Use of a conformational switching mechanism to modulate exposed polarity: discovery of CCR2 antagonist BMS-741672

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Supporting Information (1 of 2)

Characterization of BMS-741672 by X-ray crystallography and ^{1}H-NMR spectroscopy.

X-ray Crystallography Sample Preparation, Data Collection, Structure Solution and Refinement:

Compound **7**, bis-benzene sulfonic acid salt (Lactam Axial Di-Equatorial, LADE): Single crystal X-ray diffraction data was obtained using a colorless plate shaped crystal (approximate dimensions: 0.100 x 0.075 x 0.030 mm^3). Data collection was carried out at room temperature (~296K) using CuKα radiation. Indexing and processing of the measured intensity data were carried out via HKL-SCALEPACK & DENZO-SCALEPACK[1]. The crystal structure was solved by direct methods (SIR 97)[2] and refined by full-matrix least-squares procedures on F^2 using all reflections (SHELXL-2016/6)[3]. Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors and refined using a riding model.

Compound **7**, free base (Lactam Equatorial Di-Axial, LEDA): Single crystal X-ray diffraction data was obtained using a colorless plate shaped crystal (approximate dimensions: 0.170 x 0.100 x 0.030 mm^3). Data collection was carried out at room temperature (~296K) using CuKα radiation. Indexing and processing of the measured intensity data were carried out with the Bruker's APEX2 program suite[4]. The crystal structure was solved by direct methods (SHELXS-97)[5] and refined by full-matrix least-squares procedures on F^2 using all reflections (SHELXL-2016/6)[3]. The derived atomic parameters (coordinates and temperature factors) were refined through full matrix least-squares. Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors and refined using a riding model.

[1] Z. Otwinowski and W. Minor, "Processing of X-ray Diffraction Data Collected in Oscillation Mode", Methods in Enzymology, Volume 276: Macromolecular Crystallography, part A, p.307 326, 1997, C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press (New York)

[2] Cascarano al.,Acta Cryst.,1996,A52,C-79

[3] G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access)

[4] Bruker (2007). APEX2. Bruker AXS Inc., Madison, Wisconsin, USA.

[5] Sheldrick, G. M. SHELX97: Programs for Crystal Structure Analysis; University of Göttingen: Göttingen, Germany, 1997.

X-ray Crystallography Data:

Compound **7**, bis-benzene sulfonic acid salt (Lactam Axial Di-Equatorial, LADE):

CCDC deposition number	ZIGPAI
Empirical formula	$C_{37}H_{45}F_3N_6O_8S_2$
Formula weight	822.91
Temperature	296(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 15.174(3)Å α= 90°
	b = 7.6544(15)Å β= 93.76(3)°
	c = 16.772(3)Å γ = 90°
Volume	1943.8(7)Å^3
Z	2
Density (calculated)	1.406 Mg/m^3
Absorption coefficient	1.879 mm^{-1}
F(000)	864
Crystal size	0.100 x 0.075 x 0.030 mm^3
Theta range for data collection	2.640 to 61.290°
Index ranges	-17<=h<=14, -8<=k<=7, -18<=l<=18
Reflections collected	5231
Independent reflections	5231 [R(int) = 0.053]
Completeness to theta = 61.290°	98.2 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5231 / 19 / 538
Goodness-of-fit on F2	1.166
Final R indices [I>2sigma(I)]	R1 = 0.0500, wR2 = 0.1475
R indices (all data)	R1 = 0.0583, wR2 = 0.2018
Absolute structure parameter	-0.022(15)
Extinction coefficient	0.0046(9)
Largest diff. peak and hole	0.289 and -0.251 e.Å^{-3}

Compound **7**, free base (Lactam Equatorial Di-Axial, LEDA):

CCDC deposition number	ZIGNAG
Empirical formula	$C_{25}H_{33}F_3N_6O_2$
Formula weight	506.57
Temperature	296(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 11.8427(3)Å α= 90°
	b = 18.1503(7)Å β= 105.362(2)°
	c = 12.7923(4)Å γ = 90°
Volume	2651.44(15)Å^3
Z	4
Density (calculated)	1.269 Mg/m^3
Absorption coefficient	0.816 mm^{-1}
F(000)	1072
Crystal size	0.170 x 0.100 x 0.030 mm^3
Theta range for data collection	3.583 to 59.943°
Index ranges	-13<=h<=8, -19<=k<=19, -13<=l<=13
Reflections collected	16019
Independent reflections:	7312 [R(int) = 0.0228]
Completeness to theta = 59.943°	96.4 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7312 / 127 / 713
Goodness-of-fit on F2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0315, wR2 = 0.0836
R indices (all data)	R1 = 0.0372, wR2 = 0.0881
Absolute structure parameter	0.07(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.082 and -0.090 e.Å^{-3}

NMR Data Collection:

All NMR data were collected on a Bruker 500 MHz Avance III HD NMR Spectrometer with a 5 mm Bruker BBO Prodigy 500 probe at 27°C or a Bruker 600 MHz Avance III NMR Spectrometer with a 5 mm Bruker TCI 600 Cryo probe at 27°C

NMR Solvents:

Deuterium Oxide, Sigma-Aldrich 99.96 % D with d_4-TSP, ^{1}H, ^{13}C referenced to TSP at 0.0 ppm.

Acetonitrile-d_3, Cambridge Isotope Labs, 99.8 % D, ^{1}H referenced to acetonitrile at 1.94 ppm, ^{13}C referenced to acetonitrile at 1.39 ppm

Sample preparation and NMR Experiments:

Compound 7,bis-benzene sulfonic acid salt (Lactam Axial Di-Equatorial, LADE): 9.01 mg of Compound 7, the bis-acid salt, was dissolved in 600 µL Deuterium Oxide. Data from the following NMR experiments were acquired: ^{1}H-1D, ^{13}C-1D, g-COSY, g-NOESY, ^{1}H-^{13}C-dept-HSQC, ^{1}H-^{13}C-dept-HMBC, and ^{1}H-^{1}H-homonuclear decoupling.

Compound 7, free base (Lactam Equatorial Di-Axial, LEDA): 6.96 mg of Compound 7, the free base, was dissolved in 600 µL Acetonitrile-d_3 and placed in a 5mm NMR tube. Data from the following NMR experiments were acquired: ^{1}H-1D, ^{13}C-1D, g-COSY, g-NOESY, ^{1}H-^{13}C-dept-HSQC, ^{1}H-^{13}C-dept-HMBC, and ^{1}H-^{1}H-homonuclear decoupling.

Chemical Shift Data:

Compound 7,bis-benzene sulfonic acid salt (Lactam Axial Di-Equatorial, LADE): Note: 1:1 rotational isomers seen at 27°C

^{1}H NMR (500 MHz, DEUTERIUM OXIDE) δ 8.77 (s, 1H), 8.70 (s, 1H), 8.27 (dd, *J*=8.9, 1.8 Hz, 1H), 7.94 (d, *J*=8.8 Hz, 1H), 7.80 - 7.75 (m, 4H), 7.60 - 7.54 (m, 2H), 7.54 - 7.49 (m, 4H), 5.44 (dd, *J*=11.0, 9.0 Hz, 1H), 4.40 (br t, *J*=4.7 Hz, 1H), 4.21 - 4.10 (m, 1H), 3.91 - 3.86 (m, 1H), 3.85 - 3.82 (m, 1H), 3.82 - 3.78 (m, 1H), 3.64 (tt, *J*=12.4, 3.7 Hz, 1H), 2.77 (d, *J*=6.1 Hz, 3H), 2.67 (dt, *J*=12.7, 7.8 Hz, 1H), 2.44 - 2.33 (m, 1H), 2.30 - 2.23 (m, 1H), 2.22 - 2.18 (m, 1H), 2.18 (br s, 1H), 2.05 - 1.96 (m, 1H), 1.93 (s, 3H), 1.92 - 1.85 (m, 1H), 1.87 - 1.79 (m, 1H), 1.39 (d, *J*=6.5 Hz, 3H), 1.31 (d, *J*=6.2 Hz, 3H)

^{13}C NMR (126 MHz, DEUTERIUM OXIDE) δ 177.5, 176.4, 164.9, 155.2, 145.2 (s, 2C), 143.5, 135.3 (q, *J*=3.6 Hz, 1C), 134.5 (s, 2C), 132.7 (q, *J*=33.6 Hz, 1C), 131.9 (s, 4C), 128.3 (s, 4C), 125.0 (q, *J*=4.5 Hz, 1C), 124.5, 126.1 (q, *J*=267.9 Hz, 1C), 115.9, 62.92, 57.93 (0.5C), 57.87 (0.5C), 56.32, 51.67, 51.52 (0.5C), 51.49 (0.5C), 48.8, 34.31 (0.5C), 34.36 (0.5C),

32.36 (0.5C), 30.95 (0.5C), 27.42, 27.39 (0.5), 27.34 (0.5C), 26.63 (0.5C), 25.04 (0.5C), 24.94, 21.02 (0.5C), 20.99 (0.5C), 17.90 (0.5C), 17.77 (0.5C)

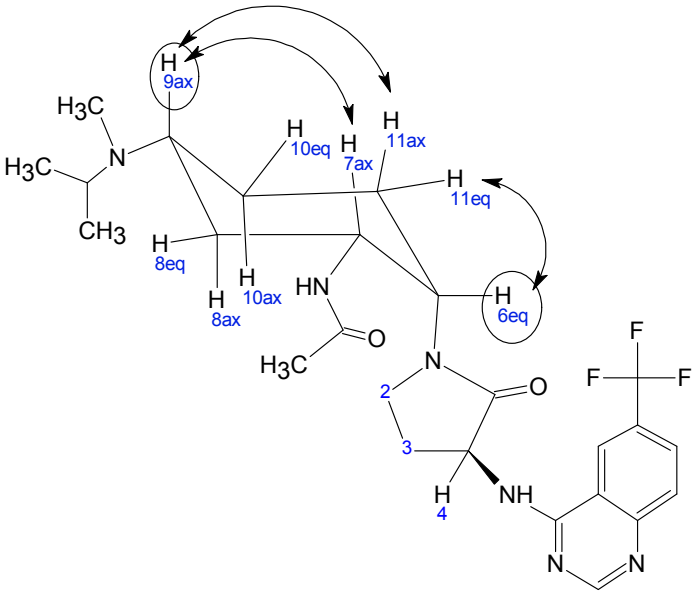
^{19}F NMR (471 MHz, DEUTERIUM OXIDE) δ -62.68 (s, 1F)

Key NOESY observations:

H-7ax to H-9 ax

H-9ax to H-11 ax

H-6eq to H-11eq



Compound **7**, free base (Lactam Equatorial Di-Axial, LEDA)**:**

^{1}H NMR (500 MHz, ACETONITRILE-d_3) δ 9.56 - 9.38 (m, 1H), 9.10 (s, 1H), 8.58 (s, 1H), 8.38 (br d, *J*=7.4 Hz, 1H), 7.96 (dd, *J*=8.7, 1.7 Hz, 1H), 7.86 (d, *J*=8.7 Hz, 1H), 4.93 (td, *J*=7.8, 1.7 Hz, 1H), 4.72 (br dtd, *J*=7.9, 4.2, 3.8 Hz, 1H), 3.96 (dt, *J*=13.0, 3.8 Hz, 1H), 3.53 (ddd, *J*=10.1, 8.8, 1.8 Hz, 1H), 3.45 - 3.40 (m, 1H), 3.40 - 3.36 (m, 1H), 2.68 (quin, *J*=2.5 Hz, 1H), 2.35 - 2.28 (m, 1H), 2.28 - 2.23 (m, 1H), 2.20 (s, 3H), 2.20 - 2.16 (m, 1H), 2.06 - 1.98 (m, 1H), 1.95 (s, 3H), 1.92 - 1.86 (m, 1H), 1.68 - 1.64 (m, 1H), 1.64 - 1.61 (m, 1H), 1.61 - 1.57 (m, 1H), 1.05 (br d, *J*=5.4 Hz, 3H), 0.99 (br d, *J*=5.7 Hz, 3H)

^{13}C NMR (126 MHz, ACETONITRILE-d_3) δ 172.7, 172.5, 161.0, 158.1, 152.7, 130.1, 129.2 (q, *J*=2.7 Hz, 1C), 127.7 (q, *J*=32.7 Hz, 1C), 122.8 (q, *J*=3.9 Hz, 1C), 125.5 (q, *J*=271.6 Hz, 1C), 116.2, 56.0 (s, 2C), 54.3, 48.2, 47.9, 44.6, 31.5 (br s, 1C), 30.8 (s, 2C), 28.4, 28.2, 24.1 (s, 2C), 20.9

^{19}F NMR (471 MHz, ACETONITRILE-d_3) δ -62.36 (s, 1F)

Key NOESY observations:

H-6ax to H-8 ax

H-6ax to H-10 ax

H-9eq to H-8 eq

H-9eq to H-10 eq

H-11_{ax} to H-2'/H-2''

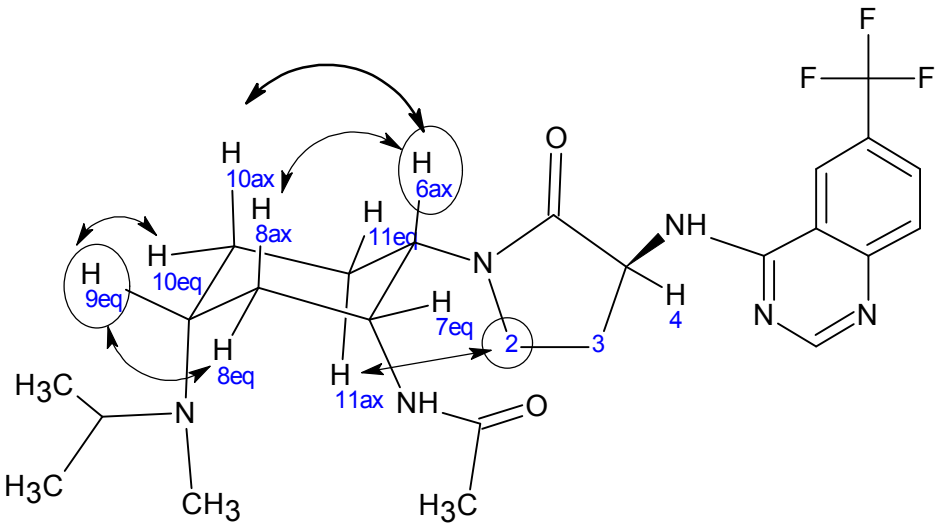


Table of Key Chemical Shifts and Coupling Constants (*J*) of BMS-741672-02/Bis-benzene sulfonic acid (LADE) in d_3-ACN and BMS-741672-03 (free base) in D_2O/TSP-d4 (LEDA), 500 MHz, 27°C

Atom No	**^{1}H BMS-741672-02 in d_3-ACN**	Atom No	**^{1}H BMS-741672-03 in D_2O with TSP-d_4**
1	-	1	-
2'/2''	3.53 (ddd, *J*=10.1, 8.8, 1.8 Hz, 1H), 3.45 - 3.40 (m, 1H)	2'/2''	3.91 - 3.86 (m, 1H) 3.82 - 3.78 (m, 1H)
3'/3''	2.35 - 2.28 (m, 1H), 1.92 - 1.86 (m, 1H)	3'/3''	2.67 (dt, *J*=12.7, 7.8 Hz, 1H), 2.44 - 2.33 (m, 1H)
4	4.93 (td, *J*=7.8, 1.7 Hz, 1H)	4	5.44 (dd, *J*=11.0, 9.1 Hz, 1H)
5	-	5	-
6ax	3.96 (dt, *J*=13.0, 3.8 Hz, 1H)	6eq	4.40 (br t, *J*=4.3 Hz, 1H)
7eq	4.72 (br dtd, *J*=7.9, 4.2, 3.8 Hz, 1H)	7ax	4.21 - 4.10 (m, 1H)
8ax	1.61 - 1.57 (m, 1H)	8ax	1.87 - 1.79 (m, 1H),
8eq	2.20 - 2.16 (m, 1H)	8eq	2.30 - 2.23 (m, 1H)
9eq	2.68 (quin, *J*=2.5 Hz, 1H)	9ax	3.64 (tt, *J*=12.4, 3.7 Hz, 1H),
10ax	1.64 - 1.61 (m, 1H)	10ax	1.92 - 1.85 (m, 1H),
10eq	2.28 - 2.23 (m, 1H)	10eq	2.22 - 2.18 (m, 1H)
11ax	2.06 - 1.98 (m, 1H)	11ax	2.05 - 1.96 (m, 1H)
11eq	1.68 - 1.64 (m, 1H)	11eq	2.18 (br s, 1H)
45	3.40 - 3.36 (m, 1H)	45	3.85 - 3.82 (m, 1H)

Experimental

General Experimental Conditions.

As appropriate, reactions were conducted under an atmosphere of dry nitrogen. For anhydrous reactions, Dri-Solv solvents from EM were employed. For other reactions, reagent grade or HPLC grade solvents were utilized. Unless otherwise stated, all commercially obtained reagents were purchased at the highest grade available and used as received.

LC/MS measurements were obtained using a Shimadzu HPLC/Waters ZQ single quadropole mass spectrometer hybrid system. Data for the peak of interest are reported from positive-mode electrospray ionization. The purity of tested compounds determined by analytical HPLC was >95%. Analytical HPLC conditions: column, YMC Combiscreen ODS-A 4.6 X 50mm 4 min; gradient elution 0–100% B over 4 min with 1 min hold (solvent A, Water 90%/MeOH 10%/H3PO4 0.2%; solvent B, MeOH 90%/Water 10%/H_3PO_4 0.2%; flow rate, 4 mL/min; 220 nm as the detection wavelength).

NMR spectra were obtained on a Bruker 400 MHz or 500 MHz instrument in the indicated solvent. All chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, sep = septet, m = multiplet), coupling constants (Hz), and integration.

The numbering below corresponds to Scheme 1 in the main text.

tert-Butyl (1R,2S,5R)-2-((S)-3-(((benzyloxy)carbonyl)amino)-2-oxopyrrolidin-1-yl)-7-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate (S.2). Step 1: The cyclic imide **S.1** (89.6 g, 0.24 mol) was dissolved in ethyl acetate (1.5 L) and the resulting solution was washed with sat. $NaHCO_3$ (2 x 0.45 L) and sat. NaCl (1 x 0.45 L). The solution was dried (Na_2SO_4) and then filtered directly into a 3-necked 3 L round-bottom flask. The solution was purged with direct nitrogen injection before being charged with 10% Pd/C (13.65 g, Caution: fire hazard) under nitrogen atmosphere. The flask was evacuated and back-filled with hydrogen; this was repeated twice more. Hydrogen was bubbled through the solution for 30 min and then the reaction was stirred under 1 atm H_2 for 18 h. The flask was evacuated, back-filled with nitrogen, and charged with fresh catalyst (6 g of 10% Pd/C). Hydrogen was bubbled through the solution for 30 min and then the reaction was stirred under 1 atm H_2 for 18 h. The flask was evacuated and back-filled with nitrogen. The mixture was filtered through Celite (Caution: fire hazard) with ethyl acetate washes. For the amine intermediate, tert-butyl (1R,2S,5R)-2-amino-7-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate, LC/MS for primary peak: ESI-MS *m/z* 263.3 ([M + Na^+]). ^{1}H-NMR (400 MHz, d_4-MeOH): δ 4.3 (m, 1H), 3.0 (m, 1H), 2.53 (m, 1H), 2.28 (m, 1H), 2.1 (m, 2H), 1.65 (m, 2H), 1.54 (s, 9H), 1.22 (m, 1H).

Step 2: The filtrate obtained from the previous step (~ 1.6 L EtOAc volume) was diluted with acetonitrile (0.3 L) and charged sequentially with Cbz-methionine (68 g, 0.24 mol), TBTU (77 g, 0.24 mol), and DIEA (42 mL, 0.24 mol). The reaction was stirred at room temperature for 4 h, during which time it changed from a suspension to a clear solution. The reaction was quenched with the addition of sat. NH_4Cl (0.75 L) and water (0.15 L); the mixture was diluted further with EtOAc (0.75 L). The phases were mixed and separated and the organic phase was washed with sat. Na_2CO_3 (2 x 0.9 L) and sat. NaCl (1 x 0.75 L). The solution was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give tert-Butyl (1R,2S,5R)-2-((S)-2-(((benzyloxy)carbonyl)amino)-4-(methylthio)butanamido)-7-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate as an oil, which was taken into the next step without further purification. LC/MS for primary peak: ESI-MS m/z 406.3 ([M – Boc + H^+]). ^{1}H-NMR (400 MHz, d_4-MeOH): δ 7.36 (m, 5H), 5.11 (s, 2H), 4.32 (m, 1H), 4.2 (m, 1H), 4.0 (m, 1H), 2.5 – 2.7 (m, 3H), 2.25 (m, 1H), 2.11 (s, 3H), 2.05 (m, 4H), 1.9 (m, 1H), 1.7 (m, 2H), 1.54 (s, 9H). Also present are EtOAc [1.26 (t), 2.03 (s), 4.12 (q)] and N,N,N,N-tetramethylurea [2.83 (s)].

Step 3: A sample of tert-Butyl (1R,2S,5R)-2-((S)-2-(((benzyloxy)carbonyl)amino)-4-(methylthio)butanamido)-7-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate (0.24 mol assumed; see previous procedure) was dissolved in iodomethane (1,250 g) and stirred for 48 h at room temperature. The reaction was concentrated *in vacuo*. The residue was dissolved in dichloromethane and concentrated *in vacuo*. This was repeated twice more. The resultant sludge was dissolved in dichloromethane (0.4 L) and poured into a rapidly stirring solution of MTBE (4.0 L). The resultant yellow solids were collected via suction filtration and dried under high vacuum to afford the sulfonium salt (179 g). This material, tert-butyl (1R,2S,5R)-2-((S)-2-(((benzyloxy)carbonyl)amino)-4-(iododimethyl-l4-sulfanyl)butanamido)-7-oxo-6 azabicyclo[3.2.1]octane-6-carboxylate, was taken into the next step without further purification. LC/MS for primary peak: ESI-MS m/z 520.4 ([M^+]). ^{1}H-NMR (400 MHz, d_4-MeOH): δ 7.35 (m, 5H), 5.09 (s, 2H), 4.33 (m, 1H), 4.28 (m, 1H), 3.98 (m, 1H), 3.3 – 3.45 (m, 2H), 2.97 (s, 3H), 2.94 (s, 3H), 2.78 (m, 1H), 2.0 – 2.3 (m, 4H), 1.7 (m, 2H), 1.52 (s, 9H). Also present are MTBE [1.18 (s), 3.2 (s)] and traces of N,N,N,N-tetramethylurea [2.81 (s)].

Step 4: All of the sulfonium salt from the previous step (0.24 mol assumed) was dissolved in DMSO (2.0 L). The resultant solution was stirred under nitrogen at room temperature and charged with cesium carbonate (216 g) portion wise (Caution: dimethylsulfide evolution). The suspension was stirred at room temperature for 3 h and then filtered to remove the solids. The solution was divided into ~ 0.22 L portions and worked up as follows: the reaction mixture (~ 0.22 L) was diluted with ethyl acetate (1.5 L) and washed successively with water (3 x 0.5 L) and brine (1 x 0.3 L). The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. **S.2** (90.8 g, 84%) was obtained as a microcrystalline foam, free from tetramethyl urea impurity. ^{1}H-NMR (400 MHz, d_4-MeOH) δ 7.35 (m, 5H), 5. 12 (s, 2H), 4. 35 (m, 2H), 4. 2(m, 1H), 3. 6 (m, 1H), 33 (m, 1H), 2. 64 (m, 1H), 2. 28-2. 42 (m, 2H), 2. 15 (m, 1H), 1. 7-2. 0 (m, 5H), 1. 55 (s, 9H). ^{13}C-NMR (126 MHz, *d*-$CDCl_3$) δ 174.6, 149.3, 136.3, 128.5, 128.1, 128.1, 83.1, 67.0 (br s, 1C), 55.0, 53.03 - 52.86 (m, 1C), 50.4, 47.4, 41.0 (br d, J = 4.5 Hz, 1C), 35.2, 28.4, 28.3 (br s, 1C), 28.1, 27.0, 26.6, 22.6. ESI-MS m/z 358.4 ([M – Boc + H^+]). HR-ESI(+)-MS: calcd for $C_{24}H_{31}N_3O_6$ 458.229 [M + H]$^+$, found 458.2292. HPLC: t_R = 2.84 min.

(1R,2S,5R)-2-((S)-3-(((Benzyloxy)carbonyl)amino)-2-oxopyrrolidin-1-yl)-5-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid (S.3) A stirring solution of **S.2** (108 g, 0.236 mol) in THF (1 L) was charged with lithium hydroxide monohydrate (21.74 g, 0.519 mol). Water (0.3 L) was added slowly, such that the temperature did not exceed 20 °C. The reaction was stirred at room temperature overnight and the volatiles were removed *in vacuo*. The pH was adjusted to ~4 through the addition of 1N HCl (450 mL) and NaH_2PO_4. The resultant white precipitates were collected by filtration and washed with water (2 x 1 L). The solid was dissolved in dichloromethane (1.5 L) and water (~ 1 L). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (0.7 L) and the resultant solution was heated at reflux for 1 h. Solids separated after cooling to room temp, and were collected via filtration. These solids were purified by recrystallization in isopropanol to afford the desired carboxylic acid **S.3** as a white solid (104.5 g, 93% yield). ^{1}H-NMR (400 MHz, d_4-MeOH) δ 7.35 (m, 5H), 5. 11 (s, 2H), 435 (m, 2H), 3. 71(m, 1H), 3. 45-3. 6 (m, 2H), 2. 99 (m, 1H), 2. 41 (m, 1H), 2. 15 (m, 1H), 2. 0 (m, 2H), 1. 6-1. 9 (m, 4H), 1. 46 (s, 9H). . ^{13}C-NMR (126 MHz, d_4-MeOH) δ 176.1, 173.6, 157.3, 156.2, 136.8, 128.1, 127.5, 127.26 - 127.26 (m, 1C), 78.5 (br d, J =10.9 Hz, 1C), 66.41 - 66.10 (m, 1C), 52.4, 49.7 (br s, 1C), 46.2 (br s, 1C), 43.4 (br s, 1C), 42.79 - 42.44 (m, 1C), 30.7 (br s, 1C), 28.9 (br s, 1C), 27.4, 26.9, 24.89 - 24.48 (m, 1C). LC/MS: ESI-MS m/z 476.23 ([M^+]). HR-ESI(+)-MS: calcd for $C_{24}H_{33}N_3O_7$ 476.2397 [M + H]$^+$, found 476.2395. HPLC: t_R = 2.87 min.

tert-Butyl ((1R,3R,4S)-3-acetamido-4-((S)-3-(((benzyloxy)carbonyl)amino)-2-oxopyrrolidin-1-yl)cyclohexyl)carbamate (S.4). Step 1: A 3 L round bottom flask was charged with **S.3** (75.5 g, 0.158 mol), EDC•HCl (33.5 g, 0.175 mol), hydroxybenzotriazole (23.6 g, 0.175 mol), and dichloromethane (1 L). The reaction was stirred at room temperature for 2 h, during which time it changed from a white suspension to a clear solution. Ammonia (gas) was bubbled into the solution until the pH was strongly basic (paper) and the reaction was stirred for 10 min;

this ammonia addition was repeated and the reaction was stirred for an additional 10 min. Water was added. The organic phase was washed with sat. $NaHCO_3$, NaH_2PO_4, and brine before being concentrated *in vacuo*. The residue was slurried with acetonitrile (0.5 L) and then concentrated in to give the carboxamide as a white solid (75.9 g, ~100%), which was used in the next step without further purification. ^{1}H-NMR (400 MHz, d_4-MeOH): δ 7.35 (m, 5H), 5.11 (s, 2H), 4.25 (m, 2H), 3.70 (m, 1H), 3.6 (m, 1H), 3.45 (m, 1H), 2.91 (m, 1H), 2.38 (m, 1H), 2.12 (m, 1H), 1.9 - 2.05 (m, 2H), 1.65 - 1.9 (m, 4H), 1.46 (s, 9H) ^{13}C-NMR (126 MHz, *d*-$CDCl_3$) δ 177.1, 172.1 (br s, 1C), 156.0 (br s, 1C), 155.55 - 155.44 (m, 1C), 136.0, 128.6, 128.3, 128.1, 78.5, 67.1, 53.1, 52.2 (br s, 1C), 42.7 (br s, 1C), 42.0 (br s, 1C), 41.6, 30.8 (br s, 1C), 30.3, 28.6, 26.4 (br s, 1C), 20.6. LC/MS: ESI-MS m/z 475.25 ([M^+]). HR-ESI(+)-MS: calcd for $C_{24}H_{34}N_4O_6$ 475.2556 [M + H]$^+$, found 475.2551. HPLC: t_R = 2.86 min.

Step 2: The reaction was run in three equal portions and combined for aqueous workup. A 5 L, 3-necked round bottom flask was charged with the carboxamide (25.3 g, 53 mmol, see previous step), acetonitrile (1.9 L), and 2.6 L of water/ice. The mixture was stirred and cooled to 0 °C. Iodobenzene diacetate (25.77 g, 80 mmol) was added and the reaction was stirred for 2 h; another 0.5 eq of iodobenzene diacetate was added. The reaction was stirred for 9 h (reaction temp < 10 °C). The mixture was charged with 8 eq DIPEA and 2 eq acetic anhydride. Over the next thirty minutes, 4 eq DIPEA and 2 eq acetic anhydride were added every ten minutes, until the reaction had proceeded to completion (HPLC). The acetonitrile was removed *in vacuo*; some solid separated from the residue, and this was collected by filtration. The remaining residue was extracted with dichloromethane (3 L, then 1 L). The organic phase was washed sequentially with water, sat. $NaHCO_3$, and brine. The collected solids were added to the organic phase, along with activated carbon (15 g). The mixture was stirred for 30 minutes at 40 °C before being filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc (1 L), and the resultant solution was stirred at 75 °C for 1 h before being allowed to cool to room temperature. A solid separated and was collected by filtration. This solid was purified further by recrystallization: it was first dissolved in 0.5 L CH_2Cl_2, then concentrated in vacuo, then re-crystallized from 1 L EtOAc; this was repeated three times. The solids obtained from the mother liquors of the above were recrystallized three times using the same method. The combined solids were recrystallized twice more from acetonitrile (0.7 L) to provide 66 g of **S.4**. The absolute stereoconfiguration of **S.4** was subsequently confirmed by an X-ray crystal structure, which is available in the Supporting Information. ^{1}H-NMR (500 MHz, d_4-MeOH): δ 7.3 – 7.4 (m, 5H), 5.11 (s, 2H), 4.35 (m, 1H), 4.15 (m, 1H), 4.04 (m, 1H), 3.8 (m, 1H), 3.6 (m, 2H), 2.44 (m, 1H), 2.12 (m, 1H), 1.87 – 2.05 (m, 4H), 1.87 (s, 3H), 1.55 – 1.7 (m, 2H), 1.46 (s, 9H). ^{13}C-NMR (126 MHz, d_4-MeOH) δ 174.4, 171.5, 156.8, 156.1, 136.8, 128.2, 127.7, 127.3, 78.76, 66.2, 60.15, 52.1, 49.0, 48.6, 45.2, 34.3, 28.1, 27.5, 25.3, 24.5, 21.6. LC/MS found: ESI-MS: m/z 489.27 ([M + H^+]). HR-ESI(+)-MS: calcd for $C_{25}H_{36}N_4O_6$ 489.2713 [M + H]$^+$, found 489.2702. HPLC: t_R = 2.90 min.

N-((1R,2S,5R)-5-(Isopropyl(methyl)amino)-2-((S)-2-oxo-3-((6-(trifluoromethyl)quinazolin-4-yl)amino)pyrrolidin-1-yl)cyclohexyl)acetamide (7, BMS-741672). Step 1: A stirring solution of **S.4** (66 g, 0.135 mol) in dichloromethane (216 mL) was charged with trifluoroacetic acid (216 mL). The reaction was stirred for 2 h at room temperature and concentrated *in vacuo*. The residue was dissolved in methanol and the resultant solution was concentrated *in vacuo*; this was repeated once. The corresponding amine, benzyl ((S)-1-((1S,2R,4R)-2-acetamido-4-aminocyclohexyl)-2-oxopyrrolidin-3-yl)carbamate, was obtained as an oil. LC/MS for primary peak: ESI-MS m/z 389.4 ([M + H^+]). ^{1}H-NMR (400 MHz, d_4-MeOH): δ 7.3 – 7.4 (m, 5H), 5.12 (s, 2H), 4.41 (br. s, 1H), 4.15 (m, 1H), 4.00 (t, J = 9.3 Hz, 1H), 3.81 (t, J = 9.1 Hz, 1H), 3.65 (q, J = 8.4 Hz, 1H), 3.3 – 3.4 (m, 1H), 2.45 (m, 1H), 1.95 – 2.24 (m, 5H), 2.00 (s, 3H), 1.6 – 1.8 (m, 2H).

Step 2: A stirring solution of the primary amine (~0.135 mol, see previous step) in methanol (675 mL) was charged sequentially with acetone (37.8 g, 4 eq), sodium acetate (33.2 g, 3 eq), and sodium cyanoborohydride (16.9 g, 2 eq; Caution: hazardous reagent). The mixture was stirred at room temperature for 6 h and filtered. The filtrate was dissolved in dichloromethane (1 L); this solution was washed with 1N NaOH (1 L). The solids collected in the filtration were dissolved in 1N NaOH (1L) at 0 °C and then extracted with dichloromethane (1 L). The organic

extracts were combined and extracted with aqueous HCl (200 mL 1N HCl + 800 mL water). The aqueous phase was basified with sat. $NaHCO_3$ (500 mL) and then 1N NaOH (100 mL) until pH 11. The aqueous phase was extracted with dichloromethane (2 L). The organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the isopropylamine. ^{1}H-NMR (500 MHz, d_4-MeOH): δ 7.3 – 7.4 (m, 5H), 5.12 (s, 2H), 4.31 (m, 1H), 4.24 (t, J = 9.4 Hz, 1H), 4.11 (m, 1H), 3.61 (t, J = 9.1 Hz, 1H), 3.52 (q, J = 8.6 Hz, 1H), 3.04 (br. s, 1H), 2.96 (sep, J = 6.3 Hz, 1H), 2.40 (m, 1H), 2.15 (m, 1H), 1.92 (s, 3H), 1.7 – 1.9 (m, 5H), 1.65 (m, 1H), 1.12 (dd, J = 6.3, 1.1 Hz, 6H). 13C NMR (126 MHz, d_4-MeOH) δ 173.8, 171.0, 157.1, 136.9, 128.1, 127.6, 127.4, 66.3, 52.5, 49.4, 48.4, 44.8, 43.6, 32.5, 29.1, 26.3, 22.0, 22.0, 21.54, 21.2. LC/MS found: ESI-MS: m/z 431.26 ([M + H$^+$]). HR-ESI(+)-MS: calcd for $C_{23}H_{34}N_4O_4$ 431.2658 [M + H]$^+$, found 431.2649. HPLC: t_R = 1.44 min.

Step 3: A stirring solution of the isopropylamine (~115 mmol, see Step 2) in dichloromethane (600 mL) was cooled to 0 °C and charged sequentially with formaldehyde (18.6 g, 37 wt% solution), triethylamine (23 mL), and sodium triacetoxyborohydride (28.7 g). The mixture was stirred at room temperature for 30 min and diluted with dichloromethane (up to 1.2 L). This solution was washed thrice with 500 mL sat. $NaHCO_3$ + NaOH (sat. $NaHCO_3$, pH to 11 w/ 1N NaOH). The organic layer was extracted with aq. HCl (200 mL 1N HCl + 600 mL water). The aqueous phase was basified with sat. $NaHCO_3$ (500 mL) and then 1N NaOH (100 mL) until pH 11. The aqueous phase was extracted with dichloromethane (1.2 L). The organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the tertiary amine as an oil. (Note: the characterization of the L-tartrate salt of this amine has been reported separately).

Step 4: To a solution of the benzylcarbamate (~0.115 mol, see Step 3) in methanol (600 mL) was added 10% Pd/C (6 g of 50% wet catalyst). The flask was evacuated and back-filled with hydrogen. The mixture was stirred under 1 atm H_2 for 2 h and the catalyst was removed by filtration through Celite (Caution: fire hazard). The filtrate was concentrated in vacuo to provide N-((1R,2S,5R)-2-((S)-3-Amino-2-oxopyrrolidin-1-yl)-5-(isopropyl(methyl)amino)cyclohexyl)acetamide as an oil, which was taken on to the next step without further purification. HR-ESI(+)-MS: calcd for $C_{16}H_{31}N_4O_2$ 311.2442 [M + H]$^+$, found 311.2445. HPLC: t_R = 0.16 min. (Note: the characterization of the bis-HCl salt of this amine has been reported separately).

Step 5: To a solution of the primary amine (~35 g, 0.115 mol, see Step 4) in isopropanol (600 mL) was added 4-chloro-6-(trifluoromethyl)quinazoline (32 g, 0.138 mol, 1.2 eq). The mixture was stirred at room temperature overnight before being charged with triethylamine (46 g, 0.46 mol, 4 eq). The mixture was stirred at 60 °C for 10 h. The solvent was removed under reduced pressure to give an oil. Azeotropic distillation with isopropanol was performed twice. The residue was dissolved in dichloromethane (600 mL) and extracted with water (250 mL, containing 4 eq acetic acid). Dichloromethane (600 mL) was added to the combined aqueous washes, and the mixture was cooled to 0 °C. Aqueous NaOH (50% by weight) was added with stirring until the pH reached 11. The water layer was extracted with dichloromethane twice (2 x 600 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give **7** (99% purity by HPLC). This was dissolved in methanol (600 mL). The resultant solution was heated at 60 °C and charged with benzenesulfonic acid (2.5 eq). The mixture was cooled to room temperature and the resultant white solid was collected by filtration to yield the bis-benzene sulfonic acid salt of BMS-741672 (**7,** 95 g, 86% yield from **S.4**). ^{1}H NMR (500 MHz, D_2O) δ 8.75 (s, 1H), 8.66 (s, 1H), 8.25 (d, *J* = 8.80 Hz, 1H), 7.90 (d, *J* =8.80 Hz, 1H), 7.75 (d, *J* = 8.25 Hz, 4H), 7.43 - 7.57 (m, 6H), 5.42 (t, 1H), 4.33 - 4.44 (m, 1H), 4.09 - 4.19 (m, 1H), 3.83 - 3.91 (m, 1H), 3.74 - 3.83 (m, 2H), 3.61 (t, *J* = 11.55 Hz, 1H), 2.75 (d, *J* = 6.60 Hz, 3H), 2.61 - 2.70 (m, 1H), 2.31 - 2.44 (m, 1H), 2.20 - 2.27 (m, 1H), 2.17 (d, *J* = 12.10 Hz, 2H), 1.94 - 2.04 (m, 1H), 1.90 - 1.95 (m, 3H), 1.72 - 1.91 (m, 2H), 1.37 (d, *J* = 6.05 Hz, 3H), 1.29 (d, *J* = 6.60 Hz, 3H). ^{13}C NMR (126 MHz, D_2O) δ 177.68, 176.34, 164.56, 155.79, 145.25 (2C), 144.94, 134.77, 134.44 (2C), 132.32 (q, *J* = 31.8 Hz), 131.88 (4C), 128.25 (s, 4C), 125.45, 124.76 (q, *J* = 4.8 Hz), 126.13 (q, *J* = 272.5 Hz), 116.03, 62.90, 57.92 (0.5C), 57.85 (0.5C), 56.21, 51.67, 51.47, 48.8, 34.29 (0.5C), 34.25 (0.5C), 32.37 (0.5C), 30.98 (0.5C), 27.42, 27.38, 26.62 (0.5C), 25.03 (0.5C), 24.93, 20.98, 17.88 (0.5C), 17.74 (0.5C). ESI-MS *m/z* 507.27 ([M + H]$^+$). HPLC: t_R = 0.78 min. Anal. Calcd for $C_{25}H_{33}N_6O_2F_3 \cdot 2C_6H_6SO_3$: C, 54.00; H, 5.51; N, 10.21; S, 7.79; F, 6.92. Found: C, 53.97; H, 5.31; N, 10.00; S, 7.79; F, 7.47. The %F was 0.55 % (absolute) higher than theoretical adjusted for found solvents based on empirical formula:

$C_{25}H_{33}N_6O_2F_3$. $2C_6H_6SO_3$. $0.02C_2H_6O$ [Note: Pd=<1ppm. Pb, Cr, Ni, Cd, and Cu are all <1ppm]. The ^{1}H-NMR and X-ray crystal structures of both the free base and bis-BSA salt of **7** are described in a separate section in the Supporting Information.

Characterization of other compounds from Table 1

(S)-1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-propylcyclohexyl)-3-((6-(trifluoromethyl)quinazolin-4-yl)amino)pyrrolidin-2-one (**1**, Table 1). Compound **1** was fully characterized and its report can be found in *ACS Med. Chem. Lett*. **2015**, *6*, 439-444. The X-ray crystal structure of **1** is available in the Supporting Information.

N-((S)-1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-((methylsulfonyl)methyl)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-(trifluoromethyl)benzamide (**2**, Table 1). ^{1}H NMR (499 MHz, METHANOL-d_4) δ 8.18 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 4.49 (dd, *J* = 10.3, 9.2 Hz, 1H), 4.37 - 4.32 (m, 1H), 3.87 - 3.80 (m, 1H), 3.72 (td, *J* = 9.4, 7.2 Hz, 1H), 3.42 (dd, *J* = 14.5, 3.3 Hz, 1H), 3.30 - 3.13 (m, 2H), 3.04 - 3.00 (m, 3H), 2.81 (br t, *J* = 11.3 Hz, 1H), 2.64 - 2.44 (m, 2H), 2.35 - 2.22 (m, 5H), 2.07 - 1.88 (m, 3H), 1.75 - 1.59 (m, 2H), 1.11 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, METHANOL-d_4) δ 176.0, 168.4, 136.6, 132.3, 132.0, 130.8, 129.4 (q, *J* = 3.6 Hz, 1C), 126.6, 125.4 (q, *J* = 4.2 Hz, 1C), 124.4, 59.8, 57.8, 53.3, 51.5, 51.1, 49.8, 47.1, 42.1, 36.6, 32.8, 32.4, 28.7, 26.6, 26.4, 19.3, 19.2. HR-ESI(+)-MS: calcd for $C_{24}H_{34}F_3N_3O_4S$ 518.2295 $[M + H]^+$, found 518.2293. HPLC: t_R = 1.8 min.

N-((S)-1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-(methylsulfonamido)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-(trifluoromethyl)benzamide (**3**, Table 1). ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.87 (br d, *J* = 8.08 Hz, 1H), 8.20 (s, 1H), 8.17 (d, *J* = 8.09 Hz, 1H), 7.94 (d, *J* = 7.78 Hz, 1H), 7.76 (t, *J* = 7.78 Hz, 1H), 4.62-4.67 (m, 1H), 3.90-3.97 (m, 1H), 3.75 (t, *J* = 8.45 Hz, 1H), 3.58-3.66 (m, 1H), 3.41-3.48 (m, 2H), 3.21-3.29 (m, 1H), 2.99 (s, 3H), 2.68 (br s, 1H), 2.28-2.33 (m, 1H), 2.17 (br d, *J* = 13.91 Hz, 1H), 2.13 (s, 3H), 2.04 (br d, *J* = 14.81 Hz, 1H), 1.94-1.98 (m, 1H), 1.83-1.89 (m, 1H), 1.59-1.64 (m, 1H), 1.57-1.64 (m, 1H), 1.56-1.62 (m, 1H), 1.21-1.31 (m, 1H), 0.97 (br d, *J* = 6.13 Hz, 6H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 173.7, 166.8, 136.8, 133.4, 131.7, 131.1 (q, *J* = 32.6 Hz, 1C), 129.97 - 129.91 (m, 1C), 125.83 - 125.74 (m, 1C), 128.27 - 123.53 (m, 1C), 56.7 (br s, 1C), 55.5, 54.5, 53.1, 48.9, 44.2, 42.2, 32.9 (br s, 1C), 32.5, 28.6, 27.9, 22.6 (br s, 1C), 19.55 - 18.30 (m, 1C). HR-ESI(+)-MS: calcd for $C_{23}H_{33}F_3N_4O_4S$ 519.2253 $[M + H]^+$, found 519.2239. HPLC: t_R = 1.83 min.

N-((S)-1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-(N-methylmethylsulfonamido)cyclohexyl)-2-oxopyrrolidin-3-yl)-3-(trifluoromethyl)benzamide (**4**, Table 1). ^{1}H NMR (700 MHz, METHANOL-d_4) δ 8.19 (s, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.85 (br d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.9 Hz, 1H), 4.59 (dd, *J* = 11.4, 8.6 Hz, 1H), 4.50 (br s, 1H), 4.07 (dt, *J* = 13.5, 4.5 Hz, 1H), 3.89 - 3.83 (m, 1H), 3.72 (td, *J* = 9.9, 6.6 Hz, 1H), 3.15 (br s, 1H), 2.98 (s, 4H), 2.97 (s, 2H), 2.96 - 2.88 (m, 1H), 2.50 - 2.44 (m, 1H), 2.32 (s, 2H), 2.23 - 2.15 (m, 1H), 2.15 - 2.06 (m, 1H), 1.98 - 1.92 (m, 1H), 1.93 - 1.87 (m, 1H), 2.03 - 1.85 (m, 3H), 1.72 - 1.64 (m, 1H), 1.12 (br dd, *J* = 6.1, 4.2 Hz, 6H). ^{13}C NMR (176 MHz, METHANOL-d_4) δ 175.7, 168.6, 136.6, 132.3, 131.9 (q, *J* = 33.1 Hz, 1C), 130.6, 129.3 (q, *J* = 3.4 Hz, 1C), 125.4 (q, *J* = 3.8 Hz, 1C), 125.4 (q, *J* = 271.7 Hz, 1C), 60.3, 58.6, 53.2, 51.9, 51.6, 47.1, 39.3, 32.4, 32.1, 31.4, 28.0, 26.9, 26.2, 19.5, 19.3. HR-ESI(+)-MS: calcd for $C_{24}H_{35}F_3N_4O_4S$ 533.2409 $[M + H]^+$, found 533.2397. HPLC: t_R = 1.93 min.

(S)-1-((1S,2R,4R)-4-(Isopropyl(methyl)amino)-2-((methylsulfonyl)methyl)cyclohexyl)-3-((6-(trifluoromethyl)quinazolin-4-yl)amino)pyrrolidin-2-one (**5**, Table 1). ^{1}H NMR (499 MHz, METHANOL-d_4) δ 8.83 (s, 1H), 8.81 (s, 1H), 8.26 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 5.14 (dd, *J* = 10.7, 9.2 Hz, 1H), 4.36 (br s, 1H), 3.92 - 3.75 (m, 3H), 3.68 - 3.56 (m, 1H), 3.46 (dd, *J* = 14.7, 3.6 Hz, 1H), 3.24 (dd, *J* = 14.6, 8.5 Hz, 1H), 3.06 (s, 3H), 2.80 (s, 3H), 2.74 - 2.64 (m, 1H), 2.62 - 2.44 (m, 3H), 2.26 - 2.12 (m, 2H), 2.10 - 1.88 (m, 3H), 1.43 (br d, *J* = 6.4 Hz, 3H), 1.36 (br d, *J* = 4.3 Hz, 3H). ^{13}C NMR (126 MHz, METHANOL-d_4) δ 174.7, 163.0, 163.0, 162.7, 154.5, 144.0, 132.9, 132.9, 131.3, 131.1, 126.0, 124.0, 123.8, 123.4, 123.4, 115.1, 62.5, 62.4, 57.6, 56.2, 55.1, 50.7, 50.6, 49.8, 47.1, 41.5,

36.2, 32.4, 32.3, 31.6, 30.2, 28.2, 28.1, 25.7, 25.4, 23.8, 19.2, 16.2, 16.0. HR-ESI(+)-MS: calcd for $C_{25}H_{34}F_3N_5O_3S$ 542.2407 $[M + H]^+$, found 542.2403. HPLC: t_R = 0.84 min.

N-((1R,2S,5R)-5-(isopropyl(methyl)amino)-2-((S)-2-oxo-3-((6-(trifluoromethyl)quinazolin-4-yl)amino)pyrrolidin-1-yl)cyclohexyl)methanesulfonamide (**6**, Table 1). ^{1}H NMR (700 MHz, METHANOL-d_4) δ 8.63 (s, 1H), 8.59 (s, 1H), 8.03 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 5.27 (br t, *J* = 8.2 Hz, 1H), 4.03 - 3.95 (m, 1H), 3.99 - 3.93 (m, 1H), 3.93 (br d, *J* = 2.8 Hz, 1H), 3.66 - 3.60 (m, 1H), 3.41 (dt, *J* = 13.0, 6.5 Hz, 1H), 3.07 (s, 3H), 2.82 - 2.78 (m, 1H), 2.58 - 2.50 (m, 1H), 2.42 - 2.35 (m, 1H), 2.27 - 2.23 (m, 3H), 2.24 (s, 3H), 2.19 - 2.11 (m, 1H), 2.11 - 2.01 (m, 1H), 1.80 - 1.73 (m, 1H), 1.73 - 1.64 (m, 1H), 1.06 (br s, 6H). ^{13}C NMR (176 MHz, METHANOL-d_4) δ 174.7, 161.8, 158.0, 152.0, 130.1 (q, *J* = 2.5 Hz, 1C), 129.4, 129.2 (q, *J* = 33.1 Hz, 1C), 125.4 (q, *J* = 270.8 Hz, 1C), 122.2 (q, *J* = 3.8 Hz, 1C), 115.9, 56.4 (br s, 1C), 55.4 (br s, 1C), 54.3, 48.8, 44.6, 40.6, 31.4, 31.2 (br s, 1C), 28.3, 27.5, 21.4 (br s, 1C). HR-ESI(+)-MS: calcd for $C_{24}H_{33}F_3N_6O_3S$ 543.2365 $[M + H]^+$, found 543.2359. HPLC: t_R = 0.87 min. The X-ray crystal structure of **6** is available in the Supporting Information.

X-ray Crystal Structures of Intermediate S.4, Compound 1, and Compound 6

X-ray Crystallography Sample Preparation, Data Collection, Structure Solution and Refinement:

Intermediate S.4: Single crystal X-ray diffraction data was obtained using a colorless rod shaped crystal (approximate dimensions: 0.780 x 0.060 x 0.040 mm^3). Data collection was carried out at room temperature (~296K) using CuKα radiation. Indexing and processing of the measured intensity data were carried out via HKL-SCALEPACK & DENZO-SCALEPACK[6]. The crystal structure was solved by direct methods (SIR 97)[7] and refined by full-matrix least-squares procedures on F^2 using all reflections (SHELXL-2016/6)[8]. Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors and refined using a riding model.

Compound 1: Single crystal X-ray diffraction data was obtained using a colorless prism shaped crystal (approximate dimensions: 0.460 x 0.180 x 0.160 mm^3). Data collection was carried out using CuKα radiation. The crystal was kept at a constant temperature (173K) during data collection using an Oxford cryo-system. Indexing and processing of the measured intensity data were carried out with the Bruker's APEX2 program suite[9]. The crystal structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares procedures on F^2 using all reflections (SHELXL-97).[10] Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors and refined using a riding model.

Compound 6 (TFA salt): Single crystal X-ray diffraction data was obtained using a colorless prism shaped crystal (of unreported dimensions). Data collection was carried out using CuKα radiation. The crystal was kept at a constant temperature (203K) during data collection using an Oxford cryo-system. Indexing and processing of the measured intensity data were carried out with the HKL-SCALEPACK & DENZO-SCALEPACK[6]. The crystal structure was solved by direct methods (SIR97)[7] and refined by full-matrix least-squares procedures on F^2 using all reflections (SHELXL-2016/6)[8]. Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors and refined using a riding model.

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[6] Z. Otwinowski and W. Minor, "Processing of X-ray Diffraction Data Collected in Oscillation Mode", Methods in Enzymology, Volume 276: Macromolecular Crystallography, part A, p.307 326, 1997, C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press (New York)

[7] Cascarano al.,Acta Cryst.,1996,A52,C-79

[8] G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access)

[9] Bruker (2007). APEX2. Bruker AXS Inc., Madison, Wisconsin, USA.

[10] Sheldrick, G. M. SHELX97: Programs for Crystal Structure Analysis; University of Göttingen: Göttingen, Germany, 1997.

X-ray Crystallography Data:

Intermediate S.4:

CCDC deposition number	XYZ
Empirical formula	$C_{25}H_{36}N_4O_6$
Formula weight	488.58
Temperature	296(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.1321(5)Å α= 90°
	b = 11.7767(12)Å β= 90°
	c = 37.324(3)Å γ = 90°
Volume	2695.4(4)Å^3
Z	4
Density (calculated)	1.204 Mg/m^3
Absorption coefficient	0.710 mm^{-1}
F(000)	1048
Crystal size	0.780 x 0.06 x 0.04 mm^3
Theta range for data collection	2.367 to 55.099°.
Index ranges	-6<=h<=6, -11<=k<=12, -39<=l<=37
Reflections collected	3148
Independent reflections	3148 [R(int) = 0.081]
Completeness to theta = 55.099°	99.6 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3148 / 0 / 321
Goodness-of-fit on F2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0563, wR2 = 0.1582
R indices (all data)	R1 = 0.0711, wR2 = 0.2170
Absolute structure parameter	0.1(3)
Extinction coefficient	0.0074(11)
Largest diff. peak and hole	0.212 and -0.186 e.Å^{-3}

Compound 1:

CCDC deposition number	1479580
Empirical formula	$C_{26}H_{36}F_3N_5O_{3.58}$
Formula weight	532.80
Temperature	173(2) K
Wavelength	1.54178 Å
Crystal system	Tetragonal
Space group	$P4_32_12$
Unit cell dimensions	a = 20.4436(4)Å α= 90°
	b = 20.4436(4)Å β= 90°
	c = 28.9325(7)Å γ = 90°
Volume	12092.1(4)Å^3
Z	16
Density (calculated)	1.171 Mg/m^3
Absorption coefficient	0.768 mm^{-1}
F(000)	4522
Crystal size	0.46 x 0.18 x 0.16 mm^3
Theta range for data collection	2.65 to 58.78°
Index ranges	-22<=h<=22, -21<=k<=22, -31<=l<=14
Reflections collected	108743
Independent reflections	8518 [R(int) = 0.1259]
Completeness to theta = 58.78°	98.6 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8518 / 22 / 713
Goodness-of-fit on F2	1.058
Final R indices [I>2sigma(I)]	R1 = 0.0770, wR2 = 0.2087
R indices (all data)	R1 = 0.0860, wR2 = 0.2178
Absolute structure parameter	0.1(2)
Largest diff. peak and hole	0.543 and -0.405 e.Å^{-3}

Compound 6:

CCDC deposition number	XYZ
Empirical formula	$C_{26}H_{36}F_6N_6O_6S$
Formula weight	674.67
Temperature	223.15 K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 10.1411(6)Å α= 90°
	b = 14.266(2)Å β= 90°
	c = 22.592(2)Å γ = 90°
Volume	3268.5(6)Å^3
Z	4
Density (calculated)	1.371 Mg/m^3
Absorption coefficient	1.613 mm^{-1}
F(000)	1408
Crystal size	unreported
Theta range for data collection	3.664 to 50.319°
Index ranges	0<=h<=10, 0<=k<=14, 0<=l<=22
Reflections collected	1965
Independent reflections	1965
Completeness to theta = 50.319°	99.5 %
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	1965 / 276 / 467
Goodness-of-fit on F2	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0483, wR2 = 0.1285
R indices (all data)	R1 = 0.0539, wR2 = 0.1344
Absolute structure parameter	0.24(5)
Extinction coefficient	0.0019(3)
Largest diff. peak and hole	0.274 and -0.184 e.Å^{-3}

Computational Experiments

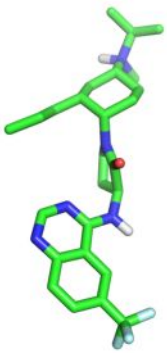
Gaussian09 rev. D.01 was used for all *ab Initio* quantum mechanical calculations. Starting geometries were derived from the small molecule crystal structures: LEDA conformations used the free base of compound **7**, LADE used the protonated form of compounds **6** and **7**. The functional group substitutions needed to construct compounds **1** and **5** from these structures were done with the 3D builder from Maestro v2017-1. The crystallographic conformations were maintained outside the functional group changes. The resulting structures were optimized using B3LYP/6-31+G(d,p) with an smd water solvent model. Stationary points were confirmed by the absence of imaginary frequencies in a frequency calculation at the same level. Final energies were calculated as single points at the B2PLYPD3/6-311+G(d,p) with a smd water solvation model.

Polar surface areas were calculated from the optimized structures using the ASA_P (Total polar surface area) descriptor in MOE version 2016.0801.

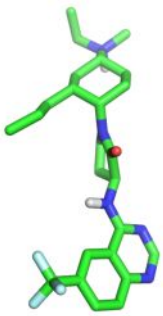
Initial calculations showed the compound **7** LADE conformation to be higher in energy than the compound **1** and **6** LADE conformations (Supplementary Table 1), so the quinazoline orientation from the compound **6** structure was used for all comparisons.

SI Table 1. Relative energies of LEDA conformations with alternate aminoquinazoline rotamers. $\Delta E = E_{(LEDA - SM\ Crystal\ Conf)} - E_{(LEDA - Bound\ conf)}$ (kcal/mol) for each rotamer pair. Energies were computed for protonated and free base forms.

	Protonated		**Free Base**
Cpd	ΔE		ΔE
1	0.5		0.1
5	0.4		0
6	5.4		4.8
7	0.7		0.2

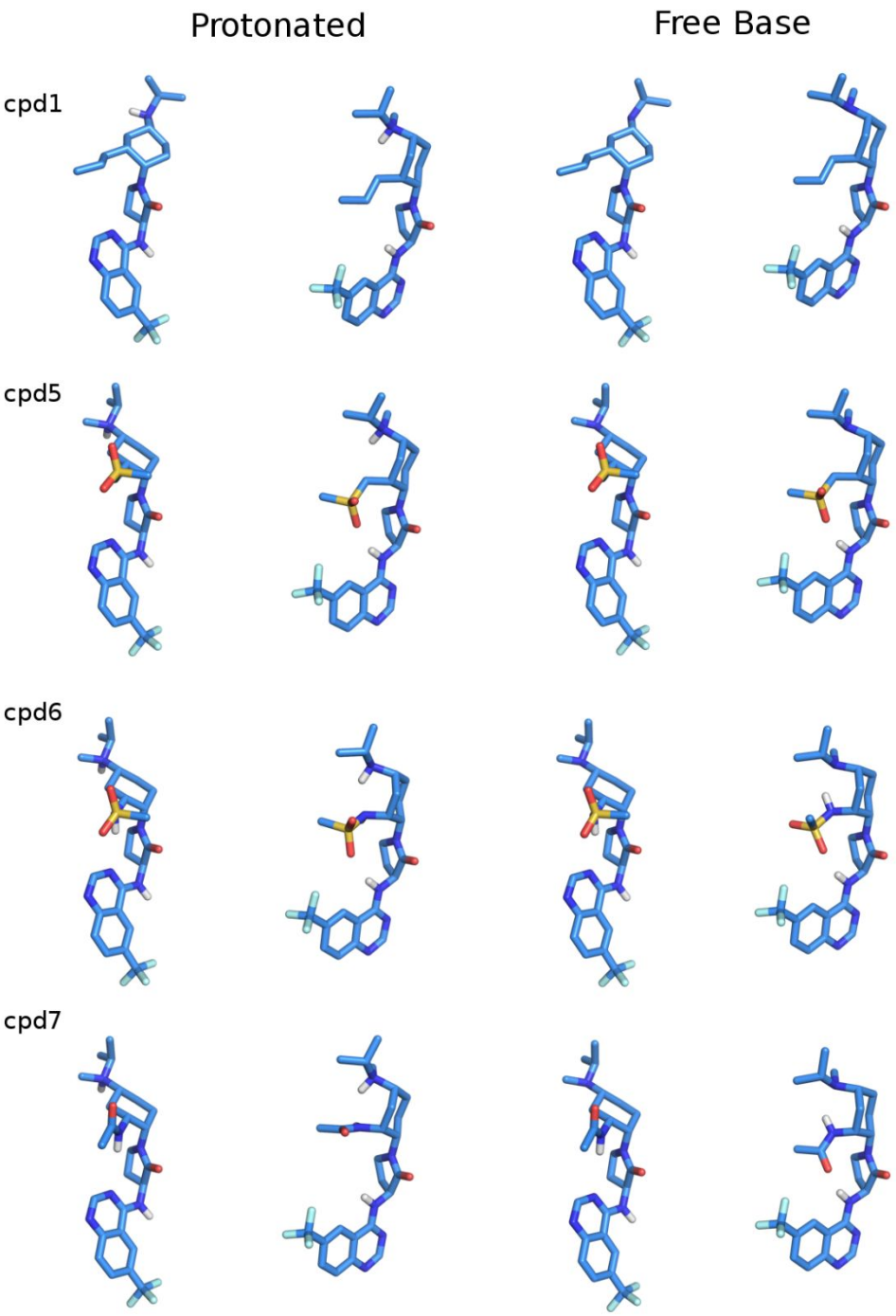


LEDA Bound conformation



LEDA SM Crystal conformation

SI Figure 1. Minimized conformations for compounds **1**, **5**, **6** and **7**



SI Figure 2. Small molecule crystal structures. Hydrogen bonds are shown as dashed lines. (A) Bisbenzenesulfonic acid salt of compound **7**. (B) TFA salt of compound **6**.