Supporting Information

Cyclic Penta- and Hexa- Leucine Peptides Without N-Methylation Are Orally Absorbed

Timothy A Hill,[§a] Rink-Jan Lohman,[§a] Huy N Hoang,[a] Daniel S Nielsen,[a] Conor CG Scully,[a] W.Mei Kok,[a] Ligong Liu,[a] Andrew J. Lucke,[a] Martin J. Stoermer,[a] Christina I. Schroeder[a], Stephanie Chaousis[a], Barbara Colless[a] Paul V. Bernhardt,[b] David J. Edmonds,[c] David A. Griffith,[c] Charles J. Rotter,[d] Roger B. Ruggeri,[c] David A. Price,[c] Spiros Liras,[c] David J. Craik,[a] and David P Fairlie[a]*

[a] Division of Chemistry and Structural Biology, Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland 4072, Australia. Fax: +61-733462990; Tel: +61-733462989; E-mail: d.fairlie@imb.uq.edu.au.

[b] School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane 4072, Australia

[c] World Wide Medicinal Chemistry, CVMED, Pfizer, Cambridge, Massachusetts, USA

[d] Pfizer Pharmacokinetics, Dynamics and Metabolism, Groton, Connecticut, USA

*Correspondence to Professor David Fairlie, Email: d.fairlie@imb.uq.edu.au

Experimental procedures

Abbreviations

DIPEA, diisopropylethylamine; DMF, dimethylformamide; ESI-MS; Fmoc, 9-fluorenylmethyloxycarbonyl; HBTU, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate: HCTU, 2-(1*H*-6-chlorobenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate; HR-MS, High-resolution mass spectroscopy; MBHA, 4-methyl-benzylhydrylamine;; PyBOP, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate; RP-HPLC, reserved-phase high performance liquid chromatography; RP-HPLC; UHPLC, reserved-phase ultra high performance liquid chromatography;; RT, room temperature; SPPS, solid-phase peptide synthesis;; TFA, trifluoroacetic acid; TFE, 2,2,2-trifluoroethanol; TIS, triisopropylsilane;.

Materials

Cyclosporin was purchased from Sigma Aldrich catalogue no 30024

All solvents and reagents used during peptide chain assembly were peptide synthesis grade and purchased from commercial suppliers unless otherwise stated.

Peptide Synthesis:

The synthesis of linear peptides from 9-fluorenylmethoxycarbonyl (Fmoc) L-amino acids was conducted manually, on 2-chlorotrityl chloride resin (0.8 mmol/g). Fmoc-Leu-OH (2eq. relative to resin) and DIPEA (2 eq.) was dissolved in dry DCM (approx. 10mL per gram of resin), then added to the dry resin and stirred overnight. The resin was then washed with DCM (3x) and DMF (3x), and the Fmoc protecting group was removed using 50% piperidine in DMF (2 x

10min). A qualitative confirmation test was carried out using the Kaiser test for free amino groups. For subsequent amino acid couplings, Fmoc-Leu-OH (4 eq.) was activated with HATU (4 eq.) and DIPEA (4 eq.) in DMF (5 ml/g). The solution was added to the resin, and the reaction allowed to proceed for 2 h. The coupling reaction was monitored for completion with the Kaiser test. When the coupling was achieved, the resin was washed with DMF. The same procedure for deprotection and coupling was repeated for the next amino acid until all amino acids in the sequence were attached. The peptidyl resin was thoroughly washed with DCM before the peptide was cleaved. The peptides were cleaved with an acid solution containing 2.5% triisopropylsilane (TIPS), 2.5% water, 95% TFA at room temperature for 2 h. The TFA was removed under a stream of nitrogen gas, and peptides precipitated with diethyl ether, then centrifuged. The product was then redissolved in 75% acetonitrile in water (v/v), and lyophilised.

Cyclisation

The linear peptide dissolved in DMF was added dropwise over 3 hr to a solution of PyBOP (4 eq.) and DIPEA (4 eq.) in DMF (0.5 mg/mL relative to peptide), and the mixture was stirred overnight at room temperature. The reaction was then concentrated *in vacuo* to give the cyclized peptide as a yellow oil. Purification of the peptide was carried out on a preparative C18 column with a linear gradient of 50-100% buffer B [buffer A: 0.1% TFA in water (v/v); buffer B: 0.1% TFA in 90% acetonitrile/water (v/v)] over 20 min, with a flow rate of 40 mL/min to yield the purified peptide. (1) Yield = 3% (2) and (3) = 20% (15:85 epimer ratio)

Analytical Methods

HPLC analysis was done measuring light absorption at wavelength 200-600 nm on a Shimadzu UHPLC system (LC-30AD, SIL-30AC, CBM-20A, SPD-M20A, CTO-20A) using solvent mixtures of H_2O/0.1 % trifluoroacetic acid (buffer A) and MeCN/H_2O (9/1) (aq)/0.1 % trifluoroacetic acid (buffer B) with a flow rate of 0.6 ml/min on a Eclipse Plus C18 column (2.1 μm x 100 mm).

Preparative HPLC of cyclic peptides was carried out on a Shimadzu preparative HPLC system (LC-20AP, CBM-20A, SPD-M20A) eluting with solvent mixtures of 0.1 % TFA in water (buffer A) and 0.1 % TFA in MeCN/H_2O 9:1 (buffer B) with a Phenomenex Luna C18 column (semi-prep 250 x 21.20 mm, prep 250 x 30.00 mm) with the only exceptions of cyc(Leu)$_5$, cyc(Leu)$_6$ and cyc(Leu$_5$leu), which was purified on a Phenomenex Luna C5 column (250 x 21.20 mm).

High-resolution mass spectrometry (HRMS) was performed on a TOF instrument by direct infusion of compounds in acetonitrile, using sodium formate clusters as an internal calibrant.

(1) Analytical UHPLC: linear gradient from 50% to 100% B over 8 min, R_t = 3.01 min.
HRMS-TOF for $[M+H]^+$: calcd $C_{30}H_{56}N_5O_5+$, 566.4201; Found 566.4277

(2) Analytical UHPLC: linear gradient from 50% to 100% B over 8 min, R_t = 3.15 min.
HRMS-TOF for $[M+H]^+$: calcd for $C_{36}H_{67}N_6O_6+$, 679.5117; found 679.5119

(3) Analytical UHPLC: linear gradient from 50% to 100% B over 8 min, R_t = 3.24 min.
HRMS-TOF for $[M+H]^+$: calcd for $C_{36}H_{67}N_6O_6+$, 679.5117; found 679.5118

RRCK Cell Permeability

Cell permeability was determined using RRCK cells (Pfizer, Inc. Groton CT). RRCK cells were generated in house as a sub-clone of Madin-Darby Canine Kidney wild type (MDCK-WT) dells that displayed low expression of endogenous p-glycoprotein (approximately 1-2% of MDCK-WT cells, based on mRNA lelvel). Cells were cultured in minimal essential medium α with supplements and passaged when 70-80% confluent. Cell monolayer flux studies were conducted five days after seeding 24-well transwell inserts (RRCK in 1.0 μm pore size (Becton Dickinson. Cowley, UK)) at 4.2 x 10^4 cells/cm^2. Donor and acceptor solutions were prepared from HBSS containing HEPES at 20 mM, pH 7.4. Stock solutions of test compounds were prepared at 10mM DMSO and used to prepare donor solutions of 8 μM compound in 0.05% (v/v) DMSO. Apparent permeability (P_{app}) was determined in apical to basolateral (AB) direction in triplicate by incubating with compound for 2h at 37° C. Samples of the medium were analysed by liquid-chromatography tandem mass spectrometry (LC-MS/MS). P_{app} values were calculated according to the equation $P_{app} = (Q/t) \times 1/C_0 \times 1/A$, where Q is the sampled concentration in the acceptor compartment, t is the incubation time, C_0 is the initial concentration in the donor compartment, and A is the area of the filter of the transwell plate.

CACO2 Permeability

Caco-2 cells were cultured in an atmosphere of 5% CO_2 and 90% relative humidity in T75 flasks (Nunc) with 10 mL of media (10% foetal bovine serum (FBS), 1% non-essential amino acids (NEAA), 1% penicillin/streptomyocin). Cells were passaged 1:10 every five days, or when 80-90% confluent, using 0.25% trypsin-EDTA (Invitrogen, Gibco Laboratories). Cells were seeded onto each membrane of the

transwell permeable support 12-well plate insert to give 50,000 cells/well. The individual feeding tray wells received 1.5 mL of cell culture medium. The cell culture medium was changed every second day. Caco-2 cell monolayers were used for experimentation 21 days post seeding. Monolayers were incubated and continuously shaken. 100 µL samples were taken from the A and B compartments at 45 min, and the buffer volume replenished. After 90 min, 200 µL of compartment A and B was also collected for Lucifer Yellow (LY) measurements. Amount of LY permeated was measured on a Tecan plate reader (excitation 485 nm, emission 530 nm). At the conclusion of the experiment TEER was measured again to confirm the integrity of the Caco-2 monolayers (TEER >300 Ω cm^2). Acceptor and donor well concentrations were measured by LCMS, Shimadzu UHPLC system (LC-30AD, SIL-30AC, CBM-20A, SPD-M20A, CTO-20A). The permeability coefficient (P_{app}) values were calculated according to the equation:

$$P_{app} = \left(\frac{Q}{t}\right) \times \frac{1}{C_0} \times \frac{1}{A}$$

Where Q is the sampled concentration in the acceptor compartment, t is the incubation time, C_0 is the initial concentration in the donor compartment, and A is the area of the filter of the transwell plate.

Animals. Male Wistar rats (aged 8-9 weeks, 250±50 g) were bred at, and obtained from, the Australian Animal Resource Centre (Canning Vale, WA). Following Australian standard animal air transport, animals were housed at The University of Queensland Biological Resources (UQBR) Animal facility at The Australian Institute for Bioengineering and Nanotechnology at The University of Queensland, Australia. Animals were housed at appropriate temperature/pressure environments in a 12 h light/dark cycle

according to the standard of holding facility with food and water provided. All experiments were approved by the animal ethics committee of The University of Queensland. At period of at least 48 h habituation in the UQBR facility was provided prior to any experimental intervention. After experimentation, animals were humanely euthanised by CO_2 inhalation as stipulated by the ethical agreements.

Pharmacokinetic Measurements

Male Wistar rats (200-250 g) were surgically implanted with a jugular vein catheter and fasted overnight, as previously described (Lohman et al, PMID 22467762 Nielsen PMID23130644). Blood samples (200uL) were collected from the indwelling catheter of an unanaesthetised, unrestrained rat, 5 min prior to peptide administration (10 mg/kg p.o. in olive oil, or 1 mg/kg in neat DMSO). Oral dosing was performed by gavage (75mm soft-tipped polyethylene 18G), i.v. dosing was directly via the indwelling catheter using a 250 µL glass Hamilton syringe. Further blood samples were collected 5 min, 15 min, 30 min and at given time points from 1 to 8 h, post administration. Volumes collected were replaced with sterile heparinised saline (20 U/mL). Blood samples were centrifuge (8000 rpm, 5 min), plasma extracted and snap frozen on dry ice. Rats were fed after the 4h sample was collected.

Plasma compound concentration (C_p) was determined by extraction using simple acetonitrile (ACN)-based techniques. Briefly, thawed plasma was diluted 1:3 in neat ACN, vortexed, sonicated and then centrifuged (13K rpm, 5min RT). Spiked samples of known concentrations of peptide (i.e. 1ug-1ng/mL) were prepared in both ACN and clean plasma using the same technique, for standard curve

preparation. The supernatant of all centrifuged samples was used directly for LCMS analysis (ABSCIEX 4000 QTRAP Triple Quadrupole, Linear Ion-Trap LCMS mass spectrometer). Chromatography was carried out on a C18 column (Phenomenex, 5 μm, 2.1 × 50mm) using a linear gradient (2-80 % Buffer B in 12 minutes, flow rate 0.3 mL/min). Buffer A was 0.1 % formic acid (aq) and Buffer B was 90/10 acetonitrile/0.1 % formic acid (aq).

LCMS data was analyzed for area under curve (AUC) of peaks corresponding to both protonated (H^+; i.e. peptide MW+1) and sodium (Na^+; i.e. peptide MW+23) moieties. These peaks were summed to give a total AUC, which corresponded to the total concentration of compound in the original plasma sample. These AUC were compared to those obtained from the plasma standard samples for conversion to concentration. The peptide fraction absorbed (i.e. oral bioavailability; F%) was determined using standard arithmetic (eq. 1).

Eq 1. $F\% = 100 \cdot \frac{AUC\ p.o.}{AUC\ i.v.} \cdot \frac{Dose\ i.v.}{Dose\ p.o.}$.

CD Spectroscopy

CD measurements were performed using a Jasco model J-710 spectropolarimeter, which was routinely calibrated with (1*S*)-(+)-10-camphorsulfonic acid. A stock solution of variable concentrations (30-500 μM) of peptide was dissolved in 1 mL of 2,2,2-trifluoroethanol (TFE). Spectra were recorded at room temperature (298K), with a 0.1 cm Jasco quartz cell over the wavelength range 260-185 nm at 50 nm/min, with a bandwidth of 1.0 nm, response time of 1 s, resolution step width of 1 nm and sensitivity of 20-50 Mdeg. Each spectrum represents the average of 5 scans. Spectra were analysed using the spectral analysis software and smoothed using 'adaptive smoothing'

function. Aggregation of compound **2** and **3** was determined by changing CD line shapes in different peptide concentrations.

Concentrations were determined using the PULCON (Dreier, L. and G. Wider, *Concentration measurements by PULCON using X-filtered or 2D NMR spectra.* Magn Reson Chem, **2006**. 44 Spec No: p. S206-12.) NMR solutions for **1** and **3** were prepared in 550 μL of DMSO-d_6. 90° pulses were accurately determined and then 1D Spectra were acquired using the standard ^{1}H sequence with a ns= 32, d1= 30s. Spectra were also acquired for a 4.76 mM solution of L-histidine as the reference standard. The fully resolved, most downfield amide resonance was integrated and used to calculate the concentration from the equation:

$$c_u = c_R \frac{S_U T_U \vartheta_{360}^U n_R r g_R}{S_R T_R \vartheta_{360}^R n_U r g_U}$$

where *c* is the concentration, *S* is the integral(in absolute units)/number of protons, *T* is the temperature in Kelvin, θ_{360} is the 360° rf pulse, *n* is the number of scans, and *rg* is the receiver gain used for measuring the reference (R) and unknown (U) samples.

NMR Spectroscopy

The samples for the NMR analyses of **1**, **2** and **3** were prepared by dissolving the peptide (about 1 mg) in 550 μL of DMSO-d6. 1D and 2D ^{1}H-NMR spectra were recorded on a Bruker Avance DRX-600 spectrometer equipped with CryoProbe. 2D ^{1}H-spectra were recorded in phase-sensitive mode using time-proportional phase incrementation for quadrature detection in the *t*1 dimension. The 2D

experiments included TOCSY (standard Bruker mlevgpph pulse program), ROESY (standard Bruker roesygpph pulse program), ROESY and dqfCOSY (standard Bruker dqfcosygpph pulse program). TOCSY spectra were acquired over 6887 Hz with 4096 complex data points in *F2*, 512 increments in *F1* and 32 scans per increment. ROESY spectra were acquired over 6887 Hz with 4096 complex data points in *F2*, 512 increments in *F1* and 32 scans per increment. TOCSY and ROESY spectra were acquired with several isotropic mixing times of 80, 100 ms for TOCSY, 250-350 ms for ROESY. The variable temperature NMR experiments were performed over the range of 288-338K. Spectra were processed using Topspin (Bruker, Germany) software and ROE intensities were collected manually. The *t*1 dimensions of all 2D spectra were zero-filled to 1024 real data points with 90˚ phase-shifted QSINE bell window functions applied in both dimensions followed by Fourier transformation and fifth order polynomial baseline correction. ^{1}H chemical shifts were referenced to DSS (δ 0.00 ppm) in water. $^{3}J_{\mathrm{NHCH}\alpha}$ coupling constants were measured from 1D ^{1}H NMR using Topspin Program.

Structure Calculations

Solution structures for **3** were calculated from Phi (ϕ) dihedral restraints using XPLOR-NIH program with CHARMm forcefield. Backbone dihedral angle restraints were inferred from $^{3}J_{\mathrm{NHCH}\alpha}$ coupling constants in 1D spectra (recorded at 298K with 32 scan and 32K complex data points), ϕ was restrained to –80 ± 30° for $^{3}J_{\mathrm{NHCH}\alpha}$ = 7.2Hz (Pardi, A.; Billeter, M.; Wuthrich, K. *J. Mol. Biol.* **1984**, *180*, 741.). There was clearly no evidence at all for *cis*-amides about peptide bonds (i.e. no CHα-CHα (*i*, *i+1*) ROEs) in the NOESY spectra so all ψ-

angles were set to *trans* (ψ = 180°). Starting structures with randomised ϕ and ψ angles and extended side chains were generated using an *ab initio* simulated annealing protocol. The calculations were performed using the standard forcefield parameter set (PARALLHDG5.2.PRO) and topology file (TOPALLHDG5.2.PRO) in XPLOR-NIH with in house modifications to generated lactam bridges between lysine and aspartic acid residues. Refinement of structures was achieved using the conjugate gradient Powell algorithm with 4000 cycles of energy minimisation and a refined forcefield based on the program CHARMm (Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comput. Chem.* **1983**, *4,* 187). Structures were visualised with InsightII and Pymol and analysed for distance (>0.2Å) and dihedral angle (>5°) violations using noe.inp files. The final 20 lowest energy structures contained no distance violations (>0.2Å) or angle violations (>5°).

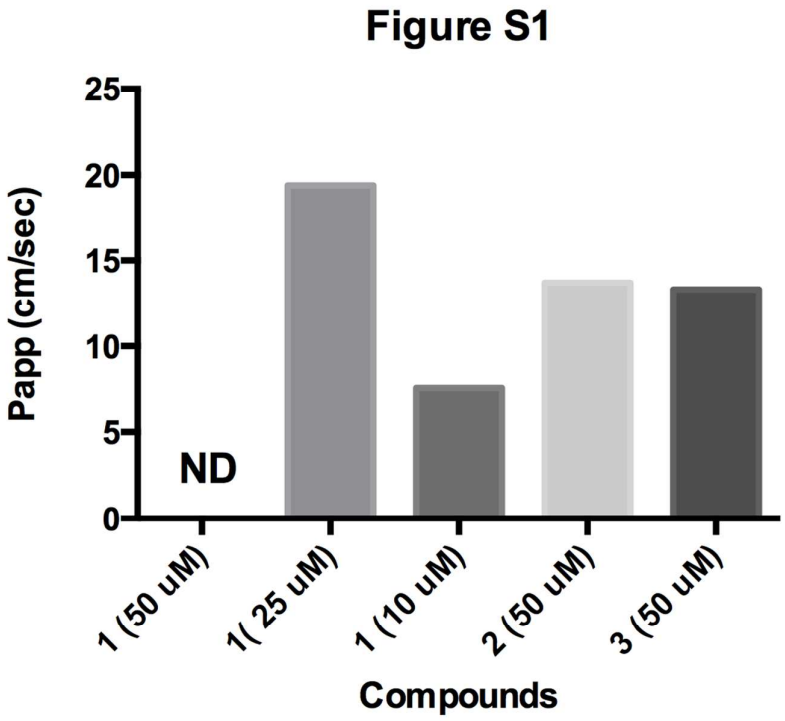

Figure S1. Permeability of **1** at 50, 25 and 10 µM; and **2** and **3** at 50 µM in CACO2 monolayers.

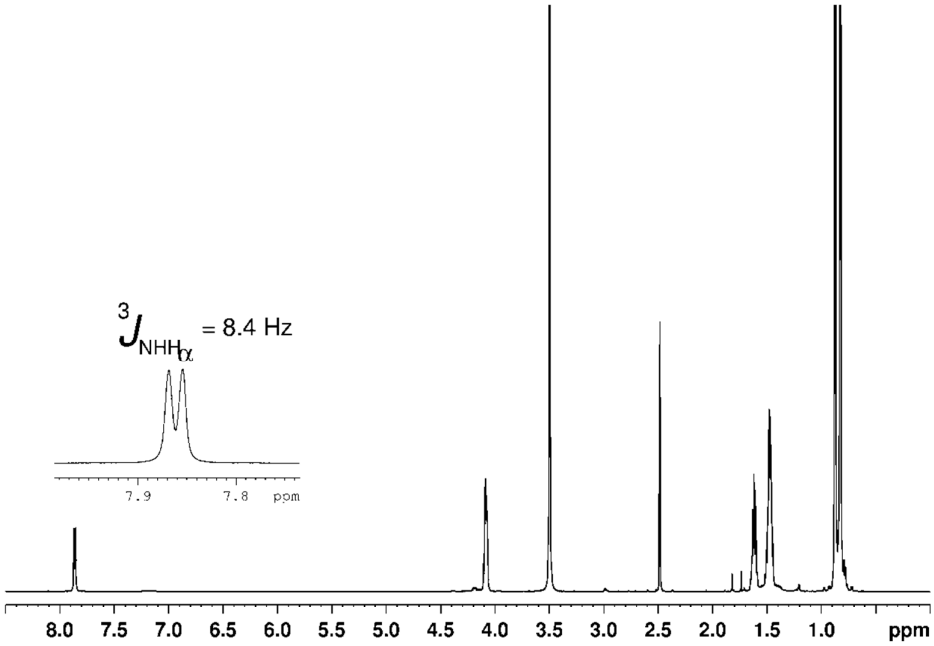

Figure S2. 600 MHz ^{1}H NMR spectrum for **1** in DMSO-d6 solution at 298K **.**

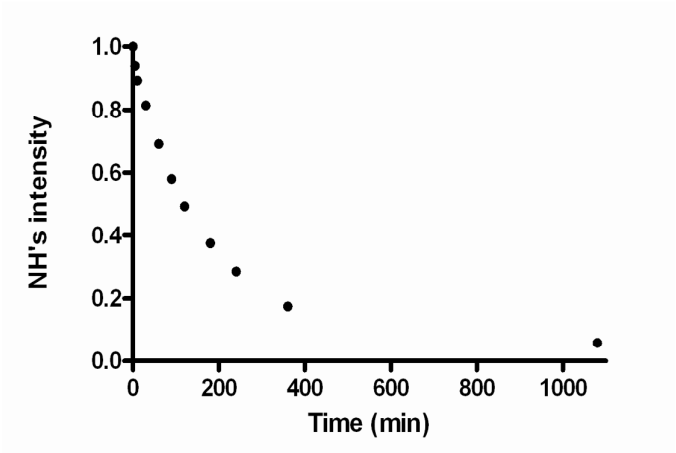

Figure S3. Amide proton H/D exchange plot for **1** in DMSO-d6 with t1/2 = 120 min.

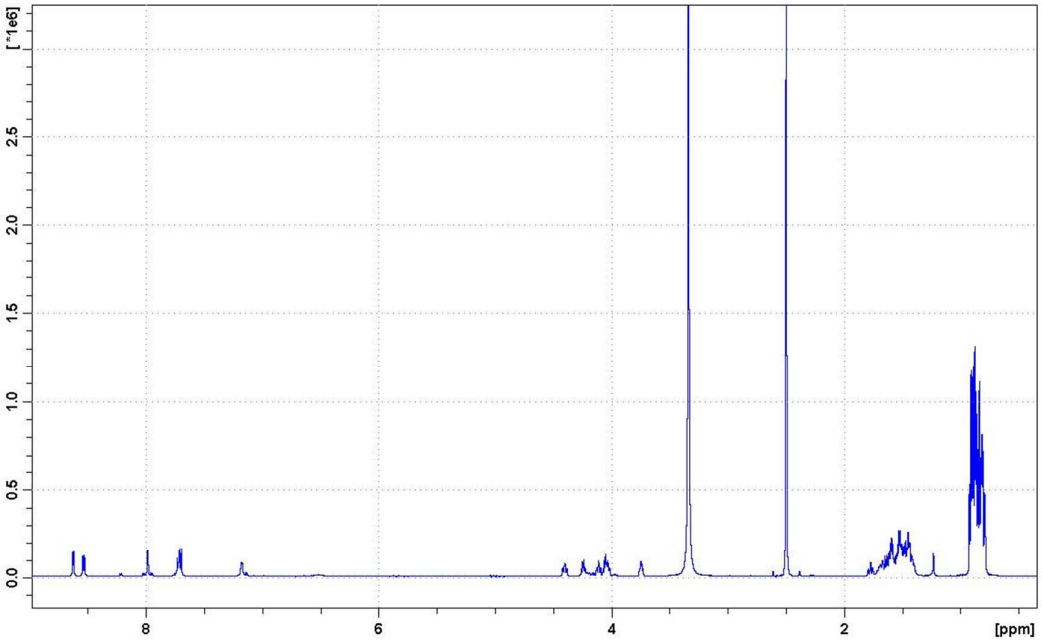

Figure S4. 600 MHz ^{1}H NMR spectrum for **2** in DMSO-d6 solution at 298K **.**

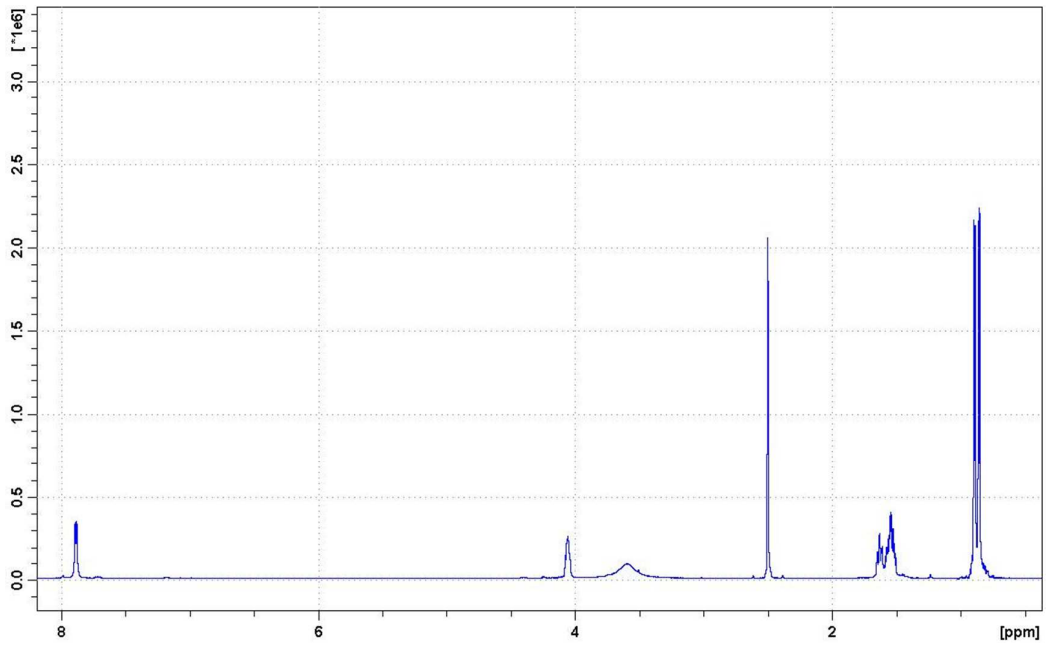

Figure S5. 600 MHz ^{1}H NMR spectrum for **3** in DMSO-$_{d6}$ solution at 298K **.**

TableS6: The amide proton's NMR Properties in DMSO-d_6. For **1** and **3** the average values are shown.

Peptide	$^3J_{NHHa}$ (Hz)	Temperature Coefficient (Δδ/K, ppb/K)	H/D Exchange, $t_{1/2}$ (min)
1 (C5L)	8.4	-2.6	120
2 (C6L-	5.2	-8.2	120
1d)	8.7	-5.4	>150
	4.3	-2.7	60
	8.7	-2.4	>150
	9.2	-4.4	>150
	4.9	1.7	150
3 (C6l)	7.2	-2.6	480

Table S1 Pharmacokinetic parameters in rats for compounds after intravenous (i.v.) or oral (p.o.) dose

	Dose (mg kg^{-1})	Route	C_{max}(ng mL)	T_{max}(min)	CL_p(mL $min^{-1}kg^{-1}$)	Vd_{ss}(L kg^{-1})	$AUC_{(0-N)}$(ng h mL^{-1})	$T_{1/2}$(min)	F(%)
1	1	i.v	N.A	N.A	13.1	0.36		N.A	
	10	p.o.	186.5	240	N.A	N.A	442	32	**4**
2	1	i.v	N.A	N.A	24.1	0.75		N.A	
	10	p.o.	174	180	N.A	N.A	642	69.4	**8.5**
3	1	i.v	N.A	N.A	4.7	0.19		N.A	
	10	p.o.	1900	180	N.A	N.A	6289	61	**17.5**
CSA	1	i.v	N.A	N.A	2.4	0.68		N.A	
	10	p.o.	2985	360	N.A	N.A	16487	133.1	**24.3**

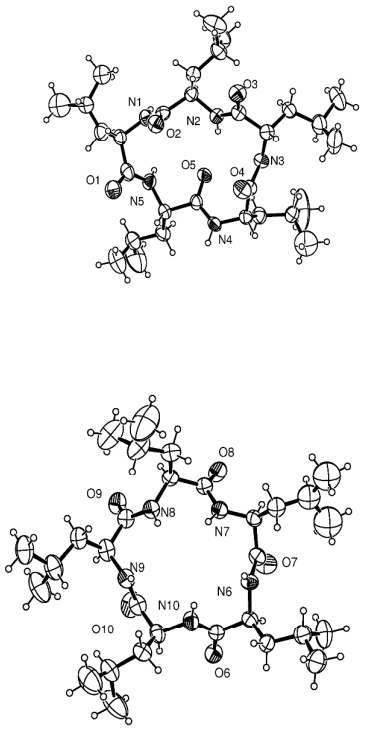

Figure S6: ORTEP drawing 1

Table S2. Crystal data and structure refinement for 1 (CCDC 1002286)

Identification code	700hh1	
Empirical formula	C_{30} H_{56} N_5 $O_{5.50}$	
Formula weight	574.80	
Temperature	293(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	$P2_1$ 2_1 2_1	
Unit cell dimensions	a = 10.8701(13) Å	α= 90°.
	b = 23.328(3) Å	β= 90°.
	c = 27.366(6) Å	γ = 90°.
Volume	6939(2) $Å^3$	
Z	8	

Density (calculated)	1.100 Mg/m^3
Absorption coefficient	0.608 mm^{-1}
F(000)	2520
Crystal size	0.5 x 0.4 x 0.02 mm^3
Theta range for data collection	3.23 to 62.46°.
Index ranges	-9<=h<=12, -24<=k<=26, -31<=l<=31
Reflections collected	20723
Independent reflections	6083 [R(int) = 0.0596]
Completeness to theta = 62.46°	99.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1 and 0.87979
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6083 / 9 / 721
Goodness-of-fit on F^2	1.056
Final R indices [I>2sigma(I)]	R1 = 0.0833, wR2 = 0.2220
R indices (all data)	R1 = 0.1119, wR2 = 0.2661
Absolute structure parameter	10(10)
Extinction coefficient	0.0013(2)
Largest diff. peak and hole	0.385 and -0.337 $e.Å^{-3}$

Table S3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **1**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2575(6)	4805(3)	3886(2)	83(2)
C(2)	2876(6)	4171(3)	3964(2)	72(2)
C(3)	3834(8)	4091(4)	4370(3)	95(2)
C(4)	3934(19)	3560(9)	4591(7)	88(7)
C(5)	4540(20)	3064(9)	4303(7)	118(7)
C(6)	4370(40)	3525(14)	5106(9)	187(13)
C(4')	3904(18)	3387(11)	4526(7)	112(8)
C(5')	5160(20)	3320(13)	4784(10)	174(11)
C(6')	2927(19)	3367(10)	4907(8)	139(8)
C(7)	2509(5)	3808(3)	3151(2)	66(1)
C(8)	2979(5)	3552(3)	2675(2)	65(1)
C(9)	4241(6)	3260(3)	2694(2)	76(2)
C(10)	4546(7)	2911(4)	2236(3)	92(2)
C(11)	5888(8)	2735(5)	2245(4)	116(3)
C(12)	3708(10)	2395(4)	2192(4)	135(4)
C(13)	2302(5)	3946(3)	1887(2)	67(1)
C(14)	2602(5)	4368(3)	1481(2)	66(1)
C(15)	3452(7)	4077(3)	1117(2)	77(2)
C(16)	3830(9)	4421(4)	665(3)	107(3)
C(17)	2779(13)	4678(7)	413(3)	163(5)
C(18)	4595(12)	4042(6)	340(4)	145(4)
C(19)	2378(5)	5312(3)	1862(2)	66(1)
C(20)	2935(6)	5885(3)	2015(2)	69(2)
C(21)	4233(7)	6011(3)	1863(2)	83(2)
C(22)	4495(8)	6077(3)	1318(2)	86(2)
C(23)	3842(17)	6574(8)	1105(6)	196(6)
C(24)	5809(13)	6146(11)	1207(5)	274(15)
C(25)	3261(5)	5548(3)	2840(2)	65(1)
C(26)	3124(6)	5647(3)	3390(2)	69(2)
C(27)	3978(8)	6130(3)	3549(2)	87(2)
C(28)	4059(10)	6222(4)	4098(3)	111(3)
C(29)	2884(12)	6440(7)	4299(4)	159(5)
C(30)	5088(16)	6660(8)	4198(5)	221(9)

N(1)	3278(5)	3898(2)	3516(2)	70(1)
N(2)	2970(4)	3998(2)	2296(2)	64(1)
N(3)	3096(4)	4916(2)	1655(2)	63(1)
N(4)	2792(5)	5939(2)	2543(2)	72(1)
N(5)	3393(5)	5092(2)	3615(2)	73(1)
O(1)	1666(6)	5020(3)	4068(2)	116(2)
O(2)	1399(4)	3915(2)	3191(2)	81(1)
O(3)	1535(4)	3568(2)	1821(2)	83(1)
O(4)	1252(4)	5229(2)	1913(2)	90(1)
O(5)	3843(4)	5125(2)	2690(2)	74(1)
C(31)	9005(6)	2383(3)	2004(2)	68(2)
C(32)	9169(6)	2625(3)	1495(2)	68(1)
C(33)	10425(6)	2449(3)	1292(2)	75(2)
C(34)	10699(8)	2630(4)	772(3)	95(2)
C(35)	11987(11)	2444(5)	643(4)	139(4)
C(36)	9768(12)	2401(6)	415(3)	144(4)
C(37)	7883(6)	3468(3)	1318(2)	74(2)
C(38)	7725(6)	4111(3)	1347(2)	71(2)
C(39)	8660(16)	4445(7)	1043(5)	91(6)
C(40)	8422(17)	4538(8)	551(7)	142(6)
C(41)	8320(30)	4074(12)	263(10)	232(13)
C(42)	9250(30)	5017(11)	328(9)	202(10)
C(39')	8730(30)	4504(13)	1142(12)	101(13)
C(40')	8560(20)	5005(11)	877(9)	125(11)
C(41')	7680(30)	4998(16)	531(13)	154(13)
C(42')	9790(30)	5270(13)	697(12)	138(12)
C(43)	6712(5)	4552(3)	2059(2)	70(2)
C(44)	6881(6)	4770(3)	2571(2)	75(2)
C(45)	7636(8)	5327(3)	2544(3)	92(2)
C(46)	8231(11)	5536(5)	3011(4)	130(4)
C(47)	9075(19)	6044(7)	2896(7)	234(10)
C(48)	7396(16)	5650(7)	3418(5)	191(7)
C(49)	6997(6)	4122(3)	3279(2)	77(2)
C(50)	7806(6)	3739(4)	3593(2)	87(2)
C(51)	8488(7)	4106(4)	3975(3)	93(2)
C(52)	9199(8)	3769(5)	4358(3)	113(3)
C(53)	9727(9)	4196(5)	4732(3)	128(4)
C(54)	8484(13)	3297(6)	4618(4)	167(6)

C(55)	8355(7)	2843(3)	3172(3)	84(2)
C(56)	9274(7)	2495(3)	2893(2)	79(2)
C(57)	10544(7)	2470(3)	3125(3)	84(2)
C(58)	10546(9)	2183(4)	3621(3)	107(3)
C(59)	10424(15)	1540(5)	3582(5)	176(6)
C(60)	11706(13)	2314(7)	3888(5)	171(5)
N(6)	8979(5)	3250(2)	1478(2)	68(1)
N(7)	7660(4)	4284(2)	1861(2)	75(1)
N(8)	7482(4)	4341(2)	2883(2)	74(1)
N(9)	8656(5)	3386(2)	3313(2)	76(1)
N(10)	9349(6)	2700(2)	2384(2)	85(2)
O(6)	8569(5)	1894(2)	2053(2)	86(1)
O(7)	7069(5)	3167(2)	1168(3)	108(2)
O(8)	5759(4)	4637(3)	1832(2)	105(2)
O(9)	5908(4)	4211(3)	3411(2)	93(2)
O(10)	7348(6)	2644(3)	3277(3)	129(2)
O(11)	-71(4)	4377(3)	2455(2)	103(2)

Table S4. Bond lengths [Å] and angles [°] for 1.

C(1)-O(1)	1.214(8)
C(1)-N(5)	1.339(8)
C(1)-C(2)	1.530(10)
C(2)-N(1)	1.451(7)
C(2)-C(3)	1.533(11)
C(2)-H(2)	0.9800
C(3)-C(4)	1.382(19)
C(3)-C(4')	1.70(3)
C(3)-H(3A)	0.9734
C(3)-H(3B)	0.9730
C(4)-C(6)	1.49(2)
C(4)-C(5)	1.55(2)
C(4)-H(4)	0.9800
C(5)-H(5A)	0.9600
C(5)-H(5B)	0.9600
C(5)-H(5C)	0.9600
C(6)-H(6A)	0.9600
C(6)-H(6B)	0.9600
C(6)-H(6C)	0.9600
C(4')-C(6')	1.49(2)
C(4')-C(5')	1.55(2)
C(4')-H(4')	0.9800
C(5')-H(5D)	0.9600
C(5')-H(5E)	0.9600
C(5')-H(5F)	0.9600
C(6')-H(6D)	0.9600
C(6')-H(6E)	0.9600
C(6')-H(6F)	0.9600
C(7)-O(2)	1.238(7)
C(7)-N(1)	1.320(8)
C(7)-C(8)	1.520(8)
C(8)-N(2)	1.471(7)
C(8)-C(9)	1.532(9)
C(8)-H(8)	0.9800
C(9)-C(10)	1.530(10)
C(9)-H(9A)	0.9700

C(9)-H(9B)	0.9700
C(10)-C(12)	1.515(13)
C(10)-C(11)	1.516(12)
C(10)-H(10)	0.9800
C(11)-H(11A)	0.9600
C(11)-H(11B)	0.9600
C(11)-H(11C)	0.9600
C(12)-H(12A)	0.9600
C(12)-H(12B)	0.9600
C(12)-H(12C)	0.9600
C(13)-O(3)	1.227(7)
C(13)-N(2)	1.339(8)
C(13)-C(14)	1.520(9)
C(14)-N(3)	1.466(7)
C(14)-C(15)	1.519(9)
C(14)-H(14)	0.9800
C(15)-C(16)	1.533(11)
C(15)-H(15A)	0.9700
C(15)-H(15B)	0.9700
C(16)-C(17)	1.462(15)
C(16)-C(18)	1.504(13)
C(16)-H(16)	0.9800
C(17)-H(17A)	0.9600
C(17)-H(17B)	0.9600
C(17)-H(17C)	0.9600
C(18)-H(18A)	0.9600
C(18)-H(18B)	0.9600
C(18)-H(18C)	0.9600
C(19)-O(4)	1.247(7)
C(19)-N(3)	1.338(7)
C(19)-C(20)	1.524(9)
C(20)-N(4)	1.460(7)
C(20)-C(21)	1.500(10)
C(20)-H(20)	0.9800
C(21)-C(22)	1.527(9)
C(21)-H(21A)	0.9700
C(21)-H(21B)	0.9700
C(22)-C(24)	1.470(15)

C(22)-C(23)	1.478(18)
C(22)-H(22)	0.9800
C(23)-H(23A)	0.9600
C(23)-H(23B)	0.9600
C(23)-H(23C)	0.9600
C(24)-H(24A)	0.9600
C(24)-H(24B)	0.9600
C(24)-H(24C)	0.9600
C(25)-O(5)	1.242(7)
C(25)-N(4)	1.324(8)
C(25)-C(26)	1.528(8)
C(26)-N(5)	1.462(8)
C(26)-C(27)	1.524(10)
C(26)-H(26)	0.9800
C(27)-C(28)	1.520(10)
C(27)-H(27A)	0.9700
C(27)-H(27B)	0.9700
C(28)-C(29)	1.479(15)
C(28)-C(30)	1.539(16)
C(28)-H(28)	0.9800
C(29)-H(29A)	0.9600
C(29)-H(29B)	0.9600
C(29)-H(29C)	0.9600
C(30)-H(30A)	0.9600
C(30)-H(30B)	0.9600
C(30)-H(30C)	0.9600
N(1)-H(1)	0.8600
N(2)-H(2A)	0.8600
N(3)-H(3)	0.8600
N(4)-H(4A)	0.8600
N(5)-H(5)	0.8600
C(31)-O(6)	1.244(7)
C(31)-N(10)	1.329(8)
C(31)-C(32)	1.513(8)
C(32)-N(6)	1.472(7)
C(32)-C(33)	1.529(9)
C(32)-H(32)	0.9800
C(33)-C(34)	1.514(10)

C(33)-H(33A)	0.9700
C(33)-H(33B)	0.9700
C(34)-C(36)	1.505(13)
C(34)-C(35)	1.507(13)
C(34)-H(34)	0.9800
C(35)-H(35A)	0.9600
C(35)-H(35B)	0.9600
C(35)-H(35C)	0.9600
C(36)-H(36A)	0.9600
C(36)-H(36B)	0.9600
C(36)-H(36C)	0.9600
C(37)-O(7)	1.202(8)
C(37)-N(6)	1.367(8)
C(37)-C(38)	1.512(10)
C(38)-N(7)	1.465(8)
C(38)-C(39)	1.527(15)
C(38)-C(39')	1.53(3)
C(38)-H(38)	0.9800
C(39)-C(40)	1.388(19)
C(39)-H(39A)	0.9700
C(39)-H(39B)	0.9700
C(40)-C(41)	1.34(3)
C(40)-C(42)	1.56(2)
C(40)-H(40A)	0.9800
C(41)-H(41A)	0.9600
C(41)-H(41B)	0.9600
C(41)-H(41C)	0.9600
C(42)-H(42A)	0.9600
C(42)-H(42B)	0.9600
C(42)-H(42C)	0.9600
C(39')-C(40')	1.389(19)
C(39')-H(39C)	0.9700
C(39')-H(39D)	0.9700
C(40')-C(41')	1.34(3)
C(40')-C(42')	1.56(2)
C(40')-H(40B)	0.9800
C(41')-H(41D)	0.9600
C(41')-H(41E)	0.9600

C(41')-H(41F)	0.9600
C(42')-H(42D)	0.9600
C(42')-H(42E)	0.9600
C(42')-H(42F)	0.9600
C(43)-O(8)	1.223(7)
C(43)-N(7)	1.321(8)
C(43)-C(44)	1.503(9)
C(44)-N(8)	1.469(8)
C(44)-C(45)	1.537(10)
C(44)-H(44)	0.9800
C(45)-C(46)	1.513(13)
C(45)-H(45A)	0.9700
C(45)-H(45B)	0.9700
C(46)-C(48)	1.460(17)
C(46)-C(47)	1.532(18)
C(46)-H(46)	0.9800
C(47)-H(47A)	0.9600
C(47)-H(47B)	0.9600
C(47)-H(47C)	0.9600
C(48)-H(48A)	0.9600
C(48)-H(48B)	0.9600
C(48)-H(48C)	0.9600
C(49)-O(9)	1.254(8)
C(49)-N(8)	1.309(8)
C(49)-C(50)	1.519(10)
C(50)-N(9)	1.455(9)
C(50)-C(51)	1.543(11)
C(50)-H(50)	0.9800
C(51)-C(52)	1.520(12)
C(51)-H(51A)	0.9700
C(51)-H(51B)	0.9700
C(52)-C(54)	1.525(14)
C(52)-C(53)	1.539(13)
C(52)-H(52)	0.9800
C(53)-H(53A)	0.9600
C(53)-H(53B)	0.9600
C(53)-H(53C)	0.9600
C(54)-H(54A)	0.9600

C(54)-H(54B)	0.9600
C(54)-H(54C)	0.9600
C(55)-O(10)	1.224(9)
C(55)-N(9)	1.363(9)
C(55)-C(56)	1.496(11)
C(56)-N(10)	1.475(8)
C(56)-C(57)	1.520(10)
C(56)-H(56)	0.9800
C(57)-C(58)	1.513(10)
C(57)-H(57A)	0.9700
C(57)-H(57B)	0.9700
C(58)-C(60)	1.489(15)
C(58)-C(59)	1.509(15)
C(58)-H(58)	0.9800
C(59)-H(59A)	0.9600
C(59)-H(59B)	0.9600
C(59)-H(59C)	0.9600
C(60)-H(60A)	0.9600
C(60)-H(60B)	0.9600
C(60)-H(60C)	0.9600
N(6)-H(6)	0.8600
N(7)-H(7)	0.8600
N(8)-H(8A)	0.8600
N(9)-H(9)	0.8600
N(10)-H(10A)	0.8600
O(11)-H(11D)	0.9004
O(11)-H(11E)	0.9001

O(1)-C(1)-N(5)	124.0(7)
O(1)-C(1)-C(2)	121.1(6)
N(5)-C(1)-C(2)	114.9(6)
N(1)-C(2)-C(1)	111.7(5)
N(1)-C(2)-C(3)	110.7(6)
C(1)-C(2)-C(3)	111.3(6)
N(1)-C(2)-H(2)	107.6
C(1)-C(2)-H(2)	107.6
C(3)-C(2)-H(2)	107.6
C(4)-C(3)-C(2)	118.6(11)

C(4)-C(3)-C(4')	11.5(12)
C(2)-C(3)-C(4')	109.2(9)
C(4)-C(3)-H(3A)	105.9
C(2)-C(3)-H(3A)	108.6
C(4')-C(3)-H(3A)	104.4
C(4)-C(3)-H(3B)	107.3
C(2)-C(3)-H(3B)	108.6
C(4')-C(3)-H(3B)	118.1
H(3A)-C(3)-H(3B)	107.4
C(3)-C(4)-C(6)	119(2)
C(3)-C(4)-C(5)	118.8(14)
C(6)-C(4)-C(5)	107.9(13)
C(3)-C(4)-H(4)	102.6
C(6)-C(4)-H(4)	102.6
C(5)-C(4)-H(4)	102.6
C(4)-C(5)-H(5A)	109.5
C(4)-C(5)-H(5B)	109.5
H(5A)-C(5)-H(5B)	109.5
C(4)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5
H(5B)-C(5)-H(5C)	109.5
C(4)-C(6)-H(6A)	109.5
C(4)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	109.5
C(4)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
C(6')-C(4')-C(5')	107.8(13)
C(6')-C(4')-C(3)	100.1(17)
C(5')-C(4')-C(3)	104.7(19)
C(6')-C(4')-H(4')	114.3
C(5')-C(4')-H(4')	114.3
C(3)-C(4')-H(4')	114.3
C(4')-C(5')-H(5D)	109.5
C(4')-C(5')-H(5E)	109.5
H(5D)-C(5')-H(5E)	109.5
C(4')-C(5')-H(5F)	109.5
H(5D)-C(5')-H(5F)	109.5

H(5E)-C(5')-H(5F)	109.5
C(4')-C(6')-H(6D)	109.5
C(4')-C(6')-H(6E)	109.5
H(6D)-C(6')-H(6E)	109.5
C(4')-C(6')-H(6F)	109.5
H(6D)-C(6')-H(6F)	109.5
H(6E)-C(6')-H(6F)	109.5
O(2)-C(7)-N(1)	121.2(6)
O(2)-C(7)-C(8)	118.9(6)
N(1)-C(7)-C(8)	119.9(5)
N(2)-C(8)-C(7)	108.9(5)
N(2)-C(8)-C(9)	110.1(5)
C(7)-C(8)-C(9)	116.6(5)
N(2)-C(8)-H(8)	106.9
C(7)-C(8)-H(8)	106.9
C(9)-C(8)-H(8)	106.9
C(10)-C(9)-C(8)	113.8(6)
C(10)-C(9)-H(9A)	108.8
C(8)-C(9)-H(9A)	108.8
C(10)-C(9)-H(9B)	108.8
C(8)-C(9)-H(9B)	108.8
H(9A)-C(9)-H(9B)	107.7
C(12)-C(10)-C(11)	111.3(8)
C(12)-C(10)-C(9)	110.9(7)
C(11)-C(10)-C(9)	109.8(7)
C(12)-C(10)-H(10)	108.2
C(11)-C(10)-H(10)	108.2
C(9)-C(10)-H(10)	108.2
C(10)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(10)-C(12)-H(12A)	109.5
C(10)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(10)-C(12)-H(12C)	109.5

H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
O(3)-C(13)-N(2)	123.9(6)
O(3)-C(13)-C(14)	120.1(5)
N(2)-C(13)-C(14)	115.8(5)
N(3)-C(14)-C(15)	112.3(5)
N(3)-C(14)-C(13)	113.9(5)
C(15)-C(14)-C(13)	108.7(5)
N(3)-C(14)-H(14)	107.2
C(15)-C(14)-H(14)	107.2
C(13)-C(14)-H(14)	107.2
C(14)-C(15)-C(16)	117.2(6)
C(14)-C(15)-H(15A)	108.0
C(16)-C(15)-H(15A)	108.0
C(14)-C(15)-H(15B)	108.0
C(16)-C(15)-H(15B)	108.0
H(15A)-C(15)-H(15B)	107.2
C(17)-C(16)-C(18)	113.2(9)
C(17)-C(16)-C(15)	112.7(8)
C(18)-C(16)-C(15)	108.5(8)
C(17)-C(16)-H(16)	107.4
C(18)-C(16)-H(16)	107.4
C(15)-C(16)-H(16)	107.4
C(16)-C(17)-H(17A)	109.5
C(16)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(16)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(16)-C(18)-H(18A)	109.5
C(16)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(16)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
O(4)-C(19)-N(3)	120.8(6)
O(4)-C(19)-C(20)	119.8(6)
N(3)-C(19)-C(20)	119.3(5)

N(4)-C(20)-C(21)	110.9(5)
N(4)-C(20)-C(19)	107.7(5)
C(21)-C(20)-C(19)	118.1(5)
N(4)-C(20)-H(20)	106.5
C(21)-C(20)-H(20)	106.5
C(19)-C(20)-H(20)	106.5
C(20)-C(21)-C(22)	117.7(6)
C(20)-C(21)-H(21A)	107.9
C(22)-C(21)-H(21A)	107.9
C(20)-C(21)-H(21B)	107.9
C(22)-C(21)-H(21B)	107.9
H(21A)-C(21)-H(21B)	107.2
C(24)-C(22)-C(23)	107.5(13)
C(24)-C(22)-C(21)	113.1(8)
C(23)-C(22)-C(21)	112.0(9)
C(24)-C(22)-H(22)	108.0
C(23)-C(22)-H(22)	108.0
C(21)-C(22)-H(22)	108.0
C(22)-C(23)-H(23A)	109.5
C(22)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(22)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(22)-C(24)-H(24A)	109.5
C(22)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(22)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
O(5)-C(25)-N(4)	122.7(5)
O(5)-C(25)-C(26)	119.6(6)
N(4)-C(25)-C(26)	117.6(5)
N(5)-C(26)-C(27)	114.3(6)
N(5)-C(26)-C(25)	105.2(5)
C(27)-C(26)-C(25)	109.5(5)
N(5)-C(26)-H(26)	109.2
C(27)-C(26)-H(26)	109.2

C(25)-C(26)-H(26)	109.2
C(28)-C(27)-C(26)	115.1(7)
C(28)-C(27)-H(27A)	108.5
C(26)-C(27)-H(27A)	108.5
C(28)-C(27)-H(27B)	108.5
C(26)-C(27)-H(27B)	108.5
H(27A)-C(27)-H(27B)	107.5
C(29)-C(28)-C(27)	111.4(9)
C(29)-C(28)-C(30)	109.5(10)
C(27)-C(28)-C(30)	108.1(9)
C(29)-C(28)-H(28)	109.3
C(27)-C(28)-H(28)	109.3
C(30)-C(28)-H(28)	109.3
C(28)-C(29)-H(29A)	109.5
C(28)-C(29)-H(29B)	109.5
H(29A)-C(29)-H(29B)	109.5
C(28)-C(29)-H(29C)	109.5
H(29A)-C(29)-H(29C)	109.5
H(29B)-C(29)-H(29C)	109.5
C(28)-C(30)-H(30A)	109.5
C(28)-C(30)-H(30B)	109.5
H(30A)-C(30)-H(30B)	109.5
C(28)-C(30)-H(30C)	109.5
H(30A)-C(30)-H(30C)	109.5
H(30B)-C(30)-H(30C)	109.5
C(7)-N(1)-C(2)	121.3(5)
C(7)-N(1)-H(1)	119.4
C(2)-N(1)-H(1)	119.4
C(13)-N(2)-C(8)	121.9(5)
C(13)-N(2)-H(2A)	119.0
C(8)-N(2)-H(2A)	119.0
C(19)-N(3)-C(14)	121.8(5)
C(19)-N(3)-H(3)	119.1
C(14)-N(3)-H(3)	119.1
C(25)-N(4)-C(20)	120.5(5)
C(25)-N(4)-H(4A)	119.7
C(20)-N(4)-H(4A)	119.7
C(1)-N(5)-C(26)	123.0(6)

C(1)-N(5)-H(5)	118.5
C(26)-N(5)-H(5)	118.5
O(6)-C(31)-N(10)	122.2(6)
O(6)-C(31)-C(32)	119.1(5)
N(10)-C(31)-C(32)	118.7(5)
N(6)-C(32)-C(31)	112.4(5)
N(6)-C(32)-C(33)	112.3(5)
C(31)-C(32)-C(33)	109.8(5)
N(6)-C(32)-H(32)	107.3
C(31)-C(32)-H(32)	107.3
C(33)-C(32)-H(32)	107.3
C(34)-C(33)-C(32)	116.2(6)
C(34)-C(33)-H(33A)	108.2
C(32)-C(33)-H(33A)	108.2
C(34)-C(33)-H(33B)	108.2
C(32)-C(33)-H(33B)	108.2
H(33A)-C(33)-H(33B)	107.4
C(36)-C(34)-C(35)	111.7(9)
C(36)-C(34)-C(33)	112.3(7)
C(35)-C(34)-C(33)	108.9(7)
C(36)-C(34)-H(34)	107.9
C(35)-C(34)-H(34)	107.9
C(33)-C(34)-H(34)	107.9
C(34)-C(35)-H(35A)	109.5
C(34)-C(35)-H(35B)	109.5
H(35A)-C(35)-H(35B)	109.5
C(34)-C(35)-H(35C)	109.5
H(35A)-C(35)-H(35C)	109.5
H(35B)-C(35)-H(35C)	109.5
C(34)-C(36)-H(36A)	109.5
C(34)-C(36)-H(36B)	109.5
H(36A)-C(36)-H(36B)	109.5
C(34)-C(36)-H(36C)	109.5
H(36A)-C(36)-H(36C)	109.5
H(36B)-C(36)-H(36C)	109.5
O(7)-C(37)-N(6)	122.3(6)
O(7)-C(37)-C(38)	120.8(6)
N(6)-C(37)-C(38)	116.9(6)

N(7)-C(38)-C(37)	109.2(5)
N(7)-C(38)-C(39)	114.5(9)
C(37)-C(38)-C(39)	113.7(8)
N(7)-C(38)-C(39')	102.7(15)
C(37)-C(38)-C(39')	119.6(15)
C(39)-C(38)-C(39')	11.8(17)
N(7)-C(38)-H(38)	107.1
C(37)-C(38)-H(38)	107.0
C(39)-C(38)-H(38)	104.8
C(39')-C(38)-H(38)	110.7
C(40)-C(39)-C(38)	119.0(14)
C(40)-C(39)-H(39A)	107.6
C(38)-C(39)-H(39A)	107.6
C(40)-C(39)-H(39B)	107.6
C(38)-C(39)-H(39B)	107.6
H(39A)-C(39)-H(39B)	107.0
C(41)-C(40)-C(39)	117.1(18)
C(41)-C(40)-C(42)	113.3(19)
C(39)-C(40)-C(42)	112.6(15)
C(41)-C(40)-H(40A)	104.0
C(39)-C(40)-H(40A)	104.0
C(42)-C(40)-H(40A)	104.0
C(40)-C(41)-H(41A)	109.5
C(40)-C(41)-H(41B)	109.5
H(41A)-C(41)-H(41B)	109.5
C(40)-C(41)-H(41C)	109.5
H(41A)-C(41)-H(41C)	109.5
H(41B)-C(41)-H(41C)	109.5
C(40)-C(42)-H(42A)	109.5
C(40)-C(42)-H(42B)	109.5
H(42A)-C(42)-H(42B)	109.5
C(40)-C(42)-H(42C)	109.5
H(42A)-C(42)-H(42C)	109.5
H(42B)-C(42)-H(42C)	109.5
C(40')-C(39')-C(38)	127(2)
C(40')-C(39')-H(39C)	105.6
C(38)-C(39')-H(39C)	105.6
C(40')-C(39')-H(39D)	105.6

C(38)-C(39')-H(39D)	105.6
H(39C)-C(39')-H(39D)	106.1
C(41')-C(40')-C(39')	117.0(18)
C(41')-C(40')-C(42')	113.2(19)
C(39')-C(40')-C(42')	112.5(15)
C(41')-C(40')-H(40B)	104.1
C(39')-C(40')-H(40B)	104.1
C(42')-C(40')-H(40B)	104.1
C(40')-C(41')-H(41D)	109.5
C(40')-C(41')-H(41E)	109.5
H(41D)-C(41')-H(41E)	109.5
C(40')-C(41')-H(41F)	109.5
H(41D)-C(41')-H(41F)	109.5
H(41E)-C(41')-H(41F)	109.5
C(40')-C(42')-H(42D)	109.5
C(40')-C(42')-H(42E)	109.5
H(42D)-C(42')-H(42E)	109.5
C(40')-C(42')-H(42F)	109.5
H(42D)-C(42')-H(42F)	109.5
H(42E)-C(42')-H(42F)	109.5
O(8)-C(43)-N(7)	122.0(6)
O(8)-C(43)-C(44)	121.4(6)
N(7)-C(43)-C(44)	116.6(5)
N(8)-C(44)-C(43)	111.5(5)
N(8)-C(44)-C(45)	111.5(5)
C(43)-C(44)-C(45)	107.8(6)
N(8)-C(44)-H(44)	108.7
C(43)-C(44)-H(44)	108.7
C(45)-C(44)-H(44)	108.7
C(46)-C(45)-C(44)	117.4(7)
C(46)-C(45)-H(45A)	108.0
C(44)-C(45)-H(45A)	108.0
C(46)-C(45)-H(45B)	108.0
C(44)-C(45)-H(45B)	108.0
H(45A)-C(45)-H(45B)	107.2
C(48)-C(46)-C(45)	115.9(10)
C(48)-C(46)-C(47)	112.8(11)
C(45)-C(46)-C(47)	109.3(11)

C(48)-C(46)-H(46)	106.0
C(45)-C(46)-H(46)	106.0
C(47)-C(46)-H(46)	106.0
C(46)-C(47)-H(47A)	109.5
C(46)-C(47)-H(47B)	109.5
H(47A)-C(47)-H(47B)	109.5
C(46)-C(47)-H(47C)	109.5
H(47A)-C(47)-H(47C)	109.5
H(47B)-C(47)-H(47C)	109.5
C(46)-C(48)-H(48A)	109.5
C(46)-C(48)-H(48B)	109.5
H(48A)-C(48)-H(48B)	109.5
C(46)-C(48)-H(48C)	109.5
H(48A)-C(48)-H(48C)	109.5
H(48B)-C(48)-H(48C)	109.5
O(9)-C(49)-N(8)	123.5(7)
O(9)-C(49)-C(50)	118.8(6)
N(8)-C(49)-C(50)	117.7(6)
N(9)-C(50)-C(49)	113.8(5)
N(9)-C(50)-C(51)	111.5(6)
C(49)-C(50)-C(51)	109.5(7)
N(9)-C(50)-H(50)	107.2
C(49)-C(50)-H(50)	107.2
C(51)-C(50)-H(50)	107.2
C(52)-C(51)-C(50)	115.1(8)
C(52)-C(51)-H(51A)	108.5
C(50)-C(51)-H(51A)	108.5
C(52)-C(51)-H(51B)	108.5
C(50)-C(51)-H(51B)	108.5
H(51A)-C(51)-H(51B)	107.5
C(51)-C(52)-C(54)	115.9(8)
C(51)-C(52)-C(53)	108.2(8)
C(54)-C(52)-C(53)	110.4(8)
C(51)-C(52)-H(52)	107.3
C(54)-C(52)-H(52)	107.3
C(53)-C(52)-H(52)	107.3
C(52)-C(53)-H(53A)	109.5
C(52)-C(53)-H(53B)	109.5

H(53A)-C(53)-H(53B)	109.5
C(52)-C(53)-H(53C)	109.5
H(53A)-C(53)-H(53C)	109.5
H(53B)-C(53)-H(53C)	109.5
C(52)-C(54)-H(54A)	109.5
C(52)-C(54)-H(54B)	109.5
H(54A)-C(54)-H(54B)	109.5
C(52)-C(54)-H(54C)	109.5
H(54A)-C(54)-H(54C)	109.5
H(54B)-C(54)-H(54C)	109.5
O(10)-C(55)-N(9)	120.1(8)
O(10)-C(55)-C(56)	120.6(7)
N(9)-C(55)-C(56)	119.2(6)
N(10)-C(56)-C(55)	110.1(6)
N(10)-C(56)-C(57)	110.9(6)
C(55)-C(56)-C(57)	114.5(6)
N(10)-C(56)-H(56)	107.0
C(55)-C(56)-H(56)	107.0
C(57)-C(56)-H(56)	107.0
C(58)-C(57)-C(56)	113.1(6)
C(58)-C(57)-H(57A)	109.0
C(56)-C(57)-H(57A)	109.0
C(58)-C(57)-H(57B)	109.0
C(56)-C(57)-H(57B)	109.0
H(57A)-C(57)-H(57B)	107.8
C(60)-C(58)-C(59)	108.2(10)
C(60)-C(58)-C(57)	110.5(9)
C(59)-C(58)-C(57)	112.1(8)
C(60)-C(58)-H(58)	108.6
C(59)-C(58)-H(58)	108.6
C(57)-C(58)-H(58)	108.6
C(58)-C(59)-H(59A)	109.5
C(58)-C(59)-H(59B)	109.5
H(59A)-C(59)-H(59B)	109.5
C(58)-C(59)-H(59C)	109.5
H(59A)-C(59)-H(59C)	109.5
H(59B)-C(59)-H(59C)	109.5
C(58)-C(60)-H(60A)	109.5

C(58)-C(60)-H(60B)	109.5
H(60A)-C(60)-H(60B)	109.5
C(58)-C(60)-H(60C)	109.5
H(60A)-C(60)-H(60C)	109.5
H(60B)-C(60)-H(60C)	109.5
C(37)-N(6)-C(32)	120.0(5)
C(37)-N(6)-H(6)	120.0
C(32)-N(6)-H(6)	120.0
C(43)-N(7)-C(38)	124.2(5)
C(43)-N(7)-H(7)	117.9
C(38)-N(7)-H(7)	117.9
C(49)-N(8)-C(44)	124.6(5)
C(49)-N(8)-H(8A)	117.7
C(44)-N(8)-H(8A)	117.7
C(55)-N(9)-C(50)	121.4(6)
C(55)-N(9)-H(9)	119.3
C(50)-N(9)-H(9)	119.3
C(31)-N(10)-C(56)	123.0(5)
C(31)-N(10)-H(10A)	118.5
C(56)-N(10)-H(10A)	118.5
H(11D)-O(11)-H(11E)	108.3

Symmetry transformations used to generate equivalent atoms:

Table S5. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	73(4)	99(5)	76(3)	-9(4)	23(3)	-7(4)
C(2)	73(4)	80(4)	63(3)	-5(3)	15(3)	-9(3)
C(3)	109(5)	103(5)	73(4)	-2(4)	-8(4)	-13(5)
C(7)	59(3)	60(3)	78(3)	3(3)	3(3)	0(3)
C(8)	63(3)	67(3)	66(3)	4(3)	4(3)	-3(3)
C(9)	69(3)	81(4)	78(3)	2(3)	1(3)	4(3)
C(10)	84(4)	101(5)	90(4)	-19(4)	-3(4)	18(4)
C(11)	93(5)	132(7)	123(6)	-9(6)	25(5)	24(6)
C(12)	113(7)	115(7)	177(10)	-56(7)	-16(7)	2(6)
C(13)	58(3)	73(4)	71(3)	-4(3)	-7(3)	-4(3)
C(14)	59(3)	70(3)	70(3)	-2(3)	-12(3)	-2(3)
C(15)	83(4)	79(4)	68(3)	-12(3)	6(3)	0(4)
C(16)	121(6)	121(6)	80(4)	-2(5)	20(5)	-3(6)
C(17)	176(11)	232(15)	82(5)	33(7)	14(7)	52(11)
C(18)	162(10)	182(10)	92(5)	-37(6)	41(6)	6(9)
C(19)	53(3)	73(4)	73(3)	-5(3)	-2(3)	5(3)
C(20)	76(4)	71(3)	60(3)	-2(3)	-1(3)	19(3)
C(21)	89(4)	87(4)	72(3)	-4(3)	-1(3)	-11(4)
C(22)	101(5)	80(4)	77(4)	9(3)	11(4)	-9(4)
C(24)	150(11)	560(40)	113(8)	26(14)	27(8)	-160(19)
C(25)	61(3)	76(4)	59(3)	1(3)	9(3)	4(3)
C(26)	70(3)	74(4)	61(3)	-5(3)	14(3)	5(3)
C(27)	106(5)	75(4)	81(4)	-18(3)	3(4)	-14(4)
C(28)	144(8)	106(6)	81(4)	-17(4)	-9(5)	-2(6)
C(29)	159(11)	213(13)	105(7)	-44(8)	14(7)	-6(11)
C(30)	228(17)	274(18)	163(12)	-102(13)	2(12)	-123(16)
N(1)	59(2)	84(3)	66(3)	-5(2)	7(2)	-5(3)
N(2)	58(2)	66(3)	67(2)	4(2)	-5(2)	-6(2)
N(3)	48(2)	65(3)	76(3)	-9(2)	0(2)	2(2)
N(4)	85(3)	73(3)	59(2)	-12(2)	-1(2)	20(3)
N(5)	70(3)	77(3)	72(3)	9(3)	9(2)	-1(3)
O(1)	117(4)	101(4)	128(4)	13(3)	66(4)	10(3)
O(2)	60(2)	93(3)	90(3)	0(3)	9(2)	4(2)

O(3)	75(3)	81(3)	94(3)	-6(2)	-18(2)	-21(2)
O(4)	57(2)	105(4)	107(3)	-11(3)	5(2)	9(2)
O(5)	76(2)	75(3)	73(2)	-5(2)	6(2)	19(2)
C(31)	63(3)	68(4)	75(3)	1(3)	2(3)	0(3)
C(32)	70(3)	58(3)	76(3)	5(3)	-3(3)	-10(3)
C(33)	83(4)	73(4)	68(3)	-4(3)	3(3)	0(3)
C(34)	101(5)	91(5)	93(4)	5(4)	16(4)	-1(5)
C(35)	141(8)	151(9)	124(7)	20(7)	61(7)	31(8)
C(36)	167(10)	191(11)	73(4)	-8(6)	-14(6)	-32(10)
C(37)	58(3)	84(4)	81(4)	4(3)	-13(3)	2(3)
C(38)	68(3)	77(4)	69(3)	6(3)	-7(3)	10(3)
C(43)	55(3)	75(4)	80(4)	-1(3)	-9(3)	2(3)
C(44)	57(3)	88(4)	81(4)	-5(3)	-10(3)	15(3)
C(45)	85(4)	80(4)	112(5)	-4(4)	-2(4)	4(4)
C(46)	123(7)	124(7)	144(8)	-45(7)	20(7)	-16(7)
C(47)	270(20)	194(14)	235(17)	-73(14)	73(17)	-126(16)
C(48)	182(13)	193(14)	198(14)	-81(12)	24(12)	-7(12)
C(49)	57(3)	91(4)	82(4)	0(3)	5(3)	-8(3)
C(50)	60(3)	122(6)	79(4)	9(4)	1(3)	-15(4)
C(51)	83(5)	116(6)	79(4)	3(4)	1(4)	-5(4)
C(52)	93(5)	155(8)	92(5)	22(5)	1(4)	-13(6)
C(53)	113(7)	179(10)	91(5)	-4(6)	-16(5)	-29(7)
C(54)	171(11)	198(13)	131(8)	67(9)	-22(8)	-59(11)
C(55)	73(4)	94(5)	86(4)	12(4)	-2(4)	-27(4)
C(56)	94(4)	77(4)	67(3)	13(3)	-2(3)	-24(4)
C(57)	75(4)	81(4)	95(4)	13(4)	-5(4)	-5(4)
C(58)	105(6)	125(7)	91(5)	22(5)	-21(5)	0(5)
C(59)	214(14)	134(9)	180(11)	70(9)	-81(11)	-61(10)
C(60)	164(11)	193(13)	157(10)	24(10)	-74(9)	-8(10)
N(6)	63(3)	55(3)	86(3)	-2(2)	-11(2)	-3(2)
N(7)	58(3)	91(4)	77(3)	-2(3)	-10(2)	19(3)
N(8)	49(2)	93(4)	79(3)	2(3)	3(2)	5(3)
N(9)	63(3)	84(4)	82(3)	9(3)	6(3)	-13(3)
N(10)	117(4)	70(3)	69(3)	5(3)	-3(3)	-26(3)
O(6)	97(3)	66(3)	95(3)	0(2)	14(3)	-23(3)
O(7)	70(3)	101(4)	153(5)	-4(4)	-34(3)	-13(3)
O(8)	65(3)	148(5)	102(3)	-29(3)	-27(3)	40(3)
O(9)	56(2)	130(4)	94(3)	-7(3)	17(2)	-1(3)

O(10)	98(4)	148(5)	140(5)	-12(4)	18(4)	-49(4)
O(11)	53(2)	146(5)	109(3)	17(3)	3(2)	2(3)

Table S6. Hydrogen bonds for **1** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(9)	0.86	2.27	2.965(7)	137.9
N(2)-H(2A)...O(5)	0.86	2.20	2.996(7)	153.6
N(3)-H(3)...O(8)	0.86	2.28	3.006(6)	142.1
N(4)-H(4A)...O(6)#1	0.86	2.03	2.894(7)	178.5
N(5)-H(5)...O(9)	0.86	2.64	3.467(7)	162.9
N(6)-H(6)...O(3)#2	0.86	2.27	3.025(7)	147.0
N(7)-H(7)...O(11)#2	0.86	2.15	2.963(7)	156.7
N(8)-H(8A)...O(11)#2	0.86	2.13	2.908(7)	150.3
N(9)-H(9)...O(2)#2	0.86	2.40	3.244(7)	168.4
O(11)-H(11D)...O(2)	0.90	1.89	2.787(7)	174.2
O(11)-H(11E)...O(4)	0.90	1.98	2.868(8)	170.2

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y+1/2,-z+1/2 #2 x+1,y,z