

# Supporting information

## **Halogenated pyrrolopyrimidines with low MIC on *Staphylococcus aureus* and synergistic effects with an antimicrobial peptide**

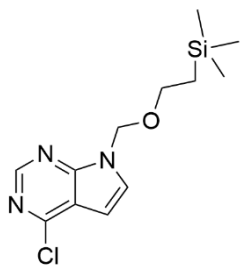
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### Contents

Synthesis of building blocks .....	2
NMR spectroscopy .....	12
Comparison of TMPK folding .....	32
References .....	32

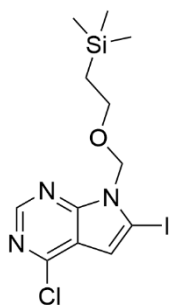
## Synthesis of building blocks

### 4-Chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-*d*]pyrimidine<sup>1</sup>



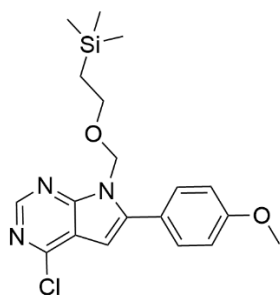
The following procedure was adapted from Reiersølmoen *et al.*<sup>2</sup> 4-Chloro-7H-pyrrolo[2,3-*d*]pyrimidine (3.06 g, 19.9 mmol) was dissolved in dry DMF (20 mL) and stirred at 0 °C under and N<sub>2</sub> atmosphere. To the mixture was added NaH (578 mg, 24.1 mmol) dissolved in dry DMF (50 mL) dropwise over 10 minutes. The solution was left to clear for 30 minutes before SEM-Cl (4.58 mL, 25.9 mmol) was added dropwise over 30 minutes. The solution was stirred for an additional 2.5 hours, and the reaction was subsequently cooled to 0 °C and quenched with H<sub>2</sub>O (500 mL). The resulting slurry was extracted with EtOAc (4 × 100 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude product was then purified twice by flash chromatography (silica-gel, EtOAc/*n*-pentane, 0:1 to 1:2), resulting in 4.06 g (14.3 mmol, 72%) of the desired product as a waxy solid. TLC (EtOAc/*n*-pentane 1:8) *R*<sub>f</sub> = 0.20; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 8.68 (s, 1H), 7.87 (d, *J* = 3.7 Hz, 1H), 6.71 (d, *J* = 3.7 Hz, 1H), 5.64 (s, 2H), 3.61 – 3.43 (m, 2H), 0.93 – 0.73 (m, 2H), -0.12 (s, 9H). The <sup>1</sup>H-NMR spectrum was in accordance with the literature<sup>1</sup>.

### 4-Chloro-6-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-*d*]pyrimidine (22)<sup>3</sup>



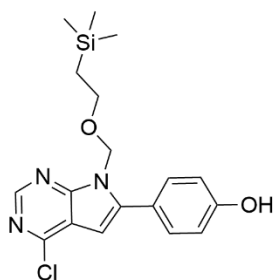
The procedure is an adaptation from Reiersølmoen *et al.*<sup>2</sup> A solution of 4-chloro-6-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-*d*]pyrimidine (3.51 g, 12.4 mmol) in dry THF (30 mL) was cooled to -78 °C and stirred under an N<sub>2</sub> atmosphere. To this was added a solution of LDA in THF (2.0 M, 9.28 mL) dropwise over 30 minutes. The solution was stirred for a further 30 minutes, before I<sub>2</sub> (3.47 g, 13.6 mmol) dissolved in THF (10 mL) was added dropwise over 30 minutes. The solution was then stirred for further 30 minutes before quenching with NH<sub>4</sub>Cl (6 M, 3.1 mL) and warming to ambient temperature. Sodium thiosulphate solution (10%, 27 mL) and CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was then added before the phases were separated. The aqueous phase was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 50 mL), and the combined organic layers dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting crude material was purified twice by gradient flash chromatography (silica, EtOAc/*n*-pentane, 0:1 to 1:10) resulting in 4.41 g (10.8 mmol, 87%) of the desired product as brown crystals. TLC (EtOAc/*n*-pentane 1:10) *R*<sub>f</sub> = 0.13; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 8.64 (s, 1H), 7.13 (s, 1H), 5.62 (s, 2H), 3.58 – 3.49 (m, 2H), 0.87 – 0.79 (m, 2H), -0.10 (s, 9H). The <sup>1</sup>H-NMR spectrum was in accordance with the literature.<sup>3</sup>

#### 4-Chloro-6-(4-methoxyphenyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]-pyrimidine (23)<sup>4</sup>



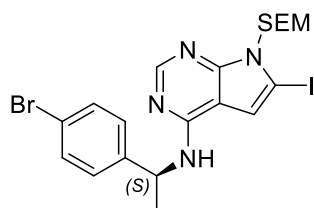
4-Chloro-6-(4-methoxyphenyl)-7-((2-(ethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (251 mg, 0.613 mmol), (4-methoxyphenyl)boronic acid (102.9 mg, 0.677 mmol), K<sub>2</sub>CO<sub>3</sub> (253 mg, 1.83 mmol) and Pd(dppf)Cl<sub>2</sub> (22.4 mg, 30.6 μmol) was added to a Schlenk tube and flushed with N<sub>2</sub>. Degassed H<sub>2</sub>O (2.5 mL) and 1,4-dioxane (2.5 mL) was added, and the reaction was stirred at 80 °C for 10 minutes. After cooling to ambient temperature, H<sub>2</sub>O (25 mL) and CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added, and the phases separated. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL) and the combined organic layers washed with brine (25 mL). They were then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. This crude was purified by gradient flash chromatography (*i*-PrOH/CH<sub>2</sub>Cl<sub>2</sub>, 0:100 to 8:92), resulting in 160 mg (0.409 mmol, 67%) of the desired product as a brown oil. TLC (*i*PrOH/CH<sub>2</sub>Cl<sub>2</sub> 2:98) *R*<sub>f</sub> = 0.34; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 8.65 (s, 1H), 7.76 – 7.69 (m, 2H), 7.06 – 7.00 (m, 2H), 6.63 (s, 1H), 5.61 (s, 2H), 3.89 (s, 3H), 3.78 – 3.71 (m, 2H), 1.01 – 0.95 (m, 2H), -0.02 (s, 9H). The <sup>1</sup>H-NMR spectrum was in accordance with the literature.<sup>4</sup>

#### (4-(4-Chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol (24)<sup>3</sup>



A mixture of 4-chloro-6-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (2.05 g, 5.01 mmol), (4-hydroxyphenyl)boronic acid (814 mg, 5.90 mmol), K<sub>2</sub>CO<sub>3</sub> (1.39 g, 10.1 mmol) and Pd<sub>2</sub>dba<sub>3</sub> (113 mg, 0.123 mmol) was flushed with N<sub>2</sub> three times. Degassed 1,4 dioxane (9 mL) and H<sub>2</sub>O (3 mL) were then added, and the mixture stirred at 60 °C for 2.5 hours. Additional degassed 1,4 dioxane (9 mL) and H<sub>2</sub>O (3 mL) were then added, and the solution stirred for a further 2.5 hours. After cooling to ambient temperature, the solvent was removed *in vacuo*, and the resulting solid suspended in H<sub>2</sub>O (100 mL). The suspension was extracted with EtOAc (4 × 100 mL) and the combined organic layers washed with brine (100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting crude was immobilized on Celite and purified by gradient flash chromatography (EtOAc/*n*-pentane/AcOH, 10:100:1 to 25:100:1) yielding 1.34 g (3.56 mmol, 71%) of the desired product as a light brown solid. TLC (AcOH/EtOAc/*n*-pentane 1:80:10) *R*<sub>f</sub> = 0.22; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 9.94 (s, 1H), 8.68 (s, 1H), 7.72 – 7.61 (m, 2H), 7.01 – 6.89 (m, 2H), 6.74 (s, 1H), 5.60 (s, 2H), 3.68 – 3.57 (m, 2H), 0.89 – 0.80 (m, 2H), -0.10 (s, 9H). The <sup>1</sup>H-NMR spectrum was in accordance with the literature.<sup>3</sup>

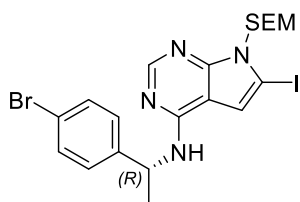
#### (S)-N-(1-(4-Bromophenyl)ethyl)-6-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine ((S)-34)



4-Chloro-6-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (**22**) (503 mg, 1.23 mmol) was treated as described in General Procedure A. The crude material was purified by gradient flash chromatography (silica-gel, Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, 0:100 to 1:3) to afford 541 mg (0.944 mmol, 77%) as an off-white waxy solid; TLC (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, 1:3): *R*<sub>f</sub> = 0.42; [α]<sub>D</sub><sup>20</sup> = +61.0 (1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ: 8.03 (s, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.49-7.47 (m, 2H), 7.34-7.33 (m, 2H), 7.11 (s, 1H), 5.47-5.39 (m, 3H),

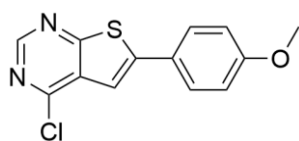
3.50-3.47 (m, 2H), 1.49 (d,  $J = 7.0$  Hz, 3H), 0.81-0.78 (m, 2H), -0.10 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz, DMSO- $d_6$ )  $\delta$ : 153.7, 151.9, 151.4, 144.7, 131.1 (2C), 128.3 (2C), 119.4, 110.1, 104.7, 79.8, 72.5, 65.4, 48.4, 22.6, 17.1, -1.4 (3C); IR (neat,  $\text{cm}^{-1}$ ): 3281, 2951, 2893, 1597, 1563, 1504, 1488, 1454, 1378, 1339, 1297, 1248, 1217, 1077, 1010, 859, 835, 749; HRMS (ASAP-TOF,  $m/z$ ): calcd. for  $\text{C}_{20}\text{H}_{27}\text{N}_4\text{OSi}^{79}\text{BrI}$ , 573.0182  $[\text{M}+\text{H}]^+$ , found 573.1087.

**(*R*)-4-(4-((1-(4-Bromophenyl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)phenol (34)**



Compound **34** was made as described in General Procedure A starting with 4-chloro-6-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**22**) (1.17 g, 2.87 mmol) and (*R*)-1-(4-bromophenyl)ethan-1-amine (1.34 mL, 9.31 mmol). The product was purified by gradient flash chromatography (silica-gel,  $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ , 0:100 to 1:3) to afford 541 mg (0.944 mmol, 77%) as an off-white waxy solid; TLC ( $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ , 1:3):  $R_f = 0.42$ . This gave 1.49 g (2.60 mmol, 91%) as an off-white waxy solid;  $[\alpha]_D^{20} = -61.2$  (1.00,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR spectroscopy corresponded with that reported for the (*S*)-enantiomer.

**4-Chloro-6-(4-methoxyphenyl)thieno[2,3-*d*]pyrimidine (44)<sup>5</sup>**

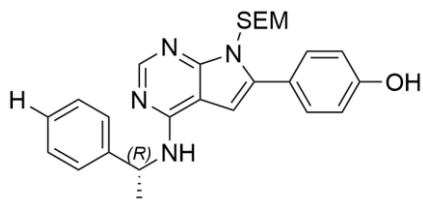


6-Bromo-4-chlorothieno[2,3-*d*]pyrimidine<sup>6</sup> (200 mg, 0.801 mmol), phenylboronic acid (150 mg, 0.987 mmol),  $\text{K}_2\text{CO}_3$  (350 mg, 2.53 mmol),  $\text{Pd}_2(\text{dba})_3$  (41 mg, 44.7  $\mu\text{mol}$ ) and degassed 1,4-dioxane (4 mL) were mixed and stirred at 130  $^\circ\text{C}$  for 4.5 h under an  $\text{N}_2$  atmosphere. The solvent was evaporated under reduced pressure. The residue was suspended in water (50 mL), extracted with  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL), dried over  $\text{MgSO}_4$  and filtered. The solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (silica, *n*-pentane/acetone, 20:1,  $R_f = 0.20$ ) to give 163 mg (0.590 mmol, 73%) of the product.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.79 (s, 1H), 7.68 (d,  $J = 8.8$  Hz, 1H), 7.47 (s, 1H), 7.00 (d,  $J = 8.8$  Hz, 1H), 3.88 (s, 1H).

The  $^1\text{H}$  NMR spectrum in  $\text{CDCl}_3$  was similar to a previously published DMSO- $d_6$  spectrum<sup>5</sup>.

**Synthesis of SEM protected 6-aryl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amines**

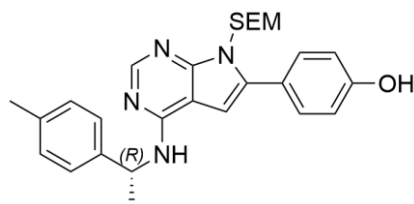
**(*R*)-4-(4-((1-Phenylethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)phenol (25)**



Compound **25** was prepared as described in General Procedure A starting with **24** (139 mg, 0.370 mmol) and (*R*)-1-phenylethan-1-amine (150  $\mu\text{L}$ , 1.18 mmol). The crude product was purified by dissolution in  $\text{CH}_2\text{Cl}_2$  and purification by two rounds of flash chromatography (first: C18 silica,  $\text{MeCN}/\text{H}_2\text{O}$  cont. 0.1%  $\text{NEt}_3$ , 3:1, then: silica-gel:  $\text{EtOAc}/n$ -pentane, 1:4 to 1:2), resulting in 106 mg (0.230 mmol, 62%) of the desired product as a light brown waxy solid, mp. 83.2-87.1  $^\circ\text{C}$ ; TLC ( $\text{EtOAc}/n$ -pentane 1:2)  $R_f = 0.23$ ;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$ : 9.71 (s, 1H), 8.11 (s, 1H), 7.84 (d,  $J = 8.2$  Hz, 1H), 7.55 – 7.48 (m, 2H), 7.45 – 7.39 (m, 2H), 7.34 – 7.27 (m, 2H), 7.22 – 7.16 (m, 1H), 6.90 – 6.84 (m, 2H), 6.78 (s, 1H), 5.50 (p,  $J = 7.2$  Hz, 1H), 5.44 (s, 2H), 3.64 – 3.55 (m, 2H), 1.53 (d,  $J = 7.1$  Hz, 3H), 0.87 – 0.78 (m, 2H), -0.09 (s, 9H);  $^{13}\text{C}$  NMR (151 MHz, DMSO- $d_6$ )  $\delta$ : 157.6, 154.8, 151.5, 151.4,

145.4, 137.1, 129.9 (2C), 128.2 (2C), 126.4, 126.0 (2C), 122.4, 115.6 (2C), 102.6, 98.2, 70.1, 65.6, 48.7, 22.8, 17.3, -1.4 (3C); IR (neat,  $\text{cm}^{-1}$ ): 2951, 1600, 1496, 1470, 1246, 1216, 1074, 858, 699; HRMS (TOF ES+,  $m/z$ ): calcd. for  $\text{C}_{26}\text{H}_{33}\text{N}_4\text{O}_2\text{Si}$   $[\text{M}+\text{H}]^+$ : 461.2373, found: 461.2370.

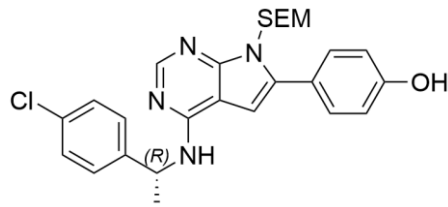
**(*R*)-4-(4-((1-(*p*-Tolyl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)phenol (26)**



Compound **26** was prepared as described in General Procedure A starting from **24** (202 mg, 0.536 mmol) and (*R*)-1-(*p*-tolyl)ethan-1-amine (220  $\mu\text{L}$ , 1.50 mmol). The crude product was purified by gradient flash chromatography (silica-gel, EtOAc/*n*-pentane, 0:1 to 1:2) resulting in 197 mg (0.415 mmol, 77%) of the desired product as a light brown solid, mp. 88.2-90.3  $^{\circ}\text{C}$ . TLC

(EtOAc/*n*-pentane 1:2)  $R_f$  = 0.30;  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 9.71 (s, 1H), 8.11 (s, 1H), 7.78 (d,  $J$  = 8.2 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.32 – 7.26 (m, 2H), 7.13 – 7.07 (m, 2H), 6.89 – 6.85 (m, 2H), 6.77 (s, 1H), 5.49 – 5.42 (m, 3H), 3.64 – 3.52 (m, 2H), 2.25 (s, 3H), 1.50 (d,  $J$  = 7.0 Hz, 3H), 0.88 – 0.78 (m, 2H), -0.09 (s, 9H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 157.5, 154.8, 151.5 (2C), 142.4, 137.0, 135.4, 129.9 (2C), 128.7 (2C), 125.9 (2C), 122.4, 115.5 (2C), 102.6, 98.2, 70.1, 65.6, 48.4, 22.8, 20.6, 17.3, -1.4 (3C); IR (neat,  $\text{cm}^{-1}$ ): 2951, 1600, 1497, 1470, 1342, 1246, 1218, 1074, 833, 764, 736, 601; HRMS (TOF ES+,  $m/z$ ): calcd. for  $\text{C}_{27}\text{H}_{35}\text{N}_4\text{O}_2\text{Si}$   $[\text{M}+\text{H}]^+$ : 475.2529, found: 475.2531.

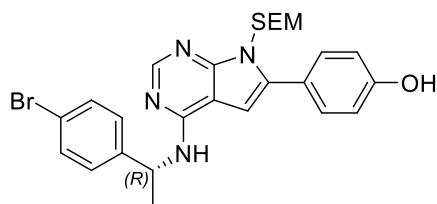
**(*R*)-4-(4-((1-(4-Chlorophenyl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo [2,3-*d*]pyrimidin-6-yl)phenol (27)**



Compound **27** was prepared as described in General Procedure A, starting from **24** (101 mg, 0.256 mmol) and (*R*)-1-(4-chlorophenyl)ethan-1-amine (115  $\mu\text{L}$ , 0.823 mmol). The crude product was purified by dissolution in  $\text{CH}_2\text{Cl}_2$  and purification by two rounds of flash chromatography (first: silica-gel: MeOH/ $\text{CH}_2\text{Cl}_2$ , 0:100 to 5:95, then: C18-silica,

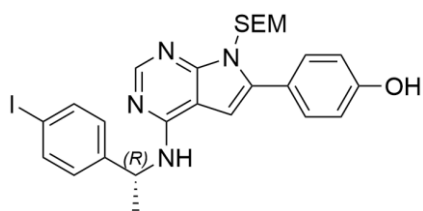
MeCN/ $\text{H}_2\text{O}$  cont. 0.1%  $\text{NEt}_3$ , 4:1). This gave 65 mg (0.132 mmol, 49%) of the desired product as a brown solid, mp. 91.0-92.7  $^{\circ}\text{C}$ ; TLC (MeOH/ $\text{CH}_2\text{Cl}_2$  3:97)  $R_f$  = 0.31;  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 9.72 (s, 1H), 8.11 (s, 1H), 7.87 (d,  $J$  = 8.0 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.45 – 7.41 (m, 2H), 7.38 – 7.34 (m, 2H), 6.89 – 6.85 (m, 2H), 6.76 (s, 1H), 5.50 – 5.41 (m, 3H), 3.64 – 3.51 (m, 2H), 1.51 (d,  $J$  = 7.0 Hz, 3H), 0.88 – 0.77 (m, 2H), -0.10 (s, 9H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 157.6, 154.7, 151.4 (2C), 144.5, 137.2, 130.9, 129.9 (2C), 128.1 (2C), 127.9 (2C), 122.4, 115.6 (2C), 102.7, 98.1, 70.1, 65.6, 48.3, 22.7, 17.3, -1.4 (3C); IR (neat,  $\text{cm}^{-1}$ ): 2951, 1600, 1493, 1470, 1342, 1075, 858; HRMS (TOF ES+,  $m/z$ ): calcd. for  $\text{C}_{26}\text{H}_{32}\text{N}_4\text{O}_2\text{Si}^{35}\text{Cl}$   $[\text{M}+\text{H}]^+$ : 495.1983, found: 495.1985.

**(*R*)-4-(4-((1-(4-Bromophenyl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)phenol (28)**



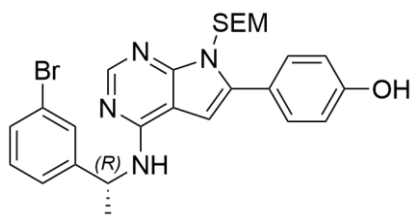
Compound **28** was prepared as described in General Procedure A from **24** (203 mg, 0.540 mmol) and (*R*)-1-(4-bromophenyl)ethan-1-amine (0.235 mL, 1.63 mmol). The crude product was immobilized on Celite and purified by gradient flash chromatography (silica, EtOAc/*n*-pentane 0:1 to 1:1). This gave 203 mg (0.376 mmol, 70%) of the desired product as an off-white waxy solid; TLC (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, 1:1) *R<sub>F</sub>* = 0.42;  $[\alpha]_D^{20}$  = -104.4 (1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 9.72 (s, 1H), 8.10 (s, 1H), 7.87 (d, 1H, *J* = 8.0 Hz), 7.52-7.48 (m, 4H), 7.38-7.36 (m, 2H), 6.88-6.86 (m, 2H), 6.76 (s, 1H), 5.47-5.42 (m, 3H), 3.59-3.56 (m, 2H), 1.51 (d, 3H, *J* = 7.1 Hz), 0.84-0.81 (m, 2H), -0.10 (s, 9H); <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 157.6, 154.7, 151.4, 145.0, 137.2, 131.0 (2C), 129.9 (2C), 128.3 (2C), 122.4, 119.4, 115.6 (2C), 102.7, 98.1, 70.1, 65.6, 48.4, 25.5, 22.7, 17.3, -1.4 (3C); IR (neat, cm<sup>-1</sup>): 3345, 3042, 2951, 2925, 1601, 1497, 1470, 1343, 1247, 1216, 1174, 1073, 1009, 858, 834, 769, 694; HRMS (ASAP-TOF, *m/z*): calcd. for C<sub>26</sub>H<sub>32</sub>N<sub>4</sub>O<sub>2</sub>Si<sup>79</sup>Br, 539.1478 [M+H]<sup>+</sup>, found 539.1473.

**(*R*)-4-(4-((1-(4-Iodophenyl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)phenol (29)**



Compound **29** was made as described in the General Procedure A starting with **24** (93 mg, 0.248 mmol) and (*R*)-1-(4-iodophenyl)-ethan-1-amine hydrochloride (227 mg, 0.801 mmol) and DIPEA (230  $\mu$ L, 1.32 mmol). The resulting crude product was purified twice by flash chromatography (first C18 silica: MeCN/H<sub>2</sub>O cont. 0.1% NEt<sub>3</sub>, 3:1, then: silica-gel, EtOAc/*n*-pentane, 3:1). This gave 71 mg (0.121 mmol, 49%) of the desired product as a light brown solid, mp. 91.3-94.4 °C. TLC (EtOAc/*n*-pentane 1:3) *R<sub>F</sub>* = 0.19; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 9.71 (s, 1H), 8.10 (s, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.55 – 7.48 (m, 2H), 7.27 – 7.19 (m, 2H), 6.90 – 6.84 (m, 2H), 6.76 (s, 1H), 5.46 – 5.35 (m, 3H), 3.63 – 3.54 (m, 2H), 1.50 (d, *J* = 7.0 Hz, 3H), 0.86 – 0.76 (m, 2H), -0.10 (s, 9H); <sup>13</sup>C NMR (151 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 157.6, 154.7, 151.4 (2C), 145.4, 137.2, 136.9 (2C), 129.9 (2C), 128.5 (2C), 122.4, 115.6 (2C), 102.7, 98.1, 92.1, 70.1, 65.6, 48.5, 22.6, 17.3, -1.4 (3C); IR (neat, cm<sup>-1</sup>): 2950, 1600, 1497, 1469, 1242, 1265, 1215, 1074, 858, 833; HRMS (TOF ES<sup>+</sup>, *m/z*): calcd. for C<sub>26</sub>H<sub>32</sub>N<sub>4</sub>O<sub>2</sub>Si [M+H]<sup>+</sup>: 587.1339, found: 587.1345.

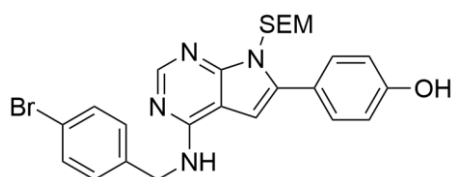
**(*R*)-4-(4-((1-(3-Bromophenyl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)phenol (30)**



Compound **30** was prepared as described in General Procedure A starting from **24** (152 mg, 0.404 mmol) and (*R*)-1-(3-bromophenyl)ethan-1-amine (185  $\mu$ L, 1.23 mmol). The crude product was immobilized on Celite and purified by gradient flash chromatography (silica, EtOAc/*n*-pentane, 0:1 to 1:3), resulting in 162 mg (0.301 mmol, 75%) of the desired product as a brown solid, mp. 147.4-148.5 °C; TLC (EtOAc/*n*-pentane 1:2) *R<sub>F</sub>* = 0.19; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 9.72

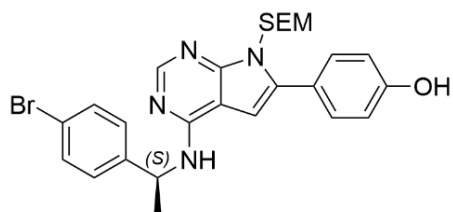
(s, 1H), 8.12 (s, 1H), 7.88 (d,  $J$  = 8.0 Hz, 1H), 7.61 (t,  $J$  = 1.9 Hz, 1H), 7.54 – 7.51 (m, 2H), 7.42 (d,  $J$  = 7.9 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.27 (t,  $J$  = 7.8 Hz, 1H), 6.90 – 6.86 (m, 2H), 6.77 (s, 1H), 5.45 (s, 3H), 3.61 – 3.55 (m, 2H), 1.52 (d,  $J$  = 7.1 Hz, 3H), 0.82 (td,  $J$  = 7.6, 0.7 Hz, 2H), -0.10 (s, 9H);  $^{13}\text{C}$  NMR (151 MHz, DMSO- $d_6$ )  $\delta$ : 157.6, 154.7, 151.4, 148.5, 137.3, 130.5, 129.9 (2C), 129.4, 128.7, 125.3, 122.4, 121.6, 115.6 (2C), 102.7, 98.1, 70.2, 65.6, 48.5, 22.8, 17.3, -1.4 (3C); IR (neat,  $\text{cm}^{-1}$ ): 3409, 2950, 1601, 1438, 1229, 1066, 835, 771, 693; HRMS (TOF ES+,  $m/z$ ): calcd. for  $\text{C}_{26}\text{H}_{32}\text{N}_4\text{O}_2\text{Si}^{79}\text{Br}$   $[\text{M}+\text{H}]^+$ : 539.1478, found: 539.1481.

**4-(4-((4-Bromobenzyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol (31)**



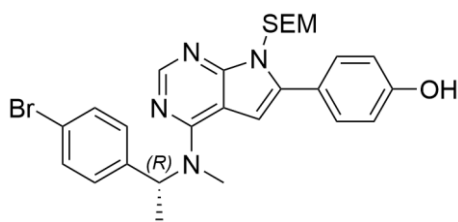
Compound **31** was prepared as described in General Procedure A, starting from **24** (150 mg, 0.399 mmol) and (4-bromophenyl)methanamine (155  $\mu\text{L}$ , 1.23 mmol). The crude product was immobilized on Celite and purified by flash chromatography (silica, EtOAc/*n*-pentane 0:1 to 1:1) resulting in 164 mg (0.313 mmol, 78%) of the desired product as a brown wax, mp. 155.5-156.0  $^{\circ}\text{C}$ . TLC (EtOAc/*n*-pentane 1:2)  $R_f$  = 0.14;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$ : 9.72 (s, 1H), 8.17 (s, 1H), 8.10 (t,  $J$  = 6.1 Hz, 1H), 7.53 – 7.47 (m, 4H), 7.33 – 7.29 (m, 2H), 6.90 – 6.84 (m, 2H), 6.65 (s, 1H), 5.45 (s, 2H), 4.70 (d,  $J$  = 6.1 Hz, 2H), 3.62 – 3.56 (m, 2H), 0.86 – 0.80 (m, 2H), -0.09 (s, 9H);  $^{13}\text{C}$  NMR (151 MHz, DMSO- $d_6$ )  $\delta$ : 157.6, 155.4, 151.5, 151.4, 139.7, 137.3, 131.1 (2C), 130.0 (2C), 129.4 (2C), 122.3, 119.6, 115.6 (2C), 102.7, 97.9, 70.2, 65.6, 42.5, 40.1, 17.3, -1.4 (3C); IR (neat,  $\text{cm}^{-1}$ ): 3414, 2949, 1606, 1486, 1242, 1236, 1068, 834, 774; HRMS (TOF ES+,  $m/z$ ): calcd. for  $\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_2\text{Si}^{79}\text{Br}$   $[\text{M}+\text{H}]^+$ : 525.1321, found: 525.1328.

**(S)-4-(4-((1-(4-Bromophenyl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol (32)**



Compound **32** was prepared as described in General Procedure A, starting from **24** (153 mg, 0.407 mmol) and (S)-1-(4-bromophenyl)ethan-1-amine (174  $\mu\text{L}$ , 1.20 mmol). The crude product was immobilized on Celite and purified by gradient flash chromatography (silica, EtOAc/*n*-pentane, 0:1 to 1:1), giving 159 mg (0.295 mmol, 72%) of the desired product as a brown solid, mp. 92.4-93.7  $^{\circ}\text{C}$ . TLC (EtOAc/*n*-pentane 1:2)  $R_f$  = 0.13;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$ : 8.23 (s, 1H), 7.56 – 7.51 (m, 4H), 7.28 (m, 2H), 6.85 (d,  $J$  = 8.6 Hz, 2H), 6.71 (s, 1H), 6.40 (s, 1H), 5.50 (s, 2H), 3.64 – 3.59 (m, 2H), 3.06 (s, 3H), 1.57 (d,  $J$  = 7.0 Hz, 3H), 0.88 – 0.83 (m, 2H), -0.07 (s, 9H);  $^{13}\text{C}$  NMR (151 MHz, DMSO- $d_6$ )  $\delta$ : 157.6, 156.3, 152.9, 150.8, 141.0, 136.9, 131.3 (2C), 130.1 (2C), 129.2 (2C), 122.1, 120.1, 115.5 (2C), 102.4, 101.0, 70.2, 65.7, 51.9, 21.3, 17.4, -1.4 (3C); IR (neat,  $\text{cm}^{-1}$ ): 2951, 1469, 1490, 1414, 1318, 1257, 1068, 1007, 832, 618; HRMS (TOF ES+,  $m/z$ ): calcd. for  $\text{C}_{26}\text{H}_{32}\text{N}_4\text{O}_2\text{Si}^{79}\text{Br}$   $[\text{M}+\text{H}]^+$ : 539.1478, found: 539.1475.

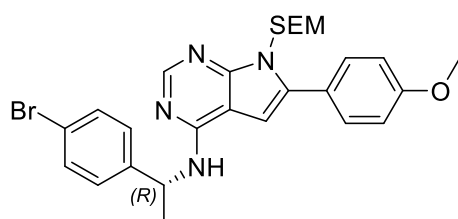
**(*R*)-4-(4-((1-(4-Bromophenyl)ethyl)(methyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)phenol (33)**



Compound **33** was prepared as described in General Procedure A, starting from **24** (190 mg, 0.505 mmol) and (*R*)-1-(4-bromophenyl)-*N*-methylethan-1-amine HCl-salt (401 mg, 1.60 mmol). The crude product was immobilized on Celite and purified by flash chromatography (silica, AcOH/EtOAc/*n*-pentane, 1:0:99 to 1:24:75), recovering 30% of the starting material and giving 89 mg, (0.161 mmol, 32%)

of the desired product as a white solid, mp. 150.8-151.8 °C. TLC (AcOH/EtOAc/*n*-pentane 1:19:80)  $R_f$  = 0.24;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$ : 8.23 (s, 1H), 7.56 – 7.51 (m, 4H), 7.28 (m, 2H), 6.85 (d,  $J$  = 8.6 Hz, 2H), 6.71 (s, 1H), 6.40 (s, 1H), 5.50 (s, 2H), 3.64 – 3.59 (m, 2H), 3.06 (s, 3H), 1.57 (d,  $J$  = 7.0 Hz, 3H), 0.88 – 0.83 (m, 2H), -0.07 (s, 9H);  $^{13}\text{C}$  NMR (151 MHz, DMSO- $d_6$ )  $\delta$ : 157.6, 156.3, 152.9, 150.8, 141.0, 136.9, 131.3 (2C), 130.1 (2C), 129.2 (2C), 122.1, 120.1, 115.5 (2C), 102.4, 101.0, 70.2, 65.7, 51.9, 21.3, 17.4, -1.4 (3C); IR (neat,  $\text{cm}^{-1}$ ): 2951 (br, w), 1469, 1490, 1414, 1318, 1257, 1068, 1007, 832, 764, 618; HRMS (TOF ES+,  $m/z$ ): calcd. for  $\text{C}_{27}\text{H}_{34}\text{N}_4\text{O}_2\text{Si}^{79}\text{Br}$   $[\text{M}+\text{H}]^+$ : 553.1634, found: 553.1634.

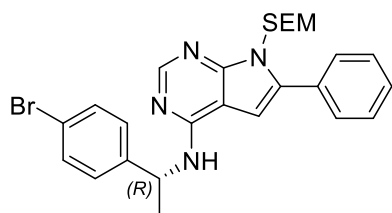
**(*R*)-*N*-(1-(4-bromophenyl)ethyl)-6-(4-methoxyphenyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (35)**



Compound **35** was prepared by Suzuki cross-coupling from **34** (205 mg, 0.358 mmol) and (4-methoxyphenyl)boronic acid as described in General Procedure B. The reaction time was 20 minutes. The crude material was purified by gradient flash chromatography (silica-gel, acetone/*n*-pentane, 0/100 to 1:4). TLC (acetone/*n*-pentane, 1:4)  $R_f$  = 0.33. This gave 146

mg (0.264 mmol, 74%) as a colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.35 (s, 1H), 7.63-7.62 (m, 2H), 7.45-7.44 (m, 2H), 7.31-7.30 (m, 2H), 6.99-6.98 (m, 2H), 6.34 (s, 1H), 5.52-5.48 (m, 3H), 5.25 (br s, 1H), 3.86 (s, 3H), 3.73-3.70 (m, 2H), 1.63 (d, 3H,  $J$  = 6.8 Hz), 0.96-0.93 (m, 2H), -0.04 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 160.0, 155.1, 152.4, 152.0, 143.4, 138.8, 131.9 (2C), 130.7 (2C), 128.0 (2C), 124.2, 121.1, 114.3 (2C), 103.1, 97.2, 70.7, 66.6, 55.5, 49.8, 23.1, 18.2, -1.3 (3C); IR (neat,  $\text{cm}^{-1}$ ): 3284, 2952, 2897, 2836, 1600, 1498, 1467, 1250, 1212, 1179, 1160, 1143, 1076, 835, 601; HRMS (ASAP-TOF,  $m/z$ ): calcd. for  $\text{C}_{27}\text{H}_{34}\text{N}_4\text{O}_2^{79}\text{BrSi}$ , 553.1634  $[\text{M}+\text{H}]^+$ , found 553.1633

**(*R*)-*N*-(1-(4-Bromophenyl)ethyl)-6-phenyl-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (36)**



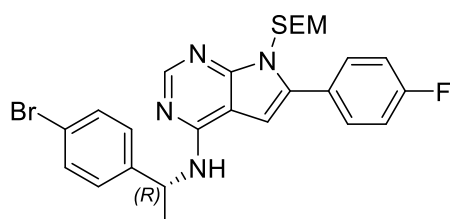
Compound **36** was synthesized as described in General Procedure B from **34** (100 mg, 0.174 mmol) and phenylboronic acid (21 mg, 0.172 mmol). The reaction time was 10 minutes. The crude material was purified by gradient flash chromatography (silica-gel, acetone/*n*-pentane, 0:100 to 1:6). This gave 63 mg (0.120 mmol, 69%) as a colorless oil; TLC (acetone/*n*-pentane, 1:6)  $R_f$  = 0.20;

$[\alpha]_D^{20}$  = -92.8 (1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.37 (s, 1H), 7.71-7.69 (m, 2H), 7.47-7.44 (m, 4H), 7.42-7.39 (m, 1H), 7.32-7.30 (m, 2H), 6.41 (s, 1H), 5.55 (s, 2H), 5.53-5.48 (m, 1H), 5.18 (br s, 1H), 3.73-3.70 (m, 2H), 1.64 (d,  $J$  = 6.9 Hz, 3H), 0.96-0.93 (m, 2H), -0.04 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )



$\delta$ : 155.3, 152.6, 152.3, 143.4, 138.9 (2C), 131.9, 131.8, 129.3 (2C), 128.8 (2C), 128.5, 128.0 (2C), 121.1, 103.1, 98.0, 70.8, 66.7, 49.8, 23.1, 18.2, -1.3 (3C); IR (neat,  $\text{cm}^{-1}$ ): 3283, 3058, 3030, 2952, 2894, 1596, 1487, 1468, 1302, 1248, 1213, 1073, 859, 834, 755, 698; HRMS (ASAP-TOF,  $m/z$ ): calcd. for  $\text{C}_{26}\text{H}_{32}\text{N}_4\text{OSi}^{79}\text{Br}$ , 523.1529  $[\text{M}+\text{H}]^+$ , found: 523.1521

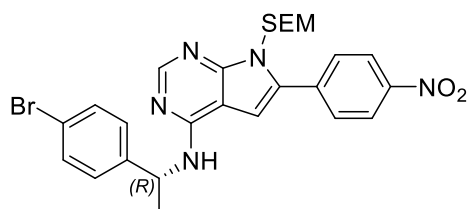
**(*R*)-*N*-(1-(4-Bromophenyl)ethyl)-6-(4-fluorophenyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (37)**



Compound **37** was made from **34** (100 mg, 0.174 mmol) and (4-fluorophenyl)boronic acid (25 mg, 0.179 mmol), as described in General Procedure B. Purification by flash chromatography (silica, acetone/*n*-pentane 1:5,  $R_f$  = 0.28) gave 63 mg (0.116 mmol, 67%) as a colorless oil;  $[\alpha]_D^{20}$  = -99.4 (1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.36 (s, 1H), 7.70-

7.67 (m, 2H), 7.47-7.45 (m, 2H), 7.31-7.30 (m, 2H), 7.16-7.13 (m, 2H), 6.37 (s, 1H), 5.53-5.48 (m, 3H), 5.16 (br d, 1H,  $J$  = 7.0 Hz), 3.74-3.71 (m, 2H), 1.64 (d, 3H,  $J$  = 6.9 Hz), 0.96-0.93 (m, 2H), -0.03 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 163.0 (d,  $J$  = 248.8 Hz), 155.3, 152.5, 152.4, 143.4, 137.8, 131.9 (2C), 131.2 (d,  $J$  = 7.9 Hz, 2C), 128.0 (2C), 127.9 (d,  $J$  = 3.3 Hz), 121.1, 115.9 (d,  $J$  = 21.8 Hz, 2C), 103.0, 98.0, 70.7, 66.7, 49.8, 23.0, 18.2, -1.3 (3C);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ,  $\text{C}_6\text{F}_6$ )  $\delta$ : -116.2 (s); IR (neat,  $\text{cm}^{-1}$ ): 3284, 3042, 2952, 2895, 1599, 1496, 1468, 1341, 1247, 1223, 1075, 1009, 858, 836, 766; HRMS (ASAP-TOF,  $m/z$ ): calcd. for  $\text{C}_{26}\text{H}_{31}\text{N}_4\text{OSi}^{79}\text{Br}$  F, 541.1435  $[\text{M}+\text{H}]^+$ , found 541.1432.

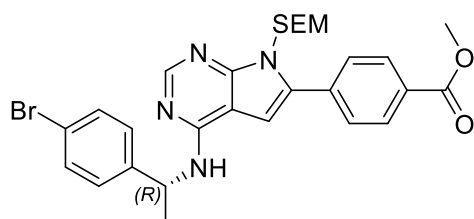
**(*R*)-*N*-(1-(4-Bromophenyl)ethyl)-6-(4-nitrophenyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (38)**



Compound **38** was made from **34** (300 mg, 0.523 mmol) and (4-nitrophenyl)boronic acid (87 mg, 0.521 mmol) as described in General Procedure B. The reaction time was 10 minutes. Purification by flash chromatography (silica, acetone/*n*-pentane, 1:4,  $R_f$  = 0.23) gave 186 mg (0.327 mmol, 63%) of a yellow-red wax;  $[\alpha]_D^{20}$  = -178.0 (1.00,  $\text{CHCl}_3$ );

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.37 (s, 1H), 8.31-8.29 (m, 2H), 7.94-7.92 (m, 2H), 7.47-7.45 (m, 2H), 7.32-7.30 (m, 2H), 6.59 (s, 1H), 5.59-5.48 (m, 4H), 3.80-3.77 (m, 2H), 1.65 (d,  $J$  = 6.7 Hz, 3H), 0.99-0.96 (m, 2H), -0.02 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 155.6, 153.3, 153.1, 147.4, 143.1, 138.2, 136.2, 132.0 (2C), 129.4 (2C), 127.9 (2C), 124.2 (2C), 121.3, 103.0, 100.8, 70.9, 67.0, 50.1, 23.0, 18.2, -1.3 (3C); IR (neat,  $\text{cm}^{-1}$ ): 3405, 3276, 3102, 3042, 2952, 2895, 1591, 1534, 1342, 1075, 1010, 856, 835, 751; HRMS (ASAP-TOF,  $m/z$ ): calcd. for  $\text{C}_{26}\text{H}_{31}\text{N}_5\text{O}_3\text{Si}^{79}\text{Br}$ , 568.1380  $[\text{M}+\text{H}]^+$ , found 568.1385.

**Methyl (*R*)-4-(4-((1-(4-bromophenyl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)benzoate (39)**

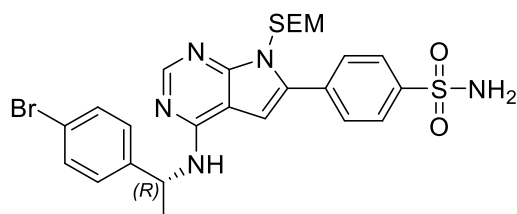


Compound **39** was prepared from **34** (301 mg, 0.525 mmol) and (4-(methoxycarbonyl)phenyl)boronic acid (94 mg, 0.522 mmol), as described in General Procedure B. The reaction time was 25 minutes. Purification by flash chromatography (silica, acetone/*n*-pentane, 1:9,  $R_f$  = 0.04) gave 170 mg (0.292 mmol, 56%) of a white wax;  $[\alpha]_D^{20}$  = -

131.0 (1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.37 (s, 1H), 8.13-8.11 (m, 2H), 7.82-7.80 (m, 2H), 7.48-7.45 (m, 2H), 7.32-7.30 (m, 2H), 6.52 (s, 1H), 5.56 (s, 2H), 5.51 (quint., 1H,  $J$  = 6.9 Hz), 5.21 (br s,

1H), 3.95 (s, 3H), 3.76-3.73 (m, 2H), 1.64 (d,  $J$  = 6.9 Hz, 3H), 0.97-0.95 (m, 2H), -0.03 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 166.9, 155.4, 152.9, 152.8, 143.2, 137.7, 136.2, 131.9 (2C), 130.1 (2C), 129.8, 128.9 (2C), 128.0 (2C), 121.2, 103.2, 99.3, 70.9, 66.8, 52.4, 49.9, 23.0, 18.2, -1.2 (3C); IR (neat,  $\text{cm}^{-1}$ ): 3378, 3277, 2951 2894, 1723, 1598, 1563, 1468, 1279, 1249, 1188, 1105, 1076, 860, 835, 772; HRMS (ASAP-TOF,  $m/z$ ): calcd. for  $\text{C}_{28}\text{H}_{34}\text{N}_4\text{O}_3^{79}\text{BrSi}$ , 581.1584  $[\text{M}+\text{H}]^+$ , found 581.1588.

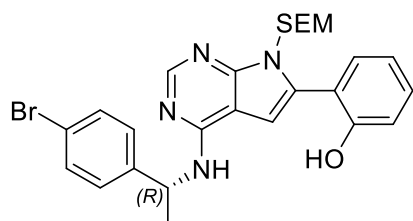
**(R)-4-(4-((1-(4-bromophenyl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzenesulfonamide (40)**



Compound **40** was prepared from **34** (200 mg, 0.349 mmol) and (4-sulfamoylphenyl)boronic acid (70 mg, 0.348 mmol) as described in General Procedure B. The reaction time was 10 minutes. Purification by gradient flash chromatography (silica-gel, acetone/*n*-pentane, 0:100 to 1:2); TLC (silica, acetone/*n*-pentane, 1:2)  $R_f$  =

0.43. This gave 136 mg (0.226 mmol, 65%) of a white wax;  $[\alpha]_D^{20}$  = -145.4 (1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.36 (s, 1H), 8.00 – 7.98 (m, 2H), 7.89 – 7.87 (m, 2H), 7.47 – 7.44 (m, 2H), 7.32 – 7.30 (m, 2H), 6.55 (s, 1H), 5.54 (s, 2H), 5.52 – 5.49 (m, 1H), 5.43 (br s, 1H), 5.08 (s, 2H), 3.77 – 3.75 (m, 2H), 1.65 (d,  $J$  = 6.8 Hz, 3H), 0.97 – 0.94 (m, 2H), -0.03 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 155.6, 153.0 (2C)\*, 143.2, 141.3, 136.6, 136.4, 131.9 (2C), 129.5 (2C), 128.0 (2C), 127.0 (2C), 121.2, 103.1, 100.1, 70.8, 66.9, 49.9, 22.4, 18.2, -1.2 (3C), \* 2C overlap seen by HMBC; IR (neat,  $\text{cm}^{-1}$ ): 3372, 3259, 3020, 2952, 2895, 1593, 1562, 1470, 1338, 1306, 1157, 1072, 834, 751, 603; HRMS (ASAP-TOF,  $m/z$ ): calcd. for  $\text{C}_{26}\text{H}_{33}\text{N}_5\text{O}_3\text{S}^{79}\text{BrSi}$ , 602.1257  $[\text{M}+\text{H}]^+$ , found 602.1257.

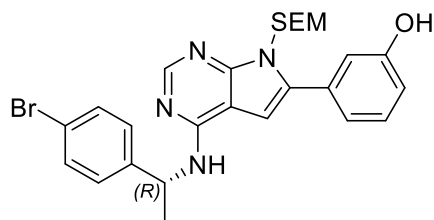
**(R)-2-(4-((1-(4-Bromophenyl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol (41)**



Compound **41** was prepared from **34** (200 mg, 0.349 mmol) and (2-hydroxyphenyl)boronic acid (48 mg, 0.348 mmol) as described in General Procedure B. Purification was by two rounds of flash chromatography (first: silica-gel EtOAc/*n*-pentane, 1:1,  $R_f$  = 0.45, then: C18 silica, acetone  $\text{H}_2\text{O}$ , 2:1, TLC (EtOAc/*n*-pentane, 1:1)  $R_f$  = 0.45). This gave 49 mg (0.091 mmol,

26%) as an off-white wax;  $[\alpha]_D^{20}$  = -88.8 (1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.35 (s, 1H), 7.47-7.44 (m, 2H), 7.38-7.35 (m, 1H), 7.31-7.28 (m, 3H), 7.20-7.06 (m, 2H), 7.01 (td,  $J$  = 7.5, 1.2 Hz, 1H), 6.36 (s, 1H), 5.49-5.43 (m, 3H), 5.21-5.19 (m, 1H), 3.68-3.65 (m, 2H), 1.63 (d,  $J$  = 6.8 Hz, 3H), 0.94-0.91 (m, 2H), -0.05 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 155.3, 154.9, 152.6, 152.0, 143.2, 133.7, 132.4, 131.9 (2C), 131.2, 128.0 (2C), 121.2, 121.0, 119.2, 118.1, 103.2, 100.1, 70.8, 67.3, 49.9, 23.1, 18.0, -1.4 (3C); IR (neat,  $\text{cm}^{-1}$ ): 3353, 3274, 3045, 2952, 2929, 1601, 1565, 1471, 1451, 1343, 1075, 859, 835, 756; HRMS (ASAP-TOF,  $m/z$ ): calcd. for  $\text{C}_{26}\text{H}_{32}\text{N}_4\text{O}_2^{79}\text{BrSi}$ , 539.1478  $[\text{M}+\text{H}]^+$ , found 539.1479.

**(R)-3-(4-((1-(4-bromophenyl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol (42)**



Compound **42** was synthesized from **34** (100 mg, 0.174 mmol) and (3-hydroxyphenyl)boronic acid (24 mg, 0.174 mmol) as described in General Procedure B. Purification by flash chromatography (silica, acetone/*n*-pentane, 1:2,  $R_f$  = 0.57) gave 50 mg (0.093 mmol, 53%) of an off-white wax;  $[\alpha]_D^{20}$  = -92.0 (1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.35 (s, 1H), 7.43-7.40 (m, 2H), 7.30-7.26 (m, 3H), 7.22-7.20 (m, 1H), 7.16-7.15 (m, 1H), 6.89-6.87 (ddd,  $J$  = 8.1, 2.5, 1.0 Hz, 1H), 6.39 (s, 1H), 5.54 (s, 2H), 5.49-5.44 (m, 1H), 5.40 (br s, 1H), 3.69-3.66 (m, 2H), 1.62 (d,  $J$  = 6.7 Hz, 3H), 0.92-0.87 (m, 2H), -0.07 (s, 9H) (OH-signal not observed);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 156.6, 155.2, 152.3, 152.0, 143.2, 138.8, 133.0, 131.9 (2C), 130.1, 127.9 (2C), 121.4, 121.1, 116.3, 115.9, 103.1, 98.4, 70.9, 66.7, 50.1, 23.3, 18.1, -1.3 (3C); IR (neat,  $\text{cm}^{-1}$ ): 3333, 3015, 2952, 2929, 2894, 1598, 1564, 1471, 1345, 1215, 1073, 858, 833, 752; HRMS (ASAP-TOF,  $m/z$ ): calcd. for  $\text{C}_{26}\text{H}_{32}\text{N}_4\text{O}_2^{79}\text{BrSi}$ , 539.1478  $[\text{M}+\text{H}]^+$ , found 539.1479.

# NMR spectroscopy

## Compound 1

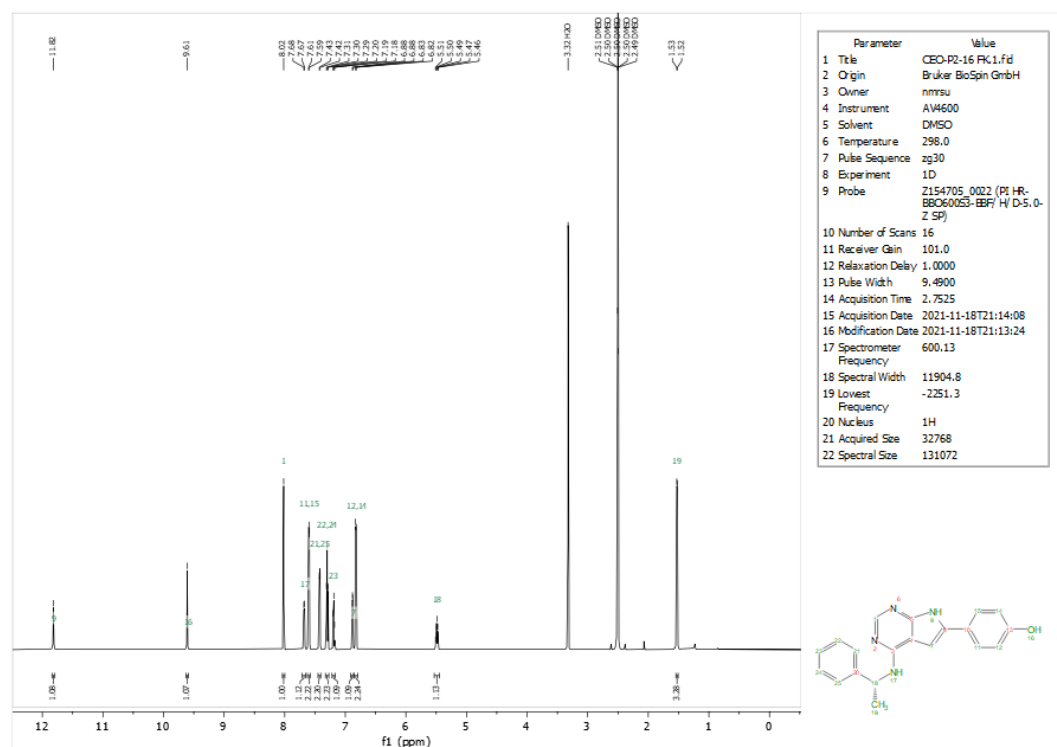


Figure S1: <sup>1</sup>H NMR spectrum of compound 1 at 600 MHz in DMSO-*d*<sub>6</sub>

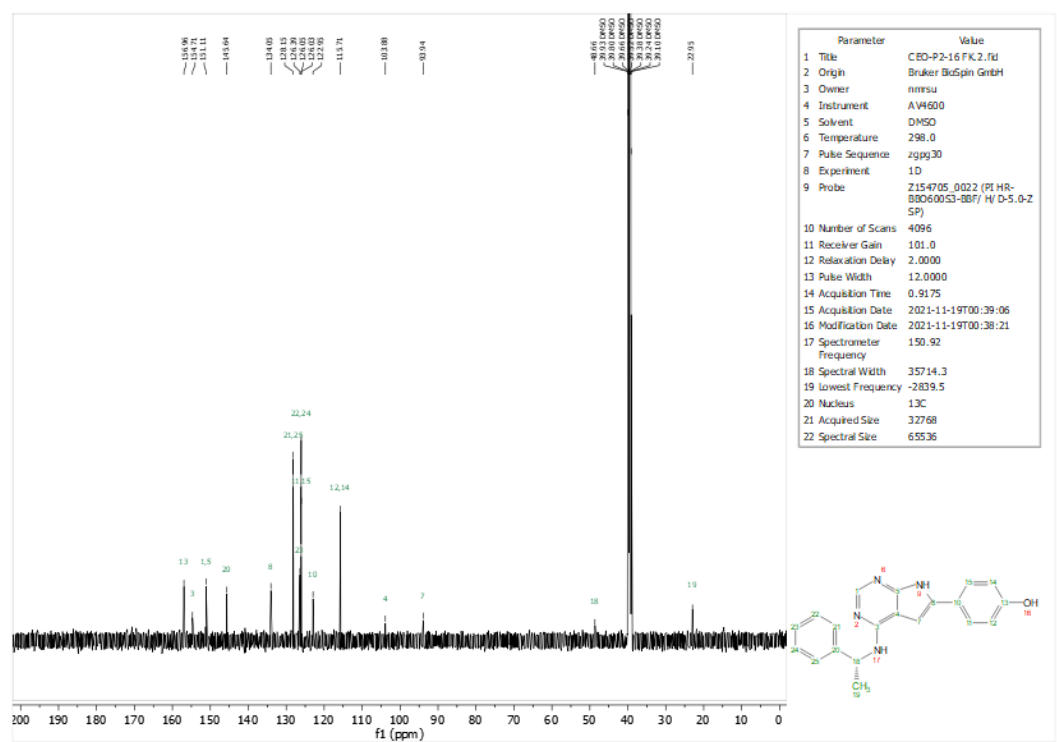


Figure S2: <sup>13</sup>C NMR spectrum of compound 1 at 150 MHz in DMSO-*d*<sub>6</sub>

## Compound 2

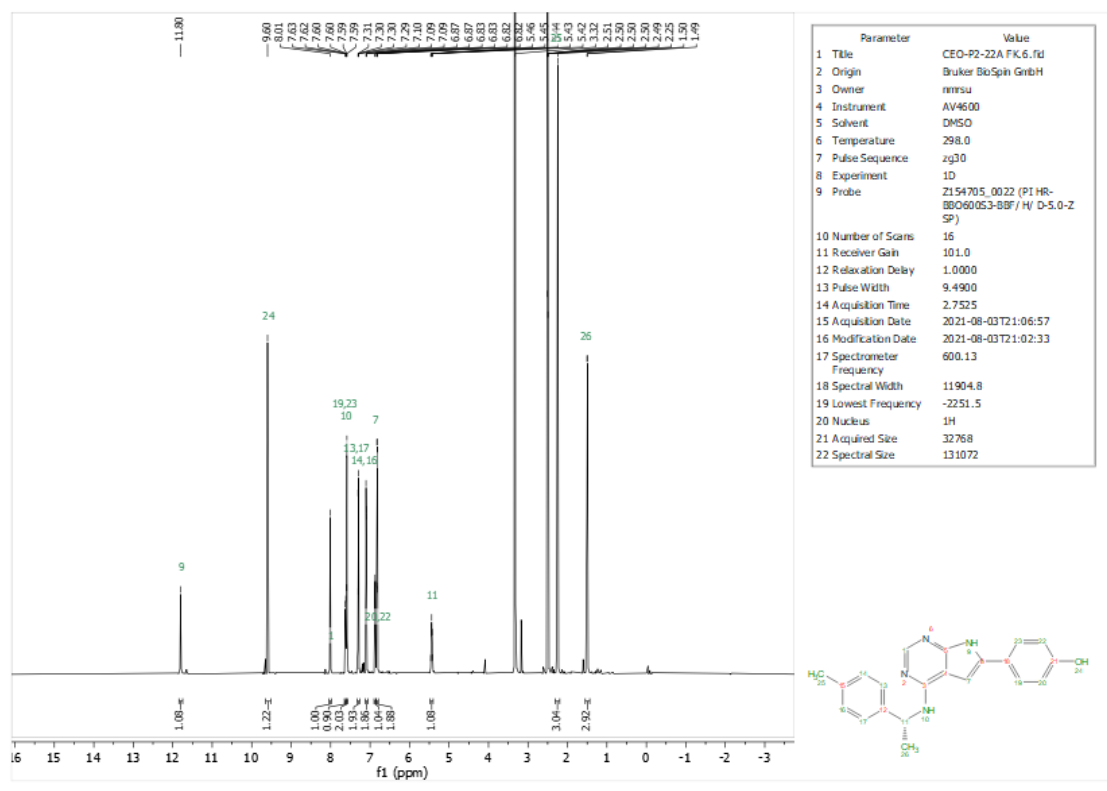
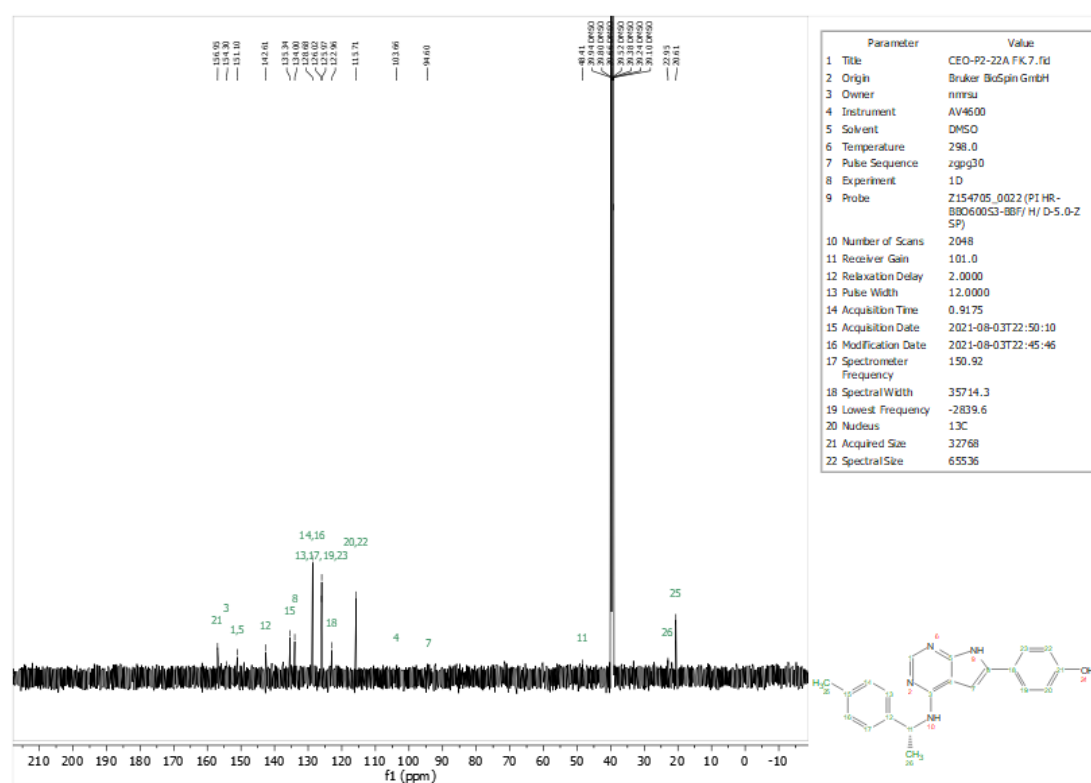


Figure S3: <sup>1</sup>H NMR spectrum of compound 2 at 600 MHz in DMSO-*d*<sub>6</sub>



## Compound 4

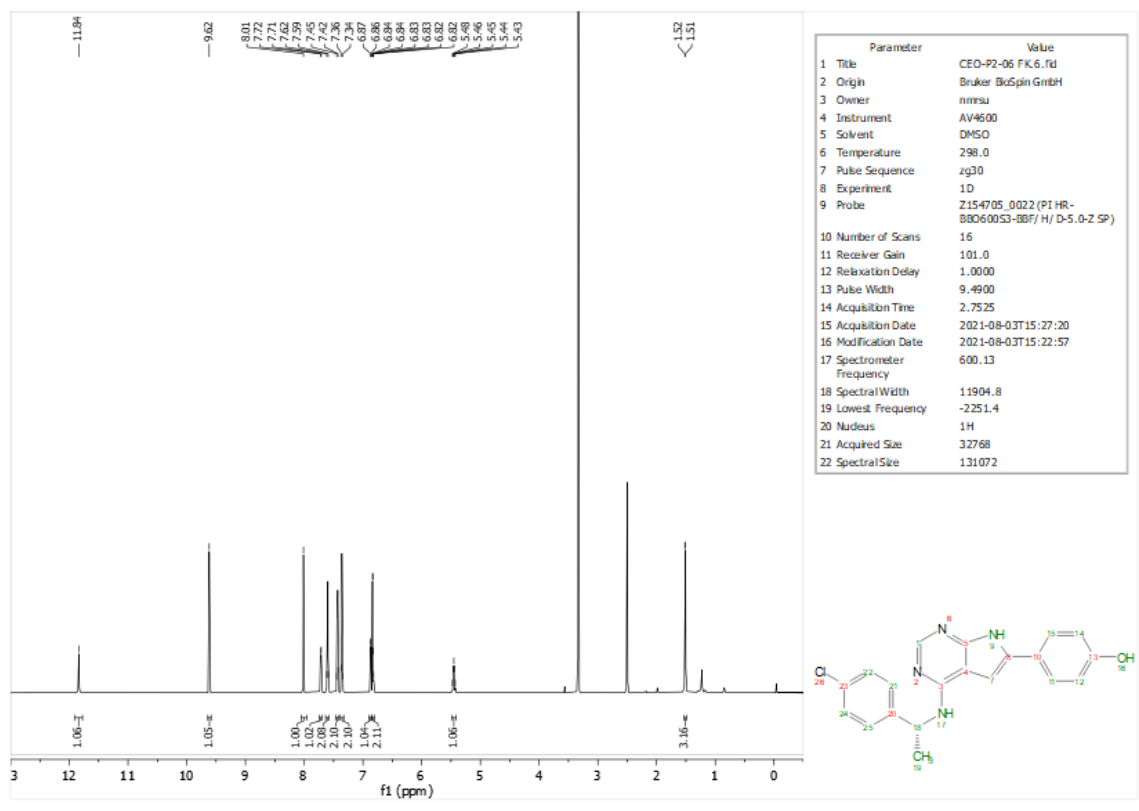


Figure S5:  $^1\text{H}$  NMR spectrum of compound 4 at 600 MHz in  $\text{DMSO}-d_6$

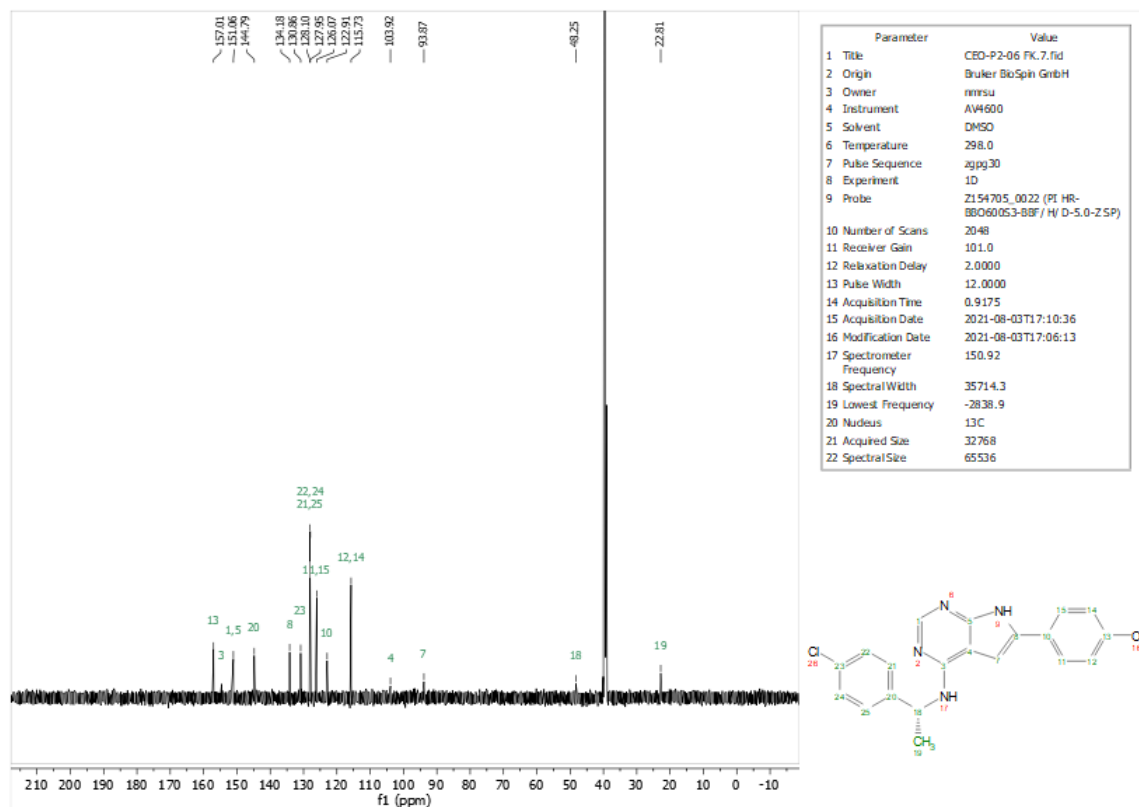
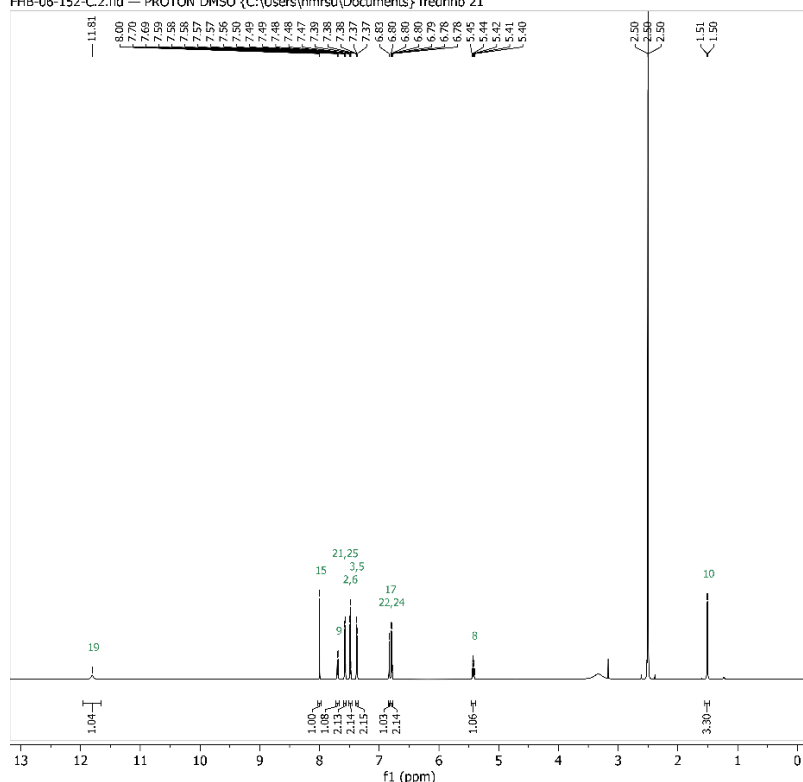


Figure S6:  $^{13}\text{C}$  NMR spectrum of compound 4 at 150 MHz in  $\text{DMSO}-d_6$

# Compound 5

FHB-06-152-C.2.fid — PROTON DMSO {C:\Users\nmrsl\Documents} fredrihb 21



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Owner	nmrsu
3 Instrument	spect
4 Solvent	DMSO
5 Temperature	298.0
6 Pulse Sequence	zg30
7 Experiment	1D
8 Probe	Z117768_0061 (CP TCI 600S3 H-C/ N-D-05 Z)
9 Number of Scans	16
10 Receiver Gain	11.5
11 Relaxation Delay	1.0000
12 Pulse Width	8.0000
13 Presaturation Frequency	
14 Acquisition Time	2.7263
15 Acquisition Date	2021-04-13T09:40:50
16 Modification Date	2021-04-13T09:40:50
17 Spectrometer Frequency	600.18
18 Spectral Width	12019.2
19 Lowest Frequency	-2303.5
20 Nucleus	1H
21 Acquired Size	32768
22 Spectral Size	131072
23 Digital Resolution	0.09

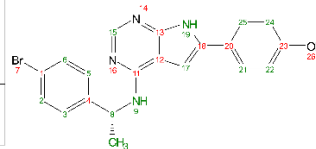
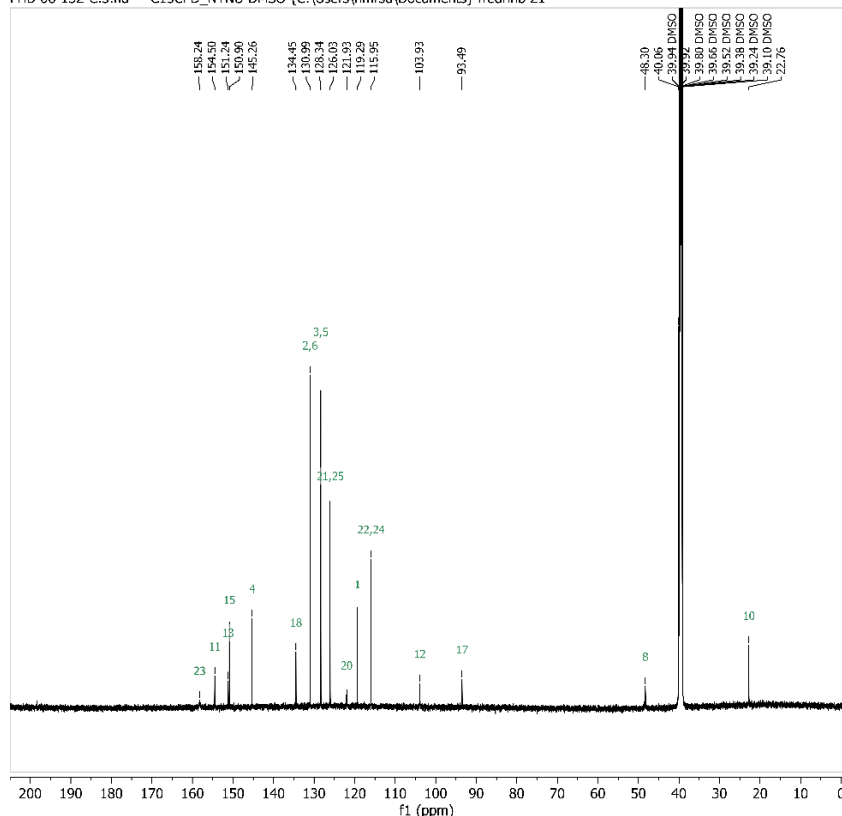


Figure S7:  $^1\text{H}$  NMR spectrum of compound 5 at 600 MHz in  $\text{DMSO}-d_6$

FHB-06-152-C.3.fid — C13CPD\_NTNU DMSO {C:\Users\nmrsl\Documents} fredrihb 21



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Owner	nmrsu
3 Instrument	spect
4 Solvent	DMSO
5 Temperature	300.0
6 Pulse Sequence	zgpg30
7 Experiment	1D
8 Probe	Z117768_0061 (CP TCI 600S3 H-C/ N-D-05 Z)
9 Number of Scans	2048
10 Receiver Gain	197.1
11 Relaxation Delay	2.0000
12 Pulse Width	11.4000
13 Presaturation Frequency	
14 Acquisition Time	0.9088
15 Acquisition Date	2021-04-13T11:24:37
16 Modification Date	2021-04-13T11:24:37
17 Spectrometer Frequency	150.93
18 Spectral Width	36057.7
19 Lowest Frequency	-3012.3
20 Nucleus	13C
21 Acquired Size	32768
22 Spectral Size	65536
23 Digital Resolution	0.55

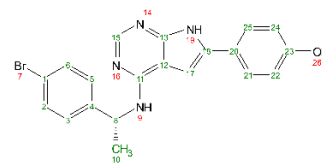


Figure S8:  $^{13}\text{C}$  NMR spectrum of compound 5 at 150 MHz in  $\text{DMSO}-d_6$

## Compound 6

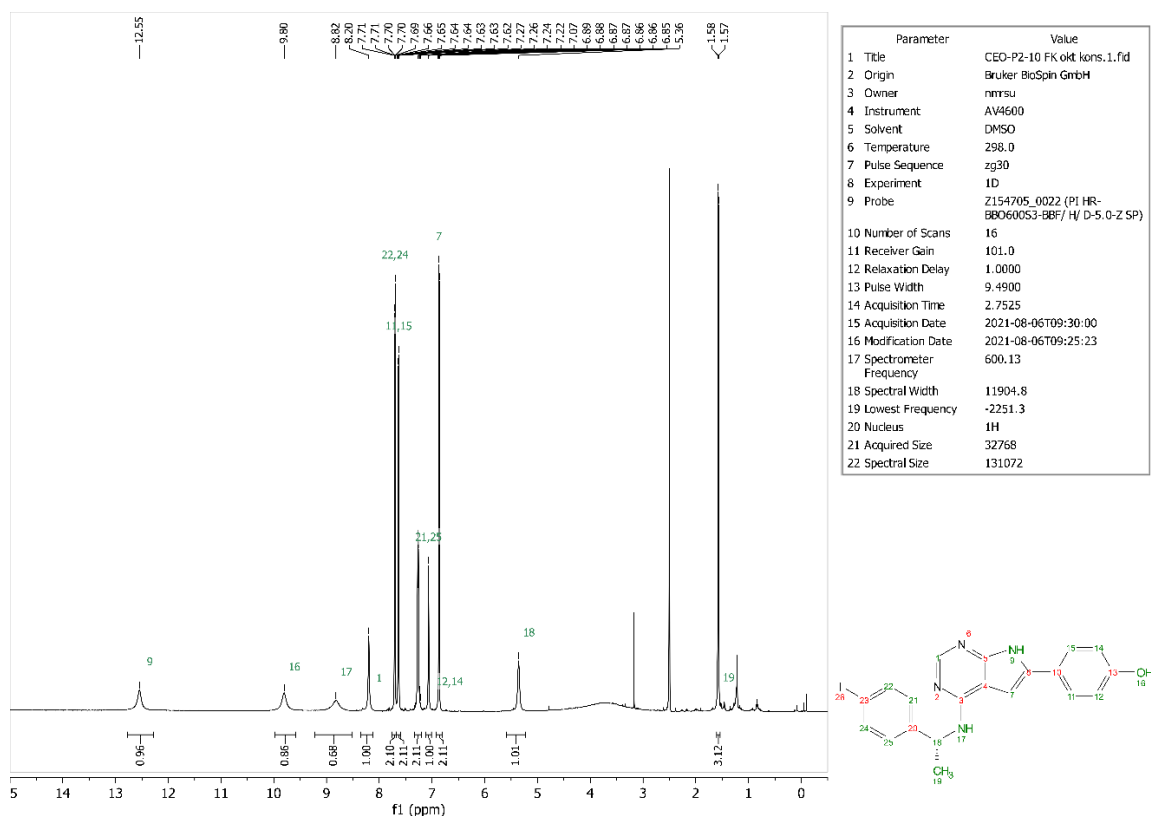


Figure S9: <sup>1</sup>H NMR spectrum of compound 6 at 600 MHz in DMSO-d<sub>6</sub>

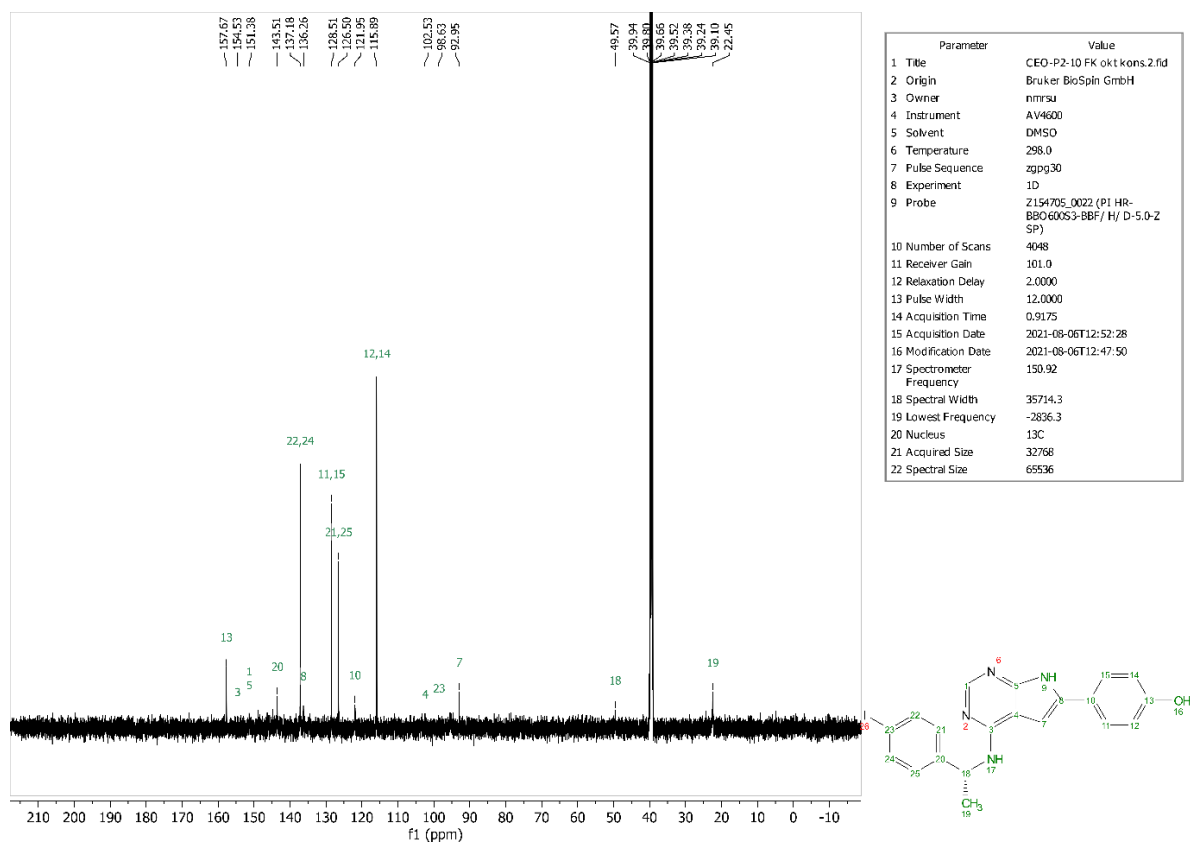


Figure S10: <sup>13</sup>C NMR spectrum of compound 6 at 150 MHz in DMSO-d<sub>6</sub>



## Compound 7

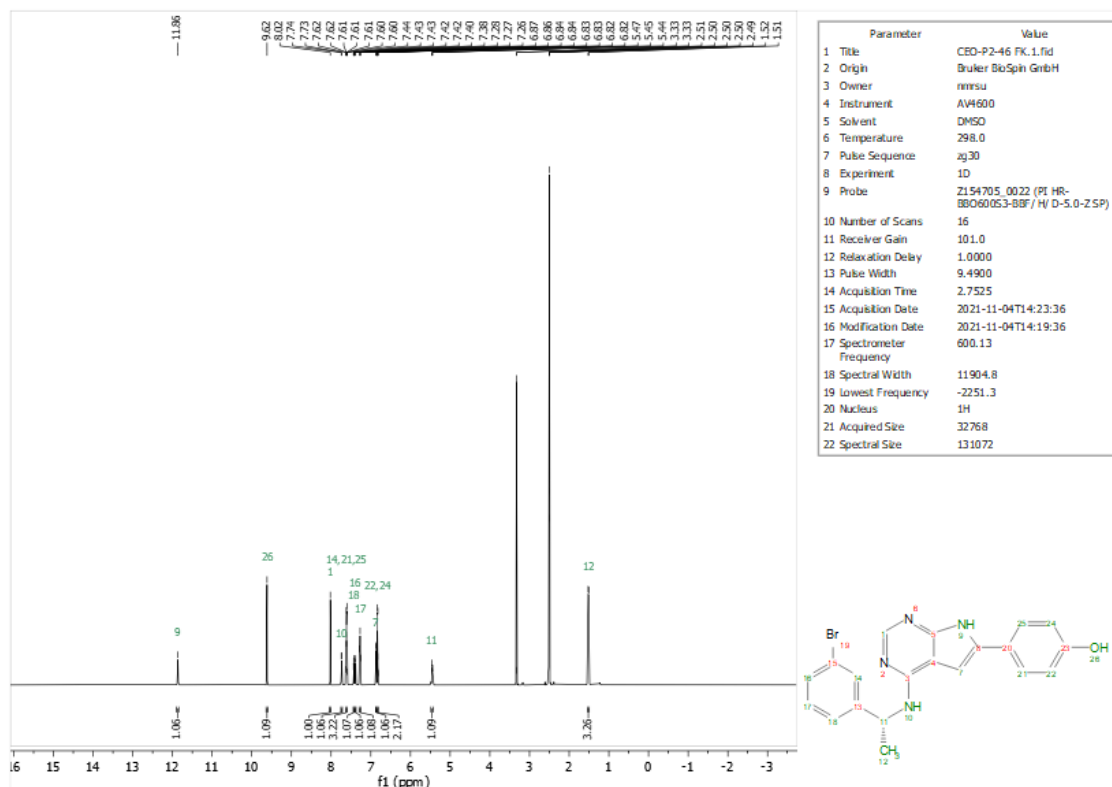


Figure S11:  $^1\text{H}$  NMR spectrum of compound 7 at 600 MHz in  $\text{DMSO}-d_6$

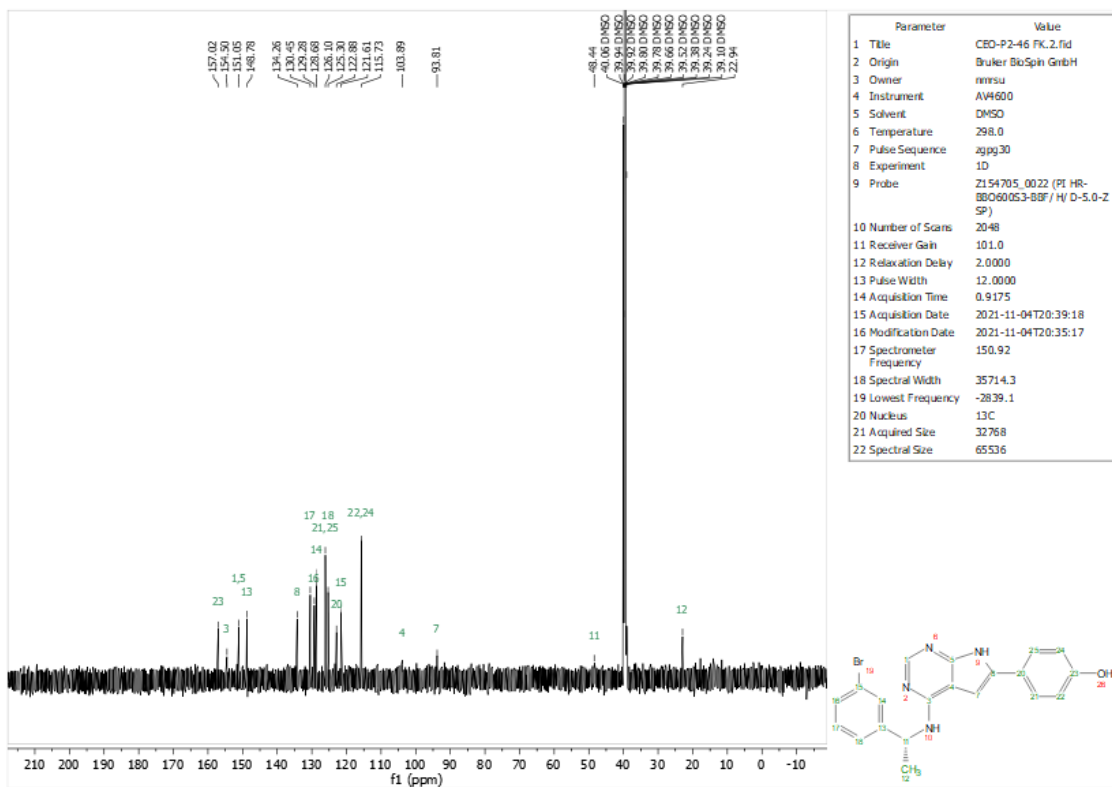


Figure S12:  $^{13}\text{C}$  NMR spectrum of compound 7 at 150 MHz in  $\text{DMSO}-d_6$

## Compound 8

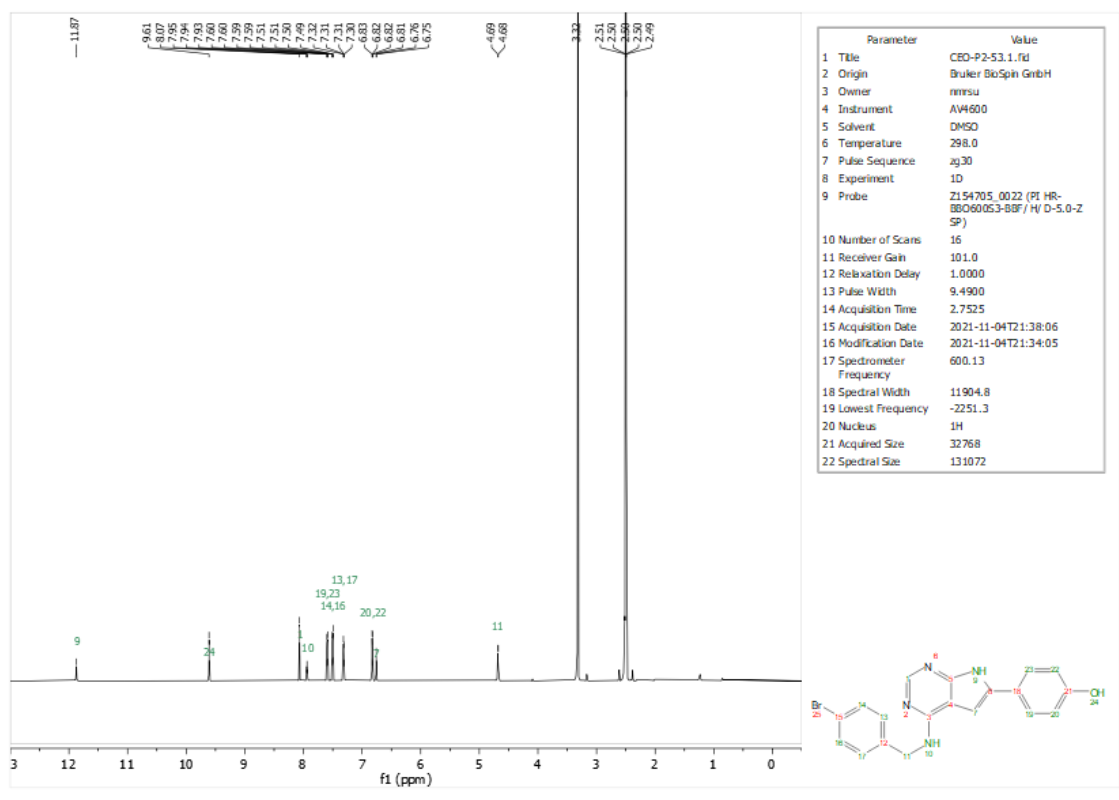


Figure S13: <sup>1</sup>H NMR spectrum of compound 8 at 600 MHz in DMSO-*d*<sub>6</sub>

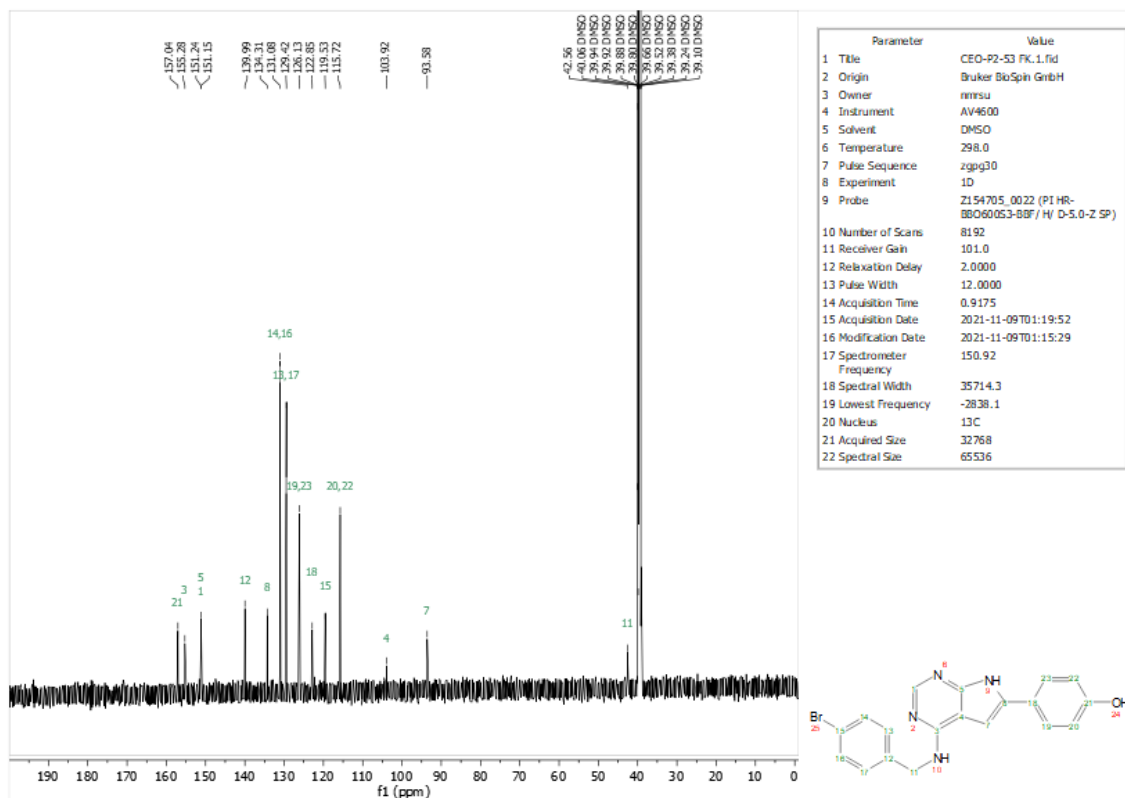


Figure S14: <sup>13</sup>C NMR spectrum of compound 8 at 150 MHz in DMSO-*d*<sub>6</sub>

## Compound 9

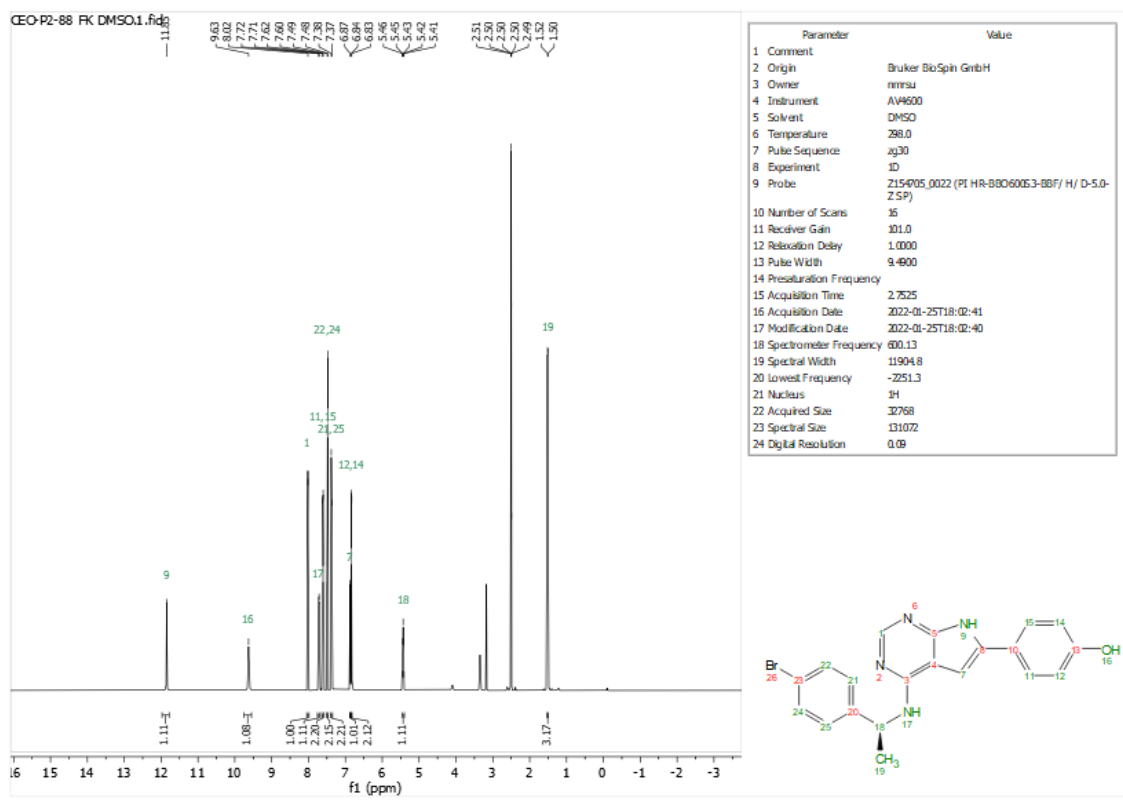


Figure S15: <sup>1</sup>H NMR spectrum of compound 9 at 600 MHz in DMSO-*d*<sub>6</sub>

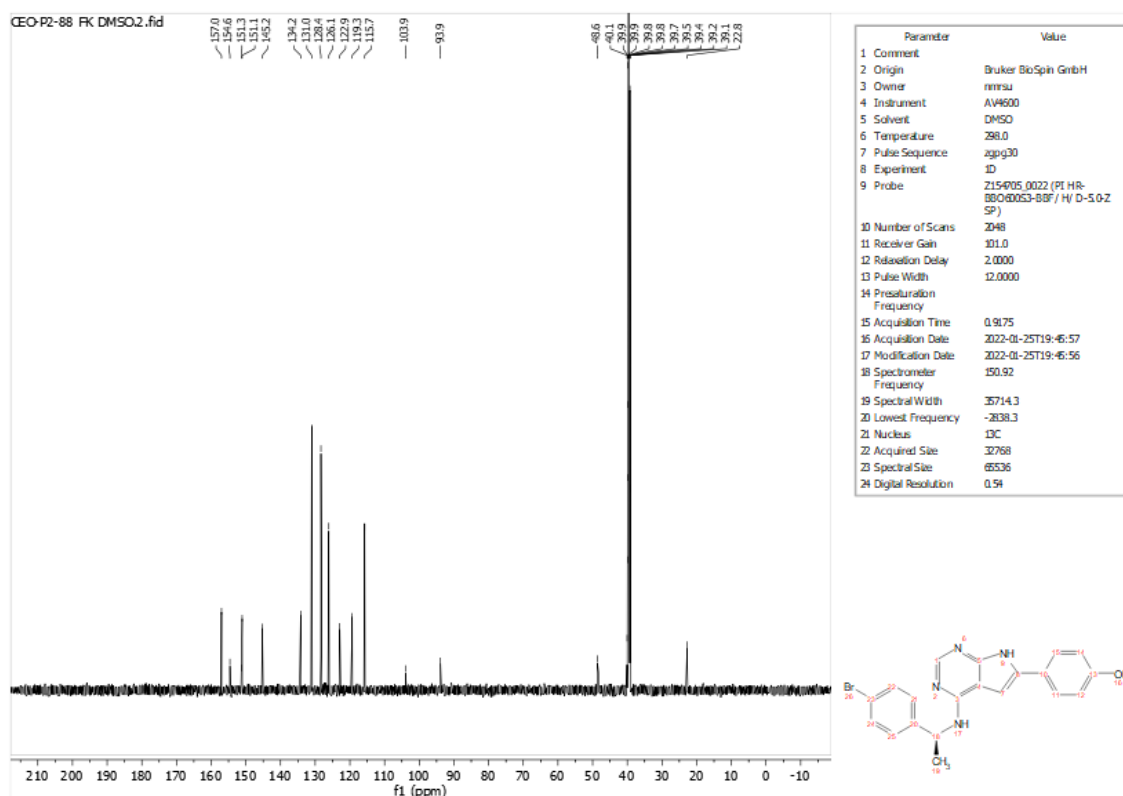


Figure S16: <sup>13</sup>C NMR spectrum of compound 9 at 150 MHz in DMSO-*d*<sub>6</sub>

## Compound 10

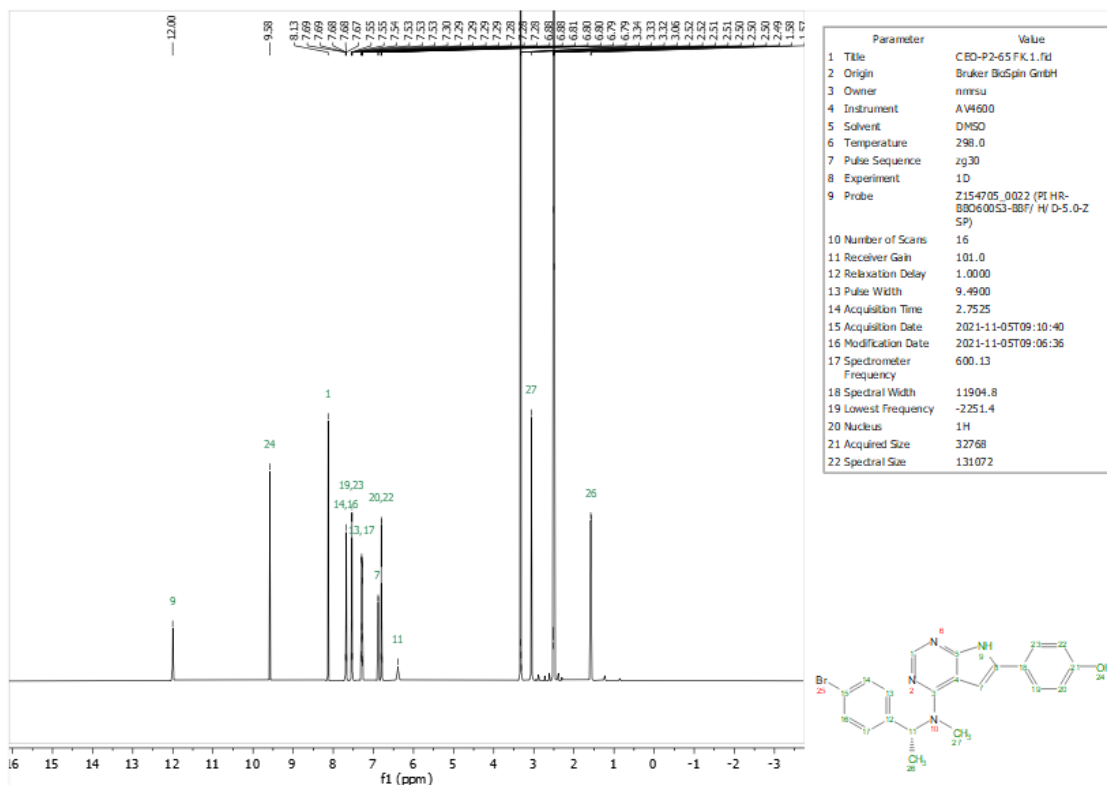


Figure S17: <sup>1</sup>H NMR spectrum of compound 10 at 600 MHz in DMSO-*d*<sub>6</sub>

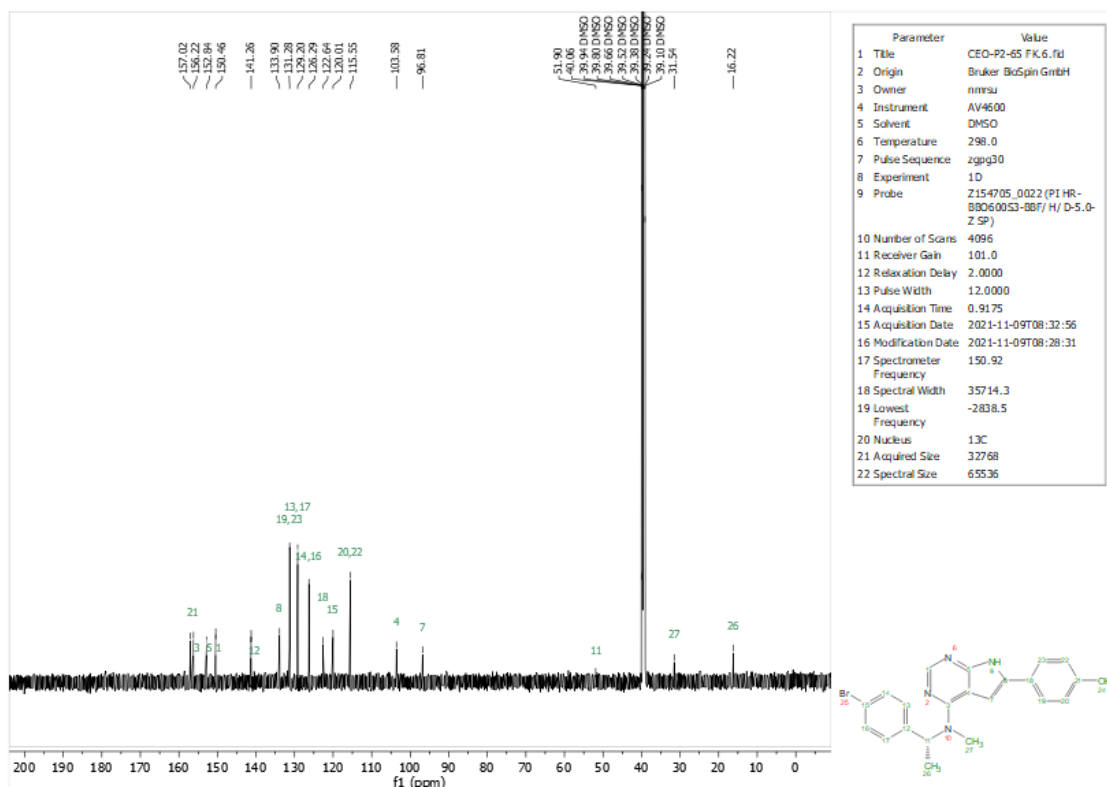


Figure S18: <sup>13</sup>C NMR spectrum of compound 10 at 150 MHz in DMSO-*d*<sub>6</sub>

# Compound 11

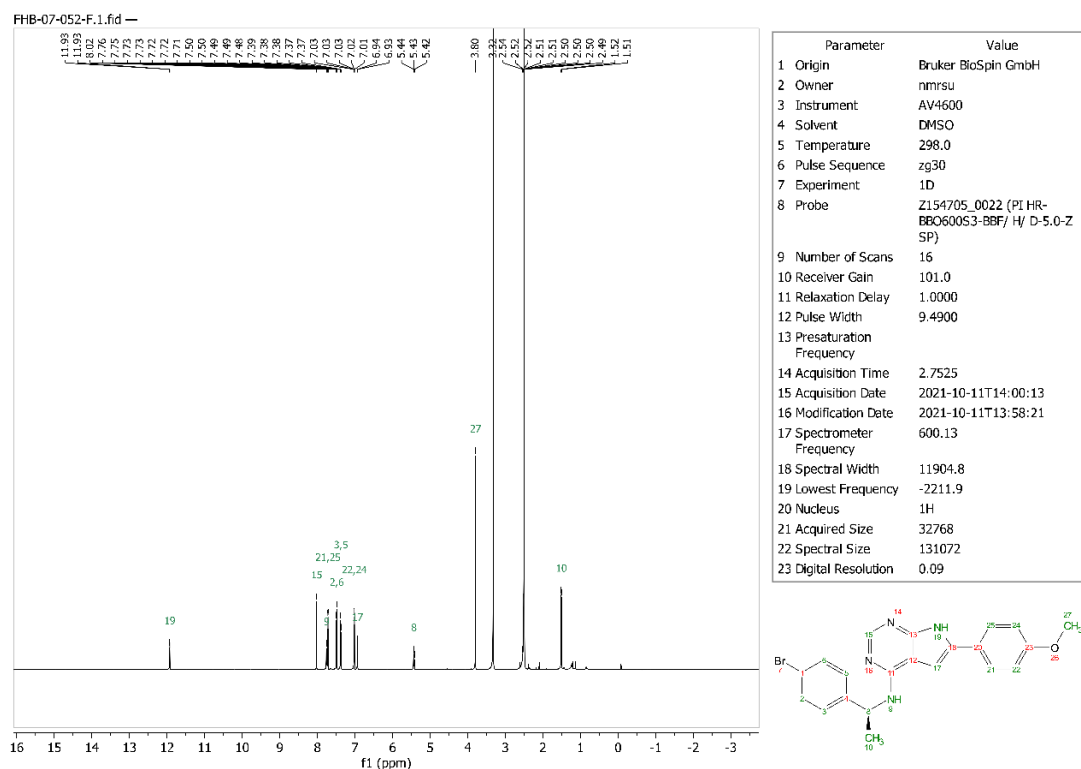


Figure S19: <sup>1</sup>H NMR spectrum of compound **11** at 600 MHz in DMSO-*d*<sub>6</sub>

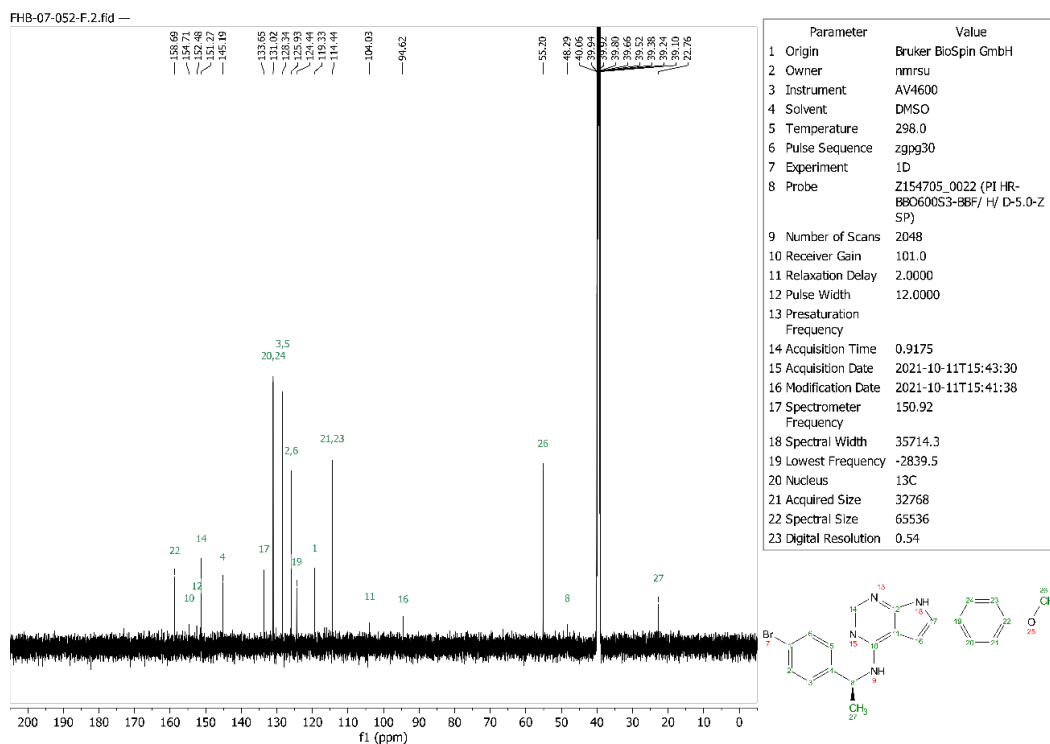
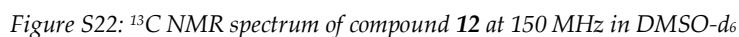
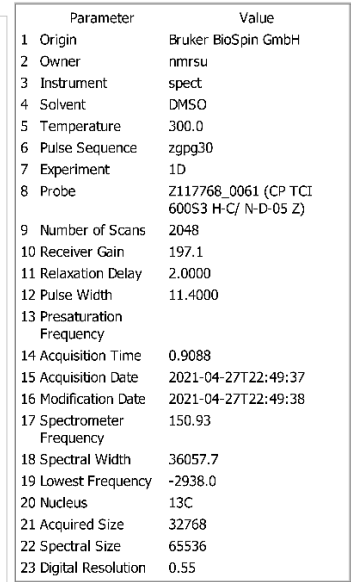
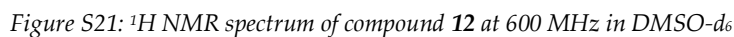
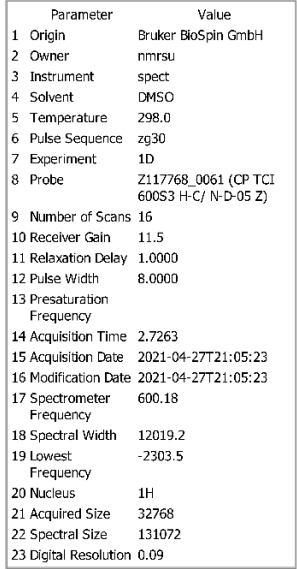


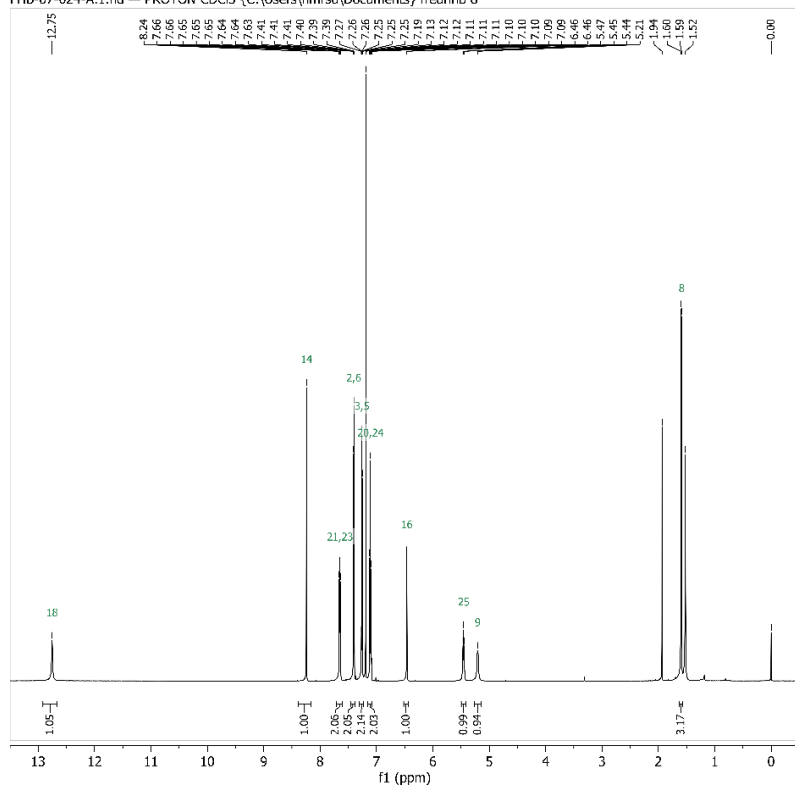
Figure S20: <sup>13</sup>C NMR spectrum of compound **11** at 150 MHz in DMSO-*d*<sub>6</sub>

## FHB-06-170-C.1.fid — PROTON DMSO {C:\Users\nmrsu\Documents} fredrihb 21



# Compound 13

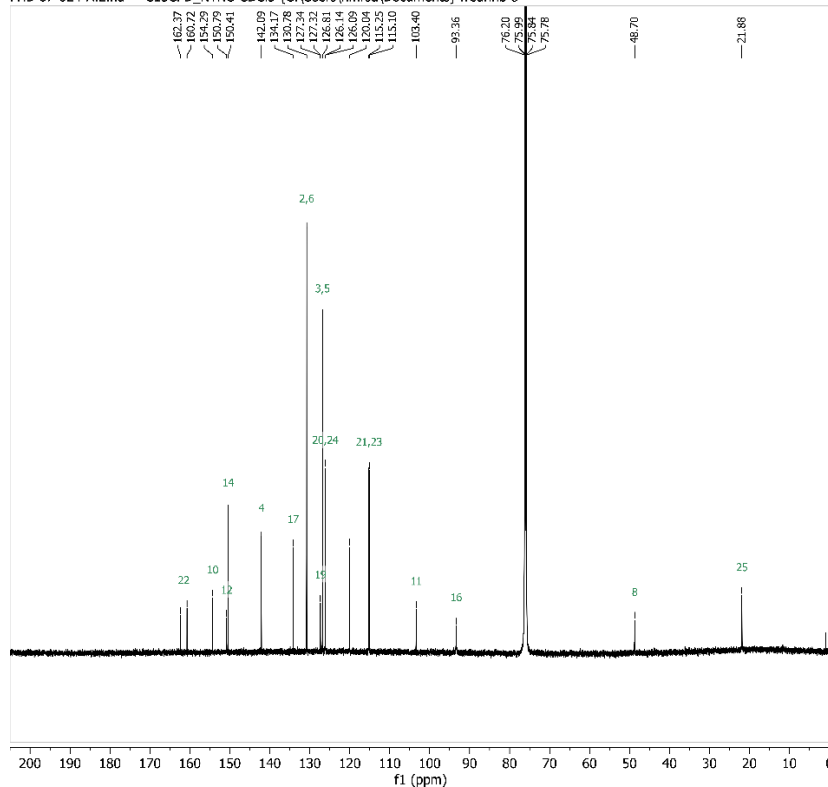
FHB-07-024-A.1.fid — PROTON CDCl<sub>3</sub> {C:\Users\nmrsl\Documents} fredrihb 8



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Owner	nmrsu
3 Instrument	spect
4 Solvent	CDCl <sub>3</sub>
5 Temperature	298.0
6 Pulse Sequence	zg30
7 Experiment	1D
8 Probe	Z117768_0061 (CP TCI 600S3 H-C/ N-D-05 Z)
9 Number of Scans	16
10 Receiver Gain	9.2
11 Relaxation Delay	1.0000
12 Pulse Width	8.0000
13 Presaturation Frequency	
14 Acquisition Time	2.7263
15 Acquisition Date	2021-08-05T14:11:02
16 Modification Date	2021-08-05T14:11:02
17 Spectrometer Frequency	600.18
18 Spectral Width	12019.2
19 Lowest Frequency	-2330.9
20 Nucleus	<sup>1</sup> H
21 Acquired Size	32768
22 Spectral Size	131072
23 Digital Resolution	0.09

Figure S23: <sup>1</sup>H NMR spectrum of compound 13 at 600 MHz in CDCl<sub>3</sub>

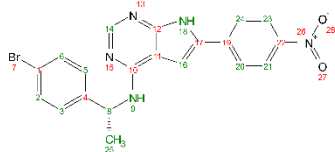
FHB-07-024-A.2.fid — C13CPD\_NTNU CDCl<sub>3</sub> {C:\Users\nmrsl\Documents} fredrihb 8



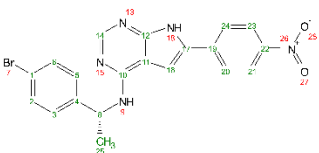
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Owner	nmrsu
3 Instrument	spect
4 Solvent	CDCl <sub>3</sub>
5 Temperature	300.0
6 Pulse Sequence	zgpg30
7 Experiment	1D
8 Probe	Z117768_0061 (CP TCI 600S3 H-C/ N-D-05 Z)
9 Number of Scans	2048
10 Receiver Gain	197.1
11 Relaxation Delay	2.0000
12 Pulse Width	11.4000
13 Presaturation Frequency	
14 Acquisition Time	0.9088
15 Acquisition Date	2021-08-05T15:54:58
16 Modification Date	2021-08-05T15:54:58
17 Spectrometer Frequency	150.93
18 Spectral Width	36057.7
19 Lowest Frequency	-3228.6
20 Nucleus	<sup>13</sup> C
21 Acquired Size	32768
22 Spectral Size	65536
23 Digital Resolution	0.55

Figure S24: <sup>13</sup>C NMR spectrum of compound 13 at 150 MHz in CDCl<sub>3</sub>

## FHB-07-032-E.1.fid — Etter sonikering — PROTON DMSO {C:\Users\nmrsl\Documents} fredrihb 3



FHB-07-032-E.2.fid — Etter sonikering — C13CPD\_NTNU DMSO {C:\Users\nmrslu\Documents} fredrihb 3

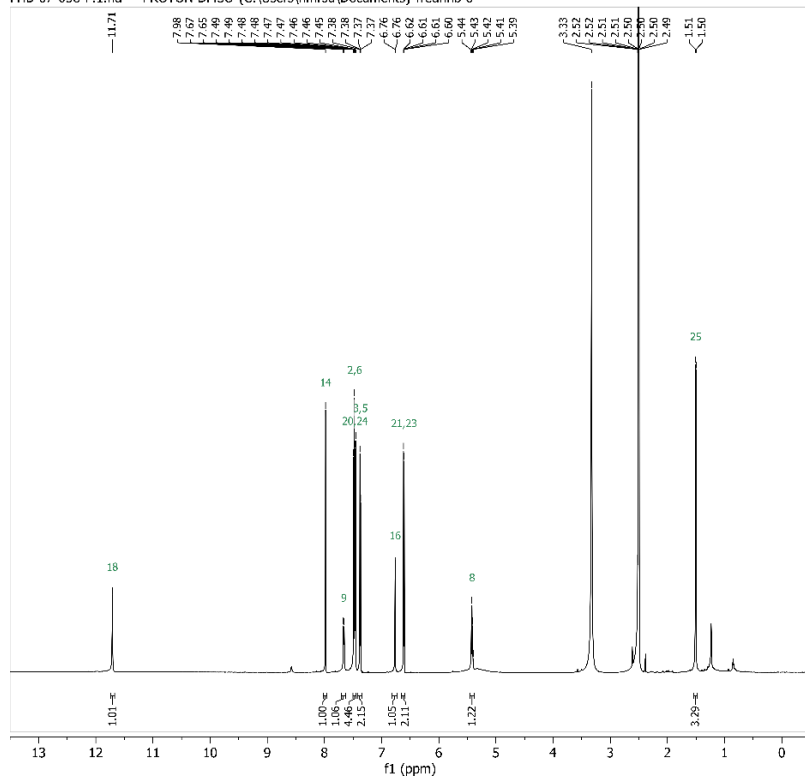


24



# Compound 15

FHB-07-038-F.1.fid — PROTON DMSO {C:\Users\nmrsu\Documents} fredrihb 6



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Owner	nmrsu
3 Instrument	spect
4 Solvent	DMSO
5 Temperature	298.0
6 Pulse Sequence	zg30
7 Experiment	1D
8 Probe	Z117768_0061 (CP TCI 600S3 H-C/ N-D-05 Z)
9 Number of Scans	16
10 Receiver Gain	9.2
11 Relaxation Delay	1.0000
12 Pulse Width	8.0000
13 Presaturation Frequency	
14 Acquisition Time	2.7263
15 Acquisition Date	2021-08-18T10:41:19
16 Modification Date	2021-08-18T10:41:19
17 Spectrometer	600.18
18 Spectral Width	12019.2
19 Lowest Frequency	-2308.4
20 Nucleus	1H
21 Acquired Size	32768
22 Spectral Size	131072
23 Digital Resolution	0.09

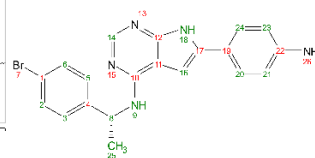
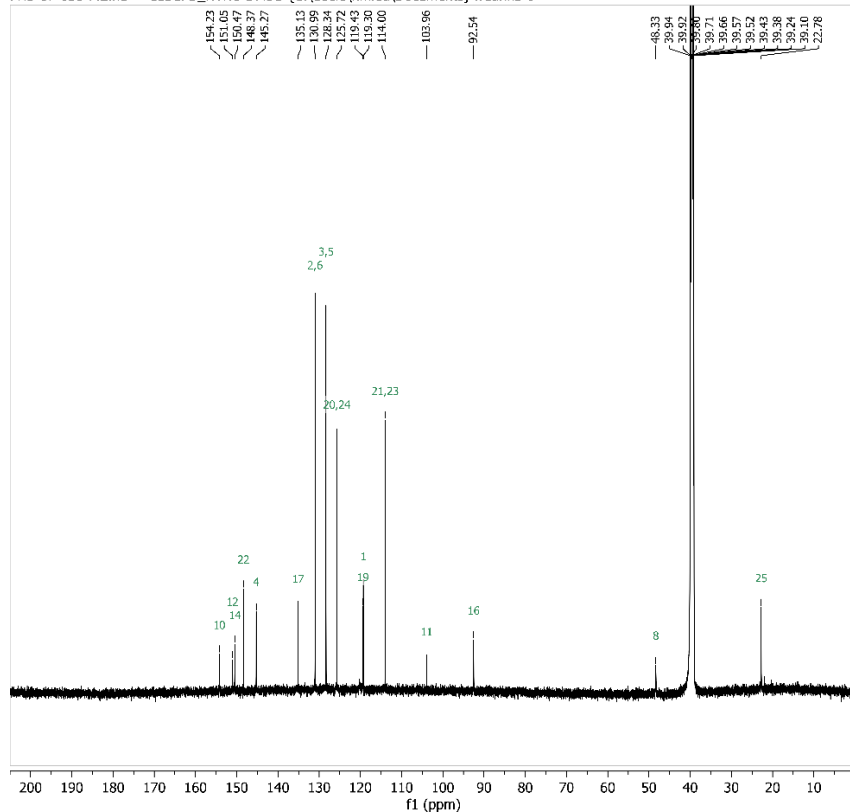


Figure S27: <sup>1</sup>H NMR spectrum of compound 15 at 600 MHz in DMSO-d<sub>6</sub>

FHB-07-038-F.2.fid — C13CPD\_NTNU DMSO {C:\Users\nmrsu\Documents} fredrihb 6



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Owner	nmrsu
3 Instrument	spect
4 Solvent	DMSO
5 Temperature	300.0
6 Pulse Sequence	zgpg30
7 Experiment	1D
8 Probe	Z117768_0061 (CP TCI 600S3 H-C/ N-D-05 Z)
9 Number of Scans	2048
10 Receiver Gain	197.1
11 Relaxation Delay	2.0000
12 Pulse Width	11.4000
13 Presaturation Frequency	
14 Acquisition Time	0.9088
15 Acquisition Date	2021-08-18T12:33:05
16 Modification Date	2021-08-18T12:33:05
17 Spectrometer	150.93
18 Spectral Width	36057.7
19 Lowest Frequency	-3011.7
20 Nucleus	13C
21 Acquired Size	32768
22 Spectral Size	65536
23 Digital Resolution	0.55

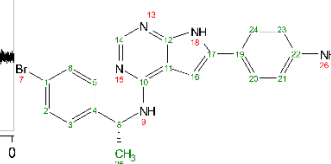
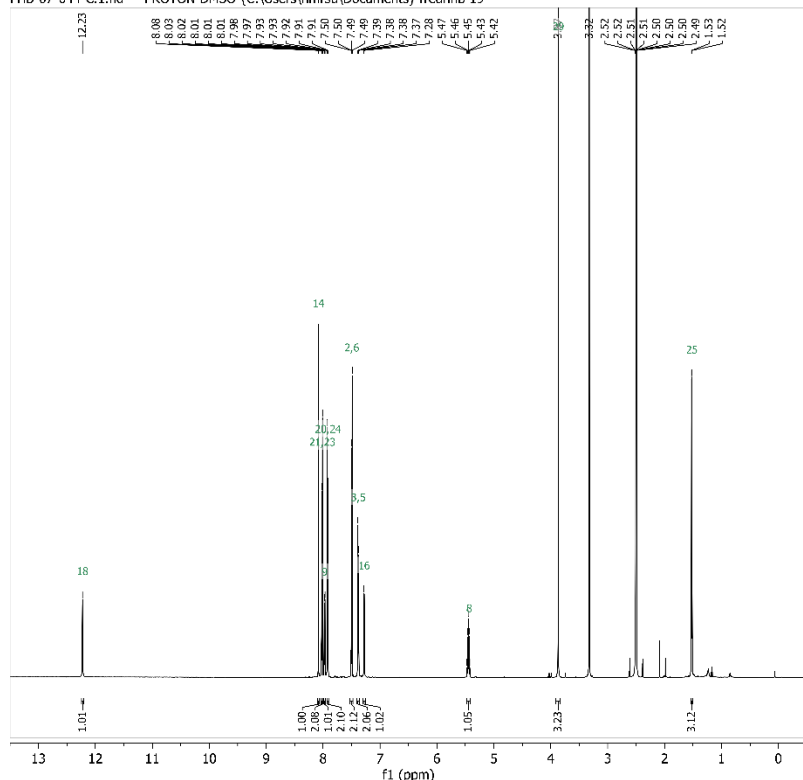


Figure S28: <sup>13</sup>C NMR spectrum of compound 15 at 150 MHz in DMSO-d<sub>6</sub>

# Compound 16

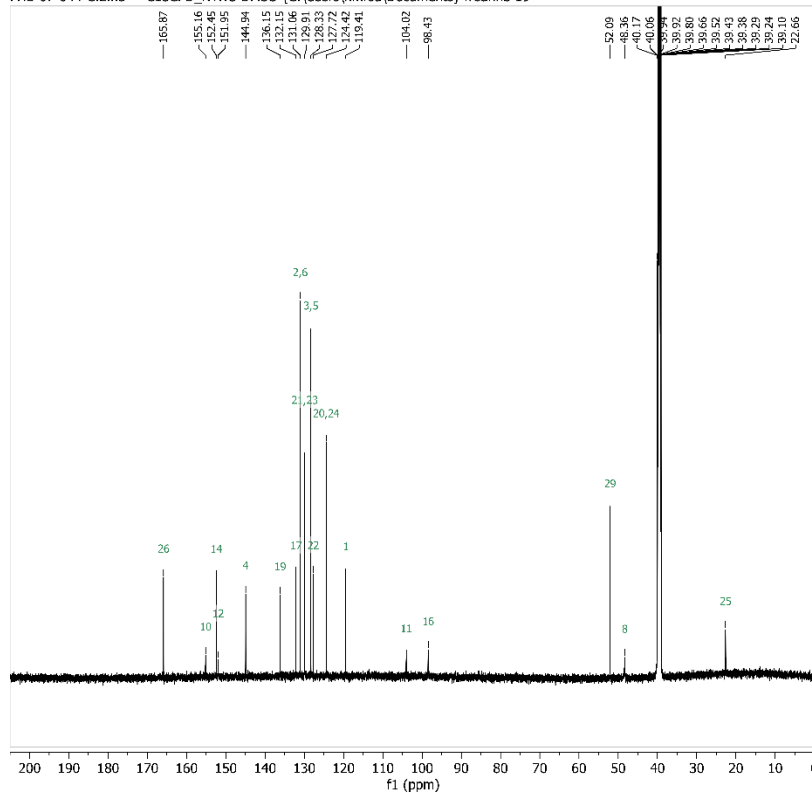
FHB-07-044-C.1.fid — PROTON DMSO {C:\Users\nmrsl\Documents} fredrihb 19



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Owner	nmrsu
3 Instrument	spect
4 Solvent	DMSO
5 Temperature	298.0
6 Pulse Sequence	zg30
7 Experiment	1D
8 Probe	Z117768_0061 (CP TCI 60053 H-C/ N-D-05 Z)
9 Number of Scans	16
10 Receiver Gain	9.2
11 Relaxation Delay	1.0000
12 Pulse Width	8.0000
13 Presaturation Frequency	
14 Acquisition Time	2.7263
15 Acquisition Date	2021-08-26T08:40:46
16 Modification Date	2021-08-26T08:40:46
17 Spectrometer Frequency	600.18
18 Spectral Width	12019.2
19 Lowest Frequency	-2344.1
20 Nucleus	<sup>1</sup> H
21 Acquired Size	32768
22 Spectral Size	131072
23 Digital Resolution	0.09

Figure S29: <sup>1</sup>H NMR spectrum of compound 16 at 600 MHz in DMSO-*d*<sub>6</sub>

FHB-07-044-C.2.fid — C13CPD\_NTNU DMSO {C:\Users\nmrsl\Documents} fredrihb 19

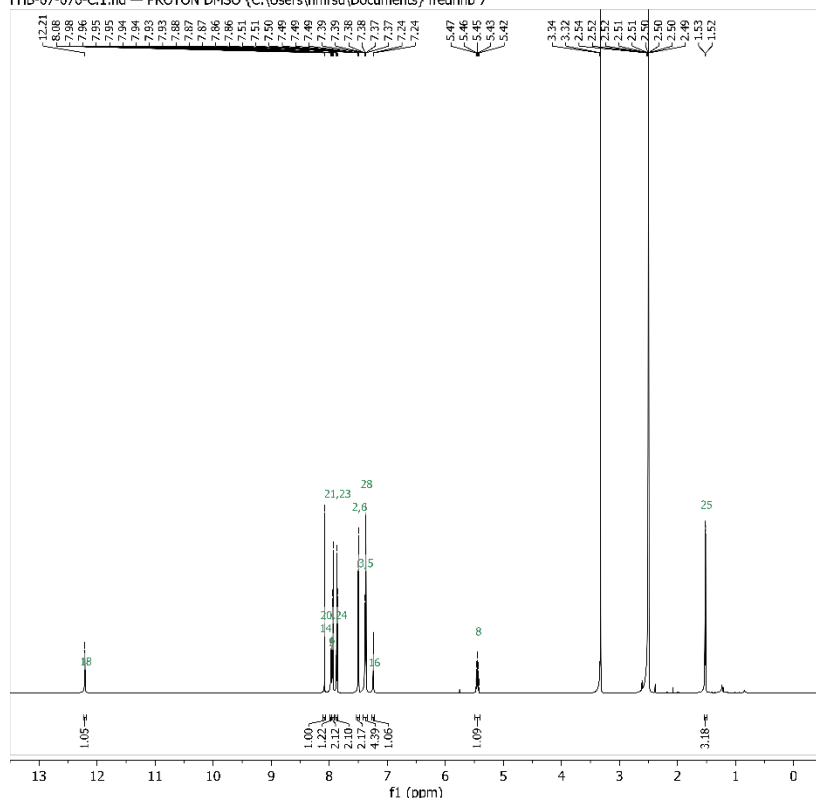


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Owner	nmrsu
3 Instrument	spect
4 Solvent	DMSO
5 Temperature	300.0
6 Pulse Sequence	zgpg30
7 Experiment	1D
8 Probe	Z117768_0061 (CP TCI 60053 H-C/ N-D-05 Z)
9 Number of Scans	2048
10 Receiver Gain	197.1
11 Relaxation Delay	2.0000
12 Pulse Width	11.4000
13 Presaturation Frequency	
14 Acquisition Time	0.9088
15 Acquisition Date	2021-08-26T10:25:46
16 Modification Date	2021-08-26T10:25:46
17 Spectrometer Frequency	150.93
18 Spectral Width	36057.7
19 Lowest Frequency	-3012.1
20 Nucleus	<sup>13</sup> C
21 Acquired Size	32768
22 Spectral Size	65536
23 Digital Resolution	0.55

Figure S30: <sup>13</sup>C NMR spectrum of compound 16 at 150 MHz in DMSO-*d*<sub>6</sub>

# Compound 17

FHB-07-076-C.1.fid — PROTON DMSO (C:\Users\nmrslu\Documents) fredrihb 7



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Owner	nmrsu
3 Instrument	spect
4 Solvent	DMSO
5 Temperature	298.0
6 Pulse Sequence	zg30
7 Experiment	1D
8 Probe	Z117768_0061 (CP TCI 600S3 H-C/ N-D-05 Z)
9 Number of Scans	16
10 Receiver Gain	9.2
11 Relaxation Delay	1.0000
12 Pulse Width	8.0000
13 Presaturation Frequency	
14 Acquisition Time	2.7263
15 Acquisition Date	2021-10-29T16:30:12
16 Modification Date	2021-10-29T16:30:12
17 Spectrometer Frequency	600.23
18 Spectral Width	12019.2
19 Lowest Frequency	-2303.2
20 Nucleus	1H
21 Acquired Size	32768
22 Spectral Size	131072
23 Digital Resolution	0.09

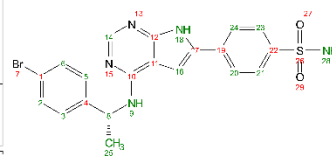
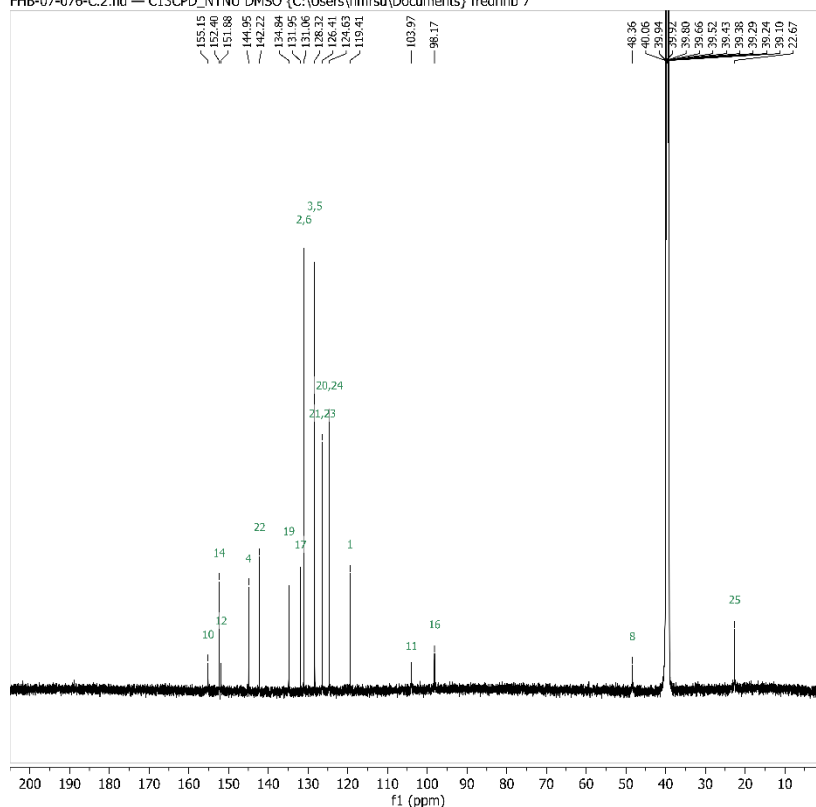


Figure S31: <sup>1</sup>H NMR spectrum of compound 17 at 600 MHz in DMSO-d<sub>6</sub>

FHB-07-076-C.2.fid — C13CPD\_NTNU DMSO (C:\Users\nmrslu\Documents) fredrihb 7



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Owner	nmrsu
3 Instrument	spect
4 Solvent	DMSO
5 Temperature	300.0
6 Pulse Sequence	zgpg30
7 Experiment	1D
8 Probe	Z117768_0061 (CP TCI 600S3 H-C/ N-D-05 Z)
9 Number of Scans	2048
10 Receiver Gain	197.1
11 Relaxation Delay	2.0000
12 Pulse Width	11.4000
13 Presaturation Frequency	
14 Acquisition Time	0.9088
15 Acquisition Date	2021-10-29T18:14:07
16 Modification Date	2021-10-29T18:14:07
17 Spectrometer Frequency	150.94
18 Spectral Width	36057.7
19 Lowest Frequency	-2936.8
20 Nucleus	13C
21 Acquired Size	32768
22 Spectral Size	65536
23 Digital Resolution	0.55

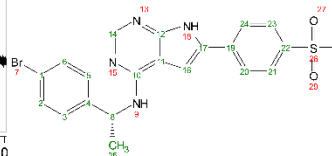
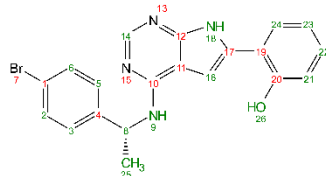
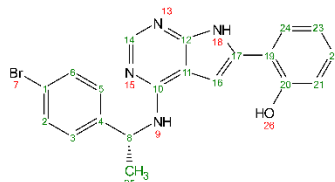


Figure S32: <sup>13</sup>C NMR spectrum of compound 17 at 150 MHz in DMSO-d<sub>6</sub>

## FHB-07-084-C.1.fid — PROTON DMSO {C:\Users\nmrsl\Documents} fredrihb 17



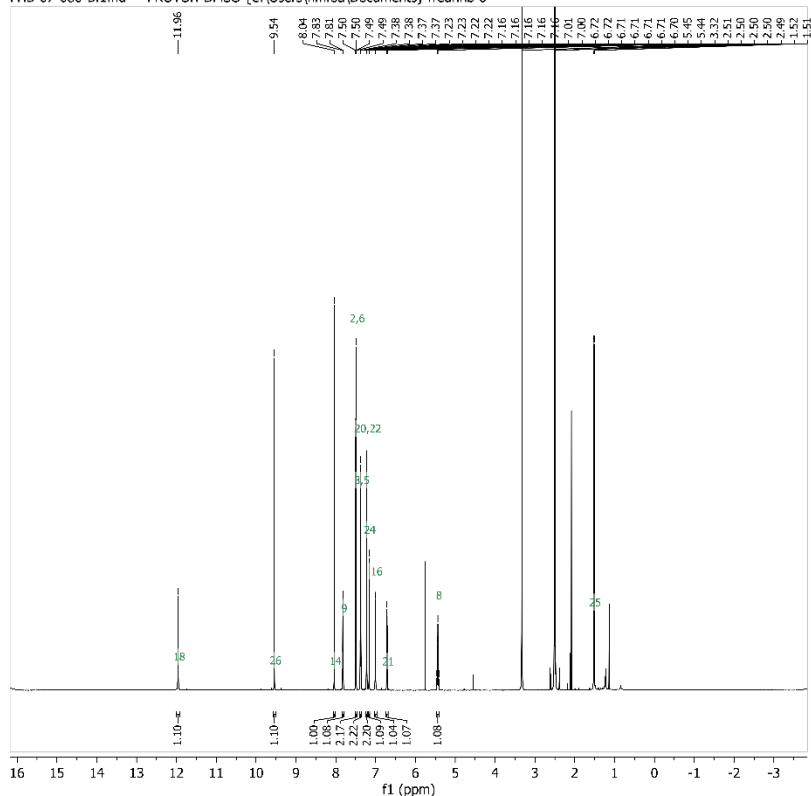
FHB-07-084-C.2.fid — C13CPD NTNU DMSO {C:\Users\nmrsl\Documents} fredrihb 17



28

# Compound 19

FHB-07-080-B.1.fid — PROTON DMSO {C:\Users\nmrsl\Documents} fredrihb 6



Parameter	Value
1 Title	FHB-07-080-B.1.fid
2 Origin	Bruker BioSpin GmbH
3 Owner	nmrsu
4 Instrument	spect
5 Solvent	DMSO
6 Temperature	298.0
7 Pulse Sequence	zg30
8 Experiment	1D
9 Probe	Z117768_0061 (CP TCI 600S3 H-C/ N-D-05 Z)
10 Number of Scans	16
11 Receiver Gain	9.2
12 Relaxation Delay	1.0000
13 Pulse Width	8.0000
14 Presaturation Frequency	
15 Acquisition Time	2.7263
16 Acquisition Date	2021-10-29T12:55:28
17 Modification Date	2021-10-29T12:55:28
18 Spectrometer Frequency	600.23
19 Spectral Width	12019.2
20 Lowest Frequency	-2307.9
21 Nucleus	1H
22 Acquired Size	32768
23 Spectral Size	131072
24 Digital Resolution	0.09

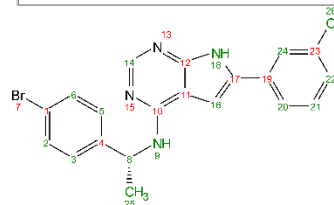
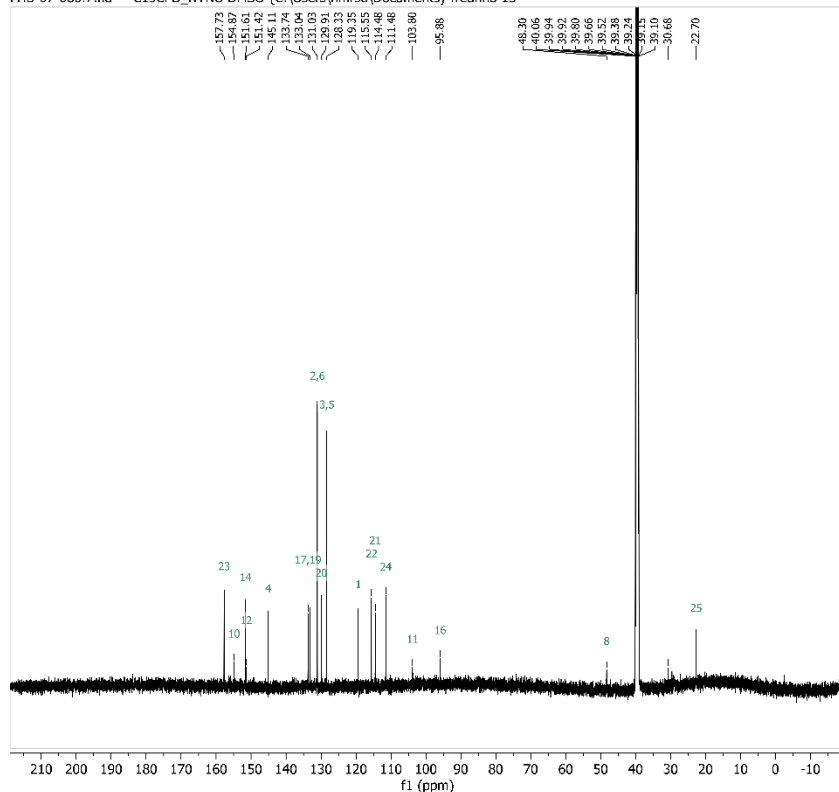


Figure S35:  $^1\text{H}$  NMR spectrum of compound **19** at 600 MHz in  $\text{DMSO}-d_6$

FHB-07-080.7.fid — C13CPD\_NTNU DMSO {C:\Users\nmrsl\Documents} fredrihb 15



Parameter	Value
1 Title	FHB-07-080.7.fid
2 Origin	Bruker BioSpin GmbH
3 Owner	nmrsu
4 Instrument	spect
5 Solvent	DMSO
6 Temperature	300.0
7 Pulse Sequence	zgpg30
8 Experiment	1D
9 Probe	Z117768_0061 (CP TCI 600S3 H-C/ N-D-05 Z)
10 Number of Scans	8192
11 Receiver Gain	197.1
12 Relaxation Delay	2.0000
13 Pulse Width	11.4000
14 Presaturation Frequency	
15 Acquisition Time	0.9088
16 Acquisition Date	2021-11-05T20:22:32
17 Modification Date	2021-11-05T20:22:32
18 Spectrometer Frequency	150.94
19 Spectral Width	36057.7
20 Lowest Frequency	-2936.8
21 Nucleus	13C
22 Acquired Size	32768
23 Spectral Size	65536
24 Digital Resolution	0.55

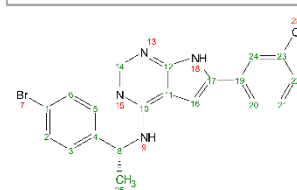


Figure S36:  $^{13}\text{C}$  NMR spectrum of compound **19** at 150 MHz in  $\text{DMSO}-d_6$

## Compound 20

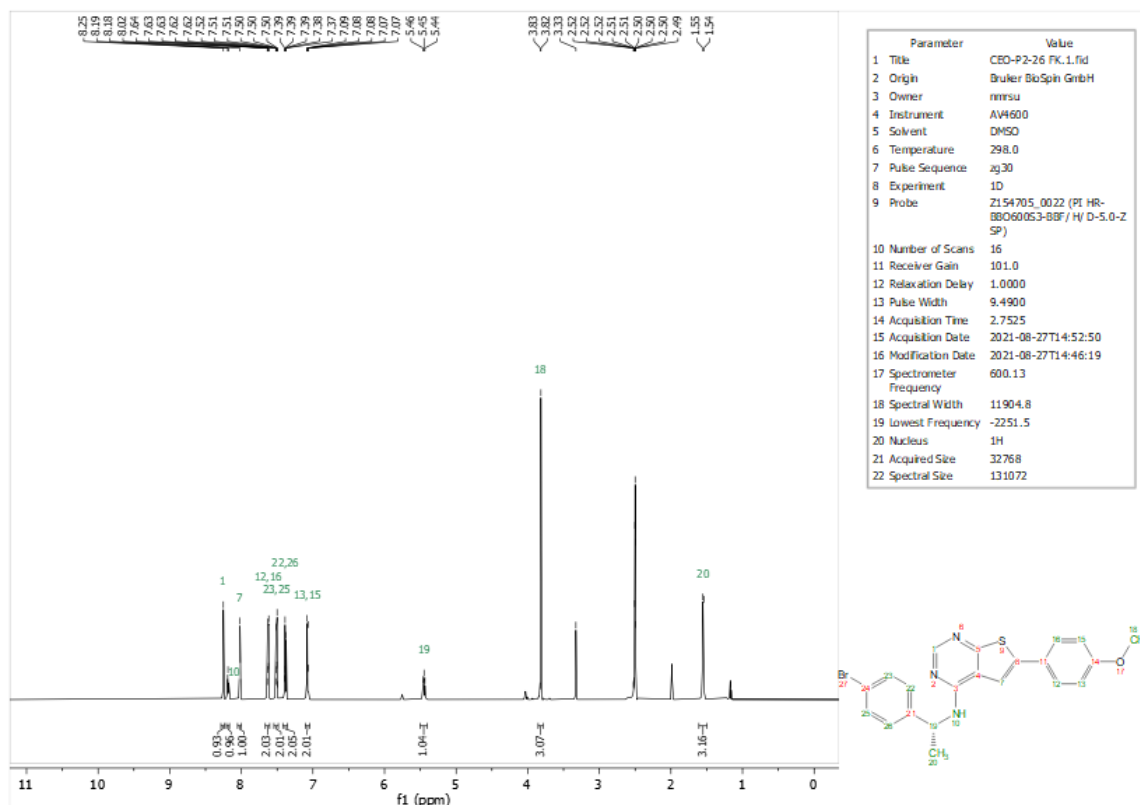


Figure S37: <sup>1</sup>H NMR spectrum of compound **20** at 600 MHz in DMSO-*d*<sub>6</sub>

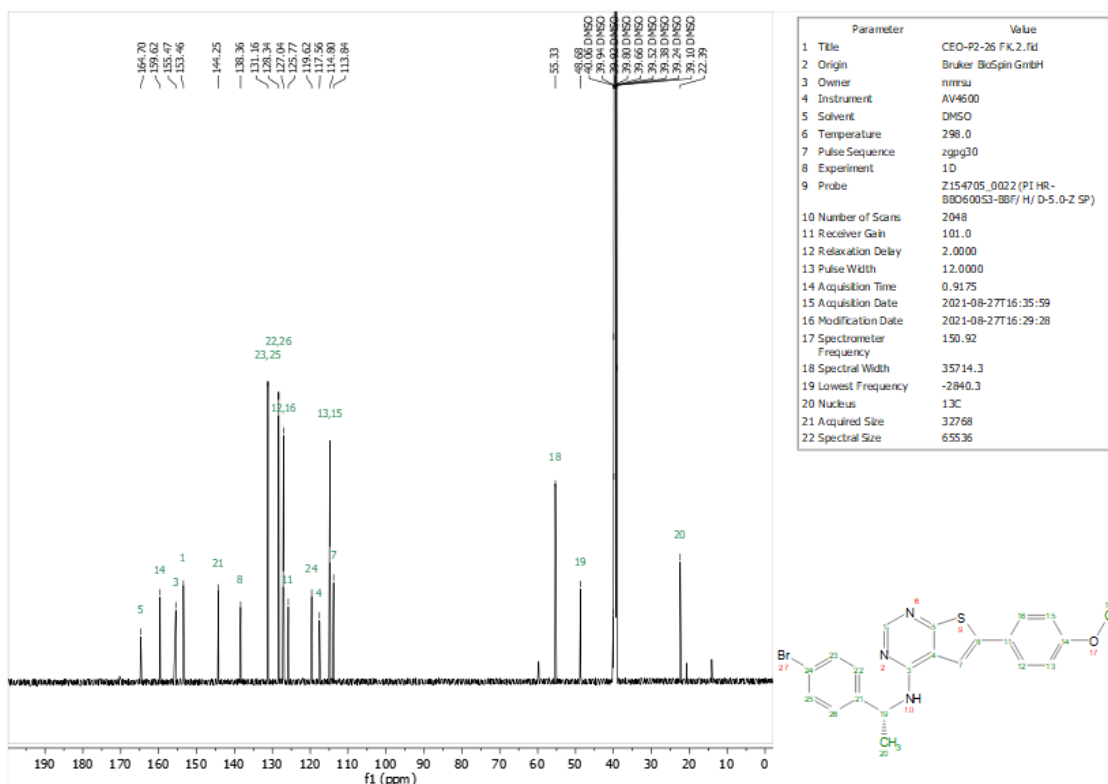


Figure S38: <sup>13</sup>C NMR spectrum of compound **20** at 150 MHz in DMSO-*d*<sub>6</sub>

## Compound 21

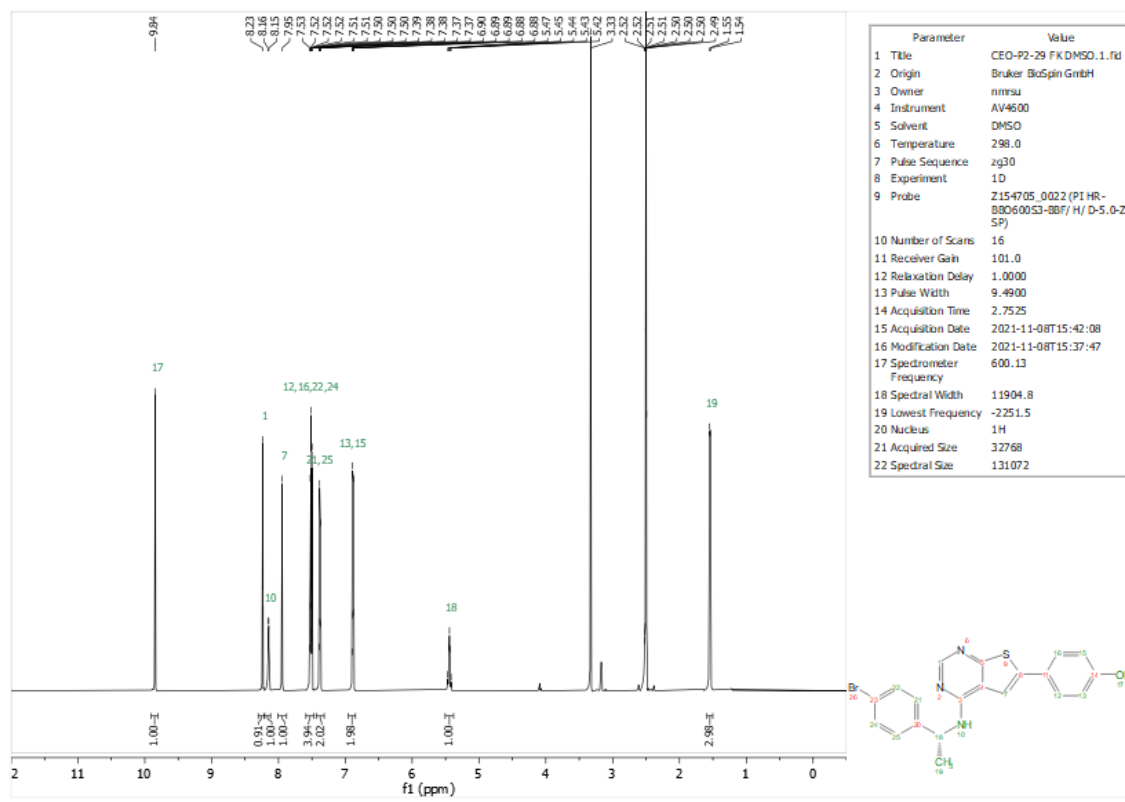


Figure S39:  $^1\text{H}$  NMR spectrum of compound **21** at 600 MHz in  $\text{DMSO}-d_6$

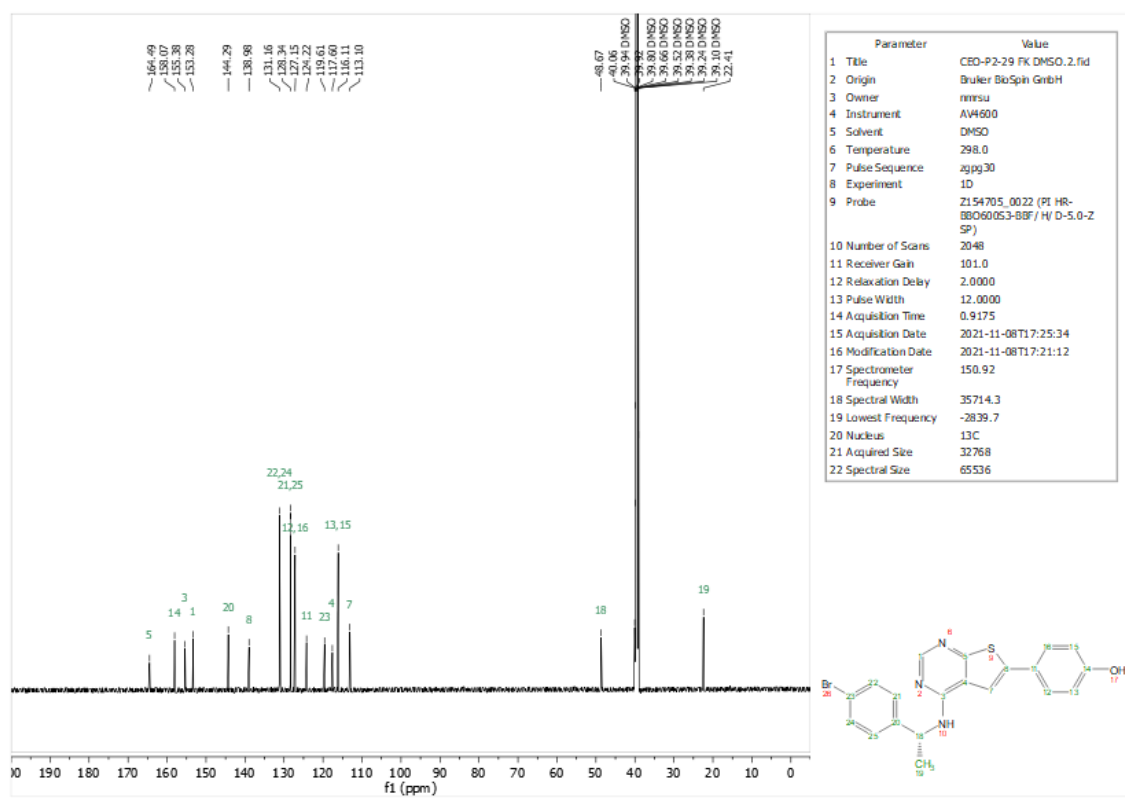


Figure S40:  $^{13}\text{C}$  NMR spectrum of compound **21** at 150 MHz in  $\text{DMSO}-d_6$ .

## Comparison of TMPK folding

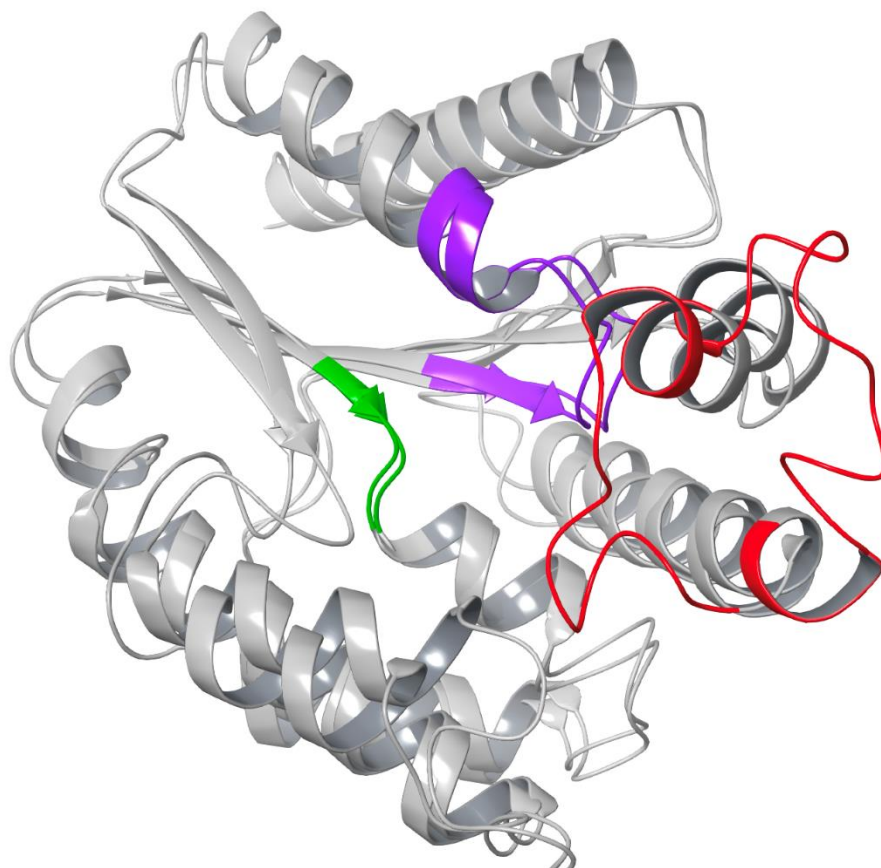


Figure S41. The crystal structures of TMPK from *E. coli* (4TMK.pdb) and *S. aureus* (4GSY.pdb) overlaid with the P-loops hightailed in purple, the DRX motif highlighted in green and the lid-structures highlighted in red. (Made using the Schrodinger Maestro suite (version 13.1.144, Release 2022-1))

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