

## Supporting Information

### Transition state analogue inhibitors of human methylthioadenosine phosphorylase and bacterial methylthioadenosine/S-adenosylhomocysteine nucleosidase incorporating acyclic ribooxacarbenium ion mimics.

Keith Clinch<sup>a\*</sup>, Gary B. Evans<sup>a</sup>, Richard F. G. Fröhlich<sup>a</sup>, Shivali A. Gulab<sup>a</sup>, Jemy A. Gutierrez<sup>b</sup>, Jennifer M. Mason<sup>a</sup>, Vern L. Schramm<sup>b</sup>, Peter C. Tyler<sup>a\*</sup> and Anthony D. Woolhouse<sup>a</sup>

<sup>a</sup> *Carbohydrate Chemistry, Industrial Research Limited, P O Box 31310, Lower Hutt 5040, New Zealand.*

<sup>b</sup> *Department of Biochemistry, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461, USA.*

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\*Corresponding authors. Fax.: +64-4-931-3055; e-mail: [k.clinch@irl.cri.nz](mailto:k.clinch@irl.cri.nz); Fax.: +64-4-931-3055 e-mail: [p.tyler@irl.cri.nz](mailto:p.tyler@irl.cri.nz)

## Experimental

### General

Air sensitive reactions were performed under argon. Organic solutions were dried over anhydrous  $\text{MgSO}_4$  and the solvents were evaporated under reduced pressure. Anhydrous and chromatography solvents were obtained commercially and used without any further purification. Thin layer chromatography was performed on glass or aluminium sheets coated with 60 F<sub>254</sub> silica gel. Organic compounds were visualized under uv light or use of a dip of ammonium molybdate (5 wt%) and cerium(IV) sulfate 4 H<sub>2</sub>O (0.2 wt%) in aq. H<sub>2</sub>SO<sub>4</sub> (2M), one of I<sub>2</sub> (0.2%) and KI (7%) in H<sub>2</sub>SO<sub>4</sub> (1M), or 0.1% ninhydrin in EtOH. Chromatography (flash column, or an automated system with continuous gradient facility) was performed on silica gel (40-63  $\mu\text{m}$ ). All reactions involving sealed pressure tubes were conducted behind a safety shield. Optical rotations were recorded at a path length of 1 dm and are in units of  $10^{-1} \text{deg cm}^2 \text{g}^{-1}$ ; concentrations are in g/100 mL. <sup>1</sup>H NMR spectra were measured in CDCl<sub>3</sub>, CD<sub>3</sub>OD, DMSO *d*<sub>6</sub> (internal Me<sub>4</sub>Si,  $\delta$  0) or D<sub>2</sub>O (HOD,  $\delta$  4.79), and <sup>13</sup>C NMR spectra in CDCl<sub>3</sub> (centre line,  $\delta$  77.0), CD<sub>3</sub>OD (centre line,  $\delta$  49.0), DMSO *d*<sub>6</sub> (centre line,  $\delta$  39.5) or D<sub>2</sub>O (no internal reference or internal CH<sub>3</sub>CN,  $\delta$  1.47 where stated). <sup>19</sup>F NMR (external CFCl<sub>3</sub>, or internal  $\delta$  0, where stated). Assignments of <sup>1</sup>H and <sup>13</sup>C resonances were based on 2D (<sup>1</sup>H-<sup>1</sup>H DQF-COSY, <sup>1</sup>H-<sup>13</sup>C HSQC, HMBC) and DEPT experiments. NMR abbreviations used: b, broad; s, singlet; d, doublet; t, triplet; m, multiplet. High resolution electrospray mass spectra (ESI-HRMS) were recorded on a Q-TOF Tandem Mass Spectrometer. Microanalyses were performed by the Campbell Microanalytical Department, University of Otago, Dunedin, New Zealand.

### Synthetic Chemistry

**5-[(Benzyloxy)methyl]-7-bromo-4-chloro-5H-pyrrolo[3,2-*d*]pyrimidine (9).** *N*-Bromosuccinimide (2.90 g, 16.3 mmol) was added in several portions to a stirred solution of chloride **8**<sup>50</sup> (4.46 g, 16.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) cooled in an ice-bath. After 1 h the

solvent was evaporated and the residue chromatographed (EtOAc-hexanes, 3:7) to give **9** as a yellow solid (4.1 g, 71%). <sup>1</sup>H NMR (500 MHz, DMSO *d*<sub>6</sub>): δ 8.76, (s, 1H), 8.44 (s, 1H), 7.27–7.20 (m, 5H), 5.91 (s, 2H), 4.58 (s, 2H). <sup>13</sup>C NMR (125.7 MHz, DMSO *d*<sub>6</sub>): δ 150.3 (CH), 149.4 (C), 142.3 (C), 137.8 (CH), 137.1 (C), 128.0 (CH), 127.5 (CH), 127.3 (CH), 123.0 (C), 90.1 (C), 77.3 (CH<sub>2</sub>), 70.0 (CH<sub>2</sub>). ESI-HRMS for C<sub>14</sub>H<sub>12</sub><sup>79</sup>Br<sup>35</sup>ClN<sub>3</sub>O<sup>+</sup> (M+H)<sup>+</sup> calcd. 351.9847, found 351.9848. X-ray crystal structure.<sup>51</sup>

**5-[(Benzyloxy)methyl]-4-chloro-5H-pyrrolo[3,2-*d*]pyrimidine-7-carbaldehyde (10).** *n*-Butyllithium (1.48M in hexanes, 9.2 mL, 13.6 mmol) was added to a solution of bromide **9** (3.73 g, 10.6 mmol) in a mixture of dry anisole (48 mL) and dry Et<sub>2</sub>O (145 mL) at -78 °C. The mixture was stirred for 2-3 min then DMF (4.11 mL, 53.0 mmol) was added at such a rate that the internal temperature remained below -68 °C. After warming to -40 °C, H<sub>2</sub>O (20 mL) was added, then the solution was warmed to rt, EtOAc (200 mL) added and the organic layer washed successively with H<sub>2</sub>O and brine then dried and the solvent evaporated. The resulting orange solid was chromatographed (EtOAc-hexanes, 2:8 then stepwise to 4:6) to give **10** as a yellow solid (1.83 g, 57%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 10.33, (s, 1H), 8.92 (s, 1H), 8.13 (s, 1H), 7.36-7.27 (m, 5H), 5.90 (s, 2H), 4.60 (s, 2H). <sup>13</sup>C NMR (125.7 MHz, CDCl<sub>3</sub>): δ 183.8 (CH), 152.4 (CH), 151.0 (C), 144.0 (C), 139.8 (CH), 135.6 (C), 128.7 (CH), 128.5 (CH), 127.7 (CH), 124.8 (C), 117.4 (C), 77.7 (CH<sub>2</sub>), 71.3 (CH<sub>2</sub>). ESI-HRMS for C<sub>15</sub>H<sub>12</sub><sup>35</sup>ClN<sub>3</sub>NaO<sub>2</sub><sup>+</sup> (M+Na)<sup>+</sup> calcd. 324.0511, found 324.0507.

***tert*-Butyl (4*R*)-2,2-dimethyl-4-[(methylsulfonyl)methyl]-1,3-oxazolidine-3-carboxylate (12 I).** Methanesulfonyl chloride (0.26 mL, 3.33 mmol) was added to a solution of *tert*-butyl (4*S*)-4-(hydroxymethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (**11 I**, 0.7 g, 3.03 mmol, prepared as for its enantiomer<sup>54</sup>) and Et<sub>3</sub>N (0.68 mL, 4.84 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C. After 30 min the mixture was washed with aq. NaHCO<sub>3</sub> (sat., 3 x 5 mL), dried and the solvent evaporated. The residue was dissolved in DMF (8 mL) and sodium thiomethoxide (0.42 g, 6.05 mmol) added. After stirring at rt for 1 h, Et<sub>2</sub>O (100 mL) was added and the mixture washed with H<sub>2</sub>O (4 x 10 mL), brine then dried and the solvent evaporated. The residue was chromatographed (EtOAc-hexanes, 5:95) to give **12 I** as a colourless oil (0.59 g, 75%). [α]<sub>D</sub><sup>20</sup> +44.3 (c 1.02, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, ~1:1 mixture of rotamers): δ 4.06 (bd, *J* = 6.2 Hz, 0.5H), 4.01-3.89 (m, 2.5H), 2.89 (bd, *J* = 13.0 Hz, 0.5H), 2.75 (bd, *J* = 13.2 Hz, 0.5H), 2.52 (dd, *J* = 13.3, 10.7 Hz, 1H), 2.16, 2.13 (2s, 3H), 1.60, 1.50 (2s, 3H), 1.48, 1.47 (2s, 12H). <sup>13</sup>C NMR (125.7 MHz, CDCl<sub>3</sub>, ~1:1 mixture of rotamers): δ 152.0, 151.3 (C's), 94.2, 93.7 (C's), 80.2, 79.9 (C's), 66.5, 66.2 (CH<sub>2</sub>'s), 56.7, 56.4 (CH<sub>2</sub>'s), 36.4, 35.6 (CH's),

28.5, 28.4 (CH<sub>3</sub>'s), 27.6, 24.4 (CH<sub>3</sub>'s), 26.9, 23.1 (CH<sub>3</sub>'s), 15.4, 15.3 (CH<sub>3</sub>'s). ESI-HRMS for C<sub>12</sub>H<sub>23</sub>NNaO<sub>3</sub>S<sup>+</sup> (M+Na)<sup>+</sup> calcd. 284.1291, found 284.1289.

**(2*R*)-2-Amino-3-(methylsulfanyl)propan-1-ol hydrochloride (14 I).** Aqueous hydrochloric acid (37%, 2 mL) was added to an ice-cold solution of **12 I** (0.54 g, 2.07 mmol) in MeOH (3 mL). The solution was warmed to rt, left for 1.5 h then the solvents evaporated to give **14 I** as a colourless gum which solidified on standing (0.326 g, 100%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -39.7 (c 1.20, H<sub>2</sub>O). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta$  3.97 (dd, *J* = 12.4, 3.9 Hz, 1H), 3.83 (dd, *J* = 12.4, 6.2 Hz, 1H), 3.62 (m, 1H), 2.95 (dd, *J* = 14.5, 5.7 Hz, 1H), 2.83 (dd, *J* = 14.5, 8.4 Hz, 1H), 2.23 (s, 3H). <sup>13</sup>C NMR (125.7 MHz, D<sub>2</sub>O, internal CH<sub>3</sub>CN):  $\delta$  60.9 (CH<sub>2</sub>), 52.2 (CH), 32.9 (CH<sub>2</sub>), 15.1 (CH<sub>3</sub>). ESI-HRMS for C<sub>4</sub>H<sub>12</sub>NOS<sup>+</sup> (M+H)<sup>+</sup> calcd. 122.0635, found 122.0634.

**Preparation of the (*R, R*) Mosher amide.** Compound **14 I** (4 mg, 0.025 mmol) was dissolved in CDCl<sub>3</sub> (0.6 mL), spiked with CFCl<sub>3</sub> then Et<sub>3</sub>N (10.5  $\mu$ L, 0.075 mmol) and (*S*)-MTPACI<sup>56</sup> (7.5 mg, 0.03 mmol) added. After 30 min at rt the sample was analysed by <sup>19</sup>F NMR. <sup>19</sup>F NMR (470.5 MHz, CDCl<sub>3</sub>, internal CFCl<sub>3</sub>):  $\delta$  -69.3 (s, 97%), -69.4 (s, 3%). The % d. e. = 94%. See **14 II** for the preparation of the (*R, S*) diastereomer.

**(2*R*)-2-[(5-[(Benzyloxy)methyl]-4-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-3-(methylsulfanyl)propan-1-ol (15 I).** A mixture of **14 I** (0.12 g, 0.76 mmol), aldehyde **10** (0.38 g, 0.76 mmol), Et<sub>3</sub>N (0.11 mL, 0.76 mmol) and 2-picoline-borane complex<sup>55</sup> (0.106 g, 0.99 mmol) were stirred together in MeOH (4 mL) at rt for 16 h. The solvent was evaporated and the residue chromatographed (CHCl<sub>3</sub>-7M NH<sub>3</sub> in MeOH, 99:1 then 98:2) to give **15 I** as a yellow solid (0.21 g, 67%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -24.0 (c 0.63, MeOH). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD):  $\delta$  8.63 (s, 1H), 7.92 (s, 1H), 7.25-7.18 (m, 5H), 5.91 (d, *J* = 11.0 Hz, 1H), 5.89 (d, *J* = 11.0 Hz, 1H), 4.56 (s, 2H), 4.07 (d, *J* = 14.2 Hz, 1H), 4.03 (d, *J* = 14.2 Hz, 1H), 3.70 (dd, *J* = 11.1, 5.1 Hz, 1H), 3.61 (dd, *J* = 11.1, 5.6 Hz, 1H), 2.81 (m, 1H), 2.67 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.59 (dd, *J* = 13.5, 6.7 Hz, 1H), 1.97 (s, 3H). <sup>13</sup>C NMR (125.7 MHz, CD<sub>3</sub>OD):  $\delta$  153.0 (C), 150.6 (CH), 143.9 (C), 138.7 (CH), 138.5 (C), 129.3 (CH), 128.8 (CH), 128.6 (CH), 125.5 (C), 116.1 (C), 78.3 (CH<sub>2</sub>), 71.7 (CH<sub>2</sub>), 63.9 (CH<sub>2</sub>), 58.2 (CH), 40.9 (CH<sub>2</sub>), 36.6 (CH<sub>2</sub>), 15.7 (CH<sub>3</sub>). ESI-HRMS for C<sub>19</sub>H<sub>24</sub><sup>35</sup>ClN<sub>4</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 407.1304, found 407.1309.

**(2*R*)-2-[(4-Amino-5-[(benzyloxy)methyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-3-(methylsulfanyl)propan-1-ol (16 I).** Compound **15 I** (0.19 g, 0.48

mmol) was dissolved in NH<sub>3</sub>-MeOH solution (7M, 25 mL) and heated at 135 °C in a sealed pressure tube for 30 h. After cooling, the solvent was evaporated and the residue chromatographed (CHCl<sub>3</sub>-7M NH<sub>3</sub> in MeOH, 98:2) to give **16 I** as a yellow solid (0.14 g, 74%).  $[\alpha]_{\text{D}}^{20}$  -35.9 (c 0.50, MeOH). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 8.17 (s, 1H), 7.49 (s, 1H), 7.32-7.24 (m, 5H), 5.66 (s, 2H), 4.57 (s, 2H), 4.00 (d, *J* = 13.8 Hz, 1H), 3.96 (d, *J* = 13.8 Hz, 1H), 3.71 (dd, *J* = 11.2, 5.0 Hz, 1H), 3.62 (dd, *J* = 11.2, 5.5 Hz, 1H), 2.84 (m, 1H), 2.67 (dd, *J* = 13.5, 6.4 Hz, 1H), 2.58 (dd, *J* = 13.5, 6.7 Hz, 1H), 1.97 (s, 3H). <sup>13</sup>C NMR (125.7 MHz, CD<sub>3</sub>OD): δ 152.8 (C), 151.6 (CH), 149.4 (C), 137.7 (C), 133.5 (CH), 129.6 (CH), 129.3 (CH), 129.2 (CH), 116.1 (C), 114.5 (C), 78.6 (CH<sub>2</sub>), 71.3 (CH<sub>2</sub>), 63.8 (CH<sub>2</sub>), 58.0 (CH), 41.0 (CH<sub>2</sub>), 36.6 (CH<sub>2</sub>), 15.7 (CH<sub>3</sub>). ESI-HRMS for C<sub>19</sub>H<sub>26</sub>N<sub>5</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 388.1802, found 388.1796.

**(2R)-2-[(4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-3-(methylsulfanyl)propan-1-ol (17 I)**. Pd black (100 mg) was added to a solution of **16 I** (0.13 g, 0.33 mmol) and hydrazine hydrate (55% in hydrazine, 1.9 mL) in NH<sub>3</sub>-MeOH solution (7M, 10 mL), and the mixture stirred at rt for 30 min. The solids were filtered off and the solvents evaporated. The residue was chromatographed (CHCl<sub>3</sub>-7M NH<sub>3</sub> in MeOH, 9:1) to give **17 I** as a colourless solid (0.074 g, 84%).  $[\alpha]_{\text{D}}^{20}$  -38.3 (c 0.90, MeOH). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 8.16 (s, 1H), 7.49 (s, 1H), 4.04 (d, *J* = 13.7 Hz, 1H), 3.99 (d, *J* = 13.7 Hz, 1H), 3.71 (dd, *J* = 11.3, 5.0 Hz, 1H), 3.62 (dd, *J* = 11.3, 5.5 Hz, 1H), 2.83 (m, 1H), 2.66 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.57 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.94 (s, 3H). <sup>13</sup>C NMR (125.7 MHz, CD<sub>3</sub>OD): δ 152.1 (C), 150.9 (CH), 146.6 (C), 129.0 (CH), 115.4 (C), 114.7 (C), 63.7 (CH<sub>2</sub>), 57.7 (CH), 41.2 (CH<sub>2</sub>), 36.5 (CH<sub>2</sub>), 15.5 (CH<sub>3</sub>). ESI-HRMS for C<sub>11</sub>H<sub>18</sub>N<sub>5</sub>OS<sup>+</sup> (M+H)<sup>+</sup> calcd. 268.1227, found 268.1231.

**tert-Butyl (4S)-2,2-dimethyl-4-[(methylsulfanyl)methyl]-1,3-oxazolidine-3-carboxylate (12 II)**. *tert*-Butyl (4*R*)-4-(hydroxymethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate<sup>54</sup> (**11 II**, 0.72 g, 3.12 mmol) was converted into **12 II** as a colourless oil (0.75 g, 91%) in the same way as that described for the preparation of enantiomer **12 I**.  $[\alpha]_{\text{D}}^{20}$  -42.3 (c 1.13, CHCl<sub>3</sub>). The <sup>1</sup>H and <sup>13</sup>C NMR spectra were identical to those of the enantiomer **12 I**. ESI-HRMS for C<sub>12</sub>H<sub>23</sub>NNaO<sub>3</sub>S<sup>+</sup> (M+Na)<sup>+</sup> calcd. 284.1291, found 284.1289.

**(2S)-2-Amino-3-(methylsulfanyl)propan-1-ol hydrochloride (14 II)**. Compound **12 II** (0.70 g, 2.68 mmol) was converted into **14 II** as a colourless solid (0.422 g, 100%) in the same way as that described for the preparation of enantiomer **14 I**.  $[\alpha]_{\text{D}}^{20}$  +40.5 (c 1.19, H<sub>2</sub>O).

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were identical to those of enantiomer **14 I**. ESI-HRMS for  $\text{C}_4\text{H}_{12}\text{NOS}^+$  ( $\text{M}+\text{H}$ ) $^+$  calcd. 122.0635, found 122.0631.

**Prep of the (R, S) Mosher amide.** Compound **14 II** (4 mg, 0.025 mmol) was dissolved in  $\text{CDCl}_3$  (0.6 mL), spiked with  $\text{CFCl}_3$  then  $\text{Et}_3\text{N}$  (10.5  $\mu\text{L}$ , 0.075 mmol) and (*S*)-MTPACl<sup>56</sup> (7.5 mg, 0.03 mmol) added. After 30 min at rt the sample was analysed by  $^{19}\text{F}$  NMR.  $^{19}\text{F}$  NMR (470.5 MHz,  $\text{CDCl}_3$ , internal  $\text{CFCl}_3$ ):  $\delta$ , -69.3 (s, 3%), -69.4 (s, 97%). The % d. e. = 94%. See **14 I** for the preparation of the (*R, R*) diastereomer.

**(2S)-2-[(5-[(Benzyloxy)methyl]-4-chloro-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-3-(methylsulfanyl)propan-1-ol (15 II).** Compound **14 II** (0.12 g, 0.76 mmol) was converted into **15 II** as a yellow solid (0.24 g, 78%) in the same way as that described for enantiomer **15 I**.  $[\alpha]_{\text{D}}^{20}$  +19.6 (c 0.58, MeOH). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were identical to those of enantiomer **15 I**. ESI-HRMS for  $\text{C}_{19}\text{H}_{24}^{35}\text{ClN}_4\text{O}_2\text{S}^+$  ( $\text{M}+\text{H}$ ) $^+$  calcd. 407.1304, found 407.1311.

**(2S)-2-[(4-Amino-5-[(benzyloxy)methyl]-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-3-(methylsulfanyl)propan-1-ol (16 II).** Compound **15 II** (0.22 g, 0.54 mmol) was converted into **16 II** as a yellow solid (0.18 g, 86%) in the same way as that described for enantiomer **16 I**.  $[\alpha]_{\text{D}}^{20}$  +37.8 (c 0.50, MeOH). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were identical to those of enantiomer **16 I**. ESI-HRMS for  $\text{C}_{19}\text{H}_{26}\text{N}_5\text{O}_2\text{S}^+$  ( $\text{M}+\text{H}$ ) $^+$  calcd. 388.1802, found 388.1803.

**(2S)-2-[(4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-3-(methylsulfanyl)propan-1-ol (17 II).** Compound **16 II** (0.168 g, 0.43 mmol) was converted into **17 II** as a colourless solid (0.091 g, 79%) in the same way as that described for enantiomer **17 I**.  $[\alpha]_{\text{D}}^{20}$  +43.8 (c 0.90, MeOH). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were identical to those of enantiomer **17 I**. ESI-HRMS for  $\text{C}_{11}\text{H}_{18}\text{N}_5\text{OS}^+$  ( $\text{M}+\text{H}$ ) $^+$  calcd. 268.1227, found 268.1225.

**(±)-(2R/S)-2-[(5-[(Benzyloxy)methyl]-4-chloro-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-3-(methylsulfanyl)propan-1-ol [15 III]** ( $\pm$ )-*tert*-Butyl *N*-{1-[(*tert*-butyldimethylsilyl)oxy]-3-(methylsulfanyl)propan-2-yl}carbamate (**13 III**, 0.200 g, 0.597 mmol)<sup>52</sup> was converted into **14 III** under the same conditions used to convert **12 I** to **14 I**. Compound **14 III** was then transformed into **15 III** (0.173 g, 71%) in the same way as that described for the preparation of **15 I** except that  $\text{NaCNBH}_3$ <sup>53</sup> was used instead of 2-picoline-

borane complex and NaHCO<sub>3</sub> was used instead of Et<sub>3</sub>N. The <sup>1</sup>H NMR (300 MHz) and <sup>13</sup>C NMR (75.5 MHz) were in agreement with the data recorded for **15 I**. ESI-HRMS for C<sub>19</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>S<sup>35</sup>Cl<sup>+</sup>, (M+H)<sup>+</sup> calcd. 407.1304, found 407.1297.

**(±)-(2R/S)-2-[(4-Amino-5-[(benzyloxy)methyl]-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-3-(methylsulfanyl)propan-1-ol [16 III]**. Compound **15 III** (0.17 g, 0.418 mmol) was converted into **16 III** as a yellow solid (0.095 g, 59%) in the same way as that described for the preparation of **16 I**. The <sup>1</sup>H NMR (300 MHz) and <sup>13</sup>C NMR (75.5 MHz) were in agreement with the data recorded for **16 I**. ESI-HRMS for C<sub>19</sub>H<sub>26</sub>N<sub>5</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 388.1802, found 388.1795.

**(±)-(2R/S)-2-[(4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-3-(methylsulfanyl)propan-1-ol [17 III]**. Compound **16 III** (0.092 g, 0.237 mmol) was converted into **17 III** as a colourless solid (0.048 g, 76%) in the same way as that described for the preparation of **17 I**. The <sup>1</sup>H NMR (300 MHz) and <sup>13</sup>C NMR (75.5 MHz) were in agreement with the data recorded for **17 I**. ESI-HRMS C<sub>11</sub>H<sub>18</sub>N<sub>5</sub>OS<sup>+</sup> (M+H)<sup>+</sup> calcd. 268.1227, found 268.1228.

**2,2-Dimethyl-5-[(methylsulfanyl)methyl]-1,3-dioxane (19)**. Methanesulfonyl chloride (0.97 mL, 12.40 mmol) was added dropwise to a stirred solution of (2,2-dimethyl-1,3-dioxan-5-yl)methanol<sup>57</sup> (**18**, 1.51 g, 10.33 mmol) and Et<sub>3</sub>N (2.18 mL, 15.49 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C. The mixture was warmed to rt and stirred for 30 min then diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and washed with aq. NaHCO<sub>3</sub> (sat., 3 x 10 mL) then dried and the solvent evaporated to give the crude mesylate as an oil. The latter was dissolved in DMF (7 mL), sodium thiomethoxide (1.45 g, 20.66 mmol) added and the mixture stirred at rt for 16 h. Diethyl ether (100 mL) was added and the solution washed with H<sub>2</sub>O (4 x 15 mL), brine (15 mL), dried and the solvent evaporated. The residue was chromatographed (EtOAc-hexanes, 5:95) to give **19** as a colourless oil (1.38 g, 76%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 4.01 (dd, *J* = 11.8, 4.3 Hz, 2H), 3.70 (dd, *J* = 11.8, 7.1 Hz, 2H), 2.54 (d, *J* = 7.3 Hz, 2H), 2.10 (s, 3H), 1.92 (m, 1H), 1.42 (s, 3H), 1.41 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 98.0 (C), 63.6 (2 x CH<sub>2</sub>), 33.8 (CH<sub>2</sub>), 33.6 (CH), 24.7 (CH<sub>3</sub>), 23.0 (CH<sub>3</sub>), 16.0 (CH<sub>3</sub>). ESI-HRMS for C<sub>8</sub>H<sub>16</sub>O<sub>2</sub>NaS<sup>+</sup> (M+Na)<sup>+</sup> calcd. 199.0764 found 199.0768.

**(±)-(2R/S)-3-[(tert-Butyldimethylsilyloxy)-2-[(methylsulfanyl)methyl]propan-1-ol [(±)-20]**. Compound **19** (1.35 g, 7.66 mmol) was dissolved in MeOH (100 mL) and acetyl chloride (5.45 mL, 77 mmol) added. The solution was stirred at rt for 1 h then neutralized

with Amberlyst A21 resin. The solids were filtered off and the solvent evaporated to leave an oil (1.05 g) which was dissolved in THF (3 mL) and added to a stirred suspension of sodium hydride (60%, 0.31 g, 7.66 mmol) in dry THF (12 mL) with ice-cooling.<sup>58</sup> After 30 min *tert*-butyldimethylsilyl chloride (1.154 g, 7.66 mmol) was added and the mixture stirred for 2 h. After quenching with H<sub>2</sub>O (6 mL) and extracting with Et<sub>2</sub>O the organic layer was washed with brine then dried and the solvent evaporated. The residue was chromatographed (EtOAc-hexanes, 1:9) to give (±)-**20** as a colourless oil (1.44 g, 75%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.86-3.64 (m, simplified after D<sub>2</sub>O exchange, 4H), 2.62 (t, *J* = 5.6 Hz, exchanged to D<sub>2</sub>O, 1H), 2.61-2.52 (m, 2H), 2.11 (s, 3H), 1.92 (m, 1H), 0.90 (s, 9H), 0.08 (s, 6H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 65.1 (2 x CH<sub>2</sub>), 41.8 (CH), 33.1 (CH<sub>2</sub>), 25.8 (CH<sub>3</sub>), 18.2 (C), 16.1 (CH<sub>3</sub>), -5.6 (CH<sub>3</sub>). ESI-HRMS for C<sub>11</sub>H<sub>26</sub>NaO<sub>2</sub>SSi<sup>+</sup> (M+Na)<sup>+</sup> calcd. 273.1316, found 273.1311.

**(±)-[(2*R/S*)-2-(Azidomethyl)-3-(methylsulfanyl)propoxy](*tert*-butyl)dimethylsilane [(±)-**21**].** Methanesulfonyl chloride (0.48 mL, 6.18 mmol) was added dropwise to a stirred solution of (±)-**20** (1.29 g, 5.15 mmol) and Et<sub>3</sub>N (1.09 mL, 7.73 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at 0 °C. The solution was warmed to rt and stirred for 30 min then washed with aq. NaHCO<sub>3</sub> (sat., 3 x 5 mL), dried and the solvent evaporated. The resulting crude mesylate was dissolved in DMF (15 mL), sodium azide (1.00 g, 15.45 mmol) added and the mixture stirred and heated at 80 °C for 3 h. After cooling, H<sub>2</sub>O (15 mL) was added to the mixture extracted with Et<sub>2</sub>O (100 mL). The extract was washed with H<sub>2</sub>O (4 x 15 mL) then brine (15 mL), dried and the solvent evaporated. The residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-hexanes, 5:95 then 1:9) to give (±)-**21** as a colourless oil (1.14 g, 80%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.71-3.62 (m, 2H), 3.51-3.40 (m, 2H), 2.55 (dd, *J* = 13.3, 7.0 Hz, 1H), 2.50 (dd, *J* = 13.3, 6.8 Hz, 1H), 2.10 (s, 3H), 1.92 (m, 1H), 0.90 (s, 9H), 0.06 (s, 6H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 62.1 (CH<sub>2</sub>), 51.5 (CH<sub>2</sub>), 40.9 (CH), 33.5 (CH<sub>2</sub>), 25.8 (CH<sub>3</sub>), 18.2 (C), 16.2 (CH<sub>3</sub>), -5.5 (CH<sub>3</sub>). ESI-HRMS for C<sub>11</sub>H<sub>25</sub>OSSi<sup>+</sup> (M-HN<sub>3</sub>+H)<sup>+</sup> calcd. 233.1390, found 233.1386.

**(±)-[(2*R/S*)-2-(Aminomethyl)-3-(methylsulfanyl)propoxy](*tert*-butyl)dimethylsilane [(±)-**22**].** Pd-Black (100 mg) was added to a stirred solution of (±)-**21** (0.99 g, 3.59 mmol) and hydrazine hydrate (55% in hydrazine, 10 mL) in MeOH (80 mL). After 1 h more Pd-black (100 mg) was added and after a further 30 min the solids were filtered off and the solvent evaporated. The residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-MeOH-Et<sub>3</sub>N, 94:5:1) to give (±)-**22** as a yellow oil (0.731g, 82%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.74-3.65 (m, 2H), 2.86-2.75 (m, 2H), 2.57 (dd, *J* = 13.0, 7.1 Hz, 1H), 2.50 (dd, *J* = 13.0, 6.6 Hz, 1H), 2.10 (s,



3H), 1.75 (m, 1H), 1.33 (s, exchanged to D<sub>2</sub>O, 2H), 0.89 (s, 9H), 0.06 (s, 6H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 63.3 (CH<sub>2</sub>), 43.3 (CH), 43.0 (CH<sub>2</sub>), 34.2 (CH<sub>2</sub>), 25.9 (CH<sub>3</sub>), 18.2 (C), 16.2 (CH<sub>3</sub>), -5.5 (CH<sub>3</sub>). ESI-HRMS for C<sub>11</sub>H<sub>28</sub>NOSSi<sup>+</sup> (M+H)<sup>+</sup> calcd. 250.1656, found 250.1650.

**(±)-(2*R*/*S*)-3-[(4-Amino-5-[(benzyloxy)methyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-2-[(methylsulfanyl)methyl]propan-1-ol [(±)-**24**].** Compound **(±)-22** (0.16 g, 0.64 mmol) was dissolved in a 1:1 mixture of aq. HCl (37%)-MeOH (6 mL) and left at rt for 2 h. The solvent was evaporated and the residue dissolved in MeOH (4 mL) to which were added aldehyde **10** (0.258 g, 0.64 mmol), NaHCO<sub>3</sub> (0.036 g, 0.42 mmol) and NaCNBH<sub>3</sub><sup>53</sup> (0.052 g, 0.83 mmol). The mixture was stirred at rt for 16 h then the solvent was evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 99:1 then 98:2) to give intermediate **(±)-(2*R*/*S*)-3-[(5-[(benzyloxy)methyl]-4-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-2-[(methylsulfanyl)methyl]propan-1-ol [(±)-**23**]** as a yellow gum (100 mg). This was dissolved in NH<sub>3</sub>-MeOH solution (7M, 10 mL) and heated at 135 °C for 24 h in a sealed tube. After cooling, the solvent was evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 98:2) to give **(±)-24** as a yellow gum (0.051 g, 20%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.17 (s, 1H), 7.45 (s, 1H), 7.32-7.23 (m 5H), 5.64 (s, 2H), 4.57 (s, 2H), 3.90 (s, 2H), 3.67 (dd, *J* = 10.9, 5.1 Hz, 1H), 3.61 (dd, *J* = 10.9, 5.9 Hz, 1H), 2.88-2.69 (m, 2H), 2.55 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.48 (dd, *J* = 13.2, 6.6 Hz, 1H), 2.04 (s, 3H), 1.94 (m, 1H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 152.8 (C), 151.6 (CH), 149.4 (C), 137.7 (C), 133.5 (CH), 129.6 (CH), 129.3 (CH), 129.2 (CH), 116.1 (C), 114.4 (C), 78.6 (CH<sub>2</sub>), 71.3 (CH<sub>2</sub>), 64.7 (CH<sub>2</sub>), 51.5 (CH<sub>2</sub>), 43.7 (CH<sub>2</sub>), 41.4 (CH), 35.6 (CH<sub>2</sub>), 16.0 (CH<sub>3</sub>). ESI-HRMS for C<sub>20</sub>H<sub>28</sub>N<sub>5</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 402.1959, found 402.1957.

**(±)-(2*R*/*S*)-3-[(4-Amino-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-2-[(methylsulfanyl)methyl]propan-1-ol [(±)-**25**].** Pd Black (30 mg) was added to a stirred solution of **(±)-24** (0.05 g, 0.125 mmol) and hydrazine hydrate (55% in hydrazine, 0.7 mL) in NH<sub>3</sub>-MeOH (7M, 4 mL) and the mixture stirred at rt 1 h. After filtering the solids off over Celite the solvent was evaporated and the residue chromatographed (CHCl<sub>3</sub>-7M NH<sub>3</sub> in MeOH, 9:1 then 85:15) to give **(±)-25** (0.019 g, 54%) as a colourless solid. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.16 (s, 1H), 7.48 (1H), 3.94 (2H), 3.67 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.60 (dd, *J* = 11.0, 6.0 Hz, 1H), 2.82-2.71 (m, 2H), 2.58-2.44 (m, 2H), 2.05 (s, 3H), 1.95 (m, 1H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 152.1 (C), 150.9 (CH), 146.6 (C), 129.1 (CH), 115.4 (C),

114.2 (C), 64.6 (CH<sub>2</sub>), 51.6 (CH<sub>2</sub>), 43.9 (CH<sub>2</sub>), 41.2 (CH), 35.5 (CH<sub>2</sub>), 16.0 (CH<sub>3</sub>). ESI-HRMS for C<sub>12</sub>H<sub>20</sub>N<sub>5</sub>OS<sup>+</sup> (M+H)<sup>+</sup> calcd. 282.1384, found 282.1384.

**(4R)-4-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one (27).** (2R)-2-Amino-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]ethan-1-ol benzoate (**26**, 7.2 g, 25.4 mmol, prepared in the same way as that described for its enantiomer<sup>61</sup>) was dissolved in MeOH (30 mL) and eluted from a column of Amberlyst A26 resin (OH) (5 x 18 cm) with MeOH. Fractions containing product were collected and the solvent evaporated to give the free base form of **26** as a yellow gum (4.1 g, 25.4 mmol). It was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (60 mL), cooled in an ice bath and Et<sub>3</sub>N (10.75 mL, 76 mmol) added followed by triphosgene (2.72 g, 9.18 mmol) in portions over 60 min. The mixture was stirred for 20 min then the solvent was evaporated and the residue chromatographed (EtOAc-hexanes, 8:2) to give **27** as a colourless solid (4.4 g, 92%). An analytical sample was recrystallized from EtOAc-hexanes. MP 126-127 °C.  $[\alpha]_D^{21}$  -50.7 (c 0.8, MeOH). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.18 (bs, exchanged to D<sub>2</sub>O, 1H), 4.44 (t, *J* = 8.8 Hz, 1H), 4.20-4.06 (m, 3H), 3.91 (m, 1H), 3.74 (dd, *J* = 8.5, 4.7 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 159.6 (C), 110.2 (C), 76.6 (CH), 66.2 (CH<sub>2</sub>), 65.4 (CH<sub>2</sub>), 54.5 (CH), 26.4 (CH<sub>3</sub>), 24.8 (CH<sub>3</sub>). ESI-HRMS for C<sub>8</sub>H<sub>13</sub>NNaO<sub>4</sub><sup>+</sup> (M+Na)<sup>+</sup> calcd. 210.0737, found 210.0732. Anal. calcd. for C<sub>8</sub>H<sub>13</sub>NO<sub>4</sub>: C, 51.33, H, 7.00, N, 7.48. Found C, 51.46, H, 6.79, N, 7.49.

**(4R)-4-[(1S)-1,2-Dihydroxyethyl]-1,3-oxazolidin-2-one (28).** Acetyl chloride (0.44 mL, 6.20 mmol) then acetal **27** (5.8 g, 31.0 mmol) were added successively to MeOH (80 mL) and the solution was stirred at rt for 4 h then the solvent was evaporated. The residue was again dissolved in MeOH (80 mL) to which more acetyl chloride (0.5 mL) had been added. The mixture was stirred a further 1 h then the solvent was evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 9:1 then 85:15) to give **28** as a colourless gum (4.23 g, 93%).  $[\alpha]_D^{21}$  -63.0 (c 0.9, MeOH). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 4.47 (t, *J* = 8.8 Hz, 1H), 4.30 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.97 (m, 1H), 3.62-3.49 (m, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 162.7 (C), 73.6 (CH), 68.6 (CH<sub>2</sub>), 64.3 (CH<sub>2</sub>), 55.9 (CH). ESI-HRMS for C<sub>5</sub>H<sub>9</sub>NNaO<sub>4</sub><sup>+</sup> (M+Na)<sup>+</sup> calcd. 170.0424, found 170.0426.

**(4R,5S)-4-(Hydroxymethyl)-5-[(methylsulfonyl)methyl]-1,3-oxazolidin-2-one (29).** *p*-Toluenesulfonyl chloride (2.21 g, 11.58 mmol) was added to a solution of **28** (1.42 g, 9.65 mmol) in dry pyridine (10 mL) at 0 °C. The mixture was warmed to rt and stirred for 3 h then more *p*-toluenesulfonyl chloride (442 mg, 2.3 mmol) added and the mixture stirred a further

16 h. The solvent was evaporated and the residue chromatographed (EtOAc-hexane, 6:4, then EtOAc) to give the intermediate primary tosylate as a colourless solid (1.77 g, 5.9 mmol). It was dissolved in DMF (7 mL) and sodium thiomethoxide (827 mg, 11.8 mmol) added. The mixture was stirred at rt for 3 h then the solvent evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 98:2 then 95:5) to give **29** as a colourless gum which solidified on standing a short while (0.75 g, 44%). An analytical sample was recrystallized from EtOH-hexanes. MP 71-72 °C.  $[\alpha]_{\text{D}}^{21} +79.5$  (c 0.8, MeOH). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.46 (s, exchanged to D<sub>2</sub>O, 1H), 4.56 (m, 1H), 3.82-3.73 (m, became a changed m after D<sub>2</sub>O exchange, 2H), 3.63 (m, became a changed m after D<sub>2</sub>O exchange, 1H), 3.41 (bt, exchanged to D<sub>2</sub>O, 1H), 2.88 (dd, *J* = 14.0, 4.9 Hz, 1H), 2.75 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.19 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 159.9 (C), 77.7 (CH), 63.5 (CH<sub>2</sub>), 58.7 (C), 37.6 (CH<sub>2</sub>), 16.2 (CH<sub>3</sub>). ESI-HRMS for C<sub>6</sub>H<sub>11</sub>NNaO<sub>3</sub>S<sup>+</sup> (M+Na)<sup>+</sup> calcd. 200.0352, found 200.0353. Anal. calcd. for C<sub>6</sub>H<sub>11</sub>NO<sub>3</sub>S: C, 40.66, H, 6.26, N, 7.90. Found C, 40.84, H, 6.46, N, 7.85. X-ray crystal structure.<sup>62</sup>

**(2R,3S)-2-Amino-4-(methylsulfanyl)butane-1,3-diol (30)**. Compound **29** (1.16 g, 6.55 mmol) was dissolved in a mixture of *i*-PrOH (32 mL) and aq. KOH (2M, 14 mL) and stirred at 80 °C for 4 h. The solvent was evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-MeOH-28% aq. NH<sub>4</sub>OH, 9:1:0.1) to give **30** as a yellow solid (0.932 g, 94%).  $[\alpha]_{\text{D}}^{21} +3.7$  (c 1.11, MeOH). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 3.75 (m, 1H), 3.60 (dd, *J* = 10.8, 5.7 Hz, 1H), 3.51 (dd, *J* = 10.8, 6.4 Hz, 1H), 2.84 (m, 1H), 2.72 (dd, *J* = 13.6, 5.5 Hz, 1H), 2.61 (dd, *J* = 13.6, 7.5 Hz, 1H), 2.13 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 71.0 (CH), 65.1 (CH<sub>2</sub>), 56.5 (CH), 39.2 (CH<sub>2</sub>), 15.9 (CH<sub>3</sub>). ESI-HRMS for C<sub>5</sub>H<sub>14</sub>NO<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 152.0740, found 152.0745.

**(2R,3S)-2-[(5-[(Benzyloxy)methyl]-4-chloro-5H-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-4-(methylsulfanyl)butane-1,3-diol (31)**. Acetyl chloride (10 μL, 0.14 mmol) was added to MeOH (5 mL) then amine **30** (0.066 g, 0.44 mmol), aldehyde **10** (0.132 g, 0.44 mmol) and NaCNBH<sub>3</sub><sup>53</sup> (0.036 g, 0.57 mmol) were added. The mixture was stirred at rt for 3 h then the solvent evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 97:3) to give **31** as a yellow gum (0.099 g, 52%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.60 (s, 1H), 7.87 (s, 1H), 7.20 (s, 5H), 5.86 (s, 2H), 4.54 (s, 2H), 4.12 (d, *J* = 13.8 Hz, 1H), 3.99 (d, *J* = 13.8 Hz, 1H), 3.84-3.73 (m, 2H), 3.64 (dd, *J* = 11.2, 5.1 Hz, 1H), 2.82-2.72 (m, 2H), 2.55 (dd, *J* = 13.5, 7.4 Hz, 1H), 2.04 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 152.9 (C), 150.5 (CH), 143.7 (C), 138.6 (CH), 138.4 (C), 129.2 (CH), 128.8 (CH), 128.6 (CH),

125.5 (C), 116.6 (C), 78.2 (CH<sub>2</sub>), 71.6 (CH<sub>2</sub>), 71.2 (CH), 62.2 (CH), 62.0 (CH<sub>2</sub>), 41.9 (CH<sub>2</sub>), 39.2 (CH<sub>2</sub>), 16.0 (CH<sub>3</sub>). ESI-HRMS for C<sub>20</sub>H<sub>26</sub><sup>35</sup>ClN<sub>4</sub>O<sub>3</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 437.1409, found 437.1411.

**(2R,3S)-2-[(4-Amino-5-[(benzyloxy)methyl]-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-4-(methylsulfanyl)butane-1,3-diol (32).** Compound **31** (0.19 g, 0.44 mmol) was stirred in NH<sub>3</sub>-MeOH solution (7M, 25 mL) for 24 h in a sealed tube at 135 °C (oil bath). After cooling to rt the solvent was evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub>-MeOH 96.5:3.5 then 95:5) to give **32** as a yellow gum (0.108 g, 60%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.17 (s, 1H), 7.46 (s, 1H), 7.28 (m, 5H), 5.63 (s, 2H), 4.57 (s, 2H), 4.07 (d, *J* = 13.6 Hz, 1H), 3.91 (d, *J* = 13.7 Hz, 1H), 3.81-3.73 (m, 2H), 3.64 (dd, *J* = 11.4, 5.0 Hz, 1H), 2.81-2.69 (m, 2H), 2.54 (dd, *J* = 13.5, 7.3 Hz, 1H), 2.04 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 152.8 (C), 151.5 (CH), 149.4 (C), 137.8 (C), 133.6 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 116.2 (C), 115.1 (C), 78.6 (CH<sub>2</sub>), 71.4 (CH<sub>2</sub>), 71.3 (CH), 62.1 (CH), 62.0 (CH<sub>2</sub>), 42.0 (CH<sub>2</sub>), 39.3 (CH<sub>2</sub>), 16.0 (CH<sub>3</sub>). ESI-HRMS for C<sub>20</sub>H<sub>28</sub>N<sub>5</sub>O<sub>3</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 418.1908, found 418.1902.

**(2R,3S)-2-[(4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-4-(methylsulfanyl)butane-1,3-diol (33).** Compound **32** (0.106 g, 0.25 mmol) was dissolved in NH<sub>3</sub>-MeOH solution (7M, 10 mL), Pd black (106 mg) was added followed by hydrazine hydrate (55% in hydrazine, 1.5 mL). The mixture was stirred for 1 h then filtered and the solvent evaporated. The residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 85:15) to give **33** as a colourless solid (0.056 g, 74%). [α]<sub>D</sub><sup>20</sup> -8.4 (c, 0.70, MeOH). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.16 (s, 1H), 7.47 (s, 1H), 4.11 (d, *J* = 13.6 Hz, 1H), 3.97 (d, *J* = 13.5 Hz, 1H), 3.84-3.74 (m, 2H), 3.64 (dd, *J* = 11.5, 5.0 Hz, 1H), 2.81 (q, *J* = 5.1 Hz, 1H), 2.72 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.55 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.06 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 152.0 (C), 150.8 (CH), 146.5 (C), 129.1 (CH), 115.5 (C), 114.9 (C), 71.2 (CH), 62.5 (CH), 61.8 (CH<sub>2</sub>), 42.2 (CH<sub>2</sub>), 39.3 (CH<sub>2</sub>), 16.0 (CH<sub>3</sub>). ESI-HRMS for C<sub>12</sub>H<sub>20</sub>N<sub>5</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 298.1333, found 298.1328.

**(4S)-4-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one (ent-27).** (2S)-2-Amino-2-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]ethan-1-ol benzoate (*ent*-**26**)<sup>61</sup> was converted into *ent*-**27** in the same way as that described for enantiomer **27**. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were identical to those of enantiomer **27**. [α]<sub>D</sub><sup>21</sup> + 50.5 (c 0.80, MeOH). ESI-HRMS for C<sub>8</sub>H<sub>13</sub>NNaO<sub>4</sub><sup>+</sup> (M+Na)<sup>+</sup> calcd. 210.0737, found 210.0736.

**(4S)-4-[(1R)-1,2-Dihydroxyethyl]-1,3-oxazolidin-2-one (*ent*-28).** Compound *ent*-27 was converted into *ent*-28 in the same way as that described for enantiomer 28. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were identical to those of enantiomer 28.  $[\alpha]_D^{21} +62.8$  (c 0.90, MeOH). ESI-HRMS for C<sub>5</sub>H<sub>9</sub>NNaO<sub>4</sub>, (M+Na)<sup>+</sup> calcd. 170.0424, found 170.0422.

**(4S,5R)-4-(Hydroxymethyl)-5-[(methylsulfonyl)methyl]-1,3-oxazolidin-2-one (*ent*-29).** Compound *ent*-28 was converted into *ent*-29 in the same way as that described for enantiomer 29. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were identical to those of enantiomer 29.  $[\alpha]_D^{21} -77.5$  (c 0.60, MeOH). ESI-HRMS for C<sub>6</sub>H<sub>11</sub>NNaO<sub>3</sub>S<sup>+</sup> (M+Na)<sup>+</sup> calcd. 200.0352, found 200.0352.

**(2S,3R)-2-Amino-4-(methylsulfonyl)butane-1,3-diol (*ent*-30).** Compound *ent*-29 was converted into *ent*-30 in the same way as that described for enantiomer 30. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were identical to those of enantiomer 30.  $[\alpha]_D^{21} -3.5$  (c1.09, MeOH). ESI-HRMS for C<sub>5</sub>H<sub>14</sub>NO<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 152.0740, found 152.0739.

**(2S,3R)-2-[(5-(Benzyloxy)methyl)-4-chloro-5H-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-4-(methylsulfonyl)butane-1,3-diol (*ent*-31).** Compound *ent*-30 was converted into *ent*-31 in the same way as that described for enantiomer 31. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were identical to those of enantiomer 31. ESI-HRMS for C<sub>20</sub>H<sub>26</sub><sup>35</sup>ClN<sub>4</sub>O<sub>3</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 437.1409, found 437.1417.

**(2S,3R)-2-[(4-Amino-5-(benzyloxy)methyl)-5H-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-4-(methylsulfonyl)butane-1,3-diol (*ent*-32).** Compound *ent*-31 was converted into *ent*-32 in the same way as that described for enantiomer 32. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were identical to those of enantiomer 32. ESI-HRMS for C<sub>20</sub>H<sub>28</sub>N<sub>5</sub>O<sub>3</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 418.1908, found 418.1904.

**(2S,3R)-2-[(4-Amino-5H-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-4-(methylsulfonyl)butane-1,3-diol (*ent*-33).** Compound *ent*-32 was converted into *ent*-33 in the same way described for the synthesis of enantiomer 33. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were identical to those of enantiomer 33.  $[\alpha]_D^{20} +8.2$  (c, 0.68, MeOH). ESI-HRMS for C<sub>12</sub>H<sub>20</sub>N<sub>5</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 298.1332, found 298.1330.

**(2R,3R)-3-Azido-2,4-dihydroxybutyl methanesulfonate (35).** A suspension of (2R,3R)-3-azidobutane-1,2,4-triol<sup>63</sup> (34, 1.0 g, 6.80 mmol) and dibutyltin oxide (1.93 g, 7.77 mmol) in toluene (60 mL) was heated under reflux in a Dean-Stark trap. After 30 min the resulting

clear solution was cooled to rt and methanesulfonyl chloride (1.0 mL, 12.95 mmol) was added. The solution was stirred overnight and then evaporated on to silica gel and the residue chromatographed (EtOAc-hexanes, 1:1) to give **35** as a pale yellow oil (1.05 g, 72%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 4.36 (dd, *J* = 10.7, 3.2 Hz, 1H), 4.30 (dd, *J* = 10.7, 5.6 Hz, 1H), 3.94 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.84 (m, 1H), 3.73 (dd, *J* = 11.6, 7.0 Hz, 1H), 3.56 (m, 1H), 3.13 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 72.6 (CH<sub>2</sub>), 69.8 (CH), 65.9 (CH), 62.8 (CH<sub>2</sub>), 37.3 (CH<sub>3</sub>). ESI-HRMS for C<sub>5</sub>H<sub>11</sub>N<sub>3</sub>NaO<sub>5</sub>S<sup>+</sup> (M+Na)<sup>+</sup> calcd. 248.0312, found 248.0315.

**(2R,3R)-2-Azido-4-(methylsulfanyl)butane-1,3-diol (36)**. The mesylate **35** (1.00 g, 4.44 mmol) was dissolved in dry DMF (12 mL), sodium thiomethoxide (0.62 g, 8.88 mmol) added and the mixture stirred for 2 h. H<sub>2</sub>O (100 mL) was added and the mixture extracted with EtOAc (5 x 5 mL) then the combined extracts were dried, the solvent evaporated and the residue chromatographed (EtOAc-hexanes, 1:1) to give **36** as a pale yellow syrup (0.40 g, 51%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.91-3.68 (m, 3H), 3.45 (m, 1H) 3.06 (d, *J* = 3.2 Hz, 1H), 2.80 (dd, *J* = 13.9, 3.3 Hz, 1H), 2.55 (dd, *J* = 13.9, 9.1 Hz, 1H), 2.36 (t, *J* = 5.7 Hz, 1H), 2.07 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 69.1 (CH), 65.8 (CH), 62.8 (CH<sub>2</sub>), 38.9 (CH<sub>2</sub>), 15.5 (CH<sub>3</sub>). ESI-HRMS for C<sub>5</sub>H<sub>11</sub>N<sub>3</sub>NaO<sub>2</sub>S<sup>+</sup> (M+Na)<sup>+</sup> calcd. 200.0465, found 200.0467.

**(2R,3R)-2-Amino-4-(methylsulfanyl)butane-1,3-diol (37)**. Lithium aluminium hydride (2M in THF, 1.79 mL, 3.58 mmol) was added to a solution of azide **36** (0.4 g, 2.26 mmol) in dry THF (12 mL) cooled in an ice bath. The solution was brought to room temperature and stirred for 1 h and then H<sub>2</sub>O (0.5 mL) was added. The resulting slurry was concentrated to dryness on silica gel and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 8:2) to give **37** as a yellow oil (0.22 g, 65%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 3.73 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.69 (m, 1H), 3.51 (dd, *J* = 10.8, 7.0 Hz, 1H), 2.86 (ddd, *J* = 7.0, 5.7, 4.2 Hz, 1H), 2.76 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.59 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.13 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 73.1 (CH), 64.2 (CH<sub>2</sub>), 57.3 (CH), 39.2 (CH<sub>2</sub>), 16.0 (CH<sub>3</sub>). ESI-HRMS for C<sub>5</sub>H<sub>14</sub>NO<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 152.0740, found 152.0734.

**(2R,3R)-2-[(5-[(Benzyloxy)methyl]-4-chloro-5H-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-4-(methylsulfanyl)butane-1,3-diol (38)**. A stirred solution of amine **37** (85 mg, 0.56 mmol), aldehyde **10** (170 mg, 0.56 mmol) and NaCNBH<sub>3</sub><sup>53</sup> (42.4 mg, 0.67 mmol) in methanol (5 mL) was brought to pH 7 by addition of HCl (2M in ether, 0.10 mL). After 3 h the solvent was evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 97:3) to give **38** as a yellow solid (149 mg, 61%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.62 (s, 1H), 7.91 (s, 1H), 7.27-7.17 (m, 5H), 5.90 (s, 2H), 4.56 (s, 2H), 4.04 (s, 2H), 3.90 (dt,

$J = 9.5, 4.8$  Hz, 1H), 3.76 (dd,  $J = 11.3, 4.6$  Hz, 1H), 3.66 (dd,  $J = 11.3, 5.9$  Hz, 1H), 2.81-2.71 (m, 2H) 2.61 (dd,  $J = 13.6, 7.8$  Hz, 1H), 2.08 (s, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  153.0 (C), 150.5 (CH), 143.9 (C), 138.7 (CH), 138.5 (C), 129.3 (CH), 128.8 (CH), 128.7 (CH), 125.6 (C), 116.5 (C), 78.3 ( $\text{CH}_2$ ), 71.7 ( $\text{CH}_2$ ), 71.5 (CH), 62.5 (CH), 61.3 ( $\text{CH}_2$ ), 41.3 ( $\text{CH}_2$ ), 39.2 ( $\text{CH}_2$ ), 16.1 ( $\text{CH}_3$ ). ESI-HRMS for  $\text{C}_{20}\text{H}_{26}^{35}\text{ClN}_4\text{O}_3\text{S}^+$  (M+H) $^+$  calcd. 437.1409, found 437.1407.

**(2R,3R)-2-[(4-Amino-5-[(benzyloxy)methyl]-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-4-(methylsulfanyl)butane-1,3-diol (39)**. A solution of chloride **38** (120 mg, 0.28 mmol) in  $\text{NH}_3$ -EtOH solution (6M, 15 mL) was heated in a sealed tube at 130 °C for 48 h, cooled to rt, then the solvent evaporated. The residue was chromatographed ( $\text{CH}_2\text{Cl}_2$ -7M  $\text{NH}_3$  in MeOH, 93:7) to give **39** as a yellow oil (84 mg, 73%).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.16 (s, 1H), 7.47 (s, 1H), 7.33-7.23 (m, 5H), 5.63 (s, 2H), 4.56 (s, 2H), 3.97 (s, 2H), 3.91 (dt,  $J = 9.4, 4.7$  Hz, 1H), 3.78 (dd,  $J = 11.3, 4.6$  Hz, 1H), 3.68 (dd,  $J = 11.3, 5.9$  Hz, 1H), 2.82 (m, 1H) 2.74 (dd,  $J = 13.5, 4.8$  Hz, 1H) 2.62 (dd,  $J = 13.5, 7.9$  Hz, 1H), 2.08 (s, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  152.8 (C), 151.5 (CH), 149.4 (C), 137.7 (C), 133.5 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 116.1 (C), 115.0 (C), 78.6 ( $\text{CH}_2$ ), 71.6 (CH), 71.3 ( $\text{CH}_2$ ), 62.5 (CH), 61.3 ( $\text{CH}_2$ ), 41.5 ( $\text{CH}_2$ ), 39.2 ( $\text{CH}_2$ ), 16.1 ( $\text{CH}_3$ ). ESI-HRMS for  $\text{C}_{20}\text{H}_{28}\text{N}_5\text{O}_3\text{S}^+$  (M+H) $^+$  calcd. 418.1903, found 418.1898.

**(2R,3R)-2-[(4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-4-(methylsulfanyl)butane-1,3-diol (40)**. Pd black (34 mg, 0.33 mmol) and hydrazine hydrate (55% in hydrazine, 0.75 mL) were added to a solution of compound **39** (34 mg, 0.081 mmol) in  $\text{NH}_3$ -MeOH (7M, 3 mL). After 0.5 h the mixture was filtered through a plug of Celite, the solvent evaporated and the residue chromatographed ( $\text{CH}_2\text{Cl}_2$ -7M  $\text{NH}_3$  in MeOH, 8:2) to give **40** as a pale yellow foam (14 mg, 61%).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.15 (s, 1H), 7.49 (s, 1H), 4.02 (s, 2H), 3.92 (dt,  $J = 9.2, 4.6$  Hz, 1H), 3.78 (dd,  $J = 11.4, 4.7$  Hz, 1H), 3.68 (dd,  $J = 11.4, 5.9$  Hz, 1H), 2.84 (m, 1H), 2.73 (dd,  $J = 13.6, 4.8$  Hz, 1H) 2.59 (dd,  $J = 13.6, 8.0$  Hz, 1H) 2.09 (s, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  152.1 (C), 150.8 (CH), 146.6 (C), 129.1 (CH), 115.4 (C), 114.8 (C), 71.4 (CH), 62.6 (CH), 61.2 ( $\text{CH}_2$ ), 41.8 ( $\text{CH}_2$ ), 39.1 ( $\text{CH}_2$ ), 16.0 ( $\text{CH}_3$ ). ESI-HRMS for  $\text{C}_{12}\text{H}_{20}\text{N}_5\text{O}_2\text{S}^+$  (M+H) $^+$  calcd. 298.1333, found 298.1333.

**(2S,3S)-3-Azido-2,4-dihydroxybutyl methanesulfonate (ent-35)**. (2R,3R)-3-Azidobutane-1,2,4-triol (*ent*-**34**)<sup>63</sup> was converted into *ent*-**35** in the same way as that described for enantiomer **35**. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were identical to those of enantiomer **35**. ESI-HRMS for  $\text{C}_5\text{H}_{11}\text{N}_3\text{O}_2\text{NaS}^+$  (M+Na) $^+$  calcd. 248.0312, found 238.0308.

**(2S,3S)-2-Azido-4-(methylsulfonyl)butane-1,3-diol (ent-36).** Compound *ent-35* was converted into *ent-36* in the same way as that described for enantiomer **36**. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were identical to those of enantiomer **36**. ESI-HRMS for  $\text{C}_5\text{H}_{11}\text{N}_3\text{O}_2\text{NaS}^+$  ( $\text{M}+\text{Na}$ ) $^+$  calcd. 200.0465, found 200.0466.

**(2S,3S)-2-Amino-4-(methylsulfonyl)butane-1,3-diol (ent-37).** Compound *ent-36* was converted into *ent-37* in the same way as that described for enantiomer **37**. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were identical to those of enantiomer **37**. ESI-HRMS for  $\text{C}_5\text{H}_{14}\text{NO}_2\text{S}^+$  ( $\text{M}+\text{H}$ ) $^+$  calcd. 152.0740, found 152.0742

**(2S,3S)-2-[(5-[(benzyloxy)methyl]-4-chloro-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-4-(methylsulfonyl)butane-1,3-diol (ent-38).** Compound *ent-37* was converted into *ent-38* in the same way as that described for enantiomer **38**. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were identical to those of enantiomer **38**. ESI-HRMS for  $\text{C}_{20}\text{H}_{26}^{35}\text{ClN}_4\text{O}_3\text{S}^+$  ( $\text{M}+\text{H}$ ) $^+$  calcd. 437.1409, found 437.1416.

**(2S,3S)-2-[(4-Amino-5-(benzyloxy)methyl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-4-(methylsulfonyl)butane-1,3-diol (ent-39).** Compound *ent-38* was converted into *ent-39* in the same way as that described for enantiomer **39**. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were identical to those of enantiomer **39**. ESI-HRMS for  $\text{C}_{20}\text{H}_{28}\text{N}_5\text{O}_3\text{S}^+$  ( $\text{M}+\text{H}$ ) $^+$  calcd 418.1908, found 418.1903.

**(2S,3S)-2-[(4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-4-(methylsulfonyl)butane-1,3-diol (ent-40).** Compound *ent-39* was converted into *ent-40* in the same way as that described for enantiomer **40**. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were identical to those of enantiomer **40**. ESI-HRMS for  $\text{C}_{12}\text{H}_{20}\text{N}_5\text{O}_2\text{S}^+$  ( $\text{M}+\text{H}$ ) $^+$  calcd. 298.1333, found 298.1334.

**2-Amino-2-[(methylsulfonyl)methyl]propane-1,3-diol hydrochloride (44).** Methanesulfonyl chloride (0.43 mL, 5.46 mmol) was added dropwise to a stirred solution of *tert*-butyl *N*-[5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl]carbamate<sup>64</sup> (**41**, 1.03 g, 4.66 mmol) and  $\text{Et}_3\text{N}$  (1.52 mL, 10.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0 °C. The reaction was allowed to warm to rt and after 1.5 h the mixture was diluted with  $\text{CH}_2\text{Cl}_2$ , washed with  $\text{H}_2\text{O}$  then brine, dried and the solvent evaporated to yield *tert*-butyl *N*-{5-[(methanesulfonyloxy)methyl]-2,2-dimethyl-1,3-dioxan-5-yl}carbamate (**42**, 1.35 g, 85%) as a pale yellow solid. To a solution of this material (0.566 g, 1.67 mmol), in DMF (3 mL) was added sodium thiomethoxide (0.292 g, 4.17 mmol) and after stirring at rt for 15 h, ethyl



acetate was added. The mixture was washed with aq. NaHCO<sub>3</sub> (sat., 3 x) then brine, dried and the solvent evaporated. The resulting pale yellow solid was chromatographed (EtOAc-hexanes, 1:5) to give *tert*-butyl *N*-{2,2-dimethyl-5-[(methylsulfanyl)methyl]-1,3-dioxan-5-yl}carbamate (**43**, 0.460 g, 95%) as a white solid. A solution of this material (2.64 g, 9.06 mmol) in MeOH (10 mL) was added to a solution of aq. HCl (37%, 8 mL) in MeOH (100 mL) and after 10 mins the solvent was evaporated and the oily residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-MeOH-7 M NH<sub>3</sub> in MeOH, 5:2:1) to give the free base form of the product. Addition of aq. HCl (37%, 1 mL) in MeOH (5 mL) followed by evaporation of the solvent gave **44** as a colourless solid (1.37 g, 81%). <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O): δ 3.83 (s, 4H), 2.97 (s, 2H), 2.28 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, DMSO-*d*<sub>6</sub>): δ 64.2 (2 x CH<sub>2</sub>), 57.7 (C), 39.3 (CH<sub>2</sub>), 17.3 (CH<sub>3</sub>). ESI-HRMS for C<sub>5</sub>H<sub>14</sub>NO<sub>2</sub>S<sup>+</sup> (M-HCl+H)<sup>+</sup> calcd. 152.0739, found 152.0740.

**2-[(4-Amino-5-[(benzyloxy)methyl]-5H-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-2-[(methylsulfanyl)methyl]propane-1,3-diol (**46**)**. A mixture of **36** (60.0 mg, 0.32 mmol), aldehyde **10** (97 mg, 0.32 mmol) and NaCNBH<sub>3</sub><sup>53</sup> (27.4 mg, 0.436 mmol) was stirred in MeOH (4 mL) for 15 h at rt. The solvent was evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH 10:1) to give *tert*-butyl *N*-{2,2-dimethyl-5-[(methylsulfanyl)methyl]-1,3-dioxan-5-yl}carbamate (**45**) as a yellow gum (110 mg, 79%). ESI-HRMS for C<sub>20</sub>H<sub>26</sub><sup>35</sup>ClN<sub>4</sub>O<sub>3</sub>S (M+H)<sup>+</sup> calcd. 437.1414, found 437.1407. A portion of **45** (20.0 mg, 0.046 mmol) in NH<sub>3</sub>-MeOH solution (7M, 3 mL) was stirred in a sealed pressure tube at 135 °C for 20 h. After cooling to rt the solvent was evaporated and the residue chromatographed (CHCl<sub>3</sub>-7 M NH<sub>3</sub> in MeOH, 9:1 then 8:2) to give **46** (19.0 mg, 99%) as a yellow gum. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 8.15 (s, 1H), 7.47 (s, 1H), 7.33-7.21 (m, 5H), 5.65 (s, 2H), 4.58 (s, 2H), 3.91 (s, 2H), 3.67 (d, *J* = 11.4 Hz, 2H), 3.64 (d, *J* = 11.4 Hz, 2H), 2.75 (s, 2H), 2.16 (s, 3H). <sup>13</sup>C NMR (125.7 MHz, CD<sub>3</sub>OD): δ 152.8 (C), 151.5 (CH), 149.2 (C), 137.8 (C), 133.2 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 116.1 (C), 115.1 (C), 78.6 (CH<sub>2</sub>), 71.4 (CH<sub>2</sub>), 62.8 (2 x CH<sub>2</sub>), 62.2 (C), 37.8 (CH<sub>2</sub>), 35.9 (CH<sub>2</sub>), 17.3 (CH<sub>3</sub>). ESI-HRMS for C<sub>20</sub>H<sub>28</sub>N<sub>5</sub>O<sub>3</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 418.1902, found 418.1908.

**2-[(4-Amino-5H-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-2-[(methylsulfanyl)methyl]propane-1,3-diol (**47**)**. To a stirred suspension of **46** (75 mg, 0.18 mmol) and Pd-black (75 mg) in NH<sub>3</sub>-MeOH solution (7M, 2 mL) was added hydrazine hydrate (55% in hydrazine, 0.5 mL) dropwise. After 1 h at rt the mixture was filtered through Celite, the solvent evaporated and the residue chromatographed (CHCl<sub>3</sub>-7M NH<sub>3</sub> in MeOH,

9:1 then 8:2) to give **47** as a colourless crystalline solid (30 mg, 56%). <sup>1</sup>H NMR (500 MHz, DMSO *d*<sub>6</sub>): δ 10.67 (s, exchanged D<sub>2</sub>O, 1H), 8.07 (s, 1H), 7.40 (s, 1H), 6.71 (s, exchanged D<sub>2</sub>O, 1H), 4.92 (s, exchanged D<sub>2</sub>O, 1H), 3.79 (s, 2H), 3.42 (m, 4H), 3.32 (d, *J* = 10.9 Hz, exchanged D<sub>2</sub>O, 3H), 2.62 (s, 2H), 2.08 (s, 3H). <sup>13</sup>C NMR (125.7 MHz, DMSO *d*<sub>6</sub>): δ 150.4 (C), 149.7 (CH), 145.2 (C), 125.6 (d, *J* = 20.5 Hz, s after D<sub>2</sub>O exchange, CH), 114.6 (C), 113.9 (d, *J* = 17.5 Hz, s after D<sub>2</sub>O exchange, C), 61.2 (CH<sub>2</sub>), 60.2 (C), 36.8 (CH<sub>2</sub>), 35.0 (CH<sub>2</sub>), 16.7 (CH<sub>3</sub>). ESI-HRMS for C<sub>12</sub>H<sub>20</sub>N<sub>5</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 298.1333, found 298.1329.

**tert-Butyl N-[(2S)-2,3-dihydroxypropyl]carbamate (49).** Benzyl({[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl})amine<sup>48</sup> (**48**, 1.5 g, 6.78 mmol) was dissolved in EtOH (30 mL), 10% Pd-C (200 mg) added and the mixture stirred under a hydrogen atmosphere at rt for 16 h. The mixture was filtered through Celite and the solvent evaporated to give [(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methanamine as a colourless oil (840 mg). The <sup>1</sup>H NMR (300 MHz) was in agreement with that reported in the literature.<sup>69</sup> The oil was dissolved in aq. HCl (6M, 2 mL) and heated at 100 °C for 30 min. The solvent was evaporated to give (2S)-3-aminopropane-1,2-diol hydrochloride as an oil (720 mg, 5.65 mmol). The <sup>1</sup>H (300 MHz) and <sup>13</sup>C NMR(75.5 MHz) spectra were in agreement with those reported.<sup>69</sup> The HCl salt (0.71 g, 5.57 mmol) was dissolved in MeOH (20 mL) and Et<sub>3</sub>N (1.5 mL, 11.1 mmol) added followed by di-*tert*-butyl dicarbonate (1.33 g, 6.1 mmol). The mixture was stirred at rt for 2 h then the solvent evaporated. The residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 92:8) to give crude **49** as a colourless gum contaminated with some Et<sub>3</sub>NHCl. The products were dissolved in MeOH and stirred with Amberlyst A26 (OH) resin, filtered and the solvent evaporated to give pure **49** (0.849 g, 66%). The <sup>1</sup>H (300 MHz) and <sup>13</sup>C NMR(75.5 MHz) spectra were in agreement with those reported.<sup>65</sup> [ $\alpha$ ]<sub>D</sub><sup>21</sup> +7.8 (c 0.90, CHCl<sub>3</sub>). Lit<sup>65</sup> [ $\alpha$ ]<sub>D</sub><sup>21</sup> +6.7 (c 0.50, CHCl<sub>3</sub>). ESI-HRMS for C<sub>8</sub>H<sub>17</sub>NNaO<sub>4</sub><sup>+</sup> (M+Na)<sup>+</sup> calcd. 214.1050, found 214.1048.

**tert-Butyl N-[(2R)-2-hydroxy-2-(methylsulfonyl)ethyl]carbamate (50).** *p*-Toluenesulfonyl chloride (0.812 g, 4.26 mmol) was added to a solution of **49** (0.74 g, 3.87 mmol) in dry pyridine (15 mL) at 0 °C. After 15 mins the solution was warmed to rt and stirred for 2 h. More *p*-toluenesulfonyl chloride (400 mg) was added and the mixture stirred for 16 h. An additional quantity of *p*-toluenesulfonyl chloride (800 mg) was added and the mixture stirred a further 24 h. The solvent was evaporated and the residue chromatographed (EtOAc-hexanes, 1:1, then EtOAc) to give first the intermediate tosylate (490 mg) then recovered alcohol (**49**) (223 mg). The latter was dissolved in dry pyridine (10 mL) and *p*-

toluenesulfonyl chloride (446 mg) added and the mixture stirred for 16 h at rt. Work-up and chromatography as above gave another 179 mg of tosylate. The combined tosylate products (625 mg 1.8 mmol) were dissolved in DMF (5 mL) cooled in an ice-bath then NaSMc (257 mg, 3.6 mmol) added. The mixture was stirred at rt for 2 h then the solvent evaporated and the residue chromatographed (EtOAc-hexanes, 2:8) to give **50** as a colourless oil (0.189 g, 22%).  $[\alpha]_D^{21}$  -9.2 (c 0.65, MeOH).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.02 (bs, exchanged to  $\text{D}_2\text{O}$ , 1H), 3.80 (bm, 1H), 3.42 (bm, 1H), 3.22 (bs, exchanged to  $\text{D}_2\text{O}$ , 1H), 3.14 (m, 1H), 2.65 (dd,  $J = 13.8, 4.6$  Hz, 1H), 2.51 (dd,  $J = 13.8, 8.3$  Hz, 1H), 2.12 (s, 3H), 1.45 (s, 9H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.7 (C), 79.7 (C), 68.6 (CH), 45.2 ( $\text{CH}_2$ ), 38.9 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_3$ ), 15.5 ( $\text{CH}_3$ ). ESI-HRMS for  $\text{C}_9\text{H}_{19}\text{NNaO}_3\text{S}^+$  ( $\text{M}+\text{Na}$ ) $^+$  calcd. 244.0978, found 244.0975. The column was further eluted with EtOAc to give the by-product (5*S*)-5-[(methylsulfonyl)methyl]-1,3-oxazolidin-2-one (**51**) as a yellow oil (88 mg, 16%).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.46 (bs, exchanged to  $\text{D}_2\text{O}$ , 1H), 4.80 (m, 1H), 3.74 (t,  $J = 8.7$  Hz, 1H), 3.44 (dd,  $J = 8.7, 6.5$  Hz, 1H), 2.87 (dd,  $J = 14.0, 5.1$  Hz, 1H), 2.76 (dd,  $J = 14.0, 7.2$  Hz, 1H), 2.20 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  159.8 (C), 75.7 (CH), 45.1 ( $\text{CH}_2$ ), 37.6 ( $\text{CH}_2$ ), 16.2 ( $\text{CH}_3$ ). ESI-HRMS for  $\text{C}_5\text{H}_{10}\text{NO}_2\text{S}^+$  ( $\text{M}+\text{H}$ ) $^+$  calcd. 148.0427, found 148.0421.

**(({5-[(Benzyloxy)methyl]-4-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methyl}[(2*S*)-2-hydroxy-3-(methylsulfonyl)propyl]amine (**52**)).** Compound **50** (0.18 g, 0.813 mmol) was dissolved in a mixture of MeOH (3 mL) and aq. HCl (37%, 2 mL) and after 5 min the solvent was evaporated. The residue was dissolved in MeOH (8 mL) then aldehyde **10** (0.270 g, 0.895 mmol) and  $\text{NaCNBH}_3$ <sup>53</sup> (0.066 g, 1.057 mmol) were added and the mixture stirred at rt for 60 h. The solvent was evaporated and the residue chromatographed ( $\text{CH}_2\text{Cl}_2$ -7M  $\text{NH}_3$ -MeOH 98:2) to give **52** as a colourless gum (0.146 g, 44%).  $^1\text{H NMR}$  (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.62 (s, 1H), 7.89 (s, 1H), 7.21 (m, 5H), 5.90 (s, 2H), 4.56 (s, 2H), 4.03 (d,  $J = 13.8$  Hz, 1H), 3.96 (d,  $J = 13.8$  Hz, 1H), 3.87 (m, 1H), 2.85 (dd,  $J = 12.1, 3.5$  Hz, 1H), 2.63 (dd,  $J = 12.1, 8.3$  Hz, 1H), 2.55 (d,  $J = 6.4$  Hz, 2H), 2.09 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  153.0 (C), 150.6 (CH), 143.9 (C), 138.7 (CH), 138.5 (C), 129.3 (CH), 128.8 (CH), 128.7 (CH), 125.5 (C), 115.6 (C), 78.3 ( $\text{CH}_2$ ), 71.7 ( $\text{CH}_2$ ), 70.3 (CH), 54.6 ( $\text{CH}_2$ ), 43.1 ( $\text{CH}_2$ ), 40.3 ( $\text{CH}_2$ ), 16.2 ( $\text{CH}_3$ ). ESI-HRMS for ( $\text{M}+\text{H}$ ) $^+$   $\text{C}_{19}\text{H}_{24}^{35}\text{ClN}_4\text{O}_2\text{S}^+$  calcd. 407.1304, found 407.1305.

**5-[(Benzyloxy)methyl]-7-({[(2*S*)-2-hydroxy-3-(methylsulfonyl)propyl]amino}methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (**53**).** Compound **52** (0.124 g, 0.305 mmol) was stirred in a solution of  $\text{NH}_3$ -MeOH (7M, 25 mL) for 24 h in a sealed tube at 135 °C (oil bath).

After cooling to rt the solvent was evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 98:2) to give **53** as a colourless gum (0.085 g, 72%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.16 (s, 1H), 7.47 (s, 1H), 7.28 (m, 5H), 5.66 (s, 2H), 4.58 (s, 2H), 3.97 (d, *J* = 13.8 Hz, 1H), 3.91-3.83 (m, 2H), 2.84 (dd, *J* = 12.2, 3.5 Hz, 1H), 2.62 (dd, *J* = 12.1, 8.4 Hz, 1H), 2.56 (d, *J* = 6.4 Hz, 2H), 2.09 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 152.8 (C), 151.6 (CH), 149.4 (C), 137.7 (C), 133.5 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 116.0 (C), 114.2 (C), 78.6 (CH<sub>2</sub>), 71.3 (CH<sub>2</sub>), 70.3 (CH), 54.6 (CH<sub>2</sub>), 43.3 (CH<sub>2</sub>), 40.4 (CH<sub>2</sub>), 16.2 (CH<sub>3</sub>). ESI-HRMS for C<sub>19</sub>H<sub>26</sub>N<sub>5</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 388.1802, found 388.1808.

**7-([(2*S*)-2-Hydroxy-3-(methylsulfanyl)propyl]amino)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (**54**). Pd black (80 mg) and hydrazine hydrate (55% in hydrazine, 1.2 mL) were added to a stirred solution of **53** (0.08 g, 0.206 mmol) in NH<sub>3</sub>-MeOH solution (7M, 8 mL). After 40 min the solids were filtered off and the solvent evaporated. The residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 85:15) to give **54** as a colourless solid (0.042 g, 76%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -12.4 (c, 0.36, MeOH). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.16 (s, 1H), 7.48 (s, 1H), 4.00 (d, *J* = 13.5 Hz, 1H), 3.92-3.84 (m, 2H), 2.85 (dd, *J* = 12.2, 3.5 Hz, 1H), 2.65 (dd, *J* = 12.2, 8.5 Hz, 1H), 2.55 (d, *J* = 6.5 Hz, 2H), 2.10 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 152.1 (C), 150.9 (CH), 146.6 (C), 129.1 (CH), 115.4 (C), 114.2 (C), 70.2 (CH), 54.5 (CH<sub>2</sub>), 43.5 (CH<sub>2</sub>), 40.4 (CH<sub>2</sub>), 16.1 (CH<sub>3</sub>). ESI-HRMS for C<sub>11</sub>H<sub>18</sub>N<sub>5</sub>OS<sup>+</sup> (M+H)<sup>+</sup> calcd. 268.1227, found 268.1236.**

**(±)-Benzyl N-([(5*R*/*S*,6*R*/*S*)-6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl]methyl)carbamate [(±)-**57**]. A mixture of *N*-benzylhydroxylamine hydrochloride (22.4 g, 140 mmol) and NaOAc (15.36 g, 187 mmol) in EtOH (120 mL) was stirred at rt for 15 mins and then aq. formaldehyde (37%, 20.91 mL, 281 mmol) was added and the resulting mixture stirred for 30 mins. 2,2-Dimethyl-4,7-dihydro-2*H*-1,3-dioxepine<sup>66</sup> (**55**, 12 g, 94 mmol) was added and the mixture was stirred and heated under reflux for 6 h before evaporating to dryness. The residue was partitioned between CHCl<sub>3</sub> and H<sub>2</sub>O with the aq. phase adjusted to pH 8 with aq. NaOH. The organic phase was separated and washed with aq. NaHCO<sub>3</sub> (sat.) then dried and the solvent evaporated to a syrup. Chromatography (EtOAc-hexanes, 1:2, then 1:1) gave (±)-(5'*a**R*/*S*,10'*a**R*/*S*)-8',8'-dimethyl-1',3',4',5'*a*,6',8',10',10'*a*-octahydro-5',7',9'-trioxo-4'-azaspiro[benzene-1,2'-heptalene] [(±)-**56**] as a yellow solid (10.47 g, 43%). To a solution of this material (10.4 g, 39.5 mmol) in EtOH (150 mL) was added 10% Pd/C (2.5 g) and the mixture was stirred under a hydrogen atmosphere for 2 days. The solids were filtered off and the solvent evaporated. The residue was dissolved in MeOH (100 mL), cooled in an ice bath**

then Et<sub>3</sub>N (11.01 mL, 79 mmol) and benzyl chloroformate (7.3 mL, 51.3 mmol) added. After stirring at rt for 30 mins, CHCl<sub>3</sub> was added and the solution was washed with H<sub>2</sub>O then dried and the solvent evaporated and the resulting residue triturated with hexanes to give the carbamate (±)-**57** (7.73 g, 63%) as a white solid which was recrystallized from EtOH. M.P. 123-124 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.35-7.28 (m, 5H), 5.31 (bt, *J* = 5.5 Hz, 1H), 5.08 (s, 2H), 3.83-3.61 (m, 4H), 3.38 (dd, *J* = 12.5, 2.4 Hz, 1H), 3.33-3.14 (m, 2H), 3.00 (bd, *J* = 7.6 Hz, 1H), 1.90 (bm, 1H), 1.33, 1.32 (2s, 6H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 156.8 (C), 136.4 (C), 128.5 (CH), 128.1 (2 x CH), 101.7 (C), 68.7 (CH), 66.7 (CH<sub>2</sub>), 64.2 (CH<sub>2</sub>), 59.4 (CH<sub>2</sub>), 45.9 (CH), 39.5 (CH<sub>2</sub>), 24.8 (CH<sub>3</sub>), 24.5 (CH<sub>3</sub>). Anal. calcd for C<sub>16</sub>H<sub>23</sub>NO<sub>5</sub>: C, 62.12, H, 7.49; N, 4.53. Found C, 62.41, H, 7.32, N, 4.54.

(±)-Benzyl *N*-{[(4*R/S*,5*R/S*)-4-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl]methyl}carbamate [(±)-**58**] and (±)-benzyl *N*-[(2*R/S*)-2-[(4*R/S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxypropyl]carbamate [(±)-**59**]. Camphorsulfonic acid (0.069 g, 0.296 mmol) was added to a solution of (±)-**57** (1.83 g, 5.92 mmol) in acetone (50 mL) and the solution was stirred at rt for 40 mins. Chloroform was added and the solution was washed with aq. NaHCO<sub>3</sub> (sat.) then dried and the solvent evaporated to leave a syrup. Chromatography (EtOAc-hexanes 1:1 then 3:1) gave firstly (±)-**59** (0.86 g, 44%) as a syrup. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.35-7.28 (m, 5H), 5.36 (bt, *J* = 5.0 Hz, 1H), 5.09 (s, 2H), 4.14-4.03 (m, 2H), 3.72 (bt, *J* = 5.1 Hz, 3H), 3.27 (bt, *J* = 6.2 Hz, 2H), 3.05 (bt, *J* = 5.2 Hz, 1H), 1.85 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 157.2 (C), 136.3 (C), 128.5 (CH), 128.1 (CH), 128.0 (CH), 108.8 (C), 75.9 (CH), 67.5 (CH<sub>2</sub>), 66.9 (CH<sub>2</sub>), 60.8 (CH<sub>2</sub>), 43.8 (CH), 39.5 (CH<sub>2</sub>), 26.5 (CH<sub>3</sub>), 25.2 (CH<sub>3</sub>). Further elution gave (±)-**58** (0.942 g, 52%) as a syrup. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.35-7.29 (m, 5H), 5.19 (bt, *J* = 5.8 Hz, 1H), 5.08 (s, 2H), 3.81 (dd *J* = 11.7, 5.3 Hz, 1H), 3.75-3.58 (m, 4H), 3.17-3.05 (m, 2H) 2.49 (bt, *J* = 5.0 Hz, 1H), 1.98 (bm, 1H), 1.40 (s, 3H), 1.37 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 156.6 (C), 136.3 (C), 128.5 (CH), 128.1 (CH), 128.0 (CH), 98.6 (C), 72.0 (CH), 66.8 (CH<sub>2</sub>), 63.8 (CH<sub>2</sub>), 61.8 (CH<sub>2</sub>), 39.8 (CH<sub>2</sub>), 36.3 (CH), 24.5 (CH<sub>3</sub>), 19.8 (CH<sub>3</sub>).

(±)-Benzyl *N*-[(2*S/R*)-2-[(4*R/S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-(methylsulfonyl)propyl]carbamate [(±)-**60**]. Methanesulfonyl chloride (0.274 mL, 3.54 mmol) was added to a solution of (±)-**59** (0.843 g, 2.73 mmol) and *i*-Pr<sub>2</sub>NEt (1.35 mL, 8.18 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and the resulting solution was stirred at rt for 15 mins. The mixture was washed successively with H<sub>2</sub>O, aq. HCl (5%), then aq. NaHCO<sub>3</sub> (sat.), dried and the solvent evaporated. The residue was dissolved in DMF (15 mL) and sodium

thiomethoxide (0.57 g, 8.18 mmol) added. After stirring the mixture at rt for 1 h, toluene was added and the mixture was washed with H<sub>2</sub>O (x 2), dried and the solvent evaporated. The residue was chromatographed (EtOAc-hexanes, 1:2) to give (±)-**60** as a syrup (0.77 g, 83%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.39-7.28 (m, 5H), 5.21 (bt, *J* ~ 5.0 Hz, 1H), 5.10 (s, 2H), 4.16-4.06 (m, 2H), 3.74 (m, 1H), 3.33 (t, *J* = 5.8 Hz, 2H), 2.74 (dd, *J* = 13.3, 4.4 Hz, 1H), 2.51 (dd, *J* = 13.3, 8.3 Hz, 1H), 2.10 (s, 3H), 1.98 (bm, 1H), 1.40 (s, 3H), 1.33 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 156.5 (C), 136.5 (C), 128.5 (CH), 128.1 (2 x CH), 108.9 (C), 76.4 (CH), 67.2 (CH<sub>2</sub>), 66.7 (CH<sub>2</sub>), 41.4 (CH + CH<sub>2</sub>), 33.2 (CH<sub>2</sub>), 26.5 (CH<sub>3</sub>), 25.1 (CH<sub>3</sub>), 16.6 (CH<sub>3</sub>).

**(±)-(2*S*/*R*)-2-[(4*R*/*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(methylsulfanyl)propan-1-amine [(±)-**61**].** A solution of (±)-**60** (50 mg, 0.15 mmol) and potassium hydroxide (248 mg, 4.42 mmol) in *i*-PrOH (2 mL) was heated under reflux for 2 h. Silica gel was added and the solvent evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 95:5, then CH<sub>2</sub>Cl<sub>2</sub>- 7M NH<sub>3</sub> in MeOH, 93:7) to give (±)-**61** as a syrup (25 mg, 83%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 4.21 (q, *J* = 6.6 Hz, 1H), 4.06 (dd, *J* = 6.3, 8.1 Hz, 1H), 3.70 (t, *J* = 7.7 Hz, 1H); 2.82-2.74 (m, 3H); 2.61 (dd, *J* = 13.0, 8.0 Hz, 1H); 2.13 (s, 3H); 1.80 (m, 1H), 1.48 (bs, 2H), 1.41 (s, 3H), 1.35 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 108.6 (C), 76.5 (CH), 67.5 (CH<sub>2</sub>), 44.1 (CH), 41.9 (CH<sub>2</sub>), 33.3 (CH<sub>2</sub>), 26.5 (CH<sub>3</sub>), 25.3 (CH<sub>3</sub>), 16.4 (CH<sub>3</sub>).

**({5-[(Benzyloxy)methyl]-4-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methyl}[(2*S*/*R*)-2-[(4*R*/*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-(methylsulfanyl)propyl]amine [(±)-**62**].** Sodium triacetoxyborohydride<sup>67</sup> (152 mg, 0.68 mmol) was added to a solution of (±)-**61** (70 mg, 0.34 mmol) and aldehyde **10** (129 mg, 0.34 mmol) in 1,2-dichloroethane (5 mL) at rt. After stirring for 40 min aq. NaHCO<sub>3</sub> (sat., 10 mL) was added to the vigorously stirred mixture then the organic layer was separated, dried and the solvent evaporated. The residue was chromatographed CHCl<sub>3</sub>-EtOAc-MeOH, 5:2:1) to give (±)-**62** as a colourless oil (107 mg, 64%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.72 (s, 1H), 7.53 (s, 1H), 7.35-7.21 (m, 5H), 5.82 (s, 2H), 4.53 (s, 2H), 4.18 (q, *J* = 6.7 Hz, 1H), 4.04 (dd, *J* = 8.1, 6.3, Hz, 1H), 4.00 (s, 2H), 3.69 (t, *J* = 7.8 Hz, 1H), 2.83-2.67 (m, 3H), 2.61 (dd, *J* = 13.1, 7.8, Hz, 1H), 2.09 (s, 3H), 2.07-1.89 (m, 2H), 1.38 (s, 3H), 1.33 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 151.8, 149.9, 142.4, 136.4, 135.0, 128.5, 128.1, 127.6, 124.4, 116.3, 108.5, 76.7, 76.5, 70.4, 67.6, 49.4, 43.4, 42.0, 34.1, 26.6, 25.3, 16.5. ESI-HRMS for C<sub>24</sub>H<sub>32</sub><sup>35</sup>ClN<sub>4</sub>O<sub>3</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 491.1879, found 491.1859.

**(({4-Azido-5-[(benzyloxy)methyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methyl})[(2*S*/*R*)-2-[(4*R*/*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-(methylsulfanyl)propyl]amine [(±)-63].**

Sodium azide (50 mg, 0.77 mmol) was added to a solution of (±)-**62** (100 mg, 0.20 mmol) in dry DMF (3 mL) and the mixture was heated at 90 °C for 1 h. After cooling the reaction mixture to rt the solvent was evaporated and the residue was suspended in CHCl<sub>3</sub>/MeOH and concentrated onto silica gel. The residue was chromatographed (EtOAc, then CHCl<sub>3</sub>-MeOH, 5:1) to give (±)-**63** as a colourless oil (101 mg, 100%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.38 (s, 1H), 7.55 (s, 1H), 7.30-7.15 (m, 5H), 6.05 (s, 2H), 4.64 (s, 2H), 4.20 (q, *J* = 6.7, Hz, 1H), 4.14-4.00 (m, 3H), 3.71 (t, *J* = 7.7 Hz, 1H), 2.98-2.69 (m, 3H), 2.62 (dd, *J* = 13.1, 7.8, Hz, 1H), 2.24 (bs, 1H), 2.10 (s, 3H), 2.07-1.91 (m, 1H), 1.38 (s, 3H), 1.33 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 141.7, 138.3, 136.3, 131.1, 129.0, 128.2, 127.9, 127.5, 119.7, 113.4, 108.5, 77.9, 76.7, 71.4, 67.6, 49.3, 43.5, 41.9, 34.1, 26.5, 25.2, 16.4. ESI-HRMS for C<sub>24</sub>H<sub>32</sub>N<sub>7</sub>O<sub>3</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 498.2282, found 498.2271.

**5-[(Benzyloxy)methyl]-7-({[(2*S*/*R*)-2-[(4*R*/*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-(methylsulfanyl)propyl]amino}methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine [(±)-64].**

Trimethylphosphine (1.0M in THF, 0.5 mL, 0.50 mmol) was added to a solution of (±)-**63** (90 mg, 0.18 mmol) in THF (2 mL) at rt and the mixture stirred for 1.5 h. Further trimethyl phosphine (1.0M in THF, 0.3 mL, 0.30 mmol) was added then after 2 h aq. NH<sub>4</sub>OH (28%, 1.5 mL) was added and the mixture stirred for an additional 15 min. The solvent was evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M. NH<sub>3</sub> in MeOH, 15:1) to give (±)-**64** as a colourless oil (78 mg, 91%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.38 (s, 1H), 7.42-7.33 (m, 3H), 7.32-7.24 (m, 2H), 7.11 (s, 1H), 5.81 (bs, exchanged to D<sub>2</sub>O, 2H), 5.49 (s, 2H), 4.56 (s, 2H), 4.19 (q, *J* = 6.9 Hz, 1H), 4.05 (dd, *J* = 8.1, 6.3, Hz, 1H), 3.95 (s, 2H), 3.70 (t, *J* = 7.7 Hz, 1H), 2.85-2.68 (m, 3H), 2.62 (dd, *J* = 13.1, 7.6, Hz, 1H), 2.21 (bs, exchanged to D<sub>2</sub>O, 1H), 2.10 (s, 3H), 2.03-1.90 (m, 1H), 1.38 (s, 3H), 1.33 (s, 3H), <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 151.3, 150.9, 149.5, 135.4, 130.1, 128.7, 128.6, 128.3, 115.3, 114.9, 108.5, 76.8, 76.7, 69.8, 67.7, 49.3, 43.6, 42.0, 34.2, 26.6, 25.4, 16.5 ESI-HRMS for C<sub>24</sub>H<sub>34</sub>N<sub>5</sub>O<sub>3</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd. 472.2377, found 472.2365.

**(2*R*/*S*,3*S*/*R*)-4-[(4-Amino-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino]-3-[(methylsulfanyl)methyl]butane-1,2-diol trifluoroacetate salt [(±)-65].**

A solution of (±)-**64** (78 mg, 0.16 mmol) in trifluoroacetic acid-H<sub>2</sub>O (9:1 2.0 mL) was allowed to stand at rt for 10 min then the solvent was evaporated. A portion (70 mg, 0.11 mmol) was dissolved in NH<sub>3</sub>-MeOH solution (7M, 5 mL) and Pd-black (95 mg) was added, followed by hydrazine

hydrate (55% in hydrazine, 0.5 mL). After 15 min, more Pd-black (101 mg) was added then after 45 min the mixture was filtered through Celite and the residue washed with MeOH. The combined filtrates were evaporated and the residue was triturated with CHCl<sub>3</sub> (5 mL). After decanting the solvent (±)-**65** was obtained as a colourless oil after drying (57 mg, 100%). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O): δ 8.40 (s, 1H), 7.92 (s, 1H), 4.48 (d, *J* = 14.4 Hz, 1H), 4.45 (d, *J* = 14.4 Hz, 1H), 3.89 (dt, *J* = 6.1, 4.3 Hz, 1H), 3.63 (dd, *J* = 11.9, 4.6 Hz, 1H), 3.59 (dd, *J* = 11.9, 6.2 Hz, 1H), 3.35 (dd, *J* = 13.0, 7.1 Hz, 1H), 3.31 (dd, *J* = 13.0, 5.4 Hz, 1H), 2.70 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.48 (dd, *J* = 13.8, 9.4 Hz, 1H), 2.26 (m, 1H), 2.05 (s, 3H). <sup>13</sup>C NMR (125.7 MHz, D<sub>2</sub>O): δ 163.6 (q, *J* = 36 Hz), 151.0, 145.4, 138.6, 134.7, 117.0 (q, *J* = 292 Hz), 113.5, 103.5, 72.3, 62.8, 48.1, 41.5, 38.5, 32.1, 15.1. ESI-HRMS for C<sub>13</sub>H<sub>22</sub>N<sub>5</sub>O<sub>2</sub>S<sup>+</sup> (M-CF<sub>3</sub>CO<sub>2</sub>H+H)<sup>+</sup> calcd. 312.1489, found 312.1494.

**(±)-[(2S/R)-2-[(4R/S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(methylsulfanyl)propyl](methyl)amine [(±)-66]** Sodium hydride (60%, 34.6 mg, 0.87 mmol) was added to a solution of (±)-**60** (210 mg, 0.62 mmol) in dry THF (5 mL) then CH<sub>3</sub>I (0.077 mL, 1.24 mmol) added and the mixture was stirred at rt for 30 mins. Chloroform was added to the mixture which was then washed with H<sub>2</sub>O, dried and the solvent evaporated. The residue was dissolved in *i*-PrOH (8 mL) and KOH (1.0 g, 17.8 mmol) added. The solution was heated under reflux for 5 h, silica gel was added and the solvent evaporated. The residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 95:5 then CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 93:7) to give (±)-**66** as a syrup (105 mg, 77%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 4.19 (q, *J* = 6.7 Hz, 1H), 4.06 (dd, *J* = 8.1, 6.3 Hz, 1H), 3.70 (dd, *J* = 8.0, 7.3 Hz, 1H), 2.76 (dd, *J* = 13.1, 4.4 Hz, 1H), 2.70-2.56 (m, 3H), 2.42 (s, 3H), 2.12 (s, 3H), 1.92 (m, 1H), 1.40 (s, 3H), 1.34 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 108.6 (C), 76.7 (CH), 67.6 (CH<sub>2</sub>), 52.2 (CH<sub>2</sub>), 41.8 (CH), 36.8 (CH<sub>3</sub>), 34.1 (CH<sub>2</sub>), 26.6 (CH<sub>3</sub>), 25.3 (CH<sub>3</sub>), 16.4 (CH<sub>3</sub>).

**(±)-7-([(3S/R)-3-[(4R/S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-(methylsulfanyl)butyl]amino)methyl]-5H-pyrrolo[3,2-*d*]pyrimidin-4-amine [(±)-68]**. 9-Deazaadenine (73 mg, 0.55 mmol), (±)-**66** (80 mg, 0.37 mmol) and aq. formaldehyde (37%, 0.44 mL, 0.55 mmol) were stirred for 1 h in a mixture of 1,4-dioxane (2 mL) and H<sub>2</sub>O (0.5 mL) at 90 °C (bath temp). The reaction mixture was cooled to rt and NH<sub>3</sub> in MeOH solution (7M, 2.5 mL) was added and the resulting reaction left to stir for a further 1 h. The solvent was evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 9:1 then CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 8:2) to afford (±)-**67** as a syrup (110 mg) which by <sup>1</sup>H NMR was contaminated with paraformaldehyde. A portion of crude (±)-**67** (65 mg) was dissolved in



MeOH (5 mL) and aq. HCl (37%, 0.5 mL) added. The solvent was evaporated and the residue dissolved in more aq. HCl (37%, 0.5 mL) then the solvent evaporated again. The residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 85:15 then CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 8:2) to give (±)-**68** as a syrup (35 mg, 61%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.16 (s, 1H), 7.49 (s, 1H), 3.84 (d, *J* = 13.5 Hz, 1H), 3.72-3.63 (m, 2H), 3.54 (d, *J* = 4.8 Hz, 2H), 2.78-2.66 (m, 2H), 2.53 (dd, *J* = 12.8, 3.8 Hz, 1H), 2.39 (dd, *J* = 13.1, 8.1 Hz, 1H), 2.28 (s, 3H), 2.14 (m, 1H), 2.08 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): 152.1 (C), 151.0 (CH), 147.2 (C), 130.2 (CH), 115.2 (C), 112.5 (C), 75.0 (CH), 65.3 (CH<sub>2</sub>), 59.3 (CH<sub>2</sub>), 51.6 (CH<sub>2</sub>), 42.3 (CH<sub>3</sub>), 40.6 (CH), 35.6 (CH<sub>2</sub>), 16.2 (CH<sub>3</sub>). ESI-HRMS for C<sub>14</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup> calcd, 326.1646, found 312.1650.

(±)-Benzyl *N*-{[(4*R*/*S*,5*R*/*S*)-2,2-dimethyl-4-[(methylsulfonyl)methyl]-1,3-dioxan-5-yl]methyl}carbamate [(±)-**69**]. Alcohol (±)-**58** (0.884 g, 2.86 mmol) was converted into syrupy (±)-**69** (0.839 g, 86%) in the same way as that described for the preparation of (±)-**60**. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 7.36-7.28 (m, 5H), 5.09 (s, 2H), 5.02 (bt, *J* = 6.2 Hz, 1H), 3.85-3.76 (m, 2H), 3.62 (t, *J* = 10.6 Hz, 1H), 3.24-3.06 (m, 2H), 2.77 (dd, *J* = 13.8, 2.4 Hz, 1H), 2.63 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.15 (s, 3H), 1.99 (bm, 1H), 1.40 (s, 3H), 1.37 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 156.5 (C), 136.3 (C), 128.5 (CH), 128.1 (CH), 128.0 (CH), 98.7 (C), 71.9 (CH), 66.8 (CH<sub>2</sub>), 61.9 (CH<sub>2</sub>), 40.0 (CH<sub>2</sub>), 39.4 (CH), 37.9 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 19.8 (CH<sub>3</sub>), 16.8 (CH<sub>3</sub>).

(±)-{[(4*R*/*S*,5*R*/*S*)-2,2-Dimethyl-4-[(methylsulfonyl)methyl]-1,3-dioxan-5-yl]methyl}(methyl)amine [(±)-**70**]. Lithium aluminium hydride in THF (2.0M 1.2 mL, 2.42 mmol) was added to a solution of (±)-**69** (82 mg, 0.242 mmol) in dry THF (1.5 mL) and stirred at rt for 18 h. Water (0.12 mL), aq. NaOH (15%, 0.12 mL) and H<sub>2</sub>O (0.36 mL) were added successively. The resulting mixture was filtered, the solids were washed with warm EtOAc and the filtrate was evaporated. The residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 95:5 then CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 95:5) to give (±)-**70** as a syrup (30 mg, 57%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.91 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.84 (ddd, *J* = 9.9, 7.0, 3.0 Hz, 1H), 3.69-3.62 (m, 2H), 2.82 (dd, *J* = 13.8, 2.9 Hz, 1H), 2.64 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.55 (dd, *J* = 12.0, 4.7 Hz, 1H), 2.44-2.38 (m, 4H), 2.18 (s, 3H), 1.95 (m, 1H), 1.44 (s, 3H), 1.39 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 98.4 (C), 73.2 (CH), 62.9 (CH<sub>2</sub>), 51.1 (CH<sub>2</sub>), 38.8 (CH), 38.1 (CH<sub>2</sub>), 36.9 (CH<sub>3</sub>), 28.9 (CH<sub>3</sub>), 19.6 (CH<sub>3</sub>), 16.9 (CH<sub>3</sub>).

(±)-7-[[{(4*R*/*S*,5*R*/*S*)-2,2-Dimethyl-4-[(methylsulfonyl)methyl]-1,3-dioxan-5-yl]methyl}(methyl)amino)methyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine [(±)-**71**]. A

mixture of ( $\pm$ )-**70** (30 mg, 0.14 mmol), 9-deazaadenine (27.5 mg, 0.21 mmol) and aq. formaldehyde (37%, 15.9  $\mu$ L, 0.21 mmol) in 1,4-dioxane (2 mL) and H<sub>2</sub>O (0.5 mL) was heated at 85 °C for 15 min, cooled to rt and NH<sub>3</sub> in MeOH solution (7M, 2.5 mL) added. The solution was allowed to stand at rt for 3 days then the solvent evaporated. Chromatography of the residue (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 9:1) gave ( $\pm$ )-**71** as a syrup (34 mg, 68%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  8.16 (s, 1H), 7.45 (s, 1H), 3.86 (dd,  $J$  = 11.9, 5.2, Hz, 1H) 3.73-3.65 (m, 3H), 3.52 (dd,  $J$  = 11.7, 10.6, Hz, 1H), 2.79 (dd,  $J$  = 14.0, 2.5, Hz, 1H), 2.53 (dd,  $J$  = 14.0, 7.1, Hz, 1H), 2.32 (dd,  $J$  = 12.7, 5.5, Hz, 1H), 2.24 (s, 3H), 2.16 (dd,  $J$  = 12.4, 8.1, Hz, 1H), 2.06 (s, 3H), 2.01 (m, 1H), 1.36 (s, 3H), 1.31 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD):  $\delta$  152.1 (C), 150.9 (CH), 147.2 (C), 130.1 (CH), 115.2 (C), 112.9 (C), 99.6 (C), 75.4 (CH), 64.2 (CH<sub>2</sub>), 56.8 (CH<sub>2</sub>), 51.9 (CH<sub>2</sub>), 43.1 (CH<sub>3</sub>), 38.8 (CH<sub>2</sub>), 37.8 (CH), 29.4 (CH<sub>3</sub>), 19.9 (CH<sub>3</sub>) 16.9 (CH<sub>3</sub>).

**( $\pm$ )-(2*R*/*S*,3*R*/*S*)-2-[[{(4-Amino-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methyl}(methylamino)methyl]-4-(methylsulfanyl)butane-1,3-diol [( $\pm$ )-**72**].** Aqueous hydrochloric acid (37%, 0.5 mL) was added to a solution of ( $\pm$ )-**71** (34 mg, 0.093 mmol) in MeOH (2 mL) and the solution was allowed to stand at rt for 2 h, then the solvent was evaporated. Chromatography (CH<sub>2</sub>Cl<sub>2</sub>-7M NH<sub>3</sub> in MeOH, 85:15 then 75:25) gave ( $\pm$ )-**72** as a syrup (24 mg, 79%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  8.16 (s, 1H), 7.49 (s, 1H), 3.83-3.75 (m, 3H), 3.67 (dd,  $J$  = 10.9, 5.0 Hz, 1H), 3.56 (dd,  $J$  = 10.8, 7.1 Hz, 1H), 2.64 (d,  $J$  = 7.2 Hz, 2H), 2.57 (dd,  $J$  = 13.6, 4.6 Hz, 1H), 2.41 (dd,  $J$  = 13.5, 8.3 Hz, 1H), 2.34 (s, 3H); 2.15 (m, 1H), 2.05 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD):  $\delta$  152.1 (C), 151.1 (CH), 147.2 (C), 130.2 (CH), 115.3 (C), 112.3 (C), 72.4 (CH), 63.4 (CH<sub>2</sub>), 58.4 (CH<sub>2</sub>), 51.9 (CH<sub>2</sub>), 42.9 (CH), 42.7 (CH<sub>3</sub>), 39.7 (CH<sub>2</sub>), 16.0 (CH<sub>3</sub>).

**( $\pm$ )-*tert*-Butyl *N*-[[{(4*S*/*R*,5*R*/*S*)-2,2-dimethyl-5-[(methylsulfanyl)methyl]-1,3-dioxolan-4-yl)methyl}carbamate [( $\pm$ )-**74**].** Di-*tert*-butyl dicarbonate (1.096 g, 5.02 mmol) and amine ( $\pm$ )-**73**<sup>48</sup> (0.736 g, 4.57 mmol) were stirred together in MeOH (10 mL) for 1 h. The solvent was evaporated and the residue chromatographed on silica gel (gradient 0  $\rightarrow$  100% EtOAc in hexanes) to give ( $\pm$ )-**74** as a colourless gum (1.01 g, 85%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  3.91-3.85 (m, 1H), 3.82-3.77 (m, 1H), 3.68 (dd,  $J$  = 11.8, 3.9 Hz, 1H), 3.61 (dd,  $J$  = 11.8, 5.2 Hz, 1H), 3.31 (dd,  $J$  = 14.2, 4.6 Hz, 1H + residual CD<sub>3</sub>OD), 3.24 (dd,  $J$  = 14.2, 5.3 Hz, 1H), 1.44 (s, 9H), 1.37 (s, 6H). <sup>13</sup>C NMR (75.5 Mz, CD<sub>3</sub>OD):  $\delta$  158.5 (C), 110.2 (C), 80.8 (CH), 80.3 (C), 78.3 (CH), 63.2 (CH<sub>2</sub>), 43.3 (CH<sub>2</sub>), 28.7 (CH<sub>3</sub>), 27.42 (CH<sub>3</sub>), 27.35 (CH<sub>3</sub>). ESI-HRMS for C<sub>12</sub>H<sub>23</sub>NNaO<sub>5</sub><sup>+</sup> (M+Na)<sup>+</sup>, calcd. 284.1463, found 284.1467.

**(±)-tert-Butyl N-[[[(4S/R,5R/S)-2,2-dimethyl-5-[(methylsulfanyl)methyl]-1,3-dioxolan-4-yl]methyl]carbamate [(±)-75].** Methanesulfonyl chloride (0.35 mL, 4.48 mmol) was added dropwise to a stirred solution of (±)-**74** (0.975 g, 3.73 mmol) and triethylamine (1.05 mL, 7.46 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) cooled in an ice-bath. The mixture was warmed to rt and stirred for 30 min then diluted with CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and washed with aq. NaHCO<sub>3</sub> (sat., 3 x 25 mL), dried and the solvent evaporated to give the intermediate mesylate as a yellow gum. The gum was dissolved in DMF (8 mL), sodium thiomethoxide (0.523 g, 7.46 mmol) added and the mixture stirred at rt for 2 h. Diethyl ether (100 mL) was added and the mixture washed with H<sub>2</sub>O (4 x 10 mL), brine, dried and the solvent evaporated. Chromatography of the residue (gradient 0 → 30% EtOAc in hexanes) gave (±)-**75** as a colourless oil (0.653 g, 60%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 4.90 (bs, exchanged D<sub>2</sub>O, 1H), 3.96-3.85 (m, 1H), 3.47 (ddd, *J* = 14.1, 5.9, 2.5 Hz, 1H), 3.31 (ddd, *J* = 14.2, 6.0, 5.5 Hz, 1H), 2.72 (d, *J* = 5.4 Hz, 2H), 2.18 (s, 3H), 1.45 (s, 9H), 1.41 (s, 6H). <sup>13</sup>C (75.5 MHz, CDCl<sub>3</sub>): δ 155.9 (C), 109.1 (C), 79.6 (CH), 79.5 (C), 77.2 (CH), 41.9 (CH<sub>2</sub>), 36.5 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>), 27.13 (CH<sub>3</sub>), 27.11 (CH<sub>3</sub>), 16.4 (CH<sub>3</sub>). ESI-HRMS for C<sub>13</sub>H<sub>25</sub>NNaO<sub>4</sub>S<sup>+</sup> (M+Na)<sup>+</sup>, calcd. 314.1397, found 314.1396.

**(±)-[[[(4S/R,5R/S)-2,2-Dimethyl-5-[(methylsulfanyl)methyl]-1,3-dioxolan-4-yl]methyl](methyl)amine [(±)-76].** Lithium aluminum hydride (2M in THF, 3.67 mL, 7.34 mmol) was added dropwise to a stirred solution of (±)-**75** (0.60 g, 2.45 mmol) in THF (5 mL) then heated under reflux for 16 h. The mixture was cooled in an ice-bath and H<sub>2</sub>O (0.3 mL), aq. NaOH (15%, 0.3 mL) and H<sub>2</sub>O (0.9 mL) added successively then filtered through Celite and the solids washed with hot EtOAc (3 x 50 mL). The combined filtrates were evaporated and the oily residue chromatographed on silica gel (gradient of 0 → 10% 3M NH<sub>3</sub>/MeOH in CHCl<sub>3</sub>) to give (±)-**76** as a colourless oil (0.37 g, 74%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 4.01-3.91 (m, 2H), 2.86 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.78-2.66 (m, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.53 (s, exchanged D<sub>2</sub>O, 1H), 1.412, 1.410 (2s, 6H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 109.0 (C), 80.0 (CH), 78.2 (CH), 54.0 (CH<sub>2</sub>), 36.9 (CH<sub>2</sub>), 36.7 (CH<sub>3</sub>), 27.3 (CH<sub>3</sub>), 27.1 (CH<sub>3</sub>), 16.6 (CH<sub>3</sub>). ESI-HRMS for C<sub>9</sub>H<sub>20</sub>NO<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup>, calcd. 206.1210, found 206.1211.

**(±)-7-([[(2S/R,3R/S)-2,3-Dihydroxy-4-(methylsulfanyl)butyl](methyl)amino]methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine [(±)-78].** A mixture of (±)-**76** (0.08 g, 0.39 mmol), 9-deazaadenine (0.078 g, 0.58 mmol) and aq. formaldehyde solution (37%, 0.036 mL, 0.43 mmol) were heated in a 4:1 mixture of 1,4-dioxane:H<sub>2</sub>O (2.5 mL) at 90 °C (bath temp.) for 1 h. Silica gel was added then the volatiles evaporated. The residue was chromatographed on

silica gel (CHCl<sub>3</sub>-7M NH<sub>3</sub> in MeOH, 93:7) to give (±)-**77** as a colourless solid. This was dissolved in a mixture of MeOH (3 mL) and aq. HCl (37%, 0.75 mL) and left to stand at rt for 30 min. The solvent was evaporated to a colourless solid which was dissolved in MeOH (5 mL) and neutralized with Amberlyst A21 resin. After filtering off the solids the filtrate was evaporated and the residue chromatographed on silica gel (CHCl<sub>3</sub>-7M NH<sub>3</sub> in MeOH, 8:2) to give (±)-**78** as a colourless solid (0.076 g, 63%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.16 (s, 1H), 7.47 (s, 1H), 3.94-3.83 (m, 2H), 3.78 (d, *J* = 13.5 Hz, 1H), 3.64 (m, 1H), 2.73-2.48 (m, 4H), 2.32 (s, 3H), 2.08 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 152.1 (C), 150.9 (CH), 147.2 (C), 130.2 (CH), 115.3 (C), 112.5 (C), 73.3 (CH), 70.5 (CH), 60.4 (CH<sub>2</sub>), 51.8 (CH<sub>2</sub>), 43.0 (CH<sub>3</sub>), 38.2 (CH<sub>2</sub>), 15.9 (CH<sub>3</sub>). ESI-HRMS for C<sub>13</sub>H<sub>21</sub>N<sub>5</sub>NaO<sub>2</sub>S<sup>+</sup> (M+Na)<sup>+</sup>, calcd. 334.1309, found 334.1308.

**(2S)-2-[(1S)-1-{4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl}-2-hydroxyethylamino]-3-(methylsulfanyl)propan-1-ol (79)**. Sodium periodate (0.070 g, 0.326 mmol) was added to a stirred solution of (2S,3S,4R,5S)-2-{4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl}-5-[(methylsulfanyl)methyl]pyrrolidine-3,4-diol dihydrochloride<sup>34</sup> (**3**, 0.1g, 0.272 mmol), in H<sub>2</sub>O (3 mL). After 1 h, sodium borohydride (0.051 g, 1.358 mmol) was added in small portions and the solution, which momentarily darkened then became almost colourless, was stirred for 15 mins. Silica gel was added, the solvent evaporated and the residue chromatographed (CH<sub>2</sub>Cl<sub>2</sub>-MeOH-28% aq. NH<sub>4</sub>OH, 50:10:1). The fractions containing product were evaporated to a gum (70 mg) which was dissolved in MeOH and eluted through Amberlyst A26 (OH<sup>-</sup>) resin with MeOH. The solvent was evaporated to a yellow gum, dissolved in water and freeze dried to give **79** as a cream coloured solid (38 mg, 47%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.14 (s, 1H), 7.54 (s, 1H), 4.26 (dd, *J* = 6.5, 4.6 Hz, 1H), 3.85 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.77 (dd, *J* = 10.9, 6.6 Hz, 1H), 3.67 (dd, *J* = 11.1, 5.1 Hz, 1H), 3.61 (dd, *J* = 11.1, 4.2 Hz, 1H), 2.77-2.66 (m, 1H), 2.64 (dd, *J* = 13.4, 5.6 Hz, 1H), 2.41 (dd, *J* = 13.3, 7.6 Hz, 1H), 1.72 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CD<sub>3</sub>OD): δ 152.1 (C), 150.7 (CH), 146.3 (C), 128.8 (CH), 116.5 (C), 115.5 (C), 66.8 (CH<sub>2</sub>), 63.5 (CH<sub>2</sub>), 55.9 (CH), 54.5 (CH), 37.6 (CH<sub>2</sub>), 15.1 (CH<sub>3</sub>). ESI-HRMS for C<sub>12</sub>H<sub>19</sub>N<sub>5</sub>NaO<sub>2</sub>S<sup>+</sup> (M+Na)<sup>+</sup> calcd. 320.1152, found 320.1149.

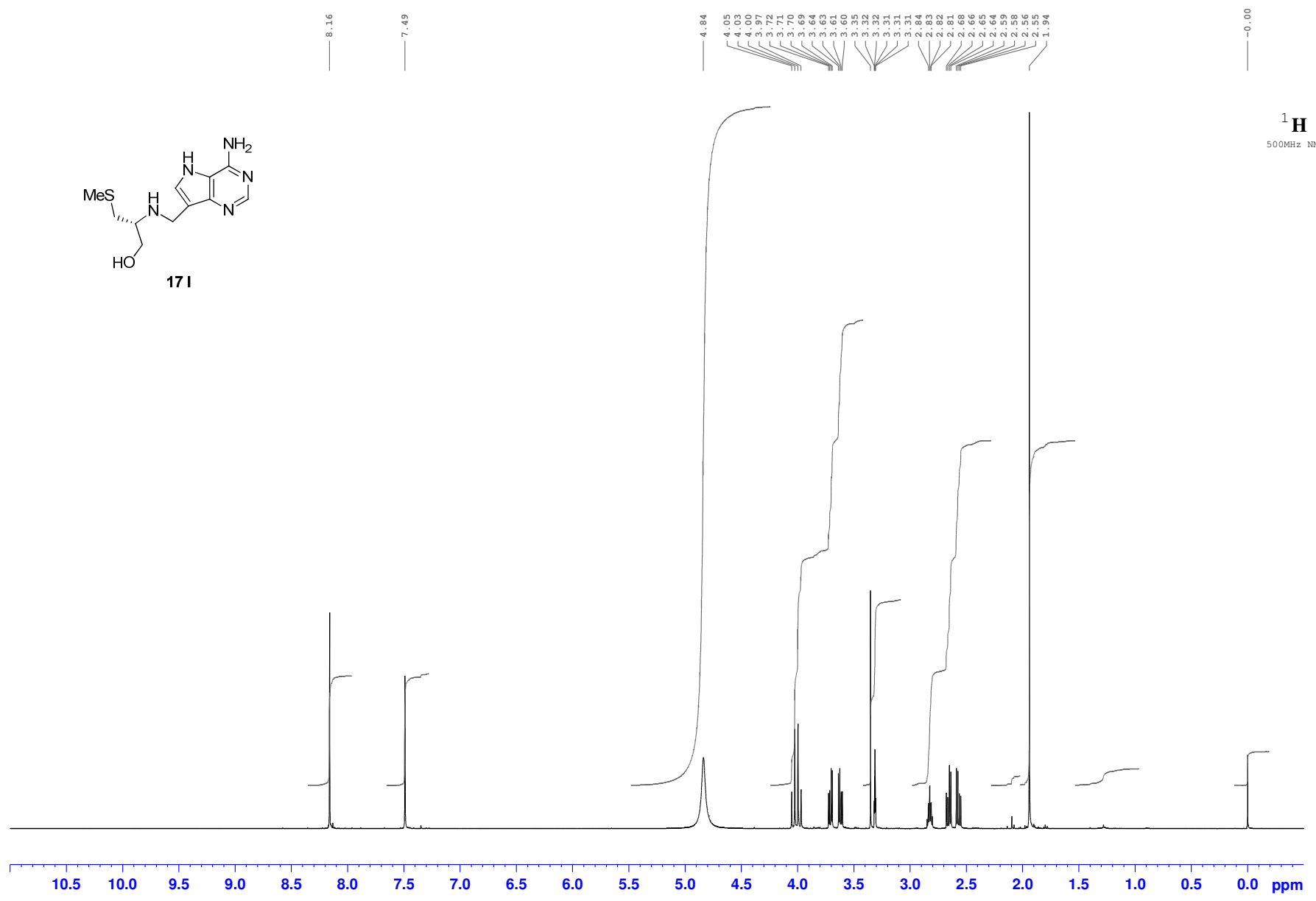
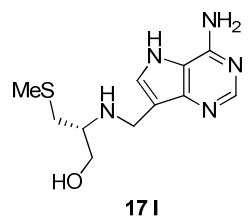
**Protein Expression and Inhibition Assays.** Human MTAP, *E. coli* MTAN and *N. meningitidis* MC58 MTAN used in the biological evaluation of the compounds were expressed and purified as previously described.<sup>40,70</sup> Enzyme inhibition assays were carried out using a xanthine oxidase-coupling enzyme that converts the adenine product of the

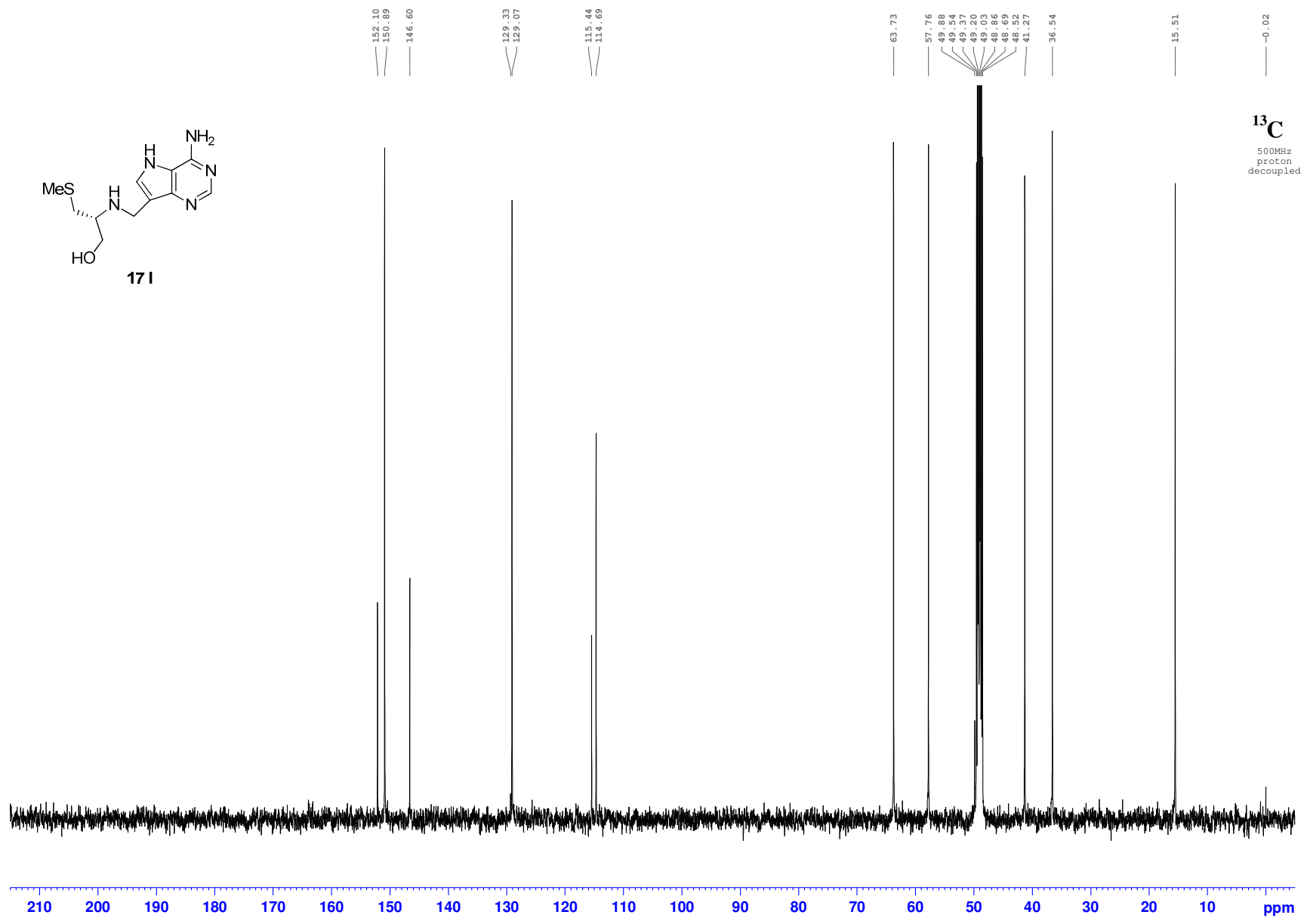
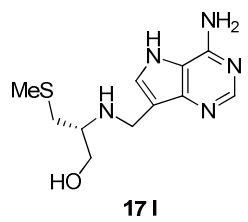
MTAP and MTAN reactions to 2,8-dihydroxyadenine; monitored at 293 nM ( $E_{293} = 15.2 \text{ mM}^{-1}\text{cm}^{-1}$ ). The  $K_m$  values used were 5.28  $\mu\text{M}$  (human MTAP), 0.43  $\mu\text{M}$  (*E. coli* MTAN) and 1.4  $\mu\text{M}$  (*N. meningitidis* MTAP). Details of the assay and experimental determination of  $K_i$  and  $K_i^*$  have been reported.<sup>70</sup>

## References

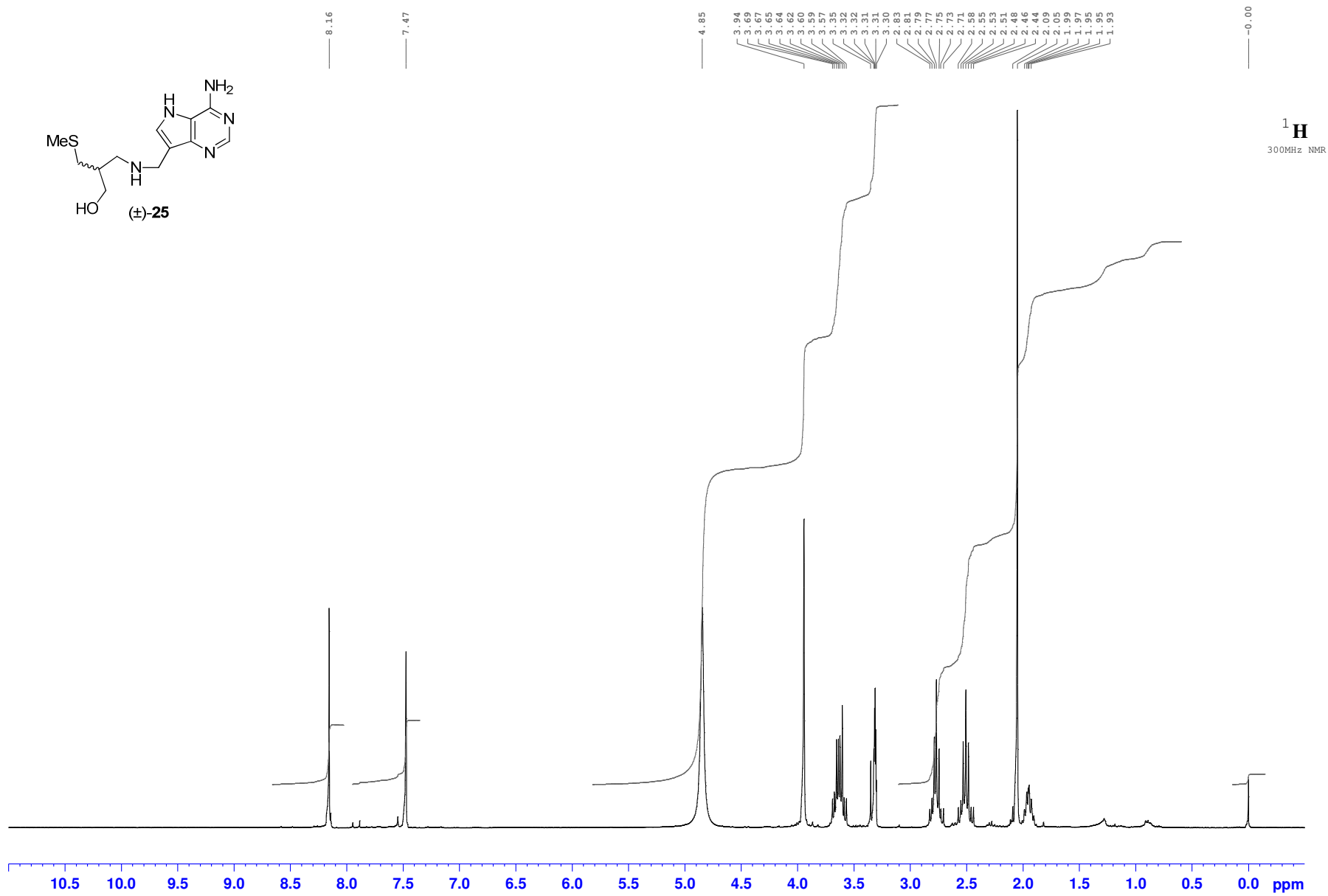
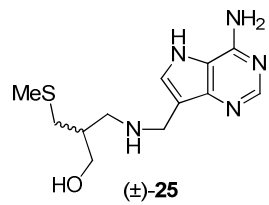
- 34 Evans, G. B.; Furneaux, R. H.; Schramm, V. L.; Singh, V.; Tyler, P. C. *J. Med. Chem.* **2004**, *47*, 3275.
- 40 Gutierrez, J. A.; Luo, M.; Singh, V.; Li, L.; Brown, R. L.; Norris, G. E.; Evans, G. B.; Furneaux, R. H.; Tyler, P. C.; Painter, G. F.; Lenz, D. H.; Schramm, V. L. *ACS Chemical Biology* **2007**, *2*, 725.
- 50 Evans, G. B.; Furneaux, R. H.; Hutchison, T. L.; Kezar, H. S.; Morris, P. E.; Schramm, V. L.; Tyler, P. C. *J. Org. Chem.* **2001**, *66*, 5723.
- 51 Gainsford, G. J.; Mason, J. M.; Gulab, S. A. *Acta Crystallogr. Sect. E* **2010**, *66*, o138.
- 52 Murkin, A. S.; Clinch, K.; Mason, J. M.; Tyler, P. C.; Schramm, V. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5900.
- 53 Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
- 54 Dondoni, A.; Perrone, D. *Org. Synth.* **2004**, *Coll. Vol. 10*, 320; *Org. Synth.* **2000**, *77*, 64.
- 55 Sato, S.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *Tetrahedron*, **2004**, *60*, 7899. 2-Picoline-borane complex is now the reagent of choice for conducting reductive amination/alkylation reactions in our laboratories.
- 56 Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165.
- 57 Harnden, M. R.; Wyatt, P. G.; Boyd, M. R.; Sutton, D. *J. Med. Chem.* **1990**, *33*, 187.
- 58 McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.
- 61 Inaba, T.; Yamada, Y.; Abe, H.; Sagawa, S.; Cho, H. *J. Org. Chem.* **2000**, *65*, 1623.
- 62 Gainsford, G. J.; Clinch, K. *Acta Crystallogr. Sect. E* **2012**, *68*, o2082.
- 63 Calderón, F.; Doyagüez, E. G.; Fernández-Mayoralas, A. *J. Org. Chem.* **2006**, *71*, 6258.
- 64 Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2004**, *69*, 7765.
- 65 Kokotos, G.; Verger, R.; Chiou, A. *Chem. Eur. J.* **2000**, *6*, 4211.
- 66 Elliott, W. J.; Fried, J. *J. Org. Chem.* **1976**, *41*, 2469.

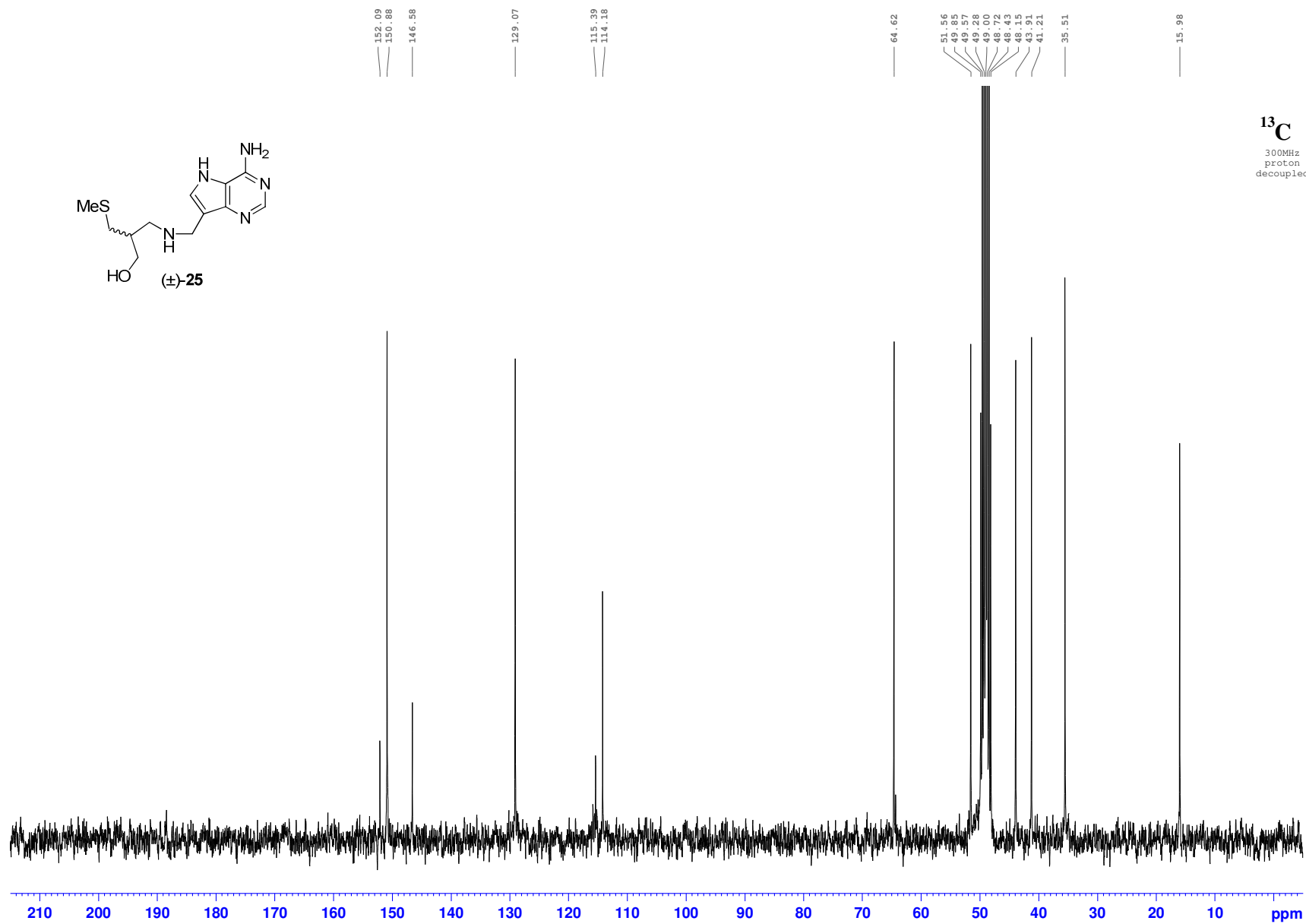
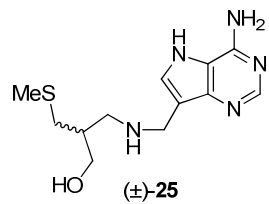
- 67 Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595.
- 69 Wang, G.; Hollingsworth, R. I. *J. Org. Chem.* **1999**, *64*, 1036.
- 70 Longshaw, A. I.; Adanitsch, F.; Gutierrez, J. A.; Evans, G. B.; Tyler, P. C.; Schramm, V. L. *J. Med. Chem.* **2010**, *53*, 6730.

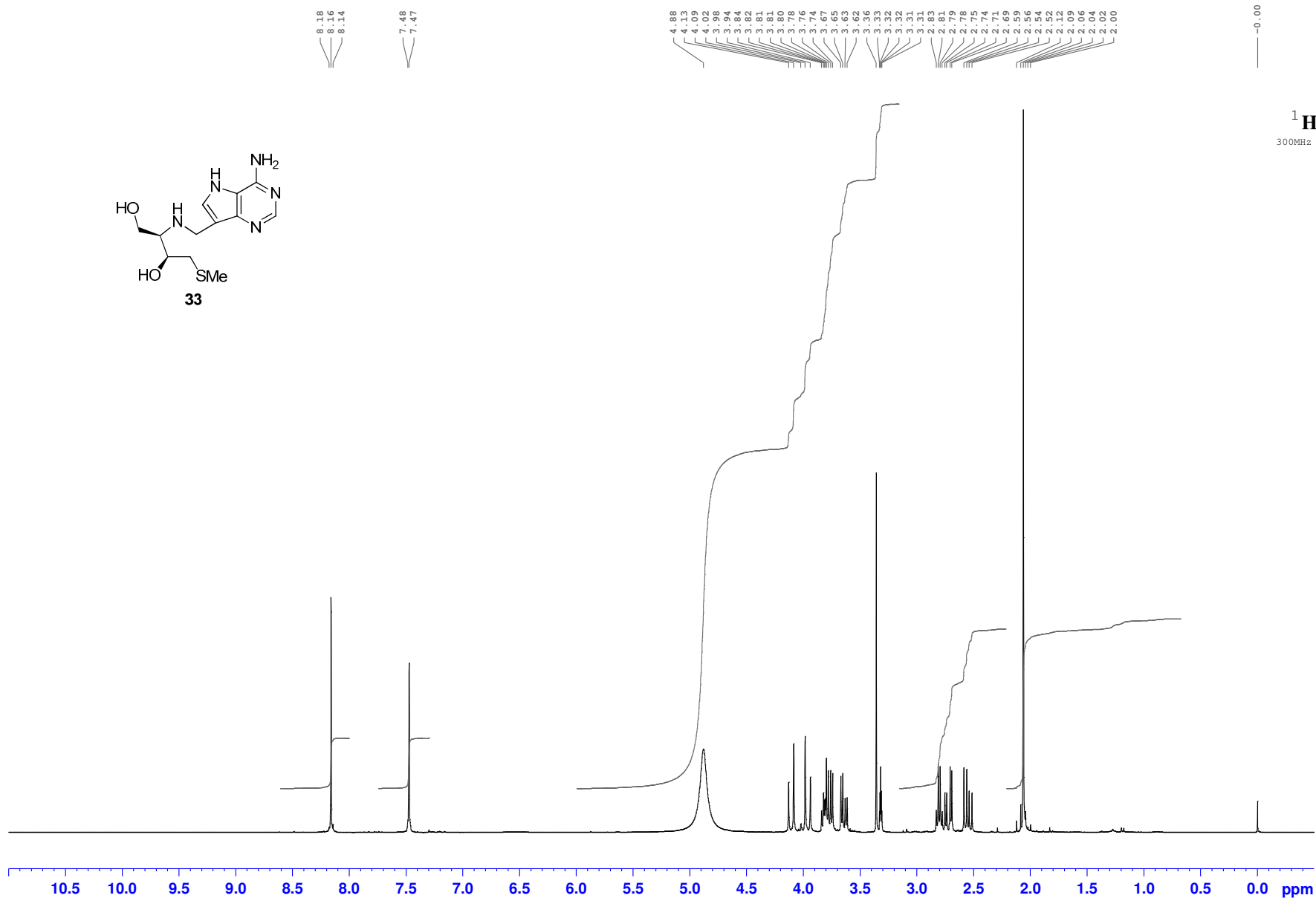
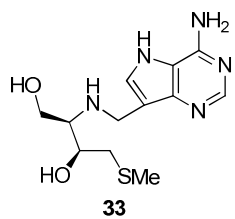




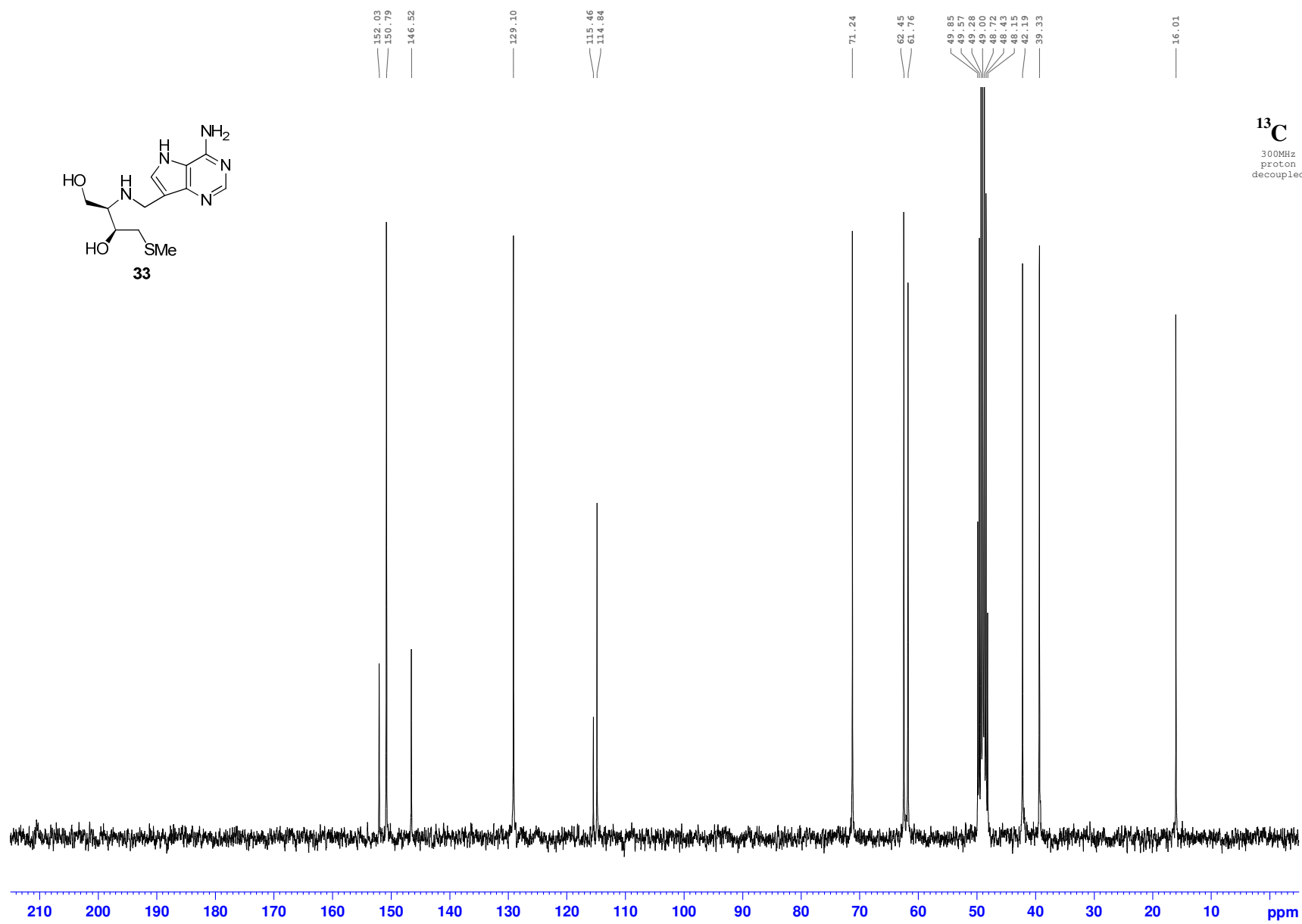
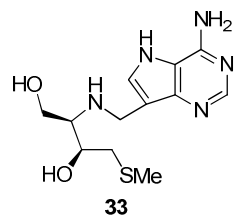


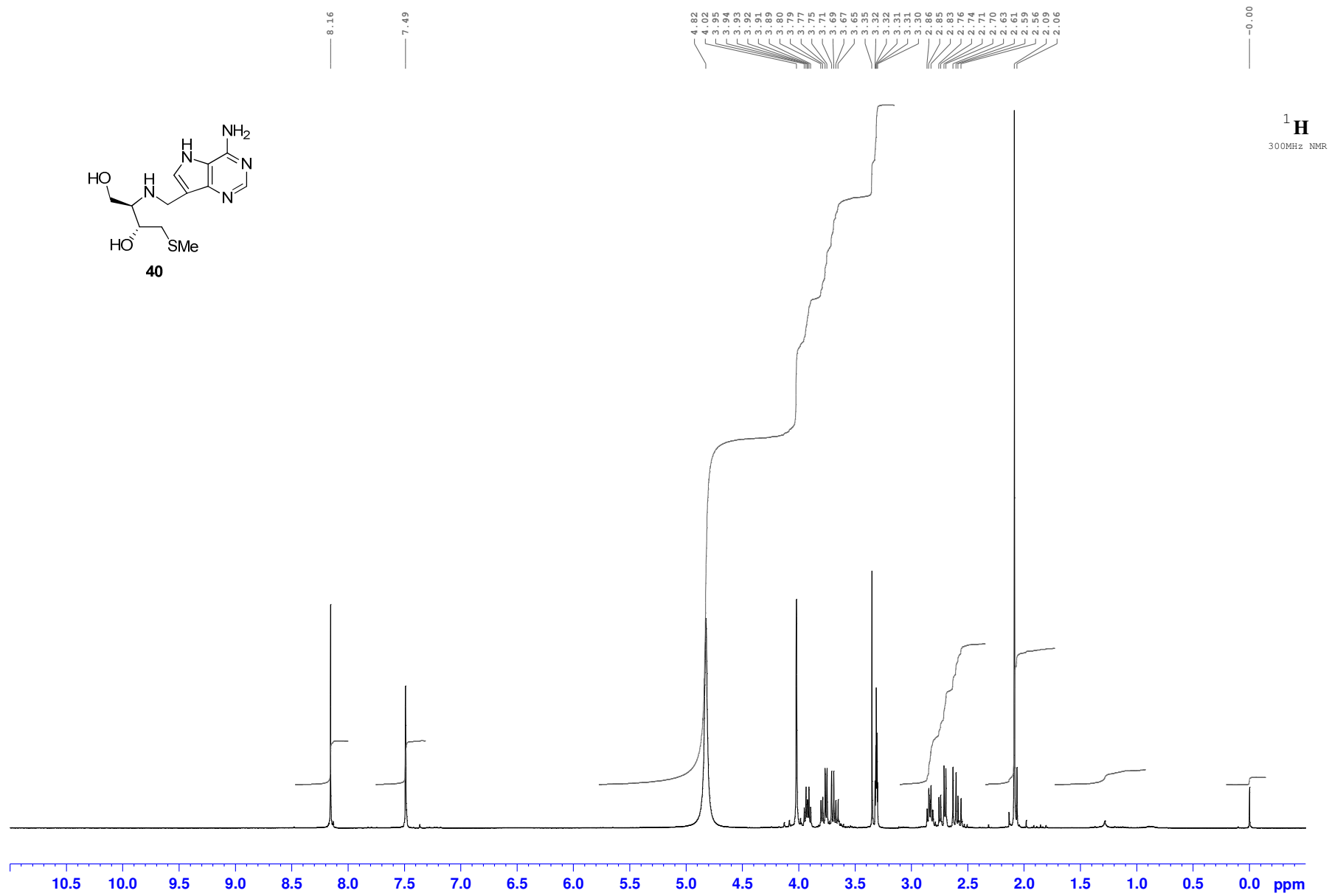
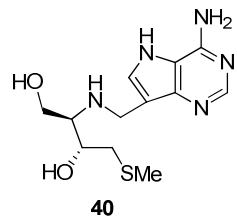


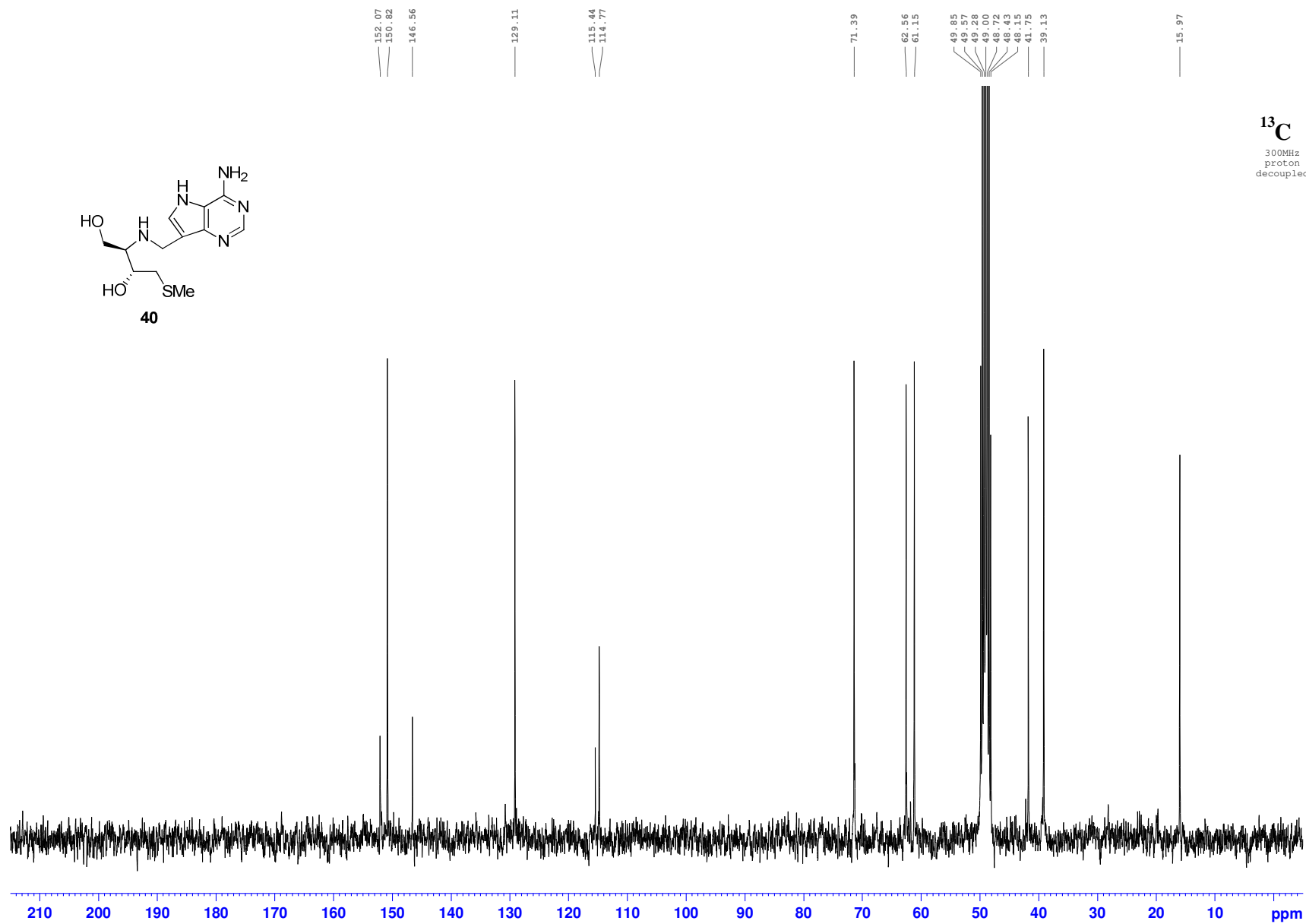
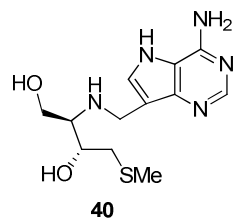


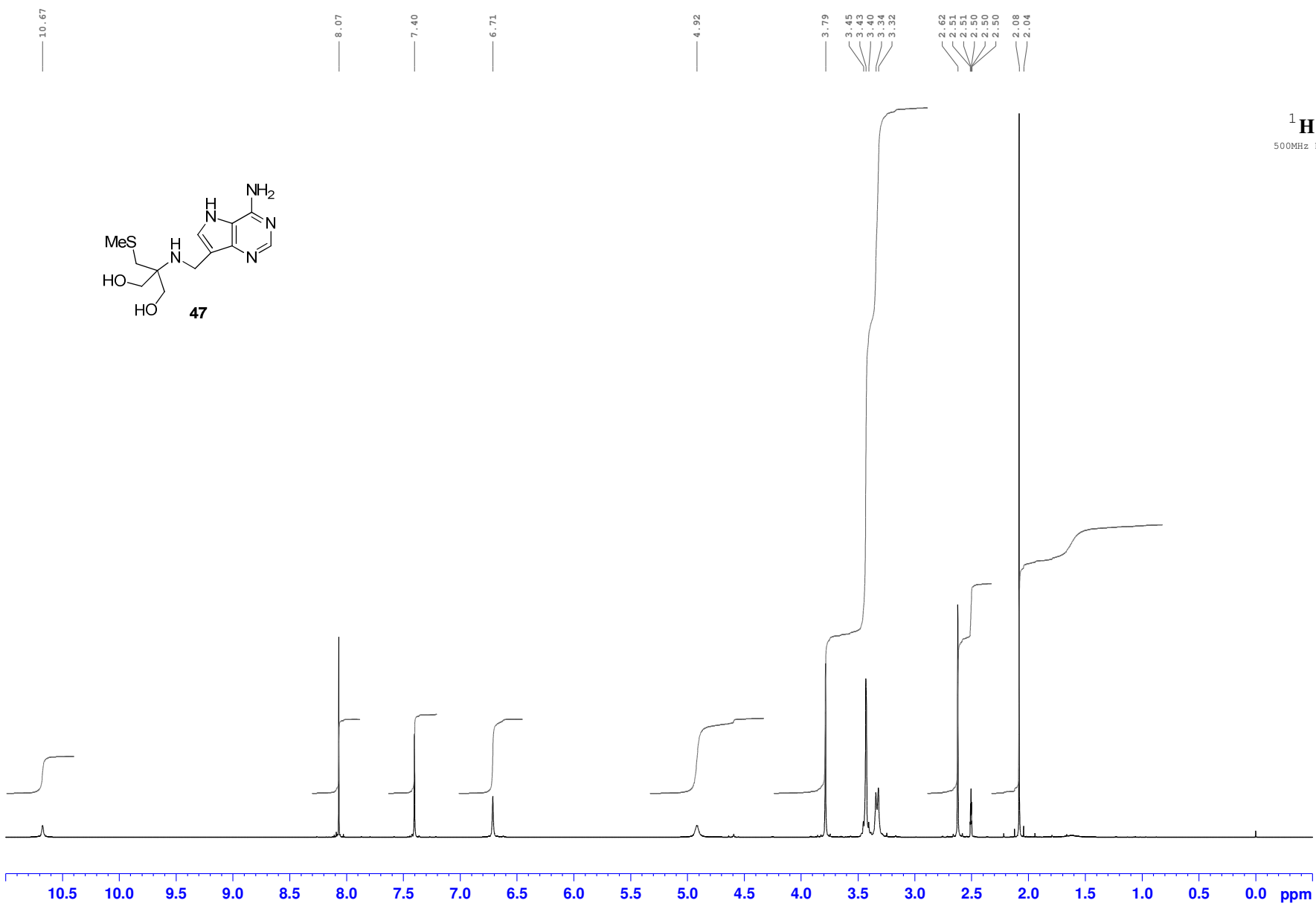


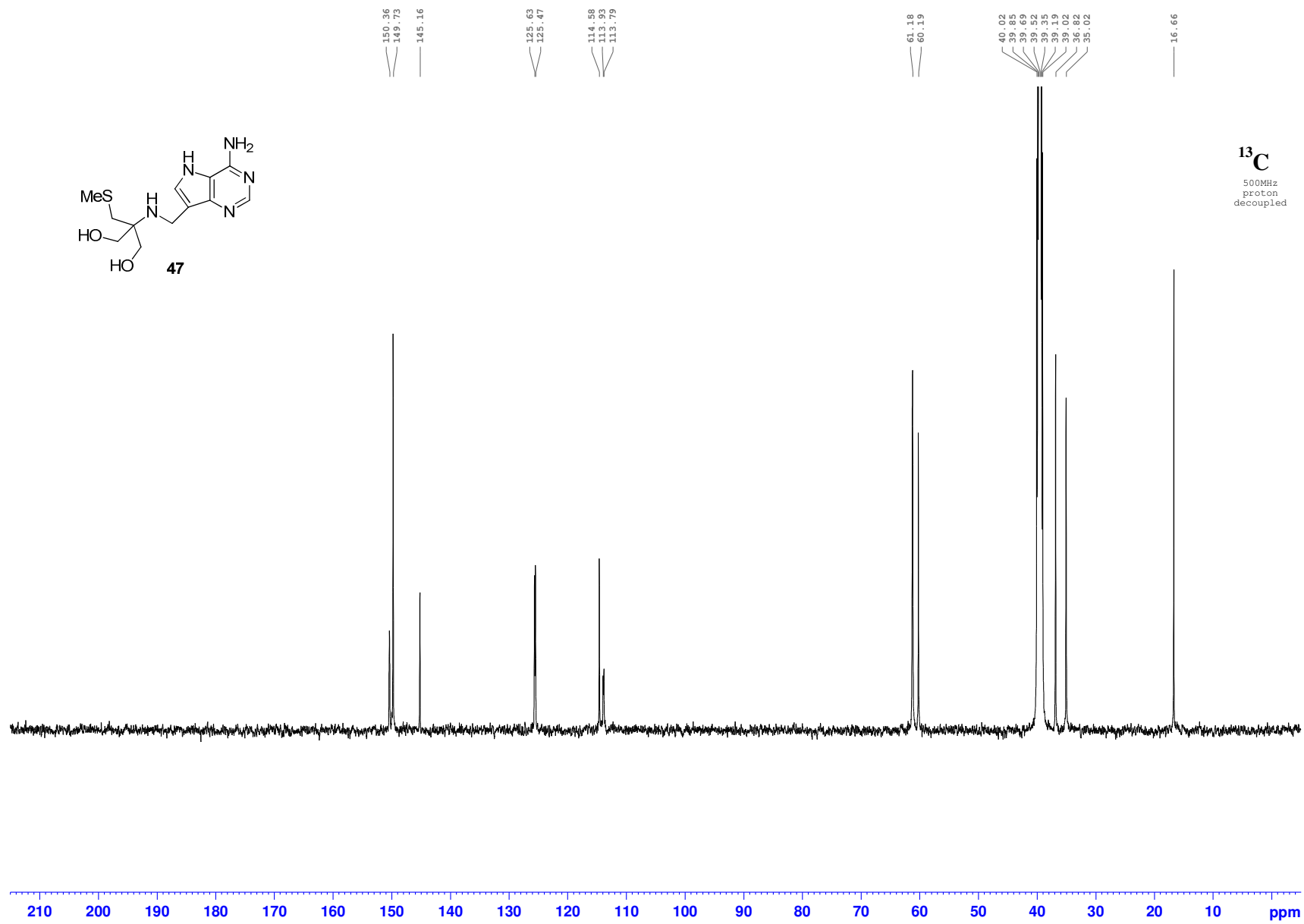
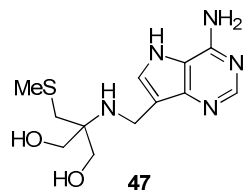
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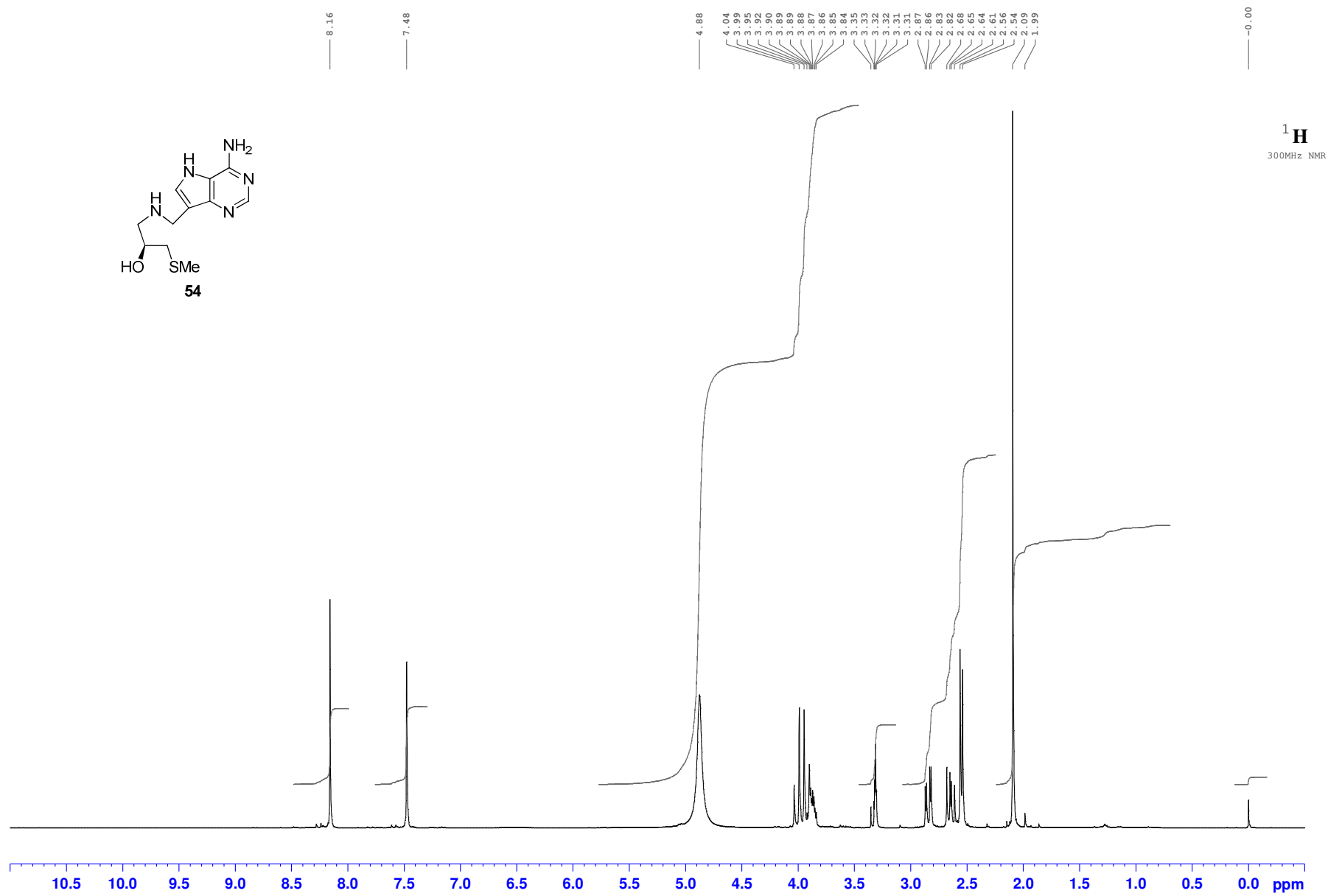
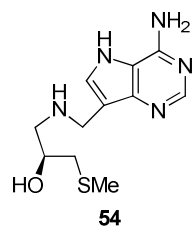


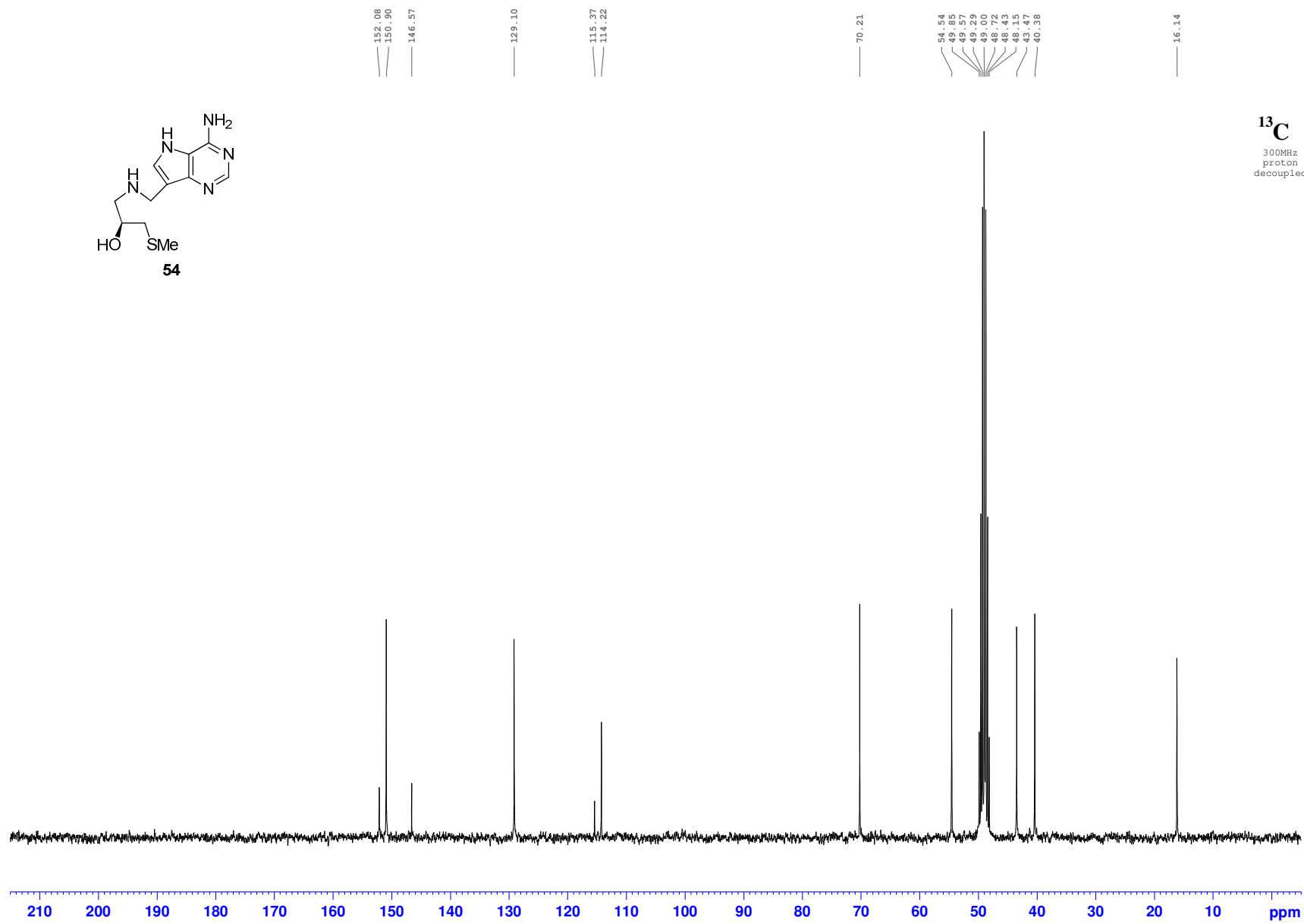
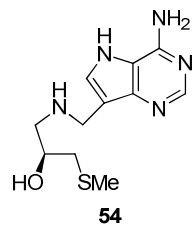


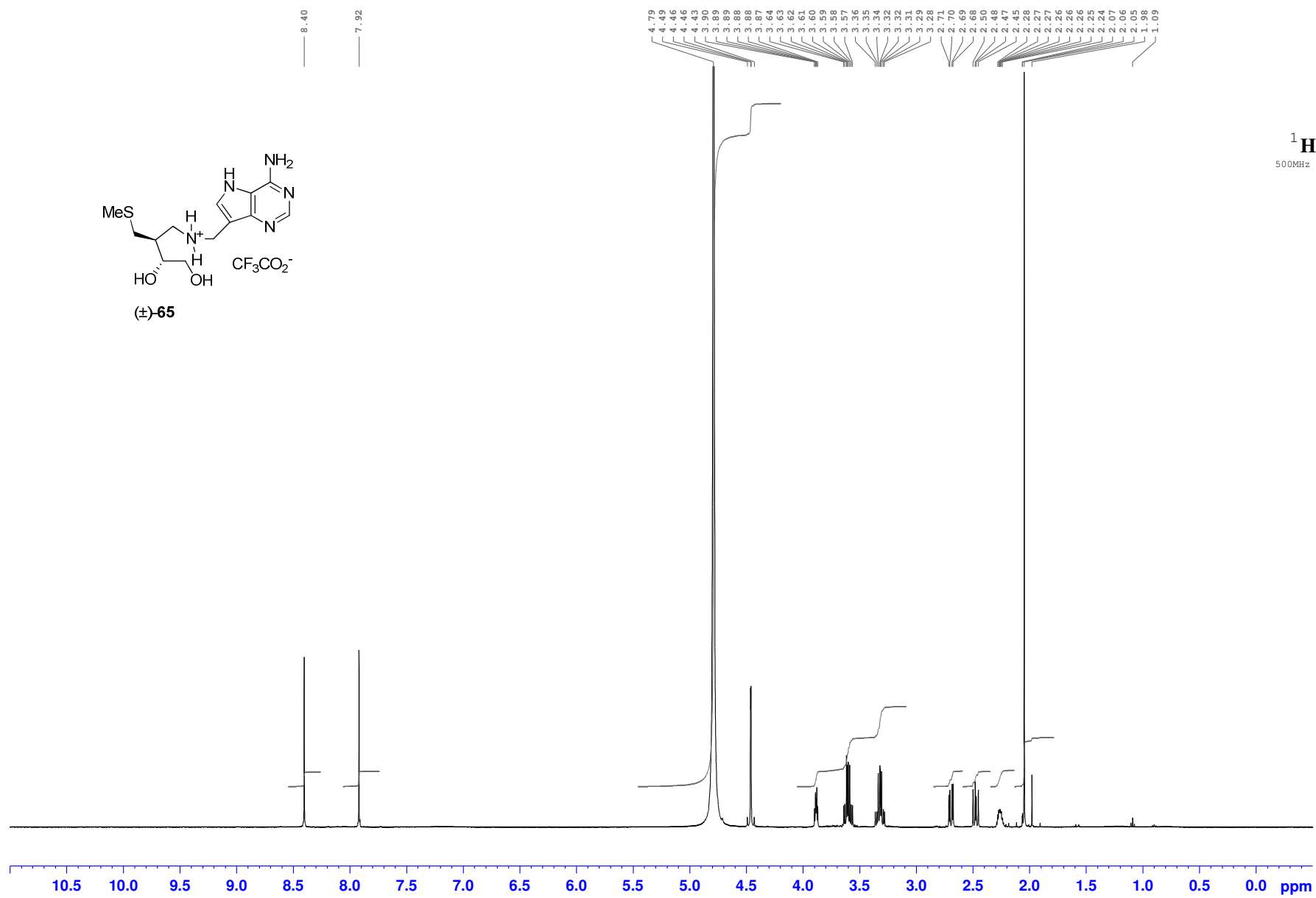
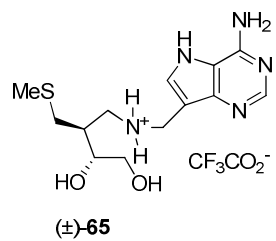




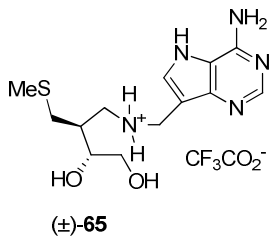
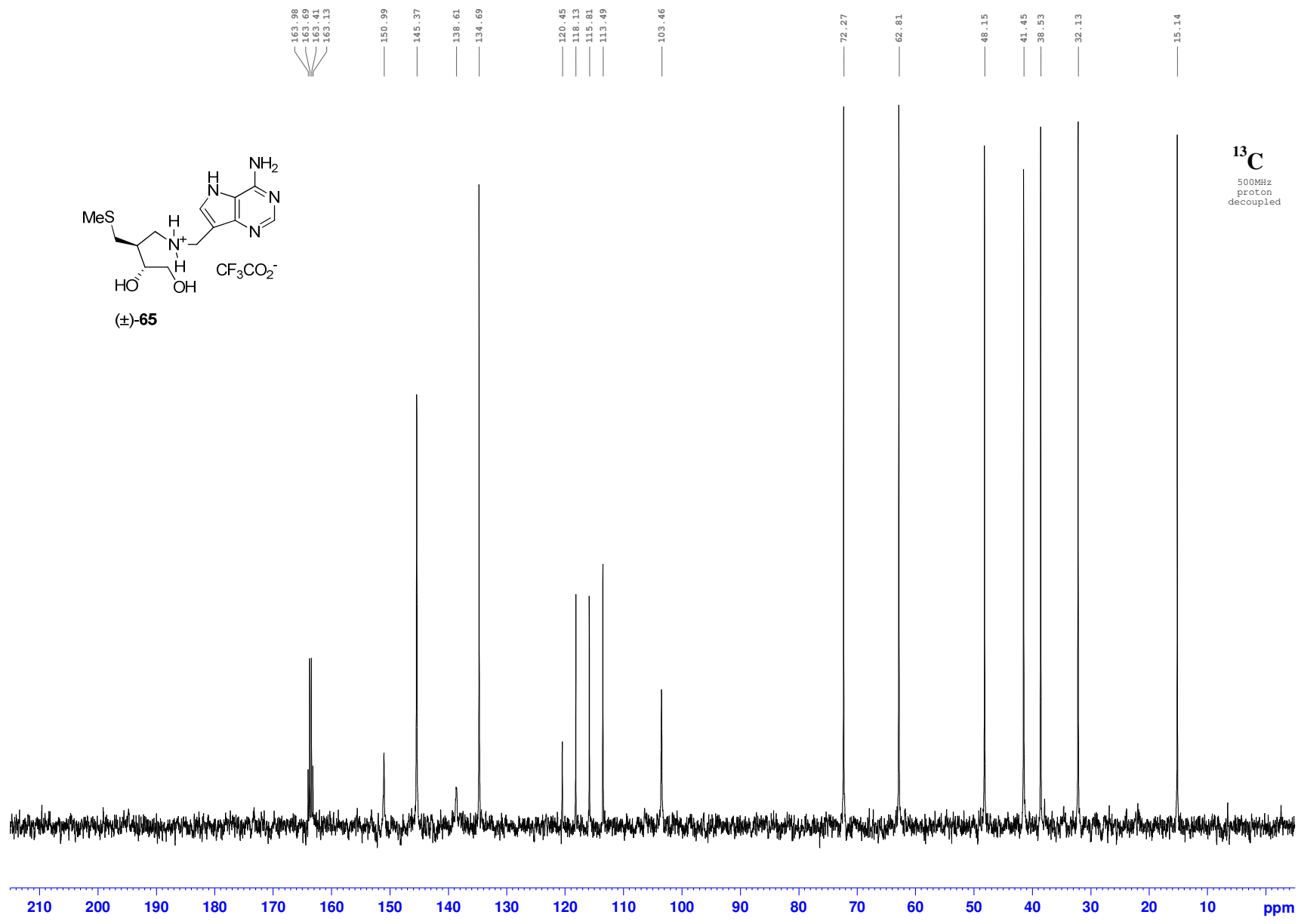


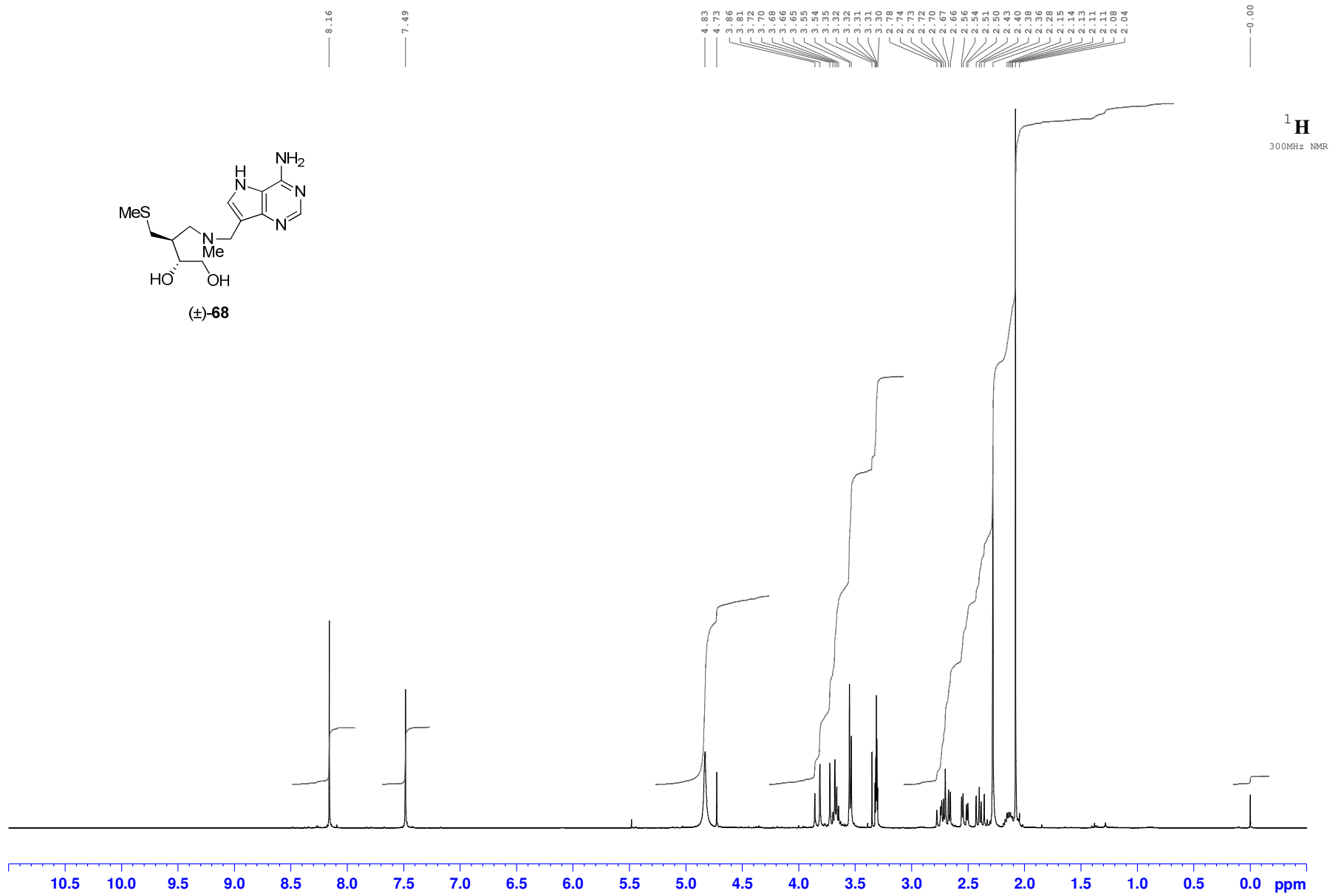
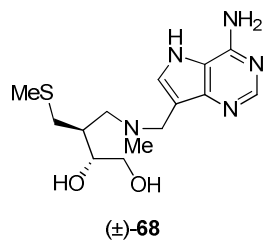


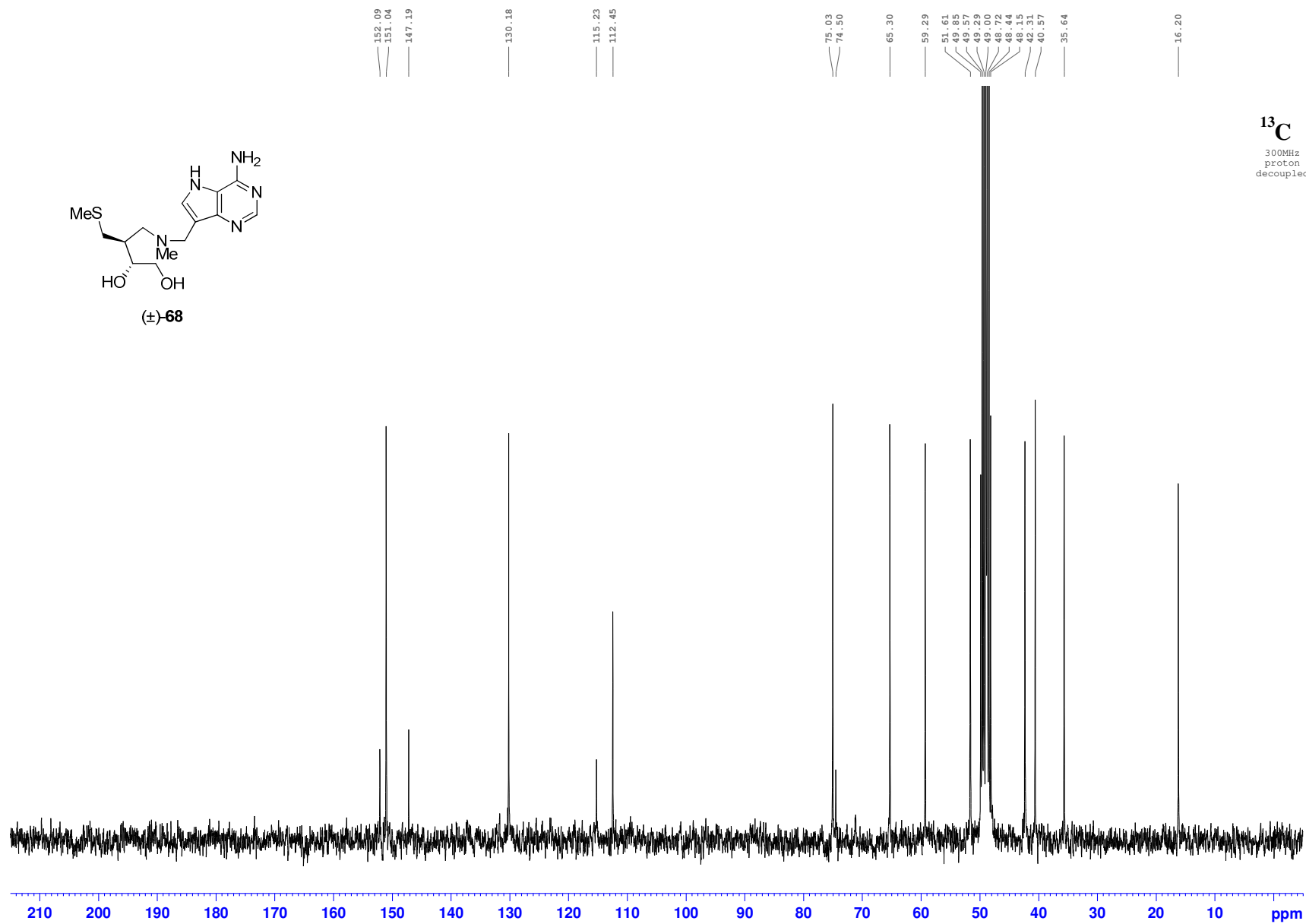
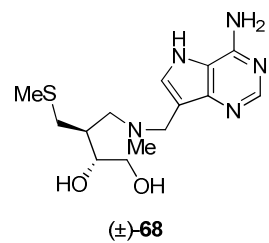




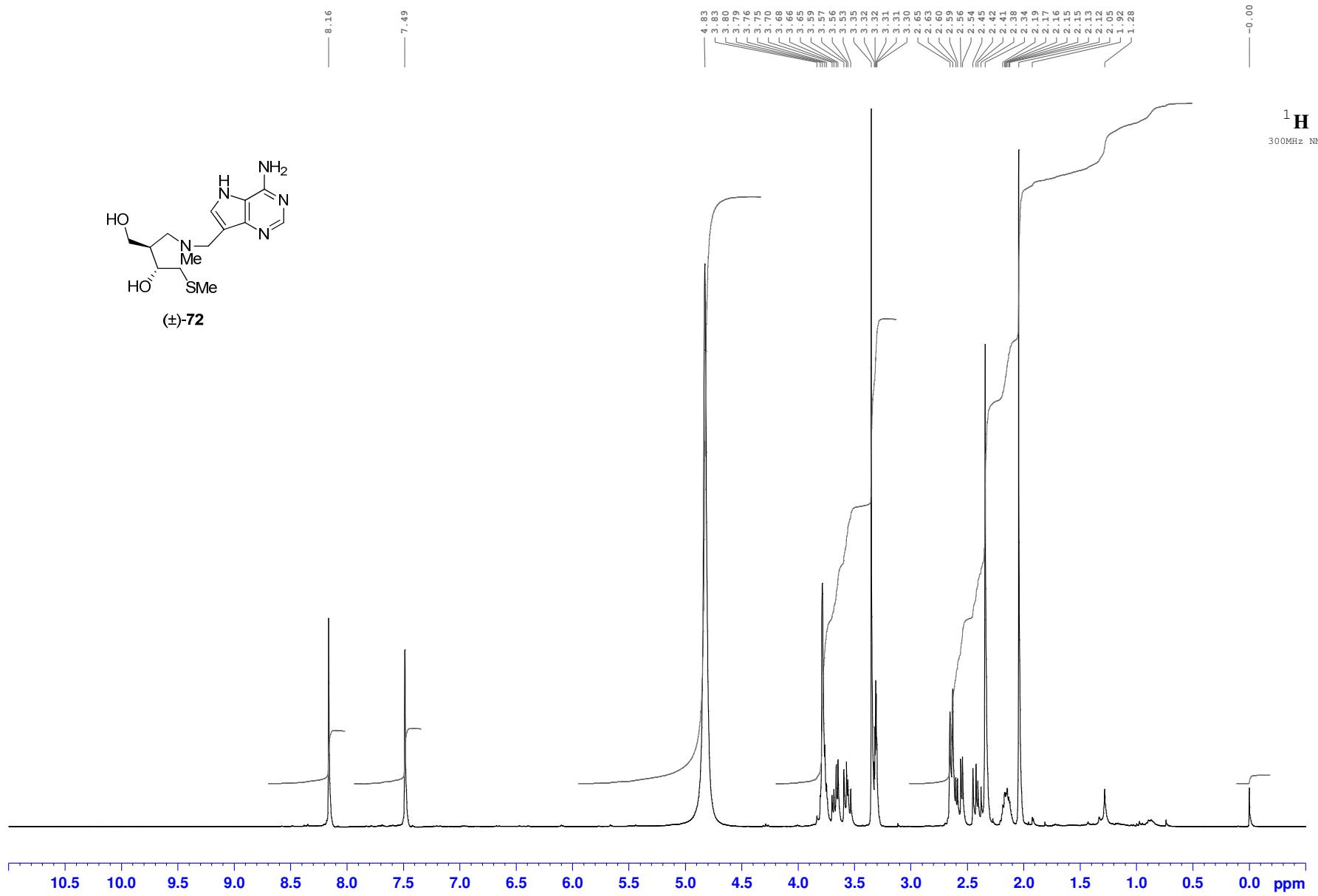
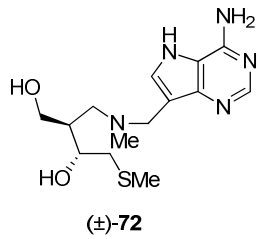
<sup>1</sup>H  
500MHz NMR



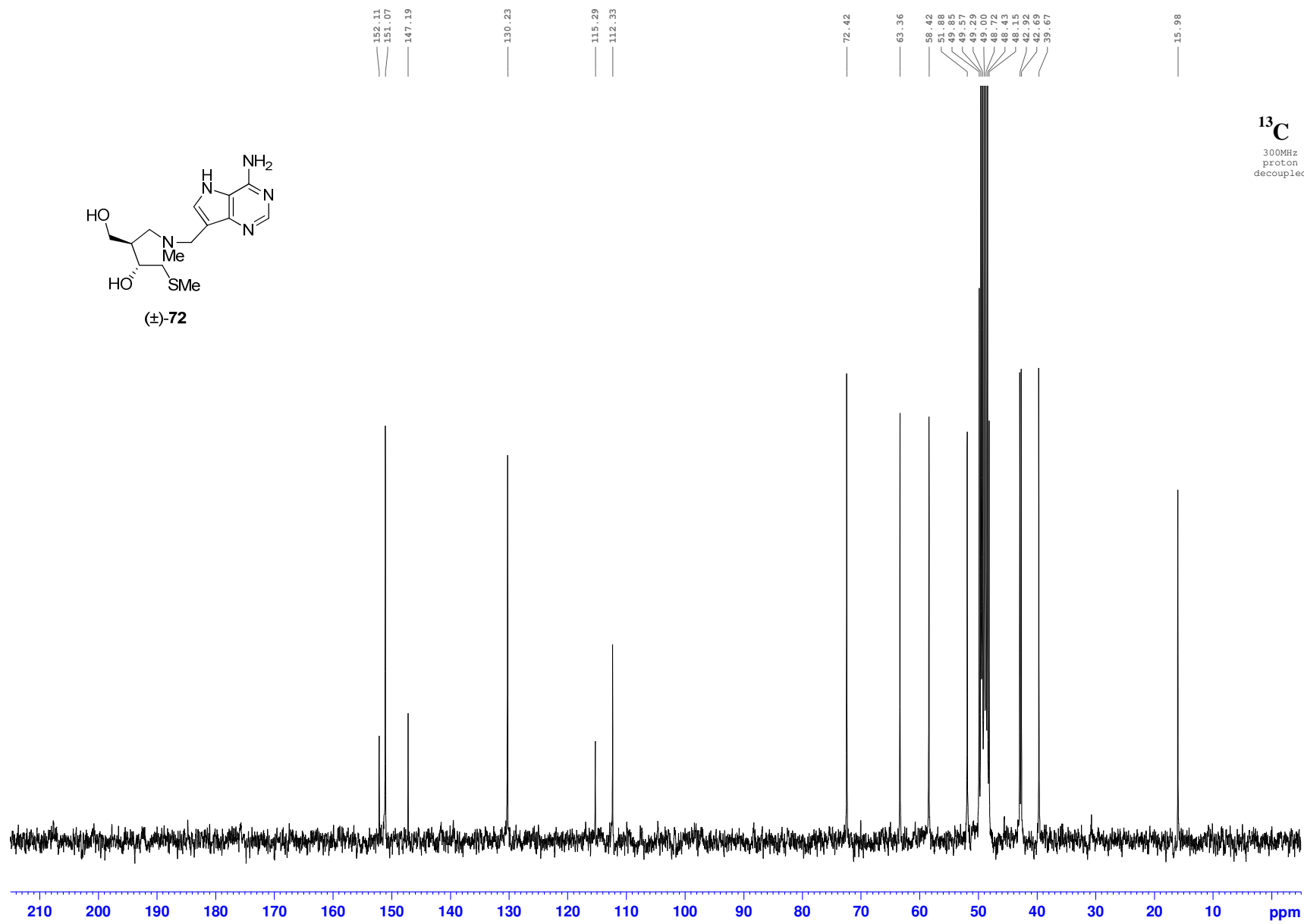
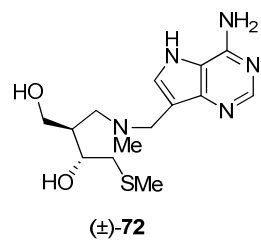




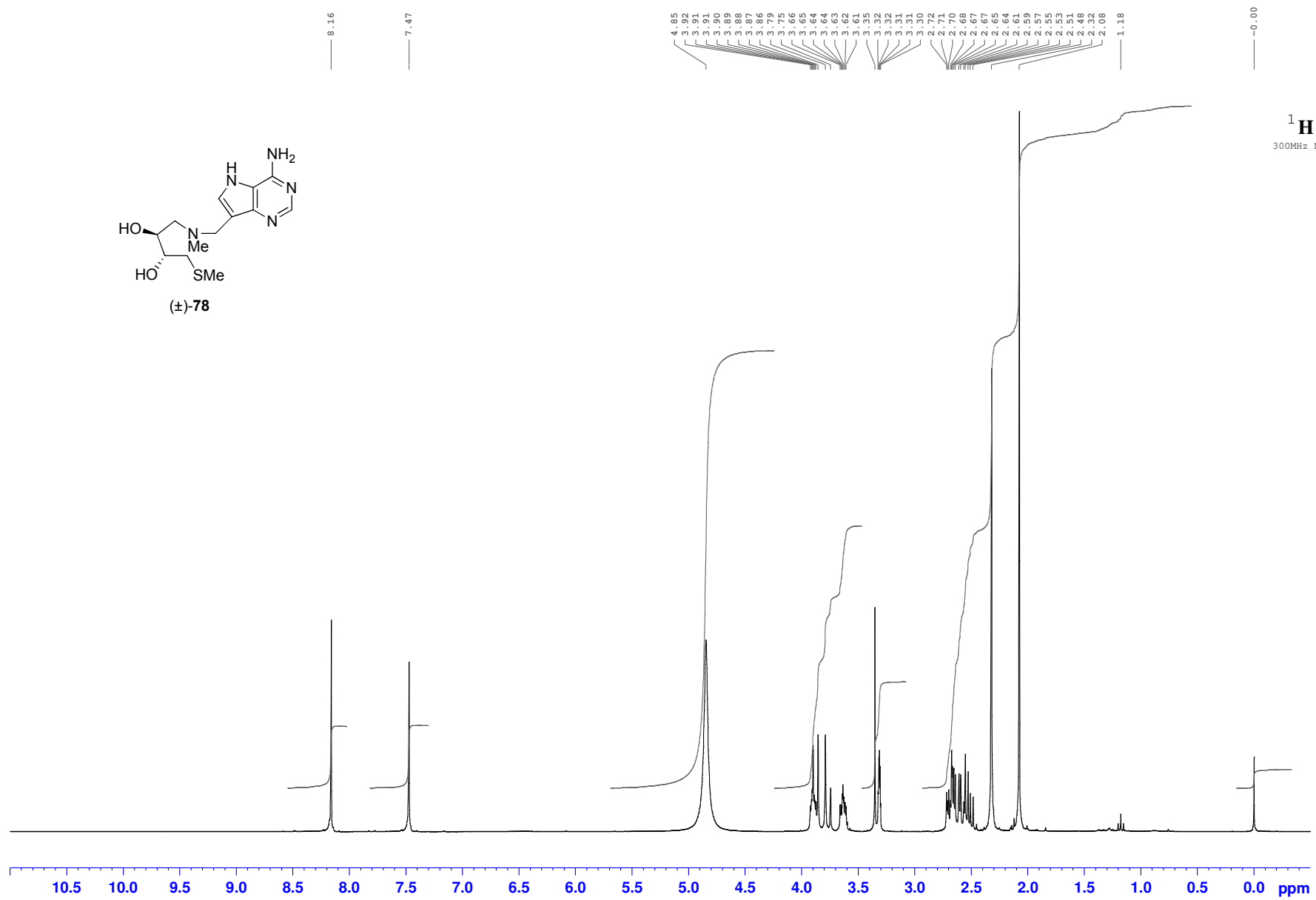
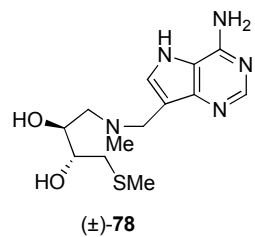
<sup>13</sup>C  
300MHz  
proton  
decoupled

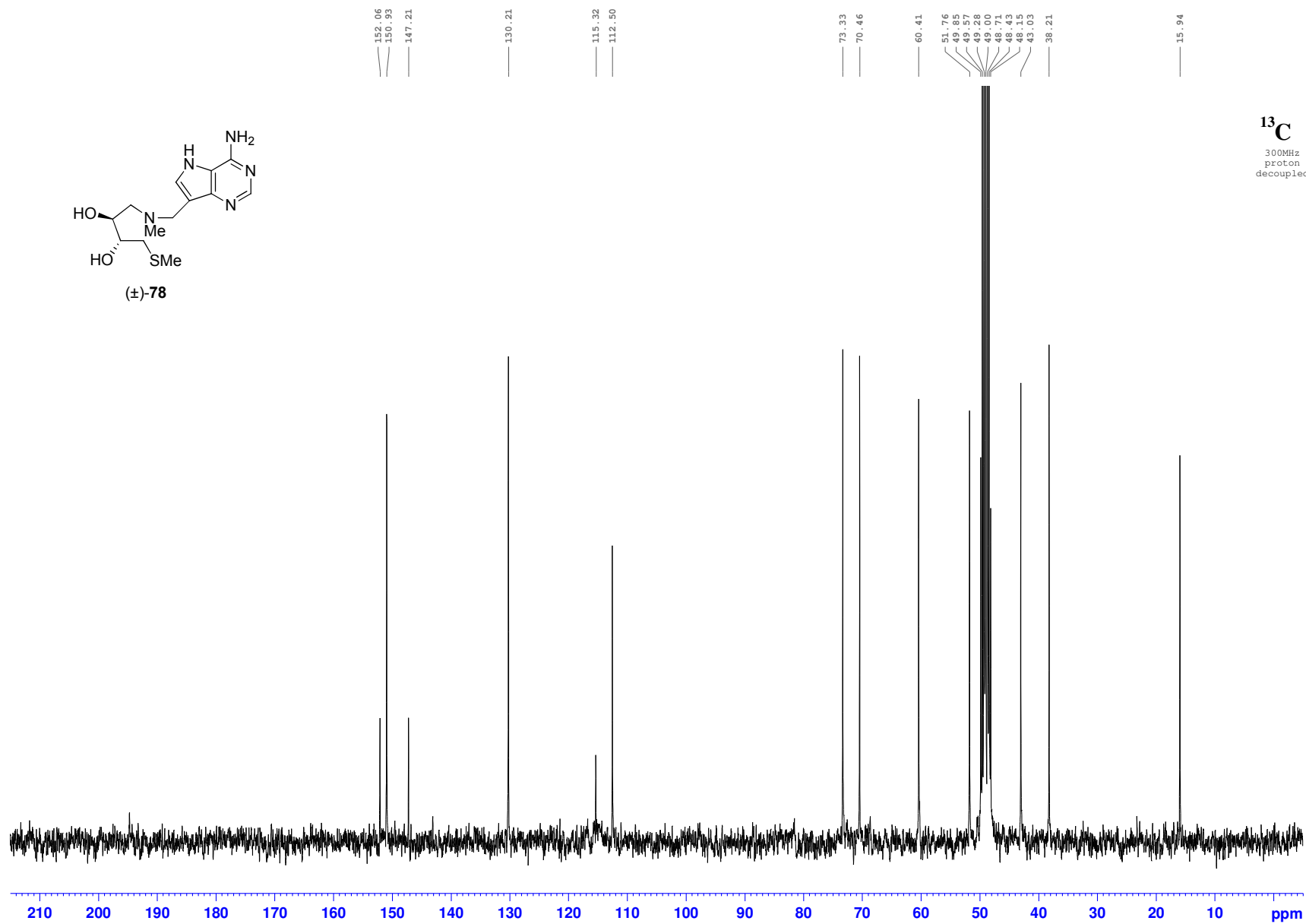
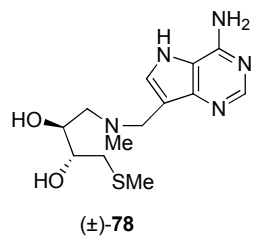


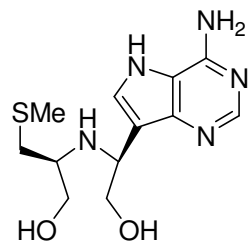
<sup>1</sup>H  
300MHz NMR



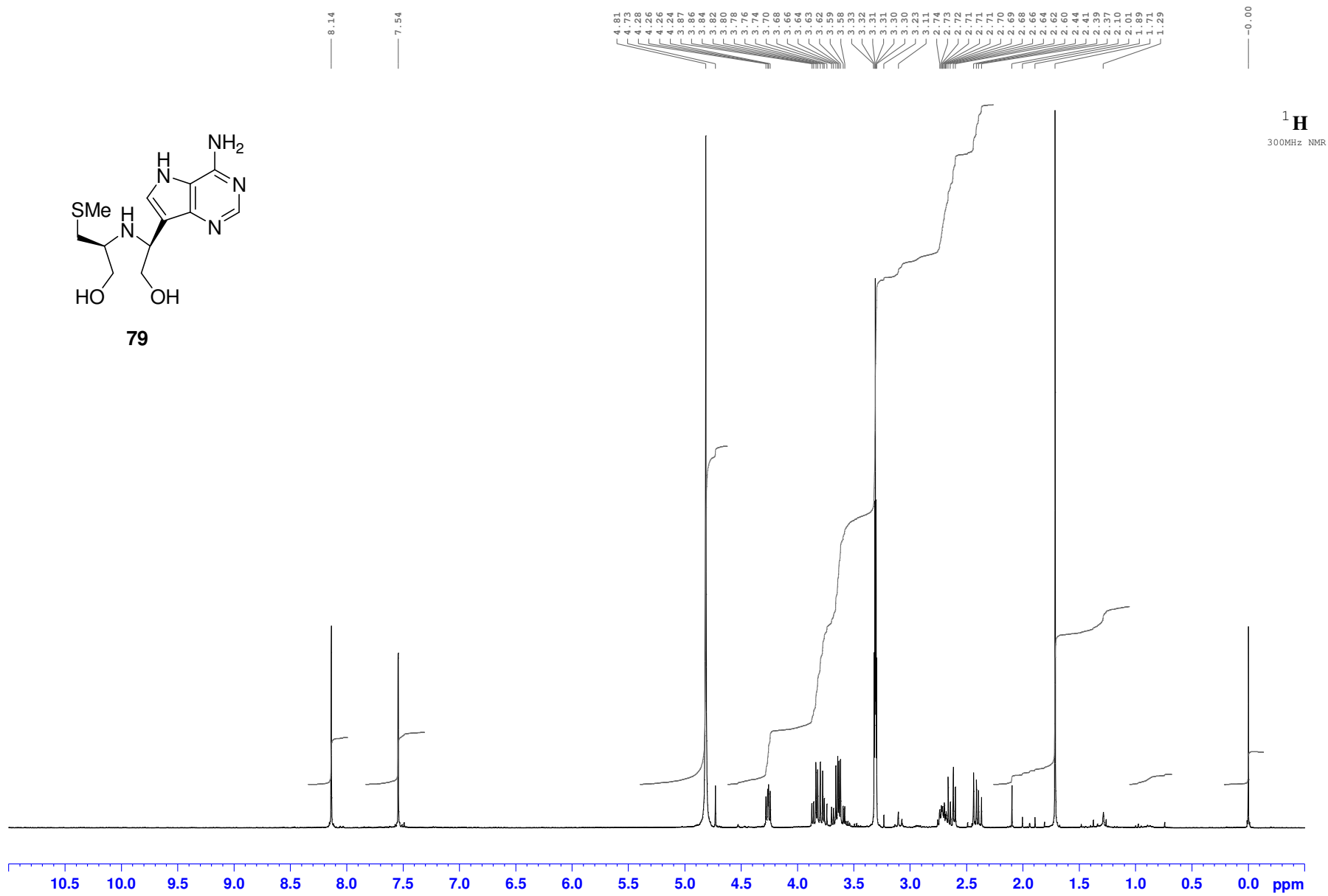




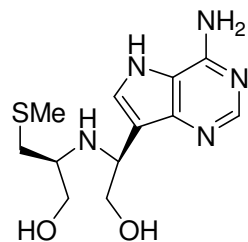




79



<sup>1</sup>H  
300MHz NMR



79



<sup>13</sup>C  
300MHz  
proton  
decoupled

