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N-Benzyltetrahydropyrido-anellated thiophene derivatives: new anti-cholinesterases

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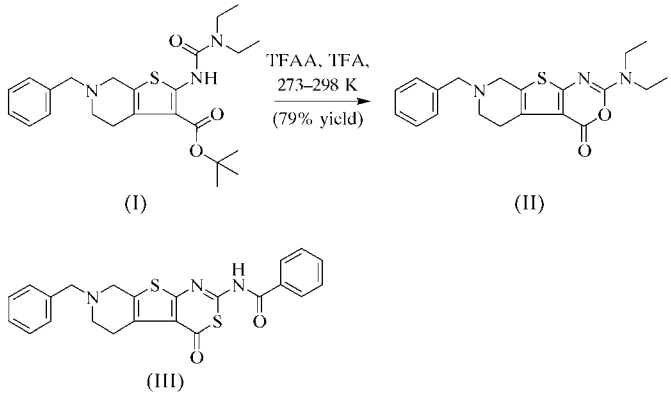
The title compounds, *tert*-butyl 6-benzyl-2-(3,3-diethylureido)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate, $C_{24}H_{33}N_3O_3S$, (I), 7-benzyl-2-diethylamino-5,6,7,8-tetrahydro-3-oxa-9-thia-1,7-diazafluoren-4-one, $C_{20}H_{23}N_3O_2S$, (II), and *N*-(7-benzyl-4-oxo-5,6,7,8-tetrahydro-4*H*-3,9-dithia-1,7-diazafluoren-2-yl)benzamide, $C_{23}H_{19}N_3O_2S_2$, (III), form monoclinic crystal systems. In (I) and (II), the molecules are linked into a three-dimensional framework by weak intermolecular C—H···O═C hydrogen bonds, whereas in (III) stronger intermolecular N—H···O═C interactions are observed. The conformation of (I) is further stabilized by an intramolecular N—H···O═C hydrogen bond, which effects the planarity of the ureidothiophenecarboxylate moiety.

Comment

As part of our search for new structures exhibiting an inhibitory potency towards members of the α/β-hydrolase family, we performed the present structure determinations. In this



context, we were especially interested in inhibitors of the enzyme acetylcholinesterase (AChE) currently being used as major therapeutic agents to alleviate the symptoms of Morbus Alzheimer (Colombres *et al.*, 2004; Muñoz-Torrero & Camps,

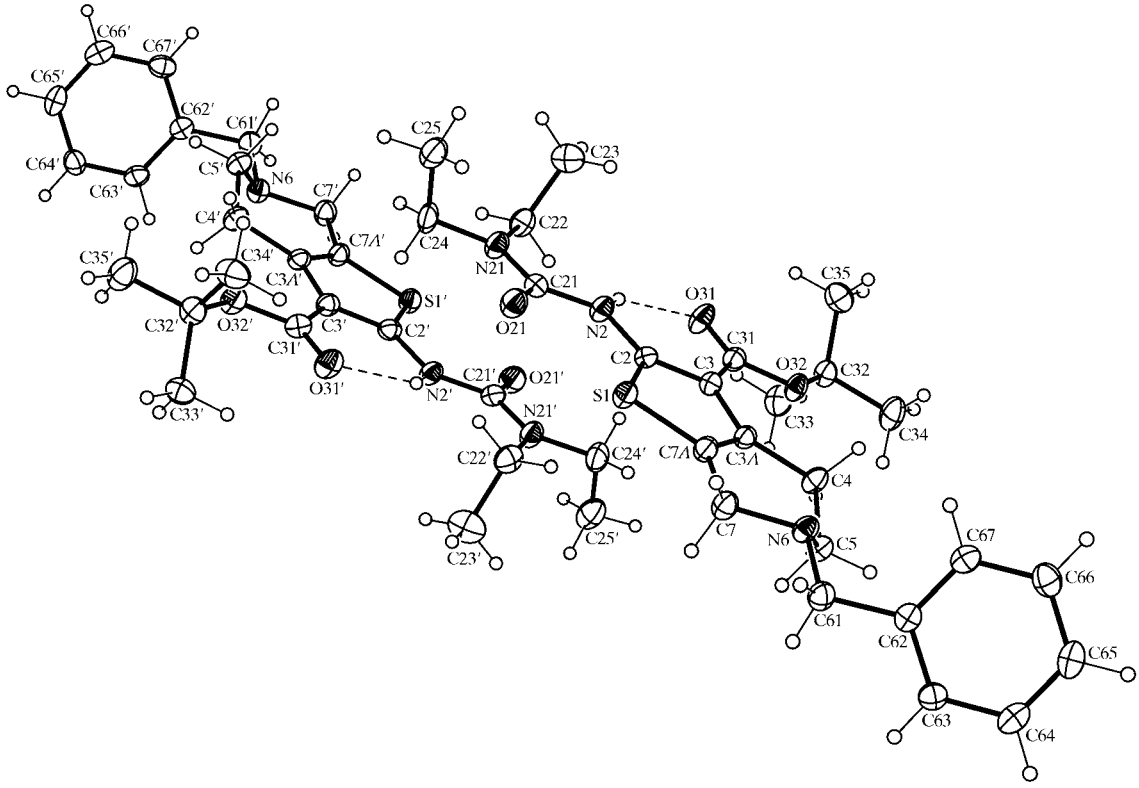


Figure 1
The molecular structure of (I), showing the atom-labelling scheme and displacement ellipsoids at the 50% probability level for the non-H atoms of the two independent molecules in the asymmetric unit. H atoms are depicted as small circles of arbitrary radii and dashed lines represent hydrogen bonds.

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2006). This disease is characterized by a selective neuronal cell death probably caused by amyloid fibrils, as well as a loss of cholinergic transmission. AChE was found to be associated with such amyloid species and may contribute to their development (Alvarez *et al.*, 1997, 1998; Inestrosa & Alarcon, 1998). In addition, the enzyme catalyzes the hydrolytic destruction of the neurotransmitter acetylcholine at cholinergic synapses (Cartaud *et al.*, 2004; Silman & Sussman, 2005). A reduction of the activity of AChE leads to an increased bioavailability of acetylcholine at the synaptic cleft and an improvement of the cholinergic neurotransmission as well as the cognitive functions (Colombres *et al.*, 2004; Muñoz-Torrero & Camps, 2006). Beside its central role in the therapy of Alzheimer's disease, AChE has been targeted in treatments for myasthenia gravis, glaucoma, obstipation and spasmolysis and to antagonize muscle relaxation in anesthesiology (Ibach & Haen, 2004). Compounds of several classes bearing a benzyl-substituted piperidine moiety, including donepezil (Aricept), have been characterized as inhibitors of AChE (Muñoz-Torrero & Camps, 2006). These findings resulted in the investigation and X-ray crystal structures of the *N*-benzyltetrahydropyrido-anellated thiophene derivatives (I)–(III) [at 123 (2) K] that are reported here. Compounds (II) and (III) are potent inhibitors of AChE (IC_{50} values of 2.1 μM and 5.2 μM, respectively), whereas the enzyme is less affected by (I), *i.e.* the educt of (II) (IC_{50} = 10 μM). Full details of the synthesis and characterization of these compounds as well as their biological activity were published elsewhere (Pietsch & Gütschow, 2005).

The structure of (I) with the atomic numbering scheme is shown in Fig. 1. Selected parameters characterizing the geometry of the ureidothiophenecarboxylic ester unit of the two independent molecules are given in Table 1. This unit is planar, with the ester group and the ureido group situated in the plane of the thiophene ring system, and with torsion angles C2—C3—C31—O32 and C2—N2—C21—N21 of 177.93 (16)/−175.24 (16) and −173.60 (17)/174.37 (17)°, respectively. The mean deviations of the atoms from the N21/C21/O21/N2/C2/S1/C7*A*/C7/C4/C3*A*/C3/C31/O31/O32/C32 planes are 0.044 and 0.053 Å. The dihedral angles between the planes delineated by the above-mentioned atoms and all the non-H atoms of the phenyl rings are 68.11 (5) and 67.11 (5)° in the two independent molecules of (I). The ester carbonyl group has a *cis* orientation with respect to the C2═C3 double bond. This leads to an intramolecular resonance-assisted N2—H2···O31 hydrogen bond (Table 2), which locks the molecular conformation by forming a pseudo-six-membered ring and eliminates conformational flexibility (Gilli *et al.*, 2000). The values of the H—*A* and *D*···*A* distances and the *D*—H···*A* angle (Table 2) characterize this bond as a strong hydrogen bond (Desiraju & Steiner, 1999; Steiner, 2002), and agree with relevant data (average values) for 11 β-enaminoesters forming intramolecular N—H···O hydrogen bonds [*D*···*A* = 2.70 (2) Å and *D*—H···*A* = 132 (4)°; Gilli *et al.*, 2000]. In addition, the O31═C31 distance of 1.225 (2) Å [O31′═C31′ = 1.222 (2) Å] in (I) is in accordance with the average value of C═O [1.221 (6) Å] for the above-mentioned β-enaminoesters, and can be calculated from the *D*···*A* distance by the equation C═O = *a* + *b*(*D*···*A*), with *a* = 2.14 (5) and *b* = −0.34 (2) (Gilli *et al.*, 2000). This calculation yielded values of 1.227 and 1.231 Å for O31═C31 and O31′═C31′, respectively,

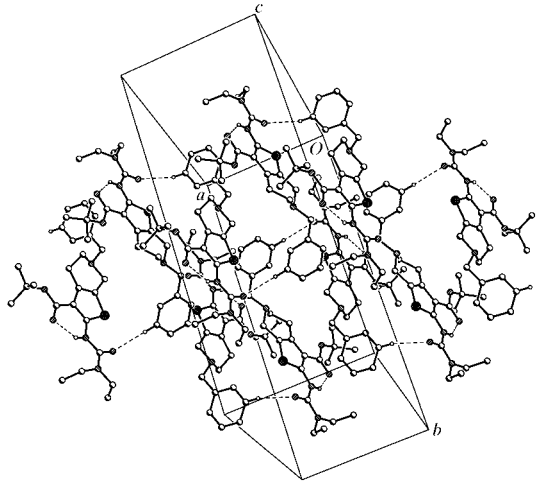

Figure 2
The arrangement of the molecules of (I) in the unit cell. The intramolecular N—H···O interactions and intermolecular C—H···O interactions are represented by dashed lines.

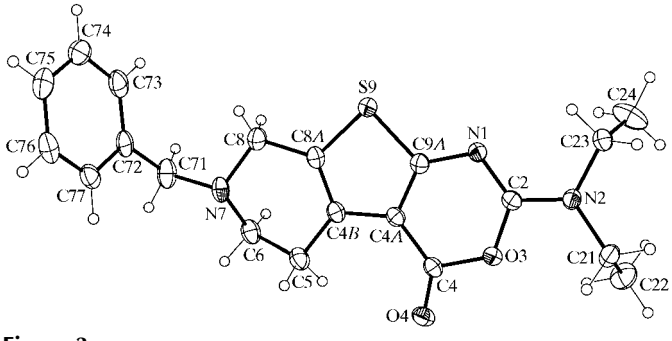

Figure 3
The molecular structure of (II), showing the atom-labelling scheme and displacement ellipsoids at the 50% probability level for non-H atoms. H atoms are depicted as small circles of arbitrary radii.

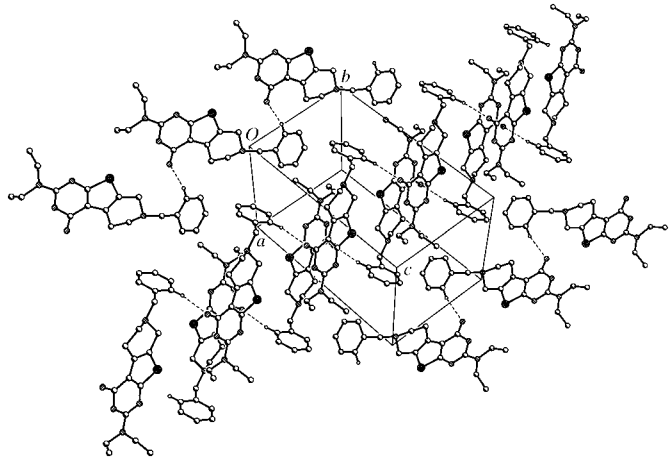

Figure 4
The arrangement of the molecules of (II) in the unit cell. The intermolecular C—H···O interactions are represented by dashed lines.

and agreed with the experimentally found data. The intramolecular hydrogen bond is weakened by the electron-attracting *tert*-butoxy group, which decreases the charge density and thus the proton affinity of the carbonyl O atom. This effect has been confirmed by calculations showing that the resonance assistance of hydrogen bonds in β-enaminoesters has become so weak that such hydrogen bonds are barely distinguishable from non-resonant ones (Gilli *et al.*, 2000). The weakening of the intramolecular hydrogen bond in (I) is further supported by IR and NMR spectroscopic data. The band of the isolated N—H stretching vibration, ν NH, is only marginally shifted to a lower frequency from approximately 3400 (Gilli *et al.*, 2000) to 3247 cm^{-1} (Pietsch & Gütschow, 2005). Likewise, the δ N—H chemical shift obtained from an NMR measurement shows only a minor downfield shift from approximately 7 (Gilli *et al.*, 2000) to 11.09 p.p.m. (Pietsch & Gütschow, 2005). In contrast, very strong hydrogen bonds are characterized by the values 2.65 $\geq D\cdots A \geq$ 2.48 Å, 3200 $\geq \nu$ NH $\geq$ 2340 cm^{-1} and 13 $\leq \delta$ N—H $\leq$ 18 p.p.m. The latter value, obtained in solution ($CDCl_3$), can be correlated with the solid-state $D\cdots A$ distance using the equation δ N—H = 91 (6) − 30 (2)($D\cdots A$) (Gilli *et al.*, 2000), the calculated values, *i.e.* 10.48 and 10.78 p.p.m., being in accordance with the experimental one. Molecules of (I) are interconnected by a framework of intermolecular C—H$\cdots$O═C hydrogen bonds, *viz*. C66—H66$\cdots$O21′ and C64′—H64′$\cdots$O21, respectively, as shown in Fig. 2 and detailed in Table 2. The values of the H—*A* and $D\cdots A$ distances, as well as the D—H$\cdots A$ angle, characterize these nearly linear hydrogen bonds (D—H$\cdots A$ = 159 and 160°) as weak ones (Desiraju, 1996; Desiraju & Steiner, 1999; Steiner, 2002) and agree with data described in the literature (Cox, 2002; Pigge *et al.*, 1999; Schulze *et al.*, 2005; Vasu *et al.*, 2004).

Compound (II) is the first thieno[1,3]oxazin-4-one that has been characterized by X-ray crystallography. The synthesis of (II) was performed by treating (I) with trifluoroacetic acid and trifluoroacetic anhydride, resulting in deesterification and cyclocondensation (Pietsch & Gütschow, 2005). The structure of (II), with the atomic numbering scheme, and the arrangement of the molecules in the asymmetric unit are shown in Figs. 3 and 4, respectively; selected bond distances and angles are given in Table 3. The thienoxazinone system in (II) is essentially planar, in agreement with earlier experimental data of bioisosteric benzoxazinones (Crane & Rogerson, 2004; Gütschow *et al.*, 1998; Kovalevsky & Ponomarev, 2000; Kovalevsky *et al.*, 2000; Yadav *et al.*, 2002). The mean deviation of the atoms from the plane formed by this heterocycle and atoms N2, C5 and C8 is 0.015 Å, with C8 deviating by a maximum of 0.041 Å. The aforementioned plane and the phenyl ring of the benzyl group in (II) are virtually perpendicular to each other, as shown by the dihedral angle of 75.50 (3)°. In compound (II), the O3—C2 bond is shorter than the O3—C4 bond. Moreover, the bond angles at C2 and C4 are distorted from their ideal values of 120°. Such observations were explained as a result of the concerted electronic effects of adjacent substituents (Kovalevsky & Ponomarev, 2000). Similar to the molecules of (I), the crystal structure of (II) is stabilized by weak intermolecular C—H$\cdots$O═C hydrogen bonds formed by C73, H73 and O4 (Table 4 and Fig. 4).

In contrast to the thieno[1,3]oxazin-4-one heterocycle in compound (II), the isosteric thieno[1,3]thiazin-4-one system in (III) (Table 5 and Fig. 5) is less planar. This is reflected in the mean deviation of the atoms from the plane formed by this system and atoms N21, C5 and C8, taking a value of 0.085 Å, with O4 deviating by a maximum of 0.229 Å. The dihedral angles between this plane and the phenyl rings of the benzyl and benzoyl groups are 55.69 (4) and 53.90 (4)°, respectively. The replacement of the ring O atom in oxazinone (II) by an S atom in thiazinone (III) results in a significant distortion of the bond angles at C2, C4 and C9*A* from 120° (Table 5), with the obtained values agreeing with reported data (Evain *et al.*, 2002; Lamiot *et al.*, 1992). As N21, and not N1, was found to be hydrogen-substituted, the structure of the tautomeric form (III) based on IR and NMR data (Pietsch & Gütschow, 2005)

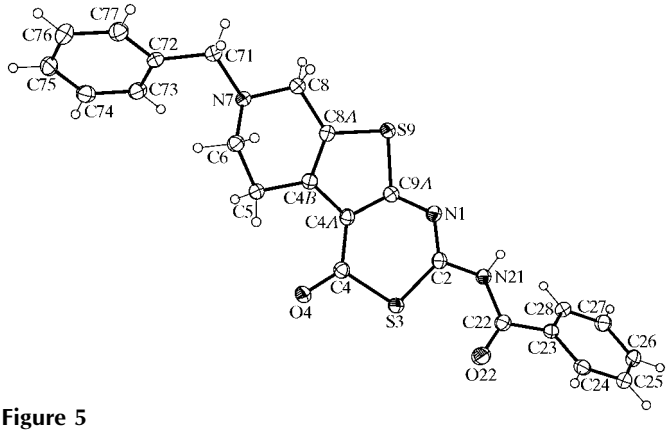

Figure 5
The molecular structure of (III), showing the atom-labelling scheme and displacement ellipsoids at the 50% probability level for non-H atoms. H atoms are depicted as small circles of arbitrary radii.

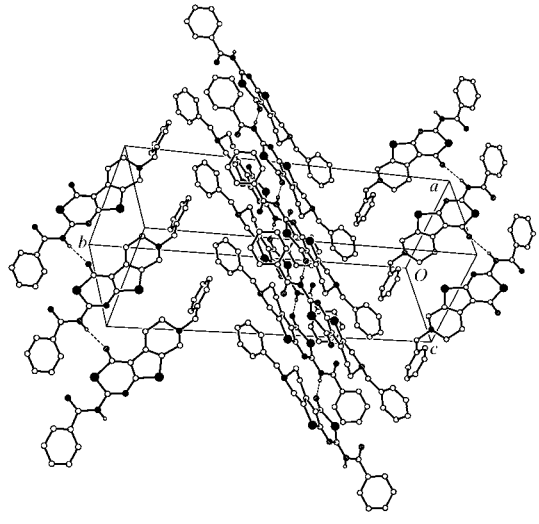

Figure 6
The arrangement of the molecules of (III) in the unit cell. The intermolecular N—H$\cdots$O interactions are represented by dashed lines.

has been proved true. The tautomer containing an exocyclic C2═N21 double bond is not observed and thus an intramolecular N1—H1···O22 hydrogen bond cannot be formed. Instead, a non-binding intramolecular interaction between atoms S3 and O22 has been taken into account as already shown for 4-acylimino-2-aminothieno[2,3-*d*][1,3]thiazines (Gütschow *et al.*, 1992). Such an interaction was not found as the S3···O22 distance exceeds the described value, and the system formed by atoms S3, C2, N21, C22 and O22 is less planar, with C2 deviating by a maximum of 0.176 Å. In contrast to compounds (I) and (II), molecules of (III) are linked *via* intermolecular N—H···O═C hydrogen bonds originating from N21, H21 and O4 (Table 6 and Fig. 6). The values of the N···O contact distance as a measure of the hydrogen-bond strength, and the C4═O4 bond length, taken as an indicator of π-delocalization in an ···O═R_n—N—H··· heteroconjugated system (Tables 5 and 6), characterize this intermolecular interaction as not assisted by resonance (Bertolasi *et al.*, 1995, 1998).

Experimental

Compounds (I)–(III) were prepared as described previously (Pietsch & Gütschow, 2005). Yellow crystals of (I) suitable for X-ray analysis were grown from methanol, while yellow crystals of (II) and (III) were obtained upon recrystallization from hexane and ethyl acetate, respectively. AChE inhibition by compound (I) was assayed spectrophotometrically in two separate experiments (each in duplicate) at a single concentration (10 μ*M*) according to the method of Ellman *et al.* (1961), as described elsewhere (Pietsch & Gütschow, 2005).

Compound (I)

Crystal data

$C_{24}H_{33}N_3O_3S$
M_r = 443.59
Monoclinic, $P2_1/c$
a = 9.7735 (2) Å
b = 24.4098 (5) Å
c = 19.7439 (5) Å
β = 93.865 (1)°
V = 4699.57 (18) Å^3
Z = 8
D_x = 1.254 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.17 mm^{-1}
T = 123 (2) K
Plate, yellow
0.50 × 0.40 × 0.20 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans
28911 measured reflections
10616 independent reflections
6646 reflections with $I > 2\sigma(I)$
R_{int} = 0.052
θ_{max} = 27.5°

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

N2—C21	1.376 (3)	N2′—C21′	1.376 (3)
C21—O21	1.235 (2)	C21′—O21′	1.229 (2)
C21—N21	1.358 (2)	C21′—N21′	1.359 (3)
C31—O31	1.225 (2)	C31′—O31′	1.222 (2)
C31—O32	1.343 (2)	C31′—O32′	1.341 (2)
N2—C2—C3	125.19 (17)	N2′—C2′—C3′	124.70 (18)
C2—C3—C31	119.94 (18)	C2′—C3′—C31′	120.17 (19)
O31—C31—C3	124.45 (19)	O31′—C31′—C3′	123.9 (2)
C2—N2—C21—N21	−173.60 (17)	C2′—N2′—C21′—N21′	174.37 (17)
C2—C3—C31—O32	177.93 (16)	C2′—C3′—C31′—O32′	−175.24 (16)

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.128
S = 0.97
10616 reflections
565 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0609P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.51 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···O31	0.881 (14)	1.961 (18)	2.684 (2)	138.4 (19)
N2′—H2′···O31′	0.870 (14)	1.983 (18)	2.674 (2)	135.5 (19)
C64′—H64′···O21^{i}	0.95	2.54	3.448 (2)	160
C66—H66···O21′^{ii}	0.95	2.50	3.403 (2)	159

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

Compound (II)

Crystal data

$C_{20}H_{23}N_3O_2S$
M_r = 369.47
Monoclinic, $P2_1/c$
a = 12.0595 (4) Å
b = 8.9892 (3) Å
c = 18.0483 (6) Å
β = 106.503 (1)°
V = 1875.93 (11) Å^3
Z = 4
D_x = 1.308 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.19 mm^{-1}
T = 123 (2) K
Block, yellow
0.60 × 0.50 × 0.30 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans
10069 measured reflections
4092 independent reflections
3374 reflections with $I > 2\sigma(I)$
R_{int} = 0.026
θ_{max} = 27.5°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.090
S = 1.08
4092 reflections
235 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0465P)^2 + 0.1983P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.28 e Å^{-3}

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

N1—C2	1.3093 (16)	O3—C4	1.4169 (14)
C2—N2	1.3334 (15)	C4—O4	1.2114 (14)
C2—O3	1.3654 (13)		
C2—N1—C9*A*	113.61 (10)	O3—C4—C4*A*	113.72 (10)
N1—C2—O3	125.16 (10)	C9*A*—C4*A*—C4	117.96 (10)
C2—O3—C4	122.20 (9)	N1—C9*A*—C4*A*	127.34 (11)

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

D—H···A	D—H	H···A	D···A	D—H···A
C73—H73···O4^{i}	0.95	2.50	3.4341 (16)	167

Symmetry code: (i) $x, y-1, z$.

Compound (III)

Crystal data

$C_{23}H_{19}N_3O_2S_2$
M_r = 433.53
Monoclinic, $P2_1/c$
a = 9.2927 (2) Å
b = 29.3299 (6) Å
c = 7.5645 (1) Å
β = 106.015 (1)°
V = 1981.72 (7) Å^3
Z = 4
D_x = 1.453 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.30 mm^{-1}
T = 123 (2) K
Plate, yellow
0.50 × 0.30 × 0.20 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans
11671 measured reflections
4398 independent reflections
3832 reflections with $I > 2\sigma(I)$
R_{int} = 0.027
θ_{max} = 27.5°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.090
S = 1.04
4398 reflections
274 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0449P)^2 + 0.6981P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.46 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}

Table 5
Selected geometric parameters (Å, °) for (III).

N1—C2	1.2920 (19)	S3—C4	1.7948 (14)
C2—N21	1.3927 (17)	C4—O4	1.2299 (17)
C2—S3	1.7562 (14)		
C2—N1—C9*A*	119.46 (12)	C4*A*—C4—S3	117.69 (10)
N1—C2—S3	126.56 (11)	C9*A*—C4*A*—C4	120.79 (12)
C2—S3—C4	103.54 (7)	N1—C9*A*—C4*A*	131.10 (13)
N1—C2—N21—C22	160.22 (14)	C2—N21—C22—O22	3.8 (2)
S3—C2—N21—C22	−20.61 (18)		

Table 6
Hydrogen-bond geometry (Å, °) for (III).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N21—H21···O4^{i}	0.855 (14)	2.188 (14)	3.0406 (16)	174.5 (16)

Symmetry code: (i) $x, y, z-1$.

All H atoms were initially located in a difference Fourier map. The methyl H atoms were then constrained to an ideal geometry, with C—H = 0.98 Å and U_{iso}(H) = 1.5U_{eq}(C). A DFIX restraint [0.88 (3) Å] was applied to each N—H bond in the refinement of the two independent molecules of (I), and in the refinement of (III), with U_{iso}(H) = 1.2U_{eq}(N). All other H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms, with C—H = 0.95–0.99 Å and U_{iso}(H) = 1.2U_{eq}(C).

For all compounds, data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Sheldrick, 2001); software used to prepare material for publication: *SHELXL97* (Sheldrick, 1997) and *DIAMOND* (Brandenburg, 2006).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3083). Services for accessing these data are described at the back of the journal.

References

Alvarez, A., Alarcon, R., Opazo, C., Campos, E. O., Munoz, F. J., Calderon, F. H., Dajas, F., Gentry, M. K., Doctor, B. P., De Mello, F. G. & Inestrosa, N. C. (1998). *J. Neurosci.* **18**, 3213–3223.
Alvarez, A., Opazo, C., Alarcon, R., Garrido, J. & Inestrosa, N. C. (1997). *J. Mol. Biol.* **272**, 348–361.
Bertolasi, V., Gilli, P., Ferretti, V. & Gilli, G. (1995). *Acta Cryst.* B**51**, 1004–1015.
Bertolasi, V., Gilli, P., Ferretti, V. & Gilli, G. (1998). *Acta Cryst.* B**54**, 50–65.
Brandenburg, K. (2006). *DIAMOND*. Version 3.1d. Crystal Impact GbR, Bonn, Germany.
Cartaud, A., Strochlic, L., Guerra, M., Blanchard, B., Lambergeon, M., Krejci, E., Cartaud, J. & Legay, C. (2004). *J. Cell Biol.* **165**, 505–515.
Colombres, M., Sagal, J. P. & Inestrosa, N. C. (2004). *Curr. Pharm. Des.* **10**, 3121–3130.
Cox, P. J. (2002). *Acta Cryst.* E**58**, o661–o662.
Crane, J. D. & Rogerson, E. (2004). *Acta Cryst.* E**60**, o669–o670.
Desiraju, G. R. (1996). *Acc. Chem. Res.* **29**, 441–449.
Desiraju, G. R. & Steiner, T. (1999). *The Weak Hydrogen Bond.* Oxford University Press.
Ellman, G. L., Courtney, K. D., Andres, V. & Featherstone, R. M. (1961). *Biochem. Pharmacol.* **7**, 88–95.
Evain, M., Landreau, C., Deniaud, D., Reliquet, A. & Meslin, J. C. (2002). *Acta Cryst.* E**58**, o288–o289.
Gilli, P., Bertolasi, V., Feretti, V. & Gilli, G. (2000). *J. Am. Chem. Soc.* **122**, 10405–10417.
Gütschow, M., Leistner, S. & Pink, M. (1992). *J. Heterocycl. Chem.* **29**, 279–282.
Gütschow, M., Neumann, U., Sieler, J. & Eger, K. (1998). *Pharm. Acta Helv.* **73**, 95–103.
Ibach, B. & Haen, E. (2004). *Curr. Pharm. Des.* **10**, 231–251.
Inestrosa, N. C. & Alarcon, R. (1998). *J. Physiol.* (*Paris*), **92**, 341–344.
Kovalevsky, A. Yu. & Ponomarev, I. I. (2000). *Acta Cryst.* C**56**, 260–262.
Kovalevsky, A. Yu., Ponomarev, I. I. & Baranova, M. A. (2000). *Acta Cryst.* C**56**, e408–e409.
Lamiot, J., Baert, F., Guelzim, A., Vicens, J., Chehna, M. & Pradere, J. P. (1992). *Acta Cryst.* C**48**, 729–731.
Muñoz-Torrero, D. & Camps, P. (2006). *Curr. Med. Chem.* **13**, 399–422.
Nonius (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Pietsch, M. & Gütschow, M. (2005). *J. Med. Chem.* **48**, 8270–8288.
Pigge, F. C., Ghasedi, F. & Rath, N. P. (1999). *Tetrahedron Lett.* **40**, 8045–8048.
Schulze, B., Taubert, K., Siegemund, A., Freysoldt, T. H. E. & Sieler, J. (2005). *Z. Naturforsch. Teil B*, **60**, 41–47.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
Sheldrick, G. M. (2001). *SHELXTL*. Version 5. Bruker AXS Inc., Madison, Wisconsin, USA.
Silman, I. & Sussman, J. L. (2005). *Curr. Opin. Pharmacol.* **5**, 293–302.
Steiner, T. (2002). *Angew. Chem. Int. Ed.* **41**, 48–76.
Vasu, Nirmala, K. A., Chopra, D., Mohan, S. & Saravanan, J. (2004). *Acta Cryst.* E**60**, o756–o757.
Yadav, B. N., Prasad, S. & Prasad, S. M. (2002). *Acta Cryst.* E**58**, o1111–o1112.