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Two biologically active thiophene-3-carboxamide derivatives

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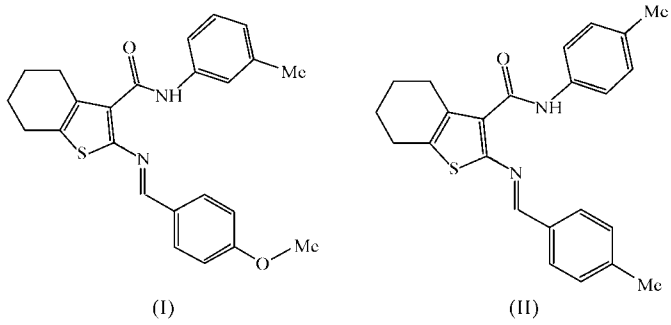
The compounds 2-{[(*E*)-(4-methoxyphenyl)methylene]amino}-*N*-(3-methylphenyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide, $C_{24}H_{24}N_2O_2S$, (I), and *N*-(4-methylphenyl)-2-{[(*E*)-(4-methylphenyl)methylene]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide, $C_{24}H_{24}N_2OS$, (II), show antibacterial and antifungal activities. The *m*-toluidine ring in (I) and the *p*-toluidine ring in (II) are coplanar with their respective thiophene rings. In (I), an intermolecular C—H···O hydrogen bond is present, whereas (II) does not exhibit any significant intermolecular interactions. However, in both compounds, an intramolecular N—H···N hydrogen bond forms a pseudo-six-membered ring, thus locking the molecular conformation and eliminating conformational flexibility.

Comment

The design of compounds that possess important pharmacological properties, such as antibacterial, anticancer, anti-inflamatory and antitoxic activities, is an important area of research, and Schiff bases (Pellis & West, 1968; Cohen *et al.*, 1977; Csaszar & Morvay, 1983; Lakshmi *et al.*, 1985) and their thiophene derivatives (El Maghraby *et al.*, 1984; Dzhurayev *et al.*, 1992; Gewald *et al.*, 1966) have been found to exhibit these activities. In this context, sulfur-containing Schiff bases are most effective. We have already reported the crystal structures of biologically active thiophene-3-carboxamide derivatives (Vasu *et al.*, 2003). In view of the medicinal applications of such classes of compounds, single-crystal studies have been carried out.

The two compounds 2-{[(*E*)-4-methoxyphenyl)methylene]-amino}-*N*-(3-methylphenyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide, (I), and *N*-(4-methylphenyl)-2-{[(*E*)-4-methylphenyl)methylene]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide, (II), belong to the same series of compounds and show antibacterial and antifungal activities (Mohan & Saravanan, 2002, 2003).

Compounds (I) and (II) contain three different structural moieties, which will be discussed separately (Figs. 1 and 2).



The thiophene ring exhibits normal geometry and is planar, with maximum deviations of 0.012 (1) and 0.007 (3) Å for the C7 atoms in (I) and (II), respectively. The six-membered cyclohexene ring adopts a half-chair conformation, with atoms C1 and C2 deviating, respectively, 0.316 (2) and −0.340 (2) Å in (I), and 0.337 (5) and −0.250 (4) Å in (II).

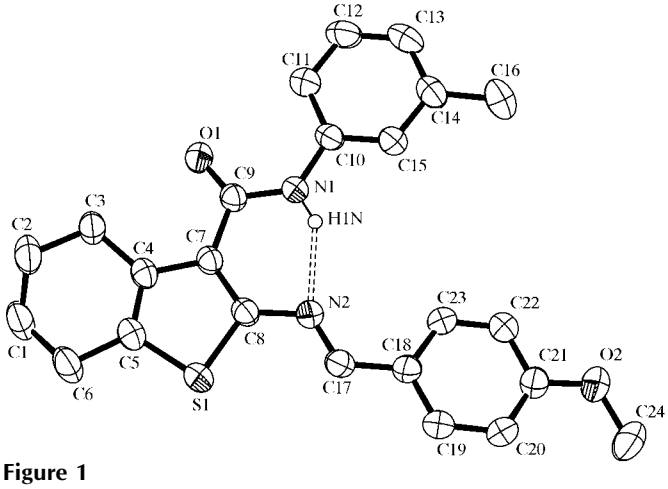


Figure 1
A view of (I), drawn with 50% probability displacement ellipsoids. The broken lines indicate the intramolecular N—H···N hydrogen bond.

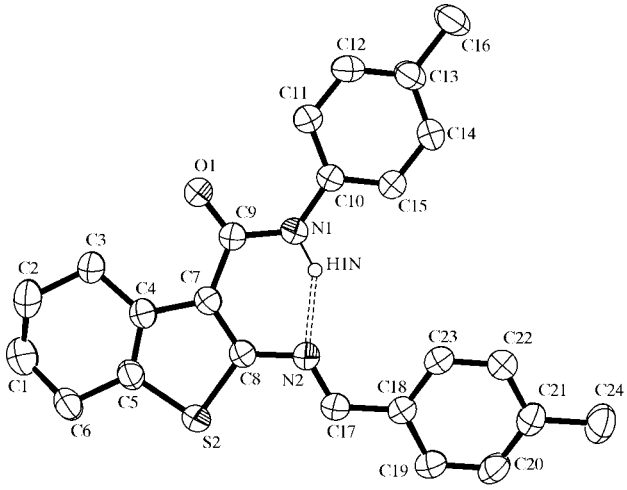


Figure 2
A view of (II), drawn with 50% probability displacement ellipsoids. The broken lines indicate the intramolecular N—H···N hydrogen bond.

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The *m*-toluidine group in (I) and the *p*-toluidine moiety in (II) are coplanar with the plane of the thiophene ring, as indicated by the C9—N1—C10—C15 torsion angles [177.5 (2) and −178.3 (3)°, respectively]. The angle between the mean planes of the *m*-toluidine and thiophene rings is 8.2 (1)°, whereas that between the planes of the *p*-toluidine and thiophene rings is 9.7 (1)°. The dihedral angle between the planes containing the *p*-methoxyphenyl group and the thiophene ring is 13.03 (5)°, which implies that the whole molecule is planar. The corresponding dihedral angle between the planes passing through the *p*-toluidine group attached to the imine moiety and thiophene ring is 14.3 (1)°.

The C—N bond lengths in the carboxamide and imine moieties are significantly different: the C9—N1 and C8—N2 bond lengths are, respectively, 1.364 (2) and 1.391 (2) Å in (I), and 1.360 (2) and 1.391 (3) Å in (II), indicating that the electronic and steric environments around these moieties are different. The C23—C18—C19 [117.5 (1)°] and C22—C21—C20 [117.9 (2)°] angles in (I) and (II), respectively, deviate significantly from the ideal value (120°) for a phenyl ring, This deviation is due to the electron-donating resonance effect of the methoxy group attached to atom C21 in (I) and the electron-donating inductive effect of the methyl group on C21 in (II).

There are no significant intermolecular hydrogen-bonding interactions in the packing of (II). An intramolecular N—H···N hydrogen-bonding interaction in each structure (Tables 1 and 2) locks the molecule into a rigid pseudo-six-membered-ring conformation and removes the conformational flexibility. Hence, the free NH group is not available for participation in intermolecular interactions. In (I), intermolecular C—H···O interactions form molecular chains (Fig. 3) running parallel to the crystallographic *c* axis and further stabilizing the packing of molecules in the crystal structure.

The packing characteristics reveal interesting features as regards the orientation of the molecules in the crystalline environment. In (I), the molecules held together by C—H···O interactions are related by the *n*-glide plane at $(\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z)$, and this feature of molecular recognition essentially steers the molecules to pack in a monoclinic centrosymmetric environment. In (II), replacement of the H atom that participates in an intermolecular interaction in (I) by a methyl group eliminates the formation of chains. This difference leads to remarkable differences in the crystal packing, and the molecules in (II) are stacked in layers that are parallel to one another and related by a center of inversion.

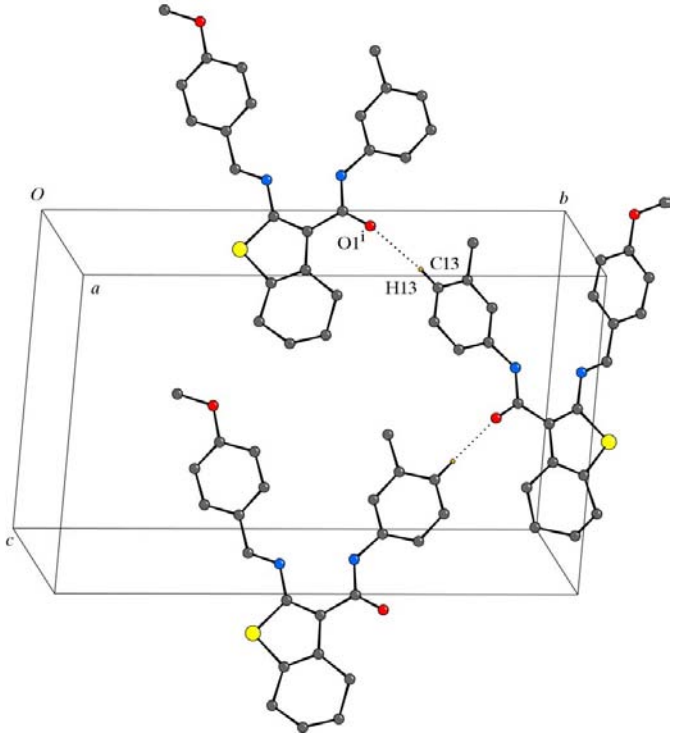

Figure 3
C—H···O interactions in (I); see Table 1 for symmetry code.

Experimental

The title compound was synthesized using the Gewald reaction (Gewald *et al.*, 1966). For (I), *m*-cyanotoluidine was refluxed with cyclohexanone in the presence of sulfur, dimethylamine and ethanol at 313–323 K for 1 h. The product was treated with an equimolar quantity of 4-methoxybenzaldehyde in the presence of ethanol, yielding (I). Compound (I) was recrystallized from a solution of *N*,*N*-dimethylformamide and ethanol (1:2) by slow evaporation. Crystals were obtained after four weeks and used for single-crystal data collection. For the preparation of (II), a similar procedure was followed using *p*-cyanotoluidine, and later 4-methylbenzaldehyde was added. The compound was purified and crystallized using the same procedure as for (I).

Compound (I)

Crystal data

$C_{24}H_{24}N_2O_2S$
M_r = 404.52
Monoclinic, $P2_1/n$
a = 8.184 (5) Å
b = 19.786 (11) Å
c = 12.884 (7) Å
β = 96.994 (10)°
V = 2071 (2) Å^3
Z = 4
D_x = 1.297 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 265 reflections
θ = 1.5–26.4°
μ = 0.18 mm^{-1}
T = 293 (2) K
Block, yellow
0.33 × 0.28 × 0.14 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1997)
T_{min} = 0.927, T_{max} = 0.975
15 741 measured reflections
4130 independent reflections
3501 reflections with $I > 2\sigma(I)$
R_{int} = 0.016
θ_{max} = 26.4°
$h = -10 \rightarrow 10$
$k = -24 \rightarrow 24$
$l = -15 \rightarrow 15$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.119
S = 0.83
4130 reflections
336 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0928P)^2 + 0.6468P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···N2	0.84 (2)	2.03 (2)	2.766 (2)	145 (2)
C13—H13···O1^{i}	0.95 (2)	2.47 (2)	3.385 (2)	160 (2)

Symmetry code: (i) $x-\frac{1}{2}, \frac{3}{2}-y, z-\frac{1}{2}$.

Compound (II)

Crystal data

$C_{24}H_{24}N_2OS$
M_r = 388.52
Triclinic, $P\overline{1}$
a = 7.658 (7) Å
b = 12.365 (11) Å
c = 12.569 (11) Å
α = 108.490 (13)°
β = 103.745 (14)°
γ = 106.020 (13)°
V = 1013.6 (16) Å^3
Z = 2
D_x = 1.273 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 650 reflections
θ = 1.4–26.2°
μ = 0.18 mm^{-1}
T = 293 (2) K
Block, yellow
0.16 × 0.11 × 0.10 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1997)
T_{min} = 0.936, T_{max} = 0.983
10 561 measured reflections
4011 independent reflections
3363 reflections with $I > 2\sigma(I)$
R_{int} = 0.018
θ_{max} = 26.4°
$h = -9 \rightarrow 9$
$k = -14 \rightarrow 15$
$l = -15 \rightarrow 15$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.057
$wR(F^2)$ = 0.192
S = 0.87
4011 reflections
295 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.1622P)^2 + 0.394P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.43 e Å^{-3}
$\Delta\rho_{min}$ = −0.43 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···N2	0.98 (4)	1.89 (4)	2.752 (4)	146 (3)

For (I), the methyl H atoms were constrained to an ideal geometry [C—H = 0.96 Å and U_{iso}(H) = 1.5U_{eq}(C)] but were allowed to rotate freely about the C—C bond. All other H atoms were located from a difference Fourier map and their parameters were refined freely. For (II), the methyl H atoms were constrained to an ideal geometry [C—H = 0.96 Å and U_{iso}(H) = 1.5U_{eq}(C)] but were allowed to rotate freely about the C—C bond. The H atoms of the cyclohexene ring (C—H = 0.93–0.97 Å) and phenyl atom H22 (C—H = 0.93 Å) were placed in idealized positions and constrained to ride on their parent atoms [U_{iso}(H) = 1.2U_{eq}(C)]. All other H atoms were located from a difference Fourier map and their parameters were refined freely.

For both compounds, data collection: *SMART* (Bruker, 1998); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1998); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997) and *CAMERON* (Watkin *et al.*, 1993); software used to prepare material for publication: *PLATON* (Spek, 2003).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DE1249). Services for accessing these data are described at the back of the journal.

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