

Crystal Structures of Large-Volume Pharmaceuticals with Z'>1

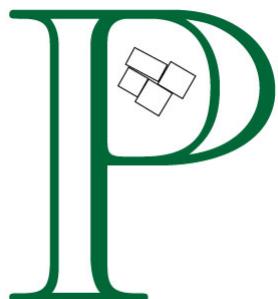
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Joel W. Reid, CLS

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This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

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PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

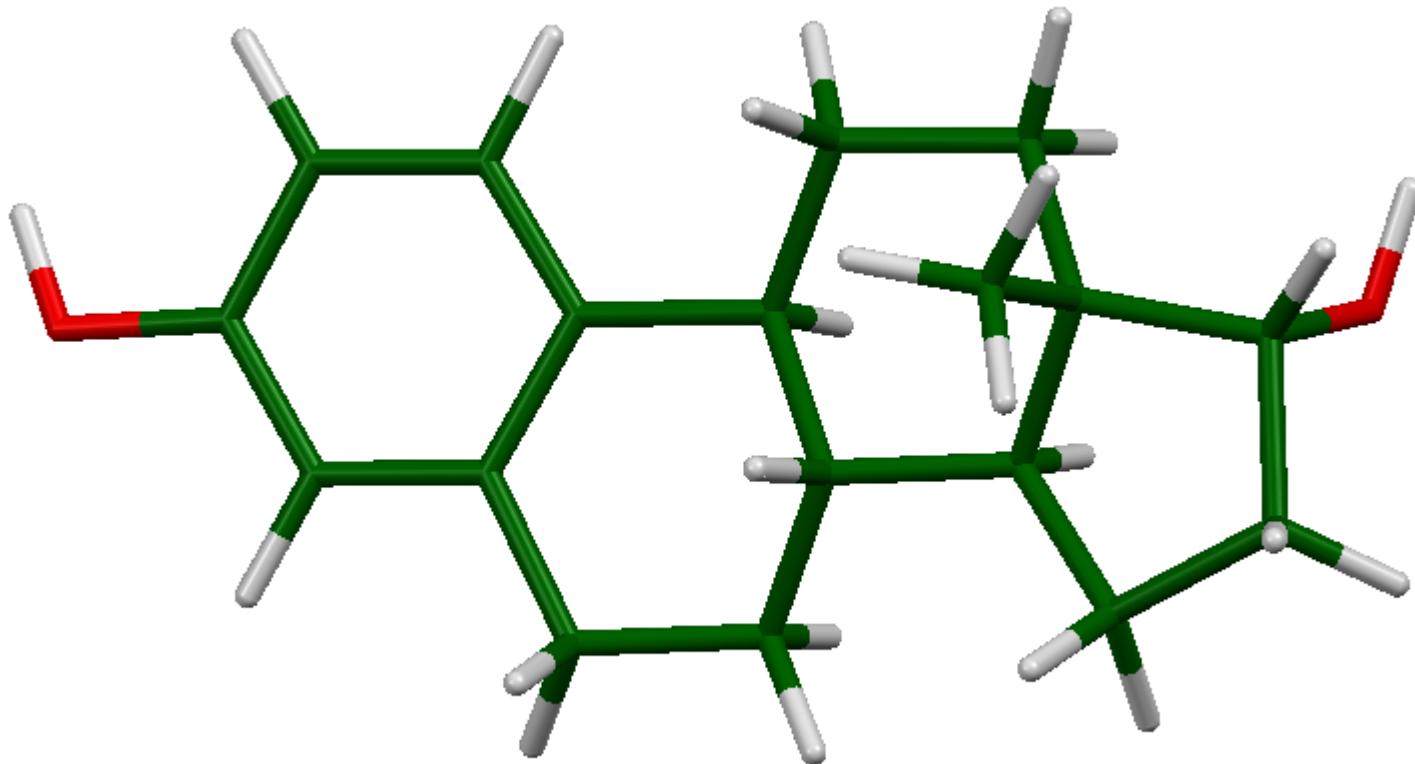
Reasons for the Project

- High-quality reference patterns for phase ID
 - Pharmaceutical, forensic, law enforcement
- New crystal structures
 - Quantitative analysis
 - Bonding and energetics (polymorphs)
- Ambient conditions

17α -Estradiol

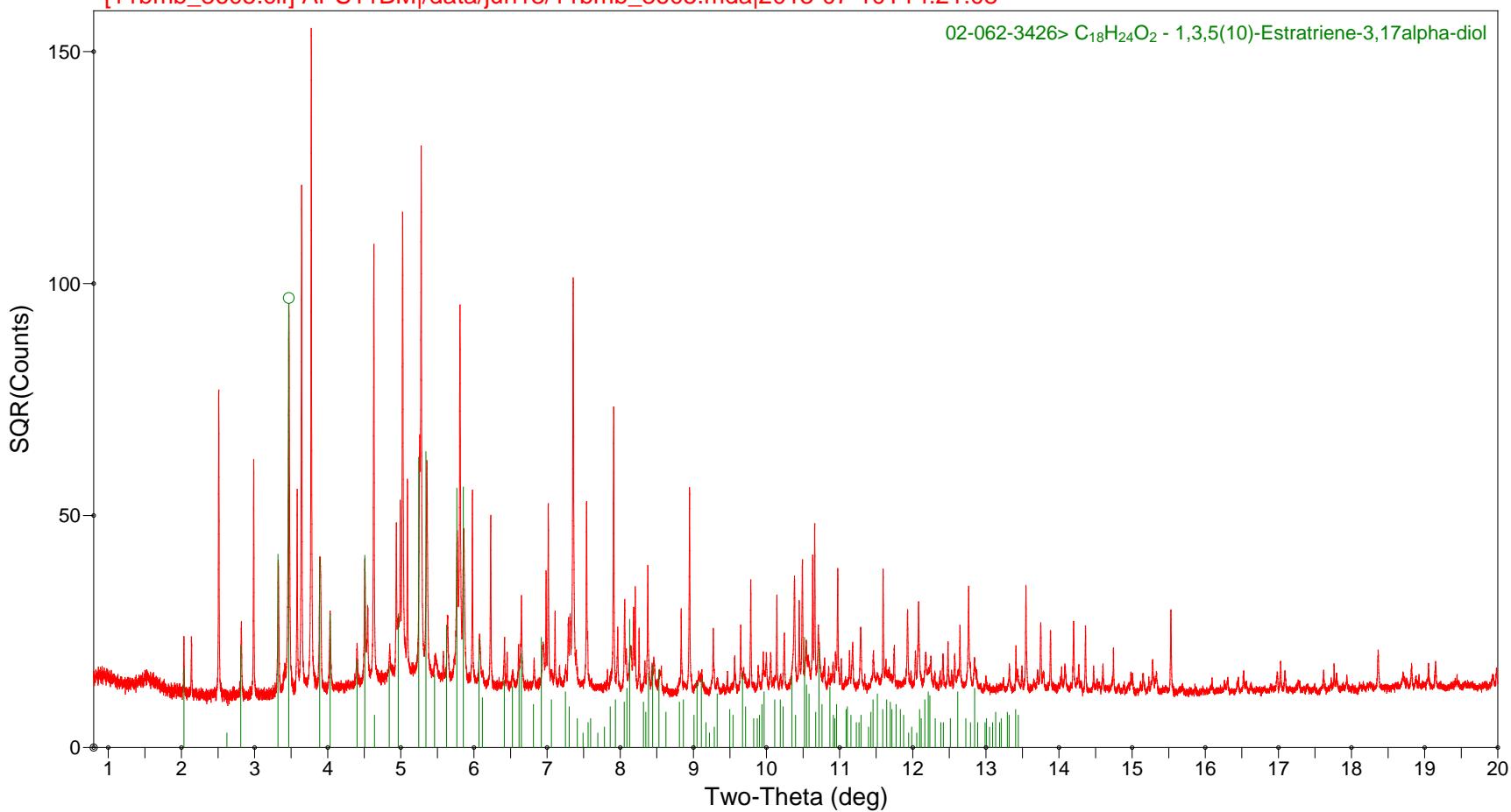
Ell-Cranell Alpha and Pantosin
hair loss in men and women

17α -Estradiol



[11bmb_8605.cif] APS11BM|/data/jun13/11bmb_8605.mda|2013-07-10T14:21:08

02-062-3426 > C₁₈H₂₄O₂ - 1,3,5(10)-Estratriene-3,17alpha-diol



Index the remaining peaks

- I -monoclinic (Jade 9.5)
- $a = 16.082539(13) \text{ \AA}$
- $b = 7.135217(40) \text{ \AA}$
- $c = 13.412559(13) \text{ \AA}$
- $\beta = 99.3291(7)^\circ$
- $V = 1518.743(21) \text{ \AA}^3$
- $Z = 4$

CCDC ConQuest (1) : search1 [Search]

File Edit Options View Databases Results Help

Build Queries Combine Queries Manage Hitlists View Results

All Text

Author/Journal

Chemical

Crystal

Experimental

Diagram

3D Visualiser

CSD Internals

Search Overview

Refcode: ESTTRD01

CSD version 5.36 (November 2014)

ESTTRD01

Analyse Hitlist

BIDKAB
BIJYID
CLMOLB
CUHQUS
ESTTRD01
FIXDIZ
KETRUX
NAHPES
NEYQOY
TAPWAI02
URESIU
YEKSIR

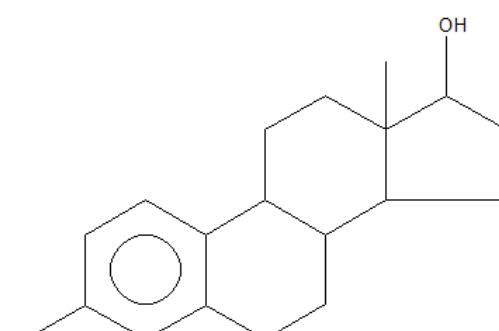
<< >>

12 hits

100%

Show terminal carbons

Use as Query... Detach Stop Search





CCDC ConQuest (1) : search1 [Search]

File Edit Options View Databases Results Help

Build Queries

Combine Queries

Manage Hitlists

View Results

All Text

Author/Journal

Chemical

Crystal

Experimental

Diagram

3D Visualiser

CSD Internals

Search Overview

Refcode: ESTTRD01

Author(s): Ohrt +

Journal: Acta Crystallogr.

Volume: 17

Page: 1611

Year: 1964

Publication DOI: [10.1107/S0365110X64003966](https://doi.org/10.1107/S0365110X64003966)

Deposition: IUCr A04438

Notes:

CSD version 5.36 (November 2014)



ESTTRD01

Analyse Hitlist

- BIDKAB
- BIJYID
- CLMOLB
- CUHQUS
- ESTTRD01
- FIXDIZ
- KETRUX
- NAHPES
- NEYQOY
- TAPWAI02
- URESIU
- YEKSIR

<< >>

12 hits

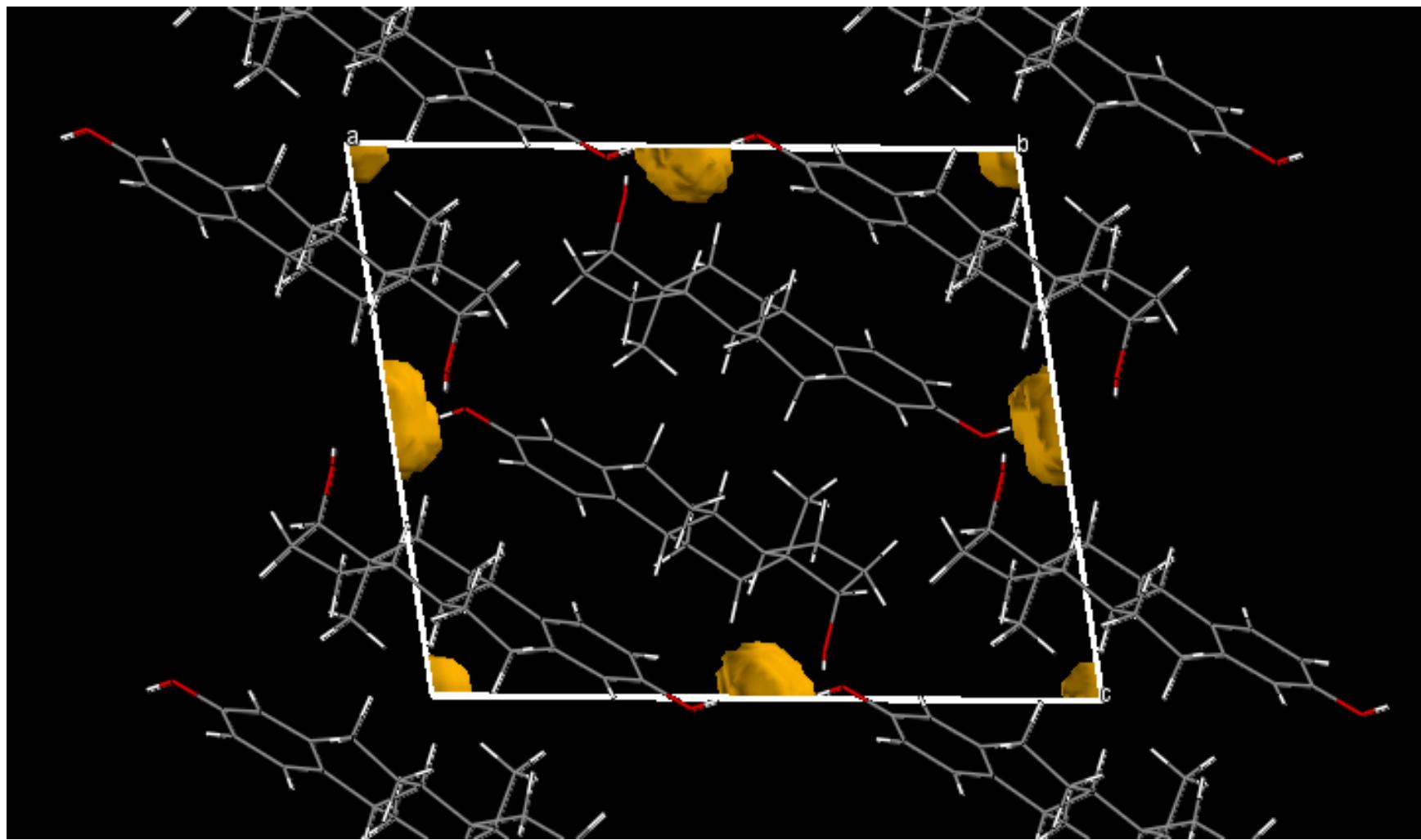
100%

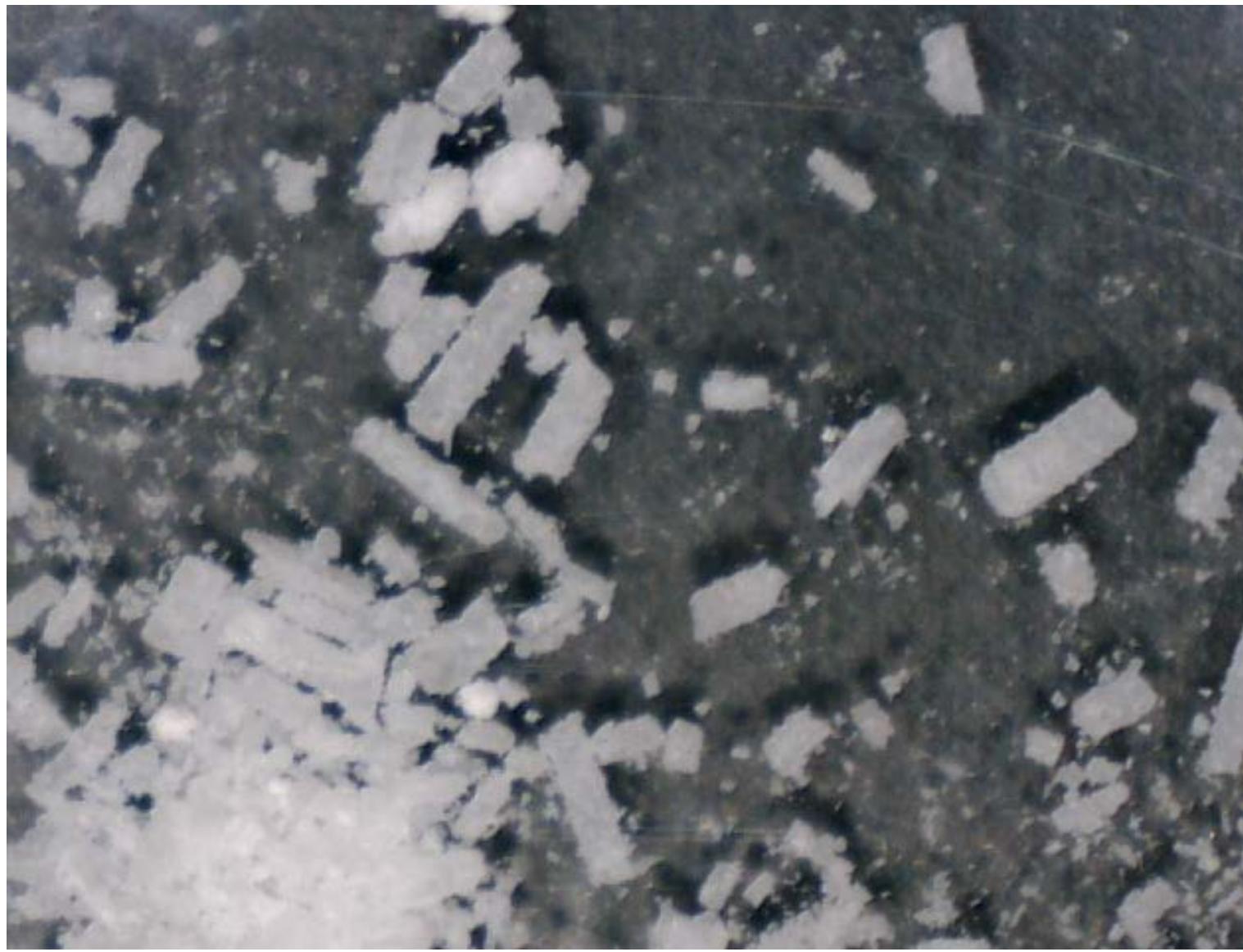
Stop Search

No 3D coordinates available

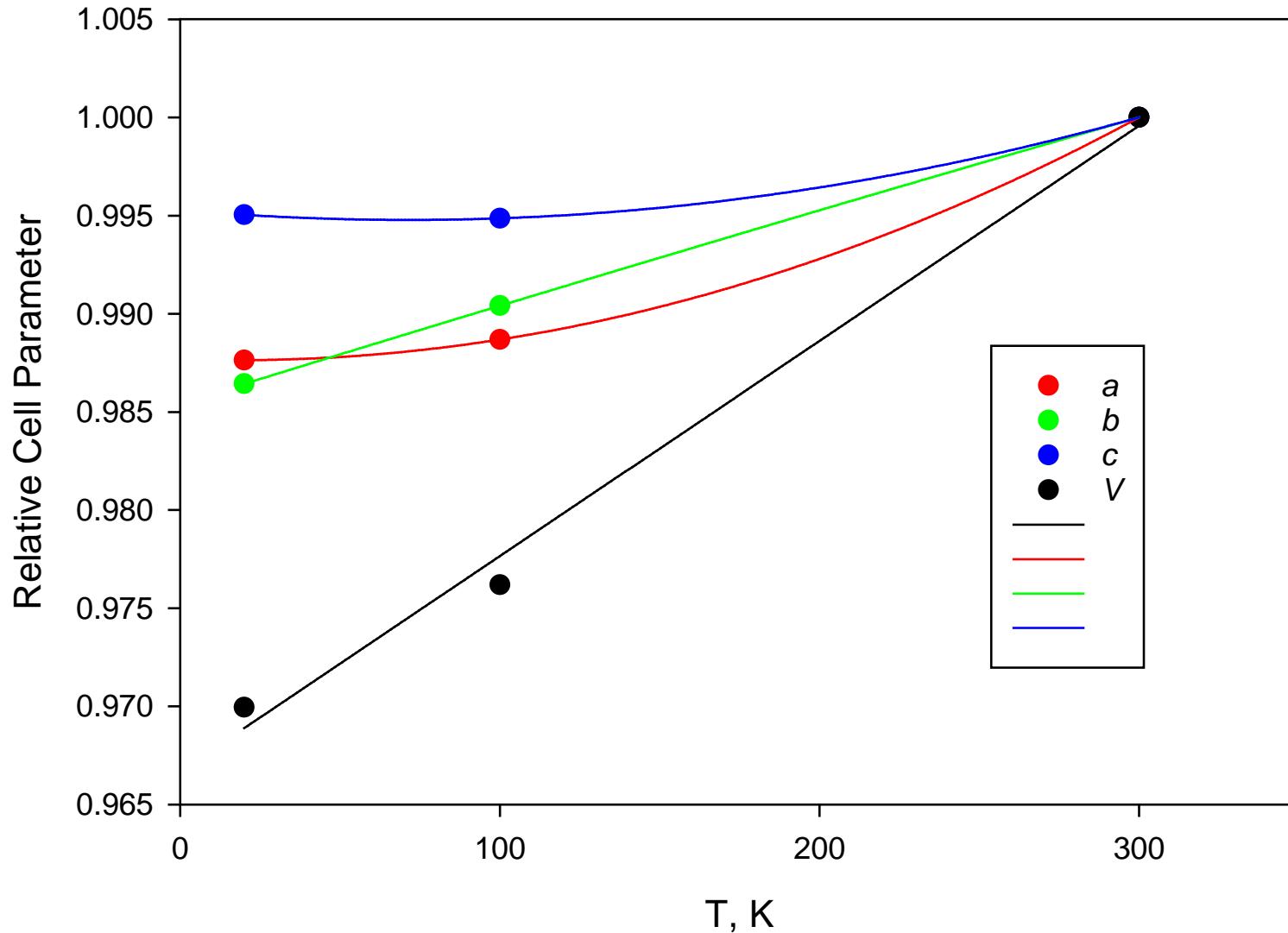
Right-click in visualiser for options menu

Detach



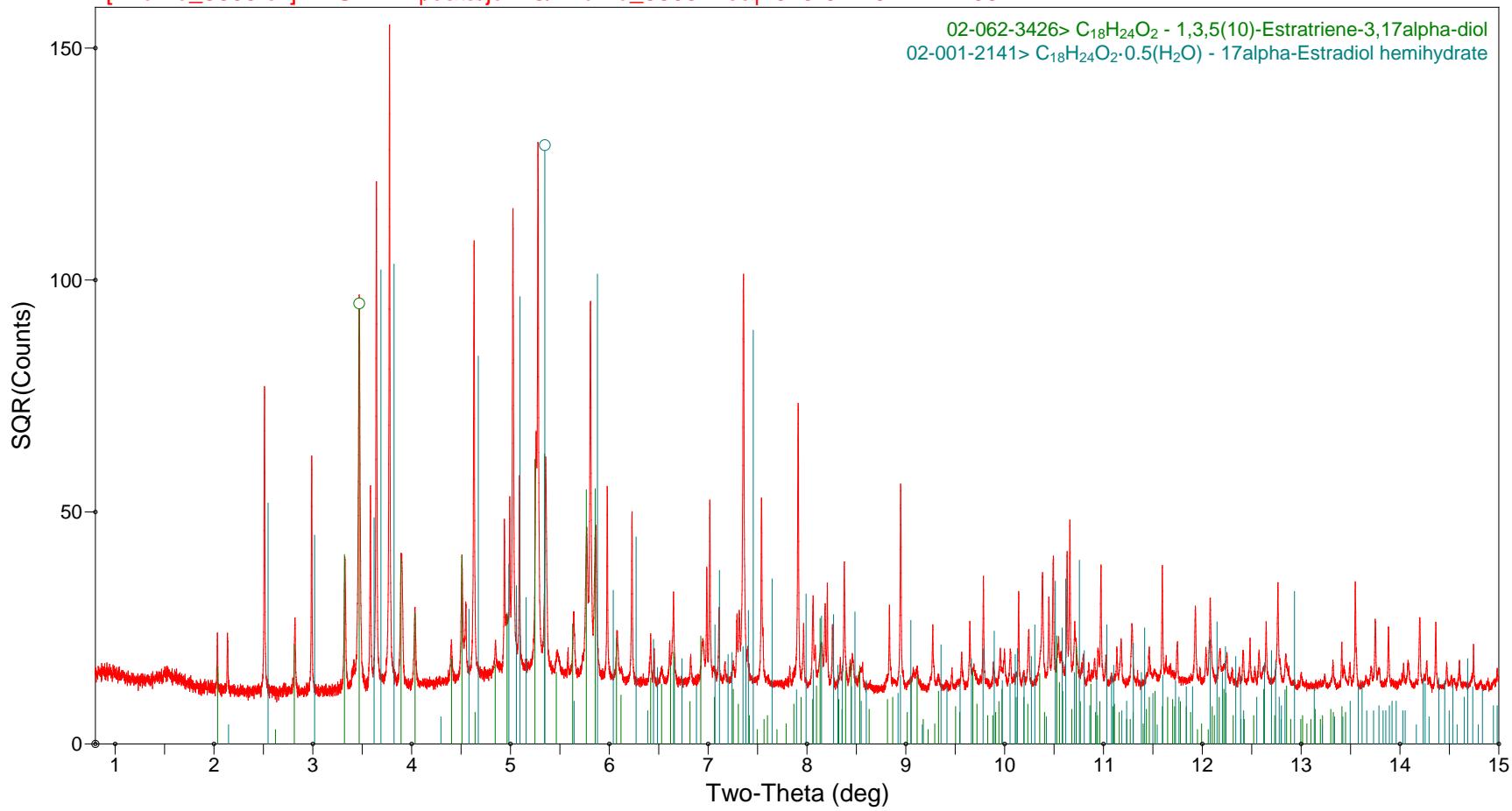


Changes in Reduced Cell Parameters of beta 17 α -estradiol with Temperature

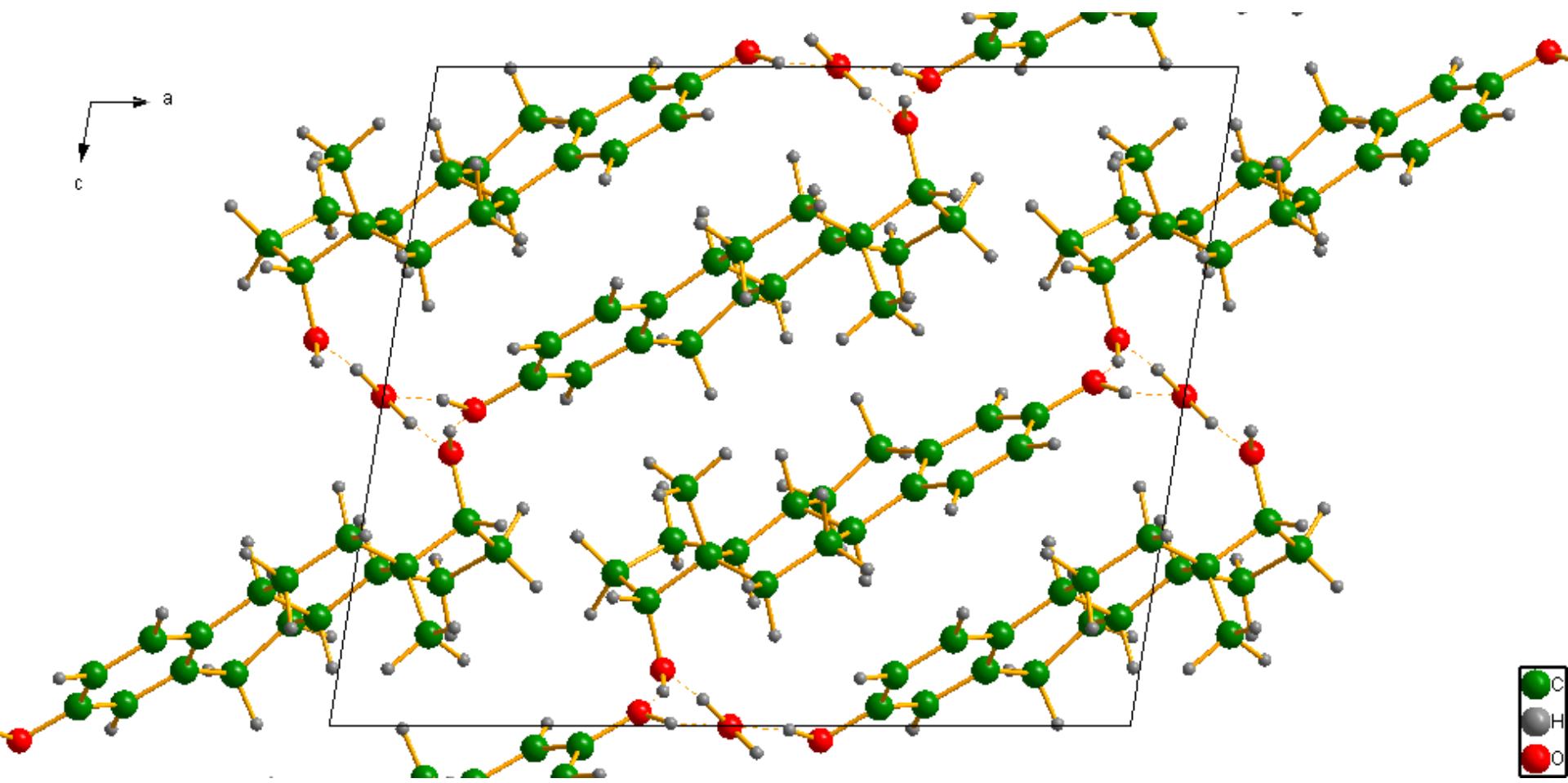


[11bmb_8605.cif] APS11BM|/data/jun13/11bmb_8605.mda|2013-07-10T14:21:08

02-062-3426> C₁₈H₂₄O₂ - 1,3,5(10)-Estratriene-3,17alpha-diol
02-001-2141> C₁₈H₂₄O₂·0.5(H₂O) - 17alpha-Estradiol hemihydrate



Beta 17 α -Estradiol Hemihydrate



Hydrogen Bonds in Beta 17 α -Estradiol Hemihydrate

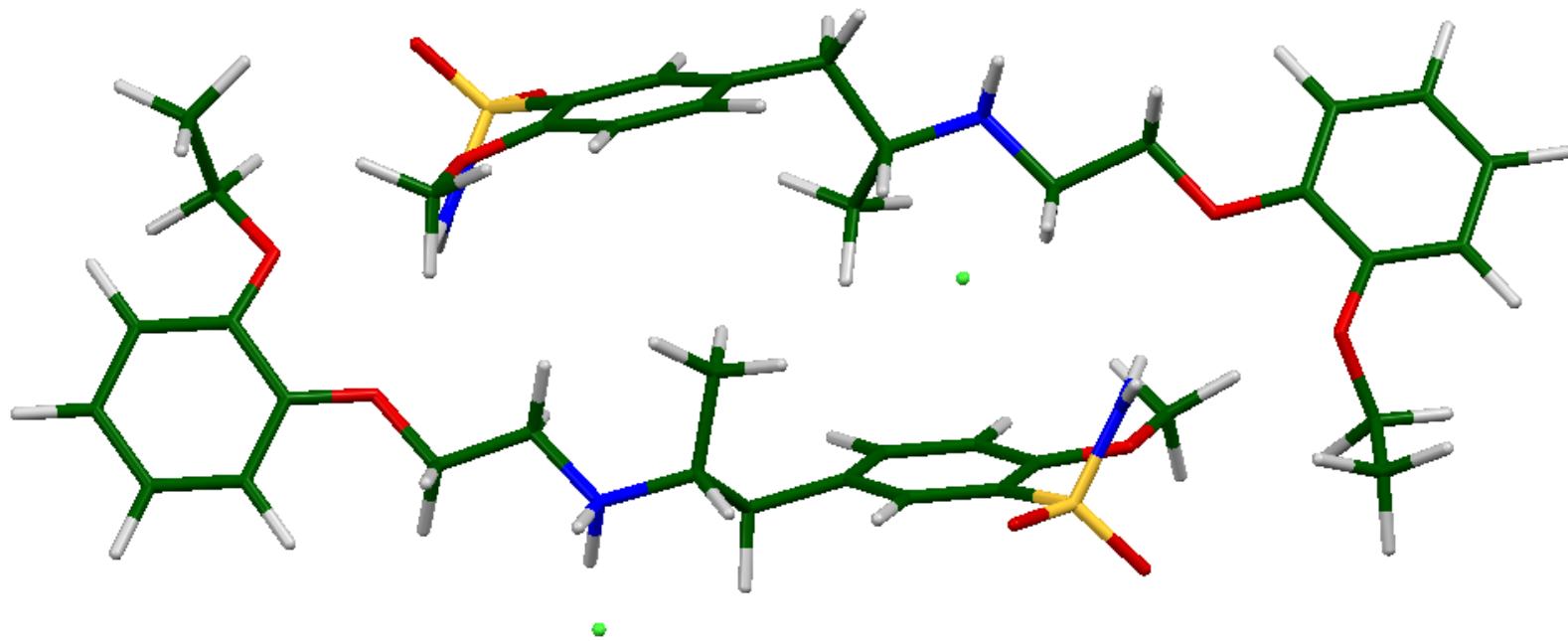
H-Bond	D-H, Å	H···A, Å	D···A, Å	D-H···A, °	Overlap, e
O1-H2···O2	0.975	1.984	2.917	159.6	0.037
O2-H22···O45	0.980	1.917	2.885	169.3	0.046
O45-H47···O1	0.984	1.839	2.792	162.2	0.054
C14-H7···O45	1.099	2.685	3.677	149.8	0.012

Tamsulosin Hydrochloride

$C_{20}H_{29}N_2O_5SCl$

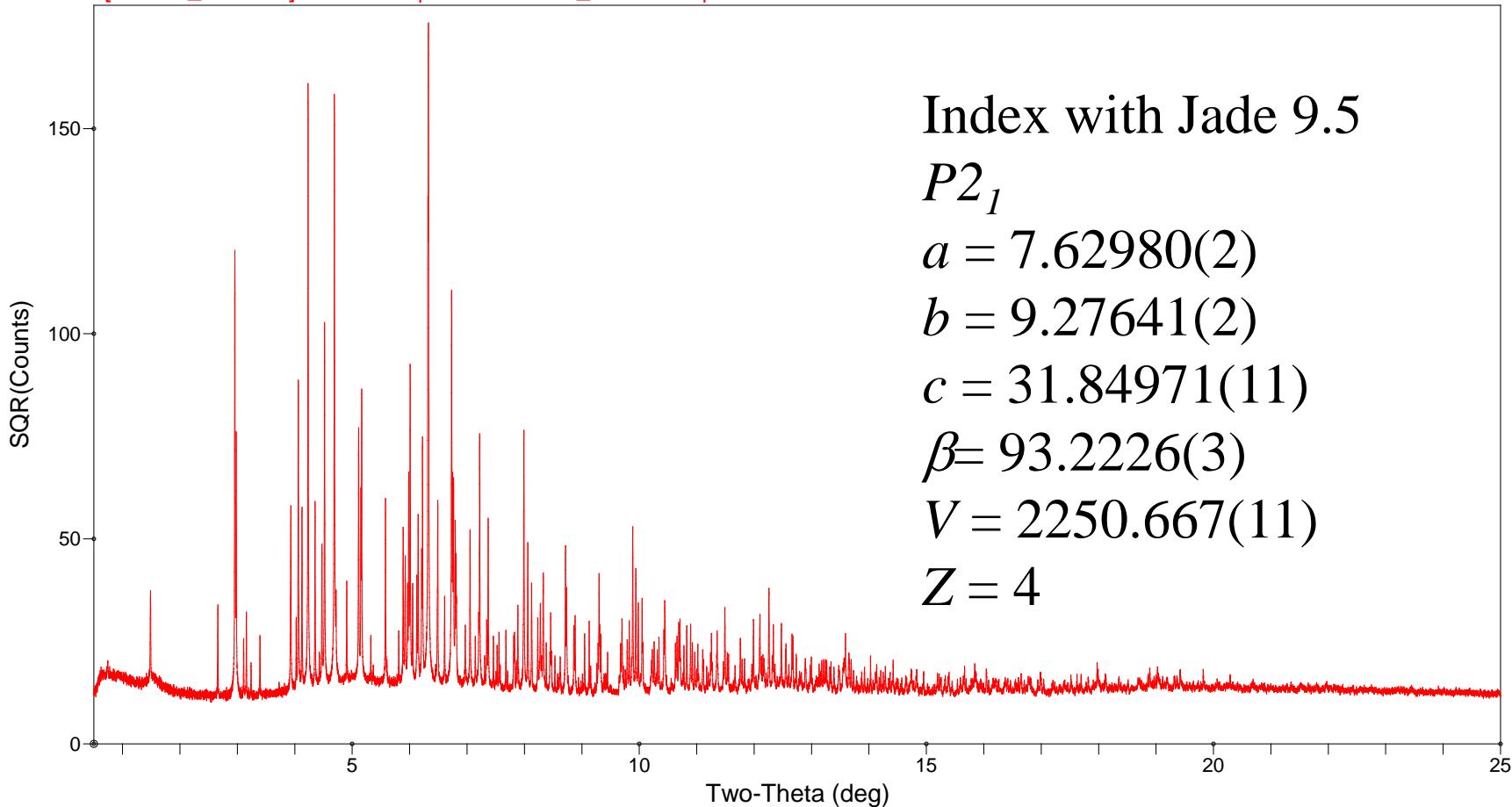
Flomax (generic in 2010)
benign prostatic hyperplasia (BPH)

Tamsulosin Hydrochloride

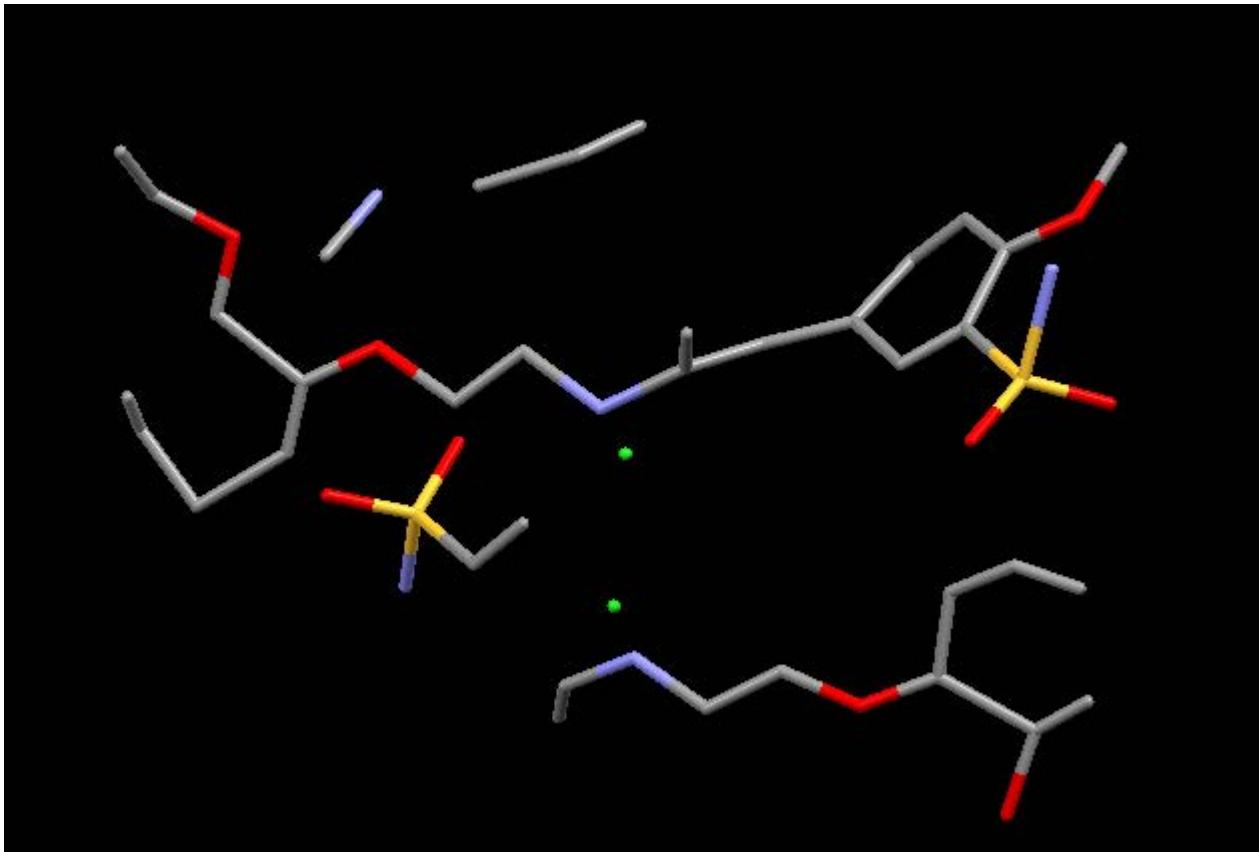


Tamsulosin Hydrochloride

[11bmb_3759.cif] APS11BM|mar14/11bmb_3759.mda|2014-03-15T03:39:39



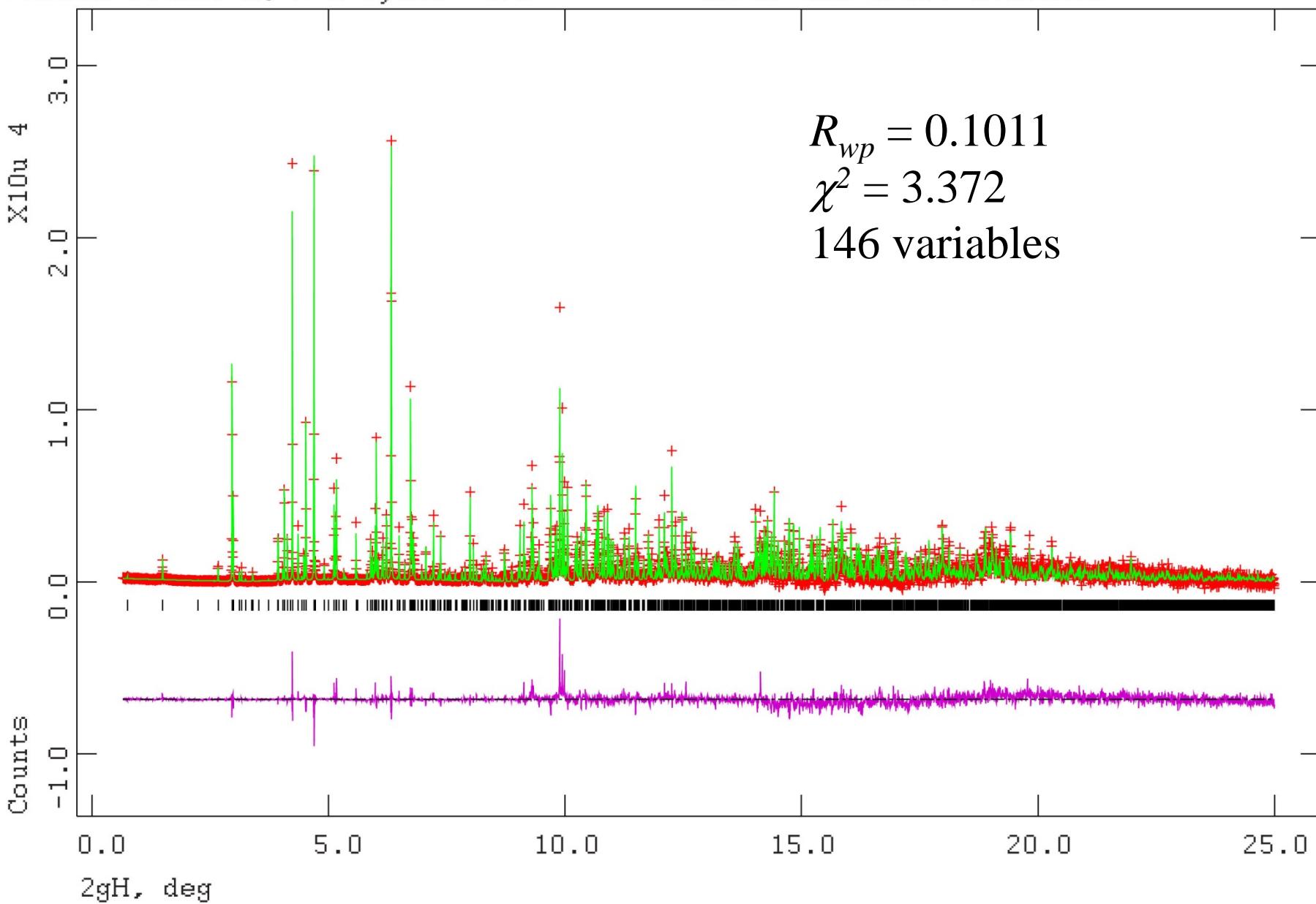
Charge Flipping Result



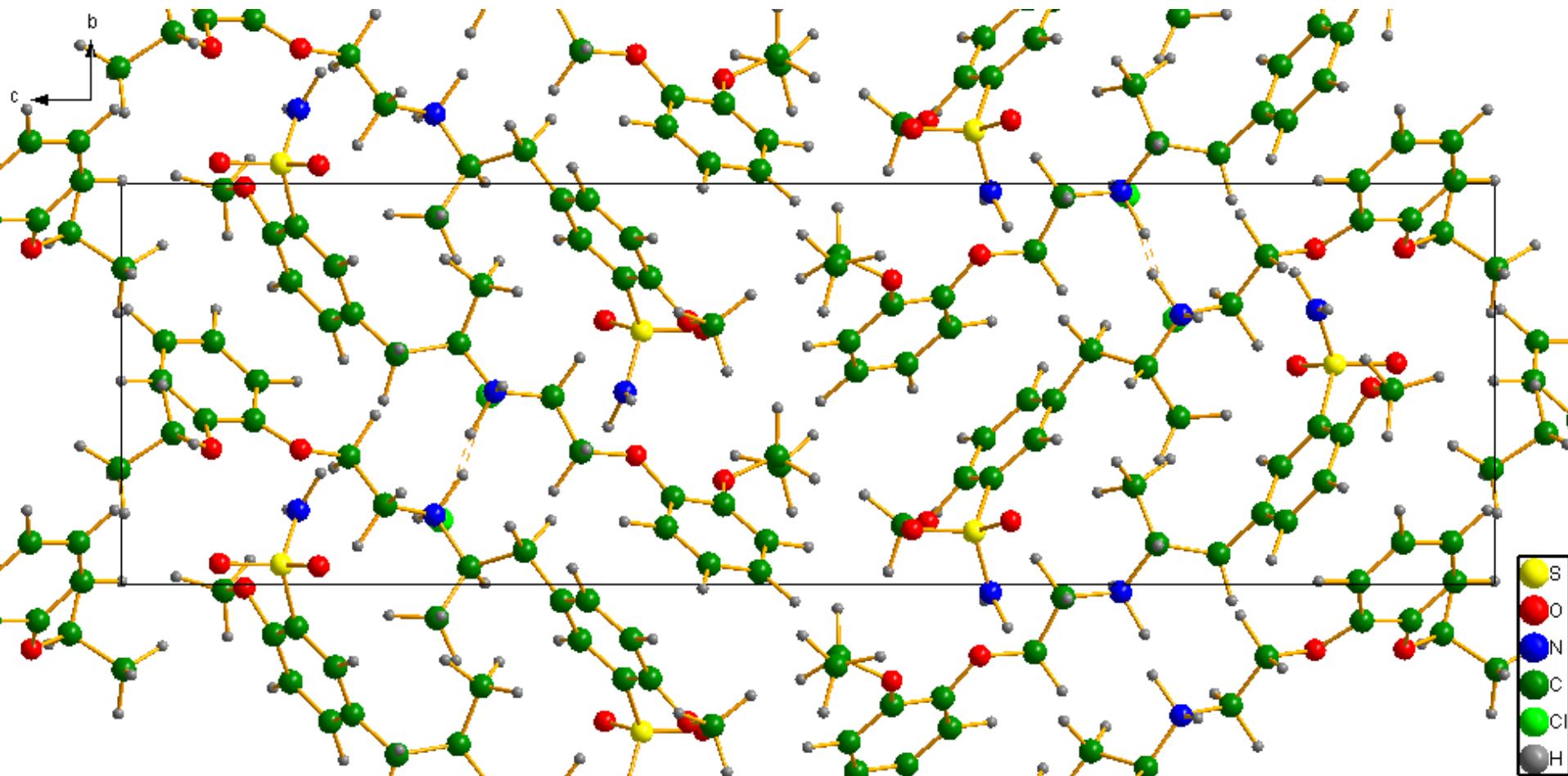
Tamsulosin Hydrochloride, C₂₀ H₂₉ N₂ O₅ S Cl (11bmb_3759) Hist 1

Lambda 0.4137 Å, L-S cycle 876

Obsd. and Diff. Profiles



Scaling: 9.0(6.0X) 14.0(20.0X)

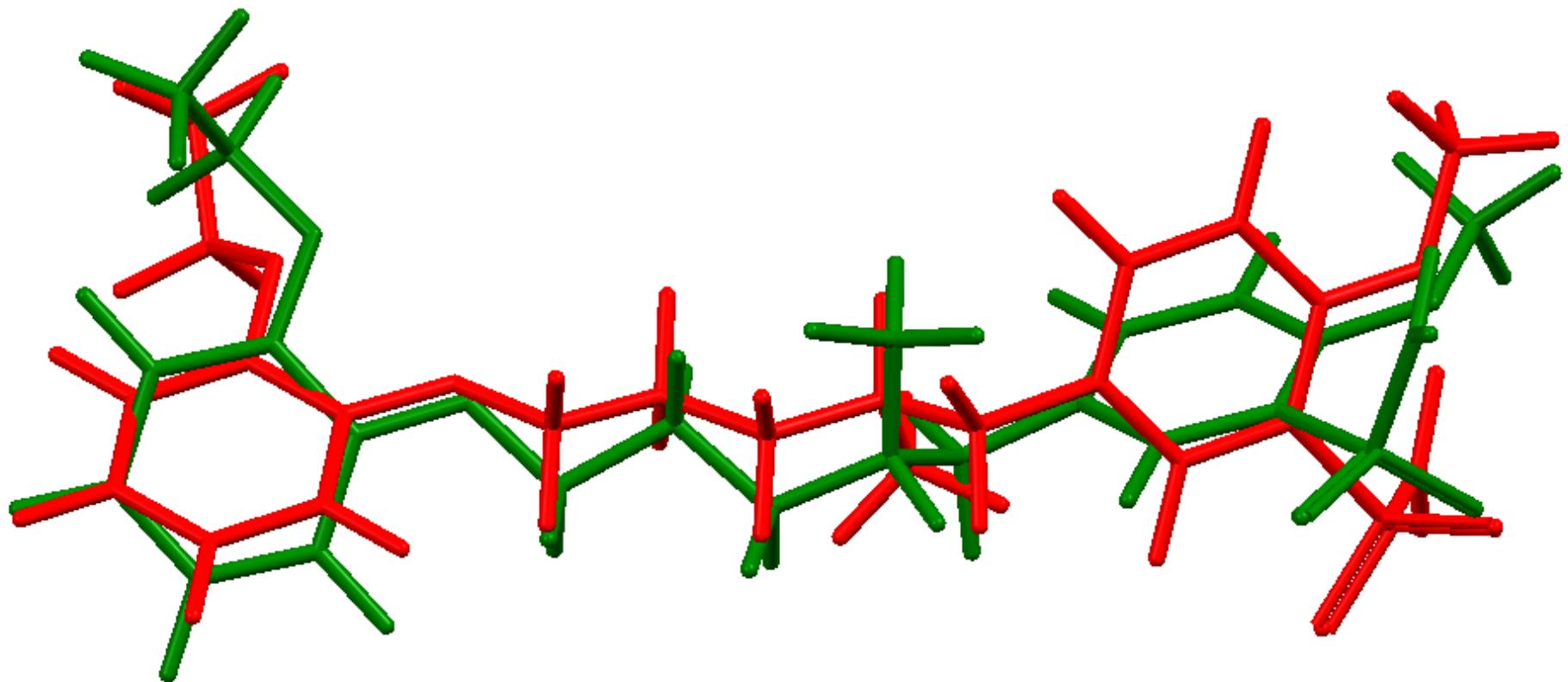


Hydrogen Bonds in Tamsulosin HCl

H-Bond	D-H, Å	H···A, Å	D···A, Å	D-H···A, °	Overlap, e
N4-H60···Cl57			3.303		
N16-H73···Cl57			3.228		
N16-H116···Cl58			3.341		
N44-H101···Cl57			3.177		
N44-H115···Cl58			3.042		
N4-H59···O11			2.867		
N32-H88···O39			3.024		

Experimental
116 atoms

Tamsulosin HCl – 2 Molecules



Experimental – rms $\Delta = 1.866 \text{ \AA}$

Red = molecule 1, green = molecule 2 (lower E by $\sim 2.2 \text{ Kcal/mole}$)

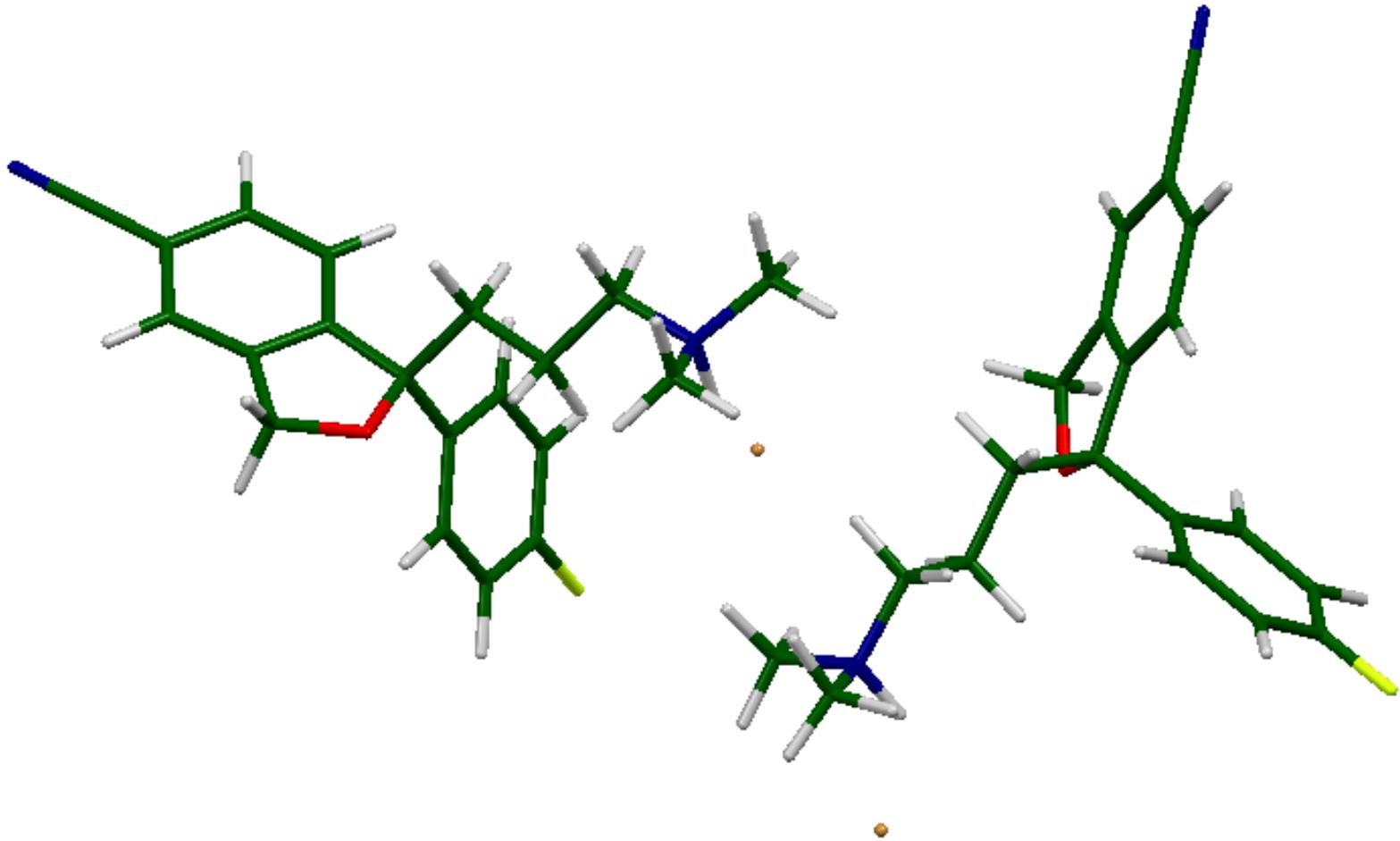
Citalopram Hydrobromide

$\text{C}_{20}\text{H}_{22}\text{FN}_2\text{OBr}$

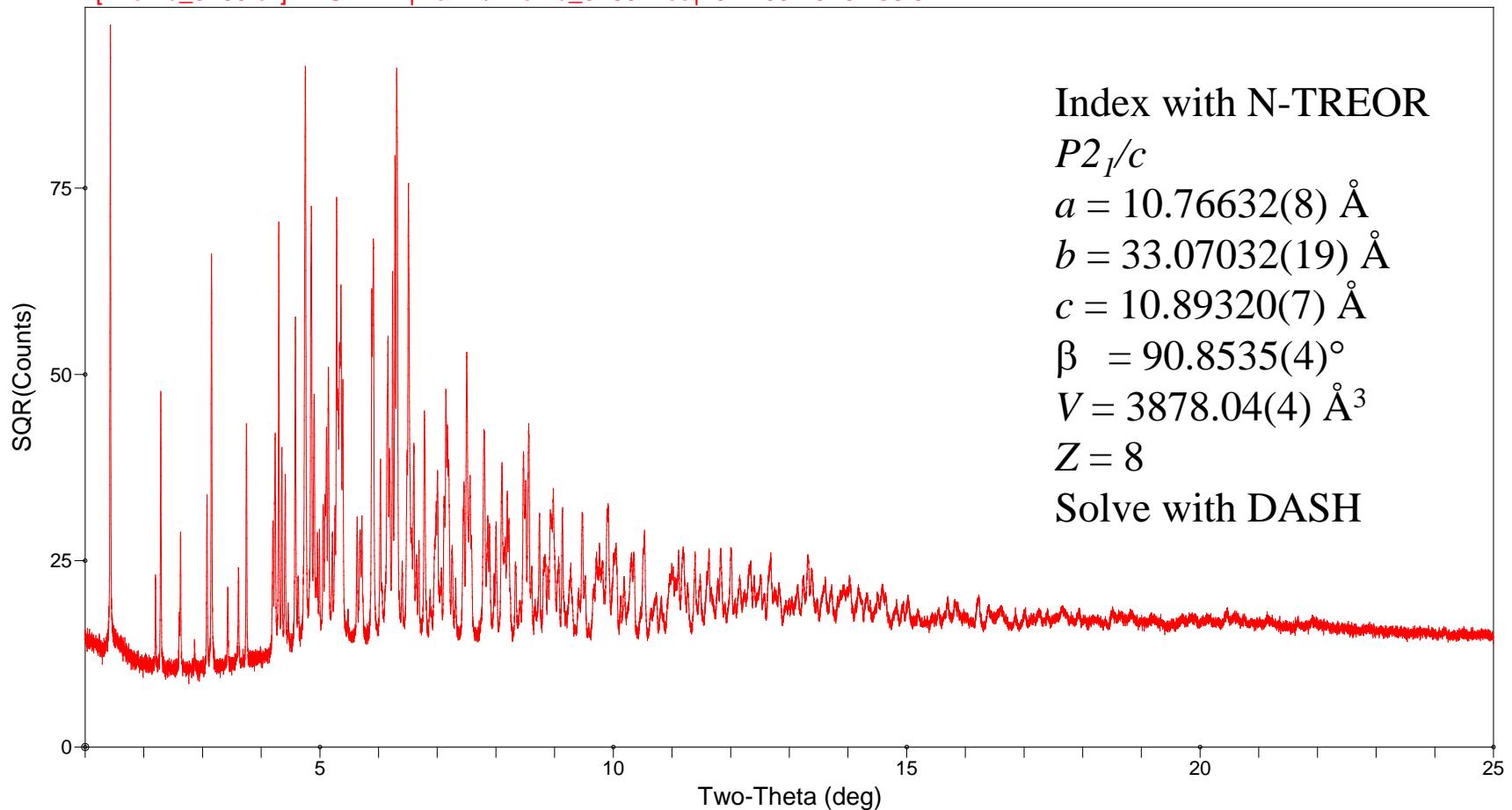
Celexa
Cipramil
depression

Citalopram Hydrobromide

$\text{C}_{20}\text{H}_{22}\text{FN}_2\text{OBr}$



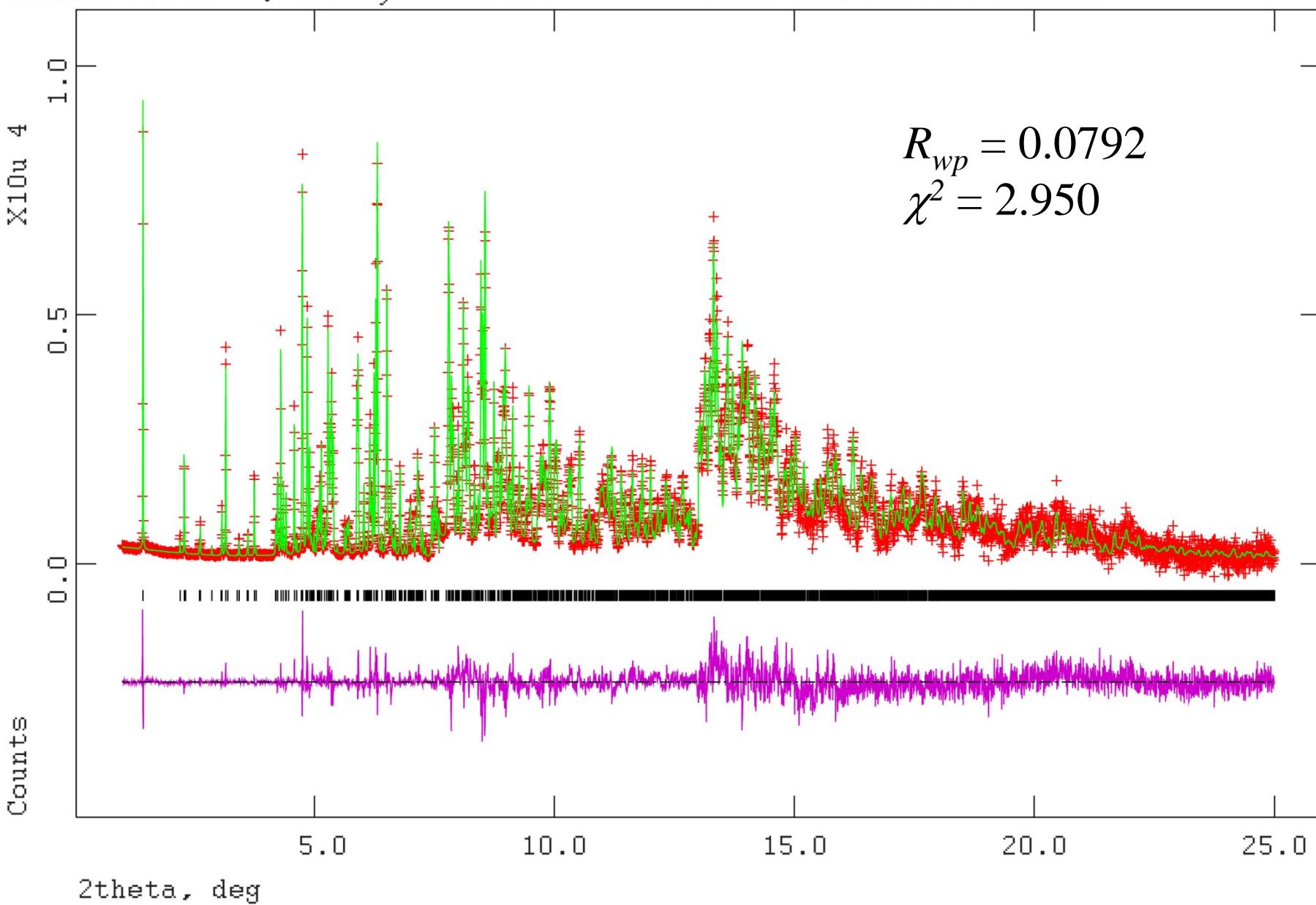
[11bmb_3760.cif] APS11BM|mar14/11bmb_3760.mda|2014-03-15T04:38:51



Citalopram Hydrobromide, C₂₀ H₂₂ F N₂ O Br (11bmb_3760) Hist 1

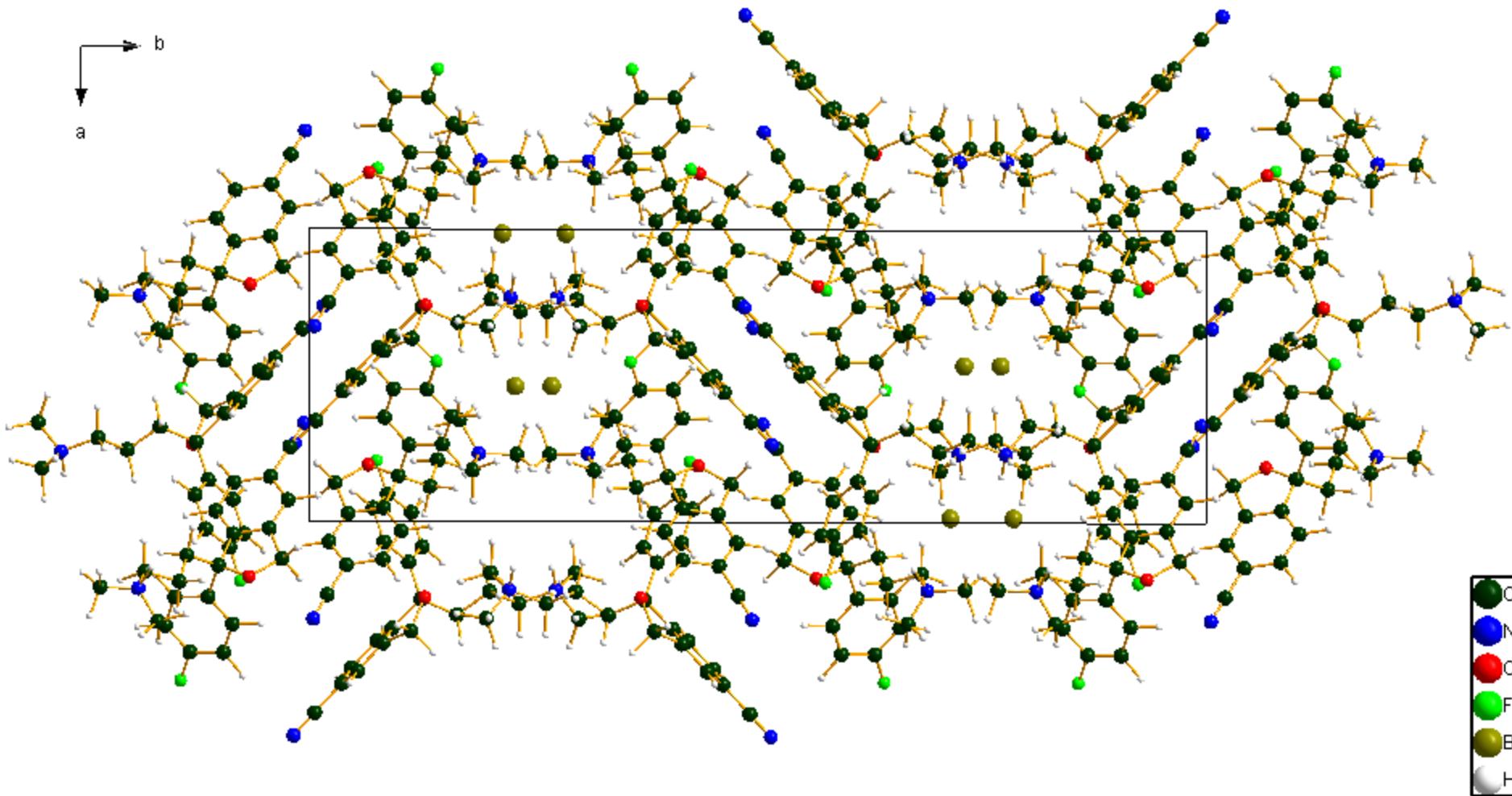
Lambda 0.4137 Å, L-S cycle 342

Obsd. and Diff. Profiles



Scaling: 7.6(4.0X) 13.0(15.0X)

Citalopram Hydrobromide

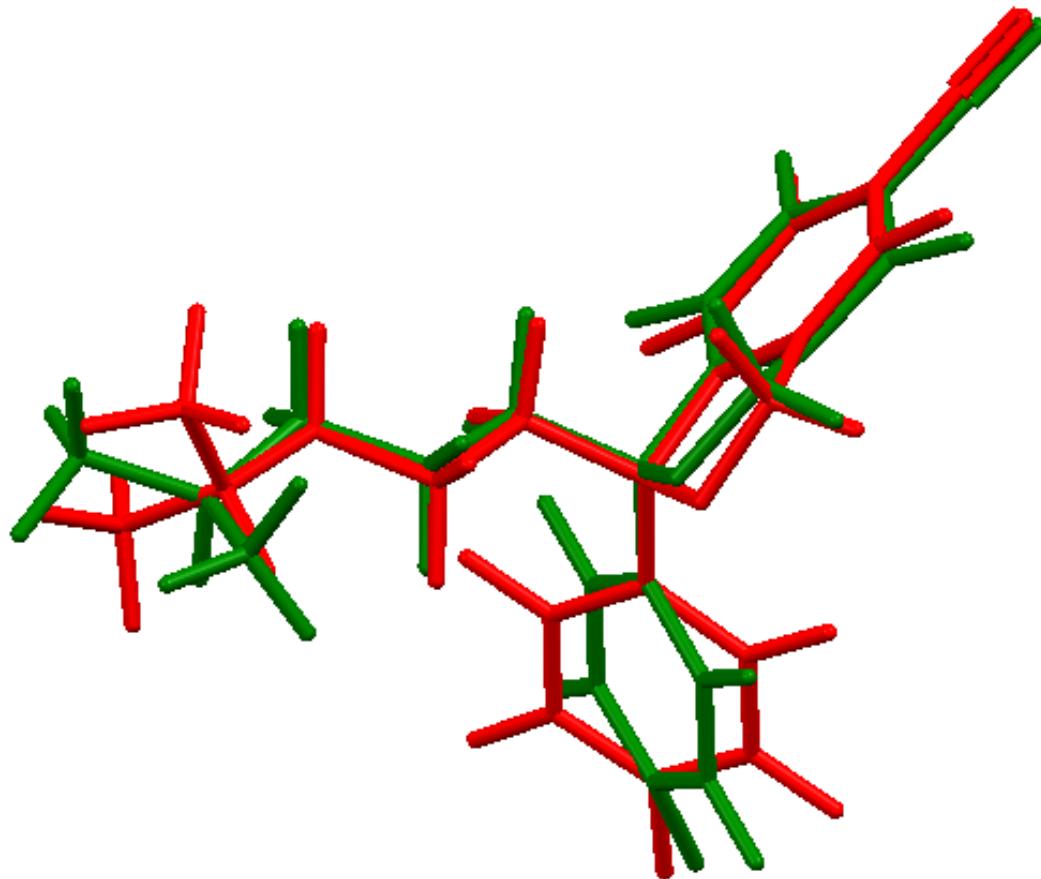


Hydrogen Bonds in Citalopram HBr

H-Bond	D-H, Å	H···A, Å	D···A, Å	D-H···A, °	Overlap, e
N45-H94···Br50			3.358		
N21-H93···Br49			3.401		

Experimental
94 atoms

Citalopram HBr – 2 Molecules



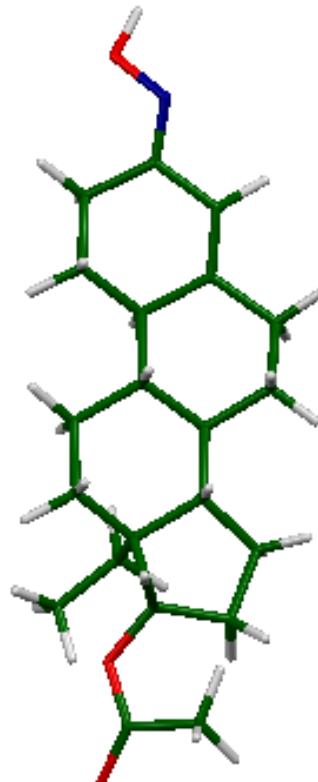
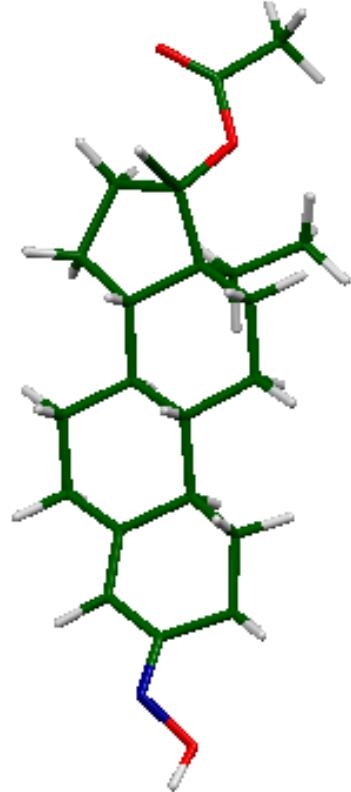
Experimental – rms $\Delta = 0.568 \text{ \AA}$

Red = molecule 1, green = molecule 2 (lower E by ~0 Kcal/mole)

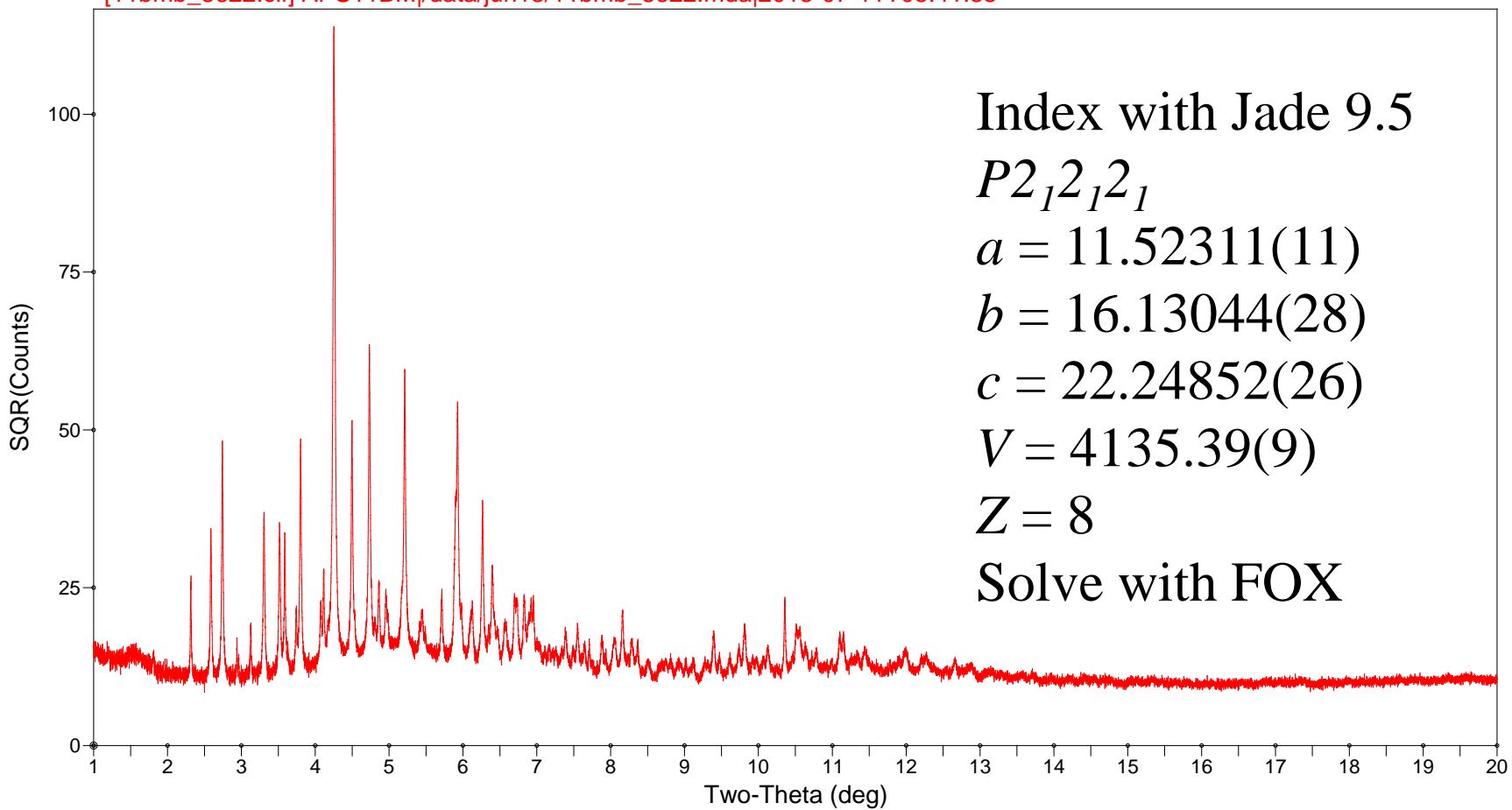
Norgestimate
 $C_{23}H_{31}NO_3$

Ortho-Prefest
oral contraceptive

Norgestimate, C₂₃H₃₁NO₃



[11bmb_8622.cif] APS11BM|/data/jun13/11bmb_8622.mda|2013-07-11T05:41:35

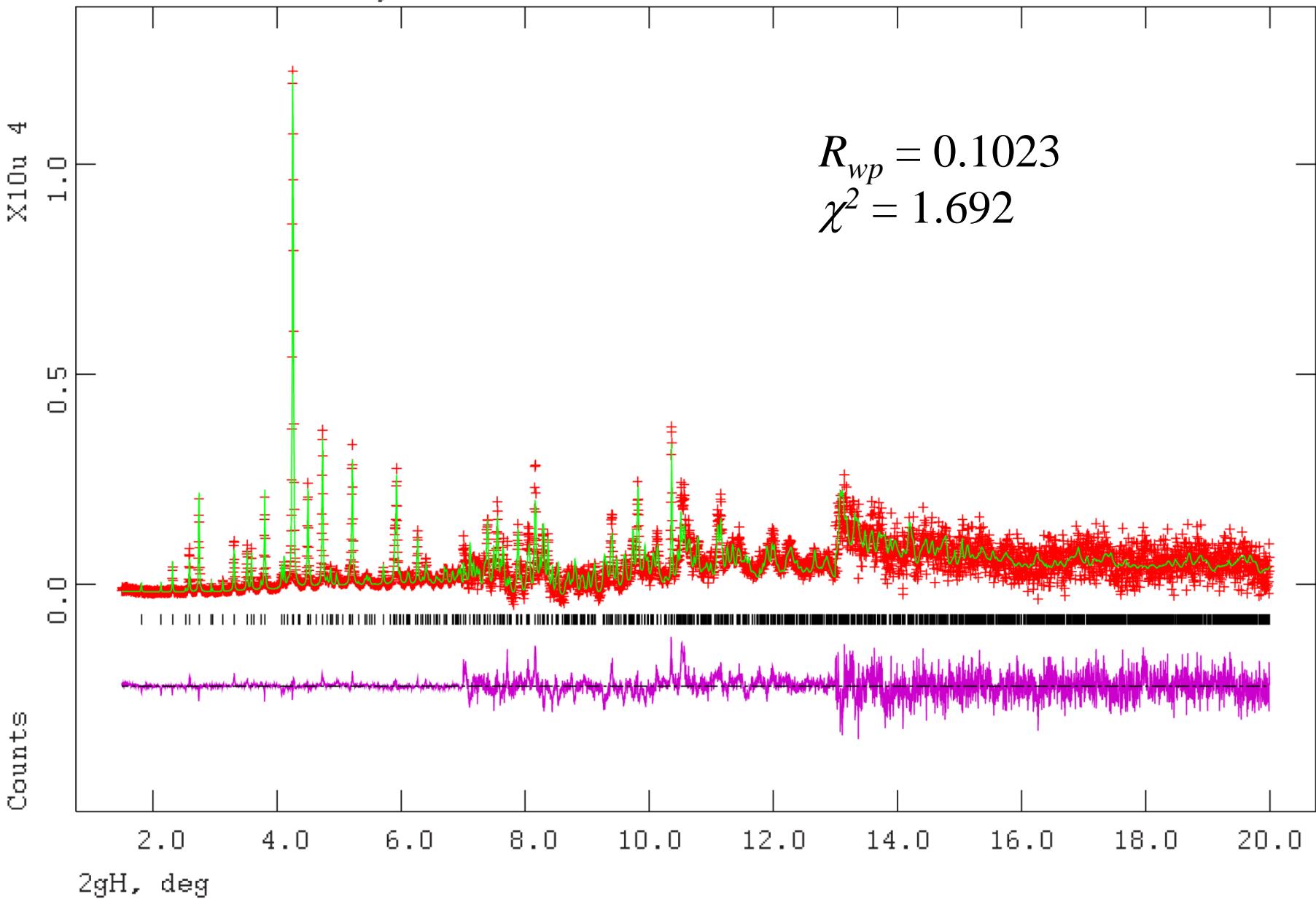


Norgestimate, C23 H31 N 03 (11bmb_8622)

Hist 1

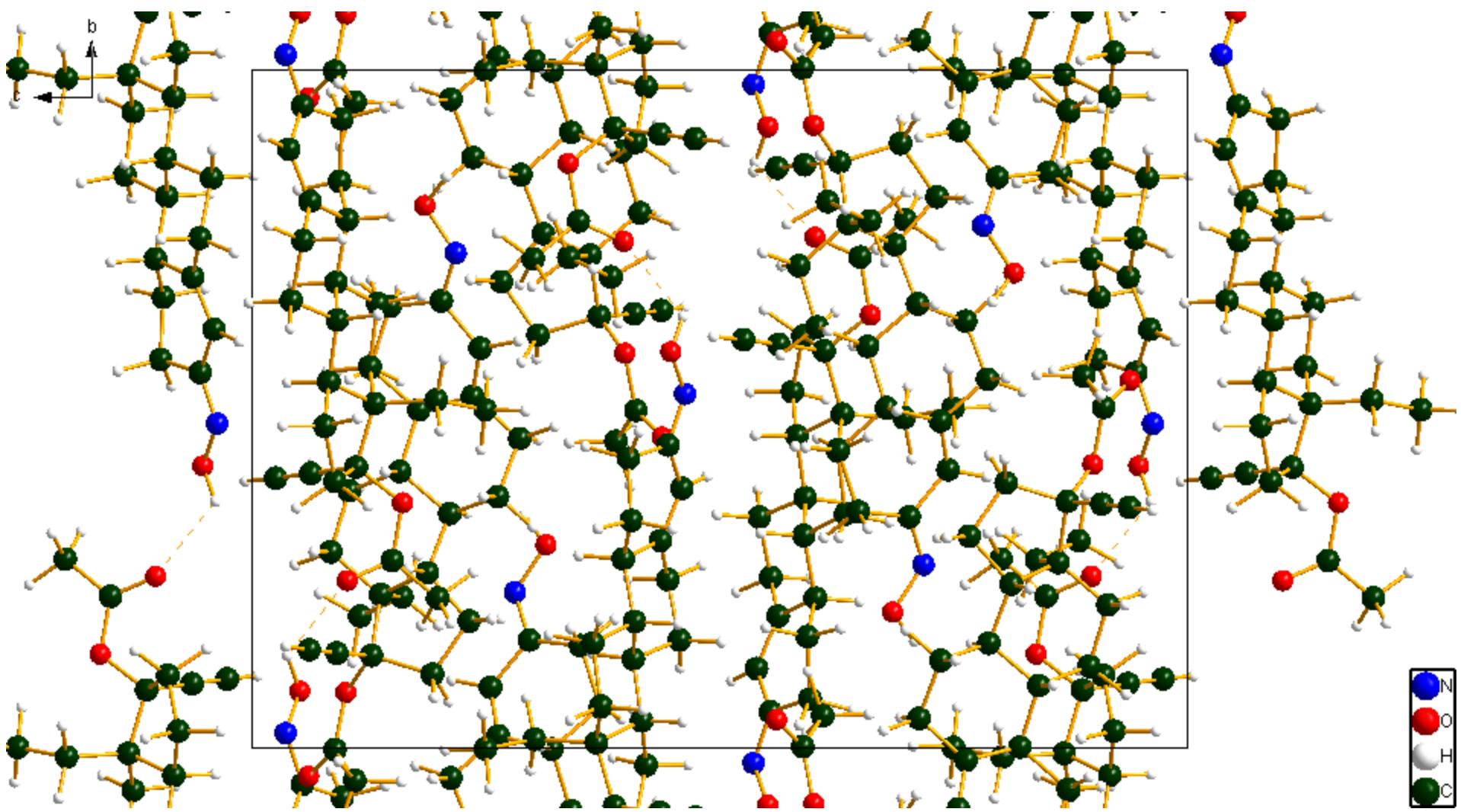
Lambda 0.4139 Å, L-S cycle 100

Obsd. and Diff. Profiles



Scaling: 7.0(10.0X) 13.0(40.0X)

Norgestimate, C₂₃H₃₁NO₃

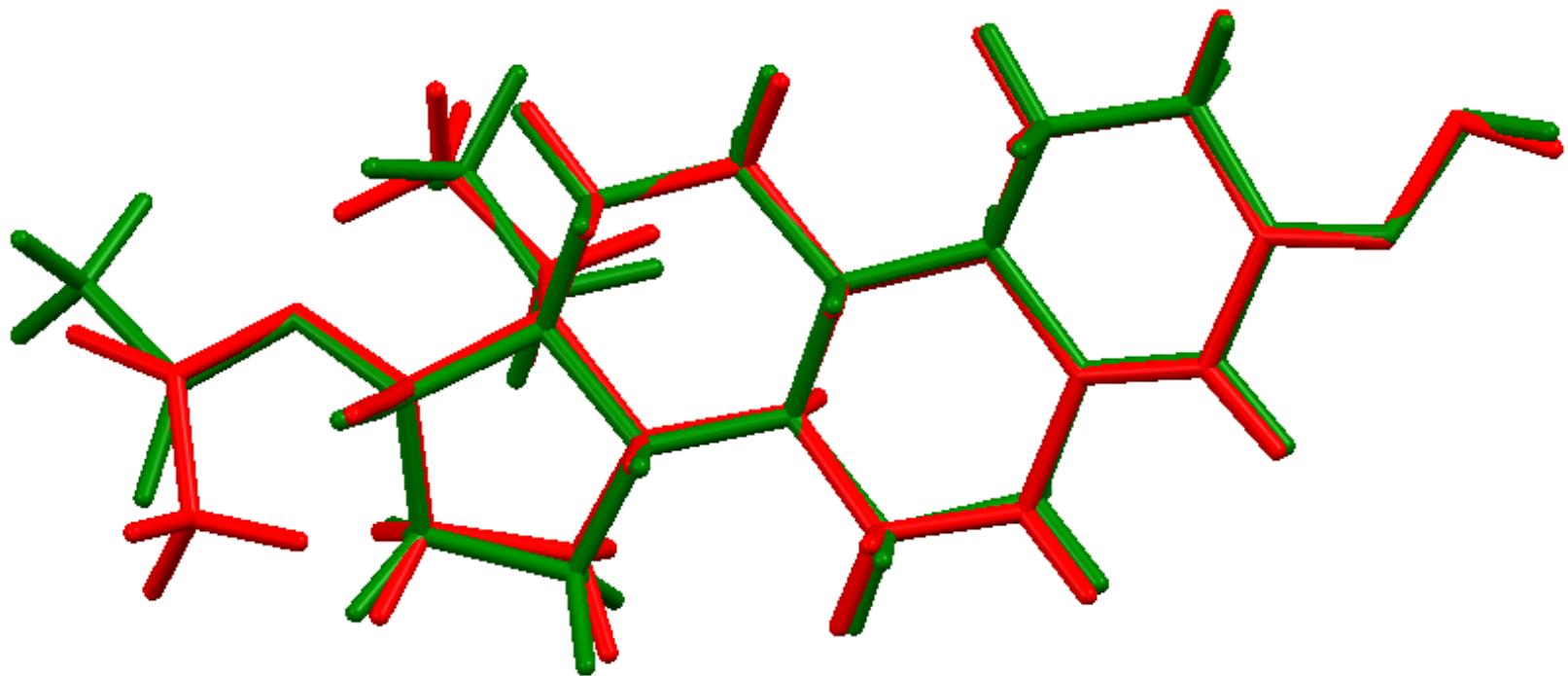


Hydrogen Bonds in Norgestimate

H-Bond	D-H, Å	H···A, Å	D···A, Å	D-H···A, °	Overlap, e
O2-H3···O51	0.985	2.337	2.734	103.1	
O60-H61···O109	0.985	1.724	2.536	137.2	

Experimental
116 atoms

Two Norgestimate Molecules



Experimental – rms $\Delta = 0.671 \text{ \AA}$

Red = molecule 1, green = molecule 2 (lower E by $\sim 7.9 \text{ Kcal/mole}$)

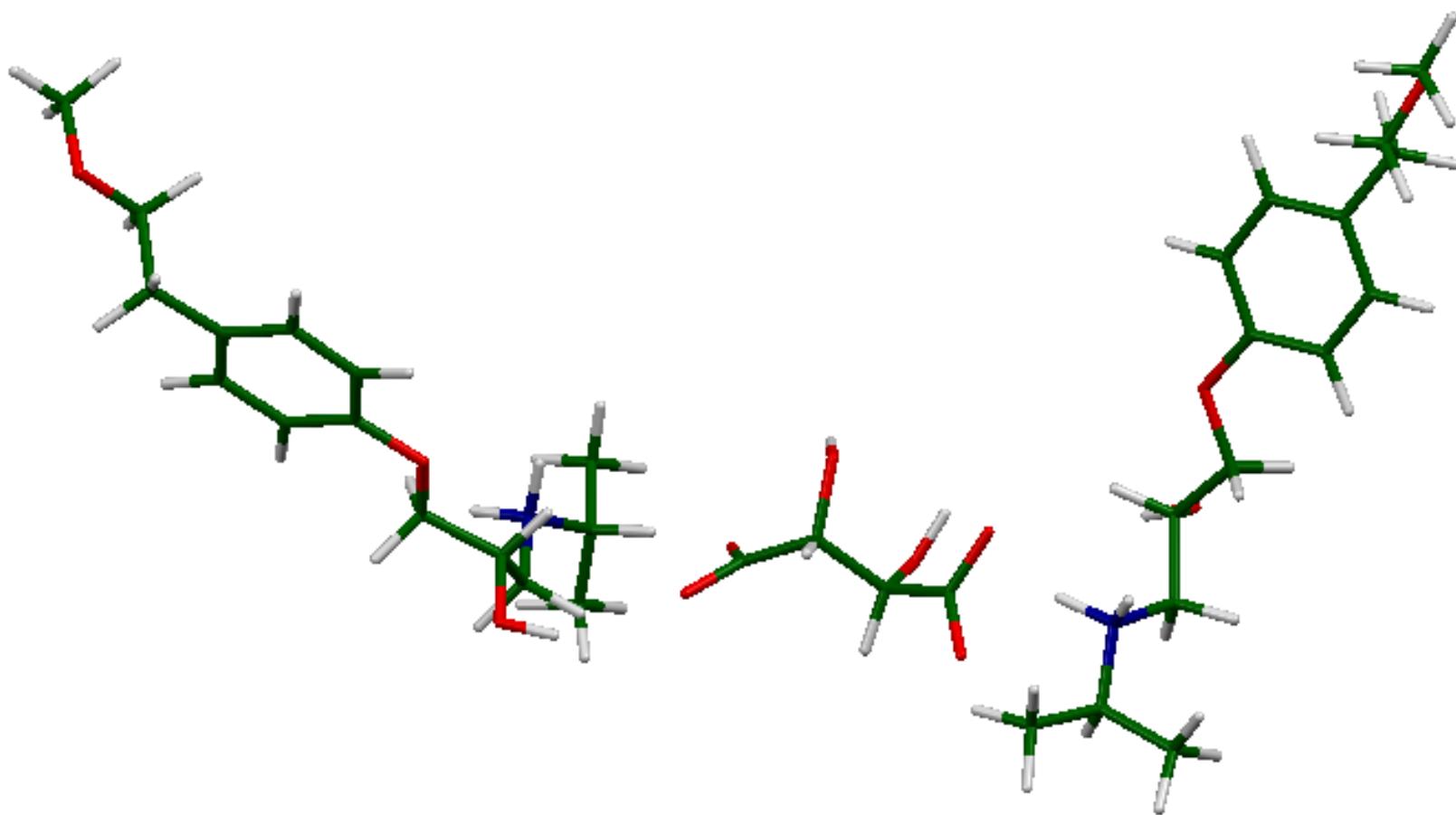
Metoprolol Tartrate $(C_{15}H_{25}NO_3)_2(C_4H_6O_6)$

selective β_1 blocker

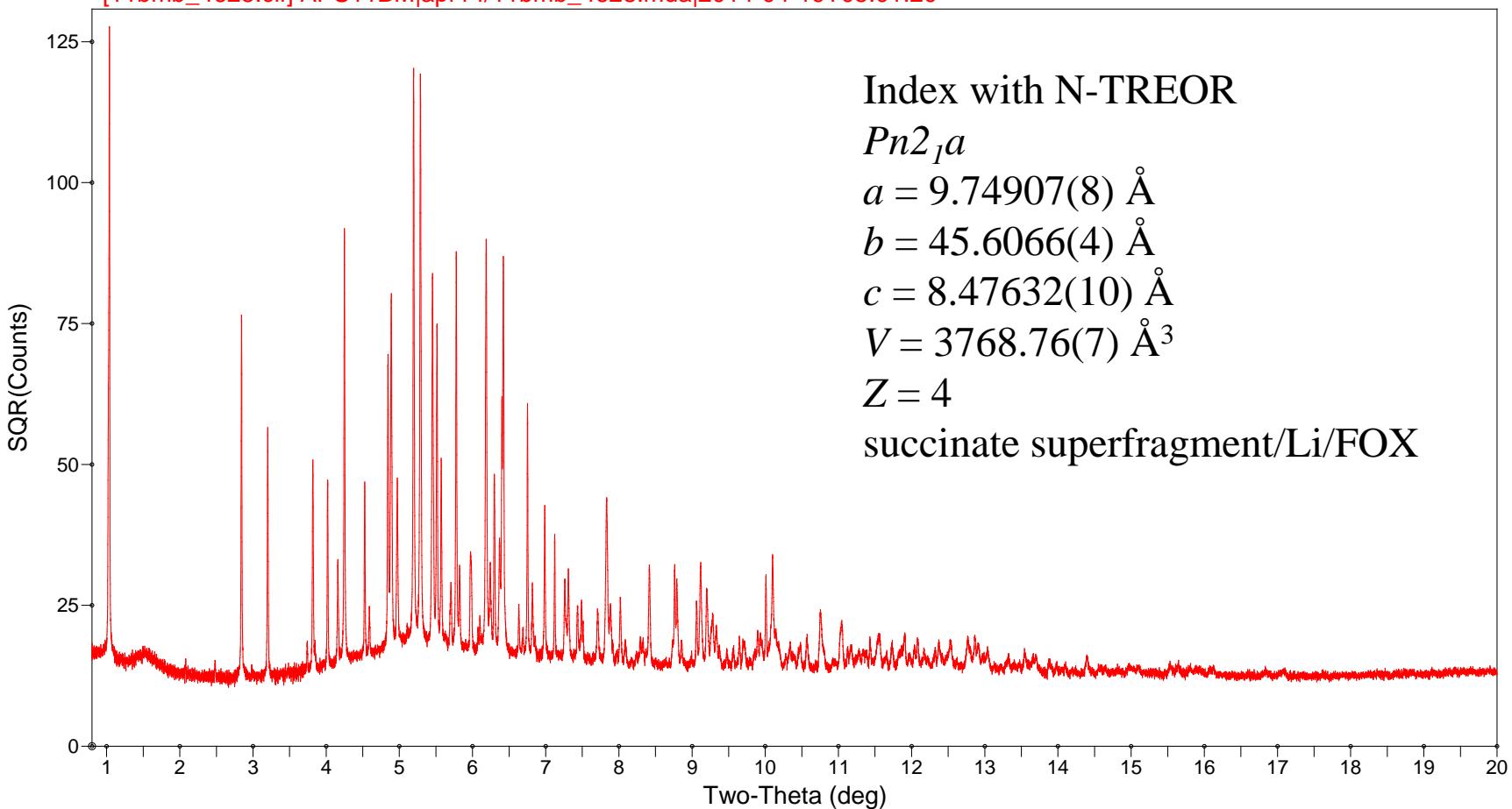
hypertension

tartrate = intermediate-release

Metoprolol Tartrate

$$(\text{C}_{15}\text{H}_{25}\text{NO}_3)_2(\text{C}_4\text{H}_6\text{O}_6)$$


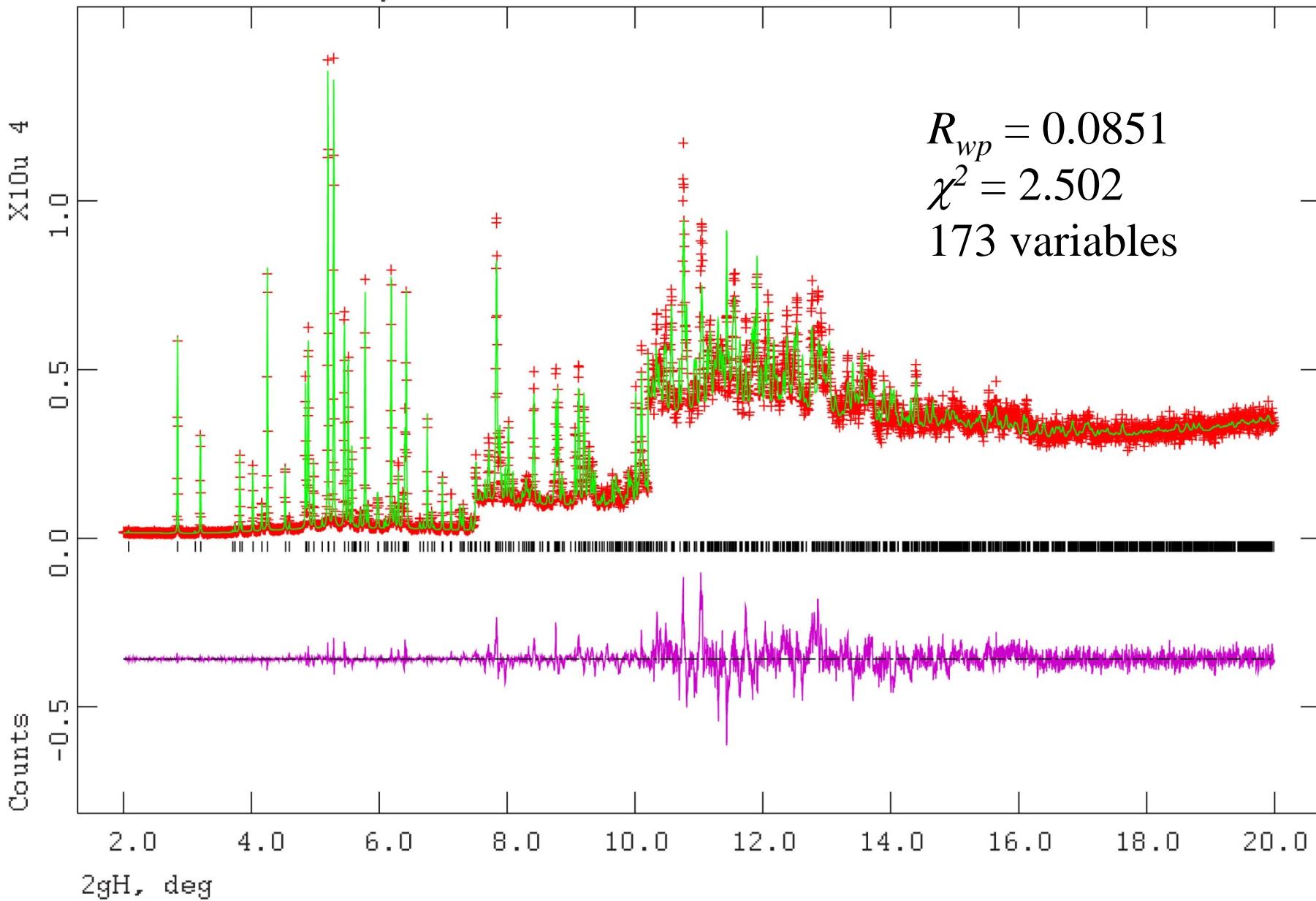
[11bmb_4628.cif] APS11BM|apr14/11bmb_4628.mda|2014-04-19T05:01:20



Metoprolol Tartrate, (C₁₅ H₂₅ N₀₃)₂ (C₄ H₆ O₆), 11bmb_46 Hist 1

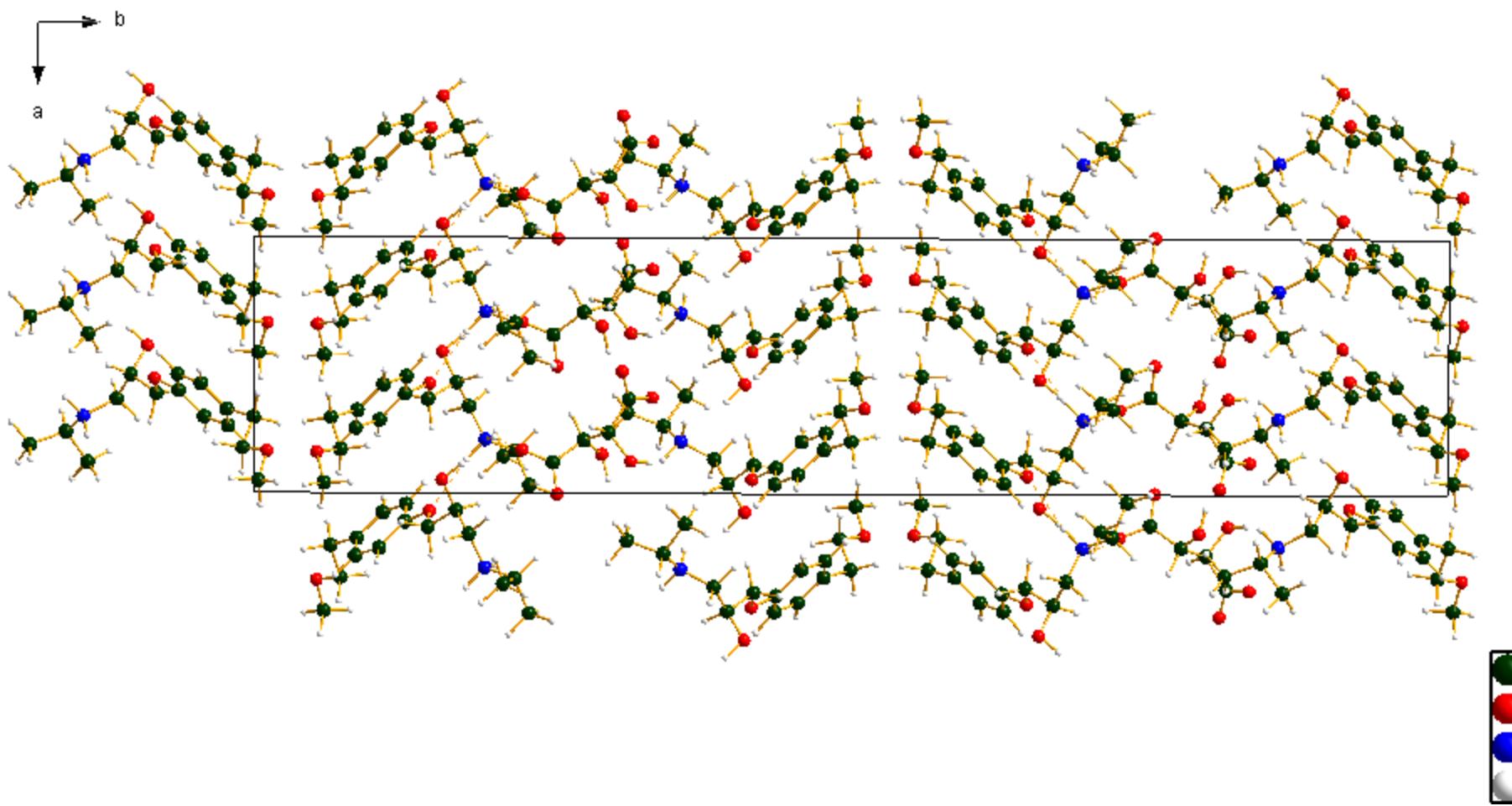
Lambda 0.4137 Å, L-S cycle 1692

Obsd. and Diff. Profiles



Scaling: 7.5(5.0X) 10.2(20.0X)

Metoprolol Tartrate

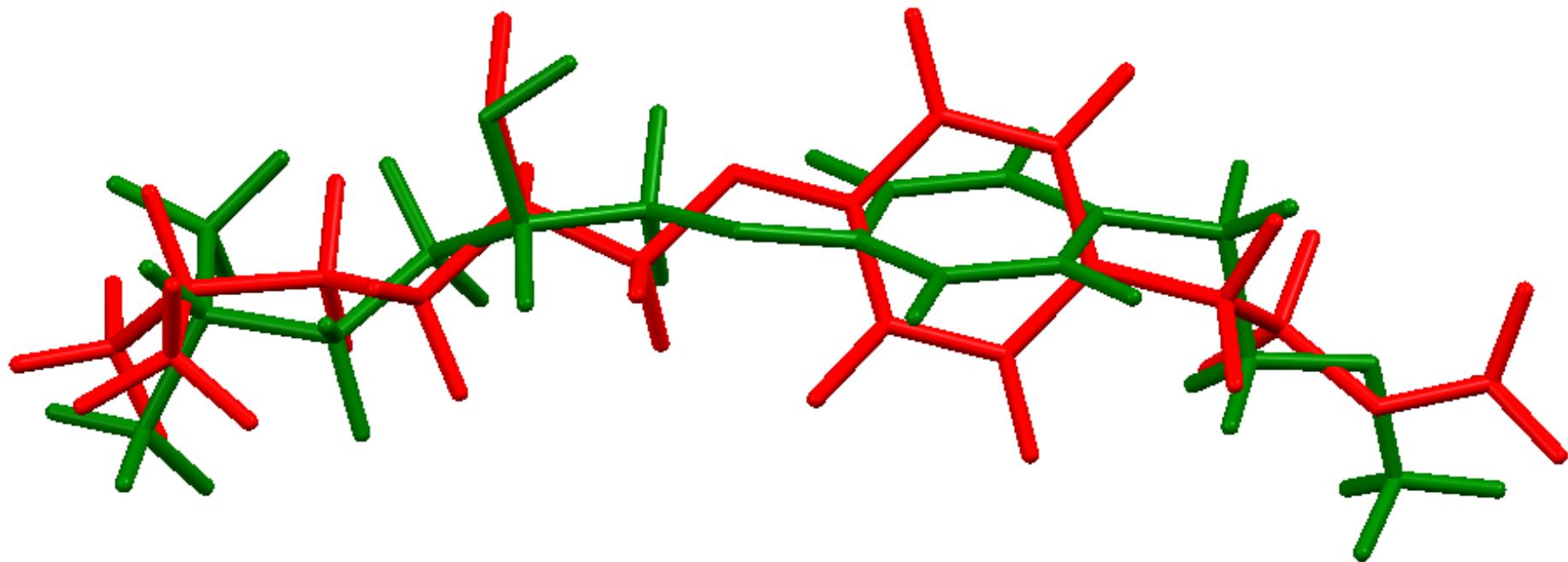


Hydrogen Bonds in Metoprolol Tartrate

H-Bond	D-H, Å	H···A, Å	D···A, Å	D-H···A, °	Overlap, e
N16-H104···O46			3.186		
N16-H66···O45			2.350		
N35-H103···O44			2.610		
N35-H91···O43			2.720		
O14-H63···O45			2.511		
O33-H88···O43			2.753		
O47-H101···O46			2.315		
O48-H102···O46?			2.757		
O48-H102···O43?			2.764		

Experimental
104 atoms

Metaprolol (Tartrate) – 2 Molecules



Experimental – rms $\Delta = 1.082 \text{ \AA}$

Red = molecule 1, green = molecule 2 (lower E by ~0 Kcal/mole)

Pantoprazole Sodium Dihydrate

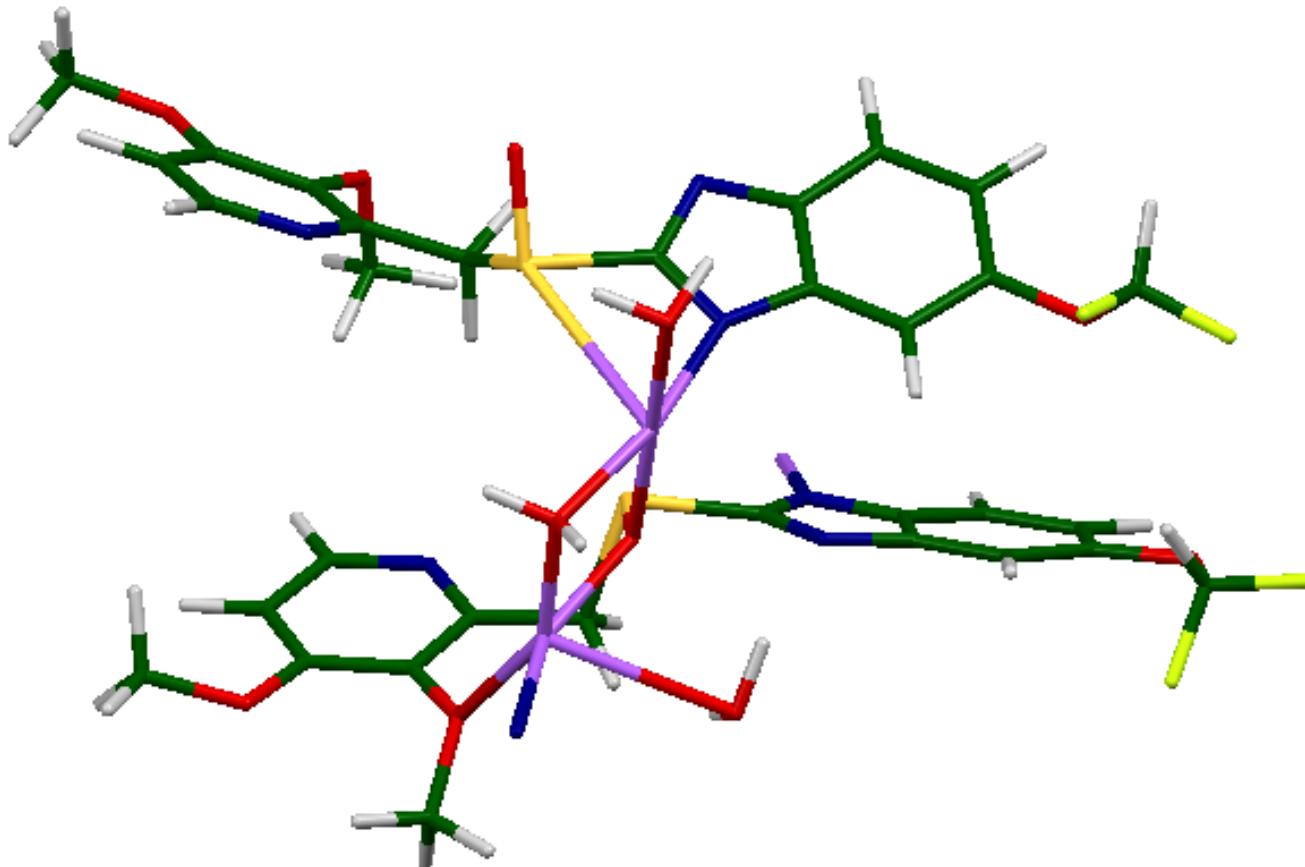
$C_{16}H_{14}N_3O_4SNa(H_2O)_2$

esophageal reflux disease (ERD)

ulcers

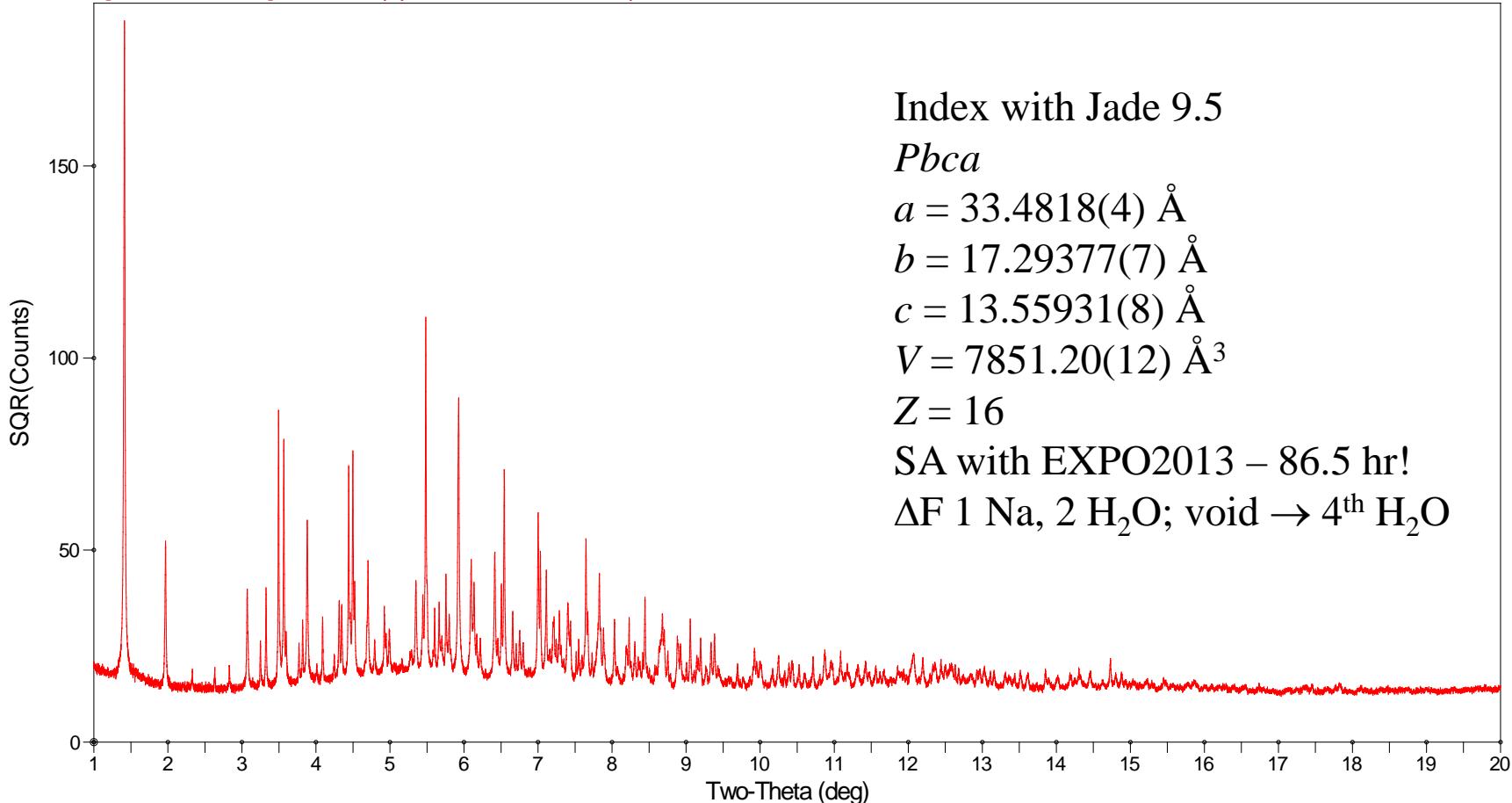
Pantoprazole Sodium Dihydrate

$C_{16}H_{14}N_3O_4SNa(H_2O)_2$

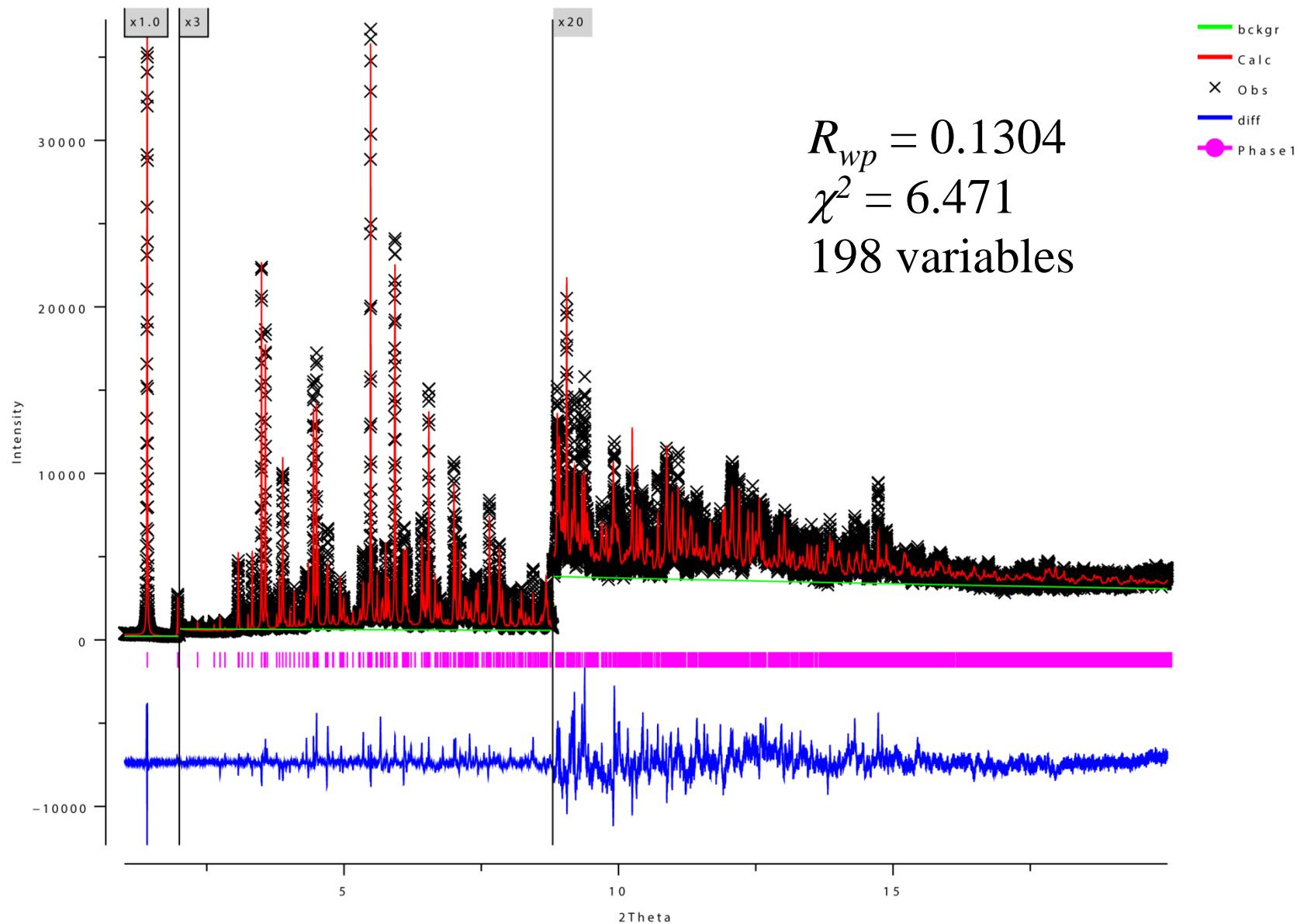


“Pantoprazole Sodium Sesquihydrate”

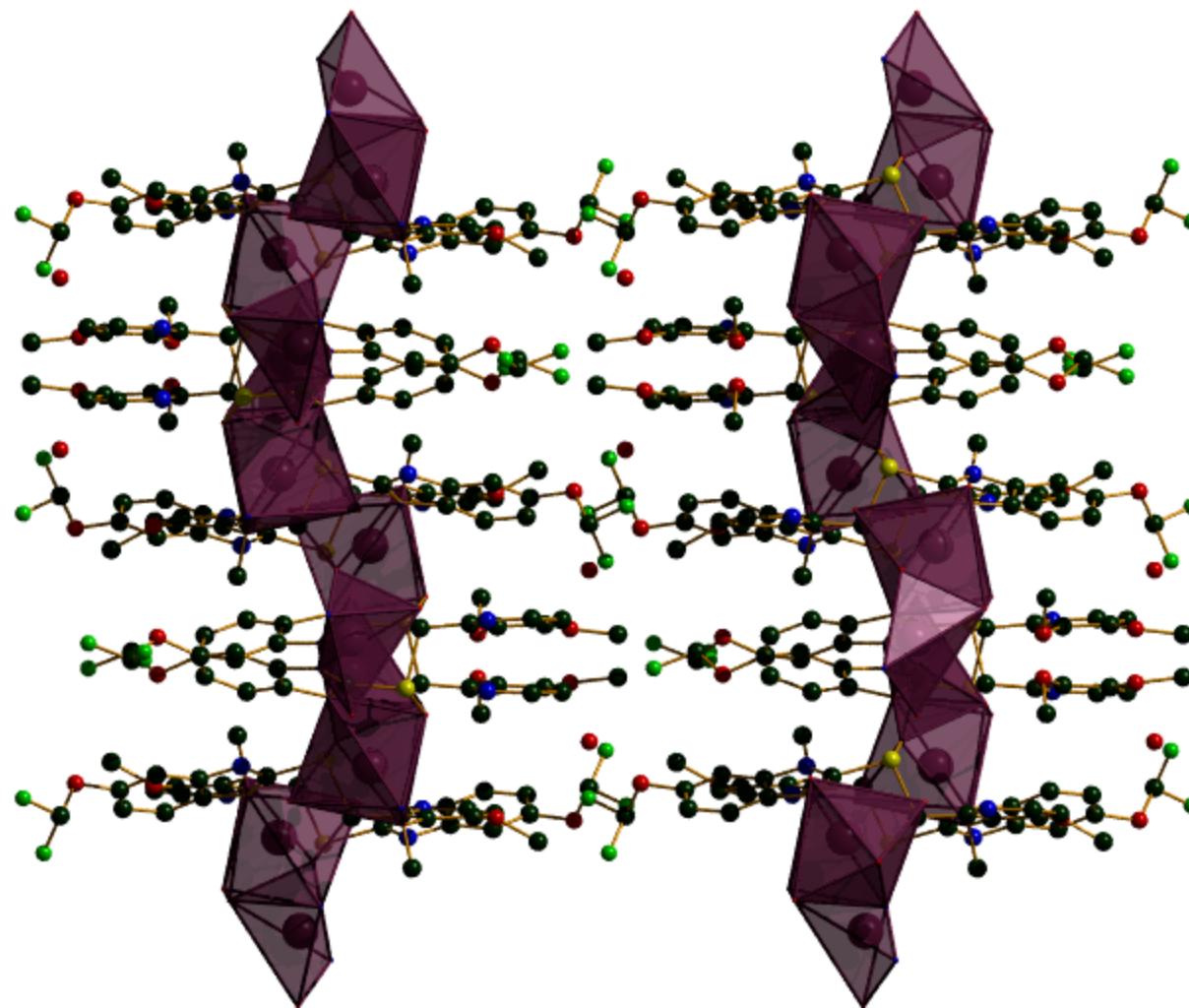
[11bmb_4465.cif] APS11BM|apr14/11bmb_4465.mda|2014-04-11T22:02:58



PANTOPRAZOLE_C cycle 1622 Hist 1



Pantoprazole Sodium Dihydrate



Na53 = 5-coord, BVS = 1.21; Na54 = 7-coord, BVS = 1.01

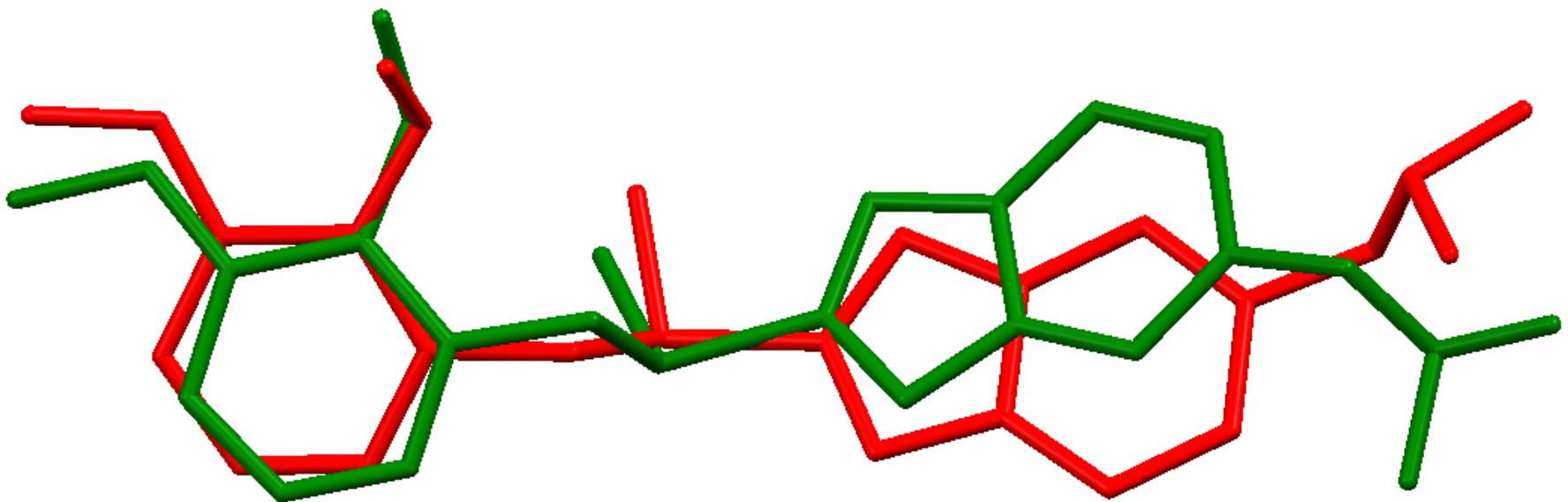
Hydrogen Bonds in Pantoprazole

H-Bond	D-H, Å	H···A, Å	D···A, Å	D-H···A, °	Overlap, e
O55-H87···O56			2.730		
O56-H89···N15			2.933		
O56-H90···N6			2.853		
O58-H93···O39			2.601		
O58-H94···N32			2.824		

Almost-converged DFT

94 atoms

Two Pantoprazole Molecules



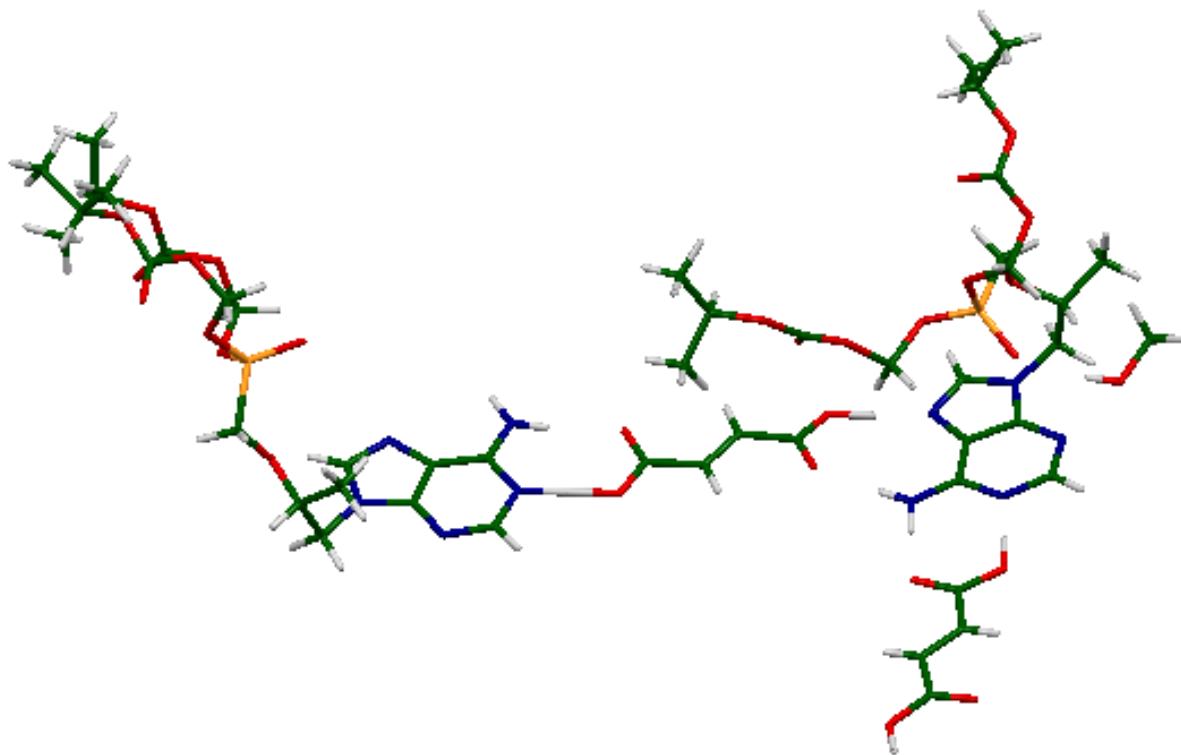
DFT – rms $\Delta = 1.655 \text{ \AA}$

Red = molecule 1, green = molecule 2 (lower E by $\sim 1.0 \text{ Kcal/mole}$)

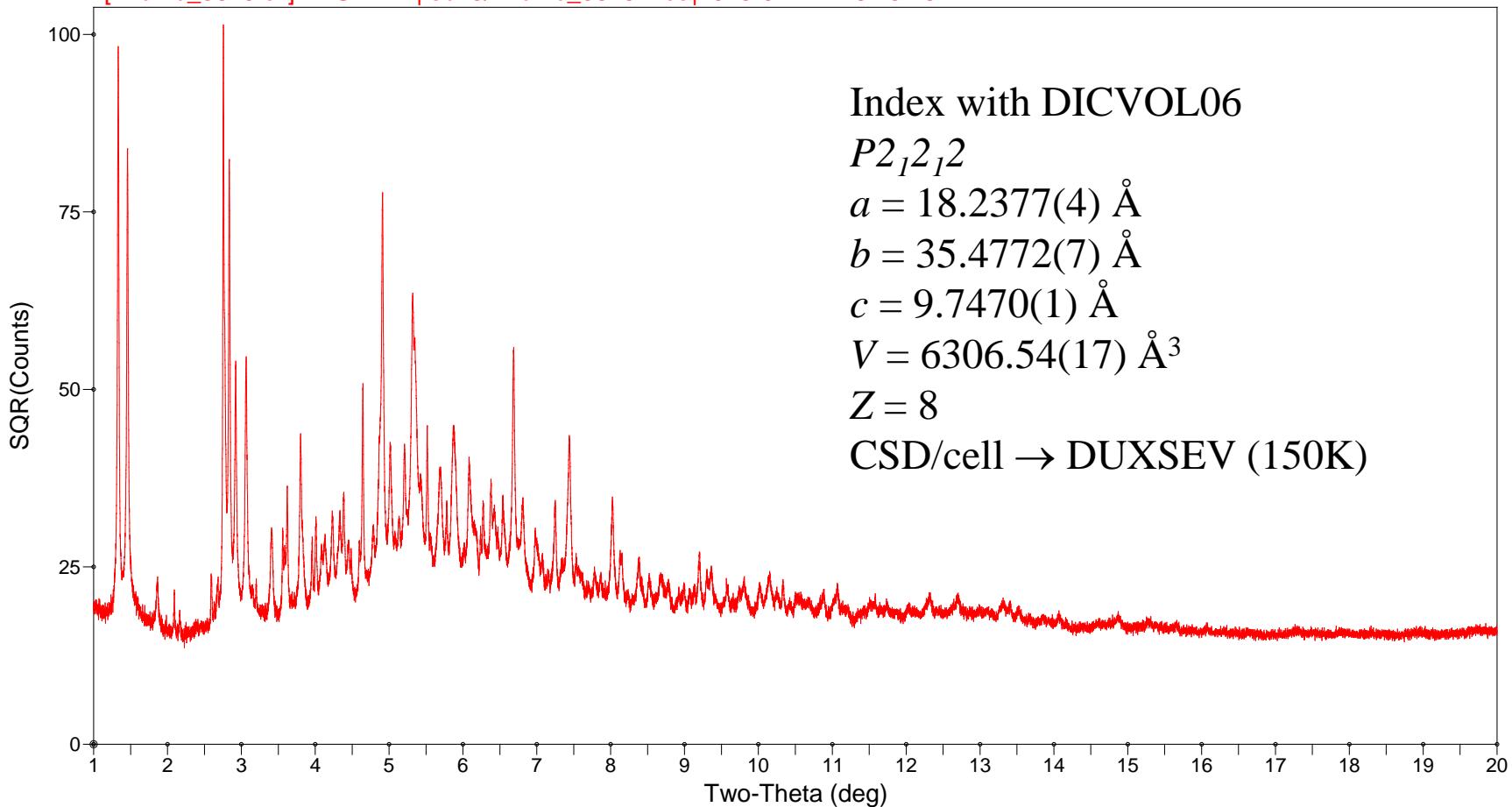
Tenofovir Disoproxil Fumarate
 $C_{19}H_{31}N_5O_{10}P(HC_4H_2O_4)(CH_3OH)_{0.5}$

Viread
HIV/AIDS

Tenofovir Disoproxil Fumarate

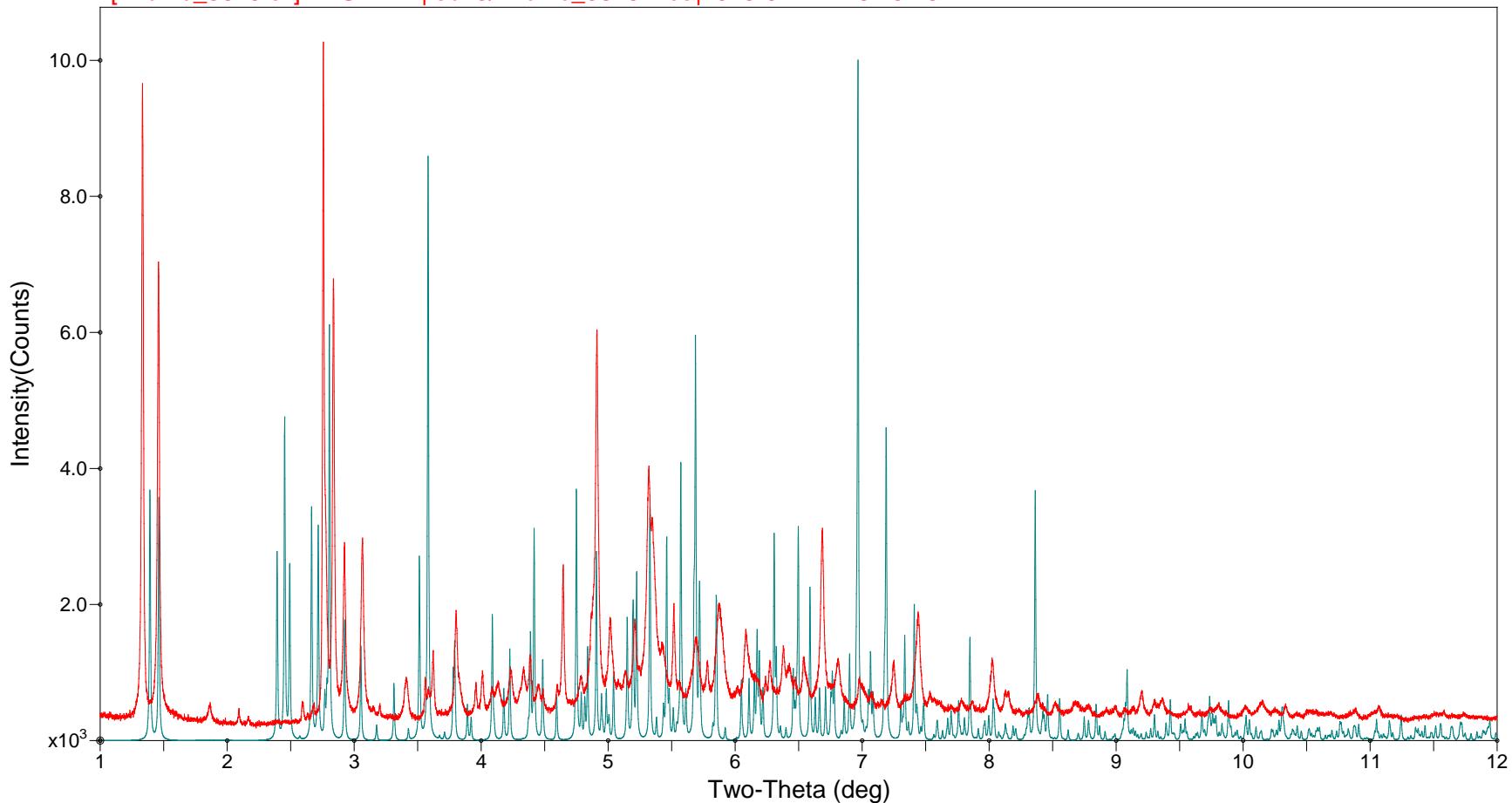


[11bmb_3679.cif] APS11BM|feb13/11bmb_3679.mda|2013-02-21T16:45:28



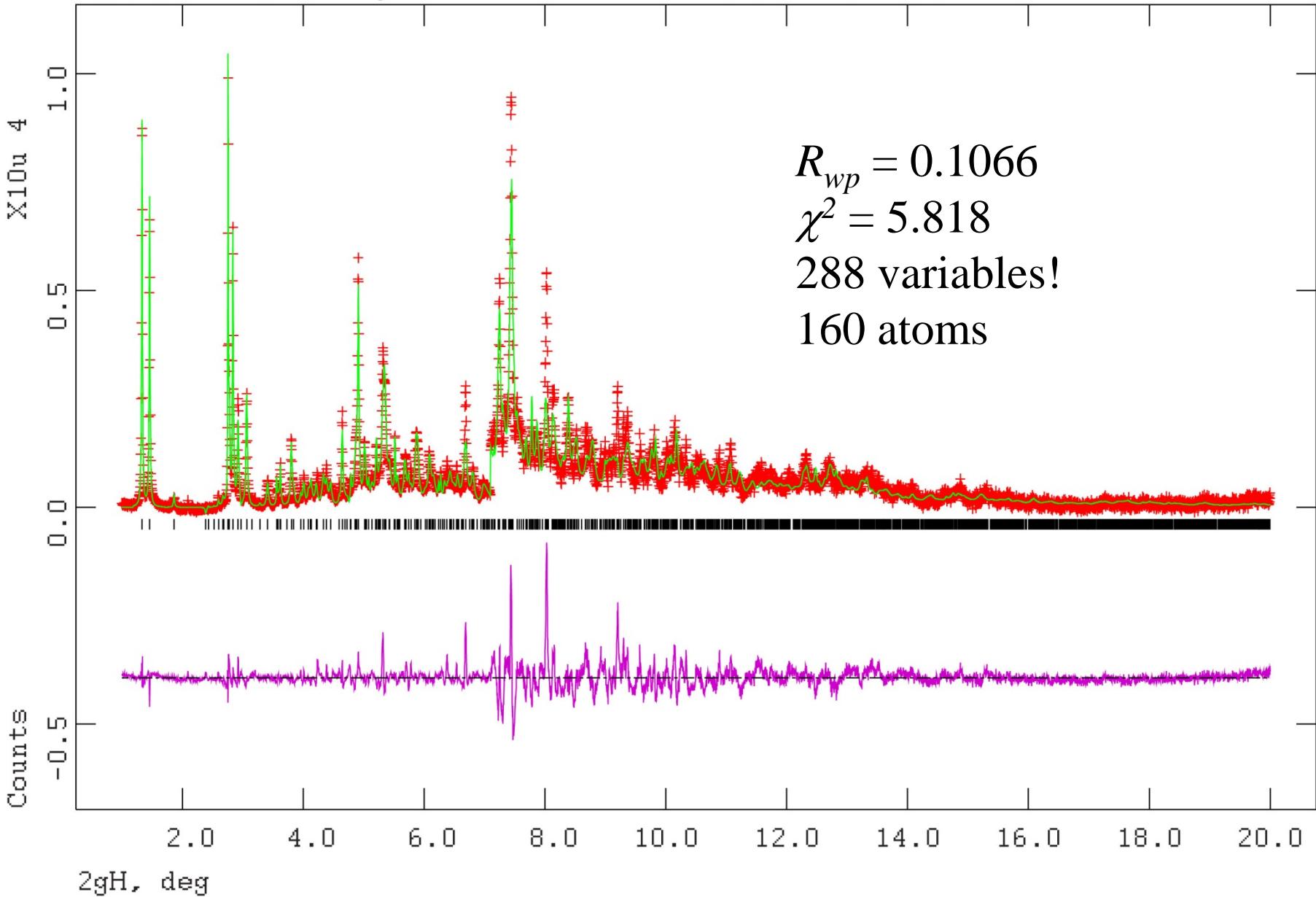
[DUXSEV.raw]

[11bmb_3679.cif] APS11BM|feb13/11bmb_3679.mda|2013-02-21T16:45:28

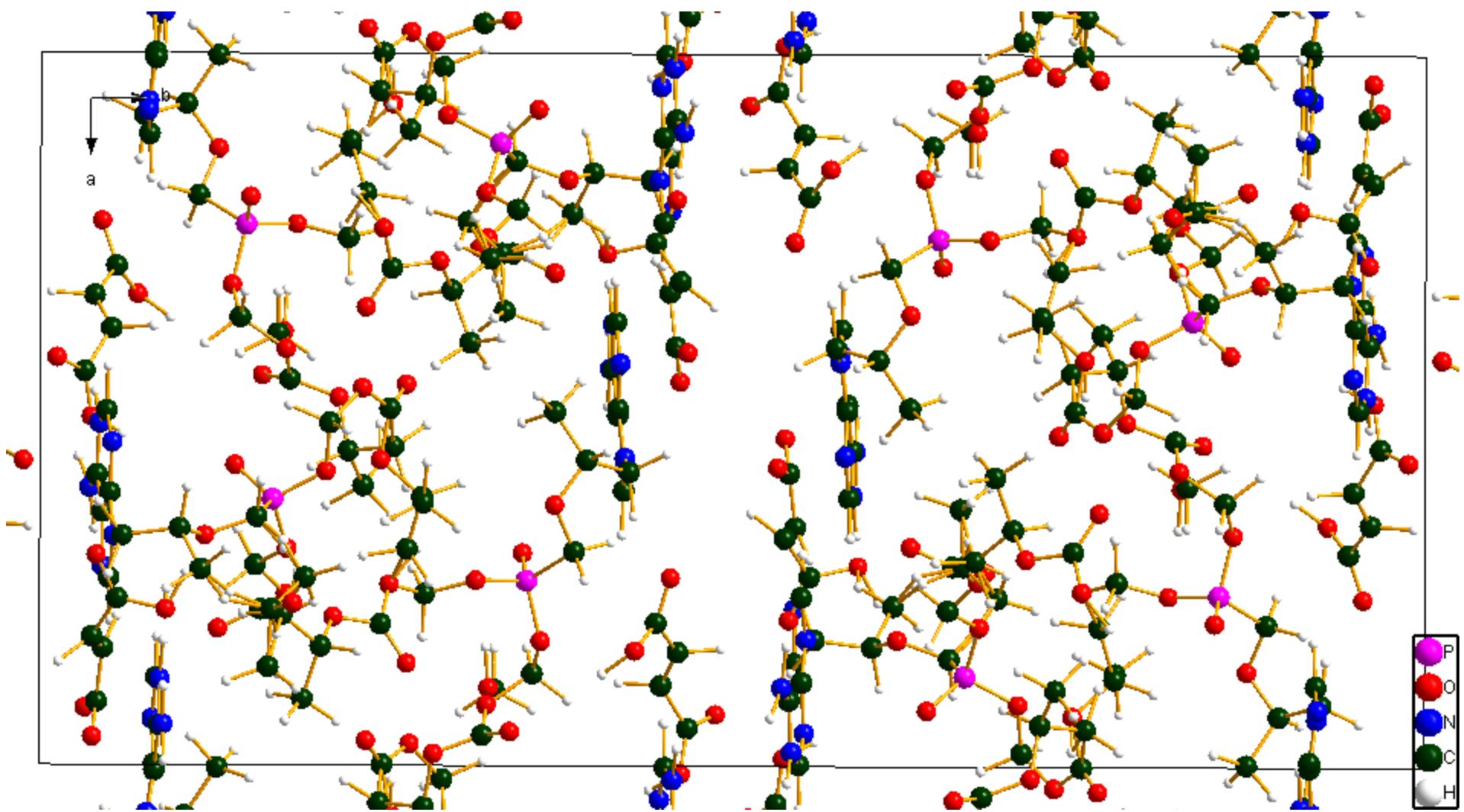


Lambda 0.4139 Å, L-S cycle 495

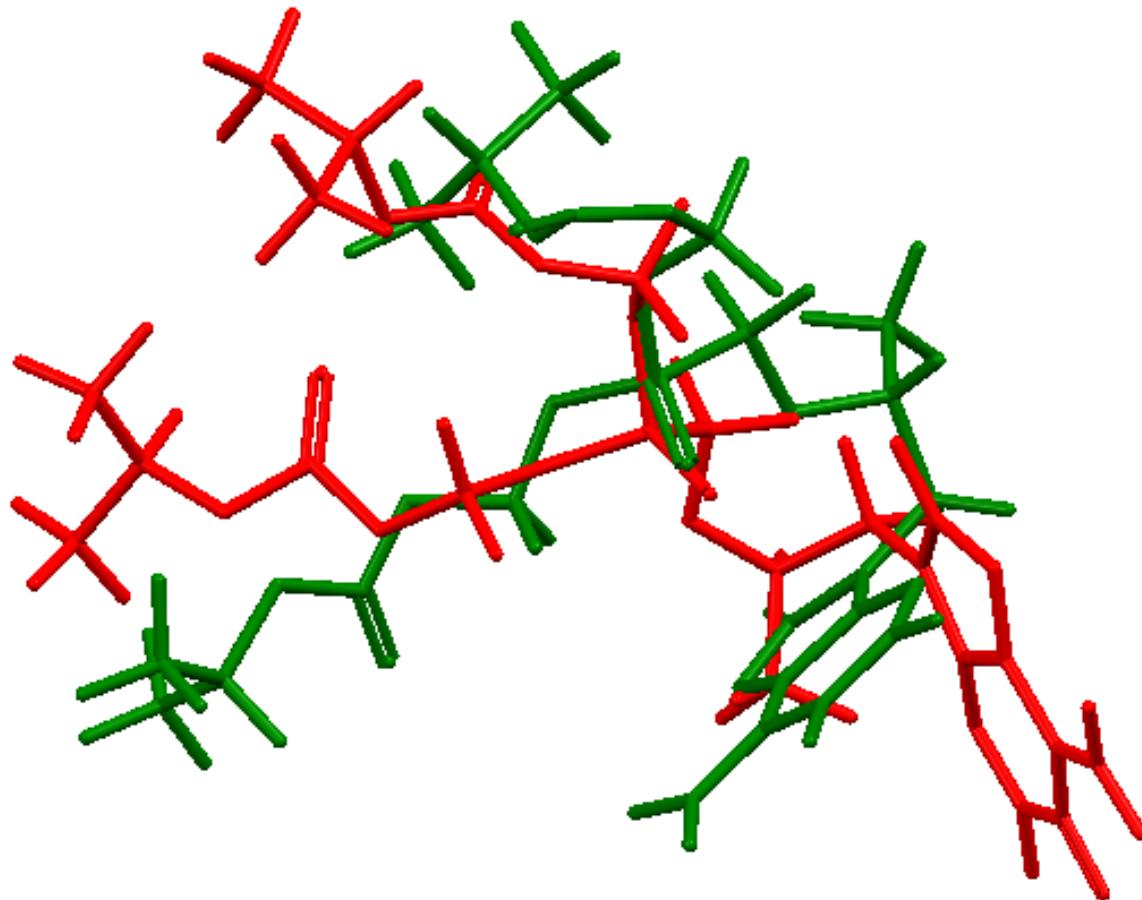
Obsd. and Diff. Profiles



Tenofovir Disoproxil Fumarate



Two Tenofovir Disoproxil Molecules



Experimental – rms $\Delta = 3.008 \text{ \AA}$

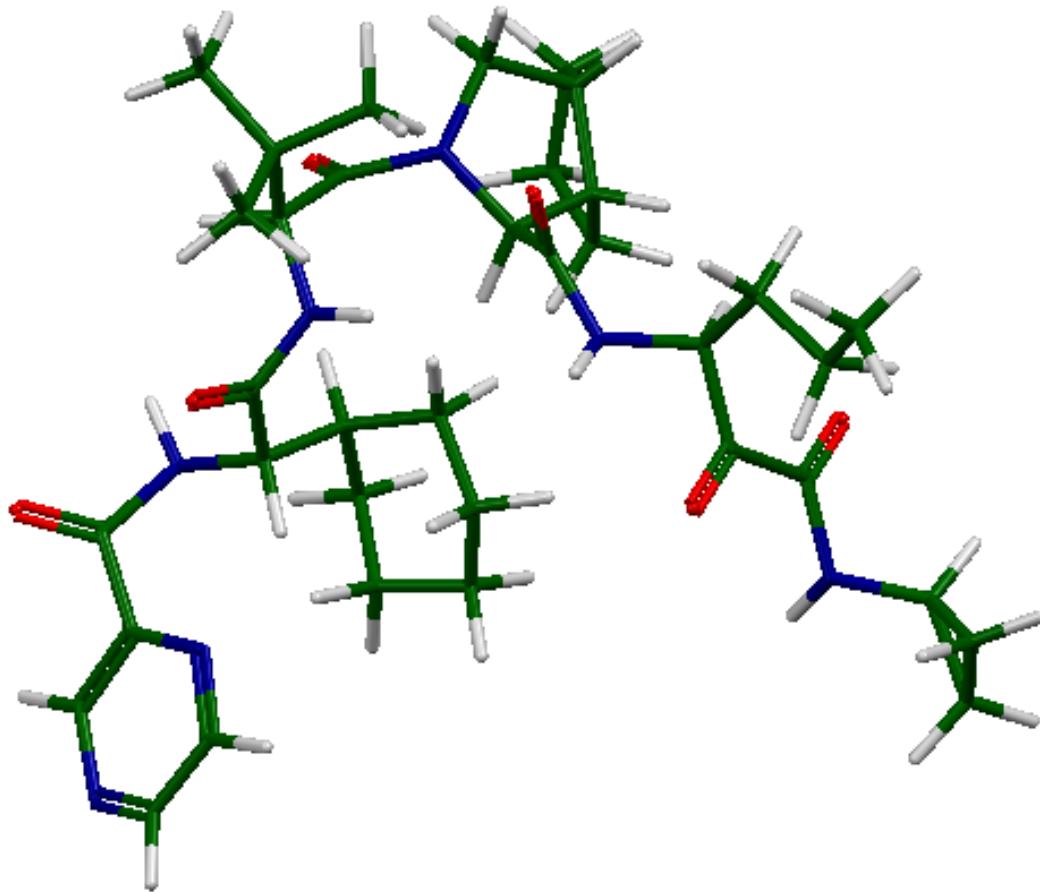
Red = molecule 1(lower E by ~3.2 Kcal/mole), green = molecule 2

Telaprevir

C₃₆H₅₃N₇O₆

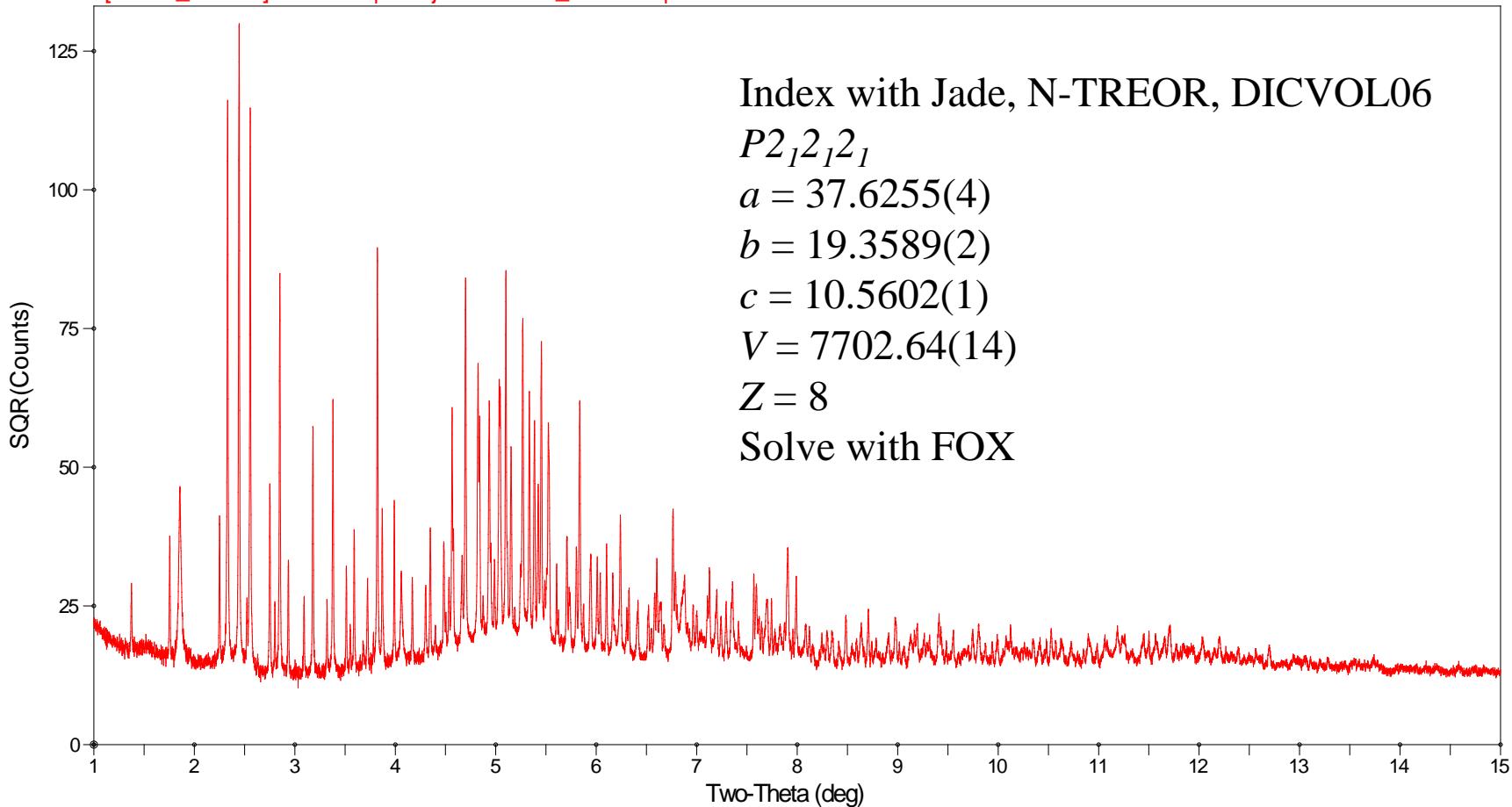
Robert Papoular
Leon Brillouin Laboratory
Incivek and Incivo
Hepatitis C

Telaprevir, C₃₆H₅₃N₇O₆



Telaprevir, C₃₆H₅₃N₇O₆

[11bmb_8616.cif] APS11BM\data\jun13\11bmb_8616.mda|2013-07-11T00:30:01

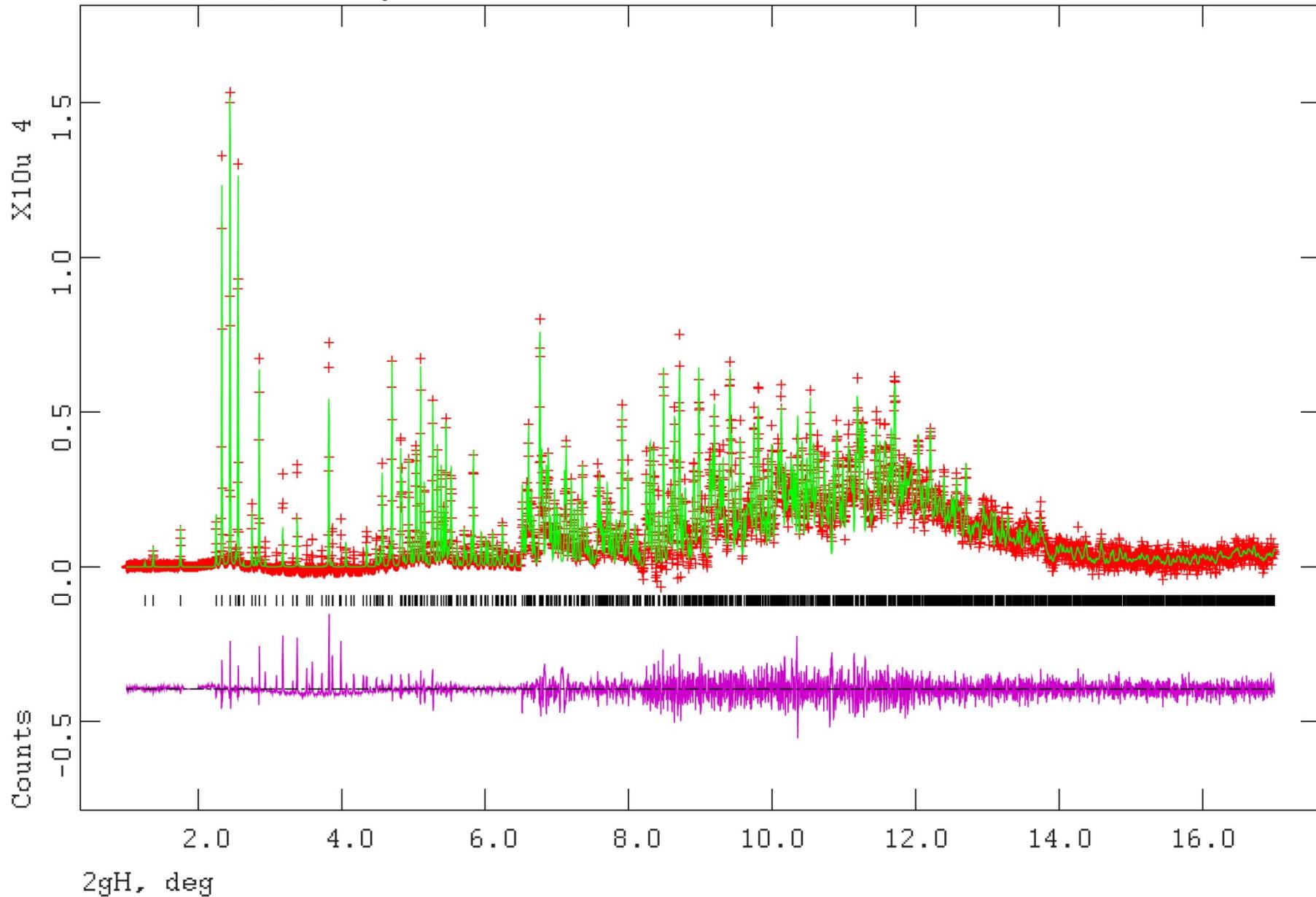


TELAPREVIR - RIETVELD

Hist 1

Lambda 0.4139 Å, L-S cycle 3723

Obsd. and Diff. Profiles



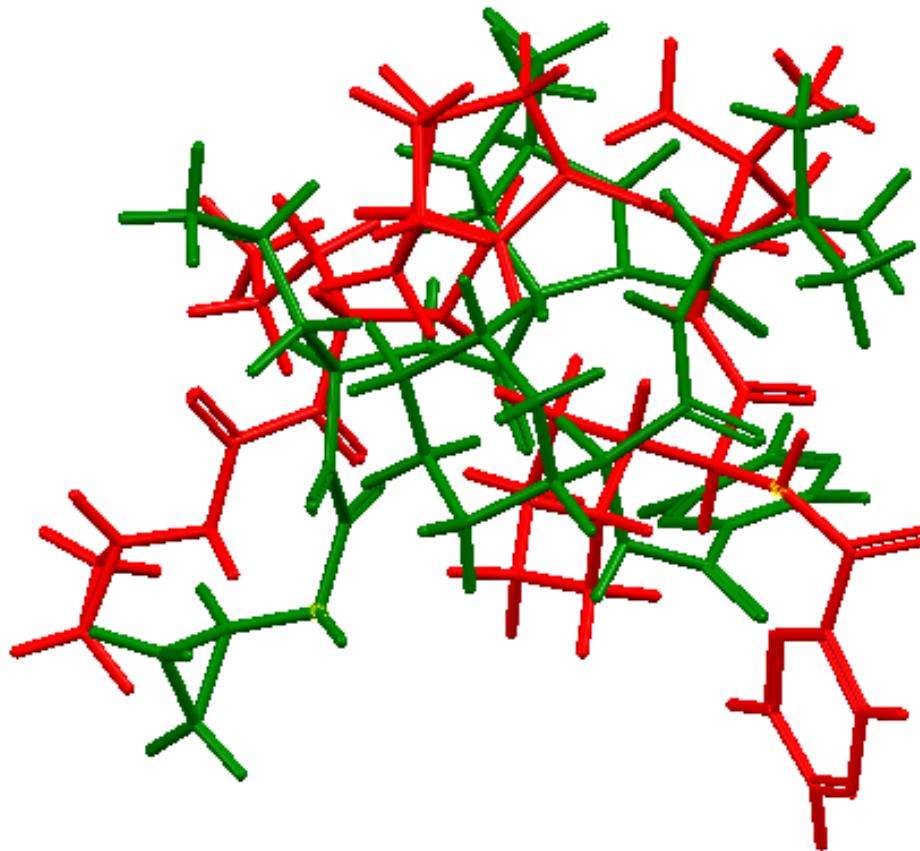
Scaling: 6.5(5.0X) 8.2(20.0X)

Hydrogen Bonds in Telaprevir

H-Bond	D-H, Å	H…A, Å	D…A, Å	D-H…A, °	Overlap, e
N9a-H21a…O8b			2.970		
N100b-H101b…O6a			2.969		

Experimental
204 atoms

Two Telaprevir Molecules



Experimental – rms $\Delta = 3.216 \text{ \AA}$

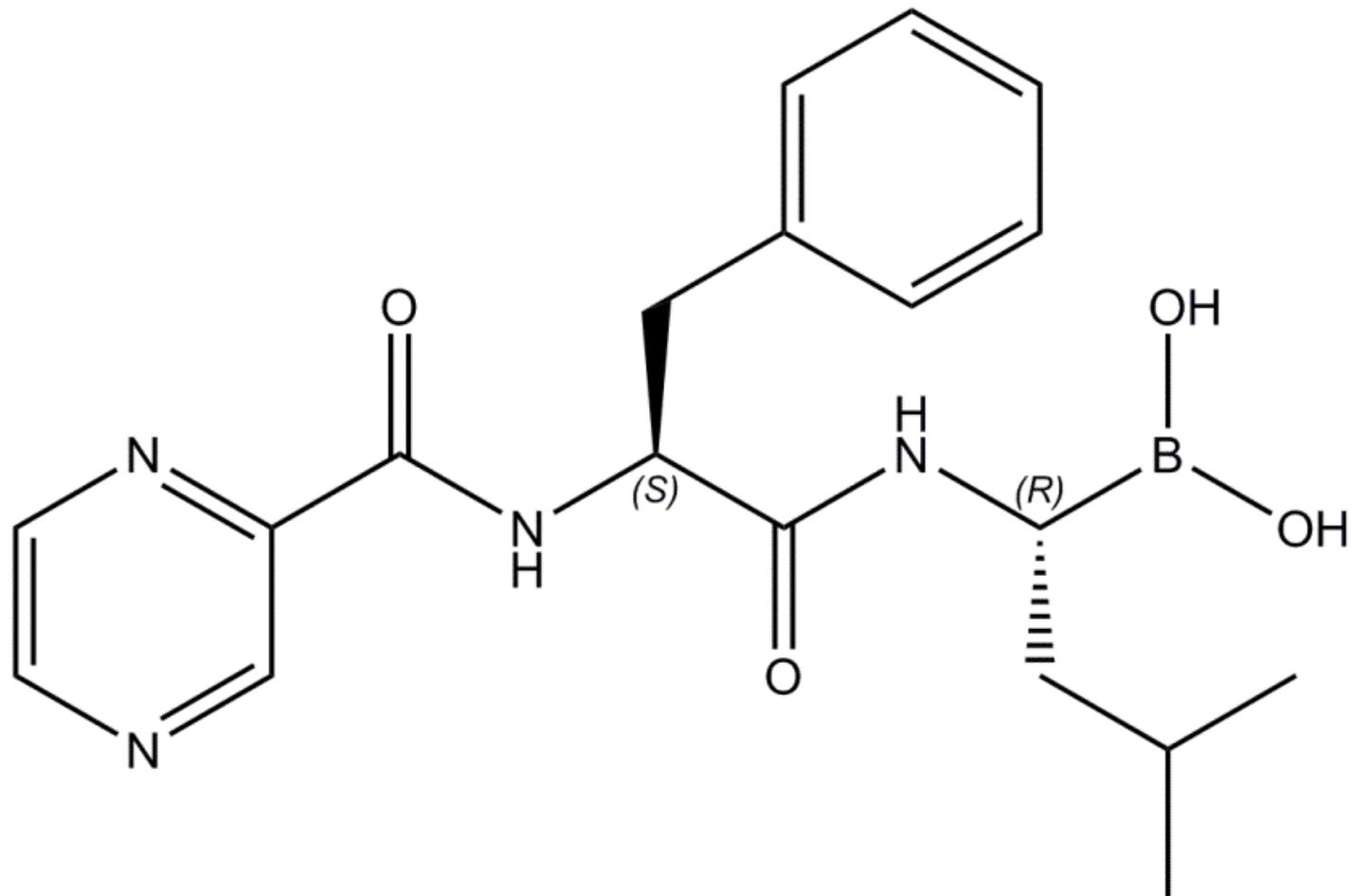
Red = molecule 1, green = molecule 2 (lower E by ~xx Kcal/mole)

Bortezomib

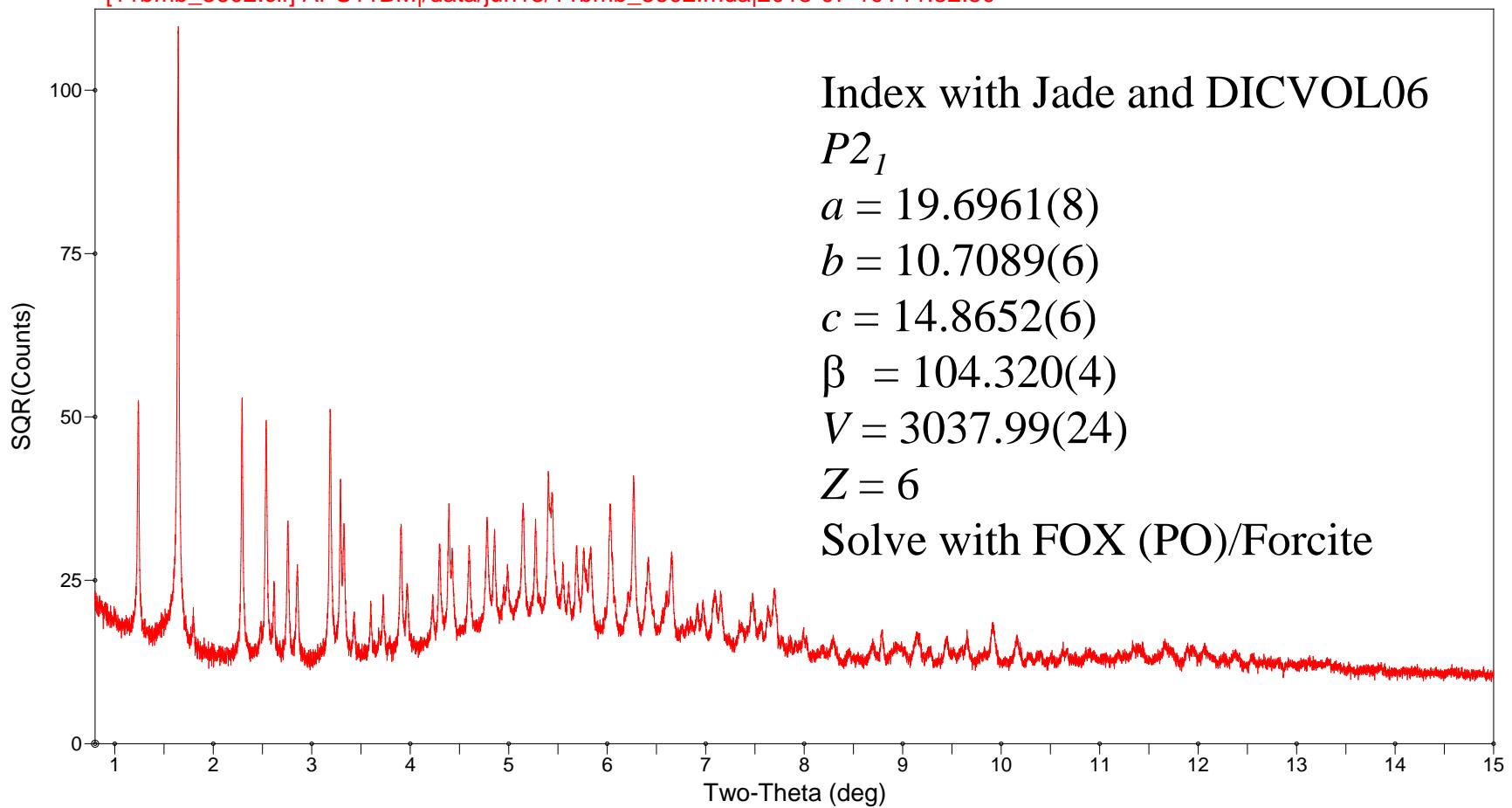
C₁₉H₂₅BN₄O₄

Joel Reid
Canadian Light Source
Velcade and Bortecad
multiple myeloma

Bortezomib, C₁₉H₂₅BN₄O₄

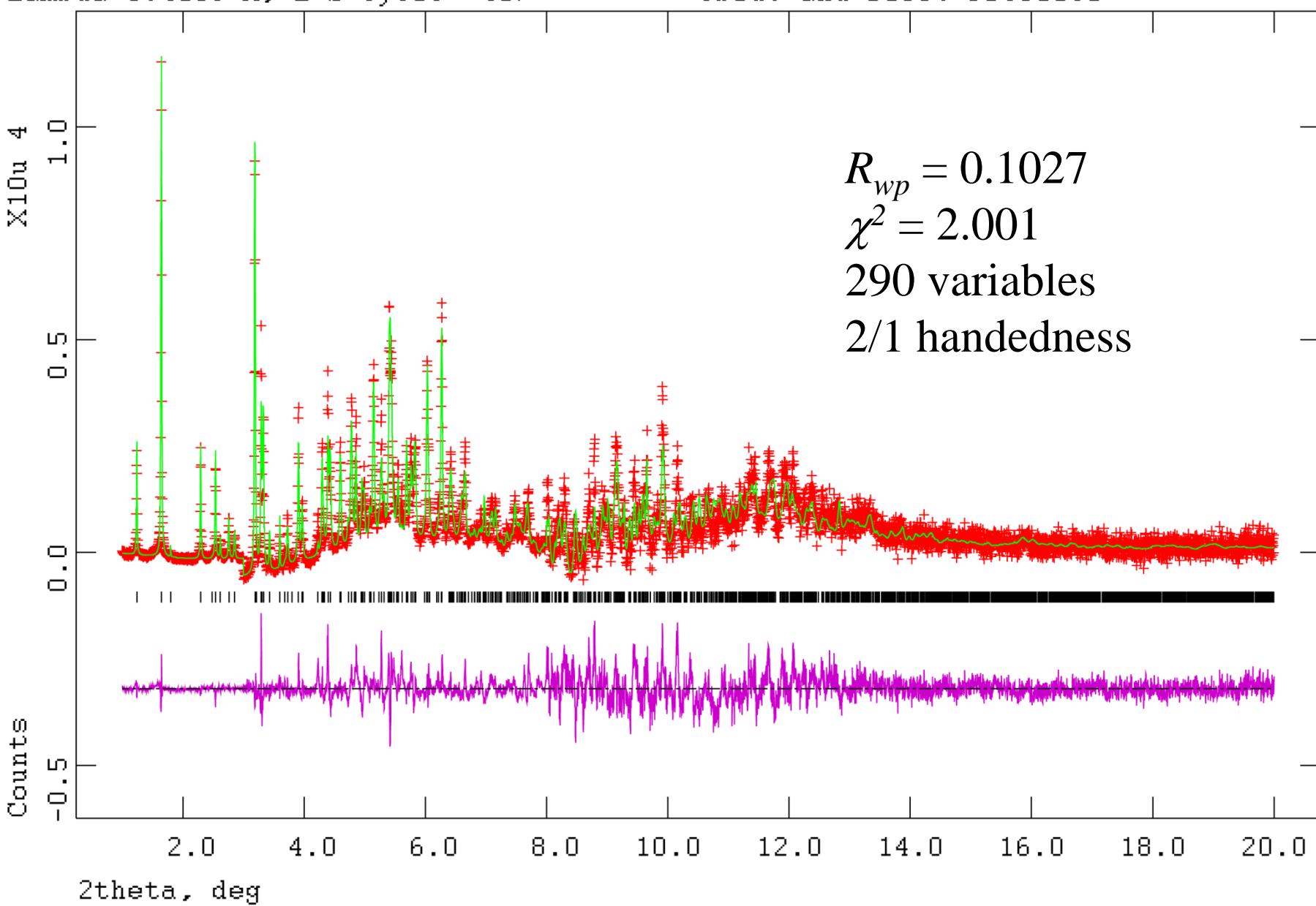


[11bmb_8602.cif] APS11BM|/data/jun13/11bmb_8602.mda|2013-07-10T11:32:50

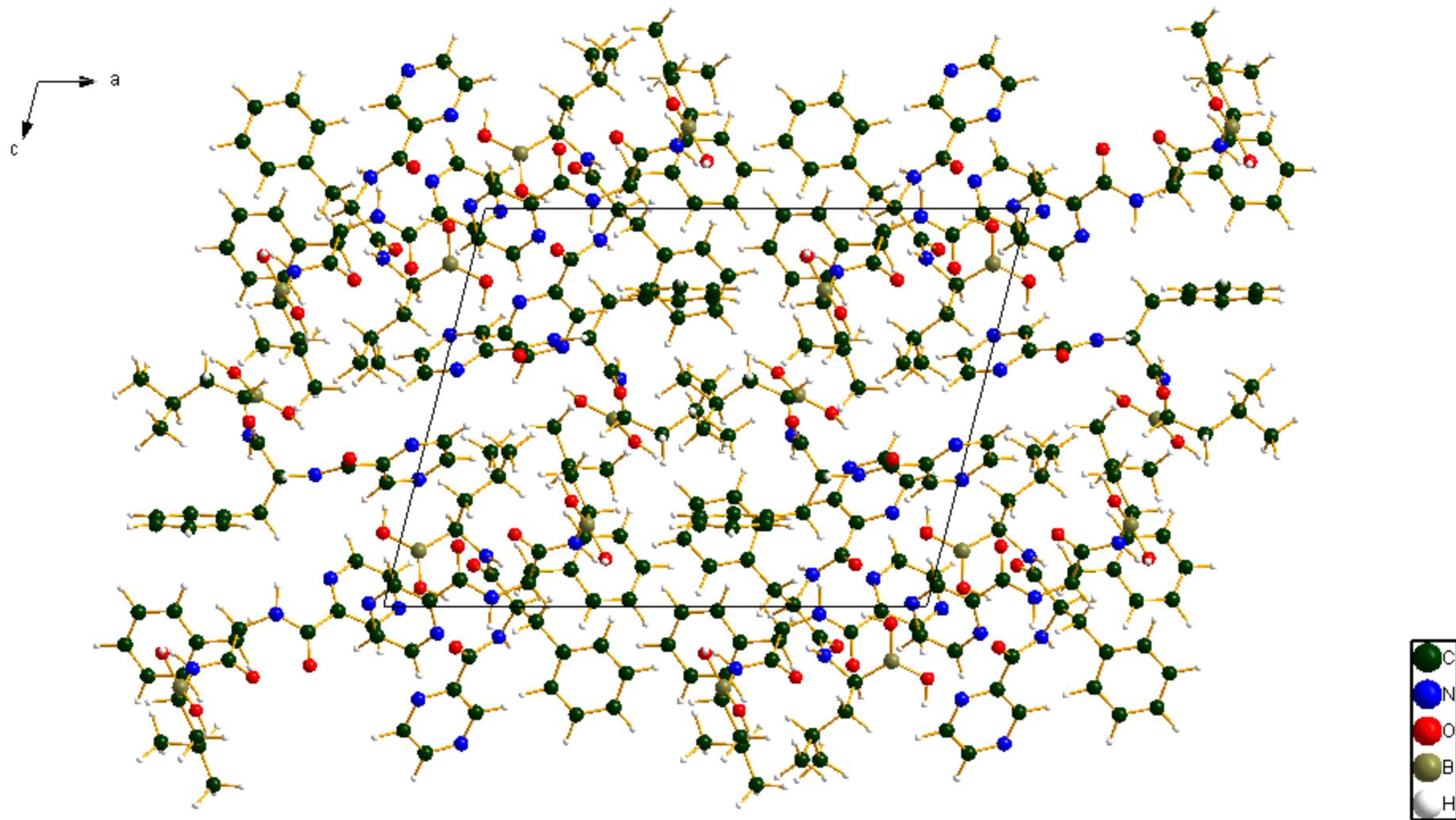


Lambda 0.4139 Å, L-S cycle 417

Obsd. and Diff. Profiles



Bortezomib, C₁₉H₂₅BN₄O₄

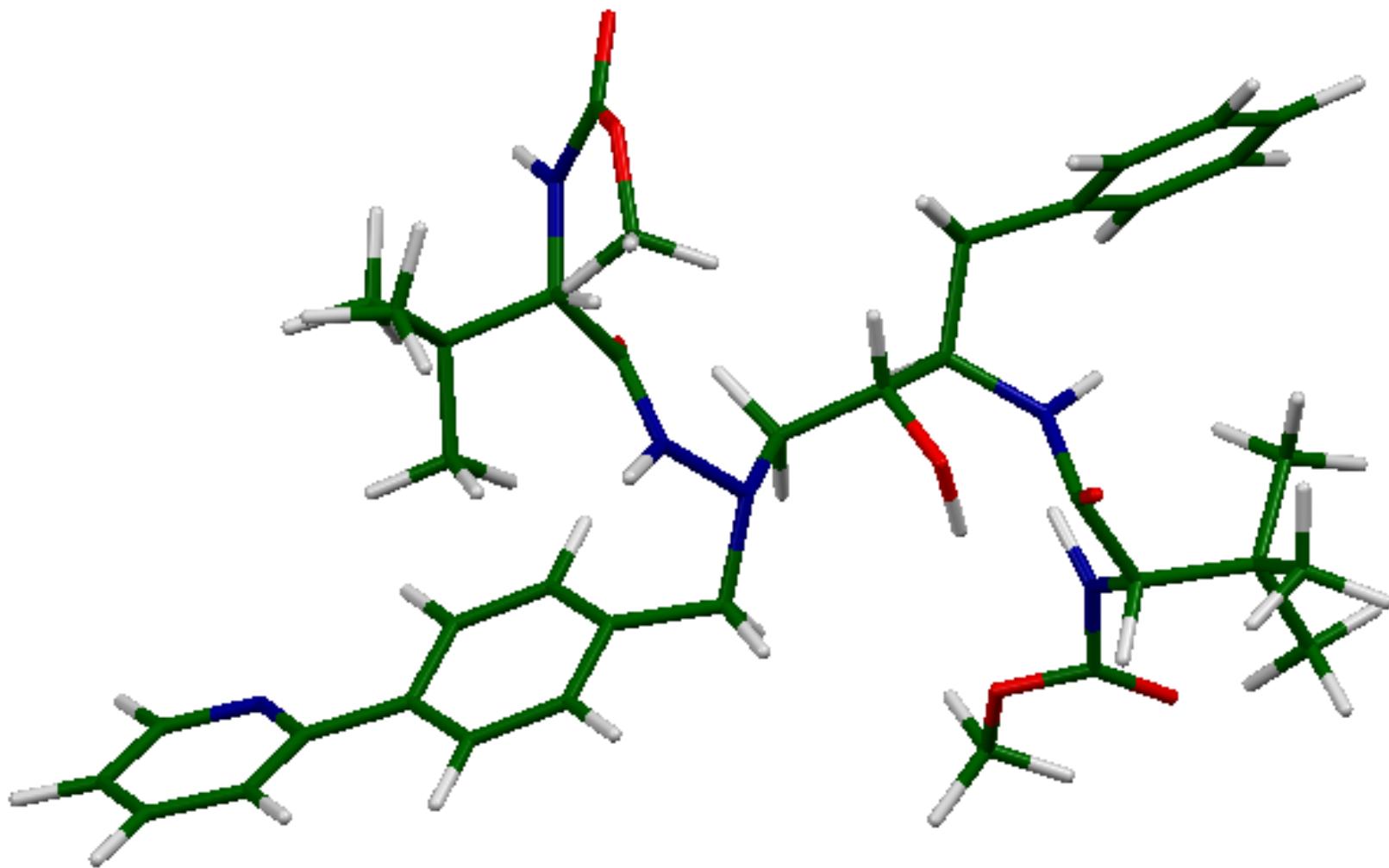


“Atazanavir Sulfate”
 $C_{38}H_{53}N_6O_7(HSO_4)$

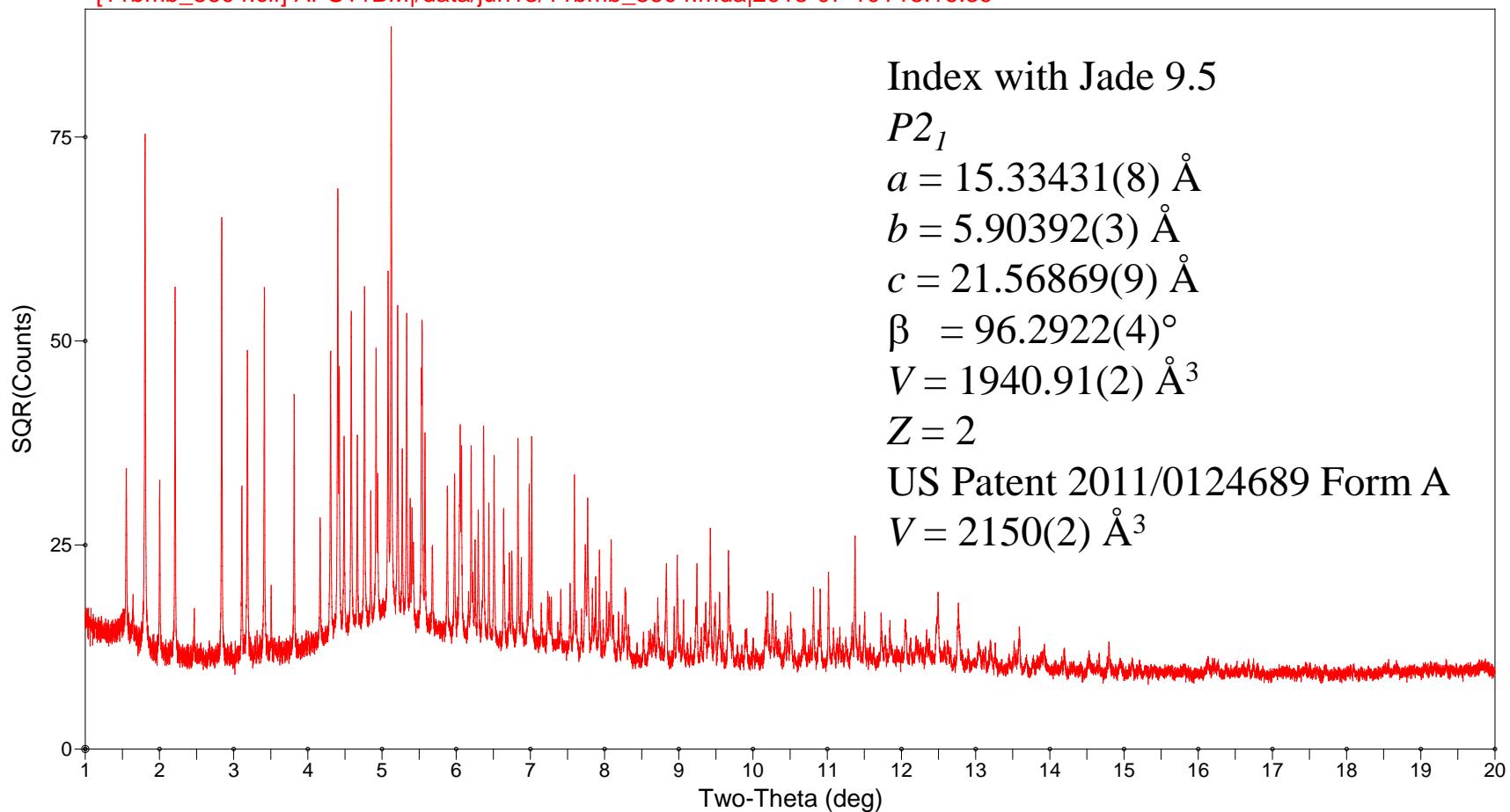
Reyataz®

HIV

Atazanavir, C₃₈H₅₂N₆O₇



[11bmb_8604.cif] APS11BM|/data/jun13/11bmb_8604.mda|2013-07-10T13:16:39

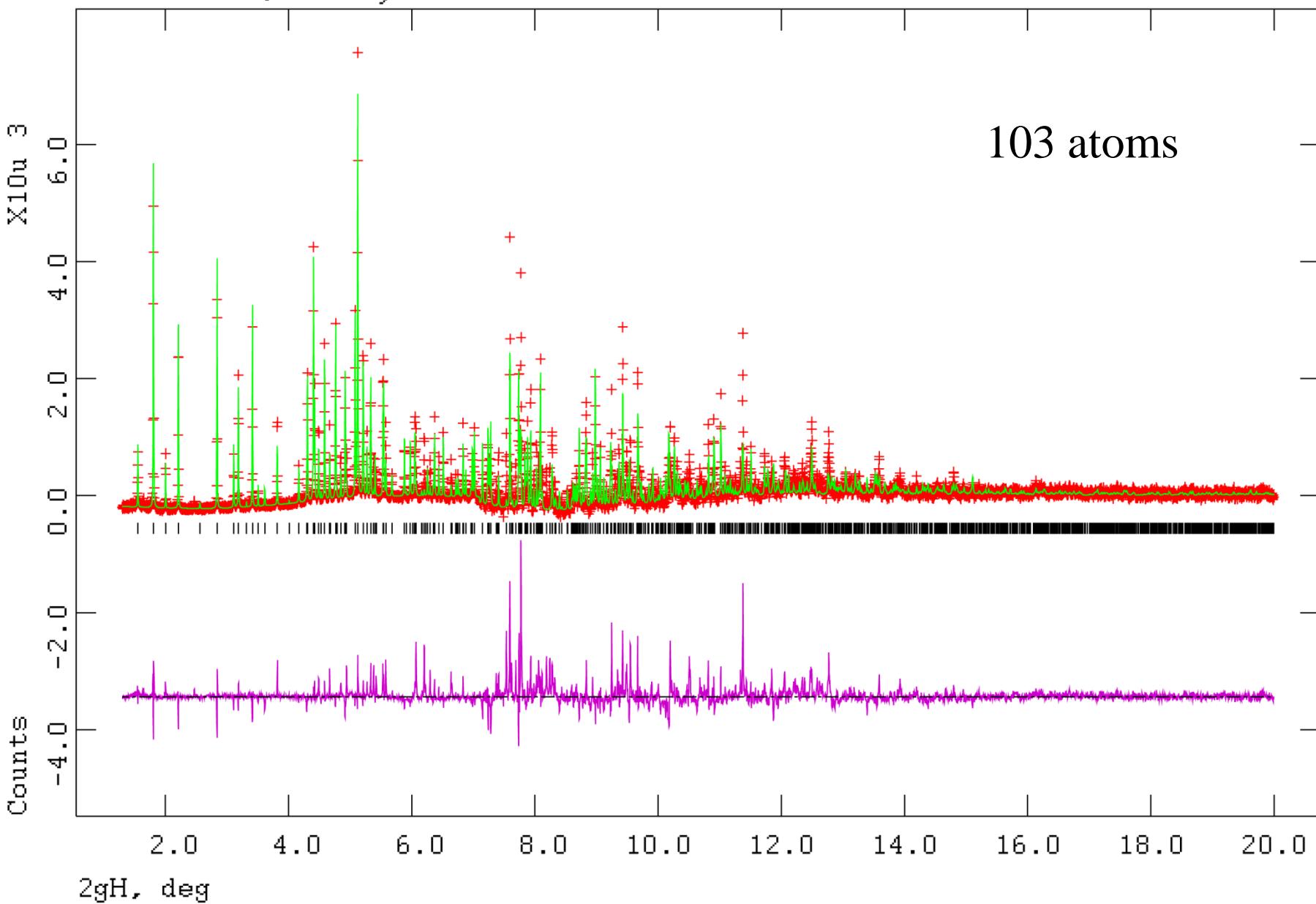


Atazanavir, C38 H52 N6 O7 (11bmb_8604)

Hist 1

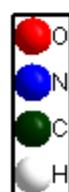
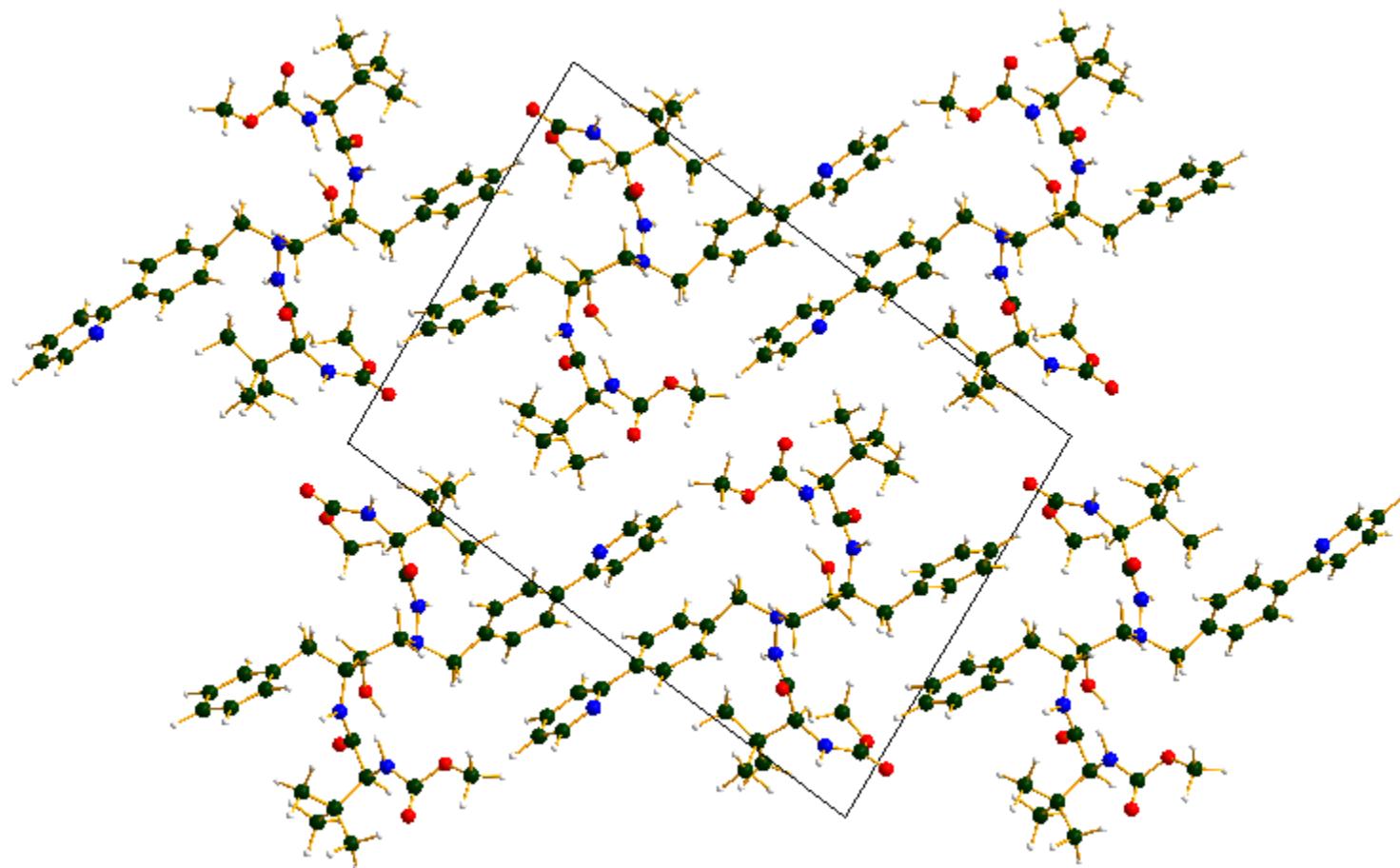
Lambda 0.4139 Å, L-S cycle 265

Obsd. and Diff. Profiles

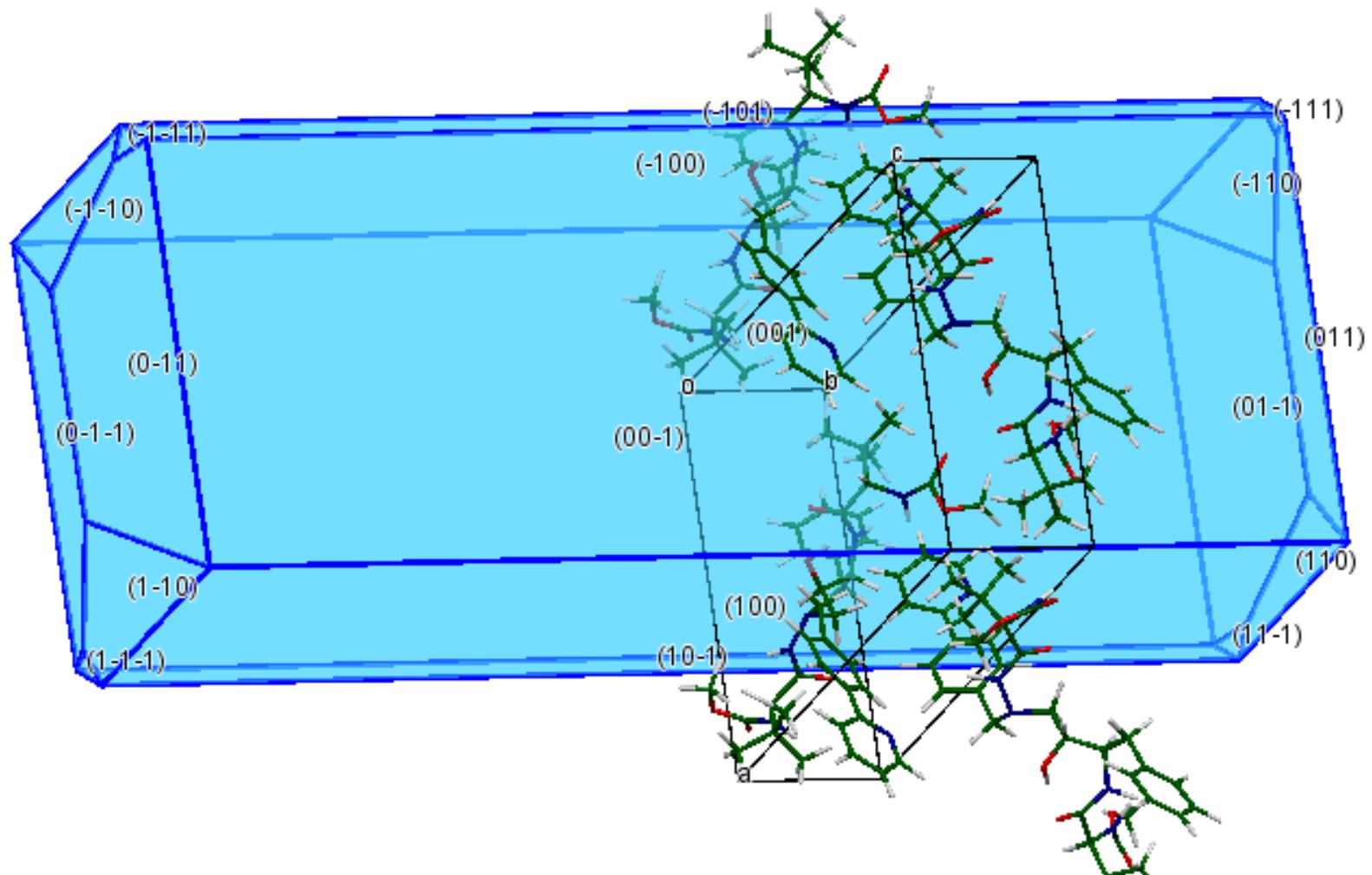


Scaling: 7.1(5.0X)

Atazanavir (free base)



BFDH Morphology of Atazanavir



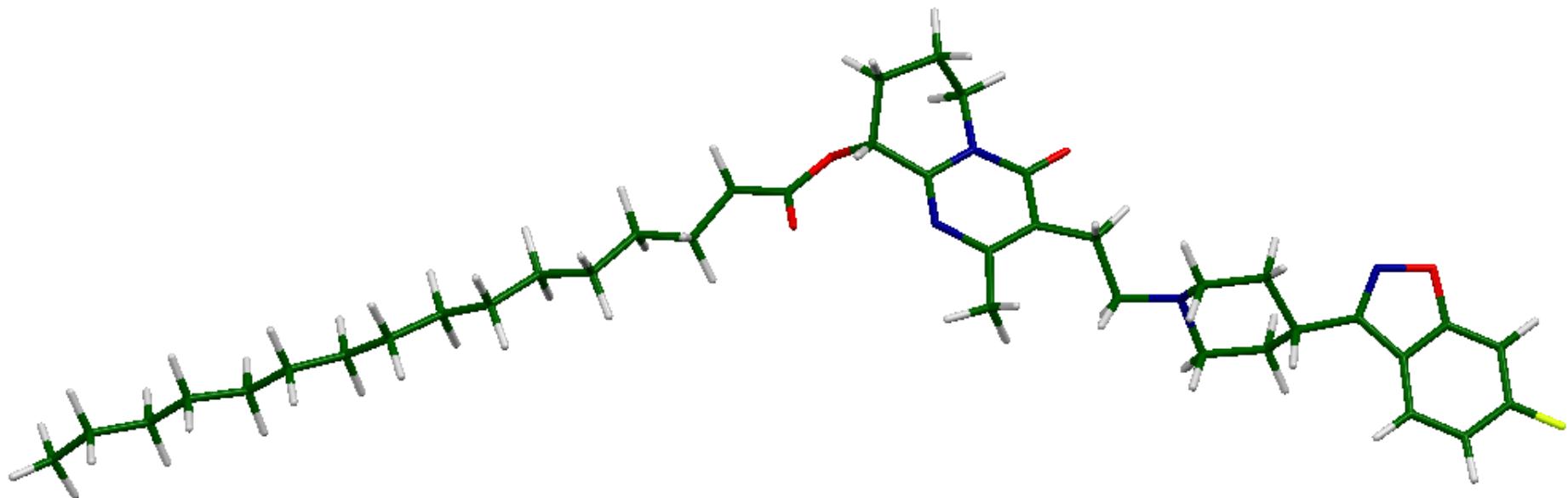
Paliperidone Palmitate

C₃₉H₅₇FN₄O₄

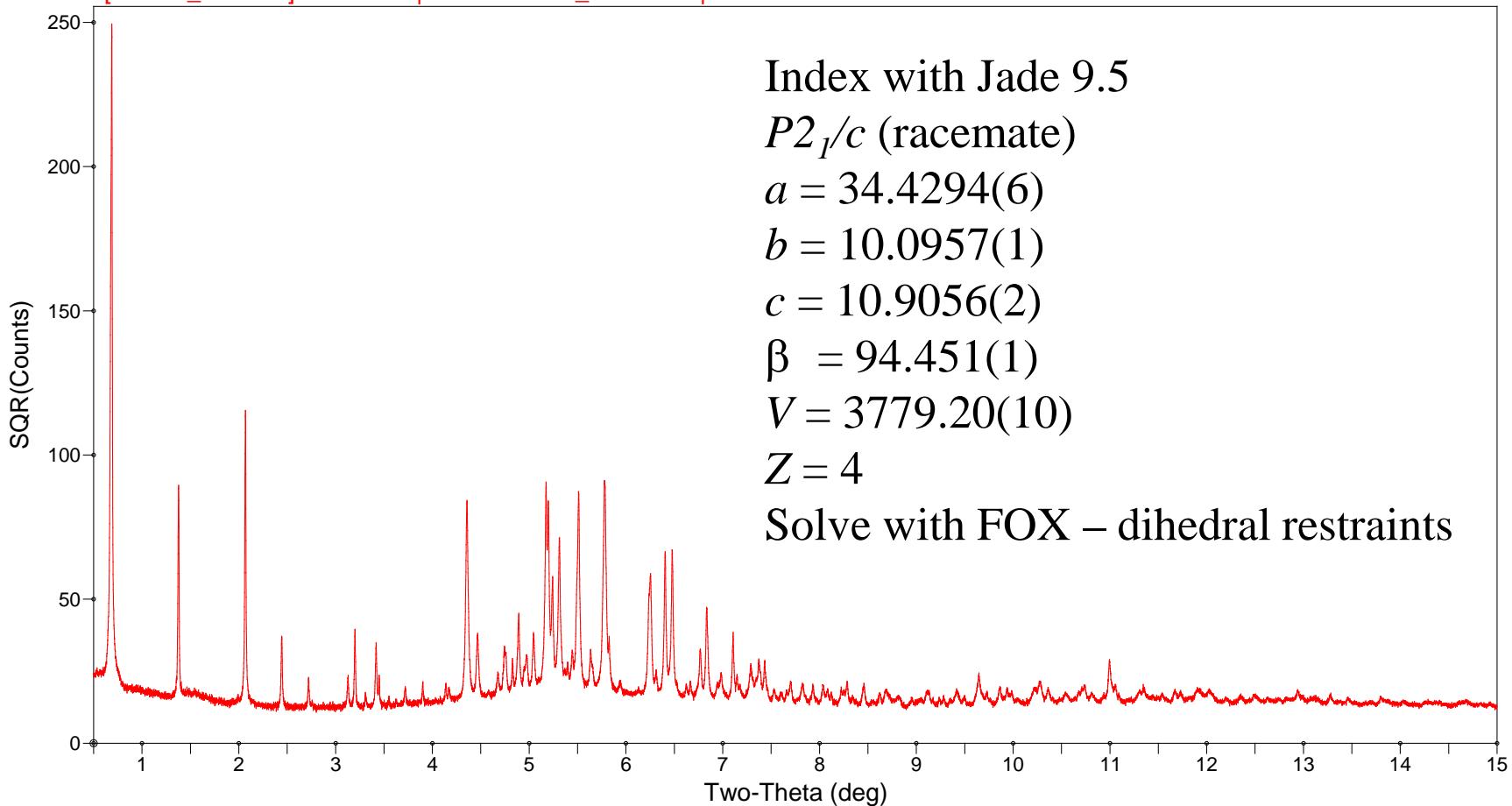
Invega® Sustenna®

antipsychotic

Paliperidone Palmitate



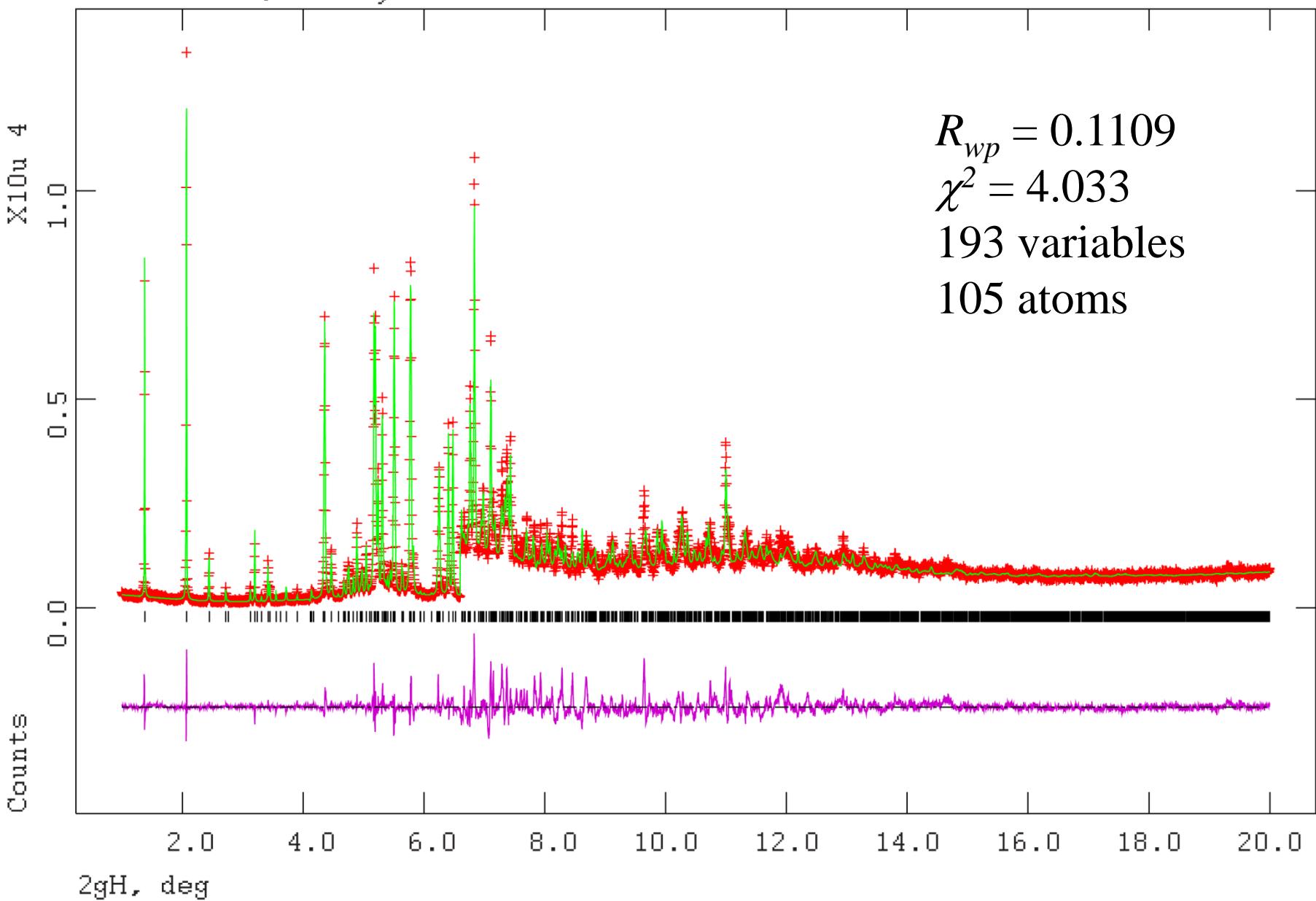
[11bmb_0176.cif] APS11BM|mar15/11bmb_0176.mda|2015-03-14T00:08:17



Paliperidone palmitate, C39 H57 F N4 O4 (11bmb_0176) Hist 1

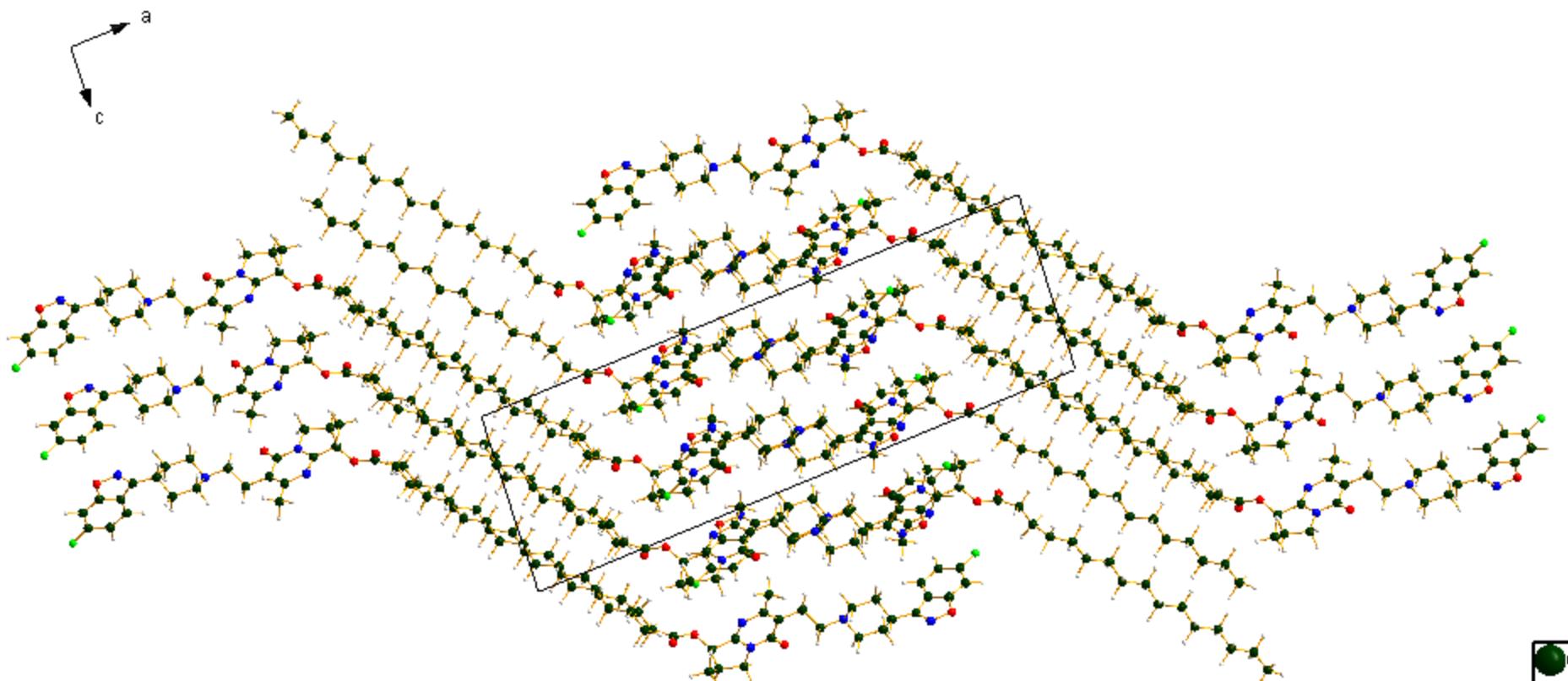
Lambda 0.4133 Å, L-S cycle 533

Obsd. and Diff. Profiles



Scaling: 6.6(5.0X)

Paliperidone Palmitate

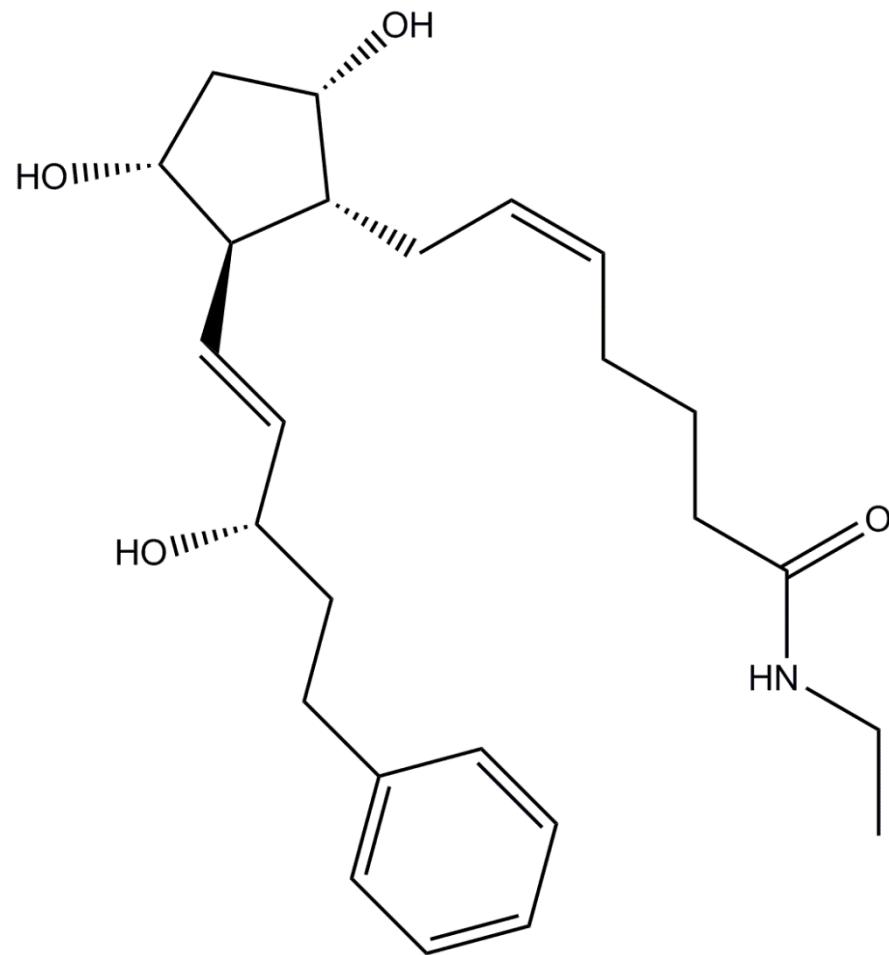


C
F
O
N
H

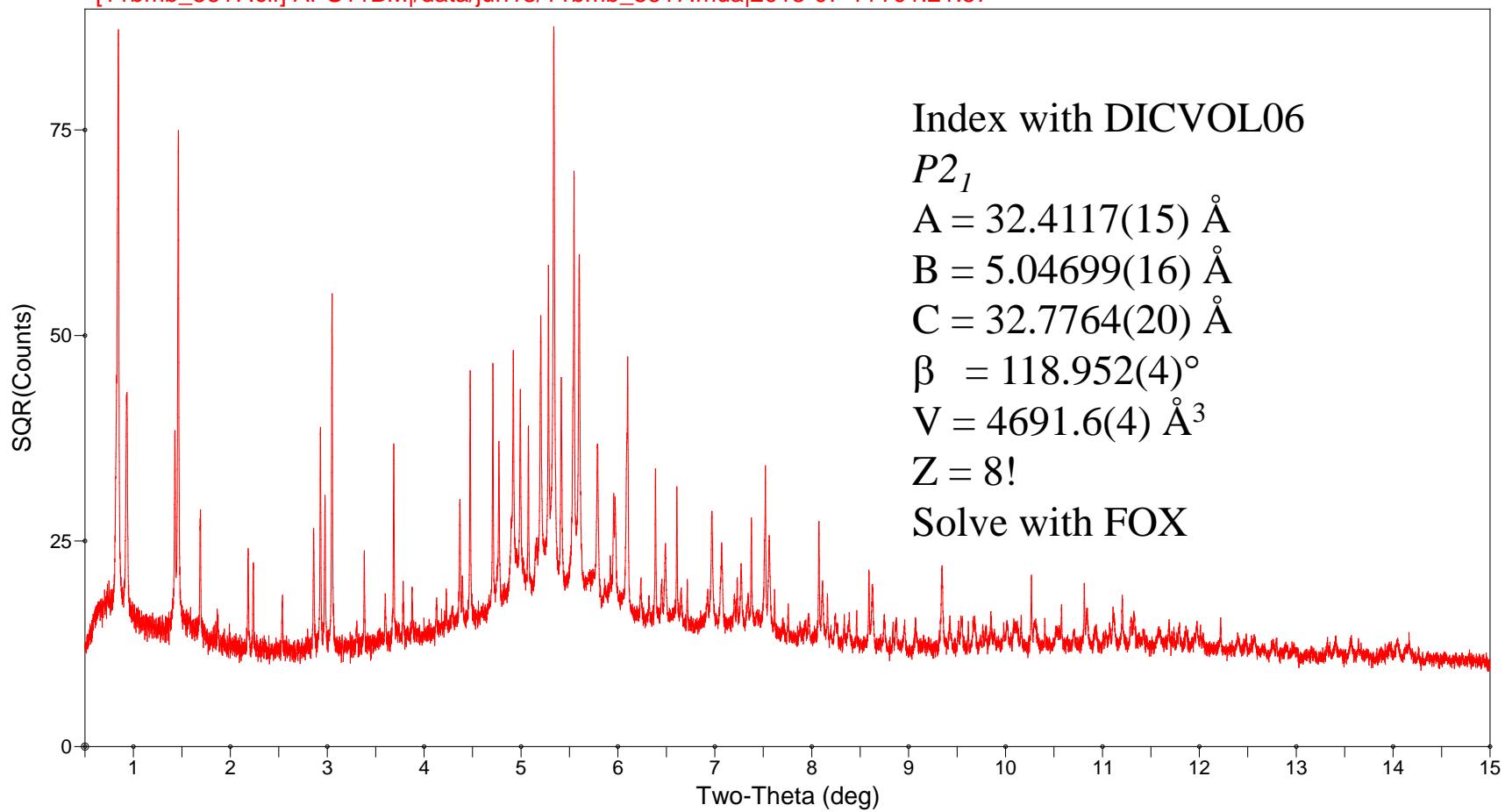
Bimatoprost
 $C_{25}H_{37}NO_4$

Lumigan – glaucoma
Latisse – lengthen eyelashes

Bimatoprost



[11bmb_8617.cif] APS11BM|/data/jun13/11bmb_8617.mda|2013-07-11T01:21:57

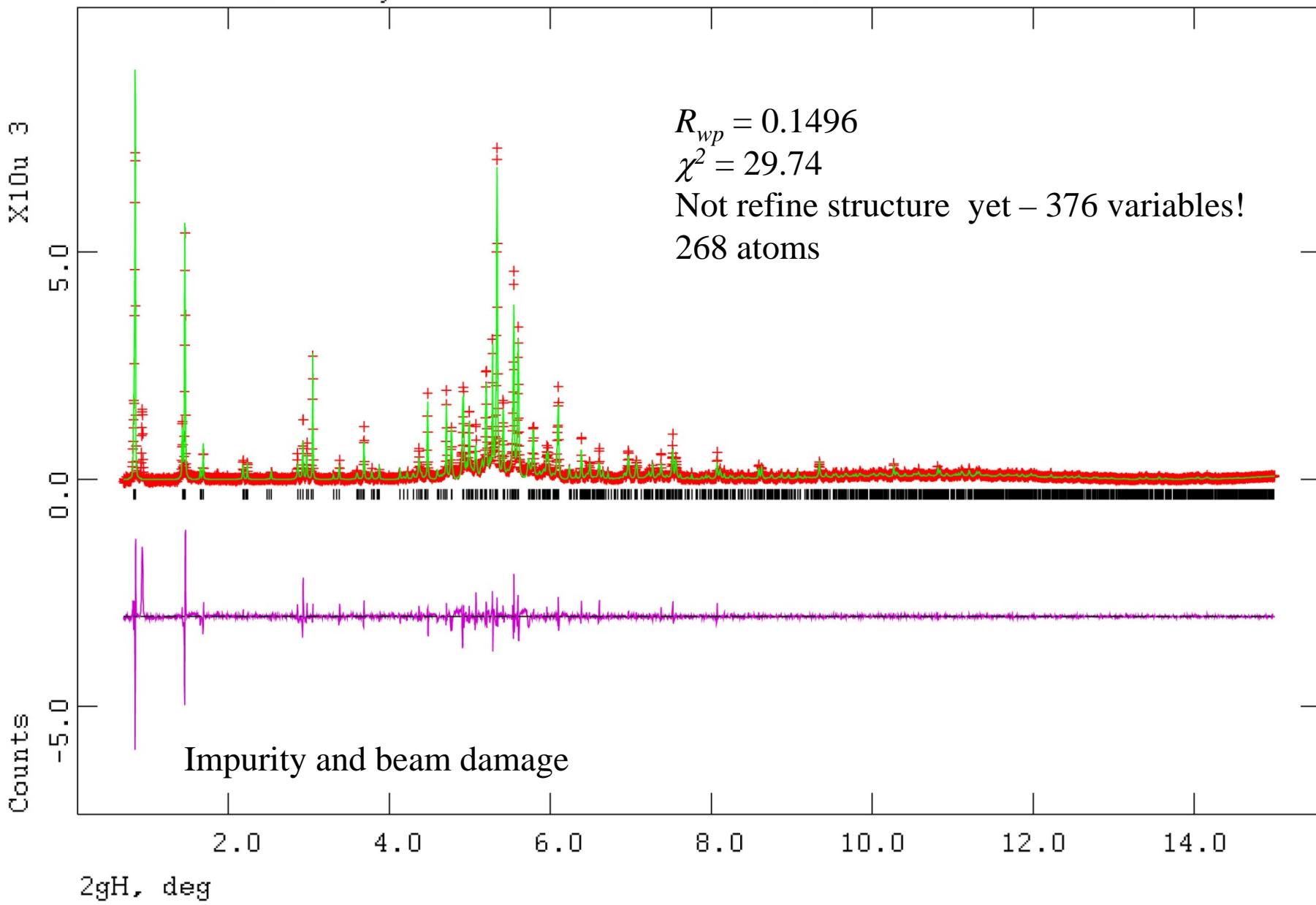


Bimatoprost, C₂₅ H₃₇ N₀₄, 11bmb_8617

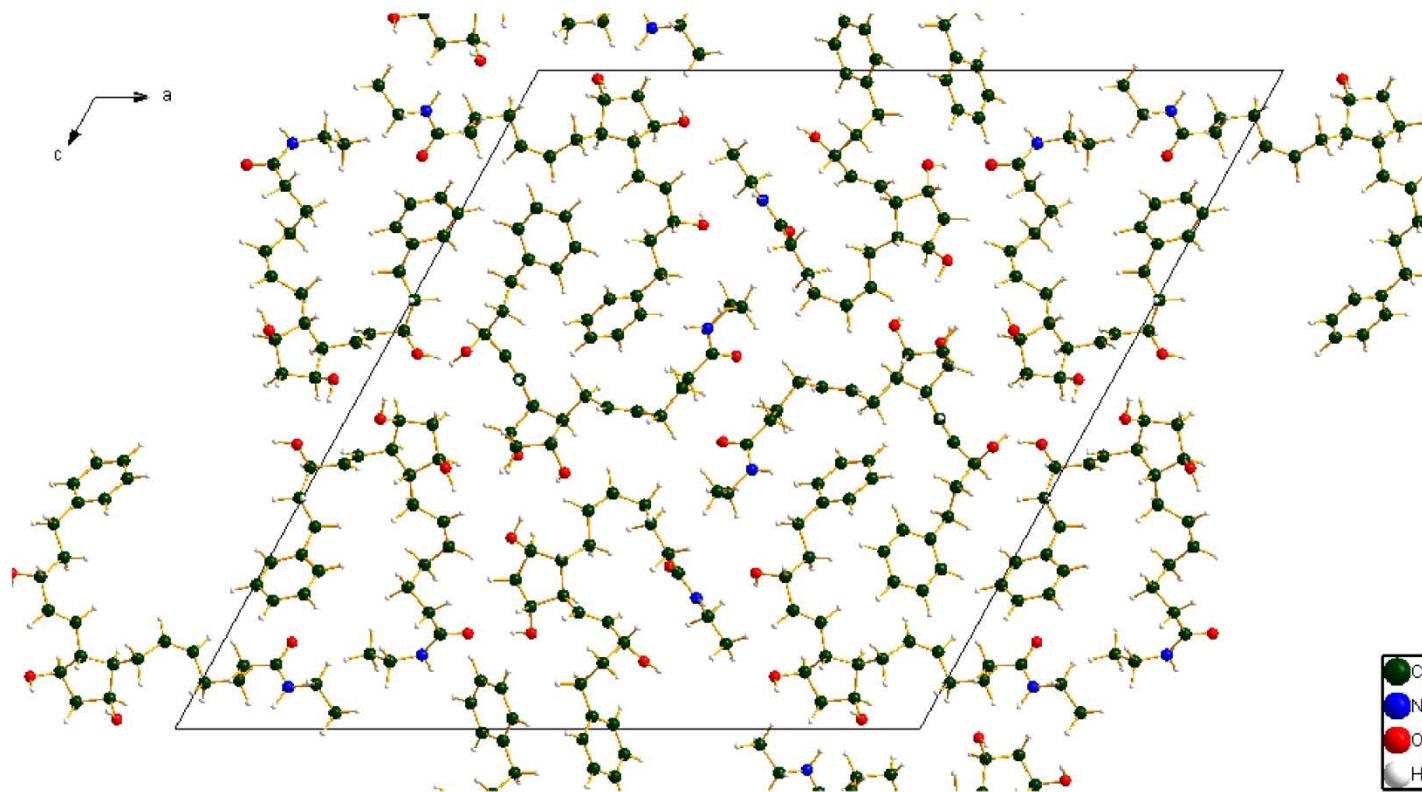
Hist 1

Lambda 0.4139 Å, L-S cycle 216

Obsd. and Diff. Profiles



Bimatoprost



Hydrogen Bonds in Bimatoprost

H-Bond	D-H, Å	H···A, Å	D···A, Å	D-H···A, °	Overlap, e
N160-H198···O97			3.193		
O28-H65···O29			3.170		
O29-H66···O28					
O30-H67···O231			3.187		
O231-H268···O30					