Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

2-[(*E*)-(4-Hydroxy-3-methoxybenzylidene)amino]-*N*-(2-methylphenyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide

Vasu,[a] K. A. Nirmala,[b] Deepak Chopra,[c]* M. D. Lakshman[d] and J. Saravanan[e]

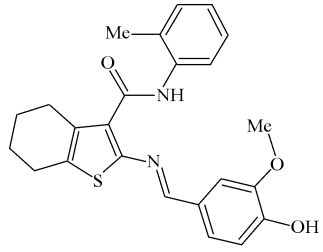
[a]Vivekananda Degree College, Bangalore 560 055, Karnataka, India, [b]Department of Physics, Bangalore University, Bangalore 560 056, Karnataka, India, [c]Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore 560 012, Karnataka, India, [d]Department of Physics, Seshadripuram College, Bangalore 560 020, Karnataka, India, and [e]MS Ramaiah College of Pharmacy, Bangalore 560 054, Karnataka, India
Correspondence e-mail: deepak@sscu.iisc.ernet.in

Received 29 November 2007
Accepted 11 January 2008
Online 23 February 2008

The title compound, $C_{24}H_{24}N_2O_3S$, exhibits antifungal and antibacterial properties. The compound crystallizes with two molecules in the asymmetric unit, with one molecule exhibiting 'orientational disorder' in the crystal structure with respect to the cyclohexene ring. The *o*-toluidine groups in both molecules are noncoplanar with the respective cyclohexene-fused thiophene ring. In both molecules, there is an intramolecular N—H···N hydrogen bond forming a pseudo-six-membered ring which locks the molecular conformation and eliminates conformational flexibility. The crystal structure is stabilized by O—H···O hydrogen bonds; both molecules in the asymmetric unit form independent chains, each such chain consisting of alternating 'ordered' and 'disordered' molecules in the crystal lattice.

Comment

The design of compounds possessing important pharmacological properties, such as antibacterial, anticancer, anti-inflammatory and antitoxic activities, is an important area of research. In this respect, Schiff bases (Pellis & West, 1968; Cohen *et al.*, 1977; Csaszar & Morvay, 1983; Lakshmi *et al.*, 1985) and their related thiophene derivatives (El-Maghraby *et al.*, 1984; Dzhurayev *et al.*, 1992; Gewald *et al.*, 1966) have been synthesized and found to exhibit such biological activities. In this context, sulfur-containing Schiff bases are the most effective. In view of the medicinal applications of such classes of compounds, single-crystal structure determinations of a series of biologically active thiophene-3-carboxamide derivatives have been performed (Vasu *et al.*, 2003). In most of these structure determinations, the molecular scaffold which remains invariant is the 2-[(*E*)-benzylideneamino]-*N*-phenyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide group. This molecular skeleton is divided into three parts, namely the cyclohexene-fused thiophene group, the *N*-phenyl part and the benzylideneamino group. It was observed that the cyclohexene ring is ordered in all the above determined crystal structures. In one such structure determination, *viz*. 2-({(1*E*)-[4-(dimethylamino)phenyl]methylene}amino)-*N*-(4-methylphenyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (Vasu *et al.*, 2003), the asymmetric unit contains two molecules. It is indeed noteworthy that in the title compound, (I), although it crystallizes with two molecules (*A* and *B*) in the asymmetric unit (Fig. 1), one molecule exhibits orientational disorder (molecule *B*) in the crystal structure. The disorder could be well resolved, with the cyclohexene rings (C25/C26*B*/C27*A*/C28–C30 and C25/C26*A*/C27*B*/C28–C30) existing in two independent conformations with a population ratio of 1:1. With this background, and in order to compare with our previous studies the changes in molecular conformation and associated intermolecular interactions due to the presence of different substituents on the invariant group, the crystal structure analysis of compound (I) has been carried out.



(I)

The thiophene ring of (I) is essentially planar, with maximum deviations of 0.005 (3) and −0.017 (3) Å for atoms C9 and C31, respectively, in the two molecules. The six-membered cyclohexene ring adopts a half-chair conformation, with atoms C13 and C14 deviating from the C10/C11/C12/C15 plane by 0.228 (4) and −0.408 (5) Å in molecule *A*; the corresponding displacements for atoms C27*A* and C26*B* (of the major conformer in molecule *B*) from the C25/C28–C30 plane are 0.23 (2) and −0.51 (2) Å, respectively. The ring-puckering parameters (Cremer & Pople, 1975) generated by *PLATON* (Spek, 2003) for the cyclohexene ring are $Q(2)$ = 0.324 (3) Å, $\varphi(2)$ = 200.2 (6)° and θ = 49.8 (4)° in molecule *A*, with corresponding values of 0.39 (2) Å, 88.0 (12)° and 131.9 (12)° in molecule *B* (major conformer).

The bond angles C20—C21—C23 and C42—C47—C46 in molecules *A* and *B* are 116.9 (2) and 117.06 (3)°, respectively, which deviate significantly from the ideal value of 120°. This deviation is due to the electron-donating inductive effect of the methyl group, and similar variations in bond angles have also been observed in 2-[(*E*)-(4-chlorophenyl)methyleneamino]-*N*-(*X*-methylphenyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (where *X* = 2 and 3; Vasu *et al.*, 2004*a*), and in 2-{[(*E*)-(4-methoxyphenyl)methylene]amino}-*N*-(3-methylphenyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide and *N*-(4-methylphenyl)-2-{[(*E*)-(4-methylphenyl)-methylene]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-car-

  DOI: 10.1107/S0108270108001133

boxamide (Vasu *et al.*, 2004*b*). Similarly, the bond angles C8—N1—C7 [121.9 (2)°] and C16—N2—C23 [123.9 (2)°] in molecule *A* around the iminomethyl N and amide N atoms are different, indicating delocalization of the N-atom lone pair of electrons. The corresponding bond angles C41—N4—C42 and C31—N3—C32 in molecule *B* are 124.2 (2) and 122.3 (2)°, respectively. This is further demonstrated by the bond lengths in the carboxamide and imine groups being significantly different. In molecule *A*, the C16—N2 and C8—N1 bond lengths are 1.342 (3) and 1.384 (3) Å, respectively. The corresponding values in molecule *B* (C41—N4 and C31—N3) are 1.343 (3) and 1.388 (3) Å, respectively, indicating that the electronic and steric environments around these groups are different (Table 1). Similarity in bond lengths has been observed previously in analogous systems (Vasu *et al.*, 2003, 2004*a*,*b*; Kumar *et al.*, 2005).

The angles between the mean planes of the *o*-toluidine and thiophene rings are 58.6 (1) and 64.4 (1)° in molecules *A* and *B*, respectively, indicating sufficient deviation from coplanarity to minimize steric repulsion between the methoxy group and the H atoms of the benzene ring (atoms H17 and H18 in molecule *A*, and H43 and H44 in molecule *B*). This is further demonstrated by the torsion angle C17—C23—N2—C16 about the C23—N2 bond in molecule *A* [−107.6 (3)°] and C43—C42—N4—C41 about the C42—N4 bond in molecule *B* [−102.7 (3)°]. The benzylideneamino group is essentially coplanar with the thiophene ring in both molecules *A* and *B*, the corresponding dihedral angles being 176.3 (1) and 172.1 (1)°, respectively. It is noteworthy that, in the case of 2-{[(*E*)-(4-methoxyphenyl)methylene]amino}-*N*-(3-methylphenyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide and *N*-(4-methylphenyl)-2-{[(*E*)-(4-methylphenyl)methylene]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (Vasu *et al.*, 2004*b*), the *m*-toluidine and *p*-toluidine rings are coplanar with the thiophene rings because of the stabilization imparted by the electron delocalization and the absence of steric interactions. The introduction of one methyl group into the *N*-phenyl ring in the *ortho* and *meta* positions, as in the case of 2-[(*E*)-(4-chlorophenyl)methyleneamino]-*N*-(2-methylphenyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (Vasu *et al.*, 2004*a*), causes loss of planarity due to steric interaction between the methyl group and the benzene H atoms bonded to the imine group. The dihedral angle between the mean planes of the *m*-toluidine and thiophene rings is 18.4 (1)°, whereas that between the *o*-toluidine and thiophene rings is 12.9 (1)°. On addition of an F atom, as in the case of 2-[(*E*)-benzylideneamino]-*N*-(2-fluorophenyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (Vasu *et al.*, 2005), the torsion angle is 151.8 (2)° between the *o*-fluorophenyl and thiophene groups, indicating the important role of steric hindrance in molecular conformation. This deviation from planarity is further increased when a methoxy group is introduced on the phenyl ring attached to the imine group, as reflected in the values of the dihedral angles observed here.

The conformations of both molecules in the asymmetric unit of (I) are stabilized by intramolecular N—H···N hydrogen bonds which lock the molecular conformations. The crystal structure is stabilized by intermolecular O—H···O hydrogen bonds involving the phenolic H atom and the carbonyl ring, forming *C*(12) chains (Bernstein *et al.*, 1995) along the crystallographic *c* axis related by a glide plane (Fig. 2 and Table 2). From the packing characteristics, it is interesting to note that the ordered molecule (*A*) forms molecular chains involving O—H···O hydrogen bonds (involving atoms H1O

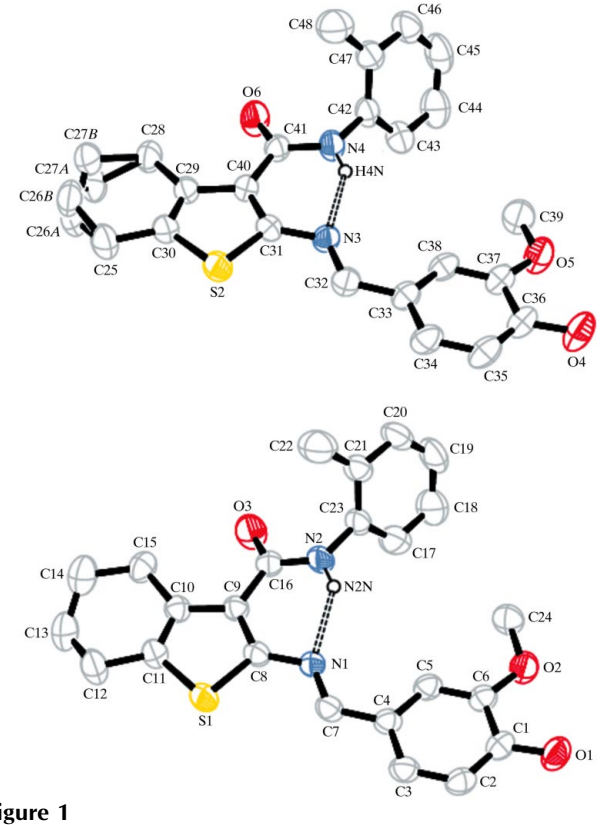


Figure 1
Views of the two molecules (*B* top and *A* bottom) of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. Dotted lines depict intramolecular N—H···N hydrogen bonds. H atoms not involved in these hydrogen bonds have been omitted for clarity.

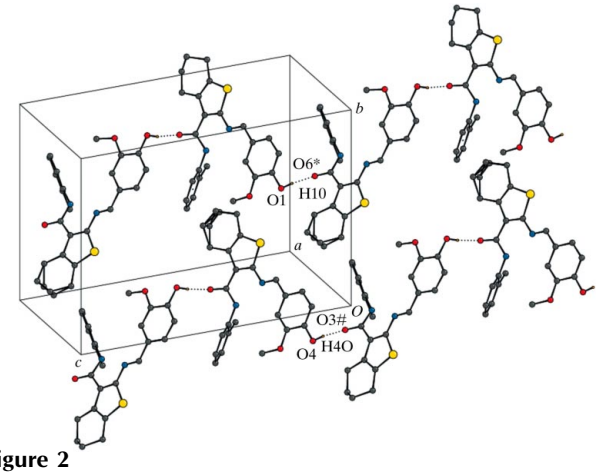


Figure 2
A packing view of the molecules, along the [001] direction, showing the O—H···O hydrogen bonds (dotted lines). Molecules labelled with an asterisk (*) or a hash (#) are at the symmetry positions $(x-\frac{1}{2}, -y+\frac{1}{2}, z-\frac{1}{2})$ and $(x+\frac{1}{2}, -y+\frac{1}{2}, z-\frac{1}{2})$, respectively.

and O6) with disordered molecules on either side. Similarly, in the parallel chain along the [001] direction, the disordered molecule *B* forms chains with ordered molecules *via* O—H···O hydrogen bonds (involving atoms H4O and O3). The crystal structure is stabilized by van der Waals forces between parallel layers of molecules (Vasu *et al.*, 2003).

In conclusion, the effect of different substituents on the conformational preferences in a series of carboxamide derivatives has been highlighted. Packing is mainly governed by strong hydrogen bonds together with van der Waals interactions.

Experimental

The title compound was synthesized using the Gewald reaction (Gewald *et al.*, 1966). *o*-Cyanotoluidine (0.04 mol) was refluxed with ethyl methyl ketone in the presence of sulfur at 313–323 K for 1 h. The product was then reacted with 4-hydroxy-5-methoxybenzaldehyde in an equimolar ratio in the presence of ethanol, which yielded the title compound (68%). This was purified by recrystallization from ethyl acetate by slow evaporation, yielding orange needle-shaped crystals of (I).

Crystal data

$C_{24}H_{24}N_2O_3S$
M_r = 420.52
Monoclinic, $P2_1/n$
a = 14.817 (8) Å
b = 13.701 (8) Å
c = 22.224 (13) Å
β = 108.807 (11)°
V = 4271 (4) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.18 mm^{-1}
T = 290 (2) K
0.18 × 0.09 × 0.08 mm

Data collection

Bruker SMART CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.936, T_{max} = 0.986
30379 measured reflections
7512 independent reflections
4900 reflections with $I > 2\sigma(I)$
R_{int} = 0.037

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.053
$wR(F^2)$ = 0.134
S = 1.02
7512 reflections
587 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}

Table 1
Selected bond lengths (Å).

N1—C7	1.283 (3)	N3—C32	1.277 (3)
N1—C8	1.384 (3)	N3—C31	1.388 (3)
N2—C16	1.342 (3)	N4—C41	1.344 (3)
N2—C23	1.431 (3)	N4—C42	1.424 (3)

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

*Cg*1 is the centroid of the C17–C23 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N4—H4N···N3	0.81 (3)	2.05 (3)	2.738 (3)	143 (2)
N2—H2N···N1	0.82 (3)	2.06 (3)	2.748 (4)	141 (2)
O4—H4O···O3^{i}	0.86 (4)	1.83 (4)	2.683 (3)	171 (4)
O1—H1O···O6^{ii}	0.88 (4)	1.82 (4)	2.697 (3)	174 (3)
C35—H35···*Cg*1^{iii}	0.93	2.89	3.670 (3)	143

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

The H atoms of the phenolic O atom, the amide N atom and the C atom connected to the imine N atom were located in a difference Fourier map and refined isotropically. The N—H and O—H bond lengths are in the ranges 0.81 (2)–0.82 (2) and 0.84 (4)–0.86 (4) Å, respectively. The disordered C26 and C27 atoms of the cyclohexene ring in molecule *B* were split with an initial occupany of 0.5 assigned to each. The H atoms on C25 and C28 were also split with occupancies of 0.5 and fixed using the riding model. The remaining H atoms were placed in calculated positions and allowed to ride on their parent C atoms, with C—H = 0.93–0.97 Å and U_{iso}(H) = 1.2 or 1.5U_{eq}(C).

Data collection: *SMART* (Bruker, 2000); cell refinement: *SAINT* (Bruker, 2000); data reduction: *SAINT*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *CAMERON* (Watkin *et al.*, 1993); software used to prepare material for publication: *PLATON* (Spek, 2003).

The authors thank Professor T. N. Guru Row, Indian Institute of Science, Bangalore, and the Department of Science and Technology, India, for data collection on the CCD facility under the IRHPA–DST scheme. Vasu thanks Vivekananda Degree College for support and DC thanks the CSIR and IISc for a Senior Research Fellowship.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV3133). Services for accessing these data are described at the back of the journal.

References

Altomare, A., Cascarano, G., Giacovazzo, C. & Guagliardi, A. (1993). *J. Appl. Cryst.* **26**, 343–350.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Bruker (2000). *SMART* (Version 5.0) and *SAINT* (Version 6.02). Bruker AXS Inc., Madison, Wisconsin, USA.
Cohen, V. I., Rist, N. & Duponchel, C. (1977). *J. Pharm. Sci.* **66**, 1332–1334.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Csaszar, J. & Morvay, J. (1983). *Acta Pharm. Hung.* **53**, 121–128.
Dzhurayev, A. D., Karimkulov, K. M., Makhsumov, A. G. & Amanov, N. (1992). *Khim. Farm. Zh.* **26**, 73–75.
El-Maghraby, A. A., Haroun, B. & Mohammed, N. A. (1984). *Egypt. J. Pharm. Sci.* **23**, 327–336.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Gewald, K., Schinke, E. & Botcher, H. (1966). *Chem. Ber.* **99**, 94–100.
Kumar, G. N. A., Kokila, M. K., Puttaraja,, Mohan, S., Shetty, K. S. M. & Kulkarni, M. V. (2005). *Acta Cryst.* E**61**, o69–o71.
Lakshmi, V. V., Sridhar, P. & Polasa, H. (1985). *Indian J. Pharm. Sci.* **47**, 202–204.
Pellis, G. & West, G. B. (1968). *Progress in Medicinal Chemistry*, Vol. 5, pp. 320–324. London: Butterworth and Co. Ltd.
Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Vasu, Nirmala, K. A., Chopra, D., Mohan, S. & Saravanan, J. (2004*a*). *Acta Cryst.* C**60**, o786–o788.
Vasu, Nirmala, K. A., Chopra, D., Mohan, S. & Saravanan, J. (2004*b*). *Acta Cryst.* C**60**, o636–o638.
Vasu, Nirmala, K. A., Chopra, D., Mohan, S. & Saravanan, J. (2005). *Acta Cryst.* E**61**, o236–o238.
Vasu, Nirmala, K. A., Choudhury, A. R., Mohan, S., Saravanan, J. & Narasimhamurthy, T. (2003). *Acta Cryst.* C**59**, o676–o678.
Watkin, D. M., Pearce, L. & Prout, C. K. (1993). *CAMERON*. Chemical Crystallography Laboratory, University of Oxford, England.