Supplemental information

Synthesis, characterization and monoamine transporter activity of the new psychoactive substance 3',4'-methylenedioxy-4-methylaminorex (MDMAR).

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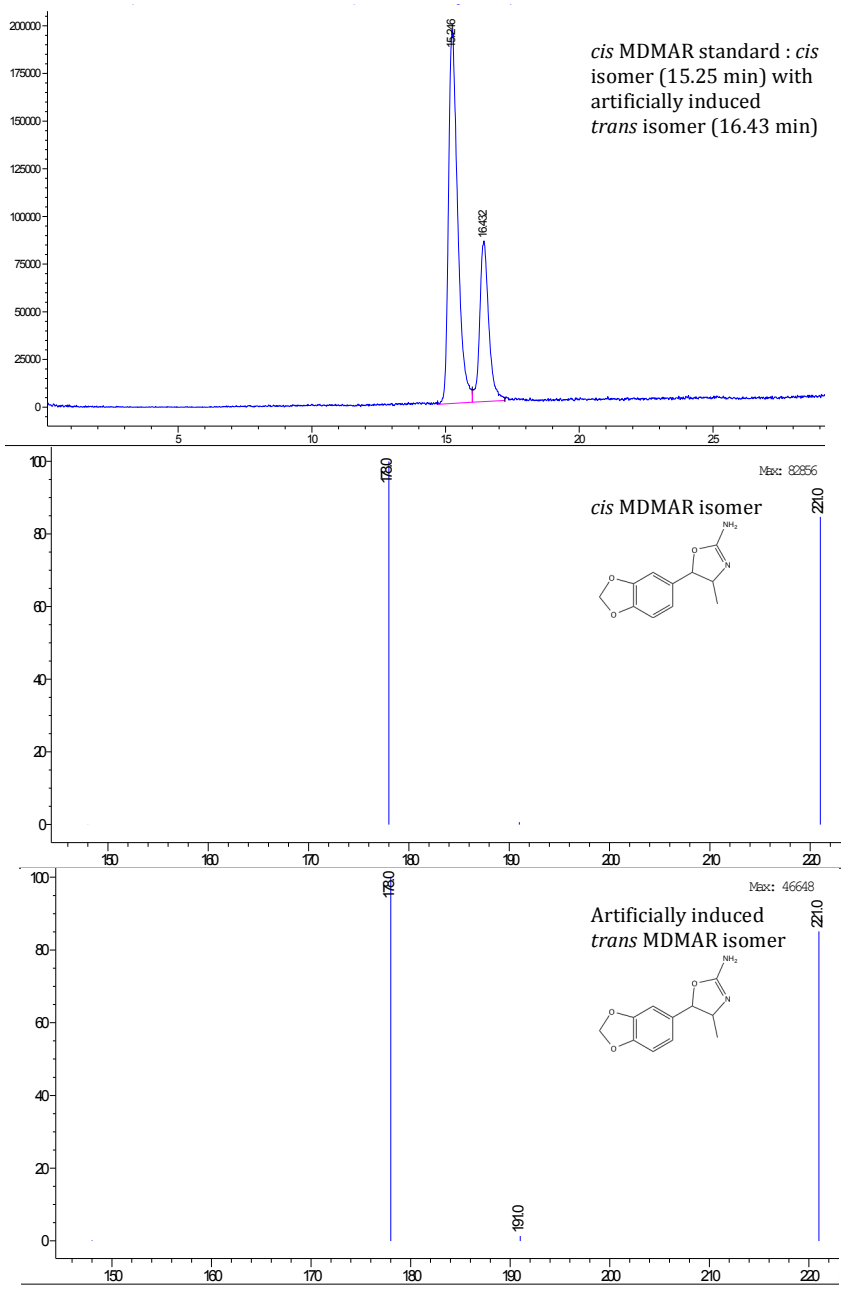
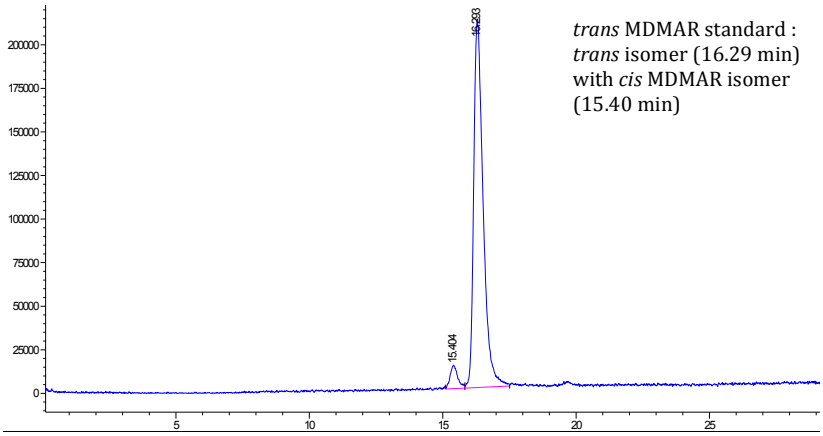
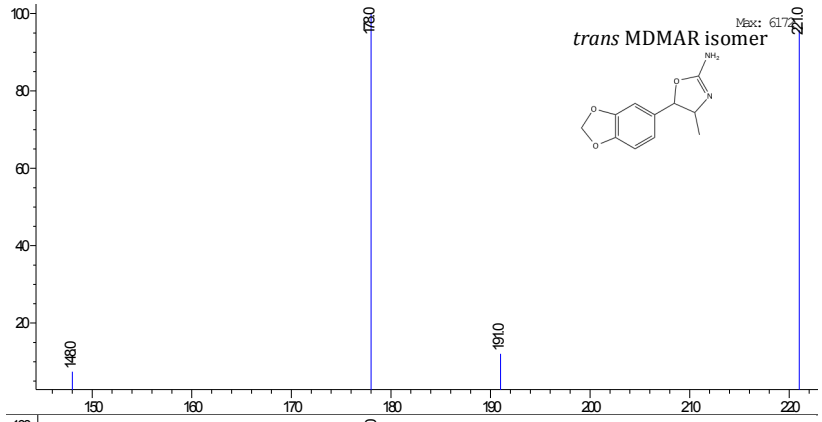
1. LC-MS data for the synthesized *cis* and *trans* MDMAR isomers and vendor sample.

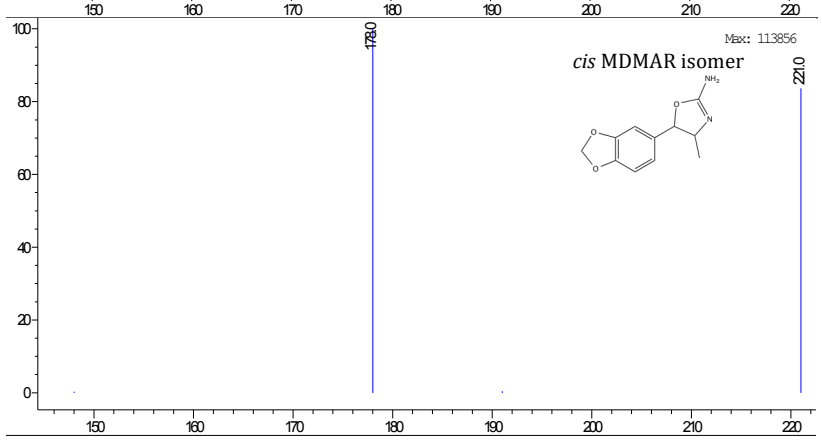




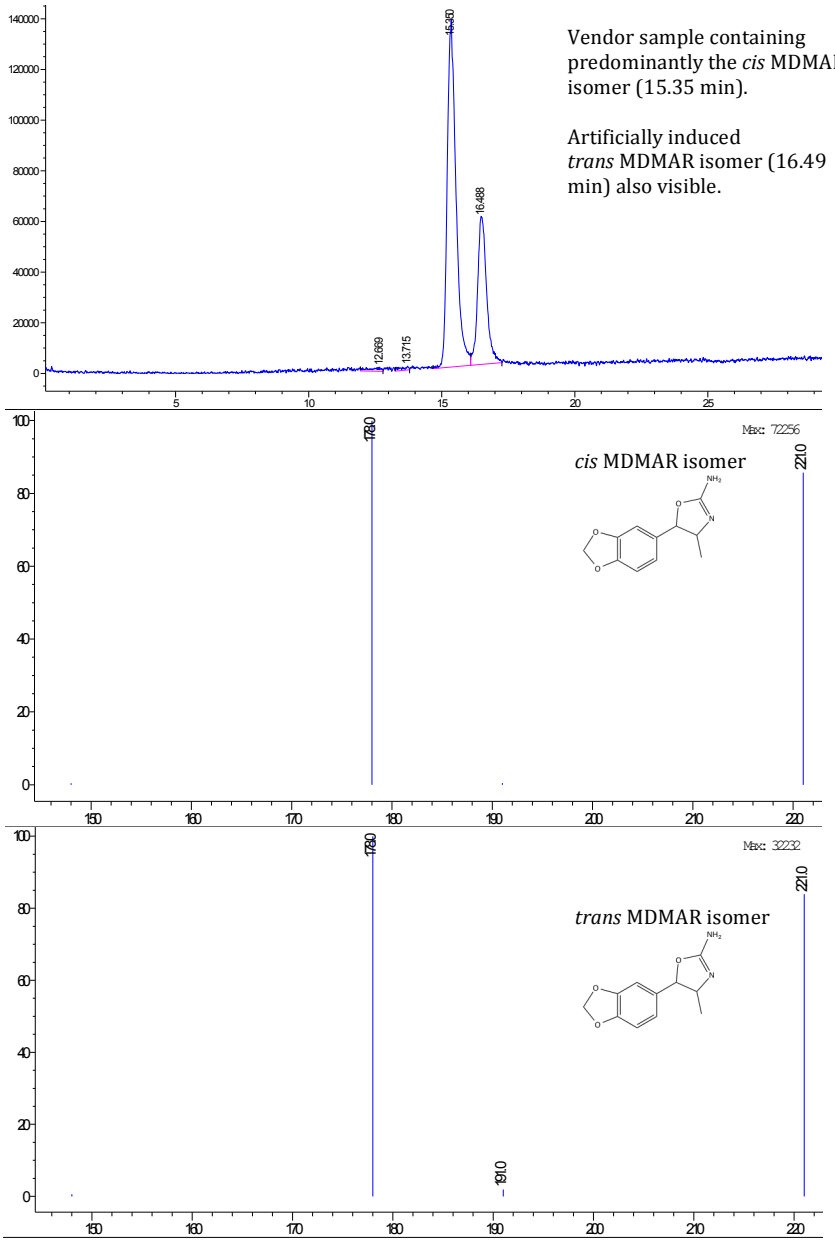
trans MDMAR standard : *trans* isomer (16.29 min) with *cis* MDMAR isomer (15.40 min)



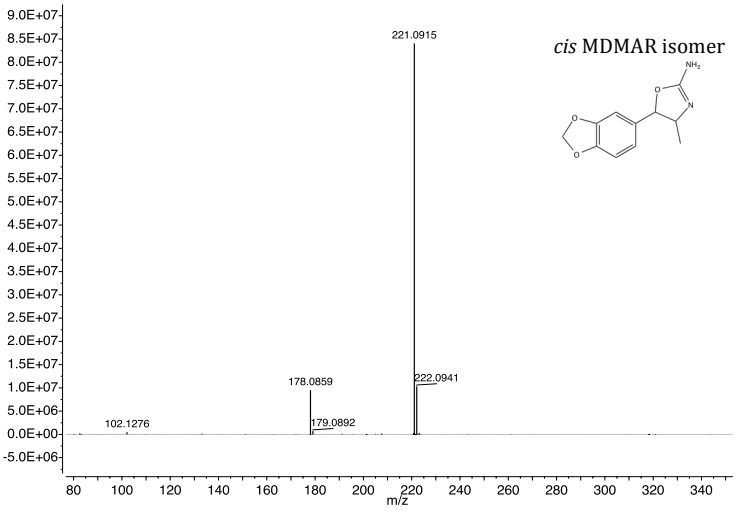
trans MDMAR isomer



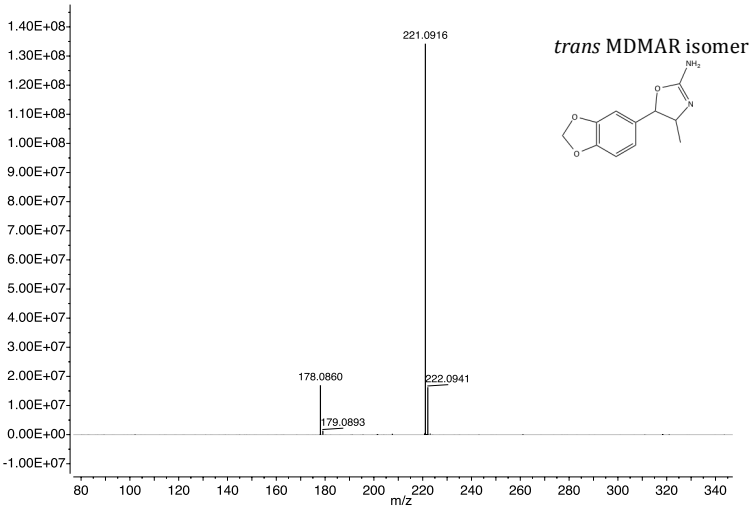
cis MDMAR isomer


12.669
13.715
15.350
16.488
Vendor sample containing predominantly the *cis* MDMAR isomer (15.35 min).
Artificially induced *trans* MDMAR isomer (16.49 min) also visible.
Max: 72256
cis MDMAR isomer
178.0
221.0
Max: 32232
trans MDMAR isomer
178.0
191.0
221.0

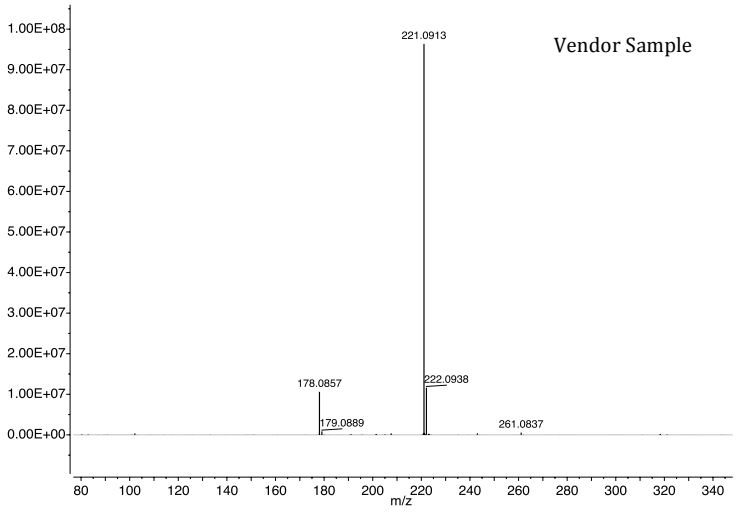
2. HR-MS data for the synthesized *cis* and *trans* MDMAR isomers and vendor sample.



cis MDMAR isomer

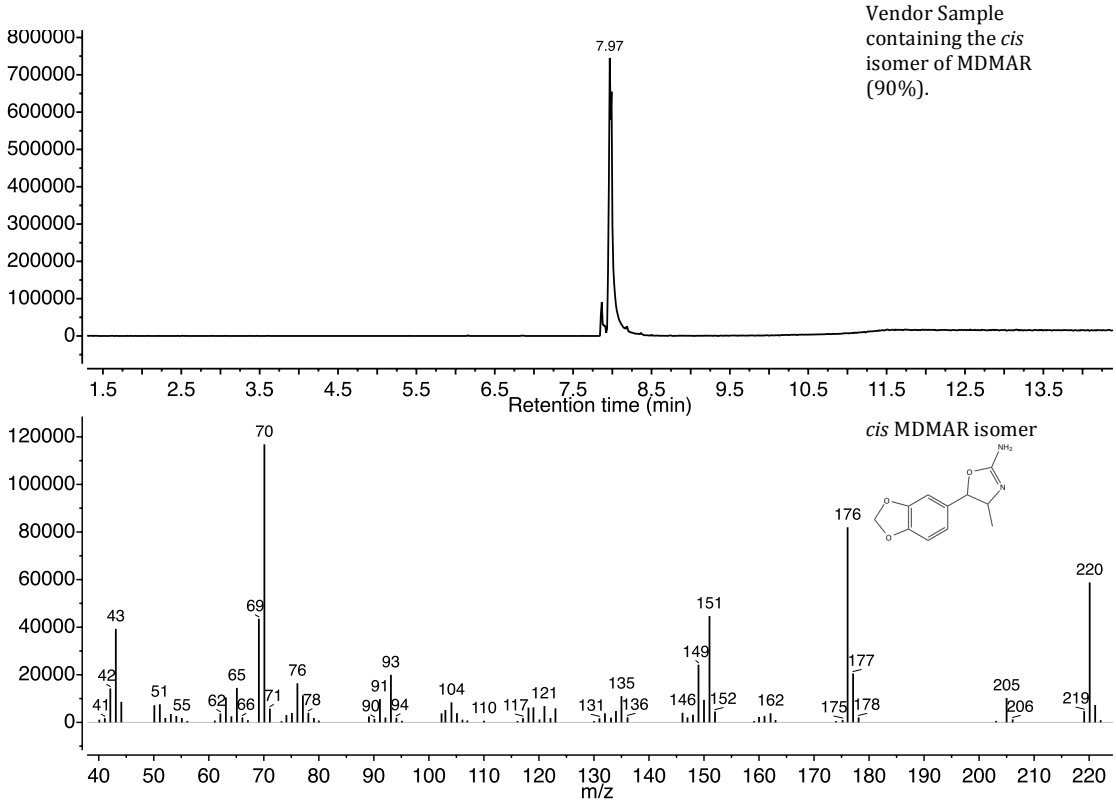


trans MDMAR isomer



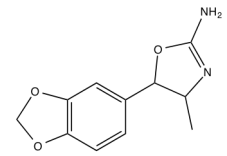
Vendor Sample

3. GC-MS data for vendor sample.

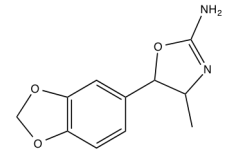


4. NMR data for the synthesized *cis* and *trans* MDMAR isomers and vendor sample.

^{1}H NMR of *cis* MDMAR

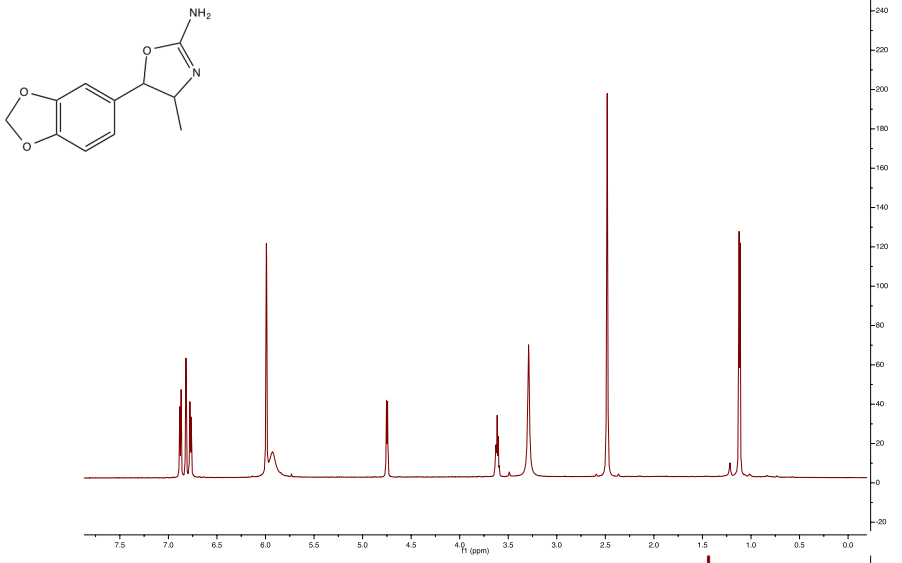


^{13}C NMR of *cis* MDMAR

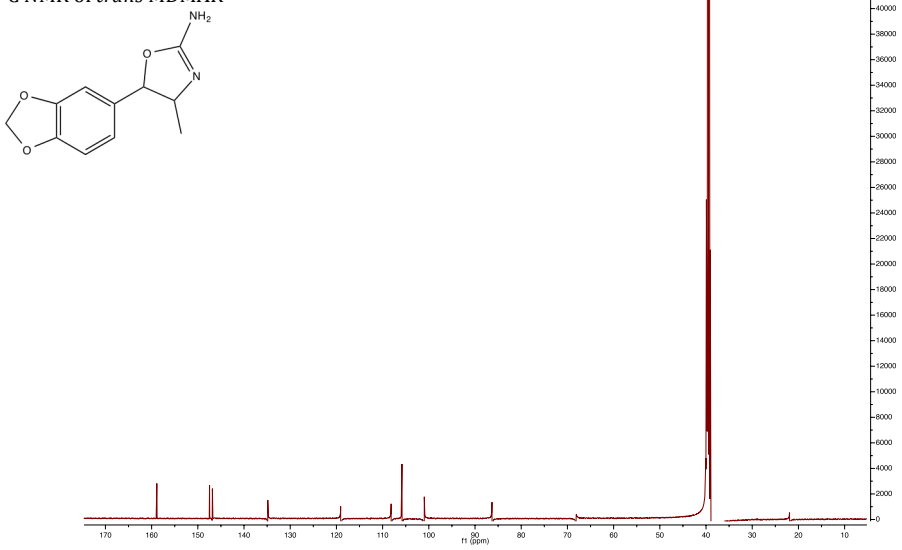


^{1}H NMR (DMSO) δ 6.90 (doublet; *J* = 7.9 Hz; 1H; Ar-H6'), 6.72 (doublet; *J* = 7.9 Hz; 1H; Ar-H2'); 6.69 (doublet; *J* = 1.8 Hz; 1H; Ar-H5'), 5.91 (singlet; *J* = 7.5 Hz; 2H; CH_2); 5.43 (doublet; *J* = 8.5 Hz; 1H; H-5), 4.14 (double quartet; *J* = 8.5, 6.8 Hz; 1H; H-4), 0.60 (doublet; *J* = 6.8Hz; 3H; CH_3); ^{13}C NMR (DMSO) δ 159.59 (C-2); 147.39 (Ar C3'); 146.69 (Ar C4'); 132.36 (Ar C1'); 119.48 (Ar C6'); 108.19 (Ar C5'); 106.64 (Ar C2'); 101.23 (CH_2); 82.52 (C-5); 63.00 (C-4); 18.90 (CH_3).

^{1}H NMR of *trans* MDMAR

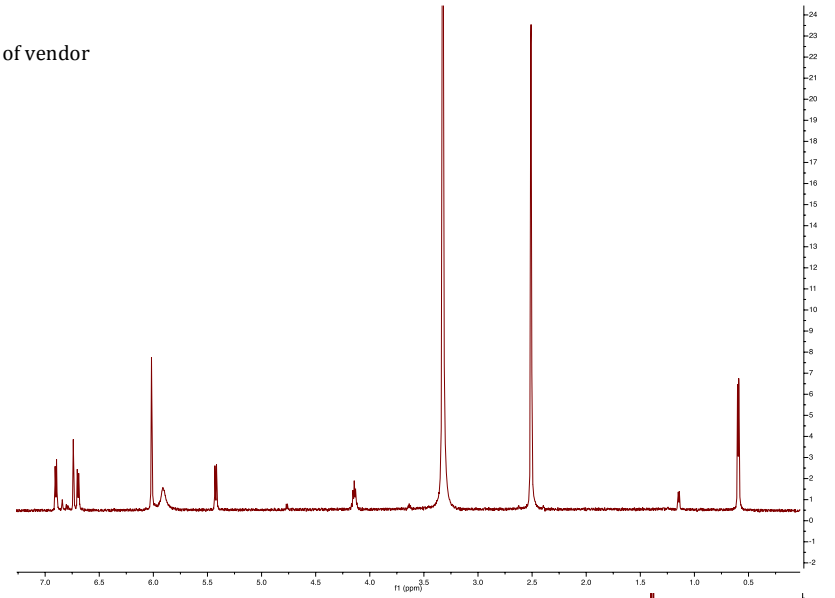


^{13}C NMR of *trans* MDMAR

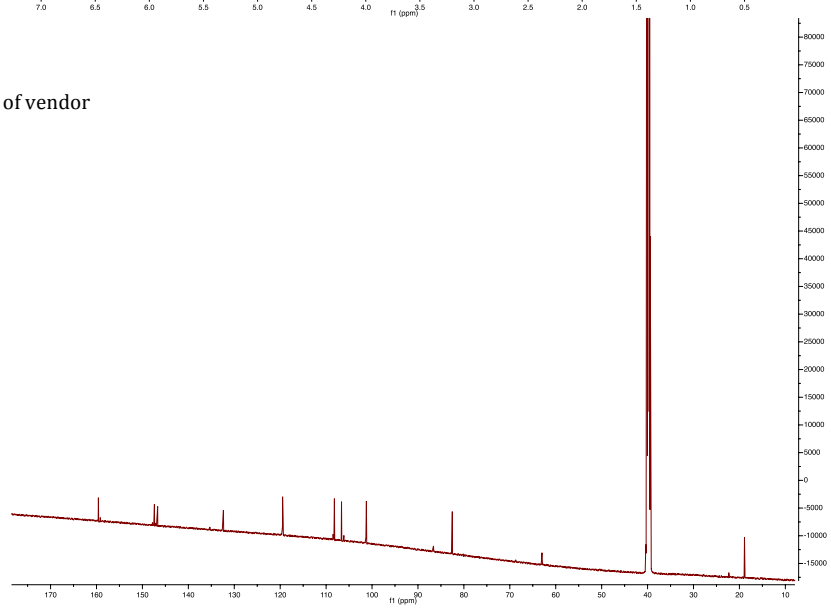


^{1}H NMR (DMSO) δ 6.88 (doublet; *J* = 1.9 Hz; 1H; Ar-H6'); 6.82 (doublet; *J* = 8.0Hz; 1H; Ar-H2'); 6.77 (doublet; J = 1.9 Hz; 1H; Ar-H5'); 5.93 (singlet; *J* = 7.5 Hz; 2H; CH_2); 4.75 (doublet; *J*= 6.5 Hz; 1H; H-5); 4.16 (double quartet; *J* = 6.5, 6.4 Hz; 1H; H-4); 1.12 (doublet; *J* = 6.4 Hz; 3H; CH_3); ^{13}C NMR (DMSO) δ 159.59 (C-2); 147.39 (Ar C3'); 146.69 (Ar C4'); 132.37 (Ar C1'); 119.47 (Ar C6'); 108.19 (Ar C5'); 106.64 (Ar C2'); 101.23 (CH_2); 82.52 (C-5); 62.99 (C-4); 18.90 (CH_3).

^{1}H NMR of vendor sample



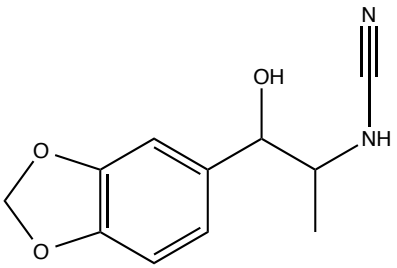
^{13}C NMR of vendor sample



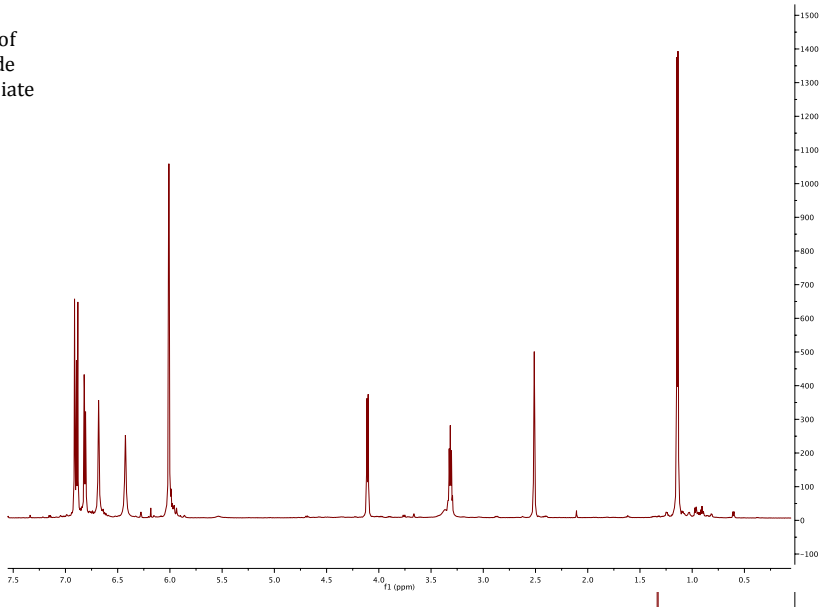
^{1}H NMR (DMSO) δ 6.90 (doublet; *J* = 8.0 Hz; 1H; Ar-H6'), 6.74 (doublet; *J* = 8.0 Hz; 1H; Ar-H2'); 6.70 (doublet; *J* = 1.8 Hz; 1H; Ar-H5'), 5.91 (singlet; *J* = 7.5 Hz; 2H; CH_2); 5.42 (doublet; *J* = 8.8 Hz; 1H; H-5), 4.14 (double quartet; *J* = 8.8, 6.6 Hz; 1H; H-4), 0.60 (doublet; *J* = 6.6Hz; 3H; CH_3); ^{13}C NMR (DMSO) δ 159.59 (C-2); 147.39 (Ar C3'); 146.69 (Ar C4'); 132.37 (Ar C1'); 119.47 (Ar C6'); 108.19 (Ar C2'); 101.23 (CH_2); 82.52 (C-5); 63.00 (C-4); 18.90 (CH_3).

5. Structure of the cyanamide intermediate, NMR and HR-MS data.

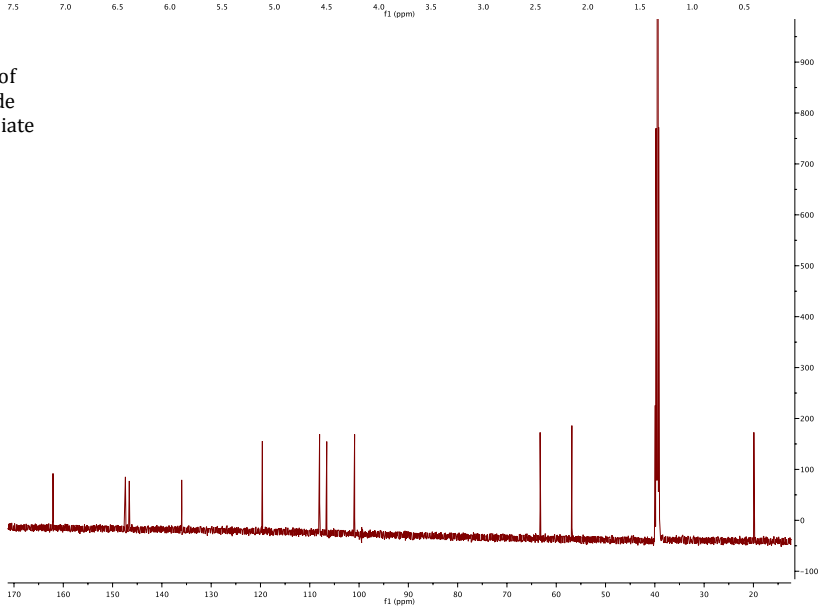
The cyanamide intermediate was formed following the literature-based methods for the synthesis of trans-DMAR.



^{1}H NMR of cyanamide intermediate



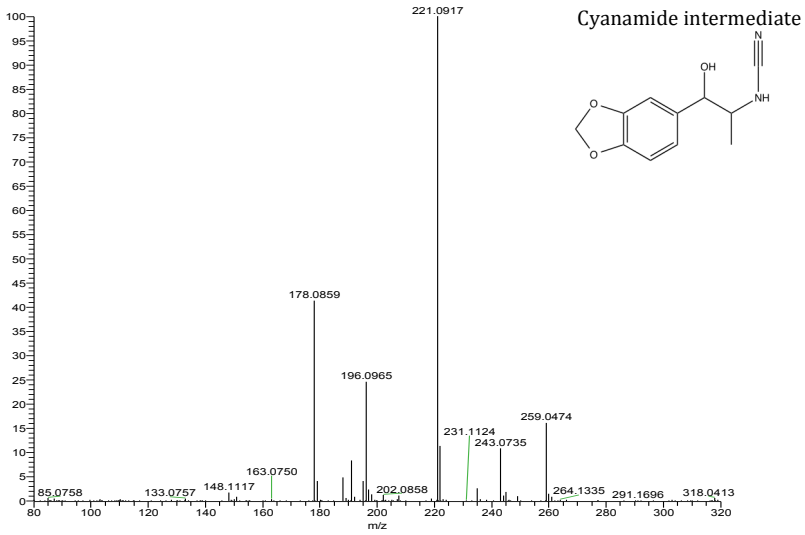
^{13}C NMR of cyanamide intermediate



^{1}H NMR (DMSO) δ 6.90 (doublet; *J* = 2.0 Hz; 1H; Ar-H), 6.81 (doublet; *J* = 8.0 Hz; 1H; Ar-H), 6.68 (double doublet; *J* = 8.0, 2.0 Hz; 1H; Ar-H), 5.97 (doublet, *J* = 2.0 Hz; 2H; CH_2), 4.11 (doublet; *J* = 7.2 Hz; 1H; C<u>H</u>(OH)), 3.32 (Pentet; *J* = 6.0 Hz; 1H; C<u>H</u>(CH_3)); 1.14 (doublet; *J* = 6.0 Hz; 3H; CH_3); ^{13}C NMR (DMSO) δ 162.08 (Ar-C); 147.40 (Ar-C); 146.61

(Ar-C); 135.98 (Ar-C); 119.62 (CN); 108.00 (Ar-C); 106.55 (Ar-C); 100.90 (CH_2); 63.27 (CH(OH)); 56.82 ($CH(CH_3)$); 19.91 (CH_3)

HR-MS data for cyanamide intermediate



6. X-Ray data for the synthesized *cis* MDMAR isomer (TCD53b).

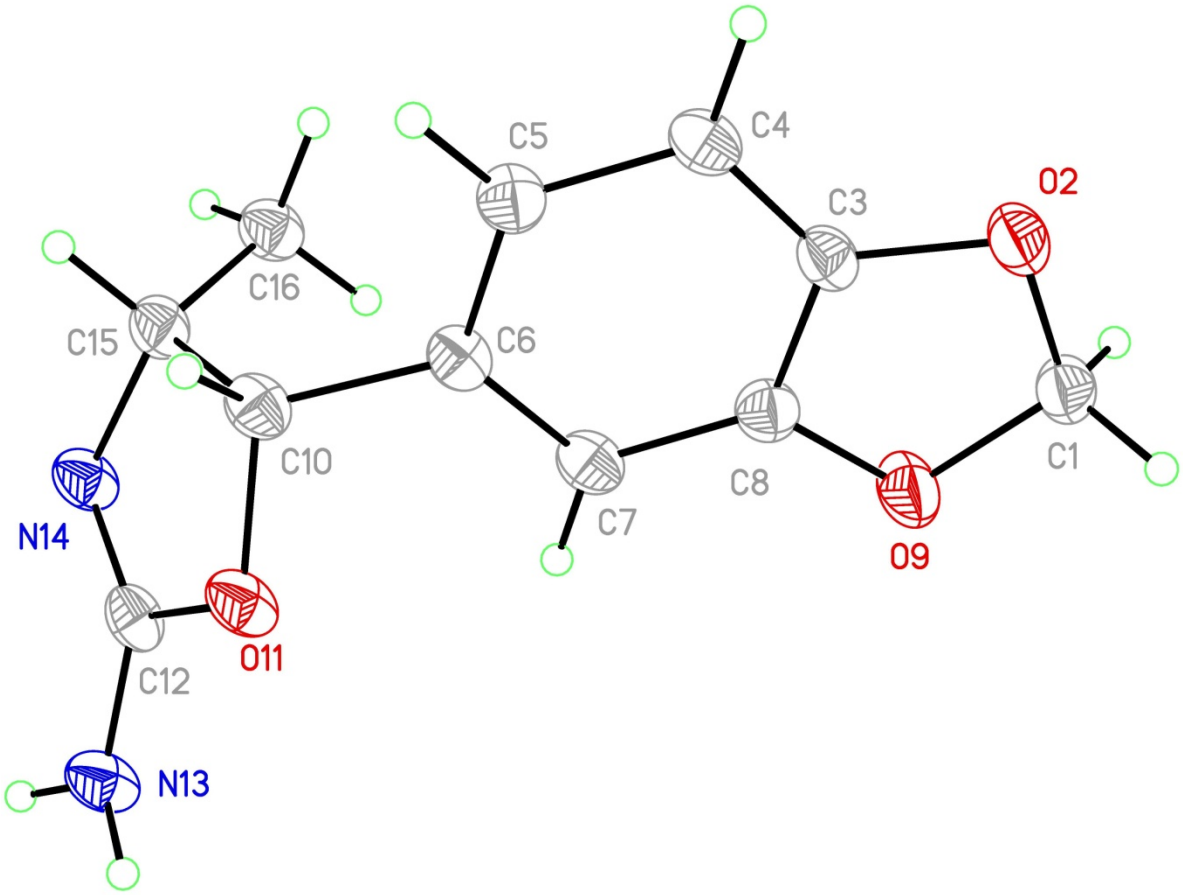


Figure depicting molecular structure of *cis* MDMAR. Displacement ellipsoids shown at 50%.

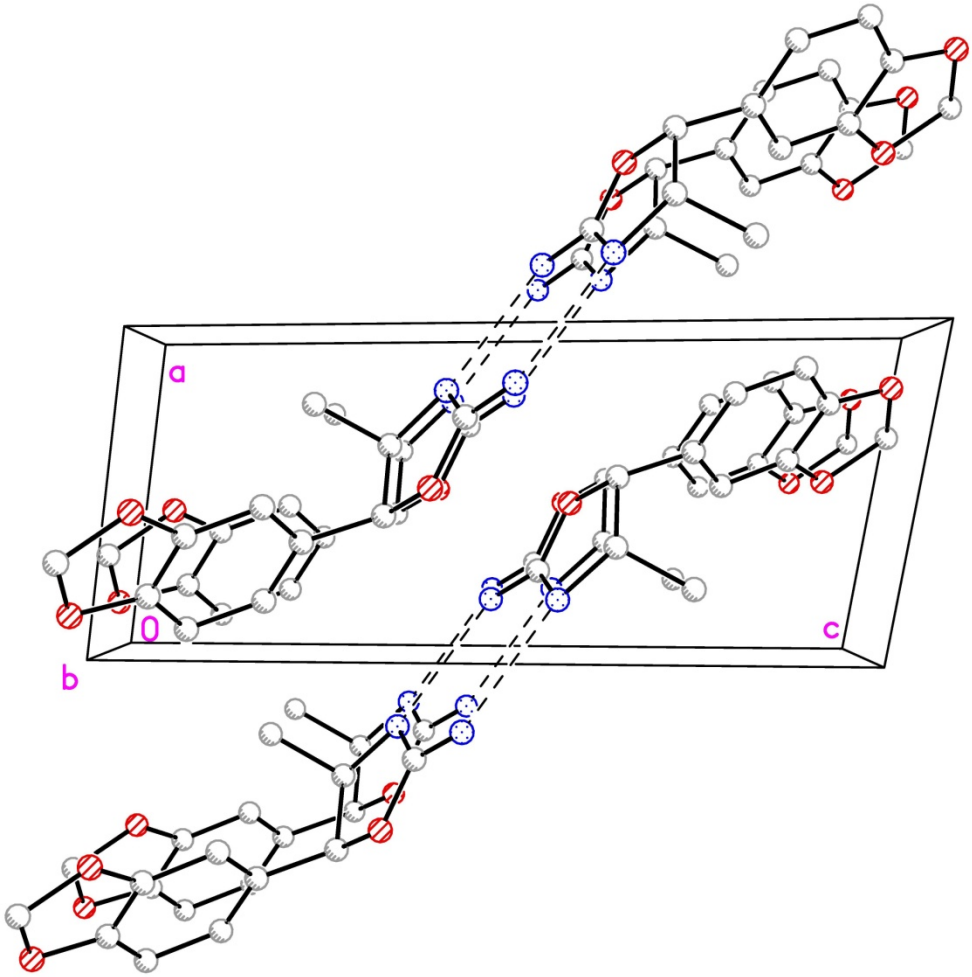


Figure showing packing diagram of *cis* MDMAR viewed down the b axis. Strong hydrogen bonding indicated by dashed lines. Hydrogen atoms omitted for clarity.

Table 2. Crystal data and structure refinement for TCD53b.

Identification code	tcd53b	
Empirical formula	C11 H12 N2 O3	
Formula weight	220.23	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 6.1800(2) Å	α= 80.360(2)°.
	b = 6.4291(3) Å	β= 78.857(2)°.
	c = 14.0726(6) Å	γ = 72.431(2)°.
Volume	519.43(4) $Å^3$	
Z	2	
Density (calculated)	1.408 Mg/m^3	
Absorption coefficient	0.868 mm^{-1}	
F(000)	232	
Crystal size	0.350 x 0.160 x 0.020 mm^3	
Theta range for data collection	3.223 to 69.908°.	
Index ranges	$-7\leq h\leq 7$, $-7\leq k\leq 7$, $-16\leq l\leq 17$	
Reflections collected	7712	
Independent reflections	1932 [R(int) = 0.0363]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7532 and 0.6506	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1932 / 0 / 154	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0960	
R indices (all data)	R1 = 0.0415, wR2 = 0.1001	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.247 and -0.187 $e.Å^{-3}$	

Table 3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for TCD53b. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3177(2)	8484(2)	36(1)	26(1)
O(2)	1680(2)	7102(2)	172(1)	30(1)
C(3)	2181(2)	5666(2)	996(1)	22(1)
C(4)	1181(2)	4045(2)	1435(1)	24(1)
C(5)	1964(2)	2854(2)	2293(1)	23(1)
C(6)	3682(2)	3286(2)	2671(1)	21(1)
C(7)	4688(2)	4946(2)	2203(1)	24(1)
C(8)	3887(2)	6102(2)	1370(1)	24(1)
O(9)	4557(2)	7816(2)	798(1)	37(1)
C(10)	4434(2)	1937(2)	3596(1)	23(1)
O(11)	5219(2)	3261(2)	4128(1)	26(1)
C(12)	7247(2)	1977(2)	4407(1)	22(1)
N(13)	8159(2)	2931(2)	4947(1)	28(1)
N(14)	8065(2)	75(2)	4118(1)	25(1)
C(15)	6490(2)	-192(2)	3512(1)	24(1)
C(16)	7713(2)	-609(2)	2489(1)	26(1)

Table 4. Bond lengths [Å] and angles [°] for TCD53b.

C(1)-O(9)	1.4287(16)	H(1A)-C(1)-H(1B)	108.4
C(1)-O(2)	1.4329(17)	C(3)-O(2)-C(1)	105.64(10)
C(1)-H(1A)	0.9900	C(4)-C(3)-O(2)	127.95(12)
C(1)-H(1B)	0.9900	C(4)-C(3)-C(8)	122.06(13)
O(2)-C(3)	1.3794(16)	O(2)-C(3)-C(8)	109.97(12)
C(3)-C(4)	1.369(2)	C(3)-C(4)-C(5)	116.51(12)
C(3)-C(8)	1.3809(19)	C(3)-C(4)-H(4)	121.7
C(4)-C(5)	1.4048(19)	C(5)-C(4)-H(4)	121.7
C(4)-H(4)	0.9500	C(6)-C(5)-C(4)	121.63(13)
C(5)-C(6)	1.3908(18)	C(6)-C(5)-H(5)	119.2
C(5)-H(5)	0.9500	C(4)-C(5)-H(5)	119.2
C(6)-C(7)	1.4021(19)	C(5)-C(6)-C(7)	120.62(12)
C(6)-C(10)	1.5077(18)	C(5)-C(6)-C(10)	118.60(12)
C(7)-C(8)	1.3725(19)	C(7)-C(6)-C(10)	120.77(12)
C(7)-H(7)	0.9500	C(8)-C(7)-C(6)	116.83(12)
C(8)-O(9)	1.3723(17)	C(8)-C(7)-H(7)	121.6
C(10)-O(11)	1.4564(16)	C(6)-C(7)-H(7)	121.6
C(10)-C(15)	1.5645(18)	O(9)-C(8)-C(7)	127.72(12)
C(10)-H(10)	1.0000	O(9)-C(8)-C(3)	109.93(12)
O(11)-C(12)	1.3653(15)	C(7)-C(8)-C(3)	122.34(13)
C(12)-N(14)	1.2765(18)	C(8)-O(9)-C(1)	106.12(10)
C(12)-N(13)	1.3422(18)	O(11)-C(10)-C(6)	109.11(11)
N(13)-H(13A)	0.91(2)	O(11)-C(10)-C(15)	103.36(10)
N(13)-H(13B)	0.89(2)	C(6)-C(10)-C(15)	118.54(11)
N(14)-C(15)	1.4746(16)	O(11)-C(10)-H(10)	108.5
C(15)-C(16)	1.5179(19)	C(6)-C(10)-H(10)	108.5
C(15)-H(15)	1.0000	C(15)-C(10)-H(10)	108.5
C(16)-H(16A)	0.9800	C(12)-O(11)-C(10)	106.69(10)
C(16)-H(16B)	0.9800	N(14)-C(12)-N(13)	128.01(12)
C(16)-H(16C)	0.9800	N(14)-C(12)-O(11)	117.72(12)
		N(13)-C(12)-O(11)	114.25(12)
O(9)-C(1)-O(2)	108.33(10)	C(12)-N(13)-H(13A)	117.1(11)
O(9)-C(1)-H(1A)	110.0	C(12)-N(13)-H(13B)	118.1(12)
O(2)-C(1)-H(1A)	110.0	H(13A)-N(13)-H(13B)	117.8(16)
O(9)-C(1)-H(1B)	110.0	C(12)-N(14)-C(15)	107.83(11)
O(2)-C(1)-H(1B)	110.0	N(14)-C(15)-C(16)	111.09(11)

N(14)-C(15)-C(10)	103.87(10)	C(15)-C(16)-H(16B)	109.5
C(16)-C(15)-C(10)	116.15(11)	H(16A)-C(16)-H(16B)	109.5
N(14)-C(15)-H(15)	108.5	C(15)-C(16)-H(16C)	109.5
C(16)-C(15)-H(15)	108.5	H(16A)-C(16)-H(16C)	109.5
C(10)-C(15)-H(15)	108.5	H(16B)-C(16)-H(16C)	109.5
C(15)-C(16)-H(16A)	109.5		

Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for TCD53b. 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)	26(1)	26(1)	27(1)	2(1)	-9(1)	-8(1)
O(2)	35(1)	33(1)	28(1)	7(1)	-16(1)	-16(1)
C(3)	20(1)	24(1)	21(1)	-3(1)	-6(1)	-3(1)
C(4)	18(1)	29(1)	26(1)	-4(1)	-6(1)	-7(1)
C(5)	20(1)	27(1)	25(1)	-1(1)	-4(1)	-8(1)
C(6)	16(1)	24(1)	21(1)	-4(1)	-3(1)	-3(1)
C(7)	19(1)	30(1)	25(1)	-4(1)	-6(1)	-8(1)
C(8)	23(1)	25(1)	24(1)	-2(1)	-5(1)	-9(1)
O(9)	48(1)	42(1)	34(1)	14(1)	-22(1)	-30(1)
C(10)	19(1)	29(1)	23(1)	-3(1)	-5(1)	-7(1)
O(11)	21(1)	29(1)	26(1)	-8(1)	-11(1)	3(1)
C(12)	18(1)	28(1)	19(1)	-1(1)	-6(1)	-2(1)
N(13)	24(1)	30(1)	30(1)	-10(1)	-12(1)	3(1)
N(14)	23(1)	27(1)	25(1)	-6(1)	-10(1)	0(1)
C(15)	22(1)	26(1)	24(1)	0(1)	-9(1)	-6(1)
C(16)	24(1)	28(1)	26(1)	-6(1)	-7(1)	-4(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for TCD53b.

	x	y	z	U(eq)
H(1A)	4168	8348	-607	31
H(1B)	2263	10038	56	31
H(4)	19	3741	1171	28
H(5)	1302	1726	2624	28
H(7)	5868	5256	2451	29
H(10)	3080	1532	4010	28
H(13A)	7210(30)	4140(30)	5218(13)	36(5)
H(13B)	9300(30)	2080(30)	5262(14)	40(5)
H(15)	5917	-1484	3817	28
H(16A)	8200	684	2165	39
H(16B)	6666	-894	2117	39
H(16C)	9061	-1886	2523	39

Table 7. Torsion angles [°] for TCD53b.

O(9)-C(1)-O(2)-C(3)	0.09(15)
C(1)-O(2)-C(3)-C(4)	178.87(14)
C(1)-O(2)-C(3)-C(8)	0.20(15)
O(2)-C(3)-C(4)-C(5)	-177.88(13)
C(8)-C(3)-C(4)-C(5)	0.7(2)
C(3)-C(4)-C(5)-C(6)	-0.7(2)
C(4)-C(5)-C(6)-C(7)	0.3(2)
C(4)-C(5)-C(6)-C(10)	-179.93(12)
C(5)-C(6)-C(7)-C(8)	0.3(2)
C(10)-C(6)-C(7)-C(8)	-179.55(12)
C(6)-C(7)-C(8)-O(9)	178.54(13)
C(6)-C(7)-C(8)-C(3)	-0.3(2)
C(4)-C(3)-C(8)-O(9)	-179.19(12)
O(2)-C(3)-C(8)-O(9)	-0.42(16)
C(4)-C(3)-C(8)-C(7)	-0.2(2)
O(2)-C(3)-C(8)-C(7)	178.61(12)
C(7)-C(8)-O(9)-C(1)	-178.51(14)
C(3)-C(8)-O(9)-C(1)	0.46(16)
O(2)-C(1)-O(9)-C(8)	-0.33(15)
C(5)-C(6)-C(10)-O(11)	-150.27(12)
C(7)-C(6)-C(10)-O(11)	29.54(16)
C(5)-C(6)-C(10)-C(15)	91.90(15)
C(7)-C(6)-C(10)-C(15)	-88.30(16)
C(6)-C(10)-O(11)-C(12)	-133.65(11)
C(15)-C(10)-O(11)-C(12)	-6.64(13)
C(10)-O(11)-C(12)-N(14)	4.06(16)
C(10)-O(11)-C(12)-N(13)	-177.29(11)
N(13)-C(12)-N(14)-C(15)	-177.56(14)
O(11)-C(12)-N(14)-C(15)	0.87(17)
C(12)-N(14)-C(15)-C(16)	120.56(13)
C(12)-N(14)-C(15)-C(10)	-5.01(14)
O(11)-C(10)-C(15)-N(14)	7.01(13)
C(6)-C(10)-C(15)-N(14)	127.83(12)
O(11)-C(10)-C(15)-C(16)	-115.27(12)
C(6)-C(10)-C(15)-C(16)	5.55(17)

Table 8. Hydrogen bonds for TCD53b [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(13)-H(13A)...O(11)#1	0.91(2)	2.09(2)	2.9969(16)	173.9(16)
N(13)-H(13B)...N(14)#2	0.89(2)	2.03(2)	2.9196(16)	174.1(17)

Symmetry transformations used to generate equivalent atoms:

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

End of supplementary data