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6-(4-Fluorophenyl)-8-phenyl-2,3-dihydro-4*H*-imidazo[5,1-*b*][1,3]thiazin-4-one: an unusual [6–5] fused-ring system

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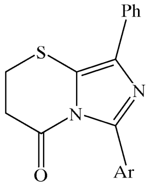
The title compound, $C_{18}H_{13}FN_2OS$, is the first structural example of a [6–5] fused ring incorporating the 2,3-dihydro-4*H*-imidazo[5,1-*b*][1,3]thiazin-4-one molecular scaffold. The six-membered 2,3-dihydro-1,3-thiazin-4-one ring adopts an envelope conformation, with the S—CH_2 C atom displaced by 0.761 (2) Å from the five-atom plane (all within 0.05 Å of the mean plane). The imidazole ring is planar. The phenyl ring is twisted from coplanarity with the imidazole ring by 23.84 (5)° and the 4-fluorophenyl ring is twisted by 53.36 (6)°, due to a close C(aryl)—H⋯O═C contact with the thiazin-4-one carbonyl O atom. The primary intermolecular interaction involves a CH_2 group with the F atom [C⋯F = 3.256 (2) Å and C—H⋯F = 137°].

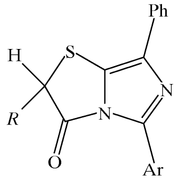
Comment

Heterocyclic compounds have been a traditional focal point for the development of new anticancer agents, with combinatorial (high-throughput) approaches to new ring systems being of current interest. In our research to develop new routes to diversely substituted drug-like heterocyclic scaffolds, classes of [5–5] [imidazo[5,1-*b*]thiazol-3-ones, (II)] and [6–5] [imidazo[5,1-*b*]thiazin-4-ones, (I)] fused-ring systems have been targeted (Le Bas *et al.*, 2005; Le Bas & O'Shea, 2005; O'Shea *et al.*, 2006). The [5–5] imidazo[2,1-*b*]thiazoles have shown promise as anticancer therapeutics (Andreani *et al.*, 2000). However, the isomeric imidazo[5,1-*b*]thiazole systems have only recently been investigated and a crystal structure reported [(II*a*); Le Bas *et al.*, 2005]. We report here the first structural example of a [6–5] imidazo[5,1*b*]thiazin-4-one fused-ring system, *viz*. the title compound, (I*a*).

The molecular structure of (I*a*) is depicted in Fig. 1, with the atomic numbering scheme, and selected bond lengths and angles are given in Table 1. Geometric data can be compared individually with different fused-ring systems. However, given that the [6–5] fused-ring in (I*a*) is thus far unique, our focus is on comparisons with both the key ring systems, *i.e.* the imidazole ring, and the [5–5] fused-ring relatives, (II). In (I*a*), geometric data for the diarylimidazole ring differ from the average values for imidazoles (Orpen *et al.*, 1994). The C1═C3 and C2═N2 bond lengths of 1.365 (2) (longer) and 1.3023 (19) Å (shorter) differ, though not significantly, from the expected values of 1.36 and 1.313 Å. However, the three C—N bond lengths for C1/C2—N1 and C3—N2 are *ca* 0.03 Å longer [1.4065 (18)/1.3986 (18) and 1.3943 (19) Å, respectively] than the corresponding average values in imidazoles (1.370/1.349 and 1.376 Å, respectively) (Orpen *et al.*, 1994), reflecting the effect of the extra ring attached at C1—N1. The imidazole ring is planar, with all five atoms within 0.002 (1) Å of the C_3N_2 mean plane. The phenyl ring is twisted from coplanarity with the imidazole ring by 23.84 (5)°, while the 4-fluorophenyl ring is twisted by 53.36 (6)° away from the central ring due to a close contact with the thiazin-4-one carbonyl atom O1 and an intermolecular interaction with a neighbouring π-arene, C22—H22⋯C24^{i} [symmetry code: (i) $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$; Table 2].



[5–6]
(I*a*) Ar=*p*-C_6H_4F
(I*b*) Ar=*p*-C_6H_4OMe
(I*c*) Ar=*p*-$C_6H_4CF_3$



[5−5]
Ar=*p*-C_6H_4OMe
(II*a*) *R*=H
(II*b*) *R*=Me
(II*c*) *R*=Et

Reactivity studies reveal distinct differences between the [5–5] imidazo[5,1-*b*]thiazol-3-ones, (II), and [6–5] imidazo[5,1-*b*]thiazin-4-ones, (I*a*)–(I*c*). Firstly, ring opening by nucleophilic attack at the C13═O1 amide carbonyl group occurs relatively quickly (under mild conditions) for the [5–5] fused rings, (II), but only under more testing conditions for the [6–5]

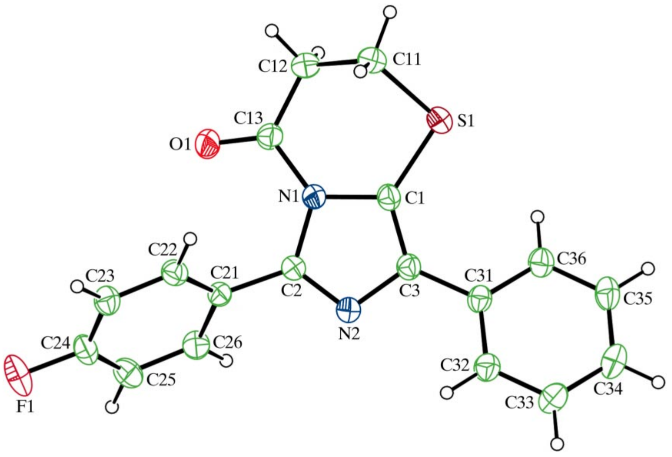
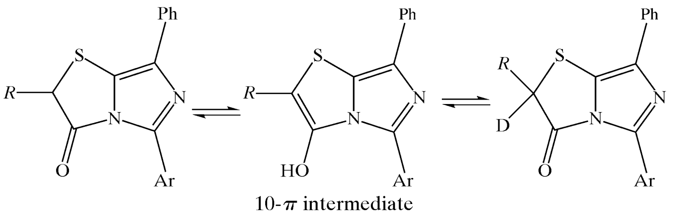


Figure 1
A view of (I*a*), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

derivatives, (I). Secondly, H/D exchange occurs at the methylene H atoms in (II) at 323 K under facile conditions, but not for (I) under similar conditions (Le Bas *et al.*, 2005). In order to rationalize these reactivity differences, the six-membered thiazin-4-one ring in (I*a*) is compared with the five-membered thiazol-3-one ring in (II). The mode of amide bond reactivity of (I*a*) is comparable with that observed for the hydrolysis and acyl transfer reactions of *N*-acetylimidazoles. This is attributed to the N-atom lone pair being part of the aromatic sextet, resulting in ineffective amide stabilization (Oakenfull & Jencks, 1971; Oakenfull *et al.*, 1971). This is further substantiated by the IR carbonyl stretch peak being observed at 1743 cm^{-1} for (I*a*), which is considerably higher than expected for a typical amide (1630–1670 cm^{-1}; Williams & Fleming, 1989) or six-membered lactam (1660–1690 cm^{-1}).

The main difference is the nature of the thiazol-3-one and thiazin-4-one rings, with ring strain evident in the former. In (II) (Le Bas *et al.*, 2005), analysis of two related systems, *viz*. (II*a*)/(II*b*), at the bridgehead atom N1 shows that all three C—N bonds range from 1.391 (2) to 1.409 (2) Å in (II*a*) and from 1.388 (3) to 1.407 (3) Å in (II*b*), whereas in (I*a*) a range of 1.3986 (18)–1.4243 (19) Å reveals a distinct difference, with C13—N1 longer by 0.02 Å. In (I*a*), the C1—N1—C2 angle is 105.7 (1)°, and C1—N1—C13 and C2—N1—C13 are similar [126.40 (12) and 126.84 (12)°, respectively], in contrast with the corresponding angles in (II*a*)/(II*b*) [106 and 115/138°, respectively], as C2—N1—C13 opens up by 11° in (II*a*)/(II*b*) compared with the value in (I*a*). The N1—C13═O1 angles differ by 6°, with a value of 120.32 (14)° in (I*a*) versus 126.0 (2)/126.7 (2)° in (II*a*)/(II*b*). Pyramidalization at atom N1 is negligible in both (I*a*) and (II*a*)/(II*b*), as all three angles sum to 360°. Reactivity could be attributed to the more open and accessible N1—C13 bond, and greater ring strain facilitates increased susceptibility to nucleophilic ring opening in (II*a*)/(II*b*). The H/D exchange at the CH_2 group in (II) can be explained by the formation of a 10-π aromatic enol intermediate which facilitates the exchange mechanism, and this is not possible for (I) (see scheme below).



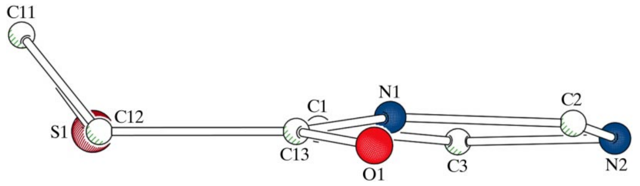


Figure 2
An edge-on view of the [6–5] fused-ring system in (I*a*), highlighting the envelope conformation.

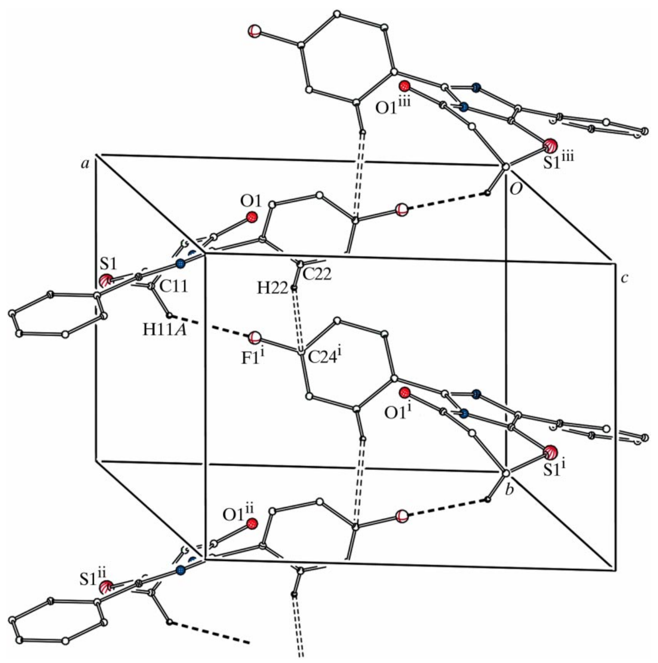


Figure 3
A packing diagram (with unit cell) of the hydrogen-bonding and contact geometry in the zigzag chain along (010) in (I*a*). Only two H atoms, H11*A* and H22, involved in these interactions and contacts have been included for clarity. [Symmetry codes: (i) $1 - x, y + \frac{1}{2}, -z + \frac{1}{2}$; (ii) $x, 1 + y, z$; (iii) $1 - x, y - \frac{1}{2}, -z + \frac{1}{2}$.]

An edge-on view of the [6–5] fused ring in (I*a*) down the S1—C12 axis is depicted in Fig. 2, showing the four-atom plane [S1/C1/C13/C12, atoms all within 0.005 (1) Å of the mean plane]. The envelope conformation of the C_4NS ring has atom C11 at the flap position displaced by 0.738 (2) Å from the four-atom plane in the same direction as atom N1, which is displaced by 0.095 (2) Å and oriented in the same direction. This envelope description is adequate, however, albeit with a small distortion towards a screw-boat; ring puckering parameters (Cremer & Pople, 1975) are Q = 0.560 (2) Å, θ = 120.5 (2)° and φ = 122.85 (18)°.

The primary intermolecular interaction involves a methylene CH_2 group with a symmetry-related F atom, with C11···F1^{i} = 3.256 (2) Å and C11—H11···F1^{i} = 137° [symmetry code: (i) $1 - x, y + \frac{1}{2}, -z + \frac{1}{2}$] (Fig. 3), in tandem with a C22···C24^{i} contact (Table 2), generating a zigzag chain along the (010) direction. Given the paucity of structural data for this and related rings, we are now developing synthetic routes to new [5–5] and [5–6] fused rings with a view to comparing structural data with reactivity in order to gain a more complete insight into the chemical reactivity of these systems.

Experimental

Brief details of the synthesis of (I*a*) have been reported previously (Le Bas *et al.*, 2005). The compound was recrystallized from ethanol

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as a pale-yellow solid in 72% yield (m.p. 495–497 K). IR (KBr disc, ν, cm^{-1}): 1743, 1623; ^{1}H NMR (CDCl$_3$): δ 7.87 (d, J = 7.0 Hz, 2H), 7.60–7.64 (m, 2H), 7.41–7.44 (m, 2H), 7.31–7.34 (m, 1H), 7.05–7.10 (m, 2H), 3.27–3.15 (m, 4H); ^{19}F NMR (CDCl$_3$): δ −111; ^{13}C NMR (CDCl$_3$): δ 166.4, 163.6 (d, $J_{\rm CF}$ = 250.0 Hz), 149.8, 138.4, 132.6, 131.6 (d, $J_{\rm CF}$ = 8.6 Hz), 128.8, 128.7, 127.9, 127.1, 119.8, 115.2 (d, $J_{\rm CF}$ = 22.4 Hz), 37.3, 26.0. ES$^+$–MS: m/z 325 $(M + {\rm H})^+$; HRMS found: 323.0641 $(M - {\rm H})^-$; $C_{18}H_{12}FN_2OS$ requires: 323.0654. Analysis calculated for $C_{18}H_{13}FN_2OS$: C 66.65, H 4.04, N 8.64, S 9.89%; found: C 66.42, H 4.01, N 8.54, S 10.07%.

Crystal data

$C_{18}H_{13}FN_2OS$
M_r = 324.36
Monoclinic, $P2_1/c$
a = 11.5195 (13) Å
b = 8.6516 (7) Å
c = 15.9173 (11) Å
β = 109.865 (5)°
V = 1492.0 (2) Å^3
Z = 4
D_x = 1.444 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.23 mm^{-1}
T = 294 (1) K
Block, colourless
0.45 × 0.45 × 0.35 mm

Data collection

Bruker $P4$ diffractometer
ω scans
4084 measured reflections
2938 independent reflections
2501 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.017
$\theta_{\rm max}$ = 26.1°
4 standard reflections
every 296 reflections
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.093
S = 1.04
2938 reflections
208 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0448P)^2 + 0.385P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max}$ = 0.001
$\Delta\rho_{\rm max}$ = 0.29 e Å^{-3}
$\Delta\rho_{\rm min}$ = −0.16 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

S1—C1	1.7392 (15)	N1—C13	1.4243 (19)
S1—C11	1.7986 (17)	O1—C13	1.1976 (19)
C11—C12	1.512 (2)	C1—C3	1.365 (2)
C12—C13	1.498 (2)	N2—C2	1.3023 (19)
N1—C1	1.4065 (18)	N2—C3	1.3943 (19)
N1—C2	1.3986 (18)		
S1—C1—N1	122.92 (11)	C1—S1—C11	98.08 (7)
S1—C1—C3	130.76 (12)	S1—C11—C12	111.10 (13)
N1—C1—C3	106.30 (12)	C11—C12—C13	115.87 (14)
C1—N1—C2	105.70 (11)	O1—C13—N1	120.32 (14)
C1—N1—C13	126.40 (12)	O1—C13—C12	123.08 (15)
C2—N1—C13	126.84 (12)	N1—C13—C12	116.59 (13)
N1—C1—S1—C11	20.39 (14)	C1—N1—C13—C12	−10.0 (2)
C1—S1—C11—C12	−52.19 (13)	S1—C1—N1—C13	9.9 (2)
S1—C11—C12—C13	61.22 (18)	N2—C2—C21—C26	−53.1 (2)
C11—C12—C13—N1	−27.8 (2)	N2—C3—C31—C32	−22.5 (2)

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

D—H···A	D—H	H···A	D···A	D—H···A
C11—H11A···F1$^{\rm i}$	0.97	2.48	3.256 (2)	137
C22—H22···C24$^{\rm i}$	0.93	2.85	3.753 (2)	164
C32—H32···N2	0.93	2.58	2.896 (2)	100
C36—H36···S1	0.93	2.67	3.3078 (18)	126

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

In (Ia), all H atoms bound to carbon were treated as riding atoms, using *SHELXL97* (Sheldrick, 1997) defaults for C—H bond lengths (range 0.93–0.97 Å), and with $U_{\rm iso}$(H) = 1.5$U_{\rm eq}$(C) for methylene H atoms or 1.2$U_{\rm eq}$(C) for aromatic H atoms.

Data collection: *XSCANS* (Siemens, 1994); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997) and *SORTX* (McArdle, 1995); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *PREP8* (Ferguson, 1998).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: HJ3028). Services for accessing these data are described at the back of the journal.

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