organic compounds

7-Chloro-1-(2,6-difluorophenyl)-1H,3H-thiazolo[3,4-a]benzimidazole and 1-(2,6-difluorophenyl)-6-methyl-1H,3H-thiazolo[3,4-a]benzimidazole

Francesco Nicoló,[a]* Giuseppe Bruno,[a] Rosario Scopelliti,[a] Silvana Grasso,[b] Angela Rao[b] and Maria Zappalá[b]

[a]Dip. di Chimica Inorganica, Chimica Analitica e Chimica Fisica, Universitá degli Studi di Messina, Via Salita Sperone 31, I-98166 Vill. S. Agata, Messina, Italy, and [b]Dip. Farmaco-Chimico, Universitá di Messina, 98168 Viale Annunziata, Messina, Italy

Correspondence e-mail: fnicolo@unime.it

The title molecules, $C_{15}H_9ClF_2N_2S$ and $C_{16}H_{12}F_2N_2S$, respectively, display the well known butterfly-like conformation with a flat thiazolobenzimidazole system. In both compounds, the mean plane through the tricyclic system is almost perpendicular to the 2,6-difluorophenyl ring. This arrangement of the aryl group is determined by two intramolecular hydrogen bonds and by an attractive F···S interaction.

Comment

As part of a structure–activity relationship study on a series of thiazolo[3,4-a]benzimidazole derivatives endowed with anti-HIV activity, we have already demonstrated (Chimirri *et al.*, 1997) that the geometric features of 1-(2,6-difluorophenyl)-1H,3H-thiazolo[3,4-a]benzimidazole (TBZ), the lead compound of the series, determine the biological activity. Moreover, we have observed (Chimirri *et al.*, 1996) that the anti-HIV activity is maintained by introducing a Cl atom at position

(I)

(II)
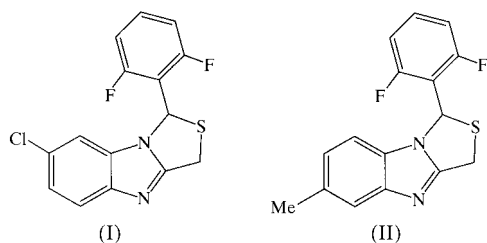
7 of the tricyclic system, whereas the presence of a methyl group at position 6 leads to a drop-off in activity. In this context, we report the crystal structures of 7-chloro-1-(2,6-difluorophenyl)-1H,3H-thiazolo[3,4-a]benzimidazole, (I), and 1-(2,6-difluorophenyl)-6-methyl-1H,3H-thiazolo[3,4-a]benzimidazole, (II), in order to determine whether the difference in activity could be related to any change in the molecular

geometry or to the presence of a substituent on the benzene ring.

Both compounds (I) and (II) are built up by three fused rings which form a flat thiazolobenzimidazole system (the atomic deviations from the weighted least-squares mean plane are within 0.02 Å); the thiazole ring in (I) has a chiral C atom at the point of attachment of the 2,6-difluorophenyl group. Since both compounds crystallize in centrosymmetric space groups, in the solid state, a racemic mixture was obtained from the synthesis. The molecular structure determinations of (I) and (II) confirm the well known butterfly conformation
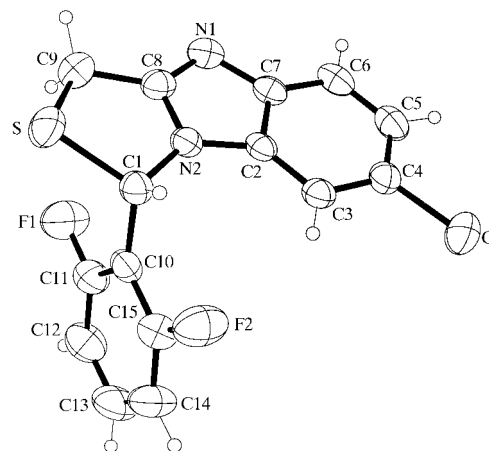
Figure 1
Perspective view of (I) showing the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level.

already shown to exist in other 1-aryl-1H,3H-thiazolo[3,4-a]-vatives (Bruno *et al.*, 1996, 1997, 1998). Such a disposition is evidenced by considering the dihedral angle between the three fused rings (the thiazolobenzimidazole system) and the 2,6-difluorophenyl substituent at C1, *i.e.* 100.28 (5) and 87.62 (6)° for (I) and (II), respectively. This arrangement is mainly due either to hindered rotation around the C1—C10 bond axis or to further stabilization through an intramolecular interaction between the H atom of the chiral Csp^3 atom and the electron-rich F atoms (see Tables 2 and 4).
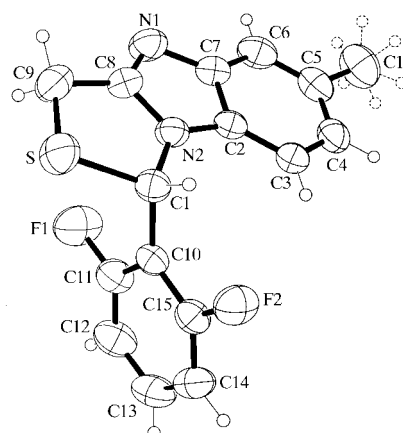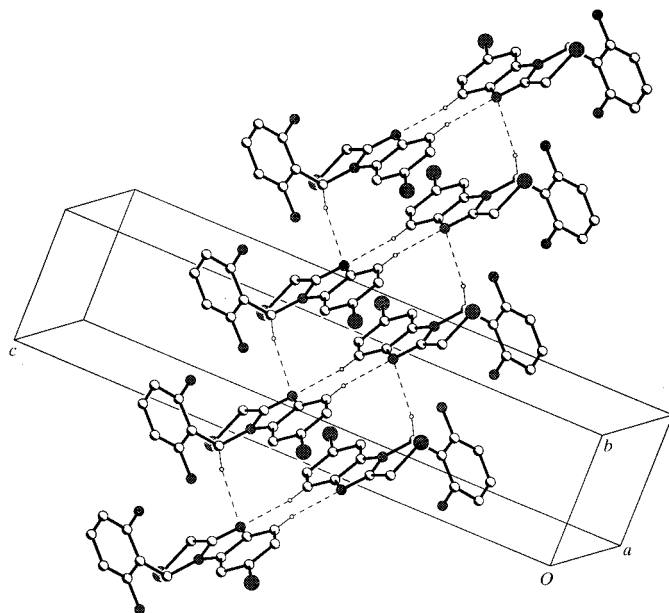

Figure 2
Perspective view of (II) showing the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level.

However, the puckering analysis (Cremer & Pople, 1975) shows that the conformations of the five-membered thiazolidine ring (S/C9/C8/N2/C1) are essentially different in (I) and (II); the conformation is intermediate between envelope ($\varphi = 180°$) and twisted ($\varphi = 90°$) in (I) [$\varphi = -145.4$ (4)°, $Q = 0.221$ (2) and $\Delta\sigma(S) = 0.005$ (1)] and a flatter envelope in (II) [$\varphi = -170$ (1)°, $Q = 0.097$ (2) and $\Delta2(C8) = 0.006$ (1)]. Such a difference may arise from the attractive F1···S [3.063 (1) Å] interaction (Bruno, Nicoló et al., 1997) that in (I) pushes the S atom up to -0.398 (1) Å out of the best mean plane through atoms C9/C8/N2/C1 on the opposite side of the F atom. In (II), the larger F···S separation of 3.236 (2) Å leaves the S atom 0.179 (1) Å out of this plane.

Bond distances of the thiazolidine ring are similar to those observed in a series of analogous TBZ compounds. In each compound, the bond distances involving the S atom, S—C1 and S—C9, are not equivalent, viz. 1.838 (2) and 1.825 (2) Å in (I) versus 1.848 (2) and 1.816 (2) Å in (II). The significant difference of 0.032 Å in (II) might be caused by the steric effect of the 2,6-difluorophenyl group linked to the C1 atom. The endocyclic C9—S—C1 bond angles of 95.3 (1) and 95.4 (1)° for (I) and (II), respectively, are in the narrow range of values reported in the Cambridge Structural Database (Allen et al., 1991) for penicillin and other biologically active substituted thiazolidines. The sum of the valence angles around N2 is 360.0 (1)° in (I) and 359.8 (2)° in (II), indicating its sp^2 hybridization. The N—C bond distances are also indicative of π-delocalization over the entire naphthoimidazole fragment.

The molecular packing for both compounds is essentially determined by normal van der Waals interactions and some weak hydrogen bonds involving the F and N atoms as acceptors. However, the H···N intermolecular network in compound (I) causes each centrosymmetric molecular pair to assume a flat head-to-tail disposition. Each molecular pair acts as a step of a staircase constituted by their overlap along the b axis like a pseudo-polymeric column, as shown in Fig. 3.

Experimental

The title compounds were obtained as described previously by Chimirri et al. (1996). Suitable single crystals were obtained by recrystallization from ethanol.

Compound (I)

Crystal data

$C_{15}H_9ClF_2N_2S$	$D_x = 1.552$ Mg m^{-3}
$M_r = 322.75$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 30
$a = 10.292$ (2) Å	reflections
$b = 5.741$ (1) Å	$\theta = 6.32–14.90°$
$c = 23.474$ (4) Å	$\mu = 0.443$ mm^{-1}
$\beta = 95.05$ (1)°	$T = 293$ (2) K
$V = 1381.6$ (4) Å^3	Prism, colourless
$Z = 4$	$0.34 \times 0.23 \times 0.17$ mm

Data collection

Siemens $P4$ diffractometer	$h = -5 \rightarrow 12$
ω–2θ scans	$k = -3 \rightarrow 7$
3993 measured reflections	$l = -29 \rightarrow 29$
2720 independent reflections	3 standard reflections
2170 reflections with $I > 2\sigma(I)$	every 197 reflections
$R_{int} = 0.013$	intensity decay: none
$\theta_{max} = 26.05°$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0452P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.031$	$+ 0.3215P]$
$wR(F^2) = 0.089$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.066$	$(\Delta/\sigma)_{max} = 0.001$
2720 reflections	$\Delta\rho_{max} = 0.20$ e Å^{-3}
191 parameters	$\Delta\rho_{min} = -0.25$ e Å^{-3}
H-atom parameters constrained	Extinction correction: *SHELXL*97
	Extinction coefficient: 0.0041 (11)

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

S—C9	1.825 (2)	N2—C2	1.3792 (19)
S—C1	1.8375 (17)	C8—N1	1.301 (2)
C1—N2	1.451 (2)	C8—C9	1.490 (2)
N2—C8	1.361 (2)	C7—N1	1.399 (2)
C9—S—C1	95.25 (8)	N1—C8—N2	114.46 (15)
N2—C1—S	102.11 (11)	N2—C8—C9	113.94 (15)
C8—N2—C2	107.06 (13)	C8—C9—S	104.41 (12)
C8—N2—C1	120.54 (13)	C8—N1—C7	103.64 (14)
C2—N2—C1	132.39 (14)		
S—C1—C10—C11	49.8 (2)		

Table 2
Contacts (Å, °) involving H atoms for (I).

D—H···A	D—H	H···A	D···A	D—H···A
C1—H1···F2	0.98	2.33	2.793 (2)	108
C9—H9A···F1	0.97	2.53	2.990 (2)	109
C1—H1···N1^i	0.98	2.44	3.399 (2)	165
C6—H6···N1^{ii}	0.93	2.59	3.502 (2)	166

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

Figure 3
The crystal packing of compound (I) showing the intermolecular hydrogen-bond interactions as dotted lines. Atom size is arbitrary. Shaded circles in rings indicate N atoms.

organic compounds

Compound (II)

Crystal data

$C_{16}H_{12}F_2N_2S$
$M_r = 302.34$
Triclinic, $P\bar{1}$
$a = 7.6160 (10)$ Å
$b = 10.202 (3)$ Å
$c = 10.868 (2)$ Å
$\alpha = 108.86 (2)°$
$\beta = 106.960 (10)°$
$\gamma = 105.46 (2)°$
$V = 701.0 (3)$ Å³

$Z = 2$
$D_x = 1.432$ Mg m⁻³
Mo $K\alpha$ radiation
Cell parameters from 40
  reflections
$\theta = 7.23–15.78°$
$\mu = 0.247$ mm⁻¹
$T = 293 (2)$ K
Irregular, colourless
$0.30 \times 0.28 \times 0.26$ mm

Data collection

Siemens $P4$ diffractometer
ω–2θ scans
3013 measured reflections
2342 independent reflections
1713 reflections with $I > 2\sigma(I)$
$R_{int} = 0.011$
$\theta_{max} = 24.55°$

$h = -4 \rightarrow 8$
$k = -11 \rightarrow 11$
$l = -12 \rightarrow 12$
3 standard reflections
  every 197 reflections
  intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.030$
$wR(F^2) = 0.073$
$S = 0.916$
2342 reflections
192 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0427P)^2]$
  where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.18$ e Å⁻³
$\Delta\rho_{min} = -0.15$ e Å⁻³
Extinction correction: $SHELXL97$
Extinction coefficient: 0.008 (2)

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

S—C9	1.8162 (19)	N2—C2	1.384 (2)
S—C1	1.8475 (18)	C8—N1	1.309 (2)
C1—N2	1.452 (2)	C8—C9	1.482 (2)
N2—C8	1.355 (2)	C7—N1	1.399 (2)
C9—S—C1	95.38 (8)	N1—C8—N2	114.16 (16)
N2—C1—S	102.96 (11)	N2—C8—C9	114.41 (15)
C8—N2—C2	107.32 (13)	C8—C9—S	105.89 (13)
C8—N2—C1	120.61 (14)	C8—N1—C7	103.81 (14)
C2—N2—C1	131.91 (14)		
S—C1—C10—C11	−63.06 (19)		

Table 4
Contacts (Å, °) involving H atoms for (II).

D—H⋯A	D—H	H⋯A	D⋯A	D—H⋯A
C1—H1⋯F2	0.98	2.31	2.782 (2)	109
C9—H9B⋯F1	0.97	2.95	3.225 (3)	98

H atoms were placed in calculated positions (the idealized geometry depending on the parent atom type) and included in the refinement as riding atoms, with a common fixed isotropic displacement parameter ($U_{iso} = 0.06$ Å²). The usual rotational disorder of the terminal methyl group in compound (II) was handled by splitting it into two staggered positions, and fixing their occupancies to the best values (0.6 versus 0.4).

For both compounds, data collection: $P3/V$ (Siemens, 1989); cell refinement: $P3/V$; data reduction: $SHELXTL-Plus$ (Sheldrick, 1990); program(s) used to solve structure: $SIR92$ (Altomare et al., 1994); program(s) used to refine structure: $SHELXL97$ (Sheldrick, 1997); molecular graphics: XPW (Siemens, 1996); software used to prepare material for publication: locally modified $PARST97$ (Nardelli, 1995) and $SHELXL97$.

References

Allen, F. H., Davies, J. E., Galloy, J. J., Johnson, O., Kennard, O., Macrae, C. F., Mitchell, E. M., Mitchell, G. F., Smith, J. M. & Watson, D. G. (1991). J. Chem. Inf. Comput. Sci. **31**, 187–204.
Altomare, A., Cascarano, O., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). J. Appl. Cryst. **27**, 435.
Bruno, G., Chimirri, A., Grasso, S., Molica, C., Monforte, A. M., Monforte, P., Nicoló, F., Zappalá, M., Rao, A., Witvrouw, M., Pannecouque, C. & De Clercq, E. (1998). Antivir. Chem. Chemother. **9**, 431–438.
Bruno, G., Chimirri, A., Monforte, A. M., Nicoló, F. & Scopelliti, R. (1997). Acta Cryst. C**53**, 1337–1341.
Bruno, G., Monforte, A. M., Nicoló, F., Scopelliti, R. & Zappalá, M. (1996). Acta Cryst. C**52**, 2533–2535.
Bruno, G., Nicoló, F., Chimirri, A., Grasso, S., Monforte, A. M., Monforte, P., Zappalá, M., Rao, A. & Scopelliti, R. (1997). Il Farmaco, **52**, 673–677.
Chimirri, A., Grasso, S., Molica, C., Monforte, A. M., Monforte, P., Zappalá, M., Bruno, G., Nicoló, F., Witvrouw, M., Jonckeere, H., Balzarini, J. & De Clercq, E. (1997). Antivir. Chem. Chemother. **8**, 363–370.
Chimirri, A., Grasso, S., Molica, C., Monforte, A. M., Monforte, P., Zappalá, M. & Scopelliti, R. (1996). Il Farmaco, **51**, 279–282.
Cremer, D. & Pople, J. A. (1975). J. Am. Chem. Soc. **97**, 1354–1358.
Nardelli, M. (1995). J. Appl. Cryst. **28**, 659.
Sheldrick, G. M. (1990). SHELXTL-Plus. Release 4.21/V. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1997). SHELXL97. University of Göttingen, Germany.
Siemens (1989). P3/V. Release 4.21. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Siemens (1996). XPW in SHELXTL. Release 5.0.5. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.