Acta Crystallographica Section C
**Crystal Structure Communications**
ISSN 0108-2701

# 1-[4-(Methylsulfonyl)phenyl]-5-phenyl-1*H*-pyrazole derivatives

**Caroline Charlier,[a]* Bernadette Norberg,[a] Laurence Goossens,[b] Jean-Pierre Hénichart[b] and François Durant[a]**

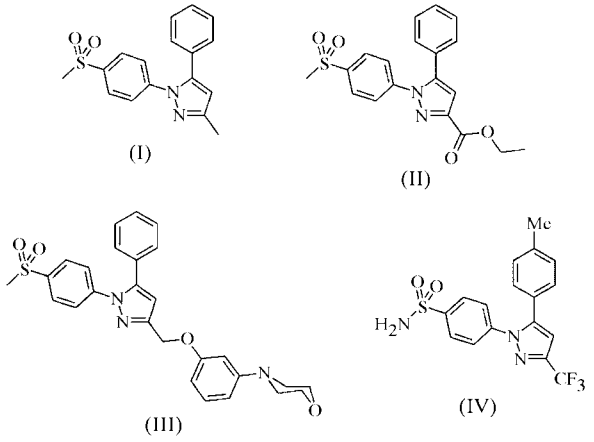
[a]Lab. Chimie Moléculaire Structurale, Facultés Universitaires N.-D. de la Paix, 61 Rue de Bruxelles, B-5000 Namur, Belgium, and [b]Institut de Chimie Pharmaceutique Albert Lespagnol, Rue J. Laguesse BP 83, 59006 Lille, France
Correspondence e-mail: caroline.charlier@fundp.ac.be

Received 17 May 2004
Accepted 1 July 2004
Online 11 August 2004

Three related compounds containing a pyrazole moiety with vicinal phenyl rings featuring a methylsulfonyl substituent are described, namely 3-methyl-1-[4-(methylsulfonyl)phenyl]-5-phenyl-1*H*-pyrazole, $C_{17}H_{16}N_2O_2S$, ethyl 1-[4-(methylsulfonyl)phenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate, $C_{19}H_{18}N_2O_4S$, and 1-[4-(methylsulfonyl)phenyl]-3-[3-(morpholino)-phenoxymethyl]-5-phenyl-1*H*-pyrazole, $C_{27}H_{27}N_3O_4S$. The design of these compounds was based on celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, in order to study the influence of various substituents on COX-2 and 5-lipoxygenase (5-LOX) inhibition.

## Comment

The three title compounds, *i.e.* (I), (II), and (III) (see scheme), have been investigated as part of a project aimed at the design of new dual 5-LOX/COX-2 inhibitors (5-LOX is 5-lipoxygenase and COX-2 is cyclooxygenase-2; Barbey *et al.*, 2002; Pommery *et al.*, 2004). This strategy also appears to be a promising approach to providing safer non-steroidal anti-inflammatory drugs (Charlier & Michaux, 2003). Moreover, it opens up new perspectives in the prophylactic treatment of several types of cancer (Romano & Claria, 2003). Celecoxib, (IV), a selective COX-2 inhibitor, was used as a starting point to investigate several pharmacomodulations and subsequently to study the influence of various substituents on COX-2 and 5-LOX inhibition. While totally inactive against 5-LOX, the three title compounds exhibit different results regarding COX-2 inhibition. Indeed, in contrast to (III), both (I) and (II), which are structurally closer to celecoxib, show an unexpected inactivity towards COX-2 (Barbey *et al.*, 2002; Pommery *et al.*, 2004). Crystal structure determination for the three compounds was carried out in order to elucidate their structural properties and to allow comparison with the previously reported structure of celecoxib (Vasu Dev *et al.*, 1999), as deposited in the Cambridge Structural Database (CSD; refcode DIBBUL; Allen, 2002).



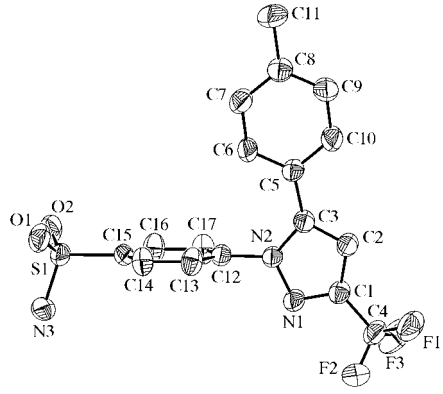




**Figure 1**
A view of parent compound celecoxib, (IV), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

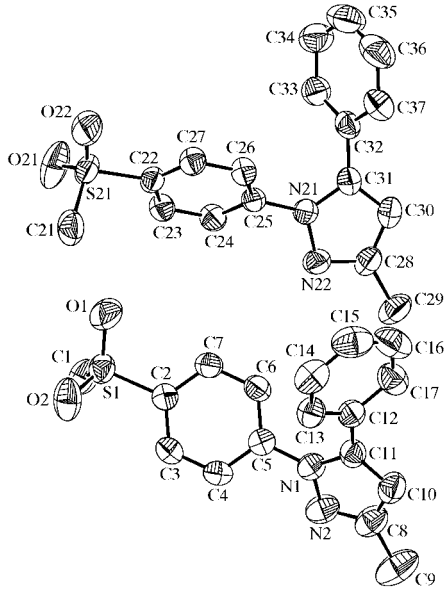



**Figure 2**
A view of the two independent molecules in (I) showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

  DOI: 10.1107/S0108270104016117 

In all three crystal structures, the asymmetric unit includes two independent molecules, which differ slightly in conformation, whereas the parent compound, (IV), has only one molecule in the asymmetric unit (Fig. 1). Except for those influenced by the different nature of the moieties characteristic to each compound, the geometric parameters (bond lengths and angles) in the three studied molecules do not differ considerably from those in (IV).

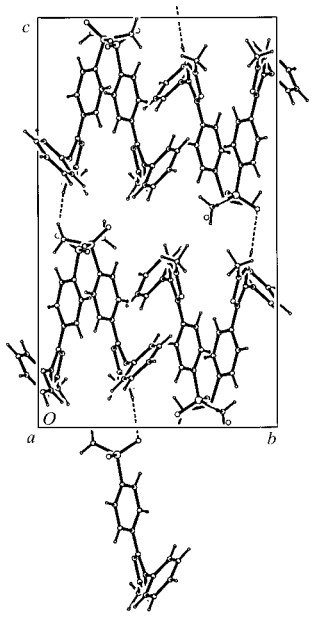



**Figure 3**
A packing diagram for (I), viewed along the *a* axis, illustrating the hydrogen-bonding network.

Compound (I) (Fig. 2) crystallizes in space group $P2_1/c$. The two independent molecules are related by a non-crystallographic pseudo-twofold rotational axis (rotation of −177.70° about the *b* axis). Superimposition of all non-H atoms in the two molecules with the quaternion transformation method (Mackay, 1984) gives a weighted (unit weight) r.m.s. fit of 0.16 Å (0.12 Å). The two vicinal phenyl rings are twisted with respect to the plane of the pyrazole ring. The extent of this deviation is not exactly the same for the two independent molecules. The C11—N1—C5—C6 and C13—C12—C11—N1 torsion angles are 39.3 (2) and 47.0 (2)°, respectively, and the C31—N21—C25—C26 and C33—C32—C31—N21 angles are −40.8 (2) and −54.7 (2)°, respectively. These orientations are significantly different from those observed in celecoxib, whose two phenyl rings are almost perpendicular [the C6—C5—C3—N2 and C3—N2—C12—C17 torsion angles are 16.0 (8) and 98.8 (6)°, respectively]. Weak intramolecular interactions in each residue of the asymmetric unit, involving a phenyl H atom (H7 and H27) and a sulfonyl O atom (O1 and O22, respectively), influence the conformation of the sulfonyl moiety with respect to the phenyl ring (Table 1). This type of interaction is also found in celecoxib, between the H atom attached to atom C16 and sulfonyl atom O2. In the crystal packing (Fig. 3), cohesion is achieved by, in addition to van der Waals interactions, weak C—H···O hydrogen bonds and C—H···$\pi$ interactions (Tables 1 and 2).

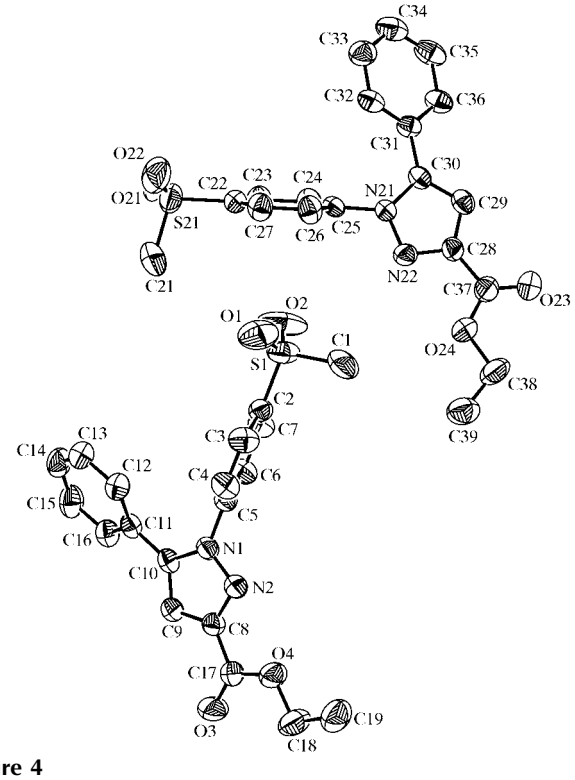



**Figure 4**
A view of the two independent molecules in (II) showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

Compound (II) (Fig. 4) crystallizes in space group $Pca2_1$. The ethyl ester chain is completely extended, with all the non-H atoms coplanar. The two residues in the asymmetric unit can be almost perfectly superimposed on one another (weighted and unit weight r.m.s. fit values of 0.065 and 0.050 Å, respectively). As observed for (I), both molecules are related by a non-crystallographic pseudo-twofold rotational axis (rotation of −179.2° about the *c* axis). The two vicinal phenyl rings are not perpendicular, in contrast to the situation

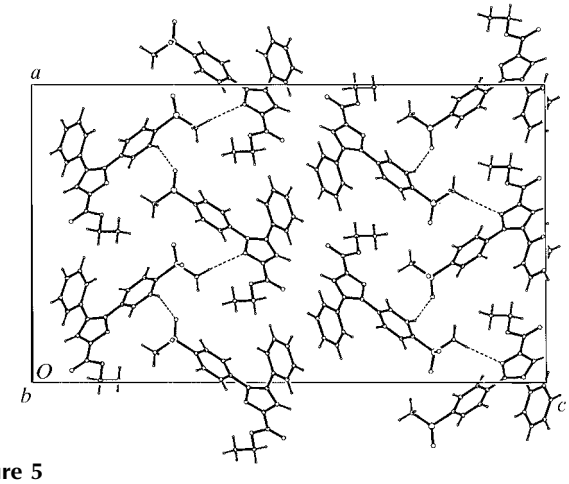



**Figure 5**
A packing diagram for (II), viewed along the *b* axis, illustrating the hydrogen-bonding network.

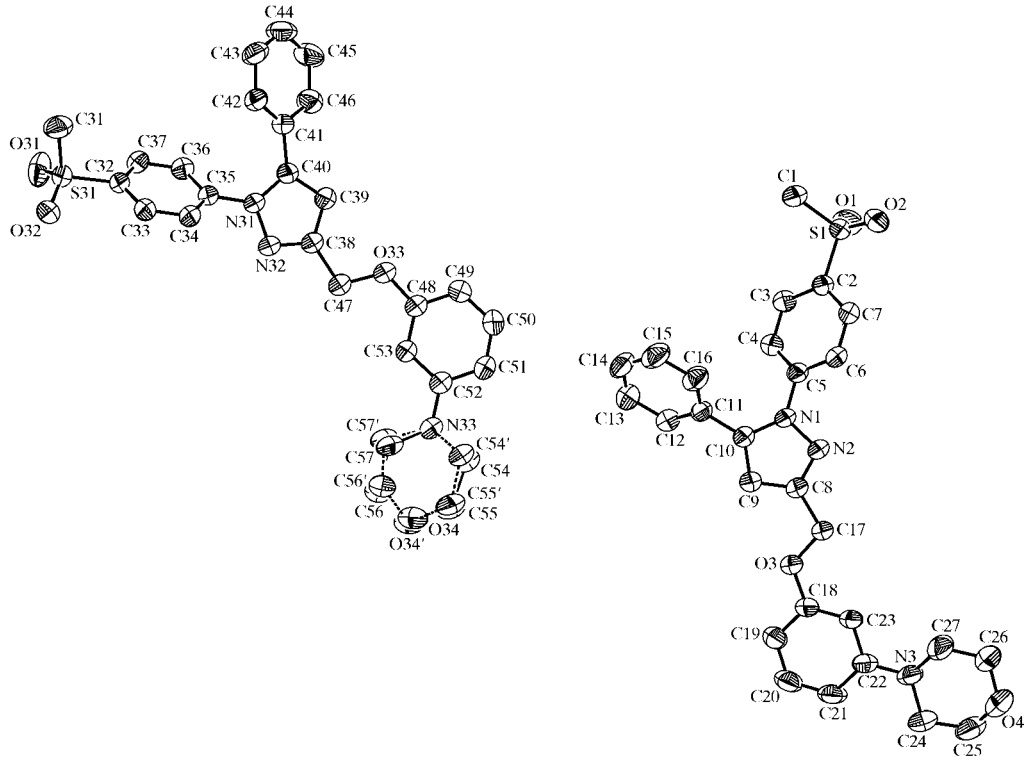



**Figure 6**
A view of the two independent molecules in (III) showing the atom-numbering scheme. Primes (′) indicate the minor-site atoms. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

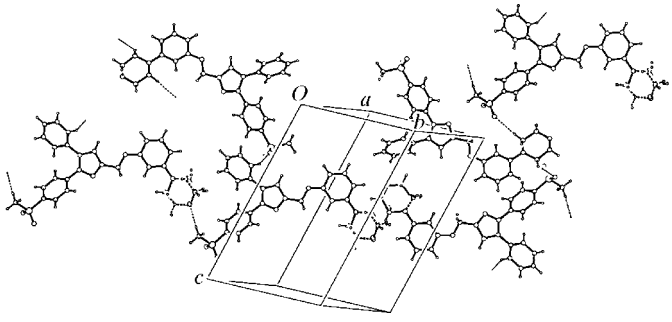



**Figure 7**
A packing diagram for (III), illustrating the hydrogen-bonding network.

in celecoxib (Table 3). Again, in both asymmetric-unit residues in (II), a weak intramolecular hydrogen bond is observed, involving a phenyl H atom (H7 and H23) and one of the sulfonyl O atoms (O2 and O22; Table 4). While no classic hydrogen bond is found in the crystal packing (Fig. 5), the methyl atom (C1 and C21) of each methylsulfonyl group is involved in a weak intermolecular C—H···N interaction with the pyrazole N atom (N2 and N22) of an adjacent molecule (Table 4). Additional weak C—H···O and C—H···$\pi$ contacts occur. Surprisingly, none of these intermolecular interactions involve the ethyl ester chain (Tables 4 and 5).

Like celecoxib, compound (III) (Fig. 6) crystallizes in space group $P\overline{1}$. One of the residues in the asymmetric unit exhibits disorder in its morpholine moiety, as evidenced by the $U_{eq}$ values. Among the three studied compounds, the two independent molecules in (III) display the most different conformations (weighted and unit weight r.m.s. fit values of 0.55 and 0.36 Å, respectively). The two vicinal phenyl rings are almost perpendicular when the two asymmetric unit residues are superimposed. The torsion angles differ slightly from those observed for (I) and (II) (Table 6). However, both independent molecules exhibit a weak intramolecular hydrogen bond between a phenyl H atom (H7 and H33) and one of the sulfonyl O atoms (O2 and O32; Table 7). In the crystal packing (Fig. 7), several intermolecular interactions exist between symmetry-related molecules, notably C—H···O and C—H···$\pi$ contacts, especially involving the morpholine moiety (Tables 7 and 8). This additional fragment could represent an important anchoring point inside the COX-2 active site, partly explaining the higher COX-2 inhibitory potency of (III) compared with that of (I) or (II).

## Experimental

Crystals of (I), (II) and (III) were obtained by slow evaporation from diethyl ether, methanol and isooctane solutions, respectively.

### Compound (I)

*Crystal data*

$C_{17}H_{16}N_2O_2S$
$M_r$ = 312.39
Monoclinic, $P2_1/c$
$a$ = 11.007 (1) Å
$b$ = 13.061 (1) Å
$c$ = 24.298 (1) Å
$\beta$ = 112.652 (5)°
$V$ = 3223.7 (4) Å$^3$
$Z$ = 8
$D_x$ = 1.287 Mg m$^{-3}$
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta$ = 30–40°
$\mu$ = 1.85 mm$^{-1}$
$T$ = 293 (2) K
Needle, colorless
0.35 × 0.30 × 0.20 mm

*Data collection*

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: analytical (Alcock, 1970)
$T_{min}$ = 0.563, $T_{max}$ = 0.708
11 113 measured reflections
6323 independent reflections
5480 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.028
$\theta_{max}$ = 71.9°
$h = -13 \rightarrow 11$
$k = 0 \rightarrow 16$
$l = -27 \rightarrow 29$
3 standard reflections
every 200 reflections
intensity decay: 4.2%

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.118
$S$ = 1.03
6323 reflections
402 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0652P)^2 + 0.6922P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.33 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.30 e Å$^{-3}$
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0048 (2)

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

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| C1—H1$B$···O22$^{i}$ | 0.96 | 2.39 | 3.344 (3) | 173 |
| C7—H7···O1 | 0.93 | 2.58 | 2.939 (2) | 104 |
| C23—H23···O1 | 0.93 | 2.56 | 3.083 (3) | 116 |
| C27—H27···O22 | 0.93 | 2.55 | 2.921 (2) | 104 |
| C30—H30···O2$^{ii}$ | 0.93 | 2.53 | 3.436 (2) | 165 |

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

**Table 2**
Analysis of C—H···$\pi$ interactions (Å, °) for (I).

*Cg*1 and *Cg*2 are the centroids of the five-membered N1—N2—C8—C10—C11 and N21—N22—C28—C30—C31 rings, respectively. *Cg*4 and *Cg*6 denote the centroids of the C12–C17 and C32–C37 phenyl rings, respectively.

| $X$—H···$Cg$ | H···$Cg$ | $X$—H···$Cg$ | $X$···$Cg$ |
|---|---|---|---|
| C1—H1···$Cg$4$^{iii}$ | 2.70 | 152 | 3.577 (2) |
| C4—H4···$Cg$2$^{iv}$ | 2.81 | 120 | 3.379 (2) |
| C21—H21$B$···$Cg$6$^{v}$ | 2.79 | 146 | 3.624 (2) |
| C24—H24···$Cg$1$^{iii}$ | 2.85 | 120 | 3.411 (2) |

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

## Compound (II)

*Crystal data*

$C_{19}H_{18}N_2O_4S$
$M_r$ = 370.41
Orthorhombic, $Pca2_1$
$a$ = 19.479 (1) Å
$b$ = 5.610 (1) Å
$c$ = 33.586 (3) Å
$V$ = 3670.2 (8) Å$^3$
$Z$ = 8
$D_x$ = 1.341 Mg m$^{-3}$
Cu $K\alpha$ radiation
Cell parameters from 24 reflections
$\theta$ = 40–45°
$\mu$ = 1.80 mm$^{-1}$
$T$ = 293 (2) K
Needle, colorless
0.42 × 0.05 × 0.04 mm

*Data collection*

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: analytical (Alcock, 1970)
$T_{min}$ = 0.519, $T_{max}$ = 0.932
6078 measured reflections
3651 independent reflections
2391 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.028
$\theta_{max}$ = 72.0°
$h = -20 \rightarrow 24$
$k = -6 \rightarrow 0$
$l = 0 \rightarrow 41$
3 standard reflections
every 200 reflections
intensity decay: 3%

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.102
$S$ = 1.01
3651 reflections
475 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.049P)^2 + 0.121P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.012
$\Delta\rho_{max}$ = 0.18 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.18 e Å$^{-3}$
Extinction correction: *SHELXL*97
Extinction coefficient: 0.00046 (7)

**Table 3**
Selected torsion angles (°) for (II).

| | | | |
|---|---|---|---|
| N1—C10—C11—C12 | −32.9 (6) | C30—N21—C25—C24 | 63.5 (6) |
| C10—N1—C5—C6 | −64.8 (6) | C32—C31—C30—N21 | 27.1 (6) |

**Table 4**
Hydrogen-bonding geometry (Å, °) for (II).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| C1—H1$C$···N22 | 0.96 | 2.58 | 3.515 (6) | 164 |
| C7—H7···O2 | 0.93 | 2.55 | 2.908 (6) | 103 |
| C21—H21$A$···N2$^{vi}$ | 0.96 | 2.60 | 3.545 (7) | 169 |
| C23—H23···O1$^{vii}$ | 0.93 | 2.47 | 3.292 (6) | 147 |
| C23—H23···O22 | 0.93 | 2.54 | 2.907 (6) | 104 |

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

**Table 5**
Analysis of C—H···$\pi$ interactions (Å, °) for (II).

*Cg*4 and *Cg*6 denote the centroids of the C11–C16 and C31–C36 phenyl rings, respectively.

| $X$—H···$Cg$ | H···$Cg$ | $X$—H···$Cg$ | $X$···$Cg$ |
|---|---|---|---|
| C14—H14···$Cg$6$^{viii}$ | 2.88 | 135 | 3.597 (6) |
| C34—H34···$Cg$4$^{ix}$ | 2.95 | 138 | 3.694 (6) |

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

## Compound (III)

*Crystal data*

$C_{27}H_{27}N_3O_4S$
$M_r$ = 489.59
Triclinic, $P\overline{1}$
$a$ = 10.325 (2) Å
$b$ = 13.874 (2) Å
$c$ = 18.094 (2) Å
$\alpha$ = 100.823 (9)°
$\beta$ = 104.704 (8)°
$\gamma$ = 91.888 (11)°
$V$ = 2453.6 (7) Å$^3$
$Z$ = 4
$D_x$ = 1.325 Mg m$^{-3}$
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta$ = 38–42°
$\mu$ = 1.49 mm$^{-1}$
$T$ = 293 (2) K
Needle, colorless
0.40 × 0.28 × 0.24 mm

*Data collection*

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: analytical (Alcock, 1970)
$T_{min}$ = 0.587, $T_{max}$ = 0.716
15 978 measured reflections
9997 independent reflections
8261 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.018
$\theta_{max}$ = 74.3°
$h = -12 \rightarrow 10$
$k = -17 \rightarrow 17$
$l = -21 \rightarrow 22$
3 standard reflections
every 200 reflections
intensity decay: 5%

*Refinement*

| | |
|---|---|
| Refinement on $F^2$ | $w = 1/[\sigma^2(F_o^2) + (0.085P)^2 + 0.8675P]$ where $P = (F_o^2 + 2F_c^2)/3$ |
| $R[F^2 > 2\sigma(F^2)] = 0.056$ | $(\Delta/\sigma)_{max} = 0.001$ |
| $wR(F^2) = 0.168$ | $\Delta\rho_{max} = 0.47$ e Å$^{-3}$ |
| $S = 1.04$ | $\Delta\rho_{min} = -0.39$ e Å$^{-3}$ |
| 9997 reflections | |
| 646 parameters | |
| H-atom parameters constrained | |

**Table 6**
Selected torsion angles (°) for (III).

| | | | |
|---|---|---|---|
| C4—C5—N1—C10 | −35.7 (3) | C36—C35—N31—C40 | 48.8 (3) |
| N1—C10—C11—C16 | −56.0 (3) | N31—C40—C41—C42 | 35.7 (3) |

**Table 7**
Hydrogen-bonding geometry (Å, °) for (III).

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| C7—H7···O2 | 0.93 | 2.50 | 2.887 (3) | 105 |
| C24—H24*A*···O31$^{x}$ | 0.97 | 2.57 | 3.378 (4) | 141 |
| C27—H27*B*···O32$^{xi}$ | 0.97 | 2.55 | 3.427 (4) | 151 |
| C31—H31*A*···O34$^{xii}$ | 0.96 | 2.53 | 3.489 (8) | 174 |
| C33—H33···O32 | 0.93 | 2.57 | 2.925 (3) | 103 |
| C46—H46···O1$^{xiii}$ | 0.93 | 2.40 | 3.223 (4) | 148 |

Symmetry codes: (x) $2-x, 1-y, 1-z$; (xi) $1+x, 1+y, z-1$; (xii) $x-1, y-1, z$; (xiii) $1-x, -y, -z$.

**Table 8**
Analysis of C—H···$\pi$ interactions (Å, °) for (III).

*Cg*1 and *Cg*2 are the centroids of the five-membered N1—N2—C8—C9—C10 and N31—N32—C28—C29—C30 rings, respectively. *Cg*6, *Cg*8, *Cg*10 and *Cg*11 denote the centroids of the C2–C7, C18–C23, C41–C47 and C48–C53 phenyl rings, respectively.

| *X*—H···*Cg* | H···*Cg* | *X*—H···Cg | *X*···*Cg* |
|---|---|---|---|
| C4—H4···*Cg*1$^{xiv}$ | 3.04 | 118 | 3.580 (2) |
| C15—H15···*Cg*6$^{xv}$ | 2.78 | 153 | 3.631 (3) |
| C26—H26*A*···*Cg*8$^{xvi}$ | 3.02 | 156 | 3.926 (3) |
| C27—H27*A*···*Cg*1$^{xvii}$ | 2.90 | 149 | 3.763 (4) |
| C34—H34···*Cg*10$^{xviii}$ | 2.78 | 143 | 3.571 (2) |
| C36—H36···*Cg*11$^{xix}$ | 2.92 | 138 | 3.669 (2) |
| C42—H42···*Cg*2$^{xviii}$ | 2.91 | 118 | 3.445 (2) |

Symmetry codes: (xiv) $2-x, 1-y, -z$; (xv) $1-x, 1-y, -z$; (xvi) $3-x, 2-y, -z$; (xvii) $2-x, 2-y, -z$; (xviii) $-x, -y, 1-z$; (xix) $1-x, -y, 1-z$.

For the three title compounds, all H atoms were fixed at idealized positions, with C—H distances in the range 0.93–0.97 Å. Compound (II) crystallized in a non-centrosymmetric space group. Refinement of the Flack (1983) parameter using the TWIN BASF option in *SHELXL*97 (Sheldrick, 1997) led to a value of 0.35 (5) and a value of 0.65 (5) for the inverted structure. In (III), the morpholine moiety of one of the molecules in the asymmetric unit is disordered. This group was refined with a split model over two positions for all atoms of the group, except for atom N33. On the basis of CSD statistics for morpholine bond geometry, distance restraints were applied to C—C, C—N and C—O distances involving disordered atoms. Constrained refinement of the site-occupation factors led to a value of 0.620 for the major conformation.

For all compounds, data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *PLATON* (Spek, 2003); program(s) used to solve structure: *SHELXS*97 (Spek, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON*; software used to prepare material for publication: *enCIFer* (Allen *et al.*, 2004).

CC thanks the FNRS for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN1055). Services for accessing these data are described at the back of the journal.

## References


Alcock, N. W. (1970). *Crystallographic Computing*, edited by F. R. Ahmed, S. R. Hall & C. P. Huber, p. 271. Copenhagen: Munksgaard.

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.

Allen, F. H., Johnson, O., Shields, G. P., Smith, B. R. & Towler, M. (2004). *J. Appl. Cryst.* **37**, 335–338.

Barbey, S., Goossens, L., Taverne, T., Cornet, J., Choesmel, V., Rouaud, C., Gimeno, G., Yannic Arnoult, S., Michaux, C., Charlier, C., Houssin, R. & Henichart, J. P. (2002). *Bioorg. Med. Chem. Lett.* **12**, 779–782.

Charlier, C. & Michaux, C. (2003). *Eur. J. Med. Chem.* **38**, 645–659.

Enraf–Nonius (1994). *CAD*-4 *EXPRESS*. Version 5.1. Enraf–Nonius, Delft, The Netherlands.

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.

Mackay, A. L. (1984). *Acta Cryst.* A**40**, 165–166.

Pommery, N., Taverne, T., Telliez, A., Goossens, L., Charlier, C., Pommery, J., Goossens, J. F., Houssin, R., Durant, F. & Henichart, J. P. (2004). *J. Med. Chem.* Submitted.

Romano, M. & Claria, J. (2003). *FASEB J.* **17**, 1986–1995.

Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.

Spek, A. L. (1997). *HELENA*. Utrecht University, The Netherlands.

Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.

Vasu Dev, R., Shashi Rekha, K., Vyas, K., Mohanti, S. B., Rajender Kumar, P. & Om Reddy, G. (1999). *Acta Cryst.* C**55**, *IUC9900161*.