Electronic Supplementary Material (ESI) for MedChemComm.

Supporting Information

On the importance of synthetic organic chemistry in drug discovery: reflections on the discovery of antidiabetic agent ertugliflozin

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X-ray data for compound 33:

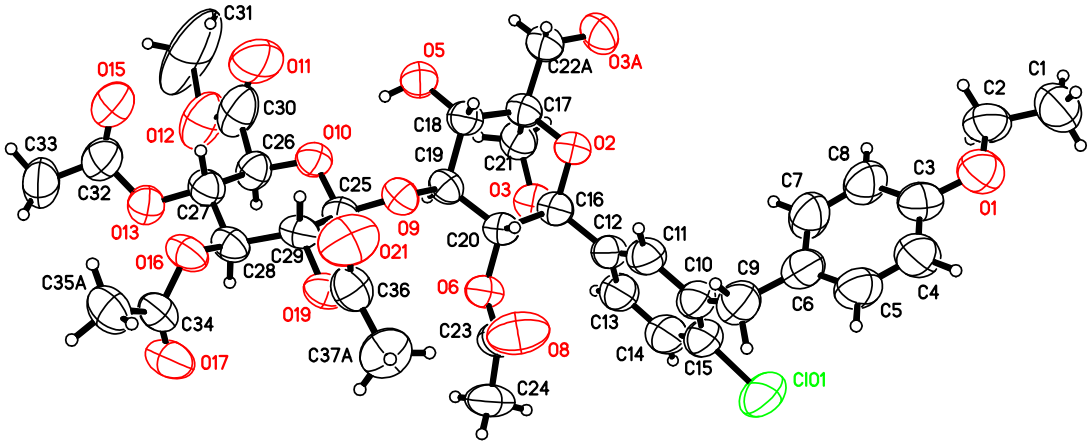

Fig. 1. ORTEP with ellipsoids drawn at 50% confidence level.

EXPERIMENTAL:

Data collection was performed on a Bruker APEX diffractometer at room temperature. Data collection consisted of 3 omega scans and low angle and three at high angle; each with 0.5 step. In addition, 2 phi scans were collected to improve the quality of the absorption correction. Resolution limited to 0.95 angstroms.

The structure was solved by direct methods using SHELX software suite in the space group P2(1). The structure was subsequently refined by the full-matrix least squares method. All non-hydrogen atoms were found and refined using anisotropic displacement parameters.

The C22-O3 group is disordered in two positions with approximately 50/50 occupancy. The O12-C31 distance is a bit long and C31 is disordered; left un-modeled. It is possible that C30-O11 and C30-O12 have a shared occupancy.

The hydrogen atoms located on disordered sites O3a and O3b were placed in an idealized position and refined; however the H3b proton refined to an unreasonable position within the hydrogen bonding network and was thus fixed into a reasonable position within the hydrogen bonding network. The remaining hydrogen atoms were placed in calculated positions and were allowed to ride on their carrier atoms. The final refinement included isotropic displacement parameters for all hydrogen atoms.

Analysis of the absolute structure was done by examining the Flack parameter. In this case, the flack parameter = 0.0291 with esd of 0.0287; within range of absolute configuration for an enantiopure compound.

The final R-index was 4%. A final difference Fourier revealed no missing or misplaced electron density.

Pertinent crystal, data collection and refinement are summarized in table 1. Atomic coordinates, bond lengths, bond angles, Torsion angles and displacement parameters are listed in tables 2 –6.

Software and References

SHELXTL, Version 5.1, Bruker AXS, 1997

PLATON, A.L. Spek, J. Appl. Cryst. 2003, 36, 7-13.

MERCURY, C.F. Macrae, P.R. Edington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Cryst.* **39**, 453-457, 2006.

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H.D. Flack, *Acta Cryst.* 1983, **A**39, 867-881.

Table 1. Crystal data and structure refinement for compound **33**.

Empirical formula	$C_{37}\ H_{43}\ Cl\ O_{17}$	
Formula weight	795.16	
Temperature	298(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 16.0735(5) Å	α= 90°.
	b = 7.0772(2) Å	β= 113.3510(10)°.
	c = 18.7585(6) Å	γ = 90°.
Volume	1959.10(10) $Å^3$	
Z	2	
Density (calculated)	1.348 Mg/m^3	
Absorption coefficient	1.507 mm^{-1}	
F(000)	836	
Crystal size	0.35 x 0.10 x 0.05 mm^3	
Theta range for data collection	2.57 to 54.23°.	
Index ranges	-16<=h<=16, -7<=k<=5, -19<=l<=19	
Reflections collected	9621	
Independent reflections	3635 [R(int) = 0.0317]	
Completeness to theta = 54.23°	94.5 %	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3635 / 2 / 513	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0418, wR2 = 0.1062	
R indices (all data)	R1 = 0.0537, wR2 = 0.1152	
Absolute structure parameter	0.03(3)	
Extinction coefficient	0.0022(3)	
Largest diff. peak and hole	0.242 and -0.171 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **33**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	17108(4)	6751(11)	11449(4)	114(2)
C(2)	16144(4)	6506(10)	10881(4)	99(2)
C(3)	14685(4)	7803(9)	10694(3)	81(2)
C(4)	14203(4)	9034(9)	10954(4)	97(2)
C(5)	13268(4)	9021(9)	10622(3)	91(2)
C(6)	12791(4)	7792(9)	10041(3)	80(2)
C(7)	13288(4)	6603(9)	9793(3)	96(2)
C(8)	14214(4)	6568(9)	10109(3)	94(2)
C(9)	11767(4)	7872(9)	9651(3)	89(2)
C(10)	11307(3)	6045(8)	9327(3)	77(2)
C(11)	11008(3)	5635(8)	8533(3)	73(1)
C(12)	10589(3)	3982(8)	8202(3)	65(1)
C(13)	10426(3)	2621(9)	8674(3)	80(2)
C(14)	10717(4)	3010(11)	9466(3)	91(2)
C(15)	11143(4)	4642(10)	9774(3)	84(2)
C(16)	10228(3)	3700(7)	7342(3)	60(1)
C(17)	10562(3)	3239(7)	6299(3)	63(1)
C(18)	9755(3)	4385(7)	5743(2)	61(1)
C(19)	9018(3)	4521(7)	6055(2)	56(1)
C(20)	9404(3)	4965(7)	6911(2)	57(1)
C(21)	10277(3)	1336(8)	6507(3)	74(1)
C(23)	8585(4)	5914(11)	7668(3)	82(2)
C(24)	8004(4)	5145(11)	8058(3)	112(2)
C(25)	7528(3)	5478(6)	5191(2)	55(1)
C(26)	6707(3)	3843(7)	4013(3)	66(1)
C(27)	6076(3)	5548(7)	3687(3)	64(1)
C(28)	6015(3)	6709(7)	4338(3)	61(1)
C(29)	6962(3)	7227(6)	4917(3)	59(1)
C(30)	6906(6)	2822(11)	3396(4)	104(2)
C(31)	6671(9)	761(19)	2424(4)	298(10)
C(32)	4956(4)	4809(10)	2440(3)	94(2)

C(33)	3993(4)	4349(10)	1991(3)	107(2)
C(34)	4806(3)	8923(8)	4138(3)	70(1)
C(36)	7285(3)	9868(9)	5791(3)	77(1)
C(22A)	11320(3)	3178(11)	6010(3)	85(2)
C(35A)	4388(4)	10610(9)	3691(3)	95(2)
C(37A)	7261(4)	10471(9)	6537(3)	94(2)
C(22B)	11320(3)	3178(11)	6010(3)	85(2)
Cl(01)	11471(1)	5017(3)	10773(1)	123(1)
O(1)	15616(3)	7935(6)	11053(2)	94(1)
O(2)	10888(2)	4196(4)	7050(2)	65(1)
O(3)	10004(2)	1778(5)	7135(2)	72(1)
O(5)	9452(2)	3518(6)	5003(2)	79(1)
O(6)	8725(2)	4588(5)	7214(2)	69(1)
O(8)	8888(4)	7469(8)	7750(3)	123(2)
O(9)	8404(2)	6029(4)	5653(2)	60(1)
O(10)	7564(2)	4528(5)	4538(2)	64(1)
O(11)	7527(4)	3265(8)	3222(3)	124(2)
O(12)	6327(4)	1486(7)	3077(3)	122(2)
O(13)	5169(2)	4939(5)	3207(2)	71(1)
O(15)	5504(3)	5007(8)	2162(2)	118(2)
O(16)	5531(2)	8398(5)	3999(2)	70(1)
O(17)	4553(2)	8061(6)	4571(2)	93(1)
O(19)	6887(2)	8119(5)	5576(2)	65(1)
O(21)	7607(3)	10696(6)	5420(3)	110(2)
O(3A)	12107(4)	2438(10)	6508(4)	90(3)
O(3B)	11630(5)	4711(14)	5860(5)	96(3)

Table 3. Bond lengths [Å] and angles [°] for **33**.

C(1)-C(2)	1.503(8)	C(23)-C(24)	1.497(8)
C(2)-O(1)	1.437(7)	C(25)-O(9)	1.385(5)
C(3)-C(8)	1.372(8)	C(25)-O(10)	1.419(5)
C(3)-C(4)	1.377(7)	C(25)-C(29)	1.500(6)
C(3)-O(1)	1.379(6)	C(26)-O(10)	1.424(5)
C(4)-C(5)	1.380(8)	C(26)-C(30)	1.503(8)
C(5)-C(6)	1.367(8)	C(26)-C(27)	1.538(7)
C(6)-C(7)	1.364(7)	C(27)-O(13)	1.443(5)
C(6)-C(9)	1.514(7)	C(27)-C(28)	1.507(6)
C(7)-C(8)	1.366(7)	C(28)-O(16)	1.431(5)
C(9)-C(10)	1.494(8)	C(28)-C(29)	1.524(6)
C(10)-C(15)	1.390(8)	C(29)-O(19)	1.436(5)
C(10)-C(11)	1.403(7)	C(30)-O(11)	1.209(9)
C(11)-C(12)	1.369(7)	C(30)-O(12)	1.295(9)
C(12)-C(13)	1.402(7)	C(31)-O(12)	1.615(9)
C(12)-C(16)	1.496(6)	C(32)-O(15)	1.197(6)
C(13)-C(14)	1.397(7)	C(32)-O(13)	1.344(6)
C(14)-C(15)	1.350(9)	C(32)-C(33)	1.475(8)
C(15)-Cl(01)	1.753(5)	C(34)-O(17)	1.208(5)
C(16)-O(2)	1.417(5)	C(34)-O(16)	1.343(5)
C(16)-O(3)	1.421(6)	C(34)-C(35A)	1.460(8)
C(16)-C(20)	1.536(6)	C(36)-O(21)	1.175(6)
C(17)-O(2)	1.460(5)	C(36)-O(19)	1.378(6)
C(17)-C(22A)	1.519(6)	C(36)-C(37A)	1.479(7)
C(17)-C(21)	1.522(7)	C(22A)-O(3A)	1.345(8)
C(17)-C(18)	1.534(6)		
C(18)-O(5)	1.416(5)	O(1)-C(2)-C(1)	107.1(5)
C(18)-C(19)	1.519(5)	C(8)-C(3)-C(4)	118.5(5)
C(19)-O(9)	1.447(5)	C(8)-C(3)-O(1)	125.5(5)
C(19)-C(20)	1.507(6)	C(4)-C(3)-O(1)	116.0(5)
C(20)-O(6)	1.440(5)	C(3)-C(4)-C(5)	120.1(6)
C(21)-O(3)	1.445(5)	C(6)-C(5)-C(4)	122.0(5)
C(23)-O(8)	1.189(7)	C(7)-C(6)-C(5)	116.4(5)
C(23)-O(6)	1.346(7)	C(7)-C(6)-C(9)	122.1(5)

C(5)-C(6)-C(9)	121.4(5)	C(19)-C(20)-C(16)	110.1(4)
C(6)-C(7)-C(8)	123.3(6)	O(3)-C(21)-C(17)	103.7(4)
C(7)-C(8)-C(3)	119.7(5)	O(8)-C(23)-O(6)	124.3(5)
C(10)-C(9)-C(6)	115.6(5)	O(8)-C(23)-C(24)	125.2(6)
C(15)-C(10)-C(11)	115.2(6)	O(6)-C(23)-C(24)	110.4(7)
C(15)-C(10)-C(9)	123.6(5)	O(9)-C(25)-O(10)	107.1(3)
C(11)-C(10)-C(9)	121.1(5)	O(9)-C(25)-C(29)	108.0(4)
C(12)-C(11)-C(10)	123.9(5)	O(10)-C(25)-C(29)	108.8(3)
C(11)-C(12)-C(13)	118.8(5)	O(10)-C(26)-C(30)	104.7(5)
C(11)-C(12)-C(16)	120.9(4)	O(10)-C(26)-C(27)	108.2(4)
C(13)-C(12)-C(16)	120.0(5)	C(30)-C(26)-C(27)	112.3(4)
C(14)-C(13)-C(12)	118.0(6)	O(13)-C(27)-C(28)	107.1(3)
C(15)-C(14)-C(13)	121.5(6)	O(13)-C(27)-C(26)	111.0(4)
C(14)-C(15)-C(10)	122.6(5)	C(28)-C(27)-C(26)	110.5(4)
C(14)-C(15)-Cl(01)	118.2(5)	O(16)-C(28)-C(27)	107.1(4)
C(10)-C(15)-Cl(01)	119.2(5)	O(16)-C(28)-C(29)	109.3(4)
O(2)-C(16)-O(3)	106.2(3)	C(27)-C(28)-C(29)	109.9(3)
O(2)-C(16)-C(12)	110.7(4)	O(19)-C(29)-C(25)	108.3(4)
O(3)-C(16)-C(12)	111.7(4)	O(19)-C(29)-C(28)	108.5(3)
O(2)-C(16)-C(20)	105.9(3)	C(25)-C(29)-C(28)	110.1(4)
O(3)-C(16)-C(20)	110.0(4)	O(11)-C(30)-O(12)	125.8(7)
C(12)-C(16)-C(20)	112.0(4)	O(11)-C(30)-C(26)	122.3(8)
O(2)-C(17)-C(22A)	109.0(4)	O(12)-C(30)-C(26)	111.9(7)
O(2)-C(17)-C(21)	101.1(4)	O(15)-C(32)-O(13)	122.6(6)
C(22A)-C(17)-C(21)	115.6(4)	O(15)-C(32)-C(33)	124.4(6)
O(2)-C(17)-C(18)	107.1(4)	O(13)-C(32)-C(33)	113.0(5)
C(22A)-C(17)-C(18)	110.7(4)	O(17)-C(34)-O(16)	122.7(5)
C(21)-C(17)-C(18)	112.5(4)	O(17)-C(34)-C(35A)	126.6(4)
O(5)-C(18)-C(19)	112.8(4)	O(16)-C(34)-C(35A)	110.7(5)
O(5)-C(18)-C(17)	107.9(4)	O(21)-C(36)-O(19)	122.5(5)
C(19)-C(18)-C(17)	110.4(4)	O(21)-C(36)-C(37A)	126.9(6)
O(9)-C(19)-C(20)	108.1(3)	O(19)-C(36)-C(37A)	110.6(5)
O(9)-C(19)-C(18)	108.7(3)	O(3A)-C(22A)-C(17)	115.5(5)
C(20)-C(19)-C(18)	111.6(3)	C(3)-O(1)-C(2)	117.8(4)
O(6)-C(20)-C(19)	108.9(3)	C(16)-O(2)-C(17)	102.7(3)
O(6)-C(20)-C(16)	108.3(3)	C(16)-O(3)-C(21)	107.7(3)

C(23)-O(6)-C(20)	117.6(4)
C(25)-O(9)-C(19)	115.7(3)
C(25)-O(10)-C(26)	113.5(3)
C(30)-O(12)-C(31)	100.5(7)
C(32)-O(13)-C(27)	117.0(4)
C(34)-O(16)-C(28)	120.3(4)
C(36)-O(19)-C(29)	117.3(4)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **33**. 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)	84(4)	127(6)	133(6)	-12(4)	44(4)	-3(4)
C(2)	101(5)	111(5)	102(5)	-21(4)	58(4)	-1(4)
C(3)	92(4)	80(4)	83(4)	1(3)	48(3)	-3(3)
C(4)	91(4)	100(5)	106(5)	-30(4)	46(4)	-13(4)
C(5)	105(5)	91(5)	89(4)	-20(3)	50(4)	0(3)
C(6)	93(4)	85(4)	66(3)	0(3)	35(3)	11(3)
C(7)	90(4)	108(5)	79(4)	-21(3)	20(3)	18(3)
C(8)	99(5)	100(5)	83(4)	-24(4)	35(4)	12(4)
C(9)	96(4)	93(5)	75(4)	1(3)	31(3)	23(4)
C(10)	75(3)	92(5)	62(3)	6(3)	27(3)	14(3)
C(11)	75(3)	80(4)	68(4)	8(3)	33(3)	9(3)
C(12)	61(3)	77(4)	59(3)	6(3)	28(2)	8(3)
C(13)	75(3)	95(5)	73(4)	21(3)	32(3)	13(3)
C(14)	84(4)	115(6)	78(4)	40(4)	37(3)	21(4)
C(15)	79(4)	111(6)	61(3)	12(3)	28(3)	16(4)
C(16)	61(3)	60(4)	63(3)	5(2)	29(2)	3(2)
C(17)	57(3)	69(4)	67(3)	-4(2)	29(2)	4(2)
C(18)	60(3)	62(3)	64(3)	-6(2)	29(2)	-4(2)
C(19)	51(3)	50(3)	66(3)	4(2)	24(2)	0(2)
C(20)	59(3)	58(3)	61(3)	2(2)	31(2)	2(2)
C(21)	74(3)	72(4)	75(3)	0(3)	28(3)	11(3)
C(23)	85(4)	94(5)	79(4)	1(3)	45(3)	23(3)
C(24)	101(4)	165(7)	99(4)	12(4)	70(4)	26(4)
C(25)	59(3)	51(3)	61(3)	3(2)	29(2)	1(2)
C(26)	73(3)	60(4)	60(3)	2(2)	22(3)	7(2)
C(27)	59(3)	67(4)	69(3)	7(2)	27(2)	1(2)
C(28)	56(3)	56(3)	76(3)	9(2)	32(2)	8(2)
C(29)	63(3)	54(3)	72(3)	9(2)	39(2)	7(2)
C(30)	130(6)	91(6)	74(4)	5(4)	21(4)	51(5)
C(31)	430(20)	290(16)	90(6)	-60(7)	17(9)	233(15)
C(32)	90(4)	115(5)	74(4)	18(4)	30(3)	-3(4)

C(33)	79(4)	136(6)	83(4)	10(4)	7(3)	-5(4)
C(34)	54(3)	75(4)	82(4)	-1(3)	30(3)	6(2)
C(36)	68(3)	67(4)	91(4)	-5(3)	28(3)	-5(3)
C(22A)	61(3)	118(6)	76(4)	-15(3)	28(3)	9(4)
C(35A)	76(4)	98(5)	109(4)	6(3)	33(3)	34(3)
C(37A)	122(5)	66(4)	97(4)	-15(3)	46(4)	-2(3)
C(22B)	61(3)	118(6)	76(4)	-15(3)	28(3)	9(4)
Cl(01)	132(1)	172(2)	63(1)	15(1)	36(1)	23(1)
O(1)	95(3)	87(3)	108(3)	-15(2)	49(2)	-5(2)
O(2)	59(2)	78(2)	64(2)	-3(2)	31(2)	4(2)
O(3)	79(2)	60(3)	83(2)	3(2)	38(2)	4(2)
O(5)	68(2)	106(3)	65(2)	-14(2)	28(2)	12(2)
O(6)	64(2)	84(3)	68(2)	1(2)	37(2)	6(2)
O(8)	169(5)	102(4)	131(4)	-17(3)	97(4)	13(4)
O(9)	57(2)	54(2)	70(2)	5(2)	26(2)	3(2)
O(10)	64(2)	70(2)	62(2)	-1(2)	28(2)	11(2)
O(11)	151(4)	130(4)	111(4)	-24(3)	71(3)	30(3)
O(12)	163(4)	91(4)	83(3)	-17(3)	19(3)	10(3)
O(13)	66(2)	79(3)	66(2)	5(2)	23(2)	0(2)
O(15)	106(3)	171(5)	74(3)	21(3)	31(2)	1(3)
O(16)	60(2)	69(2)	92(2)	19(2)	42(2)	17(2)
O(17)	80(2)	103(3)	116(3)	8(3)	59(2)	11(2)
O(19)	68(2)	55(2)	85(2)	-6(2)	43(2)	-6(2)
O(21)	152(4)	76(3)	121(4)	-6(2)	73(3)	-43(3)
O(3A)	62(5)	109(6)	95(5)	-6(4)	28(4)	21(4)
O(3B)	83(6)	106(8)	115(7)	-21(5)	55(5)	-23(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **33**.

	x	y	z	U(eq)
H(1A)	17312	8001	11400	171
H(1B)	17486	5838	11343	171
H(1C)	17143	6571	11967	171
H(2A)	16102	6651	10353	119
H(2B)	15925	5259	10933	119
H(4)	14507	9875	11353	116
H(5A)	12953	9874	10799	110
H(7)	12983	5774	9389	115
H(8)	14524	5711	9928	113
H(9A)	11537	8330	10026	107
H(9B)	11600	8788	9233	107
H(11)	11100	6540	8212	88
H(13)	10133	1493	8467	96
H(14)	10614	2126	9789	109
H(18)	9965	5664	5702	73
H(19)	8684	3325	5964	67
H(20)	9584	6297	6993	69
H(21A)	9777	803	6068	89
H(21B)	10778	450	6674	89
H(99D)	8378	4503	8526	168
H(99E)	7572	4274	7715	168
H(99F)	7690	6164	8181	168
H(26)	7280	4653	5478	66
H(27)	6450	2972	4278	79
H(28)	6311	6335	3379	77
H(29)	5691	6004	4599	73
H(30)	7249	8091	4675	71
H(90A)	7189	1488	2454	447
H(90B)	6194	913	1918	447
H(90C)	6836	-549	2510	447

H(98D)	3619	5255	2106	160
H(98E)	3867	3107	2129	160
H(98F)	3866	4386	1446	160
H(22A)	11114	2448	5534	101
H(22B)	11434	4455	5885	101
H(98A)	3749	10599	3573	143
H(98B)	4482	10623	3217	143
H(98C)	4656	11716	3990	143
H(99A)	7745	9873	6958	141
H(99B)	6691	10114	6551	141
H(99C)	7330	11818	6587	141
H(22C)	11824	2505	6396	101
H(22D)	11110	2417	5542	101
H(5)	8901	3630	4784	119
H(3A)	12025	1339	6604	135
H(3B)	11909	5892	6166	145