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New pseudopolymorphs of 5-fluorocytosine

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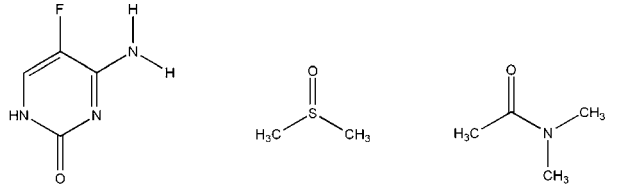
In order to better understand the interaction between the pharmaceutically active compound 5-fluorocytosine [4-amino-5-fluoropyrimidin-2(1*H*)-one] and its receptor, hydrogen-bonded complexes with structurally similar bonding patterns have been investigated. During the cocrystallization screening, three new pseudopolymorphs of 5-fluorocytosine were obtained, namely 5-fluorocytosine dimethyl sulfoxide solvate, $C_4H_4FN_3O{\cdot}C_2H_6OS$, (I), 5-fluorocytosine dimethylacetamide hemisolvate, $C_4H_4FN_3O{\cdot}0.5C_4H_9NO$, (II), and 5-fluorocytosine hemihydrate, $C_4H_4FN_3O{\cdot}0.5H_2O$, (III). Similar hydrogen-bond patterns are observed in all three crystal structures. The 5-fluorocytosine molecules form ribbons with repeated $R_2^2(8)$ dimer interactions. These dimers are stabilized by N—H···N and N—H···O hydrogen bonds. The solvent molecules adopt similar positions with respect to 5-fluorocytosine. Depending on the hydrogen bonds formed by the solvent, the 5-fluorocytosine ribbons form layers or tubes. A database study was carried out to compare the hydrogen-bond pattern of compounds (I)–(III) with those of other (pseudo)-polymorphs of 5-fluorocytosine.

Comment

5-Fluorocytosine is commonly used as a systemic antifungal drug. It becomes active by deamination within the fungal cells to 5-fluorouracil, and inhibits RNA and DNA synthesis (Morschhäuser, 2003). Furthermore, it has a novel application as a prodrug active against liver tumours (Pierrefite-Carle *et al.*, 1999). The interaction between 5-fluorocytosine and its receptor, as well as the base pairing, can be imitated by hydrogen-bonded complexes (Davis *et al.*, 2003). In order to investigate these interactions, we cocrystallized 5-fluorocytosine together with model compounds containing complementary functional groups. During the cocrystallization screening, three new pseudopolymorphs of 5-fluorocytosine were obtained, namely 5-fluorocytosine dimethyl sulfoxide solvate, (I), 5-fluorocytosine dimethylacetamide hemisolvate, (II), and 5-fluorocytosine hemihydrate, (III). Since 5-fluorocytosine is a rigid molecule, no significant geometric changes are to be expected and the molecules in (I)–(III) show the usual geometry.



5-Fluorocytosine $C_4H_4FN_3O$ | Dimethyl sulfoxide (DMSO) C_2H_6OS | Dimethylacetamide (DMAC) C_4H_9NO

(I) 5-Fluorocytosine · DMSO
(II) 5-Fluorocytosine · 0.5DMAC
(III) 5-Fluorocytosine · 0.5H_2O

Compound (I) crystallizes in the monoclinic space group $P2_1/c$, with one 5-fluorocytosine and one dimethyl sulfoxide (DMSO) molecule in the asymmetric unit (Fig. 1). The planar 5-fluorocytosine (r.m.s. deviation = 0.016 Å for all non-H atoms) is coplanar with the S and one C atom of the solvent molecule. The other methyl C and the O atom deviate from this plane by 0.753 (4) and 0.890 (3) Å, respectively. The two molecules are connected by an N—H···O hydrogen bond. The 5-fluorocytosine molecules form ribbons parallel to the $(\bar{3}02)$ plane, which are characterized by repeated $R_2^2(8)$ (Bernstein *et al.*, 1995) dimer interactions involving N—H···N and N—H···O hydrogen bonds (Fig. 2).

Compound (II) crystallizes in the triclinic space group $P\bar{1}$, with two essentially planar 5-fluorocytosine molecules (r.m.s. deviation = 0.091 Å for all non-H atoms in both molecules) and one disordered dimethylacetamide (DMAC) molecule in

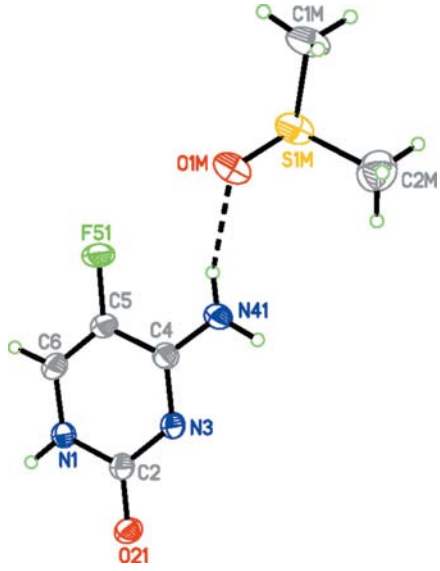


Figure 1
A perspective view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The dashed line indicates the N—H···O hydrogen bond.

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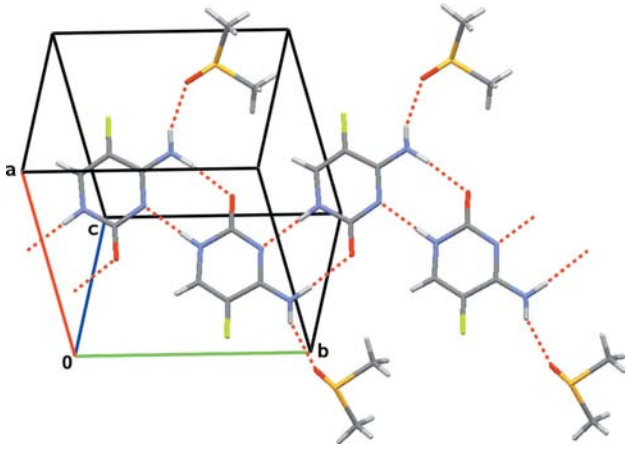

Figure 2
A partial packing diagram for (I). Hydrogen bonds are shown as dashed lines.

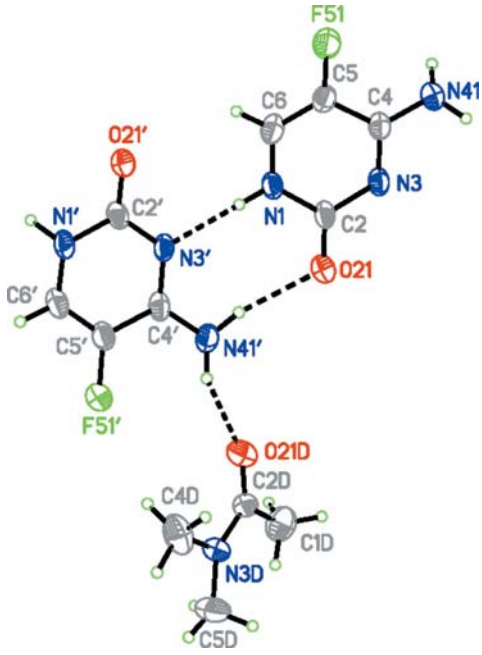

Figure 3
A perspective view of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed lines indicate hydrogen bonds. The dimethylacetamide solvent molecule is disordered and the minor occupied sites are not shown.

the asymmetric unit (Fig. 3). Although the solvent molecule is disordered over two sites, all atoms of these two sites lie in a common plane (r.m.s. deviation = 0.004 Å for all non-H atoms in both orientations). The 5-fluorocytosine molecules form planar ribbons and show exactly the same hydrogen-bond pattern as in (I). The O atom of the DMAC molecule adopts a position similar to that of the O atom of the DMSO molecule in (I). The planes through the non-H atoms of the solvent molecule and those of the 5-fluorocytosine ribbons enclose a dihedral angle of 68.0 (1)° (Fig. 4). The packing of (II) shows tubes of 5-fluorocytosine ribbons stabilized by N—H···O

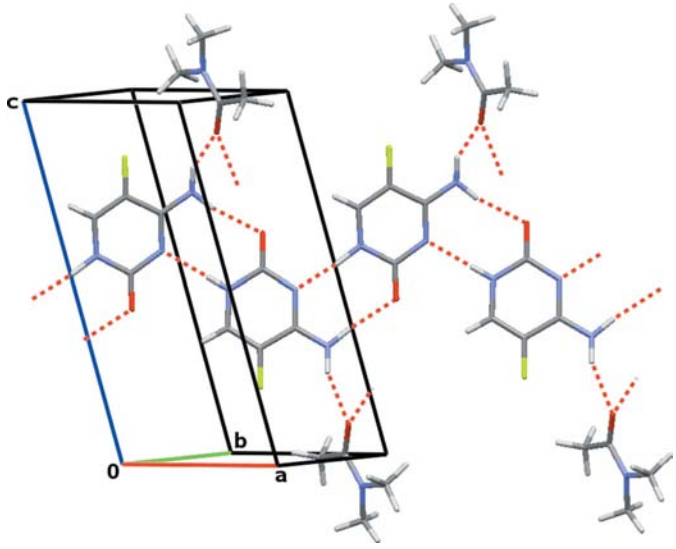

Figure 4
The hydrogen-bond pattern of (II). Hydrogen bonds are shown as dashed lines. The minor occupied sites of the dimethylacetamide molecules have been omitted.

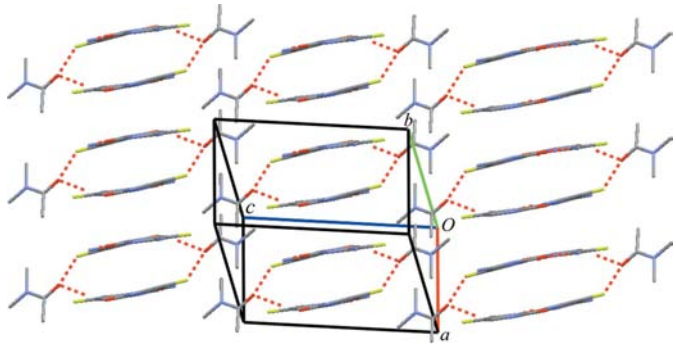

Figure 5
A packing diagram for (II), showing the tubular arrangement of the molecules. Hydrogen bonds are shown as dashed lines. The minor occupied sites of the dimethylacetamide molecules have been omitted.

hydrogen bonds between 5-fluorocytosine and dimethylacetamide molecules (Fig. 5).

Compound (III) crystallizes in the noncentrosymmetric space group *Cc*, with four 5-fluorocytosine and two water molecules in the asymmetric unit (Fig. 6). There are two planar 5-fluorocytosine dimers, each stabilized by a $R_2^2(8)$ hydrogen-bond pattern. The r.m.s. deviations for all non-H atoms of the dimers are 0.066 and 0.105 Å, respectively. The water molecules are displaced by 2.337 (4) and 2.378 (4) Å from the planes of the dimers. As in (I) and (II), the 5-fluorocytosine molecules form hydrogen-bonded ribbons (Fig. 7). Each dimer is directly connected only to its symmetry equivalents, but not to the other symmetry-independent dimer. Neighbouring layers of the two symmetry-independent dimers are held together by water-mediated O*W*—H···O and N—H···O*W* hydrogen bonds (Fig. 8).

In order to compare the hydrogen-bonding patterns of compounds (I)–(III) with other (pseudo)polymorphs of 5-fluorocytosine, a study of the Cambridge Structural Database (CSD, Version 5.3 of November 2008, plus three updates;

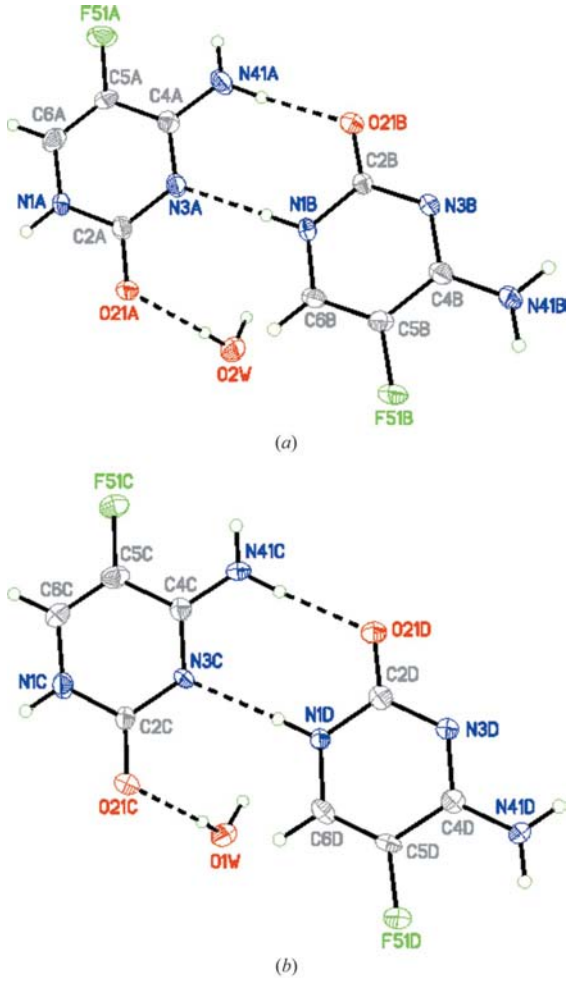

Figure 6
Perspective views of (*a*) the first dimer (including the solvent water) and (*b*) the second dimer (including the solvent water) in the asymmetric unit of (III), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed lines indicate hydrogen bonds.

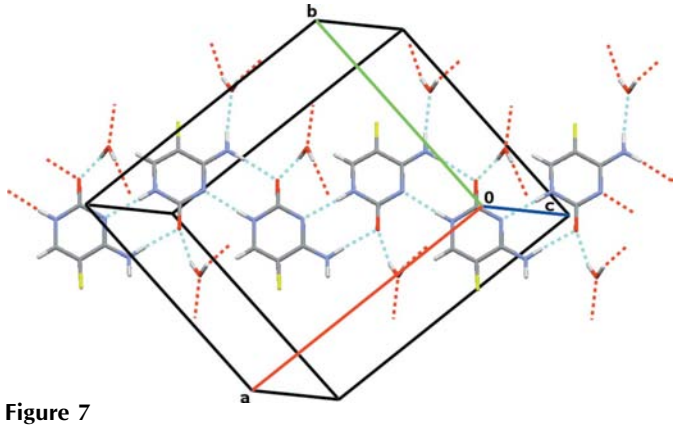

Figure 7
The hydrogen-bond pattern of (III). Hydrogen bonds are shown as dashed lines.

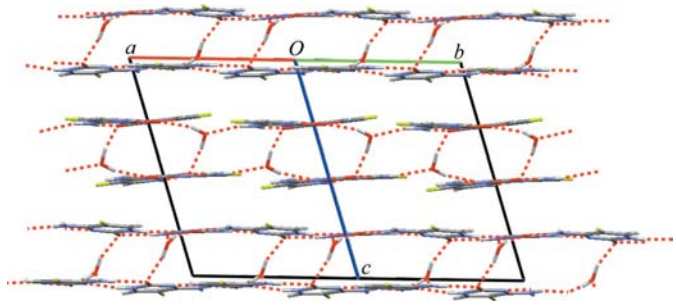

Figure 8
A packing diagram for (III). Hydrogen bonds are shown as dashed lines.

Allen, 2002) was undertaken. Since (I)–(III) contain neutral 5-fluorocytosine, we restricted the search to neutral molecules and found nine entries: two polymorphs of solvent-free 5-fluorocytosine (forms I and II according to Hulme & Tocher, 2006; CSD refcodes MEBQEQ01 and MEBQEQ), two monohydrates [forms I(*h*) and II(*h*); refcodes BIRMEU (Louis *et al.*, 1982) and BIRMEU03 (Hulme & Tocher, 2006)], a hemipentahydrate, a methanol solvate and a 2,2,2-trifluoroethanol solvate (refcodes MEBQUG, MEBQOA and MEBQIU, respectively; Hulme & Tocher, 2006). The other two entries [refcodes BIRMEU01 (Portalone & Colapietro, 2006) and BIRMEU02 (Hulme & Tocher, 2006)] were redeterminations of the I(*h*) form.

The hydrogen-bond pattern in anhydrous forms I and II is similar to that in (I)–(III). They form ribbons with repeated $R_2^2(8)$ dimer interactions stabilized by N—H···N and N—H···O hydrogen bonds. Form I crystallizes in the tetragonal space group $P4_12_12$, with one independent molecule; its crystal packing shows a zigzag arrangement of planar 5-fluorocytosine ribbons, which enclose a dihedral angle of 64.9°. Form II crystallizes in the monoclinic space group $P2_1/n$, with one independent molecule. In contrast with (I)–(III), the 5-fluorocytosine ribbons in form II are rippled and are connected with adjacent ribbons into layers by $R_2^4(8)$ N—H···O interactions.

The 5-fluorocytosine molecules in form I(*h*) and in the hemipentahydrate structure show an identical hydrogen-bond pattern to that in (I)–(III). Form I(*h*) crystallizes in the monoclinic space group $P2_1/c$, with two 5-fluorocytosine and two water molecules in the asymmetric unit. The planar 5-fluorocytosine ribbons are stabilized by the water molecules, forming a tube. The water molecules themselves form cyclic tetramers and connect the tubes into a three-dimensional hydrogen-bonded network. The 5-fluorocytosine hemipentahydrate crystallizes in the monoclinic space group $P2_1/c$, with two 5-fluorocytosine and five water molecules in the asymmetric unit. The water molecules form a hydrogen-bonded sheet parallel to the *bc* plane. The 5-fluorocytosine ribbons are stacked nearly perpendicular to the water sheet and are stabilized in columns by water-mediated hydrogen bonds. The asymmetric unit of triclinic II(*h*) consists of one 5-fluorocytosine and one water molecule. In this case, a different hydrogen-bonding pattern of the 5-fluorocytosine molecules is observed. The 5-fluorocytosine molecules are held together by two kinds of dimer interactions. Although these dimers show the same $R_2^2(8)$ graph set, the hydrogen-bond pattern consists of either two centrosymmetric N—H···O or two centrosymmetric N—H···N interactions. The planar 5-fluorocytosine

ribbons are further connected by two symmetry-equivalent water molecules.

In both the methanol solvate and the 2,2,2-trifluoroethanol solvate, the 5-fluorocytosine molecules show again the same hydrogen-bonded ribbons as in (I)–(III). The 5-fluorocytosine methanol solvate crystallizes in the monoclinic space group $P2_1/n$, with two 5-fluorocytosine and one methanol molecule in the asymmetric unit. Similar to (III), the 5-fluorocytosine molecules are directly connected only to their symmetry equivalents. The methanol molecule holds three different 5-fluorocytosine ribbons together. The 1:1 5-fluorocytosine 2,2,2-trifluoroethanol solvate crystallizes in the monoclinic space group $P2_1/c$. The packing shows some similarity to (II). The tubes of 5-fluorocytosine ribbons are stabilized by hydrogen bonds to solvent molecules which participate in N—H···O and O—H···O interactions.

Almost all the structures discussed here show the same hydrogen-bond pattern between the 5-fluorocytosine molecules. Apparently, the latter molecules prefer the formation of $R_2^2(8)$ dimers, which are further hydrogen bonded into ribbons. The dimers are usually stabilized by an N—H···O and an N—H···N interaction. Only in the case of monohydrate form II(*h*) is a different pattern observed: the 5-fluorocytosine molecules form centrosymmetric dimers, which are stabilized either by two N—H···O or by two N—H···N hydrogen bonds. The crystal packing in the various structures shows layers or tubes depending on the hydrogen bonds formed with adjacent 5-fluorocytosine ribbons or solvent molecules.

Experimental

Single crystals of (I)–(III) were obtained by cocrystallization of commercially available 5-fluorocytosine with various compounds. The crystallization method used was solvent evaporation at 323 K for (I) and (II), and at room temperature for (III). Compound (I) was obtained by crystallization of 5-fluorocytosine (2.3 mg) with carbamylurea (1.9 mg) from dimethyl sulfoxide (300 µl). 5-Fluorocytosine (2.0 mg) and *N*,*N*′-(pyridine-2,6-diyl)diacetamide (1.4 mg) dissolved in dimethylacetamide (200 µl) yielded (II). Crystals of (III) were obtained by crystallization of 5-fluorocytosine (2.8 mg) and 2-aminopyridine (1.9 mg) from dimethylacetamide (400 µl).

Compound (I)

Crystal data

$C_4H_4FN_3O\cdot C_2H_6OS$
M_r = 207.23
Monoclinic, $P2_1/c$
a = 12.4467 (12) Å
b = 9.1849 (8) Å
c = 8.5635 (8) Å
β = 107.065 (8)°
V = 935.89 (15) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.33 mm^{-1}
T = 173 K
0.31 × 0.14 × 0.05 mm

Data collection

Stoe IPDS II two-circle diffractometer
Absorption correction: multi-scan (*MULABS*; Spek, 2009; Blessing, 1995)
T_{min} = 0.903, T_{max} = 0.984
8061 measured reflections
1904 independent reflections
1509 reflections with $I > 2\sigma(I)$
R_{int} = 0.049

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.100
S = 1.03
1904 reflections
132 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Compound (II)

Crystal data

$C_4H_4FN_3O\cdot 0.5C_4H_9NO$
M_r = 172.67
Triclinic, $P\overline{1}$
a = 7.7247 (12) Å
b = 8.2840 (13) Å
c = 13.238 (2) Å
α = 90.204 (13)°
β = 104.336 (12)°
γ = 107.774 (12)°
V = 778.7 (2) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.13 mm^{-1}
T = 173 K
0.40 × 0.25 × 0.10 mm

Data collection

Stoe IPDS II two-circle diffractometer
8171 measured reflections
2911 independent reflections
1647 reflections with $I > 2\sigma(I)$
R_{int} = 0.169

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.069
$wR(F^2)$ = 0.199
S = 0.94
2911 reflections
260 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

Compound (III)

Crystal data

$C_4H_4FN_3O\cdot 0.5H_2O$
M_r = 138.11
Monoclinic, Cc
a = 14.7039 (13) Å
b = 12.4546 (10) Å
c = 13.7921 (14) Å
β = 115.474 (7)°
V = 2280.2 (4) Å^3
Z = 16
Mo $K\alpha$ radiation
μ = 0.15 mm^{-1}
T = 173 K
0.30 × 0.30 × 0.20 mm

Data collection

Stoe IPDS II two-circle diffractometer
14246 measured reflections
2141 independent reflections
1631 reflections with $I > 2\sigma(I)$
R_{int} = 0.104

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.078
S = 0.88
2141 reflections
355 parameters
8 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}

In (I) and (II), all H atoms were initially located by difference Fourier synthesis. Subsequently, H atoms bonded to C atoms were refined using a riding model, with methyl C—H = 0.98 Å and aromatic C—H = 0.95 Å, and with U_{iso}(H) = 1.5U_{eq}(C) for methyl H or 1.2U_{eq}(C) for all other H atoms. H atoms bonded to N atoms were refined isotropically. In (III), all H atoms of the 5-fluorocytosine molecules were refined using a riding model, with aromatic C—H = 0.95 Å and amide and terminal N—H = 0.88 Å, with U_{iso}(H) = 1.2U_{eq}(C,N). For the water molecules, the following restraints were applied during refinement: O—H = 0.88 (2) and H···H = 1.44 (4) Å,

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

D—H···A	D—H	H···A	D···A	D—H···A
N41—H411···O1M	0.82 (3)	2.18 (3)	2.929 (2)	152 (2)
N41—H412···O21^{i}	0.91 (3)	2.05 (3)	2.959 (2)	174 (2)
N1—H1···N3^{ii}	0.88 (3)	1.88 (3)	2.762 (2)	179 (2)

Symmetry codes: (i) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$; (ii) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$.

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···N3′	0.85 (5)	1.92 (5)	2.772 (4)	179 (5)
N41—H41A···O21′^{i}	0.94 (5)	2.03 (5)	2.965 (4)	174 (4)
N41—H41B···O21D^{ii}	0.90 (5)	2.13 (5)	2.976 (5)	157 (4)
N1′—H1′···N3^{iii}	1.06 (5)	1.72 (5)	2.774 (4)	173 (4)
N41′—H41C···O21	0.89 (5)	2.08 (5)	2.955 (4)	168 (4)
N41′—H41D···O21D	0.88 (4)	2.17 (4)	2.922 (4)	143 (3)

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

Table 3
Hydrogen-bond geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
N1A—H1A···N3B^{i}	0.88	1.98	2.853 (5)	172
N41A—H41A···O21B	0.88	1.99	2.858 (5)	170
N1B—H1B···N3A	0.88	1.97	2.854 (5)	177
N41B—H41C···O21A^{ii}	0.88	1.99	2.869 (5)	176
N41B—H41D···O1W^{iii}	0.88	2.10	2.972 (5)	170
N1C—H1C···N3D^{iv}	0.88	1.99	2.861 (5)	173
N41C—H41E···O21D	0.88	1.95	2.834 (5)	177
N1D—H1D···N3C	0.88	1.98	2.862 (5)	178
N41D—H41G···O21C^{v}	0.88	1.98	2.862 (5)	175
N41D—H41H···O2W^{vi}	0.88	2.10	2.961 (5)	164
O1W—H1WA···O21B^{vii}	0.87 (2)	2.06 (3)	2.906 (5)	163 (4)
O1W—H1WB···O21C	0.90 (2)	1.93 (3)	2.786 (5)	158 (5)
O2W—H2WA···O21A	0.90 (2)	1.95 (2)	2.826 (5)	166 (5)
O2W—H2WB···O21D^{viii}	0.88 (2)	2.05 (3)	2.898 (5)	163 (4)

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

with U_{iso}(H) = 1.2U_{eq}(O). In (II), all solvent atoms except O are disordered over two positions, with a site-occupation factor of 0.66 (2) for the major occupied orientation. However, the positions of the methyl C atoms coincide. In spite of the *E*-value distribution, which suggests a centrosymmetric space group (mean value of $|E^2 - 1| = 0.958$), the structure solution of (III) in the centrosymmetric space group *C2/c* failed. 2113 Friedel pairs were merged prior to refinement, due to the absence of anomalous scatterers. The absolute structure was arbitrarily assigned.

For all compounds, data collection: *X-AREA* (Stoe & Cie, 2001); cell refinement: *X-AREA*; data reduction: *X-AREA*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *Mercury* (Version 2.2; Macrae *et al.*, 2008) and *XP* (Sheldrick, 2008); software used to prepare material for publication: *publCIF* (Westrip, 2009).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3347). Services for accessing these data are described at the back of the journal.

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