SUPPLEMENTARY INFORMATION FOR:

Selective inhibitors of *H. pylori* methylthioadenosine nucleosidase and human methylthioadenosine phosphorylase

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ABBREVIATIONS: MTDIA: methylthio-DADMe-Immucillin-A; MTA: *S*-methyl-5' thioadenosine; All: allyl; DQF-COSY: double-quantum filtered correlation spectroscopy; Q-TOF: quadrupole time-of-flight; MTAN: 5'-methylthioadenosine/S-adenosylhomocysteine nucleosidase; *Hp*MTAN: *Helicobacter pylori* MTAN; MTAP: 5'-methylthioadenosine phosphorylase; MTR: 5-methylthio-α-D-ribose 1-phosphate; SAM: *S*-Adenosylmethionine; SAH: *S*-adenosylhomocysteine, SRH: *S*-ribosylhomocysteine; NMR: nuclear magnetic resonance; HPLC: high performance liquid chromatography; RT: room temperature; t-Bu: tert-butyl; DMF: Dimethylformamide; aq: aqueous; Et: ethyl; Me: methyl; THP: tetrahydropyranyl; BOC: tert-butyloxycarbonyl; Ac: acyl; n-Bu: n-butyl; Bn: benzyl; PRMT5: protein arginine methyltransferase 5; MAT2A: S-adenosylmethionine synthetase 2 A; HSQC: heteronuclear single quantum coherence spectroscopy; DEPT: distortionless

enhancement by polarization transfer; APT: Attached proton test

SI CONTENT

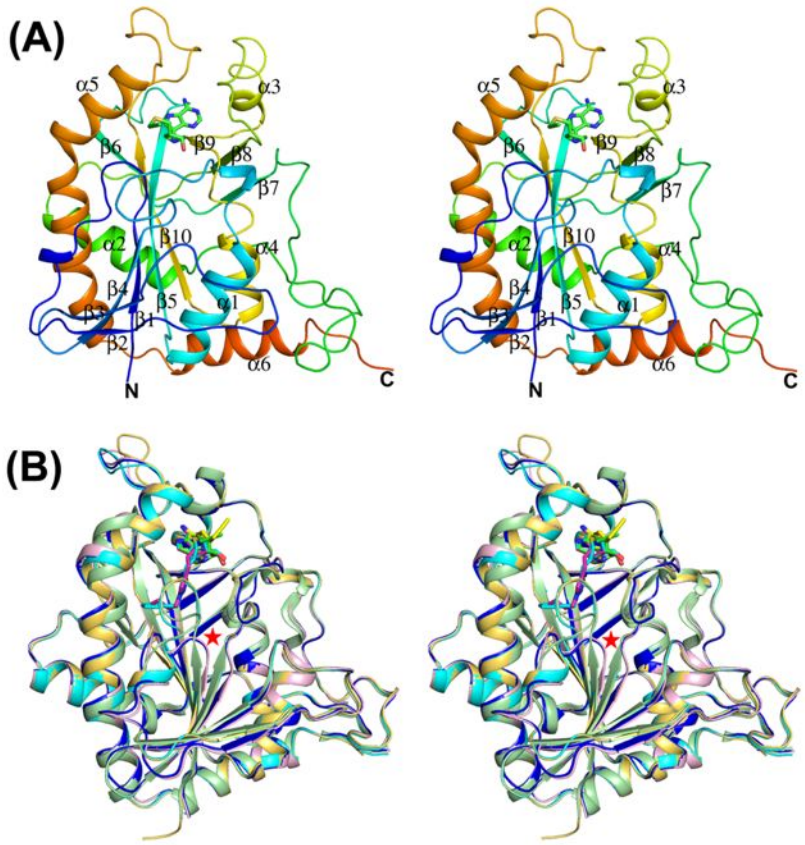

Figure S1. Stereoviews of apo- and inhibitor-bound MTAP structures. **(A)** The monomer subunit structure of MTAP in complex with **15**. The structural fold and secondary structures are highlighted. **(B)** The structural comparison of unliganded MTAP structure is superimposed with four inhibitor-bound MTAP structures. The major structural change upon inhibitor binding occurs in the β1-β2 loop conformation as indicated by the red star.

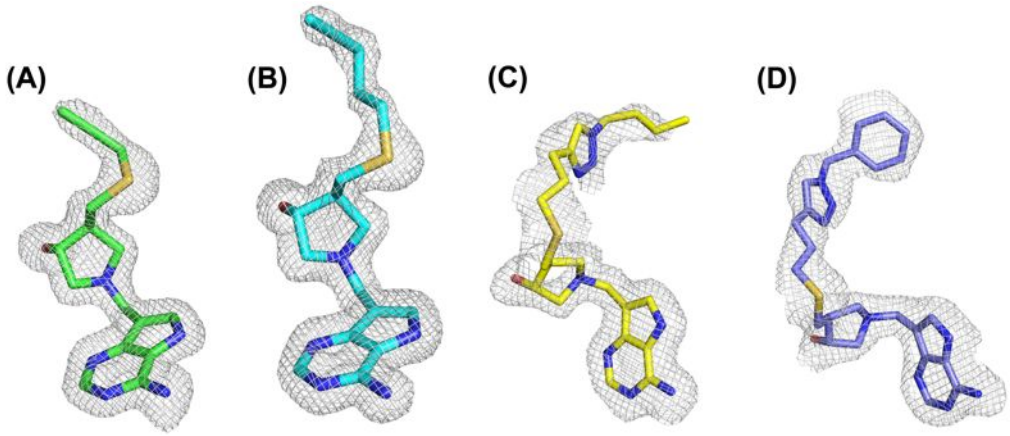

Figure S2. The omit density map (Fo−Fc) of transition-state analogue inhibitors bound at the active site of MTAP. The omit map was calculated after 15 cycles of omit refinement by REFMAC5, leaving out the active site inhibitors. The contour levels are at 2.5σ. The inhibitors **15**, **16**, **30** and **32** are shown in panels A, B, C, and D, respectively.

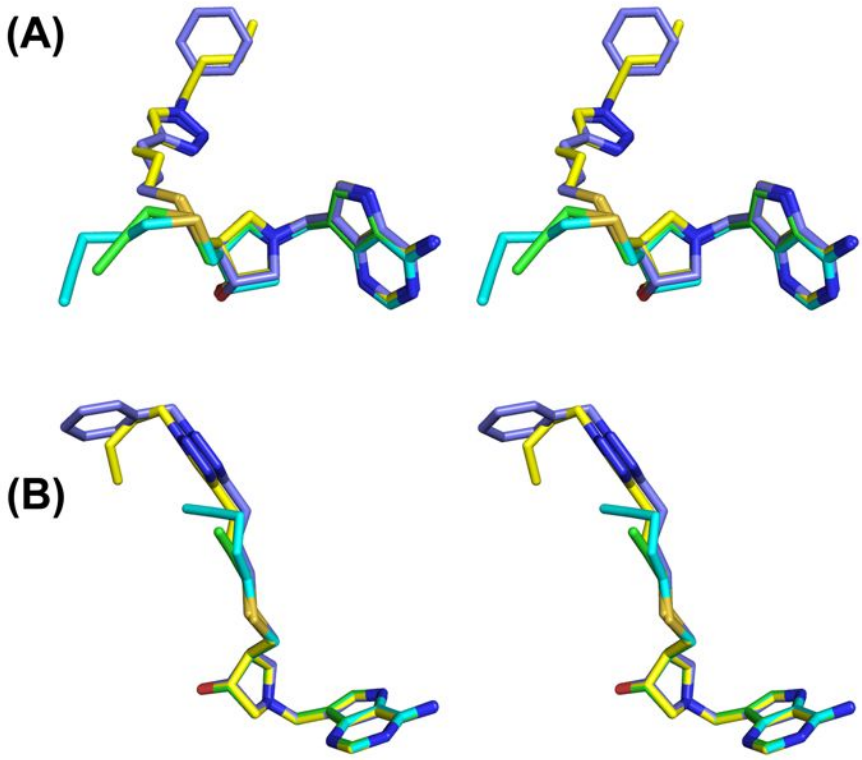

Figure S3. Stereoview superposition of the inhibitors **15**, **16**, **30** and **32** at the binding site of MTAP (A) and *Hp*MTAN (B). The 5'-alkylthio groups of the inhibitors bind in distinct conformations in MTAP and in *Hp*MTAN. Small substituents in MTAP fit a closed hydrophobic pocket but larger ones cannot, and fold under the molecule near the phosphate binding site.

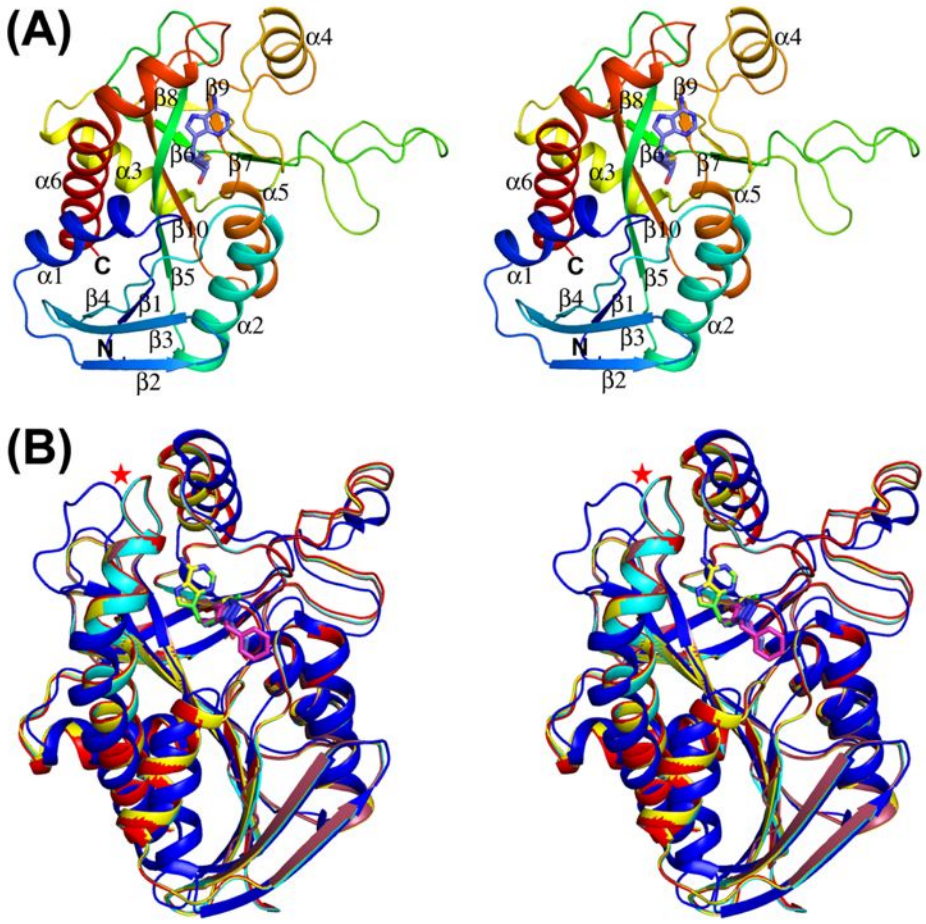

Figure S4. Stereoviews of apo- and inhibitor-bound MTAN structures. **(A)** The monomeric subunit structure of *Hp*MTAN in complex with **15** (PDB code: 6DYU). The structural fold and secondary structures are highlighted. **(B)** A structural comparison of unliganded *E. coli* MTAN structure (deep blue) is superimposed with inhibitor-bound complexes of *Hp*MTAN with **15**, **16**, **30** and **32** (other colors). The major structural change due to inhibitor binding occurs in the α6-β10 loop conformation as highlighted with red star.

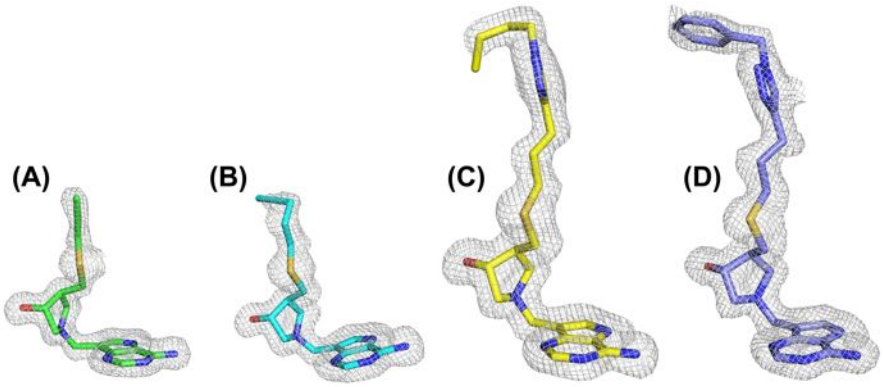

Figure S5. The omit density map (Fo−Fc) of transition-state analogue inhibitors bound at the active site of *Hp*MTAN. The omit map was calculated after 15 cycles of omit refinement by REFMAC5, leaving out the active site inhibitors. The contour levels are at 2.5σ. The inhibitors **15**, **16**, **30** and **32** are shown in panels A, B, C, and D, respectively.

Table S1. Crystallization and crystal handling.

Enzyme	Complex structures	Crystallization conditions	Cryoprotectant solution	Space group	PDB ID
H. sapiens MTAP	**MTAP + 15**	100 mM HEPES pH 7.0, 10 %(w/v) PEG 6000	100 mM HEPES pH 7.0, 10 %(w/v) PEG 6000, 20% ethylene glycol, 0.4 mM **15**	P321	6DYZ
	MTAP + 16	100 mM HEPES pH 7.0, 10 %(w/v) PEG 6000	100 mM HEPES pH 7.0, 10 %(w/v) PEG 6000, 20% ethylene glycol, 0.4 mM **16**	P321	6DZ0
	MTAP + 30	100 mM Sodium acetate trihydrate pH 4.6, 2.0 M Sodium chloride	100 mM Sodium acetate trihydrate pH 4.6, 2.0 M Sodium chloride, 20% ethylene glycol, 0.4 mM **30**	$C222_1$	6DZ2
	MTAP + 32	100 mM Sodium acetate trihydrate pH 4.6, 2.0 M Sodium chloride	100 mM Sodium acetate trihydrate pH 4.6, 2.0 M Sodium chloride, 20% ethylene glycol, 0.4 mM **32**	$C222_1$	6DZ3
H. pylori MTAN	**HpMTAN + 15**	200 mM Sodium Nitrate, 20 %(w/v) PEG 3350	200 mM Sodium Nitrate, 20 %(w/v) PEG 3350, 20% ethylene glycol, 0.4 mM **15**	$P4_12_12$	6DYU
	HpMTAN + 16	100 mM HEPES pH 7.5, 20 %(w/v) PEG 8000	100 mM HEPES pH 7.5, 20 %(w/v) PEG 8000, 20% ethylene glycol, 0.4 mM **16**	$P4_12_12$	6DYV
	HpMTAN + 30	200 mM Calcium Chloride, 20 %(w/v) PEG 3350	100 mM HEPES pH 7.5, 20 %(w/v) PEG 8000, 20% ethylene glycol, 0.4 mM **30**	$P4_12_12$	6DYY
	HpMTAN + 32	100 mM HEPES pH 7.5, 20 %(w/v) PEG 8000	200 mM Calcium Chloride, 20 %(w/v) PEG 3350, 20% ethylene glycol, 0.4 mM **32**	$P4_12_12$	6DYW

Details of chemical synthesis

All reactions were performed under an argon or nitrogen atmosphere, unless water was used as solvent or the reaction mixture was heated above 100 °C. Organic solutions were dried over anhydrous magnesium sulfate or sodium sulfate and the volatiles were evaporated under reduced pressure at 40 °C. Anhydrous and chromatography solvents were obtained commercially and used without any further purification. Thin layer chromatography (TLC) was performed on aluminum sheets coated with 60 F254 silica gel. Organic compounds were visualized under UV light or a dip [Ehrlich′s - 4-di-methylaminobenzaldehyde (1 g) in sulfuric acid (conc., aq., 25 mL) and methanol (150 mL)] or [ammonium molybdate (5 g) and cerium(IV) sulfate (0.2 g) in sulfuric acid (conc., aq., 5 mL) and water (95 mL)] or [potassium permanganate (2 g) and potassium carbonate (13 g) in sodium hydroxide (aq, 1 M, 3.5 mL) and water (200 mL)]. Chromatography (flash column or an automated system with continuous gradient facility) was performed on silica gel (40-63μm and 35-70μm). Solvent mixtures are stated as percentage of the polar solvent respective to total volume. All final compounds gave satisfactory purity (≥95%) by HPLC and NMR. ^{1}H NMR spectra were measured in $CDCl_3$ (δ=7.26), CD_3OD (center line, δ=3.31), DMSO-d6 (δ=2.50), APT and ^{13}C NMR spectra in $CDCl_3$ (center line, δ=77.16), CD_3OD (center line, δ=49.0) or DMSO-d6 (center line δ=39.52) at 500 and 300 MHz. Assignments of ^{1}H and ^{13}C resonances were based on 2D (1H-1H DQF-COSY, 1H-13C HSQC), DEPT and APT experiments. High resolution electrospray mass spectra (ESI-HRMS) were recorded on a Q-TOF Tandem Mass Spectrometer.

General Synthetic Procedures.

Thioether Formation from Thioacetate ester 12

A solution of sodium methoxide (1.1 eq, 3%) in methanol was degased with argon and treated with a solution of thioacetate ester **12** (1.0 eq) in methanol. The respective halide

(1.2 eq) was added after 30 min. After 1 h, the volatiles were removed under reduced pressure and the residue was dissolved in chloroform. Aqueous work-up gave crude products in quantitative yields. Purification (column chromatography: gradient from petrol ether to ethyl acetate) was only necessary, if excess amounts of non-volatile halides were used as reactants.

Multicomponent 1,3-Dipolar Cycloaddition

The respective alkyne (1.0 eq) was dissolved in methanol under argon atmosphere and treated with sodium azide (2.0 eq), the respective halide (1.1 eq) and a catalytic amount of copper(I) iodide (ca. 5 mol%). After the reaction mixture was stirred at room temperature overnight it was directly adsorbed onto silica and the desired product was obtained by chromatography (petroleum ether/ethyl acetate/methanol or toluene/acetone mixtures).

***N*-Boc Deprotection**

The respective Boc protected pyrrolidine (1.0 eq) was dissolved in methanol and treated with hydrochloric acid (conc., aq.) to give a volume ratio methanol/hydrochloric acid of 3:1. After full conversion was determined by tlc (1–10h) isopropyl alcohol and toluene were added and the volatiles were removed under reduced pressure. The residue was redissolved in methanol and basified with ion exchange resin Amberlyst A21 to pH=7–9. Filtration and evaporation gave crude product often with sufficient purity. This generally provided the amine which was at least partially the hydrochloride salt. If necessary, the crude product was purified by chromatography (absorbed on silica gel, gradient elution from dichloromethane to 20% methanolic ammonia (7 M) in dichloromethane).

Mannich Coupling

The respective pyrrolidine (1.0–1.2 eq) and the respective aza-amino-indole (1.0–1.2 eq) were fully dissolved in water/ethanol (1:1). The mixture was treated with formaldehyde (aq., 37 wt%, 1.2 eq) and heated to 70–100 °C in a sealed vessel conventionally or with radiation

(microwave). The limiting reactant was occasionally changed due to better separation of product and excess starting material. After full conversion (2–6 h) the volatiles were removed under reduced pressure and the product isolated by column chromatography (absorbed on silica gel, and a gradient elution of dichloromethane to 30% methanolic ammonia (7 M) in dichloromethane). If purification with methanolic ammonia did not provide pure product additional chromatography with aqueous ammonia/isopropyl alcohol or chloroform/methanol mixtures was used.

(E)-4-(2-(Dimethylamino)vinyl)-3-nitropyridin-2(1H)-one (3)

Commercial available 4-methyl-3-nitro-pyridin-2-ol (**2**, 1.64 g, 10.6 mmol) in DMF (60 mL) was treated with Bredereck′s reagent (6.25 mL, 773 mmol) and heated to 100 °C for 20 h. The product was precipitated by the addition of ice and water (150 mL) and filtered. The crude compound **3** (1.61 g, 72%) was obtained as orange solid, showed sufficient purity and was used in the next step without further purification. ^{1}H NMR ($(CD_3)_2SO$ at 2.50): δ 11.32 (bs, 1H), 7.66 (d, *J*=13.0 Hz, 1H), 7.16 (d, *J*=7.3 Hz, 1H), 6.47 (d, *J*=7.4 Hz, 1H), 4.77 (d, *J*=13.0 Hz, 1H), 2.94 (bs, 6H). ^{13}C NMR ($(CD_3)_2SO$ center line 39.5): δ 155.4 (C), 150.0 (CH), 144.5 (C), 134.0 (CH), 133.1 (C), 99.1 (CH), 85.0 (CH). MS: ESI-HRMS (TOF) *m/z* for $C_9H_{11}N_3O_3Na$ (MNa^+) Calcd 232.0698, found 232.0692.

1,6-Dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (4)

Substrate **3** (1.57 g, 7.50 mmol) in acetic acid (100 mL) was stirred at RT with zinc dust (2.48 g, 37.2 mmol). After 1.5 h the reaction mixture was filtered and the filtrate concentrated to give the crude product (2.8 g) as a green residue. The material was subject to purification by column chromatography to afford product **4** (769 mg, 5.73 mmol, 76%) as powder. ^{1}H NMR ($(CD_3)_2SO$ at 2.50): δ 11.93 (bs, 1H), 10.88 (bs, 1H), 7.27 (d, *J*=2.55 Hz, 1H), 6.86 (d, *J*=7.0 Hz, 1H), 6.45 (d, *J*=6.9 Hz, 1H), 6.30 (d, *J*=2.7 Hz, 1H). ^{13}C NMR ($(CD_3)_2SO$ center line 39.5): δ 155.0 (C), 130.4 (C), 126.5, 126, 4 (CH), 124.3, 124.2 (CH), 123.9, 123.7 (C),

102.7 (CH), 100.7 (CH). MS: ESI-HRMS (TOF) *m/z* for $C_7H_7N_2O$ (MH^+) Calcd 135.0558, found 135.0556.

7-Chloro-1H-pyrrolo[2,3-c]pyridine (5)

Compound **4** (41 mg, 0.31 mmol) was dissolved in phosphoryl chloride (1.00 mL, 10.7 mmol) and heated to 100 °C. All volatiles were evaporated after 2.5 h and the white, solid residue was partitioned between sodium hydroxide (aq., 0.2 M, 11 mL) and chloroform (3x10 mL). Combined organic layers were dried and concentrated to the give crude product (35 mg) as white solid. The material was subject to silica filtration to afford product **49** (26 mg, 0.17 mmol, 56%) as powder. ^{1}H NMR (CD_3OD center line 3.31): δ 7.85 (d, *J*=5.5 Hz, 1H), 7.56 (d, *J*=3.2 Hz, 1H), 7.55 (d, *J*=5.4 Hz, 1H), 6.63 (d, *J*=3.2 Hz, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 137.7 (CH), 136.6 (C), 135.3 (C), 131.6 (CH), 131.3 (C), 116.2 (CH), 103.5 (CH). MS: ESI-HRMS (TOF) *m/z* for $C_7H_6N_2{}^{35}Cl$ (MH^+) Calcd 153.0220, found 153.0224.

1H-Pyrrolo[2,3-c]pyridin-7-amine (6)

Chloride **5** (19 mg, 0.12 mmol) was dissolved in ammonia (aq., 2.8 mL, 25 wt%) and heated with copper(I) chloride (22 mg, 0.22 mmol) and copper dust (6.4 mg, 0.10 mmol) at 120 °C for 17 h in a sealed pressure vessel. The reaction mixture was filtered, and the solids washed with water (10 mL). The filtrate was extracted with ethyl acetate (3x25 mL) and the combined organic layers were dried and concentrated to give the crude product (21 mg). The material was purified by column chromatography to afford product **6** (16 mg, 0.12 mmol, ~ quant) as grey powder. ^{1}H NMR (CD_3OD center line 3.31): δ 7.45 (d, *J*=5.8 Hz, 1H), 7.33 (d, *J*=3.0 Hz, 1H), 6.90 (d, *J*=5.8 Hz, 1H), 6.40 (d, *J*=3.0 Hz, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 147.4 (C), 135.8 (CH), 134.4 (C), 127.9 (CH), 121.7 (C), 108.0 (CH), 102.9 (CH). MS: ESI-HRMS (TOF) *m/z* for $C_7H_8N_3$ (MH^+) Calcd 134.0718, found 134.0716.

(3R,4S)-1-((7-Amino-1H-pyrrolo[2,3-c]pyridin-3-yl)methyl)-4-((methylthio)methyl)pyrrolidin-3-ol (8)

The Mannich coupling of pyrrolidine **7** (27.3 mg, 0.185 mmol) and **6** (21.9 mg, 0.164 mmol) was carried out as described in General Synthetic Procedures in water (0.5 mL) and ethanol (0.5 mL) with formaldehyde (aq., 37 wt%, 15 mg, mmol) by conventional heating at 80 °C with a reaction time of 6h. The crude product was purified by column chromatography twice (CH_2Cl_2/ NH_3 (7 M in MeOH) 0%→30%, then ^{i}PrOH/NH_3 (aq, 25%) 0%→2.5%) to afford product **8** (25mg, 85μmol, 52%) as colorless oil. ^{1}H NMR (CD_3OD center line 3.31): δ 7.48 (d, *J*=6.1 Hz, 1H), 7. 46 (s, 1H), 7.07 (d, *J*=6.1 Hz, 1H), 4.00 (ddd, *J*=4.3, 6.4, 4.3 Hz, 1H), 3.85 (d, *J*=13.5 Hz, 1H), 3.79 (d, *J*=13.5 Hz, 1H), 3.04 (dd, *J*=10.0, 7.9 Hz, 1H), 2.89 (dd, *J*=10.4, 6.5 Hz, 1H), 2.72-2.65 (m, 2H), 2.48 (dd, *J*=12.9, 9.1 Hz, 1H), 2.42 (dd, *J*=10.0, 7.0 Hz, 1H), 2.28-2.20 (m, 1H), 2.07 (s, 3H). ^{13}C NMR (CD_3OD center line 49.0): δ 146.8 (C), 134.1 (C), 133.5 (CH), 129.6 (CH), 121.0 (C), 113.0 (C), 106.6 (CH), 76.5 (CH), 62.2 (CH_2), 58.9 (CH_2), 50.4 (CH_2), 47.8 (CH), 37.8 (CH_2), 15.5 (CH_3). MS: ESI-HRMS (TOF) *m/z* for $C_{14}H_{21}N_4OS$ (MH^+) Calcd 293.1436, found 293.1430.

(3R,4S)-1-((7-amino-2H-pyrazolo[4,3-d]pyrimidin-3-yl)methyl)-4-((methylthio)methyl)pyrrolidin-3-ol (11)

Pyrrolidine **7** (185 mg, 1.26 mmol) and aldehyde **9** (328 mg, 1.25 mmol) were added to a prepared solution of acetyl chloride (60 μL, 0.824 mmol) in methanol (2 mL) and the mixture was warmed to 40 °C. 2-Picoline-borane complex (175 mg, 1.63 mmol) was added. After 8 h, all volatiles were evaporated. The residue was purified by column chromatography (CH_2Cl_2/NH_3 (7 M in MeOH) 0%→10%) to afford **10** (353 mg, 0.897 mmol, 71%) as yellow solid. The inconsequential mixture of unseperable diastereomers (1:1 d.r.) was carried through the next two steps. A solution of compound **10** (328 mg, 0.834 mmol) in NH_3 (7 M in MeOH, 5mL) was heated to 120°C in a sealed pressure vessel for 16 h. All volatiles were evaporated *in vacuo* and the residue was purified by column chromatography (CH_2Cl_2/NH_3

(7 M in MeOH) 0%→10%) to afford a diastereomeric mixture of (3R,4S)-1-((7-amino-2-(tetrahydro-2H-pyran-2-yl)-2H-pyrazolo[4,3-d]pyrimidin-3-yl)methyl)-4-((methylthio)methyl)pyrrolidin-3-ol (243mg, 0.642mmol, 77%) as yellow foam. A solution of this material (231 mg, 610 μmol) in methanol (10 mL) was treated with hydrochloric acid (conc., aq., 0.78 mL) and stirred for 3 h. After which, the reaction mixture was diluted with isopropyl alcohol and toluene and the volatiles were removed under reduced pressure. The residue was redissolved in methanol and basified with ion exchange resin Amberlyst A21. The mixture was filtered and the filtrate concentrated *in vacuo*. Product **11** (98 mg, 0.33 mmol, 54%; 30% over three steps) was obtained after purification by column chromatography (CH_2Cl_2/NH_3 (7 M in MeOH) 5%→20%). ^{1}H NMR (CD_3OD center line 3.31): δ 8.21 (s, 1H), 4.03 (d, *J*=13.8 Hz, 1H), 4.00 (d, *J*=13.8 Hz, 1H), 3.96 (ddd, *J*=4.1, 6.3, 4.1 Hz, 1H), 3.09 (dd, *J*=7.9, 9.6 Hz, 1H), 2.90 (dd, *J*=10.2, 6.3 Hz, 1H), 2.70 (dd, *J*=10.2, 4.0 Hz, 1H), 2.66 (dd, *J*=12.9, 6.4 Hz, 1H), 2.47 (dd, *J*=12.9, 8.9 Hz, 1H), 2.41 (dd, *J*=9.7, 6.8 Hz, 1H), 2.25-2.17 (m, 1H), 2.06 (s, 3H). ^{13}C NMR (CD_3OD center line 49.0): δ = 154.1 (C), 152.9 (CH), 140.5 (C), 140.0 (C), 125.6 (C), 76.9 (CH), 62.6 (CH2), 59.1 (CH2), 49.6 (CH2), 48.2 (CH), 38.0 (CH2), 15.5 (CH3). MS: ESI-HRMS (TOF) *m/z* for $C_{12}H_{19}N_6OS$ (MH+) Calcd 295.1341, found 295.1336.

3-(((3R,4S)-3-Hydroxy-4-((methylthio)methyl)pyrrolidin-1-yl)methyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (35)

The Mannich coupling of pyrrolidine **7** (101 mg, 0.686 mmol) and **4** (77 mg, 0.574 mmol) was carried out as described in General Synthetic Procedures in water (2 mL) and ethanol (2 mL) with formaldehyde (aq., 37 wt%, 65 mg, 0.80 mmol) by conventional heating at 80 °C with a reaction time of 3 h. The crude product was subject to purification by column chromatography (iPrOH/NH_3 (aq, 25%) 0%→5%) to afford product **35** (77 mg, 0.26 mmol, 45%). ^{1}H NMR (CD_3OD center line 3.31): δ 7.34 (s, 1H), 6.99 (d, *J*=6.9 Hz, 1H), 6.78 (d, *J*=6.9 Hz, 1H), 3.98 (ddd, *J*=4.1, 6.3, 4.1 Hz, 1H), 3.75 (d, *J*=13.4 Hz, 1H), 3.70 (d,

J=13.4 Hz, 1H), 3.00 (dd, *J*=9.6, 8.3 Hz, 1H), 2.82 (dd, *J*=10.2, 6.4 Hz, 1H), 2.68 (dd, *J*=12.8, 6.3 Hz, 1H), 2.62 (dd, *J*=10.2, 4.1, 1H), 2.48 (dd, *J*=12.9, 9.0, 1H), 2.35 (dd, 9.8, 7.0, 1H), 2.26-2.18 (m, 1H), 2.06 (s, 3H). ^{13}C NMR (CD_3OD center line 49.0): δ 157.3 (C), 133.4 (C), 128.9 (CH), 125.0 (CH), 124.8 (C), 114.6 (C), 102.8 (CH), 76.8 (CH), 62.6 (CH_2), 59.1 (CH_2), 50.8 (CH_2), 48.1 (CH), 38.1 (CH_2), 15.6 (CH_3). MS: ESI-HRMS (TOF) *m/z* for $C_{14}H_{20}N_3O_2S$ (MH^+) Calcd 294.1276, found 294.1271.

3-(((3R,4R)-3-Hydroxy-4-(hydroxymethyl)pyrrolidin-1-yl)methyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (34)

The Mannich coupling of (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol (119 mg, 1.02 mmol) and **4** (164 mg, 1.22 mmol) was carried out as described in the General Synthetic Procedures in water (3 mL) and ethanol (3 mL) with formaldehyde (aq., 37 wt%, 108 mg, 1.33 mmol) in a microwave at 100 °C with a reaction time of 2 h. Product **34** (190 mg, 0.710 mmol, 71%) was obtained after purification by column chromatography (CH_2Cl_2/NH_3 (7 M in MeOH): 10%→30%). ^{1}H NMR (CD_3OD center line 3.31): δ 7.55 (s, 1H), 7.06 (d, *J*=7.1 Hz, 1H), 6.84 (d, 7.0 Hz, 1H), 4.30 (d, *J*=13.7 Hz, 1H), 4.25 (d, *J*=13.8 Hz, 1H), 4.24 (ddd, *J*=3.2, 5.8, 3.2 Hz, 1H), 3.63 (dd, *J*=10.1, 5.4 Hz, 1H), 3.59 (dd, *J*=10.9, 6.1 Hz, 1H), 3.45 (dd, *J*=11.1, 8.3 Hz, 1H), 3.25 (dd, *J*=11.4, 5.7 Hz, 1H), 3.08 (dd, *J*=11.2, 2.8 Hz, 1H), 2.97 (dd, *J*=11.1, 6.8 Hz, 1H), 2.41-2.34 (m, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 157.2 (C), 133.3 (C), 130.6 (CH), 126.1 (CH), 125.2 (C), 109.8 (C), 102.0 (CH), 73.2 (CH), 62.6 (CH_2), 61.6 (CH_2), 55.9 (CH_2), 50.5 (CH_2), 50.3 (CH). MS: ESI-HRMS (TOF) *m/z* for $C_{13}H_{18}N_3O_3$ (MH^+) Calcd 264.1348, found 264.1344.

(3R,4S)-1-((4-Amino-4a,7a-dihydro-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-((pyrimidin-2-ylthio)methyl)pyrrolidin-3-ol (33)

Thioether formation from thioacetate ester **12** (190 mg, 655 μmol) with sodium methoxide (0.750 mmol) and 2-chloropyrimidine (104 mg, 863 μmol) was carried out as described in the

General Synthetic Procedures in methanol (5 mL). tert-Butyl (3R,4S)-3-hydroxy-4-((pyrimidin-2-ylthio)methyl)pyrrolidine-1-carboxylate (135 mg, 434 μmol, 66%) was obtained as pale syrup after purification by column chromatography (PE/EA: 20%→100%). ^{1}H NMR ($CDCl_3$ at 7.26): δ 8.51 (d, J=4.9 Hz, 2H), 7.00 (t, J=4.81 Hz, 1H), 4.22-4.12 (bm, 1H), 3.75-3.58 (bm, 2H), 3.42-3.11 (bm, 5H), 2.54-2.42 (bm, 1H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$ center line 77.2): δ 172.3 (C), 157.5 (CH), 154.7 (C), 116.9 (CH), 79.6 (C), 73.2, 72.7 (CH), 51.9, 51.7 (CH_2), 48.9, 48.3 (CH_2), 46, 45.5 (CH), 31.0, 30.8 (CH_2), 28.6 (CH_3). MS: ESI-HRMS (TOF) *m/z* for $C_{14}H_{21}N_3O_3NaS$ (MNa^+) Calcd 334.1201, found 334.1199.) The Boc deprotection of this material (130 mg, 0.418 mmol) was carried out as described in the General Synthetic Procedures. Crude product of (3*R*,4*S*)-4-((Pyrimidin-2-ylthio)methyl)pyrrolidin-3-ol hydrochloride was obtained as a pale (93 mg, 0.28 mmol, 70%). (^{1}H NMR (CD_3OD center line 3.31): δ 8.59 (d, *J*=4.8 Hz, 2H), 7.18 (t, *J*=4.9 Hz, 1H), 4.37 (ddd, *J*=2.9, 5.4, 2.9 Hz, 1H), 3.60 (dd, 12.0, 7.5 Hz, 1H), 3.51 (dd, *J*=12.3, 4.7 Hz, 1H), 3.39 (dd, *J*=14.3, 7.3 Hz, 1H), 3.26-3.20 (m, 2H), 3.17 (dd, *J*=14.1, 8.1 Hz, 1H), 2.74-2.66 (m, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 172.4 (C), 159.0 (CH), 118.5 (CH), 74.6 (CH), 52.7 (CH_2), 49.4 (CH_2), 47.8 (CH), 31.9 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_9H_{14}N_3OS$ (MH^+) Calcd 212.0858, found 212.0858). The Mannich coupling of this pyrrolidine (85 mg, 0.34 mmol) and 9-deaza-adenine (65 mg, 0.49 mmol) was carried out as described in the General Synthetic Procedures in water (2 mL) and ethanol (2 mL) with formaldehyde (aq., 37 wt%, 37 mg, 0.46 mmol) in the microwave at 70 °C with a reaction time of 2 h. Product **33** (74 mg, 0.21 mmol 62%) was obtained after purification by column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→30%). ^{1}H NMR (CD_3OD center line 3.31): δ 8.51 (d, *J*=5.0 Hz, 2H), 8.17 (s, 1H), 7.68 (s, 1H), 7.11 (t, *J*=5.0 Hz, 1H), 4.31 (bs, 1H), 4.24 (ddd, *J*=3.5, 5.8, 3.5 Hz, 1H), 3.55 (dd, *J*=11.4, 7.9 Hz, 1H), 3.41-3.34 (m, 2H), 3.19-3.10 (m, 2H), 3.01 (dd, *J*=11.4, 6.9 Hz, 1H), 2.65-2.57 (m, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 172.4 (C), 158.7 (CH), 152.4 (C), 151.6 (CH), 146.6 (C), 131.8 (CH),

118.3 (CH), 115.4 (C), 107.3 (C), 75.0 (CH), 60.7 (CH_2), 57.3 (CH_2), 49.2 (CH_2), 47.8 (CH), 32.6 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{16}H_{20}N_7OS$ (MH^+) Calcd 358.1450, found 358.1443.

Pent-4-yn-1-yl methanesulfonate

A solution of commercial 4-pentyn-1-ol (909 mg, 10.5 mmol) and triethylamine (2.2 mL, 16 mmol) in dichloromethane (20 mL) was cooled to 0 °C. Addition of methanesulfonyl chloride (1.0 mL, 13 mmol) caused the precipitation of white crystals (triethylamine hydrochloride) and the mixture was warmed to room temperature after 10 min and then quenched with water (20 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with sodium bicarbonate (sat., aq., 20 mL), dried and concentrated to afford crude product **73** (1.72 g, 10.6 mmol) in quantitative yield as yellow liquid. The material showed sufficient purity by NMR and was used in the next step without further purification. ^{1}H NMR ($CDCl_3$ at 7.26): δ 4.35 (t, *J*=6.1 Hz, 2H), 3.02 (s, 3H), 2.36 (td, *J*=6.9, 2.7 Hz, 2H), 2.00 (t, *J*=2.7 Hz, 1H), 1.96 (qunit, *J*=6.58 Hz, 2H). ^{13}C NMR ($CDCl_3$ center line 77.2): δ 82.2 (C), 69.9 (CH), 68.4 (CH_2), 37.4 (CH_3), 28.0 (CH_2), 14.8 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_6H_{10}O_3NaS$ (MNa^+) Calcd 185.0248, found 185.0251.

tert-Butyl (3R,4S)-3-hydroxy-4-((prop-2-yn-1-ylthio)methyl)pyrrolidine-1-carboxylate (13)

Thioether formation from thioacetate ester **12** (5.01 mg, 17.3 mmol) with sodium methoxide (19 mmol) and propargyl bromide (80 wt% in toluene, 2.3 mL, 21 mmol) was carried out as described in the General Synthetic Procedures in methanol (25 mL). Product **13** (4.44 g, 16.4 mmol, 95%) was obtained as pale syrup after purification by column chromatography. ^{1}H NMR ($CDCl_3$ at 7.26): δ 4.25-4.16 (bs, 1H), 3.74-3.60 (bm, 2H), 3.33-3.23 (m, 3H), 3.21-3.15 (bm, 1H), 2.81-2.65 (bm, 2H), 2.40-2.29 (bm, 2H), 2.27 (t, *J*=2.6 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$ center line 77.2): δ 154.7 (C), 79.8 (C), 79.6 (C), 75.0, 74.3 (CH), 71.8 (CH), 52.7, 52.4 (CH_2), 49.3, 49.0 (CH_2), 45.5, 44.8 (CH), 33.1 (CH_2), 28.6 (CH_3), 19.8

(CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{13}H_{21}NO_3NaS$ (MNa^+) Calcd 294.1140, found 294.1134.

***tert*-Butyl (3*R*,4*S*)-3-hydroxy-4-((pent-4-yn-1-ylthio)methyl)pyrrolidine-1-carboxylate (14)**

Thioether formation from thioacetate ester **12** (1.88 g, 6.48 mmol) with sodium methoxide (6.89 mmol) and pent-4-yn-1-yl methanesulfonate (1.41 g, 7.60 mmol) was carried out as described in the General Synthetic Procedures in methanol (10 mL). Product **14** (1.23 g, 4.42 mmol, 68%) was obtained as pale syrup after purification by column chromatography. ^{1}H NMR ($CDCl_3$ at 7.26): δ 4.17 (bs, 1H), 3.72-3.59 (bm, 2H), 3.29-3.18 (bm, 1H), 3.13 (dd, *J*=11.2, 6.5 Hz, 1H), 2.66 (t, *J*=7.3 Hz, 2H), 2.63-2.48 (bm, 3H), 2.32 (td, *J*=6.9, 2.6 Hz, 2H), 2.28 (bs, 1H), 1.97 (t, *J*=2.7 Hz, 1H), 1.80 (pent, *J*=7.0 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$ center line 77.2): δ 154.7 (C), 83.4 (C), 79.7 (C), 75.1, 74.3 (CH), 69.3 (CH), 52.6, 52.4 (CH_2), 49.4, 49.1 (CH_2), 45.9, 45.1 (CH), 33.7 (CH_2), 31.3 (CH_2), 28.6 (CH_3), 28.3 (CH_2), 17.6 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{15}H_{25}NO_3NaS$ (MNa^+) Calcd 322.1453, found 322.1444.

(3*R*,4*S*)-1-((4-Amino-5*H*-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-((prop-2-yn-1-ylthio)methyl)pyrrolidin-3-ol (15).

Boc deprotection of substrate **13** (145 mg, 508 µmol) was carried out as described in the General Synthetic Procedures. Crude material was subject to purification by column chromatography to afford (3*R*,4*S*)-4-((prop-2-yn-1-ylthio)methyl)pyrrolidin-3-ol (60 mg, 129 µmol, 69%) as a yellow oil. ^{1}H NMR (CD_3OD center line 3.31): δ 4.22 (ddd, *J*=3.2, 5.3, 3.2 Hz, 1H), 3.47 (dd, *J*=11.8, 7.5 Hz, 1H), 3.34 (d, *J*=2.3 Hz, 2H), 3.27 (dd, *J*=12.2, 5.2 Hz, 1H), 3.04 (dd, *J*=12.2, 2.9 Hz, 1H), 3.00 (dd, *J*=11.8, 5.6 Hz, 1H), 2.86 (dd, *J*=13.3, 6.7 Hz, 1H), 2.63 (dd, *J*=13.3, 8.8 Hz, 1H) overlaps with 2.62 (t, *J*=2.5 Hz, 1H), 2.45-2.38 (m, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 80.8 (C), 75.8 (CH), 72.6 (CH), 53.3 (CH_2), 50.0

(CH_2), 47.6 (CH), 33.7 (CH_2), 19.8 (CH_2). MS: ESI-MS (TOF) *m/z* for $C_8H_{14}NO_3S$ (MH^+) Calcd 172.08, found 172.1. The Mannich coupling of this pyrrolidine (60 mg, 0.33 mmol) and 9-deaza-adenine (42.7 mg, 0.318 mmol) was carried out as described in the General Synthetic Procedures in water (2 mL) and ethanol (2 mL) with formaldehyde (aq., 37 wt%, 34 mg, 0.42 mmol) by conventional heating at 80 °C with a reaction time of 2 h. Product **15** (25 mg, 0.079 mmol, 24%) was obtained after purification by column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→30%). ^{1}H NMR (CD_3OD center line 3.31): δ 8.16 (s, 1H), 7.50 (s, 1H), 3.99 (ddd, *J*=4.2, 6.4, 4.2, 1H), 3.87 (d, 13.4 Hz, 1H), 3.82 (d, 13.4 Hz, 1H), 3.27 (d, *J*=2.6, 2H), 3.07 (dd, 9.8, 8.0 Hz, 1H), 2.90-2.85 (m, 2H), 2.70-2.63 (m, 2H), 2.54 (t, *J*=2.6 Hz, 1H), 2.41 (dd, *J*=10.0, 7.0 Hz, 1H), 2.29-2.19 (m, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 152.1 (C), 151.0 (CH), 147.0 (C), 130.1 (CH), 115.15 (C), 112.3 (C), 81.0 (CH), 76.8 (CH), 72.2 (C), 62.3 (CH_2), 58.8 (CH_2), 49.0 (CH_2), 48.0 (CH), 35.3 (CH_2), 19.8 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{15}H_{20}N_5OS$ (MH^+) Calcd 318.1389, found 318.1391.

(3R,4S)-1-((4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-((pent-4-yn-1-ylthio)methyl)pyrrolidin-3-ol (16)

The Boc deprotection of **14** (108 mg, 361 μmol) was carried out as described in the General Synthetic Procedures. Crude material was purified by column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→20%) to afford product (3R,4S)-4-((pent-4-yn-1-ylthio)methyl)pyrrolidin-3-ol (35 mg, 176 μmol, 48%) as a solid. ^{1}H NMR (CD_3OD center line 3.31): δ 4.06 (ddd, J=3.4, 6.9, 3.4 Hz, 1H), 3.29-3.23 (bm, 1H), 3.08-3.01 (bm, 1H), 2.84-2.78 (bm, 1H), 2.72-2.64 (m, 4H), 2.47 (dd, J=12.9, 8.8 Hz, 1H), 2.31 (td, J=7.0, 2.7 Hz, 2H), 2.23 (t, J=2.7 Hz, 1H), 2.22-2.14 (m, 1H), 1.78 (pent, J=7.1 Hz, 2H). ^{13}C NMR (CD_3OD center line 49.0): δ 84.2 (C), 77.6 (CH), 70.1 (CH), 54.6 (CH_2), 51.3 (CH_2), 49.1 (CH), 34.9 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 18.1 (CH_2). MS: ESI-HRMS (TOF) m/z for $C_{10}H_{18}NOS$ (MH^+) Calcd 200.1109, found 200.1112. Mannich coupling of this pyrrolidine (35 mg, 0.18 mmol) and 9-deaza-adenine (29 mg, 0.22 mmol) was carried out as described in the

General Synthetic Procedures in water (1 mL) and ethanol (1 mL) with formaldehyde (37% aq. solution, 25 mg, 0.31 mmol) in the microwave at 70 °C with a reaction time of 2 h. Product **16** (38 mg, 0.11 mmol, 63%) was obtained after purification by column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→20%).^{1}H NMR (CD_3OD center line 3.31): δ 8.16 (s, 1H), 7.49 (s, 1H), 3.96 (ddd, J=4.2, 8.4, 4.2 Hz, 1H), 3.86 (d, J=13.5 Hz, 1H), 3.81 (d, J=13.5 Hz, 1H), 3.07 (dd, J=9.9, 8.1 Hz, 1H), 2.86 (dd, J=10.3, 6.4 Hz, 1H), 2.73 (dd, J=12.7, 6.1 Hz, 1H), 2.67 (dd, J=10.4, 4.2 Hz, 1H), 2.60 (t, J=7.2 Hz, 2H), 2.49 (dd, J=12.8, 9.2 Hz, 1H), 2.40 (dd, J=9.9, 7.1 Hz, 1H), 2.27 (td, J=7.0, 2.7 Hz, 2H), 2.22-2.14 (m, 1H) overlaps with 2.20 (t, J=2.6 Hz, 1H), 1.73 (pent, J=7.1 Hz, 2H). ^{13}C NMR (CD_3OD center line 49.0): δ 152.1 (C), 151.0 (CH), 147.0 (C), 130.1 (CH), 115.2 (C), 112.4 (C), 84.2 (C), 76.8 (CH), 70.0 (C), 62.3 (CH_2), 58.8 (CH_2), 49.0 (CH_2), 48.6 (CH), 35.7 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 18.0 (CH_2). MS: ESI-HRMS (TOF) m/z for $C_{17}H_{24}N_5OS$ (MH^+) Calcd 346.1702, found 346.1698.

tert-Butyl (3R,4S)-3-hydroxy-4-((((1-methyl-1H-1,2,3-triazol-4-yl)methyl)thio)methyl)pyrrolidine-1-carboxylate (17)

The copper(I) catalyzed 1,3-dipolar cycloaddition of alkyne **13** (198 mg, 730 μmol), methyl iodide (117 mg, 816 μmol) and sodium azide (101 mg, 1.54 mmol) was carried out as described in the General Synthetic Procedures in methanol (2.5 mL). Product **17** (64 mg, 0.19 mmol, 27%) was obtained after purification by column chromatography. ^{1}H NMR (CD_3OD center line 3.31): δ 7.88 (s, 1H), 4.11-4.04 (bm, 1H) overlaps with 4.09 (s, 3H), 3.88 (s, 2H), 3.63-3.51 (bm, 2H), 3.22-3.14 (bm, 2H), 2.68 (dd, *J*=13.0, 5.5 Hz, 1H), 2.46 (dd, *J*=12.6, 8.8 Hz, 1H), 2.33-2.24 (bm, 1H), 1.46 (s, 9H). ^{13}C NMR (CD_3OD center line 49.0): δ 156.8 (C), 146.3 (C), 125.4 (CH), 81.0 (C), 74.9, 74.2 (CH), 53.6, 53.2 (CH_2), 50.2, 49.9 (CH_2), 46.9, 46.3 (CH), 37.2 (CH_3), 34.2 (CH_2), 28.8 (CH_3), 27.1 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{14}H_{24}N_4O_3NaS$ (MNa^+) Calcd 351.1467, found 351.1460.

tert-Butyl (3R,4S)-3-hydroxy-4-(((3-(1-methyl-1H-1,2,3-triazol-4-yl)propyl)thio)methyl)pyrrolidine-1-carboxylate (18)

The copper(I) catalyzed 1,3-dipolar cycloaddition of alkyne **14** (197 mg, 658 μmol), methyl iodide (100 mg, 698 μmol) and sodium azide (89 mg, 1.4 mmol) was carried out as described in the General Synthetic Procedures in methanol (2.5 mL). Product **18** (153 mg, 429 μmol, 65%) was obtained as syrup after purification by column chromatography. ^{1}H NMR ($CDCl_3$ at 7.26): δ 7.71 (s, 1H), 4.09 (q, *J*=7.4 Hz, 1H), 3.59 (dd, *J*=11.2, 7.4 Hz, 1H), 3.58-3.52 (m, 1H), 3.24-3.15 (m, 2H), 2.81 (t, *J*=7.4 Hz, 2H), 2.69 (dd, *J*=13.0, 6.0 Hz, 1H), 2.59 (td, *J*=7.2, 1.0 Hz, 2H), 2.43 (dd, *J*=13.0, 9.0 Hz, 1H), 2.28-2.20 (m, 1H), 1.95 (pent, *J*=7.3 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$ center line 77.2): δ 156.6 (C), 148.5 (C), 124.4 (CH), 81.0 (C), 74.9, 74.2 (CH), 53.7, 53.3 (CH_2), 50.3, 49.8 (CH_2), 47.4, 46.8 (CH), 37.0 (CH_3), 34.1 (CH_2), 32.5 (CH_2), 30.3 (CH_2), 28.8 (CH_3), 25.1 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{16}H_{28}N_4O_3NaS$ (MNa^+) Calcd 379.1780, found 379.1782.

tert-Butyl (3R,4S)-3-hydroxy-4-((((1-((Z)-prop-1-en-1-yl)-1H-1,2,3-triazol-4-yl)methyl)thio)methyl)pyrrolidine-1-carboxylate (19)

The copper(I) catalyzed 1,3-dipolar cycloaddition of alkyne **13** (43 mg, 0.16 mmol), allyl bromide (24 mg, 0.20 mmol) and sodium azide (17 mg, 0.26 mmol) was carried out as described in the General Synthetic Procedures in methanol (1.5 mL). Product **19** (43 mg, 0.12 mmol, 77%) was obtained as pale syrup after purification by column chromatography. ^{1}H NMR ($CDCl_3$ at 7.26): δ 7.49 (s, 1H), 6.01 (ddt, *J*=16.5, 10.2, 6.3 Hz, 1H), 5.36 (dq, *J*=10.3, 1.0 Hz, 1H), 5.31 (dq, *J*=17.0, 1.1 Hz, 1H), 4.95 (dt, *J*=6.3, 1.2 Hz, 2H), 4.18-4.11 (bm, 1H), 3.82 (s, 2H), 3.69-3.57 (bm, 2H), 3.43 (bs, 1H), 3.29-3.17 (bm, 1H), 3.15-3.08 (bm, 1H), 2.67-2.59 (bm, 1H), 2.57-2.49 (bm, 1H), 2.39-2.27 (bm, 1H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$ center line 77.2): δ 154.5 (C), 145.6 (C), 131.1 (CH), 121.6 (CH), 120.4 (CH_2), 79.5 (C), 74.3, 73.6 (CH), 52.9 (CH_2), 52.4, 52.1 (CH_2), 49.2, 48.7 (CH_2), 45.6, 45.1 (CH),

32.7 (CH_2), 28.5 (CH_3), 26.2(CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{16}H_{27}N_4O_3S$ (MH^+) Calcd 355.1804, found 355.1804.

tert-Butyl (3R,4S)-3-hydroxy-4-(((3-(1-((Z)-prop-1-en-1-yl)-1H-1,2,3-triazol-4-yl)propyl)thio)methyl)pyrrolidine-1-carboxylate (20)

Alkyne **14** (208 mg, 695 µmol) in methanol (2.5 mL) under argon atmosphere was treated with sodium azide (57 mg, 0.87 mmol), allyl bromide (107 mg, 876 µmol) and a catalytic amount of copper(I) iodide. Additional charges of sodium azide (91 mg, 1.4 mmol), allyl bromide (0.12 mL, 1.4 mmol) and a copper(I) iodide were added after 21 h and 48 h. After 4 days the reaction mixture was heated to 50 °C for 4 h, adsorbed onto silica and chromatography afforded **20** (149 mg, 390 µmol, 56%). ^{1}H NMR ($CDCl_3$ at 7.26): δ 7.31 (s, 1H), 6.00 (ddt, *J*=16.5, 10.2, 6.2 Hz, 1H), 5.33 (dq, *J*=10.3, 1.0 Hz, 1H), 5.28 (dq, *J*=17.1, 1.1 Hz, 1H), 4.93 (dt, *J*=6.2, 1.4 Hz, 2H), 4.25-4.15 (bm, 1H), 3.70-3.58 (bm, 2H), 3.40 (bs, 1H), 3.27-3.18 (bm, 1H), 3.14-3.08 (bm, 1H), 2.89-2.75 (m, 2H), 2.66-2.47 (bm, 2H) overlaps with 2.58 (t, *J*=7.4 Hz, 2H), 2.32-2.22 (bm, 1H), 1.97 (pent, *J*=7.2 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$ center line 77.2): δ 154.6 (C), 147.3 (C), 131.4 (CH), 120.8 (CH), 120.0 (CH_2), 79.5 (C), 74.4, 73.7 (CH), 52.7 (CH_2), 52.5, 52.2 (CH_2), 49.2, 48.8 (CH_2), 45.7, 45.1 (CH), 33.2 (CH_2), 31.5 (CH_2), 29.0 (CH_2), 28.5 (CH_3), 24.3 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{18}H_{40}N_4O_3S$ (MH^+) Calcd 383.2117, found 383.2122.

tert-Butyl (3S,4R)-3-((((1-butyl-1H-1,2,3-triazol-4-yl)methyl)thio)methyl)-4-hydroxypyrrolidine-1-carboxylate (21)

The copper(I) catalyzed 1,3-dipolar cycloaddition of alkyne **13** (352 mg, 1.30 mmol), 1-bromobutane (0.28 mL, 2.6 mmol) and sodium azide (186 mg, 2.83 mmol) was carried out as described in the General Synthetic Procedures in methanol (6 mL). Product **21** (133 mg, 359 µmol, 28%) was obtained as colorless oil after chromatography. ^{1}H NMR ($CDCl_3$ at 7.26): δ 7.46 (s, 1H), 4.33 (t, *J*=7.3 Hz, 2H), 4.18-4.12 (bm, 1H), 3.83 (s, 2H), 3.72-3.57 (bm,

2H), 3.27-3.16 (bm, 1H), 3.16-3.08 (bm, 1H), 2.67-2.59 (bm, 1H), 2.59-2.50 (bm, 1H), 2.39-2.28 (bm, 1H), 1.88 (quint, *J*=7.5 Hz, 2H), 1.44 (s, 9H), 1.36 (sext, *J*=7.5 Hz, 2H), 0.95 (t, *J*=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$ center line 77.2): δ 154.5 (C), 145.3 (C), 121.6 (CH), 79.5 (C), 74.3, 73.7 (CH), 52.4, 52.0 (CH_2), 50.2 (CH_2), 49.2, 48.7 (CH_2), 45.7, 45.1 (CH), 32.6 (CH_2), 32.2 (CH_2), 28.5 (CH_3), 26.2 (CH_2), 19.7 (CH_2), 14.1 (CH_3). MS: ESI-HRMS (TOF) *m/z* for $C_{17}H_{30}N_4O_3NaS$ (MNa^+) Calcd 393.1936, found 393.1937.

tert-Butyl (3S,4R)-3-(((3-(1-butyl-1H-1,2,3-triazol-4-yl)propyl)thio)methyl)-4-hydroxypyrrolidine-1-carboxylate (22)

The copper(I) catalyzed 1,3-dipolar cycloaddition of alkyne **14** (186 mg, 0.621 mmol), 1-bromobutane (0.14 mL, 1.3 mmol) and sodium azide (105 mg, 1.60 mmol) was carried out as described in the General Synthetic Procedures in methanol (2.5 mL). Product **22** (95 mg, 0.24 mmol, 39%) was obtained as colorless oil after purified by column chromatography. ^{1}H NMR ($CDCl_3$ at 7.26): δ 7.28 (s, 1H), 4.30 (t, *J*=7.2 Hz, 2H), 4.24-4.16 (bm, 1H), 3.74-3.57 (bm, 2H), 3.47-3.33 (bm, 1H), 3.29-3.17 (bm, 1H), 3.17-3.07 (bm, 1H), 2.89-2.75 (m, 2H), 2.67-2.47 (bm, 2H) overlaps with 2.59 (t, *J*=7.4 Hz, 2H), 2.33-2.22 (bm, 1H), 1.98 (pent, *J*=7.1 Hz, 2H), 1.86 (pent, *J*=7.4 Hz, 2H), 1.44 (s, 9H), 1.34 (sext, *J*=7.5 Hz, 2H), 0.94 (t, *J*=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$ center line 77.2): δ 154.7 (C), 147.0 (C), 120.9 (CH), 79.6 (C), 74.5, 73.8 (CH), 52.6, 52.3 (CH_2), 50.1 (CH_2), 49.3, 49.0 (CH_2), 45.8, 45.2 (CH), 33.4 (CH_2), 32.4 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 28.6 (CH_3), 24.4 (CH_2), 19.8 (CH_2), 13.6 (CH_3). MS: ESI-HRMS (TOF) *m/z* for $C_{19}H_{34}N_4O_3NaS$ (MNa^+) Calcd 421.2249, found 421.2254.

tert-Butyl (3S,4R)-3-((((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)methyl)-4-hydroxypyrrolidine-1-carboxylate (23)

The copper(I) catalyzed 1,3-dipolar cycloaddition of alkyne **13** (112 mg, 0.413 mmol), benzyl bromide (60 µg, 0.49 mmol) and sodium azide (33 mg, 0.50 mmol) was carried out as described in the General Synthetic Procedures in methanol (1.5 mL). Product **23** (88 mg,

0.22 mmol, 53%) was obtained as colorless oil after column chromatography. ^{1}H NMR (TMS at 0.00): δ 7.41 (s, 1H), 7.40-7.35 (m, 3H), 7.28-7.24 (m, 2H), 5.50 (s, 2H), 4.16-4.08 (bm, 1H), 3.79 (s, 2H), 3.69-3.56 (bm, 3H), 3.27-3.17 (bm, 1H), 3.14-3.07 (bm, 1H), 2.67-2.59 (bm, 1H), 2.54-2.46 (bm, 1H), 2.37-2.26 (bm, 1H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$ center line 77.2): δ 154.6 (C), 145.8 (C), 134.5 (C), 129.2 (CH), 128.9 (CH), 128.2 (CH), 121.9 (CH), 79.6 (C), 74.3, 73.6 (CH), 54.4 (CH_2), 52.5, 52.2 (CH_2), 49.3, 48.8 (CH_2), 45.7, 45.2 (CH), 32.8 (CH_2), 28.6 (CH_3), 26.3 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{20}H_{29}N_4O_3S$ (MH^+) Calcd 405.1960, found 405.1957.

tert-Butyl (3S,4R)-3-(((3-(1-benzyl-1H-1,2,3-triazol-4-yl)propyl)thio)methyl)-4-hydroxypyrrolidine-1-carboxylate (24)

The copper(I) catalyzed 1,3-dipolar cycloaddition of alkyne **14** (226 mg, 0.755 mmol), benzyl bromide (153 mg, 0.877 mmol) and sodium azide (62 mg, 0.94 mmol) was carried out as described in the General Synthetic Procedures in methanol (2.5 mL). Product **24** (215 mg, 0.197 mmol, 66%) was obtained as yellow oil after column chromatography. ^{1}H NMR ($CDCl_3$ at 7.26): δ 7.40-7.33 (m, 3H), 7.28-7.21 (m, 3H), 5.48 (s, 2H), 4.19 (bm, 1H), 3.72-3.57 (bm, 2H), 3.31-3.18 (bm, 2H), 3.15-3.07 (bm, 1H), 2.88-2.73 (m, 2H), 2.64-2.47 (m, 2H) overlaps with 2.58 (t, *J*=7.1 Hz, 2H), 2.32-2.21 (m, 1H), 1.96 (pent, *J*=7.3 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$ center line 77.2): δ 154.7 (C), 147.6 (C), 134.9 (C), 129.2 (CH), 128.8 (CH), 128.2 (CH), 121.0 (CH), 79.6 (C), 74.6, 73.9 (CH), 54.2(CH_2), 52.6, 52.3 (CH_2), 49.3, 49.0 (CH_2), 45.8, 45.12 (CH), 33.4 (CH_2), 31.7 (CH_2), 29.0 (CH_2), 28.6 (CH_3), 24.4 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{22}H_{33}N_4O_3S$ (MH^+) Calcd 433.2273, found 433.2274.

(3R,4S)-1-((4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-((((1-methyl-1H-1,2,3-triazol-4-yl)methyl)thio)methyl)pyrrolidin-3-ol (25).

Boc deprotection of **17** (64 mg, 0.20 mmol) was carried out as described in the General Synthetic Procedures. Crude material was subject to purification by column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→30%) to afford (3*R*,4*S*)-4-((((1-Methyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)methyl)pyrrolidin-3-ol (25 mg, 110 µmol, 56%). ^{1}H NMR (CD_3OD center line 3.31): δ 7.84 (s, 1H), 4.09-4.06 (m, 4H), 3.82 (s, 2H), 3.28 (dd, *J*=10.9, 7.9 Hz, 1H) overlaps with solvent, 3.11-3.02 (m, 1H), 2.88-2.81 (m, 1H), 2.75-2.69 (m, 1H), 2.66 (dd, *J*=13.0, 6.8 Hz, 1H), 2.47 (dd, *J*=13.0, 8.6 Hz, 1H), 2.27-2.19 (m, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 146.8 (C), 125.1 (CH), 77.1 (CH), 54.4 (CH_2), 51.1 (CH_2), 48.5 (CH), 37.1 (CH_3), 34.5 (CH_2), 26.6(CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_9H_{17}N_4OS$ (MH^+) Calcd 229.1123, found 229.1123. Mannich coupling of this material (25 mg, 0.11 mmol) and 9-deaza-adenine (18 mg, 0.13 mmol) was carried out as described in the General Synthetic Procedures in water (0.5 mL) and ethanol (0.5 mL) with formaldehyde (aq., 37 wt%, 17 mg, 0.21 mmol) in the microwave at 70 °C with a reaction time of 2 h. Product **25** (26 mg, 69 µmol, 63%) was obtained after column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→30%).^{1}H NMR (CD_3OD center line 3.31): δ 8.17 (s, 1H), 7.80 (s, 1H), 7.53 (s, 1H), 4.06 (s, 3H), 3.99 (ddd, *J*=4.1, 6.2, 4.1 Hz, 1H), 3.94 (d, *J*=13.6, 1H), 3.90 (d, *J*=13.5 Hz, 1H), 3.77 (s, 2H), 3.14 (dd, *J*=10.0, 8.0 Hz, 1H), 2.94 (dd, *J*=10.5, 6.3 Hz, 1H), 2.76 (dd, *J*=10.6, 3.9 Hz, 1H), 2.70 (dd, *J*=12.8, 6.4 Hz, 1H), 2.52-2.45 (m, 2H), 2.27-2.19 (m, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 152.2 (C), 151.1 (CH), 146.9 (C), 146.7 (C), 130.4 (CH), 125.1 (CH), 115.2 (C), 111.3 (C), 76.4 (CH), 62.0 (CH_2), 58.5 (CH_2), 49.9 (CH_2), 48.0 (CH), 37.0 (CH_3), 35.3 (CH_2), 26.6 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{16}H_{22}N_8ONaS$ (MNa^+) Calcd 397.1535, found 397.1530.

(3R,4S)-1-((4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(((3-(1-methyl-1H-1,2,3-triazol-4-yl)propyl)thio)methyl)pyrrolidin-3-ol (26).

Boc deprotection of **18** (116 mg, 325 µmol) was carried out as described in the General Synthetic Procedures. The crude product ((3*R*,4*S*)-4-(((3-(1-Methyl-1*H*-1,2,3-triazol-4-yl)propyl)thio)methyl)pyrrolidin-3-ol hydrochloride) (88 mg, 0.30 mmol, 93%) was used in the next step without further purification. ^{1}H NMR (CD_3OD center line 3.31): δ 7.75 (s, 1H), 4.35-4.29 (bm, 1H), 4.07 (s, 3H), 3.63-3.56 (bm, 1H), 3.46-3.39 (bm, 1H), 3.25-3.17 (bm, 2H), 2.81 (t, *J*=7.5 Hz, 2H), 2.74 (dd, *J*=12.9, 6.2 Hz, 1H), 2.62 (t, *J*=7.1 Hz, 2H), 2.52 (dd, *J*=12.8, 8.9 Hz, 1H), 2.49-2.42 (bm, 1H), 1.96 (pent, *J*=7.3 Hz, 2H). ^{13}C NMR (CD_3OD center line 49.0): δ 148.8 (C), 124.7 (CH), 74.5 (CH), 52.6 (CH_2), 49.4 (CH_2), 47.5 (CH), 37.0 (CH_3), 33.4 (CH_2), 32.3 (CH_2), 30.3 (CH_2), 25.1 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{11}H_{21}N_4OS$ (MH^+) Calcd 257.1436, found 257.1437. The Mannich coupling of this material (83 mg, 0.28 mmol) and 9-deaza-adenine (43 mg, 0.32 mmol) was carried out as described in the General Synthetic Procedures in water (2 mL) and ethanol (2 mL) with formaldehyde (aq., 37 wt%, 27 mg, 0.33 mmol) in the microwave at 70 °C with a reaction time of 2 h. Product **26** (54 mg, 0.13 mmol, 46%) was obtained after purification by column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→30%).^{1}H NMR (CD_3OD center line 3.31): δ 8.16 (s, 1H), 7.67 (s, 1H), 7.50 (s, 1H), 4.05 (s, 3H), 3.97 (ddd, *J*=4.1, 6.3, 4.1 Hz, 1H), 3.87 (d, *J*=13.4 Hz, 1H), 3.83 (d, *J*=13.4 Hz, 1H), 3.07 (dd, *J*=9.9, 8.1 Hz, 1H), 2.87 (dd, *J*=10.4, 6.3 Hz, 1H), 2.76 (t, *J*=7.4 Hz, 2H), 2.72 (dd, *J*=12.7, 6.2 Hz, 1H), 2.68 (dd, *J*=10.5, 4.3 Hz, 1H), 2.53 (td, *J*=7.2, 1.9 Hz, 2H) overlaps with 2.49 (dd, *J*=12.8, 9.3 Hz, 1H), 2.40 (dd, *J*=9.9, 7.1 Hz, 1H), 2.21-2.13 (m, 1H), 1.90 (pent, *J*=7.3 Hz, 2H). ^{13}C NMR (CD_3OD center line 49.0): δ 152.1 (C), 148.5 (CH), 147.0 (C), 130.1 (C), 124.3 (CH), 115.2 (CH), 115.2 (C), 112.2 (C), 76.7 (CH), 62.2 (CH_2), 58.7 (CH_2), 48.9 (CH_2), 48.5 (CH), 36.9 (CH_3), 35.6 (CH_2), 32.2 (CH_2), 30.3 (CH_2), 25.1 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{18}H_{27}N_8OS$ (MH^+) Calcd 403.2029, found 403.2032.

(3R,4S)-1-((4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-((((1-((Z)-prop-1-en-1-yl)-1H-1,2,3-triazol-4-yl)methyl)thio)methyl)pyrrolidin-3-ol (27).

Boc deprotection of **19** (64 mg, 181 μmol) was carried out as described in the General Synthetic Procedures. (3*R*,4*S*)-4-((((1-((*Z*)-Prop-1-en-1-yl)-1H-1,2,3-triazol-4-yl)methyl)thio)methyl)-pyrrolidin-3-ol hydrochloride was obtained as pale oil (45 mg, 0.15 mmol, 86%). The material showed sufficient purity by NMR and was used in the next step without further purification. ^{1}H NMR (CD_3OD center line 3.31): δ 7.90 (s, 1H), 6.08 (ddt, *J*=16.4, 10.3, 6.0 Hz, 1H), 5.32 (dq, *J*=10.4, 1.3 Hz, 1H), 5.26 (dq, *J*=17.0, 1.4 Hz, 1H), 5.02 (dt, *J*=6.0, 1.5 Hz, 2H), 4.22 (ddd, *J*=3.0, 5.3, 3.0 Hz, 1H), 3.86 (s, 2H), 3.49 (dd, *J*=11.8, 7.4 Hz, 1H), 3.29 (dd, *J*=12.4, 5.0 Hz, 1H), 3.07 (dd, *J*=9.5, 2.8 Hz, 1H), 3.02 (dd, *J*=12.0, 5.4 Hz, 1H), 2.69 (dd, *J*=13.3, 6.7 Hz, 1H), 2.51 (dd, *J*=13.2, 8.6 Hz, 1H), 2.45-2.38 (m, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 146.7 (C), 133.2 (CH), 124.2 (CH), 119.9 (CH_2), 75.4 (CH), 53.7 (CH_2), 53.2 (CH_2), 49.9 (CH_2), 47.6 (CH), 33.7 (CH_2), 26.6 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{11}H_{19}N_4OS$ (MH^+) Calcd 255.1280, found 255.1281. Mannich coupling of this material (45 mg, 0.15 mmol) and 9-deaza-adenine (28 mg, 0.21 mmol) was carried out as described in the General Synthetic Procedures in water (1.5 mL) and ethanol (1.5 mL) with formaldehyde (37% aq. solution, 24 mg, 0.30 mmol) in the microwave at 70 °C with a reaction time of 2 h. Product **27** (43 mg, 0.11 mmol, 73%) was obtained after purification by column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→30%). ^{1}H NMR (CD_3OD center line 3.31): δ 8.16 (s, 1H), 7.83 (s, 1H), 7.50 (s, 1H), 6.05 (ddt, *J*=16.8, 10.5, 6.1 Hz, 1H), 5.30 (dq, *J*=10.3, 1.3 Hz, 1H), 5.23 (dq, *J*=17.0, 1.2 Hz, 1H), 4.99 (dt, *J*=6.0, 1.4 Hz, 2H), 3.96 (ddd, *J*=4.0, 6.1, 4.0 Hz, 1H), 3.88 (d, *J*=13.6 Hz, 1H), 3.84 (d, *J*=13.6 Hz, 1H), 3.79 (s, 2H), 3.07 (dd, *J*=9.8, 8.3 Hz, 1H), 2.88 (dd, *J*=10.4, 6.3 Hz, 1H), 2.73-2.67 (m, 2H), 2.50 (dd, *J*=12.9, 8.8 Hz, 1H), 2.40 (dd, *J*=9.8, 7.0 Hz, 1H), 2.25-2.17 (m, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 152.1 (C), 151.1 (CH), 147.0 (C), 146.9(C), 133.2 (CH), 130.3 (CH), 124.2 (CH), 119.9 (CH_2), 115.2 (C), 112.0 (C), 76.6 (CH), 62.2 (CH_2), 58.7 (CH_2), 53.6 (CH_2), 49.0 (CH_2), 48.1 (CH), 35.5 (CH_2), 26.7 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{18}H_{25}N_8OS$ (MH^+) Calcd 401.1872, found 401.1874.

(3R,4S)-1-((4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(((3-(1-((Z)-prop-1-en-1-yl)-1H-1,2,3-triazol-4-yl)propyl)thio)methyl)pyrrolidin-3-ol (28).

Boc deprotection of **20** (144 mg, 377 µmol) was carried out as described in the General Synthetic Procedures. (3*R*,4*S*)-4-(((3-(1-((*Z*)-Prop-1-en-1-yl)-1H-1,2,3-triazol-4-yl)propyl)-thio)methyl)pyrrolidin-3-ol hydrochloride was obtained as pale oil (101 mg, 317 µmol, 84%). The material showed sufficient purity by NMR and was used in the next step without further purification. ^{1}H NMR (CD_3OD center line 3.31): δ 7.74 (s, 1H), 6.07 (ddt, *J*=16.4, 10.2, 6.0 Hz, 1H), 5.31 (dq, *J*=10.2, 1.2 Hz, 1H), 5.25 (dq, *J*=17.0, 1.4 Hz, 1H), 4.99 (dt, *J*=6.1, 1.4 Hz, 2H), 4.24 (ddd, *J*=3.1, 5.3, 3.1 Hz, 1H), 3.49 (dd, *J*=11.8, 7.6 Hz, 1H), 3.32-3.28 (m, 1H), 3.07 (dd, *J*=12.3, 2.8 Hz, 1H), 3.03 (dd, *J*=11.9, 5.5 Hz, 1H), 2.82 (t, *J*=7.6 Hz, 2H), 2.71 (dd, *J*=13.2, 6.6 Hz, 1H), 2.61 (t, *J*=7.1 Hz, 2H), 2.49 (dd, *J*=13.1, 8.8 Hz, 1H), 2.40-2.33 (m, 1H), 196 (pent, *J*=7.4 Hz, 2H). ^{13}C NMR (CD_3OD center line 49.0): δ 148.5 (C), 133.3 (CH), 123.4 (CH), 119.7 (CH_2), 75.4 (CH), 53.5 (CH_2), 53.2 (CH_2), 50.0 (CH_2), 48.0 (CH), 33.8 (CH_2), 32.2 (CH_2), 30.3 (CH_2), 25.1 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{13}H_{23}N_4OS$ (MH^+) Calcd 283.1593, found 283.1594. Mannich coupling of this material (101 mg, 0.317 mmol) and 9-deaza-adenine (60 mg, 0.45 mmol) was carried out as described in the General Synthetic Procedures in water (3 mL) and ethanol (3 mL) with formaldehyde (aq., 37 wt%, 34 mg, 0.42 mmol) in the microwave at 70 °C with a reaction time of 2 h. Product **28** (37 mg, 86 µmol, 27%) was obtained after purification by column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→30%). ^{1}H NMR (CD_3OD center line 3.31): δ 8.16 (s, 1H), 7.70 (s, 1H), 7.50 (s, 1H), 6.05 (ddt, *J*=16.7, 10.6, 6.0 Hz, 1H), 5.29 (dq, *J*=10.4, 1.2 Hz, 1H), 5.22 (dq, *J*=17.0, 1.4 Hz, 1H), 4.97 (dt, *J*=6.0, 1.4 Hz, 2H), 3.97 (ddd, *J*=4.3, 6.2, 4.3 Hz, 1H), 3.88 (d, *J*=13.4 Hz, 1H), 3.83 (d, *J*=13.5 Hz, 1H), 3.07 (dd, *J*=9.7, 7.9 Hz, 1H), 2.88 (dd, *J*=10.5, 6.4 Hz, 1H), 2.78 (t, *J*=7.5 Hz, 2H), 2.75-2.67 (m, 2H), 2.53 (td, *J*=7.3, 1.9 Hz, 2H), 2.49 (dd, *J*=12.7, 9.0 Hz, 1H), 2.41 (dd, *J*=10.0, 7.0 Hz, 1H), 2.21-2.14 (m, 1H), 1.91 (pent, *J*=7.3 Hz, 2H). ^{13}C NMR (CD_3OD center line 49.0): δ 152.1

(C), 151.1 (CH), 148.6 (C), 147.0 (C), 133.3 (CH), 130.2 (CH), 123.3 (CH), 119.7 (CH_2), 115.2 (C), 112.1 (C), 76.7 (CH), 62.2 (CH_2), 58.8 (CH_2), 53.5 (CH_2), 49.0 (CH_2), 48.5 (CH), 35.6 (CH_2), 32.3 (CH_2), 30.3 (CH_2), 25.2 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{20}H_{29}N_8OS$ (MH^+) Calcd 429.2185, found 429.2189.

(3R,4S)-1-((4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-((((1-butyl-1H-1,2,3-triazol-4-yl)methyl)thio)methyl)pyrrolidin-3-ol (29).

Boc deprotection of **21** (133 mg, 0.346 mmol) was carried out as described in the General Synthetic Procedures. (3*R*,4*S*)-4-((((1-Butyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)methyl)-pyrrolidin-3-ol hydrochloride was obtained as pale oil (101 mg, 330 µmol, 95%). The material was used in the next step without further purification. ^{1}H NMR (CD_3OD center line 3.31): δ 7.93 (s, 1H), 4.39 (t, *J*=7.1 Hz, 2H), 4.26 (ddd, *J*=3.0, 5.4, 3.0 Hz, 1H), 3.68 (s, 2H), 3.56 (dd, *J*=11.9, 7.0 Hz, 1H), 3.37 (dd, *J*=12.4, 4.8 Hz, 1H), 3.15 (dd, *J*=12.5, 2.9 Hz, 1H) overlaps with 3.12 (dd, *J*=11.8, 4.7 Hz, 1H), 2.70 (dd, *J*=12.8, 6.3 Hz, 1H), 2.52 (dd, *J*=13.0, 8.8 Hz, 1H) overlaps with 2.50-2.43 (m, 1H), 1.88 (pent, *J*=7.3 Hz, 2H), 1.34 (sext, *J*=7.5 Hz, 2H), 0.96 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (CD_3OD center line 49.0): δ 146.3 (C), 124.2 (CH), 74.8 (CH), 52.8 (CH_2), 51.2 (CH_2), 49.6 (CH_2), 47.3 (CH), 33.4 (CH_2), 33.3 (CH_2), 26.5 (CH_2), 20.7 (CH_2), 13.8 (CH_3). MS: ESI-HRMS (TOF) *m/z* for $C_{12}H_{22}NONaS$ (MNa^+) Calcd 293.1412, found293.1407. Mannich coupling of this material (101 mg, 330 µmol) and 9-deaza-adenine (66 mg, 0.49 mmol) was carried out as described in the General Synthetic Procedures in water (3 mL) and ethanol (3 mL) with formaldehyde (aq., 37 wt%, 38 mg, 0.47 mmol) in the microwave at 70 °C with a reaction time of 2 h. Product **29** (81 mg, 0.19 mmol, 58%) was obtained after purification by column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→30%). ^{1}H NMR (CD_3OD center line 3.31): δ 8.19 (s, 1H), 7.87 (s, 1H), 7.51 (s, 1H), 4.36 (t, *J*=7.1 Hz, 2H), 4.02-3.83 (bm, 3H), 3.78 (s, 2H), 3.15-.06 (bm, 1H), 2.96-2.86 (bm, 1H), 2.76-2.66 (bm, 2H), 2.55-2.40 (bm, 2H), 2.26-2.17 (bm, 1H), 1.86 (pent,

J=7.3 Hz, 2H), 1.31 (sext, *J*=7.5 Hz, 2H), 0.94 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (CD_3OD center line 49.0): δ 152.1 (C), 151.1 (CH), 147.0 (C), 146.6 (C), 130.3 (CH), 124.2 (CH), 115.4 (C), 111.8 (C), 76.6 (CH), 62.1 (CH_2), 58.7 (CH_2), 51.1 (CH_2), 49.0 (CH_2), 48.1 (CH), 35.4 (CH_2), 33.3 (CH_2), 26.7 (CH_2), 20.6 (CH_2), 13.7 (CH_2). MS: ESI-HRMS (TOF) *m/z* for $C_{19}H_{29}N_8OS$ (MH^+) Calcd 417.2185, found 417.2179.

(3R,4S)-1-((4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(((3-(1-butyl-1H-1,2,3-triazol-4-yl)propyl)thio)methyl)pyrrolidin-3-ol (30).

Boc deprotection of **22** (95 mg, 0.238 mmol) was carried out as described in the General Synthetic Procedures. (3*R*,4*S*)-4-(((3-(1-Butyl-1*H*-1,2,3-triazol-4-yl)propyl)thio)methyl)-pyrrolidin-3-ol hydrochloride was obtained as pale oil (69 mg, 0.21 mmol, 87%). The material was used in the next step without further purification. ^{1}H NMR (CD_3OD center line 3.31): δ = 7.75 (s, 1H), 4.36 (t, *J*=7.1 Hz, 2H), 4.12 (ddd, *J*=3.3, 5.4, 3.3 Hz, 1H), 3.33 (dd, *J*=10.5, 2.9 Hz, 1H) overlaps with solvent, 3.12 (dd, *J*=12.1, 5.3 Hz, 1H), 2.88 (dd, *J*=12.2, 3.2 Hz, 1H), 2.83-2.77 (m, 3H), 2.69 (dd, *J*=12.9, 6.7 Hz, 1H), 2.59 (t, *J*=7.2 Hz, 2H), 2.47 (dd, *J*=13.0, 8.7 Hz, 1H), 2.27-2.19 (m, 1H), 1.96 (pent, *J*=7.4 Hz, 2H), 1.87 (pent, *J*=7.3 Hz, 2H), 0.96 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (CD_3OD center line 49.0): δ = 148.3 (C), 123.3 (CH), 76.8 (CH), 54.2 (CH_2), 51.0 (CH_2), 50.9 (CH_2), 48.7 (CH), 34.5 (CH_2), 33.3 (CH_2), 32.3 (CH_2), 30.3 (CH_2), 25.2 (CH_2), 20.6 (CH_2), 13.7 (CH_3). MS: ESI-HRMS (TOF) *m/z* for $C_{14}H_{27}N_4OS$ (MH^+) Calcd 299.1906, found 299.1897. Mannich coupling of this material (51 mg, 0.15 mmol) and 9-deaza-adenine (29 mg, 0.22 mmol) was carried out as described in the General Synthetic Procedures in water (2 mL) and ethanol (2 mL) with formaldehyde (aq., 37 wt%, 18 mg, 0.22 mmol) in the microwave at 70 °C with a reaction time of 2 h. Product **30** (25 mg, 56 µmol, 37%) was obtained after purification by column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→30%). ^{1}H NMR (CD_3OD center line 3.31): δ 8.16 (s, 1H), 7.72 (s, 1H), 7.50 (s, 1H), 4.34 (t, *J*=7.1 Hz, 2H), 3.96 (ddd, *J*=4.2, 6.4,

4.2 Hz, 1H), 3.86 (d, *J*=13.5 Hz, 1H), 3.81 (d, *J*=13.5 Hz, 1H), 3.05 (dd, *J*=9.9, 8.0 Hz, 1H), 2.86 (dd, *J*=10.3, 4.2 Hz, 1H), 2.78 (t, *J*=7.4 Hz, 2H), 2.72 (dd, *J*=12.8, 6.2 Hz, 1H), 2.67 (dd, *J*=10.3, 4.2 Hz, 1H), 2.53 (td, *J*=7.2, 2.1 Hz, 2H), 2.49 (dd, *J*=12.7, 9.2 Hz, 1H), 2.39 (dd, *J*=10.0, 7.0 Hz, 1H), 2.21-2.13 (m, 1H), 1.92 (pent, *J*=7.4 Hz, 2H), 1.85 (pent, *J*=7.5 Hz, 2H), 1.31 (sext, *J*=7.5 Hz, 2H), 0.94 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (CD_3OD center line 49.0): δ 152.1 (C), 151.0 (CH), 148.3 (C), 147.0 (C), 130.1 (CH), 123.3 (CH), 115.1 (C), 112.4 (C), 76.8 (CH), 62.3 (CH_2), 58.8 (CH_2), 51.0 (CH_2), 48.9 (CH_2), 48.6 (CH), 35.7 (CH_2), 33.3 (CH_2), 32.3 (CH_2), 30.3 (CH_2), 25.2 (CH_2), 20.6 (CH_2), 13.7 (CH_3). MS: ESI-HRMS (TOF) *m/z* for $C_{21}H_{32}N_8ONaS$ (MNa^+) Calcd 467.2317, found 467.2312.

(3R,4S)-1-((4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-((((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)methyl)pyrrolidin-3-ol (31)

Boc deprotection of **23** (90 mg, 0.22 mmol) was carried out as described in the General Synthetic Procedures. (3R,4S)-4-((((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)methyl)-pyrrolidin-3-ol hydrochloride was obtained as pale oil (65 mg, 0.19 mmol, 87%) and was used in the next step without further purification. ^{1}H NMR (CD_3OD center line 3.31): δ 7.91 (s, 1H), 7.40-7.29 (m, 5H), 5.58 (s, 2H), 4.26-4.23 (m, 1H), 3.84 (s, 2H), 3.53 (dd, J=12.2, 7.4 Hz, 1H), 3.34 (dd, J=12.4, 2.0 Hz, 1H), 3.14 (dd, J=12.4, 2.0 Hz, 1H), 3.10 (dd, J=12.2, 5.0 Hz, 1H), 2.67 (dd, J=13.0, 6.4 Hz, 1H), 2.53-2.41 (m, 2H). ^{13}C NMR (CD_3OD center line 49.0): δ 146.8 (C), 136.8 (C), 130.1 (CH), 129.6 (CH), 129.2 (CH), 124.3 (CH), 74.8 (CH), 55.0 (CH_2), 52.8 (CH_2), 49.5 (CH_2), 47.3 (CH), 33.3 (CH_2), 26.5 (CH_2). MS: ESI-HRMS (TOF) m/z for $C_{15}H_{21}N_4OS$ (MH^+) Calcd 305.1436, found 305.1443. Mannich coupling of this material (61 mg, 0.18 mmol), and 9-deaza-adenine (33 mg, 0.25 mmol) was carried out as described in the General Synthetic Procedures in water (1.5 mL) and ethanol (1.5 mL) with formaldehyde (aq., 37 wt%, 22 mg, 0.27 mmol) in the microwave at 70 °C with a reaction time of 2 h. Product **31** (48 mg, 0.11 mmol, 61%) was obtained after purification by column

chromatography CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→20%. ^{1}H NMR (CD_3OD center line 3.31): δ 8.16 (s, 1H), 7.83 (s, 1H), 7.49 (s, 1H), 7.38-7.26 (m, 5H), 5.54 (s, 2H), 3.94 (ddd, J=4.2, 8.1, 4.2 Hz, 1H), 3.86 (d, J=13.5 Hz, 1H), 3.82 (d, J=13.5 Hz, 1H), 3.76 (s, 2H), 3.04 (dd, J=9.8, 8.1 Hz, 1H), 2.85 (dd, J=10.5, 6.4 Hz, 1H), 2.70-2.64 (m, 2H), 2.47 (dd, J=12.8, 8.8 Hz, 1H), 2.36 (dd, J=10.0, 7.1 Hz, 1H), 2.22-2.14 (m, 1H). ^{13}C NMR (CD_3OD center line 49.0): δ 152.1 (C), 151.1 (CH), 147.1 (C), 147.0 (C), 136.8 (C), 130.2 (CH), 130.0 (CH), 129.6 (CH), 129.1 (CH), 124.2 (CH), 115.2 (C), 112.0 (C), 76.6 (CH), 62.2 (CH_2), 58.7 (CH_2), 55.0 (CH_2), 49.0 (CH_2), 48.1 (CH), 35.5 (CH_2), 26.6 (CH_2). MS: ESI-HRMS (TOF) m/z for $C_{22}H_{27}N_8OS$ (MH^+) Calcd 451.2029, found451.2030.

(3R,4S)-1-((4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(((3-(1-benzyl-1H-1,2,3-triazol-4-yl)propyl)thio)methyl)pyrrolidin-3-ol (32).

Boc deprotection of **24** (193 mg, 446 µmol) was carried out as described in the General Synthetic Procedures. (3R,4S)-4-(((3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propyl)thio)methyl)-pyrrolidin-3-ol hydrochloride was obtained as pale oil (145 mg, 394 µmol, 88%) and was used in the next step without further purification. ^{1}H NMR (CD_3OD center line 3.31): δ 7.76 (s, 1H), 7.39-7.30 (m, 5H), 5.55 (s, 2H), 4.30 (ddd, J=2.9, 5.4, 2.9 Hz, 1H), 3.58 (dd, J=12.0, 7.1 Hz, 1H), 3.40 (dd, J=12.3, 4.8 Hz, 1H), 3.21-3.15 (m, 2H), 2.80 (t, J=7.5 Hz, 2H), 2.71 (dd, J=12.7, 6.2 Hz, 1H), 2.59 (t, J=7.2 Hz, 2H), 2.49 (dd, J=12.8, 8.8 Hz, 1H), 2.46-2.40 (m, 1H), 1.94 (pent, J=7.4 Hz, 2H). ^{13}C NMR (CD_3OD center line 49.0): δ 148.7 (C), 136.9 (C), 130.0 (CH), 129.6 (CH), 129.1 (CH), 123.5 (CH), 74.6 (CH), 54.9 (CH_2), 52.7 (CH_2), 49.4 (CH_2), 47.5 (CH), 33.4 (CH_2), 32.2 (CH_2), 30.3 (CH_2), 25.2 (CH_2). MS: ESI-HRMS (TOF) m/z for $C_{17}H_{25}N_4OS$ (MH^+) Calcd 333.1749, found 33.1755. Mannich coupling of this material (140 mg, 380 µmol) and 9-deaza-adenine (68 mg, 0.51 mmol) was carried out like described above (General Synthetic Procedures) in water (3 mL) and ethanol (3 mL) with formaldehyde (aq., 37 wt%, 35 mg, 0.43 mmol) in the microwave at 70 °C with a reaction

time of 2 h. Product **32** (85 mg, 0.18 mmol 47%) was obtained after purification by column chromatography (CH_2Cl_2/ NH_3 (7 M in MeOH): 0%→30%). ^1H NMR (CD_3OD center line 3.31): δ 8.15 (s, 1H), 7.70 (s, 1H), 7.49 (s, 1H), 7.37-7.26 (m, 5H), 5.53 (s, 2H), 3.95 (ddd, J=4.1, 6.3, 4.1 Hz, 1H), 3.86 (d, J=13.5 Hz, 1H), 3.82 (d, J=13.5 Hz, 1H), 3.05 (dd, J=9.8, 8.0 Hz, 1H), 2.86 (dd, J=10.3, 6.4 Hz, 1H), 2.76 (t, J=7.5 Hz, 2H), 2.70 (dd, J=13.1, 6.2 Hz, 1H) overlaps with 2.67 (dd, J=9.4, 4.2 Hz, 1H), 2.51 (td, J=7.1, 1.4 Hz, 2H) overlaps with 2.47 (dd, J=12.8, 9.1 Hz, 1H), 2.39 (dd, J=9.8, 7.1 Hz, 1H), 2.20-2.12 (m, 1H), 1.89 (pent, J=7.3 Hz, 2H). ^{13}C NMR (CD_3OD center line 49.0): δ 152.1 (C), 151.1 (CH), 148.8 (C), 147.0 (C), 136.9 (C), 130.2 (CH), 130.0 (CH), 129.5 (CH), 129.0 (CH), 123.4 (CH), 115.2 (C), 112.3 (C), 76.7 (CH), 62.2 (CH_2), 58.8 (CH_2), 54.9 (CH_2), 49.0 (CH_2), 48.5 (CH), 35.6 (CH_2), 32.3 (CH_2), 30.2 (CH_2), 25.2 (CH_2). MS: ESI-HRMS (TOF) m/z for $C_{24}H_{30}N_8ONaS$ (MNa^+) Calcd 501.2161, found 501.2157.

Compound_ID	SMILES
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3	O=C1NC=CC(/C=C/N(C)C)=C1[N+]([O-])=O
4	O=C1NC=CC2=C1NC=C2
5	ClC1=NC=CC2=C1NC=C2
6	NC1=NC=CC2=C1NC=C2
7	O[C@H]1CNC[C@@H]1CSC
8	O[C@H]1CN(CC2=CNC3=C2C=CN=C3N)C[C@@H]1CSC
9	COC1=NC=NC2=C(C=O)N(C3OCCCC3)N=C21
10	O[C@H]1CN(CC2=C(N=CN=C3OC)C3=NN2C4OCCCC4)C[C@@H]1CSC
11	NC1=NC=NC2=C(CN3C[C@H](O)[C@@H](CSC)C3)NN=C21
12	O[C@H]1CN(C[C@@H]1CSC(C)=O)C(OC(C)(C)C)=O
13	O[C@H]1CN(C[C@@H]1CSCC#C)C(OC(C)(C)C)=O
14	O[C@H]1CN(C[C@@H]1CSCCCC#C)C(OC(C)(C)C)=O
15	NC1=NC=NC2=C1NC=C2CN3C[C@H](O)[C@@H](CSCC#C)C3
16	NC1=NC=NC2=C1NC=C2CN3C[C@H](O)[C@@H](CSCCCC#C)C3
17	O[C@H]1CN(C[C@@H]1CSCC2=CN(C)N=N2)C(OC(C)(C)C)=O
18	O[C@H]1CN(C[C@@H]1CSCCCC2=CN(C)N=N2)C(OC(C)(C)C)=O
19	O[C@H]1CN(C[C@@H]1CSCC2=CN(CC=C)N=N2)C(OC(C)(C)C)=O
20	O[C@H]1CN(C[C@@H]1CSCCCC2=CN(CC=C)N=N2)C(OC(C)(C)C)=O
21	O[C@H]1CN(C[C@@H]1CSCC2=CN(CCCC)N=N2)C(OC(C)(C)C)=O
22	O[C@H]1CN(C[C@@H]1CSCCCC2=CN(CCCC)N=N2)C(OC(C)(C)C)=O
23	O[C@H]1CN(C[C@@H]1CSCC2=CN(CC3=CC=CC=C3)N=N2)C(OC(C)(C)C)=O
24	O[C@H]1CN(C[C@@H]1CSCCCC2=CN(CC3=CC=CC=C3)N=N2)C(OC(C)(C)C)=O
25	NC1=NC=NC2=C1NC=C2CN3C[C@H](O)[C@@H](CSCC4=CN(C)N=N4)C3
26	NC1=NC=NC2=C1NC=C2CN3C[C@H](O)[C@@H](CSCCCC4=CN(C)N=N4)C3
27	NC1=NC=NC2=C1NC=C2CN3C[C@H](O)[C@@H](CSCC4=CN(CC=C)N=N4)C3
28	NC1=NC=NC2=C1NC=C2CN3C[C@H](O)[C@@H](CSCCCC4=CN(CC=C)N=N4)C3
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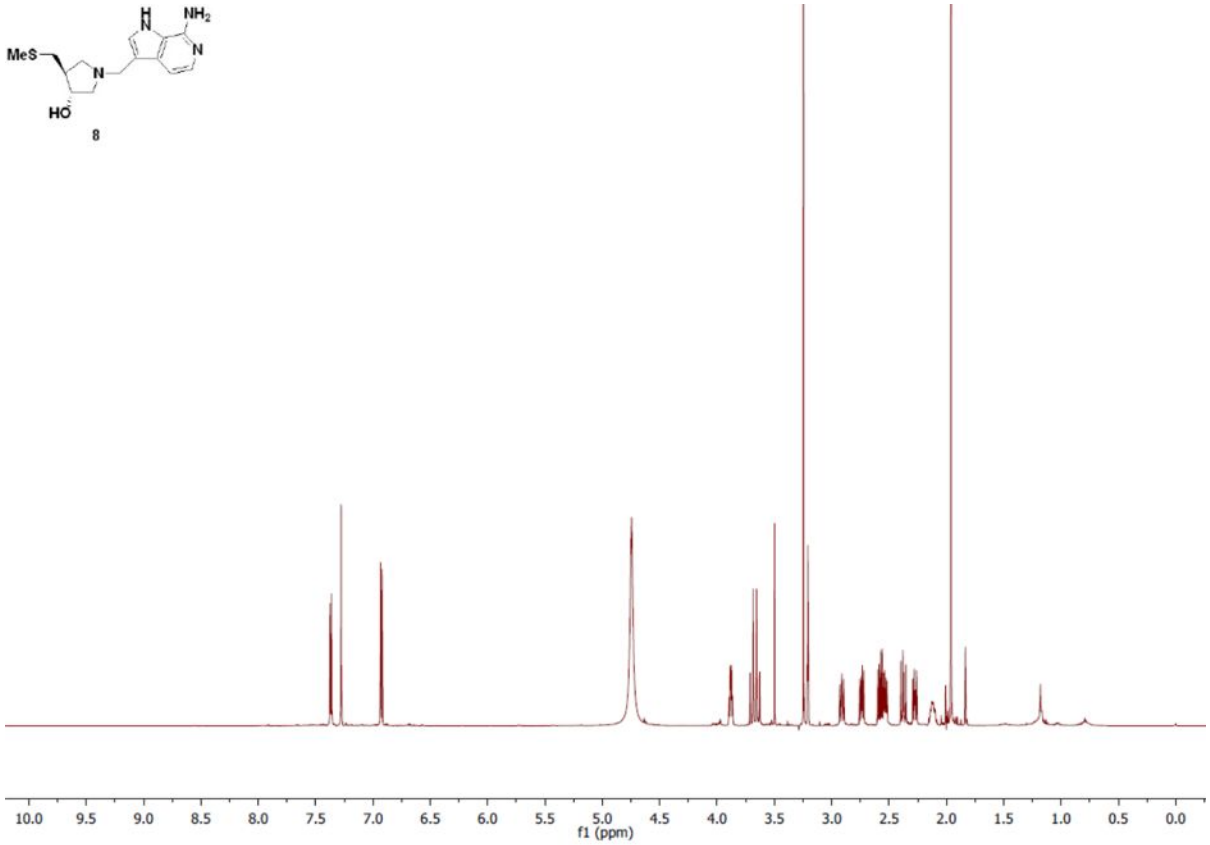
30	NC1=NC=NC2=C1NC=C2CN3C[C@H](O)[C@@H](CSCCCC4=CN(CCCC)N=N4)C3
31	NC1=NC=NC2=C1NC=C2CN3C[C@H](O)[C@@H](CSCC4=CN(CC5=CC=CC=C5)N=N4)C3
32	NC1=NC=NC2=C1NC=C2CN3C[C@H](O)[C@@H](CSCCCC4=CN(CC5=CC=CC=C5)N=N4)C3
33	NC1=NC=NC2C(CN3C[C@H](O)[C@@H](CSC4=NC=CC=N4)C3)=CNC21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N
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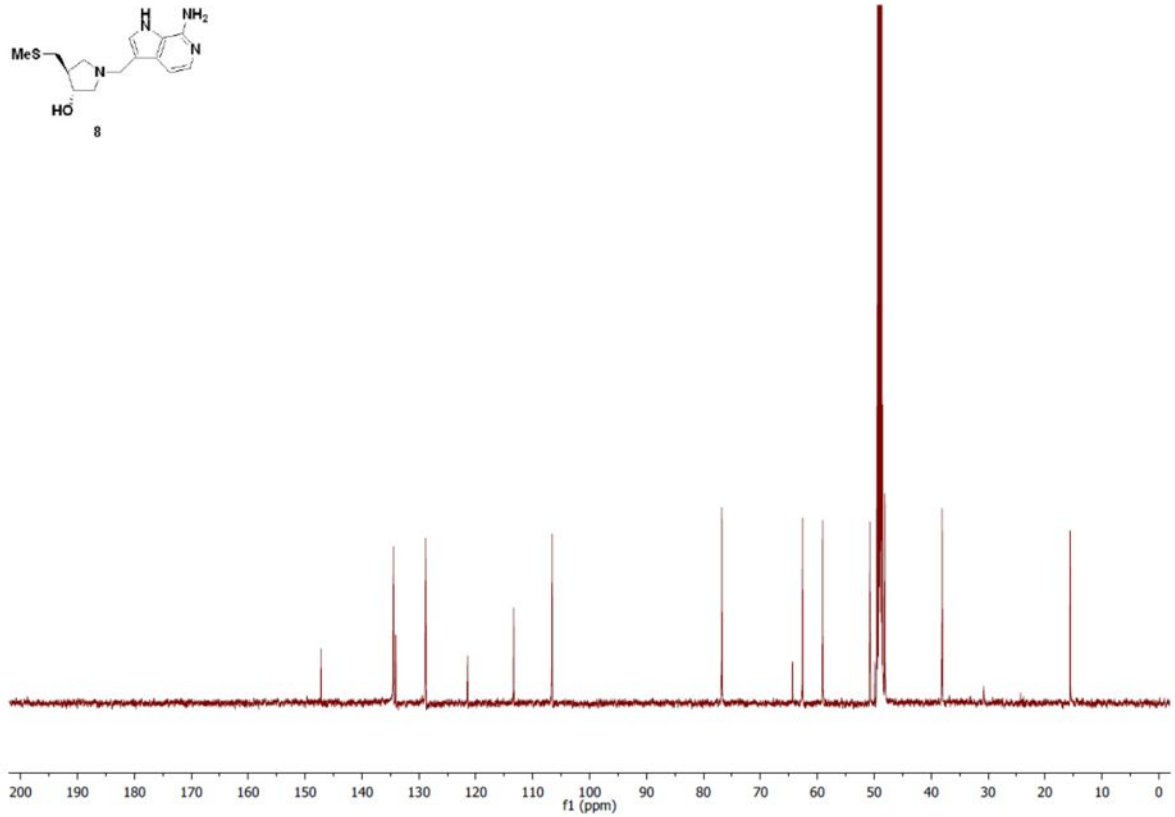
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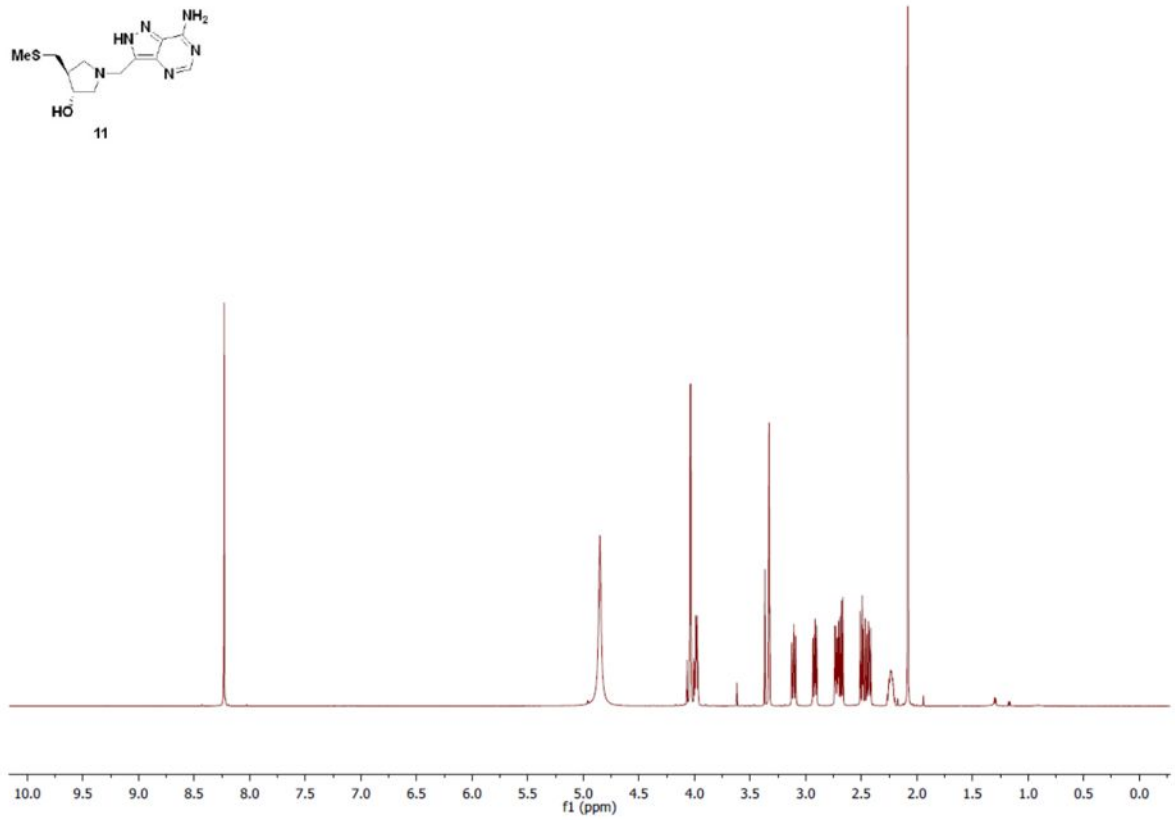
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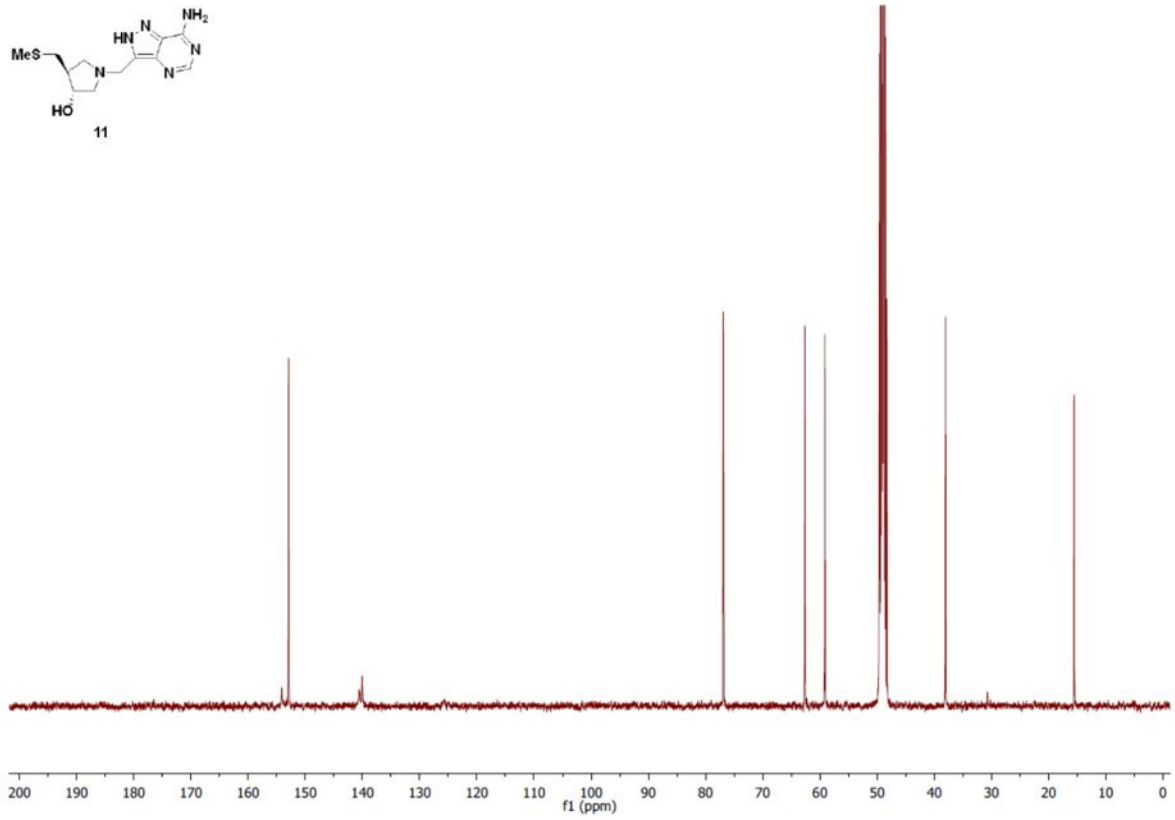
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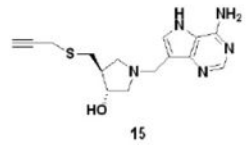

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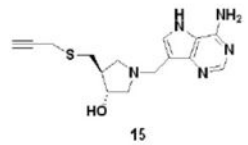

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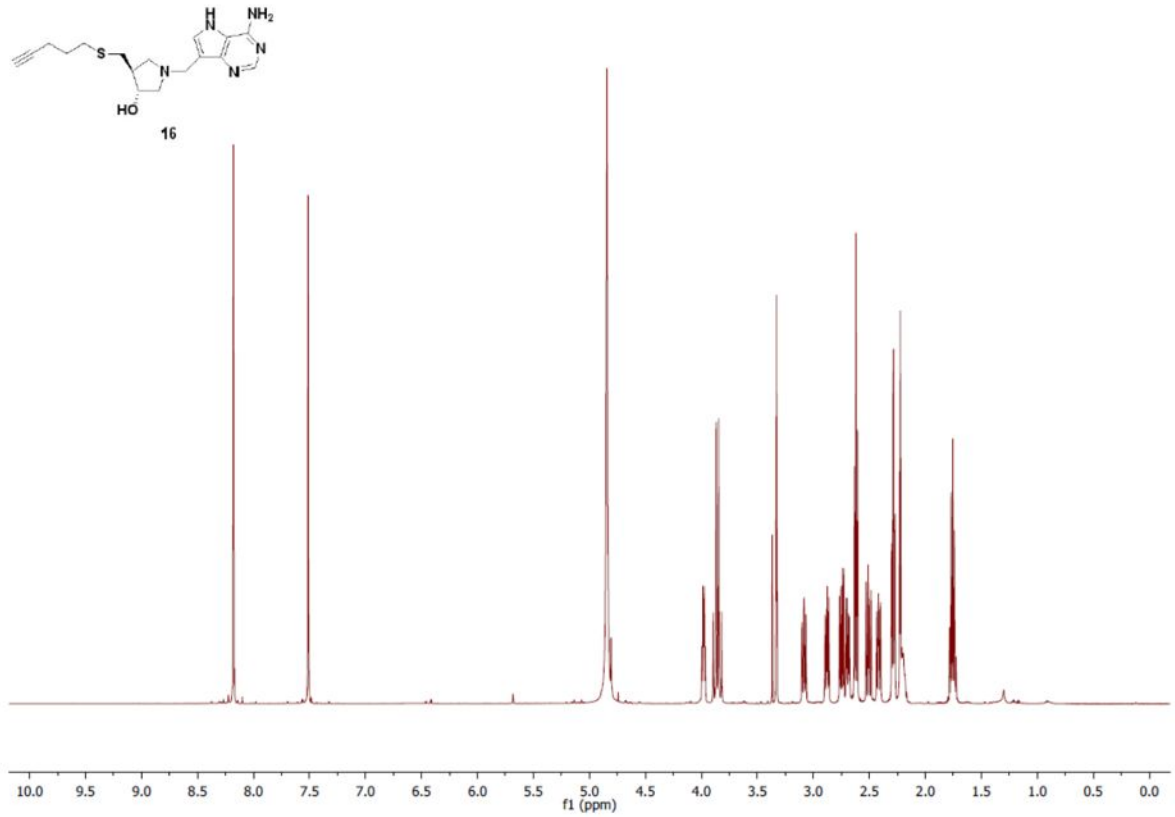
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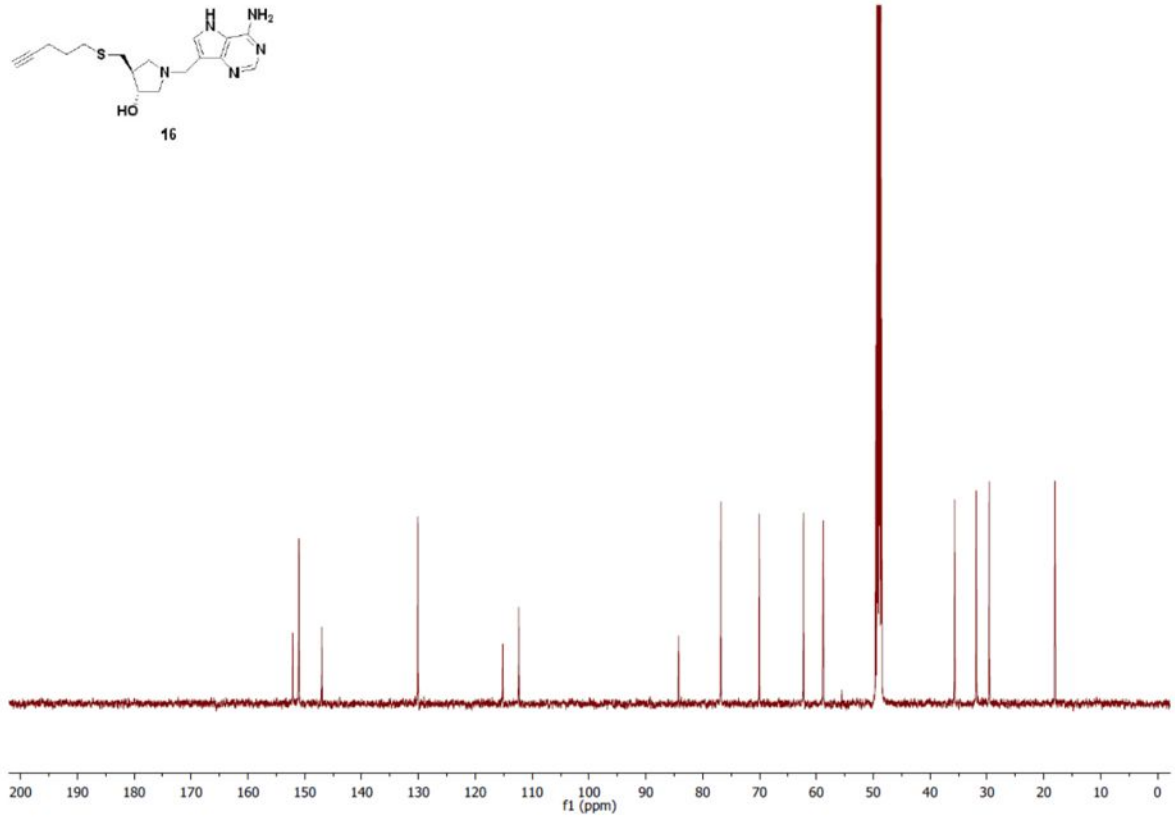
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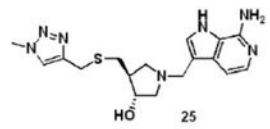
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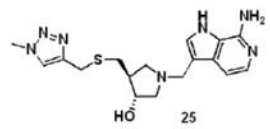
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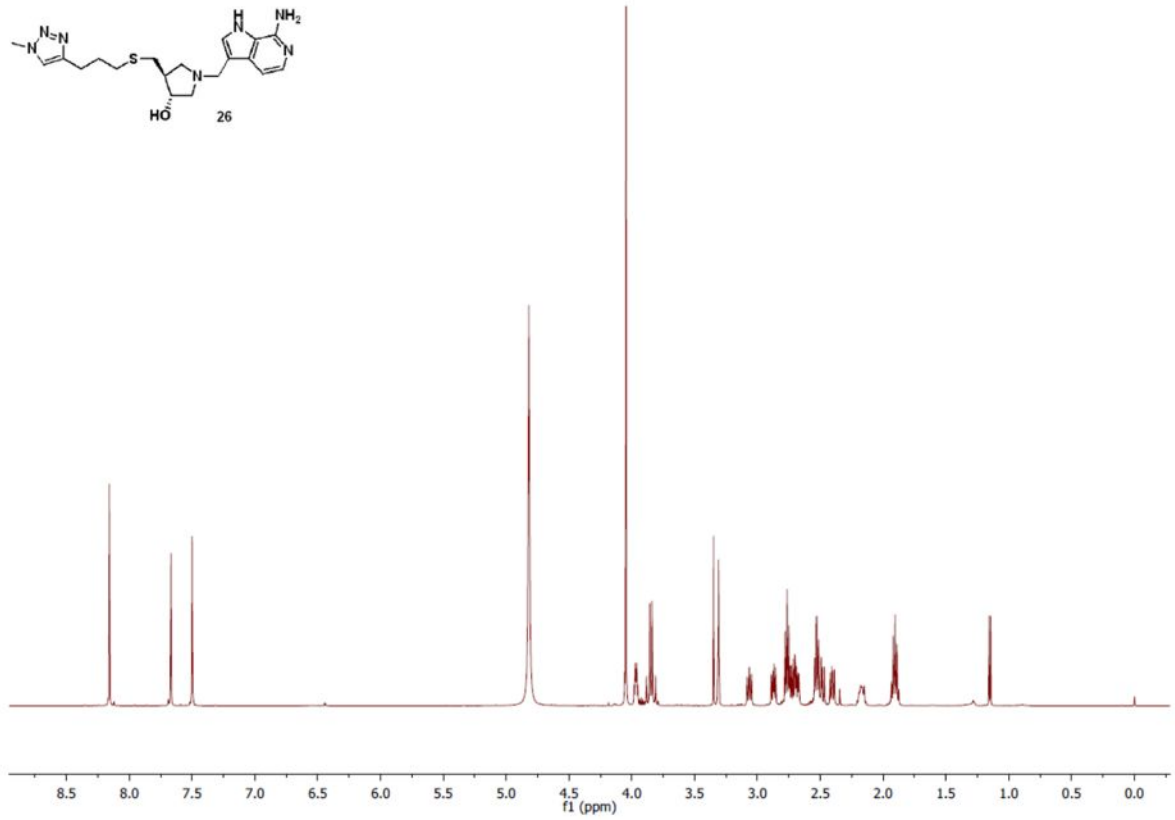
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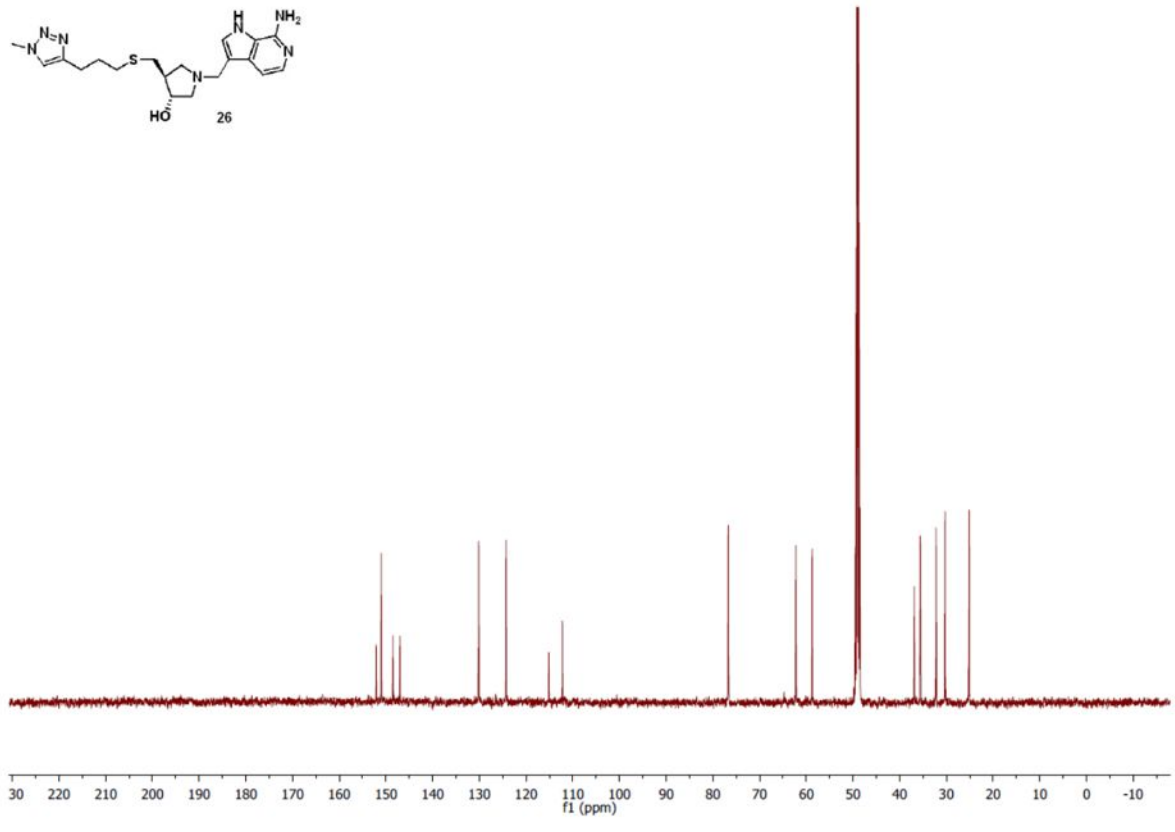
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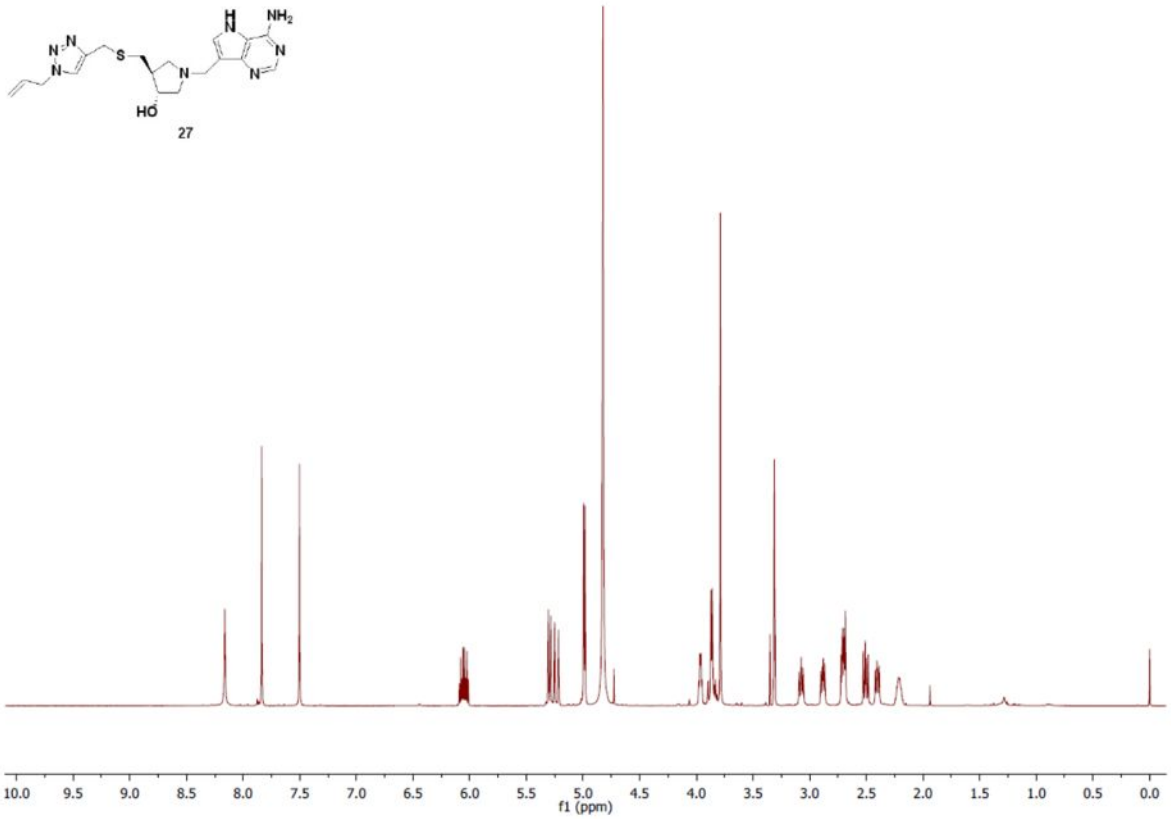
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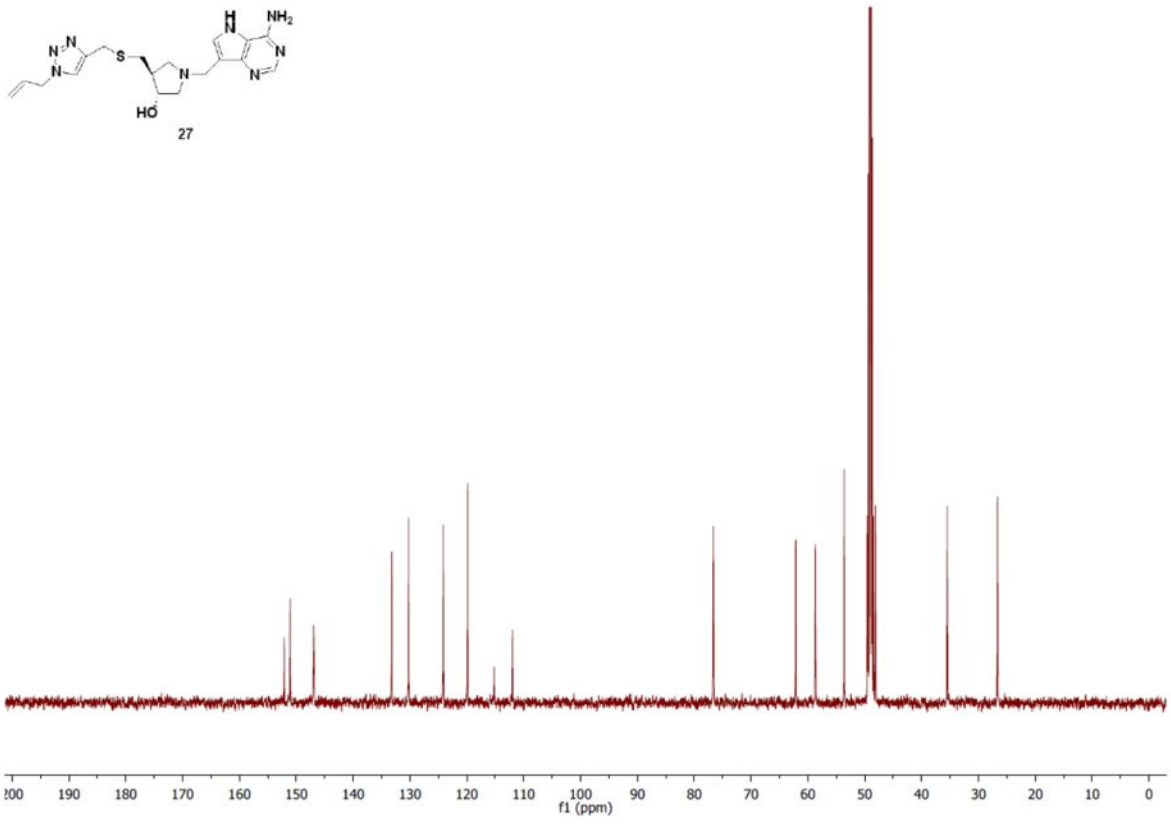
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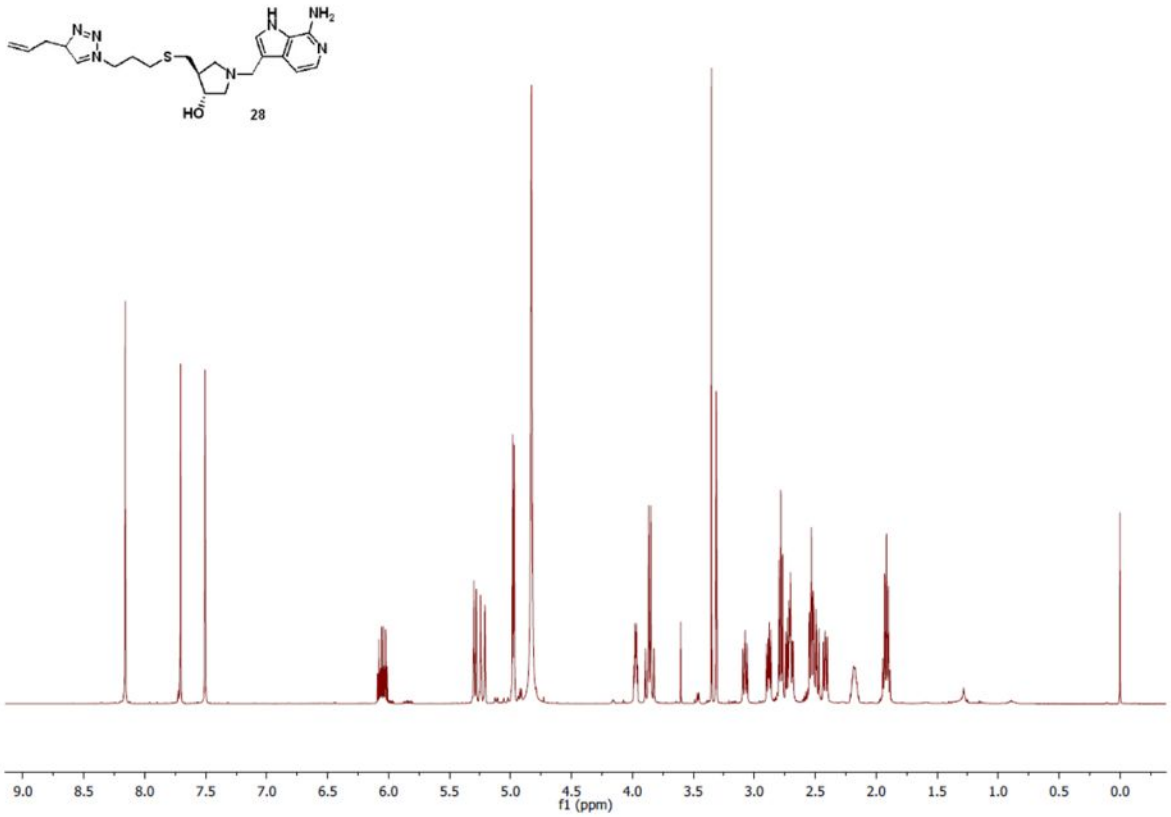
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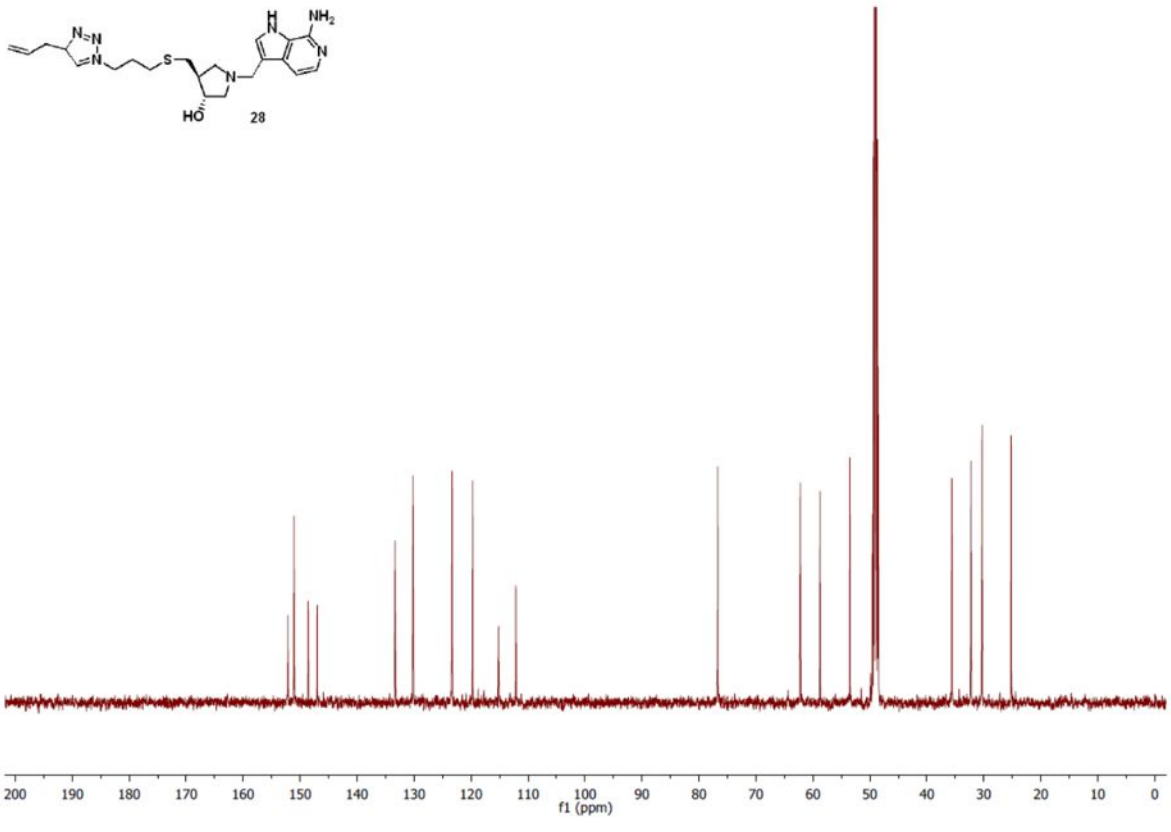
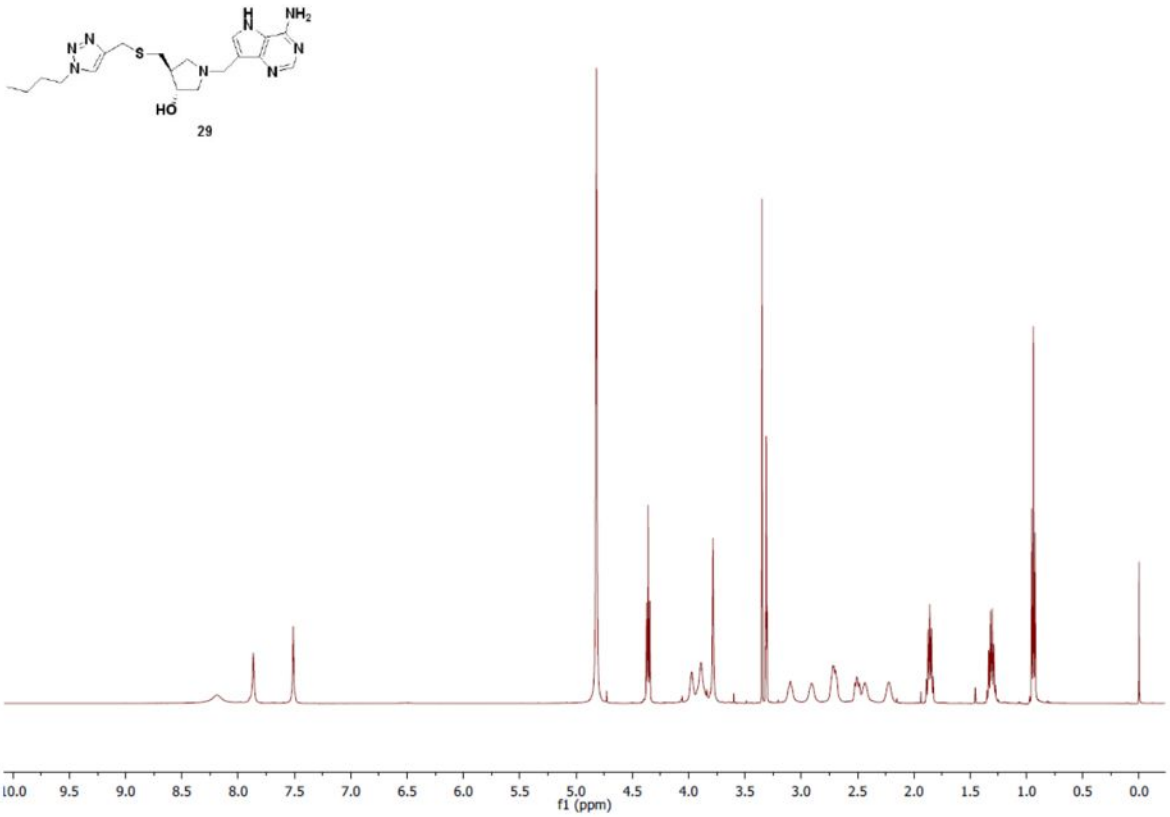
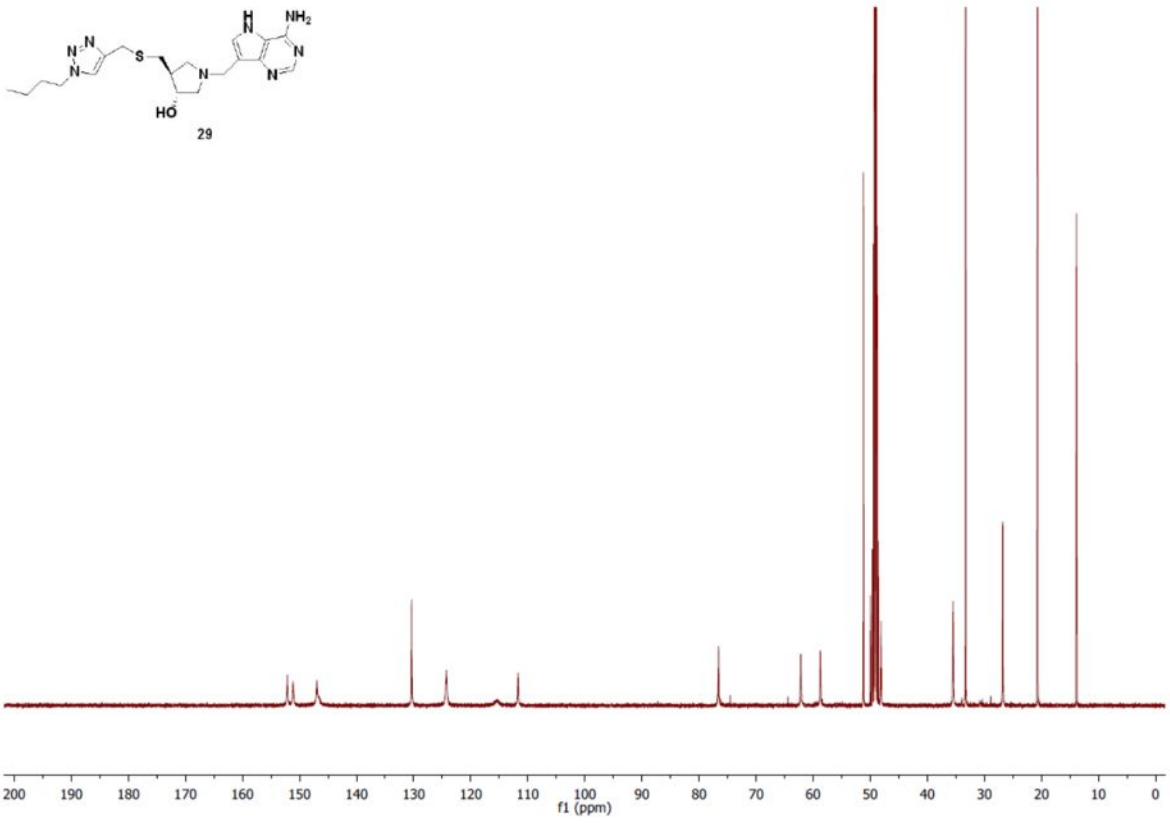
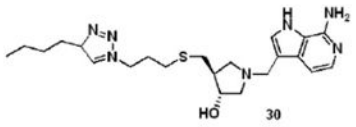
1.5
1.0
0.5
0.0
f1 (ppm)

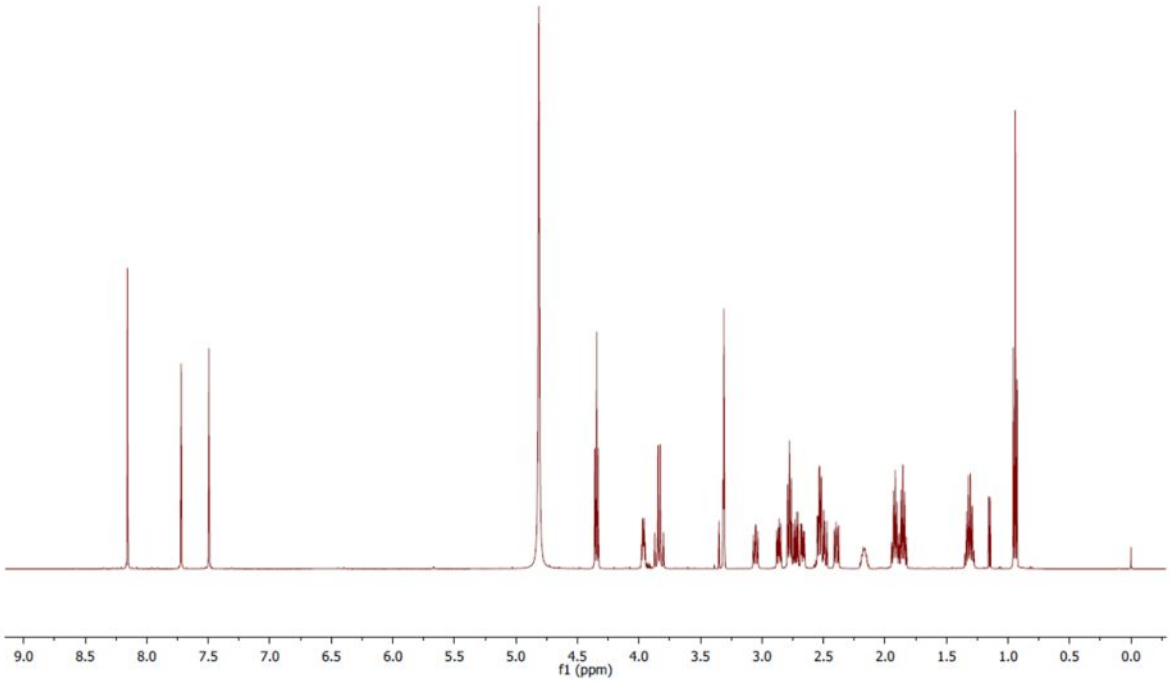

28
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

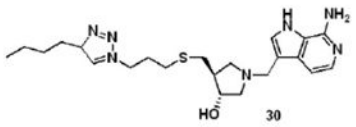

29
f1 (ppm)


29
f1 (ppm)


NH2
HO

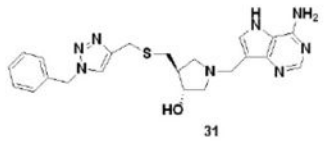
30


9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

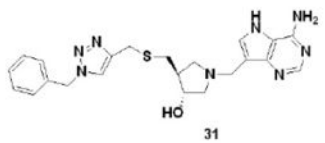

NH2
HO

30

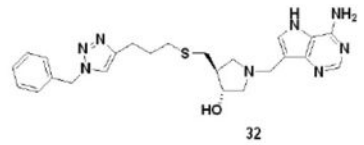
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



31

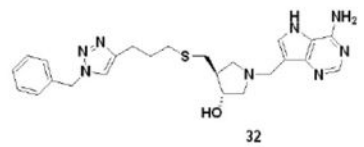


31



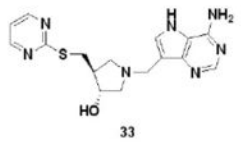
32

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

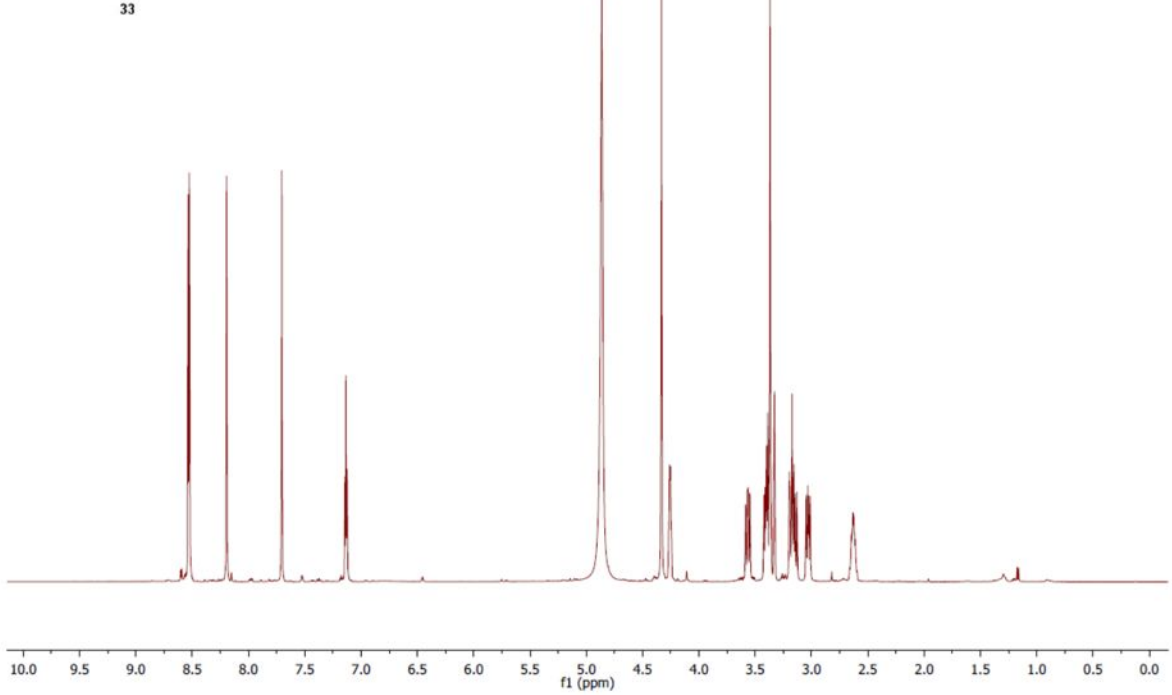


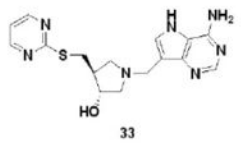
32

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



33


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



33

30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)