

A novel potent non-nucleoside reverse transcriptase inhibitor acylthiocarbamate derivative with extensive intramolecular π - π interactions

Angelo Mugnoli,^{a‡} Alberto Borassi,^{a*} Andrea Spallarossa^b and Sara Cesarini^b

^aDipartimento di Chimica e Chimica Industriale, Università degli Studi di Genova, Via Dodecaneso 31, I-16146 Genova, Italy, and ^bDipartimento di Scienze Farmaceutiche, Università degli Studi di Genova, Viale Benedetto XV 3, I-16132 Genova, Italy

Correspondence e-mail: alboris@libero.it

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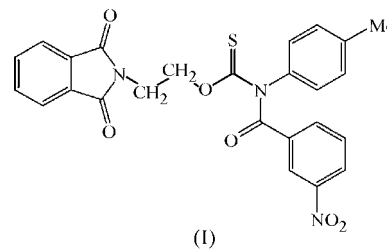
In the crystal structure of the novel acylthiocarbamate derivative *O*-[2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)ethyl] *N*-(4-methylphenyl)-*N*-(3-nitrobenzoyl)thiocarbamate, C₂₅H₁₉N₃O₆S, intra- and intermolecular π - π interactions occur between the phthalimide and *N*-benzoyl moieties. The partial atomic charges, calculated by *ab initio* methods, are consistent with the observed structure.

Comment

Acylthiocarbamates (ATCs) represent a novel chemical class, synthesized through an original highly convergent one-pot three-step procedure that combines, sequentially and covalently, three types of building blocks, namely alcohols, isothiocyanates and acyl chlorides (Ranise *et al.*, 2003). ATCs have proved to be a new class of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs), structurally related to *N*-phenyl-*N*-thiazolylthiourea derivatives. A structure-based optimization strategy led to the identification of *O*-(2-phthalimidoethyl) ATCs, which proved to be active at low nanomolar concentrations. Docking simulations suggest that phthalimidoethyl ATCs do not share the bioactive 'butterfly like' conformation typical of first-generation NNRTIs. According to this model, the ethyl linker would assume an extended conformation, with the *N*-phenyl and *N*-acyl moieties positioned at nearly 90° and located at the top of the allosteric binding site RT, while the phthalimide framework would be positioned at the entrance of the cavity.

In order to characterize this novel class of potent NNRTIs at the atomic level, and to provide insights for further chemical modifications, the crystal structure of *O*-[2-(1,3-

dioxo-2,3-dihydro-1*H*-isoindol-2-yl)ethyl] *N*-(4-methylphenyl)-*N*-(3-nitrobenzoyl)thiocarbamate, (I), one of the most potent ATCs currently available (EC₅₀ = 20 nM; Cesarini *et al.*, 2003), has been determined by single-crystal X-ray analysis and the results are presented here.



The structure of (I) is shown in Fig. 1, where the labels *A*, *B* and *C* are used to specify the ring moieties, defined as follows: 5*A* is the five-membered ring defined by atoms C1/N1/C8/C7/C2, 6*A* is the fused aromatic ring defined by atoms C2–C7, *B* is the 3-nitrobenzoyl ring and *C* is the methylphenyl ring. The shape of (I) is horseshoe-like, with the phthalimide and 3-nitrobenzoyl groups facing each other. The 'linker' connecting these two ring systems is formed by atoms C9/C10/O3/C11/N2/C19 and contains an acylthiocarbamate group. The C11–O3 bond distance is in agreement with the value found in an analogous structure of a secondary *N*-phenylthiocarbamate (1.330 Å; Sakamoto *et al.*, 1998), indicating a less marked double-bond character compared with the corresponding value reported for a primary acylthiocarbamate (1.290 Å; Morales *et al.*, 2000)

Ring *C* is rotated by a dihedral angle of 83.8 (1)° with respect to ring *B*. All rings are planar to within 0.01 Å. The thiocarbamate moiety shows a planar conformation, atoms C12, C11, C19 and N2 being coplanar to within 0.004 Å. The molecular fragment N2/C19/(O4)/Ph-NO₂ also shows a certain degree of planarity, the conformation being partially stabilized by weak intramolecular hydrogen bonds. Notably, rings 5*A* and *B* (Fig. 1) are in contact through a π - π stacking interaction. The mean planes of rings 5*A* and *B* form a dihedral angle of 9.6 (1)° and the centroid-centroid distance between the rings is 3.84 (2) Å.

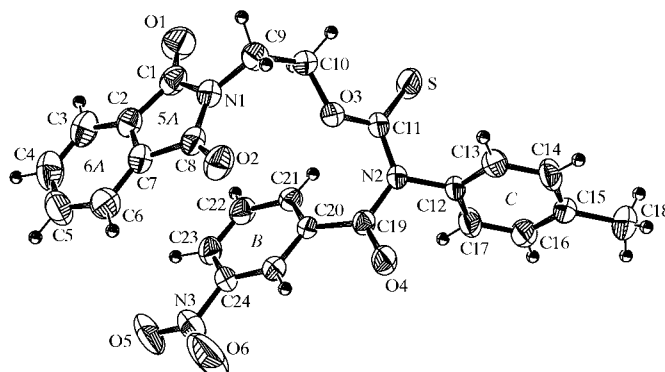


Figure 1

A drawing of (I), showing the labelling scheme for the atoms and rings. Displacement parameters are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

[‡] Deceased during the course of the present work.

In order to compare similar geometries, the Cambridge Structural Database (CSD, Version 5.27; Allen, 2002) was searched, retrieving all molecules with similar rings *A* and *B* separated by an intramolecular centroid-centroid distance

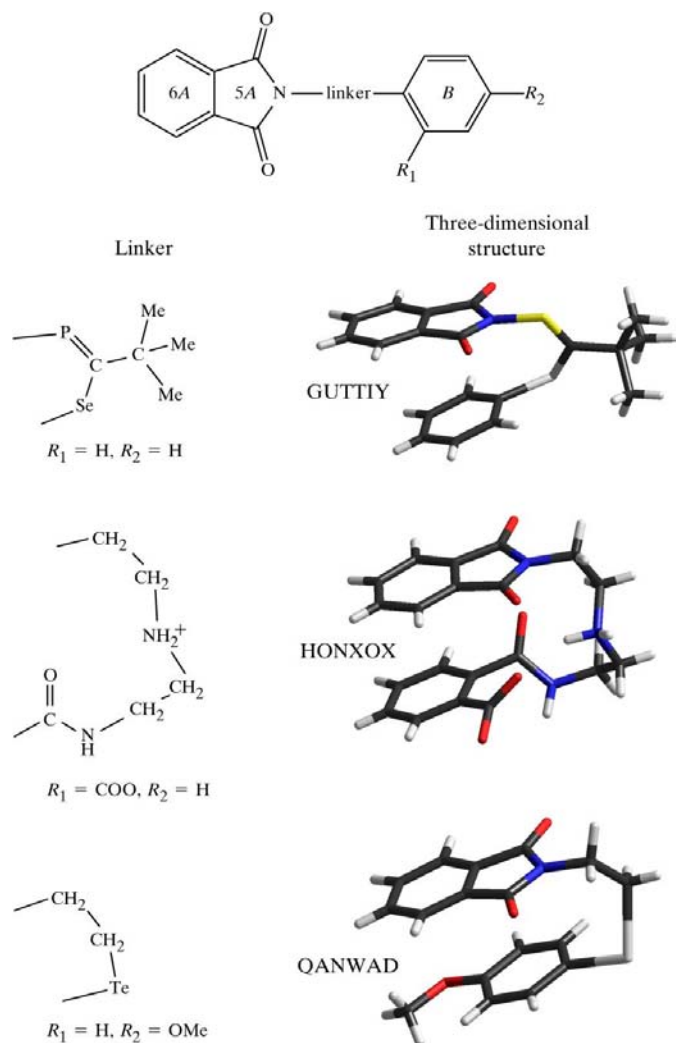


Figure 2
Schematic representations and three-dimensional structures of the three molecules selected from the CSD.

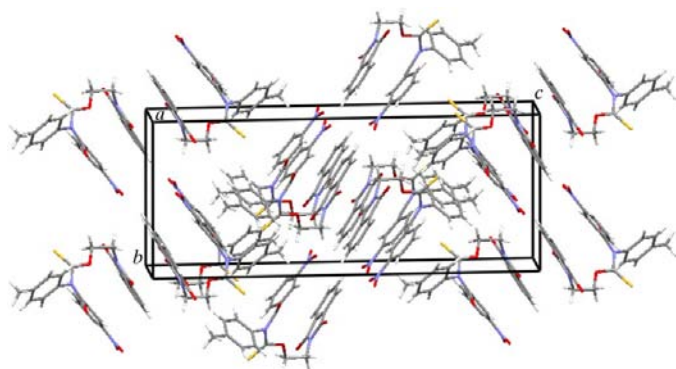


Figure 3
The crystal packing of (I), viewed along the *a* axis.

within 4.5 Å. Among the nine compounds found, only three have a dihedral angle between the stacked rings of less than 13°, *viz.* CSD refcodes GUTTIY (Aldridge *et al.*, 2003), HONXOX (Barrett *et al.*, 1998) and QANWAD (Singh *et al.*, 2000) (Fig. 2). In the HONXOX structure, the presence of a bulky carboxylate substituent at the benzene ring *B* very close to the linker causes a perturbation in the π - π interaction. In fact, among the four structures considered, it is the only case for which the centroid-centroid distance $6A \cdots B$ is less than that of $5A \cdots B$.

Owing to the importance assumed by aromatic π -systems in chemistry and physics, but mainly in biology, the nature of the π - π interaction has been widely studied (see, for example, Hobza *et al.*, 1994; Hunter & Sanders, 1990). To investigate the contribution of electrostatic components to the $5A \cdots B$ interaction, an *ab initio* calculation was performed. Mulliken atomic charges were calculated by single-point methods HF/STO-6-311G*, as implemented in *HYPERCHEM* (Hypercube, 2005). The same computations were applied to both the title compound and the three molecules selected from the CSD, and the relevant parameters obtained for these four molecules are summarized in Table 2. The charge-distribution analysis in the four molecules shows that atoms C1 and C8 of the phthalimide system have the most positive partial charges, suggesting that the π - π stacked conformation is mainly guided by the electrostatic interactions $C1 \cdots \pi$ and $C8 \cdots \pi$. Moreover, the variation of the centroid-centroid distance, as well as the relative displacement of the two rings, is surely influenced by a series of parameters, including the nature and number of atoms of the linker, the type and position of the substituent present on benzene ring *B*, and probably the occurrence of (weak) hydrogen-bond interactions.

Even considering the crystal packing (Fig. 3), the molecules tend to arrange in such a way as to realise the *A*-*B* π - π interactions. The molecules involved in the intermolecular case are the centrosymmetric pairs, but the interaction is weaker than for the intramolecular case and, therefore, the molecules also appear more shifted. In fact, the centroid-centroid distance between the two *A* rings is 4.22 (3) Å and the two rings superimpose only partially, as atoms O1/C1-C5 overlap with atoms C5'-C1'/O1' [a prime indicates symmetry operator $(-1-x, 1-y, -1-z)$, the shortest distance is $O1 \cdots C5'$ of 3.603 (4) Å]. Apart from two intermolecular contacts, which are appreciably shorter than the sum of the van der Waals radii [$C20 \cdots S(-x, y - \frac{1}{2}, -z + \frac{1}{2}) = 3.405$ (2) Å and $C21 \cdots S(-x, y - \frac{1}{2}, -z + \frac{1}{2}) = 3.205$ (3) Å], all other intermolecular distances, as well as all bond lengths and bond angles, are in normal ranges (Allen *et al.*, 1987; Pauling, 1960).

Experimental

Compound (I) was synthesized by a modified protocol of the previously reported procedure for the preparation of 2-phthalimidoethyl ATCs (reaction solvent: dry DMF; reaction time: 12 h; Ranise *et al.*, 2003). The crude product was dissolved in a dichloromethane-ethanol (3:1) mixture and the solution was kept at room temperature for 2 d. Crystals of (I) grew as colourless prisms.

Crystal data

$C_{25}H_{19}N_3O_6S$	$Z = 4$
$M_r = 489.49$	$D_x = 1.399 \text{ Mg m}^{-3}$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 7.918 (2) \text{ \AA}$	$\mu = 0.19 \text{ mm}^{-1}$
$b = 10.890 (1) \text{ \AA}$	$T = 293 \text{ K}$
$c = 27.087 (7) \text{ \AA}$	Prism, colourless
$\beta = 95.72 (2)^\circ$	$0.32 \times 0.26 \times 0.09 \text{ mm}$
$V = 2324.0 (9) \text{ \AA}^3$	

Data collection

Bruker Nonius MACH3 diffractometer	2977 reflections with $I > 2\sigma(I)$
ω/θ scans	$\theta_{\text{max}} = 27.5^\circ$
5311 measured reflections	2 standard reflections
5311 independent reflections	frequency: 90 min
	intensity decay: none

Refinement

Refinement on F^2	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.055$	
$wR(F^2) = 0.127$	$w = 1/[\sigma^2(F_o^2) + (0.0565P)^2]$
$S = 1.00$	where $P = (F_o^2 + 2F_c^2)/3$
5311 reflections	$(\Delta/\sigma)_{\text{max}} = 0.013$
381 parameters	$\Delta\rho_{\text{max}} = 0.23 \text{ e \AA}^{-3}$
	$\Delta\rho_{\text{min}} = -0.21 \text{ e \AA}^{-3}$

Table 1

 Selected geometric parameters (\AA , $^\circ$).

C9–N1	1.466 (3)	C12–N2	1.456 (3)
C11–O3	1.334 (3)	C19–O4	1.208 (2)
C11–N2	1.375 (3)	C19–N2	1.415 (3)
C11–S	1.632 (2)	C19–C20	1.497 (3)
N1–C9–C10	113.9 (2)	C11–N2–C19	125.25 (17)
O3–C10–C9	108.0 (2)	C11–O3–C10	116.77 (18)
O3–C11–N2	110.66 (19)		
C20–C19–N2–C12	–143.9 (2)		

Table 2

 Calculated charges (atomic units) and geometric parameters (\AA , $^\circ$) for compound (I) and the three compounds selected from the CSD.

Compound	Charge on C8 (a.u.)	Charge on C1 (a.u.)	5A...B distance	6A...B distance	A–B dihedral angle	Atoms in linker
(I) [†]	0.657	0.627	3.84	4.46	9.04	6
GUTTIY [‡]	0.627	0.673	3.34	3.85	11.67	3
HONXOX [§]	0.658	0.664	4.77	3.96	5.95	7
QANWAD [¶]	0.597	0.612	3.54	3.79	5.07	3

[†] This work. [‡] Aldridge *et al.* (2003). [§] Barrett *et al.* (1998). [¶] Singh *et al.* (2000).

The methyl H atoms were treated as an idealized group, with C–H = 0.96 \AA and a global U_{iso} value fixed at $1.2U_{\text{eq}}(\text{C18})$. All other

H atoms were located in a difference Fourier map and refined freely. Atom O6 of the nitro group exhibits a large displacement parameter, indicating its tendency to be disordered over two different positions. However, the structural model with the best agreement indexes was that obtained without considering the split positions.

Data collection: *MACH3 Software* (Nonius, 2000); cell refinement: *MACH3 Software*; data reduction: *NRCVAX* (Gabe *et al.*, 1989) and *CADABS* (local software); program(s) used to solve structure: *NRCVAX*; program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Version 1.05; Farrugia, 1997) and *MERCURY* (Version 1.3; Bruno *et al.*, 2002); software used to prepare material for publication: *PARST95* (Nardelli, 1995) and *HYPERCHEM* (Hypercube, 2005).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: TR1130). Services for accessing these data are described at the back of the journal.

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