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3-[1-(4-Sulfamoylphenyl)-5-*p*-tolyl-1*H*-pyrazol-3-yl]propanoic acid and 3-[5-(4-bromophenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrazol-3-yl]propanoic acid–dichloromethane–diethyl ether–water (2/0.72/1/1)

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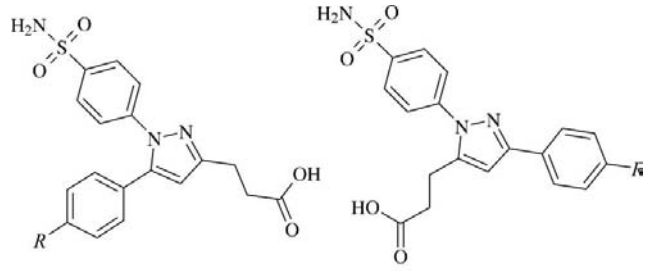
The syntheses of 3-[1-(4-sulfamoylphenyl)-5-*p*-tolyl-1*H*-pyrazol-3-yl]propanoic acid, $C_{19}H_{19}N_3O_4S$, (I), and 3-[5-(4-bromophenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrazol-3-yl]propanoic acid–dichloromethane–diethyl ether–water (2/0.72/1/1), $2C_{18}H_{16}BrN_3O_4S\cdot0.72CH_2Cl_2\cdot C_4H_{10}O\cdot H_2O$, (II), are regiospecific. However, correct identification by spectroscopic techniques of the regioisomer formed is not trivial and single-crystal X-ray analysis provided the only means of unambiguous structure determination. Both structures make extensive use of hydrogen bonding and while compound (I) forms a straightforward unsolvated $Z' = 1$ structure, compound (II) crystallizes as an unusual mixed solvate, with two crystallographically unique molecules of the pyrazole derivative present in the asymmetric unit. The structure of (II) also features Br···Br interactions.

Comment

Nonsteroidal anti-inflammatory drugs are divided into three different categories, namely classical cyclooxygenase-1 (COX1) inhibitors, cyclooxygenase-2 (COX2) inhibitors and dual inhibitors (Charlier & Michaux, 2003). In pharmacological terms, they possess analgesic, anti-inflammatory and antipyretic effects (Charlier & Michaux, 2003; Antoniou *et al.*, 2007). COX1 inhibitors were replaced by COX2 inhibitors due to problems of severe gastrointestinal irritation and renal impairment experienced by COX1 patients (Copeland *et al.*, 1995). In the USA, only the COX2 inhibitor celecoxib is approved for the treatment of various forms of arthritis and even then the Food and Drug Administration requires a warning label highlighting the potential of an increased risk of cardiovascular events (Antoniou *et al.*, 2007). This prompted us to synthesize celecoxib analogues and to investigate their pharmacological properties. In the process of synthesizing these analogues, we found that a mixture of regioisomers was possible, identified as 1 and 2 in the scheme below. Efforts to identify unambiguously the correct regioisomer by heteronuclear multiple-bond correlation (two-dimensional HMBC) and one-dimensional nuclear Overhauser effect (one-dimensional NOE) NMR spectroscopy were not successful, leaving single-crystal X-ray diffraction as the only possible means of unambiguous identification. We report here the structures of two related analogues, *viz.* the title compounds, (I) and (II).



(I) R = Me
(II) R = Br, + $\cdot0.72CH_2Cl_2\cdot C_4H_{10}O\cdot H_2O$

The asymmetric unit of (I) is shown in Fig. 1. The molecular dimensions are unexceptional and the compound is unambiguously regioisomer 1. A mean plane fitted through the central pyrazole ring has an r.m.s. deviation of 0.0036 Å, showing it to be essentially planar. The benzenesulfonamide ring is rotated by 28.73 (9)° from the plane of the pyrazole ring, while the tolyl ring is essentially planar (r.m.s. deviation of a plane fitted through all seven C atoms = 0.0137 Å) and is rotated by 70.26 (6)° from the plane of the pyrazole ring. The propanoic acid group has an extended structure but is not planar, with the C16—C17—C18—O4 torsion angle being −138.85 (16)°, and the r.m.s. deviation of a mean plane fitted

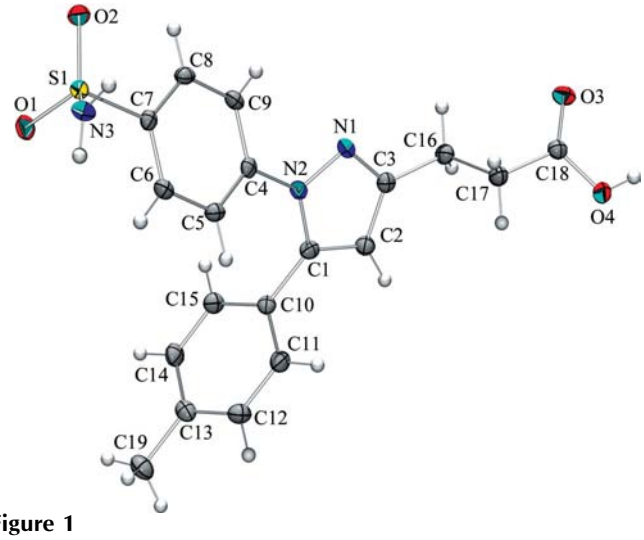


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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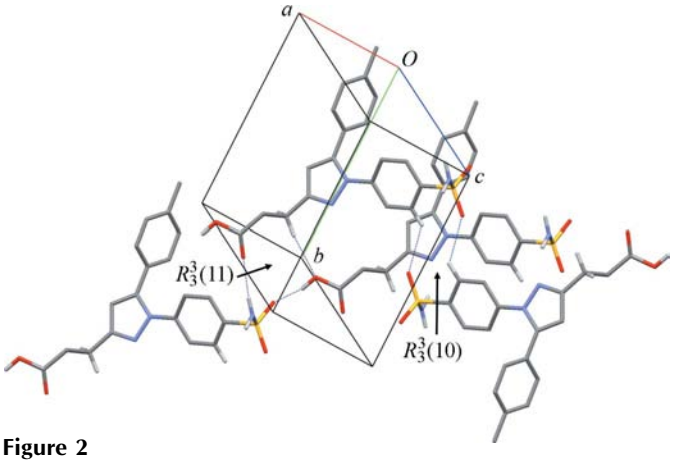

Figure 2
Hydrogen-bonding interactions (dotted lines) involving O-atom acceptor sites in (I).

through atoms C16, C17, C18, O3 and O4 is 0.2287 Å. This mean plane is rotated by 48.01 (8)° from the plane of the pyrazole ring.

The crystal packing of (I) involves O—H···O, N—H···O, N—H···N and C—H···O hydrogen-bond interactions (Table 1). Fig. 2 shows the interactions involving O-atom acceptor sites. There are two discrete motifs (Bernstein *et al.*, 1995): (i) an $R_2^2(10)$ interaction around an inversion centre formed by symmetry-related C—H···O interactions, and (ii) an $R_3^3(11)$ interaction formed by O—H···O, N—H···O and C—H···O interactions from three adjacent molecules. N—H···N interactions form a large discrete motif involving sites related by inversion symmetry. Hydrogen bonding overall forms a three-dimensional hydrogen-bonded structure.

Compound (II) crystallizes, unusually, with three separate and chemically different solvent molecules (dichloromethane, diethyl ether and water) present in the asymmetric unit, along with two molecules of the pyrazole derivative itself (Fig. 3). Thus, $Z' = 1$, since this represents the empirical chemical formula. In the following discussion, reference is made to the molecule containing atoms Br1–C18 (molecule *A*), with details for the molecule containing atoms Br51–C68 (molecule *B*) given in square brackets. Both molecules *A* and *B* are unambiguously regioisomer 1.

The presence of three separate solvent molecules is rather unusual. Diethyl ether and dichloromethane were used for recrystallization and the identity of the remaining solvent molecule was established by analysis of difference Fourier maps, which clearly showed the water H atoms; they are also involved in hydrogen bonding, which is discussed below. The source of the water is probably due to using bench, rather than rigourously dried, solvents for recrystallization. The displacement ellipsoids for dichloromethane are rather large, especially when compared with the remainder of the structure and considering that the data were measured at 115 K. In this case, free refinement of the dichloromethane atom occupancies suggests that it is only *ca* 0.72 occupied, consistent with the observation that the crystals lost solvent when removed from the mother liquor. This model also yields lower refinement residuals than a fully ordered model. The presence of three different solvent molecules is not without precedent. The Cambridge Structural Database (CSD, Version 5.30 plus two updates; Allen, 2002) has 21 examples of reported structures containing diethyl ether, dichloromethane and water solvent molecules, all of them metal complexes.

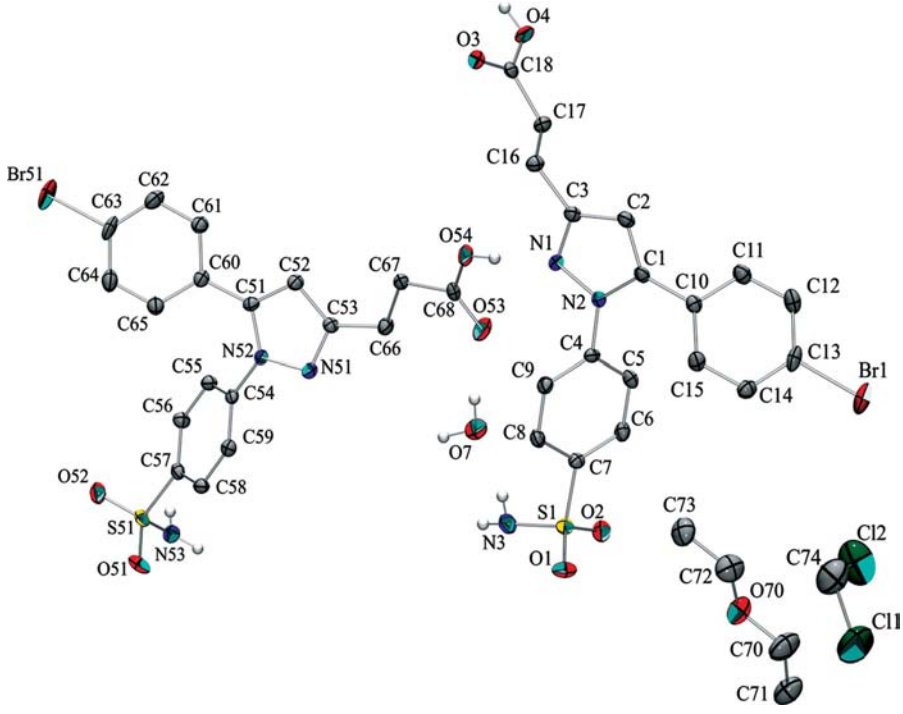

Figure 3
The asymmetric unit of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. C-bound H atoms have been omitted.

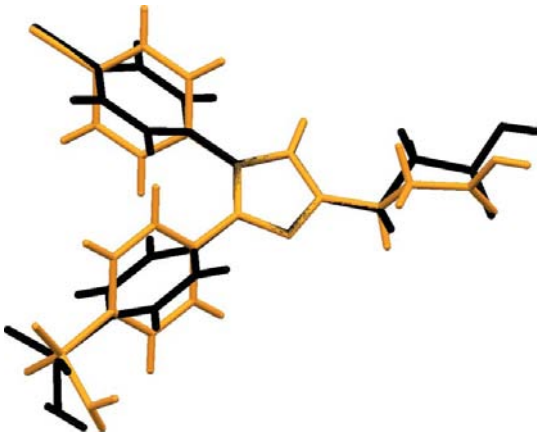

Figure 4
An overlay of molecules *A* (lighter shading) and *B* (black) in (II), formed by fitting the pyrazole rings, with an r.m.s. deviation of 0.0072 Å.

The molecular dimensions of (II) are unexceptional. A mean plane fitted through the central pyrazole ring has an r.m.s. deviation of 0.0018 Å [0.0038 Å], showing it to be essentially planar. The benzenesulfonamide ring is rotated by 46.79 (10)° [48.72 (7)°] from the plane of the pyrazole ring, while the bromobenzene ring is essentially planar (r.m.s. deviation of a plane fitted through the one Br and all six C atoms = 0.0303 Å [0.0196 Å]) and is rotated by 44.85 (8)° [35.11 (9)°] from the plane of the pyrazole ring. The propanoic acid group has an extended planar structure (r.m.s. deviation of a mean plane fitted through atoms C16, C17, C18, O3 and O4 = 0.0581 Å [0.0403 Å]) and the group is rotated by 83.07 (10)° [24.85 (12)°] from the plane of the pyrazole ring. Fig. 4 shows an overlay of the two independent molecules, formed by fitting the two pyrazole rings, and from this the differences in the relative orientations of the benzyl rings and the propanoic acid groups can be clearly seen.

The crystal structure makes extensive use of hydrogen bonding (Table 2), forming a thick two-dimensional hydrogen-bonded structure. Fig. 5 shows a *c*-axis projection of part of the structure, showing how two different hydrogen-bonding motifs, one $R_3^3(11)$ and one $R_3^3(13)$, allow the structure to propagate along the *b* axis. The role of water is crucial here since it acts as both donor (two O—H···O interactions) and acceptor (one N—H···O interaction), allowing both ring motifs to form. By contrast, the diethyl ether acts as a space-filling hydrogen-bond acceptor in a *D* interaction with one sulfonamide donor site of molecule *B*. Further *D* interactions, one N—H···O with sulfonamide as both donor and acceptor and a second N—H···O with sulfonamide as donor and an adjacent propanoic acid group as acceptor, allow the two-dimensional hydrogen-bonded sheet structure to grow. Several C—H···O interactions are also found in (II). Atoms O3 and O51 are of note, both acting as bifurcated acceptors: O3 is an acceptor from C8 and C59, and O51 acts as a bifurcated acceptor from C15 and C51.

The third direction is dominated by Br···Br interactions. The refined Br···Br distance is 3.5787 (9) Å. This is consistent with data derived from the CSD; a search for nonbonded

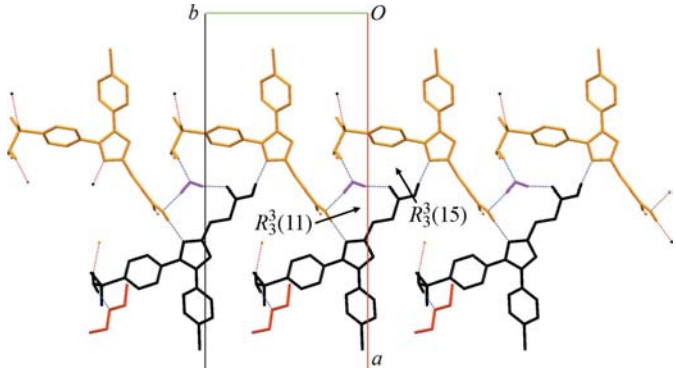

Figure 5
Part of the crystal structure of (II), projected along the *c* axis. The long *a* axis has been truncated. Molecules are coloured according to symmetry equivalence as in Fig. 4. Dashed lines indicate hydrogen bonds. The dichloromethane solvent has been omitted. (In the electronic version of the paper, water is indicated in light purple and diethyl ether is shown in red. Blue dashed lines indicate hydrogen bonds in the direction of the *b* axis, while red dashed lines indicate further hydrogen bonding which propagates the structure in the *c*-axis direction.)

Br···Br contacts between two Br atoms bonded to benzyl rings yielded 741 hits, with an average Br···Br distance of 3.576 Å. The Br···Br interactions, propagating along the [101] direction, link the hydrogen-bonded sheets together to form the overall crystal structure. Molecules of dichloromethane are also found between the sheets, although there are no significant interactions between dichloromethane and adjacent molecules.

Experimental

The title compounds were synthesized by a two-step procedure. 6-(4-Bromophenyl)-4,6-dioxohexanoic acid and 4,6-dioxo-6-*p*-tolylhexanoic acid were synthesized according to a modified literature method (Murray *et al.*, 1991), using NaHMDS in place of LiHMDS; further details are available in the archived CIF.

For the preparation of (I), a mixture of 4,6-dioxo-6-*p*-tolylhexanoic acid (1.639 g, 7 mmol), 4-sulfonamidophenylhydrazine hydrochloride (1.56 g, 7 mmol) and Et_3N (0.97 ml, 7 mmol) were combined in MeOH (8 ml) and stirred at room temperature for 6 h. The mixture was then concentrated *in vacuo* to a residue which was partitioned between Et_2O (40 ml) and 5% aqueous HCl (12.5 ml). The ether layer was separated, washed with 5% aqueous HCl (2 × 10 ml) and brine (10 ml), dried over Na_2SO_4, filtered, and concentrated to a residue. The crude residue was flash chromatographed on silica gel with a hexane–EtOAc–AcOH (6:2:1) eluant, then recrystallized from methanol, yielding colourless crystals of (I). For $C_{19}H_{19}N_3O_4S$: calculated mass = 385.4 g mol^{-1} and observed mass (LQ-ESI MS) = 386.1 g mol^{-1}.

For the preparation of (II), a mixture of 6-(4-bromophenyl)-4,6-dioxohexanoic acid (299 mg, 1 mmol), 4-sulfonamidophenylhydrazine hydrochloride (224 mg, 1 mmol) and Et_3N (0.1 ml, 1 mmol) were combined in MeOH (8 ml) and stirred at room temperature for 6 h. The mixture was then concentrated *in vacuo* to a residue, which was partitioned between Et_2O (40 ml) and 5% aqueous HCl (12.5 ml). The ether layer was separated, washed with 5% aqueous HCl (2 × 10 ml) and brine (10 ml), dried over Na_2SO_4, filtered, and concentrated to a residue. The crude residue was flash chromatographed on silica gel with a 1:1 eluant of hexane and EtOAc, and recrystallized

from diethyl ether and dichloromethane, yielding colourless crystals of (II). For $C_{18}H_{16}BrN_3O_4S$: yield 0.47 g; calculated mass = 450.31 g mol^{-1} and observed mass (LQ-ESI MS) = 452.0 g mol^{-1}.

Compound (I)

Crystal data

$C_{19}H_{19}N_3O_4S$
M_r = 385.43
Triclinic, $P\overline{1}$
a = 5.8382 (14) Å
b = 12.582 (3) Å
c = 13.279 (3) Å
α = 106.928 (3)°
β = 97.777 (3)°
γ = 101.077 (3)°
V = 896.5 (4) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.21 mm^{-1}
T = 115 K
0.52 × 0.25 × 0.15 mm

Data collection

Bruker SMART 1000 CCD area-detector diffractometer
Absorption correction: numerical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.898, T_{max} = 0.989
6690 measured reflections
3300 independent reflections
2824 reflections with $I > 2\sigma(I)$
R_{int} = 0.025

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.109
S = 1.06
3300 reflections
320 parameters
All H-atom parameters refined
$\Delta\rho_{max}$ = 0.43 e Å^{-3}
$\Delta\rho_{min}$ = −0.41 e Å^{-3}

Compound (II)

Crystal data

$2C_{18}H_{16}BrN_3O_4S\cdot 0.72CH_2Cl_2\cdot C_4H_{10}O\cdot H_2O$
M_r = 1054.11
Monoclinic, $C2/c$
a = 49.255 (15) Å
b = 11.702 (3) Å
c = 16.181 (5) Å
β = 95.567 (4)°
V = 9283 (5) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 1.98 mm^{-1}
T = 115 K
0.51 × 0.31 × 0.05 mm

Data collection

Bruker SMART 1000 CCD area-detector diffractometer
Absorption correction: numerical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.432, T_{max} = 0.908
23405 measured reflections
8605 independent reflections
6781 reflections with $I > 2\sigma(I)$
R_{int} = 0.033

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.105
S = 1.02
8605 reflections
595 parameters
2 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.84 e Å^{-3}
$\Delta\rho_{min}$ = −0.43 e Å^{-3}

In (I), all atoms, including H atoms, were freely refined. In (II), O- and N-bound H atoms were refined with U_{iso}(H) = 1.2U_{eq}(O,N), but without distance restraints. Other H atoms were placed in geometrically optimized positions and refined using a riding model with U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(methyl C), and with fixed C—H distances of 0.95 Å for aryl, 0.98 Å for methyl and 0.99 Å for methylene H atoms. The dichloromethane atom site occupancies were freely refined to 0.722 (3).

For both compounds, data collection: *SMART* (Bruker, 2007); cell refinement: *SAINT* (Bruker, 2007); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *Mercury* (Version 2.2; Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXTL* and local programs.

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

D—H···A	D—H	H···A	D···A	D—H···A
O4—H4O···O1^{i}	0.90 (3)	1.83 (3)	2.705 (2)	164 (3)
N3—H3A···N1^{ii}	0.82 (3)	2.16 (3)	2.941 (2)	160 (2)
N3—H3B···O3^{iii}	0.85 (3)	2.07 (3)	2.910 (2)	170 (2)
C8—H8···O2^{iv}	0.95 (2)	2.44 (2)	3.167 (2)	133 (2)

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

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

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3A···O7	0.84 (3)	1.97 (3)	2.796 (4)	166 (3)
N3—H3B···O3^{i}	0.88 (3)	2.22 (3)	3.094 (3)	170 (3)
O4—H4O···N51^{ii}	0.816 (10)	1.910 (13)	2.708 (3)	165 (3)
N53—H53A···O2^{iii}	0.84 (3)	2.21 (3)	3.028 (3)	165 (3)
N53—H53B···O70^{iii}	0.79 (3)	2.12 (3)	2.910 (3)	172 (3)
O54—H54O···N1	0.814 (10)	1.924 (12)	2.726 (3)	169 (3)
O7—H7A···O53	0.86 (4)	2.02 (4)	2.874 (3)	171 (3)
O7—H7B···O4^{iv}	0.98 (4)	2.28 (4)	3.164 (3)	149 (3)
C8—H8···O3^{iii}	0.95	2.39	3.327 (3)	169
C9—H9···O54^{iii}	0.95	2.42	3.364 (3)	173
C15—H15···O51^{v}	0.95	2.43	3.187 (3)	137
C52—H52···O51^{ii}	0.95	2.47	3.395 (3)	164
C59—H59···O3^{i}	0.95	2.53	3.443 (3)	160

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

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FN3023). Services for accessing these data are described at the back of the journal.

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Antoniou, K., Malamas, M. & Drosos, A. A. (2007). *Expert Opin. Pharmacother.* **8**, 1719–1732.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Bruker (2007). *SMART* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.
Charlier, C. & Michaux, C. (2003). *Eur. J. Med. Chem.* **38**, 645–659.
Copeland, R. A., Williams, J. M., Rider, N. L., Van Dyk, D. E., Giannaras, J., Nurnberg, S., Covington, M., Pinto, D., Magolda, R. L. & Trzaskos, J. M. (1995). *Med. Chem. Res.* **5**, 384–393.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Macrae, C. F., Bruno, I. J., Chisholm, J. A., Edgington, P. R., McCabe, P., Pidcock, E., Rodriguez-Monge, L., Taylor, R., van de Streek, J. & Wood, P. A. (2008). *J. Appl. Cryst.* **41**, 466–470.
Murray, W., Wachter, M., Barton, D. & Forero-Kelly, Y. (1991). *Synthesis*, **1**, 18–20.
Sheldrick, G. M. (1996). *SADABS*. Version 2008/1. University of Göttingen, Germany.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.