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The Use of X-Ray Co-Crystal Structures and Molecular Modeling to Design

Potent and Selective, Non-Peptide Inhibitors of Cathepsin K

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Supporting Information:

Cathepsin K/Inhibitor X-Ray Crystallography

Protein was prepared as described previously.¹ Crystals of mature activated cathepsin K complexed with **9** grew in about six days using vapor diffusion at 20° C from a solution of 18% PEG 8000, 0.06 M sodium acetate at pH 4.5 containing 0.12 M Li₂SO₄. Crystals of the complex are tetragonal, space group P4₃, with cell constants of a=71.5 Ångstroms, and c=55.1 Ångstroms. The structure was determined by molecular replacement using X-PLOR.² The starting model consisted of the protein atoms from the crystal structure of cathepsin K in complex with the cysteine protease inhibitor E64.¹ The structure was refined at 2.3 Ångstroms resolution with a final R_C of 0.240.

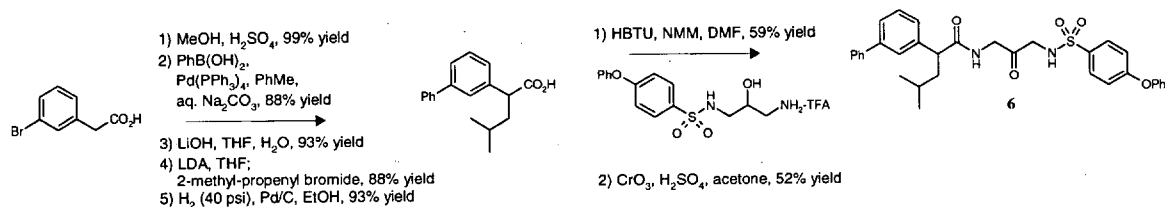
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- (1) Zhao, B., Janson, C.A.; Amegadzie, B.Y.; D'Alessio, K.; Griffin, C.; Hanning, C.R.; Jones, C.; Kurdyla, J.; McQueney, M.; Qiu, X.; Smith, W.W.; Abdel-Meguid, S.S. *Nat. Struct. Biol.* **1997**, *4*, 109-111. (j) McGrath, M.E.; Klaus, J.L.; Barnes, M.G.; Bromme, D. *Nat. Struct. Biol.* **1997**, *4*, 105-109
- (2) Brunger, A. T., Kuriyan, J., Karplus, M. *Science* **1987**, *235*, 458-460.

Synthesis

The Cbz-Leu mimetic, 2-(3-biphenyl)-4-methylvaleric acid, was prepared as shown in Scheme 1. 3-Bromophenylacetic acid was esterified and coupled with phenylboronic acid by the method of Suzuki. Hydrolysis of the ester to the 3-biphenylacetic acid, and alkylation of the dianion with 2-methylpropenylbromide, followed by hydrogenation of the olefin gave 2-(3-biphenyl)-4-methylvaleric acid as a racemate. Enantiomerically pure (R)-2-(3-biphenyl)-4-methylvaleric acid could be obtained by fractional recrystallization from EtOH/EtOAc as a (S)-p-bromo- α -methyl benzyl amine salt. Inhibitor **6** was prepared by coupling 2-(3-biphenyl)-4-methylvaleric acid to 3-amino-1-(4-phenoxyphenylsulfonyl)aminopropan-2-ol, followed by a Jones oxidation of the alcohol to the ketone. The enantiomers of **6** were separated by preparative chiral HPLC. 2-(4-Biphenyl)-4-methylvaleric acid was prepared analogously by alkylation and hydrogenation starting with the commercially available 4-biphenyl acetic acid.

Scheme 1



Experimental Section

3-Bromophenyl methyl acetate

3-Bromophenyl acetic acid (25.5 g, 118.6 mmol) was dissolved in MeOH (250 ml). Then, concentrated sulfuric acid (1.5 ml) was added and the reaction mixture was refluxed for

1.5 h. The reaction mixture was then cooled to RT, concentrated *in vacuo*, and the residue was redissolved in Et₂O, extracted with water (2x), then brine, and the combined organic extracts were dried with magnesium sulfate, filtered, concentrated *in vacuo* and used in the next reaction without further purification (27.0 g, 99%): ¹H NMR (δ, CDCl₃, 360 MHz): 7.45-7.20 (m, 4H), 3.70 (s, 3H), 3.60 (s, 2H).

3-Biphenyl methyl acetate

3-Bromophenyl methyl acetate (27.0 g, 118 mmol) was dissolved in toluene (300 ml). Then, phenyl boronic acid (17.35 g, 142 mmol) was added, followed by aqueous sodium carbonate (2M, 237 ml, 474 mmol), then tetrakis(triphenylphosphine) palladium (4.15 g, 3.6 mmol) was added, and the reaction mixture was refluxed overnight. The reaction was cooled to RT, saturated aqueous ammonium chloride was added, then the mixture was extracted with EtOAc (2x). The combined organics were dried with magnesium sulfate, filtered, concentrated, and chromatographed (silica gel, 4% EtOAc: hexanes) to provide the desired product (23.5 g, 88%): ¹H NMR (δ, CDCl₃, 360 MHz) 7.60-7.25 (m, 9H), 3.70 (s, 3H), 3.68 (s, 2H); MS(ES) 263 (M+H⁺).

3-Biphenyl acetic acid

3-Biphenyl methyl acetate (10.36 g, 45.84 mmol) was dissolved in MeOH (240 ml) and water (35 ml), then LiOH-hydrate (3.85 g, 92 mmol) was added, and the reaction was stirred at RT for 2h. The reaction was diluted with water, acidified with 6N hydrochloric acid (8 ml), then was extracted with EtOAc (2x). The combined organics were extracted with H₂O, then brine, then dried with magnesium sulfate, filtered, and concentrated to give the desired product as a white solid (9.03 g, 93%): ¹H NMR (δ, CDCl₃, 360 MHz): 7.57-7.24 (m, 9H), 3.70 (s, 2H).

2-(3-Biphenyl)-4-methyl-pent-4-enoic acid

n-BuLi (32.6 ml, 1.6 M in hexanes, 52 mmol) was added dropwise to a solution of diisopropyl amine (7.4 ml, 53 mmol) in THF (60 ml) at 0° C. The reaction was stirred for 15 minutes, then was cooled to -78° C. 3-Biphenyl acetic acid (5.0 g, 23.5 mmol) was dissolved in THF (20 ml) and was added dropwise to the LDA solution. The reaction was warmed to 0° C, stirred 40 minutes, then cooled to -78° C. Isobutenyl bromide (3.55 ml, 35.2 mmol) was added rapidly, and the reaction was stirred for 1h. Water (20 ml) was then added, then the THF was removed *in vacuo*. The reaction was acidified with 6N hydrochloric acid (10 ml), then was extracted with EtOAc (2x). The combined organics were dried with magnesium sulfate, filtered, concentrated, chromatographed twice (silica gel, 5% MeOH: CH₂Cl₂, then silica gel, 3% MeOH: CH₂Cl₂) to give the desired product (5.47 g, 88%): ¹H NMR (δ, CDCl₃, 360 MHz): 7.57-7.24 (m, 9H), 4.76 (d, J= 9.9 Hz, 2H), 3.88 (dd, J= 6.6 Hz, 8.9 Hz, 1H), 2.87 (dd, J= 9.0 Hz, 14.7 Hz, 1H), 2.50 (dd, J= 6.5 Hz, 14.7 Hz, 1H), 1.72 (s, 3H).

2-(3-Biphenyl)-4-methyl-valeric acid

2-(3-Biphenyl)-4-methyl-pent-4-enoic acid (5.2 g, 19.6 mmol) was dissolved in EtOAc (40 ml) and EtOH (60 ml). Then, 10% Pd/C (0.8 g) was added and the reaction was shaken in a Parr hydrogenator at 40 psi for 2h. The reaction was filtered, concentrated *in vacuo*, then chromatographed (silica gel, 5% MeOH: methylene chloride) to give the desired product (1.66 g, 93%): ¹H NMR (δ, CDCl₃, 360 MHz): 7.58-7.33 (m, 9H), 3.72 (dd, J= 7.8 Hz, 7.8 Hz, 1H), 2.03-1.95 (m, 1H), 1.76-1.70 (m, 1H), 1.54-1.50 (m, 1H), 0.91 (d, J= 6.6 Hz, 6H).

3-Amino-1-N-(4-phenoxy-phenyl-sulfonyl)-amino-propan-2-ol

4-Phenoxybenzene sulfonyl chloride (1.9 g, 7 mmol) was added to a mixture of 1,3-diaminoalcohol (1.9 g, 21 mmol) in DMF (15 ml) and was stirred overnight. DMF was removed *in vacuo*, then the resulting residue was chromatographed (silica gel, 5:94:1 MeOH, CH₂Cl₂, TFA to 8:91:1 MeOH, CH₂Cl₂, TFA) to yield the desired product as a TFA salt (2.3 g, 75%): MS(ES) 323.3 (M+H⁺).

1-N-(2-(3-Biphenyl)-4-methyl-valeryl)-amino-3-N-(4-phenoxy-phenyl-sulfonyl)-amino-propan-2-ol

N-methyl-morpholine (0.25 ml, 2.3 mmol), then HBTU (0.22 g, 0.58 mmol) was added to a solution of 3-amino-1-N-(4-phenoxy-phenyl-sulfonyl)-amino-propan-2-ol (0.24 g, 0.56 mmol) and 2-(3-biphenyl)-4-methyl-valeric acid (0.15 g, 0.56 mmol) in DMF (3 ml) and was stirred overnight. The reaction mixture was diluted with water, then extracted with EtOAc (2x). The combined organics were dried with magnesium sulfate, filtered, concentrated, chromatographed twice (silica gel, 45:55 EtOAc: hexanes) to give the desired product (0.19 g, 59%): ¹H NMR (δ, CDCl₃, 360 Mhz): 7.70-6.92 (m, 18H), 6.0 (2 br.d, 1H), 5.20 (2 br. d, 1H), 3.76 (dd, 8.2 Hz, 8.2 Hz, 2H), 3.33 (dd, J= 5.8 Hz, 5.8 Hz, 2H), 2.80 (dd, J= 5.8 Hz, 5.8 Hz, 1H), 1.99-1.91 (m, 1H), 1.74-1.65 (m, 1H), 1.47-1.40 (m, 1H), 0.88 (2 d, J= 6.6 Hz, 6.6 Hz, 6H).

1-N-(2-(3-Biphenyl)-4-methyl-valeryl)-amino-3-N-(4-phenoxy-phenyl-sulfonyl)-amino-propan-2-one (6)

Jones reagent (1.5 M) was added to a solution of 1-N-(2-(3-biphenyl)-4-methyl-valeryl)-amino-3-N-(4-phenoxy-phenyl-sulfonyl)-amino-propan-2-ol (0.19 g, 0.33 mmol) in acetone (5 ml) until the yellow color persisted, and the reaction mixture was stirred overnight. Isopropanol (0.5 ml) was added to quench the excess Jones reagent. The reaction mixture was concentrated *in vacuo*, then the residue was redissolved in EtOAc and was extracted with H₂O, then brine. The combined organics were dried with magnesium sulfate, filtered, concentrated, chromatographed twice (silica gel, 45:55 EtOAc: hexanes) to give the desired product (0.19 g, 52%): ¹H NMR (δ, CDCl₃, 360 Mhz): 7.70-6.96 (m, 18H), 6.0 (br.t, 1H), 5.20 (t, 5.0 Hz, 1H), 4.03 (dd, 5.2 Hz, 8.3 Hz, 2H), 3.83 (d, J= 5.0 Hz, 2H), 3.54 (dd, J= 7.0 Hz, 8.4 Hz, 1H), 2.03-1.95 (m, 1H), 1.78-1.70 (m, 1H), 1.47-1.42 (m, 1H), 0.88 (2 d, J= 6.6 Hz, 6.6 Hz, 6H).

The enantiomers were separated by chiral preparative HPLC (Daicel Chiralcel OD column (21.2 x 250mm), 20% ethanol in hexane, 10mL/min, UV detection @280nm).

(R)-2-(3-Biphenyl)-4-methyl-valeric acid

(+/-)-2-(3-biphenyl)-4-methyl-valeric acid (16.6 g, 62 mmol) was dissolved in EtOH (100 ml) and EtOAc (200 ml). (S)-p-Bromo- α -methyl benzyl amine (12.31 g, 62 mmol) was added and the solution was heated to 65 degrees C until the solid was completely in solution. The solution was cooled in a refrigerator and white crystals formed overnight. The crystals were collected then were dried in vacuo. Four recrystallizations from a 1:2 EtOAc/ EtOH yielded crystalline white solid (3.05 g, 21% recovery). Chiral HPLC indicated an enantiomeric ratio of 99.3% (R) and 0.7% (S). The solid was then dissolved in EtOAc, extracted with 1 N aqueous HCl to form the free carboxylic acid, and the combined organics were dried with magnesium sulfate, filtered, concentrated in vacuo and was used in the next reaction without further purification.

1-N-(Cbz-L-leuciny)-amino-3-N-(4-phenoxy-phenyl-sulfonyl)-amino-propan-2-one (3): $^1\text{H NMR}$ (δ , CDCl_3 , 360 MHz): 7.76 (d, 8.7 Hz, 2H), 7.40-7.00 (m, 12 H), 6.65 (br.s, 1H), 5.33 (br.t, 1H), 5.1 (br.s, 3H), 4.2 (br.s, 1H), 4.1 (br.s., 2H), 3.86 (d, J= 5.2 Hz, 2H), 1.66-1.63 (m, 2H), 1.55-1.45 (m, 2H), 0.90 (dd, J= 6.5 Hz, 5.7 Hz, 6H).

1-N-(Cbz-L-leuciny)-amino-3-N-((R,S)-2-(4-biphenyl)-4-methyl-valeryl)-amino-propan-2-one (4): $^1\text{H NMR}$ (δ , CDCl_3 , 360 MHz): 7.57-7.24 (m. 14H), 6.55 (br.d, 1H), 6.10 (br.t, 1H), 5.09 (s, 2H), 5.05 (br.s, 1H), 4.17-4.05 (m, 5H), 3.55 (dd, J= 5.2 Hz, 8.3 Hz, 1H), 2.05-1.95 (m, 1H), 1.80-1.70 (m, 1H), 1.70-1.40 (m, 4H), 0.91-0.89 (2 d, J= 6.5 Hz, 6.5 Hz, 12H).

1-N-(2-(4-Biphenyl)-4-methyl-valeryl)-amino-3-N-(4-phenoxy-phenyl-sulfonyl)-amino-propan-2-one (5): $^1\text{H NMR}$ (δ , CDCl_3 , 360 MHz): 7.74-6.97 (m. 18H), 6.0 (br.s, 1H), 5.20 (t, 5.0 Hz, 1H), 4.03 (dd, 5.2 Hz, 8.3 Hz, 2H), 3.83 (d, J= 5.0 Hz, 2H), 3.52 (dd, J= 7.0 Hz, 8.4 Hz, 1H), 2.05-1.93 (m, 1H), 1.78-1.73 (m, 1H), 1.47-1.42 (m, 1H), 0.89 (2 d, J= 6.6 Hz, 6.6 Hz, 6H).

1-N-(2-(3-Biphenyl)-acetyl)-amino-3-N-(4-phenoxy-phenyl-sulfonyl)-amino-propan-2-one (7): $^1\text{H NMR}$ (δ , CDCl_3 , 360 MHz): 7.74-6.97 (m. 18H), 6.03 (br.s, 1H), 5.24 (br.s, 1H), 4.07 (d, 5.2 Hz, 2H), 3.85 (d, J= 5.1 Hz, 2H), 3.65 (s, 2H).

1-N-(2-(4-Biphenyl)-acetyl)-amino-3-N-(4-phenoxy-phenyl-sulfonyl)-amino-propan-2-one (8): $^1\text{H NMR}$ (δ , $\text{CDCl}_3/\text{CD}_3\text{OD}$, 360 MHz): 7.65-6.89 (m. 18H), 4.00 (s, 2H), 3.68 (s, 2H), 3.52 (s, 2H).

1-N-(2-(3-Biphenyl)-4-methyl-valeryl)-amino-3-N-(2-pyridyl-phenyl-sulfonyl)-amino-propan-2-one (9): $^1\text{H NMR}$ (δ , CDCl_3 , 360 MHz): 8.54 (d, J= 4.7 Hz, 1H), 7.93-7.85 (m, 2H), 7.57-7.39 (m, 10 H), 6.0 (br.s, 1H), 5.5 (br.s, 1H), 4.16 (d, J= 5.1 Hz, 2H), 4.10 (dd, J= 5.1 Hz, 10.9 Hz, 2H), 3.55 (dd, J= 7.25 Hz, 8.2 Hz, 1H), 2.0-1.96 (m, 1H), 1.78-1.70 (m, 1H), 1.47-1.43 (m, 1H), 0.89 (d, J=6.6 Hz, 6H).

X-ray structure of the p-bromo-phenethylene salt of 2-(3-biphenyl)-4-methyl-valeric acid.

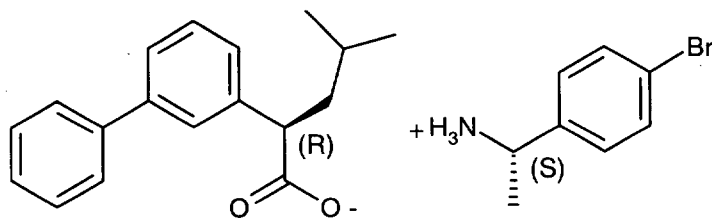


Figure 1. A view of the crystal structure.

Figure 2. A stereo view showing the hydrogen bonding interactions.

Table 1. Crystal data and structure refinement.

Table 2. Atomic coordinates and equivalent isotropic displacement parameters.

Table 3. Selected bond lengths and angles.

Table 4. Torsion angles.

Table 5. Anisotropic displacement parameters.

Table 6. Hydrogen coordinates and isotropic displacement parameters.

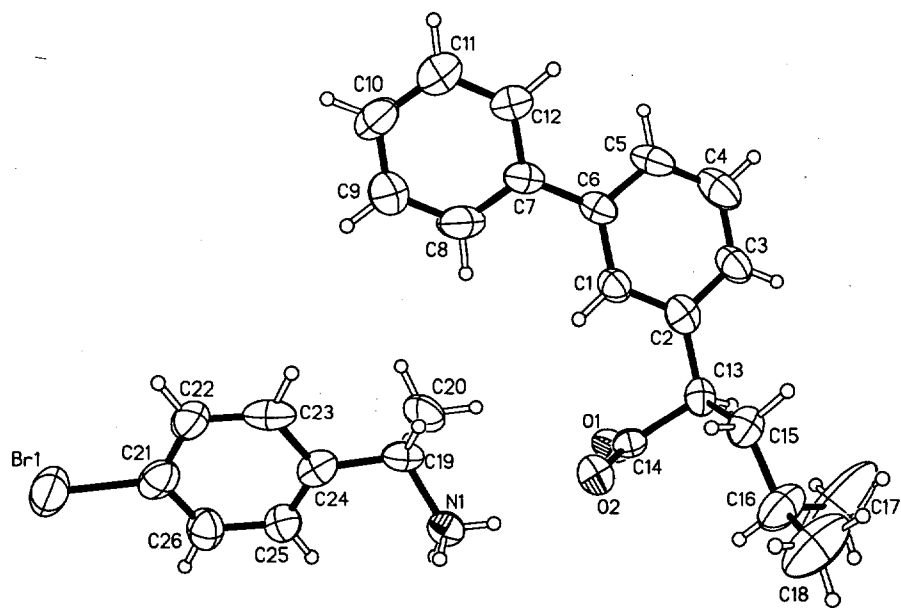


Figure 1. A view of the crystal structure showing the numbering scheme employed. Anisotropic displacement ellipsoids for non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displayed with an arbitrarily small radius.

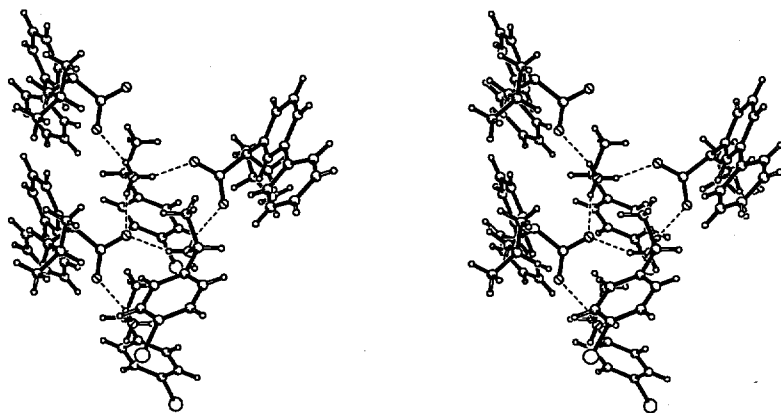


Figure 2. A stereo view showing the hydrogen bonding interactions as dotted lines. All three ammonium hydrogens form interactions with the carboxylate oxygens in adjacent molecules. O1 is an acceptor from two donors, while O2 is involved with only one. Metrical details of the hydrogen bonding interactions are:

Atom Names	X...Y, Å	X-H, Å	H...Y, Å	X-H...Y, °
N1-H1A ... O2	2.837(8)	0.859(4)	2.022(5)	158(5)
N1-H1B ... O1	2.811(8)	0.860(4)	1.981(5)	162(5)
N1-H1C ... O1	2.775(8)	0.855(4)	1.953(5)	161(5)

Table 1. Crystal data and structure refinement.

Empirical formula	[C ₈ H ₁₁ NBr] ⁺ [C ₁₈ H ₁₉ O ₂] ⁻
Formula weight	468.42
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal size	0.8 x 0.06 x 0.04 mm
Density (calculated)	1.269 Mg/m ³
Absorption coefficient	1.697 mm ⁻¹
F(000)	488
θ range for data collection ¹	2.58 to 22.70°
Index ranges	-15 ≤ h ≤ 15, -6 ≤ k ≤ 7, -15 ≤ l ≤ 15
Reflections collected	8964
Independent reflections	3172 (R _{int} = 0.108)
Refinement method ²	Full-matrix least-squares on F ²
Data / restraints / parameters	3171 / 10 / 284
Final R indices:	
2662 data; I > 2σ(I)	R1 = 0.064, wR2 = 0.144
all data	R1 = 0.080, wR2 = 0.161
Absolute structure parameter ³	-0.02(2)
Extinction coefficient	0.051(5)
Largest diff. peak and hole	0.70 and -0.57 eÅ ⁻³

1. Data were collected on an Enraf Nonius FAST diffractometer using graphite monochromated molybdenum radiation and the MADNES data collection program.
2. The structure was solved, refined and displayed using the SHELXTL program package. Weights were assigned to the data as $w = 1/[\sigma^2(F_o^2) + (0.0553P)^2 + 2.7238P]$ where $P = [\text{MAX}(F_o^2, 0) + 2F_c^2]/3$.
3. The absolute configuration was assigned on the basis of the known configuration (S) of the cation and was confirmed by the Hamilton R-factor ratio test and the least squares absolute structure parameter. The ratio of weighted R-values, 0.218/0.161= 1.35 permits assignment with a confidence level greater than 99.9%. Consistent with this, the calculated absolute structure parameter is -0.02(2). When the absolute structure parameter is refined, the value is -0.02(2) for the reported configuration and 1.02(2) for the inverted model.

Table 2. Atomic coordinates [$\times 10^4$] and equivalent isotropic displacement parameters [$\text{\AA}^2 \times 10^3$].

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
Br1	3513(1)	1885(2)	5361(1)	80(1)
O1	6131(3)	-10446(8)	10376(4)	43(1)
O2	7121(4)	-7600(8)	10775(4)	45(1)
N1	5781(5)	-4451(9)	9631(5)	40(2)
C1	8136(5)	-10606(11)	9493(5)	40(2)
C2	8245(6)	-11796(12)	10358(6)	42(2)
C3	8646(6)	-13805(12)	10442(6)	49(2)
C4	8963(7)	-14551(14)	9700(7)	66(2)
C5	8841(6)	-13389(14)	8851(6)	53(2)
C6	8422(5)	-11374(11)	8730(6)	40(2)
C7	8286(5)	-10112(12)	7816(5)	43(2)
C8	7610(9)	-8512(20)	7500(7)	99(4)
C9	7466(11)	-7363(17)	6627(9)	108(5)
C10	7976(7)	-7782(19)	6046(6)	70(3)
C11	8663(11)	-9302(22)	6360(8)	116(5)
C12	8837(9)	-10412(21)	7233(7)	107(5)
C13	7934(5)	-10980(11)	11185(5)	38(2)
C14	6993(5)	-9533(11)	10747(5)	35(2)
C15	8809(5)	-9923(13)	12050(5)	46(2)
C16	8598(7)	-9519(18)	13009(6)	73(3)
C17	8496(15)	-11442(30)	13510(9)	191(11)
C18	9395(9)	-8094(31)	13753(7)	111(4)
C19	5842(5)	-4738(12)	8622(5)	43(2)
C20	5410(8)	-6914(12)	8222(7)	64(3)
C21	4183(6)	-209(12)	6329(5)	52(2)
C22	5104(8)	-1011(13)	6373(6)	62(2)
C23	5636(7)	-2406(13)	7123(7)	63(3)
C24	5271(5)	-3061(15)	7859(4)	42(2)
C25	4341(6)	-2278(11)	7778(6)	44(2)
C26	3803(7)	-861(13)	7020(6)	53(2)

Table 3. Selected bond lengths [\AA] and angles [$^\circ$].

Br1-C21	1.908(8)	O1-C14	1.280(8)
O2-C14	1.263(9)	N1-C19	1.501(9)
C1-C6	1.406(10)	C1-C2	1.418(10)
C2-C3	1.409(11)	C2-C13	1.522(10)
C3-C4	1.401(11)	C4-C5	1.386(12)
C5-C6	1.418(12)	C6-C7	1.494(10)
C7-C8	1.367(13)	C7-C12	1.377(12)
C8-C9	1.403(14)	C9-C10	1.339(13)
C10-C11	1.34(2)	C11-C12	1.381(14)
C13-C15	1.533(10)	C13-C14	1.555(10)
C15-C16	1.548(11)	C16-C17	1.47(2)
C16-C18	1.53(2)	C19-C24	1.530(11)
C19-C20	1.555(11)	C21-C26	1.375(11)
C21-C22	1.397(12)	C22-C23	1.381(12)
C23-C24	1.420(10)	C24-C25	1.387(10)
C25-C26	1.400(11)		
C6-C1-C2	121.9(7)	C3-C2-C1	118.4(7)
C3-C2-C13	119.3(7)	C1-C2-C13	122.2(7)
C4-C3-C2	119.9(7)	C5-C4-C3	121.3(8)
C4-C5-C6	120.4(7)	C1-C6-C5	118.1(7)
C1-C6-C7	121.1(6)	C5-C6-C7	120.8(6)
C8-C7-C12	114.0(8)	C8-C7-C6	122.4(7)
C12-C7-C6	123.6(7)	C7-C8-C9	122.2(9)
C10-C9-C8	121.9(10)	C11-C10-C9	116.7(9)
C10-C11-C12	122.2(10)	C7-C12-C11	122.7(10)
C2-C13-C15	112.9(6)	C2-C13-C14	111.6(5)
C15-C13-C14	111.0(6)	O2-C14-O1	125.1(7)
O2-C14-C13	119.5(6)	O1-C14-C13	115.4(6)
C13-C15-C16	114.3(6)	C17-C16-C18	111.1(9)
C17-C16-C15	112.7(10)	C18-C16-C15	111.7(8)
N1-C19-C24	112.7(6)	N1-C19-C20	107.6(6)
C24-C19-C20	110.9(6)	C26-C21-C22	119.5(8)
C26-C21-Br1	121.1(7)	C22-C21-Br1	119.3(6)
C23-C22-C21	119.8(7)	C22-C23-C24	121.7(8)
C25-C24-C23	117.0(8)	C25-C24-C19	122.8(6)
C23-C24-C19	119.8(7)	C24-C25-C26	121.3(7)
C21-C26-C25	120.7(8)		

Table 4. Torsion angles [°].

C6-C1-C2-C3	-0.3(10)	C6-C1-C2-C13	-179.8(7)
C1-C2-C3-C4	2.4(11)	C13-C2-C3-C4	-178.2(8)
C2-C3-C4-C5	-3.4(13)	C3-C4-C5-C6	2.2(13)
C2-C1-C6-C5	-0.8(11)	C2-C1-C6-C7	178.9(6)
C4-C5-C6-C1	-0.1(11)	C4-C5-C6-C7	-179.8(7)
C1-C6-C7-C8	-21.5(12)	C5-C6-C7-C8	158.2(9)
C1-C6-C7-C12	156.9(10)	C5-C6-C7-C12	-23.3(13)
C12-C7-C8-C9	3(2)	C6-C7-C8-C9	-178.4(11)
C7-C8-C9-C10	1(2)	C8-C9-C10-C11	-3(2)
C9-C10-C11-C12	1(2)	C8-C7-C12-C11	-5(2)
C6-C7-C12-C11	176.5(12)	C10-C11-C12-C7	3(2)
C3-C2-C13-C15	88.4(8)	C1-C2-C13-C15	-92.2(8)
C3-C2-C13-C14	-145.8(6)	C1-C2-C13-C14	33.6(9)
C2-C13-C14-O2	-97.4(8)	C15-C13-C14-O2	29.5(9)
C2-C13-C14-O1	82.6(7)	C15-C13-C14-O1	-150.6(6)
C2-C13-C15-C16	-166.9(7)	C14-C13-C15-C16	67.0(9)
C13-C15-C16-C17	65.6(12)	C13-C15-C16-C18	-168.5(10)
C26-C21-C22-C23	-1.6(12)	Br1-C21-C22-C23	174.8(6)
C21-C22-C23-C24	0.1(13)	C22-C23-C24-C25	1.6(12)
C22-C23-C24-C19	175.1(7)	N1-C19-C24-C25	-39.6(9)
C20-C19-C24-C25	81.1(9)	N1-C19-C24-C23	147.3(7)
C20-C19-C24-C23	-92.0(9)	C23-C24-C25-C26	-1.7(11)
C19-C24-C25-C26	-175.0(7)	C22-C21-C26-C25	1.5(11)
Br1-C21-C26-C25	-174.9(6)	C24-C25-C26-C21	0.2(11)

Table 5. Anisotropic displacement parameters [$\text{\AA}^2 \times 10^3$].

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [(ha^*)^2 U_{11} + \dots + 2hka^*b^* U_{12}]$$

	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
Br1	120(1)	65(1)	53(1)	11(1)	32(1)	2(1)
O1	33(3)	39(3)	58(3)	-10(2)	19(2)	-3(2)
O2	39(3)	41(4)	52(3)	2(2)	16(2)	-1(2)
N1	38(4)	35(4)	46(4)	-4(3)	16(3)	-3(3)
C1	42(4)	34(4)	47(4)	4(3)	20(3)	5(3)
C2	33(4)	39(5)	48(5)	-2(3)	10(3)	-3(3)
C3	50(5)	38(5)	66(5)	13(4)	29(4)	12(4)
C4	64(6)	44(5)	94(7)	7(5)	37(5)	17(4)
C5	52(4)	48(5)	72(5)	-7(5)	39(4)	9(4)
C6	36(4)	37(4)	53(4)	-2(3)	23(4)	2(3)
C7	38(4)	48(5)	48(4)	-11(4)	19(3)	0(4)
C8	159(10)	87(9)	93(7)	26(7)	96(7)	56(8)
C9	167(12)	91(9)	98(8)	48(7)	85(9)	74(8)
C10	81(6)	89(8)	50(4)	10(6)	36(4)	4(6)
C11	145(11)	151(12)	89(8)	57(8)	86(8)	78(9)
C12	132(10)	145(11)	69(6)	39(7)	67(7)	83(9)
C13	28(4)	43(4)	42(4)	10(3)	13(3)	-1(3)
C14	35(4)	39(5)	35(4)	-2(3)	20(3)	-2(3)
C15	34(4)	60(5)	41(4)	3(4)	12(3)	-8(4)
C16	58(5)	116(8)	42(4)	-8(5)	16(4)	-12(5)
C17	249(21)	263(23)	68(8)	9(10)	70(10)	-149(19)
C18	119(9)	155(11)	59(5)	-28(11)	34(6)	-59(12)
C19	36(4)	50(5)	46(4)	-13(4)	20(3)	-1(3)
C20	85(7)	36(5)	63(5)	-15(4)	20(5)	13(5)
C21	66(5)	50(5)	36(4)	-11(4)	17(4)	-14(4)
C22	97(7)	49(5)	52(5)	8(4)	43(5)	6(5)
C23	67(6)	68(6)	72(5)	-20(5)	47(5)	-2(4)
C24	48(4)	41(4)	42(3)	-7(4)	22(3)	-17(4)
C25	47(5)	39(4)	50(4)	1(3)	23(4)	-10(3)
C26	58(5)	44(5)	53(4)	4(4)	20(4)	-2(4)

Table 6. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for X1671A1.

	x/a	y/b	z/c	U(eq)
H1A	6089(40)	-5380(72)	10074(33)	30(20)
H1B	5172(36)	-4467(88)	9608(38)	102(39)
H1C	6030(39)	-3312(76)	9925(34)	63(23)
H1	7869(5)	-9281(11)	9429(5)	48
H3A	8701(6)	-14635(12)	10989(6)	59
H4A	9260(7)	-15851(14)	9779(7)	79
H5	9036(6)	-13934(14)	8357(6)	64
H8	7233(9)	-8174(20)	7876(7)	118
H9	7002(11)	-6279(17)	6446(9)	130
H10	7859(7)	-7052(19)	5453(6)	84
H11	9036(11)	-9622(22)	5978(8)	139
H12	9348(9)	-11404(21)	7435(7)	128
H13	7730(5)	-12176(11)	11478(5)	46
H15A	8954(5)	-8616(13)	11806(5)	55
H15B	9412(5)	-10778(13)	12235(5)	55
H16A	7944(7)	-8800(18)	12788(6)	88
H17A	7992(15)	-12309(30)	13028(9)	230
H17B	8294(15)	-11116(30)	14054(9)	230
H17C	9137(15)	-12152(30)	13774(9)	230
H18A	9446(9)	-6857(31)	13409(7)	134
H18B	10041(9)	-8783(31)	14018(7)	134
H18C	9199(9)	-7747(31)	14298(7)	134
H19A	6558(5)	-4699(12)	8721(5)	51
H20A	5779(8)	-7939(12)	8712(7)	77
H20B	5480(8)	-7178(12)	7596(7)	77
H20C	4704(8)	-6969(12)	8112(7)	77
H22A	5358(8)	-606(13)	5899(6)	74
H23A	6248(7)	-2929(13)	7146(7)	75
H25A	4070(6)	-2702(11)	8237(6)	53
H26A	3182(7)	-354(13)	6982(6)	63