Supplementary information for:

2-Amino-3,4-diethylpyrrole derivatives: new building blocks for coiled structures

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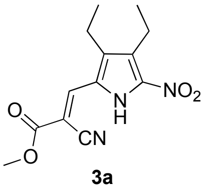
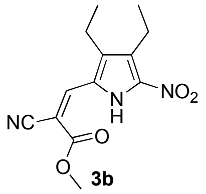
SYNTHESIS

General: All solvents were of reagent grade quality and purchased commercially. All starting materials were purchased from Aldrich Chemical Co. and used without further purification. NMR spectra used in the characterization of products were recorded on Varian INOVA 500, Varian Mercury 400 or Bruker AV 300 MHz instruments. The NMR spectra were referenced to solvent and the spectroscopic solvents were purchased from Cambridge Isotope Laboratories. All high-resolution (HR) chemical ionization (CI) mass spectra were recorded on a VG ZAB-2E instrument. TLC analyses were carried out using Baker-flex Silica gel IB-F sheets. Column chromatography was performed on Whatman silica gel 60 Å (230 – 400 mesh) unless otherwise indicated. Methyl 2-cyano-3-(3,4-diethylpyrrol-2-yl)acrylate, **2**, was synthesized according to literature procedures.[1]

Methyl 2-cyano-3-(3',4'-diethyl-5'-nitro-1'*H*-pyrrol-2'-yl)acrylate (3)



3a



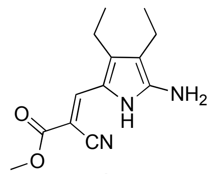
3b

Concentrated nitric acid (0.2 ml, d = 1.4 g/l, 4.32 mmol) was added in small portions to 3.4 ml of cooled (-5 °C, brine / ice bath) acetic anhydride. The mixture was stirred at this temperature for a period of 45 min, after which it was added dropwise to a cooled solution of methyl 2-cyano-3-(3,4-diethylpyrrol-2-yl)acrylate **2** (500 mg, 2.15 mmol) in 5 ml acetic anhydride. After the addition was complete (ca. 30 min.), the mixture was stirred for at -5 °C for 3h, followed by 1h stirring at room temperature. The reaction mixture was diluted with ice and quenched with $NaHCO_3$ (pH ~ 5). The aqueous mixture was extracted with Et_2O (5 × 15 ml). The organic layer was neutralized by washing with aqueous $NaHCO_3$ (pH ~ 8), dried with brine and Na_2SO_4 and concentrated *in vacuo*. The crude product obtained in this way was a dark brown deliquescent solid, which was further purified *via* column chromatography (silica gel; gradient eluent 0.5% – 2.5% MeOH in CH_2Cl_2). The product was isolated in 45% yield as a yellow-brown solid, containing a mixture of two regio isomers **3a** and **3b** in a 10:1 molar ratio as judged by ^1H NMR spectroscopy. No conditions were found that allowed for the separation of the two isomers. ^1H NMR (400 MHz, $CDCl_3$) major component: δ (ppm) = 1.17-1.23 (m, 6H, CH_3), 2.63-2.69 (q, 2H, CH_2),), 2.82-2.87 (q, 2H, CH_2), 3.94 (s, 3H, OCH_3), 8.07 (s, 1H, CH), 10.52 (bs, 1H, NH); minor component: δ (ppm) = the alkyl signals (CH_3, CH_2) overlap with the major component, 3.98 (s, 3H, OCH_3) 7.46 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = [164.37, 161.89] (C=O), [139.99, 138.55, 138.42, 138.37] (C-

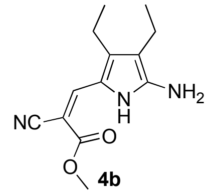
2', C-5', C-3), [128.00, 127.63, 124.32, 123.73] (C-3', C-4'), 117.00 (CN), [99.75, 98.86] (C-2), [63.53, 63.90] (OCH_3), [17.77, 17.68, 17.21, 16.85, 14.24, 14.10, 13.96] (CH_2CH_3). HRMS (CI^+): calcd for $C_{13}H_{16}N_3O_4$ $[M + H]^+$ 278.1140; found *m/z*: 278.1134.

Methyl 3-(5'-amino-3',4'-diethyl-1'*H*-pyrrol-2'-yl)-2-cyanoacrylate (4)

Nitropyrrole **3** (200 mg, 0.72 mmol) was suspended in 2.3 ml of a water : ethanol (1.3 : 1 v/v) mixture. The reaction mixture was heated at 75 °C in air, whereupon sodium dithionite was added (1 g, 5.77 mmol). The reaction mixture was maintained exposed to air at this temperature until the reaction mixture underwent a significant loss in color (i.e., a change in color from yellow-brown to pale yellow). At this point, the reaction flask was connected to an argon inlet, removed from the oil bath, and the solvent removed using a rotary evaporator. The resulting solid was suspended in deionized water by means of sonication, and transferred to a separatory funnel. The α-aminopyrrole was extracted with dichloromethane. During this process, exposure to air was kept at minimal levels. The organic layer was dried by washing with brine, followed by standing over Na_2SO_4. The solution of aminopyrrole obtained in this way was evaporated to dryness and used as such without subsequent purification or extensive spectroscopic characterization. However, this product was characterized by single crystal X-ray diffraction analysis. Single crystals, suitable for X-ray analysis, were grown by slow evaporation of a dichloromethane solution of **4**, under an argon blanket. For **4**: ^{1}H NMR (400 MHz, $CDCl_3$) major component: δ (ppm) = 1.04-1.09 (m, 6H, CH_3), 2.38 (q, 2H, CH_2), 2.55 (q, 2H, CH_2), 3.79 (s, 3H, OCH_3), 4.89 (bs, 2H, NH_2), 7.51 (s, 1H, CH), 9.38 (bs, 1H, NH); minor component: δ (ppm) = the alkyl signals (CH_3, CH_2, OCH_3) overlap with the major component, 4.57 (bs, 2H, NH_2), 6.79 (2, 1H, CH).



4a



4b

Methyl 3-(5'-(3''-aminoisoindol-1''-ylideneamino)-3',4'-diethyl-1'*H*-pyrrol-2'-yl)-2-cyanoacrylate (6)

Compound **4** (123 mg, 0.510 mmol) and 1,3-diiminoisoindoline (28 mg, 0.193 mmol) were dissolved in 10 ml *n*-butyronitrile. The reaction mixture was heated with stirring at reflux for a period of 14 h. After removing the volatile components of the reaction mixture using a rotary evaporator, the resulting crude product was subject to column chromatography (silica gel, eluent: 2% MeOH in CH_2Cl_2). The product was isolated in 51% yield from the 2nd fraction, in the form of an orange powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 1.10-1.21 (m, 6H, CH_3), 2.59-2.65 (m, 4H, CH_2), 3.76 (s, 3H, OCH_3), 7.58-7.63 (m, 2H, 5''-H, 6''-CH), 7.75 (s, 1H, 3-H), [7.80, 8.03] (2d, 2H, 4''-H, 7''-CH), 12.96 (bs, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 170.23, 164.87, 146.97, 140.30, 139.61, 133.04, 126.27, 122.35, 121.62, 111.29, 89.54, 83.30, 52.20, 17.00, 15.62. HRMS (CI^+): calcd for $C_{21}H_{22}N_5O_2$ $[M + H]^+$ 376.1773; found *m/z*: 376.1762.

***N*^{2},*N*^{6}-bis{3'-{3'',4''-diethyl-5''-[2'''-(methoxycarbonyl)-2'''-cyanovinyl]-1''*H*-pyrrol-2''-ylimino}isoindol-1'-yl}pyridine-2,6-dicarboxamide (1)**

Compound **6** (11 mg, 0.048 mmol) was dissolved in 10 ml dry CH_2Cl_2. To this mixture, pyridine-2,6-dicarbonyl dichloride, **7** (3.6 mg, 0.017 mmol) was added. The reaction mixture was heated with stirring at reflux for a period of 24 h. After removing the volatile components of the reaction mixture using a rotary evaporator, the resulting crude product was subject to column chromatography (alumina, eluent: 1% MeOH in CH_2Cl_2). The product was isolated in 47% yield as a blue powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.06 (t, 6H, CH_3), 1.35 (t, 6H, CH_3), 2.45 (m, 4H, CH_2), 2.74 (m, 4H, CH_2), 2.85 (s, 6H, OCH_3), 7.34 (s, 2H, 1'''-CH), 7.56 (m, 4H, 5'-H, 6'-H phenylene), 8.04 (m, 2H, 4'-H, phenylene), 8.26 (dd, 1H, 4-H, pyridine), 8.66 (d, 2H, 3-H, 5-H pyridine), 8.90 (m, 2H, 7'-H, phenylene), 11.77 (s, 2H, amide NH), 12.71 (bs, 2H, pyrrole NH). ^{13}C

NMR (100 MHz, $CDCl_3$) δ (ppm) = 166.43, 163.88, 162.18, 159.96, 148.20, 144.47, 140.96, 139.67, 138.76, 135.54, 132.97, 131.26, 131.01, 130.59, 128.16, 127.18, 125.31, 122.55, 119.38, 88.53, 51.46, 29.83, 17.49, 16.98, 16.90, 16.00. HRMS (CI^+): calcd for $C_{49}H_{44}N_{11}O_6$ $[M + H]^+$ 882.3476; found *m/z*: 882.3454.

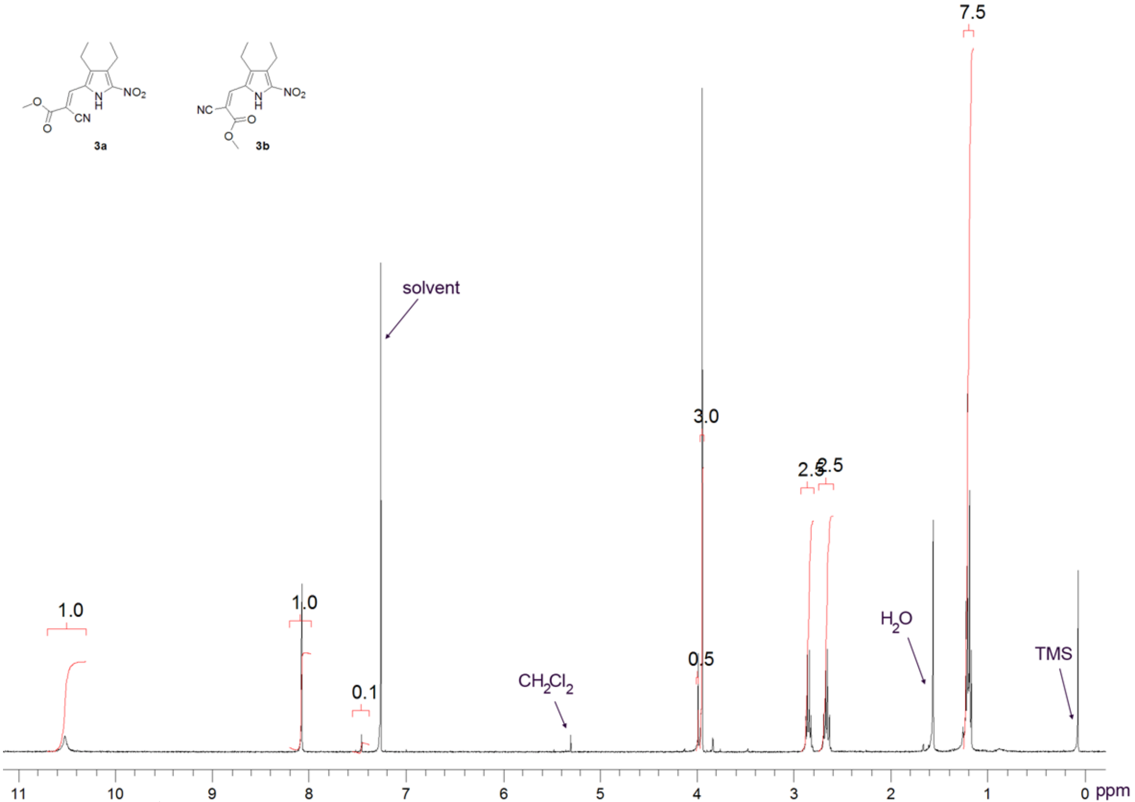


Figure S1: ^{1}H-NMR spectrum (400MHz, $CDCl_3$) of **3** as a mixture of isomers **3a** and **3b**.

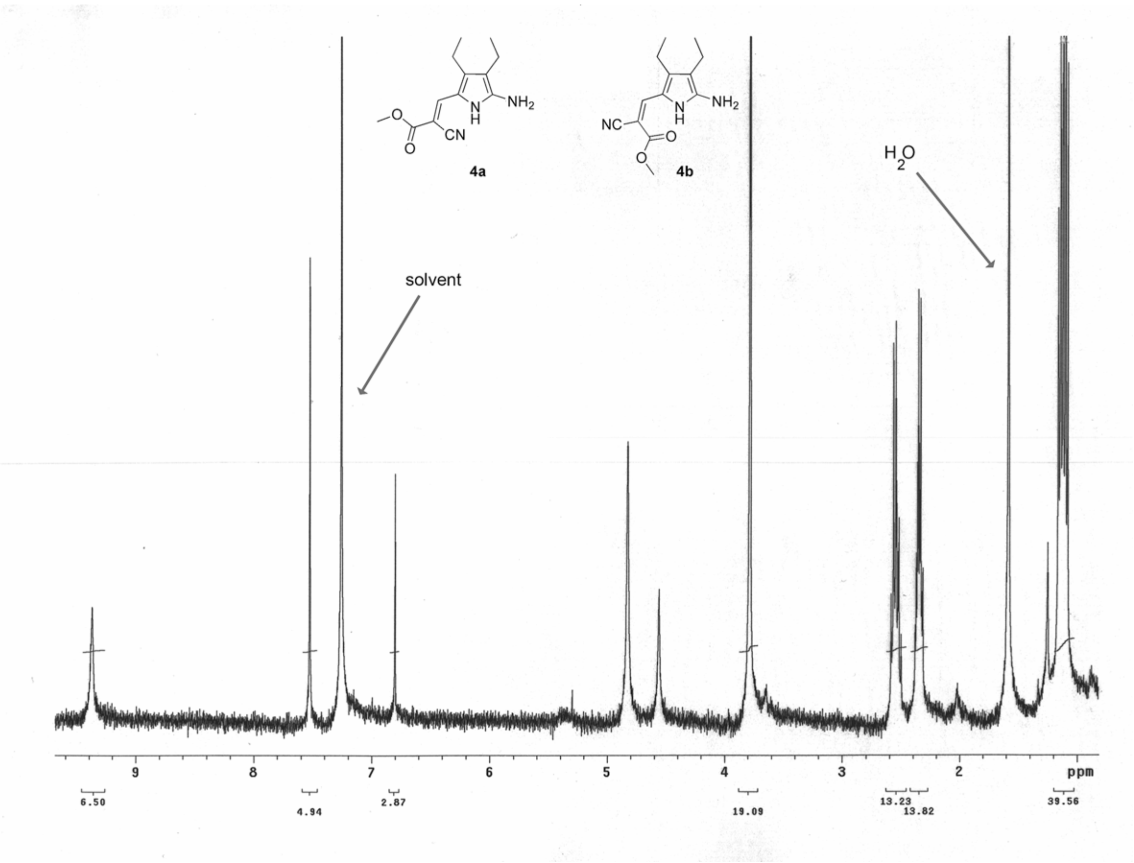


Figure S2: ^{1}H-NMR spectrum (400MHz, $CDCl_3$) of **4** as a mixture of isomers **4a** and **4b**.

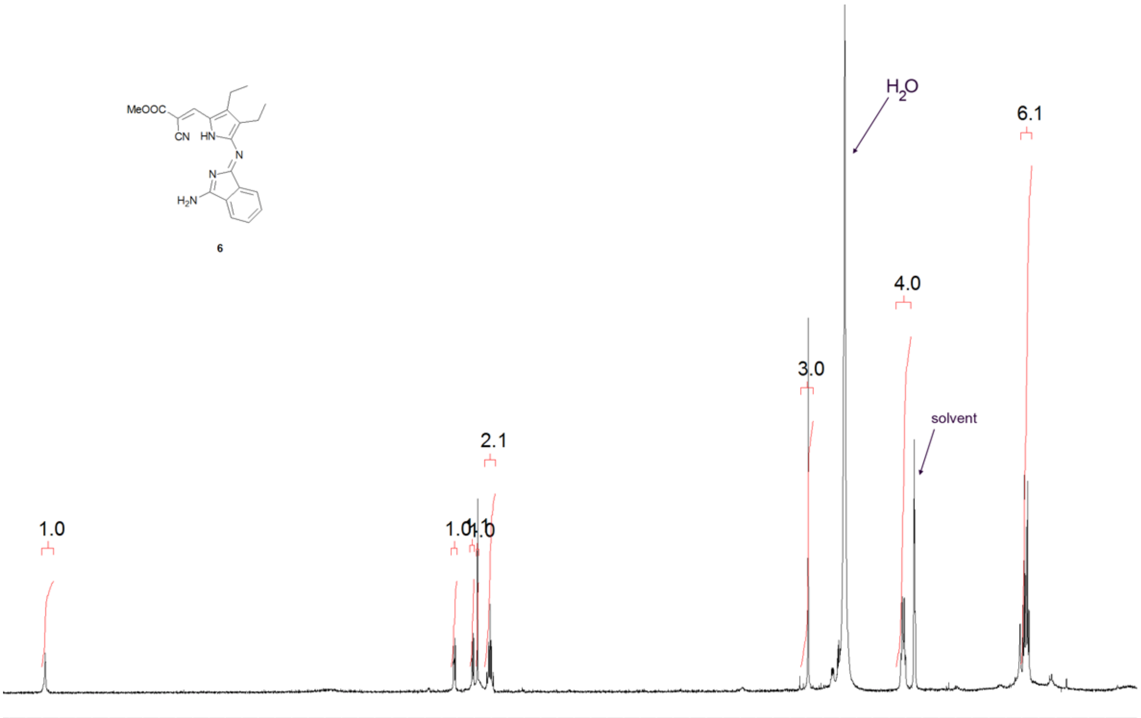


Figure S3: ^{1}H-NMR spectrum (400MHz, DMSO-d_6) of **6**.

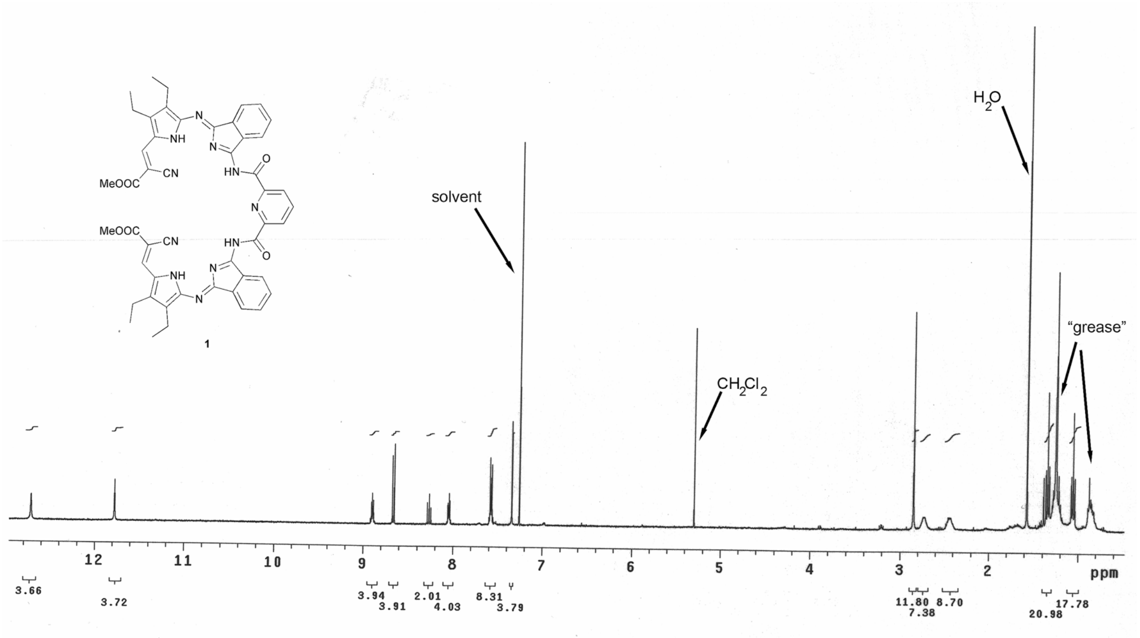


Figure S4: ^{1}H-NMR spectrum (400MHz, $CDCl_3$) of **1**.

X-ray Crystallography Data

Crystallographic Material for **4**.

X-ray Experimental.

Table S1. Crystallographic Data for **4**.

Figure S5. View of **4** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

Figure S6. Unit cell packing diagram for **4**. The view is approximately down the **b** axis. Dashed lines are indicative of H-bonding interactions. The geometry of these interactions is listed in Table 7.

X-ray Experimental for $C_{13}H_{17}N_3O_2$ (**4**):

Crystals grew as thin yellow plates by slow evaporation of a dichloromethane solution under inert atmosphere (Ar). The data crystal was a long lathe that had approximate dimensions; 0.22 x 0.20 x 0.04 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 200 frames of data were collected using ω-scans with a scan range of 2° and a counting time of 264 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[2] The structure was solved by direct methods using SIR97[3] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[4] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.02*P)^2 + (2.5*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.189, with R(F) equal to 0.119 and a goodness of fit, S, = 1.25. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[5] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[6] All figures were generated using SHELXTL/PC.[7] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, and H-bonding interactions are located in tables S1 through S7.

Table S1. Crystal data and structure refinement for **4**.

Empirical formula	C13 H17 N3 O2	
Formula weight	247.30	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 10.5504(10) Å	
	b = 9.0899(8) Å	β= 96.867(4)°
	c = 13.5949(14) Å	
Volume	1294.4(2) Å^3	
Z	4	
Density (calculated)	1.269 mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	528	
Crystal size	0.22 x 0.20 x 0.04 mm	
Theta range for data collection	2.97 to 25.00°.	
Index ranges	-12<=h<=12, -9<=k<=10, -16<=l<=16	
Reflections collected	3999	
Independent reflections	2273 [R(int) = 0.0875]	
Completeness to theta = 25.00°	99.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2273 / 0 / 174	
Goodness-of-fit on F^2	1.252	
Final R indices [I>2sigma(I)]	R1 = 0.1189, wR2 = 0.1647	
R indices (all data)	R1 = 0.1945, wR2 = 0.1888	
Largest diff. peak and hole	0.306 and -0.346 e.Å^{-3}	

Figure S5. View of **4** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

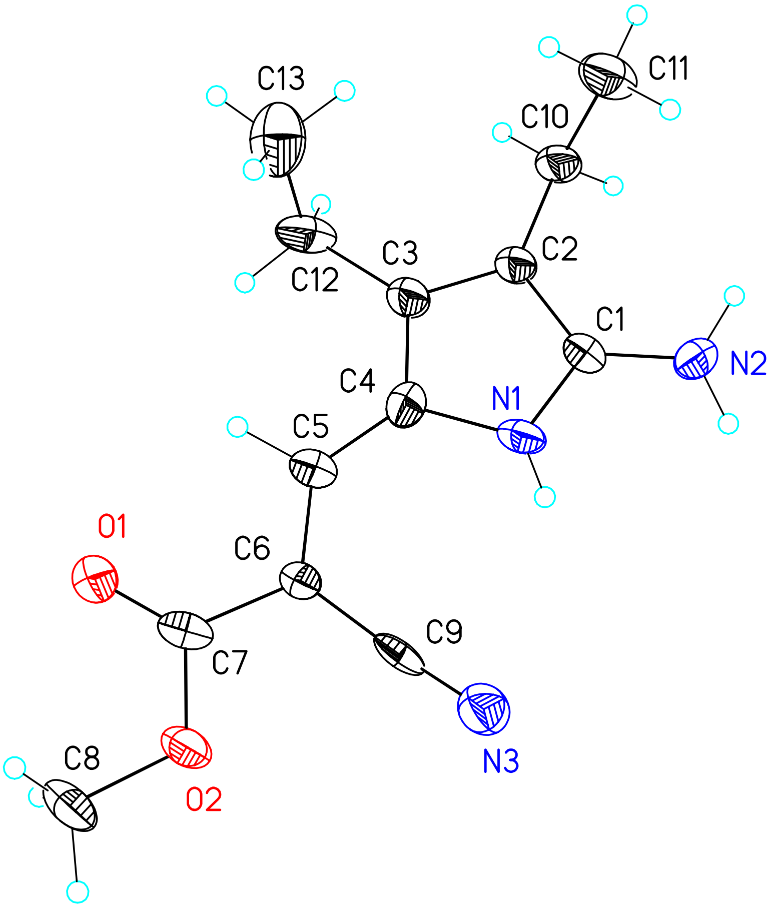
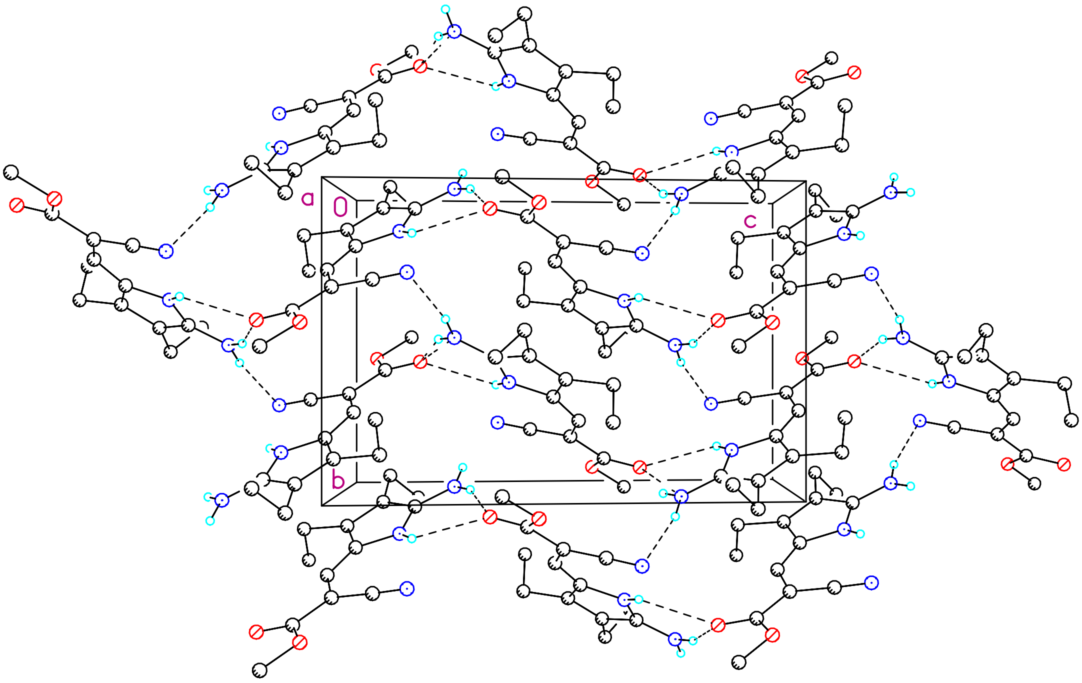


Figure S6. Unit cell packing diagram for **4**. The view is approximately down the **b** axis. Dashed lines are indicative of H-bonding interactions. The geometry of these interactions is listed in Table S7.



Crystallographic Material for **1**.

X-ray Experimental.

Table S2. Crystallographic Data for **1**.

Figure S7. View of **1** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Most hydrogen atoms have been removed for clarity.

Figure S8. Unit cell packing diagram for **1**. The view is approximately along an **ab** face diagonal.

X-ray Experimental for $C_{28}H_{44}N_4O_4$ (**1**):

Crystals grew as dark blue needles by slow evaporation in an NMR tube. The data crystal was cut from a long needle and had approximate dimensions; 0.35 x 0.16 x 0.12 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation ($\lambda = 0.71073$Å). A total of 452 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 122 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[2] The structure was solved by direct methods using SIR97[3] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[4] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atoms bound to nitrogen were located in a ΔF map and refined with isotropic displacement parameters. The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0328*P)^2 + (1.8006*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.147, with R(F) equal to 0.0621 and a goodness of fit, S, = 1.05. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[5] The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1 + (7.4(10)x10^{-6})* F_c^2 \lambda^3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[6] All figures were generated using SHELXTL/PC.[7] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, and H-bonding interactions are located in tables S8 through S14.

Table S2. Crystal data and structure refinement for **1**.

Empirical formula	C49 H43 N11 O6	
Formula weight	881.94	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 12.7239(4) Å	α= 65.588(2)°.
	b = 13.6559(5) Å	β= 69.964(2)°.
	c = 15.0447(7) Å	γ = 67.954(2)°.
Volume	2151.24(14) Å^3	
Z	2	
Density (calculated)	1.362 mg/m^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	924	
Crystal size	0.35 x 0.16 x 0.12 mm	
Theta range for data collection	3.03 to 25.00°.	
Index ranges	0<=h<=15, -14<=k<=16, -16<=l<=17	
Reflections collected	7477	
Independent reflections	7477	
Completeness to theta = 25.00°	98.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7477 / 0 / 612	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0621, wR2 = 0.1211	
R indices (all data)	R1 = 0.1187, wR2 = 0.1466	
Extinction coefficient	7.4(10)x10^{-6}	
Largest diff. peak and hole	0.267 and -0.264 e.Å^{-3}	

Figure S7. View of **1** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Most hydrogen atoms have been removed for clarity.

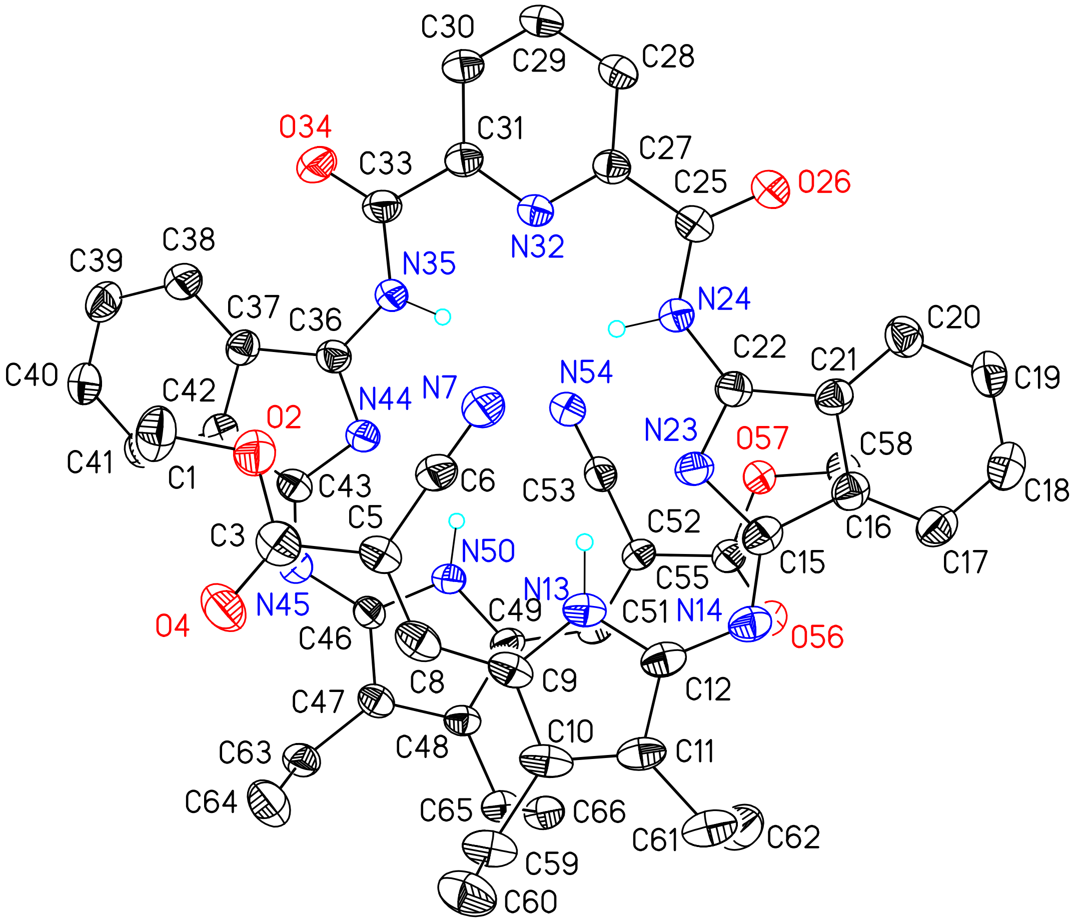
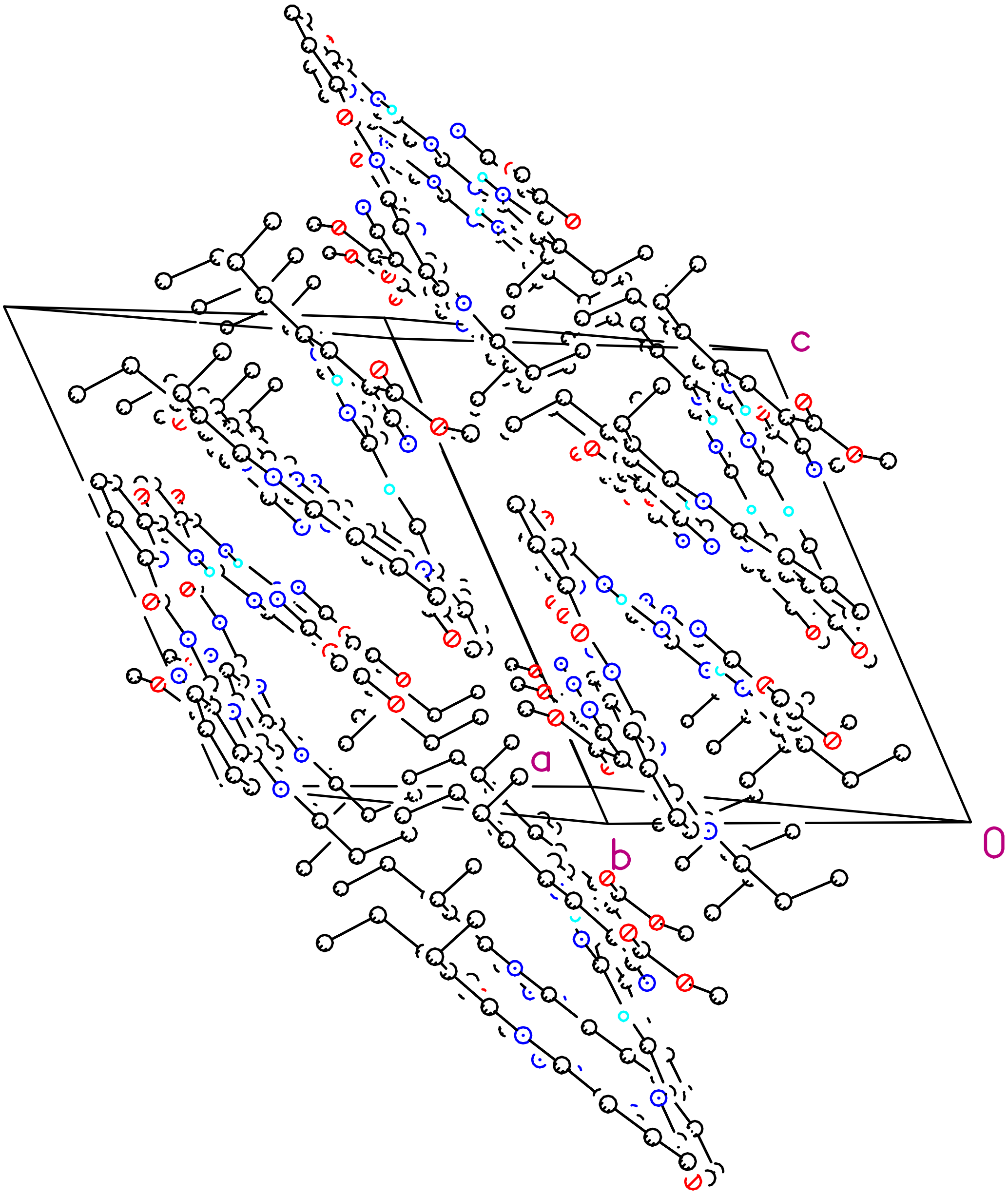


Figure S8. Unit cell packing diagram for **1**. The view is approximately along an **ab** face diagonal.



References:

1) J. B. Paine III, R. B. Woodward, and D. Dolphin, *J. Org. Chem.*, 1976, **41**, 2826

2) DENZO-SMN: Z. Otwinowski and W. Minor, *Methods in Enzymology*, 1997, **276**: Macromolecular Crystallography, part A, 307 – 326, C. W. Carter, Jr. and R. M. Sweets, Editors, Academic Press.

3) SIR97: A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Cryst.*, 1999, **32**, 115.

4) G. M. Sheldrick, SHELXL97. Program for the Refinement of Crystal Structures. University of Gottingen, 1994, Germany.

5) $R_W(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$ where w is the weight given each reflection.
$R(F) = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|\}$ for reflections with $F_o > 4(\sigma(F_o))$.
$S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.

6) International Tables for X-ray Crystallography (1992). Vol. C, Tables 4.2.6.8 and 6.1.1.4, A. J. C. Wilson, editor, Boston: Kluwer Academic Press.

7) G. M. Sheldrick, SHELXTL/PC (Version 5.03). Siemens Analytical X-ray Instruments, Inc., 1994, Madison, Wisconsin, USA.