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The Crystal Structure of Trandolapril, $C_{24}H_{34}N_2O_5$: An Example of the Utility of Raw Data Deposition in the Powder Diffraction File

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Abstract

The crystal structure of trandolapril has been solved by parallel tempering using the FOX software package with laboratory powder diffraction data submitted to and published in the Powder Diffraction File. Rietveld refinement was performed with the software package GSAS yielding orthorhombic lattice parameters of a = 19.7685(4) Å, b = 15.0697(4) Å and c = 7.6704(2) Å ($C_{24}H_{34}N_2O_5$, Z = 4, space group $P2_12_12_1$). The Rietveld refinement results were compared with density functional theory (DFT) calculations performed with CRYSTAL14. While the structures are similar, discrepancies are observed in the configuration of the octahydroindole ring between the Rietveld and DFT structures, suggesting the refined and calculated molecules are diastereomers.

Keywords: trandolapril, powder diffraction, structure solution, density functional theory

I. INTRODUCTION

Trandolapril is a common angiotensin converting enzyme (ACE) inhibitor used to treat hypertension or high blood pressure (Wiseman and McTavish, 1994; Guay, 2003), either by itself or in combination with verapamil (Reynolds *et al*., 2005). The systematic name is (2S,3aR,7aS)-1-[(2S)-2-[[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2-carboxylic acid, and the 2D molecular structure is given in Figure 1. Despite widespread usage for over 20 years (Wiseman and McTavish, 1994), to the best of our knowledge the crystal structure of trandolapril has not been published in the open literature.

While the International Centre for Diffraction Data (ICDD) has collected raw powder diffraction data for many years, submitted both by Grant-in-Aid recipients and private contributors, in the 2008 release of Powder Diffraction File PDF-4 products the ICDD began publishing raw data as part of both new and legacy PDF entries. The powder diffraction data used here for the solution of the crystal structure of trandolapril was part of set of high quality pharmaceutical patterns submitted to the PDF by Martin Vickers of the Department of Chemistry at University College London (UCL). This work illustrates one of the advantages of including raw data in the PDF, the potential for collaborative work within the powder diffraction community to solve new structures. Raw powder diffraction data also provides significantly improved illustration of materials with anisotropic broadening features or poor crystallinity such as clays, polymers and amorphous materials.

II. EXPERIMENTAL

Laboratory PXRD data was obtained at University College London (UCL) using a Stoe StadiP diffractometer in transmission mode. The diffractometer was equipped with a copper anode operated at 40 kV and 30 mA, and an incident beam germanium monochromator (λ = 1.54059 Å). The sample was mounted in a 0.6 mm diameter glass capillary and using a 6° linear position sensitive detector, data was collected between 2 and 40° 2θ in 0.2° steps, re-binned to give a data-step of 0.02°. The raw data was published on-line (Vickers, 2008) and in the PDF (ICDD, 2013) as part of PDF entry 00-060-1211.

Pattern indexing with DICVOL06 (Boultif and Louer, 2004) suggested an orthorhombic unit cell with lattice parameters a = 19.7145 Å, b = 15.0499 Å, c = 7.6534 Å and a cell volume of 2270.8 Å^3 (M_{20} = 33.1, F_{20} = 93.9), in strong agreement with the initial assessment made at UCL (Vickers, 2008) and tabulated in the PDF entry. Space group determination with ChekCell (Laugier and Bochu, 2000) suggested space group $P2_12_12_1$ as the most plausible option (space group $Pmn2_1$ was also identified based on the observed reflections, but is incompatible with chiral molecules).

A trandolapril molecule was created using fragments of the Cambridge Structural Database (CSD, Allen, 2002) entries SIWCAC (Hausin and Codding, 1991) and FEFKEI (Bojarska *et al*., 2012), as illustrated in Figure 1. The molecule was prepared from the fragments using the molecular modeling software Avogadro (Hanwell *et al*., 2012). The molecule was converted to a Fenske-Hall Z-matrix with Open Babel (O'Boyle *et al*., 2011) and used to solve the structure with FOX (Favre-Nicolin and Černý, 2002), using 24 sets of parallel tempering

with 2×10^6 trials/set. These sets yielded two solutions with cost functions of ~20,000 that were significantly lower than the other sets.

Initial refinement was performed using the Le Bail method with the program FullProf (Rodriguez-Carvajal, 2001) in order to determine the profile parameters, given the absence of an initial instrumental parameter file. The final profile parameters determined with FullProf were converted to their GSAS equivalents (Kaduk and Reid, 2011) for the Rietveld refinement.

Rietveld refinement of the crystal structure was performed with the GSAS/EXPGUI program (Larson and Von Dreele, 2004; Toby, 2001). Restraints on the bonds, angles and planar restraints on the phenyl ring were applied using values determined by the Mogul 1.7 module of the CSD (Bruno *et al.*, 2004). The background was refined using a Chebyshev polynomial with 14 terms. The positions of the C, N and O atoms were refined, while the positions of the H atoms remained fixed but were periodically optimized using Avogadro. An overall isotropic displacement parameter was refined for the C, N and O atoms, with the H atoms constrained to 1.3 times this value. A fourth order spherical harmonic correction (Von Dreele, 1997) was used to model preferred orientation, which yielded a small texture index (1.023).

The crystal data, data collection and refinement details are summarized in Table I.

A density functional geometry optimization (using fixed experimental unit cell) was carried out using CRYSTAL14 (Dovesi *et al*., 2014). The basis sets for the H, C, N and O atoms were those of Gatti *et al*. (1994). The calculation was run on eight 2.1 GHz Xeon cores (each

with 6 Gb RAM) of a 304-core Dell Linux cluster at the Illinois Institute of Technology (IIT), used 8 k-points and the B3LYP functional, and took approximately 7 days.

III. RESULTS & DISCUSSION

The final Rietveld refinement obtained for trandolapril is illustrated in Figure 2, while the refined atomic coordinates and DFT optimized coordinates are presented in Tables II and III respectively. The atomic labeling used for both models is illustrated in Figure 3. The root-mean-square (RMS) difference between the Rietveld and DFT coordinates for the non-hydrogen atoms is 0.332 Å, which is towards the upper end of the range expected for correct powder structures from laboratory PXRD data (Van de Streek and Neumann, 2014). The DFT optimized and Rietveld refined structures are overlaid for comparison in Figure 4. The largest source of discrepancy in the heavy atoms relates to atoms C15, C18 and C19, which suggest different configurations of the octahydroindole ring, with the two molecules being diastereomers. The H53 (C18) and H56 (C20) atoms exhibit a *syn* configuration in the DFT calculated molecule and an *anti* configuration in the Rietveld refined molecule. To confirm the refinement results were consistent independent of the starting model, separate Rietveld refinements were performed starting with both the model obtained from FOX and the DFT solution. The Rietveld refinements obtained from both starting models yielded identical results.

The discrepancy between the DFT and Rietveld results may be due to the relatively low amount of powder data, with an upper 2θ limit of 40°. The pattern contains 144 reflections, and after accounting for reflection overlap (Altomare *et al.*, 1995), the effective number of

reflections varies between 123.8 (optimistic estimate) and 80.5 (pessimistic estimate). Using either estimate, the model is significantly underdetermined, emphasizing the importance of the restraints in the refinement and the use of DFT modeling for comparison. Given the low observation-to-parameter ratio, it is possible that the DFT model is more accurate than the Rietveld refined model. However, it has been observed by crystal energy landscape calculations (Price, 2009; Price, 2008) that many thermodynamically plausible structures can fall within a narrow energy band of possible polymorphs (a few kJ/mol), including numerous structures which are not observed experimentally. Different plausible structures are a trade-off between factors including hydrogen bonding and close packing. Observed polymorphs are often metastable local energy minima that do not necessarily correspond to the most thermodynamically stable structure, due to kinetic barriers associated with crystal nucleation or growth.

The Rietveld refined structure is illustrated in Figure 5. Visually, the Rietveld fit looks excellent (Figure 2) with slight residuals in the difference plot due to the strong reflection asymmetry observed at low angles. Examination of the Rietveld refined structure with Mogul yields three angles which are unusual (z-scores greater than 3) including two angles through atom C18 (C15-C18-C19 and C15-C18-C20 with z-scores of 4.04 and 3.03 respectively). One angle is highlighted in the DFT structure (C20-N23-C24, z-score of 3.88).

The DFT results suggest minimal hydrogen bonding, tabulated in Table IV, with one prominent intermolecular bond, N28-H62···O29. The hydrogen bonds through H41 and H61 are both intramolecular. It is possible that the carboxyl group (O27) is deprotonated, yielding an additional hydrogen at N28. Zwitterionic behaviour is well documented with amino acids (Tilborg *et al.*, 2014; Sarkar and Nahar, 2007) and observed in both pharmaceuticals and

drug delivery moieties (Kostic *at al.*, 2014; Jin *et al.*, 2014). Deprotonating the carboxyl group (removing H61) and adding a second H atom at N28 yields a refinement which quickly converges with a comparable fit to the tabulated data (reduced χ^2 of 2.71).

In order to test whether more complete data would change the refined structure, a second data set was collected on the same diffractometer with an expanded 2θ range of 5 to 60° using an 18° Dectris® Mythen 1K detector (data not shown). The structure was refined using the same strategy and restraints as the initial refinement, yielding a final R_{wp} value of 0.0328. The RMS difference between the coordinates of the non-hydrogen atoms for the two experimental refinements was less than 0.05 Å, suggesting only marginal change in the experimental structure with more complete data. Crystallographic information files (CIF) for the Rietveld refinements of both experimental data sets and the DFT optimized structure are included in the supplementary material.

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TABLES

Table I. The crystal data, data collection and refinement parameters obtained for trandolapril.

Crystal Data	
Formula, Z	$C_{24}H_{34}N_2O_5$, $Z = 4$
Molecular mass (M_r)	430.545 g/mol
Symmetry, space group	Orthorhombic, $P2_12_12_1$
Unit cell parameters	a = 19.7685(4) Å, b = 15.0697(4) Å, c = 7.6704(2) Å
Volume	2285.0 (1) Å^3
Density (ρ_{calc})	1.251 g/cm^3
Data Collection	
Diffractometer	Stoe StadiP (40 kV, 30 mA), germanium monochromator
Specimen mounting	0.6 mm capillary
Collection mode	Transmission
Anode, wavelength	Cu $K\alpha1$, λ = 1.54059 Å
Collection range, step size	2° to 40° (2θ), 0.02°/step
Refinement	
Number of data points	1900
Distance restraints	33 (weight factor 25)
Angle restraints	44 (weight factor 25)
Planar restraints	1 (weight factor 50)
Background correction	14-term Chebyshev polynomial
Number of refined parameters	121
R_p	0.0184
R_{wp}	0.0236
R_{exp}	0.0157
χ^2	2.75

Table II. The refined crystal structure of trandolapril with lattice parameters a = 19.7685(4) Å, b = 15.0697(4) Å, and c = 7.6704(2) Å.

Atom	*x/a*	*y/b*	*z/c*	U_{iso} (Å^2)
C1	0.2159(5)	0.6687(6)	0.5952(15)	0.0335(23)
C2	0.1463(4)	0.7061(7)	0.5618(18)	0.0335(23)
O3	0.1344(4)	0.7727(7)	0.4797(14)	0.0335(23)
O4	0.0991(5)	0.6628(7)	0.6459(15)	0.0335(23)
C5	0.0294(6)	0.6934(9)	0.6149(19)	0.0335(23)
C6	-0.0161(7)	0.6372(12)	0.7185(19)	0.0335(23)
C7	0.2433(9)	0.7066(8)	0.7658(15)	0.0335(23)
C8	0.2508(9)	0.8059(8)	0.7654(15)	0.0335(23)
C9	0.2750(6)	0.8460(8)	0.9358(14)	0.0335(23)
C10	0.2367(6)	0.8365(9)	1.0859(18)	0.0335(23)
C11	0.2524(8)	0.8839(11)	1.2357(12)	0.0335(23)
C12	0.3025(8)	0.9471(10)	1.2324(14)	0.0335(23)
C13	0.3388(7)	0.9606(8)	1.0812(18)	0.0335(23)
C14	0.3253(7)	0.9102(10)	0.9347(13)	0.0335(23)
C15	0.5608(5)	0.5398(9)	0.8908(19)	0.0335(23)
C16	0.5621(6)	0.6197(11)	1.0143(13)	0.0335(23)
C17	0.5359(7)	0.7042(8)	0.9295(18)	0.0335(23)
C18	0.4914(5)	0.5309(6)	0.8081(14)	0.0335(23)
C19	0.4706(6)	0.4611(7)	0.6756(18)	0.0335(23)
C20	0.4740(4)	0.6152(6)	0.7136(11)	0.0335(23)
C21	0.4687(6)	0.6919(7)	0.8381(17)	0.0335(23)
C22	0.4021(4)	0.4974(6)	0.6079(12)	0.0335(23)
N23	0.4103(4)	0.5944(6)	0.6236(12)	0.0335(23)
C24	0.3738(6)	0.6527(5)	0.5277(16)	0.0335(23)
C25	0.3138(4)	0.6186(5)	0.4238(11)	0.0335(23)
C26	0.3469(10)	0.4535(5)	0.7190(25)	0.0335(23)
O27	0.3171(5)	0.5069(6)	0.8256(17)	0.0335(23)
N28	0.2561(6)	0.6795(8)	0.4361(14)	0.0335(23)
O29	0.3324(6)	0.3748(6)	0.7099(16)	0.0335(23)
O30	0.3844(5)	0.7324(5)	0.5327(14)	0.0335(23)
C31	0.3358(7)	0.6113(10)	0.2352(15)	0.0335(23)
H32	0.21682	0.59837	0.62499	0.0436(30)
H33	0.01662	0.68628	0.47591	0.0436(30)
H34	0.02572	0.76146	0.64516	0.0436(30)
H35	-0.01058	0.57061	0.68101	0.0436(30)

H36	-0.06654	0.65993	0.69813	0.0436(30)
H37	-0.00223	0.64637	0.85211	0.0436(30)
H38	0.29166	0.67676	0.79582	0.0436(30)
H39	0.20764	0.69136	0.87065	0.0436(30)
H40	0.20418	0.83428	0.72892	0.0436(30)
H41	0.29105	0.81862	0.67155	0.0436(30)
H42	0.19825	0.7905	1.08536	0.0436(30)
H43	0.22484	0.87242	1.34679	0.0436(30)
H44	0.3123	0.98385	1.34253	0.0436(30)
H45	0.3759	1.00911	1.07849	0.0436(30)
H46	0.3544	0.91993	0.82328	0.0436(30)
H47	0.59836	0.5495	0.79702	0.0436(30)
H48	0.57205	0.48196	0.96945	0.0436(30)
H49	0.61112	0.63144	1.06486	0.0436(30)
H50	0.52643	0.60743	1.12223	0.0436(30)
H51	0.53255	0.75707	1.02148	0.0436(30)
H52	0.57314	0.72141	0.82824	0.0436(30)
H53	0.46653	0.51093	0.92862	0.0436(30)
H54	0.5082	0.45808	0.57433	0.0436(30)
H55	0.46961	0.39558	0.72935	0.0436(30)
H56	0.51164	0.63519	0.62431	0.0436(30)
H57	0.43064	0.68103	0.93393	0.0436(30)
H58	0.45575	0.75195	0.76713	0.0436(30)
H59	0.38958	0.48048	0.47985	0.0436(30)
H60	0.30014	0.55377	0.47057	0.0436(30)
H61	0.32968	0.56799	0.82691	0.0436(30)
H62	0.22395	0.66411	0.33551	0.0436(30)
H63	0.34911	0.67691	0.1869	0.0436(30)
H64	0.29399	0.58763	0.15616	0.0436(30)
H65	0.37759	0.56844	0.21984	0.0436(30)

Table III. The DFT optimized crystal structure of trandolapril calculated with fixed lattice parameters a = 19.7695 Å, b = 15.0705 Å and c = 7.6706 Å.

Atom	*x/a*	*y/b*	*z/c*
C1	0.20541	0.66598	0.62176
C2	0.13594	0.70507	0.58108
O3	0.12587	0.76893	0.48756
O4	0.08598	0.66089	0.66337
C5	0.01823	0.69322	0.62486
C6	-0.03298	0.64430	0.73432
C7	0.23255	0.70700	0.79311
C8	0.24624	0.80686	0.77863
C9	0.26861	0.85211	0.94507
C10	0.24026	0.83126	1.10752
C11	0.25762	0.87872	1.25725
C12	0.30350	0.94878	1.24650
C13	0.33232	0.97036	1.08586
C14	0.31552	0.92180	0.93716
C15	0.52827	0.52460	0.91896
C16	0.56180	0.59995	1.02484
C17	0.54459	0.69255	0.95062
C18	0.52253	0.54994	0.72618
C19	0.48884	0.47957	0.61041
C20	0.47944	0.63463	0.69872
C21	0.47476	0.69224	0.86348
C22	0.41357	0.50637	0.59461
N23	0.41281	0.60205	0.63333
C24	0.36988	0.66241	0.55272
C25	0.30774	0.62520	0.45472
C26	0.36754	0.45367	0.71691
O27	0.34194	0.49859	0.85322
N28	0.24939	0.68286	0.47260
O29	0.35430	0.37600	0.69274
O30	0.38231	0.74198	0.55727
C31	0.32750	0.61915	0.26073
H32	0.19762	0.59441	0.64438
H33	0.00894	0.68343	0.48590
H34	0.01698	0.76451	0.65027
H35	-0.02779	0.57264	0.71897

H36	-0.08358	0.66283	0.69047
H37	-0.02846	0.66058	0.87236
H38	0.27941	0.67248	0.82886
H39	0.19622	0.69165	0.89655
H40	0.20005	0.83979	0.73239
H41	0.28396	0.81730	0.67661
H42	0.20374	0.77780	1.11851
H43	0.23497	0.86035	1.38063
H44	0.31611	0.98642	1.36246
H45	0.36721	1.02587	1.07607
H46	0.33730	0.93946	0.81183
H47	0.55769	0.46336	0.93075
H48	0.47786	0.50949	0.97136
H49	0.54564	0.59533	1.16142
H50	0.61677	0.59140	1.02432
H51	0.54776	0.74276	1.05274
H52	0.58212	0.71188	0.85270
H53	0.57362	0.56328	0.67805
H54	0.51100	0.48108	0.48043
H55	0.49445	0.41196	0.65975
H56	0.50251	0.67452	0.59614
H57	0.43665	0.66528	0.95348
H58	0.45753	0.75875	0.82832
H59	0.39563	0.49125	0.46331
H60	0.29635	0.55782	0.50265
H61	0.35825	0.55971	0.84270
H62	0.22121	0.67985	0.36211
H63	0.33657	0.68599	0.21057
H64	0.28640	0.58890	0.18619
H65	0.37308	0.57914	0.24126

Table IV. Hydrogen bonds observed in the trandolapril structure and their parameters as determined by the DFT modeling.

D-H···A	D-H, Å	H···A, Å	D···A, Å	D-H···A,°	Overlap, *e*
O27-H61···N23	0.979	2.038	2.691	122.3	0.040
N28-H62···O29	1.015	2.151	3.098	154.5	0.027
C8-H41···O30	1.092	2.430	3.328	138.5	0.015

Figure Captions

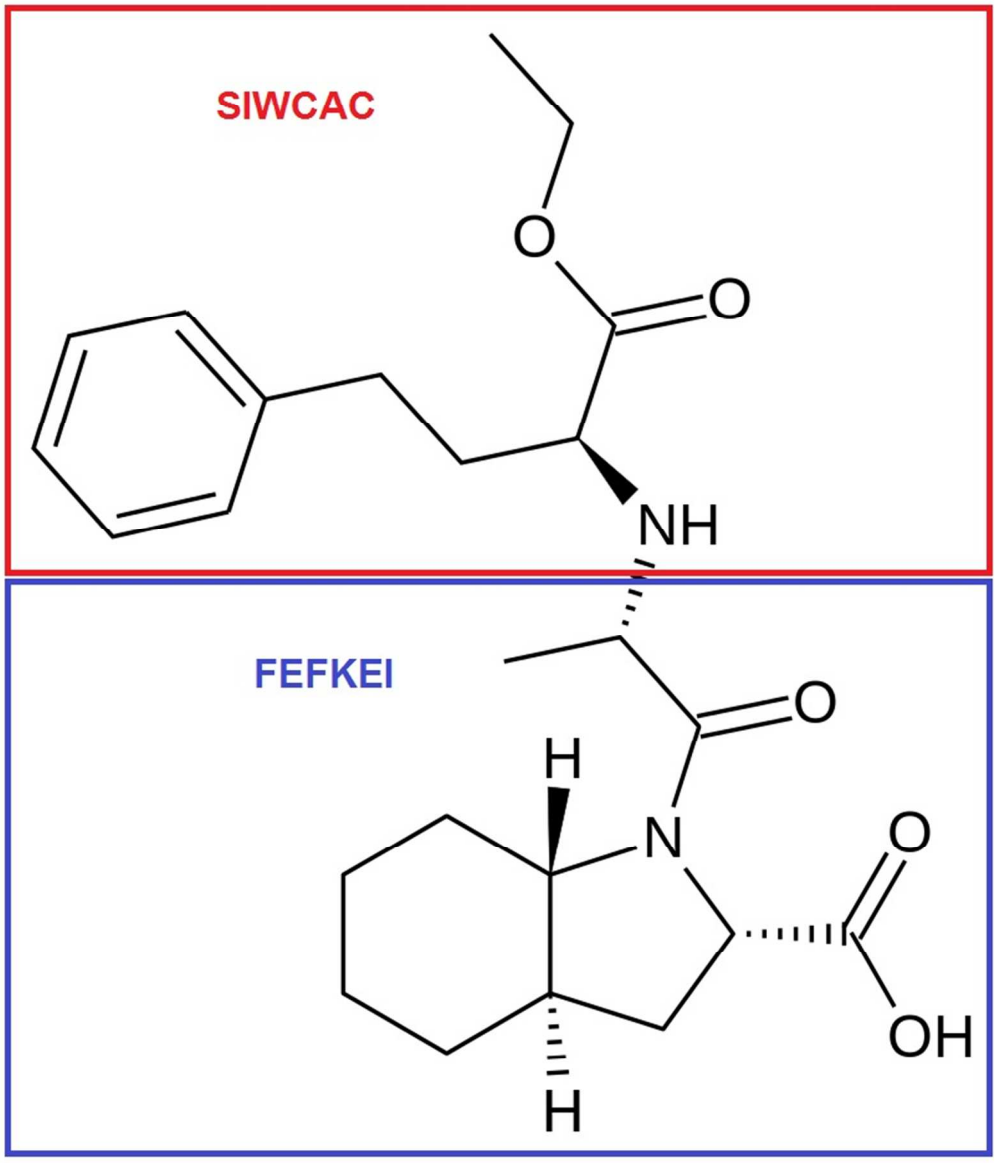
Figure 1. The 2D molecular structure of trandolapril, illustrating the fragments of the molecule prepared from edited portions of the CSD entries SIWCAC and FEFKEI.

Figure 2. A plot illustrating the final Rietveld refinement of trandolapril obtained with GSAS.

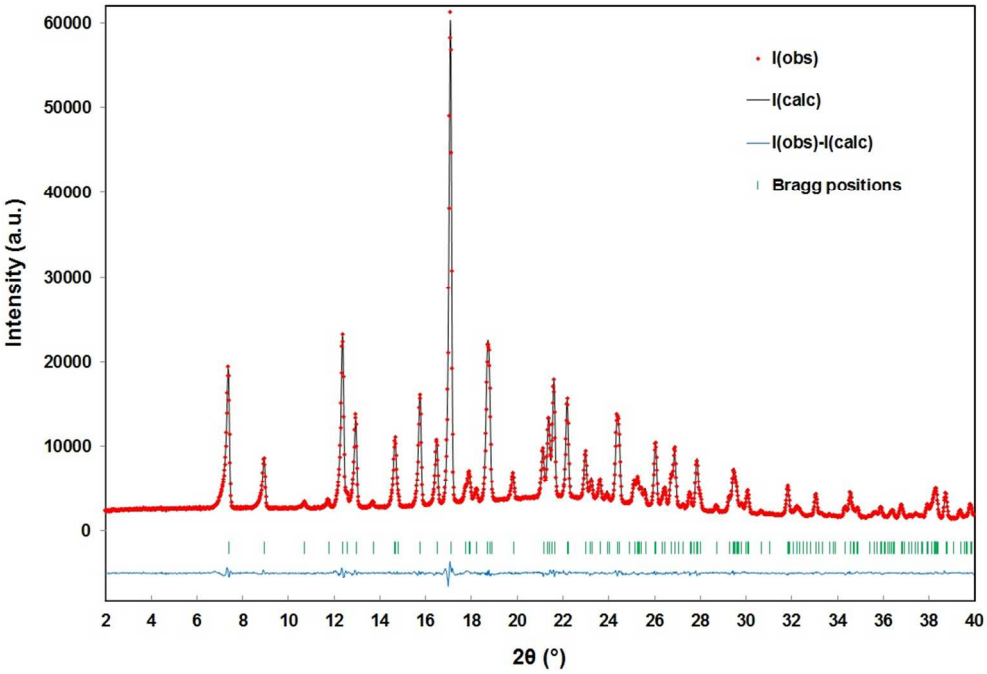
Figure 3. The molecular structure of trandolapril, illustrating the atomic labeling used in the tables.

Figure 4. Molecular overlay of the DFT (red) and Rietveld (blue) refined crystal structures of trandolapril.

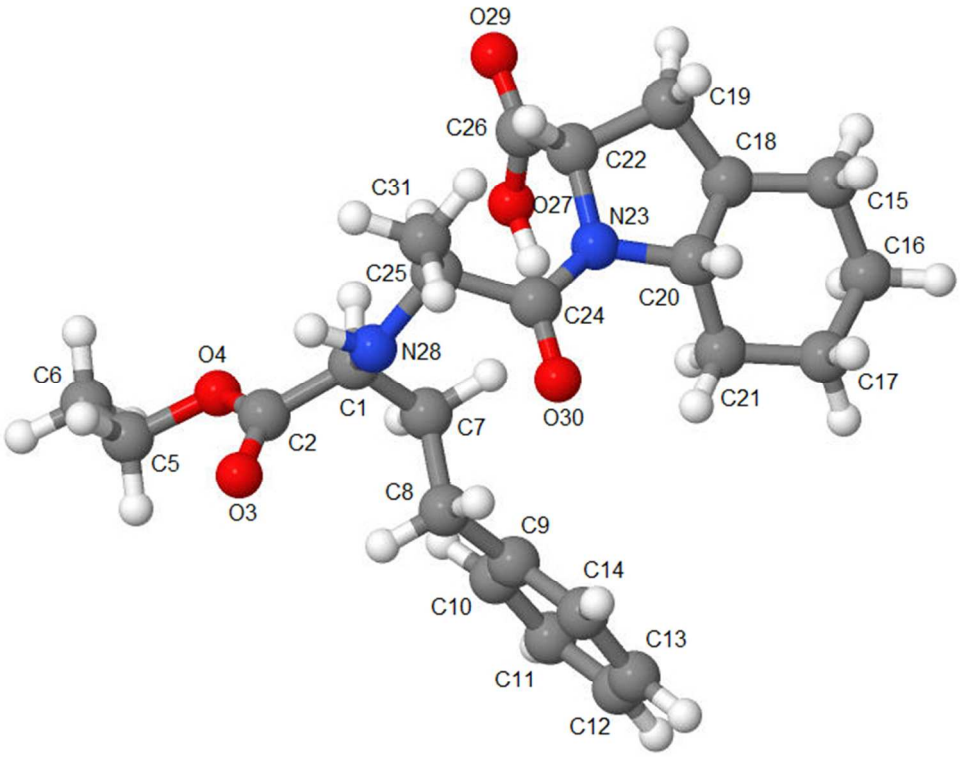
Figure 5. The crystal structure of trandolapril, viewed along to the c-axis, with the C, H, N and O atoms coloured in grey, white, blue and red respectively.



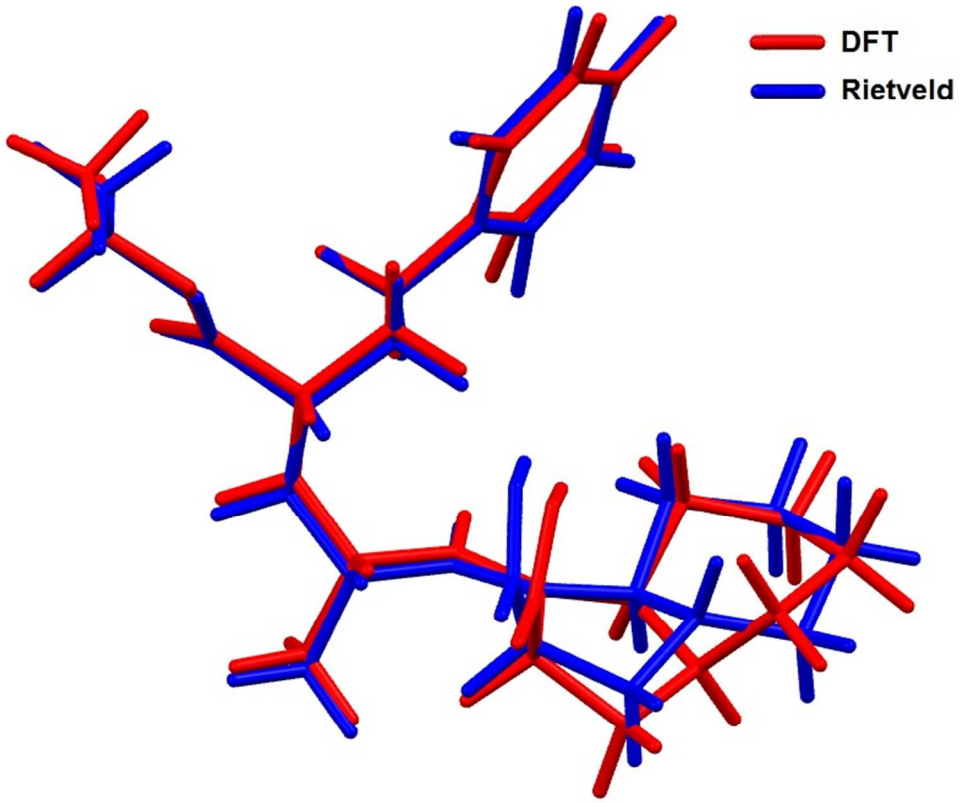
The 2D molecular structure of trandolapril, illustrating the fragments of the molecule prepared from edited portions of the CSD entries SIWCAC and FEFKEI.
213x248mm (96 x 96 DPI)



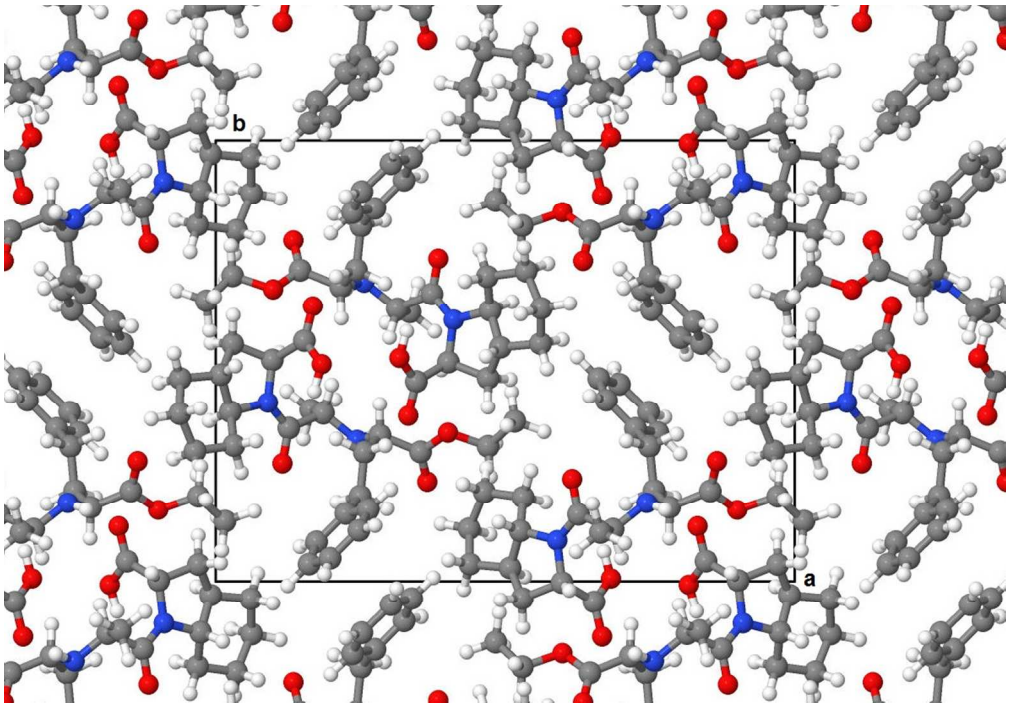
A plot illustrating the final Rietveld refinement of trandolapril obtained with GSAS.
290x197mm (96 x 96 DPI)



The molecular structure of trandolapril, illustrating the atomic labeling used in the tables.
191x151mm (96 x 96 DPI)



Molecular overlay of the DFT (red) and Rietveld (blue) refined crystal structures of trandolapril.
216x180mm (96 x 96 DPI)



The crystal structure of trandolapril, viewed along to the c-axis, with the C, H, N and O atoms coloured in grey, white, blue and red respectively.
313x218mm (96 x 96 DPI)