Supporting information

Design of reversible, cysteine-targeted Michael acceptors guided by kinetic and computational analysis

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1. Supplementary Figures

Figure S1 (related to Table 1). A. ^{1}H NMR spectrum of cyanoacrylamide **3** in 3:1 DMSO-*d*6:PBS-*d*;
B. ^{1}H NMR spectrum of cyanoacrylamide **3** upon treatment with BME-*d*6. Upon dilution, β-elimination was too fast to follow by ^{1}H NMR.

Figure S2 (related to Table 1). A. ^{1}H NMR spectrum of acrylonitrile **4** in 3:1 DMSO-*d*6:PBS-*d*; **B.** ^{1}H NMR spectrum of acrylonitrile **4** upon treatment with BME-*d*6. Upon dilution, β-elimination was too fast to follow by ^{1}H NMR.
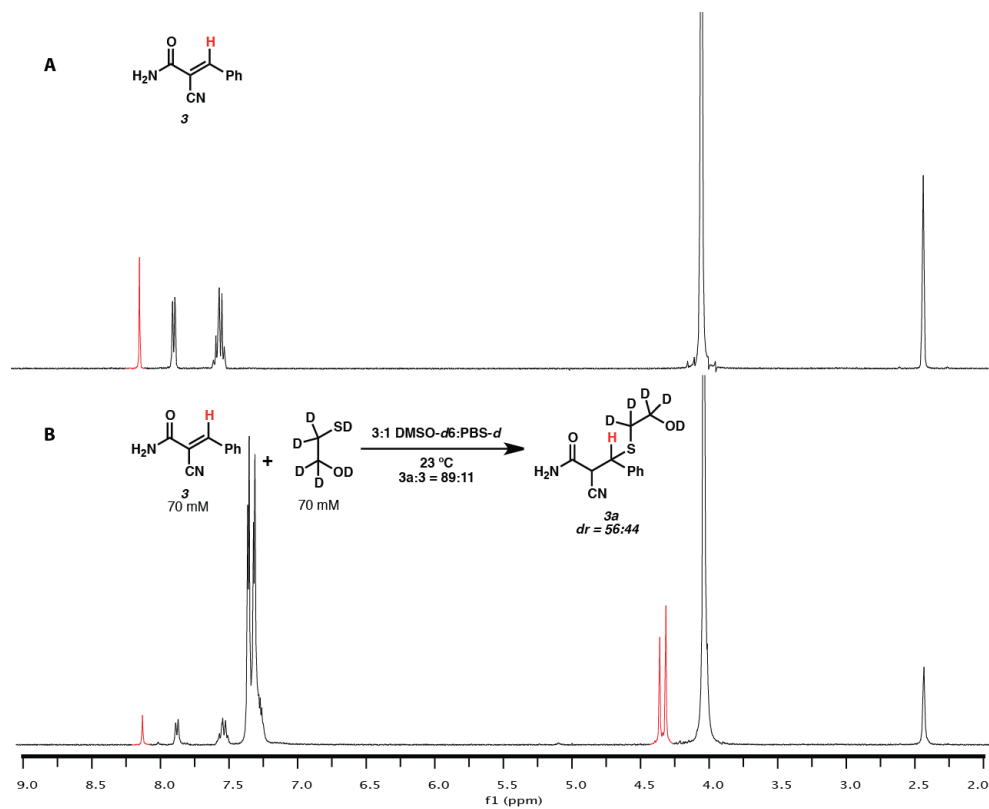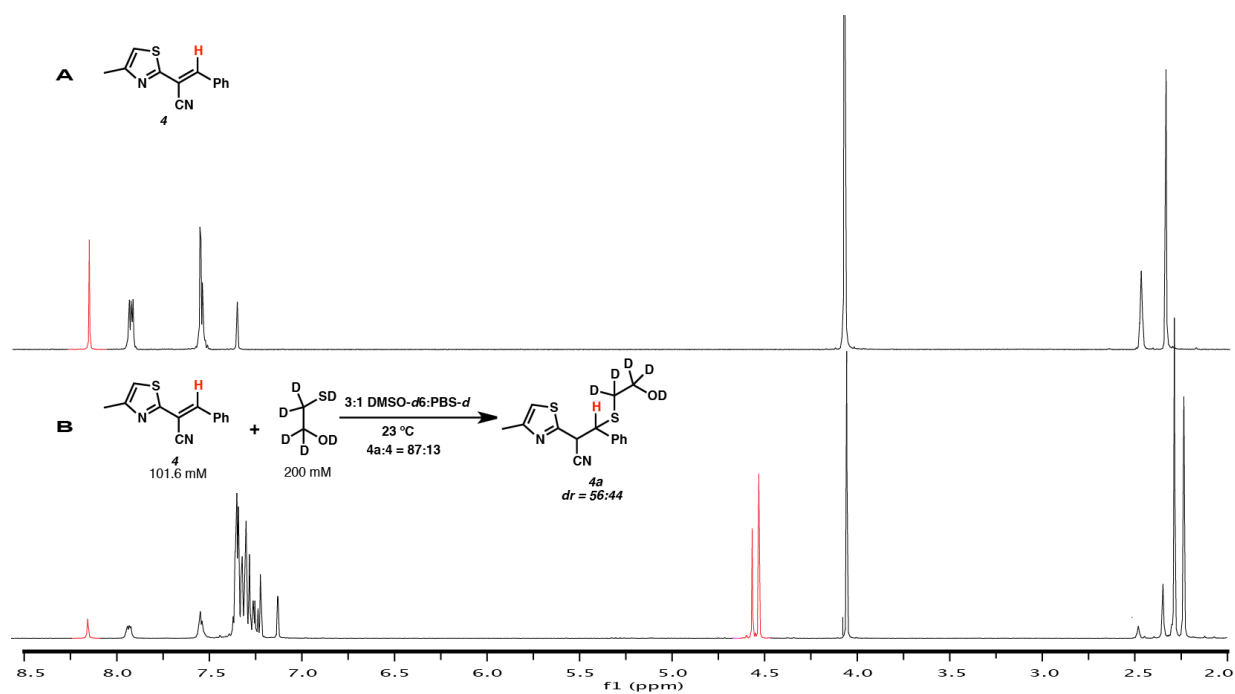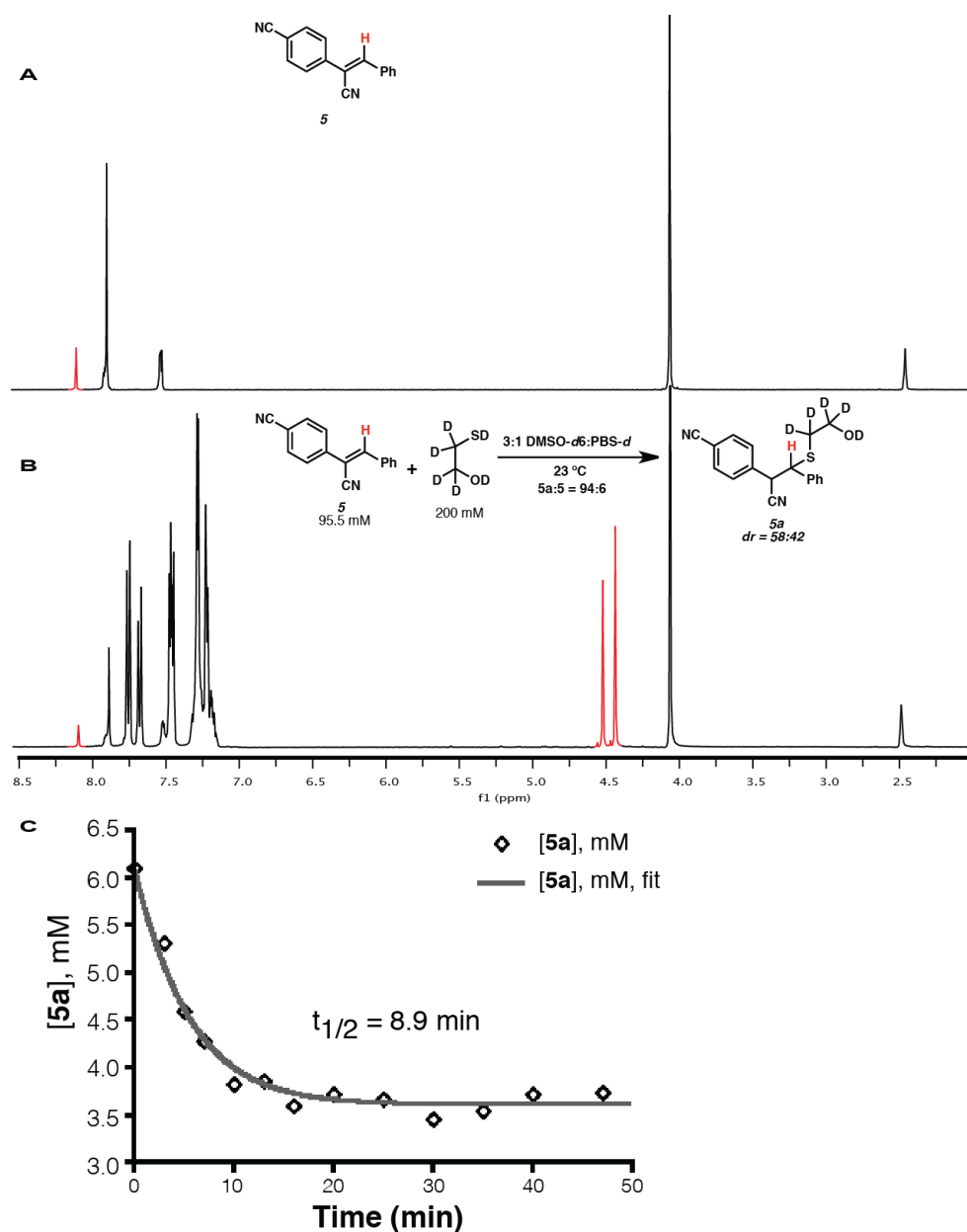
Figure S3 (related to Table 1). A. ^{1}H NMR spectrum of acrylonitrile **5** in 3:1 DMSO-*d*6:PBS-*d*; **B.** ^{1}H NMR spectrum of acrylonitrile **5** upon treatment with BME-*d*6; **C.** To acrylonitrile **5** (0.07 mmol) in 0.75 mL DMSO-*d*6 was added a solution of BME-*d*6 (0.105 mmol) in 0.25 mL PBS-*d*. The reaction mixture was maintained at room temperature for 2 hours, and the equilibrium ratio of the thioether adducts to the starting acrylonitrile was determined by ^{1}H NMR. The reaction mixture was then diluted 10-fold into DMSO-*d*6:PBS-*d* (3:1 v/v) and ^{1}H NMR spectra were recorded at multiple time points to follow the reversion of the thioether adduct to the corresponding acrylonitrile and the establishment of a new equilibrium. The concentration of the thioether adduct was determined at each time point by integration of peaks corresponding to the acrylonitrile and acrylonitrile-BME adducts (shown in red, spectra in **A** and **B**).

We analyzed the data by first estimating the dissociation equilibrium constants (K_d) for each compound from the concentrations of adduct and acrylonitrile before and after step dilution. We calculated the concentrations of free acrylonitrile, free BME, and adduct from the measured free

acrylonitrile:adduct ratio (based on ^{1}H NMR peak integration) and the known total amount of acrylonitrile and BME added to the reaction.

We then used the formula: $K_d = [A][B]/[AB]$, where A is the acrylonitrile, B is BME, and AB is the acrylonitrile-BME adduct.

In all cases, the K_d estimates from before and after step-dilution differed by less than 10%. To calculate the rate constants, we fit the dissociation time course to a simple bimolecular interaction model, using the program Berkeley Madonna (Macey and Oster).[1]

$$A \ + \ B \ \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \ AB$$
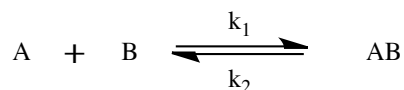
The three equations describing this model are:

$d[AB]/dt = k_1[A][B] - k_2[AB]$,

$d[A]/dt = -k_1[A][B] + k_2[AB]$,

$d[B]/dt = -k_1[A][B] + k_2[AB]$.

We further constrained the model by requiring that ratio of the dissociation and association rate constants match the estimated dissociation equilibrium constant: $k_2/k_1 = K_d$.

From the fitted data, we derived k_1 and k_2. k_2 corresponds to the first-order rate constant for the β-elimination reaction, from which $t_{1/2}$ was calculated ($0.69/k_2$).

Figure S4 (related to Table 1). A. ^{1}H NMR spectrum of acrylonitrile **6** in 3:1 DMSO-*d*6:PBS-*d*; **B.** ^{1}H NMR spectrum of acrylonitrile **6** upon treatment with BME-*d*6; **C.** The β-elimination $t_{1/2}$ was determined as described in Figure S3.

$t_{1/2} = 61.2$ min

Figure S5 (related to Table 1). A solution of thioether **7a** in DMSO (500 µM) was diluted 100-fold into PBS, pH 7.4, to afford a 5 µM solution. Aliquots of the solution were quenched by addition of an equal volume of 4% formic acid in MeCN, prior to analysis immediately and at subsequent time points by LC-MS/MS. The amount of adduct remaining at each time point was quantified and the apparent first-order rate constant was determined by fitting the data to a first-order decay curve using PRISM (4.0).

$t_{1/2} = 81.8$ min

Figure S6 (related to Table 1). A solution of thioether **8a** in DMSO (500 µM) was diluted into PBS (pH 7.4) to afford a 5 µM solution, and the apparent first-order rate constant was determined as described in Figure S5.

$t_{1/2}$ = 3482 min
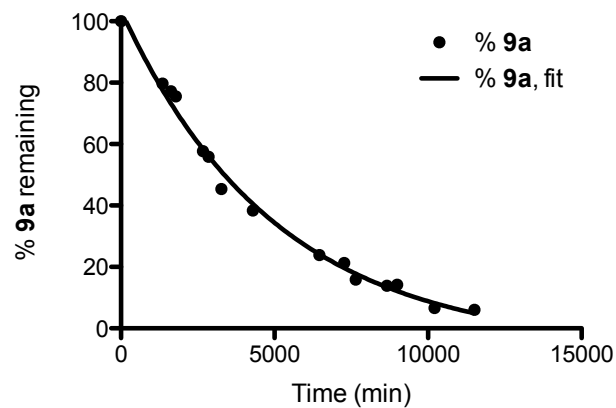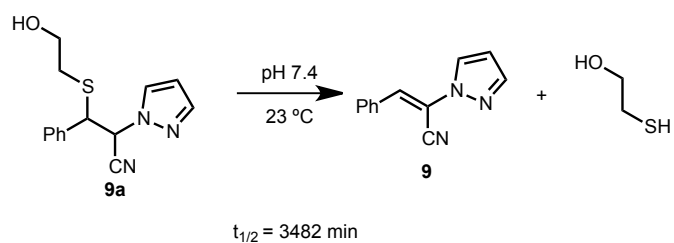
Figure S7 (related to Table 1). A solution of thioether **9a** (1:1 mixture of diastereomers) in DMSO (500 µM) was diluted into PBS (pH 7.4) to afford a 5 µM solution, and the apparent first-order rate constants were determined as described in Figure S5.
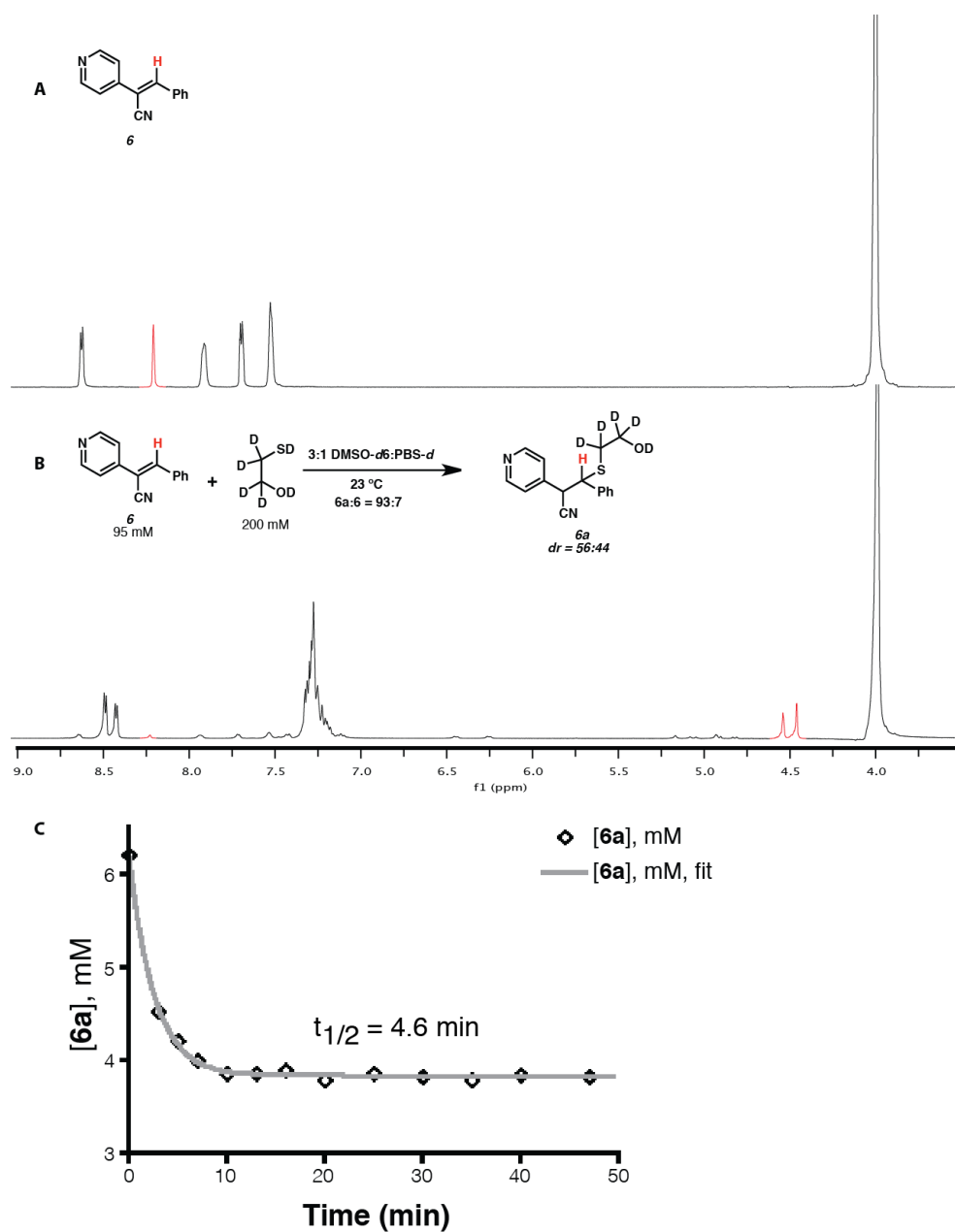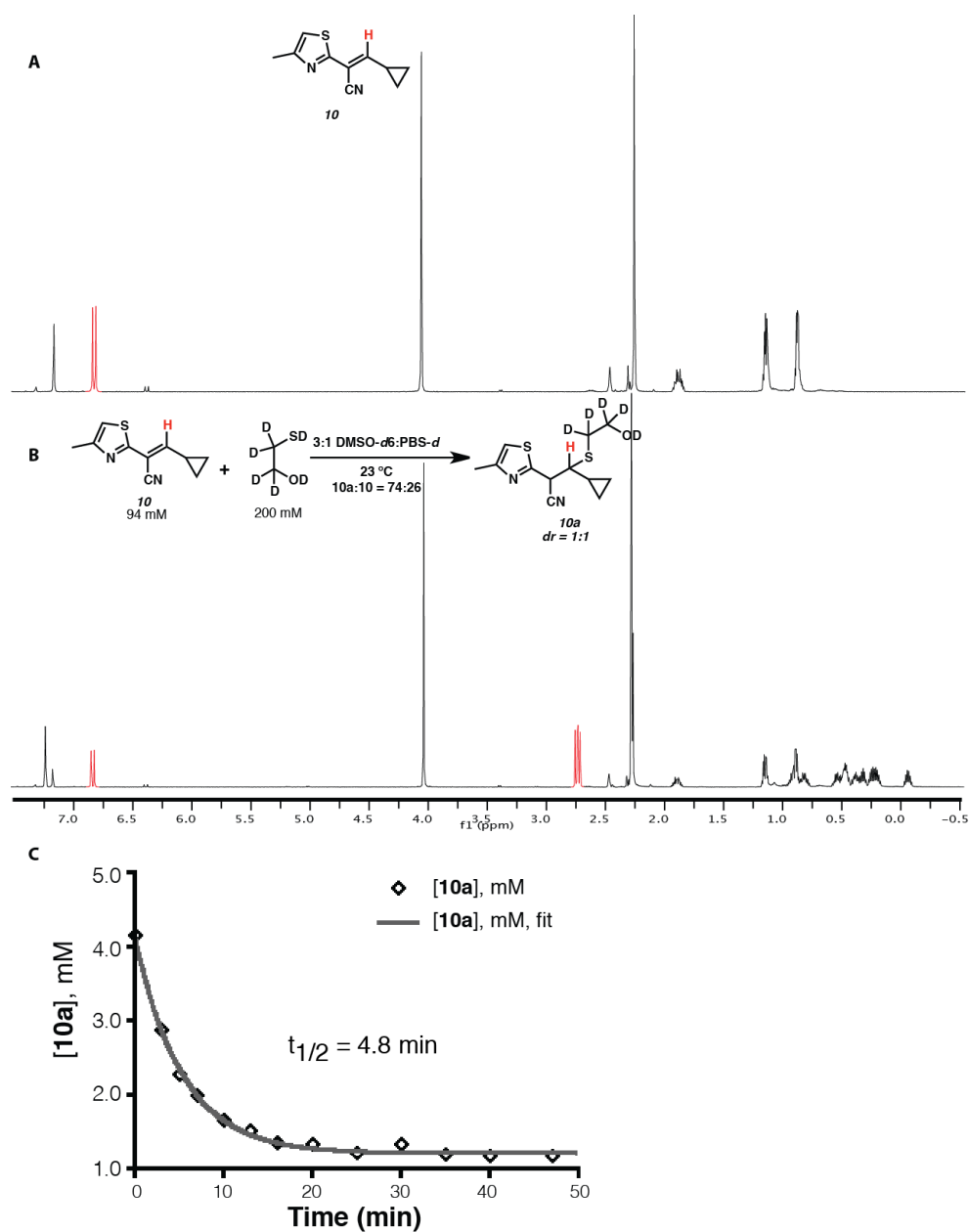
Figure S8 (related to Table 2). A. ^{1}H NMR spectrum of acrylonitrile **10** in 3:1 DMSO-*d*6:PBS-*d*; **B.** ^{1}H NMR spectrum of acrylonitrile **10** upon treatment with BME-*d*6; C. The β-elimination $t_{1/2}$ was determined as described in Figure S3.
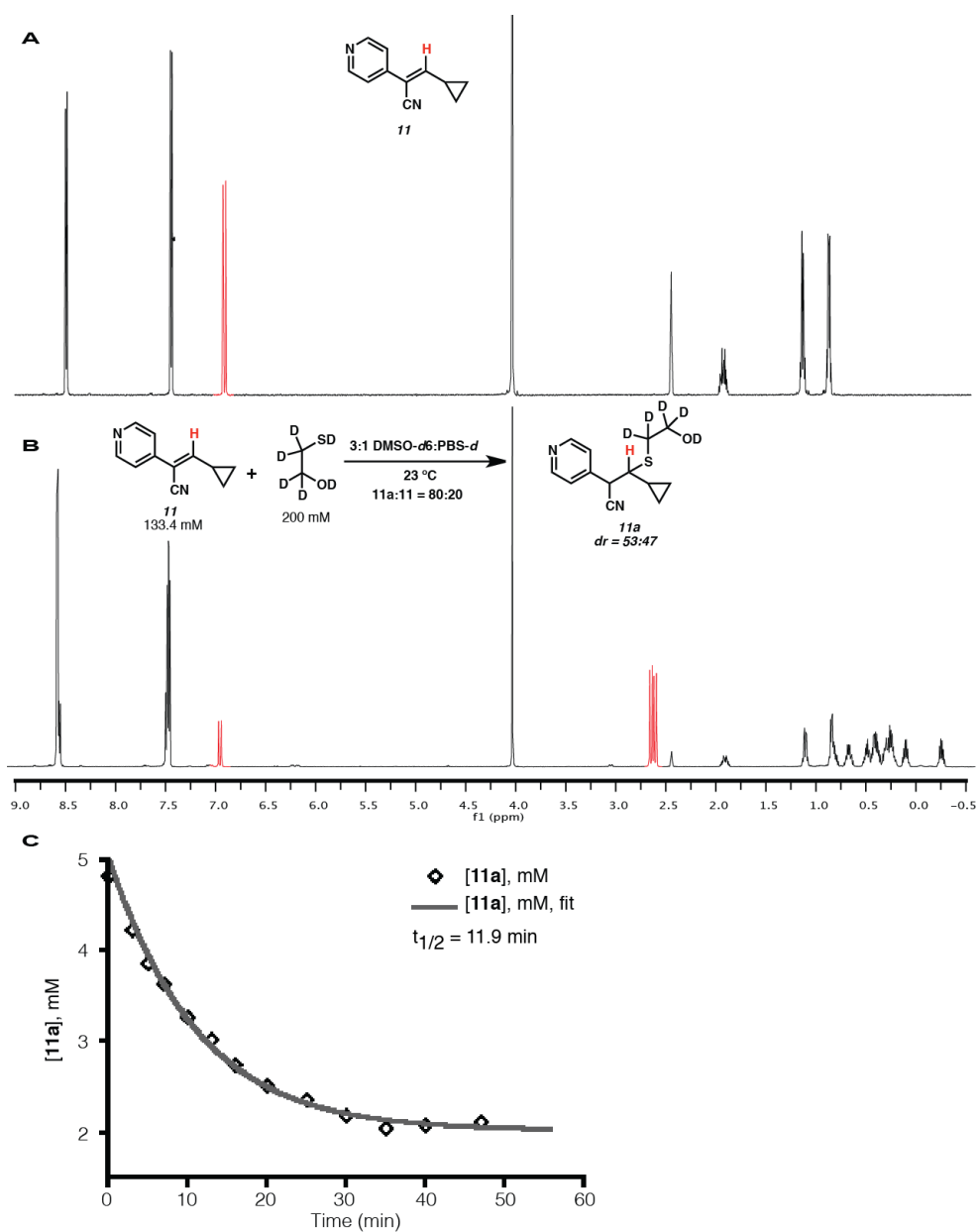
Figure S9 (related to Table 2). A. ^{1}H NMR spectrum of acrylonitrile **11** in 3:1 DMSO-*d*6:PBS-*d*; **B.** ^{1}H NMR spectrum of acrylonitrile **11** upon treatment with BME-*d*6; **C.** The β-elimination t$_{1/2}$ was determined as described in Figure S3.
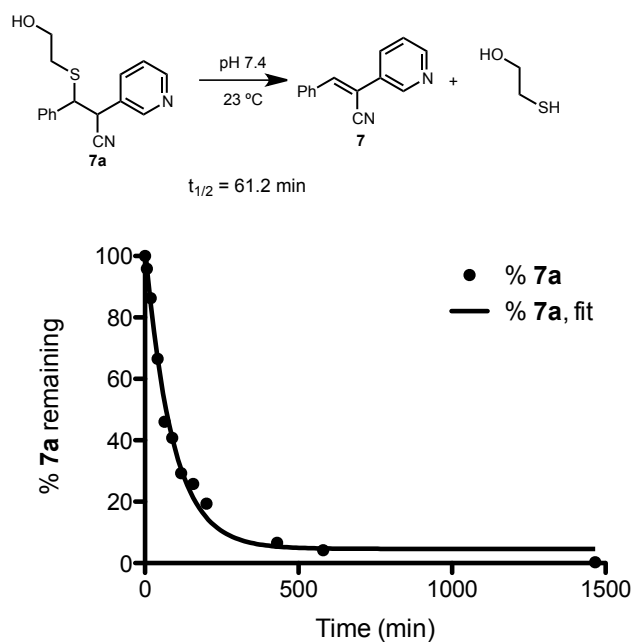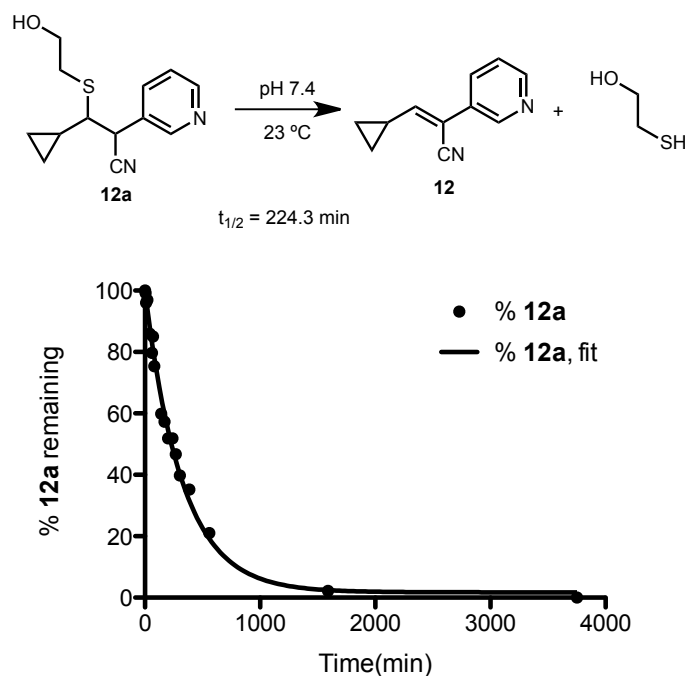
Figure S10 (related to Table 2). A solution of thioether **12a** in DMSO (500 µM) was diluted into PBS (pH 7.4) to afford a 5 µM solution, and the apparent first-order rate constant was determined as described in Figure S5.
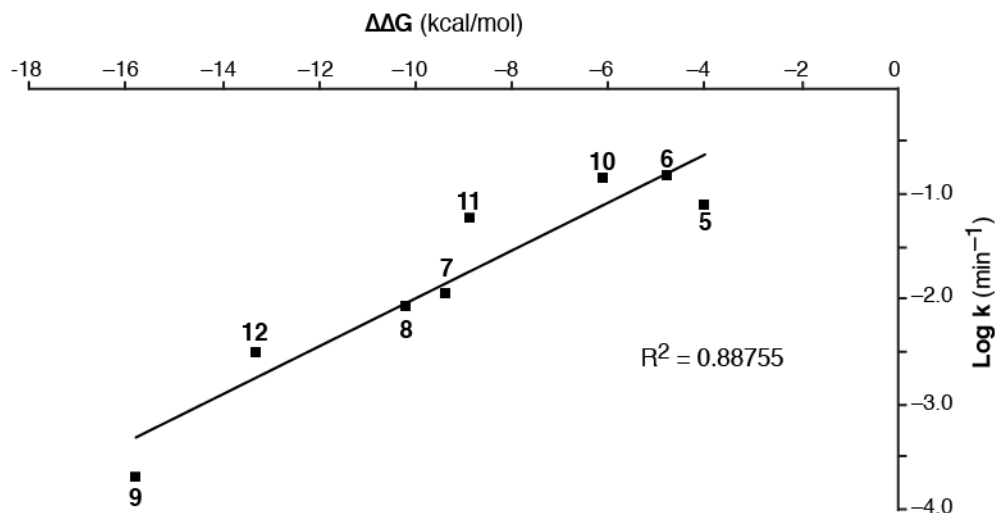
Figure S11 (related to Figure 2). Brønsted-type plot of computed proton affinity ($\Delta\Delta G_{aq}$) for *anti*-diastereomers of **5a–12a** vs. the measured β-elimination rates (log k, min^{-1}) (Table 1 and 2). BME/acrylonitrile adducts with higher proton affinity (more negative $\Delta\Delta G_{aq}$) undergo β-elimination at slower rates.
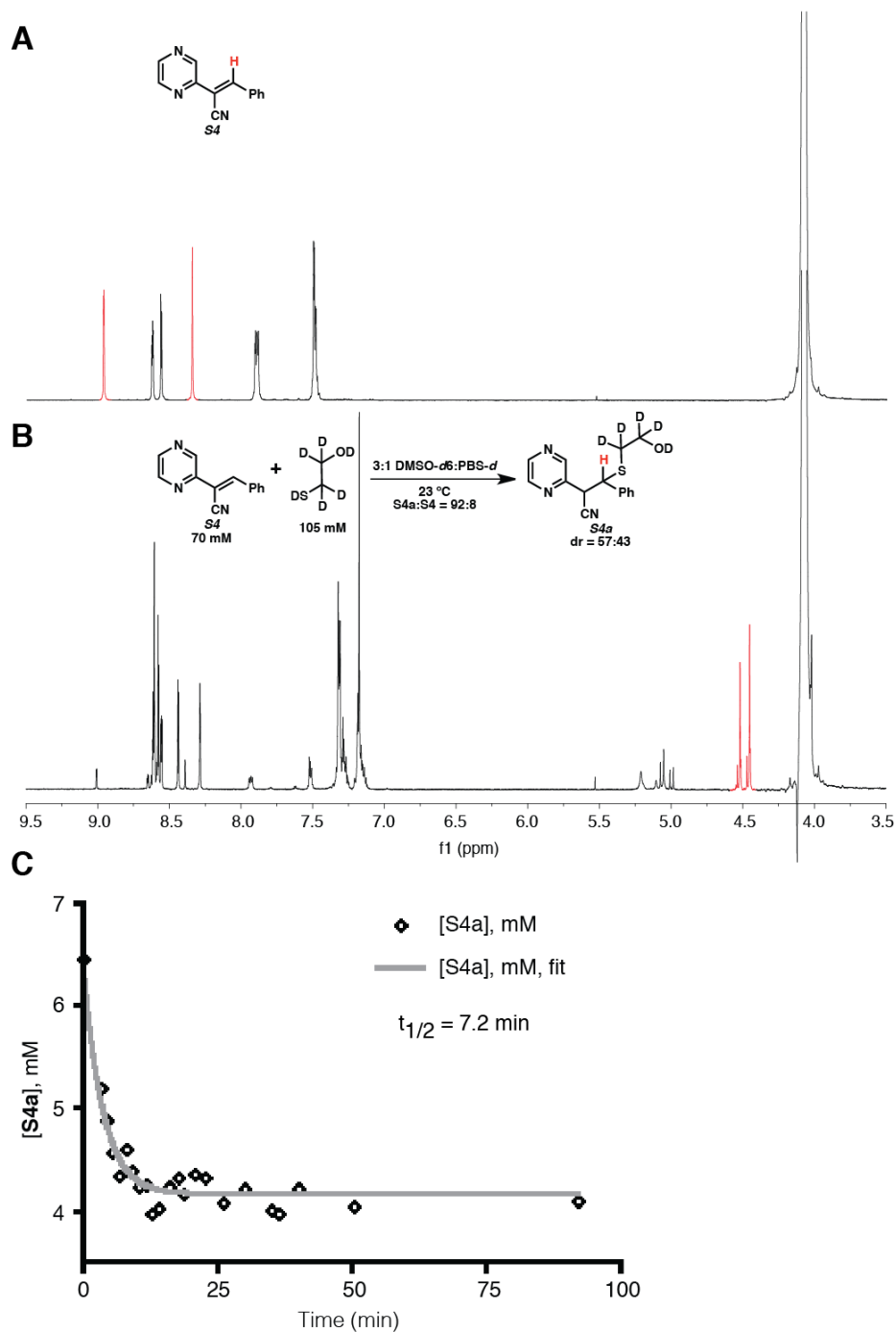
Figure S12 (related to Supplementary Table S3). A. ^{1}H NMR spectrum of acrylonitrile **S4** in 3:1 DMSO-*d*6:PBS-*d*; **B**. ^{1}H NMR spectrum of acrylonitrile **S4** upon treatment with BME-*d*6; **C.** The β-elimination $t_{1/2}$ was determined as described in Figure S3.
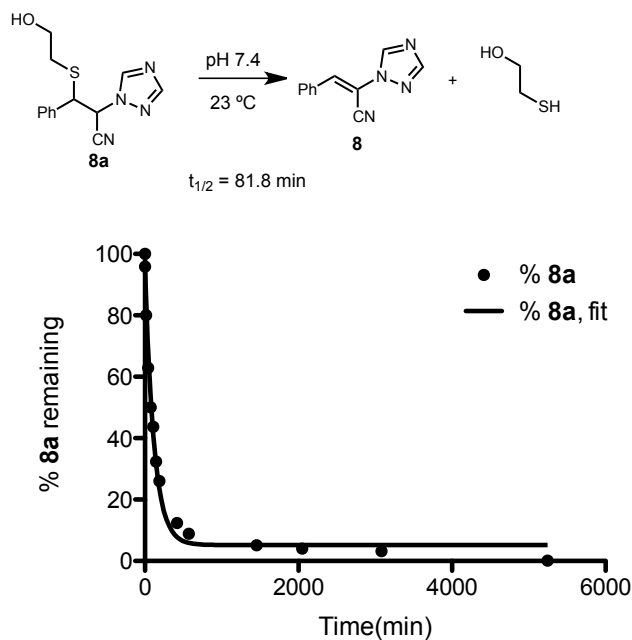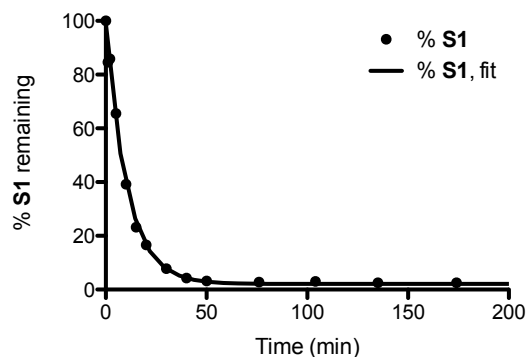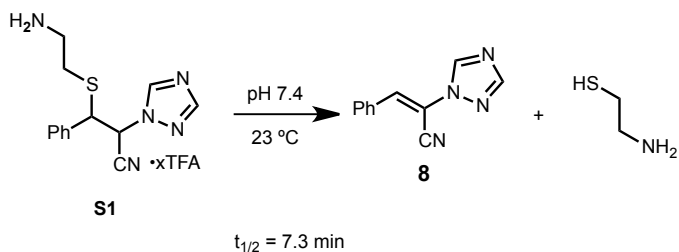
Figure S13 (related to Table 1). A solution of thioether **S1** in DMSO (500 µM) was diluted into PBS (pH 7.4) to afford a 5 µM solution, and the apparent first-order rate constant was determined as described in Figure S5.
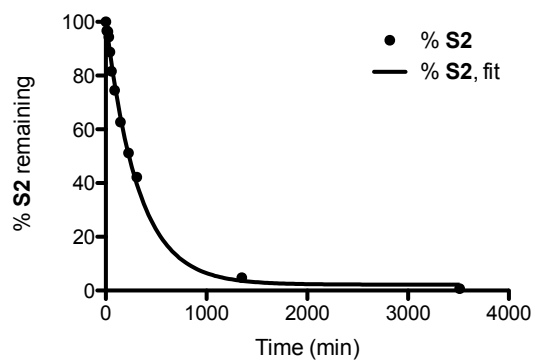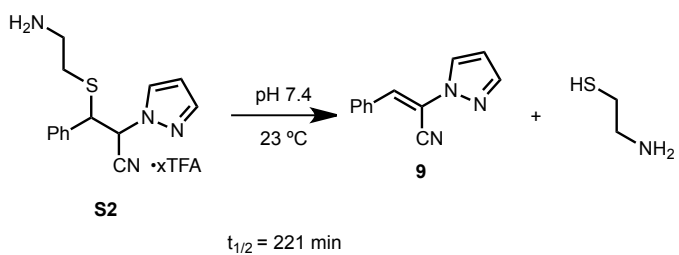
Figure S14 (related to Table 1). A solution of thioether **S2** in DMSO (500 µM) was diluted into PBS (pH 7.4) to afford a 5 µM solution, and the apparent first-order rate constant was determined as described in Figure S5.

Figure S15 (related to Figure 4). Triazole **20** inhibits HA-MSK1 autophosphorylation in PMA-stimulated cells. The assay was performed as previously described.[4]
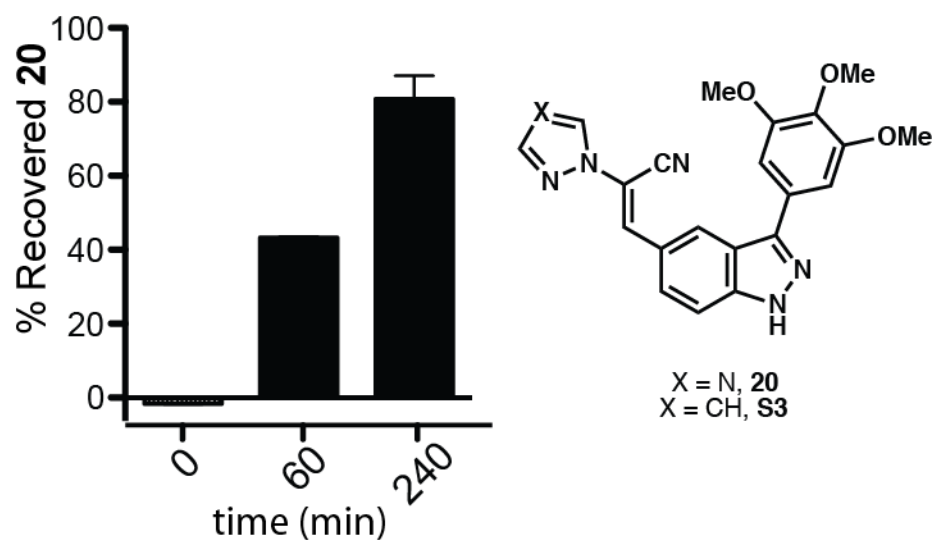
Figure S16 (related to Figure 4). Triazole **20** dissociates from RSK2 CTD upon unfolding. To a solution of **20** in 50 µL PBS (4 µM) was added 50 µL of RSK2 (8 µM, 2.0 equiv) in PBS. After 2 hours at 23 ºC, 100 µL of 6 M guanidine (pH 7.4) was added and the reaction mixture was incubated for 2 hours at 23 ºC to unfold RSK2 CTD. MeCN (200 µL) was added, and the recovery of free acrylonitrile was quantified by LC-MS/MS, relative to a control sample containing the acrylonitrile but lacking RSK2. Under the same conditions, only 2.2% of the pyrazole analog **S3** was recovered after 4 hours.

2. Supplementary Tables

Table S1 (related to Table 1 and Figure 2). Rate constants (k_1 and k_2) and equilibrium dissociation constants (K_D) for the reaction of Michael acceptors **3–12**, **S1–2** and **S4** with BME.
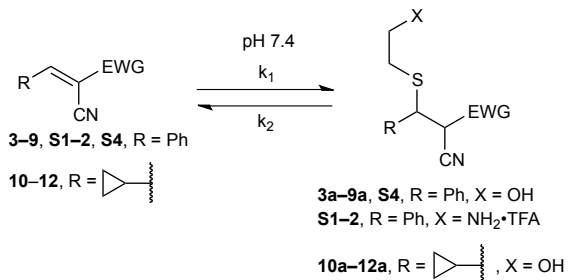
EWG	$t_{1/2}$ (min)	k_1 (mM^{-1}min^{-1})	k_2 (min^{-1})	K_D (mM)
CONH$_2$ **3**	<1	–	> 0.69	0.9
4	<1	–	> 0.69	14.9
5	8.9	0.012	0.078	6.4
6	4.6	0.028	0.152	5.5
7	61.2	–	0.011	–
8	81.8	–	0.009	–
9	3482	–	0.0002	–
10	4.8	0.003	0.144	44.3
11	11.9	0.003	0.058	22.6
12	224.3	–	0.003	–
S1	7.3	–	0.095	–
S2	221.0	–	0.003	–
S4	7.2	0.023	0.096	4.2

Table S2 (related to Figure 2). Computed proton affinities (normalized to adduct **3a**, Table 1) and predicted β-elimination half-lives of thioether adducts derived from as-yet-untested acrylonitriles. β-elimination half-lives were calculated based on the Brønsted relationship derived in Figure 2: Log k = 0.2207 (ΔΔG) – 0.1932, with $t_{1/2} = 0.69/k$.
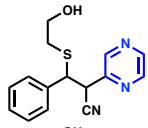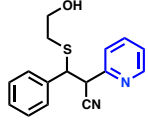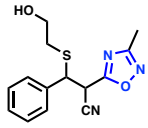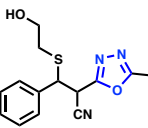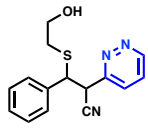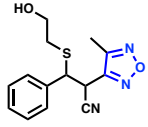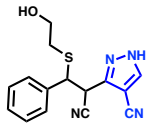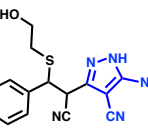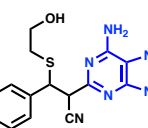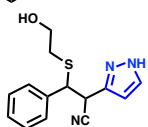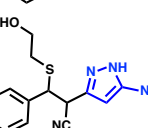
Entry	Structure	Proton affinity, $\Delta\Delta G_{aq}$ (kcal/mol) syn	anti	Estimated $t_{1/2}$ (min)
S4		−3.4	−3.2	6.1
S5		−7.5	−6.8	48.7
S6		6.8	5.0	< 1
S7		3.4	1.4	< 1
S8		−3.1	−4.4	5.2
S9		−1.6	−4.8	2.4
S10		−6.0	−6.4	22.7
S11		−5.0	−7.3	13.7
S12		−5.8	−7.8	20.5
S13		−10.2	−12.5	192.0
S14		−10.8	−13.3	260.4

S16

Table S3 (related to Figure 3). Recovery of acrylonitriles **13**–**18** after unfolding the inhibitor–RSK2 CTD complex**.**

Compound	% Recovery (mean ± s.d., n=3)
13	83.6 ± 10.2
14	91.7 ± 2.9
15	93.3 ± 2.2
16	87.0 ± 11.4
17	84.9 ± 9.4
18	91.1 ± 7.6

To 25 µL of inhibitor solution (3.2 µM in PBS) was added 25 µL of RSK2 (6.4 µM, 2.0 equiv) in PBS. After 2 hours at 23 ºC, 50 µL of 6 M guanidine (pH 7.4) was added and the reaction mixture was incubated for 2 hours at 23 ºC to unfold RSK2 CTD. MeCN (100 µL) was added, and the recovery of free acrylonitrile was quantified by LC-MS/MS, relative to a control sample containing the acrylonitrile but lacking RSK2. Absolute compound recovery in the absence of added RSK2 (control samples) was measured by LC-MS/MS using calibration curves for each compound and ranged from 52–100%.

Table S4. Kinase selectivity of compounds **19** and **20** (both at 1 μM) using [ATP] = K$_m$.

Kinase	% Inhibition with **19**	% Inhibition with **20**
AKT3	−1	−4
AURORA-A	−9	2
AURORA-B	10	8
BTK	0	7
CDK2-CYCLIN A	0	4
CRAF	3	6
EGFR	5	5
JAK1	−4	−4
JAK3	5	16
KDR	−13	−7
LYN A	4	6
MAPK1	1	−2
MAPK14-P38-ALPHA	−2	1
MEK1	3	−2
SRC	8	4
SYK	−9	1
TEC	4	5
TTK	64	6

Table S5: X-ray data collection and refinement statistics for T493M RSK2 bound to 20.

Data Collection	RSK2 T493M: **20**
space group	$P4_12_12$
unit-cell parameters	a=47.5; b=47.5; c=288.5; a=90°; b=90°; g=90°
resolution range (Å)	47.5 – 2.6
highest resolution shell (Å)	2.74 – 2.60
measured reflections	93608 (12711)
unique reflections	10976 (1587)
redundancy	8.5
completeness (%)	97.5 (92.1)
average I/s	28.2
R_{sym} (%)	6.1

Refinement	
resolution range (Å)	45.1 – 2.6
highest resolution shell (Å)	2.9 – 2.6
R_{work}	23.5 (29.7)
R_{free}	29.2 (35.4)
no. protein atoms	4671
no. water molecule	41
Wilson B-value ($Å^2$)	44.3
Average B factors ($Å^2$)	57.2
Protein	52.7
Solvent	39.7
Ligand	54.2
Ramachandran (%)	
favoured	94.9
outliers	0.3
rms deviations	
bond lengths (Å)	0.009
bond angles (°)	0.99

3. General materials and methods

Unless otherwise indicated, reactions were carried out under dry argon or nitrogen with dry, freshly distilled solvents. Dry solvents were dispensed from a delivery system that passes the solvents through packed columns (tetrahydrofuran, diethyl ether, acetonitrile, and methylene chloride: dry neutral alumina; hexane, benzene, and toluene: dry neutral alumina and Q5 reactant; dimethylformamide: activated molecular sieves). All other reagents were purchased from commercial sources and used as received.

Yields of reactions refer to chromatographically and spectroscopically pure compounds. Reactions were monitored by thin layer chromatography (TLC) using glass plates precoated with Merck silica gel 60 F_{254} or aluminum oxide 60 F_{254}. Visualization was by UV illumination or by staining with ceric ammonium molybdate, *p*-anisaldehyde, potassium permanganate and Iodoplatinate stains. Proton magnetic resonance spectra were recorded on a Varian Mercury400 (400 MHz) spectrometer. Chemical shifts (δ_H) are quoted in ppm and are referenced to tetramethylsilane (internal). Coupling constants (*J*) are reported in Hertz to the nearest 0.1 Hz. Data are reported as follows: chemical shift, integration, multiplicity [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; or as a combination of these (*e.g.* dd, dt, *etc.*)], coupling constant(s) and number of protons. Carbon magnetic resonance spectra were recorded on Varian Mercury400 (100MHz) or Bruker 500 (125 MHz) spectrometers. Chemical shifts (δ_C) are quoted in ppm to the nearest 0.1 ppm. High resolution Electrospray ionization (ESI) mass spectra were acquired using an LTQ-FT instrument (Thermo Finnigan, US) with Excalibur software used for instrument operation and data collection. The samples were introduced by direct infusion with a flow rate of 10 µL/min. Electron impact (EI) mass spectra were acquired on an Autospec from Waters (Manchester, UK) with MassLynx software for instrument operation and data collection.

Quantitative LC-MS/MS experiments were performed using a Waters Acquity UPLC/ESI-TQD instrument with a 2.1 x 50 mm Acquity UPLC BEH C_{18} column and gradient methods of 2.5 or 5 minutes using 0.1% formic acid/water and 0.1% formic acid/MeCN as eluents. LC-MS/MS methods specific to each compound were validated with calibration curves to ensure that the concentrations employed were within the linear range for detection. Phosphate buffered saline (PBS) was purchased from Invitrogen (catalog # 14190) and comprised KCl (2.7 mM), KH_2PO4 (1.5 mM), NaCl (137.9 mM) and $Na_2HPO4 \cdot 7H_2O$ (8.1 mM) and the pH was adjusted to 7.4. Deuterated phosphate buffered saline (PBS-*d*) was prepared by dissolution of 400 mg NaCl, 10 mg KCl, 30.7 mg Na_2DPO_4 and 9.7 mg KD_2PO_4 in 40 mL of D_2O. The pH was adjusted to 7.4 using NaOD (solution in D_2O) and DCl (solution in D_2O), and the volume was made up to 50 mL.

4. Synthesis and characterization of new compounds
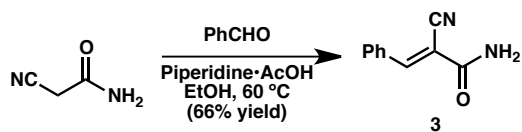
(*E*)-2-cyano-3-phenylacrylamide, **3**. Benzaldehyde (126.0 mg, 1.19 mmol), cyanoacetamide (99.8 mg, 1.0 equiv.) and piperidine-AcOH (86.3 mg, 0.5 equiv.) were heated in EtOH (2 mL) to 60 ºC for 4 hours. The reaction mixture was then cooled to ambient temperature and the reaction mixture was purified by preparative TLC (1:1 hexanes/EtOAc) to afford 135 mg (66% yield) of the cyanoacrylamide **3** as a white solid. R_f 0.37 (SiO_2, 1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): 8.34 (s, 1H), 7.95 (d, J = 7.1 Hz, 2H), 7.57–7.48 (m, 3H), 6.40 (bs, 1H), 6.31 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 162.1, 154.0, 133.0, 131.6, 130.8, 129.2, 117.0, 103.1.
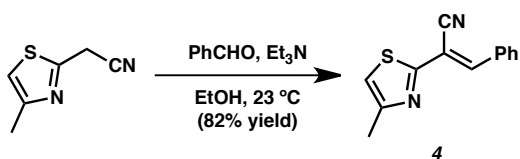
(*E*)-2-(4-methylthiazol-2-yl)-3-phenylacrylonitrile, **4**. To 2-(4-methylthiazol-2-yl)acetonitrile (47.5 mg, 0.34 mmol) and benzaldehyde (35 μL, 0.34 mmol, 1.0 equiv.) in EtOH (0.5 mL) was added triethylamine (24 μL, 0.17 mmol, 0.5 equiv.). The reaction mixture was stirred at ambient temperature for 42 hours, then concentrated and the residue obtained was purified by preparative TLC (4:1 hexanes/EtOAc, 2 elutions) to afford 63.6 mg (82% yield) of the desired vinyl nitrile **4** as a yellow solid. R_f 0.65 (SiO$_2$, 3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$): 8.13 (s, 1H), 7.95 (m, 2H), 7.50-7.46 (m, 3H), 6.98 (q, *J* = 0.7 Hz, 1H), 2.51 (d, *J* = 0.7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): 161.9, 154.7, 143.7, 132.6, 131.5, 129.9, 129.1, 116.8, 115.2, 105.0, 17.2; HRMS (ESI) found 227.0634, C$_{13}$H$_{11}$N$_2$S$^+$ (MH$^+$) requires 227.0637. The olefin geometry of the product as well as other β-aryl-α-aryl (or α-heteroaryl) nitriles was assigned based on literature precedent for related compounds.[2]
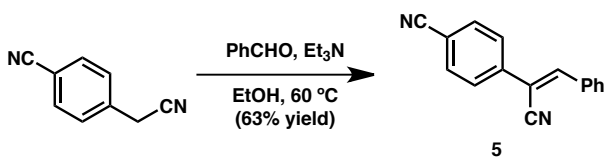
(*Z*)-4-(1-cyano-2-phenylvinyl)benzonitrile, **5**. 2-(4-cyanophenyl)acetonitrile (106 mg, 0.746 mmol) was dissolved in 2- propanol (3 mL) and benzaldehyde (113 μL, 1.12 mmol, 1.5 equiv.) was added, followed by triethylamine (312 μL, 2.24 mmol, 3.0 equiv.). The reaction mixture was heated to 60 °C for 5 hours, then cooled to ambient temperature and filtered. The solid isolated was dried in vacuo to afford 109 mg (63% yield) of the desired vinyl nitrile **5** as a white solid. R_f 0.24 (SiO$_2$, 6:1 hexanes: EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$): 7.92 (m, 2H), 7.77 (ABq, J_{AB} = 8.4 Hz, 4H), 7.63 (s, 1H), 7.50 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): 144.9, 138.8, 132.9, 132.8, 131.5, 129.6, 129.2, 126.5, 118.2, 117.1, 112.7, 109.9; HRMS (EI) found 230.0841, C$_{16}$H$_{10}$N$_2$$^+$ (M$^+$) requires 230.0844.

(*Z*)-3-phenyl-2-(pyridin-4-yl)acrylonitrile, **6**. 2-(Pyridine-4-yl)acetonitrile hydrochloride (522 mg, 3.38 mmol) was dissolved in EtOH (8 mL) and benzaldehyde (378 μL, 3.71 mmol, 1.1 equiv.) was added, followed by triethylamine (941 μL,6.75 mmol, 2.0 equiv.). The reaction mixture was heated to 40 °C for 24 hours, then cooled and concentrated and the residue was purified by silica gel chromatography (3:2 hexanes/EtOAc) to afford 636 mg (91% yield) of the desired vinyl nitrile **6** as a white solid. R_f 0.27 (SiO$_2$, 1:1 hexanes: EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$): 8.70 (d, *J* = 5.8 Hz, 2H), 7.94 (m, 2H), 7.72 (s, 1H), 7.56 (d, *J* = 5.8 Hz, 2H), 7.50 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): 150.6, 145.1, 141.7,

132.8, 131.6, 129.7, 129.1, 119.9, 116.9, 109.3; HRMS (ESI) found 207.0912, $C_{14}H_{11}N_2^+$ (MH$^+$) requires 207.0917.

(Z)-3-phenyl-2-(pyridin-3-yl)acrylonitrile, **7**. Pyridine-3-acetonitrile (58.1 mg, 0.492 mmol) and benzaldehyde (50 μL, 0.492 mmol, 1.0 equiv.) were combined in EtOH (1 mL). Triethylamine (34.3 μL, 0.5 equiv.) was added and the reaction mixture was stirred at ambient temperature for 71 hours. As the reaction had not progressed sufficiently, DBU (73.6 μL, 0.5 equiv.) was added and the reaction mixture was maintained at ambient temperature for a further 24 hours, then diluted with saturated aqueous ammonium chloride (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were concentrated and the residue obtained was purified by preparative TLC (1:1 hexanes/EtOAc) to afford 73.4 mg (72% yield) of the desired vinyl nitrile, **7**, as a white solid. R_f (SiO$_2$, 3:1 hexanes/EtOAc): 0.24; ^{1}H NMR (400 MHz, CDCl$_3$): 8.94 (d, J = 2.2 Hz, 1H), 8.64 (dd, J = 4.8 Hz, 1.3 Hz, 1H), 7.97 (m, 1H), 7.91 (m, 2H), 7.58 (s, 1H), 7.49 (m, 3H), 7.40 (dd, J = 8.0 Hz, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): 150.1, 147.0, 143.8, 133.4, 133.2, 131.1, 130.6, 129.4, 129.1, 123.6, 117.2, 108.5; HRMS (ESI) found 207.0915, $C_{14}H_{11}N_2$ (MH$^+$) requires 207.0917.

(E)-3-phenyl-2-(1H-1,2,4-triazol-1-yl)acrylonitrile, **8** and (Z)-3-phenyl-2-(1H-1,2,4-triazol-1-yl)acrylonitrile, **S15**. To a solution of benzaldehyde (105 mg, 0.99 mmol), and 1H-1,2,4-triazol-1-yl)acetonitrile (150 mg, 1.4 equiv.) in CH$_2$Cl$_2$ (5 mL) cooled to 0–5 ºC was added TiCl$_4$ (130 μL, 1.2 equiv.), followed by DIPEA (258 μL, 1.5 equiv.). The reaction mixture was maintained at 0 ºC for 30 minutes, then poured into saturated aqueous NaHCO$_3$ (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried (Na$_2$SO$_4$) and concentrated to afford a brown oil. Purification of the oil by preparative TLC (5:1 PhH/MeCN) afforded 51.9 mg (27% yield) of the (E)-isomer as a white solid and 16.7 mg (9% yield) of the (Z)-isomer as a white solid. (E)-3-phenyl-2-(1H-1,2,4-triazol-1-yl)acrylonitrile, **8**. R_f (SiO$_2$, 5:1 PhH/MeCN): 0.30; ^{1}H NMR (400 MHz, CDCl$_3$): 8.56 (s, 1H), 8.09 (s, 1H), 7.99 (s, 1H), 7.82 (m, 2H), 7.50 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): 153.1, 142.1, 135.6, 131.6, 130.2, 129.34, 129.28, 113.8, 107.1; HRMS (EI) found 196.0746, $C_{11}H_8N_4$ (M$^+$) requires 196.0749.

(Z)-3-phenyl-2-(1H-1,2,4-triazol-1-yl)acrylonitrile, **S15**. R_f (SiO$_2$, 5:1 PhH/MeCN): 0.40; ^{1}H NMR (400 MHz, CDCl$_3$): 8.19 (s, 1H), 8.11 (s, 1H), 7.42 (m, 2H), 7.33 (m, 2H), 6.95 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): 153.4, 144.1, 143.0, 132.0, 130.0, 129.6, 129.4, 114.8, 108.3. HRMS (EI) found 196.0746, $C_{11}H_8N_4$ (M$^+$) requires 196.0749.

ClCH$_2$CN, Cs$_2$CO$_3$ / MeCN, 23 ºC / (75% yield) → **S16** → PhCHO, DBU, IPA / 60 ºC / (66% yield) → **9**

(*E*)-3-phenyl-2-(1*H*-pyrazol-1-yl)acrylonitrile **9**: To a slurry of pyrazole (1.04 g, 15.3 mmol) and cesium carbonate (7.47 g, 22.9 mmol, 1.5 equiv.) in MeCN (21 mL) was added chloroacetonitrile (1.16 mL, 18.3 mmol, 1.2 equiv.) over three minutes (**CAUTION**: exothermic reaction!). The reaction mixture was stirred at 23 ºC for 2 hours and the reaction mixture was filtered. The filter cake was washed with MeCN (2 x 20 mL). The combined filtrate and washes were concentrated to afford a brown oil, which was purified by silica gel chromatography (3:1 hexanes: EtOAc) to afford 1.23 g (75% yield) of 2-(1*H*-pyrazol-1-yl)acetonitrile, **S16**, as a brown oil. R$_f$ 0.57 (SiO$_2$, 1:1 hexanes: EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$): 7.58 (d, *J* = 1.7 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 6.35 (app. t, *J* = 2.2 Hz, 1H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): 141.2, 129.6, 113.8, 107.6, 39.4; LRMS (EI): 107 (C$_5$H$_5$N$_3$$^+$, M$^+$).
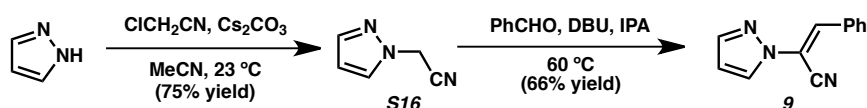
To acetonitrile **S16** (228 mg, 2.13 mmol) in 2-propanol (10 mL) was added benzaldehyde (639 µL, 6.39 mmol, 3.0 equiv.), followed by DBU (637 µL, 4.26 mmol, 2.0 equiv.). The reaction mixture was heated to 60 ºC for 5 hours, then allowed to cool to ambient temperature and diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), then concentrated to afford a brown oil that was purified by preparative TLC (10:1 hexanes: diisopropyl ether, 2 elutions) to afford 276 mg (66% yield) of (*E*)-3-phenyl-2-(1*H*-pyrazol-1-yl)acrylonitrile **9** as a pale yellow oil. R$_f$ 0.67 (SiO$_2$, 3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$): 7.89 (m, 2H), 7.77 (m, 2H), 7.70 (s, 1H), 7.43 (m, 3H), 6.46 (app. t, *J* = 2.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): 142.0, 131.9, 131.0, 130.4, 128.9, 128.8, 128.2, 113.9, 110.5, 108.1; HRMS (ESI) found 196.0867, C$_{12}$H$_{10}$N$_3$$^+$ (MH$^+$) requires 196.0869.

[cyclopropyl]–CHO / Et$_3$N / EtOH, 23 ºC / (79% yield) → **10**
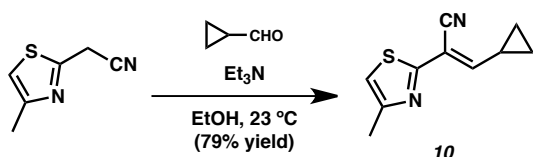
To 2-(4-methylthiazol-2-yl)acetonitrile (392.4 mg, 2.84 mmol) and cyclopropanecarboxaldehyde (424 µL, 5.68 mmol, 2.0 equiv.) in EtOH (6 mL) was added triethylamine (594 µL, 4.26 mmol, 1.5 equiv.). The reaction mixture was heated to 40 ºC for 24 hours, then concentrated to a residue that was purified by silica gel chromatography (12:1→9:1 hexanes/EtOAc) to afford 427 mg (79% yield) of the desired vinyl nitrile **10** as a colorless oil.

E:*Z* = 93:7. (*E*)-3-cyclopropyl-2-(4-methylthiazol-2-yl)acrylonitrile, **10**. R$_f$ (SiO$_2$, 3:1 hexanes/EtOAc): 0.57; ^{1}H NMR (400 MHz, CDCl$_3$): 6.87 (s, 1H), 6.77 (d, *J* = 11.0 Hz, 1H), 2.44 (s, 3H), 2.12 (m, 1H), 1.23 (m, 2H), 0.88 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): 160.8, 155.4, 154.0, 116.0, 113.9, 107.0, 17.1, 15.6, 10.2; HRMS (ESI) found 191.0634, C$_{10}$H$_{11}$N$_2$S$^+$ (MH$^+$) requires 191.0637.
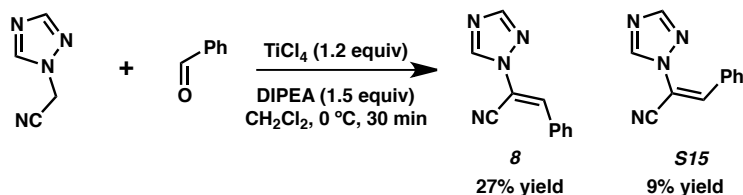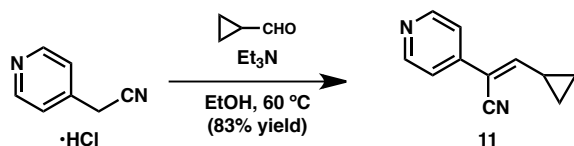
(*Z*)-3-cyclopropyl-2-(pyridin-4-yl)acrylonitrile, **11**. 2-(Pyridine-4-yl)acetonitrile hydrochloride (123.8 mg, 0.801 mmol) was dissolved in EtOH (3 mL) and cyclopropane carboxaldehyde (179.5 μL, 2.40 mmol, 3.0 equiv.) was added, followed by triethylamine (335 μL, 2.40 mmol, 3.0 equiv.). The reaction mixture was heated to 60 ºC for 5.5 hours, then cooled and concentrated and the residue was purified by preparative TLC (1:1 hexanes/EtOAc) to afford 113.6 mg (83% yield) of the desired vinyl nitrile **11** as a white solid. R_f 0.25 (SiO$_2$, 1:1 hexanes: EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$): 8.60 (d, J = 5.0 Hz, 2H), 7.36 (d, J = 5.0 Hz, 2H), 6.43 (d, J = 10.6 Hz, 1H), 2.19 (m, 1H), 1.26 (m, 2H), 0.88 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): 155.7, 150.3, 140.4, 119.1, 116.0, 110.4, 15.8, 10.0; HRMS (ESI) found 171.0913, C$_{11}$H$_{11}$N$_2^+$ (MH$^+$) requires 171.0917.
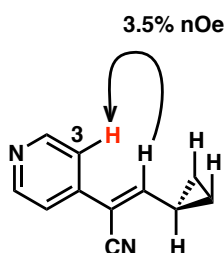
Olefin geometry was assigned as (*Z*) using a GOESY experiment, which indicated a strong nOe between the vinyl proton and C(3)–<u>H</u> of the pyridine ring.
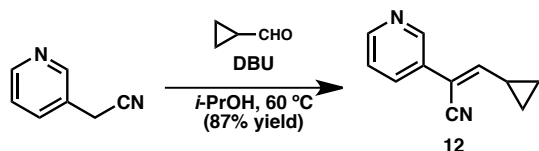
(*Z*)-3-cyclopropyl-2-(pyridin-3-yl)acrylonitrile, **12**. Pyridine-3-acetonitrile (134 mg, 1.13 mmol) and cyclopropane carboxaldehyde (254 μL, 3.40 mmol, 3.0 equiv.) were dissolved in 2-propanol (2 mL). DBU (339 μL, 2.0 equiv.) was added and the reaction mixture was heated to 60 ºC for 15 hours. The reaction mixture was then concentrated and purified by preparative TLC (1:1 hexanes/EtOAc) to afford 167.4 mg (87% yield) of the desired vinyl nitrile **12** as a white solid. R_f (SiO$_2$, 2:1 hexanes/EtOAc): 0.24; ^{1}H NMR (400 MHz, CDCl$_3$): 8.73 (m, 1h), 8.54 (m, 1H), 7.77 (m, 1H), 7.31 (m, 1H), 6.26 (d, J = 10.6 Hz, 1H), 2.12 (m, 1H), 1.21 (m, 2H), 0.85 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): 153.7, 149.2, 146.1, 132.2, 129.1, 123.3, 116.3, 109.1, 15.5, 9.5; HRMS (ESI) found 171.0916, C$_{11}$H$_{11}$N$_2$ (MH$^+$) requires 171.0917.
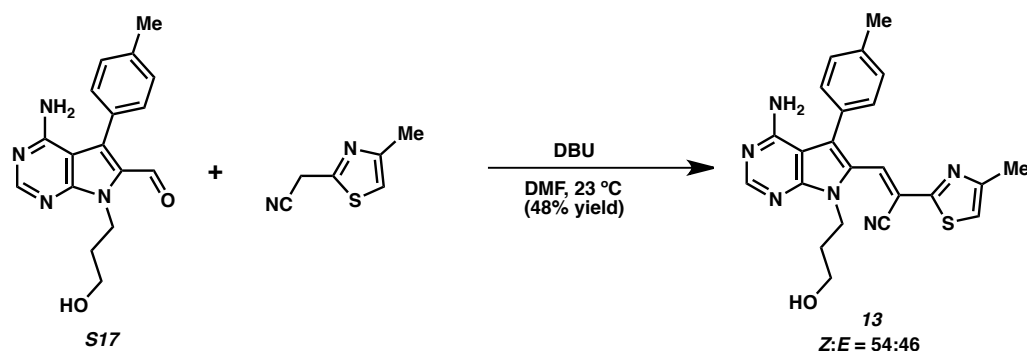
3-(4-amino-7-(3-hydroxypropyl)-5-(*p*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)-2-(4-methylthiazol-2-yl)acrylonitrile, **13**: Aldehyde **S17**[3] (19.0 mg, 61.2 μmol) and 2-(4-methylthiazol-2-yl)acetonitrile (9.3 mg, 67.3 μmol, 1.1 equiv.) were dissolved in DMF (1 mL) and DBU (18.3 μL, 122 μmol, 2.0 equiv.) was added. The reaction mixture was maintained at ambient temperature for 6 hours, then purified by HPLC (gradient of 5%B→80%B, 30 min; A = water with 0.1% TFA and B = MeCN with 0.1% TFA). The residue obtained from the purification was treated in solution in MeOH (5 mL) with amberlyst A-21 resin (100 mg) for 3 hours to remove residual TFA. The solution was then filtered and the filtrate was concentrated to afford 12.7 mg (48% yield, orange-brown oil) of vinyl nitrile **13** as a mixture of *Z* and *E* isomers, *Z*:*E* = 54:46; R_f 0.50 (SiO$_2$; 9:1 EtOAc:MeOH); ^{1}H NMR (400 MHz, CDCl$_3$): 8.31 (s, 1H, both isomers), 8.11 (s, 1H, major isomer), 7.40 (s, 1H, minor isomer), 7.33 (ABq, J_{AB} = 8.0 Hz, 4H, minor isomer), 7.15 (d, *J* = 7.8 Hz, 2H, major isomer), 7.06 (d, *J* = 7.8 Hz, 2H, major isomer), 6.99 (s, 1H, minor isomer), 6.82 (s, 1H, major isomer), 5.49 (bs, 2H, major isomer), 5.36 (bs, 2H, minor isomer), 4.48 (app. t, *J* = 5.8 Hz, 2H, minor isomer), 4.29 (app. t, *J* = 5.9 Hz, 2H, major isomer), 3.47 (app. t, *J* = 5.4 Hz, 2H, major isomer), 3.41 (app. t, *J* = 5.3 Hz, 2H, minor isomer), 2.49 (s, 3H, minor isomer), 2.40 (s, 3H, major isomer), 2.36 (s, 3H, major isomer), 2.35 (s, 3H, minor isomer), 1.98 (m, 2H, minor isomer), 1.86 (m, 2H, major isomer); ^{13}C NMR (100 MHz, CDCl$_3$): 160.6, 157.7, 157.43, 157.35, 155.1, 154.0, 153.3, 152.8, 151.9, 138.2, 138.1, 133.0, 130.6, 130.5, 129.9, 129.85, 129.7, 129.6, 129.5, 129.2, 126.6, 125.7, 121.2, 118.3, 116.9, 116.8, 116.1, 115.3, 115.0, 110.2, 102.1, 101.6, 57.3, 57.27, 39.2, 38.8, 32.8, 32.7, 21.3, 21.2, 17.2, 17.1; HRMS (ESI) found 431.1649, C$_{23}$H$_{23}$N$_6$OS (MH$^+$) requires 431.1649.
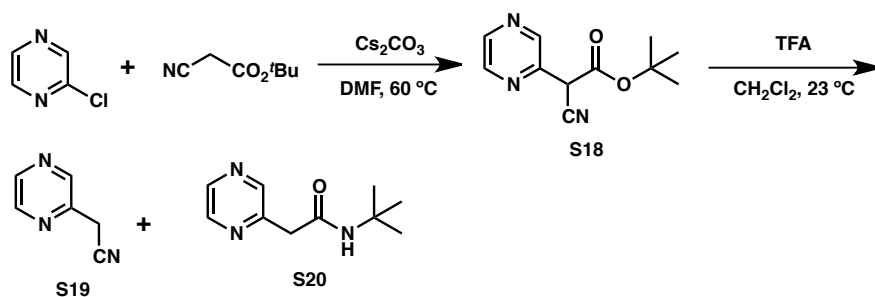
2-(Pyrazine-2-yl)-acetonitrile, **S19**: To 2-chloropyrazine (866 mg, 7.56 mmol) in DMF (12 mL) was added *tert*-butylcyanoacetate (2.16 mL, 15.1 mmol, 2.0 equiv), followed by cesium carbonate (6.16 g, 18.9 mmol, 2.5 equiv.). The slurry was stirred for 4 hours and heated to 60 ºC at which point consumption of the chloropyrazine was complete. The reaction mixture was cooled to ambient temperature and filtered. The filter cake was washed with EtOAc (100 mL). The filtrate and washes were combined and washed with 1M HCl (100 mL) and saturated aqueous ammonium chloride (3 x 50 mL). The combined aqueous washes were back-extracted with EtOAc (100 mL). The organic extracts

were combined, washed with brine (100 mL), dried (MgSO$_4$) and concentrated to afford a residue, which was purified by silica gel chromatography (3:1 hexanes/EtOAc) to afford 908 mg (55% yield) of the cyanoacetate **S18** as a yellow solid. R$_f$ 0.15 (SiO$_2$, 3:1 hexanes: EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$): 8.76 (bs, 1H), 7.66 (dd, J = 4.1 Hz, 1.7 Hz, 1H), 7.30 (m, 1H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$): 169.7, 148.4, 147.6, 129.5, 124.2, 116.9, 82.3, 66.1, 28.3; HRMS (ESI) found 220.1077, C$_{11}$H$_{14}$N$_3$O$_2^+$ (MH$^+$) requires 220.1081.

The cyanoacetate **S18** (132.3 mg, 0.603 mmol) was dissolved in CH$_2$Cl$_2$ (2 mL). TFA (2 mL) was added to afford a deep red solution. The reaction mixture was maintained at ambient temperature for 3 hours whereupon the color of the solution changed to pale yellow. The reaction mixture was concentrated and the residue obtained was purified by preparative TLC (1:1 hexanes/EtOAc, 3 elutions) to afford 43.8 mg (61% yield) of the desired nitrile **S19** as a white solid. and 34.6 mg (30% yield) of the side product, amide **S20** as a colorless oil.

Nitrile **S19**: R$_f$ 0.25 (SiO$_2$, 1:1 hexanes: EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$): 8.68 (s, 1H), 8.56 (m, 2H), 3.97 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): 146.5, 144.4, 144.3, 143.6, 115.7, 24.2; LRMS (EI): 119 (C$_6$H$_5$N$_3^+$, M$^+$).
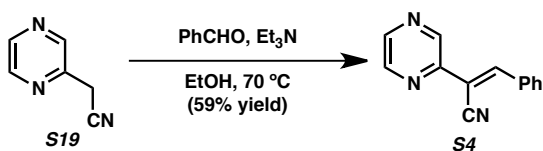
(*Z*)-3-phenyl-2-(pyrazin-2-yl)acrylonitrile, **S4**. To a solution of 2-(Pyrazine-2-yl)-acetonitrile, **S19** (67.9 mg, 0.57 mmol) and benzaldehyde (1.5 equiv.) in EtOH (1 mL) was added triethylamine (159 µL, 2.0 equiv.). The reaction mixture was heated to 70 ºC for 2.5 hours, then cooled to ambient temperature and concentrated, then purified by preparative TLC (4:1 Hexanes/EtOAc and then 7:1 PhH/MeCN) to afford acrylonitrile **S4** (69 mg, 59% yield) as a white solid. R$_f$ (4:1 Hexanes/EtOAc), 0.30. ^{1}H NMR (400 MHz, CDCl$_3$): 9.03 (d, J = 1.4 Hz, 1H), 8.59 (m, 2H), 8.46 (s, 1H), 8.01 (m, 2H), 7.50 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): 146.9, 144.4, 143.9, 142.3, 132.8, 131.8, 130.1, 129.1, 116.7, 107.0; ESI-MS: 208 (MH$^+$): 100%.
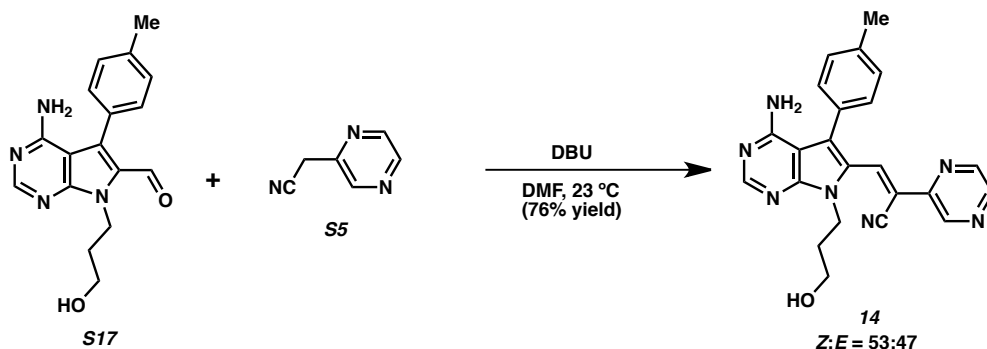
3-(4-amino-7-(3-hydroxypropyl)-5-*p*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)-2-pyrazin-2-yl)acrylonitrile, **14**: Aldehyde **S17** (23.2 mg, 74.8 µmol) and 2-(2-pyrazinyl)acetonitrile (10.7 mg, 89.7 µmol, 1.2 equiv.) were dissolved in DMF (1 mL) and DBU (16.8 µL, 112 µmol, 1.5 equiv.) was added. The reaction mixture was maintained at ambient temperature for 2.5 hours, then purified by HPLC

(gradient of 5%B→80%B, 30 min; A = water with 0.1% TFA and B = MeCN with 0.1% TFA) and preparative TLC (3:1 toluene/2-propanol, 2 elutions) to afford 28.4 mg (76% yield, yellow solid) of vinyl nitrile **14** as a mixture of Z and E isomers, $Z:E$ =53:47; R_f 0.26, 0.18 (SiO_2; 3:1 toluene/2-propanol); ^{1}H NMR (400 MHz, $CDCl_3$): 8.80 (s, 1H), 8.58 (m, 2H), 8.46 (s, 1H), 8.32 (m, 3H), 8.19 (m, 2H), 7.58 (s, 1H), 7.33 (ABq, J_{AB} = 8.1 Hz, 2H x 2, both isomers), 7.01 (d, J = 8.0 Hz, 2 x 1H, both isomers), 6.78 (d, J = 7.9 Hz, 2 x 1H, both isomers), 5.37 (bs, 2H), 5.10 (bs, 2H), 4.47 (m, 2 x 2H, both isomers), 3.49 (m, 2 x 2H, both isomers), 2.41 (s, 3H, minor isomer), 2.32 (s, 3H, major isomer), 2.03 (m, 2H), 1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.9, 157.5, 153.8, 153.6, 152.1, 151.9, 147.9, 145.8, 144.9, 144.03, 144.00, 143.9, 143.7, 142.5, 138.2, 137.9, 134.3, 133.5, 130.7, 130.5, 130.0, 129.61, 129.59, 129.2, 126.9, 126.5, 121.4, 118.5, 117.8, 115.1, 115.0, 112.3, 102.2, 101.6, 57.3, 39.2, 38.9, 32.8, 32.7, 21.3, 21.1; HRMS (ESI) found 412.1878, $C_{23}H_{22}N_7O^+$ (MH$^+$) requires 412.1880.
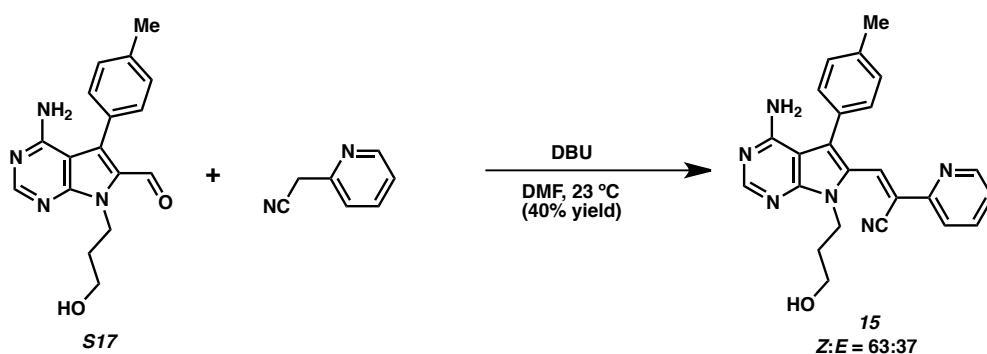
3-(4-amino-7-(3-hydroxypropyl)-5-(p-tolyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-2-(pyridin-2-yl)acrylonitrile, **15**: Aldehyde **S17** (30.5 mg, 98.3 µmol) and 2-(2-pyridyl)acetonitrile (13.9 mg, 117.9 µmol, 1.2 equiv.) were dissolved in DMF (2 mL) and DBU (29.4 µL, 197 µmol, 2.0 equiv.) was added. The reaction mixture was maintained at ambient temperature for 5 hours, then diluted with brine (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated to afford a residue that was then purified by HPLC (gradient of 5%B→80%B, 30 min; A = water with 0.1% TFA and B = MeCN with 0.1% TFA). The residue obtained from the purification was treated in solution in MeOH (5 mL) with amberlyst A-21 resin (100 mg) for 3 hours to remove residual TFA. The solution was then filtered and the filtrate was concentrated to afford 16.3 mg (40% yield, yellow solid) of the desired nitrile **15** as a mixture of Z and E isomers, Z:E = 63:37; ^{1}H NMR (400 MHz, $CDCl_3$): 8.62 (m, 1H, major isomer), 8.47 (s, 1H, major isomer), 8.30 (m, 3H, both isomers), 7.73 (td, J = 7.8 Hz, 1.8 Hz, 1H, major isomer), 7.53 (d, J = 7.9 Hz, 1H, major isomer), 7.44 (s, 1H, minor isomer), 7.40 (td, J = 7.8 Hz, 1.8 Hz, 1H, major isomer), 7.36 (m, 3H, both isomers), 7.29 (m, 4H, both isomers), 7.07 (m, 1H, minor isomer), 7.02 (d, J = 7.8 Hz, 1H, major isomer), 6.88 (d, J = 7.9 Hz, 1H, minor isomer), 6.82 (d, J = 7.9 Hz, 1H, major isomer), 5.39 (bs, 2H, major isomer), 5.14 (bs, 2H, minor isomer), 4.87 (bs, 1H, both isomers), 4.47 (m, 2H, major isomer), 4.35 (m, 2H, minor isomer), 3.49–3.42 (m, 2H, both isomers), 2.39 (3H, major isomer), 2.32 (s, 3H, minor isomer), 2.01–1.94 (m, 2H, both isomers); ^{13}C NMR (100 MHz, $CDCl_3$): 157.7, 157.4, 153.3, 153.0, 151.9, 151.6, 151.2, 149.9, 149.7, 149.5, 137.8, 137.4, 136.6, 133.4, 131.9, 130.9, 130.3, 129.9, 129.73, 129.72, 129.3, 127.3, 127.27, 124.0, 123.4, 123.2, 121.5, 120.2, 118.6, 118.3, 117.8, 116.2, 116.0, 102.0, 101.6, 57.3, 39.4, 38.8, 32.8, 32.3, 21.3, 21.1; HRMS (ESI) found 411.1929, $C_{24}H_{23}N_6O^+$ (MH$^+$) requires 411.1928.

3-(4-amino-7-(3-hydroxypropyl)-5-(*p*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)-2-(pyridin-3-yl)acrylonitrile, **16**: Aldehyde **S17** (22.0 mg, 70.9 µmol) and 2-(3-pyridyl)acetonitrile (16.8 mg, 141.8 µmol, 1.2 equiv.) were suspended in EtOH (2 mL) and DBU (21.2 µL, 142 µmol, 2.0 equiv.) was added. The reaction mixture was heated to 60 ºC for 21 hours, then cooled to ambient temperature and concentrated. The residue obtained was purified by preparative TLC (9:1 EtOAc/MeOH, 2 elutions) and then by HPLC to afford 25.3 mg (87% yield, yellow solid) of vinyl nitrile **16** as a mixture of *Z* and *E* isomers, Z:E = 64:36; ^{1}H NMR (400 MHz, CDCl$_3$): 8.82 (s, 1H, major isomer), 8.64 (d, *J* = 4.6 Hz, 1H, major isomer), 8.37 (d, *J* = 4.1 Hz, 1H, minor isomer), 8.31 (s, 1H, major isomer), 8.27 (s, 1H, minor isomer), 8.11 (m, 1H, minor isomer), 7.83 (m, 1H, major isomer), 7.56 (s, 1H, major isomer), 7.41 (s, 1H, minor isomer), 7.36–7.27 (m, 3H), 7.01–6.95 (m, 1H), 6.74 (d, *J* = 7.8 Hz, 1H, major isomer), 5.52 (bs, 2H, major isomer), 5.30 (bs, 2H, minor isomer), 4.44 (app t, *J* = 5.8 Hz, 2H), 3.51 (m, 2H), 2.39 (s, 3H, major isomer), 2.33 (s, 3H, minor isomer), 2.04–1.93 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): 157.8, 157.6, 153.3, 153.2, 151.74, 151.66, 150.6, 149.5, 148.3, 146.9, 138.1, 137.5, 134.9, 133.6, 132.1, 130.5, 130.31, 130.29, 129.89, 129.85, 129.7, 129.5, 129.3, 129.1, 127.1, 126.3, 123.6, 123.3, 120.1, 118.5, 118.0, 115.6, 115.3, 115.1, 101.8, 101.5, 57.34, 57.25, 39.00, 38.95, 32.9, 32.7, 21.3, 21.1; HRMS (ESI) found 411.1926, C$_{24}$H$_{23}$N$_6$O$^+$ (MH$^+$) requires 411.1928.
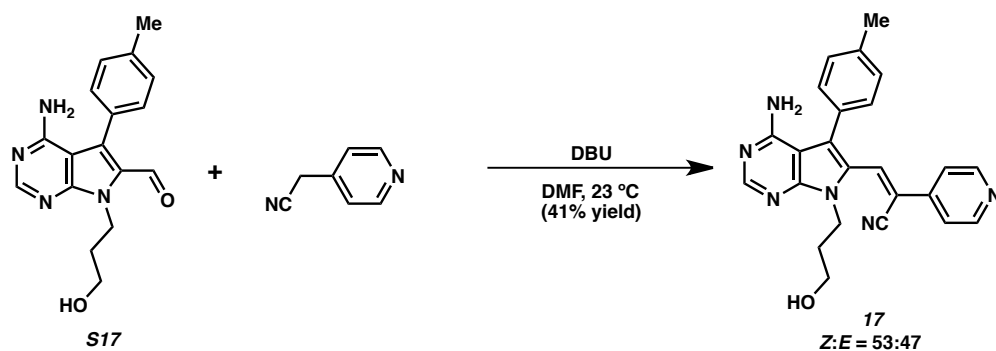
3-(4-amino-7-(3-hydroxypropyl)-5-(*p*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)-2-(pyridin-4-yl)acrylonitrile, **17**: Aldehyde **S17** (26.7 mg, 86.2 µmol) and 2-(4-pyridyl)acetonitrile hydrochloride (16.0 mg, 103.2 µmol, 1.2 equiv.) were dissolved in DMF (2 mL) and DBU (25.7 µL, 172 µmol, 2.0 equiv.) was added. The reaction mixture was maintained at ambient temperature for 6 hours, then diluted with brine (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated to afford a residue that was then purified by preparative TLC (9:1 EtOAc/MeOH) and preparative HPLC to afford 14.3 mg (41% yield, yellow solid) of the desired vinyl nitrile **17** as a mixture of *Z* (major) and *E* (minor) isomers, Z:E = 53:47; ^{1}H NMR (400 MHz, CDCl$_3$): 8.68 (s, 0.6H), 8.67 (s, 0.4H), 7.70 (s, 0.5H), 7.43 (m, 1.5H), 7.31 (ABq, J$_{AB}$ = Hz, 2H, both isomers),

7.02 (d, J = 7.9 Hz, 1H, both isomers), 6.74 (d, J = 7.8 Hz, 1H, both isomers), 6.70 (d, J = 5.4 Hz, 1H, both isomers), 5.39 (bs, 2H, major isomer), 5.18 (bs, 2H, minor isomer), 4.44 (m, 2H, both isomers), 3.51 (m, 2H, both isomers), 2.40 (s, 3H, major isomer), 2.34 (s,3H, minor isomer), 1.98 (m, 2H, both isomers); ^{13}C NMR (100 MHz, CDCl$_3$): 157.8, 157.6, 153.7, 153.5, 152.0, 151.8, 150.7, 150.5, 149.9, 140.5, 140.3, 138.2, 137.5, 133.1, 131.8, 130.5, 130.4, 130.1, 129.8, 129.6, 129.0, 126.8, 125.8, 121.9, 120.9, 119.8, 118.9, 118.2, 115.9, 115.6, 115.3, 102.0, 101.6, 57.4, 57.3, 39.0, 38.98, 32.9, 32.8, 21.3, 21.1; HRMS (ESI) found 411.1927, C$_{24}$H$_{23}$N$_6$O$^+$ (MH$^+$) requires 411.1928.
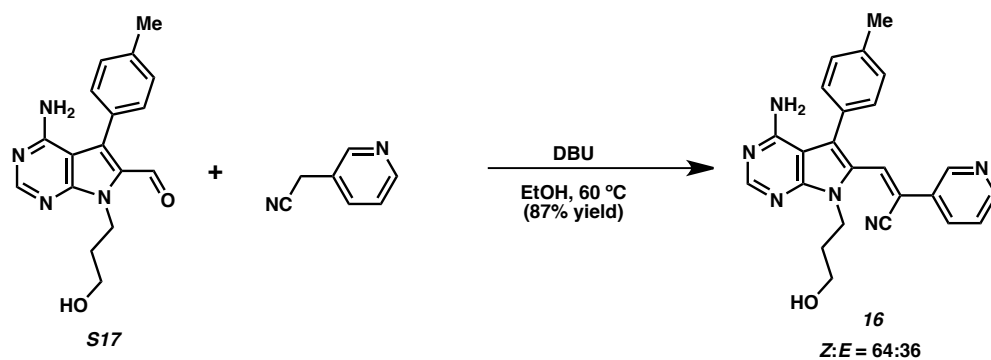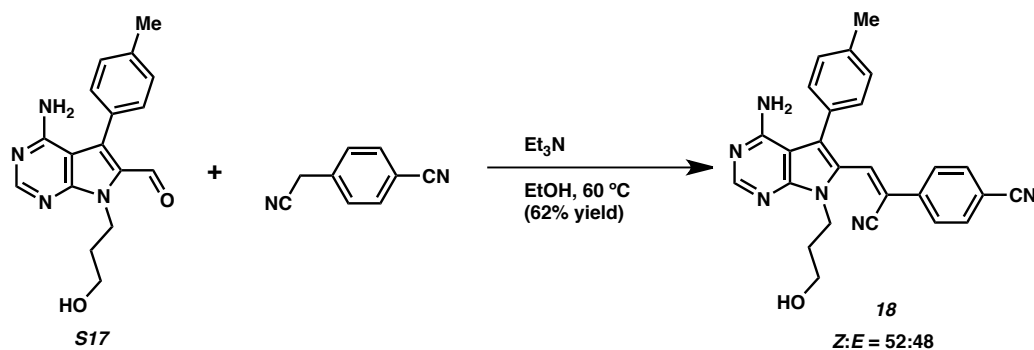

(*Z*) and (*E*)-4-(2-(4-amino-7-(3-hydroxypropyl)-5-(*p*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)-1-cyanovinyl)benzonitrile, **18**: Aldehyde **S17** (12.8 mg, 41.2 μmol) and 2-(4-cyanophenyl)acetonitrile (8.8 mg, 61.9 μmol, 1.5 equiv.) were dissolved in EtOH (3 mL) and triethylamine (17.2 μL, 124 μmol, 3.0 equiv.) was added. The reaction mixture was heated to 60 ºC whereupon a clear solution resulted. After 70 hours, the reaction mixture was concentrated and purified by preparative TLC (4:1 toluene/2-propanol) and then by preparative HPLC (gradient of 5%B→80%B, 30 min; A = water with 0.1% TFA and B = MeCN with 0.1% TFA). The residue obtained from the purification was treated in solution in MeOH (5 mL) with amberlyst A-21 resin (100 mg) for 3 hours to remove residual TFA. The solution was then filtered and the filtrate was concentrated to afford 11.1 mg (62% yield, yellow solid) of the desired vinyl nitrile **18** as a mixture of geometric isomers (Z:E = 52:48); R$_f$ 0.21 (SiO$_2$, 4:1 toluene/2-propanol) ^{1}H NMR (400 MHz, CDCl$_3$): 8.33 (s, 1H, major isomer), 8.30 (s, 1H, minor isomer), 7.71 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.60 (s, 1H, major isomer), 7.42 (s, 1H, minor isomer), 7.34–7.27 (m, 3H), 7.01 (d, J = 7.8 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 5.36 (bs, 2H, major isomer), 5.14 (bs, 2H, minor isomer), 4.64 (t, J = 6.9 Hz, 1H), 4.44 (m, 2H), 3.50 (m, 2H), 2.39 (s, 3H, major isomer), 2.34 (s, 3H, minor isomer), 2.03–1.92 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): 157.8, 157.5, 153.7, 153.6, 152.0, 151.9, 138.2, 137.6, 137.5, 137.3, 132.8, 132.6, 132.1, 131.4, 130.6, 130.4, 129.9, 129.7, 129.1, 128.5, 126.9, 126.6, 126.0, 120.7, 118.7, 118.3, 118.0, 116.4, 116.3, 115.6, 113.3, 112.4, 102.0, 101.6, 57.4, 57.3, 39.0, 32.9, 32.8, 21.3, 21.1; HRMS (ESI) found 435.1925, C$_{26}$H$_{23}$N$_6$O$^+$ (MH$^+$) requires 435.1928.
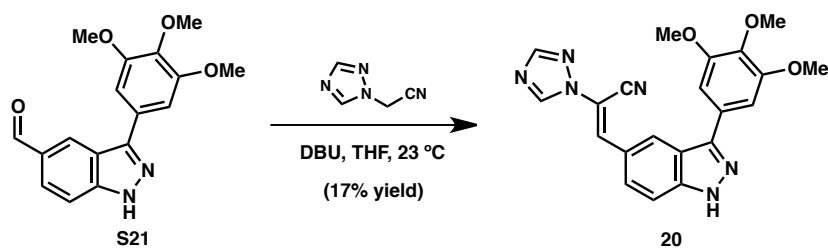
(*E*)-(2-(1*H*-1,2,4-triazol-1-yl)-3-(3-(3,4,5-trimethoxyphenyl)-1*H*-indazol-5-yl)acrylonitrile **20**: To a solution of 3-(3,4,5-trimethoxyphenyl)-1*H*-indazole-5-carbaldehyde **S21**[4] (400 mg, 1.28 mmol) and 2-(1*H*-1,2,4-triazol-1-yl)acetonitrile (140 mg, 1.28 mmol) in THF (5 mL) was added DBU (192 µL, 1.28 mmol). The yellowish solution became bright orange as the reaction progressed. After 16 h, the reaction mixture was concentrated and the crude residue was purified by silica gel chromatography, (49:49:2 EtOAc:hexanes:MeOH), to afford 85 mg (17%) of acrylonitrile **20** as a bright yellow solid. R_f (SiO$_2$, 49:49:2 EtOAc:hexanes:MeOH): 0.17 ^{1}H NMR (400 MHz, DMSO) δ 9.13 (s, 1H), 8.72 (s, 1H), 8.33 (s, 1H), 8.31 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.22 (s, 2H), 3.92 (s, 6H), 3.74 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 153.37, 152.63, 144.78, 143.78, 143.75, 142.25, 138.68, 137.73, 128.44, 127.22, 123.50, 123.35, 120.27, 114.45, 111.68, 105.43, 104.23, 60.13, 56.03. HRMS (ESI) found 401.1362, C$_{21}$H$_{17}$N$_6$O$_3^-$ (M–H$^-$) requires 401.1368.
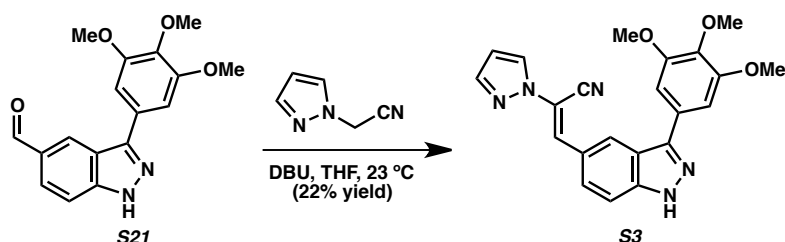
2-(1*H*-pyrazol-1-yl)-3-(3-(3,4,5-trimethoxyphenyl)-1*H*-indazol-5-yl)acrylonitrile, **S3**: To a solution of 3-(3,4,5-trimethoxyphenyl)-1*H*-indazole-5-carbaldehyde **S21**[4] (50 mg, 0.16 mmol) and 2-(1*H*-pyrazol-1-yl)acetonitrile (17.1 mg, 1.0 equiv.) in THF (1 mL) was added DBU (24 µL, 1.0 equiv.). The reaction mixture was maintained at ambient temperature for 17 hours. The reaction mixture was concentrated and purified by preparative TLC (2:1 Hexanes/Acetone) to afford 14 mg (22% yield, E:Z = 77:23) of acrylonitrile **S3** as a yellow solid. R_f (SiO$_2$, 3:2 Hexanes/Acetone) 0.32. ^{1}H NMR (CDCl$_3$, 400 MHz): 8.61 (m, 1H, major isomer), 8.09 (s, 1H, major isomer), 7.94 (dd, J = 2.5, 0.6 Hz, 1H, major isomer), 7.80–7.76 (m, 2H, minor isomer, 1H, major isomer), 7.74 (d, J = 1.6 Hz, 1H, major isomer), 7.59 (d, J = 8.8 Hz, 1H, major isomer), 7.51 (dd, J = 2.5, 0.6 Hz, 1H, minor isomer), 7.39 (m, 2H, minor isomer), 7.21 (s, 2H, major isomer), 7.03 (s, 2H, minor isomer), 6.90 (m, 1H, minor isomer), 6.51 (dd, J = 2.5, 1.8 Hz, 1H, major isomer), 6.43 (dd, J = 2.5, 1.9 Hz, 1H, minor isomer), 4.00 (s, 6H, major isomer), 3.95 (s, 6H, minor isomer), 3.94 (s, 3H, major isomer), 3.93 (s, 3H, minor isomer); ^{13}C NMR (CDCl$_3$, 125 MHz): 153.8, 153.7, 147.1, 142.3, 142.2, 142.1, 140.7, 138.6, 132.9, 130.5, 128.5, 128.4, 128.2, 128.0, 127.9, 124.90, 124.87, 124.6, 122.3, 121.3, 114.7, 110.9, 110.7, 109.7, 108.6, 108.3, 105.1, 104.7, 61.1, 61.0, 56.5, 56.4. ESI-MS: 400 (M–H$^-$): 100%

Thioethers **3a–6a**, **10a**, and **11a** could not be isolated for characterization, but were generated in the presence of 1.0–2.0 equiv of BME-*d*6. ^{1}H NMR data for these non-isolable thioether adducts are shown below.
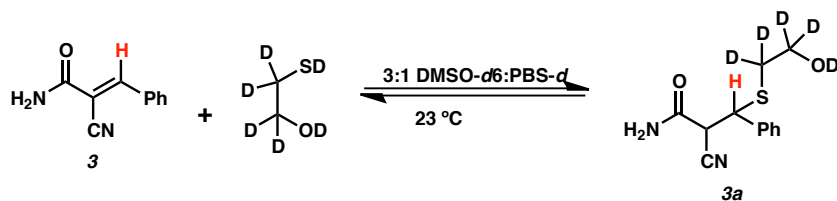
Thioether **3a** (mixture of diastereomers). ^{1}H NMR (400 MHz, 3:1 DMSO-*d6*: PBS-*d*): 7.34–7.24 (m, 5H), 4.37 (s, 1H, minor diastereomer), 4.33 (s, 1H, major diastereomer).
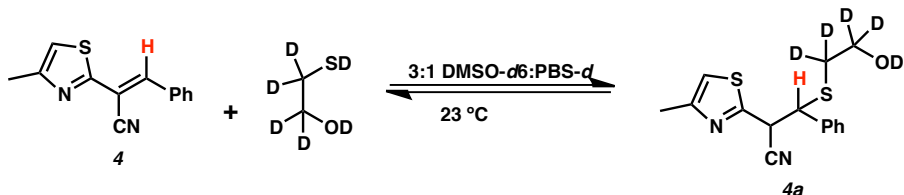
Thioether **4a** (mixture of diastereomers). ^{1}H NMR (400 MHz, 3:1 DMSO-*d6*: PBS-*d*): 7.31–7.18 (m, 5H), 7.17 (m, 1H, major diastereomer), 7.07 (m, 1H, minor diastereomer), 4.54 (s, 1H, minor diastereomer), 4.50 (s, 1H, major diastereomer), 2.28 (d, *J* = 1.0 Hz, 3H, major diastereomer), 2.23 (d, *J* = 1.0 Hz, 3H, minor diastereomer).
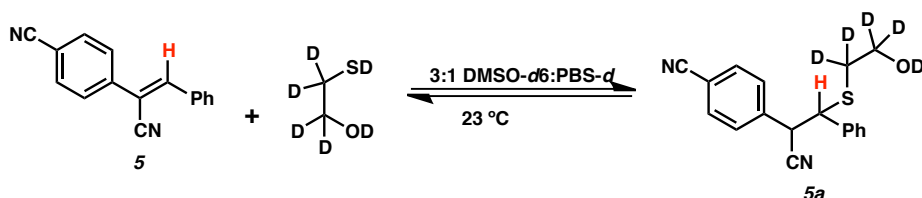
Thioether **5a** (mixture of diastereomers). ^{1}H NMR (400 MHz, 3:1 DMSO-*d6*: PBS-*d*): 7.67 (d, *J* = 8.1 Hz, 2H, major diastereomer), 7.59 (d, *J* = 8.1 Hz, 2H, minor diastereomer), 7.38 (m, 2H), 7.24–7.08 (m, 5H), 4.46 (s, 1H, minor diastereomer), 4.37 (s, 1H, major diastereomer).
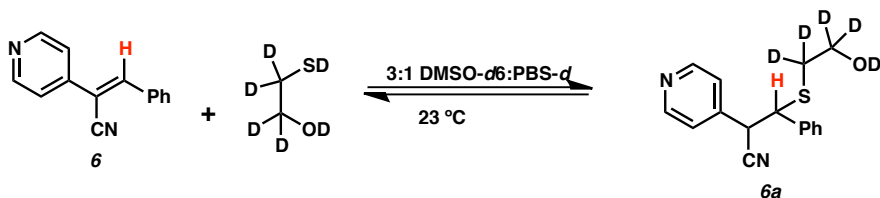
Thioether **6a** (mixture of diastereomers). ^{1}H NMR (400 MHz, 3:1 DMSO-*d6*: PBS-*d*): 8.46 (m, 2H), 8.39 (m, 2H), 7.30–7.15 (m, 5H), 4.53 (s, 1H, minor diastereomer), 4.45 (s, 1H, major diastereomer).
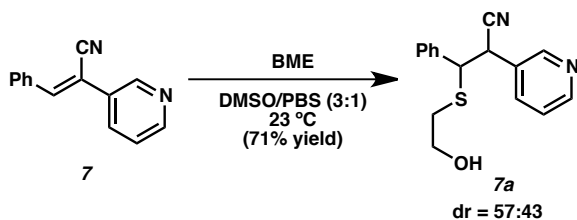
3-((2-hydroxyethyl)thio)-3-phenyl-2-(pyridin-3-yl)propanenitrile, **7a**. Vinyl nitrile **7** (35.6 mg, 0.173 mmol) was dissolved in DMSO (1.5 mL) and PBS (0.5 mL). β-mercaptoethanol (BME, 150 μL, 12.4 equiv.) was then added. After 2 hours at ambient temperature, complete conversion to the adducts was observed. The reaction mixture was diluted with brine (10 mL) and extracted with EtOAc (3 x 5 mL). The combined EtOAc extracts were dried (MgSO$_4$), concentrated and the residue obtained was purified by preparative TLC (6:1 toluene: 2-propanol, 2 elutions) to afford 34.7 mg (71% combined yield, dr =

57:43) of the BME adducts **7** as a colorless oil. The relative stereochemistry of each diastereomer was not determined. R_f (SiO$_2$, 6:1 toluene/2-propanol): 0.34; ^{1}H NMR (400 MHz, CDCl$_3$): 8.55 (dd, J = 4.8Hz, 1.6Hz, 0.57H, major diastereomer), 8.50 (dd, J = 4.8Hz, 1.6Hz, 0.43H, minor diastereomer), 8.42 (d, J = 2.3Hz, 0.57H, major diastereomer), 8.31 (d, J = 2.4Hz, 0.43H, minor diastereomer), 7.50 (dt, J = 8.0Hz, 2.0Hz, 0.47H, minor diastereomer), 7.42 (dt, J = 7.9Hz, 2.0Hz, 0.53H, major diastereomer), 7.31 (m, 2H), 7.27–7.20 (m, 3H), 7.17 (m, 1H), 4.42 (d, J = 6.7Hz, 0.57H, major diastereomer), 4.28 (d, J = 7.8Hz, 0.57H, major diastereomer), 4.27 (d, J = 6.7Hz, minor diastereomer), 4.23 (d, J = 7.8Hz, minor diastereomer), 3.90 (t, J = 5.8Hz, 0.43H, minor diastereomer), 3.65 (m, 2H), 2.88 (t, J = 5.8Hz, 0.57H, major diastereomer), 2.65–2.55 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): 149.8, 149.7, 149.3, 137.1, 136.5, 135.9, 135.8, 129.4, 129.3, 128.9, 128.8, 128.7, 128.5, 128.2, 123.44, 123.36, 118.3, 117.8, 61.4, 61.0, 53.9, 53.5, 42.7, 42.4, 35.3, 35.0
HRMS (ESI) found 285.1056, C$_{16}$H$_{17}$ON$_2$S (MH$^+$) requires 285.1056.
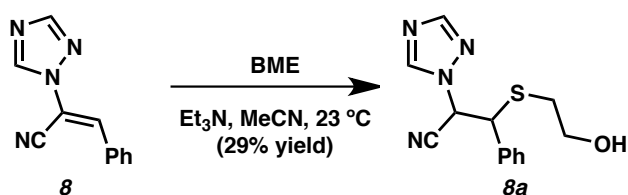
3-((2-hydroxyethyl)thio)-3-phenyl-2-(1H-1,2,4-triazol-1-yl)propanenitrile, **8a**. To vinyl nitrile **8** (14.9 mg, 0.076 mmol) in MeCN (1 mL) was added Et3N (21 µL, 2.0 equiv.), followed by BME (16 µL, 3.0 equiv). The reaction mixture was maintained at ambient temperature for 2 hours, then concentrated under reduced pressure. The residue was purified by preparative TLC (5:1 v/v PhH/IPA, 2 elutions) to afford 2.6 mg (13% yield) of the minor (higher R_f) diastereomer and 3.4 mg (16% yield) of the (lower R_f) major diastereomer. The relative configuration of each diastereomer was not determined.

Major diastereomer, **8a1**. R_f (5:1 PhH/IPA): 0.21; ^{1}H NMR (400 MHz, CD$_3$CN): 8.34 (s, 1H), 8.03 (s, 1H), 7.44–7.40 (m, 5H), 6.00 (d, J = 9.7Hz, 1H), 4.68 (d, J = 9.7Hz, 1H), 3.47 (m, 2H), 2.90 (t, J = 5.6Hz, 1H), 2.32 (app. t, J = 6.2Hz, 2H); ^{13}C NMR (100 MHz, CD$_3$CN): 153.8, 145.9, 137.8, 130.1, 129.9, 129.3, 115.6, 62.1, 56.1, 53.4, 35.0; HRMS (ESI) found 273.0821, C$_{13}$H$_{13}$ON$_4$S [(M–H)$^-$] requires 273.0816.

Minor diastereomer, **8a2**. R_f (5:1 PhH/IPA): 0.28; ^{1}H NMR (400 MHz, CDCl$_3$): 7.97 (s, 1H), 7.89 (s, 1H), 7.32 (m, 3H), 7.22 (m, 2H), 5.54 (d, J = 8.1Hz, 1H), 4.65 (d, J = 8.1Hz, 1H), 3.74 (m, 2H), 2.74 (m, 2H), 2.12 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): 152.9, 143.4, 135.5, 129.3, 129.2, 127.7, 114.1, 61.4, 56.7, 52.8, 35.9; HRMS (ESI) found 273.0817, C$_{13}$H$_{13}$ON$_4$S [(M–H)$^-$] requires 273.0816.
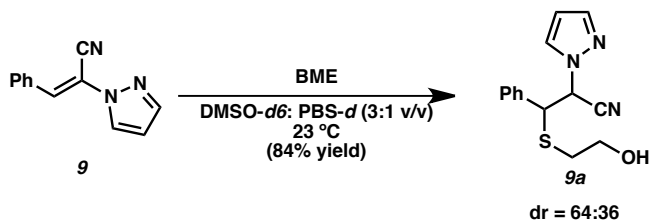
3-[(2-hydroxyethyl)thio)-3-phenyl-2-(1H-pyrazol-1-yl]propanenitrile, **9a**. Vinyl nitrile **9** (34.2 mg, 0.175 mmol) was dissolved in DMSO (0.75 mL). Phosphate-buffered saline (PBS, 0.25 mL) was

added, followed by BME (123 µL, 10.0 equiv.). The reaction was maintained at ambient temperature for 72 hours, then diluted with brine (10 mL) and extracted with EtOAc (3 x 5mL). The combined extracts were concentrated to afford a colorless oil, which was purified by preparative TLC (1:1 hexanes/EtOAc, 3 elutions) to afford 17.1 mg (36% yield) of a colorless oil (minor diastereomer) and 21.6 mg (45% yield) of a white solid (major diastereomer, dr = 56:44). The relative stereochemistry of each diastereomer was not determined.

3-[(2-hydroxyethyl)thio)-3-phenyl-2-(1H-pyrazol-1-yl]propanenitrile, **9a1**, 'major' diastereomer: R_f 0.33(SiO$_2$, 1:1 hexanes: EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$): 7.64 (d, J = 1.8 Hz, 1H), 7.37–7.27 (m, 6H), 6.27 (app. t, J = 2.2 Hz, 1H), 5.63 (d, J = 8.2 Hz, 1H), 4.65 (d, J = 8.2 Hz, 1H), 3.68 (app. q, J = 5.3 Hz, 2H), 2.53 (m, 2H), 2.32 (t, J = 5.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): 141.5, 135.6, 130.0, 129.1, 128.2, 114.5, 106.9, 61.3, 58.3, 52.6, 35.0; HRMS (ESI) found 274.1008, C$_{14}$H$_{16}$N$_3$OS$^+$ (MH$^+$) requires 274.1009.

3-[(2-hydroxyethyl)thio)-3-phenyl-2-(1H-pyrazol-1-yl]propanenitrile, **9a2**, 'minor' diastereomer: R_f 0.39(SiO$_2$, 1:1 hexanes: EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$): 7.56 (d, J = 1.9 Hz, 1H), 7.31–7.24 (m, 6H), 6.18 (app. t, J = 2.2 Hz, 1H), 5.48 (d, J = 7.7 Hz, 1H), 4.64 (d, J = 7.7 Hz, 1H), 3.69 (m, 2H), 2.68 (m, 2H), 2.25 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): 141.4, 136.2, 129.8, 129.0, 128.7, 127.9, 115.1, 106.6, 61.1, 58.9, 53.1, 53.0; MS(ESI): found 274.1 [C$_{14}$H$_{16}$N$_3$OS$^+$ (MH$^+$)].
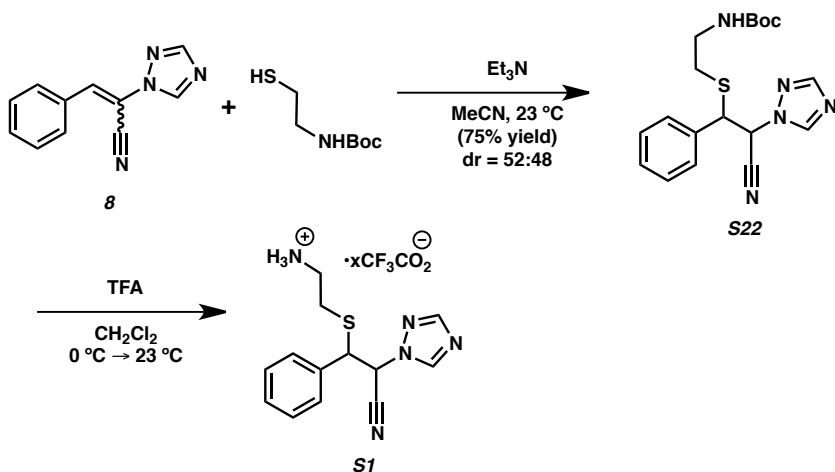
2-((2-cyano-1-phenyl-2-(1H-1,2,4-triazol-1-yl)ethyl)thio)ethanaminium 2,2,2-trifluoroacetate, **S1**. Vinyl nitrile **8** (mixture of E and Z isomers, 35.6 mg, 181 µmol) was dissolved in MeCN (1 mL) in the presence of triethylamine (30 µL, 1.2 equiv.). N-Boc-2-aminoethanethiol (123 µL, 4.0 equiv.) was added in one portion. The reaction mixture was maintained at ambient temperature for 2 hours, then purified by preparative TLC (2 elutions with 5:1 PhH/MeCN) to afford thioether **S22** as a colorless oil (50.5 mg, 75% yield, dr = 52:48). R_f (4:1 PhH/MeCN) 0.31. ^{1}H NMR (CDCl$_3$, 400 MHz): 8.03 (s, 1H, minor diastereomer), 7.97 (s, 1H, major diastereomer), 7.95 (s, 1H, minor diastereomer), 7.89 (s, 1H, major diastereomer), 7.37 (m, 2H), 7.28 (m, 2H), 7.23 (m, 1H), 5.68 (d, 1H, J = 7.5 Hz, major diastereomer), 5.51 (d, J = 8.3 Hz, 1H, minor diastereomer), 4.81 (m, 1H), 4.55 (m, 1H), 3.23 (m, 2H), 2.64 (m, 2H, major diastereomer), 2.51 (m, 2H, minor diastereomer), 1.44 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz): 155.7, 152.94, 152.86, 143.5, 143.4, 135.5, 134.7, 129.4, 129.23, 129.2, 129.1, 128.1, 127.6, 79.7, 56.4, 56.0, 52.42, 52.39, 51.9, 33.5, 33.1, 32.5, 28.3;
Thioether **S22** was dissolved in CH$_2$Cl$_2$ (1 mL). The solution was cooled in an ice-water bath, and TFA (1 mL) was added over 1 minute. The reaction mixture was allowed to warm to ambient temperature

and after 45 minutes was concentrated in vacuo to afford the crude thioether **S1** as a trifluoroacetate salt, which was not purified further. ^{1}H NMR (DMSO-$d6$, 400 MHz): 8.69 (s, major diastereomer, 1H), 8.27 (s, minor diastereomer, 1H), 8.22 (s, major diastereomer, 1H), 8.03 (s, minor diastereomer, 1H), 7.87 (bs, minor diastereomer, 3H), 7.77 (bs, major diastereomer, 3H), 7.52–7.37 (m, 3H), 7.27–7.22 (m, 2H), 6.71 (d, J = 10.5 Hz, 1H), 4.88 (d, J = 10.5 Hz, minor diastereomer,1H), 4.84 (d, J = 10.5 Hz, major diastereomer,1H); ^{13}C NMR (DMSO-$d6$, 100 MHz): 158.5 (q, J_{CF} = 37.1 Hz), 152.9, 152.5, 145.5, 144.7, 136.8, 136.2, 129.0, 128.8, 128.7, 128.4, 128.2, 127.8, 116.9, 115.5 (q, J_{CF} = 96.4 Hz), 53.64, 53.62, 51.4, 50.7, 31.3, 29.2, 28.2, ESI-MS: 274 (M[+], 100%).
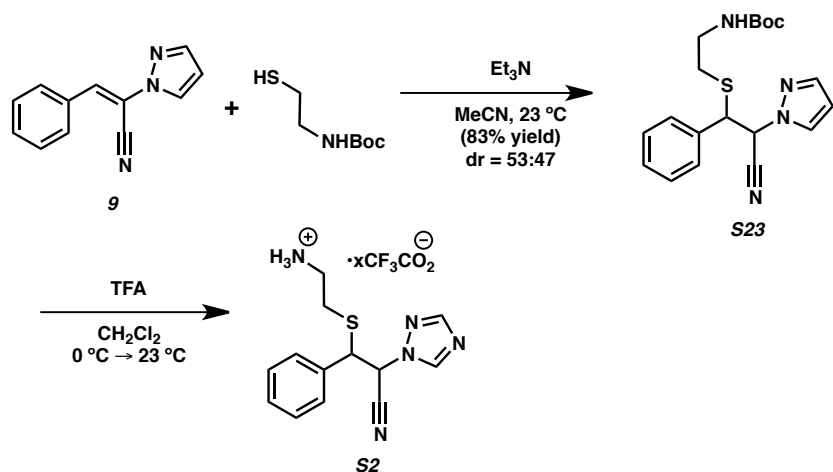
2-((2-cyano-1-phenyl-2-(1*H*-pyrazol-1-yl)ethyl)thio)ethanaminium 2,2,2-trifluoroacetate, **S2**. Vinyl nitrile **9** (28.8 mg, 147.5 μmol) was dissolved in MeCN (1 mL) in the presence of triethylamine (21 μL, 1.0 equiv.). *N*-Boc-2-aminoethanethiol (100 μL, 4.0 equiv.) was added in one portion. The reaction mixture was maintained at ambient temperature for 3 hours, then purified by preparative TLC (2 elutions with 4:1 Hexanes/EtOAc) to afford thioether **S23** as a colorless oil (45.4 mg, 83% yield, dr = 53:47). R_f (2:1 Hexanes/EtOAc): 0.39. ^{1}H NMR (CDCl$_3$, 400 MHz): 7.62 (d, J = 1.5 Hz, 1H, minor diastereomer), 7.55 (d, J = 1.5 Hz, 1H, major diastereomer), 7.36–7.24 (m, 6H), 6.25 (m, 1H, minor diastereomer), 6.17 (m, 1H, major diastereomer), 5.55 (d, J = 7.9 Hz, 1H, minor diastereomer), 5.44 (d, J = 8.0 Hz, 1H, major diastereomer), 4.79 (bs, 1H), 4.56 (m, 1H), 3.20 (m, 2H), 2.57 (app. t, J = 6.4 Hz, 1H), 2.42 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz): 158.5 (q, J_{CF} = 37.4 Hz), 155.6, 141.4, 136.3, 135.5, 129.9, 129.7, 129.08, 129.05, 128.9, 128.7, 128.2, 127.8, 115.0, 114.4, 106.8, 106.6, 79.5, 58.8, 58.4, 52.9, 52.5, 33.1, 32.4, 28.3; ESI-MS: 417.8 (M+HCOO[−]): 100%

Thioether **S23** was dissolved in CH$_2$Cl$_2$ (1 mL) and TFA (1 mL) was added over 1 minute. The reaction mixture was concentrated in vacuo after 1 hour to afford the crude thioether **S2** as a trifluoroacetate salt, which was not purified further. ^{1}H NMR (DMSO-$d6$, 400 MHz): 7.91–7.80 (m, 4H), 7.52–7.19 (m, 6H), 6.48 (t, J = 10.0 Hz, 1H), 6.39 (m, 1H, major diastereomer), 6.09 (m, 1H, minor diastereomer), 4.87 (d, J = 10.9 Hz, 1H, major diastereomer), 4.83 (d, J = 10.3 Hz, 1H, minor diastereomer), 2.95–2.69 (m, 3H), 2.33 (m, 1H); ^{13}C NMR (DMSO-$d6$, 100 MHz): 158.7, 158.3, 141.1, 140.8, 131.7, 130.8, 128.9, 128.6, 128.4, 128.3, 128.1, 127.8, 116.9, 116.0, 106.5, 106.1, 55.9, 55.7, 51.8, 51.0, 29.1, 28.1; ESI-MS: 273 (MH[+]): 100%
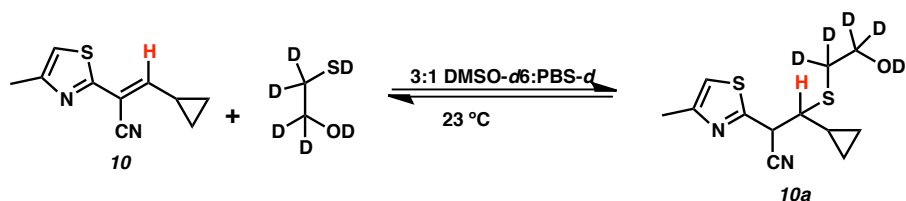
Thioether **10a** (mixture of diastereomers). ^{1}H NMR (400 MHz, 3:1 DMSO-$d6$: PBS-d): 7.17 (m, 1H), 2.72 (d, $J = 6.8$ Hz, 1H, diastereomer 1), 2.70 (d, $J = 6.8$ Hz, 1H, diastereomer 2), 2.26 (d, $J = 0.9$ Hz, 3H), 0.80 (m, 0.6H), 0.57–0.17 (m, 3.9H), –0.06 (m, 0.5H).
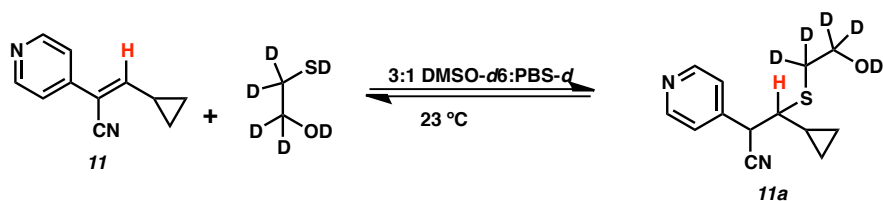
Thioether **11a** (mixture of diastereomers). ^{1}H NMR (400 MHz, 3:1 DMSO-$d6$: PBS-d): 8.47 (m, $J = 2$H), 7.37 (m, 2H), 7.63–7.60 (m, 1H), 2.64 (d, $J = 9.9$ Hz, 1H, major diastereomer), 2.60 (d, $J = 9.5$ Hz, 1H, minor diastereomer), 0.82 (m, 0.5H), 0.70 (m, 0.5H), 0.56-0.23 (m, 3H), 0.14 (m, 0.5H), –0.21 (m, 0.5H).
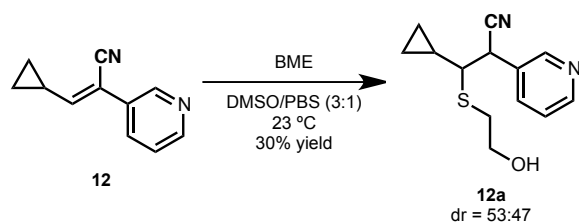
3-cyclopropyl-3-((2-hydroxyethyl)thio)-2-(pyridin-3-yl)propanenitrile, **12a**. Vinyl nitrile **12** (33.8 mg, 0.199 mmol) was dissolved in DMSO (1.5 mL) and PBS (0.5 mL). BME (150 µL, 10.8 equiv.) was then added. After 3.5 hours at ambient temperature, 89% conversion to the adducts was observed. Additional BME (150 µL) was added and the reaction mixture was maintained at ambient temperature for a further 18 hours. The reaction mixture was then diluted with brine (10 mL) and extracted with EtOAc (3 x 5 mL). The combined EtOAc extracts were dried (MgSO$_4$), concentrated and the residue obtained was purified by preparative TLC (6:1 toluene: 2-propanol, followed by 2:1 toluene/TBME) to afford 14.8 mg (30% combined yield, dr = 53:47) of a mixture of the BME adducts, **12a** as a colorless oil. The relative stereochemistry of each diastereomer was not determined. R$_f$ (SiO$_2$, 6:1 toluene/2-propanol): 0.29; ^{1}H NMR (400 MHz, CDCl$_3$): 8.61 (m, 2H), 7.85 (m, 1H), 7.35 (m, 1H), 4.37 (d, $J = 4.9$Hz, 0.53H, major diastereomer), 4.29 (d, $J = 5.0$Hz, 0.47H, minor diastereomer), 3.91 (t, $J = 5.8$Hz, 0.28H), 3.79 (t, $J = 5.8$Hz, 1.06H, major diastereomer), 3.66 (t, $J = 5.8$Hz, 0.94H, minor diastereomer), 2.90–2.68 (m, 2H), 2.63–2.55 (m, 1.13H), 2.50 (m, 0.59H), 0.94 (m, 1H), 0.75–0.58 (m, 2H), 0.46–0.31 (m, 1.47H), 0.05 (m, 0.53H, major diastereomer); ^{13}C NMR (100 MHz, CDCl$_3$): 149.7, 149.6, 149.5, 149.4, 136.1, 129.5, 129.4, 123.53, 129.45, 118.5, 118.4, 61.9, 61.4, 54.9, 54.4, 42.2, 42.1, 35.0, 34.9, 15.3, 13.9, 7.0, 6.3, 5.2, 4.8; HRMS (ESI) found 249.1055, C$_{13}$H$_{17}$ON$_2$S (MH$^+$) requires 249.1056.
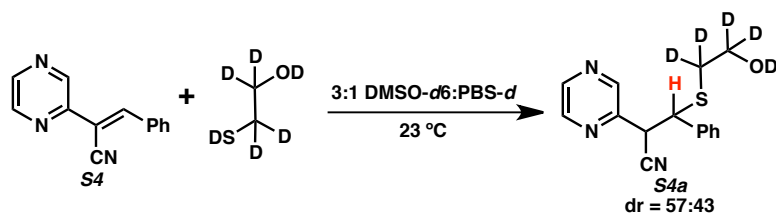
Thioether **S4a** (57:43 mixture of diastereomers). ^{1}H NMR (400 MHz, 3:1 DMSO-*d6*: PBS-*d*): 8.63 (m, 2H, major diastereomer), 8.60 (m, 1H, major diastereomer), 8.58 (dd, J = 2.5, 1.5 Hz, 1H, minor diastereomer), 8.46 (d, J = 2.6 Hz, 1H, minor diastereomer), 8.31 (m, 1H, minor diastereomer), 7.33 (m, 5H, major diastereomer), 7.18 (m, 5H, minor diastereomer), 5.08 (d, J = 9.4 Hz, 1H, major diastereomer), 5.02 (d, J = 9.6 Hz, 1H, minor diastereomer), 4.55 (d, J = 9.6 Hz, 1H, minor diastereomer), 4.54 (s, 1H, minor diastereomer), 4.48 (d, J = 9.4 Hz, 1H, major diastereomer), 4.47 (s, 1H, major diastereomer). The adduct had undergone ~ 33% D/H exchange at the methine bearing the heteroaryl and nitrile groups. As a result, the doublets at 4.55 ppm and 4.48 ppm are visible, along with the corresponding singlets at 4.54 ppm and 4.47 ppm.

5. Determination of thioether β-elimination kinetics using LC-MS/MS

A solution (500 µM) of the thioether in DMSO was diluted into PBS, pH 7.4 to afford a 5 µM solution. Aliquots of the solution were quenched by addition of an equal volume of 4% formic acid in MeCN, prior to analysis immediately and at subsequent time points by LC-MS/MS using a method specific to each compound. LC-MS/MS analysis was performed using a Waters Acquity UPLC/ESI-TQD instrument with a 2.1 x 50 mm Acquity UPLC BEH C$_{18}$ column and gradient methods of 2.5 or 5 minutes using 0.1% formic acid/water and 0.1% formic acid/MeCN as eluents. The amount of adduct remaining at each time point was quantified and the apparent first-order rate constant was determined by fitting the data to a first-order decay curve using PRISM (4.0). All reactions were followed to >90% completion, and no side products were detected. Pyridines **7** and **12** and pyrazoles **9** and **S2**, and triazole **S1** were evaluated as diastereomeric mixtures. For triazole **8**, a single diastereomer was employed; however, this equilibrated to an equilibrium diastereomeric mixture faster than β-elimination.

6. Expression and Purification of RSK2-CTD WT, C436V and T493M mutant

RSK2-CTD (mouse RSK2 399-740) was expressed in *E. coli* as described previously[5] and purified by Ni/NTA affinity chromatography (50 mM Tris pH 8.0, 0.5 M NaCl) with gradient elution (10–500 mM imidazole), followed by cleavage of the His6-tag with enterokinase (EMD Biosciences) and further purification by HiLoad 16/60 Superdex-75 size exclusion chromatography (20 mM Tris pH 8.0, 50 mM NaCl, 1 mM DTT). Purified protein was concentrated and stored in 20 mM Tris pH 8.0, 50 mM NaCl, 1 mM DTT, 12% glycerol.

7. In vitro kinase assays

WT or mutant RSK2-CTD (10 µM) was first activated by His6-ERK2 (10 µM in 20 mM Hepes pH 8.0, 10 mM MgCl$_2$, 2.5 mM TCEP, 0.2 mg/mL BSA, 200 µM ATP) for 30 min at room temp. Active RSK2-CTD (5 nM in 20 mM Hepes pH 8.0, 10 mM MgCl$_2$, 2.5 mM TCEP, 0.25 mg/mL BSA, 100 µM ATP) was then treated with inhibitors (ten concentrations, in duplicate) for 30 min. Kinase reactions were initiated by the addition of 5 µCi of [γ-^{32}P]ATP (6000 Ci/mmol, NEN) and 167 µM peptide substrate (RRQLFRGFSFVAK, CTD-tide) and incubated at room temp for 30 min. Kinase activity was determined by spotting 5 µL of each reaction onto P81 cation exchange paper (Whatman). Each blot was washed once with 1% AcOH solution, twice with 0.1% H$_3$PO$_4$ solution, and once with

MeOH (5-10 minutes per wash). Dried blots were exposed for 30 min to a storage phosphor screen and scanned by a Typhoon imager (GE Life Sciences). The data were quantified using ImageQuant 5.2 software and fit using PRISM 4.0. Inhibitor IC50s are averaged over two (RSK2 CTD C436V mutant) or three (RSK2 CTD WT) independent measurements. NEK2 and PLK1 were assayed as described[4].

8. Assay for RSK1/2 occupancy using MDA-MB-231 cells
For compounds **13–18**:

MDA-MB-231 cells were seeded into 6-well plates at 300,000 cells/well. After 48 h, the media was exchanged with fresh DMEM supplemented with 10% FBS, and the cells were treated for 2 h with the indicated concentrations of inhibitors, followed by 1 h incubation with 2 µM of the **FMK-BODIPY** probe in serum-free DMEM. The media was aspirated and the cells were washed with 2 mL of cold PBS and lysed with 70 µL CelLytic lysis buffer (Sigma) supplemented with protease (Complete, Roche) and phosphatase (PhoStop, Roche) inhibitors. The lysates were cleared by centrifugation at 14K rpm for 15 min at 4 ˚C and normalized by Bradford assay. Laemmli sample buffer was added to the lysates and the proteins were separated by 7.5% SDS-PAGE and detected by in-gel fluorescence scanning with a Typhoon 9400 flatbed laser-induced scanner, and transferred to nitrocellulose with a semi-dry transfer apparatus. Membranes were blocked for 1 hour using Odyssey Blocking Buffer and followed by incubation with 1:500 dilutions of RSK1 (C-21, Santa Cruz sc-231) and RSK2 (E-1, Santa Cruz sc-9986) antibodies at 4 ºC for 16 h. After incubation with primary antibodies, immunoblots were washed with TBST and incubated for 1 hour with 1:10,000 dilutions of infra-red dye-labeled secondary antibodies (IR680 or IR800) in TBST supplemented with 5% milk. Blots were washed and then visualized using the LI-COR Odyssey infrared imaging system (LI-COR Biosciences, Lincoln, NE).

Comparison of **19** and **20**:
MB-MDA-231 cells were seeded into 6-well plates at an initial density of 300,000 cells/well in 2 mL media and grown overnight. Each well was treated with 1 µM inhibitor (or DMSO) for 2 or 24 hours, followed by treatment with 0.6 mL of 2 µM **BODIPY-FMK** for 1 hour. Cells were washed with cold PBS and frozen at –80 °C prior to lysis in 60 µL of lysis buffer (50 mM HEPES, pH 7.4, 150 mM NaCl, 0.1% Triton X100 supplemented with phosphatase and protease inhibitor cocktails (Roche)). Lysates were clarified by centrifugation at 14,000 rpm, normalized by Bradford assay, denatured in SDS and separated by 7.5% SDS-PAGE. Gels were scanned with a Typhoon imaging system (Amersham Biosciences) and transferred to nitrocellulose with a semi-dry transfer apparatus. Membranes were blocked for 1 hour using Odyssey Blocking Buffer and incubated with 1:500 dilutions of antibodies against RSK1 and RSK2 (Santa Cruz Biotechnology, Inc.) at 4 °C overnight. Membranes were washed with TBST and incubated for 1 hour with 1:10,000 dilutions of fluorescently labeled secondary antibodies (Odyssey LiCOR) in TBST supplemented with 5% milk. Blots were washed thoroughly and scanned using an Odyssey LiCOR instrument.

9. X-ray crystallography
RSK2 T493M CTD was crystallized by hanging drop vapor diffusion as described previously[4]. Briefly, diffraction data was collected at the ALS beamline 8.2.1, and diffraction images integrated and indexed using the XDS suite. Molecular replacement and refinement was carried out using the Phaser and Phenix.Refine modules of the Phenix program suite. Data collection and refinement statistics can be found in Supplementary Table S3.

10. Computational Methods

Density Functional Theory (DFT) method B3LYP[6,7,8] was used to predict the proton affinities in aqueous solution for the compounds reported in this study. To take the solvent effect into account, all geometry optimizations were performed with inclusion of an implicit solvent model, i.e. the integral equation formalism of the polarised continuum model (IEFPCM)[9,10] with the UAHF radii. Geometries were optimized at the B3LYP/6-311+G (d) level, followed by frequency calculations at the same level of theory to ensure that these were stationary structures on their respective energy surfaces and to extract Gibbs free energy corrections at 298 K. Proton affinities are obtained by taking the Gibbs free energy differences between the protonated and deprotonated forms of the compounds. The Gaussian 09 software[11] was used for all the DFT calculations. The use of B3LYP/PCM for pK_a predictions has been previously shown to produce excellent agreement with experimental pK_as [12,13,14,15].

11. Cartesian coordinates and electronic energies of thioether adducts
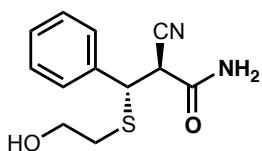
(±)–anti-**3**

Energy (in a.u.) = -1124.06060284
Gibbs correction(298K; in a.u.) =   0.194177

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C        -0.485895  -2.696174   1.293716
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C        -0.099834  -0.316524   0.627545
H         0.323461  -0.269418   1.632300
S         1.323543  -0.698999  -0.492472
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H         2.726756   0.210128   1.263530
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H         4.262343  -0.630146  -0.523296
H         3.683892   0.643859  -1.617533
O         4.755953   1.314725   0.038949
H         5.597221   1.286164  -0.433267
C        -0.794593   1.007213   0.349815
C        -1.215137   1.779639   1.439499
C        -1.044272   1.476633  -0.943644
C        -1.881237   2.988924   1.242688
H        -1.019928   1.436017   2.451319
C        -1.709581   2.684990  -1.142446
H        -0.707107   0.904813  -1.800474
C        -2.131800   3.444704  -0.050900
H        -2.195728   3.575534   2.099613
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N        -1.132397  -2.732255  -1.487871
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(±)–syn-**3**
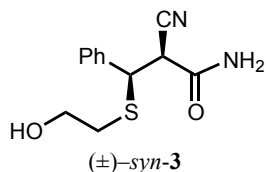
energy (in a.u.) = -1124.06537088
Gibbs correction(298K;in a.u.) =   0.195574

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C	-0.394497	0.978794	0.015493
C	-0.484559	1.775210	1.161625
C	-0.543810	1.583158	-1.239807
C	-0.722862	3.146843	1.059569
H	-0.369832	1.321720	2.141133
C	-0.786545	2.950222	-1.343185
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C	-0.876281	3.737320	-0.192869
H	-0.786609	3.749800	1.959336
H	-0.900578	3.403299	-2.322497
H	-1.061272	4.803245	-0.275192
C	-2.635675	-0.980919	0.388430
O	-2.676022	-1.065667	1.607262
N	-3.662813	-0.579996	-0.379026
H	-3.609358	-0.521711	-1.383279
H	-4.536294	-0.326150	0.059685

(±)-**3-cB**
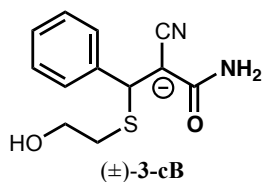
energy (in a.u.) = -1123.59698722
Gibbs correction(298K;in a.u.) =   0.181900

C	1.805208	-0.592323	0.095779
C	2.359792	-0.034076	1.244752
N	2.848295	0.425213	2.205916
C	0.386837	-0.294731	-0.301941
H	0.276781	-0.652850	-1.324801
S	-0.779716	-1.389472	0.704271
C	-2.397402	-1.032758	-0.097045
H	-2.708532	-0.014114	0.142494
H	-2.277099	-1.114060	-1.180096
C	-3.448009	-2.021218	0.379486
H	-3.160744	-3.043877	0.111027
H	-3.558240	-1.971731	1.469103

O	-4.684465	-1.669406	-0.257756
H	-5.367038	-2.292732	0.020104
C	-0.004537	1.171975	-0.256864
C	-0.062931	1.891605	-1.457650
C	-0.280046	1.851397	0.936273
C	-0.371423	3.252235	-1.468711
H	0.138459	1.382050	-2.395689
C	-0.587859	3.211532	0.929901
H	-0.265399	1.310125	1.875632
C	-0.634354	3.919140	-0.272335
H	-0.412631	3.787342	-2.412369
H	-0.797295	3.718842	1.866647
H	-0.879597	4.976357	-0.276458
C	2.575744	-1.490055	-0.712438
O	2.138379	-2.049939	-1.745501
N	3.912825	-1.708975	-0.362680
H	4.182321	-1.552984	0.598829
H	4.299190	-2.556069	-0.754605

(±)–*anti*-**4**
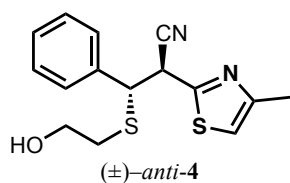
Energy (in a.u.) = -1562.55261522
Gibbs correction(298K; in a.u.) = 0.226960

C	-0.702709	-0.314313	1.528302
C	-0.677835	-1.537293	2.342296
N	-0.667127	-2.476741	3.010973
C	0.722919	0.009832	0.953303
H	1.386934	-0.012196	1.819640
S	1.315134	-1.345269	-0.160045
C	3.111384	-0.957806	-0.103440
H	3.271203	0.059038	-0.466600
H	3.462014	-1.025199	0.928515
C	3.871933	-1.944014	-0.975662
H	3.714037	-2.970065	-0.624633
H	3.530247	-1.880274	-2.014848
O	5.257780	-1.595019	-0.884793
H	5.769402	-2.201800	-1.434047
C	-1.824679	-0.393396	0.512600
C	-3.066135	-1.171237	-1.159200
C	-3.789198	-0.046384	-0.874947
H	-4.687190	0.314812	-1.353678
S	-3.073487	0.824152	0.436594
N	-1.957337	-1.351515	-0.355237
C	-3.376838	-2.176359	-2.225683
H	-4.277345	-1.902122	-2.776646
H	-2.550209	-2.255760	-2.937323
H	-3.529245	-3.168631	-1.791676
C	0.779387	1.401517	0.347379
C	1.245715	2.459903	1.136740
C	0.356846	1.671885	-0.959020
C	1.282357	3.761565	0.636619
H	1.585223	2.267243	2.150431
C	0.392678	2.971891	-1.460184
H	0.014851	0.862057	-1.593240
C	0.854080	4.021212	-0.664335
H	1.651499	4.567985	1.261722
H	0.063183	3.164325	-2.476014

H   0.885368   5.031800   -1.058083
H   -0.926739   0.502595   2.221283
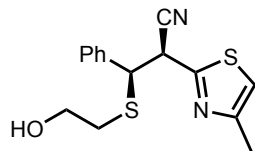
(±)–*syn*-**4**

energy (in a.u.) =   -1562.55430794
Gibbs correction(298K;in a.u.) =   0.226959

C   -0.482043   -1.273251   -0.669326
H   -0.494496   -1.028212   -1.735373
C   -0.298821   -2.728088   -0.566854
N   -0.194798   -3.873663   -0.483283
C   0.686040   -0.490401   0.017643
H   0.742302   -0.812292   1.058896
S   2.272220   -1.030206   -0.785388
C   3.468166   -0.278283   0.388234
H   3.306470   0.800211   0.422877
H   3.301116   -0.695734   1.383008
C   4.887295   -0.576722   -0.070138
H   5.060803   -1.657854   -0.108502
H   5.062136   -0.164532   -1.070282
O   5.763684   0.035242   0.882066
H   6.677188   -0.144068   0.627077
C   -1.850304   -0.878122   -0.146121
C   -3.889823   0.008669   -0.185522
C   -3.879173   -0.415663   1.111873
H   -4.655346   -0.325761   1.857228
S   -2.376432   -1.186566   1.493906
N   -2.728019   -0.267034   -0.884074
C   -5.015840   0.713458   -0.878008
H   -5.861882   0.861137   -0.205728
H   -4.694584   1.692298   -1.245156
H   -5.360745   0.138668   -1.742235
C   0.477651   1.009501   -0.030859
C   0.346169   1.726503   1.162469
C   0.414358   1.704435   -1.245539
C   0.149925   3.108768   1.146401
H   0.396980   1.204239   2.112884
C   0.214082   3.081768   -1.263862
H   0.534263   1.172962   -2.183999
C   0.081503   3.789544   -0.066801
H   0.052983   3.648777   2.082474
H   0.165648   3.604994   -2.213207
H   -0.070310   4.863751   -0.082824
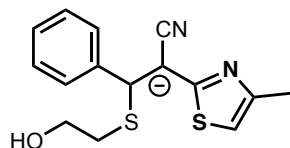
(±)-**4-cB**

energy (in a.u.) =   -1562.08435833
Gibbs correction(298K;in a.u.) =   0.213027

C   0.872398   -0.674716   -0.552747
C   0.792639   -1.661849   -1.529789

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N      0.745476  -2.497082  -2.350756
C     -0.369325  -0.065452   0.040647
H     -0.057435   0.470982   0.935718
S     -1.006261   1.290880  -1.115242
C     -2.326102   2.050282  -0.082559
H     -3.131790   1.328826   0.066730
H     -1.905407   2.309694   0.891944
C     -2.868066   3.298484  -0.757942
H     -2.071801   4.039198  -0.891833
H     -3.278446   3.054831  -1.744769
O     -3.898818   3.825992   0.089277
H     -4.256580   4.626147  -0.314948
C      2.147192  -0.198697  -0.140753
C      3.722063   0.976260   0.957848
C      4.573964   0.216319   0.217725
H      5.653732   0.222998   0.208152
S      3.668841  -0.875616  -0.817271
N      2.374775   0.747968   0.757201
C      4.137205   2.020973   1.952077
H      5.223975   2.102973   2.013579
H      3.735528   3.002289   1.679604
H      3.755462   1.784916   2.950685
C     -1.451488  -1.057354   0.427133
C     -1.616085  -1.383536   1.779757
C     -2.279677  -1.685010  -0.511812
C     -2.568602  -2.319129   2.184706
H     -0.990798  -0.901065   2.525602
C     -3.231357  -2.622108  -0.111329
H     -2.188248  -1.430567  -1.561647
C     -3.380311  -2.944334   1.238593
H     -2.679383  -2.552995   3.238961
H     -3.862527  -3.097827  -0.855603
H     -4.125465  -3.669579   1.549378
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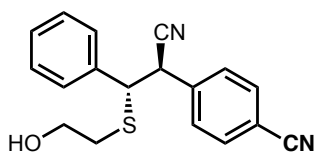

(±)–*anti*-**5**

Energy (in a.u.) = -1278.67956660
Gibbs correction(298K; in a.u.) =   0.242368

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C      3.450231  -1.468311  -1.169277
C      2.175068  -1.764299  -0.705640
C      1.614591  -1.042442   0.353639
C      2.354850  -0.018279   0.951181
C      3.633011   0.286565   0.500056
C      4.185481  -0.437637  -0.565672
H      3.877276  -2.034959  -1.987867
H      1.616840  -2.568684  -1.172659
H      1.940736   0.547124   1.777899
H      4.201064   1.080169   0.970254
C      0.192599  -1.379302   0.796232
C      0.022648  -1.216939   2.244015
N     -0.098205  -1.112619   3.386123
C     -0.882943  -0.598420  -0.041318
H     -0.693418  -0.891767  -1.075000
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S	-2.544185	-1.303196	0.391164
C	-3.542457	-0.561442	-0.960515
H	-3.496696	0.525959	-0.885116
H	-3.125248	-0.869635	-1.921195
C	5.501305	-0.129563	-1.033357
N	6.564863	0.119990	-1.412119
C	-4.984443	-1.030551	-0.844404
H	-5.041983	-2.121998	-0.921597
H	-5.409173	-0.731285	0.120343
O	-5.705092	-0.416498	-1.918223
H	-6.628816	-0.692807	-1.873097
C	-0.802207	0.912297	0.054688
C	-0.296271	1.633999	-1.032803
C	-1.213909	1.615809	1.194050
C	-0.188489	3.023949	-0.981371
H	0.017591	1.106473	-1.928290
C	-1.102142	3.003467	1.249190
H	-1.638841	1.082675	2.036584
C	-0.588456	3.712788	0.162133
H	0.203887	3.565048	-1.836095
H	-1.424912	3.532311	2.140049
H	-0.508605	4.794030	0.204873
H	0.020581	-2.441269	0.595070
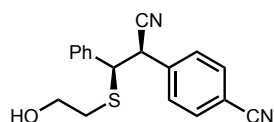
(±)–*syn*-**5**

energy (in a.u.) = -1278.68037048

Gibbs correction(298K;in a.u.) = 0.242188

C	3.342110	-0.935188	-1.265488
C	2.053589	-1.288027	-0.888420
C	1.568847	-0.961955	0.382662
C	2.397188	-0.281933	1.278578
C	3.689708	0.077955	0.914952
C	4.166427	-0.247203	-0.362138
H	3.710733	-1.191731	-2.251345
H	1.430175	-1.827101	-1.593434
H	2.036174	-0.029156	2.269123
H	4.325792	0.604537	1.616143
C	0.143542	-1.330862	0.795688
H	0.029561	-1.120335	1.862952
C	-0.060484	-2.777592	0.635011
N	-0.177021	-3.918418	0.510030
C	-0.932821	-0.507370	0.011987
H	-0.862415	-0.781073	-1.042078
S	-2.610566	-1.062919	0.586403
C	-3.653043	-0.185650	-0.645289
H	-3.548908	0.891177	-0.505242
H	-3.312687	-0.448162	-1.648887
C	5.495776	0.117376	-0.743226
N	6.570403	0.412567	-1.051180
C	-5.106692	-0.595337	-0.465572
H	-5.226155	-1.671205	-0.633468
H	-5.448886	-0.365553	0.549968
O	-5.865175	0.147324	-1.426063
H	-6.795014	-0.099641	-1.348675
C	-0.724850	0.986896	0.151768
C	-0.434507	1.751010	-0.982867
C	-0.816188	1.630904	1.392487
C	-0.229854	3.128186	-0.882734

H	-0.366258	1.269045	-1.953209
C	-0.607433	3.003588	1.495427
H	-1.065602	1.063810	2.283565
C	-0.312675	3.757653	0.357252
H	-0.007742	3.704983	-1.774500
H	-0.679630	3.486842	2.464255
H	-0.154195	4.827931	0.438468
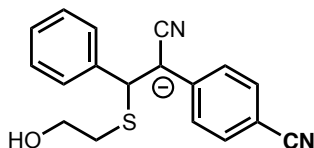
(±)-**5-cB**

energy (in a.u.) = -1278.20778414
Gibbs correction(298K;in a.u.) =   0.228331

C	4.241135	-0.947973	-0.467389
C	2.930545	-1.275189	-0.731037
C	1.830778	-0.521270	-0.208483
C	2.185847	0.606204	0.596825
C	3.499264	0.933494	0.863540
C	4.563616	0.167287	0.341407
H	5.038404	-1.554127	-0.885466
H	2.726838	-2.139386	-1.354063
H	1.413745	1.245007	1.006932
H	3.716956	1.800088	1.479630
C	0.475919	-0.884376	-0.476908
C	0.224626	-1.950950	-1.343810
N	0.040323	-2.849303	-2.071533
C	-0.690201	-0.124667	0.100531
H	-0.379596	0.323414	1.044816
S	-1.067528	1.361670	-1.009954
C	-2.274815	2.291778	0.021908
H	-3.226345	1.757329	0.046824
H	-1.885936	2.358607	1.041032
C	5.909555	0.507989	0.611868
N	7.015996	0.787549	0.834009
C	-2.478772	3.687298	-0.543421
H	-1.536794	4.246513	-0.529942
H	-2.831432	3.635728	-1.580119
O	-3.456829	4.340416	0.278044
H	-3.600997	5.233465	-0.058696
C	-1.923919	-0.962804	0.392529
C	-2.147478	-1.393530	1.706738
C	-2.837598	-1.345603	-0.595869
C	-3.245264	-2.193139	2.025334
H	-1.454303	-1.101331	2.490564
C	-3.936110	-2.145240	-0.281807
H	-2.696099	-1.006060	-1.615613
C	-4.145093	-2.573174	1.029725
H	-3.399317	-2.512297	3.051333
H	-4.633210	-2.430488	-1.063584
H	-5.003267	-3.191060	1.273836

(±)–*anti*-**6**
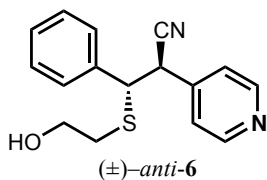
Energy (in a.u.) =   -1202.45129293
Gibbs correction(298K; in a.u.) =   0.235299

C	3.756614	-1.358239	-1.730877
C	2.537669	-1.693158	-1.148295
C	2.132622	-1.022798	0.007260
C	2.983562	-0.046513	0.522985
C	4.184602	0.214628	-0.133479
H	4.089271	-1.872410	-2.627970
H	1.924331	-2.469375	-1.593216
H	2.734522	0.505910	1.421572
H	4.860453	0.971169	0.254824
C	0.780420	-1.361233	0.629031
C	0.787691	-1.175250	2.083528
N	0.806782	-1.053278	3.230031
C	-0.393085	-0.600645	-0.085871
H	-0.317663	-0.901129	-1.132019
S	-1.986028	-1.320966	0.537340
C	-3.139489	-0.595415	-0.694550
H	-3.081298	0.492783	-0.641642
H	-2.842248	-0.919474	-1.693787
C	-4.558457	-1.055744	-0.399322
H	-4.627461	-2.148198	-0.447631
H	-4.865618	-0.735640	0.602676
O	-5.398807	-0.459420	-1.393164
H	-6.310579	-0.735648	-1.238562
N	4.578393	-0.420463	-1.243144
C	-0.320880	0.911756	-0.010079
C	0.039759	1.632064	-1.154856
C	-0.601051	1.617958	1.166907
C	0.135199	3.023612	-1.124018
H	0.247576	1.102775	-2.079697
C	-0.501684	3.007129	1.200818
H	-0.913434	1.084742	2.057248
C	-0.132240	3.715182	0.055844
H	0.413375	3.563692	-2.023055
H	-0.721310	3.538221	2.121257
H	-0.061954	4.797603	0.082697
H	0.595213	-2.428011	0.466807

(±)–*syn*-**6**
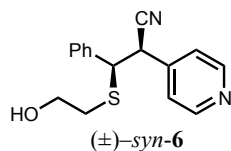
energy (in a.u.) =   -1202.45212569
Gibbs correction(298K;in a.u.) =   0.234977

C	-3.801802	-0.724125	1.548736
C	-2.548054	-1.159009	1.128899
C	-2.121291	-0.840462	-0.161224
C	-2.985398	-0.104081	-0.969336
C	-4.221250	0.284870	-0.456016
H	-4.152107	-0.962164	2.548957
H	-1.929959	-1.739572	1.805212
H	-2.713103	0.166340	-1.983285
H	-4.908103	0.859216	-1.071090

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C    -0.749369  -1.269941  -0.680424
H    -0.701504  -1.047628  -1.750297
C    -0.606607  -2.726799  -0.551079
N    -0.537524  -3.873603  -0.448053
C     0.418277  -0.509907   0.033982
H     0.409020  -0.794730   1.087250
S     2.020700  -1.136471  -0.667936
C     3.193022  -0.322922   0.488490
H     3.093952   0.759830   0.398521
H     2.948266  -0.619152   1.510376
C     4.614720  -0.744852   0.151226
H     4.729217  -1.829350   0.255430
H     4.862902  -0.470114  -0.880279
O     5.475106  -0.061962   1.069364
H     6.388123  -0.321726   0.894620
N    -4.635947  -0.011513   0.780608
C     0.272680   0.994236  -0.074252
C     0.093240   1.754140   1.085881
C     0.310096   1.650827  -1.311153
C    -0.055399   3.140337   1.015063
H     0.067340   1.261644   2.053098
C     0.157324   3.032693  -1.384444
H     0.472403   1.084994  -2.222932
C    -0.026503   3.782907  -0.220658
H    -0.191748   3.713705   1.926049
H     0.186547   3.526019  -2.350450
H    -0.141117   4.860244  -0.279153
```
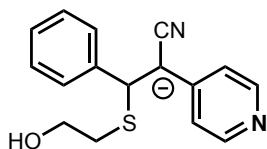

(±)-6-cB

energy (in a.u.) = -1201.97811464
Gibbs correction(298K;in a.u.) =   0.221054

```
C     4.867542  -0.160646  -0.052759
C     3.656767  -0.681068  -0.465961
C     2.425363  -0.128136  -0.003195
C     2.592829   0.979606   0.877562
C     3.859050   1.418488   1.226852
H     5.790244  -0.606747  -0.419591
H     3.653649  -1.526066  -1.146530
H     1.739642   1.510891   1.282174
H     3.955369   2.266721   1.902551
C     1.150848  -0.651095  -0.388567
C     1.107870  -1.691144  -1.317805
N     1.100264  -2.567392  -2.095679
C    -0.137257  -0.083671   0.143823
H     0.058342   0.362473   1.119346
S    -0.664447   1.387477  -0.932657
C    -2.051560   2.082939   0.055942
H    -2.870486   1.361756   0.089827
H    -1.703006   2.263088   1.075902
C    -2.534607   3.385025  -0.560115
H    -1.725670   4.123776  -0.580583
H    -2.874530   3.220791  -1.589161
O    -3.620039   3.860573   0.248779
H    -3.942299   4.692852  -0.118825
N     5.014057   0.882365   0.791042
C    -1.258328  -1.091502   0.333617
C    -1.509213  -1.584424   1.620779
C    -2.041159  -1.569375  -0.723557
```

C	-2.504638	-2.535364	1.846636
H	-0.918817	-1.220721	2.457107
C	-3.037080	-2.520235	-0.502486
H	-1.879621	-1.185097	-1.724252
C	-3.273589	-3.008129	0.783343
H	-2.682706	-2.899650	2.853588
H	-3.633099	-2.876998	-1.336776
H	-4.052821	-3.743712	0.955303
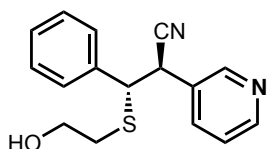
(±)–*anti*-**7**

Energy (in a.u.) =   -1202.45115256
Gibbs correction(298K; in a.u.) =   0.235157

C	2.646895	-1.769262	-1.036385
C	2.153374	-0.992368	0.015617
C	2.924464	0.090522	0.439097
C	4.131907	0.349239	-0.201420
H	2.082584	-2.629185	-1.389745
H	2.596376	0.720815	1.258471
H	4.757557	1.180128	0.103187
C	0.798920	-1.343944	0.621465
C	0.801841	-1.162146	2.077164
N	0.824077	-1.038515	3.223646
C	-0.382523	-0.597417	-0.093936
H	-0.298399	-0.894065	-1.140624
S	-1.967804	-1.341130	0.522639
C	-3.131485	-0.618597	-0.701366
H	-3.085306	0.469728	-0.639648
H	-2.832495	-0.930867	-1.703847
C	-4.544775	-1.096687	-0.407251
H	-4.602541	-2.189293	-0.465874
H	-4.852677	-0.789475	0.598559
O	-5.394126	-0.499703	-1.393109
H	-6.302897	-0.784858	-1.237044
C	4.527464	-0.483699	-1.244733
H	5.464889	-0.309112	-1.764847
N	3.803339	-1.529957	-1.661379
C	-0.334577	0.915613	-0.014429
C	0.013998	1.645133	-1.157058
C	-0.625595	1.614045	1.164730
C	0.086329	3.038015	-1.122492
H	0.231080	1.121675	-2.083151
C	-0.548994	3.004552	1.202588
H	-0.928413	1.073291	2.053845
C	-0.191920	3.721843	0.059380
H	0.355402	3.585135	-2.020054
H	-0.776563	3.529322	2.124731
H	-0.139362	4.805194	0.089305
H	0.624783	-2.412482	0.457692
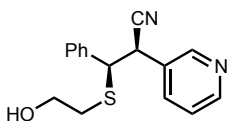
(±)–*syn*-**7**

energy (in a.u.) =   -1202.45172430

Gibbs correction(298K;in a.u.) =   0.234978

```
C      -2.555085  -1.155065   1.119823
C      -2.124966  -0.835919  -0.171306
C      -2.990743  -0.102298  -0.981160
C      -4.226127   0.286083  -0.471620
H      -1.920666  -1.739069   1.782306
H      -2.707626   0.161411  -1.994737
H      -4.923836   0.856856  -1.073281
C      -0.750391  -1.268003  -0.678174
H      -0.698590  -1.050288  -1.749134
C      -0.605759  -2.725091  -0.546802
N      -0.535870  -3.871811  -0.441735
C       0.417870  -0.506758   0.033771
H       0.411091  -0.790969   1.087312
S       2.020808  -1.130307  -0.669761
C       3.193838  -0.318302   0.487010
H       3.096699   0.764620   0.396717
H       2.947827  -0.613704   1.508849
C       4.615029  -0.742835   0.151012
H       4.727719  -1.827365   0.256753
H       4.864125  -0.469984  -0.880796
O       5.476359  -0.060075   1.068425
H       6.388741  -0.323516   0.895875
C      -4.552848  -0.076803   0.831889
H      -5.508276   0.210374   1.261325
N      -3.737695  -0.788531   1.621460
C       0.269202   0.997070  -0.074380
C       0.087140   1.756785   1.085498
C       0.304601   1.653652  -1.311305
C      -0.065695   3.142536   1.014511
H       0.062467   1.264395   2.052832
C       0.147381   3.035096  -1.384901
H       0.468731   1.088116  -2.222951
C      -0.038739   3.785036  -0.221321
H      -0.203876   3.715615   1.925415
H       0.175087   3.528320  -2.351016
H      -0.156702   4.862002  -0.280037
```


(±)-7-cB
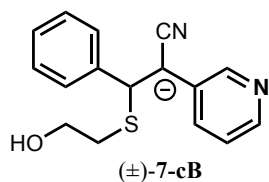
energy (in a.u.) = -1201.97070295
Gibbs correction(298K;in a.u.) =   0.220980

```
C       3.650702  -0.738937  -0.410191
C       2.425145  -0.150937   0.020886
C       2.585829   0.995598   0.840510
C       3.856394   1.447650   1.175610
H       3.616604  -1.618179  -1.049020
H       1.723136   1.541109   1.204493
H       3.975058   2.325360   1.803891
C       1.143290  -0.699431  -0.352043
C       1.100848  -1.768218  -1.241897
N       1.094207  -2.674242  -1.988341
C      -0.137362  -0.105871   0.155451
H       0.047699   0.348202   1.130309
S      -0.630478   1.380627  -0.936596
C      -2.005491   2.114522   0.041487
H      -2.850551   1.423272   0.055564
```

H	-1.664723	2.268574	1.068463
C	-2.432108	3.441228	-0.563123
H	-1.596960	4.150472	-0.559679
H	-2.760064	3.303678	-1.599948
O	-3.514025	3.945502	0.233732
H	-3.798966	4.793869	-0.127969
C	4.978866	0.777876	0.694861
H	5.984541	1.109338	0.936794
N	4.868443	-0.305641	-0.094464
C	-1.285045	-1.084095	0.330651
C	-1.579326	-1.554674	1.617128
C	-2.053384	-1.556872	-0.739465
C	-2.602548	-2.478802	1.830025
H	-1.000852	-1.194489	2.463282
C	-3.076672	-2.481328	-0.531588
H	-1.858400	-1.188977	-1.740299
C	-3.356468	-2.946865	0.753908
H	-2.813734	-2.825898	2.836682
H	-3.660354	-2.834805	-1.375985
H	-4.157170	-3.661473	0.915486

(±)-anti-**8**
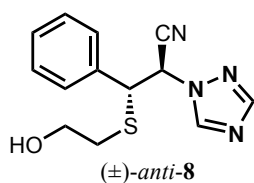
Energy (in a.u.) = -1196.41459669
Gibbs correction(298K; in a.u.) =   0.207261

C	-1.089774	-0.892359	1.142987
C	-0.879065	-2.256510	1.657635
N	-0.723695	-3.306474	2.105043
C	0.257656	-0.175386	0.812929
H	0.825747	-0.232829	1.743878
S	1.246555	-1.123431	-0.433545
C	2.903360	-0.453842	0.000407
H	2.883197	0.634398	-0.081082
H	3.143268	-0.729403	1.029260
C	3.946504	-1.025672	-0.946758
H	3.957971	-2.120135	-0.891703
H	3.726574	-0.735892	-1.980251
O	5.211047	-0.493966	-0.537494
H	5.899183	-0.842479	-1.117650
C	-2.970532	-1.396316	-1.760006
N	-1.890591	-1.672531	-1.052843
C	0.038844	1.287449	0.470763
C	0.237024	2.252840	1.465000
C	-0.377671	1.702030	-0.799836
C	0.015632	3.604335	1.199540
H	0.569065	1.949093	2.453402
C	-0.602369	3.051334	-1.064827
H	-0.509964	0.971852	-1.590336
C	-0.407106	4.006638	-0.066322
H	0.179942	4.339681	1.980175
H	-0.924869	3.357089	-2.054677
H	-0.576850	5.057422	-0.276635
H	-1.551699	-0.320589	1.951682
N	-2.067338	-0.913126	0.062281
N	-3.828272	-0.512506	-1.174488
C	-3.230915	-0.231200	-0.031743
H	-3.586613	0.437606	0.737209

H   -3.148460 -1.846777 -2.725157

(±)-*syn*-**8**
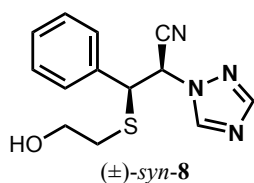
Energy (in a.u.) =   -1196.41470829
Gibbs correction(298K; in a.u.) =   0.207303

C   -0.914967 -1.318898 -0.533337
H   -0.968376 -1.139248 -1.608899
C   -0.728186 -2.766549 -0.332091
N   -0.617691 -3.901247 -0.165948
C   0.245307 -0.477937   0.083079
H   0.328722 -0.744073   1.138037
S   1.818533 -1.041754 -0.724163
C   3.019242 -0.293036   0.447945
H   2.857944   0.785432   0.483254
H   2.854201 -0.712332   1.442030
C   4.436402 -0.592552 -0.016191
H   4.607583 -1.673877 -0.059065
H   4.609259 -0.176508 -1.014986
O   5.314581   0.014254   0.936964
H   6.227609 -0.162857   0.678743
C   -4.153544 -0.109551 -0.034986
N   -3.134715 -0.331986 -0.843188
C   -0.001815   1.011556 -0.039753
C   -0.170957   1.776633   1.118493
C   -0.069105   1.646585 -1.286461
C   -0.407797   3.149996   1.036085
H   -0.117102   1.299791   2.092452
C   -0.309556   3.014889 -1.370121
H   0.079208   1.076810 -2.197955
C   -0.479668   3.771525 -0.208327
H   -0.533464   3.729352   1.944665
H   -0.360458   3.492848 -2.342805
H   -0.663307   4.838696 -0.275725
H   -5.062584   0.358614 -0.382166
N   -2.225231 -0.920518 -0.017266
N   -3.963493 -0.517963   1.252307
C   -2.743358 -1.021493   1.227713
H   -2.216487 -1.463631   2.059694

(±)–**8-cB**
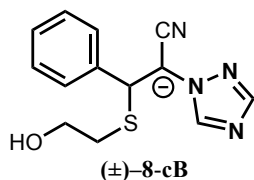
Energy (in a.u.) =   -1195.93201552
Gibbs correction(298K; in a.u.) =   0.192319

C   -1.181320 -1.024167   0.892446
C   -1.385054 -2.128033   1.702808
N   -1.554385 -3.043395   2.422089
C   0.162499 -0.399262   0.785123
H   0.681559 -0.572940   1.728377
S   1.297662 -1.322862 -0.484101
C   2.925883 -0.541609 -0.131888

```
H      2.920818   0.492722  -0.481730
H      3.090806  -0.540605   0.948762
C      4.040504  -1.312828  -0.817949
H      4.074533  -2.344152  -0.449738
H      3.878424  -1.341747  -1.901697
O      5.273549  -0.639778  -0.521915
H      5.999023  -1.120063  -0.939953
C     -3.311648  -0.835891  -1.875133
N     -2.244276  -1.377782  -1.320676
C      0.153856   1.092661   0.511928
C      0.452803   1.978336   1.555150
C     -0.174065   1.628722  -0.739919
C      0.415780   3.359493   1.360416
H      0.715511   1.583957   2.532672
C     -0.216108   3.008304  -0.937376
H     -0.384001   0.962796  -1.569350
C      0.078555   3.880718   0.111675
H      0.655802   4.025752   2.183166
H     -0.474343   3.402895  -1.915245
H      0.051747   4.954296  -0.044975
H     -3.643239  -1.110941  -2.866911
N     -2.185609  -0.759562  -0.091360
N     -3.956923   0.086179  -1.103555
C     -3.218774   0.101285  -0.004079
H     -3.386742   0.707581   0.872870
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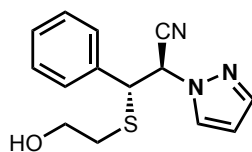

(±)–*anti*-**9**

Energy (in a.u.) =   -1180.35482800
Gibbs correction(298K; in a.u.) =   0.218441

```
C     -1.136360  -0.863377   1.122735
C     -0.984556  -2.219437   1.679922
N     -0.878915  -3.268345   2.145179
C      0.248642  -0.197341   0.839344
H      0.788673  -0.277929   1.785370
S      1.218891  -1.193343  -0.383438
C      2.883585  -0.481785  -0.070092
H      2.875203   0.577470  -0.331448
H      3.121142  -0.586561   0.990178
C      3.915043  -1.218924  -0.910288
H      3.939347  -2.281011  -0.642711
H      3.672642  -1.137880  -1.975904
O      5.179647  -0.606528  -0.638629
H      5.861959  -1.058518  -1.150289
C      0.108235   1.272192   0.487832
C      0.350659   2.228994   1.480216
C     -0.275001   1.704100  -0.787065
C      0.203654   3.589640   1.209666
H      0.657581   1.911045   2.472258
C     -0.424570   3.062422  -1.057810
H     -0.446994   0.979502  -1.574829
C     -0.186441   4.009774  -0.060775
H      0.400224   4.317589   1.989847
H     -0.723257   3.381708  -2.050937
H     -0.298005   5.067440  -0.275686
C     -2.092274  -1.625691  -1.117737
H     -1.323772  -2.353528  -1.323547
```

C	-3.214825	-1.262817	-1.829182
C	-3.839445	-0.276221	-1.034685
H	-3.538537	-1.657672	-2.779418
H	-4.752511	0.268336	-1.229073
N	-2.087008	-0.871031	0.018032
N	-3.161948	-0.042990	0.084444
H	-1.616109	-0.256893	1.894157

(±)–*syn*-**9**
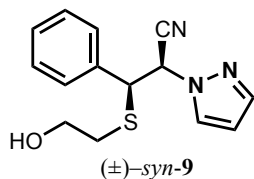
energy (in a.u.) = -1180.35867845
Gibbs correction(298K;in a.u.) =   0.218544

C	-0.962995	-1.251066	-0.617100
H	-0.998259	-1.025366	-1.685031
C	-0.808666	-2.713177	-0.482846
N	-0.728097	-3.858515	-0.385037
C	0.212581	-0.467490	0.040884
H	0.233407	-0.743017	1.095633
S	1.794970	-1.084063	-0.707716
C	2.979267	-0.333129	0.479309
H	2.867149	0.751960	0.458469
H	2.753302	-0.696299	1.483497
C	4.399498	-0.717084	0.093707
H	4.524911	-1.805092	0.120325
H	4.630396	-0.368267	-0.919111
O	5.265361	-0.091488	1.046364
H	6.178422	-0.329361	0.843047
C	0.027401	1.030479	-0.085892
C	-0.152606	1.801173	1.066805
C	0.024756	1.668702	-1.332988
C	-0.337188	3.181996	0.978675
H	-0.150452	1.321070	2.040258
C	-0.165367	3.044928	-1.423135
H	0.186153	1.093991	-2.239474
C	-0.346870	3.806669	-0.266576
H	-0.472052	3.765327	1.883500
H	-0.166501	3.524703	-2.396319
H	-0.490373	4.879743	-0.338159
C	-3.294744	-0.275036	-0.714294
H	-3.246420	-0.045897	-1.767215
C	-4.289993	-0.092043	0.221658
C	-3.748862	-0.601502	1.422722
H	-5.263436	0.343879	0.060916
H	-4.206584	-0.651306	2.400534
N	-2.249598	-0.854613	-0.061684
N	-2.513639	-1.063969	1.250450

(±)–**9-cB**
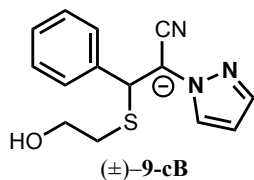
energy (in a.u.) = -1179.86364614
Gibbs correction(298K;in a.u.) =   0.203692

```
C    -0.930936  -1.370146  -0.244499
C    -0.826579  -2.755080  -0.229226
N    -0.764299  -3.930409  -0.269688
C     0.221745  -0.510795   0.242059
H     0.455840  -0.661528   1.305532
S     1.767638  -1.096407  -0.646304
C     3.059043  -0.344573   0.423270
H     2.911295   0.736670   0.463349
H     2.966629  -0.746644   1.434872
C     4.438525  -0.656308  -0.131835
H     4.599469  -1.739344  -0.178858
H     4.546168  -0.250194  -1.144034
O     5.395850  -0.051770   0.748614
H     6.283818  -0.241403   0.421170
C     0.012214   0.976422   0.024481
C     0.119480   1.863139   1.100239
C    -0.275993   1.499746  -1.243316
C    -0.056578   3.238086   0.920775
H     0.339340   1.476126   2.091174
C    -0.452731   2.867910  -1.427910
H    -0.357255   0.823798  -2.088059
C    -0.343101   3.745070  -0.344469
H     0.031456   3.908109   1.770331
H    -0.675181   3.254322  -2.417885
H    -0.479627   4.812080  -0.489211
C    -3.187207  -0.466765  -0.847879
H    -2.971152  -0.472024  -1.904320
C    -4.317087  -0.094322  -0.144521
C    -3.969251  -0.311746   1.205744
H    -5.247906   0.280100  -0.542935
H    -4.569044  -0.142625   2.090588
N    -2.252312  -0.877213   0.047423
N    -2.730836  -0.787321   1.325518
```
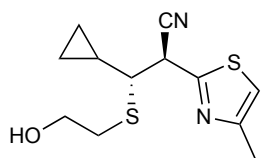

(±)-*anti*-**10**
Energy (in a.u.) = -1448.17462169
Gibbs correction(298K; in a.u.) =   0.211719

```
C    -0.629251   0.649147   1.231560
C    -0.463365  -0.145159   2.454337
N    -0.332852  -0.734488   3.436832
C     0.736065   0.844794   0.487108
H     1.441000   1.205588   1.240664
S     1.388029  -0.792204  -0.094892
C     3.179037  -0.392931  -0.222786
H     3.344794   0.303253  -1.044994
H     3.509549   0.070443   0.708927
C     0.615466   1.863058  -0.623996
C     0.508902   3.336896  -0.290597
C     1.758207   2.797890  -0.939934
H     0.033517   1.528910  -1.476593
H     0.574953   3.632730   0.751574
H    -0.170329   3.938907  -0.883060
H     1.944634   3.031257  -1.981862
H     2.651377   2.738417  -0.328103
C     3.959816  -1.674972  -0.467627
H     3.835561  -2.365632   0.373570
H     3.605748  -2.174361  -1.376858
```

```
O        5.335549   -1.303073   -0.609958
H        5.860806   -2.099030   -0.759044
C       -1.752204    0.080486    0.386000
C       -3.001532   -1.416275   -0.684259
C       -3.692819   -0.290408   -1.032079
H       -4.575523   -0.206527   -1.648327
S       -2.964482    1.114298   -0.331597
N       -1.905598   -1.183333    0.124962
C       -3.332383   -2.818892   -1.093569
H       -4.220510   -2.845884   -1.726143
H       -2.503109   -3.268245   -1.647258
H       -3.516228   -3.446459   -0.216876
H       -0.923873    1.650671    1.560361
```


(±)-*syn*-**10**
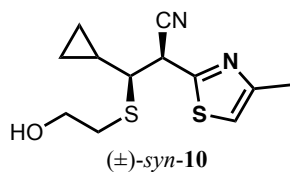
energy (in a.u.) = -1448.17341577
Gibbs correction(298K;in a.u.) =   0.211113

```
C        0.406018    0.851481   -0.647871
H        0.442002    0.782288   -1.740253
C        0.070005    2.242845   -0.315567
N       -0.151147    3.341402   -0.042475
C       -0.689242   -0.145812   -0.134555
H       -0.825972    0.003749    0.939146
S       -2.277305    0.363771   -0.961186
C       -3.533721   -0.320729    0.193957
H       -3.619130   -1.397749    0.052338
H       -3.218401   -0.119138    1.219107
C       -0.331189   -1.583178   -0.431159
C        0.512551   -2.405060    0.519799
C       -0.952588   -2.712254    0.358714
H       -0.175378   -1.783513   -1.487414
H        0.827401   -1.949295    1.451273
H        1.240428   -3.079301    0.083619
H       -1.244485   -3.604041   -0.183928
H       -1.606160   -2.459430    1.185834
C       -4.875081    0.344933   -0.075087
H       -4.816686    1.418301    0.134471
H       -5.167758    0.215151   -1.123590
O       -5.829321   -0.284482    0.787033
H       -6.692804    0.124028    0.648774
C        1.810961    0.525140   -0.178538
C        3.889362   -0.258420   -0.299007
C        3.902556    0.146940    1.004394
H        4.709365    0.089520    1.719833
S        2.379035    0.841810    1.446730
N        2.692742   -0.029589   -0.954504
C        5.025305   -0.894834   -1.039877
H        5.897518   -1.016018   -0.396295
H        4.739243   -1.880028   -1.419012
H        5.316921   -0.286982   -1.901229
```

(±)-**10-cB**
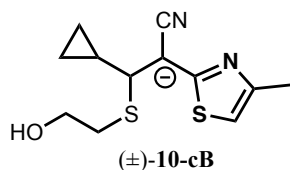
energy (in a.u.) = -1447.70059680
Gibbs correction(298K;in a.u.) =   0.198739

C	0.657032	1.127339	-0.074974
C	0.813705	2.432479	-0.532306
N	0.939175	3.536341	-0.909025
C	-0.707723	0.743522	0.442696
H	-1.288002	1.661025	0.568812
S	-1.615487	-0.193887	-0.935815
C	-3.343449	-0.294009	-0.308925
H	-3.390135	-0.971204	0.544416
H	-3.663570	0.698880	0.015630
C	-0.726543	-0.017562	1.752549
C	-0.508760	0.741507	3.041958
C	-1.864556	0.154221	2.730532
H	-0.273751	-0.999242	1.705051
H	-0.402528	1.820105	2.983063
H	0.097616	0.275822	3.811441
H	-2.196111	-0.714424	3.289726
H	-2.659522	0.847147	2.475584
C	-4.259950	-0.792878	-1.413582
H	-4.254148	-0.097532	-2.260310
H	-3.929481	-1.773870	-1.774621
O	-5.580711	-0.890552	-0.860620
H	-6.184336	-1.199782	-1.547409
C	1.748134	0.224666	-0.180146
C	2.991385	-1.651227	-0.087053
C	3.967748	-0.839542	-0.576282
H	4.989930	-1.084311	-0.824082
S	3.351113	0.788946	-0.792870
N	1.761955	-1.061879	0.131681
C	3.156884	-3.111108	0.220235
H	4.171815	-3.450864	0.005247
H	2.944628	-3.316664	1.274427
H	2.461907	-3.717291	-0.369857

(±)–*anti*-**11**
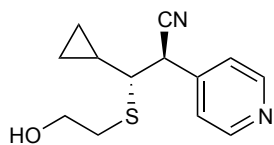
Energy (in a.u.) = -1088.07199618
Gibbs correction(298K; in a.u.) =   0.219104

C	-3.815486	0.271872	-1.214854
C	-2.858549	0.742893	-0.319717
C	-1.986969	-0.166273	0.282783
C	-2.136414	-1.515593	-0.041319
C	-3.126495	-1.886882	-0.947936
H	-4.501723	0.966514	-1.690829
H	-2.806382	1.802450	-0.096742
H	-1.506805	-2.277580	0.403078
H	-3.256338	-2.933130	-1.209579
C	-0.914146	0.335345	1.245750
C	-0.688951	-0.607111	2.346624

```
N     -0.515398   -1.325342    3.232261
C      0.446040    0.739043    0.575157
H      1.127724    0.988357    1.392296
S      1.181270   -0.731449   -0.287868
C      2.960113   -0.265252   -0.278071
H      3.124633    0.568934   -0.959936
H      3.242087    0.038154    0.731896
C      0.289804    1.936734   -0.333227
C      0.124264    3.319437    0.261532
C      1.398939    2.954269   -0.456303
H     -0.270956    1.742717   -1.241516
H      0.170804    3.421854    1.341014
H     -0.572180    3.995236   -0.221423
H      1.585771    3.380747   -1.435114
H      2.288174    2.816778    0.149000
C      3.795820   -1.459887   -0.711381
H      3.672197   -2.289331   -0.006624
H      3.489658   -1.805261   -1.705629
O      5.159123   -1.022541   -0.735866
H      5.720478   -1.762500   -0.998371
N     -3.959014   -1.019652   -1.535825
H     -1.287389    1.252958    1.712017
```
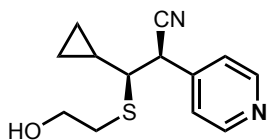

(±)-syn-**11**
energy (in a.u.) = -1088.07123079
Gibbs correction(298K;in a.u.) =   0.219628

```
C     -3.823457   -0.214377    1.466687
C     -2.530863   -0.610154    1.135845
C     -2.099671   -0.473449   -0.184403
C     -3.000464    0.048751   -1.110544
C     -4.274039    0.415714   -0.680674
H     -4.176560   -0.312762    2.489219
H     -1.884667   -1.021297    1.903798
H     -2.726696    0.172613   -2.152509
H     -4.989433    0.823934   -1.388971
C     -0.691291   -0.879119   -0.617441
H     -0.671618   -0.910168   -1.712103
C     -0.411745   -2.246711   -0.157879
N     -0.241859   -3.325970    0.212544
C      0.420434    0.120901   -0.150421
H      0.505978    0.068018    0.937781
S      2.024135   -0.515022   -0.851708
C      3.255979    0.265948    0.267918
H      3.364653    1.321515    0.020603
H      2.905471    0.174376    1.297594
C      0.133731    1.537070   -0.593040
C     -0.715926    2.471900    0.241348
C      0.764745    2.712309    0.118675
H      0.032366    1.644885   -1.669425
H     -1.087491    2.111705    1.193702
H     -1.399305    3.128861   -0.284318
H      1.112759    3.539894   -0.488791
H      1.374200    2.513238    0.992796
C      4.593314   -0.441981    0.110251
H      4.510780   -1.487755    0.424759
H      4.919521   -0.422794   -0.936276
O      5.532011    0.257983    0.934287
H      6.389976   -0.179716    0.871998
```

N   -4.693380   0.293276   0.583921
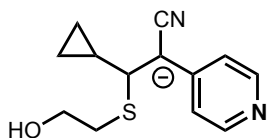
(±)-11-cB
energy (in a.u.) =   -1087.59401501
Gibbs correction(298K;in a.u.) =   0.206629

C   -4.347033 -0.855721   0.238092
C   -3.341335 -0.042957   0.722549
C   -2.014998 -0.118273   0.196089
C   -1.868944 -1.100221 -0.827909
C   -2.949290 -1.862859 -1.237126
H   -5.347751 -0.769299   0.658063
H   -3.574943   0.664723   1.511395
H   -0.905935 -1.289551 -1.282992
H   -2.803142 -2.606066 -2.019388
C   -0.958011   0.713882   0.673529
C   -1.197017   1.535963   1.774925
N   -1.384600   2.232053   2.700476
C   0.442126   0.790333   0.106282
H   0.968850   1.582573   0.643368
S   1.382524 -0.786012   0.585153
C   3.119335 -0.395458   0.116345
H   3.203967 -0.323779 -0.968308
H   3.399173   0.565943   0.553173
C   0.556086   1.093139 -1.378521
C   0.284182   2.500490 -1.858327
C   1.687126   1.946173 -1.904950
H   0.223224   0.306666 -2.044828
H   0.063557   3.254114 -1.109374
H   -0.257417   2.626344 -2.789521
H   2.114419   1.693333 -2.869473
H   2.403227   2.339005 -1.190996
C   4.043515 -1.484280   0.635941
H   3.989585 -1.544373   1.728657
H   3.757679 -2.459669   0.225278
O   5.375550 -1.146174   0.222978
H   5.983164 -1.823728   0.544684
N   -4.197812 -1.773755 -0.740124
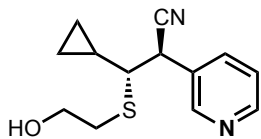
(±)–anti-12
Energy (in a.u.) =   -1088.07182833
Gibbs correction(298K; in a.u.) =   0.218985

C   -2.891686   0.714324 -0.285860
C   -1.985557 -0.188537   0.279330
C   -2.108181 -1.532937 -0.076609
C   -3.098740 -1.905968 -0.979291
H   -2.846506   1.767293 -0.020094
H   -1.449414 -2.282657   0.347717
H   -3.221427 -2.941309 -1.275352
C   -0.915959   0.326534   1.237420

```
C    -0.689503   -0.607785    2.345184
N    -0.516253   -1.324682    3.232149
C     0.443126    0.736813    0.570590
H     1.122676    0.996789    1.386277
S     1.192061   -0.731480   -0.284734
C     2.968512   -0.256730   -0.267583
H     3.130994    0.580296   -0.946446
H     3.245931    0.044932    0.744162
C     0.275450    1.927305   -0.345194
C     0.103263    3.312801    0.241186
C     1.376313    2.951953   -0.481824
H    -0.289278    1.723263   -1.249042
H     0.155316    3.422504    1.319703
H    -0.600797    3.980461   -0.242008
H     1.554125    3.373404   -1.464499
H     2.270208    2.824979    0.118813
C     3.811348   -1.445790   -0.702382
H     3.689568   -2.278347   -0.000975
H     3.509929   -1.789065   -1.698801
O     5.172630   -1.001893   -0.721025
H     5.738381   -1.738508   -0.983486
C    -3.939007   -0.922302   -1.493955
H    -4.723081   -1.180372   -2.199957
N    -3.846799    0.369324   -1.154542
H    -1.295542    1.244579    1.698613
```


(±)-*syn*-**12**
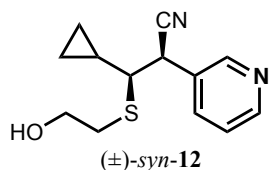
energy (in a.u.) =   -1088.07078557
Gibbs correction(298K;in a.u.) =   0.219990

```
C    -2.554093   -0.611679    1.119566
C    -2.107427   -0.470176   -0.197140
C    -2.997574    0.060854   -1.129240
C    -4.271480    0.434159   -0.711921
H    -1.900766   -1.035243    1.878454
H    -2.702546    0.183217   -2.166337
H    -4.988496    0.850030   -1.410261
C    -0.695021   -0.880422   -0.608663
H    -0.665373   -0.919012   -1.703182
C    -0.418757   -2.247016   -0.142269
N    -0.250434   -3.324935    0.233153
C     0.418324    0.118066   -0.142010
H     0.505772    0.064528    0.946080
S     2.020169   -0.519161   -0.846639
C     3.257174    0.267089    0.263370
H     3.361678    1.322438    0.013284
H     2.913676    0.176796    1.295535
C     0.132806    1.535125   -0.582233
C    -0.716807    2.468320    0.253870
C     0.763912    2.708899    0.132093
H     0.031615    1.645351   -1.658415
H    -1.088589    2.106470    1.205669
H    -1.399888    3.127052   -0.269983
H     1.111974    3.538065   -0.473208
H     1.373317    2.507536    1.005725
C     4.595138   -0.437882    0.098403
H     4.516837   -1.483620    0.414192
H     4.914994   -0.418785   -0.950078
O     5.537342    0.264700    0.916264
```

```
H        6.396477  -0.169633   0.846912
C       -4.612115   0.259247   0.626439
H       -5.597826   0.539816   0.986287
N       -3.773676  -0.256998   1.534540
```
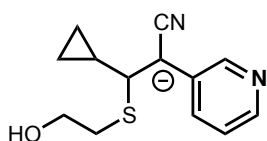

(±)-**12-cB**

energy (in a.u.) = -1087.58642749
Gibbs correction(298K;in a.u.) =   0.206109

```
C       -3.352910  -0.018103   0.684909
C       -2.019625  -0.131157   0.186890
C       -1.854648  -1.141759  -0.796008
C       -2.937365  -1.908366  -1.208318
H       -3.567174   0.726716   1.448005
H       -0.876762  -1.344951  -1.212755
H       -2.803279  -2.681673  -1.959024
C       -0.962057   0.717661   0.673249
C       -1.200824   1.532647   1.774449
N       -1.388937   2.226958   2.704371
C        0.431175   0.796004   0.102048
H        0.954214   1.604435   0.617967
S        1.399698  -0.764786   0.615191
C        3.128221  -0.384457   0.106867
H        3.195929  -0.346640  -0.980730
H        3.411197   0.591275   0.508525
C        0.542463   1.057764  -1.390790
C        0.260041   2.449390  -1.908655
C        1.666696   1.903541  -1.942881
H        0.214390   0.251607  -2.035905
H        0.035270   3.220645  -1.179154
H       -0.283831   2.546882  -2.841977
H        2.094013   1.627670  -2.901149
H        2.381547   2.321009  -1.241701
C        4.065032  -1.452594   0.646021
H        4.025839  -1.480332   1.740698
H        3.778807  -2.441232   0.268621
O        5.390396  -1.121235   0.205843
H        6.004883  -1.787296   0.538327
C       -4.194166  -1.692576  -0.647383
H       -5.059487  -2.275616  -0.949337
N       -4.390504  -0.754675   0.296687
```
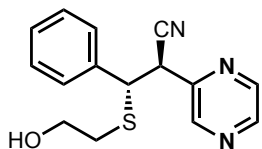

(±)–*anti*-**S4**

Energy (in a.u.) = -1218.48915784
Gibbs correction(298K; in a.u.) =   0.222251

```
C       -2.031646  -0.657374   0.261812
C       -2.169134  -1.726761  -0.629165
H       -1.532679  -2.603097  -0.560215
```

```
C      -0.971952   -0.620757    1.359688
C      -0.879215   -1.906219    2.060625
N      -0.816682   -2.902722    2.637924
C       0.455383   -0.119382    0.927674
H       1.071349   -0.205021    1.824808
S       1.196705   -1.281627   -0.306215
C       2.951185   -0.753993   -0.169116
H       3.028690    0.300703   -0.437860
H       3.282266   -0.884231    0.863027
C       3.810253   -1.592844   -1.102311
H       3.737610   -2.654751   -0.842194
H       3.482593   -1.469489   -2.140604
O       5.156555   -1.132308   -0.946054
H       5.732117   -1.644568   -1.527393
C      -3.885016   -0.658162   -1.666110
H      -4.638823   -0.645540   -2.446651
C       0.443936    1.339288    0.501059
C       0.740722    2.316271    1.459254
C       0.131593    1.747164   -0.799929
C       0.716290    3.670940    1.129412
H       0.996070    2.017543    2.471847
C       0.106892    3.100599   -1.131899
H      -0.077454    1.005608   -1.562461
C       0.397411    4.067402   -0.168762
H       0.953628    4.412941    1.884722
H      -0.135824    3.399452   -2.146454
H       0.382366    5.120403   -0.430081
C      -3.763658    0.402005   -0.769647
H      -4.424595    1.260904   -0.826380
N      -2.841872    0.403030    0.194966
N      -3.091002   -1.729027   -1.593996
H      -1.328419    0.105612    2.095996
```
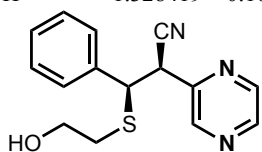

(±)–*syn*-**S4**

energy (in a.u.) = -1218.49358078
Gibbs correction(298K;in a.u.) =   0.223021

```
C      -2.118871   -0.838777   -0.143366
C      -3.045550   -0.179704   -0.952909
H      -2.829570    0.030488   -1.995751
C      -0.758294   -1.271312   -0.685429
H      -0.726485   -1.057732   -1.757729
C      -0.622974   -2.726399   -0.537708
N      -0.560419   -3.872549   -0.425472
C       0.405779   -0.503817    0.020774
H       0.387833   -0.785598    1.074298
S       2.011037   -1.126066   -0.674936
C       3.174988   -0.322878    0.497072
H       3.069116    0.760513    0.423306
H       2.929063   -0.636206    1.513522
C       4.600439   -0.730071    0.157749
H       4.720999   -1.815667    0.242225
H       4.850809   -0.434719   -0.867482
O       5.453366   -0.059553    1.091837
H       6.368805   -0.308348    0.913832
C      -4.487918   -0.046805    0.797104
H      -5.447944    0.270124    1.191478
C       0.249053    0.998955   -0.096715
```

C	0.070565	1.764838	1.059875
C	0.271742	1.647902	-1.338178
C	-0.089861	3.149278	0.981229
H	0.055159	1.277885	2.030002
C	0.105930	3.027904	-1.419196
H	0.432795	1.077717	-2.247528
C	-0.075613	3.783956	-0.258845
H	-0.224548	3.727451	1.889426
H	0.123583	3.515257	-2.388491
H	-0.200291	4.859822	-0.323455
C	-3.564615	-0.709415	1.606861
H	-3.785941	-0.923699	2.647481
N	-2.381982	-1.106469	1.137622
N	-4.231270	0.218199	-0.485116
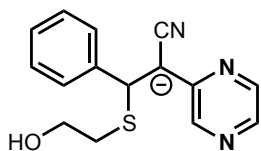
(±)-**S4-cB**

energy (in a.u.) = -1218.01936339
Gibbs correction(298K;in a.u.) =   0.208914

C	2.440656	-0.136434	-0.000949
C	2.594622	0.994702	0.867814
H	1.726501	1.525077	1.244186
C	1.166785	-0.661828	-0.374088
C	1.127855	-1.712720	-1.293524
N	1.091731	-2.596932	-2.059808
C	-0.121048	-0.087763	0.152870
H	0.064517	0.350122	1.134130
S	-0.629717	1.393076	-0.918676
C	-2.022591	2.089161	0.061250
H	-2.852445	1.379870	0.067506
H	-1.687792	2.243462	1.089998
C	-2.475941	3.410501	-0.536211
H	-1.656982	4.138250	-0.524491
H	-2.797098	3.272971	-1.575170
O	-3.571196	3.883165	0.260860
H	-3.872994	4.728909	-0.093146
C	4.871460	0.849591	0.773070
H	5.838837	1.232307	1.080885
C	-1.248950	-1.091594	0.326336
C	-1.502850	-1.602815	1.605586
C	-2.034719	-1.546766	-0.738244
C	-2.504856	-2.550257	1.816429
H	-0.909637	-1.256755	2.447398
C	-3.037475	-2.493770	-0.532096
H	-1.869540	-1.148587	-1.732828
C	-3.277226	-3.000375	0.745803
H	-2.685308	-2.929417	2.817420
H	-3.635948	-2.833051	-1.371879
H	-4.061612	-3.733092	0.906125
C	4.748843	-0.229727	-0.092523
H	5.638030	-0.715890	-0.489939
N	3.575669	-0.725167	-0.483915
N	3.769618	1.466652	1.246954
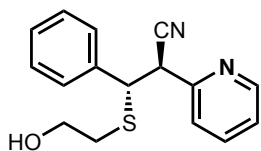
(±)–*anti*-**S5**

Energy (in a.u.) = -1202.45163927
Gibbs correction(298K; in a.u.) =   0.235026

C	-2.015286	-0.715286	0.277829
C	-2.096554	-1.729856	-0.678038
C	-3.110513	-1.671490	-1.630100
H	-1.392517	-2.553468	-0.676388
H	-3.197503	-2.445733	-2.384370
C	-0.924738	-0.682912	1.350260
C	-0.783478	-1.985192	2.010645
N	-0.686528	-2.997334	2.555759
C	0.479359	-0.130356	0.908975
H	1.106856	-0.200574	1.799589
S	1.263961	-1.249396	-0.340470
C	3.001064	-0.675592	-0.170355
H	3.052488	0.385904	-0.418388
H	3.323099	-0.815436	0.863493
C	3.896046	-1.472589	-1.106155
H	3.849473	-2.540658	-0.865894
H	3.579252	-1.339813	-2.146669
O	5.227346	-0.978652	-0.923393
H	5.825058	-1.468812	-1.501428
C	-4.009473	-0.609826	-1.591134
H	-4.816151	-0.525669	-2.309984
C	0.414332	1.328691	0.491525
C	0.732041	2.310876	1.437124
C	0.029758	1.731395	-0.791985
C	0.658685	3.665591	1.112890
H	1.041569	2.016447	2.435784
C	-0.044553	3.084073	-1.118200
H	-0.200088	0.985714	-1.544500
C	0.268299	4.056348	-0.167077
H	0.913174	4.411856	1.858414
H	-0.343975	3.378871	-2.118754
H	0.214636	5.109124	-0.424333
C	-3.856167	0.346395	-0.590654
H	-4.543431	1.184374	-0.517840
N	-2.885662	0.300836	0.329375
H	-1.281683	0.011277	2.116673
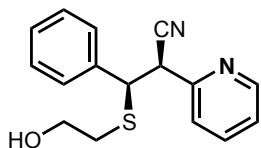
(±)–*syn*-**S5**

energy (in a.u.) = -1202.45596695
Gibbs correction(298K;in a.u.) =   0.235033

C	-2.126835	-0.827031	-0.160482
C	-3.049263	-0.176649	-0.978044
C	-4.269952	0.208484	-0.427490
H	-2.820728	0.025075	-2.018091
H	-5.009115	0.717056	-1.036585
C	-0.762229	-1.257698	-0.705484
H	-0.726160	-1.034384	-1.775355
C	-0.631484	-2.714726	-0.573522
N	-0.573108	-3.862912	-0.477662

```
C      0.403207   -0.503065    0.009791
H      0.375694   -0.787443    1.062131
S      2.011333   -1.133263   -0.674700
C      3.171624   -0.336651    0.505296
H      3.070327    0.747298    0.432849
H      2.918217   -0.650259    1.519876
C      4.597674   -0.748365    0.174659
H      4.713922   -1.834527    0.258170
H      4.855700   -0.452412   -0.848528
O      5.447603   -0.082484    1.115064
H      6.363021   -0.335340    0.942812
C     -4.520979   -0.072082    0.911627
H     -5.456485    0.207813    1.381686
C      0.261483    1.001334   -0.104657
C      0.084580    1.766598    1.052459
C      0.297696    1.653479   -1.344116
C     -0.060912    3.152916    0.976603
H      0.058120    1.277217    2.021086
C      0.147390    3.035402   -1.422770
H      0.456562    1.083510   -2.254003
C     -0.032764    3.790728   -0.261648
H     -0.194891    3.730161    1.885563
H      0.175664    3.524909   -2.390800
H     -0.145439    4.868079   -0.324206
C     -3.535601   -0.731094    1.645024
H     -3.695008   -0.971501    2.692254
N     -2.361656   -1.104610    1.126569
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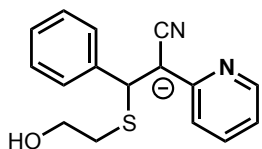

(±)-**S5-cB**

energy (in a.u.) = -1201.97493718
Gibbs correction(298K;in a.u.) =   0.220536

```
C      2.440652   -0.118842    0.006189
C      2.580349    1.006164    0.873573
C      3.837644    1.455243    1.231088
H      1.707658    1.527296    1.246788
H      3.934167    2.311946    1.892299
C      1.163624   -0.652929   -0.378858
C      1.128187   -1.697418   -1.302597
N      1.086382   -2.578322   -2.074776
C     -0.125671   -0.088011    0.144540
H      0.058800    0.361989    1.120348
S     -0.658847    1.388191   -0.934537
C     -2.053131    2.078191    0.048374
H     -2.881212    1.366706    0.054869
H     -1.717344    2.230778    1.077182
C     -2.512119    3.399830   -0.543685
H     -1.695552    4.130268   -0.531201
H     -2.834760    3.264710   -1.582517
O     -3.607855    3.867330    0.256532
H     -3.914717    4.711577   -0.096709
C      4.978047    0.812367    0.731573
H      5.980852    1.136443    0.985083
C     -1.248516   -1.094808    0.329525
C     -1.500460   -1.591862    1.615019
C     -2.033394   -1.567004   -0.728535
C     -2.498153   -2.541058    1.838228
H     -0.908573   -1.232791    2.452360
C     -3.031819   -2.516001   -0.510334
```

H	-1.870638	-1.180114	-1.727894
C	-3.269158	-3.008009	0.773749
H	-2.676521	-2.908411	2.844052
H	-3.629075	-2.868305	-1.345695
H	-4.050311	-3.742102	0.943505
C	4.764539	-0.264911	-0.123491
H	5.616127	-0.794480	-0.549436
N	3.565298	-0.726086	-0.483629
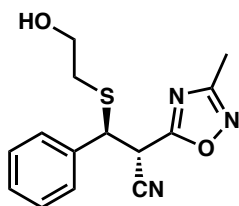
(±)–anti-**S6**

Energy (in a.u.) =   -1255.59996483
Gibbs correction(298K; in a.u.) =   0.219403

C	0.623687	-1.491235	0.396474
C	0.678623	-1.505198	1.860815
N	0.704611	-1.547752	3.011557
C	-0.527123	-0.596202	-0.189406
H	-0.495982	-0.775333	-1.264945
S	-2.129015	-1.310082	0.406779
C	-3.278893	-0.396414	-0.696665
H	-3.176876	0.673849	-0.511913
H	-3.017708	-0.606534	-1.735538
C	-4.707225	-0.839191	-0.418705
H	-4.819958	-1.913369	-0.602457
H	-4.975906	-0.638332	0.624498
O	-5.547267	-0.091117	-1.303475
H	-6.464735	-0.355546	-1.162122
C	-0.354044	0.888872	0.064594
C	0.051518	1.711876	-0.992749
C	-0.577370	1.466585	1.320973
C	0.244111	3.080022	-0.798936
H	0.214189	1.284790	-1.977565
C	-0.381234	2.831759	1.516195
H	-0.921448	0.854490	2.146561
C	0.030614	3.643130	0.457528
H	0.554498	3.702425	-1.631597
H	-0.558168	3.263958	2.495537
H	0.176327	4.707243	0.610977
H	0.419861	-2.519283	0.077041
C	1.961350	-1.097989	-0.169017
O	2.153957	-1.319377	-1.472168
C	3.895970	-0.430396	-0.604469
N	2.977473	-0.560038	0.423963
N	3.460949	-0.864034	-1.757152
C	5.253680	0.147799	-0.418861
H	5.802352	0.153864	-1.359787
H	5.178205	1.170711	-0.043389
H	5.812856	-0.435415	0.316190

(±)–*syn*-**S6**
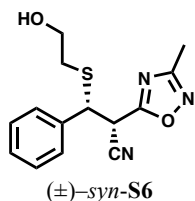
Energy (in a.u.) =   -1255.60032776
Gibbs correction(298K; in a.u.) =   0.219294

```
C     -0.728257  -1.314991   0.028566
C     -0.636298  -1.814804   1.403309
N     -0.545073  -2.229542   2.473908
C      0.367624  -0.250471  -0.328685
H      0.133753   0.060047  -1.348001
S      0.125950   1.235327   0.744515
C      1.205524   2.417252  -0.156665
H      2.233903   2.054121  -0.129532
H      0.875129   2.477774  -1.195272
C      1.118493   3.786396   0.499872
H      0.091182   4.165418   0.463885
H      1.428006   3.729813   1.549554
O      1.994987   4.648402  -0.232682
H      1.967867   5.529375   0.160641
C      1.765624  -0.843551  -0.317194
C      2.322041  -1.264027  -1.531270
C      2.504992  -1.010830   0.859031
C      3.586737  -1.850084  -1.569967
H      1.764685  -1.131770  -2.453941
C      3.768375  -1.598506   0.821343
H      2.101546  -0.668582   1.805076
C      4.312690  -2.020681  -0.391950
H      4.004481  -2.166172  -2.520074
H      4.330427  -1.720713   1.741341
H      5.298701  -2.472579  -0.419250
C     -2.121718  -0.820020  -0.255485
O     -2.379434  -0.428491  -1.505762
C     -4.129651  -0.232847  -0.290807
N     -3.139813  -0.732669   0.538538
N     -3.735641  -0.029884  -1.519377
C     -5.515991   0.048021   0.169141
H     -6.123296   0.433420  -0.648888
H     -5.975673  -0.864679   0.554857
H     -5.502323   0.780919   0.978929
H     -0.545420  -2.171412  -0.630934
```


(±)–**S6-cb**
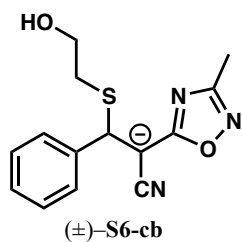
Energy (in a.u.) =   -1255.14364101
Gibbs correction(298K; in a.u.) =   0.206435

```
C     -1.067773  -0.533056   0.494691
C     -1.084570  -1.424847   1.569929
N     -1.092424  -2.173400   2.467215
C      0.228792  -0.044780  -0.099922
H      0.001249   0.387438  -1.073654
```

S	0.856474	1.410267	0.923334
C	2.263898	1.992741	-0.109062
H	3.070168	1.257632	-0.078208
H	1.922781	2.093993	-1.142170
C	2.765916	3.333432	0.400588
H	1.973151	4.087219	0.340583
H	3.084278	3.253730	1.446542
O	3.875368	3.712113	-0.425738
H	4.209805	4.566847	-0.126897
C	1.279644	-1.123370	-0.302453
C	1.469199	-1.646994	-1.587602
C	2.049886	-1.639047	0.746341
C	2.391980	-2.667309	-1.819117
H	0.887698	-1.254415	-2.416942
C	2.972116	-2.659912	0.519027
H	1.936866	-1.231840	1.744670
C	3.146895	-3.179580	-0.764312
H	2.524114	-3.055727	-2.824067
H	3.559042	-3.046825	1.346203
H	3.868509	-3.970669	-0.940938
C	-2.301249	-0.054472	0.021224
O	-2.320913	0.847810	-1.000831
C	-4.330830	0.384144	-0.402629
N	-3.539981	-0.359173	0.419192
N	-3.700718	1.129897	-1.277221
C	-5.822260	0.366351	-0.330655
H	-6.256348	1.035767	-1.073528
H	-6.199765	-0.644340	-0.504686
H	-6.158778	0.676473	0.661723

(±)–*anti*-**S7**
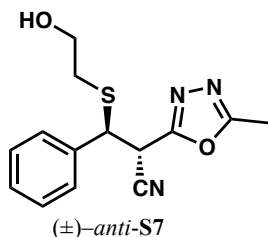
Energy (in a.u.) =   -1255.61276892
Gibbs correction(298K; in a.u.) =   0.219214

C	0.565275	-1.596252	0.264677
C	0.660680	-1.671818	1.727400
N	0.739071	-1.754157	2.873979
C	-0.556674	-0.624549	-0.249869
H	-0.567889	-0.774173	-1.330404
S	-2.173993	-1.277951	0.379288
C	-3.310781	-0.283895	-0.666975
H	-3.152310	0.775513	-0.460742
H	-3.089991	-0.480185	-1.717886
C	-4.750313	-0.664767	-0.357060
H	-4.920249	-1.727430	-0.562476
H	-4.978995	-0.476935	0.698000
O	-5.577989	0.144658	-1.198739
H	-6.503139	-0.074934	-1.032722
C	-0.310880	0.843020	0.036976
C	0.073867	1.680499	-1.016441
C	-0.445335	1.390753	1.319095
C	0.335364	3.032745	-0.794335
H	0.170369	1.275429	-2.019234
C	-0.179687	2.739656	1.542897
H	-0.772616	0.767858	2.143601
C	0.212699	3.565131	0.487529

H	0.629710	3.666935	-1.623970
H	-0.286223	3.148536	2.542246
H	0.413875	4.616651	0.663593
H	0.303291	-2.597916	-0.088655
C	1.901371	-1.278487	-0.340870
N	3.641026	-1.153064	-1.598011
N	2.404790	-1.782628	-1.414769
C	3.786827	-0.324347	-0.614802
O	2.711126	-0.350993	0.226732
C	4.913520	0.585183	-0.310639
H	5.675372	0.486908	-1.082005
H	4.573465	1.622534	-0.274400
H	5.354309	0.340844	0.658610

(±)–*syn*-**S7**
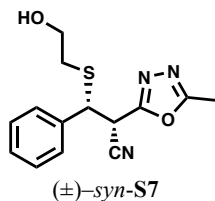
Energy (in a.u.) = -1255.61227478
Gibbs correction(298K; in a.u.) = 0.218519

C	-0.689225	-1.372160	-0.063478
C	-0.648810	-1.843384	1.324896
N	-0.614107	-2.231324	2.409087
C	0.384160	-0.269916	-0.384192
H	0.183273	0.009603	-1.419597
S	0.049092	1.229900	0.643441
C	1.141576	2.422829	-0.227297
H	2.175114	2.081609	-0.153082
H	0.853790	2.464550	-1.279457
C	0.999272	3.797729	0.407162
H	-0.034703	4.151645	0.329720
H	1.272398	3.761820	1.467774
O	1.880761	4.671214	-0.305713
H	1.818207	5.556507	0.073638
C	1.800254	-0.811279	-0.296250
C	2.438240	-1.210766	-1.476970
C	2.480161	-0.951102	0.919106
C	3.724033	-1.749513	-1.444636
H	1.928854	-1.099215	-2.429576
C	3.764174	-1.492285	0.952482
H	2.013452	-0.623048	1.840769
C	4.389928	-1.893642	-0.228264
H	4.204940	-2.049602	-2.369746
H	4.278683	-1.593685	1.902371
H	5.391952	-2.308794	-0.200497
C	-2.079004	-0.955938	-0.457110
N	-3.876909	-0.461361	-1.527327
N	-2.576675	-0.966068	-1.645367
C	-4.061622	-0.196732	-0.274452
O	-2.952520	-0.488902	0.468103
C	-5.259070	0.344009	0.406237
H	-6.044374	0.516760	-0.327626
H	-5.623815	-0.357832	1.159756
H	-5.026060	1.285985	0.907746
H	-0.433686	-2.229023	-0.694527

(±)–**S7-cb**
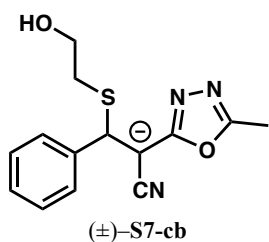
Energy (in a.u.) = -1255.14957454
Gibbs correction(298K; in a.u.) =   0.205059

C	-1.080183	-0.429448	0.408630
C	-1.188149	-1.289450	1.497418
N	-1.274828	-2.018107	2.410308
C	0.254827	-0.015142	-0.147958
H	0.072850	0.413251	-1.133414
S	0.923993	1.429550	0.871957
C	2.381534	1.937197	-0.130344
H	3.134266	1.146956	-0.105664
H	2.063763	2.084451	-1.165404
C	2.968374	3.227381	0.416836
H	2.229451	4.035008	0.369777
H	3.269840	3.099510	1.462965
O	4.109625	3.551293	-0.389765
H	4.500425	4.370934	-0.062413
C	1.261877	-1.141363	-0.298599
C	1.495621	-1.674073	-1.572864
C	1.949004	-1.694454	0.788778
C	2.378135	-2.738995	-1.756752
H	0.979849	-1.253525	-2.431430
C	2.830094	-2.760074	0.609302
H	1.802645	-1.282512	1.780751
C	3.048242	-3.288305	-0.664042
H	2.545064	-3.133683	-2.754102
H	3.351310	-3.175607	1.466164
H	3.737903	-4.114630	-0.803148
C	-2.251260	0.129717	-0.153755
N	-3.767203	1.187868	-1.314979
N	-2.386082	0.983087	-1.152803
C	-4.370521	0.474846	-0.429973
O	-3.486977	-0.226365	0.350545
C	-5.821546	0.327967	-0.162701
H	-6.384190	0.945374	-0.862049
H	-6.140279	-0.711793	-0.277543
H	-6.067465	0.639274	0.856405

(±)–*anti*-**S8**
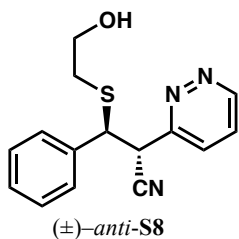
Energy (in a.u.) = -1218.46506499
Gibbs correction(298K; in a.u.) =   0.223346

C	3.764428	-1.211565	-1.794254
C	2.550336	-1.615215	-1.280363
C	2.140917	-1.031986	-0.073686
C	4.482412	-0.258078	-1.067225

H	4.157441	-1.615841	-2.719267
H	1.939242	-2.356683	-1.782368
C	0.794779	-1.400052	0.540885
C	0.820406	-1.276119	2.001776
N	0.822024	-1.230216	3.153655
C	-0.381735	-0.607316	-0.131952
H	-0.320584	-0.864282	-1.190976
S	-1.970189	-1.348584	0.477867
C	-3.137187	-0.553240	-0.696686
H	-3.065716	0.530350	-0.592034
H	-2.862504	-0.831356	-1.716045
C	-4.555540	-1.012288	-0.396386
H	-4.638134	-2.100354	-0.495567
H	-4.839862	-0.737440	0.625583
O	-5.407600	-0.360054	-1.344022
H	-6.319682	-0.632055	-1.183703
C	-0.303000	0.900470	0.004772
C	0.045303	1.665360	-1.114402
C	-0.568155	1.559116	1.212290
C	0.145334	3.054430	-1.028704
H	0.239548	1.174251	-2.063063
C	-0.465943	2.945436	1.300405
H	-0.868549	0.990976	2.084899
C	-0.107449	3.698410	0.180746
H	0.414712	3.629556	-1.908476
H	-0.673370	3.439563	2.243966
H	-0.034026	4.778707	0.250490
H	0.609420	-2.458878	0.332427
H	5.444702	0.107544	-1.408577
N	2.876805	-0.133409	0.576840
N	4.051422	0.257847	0.081750
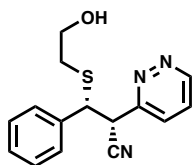
(±)–*syn*-**S8**

Energy (in a.u.) =   -1218.46519234
Gibbs correction(298K; in a.u.) =   0.222164

C	-4.409185	0.114561	0.420480
C	-3.175897	-0.319323	0.862912
C	-2.278890	-0.785056	-0.104312
C	-4.656292	0.055528	-0.952328
H	-5.161414	0.488710	1.104323
H	-2.915553	-0.304432	1.914332
C	-0.866062	-1.280509	0.199479
C	-0.717421	-1.716223	1.590237
N	-0.613645	-2.071063	2.682317
C	0.231207	-0.252789	-0.245271
H	-0.069453	0.041362	-1.251976
S	0.116811	1.267280	0.802800
C	1.126478	2.402141	-0.230370
H	2.134087	1.995150	-0.328172
H	0.674925	2.476544	-1.221493
C	1.181097	3.774392	0.422464
H	0.173988	4.194686	0.520545
H	1.624371	3.706737	1.422324
O	1.986011	4.601225	-0.424603
H	2.038964	5.484904	-0.040037
C	1.614797	-0.874784	-0.315861
C	2.095513	-1.301209	-1.559977

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C     2.414729   -1.066955    0.816624
C     3.342557   -1.915988   -1.670841
H     1.491051   -1.151932   -2.449848
C     3.660032   -1.683674    0.707615
H     2.072772   -0.721131    1.785339
C     4.127897   -2.110960   -0.535590
H     3.700121   -2.235961   -2.644047
H     4.268058   -1.824772    1.595219
H     5.099868   -2.585940   -0.618975
H    -5.601328    0.380530   -1.373448
N    -2.580040   -0.826489   -1.403056
N    -3.766940   -0.402198   -1.832411
H    -0.706518   -2.167403   -0.421583
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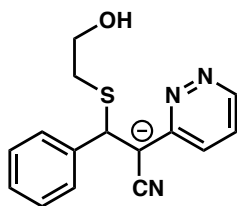

(±)–**S8-cb**

Energy (in a.u.) =   -1217.99213212
Gibbs correction(298K; in a.u.) =   0.208697

```
C     3.839201    1.432693    1.193223
C     2.577736    1.008935    0.866992
C     2.432714   -0.133126    0.019513
C     4.933902    0.728614    0.664545
H     3.995508    2.294755    1.833378
H     1.711903    1.543890    1.235852
C     1.163824   -0.671719   -0.356785
C     1.127537   -1.733543   -1.263223
N     1.082998   -2.626711   -2.018840
C    -0.125396   -0.091957    0.157529
H     0.054013    0.349529    1.138717
S    -0.622219    1.390507   -0.921192
C    -2.013290    2.098602    0.052801
H    -2.853762    1.401892    0.046125
H    -1.684569    2.238467    1.085622
C    -2.441511    3.432157   -0.535839
H    -1.611779    4.147232   -0.509683
H    -2.755073    3.309518   -1.578973
O    -3.536920    3.913997    0.255635
H    -3.824520    4.766058   -0.095052
C    -1.260011   -1.088759    0.325859
C    -1.525561   -1.595153    1.604698
C    -2.042042   -1.541369   -0.742536
C    -2.535802   -2.534683    1.811649
H    -0.935252   -1.251166    2.449405
C    -3.052959   -2.480515   -0.540354
H    -1.867569   -1.147076   -1.737052
C    -3.304710   -2.981868    0.737308
H    -2.725323   -2.909900    2.812457
H    -3.648430   -2.817771   -1.383092
H    -4.095597   -3.708253    0.894503
H     5.959441    1.010514    0.877969
N     3.558080   -0.751635   -0.463529
N     4.771791   -0.318458   -0.138841
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HO

S

N
O
N

CN
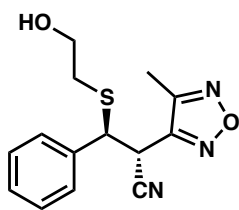
(±)–anti-**S9**

Energy (in a.u.) = -1255.55486906
Gibbs correction(298K; in a.u.) =   0.219384

C	0.919402	-1.065587	0.839268
C	0.915041	-0.670710	2.252425
N	0.911063	-0.392294	3.370535
C	-0.298125	-0.492974	0.026704
H	-0.209777	-0.936427	-0.966463
S	-1.834925	-1.214950	0.771732
C	-3.042639	-0.742116	-0.528777
H	-3.076334	0.345321	-0.607759
H	-2.718604	-1.160229	-1.483692
C	-4.417776	-1.280750	-0.164644
H	-4.394871	-2.373209	-0.084784
H	-4.748493	-0.872228	0.796881
O	-5.306551	-0.875718	-1.210843
H	-6.192740	-1.202636	-1.012372
C	-0.312561	1.015821	-0.116883
C	0.017795	1.580736	-1.354197
C	-0.641294	1.867503	0.945547
C	0.036575	2.965041	-1.525590
H	0.261647	0.935783	-2.192901
C	-0.618665	3.250046	0.776914
H	-0.931028	1.452880	1.904058
C	-0.278683	3.803836	-0.458541
H	0.292951	3.383874	-2.493052
H	-0.874373	3.896012	1.610372
H	-0.267260	4.880923	-0.588676
H	0.816582	-2.155463	0.828611
C	2.237293	-0.725131	0.188173
N	2.965497	0.289584	0.552455
N	3.995566	-0.765834	-1.161256
O	4.056585	0.284113	-0.269813
C	2.888636	-1.403341	-0.901861
C	2.465942	-2.623229	-1.648808
H	2.324269	-3.465467	-0.967483
H	1.522367	-2.456531	-2.173288
H	3.223658	-2.895624	-2.382436

HO

S

N
O
N

CN
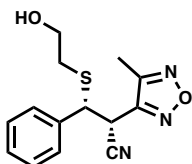
(±)–syn-**S9**

Energy (in a.u.) = -1255.55331133
Gibbs correction(298K; in a.u.) =   0.219482

C	-0.861748	-1.286232	-0.040117
C	-0.855640	-1.736520	1.355650
N	-0.848340	-2.113426	2.444604
C	0.272465	-0.251532	-0.368959
H	0.086390	0.031910	-1.406191
S	0.040014	1.278234	0.640207

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C       1.144711    2.407818   -0.297027
H       2.165633    2.025645   -0.252638
H       0.819469    2.437775   -1.338617
C       1.082895    3.801001    0.309832
H       0.062772    4.197419    0.259900
H       1.391800    3.776664    1.360922
O       1.974627    4.620014   -0.453038
H       1.960199    5.515971   -0.094387
C       1.655309   -0.873891   -0.280488
C       2.256460   -1.336456   -1.457526
C       2.337013   -1.030212    0.931797
C       3.507857   -1.950842   -1.425013
H       1.744800   -1.214557   -2.407741
C       3.586801   -1.646580    0.965537
H       1.900164   -0.655979    1.850523
C       4.175738   -2.109644   -0.211489
H       3.960823   -2.298326   -2.347641
H       4.103485   -1.759293    1.912995
H       5.151193   -2.583843   -0.183224
C      -2.233395   -0.820953   -0.481270
N      -2.579073   -1.006806   -1.723612
N      -4.271793    0.035313   -0.655757
O      -3.829787   -0.478068   -1.854689
C      -3.313873   -0.160368    0.208031
C      -3.449117    0.260701    1.633305
H      -3.397137   -0.600744    2.301566
H      -2.650751    0.950034    1.912685
H      -4.407244    0.758052    1.780742
H      -0.628965   -2.171338   -0.640624
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(±)–**S9-cb**
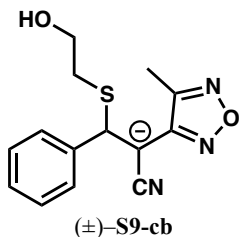
Energy (in a.u.) =   -1255.08220638
Gibbs correction(298K; in a.u.) =   0.205611

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C       1.243592   -0.724148   -0.418281
C       1.178567   -1.722704   -1.390341
N       1.142716   -2.570372   -2.197871
C      -0.027872   -0.130524    0.117611
H       0.169048    0.334213    1.079917
S      -0.553302    1.324773   -0.992399
C      -1.992595    2.009543   -0.071893
H      -2.818910    1.297163   -0.106080
H      -1.706180    2.161005    0.971719
C      -2.422588    3.331786   -0.684462
H      -1.609611    4.063923   -0.625689
H      -2.687694    3.198748   -1.739734
O      -3.561288    3.794150    0.055931
H      -3.850745    4.638445   -0.311651
C      -1.155263   -1.128185    0.329689
C      -1.400674   -1.599854    1.625785
C      -1.948004   -1.616343   -0.715051
C      -2.400446   -2.540900    1.872118
H      -0.801774   -1.228817    2.452790
C      -2.947781   -2.558269   -0.473418
H      -1.791333   -1.247720   -1.722253
C      -3.178861   -3.025340    0.820884
```

H	-2.574254	-2.888946	2.885516
H	-3.551288	-2.923622	-1.298536
H	-3.961143	-3.753715	1.008812
C	2.546075	-0.221565	-0.095663
N	3.656296	-0.671898	-0.672663
N	4.245846	0.922582	0.840582
O	4.719118	0.033928	-0.085975
C	2.952198	0.803063	0.868424
C	2.153599	1.649211	1.808851
H	1.383843	2.215250	1.280243
H	1.662449	1.041709	2.573472
H	2.814077	2.354565	2.314360

(±)–anti-**S10**
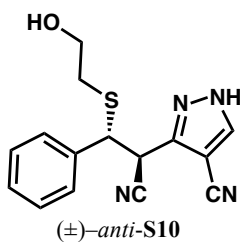
Energy (in a.u.) =   -1272.64246088
Gibbs correction(298K; in a.u.) =   0.215797

C	0.660007	-1.453544	0.523078
C	0.843990	-1.142107	1.944549
N	0.987951	-0.928294	3.068135
C	-0.523770	-0.668038	-0.144336
H	-0.567329	-1.061863	-1.160731
S	-2.085095	-1.223657	0.689445
C	-3.312928	-0.502401	-0.470710
H	-3.209700	0.583653	-0.473429
H	-3.117083	-0.881612	-1.475487
C	-4.716627	-0.890335	-0.032298
H	-4.834237	-1.979605	-0.035930
H	-4.916956	-0.525959	0.981563
O	-5.619582	-0.288181	-0.965830
H	-6.524169	-0.514984	-0.717026
C	-0.351252	0.836539	-0.212679
C	-0.000768	1.421674	-1.435450
C	-0.537644	1.666467	0.900343
C	0.173526	2.801496	-1.543974
H	0.133241	0.795784	-2.312439
C	-0.363335	3.044383	0.793611
H	-0.837173	1.239189	1.850450
C	-0.006331	3.616982	-0.428208
H	0.441927	3.236177	-2.501199
H	-0.512879	3.672884	1.665394
H	0.122761	4.691178	-0.510153
H	0.384603	-2.512066	0.480021
C	1.949985	-1.326966	-0.256034
N	3.358742	-1.834390	-1.765423
N	2.176320	-2.197095	-1.230259
C	3.909426	-0.769812	-1.166844
C	3.022234	-0.389875	-0.164605
C	3.212222	0.687500	0.729488
N	3.391503	1.570570	1.454636
H	3.741975	-2.368112	-2.532289
H	4.859165	-0.357996	-1.468422

(±)–syn-**S10**
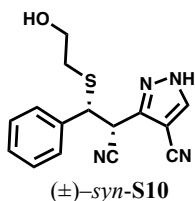
Energy (in a.u.) =   -1272.64339467
Gibbs correction(298K; in a.u.) =   0.214076

C	0.988517	-0.985183	-0.586557
C	0.767442	-1.243324	-2.014131
N	0.589428	-1.473713	-3.129180
C	-0.188673	-0.185968	0.079938
H	0.134897	-0.005159	1.106354
S	-0.337804	1.477068	-0.716398
C	-1.507000	2.256287	0.467195
H	-2.436874	1.685994	0.483567
H	-1.064071	2.243532	1.465079
C	-1.782533	3.689263	0.038938
H	-0.854070	4.270695	0.018659
H	-2.224458	3.711999	-0.963556
O	-2.693077	4.237769	0.997771
H	-2.890086	5.150849	0.754843
C	-1.475903	-0.991996	0.124633
C	-1.805760	-1.662872	1.308630
C	-2.330660	-1.112521	-0.977314
C	-2.956642	-2.446604	1.388485
H	-1.159722	-1.572271	2.176798
C	-3.479922	-1.897250	-0.899403
H	-2.108604	-0.580873	-1.895297
C	-3.796529	-2.567903	0.282569
H	-3.197398	-2.955572	2.316015
H	-4.132084	-1.979775	-1.762719
H	-4.694293	-3.174277	0.342476
C	2.343267	-0.357614	-0.356836
N	4.133567	0.721897	-0.727824
N	2.991796	0.295349	-1.306753
C	4.246618	0.363214	0.558656
C	3.093627	-0.354574	0.857177
C	2.766870	-0.962048	2.088920
N	2.483955	-1.468496	3.090181
H	4.800423	1.247113	-1.274568
H	5.102963	0.618787	1.161944
H	0.985333	-1.966988	-0.099756

(±)–**S10-cb**
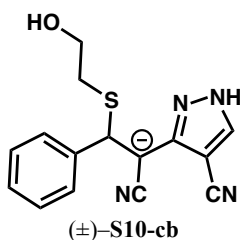
Energy (in a.u.) =   -1272.16639415
Gibbs correction(298K; in a.u.) =   0.201295

C	-1.109531	0.239068	-0.218933
C	-1.351760	1.157211	-1.231937
N	-1.519774	1.942574	-2.087829
C	0.305397	-0.041724	0.209003
H	0.256405	-0.558605	1.166675

S	1.071133	-1.326144	-0.961477
C	2.653203	-1.712535	-0.103428
H	3.311348	-0.842219	-0.141930
H	2.439090	-1.940698	0.943698
C	3.329690	-2.903263	-0.760939
H	2.689200	-3.790076	-0.698478
H	3.527230	-2.697878	-1.819466
O	4.563583	-3.132928	-0.064829
H	5.008149	-3.892897	-0.460601
C	1.186546	1.183085	0.376727
C	1.417006	1.674228	1.669039
C	1.761316	1.865314	-0.702393
C	2.184385	2.819996	1.879297
H	0.988394	1.155116	2.521787
C	2.528053	3.012157	-0.496879
H	1.617236	1.490502	-1.709203
C	2.743188	3.495714	0.794369
H	2.350459	3.178910	2.890319
H	2.963423	3.526283	-1.348318
H	3.344933	4.384879	0.953214
C	-2.176909	-0.510048	0.375802
N	-3.169315	-1.941865	1.664143
N	-1.942920	-1.457909	1.308335
C	-4.179000	-1.368892	1.011826
C	-3.612030	-0.426334	0.154367
C	-4.362897	0.402297	-0.697475
N	-5.025770	1.066443	-1.381727
H	-3.228393	-2.672629	2.355797
H	-5.209773	-1.641318	1.177636

(±)–*anti*-**S11**
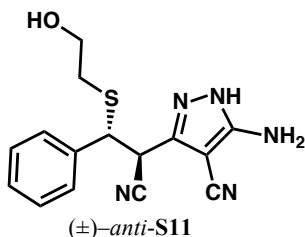
Energy (in a.u.) =   -1328.02173060
Gibbs correction(298K; in a.u.) =   0.230762

C	0.389699	-1.417269	0.672331
C	0.494691	-1.057642	2.090436
N	0.576534	-0.806069	3.212580
C	-0.761243	-0.665735	-0.084986
H	-0.732626	-1.082497	-1.092589
S	-2.365927	-1.230789	0.657701
C	-3.523957	-0.574564	-0.608045
H	-3.411544	0.508980	-0.669008
H	-3.277598	-1.013188	-1.576882
C	-4.952501	-0.928802	-0.225034
H	-5.075906	-2.015523	-0.158617
H	-5.208282	-0.493347	0.747382
O	-5.797280	-0.393397	-1.249297
H	-6.715619	-0.602441	-1.038300
C	-0.614385	0.840034	-0.177177
C	-0.207635	1.407244	-1.390910
C	-0.881460	1.688907	0.904651
C	-0.056093	2.787996	-1.519998
H	-0.010888	0.766155	-2.244821
C	-0.729380	3.067763	0.777776
H	-1.226734	1.274963	1.845095
C	-0.315427	3.622464	-0.434298

H	0.256951	3.208402	-2.470044
H	-0.941254	3.710962	1.625643
H	-0.203908	4.697294	-0.532400
H	0.123550	-2.478843	0.650238
C	1.719172	-1.311046	-0.041365
N	3.221544	-1.861068	-1.449938
N	2.001643	-2.219524	-0.952337
C	3.731864	-0.756234	-0.869804
C	2.769204	-0.347757	0.073319
N	4.908373	-0.177812	-1.235075
H	5.307780	0.483656	-0.585148
H	5.600687	-0.761604	-1.682523
C	2.900264	0.763513	0.922760
N	3.052971	1.685714	1.608622
H	3.644124	-2.425081	-2.171781

(±)–*syn*-**S11**
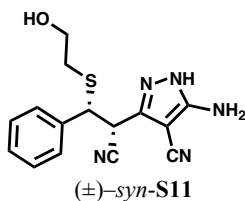
Energy (in a.u.) = -1328.02000353
Gibbs correction(298K; in a.u.) =   0.229408

C	-0.716501	-0.770087	0.070371
C	-0.807764	-1.173057	1.481359
N	-0.877044	-1.496047	2.585948
C	0.653621	-0.096991	-0.265886
H	0.497477	0.408194	-1.218213
S	1.027475	1.234537	0.967327
C	2.301512	2.148625	0.010731
H	3.122241	1.470952	-0.231025
H	1.855679	2.512493	-0.917188
C	2.817953	3.317538	0.834381
H	2.000244	4.002269	1.085737
H	3.266454	2.960320	1.768182
O	3.798939	3.986620	0.034256
H	4.137451	4.745658	0.525078
C	1.766951	-1.117231	-0.429574
C	2.187937	-1.454911	-1.721237
C	2.370407	-1.754277	0.661717
C	3.181497	-2.413897	-1.921420
H	1.736792	-0.964924	-2.579000
C	3.359229	-2.716049	0.463455
H	2.079240	-1.489252	1.671736
C	3.768547	-3.049462	-0.828686
H	3.497899	-2.658199	-2.930226
H	3.815482	-3.200810	1.320430
H	4.543166	-3.793867	-0.980847
C	-1.925878	0.049783	-0.344661
N	-3.072060	1.552358	-1.328319
N	-1.796827	1.118272	-1.097306
C	-4.012955	0.784466	-0.742098
C	-3.303526	-0.232536	-0.076477
N	-5.352759	0.976466	-0.880526
H	-5.947372	0.522007	-0.202925
H	-5.674155	1.899529	-1.134856
C	-3.881004	-1.293549	0.639620
N	-4.381403	-2.165405	1.218066
H	-3.214994	2.373509	-1.896609
H	-0.746215	-1.703131	-0.506157

(±)–**S11-cb**
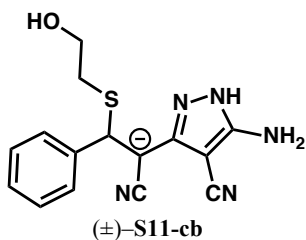
Energy (in a.u.) = -1327.54363005
Gibbs correction(298K; in a.u.) =   0.215679

C	0.788406	-0.392588	-0.309433
C	0.912404	-1.338789	-1.317177
N	0.982166	-2.143535	-2.169556
C	-0.577573	0.016704	0.166692
H	-0.442346	0.556298	1.103263
S	-1.290919	1.326619	-1.011106
C	-2.792167	1.868082	-0.094065
H	-3.514341	1.049820	-0.061183
H	-2.506853	2.120867	0.930177
C	-3.414082	3.079104	-0.767993
H	-2.708014	3.916931	-0.778544
H	-3.684400	2.846472	-1.804550
O	-4.587437	3.428816	-0.018993
H	-5.000935	4.199140	-0.428025
C	-1.548208	-1.123612	0.414500
C	-1.763785	-1.548378	1.732757
C	-2.221701	-1.793417	-0.614185
C	-2.612886	-2.618041	2.016710
H	-1.258918	-1.036788	2.547482
C	-3.070320	-2.864572	-0.335017
H	-2.090304	-1.467103	-1.639370
C	-3.270185	-3.282781	0.981267
H	-2.765289	-2.926028	3.046544
H	-3.581301	-3.370501	-1.148521
H	-3.935310	-4.112677	1.197676
C	1.937891	0.277044	0.229495
N	3.120685	1.644379	1.434825
N	1.823158	1.259222	1.135858
C	4.048382	0.959792	0.757274
C	3.347905	0.047786	-0.052474
N	5.401514	1.110255	0.936700
H	5.974795	0.770558	0.176912
H	5.713259	2.013071	1.267760
C	3.986905	-0.866344	-0.897272
N	4.583492	-1.601035	-1.574168
H	3.271149	2.378565	2.107926

(±)–*anti*-**S12**
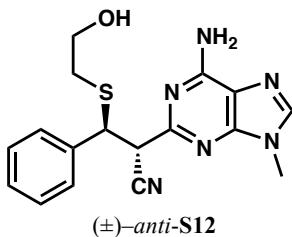
Energy (in a.u.) = -1460.87943470
Gibbs correction(298K; in a.u.) =   0.278163

C	-0.227628	-0.239996	1.567889
C	-0.519769	0.821007	2.534267
N	-0.771849	1.618502	3.328077

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C      -1.284343   -0.346691    0.415997
H      -0.979378   -1.229943   -0.146128
S      -2.919958   -0.769744    1.183424
C      -3.842695   -1.237527   -0.334391
H      -3.928065   -0.366787   -0.986326
H      -3.289794   -2.020178   -0.857780
C      -5.227056   -1.741719    0.042029
H      -5.153043   -2.630175    0.678751
H      -5.781539   -0.971301    0.589753
O      -5.896209   -2.060144   -1.183149
H      -6.783165   -2.382493   -0.980824
C      -1.325447    0.839575   -0.527207
C      -0.786340    0.701204   -1.811567
C      -1.876636    2.074050   -0.160184
C      -0.780951    1.773078   -2.704966
H      -0.367373   -0.252260   -2.118444
C      -1.868606    3.146415   -1.049251
H      -2.325346    2.196735    0.818835
C      -1.319183    3.000769   -2.324474
H      -0.360968    1.644488   -3.697223
H      -2.298290    4.096300   -0.748011
H      -1.318783    3.836005   -3.017145
H      -0.279302   -1.183560    2.119630
C       1.189974   -0.129327    1.002345
C       3.018760    1.210170    0.534809
C       2.898209   -1.106379   -0.013592
C       3.636684    0.079747   -0.036344
C       4.858692   -1.394723   -0.954646
H       5.666640   -1.917432   -1.446569
N       1.780530    1.068887    1.051165
N       1.669682   -1.264787    0.496837
N       4.866986   -0.121200   -0.632415
N       3.699859   -2.050115   -0.609202
N       3.601902    2.423850    0.574672
H       3.147948    3.182304    1.058110
H       4.553570    2.549035    0.270852
C       3.379944   -3.456808   -0.820875
H       3.197022   -3.949054    0.134524
H       2.494655   -3.551475   -1.449930
H       4.222797   -3.936184   -1.314620
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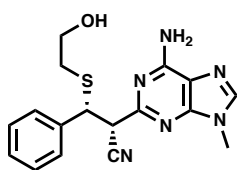

(±)–*syn*-**S12**

Energy (in a.u.) = -1460.87928704
Gibbs correction(298K; in a.u.) =   0.277958

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C      -0.218560   -1.393476   -0.285356
C      -0.618044   -2.014101   -1.550598
N      -0.964831   -2.533599   -2.519763
C      -1.189126   -0.252966    0.171761
H      -0.735524    0.133383    1.084973
S      -1.135383    1.127743   -1.060209
C      -2.025150    2.411078   -0.092905
H      -3.042792    2.071587    0.106839
H      -1.508243    2.560814    0.857108
C      -2.056241    3.712130   -0.879178
H      -1.038579    4.069037   -1.072782
H      -2.558772    3.567153   -1.842221
```

|			
O	-2.773682	4.660184	-0.081219
H	-2.810214	5.501552	-0.552728
C	-2.581993	-0.761391	0.501048
C	-2.896846	-1.029291	1.839138
C	-3.553726	-0.998508	-0.477876
C	-4.148888	-1.532351	2.191973
H	-2.158240	-0.842059	2.613199
C	-4.805194	-1.502667	-0.127325
H	-3.338091	-0.774379	-1.516107
C	-5.107101	-1.772381	1.208035
H	-4.375346	-1.729646	3.234713
H	-5.547554	-1.679383	-0.898899
H	-6.083658	-2.159740	1.479456
C	1.244235	-0.939554	-0.294932
C	3.162417	-0.509155	-1.517243
C	2.999349	-0.208951	0.841159
C	3.784076	-0.126407	-0.312239
C	5.022301	0.511135	1.291305
H	5.848499	0.867542	1.889921
N	1.876019	-0.913357	-1.472800
N	1.724683	-0.615062	0.904251
N	5.053331	0.328812	-0.009170
N	3.812003	0.204650	1.868975
N	3.797826	-0.501645	-2.705338
H	3.287515	-0.711892	-3.548188
H	4.730555	-0.131898	-2.788290
C	3.453774	0.297895	3.279147
H	2.625033	0.993617	3.411954
H	3.165797	-0.682028	3.660364
H	4.316474	0.658581	3.835587
H	-0.306204	-2.172415	0.479646

(±)–**S12-cb**
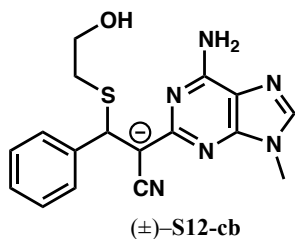
Energy (in a.u.) = -1460.40356838
Gibbs correction(298K; in a.u.) =   0.266081

|			
C	-0.014690	-1.071383	-0.572465
C	-0.331879	-2.207543	-1.315737
N	-0.629852	-3.156370	-1.935415
C	-1.113041	-0.189396	-0.049330
H	-0.658803	0.471483	0.686452
S	-1.678487	0.979944	-1.427782
C	-2.798825	2.118028	-0.512282
H	-3.696967	1.579610	-0.202908
H	-2.281826	2.474478	0.382049
C	-3.179930	3.297196	-1.390893
H	-2.287516	3.862273	-1.682026
H	-3.679033	2.951655	-2.303683
O	-4.066928	4.128994	-0.628786
H	-4.324651	4.886891	-1.168150
C	-2.272407	-0.918213	0.607677
C	-2.312844	-0.992540	2.006716
C	-3.292184	-1.546813	-0.116998

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C      -3.330172  -1.685173   2.663557
H      -1.536800  -0.504407   2.589587
C      -4.310940  -2.241025   0.535348
H      -3.295670  -1.482757  -1.199115
C      -4.334980  -2.314702   1.928754
H      -3.340542  -1.725643   3.748397
H      -5.091297  -2.721341  -0.047044
H      -5.131226  -2.850467   2.435611
C       1.358118  -0.727222  -0.363092
C       3.600505  -1.329971  -0.703351
C       2.950996   0.622763   0.478138
C       3.996405  -0.177320   0.007851
C       4.926874   1.458042   1.003928
H       5.640501   2.149446   1.429495
N       2.307423  -1.580979  -0.878745
N       1.645635   0.412214   0.330623
N       5.228447   0.363265   0.346979
N       3.568744   1.677144   1.121482
N       4.518878  -2.229460  -1.182515
H       4.189542  -2.870334  -1.889721
H       5.464849  -1.902095  -1.309530
C       2.910027   2.793131   1.781106
H       2.311020   3.360434   1.066878
H       2.260508   2.433623   2.580677
H       3.668019   3.448245   2.207422
```


(±)–*anti*-**S13**
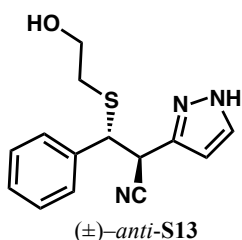
Energy (in a.u.) =   -1180.37174408
Gibbs correction(298K; in a.u.) =   0.219223

```
C       0.991648  -1.418425   0.413228
C       1.061490  -1.369650   1.877874
N       1.130660  -1.350623   3.028915
C      -0.208928  -0.604105  -0.182424
H      -0.175819  -0.823177  -1.250589
S      -1.776677  -1.370281   0.450915
C      -2.984490  -0.531818  -0.649893
H      -2.921244   0.546214  -0.494301
H      -2.734962  -0.756245  -1.688909
C      -4.389193  -1.020944  -0.334186
H      -4.465095  -2.102834  -0.489940
H      -4.645523  -0.805038   0.709155
O      -5.275756  -0.327341  -1.219104
H      -6.179782  -0.619036  -1.048123
C      -0.131191   0.897466   0.007059
C       0.166626   1.705032  -1.096721
C      -0.347345   1.511234   1.247744
C       0.263022   3.090623  -0.965528
H       0.324610   1.248432  -2.068958
C      -0.246952   2.894413   1.382041
H      -0.610765   0.911014   2.110932
C       0.059412   3.689476   0.276218
H       0.492217   3.698770  -1.834494
```

H	-0.416578	3.352937	2.350856
H	0.130353	4.767076	0.381699
H	0.810963	-2.465974	0.151270
C	2.315900	-1.023396	-0.201106
N	3.869680	-1.034216	-1.642642
N	2.694654	-1.614148	-1.335862
C	4.252828	-0.104572	-0.736855
C	3.261390	-0.064047	0.223773
H	4.367690	-1.328180	-2.468917
H	5.177599	0.440908	-0.841891
H	3.228961	0.563531	1.100178

(±)–*syn*-**S13**
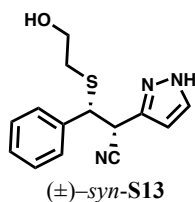
Energy (in a.u.) = -1180.37122525
Gibbs correction(298K; in a.u.) =   0.218891

C	-1.126317	-1.224637	0.058754
C	-1.052666	-1.669345	1.455513
N	-0.985115	-2.046924	2.542764
C	0.036273	-0.245609	-0.331470
H	-0.186592	0.058087	-1.355770
S	-0.071627	1.287397	0.699030
C	1.156768	2.323311	-0.190830
H	2.143090	1.863231	-0.113674
H	0.874100	2.382777	-1.243908
C	1.183929	3.715746	0.419714
H	0.201995	4.193672	0.331411
H	1.446901	3.664443	1.482407
O	2.169061	4.464416	-0.300885
H	2.211572	5.357001	0.063990
C	1.395518	-0.923766	-0.322397
C	1.925439	-1.377927	-1.536407
C	2.125940	-1.140501	0.851956
C	3.150705	-2.043248	-1.577840
H	1.377023	-1.209562	-2.458687
C	3.349877	-1.806456	0.812596
H	1.746362	-0.774855	1.799076
C	3.866212	-2.261183	-0.401425
H	3.546100	-2.384153	-2.529108
H	3.903694	-1.965117	1.732213
H	4.821451	-2.775008	-0.430165
C	-2.498761	-0.687289	-0.279088
N	-4.443567	0.111421	-0.012361
N	-3.362640	-0.318915	0.665436
C	-4.294121	0.024106	-1.354589
C	-3.034163	-0.495756	-1.573862
H	-5.250107	0.439204	0.496439
H	-5.077472	0.324964	-2.032661
H	-2.574052	-0.710160	-2.525936
H	-0.959056	-2.121949	-0.547639

(±)–**S13-cb**
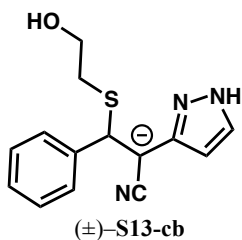
Energy (in a.u.) = -1179.88510915
Gibbs correction(298K; in a.u.) =   0.203762

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C       1.412888  -0.510977  -0.400866
C       1.501926  -1.439743  -1.424065
N       1.603510  -2.233372  -2.287597
C       0.092255  -0.060406   0.130263
H       0.268515   0.407070   1.098708
S      -0.579246   1.391223  -0.933208
C      -2.010738   1.967469   0.071495
H      -2.783616   1.196166   0.082098
H      -1.675415   2.136074   1.098051
C      -2.576244   3.255545  -0.501231
H      -1.816445   4.044981  -0.492750
H      -2.902015   3.105322  -1.537054
O      -3.693837   3.635308   0.316507
H      -4.069208   4.454606  -0.029359
C      -0.949995  -1.146849   0.306842
C      -1.219150  -1.624176   1.596868
C      -1.640830  -1.722289  -0.767256
C      -2.136073  -2.654118   1.809251
H      -0.701853  -1.186645   2.446188
C      -2.556337  -2.753643  -0.559999
H      -1.468759  -1.353448  -1.771870
C      -2.808713  -3.225601   0.729113
H      -2.328248  -3.004241   2.818812
H      -3.078355  -3.186288  -1.408094
H      -3.525486  -4.024579   0.889919
C       2.635743   0.087595   0.096293
N       3.963373   1.319022   1.269094
N       2.642471   1.030595   1.061389
C       4.783794   0.603331   0.469094
C       3.980839  -0.204308  -0.305894
H       4.217676   2.016157   1.948922
H       5.856717   0.719191   0.511144
H       4.303457  -0.911074  -1.055077
```


(±)–*anti*-**S14**
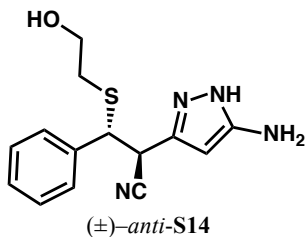
Energy (in a.u.) = -1235.74627533
Gibbs correction(298K; in a.u.) =   0.233326

```
C       0.629362  -1.479817   0.467012
C       0.649611  -1.447928   1.933663
N       0.678444  -1.443049   3.086695
C      -0.518124  -0.614074  -0.159876
H      -0.456533  -0.823567  -1.228634
S      -2.134309  -1.327986   0.411474
```

C	-3.273702	-0.437749	-0.720978
H	-3.193579	0.635067	-0.539546
H	-2.984422	-0.646193	-1.752917
C	-4.701238	-0.901452	-0.477611
H	-4.793641	-1.977338	-0.662964
H	-4.998016	-0.704569	0.558816
O	-5.533479	-0.167169	-1.382272
H	-6.449557	-0.445727	-1.260627
C	-0.393758	0.881760	0.048238
C	-0.032384	1.688644	-1.036813
C	-0.628752	1.491209	1.287574
C	0.107087	3.068817	-0.888465
H	0.142449	1.235535	-2.007787
C	-0.485111	2.868813	1.439353
H	-0.940246	0.892377	2.135617
C	-0.116178	3.663035	0.352184
H	0.385512	3.676545	-1.743252
H	-0.670051	3.323996	2.406967
H	-0.011731	4.736520	0.471048
H	0.417078	-2.516762	0.187258
C	1.988863	-1.135188	-0.099360
N	3.606777	-1.207338	-1.470444
N	2.391245	-1.760873	-1.201381
C	3.977646	-0.273537	-0.558272
C	2.936427	-0.194702	0.358487
N	5.147606	0.458115	-0.675346
H	5.416763	0.926494	0.178896
H	5.934230	-0.044267	-1.066766
H	4.128031	-1.524427	-2.273095
H	2.883490	0.446491	1.224093

(±)−*syn*-**S14**
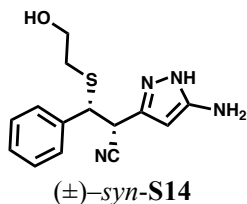
Energy (in a.u.) =   -1235.74596861
Gibbs correction(298K; in a.u.) =   0.233619

C	-0.760325	-1.304551	0.211406
C	-0.518140	-1.797040	1.572452
N	-0.311782	-2.210607	2.628736
C	0.310145	-0.256526	-0.253955
H	-0.025715	0.065929	-1.240817
S	0.226834	1.238436	0.833128
C	1.282948	2.371649	-0.154093
H	2.289165	1.956302	-0.228332
H	0.862140	2.463432	-1.157513
C	1.331767	3.735742	0.515877
H	0.326941	4.167074	0.584687
H	1.739632	3.651680	1.529589
O	2.175098	4.563845	-0.292527
H	2.222862	5.442425	0.104207
C	1.696116	-0.862199	-0.396878
C	2.124674	-1.265404	-1.667639
C	2.550147	-1.062837	0.694029
C	3.370872	-1.866408	-1.844988
H	1.480033	-1.108264	-2.527542
C	3.795311	-1.664485	0.518930
H	2.248823	-0.735115	1.682246
C	4.209957	-2.069516	-0.750405

H	3.685953	-2.168758	-2.838383
H	4.444969	-1.811311	1.375660
H	5.181758	-2.532889	-0.885494
C	-2.182663	-0.817869	0.045149
N	-4.145834	-0.183891	0.542424
N	-2.978137	-0.625762	1.089882
C	-4.098594	-0.105599	-0.811818
C	-2.822876	-0.515838	-1.178033
N	-5.149218	0.385655	-1.567325
H	-5.083516	0.156140	-2.549372
H	-6.074022	0.176205	-1.213986
H	-4.920770	0.040417	1.146983
H	-2.431187	-0.592288	-2.180470
H	-0.618420	-2.169199	-0.447519

(±)–**S14-cb**
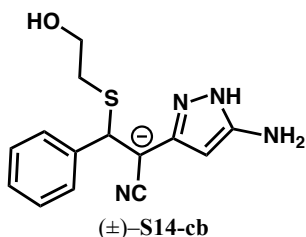
Energy (in a.u.) = -1235.25852678
Gibbs correction(298K; in a.u.) =   0.218058

| C	-1.037875	-0.597263	0.459960
C	-1.053870	-1.502999	1.506961
N	-1.087978	-2.277483	2.393311
C	0.246491	-0.082552	-0.101435
H	0.021467	0.382188	-1.060822
S	0.876500	1.390976	0.955626
C	2.266469	2.030807	-0.068884
H	3.092722	1.317004	-0.054027
H	1.920740	2.138821	-1.100144
C	2.737525	3.375632	0.457072
H	1.924921	4.109342	0.414521
H	3.065233	3.288337	1.499567
O	3.832547	3.800450	-0.369112
H	4.145830	4.658020	-0.055722
C	1.333284	-1.117611	-0.314097
C	1.589808	-1.573111	-1.614662
C	2.079746	-1.666661	0.736423
C	2.548372	-2.556830	-1.859696
H	1.029923	-1.154679	-2.446419
C	3.037155	-2.651910	0.496499
H	1.918447	-1.311929	1.747893
C	3.276464	-3.102938	-0.802599
H	2.729590	-2.890543	-2.876836
H	3.602346	-3.064457	1.326771
H	4.025978	-3.865499	-0.988966
C	-2.299782	-0.074753	-0.027401
N	-3.722967	1.065782	-1.184755
N	-2.368730	0.839895	-1.011844
C	-4.484479	0.323172	-0.348251
C	-3.614665	-0.424443	0.424121
N	-5.878286	0.333804	-0.412790
H	-6.308265	-0.076505	0.405592
H	-6.279348	1.248325	-0.583544
H	-4.033398	1.673784	-1.924491
H	-3.882687	-1.116645	1.207992

## 12. Full images of gels and Western blots
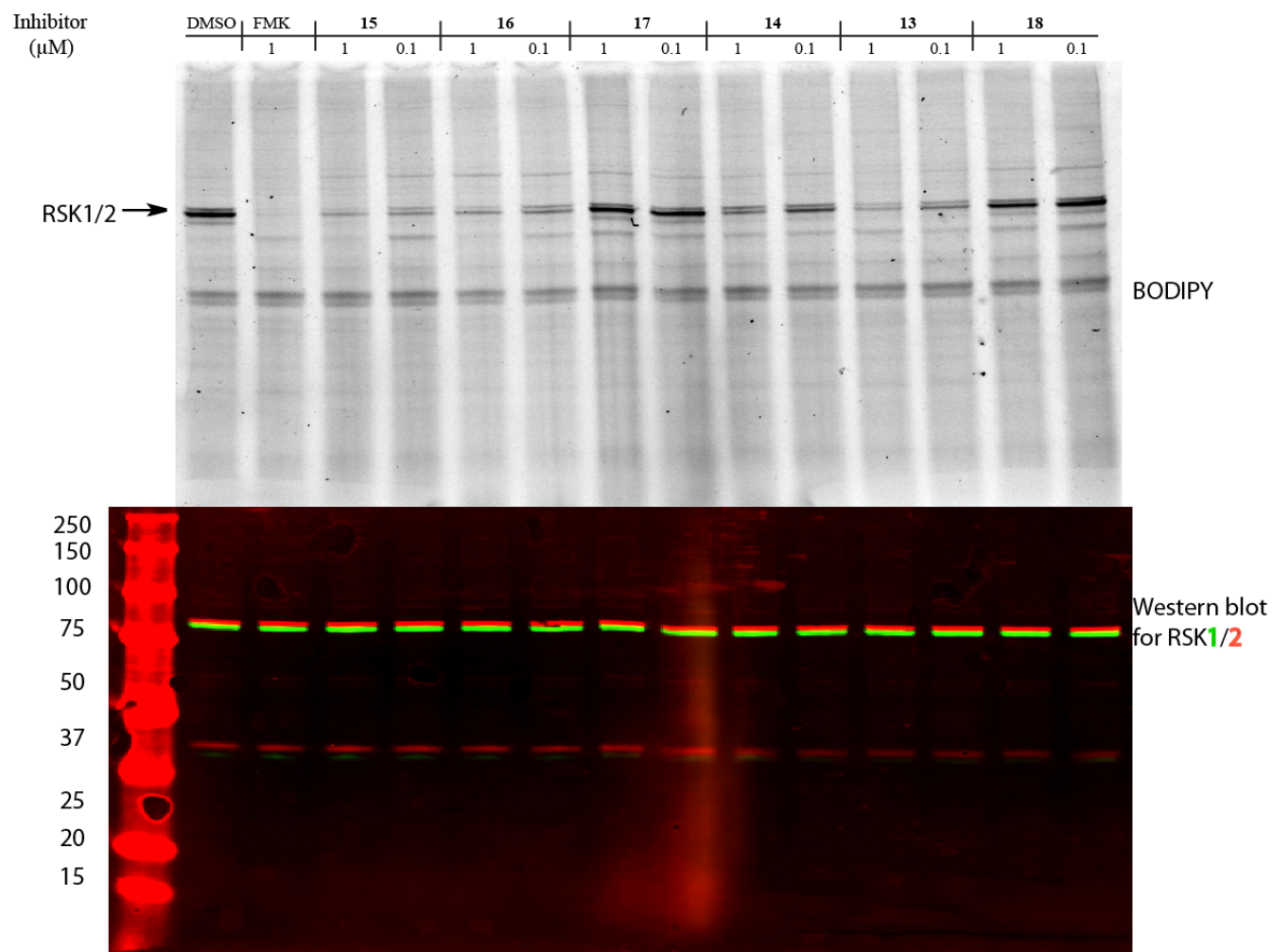
Assay with compounds **13-18** in MDA-MB-231 cells followed by labeling of RSK1/2 with BODIPY-FMK and immunoblotting (related to Figure 3).
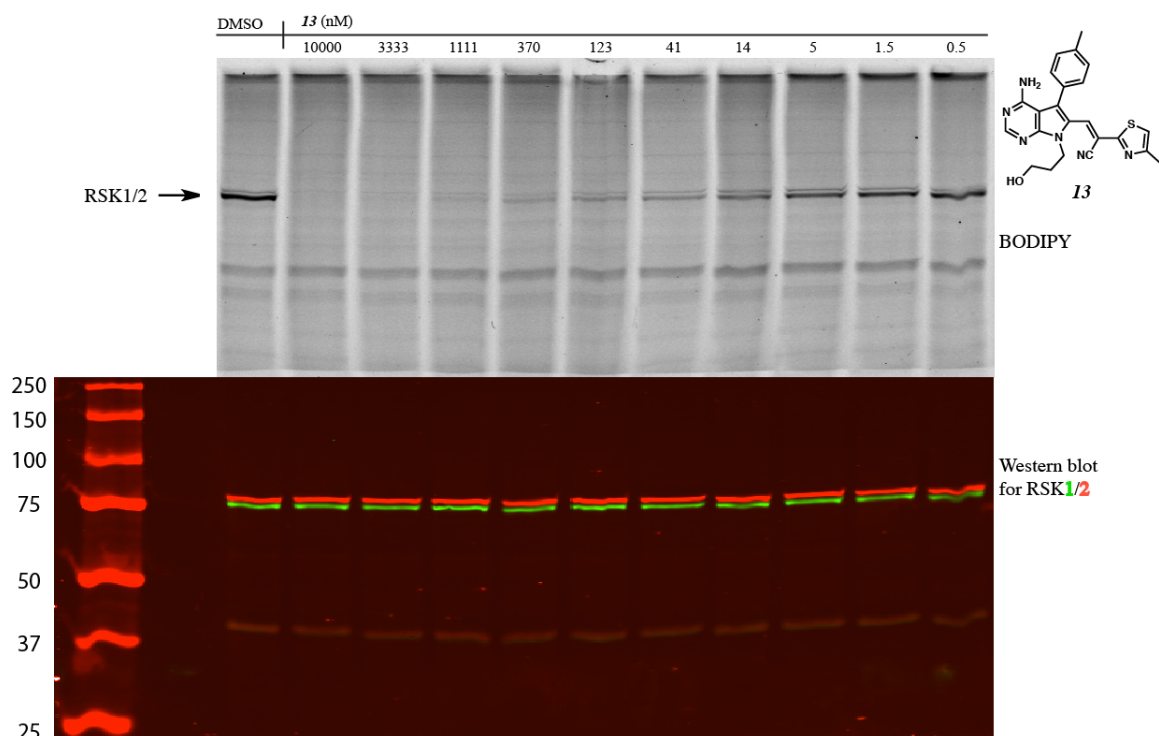
Dose response with compound **13** in MDA-MB-231 cells followed by labeling of RSK1/2 with BODIPY-FMK and immunoblotting (related to Figure 3).
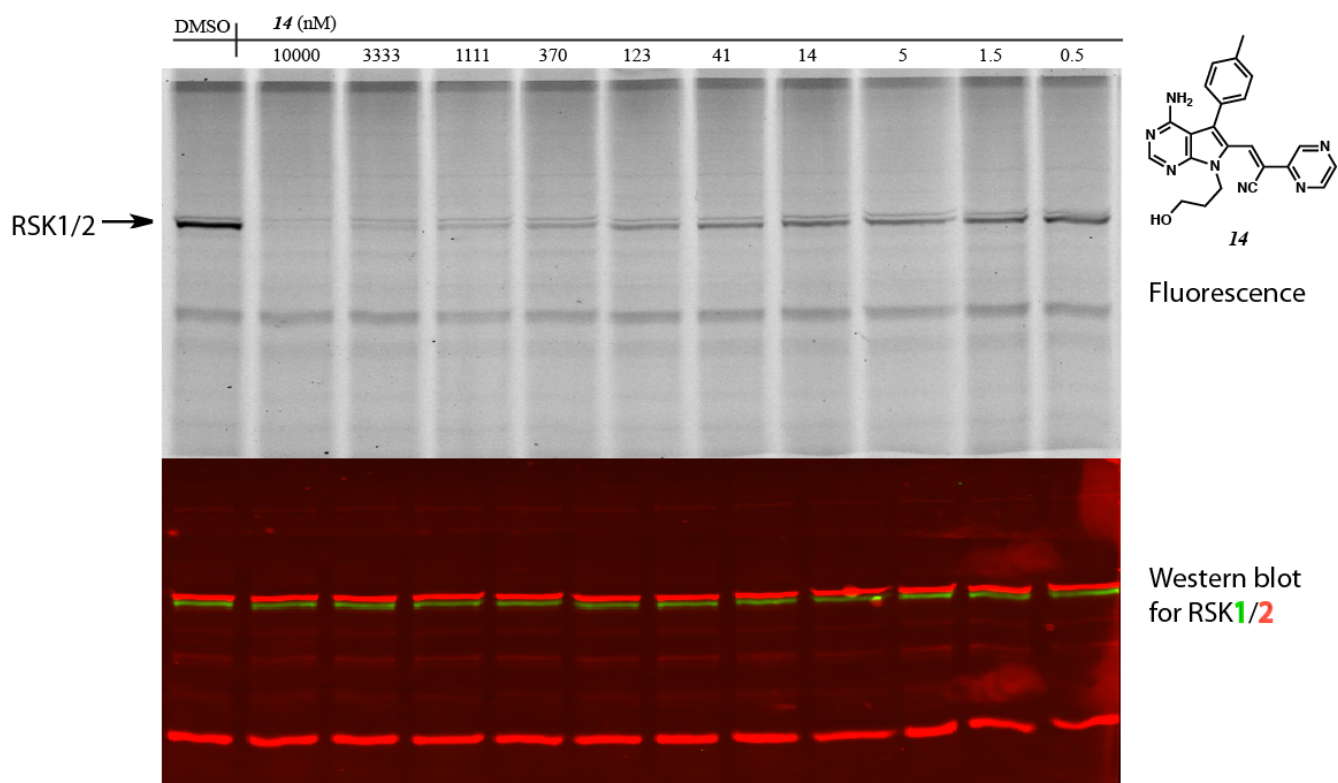
Dose response with compound **14** in MDA-MB-231 cells followed by labeling of RSK1/2 with BODIPY-FMK and immunoblotting (related to Figure 3).
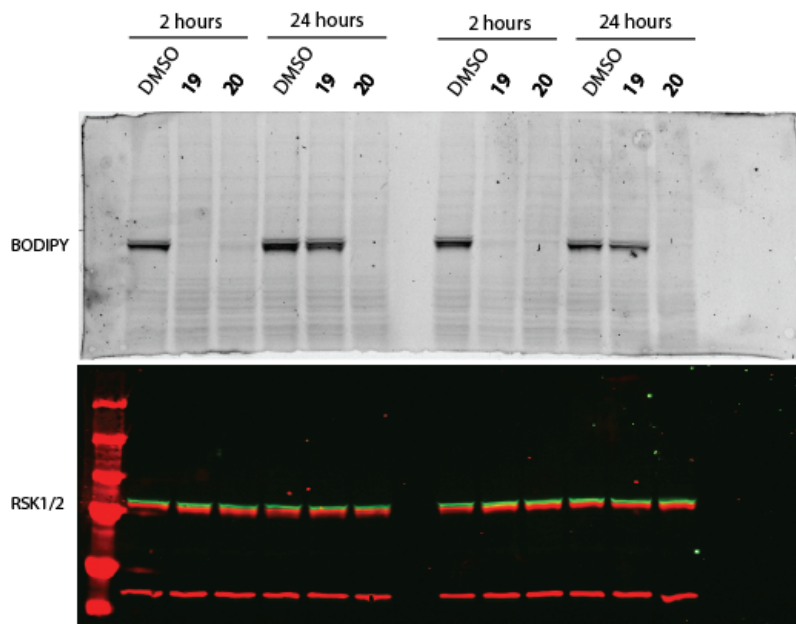
MB-MDA-231 cells treated with inhibitors **19** or **20** (1 µM) or DMSO for the indicated time period, followed by labeling of RSK1/2 with BODIPY-FMK and immunoblotting (related to Figure 4).

13. Supplementary references

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