Supporting Information (SI)

CJ-1639: A Potent and Highly Selective Dopamine D3 Receptor Full Agonist

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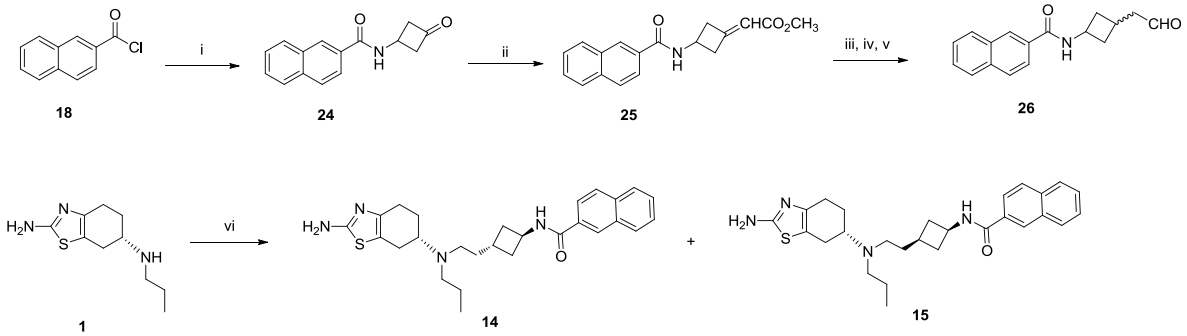
I. Chemistry

General Methods. Solvents and reagents were obtained commercially and used without further purification. Reactions were monitored by TLC carried out on 250 µm E. Merck silica gel plates (60F-254) using UV light for visualization. E. Merck silica gel (60, particle size 15-40 µm) was used for flash column chromatography. NMR spectra were recorded on a Bruker Avance300 spectrometer (300 MHz). Chemical shifts (δ) are reported as δ values (ppm) downfield relative to TMS as an internal standard, with multiplicities reported in the usual manner.

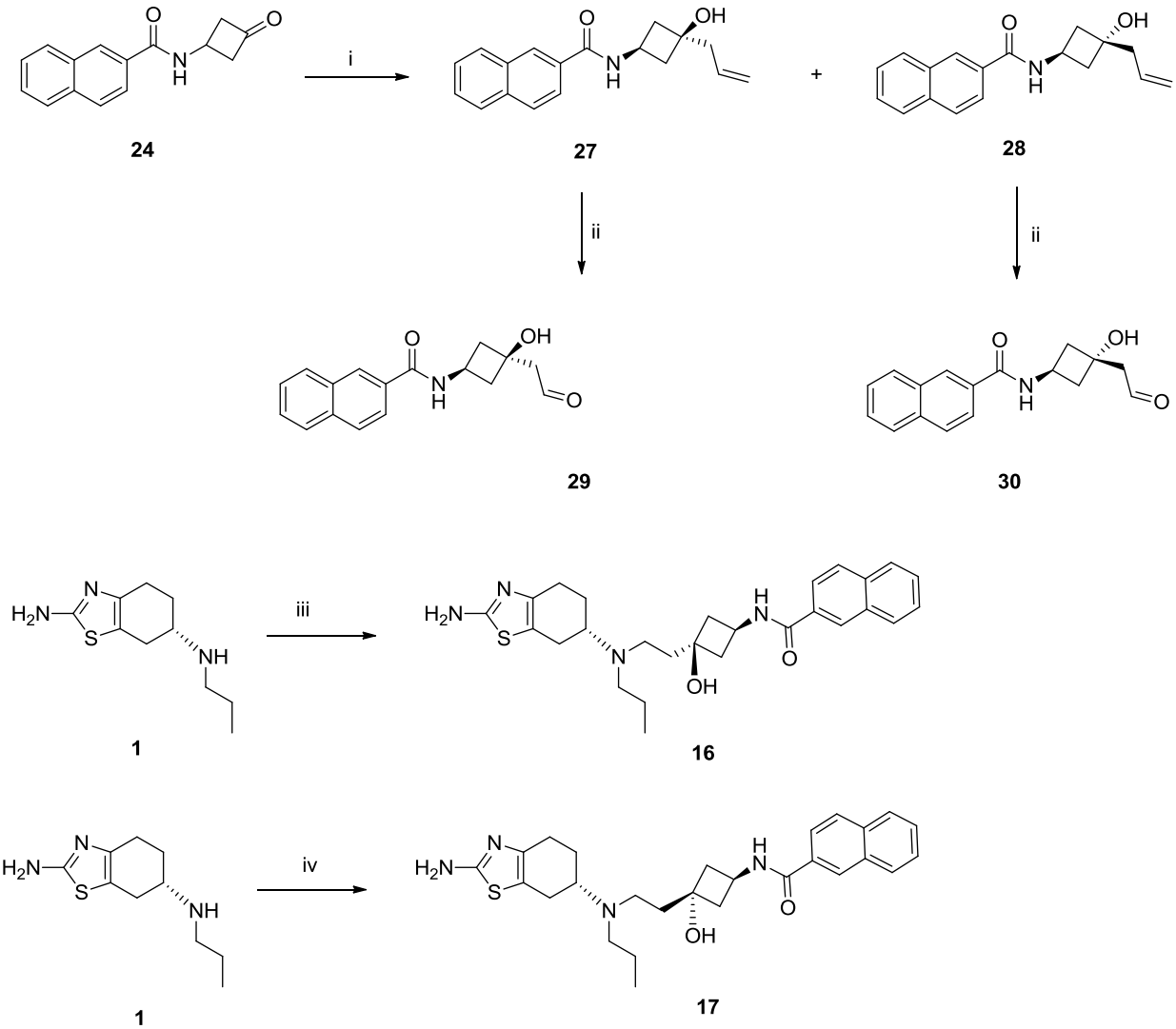
Synthesis

The synthesis of compounds **14** and **15** was outlined in **Scheme S1**. 2-Naphthoyl chloride was reacted with 3-aminocyclobutanone to give ketone **24**. Wittig reaction of **24** with methyl (triphenylphosphoranylidede)acetate in toluene gave olefin **25**. Hydrogenation of **25**, followed by reduction of methyl ester using LiBH4 and Dess-Martin oxidation afforded *cis*- and *trans*-aldehyde **26** as an inseparable mixture. Reductive amination of pramipexole **1** with **26** followed by preparative HPLC purification gave compounds **14** and **15**.



Scheme S1. Synthesis of compounds **14** and **15.** Conditions and reagents: (i) 2-naphthoyl chloride,3-aminocyclobutanone, triethylamine, DCM; (ii) Methyl (triphenylphosphoranylidene)acetate, tolune, reflux, 12 hr; (iii) H2, 10 % Pd-C, MeOH; (iv) LiBH4, THF, RT, 2 hr; (v) Dess-Martin, DCM; (v) **26**, NaBH(OAc)3, CH3CO2H, DCM.

The synthesis of compounds **16** and **17** was outlined in **Scheme S2**. Ketone **24** was treated with allymagnesium bromide at -78 °C to afford cis-cyclobutanol **27** and trans-cyclobutanol **28**. Compounds **27** and **28** can be separated easily by silica gel chromatography. *Cis*-aldehyde **29** was obtained by the treatment of cis-cyclobutanol **27** with Osium tetraoxide followed by sodium periodate. *Trans*-aldehyde **30** was obtained in a similar manner. Reductive amination of pramipexole **1** with **29** and **30** gave compounds **16** and **17**, respectively.



Scheme S2. Synthesis of compounds **16** and **17.** Conditions and reagents: (i) allylmagnesium bromide, THF, -78 °C, 2 hr; (ii) OsO_4, $NaIO_4$, THF-H_2O, RT, 30 min; (iii) **29**, $NaBH(OAc)_3$, CH_3CO_2H, DCM; (iv) **30**, $NaBH(OAc)_3$, CH_3CO_2H, DCM.

***N*-(4-oxocyclohexyl)-2-naphthamide** (**19**)

2-Naphthoyl chloride (3.0 g, 15.8 mmol) and triethylamine (1.6 g, 15.8 mmol) were added to a solution of *trans*-4-aminocyclohexanol (1.51 g, 13.2 mmol) in CH_2Cl_2 (30 mL) and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2. Organic solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (30 mL). PCC (4.27 g, 19.8 mmol) was then added to the solution and the mixture was stirred at room temperature for 12 h. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (30 mLx3). The organic layer was combined and evaporated under vacuum. The residue was subjected to flash column chromatography (hexane : EtOAc = 1 : 1) to give **19** (1.2 g, 51 % yield for two steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 7.95-7.75 (m, 4H), 7.60-7.50 (m, 2H), 6.31 (d, *J* = 7.1 Hz, 1H), 4.60-4.40 (m, 1H), 2.70-2.35 (m, 6H), 1.90-1.75 (m, 2H).

_N_-cis-4-allyl-4-hydroxycyclohexyl)-2-naphthamide (20) and _N_-trans-4-allyl-4-hydroxy-cyclohexyl)-2-naphthamide (21)

1.0 M allymagnesium bromide (6 mL, 6.0 mmol) in Et_2O was added to a solution of **19** (800 mg, 3.0 mmol) in dry THF (30 mL) at -78 ºC and the reaction mixture was stirred at -78 ºC for 2 h. The reaction was quenched with a saturated solution of NH_4Cl (20 mL) and the mixture was allowed to warm up to room temperature. The reaction mixture was extracted with EtOAc (30 mLx3). The organic solvent was removed under vacuum and the residue was chromatographed (hexane : EtOAc = 1 : 1) to give **20** (180 mg, 19 % yield) and **21** (100 mg, 11 % yield), respectively, as colorless oils. ^{1}H NMR ($CDCl_3$, 300 MHz) of **20** δ 8.26 (s, 1H), 7.93-7.75 (m, 4H), 7.65-7.50 (m, 2H), 6.14 (d, *J* = 7.6 Hz, 1H), 6.00-5.75 (m, 1H), 5.25-5.10 (m, 2H), 4.15-3.95 (m, 1H), 2.25 (d, *J* = 7.5 Hz, 2H), 2.00-1.85 (m, 2H), 1.75-1.50 (m, 6H), 1.35 (s, 1H). ^{1}H NMR ($CDCl_3$, 300 MHz) of **21** δ 8.25 (s, 1H), 7.95-7.75 (m, 4H), 7.80-7.60 (m, 2H), 6.21 (d, *J* = 6.5 Hz, 1H), 5.95-5.75 (m, 1H), 5.25-5.05 (m, 2H), 4.25-4.00 (m, 1H), 2.35(d, *J* = 7.4 Hz, 2H), 2.20-2.00 (m, 2H),

1.80-1.50 (m, 7H). Recyrstallization of **20** in a mixed solvent (DCM:Hexane=1:1) gave nice crystals for X-ray analysis.

***N*-cis-4-hydroxy-4-(2-oxoethyl)cyclohexyl)-2-naphthamide (22)**

OsO_4 (33 mg, 0.129 mmol) was added to a solution of **20** (400 mg, 1.29 mmol) in THF-H2O (30 mL, 1:1 mixture) and the reaction mixture was stirred at room temperature for 30 min. $NaIO_4$ (690 mg, 3.23 mmol) was then added and the reaction mixture was stirred for 1 hr at room temperature. The mixture was extracted with EtOAc and the solvent was removed under vacuum. The residue was chromatographed and eluted with EtOAc to give **22** (280 mg, 71 % yield) as a colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.89 (s, 1H), 8.26 (s, 1H), 7.90-7.75 (m, 4H), 7.65-7.50 (m, 2H), 6.17 (d, *J* = 7.8 Hz, 1H), 4.15-3.95 (m, 1H), 2.80 (s, 1H), 2.65 (s, 2H), 2.00-1.49 (m, 8H).

***N*-trans-4-hydroxy-4-(2-oxoethyl)cyclohexyl)-2-naphthamide (23)**

Compound **23** was prepared from **21** in 65 % yield, using a procedure similar to that for compound **22**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.90 (s, 1H), 8.26 (s, 1H), 7.90-7.70 (m, 4H), 7.65-7.50 (m, 2H), 6.20 (d, *J* = 7.6 Hz, 1H), 4.25-4.00 (m, 1H), 2.70 (s, 2H), 2.60 (s, 1H), 2.20-1.50 (m, 8H).

***N*-(cis-4-(2-(((S)-2-amino-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl)(propyl)amino)ethyl)-4-hydroxycyclohexyl)-2-naphthamide (12)**

Compound **22** (25 mg, 0.08 mmol), sodium triacetoxyborohydride (25 mg, 0.12 mmol), and AcOH (7 mg, 0.12 mmol) were added to a solution of pramipexole (17 mg, 0.08 mmol) in CH_2Cl_2 (30 mL) and the mixture was stirred at room temperature for 4 h. The reaction was quenched by adding water (30 mL) and the mixture was extracted with CH_2Cl_2 (30 mL x 3). The organic solvent was removed under vacuum and the residue was chromatographed (MeOH : EtOAc = 10 : 90) to give **12** (25 mg, 62 % yield) as a colorless oil. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.38 (s, 1H), 8.02-7.90 (m, 4H), 7.70-7.52 (m, 2H), 4.02-

3.87 (m, 2H), 3.60-2.67 (m, 8H), 2.45-2.08 (m, 2H), 2.05-1.52 (m, 12H), 1.08 (t, *J*=7.3 Hz, 3H); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.09 (d, *J* = 6.3 Hz, 1H), 8.47 (s, 1H), 8.10-7.90 (m, 4H), 7.70-7.52 (m, 2H), 4.70-4.50 (m, 1H), 3.52-3.20 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 206.53, 166.45, 134.18, 132.12, 131.51, 128.83, 127.93, 127.66, 127.49, 126.81, 124.14, 53.96, 35.67.

***N*-(trans-4-(2-(((S)-2-amino-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl)(propyl)amino)ethyl)-4-hydroxycyclohexyl)-2-naphthamide (13)**

Compound **13** was similarly prepared as **12** in 68 % yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.36 (s, 1H), 8.00-7.80 (m, 4H), 7.65-7.50 (m, 2H), 4.10-3.95 (m, 1H), 3.35-3.23 (m, 1H), 3.00-2.50 (m, 8H), 2.20-1.50 (m, 14H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 169.89, 169.77, 144.86, 136.17, 133.99, 133.18, 129.96, 129.23, 128.75, 127.80, 125.03, 115.28, 72.96, 58.49, 53.47, 47.26, 37.45, 37.19, 33.69, 29.55, 26.95, 25.79, 25.05, 22.21, 12.05.

***N*-(3-oxocyclobutyl)-2-naphthamide (24)**

2-Naphthoyl chloride (1.73 g, 9.1 mmol) and triethylamine (2.02 g, 20.0 mmol) were added to a solution of 3-aminobutanone (0.774 g, 9.1 mmol) in CH_2Cl_2 (30 mL) and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2. Organic solvent was removed under vacuum and the residue was purified by silica gel chromatography (hexane : EtOAc = 1 : 1) to give **24** as a colorless oil (1.65 g, 76 % yield). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.09 (d, *J* = 6.3 Hz, 1H), 8.47 (s, 1H), 8.10-7.90 (m, 4H), 7.70-7.52 (m, 2H), 4.70-4.50 (m, 1H), 3.52-3.20 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 206.53, 166.45, 134.18, 132.12, 131.51, 128.83, 127.93, 127.66, 127.49, 126.81, 124.14, 53.96, 35.67.

Methyl 2-(3-(2-naphthamido)cyclobutylidene)acetate (25)

Methyl (triphenylphosphoranylidene)acetate (1.34 g, 4.02 mmol) was added to a solution of **24** (0.64 g, 2.68 mmol) in toluene (30 mL) and the mixture was refluxed at 135 ºC for 12 h. Solvent was removed under vacuum and the residue was purified by silica gel chromatography (hexane : EtOAc = 60 : 40) to give **25** as a colorless solid (0.52 g, 66 % yield). ^{1}H NMR (CDCl3, 300 MHz) δ 8.31 (s, 1H), 7.95-7.80 (m, 4H), 7.15-7.00 (m, 2H), 6.60 (d, J = 6.3 Hz, 1H), 5.80-5.75 (m, 1H), 4.80-4.65 (m, 1H), 3.80-3.75 (m, 1H), 3.73 (s, 3H), 3.45-3.30 (m, 1H), 3.20-3.15 (m, 1H), 2.90-2.80 (m, 1H).

***N*-(3-(2-oxoethyl)cyclobutyl)-2-naphthamide (26)**

Compound **25** (400 mg, 1.36 mmol) was dissolved in MeOH (20 mL) and hydrogenated using 10% Pd-C as a catalyst for 12 h. The catalyst was filtered off and solvent was evaporated under vacuum. The residue was dissolved in anhydrous THF (15 mL) and 2.0 M lithium borohydride solution in THF (1.36 mL) was then added and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated ammonium chloride solution and the mixture was extracted with EtOAc. Organic solvent was evaporated under vacuum and the residue was dissolved in CH_2Cl_2 (20 mL). Dess-Martin reagent (864 mg, 2.0 mmol) was then added to the solution and the mixture was stirred at room temperature for 2 h. Solvent was removed under vacuum and the residue was subjected to silica gel chromatography (hexane : EtOAc = 1 : 1) to give **26** as *cis* and *trans* isomers (130 mg) which were inseparable.

***N*-(*trans*-3-(2-(((S)-2-amino-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl)(propyl)amino)-ethyl)-cyclobutyl)-2-naphthamide (14) and *N*-(*trans*-3-(2-(((S)-2-amino-4,5,6,7-tetrahydrobenzo-[d]thiazol-6-yl)(propyl)amino)ethyl)cyclobutyl)-2-naphthamide (15)**

Compound **26** (130 mg, 0.49 mmol), sodium triacetoxyborohydride (156 mg, 0.74 mmol), and AcOH (44 mg, 0.74 mmol) were added to a solution of pramipexole (103 mg, 0.49 mmol) in CH_2Cl_2 (30 mL) and the mixture was stirred at room temperature for 4 h. The reaction was quenched by adding

water (30 mL) and the mixture was extracted with CH_2Cl_2 (30 mLx3). The organic solvent was removed under vacuum and the residue was purified by preparative HPLC (Waters Sunfire Preparative C18 OBD 19x150 mm column, mobile phase flow 10.0 mL/min, gradient water with 0.1 % TFA/CH_3CN with 0.1 % TFA 0~50%, and UV detection at 254 nm) to give **14** (50 mg) and **15** (43 mg) as colorless oil. ^{1}H NMR (CD_3OD, 300 MHz) of **14** δ 8.37 (s, 1H), 7.95-7.78 (m, 4H), 7.60-7.50 (m, 2H), 4.50-4.33 (m, 1H), 3.95-3.80 (m, 1H), 3.30-2.55 (m, 10H), 2.40-1.70 (m, 9H), 1.06 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (CD_3OD, 75 MHz) of **14** δ 171.76, 169.58, 136.29, 134.36, 134.04, 132.77, 129.99, 129.33, 128.88, 128.79, 127.89, 124.90, 112.97, 60.32, 43.26, 36.90, 27.41, 23.91, 23.46, 22.87, 11.23. ^{1}H NMR (CD_3OD, 300 MHz) of **15** δ 8.38 (s, 1H), 7.95-7.78 (m, 4H), 7.60-7.51 (m, 2H), 4.75-4.60 (m, 1H), 3.95-3.80 (m, 1H), 3.30-2.70 (m, 8H), 2.45-1.70 (m, 11H), 1.08 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (CD_3OD, 75 MHz) of **15** δ 170.36, 168.36, 134.89, 132.98, 132.63, 131.33, 128.58, 127.91, 127.43, 127.37, 126.47, 123.51, 111.59, 58.87, 43.42, 33.59, 26.59, 22.51, 22.05, 21.48, 9.81.

_N_-(cis-3-allyl-3-hydroxycyclobutyl)-2-naphthamideand (27) and _N_-(trans-3-allyl-3-hydroxy-cyclobutyl)-2-naphthamideand (28)

1.0 M allymagnesium bromide in Et_2O (5 mL, 5.0 mmol) was added to a solution of **24** (600 mg, 2.51 mmol) in dry THF (30 mL) at -78 ºC and the reaction mixture was stirred at -78 ºC for 2 h. The reaction was quenched with saturated ammonium chloride (20 mL) and the mixture was warmed up to room temperature. The reaction mixture was extracted with EtOAc (30 mL x 3). The organic solvent was removed under vacuum and the residue was chromatographed (Silical gel, hexane : EtOAc = 1 : 1) to give **27** (240 mg, 34 % yield) as a colorless solid and **28** (200 mg, 28 % yield) as a colorless oil. ^{1}H NMR (CDCl3, 300 MHz) of **27** δ 8.27 (s, 1H), 7.95-7.75 (m, 4H), 7.65-7.50 (m, 2H), 6.51 (d, *J* = 6.5 Hz, 1H), 6.00-5.80 (m, 1H), 5.30-5.20 (m, 2H), 4.45-4.27 (m, 1H), 2.80-2.70 (m, 2H), 2.43 (d, J = 7.1 Hz, 2H), 2.36 (s, 1H), 2.25-2.15 (m, 2H). ^{1}H NMR (CDCl3, 300 MHz) of **28** δ 8.27 (s, 1H), 7.90-7.75 (m, 4H), 7.65-7.50 (m, 2H), 6.44

(d, *J* = 6.1 Hz, 1H), 5.90-5.75 (m, 1H), 5.25-5.15 (m, 2H), 4.90-4.75 (m, 1H), 2.70-2.51 (m, 2H), 2.44 (d, *J* = 7.2 Hz, 2H), 2.25-2.15 (m, 2H), 1.80 (s, 1H).

The stereochemistry of compound **27** was confirmed by x-ray crystallographic analysis and the result is provided in Figure S1.

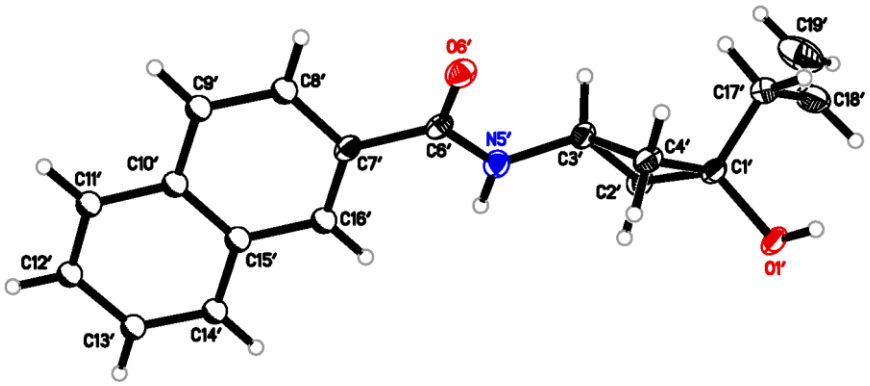


Figure S1. Crystal structure of key intermediate **27.**

***N*-(cis-3-hydroxy-3-(2-oxoethyl)cyclobutyl)-2-naphthamide (29)**

OsO_4 (21 mg, 0.084 mmol) was added to a solution of **27** (235 mg, 0.84 mmol) in THF-H2O (30 mL, 1:1 mixture) and the reaction mixture was stirred at room temperature for 30 min. NaIO4 (450 mg, 2.1 mmol) was then added and the reaction mixture was stirred for 1 hr at room temperature. The mixture was extracted with EtOAc and the solvent was removed under vacuum. The residue was chromatographed and eluted with EtOAc : CH2CL2 = 4 : 1 to give **29** (120 mg, 50 % yield) as a colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.88 (s, 1H), 8.27 (s, 1H), 7.90-7.75 (m, 4H), 7.65-7.50 (m, 2H), 6.58 (d, *J* = 6.8 Hz, 1H), 4.40-4.25 (m, 1H), 3.66 (s, 1H), 2.90 (s, 2H), 2.80-2.71 (m, 2H), 2.40-2.25 (m, 2H).

***N*-(trans-3-hydroxy-3-(2-oxoethyl)cyclobutyl)-2-naphthamide (30)**

Compound **30** was similarly prepared as compound **29** and was used directly without further purification.

***N*-(cis-3-(2-(((S)-2-amino-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl)(propyl)amino)ethyl)-3-hydroxycyclobutyl)-2-naphthamide (16)**

Compound **29** (130 mg, 0.46 mmol), sodium triacetoxyborohydride (146 mg, 0.69 mmol), and AcOH (41 mg, 0.69 mmol) were added to a solution of pramipexole (97 mg, 0.46 mmol) in CH_2Cl_2 (30 mL) and the mixture was stirred at room temperature for 4 h. The reaction was quenched by adding water (30 mL) and the mixture was extracted with CH_2Cl_2 (30 mL x 3). The organic solvent was removed under vacuum and the residue was chromatographed (MeOH:EA = 10:90) to give **16** (80 mg, 36 % yield) as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.28 (s, 1H), 8.00-7.78 (m, 4H), 7.65-7.50 (m, 2H), 6.68 (d, *J* = 7.7 Hz, 1H), 5.05 (s, 2H), 4.31-4.20 (m, 1H), 3.25-3.08 (m, 1H), 2.85-2.40 (m, 9H), 2.25-1.45 (m, 9H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.15, 166.13, 144.90, 134.82, 132.72, 131.76, 129.05, 128.55, 127.85, 127.73, 127.50, 126.84, 123.72, 116.49, 70.99, 56.01, 52.25, 47.11, 44.67, 44.48, 37.45, 34.38, 26.42, 24.53, 24.31, 21.66, 11.93.

***N*-(trans-3-(2-(((S)-2-amino-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl)(propyl)amino)ethyl)-3-hydroxycyclobutyl)-2-naphthamide (17)**

Compound **17** was similarly prepared as **16** in 49 % yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 7.95-7.75 (m, 4H), 7.65-7.45 (m, 2H), 6.50 (s, 1H), 4.90 (s, 2H), 4.75-4.63 (m, 1H), 3.30-3.10 (m, 1H), 2.85-2.40 (m, 9H), 2.25-1.45 (m, 9H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.22, 165.92, 144.84, 134.72, 132.63, 131.73, 128.93, 128.46, 127.77, 127.65, 127.34, 126.78, 123.60, 73.58, 55.99, 52.10, 46.52, 43.64, 40.61, 37.09, 29.73, 26.33, 24.54, 24.01, 21.43, 11.84.

II. *In vitro* binding assays to dopamine receptors using rat brain membrane preparation

All the synthesized compounds were determined for the binding affinities at the D_3, D_1-like and D_2-like receptors in membranes prepared from the brains of adult, male Sprague-Dawley rats (Pel-Freez, Rogers, AR). All compounds were dissolved in 100% EtOH at a concentration of 5 mM.

[^{3}H]R(+)-7-OH-DPAT binding assay. [^{3}H]*R*-(+)-7-OH-DPAT binding assays for the D_3 dopamine receptors were performed as previously described in detail.[1,2] Rat ventral striatum (nucleus accumbens and olfactory tubercles) was prepared in assay buffer (50 mM Tris, 1 mM EDTA; pH 7.4 at 23° C) to yield a final concentration of 10 mg original wet weight (o.w.w.)/ml. Membranes were incubated with [^{3}H]*R*-(+)-7-OH-DPAT (0.15 nM, SA = 163 Ci/mmol; GE Healthcare) and various concentrations of competing compounds (10^{-10} to 10^{-4} M). Nonspecific binding was defined by 1 µM spiperone. Assay tubes were incubated at 23° C for 90 min. The reaction was terminated by rapid vacuum filtration. Data were analyzed using SigmaPlot 8.0.2. using the K_D value for [^{3}H]7-OH-DPAT of 0.15 nM.**1** K_i values are expressed as the mean ± SEM of 3-6 independent determinations.

[^{3}H]Spiperone binding assays. [^{3}H]Spiperone binding assays for D_2-like receptors were performed as previously described in detail[2,3] and as described for [^{3}H] 7-OH-DPAT except for the following. Assays were performed using membranes prepared from rat caudate-putamen, which expresses D_2 receptors in high density but very low levels of D_3 receptors, and the final membrane homogenate concentration was 1.5 mg o.w.w./ml. The assay buffer was 50 mM Tris-HCl, 5 mM KCl, 2 mM $MgCl_2$, and 2 mM $CaCl_2$, pH 7.4 at 23°C; the concentration of [^{3}H]spiperone (24 Ci/mmol; GE Healthcare) was 0.2 nM; and the incubation time was 90 min at 23° C. Nonspecific binding was defined in the presence of 1 µM (+)-butaclamol. K_i values were calculated using the experimentally-determined K_D value of 0.4 nM for [^{3}H]spiperone.

[^{3}H]SCH 23390 binding assays. [^{3}H] SCH 23390 binding assays for D_1-like dopamine receptors were performed as previously described in detail[2] and as described for [^{3}H]spiperone binding except the

concentration of [^{3}H]SCH 23390 (73 Ci/mmol; GE Healthcare) was 0.3 nM. K_i values were calculated using the K_D value of 0.3 nM for [^{3}H]SCH 23390.[2]

III. *In vitro* binding assays and functional assays using cloned human dopamine receptors

Compound **17** was weighed and dissolved in DMSO to make a 10 mM stock solution. An initial dilution to 50 μM in assay buffer or water for binding was made. Subsequent dilutions were made with assay buffer supplemented with DMSO, maintaining a final concentration of 0.1% DMSO in all wells. Pipetting was conducted using a Biomek 2000 robotic workstation.

In vitro binding assays to cloned human dopamine receptors

Binding assay for human dopamine D1 receptor

Mouse fibroblast cells expressing the human D1 receptor at high density (LhD1 cells) were used. The cells were grown to confluence in Dulbecco's Minimal Essential Medium (DMEM) containing 10% FetalClone1 serum (FCS, HyClone), 0.05% penicillin-streptomycin (pen-strep), and 400 μg/ml of Geneticin (G418). Three confluent 150 mm plates yielded enough membranes for 3 assay plates with ~10-15 μg protein per well. The cells from three 150 mm plates were scraped and centrifuged at 500 x g for 5 minutes. The pellet was overlaid with 2 ml assay buffer (50 mM tris-HCl containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$) and frozen at -70^{o}C. On the day of experiment, the pellet was homogenized in 30 ml assay buffer with a polytron. Cell homogenate (100 μl) was added to wells containing 800 μl of test drug or buffer. After 10 minute preincubation, 100 μl of [^{3}H]SCH-23390 (0.18 nM final concentration) was added. The plates were incubated at 25^{o}C for 60 minutes. The reaction was terminated by filtration using a Tomtec 96 well harvester and the radioactivity on the filters was counted using a Perkin Elmer microbeta scintillation counter. Nonspecific binding was determined with 1 μM SCH-23390.

Binding assays for human dopamine D2 and D3 receptors

Chinese hamster ovary cells expressing the human D2 or D3 receptor (CHOp-D2 or CHOp-D3) were used. Cells were grown to confluence in alpha-minimal essential medium (alpha-MEM) containing 10% fetal bovine serum (FBS, Atlas Biologicals), 0.05% pen-strep, and 400 µg/ml of G418. Membranes were prepared according to the procedures described for D1 cells, using the D2/D3 binding buffer (50 mM tris containing 120 mM NaCl, 5 mM KCl, 1.5 mM $CaCl_2$, 4 mM $MgCl_2$, and 1 mM EDTA, pH 7.4). Three confluent 150 mm plates of D2 cells, resuspended in 30 ml of binding buffer, yielded enough membranes for 3 assay plates with ~10-15 µg protein per well. Two plates of D3 cells, resuspended in 30 ml, yielded enough membranes for 3 assay plates with ~7-10 µg protein per well. Cell homogenate (100 µl) was added to wells containing 800 µl of test drug or buffer. After 10 minutes, 100 µl of [^{3}H]YM-09151-2 (0.2-0.5 nM final concentration) was added. The plates were incubated at 25^{o}C for 60 minutes. The reaction was terminated by filtration through polyethylenimine-soaked (0.05%) filters using a Tomtec 96 well harvester. Radioactivity on the filters was counted using a Perkin Elmer microbeta scintillation counter. Nonspecific binding was determined with 1 µM chlorpromazine.

Functional assays for human dopamine receptors

Human dopamine D2 mitogenesis functional assay

CHOp-D2 cells were maintained in alpha-MEM with 10% FBS, 0.05% pen-strep, and 400 µg/ml of G418. To measure D2 stimulation of mitogenesis (agonist assay) or inhibition of quinpirole stimulation of mitogenesis (antagonist assay), CHOp-D2 cells were seeded in a 96-well plate at a concentration of 5,000 cells/well. The cells were incubated at 37°C in alpha-MEM with 10% FBS. After 48-72 hours, the cells were rinsed twice with serum-free alpha-MEM and incubated for 24 hours at 37°C. Serial dilutions of test compounds were made by the Biomek robotics system in serum-free alpha-MEM. In the functional assay for agonists, the medium was removed and replaced with 100 µl of test compound in

serum-free alpha-MEM. In the antagonist assay, the serial dilution of the putative antagonist test compound was added in 90 µl (1.1 times of final concentration) and 300 nM quinpirole (30 nM final) was added in 10 µl. After another 24-hour incubation at 37°C, 0.25 µCi of [^{3}H]thymidine in alpha-MEM supplemented with 10% FCS was added to each well and the plates were further incubated for 2 hours at 37°C. The cells were trypsinized by addition of 10 times trypsin solution (1% trypsin in calcium-magnesium-free phosphate-buffered saline) and the plates were filtered and counted as usual. Quinpirole was run each day as an internal control and dopamine was included for comparative purposes.

Human dopamine D3 mitogenesis functional assay

CHOp-D3 cells were maintained in alpha-MEM with 10% fetal bovine serum (FBS, Atlas Biologicals), 0.05% pen-strep, and 400 µg/ml of G418. To measure D3 stimulation of mitogenesis (agonist assay) or inhibition of quinpirole stimulation of mitogenesis (antagonist assay), CHOp-D3 cells were seeded in a 96-well plate at a concentration of 5,000 cells/well. The cells were incubated at 37°C in alpha-MEM with 10% FBS. After 48-72 hours, the cells were rinsed twice with serum-free alpha-MEM and incubated for 24 hours at 37°C. Serial dilutions of test compounds were made by the Biomek robotics system in serum-free alpha-MEM. In the functional assay for agonists, the medium was removed and replaced with 100 µl of test compound in serum-free alpha-MEM. In the antagonist assay, the serial dilution of the putative antagonist test compound was added in 90 µl (1.1X of final concentration) and 300 nM quinpirole (30 nM final) was added in 10 ul. After another 16-hour incubation at 37°C, 0.25 µCi of [3H]thymidine in alpha-MEM supplemented with 10% FBS was added to each well and the plates were further incubated for 2 hours at 37°C. The cells were trypsinized by addition of 10X trypsin solution (1% trypsin in calcium-magnesium-free phosphate-buffered saline) and

the plates were filtered and counted as usual. Quinpirole was run each day as an internal control and dopamine was included for comparative purposes.

Data analysis: For binding, data were normalized to the binding in the absence of drug. Three or more independent competition experiments were conducted with duplicate determinations. GraphPAD Prism was used to analyze the ensuing data, with IC_{50} values converted to K_i values using the Cheng-Prusoff equation ($K_i=IC_{50}/(1+([drug^*]/K_d\ drug^*))$), where drug* was the labeled ligand used in the binding assays. The K_d values used in the equations were 0.62 nM for [^{3}H]SCH-23390 at dopamine D1 receptors, 0.06 nM for [^{3}H]YM-09151-2 at dopamine D2 receptors, and 0.12 nM for [^{3}H]YM-09151-2 at dopamine D3 receptors. For functional assays, GraphPAD Prism was used to calculate either EC_{50} (agonists) or IC_{50} (antagonists) values using data expressed as pg cAMP for adenylate cyclase activity and % quinpirole-stimulation for mitogenesis.

IV. *In vivo* Yawning and hypothermia assays in rats

Rats were purchased from Harlan (Indianapolis, IN) and housed three to a cage for yawning studies, or one to a cage for hypothermia studies. For hypothermia studies, a radio-telemetric probe (E-4000 E-Mitter, Mini-Mitter, Bend, OR, USA) was implanted in the rats as previously described,[4] and the rats were allowed a 7-day recovery period. Yawning, defined as a prolonged (~1 sec.) wide opening of the mouth followed by a rapid closure, was evaluated using previously described methods.[4,5] The *in vivo* profiles of activity for pramipexole, **16** (CJ-1638), and **17** (CJ-1639) were assessed over a range of doses, with yawning and hypothermia recorded for a period of 60-min after the s.c. administration of compounds (1ml/kg). In order to determine whether the induction of yawning by **17** (CJ-1639) was mediated by its activation of the D3 receptor, rats were pretreated with a D3-selective dose of SB-277011A 30 min prior to the maximally effective dose of pramipexole (0.1 mg/kg) or CJ-1639 (1.0 mg/kg) to induce yawning. Pretreatments with a D2-selective dose of L-741,626 were used to determine if the

inhibition of yawning and induction of hypothermia observed at doses of 10.0 mg/kg CJ-1639 and 0.32 mg/kg pramipexole were similarly mediated by D2 agonist activity. The effects of compounds on core body temperature represent the change in body temperature (°C) observed 60 min after the administration of pramipexole or **17** (CJ-1639) as compared to the body temperature obtained 1 min prior to injection of that compound. Yawns and changes in core body temperature are presented as the mean ± standard error of the mean (SEM) with 6 rats per group. A one-way, repeated-measures ANOVA with post-hoc Newman-Keuls tests was used to determine significant changes in yawning or body temperature compared to vehicle, as well as to determine significant differences in pramipexole- and **17** (CJ-1639)-induced yawning and hypothermia following antagonist pretreatments (GraphPad Prism; GraphPad Software Inc., San Diego, CA).

Animals

Male Sprague-Dawley rats (Harlan; Indianapolis, IN) weighing 250-300 g housed three to a cage for yawning studies, and one to a cage for hypothermia studies, were maintained on a 12-h dark/light cycle with lights on at 7:00 AM in a temperature (21-23 ºC) and humidity controlled environment with free access to standard Purina rodent chow and water. All studies were performed in accordance with the Guide for the Care and Use of Laboratory Animals, as adopted and promulgated by the National Institutes of Health, and all experimental procedures were approved by the University of Michigan Committee on the Use and Care of Animals.

Induction of Yawning Behavior

On the day of testing, rats were transferred from their home cage to a test chamber (48 cm x 23 cm x 20 cm clear rodent cage with standard cob bedding), and allowed to habituate to the chamber for a period of 30 min prior to a sterile water injection which was administered 30 min prior to the injection of the compound of interest. Yawns were then scored for a period of 60 min. Each compound was

assessed in groups of 6 rats, with each rat receiving a single dose of a compound. Food and water were unavailable during test sessions, and all experiments were conducted between the hours of 12:00 PM and 6:00 PM with at least 72 hrs between test sessions to allow for drug washout.

Measurement of Core Body Temperature

Rats were anesthetized with ketamine/xylazine (100/10 mg/kg; i.p.) and their abdominal area was shaved and cleaned with alternating betadine and alcohol swabs prior to surgical implantation of radio-telemetric probes (E-4000 E-Mitter, Mini-Mitter, Bend, OR, USA). A small rostral-caudal incision was made in the abdominal wall to allow for insertion of the probe, and the abdominal wall was closed using absorbable, 5-0 chromic gut suture, and the skin was closed using 5-0 Ethilon® suture. A 7-day recovery period was provided prior to experimentation.

On the day of testing, rats were weighed and returned to their home cages, which were placed onto a receiving pad (ER-4000 Receiver, Mini-mitter, Bend, OR) to allow for the collection of core body temperature. Temperature measurements were taken every min with at least 30 min of baseline temperature data recorded prior to the administration of antagonist or vehicle. Agonist or vehicle injections were administered 30 min thereafter, and core body temperature was recorded for a period of at least the next 60 min. Rats were removed from the receivers for a period of 5 min to allow for injections to be administered, but were otherwise uninterrupted. Each rat was tested at each dose condition, with at least 72 hrs between test sessions. All experiments were carried out between the hours of 12:00 PM and 6:00 PM.

Effects of SB-277011A and L-741,626 on the Induction of Yawning and Hypothermia by **17** (CJ-1639) *and Pramipexole*

Measures of yawning behavior and core body temperature were performed as described above with the exception that 32.0 mg/kg SB-277011A, or 1.0 mg/kg L-741,626 were administered 30 min prior to doses of 0.1 or 0.32 mg/kg pramipexole, and doses of 1.0 or 10.0 mg/kg **17** (CJ-1639). The observation of yawning was initiated immediately after the administration of pramipexole or **17** (CJ-1639), and the total number of yawns was recorded for 60 min thereafter. Core body temperature was continuously measured for at least 60 min after the administration of pramipexole, or **17** (CJ-1639). Separate groups of 6 rats were used for each agonist in the yawning studies, and for each agonist in the hypothermia studies.

Drugs

Pramipexole, **16** (CJ-1638), and **17** (CJ-1639) were dissolved in sterile water, whereas SB-277011A was dissolved in 20% β-cyclodextrin, and L-741,626 was dissolved in 5% EtOH and water. All drugs were administered subcutaneously (s.c.) in a volume of 1 ml/kg, with the exception of the 10.0 mg/kg doses of **16** (CJ-1638) and **17** (CJ-1639) which were administered in a volume of 3 ml/kg.

Data Analysis

Dose-response curves for the induction of yawning and hypothermia were determined with 6 rats per group, and results expressed as the mean number of yawns, or change in body temperature 60 min post agonist injection compared to the body temperature 1 min prior to the agonist injection ± standard error of the mean (SEM). The effects antagonists on pramipexole- or **17** (CJ-1639)-induced yawning and hypothermia are expressed as the mean number of yawns or change in body temperature observed during the 60-min period immediately following the administration of pramipexole or **17** (CJ-1639). One-way, repeated-measures ANOVA with post-hoc Newman-Keuls tests were used to determine if compounds induced significantly more yawning or hypothermia as compared to vehicle, as well as to

determine if pretreatments significantly altered pramipexole-induced yawning or hypothermia (GraphPad Prism; GraphPad Software Inc., San Diego, CA).

V. **Single Crystal X-ray Diffraction Analysis**

Single-crystal X-ray diffraction data on compounds **20**, and **27** were collected using MoKα radiation (λ = 0.71073 Å) and a Bruker APEX 2 CCD area detector. Crystals were prepared for data collection by coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was placed on a MicroMesh mount (MiTeGen, Ithaca, NY) and transferred immediately to the diffractometer. Data was collected at 296°K (room temperature). Corrections were applied for Lorentz, polarization, and absorption effects. The structures were solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C-H distance set at 0.96 Å.

20. The 0.521 x 0.414 x 0.107 mm^3 crystal was triclininc in space group *P* -1 with unit cell dimensions *a* = 10.1477(11) Å, *b* = 13.4374(15) Å, *c* = 13.9713(15) Å, α= 116.199(3)°, β= 96.488(4)°, and γ = 90.972(4)°. Data were 97.4% complete to 29.62° θ (approximately 0.73 Å) with an average redundancy of 2.14.

27. The 0.490 x 0.096 x 0.059 mm^3 crystal was monolininc in space group *P* c with unit cell dimensions *a* = 14.8651(7) Å, *b* = 11.9815(6) Å, *c* = 8.6798(4) Å, and β = 101.688(2)°. Data were 98.8% complete to 28.42° θ (approximately 0.73 Å) with an average redundancy of 4.05.

Table S1. Crystal data and structure refinement for **20**.

Identification code	wang41	
Empirical formula	$C_{20}H_{23}NO_2$	
Formula weight	309.39	
Temperature	296(2) °K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.1477(11) Å	α= 116.199(3)°
	b = 13.4374(15) Å	β= 96.488(4)°
	c = 13.9713(15) Å	γ = 90.972(4)°
Volume	1693.7(3) $Å^3$	
Z	4	
Density (calculated)	1.213 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	664	
Crystal size	0.521 x 0.414 x 0.107 mm^3	
θ range for data collection	1.64 to 29.62°.	
Index ranges	-14<=h<=14, -18<=k<=17, -19<=l<=19	
Reflections collected	20429	
Independent reflections	9294 [R(int) = 0.0174]	
Completeness to θ = 25.00°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9917 and 0.9606	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9294 / 0 / 417	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2σ(I)]	R1 = 0.0527, wR2 = 0.1466	
R indices (all data)	R1 = 0.0761, wR2 = 0.1637	
Largest diff. peak and hole	0.391 and -0.278 $e.Å^{-3}$	

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **20**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9555(1)	7176(1)	6123(1)	52(1)
C(2)	8243(1)	6622(1)	6140(1)	57(1)
C(3)	8228(1)	6498(1)	7164(1)	56(1)
C(4)	9383(1)	5861(1)	7357(1)	52(1)
O(4)	9265(1)	4741(1)	6515(1)	57(1)
C(5)	10698(1)	6401(1)	7307(1)	57(1)
C(6)	10714(1)	6543(1)	6287(1)	56(1)
N(7)	9556(1)	7277(1)	5121(1)	56(1)
C(8)	9009(1)	8123(1)	5003(1)	53(1)
O(8)	8596(1)	8894(1)	5764(1)	70(1)
C(9)	8889(1)	8120(1)	3923(1)	52(1)
C(10)	8701(1)	9109(1)	3885(1)	53(1)
C(11)	8428(1)	9172(1)	2907(1)	55(1)
C(12)	8180(2)	10183(1)	2857(1)	66(1)
C(13)	7839(2)	10201(2)	1898(2)	79(1)
C(14)	7730(2)	9210(2)	935(2)	85(1)
C(15)	7972(2)	8232(2)	950(1)	79(1)
C(16)	8336(1)	8174(1)	1930(1)	60(1)
C(17)	8579(2)	7169(1)	1988(1)	69(1)
C(18)	8856(2)	7137(1)	2949(1)	63(1)
C(19)	9432(2)	5832(1)	8449(1)	65(1)
C(20)	8224(2)	5297(2)	8603(1)	75(1)
C(21)	8203(2)	4567(2)	8968(2)	92(1)
C(1')	5921(1)	12223(1)	6111(1)	45(1)
C(2')	4799(1)	11610(1)	6320(1)	50(1)
C(3')	5185(1)	11459(1)	7328(1)	53(1)
C(4')	6470(1)	10887(1)	7308(1)	47(1)
O(4')	6218(1)	9775(1)	6451(1)	53(1)
C(5')	7588(1)	11500(1)	7084(1)	49(1)
C(6')	7204(1)	11645(1)	6068(1)	49(1)
N(7')	5538(1)	12306(1)	5107(1)	50(1)
C(8')	5965(1)	13171(1)	4960(1)	46(1)
O(8')	6622(1)	13986(1)	5692(1)	61(1)
C(9')	5635(1)	13130(1)	3870(1)	44(1)
C(10')	5824(1)	14098(1)	3781(1)	47(1)
C(11')	5658(1)	14117(1)	2774(1)	48(1)
C(12')	5893(2)	15108(1)	2671(1)	63(1)
C(13')	5787(2)	15087(2)	1684(2)	75(1)
C(14')	5420(2)	14095(2)	753(2)	76(1)
C(15')	5172(2)	13127(2)	819(1)	68(1)
C(16')	5283(1)	13114(1)	1833(1)	52(1)
C(17')	5051(2)	12131(1)	1946(1)	61(1)
C(18')	5217(2)	12135(1)	2929(1)	56(1)
C(19')	6792(2)	10833(2)	8390(1)	68(1)

C(20')	7984(3)	10257(2)	8487(2)	112(1)
C(21')	8846(3)	10455(5)	9173(3)	219(2)

Table S3. Bond lengths [Å] and angles [°] for **20**.

C(1)-N(7)	1.4647(18)	C(1)-C(6)	1.5181(18)
C(1)-C(2)	1.5218(19)	C(1)-H(1A)	0.9800
C(2)-C(3)	1.513(2)	C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700	C(3)-C(4)	1.5322(19)
C(3)-H(3A)	0.9700	C(3)-H(3B)	0.9700
C(4)-O(4)	1.4359(15)	C(4)-C(5)	1.5305(19)
C(4)-C(19)	1.539(2)	O(4)-H(4)	0.8200
C(5)-C(6)	1.522(2)	C(5)-H(5A)	0.9700
C(5)-H(5B)	0.9700	C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700	N(7)-C(8)	1.3393(18)
N(7)-H(7A)	0.8600	C(8)-O(8)	1.2345(16)
C(8)-C(9)	1.498(2)	C(9)-C(10)	1.370(2)
C(9)-C(18)	1.4133(18)	C(10)-C(11)	1.403(2)
C(10)-H(10A)	0.9300	C(11)-C(12)	1.416(2)
C(11)-C(16)	1.421(2)	C(12)-C(13)	1.356(2)
C(12)-H(12A)	0.9300	C(13)-C(14)	1.406(3)
C(13)-H(13A)	0.9300	C(14)-C(15)	1.350(3)
C(14)-H(14A)	0.9300	C(15)-C(16)	1.413(2)
C(15)-H(15A)	0.9300	C(16)-C(17)	1.412(2)
C(17)-C(18)	1.360(2)	C(17)-H(17A)	0.9300
C(18)-H(18A)	0.9300	C(19)-C(20)	1.494(2)
C(19)-H(19A)	0.9700	C(19)-H(19B)	0.9700
C(20)-C(21)	1.290(3)	C(20)-H(20A)	0.9300
C(21)-H(21A)	0.9300	C(21)-H(21B)	0.9300
C(1')-N(7')	1.4651(16)	C(1')-C(6')	1.5211(17)
C(1')-C(2')	1.5216(18)	C(1')-H(1'A)	0.9800
C(2')-C(3')	1.5194(19)	C(2')-H(2'A)	0.9700
C(2')-H(2'B)	0.9700	C(3')-C(4')	1.5211(18)
C(3')-H(3'A)	0.9700	C(3')-H(3'B)	0.9700
C(4')-O(4')	1.4378(15)	C(4')-C(5')	1.5294(19)
C(4')-C(19')	1.5446(19)	O(4')-H(4'A)	0.8200
C(5')-C(6')	1.5262(19)	C(5')-H(5'A)	0.9700
C(5')-H(5'B)	0.9700	C(6')-H(6'A)	0.9700
C(6')-H(6'B)	0.9700	N(7')-C(8')	1.3398(16)
N(7')-H(7'A)	0.8600	C(8')-O(8')	1.2334(15)
C(8')-C(9')	1.4983(18)	C(9')-C(10')	1.3718(17)
C(9')-C(18')	1.4142(18)	C(10')-C(11')	1.4104(19)
C(10')-H(10B)	0.9300	C(11')-C(16')	1.4119(19)
C(11')-C(12')	1.4205(19)	C(12')-C(13')	1.359(2)
C(12')-H(12B)	0.9300	C(13')-C(14')	1.397(3)
C(13')-H(13B)	0.9300	C(14')-C(15')	1.365(2)
C(14')-H(14B)	0.9300	C(15')-C(16')	1.417(2)
C(15')-H(15B)	0.9300	C(16')-C(17')	1.417(2)
C(17')-C(18')	1.362(2)	C(17')-H(17B)	0.9300
C(18')-H(18B)	0.9300	C(19')-C(20')	1.472(3)
C(19')-H(19C)	0.9700	C(19')-H(19D)	0.9700
C(20')-C(21')	1.154(4)	C(20')-H(20B)	0.9300

C(21')-H(21C)	0.9300	C(21')-H(21D)	0.9300
N(7)-C(1)-C(6)	110.80(11)	N(7)-C(1)-C(2)	111.13(12)
C(6)-C(1)-C(2)	110.69(11)	N(7)-C(1)-H(1A)	108.0
C(6)-C(1)-H(1A)	108.0	C(2)-C(1)-H(1A)	108.0
C(3)-C(2)-C(1)	111.99(12)	C(3)-C(2)-H(2A)	109.2

Table S3. (continued)

C(1)-C(2)-H(2A)	109.2	C(3)-C(2)-H(2B)	109.2
C(1)-C(2)-H(2B)	109.2	H(2A)-C(2)-H(2B)	107.9
C(2)-C(3)-C(4)	112.44(11)	C(2)-C(3)-H(3A)	109.1
C(4)-C(3)-H(3A)	109.1	C(2)-C(3)-H(3B)	109.1
C(4)-C(3)-H(3B)	109.1	H(3A)-C(3)-H(3B)	107.8
O(4)-C(4)-C(5)	106.58(10)	O(4)-C(4)-C(3)	109.96(11)
C(5)-C(4)-C(3)	109.56(12)	O(4)-C(4)-C(19)	109.05(12)
C(5)-C(4)-C(19)	109.54(12)	C(3)-C(4)-C(19)	112.00(11)
C(4)-O(4)-H(4)	109.5	C(6)-C(5)-C(4)	113.64(11)
C(6)-C(5)-H(5A)	108.8	C(4)-C(5)-H(5A)	108.8
C(6)-C(5)-H(5B)	108.8	C(4)-C(5)-H(5B)	108.8
H(5A)-C(5)-H(5B)	107.7	C(1)-C(6)-C(5)	111.24(11)
C(1)-C(6)-H(6A)	109.4	C(5)-C(6)-H(6A)	109.4
C(1)-C(6)-H(6B)	109.4	C(5)-C(6)-H(6B)	109.4
H(6A)-C(6)-H(6B)	108.0	C(8)-N(7)-C(1)	121.00(11)
C(8)-N(7)-H(7A)	119.5	C(1)-N(7)-H(7A)	119.5
O(8)-C(8)-N(7)	121.10(14)	O(8)-C(8)-C(9)	119.84(13)
N(7)-C(8)-C(9)	119.05(11)	C(10)-C(9)-C(18)	119.08(14)
C(10)-C(9)-C(8)	117.68(12)	C(18)-C(9)-C(8)	123.04(13)
C(9)-C(10)-C(11)	121.97(12)	C(9)-C(10)-H(10A)	119.0
C(11)-C(10)-H(10A)	119.0	C(10)-C(11)-C(12)	122.50(13)
C(10)-C(11)-C(16)	118.66(14)	C(12)-C(11)-C(16)	118.77(15)
C(13)-C(12)-C(11)	120.86(16)	C(13)-C(12)-H(12A)	119.6
C(11)-C(12)-H(12A)	119.6	C(12)-C(13)-C(14)	120.16(18)
C(12)-C(13)-H(13A)	119.9	C(14)-C(13)-H(13A)	119.9
C(15)-C(14)-C(13)	120.66(18)	C(15)-C(14)-H(14A)	119.7
C(13)-C(14)-H(14A)	119.7	C(14)-C(15)-C(16)	121.11(17)
C(14)-C(15)-H(15A)	119.4	C(16)-C(15)-H(15A)	119.4
C(17)-C(16)-C(15)	123.19(15)	C(17)-C(16)-C(11)	118.37(14)
C(15)-C(16)-C(11)	118.42(15)	C(18)-C(17)-C(16)	121.52(14)
C(18)-C(17)-H(17A)	119.2	C(16)-C(17)-H(17A)	119.2
C(17)-C(18)-C(9)	120.28(14)	C(17)-C(18)-H(18A)	119.9
C(9)-C(18)-H(18A)	119.9	C(20)-C(19)-C(4)	115.60(13)
C(20)-C(19)-H(19A)	108.4	C(4)-C(19)-H(19A)	108.4
C(20)-C(19)-H(19B)	108.4	C(4)-C(19)-H(19B)	108.4
H(19A)-C(19)-H(19B)	107.4	C(21)-C(20)-C(19)	126.5(2)
C(21)-C(20)-H(20A)	116.8	C(19)-C(20)-H(20A)	116.8
C(20)-C(21)-H(21A)	120.0	C(20)-C(21)-H(21B)	120.0
H(21A)-C(21)-H(21B)	120.0	N(7')-C(1')-C(6')	110.75(11)
N(7')-C(1')-C(2')	109.79(10)	C(6')-C(1')-C(2')	110.98(10)
N(7')-C(1')-H(1'A)	108.4	C(6')-C(1')-H(1'A)	108.4
C(2')-C(1')-H(1'A)	108.4	C(3')-C(2')-C(1')	111.33(11)
C(3')-C(2')-H(2'A)	109.4	C(1')-C(2')-H(2'A)	109.4
C(3')-C(2')-H(2'B)	109.4	C(1')-C(2')-H(2'B)	109.4
H(2'A)-C(2')-H(2'B)	108.0	C(2')-C(3')-C(4')	113.10(11)

C(2')-C(3')-H(3'A)	109.0	C(4')-C(3')-H(3'A)	109.0
C(2')-C(3')-H(3'B)	109.0	C(4')-C(3')-H(3'B)	109.0
H(3'A)-C(3')-H(3'B)	107.8	O(4')-C(4')-C(3')	106.73(10)
O(4')-C(4')-C(5')	109.68(10)	C(3')-C(4')-C(5')	110.22(11)
O(4')-C(4')-C(19')	109.19(11)	C(3')-C(4')-C(19')	108.28(11)
C(5')-C(4')-C(19')	112.56(11)	C(4')-O(4')-H(4'A)	109.5
C(6')-C(5')-C(4')	112.05(10)	C(6')-C(5')-H(5'A)	109.2
C(4')-C(5')-H(5'A)	109.2	C(6')-C(5')-H(5'B)	109.2

Table S3. (continued)

C(4')-C(5')-H(5'B)	109.2	H(5'A)-C(5')-H(5'B)	107.9
C(1')-C(6')-C(5')	111.71(11)	C(1')-C(6')-H(6'A)	109.3
C(5')-C(6')-H(6'A)	109.3	C(1')-C(6')-H(6'B)	109.3
C(5')-C(6')-H(6'B)	109.3	H(6'A)-C(6')-H(6'B)	107.9
C(8')-N(7')-C(1')	122.14(10)	C(8')-N(7')-H(7'A)	118.9
C(1')-N(7')-H(7'A)	118.9	O(8')-C(8')-N(7')	121.80(12)
O(8')-C(8')-C(9')	119.86(12)	N(7')-C(8')-C(9')	118.34(11)
C(10')-C(9')-C(18')	118.96(12)	C(10')-C(9')-C(8')	117.83(11)
C(18')-C(9')-C(8')	123.10(11)	C(9')-C(10')-C(11')	121.70(12)
C(9')-C(10')-H(10B)	119.1	C(11')-C(10')-H(10B)	119.1
C(10')-C(11')-C(16')	119.07(12)	C(10')-C(11')-C(12')	122.09(13)
C(16')-C(11')-C(12')	118.81(13)	C(13')-C(12')-C(11')	120.56(15)
C(13')-C(12')-H(12B)	119.7	C(11')-C(12')-H(12B)	119.7
C(12')-C(13')-C(14')	120.63(15)	C(12')-C(13')-H(13B)	119.7
C(14')-C(13')-H(13B)	119.7	C(15')-C(14')-C(13')	120.56(16)
C(15')-C(14')-H(14B)	119.7	C(13')-C(14')-H(14B)	119.7
C(14')-C(15')-C(16')	120.46(16)	C(14')-C(15')-H(15B)	119.8
C(16')-C(15')-H(15B)	119.8	C(11')-C(16')-C(15')	118.97(13)
C(11')-C(16')-C(17')	118.31(13)	C(15')-C(16')-C(17')	122.72(14)
C(18')-C(17')-C(16')	121.45(13)	C(18')-C(17')-H(17B)	119.3
C(16')-C(17')-H(17B)	119.3	C(17')-C(18')-C(9')	120.44(13)
C(17')-C(18')-H(18B)	119.8	C(9')-C(18')-H(18B)	119.8
C(20')-C(19')-C(4')	115.26(14)	C(20')-C(19')-H(19C)	108.5
C(4')-C(19')-H(19C)	108.5	C(20')-C(19')-H(19D)	108.5
C(4')-C(19')-H(19D)	108.5	H(19C)-C(19')-H(19D)	107.5
C(21')-C(20')-C(19')	132.7(3)	C(21')-C(20')-H(20B)	113.6
C(19')-C(20')-H(20B)	113.6	C(20')-C(21')-H(21C)	120.0
C(20')-C(21')-H(21D)	120.0	H(21C)-C(21')-H(21D)	120.0

Table S4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **20**. 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)	46(1)	40(1)	60(1)	13(1)	15(1)	6(1)
C(2)	40(1)	48(1)	77(1)	21(1)	13(1)	8(1)
C(3)	45(1)	44(1)	73(1)	16(1)	22(1)	8(1)
C(4)	46(1)	40(1)	56(1)	9(1)	14(1)	4(1)
O(4)	52(1)	41(1)	63(1)	10(1)	14(1)	8(1)
C(5)	43(1)	56(1)	66(1)	20(1)	8(1)	2(1)
C(6)	40(1)	53(1)	68(1)	20(1)	14(1)	5(1)
N(7)	54(1)	44(1)	63(1)	15(1)	20(1)	13(1)
C(8)	44(1)	41(1)	62(1)	12(1)	11(1)	6(1)
O(8)	78(1)	54(1)	64(1)	12(1)	19(1)	26(1)
C(9)	39(1)	43(1)	61(1)	11(1)	10(1)	6(1)
C(10)	43(1)	41(1)	63(1)	11(1)	9(1)	3(1)
C(11)	39(1)	49(1)	68(1)	19(1)	9(1)	1(1)
C(12)	58(1)	56(1)	82(1)	28(1)	9(1)	2(1)
C(13)	71(1)	77(1)	98(1)	48(1)	10(1)	4(1)
C(14)	81(1)	101(2)	81(1)	49(1)	10(1)	8(1)
C(15)	79(1)	80(1)	66(1)	22(1)	12(1)	6(1)
C(16)	48(1)	60(1)	64(1)	19(1)	12(1)	5(1)
C(17)	75(1)	52(1)	61(1)	6(1)	14(1)	11(1)
C(18)	65(1)	43(1)	66(1)	11(1)	13(1)	11(1)
C(19)	66(1)	60(1)	60(1)	16(1)	15(1)	0(1)
C(20)	74(1)	76(1)	72(1)	27(1)	24(1)	3(1)
C(21)	101(2)	74(1)	91(1)	27(1)	26(1)	-8(1)
C(1')	47(1)	37(1)	50(1)	18(1)	4(1)	1(1)
C(2')	41(1)	49(1)	62(1)	26(1)	9(1)	6(1)
C(3')	52(1)	53(1)	58(1)	25(1)	17(1)	9(1)
C(4')	51(1)	41(1)	45(1)	18(1)	5(1)	3(1)
O(4')	55(1)	38(1)	61(1)	19(1)	7(1)	1(1)
C(5')	43(1)	43(1)	57(1)	19(1)	-1(1)	0(1)
C(6')	43(1)	46(1)	61(1)	25(1)	10(1)	0(1)
N(7')	54(1)	42(1)	53(1)	23(1)	-3(1)	-6(1)
C(8')	40(1)	40(1)	58(1)	21(1)	5(1)	1(1)
O(8')	66(1)	49(1)	62(1)	23(1)	-4(1)	-14(1)
C(9')	37(1)	40(1)	57(1)	22(1)	7(1)	2(1)
C(10')	42(1)	40(1)	59(1)	21(1)	7(1)	3(1)
C(11')	39(1)	47(1)	66(1)	30(1)	12(1)	8(1)
C(12')	64(1)	53(1)	81(1)	38(1)	12(1)	5(1)
C(13')	80(1)	75(1)	97(1)	60(1)	17(1)	8(1)
C(14')	85(1)	87(1)	77(1)	53(1)	21(1)	15(1)
C(15')	76(1)	70(1)	63(1)	33(1)	16(1)	12(1)
C(16')	48(1)	53(1)	61(1)	28(1)	13(1)	9(1)
C(17')	77(1)	46(1)	55(1)	19(1)	6(1)	-2(1)
C(18')	66(1)	40(1)	61(1)	23(1)	7(1)	-3(1)
C(19')	79(1)	75(1)	54(1)	31(1)	11(1)	13(1)

C(20')	110(2)	179(2)	79(1)	81(2)	25(1)	65(2)
C(21')	104(2)	463(7)	215(3)	263(4)	26(2)	63(3)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for **20**.

	x	y	z	U(eq)
H(1A)	9662	7927	6722	62
H(2A)	7523	7063	6075	68
H(2B)	8094	5894	5527	68
H(3A)	7394	6108	7123	68
H(3B)	8275	7230	7770	68
H(4)	8476	4523	6322	85
H(5A)	10870	7125	7925	69
H(5B)	11412	5948	7357	69
H(6A)	11543	6942	6333	67
H(6B)	10668	5817	5672	67
H(7A)	9913	6785	4601	67
H(10A)	8756	9759	4526	64
H(12A)	8251	10843	3490	80
H(13A)	7676	10871	1878	95
H(14A)	7490	9228	281	102
H(15A)	7896	7584	304	95
H(17A)	8550	6514	1354	83
H(18A)	9025	6467	2965	75
H(19A)	10195	5439	8537	78
H(19B)	9576	6589	9015	78
H(20A)	7406	5511	8417	90
H(21A)	8996	4326	9165	110
H(21B)	7396	4282	9034	110
H(1'A)	6069	12977	6703	54
H(2'A)	4013	12026	6401	60
H(2'B)	4583	10887	5707	60
H(3'A)	4473	11023	7408	64
H(3'B)	5286	12182	7949	64
H(4'A)	6923	9530	6248	79
H(5'A)	7804	12225	7693	59
H(5'B)	8375	11086	7006	59
H(6'A)	7915	12080	5984	59
H(6'B)	7095	10921	5446	59
H(7'A)	5023	11781	4594	60
H(10B)	6068	14758	4402	57
H(12B)	6122	15778	3285	75
H(13B)	5960	15740	1627	90
H(14B)	5344	14094	83	91
H(15B)	4929	12471	193	82
H(17B)	4779	11468	1335	73
H(18B)	5055	11479	2981	67
H(19C)	6906	11586	8965	82
H(19D)	6034	10461	8496	82
H(20B)	8058	9603	7872	135

H(21C)	8860	11092	9821	262
H(21D)	9525	9978	9079	262

Table S6. Torsion angles [°] for **20**.

N(7)-C(1)-C(2)-C(3)	179.33(10)
C(6)-C(1)-C(2)-C(3)	55.77(15)
C(1)-C(2)-C(3)-C(4)	-55.90(15)
C(2)-C(3)-C(4)-O(4)	-63.79(15)
C(2)-C(3)-C(4)-C(5)	53.03(15)
C(2)-C(3)-C(4)-C(19)	174.79(12)
O(4)-C(4)-C(5)-C(6)	66.17(15)
C(3)-C(4)-C(5)-C(6)	-52.75(15)
C(19)-C(4)-C(5)-C(6)	-175.98(12)
N(7)-C(1)-C(6)-C(5)	-178.15(11)
C(2)-C(1)-C(6)-C(5)	-54.39(15)
C(4)-C(5)-C(6)-C(1)	54.45(16)
C(6)-C(1)-N(7)-C(8)	-153.41(12)
C(2)-C(1)-N(7)-C(8)	83.08(15)
C(1)-N(7)-C(8)-O(8)	6.6(2)
C(1)-N(7)-C(8)-C(9)	-172.85(11)
O(8)-C(8)-C(9)-C(10)	19.25(19)
N(7)-C(8)-C(9)-C(10)	-161.31(13)
O(8)-C(8)-C(9)-C(18)	-155.60(14)
N(7)-C(8)-C(9)-C(18)	23.85(19)
C(18)-C(9)-C(10)-C(11)	2.4(2)
C(8)-C(9)-C(10)-C(11)	-172.67(11)
C(9)-C(10)-C(11)-C(12)	177.42(14)
C(9)-C(10)-C(11)-C(16)	0.5(2)
C(10)-C(11)-C(12)-C(13)	-175.90(15)
C(16)-C(11)-C(12)-C(13)	1.1(2)
C(11)-C(12)-C(13)-C(14)	-0.2(3)
C(12)-C(13)-C(14)-C(15)	-0.4(3)
C(13)-C(14)-C(15)-C(16)	0.1(3)
C(14)-C(15)-C(16)-C(17)	179.07(19)
C(14)-C(15)-C(16)-C(11)	0.8(3)
C(10)-C(11)-C(16)-C(17)	-2.6(2)
C(12)-C(11)-C(16)-C(17)	-179.71(14)
C(10)-C(11)-C(16)-C(15)	175.74(13)
C(12)-C(11)-C(16)-C(15)	-1.3(2)
C(15)-C(16)-C(17)-C(18)	-176.30(16)
C(11)-C(16)-C(17)-C(18)	2.0(2)
C(16)-C(17)-C(18)-C(9)	0.9(2)
C(10)-C(9)-C(18)-C(17)	-3.1(2)
C(8)-C(9)-C(18)-C(17)	171.71(14)
O(4)-C(4)-C(19)-C(20)	-62.13(16)
C(5)-C(4)-C(19)-C(20)	-178.42(13)
C(3)-C(4)-C(19)-C(20)	59.81(17)
C(4)-C(19)-C(20)-C(21)	132.7(2)
N(7')-C(1')-C(2')-C(3')	177.27(10)
C(6')-C(1')-C(2')-C(3')	54.50(14)
C(1')-C(2')-C(3')-C(4')	-54.85(15)

C(2')-C(3')-C(4')-O(4')	-65.29(14)
C(2')-C(3')-C(4')-C(5')	53.75(15)
C(2')-C(3')-C(4')-C(19')	177.27(12)
O(4')-C(4')-C(5')-C(6')	63.71(13)
C(3')-C(4')-C(5')-C(6')	-53.52(14)
C(19')-C(4')-C(5')-C(6')	-174.51(11)

Table S6. (continued)

N(7')-C(1')-C(6')-C(5')	-177.27(10)
C(2')-C(1')-C(6')-C(5')	-55.07(14)
C(4')-C(5')-C(6')-C(1')	55.16(14)
C(6')-C(1')-N(7')-C(8')	-88.91(14)
C(2')-C(1')-N(7')-C(8')	148.19(12)
C(1')-N(7')-C(8')-O(8')	-5.60(19)
C(1')-N(7')-C(8')-C(9')	173.94(11)
O(8')-C(8')-C(9')-C(10')	-13.88(18)
N(7')-C(8')-C(9')-C(10')	166.56(12)
O(8')-C(8')-C(9')-C(18')	162.31(13)
N(7')-C(8')-C(9')-C(18')	-17.24(18)
C(18')-C(9')-C(10')-C(11')	-2.31(19)
C(8')-C(9')-C(10')-C(11')	174.04(11)
C(9')-C(10')-C(11')-C(16')	0.25(18)
C(9')-C(10')-C(11')-C(12')	-177.92(13)
C(10')-C(11')-C(12')-C(13')	176.77(14)
C(16')-C(11')-C(12')-C(13')	-1.4(2)
C(11')-C(12')-C(13')-C(14')	1.2(3)
C(12')-C(13')-C(14')-C(15')	-0.5(3)
C(13')-C(14')-C(15')-C(16')	0.0(3)
C(10')-C(11')-C(16')-C(15')	-177.34(12)
C(12')-C(11')-C(16')-C(15')	0.9(2)
C(10')-C(11')-C(16')-C(17')	1.80(19)
C(12')-C(11')-C(16')-C(17')	-179.98(13)
C(14')-C(15')-C(16')-C(11')	-0.2(2)
C(14')-C(15')-C(16')-C(17')	-179.31(17)
C(11')-C(16')-C(17')-C(18')	-1.8(2)
C(15')-C(16')-C(17')-C(18')	177.31(15)
C(16')-C(17')-C(18')-C(9')	-0.3(2)
C(10')-C(9')-C(18')-C(17')	2.3(2)
C(8')-C(9')-C(18')-C(17')	-173.82(13)
O(4')-C(4')-C(19')-C(20')	61.7(2)
C(3')-C(4')-C(19')-C(20')	177.53(18)
C(5')-C(4')-C(19')-C(20')	-60.4(2)
C(4')-C(19')-C(20')-C(21')	137.2(4)

Symmetry transformations used to generate equivalent atoms:

Table S7. Crystal data and structure refinement for **27**.

Identification code	wang43	
Empirical formula	$C_{18}H_{19}NO_2$	
Formula weight	281.34	
Temperature	296(2) °K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P c	
Unit cell dimensions	a = 14.8651(7) Å	α= 90°
	b = 11.9815(6) Å	β= 101.688(2)°
	c = 8.6798(4) Å	γ = 90°
Volume	1513.87(13) $Å^3$	
Z	4	
Density (calculated)	1.234 Mg/m^3	
Absorption coefficient	0.080 mm^{-1}	
F(000)	600	
Crystal size	0.490 x 0.096 x 0.059 mm^3	
θ range for data collection	1.40 to 28.42°	
Index ranges	-19<=h<=19, -15<=k<=15, -10<=l<=11	
Reflections collected	15844	
Independent reflections	6947 [R(int) = 0.0404]	
Completeness to θ = 28.42°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9951 and 0.9603	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6947 / 2 / 380	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2σ(I)]	R1 = 0.0502, wR2 = 0.1139	
R indices (all data)	R1 = 0.0718, wR2 = 0.1254	
Absolute structure parameter	1.3(10)	
Largest diff. peak and hole	0.387 and -0.344 $e.Å^{-3}$	

Table S8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **27**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6313(1)	7123(1)	-968(2)	28(1)
C(1)	6839(2)	6630(2)	393(3)	20(1)
C(2)	7865(2)	6967(2)	850(3)	22(1)
C(3)	8091(2)	5743(2)	1275(3)	19(1)
C(4)	7156(2)	5412(2)	264(3)	20(1)
N(5)	8923(1)	5281(2)	869(2)	20(1)
O(6)	9029(1)	3877(1)	2629(2)	21(1)
C(6)	9351(2)	4393(2)	1608(3)	18(1)
C(7)	10234(2)	4022(2)	1203(3)	18(1)
C(8)	10586(2)	2964(2)	1752(3)	20(1)
C(9)	11423(2)	2606(2)	1519(3)	20(1)
C(10)	11962(2)	3286(2)	726(3)	19(1)
C(11)	12846(2)	2962(2)	506(3)	23(1)
C(12)	13350(2)	3649(2)	-248(3)	25(1)
C(13)	12998(2)	4699(2)	-836(3)	23(1)
C(14)	12149(2)	5038(2)	-642(3)	21(1)
C(15)	11611(2)	4345(2)	146(3)	18(1)
C(16)	10744(2)	4691(2)	410(3)	17(1)
C(17)	6313(2)	6814(2)	1704(3)	23(1)
C(18)	5396(2)	6238(2)	1373(3)	26(1)
C(19)	5097(2)	5533(2)	2307(3)	32(1)
O(1')	7267(1)	12898(1)	1546(2)	21(1)
C(1')	7360(2)	11731(2)	1283(3)	18(1)
C(2')	7801(2)	11390(2)	-105(3)	20(1)
C(3')	8284(2)	10444(2)	950(3)	17(1)
C(4')	8140(2)	11122(2)	2392(3)	19(1)
N(5')	9204(1)	10170(2)	757(2)	19(1)
O(6')	9402(1)	8940(1)	2764(2)	21(1)
C(6')	9677(2)	9361(2)	1643(3)	16(1)
C(7')	10558(2)	8979(2)	1230(3)	17(1)
C(16')	11040(2)	9618(2)	353(3)	18(1)
C(15')	11895(2)	9237(2)	50(3)	18(1)
C(14')	12406(2)	9893(2)	-829(3)	22(1)
C(13')	13227(2)	9504(2)	-1113(3)	26(1)
C(12')	13580(2)	8457(2)	-500(3)	26(1)
C(11')	13098(2)	7819(2)	351(3)	23(1)
C(10')	12239(2)	8190(2)	654(3)	19(1)
C(9')	11721(2)	7539(2)	1518(3)	19(1)
C(8')	10901(2)	7929(2)	1816(3)	20(1)
C(17')	6418(2)	11184(2)	1214(3)	22(1)
C(18')	5688(2)	11664(2)	-49(4)	33(1)
C(19')	5220(2)	11100(3)	-1247(4)	44(1)

Table S9. Bond lengths [Å] and angles [°] for **27**.

O(1)-C(1)	1.407(3)	O(1)-H(1A)	0.8200
C(1)-C(17)	1.522(3)	C(1)-C(4)	1.544(3)
C(1)-C(2)	1.549(3)	C(2)-C(3)	1.532(3)
C(2)-H(2A)	0.9700	C(2)-H(2B)	0.9700
C(3)-N(5)	1.461(3)	C(3)-C(4)	1.537(3)
C(3)-H(3A)	0.9800	C(4)-H(4A)	0.9700
C(4)-H(4B)	0.9700	N(5)-C(6)	1.335(3)
N(5)-H(5A)	0.8600	O(6)-C(6)	1.253(3)
C(6)-C(7)	1.495(3)	C(7)-C(16)	1.379(3)
C(7)-C(8)	1.417(3)	C(8)-C(9)	1.369(3)
C(8)-H(8A)	0.9300	C(9)-C(10)	1.415(3)
C(9)-H(9A)	0.9300	C(10)-C(11)	1.420(3)
C(10)-C(15)	1.424(3)	C(11)-C(12)	1.367(4)
C(11)-H(11A)	0.9300	C(12)-C(13)	1.417(3)
C(12)-H(12A)	0.9300	C(13)-C(14)	1.368(3)
C(13)-H(13A)	0.9300	C(14)-C(15)	1.421(3)
C(14)-H(14A)	0.9300	C(15)-C(16)	1.416(3)
C(16)-H(16A)	0.9300	C(17)-C(18)	1.503(3)
C(17)-H(17A)	0.9700	C(17)-H(17B)	0.9700
C(18)-C(19)	1.310(4)	C(18)-H(18A)	0.9300
C(19)-H(19A)	0.9300	C(19)-H(19B)	0.9300
O(1')-C(1')	1.428(3)	O(1')-H(1'A)	0.8200
C(1')-C(4')	1.534(3)	C(1')-C(17')	1.536(3)
C(1')-C(2')	1.539(3)	C(2')-C(3')	1.539(3)
C(2')-H(2'A)	0.9700	C(2')-H(2'B)	0.9700
C(3')-N(5')	1.449(3)	C(3')-C(4')	1.542(3)
C(3')-H(3'A)	0.9800	C(4')-H(4'A)	0.9700
C(4')-H(4'B)	0.9700	N(5')-C(6')	1.344(3)
N(5')-H(5'A)	0.8600	O(6')-C(6')	1.237(3)
C(6')-C(7')	1.497(3)	C(7')-C(16')	1.379(3)
C(7')-C(8')	1.414(3)	C(16')-C(15')	1.425(3)
C(16')-H(16B)	0.9300	C(15')-C(10')	1.415(3)
C(15')-C(14')	1.418(3)	C(14')-C(13')	1.375(3)
C(14')-H(14B)	0.9300	C(13')-C(12')	1.421(4)
C(13')-H(13B)	0.9300	C(12')-C(11')	1.363(4)
C(12')-H(12B)	0.9300	C(11')-C(10')	1.426(3)
C(11')-H(11B)	0.9300	C(10')-C(9')	1.414(3)
C(9')-C(8')	1.377(3)	C(9')-H(9'A)	0.9300
C(8')-H(8'A)	0.9300	C(17')-C(18')	1.492(4)
C(17')-H(17C)	0.9700	C(17')-H(17D)	0.9700
C(18')-C(19')	1.315(4)	C(18')-H(18B)	0.9300
C(19')-H(19C)	0.9300	C(19')-H(19D)	0.9300
C(1)-O(1)-H(1A)	109.5	O(1)-C(1)-C(17)	106.48(19)
O(1)-C(1)-C(4)	117.5(2)	C(17)-C(1)-C(4)	113.71(19)
O(1)-C(1)-C(2)	117.16(19)	C(17)-C(1)-C(2)	113.5(2)
C(4)-C(1)-C(2)	88.03(16)	C(3)-C(2)-C(1)	88.20(17)

C(3)-C(2)-H(2A)	114.0	C(1)-C(2)-H(2A)	114.0
C(3)-C(2)-H(2B)	114.0	C(1)-C(2)-H(2B)	114.0
H(2A)-C(2)-H(2B)	111.2	N(5)-C(3)-C(2)	117.34(19)
N(5)-C(3)-C(4)	118.43(19)	C(2)-C(3)-C(4)	88.88(17)
N(5)-C(3)-H(3A)	110.2	C(2)-C(3)-H(3A)	110.2
C(4)-C(3)-H(3A)	110.2	C(3)-C(4)-C(1)	88.24(17)

Table S9. (continued)

C(3)-C(4)-H(4A)	113.9	C(1)-C(4)-H(4A)	113.9
C(3)-C(4)-H(4B)	113.9	C(1)-C(4)-H(4B)	113.9
H(4A)-C(4)-H(4B)	111.1	C(6)-N(5)-C(3)	122.0(2)
C(6)-N(5)-H(5A)	119.0	C(3)-N(5)-H(5A)	119.0
O(6)-C(6)-N(5)	121.3(2)	O(6)-C(6)-C(7)	120.0(2)
N(5)-C(6)-C(7)	118.7(2)	C(16)-C(7)-C(8)	119.1(2)
C(16)-C(7)-C(6)	122.8(2)	C(8)-C(7)-C(6)	118.0(2)
C(9)-C(8)-C(7)	121.0(2)	C(9)-C(8)-H(8A)	119.5
C(7)-C(8)-H(8A)	119.5	C(8)-C(9)-C(10)	120.8(2)
C(8)-C(9)-H(9A)	119.6	C(10)-C(9)-H(9A)	119.6
C(9)-C(10)-C(11)	122.6(2)	C(9)-C(10)-C(15)	118.8(2)
C(11)-C(10)-C(15)	118.6(2)	C(12)-C(11)-C(10)	120.8(2)
C(12)-C(11)-H(11A)	119.6	C(10)-C(11)-H(11A)	119.6
C(11)-C(12)-C(13)	120.6(2)	C(11)-C(12)-H(12A)	119.7
C(13)-C(12)-H(12A)	119.7	C(14)-C(13)-C(12)	120.1(2)
C(14)-C(13)-H(13A)	120.0	C(12)-C(13)-H(13A)	120.0
C(13)-C(14)-C(15)	120.6(2)	C(13)-C(14)-H(14A)	119.7
C(15)-C(14)-H(14A)	119.7	C(16)-C(15)-C(14)	121.8(2)
C(16)-C(15)-C(10)	118.9(2)	C(14)-C(15)-C(10)	119.3(2)
C(7)-C(16)-C(15)	121.4(2)	C(7)-C(16)-H(16A)	119.3
C(15)-C(16)-H(16A)	119.3	C(18)-C(17)-C(1)	112.0(2)
C(18)-C(17)-H(17A)	109.2	C(1)-C(17)-H(17A)	109.2
C(18)-C(17)-H(17B)	109.2	C(1)-C(17)-H(17B)	109.2
H(17A)-C(17)-H(17B)	107.9	C(19)-C(18)-C(17)	125.9(2)
C(19)-C(18)-H(18A)	117.1	C(17)-C(18)-H(18A)	117.1
C(18)-C(19)-H(19A)	120.0	C(18)-C(19)-H(19B)	120.0
H(19A)-C(19)-H(19B)	120.0	C(1')-O(1')-H(1'A)	109.5
O(1')-C(1')-C(4')	116.83(18)	O(1')-C(1')-C(17')	107.82(18)
C(4')-C(1')-C(17')	112.90(19)	O(1')-C(1')-C(2')	117.12(18)
C(4')-C(1')-C(2')	88.69(16)	C(17')-C(1')-C(2')	112.69(19)
C(1')-C(2')-C(3')	87.20(17)	C(1')-C(2')-H(2'A)	114.1
C(3')-C(2')-H(2'A)	114.1	C(1')-C(2')-H(2'B)	114.1
C(3')-C(2')-H(2'B)	114.1	H(2'A)-C(2')-H(2'B)	111.3
N(5')-C(3')-C(2')	115.80(19)	N(5')-C(3')-C(4')	120.13(19)
C(2')-C(3')-C(4')	88.35(17)	N(5')-C(3')-H(3'A)	110.3
C(2')-C(3')-H(3'A)	110.3	C(4')-C(3')-H(3'A)	110.3
C(1')-C(4')-C(3')	87.26(17)	C(1')-C(4')-H(4'A)	114.1
C(3')-C(4')-H(4'A)	114.1	C(1')-C(4')-H(4'B)	114.1
C(3')-C(4')-H(4'B)	114.1	H(4'A)-C(4')-H(4'B)	111.3
C(6')-N(5')-C(3')	119.62(19)	C(6')-N(5')-H(5'A)	120.2
C(3')-N(5')-H(5'A)	120.2	O(6')-C(6')-N(5')	121.7(2)
O(6')-C(6')-C(7')	120.6(2)	N(5')-C(6')-C(7')	117.7(2)
C(16')-C(7')-C(8')	120.2(2)	C(16')-C(7')-C(6')	122.7(2)
C(8')-C(7')-C(6')	117.1(2)	C(7')-C(16')-C(15')	120.5(2)
C(7')-C(16')-H(16B)	119.8	C(15')-C(16')-H(16B)	119.8
C(10')-C(15')-C(14')	119.9(2)	C(10')-C(15')-C(16')	119.0(2)

C(14')-C(15')-C(16')	121.1(2)	C(13')-C(14')-C(15')	120.0(2)
C(13')-C(14')-H(14B)	120.0	C(15')-C(14')-H(14B)	120.0
C(14')-C(13')-C(12')	120.4(2)	C(14')-C(13')-H(13B)	119.8
C(12')-C(13')-H(13B)	119.8	C(11')-C(12')-C(13')	120.2(2)
C(11')-C(12')-H(12B)	119.9	C(13')-C(12')-H(12B)	119.9
C(12')-C(11')-C(10')	121.0(2)	C(12')-C(11')-H(11B)	119.5
C(10')-C(11')-H(11B)	119.5	C(9')-C(10')-C(15')	119.4(2)

Table S9. (continued)

C(9')-C(10')-C(11')	122.0(2)	C(15')-C(10')-C(11')	118.5(2)
C(8')-C(9')-C(10')	120.7(2)	C(8')-C(9')-H(9'A)	119.7
C(10')-C(9')-H(9'A)	119.7	C(9')-C(8')-C(7')	120.2(2)
C(9')-C(8')-H(8'A)	119.9	C(7')-C(8')-H(8'A)	119.9
C(18')-C(17')-C(1')	112.7(2)	C(18')-C(17')-H(17C)	109.0
C(1')-C(17')-H(17C)	109.0	C(18')-C(17')-H(17D)	109.0
C(1')-C(17')-H(17D)	109.0	H(17C)-C(17')-H(17D)	107.8
C(19')-C(18')-C(17')	124.9(3)	C(19')-C(18')-H(18B)	117.5
C(17')-C(18')-H(18B)	117.5	C(18')-C(19')-H(19C)	120.0
C(18')-C(19')-H(19D)	120.0	H(19C)-C(19')-H(19D)	120.0

Symmetry transformations used to generate equivalent atoms:

Table S10. Anisotropic displacement parameters ($Å^2$ x 10^3) for **27**. 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}
O(1)	25(1)	29(1)	30(1)	11(1)	6(1)	6(1)
C(1)	23(1)	15(1)	23(1)	4(1)	9(1)	2(1)
C(2)	23(1)	17(1)	27(1)	-1(1)	9(1)	0(1)
C(3)	20(1)	18(1)	21(1)	0(1)	9(1)	3(1)
C(4)	19(1)	17(1)	25(1)	-1(1)	5(1)	1(1)
N(5)	17(1)	23(1)	21(1)	4(1)	8(1)	3(1)
O(6)	22(1)	20(1)	22(1)	2(1)	8(1)	-4(1)
C(6)	19(1)	19(1)	16(1)	-3(1)	5(1)	-2(1)
C(7)	18(1)	16(1)	18(1)	-2(1)	2(1)	0(1)
C(8)	24(1)	15(1)	23(1)	0(1)	8(1)	-3(1)
C(9)	25(1)	12(1)	24(1)	0(1)	3(1)	0(1)
C(10)	20(1)	16(1)	21(1)	-2(1)	3(1)	1(1)
C(11)	22(1)	21(1)	26(1)	-3(1)	2(1)	4(1)
C(12)	20(1)	26(1)	30(1)	-3(1)	7(1)	3(1)
C(13)	22(1)	21(1)	27(1)	1(1)	7(1)	-1(1)
C(14)	22(1)	16(1)	24(1)	2(1)	6(1)	-1(1)
C(15)	21(1)	13(1)	21(1)	-2(1)	4(1)	0(1)
C(16)	18(1)	16(1)	17(1)	0(1)	2(1)	-1(1)
C(17)	25(1)	19(1)	26(1)	-2(1)	8(1)	2(1)
C(18)	20(1)	31(1)	27(1)	0(1)	6(1)	6(1)
C(19)	24(1)	36(2)	36(2)	5(1)	4(1)	-1(1)
O(1')	28(1)	11(1)	27(1)	0(1)	12(1)	4(1)
C(1')	21(1)	11(1)	21(1)	1(1)	7(1)	2(1)
C(2')	23(1)	18(1)	20(1)	4(1)	6(1)	4(1)
C(3')	19(1)	14(1)	19(1)	1(1)	4(1)	3(1)
C(4')	25(1)	13(1)	19(1)	-1(1)	7(1)	0(1)
N(5')	19(1)	17(1)	20(1)	3(1)	5(1)	3(1)
O(6')	26(1)	17(1)	20(1)	2(1)	7(1)	1(1)
C(6')	21(1)	12(1)	16(1)	-3(1)	2(1)	0(1)
C(7')	19(1)	13(1)	18(1)	-2(1)	0(1)	1(1)
C(16')	21(1)	14(1)	19(1)	-1(1)	2(1)	2(1)
C(15')	19(1)	15(1)	18(1)	-3(1)	1(1)	0(1)
C(14')	23(1)	17(1)	25(1)	0(1)	3(1)	-2(1)
C(13')	22(1)	26(1)	31(2)	2(1)	7(1)	-3(1)
C(12')	18(1)	26(1)	34(2)	-3(1)	5(1)	1(1)
C(11')	21(1)	19(1)	28(1)	-1(1)	3(1)	3(1)
C(10')	21(1)	16(1)	19(1)	-2(1)	-1(1)	0(1)
C(9')	22(1)	13(1)	21(1)	1(1)	1(1)	2(1)
C(8')	26(1)	14(1)	20(1)	2(1)	6(1)	-1(1)
C(17')	22(1)	17(1)	27(1)	-1(1)	9(1)	-2(1)
C(18')	19(1)	27(1)	51(2)	13(1)	5(1)	-2(1)
C(19')	26(2)	59(2)	41(2)	15(2)	-4(1)	-11(1)

Table S11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **27**.

	x	y	z	U(eq)
H(1A)	5896	6699	-1359	42
H(2A)	8119	7236	-25	26
H(2B)	8003	7473	1739	26
H(3A)	8093	5614	2390	23
H(4A)	6820	4872	760	24
H(4B)	7185	5186	-798	24
H(5A)	9143	5591	132	23
H(8A)	10243	2505	2278	24
H(9A)	11640	1907	1887	24
H(11A)	13085	2273	881	28
H(12A)	13929	3425	-377	30
H(13A)	13345	5159	-1354	28
H(14A)	11922	5728	-1030	25
H(16A)	10513	5383	41	21
H(17A)	6674	6535	2685	27
H(17B)	6221	7608	1826	27
H(18A)	5005	6397	418	31
H(19A)	5464	5349	3273	38
H(19B)	4517	5215	2004	38
H(1'A)	7026	12990	2307	32
H(2'A)	8216	11943	-385	24
H(2'B)	7365	11133	-1023	24
H(3'A)	7898	9774	827	21
H(4'A)	7940	10678	3196	23
H(4'B)	8655	11596	2843	23
H(5'A)	9446	10523	80	22
H(16B)	10805	10303	-43	22
H(14B)	12185	10587	-1213	26
H(13B)	13553	9928	-1711	31
H(12B)	14142	8206	-679	31
H(11B)	13333	7133	740	27
H(9'A)	11935	6840	1888	23
H(8'A)	10573	7500	2406	23
H(17C)	6467	10390	1033	26
H(17D)	6240	11280	2221	26
H(18B)	5554	12419	17	39
H(19C)	5334	10344	-1352	52
H(19D)	4774	11458	-1989	52

Table S12. Torsion angles [°] for **27**.

O(1)-C(1)-C(2)-C(3)	-139.4(2)
C(17)-C(1)-C(2)-C(3)	95.8(2)
C(4)-C(1)-C(2)-C(3)	-19.28(17)
C(1)-C(2)-C(3)-N(5)	141.1(2)
C(1)-C(2)-C(3)-C(4)	19.36(17)
N(5)-C(3)-C(4)-C(1)	-140.2(2)
C(2)-C(3)-C(4)-C(1)	-19.43(17)
O(1)-C(1)-C(4)-C(3)	139.0(2)
C(17)-C(1)-C(4)-C(3)	-95.7(2)
C(2)-C(1)-C(4)-C(3)	19.22(17)
C(2)-C(3)-N(5)-C(6)	157.2(2)
C(4)-C(3)-N(5)-C(6)	-98.0(3)
C(3)-N(5)-C(6)-O(6)	3.9(3)
C(3)-N(5)-C(6)-C(7)	-175.7(2)
O(6)-C(6)-C(7)-C(16)	-163.1(2)
N(5)-C(6)-C(7)-C(16)	16.5(3)
O(6)-C(6)-C(7)-C(8)	12.7(3)
N(5)-C(6)-C(7)-C(8)	-167.7(2)
C(16)-C(7)-C(8)-C(9)	0.6(4)
C(6)-C(7)-C(8)-C(9)	-175.3(2)
C(7)-C(8)-C(9)-C(10)	0.1(4)
C(8)-C(9)-C(10)-C(11)	177.9(2)
C(8)-C(9)-C(10)-C(15)	-1.1(3)
C(9)-C(10)-C(11)-C(12)	-179.1(2)
C(15)-C(10)-C(11)-C(12)	-0.2(3)
C(10)-C(11)-C(12)-C(13)	-0.3(4)
C(11)-C(12)-C(13)-C(14)	0.4(4)
C(12)-C(13)-C(14)-C(15)	0.0(4)
C(13)-C(14)-C(15)-C(16)	177.8(2)
C(13)-C(14)-C(15)-C(10)	-0.4(4)
C(9)-C(10)-C(15)-C(16)	1.2(3)
C(11)-C(10)-C(15)-C(16)	-177.8(2)
C(9)-C(10)-C(15)-C(14)	179.5(2)
C(11)-C(10)-C(15)-C(14)	0.5(3)
C(8)-C(7)-C(16)-C(15)	-0.5(3)
C(6)-C(7)-C(16)-C(15)	175.3(2)
C(14)-C(15)-C(16)-C(7)	-178.7(2)
C(10)-C(15)-C(16)-C(7)	-0.5(3)
O(1)-C(1)-C(17)-C(18)	63.1(2)
C(4)-C(1)-C(17)-C(18)	-67.9(3)
C(2)-C(1)-C(17)-C(18)	-166.53(19)
C(1)-C(17)-C(18)-C(19)	125.8(3)
O(1')-C(1')-C(2')-C(3')	141.56(19)
C(4')-C(1')-C(2')-C(3')	21.86(17)
C(17')-C(1')-C(2')-C(3')	-92.5(2)
C(1')-C(2')-C(3')-N(5')	-144.68(19)
C(1')-C(2')-C(3')-C(4')	-21.74(17)

O(1')-C(1')-C(4')-C(3')	-141.78(19)
C(17')-C(1')-C(4')-C(3')	92.3(2)
C(2')-C(1')-C(4')-C(3')	-21.81(17)
N(5')-C(3')-C(4')-C(1')	140.9(2)
C(2')-C(3')-C(4')-C(1')	21.80(17)
C(2')-C(3')-N(5')-C(6')	179.4(2)

Table S12. (continued)

C(4')-C(3')-N(5')-C(6')	75.3(3)
C(3')-N(5')-C(6')-O(6')	-9.7(3)
C(3')-N(5')-C(6')-C(7')	170.32(19)
O(6')-C(6')-C(7')-C(16')	-159.3(2)
N(5')-C(6')-C(7')-C(16')	20.7(3)
O(6')-C(6')-C(7')-C(8')	19.0(3)
N(5')-C(6')-C(7')-C(8')	-161.0(2)
C(8')-C(7')-C(16')-C(15')	-1.0(3)
C(6')-C(7')-C(16')-C(15')	177.3(2)
C(7')-C(16')-C(15')-C(10')	0.4(3)
C(7')-C(16')-C(15')-C(14')	-179.0(2)
C(10')-C(15')-C(14')-C(13')	1.0(3)
C(16')-C(15')-C(14')-C(13')	-179.6(2)
C(15')-C(14')-C(13')-C(12')	-1.5(4)
C(14')-C(13')-C(12')-C(11')	1.3(4)
C(13')-C(12')-C(11')-C(10')	-0.5(4)
C(14')-C(15')-C(10')-C(9')	-179.5(2)
C(16')-C(15')-C(10')-C(9')	1.1(3)
C(14')-C(15')-C(10')-C(11')	-0.3(3)
C(16')-C(15')-C(10')-C(11')	-179.6(2)
C(12')-C(11')-C(10')-C(9')	179.3(2)
C(12')-C(11')-C(10')-C(15')	0.0(4)
C(15')-C(10')-C(9')-C(8')	-2.0(3)
C(11')-C(10')-C(9')-C(8')	178.8(2)
C(10')-C(9')-C(8')-C(7')	1.4(4)
C(16')-C(7')-C(8')-C(9')	0.1(3)
C(6')-C(7')-C(8')-C(9')	-178.2(2)
O(1')-C(1')-C(17')-C(18')	58.6(3)
C(4')-C(1')-C(17')-C(18')	-170.8(2)
C(2')-C(1')-C(17')-C(18')	-72.2(3)
C(1')-C(17')-C(18')-C(19')	118.5(3)

Symmetry transformations used to generate equivalent atoms:

Table S13. Hydrogen bonds for **27** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(5)-H(5A)...O(6)#1	0.86	2.24	3.021(3)	151.7
O(1')-H(1'A)...O(1)#2	0.82	2.01	2.812(2)	167.1
N(5')-H(5'A)...O(6')#3	0.86	2.10	2.878(3)	150.4

Symmetry transformations used to generate equivalent atoms:
#1 x,-y+1,z-1/2 #2 x,-y+2,z+1/2 #3 x,-y+2,z-1/2

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