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A 1:1 cocrystal of fluconazole with salicylic acid

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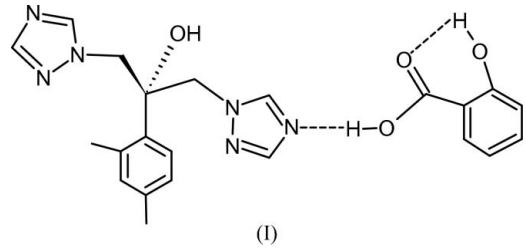
The interaction of the antifungal pharmaceutical agent fluconazole with salicylic acid in acetonitrile solution yields the 1:1 cocrystal 2-(2,4-difluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol–2-hydroxybenzoic acid (1/1), $C_{13}H_{12}F_2N_6O\cdot C_7H_6O_3$. The asymmetric unit consists of one molecule of fluconazole and one molecule of salicylic acid, both in their neutral forms. Both crystal agents form head-to-tail hydrogen-bonded dimers, which are further connected into hydrogen-bonded extended zigzag tapes propagating along the *ac* diagonal.

Comment

An important goal of the solid-state formulation and development of drugs with multicomponent crystalline phases is a search for new pharmaceutical cocrystal forms. A pharmaceutical cocrystal can be defined as a multicomponent crystal system of the active pharmaceutical ingredient (API) with another pharmaceutically acceptable molecule, both existing as solids under ambient conditions. The presence of a cocrystal former in the solid form can have an impact on the chemical and physical properties of APIs, which can lead to improved and optimized drug formulations. Thus, cocrystals have become a complementary tool, in addition to polymorphs, pseudopolymorphs (solvates) and salts, in the development of pharmaceuticals in solid form (Schultheiss & Newman, 2009; Chen *et al.*, 2011, and references therein).

Fluconazole is a wide-spectrum triazole antifungal agent used in the treatment of localized candidiasis and systematic therapy of candidial infections, dermatophytic fungal infections and cryptococcal meningitis. It is commonly used as an accompanying therapy for immunodeficient patients with AIDS or cancer and patients taking immunodepresive agents (Sweetman *et al.*, 2007). It is only slightly soluble in water. Thus, its cocrystallization with pharmaceutically acceptable cocrystal formers presents an attractive option to increase its solubility. Along these lines, we have focused our research on the preparation of new fluconazole cocrystals and have recently reported the crystal structures of three fluconazole cocrystals with three dicarboxylic acids, namely maleic, glutaric and fumaric acids (Kastelic *et al.*, 2010). We have extended our research to the preparation and investigation of further fluconazole cocrystals, not only with aliphatic dicarboxylic acids which proved to be appropriate cocrystal formers, but also with aromatic and/or monocarboxylic acids. We present here the crystal structure of a 1:1 cocrystal of fluconazole and salicylic acid, (I).



(I)

The asymmetric unit of (I) consists of one fluconazole and one salicylic acid molecule (Fig. 1), both in their neutral forms. An intramolecular hydrogen bond of type *S*(6) (Bernstein *et al.*, 1995) is observed in the salicylic acid molecule, with the OH group at the *ortho* position as donor and the carbonyl O atom of the carboxylic acid group as acceptor. The hydrogen-bonding details are given in Table 1. The fluconazole and salicylic acid molecules each form homomeric centrosymmetric dimers *via* hydrogen bonds. The two fluconazole molecules, related by an inversion centre, are linked through an O—H···N hydrogen bond, forming an $R_2^2(14)$ motif. The fluconazole OH group serves as the hydrogen-bond donor to triazole atom N24 at position 4 of an adjacent fluconazole molecule. The salicylic acid molecules form centrosymmetric head-to-tail dimers through O—H···O interactions between neighbouring molecules, involving the *ortho*-OH group as the hydrogen-bond donor to the carbonyl O atom of an adjacent

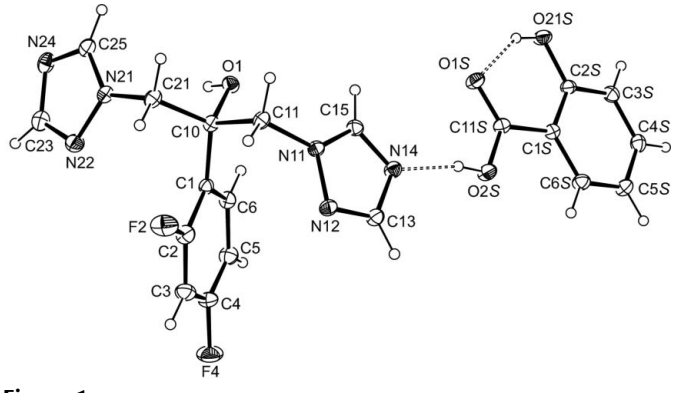


Figure 1
The asymmetric unit of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. Dashed lines indicate the intramolecular hydrogen bond in the salicylic acid molecule and the hydrogen bond between the fluconazole and salicylic acid molecules.

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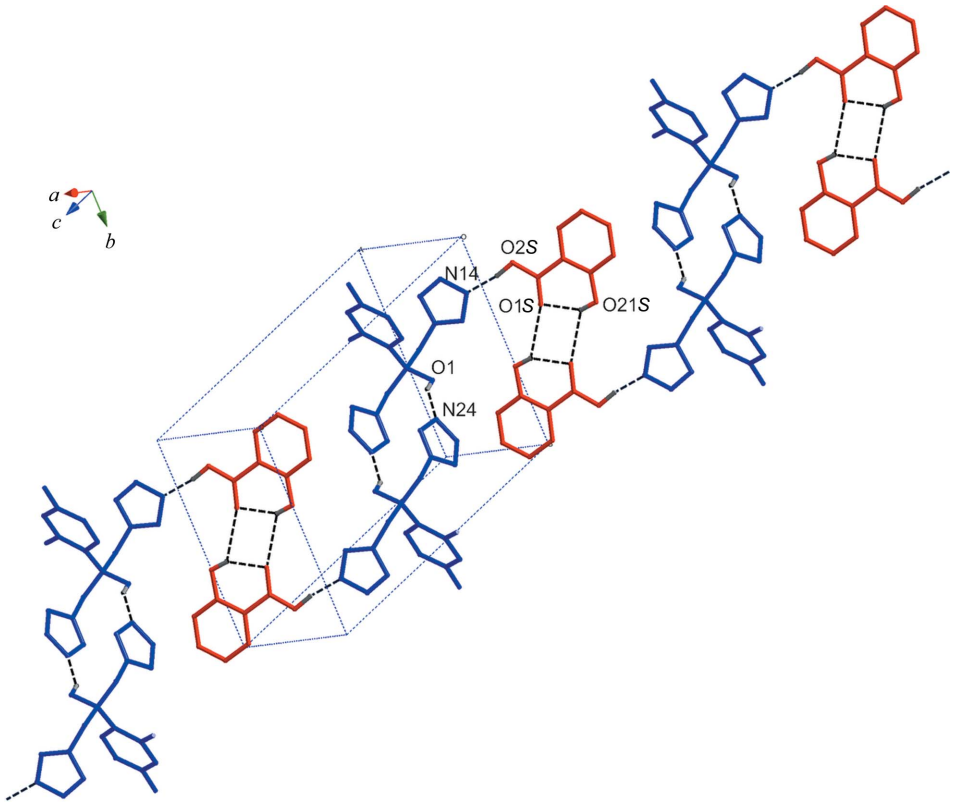

Figure 2
The one-dimensional hydrogen-bonded structure of (I), with alternating fluconazole and salicylic acid molecules.

salicylic acid molecule, forming an $R_2^2(4)$ motif. Such a pattern differs from the hydrogen-bonding motif observed in the crystal structure of pure salicylic acid, where the typical head-to-tail interaction through the carboxylic acid groups is observed (Munshi *et al.*, 2006). Thus, the carboxylic acid OH group remains available for further hydrogen-bond formation in (I). Indeed, the fluconazole and salicylic acid dimers in (I) are linked through an intermolecular O—H···N hydrogen bond, involving the carboxylic acid OH group and triazole atom N14 of an adjacent fluconazole moiety (Fig. 2). In this way, an extended zigzag tape of alternating fluconazole and salicylic acid dimers is formed, which runs along the *ac* diagonal. Additionally, two short C—H···*X* intermolecular contacts were observed (Table 1). The C15—H15···O21*S*($-x-1, -y+1, -z$) contact connects the fluconazole and salicylic acid molecules within the tape and thus stabilizes its formation. F atoms (F4) protrude from the tape on both sides. The C25—H25···F4($x, y+1, z$) interaction brings adjacent parallel tapes closer and increases the dimensionality to a three-dimensional supramolecular structure.

Experimental

Equimolar amounts of fluconazole (100 mg, 0.33 mmol) and salicylic acid (45.1 mg, 0.33 mmol) were dissolved in acetonitrile (3.0 ml) by mixing at 323 K. After cooling to ambient temperature, the solvent was allowed to evaporate slowly. Colourless crystals of (I) appeared after 72 h.

Crystal data

$C_{13}H_{12}F_2N_6O\cdot C_7H_6O_3$
$M_r = 444.40$
Triclinic, $P\overline{1}$
$a = 6.8522$ (2) Å
$b = 10.5580$ (4) Å
$c = 14.3009$ (6) Å
$\alpha = 82.862$ (3)°
$\beta = 84.892$ (2)°
$\gamma = 86.091$ (3)°
$V = 1020.80$ (6) Å^3
$Z = 2$
Mo $K\alpha$ radiation
$\mu = 0.12$ mm^{-1}
$T = 150$ K
0.18 × 0.16 × 0.15 mm

Data collection

Nonius KappaCCD area-detector diffractometer
8238 measured reflections
4579 independent reflections
3385 reflections with $I > 2\sigma(I)$
$R_{int} = 0.028$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.044$
$wR(F^2) = 0.114$
$S = 1.03$
4579 reflections
292 parameters
H-atom parameters constrained
$\Delta\rho_{max} = 0.23$ e Å^{-3}
$\Delta\rho_{min} = -0.23$ e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O2*S*—H2*S*···N14	0.82	1.79	2.6012 (17)	168
O21*S*—H21*S*···O1*S*	0.82	1.89	2.6082 (16)	146
O1—H1···N24^{i}	0.82	2.07	2.8190 (18)	152
C15—H15···O21*S*^{ii}	0.93	2.31	3.2077 (19)	163
C25—H25···F4^{iii}	0.93	2.32	3.184 (2)	155

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

All H atoms were initially found in a difference Fourier map, but they were repositioned in their calculated positions and refined using a riding model. Aromatic H atoms were permitted to ride with C—H distances of 0.93 Å and $U_{iso}(H) = 1.2U_{eq}(C)$, H atoms bonded to O atoms with O—H distances of 0.82 Å and $U_{iso}(H) = 1.5U_{eq}(O)$, and H atoms of the CH_2 group with C—H distances of 0.97 Å and $U_{iso}(H) = 1.2U_{eq}(C)$.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2009).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: EM3042). Services for accessing these data are described at the back of the journal.

References

Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Chen, J., Sarma, B., Evans, J. M. B. & Myerson, A. S. (2011). *Cryst. Growth Des.* **11**, 887–895.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Kastelic, J., Hodnik, Ž., Šket, P., Plavec, J., Lah, N., Leban, I., Pajk, M., Planinšek, O. & Kikelj, D. (2010). *Cryst. Growth Des.* **10**, 4943–4953.
Munshi, P. & Guru Row, T. N. (2006). *Acta Cryst.* B**62**, 612–626.
Nonius (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Schultheiss, N. & Newman, A. (2009). *Cryst. Growth Des.* **9**, 2950–2967.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Spek, A. L. (2009). *Acta Cryst.* D**65**, 148–155.
Sweetman, S. C., Blake, S. C., McGlashan, J. M. & Neatherco, G. C. (2007). *The Complete Drug Reference*, 35th ed., pp. 479–481. Martindale: Pharmaceutical Press.