Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Two quinazolinones: a ring conformational study

G. Y. S. K. Swamy,[a]* B. Sridhar,[a] K. Ravikumar[a] and Y. S. Sadanandam[b]

[a]Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India, and [b]Organic Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India
Correspondence e-mail: swamy@iict.res.in

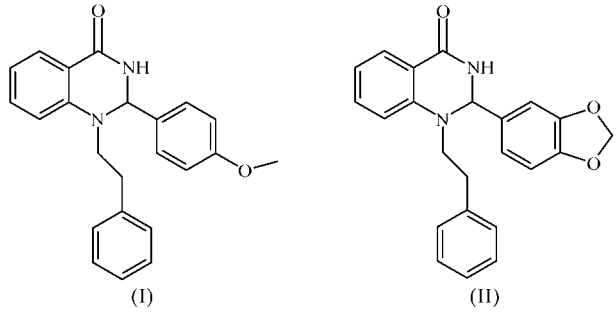
Received 28 December 2007
Accepted 31 December 2007
Online 22 January 2008

The molecules of (±)-2-(4-methoxyphenyl)-1-phenethyl-2,3-dihydroquinazolin-4(1*H*)-one, $C_{23}H_{22}N_2O_2$, (I), and (±)-2-(1,3-benzodioxol-5-yl)-1-phenethyl-2,3-dihydroquinazolin-4(1*H*)-one, $C_{23}H_{20}N_2O_3$, (II), have T-shaped forms in the crystal structure. The tetrahydropyrimidine ring in both structures adopts a sofa conformation. Both molecules are linked by N—H···O and C—H···O hydrogen bonds to form sheets built from alternating $R_2^2(8)$ and $R_4^4(26)$ [$R_4^4(24)$ in (II)] edge-fused rings. Additionally, the structures are stabilized by extensive C—H···π interactions.

Comment

Quinazolinone is a naturally occurring alkaloid and is an important pharmacophore which occurs frequently in medicinal chemistry (Fry *et al.*, 1994; Liu *et al.*, 2006); it is also considered to be a privileged structure in drug discovery (Horton *et al.*, 2003). Structural analysis of these compounds provides an opportunity to study the biological activity and its implications for the structural requirements for binding to the receptors. Ring conformation will often play a crucial role in the structure–activity relationship of the molecule (Fossheim *et al.*, 1982). Furthermore, the substituents on the ring make a substantial contribution to the ring conformation. In continuation of our earlier studies (Swamy & Ravikumar, 2005*a*,*b*, 2006) on the influence of substituents on the dihydropyrimidine ring (DHPM) conformation, we report here the crystal structures of two quinazolinone compounds, (I) and (II) (see scheme).

Compounds (I) and (II) possess a stereogenic centre with a relative configuration at C2(*S*/*R*). The two molecules are in a T-shaped form (Figs. 1 and 2), with the tetrahydropyrimidine ring (C2–C5/N1/N2) as the junction point. The bond lengths and angles about the molecular framework common to structures (I) and (II) are similar. The bond lengths and angles within the central tetrahydropyrimidine ring are affected by conjugation. The formal single bonds N1—C5 and N2—C3 in both compounds have partial double-bond character (Tables 1 and 3) and are all shorter than the typical Csp^2—N bond distance (1.426 Å; Lorente *et al.*, 1995).



As expected, the tetrahydropyrimidine ring adopts a sofa conformation, with a Csp^3 atom (*i.e.* atom C2) deviating by −0.624 (3) Å [0.626 (3) Å for (II)] from the least-squares plane defined by the remaining endocyclic atoms. The Cremer & Pople (1975) puckering parameters for (I) are Q_T = 0.453 (3) Å, θ = 64.4 (4)° and φ = 69.4 (4)° [0.460 (6) Å, 64.6 (7)° and 71.2 (8)° for (II)]. The sum of the absolute values of the internal torsion angles (close to zero) of the heterocyclic ring is a measure of planarity. It has been reported by Triggle *et al.* (1980) that there is an apparent correlation between the pharmacological activity and the planarity of the heterocyclic ring, meaning that increased planarity of the ring correlates with higher activity of the compound. Furthermore, it has been observed by Swamy & Ravikumar (2005*a*,*b*) that the substituent at the C2-position in the DHPM ring plays a crucial role in determining the ring conformation. A correlation has been observed between the bulkiness of the substituent and the tetrahydropyrimidine ring conformation (Table 5). In Fig. 3, the molecular weight of the substituent (at the C2-position) is plotted *versus* θ_{av} (the average of the C2—

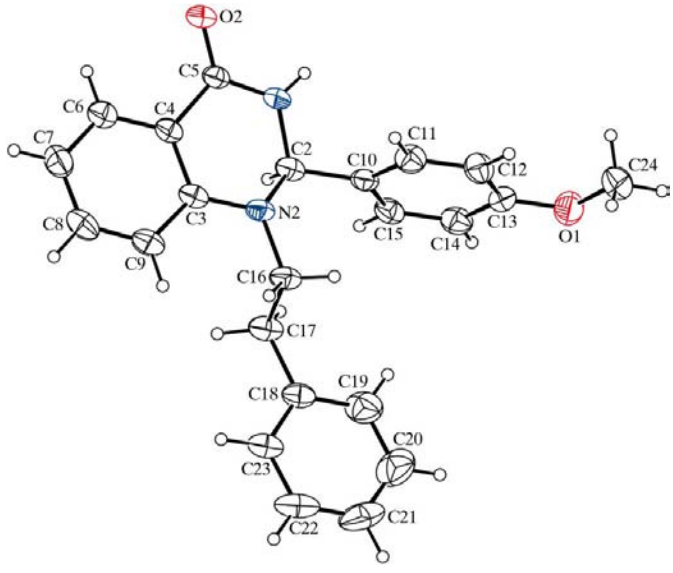


Figure 1
The asymmetric unit of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

  DOI: 10.1107/S0108270107068850

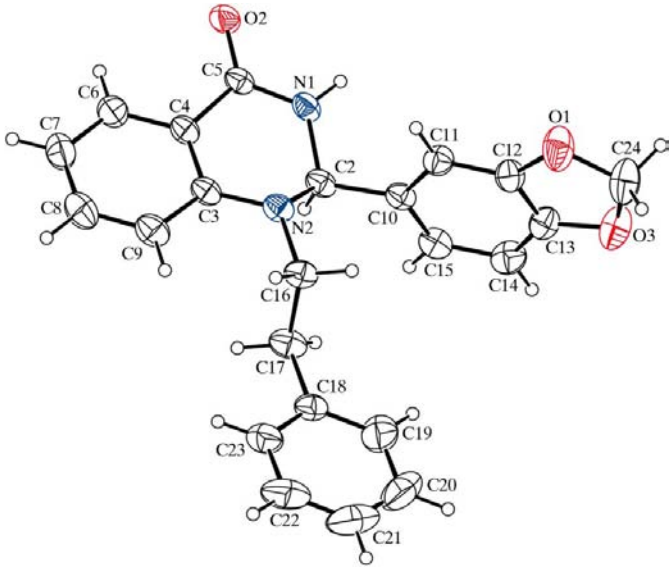


Figure 2
The asymmetric unit of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

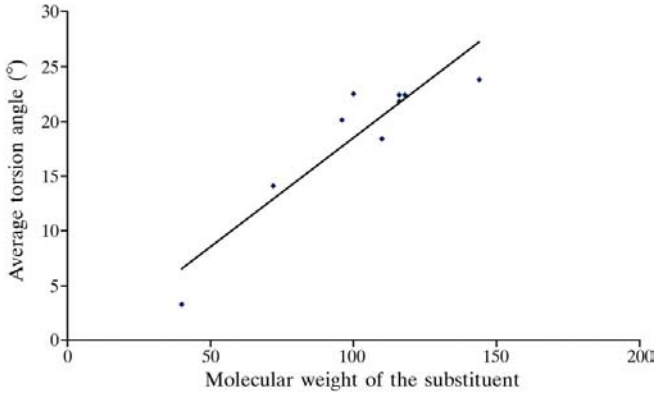


Figure 3
The correlation of DHPM ring distortion with the bulkiness of the substituent group at the C2-position in the ring. The slope, intercept and correlation coefficient obtained by linear regression are 0.198, −1.40 and 0.92, respectively.

N2—C3—C4 and C2—N1—C5—C4 torsion angles) for several quinazolinones obtained from the literature. One can see that there is a near linear correlation between θ_{av} and the molecular weight of the substituent at the C2-position. The C5—O2 bond distance of 1.234 (3) Å in compounds (I) and (II) is consistent with but slightly longer than the normal C═O distance (1.20 Å) due to the effect of substantial conjugation involving atom O2 (Tiekink, 1989). The sum of the bond angles around atoms N1 and N2 [352.3 (1) and 350.7 (2)° in (I), and 356.6 (11) and 351.5 (2)° in (II)] indicates a pyramidal configuration.

In both compounds, the phenethyl group has a fully extended conformation with respect to the central pyrimidine ring (Tables 1 and 3). In (I), with respect to the C12—C13 bond, the *cis* orientation of the C24—O1 bond about the O1—C13 bond [C24—O1—C13—C12 = −1.6 (4)°] results in repulsion between the H atoms attached to atoms C12 and C24, thereby causing the widening of the C12—C13—O1 angle and the narrowing of C14—C13—O1 from 120° (Table 1). Similar observations have been reported in the literature (Mukherjee *et al.*, 2000, 2001).

The methoxyphenyl group of (I) is positioned equatorially at atom C2 of the pyrimidine ring, as defined by the average of the torsion angles C10—C2—N2—C3 and C10—C2—N1—C5 [172.5 (2)°]. Similarly, in (II), the benzodioxole group is also oriented equatorially [the average torsion angle for (II) is 173.4 (3)°] at C2.

In both structures, atom N1 of the pyrimidine ring acts as a hydrogen-bond donor to quinazolinone atom O2 (Tables 2 and 4), so forming symmetric dimers of $R_2^2(8)$ type (Bernstein *et al.*, 1995) along the *c* axis [the *a* axis in (II); Figs. 4 and 5]. These dimers are further connected into a continuous ladder-like chain of $C(10)$ type along the *c* axis. The combination of these two then generates a supramolecular two-dimensional network that consists of $R_2^2(26)$-type [$R_2^2(24)$ in (II)] rings. The aromatic ring of the quinazolinone unit in (I) is involved in a C—H$\cdots\pi$ interaction (Table 2) with atom C24 of the methoxy group. In (II), the supramolecular network is further strengthened by weak π–π [the ring-centroid separation is 3.873 (4) Å] and extensive C—H$\cdots\pi$ interactions (Table 4).

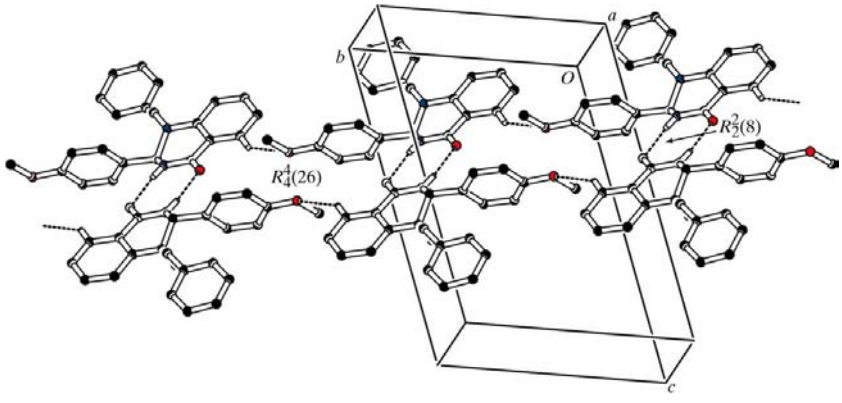


Figure 4
Part of the crystal structure of (I), highlighting the formation of centrosymmetric dimers through $R_2^2(8)$ and $R_4^4(26)$ edge-fused rings along the *c* axis. Dashed lines indicate hydrogen bonds. For the sake of clarity, H atoms not involved in the motifs have been omitted.

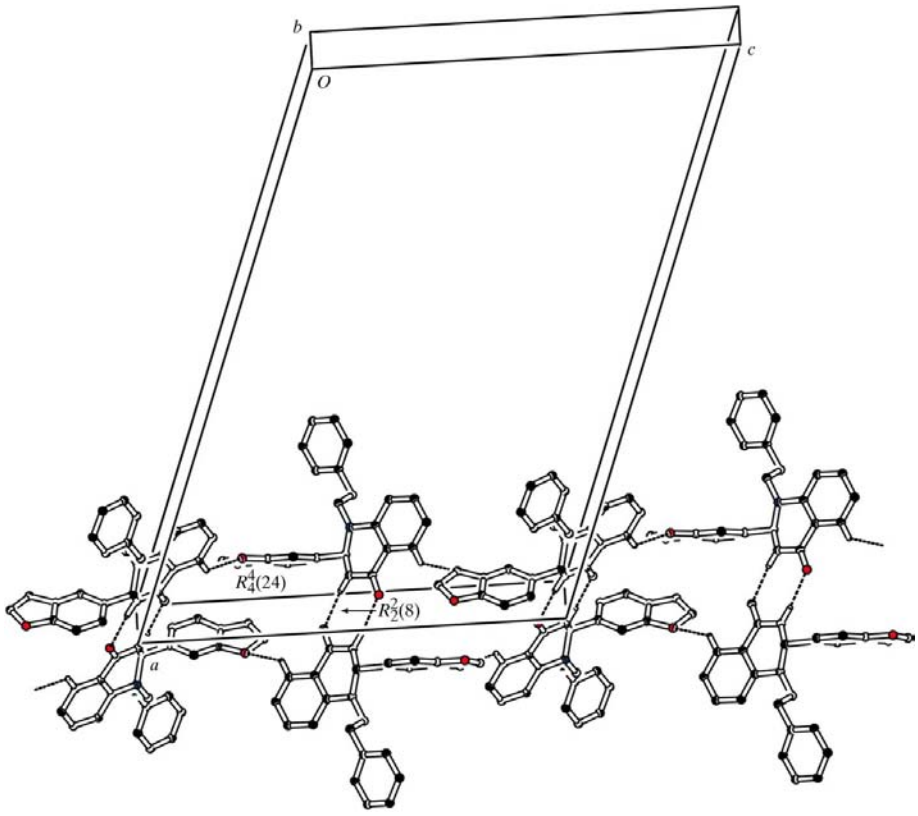


Figure 5
Part of the crystal structure of (II), highlighting the formation of centrosymmetric dimers through $R_2^2(8)$ and $R_4^4(24)$ edge-fused rings along the *c* axis. Dashed lines indicate hydrogen bonds. For the sake of clarity, H atoms not involved in the motifs have been omitted.

In summary, substitution at the C2-position in the DHPM ring plays an important role in determining the ring conformation; increasing the bulkiness of the substituent group at C2 leads to more distortion in the DHPM ring, which in turn affects the ring conformation. Interestingly, the DHPM ring adopts a sofa conformation if the substituent at C2 is more bulky. Otherwise, if the substituent is compact (*e.g.* O, S, *etc.*), the ring acquires a half-chair or boat conformation (Chandra Mohan *et al.*, 2003).

Experimental

Compounds (I) and (II) were prepared according to a literature procedure (Sadanandam *et al.*, 1987) and were recrystallized from methanol.

Compound (I)

Crystal data

$C_{23}H_{22}N_2O_2$
M_r = 358.43
Triclinic, $P\overline{1}$
a = 6.7224 (15) Å
b = 10.326 (2) Å
c = 14.694 (3) Å
α = 109.331 (4)°
β = 100.233 (4)°
γ = 90.803 (4)°
V = 944.3 (3) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.08 mm^{-1}
T = 293 (2) K
0.22 × 0.17 × 0.15 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
6526 measured reflections
3281 independent reflections
2172 reflections with $I > 2\sigma(I)$
R_{int} = 0.032

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.064
$wR(F^2)$ = 0.190
S = 1.05
3281 reflections
249 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (I).

C3—N2	1.379 (3)	C5—N1	1.333 (3)
C5—O2	1.234 (3)		
O1—C13—C14	117.1 (2)	O1—C13—C12	123.9 (2)
N2—C3—C4—C6	179.1 (2)	N1—C2—N2—C3	51.5 (2)
C3—C4—C5—N1	12.0 (3)	C4—C5—N1—C2	17.6 (3)
N2—C16—C17—C18	176.5 (2)	N2—C2—N1—C5	−48.4 (3)
C4—C3—N2—C2	−27.4 (3)	C12—C13—O1—C24	−1.6 (4)

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

*Cg*1 is the centroid of the C3/C4/C6–C9 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1N···O2^{i}	0.79 (3)	2.11 (3)	2.888 (3)	169 (3)
C6—H6···O1^{ii}	0.93	2.52	3.340 (4)	147
C24—H24*C*···*Cg*1^{iii}	0.96	2.83	3.513	129

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

Compound (II)

Crystal data

$C_{23}H_{20}N_2O_3$
M_r = 372.41
Monoclinic, $C2/c$
a = 29.840 (5) Å
b = 6.6467 (10) Å
c = 20.587 (3) Å
β = 109.529 (2)°
V = 3848.2 (10) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 293 (2) K
0.22 × 0.18 × 0.16 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
17515 measured reflections
3385 independent reflections
2799 reflections with $I > 2\sigma(I)$
R_{int} = 0.046

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.087
$wR(F^2)$ = 0.194
S = 1.28
3385 reflections
257 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}

Table 3
Selected geometric parameters (Å, °) for (II).

C3—N2	1.383 (4)	C5—N1	1.337 (4)
C5—O2	1.234 (3)		
C5—N1—C2	121.9 (3)	C3—N2—C16	119.4 (2)
C5—N1—H1N	118 (2)	C3—N2—C2	114.3 (2)
C2—N1—H1N	117 (2)	C16—N2—C2	117.8 (2)
N2—C3—C4—C6	−179.9 (3)	C4—C5—N1—C2	−16.5 (4)
C3—C4—C5—N1	−13.0 (4)	N2—C2—N1—C5	48.4 (3)
C11—C12—C13—O3	−179.5 (3)	C4—C3—N2—C2	28.4 (4)
N2—C16—C17—C18	178.1 (3)		

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

*Cg*1 and *Cg*2 are the centroids of the C18–C23 and C3/C4/C6–C9 rings.

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···O2^{i}	0.88 (3)	2.01 (3)	2.875 (3)	171 (3)
C6—H6···O1^{ii}	0.93	2.51	3.217 (4)	133
C20—H20···*Cg*1^{iii}	0.93	2.96	3.783	148
C24—H24*A*···*Cg*2^{iv}	0.97	2.77	3.580	142

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

H atoms attached to N atoms were located in a difference density map and refined isotropically. All other H atoms were placed in geometrically idealized positions and allowed to ride on their parent atoms, with C—H distances in the range 0.93–0.98 Å, and with U_{iso}(H) values of $1.5U_{eq}$(C) for methyl H atoms and $1.2U_{eq}$(C) for all other H atoms.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3* (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *PARST* (Nardelli, 1995).

Table 5
Conformational analysis of the DHPM ring.

Substituent at C2	Molecular weight of the substituent	θ_{av} (°)
Biphenyl[a]	144	23.4
Hydroxy-3-methoxyphenyl[b]	116	21.8
Acetyl[c]	40	3.3
Dimethylaminophenyl[d]	110	18.4
Methoxyphenyl[e]	96	20.1
Phenyl[e]	72	14.1
Nitrophenyl[e]	118	22.4
Methoxyphenyl[f]	100	22.5
Benzodioxole[f]	116	22.4

References: (*a*) Chruszcz *et al.* (2007); (*b*) Swamy & Ravikumar (2005*a*); (*c*) Chadwick & Easton (1983); (*d*) Swamy & Ravikumar (2005*b*); (*e*) Escalante *et al.* (2004); (*f*) this work.

The authors thank Dr J. S. Yadav, Director, IICT, Hyderabad, India, for his kind encouragement.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3077). 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.
Bruker (2001). *SAINT* (Version 6.28a) and *SMART* (Version 5.625). Bruker AXS Inc., Madison, Wisconsin, USA.
Chadwick, D. J. & Easton, I. W. (1983). *Acta Cryst.* C**39**, 454–456.
Chandra Mohan, K., Ravikumar, K., Shetty, M. M. & Velmurugan, D. (2003). *Z. Kristallogr.* **218**, 46–55.
Chruszcz, M., Chinigo, G. M., Capitosti, S. M., Brown, M. L. & Minor, W. (2007). *Acta Cryst.* E**63**, o891–o893.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Escalante, J., Flores, P. & Priego, J. M. (2004). *Heterocycles*, **63**, 2019–2032.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Fossheim, R., Svarteng, K., Mostad, A., Romming, C., Shefter, E. & Triggle, D. J. (1982). *J. Med. Chem.* **25**, 126–131.
Fry, D. W., Kraker, A. J., McMichael, A., Ambroso, L. A., Nelson, J. M., Leopold, W. R., Connors, R. W. & Bridges, A. L. (1994). *Science*, **265**, 1093–1095.
Horton, D. A., Bourne, G. T. & Smythe, M. L. (2003). *Chem. Rev.* **103**, 893–930.
Liu, J. F., Kaselj, M., Isome, Y., Ye, P., Sargent, K., Sprague, K., Cherrak, D., Wilson, C. J., Si, Y., Yohannes, D. & Ng, S.-C. (2006). *J. Comb. Chem.* **8**, 7–10.
Lorente, A., Galan, C., Fonswca, I. & Sanz-Aparico, J. (1995). *Can. J. Chem.* **73**, 1546–1555.
Mukherjee, A. K., Guha, S., Khan, M. W., Kundu, N. G. & Helliwell, M. (2000). *Acta Cryst.* C**56**, 85–87.
Mukherjee, M., Maiti, S., Chaudhuri, G., Helliwell, M. & Kundu, N. G. (2001). *Acta Cryst.* E**57**, o247–o249.
Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.
Sadanandam, Y. S., Ram Mohan Reddy, K. & Bhaskar Rao, A. (1987). *Eur. J. Med. Chem.* **22**, 169–173.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Swamy, G. Y. S. K. & Ravikumar, K. (2005*a*). *Acta Cryst.* E**61**, o4238–o4240.
Swamy, G. Y. S. K. & Ravikumar, K. (2005*b*). *J. Chem. Crystallogr.* **3**, 183–189.
Swamy, G. Y. S. K. & Ravikumar, K. (2006). *Anal. Sci.* **22**, 71–72.
Tiekink, E. R. T. (1989). *Z. Kristallogr.* **187**, 79–84.
Triggle, A. M., Shefter, E. & Triggle, D. J. (1980). *J. Med. Chem.* **23**, 1442–1445.