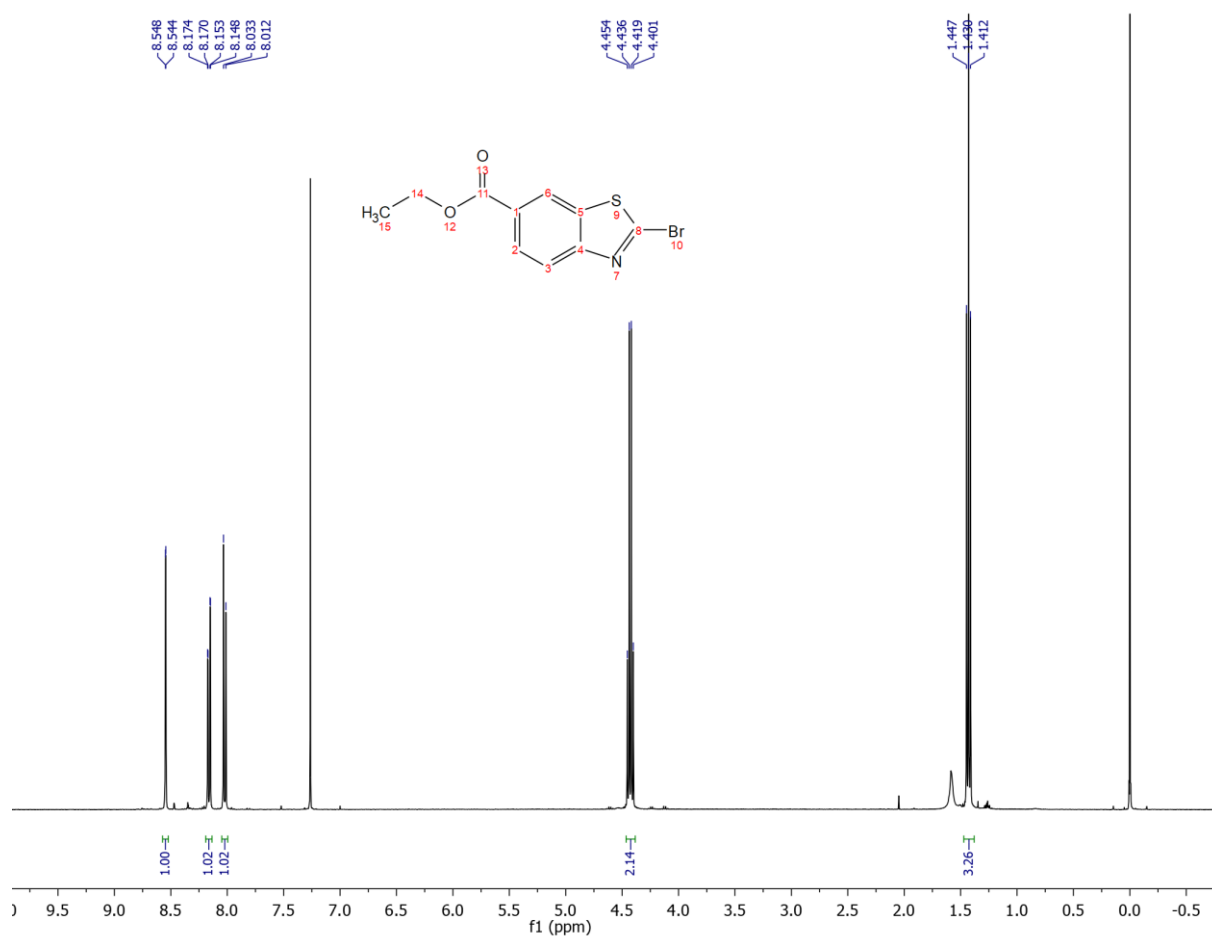


# Supplementary Materials: Structure–Activity Relationships of Benzothiazole-Based Hsp90 C-Terminal-Domain Inhibitors

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## Representative $^1\text{H}$ NMR, $^{13}\text{C}$ NMR spectra and HPLC chromatograms

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 25 °C, TMS):  $\delta$  = 8.55 (d,  $J$  = 1.5 Hz, 1H, Ar- $H_7$ ), 8.16 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.5 Hz, 1H, Ar- $H_5$ ), 8.02 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 4.43 (q,  $J$  = 7.1 Hz, 2H,  $\text{COO-CH}_2\text{-CH}_3$ ), 1.43 ppm (t,  $J$  = 7.1 Hz, 3H,  $\text{COO-CH}_2\text{-CH}_3$ )



**Figure S1.**  $^1\text{H}$  NMR spectrum of compound 1.

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ , 25 °C, TMS):  $\delta$  = 165.8, 155.1, 142.4, 137.3, 127.9, 127.8, 122.9, 122.5, 61.5, 14.4 ppm.

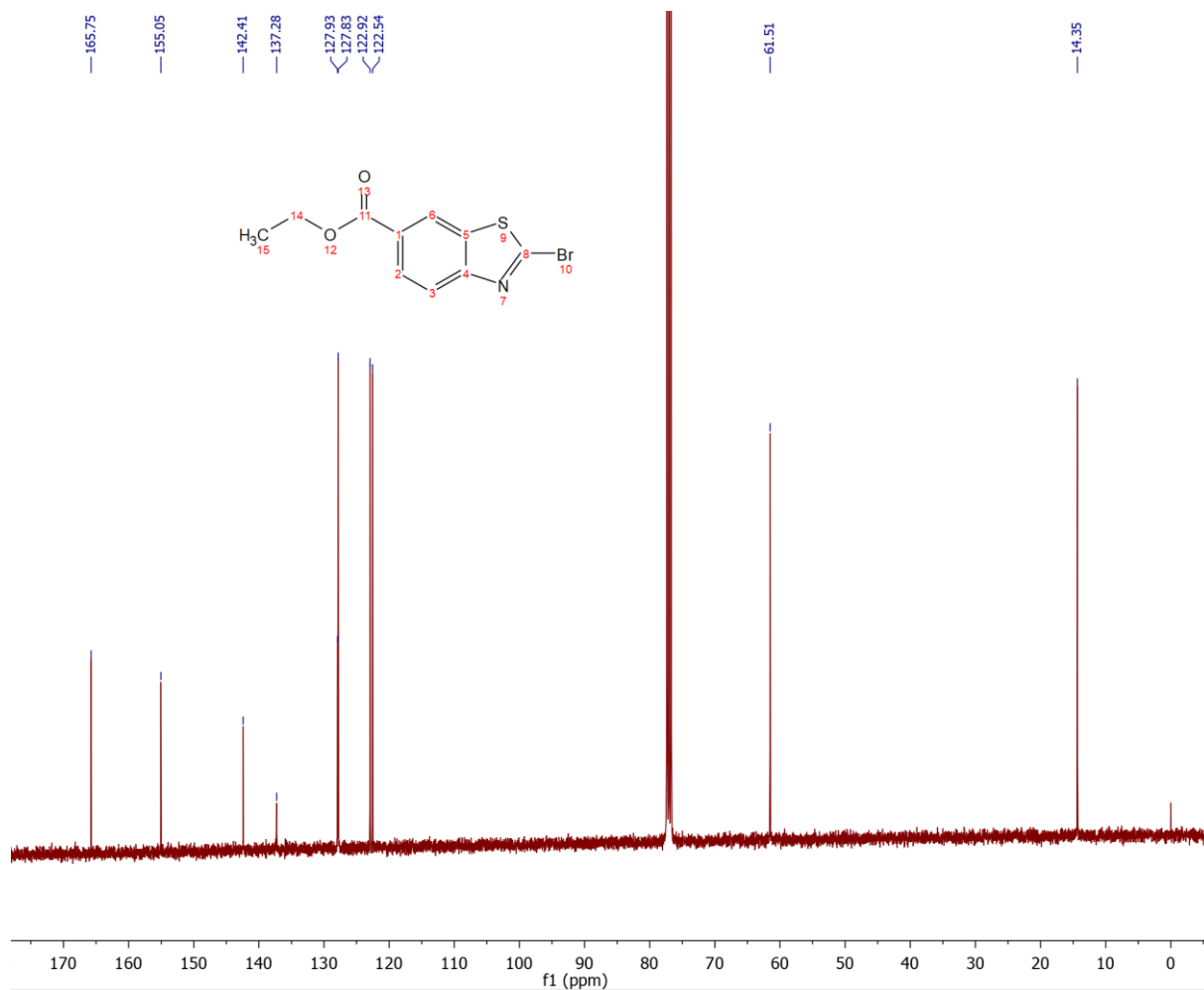


Figure S2.  $^{13}\text{C}$  NMR spectrum of compound 1.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 8.32 (d,  $J$  = 1.5 Hz, 1H, Ar- $H_7$ ), 8.01 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.53 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 4.38 (q,  $J$  = 7.1 Hz, 2H,  $\text{COO-CH}_2\text{-CH}_3$ ), 3.69 – 3.63 (m, 4H,  $2 \times$  piperazine- $\text{CH}_2$ ), 3.63 – 3.56 (m, 4H,  $2 \times$  piperazine- $\text{CH}_2$ ), 1.49 (s, 9H,  $\text{COC}(\text{CH}_3)_3$ ), 1.40 ppm (t,  $J$  = 7.1 Hz, 3H,  $\text{COO-CH}_2\text{-CH}_3$ )

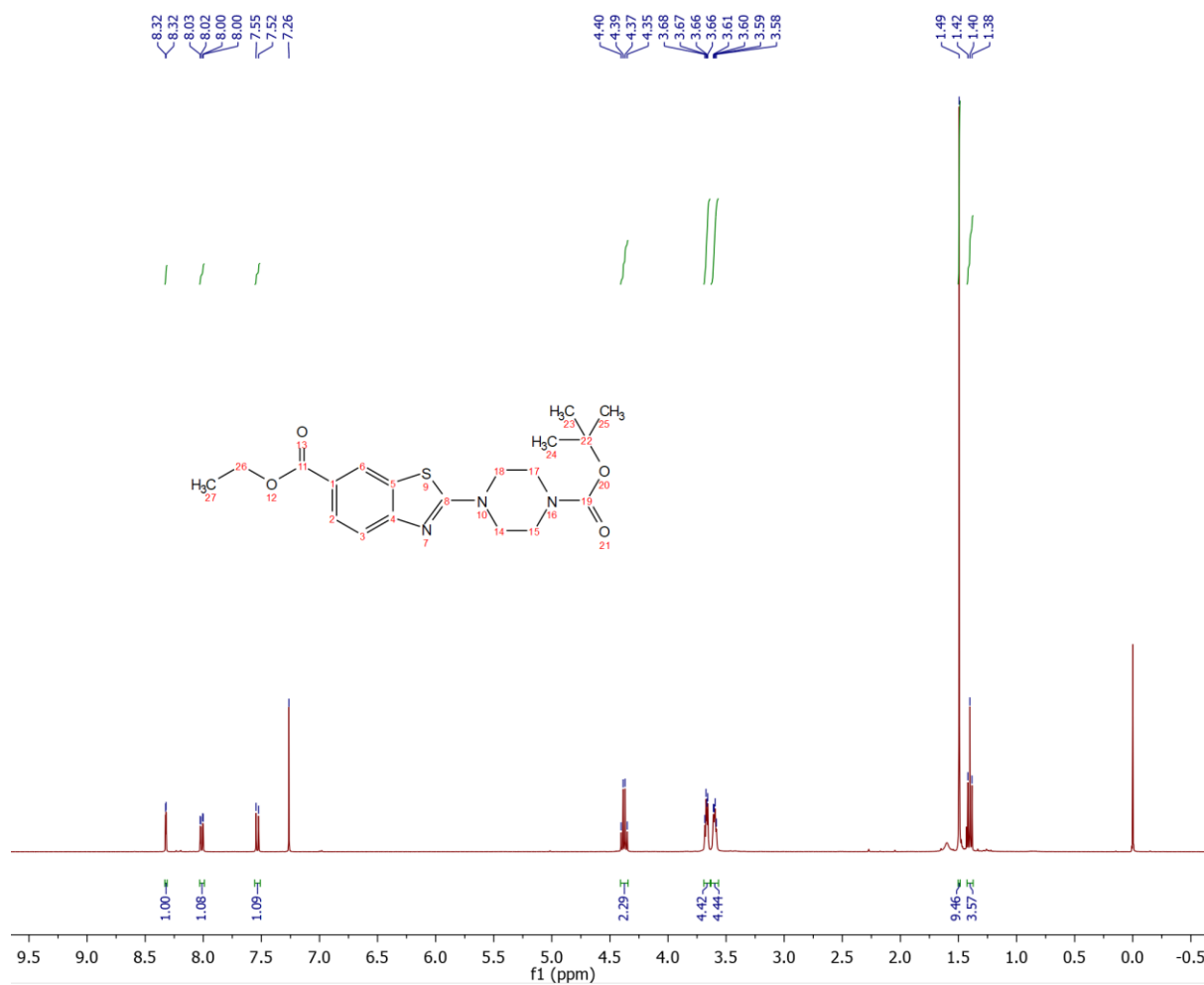


Figure S3.  $^1\text{H}$  NMR spectrum of compound 2.

Chemical structure of 1,3-bis(4-methoxyphenyl)-4,5-dimethyl-1H-imidazole-2-thione is shown above the spectrum. The structure includes atom numbering (1-27) and atom types (C, N, O, S).

<sup>13</sup>C NMR spectrum (f1 (ppm)) showing peaks corresponding to the structure. The x-axis ranges from 0 to 180 ppm.

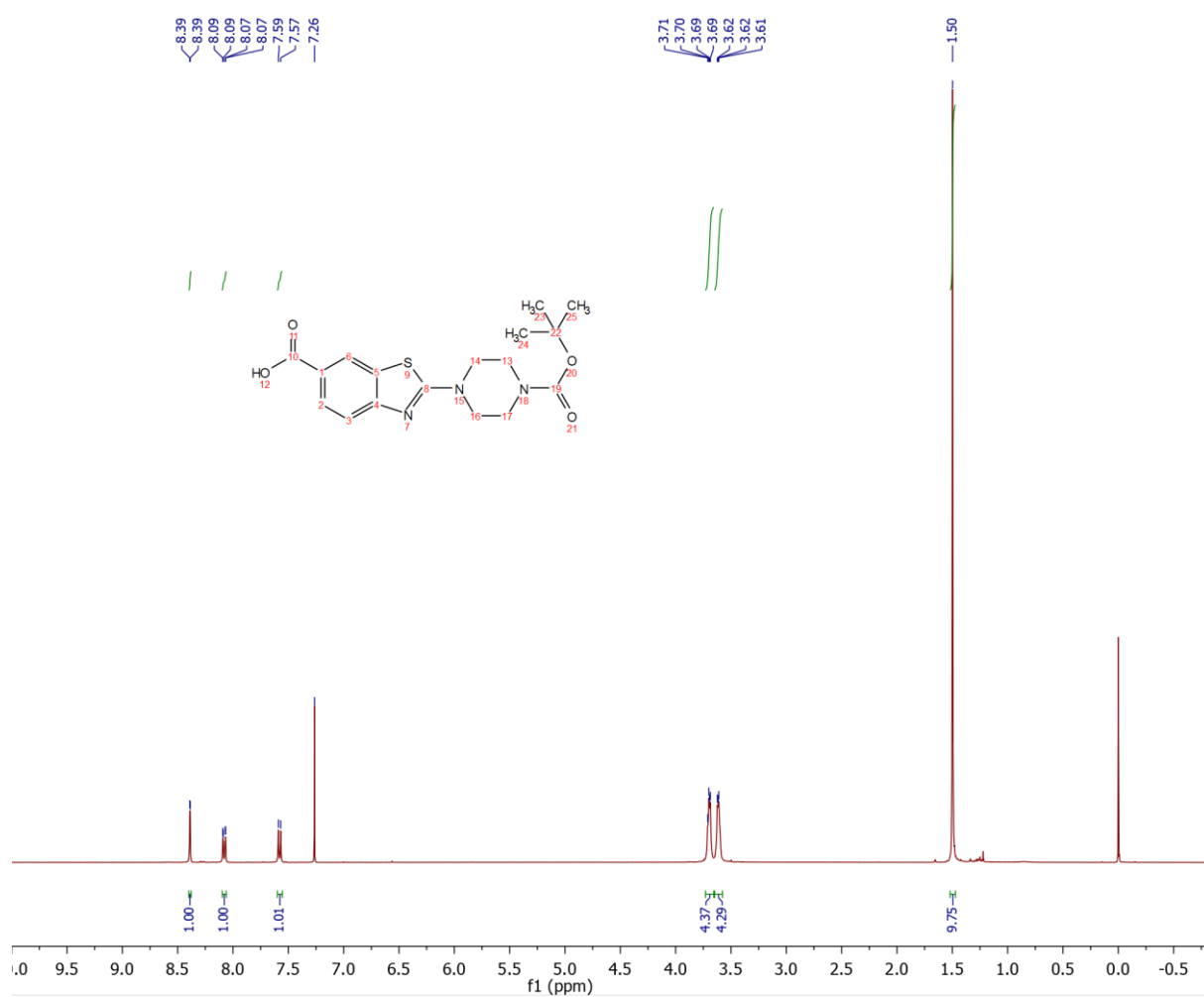
Peak list (ppm):

Peak (ppm)
170.70
166.44
156.34
154.51
130.56
128.01
123.65
122.77
118.48
80.57
60.87
48.24
28.39
14.42

**Figure S4.**  $^{13}\text{C}$  NMR spectrum of compound **2**.

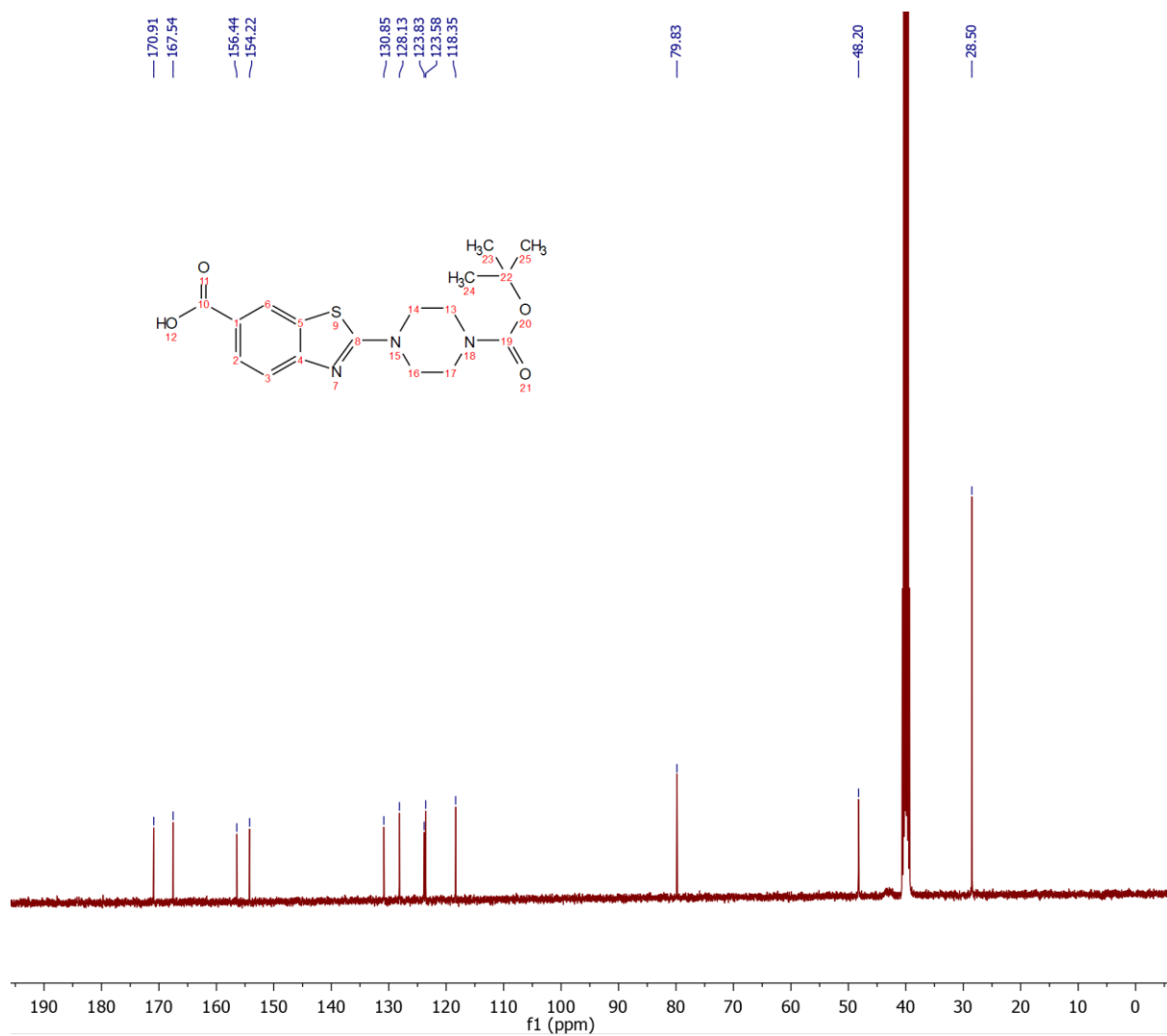


$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 8.39 (d,  $J$  = 1.6 Hz, 1H, Ar- $H_7$ ), 8.08 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.6 Hz, 1H, Ar- $H_5$ ), 7.58 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 3.73 – 3.66 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 3.65 – 3.58 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 1.50 ppm (s, 9H,  $\text{COC}(\text{CH}_3)_3$ )



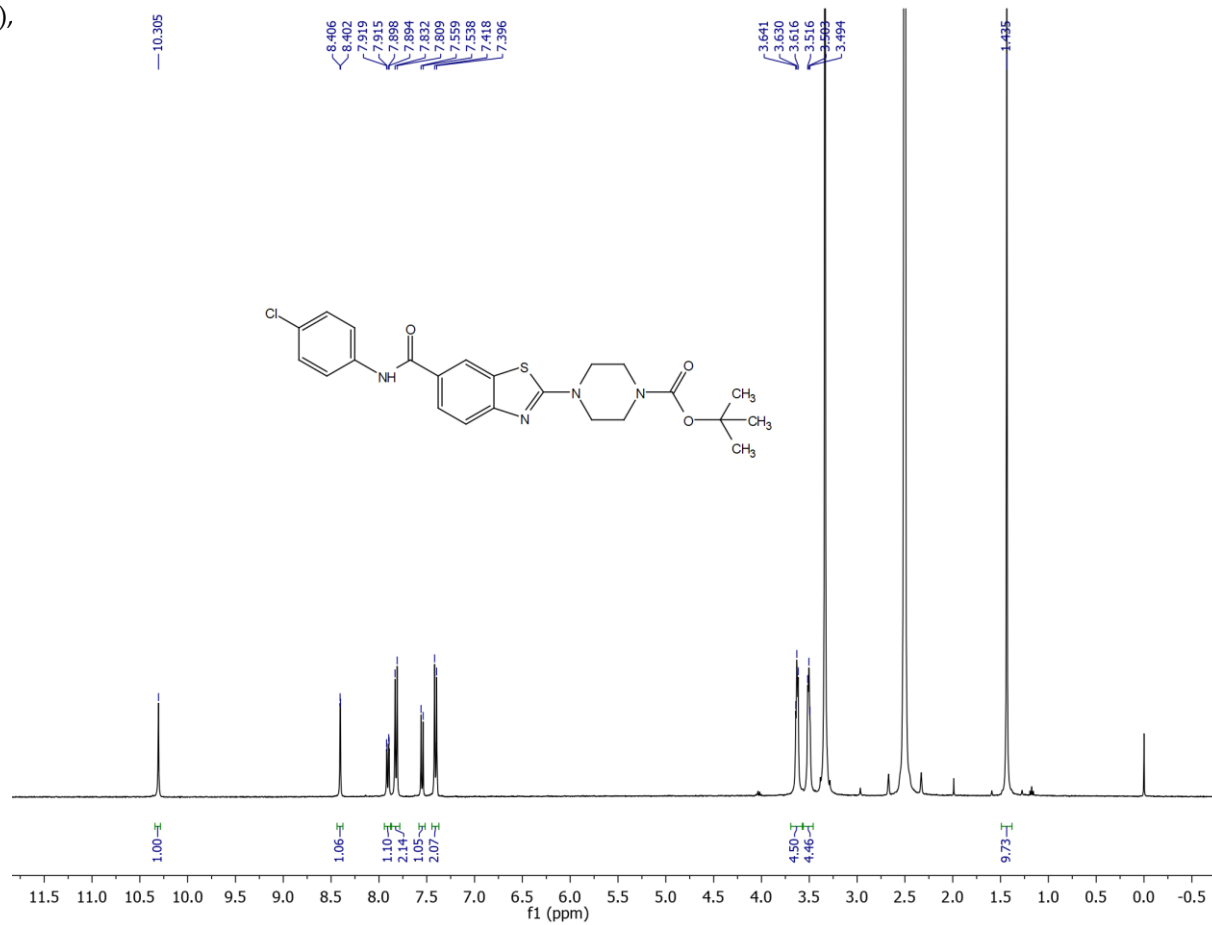
**Figure S5.**  $^1\text{H}$  NMR spectrum of compound 3.

$^{13}\text{C}$  NMR (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.9, 167.6, 156.5, 154.2, 130.9, 128.1, 123.8, 123.6, 118.4, 79.8 (2C), 48.2 (2C), 28.5 (3C) ppm



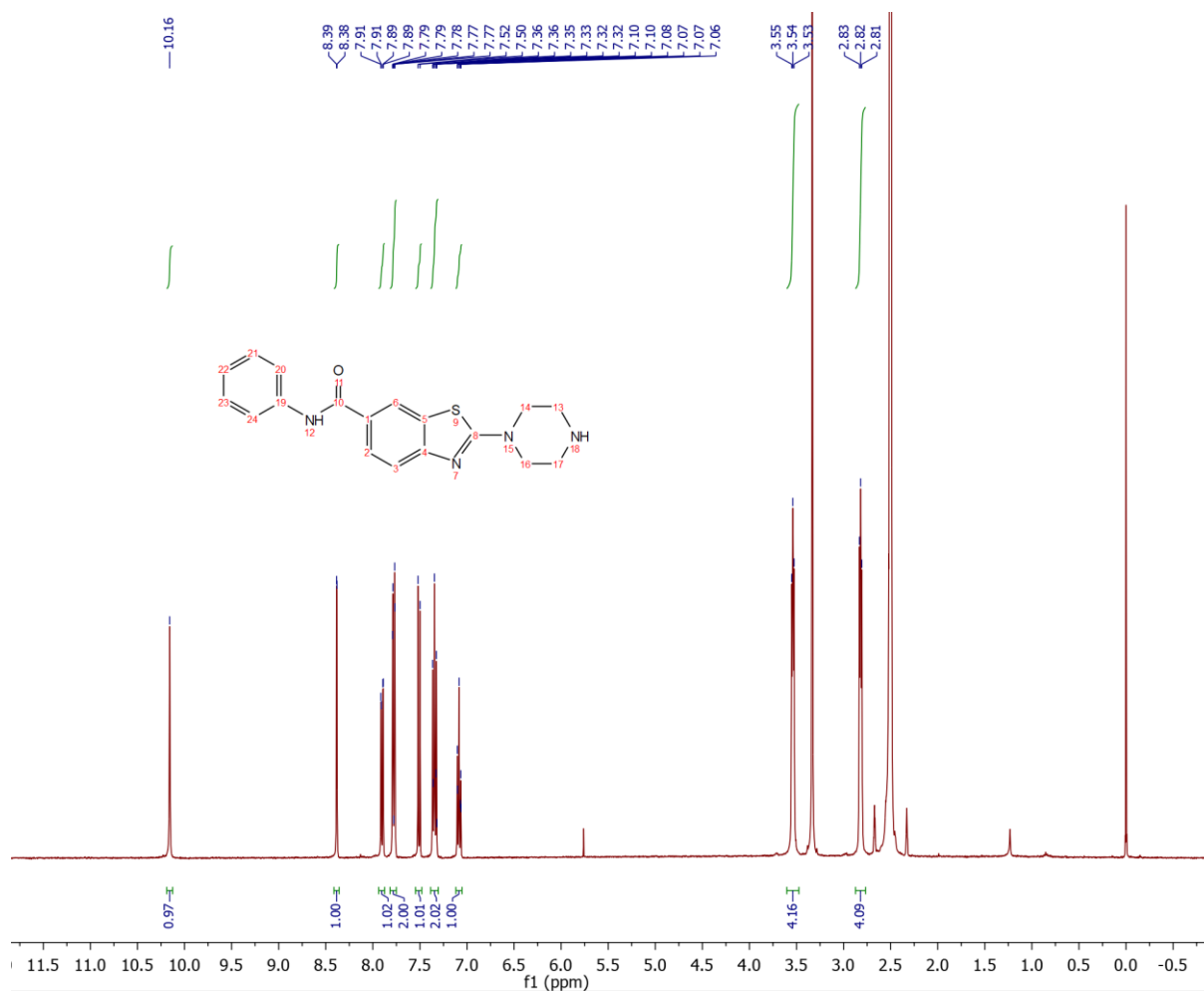
**Figure S6.**  $^{13}\text{C}$  NMR spectrum of compound 3.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.31 (s, 1H, Ar-NH-COR), 8.40 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.91 (dd,  $J_1$  = 8.5,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.82 (d,  $J$  = 8.9 Hz, 2H, 2  $\times$  Ar- $H$ ), 7.55 (d,  $J$  = 8.4 Hz, 1H, Ar- $H_4$ ), 7.41 (d,  $J$  = 8.9 Hz, 2H, 2  $\times$  Ar- $H$ ),



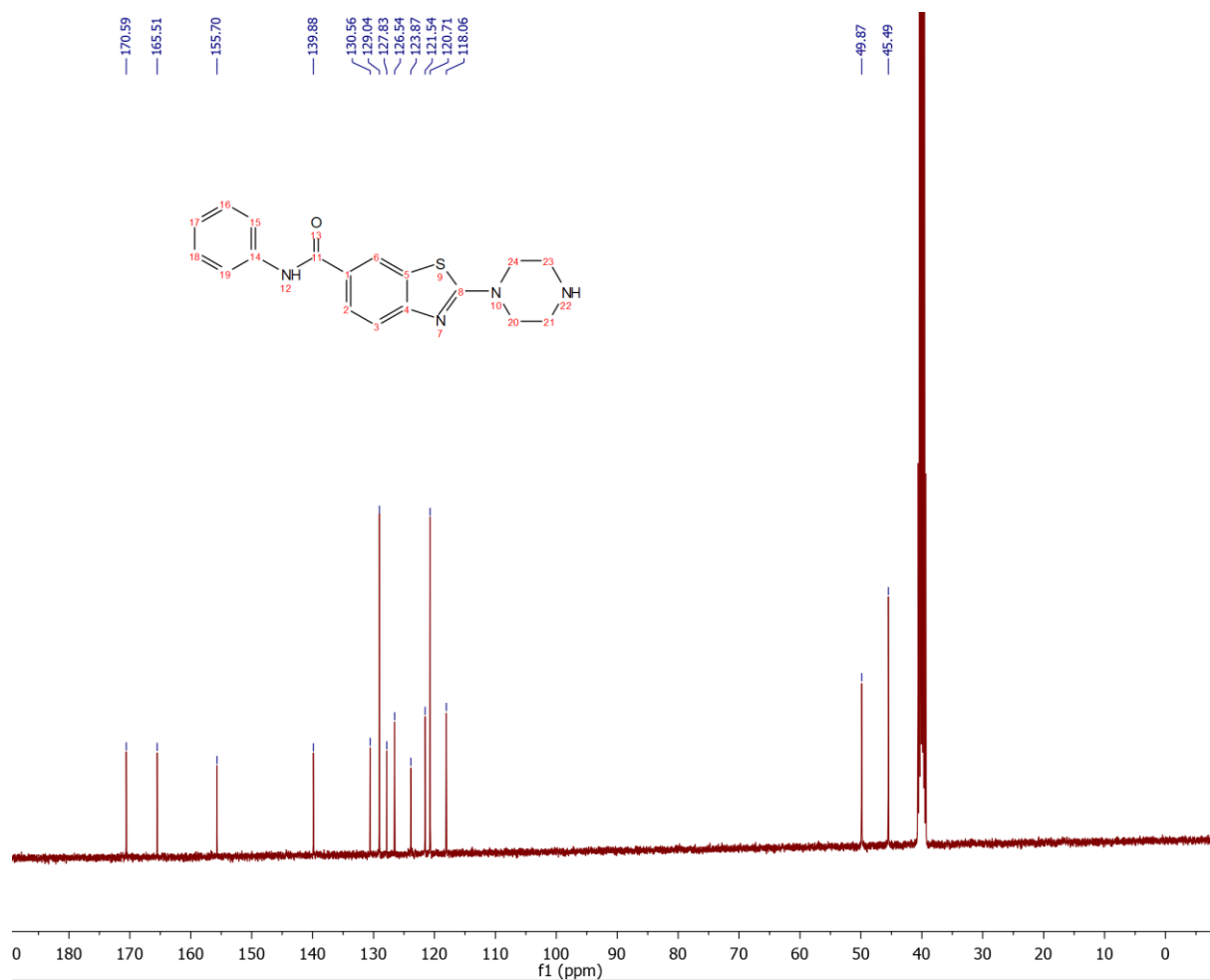
**Figure S7.**  $^1\text{H}$ NMR spectrum of compound **4c**.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.16 (s, 1H, Ar-NH-COR), 8.38 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.90 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.82 – 7.75 (m, 2H, 2  $\times$  Ar- $H$ ), 7.51 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.39 – 7.30 (m, 2H, 2  $\times$  Ar- $H$ ), 7.13 – 7.04 (m, 1H, Ar- $H$ ), 3.58 – 3.48 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 2.87 – 2.76 ppm (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ )



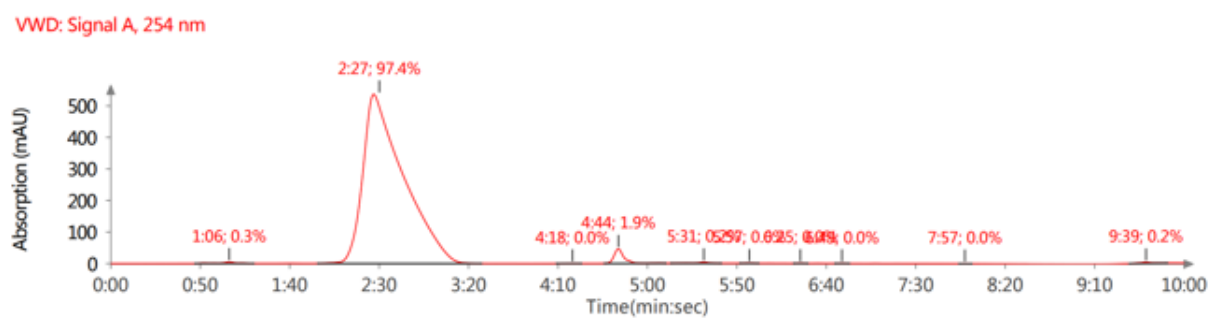
**Figure S8.**  $^1\text{H}$  NMR spectrum of compound 5a.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.6, 165.5, 155.7, 139.9, 130.6, 129.0 (2C), 127.8, 126.5, 123.9, 121.5, 120.7 (2C), 118.1, 49.9 (2C), 45.5 ppm (2C);



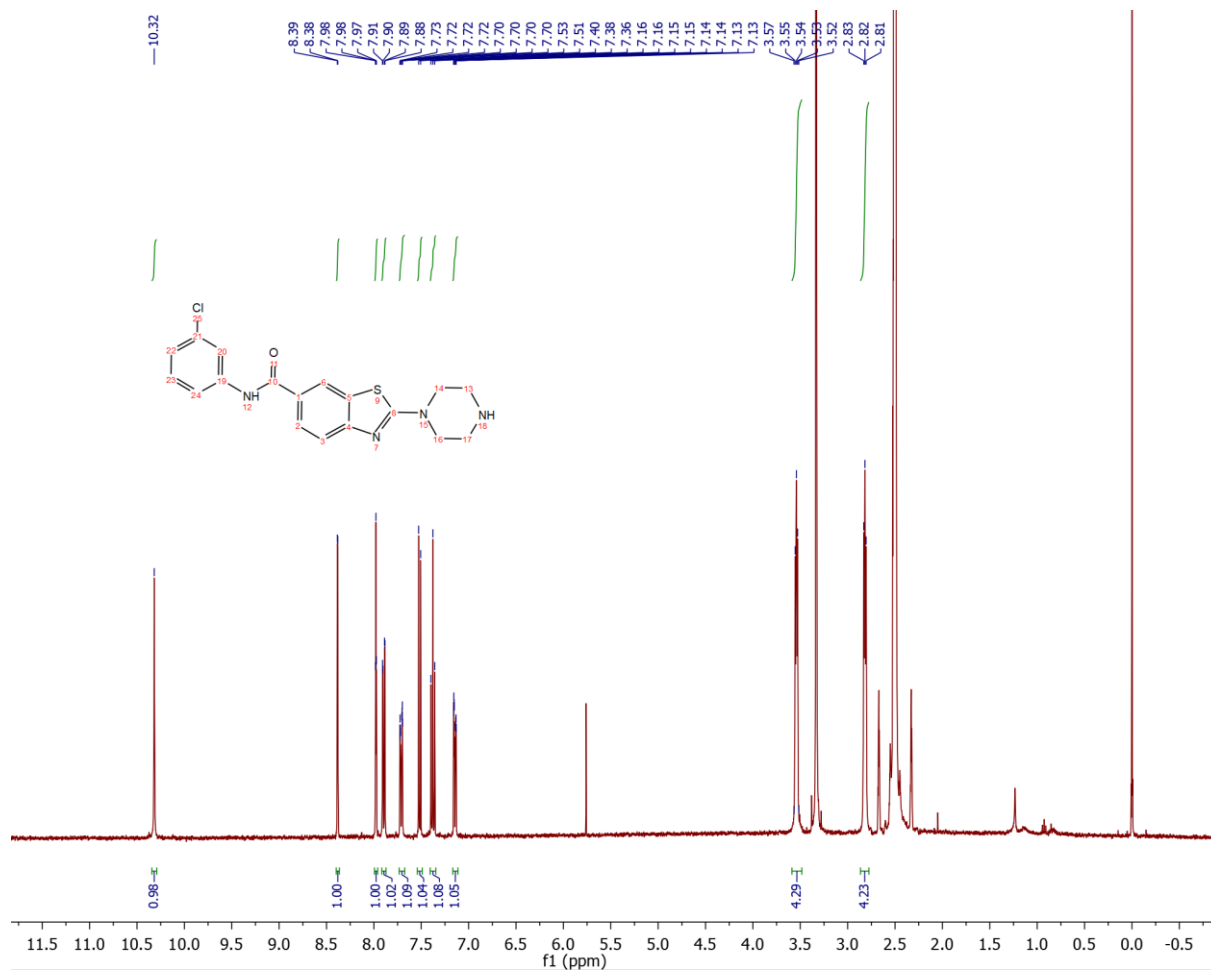
**Figure S9.**  $^{13}\text{C}$  NMR spectrum of compound 5a.

HPLC:  $t_r$  = 2.27 min (97.4 % at 254 nm)



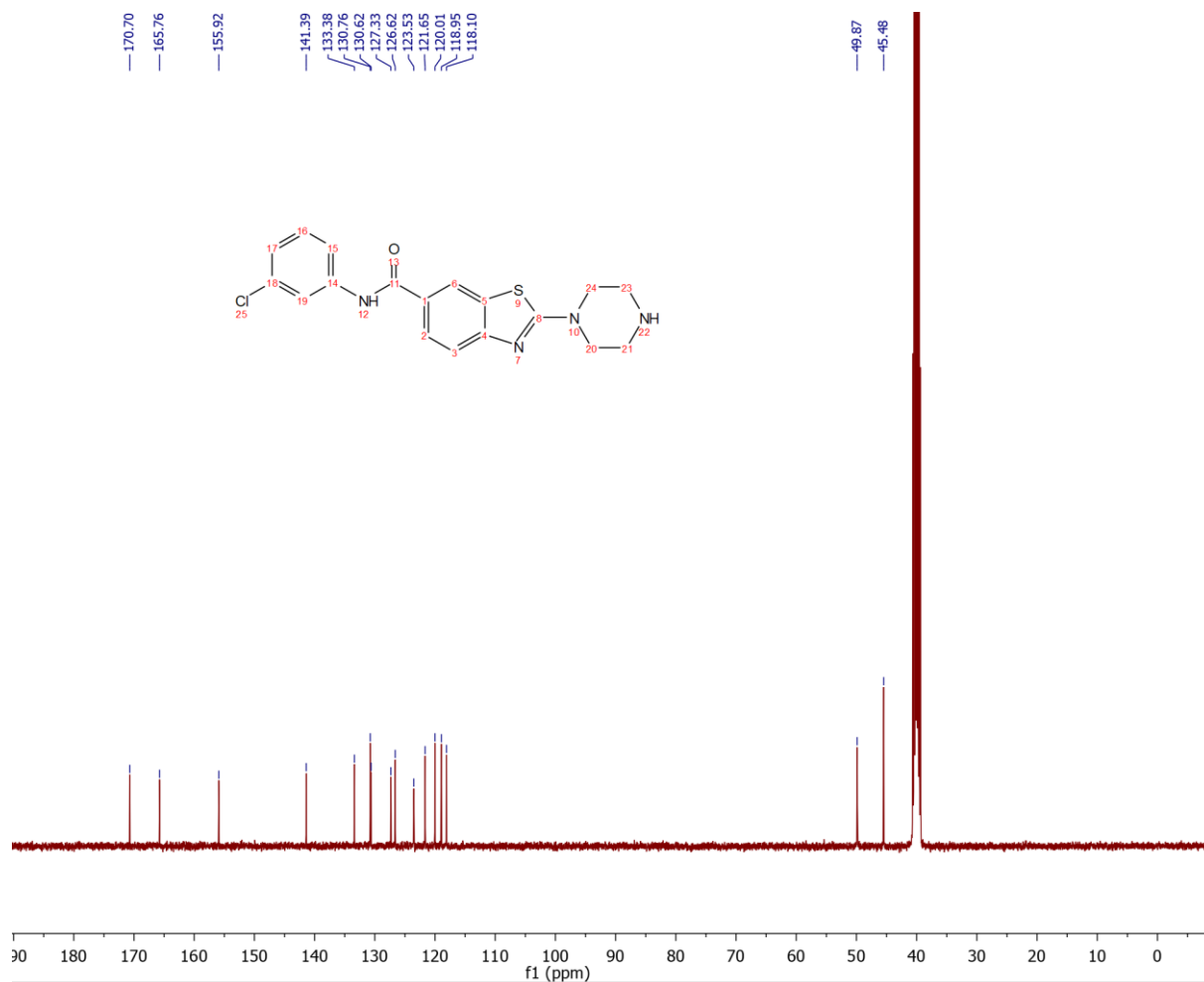
**Figure S10.** HPLC chromatogram for compound 5a.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 10.32 (s, 1H, Ar-NH-COR), 8.38 (d,  $J$  = 1.9 Hz, 1H, Ar- $H_7$ ), 7.98 (t,  $J$  = 2.0 Hz, 1H, Ar- $H$ ), 7.90 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.9 Hz, 1H, Ar- $H_5$ ), 7.71 (ddd,  $J_1$  = 8.1 Hz,  $J_2$  = 2.0 Hz,  $J_3$  = 0.9 Hz, 1H, Ar- $H$ ), 7.52 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.38 (t,  $J$  = 8.1 Hz, 1H, Ar- $H$ ), 7.14 (ddd,  $J_1$  = 8.1 Hz,  $J_2$  = 2.0 Hz,  $J_3$  = 0.9 Hz, 1H, Ar- $H$ ), 3.58 – 3.51 (m, 4H,  $2 \times$  piperazine- $\text{CH}_2$ ), 2.85 – 2.79 ppm (m, 4H,  $2 \times$  piperazine- $\text{CH}_2$ ), not visible (NH)



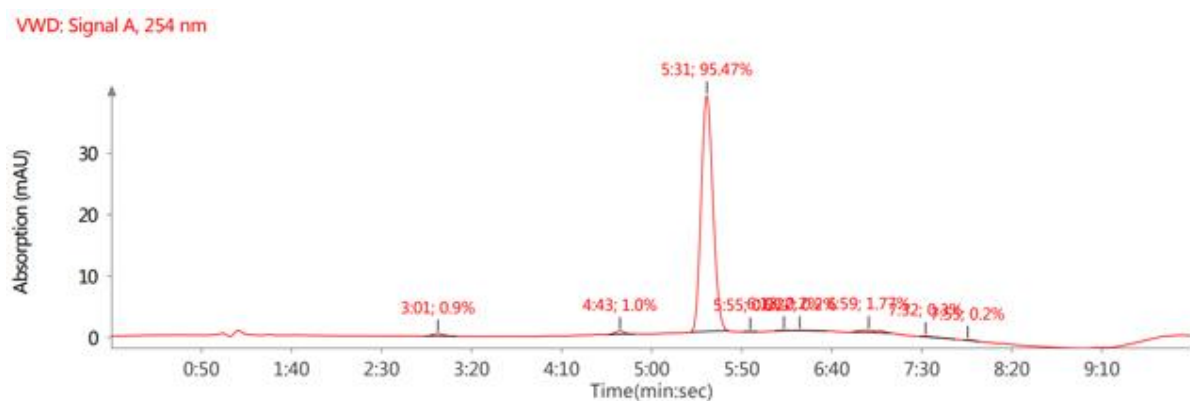
**Figure S11.**  $^1\text{H}$  NMR spectrum of compound **5b**.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.7, 165.8, 155.9, 141.4, 133.4, 130.8, 130.6, 127.3, 126.6, 123.5, 121.7, 120.0, 119.0, 118.1, 49.9 (2C), 45.5 ppm (2C)



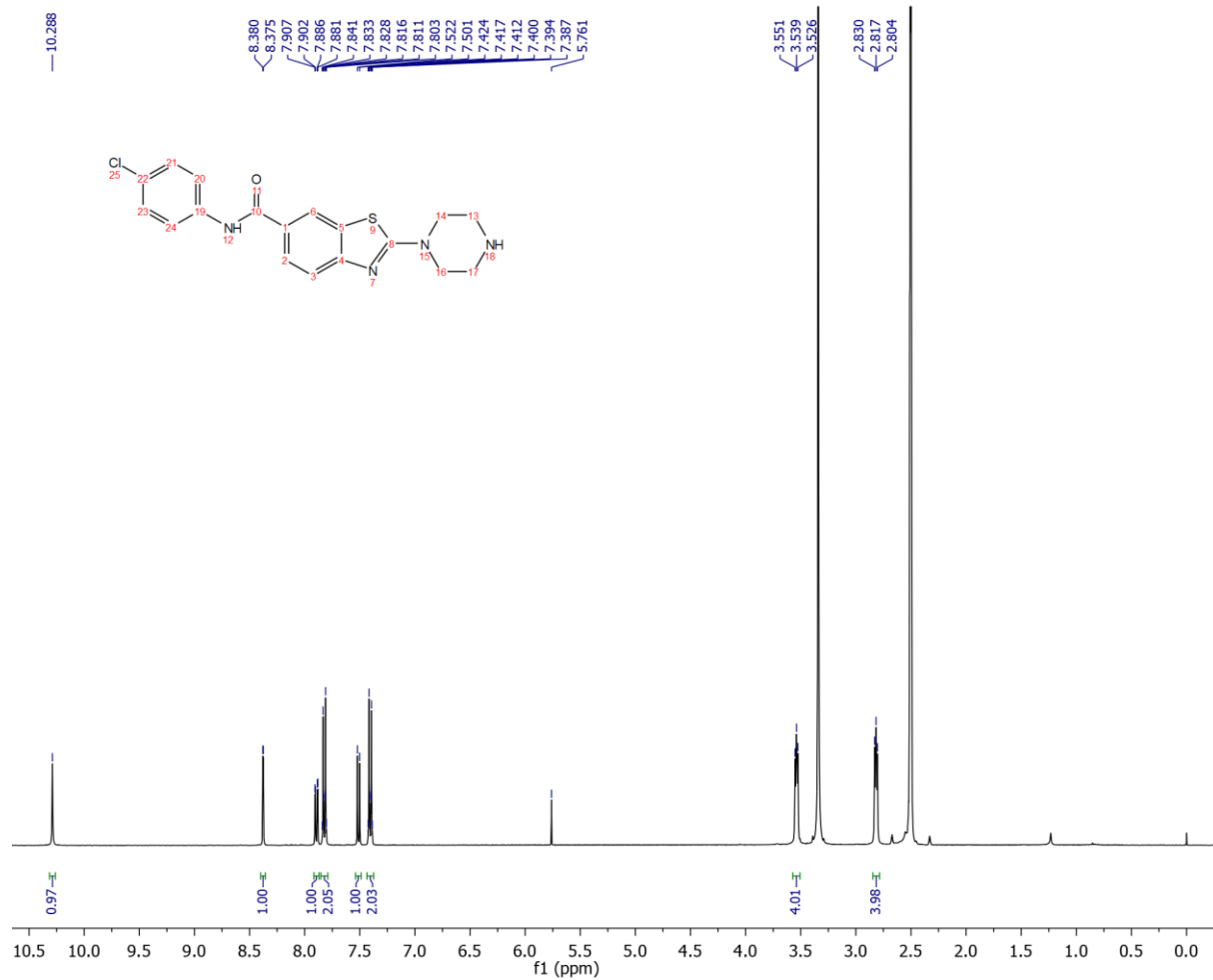
**Figure S12.**  $^{13}\text{C}$  NMR spectrum of compound 5b.

HPLC:  $t_r$  = 5.31 min (95.5 % at 254 nm)



**Figure S13.** HPLC chromatogram of compound 5b.

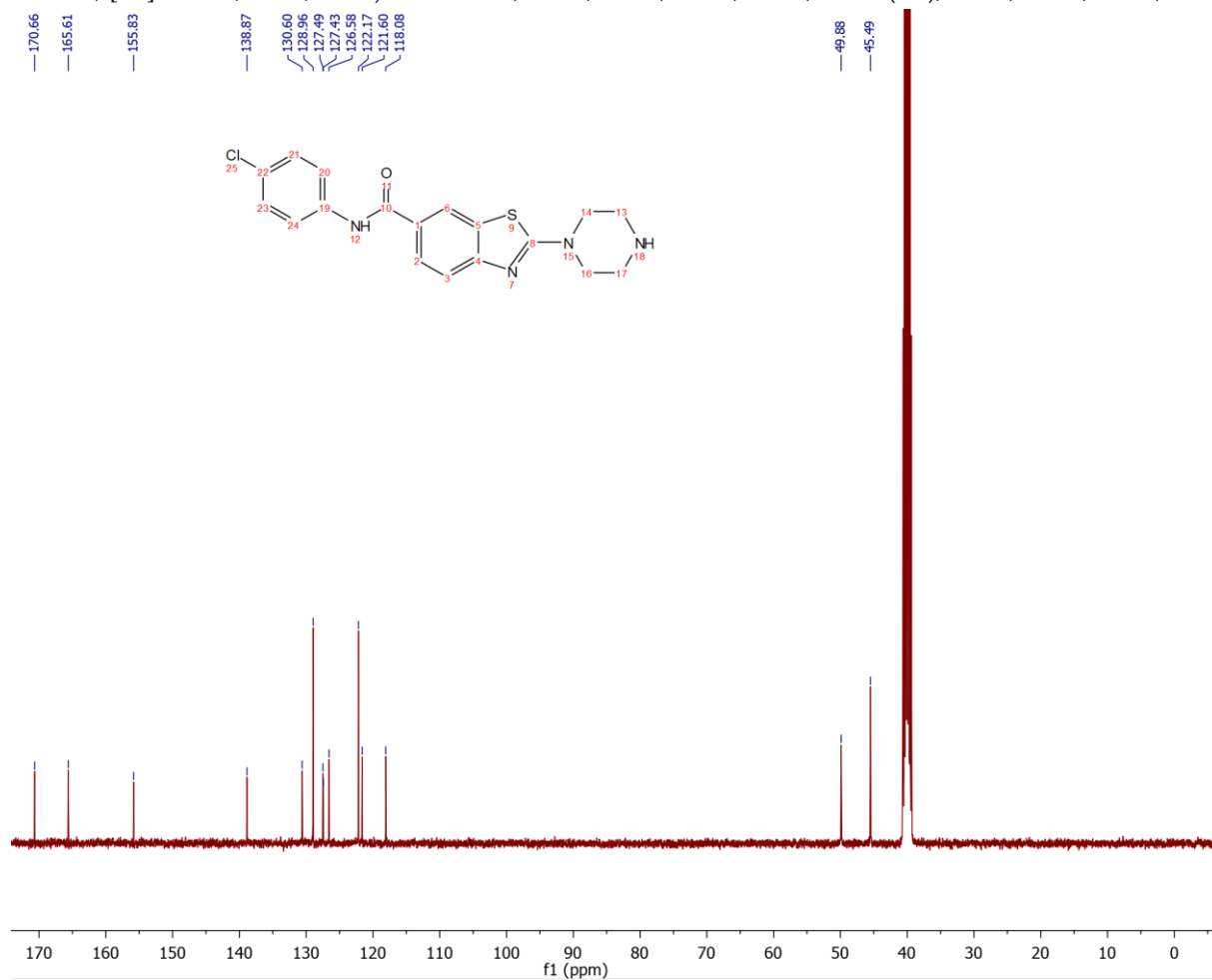
$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 10.29 (s, 1H, Ar-NH-COR), 8.38 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.85 – 7.78 (m, 2H,  $2 \times$  Ar- $H$ ), 7.51 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.44 – 7.37 (m, 2H,  $2 \times$  Ar- $H$ ), 3.57 – 3.50 (m, 4H,  $2 \times$  piperazine CH), 2.84 – 2.78 ppm (m, 4H,  $2 \times$  piperazine CH), not visible (NH).



**Figure S14.**  $^1\text{H}$  NMR spectrum of compound 5c.



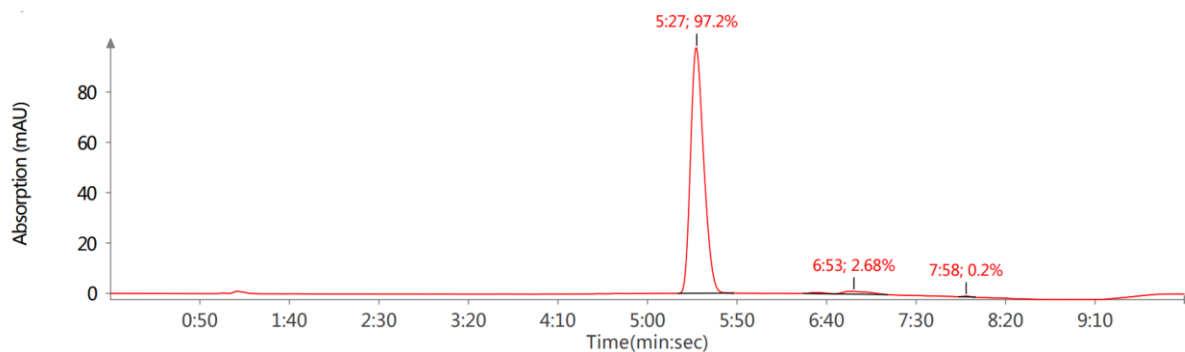
$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.7, 165.6, 155.8, 138.9, 130.6, 129.0 (2C), 127.5, 127.4, 126.6, 122.2 (2C),



**Figure S15.**  $^{13}\text{C}$  NMR spectrum of compound 5c.

HPLC:  $t_r$  = 5.27 min (97.2 % at 254 nm)

VWD: Signal A, 254 nm



**Figure S16.** HPLC chromatogram of compound 5c.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 8.20 (d,  $J$  = 1.9 Hz, 1H, Ar- $H_7$ ), 7.90 (d,  $J$  = 2.4 Hz, 1H, Ar- $H_{20}$ ), 7.79 (s, 1H, Ar-NH-COR), 7.73 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.9 Hz, 1H, Ar- $H_5$ ), 7.57 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.48 (dd,  $J_1$  = 8.7 Hz,  $J_2$  = 2.4 Hz, 1H, Ar- $H_{24}$ ), 7.42 (d,  $J$  = 8.7 Hz, 1H, Ar- $H_{23}$ ), 3.70–3.65 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 3.06–2.99 ppm (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), not visible (NH)

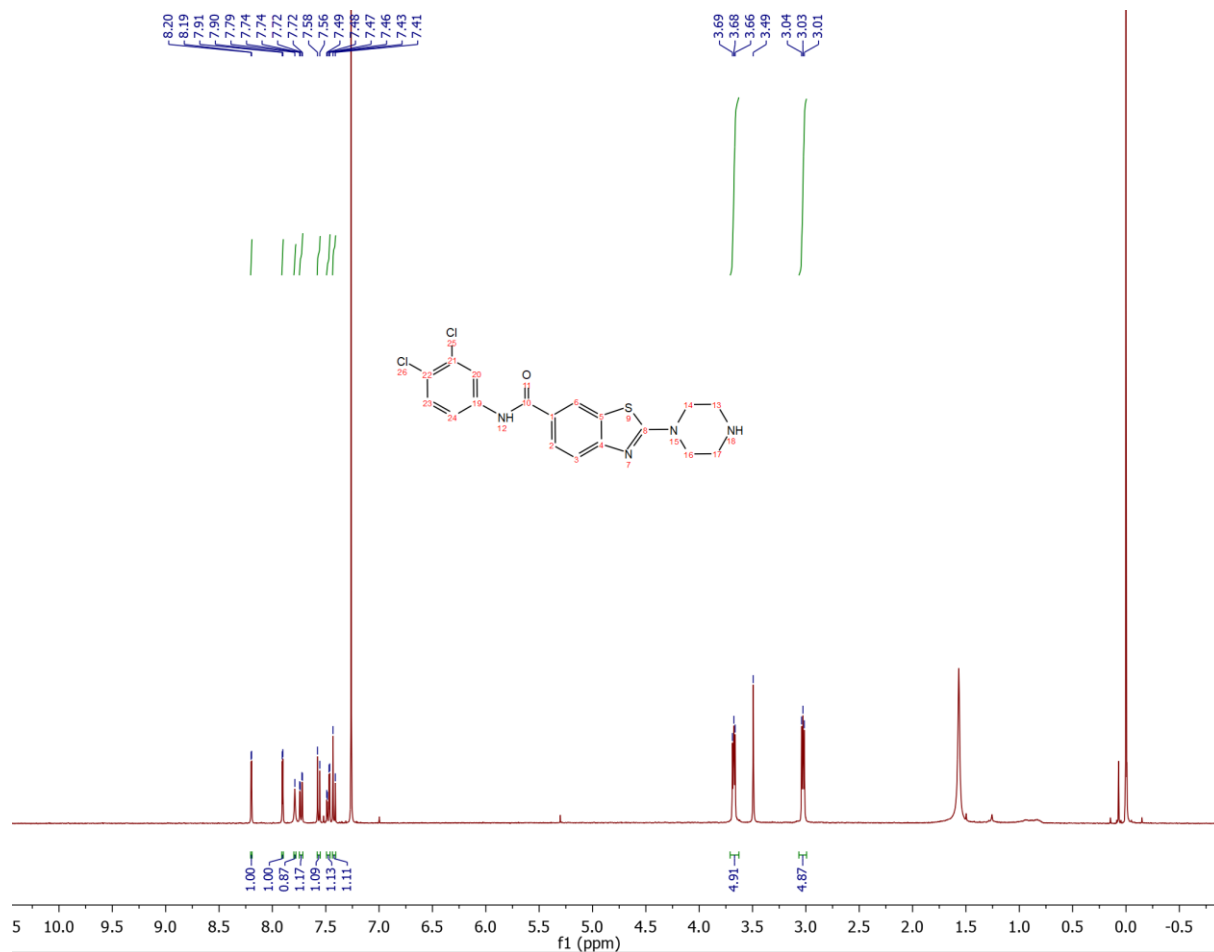


Figure S17.  $^1\text{H}$  NMR spectrum of compound 5d.

$^{13}\text{C}$  NMR (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.8, 165.8, 156.0, 140.1, 131.3, 131.0, 130.7, 127.1, 126.7, 125.2, 121.7,

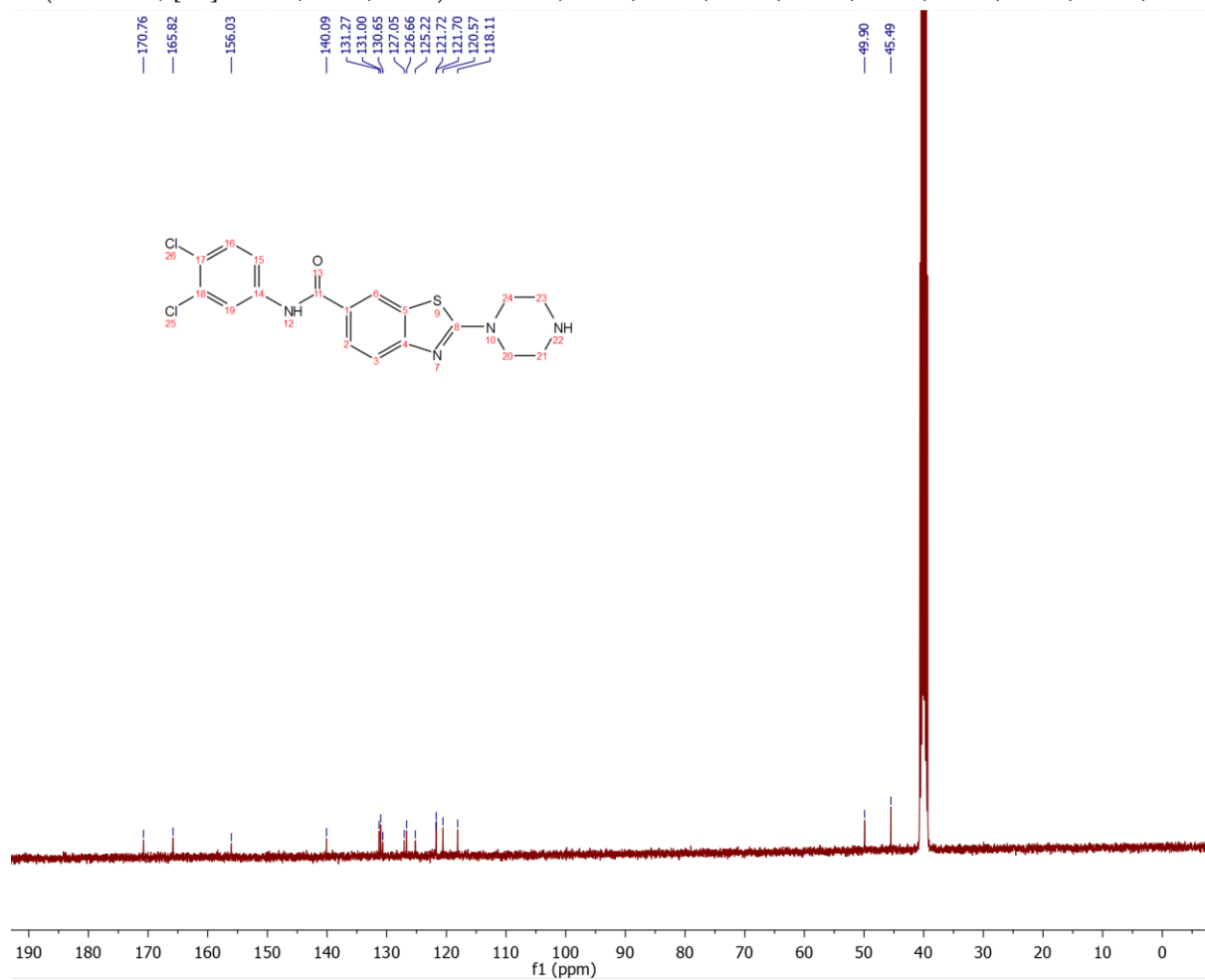


Figure S18.  $^{13}\text{C}$  NMR spectrum of compound 5d.

HPLC:  $t_r$  = 6.57 min (95.3 % at 254 nm)

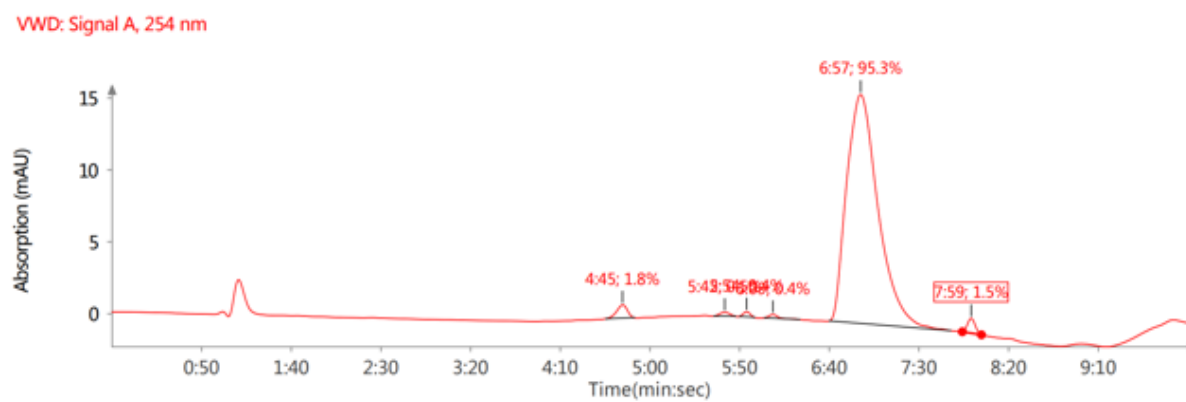
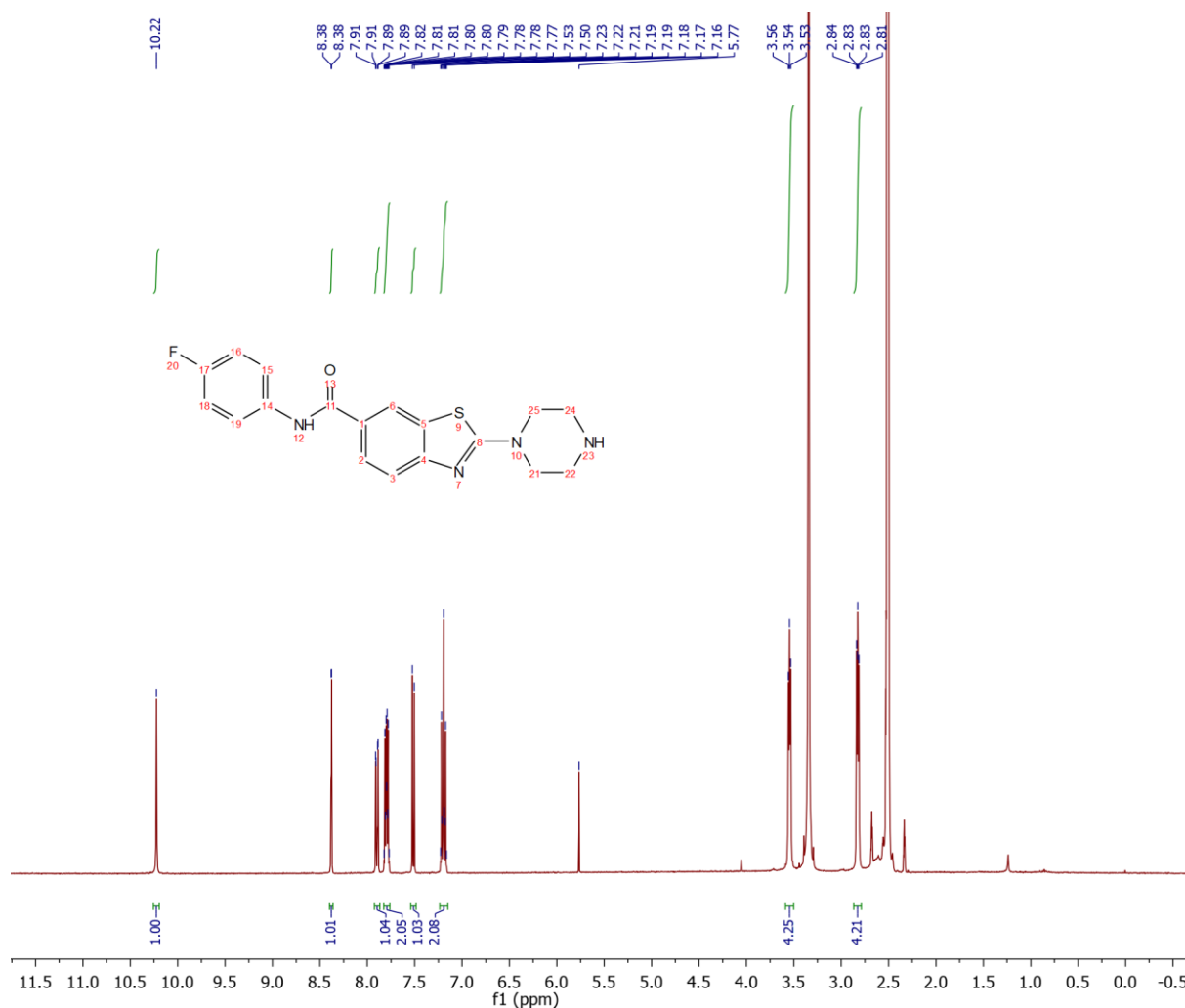


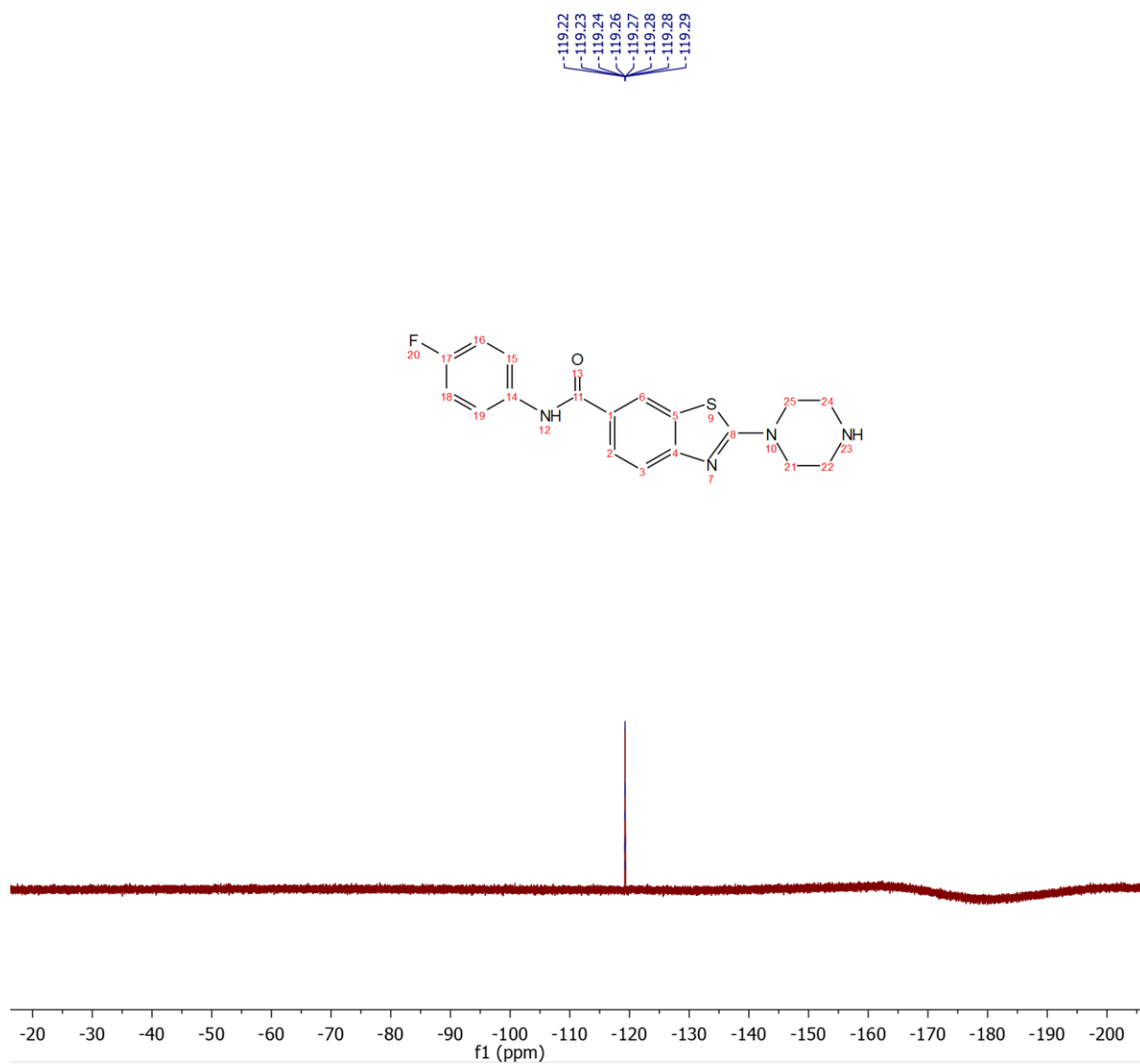
Figure S19. HPLC chromatogram of compound 5d.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.22 (s, 1H, Ar-NH-COR), 8.38 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.90 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.84 – 7.74 (m, 2H, 2  $\times$  Ar- $H$ ), 7.52 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.24 – 7.14 (m, 2H, 2  $\times$  Ar- $H$ ), 3.59 – 3.50 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 2.83 ppm (m, 4.3 Hz, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), not visible (NH)



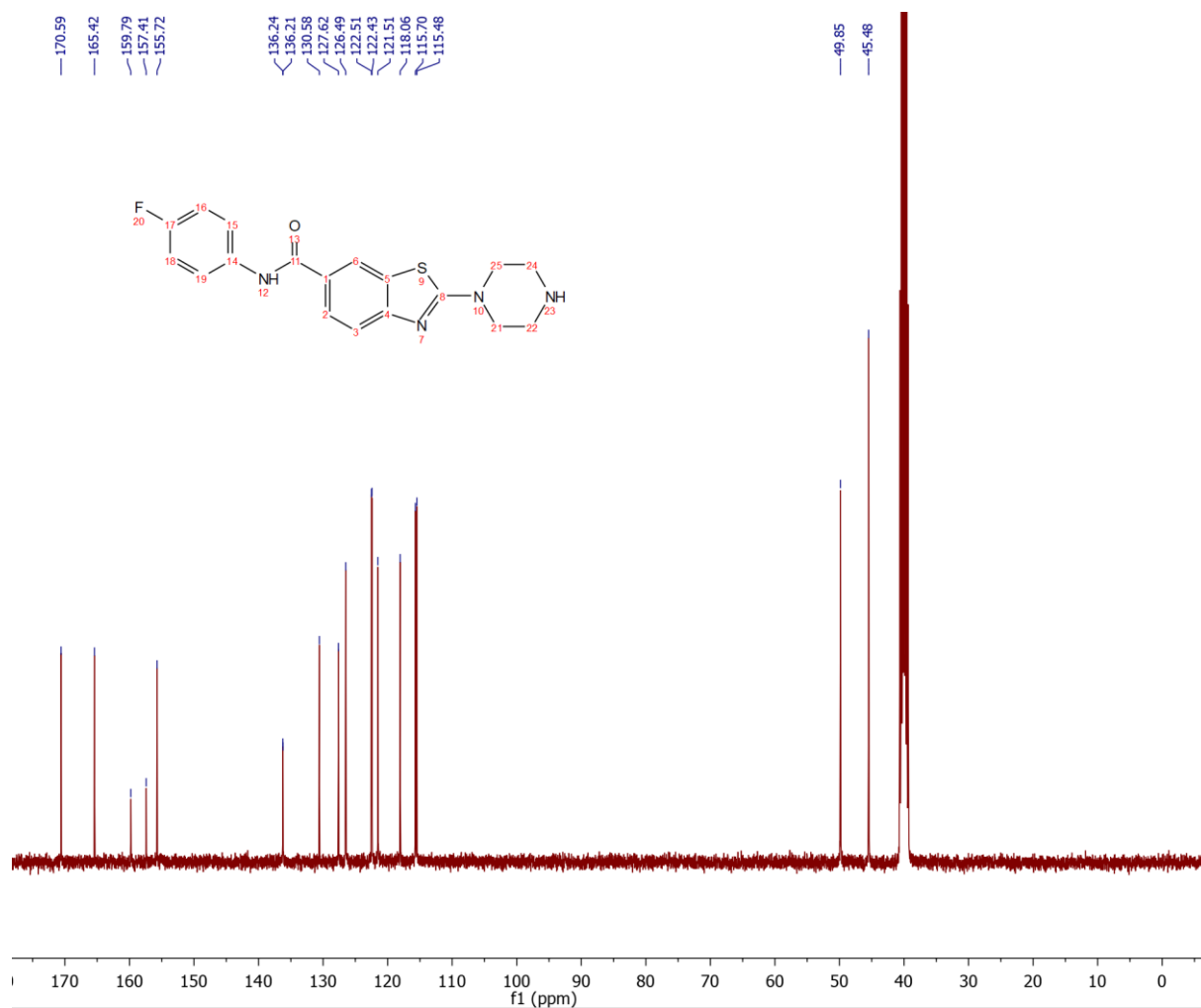
**Figure S20.**  $^1\text{H}$  NMR spectrum of compound 5e.

$^{19}\text{F}$  NMR (376 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta = -119.26$  ppm



**Figure S21.**  $^{19}\text{F}$  NMR spectrum of compound **5e**.

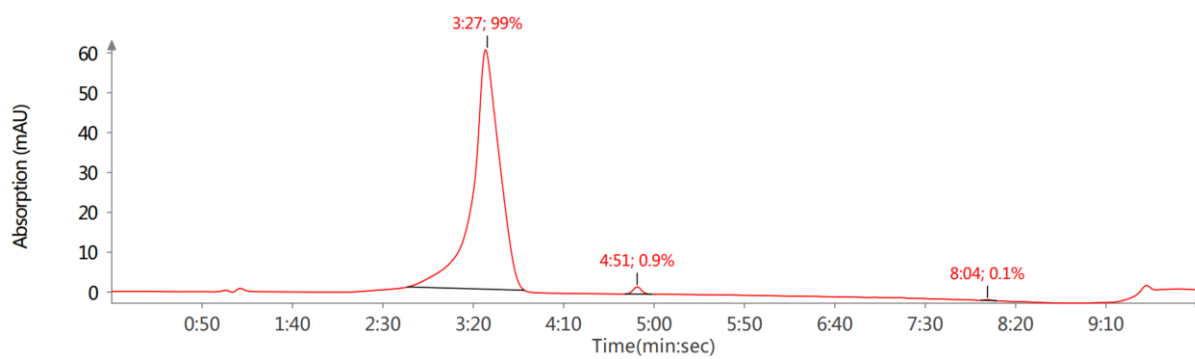
$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.6, 165.4, 158.60 (d,  $J$  = 239.8 Hz), 155.7, 136.2 (d,  $J$  = 2.6 Hz, 2C), 130.6, 127.6, 126.5, 122.5, 122.4, 121.5, 118.1, 115.7, 115.5, 49.9 (2C), 45.5 ppm (2C)



**Figure S22.**  $^{13}\text{C}$  NMR spectrum of compound **5e**.

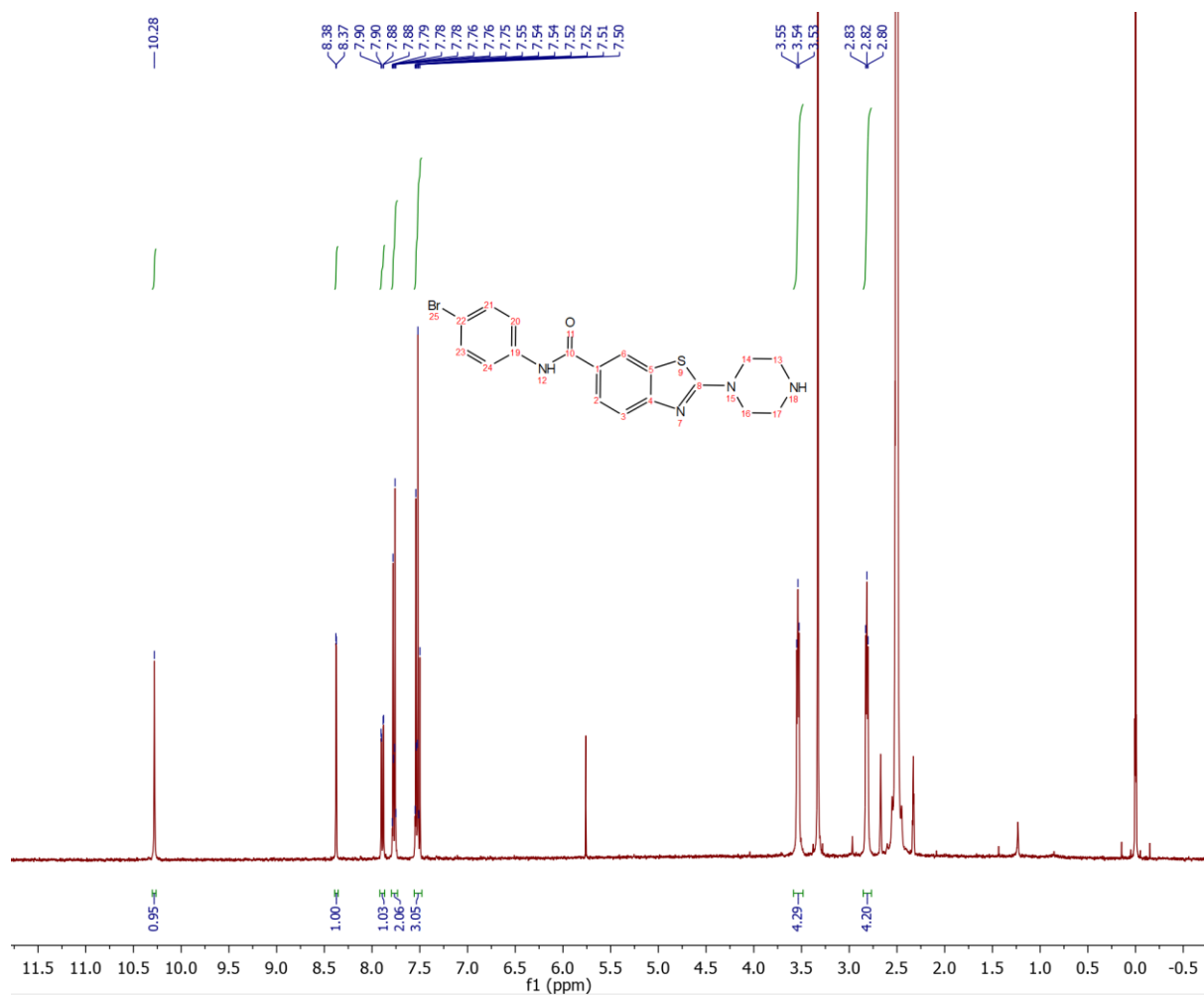
HPLC:  $t_r$  = 3.27 min (99,0 % at 254 nm)

VWD: Signal A, 254 nm



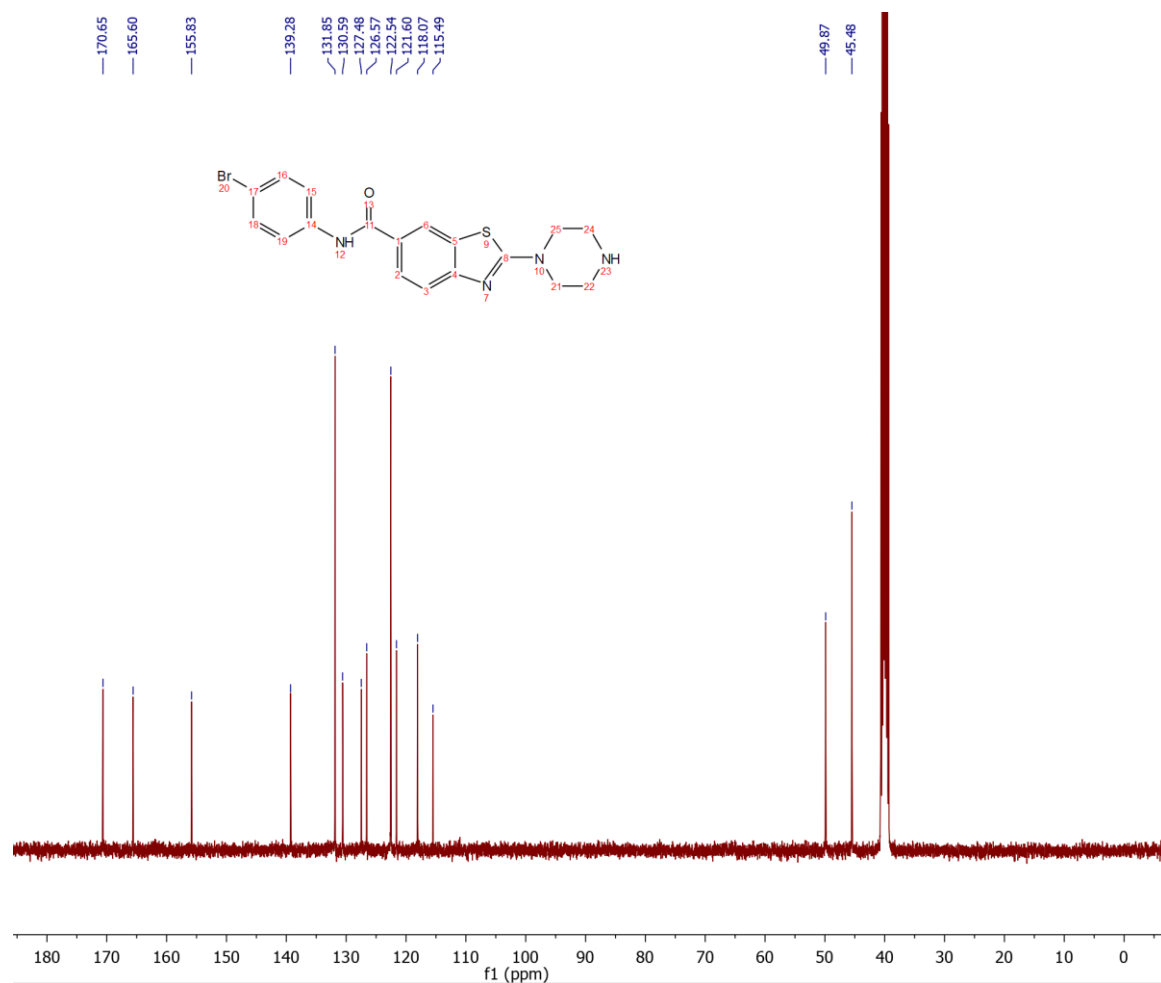
**Figure S23.** HPLC chromatogram of compound **5e**.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.28 (s, 1H, Ar-NH-COR), 8.38 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.79 – 7.73 (m, 2H, 2  $\times$  Ar- $H$ ), 7.56 – 7.47 (m, 3H, 3  $\times$  Ar- $H$ ), 3.59 – 3.48 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 2.86 – 2.77 ppm (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), not visible (NH)



**Figure S24.**  $^1\text{H}$ NMR spectrum of compound 5f.

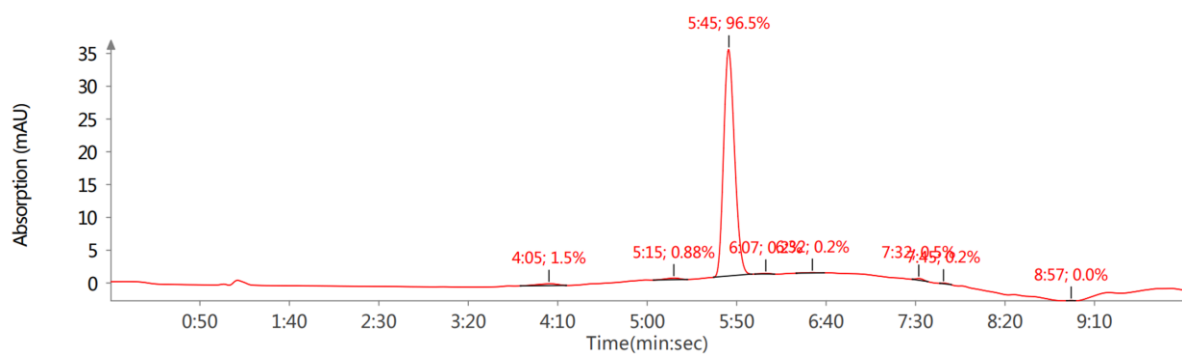
$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.7, 165.6, 155.8, 139.3, 131.9 (2C), 130.6, 127.5, 126.6, 122.6 (2C), 121.6, 118.1, 115.5, 49.9 (2C), 45.5 ppm (2C)



**Figure S25.**  $^{13}\text{C}$ NMR spectrum of compound 5f.

HPLC:  $t_r$  = 5.45 min (96.5 % at 254 nm)

VWD: Signal A, 254 nm



**Figure S26.** HPLC chromatogram of compound 5f.



$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.25 (s, 1H, Ar-NH-COR), 8.37 (s, 1H, Ar-H), 7.89 (d,  $J$  = 8.5 Hz, 1H, Ar-H), 7.71 – 7.60 (m, 4H, 4  $\times$  Ar-H), 7.50 (d,  $J$  = 8.1 Hz, 1H, Ar-H), 3.57 – 3.51 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 2.84 – 2.79 ppm (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), not visible (NH)

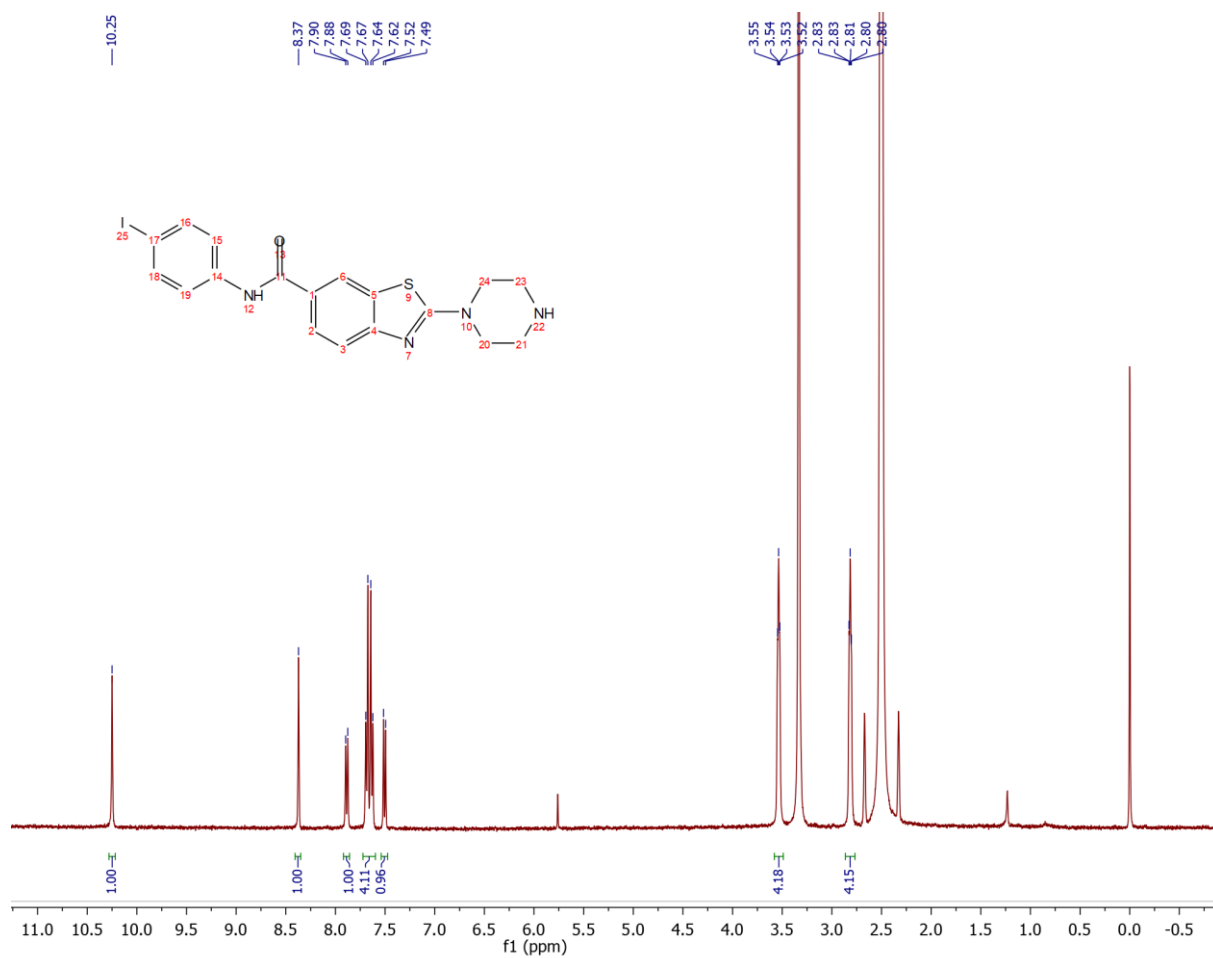
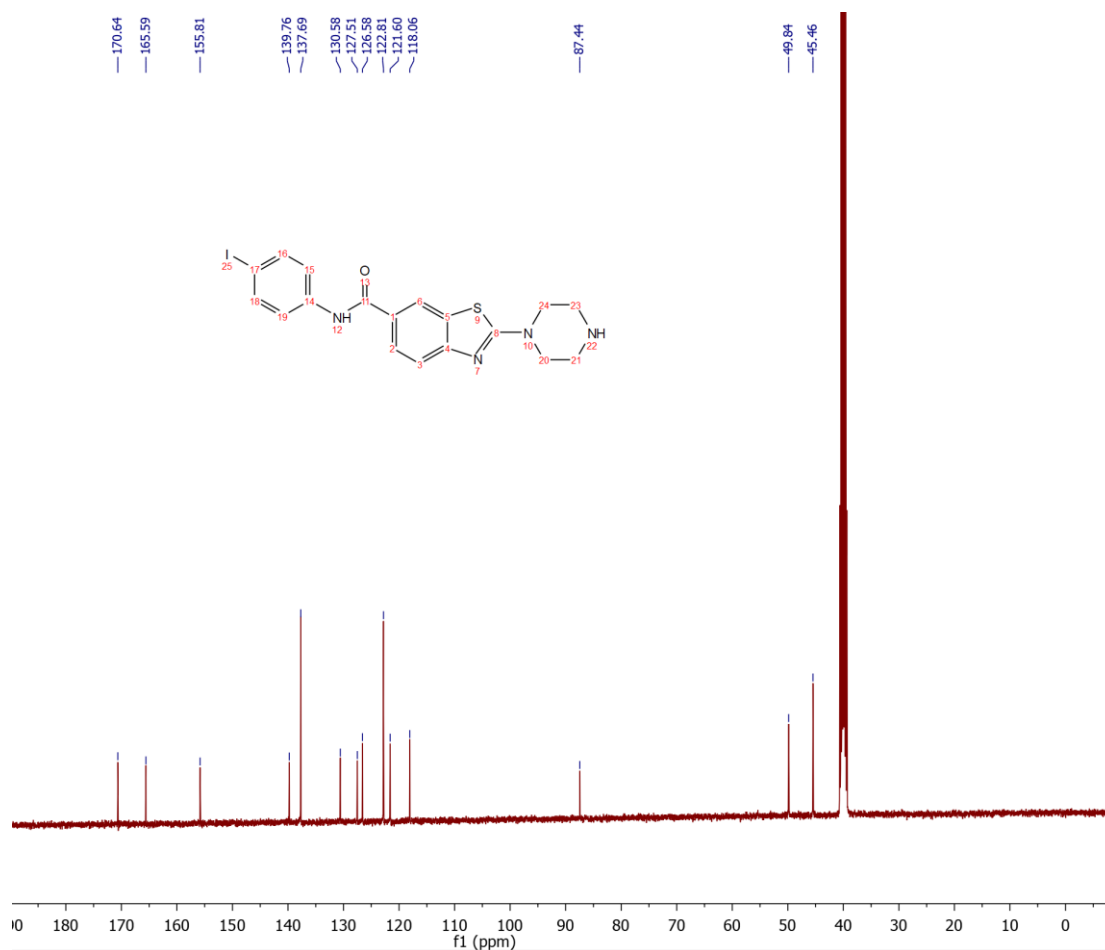


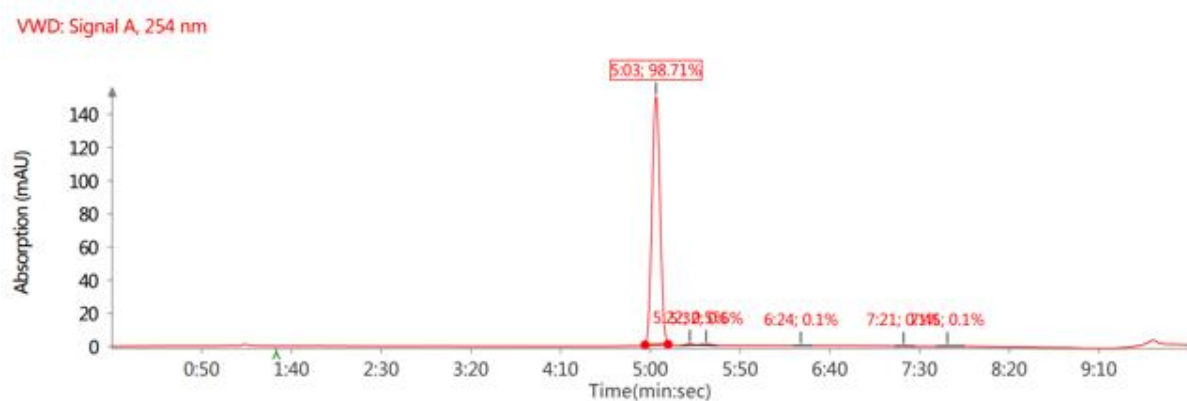
Figure S27.  $^1\text{H}$  NMR spectrum of compound 5g.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.6, 165.6, 155.8, 139.8, 137.7 (2C), 130.6, 127.5, 126.6, 122.8 (2C), 121.6, 118.1, 87.4, 49.8 (2C), 45.5 ppm (2C)



**Figure S28.**  $^{13}\text{C}$  NMR spectrum of compound **5g**.

HPLC:  $t_r$  = 5.03 min (98.7 % at 254 nm)



**Figure S29.** HPLC chromatogram of compound **5g**.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.08 (s, 1H, Ar-NH-COR), 8.37 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.68 (d,  $J$  = 8.6 Hz, 2H, 2  $\times$  Ar- $H$ ), 7.50 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.21 (d,  $J$  = 8.6 Hz, 2H, 2  $\times$  Ar- $H$ ), 3.58 – 3.47 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 2.90 – 2.78 (m, 5H, Ar- $\text{CH}-(\text{CH}_3)_2$  + 2  $\times$  piperazine- $\text{CH}_2$ ), 1.20 ppm (d,  $J$  = 6.9 Hz, 6H, Ar- $\text{CH}-(\text{CH}_3)_2$ )

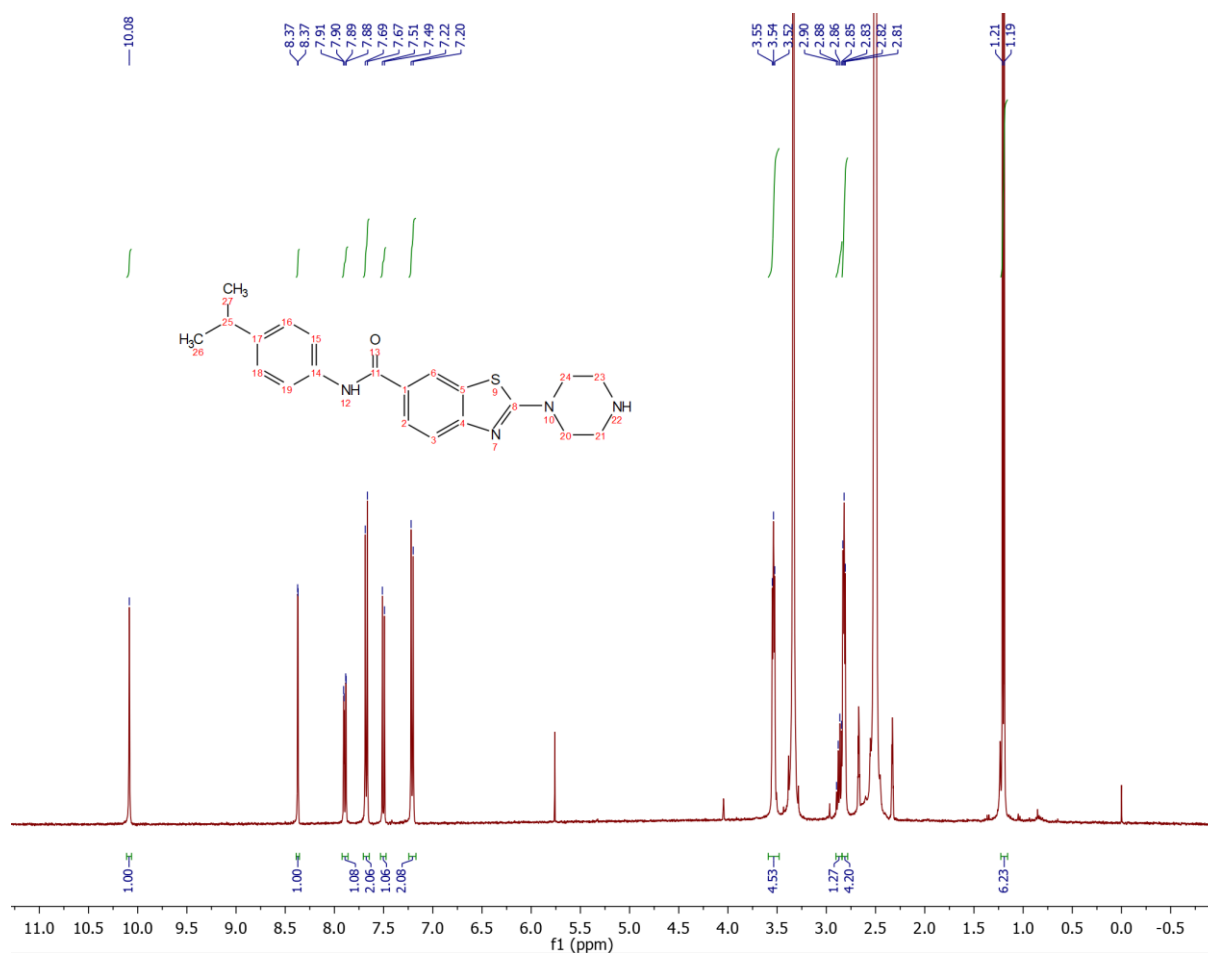
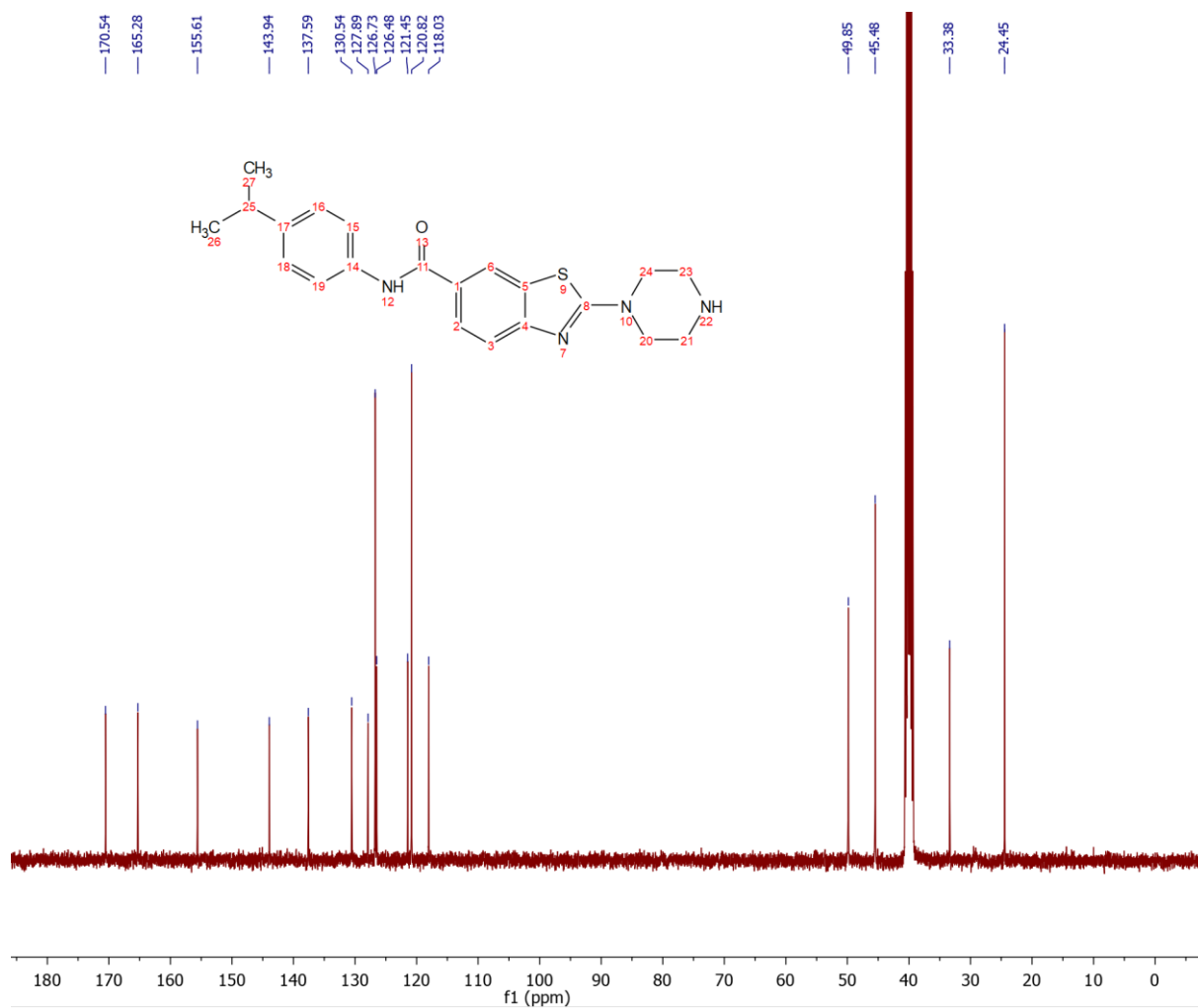


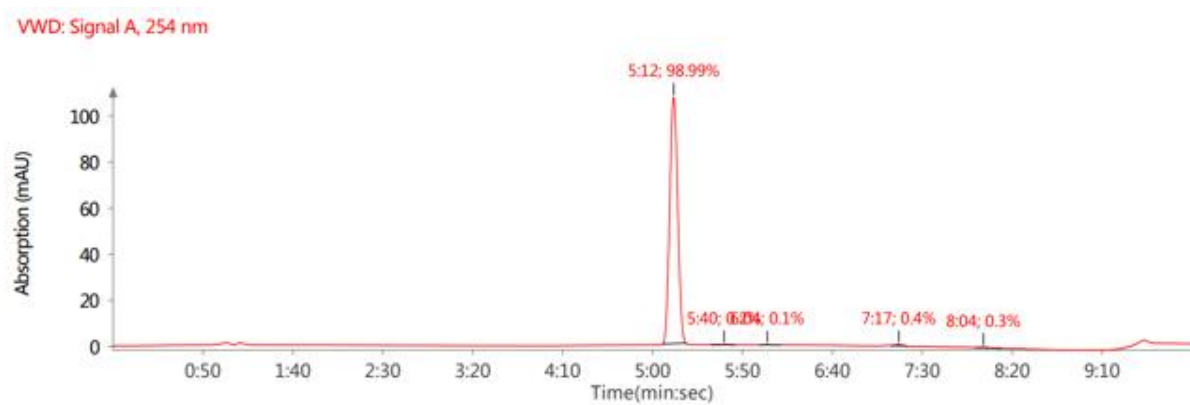
Figure S30.  $^1\text{H}$  NMR spectrum of compound 5h.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 170.5, 165.3, 155.6, 143.9, 137.6, 130.5, 127.9, 126.7 (2C), 126.5, 121.5, 120.8 (2C), 118.0, 49.9 (2C), 45.5 (2C), 33.4, 24.5 ppm (2C)



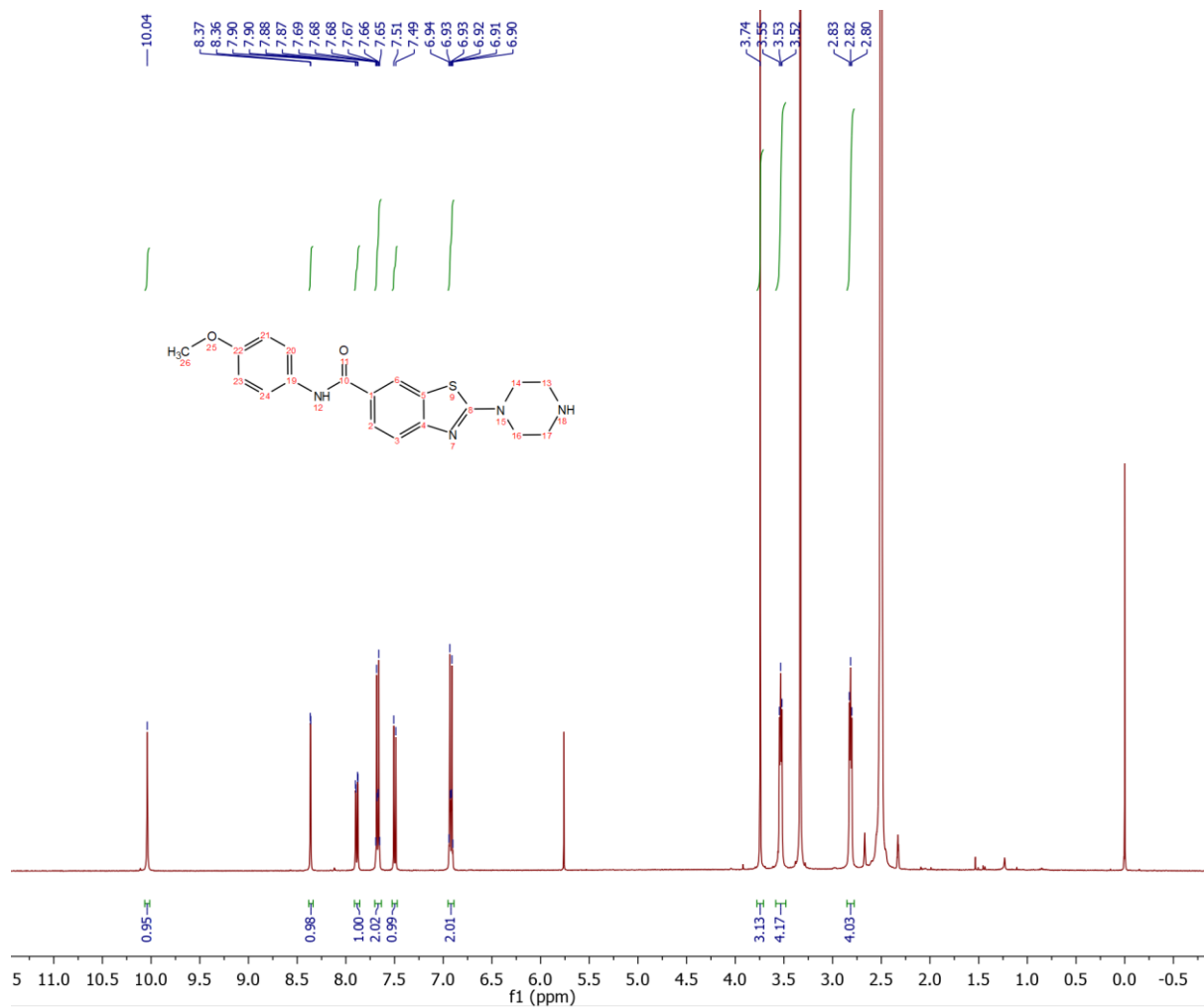
**Figure S31.**  $^{13}\text{C}$  NMR spectrum of compound 5h.

HPLC:  $t_r$  = 5.12 min (99,0 % at 254 nm)



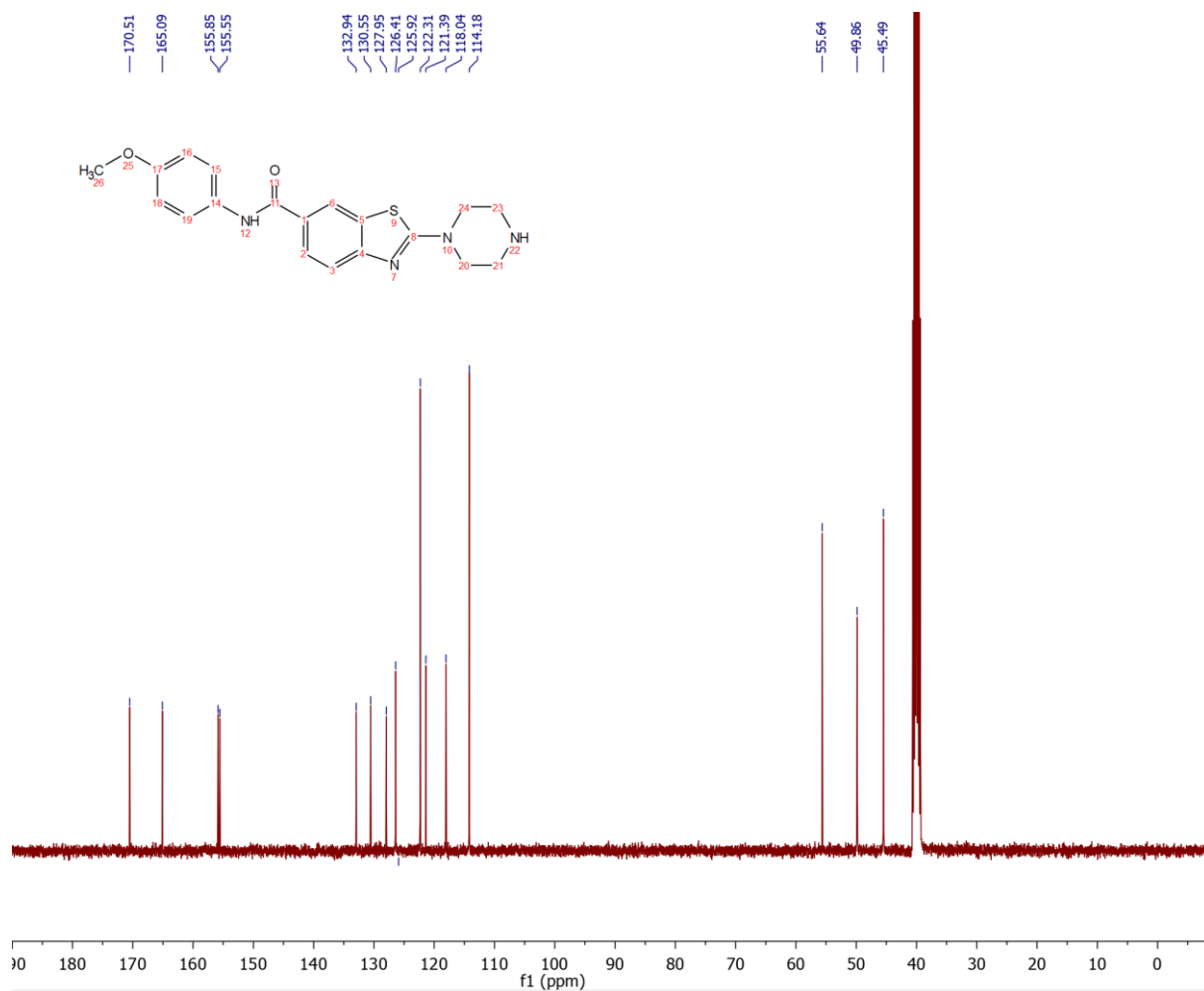
**Figure S32.** HPLC chromatogram of compound 5h.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.04 (s, 1H, Ar-NH-COR), 8.36 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.71 – 7.63 (m, 2H, 2  $\times$  Ar- $H$ ), 7.50 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 6.95 – 6.89 (m, 2H, 2  $\times$  Ar- $H$ ), 3.74 (s, 3H, Ar-O- $\text{CH}_3$ ), 3.58 – 3.48 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 2.85 – 2.78 ppm (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), not visible (NH)



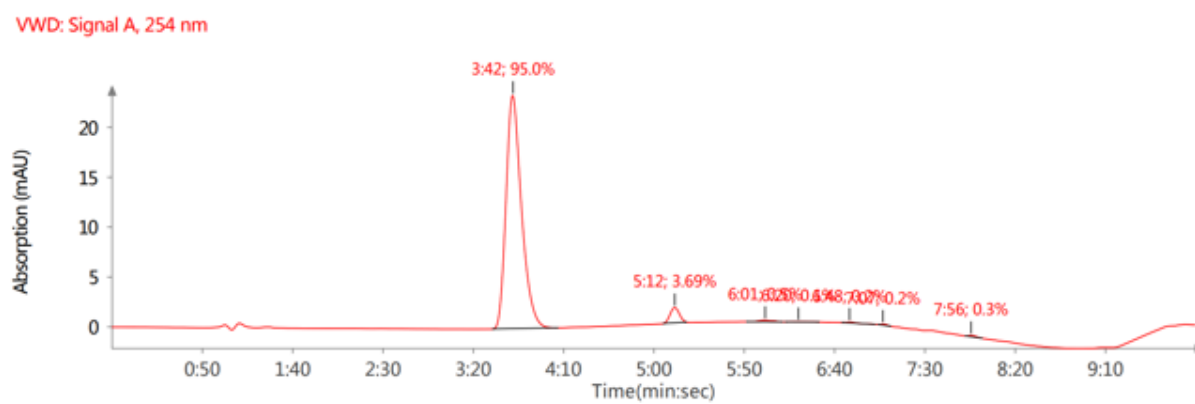
**Figure S33.**  $^1\text{H}$ NMR spectrum of compound **5i**.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.5, 165.1, 155.9, 155.6, 132.9, 130.6, 128.0, 125.9, 122.3 (2C), 121.4, 118.0, 114.2 (2C), 55.6, 49.9 (2C), 45.5 ppm (2C)



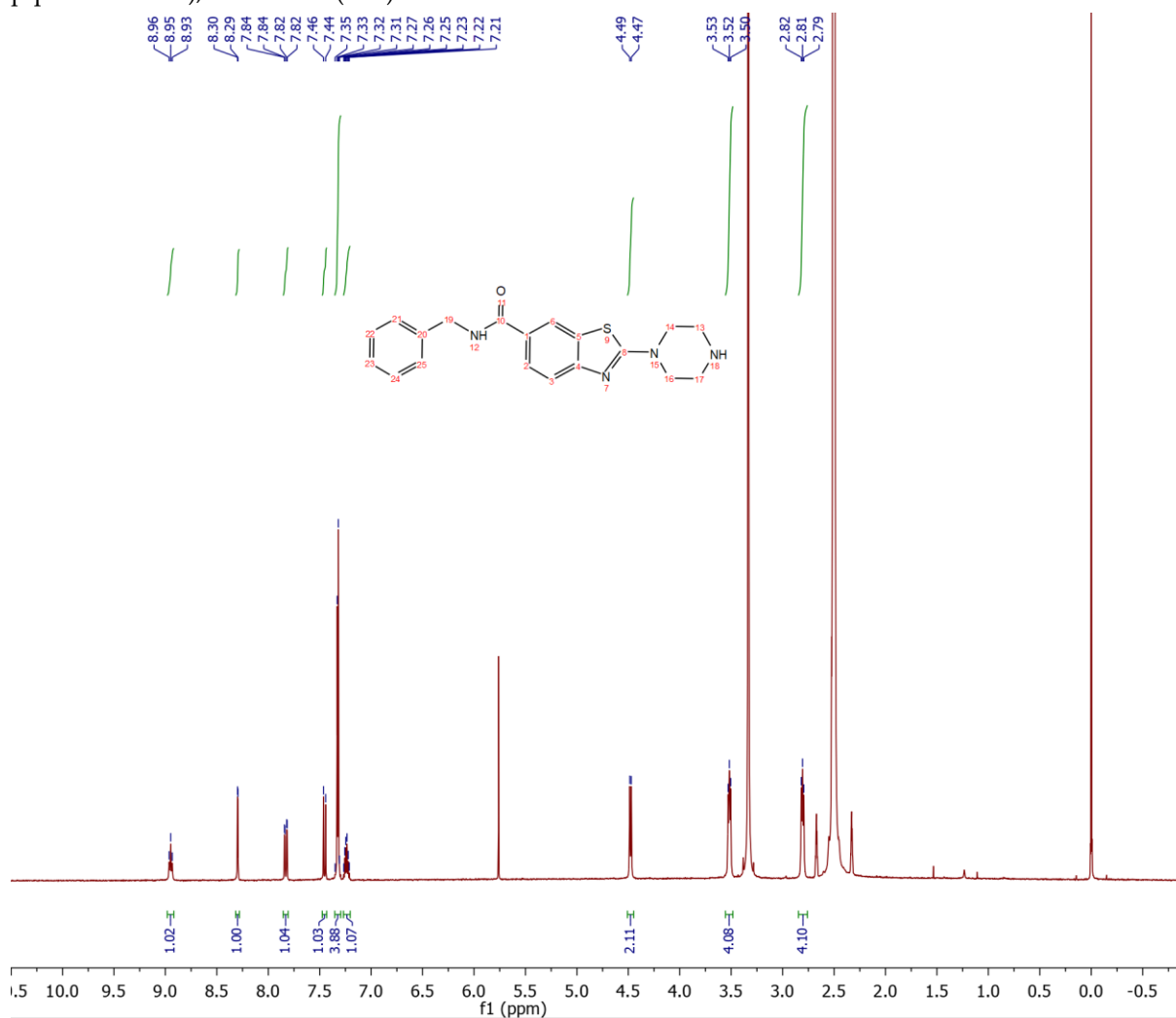
**Figure S34.**  $^{13}\text{C}$ NMR spectrum of compound 5i.

HPLC:  $t_r$  = 3.42 min (95.0 % at 254 nm)



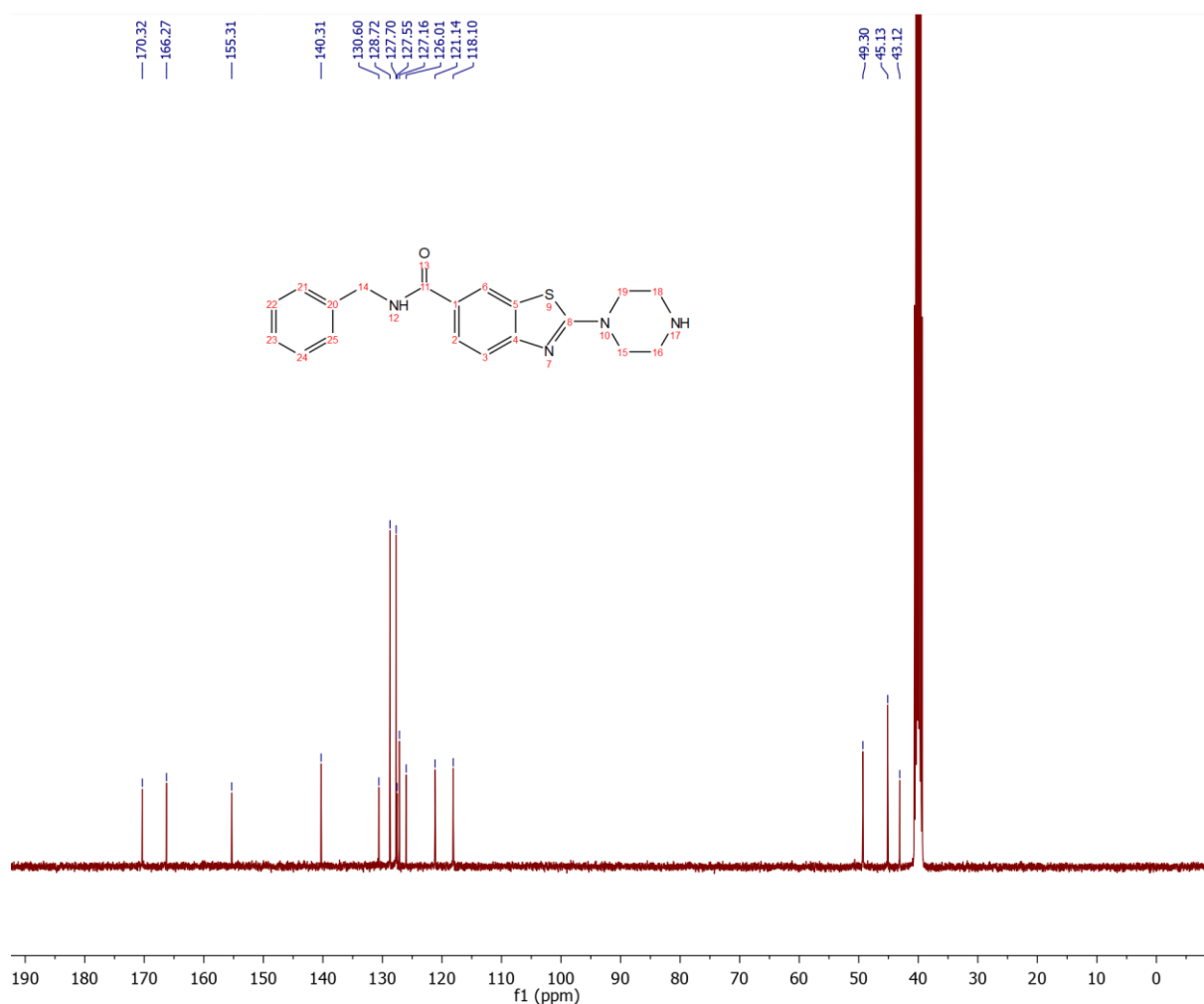
**Figure S35.** HPLC chromatogram of compound 5i.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 8.95 (t,  $J$  = 6.0 Hz, 1H, Ar-CH<sub>2</sub>-NH-COR), 8.30 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.83 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.45 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.35 – 7.29 (m, 4H, 4  $\times$  Ar- $H$ ), 7.26 – 7.20 (m, 1H, Ar- $H$ ), 4.48 (d,  $J$  = 6.0 Hz, 2H, Ar-CH<sub>2</sub>-NHCO), 3.56 – 3.48 (m, 4H, 2  $\times$  piperazine-CH<sub>2</sub>), 2.84 – 2.76 ppm (m, 4H, 2  $\times$  piperazine-CH<sub>2</sub>), not visible (NH)



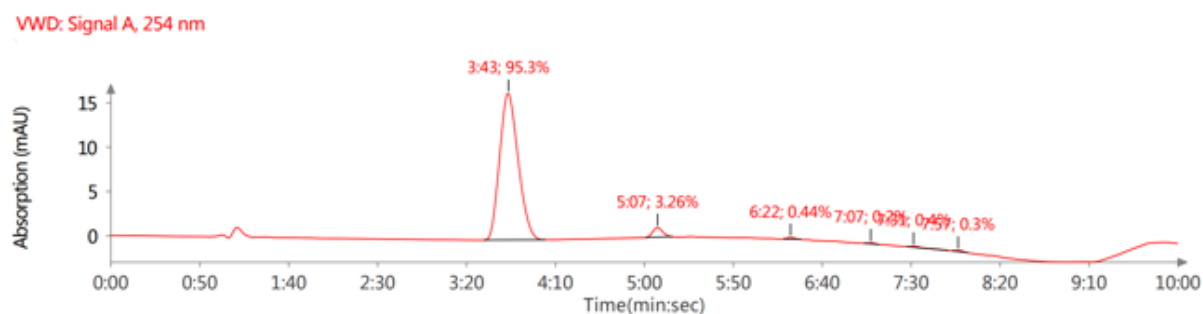
**Figure S36.**  $^1\text{H}$  NMR spectrum of compound 5j.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.3, 166.3, 155.3, 140.3, 130.6, 128.7 (2C), 127.7 (2C), 127.6, 127.2, 126.0, 121.1, 118.1, 49.3 (2C), 45.1 (2C), 43.1 ppm



**Figure S37.**  $^{13}\text{C}$ NMR spectrum of compound 5j.

HPLC:  $t_r$  = 3.43 min (95.3 % at 254 nm)



**Figure S38.** HPLC chromatogram of compound 5j.



$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 8.99 (t,  $J$  = 6.0 Hz, 1H,  $\text{CH}_2\text{-NH-COR}$ ), 8.30 (d,  $J$  = 1.9 Hz, 1H, Ar- $H_7$ ), 7.82 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.9 Hz, 1H, Ar- $H_5$ ), 7.46 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.39 – 7.33 (m, 2H,  $2 \times$  Ar- $H$ ), 7.33 – 7.27 (m, 2H,  $2 \times$  Ar- $H$ ), 4.47 (d,  $J$  = 6.0 Hz, 2H), 3.56 – 3.48 (m, 4H,  $2 \times$  piperazine- $\text{CH}_2$ ), 2.85 – 2.76 ppm (m, 4H,  $2 \times$  piperazine- $\text{CH}_2$ ), not visible (NH)

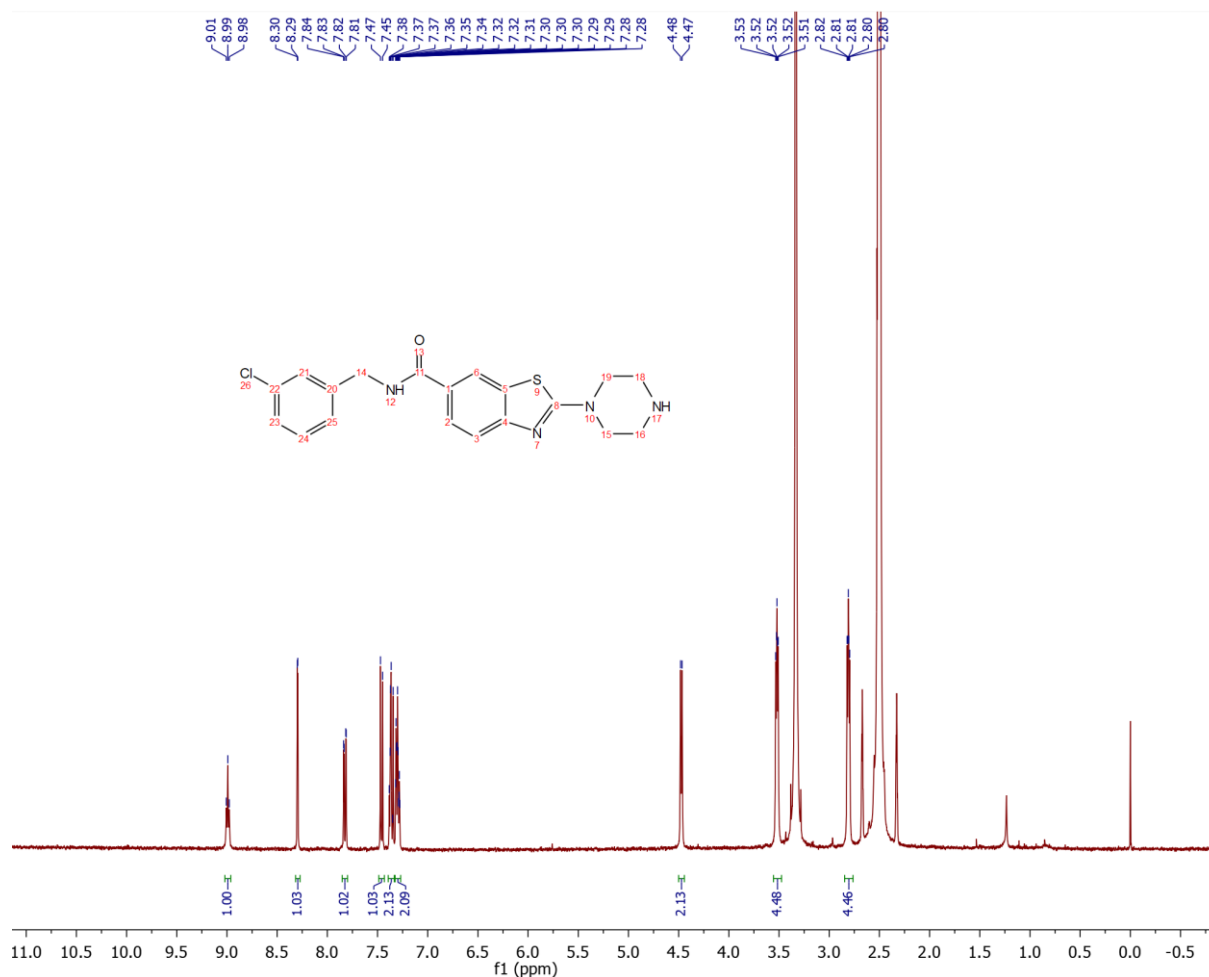


Figure S39.  $^1\text{H}$  NMR spectrum of compound 5k.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.4, 166.4, 155.5, 142.9, 133.4, 130.6, 130.6, 127.5, 127.2, 127.1, 126.4, 126.0, 121.1, 118.1, 49.8 (2C), 45.5 (2C), 42.7 ppm

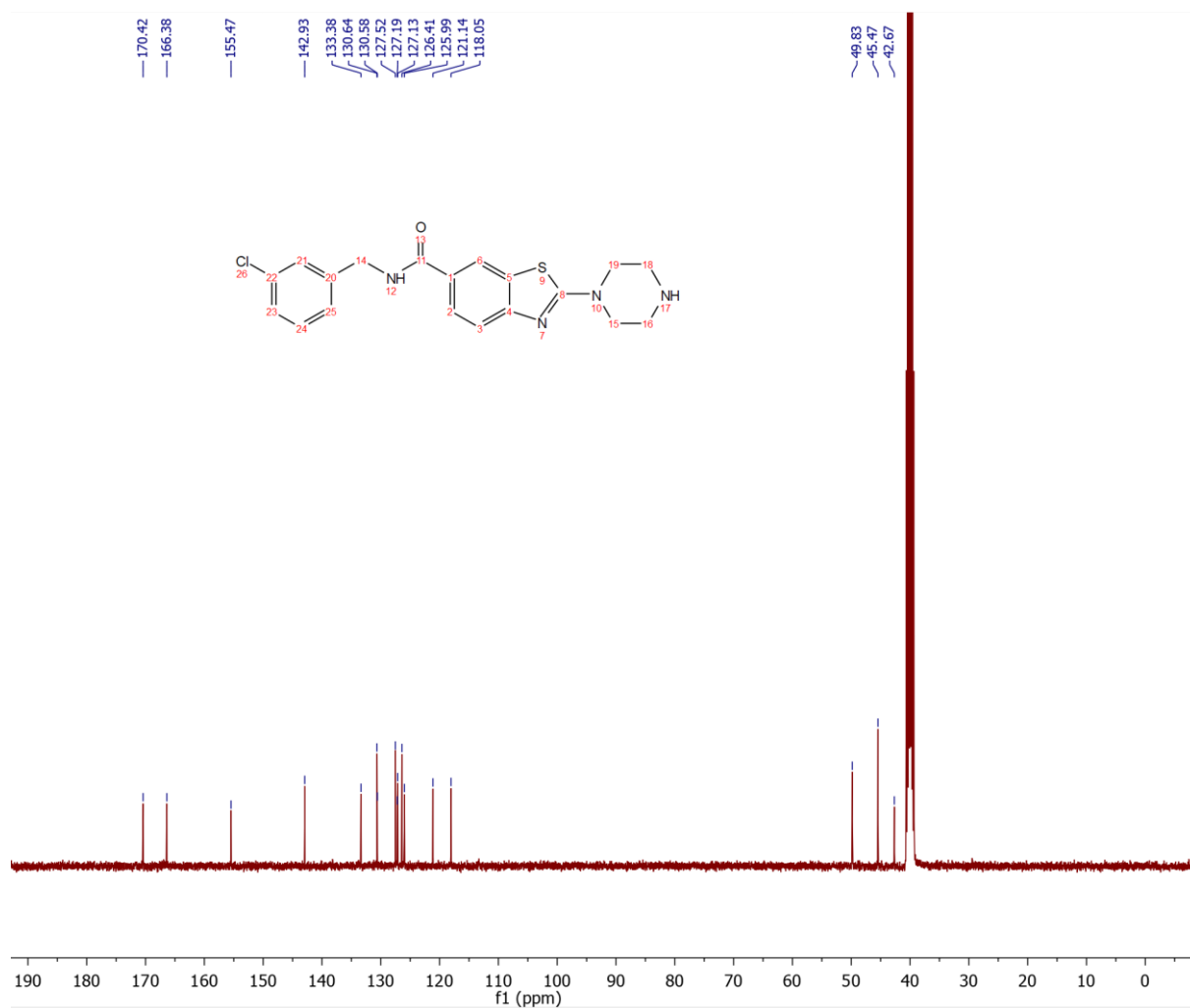


Figure S40.  $^{13}\text{C}$  NMR spectrum of compound 5k.

HPLC:  $t_r$  = 4.26 min (98.0 % at 254 nm).

VWD: Signal A, 254 nm

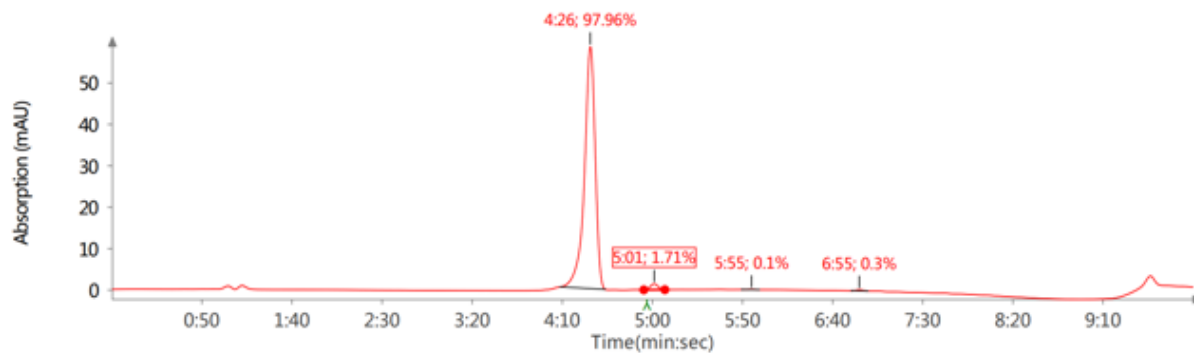
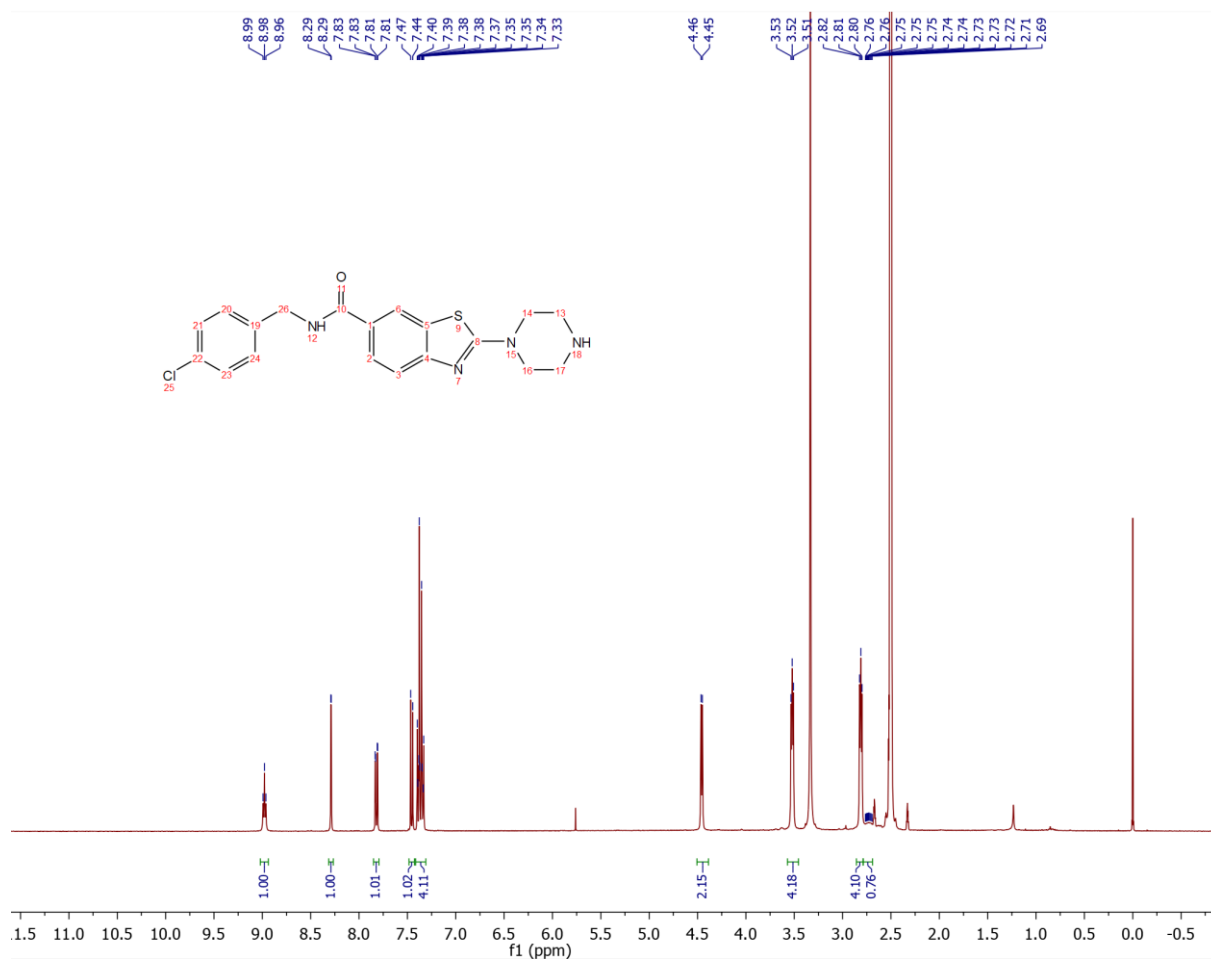


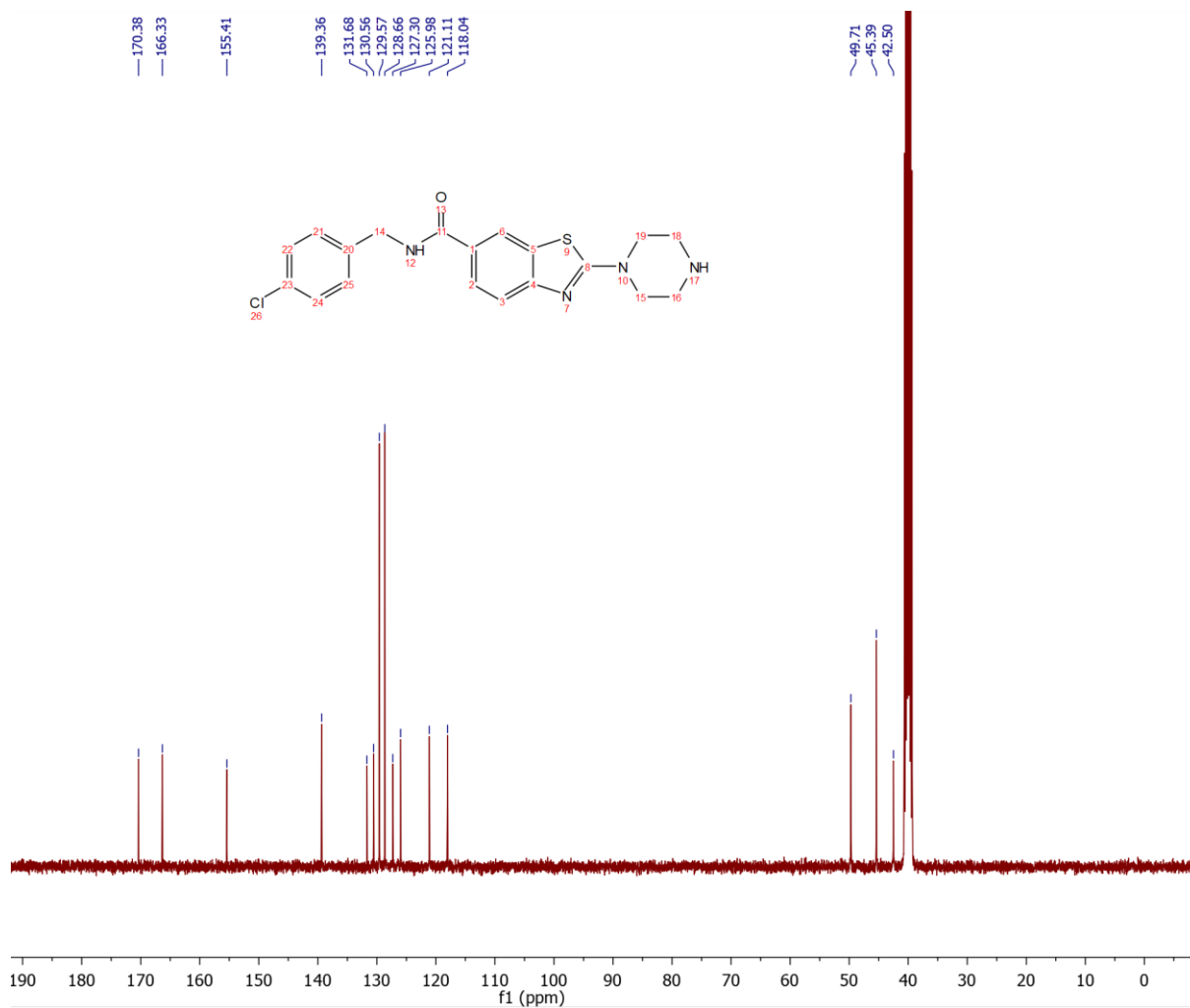
Figure S41. HPLC chromatogram of compound 5k.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 8.98 (t,  $J$  = 6.0 Hz, 1H, t,  $J$  = 5.9 Hz, 1H,  $\text{CH}_2\text{-NH-COR}$ ), 8.29 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.82 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.46 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.41 – 7.30 (m, 4H, 4  $\times$  Ar- $H$ ), 4.46 (d,  $J$  = 6.0 Hz, 2H,  $\text{RCO-NH-CH}_2\text{-Ph}$ ), 3.57 – 3.46 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 2.86 – 2.77 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 2.77 – 2.69 ppm (m, 1H, NH)



**Figure S42.**  $^1\text{H}$  NMR spectrum of compound 5l.

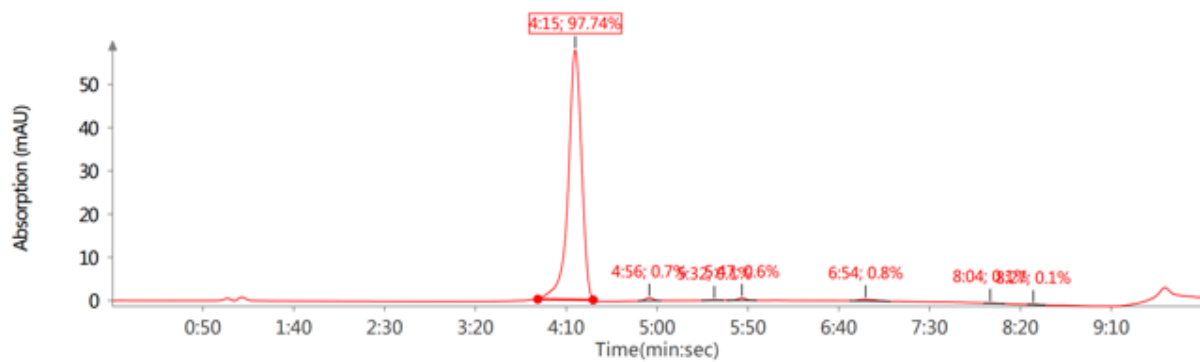
$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.4, 166.3, 155.4, 139.4, 131.7, 130.6, 129.6 (2C), 128.7 (2C), 127.3, 126.0, 121.1, 118.0, 49.7 (2C), 45.4 (2C), 42.5 ppm



**Figure S43.**  $^{13}\text{C}$ NMR spectrum of compound 51.

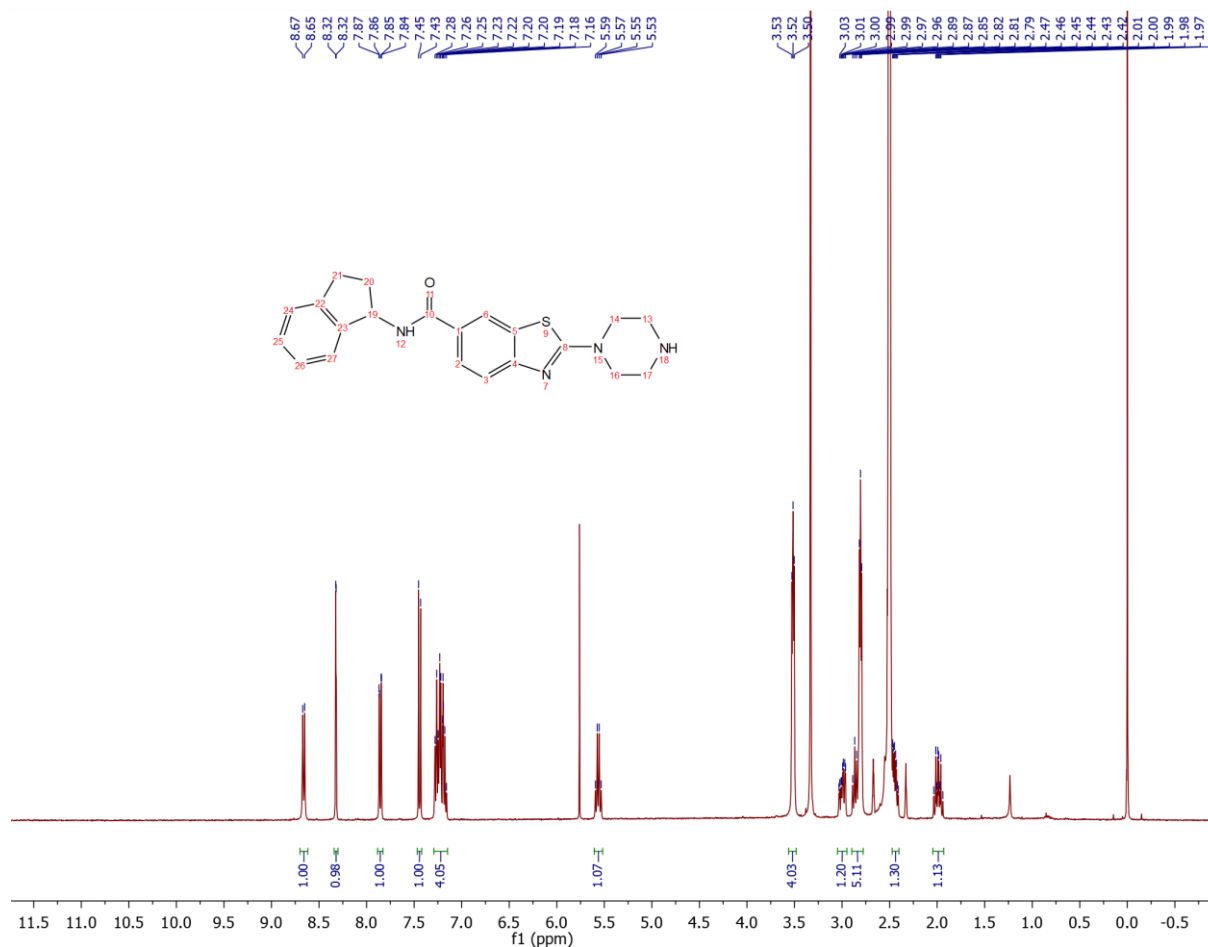
HPLC:  $t_r$  = 4.15 min (97.7 % at 254 nm)

VWD: Signal A, 254 nm



**Figure S44.** HPLC chromatogram of compound 51.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 8.66 (d,  $J$  = 8.3 Hz, 1H, CH-NH-CO), 8.32 (d,  $J$  = 1.7 Hz, 1H, Ar- $H_7$ ), 7.86 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.7 Hz, 1H, Ar- $H_5$ ), 7.44 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.29 – 7.14 (m, 4H, 4  $\times$  Ar- $H$ ), 5.56 (q,  $J$  = 8.3 Hz, 1H, indane- $H$ ), 3.55 – 3.48 (m, 4H, 2  $\times$  piperazine- $\text{CH}_2$ ), 3.00 (ddd,  $J_1$  = 15.6 Hz,  $J_2$  = 8.8 Hz,  $J_3$  = 2.9 Hz, 1H, indane- $H$ ), 2.90 – 2.77 (m, 5H, 2  $\times$  piperazine- $\text{CH}_2$ , and indane- $H$ ), 2.47 – 2.40 (m, 1H), 2.05 – 1.92 ppm (m, 1H, indane- $H$ ), not visible (NH)



**Figure S45.**  $^1\text{H}$  NMR spectrum of compound 5m.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.3, 166.2, 155.3, 144.8, 143.4, 130.4, 127.8, 127.5, 126.8, 126.2, 124.9, 124.5, 121.2, 118.0, 54.7, 49.8 (2C), 45.5 (2C), 33.2, 30.3 ppm

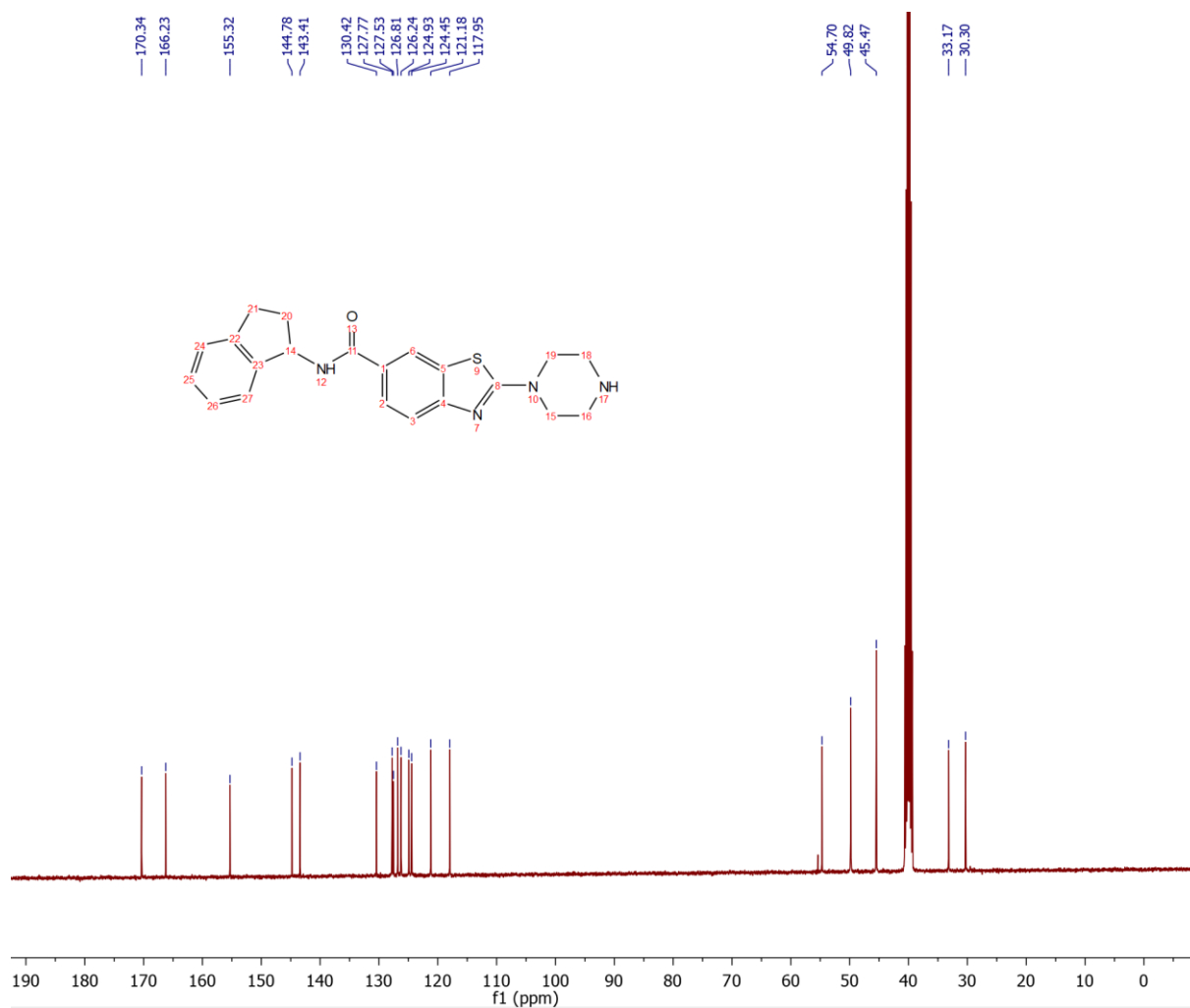


Figure S46.  $^{13}\text{C}$  NMR spectrum of compound 5m.

HPLC:  $t_r$  = 4.22 min (96.6 % at 254 nm)

VWD: Signal A, 254 nm

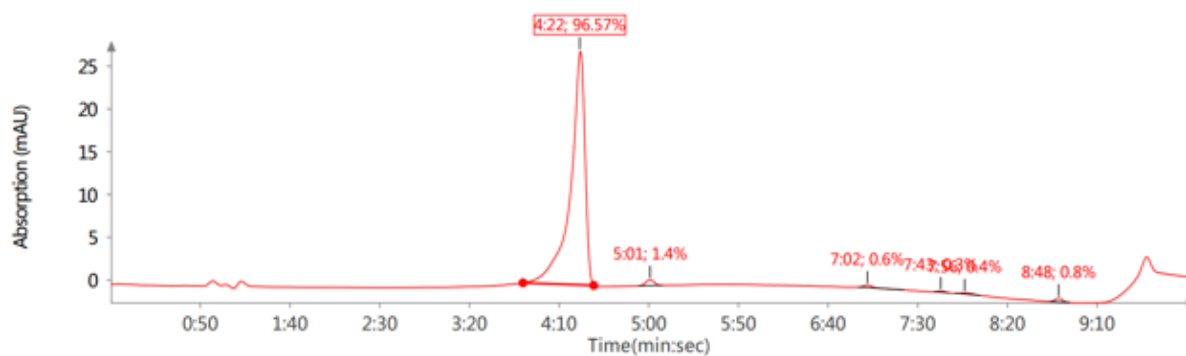
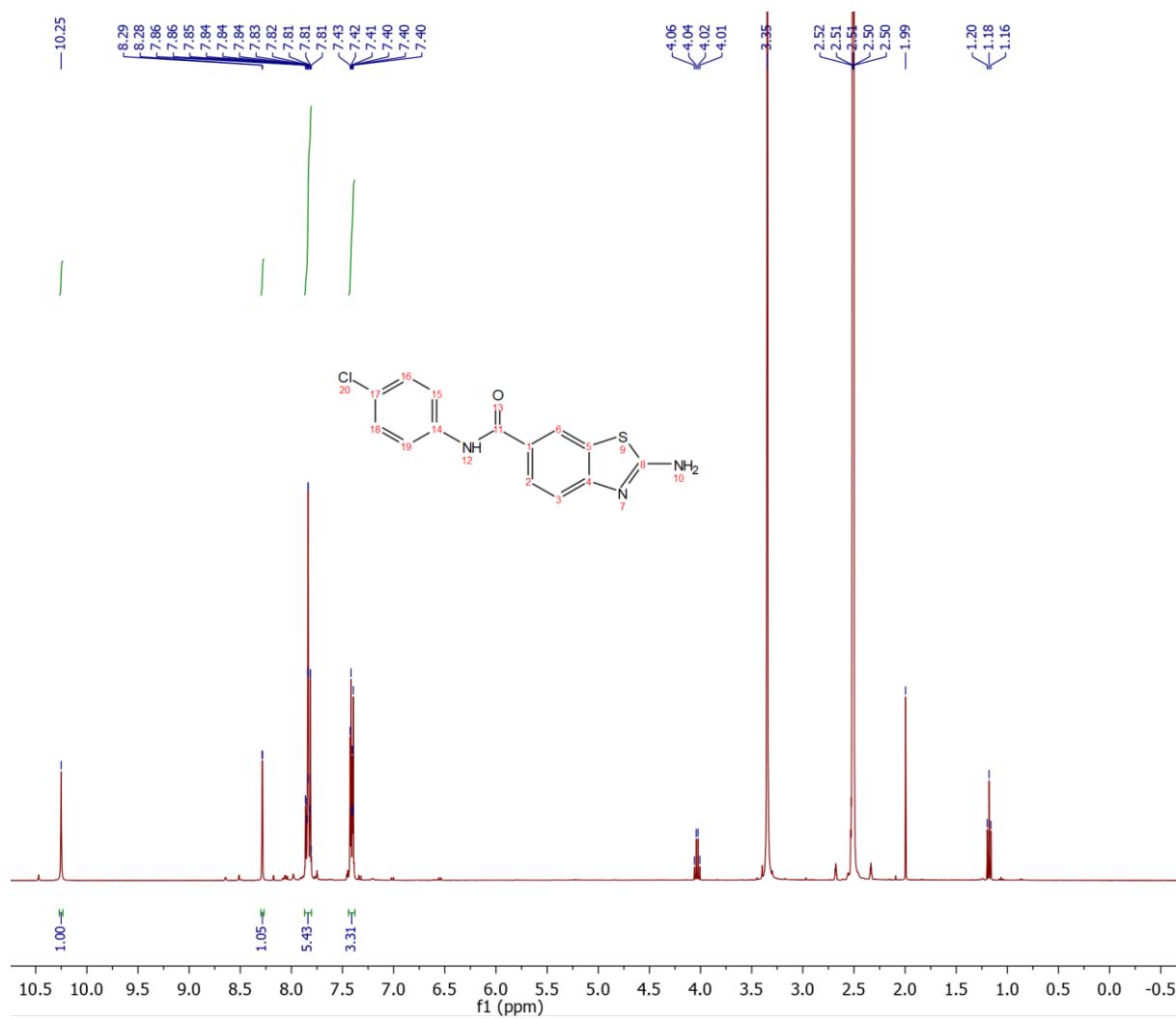


Figure S47. HPLC chromatogram of compound 5m.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.25 (s, 1H, Ar-NH-COR) 8.29 (d,  $J$  = 1.7 Hz, 1H, Ar-NH-COR), 7.87 – 7.80 (m, 5H, 5  $\times$  Ar- $H$ ), 7.45 – 7.37 ppm (m, 3H, Ar- $H$  and  $\text{NH}_2$ );



**Figure S48.**  $^1\text{H}$  NMR spectrum of compound 6.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 169.3, 165.7, 156.2, 138.9, 131.4, 129.0 (2C), 127.4; 127.4, 126.2, 122.1 (2C), 121.3, 117.4 ppm

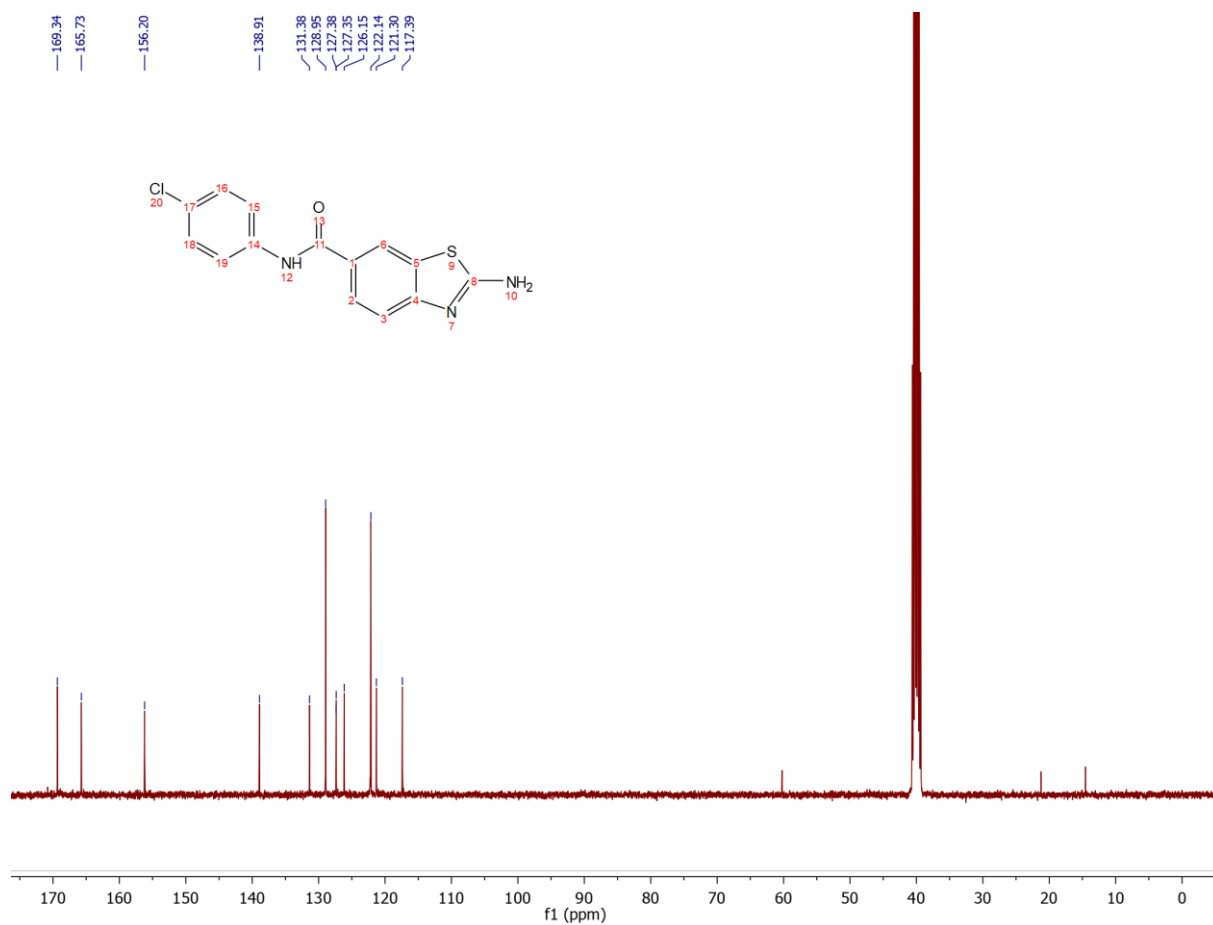
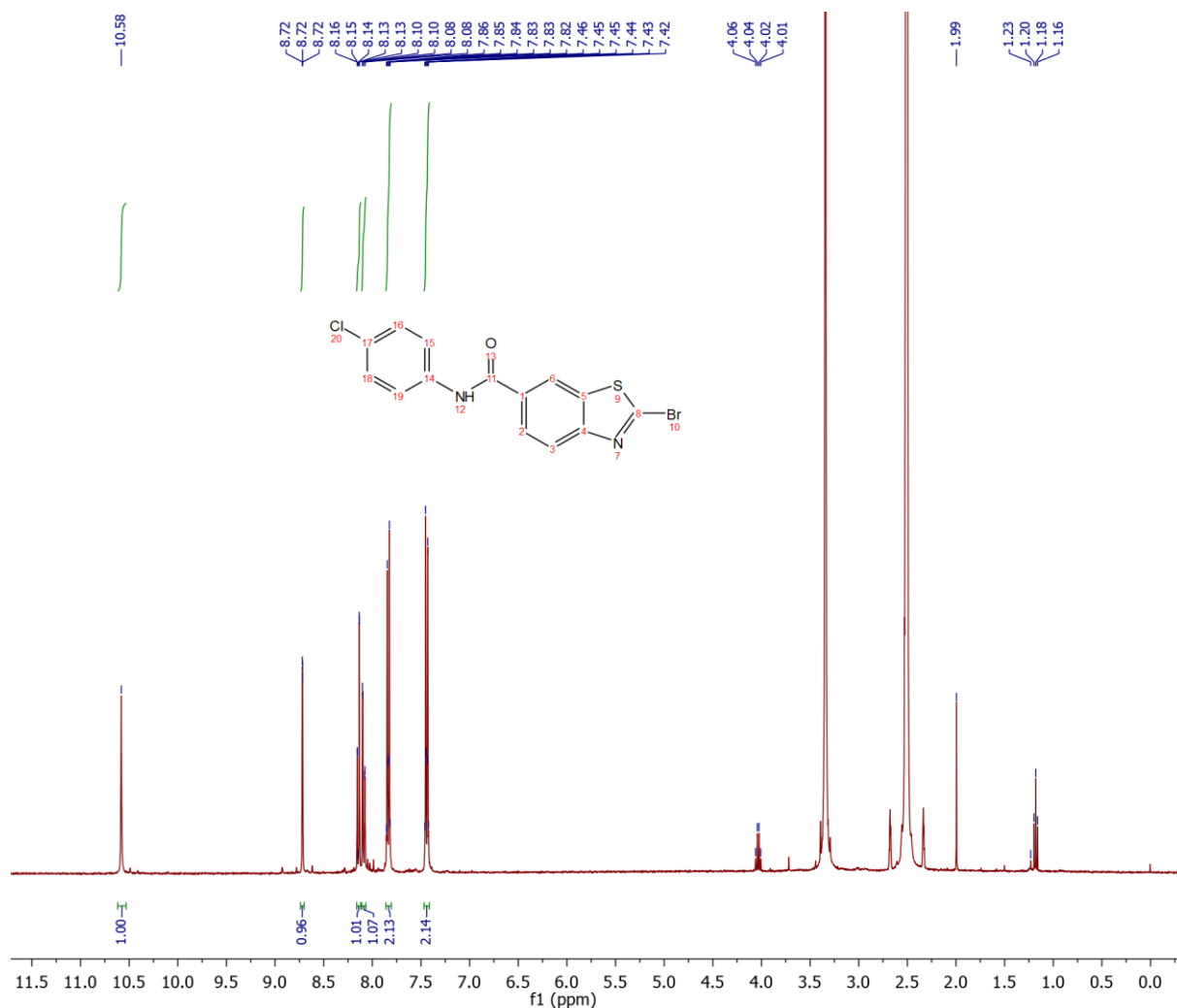


Figure S49.  $^{13}\text{C}$  NMR spectrum of compound 6.

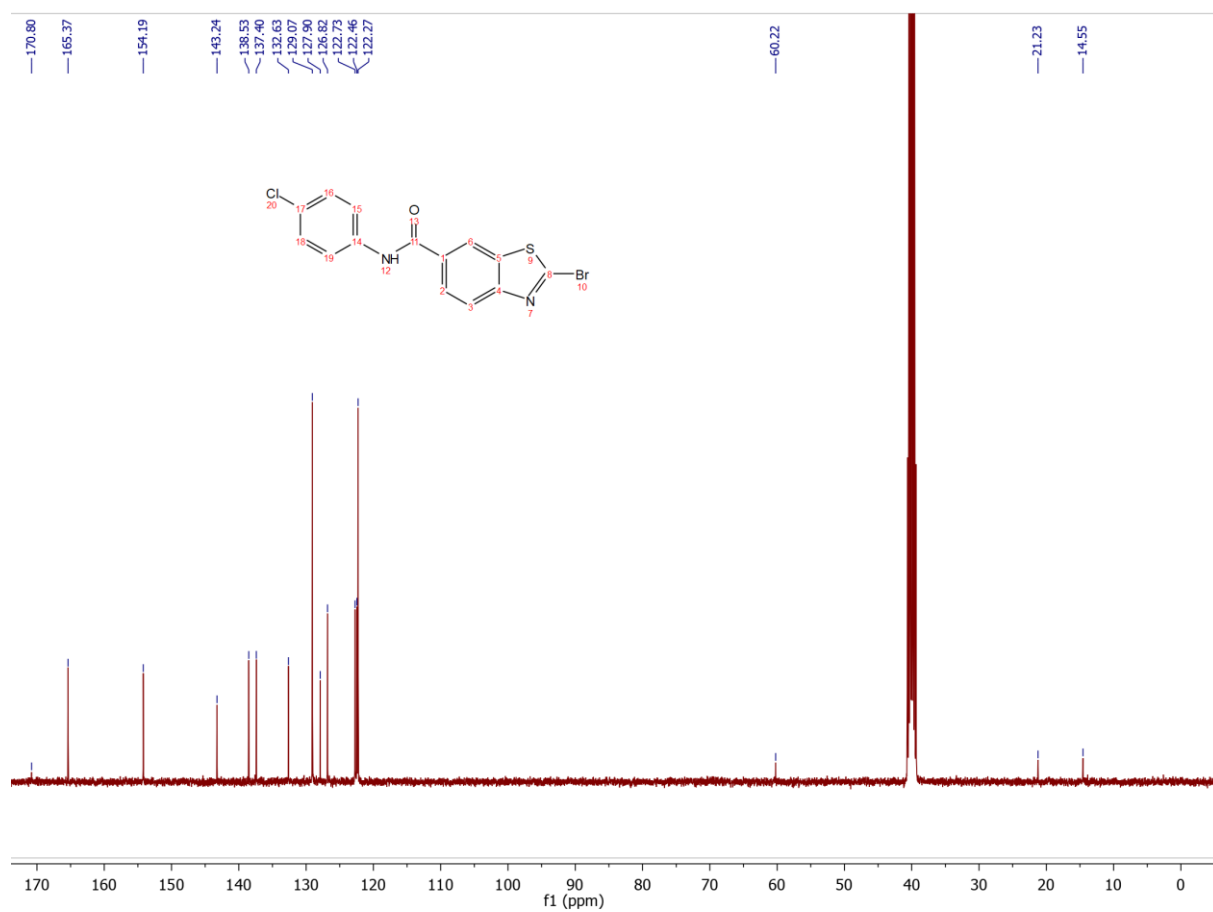


$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.58 (s, 1H, Ar-NH-COR), 8.73 – 8.70 (m, 1H, Ar-H), 8.16 – 8.12 (m, 1H, Ar-H), 8.09 (m, 1H, Ar-H), 7.87 – 7.80 (m, 2H, 2  $\times$  Ar-H), 7.48 – 7.40 ppm (m, 2H, 2  $\times$  Ar-H);



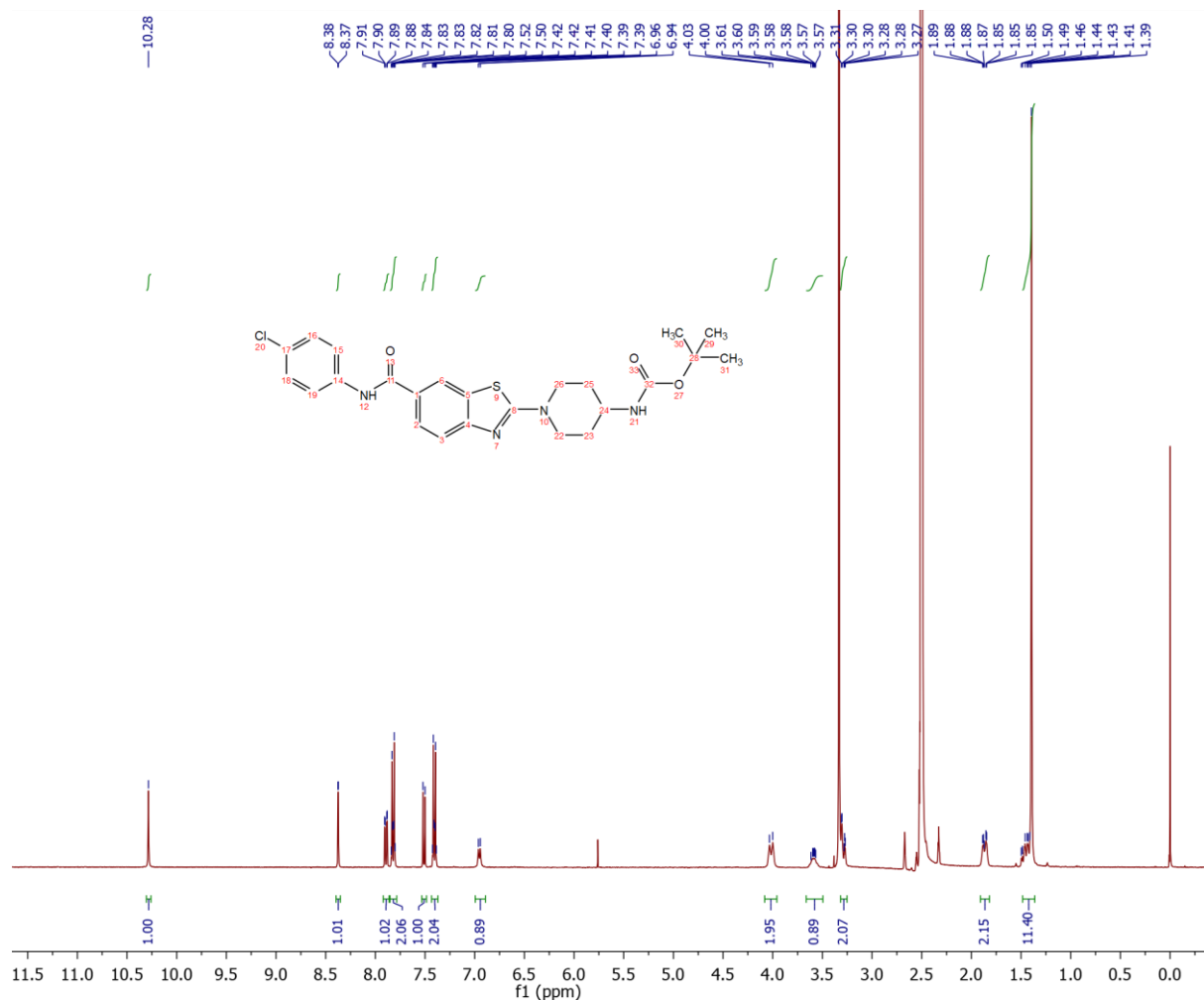
**Figure S50.**  $^1\text{H}$  NMR spectrum of compound 7.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 165.4, 154.2, 143.2, 138.5, 137.4, 132.6, 129.1 (2C), 127.9, 126.8, 122.7, 122.5, 122.3 ppm (2C)



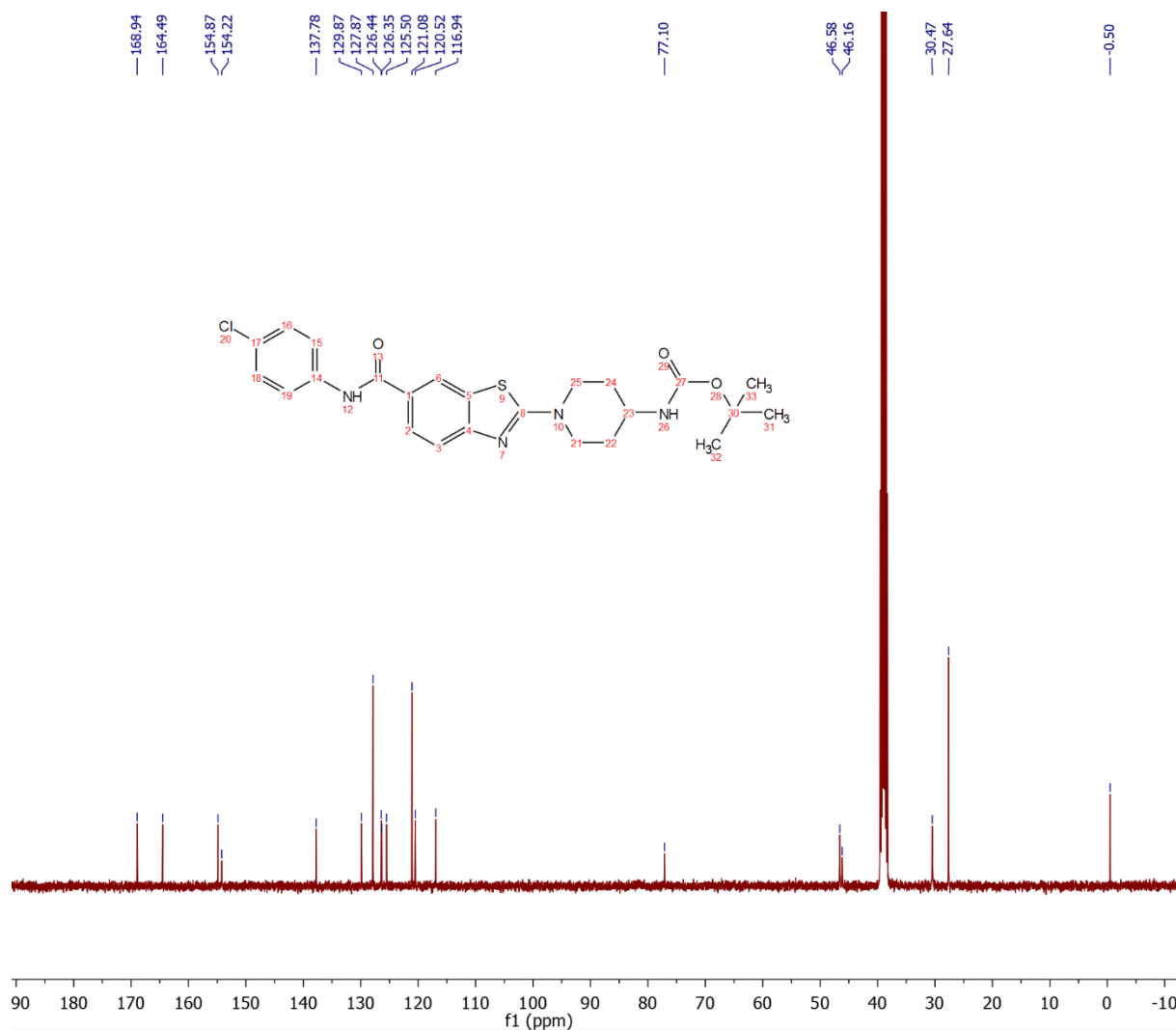
**Figure S51.**  $^{13}\text{C}$  NMR spectrum of compound 7.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.28 (s, 1H, Ar-NH-COR), 8.37 (d,  $J$  = 1.9 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.9 Hz, 1H, Ar- $H_5$ ), 7.86 – 7.78 (m, 2H, 2  $\times$  Ar- $H$ ), 7.51 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.43 – 7.37 (m, 2H, 2  $\times$  Ar- $H$ ), 6.95 (d,  $J$  = 7.9 Hz, 1H, CH-NH-Boc), 4.02 (d,  $J$  = 13.5 Hz, 2H, 2  $\times$  piperidine- $H$ ), 3.58 (s, 1H, piperidine- $H$ ), 3.27 (m, 2H, 2  $\times$  piperidine- $H$ ), 1.87 (m, 2H, 2  $\times$  piperidine- $H$ ), 1.50 – 1.41 (m, 2H, 2  $\times$  piperidine- $H$ ), 1.39 ppm (s, 9H,  $\text{COC}(\text{CH}_3)_3$ )



**Figure S52.**  $^1\text{H}$  NMR spectrum of compound 8i.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 168.9, 164.5, 154.9, 154.2, 137.8, 129.9, 127.9 (2C), 126.4, 126.4, 125.5, 121.1 (2C), 120.5, 116.9, 77.1, 46.6 (2C), 46.2, 30.5 (2C), 27.6 ppm (3C)



**Figure S53.**  $^{13}\text{C}$ NMR spectrum of compound 8i.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 10.29 (s, 1H, Ar-NH-COR), 8.38 (d,  $J$  = 1.9 Hz, 1H, Ar- $H_7$ ), 7.90 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.9 Hz, 1H, Ar- $H_5$ ), 7.85 – 7.79 (m, 2H, 2  $\times$  Ar- $H$ ), 7.52 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.43 – 7.38 (m, 2H, 2  $\times$  Ar- $H$ ), 7.36 (s, 1H, CH-CONH $_a$ ), 6.87 (s, 1H, CH-CONH $_b$ ), 4.08 (d,  $J$  = 13.0 Hz, 2H, 2  $\times$  piperidine- $H$ ), 3.29 – 3.21 (m, 2H, 2  $\times$  piperidine- $H$ ), 2.45 – 2.39 (m, 1H, piperidine- $H$ ), 1.90 – 1.79 (m, 2H, 2  $\times$  piperidine- $H$ ), 1.68 – 1.56 ppm (m, 2H, 2  $\times$  piperidine- $H$ )

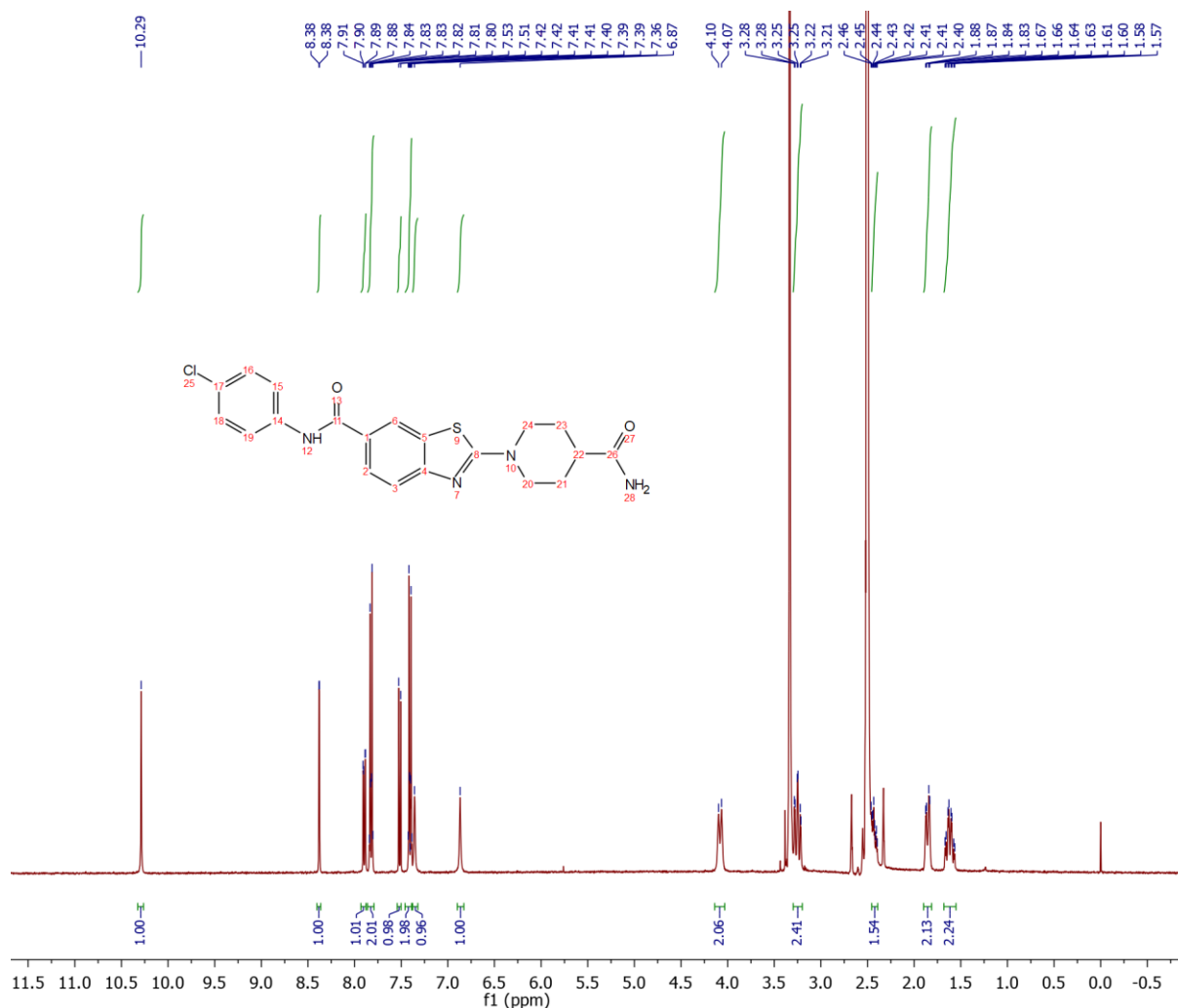
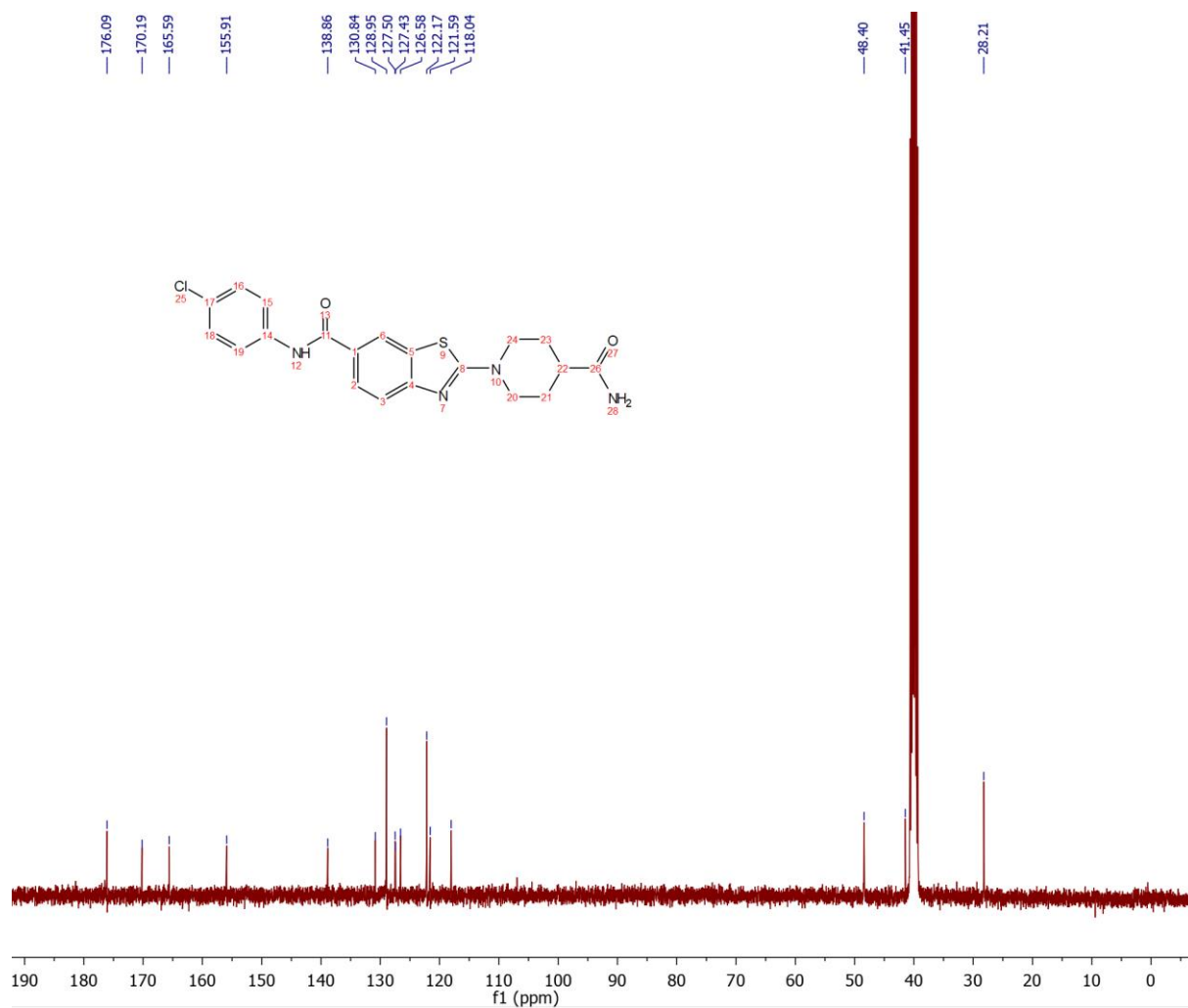


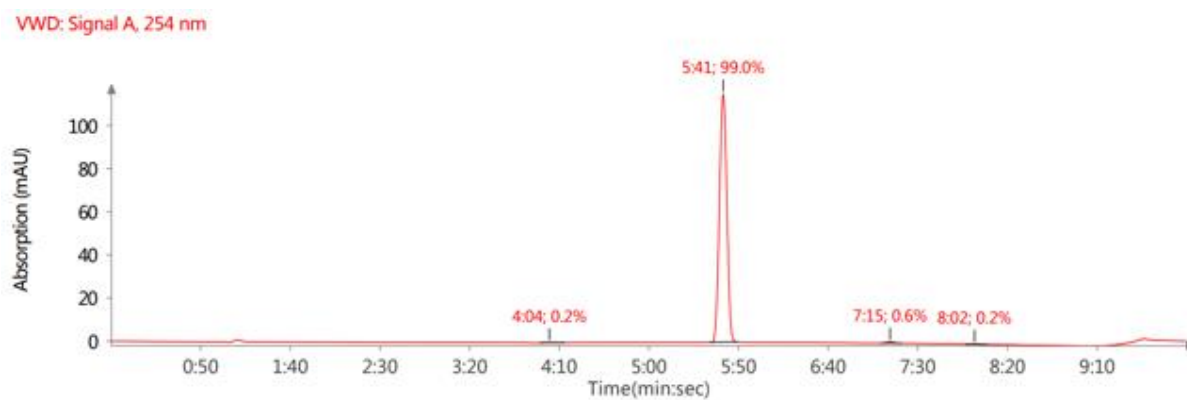
Figure S54.  $^1\text{H}$  NMR spectrum of compound 8k.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 176.1, 170.2, 165.6, 155.9, 138.9, 130.8, 129.0 (2C), 127.5, 127.4, 126.6, 122.2 (2C), 121.6, 118.0, 48.4, 41.5 (2C), 28.2 ppm (2C)



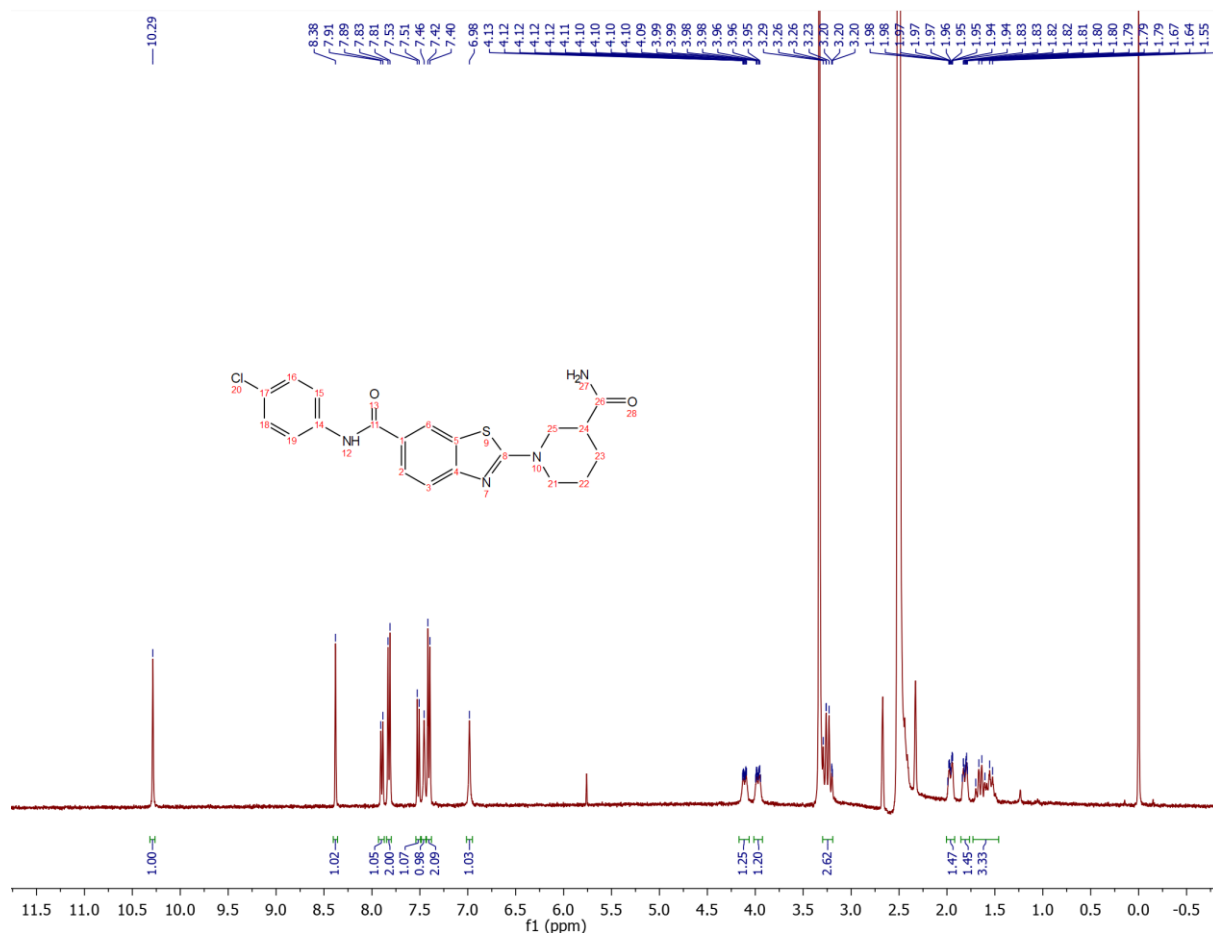
**Figure S55.**  $^{13}\text{C}$  NMR spectrum of compound 8k.

HPLC:  $t_r$  = 5.41 min (99.0 % at 254 nm)



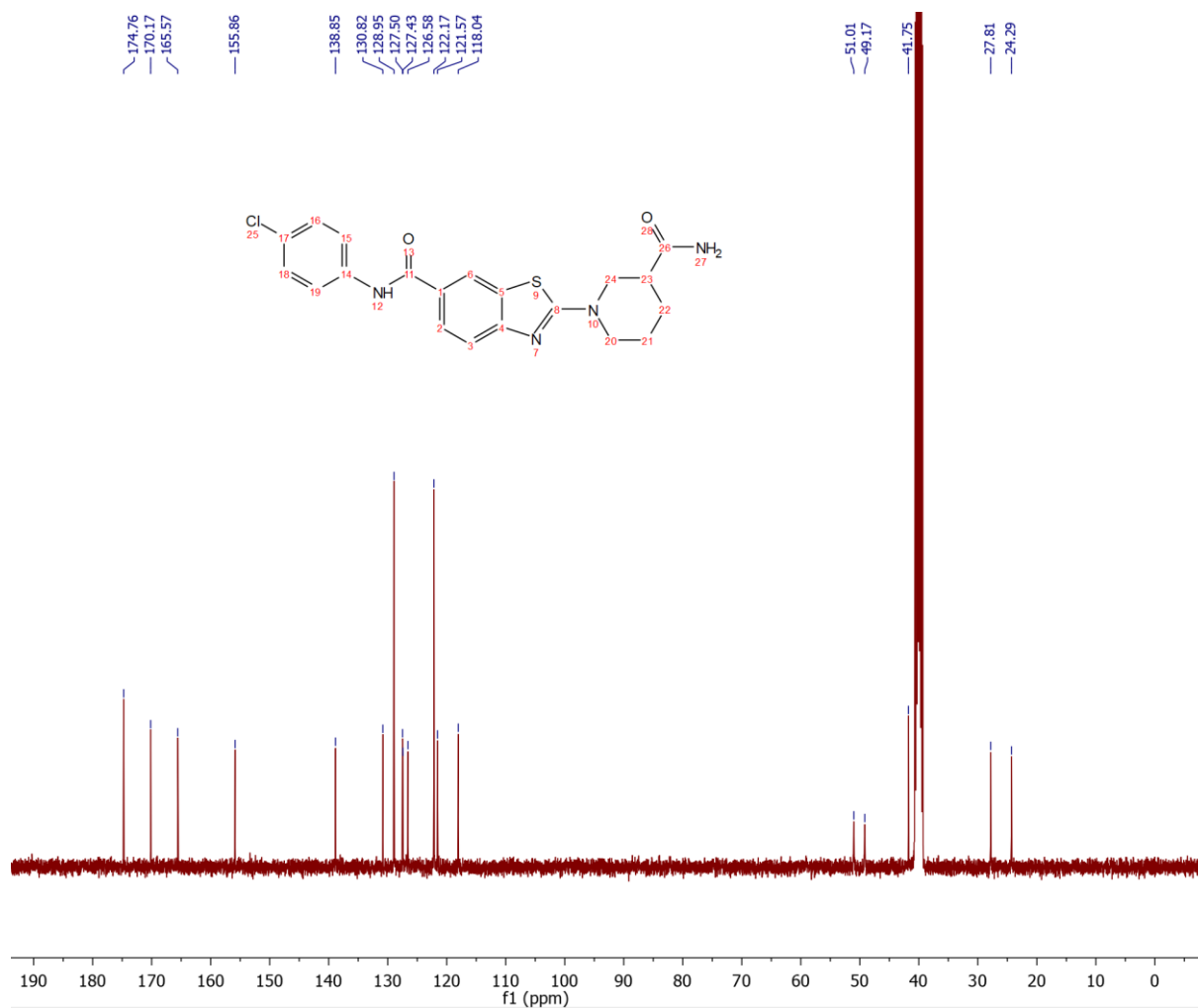
**Figure S56.** HPLC chromatogram of compound 8k.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.29 (s, 1H, Ar-NH-COR), 8.38 (s, 1H, Ar-H), 7.90 (d,  $J$  = 8.5 Hz, 1H, Ar-H), 7.82 (d,  $J$  = 8.4 Hz, 2H, 2  $\times$  Ar-H), 7.52 (d,  $J$  = 8.5 Hz, 1H, Ar-H), 7.46 (s, 1H, CO-NH<sub>a</sub>), 7.41 (d,  $J$  = 8.4 Hz, 2H, 2  $\times$  Ar-H), 6.98 (s, 1H, CO-NH<sub>b</sub>), 4.15 – 4.07 (m, 1H, piperidine-H), 4.00 – 3.93 (m, 1H, piperidine-H), 3.30 – 3.19 (m, 2H, 2  $\times$  piperidine-H), 2.00 – 1.92 (m, 1H, piperidine-H), 1.85 – 1.77 (m, 1H, piperidine-H), 1.71 – 1.50 ppm (m, 3H, 3  $\times$  piperidine-H)



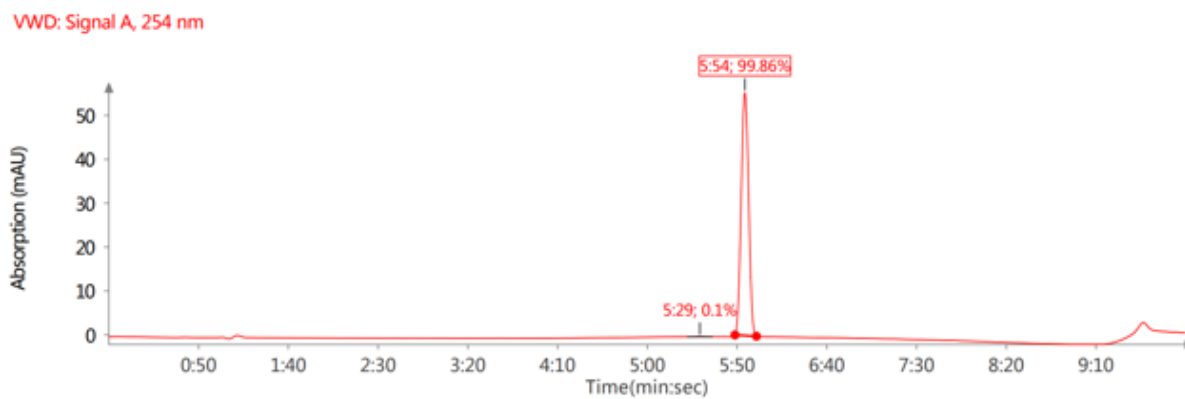
**Figure S57.**  $^1\text{H}$  NMR spectrum of compound 8l.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 174.8, 170.2, 165.6, 155.9, 138.9, 130.8, 129.0 (2C), 127.5, 127.4, 126.6, 122.2 (2C), 121.6, 118.0, 51.0, 49.2, 41.8, 27.8, 24.3 ppm



**Figure S58.**  $^{13}\text{C}$ NMR spectrum of compound 81.

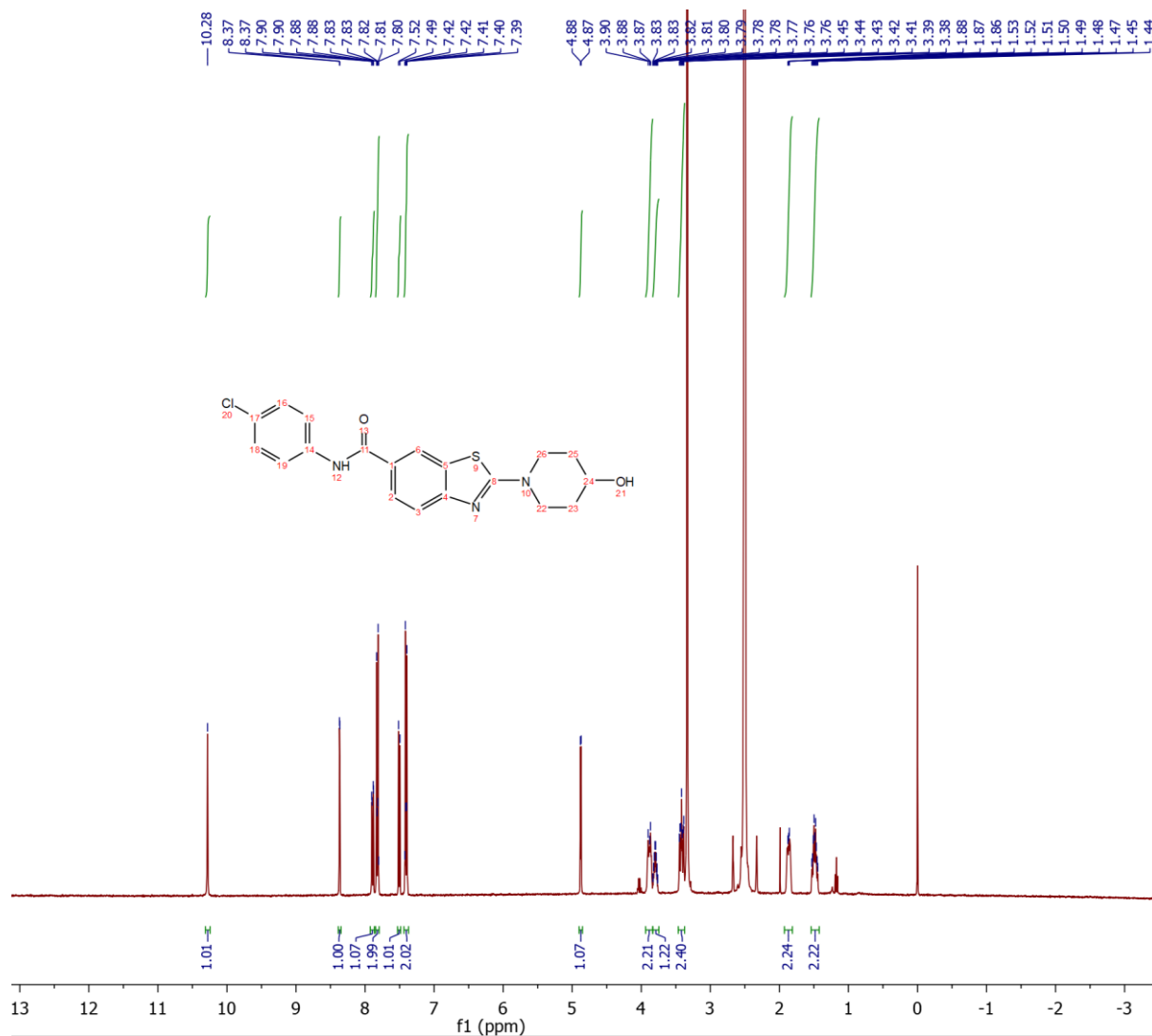
HPLC:  $t_r$  = 5.54 min (99.9 % at 254 nm)



**Figure S59.** HPLC chromatogram of compound 81.



$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.28 (s, 1H, Ar-NH-COR), 8.37 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.86 – 7.79 (m, 2H, 2  $\times$  Ar- $H$ ), 7.50 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.44 – 7.37 (m, 2H, 2  $\times$  Ar- $H$ ), 4.88 (d,  $J$  = 4.1 Hz, 1H, CH-OH), 3.94 – 3.83 (m, 2H, 2  $\times$  piperidine- $H$ ), 3.84 – 3.76 (m, 1H, piperidine- $H$ ), 3.46 – 3.37 (m, 2H, 2  $\times$  piperidine- $H$ ), 1.93 – 1.80 (m, 2H, 2  $\times$  piperidine- $H$ ), 1.56 – 1.41 ppm (m, 2H, 2  $\times$  piperidine- $H$ )



**Figure S60.**  $^1\text{H}$  NMR spectrum of compound **8m**.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.1, 165.6, 156.0, 138.9, 130.9, 129.0 (2C), 127.4, 126.6, 122.2 (2C), 121.6, 118.0, 65.5, 46.41 (2C), 33.81 (2C) ppm

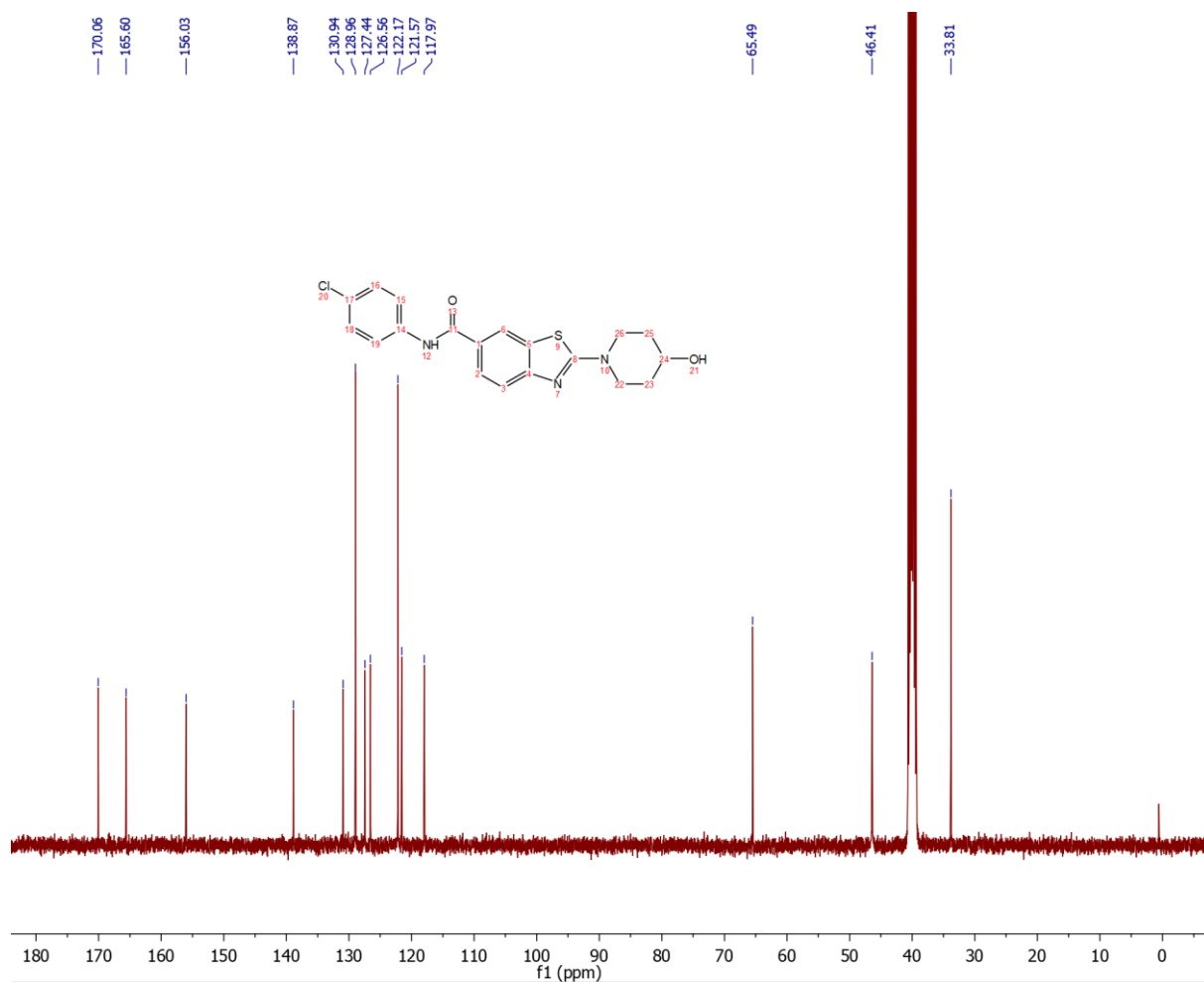


Figure S61.  $^{13}\text{C}$ NMR spectrum of compound 8m.

HPLC:  $t_r$  = 6.00 min (96.2 % at 254 nm)

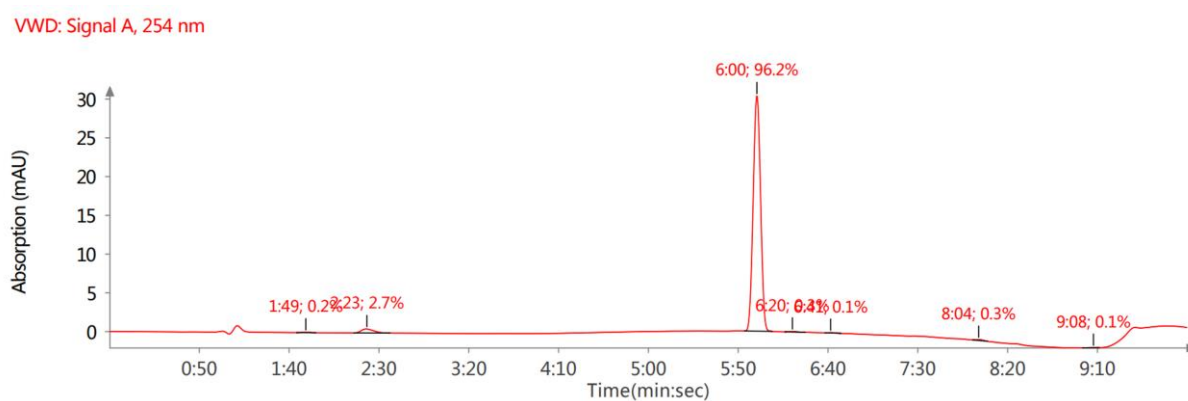
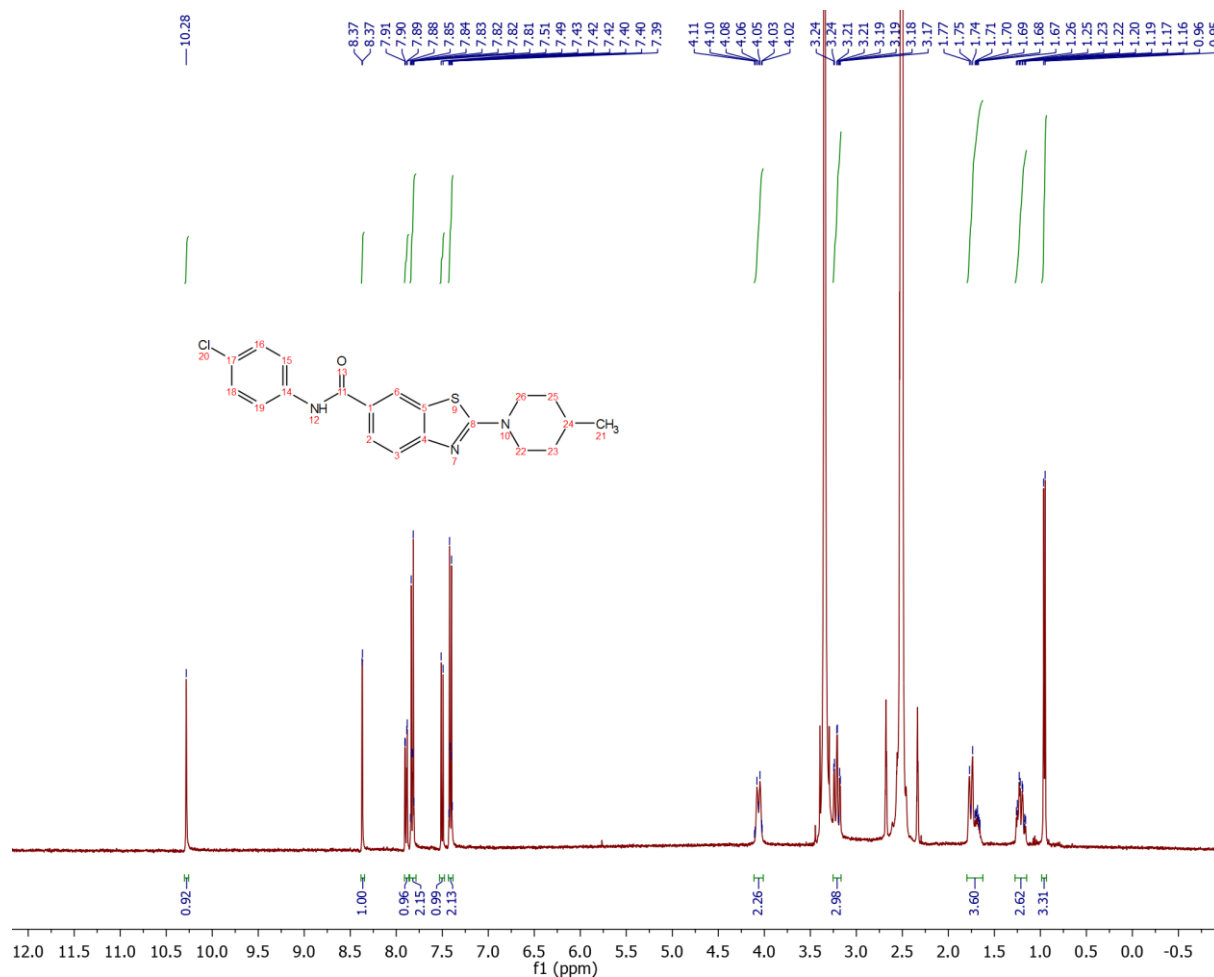


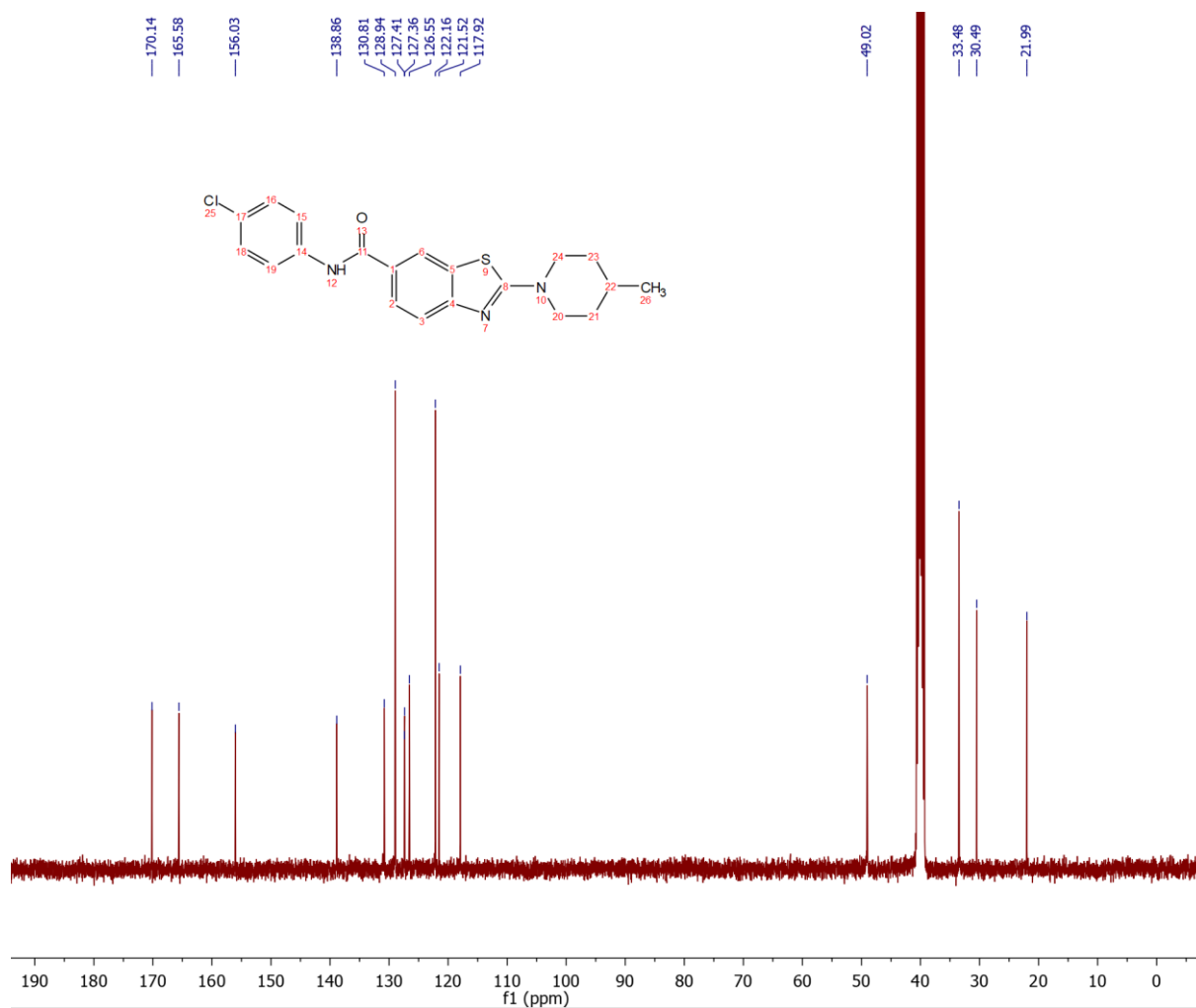
Figure S62. HPLC chromatogram of compound 8m.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.28 (s, 1H, Ar-NH-COR), 8.37 (d,  $J$  = 1.9 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.9 Hz, 1H, Ar- $H_5$ ), 7.85 – 7.78 (m, 2H, 2  $\times$  Ar- $H$ ), 7.50 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.44 – 7.38 (m, 2H, 2  $\times$  Ar- $H$ ), 4.11 – 4.02 (m, 2H, 2  $\times$  piperidine- $H$ ), 3.25 – 3.17 (m, 2H, 2  $\times$  piperidine- $H$ ), 1.80 – 1.62 (m, 3H, 3  $\times$  piperidine- $H$ ), 1.28 – 1.14 (m, 2H, 2  $\times$  piperidine- $H$ ), 0.96 ppm (d,  $J$  = 6.4 Hz, 3H,  $\text{CH}_3$ )



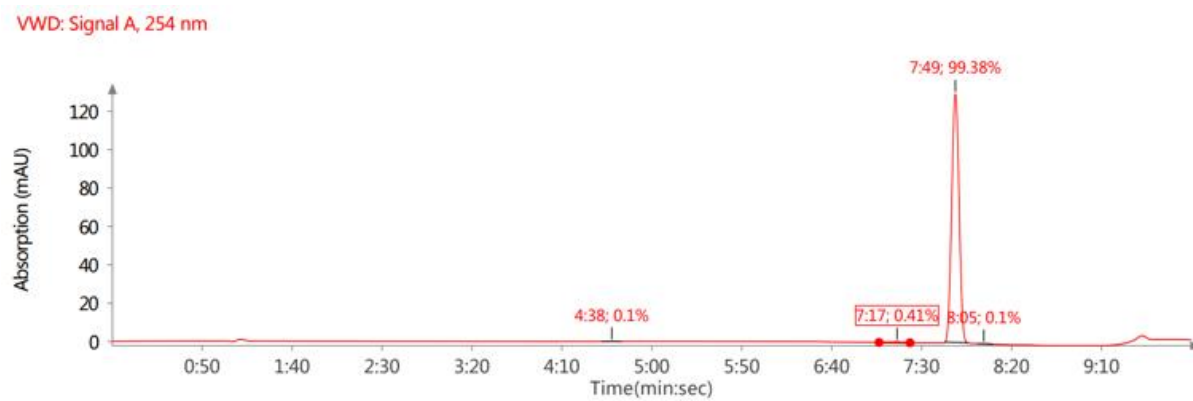
**Figure S63.**  $^1\text{H}$  NMR spectrum of compound 8n.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 170.1, 165.6, 156.0, 138.9, 130.8, 128.9 (2C), 127.4, 127.4, 126.6, 122.2 (2C), 121.5, 117.9, 49.0 (2C), 33.5 (2C), 30.5, 22.0 ppm



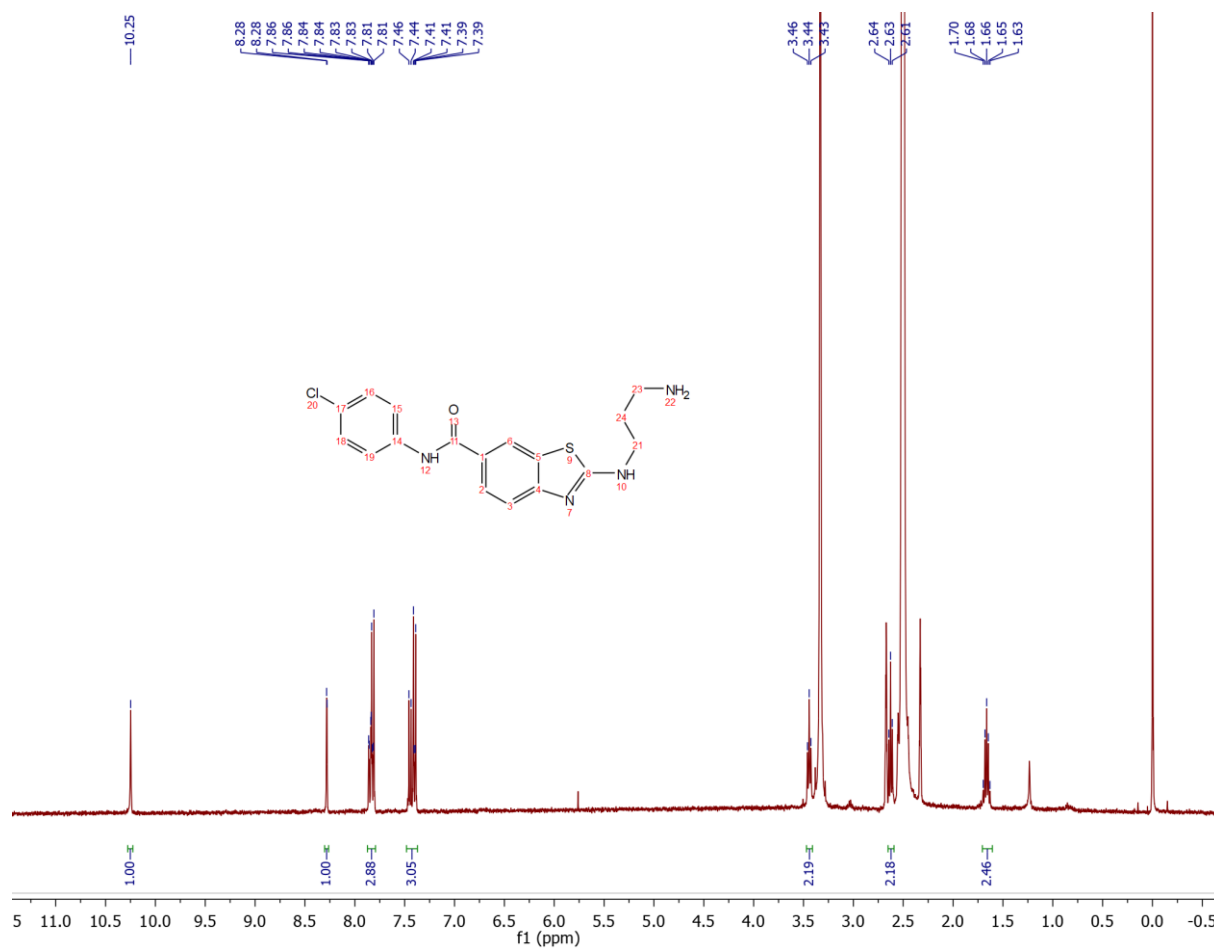
**Figure S64.**  $^{13}\text{C}$  NMR spectrum of compound **8n**.

HPLC:  $t_r$  = 7.49 min (99,4 % at 254 nm)



**Figure S65.** HPLC chromatogram of compound **8n**.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 10.25 (s, 1H, Ar-NH-COR), 8.28 (d,  $J$  = 1.8 Hz, 1H, Ar-H), 7.88 – 7.78 (m, 3H, 3  $\times$  Ar-H), 7.48 – 7.36 (m, 3H, 3  $\times$  Ar-H), 3.44 (t,  $J$  = 6.8 Hz, 2H, N-CH<sub>2</sub>-CH<sub>2</sub>), 2.63 (t,  $J$  = 6.8 Hz, 2H, N-CH<sub>2</sub>-CH<sub>2</sub>), 1.66 ppm (p,  $J$  = 6.8 Hz, 2H), not visible (NH and NH<sub>2</sub>);



**Figure S66.**  $^1\text{H}$  NMR spectrum of compound 9a.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 168.8, 165.7, 156.0, 138.9, 130.7, 128.9 (2C), 127.4, 127.2, 126.2, 122.1 (2C), 121.3, 117.5, 42.4 (2C), 33.0 ppm

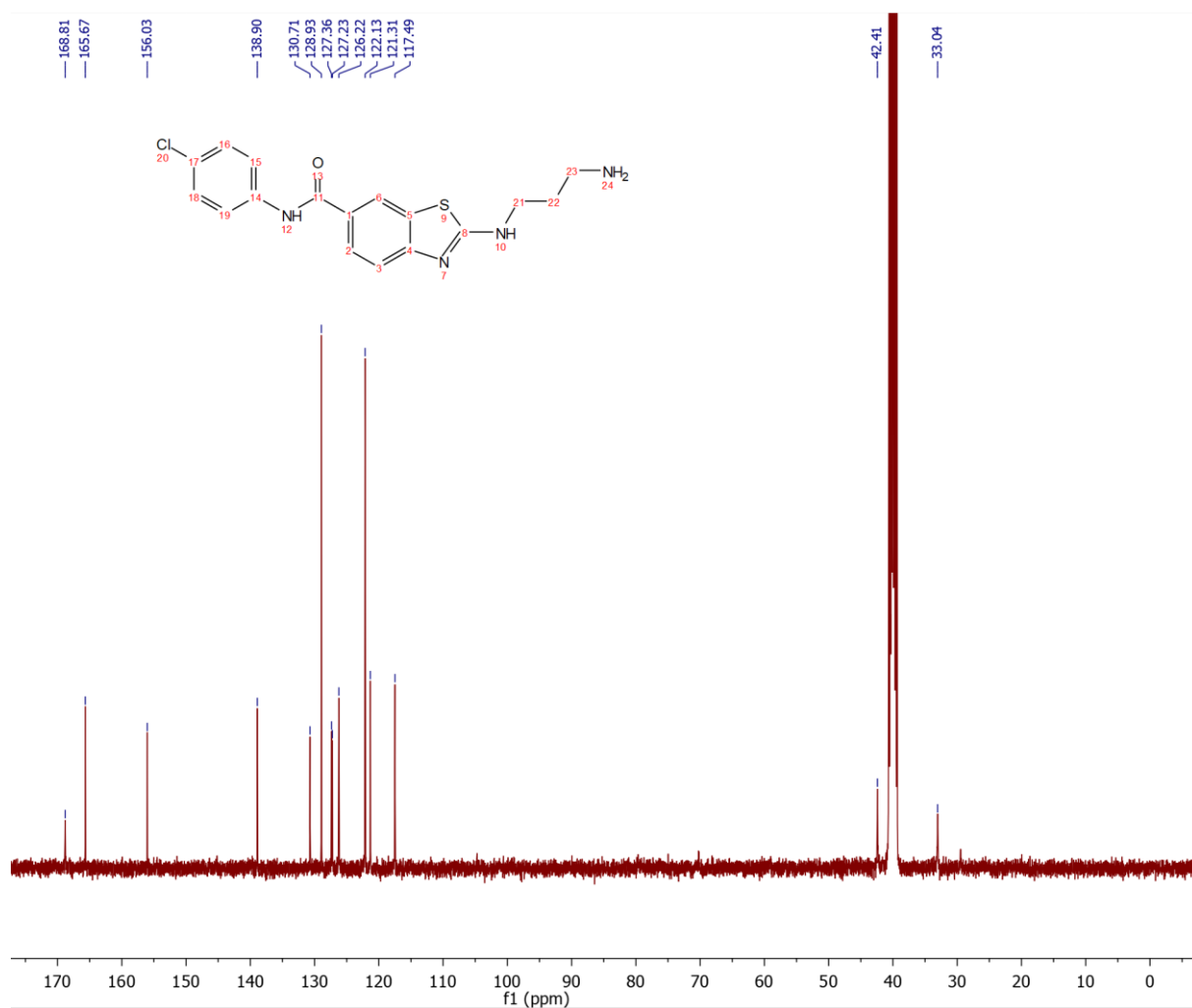


Figure S67.  $^{13}\text{C}$  NMR spectrum of compound 9a.

HPLC:  $t_r$  = 4.40 min (99.8 % at 254 nm).

VWD: Signal A, 254 nm

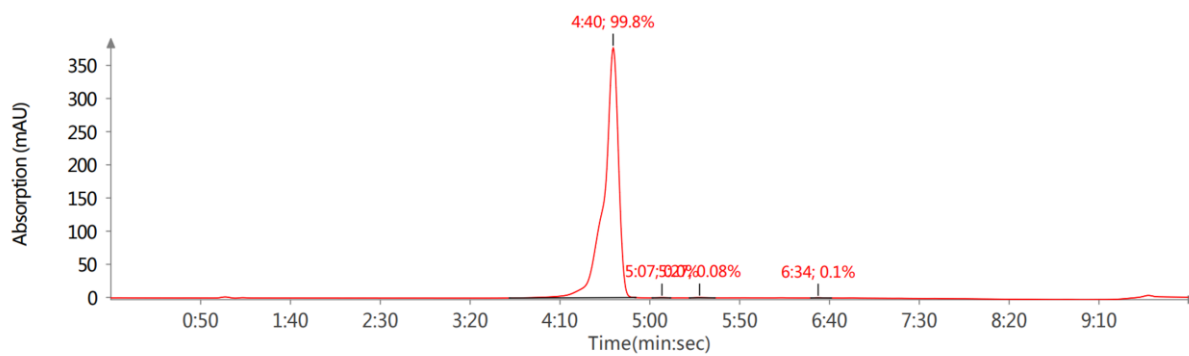


Figure S68. HPLC chromatogram of compound 9a.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.27 (s, 1H, Ar-NH-COR), 8.36 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.85 – 7.78 (m, 2H, 2  $\times$  Ar- $H$ ), 7.49 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.43 – 7.38 (m, 2H, 2  $\times$  Ar- $H$ ), 3.95 (dd,  $J_1$  = 29.1 Hz,  $J_2$  = 12.8 Hz, 2H, CH- $\text{NH}_2$ ), 3.23 – 3.14 (m, 1H, piperidine- $H$ ), 2.93 – 2.86 (m, 1H, piperidine- $H$ ), 2.79 – 2.70 (m, 1H, piperidine- $H$ ), 1.93 – 1.84 (m, 1H, piperidine- $H$ ), 1.83 – 1.70 (m, 3H, 3  $\times$  piperidine- $H$ ), 1.60 – 1.46 (m, 1H, piperidine- $H$ ), 1.34 – 1.21 ppm (m, 1H, piperidine- $H$ )

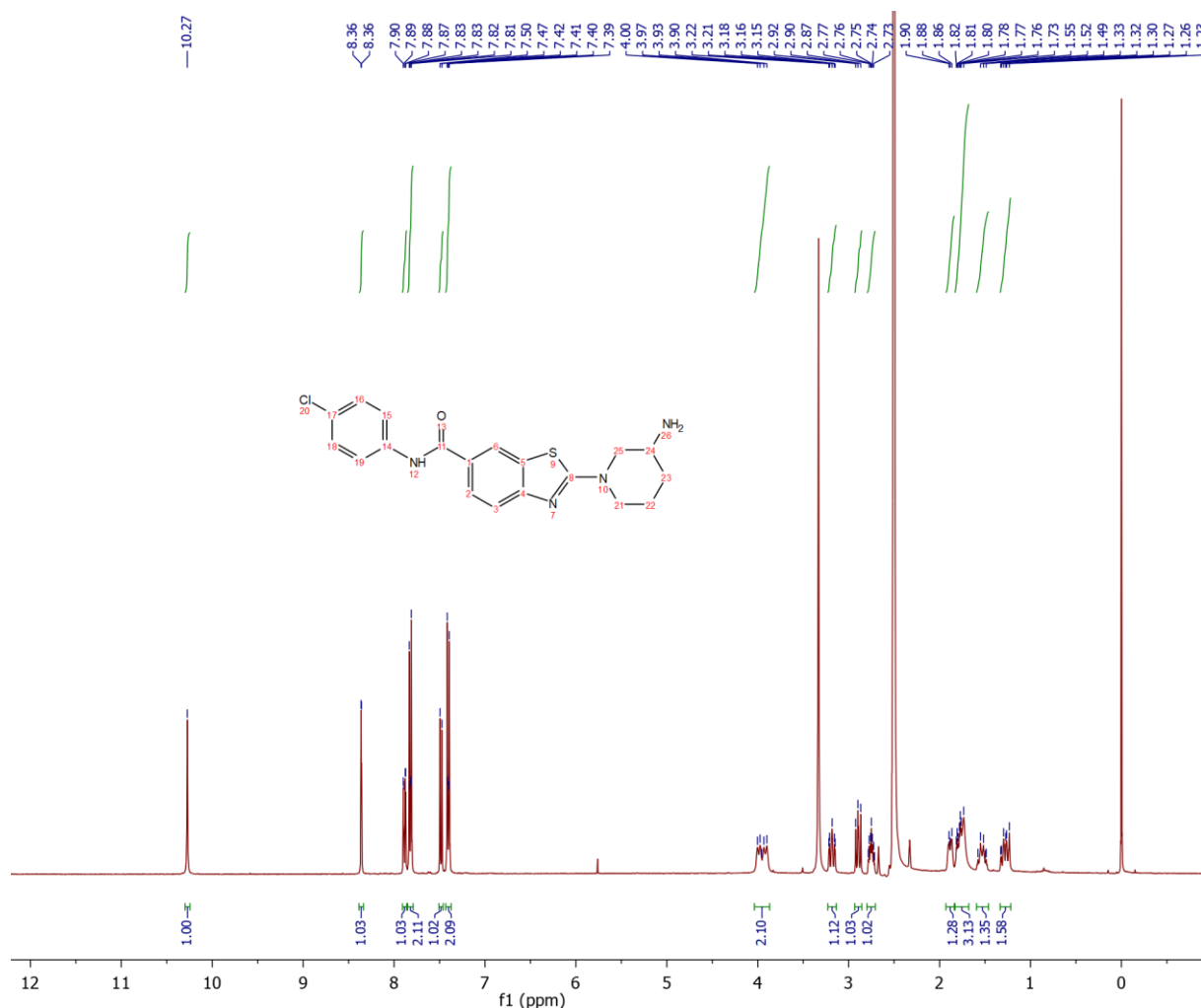
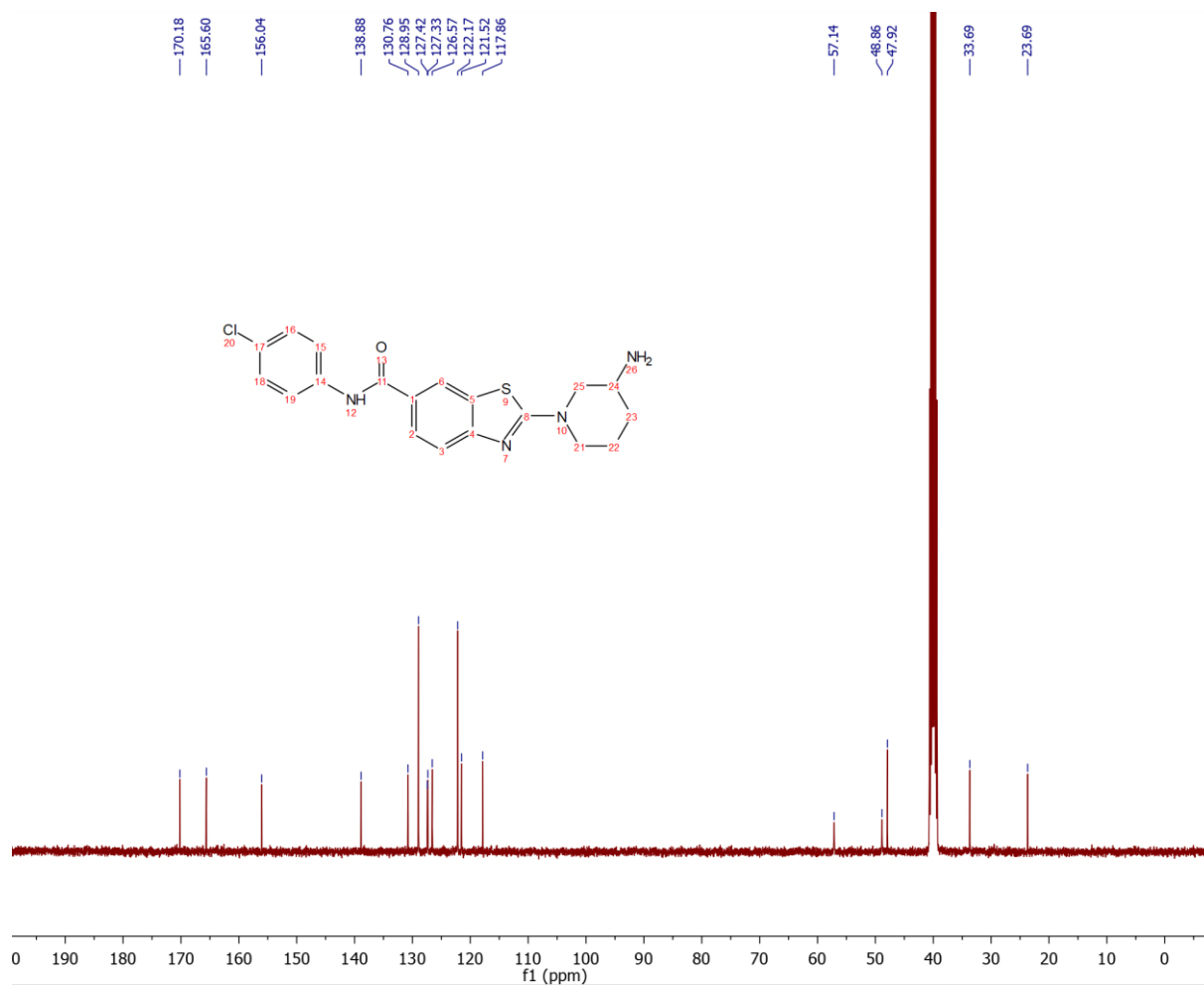


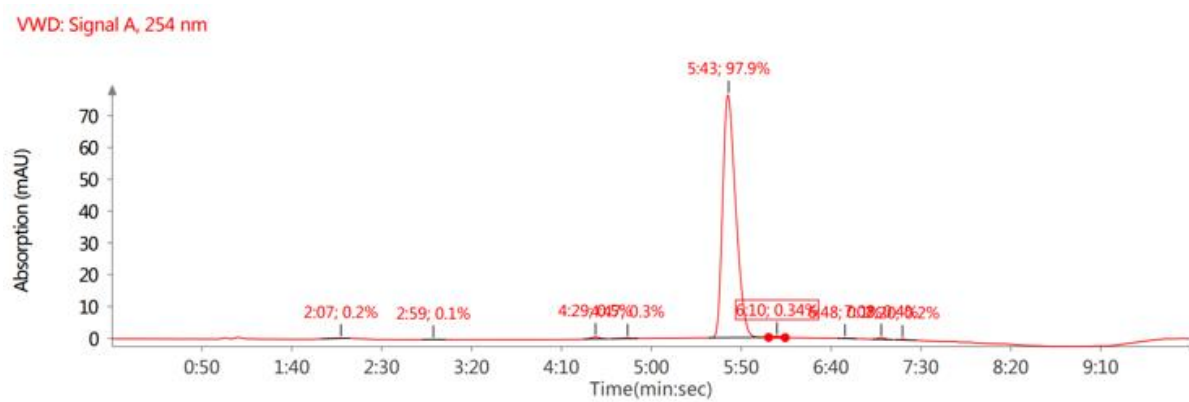
Figure S69.  $^1\text{H}$  NMR spectrum of compound 9b.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.2, 165.6, 156.0, 138.9, 130.8, 129.0 (2C), 127.4, 127.3, 126.6, 122.2 (2C), 121.5, 117.9, 57.1, 48.9, 47.9, 33.7, 23.7 ppm



**Figure S70.**  $^{13}\text{C}$  NMR spectrum of compound **9b**.

HPLC:  $t_r$  = 5.43 min (97.9 % at 254 nm)



**Figure S71.** HPLC chromatogram of compound **9b**.



$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.27 (s, 1H, Ar-NH-COR), 8.37 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.88 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.9 Hz, 1H, Ar- $H_5$ ), 7.84 – 7.78 (m, 2H, 2  $\times$  Ar- $H$ ), 7.52 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.44 – 7.37 (m, 2H, 2  $\times$  Ar- $H$ ), 3.73 – 3.46 (m, 4H, CH- $\text{NH}_2$  + 2  $\times$  pyrrolidine- $H$ ), 3.29 – 3.15 (m, 1H, pyrrolidine- $H$ ), 2.17 – 2.04 (m, 1H, pyrrolidine- $H$ ), 1.90 – 1.74 ppm (m, 3H, 3  $\times$  pyrrolidine- $H$ )

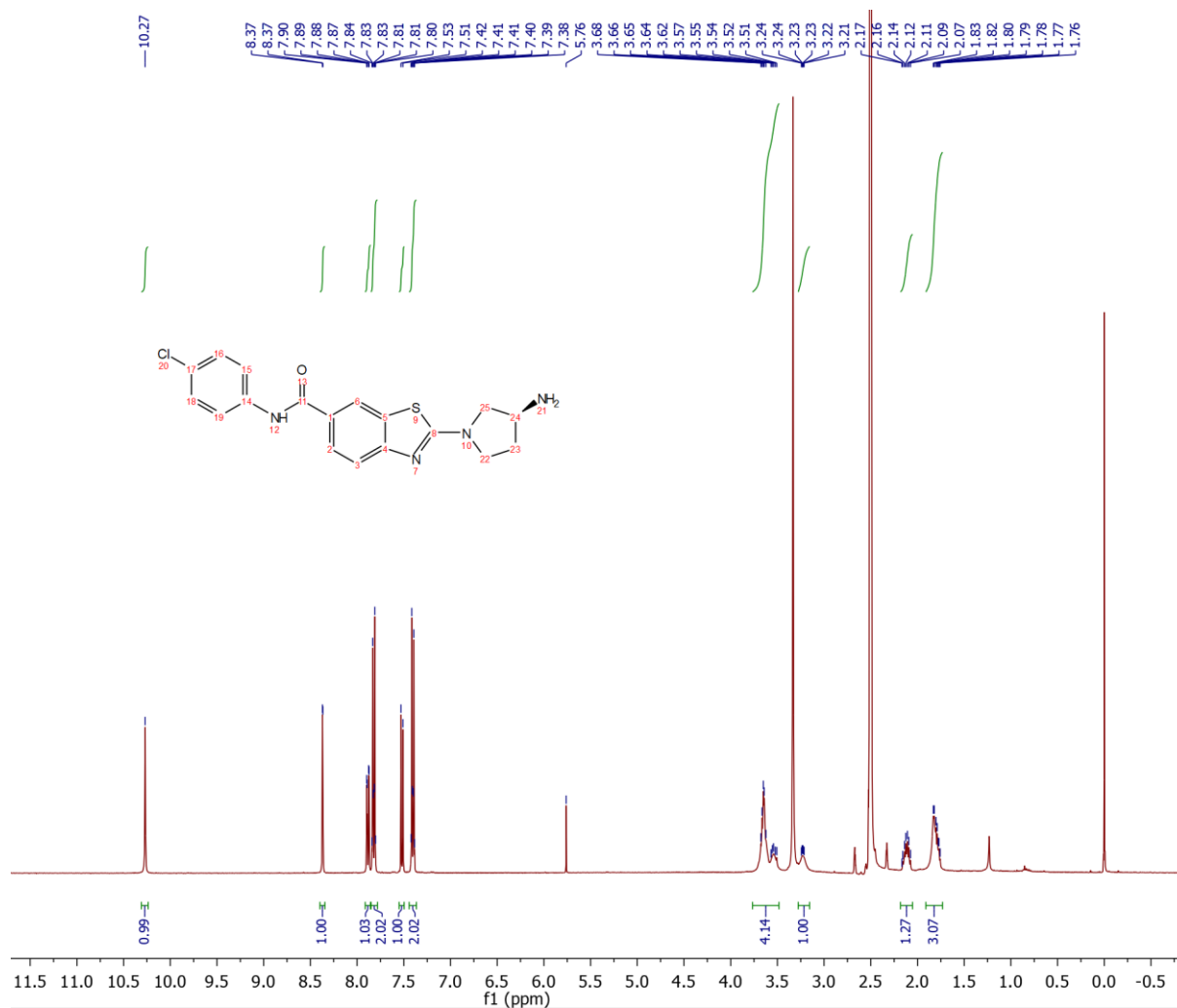
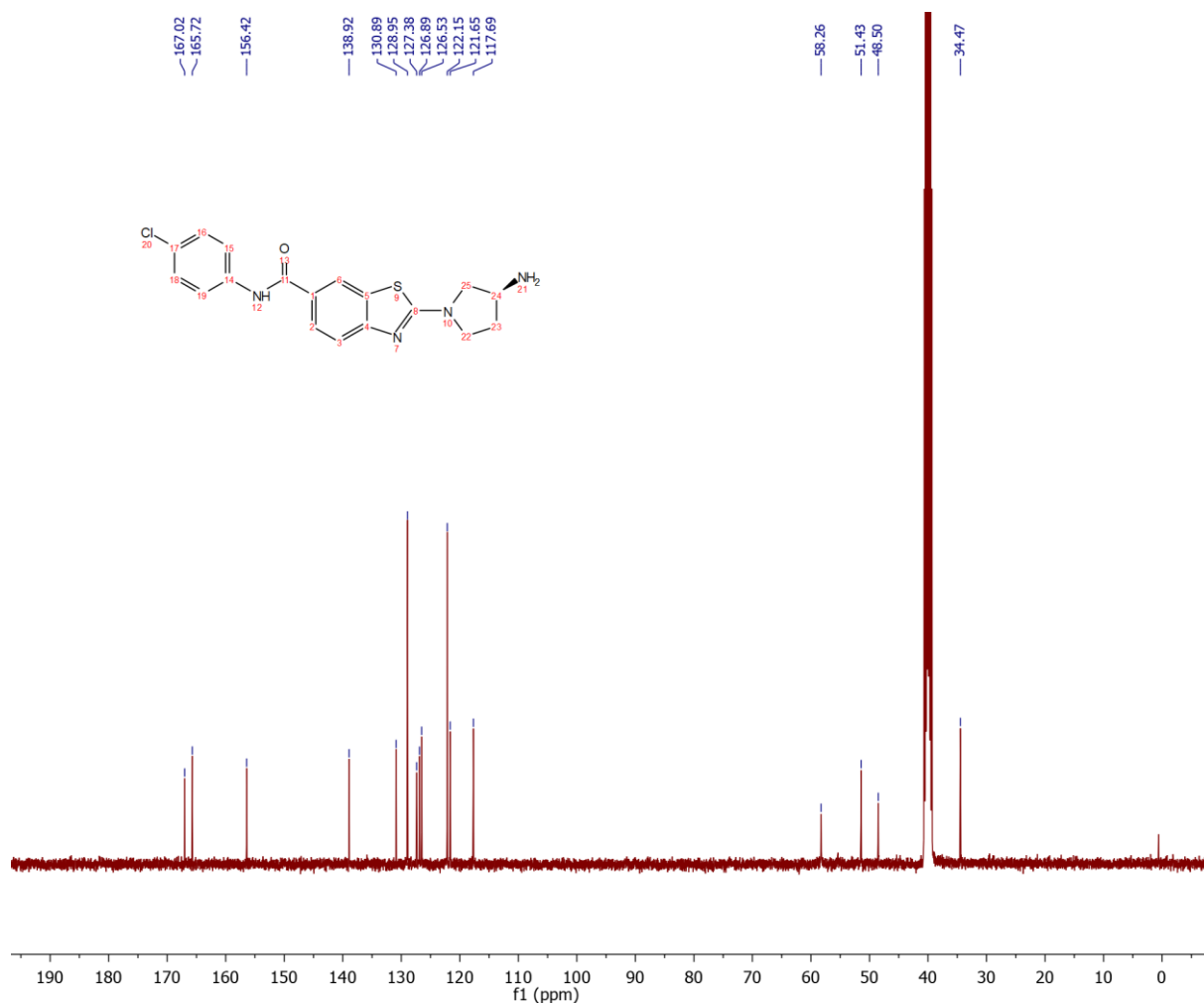


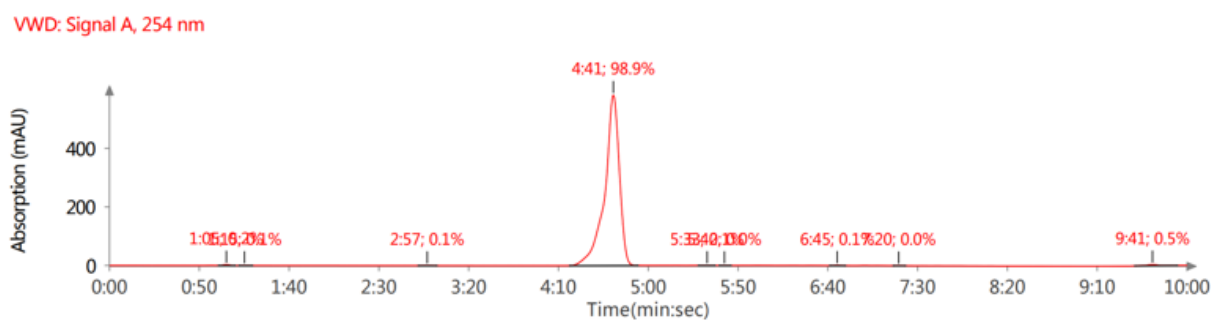
Figure S72.  $^1\text{H}$ NMR spectrum of compound 9c.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 167.0, 165.7, 156.4, 138.9, 130.9, 129.0 (2C), 127.4, 126.9, 126.5, 122.2 (2C), 121.7, 117.7, 58.3, 51.4, 48.5, 34.5 ppm



**Figure S73.**  $^{13}\text{C}$  NMR spectrum of compound 9c.

HPLC:  $t_r$  = 4.41 min (98.9 % at 254 nm).



**Figure S74.** HPLC chromatogram of compound 9c.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 10.27 (s, 1H, Ar-NH-COR), 8.37 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.88 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.9 Hz, 1H, Ar- $H_5$ ), 7.85 – 7.79 (m, 2H, 2  $\times$  Ar- $H$ ), 7.52 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.44 – 7.37 (m, 2H, 2  $\times$  Ar- $H$ ), 3.73 – 3.48 (m, 4H, CH- $\text{NH}_2$  and 2  $\times$  pyrrolidine- $H$ ), 3.27 – 3.18 (m, 1H, pyrrolidine- $H$ ), 2.16 – 2.07 (m, 1H, pyrrolidine- $H$ ), 1.96 – 1.74 ppm (m, 3H, 3  $\times$  pyrrolidine- $H$ )

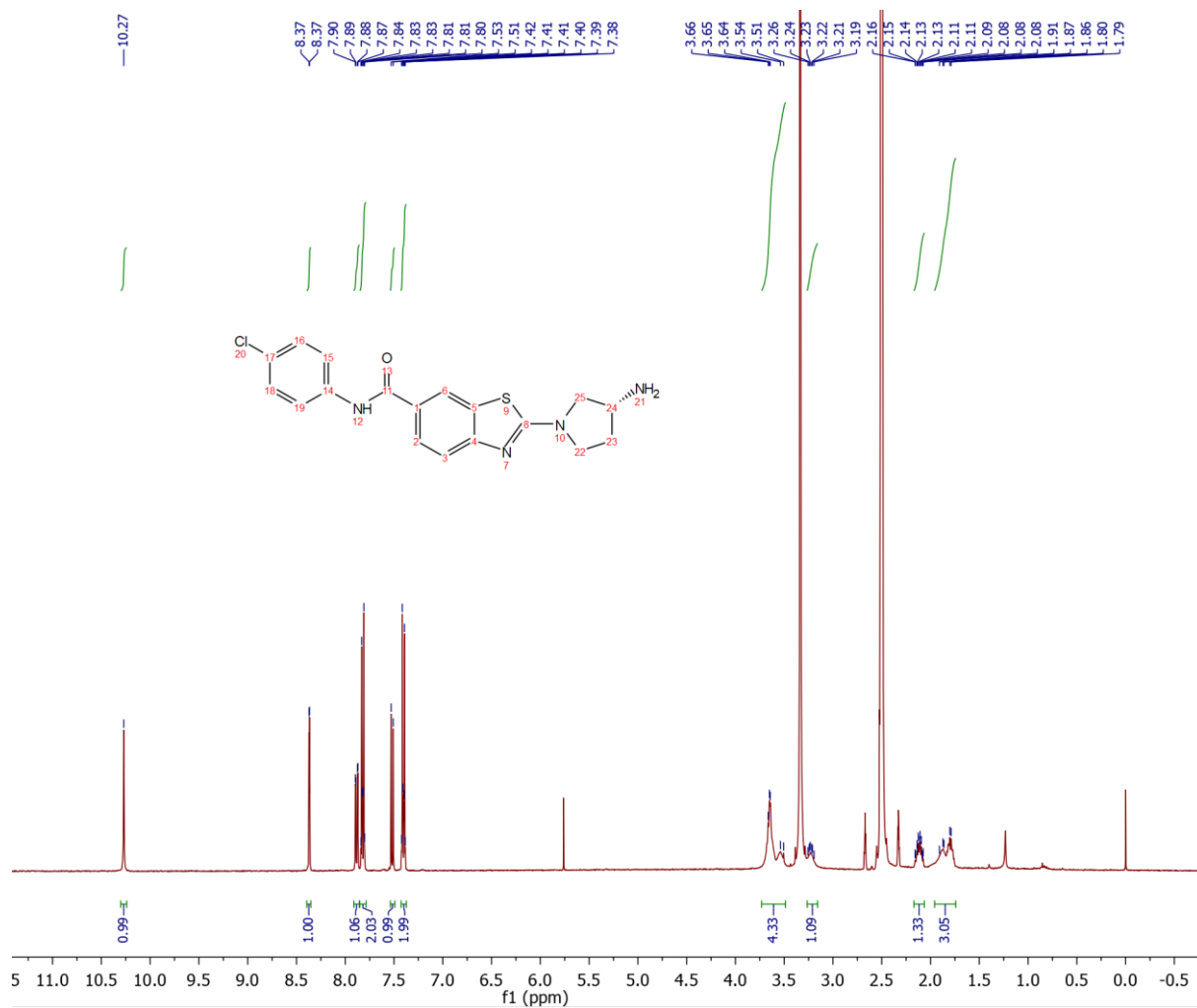
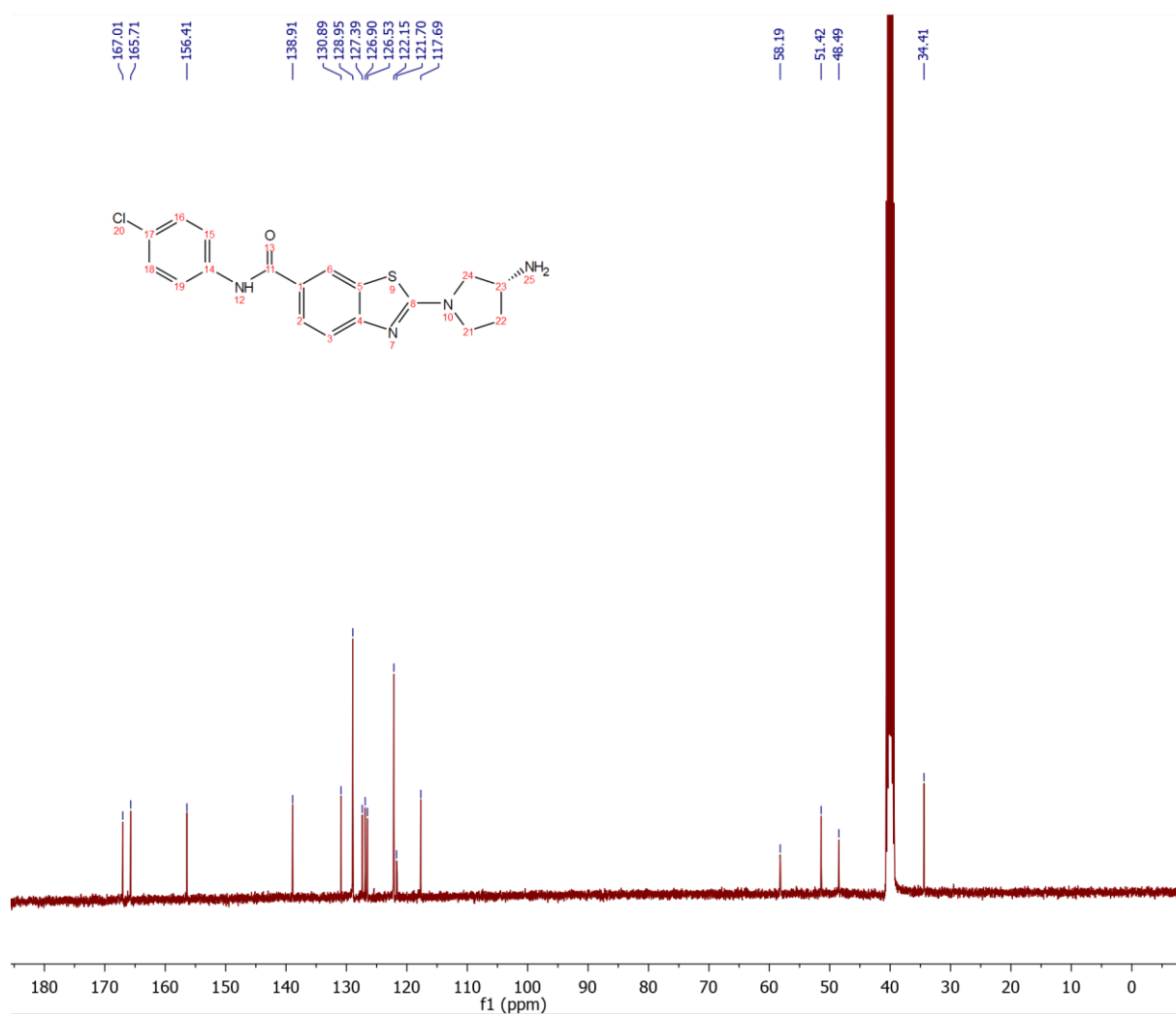


Figure S75.  $^1\text{H}$  NMR spectrum of compound 9d.

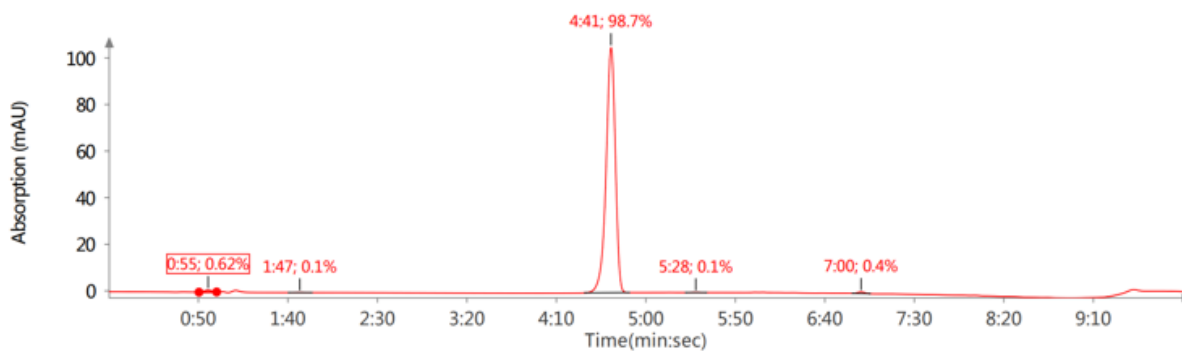
$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 167.0, 165.7, 156.4, 138.9, 130.9, 129.0 (2C), 127.4, 126.9, 126.5, 122.2 (2C), 121.7, 117.7, 58.2, 51.4, 48.5, 34.4 ppm



**Figure S76.**  $^{13}\text{C}$  NMR spectrum of compound 9d.

HPLC:  $t_r$  = 4.41 min (98.7 % at 254 nm)

VWD: Signal A, 254 nm



**Figure S77.** HPLC chromatogram of compound 9d.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.28 (s, 1H, Ar-NH-COR), 8.36 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.84 – 7.80 (m, 2H, 2  $\times$  Ar- $H$ ), 7.50 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.43 – 7.38 (m, 2H, 2  $\times$  Ar- $H$ ), 4.13 – 4.05 (m, 2H,  $\text{CH}_2\text{-NH}_2$ ), 3.19 (td,  $J_1$  = 12.7 Hz,  $J_2$  = 2.6 Hz, 2H,  $\text{CH-CH}_2\text{-NH}_2$ ), 2.47 – 2.44 (m, 2H, 2  $\times$  piperidine- $H$ ), 1.87 – 1.80 (m, 2H, 2  $\times$  piperidine- $H$ ), 1.59 – 1.40 (m, 3H, 3  $\times$  piperidine- $H$ ), 1.26 – 1.12 ppm (m, 2H, 2  $\times$  piperidine- $H$ )

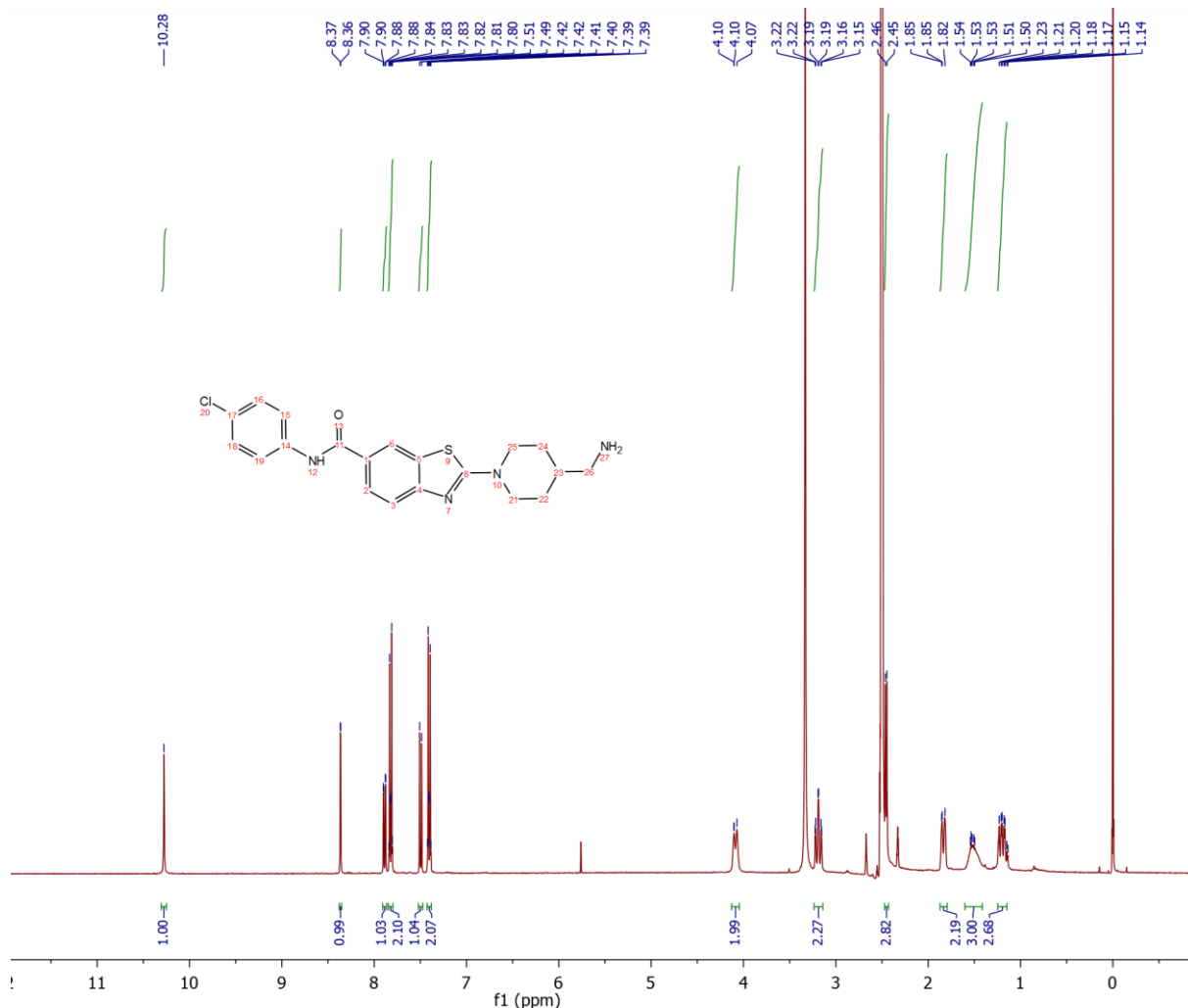
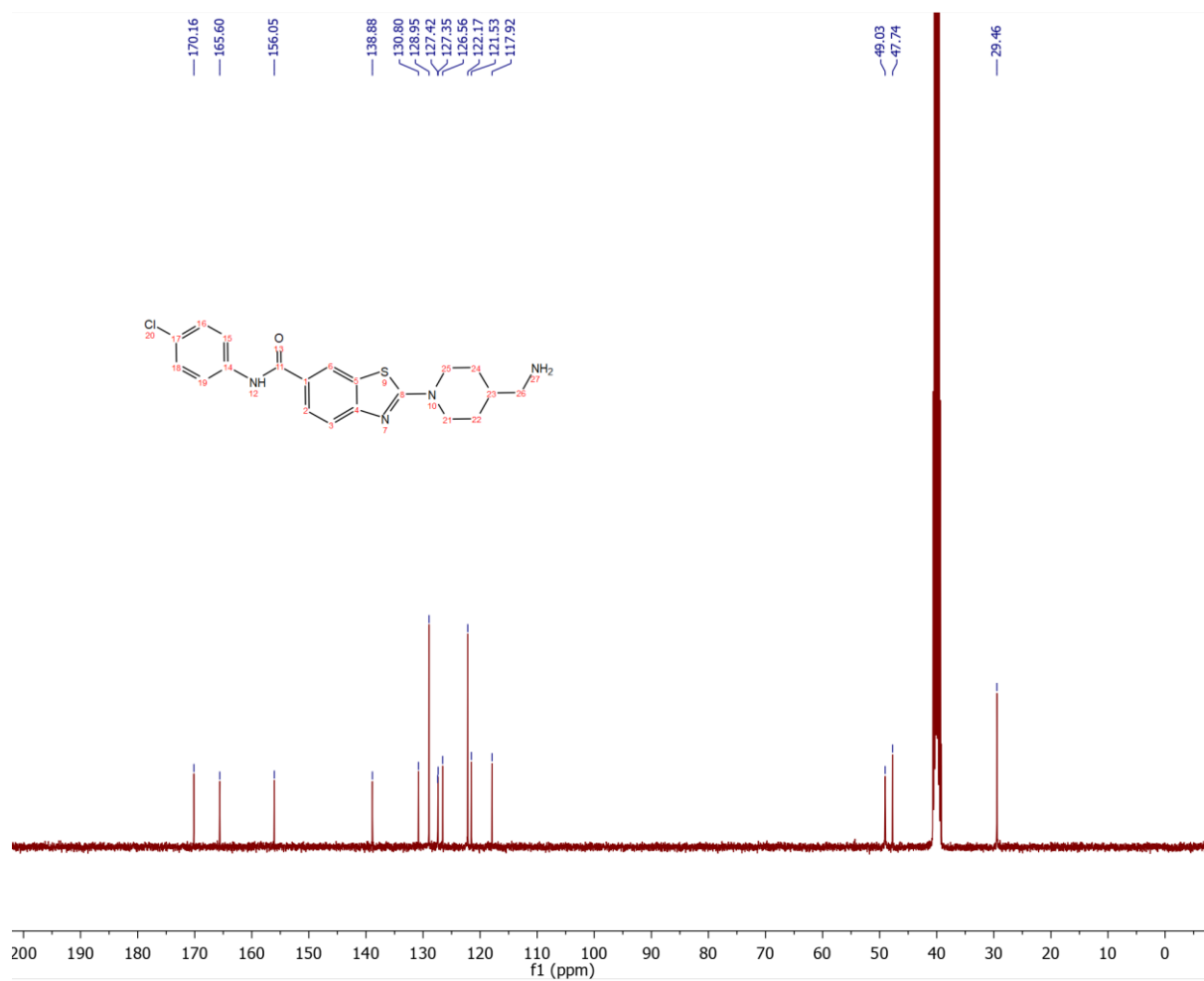


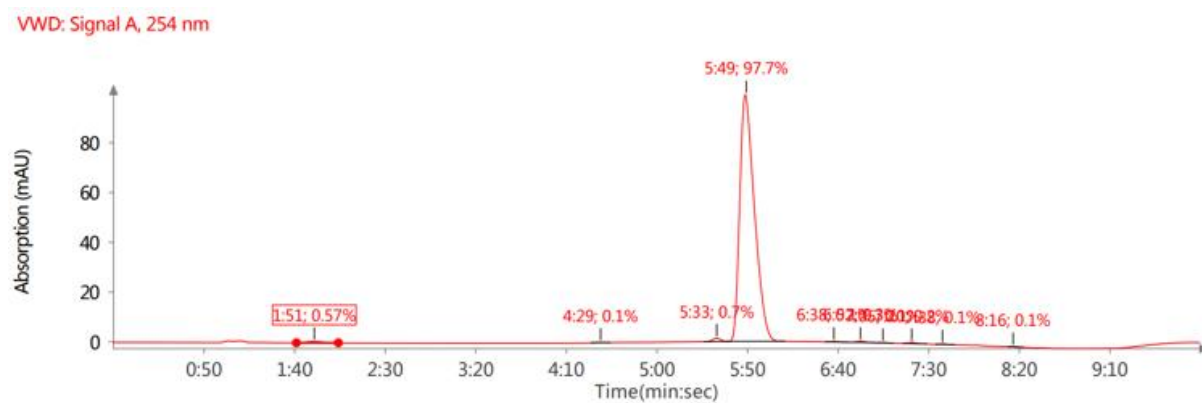
Figure S78.  $^1\text{H}$  NMR spectrum of compound 9e.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.2, 165.6, 156.1, 138.9, 130.8, 129.0 (2C), 127.4, 127.4, 126.6, 122.2 (2C), 121.5, 117.9, 49.0 (2C), 47.7, 29.5 ppm (3C)



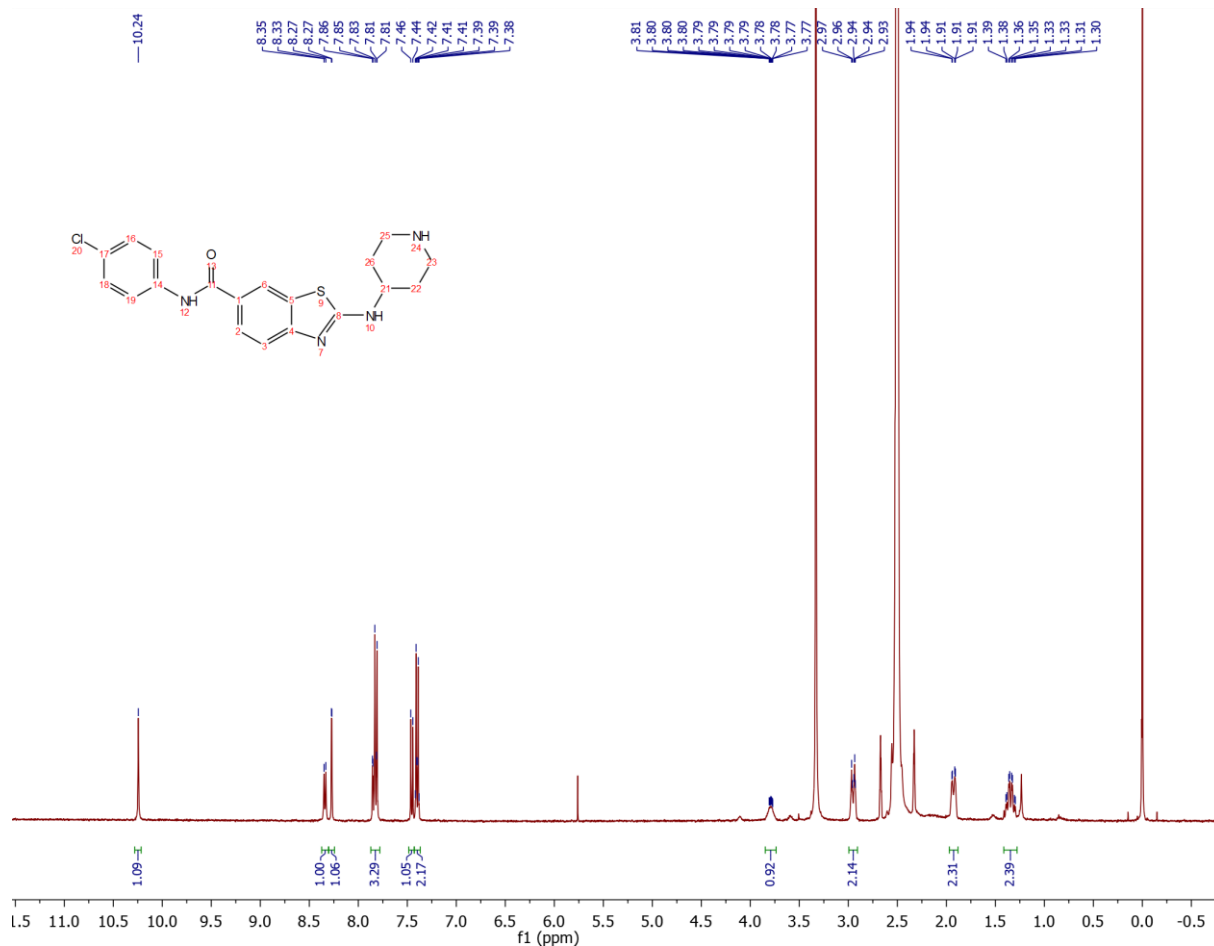
**Figure S79.**  $^{13}\text{C}$  NMR spectrum of compound 9e.

HPLC:  $t_r$  = 5.49 min (97.7 % at 254 nm)



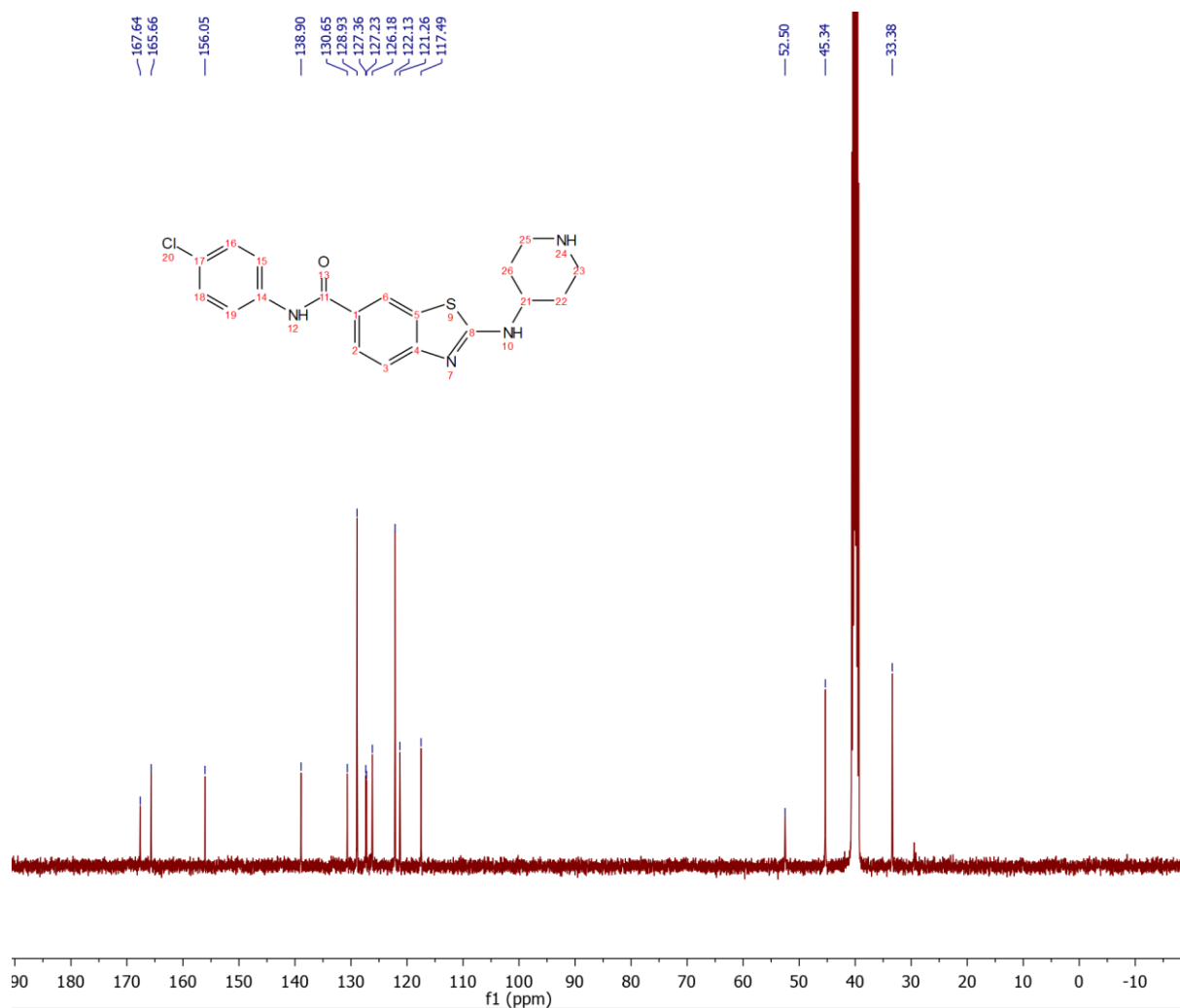
**Figure S80.** HPLC chromatogram of compound 9e.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.24 (s, 1H, Ar-NH-COR), 8.34 (d,  $J$  = 7.3 Hz, 1H, Ar-NH-CH), 8.27 (d,  $J$  = 1.7 Hz, 1H, Ar-H), 7.87 – 7.79 (m, 3H, 3  $\times$  Ar-H), 7.45 (d,  $J$  = 8.4 Hz, 1H, Ar-H), 7.42 – 7.37 (m, 2H, 2  $\times$  Ar-H), 3.82 – 3.76 (m, 1H, piperidine-H), 2.99 – 2.90 (m, 2H, 2  $\times$  piperidine-H), 1.98 – 1.88 (m, 2H, 2  $\times$  piperidine-H), 1.34 ppm (ddd,  $J_1$  = 14.9 Hz,  $J_2$  = 11.7 Hz,  $J_3$  = 3.8 Hz, 2H, 2  $\times$  piperidine-H), not visible (2  $\times$  piperidine-H and NH)



**Figure S81.**  $^1\text{H}$ NMR spectrum of compound **9f**.

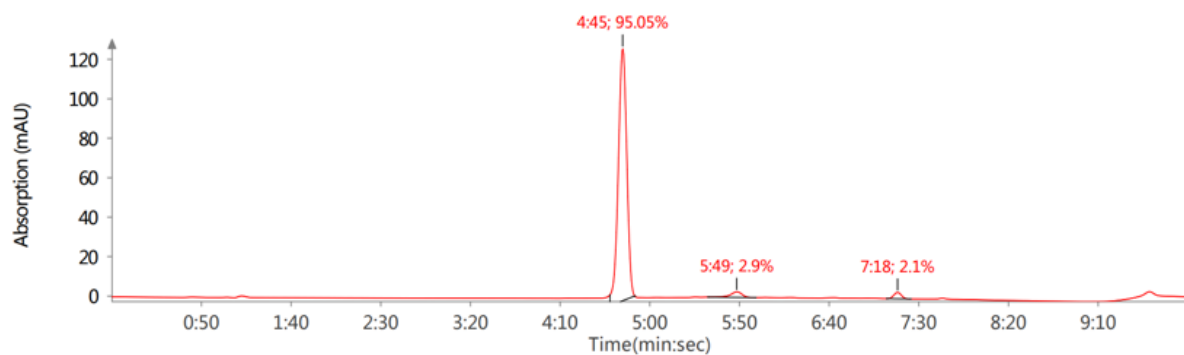
$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 167.6, 165.7, 156.1, 138.9, 130.7, 128.9 (2C), 127.4, 127.2, 126.2, 122.1 (2C), 121.3, 117.5, 52.5, 45.3 (2C), 33.4 ppm (2C)



**Figure S82.**  $^{13}\text{C}$  NMR spectrum of compound 9f.

HPLC:  $t_r$  = 4.45 min (95.1 % at 254 nm)

VWD: Signal A, 254 nm



**Figure S83.** HPLC chromatogram of compound 9f.



$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.27 (s, 1H, Ar-NH-COR), 8.39 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.84 – 7.79 (m, 2H, 2  $\times$  Ar- $H$ ), 7.52 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.43 – 7.37 (m, 2H, 2  $\times$  Ar- $H$ ), 3.69 – 3.40 (m, 4H, 2  $\times$   $\text{CH}_2$ ), 2.94 – 2.86 (m, 2H,  $\text{CH}_2$ ), 2.81 – 2.70 (m, 2H,  $\text{CH}_2$ ), 2.07 – 1.97 (m, 2H,  $\text{CH}_2$ ), 1.81 – 1.68 ppm (m, 2H,  $\text{CH}_2$ ), not visible (NH)

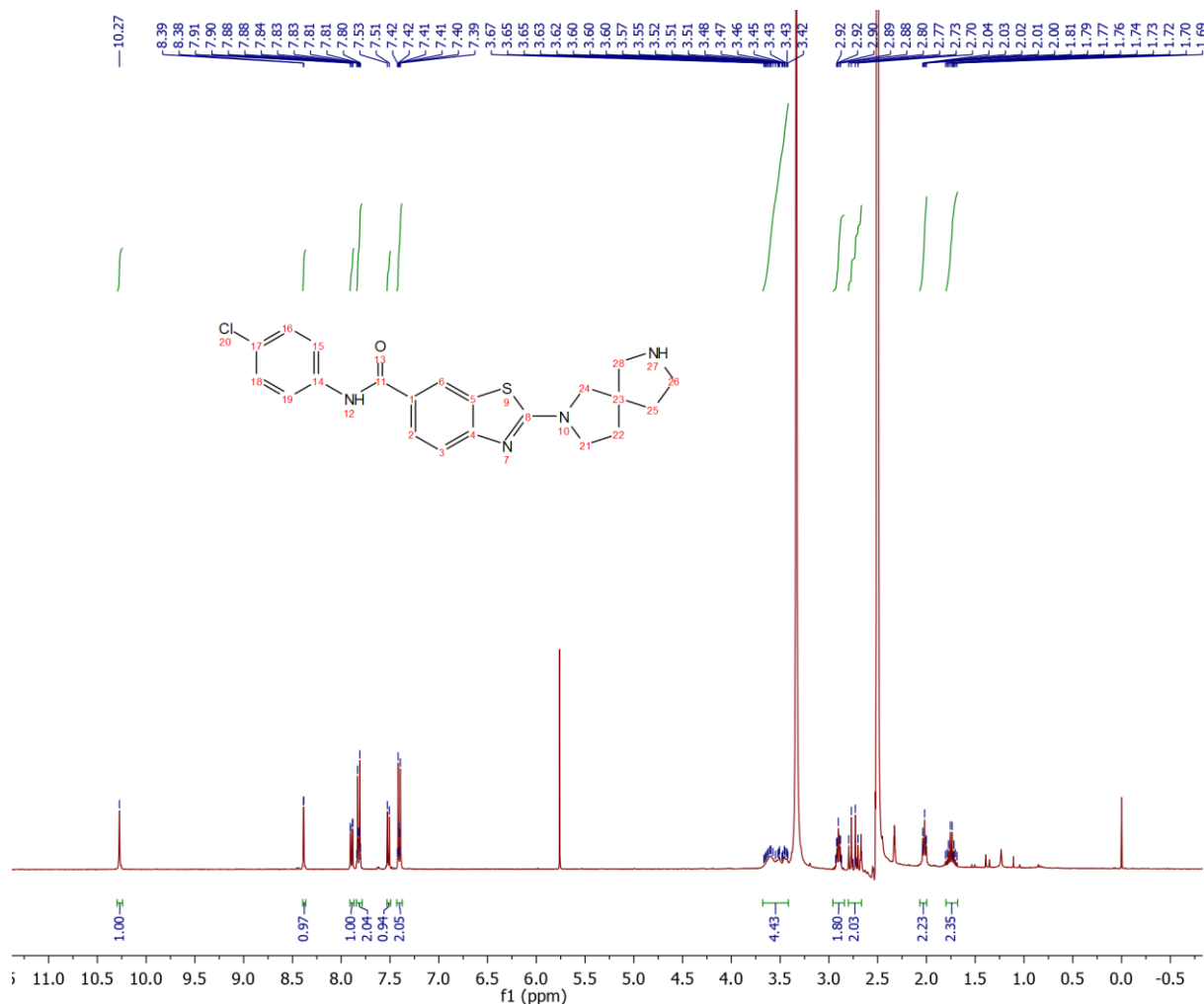
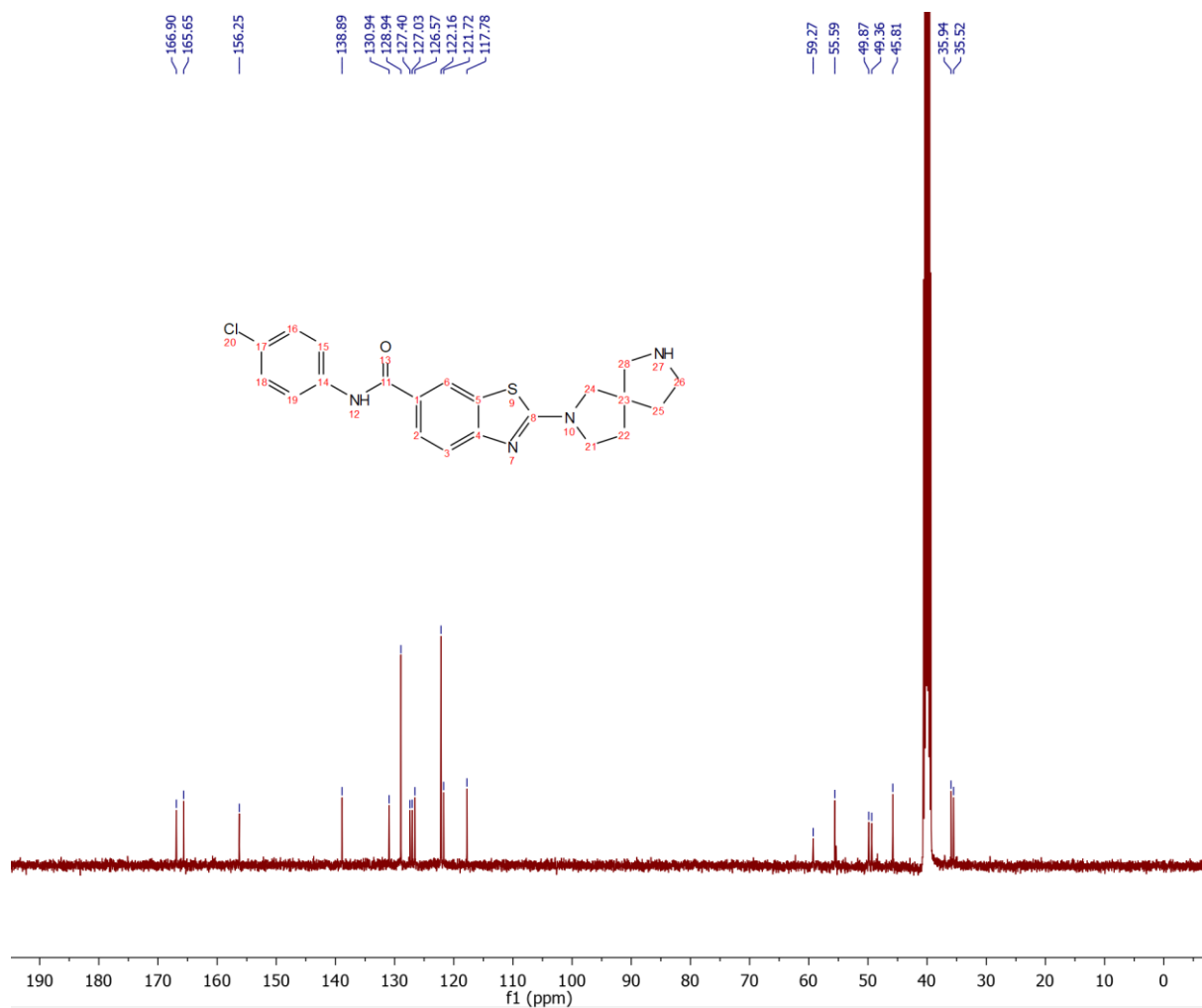


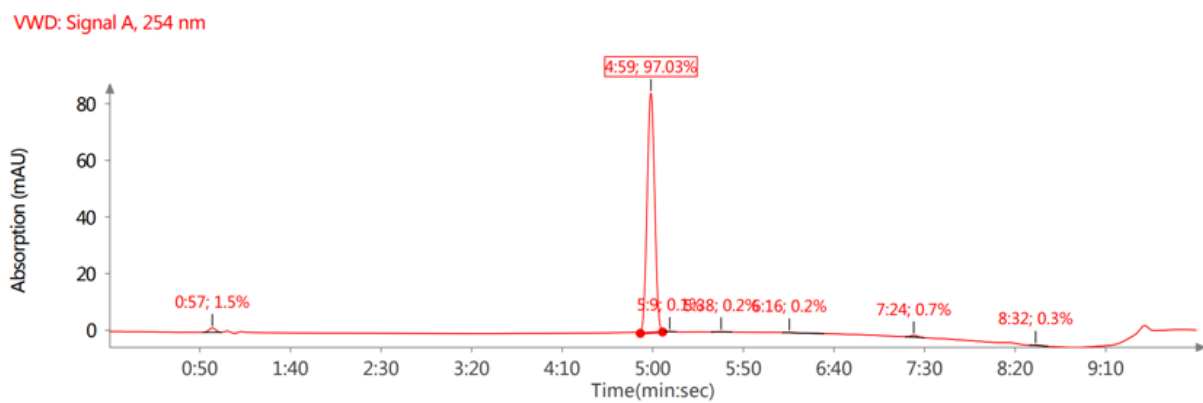
Figure S84.  $^1\text{H}$  NMR spectrum of compound 9g.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 166.9, 165.7, 156.3, 138.9, 130.9, 128.9 (2C), 127.4, 127.0, 126.6, 122.2 (2C), 121.7, 117.8, 59.3, 55.6, 49.9, 49.4, 45.8, 35.9, 35.5 ppm



**Figure S85.**  $^{13}\text{C}$  NMR spectrum of compound 9g.

HPLC:  $t_r$  = 4.59 min (97.0 % at 254 nm)



**Figure S86.** HPLC chromatogram of compound 9g.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.28 (s, 1H, Ar-NH-COR), 8.38 (d,  $J$  = 1.9 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.9 Hz, 1H, Ar- $H_5$ ), 7.85 – 7.79 (m, 2H, 2  $\times$  Ar- $H$ ), 7.53 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.43 – 7.38 (m, 2H, 2  $\times$  Ar- $H$ ), 3.82 – 3.75 (m, 2H, 2  $\times$  CH), 3.39 – 3.37 (m, 2H, 2  $\times$  CH), 2.96 – 2.88 (m, 4H, 4  $\times$  CH), 2.74 – 2.69 ppm (m, 2H, 2  $\times$  CH), not visible (NH)

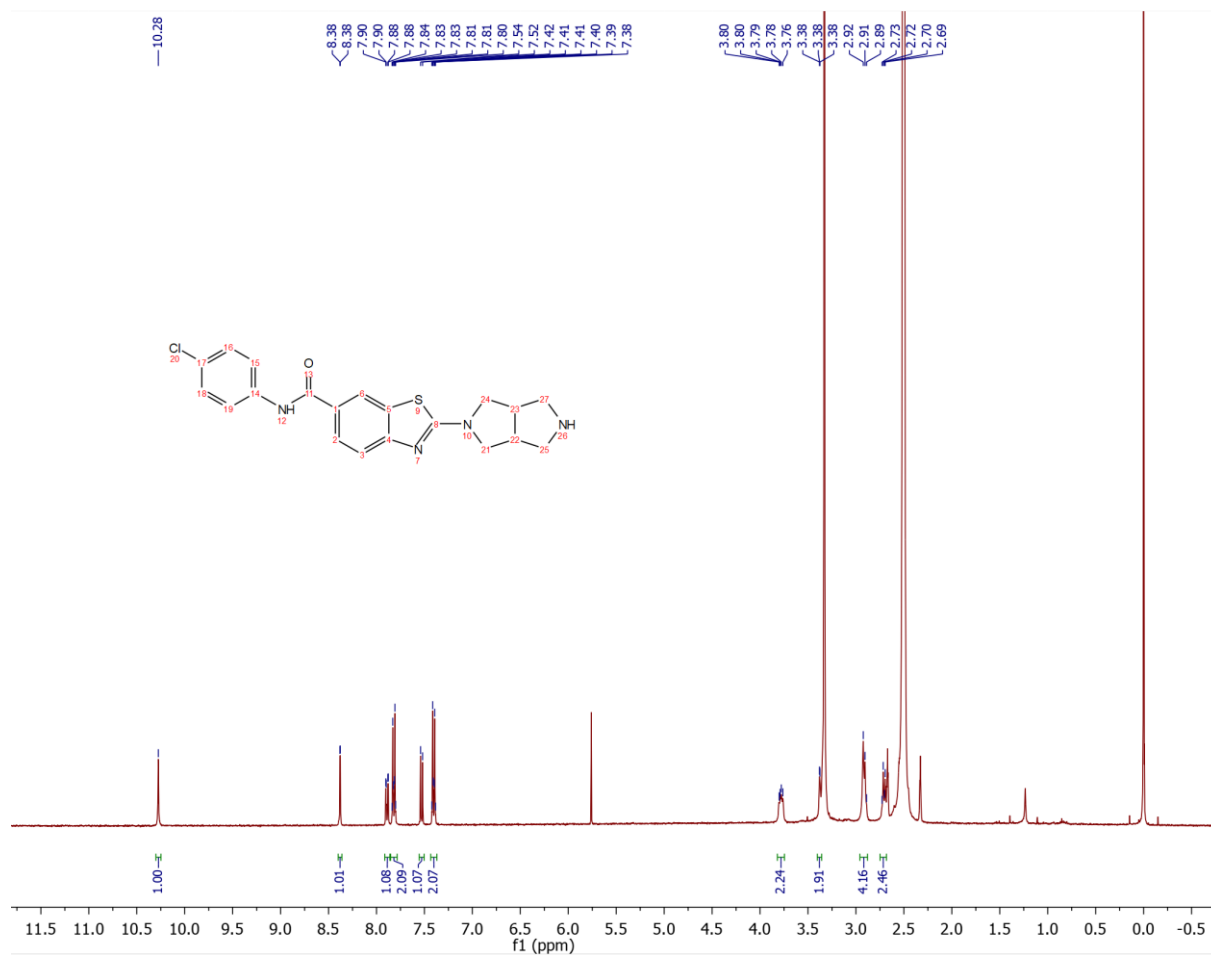


Figure S87.  $^1\text{H}$  NMR spectrum of compound 9h.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 166.6, 165.7, 156.2, 138.9, 131.1, 128.9 (2C), 127.4, 127.1, 126.5, 122.2 (2C), 121.7, 117.9, 55.3 (2C), 53.2 (2C), 43.8 ppm (2C)

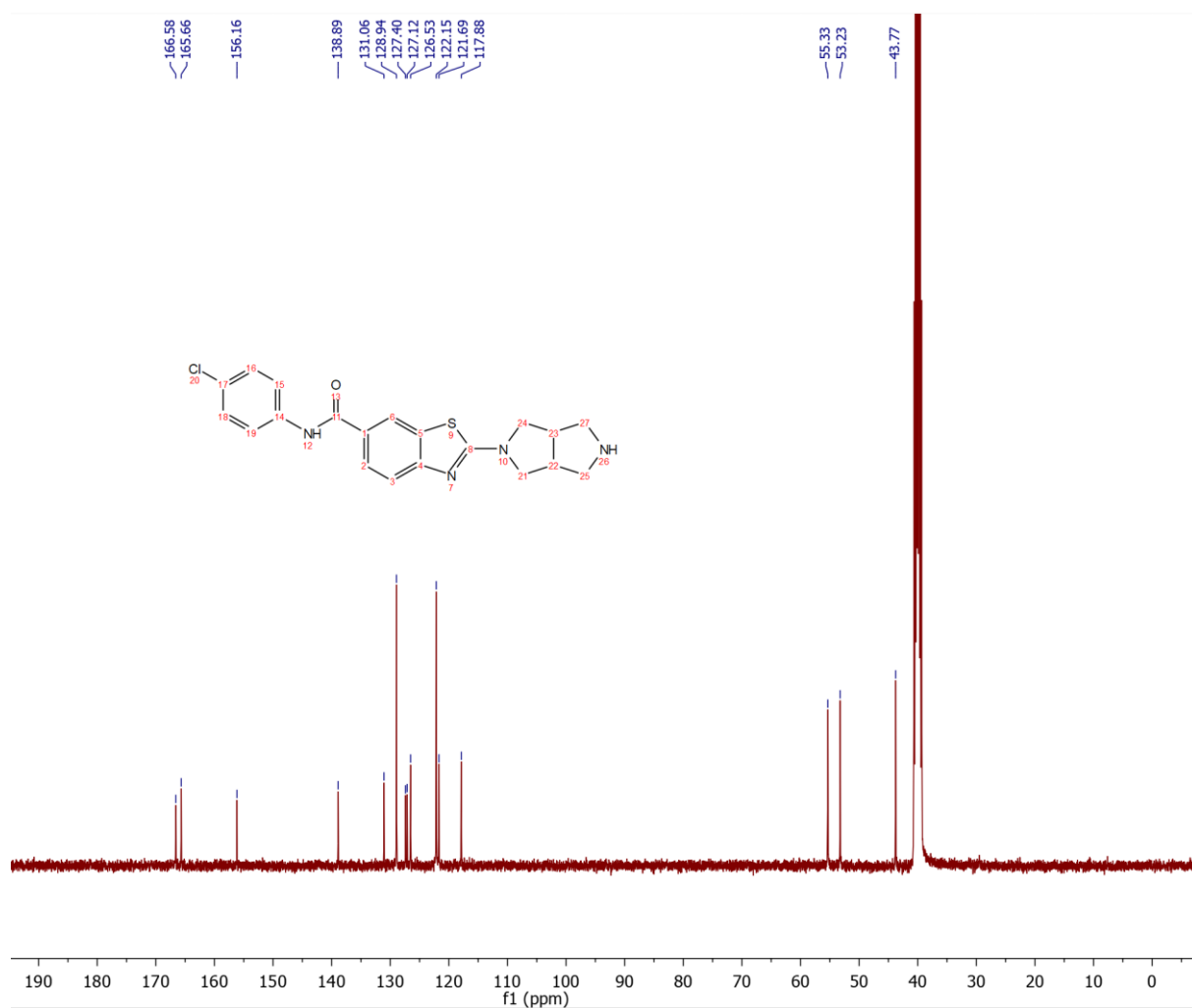


Figure S88.  $^{13}\text{C}$  NMR spectrum of compound 9h.

HPLC:  $t_r$  = 4.47 min (98.8 % at 254 nm)

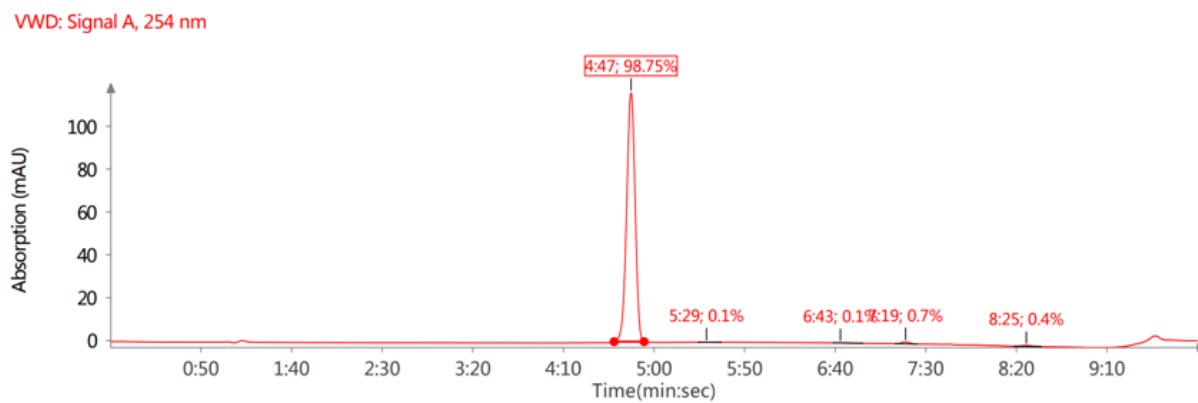
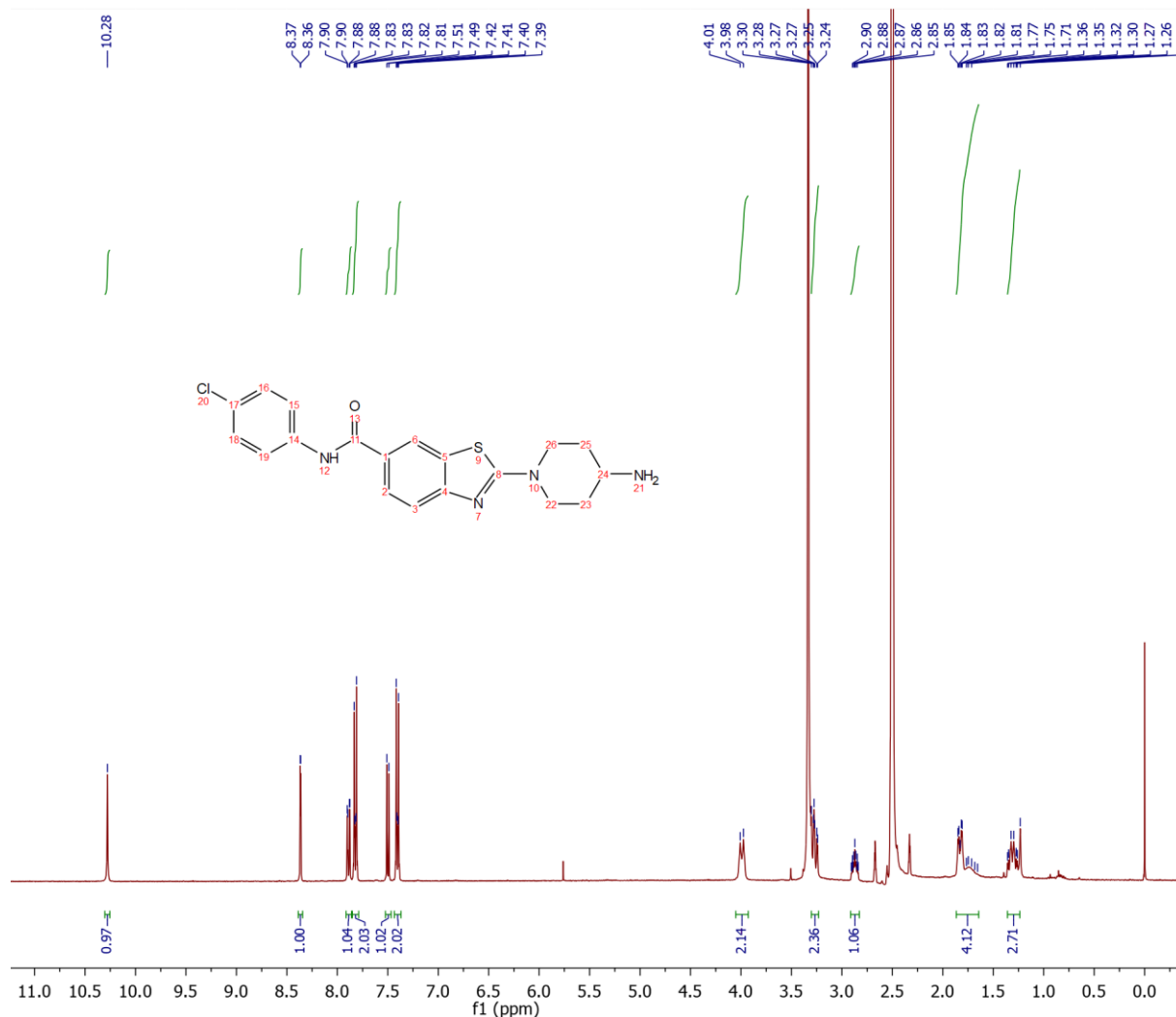


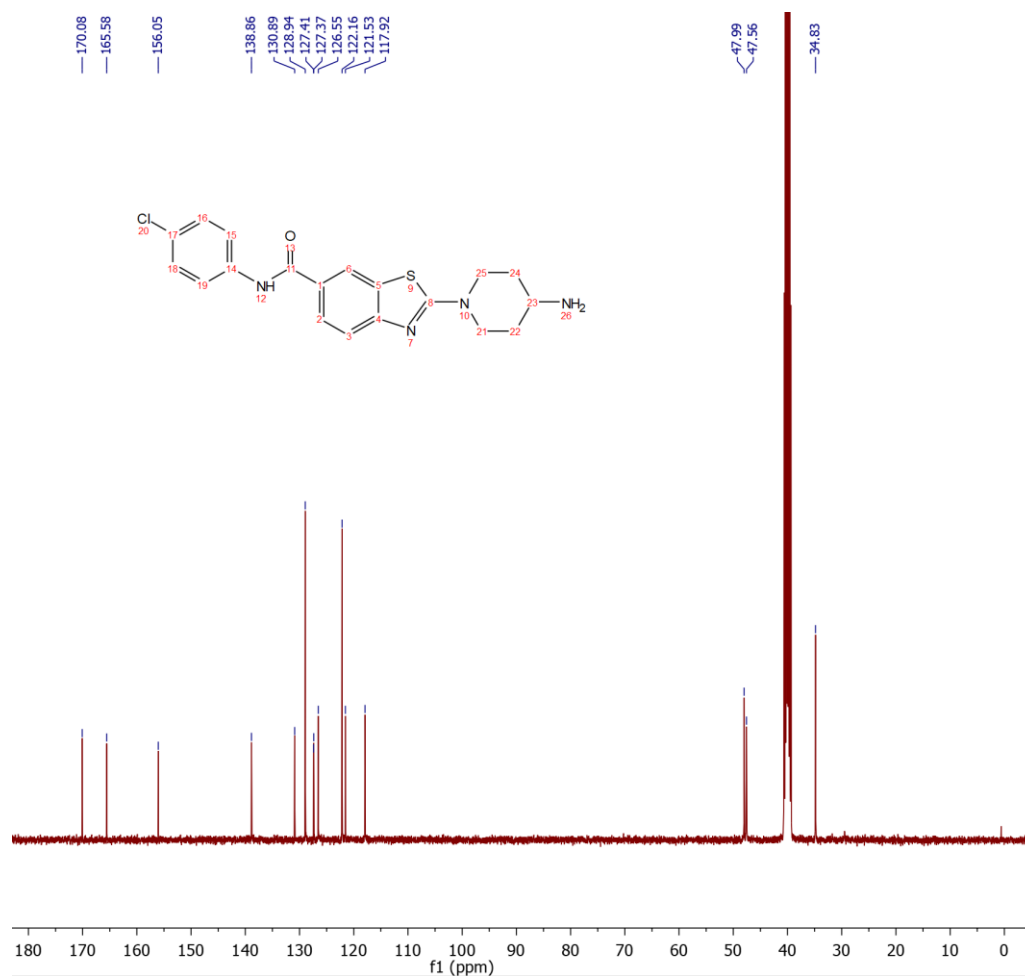
Figure S89. HPLC chromatogram of compound 9h.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 10.28 (s, 1H, Ar-NH-COR), 8.37 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.85 – 7.79 (m, 2H, 2  $\times$  Ar- $H$ ), 7.50 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.43 – 7.37 (m, 2H, 2  $\times$  Ar- $H$ ), 3.99 (d,  $J$  = 13.1 Hz, 2H, CH- $\text{NH}_2$ ), 3.30 – 3.23 (m, 2H, 2  $\times$  piperidine- $H$ ), 2.91 – 2.83 (m, 1H, piperidine- $H$ ), 1.87 – 1.64 (m, 4H, 4  $\times$  piperidine- $H$ ), 1.37 – 1.23 ppm (m, 2H, 2  $\times$  piperidine- $H$ )



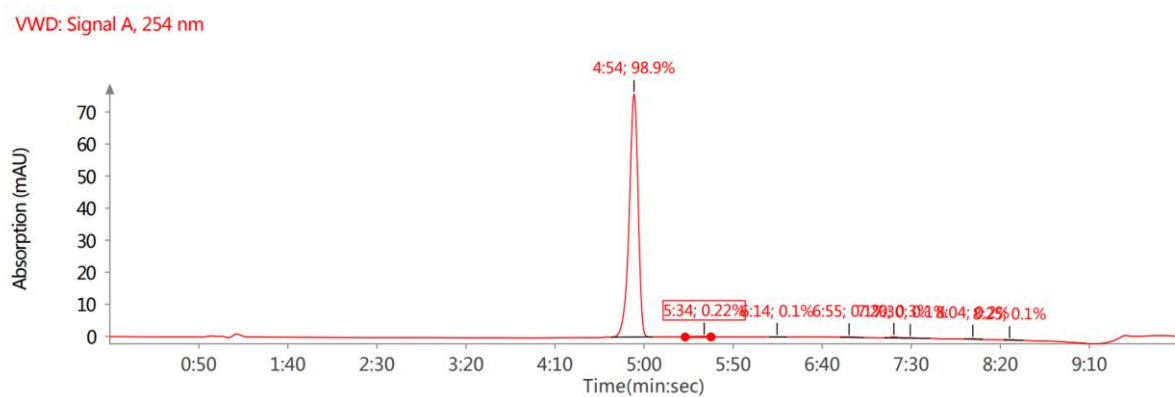
**Figure S90.**  $^1\text{H}$  NMR spectrum of compound 9i.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.1, 165.6, 156.1, 138.9, 130.9, 128.9 (2C), 127.4, 127.4, 126.6, 122.2 (2C), 121.5, 117.9, 48.0, 47.6 (2C), 34.8 ppm (2C)



**Figure S91.**  $^{13}\text{C}$ NMR spectrum of compound **9i**.

HPLC:  $t_r$  = 4.54 min (98.9 % at 254 nm)



**Figure S92.** HPLC chromatogram of compound **9i**.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.28 (s, 1H, Ar-NH-COR), 8.37 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 7.89 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.85 – 7.78 (m, 2H, 2  $\times$  Ar- $H$ ), 7.50 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.44 – 7.37 (m, 2H, 2  $\times$  Ar- $H$ ), 3.93 – 4.00 (m, 2H, 2  $\times$  piperidine- $H$ ), 3.32 – 3.26 (m, 2H, 2  $\times$  piperidine- $H$ ), 2.63 – 2.54 (m, 1H, piperidine- $H$ ), 2.30 (s, 3H, NH- $\text{CH}_3$ ), 1.97 – 1.86 (m, 2H, 2  $\times$  piperidine- $H$ ), 1.83 – 1.67 (m, 1H, NH), 1.39 – 1.28 ppm (m, 2H, 2  $\times$  piperidine- $H$ )

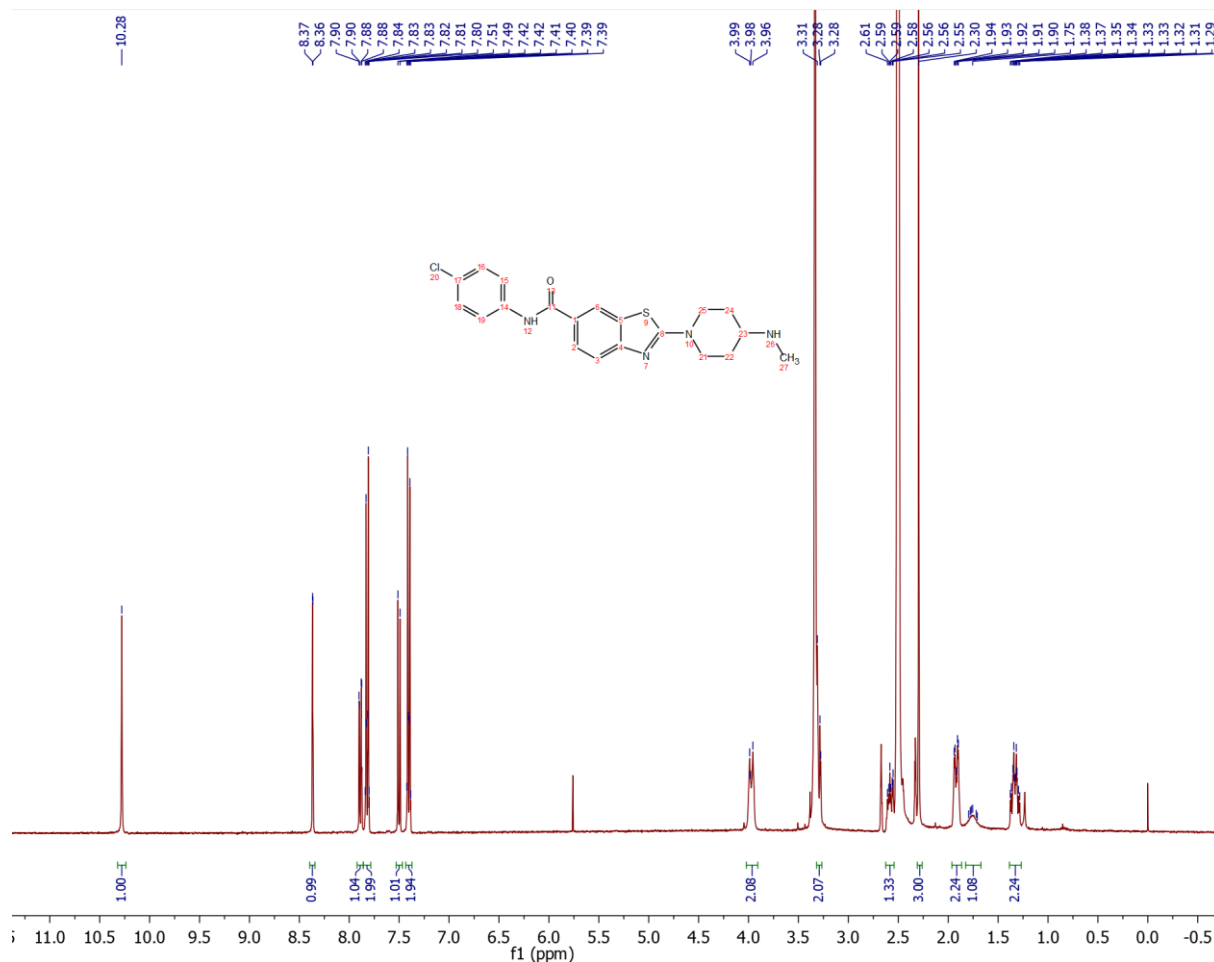
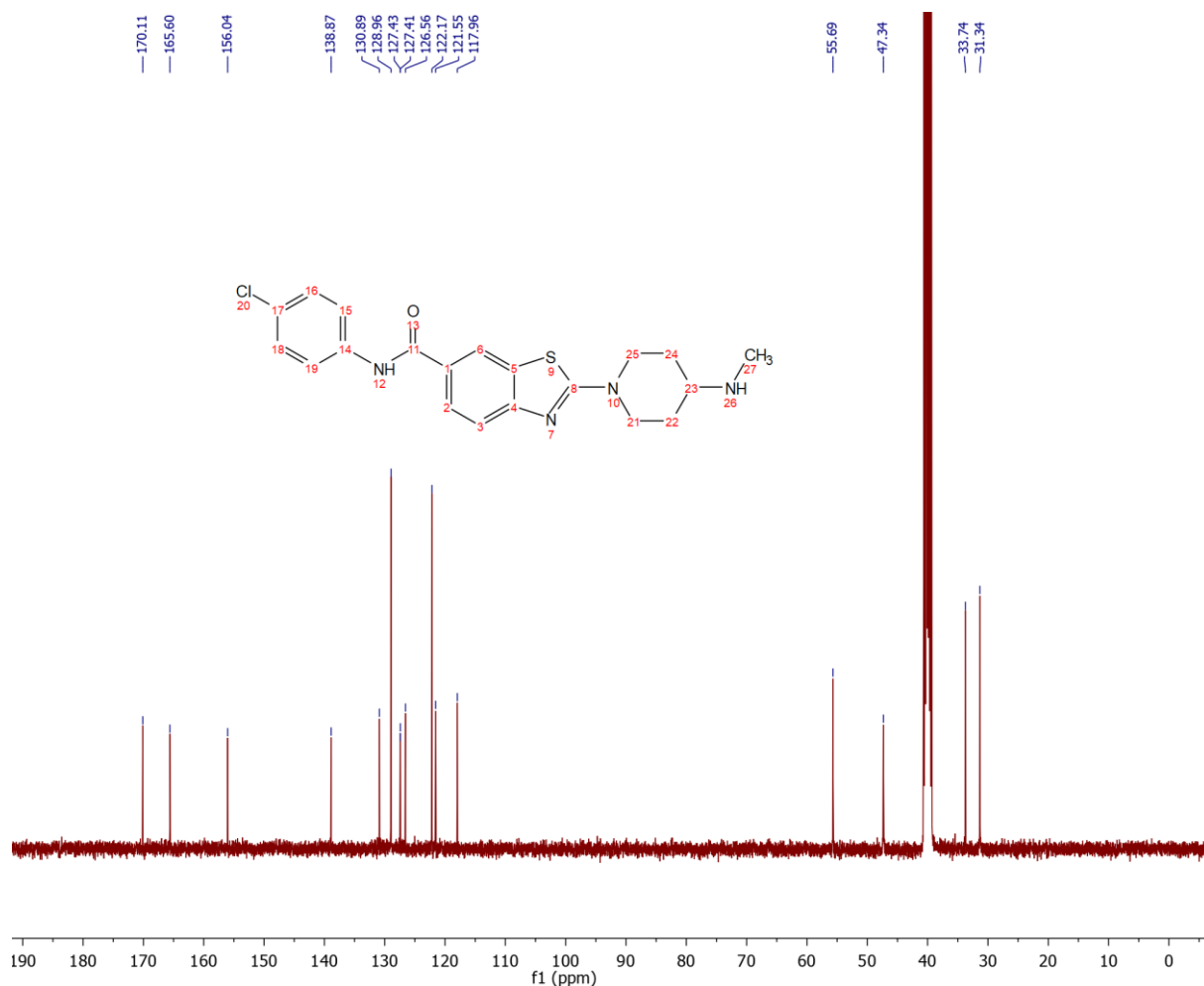


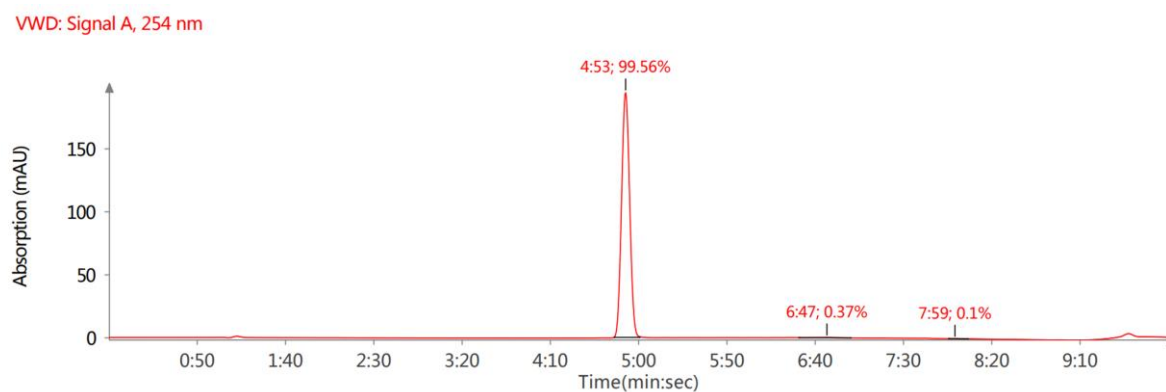
Figure S93.  $^1\text{H}$ NMR spectrum of compound 9j.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.1, 165.6, 156.0, 138.9, 130.9, 128.9 (2C), 127.4, 127.4, 126.6, 122.2 (2C), 121.5, 118.0, 55.7, 47.3 (2C), 33.7, 31.3 ppm (2C)



**Figure S94.**  $^{13}\text{C}$ NMR spectrum of compound 9j.

HPLC:  $t_r$  = 4.53 min (99.6 % at 254 nm)



**Figure S95.** HPLC chromatogram of compound 9j.



$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 10.29 (s, 1H, Ar-NH-COR), 8.38 (d,  $J$  = 1.9 Hz, 1H, Ar- $H_7$ ), 7.90 (dd,  $J_1$  = 8.5 Hz,  $J_2$  = 1.9 Hz, 1H, Ar- $H_5$ ), 7.88 – 7.78 (m, 2H, 2  $\times$  Ar- $H$ ), 7.51 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 7.44 – 7.37 (m, 2H, 2  $\times$  Ar- $H$ ), 4.08 (d,  $J$  = 13 Hz, 2H, 2  $\times$  piperidine- $H$ ), 3.29 – 3.16 (m, 2  $\times$  piperidine- $H$ ), 2.20 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.92 – 1.84 (m, 2H, 2  $\times$  piperidine- $H$ ), 1.55 – 1.42 ppm (m, 2H, 2  $\times$  piperidine- $H$ ), covered with solvent (1H, piperidine- $H$ )

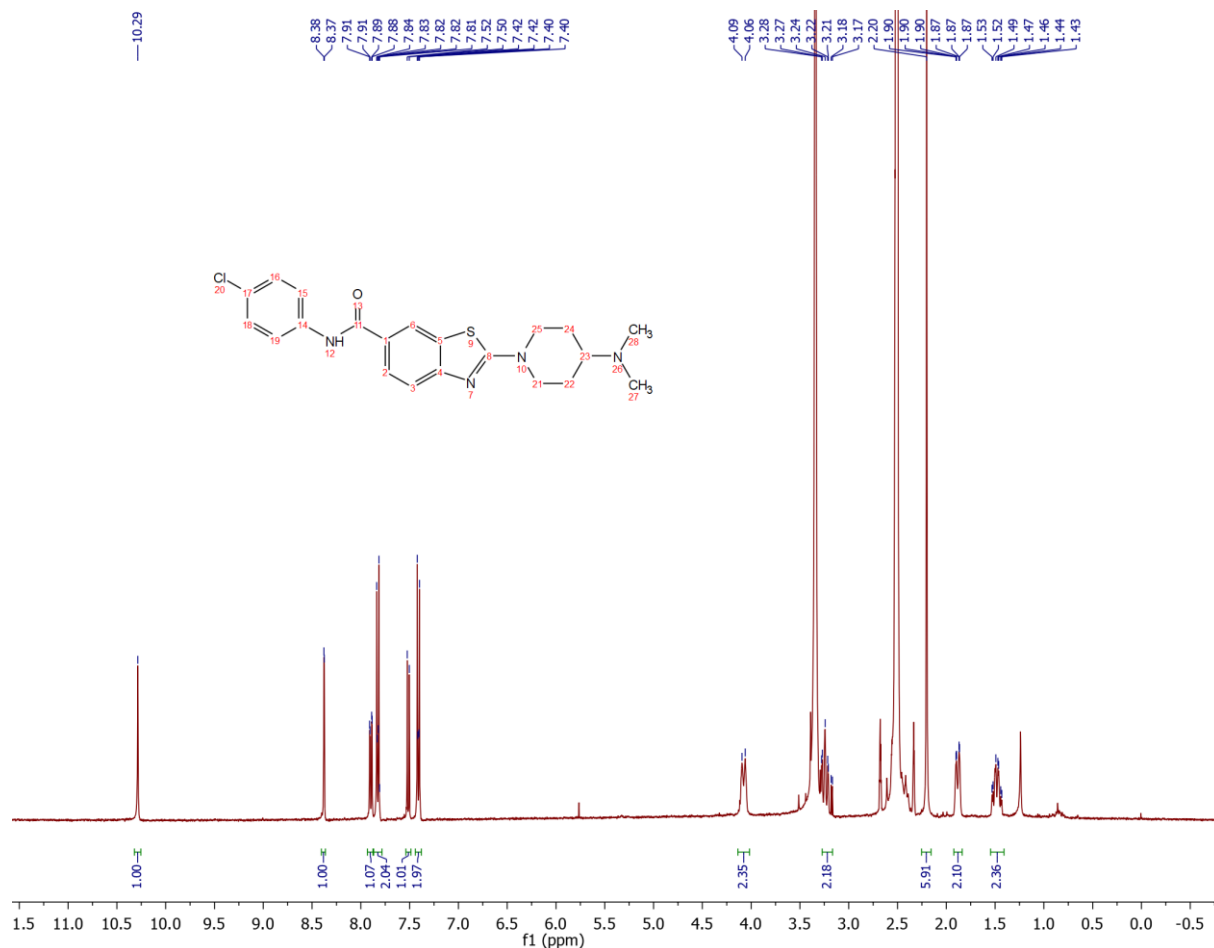
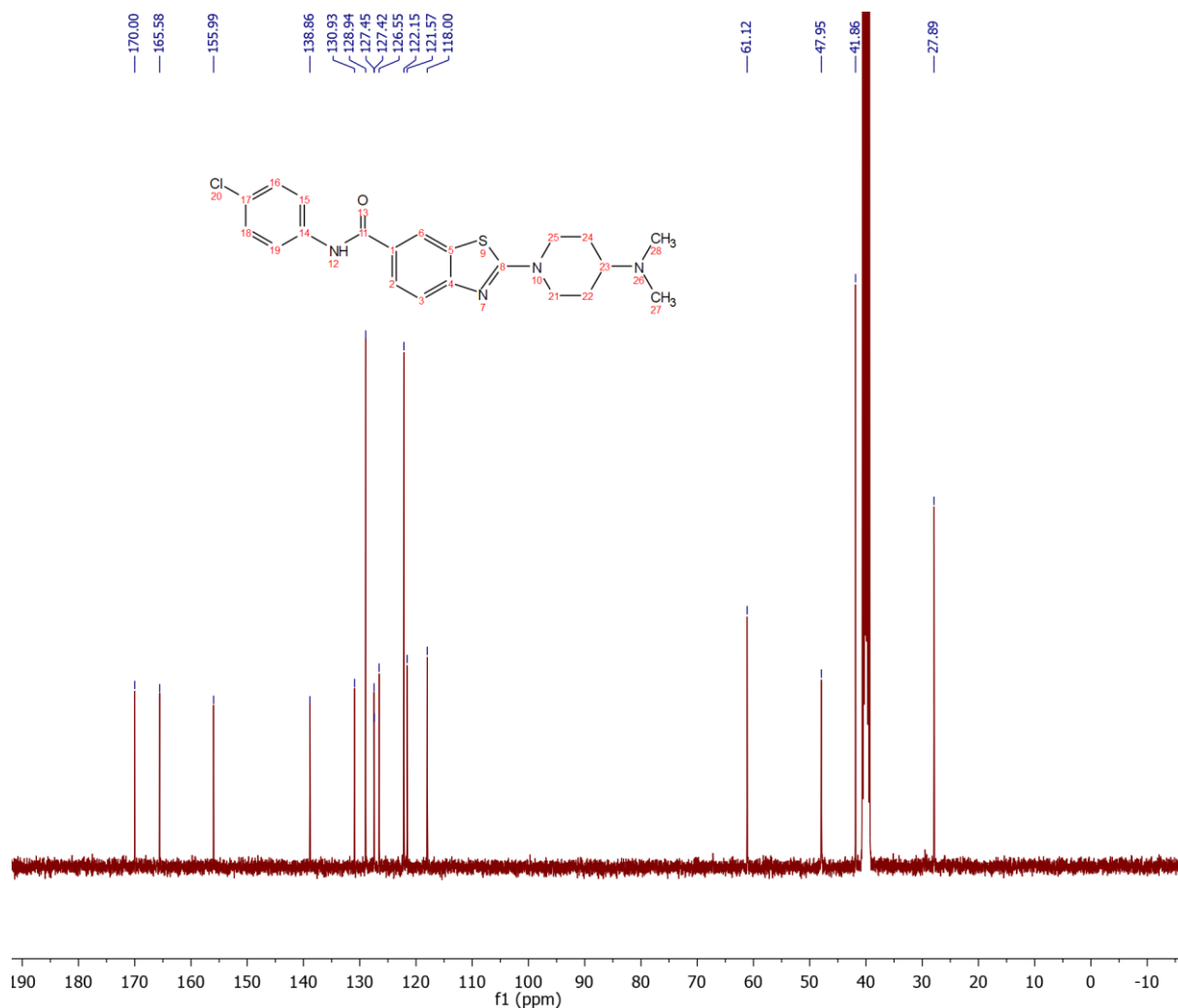


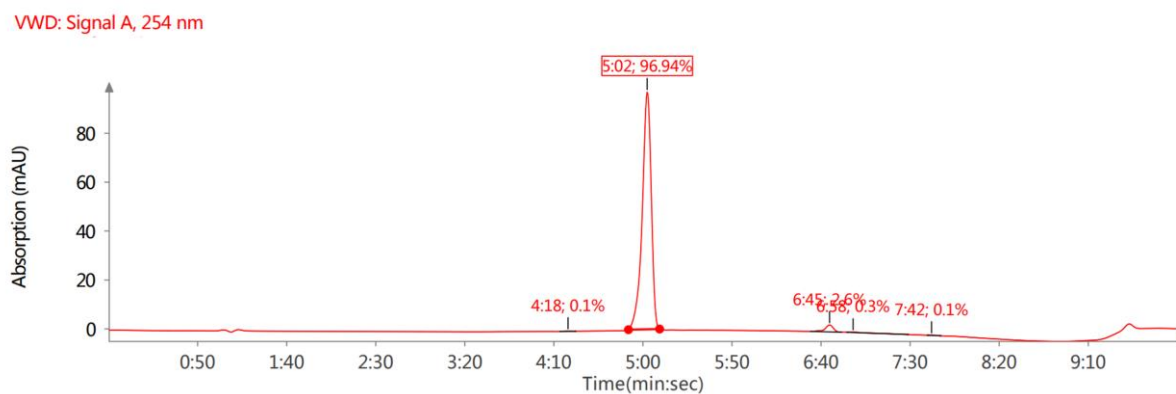
Figure S96.  $^1\text{H}$  NMR spectrum of compound 10.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.0, 165.6, 156.0, 138.9, 130.9, 128.9 (2C), 127.5, 127.4, 126.6, 122.2 (2C), 121.6, 118.0, 61.1, 48.0 (2C), 41.9 (2C), 27.9 ppm (2C)



**Figure S97.**  $^{13}\text{C}$  NMR spectrum of compound 10.

HPLC:  $t_r$  = 5.02 min (96.9 % at 254 nm)



**Figure S98.** HPLC chromatogram of compound 10.

$^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $25^\circ\text{C}$ , TMS):  $\delta$  = 10.47 (s, 1H, Ar-NH-COR), 8.40 (d,  $J$  = 1.8 Hz, 1H, Ar- $H_7$ ), 8.19 (d,  $J$  = 2.4 Hz, 1H, Ar- $H_{20}$ ), 7.91 (dd,  $J_1$  = 8.5,  $J_2$  = 1.8 Hz, 1H, Ar- $H_5$ ), 7.79 (dd,  $J$  = 8.9, 2.4 Hz, 1H, Ar- $H_{24}$ ), 7.61 (d,  $J$  = 8.9 Hz, 1H, Ar- $H_{23}$ ), 7.50 (d,  $J$  = 8.5 Hz, 1H, Ar- $H_4$ ), 3.99 (d,  $J$  = 13.2 Hz, 2H, CH- $\text{NH}_2$ ), 3.33 – 3.20 (m, 2H, 2  $\times$  piperidin- $H$ ), 2.91 – 2.83 (m, 1H, CH- $\text{NH}_2$ ), 1.88 – 1.78 (m, 2H, 2  $\times$  piperidin- $H$ ), 1.88 – 1.58 (m, 4H, 4  $\times$  piperidin- $H$ ), 1.37 – 1.25 ppm (m, 2H, 2  $\times$  piperidin- $H$ )

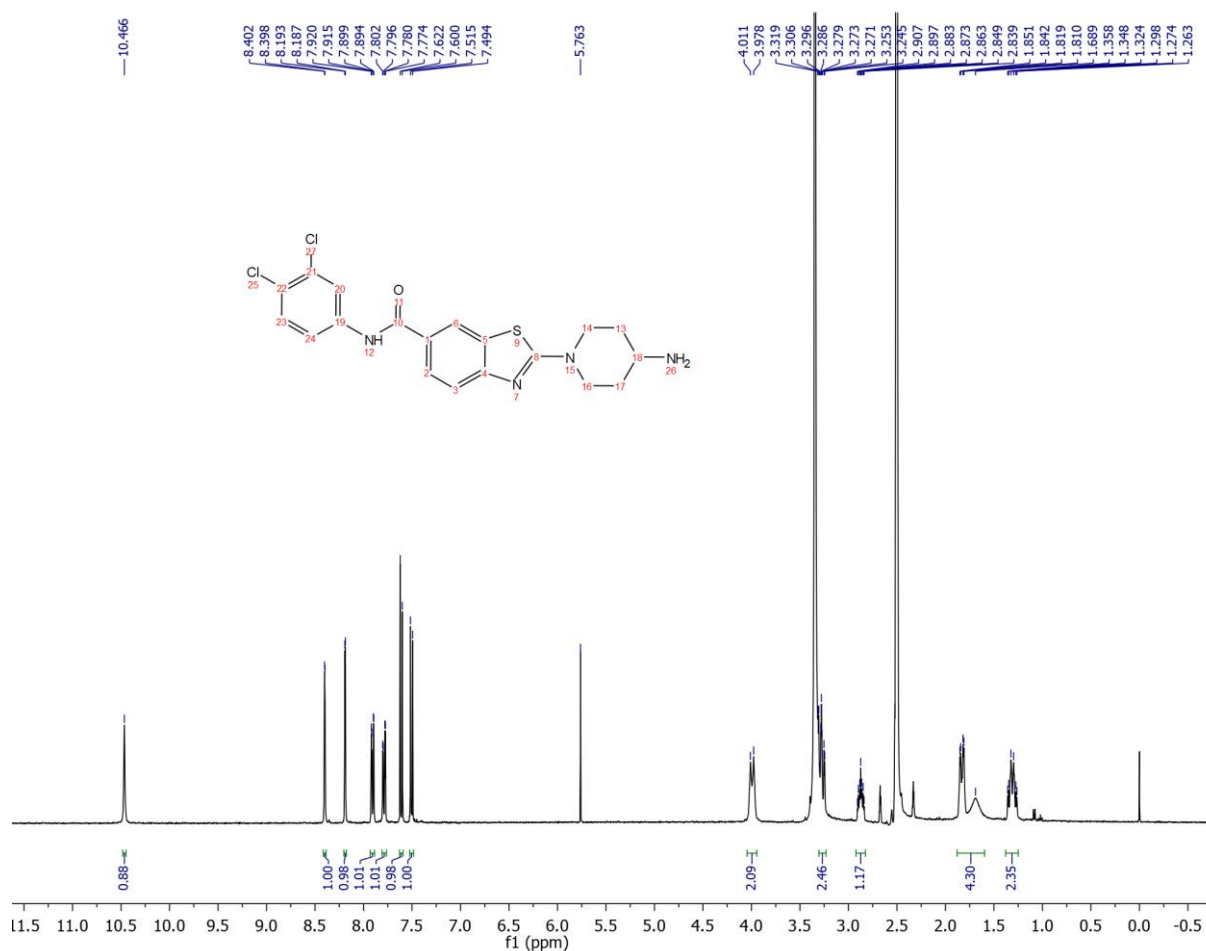
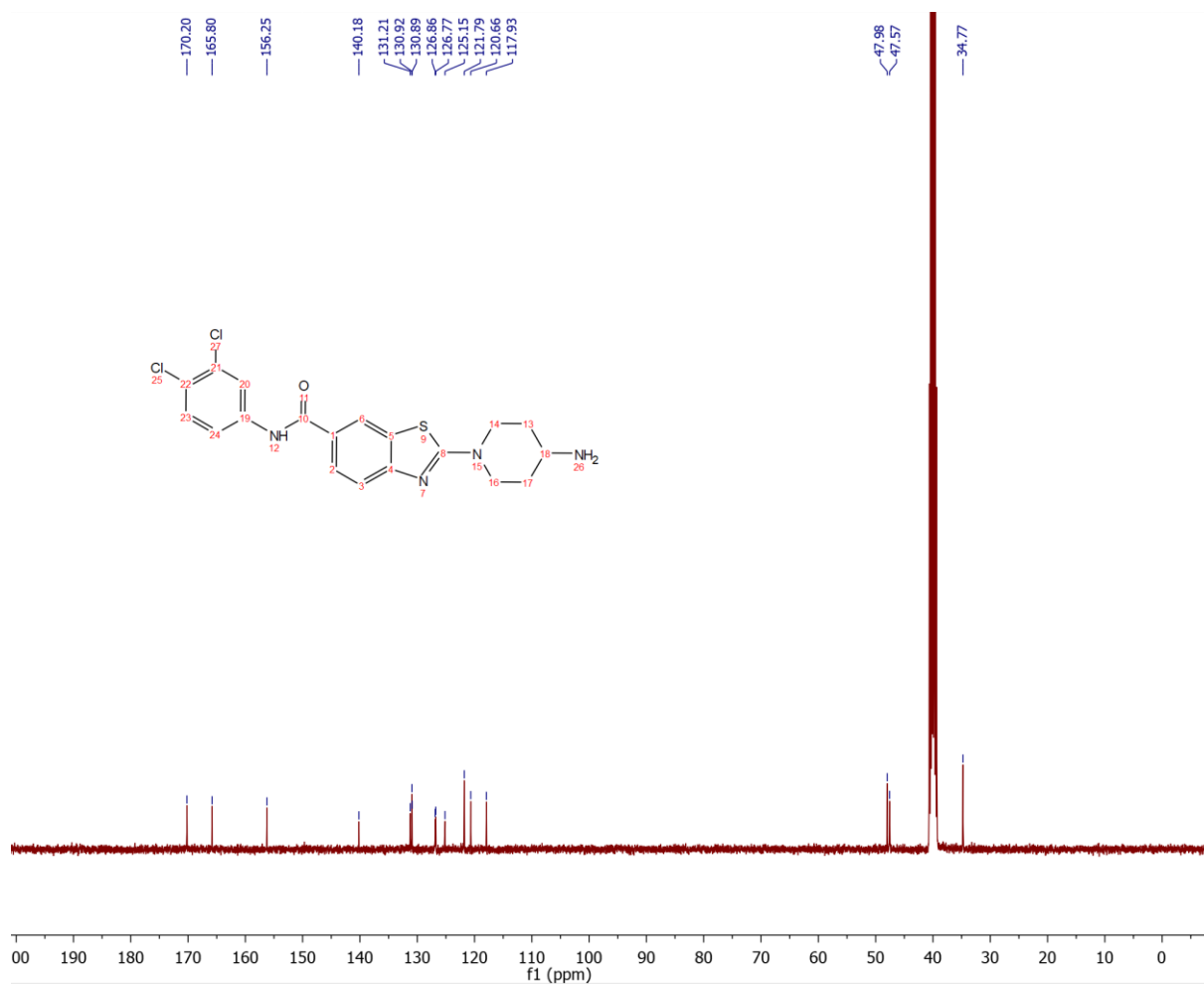


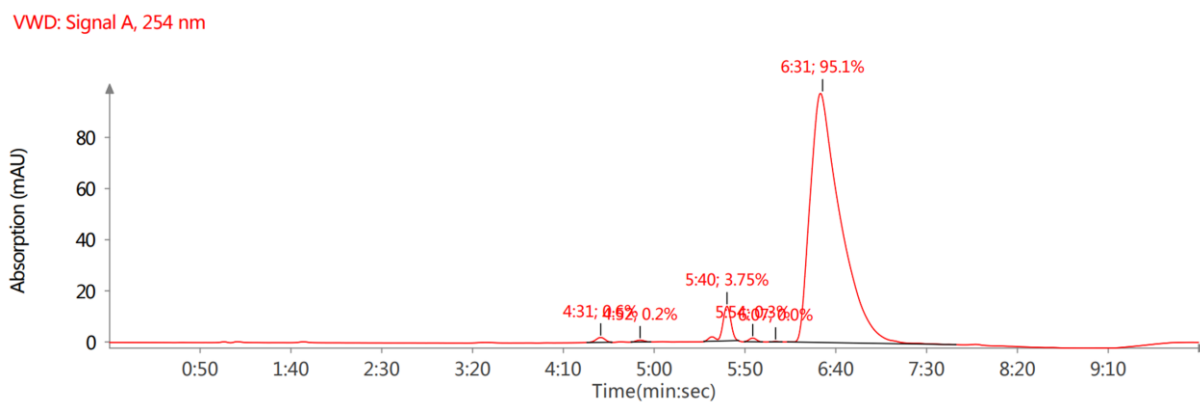
Figure S99.  $^1\text{H}$  NMR spectrum of compound 14.

$^{13}\text{C}$  (101 MHz,  $[\text{D}_6]\text{DMSO}$ , 25°C, TMS):  $\delta$  = 170.2, 165.8, 156.3, 140.2, 131.2, 130.9 (2C), 126.9, 126.8, 125.2, 121.8 (2C), 120.7, 117.9, 48.0 (2C), 47.6 (2C), 34.8 ppm



**Figure S100.**  $^{13}\text{C}$  NMR spectrum of compound 14.

HPLC:  $t_r$  = 6.31 min (95.1 % at 254 nm)



**Figure S101.** HPLC chromatogram of compound 14.