Supporting Information

Design and Synthesis of C-2 Substituted Thiazolo and Dihydrothiazolo Ring-Fused 2-Pyridones; Pilicides with Increased Antivirulence Activity

Erik Chorell, Jerome S. Pinkner, Gilles Phan, Sofie Edvinsson, Floris Buelens, Han Remaut, Gabriel Waksman, Scott J. Hultgren, and Fredrik Almqvist

Biofilm and HA-titer assays

Biofilm and HA-titer (*E. coli* grown at 250 µM pilicide compared to 3.6 mM previously) evaluations was performed as reported.[1]

Figure S1

Biofilm inhibition of compounds 9, 5a, 7h, 7g, 7n, 7k, 7l, and 7m. The values and standard deviations are averaged from 16-32 data points on every concentration.

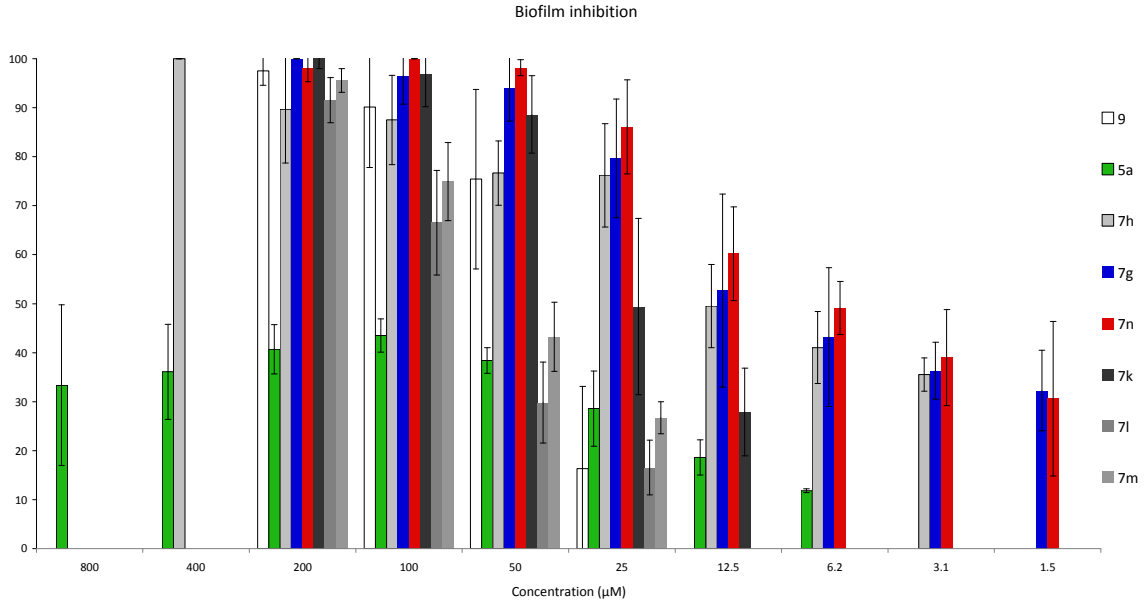
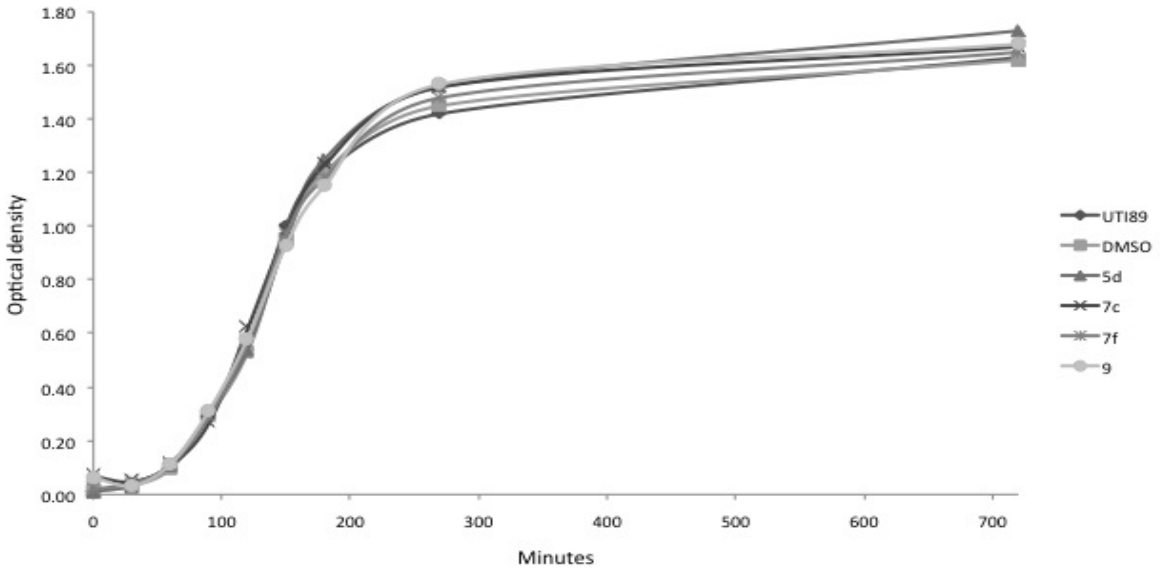


Figure S2

Growth curves for a selected set of C-2 substituted ring-fused 2-pyridones at 400 µM show that the compounds do not effect the bacterial growth (*E*. *coli* clinical isolate UTI89).



Structure determination

Diffraction data for the PapD-PapH – pilicide **1** and pilicide **5d** to 2.4 Å and 2.0 Å resolution, respectively, were collected on beamlines ID29 and MX3 at ESRF, Grenoble – France and Diamond, UK, respectively. Data were indexed, integrated and scaled using Scalepack and the XDS package, respectively.[2, 3] Crystals are in the space group C222(1) with unit cell dimensions of 104.1 Å, 148.7 Å and 82.6 Å (pilicide **1**), and a=103.6 Å, b=149.8 Å and c=82.9 Å (pilicide **5d**), and are isomorphous with the diffraction data from the pilicide free PapD-PapH complex. Difference Fourier maps calculated after an initial rigid body refinement using the PapD-PapH model showed clear density for the respective pilicides. Pilicides were modelled in using Coot and refined using Refmac5.0, applying geometry restrains generated using Sketcher.[2] Refinement statistics are given in Table S1. For pilicide **5d**, difference Fourier maps calculated using a model including the pilicide **5d**, showed additional positive density above the sulphur in the pilicide as well as negative density at the C2 position. This density corresponds with a X-ray induced ring-opened breakdown product of pilicide **5d**. Electron density and mass spectrometry are both in agreement with pilicide **5d'** (Figure S3) as the radiolysis product, likely formed by a hydroxyl radical mediated homolytic hydrolysis of the S-C2 bond in pilicide **5d**. The occupancies of pilicide **5d** and its radiolysis product **5d'** were arbitrarily set to 0.2 and 0.8, respectively, judged on the electron density

Table S1

Table S1. Data collection and Refinement

Data Collection

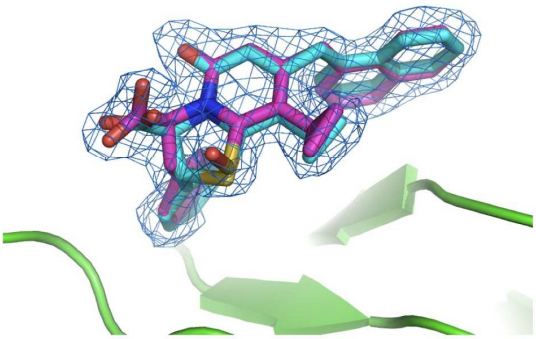
Data Set	Radiation (Å)	Resol. (Å)	Reflections Total/Unique	I/σ(I)	Completeness (%)	R_{merge}
PapD:PapH						
pilicide **1**	0.98023, ID29	20–2.4	128569 / 24104	15.5 (7.3)	99.9 (99.3)	10.5 (39.9)
pilicide **5d**	0.9763, MX3	20–2.0	182178/ 37302	8.8 (7.5)	89.5 (92.6)	5.4 (9.5)

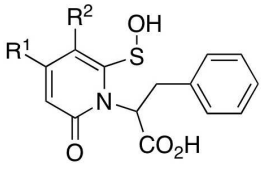
Refinement

	pilicid*e* **1**	pilicide **5d**		pilicide **1**	pilicide **5d**
Resolution (Å)	20.0 – 2.4	20.0 – 2.0	Wilson B (Å^2)	32.0	18.5
Number of reflections			Average B-factor (Å^2)	32.2	22.8
Total	24104	37302	main chain	31.0	23.2
work set	22814	35332	side chain	33.0	24.0
test set	1290	1970	RMSD stereochemistry		
R_{work} (%)	18.3	18.9	bonds (Å)	0.026	0.026
R_{free} (%)	21.7	21.5	angles (Å)	1.941	1.828
Numbers of atoms	2924	3109	RMSD B-factor (Å^2)		
Protein	2806	2828	main chain	1.10	0.93
Water	93	202	side chain	3.58	2.19
pilicide	24	67			

Values for high-resolution shell in parenthesis. R_{merge} = $\sum|I - \langle I\rangle| / \sum I$, where I = observed intensity and $\langle I\rangle$ = average intensity of multiple observations of symmetry-related reflections. RMSD stereochemistry is the deviation from ideal values, RMSD B-factors is the deviation between bonded atoms.

Figure S3





5d'

FoFc difference density map contoured at 2σ showing the pilicide binding site for the PapD-PapH – pilicide **5d** complex (left; FoFc density in blue, PapD in green, **5d** an **5d'** in cyan and pink, respectively). Chemical structure of pilicide **5d'**, the observed radiolysis product of pilicide **5d** (right).

Synthetic experimental section

General Synthesis

All reactions were carried out under inert atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. THF was freshly distilled from potassium, CH_2Cl_2 was distilled from calcium hydride, MeCN and MeOH was dried over activated 3 Å molecular sieves. TLC was performed on Silica Gel 60 F254 (Merck) with detection by UV light (254 nm). Flash column chromatography (eluents given in brackets) was performed on silica gel (Matrex, 60 Å, 35-70 µm, Grace Amicon). Parallel flash chromatography was performed on a Gradmaster parallel, Jones Chromatography using silica gel (Matrex, 60 Å, 35-70 µm, Grace Amicon). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 or Bruker DRX-360 in $CDCl_3$ [residual $CHCl_3$ (δ_H 7.26 ppm) or $CDCl_3$ (δ_C 77.0 ppm) as internal standard], CD_3OD [residual CD_3OD (δ_H 3.31 ppm) or CD_3OD (δ_C 49.0 ppm) as internal standard], DMSO-d_6 [residual DMSO (δ_H 2.50 ppm) or DMSO-d_6 (δ_C 40.0 ppm) as internal standard] or $CDCl_3$:CD_3OD mixtures using CD_3OD (see above) as internal standard at 298 K. IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. Microwave reactions were carried out using a monomode reactor (Smith Creator, Biotage AB) in Teflon septa capped 0.5-2 ml or 2-5 ml Smith TM process vials with stirring. Reaction times refer to irradiation time at target temperature, as measured by IR sensor. Purities of key compounds were >95% as determined by ^{1}H NMR and HPLC.

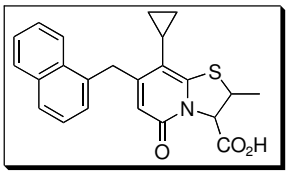
Procedures and characterization data

4a,b,d, **5a-d**, **6**, **6a-f**, **7e** and **9** was prepared according to published procedures.[4-7] For **4a**, **5a**, **5c**, and **6** the data was in agreement with published data.[4-6]

General hydrolysis method 1**:** 0.1 M LiOH(aq) (1.05 equiv) was added to **X** in THF (42 ml/mmol) at rt. The reaction mixture was stirred for approximately 12 h before being concentrated. Purification by column chromatography [CH_2Cl_2:MeOH 97:3→ CH_2Cl_2:MeOH 95:5 and 1% AcOH] gave X-X.

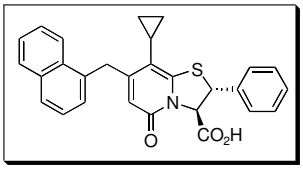
General hydrolysis method 2[6]**:** LiBr (10 equiv) was added to a stirred suspension of **X** in MeCN (12 ml/mmol, 2 v/v % water) cooled on ice. TEA (3 equiv) was added dropwise and the reaction mixture was stirred on ice for 45 min before stirring was continued at rt. After 5 h at rt the reaction mixture was diluted with EtOAc, washed with 2% $KHSO_4$(aq.) and the aqueous layer was extracted with EtOAc. The combined organic layers were concentrated under reduced pressure and purified by column chromatography [CH_2Cl_2:MeOH 97:3→ CH_2Cl_2:MeOH 95:5 and 1% AcOH] to give X-X.

General hydrolysis method 3**:** KOH(s) (25 equiv) was added to X dissolved in THF (12 ml/mmol) and MeOH (6 ml/mmol). The suspension was heated by microwave irradiation for 25 min at 90 °C before being cooled to rt. The reaction mixture was diluted in CH_2Cl_2 and washed twice with 1M HCl. The combined organic layers were concentrated under reduced pressure and purified by column chromatography [CH_2Cl_2:MeOH 97:3→ CH_2Cl_2:MeOH 95:5 and 1% AcOH] to give X-X.



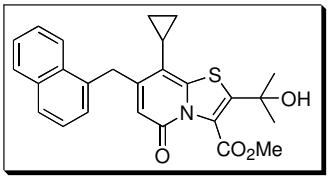
8-Cyclopropyl-2-methyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (5b).

By following general hydrolysis method 1, **4b** (12.5 mg, 0.0308 mmol) gave **5b** (11 mg, 92% yield) which was lyophilized from MeCN/H_2O to give a white solid IR (neat) 3316, 1623, 1562, 1484, 1388, and 775 cm^{-1}. ^1H NMR (360 MHz, CD_3OD) δ 0.69-0.83 (m, 2H), 0.83-1.03 (m, 2H), 1.50 (d, *J* = 6.92 Hz, 3H), 1.63-1.77 (m, 1H), 4.04 (q, *J* = 6.89 Hz, 1H), 4.45-4.59 (m, 2H), 5.06 (s, 1H), 5.60 (s, 1H), 7.32-7.38 (m, 1H), 7.41-7.53 (m, 3H), 7.77-7.84 (m, 1H), 7.85-7.92 (m, 2H). ^{13}C NMR (90 MHz, CD_3OD) δ 7.9, 8.5, 12.0, 24.5, 37.2, 45.7, 74.0, 114.7, 116.0, 125.1, 126.7, 126.8, 127.3, 128.6, 128.8, 129.8, 133.5, 135.5, 135.9, 150.1, 158.7, 164.1, 173.7.



8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-phenyl-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (5d).

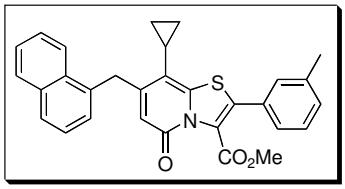
By following general hydrolysis method 1, **4d** (22.5 mg, 0.048 mmol) gave **5d** (20.5 mg, 95% yield) which was lyophilized from MeCN/H_2O to give a light yellow solid. IR (neat) 3062, 3004, 1727, 1623, 1484, 1172, 779, 732, and 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.71-0.83 (m, 2H), 0.89-1.05 (m, 2H), 1.71-1.82 (m, 1H), 4.55 (s, 2H), 5.20 (s, 1H), 5.51 (s, 1H), 5.65 (s, 1H), 7.27-7.39 (m, 6H), 7.43-7.53 (m, 3H), 7.79-7.93 (m, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 8.2, 8.6, 12.0, 37.2, 52.0, 72.0, 115.3, 116.1, 125.0, 126.7, 126.8, 127.3(3C), 128.8 (2C), 129.6, 129.8, 130.3 (2C), 133.4, 135.5, 135.6, 142.1, 149.4, 159.9, 163.5, 170.7.



8-Cyclopropyl-2-(1-hydroxy-1-methyl-ethyl)-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6b).

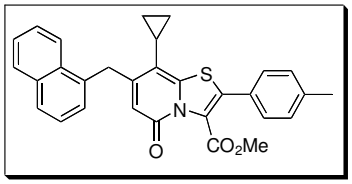
By following a published procedure.[5] To a solution of **6** (30 mg, 0.077 mmol) in 2 ml of THF at -78 °C was rapidly added freshly prepared LDA (1.05 equiv, 0.36 M). After stirring for 60 s at -78 °C acetone (14 µl, 0.1925 mmol) was added and the solution was left stirring for 10 min at -78 °C before quenching with 2% (aq.) $KHSO_4$. The solution was extracted three times with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtrated and concentrated; the residue was purified by column chromatography (heptane:EtOAc, 1:1) giving **6b** in 82% yield as a yellow foam; IR (in CH_2Cl_2) 3051, 2984, 1735, 1651, 1477, 1421, 1265, 896, 742, and 705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.71-0.77 (m, 2H), 0.97-1.04 (m, 2H), 1.64 (s, 6H), 1.67 (s, 6H), 1.69-1.78 (m, 1H), 2.93 (bs, 1H), 3.90 (s, 3H), 4.51 (m, 2H), 5.90 (s, 1H), 7.17-7.22 (m, 1H), 7.35-7.41 (m, 1H), 7.42-7.50 (m, 2H), 7.72-7.89 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9 (2C), 10.8, 31.0 (2C), 36.1, 53.2, 71.1, 111.4, 111.9, 123.6, 124.4, 125.5, 125.7, 126.2, 127.2, 127.5, 128.8, 131.9, 133.9, 134.3, 139.1, 146.4, 153.2, 158.9, 162.6. HRMS (FAB) calcd for $[M + H]^+$ $C_{26}H_{26}NO_4S^+$ 448,1577, obsd 448.1593.

General procedure for Suzuki-Miyaura couplings:



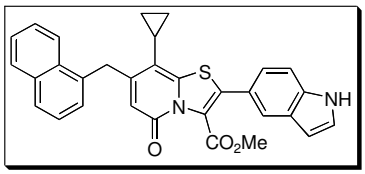
8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-*m*-tolyl-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6g).

Dry MeOH (0.9. ml) was added to pyridone **8** (20mg, 0.043 mmol), $Pd(OAc)_2$ (1 mg, 0.004 mmol), KF (5 mg, 0.81 mmol) and boronic acid (12 mg, 0.085 mmol). The reaction mixture was heated in a sealed tube by microwave irradiation (MWI) at 100 °C for 10 min. The resulting mixture was diluted with CH_2Cl_2, washed with sat. (aq.) $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were concentrated under reduced pressure and purification by parallel flash chromatography [heptane:EtOAc 100:0→0:100] gave pyridone **6g** (20 mg, 96 % yield) as yellow foam. IR (neat) 3056, 2934, 1771, 1688, 1588, 1468, 1249, 1200, 786, 763 and 711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.77-0.84 (m, 2H), 1.02-1.10 (m, 2H), 1.76-1.86 (m, 1H), 2.41 (s, 3H), 3.88 (s, 3H), 4.55 (s, 2H), 5.94 (s, 1H), 7.21-7.26 (m, 2H), 7.30-7.36 (m, 1H), 7.37-7.44 (m, 3H), 7.45-7.52 (m, 2H), 7.75-7.81 (m, 1H), 7.81-7.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9 (2C), 10.9, 21.4, 36.2, 53.3, 111.7, 111.9, 123.7, 125.4, 125.5(2C), 125.7, 126.2, 127.3, 127.6, 128.6, 128.8, 128.9, 129.0, 129.1, 130.8, 131.9, 133.9, 134.2, 139.0, 146.3, 153.4, 158.9, 161.8. HRMS (FAB) calcd for $[M + H]^+$ $C_{30}H_{26}NO_3S^+$ 480.1628, obsd 480.1632.



8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-*p*-tolyl-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6h).

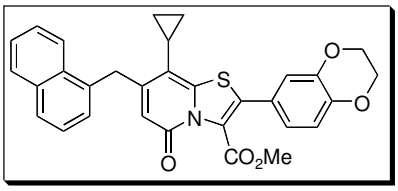
By following the same procedure as for the preparation of **6g**, **8** (20 mg, 0.043 mmol) gave **6h** (20 mg, 96 % yield) as a yellow foam. IR (neat) 2992, 2934, 1771, 1690, 1613, 1440, 1247, 1177, 1023, 784 and 711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.77-0.83 (m, 2H), 1.02-1.08 (m, 2H), 1.76-1.85 (m, 1H), 2.40 (s, 3H), 3.88 (s, 3H), 4.55 (s, 2H), 5.94 (s, 1H), 7.21-7.26 (m, 3H), 7.38-7.51 (m, 5H), 7.76-7.90 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9 (2C), 10.9, 21.3, 36.2, 53.3, 111.7, 111.9, 123.6, 125.1, 125.5, 125.70, 125.73, 126.2, 127.3, 127.6, 128.3 (2C), 128.8, 129.0, 129.9 (2C), 131.9, 133.9, 134.2, 140.2, 146.3, 153.3, 158.9, 161.9. HRMS (FAB) calcd for $[M + H]^+$ $C_{30}H_{26}NO_3S^+$ 480.1628, obsd 480.1627.



8-Cyclopropyl-2-(1H-indol-5-yl)-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6i).

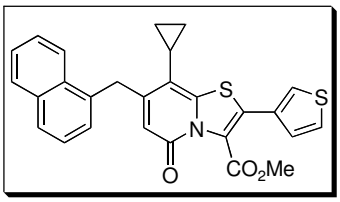
By following the same procedure as for the preparation of **6g**, **8** (20 mg, 0.043 mmol) gave **6i** (16 mg, 72 % yield) as a yellow solid. IR (neat) 1688, 1602, 1517, 1467, 784 and 747 cm^{-1}. ^1H NMR (400 MHz, DMSO, d_6) δ 0.79-0.86 (m, 2H), 1.00-1.07 (m, 2H), 1.87-1.96 (m, 1H), 3.72 (s, 3H), 4.60 (s, 2H), 5.56(s, 1H), 6.56 (s, 1H), 7.27-7.31 (m, 1H), 7.36-7.40 (m, 1H), 7.46-7.57 (m, 5H), 7.80-7.82 (m, 1H), 7.86-7.95 (m, 2H), 7.95-8.00 (m, 1H), 11.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0 (2C), 11.1, 35.9, 53.3, 102.4, 110.2, 112.0, 112.9, 118.9, 120.9, 121.3, 123.7, 124.5, 126.2, 126.3, 126.9, 127.8

(2C), 128.0, 128.5, 129.1, 130.9, 132.0, 134.0, 135.1, 137.0, 146.3, 154.0, 158.0, 161.8. HRMS (FAB) calcd for $[M + H]^+$ $C_{31}H_{25}N_2O_3S^+$ 505.1580, obsd 505.1585.



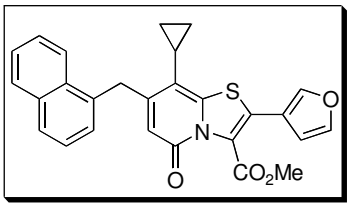
8-Cyclopropyl-2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6j).

By following the same procedure as for the preparation of **6g**, **8** (40 mg, 0.085 mmol) gave **6j** (42 mg, 94 % yield) as a yellow foam. IR (neat) 2979, 1735, 1648, 1471, 1288, 1247, 1068 and 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.75-0.81 (m, 2H), 1.00-1.07 (m, 2H), 1.75-1.84 (m, 1H), 3.90 (s, 3H), 4.28 (s, 4H), 4.54 (s, 2H), 5.93 (s, 1H), 6.89-6.94 (m, 1H), 7.05-7.14 (m, 2H), 7.20-7.25 (m, 1H), 7.37-7.43 (m, 1H), 7.44-7.51 (m, 2H), 7.75-7.80 (m, 1H), 7.80-7.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8 (2C), 10.9, 36.2, 53.3, 64.2, 64.4, 111.6, 111.8, 117.4, 118.0, 121.6, 121.7, 123.6, 124.8, 125.5, 125.7, 126.2, 127.2, 127.6, 128.5, 128.8, 131.9, 133.9, 134.2, 143.9, 145.2, 146.1, 153.2, 158.8, 161.8. HRMS (FAB) calcd for $[M + H]^+$ $C_{31}H_{26}NO_5S^+$ 524.1526, obsd 524.1532.



8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-thiophen-3-yl-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6k).

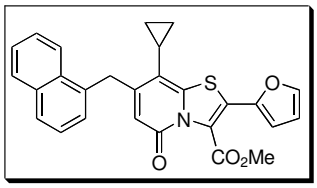
By following the same procedure as for the preparation of **6g**, **8** (50 mg, 0.107 mmol) gave **6k** (45.5 mg, 90 % yield) as a foam. IR (neat) 3052, 2985, 1737, 1653, 1476, 1421, 1265, 896, 740, and 705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.76-0.82 (m, 2H), 1.02-1.09 (m, 2H), 1.75-1.85 (m, 1H), 3.92 (s, 3H), 4.54 (s, 2H), 5.92 (s, 1H), 7.21-7.25 (m, 1H), 7.28-7.32 (m, 1H), 7.38-7.51 (m, 4H), 7.61-7.65 (m, 1H), 7.75-7.90 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9 (2C), 10.9, 36.2, 53.4, 111.7, 111.9, 123.6, 123.8, 124.9, 125.5, 125.6, 125.7, 126.2, 126.7, 127.29, 127.32, 127.6, 128.7, 128.8, 131.9, 133.9, 134.1, 145.6, 153.5, 158.8, 161.9. HRMS (FAB) calcd for $[M + H]^+$ $C_{27}H_{22}NO_3S_2^+$ 472.1036, obsd 472.1038.



8-Cyclopropyl-2-furan-3-yl-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6l).

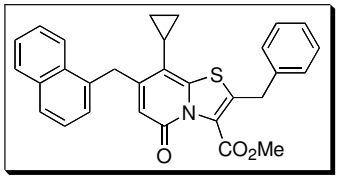
By following the same procedure as for the preparation of **6g**, **8** (50 mg, 0.107 mmol) gave **6l** (22.6 mg, 46 % yield) as a red oil. IR (neat) 3052, 2985, 1653, 1421, 1265, 896, 740, and 705 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 0.75-0.82 (m, 2H), 1.01-1.09 (m, 2H), 1.74-1.85 (m, 1H), 3.93 (s, 3H), 4.54 (s, 2H), 5.91 (s, 1H), 6.60-6.64 (m, 1H), 7.21-7.25 (m, 1H), 7.37-7.52 (m, 4H), 7.75-7.90 (m, 4H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 7.9 (2C), 10.9, 36.2, 53.4, 109.5, 111.8, 112.0, 114.6, 121.0, 123.6, 125.1, 125.5, 125.7, 126.2, 127.3,

127.6, 128.8, 131.9, 133.9, 134.1, 141.7, 144.3, 145.5, 153.6, 158.8, 161.8. HRMS (FAB) calcd for $[M + H]^+$ $C_{27}H_{22}NO_4S^+$ 456.1264, obsd 456.1275.



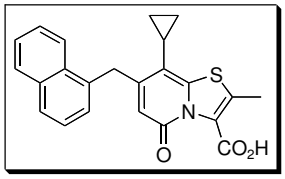
8-Cyclopropyl-2-(furan-2-yl)-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6m).

By following the same procedure as for the preparation of **6g**, **8** (40 mg, 0.085 mmol) gave **6m** (13 mg, 34 % yield) as a red oil. IR (neat) 3117, 2932, 1702, 1603, 1588, 1440, 1251, 1220, 765 and 713 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.77-0.83 (m, 2H), 1.03-1.10 (m, 2H), 1.76-1.84 (m, 1H), 3.97 (s, 3H), 4.54 (s, 2H), 5.91 (s, 1H), 6.50-6.53 (m, 1H), 6.72-6.75 (m, 1H), 7.21-7.25 (m, 1H), 7.38-7.43 (m, 1H), 7.44-7.50 (m, 2H), 7.51-7.53 (m, 1H), 7.75-7.80 (m, 1H), 7.80-7.84 (m, 1H), 7.85-7.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9 (2C), 10.9, 36.2, 53.4, 110.8, 111.9, 112.0, 112.4, 119.0, 123.6, 123.9, 125.5, 125.7, 126.3, 127.3, 127.7, 128.9, 131.9, 133.9, 134.1, 143.3, 144.2, 145.3, 153.7, 158.9, 161.6. . HRMS (FAB) calcd for $[M + H]^+$ $C_{27}H_{22}NO_4S^+$ 456.1264, obsd 456.1273.



2-Benzyl-8-cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6n).

By following a published procedure.[5] To a solution of **6** (40 mg, 0.103 mmol) in 2 mL of THF at -78 °C was rapidly added freshly prepared LDA (1.05 equiv, 0.36 M). After stirring for 60 s at -78 °C bensylbromine (31 µl, 0.2575 mmol) was added and the solution was left stirring for 10 min at -78 °C before quenching with 2% (aq.) $KHSO_4$. The solution was extracted three times with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtrated and concentrated; the residue was purified by column chromatography (heptane:EtOAc, 3:2) giving **6n** in 75% yield as a yellow foam. IR (neat) 3052, 2984, 1734, 1653, 1477, 1421, 1265, 896, 739, and 705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.66-0.72 (m, 2H), 0.92-0.99 (m, 2H), 1.65-1.74 (m, 1H), 3.95 (s, 3H), 4.03 (s, 2H), 4.50 (s, 2H), 5.91 (s, 1H), 7.18-7.23 (m, 1H), 7.27-7.51 (m, 8H), 7.74-7.89 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8 (2C), 10.9, 32.7, 36.2, 53.2, 111.8, 112.1, 123.6, 125.5, 125.7, 126.2, 126.9, 127.3, 127.5, 127.6, 128.7 (2C), 128.8, 129.0 (2C), 130.7, 131.9, 133.9, 134.2, 136.9, 146.7, 153.3, 158.8, 161.5. HRMS (FAB) calcd for $[M + H]^+$ $C_{30}H_{26}NO_3S^+$ 480.1628, obsd 480.1639.

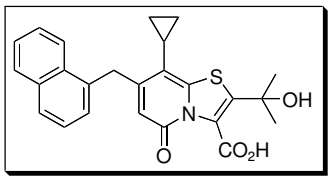


8-Cyclopropyl-2-methyl-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid

(7a).

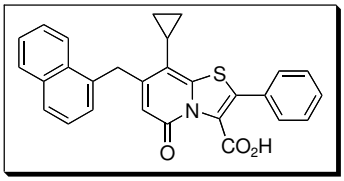
By following general hydrolysis method 3 but heated at 60 °C for 15 min, **6a** (20 mg, 0.05 mmol) gave **7a** (16.5 mg, 85 % yield) which was lyophilized from $MeCN/H_2O$ to give a white solid. IR (neat) 3046, 2923, 1693, 1654, 1569, 1508, 1400, and 782 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.81-0.87 (m, 2H), 1.16-1.22 (m, 2H), 1.85-1.94 (m, 1H), 2.83 (s, 3H), 4.60 (m, 2H), 6.13 (s, 1H), 7.22-7.26 (m, 1H), 7.40-7.52 (m, 3H), 7.71-7.75 (m, 1H), 7.79-7.84 (m, 1H), 7.87-7.92 (m 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4 (2C), 11.0, 17.3,

35.8, 112.2, 116.5, 123.4, 125.5, 125.9, 126.5, 127.7, 128.1, 129.0, 129.6, 131.7, 133.3, 134.0, 143.6, 147.1, 154.2, 159.3, 160.8.



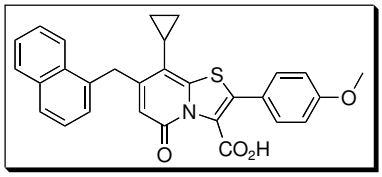
8-Cyclopropyl-2-(1-hydroxy-1-methyl-ethyl)-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7b).

By following general hydrolysis method 1, **6b** (10 mg, 0.0223 mmol) gave **7b** (9 mg, 93% yield) which was lyophilized from MeCN/H_2O to give a white solid. IR (neat) 3301, 2973, 1716, 1631, 1473, 1365, 1230, 1176, and 779 cm^{-1}. ^1H NMR (360 MHz, CD_3OD) δ 0.78-0.85 (m, 2H), 1.05-1.13 (m, 2H), 1.67 (s, 6H), 1.85-1.95 (m, 1H), 4.62 (m, 2H), 5.74 (s, 1H), 7.27-7.32 (m, 1H), 7.40-7.50 (m, 3H), 7.77-7.92 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6 (2C), 11.7, 30.7 (2C), 37.2, 71.5, 110.7, 114.1, 125.0, 126.6, 126.8, 127.2, 128.4, 128.6 (2C), 129.8, 133.3, 135.5, 136.0, 140.9, 149.2, 155.0, 160.8, 165.8.



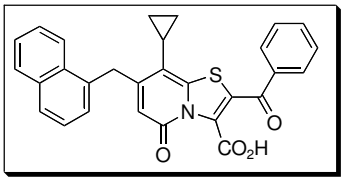
8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-phenyl-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7c).

By following general hydrolysis method 3, **6c** (37.5 mg, 0.081 mmol) gave **7c** (31 mg, 85 % yield) which was lyophilized from MeCN/H_2O to give a light yellow solid. IR (neat) 3050, 2973, 2927, 1720, 1635, 1469, 1180, 775, 759, and 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.74-0.82 (m, 2H), 1.01-1.10 (m, 2H), 1.74-1.85 (m, 1H), 4.54 (s, 2H), 6.11 (s, 1H), 7.12-7.20 (m, 1H), 7.33-7.42 (m, 4H), 7.43-7.52 (m, 2H), 7.54-7.61 (m, 2H), 7.74-7.82 (m, 2H), 7.85-7.91 (m, 1H), 9.15 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.3 (2C), 11.4, 36.6, 111.3, 113.7, 124.1, 125.9, 126.2, 126.7, 127.9, 128.1, 128.6, 128.7, 129.0 (2C), 129.2, 129.3, 129.5 (2C), 130.3, 132.4, 134.5, 134.7, 147.8, 154.5, 159.9, 163.9.



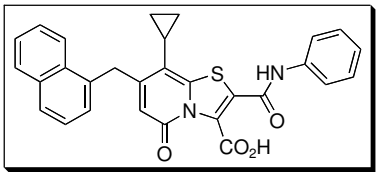
8-Cyclopropyl-2-(4-methoxy-phenyl)-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7d).

By following general hydrolysis method 3, **6d** (20 mg, 0.040 mmol) gave **7d** (17.5 mg, 90 % yield) which was lyophilized from MeCN/H_2O to give a light yellow solid. IR (neat) 3062, 2927, 1712, 1639, 1469, 1253, 1180, 1025, and 782 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.78-0.84 (m, 2H), 1.00-1.08 (m, 2H), 1.86-1.96 (m, 1H), 3.82 (s, 3H), 4.59 (s, 2H), 5.53 (s, 1H), 7.03-7.09 (m, 2H), 7.37-7.41 (m, 1H), 7.48-7.58 (m, 3H), 7.60-7.66 (m, 2H), 7.87-8.01 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.6 (2C), 10.7, 35.4, 55.4 109.8, 111.2, 113.5, 113.8, 114.7 (2C), 120.8, 124.0, 125.7, 125.8, 126.4, 127.3, 127. 5, 128.6, 129.6 (2C), 131.5, 133.5, 134.7, 145.9, 153.3, 157.6, 160.4, 161.7.



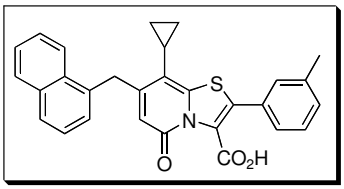
2-Benzoyl-8-cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7e).

By following general hydrolysis method 2, **6e** (20 mg, 0.0405 mmol) gave **7e** (15.5 mg, 80% yield) which was lyophilized from MeCN/H_2O to give a light yellow solid. IR (neat) 3035, 2923, 1639, 1565, 1469, 1257, 779, and 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.76-0.86 (m, 2H), 1.06-1.13 (m, 2H), 1.80-1.91 (m, 1H), 4.58 (s, 2H), 5.96 (s, 1H), 7.21-7.27 (m, 1H), 7.37-7.53 (m, 5H), 7.58-7.66 (m, 1H), 7.71-7.81 (m, 2H), 7.82-7.89 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4 (2C), 11.0, 36.1, 112.7, 117.5, 123.3, 125.6, 126.0, 126.6, 127.8, 128.3(3C), 128.9 (2C), 129.1, 131.6, 132.2 (2C), 132.8, 134.0, 134.2, 135.3, 141.6, 148.6, 156.0, 157.1, 161.3, 186.0.



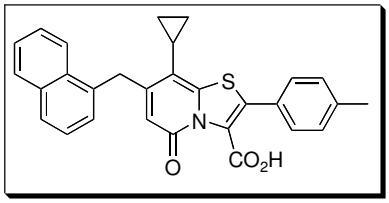
8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-phenylcarbamoyl-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7f).

By following general hydrolysis method 3, **6f** (15 mg, 0.029 mmol) gave **7f** (12.6 mg, 88 % yield) which was lyophilized from MeCN/H_2O to give a yellow solid. IR (neat) 3062, 1643, 1596, 1542, 1469, 1238, and 1191 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 0.83-0.89 (m, 2H), 1.10-1.19 (m, 2H), 1.90-2.00 (m, 1H), 4.66 (s, 2H), 5.76 (s, 1H), 7.07-7.13 (m, 1H), 7.25-7.36 (m, 3H), 7.40-7.50 (m, 3H), 7.52-7.59 (m, 2H), 7.78-7.92 (m, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 8.7 (2C), 11.8, 37.3, 111.7, 114.5, 121.6 (2C), 122.9, 124.9, 125.6, 126.6, 126.9, 127.3, 128.8 (2C), 129.7 (2C), 129.9, 133.2, 135.6 (2C), 138.9, 139.5, 149.3, 157.3, 160.1, 161.2, 162.5.



8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-m-tolyl-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7g).

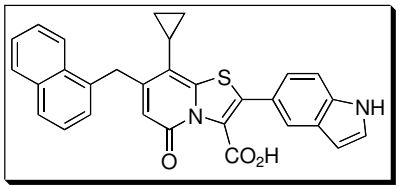
By following general hydrolysis method 3, **6g** (17 mg, 0.0355 mmol) gave **7g** (15.2 mg, 92 % yield) which was lyophilized from MeCN/H_2O to give a light yellow solid. IR (KBr) 3047, 2921, 2855, 1719, 1638, 1474, 1269, 1178, and 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.68-0.75 (m, 2H), 0.94-1.03 (m, 2H), 1.66-1.76 (m, 1H), 2.32 (s, 3H), 4.45 (s, 2H), 6.12 (s, 1H), 7.02-7.09 (m, 1H), 7.14-7.18 (m, 1H), 7.20-7.25 (m, 1H), 7.27-7.38 (m, 1H), 7.37-7.41 (m, 1H), 7.41-7.50 (m, 3H), 7.70-7.80 (m, 2H), 7.82-7.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.3 (2C), 11.4, 21.5, 36.7, 111.3, 113.7, 124.2, 126.0, 126.1, 126.2, 126.7, 127.9, 128.1, 128.3, 128.7, 129.26, 129.38, 129.43, 129.6, 131.1, 132.4, 134.5, 134.8, 139.4, 148.0, 154.4, 160.0, 164.5.



8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-p-tolyl-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7h).

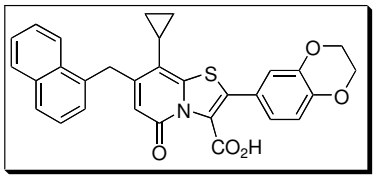
By following general hydrolysis method 3, **6h** (40 mg, 0.08 mmol) gave **7h** (34 mg, 91 % yield) which was lyophilized from MeCN/H_2O to give a light yellow solid. IR (neat)

3000, 2904, 1720, 1631, 1465, 1180, and 775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.67-0.75 (m, 2H), 0.93-1.03 (m, 2H), 1.66-1.77 (m, 1H), 2.33 (s, 3H), 4.47 (s, 2H), 6.12 (s, 1H), 7.03-7.20 (m, 3H), 7.28-7.35 (m, 1H), 7.42-7.55 (m, 4H), 7.69-7.89 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2 (2C), 11.3, 21.4, 36.6, 111.3, 113.5, 124.0, 125.9, 126.1, 126.3, 126.6, 127.7, 127.9, 128.0, 128.6, 128.8 (2C), 129.2, 130.1 (2C), 132.3, 134.4, 134.7, 140.5, 147.7, 154.2, 159.8, 164.2.



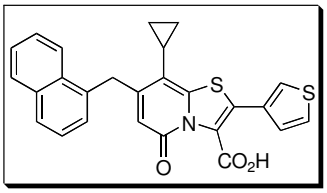
8-Cyclopropyl-2-(1H-indol-5-yl)-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7i).

By following general hydrolysis method 3, **6i** (26 mg, 0.0515 mmol) gave **7i** (20.5 mg, 80 % yield) which was lyophilized from $MeCN/H_2O$ to give a yellow solid. IR (KBr) 2932, 1708, 1627, 1466, 1379, 1254, and 1056 cm^{-1}. ^1H NMR (400 MHz, DMSO, d_6) δ 0.76-0.84 (m, 2H), 0.99-1.08 (m, 2H), 1.83-1.95 (m, 1H), 4.57 (s, 2H), 5.51(s, 1H), 6.51 (s, 1H), 7.35-7.57 (m, 7H), 7.85-8.01 (m, 4H), 11.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.6 (2C), 10.7, 35.3, 101.6 (splitted), 109.7, 110.8, 111.9 (splitted), 119.9, 120.1, 121.1, 124.0, 125.7, 125.8, 126.3, 126.7, 126.9, 127.3, 127.4, 127.8 (splitted), 128.6, 131.5, 133.5, 134.9, 136.0, 136.1, 146.6, 152.4, 157.8, 162.3.



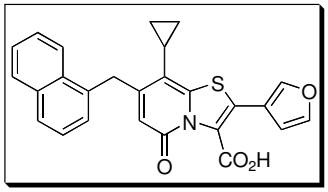
8-Cyclopropyl-2-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7j).

By following general hydrolysis method 3, **6j** (25 mg, 0.048 mmol) gave **7j** (19 mg, 78 % yield) which was lyophilized from $MeCN/H_2O$ to give a light yellow solid. IR (neat) 3000, 2927, 2873, 1724, 1616, 1461, 1284, 1245, 1180, 1064, 887, and 775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.77-0.83 (m, 2H), 0.99-1.06 (m, 2H), 1.85-1.94 (m, 1H), 4.29 (s, 4H), 4.58 (s, 2H), 5.53(s, 1H), 6.97-7.02 (m, 1H), 7.08-7.13 (m, 1H), 7.15-7.18 (m, 1H), 7.35-7.40 (m, 1H), 7.46-7.56 (m, 3H), 7.86-7.93 (m, 2H), 7.94-8.00 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.5 (2C), 10.7, 35.4, 64.1, 64.3, 109.7, 111.2, 116.6 (2C), 117.9 (2C), 121.4 (2C), 124.0, 125.7, 125.8, 126.4, 127.3, 127.5, 128.6, 131.5, 133.5, 134.6, 143.7, 144.9, 145.8, 153.4, 157.5, 161.6.



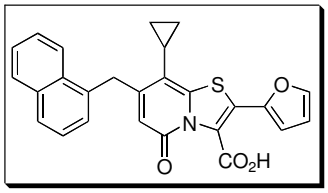
8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-thiophen-3-yl-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7k).

By following general hydrolysis method 3, **6k** (35 mg, 0.074 mmol) gave **7k** (27.5 mg, 81 % yield) which was lyophilized from $MeCN/H_2O$ to give a yellow solid IR (neat) 2996, 2927, 1727, 1619, 1542, 1465, 1172, 775, and 678 cm^{-1}. ^1H NMR (400 MHz, CD_3OD:$CDCl_3$ 1:3) δ 0.77-0.84 (m, 2H), 1.04-1.11 (m, 2H), 1.78-1.88 (m, 1H), 4.56 (s, 2H), 5.88 (s, 1H), 7.20-7.25 (m, 1H), 7.36-7.39 (m, 1H), 7.41-7.50 (m, 3H), 7.70-7.90 (m, 4H). ^{13}C NMR (100 MHz, CD_3OD:$CDCl_3$ 1:3) δ 8.1 (2C), 11.2, 36.4, 111.3, 113.3, 123.1, 123.9, 125.71, 125.73, 126.0, 126.5, 127.1, 127.3, 127.5, 127.7, 127.9, 129.0, 129.2, 132.1, 134.2, 134.4, 146.9, 154.1, 159.6, 164.5.



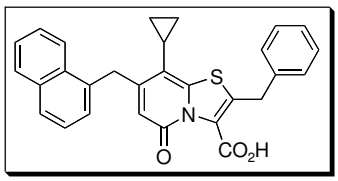
8-Cyclopropyl-2-furan-3-yl-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7l).

By following general hydrolysis method 3, **6l** (19 mg, 0.042 mmol) gave **7l** (13 mg, 70 % yield) which was lyophilized from MeCN/H_2O to give a yellow solid IR (neat) 3135, 3000, 1708, 1631, 1473, 1164, and 779 cm^{-1}. ^1H NMR (400 MHz, CD_3OD:$CDCl_3$ 2:3) δ 0.76-0.82 (m, 2H), 1.04-1.11 (m, 2H), 1.77-1.88 (m, 1H), 4.54 (s, 2H), 5.82 (s, 1H), 6.74 (s, 1H), 7.19-7.24 (m, 1H), 7.35-7.46 (m, 3H), 7.48-7.51 (m, 1H), 7.73-7.81 (m, 2H), 7.82-7.89 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD:$CDCl_3$ 2:3) δ 8.2 (2C), 11.4, 36.6, 110.0, 111.4, 113.7, 115.5, 119.0, 124.1, 125.9, 126.2, 126.7, 127.9, 128.1, 129.2, 129.5, 132.4, 134.5, 134.7, 142.1, 144.6, 147.3, 154.3, 159.9, 165.3.



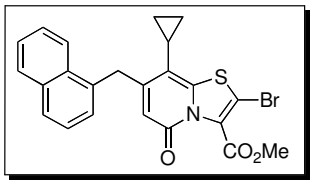
8-Cyclopropyl-2-furan-2-yl-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7m).

By following general hydrolysis method 3, **6m** (11.8 mg, 0.026 mmol) gave **7m** (5.8 mg, 50 % yield) which was lyophilized from MeCN/H_2O to give a yellow solid. IR (neat) 3043, 3004, 2850, 1720, 1639, 1465, 1207, 1149, 1018, and 779 cm^{-1}. ^1H NMR (400 MHz, CD_3OD:$CDCl_3$ 3:7) δ 0.76-0.84 (m, 2H), 1.04-1.11 (m, 2H), 1.77-1.88 (m, 1H), 4.55 (s, 2H), 5.84 (s, 1H), 6.49-6.54 (m, 1H), 6.84-6.88 (m, 1H), 7.19-7.24 (m, 1H), 7.35-7.48 (m, 4H), 7.73-7.87 (m, 3H). ^{13}C NMR (100 MHz, CD_3OD:$CDCl_3$ 3:7) δ 8.2 (2C), 11.2, 36.5, 111.4, 112.8, 113.5, 119.6, 123.9, 125.3, 125.8, 126.1, 126.6, 127.7, 128.0, 129.1, 132.2, 134.3, 134.4, 143.6, 144.6, 146.5, 154.6, 159.7, 162.9.



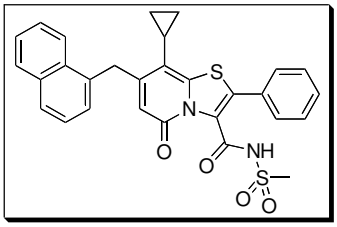
2-Benzyl-8-cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7n).

By following general hydrolysis method 3, **6n** (21 mg, 0.044 mmol) gave **7n** (14.5 mg, 70 % yield) which was lyophilized from MeCN/H_2O to give a light yellow solid. IR (neat) 3046, 2919, 1693, 1654, 1569, 1473, 1392, 779, and 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.68-0.76 (m, 2H), 1.03-1.11 (m, 2H), 1.72-1.83 (m, 1H), 4.56 (s, 2H), 4.68 (s, 2H), 6.13 (s, 1H), 7.18-7.24 (m, 1H), 7.30-7.52 (m, 8H), 7.67-7.73 (m, 1H), 7.77-7.83 (m, 1H), 7.86-7.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4 (2C), 10.9, 35.8, 36.5, 112.2, 116.7, 123.4, 125.5, 125.9, 126.5, 127.6, 127.8, 128.1, 128.97 (2C), 129.02 129.2, 129.6 (2C), 131.7, 133.3, 134.0, 137.3, 147.8, 149.1, 154.2, 159.6, 160.8.



2-Bromo-8-cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-5H-thiazolo[3,2-*a*]pyridine-3-carboxylic acid methyl ester (8).

NaH (74 mg, 3.07 mmol, washed with *n* -pentane) was added to a stirred solution of pyridone **4a** (400 mg, 1.02 mmol) in dry MeCN (8 ml) at 0 °C. After 10 min $BrCCl_3$ (302 µl, 3.07 mmol) was added dropwise and stirring was continued for 35 min at 0 °C before the reaction mixture was allowed to attain rt. After 15 min at rt 83 µl dry MeOH (2 eq) was added dropwise. Upon the addition of dry MeOH the reaction mixture turned brown and was quenched by dropwise addition of 2% $KHSO_4$ (aq.). The mixture was acidified with 2 M HCl and extracted three times with EtOAc. The combined organic layers were washed with brine, aqueous layer extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography [heptane:EtOAc 3:1] gave pyridone **8** (435 mg, 91% yield) as yellow foam. Data in agreement with published data.[5]

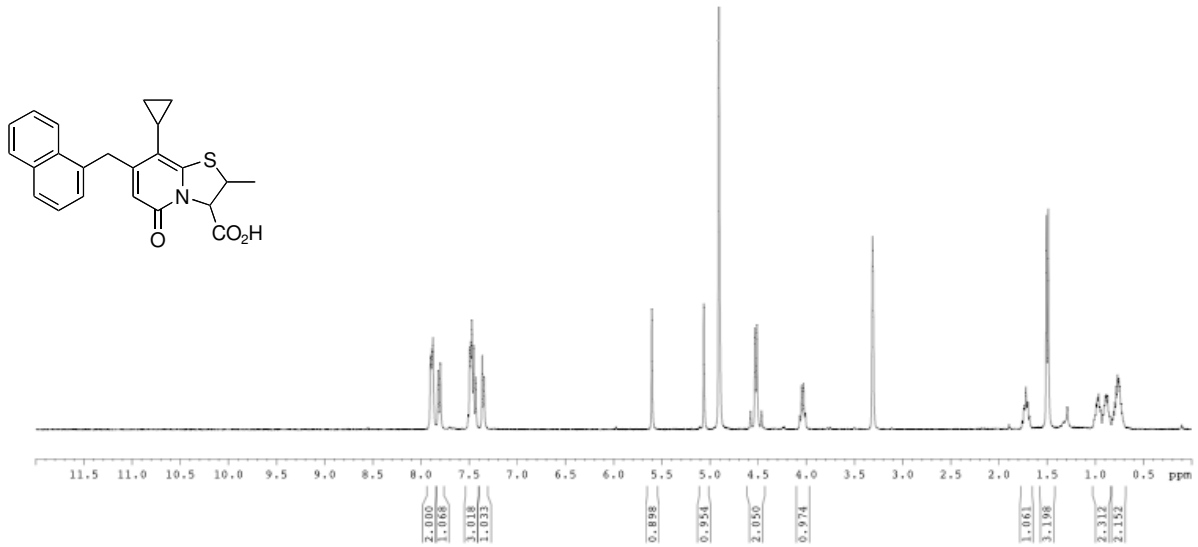


N-(8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-phenyl-5H-thiazolo[3,2-a]pyridine-3-carbonyl)-methanesulfonamide (9).

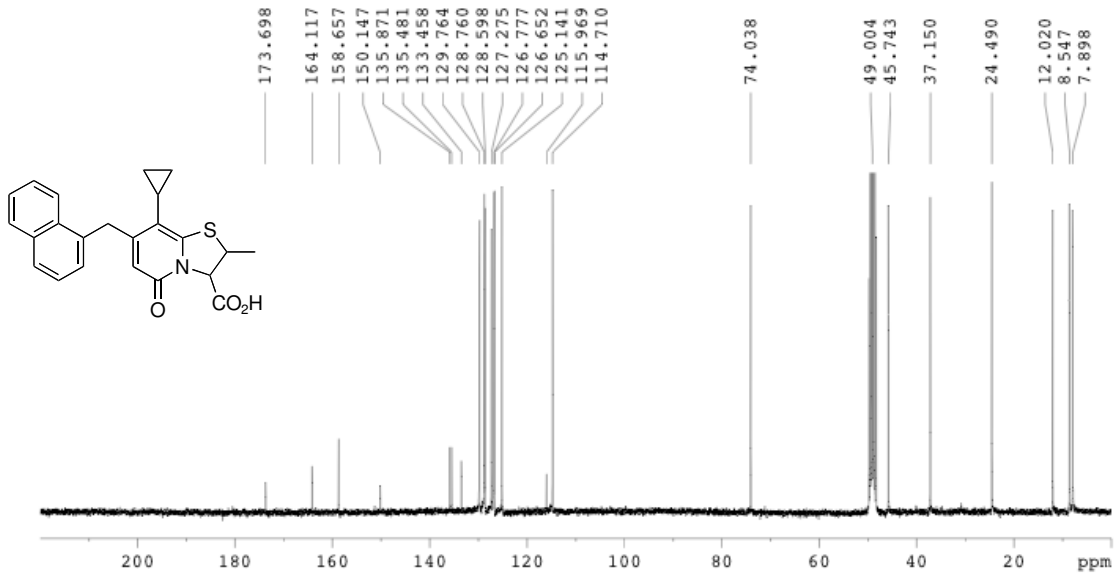
By following a published procedure.[4] **6c** (28.8 mg, 0.064 mmol) was suspended in CH_2Cl_2 (2 ml) in a microwave vial. To the suspension was added *N,N´*-carbonyldiimidazole (31 mg, 0.191 mmol) in one portion at rt. After 1 hour and 45 minutes, methane sulfonamide (24 mg, 0.255 mmol) was added in one portion at rt. The vial was capped and heated with microwave irradiation (normal absorption) at 150 °C for 55 min. The solution was diluted with CH_2Cl_2 and washed with 1 M HCl. The combined aqueous layers were extracted with CH_2Cl_2 and the combined organic layers were dried, filtrated and concentrated. Purification by silica gel chromatography (CH_2Cl_2:MeOH, 97:3) gave **9** (20 mg, 60%) IR (neat) 3016, 2927, 1704, 1635, 1465, 1326, 1133, and 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.74-0.84 (m, 2H), 1.02-1.12 (m, 2H), 1.76-1.86 (m, 1H), 3.29 (s, 3H), 4.44 (s, 2H), 5.73 (s, 1H), 6.98-7.03 (m, 1H), 7.29-7.35 (m, 1H), 7.39-7.52 (m, 5H), 7.57-7.62 (m, 2H), 7.68-8.80 (m, 2H) 7.85-7.91 (m, 1H), 7.52 (bs, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 7.9 (2C), 11.0, 36.2, 40.3, 111.1, 113.2, 123.5, 125.6, 125.7, 125.9, 126.4, 127.3, 127.6, 127.8, 128.4 (2C), 128.9, 129.5 (2C), 130.6, 131.5, 131.7, 133.7, 133.9, 146.4, 154.4, 159.1, 159.6.

^{1}H-NMR and ^{13}C-NMR spectra of all new compounds

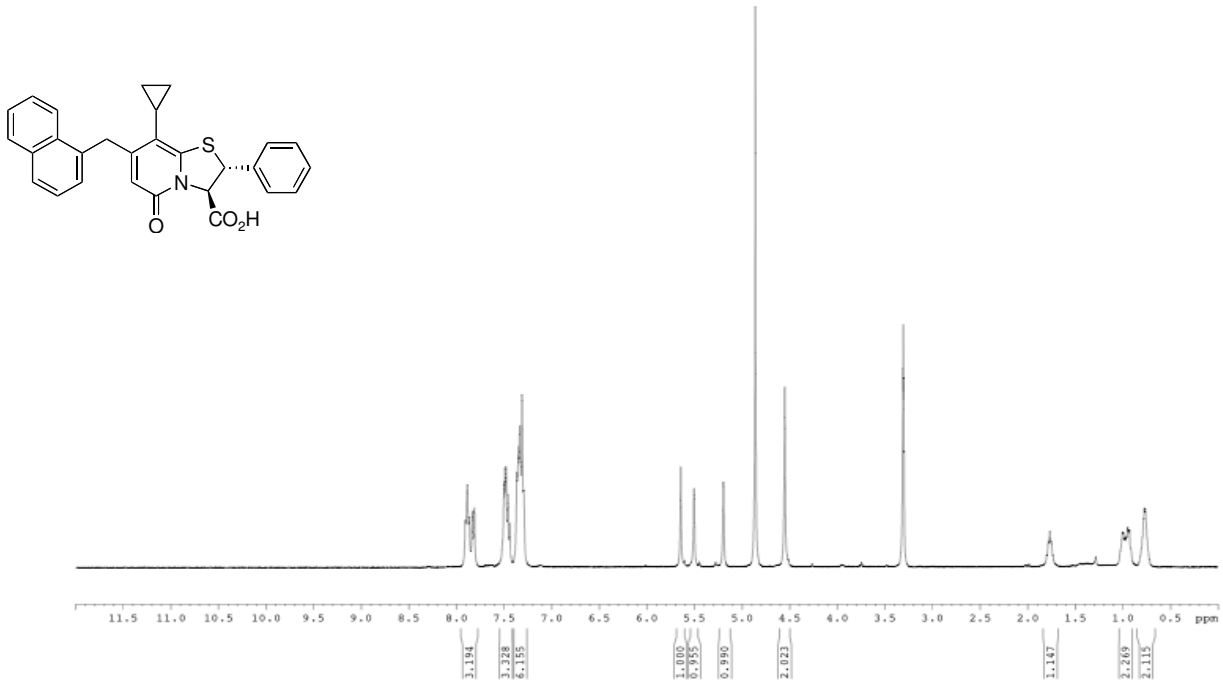
^{1}H-NMR spectra of compound **5b**



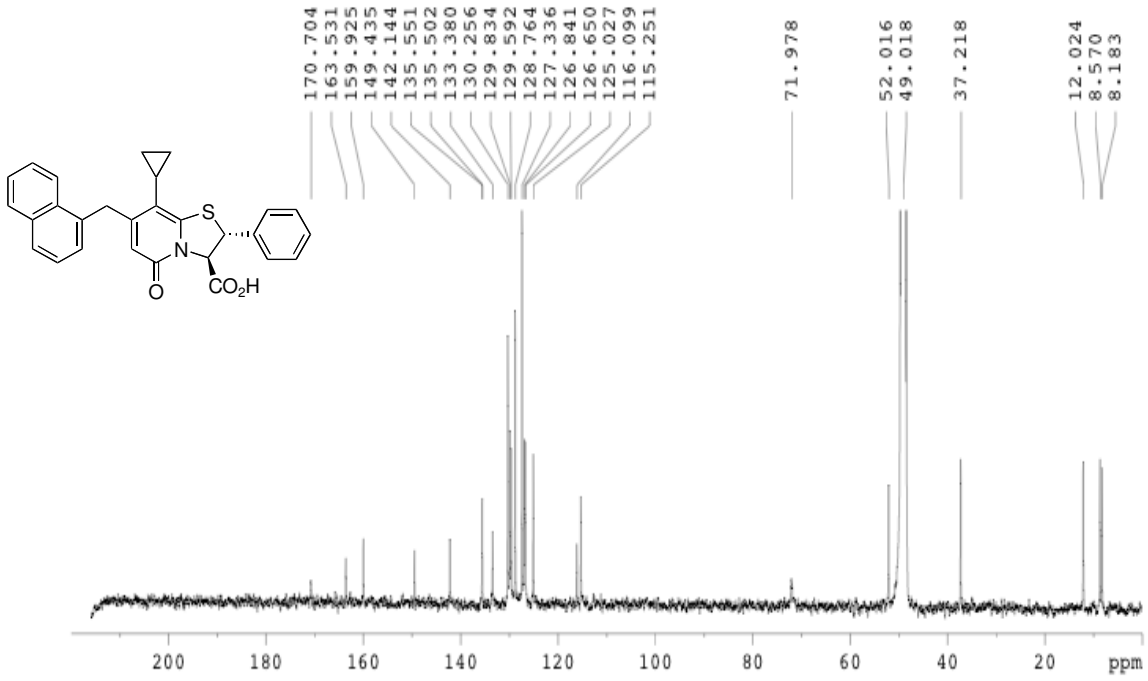
^{13}C-NMR spectra of compound **5b**



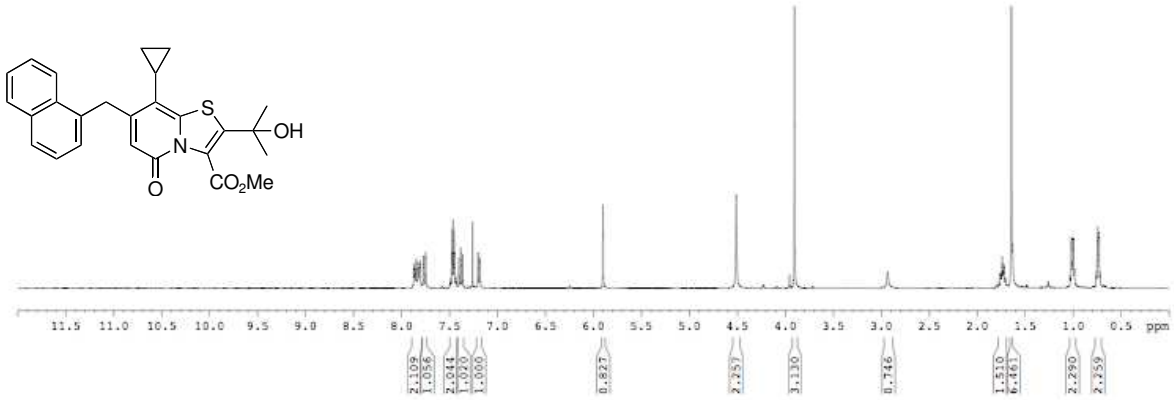
[1]H-NMR spectra of compound **5d**



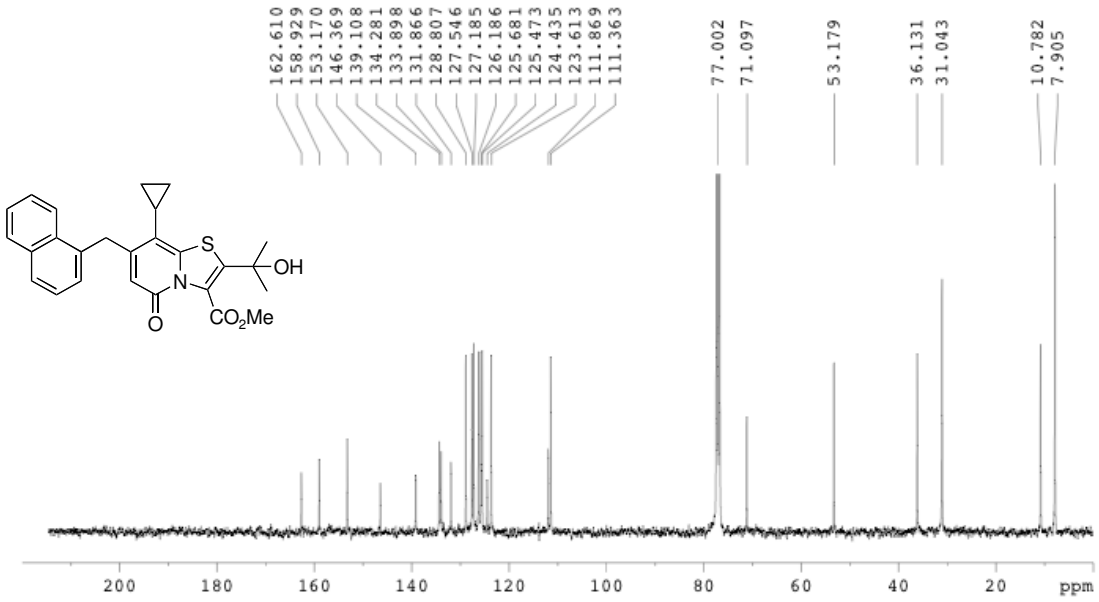
[13]C-NMR spectra of compound **5d**



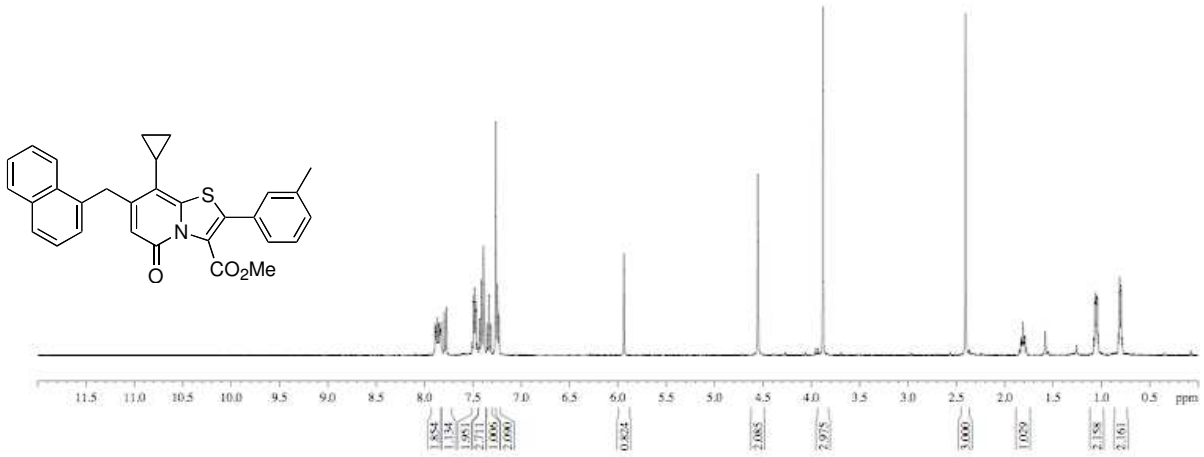
^{1}H-NMR spectra of compound **6b**



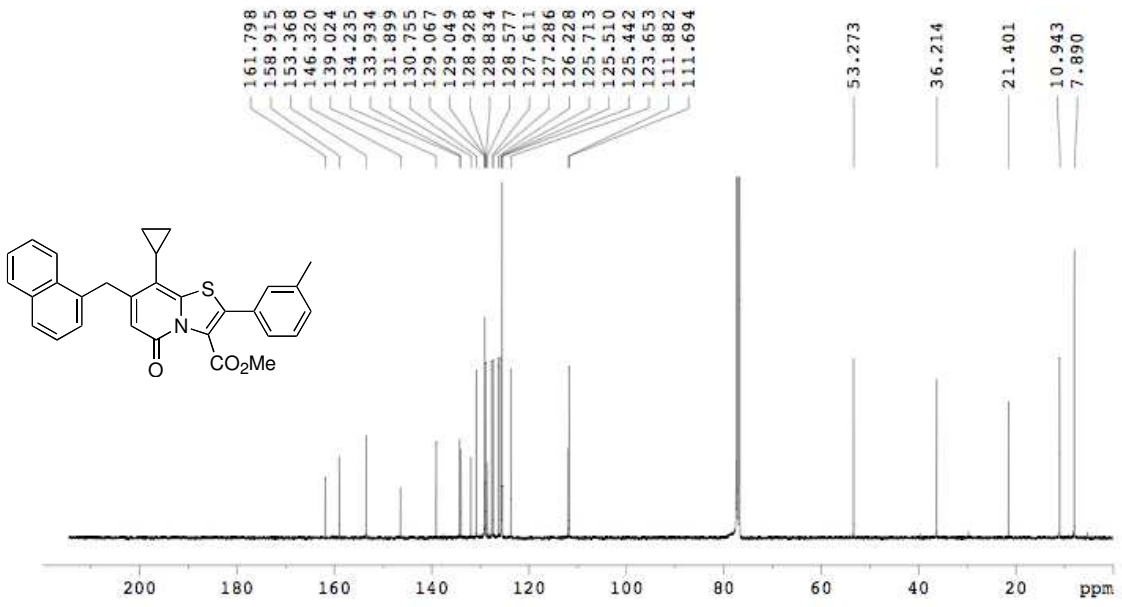
^{13}C-NMR spectra of compound **6b**



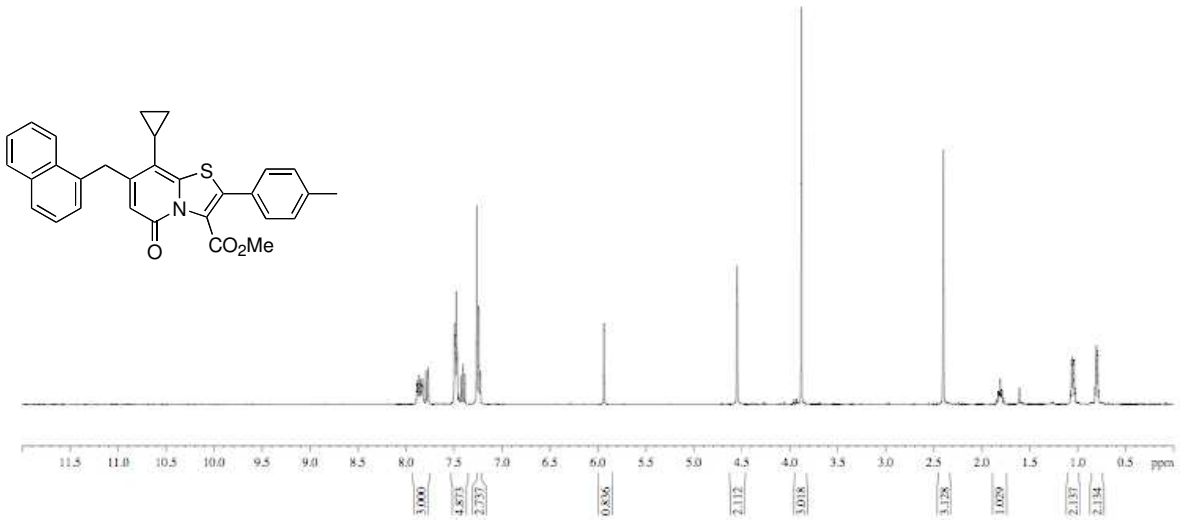
^{1}H-NMR spectra of compound **6g**



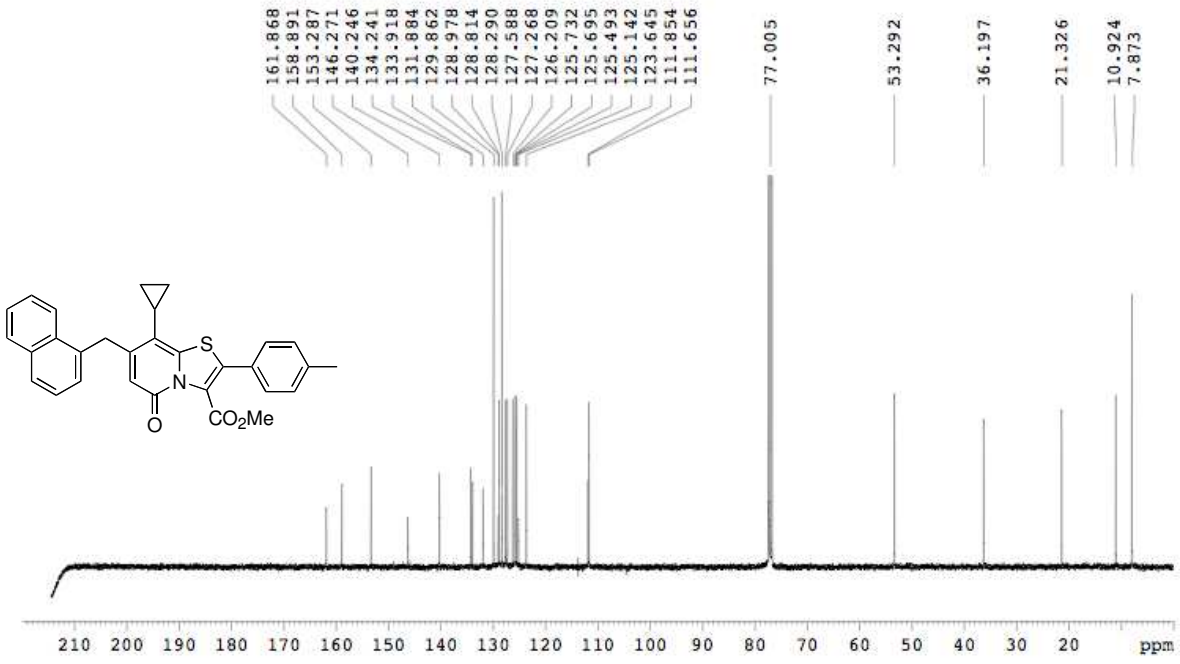
^{13}C-NMR spectra of compound **6g**



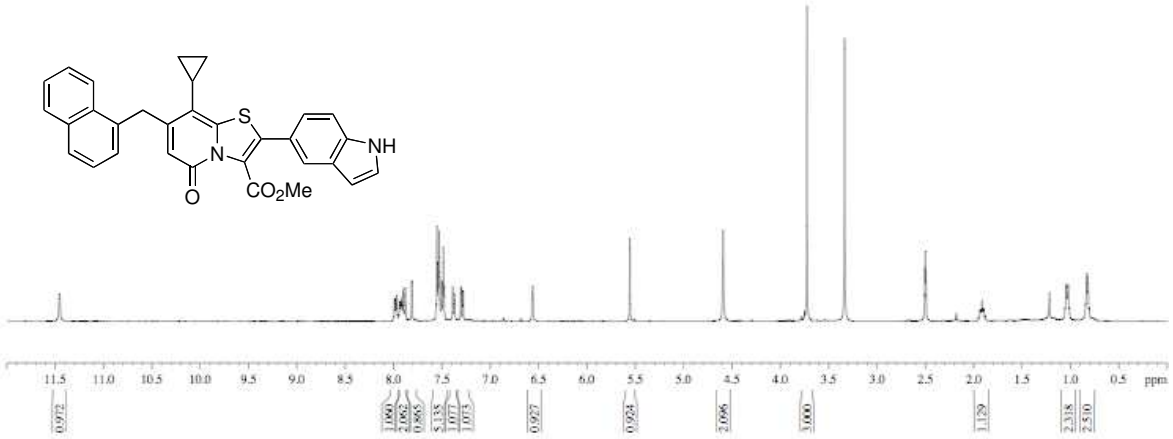
^{1}H-NMR spectra of compound **6h**



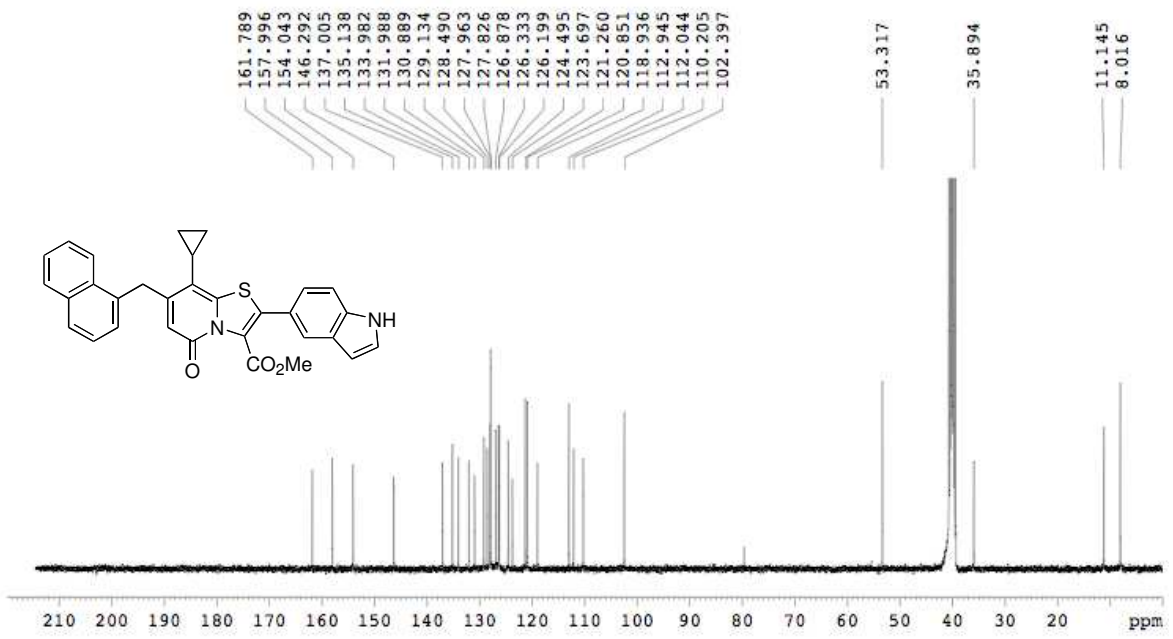
^{13}C-NMR spectra of compound **6h**



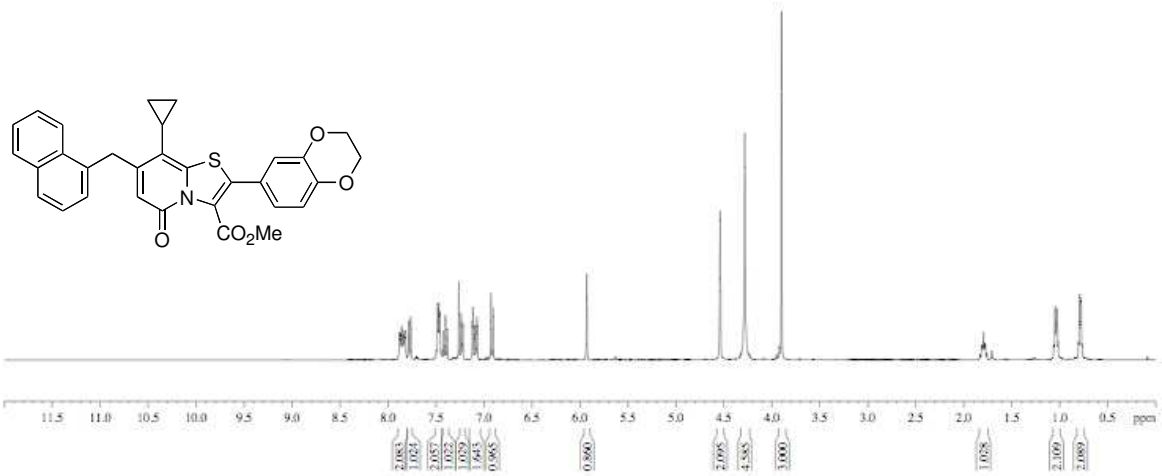
^{1}H-NMR spectra of compound **6i**



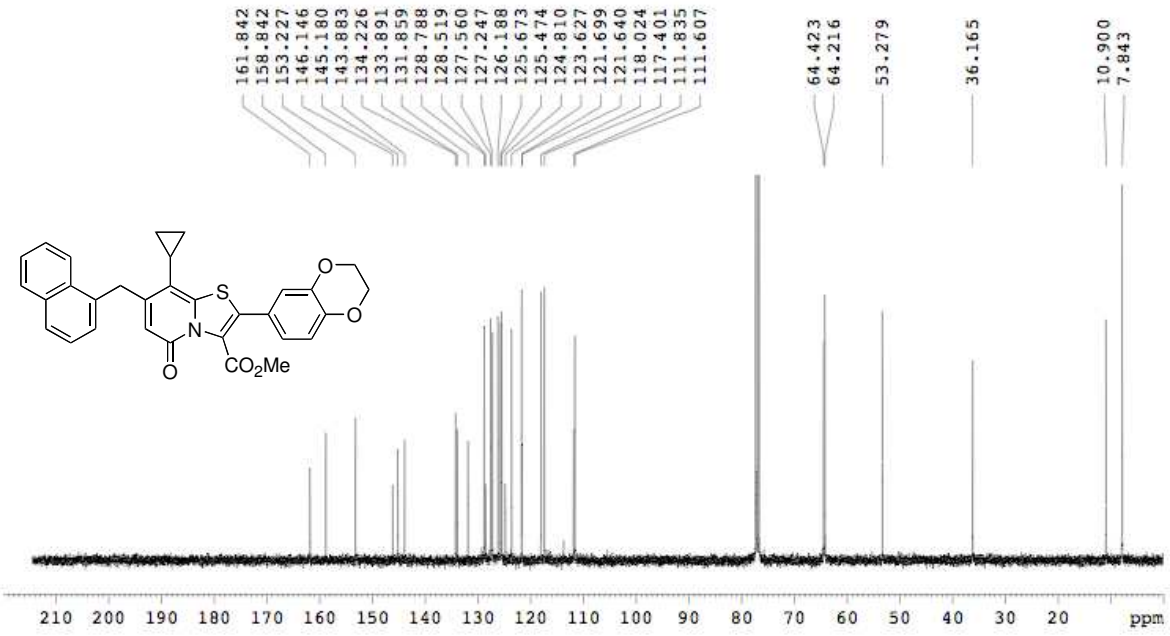
^{13}C-NMR spectra of compound **6i**



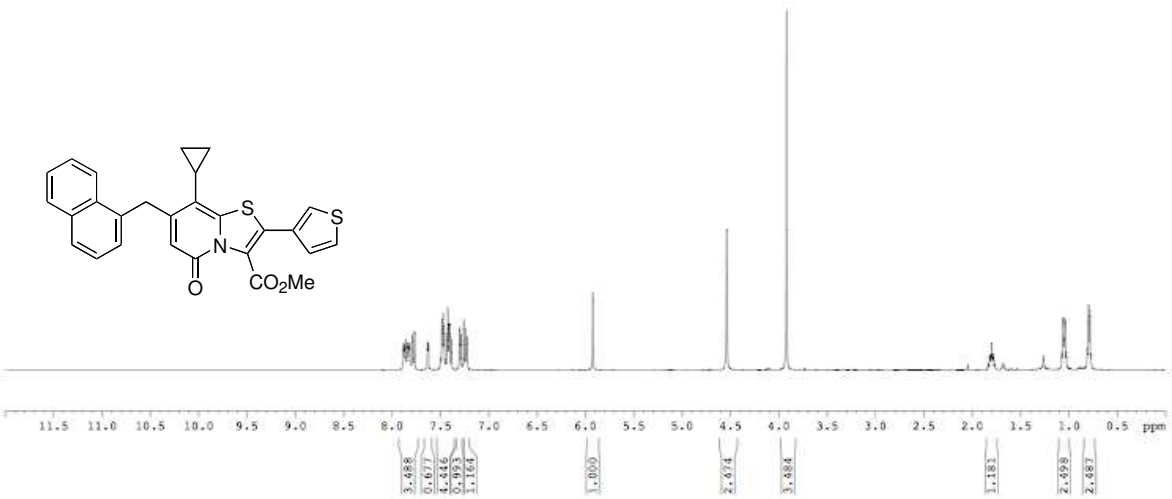
^{1}H-NMR spectra of compound **6j**



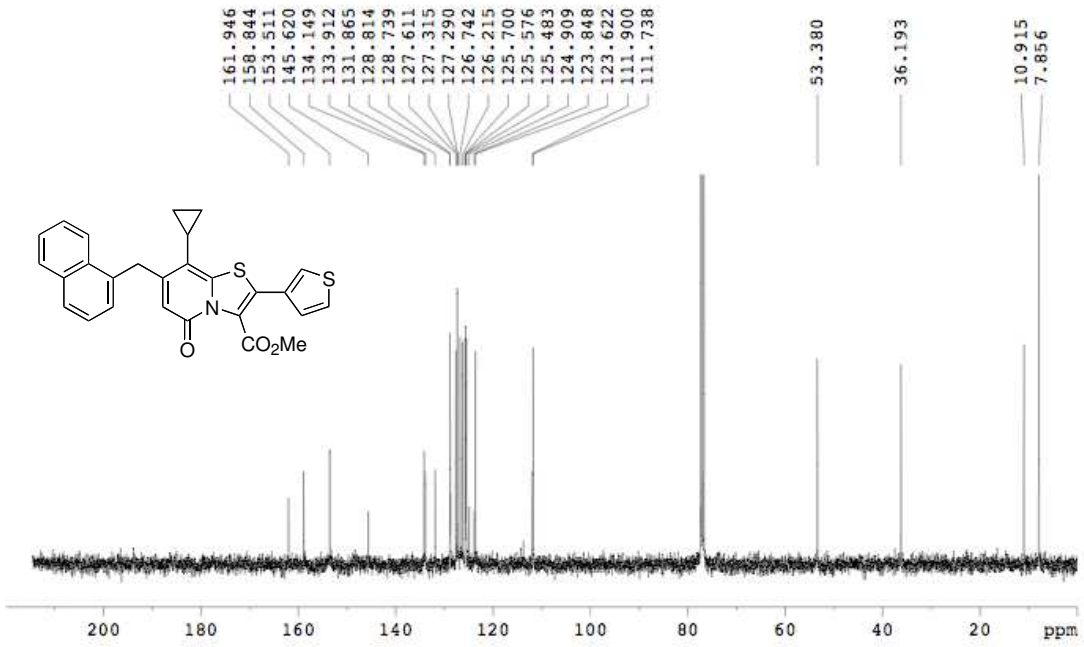
^{13}C-NMR spectra of compound **6j**



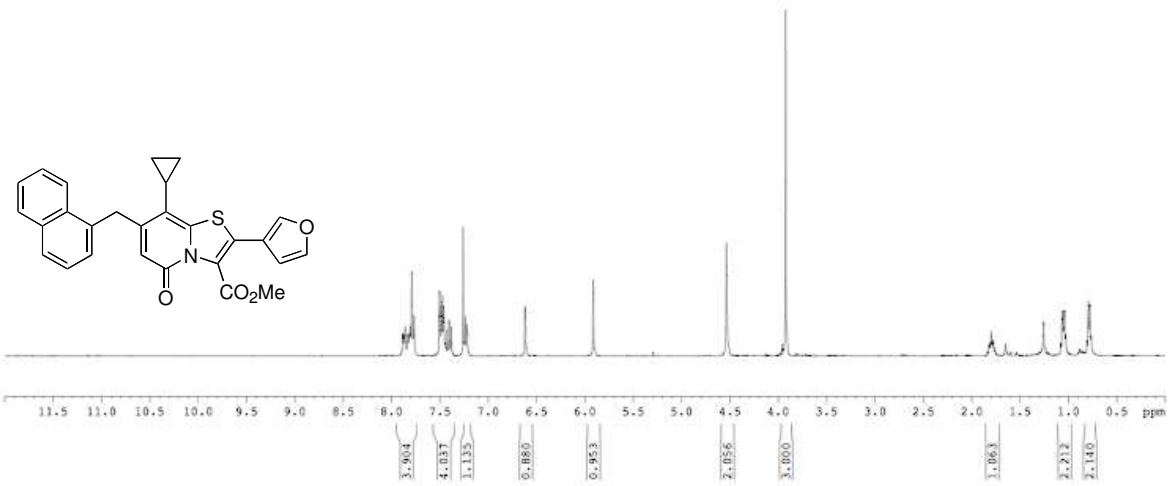
[1]H-NMR spectra of compound **6k**



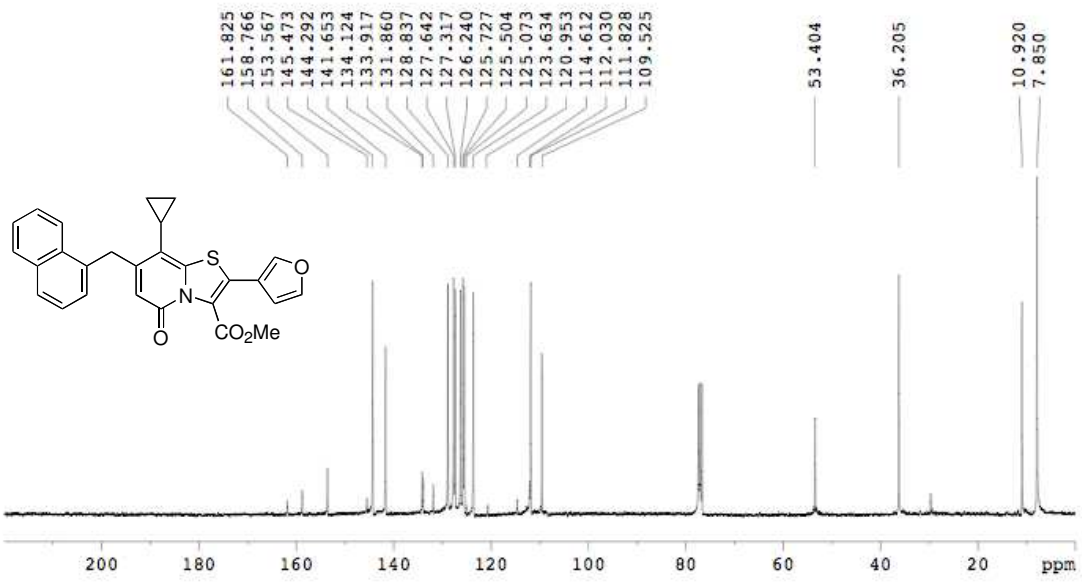
[13]C-NMR spectra of compound **6k**



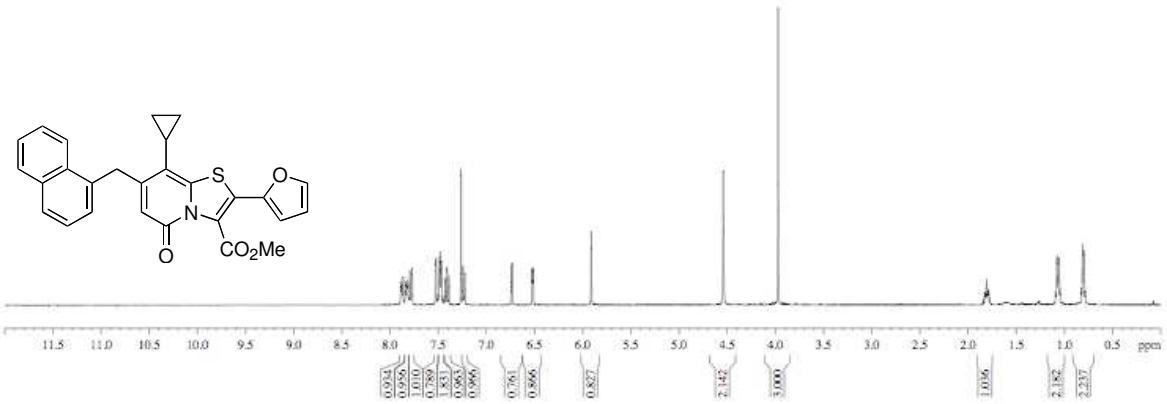
^{1}H-NMR spectra of compound **6l**



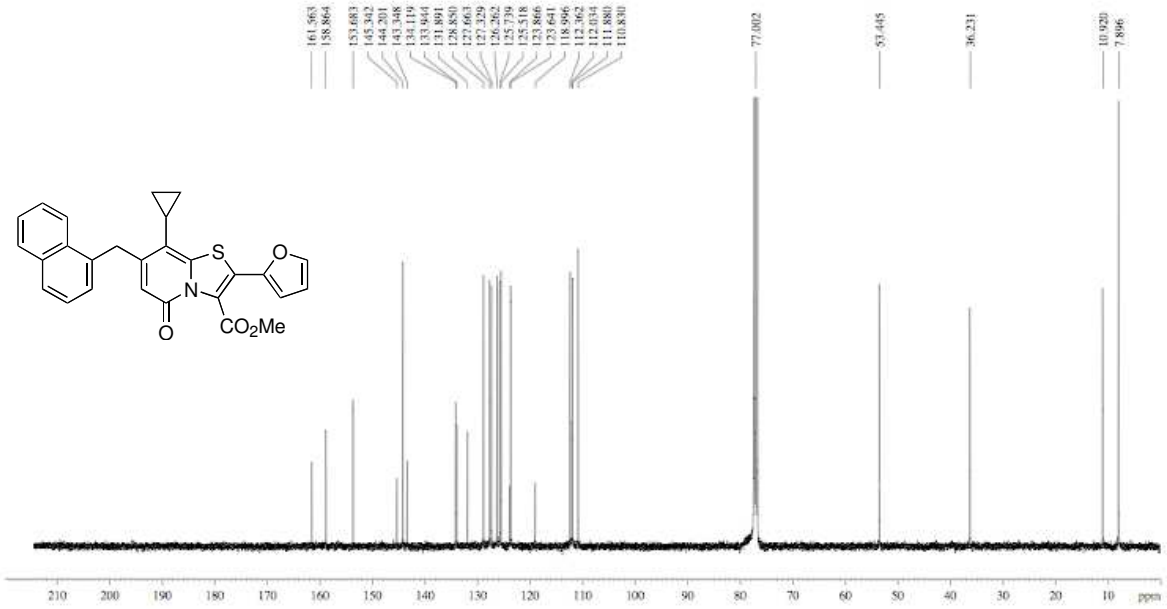
^{13}C-NMR spectra of compound **6l**



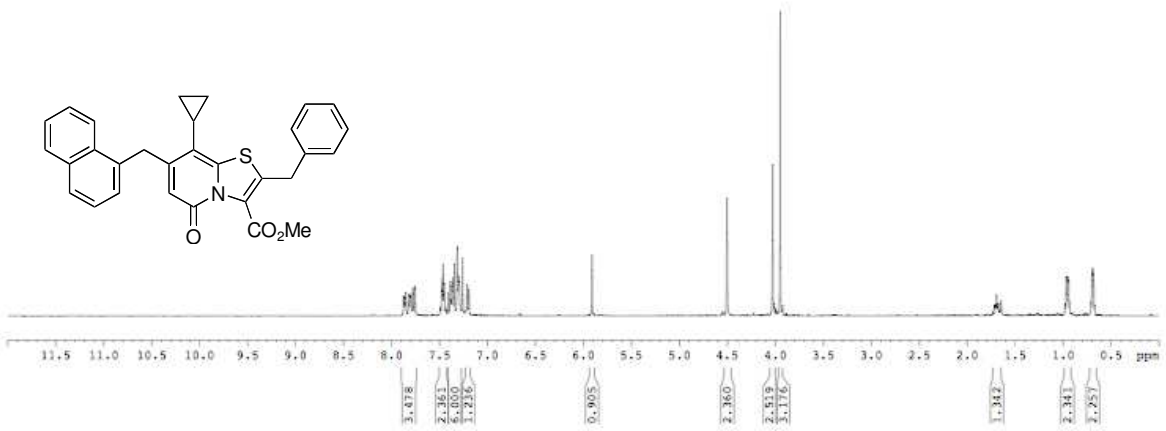
^{1}H-NMR spectra of compound **6m**



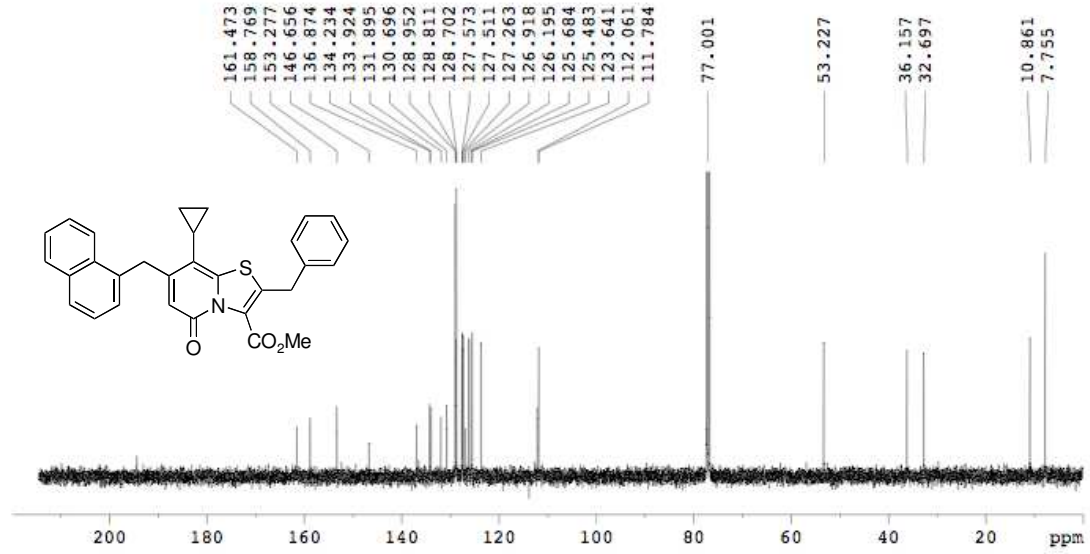
^{13}C-NMR spectra of compound **6m**



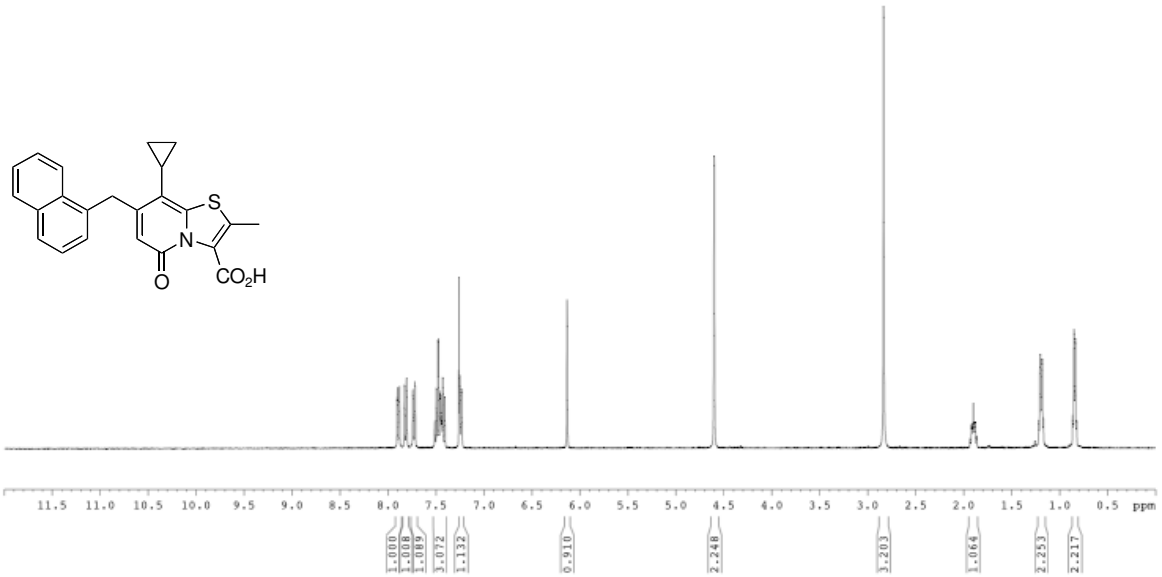
^{1}H-NMR spectra of compound **6n**



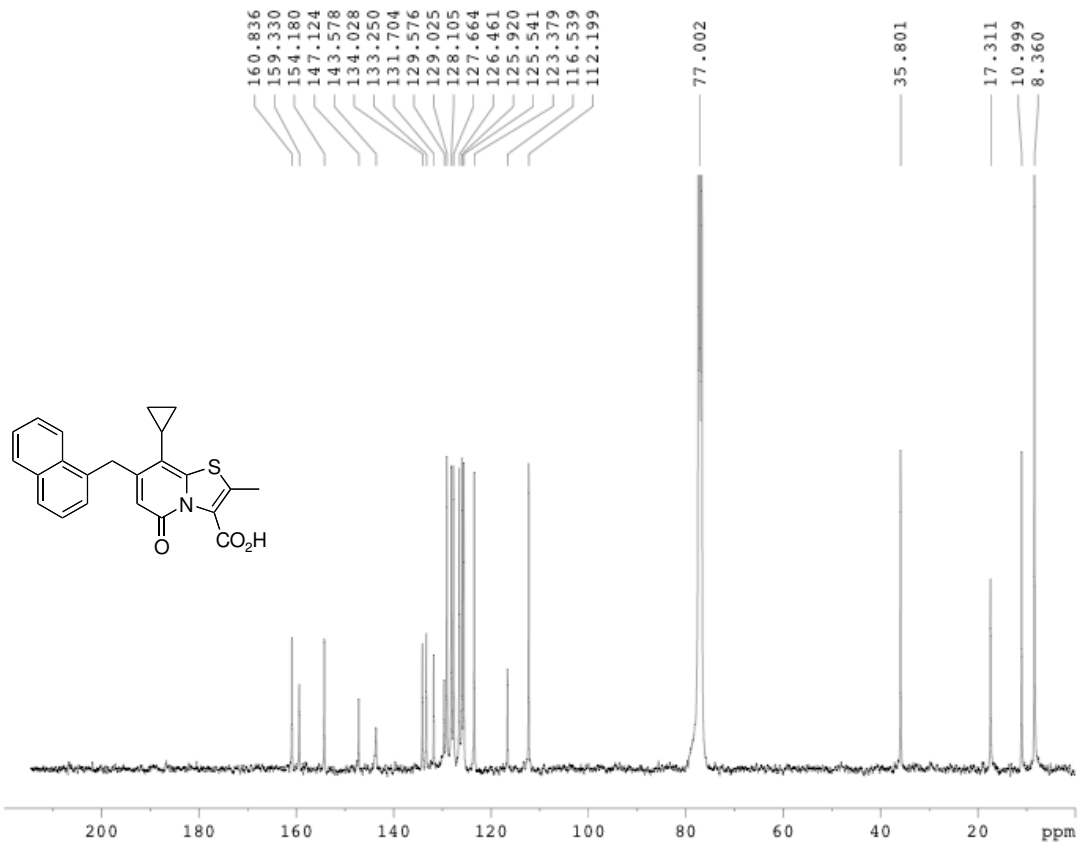
^{13}C-NMR spectra of compound **6n**



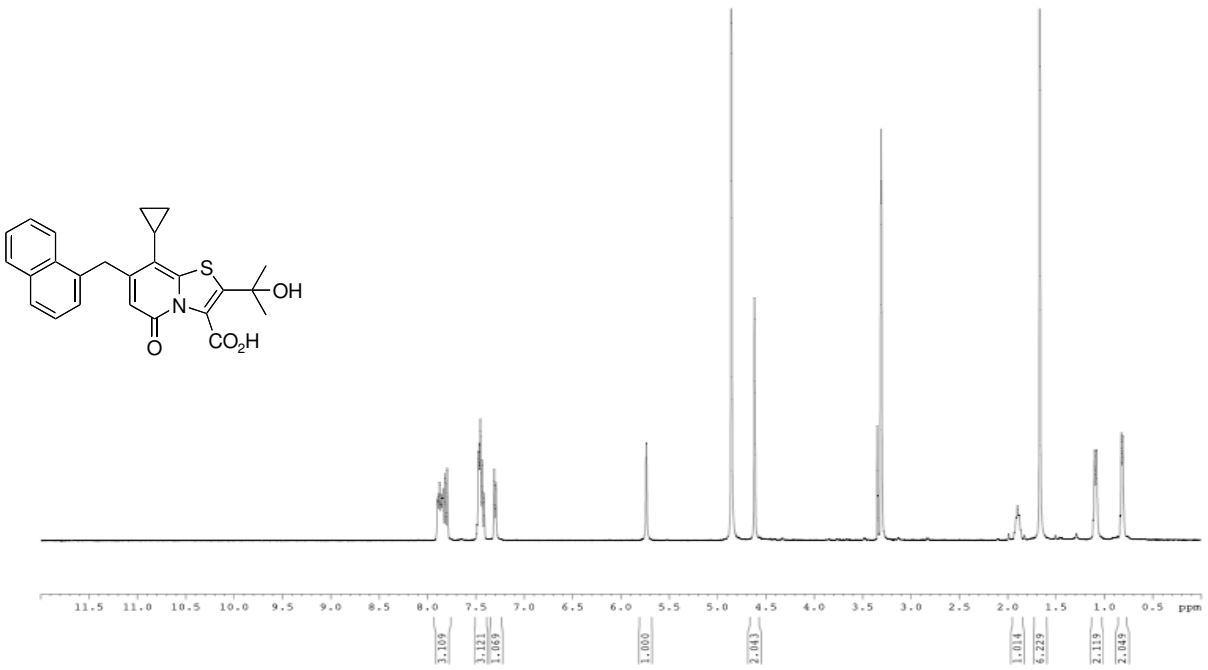
^{1}H-NMR spectra of compound **7a**



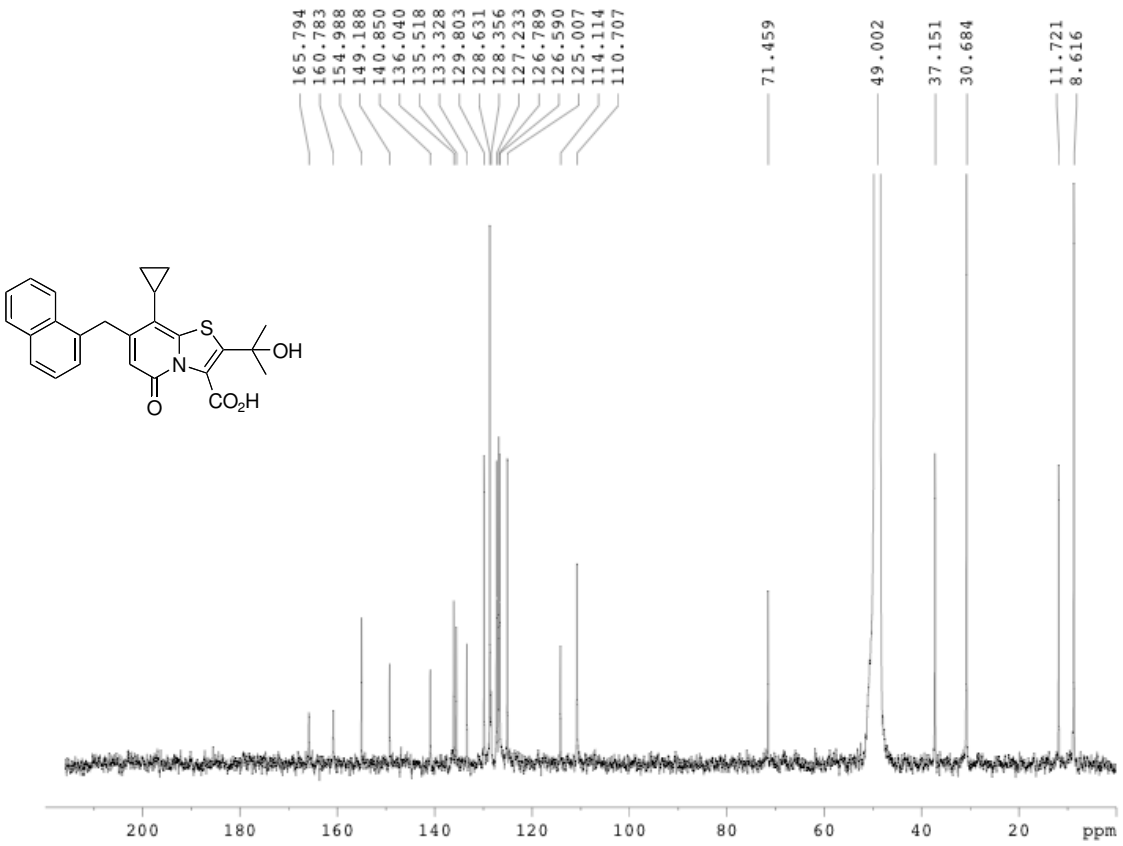
^{13}C-NMR spectra of compound **7a**



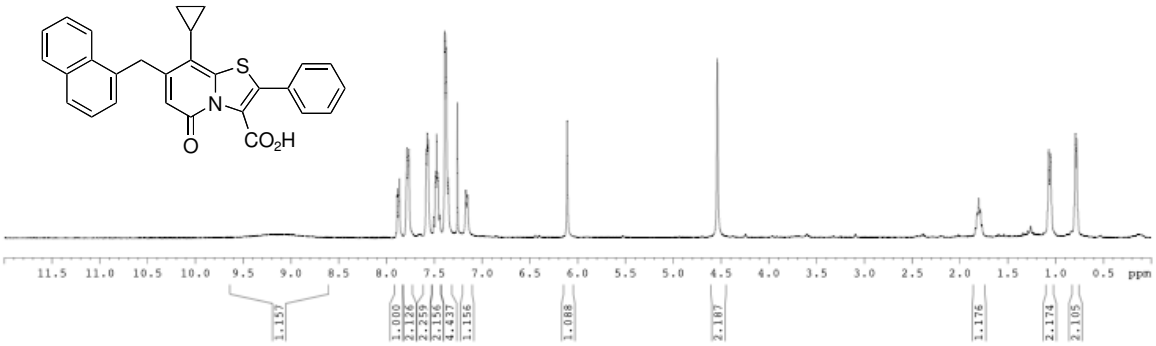
^{1}H-NMR spectra of compound **7b**



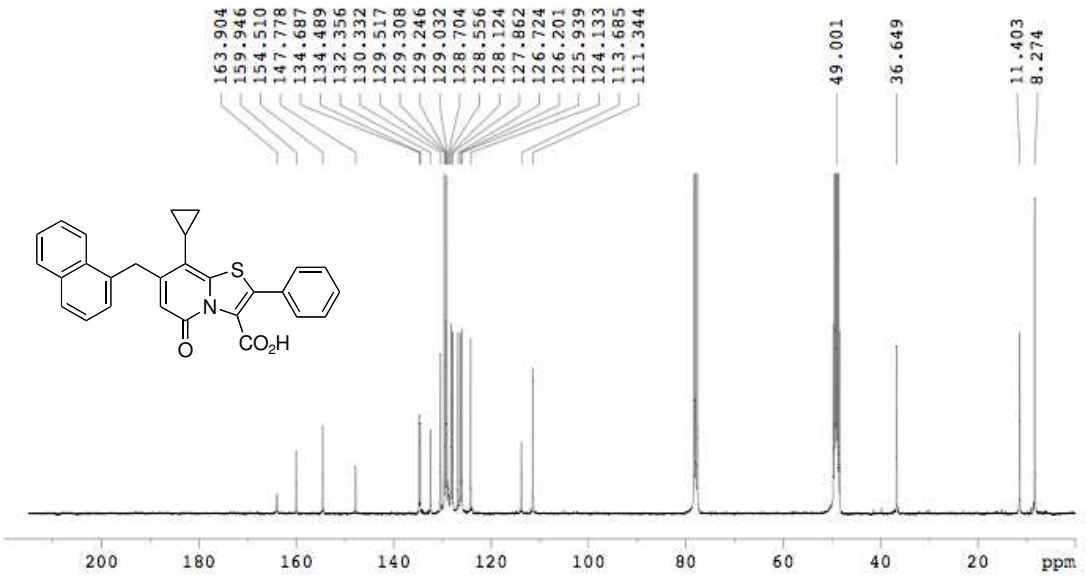
^{13}C-NMR spectra of compound **7b**



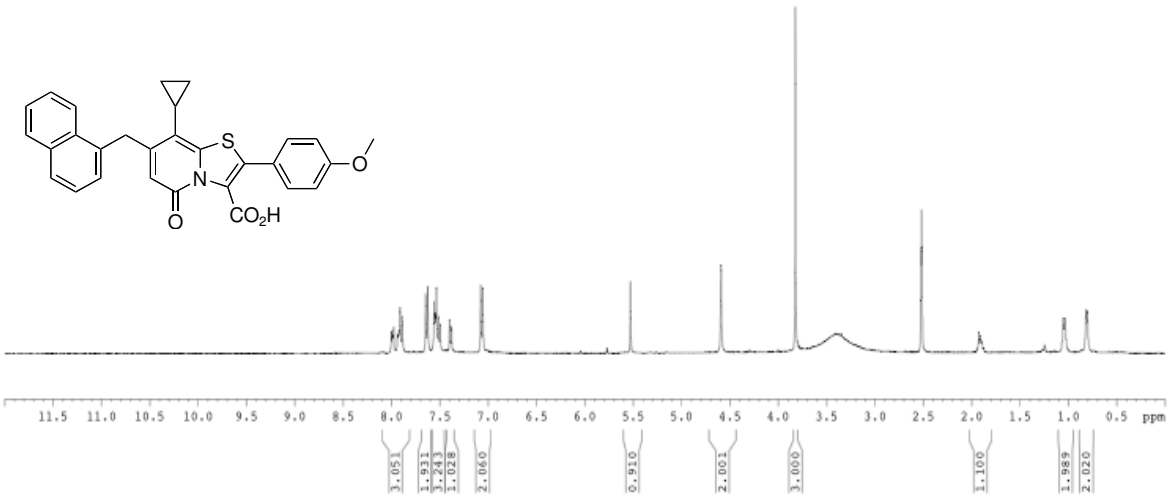
^{1}H-NMR spectra of compound **7c**



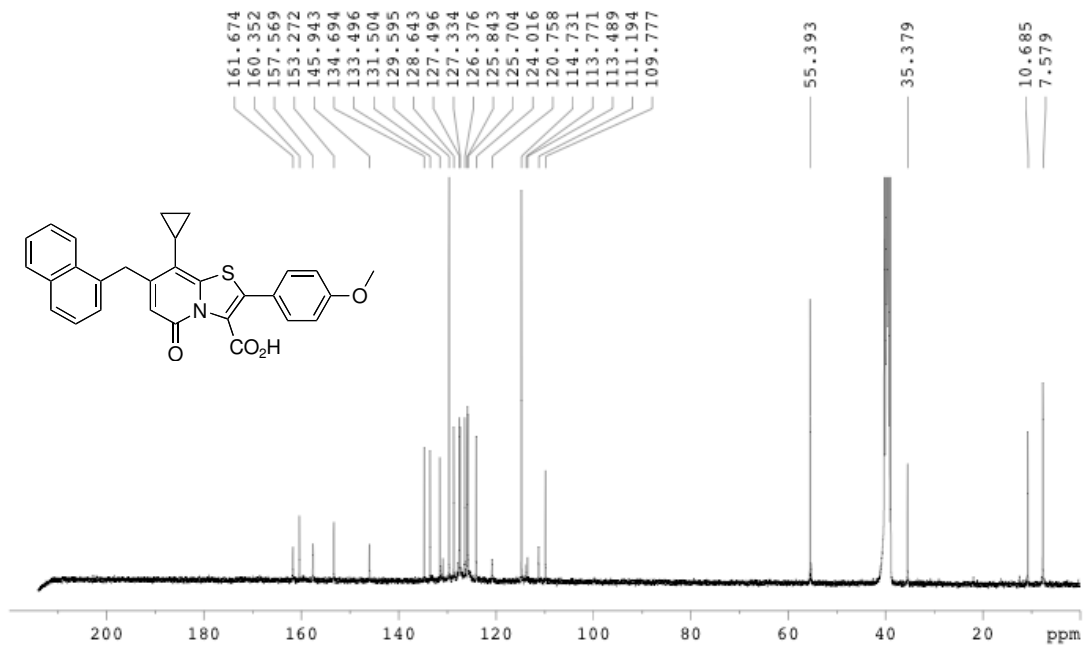
^{13}C-NMR spectra of compound **7c**



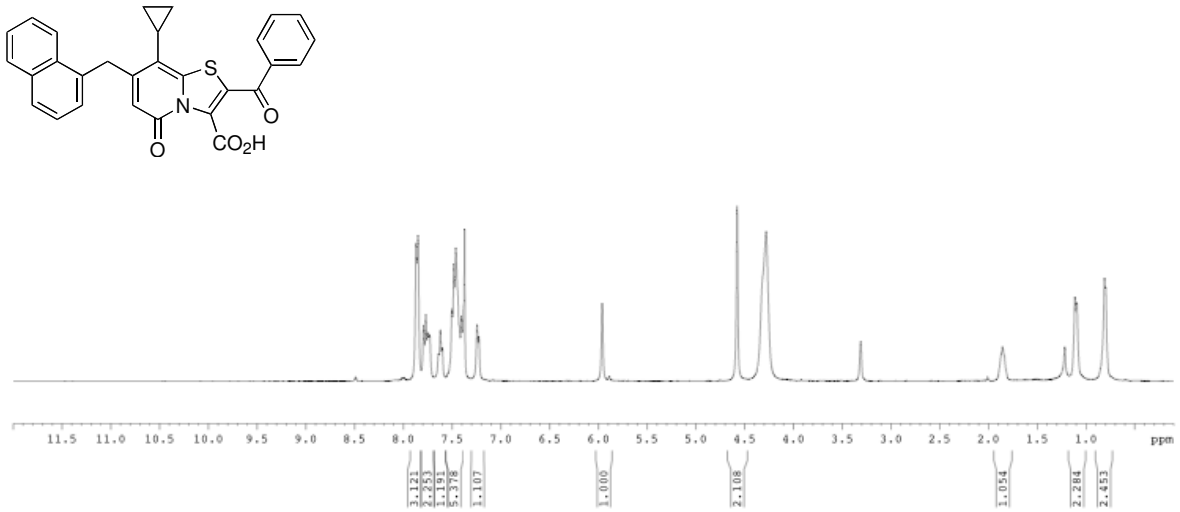
[1]H-NMR spectra of compound **7d**



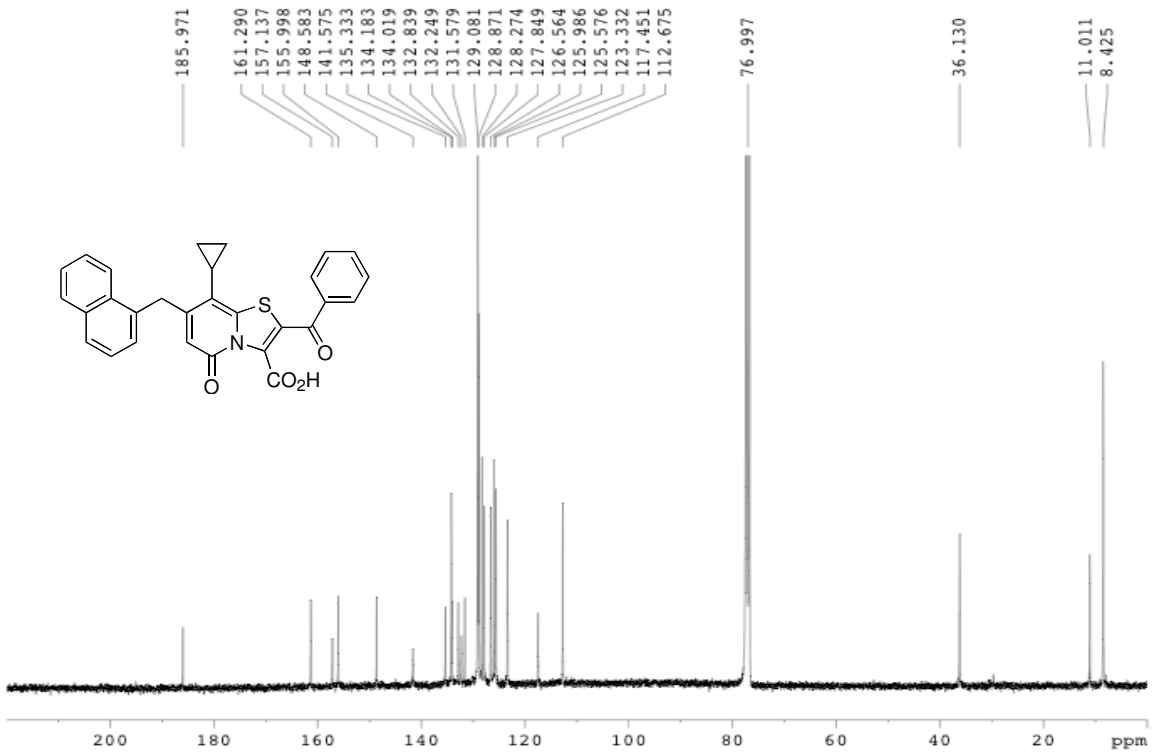
[13]C-NMR spectra of compound **7d**



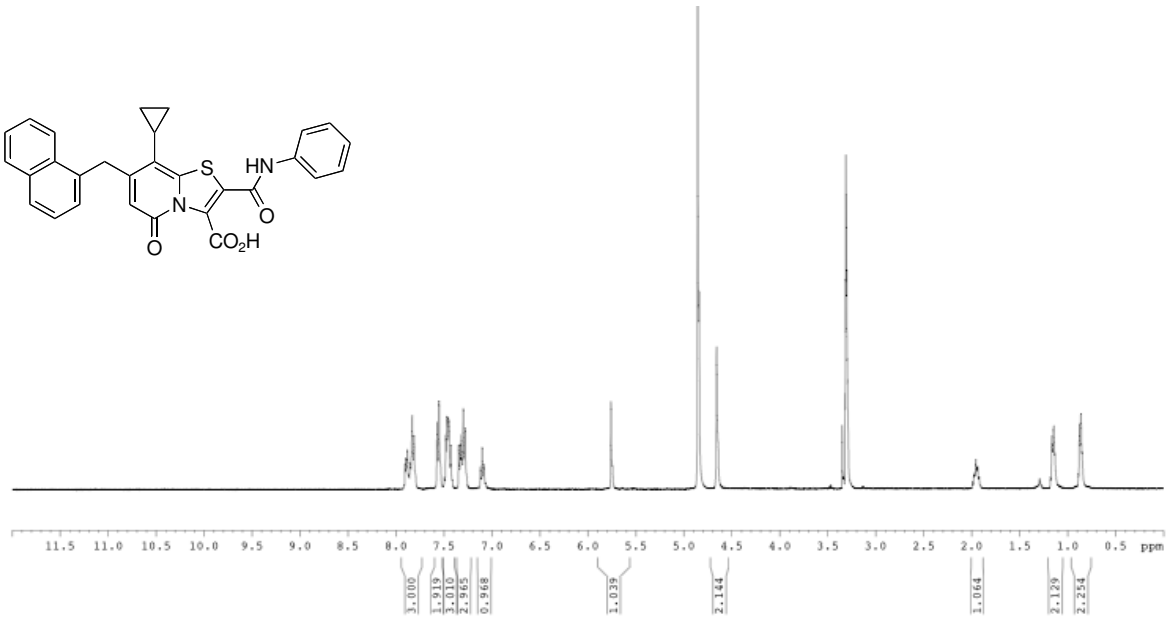
[1]H-NMR spectra of compound **7e**



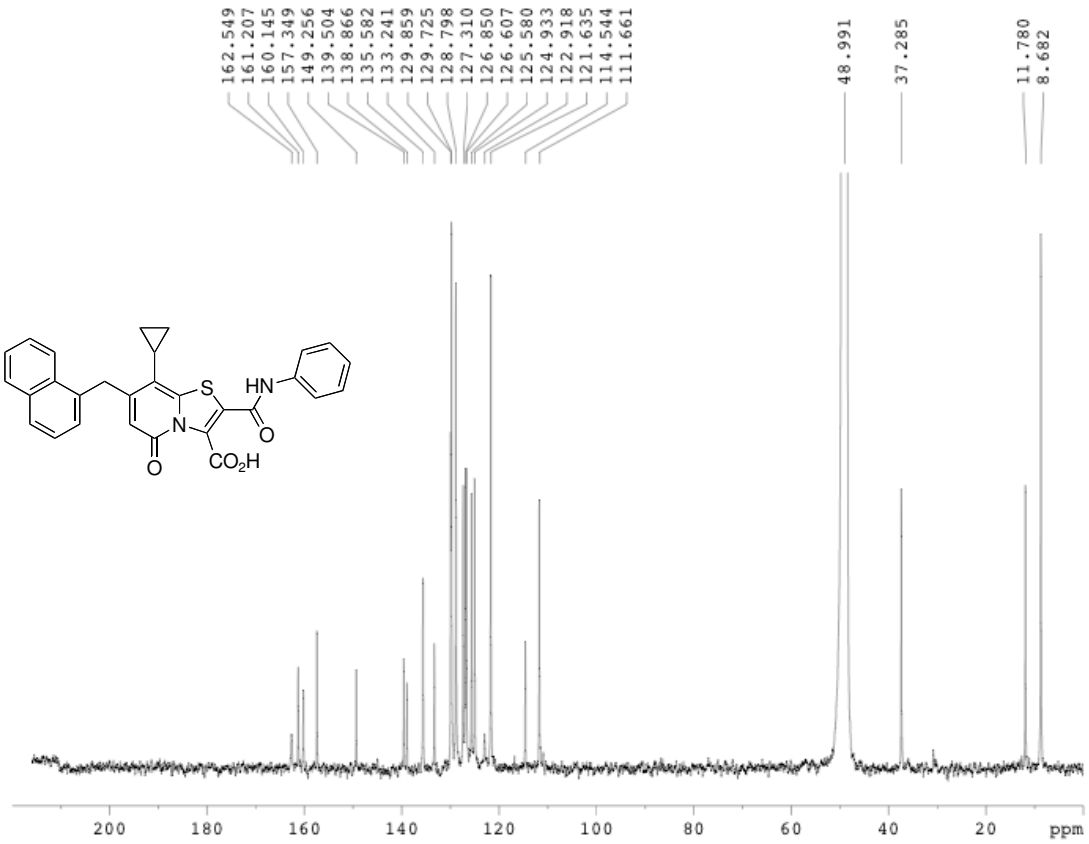
[13]C-NMR spectra of compound **7e**



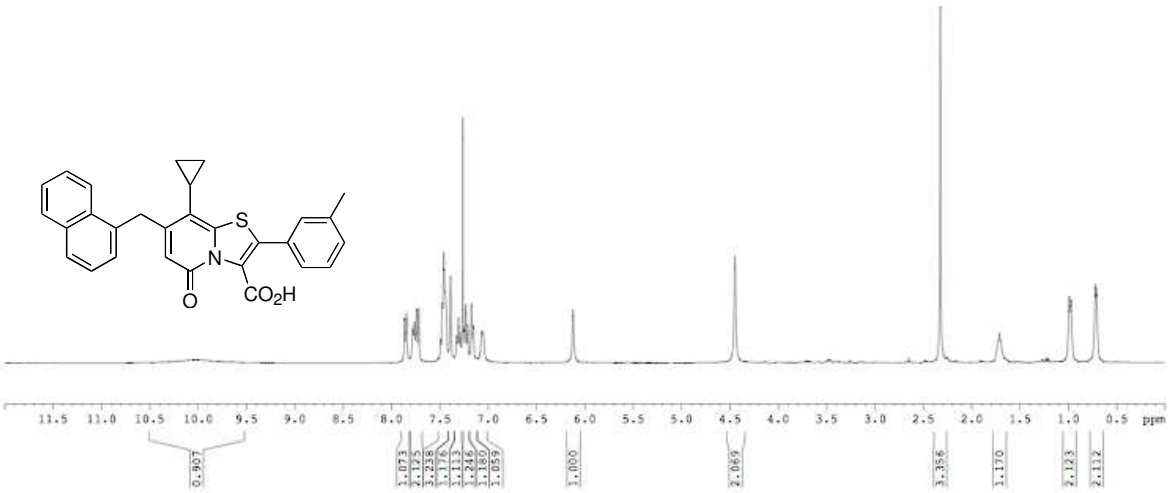
^{1}H-NMR spectra of compound **7f**



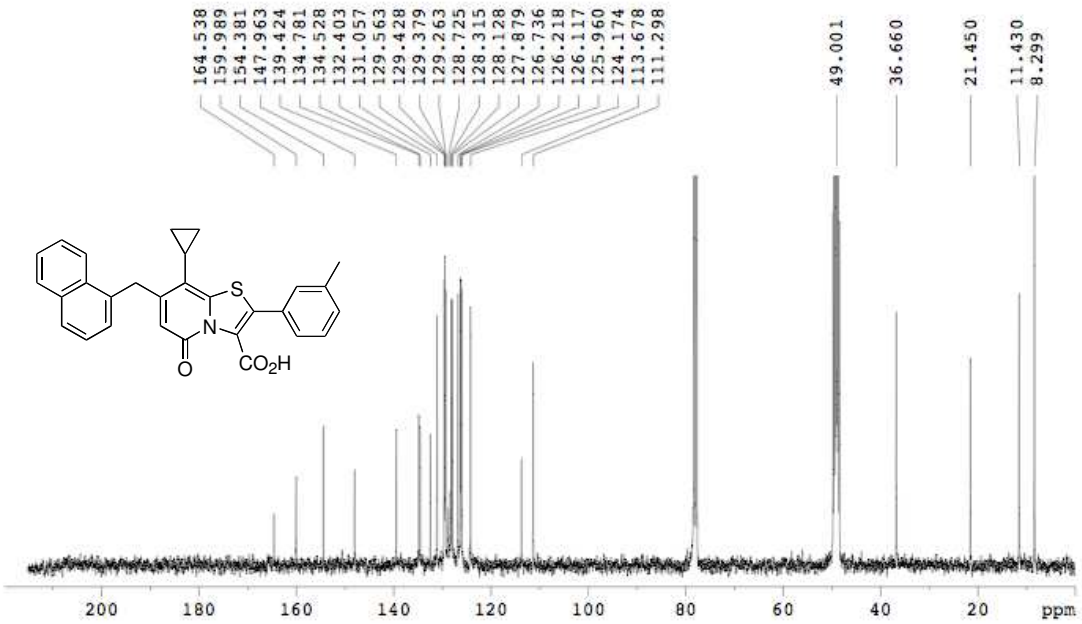
^{13}C-NMR spectra of compound **7f**



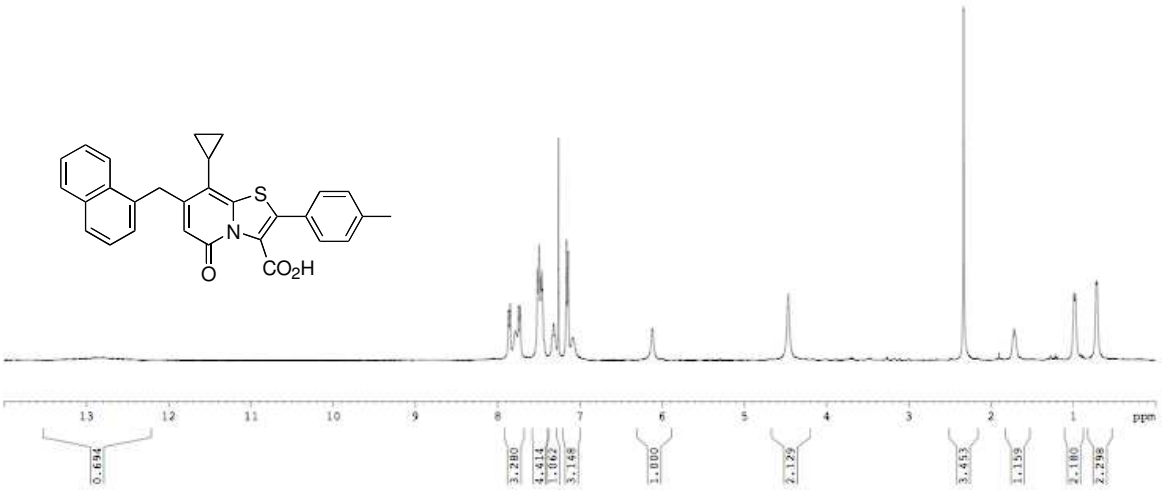
[1]H-NMR spectra of compound **7g**



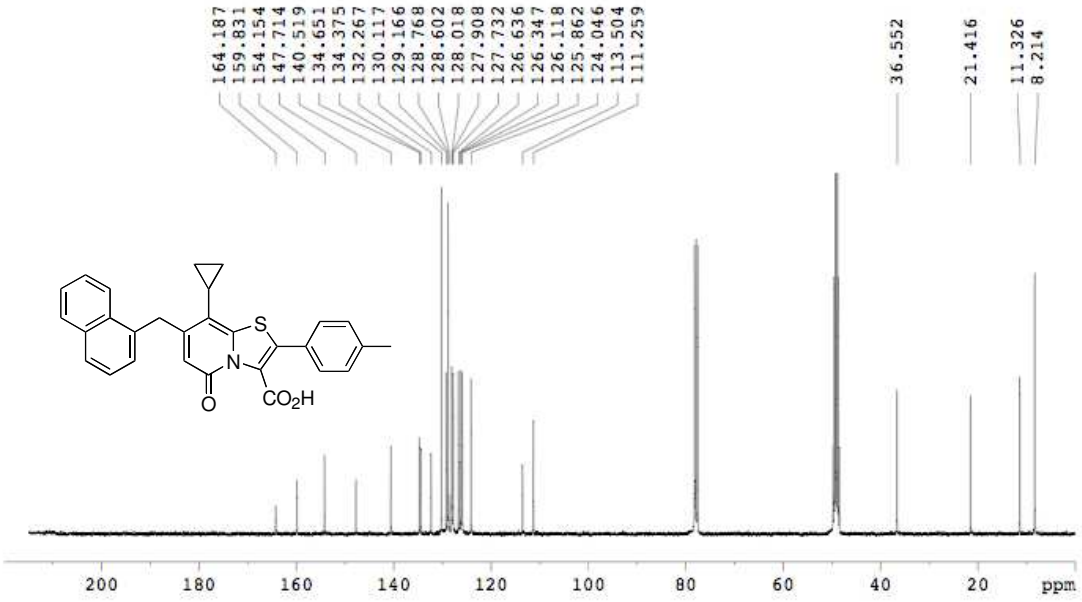
[13]C-NMR spectra of compound **7g**



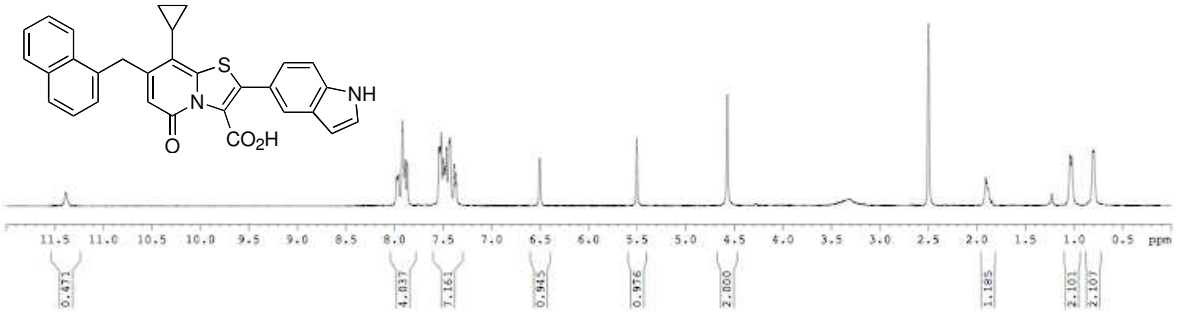
^{1}H-NMR spectra of compound **7h**



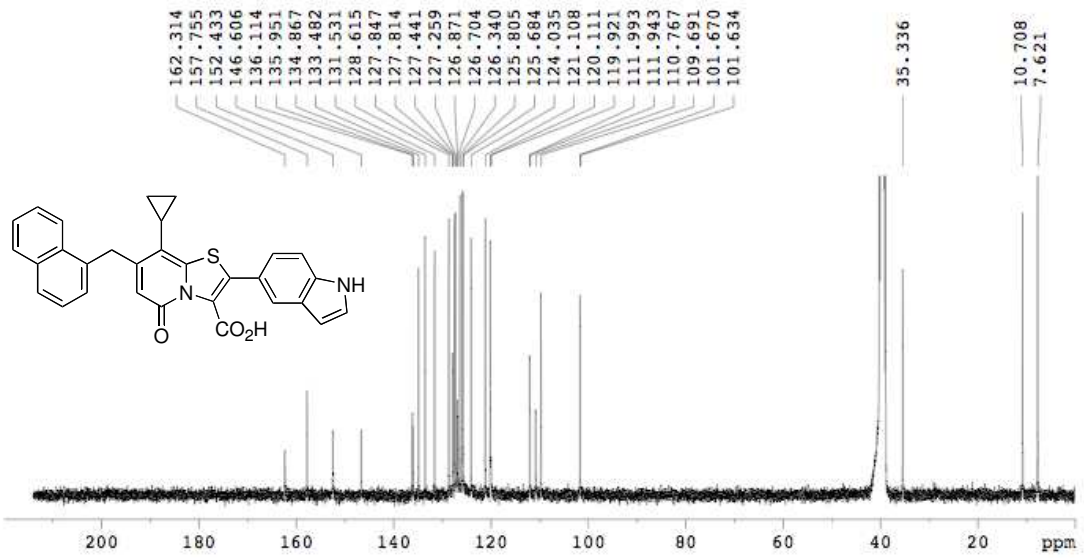
^{13}C-NMR spectra of compound **7h**



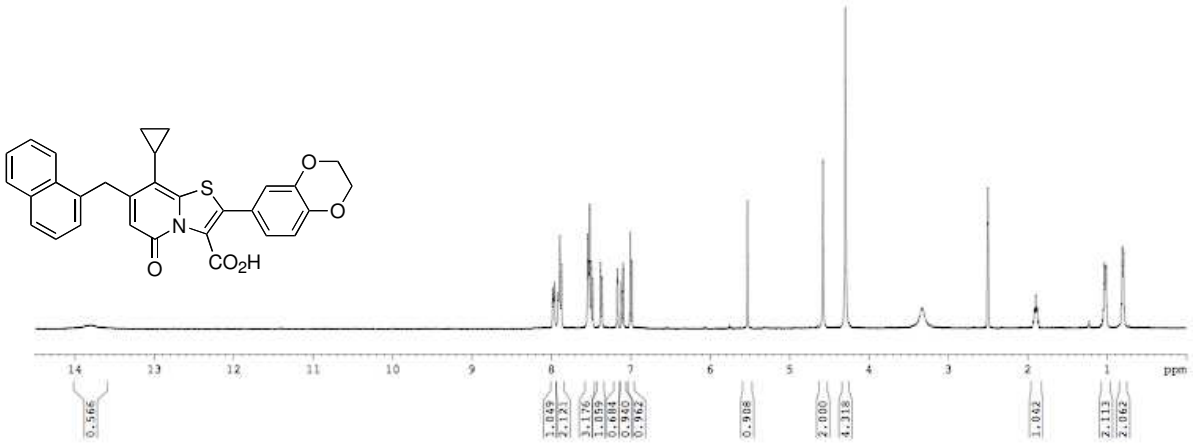
^{1}H-NMR spectra of compound **7i**



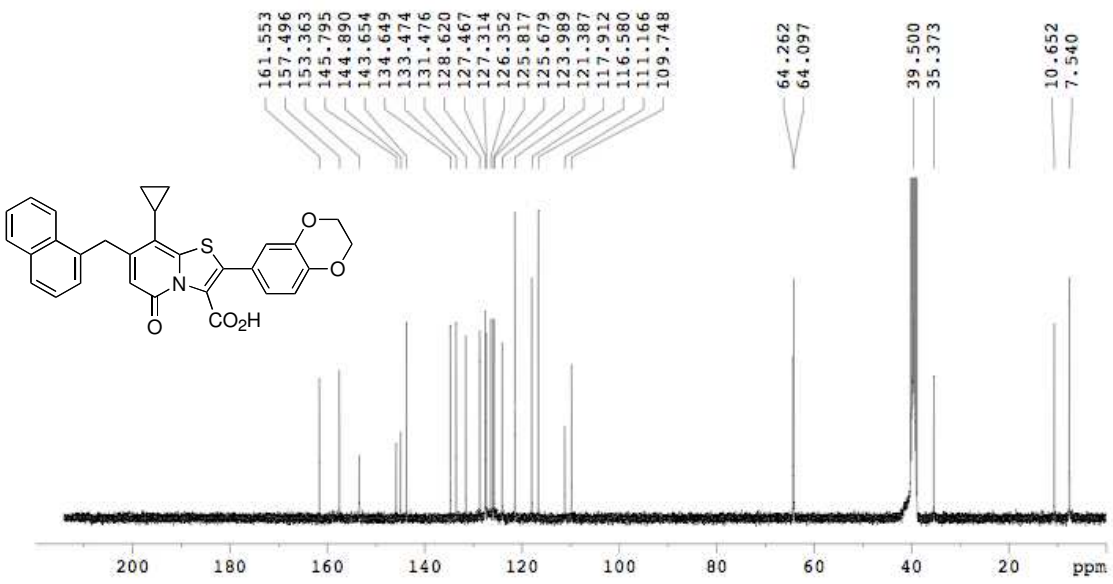
^{13}C-NMR spectra of compound **7i**



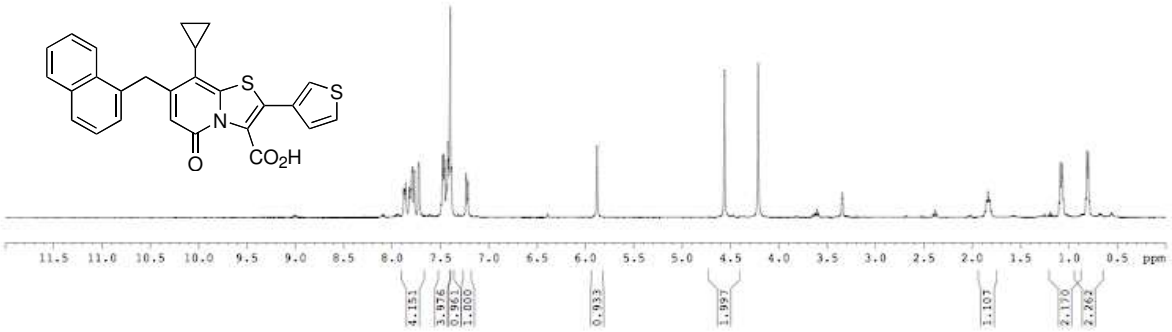
^{1}H-NMR spectra of compound **7j**



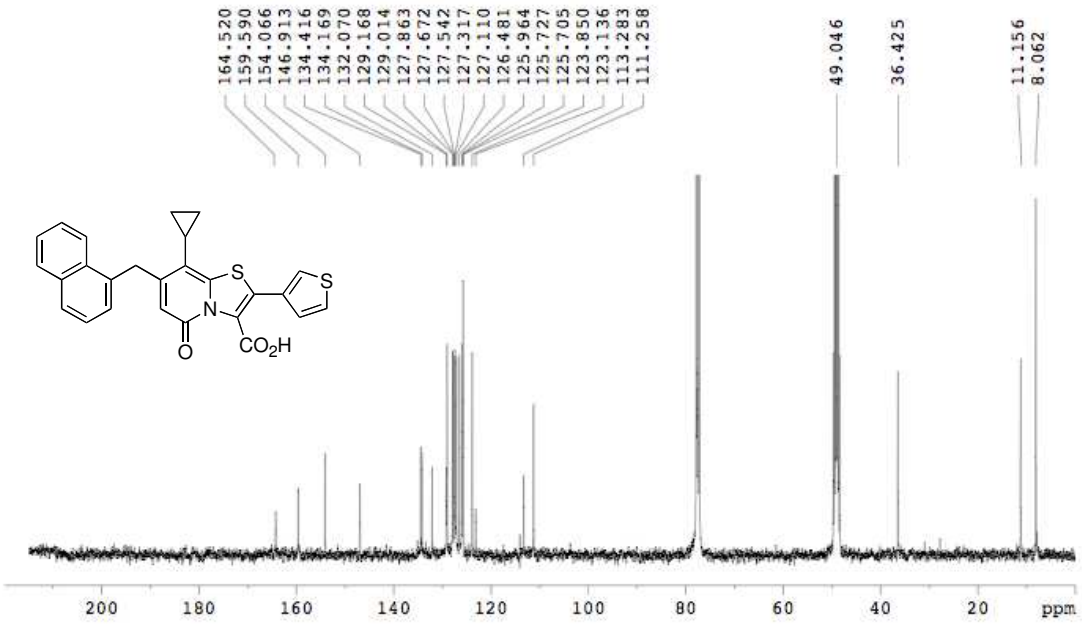
^{13}C-NMR spectra of compound **7j**



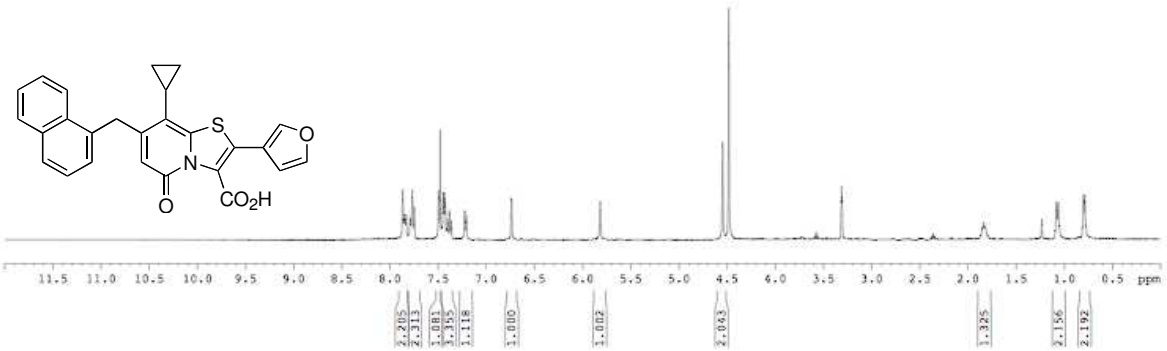
^{1}H-NMR spectra of compound **7k**



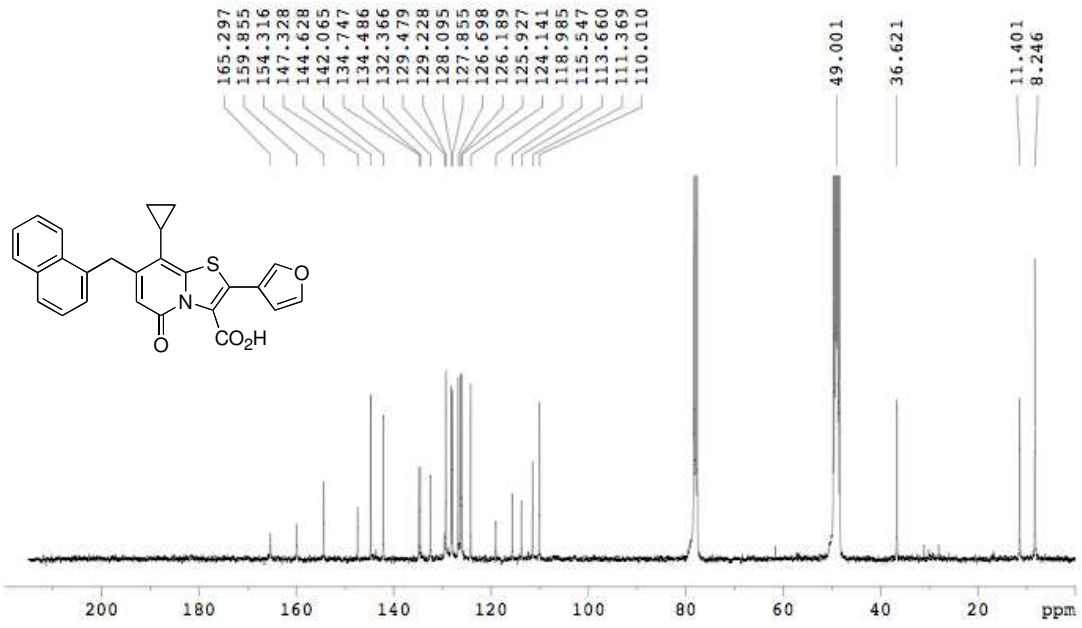
^{13}C-NMR spectra of compound **7k**



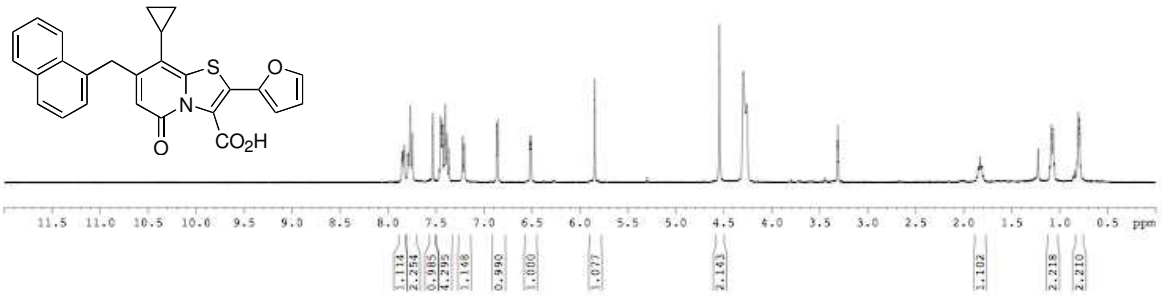
^{1}H-NMR spectra of compound **7l**



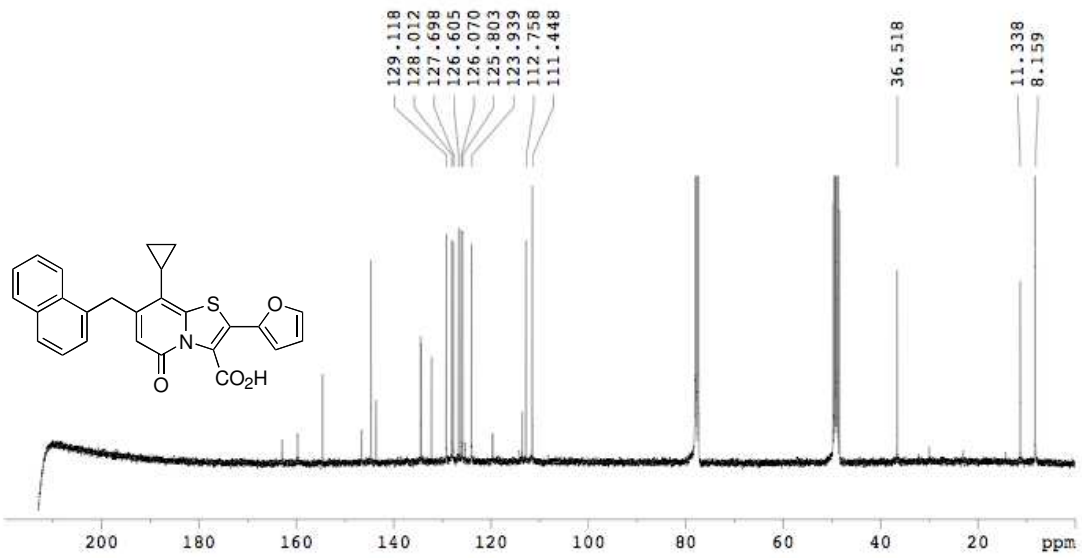
^{13}C-NMR spectra of compound **7l**



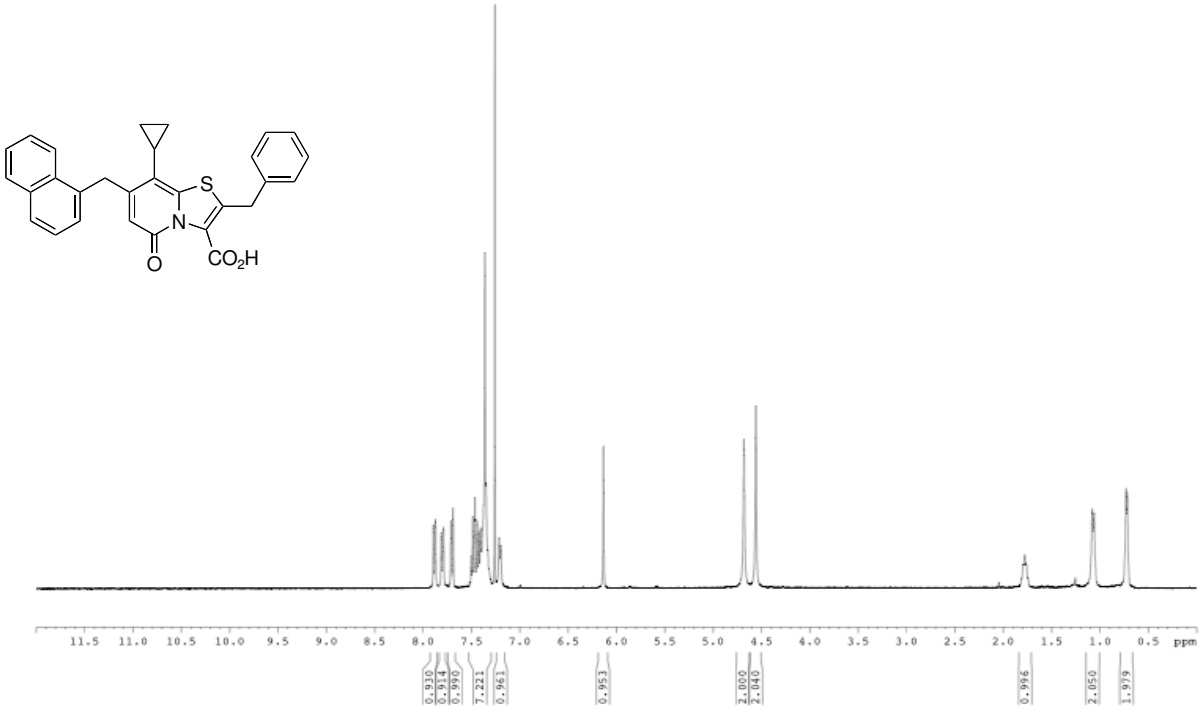
[1]H-NMR spectra of compound **7m**



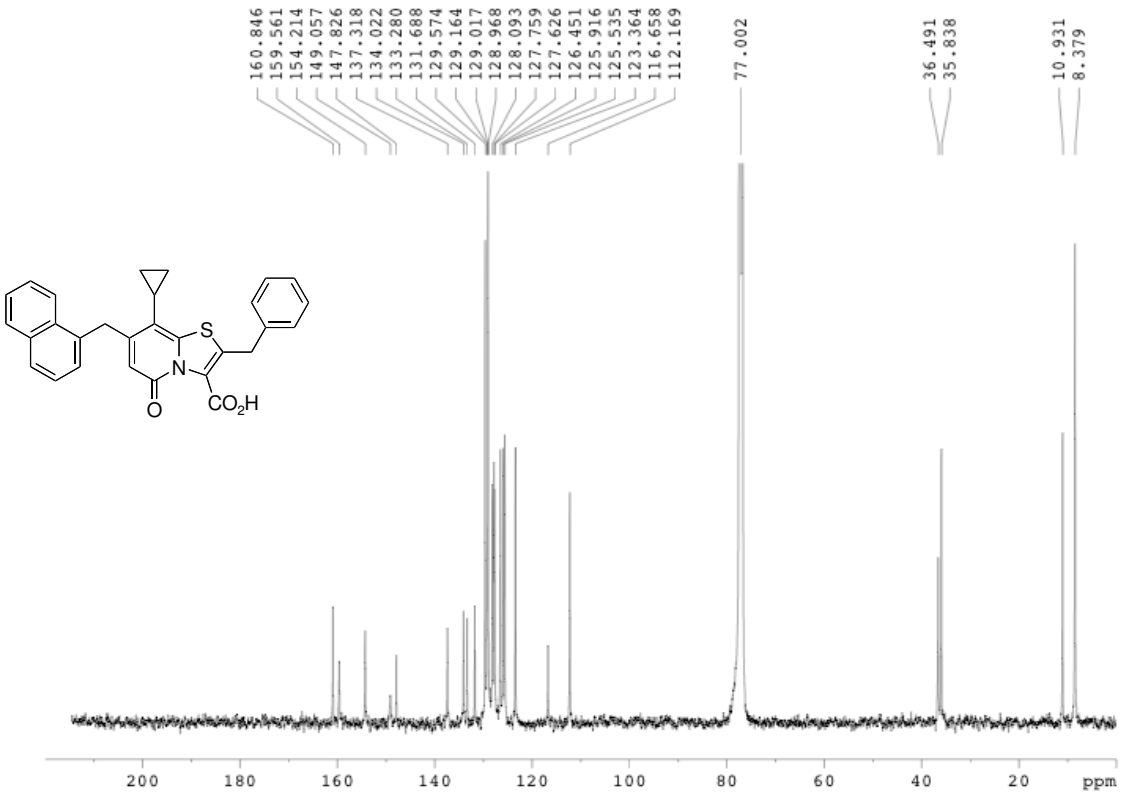
[13]C-NMR spectra of compound **7m**



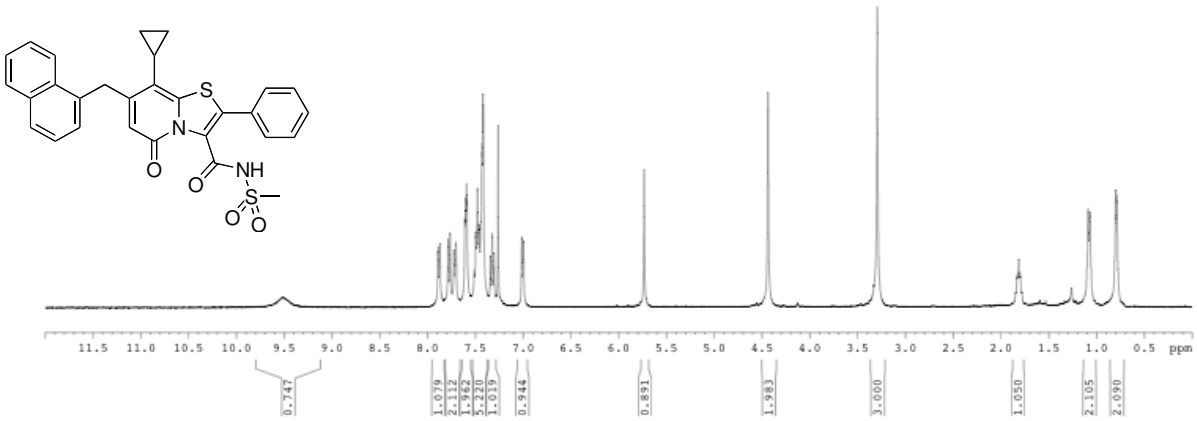
^{1}H-NMR spectra of compound **7n**



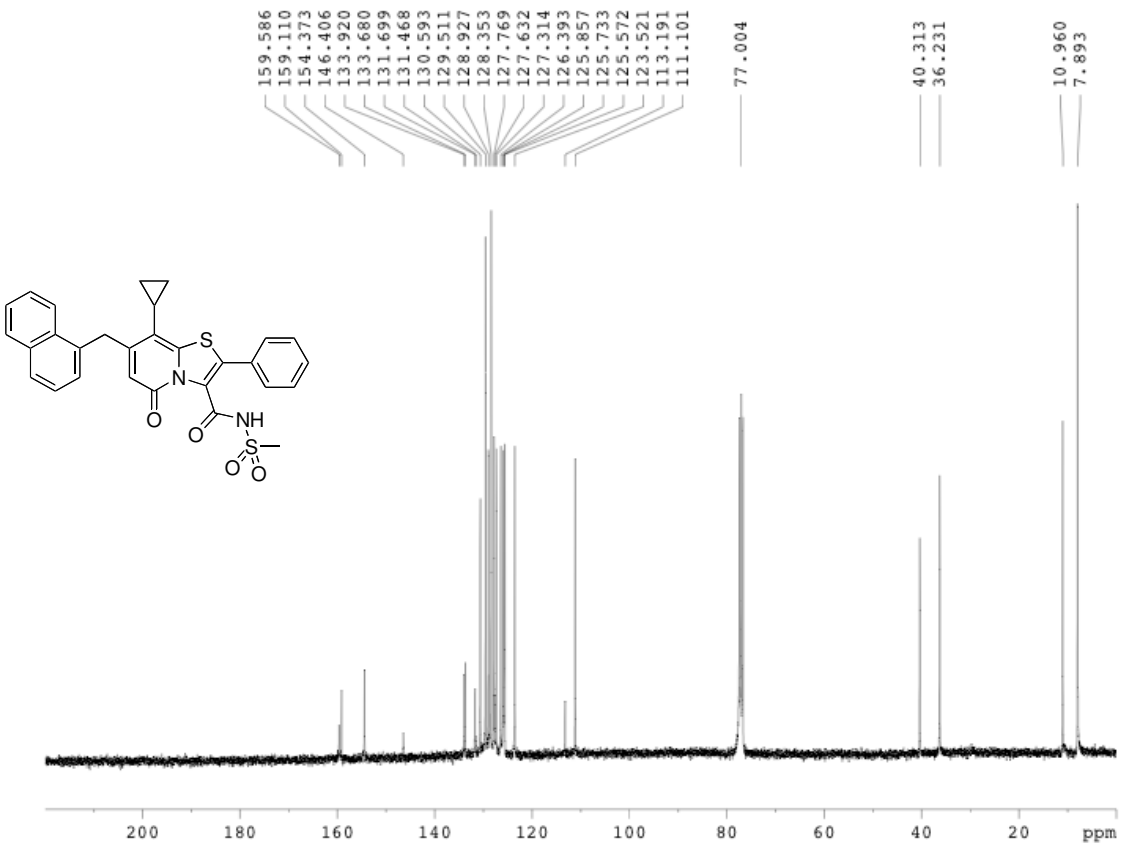
^{13}C-NMR spectra of compound **7n**



^{1}H-NMR spectra of compound **9**



^{13}C-NMR spectra of compound **9**



References

1. Pinkner, J. S.; Remaut, H.; Buelens, F.; Miller, E.; Åberg, V.; Pemberton, N.; Hedenström, M.; Larsson, A.; Seed, P.; Waksman, G.; Hultgren, S. J.; Almqvist, F. Rationally designed small compounds inhibit pilus biogenesis in uropathogenic bacteria. *Proc. Natl. Acad. Sci. USA* **2006,** 103, 17897-17902.

2. CCP4. The CCP4 (Collaborative Computational Project Number 4) suite: programmes for protein crystallography. *Acta Crystallogr D Biol Crystallogr* **1994**, 50, 760-763

3. Kabsch, W. Automatic processing of rotation diffraction data from crystals of initially unknown symmetry and cell constants. *J. Appl. Cryst.* **1993,** 26, 795-800.

4. Emtenäs, H.; Alderin, L.; Almqvist, F. An enantioselective ketene-imine cycloaddition method for synthesis of substituted ring-fused 2-pyridinones. *J. Org. Chem.* **2001,** 66, 6756-6761.

5. Aberg, V.; Das, P.; Chorell, E.; Hedenstrom, M.; Pinkner, J. S.; Hultgren, S. J.; Almqvist, F. Carboxylic acid isosteres improve the activity of ring-fused 2-pyridones that inhibit pilus biogenesis in E-coli. *Bioorg. Med. Chem. Lett.* **2008**, 18, 3536-3540.

6. Chorell, E.; Das, P.; Almqvist, F. Diverse functionalization of thiazolo ring-fused 2-pyridones. *J. Org. Chem.* **2007**, 72, 4917-4924.

7. Mattsson, S.; Dahlstrom, M.; Karlsson, S. A mild hydrolysis of esters mediated by lithium salts. *Tetrahedron Lett.* **2007**, 48, 2497-2499.