Combined Computational/Experimental Investigation of new cocrystals of the drug bosentan

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Electronic Supplementary Information

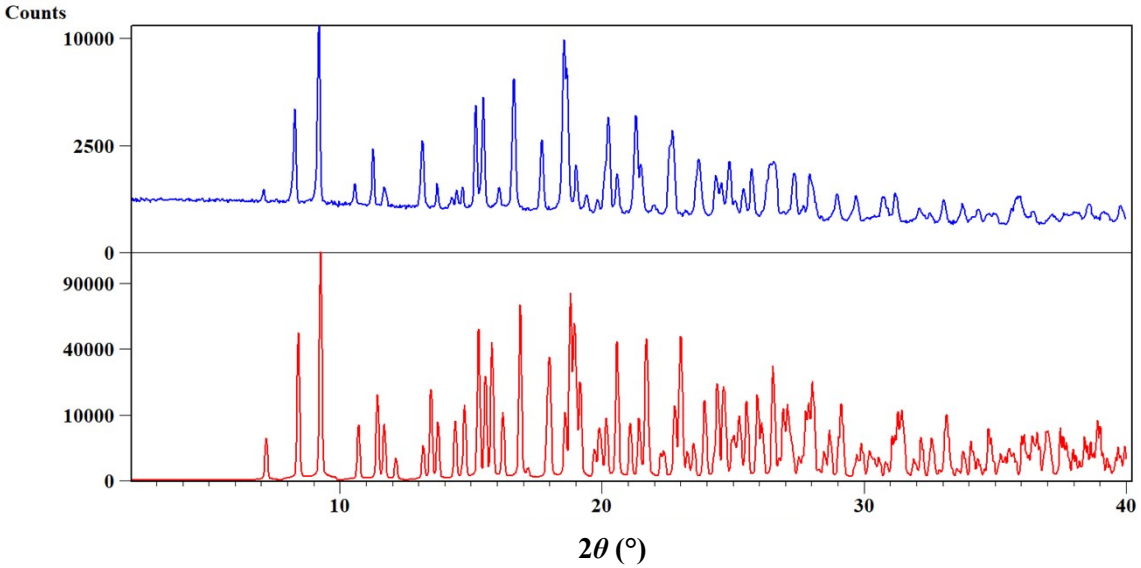
1. Materials and experimental methods

1.1 Materials

1.1.1 Bosentan

Bosentan used in this study corresponds to its monohydrate crystal form, Figure S1.

Figure S1: Comparative PXRD diffractograms of bosentan monohydrate powder used as starting material (blue) and simulated from the cif: bosentan monohydrate (CCDC refcode: NEQHEY01) (red)



1.1.2. Qualitative determination of bosentan monohydrate solubility

The solvents selected to be used in the cocrystal screening are highlighted in black. Bosentan monohydrate was dissolved in 30 solvents in a temperature range of 25-90 ºC. Bosentan monohydrate is soluble at 25 ºC in the following solvents: **methanol** (1.7 mL), **ethanol** (1.2 mL), **IPA** (1.3 mL), butanol (1.3 mL), formic acid (0.2 mL), **ACN** (0.3 mL), MEK (0.3 mL), **acetone** (0.3 mL), **MiBK** (2.0 mL), DMF (0.1 mL), **DMSO** (0.1 mL), **AcOEt** (1.5 mL), **THF** (0.3 mL), **dimethyl ethylene glycol** (0.2 mL), **dioxane** (0.3 mL), **dichloromethane** (0.2 mL), **chloroform** (0.3 mL), acetic acid (0.2 mL), **benzyl alcohol** (0.2 mL), NH_3 (32 %) in water (0.2 mL) and diethylamine (0.5 mL). At 50 ºC it is soluble in ethylene glycol (2.0 mL) and **toluene** (2.0 mL). At 70 ºC it is soluble in **xylene** (2.0 mL). At 90 ºC it is partially soluble in **heptane** (2.0 mL) and cyclohexane (2.0 mL). It is insoluble in **water** (2.0 mL), pentane (2.0 mL), **diethyl ether** (2.0 mL) and **diisopropyl ether** (2.0 mL).

1.2.1 Coformers selection

The following 10 coformers have been chosen based on the difference between the interaction site pairing energies of bosentan and the pure components, ΔE (Table S1): resorcinol, tartaric acid, citric acid, malic acid, fumaric acid, 4-hydroxybenzoic acid, inositol, succinic acid, rhamnose and urea. The coformers were purchased from Sigma-Aldrich.

Table S1. Coformers chosen in this study based on the difference between the interaction site pairing energies of bosentan and the pure components, ΔE.

Coformers	**ΔE / kJ mol^{-1}**
Resorcinol	23.7
Tartaric acid	21.0
Citric acid	20.2
Malic acid	19.6
Fumaric acid	19.1
4-Hydroxybenzoic acid	18.1
Inositol	16.9
Succinic acid	15.7
Rhamnose	14.6
Urea	13.9

Table S2. Cocrystal screening of bosentan monohydrate

Methodology	Coformers	Nº Experiments	Nº Solids	Positive results[a]	Coformers	Form obtained (according to XRPD)
Solubility Study	-	30	27	-	-	Bosentan monohydrate
Liquid assisted grinding at 25 ºC	10	88	87	1 / 2	4 / 2	3 new evidences Bosentan-Succinic acid Bosentan-Resorcinol
Reaction Crystallization at 25 ºC	6[b]	40	39	2	2	Bosentan-Succinic acid Bosentan-4-Hydroxybenzoic acid
Solvent mediated transformation at 25 ºC	1	1	1	2	1	Bosentan-Succinic acid
Solution crystallization at different temperatures	2	34	9	2	1	Bosentan-Succinic acid
Preparation of the solid forms: scale up batches	1	1	1	2	1	Bosentan-Succinic acid

[a] (1) positive: Bosentan + coformer + new peaks observed in XRPD and (2) positive: cocrystal

[b] The following 6 coformers have been tested through reaction crystallization methodology: citric acid, inositol, succinic acid, urea, resorcinol and 4-hydroxybenzoic acid.

2. Synthesis of bosentan cocrystals

Synthesis of the new multicomponent solid forms of bosentan was conducted by solvent mediated transformation (SMT), reaction crystallization (RC) or solution crystallization methodologies. Stoichiometry has been assessed based on NMR when crystal structure is not available. Details of synthesis of the bulk powder and single crystal are as follows:

2.1 Bosentan: succinic acid cocrystal (1:1)

Bulk powder

Bosentan monohydrate (2.55 g, 4.48 mmol) and succinic acid (0.53g, 4.48 mmol) were mixed and stirred overnight in acetone (25 mL) at 25 °C. The resulting suspension was filtered and dried under vacuum.

In order to obtain a single crystal of bosentan: succinic acid cocrystal, qualitative solubility was determined. Thus, the bosentan: succinic acid cocrystal was dissolved in 30 solvents in a temperature range of 25-90 ºC. Bosentan: succinic acid cocrystal is soluble at 25 ºC in the following solvents: ethanol (0.5 mL), butanol (1.0 mL), formic acid (0.05 mL), ACN (0.7 mL), MEK (0.6 mL), acetone (0.3 mL), DMF (0.05 mL), DMSO (0.05 mL), THF (0.2 mL), dimethyl ethylene glycol (0.2 mL), dioxane (0.3 mL), acetic acid (0.1 mL), benzyl alcohol (0.15 mL) and NH_3 (32 %) in water (0.2 mL). At 50 ºC it is soluble in methanol (1.0 mL), IPA (1.0 mL), ethylene glycol (1.0 mL) and AcOEt (1.0 mL). At 70 ºC it is soluble in MiBK (1.0 mL) and diethyl ether (1.0 mL). It is insoluble in water (1.0 mL), pentane (1.0 mL), heptane (1.0 mL), cyclohexane (1.0 mL), toluene (1.0 mL), xylene (1.0 mL), diisopropyl ether (1.0 mL), dichloromethane (1.0 mL), chloroform (1.0 mL) and diethylamine (1.0 mL).

Single crystal

Bosentan: succinic acid cocrystal (10 mg, 0.015 mmol) was mixed and dissolved in ACN (0.6 mL) at 25 ºC. Then, the solution was kept sealed at 25 ºC. Single crystals were observed after one week.

2.2 Bosentan: resorcinol cocrystal (1:1). It was obtained by liquid assisted grinding in THF. Its PXRD diagram has been indexed.

2.3 Bosentan: 4-hydroxybenzoic acid cocrystal (1:2). It was obtained by reaction crystallization in AcOEt. Its PXRD diagram has been indexed.

3.- Crystal data and structure refinement

3.1 Bosentan: succinic acid cocrystal (mo_023rb78_0m)

Table S3. Crystal data and structure refinement for mo_023rb78_0m.

Identification code	mo_023rb78_0m	
Empirical formula	C31 H35 N5 O10 S	
Formula weight	669.70	
Temperature	300(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 5.9031(14) Å	α= 70.166(10)°.
	b = 14.188(4) Å	β= 89.202(10)°.
	c = 20.665(5) Å	γ = 83.142(11)°.
Volume	1615.8(7) $Å^3$	
Z	2	
Density (calculated)	1.377 Mg/m^3	
Absorption coefficient	0.165 mm^{-1}	
F(000)	704	
Crystal size	0.300 x 0.300 x 0.030 mm^3	
Theta range for data collection	2.096 to 25.217°.	
Index ranges	-7<=h<=7, -16<=k<=17, -24<=l<=24	
Reflections collected	30072	
Independent reflections	5813 [R(int) = 0.1209]	
Completeness to theta = 25.217°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7452 and 0.5283	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5813 / 22 / 436	
Goodness-of-fit on F^2	1.015	
Final R indices [I>2sigma(I)]	R1 = 0.0712, wR2 = 0.1516	
R indices (all data)	R1 = 0.1388, wR2 = 0.1829	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.574 and -0.499 $e.Å^{-3}$	
CCDC	2168576	

Table S4. Hydrogen bonds for mo_023rb78_0m. Bond lengths [Å] and angles [°]

Donor --- H....Acceptor	[ARU]	D - H	H...A	D...A	D - H...A
N(1) --H(1N) ..O(3)	[ ]	0.86	2.44	2.765(4)	103
O(5) --H(5O) ..O(9)	[2-x,1-y,1-z]	0.80(7)	1.94(7)	2.727(6)	168(5)
O(8) --H(8O) ..N(5)	[2-x,1-y,1-z]	0.85(6)	1.96(6)	2.773(5)	162(5)
O(10) --H(10O) ..O(5)	[ ]	0.98(7)	1.62(7)	2.591(6)	176(4)

4.- Characterization of the solids

Figure S2: Differential Scanning Calorimetry (DSC) of bosentan: succinic acid cocrystal analysis was carried out by means of a Mettler-Toledo DSC-822e calorimeter. Experimental conditions: aluminum crucibles of 40 µL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10 °C/min. The calorimeter was calibrated with indium of 99.99% purity (m.p.: 156.8 ºC, ΔH: 28.47 J/g).

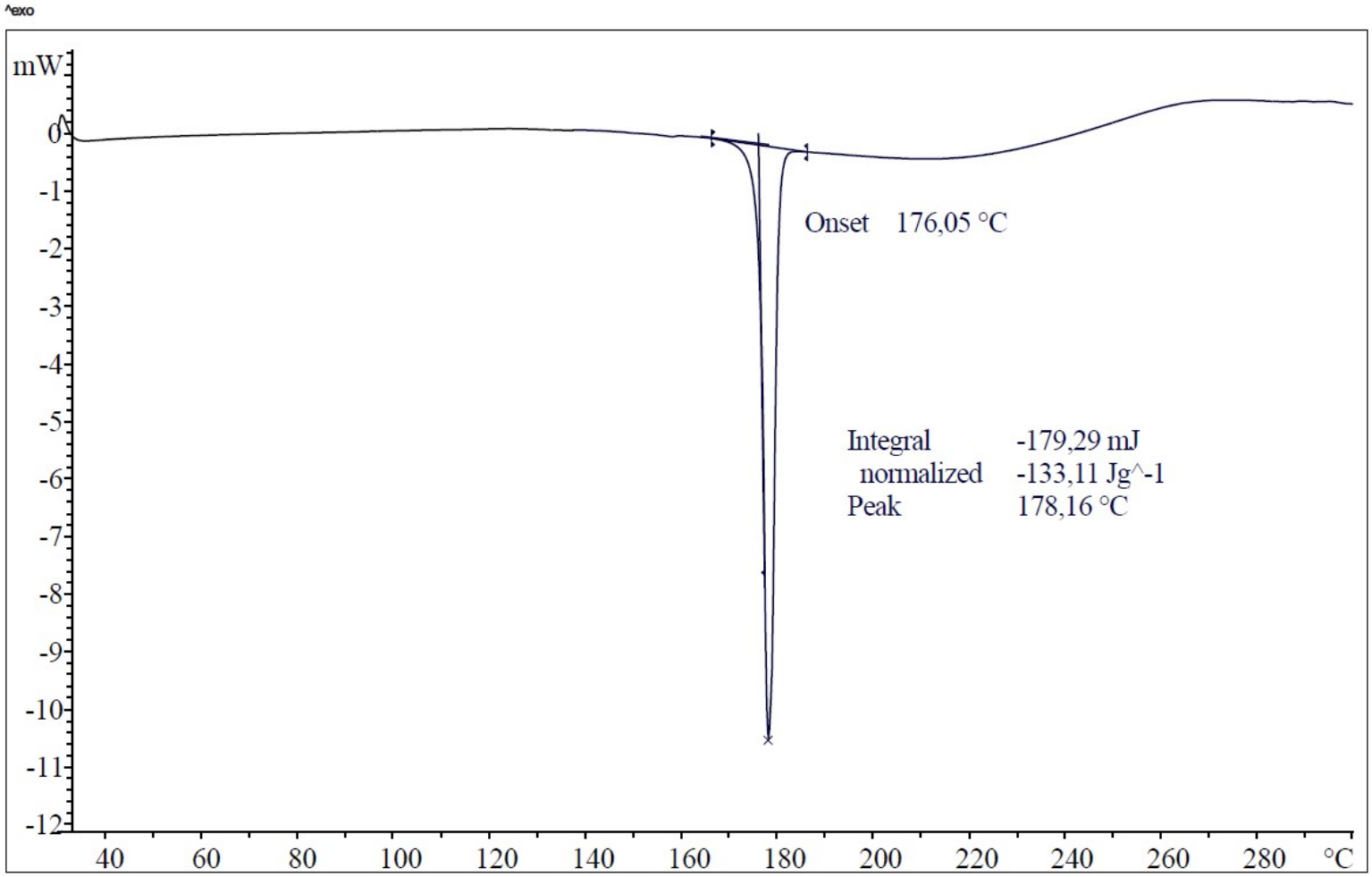


Figure S3: Thermogravimetric Analysis (TGA) of bosentan: succinic acid cocrystal was performed on a Mettler-Toledo TGA-851e thermobalance. Experimental conditions: alumina crucibles of 70 µL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10 °C/min.

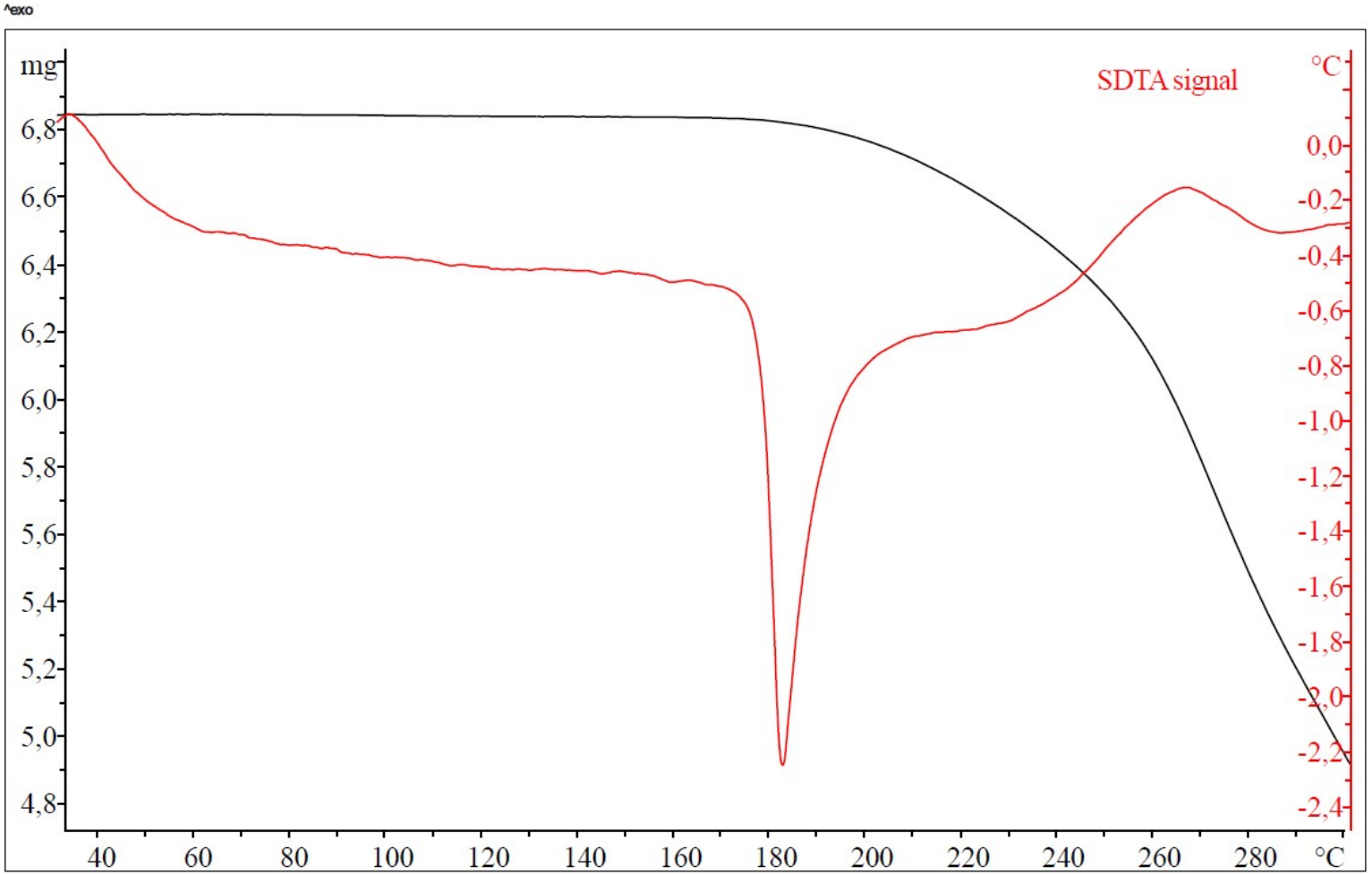


Figure S4: Comparative XRPD diffractograms of bosentan monohydrate (blue), succinic acid (green), bosentan: succinic acid bulk powder cocrystal (black) and simulated from the cif file (red).

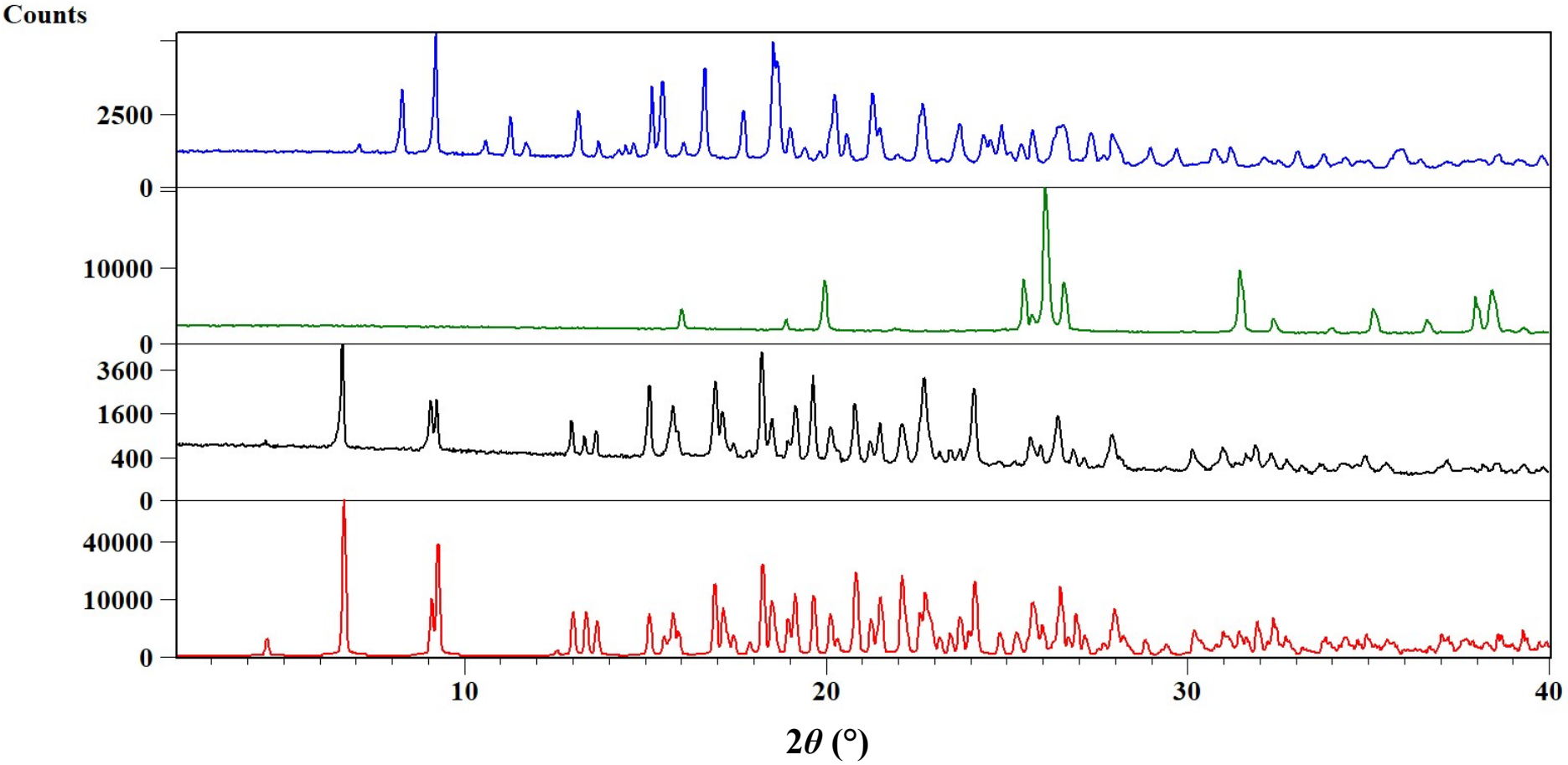


Figure S5: ^{1}H-NMR (dmso-d_6: delay: 1 second /pulse: 45º/scans: 32) of bosentan: succinic acid cocrystal (1:1)

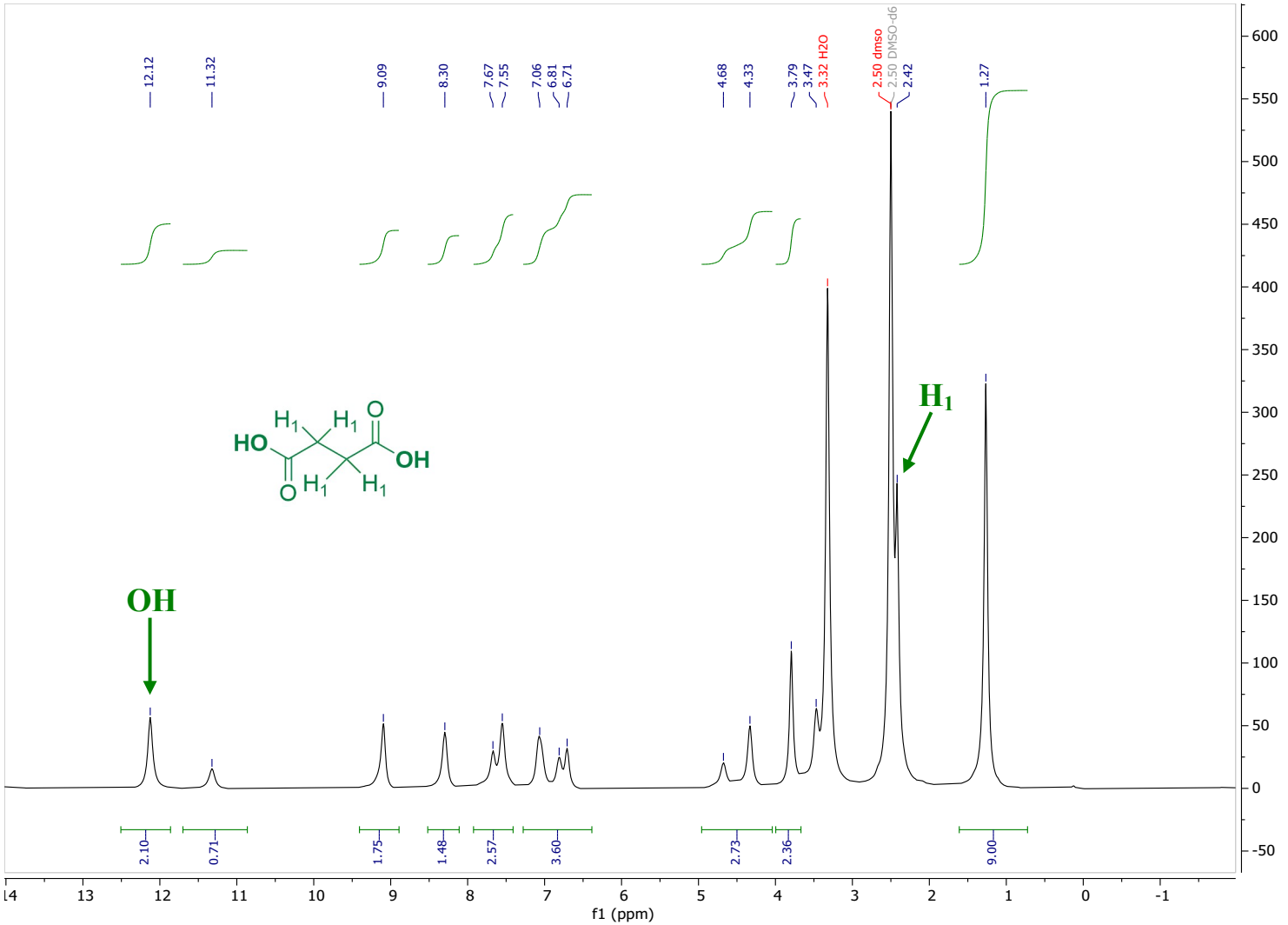


Figure S6: ORTEP representation of the asymmetric unit of bosentan: succinic acid cocrystal

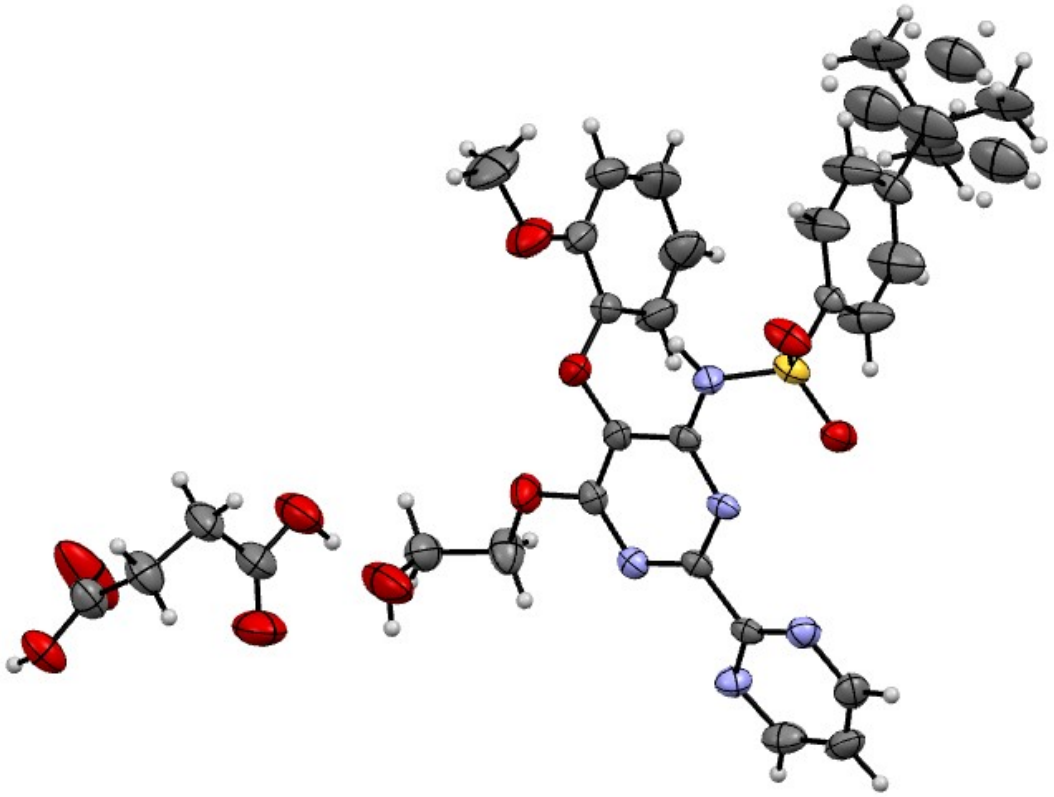


Figure S7: Comparative XRPD diffractograms of bosentan monohydrate (blue), resorcinol (green) and bosentan: resorcinol cocrystal (black).

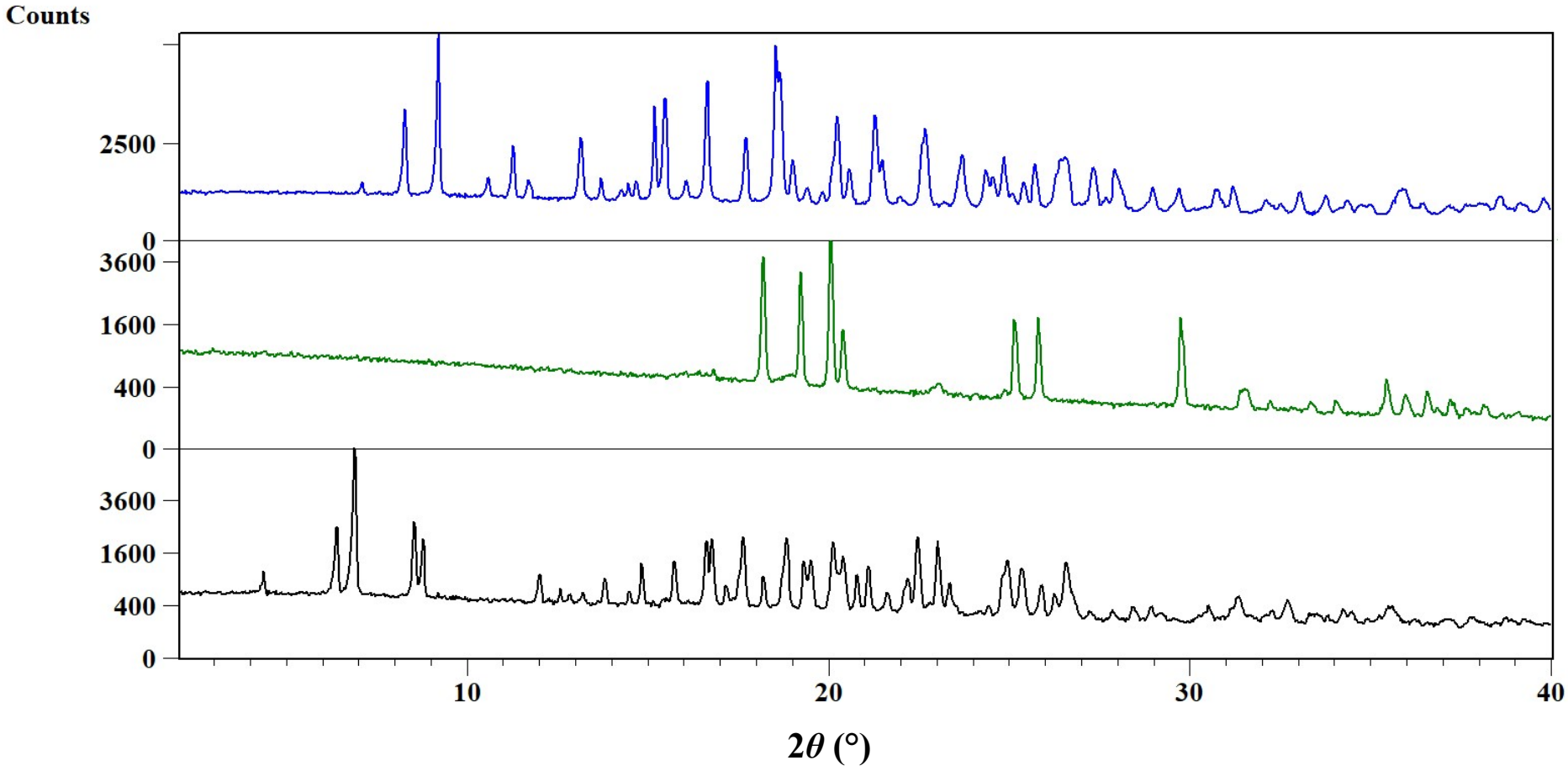


Figure S8: The XRPD of bosentan: resorcinol cocrystal has been indexed with the following proposed monoclinic cell: a= 38.57(1) Å, b= 8.030(1) Å, c= 22.174(4) Å, β= 96.14(1)º, V= 6827(20) Å^3 (Figures of Merit: M_{20}= 13.6, F_{20}= 49.6 ((0.0050, 81)), with number of impurities equal to zero. A $P2_1/m$ space group is suggested and the cell volume is compatible with 1 molecule of bosentan and 1 molecule of resorcinol. (R_{wp}: 8.65; Chi-square: 3.36), Z=8.

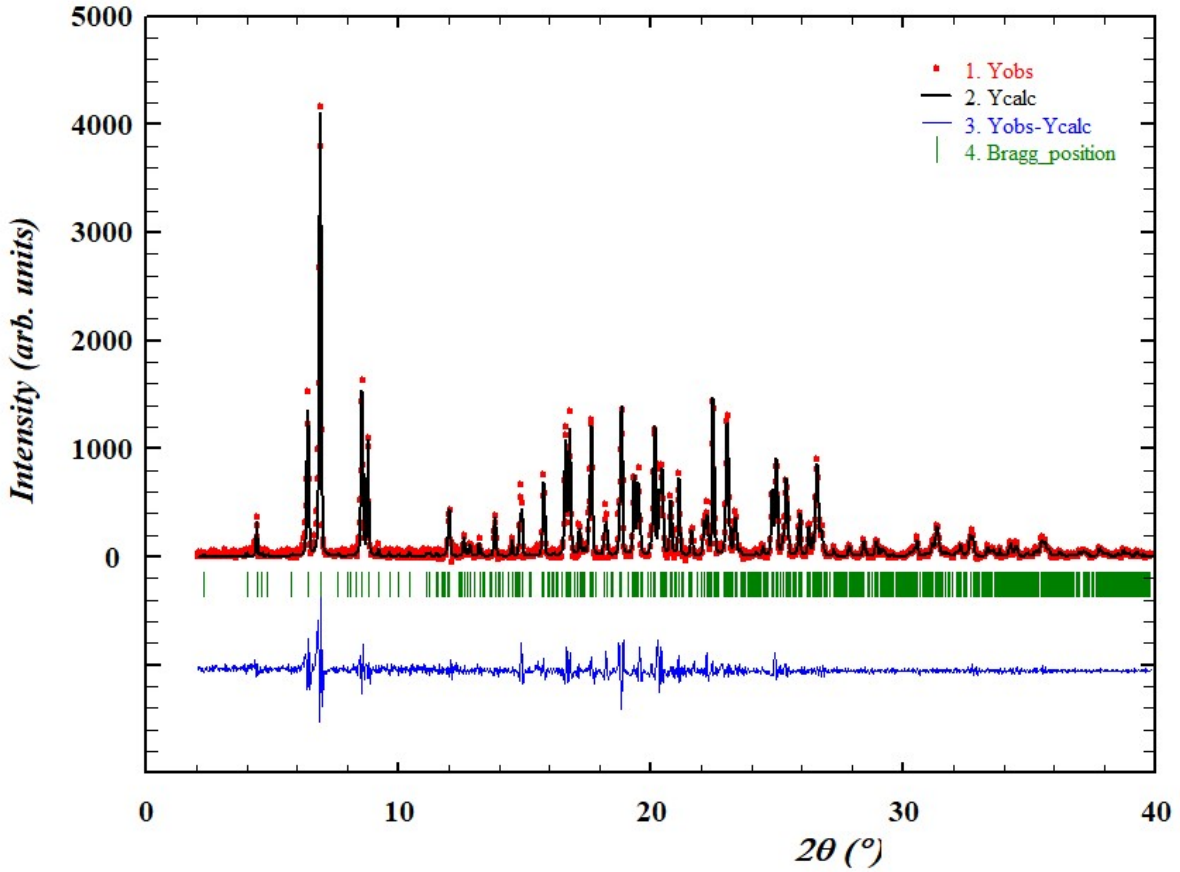


Figure S9: ^{1}H-NMR (dmso-d_6: delay: 1 second /pulse: 45º/scans: 32) of bosentan: resorcinol cocrystal (1:1)

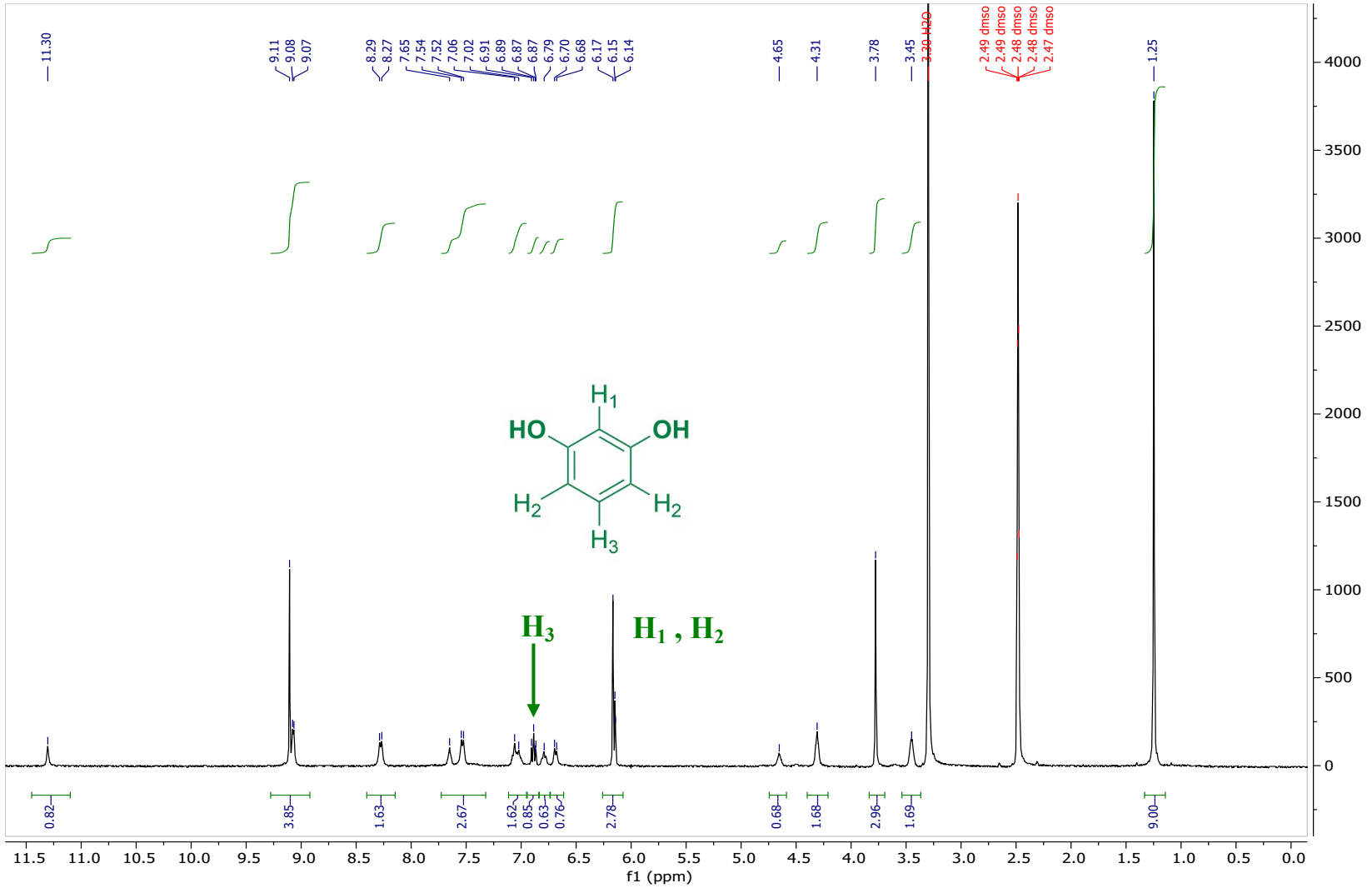


Figure S10: Comparative XRPD diffractograms of bosentan monohydrate (blue), 4-hydroxybenzoic acid (green), 4-hydroxybenzoic acid monohydrate (simulated from cif file: CCDC refcode: PHBZAC01) (red) and bosentan: 4-hydroxybenzoic acid cocrystal (black).

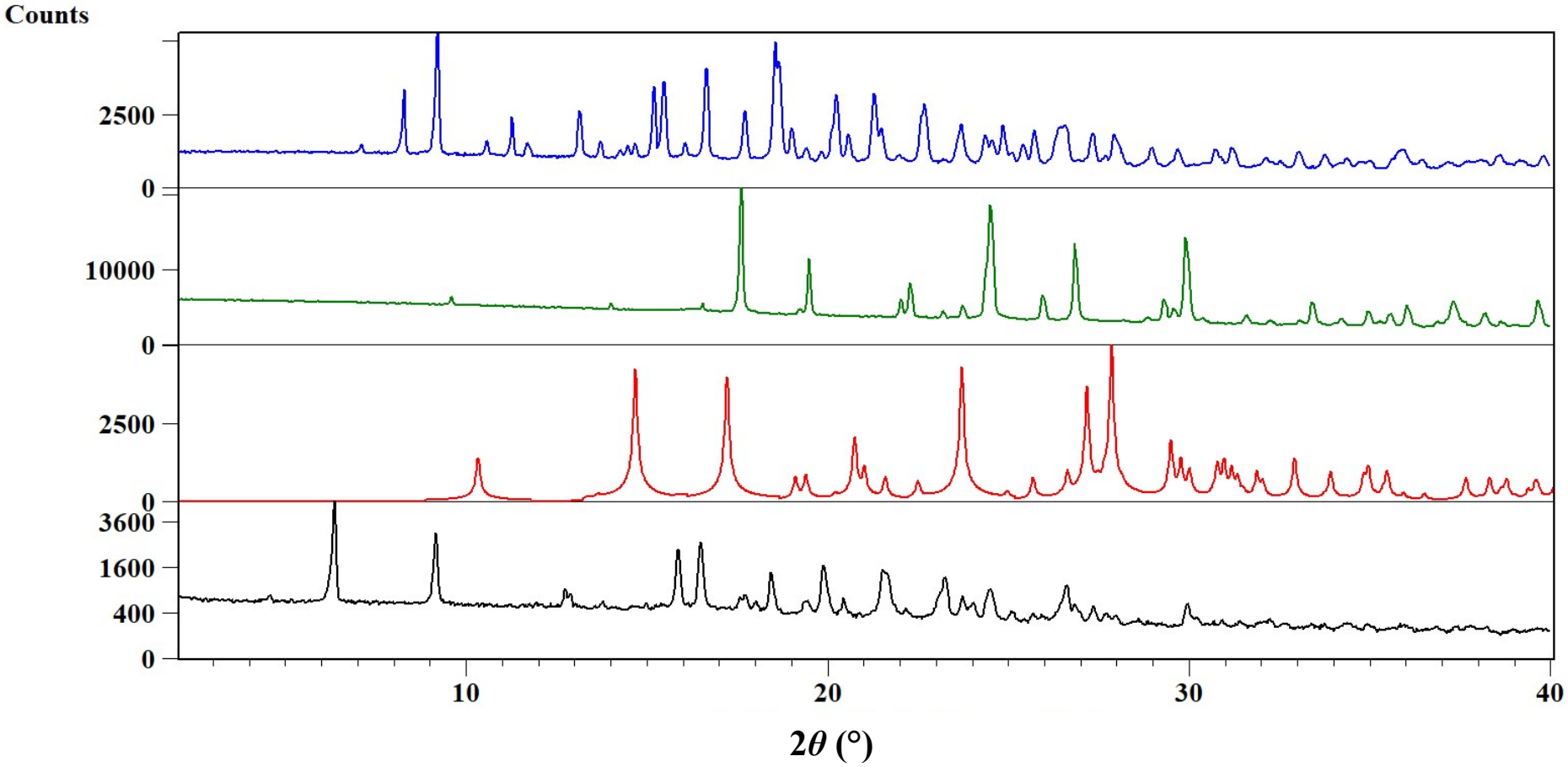


Figure S11: The XRPD of bosentan: 4-hydroxybenzoic acid cocrystal has been indexed with the following proposed monoclinic cell: a= 38.43(1) Å, b= 9.411(3) Å, c= 14.766(6) Å, β= 90.85(3)º, V= 5340(5) Å^3 (Figures of Merit: M_{20}= 10.2, F_{20}= 28.8 ((0.0060, 115)), with number of impurities equal to zero. A $P2_1/m$ space group is suggested and the cell volume is compatible with 1 molecule of bosentan and 2 molecules of 4-hydroxybenzoic acid. (R_{wp}: 7.84; Chi-square: 2.57). Z=4.

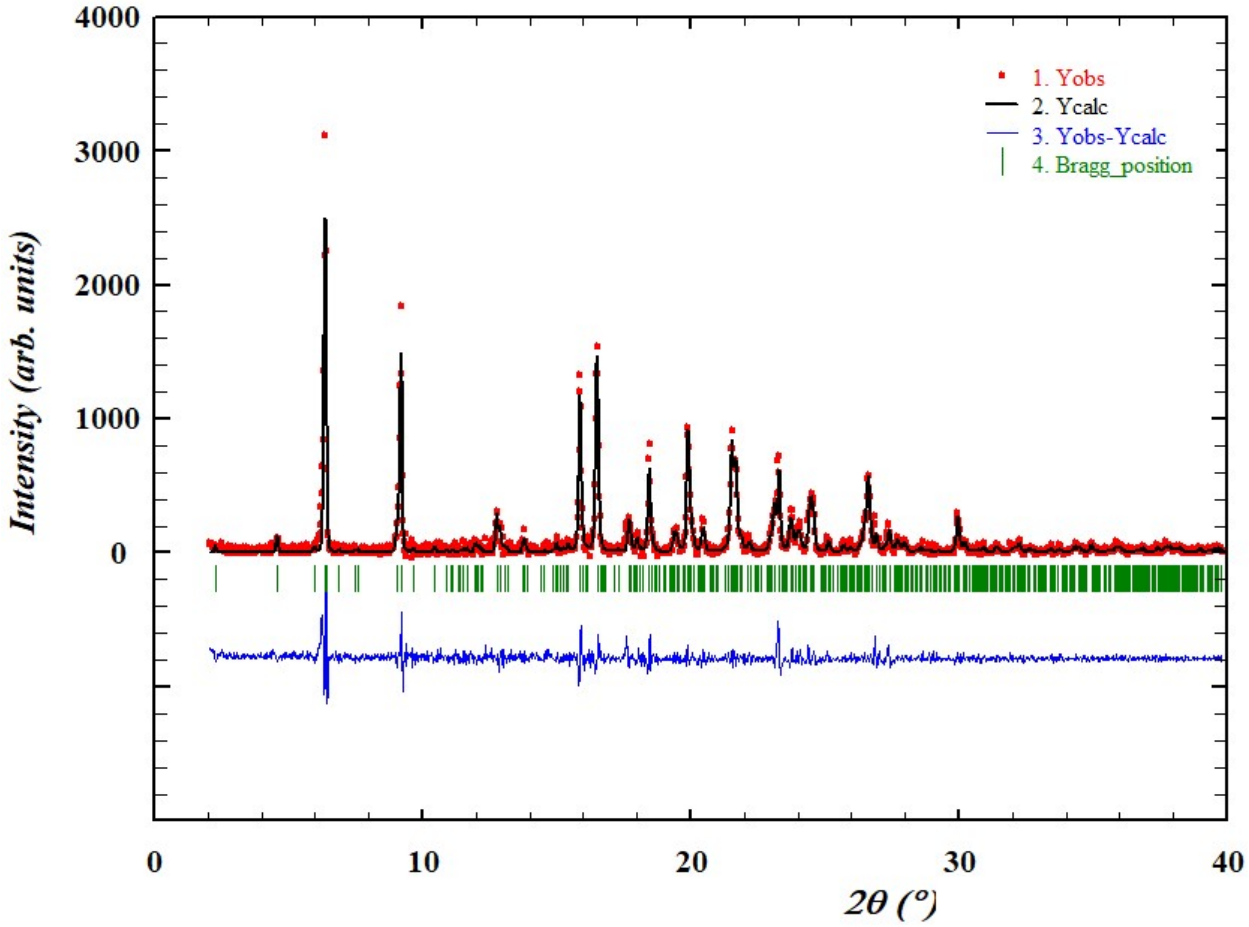
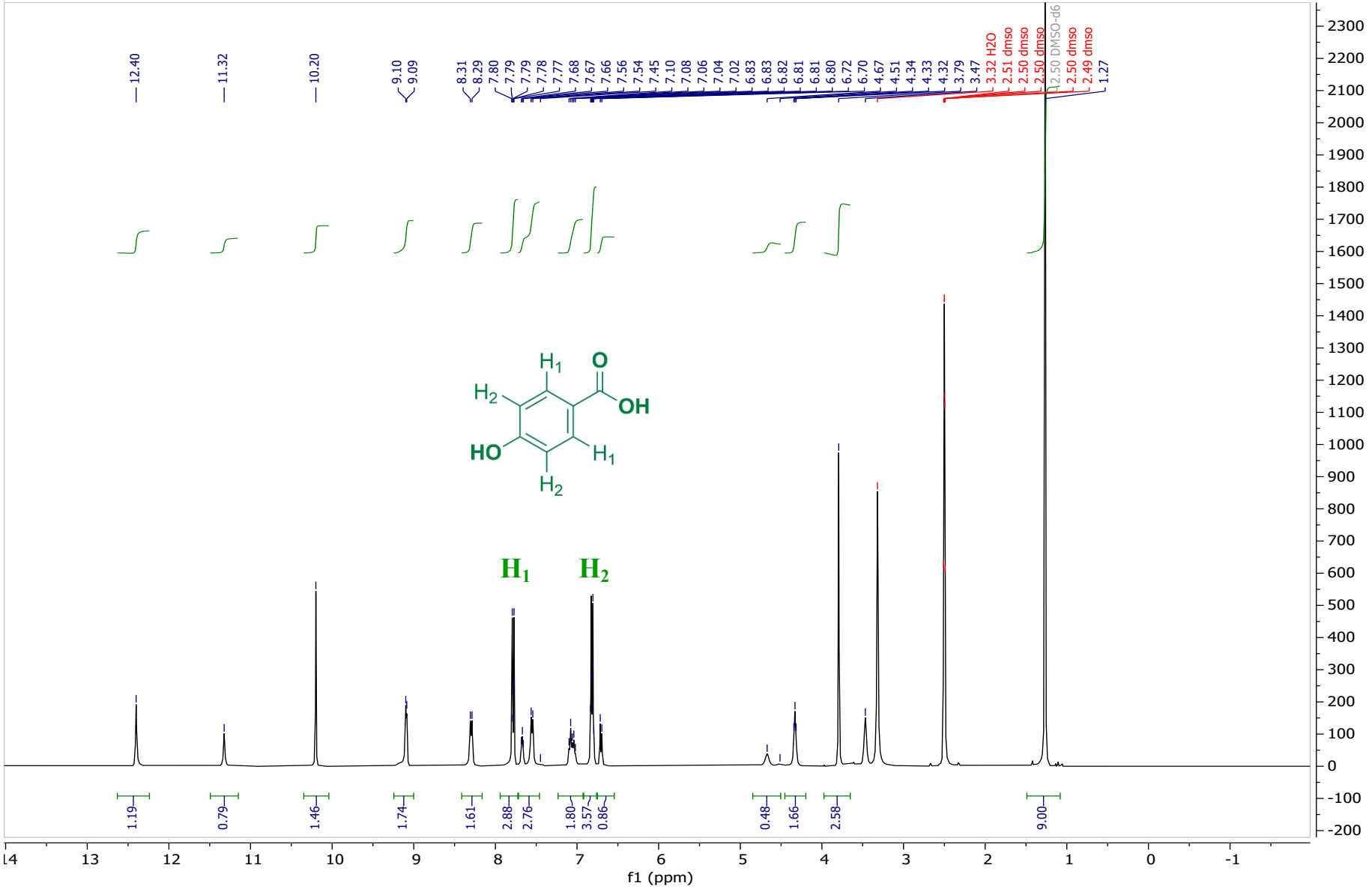
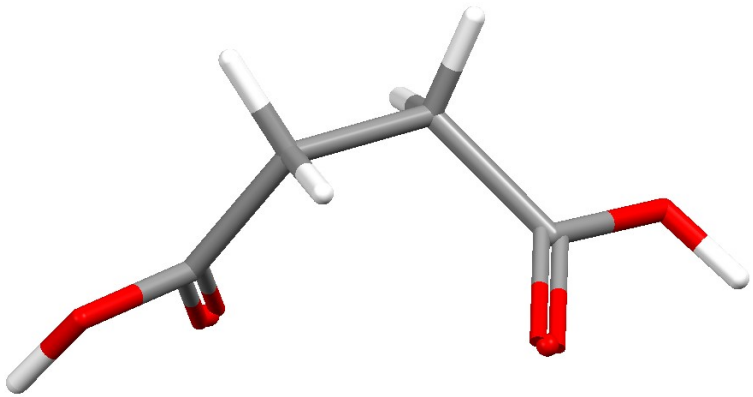
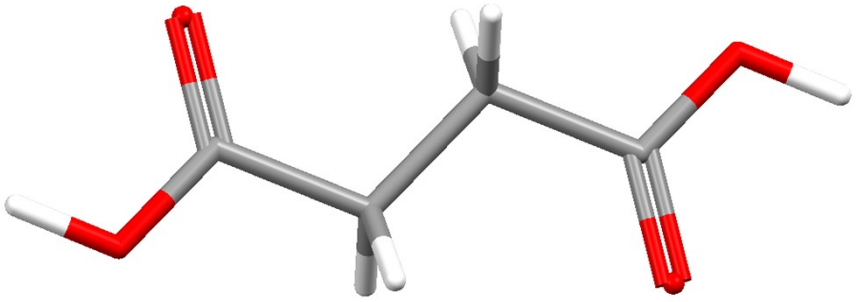


Figure S12:H-NMR (dmso-d_6: delay: 1 second /pulse: 45º/scans: 32) of bosentan: 4-hydroxybenzoic acid cocrystal (1:2).



5.- CSD Survey of succinic acid crystal structures in *gauche* conformation

Table S5. CSD Survey of succinic acid showing *gauche* conformation.

CCDC	
CIRXAD DUWLAK GADBEV GEKNAO HELFEL HOGFIU HOGJEV JEDLAG JEDLAG01 JEKDUY KIJSEC KITSUC NAQMOK NAQMOK01 OLOFUQ OMEKIC ORAMAX PEKQOM QEVMEJ SERMOR SERMOR10 SUCACB19 TAJVOP VARHUS XECRU XOBCIB XUBVEW	 *gauche*-conformation (SUCACB19)  *anti*-conformation (SUCACB02)