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Lenalidomide, an antineoplastic drug, and its hemihydrate

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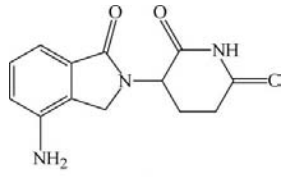
The crystal structures of lenalidomide [systematic name: (*RS*)-3-(4-amino-1-oxoisoindolin-2-yl)piperidine-2,6-dione], $C_{13}H_{13}N_3O_3$, (I), an antineoplastic drug, and its hemihydrate, $C_{13}H_{13}N_3O_3{\cdot}0.5H_2O$, (II), have been determined by single-crystal X-ray diffraction analysis. The overall conformation of the molecule defined by the orientation of the two ring portions, *viz*. pyridinedione and isoindolinone, is twisted in both structures. The influence of the self-complementary pyridinedione ring is seen in the crystal packing of both structures through its involvement in forming hydrogen-bonded dimers, although alternate dione O atoms are utilized. An extensive series of N—H···O hydrogen bonds link the dimers into two-dimensional supramolecular arrays built up from infinite chains. The water molecule in (II) has a cohesive function, connecting three lenalidomide molecules by hydrogen bonds. The significance of this study lies in the analysis of the interactions in these structures and the aggregations occurring *via* hydrogen bonds in the hydrated and dehydrated crystalline forms of the title compound.

Comment

Lenalidomide, initially known as CC-5013 and marketed as Revlimid by Celgene Europe Ltd, is one of a number of novel compounds based on the molecular structure of thalidomide that were developed with a view to improving the immunomodulatory effect of the parent compound, whilst also providing a better safety profile (Bartlett *et al.*, 2004; Richardson *et al.*, 2002). It is a synthetic derivative of glutamic acid and is structurally close to thalidomide, in that it has an identical backbone but has been subject to removal of an O atom from the phthalyl ring and addition of an amine group. Although it is chiral and possesses an asymmetric C atom, it has been developed as a racemic mixture since it undergoes racemization under physiological conditions. In a phase III clinical study, Weber *et al.* (2007) found that treatment with lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma was superior to the old treatment of multiple myeloma consisting of high-dose dexamethasone alone. On June 29 2006, lenalidomide received US Food and Drug Administration (FDA) clearance for use in combination with dexamethasone in patients with multiple myeloma who have received at least one prior therapy.



(I)
(II) = (I)·0.5H_2O

In the course of our investigations on the structural characterization of pharmaceutical compounds (Ravikumar *et al.*, 2008*a*,*b*), the title compound was obtained in two crystal types, as blocks and a small number of fine needles. The data collected suggested the structure of lenalidomide, (I) (triclinic, $P\overline{1}$), in the case of the blocks, whereas for the needles, the larger asymmetric unit indicates the presence of two molecules (monoclinic, $P2_1/c$, Z = 8) and proved to contain a water molecule as well, considered as lenalidomide hemihydrate, (II). The crystal structures of (I) and (II) are presented here.

Views of the molecules of (I) and (II), showing the atom labelling, are presented in Figs. 1 and 2, respectively. The significant difference between the two molecules of (II) is seen in the central C5—C4—N2—C13 torsion angle, defining the twist between the pyridinedione ring and the amino-isoindolinone portion; this angle is 121.97 (14)° in molecule *A* and 87.42 (16)° in molecule *B*. This is the only available point for conformation flexibility in the molecule. The corresponding angle in (I) is 87.61 (14)°. This twist is further illustrated by the nonbonding distance between the carbonyl O atoms of the two rings: O2···O3 = 3.566 (2) Å in (I), 4.317 (2) Å in molecule *A* of (II) and 3.536 (2) Å in molecule *B* of (II). An overlay of the molecules of (I) and (II) with thalidomide polymorphs [α form (Allen & Trotter, 1971) and β form (Reepmeyer *et al.*, 1994)], superimposing the planar isoindolinone systems, reveals the conformational flexibility (Fig. 3). The pyridinedione ring in both structures has a distorted half-chair conformation in which atoms C3 and C4 lie on opposite sides of the plane defined by atoms C1/C2/N1/

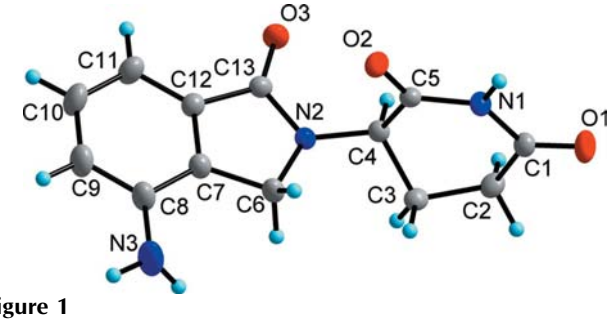


Figure 1
A view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

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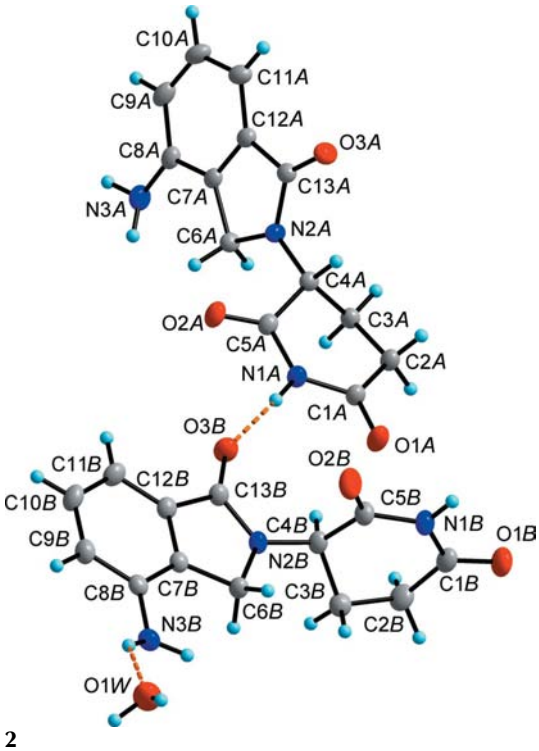

Figure 2
A view of the two lenalidomide molecules (suffixes *A* and *B*) and the water molecule in the asymmetric unit of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed lines indicate hydrogen bonds.

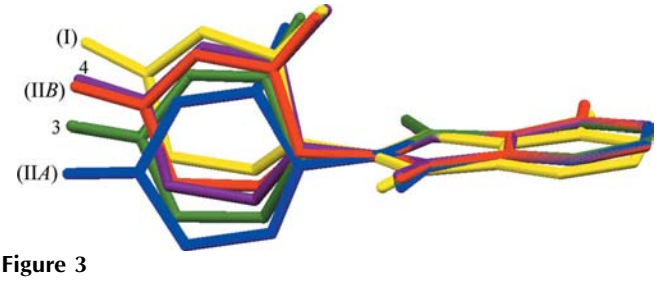

Figure 3
A superposition of the molecular conformations of the lenalidomide molecules of (I) and (II) with thalidomide. The overlay was made by making a least-squares fit through the isoindolinone ring system of (I). The labels and r.m.s deviations (Å) are as follows: molecule *A* of (II) [labelled (II*A*)] 0.019; molecule *B* of (II) [labelled (II*B*)] 0.020; thalidomide α form (labelled 3) 0.028; thalidomide β form 2 (labelled 4) 0.035.

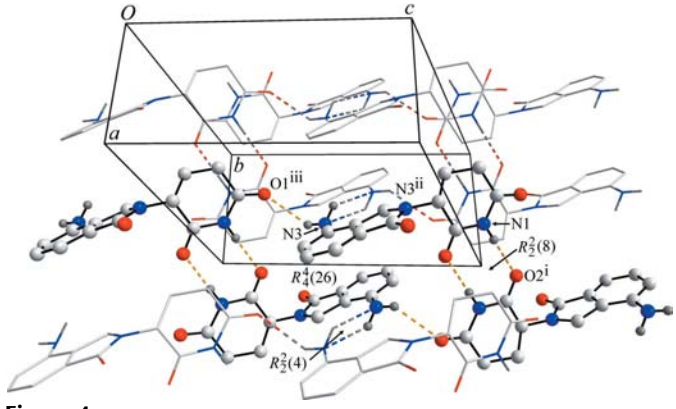

Figure 4
Part of the crystal packing of (I), showing the centrosymmetric tetramolecular $R_4^4(26)$ (in ball-and-stick representation) and dimeric $R_2^2(8)$ ring motifs, forming infinite chains parallel to the *c* axis, for which the complete graph-set notation is $C(11)[R_2^2(8)R_4^4(26)]$. Also shown are the centrosymmetric dimeric $R_2^2(4)$ ring motifs formed by N—H···N hydrogen bonds. Hydrogen bonds are shown as dashed lines and H atoms not involved in hydrogen bonding have been omitted for clarity. Selected atoms are labelled, primarily to provide a key for the coding of the atoms. [Symmetry codes: (i) $-x+2, -y+2, -z+2$; (ii) $-x+1, -y+2, -z+1$; (iii) $x, y, z-1$.]

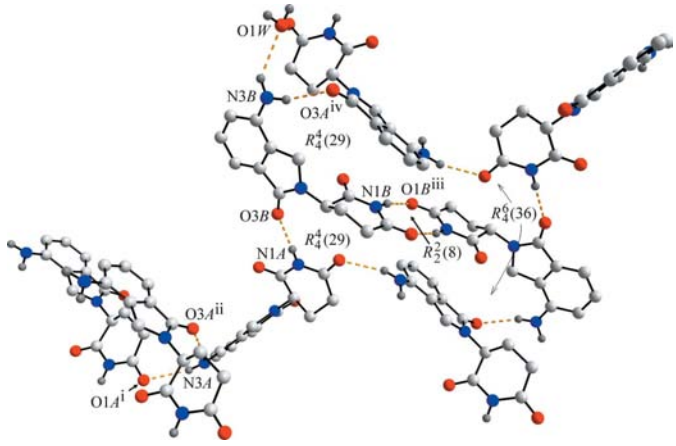

Figure 5
Part of the crystal structure of (II), showing the formation of the centrosymmetric hexamolecular $R_6^6(36)$ and dimeric $R_2^2(8)$ ring motifs, along with the tetramolecular $R_4^4(29)$ ring motif. Hydrogen bonds are shown as dashed lines. Selected atoms of the molecules present in the asymmetric unit are labelled, primarily to provide a key for the coding of the atoms. The hydrogen bonding of the water molecule is not shown. For the sake of clarity, the unit-cell outline has been omitted, together with H atoms not involved in hydrogen bonding. [Symmetry codes: (i) $x+1, -y+\frac{3}{2}, z+\frac{1}{2}$; (ii) $x, -y+\frac{3}{2}, z+\frac{1}{2}$; (iii) $-x-1, -y+1, -z+1$; (iv) $-x, y-\frac{1}{2}, -z+\frac{3}{2}$.]

C5. The half-chair conformation is distorted towards a C3 envelope.

In both (I) and (II), the main interest centres on the crystal packing features, where hydrogen bonds (Tables 1 and 2) play a major part in controlling the supramolecular assembly of the molecules.

In the crystal packing (Fig. 4) of (I), the self-complementary pyridinedione ring forms centrosymmetric dimers [N1—H1N···O2($-x+2, -y+2, -z+2$)] the hydrogen-bonding motif of which has graph set $R_2^2(8)$ (Etter, 1990; Etter *et al.*, 1990; Bernstein *et al.*, 1995). Amino atom N3 donates one of its H atoms to dione atom O1 at ($x, y, z-1$), linking the dimers to generate a cyclic centrosymmetric tetramer of graph set $R_4^4(26)$. These self-complementary tetramers form infinite chains parallel to the *c* axis, for which the complete graph set can be written as $C(11)[R_2^2(8)R_4^4(26)]$. In addition, the molecules are further linked into an additional centrosymmetric dimeric aggregate by N—H···N hydrogen bonds along the *a* axis, wherein amino atom N3 acts as both donor and acceptor [N3—H2···N2($-x+1, -y+2, -z+1$)] to generate a motif of graph set $R_2^2(4)$ propagating along the *b* axis. Carbonyl atom O3 of the indolinone ring is not involved in any conventional

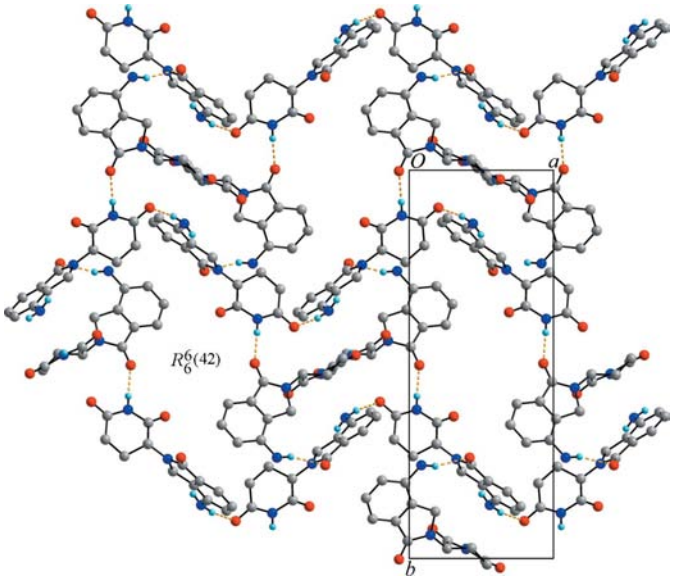

Figure 6
A more extensive view of the hydrogen bonding within a layer of molecules of (II), showing the formation of the centrosymmetric hexamolecular $R_6^6(42)$ ring motif. The representation is the same as in Fig. 5. The water molecules and H atoms not involved in hydrogen bonding have been omitted for clarity. Hydrogen bonds are shown as dashed lines. Symmetry codes and atom labelling have been omitted and the outline of the unit cell is shown.

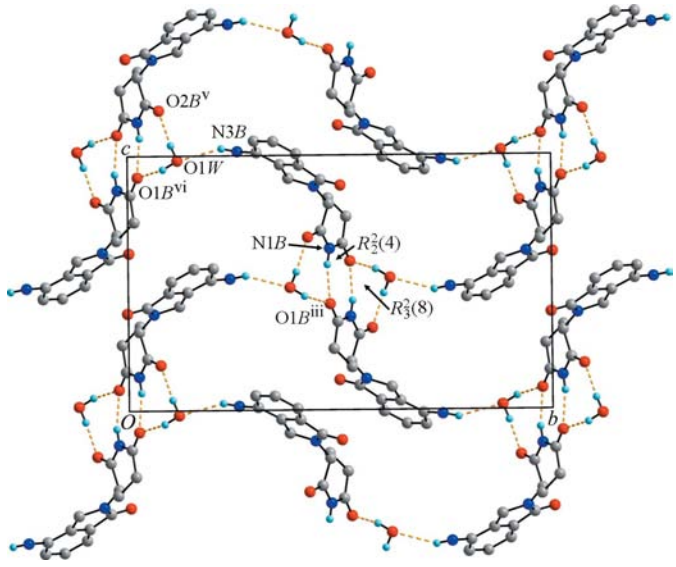

Figure 7
A partial packing view of (II), showing the water molecule involved in hydrogen-bonding interactions (dashed lines) with molecule *B*. H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry codes: (v) $x, -y+\frac{1}{2}, z+\frac{1}{2}$; (vi) $-x-1, y-\frac{1}{2}, -z+\frac{3}{2}$.]

hydrogen bonds, but participates in an acceptable C—H···O interaction (Table 1).

In hemihydrate (II), the crystal structure is built up from two lenalidomide molecules, denoted *A* and *B*, in the asymmetric unit, and solvent water molecules *via* hydrogen-bonding interactions. The self-complementary pyridinedione ring dimer found in (I) forms only between *B* molecules through N1*B*—H4N···O1*B*($-x+1, -y+1, -z+1$) hydrogen bonds (Fig. 5). Molecule *A* links to molecule *B* through pyridine atom N1*A* and carbonyl atom O3*B*. It is interesting to note that whilst the dimer formation in (I) is through dione atom O1, it is through atom O2 in (II), thus making use of the alternate presence of dione atoms O1 and O2. Amine atom N3 of both molecules connects neighbouring lenalidomide molecules *via* N—H···O hydrogen bonds and generates tetramers based on the $R_4^4(29)$ synthon along the *c* axis.

Two adjacent tetramers thus generate a centrosymmetic hexamer along the *a* axis, based on the $R_4^6(36)$ synthon, accommodating the N—H···O dimers in its cavity. Symmetry-related N—H···O hydrogen bonds generate an additional centrosymmetic hexamer of $R_6^6(42)$ motif along the *b* axis, which links the earlier formed $R_4^6(36)$ hexamers, resulting in a continuous linkage of molecules along the *c* and *b* axes (Fig. 6).

The cohesive role of water is embodied by its interaction as an acceptor of a hydrogen bond donated by amine atom N3*B*, and as a donor to the two different carbonyl atoms O1*B* and O2*B* of the pyridinedione ring, generating a graph-set motif of $R_3^2(8)$ (Fig. 7). It is interesting to note that the water molecule interacts only with molecule *B*. Carbonyl atom O2*A* of the pyridinedione ring is not involved in any conventional hydrogen bonds, but participates in an acceptable C—H···O interaction (Table 2).

To sum up, the crystal structure analysis of (I) and (II) illustrates the arrangements of supramolecular aggregates formed by hydrogen-bonding interactions in the hydrated and dehydrated forms of lenalidomide. The observed crystal packing features, with and without the interposition of water molecules, may provide some insight to understand ways of improving the tablet-formation ability and densification properties of drug substances.

Experimental

Lenalidomide (Pharmacology Department, IICT, Hyderabad) (80 mg) was dissolved in a mixture of methanol (5 ml) and water (1 ml). After 3 d, crystals of (I) and (II) were obtained and were distinguished by their distinct crystal habits.

Compound (I)

Crystal data

$C_{13}H_{13}N_3O_3$
$M_r = 259.26$
Triclinic, $P\overline{1}$
$a = 5.9983\ (5)$ Å
$b = 8.9198\ (8)$ Å
$c = 11.5785\ (10)$ Å
$\alpha = 75.711\ (1)^\circ$
$\beta = 84.660\ (1)^\circ$
$\gamma = 86.038\ (1)^\circ$
$V = 597.04\ (9)$ Å^3
$Z = 2$
Mo $K\alpha$ radiation
$\mu = 0.11$ mm^{-1}
$T = 294$ K
$0.19 \times 0.15 \times 0.12$ mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
5703 measured reflections
2092 independent reflections
1975 reflections with $I > 2\sigma(I)$
$R_{int} = 0.016$

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···O2^{i}	0.88 (2)	2.02 (2)	2.899 (2)	179 (2)
N3—H2N···N3^{ii}	0.91 (4)	2.62 (4)	3.260 (4)	128 (3)
N3—H3N···O1^{iii}	0.81 (3)	2.50 (3)	3.180 (2)	142 (3)
C3—H3A···O2^{iv}	0.97	2.56	3.213 (2)	125
C3—H3B···O3^{iv}	0.97	2.58	3.461 (2)	152
C4—H4···O3^{v}	0.98	2.36	3.205 (2)	144

Symmetry codes: (i) $-x+2, -y+2, -z+2$; (ii) $-x+1, -y+2, -z+1$; (iii) $x, y, z-1$; (iv) $x-1, y, z$; (v) $-x+2, -y+1, -z+2$.

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.039$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.104$	$\Delta\rho_{max} = 0.22$ e Å^{-3}
$S = 1.05$	$\Delta\rho_{min} = -0.20$ e Å^{-3}
2092 reflections	
185 parameters	

Compound (II)

Crystal data

$C_{13}H_{13}N_3O_3\cdot 0.5H_2O$	$V = 2523.0$ (4) Å^3
$M_r = 268.27$	$Z = 8$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 8.4425$ (7) Å	$\mu = 0.11$ mm^{-1}
$b = 22.2874$ (19) Å	$T = 294$ K
$c = 13.6627$ (12) Å	0.18 × 0.11 × 0.07 mm
$\beta = 101.069$ (1)°	

Data collection

Bruker SMART APEX CCD area-detector diffractometer	4430 independent reflections
23782 measured reflections	3972 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.022$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.036$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.105$	$\Delta\rho_{max} = 0.39$ e Å^{-3}
$S = 1.02$	$\Delta\rho_{min} = -0.18$ e Å^{-3}
4430 reflections	
383 parameters	
2 restraints	

All N-bound H atoms of (I) and (II), and the O-bound H atoms of (II), were located in difference Fourier maps and their positions and isotropic displacement parameters were refined. All other H atoms were located in a difference density map, positioned geometrically and included as riding atoms, with C—H = 0.93–0.98 Å and U_{iso}(H) = 1.2U_{eq}(C). Distance restraints were applied to O1W—H1W and O1W—H2W of the water molecule of (II), with a set value of 0.89 (1) Å and U_{iso}(H) = 1.5U_{eq}(O).

Table 2
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N3A—H2N···O1A^{i}	0.90 (2)	2.29 (2)	3.1539 (18)	160 (2)
N3A—H3N···O3A^{ii}	0.91 (2)	2.18 (2)	3.076 (2)	168 (2)
N1A—H1N···O3B	0.893 (19)	2.00 (2)	2.8921 (17)	177 (2)
N3B—H5N···O3A^{iii}	0.89 (2)	2.22 (2)	3.0808 (19)	164 (2)
N3B—H6N···O1W	0.90 (2)	2.47 (2)	3.199 (2)	138 (2)
N1B—H4N···O1B^{iv}	0.88 (2)	2.15 (2)	3.016 (2)	169 (2)
O1W—H1W···O2B^{v}	0.978 (10)	1.951 (12)	2.918 (2)	170 (3)
O1W—H2W···O1B^{vi}	0.977 (10)	2.41 (3)	2.966 (2)	116 (2)
C3A—H3A···N3B^{vii}	0.97	2.61	3.491 (2)	150
C4A—H4A···O1W^{viii}	0.98	2.57	3.471 (2)	154
C4B—H4B···O1A	0.98	2.39	3.171 (2)	136
C10B—H10B···O2A^{ix}	0.93	2.46	3.335 (2)	156

Symmetry codes: (i) $x+1, -y+\frac{3}{2}, z+\frac{1}{2}$; (ii) $x, -y+\frac{3}{2}, z+\frac{1}{2}$; (iii) $-x, y-\frac{1}{2}, -z+\frac{3}{2}$; (iv) $-x-1, -y+1, -z+1$; (v) $x, -y+\frac{1}{2}, z+\frac{1}{2}$; (vi) $-x-1, y-\frac{1}{2}, -z+\frac{3}{2}$; (vii) $-x, -y+1, -z+2$; (viii) $-x, y+\frac{1}{2}, -z+\frac{3}{2}$; (ix) $-x+1, -y+1, -z+2$.

For both compounds, data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *DIAMOND* (Brandenburg & Putz, 2005); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3114). Services for accessing these data are described at the back of the journal.

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