# Carboxylic acid isosteres improve the activity of ring-fused 2-pyridones that inhibit pilus biogenesis in *E. coli*

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## Supporting information

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## *Experimental*

*General synthesis:* All reactions were carried out under inert atmosphere, with dry solvents and anhydrous conditions, unless otherwise stated. MeCN, $CH_2Cl_2$ and 1,2-dichlorethane were distilled from calcium hydride and THF was distilled from potassium. DMF was distilled and dried over 3Å molecular sieves. EtOH was dried over 3 Å molecular sieves. HCl (g) was passed through concentrated $H_2SO_4$ prior to use. All microwave reactions were carried out in a monomode reactor (Smith Synthesizer, Biotage AB) using Smith Process Vials™ sealed with Teflon septa and aluminum crimp tops. TLC was performed on Silica Gel 60 $F_{254}$ (Merck) using UV light detection. Flash column chromatography (eluents given in brackets) employed normal phase silica gel (Matrex, 60 Å, 35-70 μm, Grace Amicon). The $^1$H and $^{13}$C NMR spectra were recorded at 298 K with a Bruker DRX-400 spectrometer in $CDCl_3$ [residual $CHCl_3$ ($\delta_H$ 7.26 ppm) or $CDCl_3$ ($\delta_C$ 77.0 ppm) as internal standard], or MeOD-$d_4$ [residual $CD_2HOD$ ($\delta_H$ 3.30 ppm) or $CD_3OD$ ($\delta_C$ 49.0 ppm) as internal standard], or DMSO-$d_6$ [residual DMSO ($\delta_H$ 2.49 ppm) or DMSO ($\delta_C$ 40.0 ppm) as internal standard]. Overlapping carbon signals were resolved by HSQC experiments on a Bruker DRX-500. IR spectra were recorded on an ATI Mattson Genesis Series FTIR™ spectrometer. Optical rotations were measured with a Perkin-Elmer 343 polarimeter at 20 ºC. HRMS data were recorded with fast atom bombardment (FAB+) ionization on a JEOL JMS-SX 102 spectrometer.

**Compounds 1-4, 7 and 8 were synthesized according to published procedures. Data in agreement with published data.** [18, 26, 27]

**(3*R*)-7-Naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic acid hydroxyamide (5)**

Prepared as described for **6**; Starting from **3** (50 mg, 0.12 mmol) gave **5** as a white powder (50 mg, quant.). $[\alpha]_D$ –93 (*c* 0.5, MeOH); IR ν/cm$^{-1}$ 3050, 1634, 1558, 1482, 1426; $^1$H NMR (400 MHz, MeOD-$d_4$) $\delta$ 7.80 (dd, $J$ = 2.1, 6.3 Hz, 1H), 7.72 (d, $J$ = 8.2, 1H), 7.60 (dd, $J$ = 2.1, 7.0 Hz, 1H), 7.44-7.31 (m, 8H), 7.21 (d, $J$ = 6.5 Hz, 1H), 5.69 (s, 1H), 5.38 (dd, $J$ = 3.0, 9.1 Hz, 1H), 4.03-3.90 (m, 2H), 3.67 (dd, $J$ = 9.1, 11.8 Hz, 1H), 3.36 (dd, $J$ = 3.0, 11.8 Hz, 1H); $^{13}$C NMR (100 MHz, MeOD-$d_4$) $\delta$ 167.38, 163.35, 157.01, 150.70, 137.59, 135.33, 135.24, 132.96, 131.37, 131.01, 130.11, 130.06, 129.71, 129.58, 128.93, 128.71, 127.18, 126.72, 126.48, 124.81, 118.31, 114.63, 64.44, 37.64, 32.61; HRMS (FAB+) calcd for $[M+H]^+$ $C_{25}H_{21}N_2O_5S$ 429.1273, obsd 429.1269.

**(3*R*)-8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic acid hydroxyamide (6)**

**4** (46 mg, 0.12 mmol) was dissolved in MeOH (3 ml) and 50 wt % aqueous $NH_2OH$ (1.7 ml, 28 mmol) was added dropwise to the stirred solution at room temperature. The solution was concentrated and lyophilized from MeCN:$H_2O$ (1:1) to give **6** as a white powder (46 mg, quant.). $[\alpha]_D$ –140 (*c* 0.5, MeOH); IR ν/cm$^{-1}$ 3020, 1637, 1561, 1486, 1429; $^1$H NMR (400 MHz, MeOD-$d_4$) $\delta$ 7.91-7.74 (m, 3H), 7.51-7.36 (m, 3H), 7.30 (d, $J$ = 7.0 Hz, 1H), 5.55 (s, 1H), 5.30 (dd, $J$ = 2.7, 9.1 Hz, 1H), 4.55-4.38 (m, 2H), 3.68 (dd, $J$ = 9.1, 11.8 Hz, 1H), 3.41 (dd, $J$ = 2.7, 11.8 Hz, 1H), 1.68 (m, 1H), 1.02-0.81 (m, 2H), 0.80-0.66 (m, 2H); $^{13}$C NMR (100 MHz, MeOD-$d_4$) $\delta$ 167.47, 163.30, 159.67, 151.05, 135.55, 135.44, 133.26, 129.80, 128.77, 128.70, 127.28, 126.81, 126.61, 124.99, 115.99, 114.68, 63.60, 37.12, 32.57, 12.08, 8.58, 8.13; HRMS (FAB+) calcd for $[M+H]^+$ $C_{22}H_{21}N_2O_5S$ 393.1273, obsd 393.1288.

**(3*R*)-*N*-(7-Naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carbonyl)-methanesulfonamide (9)**

Prepared as described for **12**; Starting from **7** (40 mg, 0.10 mmol), *N,N*-carbonyldiimidazole (47 mg, 0.29 mmol) and methane sulfonamide (37 mg, 0.39 mmol) gave, after purification with silica gel chromatography (heptane:EtOAc, 1:9 → MeOH: $CH_2Cl_2$, 1:9), **9** (41 mg, 86 %). $[\alpha]_D$ –5 (*c* 0.25, DMSO); IR ν/cm$^{-1}$ 2912, 1716, 1623, 1554, 1483; $^1$H NMR (400 MHz, DMSO-*d*$_6$) 12.32 (bs, 1H), 7.92 (m, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.68 (m, 1H), 7.53-7.32 (m, 8H), 5.45 (s, 1H), 5.41 (dd, *J* = 2.5, 9.1 Hz, 1H), 3.98 (s, 2H), 3.83 (dd, *J* = 9.1, 12.2 Hz, 1H), 3.47 (dd, *J* = 2.5, 12.2 Hz, 1H), 3.23 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$) δ 167.72, 160.28 154.39, 148.90, 136.63, 134.58, 133.83, 131.69, 130.37 (2C), 129.37 (2C), 129.06, 128.71, 128.08, 127.83, 126.78, 126.23, 126.03, 124.16, 114.95, 113.79, 64.60, 41.35, 36.30, 31.42; HRMS (FAB+) calcd for $[M+H]^+$ $C_{26}H_{23}N_2O_4S_2$ 491.1099, obsd 491.1098.

**(3*R*)-*N*-(8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carbonyl)-methanesulfonamide (10)**

Prepared as described for **12**; Starting from **8** (36 mg, 0.09 mmol), *N,N'*-carbonyldiimidazole (47 mg, **0.29** mmol) and methane sulfonamide (37 mg, 0.39 mmol) gave, after trituration of the crude product with first MeOH and then $CH_2Cl_2$, **10** (26 mg, 60 %). Using the same method but with increased temperature to 150 °C for 55 min giving **10** (95%). $[\alpha]_D$ –7 (*c* 0.5, DMSO); IR ν/cm$^{-1}$ 3045, 2925, 2854, 1729, 1637, 1552, 1483; $^1$H NMR (400 MHz, DMSO-*d*$_6$) δ 12.27 (bs, 1H), 7.96 (m, 1H), 7.91-7.83 (m, 2H), 7.58-7.44 (m, 3H), 7.36 (d, *J* = 7.0 Hz, 1H), 5.31 (dd, *J* = 1.9, 9.3 Hz, 1H), 5.26 (s, 1H), 4.53-4.36 (m, 2H), 3.81 (dd, *J* = 9.3, 12.0 Hz, 1H), 3.50 (dd, *J* = 1.9, 12.0 Hz, 1H), 3.21 (s, 3H), 1.71 (m, 1H), 0.97-0.84 (m, 2H), 0.78-0.60 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$) δ 167.83, 160.27, 157.28, 149.02, 134.97, 133.95, 132.01, 129.11, 128.03, 127.82, 126.84, 126.31, 126.16, 124.49, 113.73, 112.49, 63.68, 41.34, 35.79, 31.33, 11.22, 7.89, 7.72; HRMS (FAB+) calcd for $[M+H]^+$ $C_{23}H_{23}N_2O_4S_2$ 455.1099, obsd 455.1104.

**(3*R*)-*N*-(7-Naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carbonyl)-benzenesulfonamide (11)**

Prepared as described for **12**; Starting from **7** (31 mg, 0.07 mmol), *N,N'*-carbonyldiimidazole (34 mg, 0.21 mmol) and benzene sulfonamide (44 mg, 0.28 mmol) gave, after purification with silica gel chromatography (heptane:EtOAc, 1:9 → MeOH: $CH_2Cl_2$, 1:9), **11** (37 mg, 90 %). $[\alpha]_D$ 0 (*c* 0.5, DMSO); IR ν/cm$^{-1}$ 3058, 2924, 1729, 1631, 1556, 1481; $^1$H NMR (400 MHz, DMSO-*d*$_6$) δ 11.93 (bs, 1H), 7.89 (dd, *J* = 2.7, 6.0 Hz, 1H), 7.80 (d, *J* = 8.0, 1H), 7.77-7.62 (m, 3H), 7.53-7.22 (m, 12H), 5.32 (s, 1H), 5.18 (dd, *J* = 1.9, 9.1 Hz, 1H), 4.00-3.84 (m, 2H), 3.69 (dd, *J* = 9.1, 12.2 Hz, 1H), 3.41 (dd, *J* = 1.9, 12.2 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$) δ 170.94, 160.43, 152.81, 149.01, 137.13, 134.82, 133.81, 131.78, 130.60 (broad, 4C) 129.24 (2C), 129.02, 128.41, 128.25 (2C), 128.03, 127.72, 126.95 (2C), 126.77, 126.19, 126.03, 124.26, 114.23, 113.93, 66.92, 36.27, 33.33; HRMS (FAB+) calcd for $[M+H]^+$ $C_{31}H_{25}N_2O_4S_2$ 553.1256, obsd 553.1262.

**(3*R*)-*N*-(8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carbonyl)-benzenesulfonamide (12)**

**8** (35 mg, 0.09 mmol) was suspended in $CH_2Cl_2$ (1 ml) in a microwave vial. To the suspension was added *N,N'*-carbonyldiimidazole (47 mg, 0.29 mmol) in one portion at room temperature. After 1 hour and 45 minutes, benzene sulfonamide (61 mg, 0.39 mmol) was added in one portion at rt. The vial was capped and heated with microwave irradiation (normal absorption) at 80 °C for 7 hours. The solution was diluted with $CH_2Cl_2$ and washed with 5% aqueous citric acid. The combined aqueous layers were reextracted with $CH_2Cl_2$ and the combined organic layers were dried, filtrated and concentrated. Purification by silica gel chromatography (heptane:EtOAc, 1:9) gave **12** (32 mg, 67%): $[\alpha]_D$ -6 (*c* 0.5, DMSO); IR ν/cm$^{-1}$ 3102, 2996, 2853, 1723, 1673, 1552, 1481; $^1$H NMR (400 MHz, DMSO-*d*$_6$) δ 12.70 (bs, 1H), 7.94 (dd, *J* = 3.4, 6.3 Hz, 1H), 7.91-7.80 (m, 4H), 7.70 (m, 1H), 7.63-7.56 (m, 2H), 7.54-7.43 (m, 3H), 7.33 (d, *J* = 7.2 Hz, 1H), 5.29 (dd, *J* = 1.9, 9.3 Hz, 1H), 5.17 (s, 1H), 4.49-4.30 (m, 2H), 3.80 (dd, *J* = 9.3, 12.2 Hz, 1H), 3.36 (dd, *J* = 1.9, 12.2 Hz, 1H), 1.67 (m, 1H), 0.96-0.78 (m, 2H), 0.75-0.52 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$) δ 166.80, 160.07, 157.17, 148.78, 139.35, 134.89, 134.35, 133.92, 131.99, 129.70 (2C), 129.09, 128.02, 127.80 (3C), 126.82, 126.29, 126.13,

124.46, 113.65, 112.44, 63.48, 35.74, 31.43, 11.18, 7.86, 7.63; HRMS (FAB+) calcd for $[M+H]^+$ $C_{28}H_{25}N_2O_4S_2$ 517.1256, obsd 517.1247.

**(3*R*)-7-Naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic acid amide (13)**

Prepared as described for **14**; Starting from **3** (300 mg, 0.70 mmol) gave **13** as a pale yellow foam (289 mg, quant.). $[\alpha]_D$ –26 (*c* 0.5, MeOH); IR ν/cm$^{-1}$ 3056, 2935, 1634, 1563, 1480, 1412; $^1$H NMR (400 MHz, MeOD-*d*$_4$) $\delta$ 7.80 (dd, *J* = 2.5, 5.7 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.61 (dd, *J* = 2.3, 7.0 Hz, 1H), 7.44-7.31 (m, 10H), 7.21 (d, *J* = 7.0 Hz, 1H), 5.71 (s, 1H), 5.52 (dd, *J* = 2.1, 8.9 Hz, 1H), 4.04-3.90 (m, 2H), 3.71 (dd, *J* = 8.9, 11.8 Hz, 1H), 3.41 (dd, *J* = 2.1, 11.8 Hz, 1H); $^{13}$C NMR (100 MHz, MeOD-*d*$_4$) $\delta$ 171.98, 163.49, 156.89, 150.57, 137.67, 135.37, 135.30, 133.02, 131.42, 131.01, 130.07 (2C), 129.72, 129.54, 128.93, 128.70, 127.18, 126.71, 126.49, 124.83, 118.34, 114.77, 66.06, 37.65, 32.99; HRMS (FAB+) calcd for $[M+H]^+$ $C_{25}H_{21}N_2O_2S$ 413.1324, obsd 413.1327.

**(3*R*)-8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic acid amide (14)**

**4** (300 mg, 0.77 mmol) was dissolved in $NH_3$(g) saturated MeOH (5 ml) at rt and the solution was then heated to 40 °C in a flask that was sealed with a rubber septum. Additional $NH_3$(g) saturated MeOH was added portion wise (3×1 ml) to the reaction over a total of 29 hours to obtain full conversion into the amide. Concentration from $CH_2Cl_2$ gave **14** as a pale yellow foam (288 mg, quant.). $[\alpha]_D$ –92 (*c* 0.5, MeOH); IR ν/cm$^{-1}$ 3290, 3173, 3065, 1689, 1637, 1558, 1483; $^1$H NMR (400 MHz, MeOD-*d*$_4$) $\delta$ 7.94-7.74 (m, 4H), 7.49-7.37 (m, 4H), 7.30 (d, *J* = 6.7 Hz, 1H), 5.58 (s, 1H), 5.44 (dd, *J* = 1.9, 8.9 Hz, 1H), 4.55-4.36 (m, 2H), 3.69 (dd, *J* = 8.9, 11.8 Hz, 1H), 3.46 (dd, *J* = 1.9, 11.8 Hz, 1H), 1.67 (m, 1H), 1.03-0.82 (m, 2H), 0.79-0.66 (m, 2H); $^{13}$C NMR (100 MHz, MeOD-*d*$_4$) $\delta$ 172.09, 163.40, 159.52, 150.89, 135.60, 135.46, 133.30, 129.81, 128.75, 128.70, 127.28, 126.80, 126.61, 125.00, 115.98, 114.81, 65.20, 37.13, 32.91, 12.09, 8.55, 8.09; HRMS (FAB+) calcd for $[M+H]^+$ $C_{22}H_{21}N_2O_2S$ 377.1324, obsd 377.1319.

**(3*R*)-7-Naphthalen-1-ylmethyl-8-phenyl-3-(1*H*-tetrazol-5-yl)-2,3-dihydro-thiazolo[3,2-*a*]pyridin-5-one (15)**

Prepared as described for **16**; Starting from **13** (100 mg, 0.24 mmol) gave **15** as a pale yellow foam (19 mg, 18%) after purification by silica gel chromatography (MeOH:$CH_2Cl_2$, 1:4→ MeOH). $[\alpha]_D$ –9 (*c* 0.3, DMSO); IR ν/cm$^{-1}$ 3062, 2933, 1634, 1562, 1482; $^1$H NMR (400 MHz, MeOD-*d*$_4$) $\delta$ 7.82 (m, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.68 (m, 1H), 7.56-7.32 (m, 8H), 7.28 (d, *J* = 7.0 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 5.72 (s, 1H), 4.11-3.91 (m, 3H), 3.34 (m, 1H); $^{13}$C NMR (100 MHz, MeOD-*d*$_4$) $\delta$ 163.30, 161.01, 156.59, 150.18, 137.96, 135.40, 135.38, 133.11, 131.78, 130.97, 130.06, 129.95, 129.69, 129.46, 129.00, 128.66, 127.21, 126.71, 126.52, 124.96, 118.84, 115.07, 60.70, 37.71, 36.05; HRMS (FAB+) calcd for $[M+Na]^+$ $C_{22}H_{19}N_5NaOS$ 424.1208, obsd 424.1211.

**(3*R*)-8-Cyclopropyl-7-naphthalen-1-ylmethyl-3-(1*H*-tetrazol-5-yl)-2,3-dihydro-thiazolo[3,2-*a*]pyridin-5-one (16)**

**14** (100 mg, 0.27 mmol) was dissolved in MeCN (8 ml) and $NaN_3$ (37 mg, 0.56 mmol) was added. Then $SiCl_4$ (65 µl, 0.56 mmol) was added dropwise at room temperature. The reaction mixture was heated to reflux overnight. If starting material remained, additional $NaN_3$ and $SiCl_4$ were added under maintained refluxing. The reaction mixture was allowed to reach room temperature and was then diluted with EtOAc and washed with aq. $Na_2CO_3$ and $H_2O$. The combined aqueous layers were reextracted with EtOAc. The combined organic layers were dried, filtrated and concentrated. Purification by silica gel chromatography (MeOH:$CH_2Cl_2$, 1:4→ MeOH) gave **16** (15 mg, 14%). $[\alpha]_D$ –2 (*c* 0.4, MeOH); IR ν/cm$^{-1}$ 2923, 2850, 1637, 1555, 1485, 1427; $^1$H NMR (400 MHz, MeOD-*d*$_4$) $\delta$ 7.93-7.82 (m, 2H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.51-7.38 (m, 3H), 7.33 (d, *J* = 6.5 Hz, 1H), 6.41 (d, *J* = 7.0 Hz, 1H), 5.57 (s, 1H), 4.58 (d, *J* = 17.5 Hz, 1H), 4.43 (d, *J* = 17.5 Hz, 1H), 3.92 (dd, *J* = 8.0,

12.0 Hz, 1H), 3.41 (m, 1H), 1.76 (m, 1H), 1.05-0.95 (m, 1H), 0.94-0.75 (m, 3H); $^{13}$C NMR (100 MHz, MeOD-$d_4$) $\delta$ 160.25, 159.14, 155.78, 149.10, 135.22, 133.93, 132.12, 129.07, 127.99, 127.72, 126.80, 126.27, 126.16, 124.60, 114.09, 112.04, 58.76, 35.78, 31.16, 11.37, 8.01, 7.53; HRMS (FAB+) calcd for $[M+H]^+$ $C_{25}H_{20}N_5OS$ 438.1389, obsd 438.1367.

**(3*R*)-2-(5-Cyclopropyl-4-naphthalen-1-ylmethyl-2-oxo-2*H*-pyridin-1-yl)-propionic acid methyl ester (18)**
**4** (98 mg, 0.25 mmol) was dissolved in MeOH (11 ml). Raney® 2800 nickel (water slurry, 500 mg) was added at room temperature and the reaction mixture was heated to reflux. After 2+2 hours the reaction was fed with two additional portions of Raney® 2800 nickel (water slurry, 500+500 mg). Addition was carried out under continuous refluxing. The reaction was monitored by LC-MS to avoid reduction of the 2-pyridone ring. After a total of 7 hours, the reaction mixture was allowed to reach room temperature and filtrated through a pad of Celite. The solid phase was washed with $CH_2Cl_2$:MeOH (4:1). The filtrate was concentrated from $CH_2Cl_2$ to give **18** as a white foam (67 mg, 74%). $[\alpha]_D$ –28 (*c* 0.5, $CHCl_3$); IR $\nu$/cm$^{-1}$ 3004, 2924, 2853, 1743, 1664, 1589, 1529, 1439, 1378, 1260, 1213, 1105; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.91-7.73 (m, 3H), 7.52-7.36 (m, 3H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.07 (s, 1H), 5.97 (s, 1H), 5.48 (q, *J* = 7.4 Hz, 1H), 4.49-4.35 (m, 2H), 3.73 (s, 3H), 1.68 (m, 1H), 1.61 (d, *J* = 7.4 Hz, 3H), 0.93-0.80 (m, 2H), 0.65-0.56 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.27, 161.51, 154.79, 133.90, 131.94, 131.87, 128.78, 127.66, 127.53, 126.18, 125.67, 125.49, 123.70, 120.61, 119.07, 53.23, 52.58, 35.47, 16.68, 10.70, 5.56, 5.50; HRMS (FAB+) calcd for $[M+H]^+$ $C_{23}H_{24}NO_3$ 362.1756, obsd 362.1753.

**(3*R*)-2-(4-Naphthalen-1-ylmethyl-2-oxo-5-phenyl-2*H*-pyridin-1-yl)-propionic acid (19)**
According to the procedure described for synthesis of **18** from **4**, **3** (53 mg, 0.12 mmol) was desulfurized. The obtained methyl ester **17** was purified by silica gel chromatography (heptane:EtOAc, 3:7), and then hydrolysed to the corresponding lithium carboxylate (as described for the synthesis of **20** from **18**), which was protonated with Amberlite® IR-120 $H^+$ to give **19** (39 mg, 80% over two steps). $[\alpha]_D$ –28 (*c* 0.3, MeOH); IR $\nu$/cm$^{-1}$ 3014, 1728, 1652, 1543, 1435, 1376; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.84 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.77 (d, *J* = 8.2, 1H), 7.61 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.54 (s, 1H), 7.46-7.35 (m, 8H), 7.27 (d, *J* = 6.5 Hz, 1H), 5.98 (s, 1H), 5.27 (q, *J* = 7.4 Hz, 1H), 4.18 (s, 2H), 1.65 (d, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, MeOD-$d_4$) $\delta$ 173.28, 163.64, 155.81, 137.48, 136.57, 135.48, 135.29, 133.01, 130.99 (2C), 129.80, 129.76, 129.08, 129.02 (2C), 128.82, 127.27, 126.79, 126.56, 125.10, 124.85, 119.36, 57.19, 37.60, 16.39; HRMS (FAB+) calcd for $[M+H]^+$ $C_{25}H_{22}NO_3$ 384.1600, obsd 384.1594.

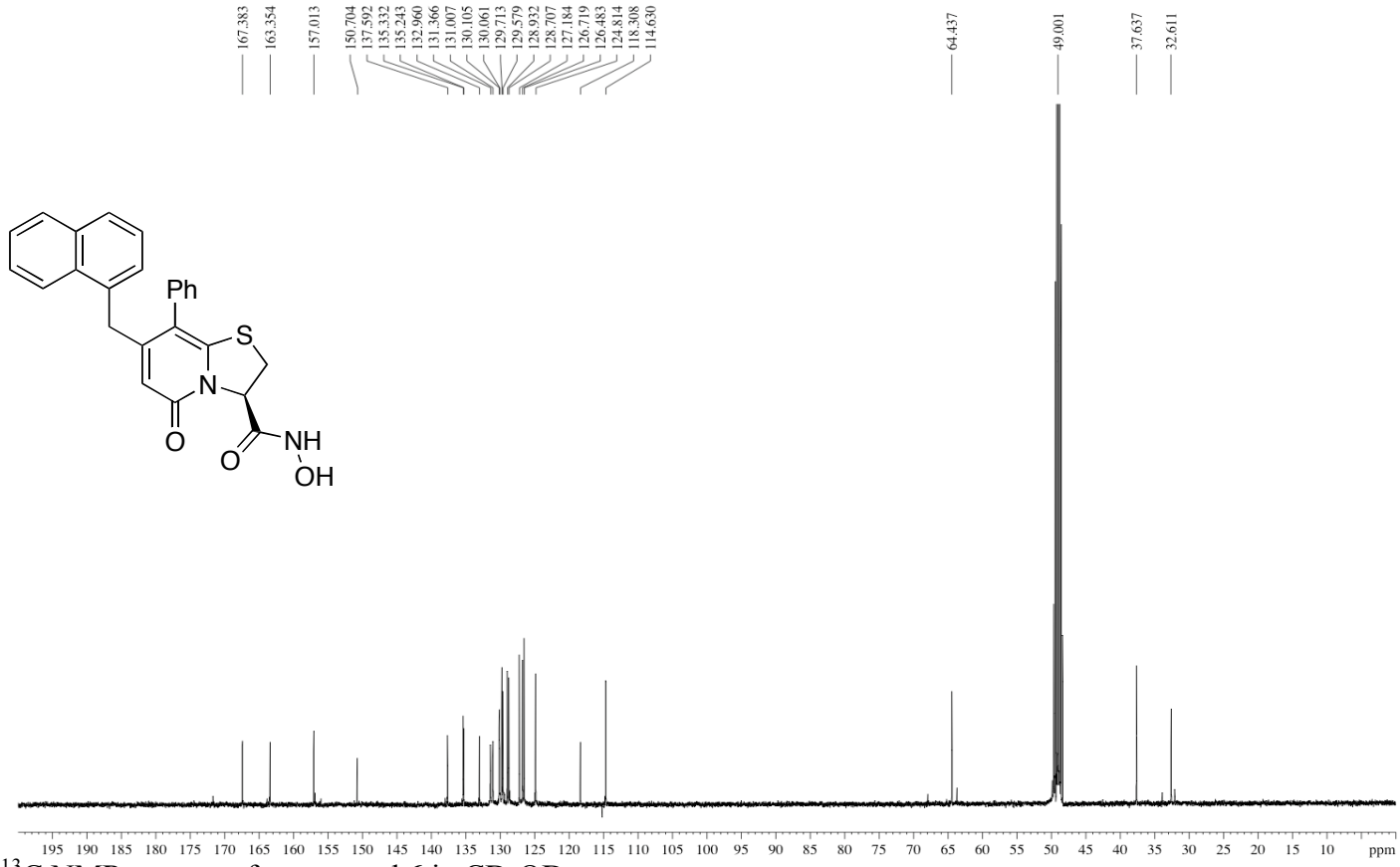
**(3*R*)-2-(5-Cyclopropyl-4-naphthalen-1-ylmethyl-2-oxo-2*H*-pyridin-1-yl)-propionic lithium carboxylate (20)**
**18** (49 mg, 0.14 mmol) was dissolved in THF (2 ml) at room temperature and then MeOH (4 ml) was added slowly to avoid precipitation. 0.1 M aqueous LiOH (1.35 ml, 0.14 mmol) was added dropwise to the stirred solution at room temperature. The solution was concentrated and lyophilized from MeCN:$H_2O$ (2:3) to give **20** as a white powder (48 mg, quant.). $[\alpha]_D$ –14 (*c* 0.5, MeOH); IR $\nu$/cm$^{-1}$ 3035, 2922, 1660, 1572, 1447, 1399; $^1$H NMR (400 MHz, MeOD-$d_4$) $\delta$ 7.95-7.75 (m, 3H), 7.50-7.40 (m, 3H), 7.39-7.32 (m, 2H), 5.81 (s, 1H), 5.36 (q, *J* = 7.4 Hz, 1H), 4.53-4.48 (s, 2H), 3.73 (s, 3H), 1.77 (m, 1H), 1.53 (d, *J* = 7.4 Hz, 3H), 0.90-0.86 (m, 2H), 0.70-0.63 (m, 2H); $^{13}$C NMR (100 MHz, MeOD-$d_4$) $\delta$ 177.18, 163.91, 157.17, 135.50, 135.31, 134.95, 133.40, 129.80, 128.83, 128.70, 127.27, 126.80, 126.66, 125.08, 122.92, 118.48, 57.20, 36.44, 18.73, 11.57, 6.17, 6.01; HRMS (FAB+) calcd for $[M+H]^+$ $C_{22}H_{21}LiNO_3$ 354.1681, obsd 354.1679.

**Ranking of binding affinities for PapD was performed according to a published pocedure.**[19]

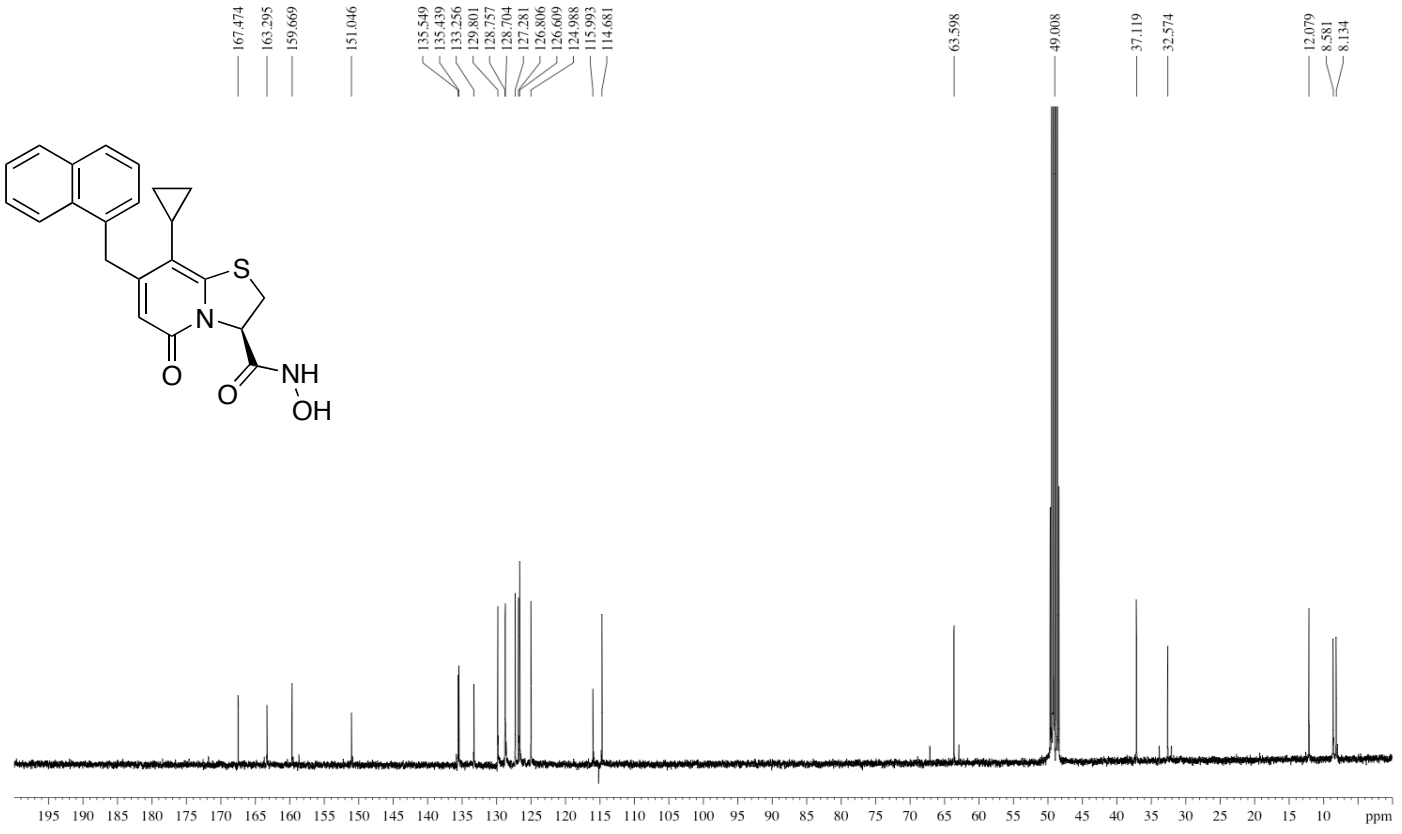
**Evaluation of ability to block P pilus biogenesis for compounds 2, 5, 6, 9-16, 19 and 20.**
HB101/pPAP5 was cultured for 24 hours at 37 °C in the presence of 1.8 mM compound in TSA with 2.5% DMSO and 100 μg/ml Ampicillin. Bacteria were harvested from the plate and suspended in 3 ml PBS pH 7.4 to

$OD_{600}$ = 1.0. 1 ml of the cells was centrifuged at 2000g × 5 min and resuspended in 80 µl PBS. The bacterial suspensions were then serially diluted in a V-bottomed 96-well plate (25 µl PBS in each well + 40 µl bacterial suspension in first well, transfer 25 µl). Subsequently, 25 µl human blood in PBS ($OD_{640}$ ~2.0) was added to each well and the plate was kept at 4 °C. The last wells in which hemagglutination occurred were visually assessed after 4 hours.

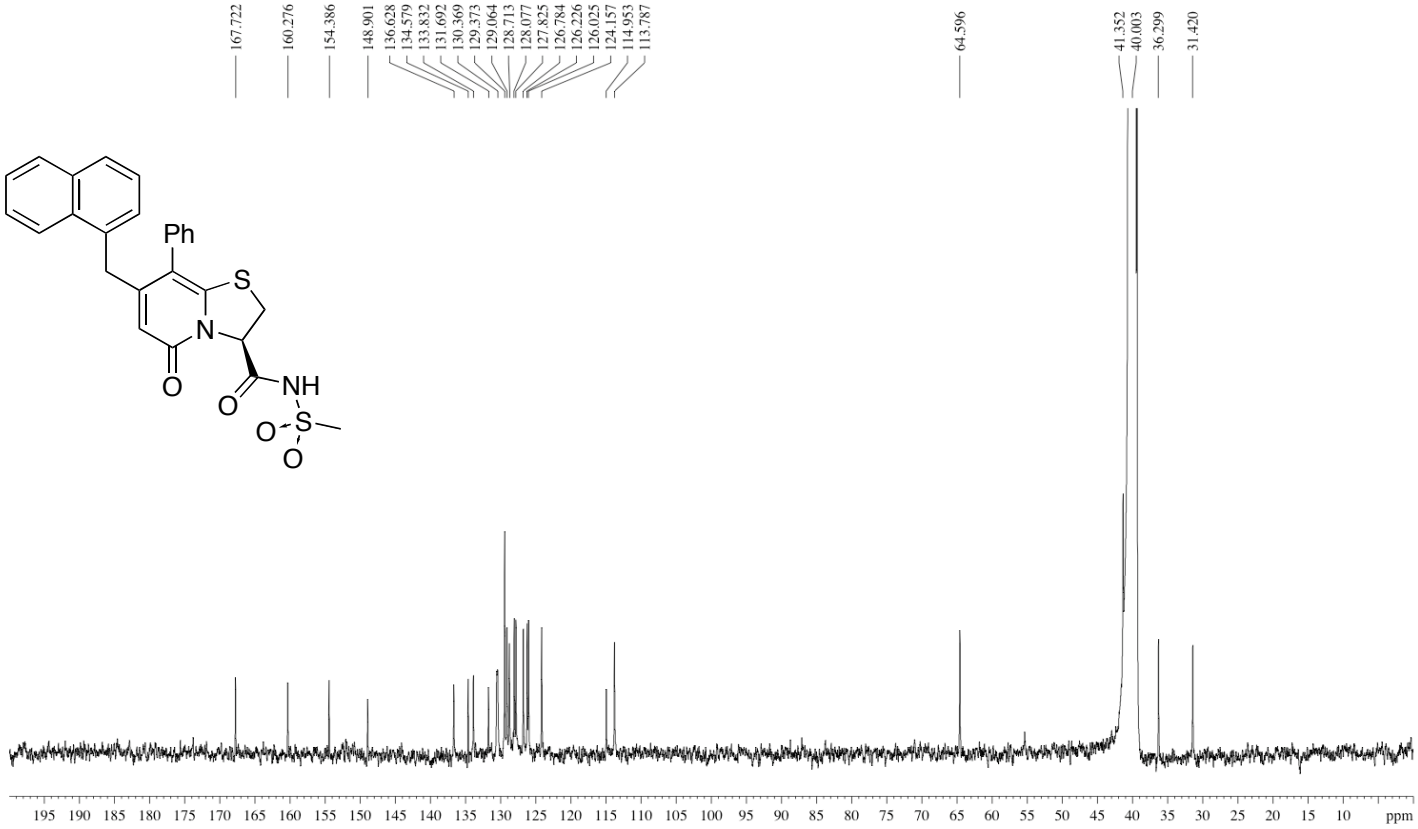
$^{13}$C NMR spectra of compound **5** in $CD_3OD$.



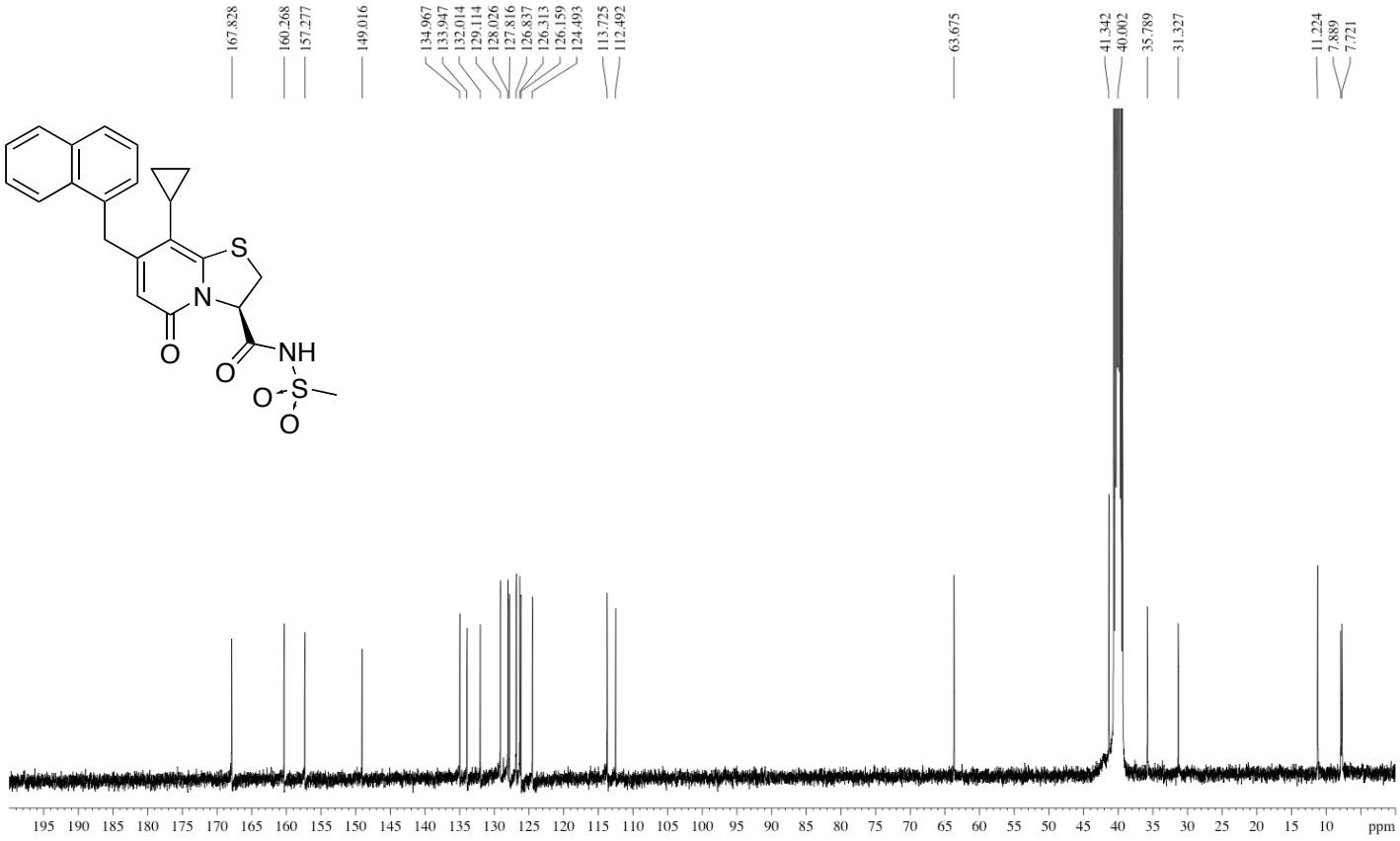

$^{13}$C NMR spectra of compound **6** in $CD_3OD$.



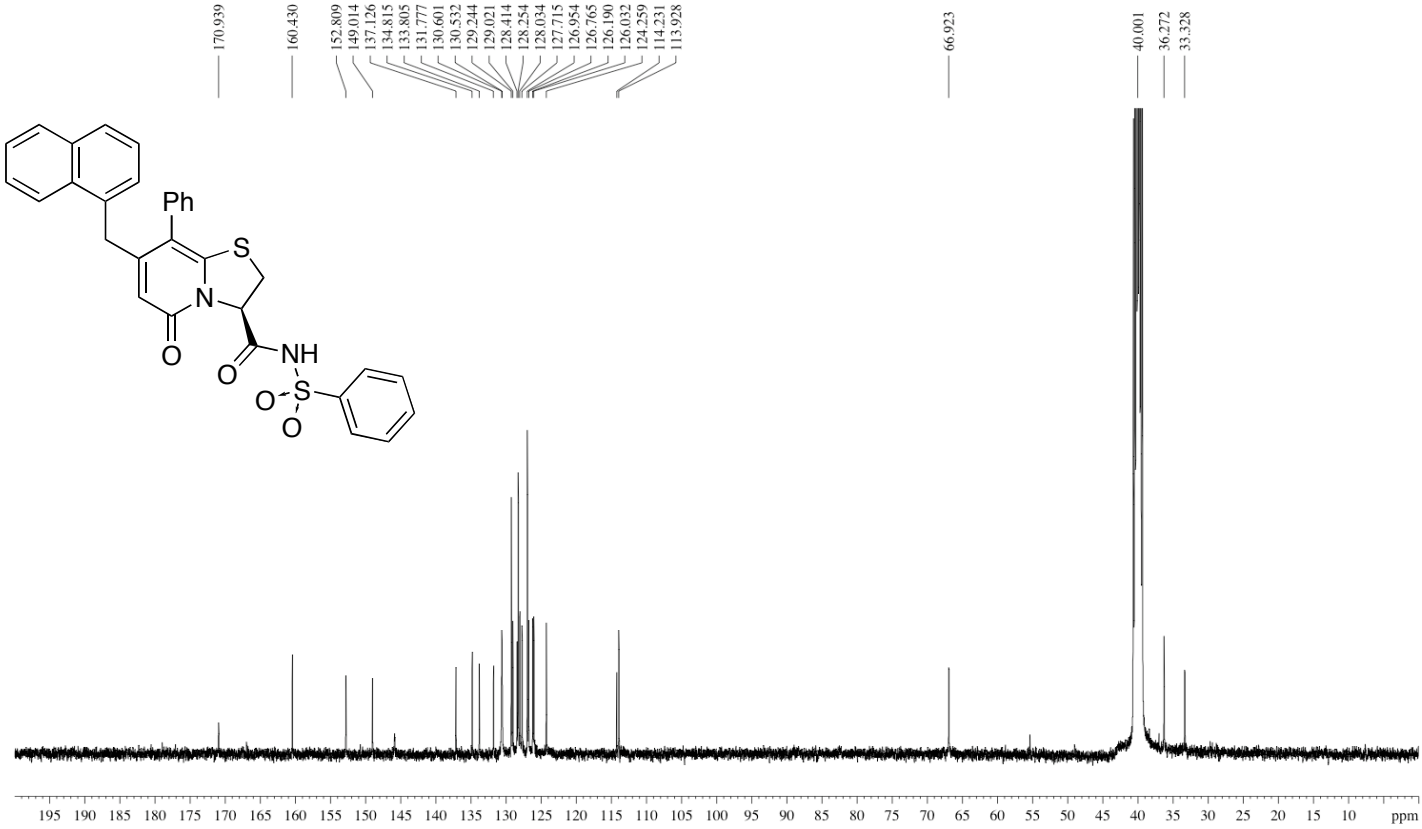
$^{13}$C NMR spectra of compound **9** in DMSO-d6.



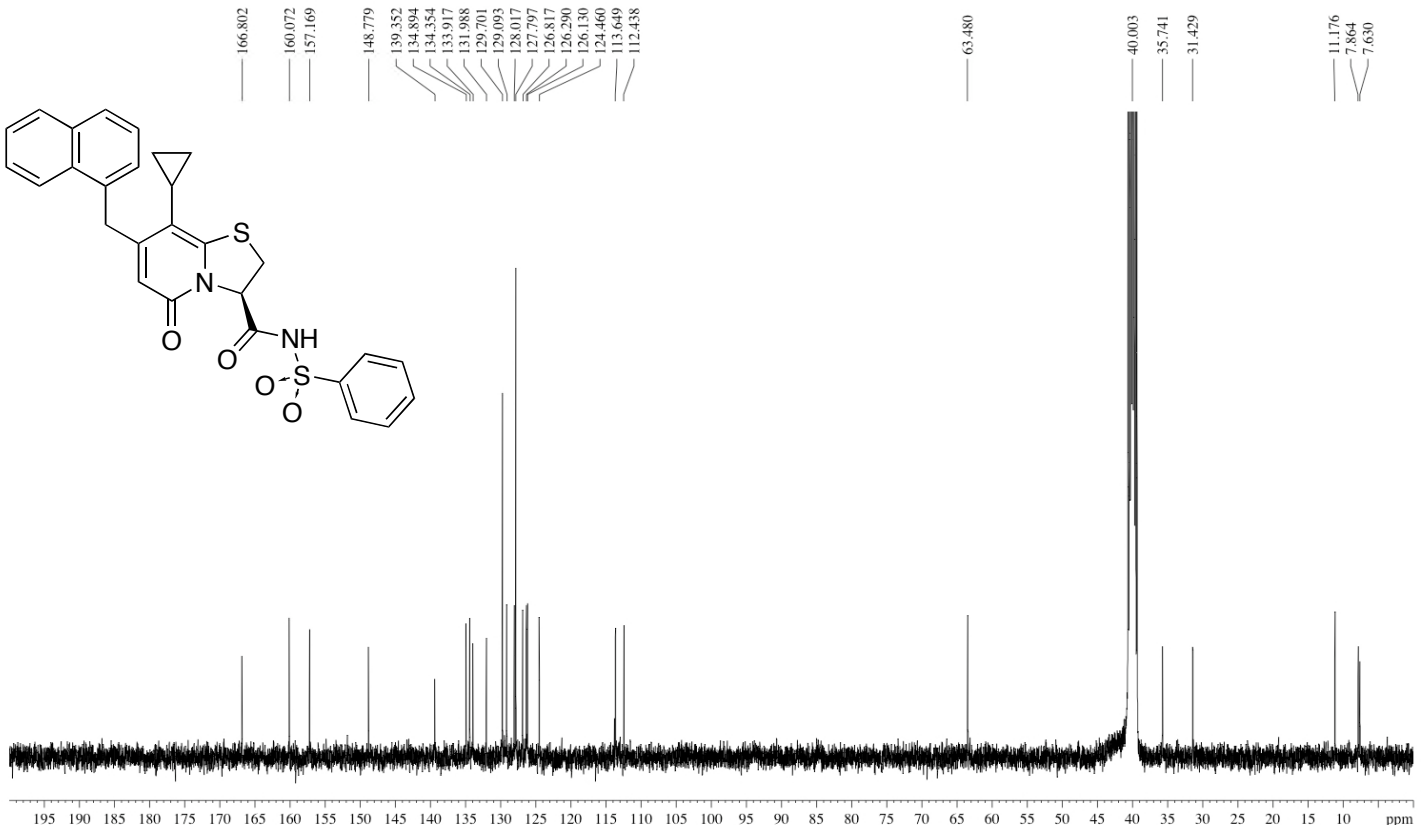

$^{13}$C NMR spectra of compound **10** in DMSO-d6.



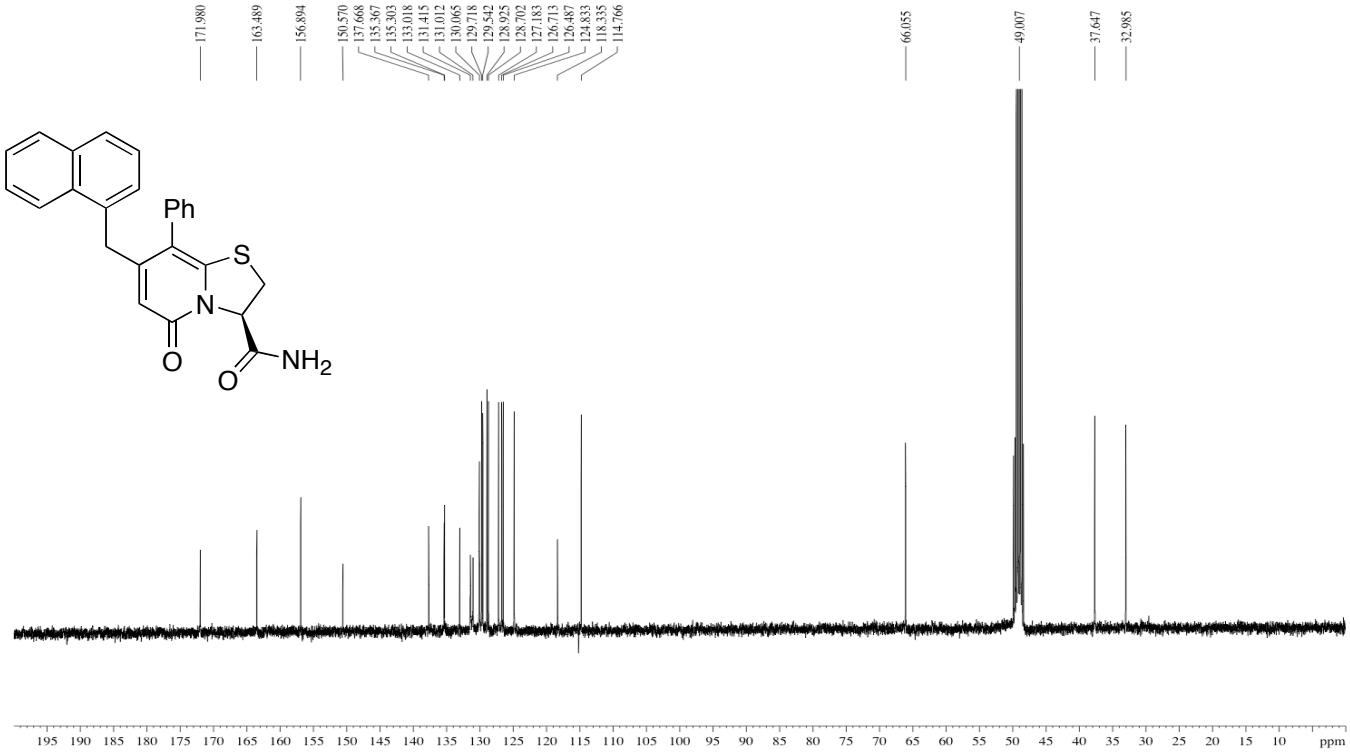
$^{13}$C NMR spectra of compound **11** in DMSO-d6.



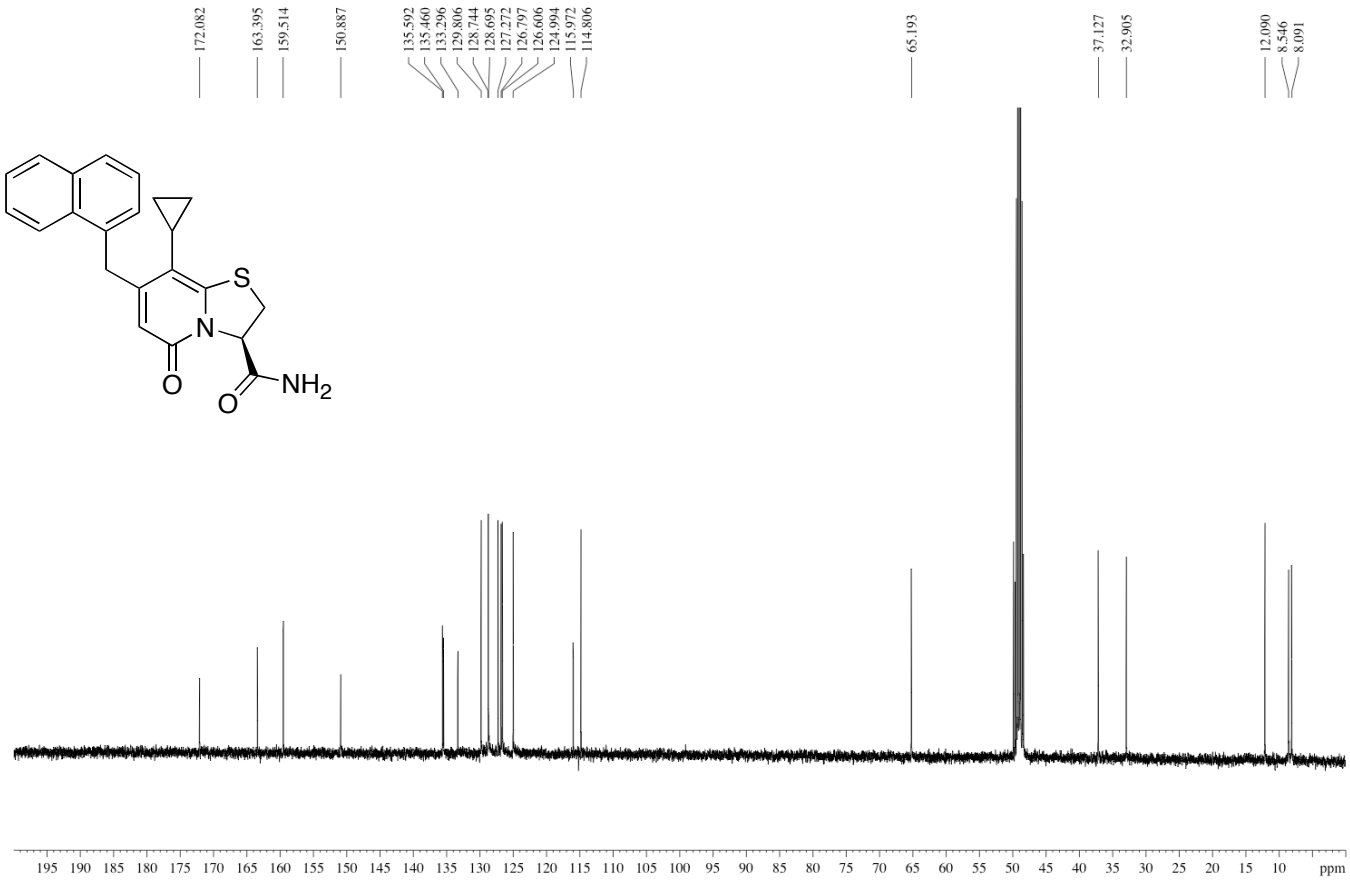

$^{13}$C NMR spectra of compound **12** in DMSO-d6.



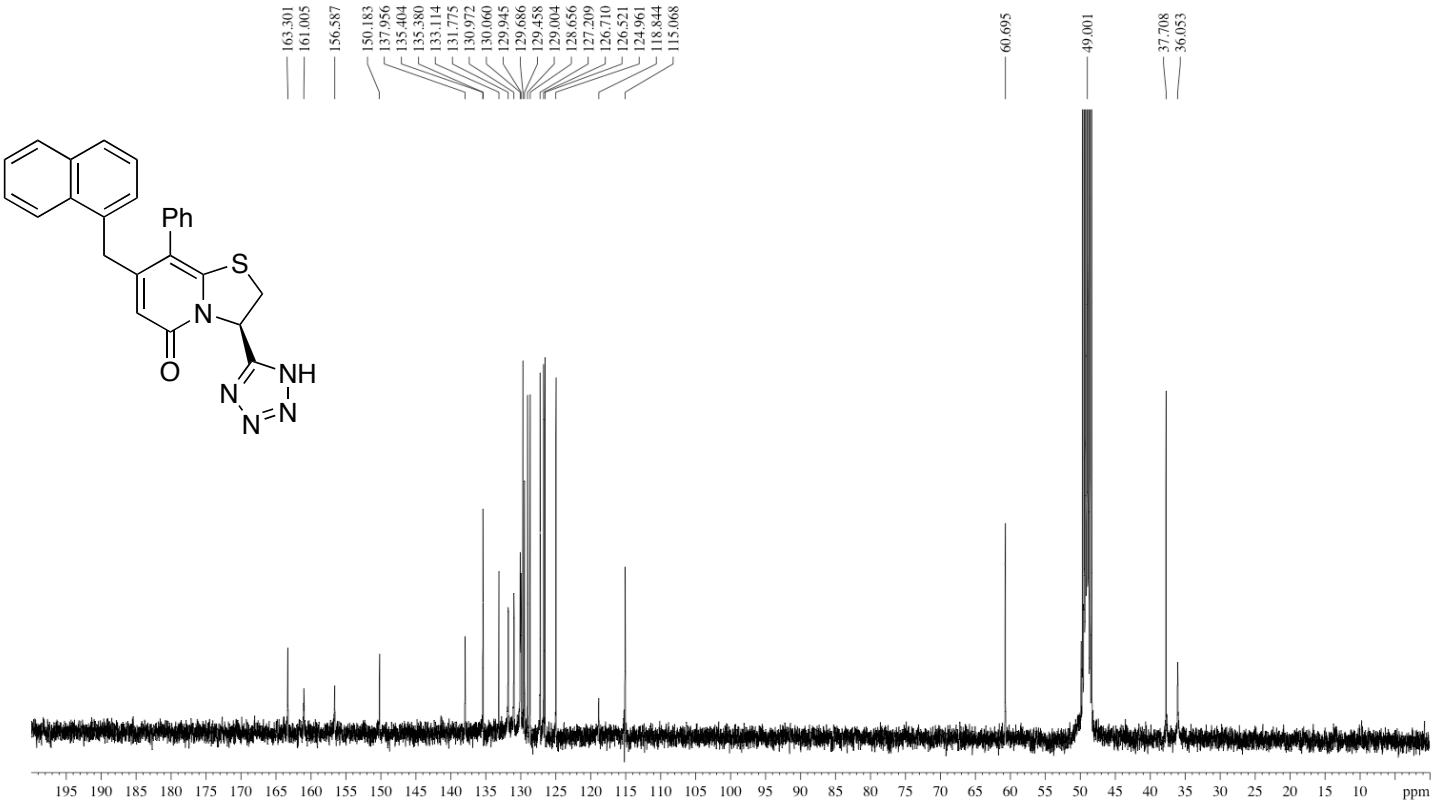
$^{13}C$ NMR spectra of compound **13** in $CD_3OD$.



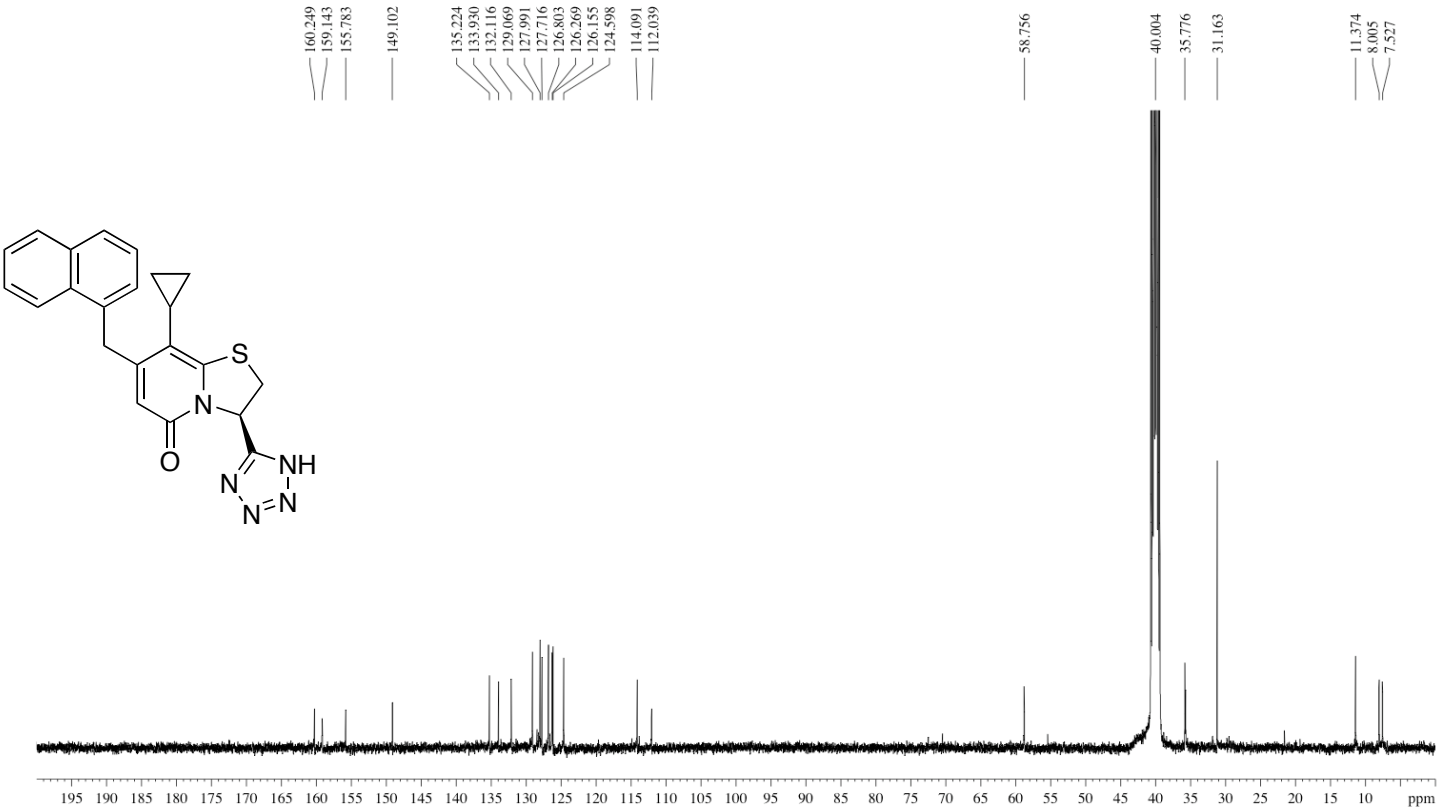

$^{13}C$ NMR spectra of compound **14** in $CD_3OD$.



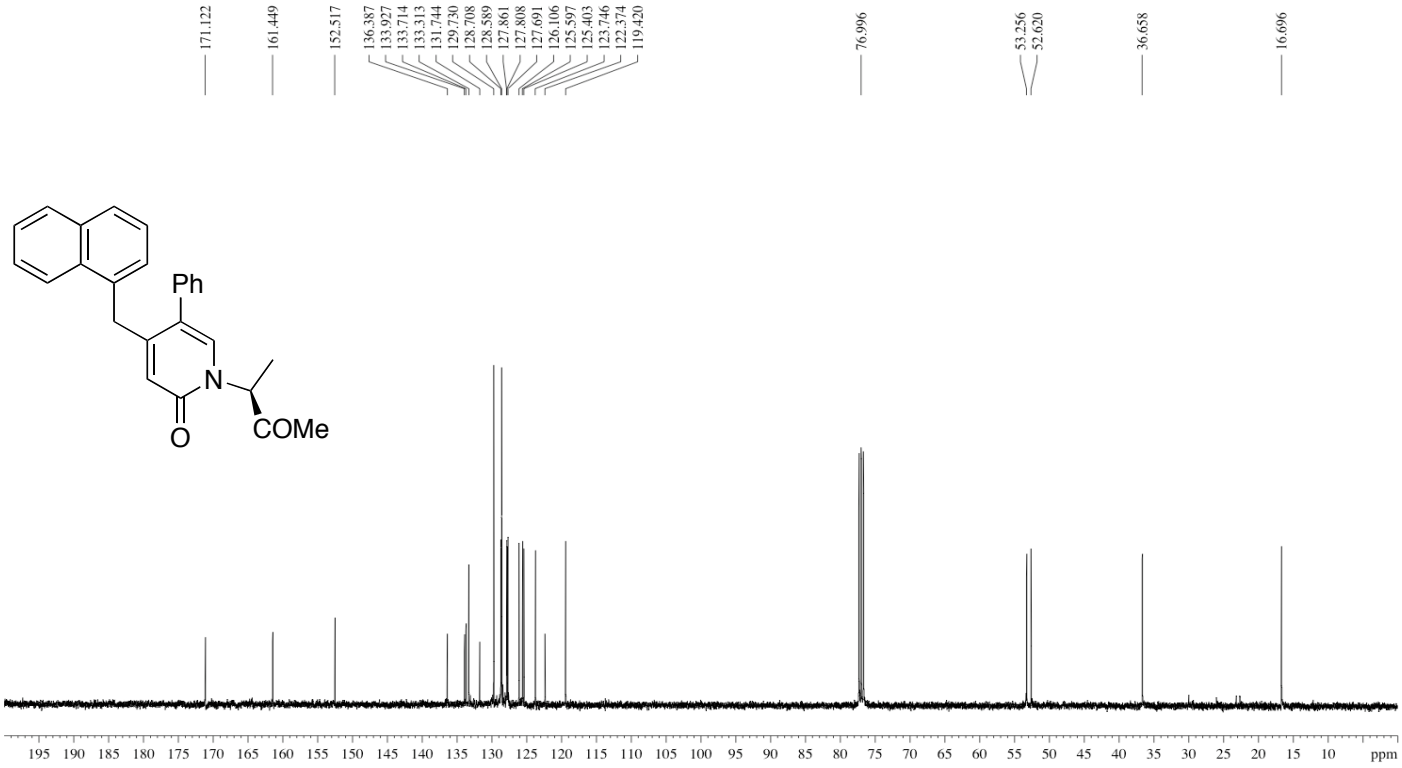
$^{13}$C NMR spectra of compound **15** in $CD_3OD$.



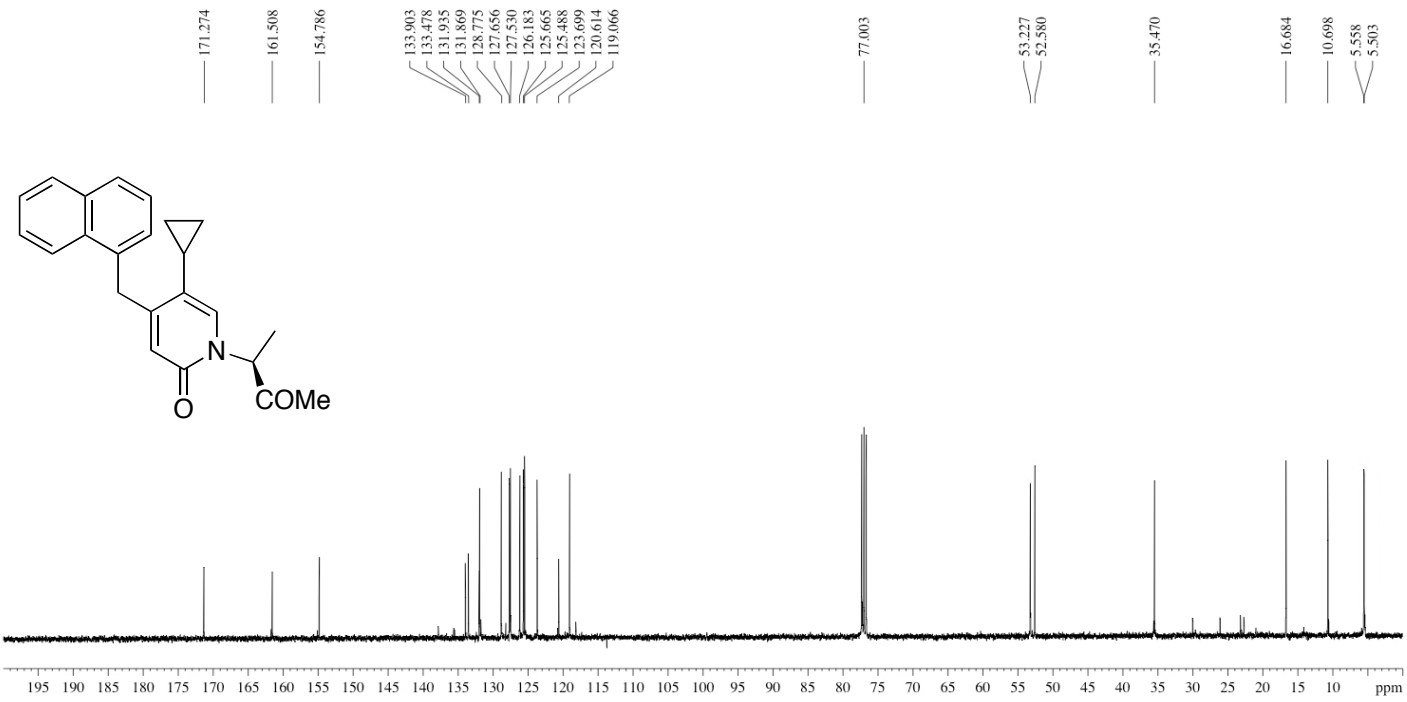

$^{13}$C NMR spectra of compound **16** in DMSO-d6.



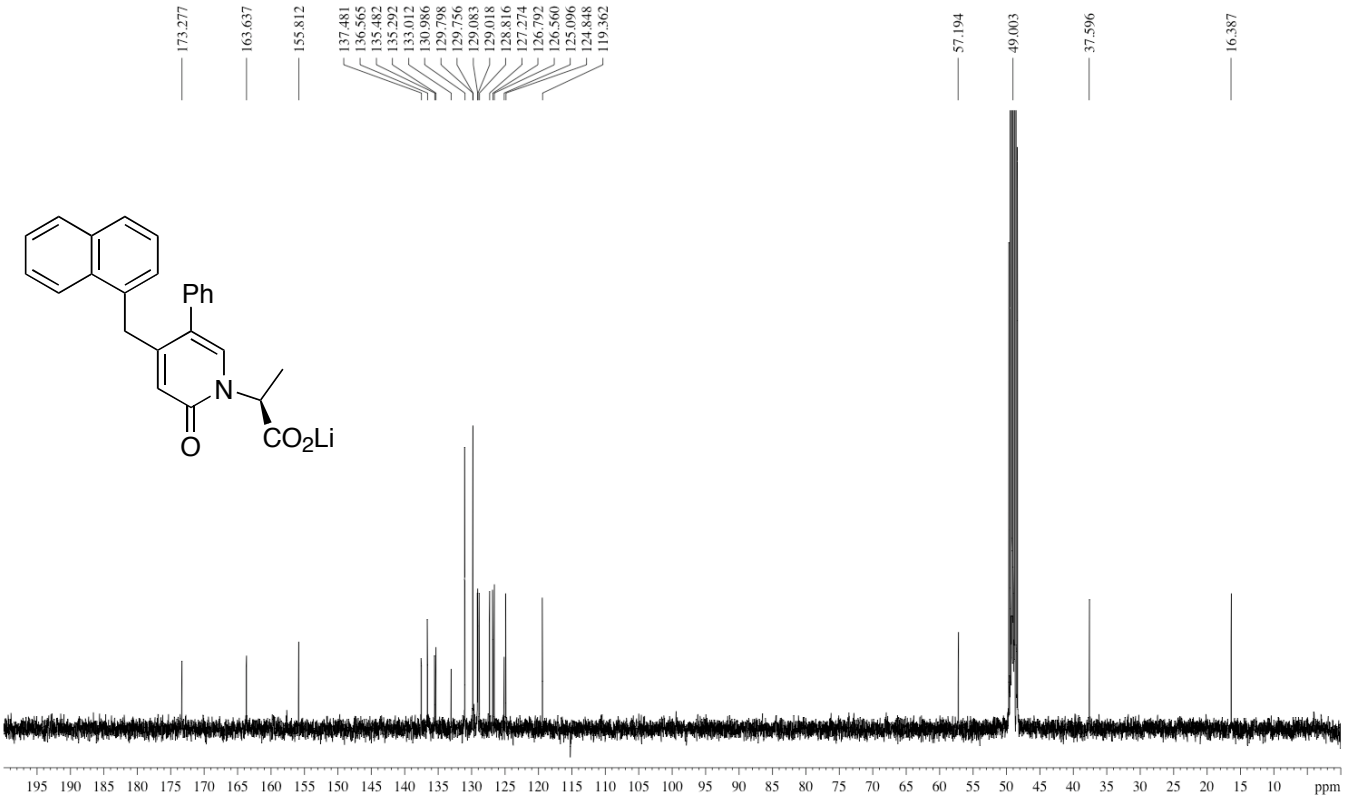
$^{13}C$ NMR spectra of compound **17** in $CDCl_3$




$^{13}C$ NMR spectra of compound **18** in $CDCl_3$



$^{13}C$ NMR spectra of compound **19** in $CD_3OD$.




$^{13}C$ NMR spectra of compound **20** in $CD_3OD$.