# Supplementary Materials for:

**Disruption of Crystal Packing in Thieno[2,3-*b*]pyridines Improves Anti-proliferative Activity**

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*General Procedure A: Synthesis of thieno[2,3-*b*]pyridine-2-carboxamide derivatives* ***4a-e***

A mixture of carbonitrile **2** (1 equiv.), acetamides **3a-e** (1 equiv.), and anhydrous sodium carbonate (1.06-2 equiv.) in absolute ethanol (4.00 mL per mmol acetamide) was stirred at reflux for 24-48 h. The ethanol was then removed *in vacuo* and the remaining residue

recrystallised from methanol to give the thieno[2,3-*b*]pyridine-2-carboxamide derivatives **4a-e**.

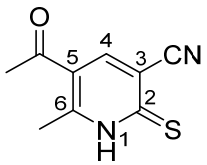
*General procedure B: Synthesis of thieno[2,3-*b*]pyridine-2-carboxamide alcohols **5a-e***

To a solution of ketones **4a-e** (1 equiv.) in dry THF was added a solution of sodium borohydride (1 equiv.) in methanol, dropwise, over 15 min. The mixture was stirred at r.t. for 2 h, water added and stirred for a further 5 min before the volatiles were removed *in vacuo.* The residue was diluted with water, extracted with ethyl acetate, washed with $H_2O$ and dried with $MgSO_4$ to give the thieno[2,3-*b*]pyridine-2-carboxamide alcohols **5a-e**.

*General Procedure C: Synthesis of esters and carbonates **6a-e**, **7a-e** and **8a-e***

To a stirred solution of alcohol (1 equiv.) and DMAP (2.5 equiv.) in dry pyridine under an atmosphere of $N_2$ at r.t. was added Boc or acetic anhydride, or methyl chloroformate (2.0 equiv.) dropwise. The mixture was monitored by TLC over 20 min, after which the mixture was quenched with equivalent portions of sat. aq. $NaHCO_3$ followed by 1 M HCl. The mixture was extracted with ethyl acetate, washed with water, dried with $MgSO_4$, and the solvent removed *in vacuo* to give the crude product, which was purified using flash chromatography to give the desired product.

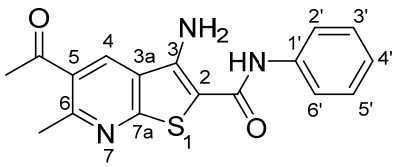
**5-Acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 2**




A mixture of acetylacetone **1** (1.00 mL, 10.0 mmol) and *N,N*-dimethylformamide dimethyl acetal (1.33 mL, 10.0 mmol) in dry dioxane (10.0 mL) was stirred under an atmosphere of nitrogen at r.t. overnight. A second mixture of sodium methoxide was prepared by adding sodium (0.46 g, 20.0 mmol) to dry methanol (10.5 mL, 0.260 mol). Cyanothioacetamide (1.00 g, 10.0 mmol) was added to the sodium methoxide and stirred for 10 min, after which the thioacetamide mixture was added to the acetone mixture and stirred for 1 h at r.t.. This was followed by heating at reflux for 4 h. After cooling, the mixture was acidified with ice cold 2 M HCl and water (10 mL) added. The resulting solid was collected by filtration to give the *title compound* **2** (1.86 g, 97%) as a light brown solid. m.p. 200-202 °C (Lit. 230-232 °C).[1] $\delta_H$ (400

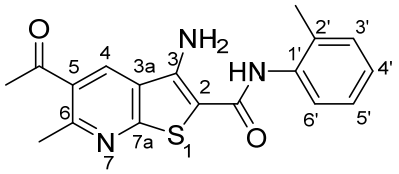
MHz, $(CD_3)_2SO$) 2.51 (3H, s, $COCH_3$), 2.64 (3H, s, 6-$CH_3$), 8.55 (1H, s, H-4), 14.26 (1H, br s, NH). The $^1H$ NMR values were in agreement with literature values.[26]

**5-Acetyl-3-amino-6-methyl-*N*-phenylthieno[2,3-*b*]pyridine-2-carboxamide 4a**



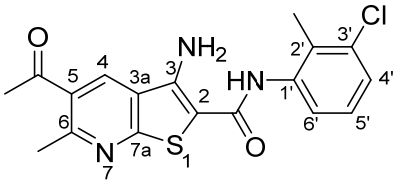

The reaction was carried out following general procedure A using carbonitrile **2** (100 mg, 0.52 mmol), acetamide **3a** (110 mg, 0.52 mmol) and anhydrous sodium carbonate (60.0 mg, 0.55 mmol) in absolute ethanol (4.00 mL) to give the *title compound* **4a** (116 mg, 69%) as a light brown solid. m.p. 228-230 °C (Lit. 228-230 °C).[2] $\delta_H$ (400 MHz, $(CD_3)_2SO$) 2.66 (3H, s, 5-$COCH_3$), 2.75 (3H, s, 6-$CH_3$), 7.07 (1H, t, $J$ = 7.8 Hz, H-4'), 7.32 (2H, t, $J$ = 7.8 Hz, H-3' and H-5'), 7.50 (2H, br s, $NH_2$), 7.68 (2H, d, $J$ = 7.8 Hz, H-2' and H-6'), 9.05 (1H, s, H-4), 9.40 (1H, br s, NH). The $^1H$ NMR values were in agreement with literature values.[1]

**5-Acetyl-3-amino-6-methyl-*N*-(*o*-tolyl)thieno[2,3-*b*]pyridine-2-carboxamide 4b**



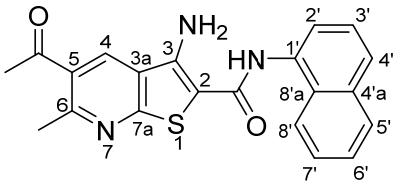

The reaction was carried out following general procedure A using carbonitrile **2** (100 mg, 0.52 mmol), acetamide **3b** (100 mg, 0.52 mmol) and anhydrous sodium carbonate (60.0 mg, 0.55 mmol) in absolute ethanol (4.00 mL) to give the *title compound* **4b** (112 mg, 63%) as a yellow solid. m.p. > 230 °C (Lit. > 230 °C).[2] $\delta_H$ (400 MHz, $(CD_3)_2SO$) 2.23 (3H, s, 2'-$CH_3$), 2.66 (3H, s, 5-$COCH_3$), 2.75 (3H, s, 6-$CH_3$), 7.13 (1H, t, $J$ = 7.3 Hz, H-4'), 7.19 (1H, t, $J$ = 7.3 Hz, H-5'), 7.26 (1H, d, $J$ = 7.3 Hz, H-3'), 7.33 (1H, d, $J$ = 7.3 Hz, H-6'), 7.35 (2H, br s, $NH_2$), 9.02 (1H, s, H-4), 9.18 (1H, br s, NH). The $^1H$ NMR values were in agreement with literature values.[1]

**5-Acetyl-3-amino-*N*-(3'-chloro-2'-methylphenyl)-6-methylthieno[2,3-*b*]pyridine-2-carboxamide 4c**



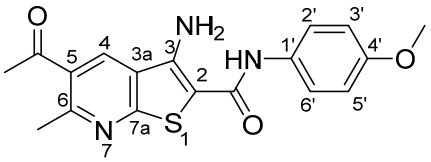
The reaction was carried out following general procedure A using carbonitrile **2** (100 mg, 0.52 mmol), acetamide **3c** (110 mg, 0.52 mmol) and anhydrous sodium carbonate (110 mg, 1.04 mmol) in absolute ethanol (4.00 mL) to give the *title compound* **4c** (207 mg, quant.) as a yellow/cream solid. m.p. > 230 °C (Lit. > 230 °C).[2] $\delta_H$ (400 MHz, $(CD_3)_2SO$) 2.24 (3H, s, 2'-$CH_3$), 2.66 (3H, s, 5-$COCH_3$), 2.75 (3H, s, 6-$CH_3$), 7.21 (1H, t, *J* = 8.0 Hz, H-5'), 7.31 (2H, d, *J* = 8.0 Hz, H-4' and H-6'), 7.40 (2H, br s, $NH_2$), 9.03 (1H, s, H-4), 9.41 (1H, br s, NH). The $^1$H NMR values were in agreement with literature values.[1]

**5-Acetyl-3-amino-6-methyl-*N*-(naphthalen-1'-yl)thieno[2,3-*b*]pyridine-2-carboxamide 4d**



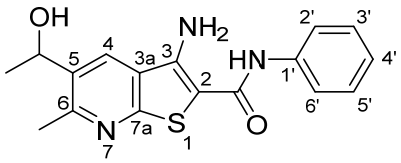
The reaction was carried out following general procedure A using carbonitrile **2** (100 mg, 0.52 mmol), acetamide **3d** (110 mg, 0.52 mmol) and anhydrous sodium carbonate (110 mg, 1.04 mmol) in absolute ethanol (4.00 mL) to give the *title compound* **4d** (93.0 mg, 47%) as a light yellow solid. m.p. >230 °C (Lit. > 230 °C).[2] $\delta_H$ (400 MHz, $(CD_3)_2SO$) 2.67 (3H, s, 5-$COCH_3$), 2.76 (3H, s, 6-$CH_3$), 7.40 (2H, br s, $NH_2$), 7.46-7.51 (3H, m, 3 × Ar-CH), 7.66-7.71 (2H, m, 2 × Ar-CH), 7.90-7.91 (1H, m, Ar-CH), 8.07 (1H, br, s, Ar-CH), 8.99 (1H, s, H-4), 9.66 (1H, br s, NH). The $^1$H NMR values were in agreement with literature values.[1]

**5-Acetyl-3-amino-*N*-(4'-methoxyphenyl)-6-methylthieno[2,3-*b*]pyridine-2-carboxamide 4e**



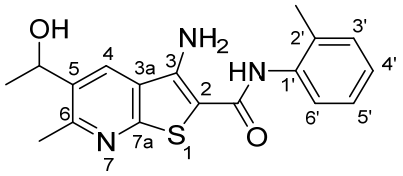
The reaction was carried out following general procedure A using carbonitrile **2** (100 mg, 0.52 mmol), acetamide **3e** (100 mg, 0.52 mmol) and anhydrous sodium carbonate (110 mg, 1.04 mmol) in absolute ethanol (4.00 mL) to give the *title compound* **4e** (159 mg, 88%) as a yellow solid. m.p. 218-220 °C (Lit. 219-221°C).[2] $\delta_H$ (400 MHz, $(CD_3)_2SO$) 2.66 (3H, s, 5-$COCH_3$), 2.75 (3H, s, 6-$CH_3$), 3.74 (3H, s, 4'-$OCH_3$), 6.89 (2H, d, *J* = 9.0 Hz, H-3' and H-5'), 7.44 (2H, br s, $NH_2$), 7.57 (2H, d, *J* = 9.0 Hz, H-2' and H-6'), 9.03 (1H, s, H-4), 9.36 (1H, br s, NH). The $^1$H NMR values were in agreement with literature values.[1]

**3-Amino-5-(1-hydroxyethyl)-6-methyl-*N*-phenylthieno[2,3-*b*]pyridine-2-carboxamide 5a**



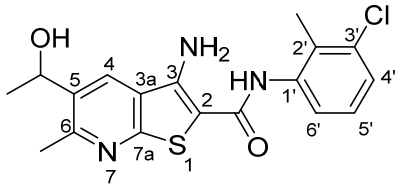
The reaction was carried out following general procedure B using ketone **4a** (0.05 g, 0.15 mmol), $NaBH_4$ (6.00 mg, 0.15 mmol) and methanol (0.51 mL) in THF (7.70 mL) to give the *title compound* **5a** (32.0 mg, 64%) as a yellow solid. m.p. >230 °C (Lit. > 230 °C).[2] $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.40 (3H, d, *J* = 6.4 Hz, $CHC\underline{H}_3$), 2.61 (3H, s, 6-$CH_3$), 5.02 (1H, dq, *J* = 6.4, 3.6 Hz, C<u>H</u>OH), 5.34 (1H, d, *J* = 3.6 Hz, CHO<u>H</u>), 7.06 (1H, t, *J* = 7.6 Hz, H-4'), 7.31 (2H, d, *J* = 7.6 Hz, H-3' and H-5'), 7.41 (2H, br s, $NH_2$), 7.68 (2H, d, *J* = 7.6 Hz, H-2' and H-6'), 8.54 (1H, s, H-4), 9.34 (1H, br s, NH). The $^1$H NMR values were in agreement with literature values.[1]

**3-Amino-5-(1-hydroxyethyl)-6-methyl-*N*-(*o*-tolyl)thieno[2,3-*b*]pyridine-2-carboxamide 5b**



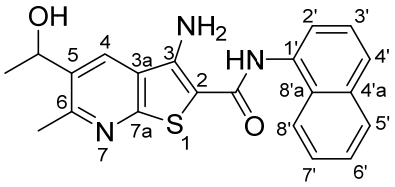

The reaction was carried out following general procedure B using ketone **4b** (0.05 g, 0.15 mmol), $NaBH_4$ (5.60 mg, 0.15 mmol) and methanol (0.50 mL) in THF (7.40 mL) to give the *title compound* **5b** (25.0 mg, 50%) as a yellow solid. m.p. 143-145 °C (Lit. 142-144 °C).[2] $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.40 (3H, d, $J$ = 6.3 Hz, CHC<u>H</u>$_3$), 2.22 (3H, s, 2'-$CH_3$), 2.61 (3H, s, 6-$CH_3$), 5.02 (1H, dq, $J$ = 6.3, 3.8 Hz, C<u>H</u>OH), 5.35 (1H, d, $J$ = 3.8 Hz, CHO<u>H</u>), 7.16 (1H, dd, $J$ = 7.4, 1.8 Hz, H-4'), 7.19 (1H, dd, $J$ = 7.4, 1.8 Hz, H-5'), 7.26-7.32 (4H, m, H-3', H-6' and $NH_2$), 8.52 (1H, s, H-4), 9.03 (1H, br s, NH). The $^1$H NMR values were in agreement with literature values.[1]

**3-Amino-*N*-(3'-chloro-2'-methylphenyl)-5-(1-hydroxyethyl)-6-methylthieno[2,3-*b*]pyridine-2-carboxamide 5c**



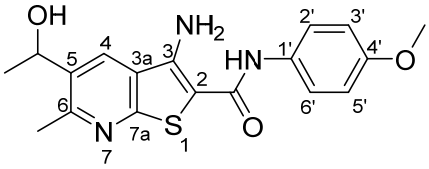

The reaction was carried out following general procedure B using ketone **4c** (0.08 g, 0.21 mmol), $NaBH_4$ (8.10 mg, 0.21 mmol) and methanol (0.71 mL) in THF (10.7 mL) to give the *title compound* **5c** (49.0 mg, 61%) as a yellow solid. m.p. >230 °C (Lit. > 230 °C).[2] $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.40 (3H, d, $J$ = 6.4 Hz, CHC<u>H</u>$_3$), 2.23 (3H, s, 2'-$CH_3$), 2.61 (3H, s, 6-$CH_3$), 5.02 (1H, dq, $J$ = 6.4, 3.6 Hz, C<u>H</u>OH), 5.35 (1H, d, $J$ = 3.6 Hz, CHO<u>H</u>), 7.22 (1H, t, $J$ = 7.8 Hz, H-5'), 7.26 (1H, d, $J$ = 7.8 Hz, H-6'), 7.28-7.35 (3H, m, H-4' and $NH_2$), 8.53 (1H, s, H-4), 9.30 (1H, br s, NH). The $^1$H NMR values were in agreement with literature values.[1]

**3-Amino-5-(1-hydroxyethyl)-6-methyl-*N*-(naphthalen-1-yl)thieno[2,3-*b*]pyridine-2-carboxamide 5d**



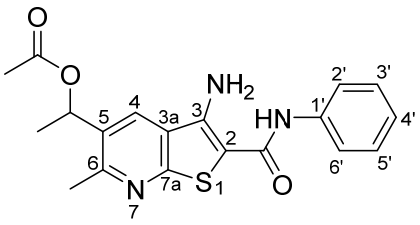

The reaction was carried out following general procedure B using ketone **4d** (0.04 g, 0.107 mmol), $NaBH_4$ (4.00 mg, 0.107 mmol) and methanol (0.35 mL) in THF (5.30 mL) to give the *title compound* **5d** (44.0 mg, quant.) as a yellow solid. m.p. 216-218 °C (Lit. 216-218 °C).[2] $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.40 (3H, d, $J$ = 6.4 Hz, CHC<u>H</u>$_3$), 2.63 (3H, s, 6-$CH_3$), 5.04 (1H, dq, $J$ = 6.4, 3.7 Hz, C<u>H</u>OH), 5.37 (1H, d, $J$ = 3.7 Hz, CHO<u>H</u>), 7.33 (2H, br s, $NH_2$), 7.52-7.56 (4H, m, 4 × Ar-CH), 7.84-7.86 (1H, m, Ar-CH), 7.91-7.98 (2H, m, 2 × Ar-CH), 8.54 (1H, s, H-4), 9.62 (1H, br s, NH). The $^1$H NMR values were in agreement with literature values.[1]

**3-Amino-5-(1-hydroxyethyl)-*N*-(4'-methoxyphenyl)-6-methylthieno[2,3-*b*]pyridine-2-carboxamide 5e**



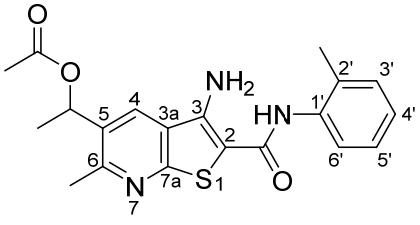

The reaction was carried out following general procedure B using ketone **4e** (0.08 g, 0.23 mmol), $NaBH_4$ (8.50 mg, 0.23 mmol) and methanol (0.74 mL) in THF (11.3 mL) to give the *title compound* **5e** (90.0 mg, quant.) as a yellow solid. m.p. >230 °C (Lit. > 230 °C).[2] $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.40 (3H, d, $J$ = 6.3 Hz, CHC<u>H</u>$_3$), 2.61 (3H, s, 6-$CH_3$), 3.74 (3H, s, 4'-$OCH_3$), 5.02 (1H, dq, $J$ = 6.3, 3.4 Hz, C<u>H</u>OH), 5.34 (1H, d, $J$ = 3.4 Hz, CHO<u>H</u>), 6.89 (2H, d, $J$ = 8.8 Hz, H-3' and H-5'), 7.35 (2H, br s, $NH_2$), 7.56 (2H, d, $J$ = 8.8 Hz, H-2' and H-6'), 8.52 (1H, s, H-4), 9.24 (1H, br s, NH). The $^1$H NMR values were in agreement with literature values.[1]

**1-(3-Amino-6-methyl-2-(phenylcarbamoyl)thieno[2,3-*b*]pyridin-5-yl)ethyl acetate 6a**



The reaction was carried out following General Procedure C using alcohol **5a** (14.0 mg, 0.04 mmol), DMAP (13.0 mg, 0.11 mmol) and acetic anhydride (0.08 mL, 0.09 mmol) in dry pyridine (0.50 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **6a** (10.0 mg, 63%) as a pale yellow crystalline solid. m.p. 203-205 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.55 (3H, d, *J* = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.08 (3H, s, acetyl COC<u></u>H$_3$), 2.64 (3H, s, 6-CH$_3$), 6.01 (1H, q, *J* = 6.5 Hz, 5-C<u>H</u>CH$_3$), 7.07 (1H, tt, *J* = 7.5, 1.1 Hz, H-4'), 7.32 (2H, t, *J* = 7.5 Hz, H-3' and H-5'), 7.41 (2H, br s, NH$_2$), 7.69 (2H, dd, *J* = 7.5, 1.1 Hz, H-2' and H-6'), 8.52 (1H, s, H-4), 9.39 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 20.8 and 20.9 (5-CH<u>C</u>H$_3$ and acetyl CO<u>C</u>H$_3$), 22.4 (6-CH$_3$), 68.4 (5-<u>C</u>HCH$_3$), 96.0 (C-2), 121.1 (C-2' and C-6'), 123.3 (C-4'), 124.5 (C-3a), 128.1 (C-4), 128.4 (C-3' and C-5'), 132.0 (C-5), 138.0 (C-1'), 147.0 (C-3), 156.8 (C-6), 157.2 (C-7a), 163.9 (2-CONH), 169.8 (acetyl <u>C</u>OCH$_3$). $\nu_{max}$ (ATR)/cm$^{-1}$ 3437 (N-H amide), 3329 (N-H amine), 2929 (C-H aromatic), 2825 (C-H alkane), 1735 (C=O carbonyl), 1608 (C=O amide), 1529 (C=C aromatic), 1438 (-C-H bending), 1223 (C-N aromatic), 1102 (C-O ether), 1075 (C-N aliphatic). *m/z* (ESI$^+$): 370 (MH$^+$, 100%). HRMS (ESI$^+$) found (MH$^+$): 370.1214 $C_{19}H_{20}N_3O_3S$ requires 370.1220.

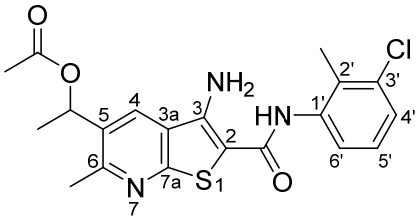
**1-(3-Amino-6-methyl-2-(o-tolylcarbamoyl)thieno[2,3-*b*]pyridin-5-yl)ethyl acetate 6b**



The reaction was carried out following General Procedure C using alcohol **5b** (26 mg, 0.08 mmol), DMAP (23.0 mg, 0.19 mmol) and acetic anhydride (0.01 mL, 0.15 mmol) in dry pyridine (0.60 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **6b** (15.0 mg, 54%) as a pale yellow crystalline solid.

m.p. 196-198 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.56 (3H, d, *J* = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.08 (3H, s, acetyl COC<u>H</u>$_3$), 2.22 (3H, s, 2'-C<u>H</u>$_3$), 2.64 (3H, s, 6-C<u>H</u>$_3$), 6.01 (1H, q, *J* = 6.5 Hz, 5-C<u>H</u>CH$_3$), 7.15 (1H, td, *J* = 7.3, 1.3 Hz, H-4'), 7.20 (1H, td, *J* = 7.3, 1.3 Hz, H-5'), 7.25 (1H, dd, *J* = 7.3, 1.3 Hz, H-3'), 7.29 (2H, br s, $NH_2$), 7.32 (1H, dd, *J* = 7.3, 1.3 Hz, H-6'), 8.50 (1H, s, H-4), 9.08 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 17.9 (2'-CH$_3$), 20.8 and 20.9 (5-CH<u>C</u>H$_3$ and acetyl CO<u>C</u>H$_3$), 22.2 (6-CH$_3$), 68.4 (5-<u>C</u>HCH$_3$), 96.5 (C-2), 124.6 (C-3a), 125.8 and 125.9 (C-4' and C-5'), 126.8 (C-6'), 128.0 (C-4), 130.1 (C-3'), 131.9 (C-5), 133.9 (C-2'), 136.4 (C-1'), 146.3 (C-3), 156.6 (C-6), 157.1 (C-7a), 163.9 (2-CONH), 169.8 (acetyl <u>C</u>OCH$_3$). $\nu_{max}$ (ATR)/cm$^{-1}$ 3406 (N-H amide), 3294 (N-H amine), 2970 (C-H aromatic), 2930 (C-H alkane), 1738 (C=O carbonyl), 1610 (C=O amide), 1514 (C=C aromatic), 1489 (-C-H bending), 1232 (C-N aromatic), 1114 (C-O ether), 1072 (C-N aliphatic). *m/z* (ESI$^+$): 384 (MH$^+$, 100%), 346 (97%), 324 (55%). HRMS (ESI$^+$) found (MH$^+$): 384.1370 $C_{20}H_{22}N_3O_3S$ requires 384.1376.

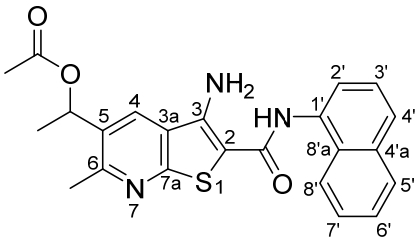
**1-(3-Amino-2-((3'-chloro-2'-methylphenyl)carbamoyl)-6-methylthieno[2,3-*b*]pyridin-5-yl)ethyl acetate 6c**




The reaction was carried out following General Procedure C using alcohol **5c** (0.10 g, 0.27 mmol), DMAP (81.0 mg, 0.67 mmol) and acetic anhydride (0.05 mL, 0.53 mmol) in dry pyridine (2 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **6c** (62.0 mg, 56%) as a pale yellow crystalline solid. m.p. 209-211 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.55 (3H, d, *J* = 6.4 Hz, 5-CHC<u>H</u>$_3$), 2.08 (3H, s, acetyl COC<u>H</u>$_3$), 2.23 (3H, s, 2'-C<u>H</u>$_3$), 2.64 (3H, s, 6-C<u>H</u>$_3$), 6.01 (1H, q, *J* = 6.4 Hz, 5-C<u>H</u>CH$_3$), 7.22 (1H, t, *J* = 7.5 Hz, H-5'), 7.28 (1H, dd, *J* = 7.5, 1.4 Hz, H-6'), 7.34 (1H, dd, *J* = 7.5, 1.4 Hz, H-4'), 7.33 (2H, br s, $NH_2$), 8.51 (1H, s, H-4), 9.36 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 15.4 (2'-CH$_3$), 20.8 and 20.9 (5-CH<u>C</u>H$_3$ and acetyl CO<u>C</u>H$_3$), 22.3 (6-CH$_3$), 68.4 (5-<u>C</u>HCH$_3$), 95.8 (C-2), 124.5 (C-3a), 126.2 (C-6'), 126.5 (C-4'), 126.7 (C-5'), 128.1 (C-4), 132.0 (C-5), 132.5 (C-2'), 133.6 (C-3'), 138.1 (C-1'), 146.8 (C-3), 156.8 (C-6), 157.2 (C-7a), 164.1 (2-CONH), 169.8 (acetyl <u>C</u>OCH$_3$). $\nu_{max}$ (ATR)/cm$^{-1}$ 3404 (N-H amide), 3351 (N-H amine), 2982 (C-H aromatic), 2936 (C-H alkane), 1740 (C=O carbonyl), 1645 (C=O amide), 1578 (C=C aromatic),

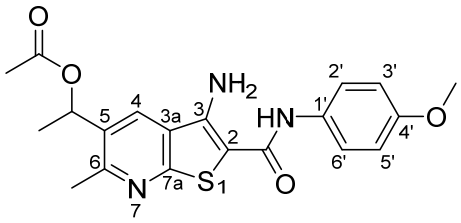
1432 (-C-H bending), 1234 (C-N aromatic), 1183 (C-O ether), 1074 (C-N aliphatic), 768 (C-Cl). *m/z* (ESI$^+$): 442 ($^{37}$ClMNa$^+$, 40%), 440 ($^{35}$ClMNa$^+$, 100%). HRMS (ESI$^+$) found ($^{37}$ClMNa$^+$): 442.0854 $C_{20}H_{20}{}^{37}ClN_3NaO_3S$ requires 442.0781. Found ($^{35}$ClMNa$^+$): 440.0797 $C_{20}H_{20}{}^{35}ClN_3NaO_3S$ requires 440.0806.

**1-(3-Amino-6-methyl-2-(naphthalen-1'-ylcarbamoyl)thieno[2,3-*b*]pyridin-5-yl)ethyl acetate 6d**



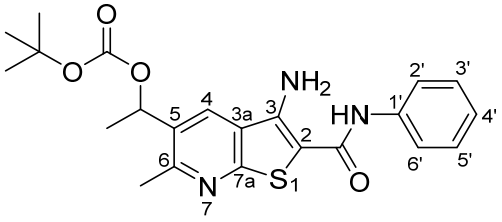

The reaction was carried out following General Procedure C using alcohol **5d** (20.0 mg, 0.05 mmol), DMAP (16.0 mg, 0.13 mmol) and acetic anhydride (0.01 mL, 0.11 mmol) in dry pyridine (0.40 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **6d** (10.0 mg, 45%) as a pale yellow crystalline solid. m.p. 190-192 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.57 (3H, d, *J* = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.09 (3H, s, acetyl COC<u>H</u>$_3$), 2.66 (3H, s, 6-C<u>H</u>$_3$), 6.02 (1H, q, *J* = 6.5 Hz, 5-C<u>H</u>CH$_3$), 7.34 (2H, br s, NH$_2$), 7.52-7.56 (4H, m, 4 × Ar-CH), 7.83-7.87 (1H, m, Ar-CH), 7.91-7.93 (1H, m, Ar-CH), 7.96-7.98 (1H, m, Ar-CH), 8.52 (1H, s, H-4), 9.67 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 20.8 and 20.9 (5-CH<u>C</u>H$_3$ and acetyl CO<u>C</u>H$_3$), 22.3 (6-CH$_3$), 68.4 (5-<u>C</u>HCH$_3$), 96.2 (C-2), 123.5 (Ar-CH), 124.3 (Ar-CH), 124.6 (C-3a), 125.5 (Ar-CH), 125.86 (Ar-CH), 125.94 (Ar-CH), 126.2 (Ar-CH), 128.0 (Ar-CH), 128.1 (C-4), 129.7 (Ar-C), 131.9 (C-5), 133.7 (C-1'), 133.9 (Ar-C), 146.7 (C-3), 156.7 (C-6), 157.3 (C-7a), 164.8 (2-CONH), 169.8 (acetyl <u>C</u>OCH$_3$). $\nu_{max}$ (ATR)/cm$^{-1}$ 3394 (N-H amide), 3308 (N-H amine), 2923 (C-H aromatic), 2852 (C-H alkane), 1731 (C=O carbonyl), 1607 (C=O amide), 1516 (C=C aromatic), 1464 (-C-H bending), 1236 (C-N aromatic), 1112 (C-O ether), 1089 (C-N aliphatic). *m/z* (ESI$^+$): 420 (MH$^+$, 100%), 413 (65%), 397 (20%), 382 (90%), 360 (45%). HRMS (ESI$^+$) found (MH$^+$): 420.1367 $C_{23}H_{22}N_3O_3S$ requires 420.1376.

**1-(3-Amino-2-((4'-methoxyphenyl)carbamoyl)-6-methylthieno[2,3-*b*]pyridin-5-yl)ethyl acetate 6e**



The reaction was carried out following General Procedure C using alcohol **5e** (20.0 mg, 0.06 mmol), DMAP (17.0 mg, 0.14 mmol) and acetic anhydride (0.01 mL, 0.11 mmol) in dry pyridine (1 mL) for 20 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **6e** (15.0 mg, 68%) as a pale yellow crystalline solid. m.p. > 230 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.56 (3H, d, $J$ = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.08 (3H, s, acetyl COC<u>H</u>$_3$), 2.63 (3H, s, 6-C<u>H</u>$_3$), 3.74 (3H, s, 4'-OC<u>H</u>$_3$), 6.00 (1H, q, $J$ = 6.5 Hz, 5-C<u>H</u>CH$_3$), 6.89 (2H, d, $J$ = 8.7 Hz, H-3' and H-5'), 7.35 (2H, br s, $NH_2$), 7.57 (2H, d, $J$ = 8.7 Hz, H-2' and H-6'), 8.50 (1H, s, H-4), 9.29 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 20.8 and 20.9 (5-CH<u>C</u>H$_3$ and acetyl CO<u>C</u>H$_3$), 22.2 (6-CH$_3$), 55.2 (4'-O<u>C</u>H$_3$), 68.4 (5-<u>C</u>HCH$_3$), 96.2 (C-2), 113.5 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.6 (C-3a), 128.0 (C-4), 131.88 and 131.95 (C-1' and C-5), 146.6 (C-3), 155.5 (C-4'), 156.7 (C-6), 157.1 (C-7a), 163.7 (2-CONH), 169.8 (acetyl <u>C</u>OCH$_3$). $\nu_{max}$ (ATR)/cm$^{-1}$ 3431 (N-H amide), 3327 (N-H amine), 2982 (C-H aromatic), 2891 (C-H alkane), 1737 (C=O carbonyl), 1600 (C=O amide), 1509 (C=C aromatic), 1411 (-C-H bending), 1227 (C-N aromatic), 1168 (C-O ether), 1098 (C-N aliphatic). *m/z* (ESI$^+$): 422 (MNa$^+$, 100%). HRMS (ESI$^+$) found (MNa$^+$): 422.1135 $C_{20}H_{21}N_3NaO_4S$ requires 422.1145.

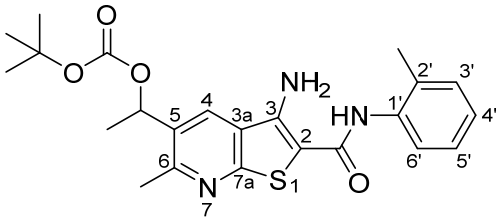
**1-(3-Amino-6-methyl-2-(phenylcarbamoyl)thieno[2,3-*b*]pyridin-5-yl)ethyl *tert*-butyl carbonate 7a**



The reaction was carried out following General Procedure C using alcohol **5a** (30.0 mg, 0.09 mmol), DMAP (28.0 mg, 0.23 mmol) and Boc anhydride (40.0 mg, 0.18 mmol) in dry pyridine

(0.70 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **7a** (15.0 mg, 38%) as a pale yellow crystalline solid. m.p. 190-192 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.39 (9H, s, 3 × *t*-butyl $CH_3$), 1.56 (3H, d, *J* = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.65 (3H, s, 6-$CH_3$), 5.88 (1H, q, *J* = 6.5 Hz, 5-C<u>H</u>$CH_3$), 7.07 (1H, tt, *J* = 7.4, 1.2 Hz, H-4'), 7.32 (2H, t, *J* = 7.4 Hz, H-3' and H-5'), 7.44 (2H, br s, $NH_2$), 7.69 (2H, d, *J* = 7.4 Hz, H-2' and H-6'), 8.54 (1H, s, H-4), 9.39 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 21.1 (5-CH<u>C</u>$H_3$), 22.2 (6-$CH_3$), 27.3 (3 × *t*-butyl $CH_3$), 71.2 (5-<u>C</u>H$CH_3$), 81.9 (*t*-butyl quat.), 96.0 (C-2), 121.1 (C-2' and C-6'), 123.3 (C-4'), 124.5 (C-3a), 128.1 (C-4), 128.4 (C-3' and C-5'), 131.9 (C-5), 139.0 (C-1'), 147.0 (C-3), 152.3 (carbonate C=O), 156.7 (C-6), 157.3 (C-7a), 163.9 (2-CONH). $\nu_{max}$ (ATR)/$cm^{-1}$ 3409 (N-H amide), 3303 (N-H amine), 2983 (C-H aromatic), 2852 (C-H alkane), 1731 (C=O carbonyl), 1630 (C=O amide), 1591 (C=C aromatic), 1432 (-C-H bending), 1251 (C-N aromatic), 1163 (C-O ether), 1082 (C-N aliphatic). *m/z* ($ESI^+$): 428 ($MH^+$, 100%), 372 (20%), 332 (40%). HRMS ($ESI^+$) found ($MH^+$): 428.1626 $C_{22}H_{26}N_3O_4S$ requires 428.1639.

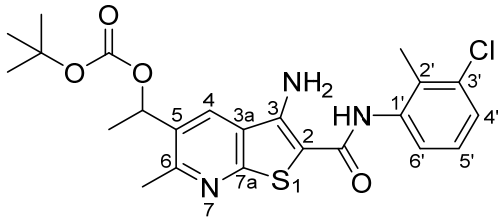
**1-(3-Amino-6-methyl-2-(o-tolylcarbamoyl)thieno[2,3-*b*]pyridin-5-yl)ethyl *tert*-butyl carbonate 7b**




The reaction was carried out following General Procedure C using alcohol **5b** (70.0 mg, 0.21 mmol), DMAP (63.0 mg, 0.51 mmol) and Boc anhydride (89.0 mg, 0.41 mmol) in dry pyridine (1.5 mL) for 30 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **7b** (25.0 mg, 27%) as a pale yellow crystalline solid. m.p. 187-189 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.39 (9H, s, 3 × *t*-butyl $CH_3$), 1.56 (3H, d, *J* = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.22 (3H, s, 2'-$CH_3$), 2.65 (3H, s, 6-$CH_3$), 5.87 (1H, q, *J* = 6.5 Hz, 5-C<u>H</u>$CH_3$), 7.15 (1H, td, *J* = 7.3, 1.3 Hz, H-4'), 7.19 (1H, td, *J* = 7.3, 1.3 Hz, H-5'), 7.25 (1H, dd, *J* = 7.3, 1.3 Hz, H-3'), 7.31 (1H, dd, *J* = 7.3, 1.3 Hz, H-6'), 7.32 (2H, br s, $NH_2$), 8.52 (1H, s, H-4), 9.09 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 17.9 (2'-$CH_3$), 21.1 (5-CH<u>C</u>$H_3$), 22.2 (6-$CH_3$), 27.3 (3 × *t*-butyl $CH_3$), 71.2 (5-<u>C</u>H$CH_3$), 81.9 (*t*-butyl quat.), 96.4 (C-2), 124.7 (C-3a), 125.8 and 125.9 (C-4' and C-5'), 126.9 (C-6'), 128.0 (C-4), 130.1 (C-3'), 131.8 (C-5), 134.0 (C-2'), 136.4

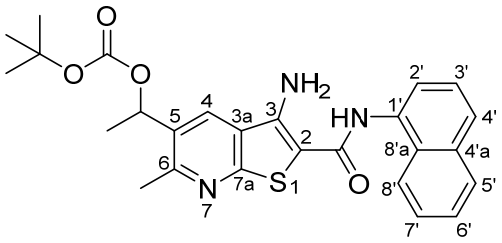
(C-1'), 146.4 (C-3), 152.3 (carbonate C=O), 156.5 (C-6), 157.3 (C-7a), 163.9 (2-CONH). $\nu_{max}$ (ATR)/cm$^{-1}$ 3400 (N-H amide), 3279 (N-H amine), 2978 (C-H aromatic), 2880 (C-H alkane), 1739 (C=O carbonyl), 1609 (C=O amide), 1513 (C=C aromatic), 1283 (C-N aromatic), 1165 (C-O ether), 1089 (C-N aliphatic). *m/z* (ESI$^+$): 442 (MH$^+$, 100%), 386 (20%), 346 (60%). HRMS (ESI$^+$) found (MH$^+$): 442.1787 $C_{23}H_{28}N_3O_4S$ requires 442.1795.

**1-(3-Amino-2-((3'-chloro-2'-methylphenyl)carbamoyl)-6-methylthieno[2,3-*b*]pyridin-5-yl)ethyl *tert*-butyl carbonate 7c**



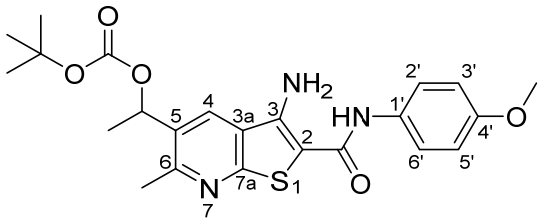

The reaction was carried out following General Procedure C using alcohol **5c** (40.0 mg, 0.11 mmol), DMAP (32.0 mg, 0.27 mmol) and Boc anhydride (46.0 mg, 0.21 mmol) in dry pyridine (1.0 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **7c** (10.0 mg, 20%) as a pale yellow crystalline solid. m.p. 199-201 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.39 (9H, s, 3 × *t*-butyl $CH_3$), 1.56 (3H, d, *J* = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.23 (3H, s, 2'-$CH_3$), 2.65 (3H, s, 6-$CH_3$), 5.87 (1H, q, *J* = 6.5 Hz, 5-C<u>H</u>$CH_3$), 7.22 (1H, t, *J* = 7.8 Hz, H-5'), 7.27 (1H, dd, *J* = 7.8, 1.4 Hz, H-6'), 7.34 (1H, dd, *J* = 7.8, 1.4 Hz, H-4'), 7.36 (2H, br s, $NH_2$), 8.53 (1H, s, H-4), 9.36 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 15.4 (2'-$CH_3$), 21.1 (5-CH<u>C</u>H$_3$), 22.2 (6-$CH_3$), 27.3 (3 × *t*-butyl $CH_3$), 71.2 (5-<u>C</u>HCH$_3$), 81.9 (*t*-butyl quat.), 95.8 (C-2), 124.6 (C-3a), 126.2 (C-6'), 126.6 (C-4'), 126.7 (C-5'), 128.1 (C-4), 131.9 (C-5), 132.5 (C-2'), 133.6 (C-3'), 138.1 (C-1'), 146.8 (C-3), 152.2 (carbonate C=O), 156.6 (C-6), 157.3 (C-7a), 164.1 (2-CONH). $\nu_{max}$ (ATR)/cm$^{-1}$ 3406 (N-H amide), 3290 (N-H amine), 2927 (C-H aromatic), 2845 (C-H alkane), 1742 (C=O carbonyl), 1607 (C=O amide), 1510 (C=C aromatic), 1460 (-C-H bending), 1283 (C-N aromatic), 1168 (C-O ether), 1088 (C-N aliphatic), 779 (C-Cl). *m/z* (ESI$^+$): 478 ($^{37}$ClMH$^+$, 40%), 476 ($^{35}$ClMH$^+$, 100%), 413 (43%), 380 (55%). HRMS (ESI$^+$) found ($^{37}$ClMH$^+$): 478.1369 $C_{23}H_{27}{}^{37}ClN_3O_4S$ requires 478.1383. Found ($^{35}$ClMH$^+$): 476.1392 $C_{23}H_{27}{}^{35}ClN_3O_4S$ requires 476.1405.

**1-(3-Amino-6-methyl-2-(naphthalen-1'-ylcarbamoyl)thieno[2,3-*b*]pyridin-5-yl)ethyl *tert*-butyl carbonate 7d**



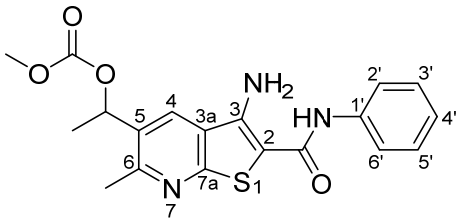
The reaction was carried out following General Procedure C using alcohol **5d** (0.10 g, 0.27 mmol), DMAP (81.0 mg, 0.66 mmol) and Boc anhydride (0.12 g, 0.53 mmol) in dry pyridine (2.0 mL) for 20 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **7d** (20.0 mg, 17%) as a pale yellow crystalline solid. m.p. 202-204 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.40 (9H, s, 3 × *t*-butyl $CH_3$), 1.57 (3H, d, $J$ = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.67 (3H, s, 6-$CH_3$), 5.89 (1H, q, $J$ = 6.5 Hz, 5-C<u>H</u>$CH_3$), 7.36 (2H, br s, $NH_2$), 7.53-7.56 (4H, m, 4 × Ar-CH), 7.84-7.87 (1H, m, Ar-CH), 7.91-7.93 (1H, m, Ar-CH), 7.95-7.98 (1H, m, Ar-CH), 8.54 (1H, s, H-4), 9.67 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 21.2 (5-CH<u>C</u>$H_3$), 22.3 (6-$CH_3$), 27.3 (3 × *t*-butyl $CH_3$), 71.2 (5-<u>C</u>$HCH_3$), 81.9 (*t*-butyl quat.), 96.2 (C-2), 123.5 (Ar-CH), 124.4 (Ar-CH), 124.6 (C-3a), 125.5 (Ar-CH), 125.9 (Ar-CH), 126.0 (Ar-CH), 126.2 (Ar-CH), 127.99 (Ar-CH), 128.04 (C-4), 129.7 (Ar-C), 131.8 (C-5), 133.7 (C-1'), 133.9 (Ar-C), 146.8 (C-3), 152.3 (carbonate C=O), 156.6 (C-6), 157.4 (C-7a), 164.8 (2-CONH). $\nu_{max}$ (ATR)/$cm^{-1}$ 3400 (N-H amide), 3285 (N-H amine), 2978 (C-H aromatic), 2923 (C-H alkane), 1734 (C=O carbonyl), 1605 (C=O amide), 1501 (C=C aromatic), 1262 (C-N aromatic), 1158 (C-O ether), 1081 (C-N aliphatic). *m/z* ($ESI^+$): 500 ($MNa^+$, 100%), 478 (50%), 413 (35%). HRMS ($ESI^+$) found ($MNa^+$): 500.1606 $C_{26}H_{27}N_3NaO_4S$ requires 500.1614.

**1-(3-Amino-2-((4'-methoxyphenyl)carbamoyl)-6-methylthieno[2,3-*b*]pyridin-5-yl)ethyl *tert*-butyl carbonate 7e**



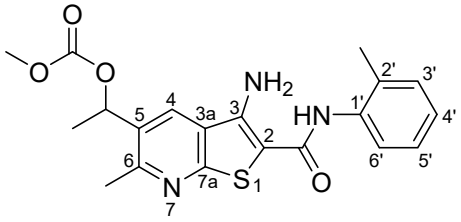

The reaction was carried out following General Procedure C using alcohol **5e** (60.0 mg, 0.17 mmol), DMAP (51.0 mg, 0.42 mmol) and Boc anhydride (73.0 mg, 0.42 mmol) in dry pyridine (1.3 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **7e** (20.0 mg, 26%) as a pale yellow crystalline solid. m.p. 196-198 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.39 (9H, s, 3 × *t*-butyl $CH_3$), 1.56 (3H, d, *J* = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.65 (3H, s, 6-$CH_3$), 3.74 (3H, s, 4'-$OCH_3$), 5.87 (1H, q, *J* = 6.5 Hz, 5-C<u>H</u>$CH_3$), 6.89 (2H, d, *J* = 8.9 Hz, H-3' and H-5'), 7.38 (2H, br s, $NH_2$), 7.57 (2H, d, *J* = 8.9 Hz, H-2' and H-6'), 8.52 (1H, s, H-4), 9.29 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 21.1 (5-CH<u>C</u>$H_3$), 22.2 (6-$CH_3$), 27.3 (3 × *t*-butyl $CH_3$), 55.1 (4'-$OCH_3$), 71.2 (5-<u>C</u>H$CH_3$), 81.9 (*t*-butyl quat.), 96.2 (C-2), 113.5 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.6 (C-3a), 128.0 (C-4), 131.8 and 131.9 (C-1' and C-5), 146.6 (C-3), 152.3 (carbonate C=O), 155.5 (C-4'), 156.5 (C-6), 157.3 (C-7a), 163.7 (2-CONH). $\nu_{max}$ (ATR)/$cm^{-1}$ 3408 (N-H amide), 3292 (N-H amine), 2981 (C-H aromatic), 2925 (C-H alkane), 1745 (C=O carbonyl), 1603 (C=O amide), 1506 (C=C aromatic), 1465 (-C-H bending), 1248 (C-N aromatic), 1166 (C-O ether), 1092 (C-N aliphatic). *m/z* ($ESI^+$): 480 ($MNa^+$, 45%), 402 (35%), 362 (100%), 275 (50%). HRMS ($ESI^+$) found ($MNa^+$): 480.1561 $C_{23}H_{27}N_3NaO_5S$ requires 480.1564.

**1-(3-Amino-6-methyl-2-(phenylcarbamoyl)thieno[2,3-*b*]pyridin-5-yl)ethyl methyl carbonate 8a**



The reaction was carried out following General Procedure C using alcohol **5a** (90.0 mg, 0.28 mmol), DMAP (67.0 mg, 0.55 mmol) and methyl chloroformate (0.02 mL, 0.28 mmol) in dry pyridine (2.0 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **8a** (20.0 mg, 22%) as a pale yellow crystalline solid. m.p. 194-196 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.60 (3H, d, *J* = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.67 (3H, s, 6-$CH_3$), 3.69 (3H, s, $OCH_3$), 5.94 (1H, q, *J* = 6.5 Hz, 5-C<u>H</u>$CH_3$), 7.07 (1H, tt, *J* = 7.5, 1.2 Hz, H-4'), 7.32 (2H, t, *J* = 7.5 Hz, H-3' and H-5'), 7.42 (2H, br s, $NH_2$), 7.69 (2H, d, *J* = 7.5 Hz, H-2' and H-6'), 8.55 (1H, s, H-4), 9.40 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 21.1 (5-CH<u>C</u>$H_3$), 22.3 (6-$CH_3$), 54.7 ($OCH_3$), 72.3 (5-<u>C</u>$HCH_3$), 96.1 (C-2), 121.1 (C-2' and C-6'), 123.3 (C-4'), 124.5 (C-3a), 128.3 (C-4), 128.4 (C-3' and C-5'), 131.5 (C-5), 139.0 (C-1'), 147.0 (C-3), 154.5 (carbonate C=O), 156.8 (C-6), 157.4 (C-7a), 163.9 (2-CONH). $\nu_{max}$ (ATR)/$cm^{-1}$ 3449 (N-H amide), 3327 (N-H amine), 2926 (C-H aromatic), 2852 (C-H alkane), 1741 (C=O carbonyl), 1626 (C=O amide), 1588 (C=C aromatic), 1495 (-C-H bending), 1255 (C-N aromatic), 1100 (C-O ether), 1071 (C-N aliphatic). *m/z* ($ESI^+$): 386 ($MH^+$, 100%), 332 (45%). HRMS ($ESI^+$) found ($MH^+$): 386.1163 $C_{19}H_{20}N_3O_4S$ requires 386.1169.

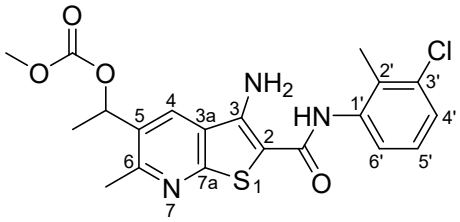
**1-(3-Amino-6-methyl-2-(o-tolylcarbamoyl)thieno[2,3-*b*]pyridin-5-yl)ethyl methyl carbonate 8b**



The reaction was carried out following General Procedure C using alcohol **5b** (0.10 g, 0.29 mmol), DMAP (72.0 mg, 0.59 mmol) and methyl chloroformate (0.02 mL, 0.29 mmol) in dry

pyridine (2.0 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **8b** (40.0 mg, 40%) as a pale yellow crystalline solid. m.p. 213-215 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.60 (3H, d, $J$ = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.22 (3H, s, 2'-$CH_3$), 2.66 (3H, s, 6-$CH_3$), 3.69 (3H, s, $OCH_3$), 5.94 (1H, q, $J$ = 6.5 Hz, 5-C<u>H</u>$CH_3$), 7.15 (1H, td, $J$ = 7.3, 1.3 Hz, H-4'), 7.20 (1H, td, $J$ = 7.3, 1.3 Hz, H-5'), 7.25 (1H, dd, $J$ = 7.3, 1.3 Hz, H-3'), 7.30 (2H, br s, $NH_2$), 7.31 (1H, dd, $J$ = 7.3, 1.3 Hz, H-6'), 8.53 (1H, s, H-4), 9.10 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 17.9 (2'-$CH_3$), 21.1 (5-CH<u>C</u>$H_3$), 22.3 (6-$CH_3$), 54.7 ($OCH_3$), 72.4 (5-<u>C</u>$HCH_3$), 96.5 (C-2), 124.7 (C-3a), 125.8 and 125.9 (C-4' and C-5'), 126.9 (C-6'), 128.2 (C-4), 130.2 (C-3'), 131.4 (C-5), 133.9 (C-2'), 136.4 (C-1'), 146.4 (C-3), 154.5 (carbonate C=O), 156.6 (C-6), 157.4 (C-7a), 163.9 (2-CONH). $\nu_{max}$ (ATR)/cm$^{-1}$ 3400 (N-H amide), 3291 (N-H amine), 2955 (C-H aromatic), 2850 (C-H alkane), 1747 (C=O carbonyl), 1609 (C=O amide), 1596 (C=C aromatic), 1439 (-C-H bending), 1262 (C-N aromatic), 1108 (C-O ether), 1069 (C-N aliphatic). *m/z* (ESI$^+$): 400 (MH$^+$, 100%), 346 (73%). HRMS (ESI$^+$) found (MH$^+$): 400.1314 $C_{20}H_{22}N_3O_4S$ requires 400.1326

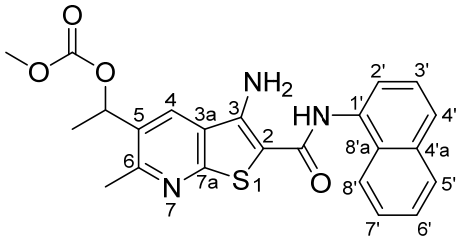
**1-(3-Amino-2-((3'-chloro-2'-methylphenyl)carbamoyl)-6-methylthieno[2,3-*b*]pyridin-5-yl)ethyl methyl carbonate 8c**




The reaction was carried out following General Procedure C using alcohol **5c** (30.0 mg, 0.08 mmol), DMAP (19.0 mg, 0.18 mmol) and methyl chloroformate (0.01 mL, 0.08 mmol) in dry pyridine (1.0 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **8c** (10.0 mg, 33%) as a pale yellow crystalline solid. m.p. 202-204 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.60 (3H, d, $J$ = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.23 (3H, s, 2'-$CH_3$), 2.67 (3H, s, 6-$CH_3$), 3.69 (3H, s, $OCH_3$), 5.94 (1H, q, $J$ = 6.5 Hz, 5-C<u>H</u>$CH_3$), 7.23 (1H, t, $J$ = 7.8 Hz, H-5'), 7.28 (1H, dd, $J$ = 7.8, 1.4 Hz, H-6'), 7.33-7.35 (3H, m, H-4' and $NH_2$), 8.54 (1H, s, H-4), 9.36 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 15.4 (2'-$CH_3$), 21.1 (5-CH<u>C</u>$H_3$), 22.3 (6-$CH_3$), 54.7 ($OCH_3$), 72.3 (5-<u>C</u>$HCH_3$), 95.8 (C-2), 124.6 (C-3a), 126.2 (C-6'), 126.6 (C-4'), 126.7 (C-5'), 128.3 (C-4), 131.5 (C-5), 132.5 (C-2'), 133.6 (C-3'), 138.1 (C-1'), 146.8 (C-3), 154.5 (carbonate C=O), 156.7 (C-6), 157.5 (C-7a), 164.1 (2-CONH). $\nu_{max}$

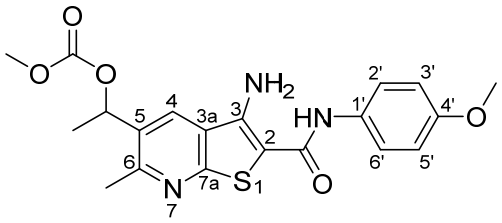
(ATR)/cm$^{-1}$ 3400 (N-H amide), 3291 (N-H amine), 2952 (C-H aromatic), 2851 (C-H alkane), 1747 (C=O carbonyl), 1607 (C=O amide), 1590 (C=C aromatic), 1436 (-C-H bending), 1240 (C-N aromatic), 1106 (C-O ether), 1071 (C-N aliphatic), 774 (C-Cl). *m/z* (ESI$^+$): 436 ($^{37}$ClMH$^+$, 40%), 434 ($^{35}$ClMH$^+$, 100%), 380 (45%). HRMS (ESI$^+$) found ($^{37}$ClMH$^+$): 436.0903 $C_{20}H_{21}{}^{37}ClN_3O_4S$ requires 436.0912. Found ($^{35}$ClMH$^+$): 434.0930 $C_{20}H_{21}{}^{35}ClN_3O_4S$ requires 434.0936.

**1-(3-Amino-6-methyl-2-(naphthalen-1'-ylcarbamoyl)thieno[2,3-*b*]pyridin-5-yl)ethyl methyl carbonate 8d**




The reaction was carried out following General Procedure C using alcohol **5d** (60.0 mg, 0.16 mmol), DMAP (39.0 mg, 0.32 mmol) and methyl chloroformate (0.01 mL, 0.16 mmol) in dry pyridine (1.0 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **8d** (28.0 mg, 47%) as a pale yellow crystalline solid. m.p. 188-190 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.61 (3H, d, $J$ = 6.5 Hz, 5-CHC<u>H</u>$_3$), 2.68 (3H, s, 6-CH$_3$), 3.70 (3H, s, OCH$_3$), 5.96 (1H, q, $J$ = 6.5 Hz, 5-C<u>H</u>CH$_3$), 7.35 (2H, br s, NH$_2$), 7.53-7.56 (4H, m, 4 × Ar-CH), 7.84-7.88 (1H, m, Ar-CH), 7.91-7.94 (1H, m, Ar-CH), 7.96-7.98 (1H, m, Ar-CH), 8.56 (1H, s, H-4), 9.68 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 21.1 (5-CH<u>C</u>H$_3$), 22.3 (6-CH$_3$), 54.8 (OCH$_3$), 72.4 (5-<u>C</u>HCH$_3$), 96.3 (C-2), 123.4 (Ar-CH), 124.3 (Ar-CH), 124.6 (C-3a), 125.5 (Ar-CH), 125.87 (Ar-CH), 125.95 (Ar-CH), 126.2 (Ar-CH), 128.0 (Ar-CH), 128.3 (C-4), 129.7 (Ar-C), 131.4 (C-5), 133.7 (C-1'), 133.9 (Ar-C), 146.7 (C-3), 154.5 (carbonate C=O), 156.7 (C-6), 157.6 (C-7a), 164.8 (2-CONH). $\nu_{max}$ (ATR)/cm$^{-1}$ 3393 (N-H amide), 3308 (N-H amine), 2985 (C-H aromatic), 2851 (C-H alkane), 1748 (C=O carbonyl), 1607 (C=O amide), 1501 (C=C aromatic), 1439 (-C-H bending), 1259 (C-N aromatic), 1106 (C-O ether), 1067 (C-N aliphatic). *m/z* (ESI$^+$): 436 (MH$^+$, 100%), 382 (73%). HRMS (ESI$^+$) found (MH$^+$): 436.1318 $C_{23}H_{22}N_3O_4S$ requires 436.1326.

**1-(3-Amino-2-((4'-methoxyphenyl)carbamoyl)-6-methylthieno[2,3-*b*]pyridin-5-yl)ethyl methyl carbonate 8e**



The reaction was carried out following General Procedure C using alcohol **5e** (90.0 mg, 0.25 mmol), DMAP (62.0 mg, 0.50 mmol) and methyl chloroformate (0.02 mL, 0.25 mmol) in dry pyridine (2.0 mL) for 15 min then purified with flash chromatography (3:1 petroleum ether, ethyl acetate) to give the *title compound* **8e** (25.0 mg, 28%) as a pale yellow crystalline solid. m.p. > 230 °C. $\delta_H$ (400 MHz, $(CD_3)_2SO$) 1.60 (3H, d, $J$ = 6.5 Hz, 5-CHC$\underline{H}_3$), 2.66 (3H, s, 6-$CH_3$), 3.69 (3H, s, $OCH_3$), 3.74 (3H, s, 4'-$OCH_3$), 5.93 (1H, q, $J$ = 6.5 Hz, 5-C$\underline{H}CH_3$), 6.89 (2H, d, $J$ = 8.9 Hz, H-3' and H-5'), 7.37 (2H, br s, $NH_2$), 7.57 (2H, d, $J$ = 8.9 Hz, H-2' and H-6'), 8.53 (1H, s, H-4), 9.29 (1H, br s, NH). $\delta_C$ (100 MHz, $(CD_3)_2SO$) 21.1 (5-CH$\underline{C}H_3$), 22.2 (6-$CH_3$), 54.7 ($OCH_3$), 55.1 (4'-$OCH_3$), 72.3 (5-$\underline{C}HCH_3$), 96.2 (C-2), 113.5 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.6 (C-3a), 128.2 (C-4), 131.4 (C-5), 131.9 (C-1'), 146.6 (C-3), 154.5 (carbonate C=O), 155.5 (C-4'), 156.6 (C-6), 157.4 (C-7a), 163.7 (2-CONH). $\nu_{max}$ (ATR)/$cm^{-1}$ 3413 (N-H amide), 3295 (N-H amine), 2955 (C-H aromatic), 2850 (C-H alkane), 1752 (C=O carbonyl), 1601 (C=O amide), 1507 (C=C aromatic), 1464 (-C-H bending), 1263 (C-N aromatic), 1106 (C-O ether), 1071 (C-N aliphatic). *m/z* ($ESI^+$): 416 ($MH^+$, 100%). HRMS ($ESI^+$) found ($MH^+$): 416.1265 $C_{20}H_{22}N_3O_5S$ requires 416.1275.

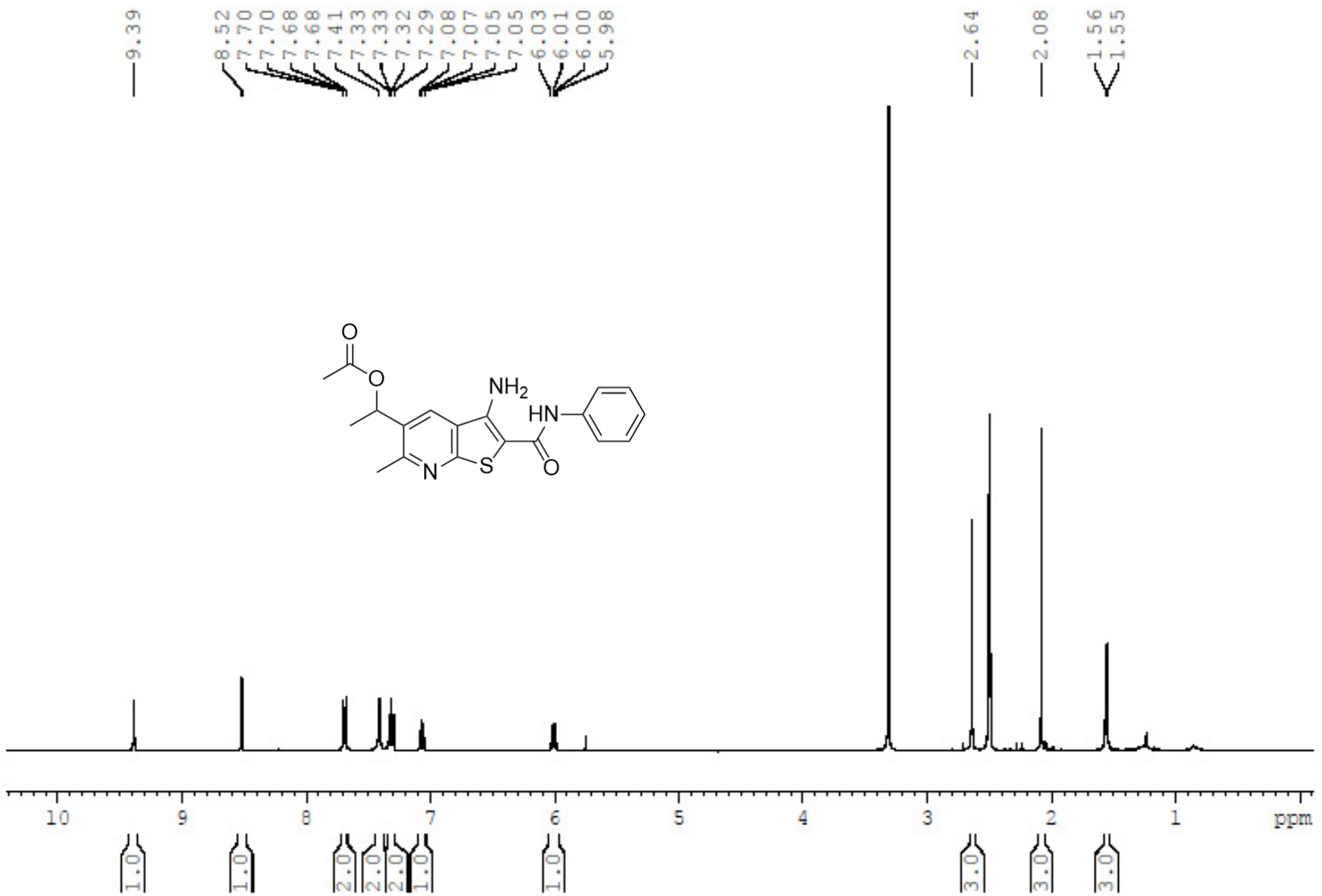



**Figure S1:** $^{1}$H NMR spectrum of **6a** (400 MHz; DMSO-*d*$_6$).

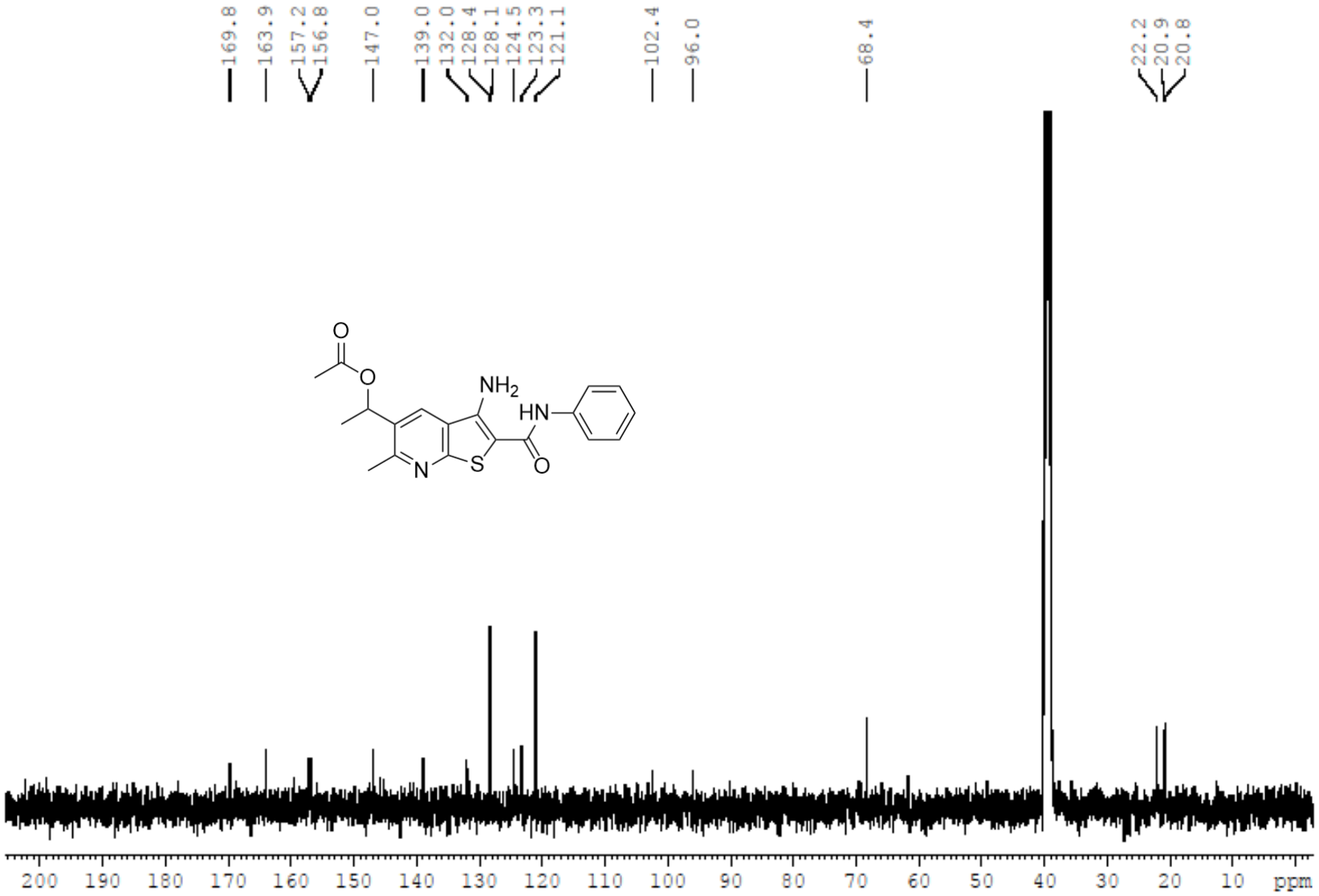



**Figure S2:** $^{13}$C NMR spectrum of **6a** (100 MHz; DMSO-*d*$_6$).

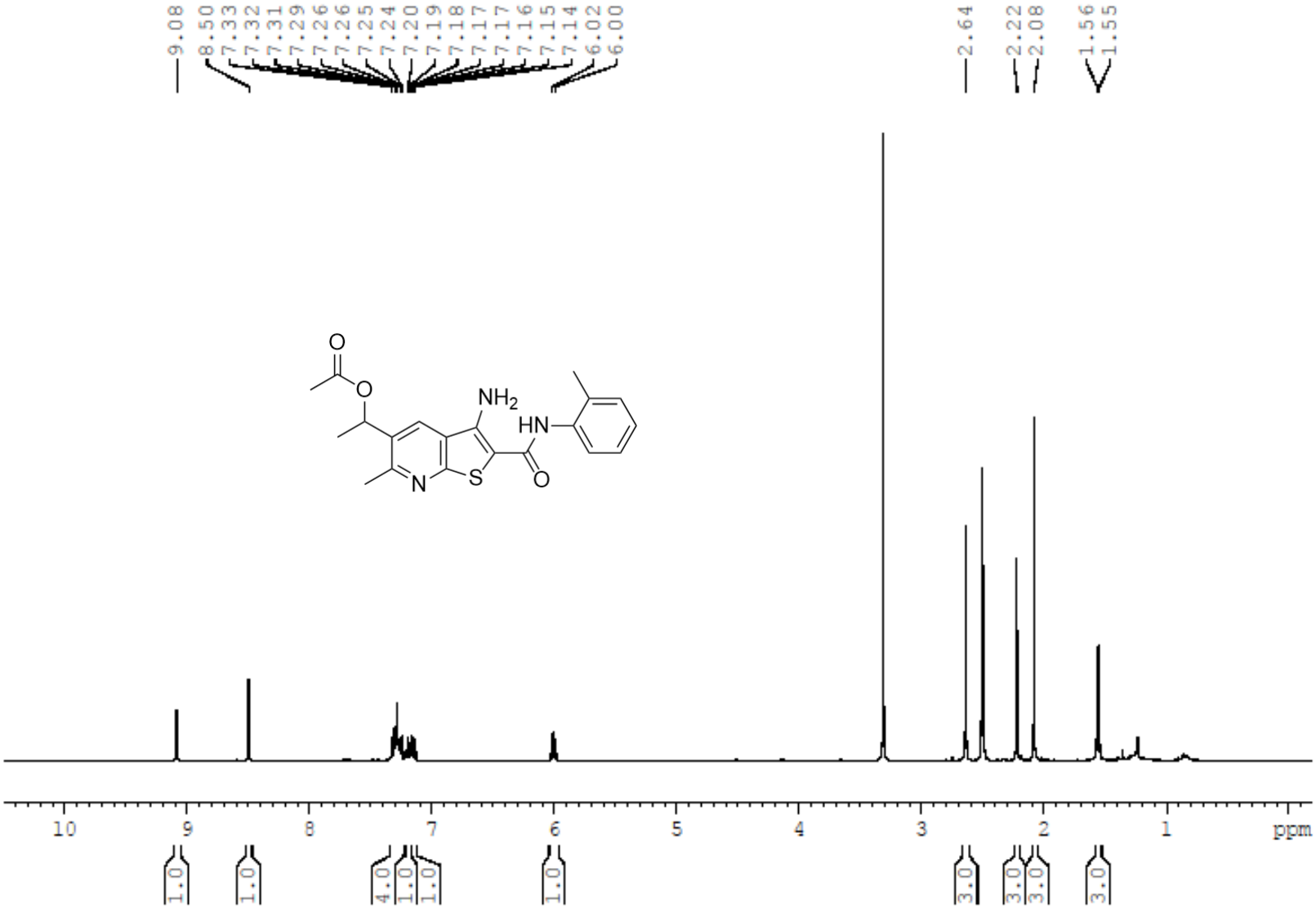



**Figure S3:** $^{1}$H NMR spectrum of **6b** (400 MHz; DMSO-*d*$_6$).

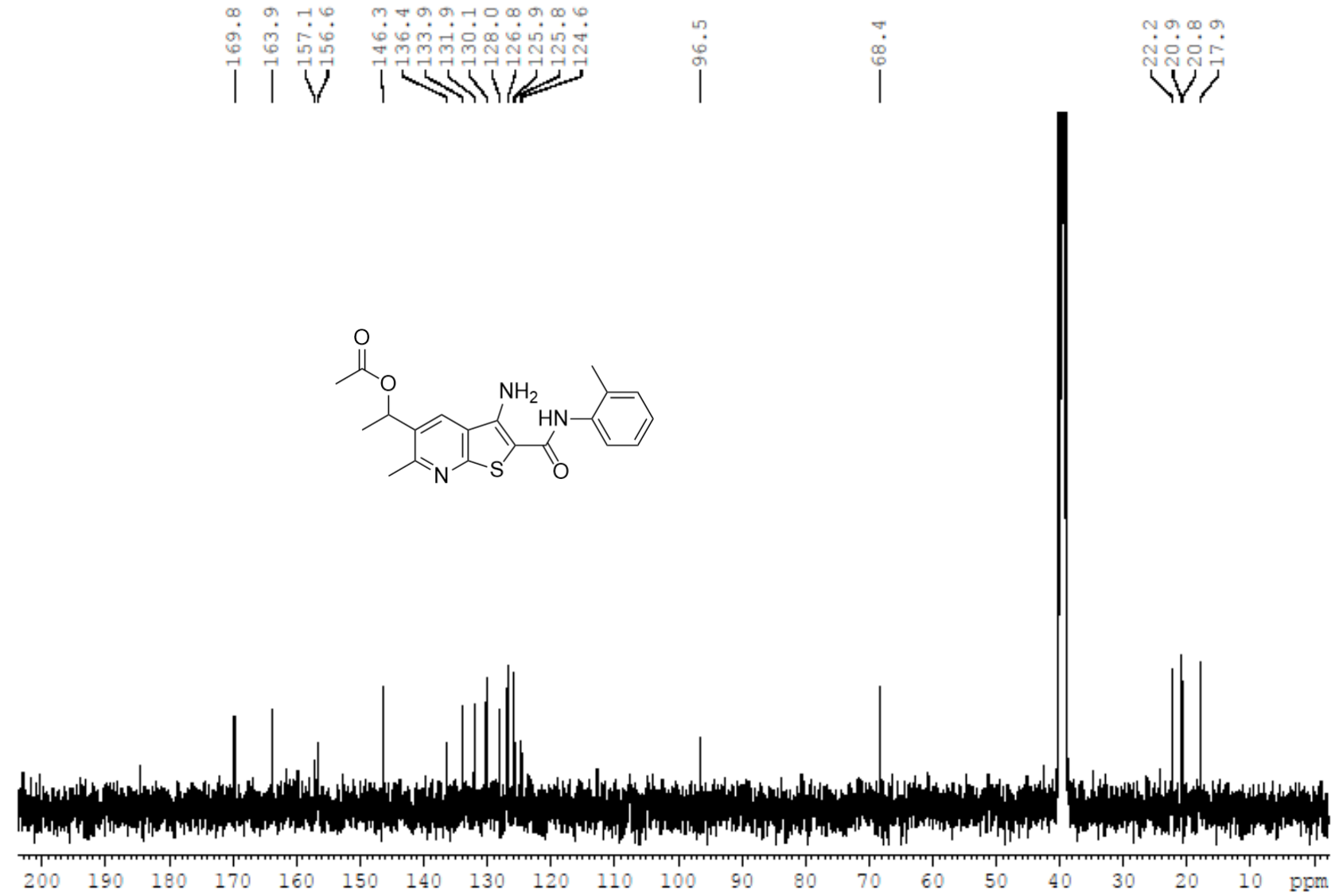



**Figure S4:** $^{13}$C NMR spectrum of **6b** (100 MHz; DMSO-*d*$_6$).

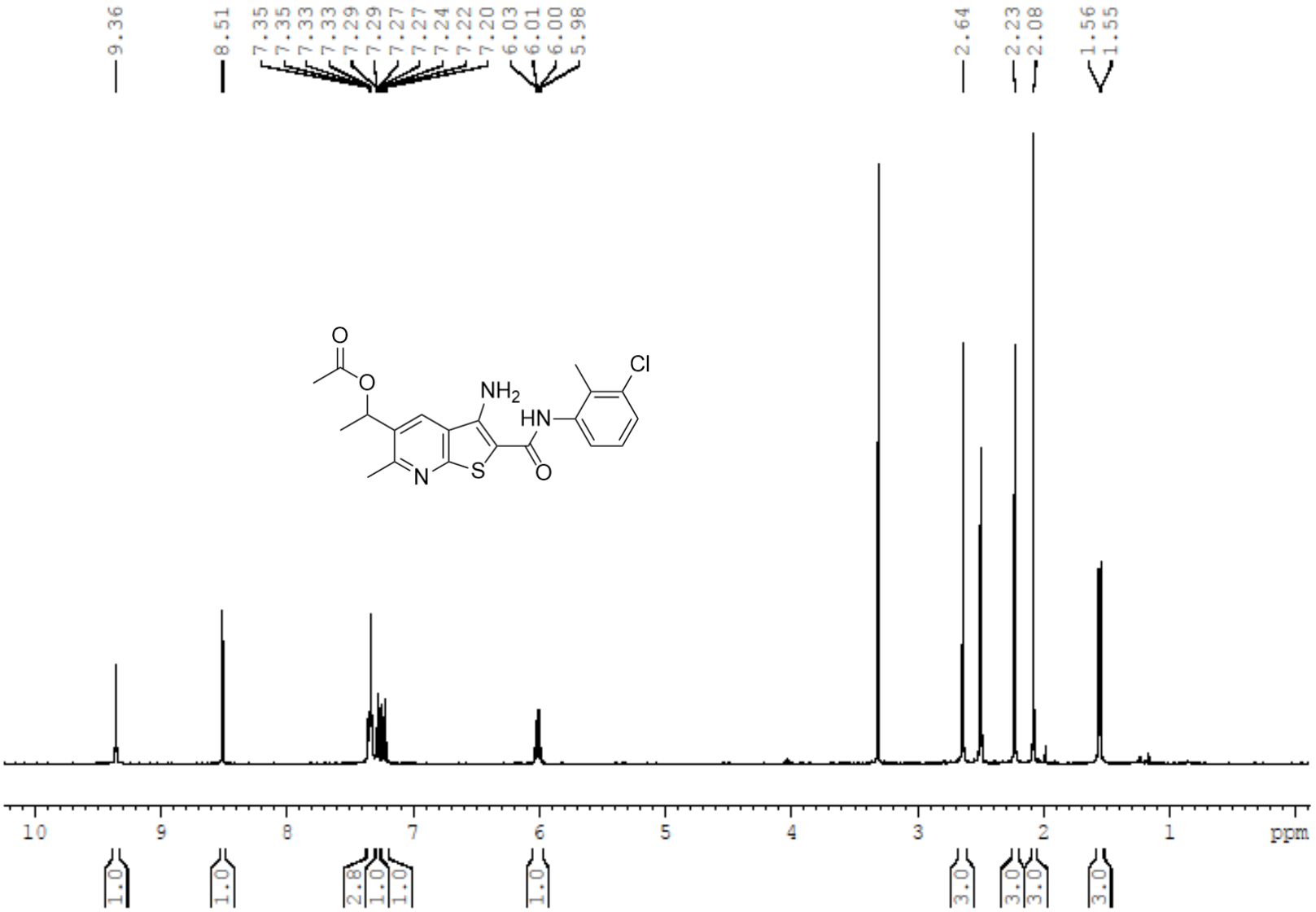



**Figure S5:** $^{1}$H NMR spectrum of **6c** (400 MHz; DMSO-*d*$_6$).

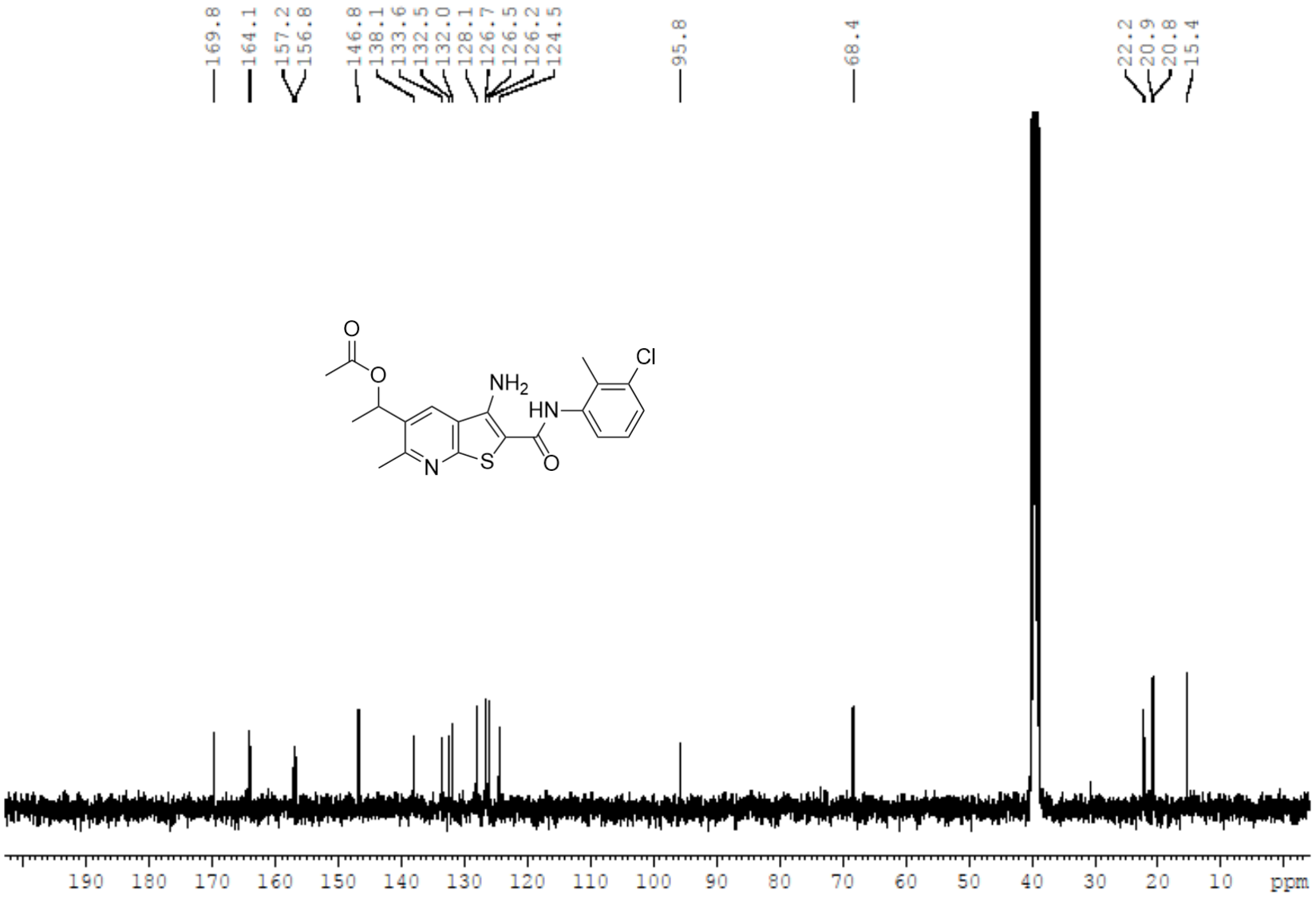



**Figure S6:** $^{13}$C NMR spectrum of **6c** (100 MHz; DMSO-*d*$_6$).

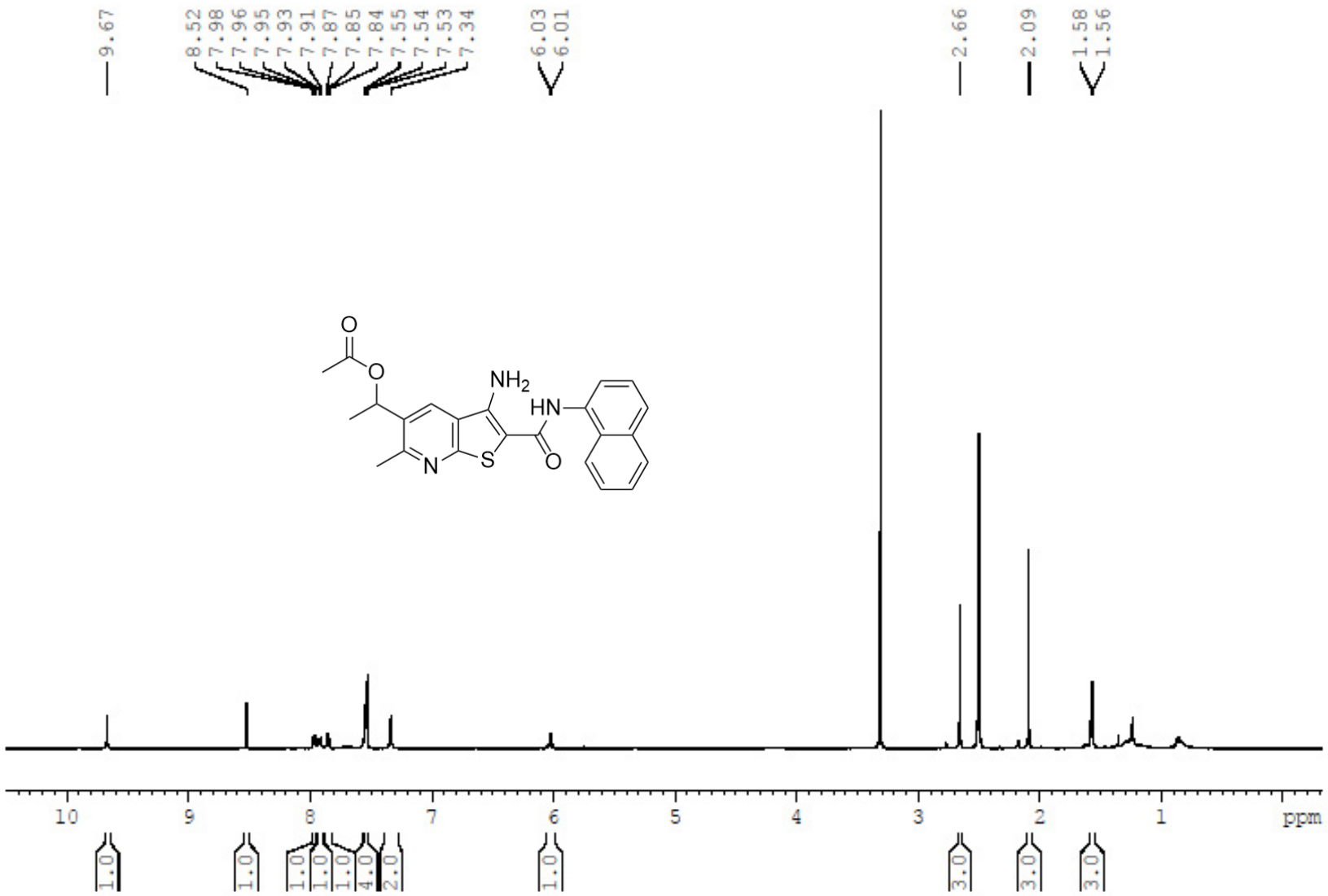



**Figure S7:** $^{1}$H NMR spectrum of **6d** (400 MHz; DMSO-*d*$_6$).

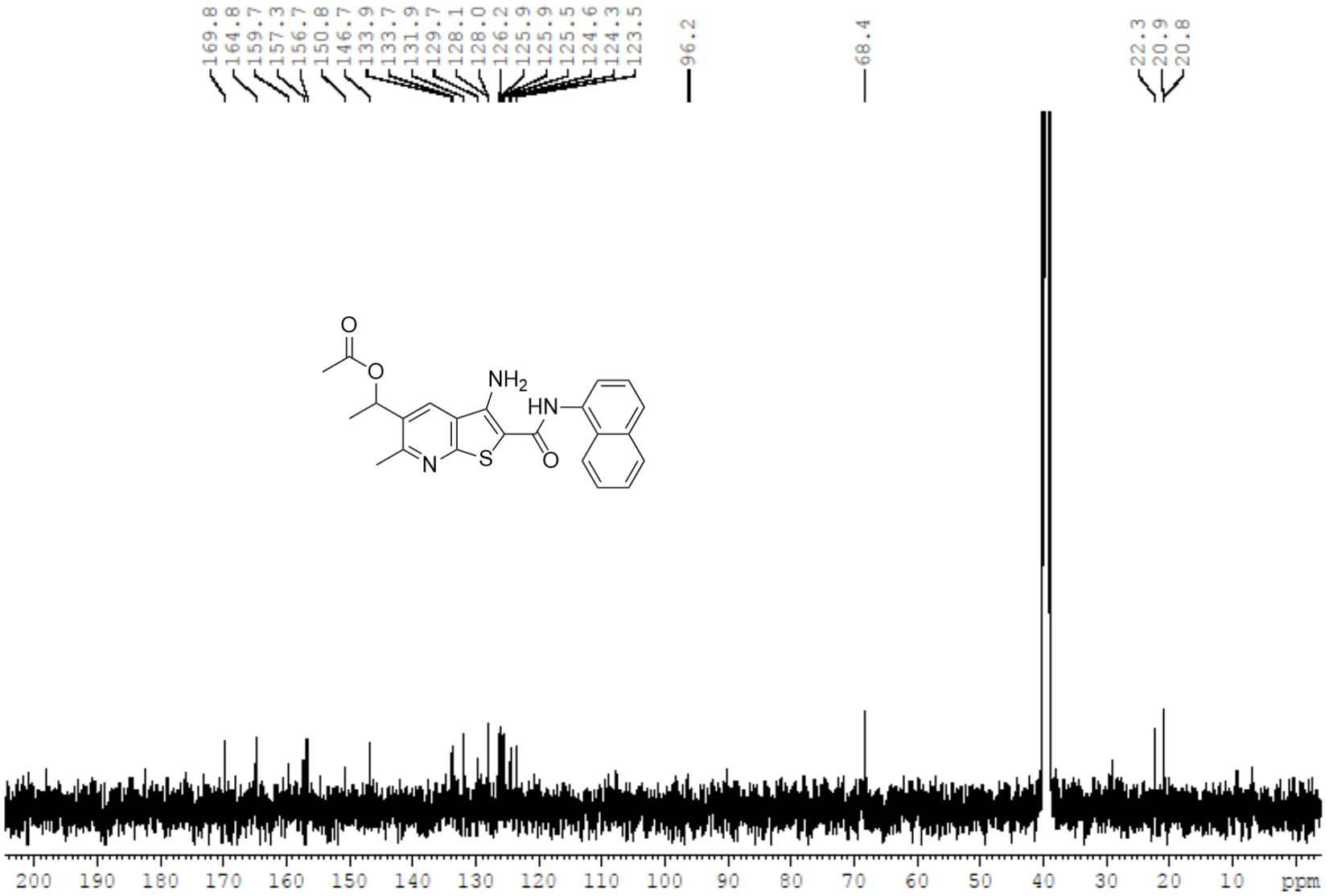



**Figure S8:** $^{13}$C NMR spectrum of **6d** (100 MHz; DMSO-$d_6$).

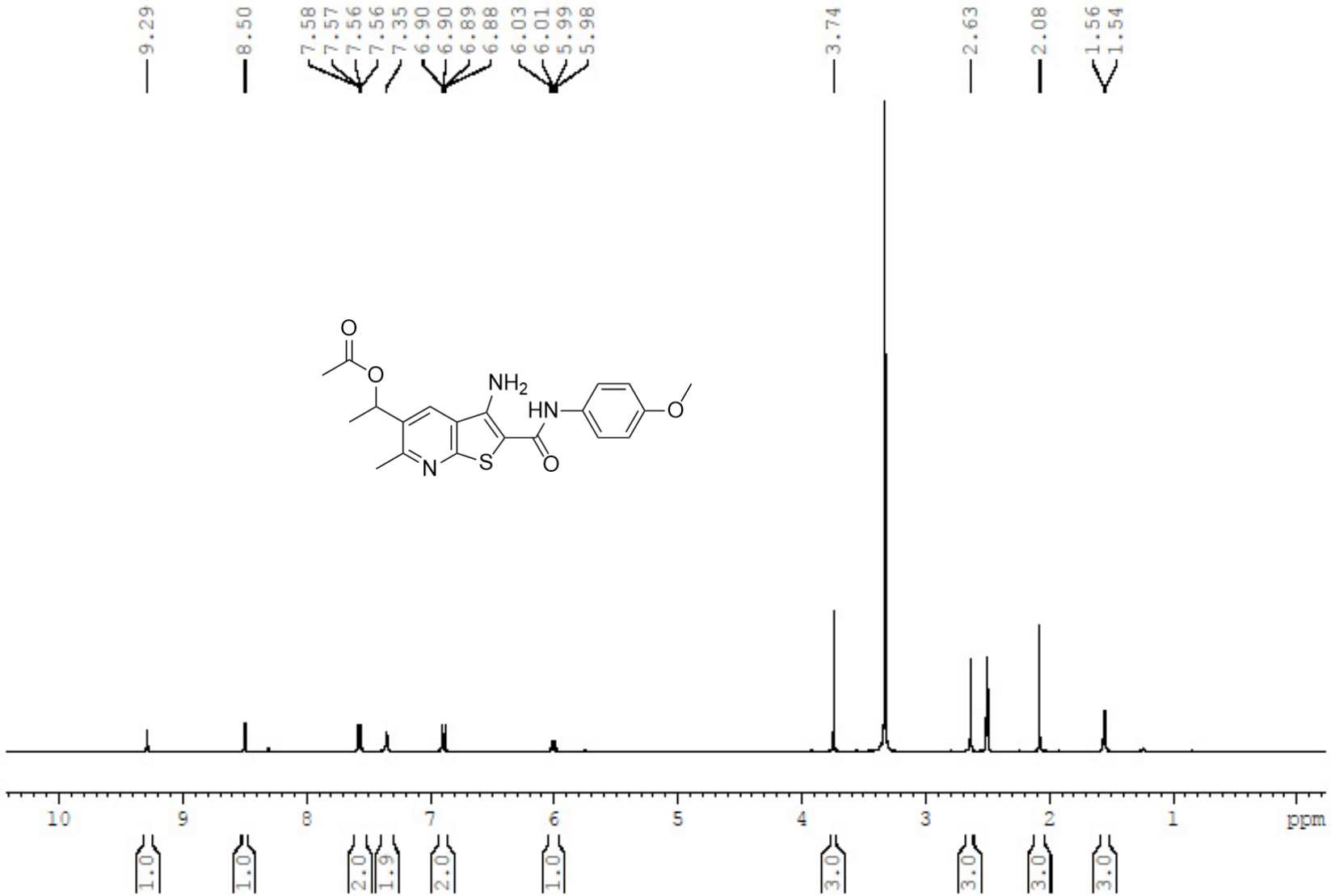



**Figure S9:** $^{1}$H NMR spectrum of **6e** (400 MHz; DMSO-$d_6$).

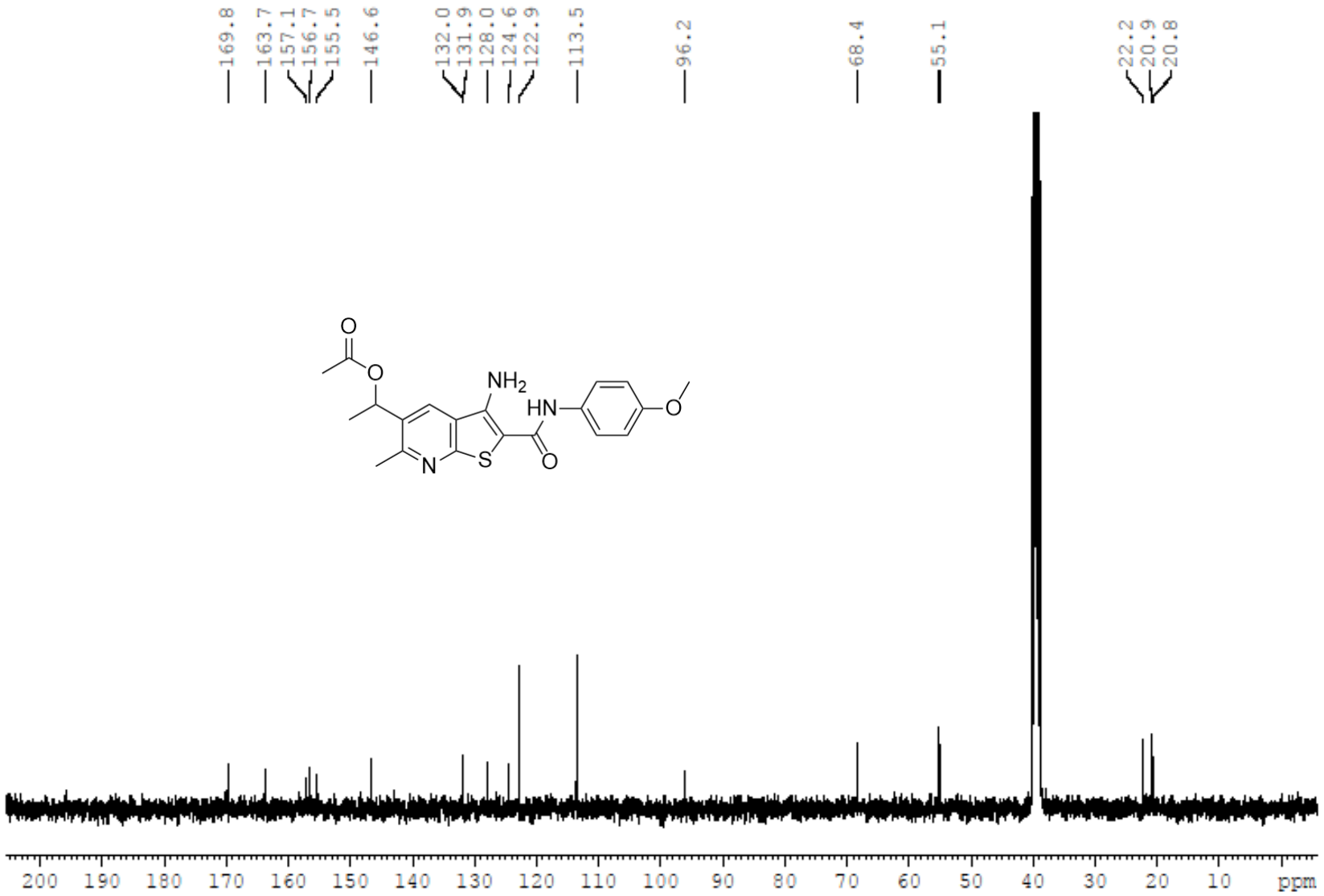



**Figure S10:** $^{13}$C NMR spectrum of **6e** (100 MHz; DMSO-*d*$_6$).

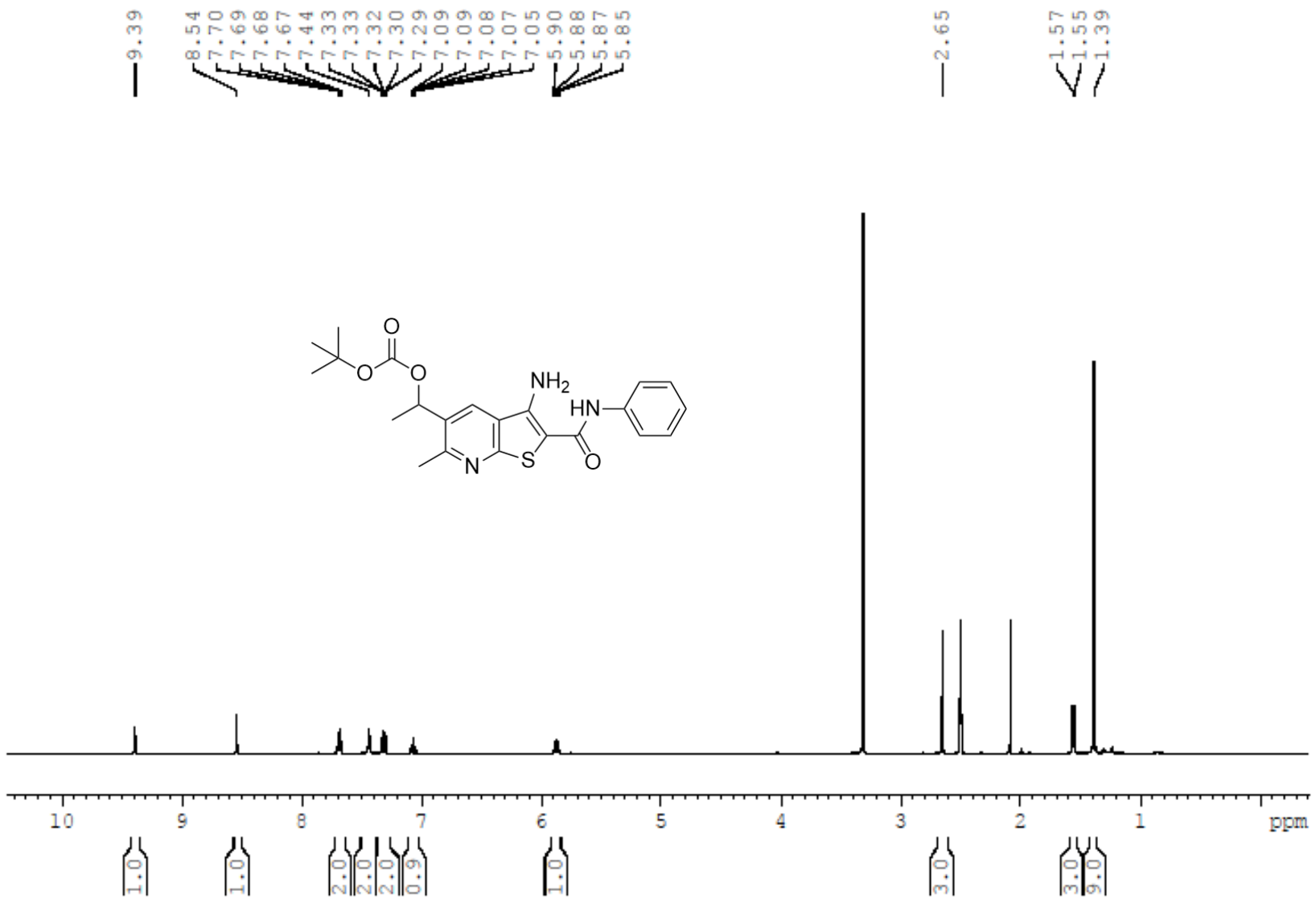



**Figure S11:** $^{1}$H NMR spectrum of **7a** (400 MHz; DMSO-*d*$_6$).

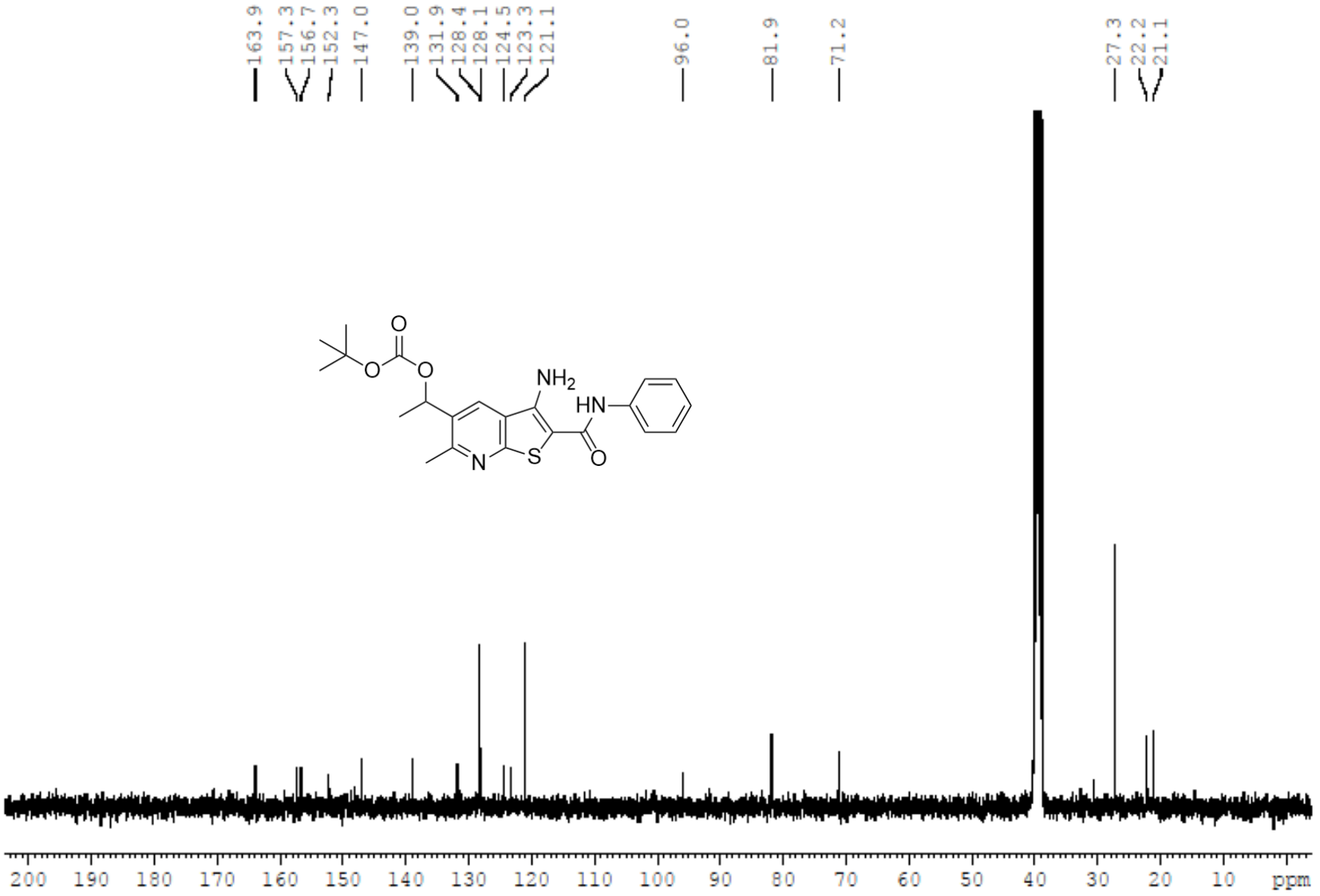



**Figure S12:** $^{13}$C NMR spectrum of **7a** (100 MHz; DMSO-*d*$_6$).

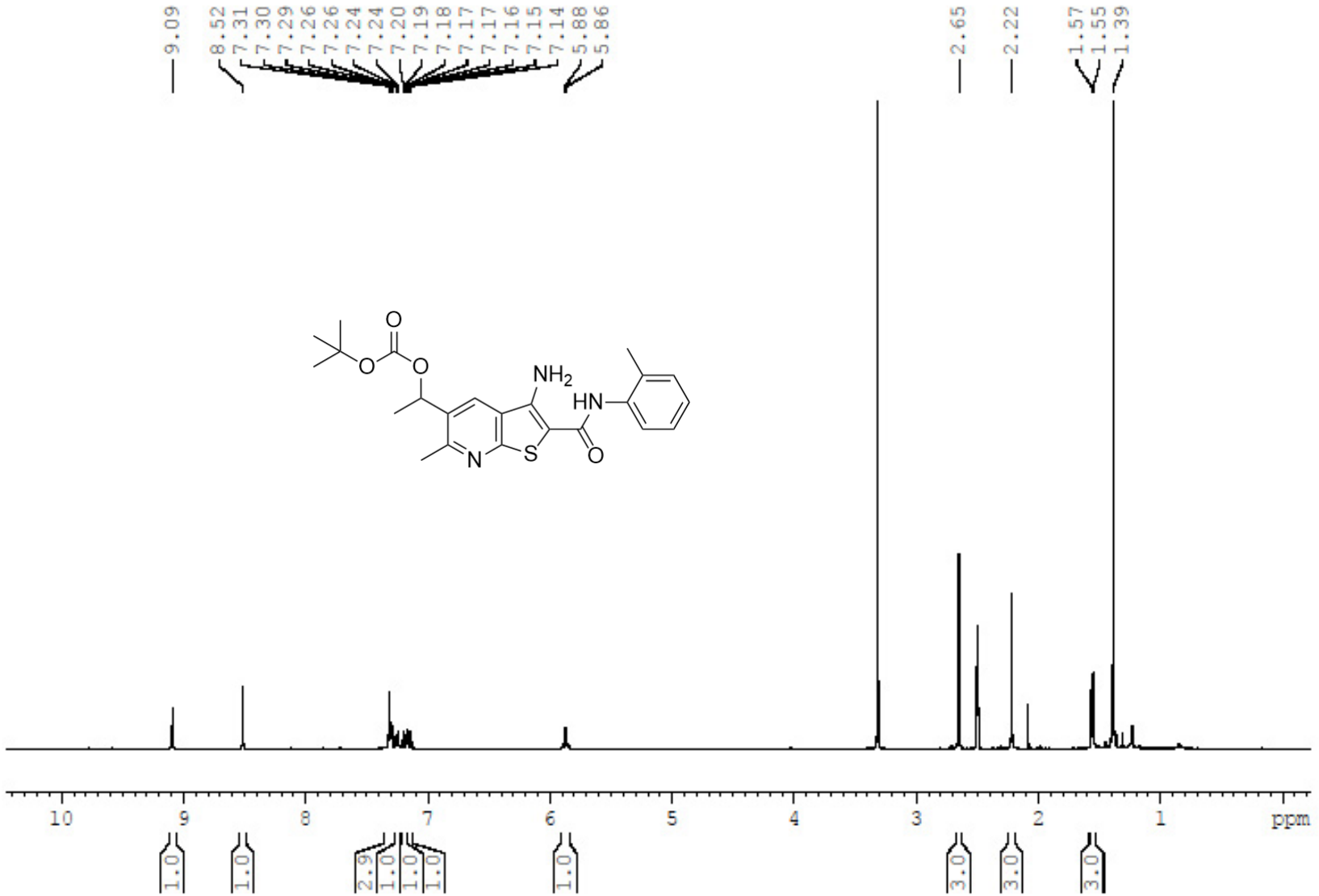



**Figure S13:** [1]H NMR spectrum of **7b** (400 MHz; DMSO-$d_6$).

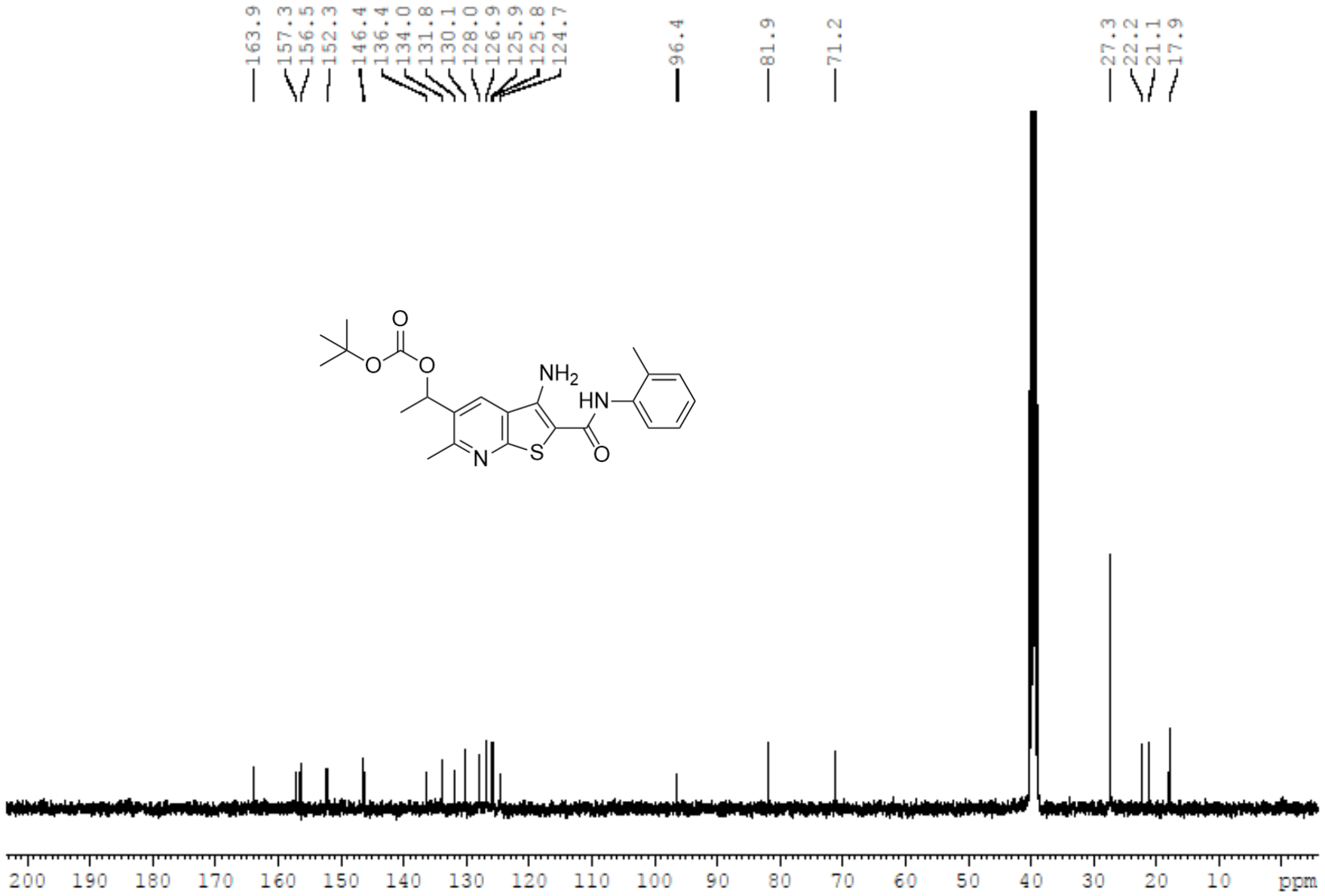



**Figure S14:** $^{13}$C NMR spectrum of **7b** (100 MHz; DMSO-*d*$_6$).

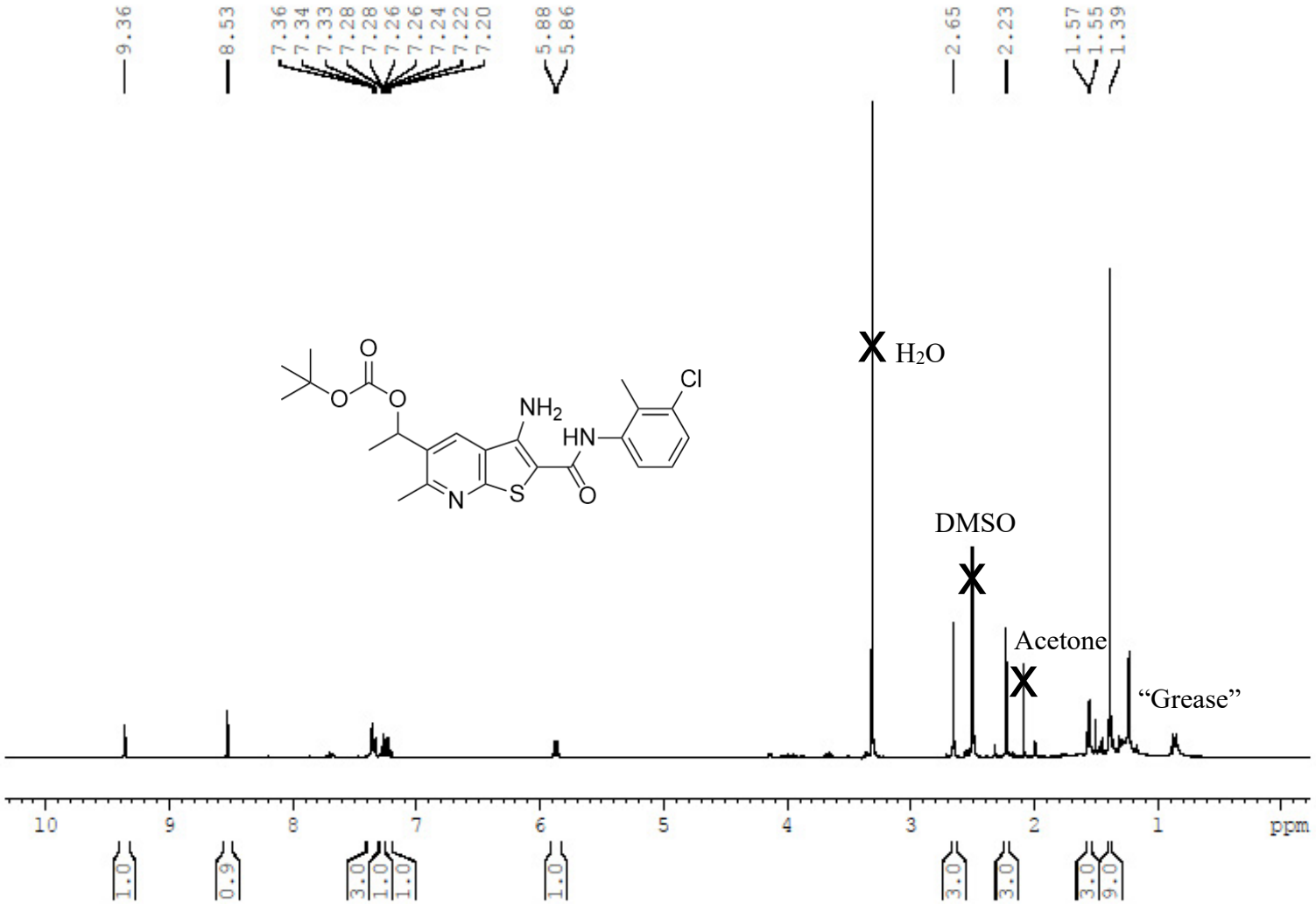



**Figure S15:** [1]H NMR spectrum of **7c** (400 MHz; DMSO-*d*$_6$).

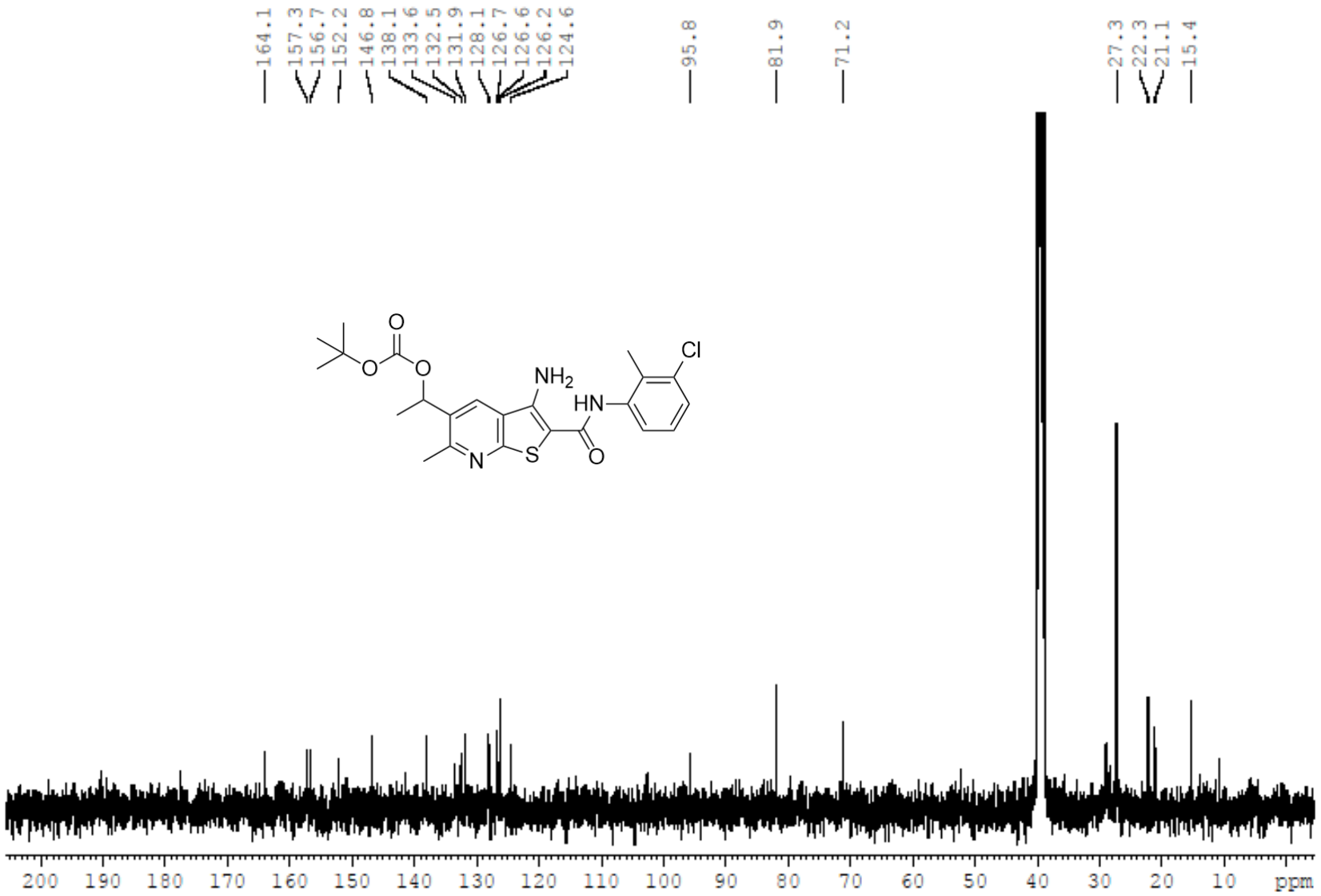



**Figure S16:** $^{13}$C NMR spectrum of **7c** (100 MHz; DMSO-*d*$_6$).

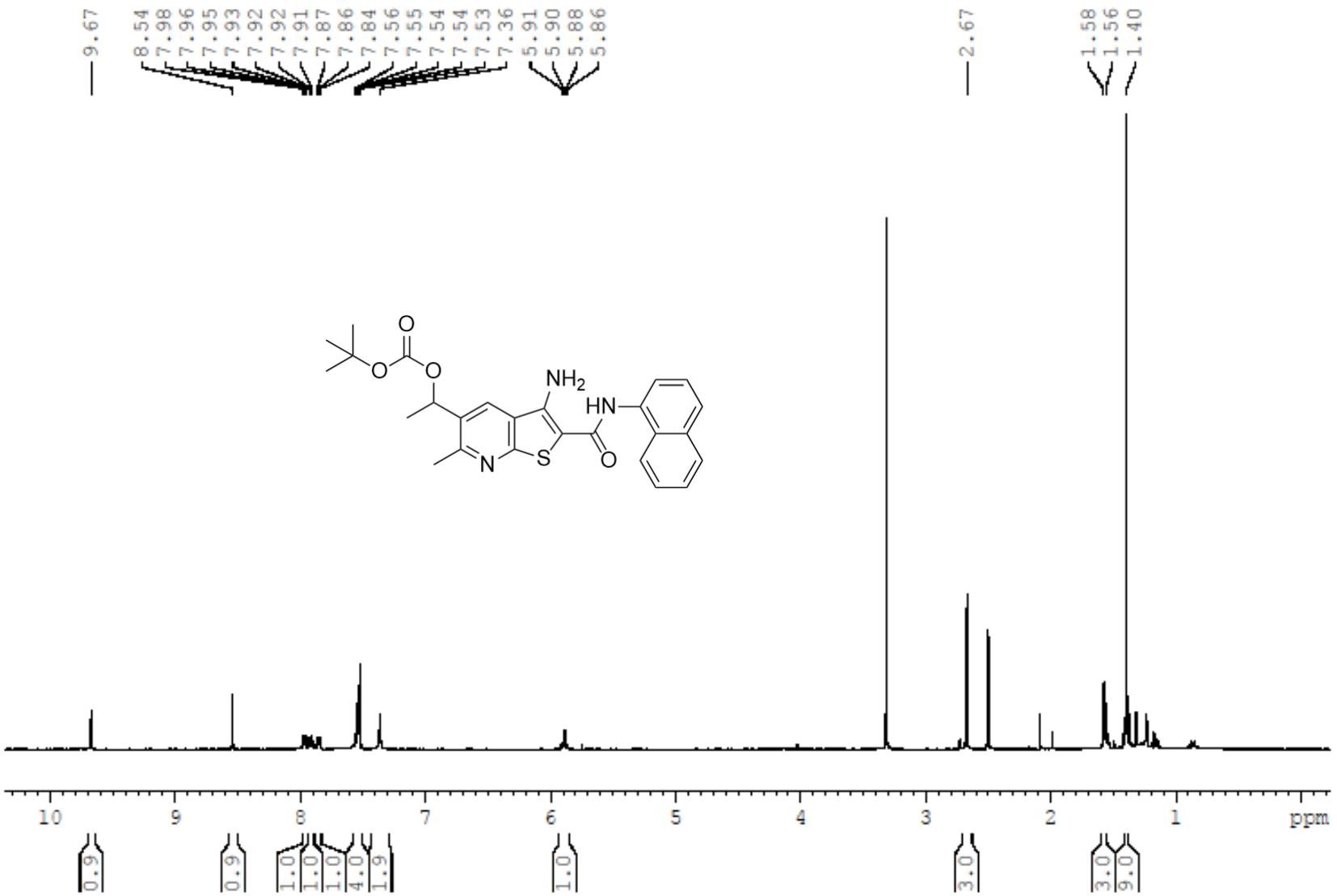



**Figure S17:** $^{1}$H NMR spectrum of **7d** (400 MHz; DMSO-*d*$_6$).

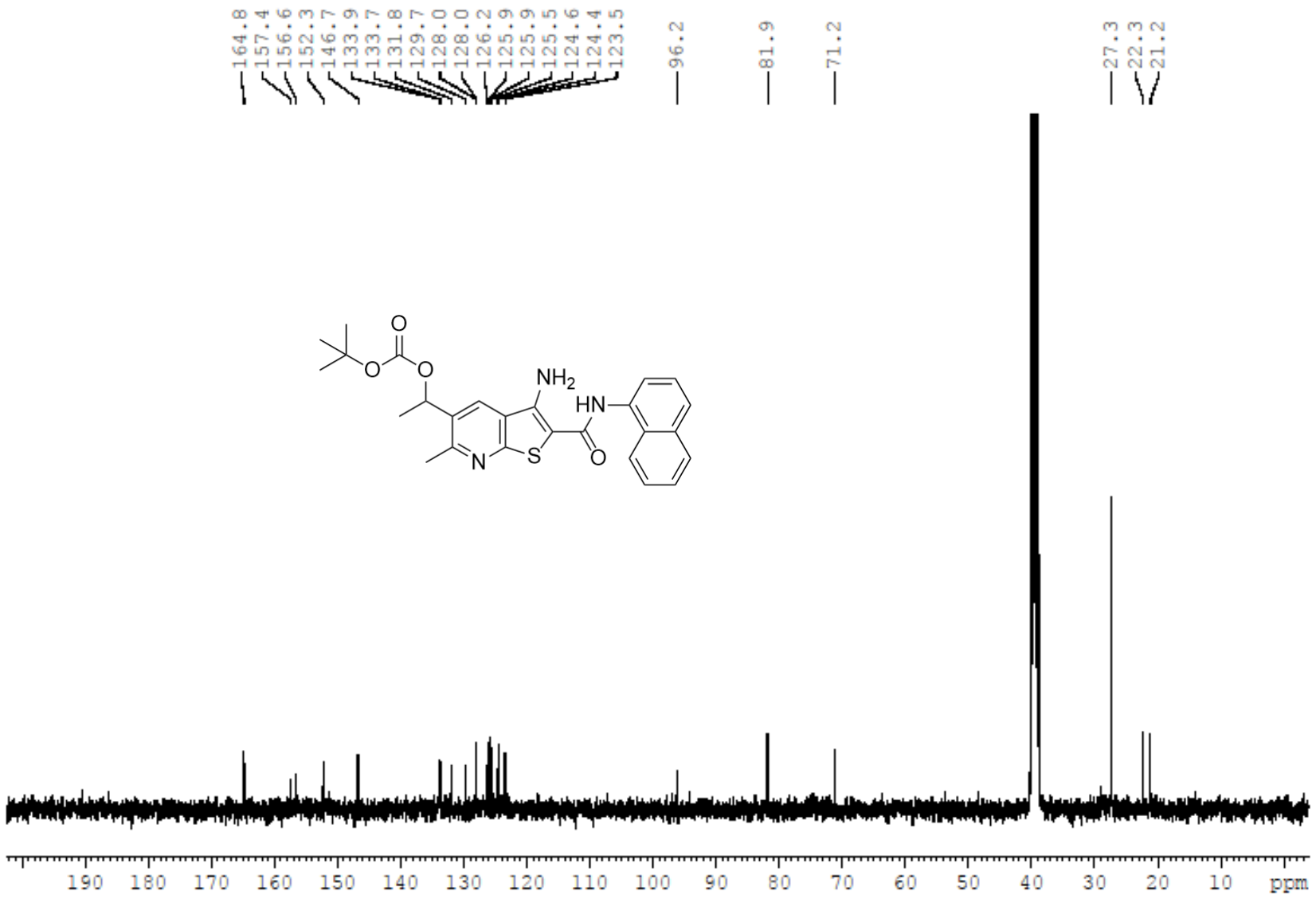



**Figure S18:** $^{13}$C NMR spectrum of **7d** (100 MHz; DMSO-*d*$_6$).

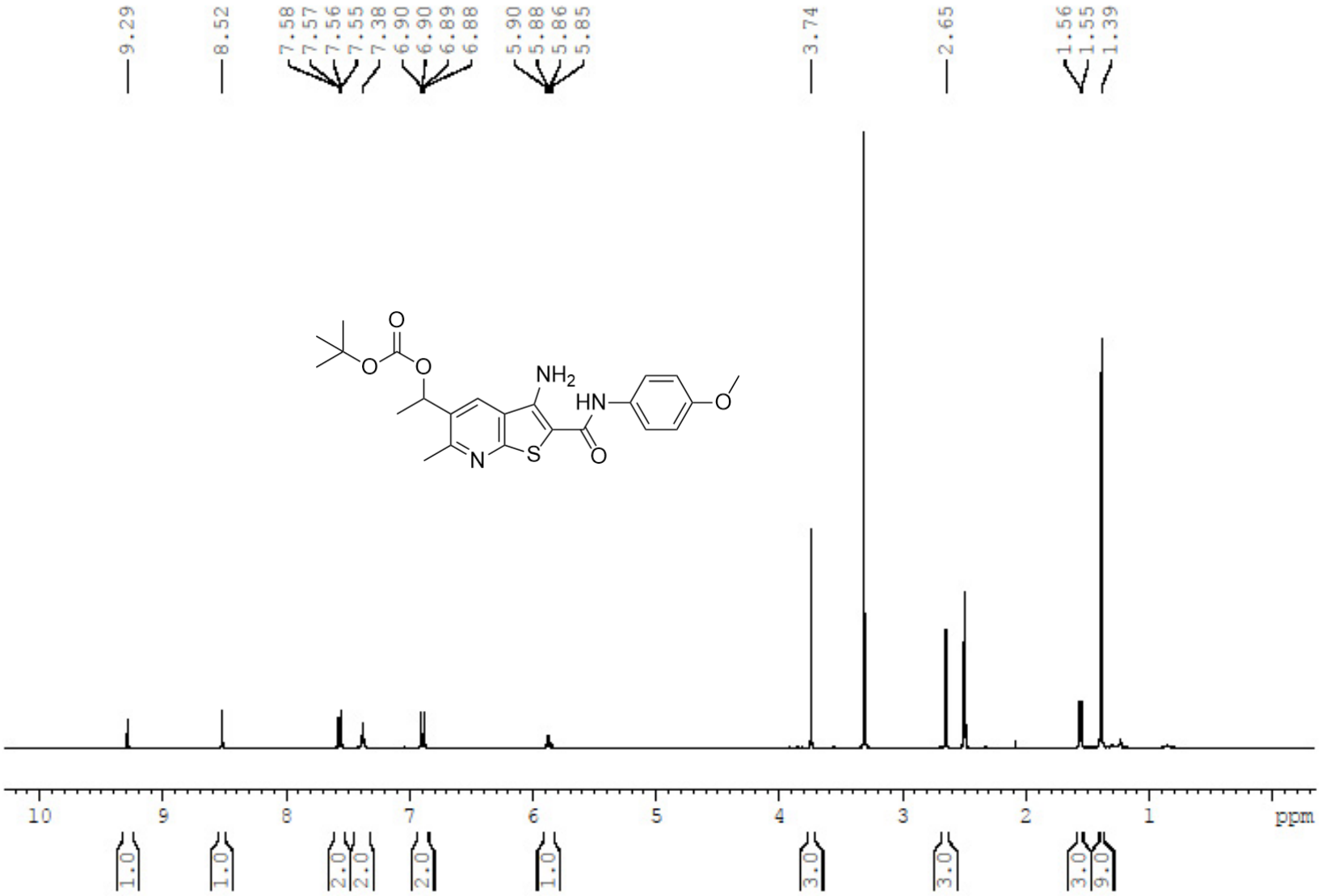



**Figure S19:** $^{1}$H NMR spectrum of **7e** (400 MHz; DMSO-*d*$_6$).

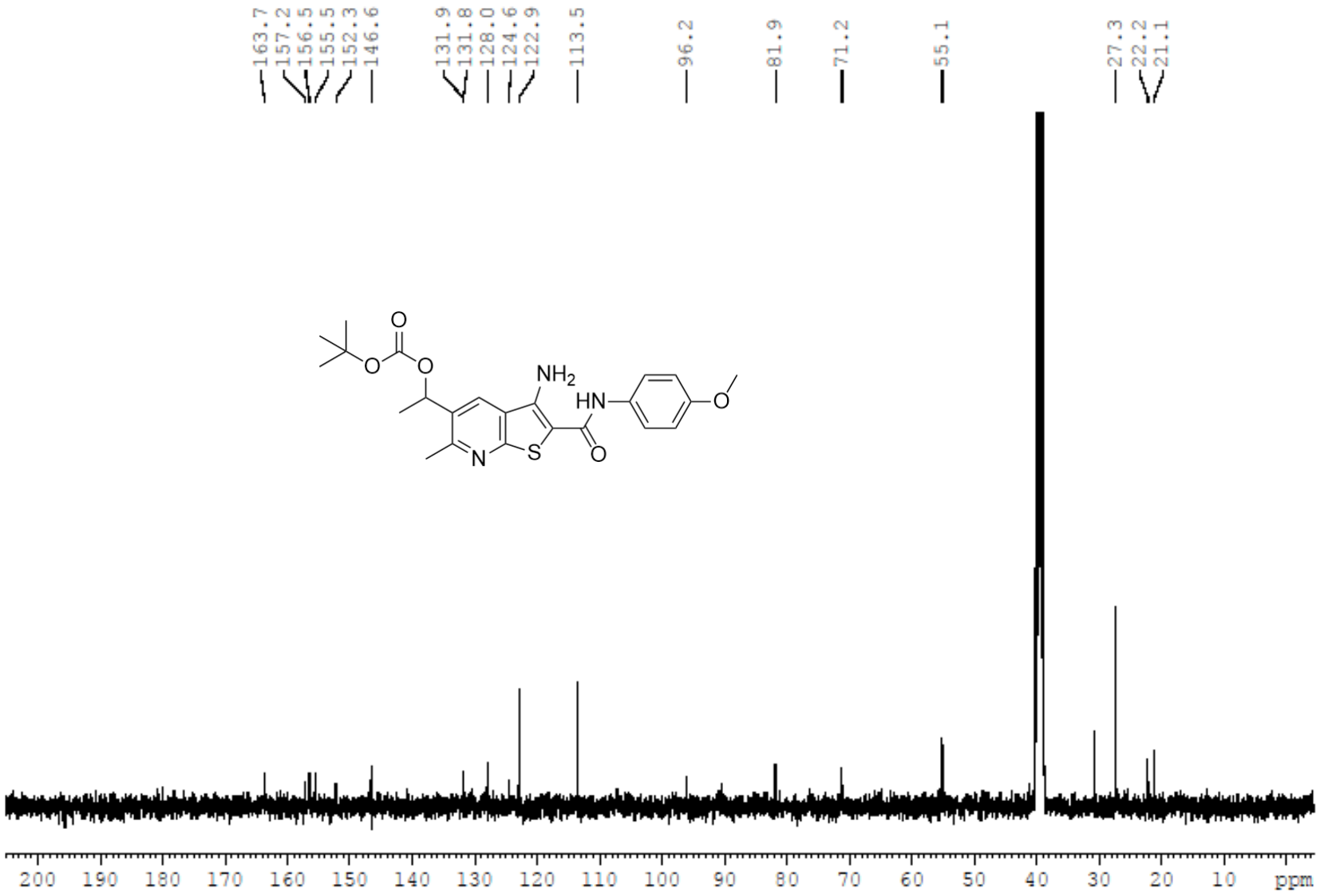



**Figure S20:** $^{13}$C NMR spectrum of **7e** (100 MHz; DMSO-*d*$_6$).

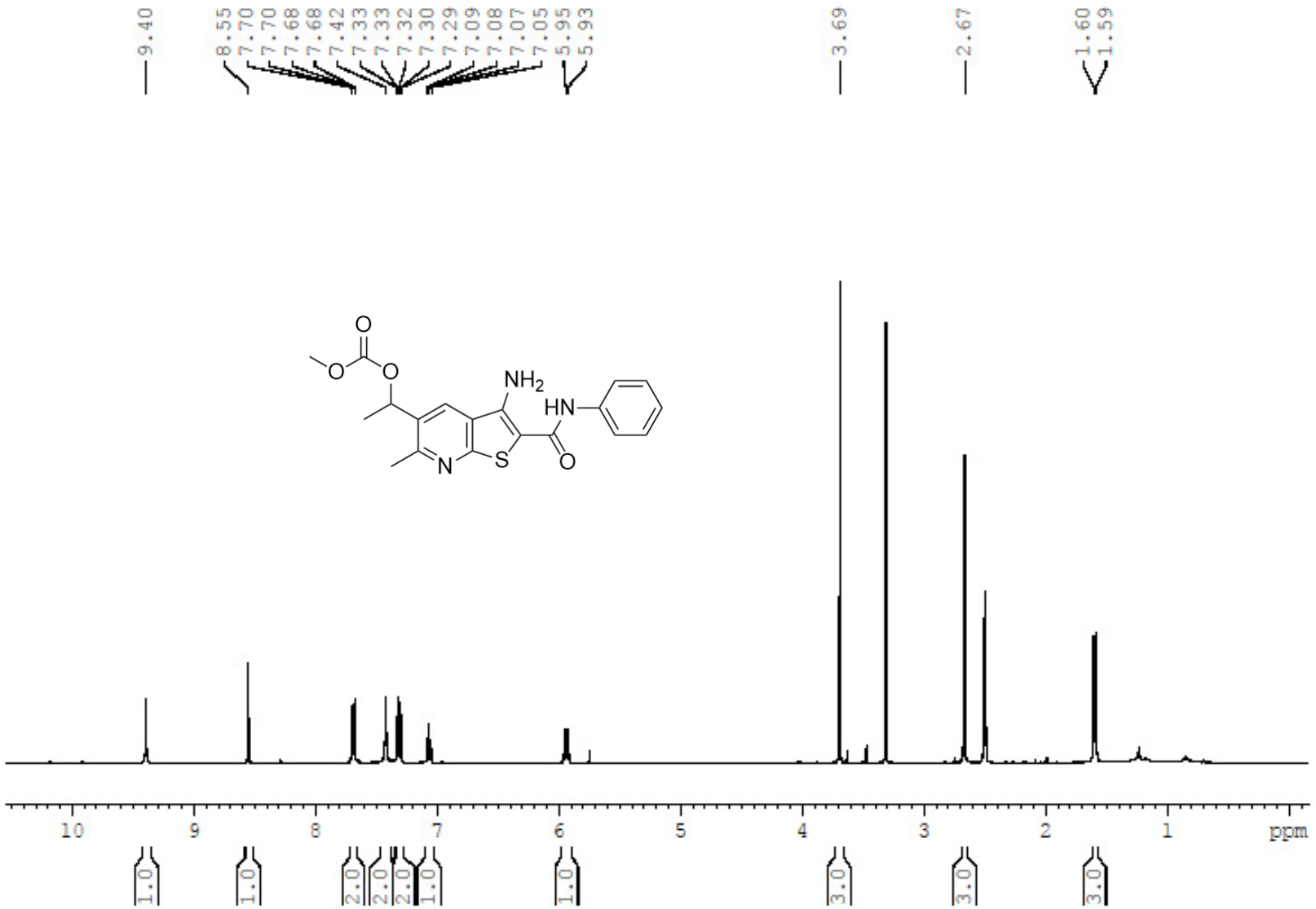



**Figure S21:** $^{1}$H NMR spectrum of **8a** (400 MHz; DMSO-$d_6$).

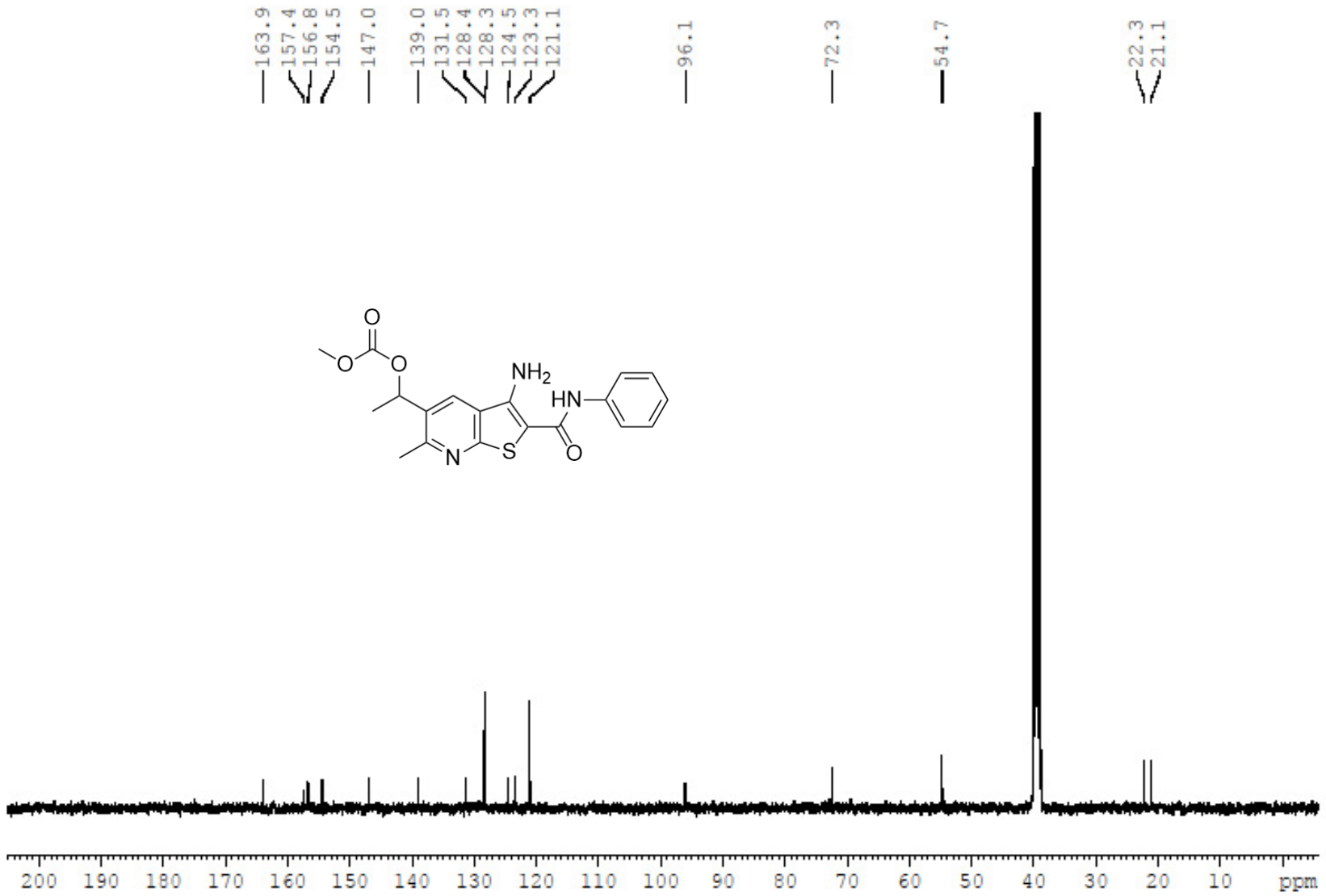



**Figure S22:** $^{13}$C NMR spectrum of **8a** (100 MHz; DMSO-$d_6$).

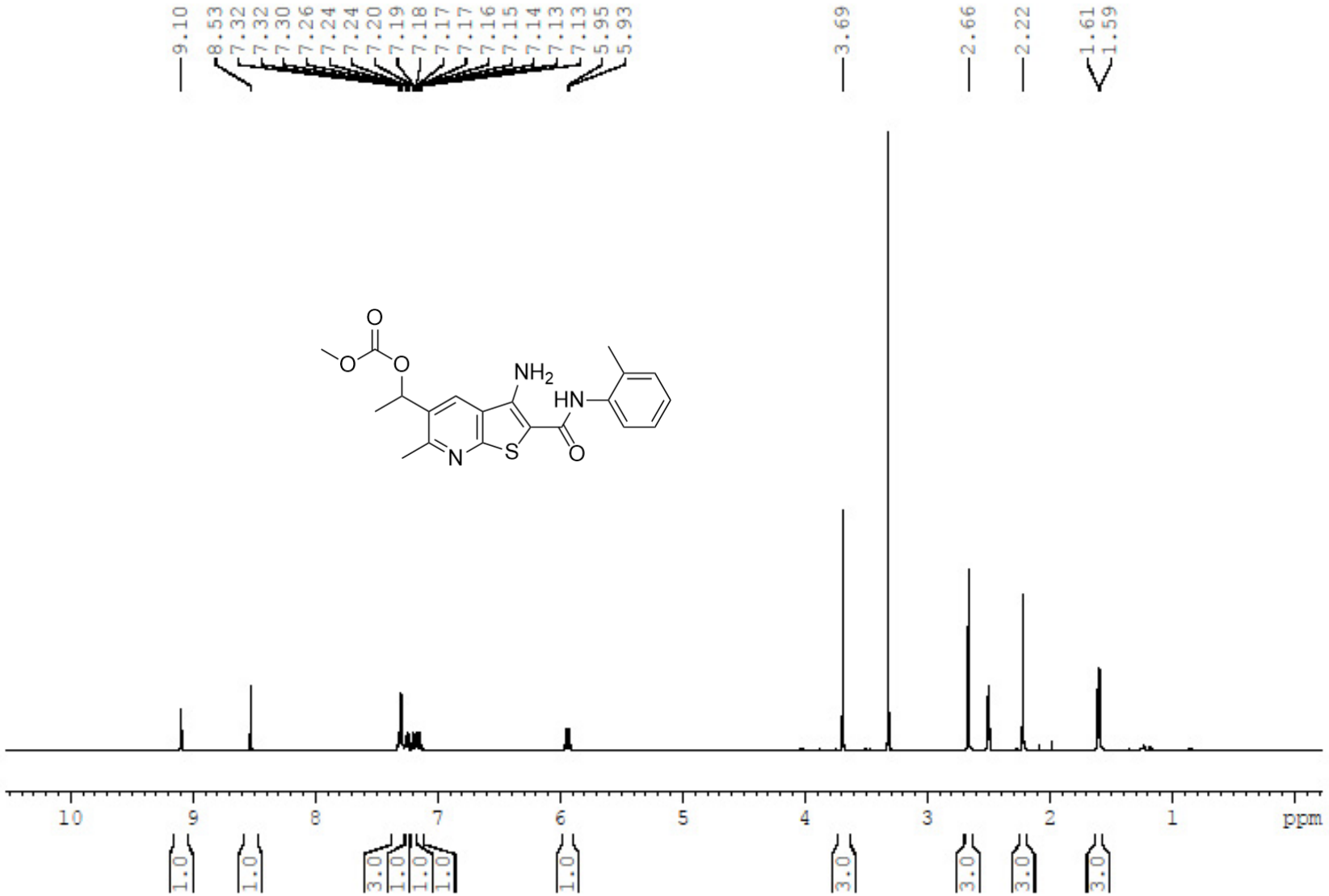



**Figure S23:** $^{1}$H NMR spectrum of **8b** (400 MHz; DMSO-*d*$_6$).

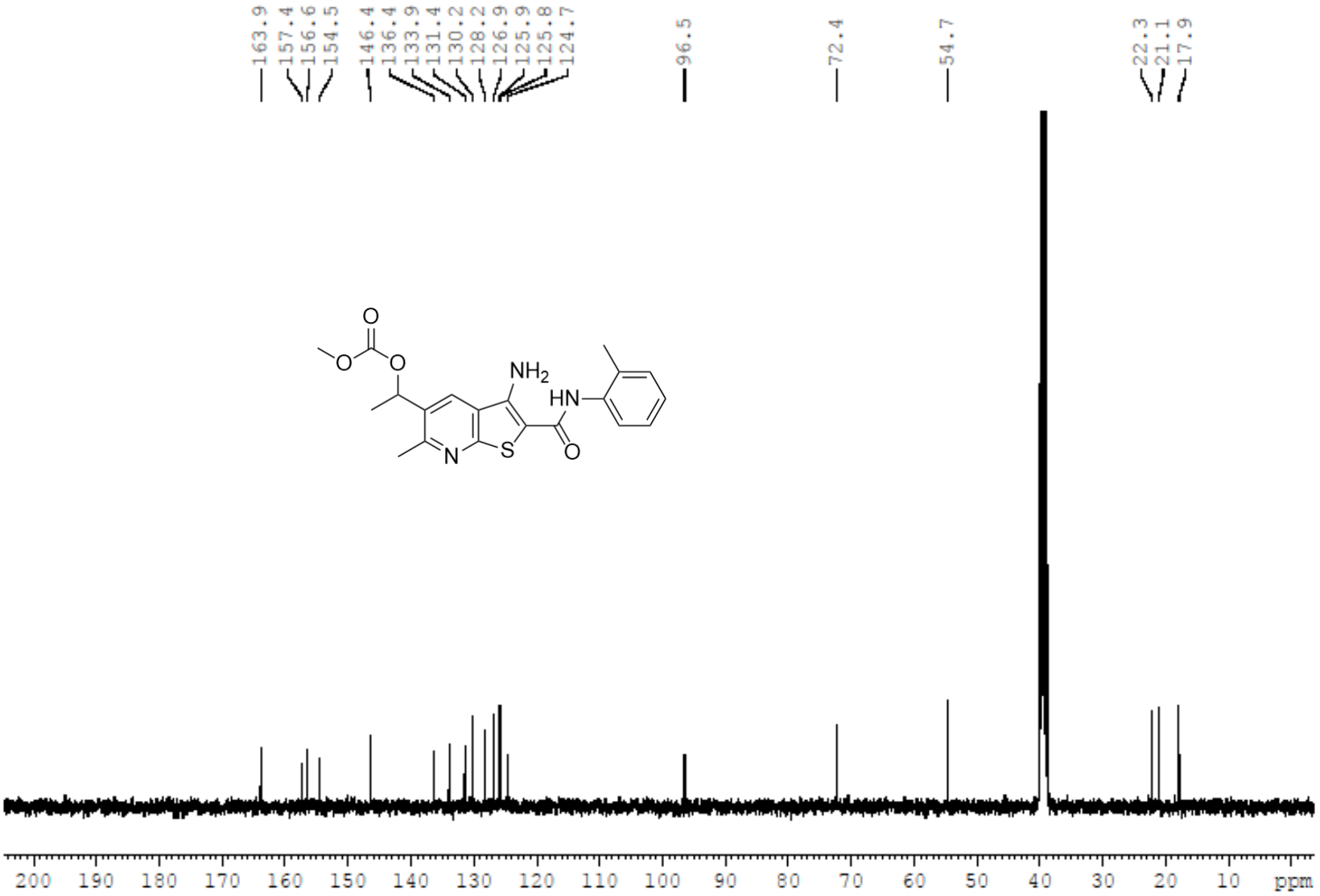



**Figure S24:** $^{13}$C NMR spectrum of **8b** (100 MHz; DMSO-*d*$_6$).

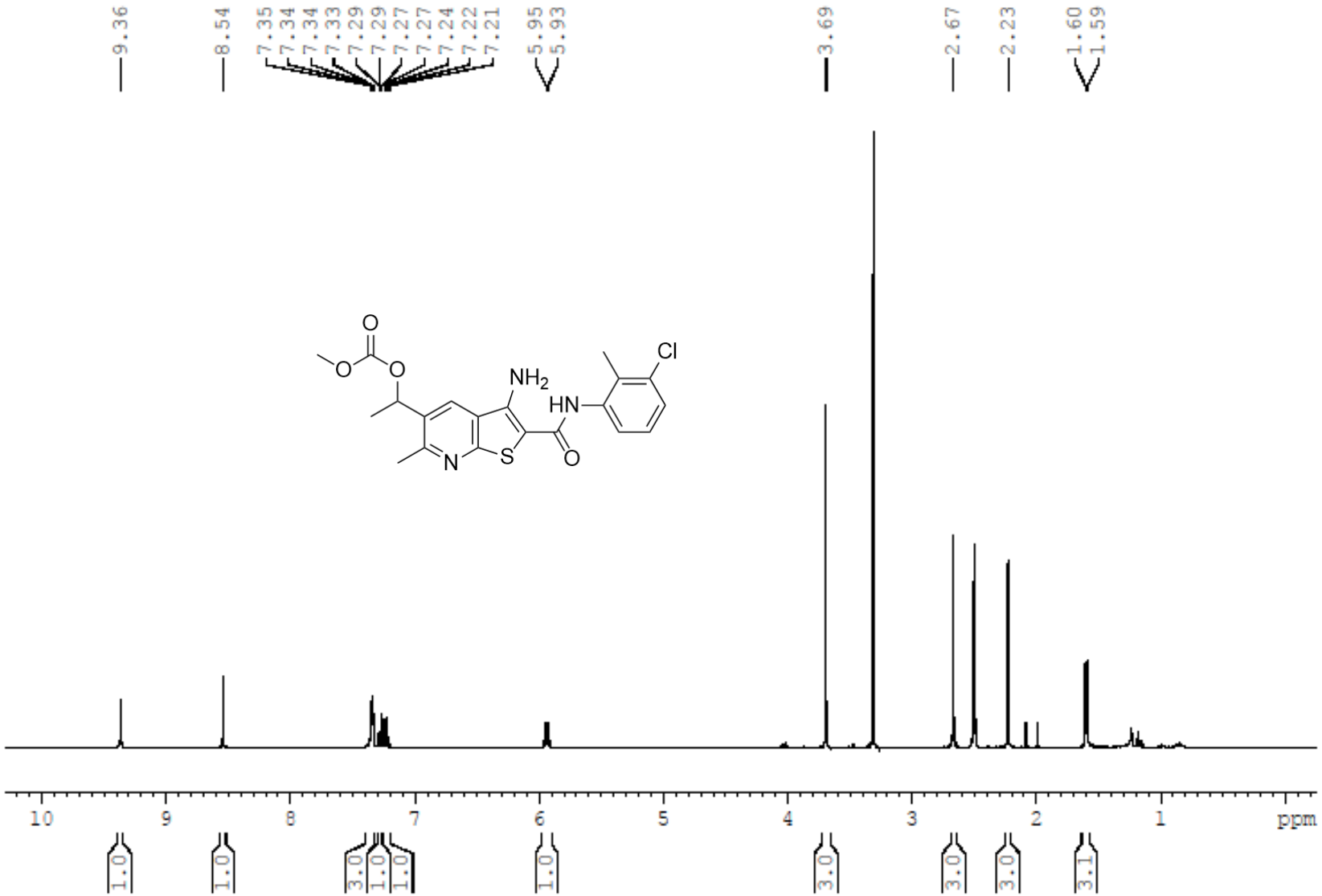



**Figure S25:** $^{1}$H NMR spectrum of **8c** (400 MHz; DMSO-*d*$_6$).

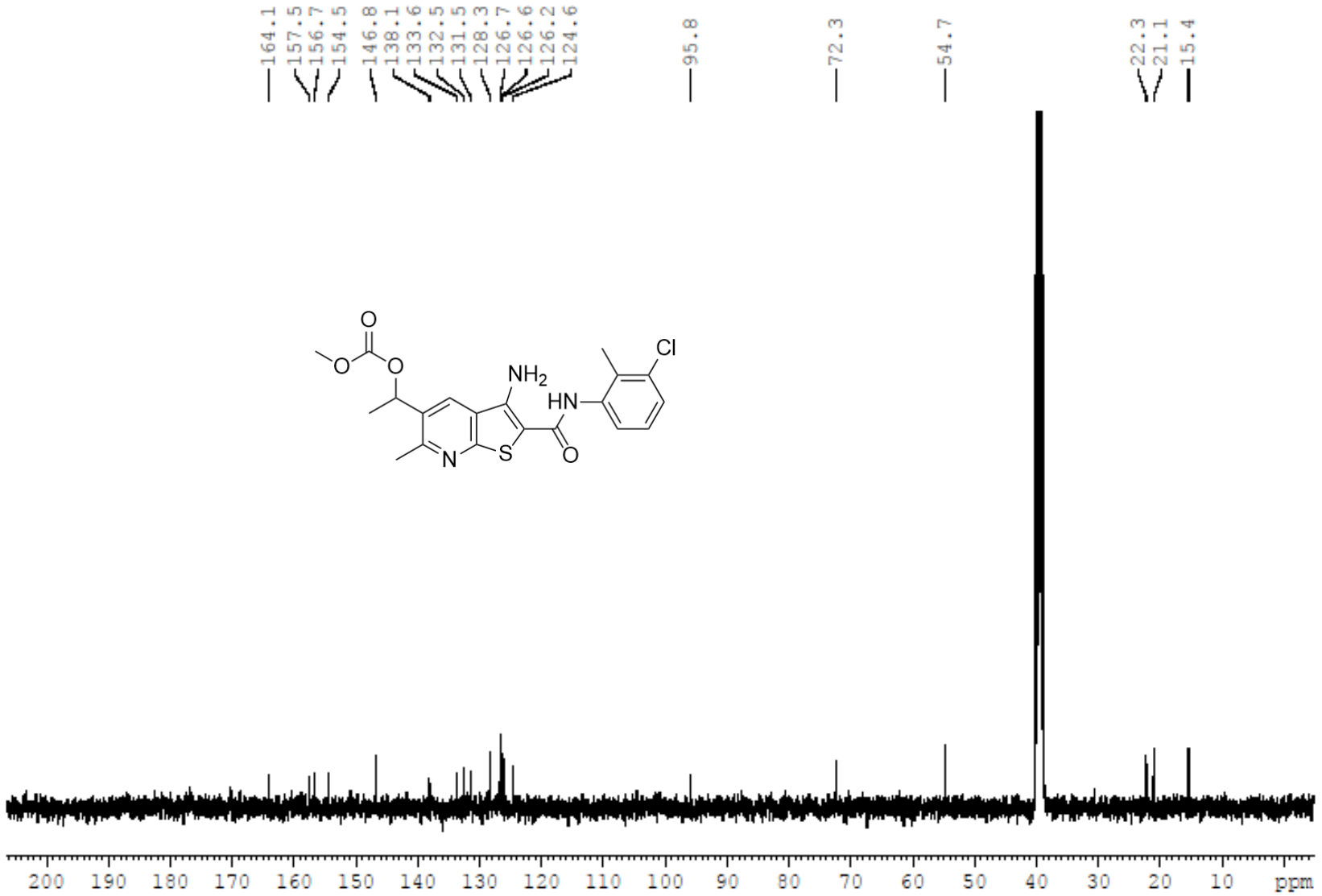



**Figure S26:** $^{13}$C NMR spectrum of **8c** (100 MHz; DMSO-*d*$_6$).

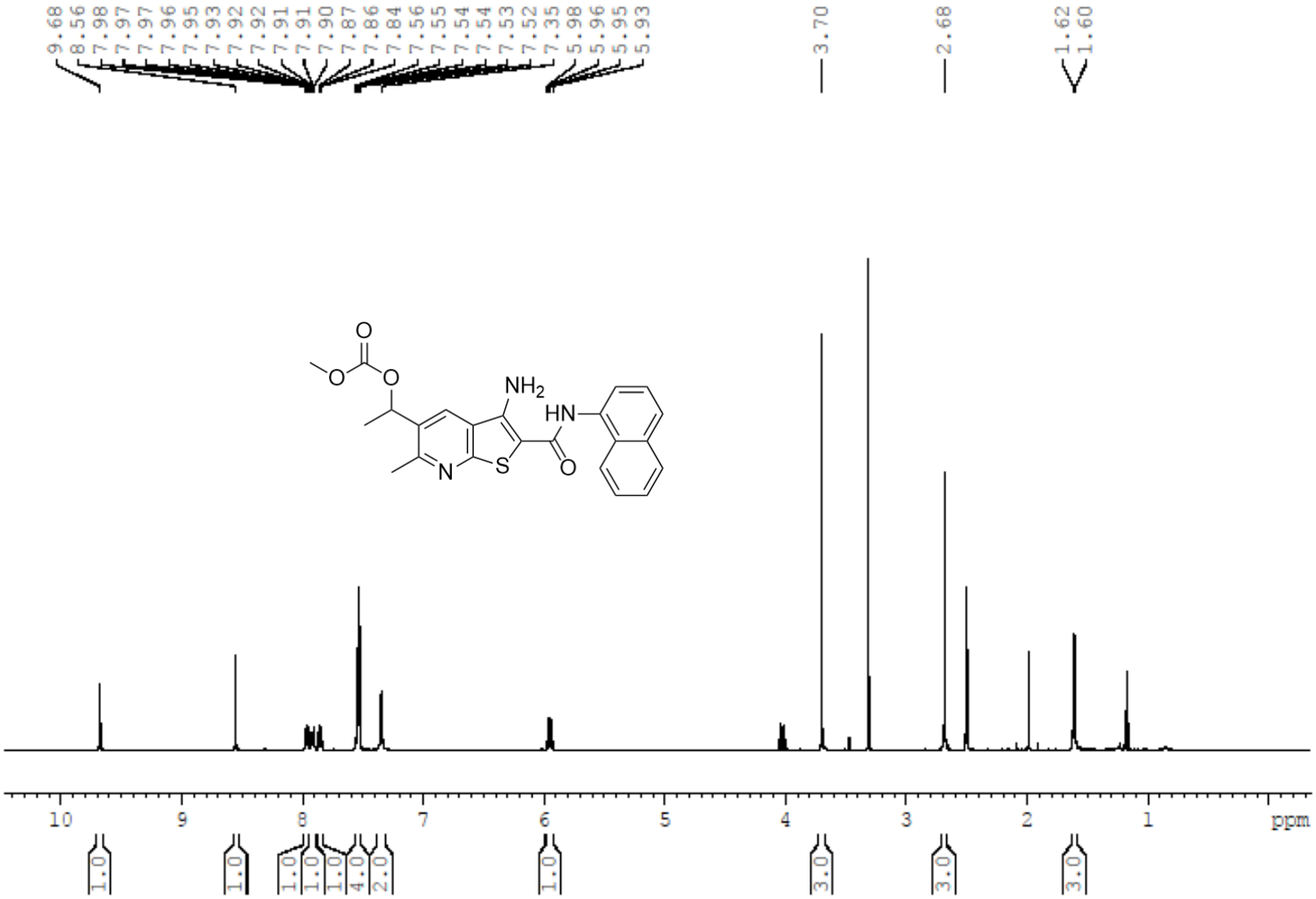



**Figure S27:** $^{1}$H NMR spectrum of **8d** (400 MHz; DMSO-*d*$_6$).

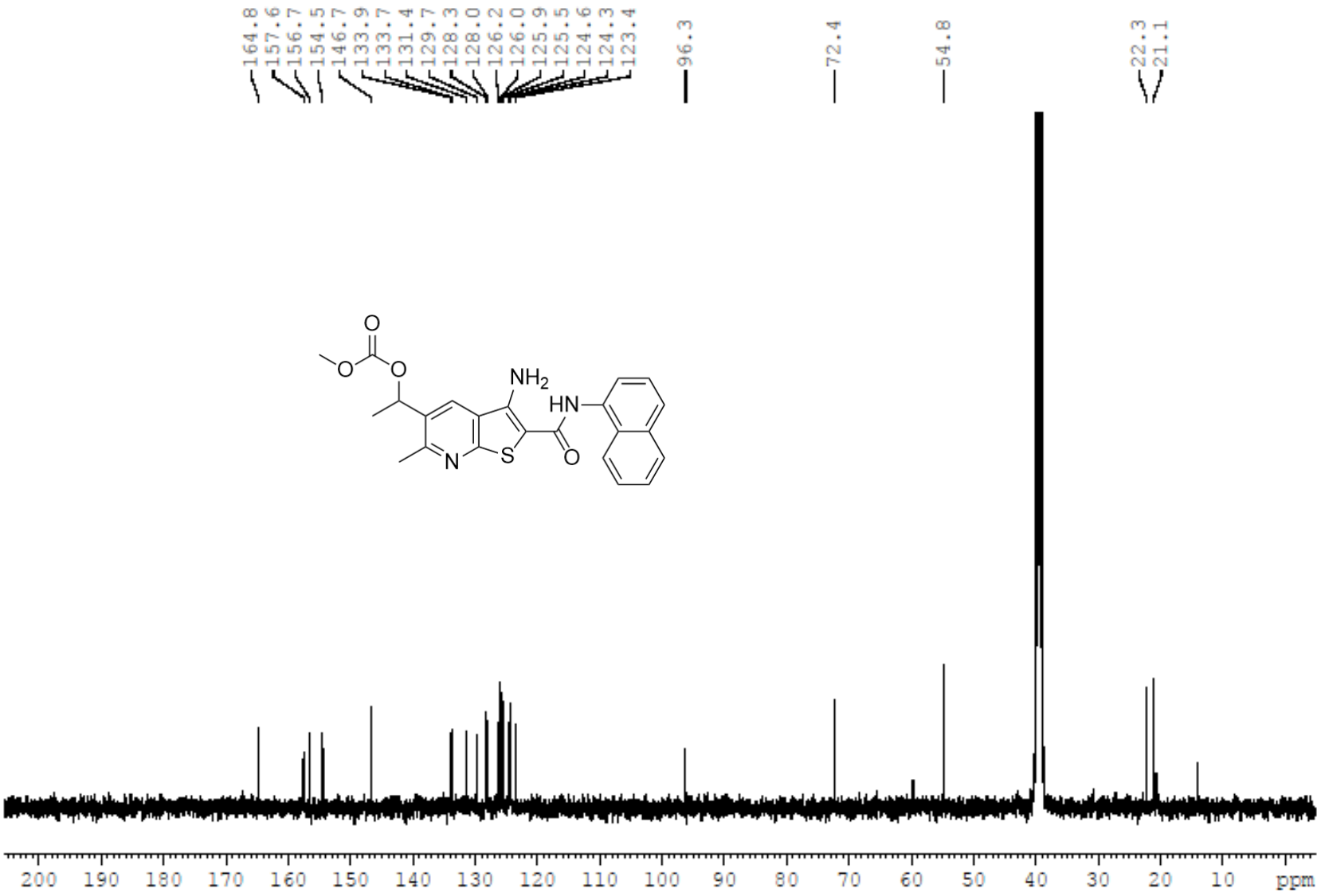



**Figure S28:** $^{13}$C NMR spectrum of **8d** (100 MHz; DMSO-*d*$_6$).

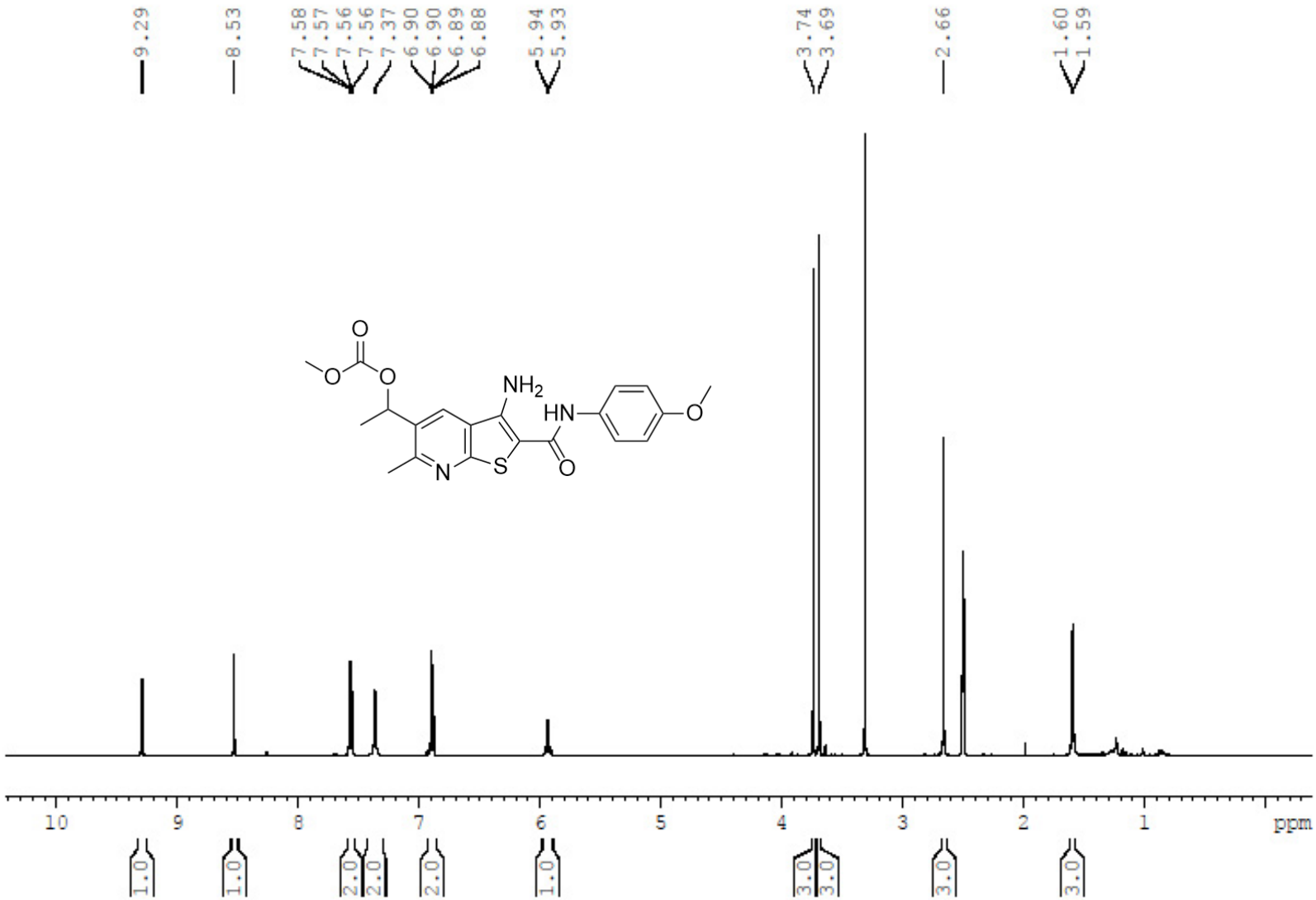



**Figure S29:** $^{1}$H NMR spectrum of **8e** (400 MHz; DMSO-*d*$_6$).

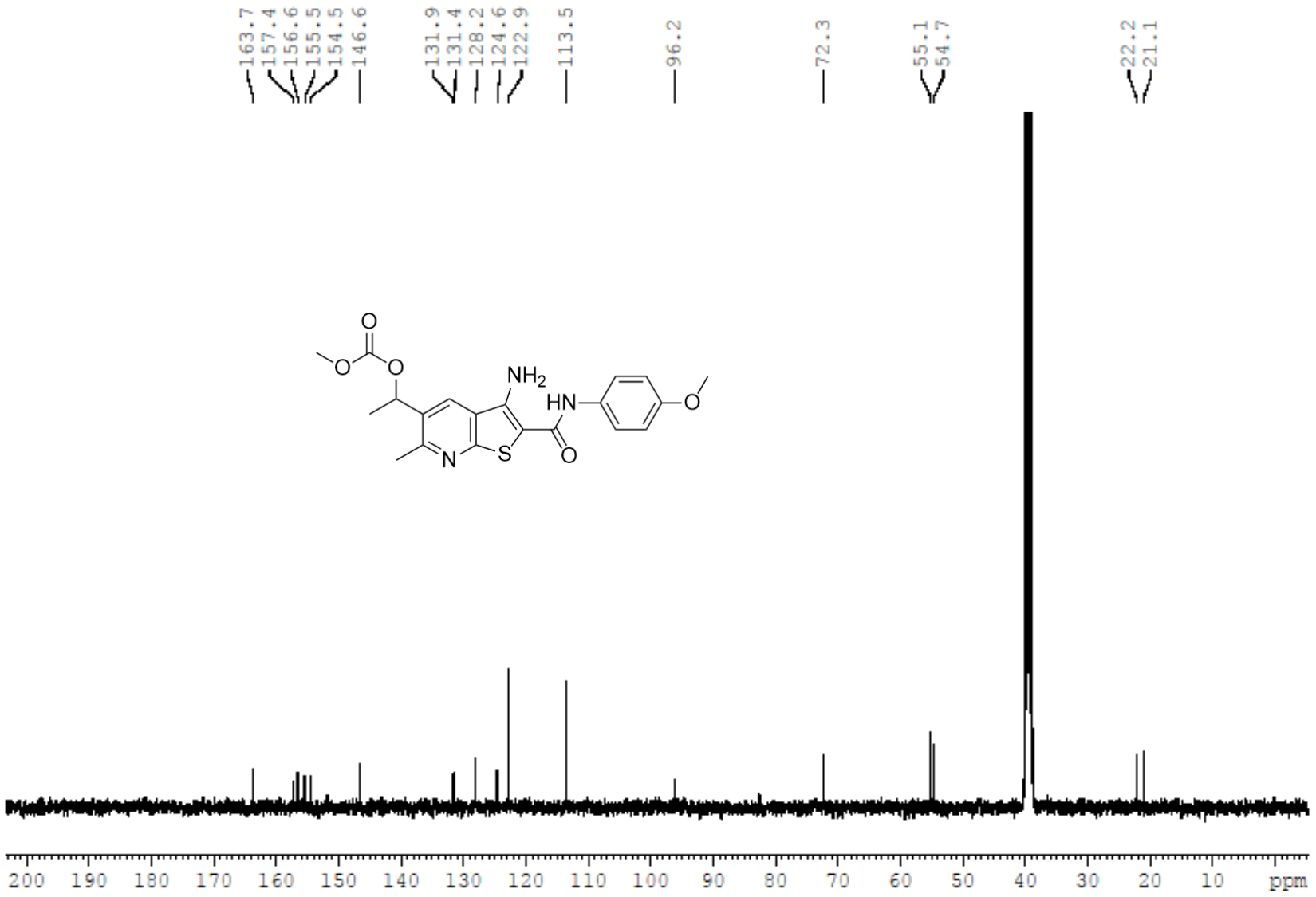



**Figure S30:** $^{13}$C NMR spectrum of **8e** (100 MHz; DMSO-*d*$_6$).

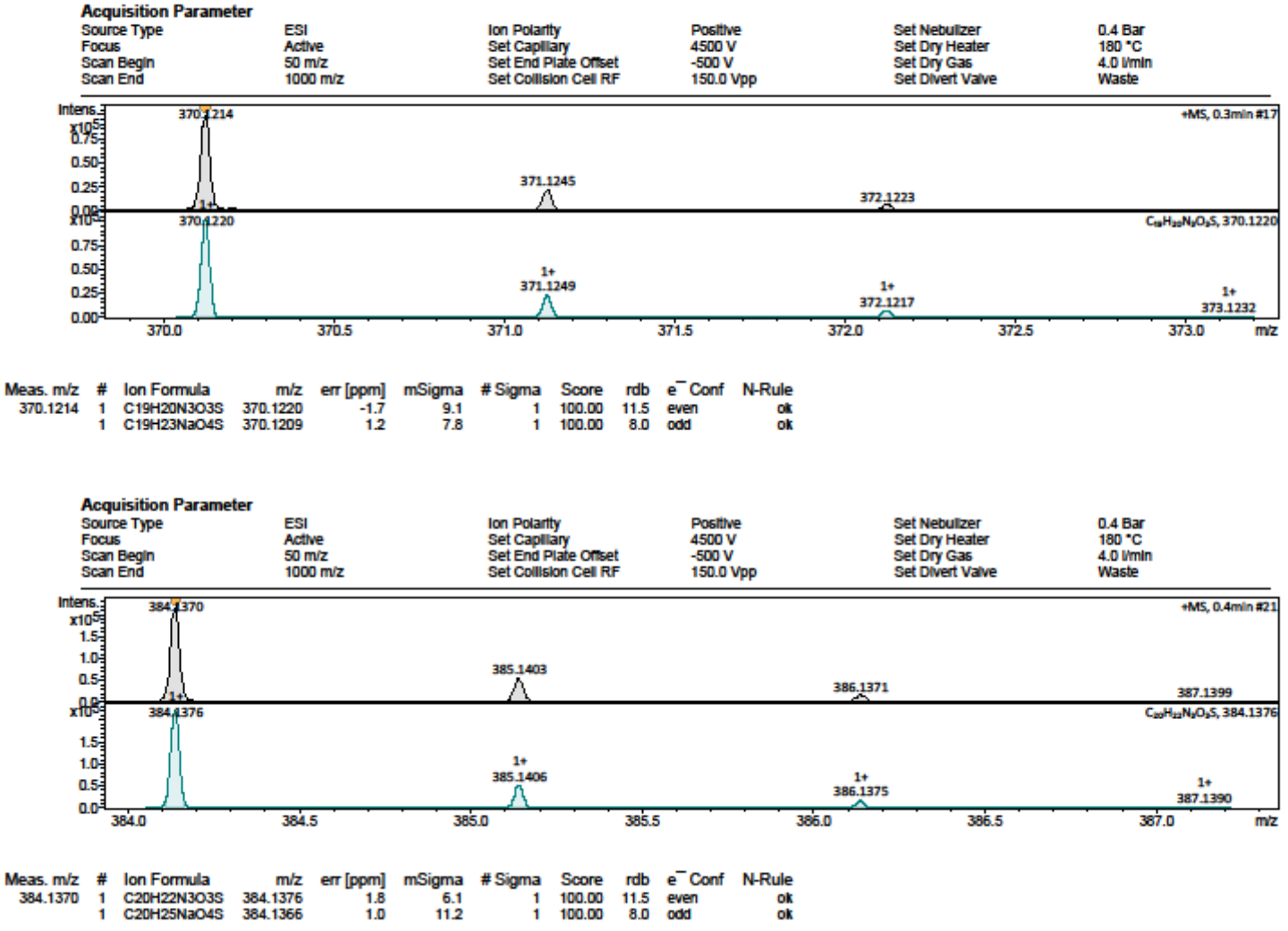
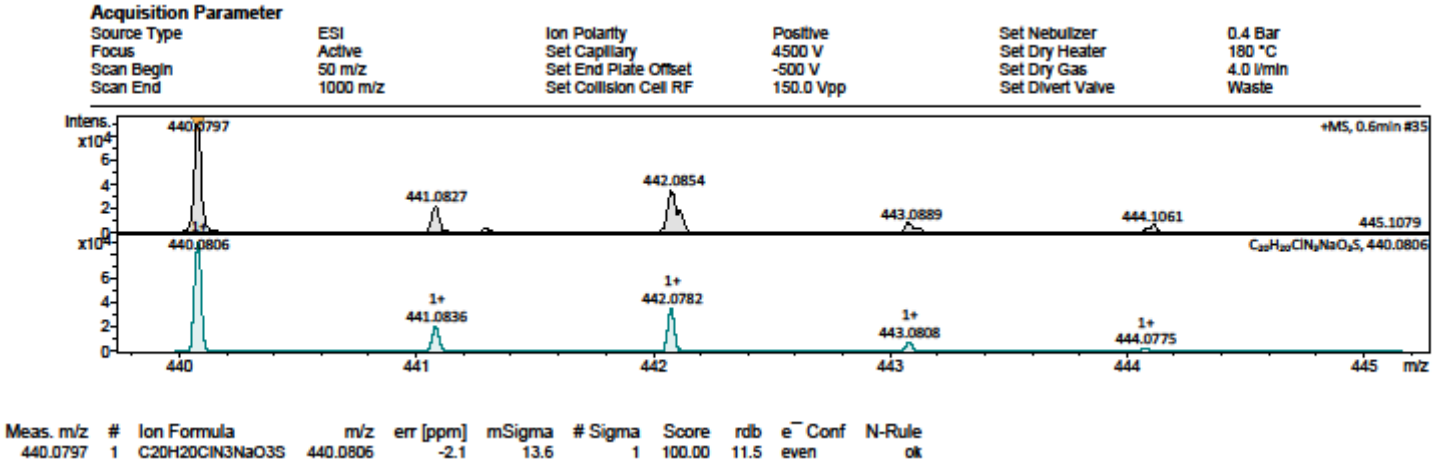
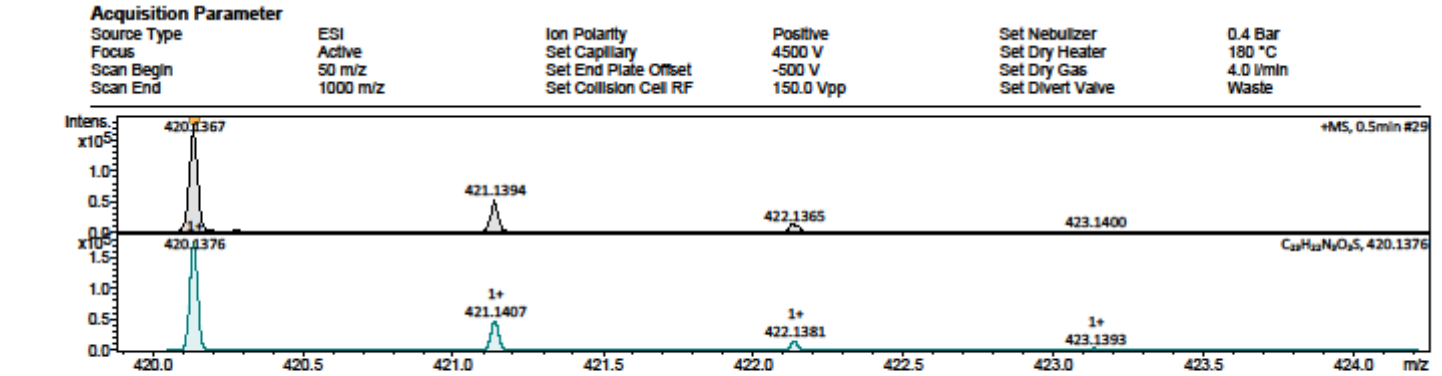



**Figure S31:** HRMS of **6a** (top) and **6b** (bottom).

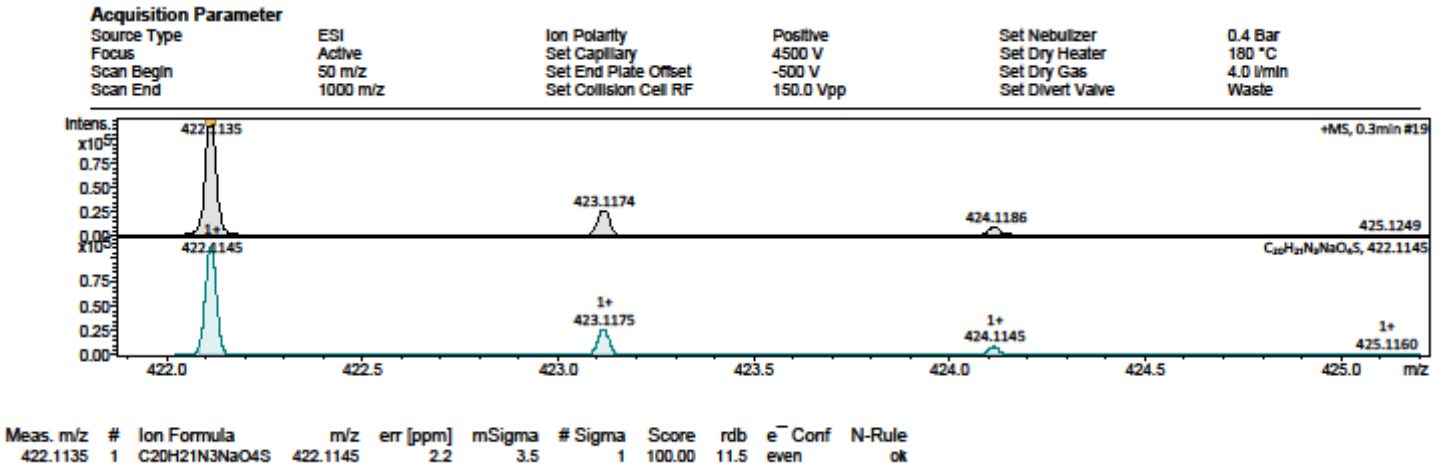



| Meas. m/z | # | Ion Formula | m/z | err [ppm] | mSigma | # Sigma | Score | rdb | e⁻ Conf | N-Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| 440.0797 | 1 | C20H20ClN3NaO3S | 440.0806 | -2.1 | 13.6 | 1 | 100.00 | 11.5 | even | ok |

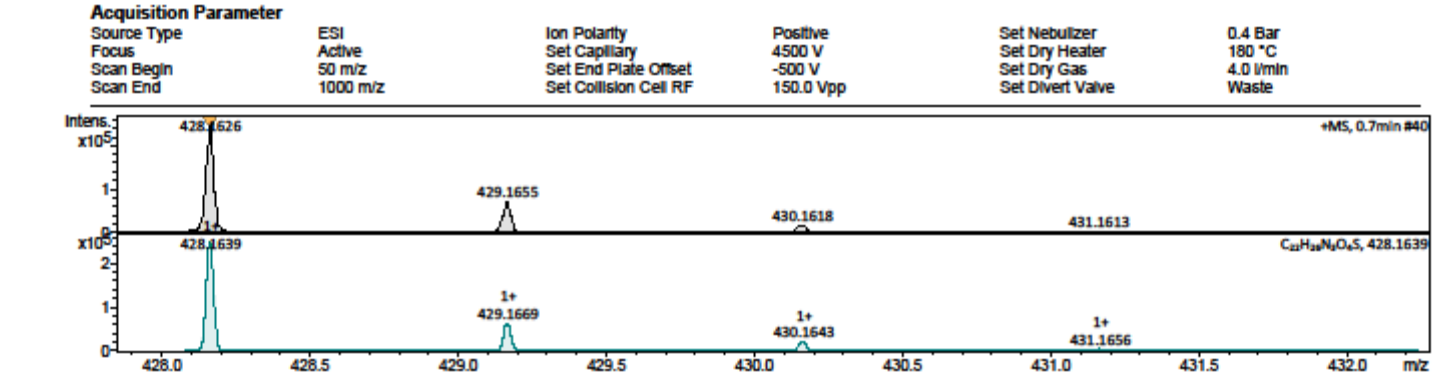



| Meas. m/z | # | Ion Formula | m/z | err [ppm] | mSigma | # Sigma | Score | rdb | e⁻ Conf | N-Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| 420.1367 | 1 | C23H22N3O3S | 420.1376 | -2.2 | 16.3 | 1 | 100.00 | 14.5 | even | ok |
| | 1 | C23H25NaO4S | 420.1366 | -0.3 | 21.3 | 1 | 100.00 | 11.0 | odd | ok |

**Figure S32:** HRMS of **6c** (top) and **6d** (bottom).

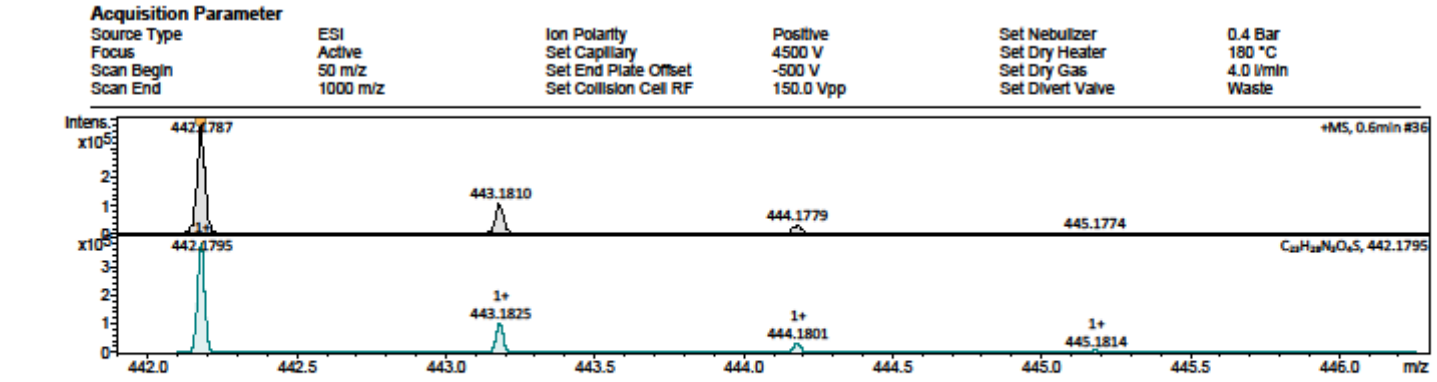



| Meas. m/z | # | Ion Formula | m/z | err [ppm] | mSigma | # Sigma | Score | rdb | e⁻ Conf | N-Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| 422.1135 | 1 | C20H21N3NaO4S | 422.1145 | 2.2 | 3.5 | 1 | 100.00 | 11.5 | even | ok |

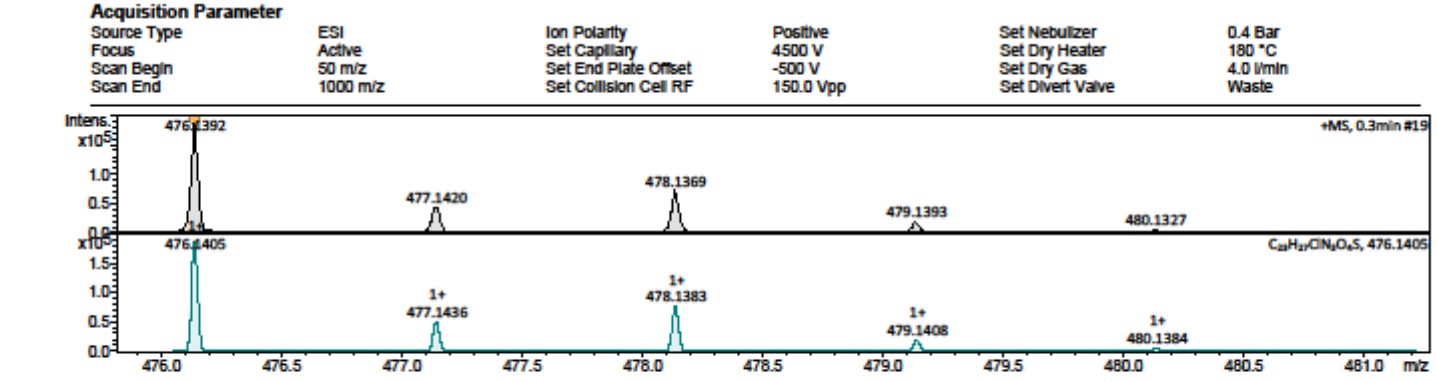



| Meas. m/z | # | Ion Formula | m/z | err [ppm] | mSigma | # Sigma | Score | rdb | e⁻ Conf | N-Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| 428.1626 | 1 | C22H26N3O4S | 428.1639 | 3.0 | 11.3 | 1 | 100.00 | 11.5 | even | ok |
| | 1 | C22H29NaO5S | 428.1628 | 0.5 | 16.0 | 1 | 100.00 | 8.0 | odd | ok |

**Figure S33:** HRMS of **6e** (top) and **7a** (bottom).




| Meas. m/z | # | Ion Formula | m/z | err [ppm] | mSigma | # Sigma | Score | rdb | e⁻ Conf | N-Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| 442.1787 | 1 | C23H28N3O4S | 442.1795 | -1.7 | 8.2 | 1 | 100.00 | 11.5 | even | ok |
| | 1 | C23H31NaO5S | 442.1784 | -0.7 | 12.9 | 1 | 100.00 | 8.0 | odd | ok |




| Meas. m/z | # | Ion Formula | m/z | err [ppm] | mSigma | # Sigma | Score | rdb | e⁻ Conf | N-Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| 476.1392 | 1 | C23H27ClN3O4S | 476.1405 | -2.8 | 16.2 | 1 | 100.00 | 11.5 | even | ok |
| | 1 | C23H30ClNaO5S | 476.1395 | 0.6 | 12.6 | 1 | 100.00 | 8.0 | odd | ok |

**Figure S34:** HRMS of **7b** (top) and **7c** (bottom).

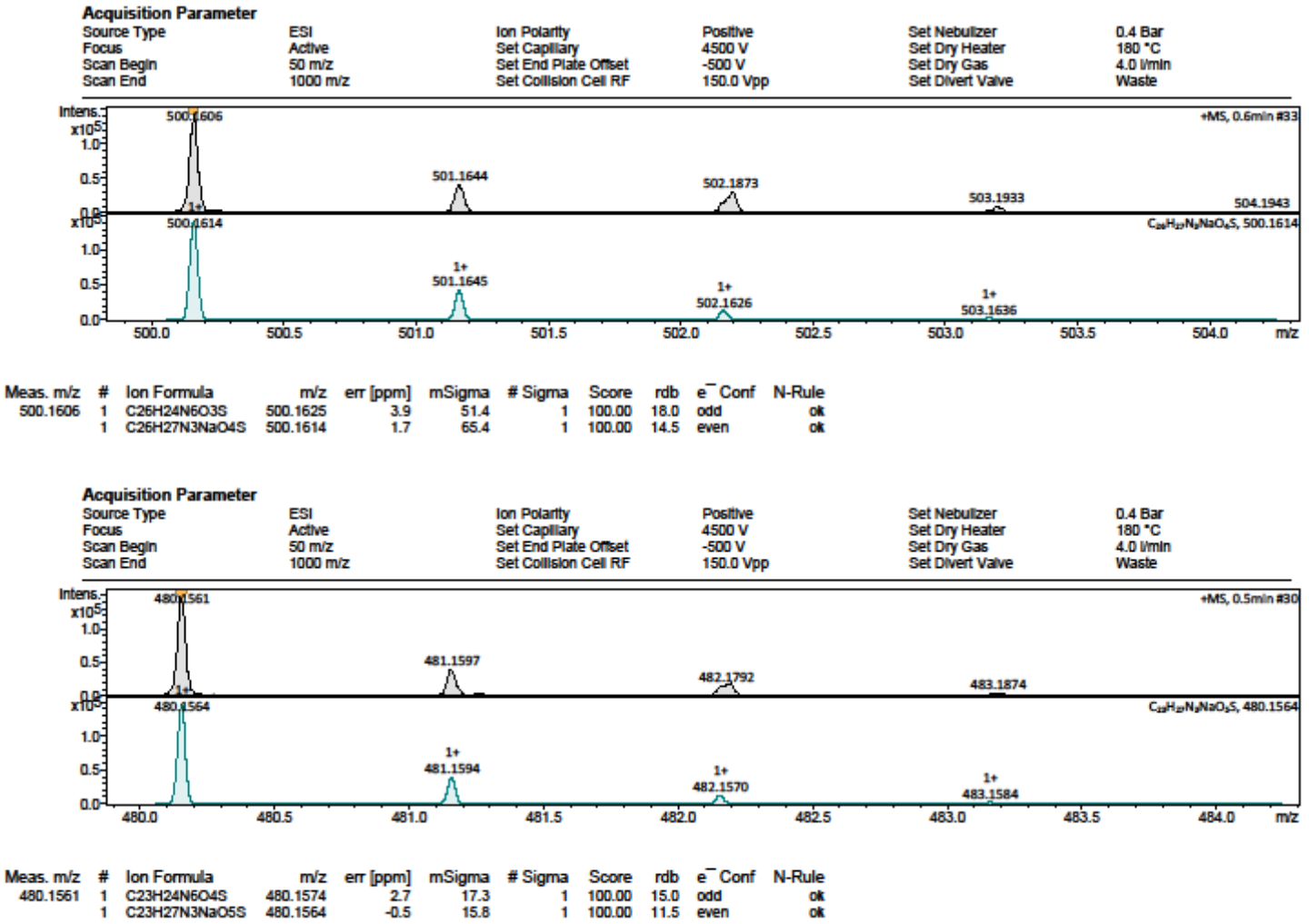



**Figure S35:** HRMS of **7d** (top) and **7e** (bottom).

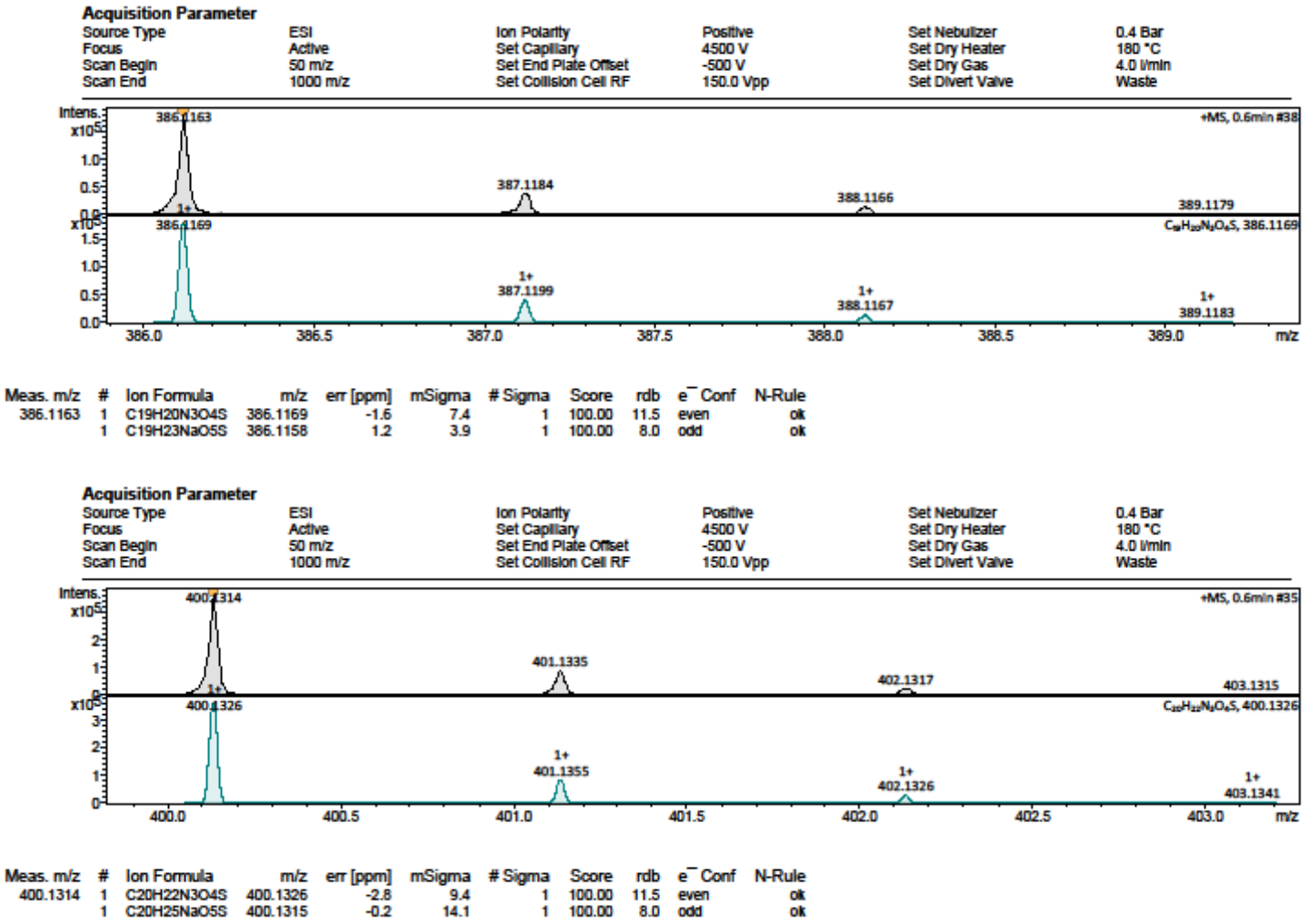



**Figure S36:** HRMS of **8a** (top) and **8b** (bottom).

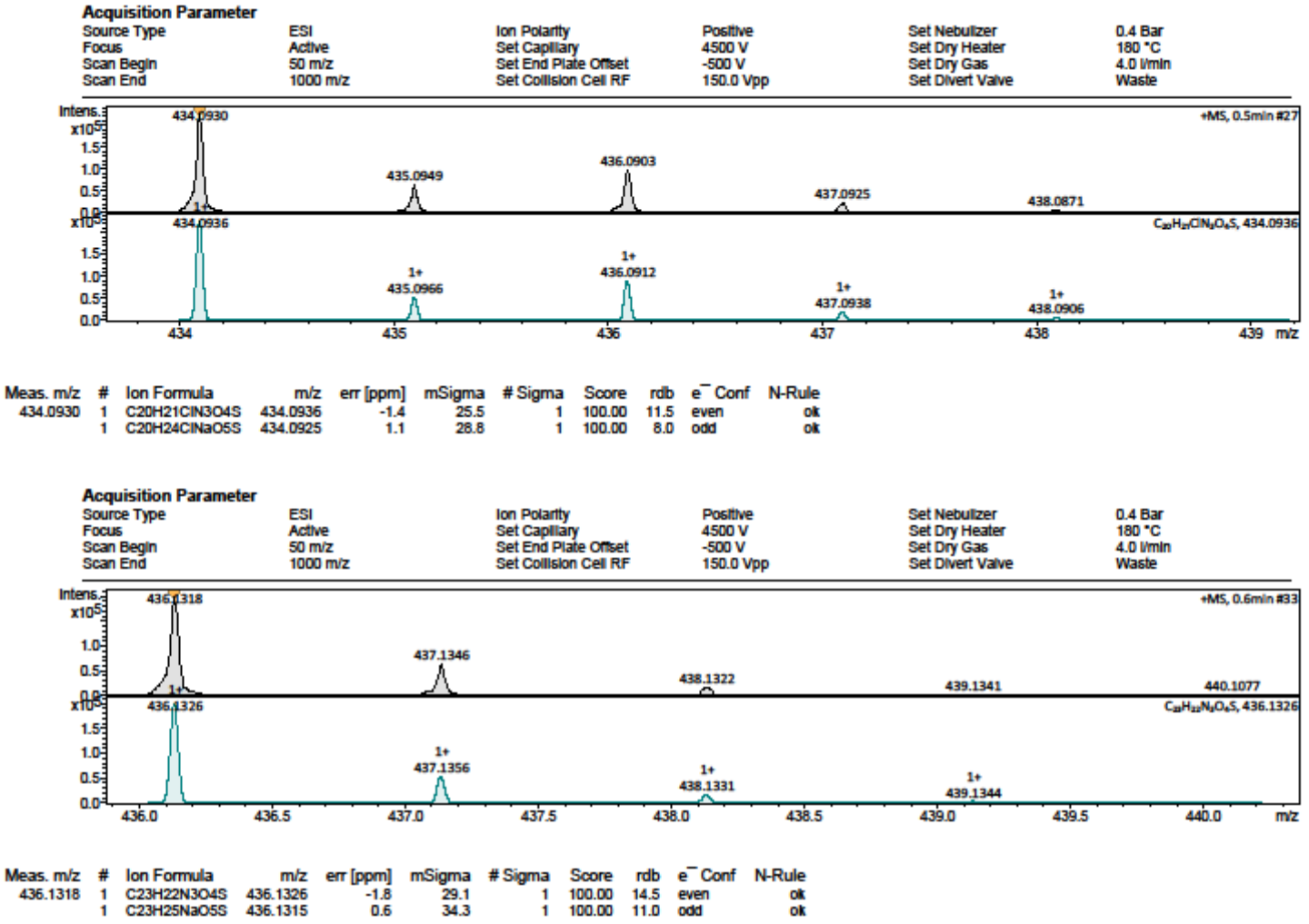
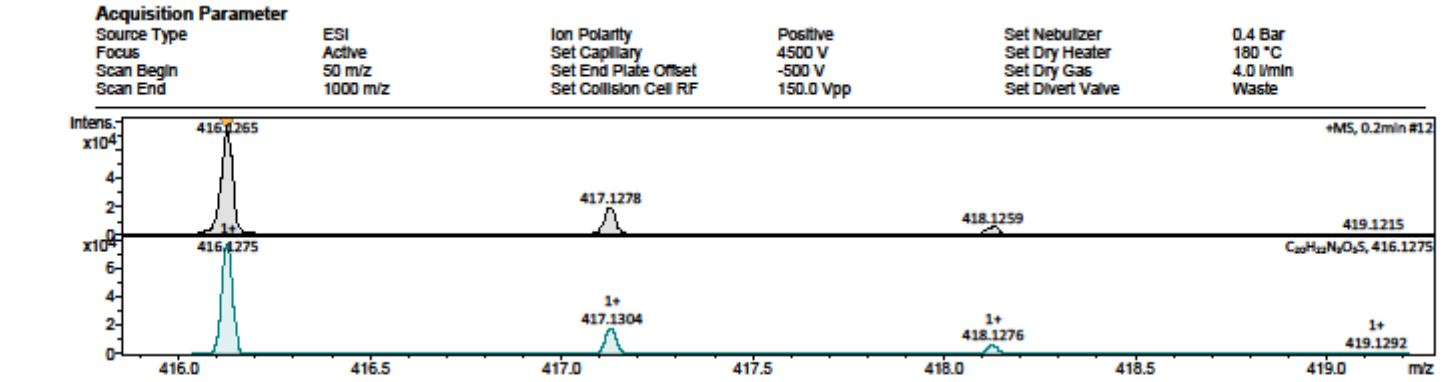



**Figure S37:** HRMS of **8c** (top) and **8d** (bottom).




| Meas. m/z | # | Ion Formula | m/z | err [ppm] | mSigma | # Sigma | Score | rdb | e⁻ Conf | N-Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| 416.1265 | 1 | C20H22N3O5S | 416.1275 | -2.4 | 10.2 | 1 | 100.00 | 11.5 | even | ok |
| | 1 | C20H25NaO6S | 416.1264 | -0.2 | 15.3 | 1 | 100.00 | 8.0 | odd | ok |

**Figure S38:** HRMS of **8e**.

**Table S1:** Computational logP and logS values for thieno[2,3-*b*]pyridines **5a-e**, **6a-e**, **7a-e**, and **8a-e** as calculated by ChemDraw Professional 19.1.1.21. * denotes previously tested parent alcohol-containing thienopyridines.[1]

| | LogP | LogS |
|---|---|---|
| **5a*** | 2.93 | -4.02 |
| **5b*** | 3.41 | -4.22 |
| **5c*** | 3.97 | -4.92 |
| **5d*** | 3.92 | -5.92 |
| **5e*** | 2.80 | -4.07 |
| **6a** | 3.16 | -4.79 |
| **6b** | 3.64 | -4.99 |
| **6c** | 4.20 | -5.68 |
| **6d** | 4.15 | -6.19 |
| **6e** | 3.03 | -4.84 |
| **7a** | 4.62 | -6.05 |
| **7b** | 5.10 | -6.25 |
| **7c** | 5.66 | -6.95 |
| **7d** | 5.61 | -7.46 |
| **7e** | 4.49 | -6.10 |
| **8a** | 3.74 | -5.00 |
| **8b** | 4.23 | -5.20 |
| **8c** | 4.79 | -5.90 |
| **8d** | 4.74 | -6.41 |
| **8e** | 3.62 | -5.05 |

**Table S2:** Melting points of compounds **5a-e**, **6a-e**, **7a-e**, and **8a-e**. * denotes previously tested parent alcohol-containing thienopyridines.[1]

| | Melting point (°C) |
|---|---|
| **5a*** | > 230 |
| **5b*** | 143-145 |
| **5c*** | > 230 |
| **5d*** | 216-218 |
| **5e*** | > 230 |
| **6a** | 203-205 |
| **6b** | 196-198 |
| **6c** | 209-211 |
| **6d** | 190-192 |
| **6e** | > 230 |
| **7a** | 190-192 |
| **7b** | 187-189 |
| **7c** | 199-201 |
| **7d** | 202-204 |
| **7e** | 196-198 |
| **8a** | 194-196 |
| **8b** | 213-215 |
| **8c** | 202-204 |
| **8d** | 188-190 |
| **8e** | > 230 |

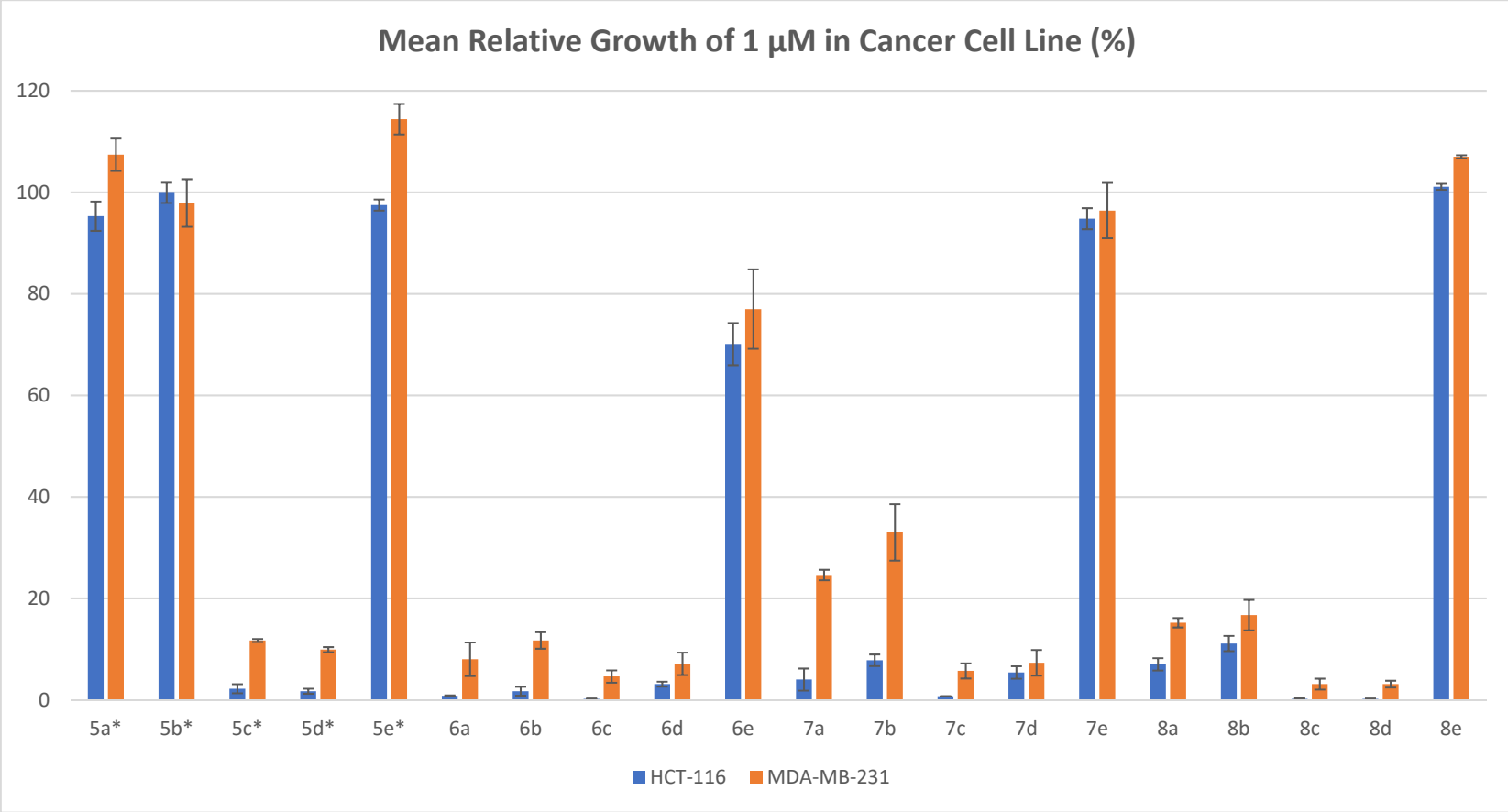



**Figure S39:** Antiproliferative results of compounds **5a-e**, **6a-e**, **7a-e**, and **8a-e**. * denotes previously tested parent alcohol-containing thienopyridines.[1]