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A new polymorph and two pseudo-polymorphs of pyrimethamine

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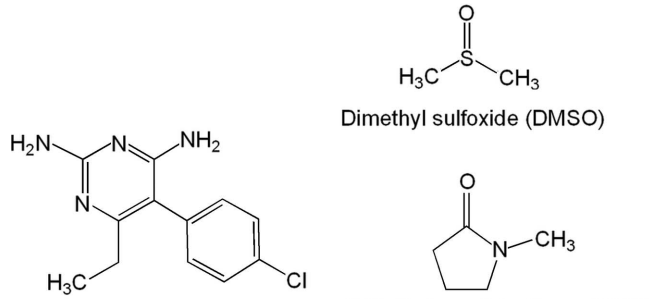
Due to its donor–acceptor–donor site, the antimalarial drug pyrimethamine [systematic name: 5-(4-chlorophenyl)-6-ethylpyrimidine-2,4-diamine] is a potential component of a supramolecular synthon. During a cocrystallization screen, one new polymorph of solvent-free pyrimethamine, $C_{12}H_{13}ClN_4$, (I), and two pseudopolymorphs, pyrimethamine dimethyl sulfoxide monosolvate, $C_{12}H_{13}ClN_4{\cdot}C_2H_6OS$, (I*a*), and pyrimethamine *N*-methylpyrrolidin-2-one monosolvate, $C_{12}H_{13}ClN_4{\cdot}C_5H_9NO$, (I*b*), were obtained. In (I), (I*a*), (I*b*) and the previously reported polymorph, the pyrimethamine molecules exhibit similar conformations and form $R_2^2(8)$ dimers stabilized by a pair of N—H···N hydrogen bonds. However, the packing arrangements are completely different. In (I), the dimers are connected by two additional N—H···N hydrogen bonds to form ribbons and further connected into a two-dimensional network parallel to (100), while layers containing N—H···Cl hydrogen-bonded pyrimethamine ribbons are observed in the packing of the known polymorph. In the two pseudopolymorphs, two pyrimethamine molecules are linked to form $R_2^2(8)$ dimers and the solvent molecules are connected to the dimers by $R_3^2(8)$ interactions involving two N—H···O hydrogen bonds. These arrangements are connected to form zigzag chains by N—H···Cl interactions in (I*a*) and to form ribbons by N—H···N interactions in (I*b*). Unexpectedly, a reaction between pyrimethamine and *N*-methylpyrrolidin-2-one occurred during another cocrystallization experiment from a solvent mixture of *N*-methylpyrrolidin-2-one and dimethyl sulfoxide, yielding solvent-free 5,5′-{[5-(4-chlorophenyl)-6-ethylpyrimidine-2,4-diyl]bis(azanediyl)}bis(1-methylpyrrolidin-2-one), $C_{22}H_{27}ClN_6O_2$, (II). In the packing of (II), the pyrimethamine derivatives are N—H···O hydrogen bonded to form ribbons. A database study was carried out to compare the molecular conformations and hydrogen-bonding interactions of pyrimethamine.

Comment

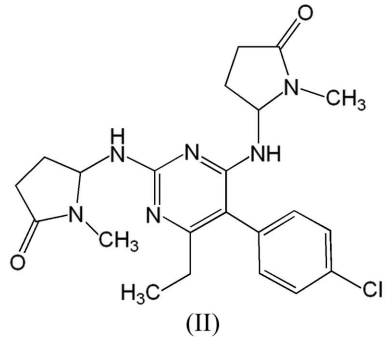
Pyrimethamine is an antifolate drug used for the prevention and treatment of malaria by inhibiting the enzyme dihydrofolate reductase (Sardarian *et al.*, 2003). Like most antifolates, pyrimethamine contains a 2,4-diaminopyrimidine group and a benzene ring, separated by one rotatable bond (Schwalbe & Cody, 2006). Previous theoretical and structural studies revealed that the relative orientation of the two rings and the protonation state of the 2,4-diaminopyrimidine play a key role in drug binding (Sansom *et al.*, 1989; Kongsaeree *et al.*, 2005). Moreover, pyrimethamine exhibits a donor–acceptor–donor site, so that together with a complementary molecule it can form three hydrogen bonds, yielding a robust supramolecular synthon (Desiraju, 1995).

In order to study the molecular geometry of pyrimethamine and its hydrogen-bonding interactions, we cocrystallized pyrimethamine with several potential receptors. Various cocrystallization experiments yielded a complex of pyrimethamine and orotic acid. Unfortunately, all of these crystals were of poor quality (Tutughamiarso & Bolte, 2011). In addition to the complex, one new polymorph of solvent-free pyrimethamine, (I), and two pseudopolymorphs were obtained, *viz*. the dimethyl sulfoxide monosolvate, (I*a*), and the *N*-methylpyrrolidin-2-one monosolvate, (I*b*). Furthermore, solvent-free 5,5′-{[5-(4-chlorophenyl)-6-ethylpyrimidine-2,4-diyl]bis(azanediyl)}bis(1-methylpyrrolidin-2-one), (II), was formed during an attempt at crystallizing pyrimethamine with N^2,9-diacetylguanine from a solvent mixture of *N*-methylpyrrolidin-2-one (NMP) and dimethyl sulfoxide (DMSO).



(I)

(I*a*): (I) · DMSO
(I*b*): (I) · NMP



(II)

The new polymorph, (I), crystallizes in the monoclinic space group $P2_1/c$ (Fig. 1), whereas the previously known modification of this compound [Cambridge Structural Database (CSD; Allen, 2002) refcode MUFMAB; Sethuraman &

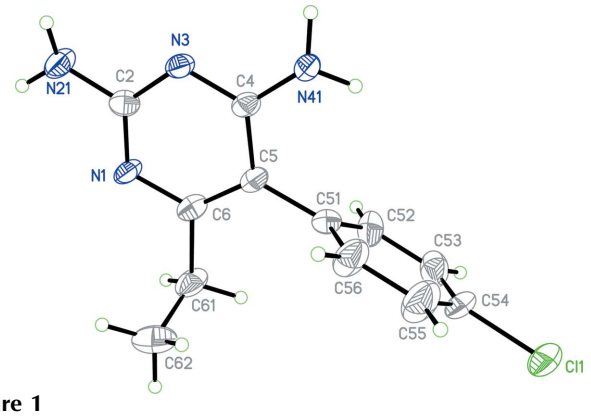


Figure 1
A perspective view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Thomas Muthiah (2002)] is triclinic. In (I), the pyrimidine and benzene ring planes enclose a dihedral angle of 75.9 (3)°, with atom C5 anticlinal to atom C62 [torsion angle = 97.0 (9)°]. The asymmetric unit of MUFMAB contains two pyrimethamine molecules, which show some similarity to (I): the dihedral angles between the two ring planes in each molecule are 74.4 (1) and 82.4 (1)°, while the torsion angles between the methyl C atom and the pivot pyrimidine C atom are 97.3 (3) and −97.2 (3)°. In both polymorphs, the pyrimethamine molecules form ribbons stabilized by repeated $R_2^2(8)$ motifs (Bernstein *et al.*, 1995) involving pairs of N—H···N hydrogen bonds [see Fig. 2 for the packing of (I)]. In (I), another $R_2^2(8)$ motif involving two N—H···N hydrogen bonds connects adjacent ribbons to form a two-dimensional network parallel to (100) (Table 1), while the packing of the triclinic polymorph shows layers consisting of N—H···Cl hydrogen-bonded ribbons.

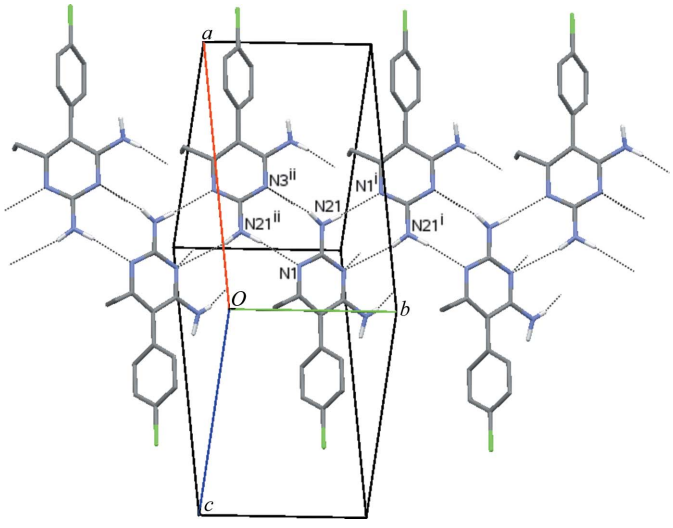


Figure 2
A partial packing diagram for (I), showing ribbons running along the *b* axis. Dashed lines indicate hydrogen bonds and only amine H atoms are shown. (Symmetry codes are as in Table 1.)

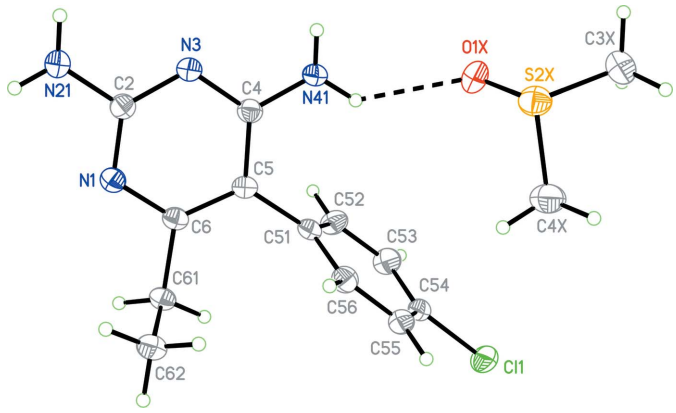


Figure 3
A perspective view of (I*a*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The N—H···O hydrogen bond is shown as a dashed line. The solvent molecule is disordered and its minor occupied site has been omitted.

Compound (I*a*) crystallizes as a DMSO solvate, with the S atom of the solvent molecule disordered over two sites (Fig. 3). A dihedral angle of 76.1 (1)° is formed between the plane through the pyrimidine and benzene rings, while atoms C5 and C62 are in an anticlinal arrangement [torsion angle = 101.5 (2)°]. In the packing, two pyrimethamine and two DMSO molecules form a centrosymmetric dimer held together by six hydrogen bonds (Fig. 4). The pyrimethamine molecules are connected by a pair of N—H···N hydrogen bonds with an $R_2^2(8)$ motif, while the pyrimethamine and the

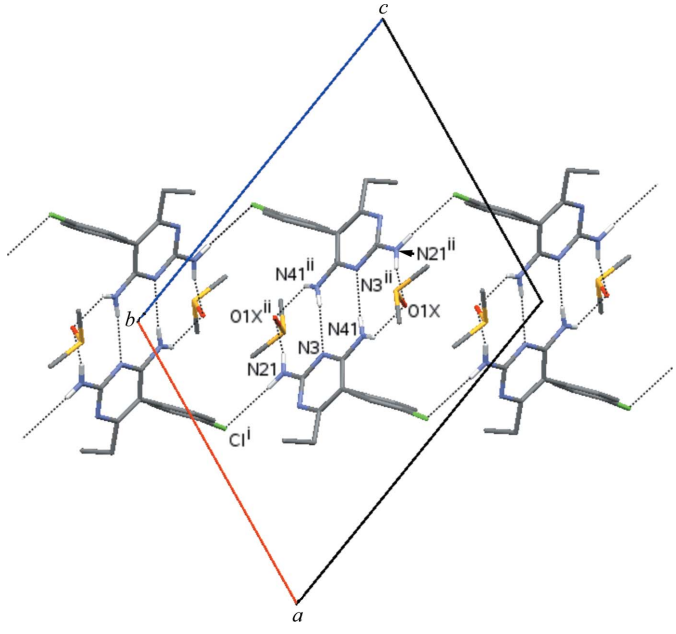


Figure 4
A partial packing diagram for (I*a*), viewed down the *b* axis. Dashed lines indicate hydrogen bonds. Only the major occupied sites of the solvent molecules and the H atoms involved in the hydrogen bonding are shown. (Symmetry codes are as in Table 2.)

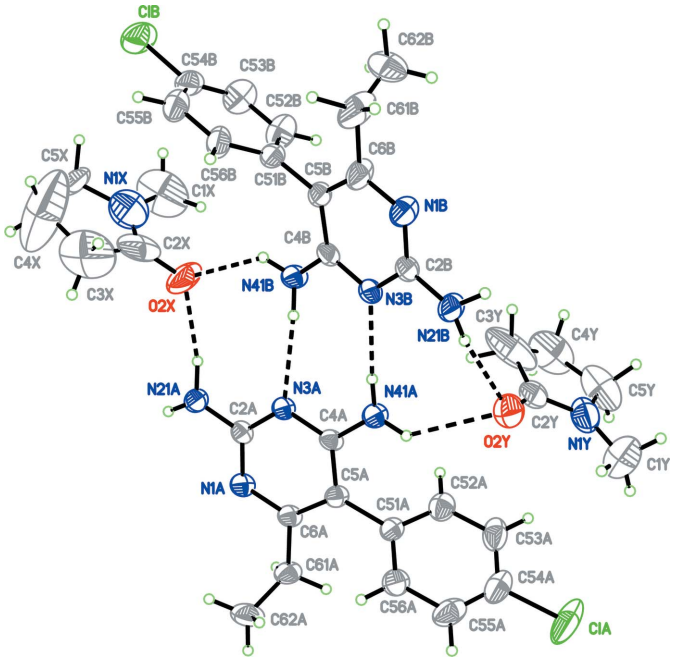


Figure 5
A perspective view of (I*b*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Hydrogen bonds are shown as dashed lines. One of the methyl groups (C62*B*) and one of the NMP molecules (molecule *Y*) are disordered and their minor occupied sites have been omitted.

solvent molecules are linked by an $R_3^2(8)$ motif involving two additional N—H···O hydrogen bonds per solvent molecule (Table 2). Within the dimer, the pyrimidine rings are coplanar but do not lie in a common plane; the planes are displaced by *ca* 0.6 Å with respect to each other. The dimers are N—H···Cl hydrogen bonded to form zigzag chains running parallel to [$\bar{1}$01].

The asymmetric unit of (I*b*) contains of two pyrimethamine and two NMP molecules (Fig. 5). The terminal C atom of the ethyl group of pyrimethamine molecule *B* and one NMP molecule (atoms labelled with suffix *Y*) are disordered over two sites. However, similar conformations of both pyrimethamine molecules are observed: dihedral angles of 62.6 (1) and 76.1 (2)° are enclosed between the planes of the pyrimidine and benzene rings in molecules *A* and *B*, with the ethyl groups nearly perpendicular to the pyrimidine ring planes [dihedral angles = 72.0 (4) (molecule *A*), and 84.0 (6) and 86.2 (8)° (molecule *B*)]. The pyrimidine rings are planar [r.m.s. deviations = 0.014 (molecule *A*) and 0.005 Å (molecule *B*) for all non-H atoms] and are twisted by 19.0 (1)° with respect to each other. In the packing, the solvent molecules are perpendicular to the *bc* plane. The hydrogen-bonding interactions between the molecules in the asymmetric unit are identical to those in the centrosymmetric dimer of (I*a*) (Table 3): the pyrimethamine molecules are connected by an $R_2^2(8)$ motif involving two N—H···N hydrogen bonds, while four N—H···O hydrogen bonds link the pyrimethamine and NMP molecules. Furthermore, the dimers are joined to form

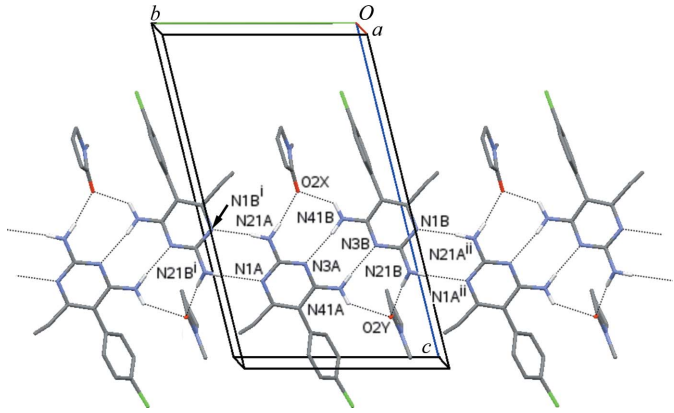


Figure 6
A partial packing diagram for (I*b*). Dashed lines indicate hydrogen bonds and only H atoms involved in the hydrogen bonding are shown. The minor occupied sites of the methyl groups and those of the solvent molecules have been omitted. (Symmetry codes are as in Table 3.)

ribbons running along the *b* axis by another $R_2^2(8)$ motif involving two N—H···N hydrogen bonds (Fig. 6).

Unexpectedly, crystals of (II) were obtained by cocrystallization attempts from a solvent mixture of NMP and DMSO (Fig. 7). The DMSO molecule probably reacted as a mild oxidizing agent, so that pyrimethamine and NMP could undergo a dehydrogenation reaction, yielding compound (II). However, no such reaction has yet been reported for pyrimethamine. The dihedral angle between the planes through the pyrimidine and benzene rings is 76.1 (1)°, with atoms C5 and C62 in an anticlinal arrangement (Table 4). Pyrimidine atom N3 is antiperiplanar to atom C5*X* and synperiplanar to atom C5*Y*, while the planes through the amide groups and the pyrimidine ring enclose dihedral angles of 18.2 (2) (N21—H) and 11.7 (5)° (N41—H). The C1*X* and N21 atoms, as well as the C1*Y* and N41 atoms, are in a synclinal arrangement (Table 4), but both methyl groups are opposite to each other.

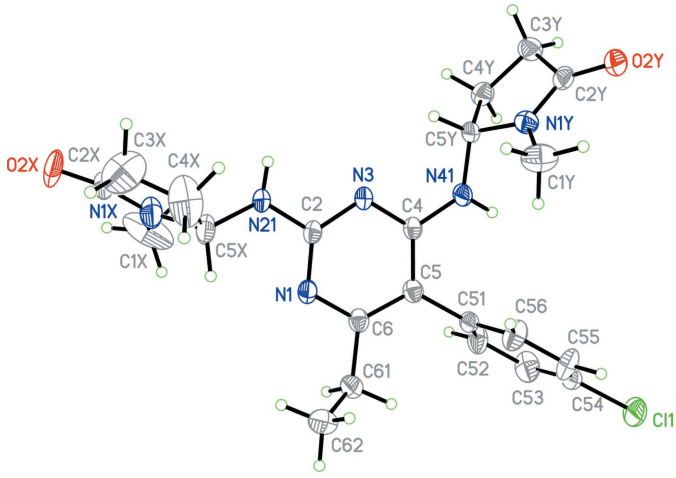


Figure 7
A perspective view of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

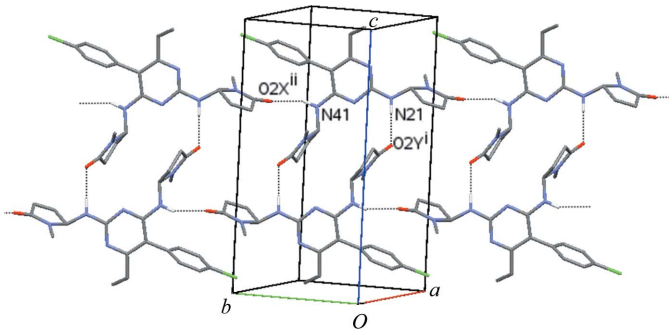


Figure 8
A packing diagram for (II). Dashed lines indicate hydrogen bonds and only H atoms involved in the hydrogen bonding are shown. (Symmetry codes are as in Table 5.)

In the crystal structure, two N—H···O hydrogen bonds stabilize the centrosymmetric dimers (Table 5), which are further N—H···O hydrogen-bonded to form ribbons running parallel to (110) (Fig. 8).

The conformation of the pyrimethamine molecule is characterized by the dihedral angle between the plane through the two rings and the C5—C6—C61—C62 torsion angle, representing the deviation of the ethyl group from the pyrimidine ring. The latter is not essential for drug binding, since the orientation of the ethyl group does not affect the overall binding energy of the enzyme–drug complex (Sansom *et al.*, 1989). In these four structures, *viz.* (I), (I*a*), (I*b*) and (II), similar molecular geometries are observed: the dihedral angle between the planes through the pyrimidine ring and the substituted benzene ring varies from 62.6 (1) to 76.1 (2)°, while the C5—C6—C61—C62 torsion angle ranges from 84.7 (8) to 125.6 (4)°. In the cocrystal of pyrimethamine and orotic acid (Fig. 9), the protonated pyrimethamine molecules also show similar conformations: the pyrimidine and benzene ring planes are twisted by 86.2 and 83.6° from each other, with atoms C5 anticlinal to atoms C62.

A search of the CSD (Version 5.32 of November 2010 plus three updates) for structures containing pyrimethamine yielded 30 entries. Since the protonation state of pyrimethamine is important for its drug binding, it is protonated in almost all entries, and in fact in one of them (refcode LAVZOY; Balasubramani *et al.*, 2005) both pyrimidine N atoms of the pyrimethamine molecule are protonated. Only MUFMAB revealed neutral pyrimethamine molecules. However, the values of the characteristic dihedral and torsion angles are in agreement with those in our four structures: the dihedral angle between the planes of the two rings varies from 61.4 to 89.7°, and the torsion angle between the terminal C atom of the ethyl group and the pivot pyrimidine C atom varies from 67.5 to 110.9°. In the structure of pyrimethamine hydrochloride (refcode CIVDEQ01; Tanaka *et al.*, 2004), the terminal C atom of the ethyl group is disordered over two sites. Thus, torsion angles of 143.2 and −155.3° are formed between these disordered C atoms and the pivot pyrimidine C atom.

As observed in (I), (I*a*), (I*b*) and 18 CSD entries, the pyrimethamine molecules form dimers characterized by the $R_2^2(8)$ motif involving N—H···O hydrogen bonds. Although different solvent molecules are included in (I*a*) and (I*b*), similar arrangements consisting of two pyrimethamine and two solvent molecules held together by six hydrogen bonds are formed. These so-called *DADA* array motifs (Sethuraman *et al.*, 2003) are also shown in 15 out of 18 CSD entries; the pyrimidine molecules are bridged by O atoms of the carboxylate groups [refcodes BOJGEN (Balasubramani & Muthiah, 2008), KUQQUJ (Thanigaimani & Muthiah, 2010), LENKEV (Devi, Muthiah, Rychlewska & Plutecka, 2006), PARXAI, PARXEM, PARXIQ (Stanley *et al.*, 2005), UHAYEH, UHAYIL (Stanley *et al.*, 2002), ULAXOU, ULAXUA and ULAYAH (Sethuraman *et al.*, 2003)], solvent molecules (refcode QOVQAU; Thanigaimani *et al.*, 2009) or anions [refcodes CIVDEQ01 (Tanaka *et al.*, 2004), DUTTOC (Nirmalram & Thomas Muthiah, 2010) and YIZCOA (Balasubramani, Muthiah & Lynch, 2007)]. In seven CSD entries, the pyrimethamine molecules are linked to the other compounds, rather than forming $R_2^2(8)$ homodimers [refcodes AFESOU (Subashini *et al.*, 2007), GINNIB (Balasubramani, Muthiah, Bocelli & Cantoni, 2007), KUQRAQ, KUQREU (Thanigaimani & Muthiah, 2010), LAVZOY (Balasubramani *et al.*, 2005), ULAXIO (Sethuraman *et al.*, 2003) and VEVNIU (Devi, Muthiah, Bocelli & Cantoni, 2006)]. In the cocrystal of pyrimethamine and orotic acid (Fig. 9), both molecules exhibit the desired arrangement of donor and acceptor groups, being held together by three hydrogen bonds forming complementary complexes. No other CSD entry with pyrimethamine shows a similar hydrogen-bonding pattern. Furthermore, the N—H···Cl hydrogen bond does not seem to be a favourable interaction in the solid state, therefore it is only formed in (I*a*)

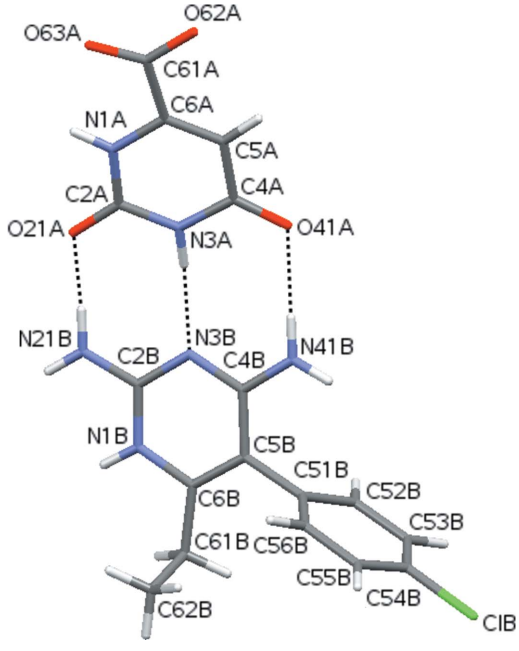


Figure 9
The complex of pyrimethamine and orotic acid (Tutughamiarso & Bolte, 2011), connected by three hydrogen bonds, which are shown as dashed lines.

and four other CSD entries [refcodes GAMFAC (Hemamalini *et al.*, 2005), MUFMAB (Sethuraman & Thomas Muthiah, 2002), ULAXIO (Sethuraman *et al.*, 2003) and VEVNIU (Devi, Muthiah, Bocelli & Cantoni, 2006)].

In summary, pyrimethamine, either neutral or protonated, always adopts approximately the same conformation, which represents the molecular geometry observed in previous studies of drug–enzyme complexes. The formation of homodimers exhibiting the $R_2^2(8)$ hydrogen-bonding motif is obviously predominant for pyrimethamine molecules in the solid state, but such homodimers are not observed in the cocrystal of pyrimethamine and orotic acid. Since both molecules exhibit complementary functional groups, the pyrimethamine molecule is hydrogen bonded to the orotic acid molecule rather than forming the supposedly preferred $R_2^2(8)$ homodimer. Altogether, our study confirms the robustness of the supramolecular synthon containing molecules with a donor–acceptor–donor site and an acceptor–donor–acceptor site.

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

D—H···A	D—H	H···A	D···A	D—H···A
N21—H211···N1^{i}	0.91 (11)	2.14 (11)	3.043 (10)	172 (8)
N21—H212···N3^{ii}	0.86 (10)	2.50 (11)	3.339 (10)	166 (8)
N41—H412···N3^{iii}	0.88 (2)	2.17 (3)	3.032 (8)	167 (8)

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

Table 2
Hydrogen-bond geometry (Å, °) for (I*a*).

D—H···A	D—H	H···A	D···A	D—H···A
N21—H211···Cl1^{i}	0.85 (2)	2.72 (3)	3.5607 (18)	170 (2)
N21—H212···O1X^{ii}	0.85 (3)	2.14 (3)	2.958 (2)	164 (2)
N41—H411···N3^{ii}	0.84 (3)	2.26 (3)	3.102 (2)	174 (2)
N41—H412···O1X	0.88 (3)	2.22 (3)	2.921 (2)	137 (2)

Symmetry codes: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, z-\frac{1}{2}$; (ii) $-x+1, -y+2, -z+1$.

Experimental

Single crystals of (I) were obtained during attempts to cocrystallize pyrimethamine (2.5 mg, 0.010 mmol) with 2,4-dihydroxypteridine (2.0 mg, 0.012 mmol) and 2,6-diaminopurine hydrate (1.3 mg, 0.009 mmol) from dimethyl sulfoxide (DMSO; 250 µl) at room temperature. Solvent-evaporation experiments with mixtures of pyrimethamine (2.2 mg, 0.088 mmol) and 2-acetamidothiazole (1.7 mg, 0.012 mmol) from DMSO (150 µl) at room temperature yielded (I*a*). Cocrystallization attempts of pyrimethamine (3.5 mg, 0.014 mmol) and N^2,9-diacetylguanine (2.5 mg, 0.011 mmol) from *N*-methylpyrrolidin-2-one (NMP; 350 µl) at room temperature yielded (I*b*), while crystals of (II) were obtained by crystallization attempts of pyrimethamine (2.8 mg, 0.011 mmol) with N^2,9-diacetylguanine (3.1 mg, 0.013 mmol) from a solvent mixture of NMP (150 µl) and DMSO (150 µl) at 323 K. All chemical substances are commercially available and none of the solvents used in the experiments was water-free.

Compound (I)

Crystal data

$C_{12}H_{13}ClN_4$
M_r = 248.71
Monoclinic, $P2_1/c$
a = 14.4471 (18) Å
b = 7.5774 (7) Å
c = 11.7526 (15) Å
β = 107.279 (10)°
V = 1228.5 (2) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.29 mm^{-1}
T = 173 K
0.50 × 0.40 × 0.20 mm

Data collection

Stoe IPDS II two-circle diffractometer
15453 measured reflections
2149 independent reflections
1616 reflections with $I > 2\sigma(I)$
R_{int} = 0.221

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.131
$wR(F^2)$ = 0.333
S = 1.11
2149 reflections
167 parameters
2 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.58 e Å^{-3}
$\Delta\rho_{min}$ = −0.53 e Å^{-3}

Pseudopolymorph (I*a*)

Crystal data

$C_{12}H_{13}ClN_4{\cdot}C_2H_6OS$
M_r = 326.84
Monoclinic, $P2_1/n$
a = 13.5596 (9) Å
b = 7.7212 (4) Å
c = 16.2870 (11) Å
β = 111.609 (5)°
V = 1585.35 (17) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.38 mm^{-1}
T = 173 K
0.50 × 0.40 × 0.30 mm

Data collection

Stoe IPDS II two-circle diffractometer
Absorption correction: multi-scan (*MULABS*; Spek, 2009; Blessing, 1995)
T_{min} = 0.834, T_{max} = 0.895
7296 measured reflections
2939 independent reflections
2615 reflections with $I > 2\sigma(I)$
R_{int} = 0.047

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.110
S = 1.00
2939 reflections
217 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}

Pseudopolymorph (I*b*)

Crystal data

$C_{12}H_{13}ClN_4{\cdot}C_5H_9NO$
M_r = 347.85
Triclinic, $P\overline{1}$
a = 9.5221 (14) Å
b = 10.8372 (15) Å
c = 18.650 (2) Å
α = 101.937 (11)°
β = 99.555 (11)°
γ = 98.892 (12)°
V = 1820.9 (4) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.22 mm^{-1}
T = 173 K
0.60 × 0.60 × 0.20 mm

Data collection

Stoe IPDS II two-circle diffractometer
16150 measured reflections
6800 independent reflections
3240 reflections with $I > 2\sigma(I)$
R_{int} = 0.107

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

D—H···A	D—H	H···A	D···A	D—H···A
N21A—H212···N1B^{i}	0.90 (2)	2.19 (2)	3.087 (5)	176 (4)
N21A—H211···O2X	0.88 (2)	2.06 (2)	2.931 (5)	168 (4)
N41A—H411···N3B	0.89 (5)	2.14 (5)	3.025 (5)	176 (4)
N41A—H412···O2Y	0.87 (5)	2.44 (5)	3.126 (5)	136 (4)
N21B—H214···N1A^{ii}	0.87 (6)	2.21 (6)	3.082 (5)	176 (5)
N21B—H213···O2Y	0.91 (5)	2.21 (5)	3.117 (5)	172 (5)
N41B—H413···N3A	0.89 (2)	2.21 (2)	3.097 (5)	173 (4)
N41B—H414···O2X	0.88 (2)	2.10 (4)	2.808 (5)	137 (4)

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

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.079	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2)$ = 0.226	$\Delta\rho_{max}$ = 0.83 e Å^{-3}
S = 0.93	$\Delta\rho_{min}$ = −0.46 e Å^{-3}
6800 reflections	
486 parameters	
36 restraints	

Compound (II)

Crystal data

$C_{22}H_{27}ClN_6O_2$	γ = 93.783 (7)°
M_r = 442.95	V = 1075.06 (16) Å^3
Triclinic, $P\overline{1}$	Z = 2
a = 6.7742 (6) Å	Mo $K\alpha$ radiation
b = 9.2265 (8) Å	μ = 0.21 mm^{-1}
c = 17.3345 (15) Å	T = 173 K
α = 95.363 (7)°	0.50 × 0.20 × 0.10 mm
β = 92.435 (7)°	

Data collection

Stoe IPDS II two-circle diffractometer	15311 measured reflections
Absorption correction: multi-scan (*MULABS*; Spek, 2009; Blessing, 1995)	3776 independent reflections
T_{min} = 0.902, T_{max} = 0.979	2262 reflections with $I > 2\sigma(I)$
	R_{int} = 0.115

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.061	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2)$ = 0.161	$\Delta\rho_{max}$ = 0.97 e Å^{-3}
S = 0.90	$\Delta\rho_{min}$ = −0.34 e Å^{-3}
3776 reflections	
288 parameters	
2 restraints	

The H atoms, except those bonded to disordered atoms, were initially located by difference Fourier synthesis. H atoms bonded to C atoms were refined using a riding model, with methyl C—H = 0.98 Å, secondary C—H = 0.99 Å, tertiary C—H = 1.00 Å and aromatic C—H = 0.95 Å, and with U_{iso}(H) = 1.5U_{eq}(C) for methyl or 1.2U_{eq}(C) for secondary, tertiary and aromatic H atoms. The positions of all amine H atoms in the structures were refined, although a bond-length restraint of 0.88 (2) Å was applied to the N—H distances involving N41 in (I), N21A and N41B in (Ib), and N21 and N41 in (II). The displacement parameters of the amine H atoms in (Ia) were refined isotropically, while in the other structures, their isotropic displacement parameters were coupled to those of the parent N atoms, with U_{iso}(H) = 1.2U_{eq}(N).

The crystal of (I) is a nonmerohedral twin indicated by its systematically high K value for reflections with low intensity [K = mean(F_o^2)/mean(F_c^2)]. The twin law (1 0 0.73/0 $\overline{1}$ 0/0 0 $\overline{1}$) and the reflection data file for refinement was prepared using *PLATON* (Spek, 2009). *PLATON* produces a file containing 1588 non-overlaps from the main domain, plus those 719 reflections that it considers would be overlaps from both domains flagged as such so that the domain ratio can be refined. For refinement, the data were read in *via* HKLF5 (*SHELXL97*; Sheldrick, 2008) and an additional variable was introduced (using the BASF command in *SHELXL97*) describing the fractional contributions of the two twin components; the ratio refined to 0.38 (1):0.62 (1). The approximations inherent in the *PLATON* method of generating a HKLF5 file may be responsible for the relatively poor final agreement factors and reduced precision of the geometric parameters for this structure.

Table 4
Selected torsion angles (°) for (II).

N3—C2—N21—C5X	−161.7 (3)	C1X—N1X—C5X—N21	64.9 (5)
N3—C4—N41—C5Y	11.4 (5)	C1Y—N1Y—C5Y—N41	−51.6 (4)
C5—C6—C61—C62	125.6 (4)		

Table 5
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N21—H21···O2Y^{i}	0.87 (2)	2.04 (2)	2.906 (4)	179 (4)
N41—H41···O2X^{ii}	0.87 (2)	2.10 (2)	2.900 (4)	154 (3)

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

In (Ia), the S atom of the DMSO solvent molecule is disordered over two positions, with a site-occupation factor of 0.564 (2) for the major occupied orientation.

In (Ib), the terminal C atom of the ethyl group in pyrimethamine molecule B is disordered over two sites. Furthermore, NMP molecule Y is disordered over a pseudo-mirror plane along the O2Y and C5Y atoms. The site-occupation factors for the major occupied orientations are 0.61 (1) for the methyl group and 0.72 (1) for the solvent molecule. The minor-occupied orientations of the disordered atoms were refined isotropically. Bond-length and bond-angle restraints were applied for the ethyl group of molecule B, the NMP molecule X and the major occupied orientation of the NMP molecule Y, while similarity restraints were applied for the 1,2- and 1,3-distances of the minor occupied orientation of molecule Y.

The presence of relatively high residual electron-density peaks in (Ib) and (II) indicates possible disorder of NMP molecule X [in (Ib)] and the 'X' ring [in (II)]. However, the heights of these peaks are less than 1 e Å^{-3} and attempts to model a second component failed. The NMP molecule X [in (Ib)] and the 'X' ring [in (II)] seem to be planar (r.m.s. deviations = 0.034 and 0.018 Å for all non-H atoms, respectively), but the apparent planarity is probably merely a consequence of the untreated disorder.

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, 2010).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3416). Services for accessing these data are described at the back of the journal.

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