Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
C(1)	0.9657 (9)	0.0888 (6)	0.8272 (3)	0.047 (2)
C(2)	0.9204 (9)	−0.0299 (6)	0.8612 (3)	0.050 (2)
C(3)	0.7392 (9)	−0.0436 (6)	0.8958 (3)	0.053 (2)
C(4)	0.5822 (9)	0.0564 (6)	0.8932 (3)	0.063 (2)
C(5)	0.6625 (9)	0.1823 (5)	0.8718 (3)	0.048 (2)
C(6)	0.4911 (9)	0.2756 (6)	0.8662 (3)	0.057 (2)
C(7)	0.5638 (9)	0.4019 (6)	0.8468 (3)	0.054 (2)
C(8)	0.6753 (9)	0.3956 (6)	0.7840 (3)	0.049 (2)
C(9)	0.8541 (9)	0.3019 (6)	0.7931 (3)	0.047 (2)
C(10)	0.7825 (9)	0.1709 (5)	0.8115 (3)	0.044 (2)
C(11)	0.9786 (9)	0.3018 (6)	0.7303 (3)	0.063 (2)
C(12)	1.0522 (9)	0.4337 (6)	0.7142 (3)	0.056 (2)
C(13)	0.8761 (9)	0.5221 (6)	0.7039 (3)	0.050 (2)
C(14)	0.7606 (9)	0.5204 (5)	0.7666 (3)	0.050 (2)
C(15)	0.6159 (9)	0.6293 (6)	0.7592 (3)	0.065 (2)
C(16)	0.7355 (9)	0.7261 (6)	0.7245 (3)	0.059 (2)
C(17)	0.9285 (9)	0.6603 (6)	0.6993 (3)	0.053 (2)
C(18)	0.7339 (9)	0.4872 (6)	0.6418 (3)	0.063 (2)
C(19)	0.6480 (9)	0.1113 (6)	0.7526 (3)	0.058 (2)
C(20)	1.0021 (10)	0.7164 (6)	0.6374 (3)	0.066 (2)
C(21)	1.1732 (11)	0.6470 (7)	0.6078 (4)	0.090 (3)
C(22)	1.0650 (11)	0.8508 (7)	0.6505 (4)	0.095 (3)
C(23)	1.1242 (14)	0.9208 (8)	0.5896 (4)	0.112 (3)
C(24)	1.1774 (14)	1.0539 (8)	0.6036 (5)	0.120 (4)
C(25)	1.2751 (16)	1.1233 (9)	0.5528 (4)	0.122 (4)
C(26)	1.2745 (21)	1.2539 (9)	0.5634 (5)	0.210 (6)
C(27)	1.4855 (16)	1.0731 (14)	0.5439 (5)	0.206 (6)
C(28)	1.0600 (9)	−0.1263 (6)	0.8637 (3)	0.046 (2)
C(29)	1.0342 (9)	−0.2362 (6)	0.8993 (3)	0.051 (2)
C(30)	1.1759 (9)	−0.3325 (6)	0.9017 (3)	0.051 (2)
C(31)	1.1445 (10)	−0.4347 (6)	0.9359 (3)	0.064 (2)
C(32)	0.9662 (10)	−0.4493 (6)	0.9691 (3)	0.059 (2)
C(33)	0.8246 (10)	−0.3588 (7)	0.9664 (3)	0.060 (2)
C(34)	0.8540 (9)	−0.2493 (6)	0.9316 (3)	0.049 (2)
C(35)	0.7112 (9)	−0.1511 (7)	0.9282 (3)	0.059 (2)

Space group $P2_1$ or $P2_1/m$ from the systematic absences $0k0$, $k = 2n + 1$; the former was chosen and confirmed by successful solution and refinement of the structure. The terminal C atoms C(26) and C(27) of the aliphatic chain exhibit large thermal motions showing a small degree of disorder.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN* (Molecular Structure Corporation, 1994). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *TEXSAN*. Software used to prepare material for publication: *TEXSAN*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: FG1167). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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6-(3-Methylbenzyl)-2-(2-methylpropyl)thio-4(3*H*)-pyrimidinone (DABO 622)

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Abstract

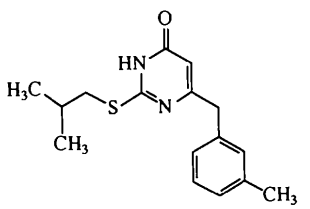
The title compound, $C_{16}H_{20}ON_2S$, shows the pyrimidine and benzene rings arranged in 'butterfly-like' conformation as observed for TIBO, nevirapine and other non-nucleoside inhibitors of HIV-1 Reverse Transcriptase.

Comment

Virally encoded reverse transcriptase (RT) of human immunodeficiency virus type 1 (HIV-1) catalyses the retrotranscription of single-stranded viral RNA into double-stranded DNA before the viral genome is integrated into the DNA of the host cell (Mitsuya, Yarchoan & Broder, 1990). Currently two classes of *anti*-AIDS agents targeted at RT have been developed, *i.e.* nucleoside analogues such as AZT, ddC, ddI and D4T, which have been approved for the treatment of AIDS, and non-nucleoside inhibitors (NNRTIs). Among these, the first compounds described were TIBO, HEPT and nevirapine, followed by BHAP, PETT α-APA and, more recently, by DABO

(3,4-dihydro-6-alkyl-2-benzyl-4-oxopyrimidine) derivatives (De Clercq, 1995, and references therein; Artico *et al.*, 1993; Massa *et al.*, 1995; Mai *et al.*, 1995). All NNRTI agents are specific for HIV-1 RT and act as non-competitive inhibitors that bind to the enzyme in a region close to, but distinct from, the polymerase active site (Wu *et al.*, 1991; Tramontano *et al.*, 1994).

The crystal structure of the HIV-1 RT–nevirapine complex was first reported at 3.5 Å resolution (Kohlstaed, Wang, Friedman, Rice & Steitz, 1992), then has been partially refined at 2.9 Å (Smerdon *et al.*, 1994), and finally fully refined at 2.2 Å (Ren *et al.*, 1995). These studies revealed that nevirapine binds the enzyme close to the catalytically relevant aspartic acid residues (110, 185 and 186) and maintains a butterfly-like conformation, in good agreement with the previously reported X-ray structure of unbonded nevirapine (Mui, Jacober, Hargrave & Adams, 1992). More recently, a detailed comparison of the crystal structures of six HIV-1 RT-inhibitor complexes revealed that the binding mode of different NNRTIs is strikingly similar. In fact, all NNRTIs occupy the same binding site and adopt a similar 'butterfly-like' shape, with two hydrophobic moieties connected by a linker group (usually with tetrahedral geometry) that allows the two wings to bend with an angle of 110–115° (Ren *et al.*, 1995; Ding *et al.*, 1995). In order to investigate whether DABO derivatives possess the same structural requirements reported for the most active compounds belonging to other NNRTI classes, we determined the crystal structure of DABO derivative 622.



DABO 622

As detailed below, DABO 622 is arranged in a butterfly-like orientation, the valence angle C3—C8—C9 between the two rings being 112.0 (5)° which is in the range considered optimal for NNIs, and with an N2—C9—C8—C3 torsion angle of −45.2 (7)°. The S1—C13—C14—C15 fragment is approximately planar [maximum displacement from the weighted least-squares plane 0.03 (1) Å]. The dihedral angle this fragment forms with the phenyl ring is 27.3 (4)°. Nevirapine, with the linker angle between the rings of 115.0° (Ding *et al.*, 1995), was found to be more potent than the title compound (Mai *et al.*, 1995) in inhibiting the HIV-1 virus, thus suggesting that other parameters, in addition to spatial orientation, must be taken into consideration to explain the different degree of potency. Therefore, further SAR (structure–activity relationship) and 3D-SAR studies on DABO derivatives may be warranted in order to determine which steric and structural changes are required for improving their anti-HIV-1 activity.

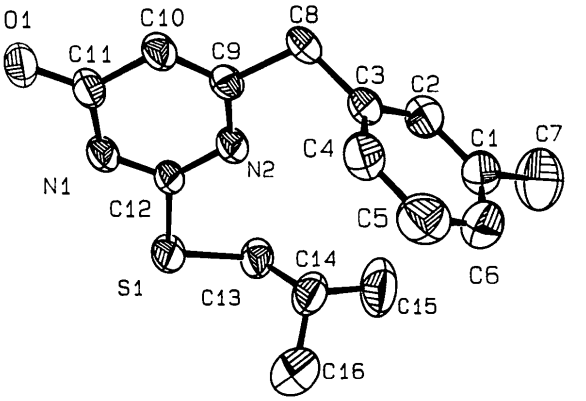


Fig. 1. A view of the molecule showing the labelling of the non-H atoms. Displacement ellipsoids are shown at 40% probability levels.

Experimental

The title compound, (1), was synthesized previously by Mai *et al.* (1995). Single crystals suitable for X-ray diffraction analysis were obtained by recrystallization from a hot cyclohexane solution.

Crystal data

$C_{16}H_{20}N_2OS$
M_r = 288.41
Triclinic
$P\bar{1}$
a = 8.566 (2) Å
b = 14.191 (4) Å
c = 7.246 (2) Å
α = 91.63 (2)°
β = 114.41 (9)°
γ = 91.42 (2)°
V = 801.1 (4) Å^3
Z = 2
D_x = 1.195 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 25 reflections
θ = 31.4–47.4°
μ = 1.725 mm^{-1}
T = 295 K
Prism
0.6 × 0.4 × 0.1 mm
Transparent

Data collection

Rigaku AFC-5*R* diffractometer
Profile data from ω–2θ scans
Absorption correction: empirical with ψ scan at χ = 90° (North, Phillips & Mathews, 1968)
T_{min} = 0.8, T_{max} = 1.0
2725 measured reflections
2531 independent reflections

1290 observed reflections [$I > 3\sigma(I)$]
R_{int} = 0.054
θ_{max} = 62.0°
$h = 0 \rightarrow 9$
$k = -15 \rightarrow 16$
$l = -8 \rightarrow 7$
3 standard reflections monitored every 150 reflections
intensity decay: none

Refinement

Refinement on F
$R = 0.0560$
$wR = 0.0670$
$S = 1.90$
1198 reflections
181 parameters
All H-atom parameters refined
Weighting scheme based on measured e.s.d.'s; $w = 1/[\sigma^2(F_o)]$
$(\Delta/\sigma)_{max} = 0.07$
$\Delta\rho_{max} = 0.30$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Tables 2.2A, 2.2C, 2.3.1)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	B_{eq}
S1	0.2660 (2)	0.3249 (1)	0.5371 (3)	5.38 (8)
O1	0.7121 (5)	0.5317 (3)	1.0339 (6)	5.7 (2)
N1	0.5182 (6)	0.4336 (3)	0.7895 (7)	4.2 (2)
N2	0.5639 (6)	0.3695 (3)	0.5156 (7)	4.3 (2)
C1	0.7472 (9)	0.1722 (6)	0.150 (1)	5.8 (3)
C2	0.7578 (8)	0.2659 (5)	0.216 (1)	5.4 (3)
C3	0.8247 (7)	0.2937 (4)	0.419 (1)	4.1 (3)
C4	0.8845 (8)	0.2253 (5)	0.555 (1)	5.5 (3)
C5	0.874 (1)	0.1313 (6)	0.495 (1)	7.0 (4)
C6	0.804 (1)	0.1059 (5)	0.290 (1)	6.8 (4)
C7	0.672 (1)	0.1446 (7)	−0.076 (1)	10.7 (5)
C8	0.8325 (7)	0.3952 (4)	0.4843 (9)	4.6 (3)
C9	0.7232 (7)	0.4126 (4)	0.601 (1)	3.9 (2)
C10	0.7823 (7)	0.4666 (4)	0.7736 (9)	4.3 (3)
C11	0.6740 (7)	0.4818 (4)	0.877 (1)	4.3 (3)
C12	0.4675 (7)	0.3804 (4)	0.6160 (9)	3.8 (2)
C13	0.2348 (8)	0.2728 (5)	0.291 (1)	5.4 (3)
C14	0.3298 (9)	0.1838 (5)	0.296 (1)	6.5 (4)
C15	0.293 (1)	0.1561 (6)	0.075 (1)	10.2 (5)
C16	0.283 (1)	0.1040 (6)	0.393 (1)	9.7 (5)

Table 2. *Selected geometric parameters (Å, °)*

S1—C12	1.738 (5)	C3—C4	1.356 (8)
S1—C13	1.823 (6)	C3—C8	1.495 (8)
O1—C11	1.237 (6)	C4—C5	1.379 (9)
N1—C11	1.371 (7)	C5—C6	1.39 (1)
N1—C12	1.348 (6)	C8—C9	1.519 (7)
N2—C9	1.363 (6)	C9—C10	1.346 (7)
N2—C12	1.315 (6)	C10—C11	1.432 (7)
C1—C2	1.387 (8)	C13—C14	1.513 (9)
C1—C6	1.35 (1)	C14—C15	1.54 (1)
C1—C7	1.53 (1)	C14—C16	1.48 (1)
C2—C3	1.379 (8)		
C12—S1—C13	101.6 (3)	C2—C3—C4	117.1 (6)
N2—C9—C8	114.4 (5)	S1—C12—N1	114.8 (4)
C11—N1—C12	123.4 (4)	C2—C3—C8	121.1 (6)
N2—C9—C10	124.2 (5)	S1—C12—N2	122.3 (4)
C9—N2—C12	116.1 (5)	C4—C3—C8	121.8 (6)
C8—C9—C10	121.5 (5)	N1—C12—N2	122.9 (5)
C2—C1—C6	118.6 (7)	C3—C4—C5	122.1 (7)
C9—C10—C11	119.5 (5)	S1—C13—C14	115.8 (5)
C2—C1—C7	120.8 (8)	C4—C5—C6	119.1 (7)
O1—C11—N1	120.8 (5)	C13—C14—C15	106.7 (7)
C6—C1—C7	120.6 (8)	C1—C6—C5	120.5 (7)
O1—C11—C10	125.4 (5)	C13—C14—C16	114.8 (6)
C1—C2—C3	122.6 (7)	C3—C8—C9	112.0 (5)
N1—C11—C10	113.8 (5)	C15—C14—C16	110.0 (6)
N2—C9—C8—C3	−45.2 (7)		

An ω scan width of $(1.47 + 0.30\tan\theta)°$, an ω scan rate of 8° min^{-1} and background counts at the beginning and end of scan, each for 50% of the total scan time, were used. The weak reflections, $I < 10\sigma(I)$, were rescanned and the counts accumulated to assure good counting statistics. The structure was solved by direct methods and refined by full-matrix least-squares methods. The H atoms were introduced at calculated positions and not refined. All the non-H atoms were refined anisotropically.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN* (Molecular Structure Corporation, 1985). Program(s) used to solve structure: *TEXSAN*. Program(s) used to refine structure: *TEXSAN*. Molecular graphics: *TEXSAN*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA1234). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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