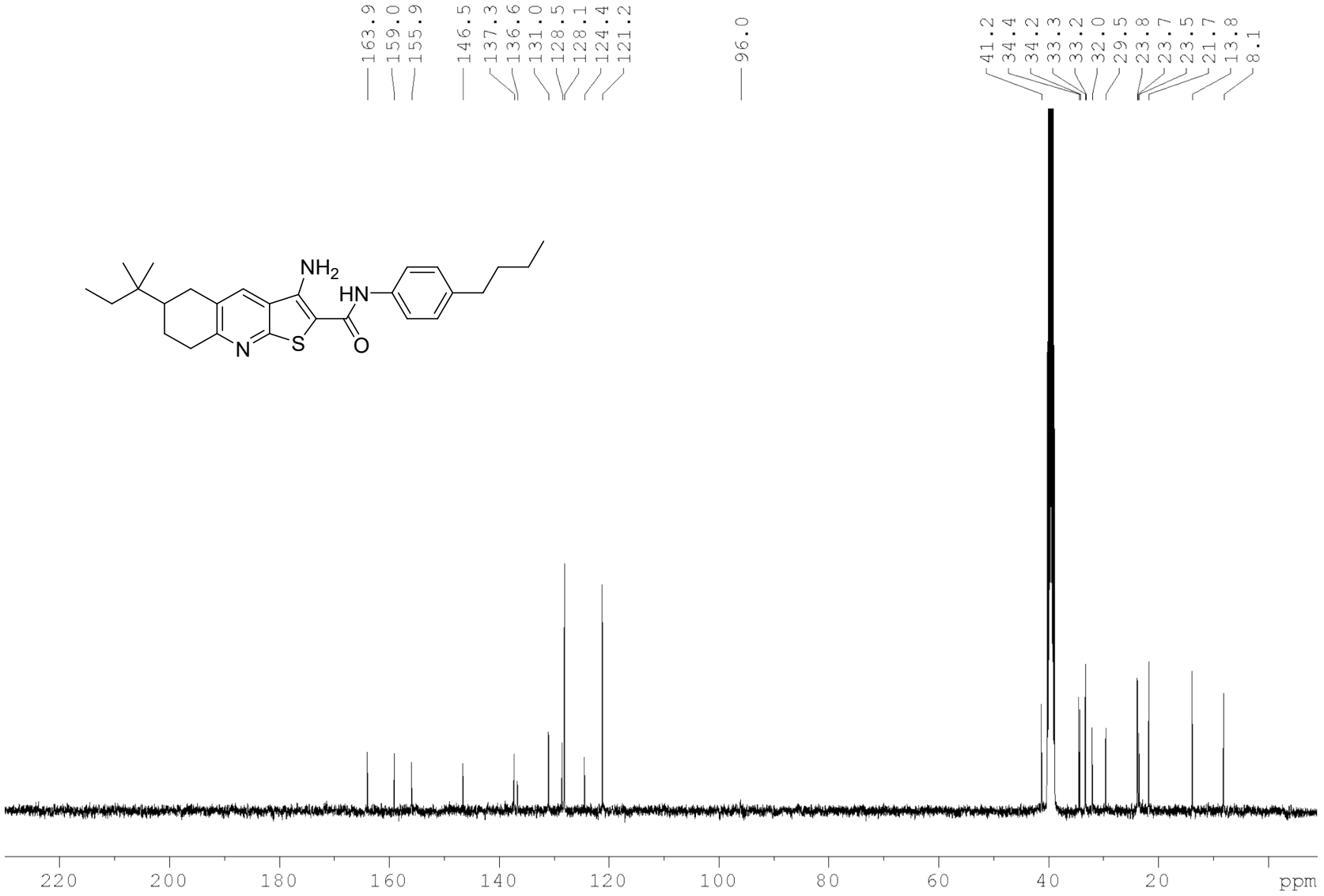


Figure S48: ^{13}C NMR spectrum of **10b** (100 MHz; DMSO-d_6).

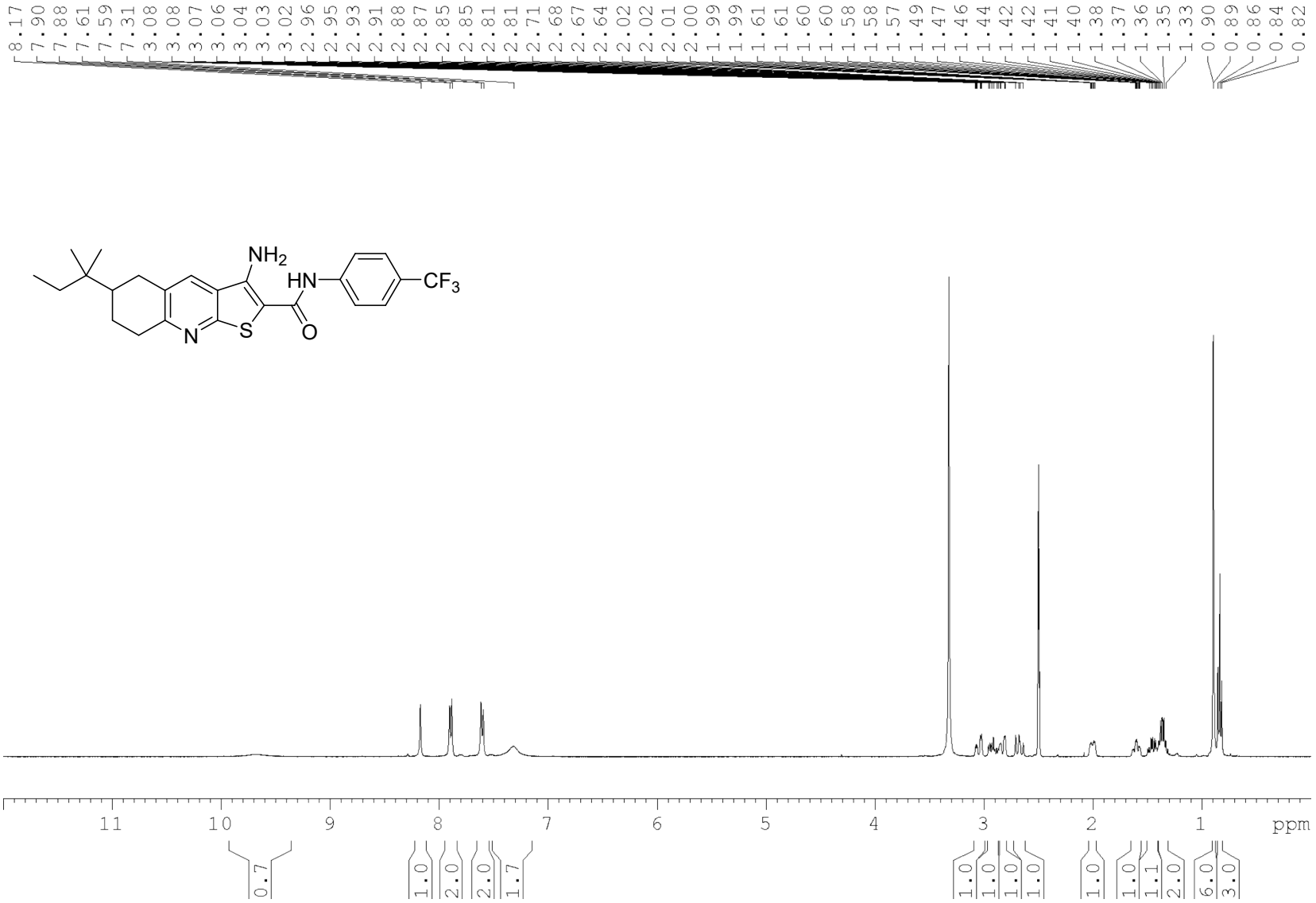


Figure S49: ^{1}H NMR spectrum of **10c** (400 MHz; DMSO-d_6).

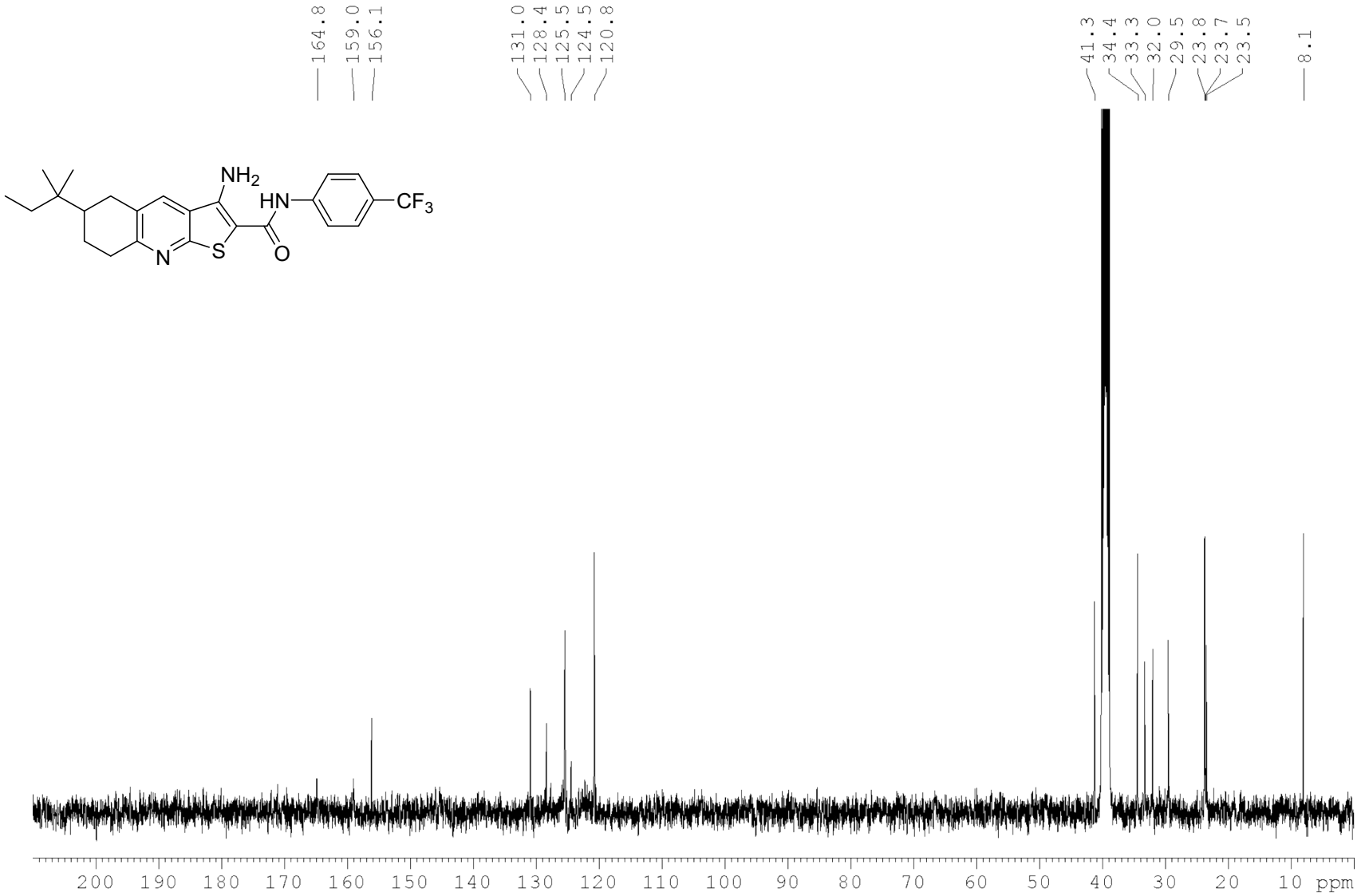


Figure S50: ^{13}C NMR spectrum of **10c** (100 MHz; DMSO-d_6).

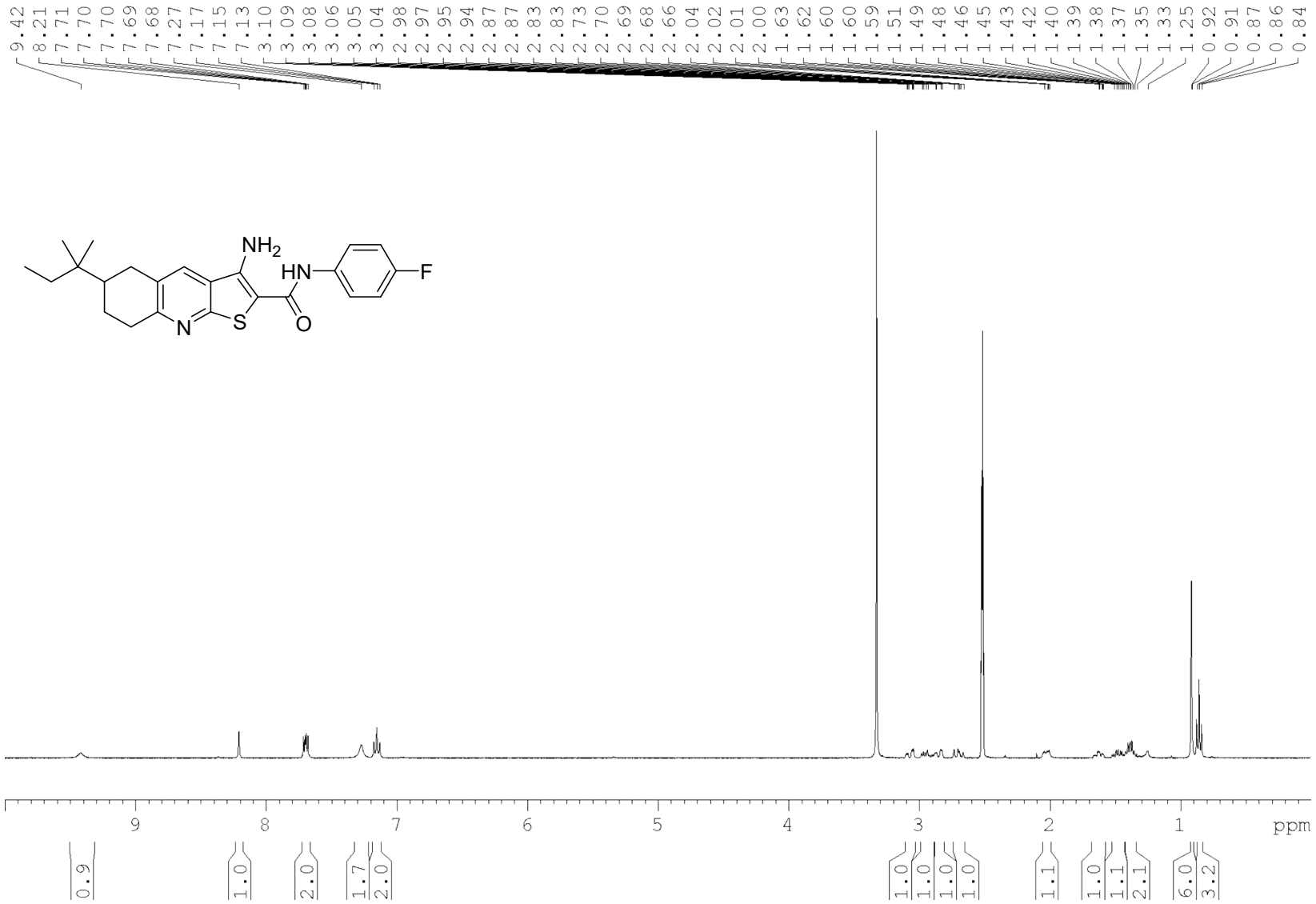


Figure S51: ^{1}H NMR spectrum of **10d** (400 MHz; DMSO-d_6).

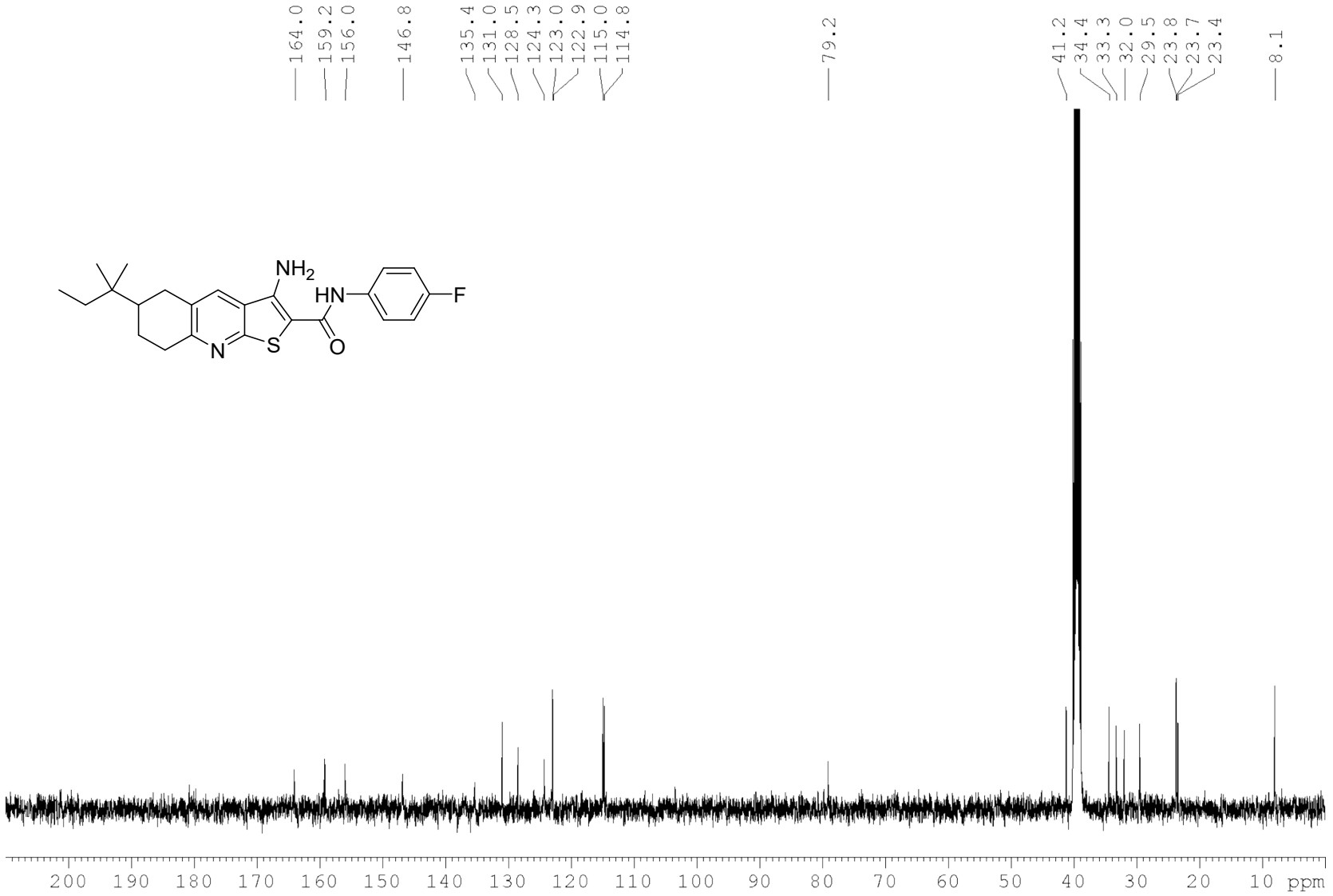


Figure S52: ^{13}C NMR spectrum of **10d** (100 MHz; DMSO-d_6).

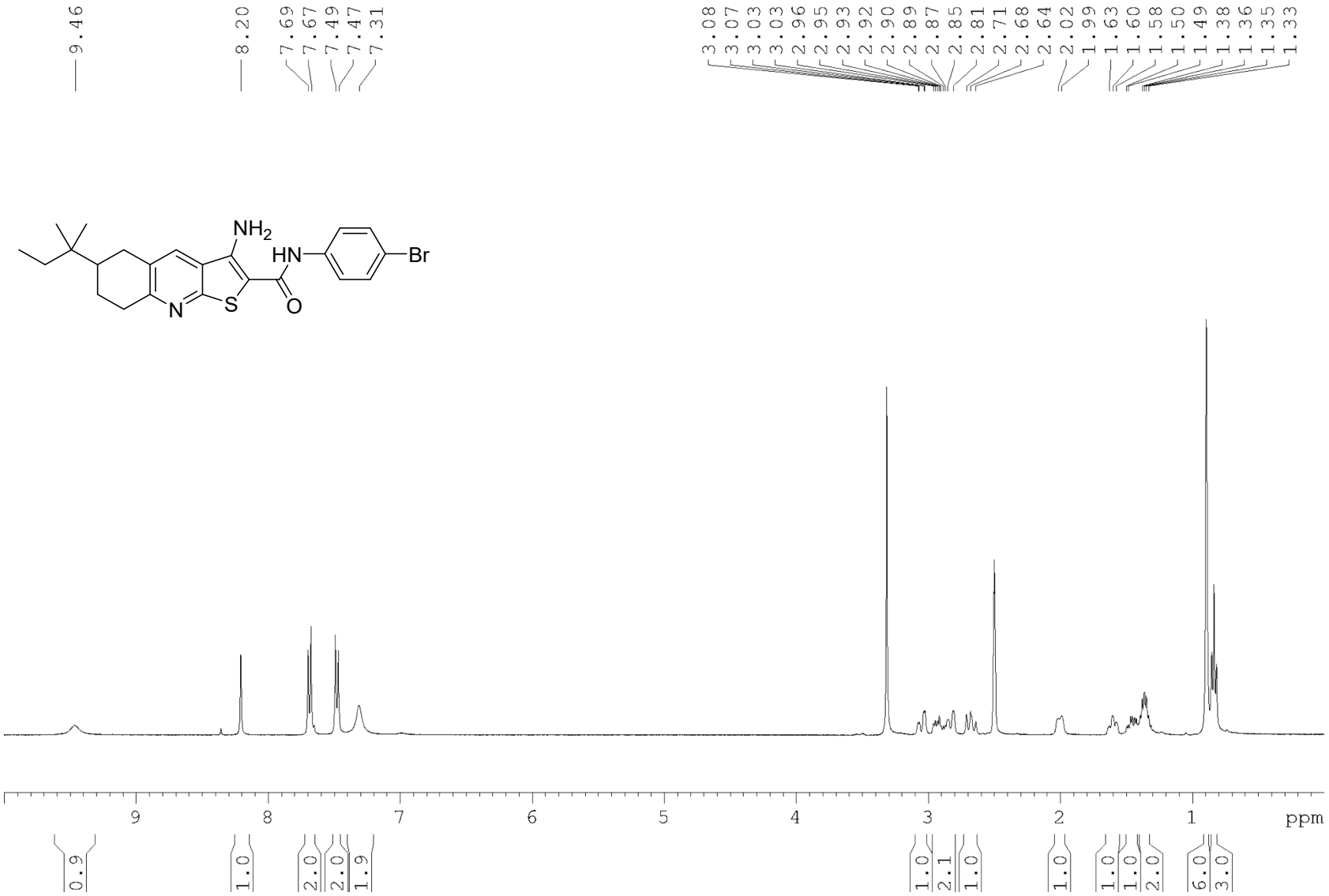


Figure S53: ^{1}H NMR spectrum of **10e** (400 MHz; DMSO-d_6).

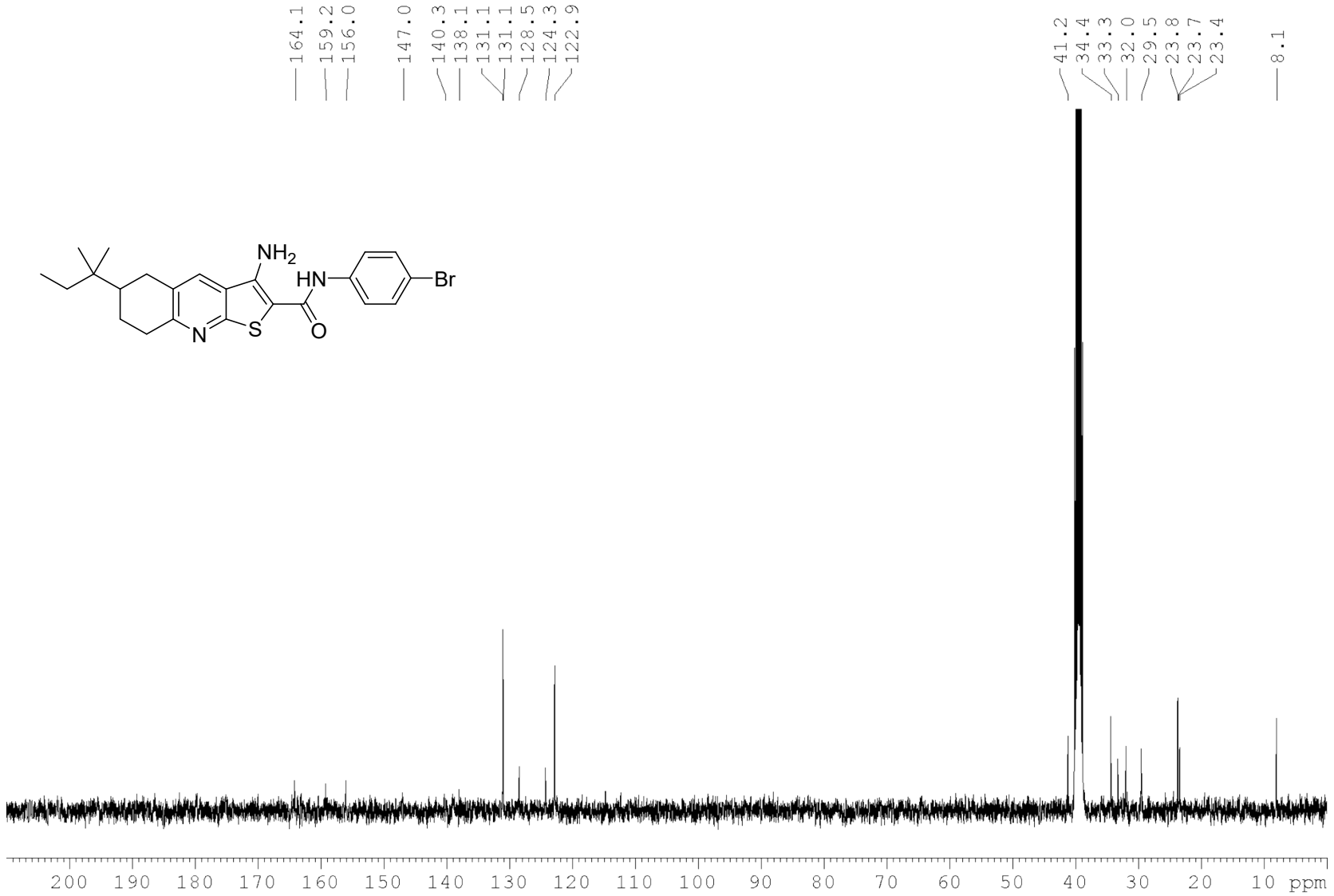


Figure S54: ^{13}C NMR spectrum of **10e** (100 MHz; DMSO-d_6).

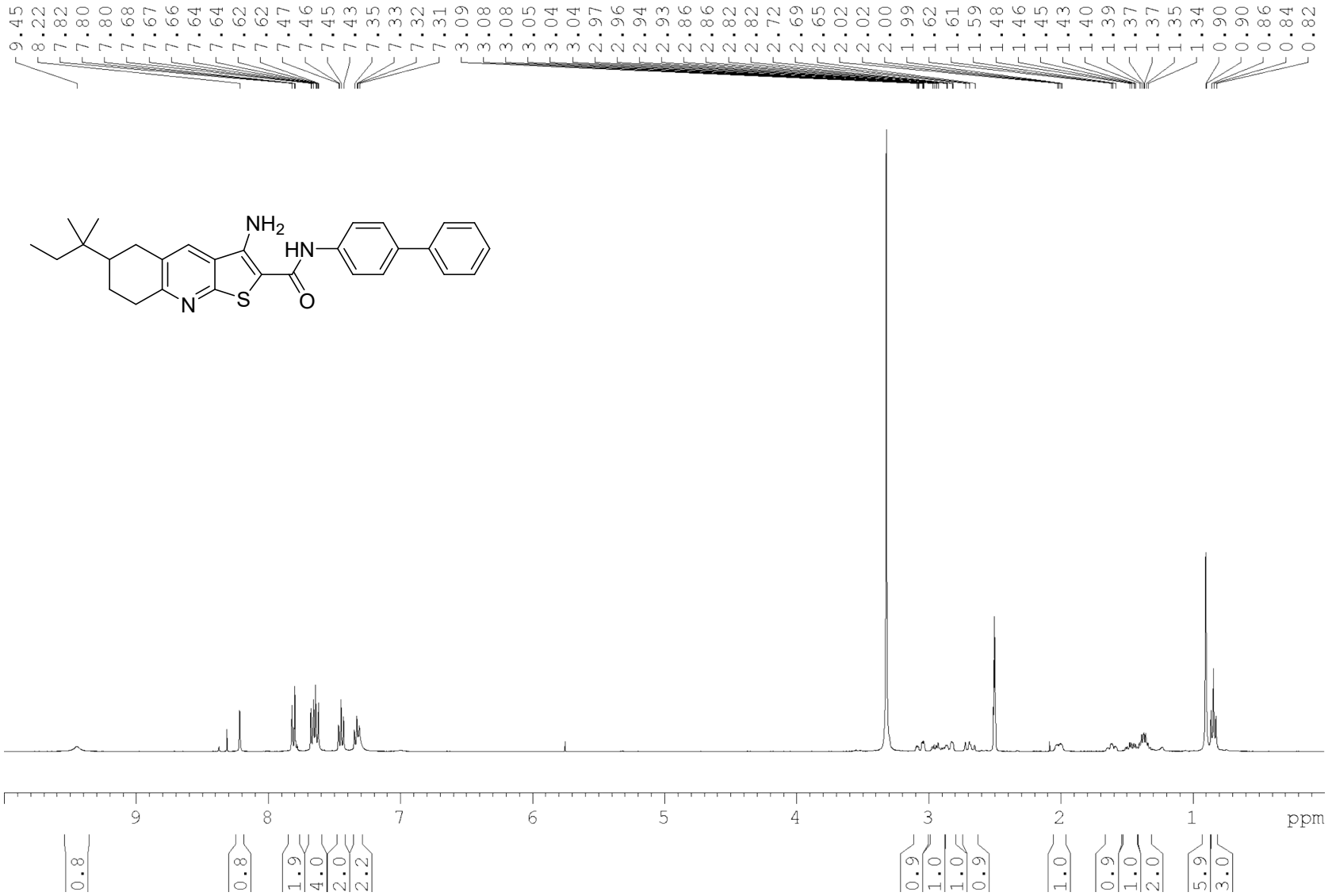


Figure S55: ^{1}H NMR spectrum of **10f** (400 MHz; DMSO-d_6).

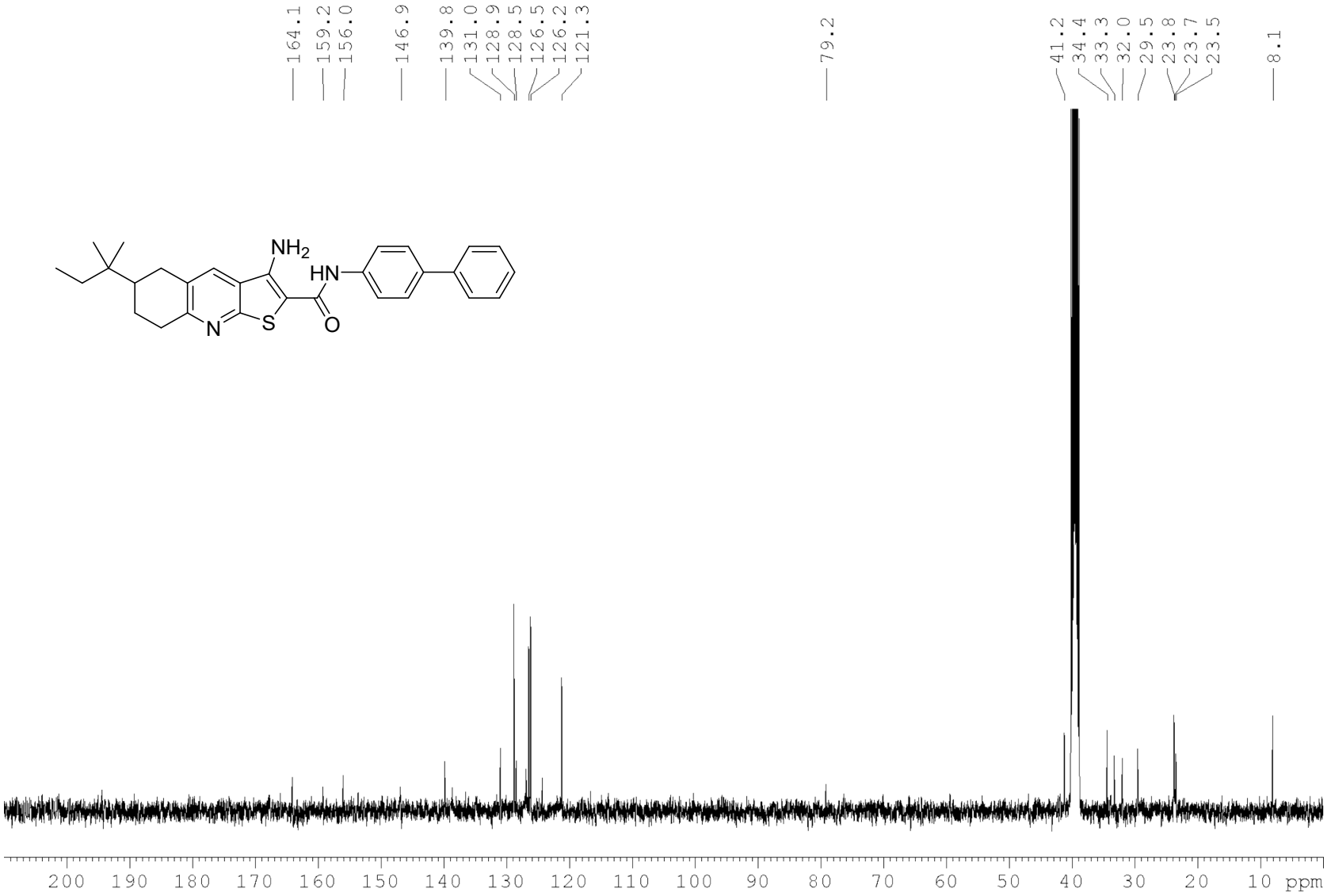


Figure S56: ^{13}C NMR spectrum of **10f** (100 MHz; DMSO-d_6).

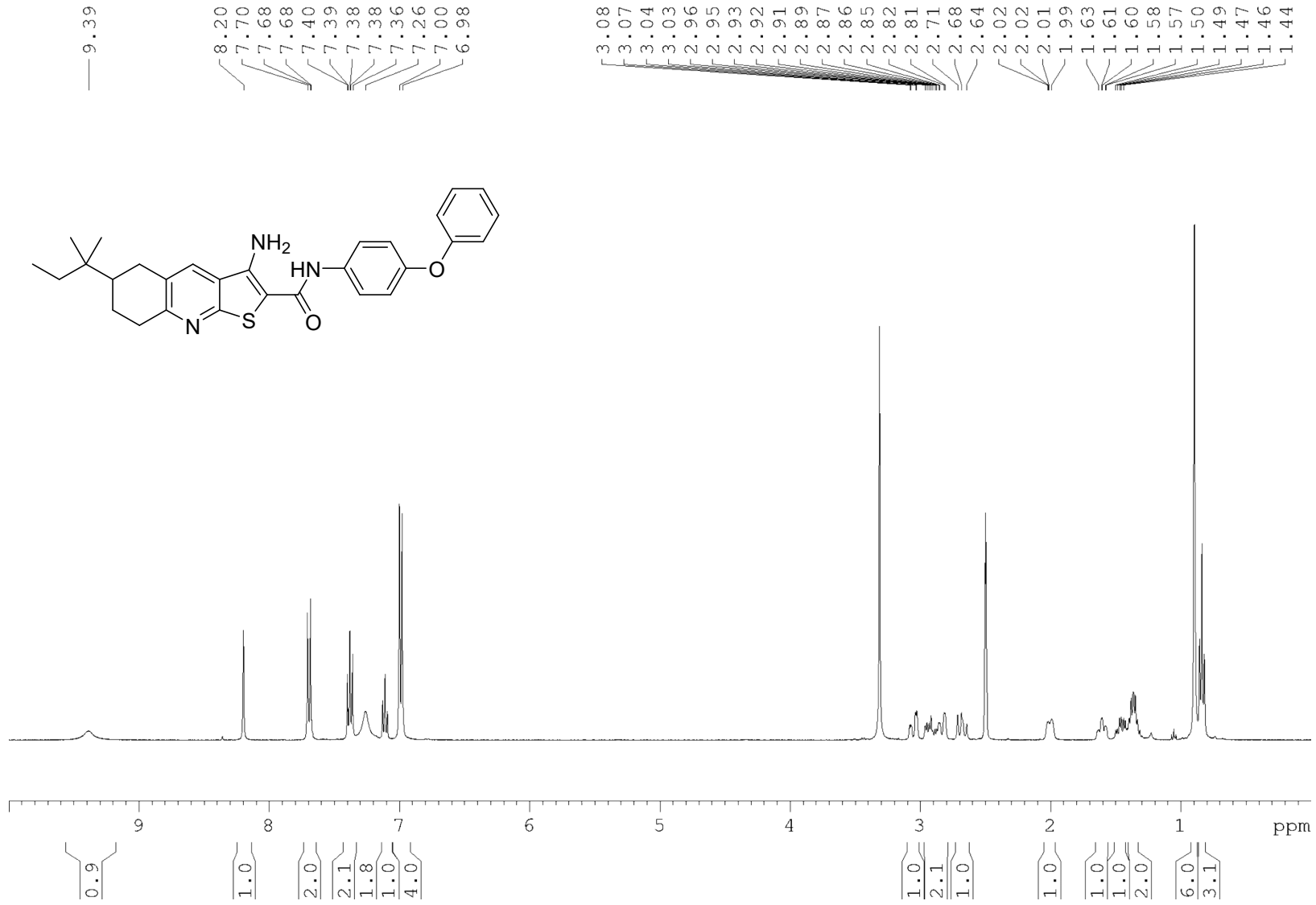


Figure S57: ^{1}H NMR spectrum of **10g** (400 MHz; DMSO-d_6).

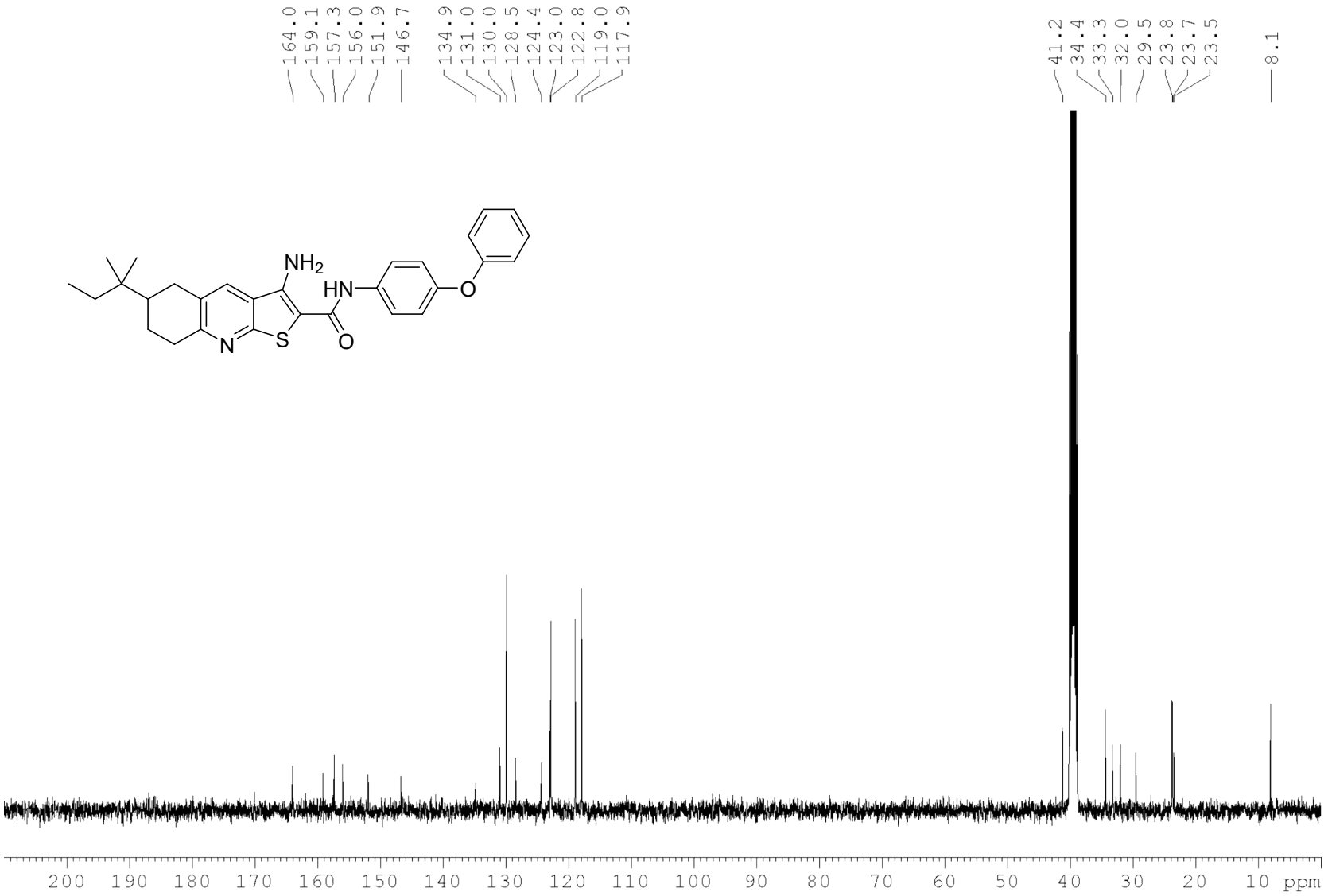


Figure S58: ^{13}C NMR spectrum of **10g** (100 MHz; DMSO-d_6).

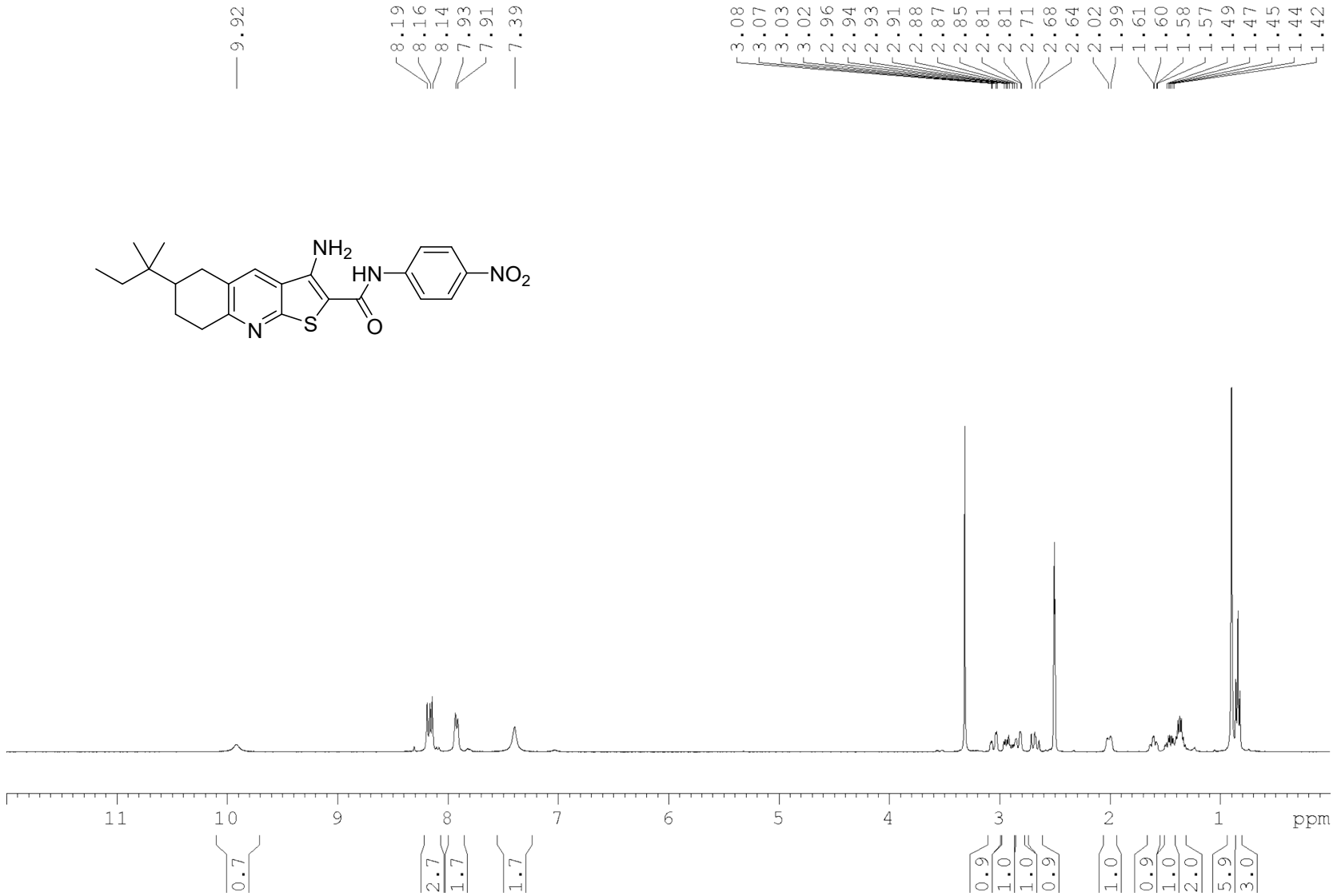


Figure S59: ^{1}H NMR spectrum of **10h** (400 MHz; DMSO-d_6).

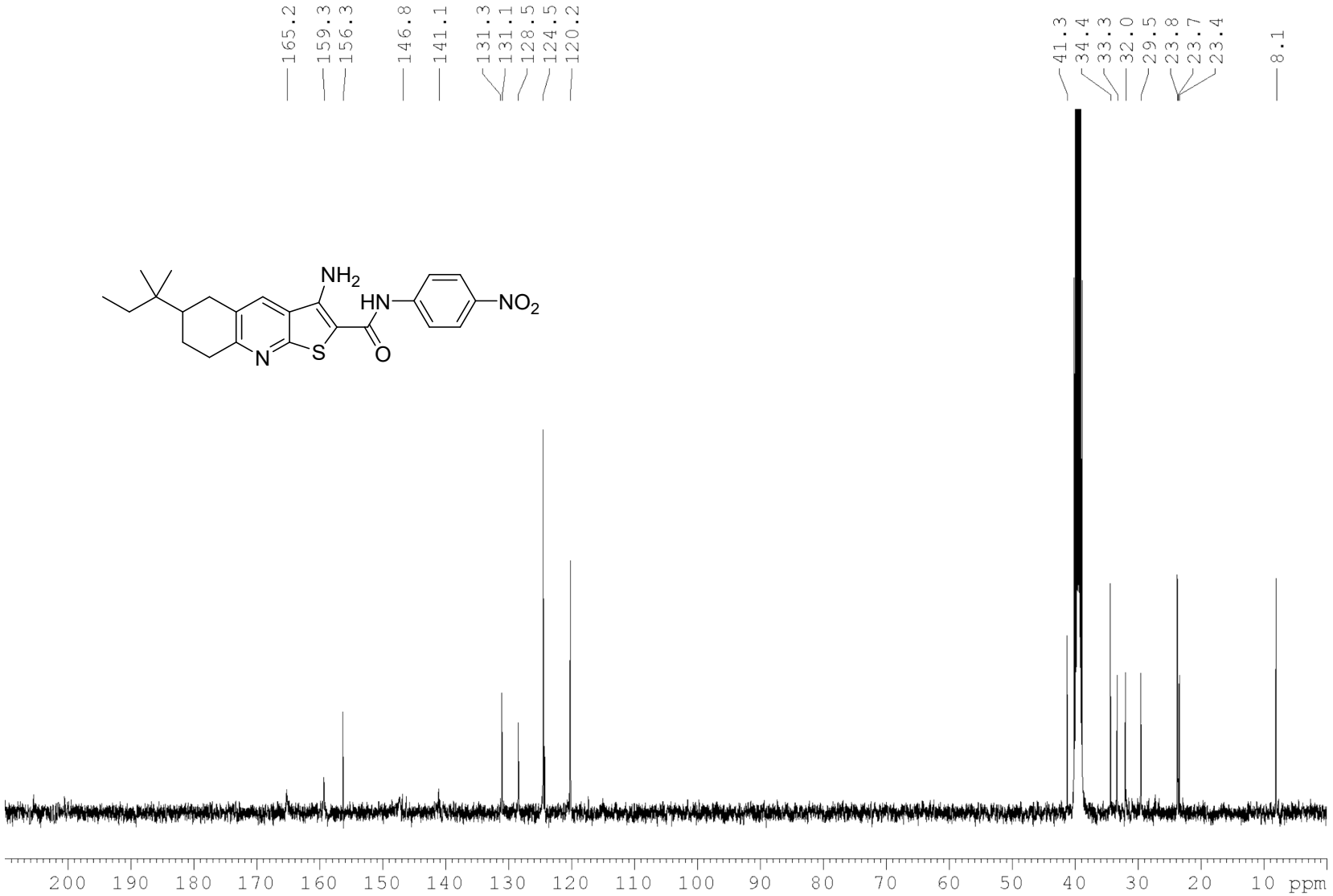


Figure S60: ^{13}C NMR spectrum of **10h** (100 MHz; DMSO-d_6).

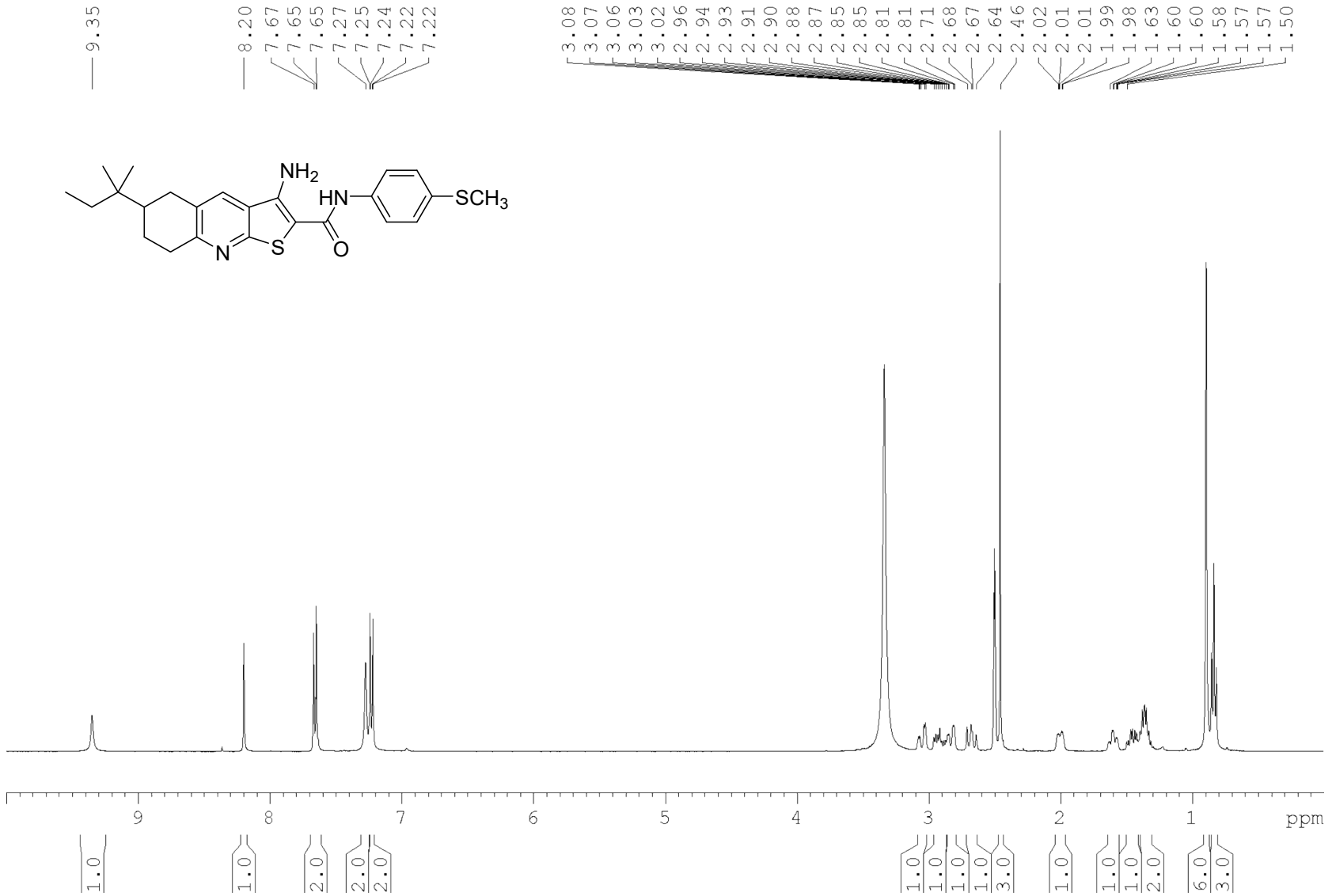


Figure S61: ^{1}H NMR spectrum of **10i** (400 MHz; DMSO-d_6).

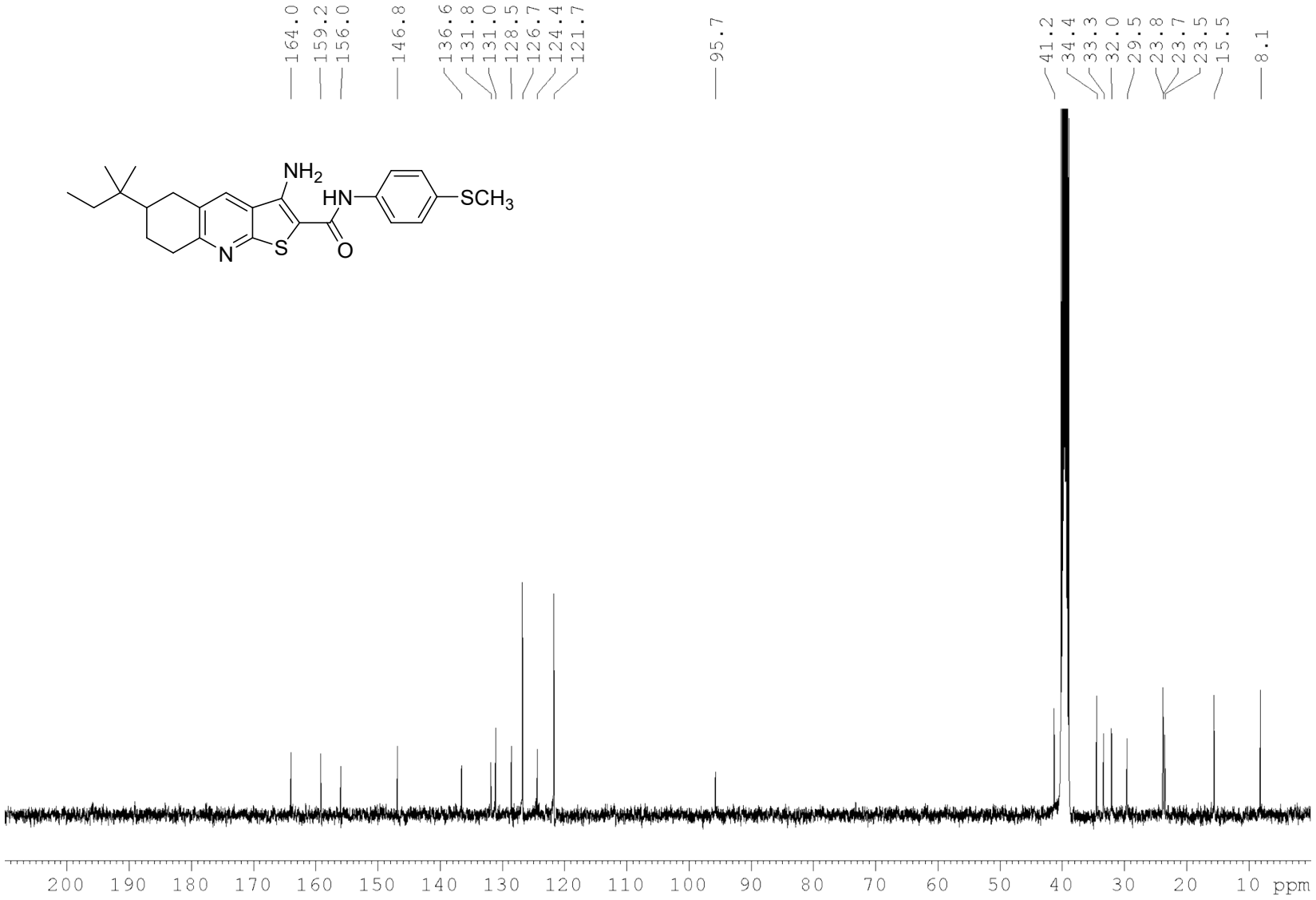


Figure S62: ^{13}C NMR spectrum of **10i** (100 MHz; DMSO-d_6).

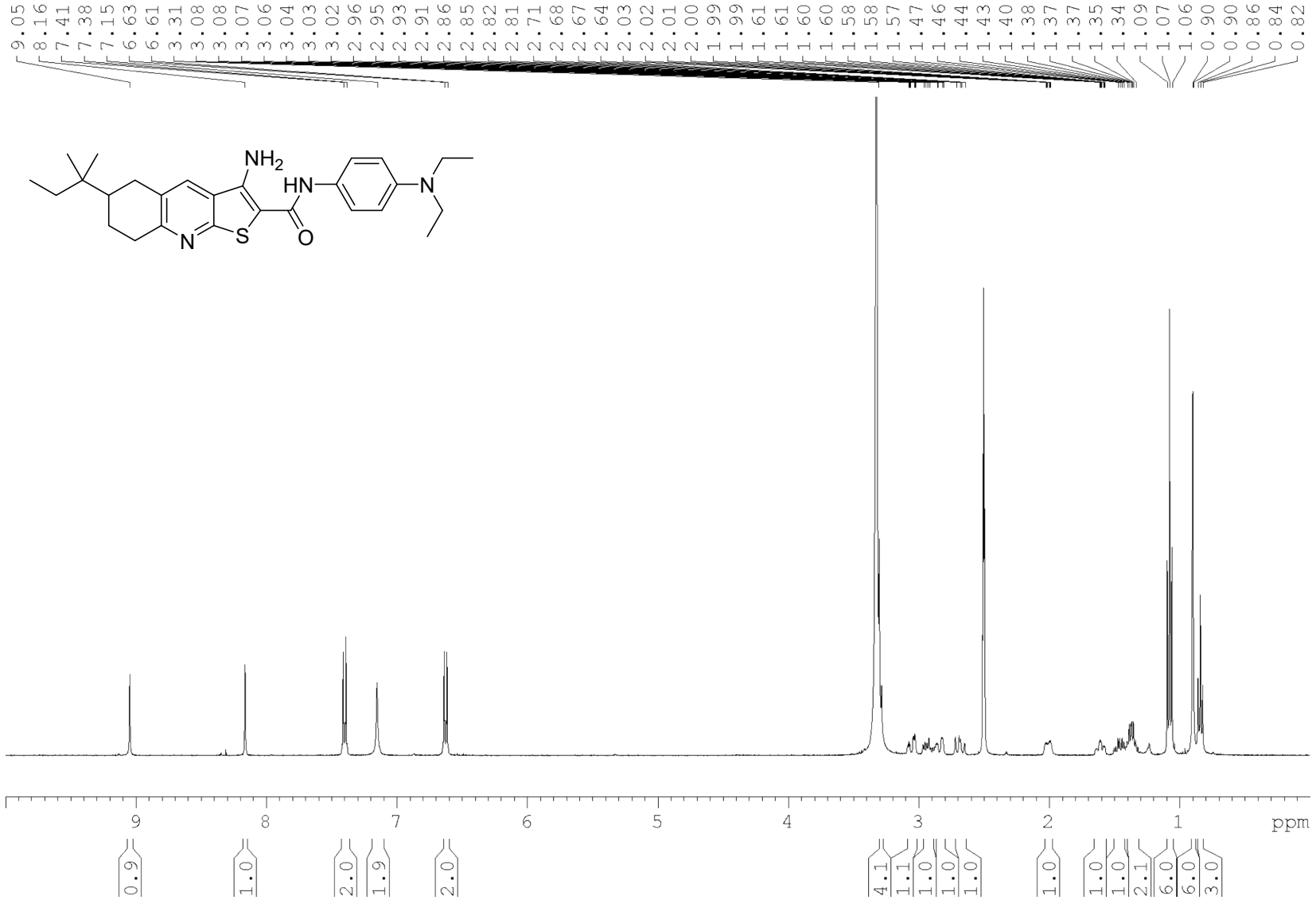


Figure S63: ^{1}H NMR spectrum of **10j** (400 MHz; DMSO-d_6).

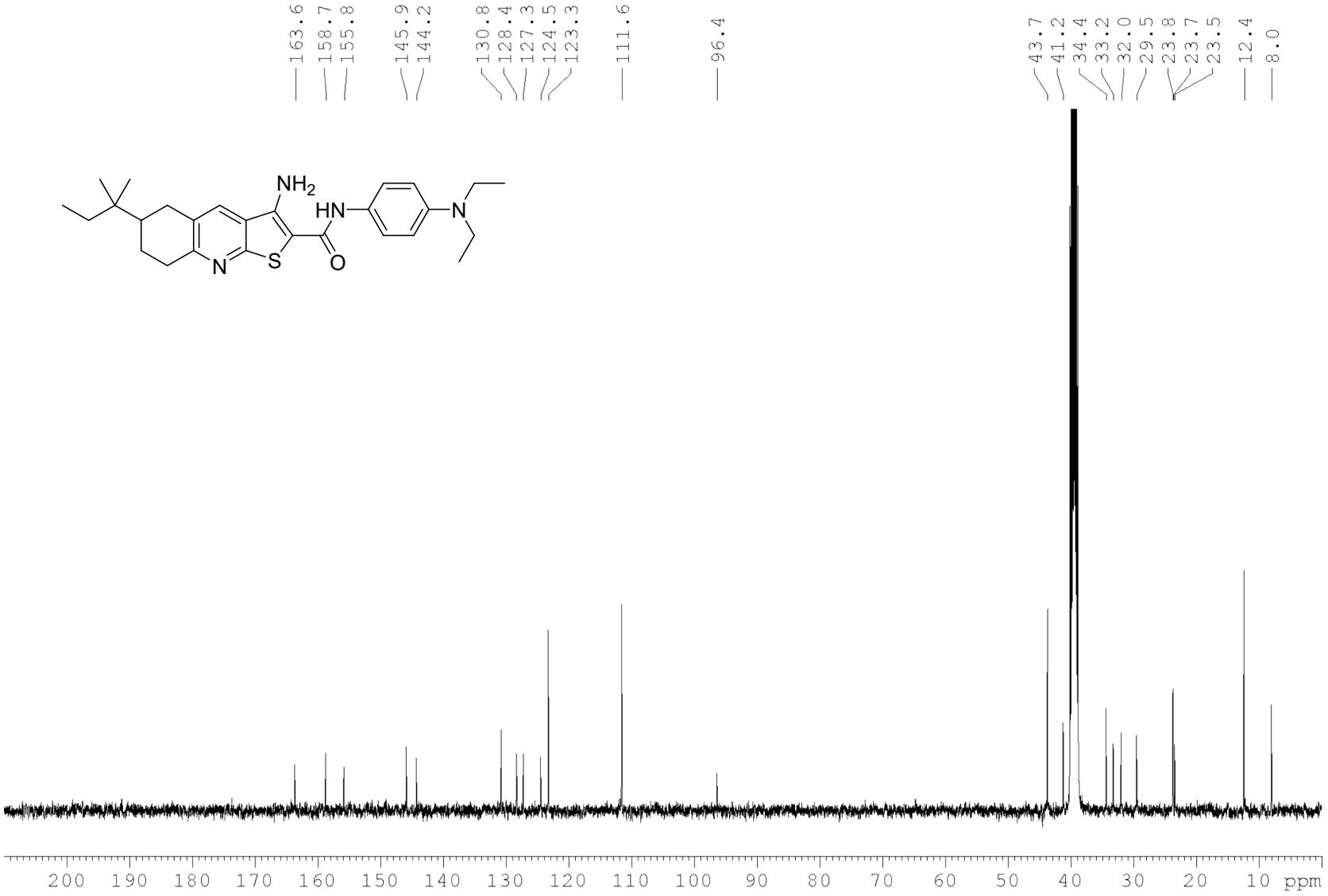


Figure S64: ^{13}C NMR spectrum of **10j** (100 MHz; DMSO-d_6).

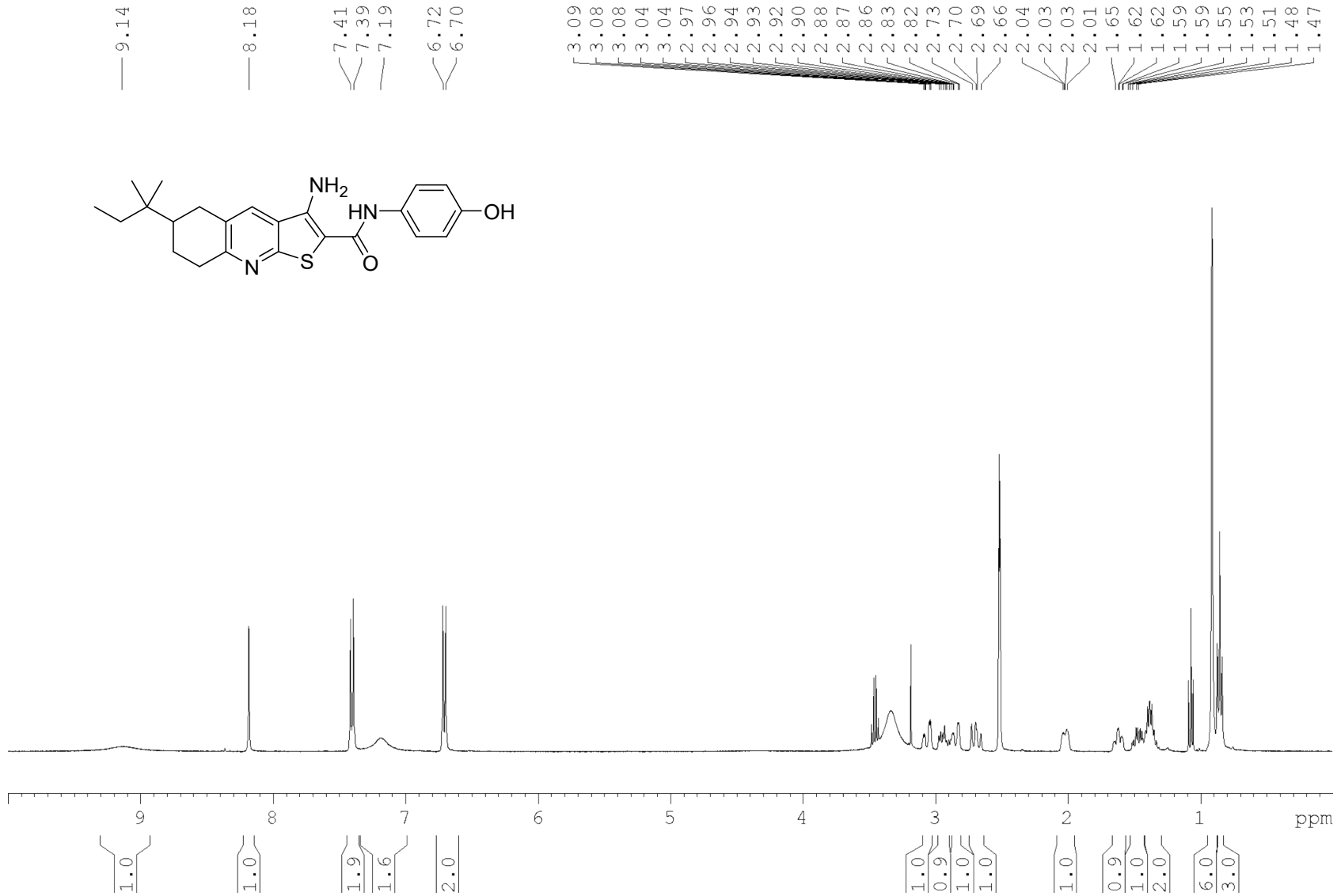


Figure S65: ^{1}H NMR spectrum of **10k** (400 MHz; DMSO-d_6).

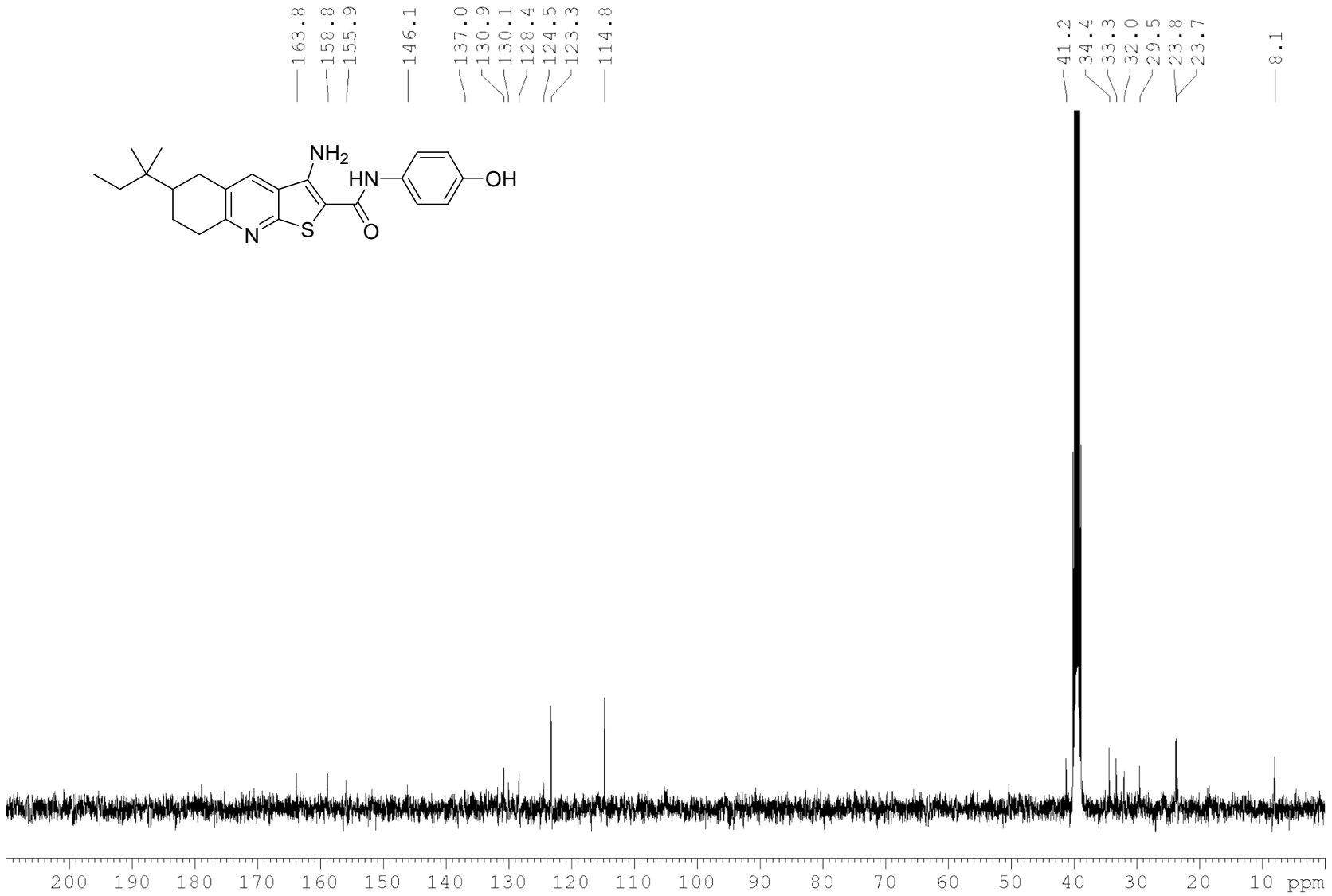


Figure S66: ^{13}C NMR spectrum of **10k** (100 MHz; DMSO-d_6).

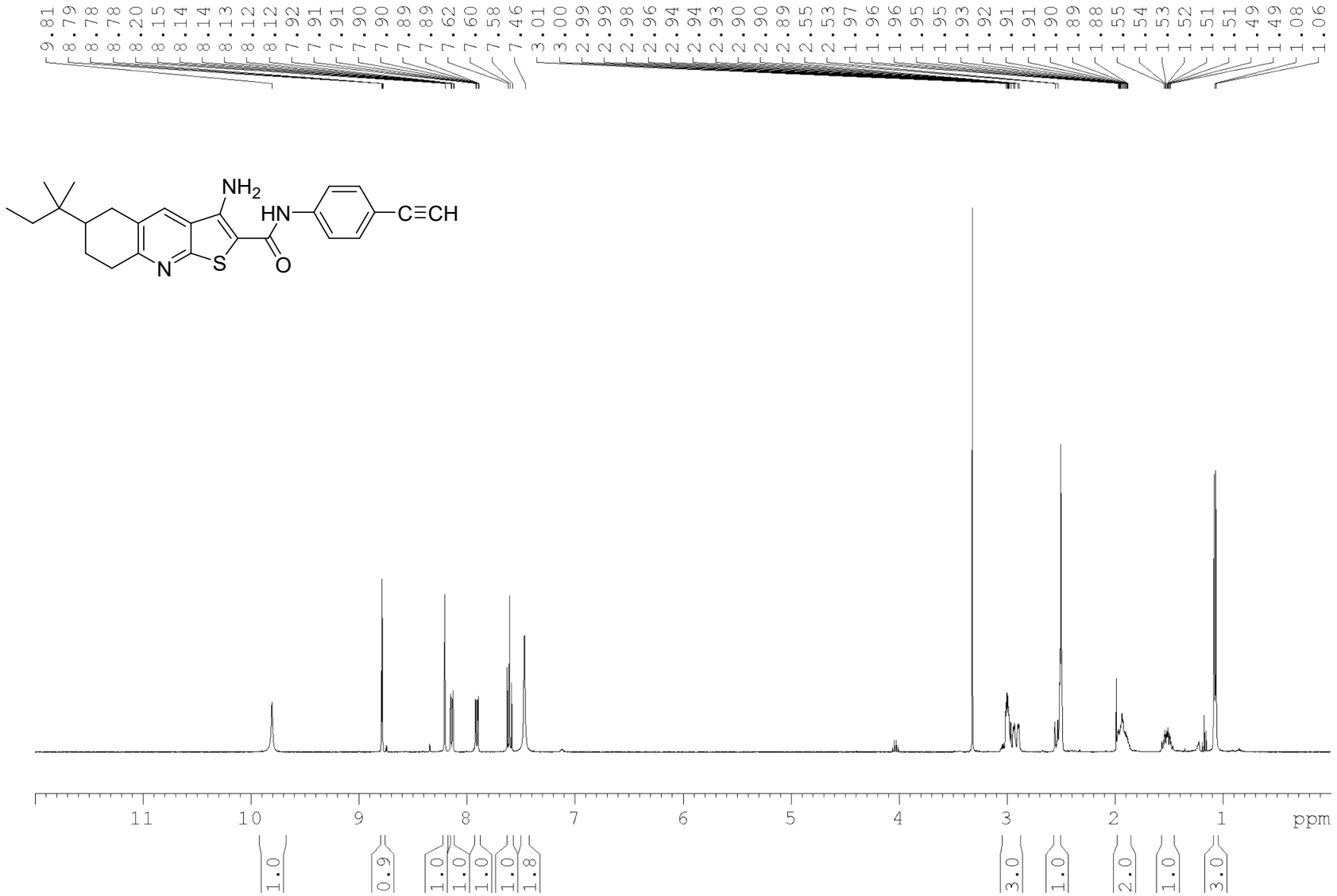


Figure S67: ^{1}H NMR spectrum of **10l** (400 MHz; DMSO-d_6).

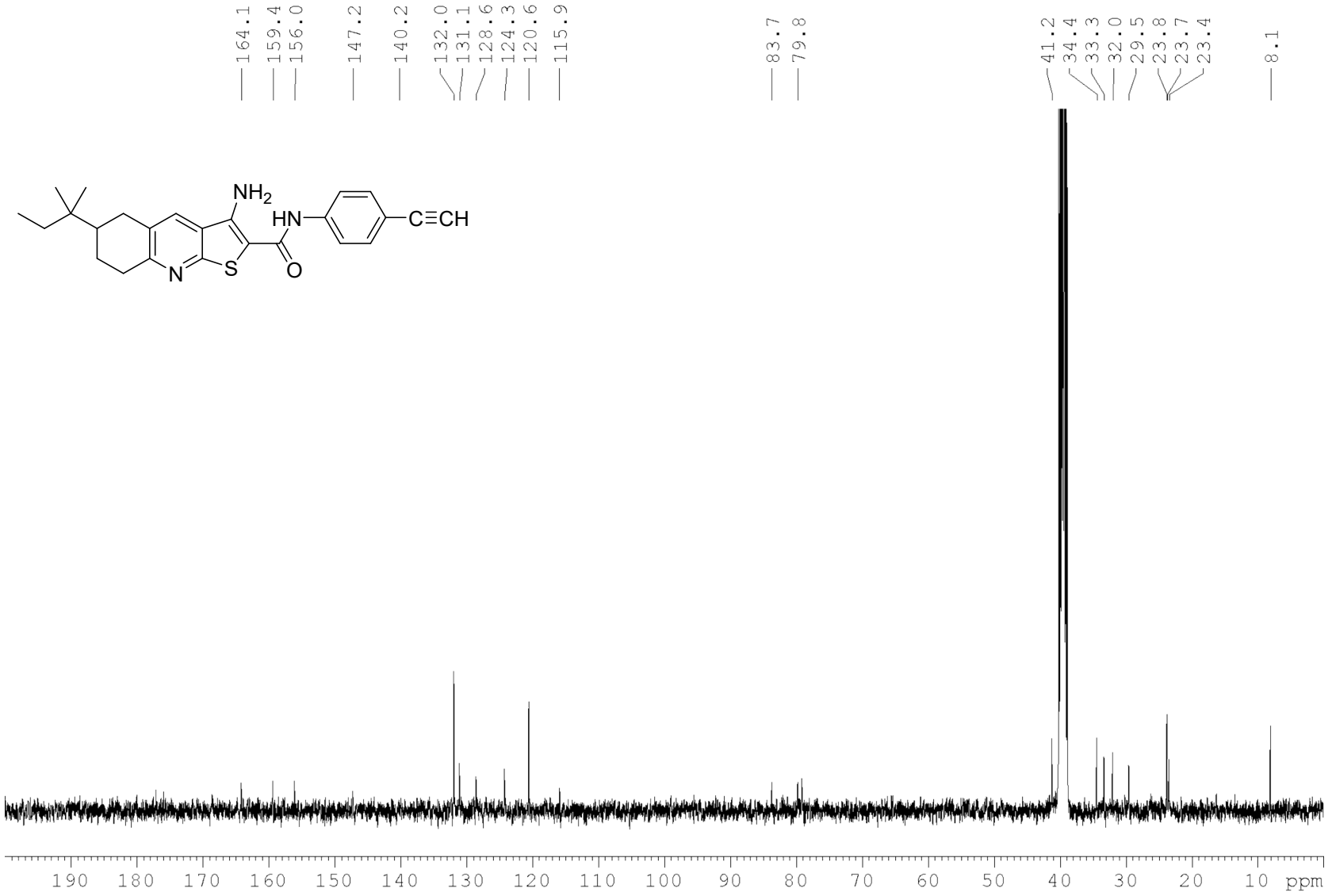


Figure S68: ^{13}C NMR spectrum of **10l** (100 MHz; DMSO-d_6).

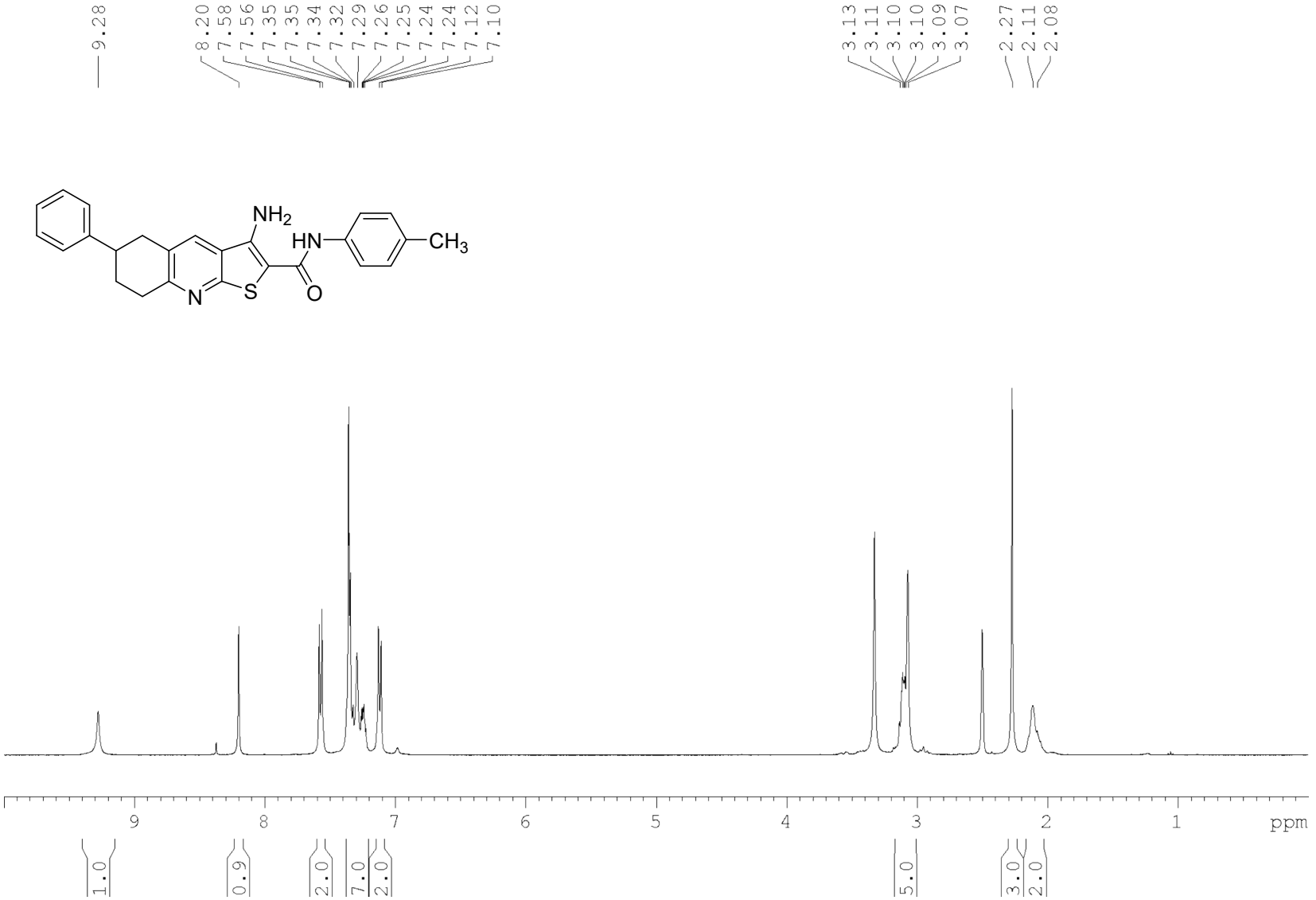


Figure S69: ^{1}H NMR spectrum of **9a** (400 MHz; DMSO-d_6).

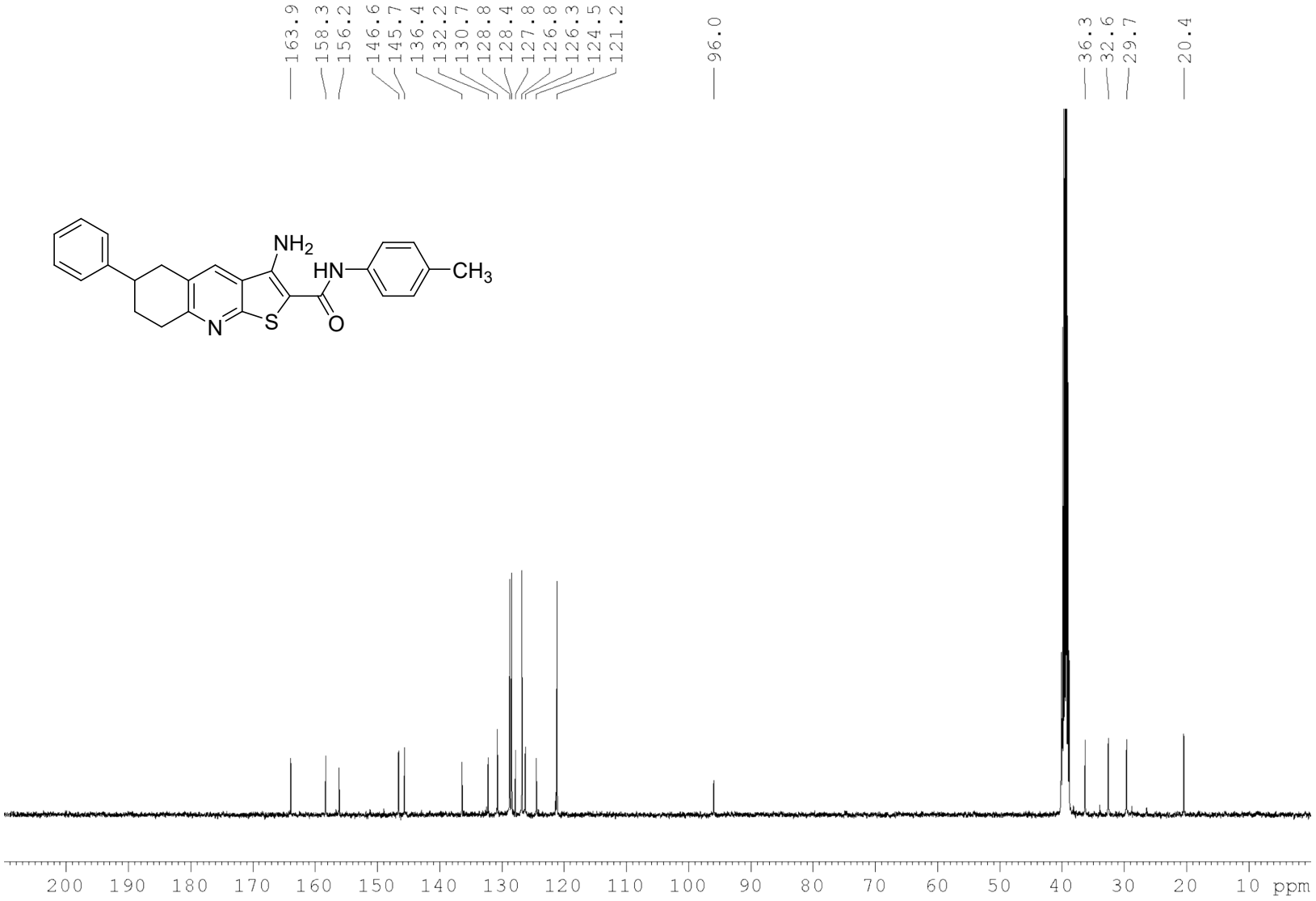


Figure S70: ^{13}C NMR spectrum of **9a** (100 MHz; DMSO-d_6).

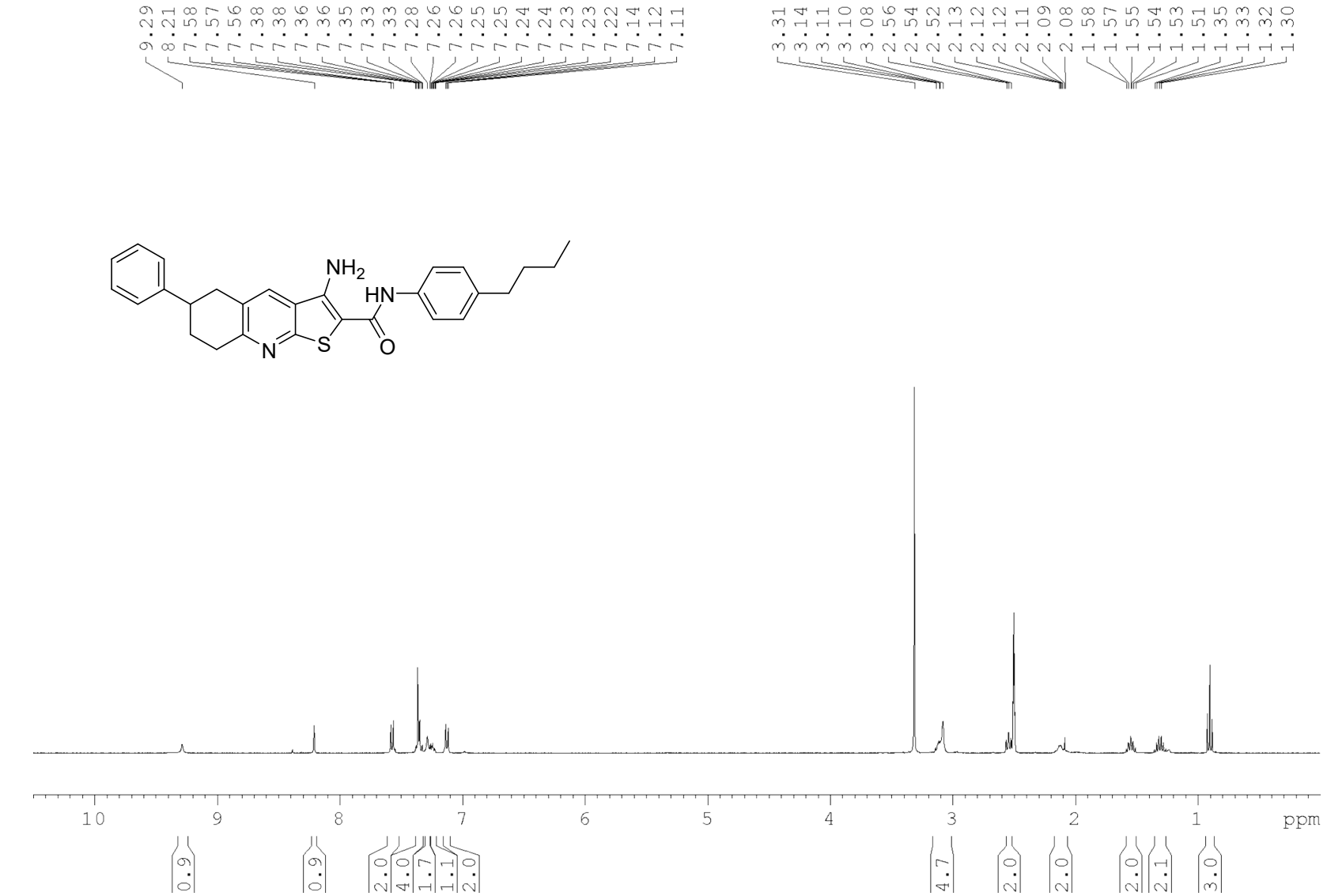


Figure S71: ^{1}H NMR spectrum of **9b** (400 MHz; DMSO-d_6).

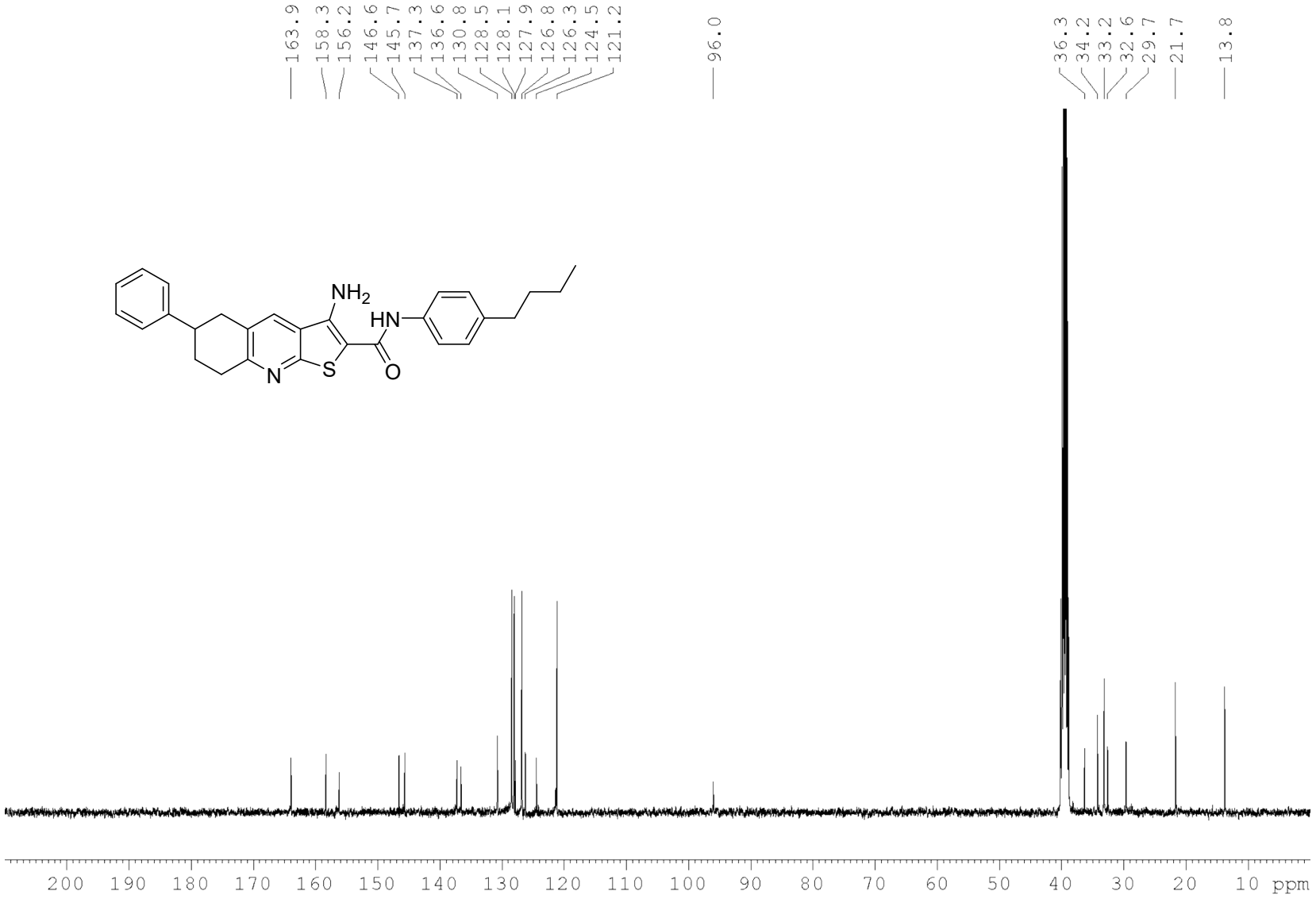


Figure S72: ^{13}C NMR spectrum of **9b** (100 MHz; DMSO-d_6).

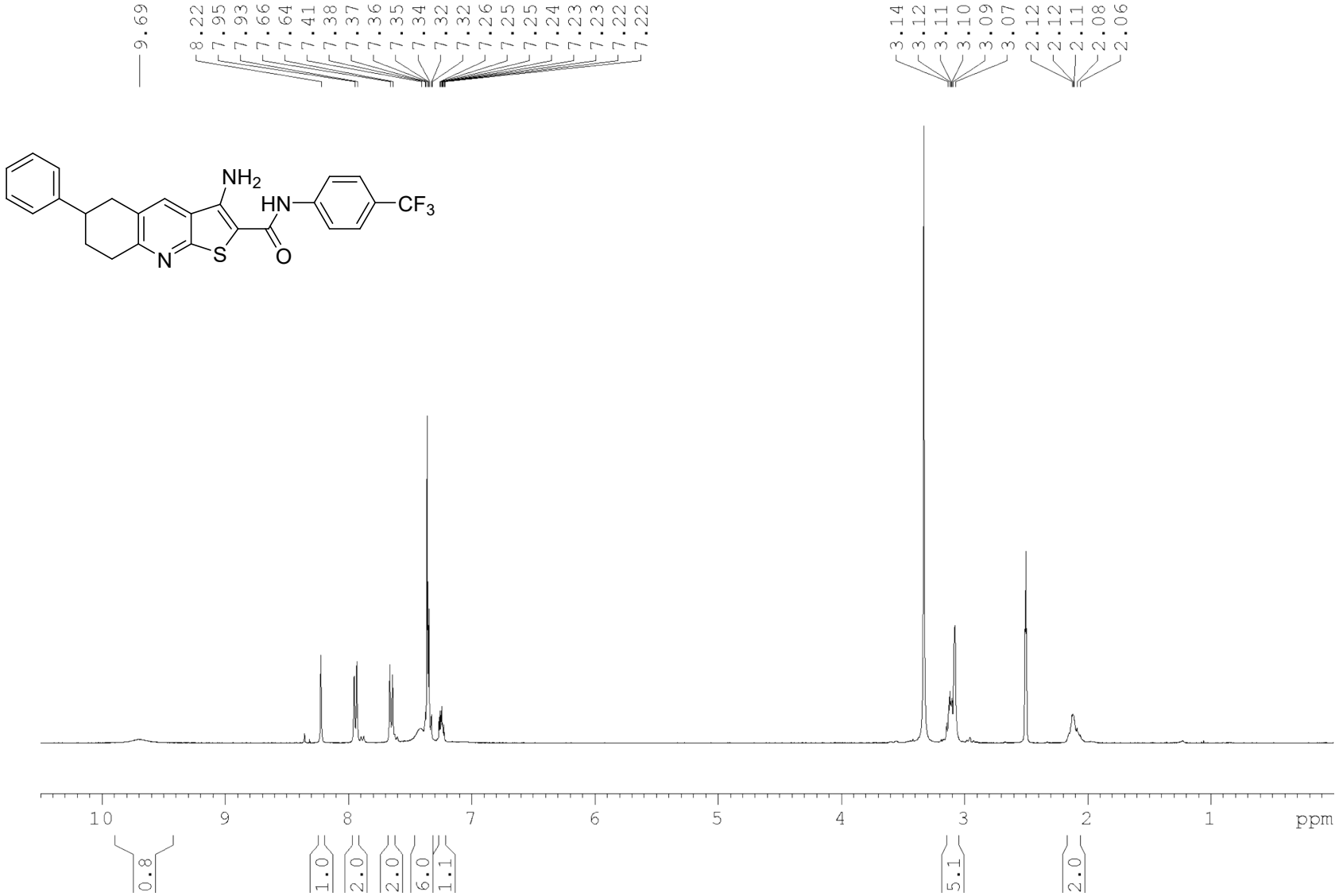


Figure S73: ^{1}H NMR spectrum of **9c** (400 MHz; DMSO-d_6).

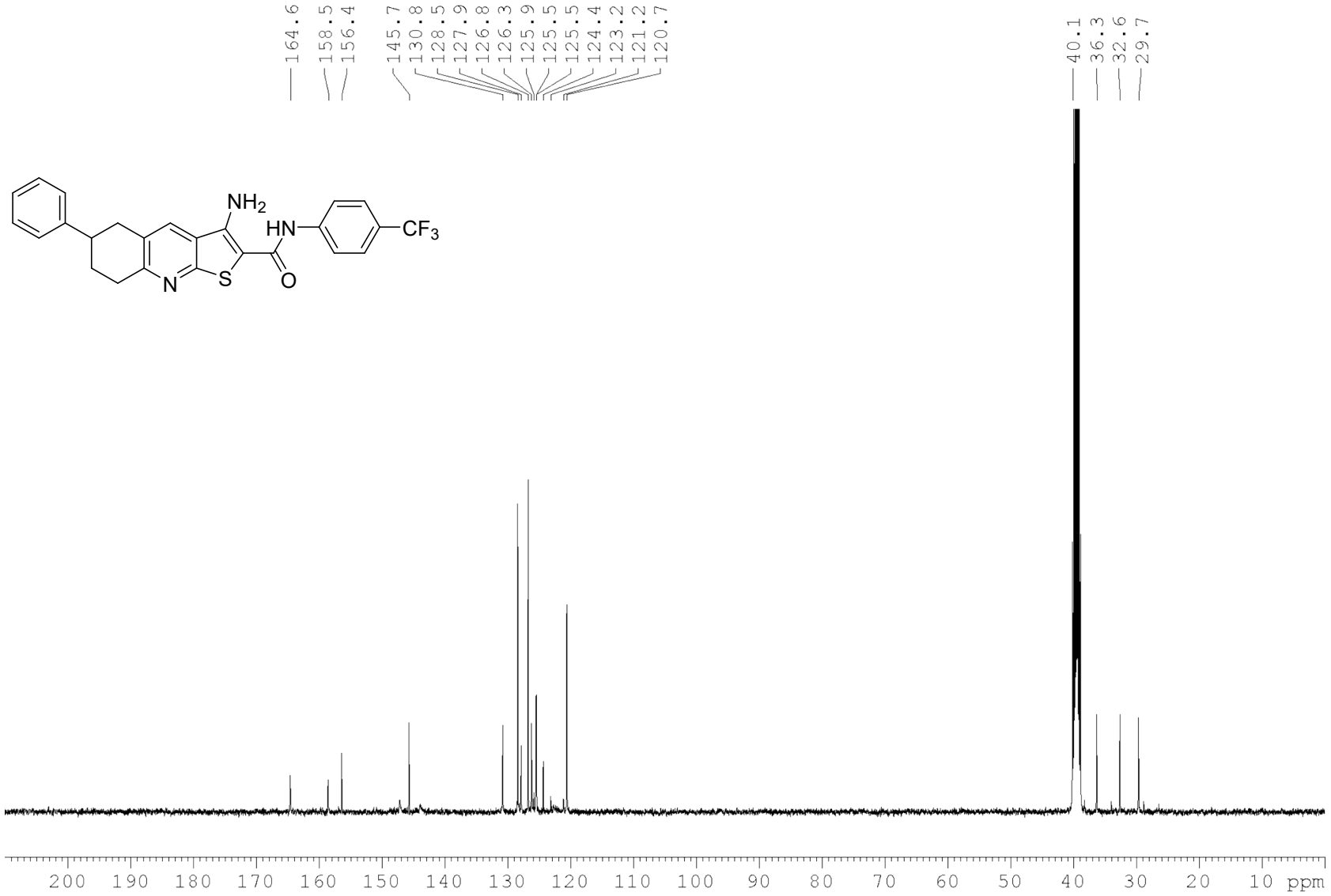


Figure S74: ^{13}C NMR spectrum of **9c** (100 MHz; DMSO-d_6).

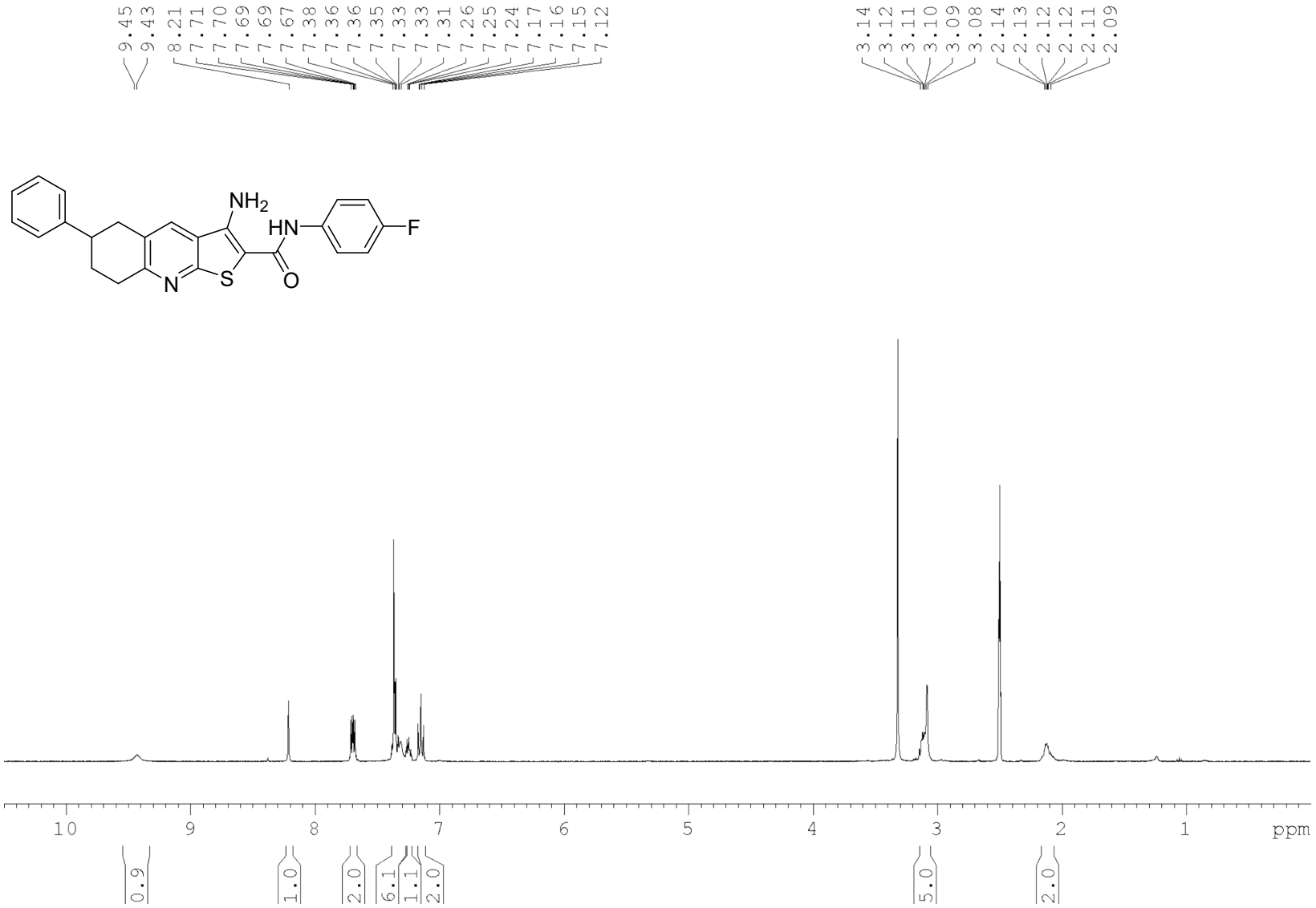


Figure S75: ^{1}H NMR spectrum of **9d** (400 MHz; DMSO-d_6).

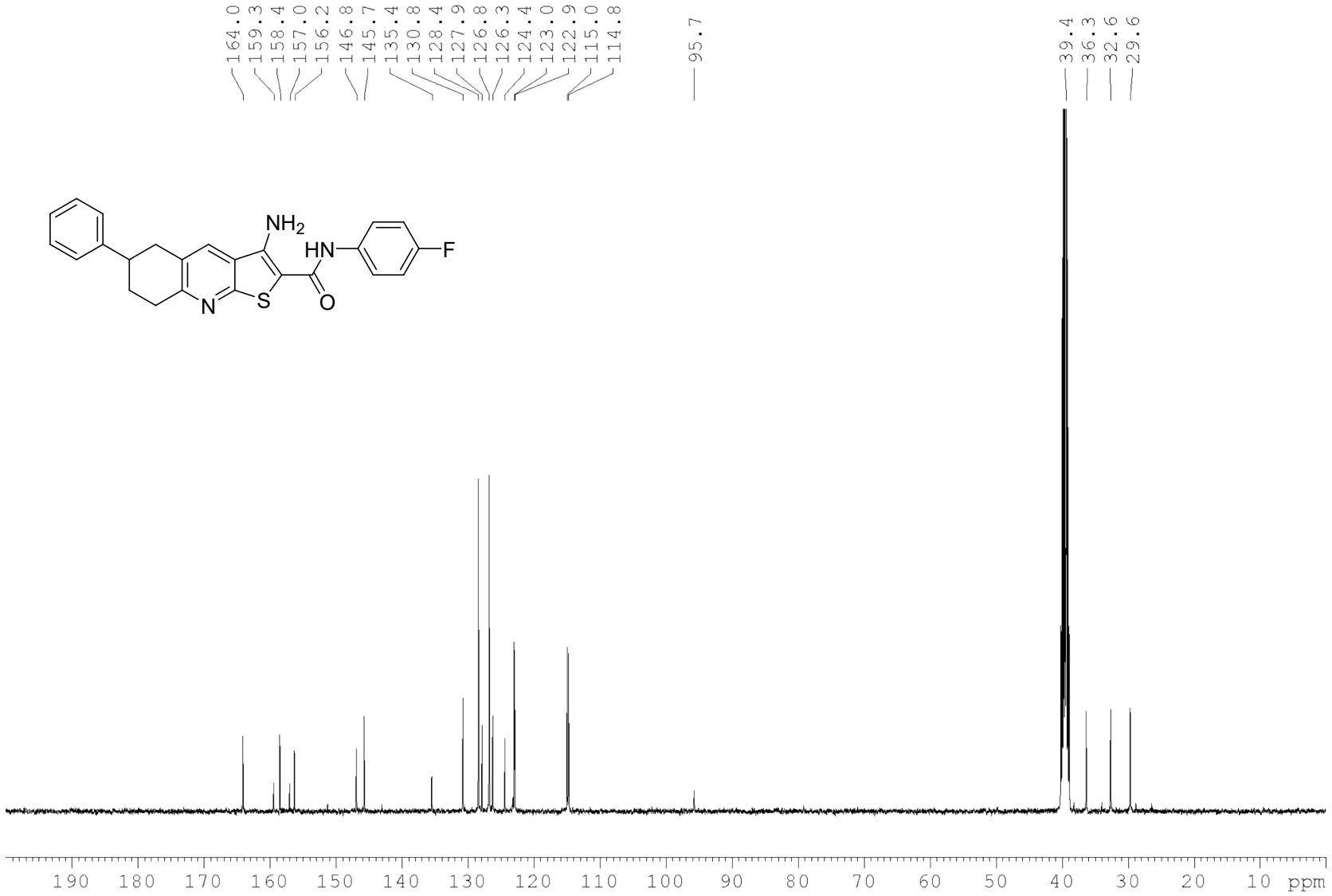


Figure S76: ^{13}C NMR spectrum of **9d** (100 MHz; DMSO-d_6).

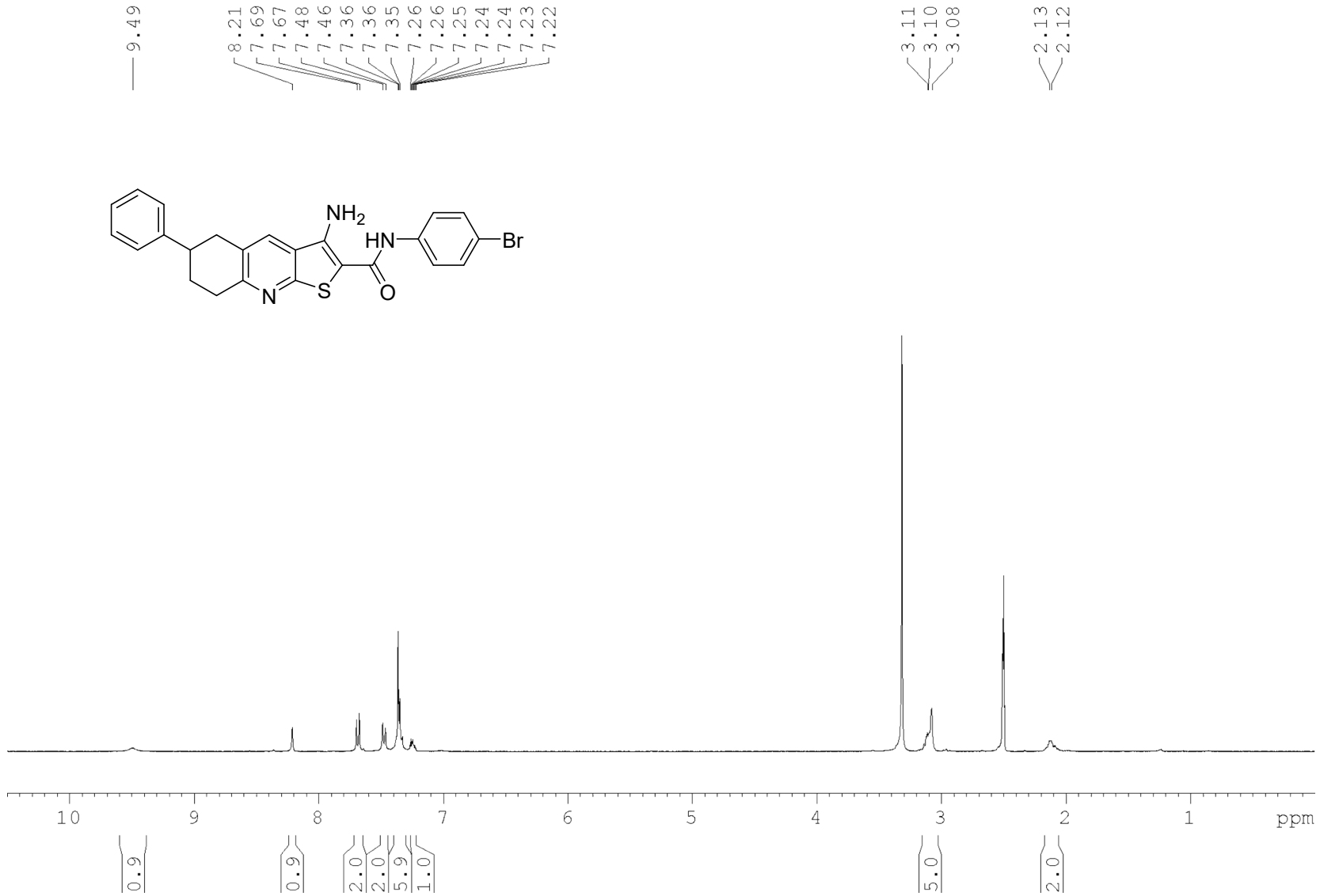


Figure S77: ^{1}H NMR spectrum of **9e** (400 MHz; DMSO-d_6).

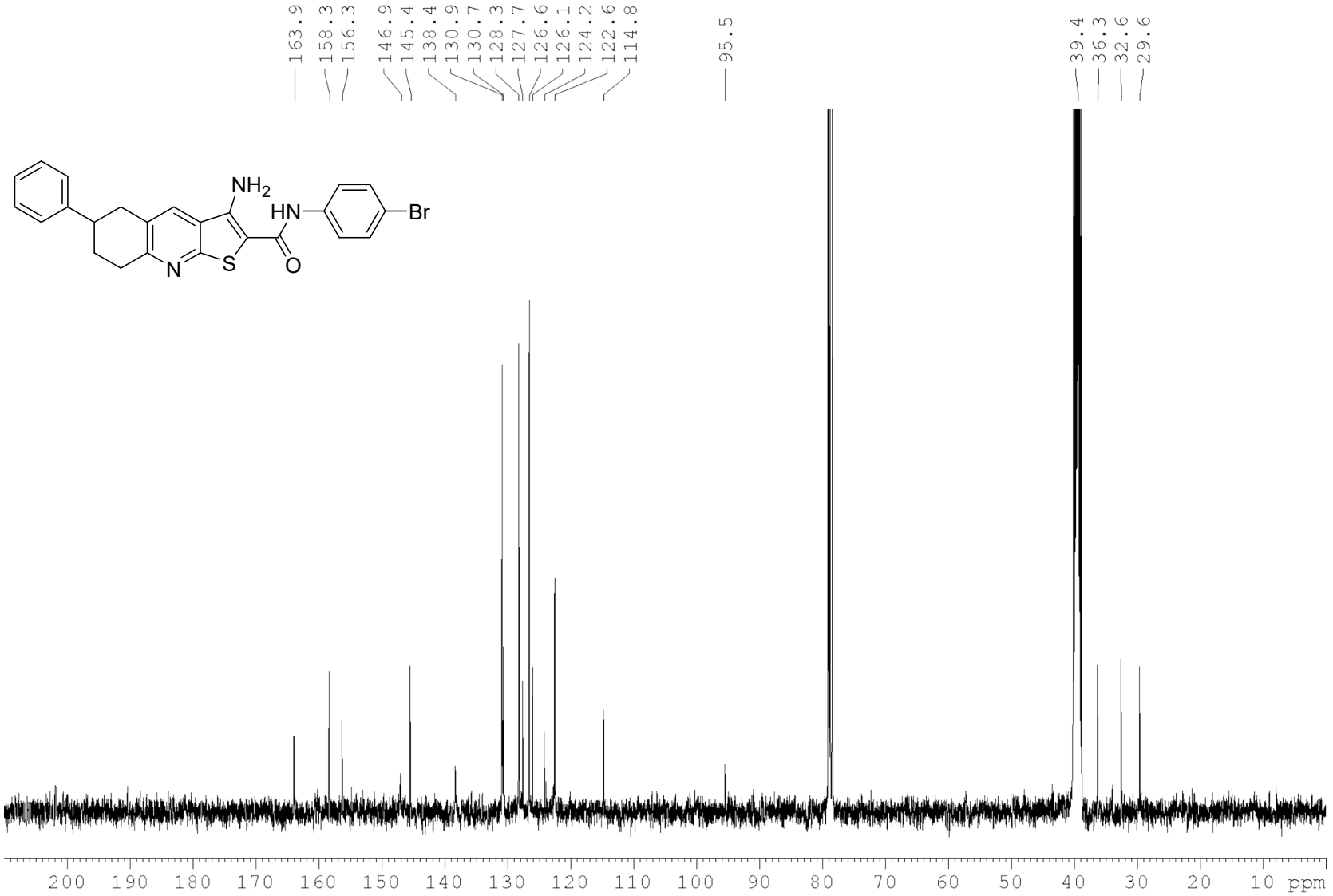


Figure S78: ^{13}C NMR spectrum of **9e** (100 MHz; DMSO-d_6; $CDCl_3$).

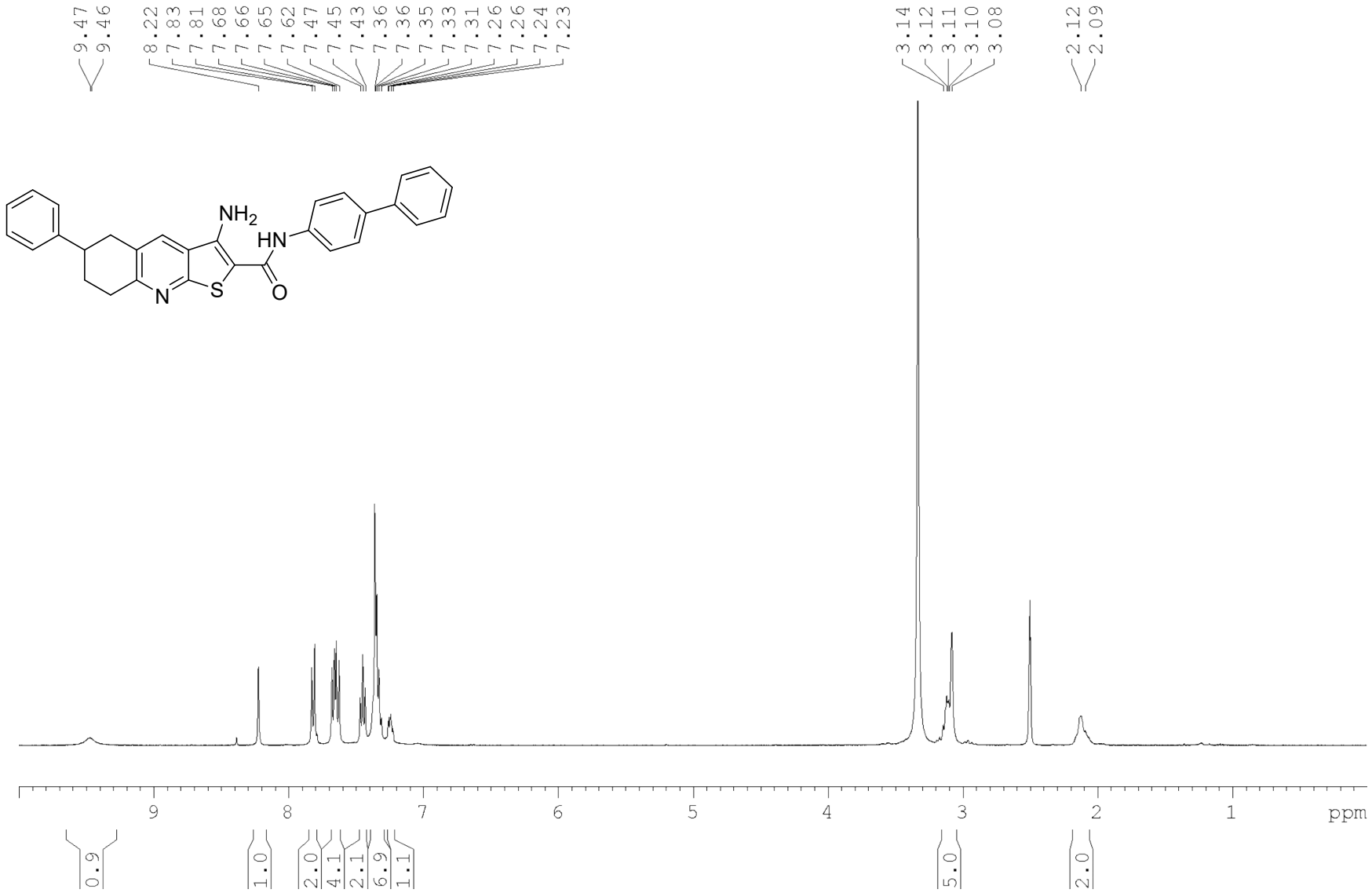

9.47
9.46
8.22
7.83
7.81
7.68
7.66
7.65
7.62
7.47
7.45
7.43
7.36
7.36
7.35
7.33
7.31
7.26
7.26
7.24
7.23
3.14
3.12
3.11
3.10
3.08
2.12
2.09
NH2
HN
O
N
S
9
8
7
6
5
4
3
2
1
ppm
0.9
1.0
2.0
4.1
2.1
6.9
1.1
5.0
2.0

Figure S79: ^{1}H NMR spectrum of **9f** (400 MHz; DMSO-d_6).

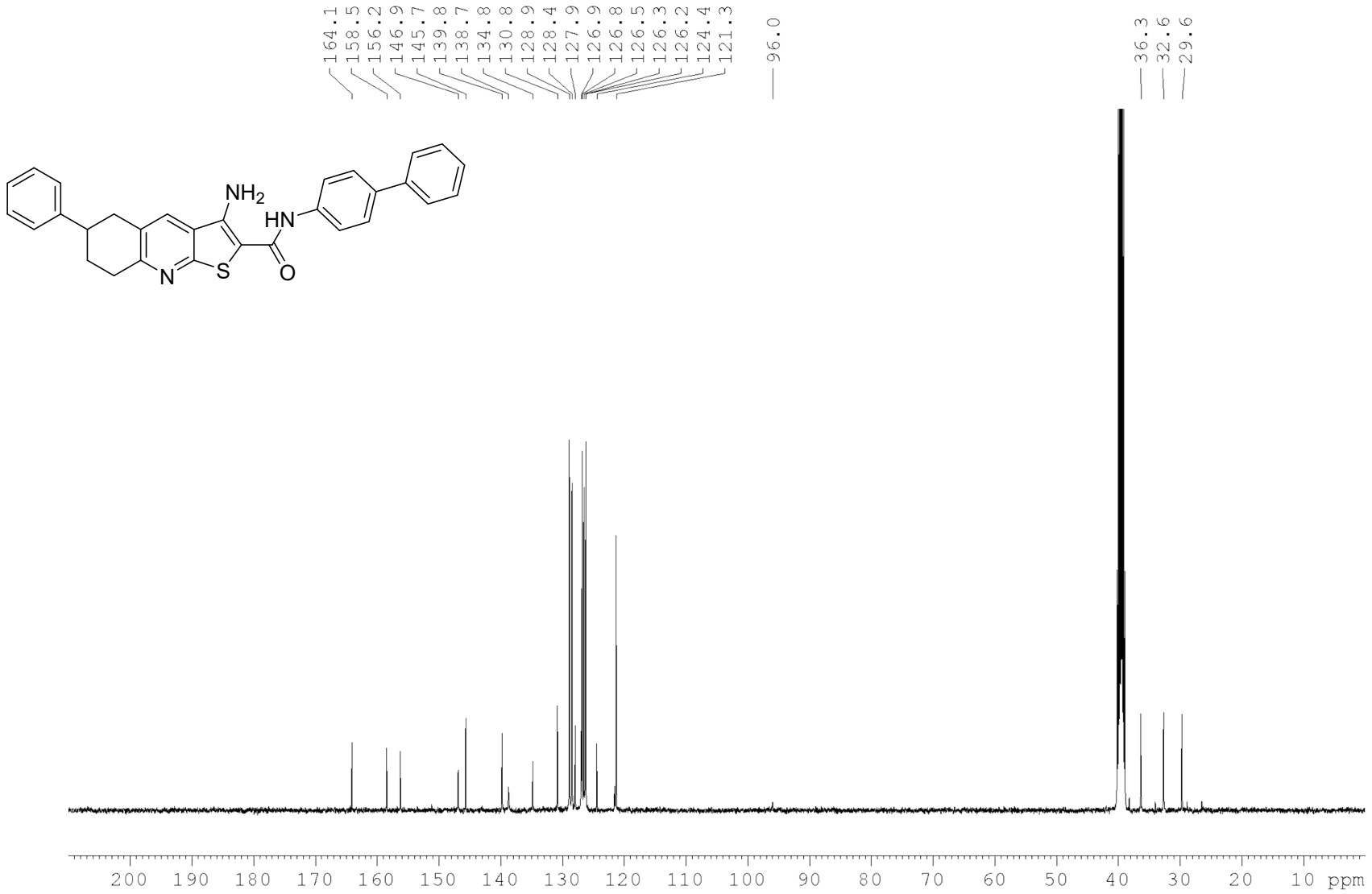


Figure S80: ^{13}C NMR spectrum of **9f** (100 MHz; DMSO-d_6).

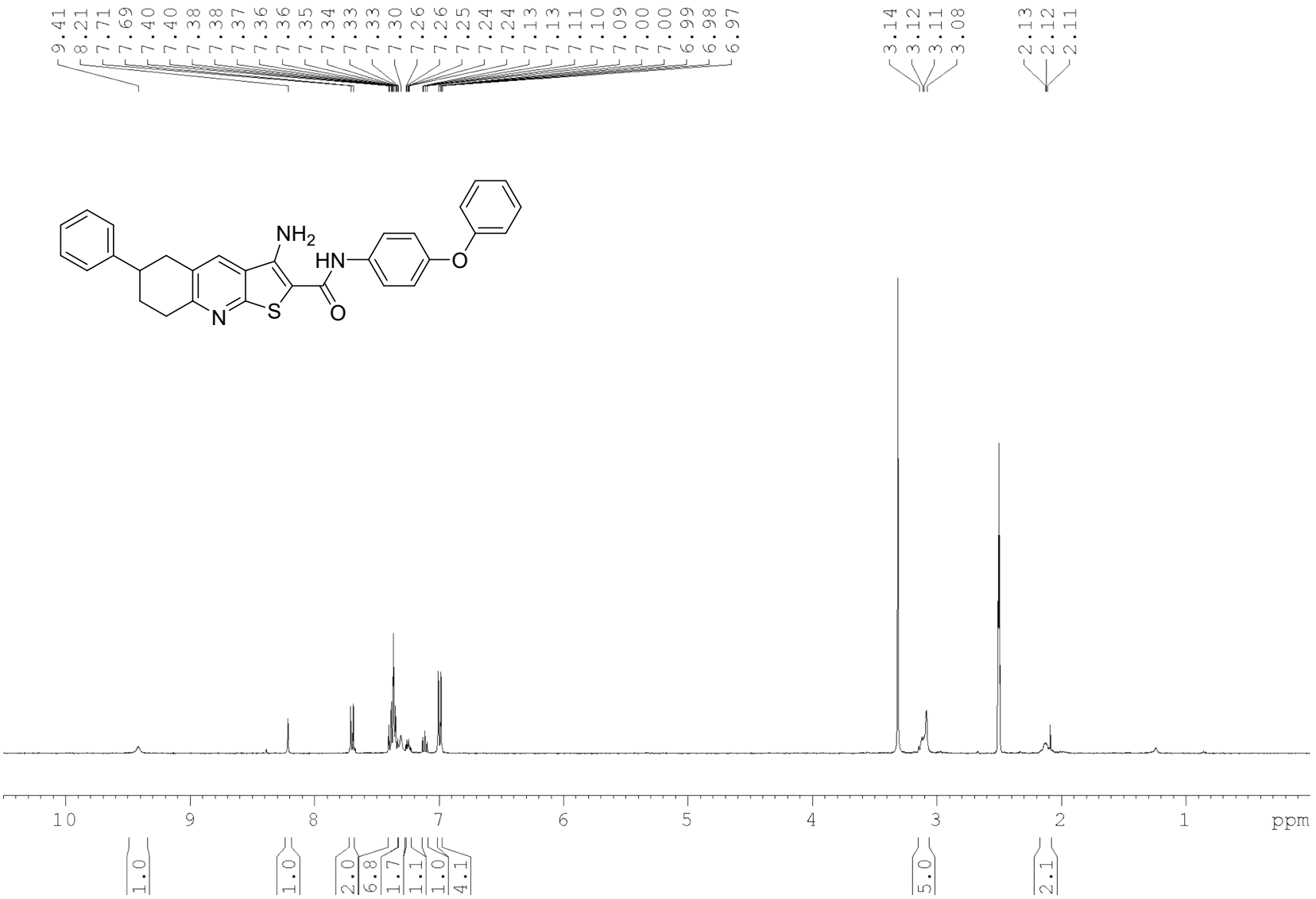


Figure S81: ^{1}H NMR spectrum of **9g** (400 MHz; DMSO-d_6).

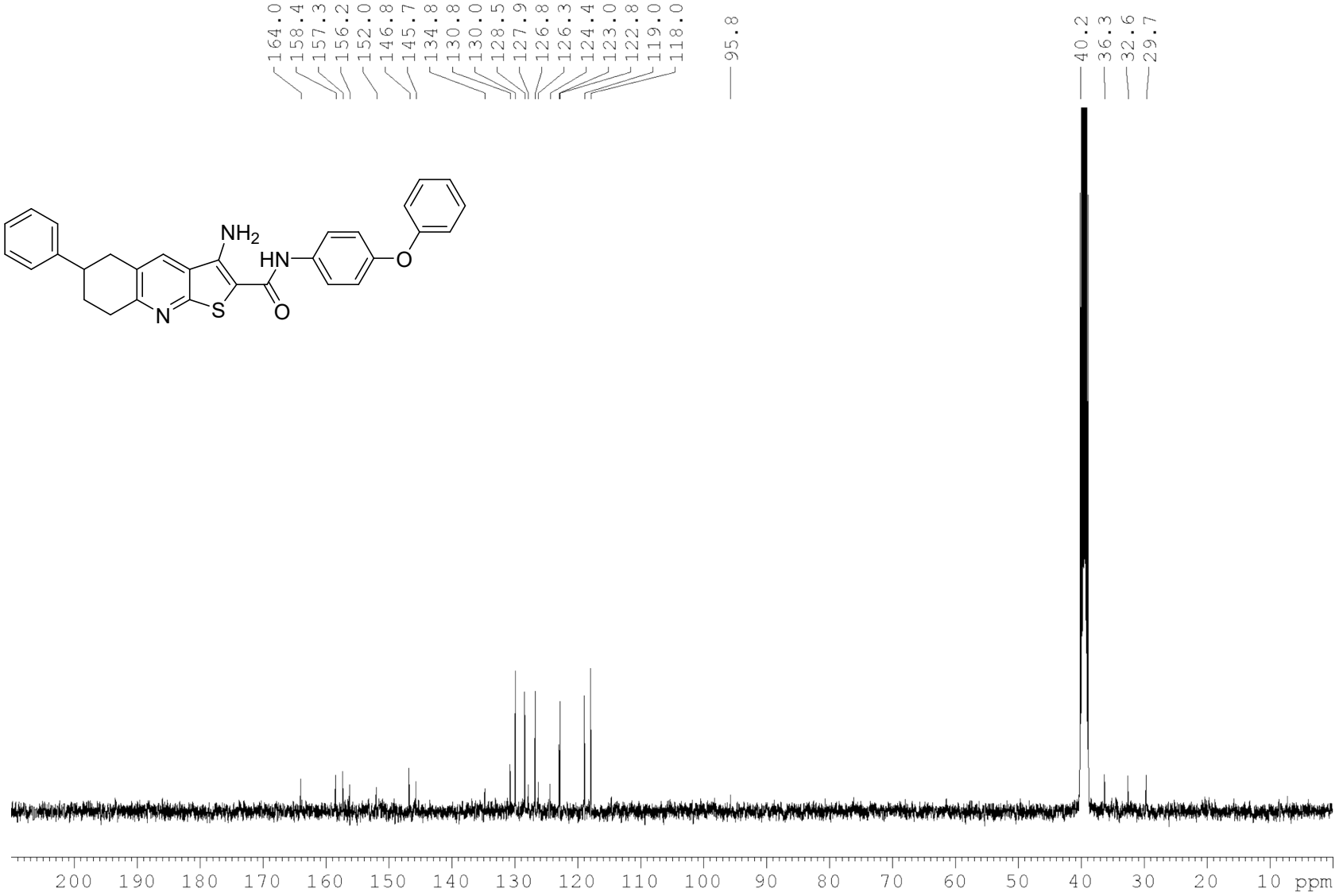


Figure S82: ^{13}C NMR spectrum of **9g** (100 MHz; DMSO-d_6).

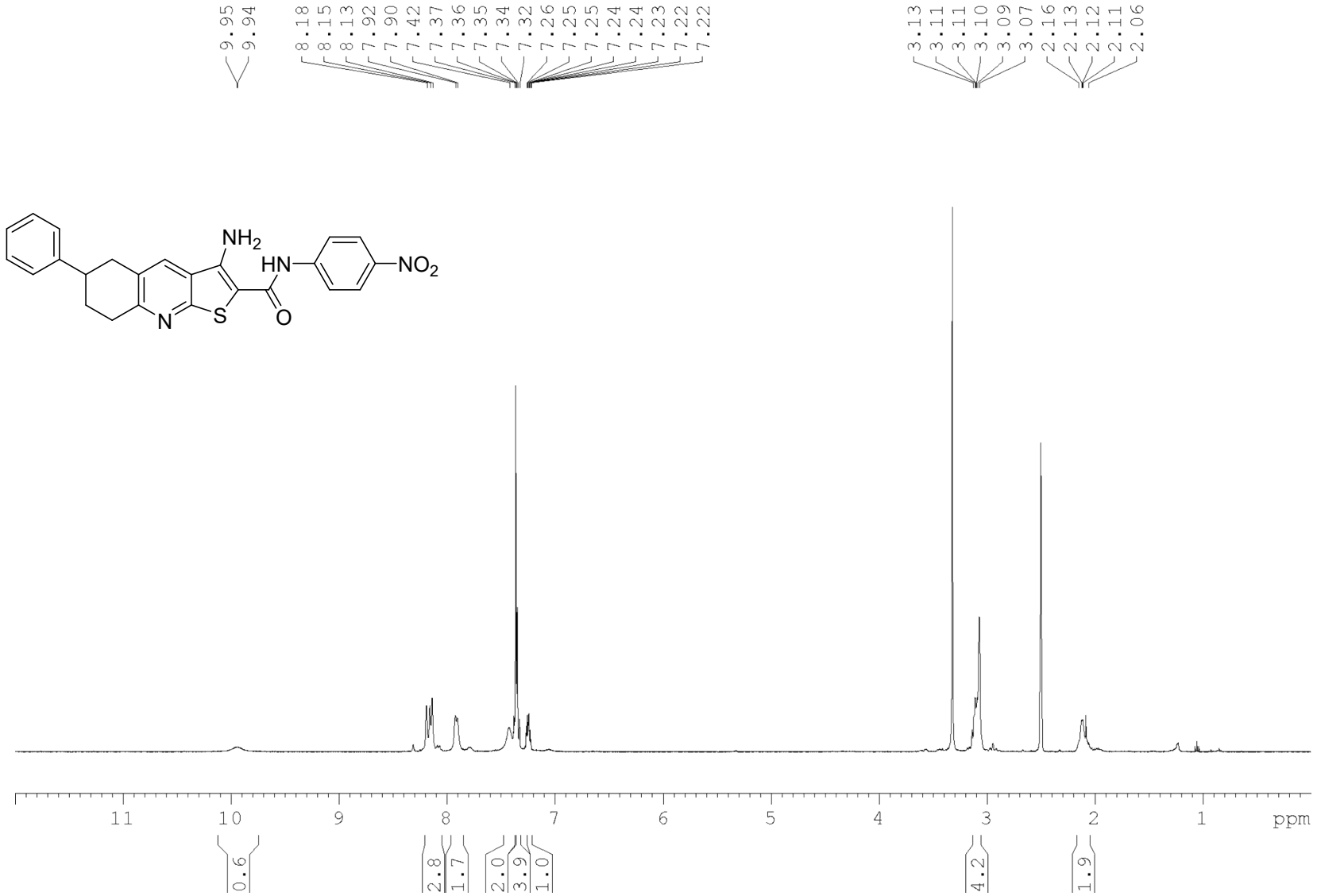


Figure S83: ^{1}H NMR spectrum of **9h** (400 MHz; DMSO-d_6).

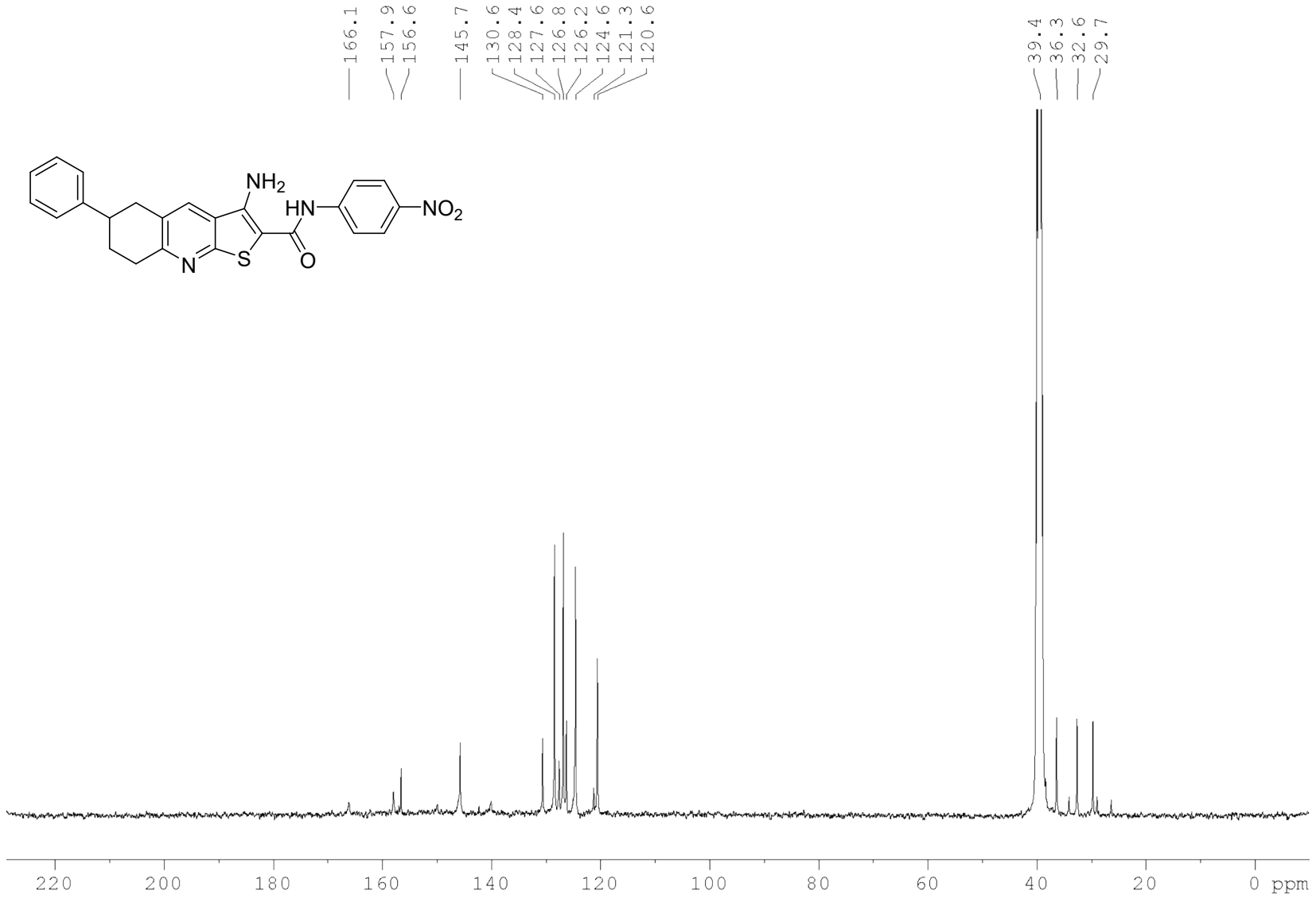


Figure S84: ^{13}C NMR spectrum of **9h** (100 MHz; DMSO-d_6).

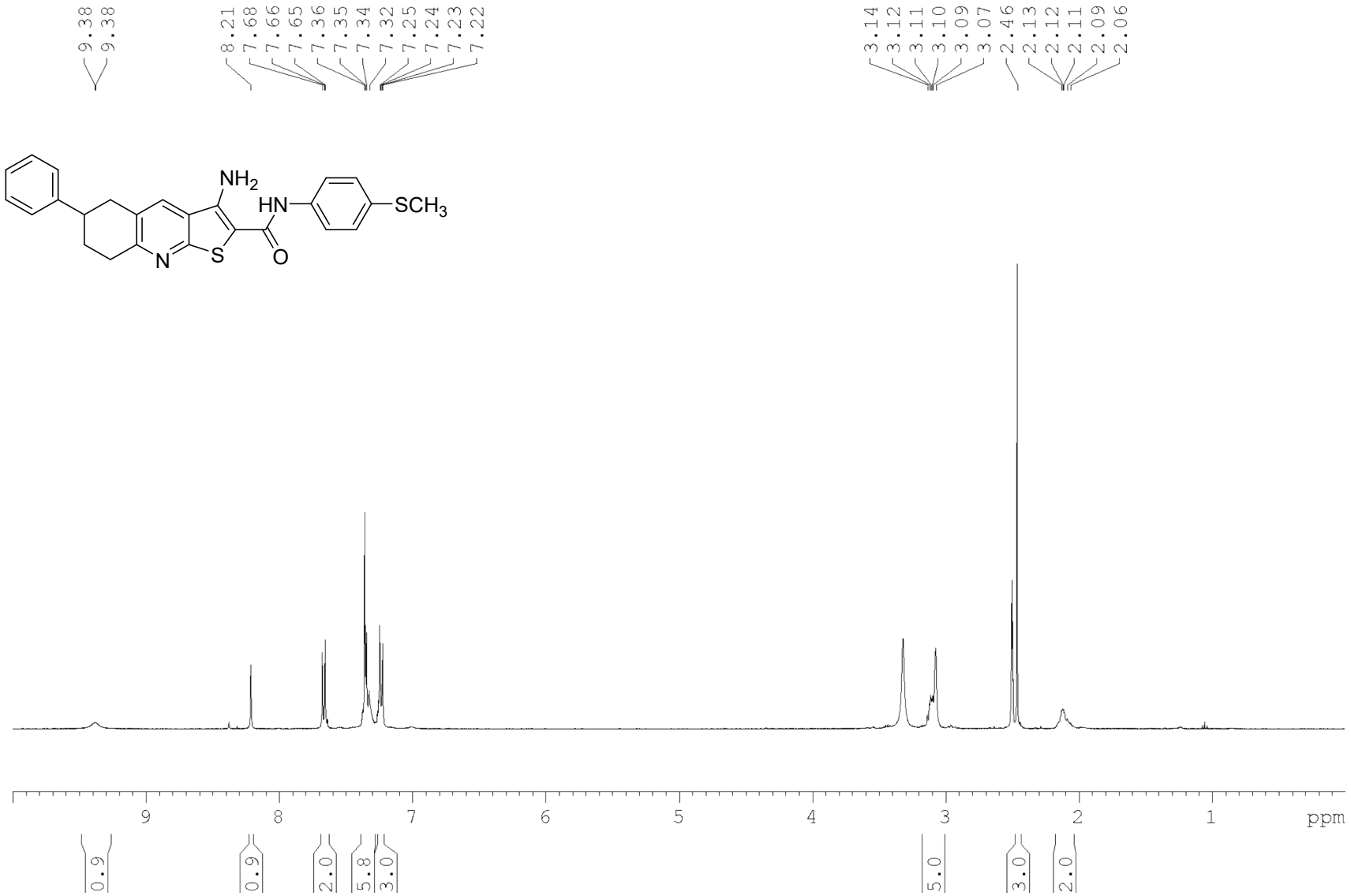


Figure S85: ^{1}H NMR spectrum of **9i** (400 MHz; DMSO-d_6).

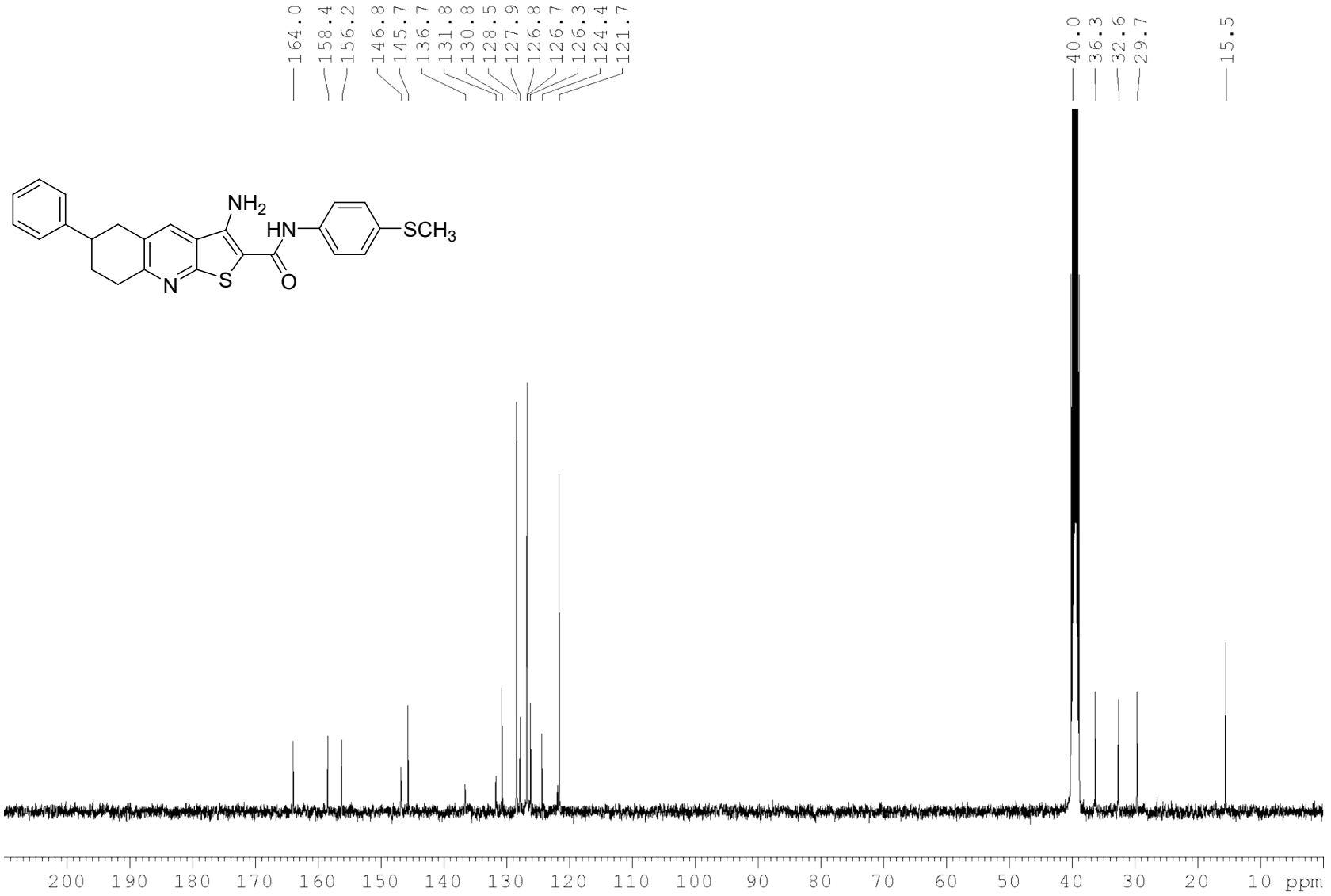


Figure S86: ^{13}C NMR spectrum of **9i** (100 MHz; DMSO-d_6).

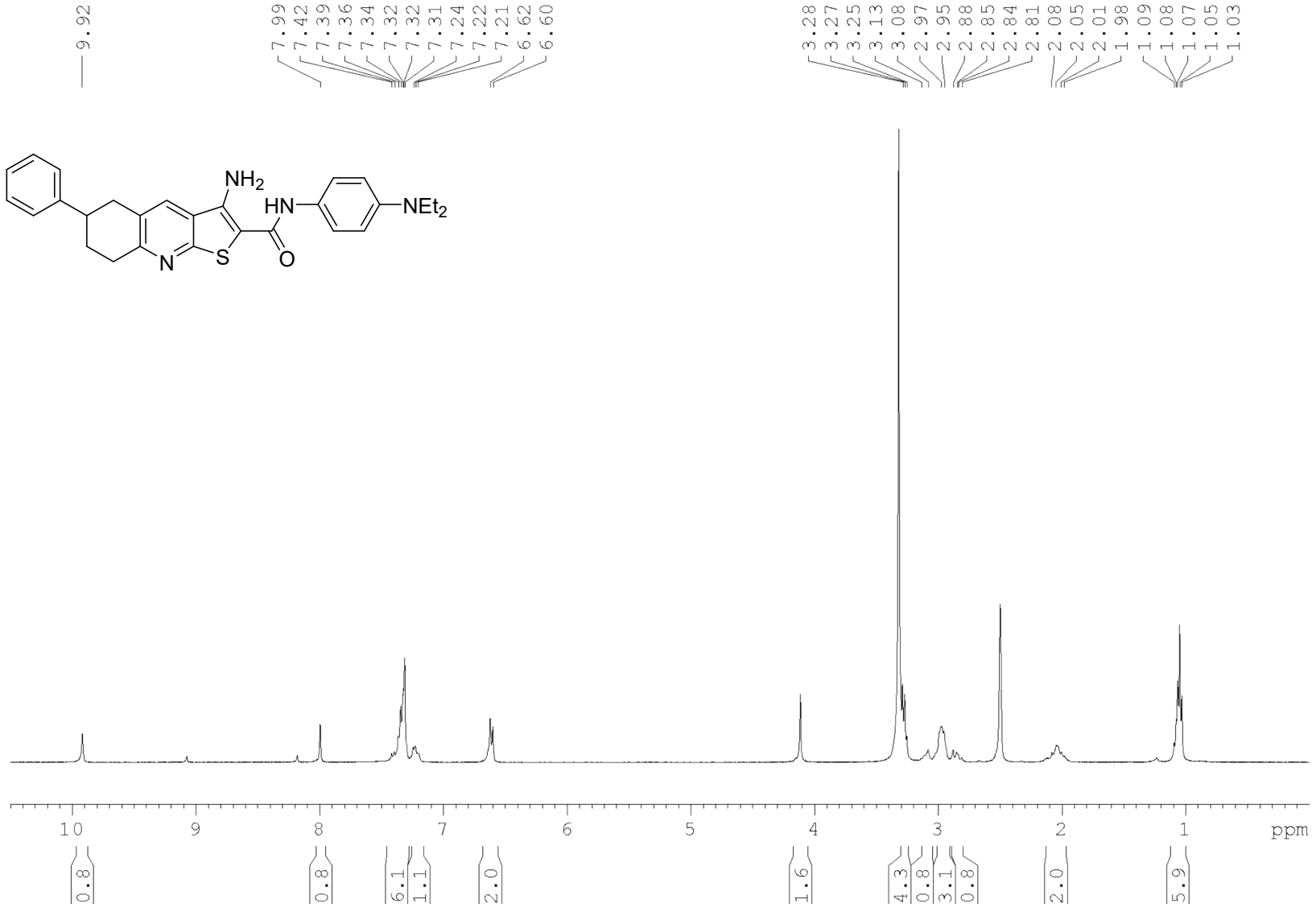


Figure S87: ^{1}H NMR spectrum of **9j** (400 MHz; DMSO-d_6).

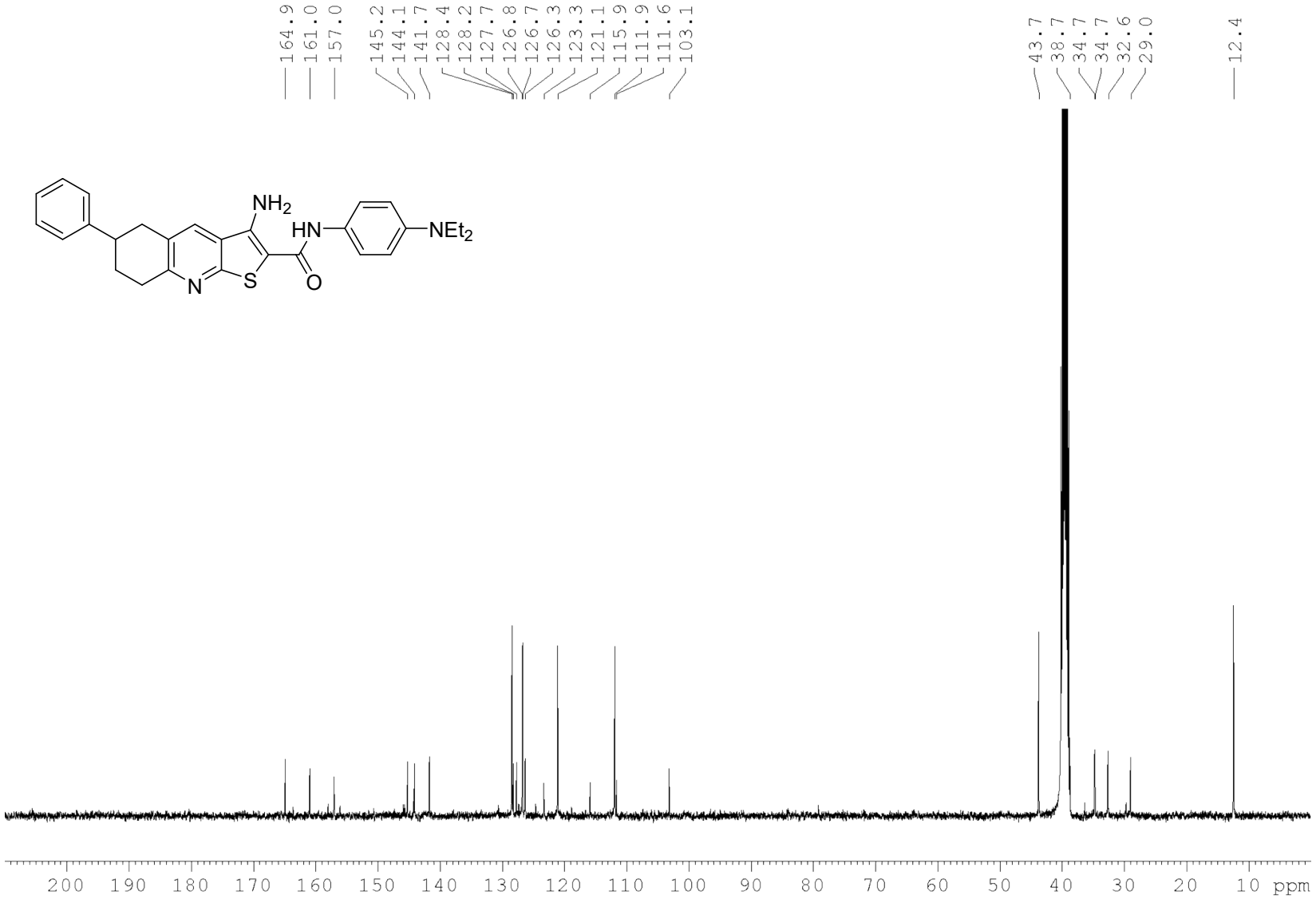


Figure S88: ^{13}C NMR spectrum of **9j** (100 MHz; DMSO-d_6).

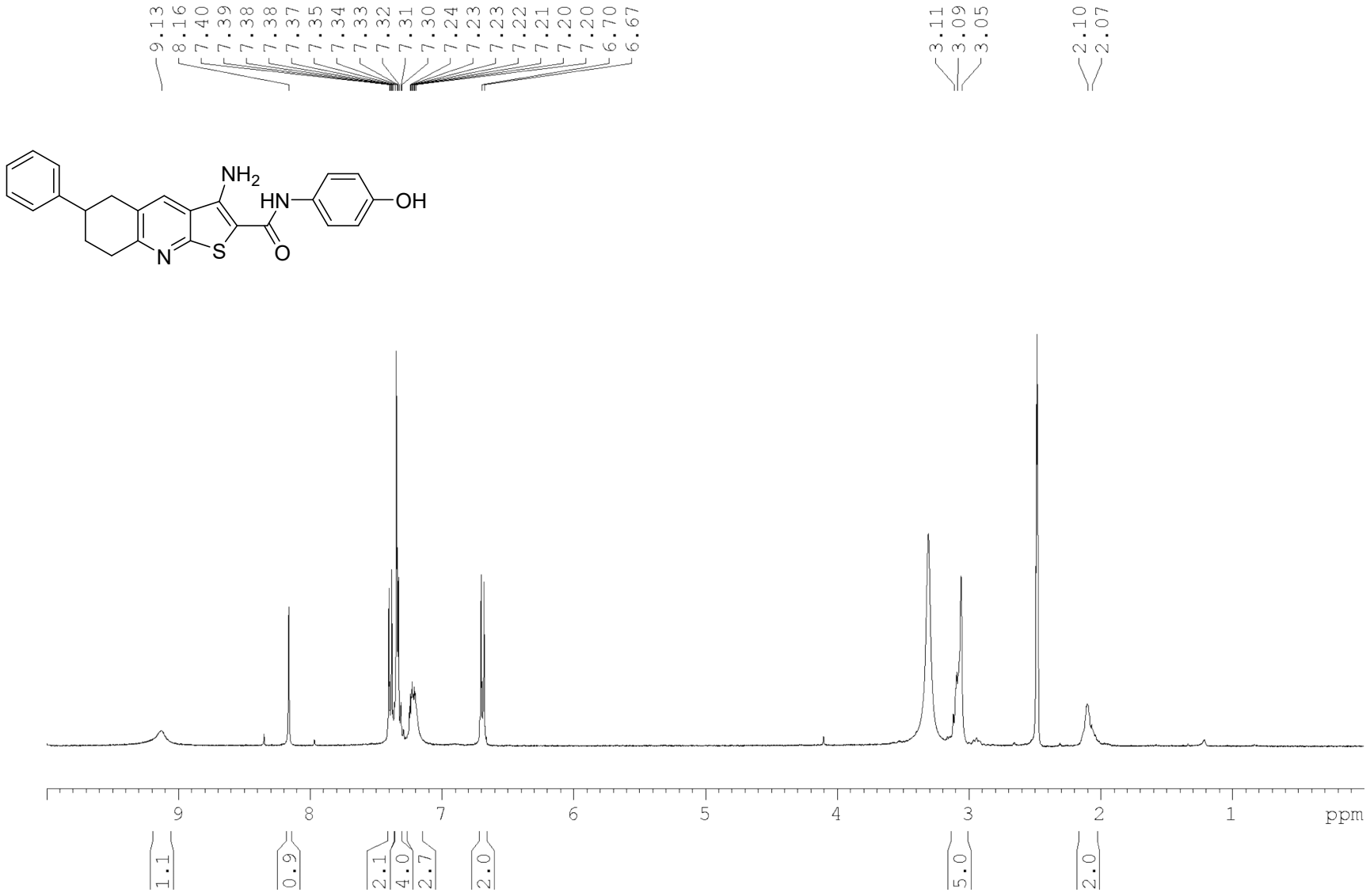


Figure S89: ^{1}H NMR spectrum of **9k** (400 MHz; DMSO-d_6).

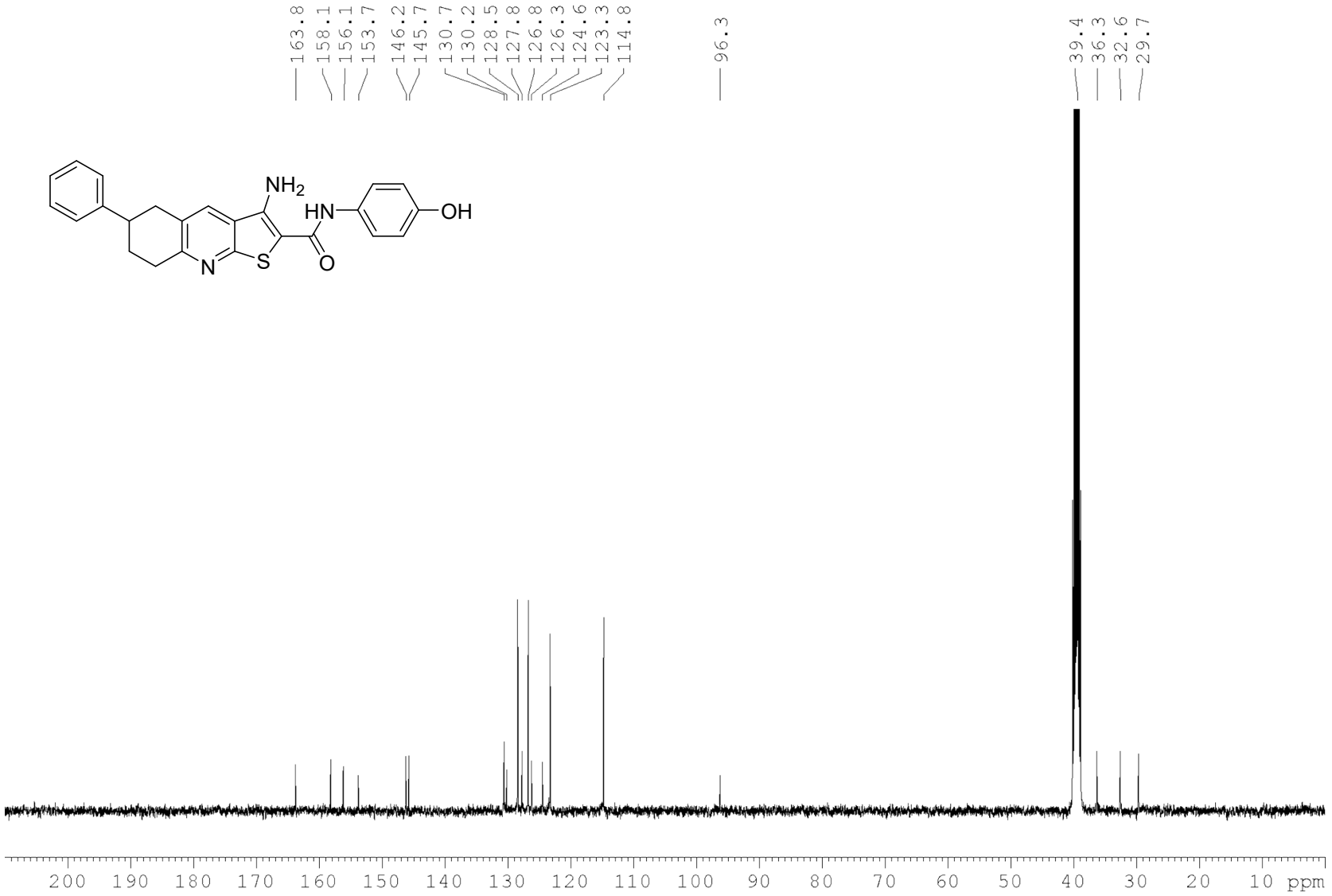


Figure S90: ^{13}C NMR spectrum of **9k** (100 MHz; DMSO-d_6).

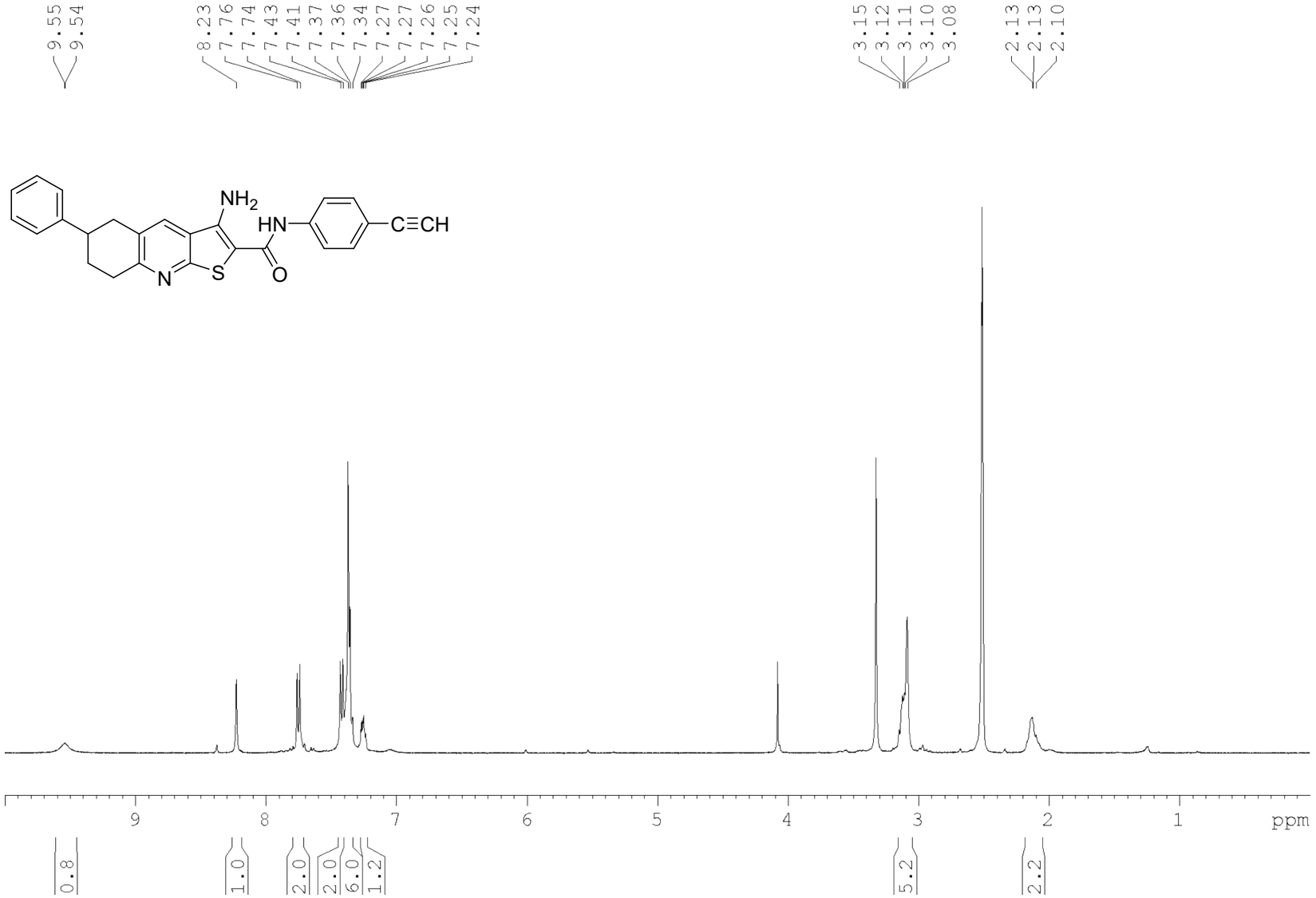


Figure S91: ^{1}H NMR spectrum of **9l** (400 MHz; DMSO-d_6).

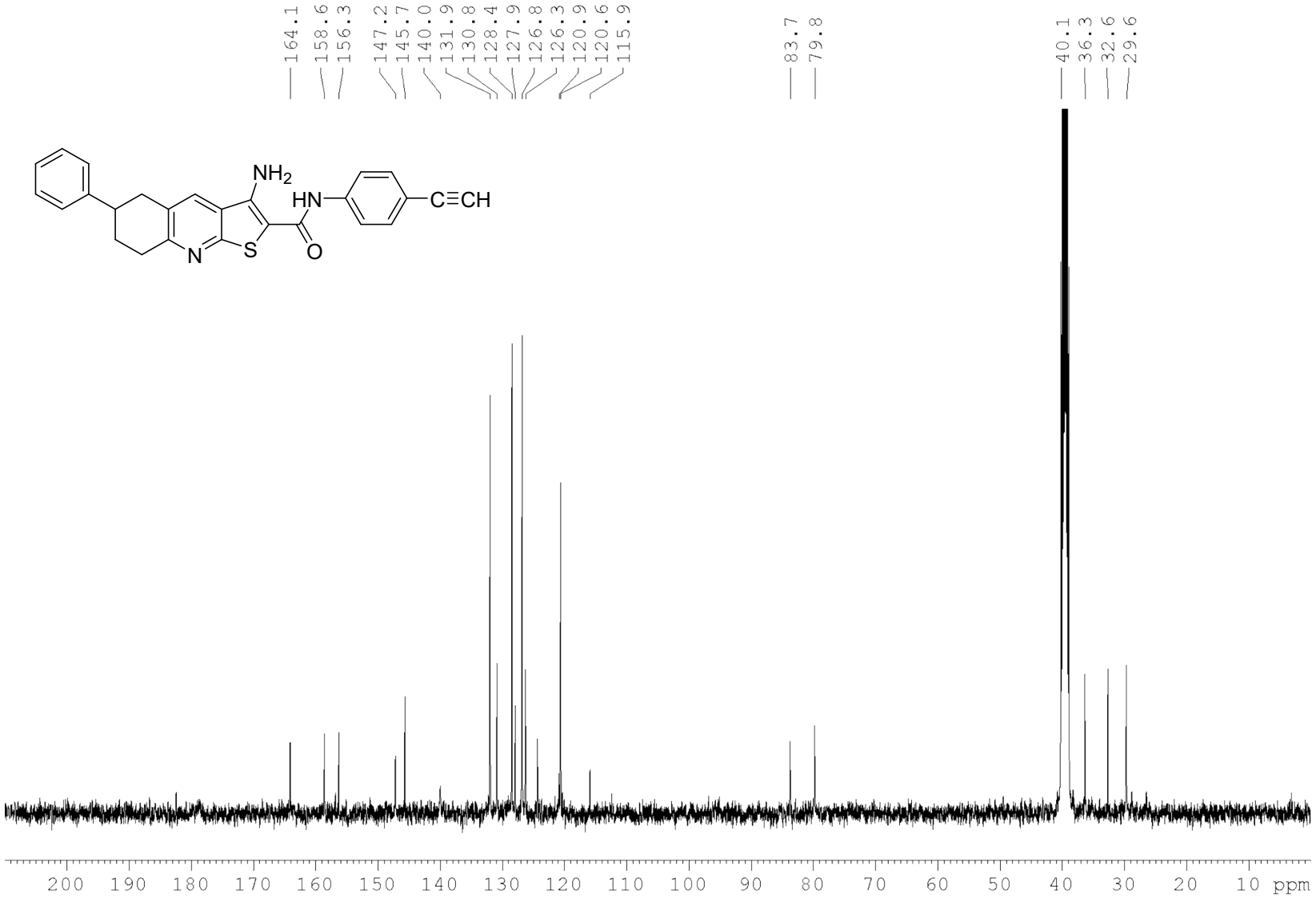


Figure S92: ^{13}C NMR spectrum of **9l** (100 MHz; DMSO-d_6).

Supplementary Figures

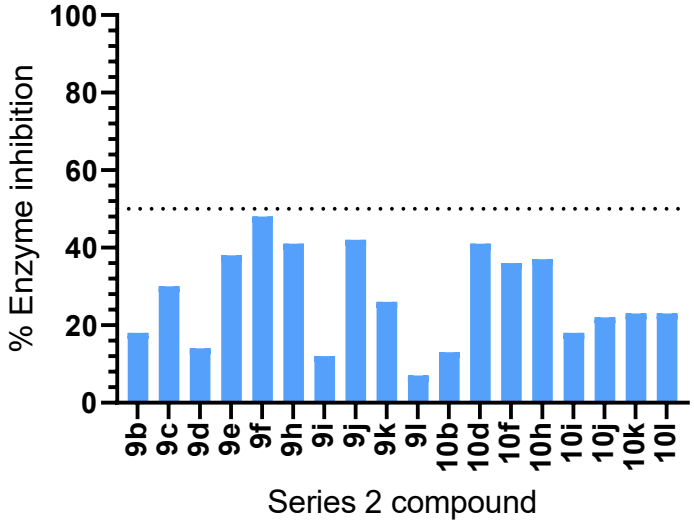


Figure S93. TDP1 enzyme inhibition after treatment with series 2 compounds (50 μM). Data are mean of three independent experiments. The dashed horizontal line represents 50% enzyme inhibition.

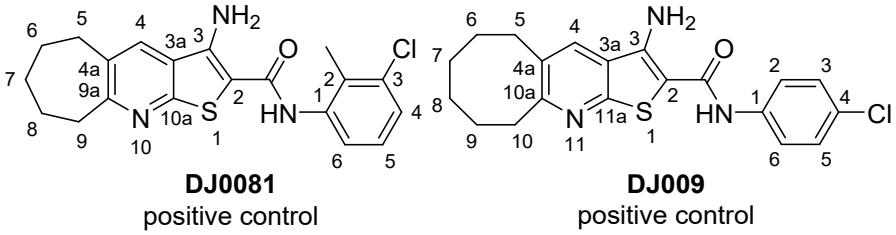


Figure S94. Structures of anti-proliferative thieno[2,3-*b*]pyridine positive controls: **DJ0081** used in ^{3}H thymidine incorporation assays (left) and **DJ009** used in synergy and pharmacokinetic assays (right).

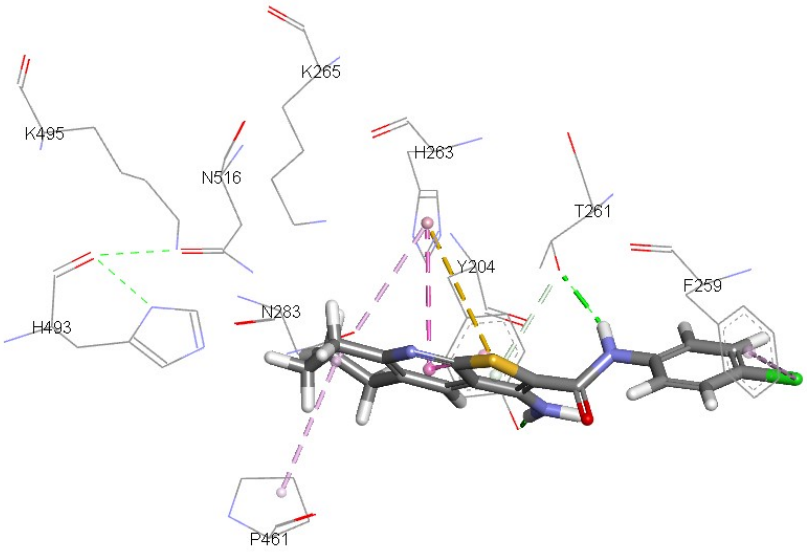


Figure S95. Bonding interactions of **6a** with TDP1 protein (PDB ID: 6DIE) and the HKN motifs. Dashed lines represent different interaction types; π-alkyl (light pink), π-π (dark pink), π-sulfur (yellow), hydrogen bonding (green).

Bliss score charts from topotecan synergy assays

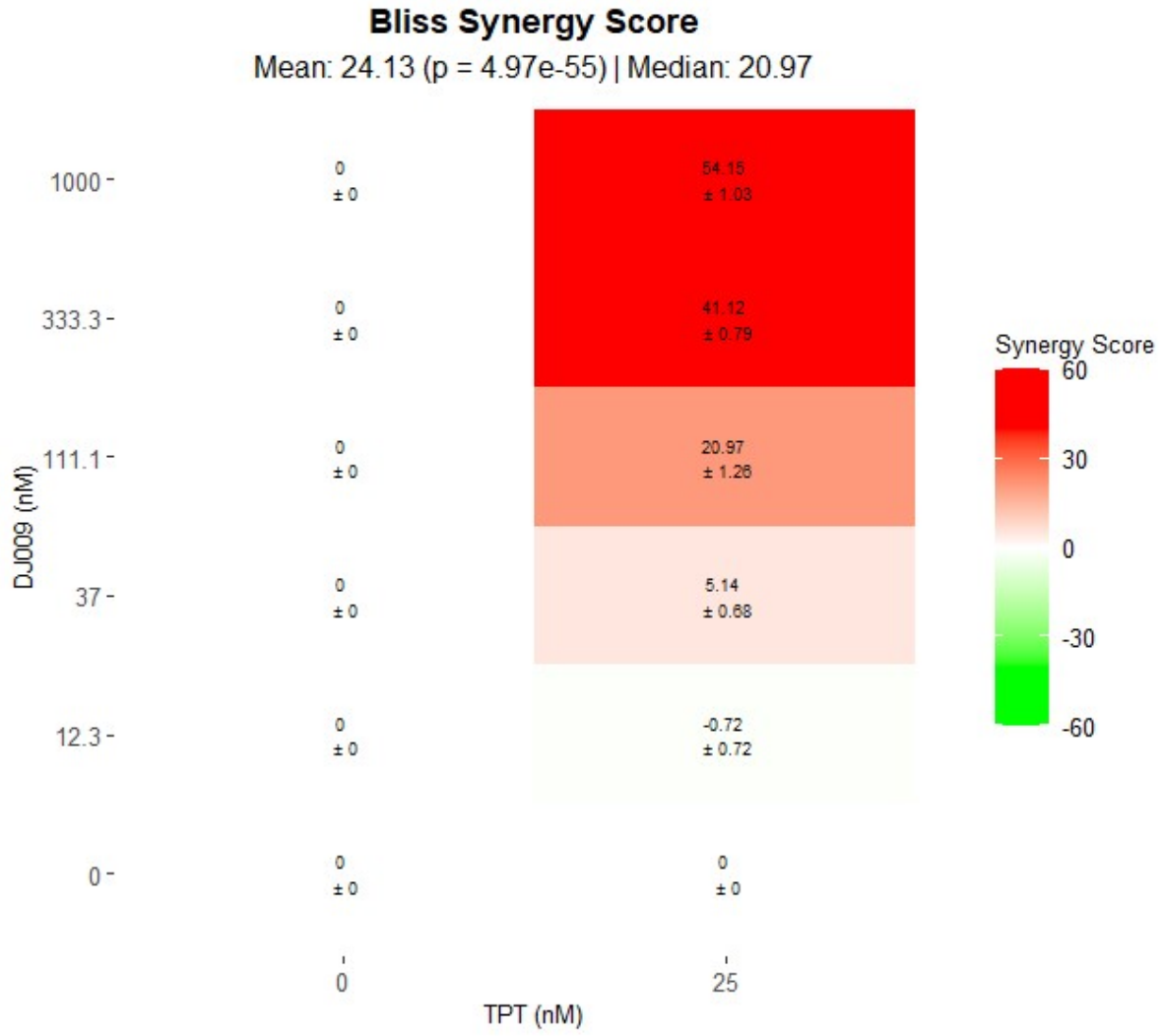


Figure S96. Bliss synergy chart of **DJ009** (positive control) and topotecan/TPT, expressed in nM. Values are the mean ± SEM at each tested concentration.

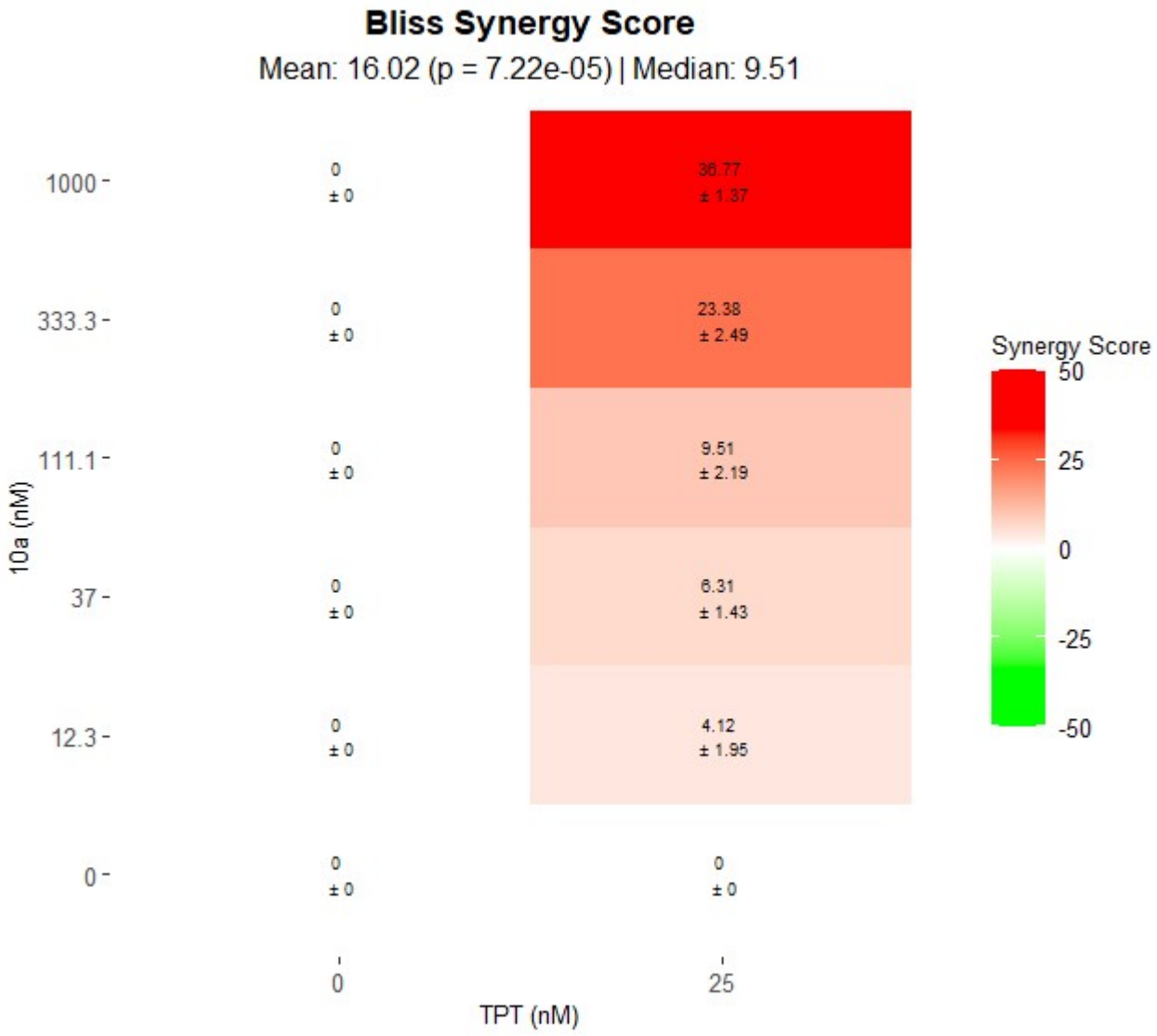


Figure S97. Bliss synergy chart of **10a** and topotecan/TPT, expressed in nM. Values are the mean ± SEM at each tested concentration.

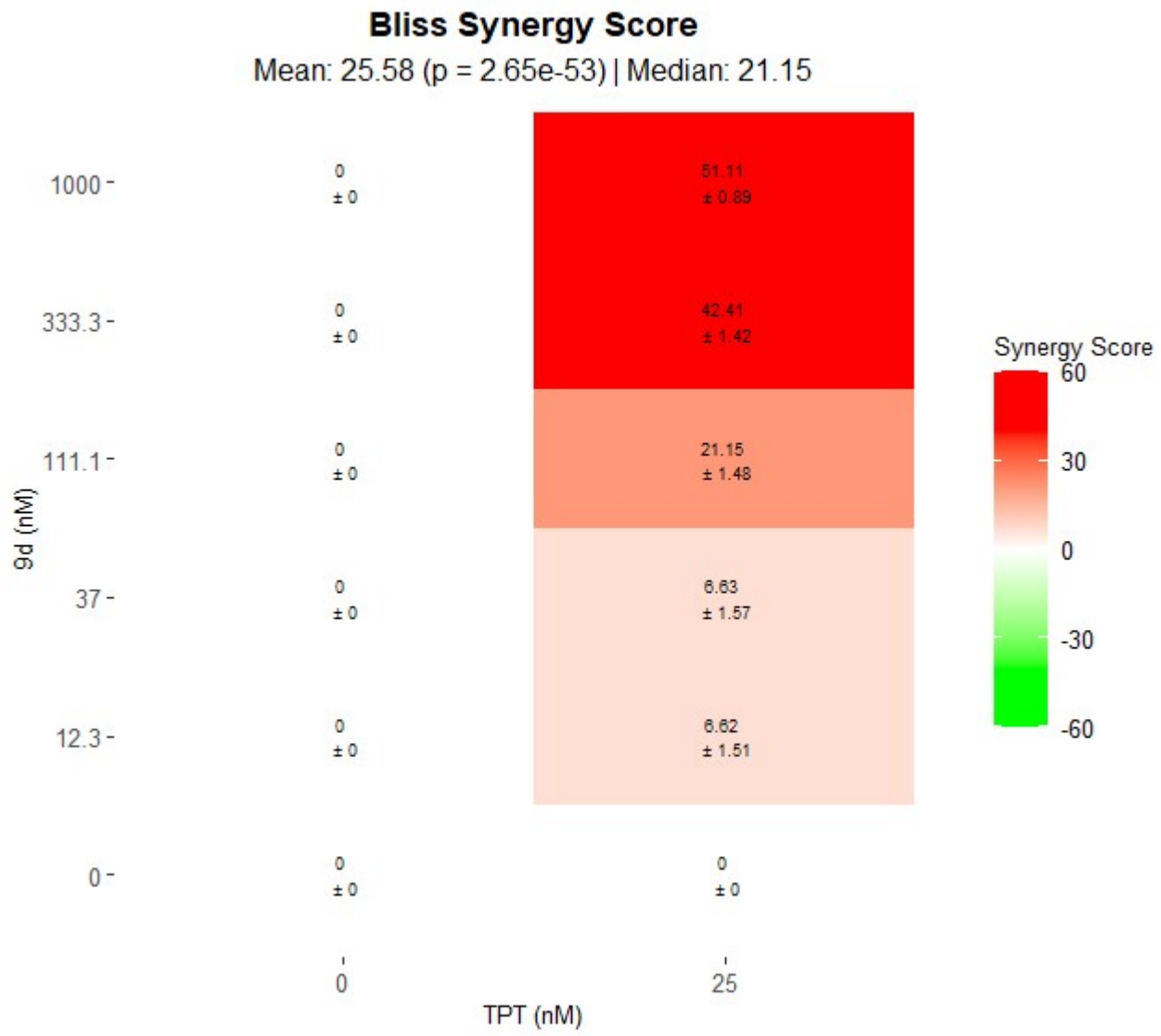


Figure S98. Bliss synergy chart of **9d** and topotecan/TPT, expressed in nM. Values are the mean ± SEM at each tested concentration.

Pharmacokinetic data

Table S1. Chromatography time gradient of mobile phase composition.

Time (min)	Mobile phase A %	Mobile phase B %
0.0	90	10
0.2	90	10
0.5	10	90
2.5	10	90
2.75	90	10
5.00	90	10

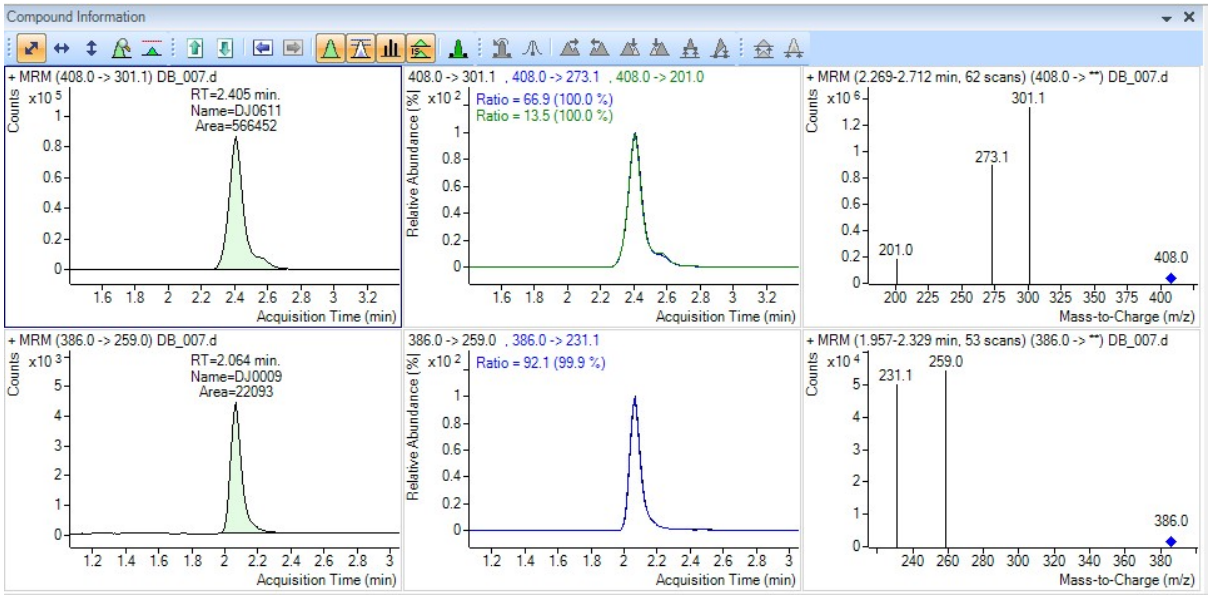


Figure S99. Representative MS peaks of **10a**. Blue curve = control DJ009, green curve = compound.

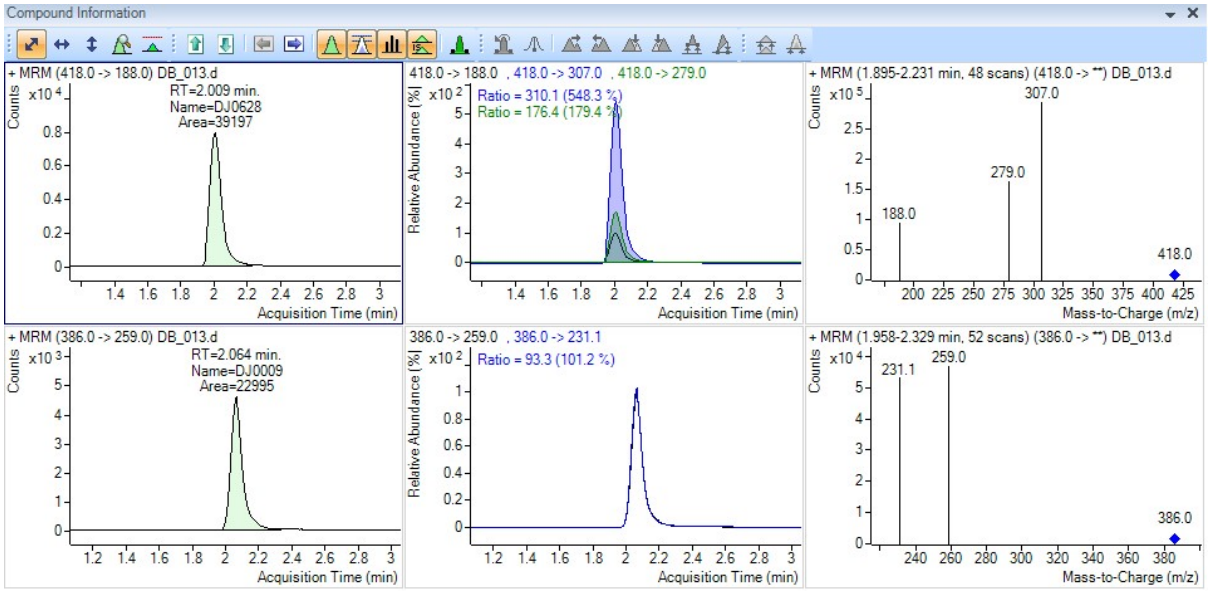


Figure S100. Representative MS peaks of **9d**. Blue curve = control DJ009, green curve = compound.

Table S2. Plasma concentrations of **10a** and **9d** in CD1 male mice after a single dose of 10 mg/kg, ip injection. Data are mean ± SE, n = 3 mice/time.

Time (h)	Plasma concentration (μM)	
	10a	**9d**
0.5	0.19 ± 0.06	3.56 ± 0.67
1	2.14 ± 0.29	2.17 ± 0.22
2	1.16 ± 0.21	0.75 ± 0.31
4	0.32 ± 0.12	0.43 ± 0.11
6	0.13 ± 0.01	0.31 ± 0.04

References

1. R. S, R.; Sugunan, A.; S, R.; Suresh, C. H.; Rajendar, G., A Method for the Preparation of β-Amino-α,β-unsaturated Carbonyl Compounds: Study of Solvent Effect and Mechanism. *Organic Letters* **2020,** *22* (3), 1040-1045.
2. Arabshahi, H. J.; van Rensburg, M.; Pilkington, L. I.; Jeon, C. Y.; Song, M.; Gridel, L.-M.; Leung, E.; Barker, D.; Vuica-Ross, M.; Volcho, K. P.; Zakharenko, A. L.; Lavrik, O. I.; Reynisson, J., A synthesis, in silico, in vitro and in vivo study of thieno[2,3-b]pyridine anticancer analogues. *MedChemComm* **2015,** *6* (11), 1987-1997.
3. Dyachenko, I. V.; Dyachenko, V. D., A simple one-pot synthesis of new 4-unsubstituted 2-oxo(thioxo)-1,2-dihydropyridine-3-carbonitriles, -3-carboxamides, and -3-carboxylic acid esters and 2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitriles. *Russian Journal of Organic Chemistry* **2015,** *51* (9), 1293-1300.
4. Elgemeie, G. E. H.; Hussain, B. A. W., A convenient synthesis of 5-deaza nonclassical antifolates: reaction of cyanothioacetamide with sodium salts of 2-(hydroxymethylene)-1-cycloalkanones. *Tetrahedron* **1994,** *50* (1), 199-204.
5. Rodinovskaya, L. A.; Belukhina, E. V.; Shestopalov, A. M.; Litvinov, V. P., Regioselective synthesis of 5,6-polymethylene-3-cyanopyridine-2(1H)-thiones and fused heterocycles based on them. *Russian Chemical Bulletin* **1994,** *43* (3), 449-457.
6. Patel, R. V.; Patel, P. K.; Kumari, P.; Rajani, D. P.; Chikhalia, K. H., Synthesis of benzimidazolyl-1,3,4-oxadiazol-2ylthio-N-phenyl (benzothiazolyl) acetamides as antibacterial, antifungal and antituberculosis agents. *European Journal of Medicinal Chemistry* **2012,** *53*, 41-51.
7. Rahaim, R. J., Jr.; Maleczka, R. E., Jr., Palladium-catalyzed silane/siloxane reductions in the one-pot conversion of nitro compounds into their amines, hydroxylamines, amides, sulfonamides, and carbamates. *Synthesis* **2006,** (19), 3316-3340.