organic compounds

Five pseudopolymorphs and a cocrystal of nitrofurantoin

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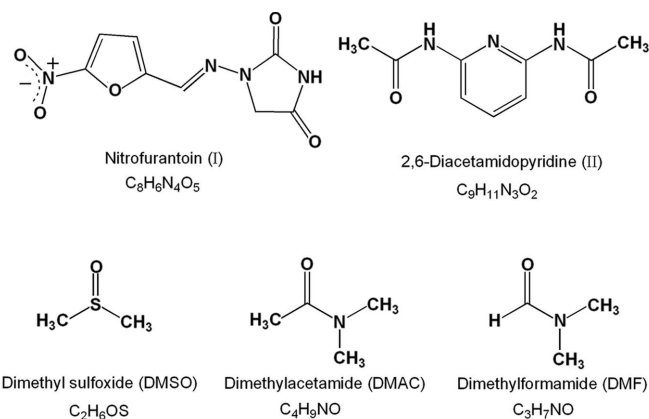Correspondence e-mail: egert@chemie.uni-frankfurt.de

The antibiotic nitrofurantoin {systematic name: (E)-1-[(5-nitro-2-furyl)methylideneamino]imidazolidine-2,4-dione} is not only used for the treatment of urinary tract infections, but also illegally applied as an animal food additive. Since derivatives of 2,6-diaminopyridine might serve as artificial receptors for its recognition, we crystallized one potential drug–receptor complex, nitrofurantoin–2,6-diacetamidopyridine (1/1), $C_8H_6N_4O_5 \cdot C_9H_{11}N_3O_2$, (I·II). It is characterized by one N—H···N and two N—H···O hydrogen bonds and confirms a previous NMR study. During the crystallization screening, several new pseudopolymorphs of both components were obtained, namely a nitrofurantoin dimethyl sulfoxide monosolvate, $C_8H_6N_4O_5 \cdot C_2H_6OS$, (Ia), a nitrofurantoin dimethyl sulfoxide hemisolvate, $C_8H_6N_4O_5 \cdot 0.5C_2H_6OS$, (Ib), two nitrofurantoin dimethylacetamide monosolvates, $C_8H_6N_4O_5 \cdot C_4H_9NO$, (Ic) and (Id), and a nitrofurantoin dimethylacetamide disolvate, $C_8H_6N_4O_5 \cdot 2C_4H_9NO$, (Ie), as well as a 2,6-diacetamidopyridine dimethylformamide monosolvate, $C_9H_{11}N_3O_2 \cdot C_3H_7NO$, (IIa). Of these, (Ia), (Ic) and (Id) were formed during cocrystallization attempts with 1-(4-fluorophenyl)biguanide hydrochloride. Obviously nitrofurantoin prefers the higher-energy conformation in the crystal structures, which all exhibit N—H···O and C—H···O hydrogen-bond interactions. The latter are especially important for the crystal packing. 2,6-Diacetamidopyridine shows some conformational flexibility depending on the hydrogen-bond pattern.

Comment

Nitrofurantoin is an antibacterial drug used for the treatment of urinary tract infections. It is reduced by bacterial flavoproteins to reactive intermediates, which inhibit the processes of protein synthesis, and aerobic energy metabolism as well as DNA, RNA and cell-wall synthesis (Cadwallader & Jun, 1976). The resistance of E. coli to other antibiotics has led to

an increased interest in this drug in spite of its severe side effects (Cunha, 2006). In many countries, it is illegally applied as an animal food additive, which can further be passed to humans through the food chain and cause a range of diseases. Since the present quantification of nitrofurantoin is time-consuming and costly, diaminopyridine derivatives are developed as artificial receptors for its recognition. The drug–receptor complex is characterized by one N—H···N and two N—H···O hydrogen bonds and has been examined by NMR spectroscopy (Athikomrattanakul et al., 2009).

Nitrofurantoin (I)
$C_8H_6N_4O_5$

2,6-Diacetamidopyridine (II)
$C_9H_{11}N_3O_2$

Dimethyl sulfoxide (DMSO)
C_2H_6OS

Dimethylacetamide (DMAC)
C_4H_9NO

Dimethylformamide (DMF)
C_3H_7NO

(Ia) Nitrofurantoin · DMSO
(Ib) Nitrofurantoin · 0.5 DMSO
(Ic) Nitrofurantoin · DMAC
(Id) Nitrofurantoin · DMAC
(Ie) Nitrofurantoin · 2 DMAC
(IIa) 2,6-Diacetamidopyridine · DMF
(I·II) Nitrofurantoin · 2,6-Diacetamidopyridine

A study of the Cambridge Structural Database (CSD, Version 5.31 of November 2009, plus three updates; Allen, 2002) revealed that similar hydrogen-bond patterns are observed in cocrystals of 2,6-diaminopyridine derivatives and six-membered ring compounds with complementary functional groups [CSD refcodes: DOPCUG (Feibush et al., 1986), FODTIB (Hamilton & Van Engen, 1987), MAWPUW (Li et al., 2005), VABVID and VABVOJ (Muehldorf et al., 1988), and XESSAQ (Spange et al., 2006)]. Since no such cocrystal with five-membered ring compounds has been reported, we cocrystallized nitrofurantoin and 2,6-diacetamidopyridine. In addition to the desired cocrystal, denoted (I·II), five pseudo-
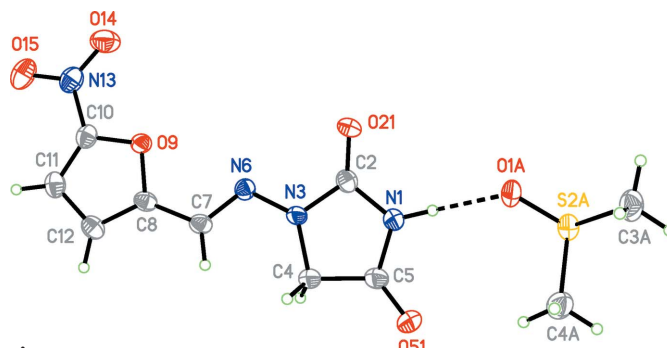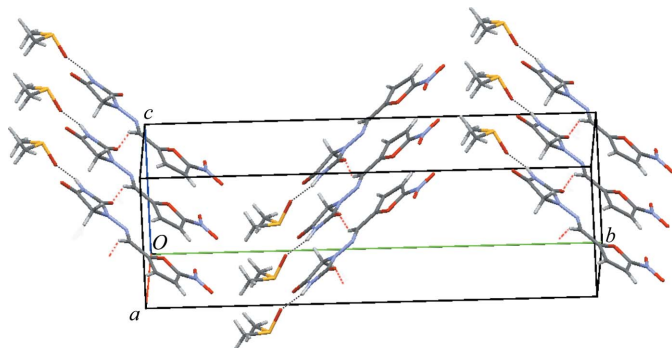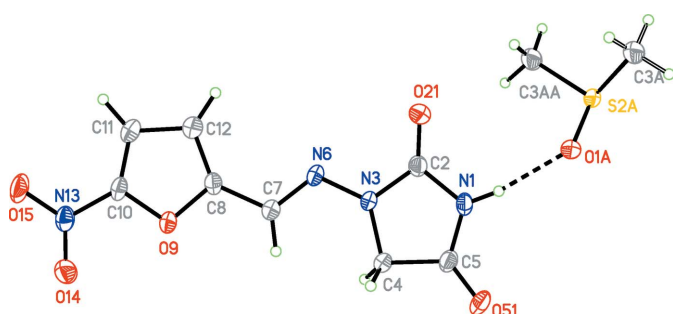

Figure 1
A perspective view of (Ia), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The dashed line indicates the N—H···O hydrogen bond.
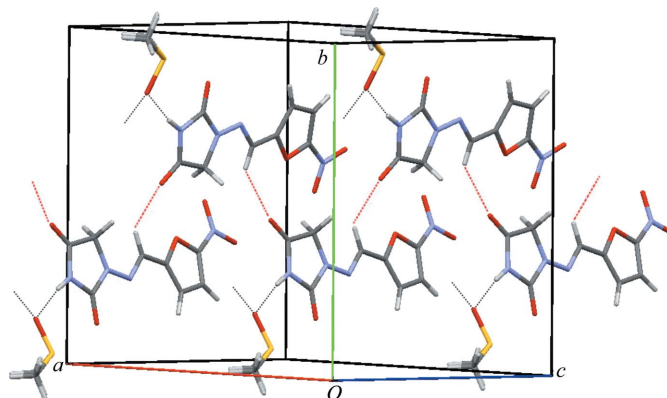
Figure 2
A packing diagram for (I*a*). N—H···O and C—H···O hydrogen bonds are shown as dashed lines.

Figure 3
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. The dashed line indicates the N—H···O hydrogen bond. The dimethyl sulfoxide solvent molecule lies on a twofold axis and only one of the two disordered positions is shown.

Figure 4
A packing diagram for (I*b*). N—H···O and C—H···O hydrogen bonds are shown as dashed lines. Only one site of the disordered dimethyl sulfoxide solvent molecule is shown.
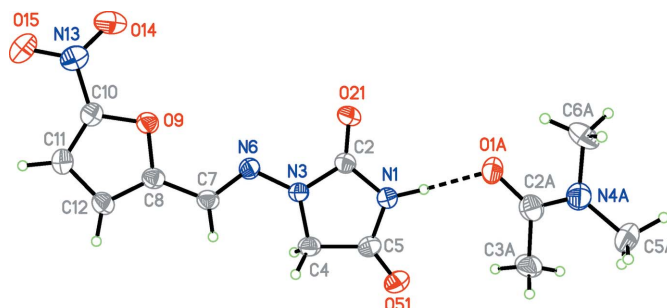

Figure 5
A perspective view of (I*c*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The dashed line indicates the N—H···O hydrogen bond. The dimethylacetamide solvent molecule is disordered and only the major occupied site is shown.
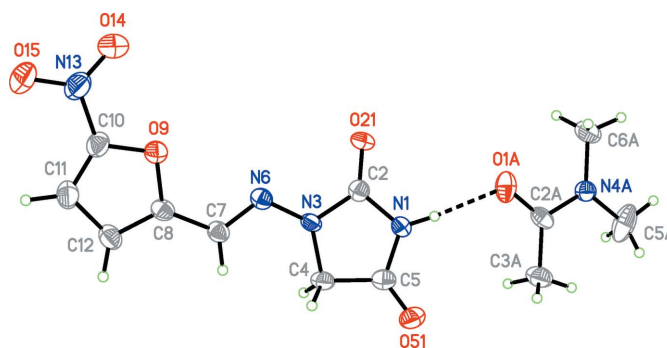
Figure 6
A perspective view of (I*d*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The dashed line indicates the N—H···O hydrogen bond. The dimethylacetamide solvent molecule is disordered and only the major occupied site is shown.

polymorphs of nitrofurantoin crystallized during the various cocrystallization experiments, namely a dimethyl sulfoxide monosolvate, (I*a*), a dimethyl sulfoxide hemisolvate, (I*b*), two dimethylacetamide monosolvates, (I*c*) and (I*d*), and a dimethylacetamide disolvate, (I*e*). Furthermore, a 2,6-diacetamidopyridine dimethylformamide monosolvate, (II*a*), was obtained. The pseudopolymorphs (I*a*), (I*c*) and (I*d*) were formed during cocrystallization attempts with 1-(4-fluorophenyl)biguanide hydrochloride whose nonplanar geometry possibly prevented the formation of a complex (Tutughamiarso & Bolte, 2010).

Compounds (I*a*) and (I*b*) formed during cocrystallization attempts from dimethyl sulfoxide (DMSO). (I*a*) crystallized in the monoclinic space group $P2_1/c$ with one nitrofurantoin and one DMSO molecule in the asymmetric unit. Both molecules are linked by an N—H···O hydrogen bond (Fig. 1). C—H···O interactions between nitrofurantoin molecules lead to ribbons running along the *a* axis, which are further stabilized by van der Waals interactions to give a herringbone pattern (Fig. 2). Compound (I*b*) crystallized in the monoclinic space group $C2/c$ as a hemisolvate. The DMSO molecule lies on a twofold axis with the S atom disordered over two positions (Fig. 3). The packing of (I*b*) shows zigzag chains of C—H···O hydrogen-bonded nitrofurantoin molecules running along the *a* axis (Fig. 4).

Crystallization attempts from dimethylacetamide (DMAC) yielded another three nitrofurantoin solvates, *viz.* (I*c*), (I*d*) and (I*e*). (I*c*) and (I*d*) crystallized with one nitrofurantoin and one DMAC molecule in the asymmetric unit (Figs. 5 and 6). In both structures, the DMAC molecule is disordered over two sites with all non-H atoms of these two sites in a common
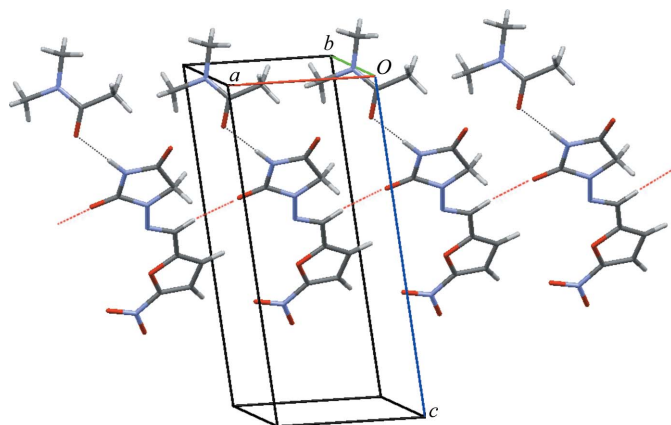
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Figure 7
A partial packing diagram for (I*c*). N—H···O and C—H···O hydrogen bonds are shown as dashed lines. The minor occupied site of the dimethylacetamide solvent molecules has been omitted.

Figure 9
A perspective view of (I*e*), 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 lines indicate hydrogen bonds. The dimethylacetamide solvent molecules are disordered and only the major occupied sites are shown.

Figure 8
A partial packing diagram for (I*d*). N—H···O and C—H···O hydrogen bonds are shown as dashed lines. The minor occupied site of the dimethylacetamide solvent molecules has been omitted.

Figure 10
A partial packing diagram for (I*e*). N—H···O and C—H···O hydrogen bonds are shown as dashed lines. The minor occupied sites of the dimethylacetamide solvent molecules have been omitted.
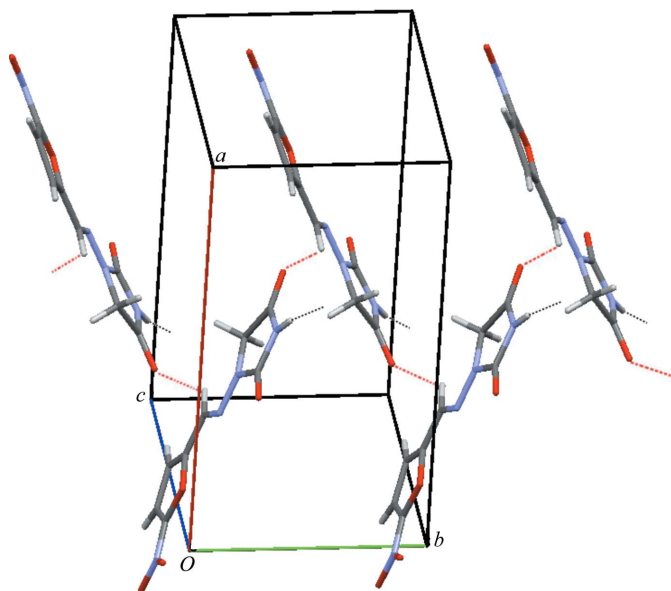
plane (r.m.s. deviation = 0.024 Å for both structures). (I*c*) crystallized in the triclinic space group $P\bar{1}$ and (I*d*) in the monoclinic space group $P2_1/c$. A similar hydrogen-bond pattern is observed; the nitrofurantoin molecules are linked to each other by C—H···O and to the solvent molecules by N—H···O interactions. However, the packing motifs of the two polymorphs are quite different. Nitrofurantoin and the solvent molecules form ribbons parallel to the $(0\bar{2}3)$ plane in (I*c*) and zigzag chains running along the *b* axis in (I*d*) (Figs. 7 and 8). In (I*e*), which crystallized in the monoclinic space group $P2_1/c$, there are two independent solvent molecules (Fig. 9). Again, each DMAC molecule is disordered over two sites with a planar arrangement of all non-H atoms (r.m.s. deviations = 0.024 and 0.038 Å). The nitrofurantoin molecules are linked to
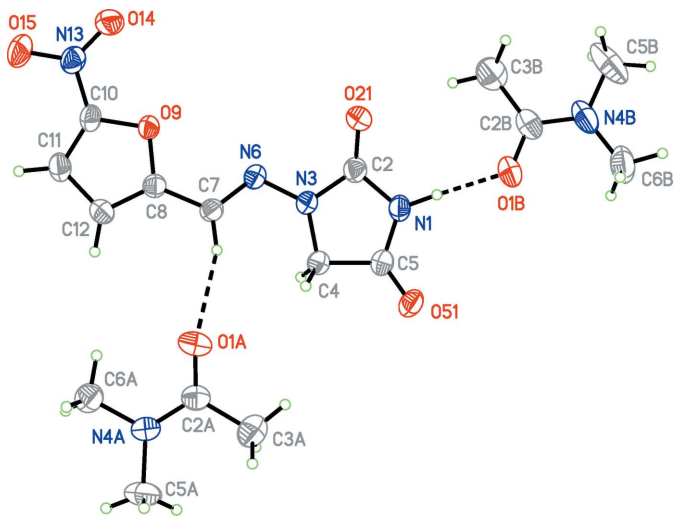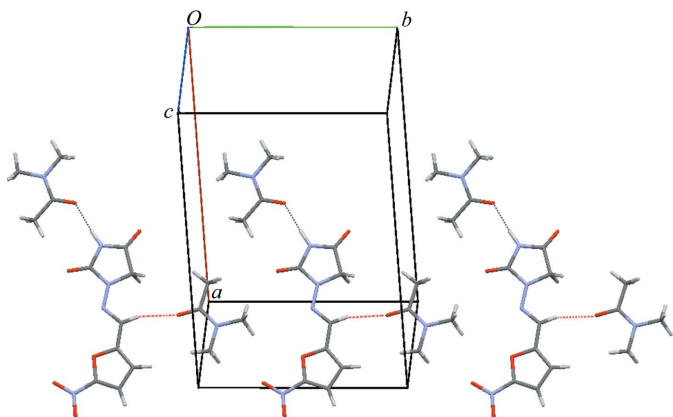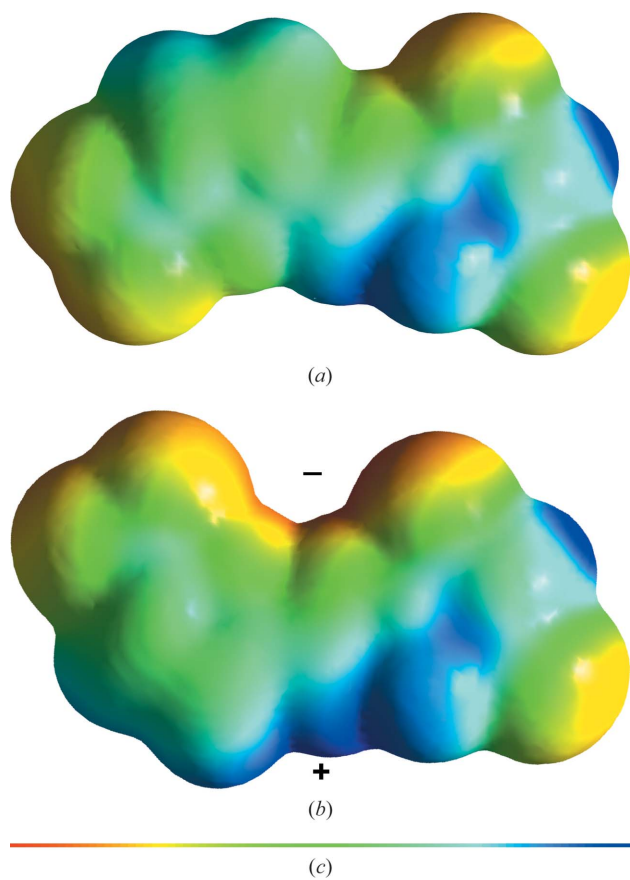
one of these by an N—H···O and to the other one by a C—H···O hydrogen bond to give discrete trimeric units. The packing shows layers parallel to the $(50\bar{2})$ plane (Fig. 10).

In the five pseudopolymorphs, (I*a*)–(I*e*), the configuration of nitrofurantoin with respect to the C7=N6 double bond is *E*, with the C7—H group pointing towards the methylene group of the imidazolidinedione ring. The dihedral angle between the planes through the two rings varies from 5.9 (1) to 12.4 (1)°. Since the nitro group is rotated by less than 10° with respect to the furan ring, the molecules are almost planar (Table 10). Because of the rotatable C7—C8 bond, nitrofurantoin can adopt two forms, *viz.* an antiperiplanar conformation between N6 and the furan O9 atom [as in (I*b*)], and a synperiplanar conformation (observed in the other four

Figure 12
A perspective view of (II*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 dashed line indicates the N—H···O hydrogen bond. The rotational disorder of the methyl groups is not shown.

Figure 13
A partial packing diagram for (II*a*). Hydrogen bonds are shown as dashed lines.
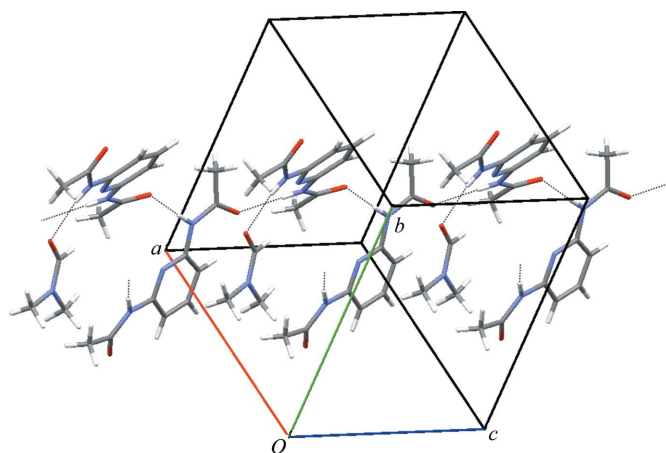

Figure 11
(*a*) The molecular charge distribution of the antiperiplanar conformer of nitrofurantoin. The electrostatic potential was calculated on an isosurface at 0.0004 e b^{-3}; the colour scale ranges from −0.07 to +0.07 h (e: elementary charge; b: bohr, the atomic unit of length; h: hartree, the atomic unit of energy). (*b*) The molecular charge distribution of the synperiplanar conformer of nitrofurantoin. (*c*) The colour scale for the molecular charge distribution. (In the electronic version of the paper, regions of high relative negative charge are red and those of high relative positive charge are blue.)

pseudopolymorphs). According to an *ab initio* energy calculation with geometry optimization [*GAUSSIAN*; basis set: RHF/6–31+G(*d*); Frisch *et al.*, 2004], the synperiplanar conformation is less stable by 11.8 kJ mol^{-1} than the antiperiplanar one. Since high-energy conformers are rarely observed in crystal structures (Weng *et al.*, 2008), we examined all five structures involving nitrofurantoin recorded in the CSD [refcodes: HAXBUD, HAXBUD01 (Pienaar *et al.*, 1993*a*), LABJON (Bertolasi *et al.*, 1993), and LABJON01 and LABJON02 (Pienaar *et al.*, 1993*b*)], which confirmed that apparently the higher-energy conformer is preferred in the solid state. A detailed analysis with our force-field program *MOMO* (Wagner *et al.*, 2009), which also clearly favoured the antiperiplanar conformation, revealed that the energy difference is caused by electrostatic interactions. A closer examination of the molecular charge distribution calculated by *GAUSSIAN* shows that the positive and negative charges are equally distributed in the antiperiplanar conformation, while in the synperiplanar one the molecule has positive and nega-
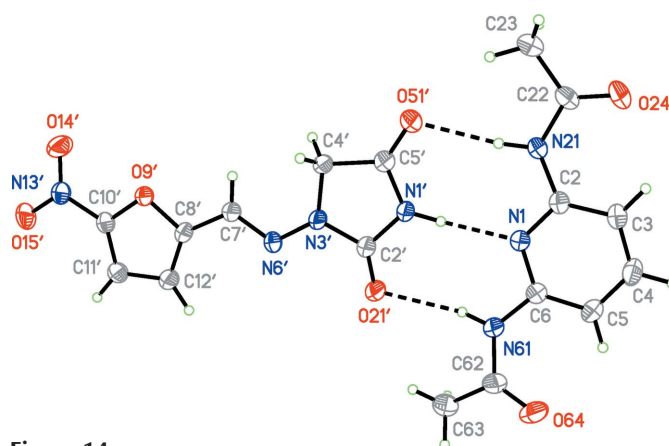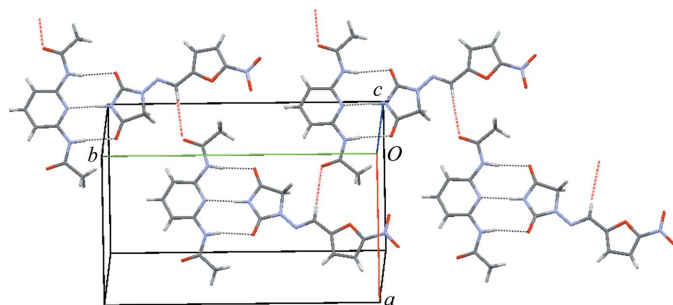

Figure 14
A perspective view of (I·II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The dashed lines indicate hydrogen bonds.

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Figure 15
A partial packing diagram for (I·II). N—H···O, N—H···N and C—H···O hydrogen bonds are shown as dashed lines.

tive sides (Fig. 11). This may promote a more compact crystal packing, which would explain why the less stable conformer is favoured in the solid phase.

During the preparation of the nitrofurantoin receptor, 2,6-diacetamidopyridine crystallized as a dimethylformamide (DMF) monosolvate, (IIa), in the monoclinic space group $P2_1/c$. Both methyl groups of the 2,6-diacetamidopyridine molecule show rotational disorder and are antiperiplanar to the pyridine ring atoms. Thus, the two N—H bonds are directed to the same side as the pyridine N atom (Fig. 12). The 2,6-diacetamidopyridine and DMF molecules are connected by an N—H···O hydrogen bond from one amide group. These entities form zigzag chains along the c axis stabilized by further N—H···O bonds between the other amide groups (Fig. 13). Similar conformations are observed in the crystal structures of solvent-free 2,6-diacetamidopyridine [refcodes: DOPDAN (Feibush *et al.*, 1986) and DOPDAN01 (Mahapatra *et al.*, 2009)].

The desired complex, (I·II), crystallized in the monoclinic space group $P2_1/n$, with nitrofurantoin and 2,6-diacetamido-pyridine connected by one N—H···N and two N—H···O hydrogen bonds (Fig. 14). As in (Ib), the nitrofurantoin molecule adopts the antiperiplanar conformation as well as the usual E configuration of the C=N double bond. The nitro group and the furan ring are coplanar and the planes through the furan and imidazolidinedione moieties form a dihedral angle of 9.0 (1)°. Similar to (IIa), the carbonyl O atoms of the 2,6-diacetamidopyridine molecule point away from the pyridine N atom. One of the amide groups is coplanar with the pyridine ring, while the other one encloses a dihedral angle of 16.7 (1)° with it. The crystal packing shows layers parallel to the (103) plane, which are stabilized by C—H···O interactions between both components (Fig. 15).

Nitrofurantoin forms an N—H···O and a C—H···O hydrogen bond in all (pseudo)polymorphs. Interestingly, the N—H···O bond connects two nitrofurantoin molecules only in the solvent-free forms (LABJON, LABJON01 and LABJON02); in the solvates [(Ia)–(Ie), HAXBUD and HAXBUD01], the interaction is with the solvent molecule. The C—H···O interaction (always with participation of the C—H bond of the hydrazone moiety N—N=C—H) usually connects two nitrofurantoin molecules and thus plays a

significant role in the crystal packing. This also occurs in the structure of complex (I·II). Even though its molecular structure in solvent-free forms and the dimethylformamide solvate, (IIa), is very similar, 2,6-diacetamidopyridine shows some conformational flexibility. The dihedral angle between the planes through the amide groups and the pyridine ring varies from 2.8 (2) to 33.4 (2)° depending on the hydrogen-bonding interactions. In the cocrystal, (I·II), the hydrogen-bonded complexes are further linked by C—H···O interactions involving one of the amide groups. As a result of that, the 2,6-diacetamidopyridine molecule is not planar. Altogether, since no crystal structure of a complex between nitrofurantoin and a 2,6-diaminopyridine derivative has yet been published, cocrystal (I·II) confirms the NMR study (Athikomrattanakul *et al.*, 2009) of this drug–receptor complex.

Experimental

Single crystals of (Ia), (Ic) and (Id) were obtained during attempts to cocrystallize commercially available nitrofurantoin (541 K) with 1-(4-fluorophenyl)biguanide hydrochloride (523–527 K) in DMSO or DMAC (Table 8). Solvent evaporation experiments with mixtures of nitrofurantoin and 2,6-diacetamidopyridine (454 K) yielded (Ib), (Ie) and cocrystal (I·II) (Table 9).

For the preparation of compound (II), 2,6-diaminopyridine (5 g, 0.046 mol) was added to a solution of acetic acid anhydride (10.4 ml, 0.055 mol) in 1,4-dioxane (100 ml) under a nitrogen atmosphere. The reaction mixture was heated at reflux for 24 h. After cooling to room temperature, the solvent was removed using a rotary evaporator. Unreacted 2,6-diaminopyridine and acetic acid anhydride were rinsed away with water. 11.5 mg (0.060 mmol) of 2,6-diacetamidopyridine dissolved in dimethylformamide (200 μl) at 323 K yielded (IIa).

Pseudopolymorph (Ia)

Crystal data

$C_8H_6N_4O_5 \cdot C_2H_6OS$	$V = 1381.73\ (16)$ Å^3
$M_r = 316.30$	$Z = 4$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 6.6257\ (4)$ Å	$\mu = 0.27$ mm^{-1}
$b = 26.488\ (2)$ Å	$T = 173$ K
$c = 8.0032\ (5)$ Å	$0.40 \times 0.20 \times 0.20$ mm
$\beta = 100.347\ (5)°$	

Data collection

Stoe IPDS II two-circle diffractometer	15878 measured reflections
	2437 independent reflections
Absorption correction: multi-scan (*MULABS*; Spek, 2009; Blessing, 1995)	1588 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.176$
$T_{min} = 0.900$, $T_{max} = 0.948$	

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O1A	0.89 (4)	1.86 (4)	2.733 (4)	167 (3)
C7—H7···O21^i	0.95	2.24	3.065 (4)	145

Symmetry code: (i) $x - 1, y, z$.

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

$D-\text{H}\cdots A$	$D-\text{H}$	$\text{H}\cdots A$	$D\cdots A$	$D-\text{H}\cdots A$
N1—H1···O1A	0.85 (3)	1.94 (3)	2.7841 (16)	171 (2)
C7—H7···O51^i	0.95	2.49	3.235 (2)	136

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

Table 3
Hydrogen-bond geometry (Å, °) for (I*c*).

$D-\text{H}\cdots A$	$D-\text{H}$	$\text{H}\cdots A$	$D\cdots A$	$D-\text{H}\cdots A$
N1—H1···O1A	0.94 (3)	1.82 (3)	2.7533 (19)	169 (2)
C7—H7···O21^i	0.95	2.34	3.123 (2)	139

Symmetry code: (i) $x+1, y, z$.

Table 4
Hydrogen-bond geometry (Å, °) for (I*d*).

$D-\text{H}\cdots A$	$D-\text{H}$	$\text{H}\cdots A$	$D\cdots A$	$D-\text{H}\cdots A$
N1—H1···O1A	0.86 (3)	1.88 (3)	2.736 (3)	172 (3)
C7—H7···O51^i	0.95	2.45	3.137 (3)	129

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

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.110$
$S = 0.89$
2437 reflections
196 parameters

H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.28$ e Å^{-3}
$\Delta\rho_{min} = -0.53$ e Å^{-3}

Pseudopolymorph (I*b*)

Crystal data

$C_8H_6N_4O_5 \cdot 0.5(C_2H_6OS)$
$M_r = 277.23$
Monoclinic, $C2/c$
$a = 16.1710$ (11) Å
$b = 13.7985$ (8) Å
$c = 10.3465$ (8) Å
$\beta = 102.358$ (6)°

$V = 2255.2$ (3) Å^3
$Z = 8$
Mo $K\alpha$ radiation
$\mu = 0.22$ mm^{-1}
$T = 173$ K
$0.50 \times 0.40 \times 0.20$ mm

Data collection

Stoe IPDS II two-circle diffractometer
Absorption correction: multi-scan (*MULABS*; Spek, 2009; Blessing, 1995)
$T_{min} = 0.896$, $T_{max} = 0.957$

13781 measured reflections
2116 independent reflections
1806 reflections with $I > 2\sigma(I)$
$R_{int} = 0.098$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.039$
$wR(F^2) = 0.100$
$S = 1.09$
2116 reflections
181 parameters

H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.28$ e Å^{-3}
$\Delta\rho_{min} = -0.32$ e Å^{-3}

Pseudopolymorph (I*c*)

Crystal data

$C_8H_6N_4O_5 \cdot C_4H_9NO$
$M_r = 325.29$
Triclinic, $P\bar{1}$
$a = 6.6544$ (5) Å
$b = 7.9842$ (6) Å
$c = 14.3515$ (11) Å
$\alpha = 100.021$ (6)°
$\beta = 93.566$ (6)°

$\gamma = 99.274$ (6)°
$V = 737.85$ (10) Å^3
$Z = 2$
Mo $K\alpha$ radiation
$\mu = 0.12$ mm^{-1}
$T = 173$ K
$0.30 \times 0.30 \times 0.20$ mm

Data collection

Stoe IPDS II two-circle diffractometer
24053 measured reflections

2770 independent reflections
2111 reflections with $I > 2\sigma(I)$
$R_{int} = 0.062$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.038$
$wR(F^2) = 0.100$
$S = 0.97$
2770 reflections
232 parameters

H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.28$ e Å^{-3}
$\Delta\rho_{min} = -0.16$ e Å^{-3}

Pseudopolymorph (I*d*)

Crystal data

$C_8H_6N_4O_5 \cdot C_4H_9NO$
$M_r = 325.29$
Monoclinic, $P2_1/c$
$a = 16.2038$ (16) Å
$b = 7.4215$ (5) Å
$c = 13.1195$ (12) Å
$\beta = 111.681$ (7)°

$V = 1466.1$ (2) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.12$ mm^{-1}
$T = 173$ K
$0.30 \times 0.20 \times 0.20$ mm

Data collection

Stoe IPDS II two-circle diffractometer
17332 measured reflections

2743 independent reflections
1584 reflections with $I > 2\sigma(I)$
$R_{int} = 0.147$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.106$
$S = 0.85$
2743 reflections
231 parameters

H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.20$ e Å^{-3}
$\Delta\rho_{min} = -0.26$ e Å^{-3}

Pseudopolymorph (I*e*)

Crystal data

$C_8H_6N_4O_5 \cdot 2C_4H_9NO$
$M_r = 412.41$
Monoclinic, $P2_1/c$
$a = 20.874$ (2) Å
$b = 11.5433$ (9) Å
$c = 8.7162$ (9) Å
$\beta = 100.708$ (9)°

$V = 2063.6$ (3) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.11$ mm^{-1}
$T = 173$ K
$0.60 \times 0.60 \times 0.20$ mm

Data collection

Stoe IPDS II two-circle diffractometer
9751 measured reflections

3844 independent reflections
2943 reflections with $I > 2\sigma(I)$
$R_{int} = 0.078$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.047$
$wR(F^2) = 0.126$
$S = 0.97$
3844 reflections
285 parameters
22 restraints

H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.26$ e Å^{-3}
$\Delta\rho_{min} = -0.24$ e Å^{-3}

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N1—H1$\cdots$O1B	0.95 (3)	1.81 (3)	2.7463 (19)	169 (3)
C7—H7$\cdots$O1A	0.95	2.30	3.175 (2)	152

Compound (IIa)

Crystal data

$C_9H_{11}N_3O_2 \cdot C_3H_7NO$	$V = 1393.00\ (14)$ Å^3
$M_r = 266.30$	$Z = 4$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 11.3031\ (7)$ Å	$\mu = 0.09$ mm^{-1}
$b = 13.1539\ (8)$ Å	$T = 173$ K
$c = 9.3959\ (5)$ Å	$0.50 \times 0.40 \times 0.40$ mm
$\beta = 94.327\ (5)°$	

Data collection

Stoe IPDS II two-circle diffractometer	2603 independent reflections
	1967 reflections with $I > 2\sigma(I)$
12406 measured reflections	$R_{int} = 0.100$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.042$	H atoms treated by a mixture of
$wR(F^2) = 0.099$	independent and constrained
$S = 0.93$	refinement
2603 reflections	$\Delta\rho_{max} = 0.24$ e Å^{-3}
187 parameters	$\Delta\rho_{min} = -0.19$ e Å^{-3}

Table 6
Hydrogen-bond geometry (Å, °) for (IIa).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N21—H21$\cdots$O1A	0.91 (2)	2.00 (2)	2.8979 (18)	168.8 (17)
N61—H61$\cdots$O64^i	0.87 (2)	2.01 (2)	2.8757 (16)	177.4 (18)

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

Cocrystal (I·II)

Crystal data

$C_8H_6N_4O_5 \cdot C_9H_{11}N_3O_2$	$V = 1922.56\ (19)$ Å^3
$M_r = 431.38$	$Z = 4$
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation
$a = 9.8407\ (6)$ Å	$\mu = 0.12$ mm^{-1}
$b = 17.9443\ (10)$ Å	$T = 173$ K
$c = 10.9902\ (6)$ Å	$0.50 \times 0.50 \times 0.40$ mm
$\beta = 97.839\ (5)°$	

Data collection

Stoe IPDS II two-circle diffractometer	3619 independent reflections
	2802 reflections with $I > 2\sigma(I)$
32493 measured reflections	$R_{int} = 0.138$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.044$	H atoms treated by a mixture of
$wR(F^2) = 0.122$	independent and constrained
$S = 1.00$	refinement
3619 reflections	$\Delta\rho_{max} = 0.24$ e Å^{-3}
295 parameters	$\Delta\rho_{min} = -0.25$ e Å^{-3}

Table 7
Hydrogen-bond geometry (Å, °) for (I·II).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N21—H21$\cdots$O51$'$	0.94 (2)	2.16 (2)	3.0640 (19)	162.4 (17)
N61—H61$\cdots$O21$'$	0.88 (2)	2.25 (2)	3.1069 (19)	167 (2)
N1$'$—H1$'\cdots$N1	0.88 (2)	1.99 (2)	2.868 (2)	171.6 (19)
C7$'$—H7$'\cdots$O24^i	0.95	2.69	3.592 (2)	159

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

Crystals of (Ia), (Id) and (I·II) show R_{int} values higher than 0.100 [0.176 for (Ia), 0.147 for (Id) and 0.138 for (I·II)], although the data sets were collected with high redundancy [6.52 for (Ia), 6.32 for (Id) and 8.98 for (I·II)]. (Ia) and (Id) did not diffract very strongly [R_σ values: 0.106 for (Ia) and 0.099 for (Id)], but there is no obvious reason for (I·II). However, all other important quality criteria are satisfied.

The H atoms, except those bonded to disordered solvent 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, secondary C—H = 0.99 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 and aromatic H atoms. H atoms bonded to N atoms were refined isotropically.

In (Ib), the O atom of the dimethyl sulfoxide solvent molecule lies on a twofold axis so that the S atom is disordered. In (Ic), (Id) and (Ie), all solvent atoms except O atoms are disordered over two positions, but the disordered methyl C atoms coincide pairwise thus forming a rectangular arrangement together with the O atom. The site-occupation factors for the major occupied orientations are 0.646 (7) in (Ic), 0.532 (12) in (Id), and 0.926 (5) and 0.881 (6) in (Ie). For the 1,2 and 1,3 distances of both solvent molecules in (Ie), similarity restraints were applied and the carbonyl C and the N atoms of the minor occupied orientations were refined isotropically.

Table 8
Cocrystallization of nitrofurantoin and 1-(4-fluorophenyl)biguanide hydrochloride.

Crystal	Nitrofurantoin (mg mmol^{-1})	1-(4-Fluorophenyl)-biguanide hydro-chloride (mg mmol^{-1})	Solvent	Temperature
(Ia)	2.4/0.010	1.9/0.008	DMSO (100 µl)	277 K
(Ic)	1.4/0.006	1.6/0.007	DMAC (100 µl)	Room temperature
(Id)	2.2/0.009	2.4/0.010	DMAC (100 µl)	277 K

Table 9
Cocrystallization of nitrofurantoin and 2,6-diacetamidopyridine.

Crystal	Nitrofurantoin (mg mmol^{-1})	2,6-Diacetamido-pyridine (mg mmol^{-1})	Solvent	Temperature
(Ib)	2.6/0.011	2.2/0.011	DMSO (150 µl)	Room temperature
(Ie)	2.9/0.012	3.4/0.018	DMAC (100 µl)	277 K
(I·II)	2.8/0.012	3.7/0.019	DMAC (100 µl)	323 K

Table 10
Selected geometric parameters (°) of nitrofurantoin.

The dihedral angle between the furan and the imidazolidinedione ring is designated by α.

Crystal	N3—N6—C7—C8	N6—C7—C8—O9	O9—C10—N13—O14	α (°)
(I*a*)	179.7 (3)	1.8 (5)	−5.0 (5)	8.5 (7)
(I*b*)	−179.37 (13)	175.15 (13)	−2.9 (2)	5.9 (2)
(I*c*)	179.04 (14)	5.3 (2)	−6.2 (2)	12.4 (2)
(I*d*)	178.3 (2)	2.8 (4)	3.4 (4)	8.8 (2)
(I*e*)	−179.32 (14)	4.1 (2)	−1.0 (2)	6.4 (2)
(I·II)	−178.99 (14)	−174.36 (15)	1.0 (3)	9.0 (2)

In (II*a*), the methyl groups of 2,6-diacetamidopyridine are rotationally disordered over two positions, with site-occupation factors of 0.58 (5) and 0.66 (2) for the major occupied orientations.

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* (Macrae *et al.*, 2008) and *XP* (Sheldrick, 2008); software used to prepare material for publication: *publCIF* (Westrip, 2010).

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