Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Intermolecular stacking in pyrazolo[3,4-*d*]pyrimidine-based pentamethylene-linked flexible molecules[1]

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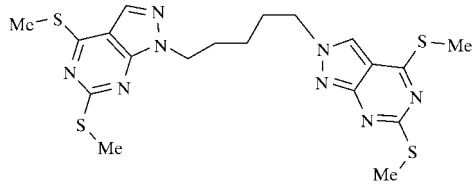
Received 9 September 2002
Accepted 13 November 2002
Online 17 December 2002

The crystal structures of 1-{5-[4,6-bis(methylsulfanyl)-2*H*-pyrazolo[3,4-*d*]pyrimidin-2-yl]pentyl}-6-methylsulfanyl-4-(pyrrolidin-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine, $C_{22}H_{29}N_9S_3$, and 6-methylsulfanyl-1-{5-[6-methylsulfanyl-4-(pyrrolidin-1-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidin-2-yl]pentyl}-4-(pyrrolidin-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine, $C_{25}H_{34}N_{10}S_2$, which differ in having either a pyrrolidine substituent or a methylsulfanyl group, show intermolecular stacking due to aromatic π–π interactions between the pyrazolo[3,4-*d*]pyrimidine rings.

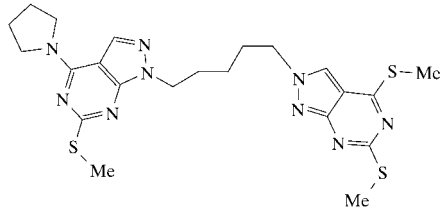
Comment

Interactions between aromatic moieties are known to play an important role in chemistry (Tsuzuki *et al.*, 2002; Hunter *et al.*, 2001) and biology. These interactions play a significant role in molecular recognition, stabilization of DNA/RNA structures (Hobza & Sponer, 1999) and crystal engineering (Desiraju, 1995). Use of a polymethylene, and especially a trimethylene (propylene), linker for studying intramolecular π–π interactions was pioneered by Leonard (Browne *et al.*, 1968) and early work was reviewed by Leonard (1979).

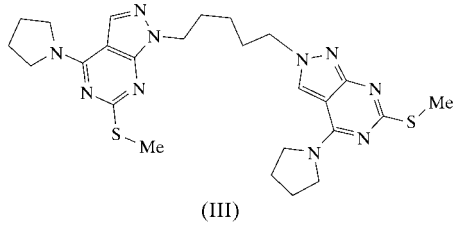
In 1995, we reported the first synthesis (Avasthi *et al.*, 1995) and crystal structure determination (Biswas *et al.*, 1995) of a trimethylene-linked molecule based on the pyrazolo[3,4-*d*]-pyrimidine core, which is isomeric with the biologically important purine system. The robustness of the U-motif formed by intramolecular stacking has been further demonstrated by crystal structure determinations of other closely related propylene-linked compounds (Maulik *et al.*, 1998; Avasthi, Aswal & Maulik, 2001; Avasthi, Rawat *et al.*, 2001). Interestingly, no intramolecular stacking is observed when the trimethylene linker is replaced by an ethylene (Avasthi, Rawat *et al.*, 2001) or tetramethylene linker (Maulik *et al.*, 2000). Importantly, symmetrical compounds involving ethylene, trimethylene, tetramethylene and pentamethylene linkers based on the pyrazolo[3,4-*d*]pyrimidine core show varying and unusual degrees of upfield shifts in their high-resolution (400 MHz) ^{1}H NMR spectra when compared with those of monomeric compounds (Garg *et al.*, 1989). These observations indicate the possibility of intramolecular stacking in solution (Avasthi *et al.*, 1995). Here, we report the structures of two pentamethylene-linked flexible molecules, *viz.* 1-{5-[4,6-bis-(methylsulfanyl)-2*H*-pyrazolo[3,4-*d*]pyrimidin-2-yl]pentyl}-6-methylsulfanyl-4-(pyrrolidin-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine, (II), and 6-methylsulfanyl-1-{5-[6-methylsulfanyl-4-(pyrrolidin-1-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidin-2-yl]pentyl}-4-(pyrrolidin-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine, (III), based on the same pyrazolo[3,4-*d*]pyrimidine core. Although many attempts have been made to crystallize the parent compound, 4,6-dimethylthio-1-[5-(4,6-dimethylthio-2*H*-pyrazolo-[3,4-*d*]-pyrimidin-2-yl)pentyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, (I) (Avasthi *et al.*, 1995), none of these has proved successful.



(I)



(II)



(III)

The crystal structure of (II) (Fig. 1) does not show any intramolecular stacking [N1···N2′ = 6.656 (3) Å]. The C—C—C angles in the five-atom linker bridge range between 111.3 (2) and 114.0 (2)°. The planar pyrazolo[3,4-*d*]pyrimidine rings are twisted [dihedral angle 62.82 (4)°] Interestingly, this twist allows intermolecular stacking (Fig. 2) between the pyrazolo[3,4-*d*]pyrimidine rings related by the symmetry operation $(1-x, 1-y, 1-z)$ about the body centre of the cell, with an interplanar separation of 3.534 (2) Å in a 'parallel-displaced' orientation, the rings being parallel by

[1] CDRI communication No. 6331.

  DOI: 10.1107/S0108270102020681

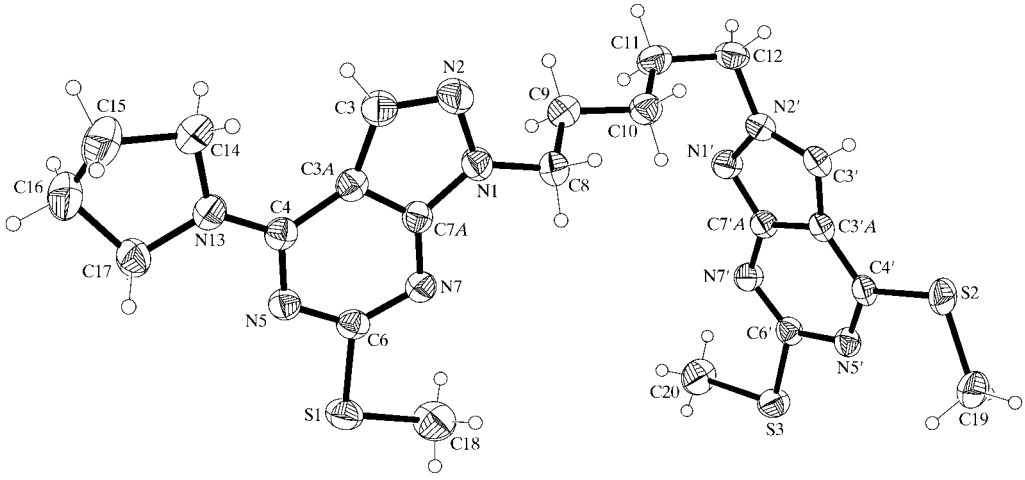


Figure 1
A view of the molecular structure of (II) with the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

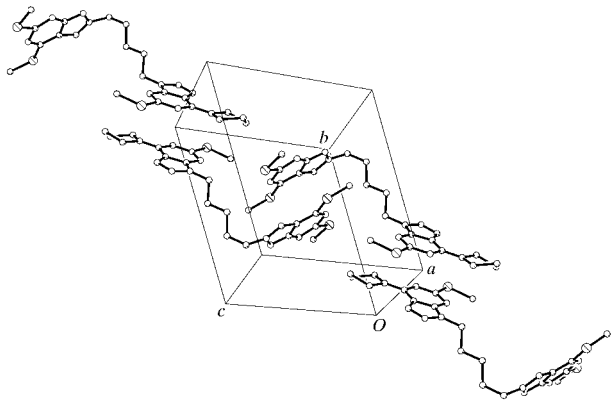


Figure 2
A crystal packing diagram for (II), showing the intermolecular π–π stacking between pyrazolo[3,4-*d*]pyrimidine rings.

symmetry. In addition, the other pyrazolo[3,4-*d*]pyrimidine ring, carrying a pyrrolidine group, similarly interacts with a neighbouring molecule, related by the symmetry operation $(2 - x, -y, -z)$, at an interplanar distance of 3.512 (2) Å (Fig. 2). These two stacking interactions link the molecules into chains running parallel to [100].

The molecular structure and conformation of (III), which differs from (II) in having an additional pyrrolidine group, rather than a methylsulfanyl group, at position C4′, is shown in Fig. 3. The planar pyrazolo[3,4-*d*]pyrimidine rings are closer to coplanarity [dihedral angles 8.3 (1) and 5.70 (4)° for the two molecules of the asymmetric unit]. Again, the crystal structure does not show any intramolecular stacking [N1···N2′ = 5.824 (3) and 5.797 (4) Å for the two molecules of the asymmetric unit]. The C—C—C angles in the five-atom linker range from 112.7 (3) to 113.6 (3)° in one molecule and from 113.0 (3)

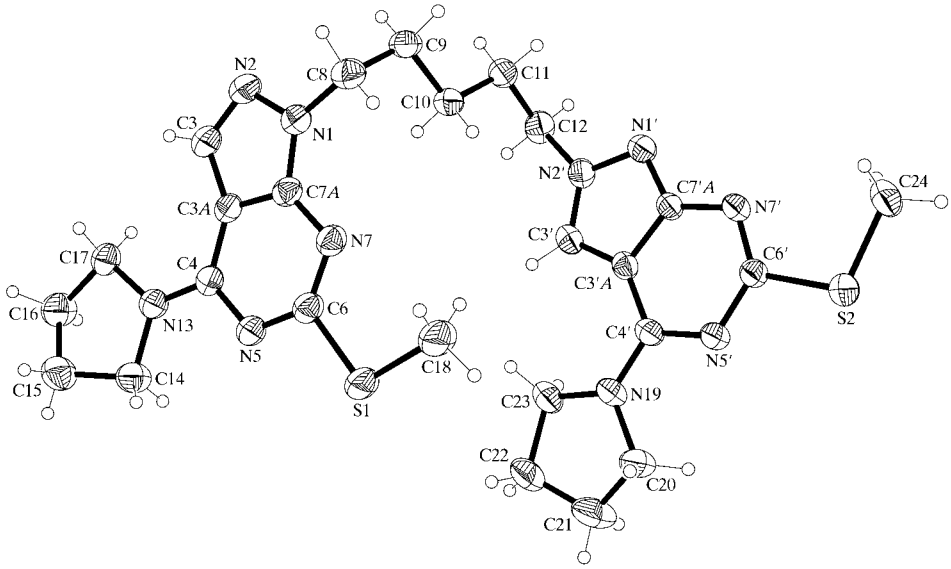


Figure 3
A view of the structure of one of the independent molecules of (III) with the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

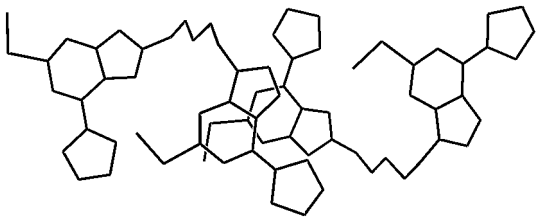


Figure 4
A view of the molecules of (III) in one asymmetric unit, showing the partial overlapping of the rings due to intermolecular stacking.

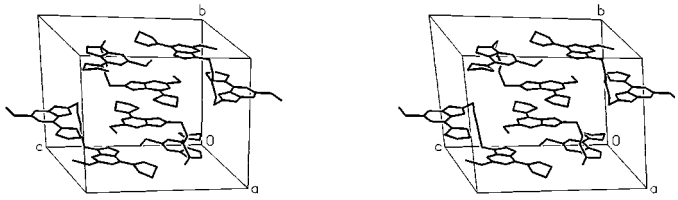


Figure 5
A stereopacking diagram for (III), showing the intermolecular π–π stacking between pyrazolo[3,4-*d*]pyrimidine rings.

to 114.2 (3)° in the other. However, intermolecular stacking due to aromatic π–π interactions is still present, with the two molecules in the asymmetric unit stacking through partial overlap of their pyrazolo[3,4-*d*]pyrimidine rings (Fig. 4). The average intermolecular spacing is 3.506 (4) Å and the minimum atom–atom distance is 3.580 (4) Å for N5′···C3″. In addition, there is also a face-to-face overlap of the pyrazolo[3,4-*d*]pyrimidine rings related by $(1-x, 1-y, 1-z)$, with an interplanar separation of 3.430 (2) Å; the rings are parallel by symmetry (Fig. 5). Thus, the crystal structures of (II) and (III) are stabilized mainly by aromatic π–π interactions.

Experimental

Compounds (II) and (III) were prepared by refluxing a solution of (I) with pyrrolidine in benzene. Diffraction quality crystals of (II) were obtained from a solution in ethyl acetate, while crystals of (III) were isolated from a chloroform–ethyl acetate (1:1) solution by slow evaporation of the solvent at room temperature.

Compound (II)

Crystal data

$C_{22}H_{29}N_9S_3$
M_r = 515.72
Triclinic, $P\overline{1}$
a = 10.1195 (8) Å
b = 11.865 (1) Å
c = 12.271 (1) Å
α = 70.563 (7)°
β = 70.092 (8)°
γ = 73.452 (7)°
V = 1281.7 (2) Å^3
Z = 2
D_x = 1.336 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 39 reflections
θ = 4.9–12.5°
μ = 0.32 mm^{-1}
T = 293 (2) K
Block, colourless
0.44 × 0.30 × 0.22 mm

Data collection

Bruker *P*4 diffractometer
$\theta/2\theta$ scans
5878 measured reflections
4980 independent reflections
3921 reflections with $I > 2\sigma(I)$
R_{int} = 0.018
θ_{max} = 26°
$h = -1 \rightarrow 12$
$k = -13 \rightarrow 14$
$l = -14 \rightarrow 15$
3 standard reflections
every 97 reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.119
S = 1.03
4980 reflections
310 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0519P)^2 + 0.4512P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.34 e Å^{-3}

Table 1
Selected torsion angles (°) for (II).

C7*A*—N1—C8—C9	113.2 (3)	C10—C11—C12—N2′	58.0 (3)
N2—N1—C8—C9	−65.6 (3)	C7′*A*—N1′—N2′—C12	−177.63 (18)
N1—C8—C9—C10	170.11 (19)	C11—C12—N2′—C3′	−114.4 (2)
C8—C9—C10—C11	175.6 (2)	C11—C12—N2′—N1′	63.1 (3)
C9—C10—C11—C12	177.9 (2)	C12—N2′—C3′—C3′*A*	177.88 (19)

Compound (III)

Crystal data

$C_{25}H_{34}N_{10}S_2$
M_r = 538.74
Triclinic, $P\overline{1}$
a = 10.006 (1) Å
b = 15.283 (1) Å
c = 18.411 (2) Å
α = 74.164 (7)°
β = 89.970 (9)°
γ = 86.359 (9)°
V = 2702.7 (4) Å^3
Z = 4
D_x = 1.324 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 41 reflections
θ = 5.3–12.5°
μ = 0.23 mm^{-1}
T = 293 (2) K
Block, colourless
0.38 × 0.33 × 0.23 mm

Data collection

Bruker *P*4 diffractometer
$\theta/2\theta$ scans
12 443 measured reflections
10 538 independent reflections
6258 reflections with $I > 2\sigma(I)$
R_{int} = 0.018
θ_{max} = 26°
$h = -1 \rightarrow 12$
$k = -18 \rightarrow 18$
$l = -22 \rightarrow 22$
3 standard reflections
every 97 reflections
intensity decay: none

Table 2
Selected torsion angles (°) for (III).

C7*A*—N1—C8—C9	110.2 (3)	C7″*A*—N1″—C8″—C9″	−107.7 (4)
N2—N1—C8—C9	−75.1 (3)	N2″—N1″—C8″—C9″	75.9 (4)
N1—C8—C9—C10	−61.8 (4)	N1″—C8″—C9″—C10″	61.9 (4)
C8—C9—C10—C11	−178.0 (3)	C8″—C9″—C10″—C11″	177.7 (3)
C9—C10—C11—C12	−176.4 (3)	C9″—C10″—C11″—C12″	176.1 (3)
C10—C11—C12—N2′	−63.4 (3)	C10″—C11″—C12″—N32	63.6 (4)
C7′*A*—N1′—N2′—C12	−179.3 (2)	C37*A*—N31—N32—C12″	176.4 (2)
C11—C12—N2′—C3′	109.3 (3)	C11″—C12″—N32—C33	−115.7 (3)
C11—C12—N2′—N1′	−71.4 (3)	C11″—C12″—N32—N31	67.2 (3)
C12—N2′—C3′—C3′*A*	179.6 (3)	C12″—N32—C33—C33*A*	−176.8 (3)

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0618P)^2 + 0.6880P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.057$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.150$	$\Delta\rho_{max} = 0.27$ e Å^{-3}
$S = 1.02$	$\Delta\rho_{min} = -0.30$ e Å^{-3}
10 538 reflections	
671 parameters	
H-atom parameters constrained	

For both compounds, data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXTL* (Bruker, 1997); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

AKT thanks CSIR, India, for a Research Associateship and SMF is grateful to DST, India (grant No. SP/S1/G-44/99), for a Junior Research Fellowship.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1510). Services for accessing these data are described at the back of the journal.

References

Avasthi, K., Aswal, S. & Maulik, P. R. (2001). *Acta Cryst.* C**57**, 1324–1325.
Avasthi, K., Chandra, T. & Bhakuni, D. S. (1995). *Indian J. Chem. Sect. B*, **34**, 944–949.
Avasthi, K., Rawat, D. S., Maulik, P. R., Sarkhel, S., Broder, C. K. & Howard, J. A. K. (2001). *Tetrahedron Lett.* **42**, 7115–7117.
Biswas, G., Chandra, T., Avasthi, K. & Maulik, P. R. (1995). *Acta Cryst.* C**51**, 2453–2455.
Browne, D. T., Eisinger, J. & Leonard, N. J. (1968). *J. Am. Chem. Soc.* **90**, 7302–7323.
Bruker (1997). *SHELXTL.* Version 5.10. Bruker AXS Inc., Madison, Wisconsin, USA.
Desiraju, G. R. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 2311–2327.
Garg, N., Avasthi, K. & Bhakuni, D. S. (1989). *Synthesis*, pp. 876–878.
Hobza, P. & Sponer, J. (1999). *Chem. Rev.* **99**, 3247–3276.
Hunter, C. A., Lawson, K. R., Perkins, J. & Urch, C. J. (2001). *J. Chem. Soc. Perkin Trans.* 2, pp. 651–669.
Leonard, N. J. (1979). *Acc. Chem. Res.* **12**, 423–429.
Maulik, P. R., Avasthi, K., Biswas, G., Biswas, S., Rawat, D. S., Sarkhel, S., Chandra, T. & Bhakuni, D. S. (1998). *Acta Cryst.* C**54**, 275–277.
Maulik, P. R., Avasthi, K., Sarkhel, S., Chandra, T., Rawat, D. S., Logsdon, B. & Jacobson, R. A. (2000). *Acta Cryst.* C**56**, 1361–1363.
Siemens (1996). *XSCANS.* Version 2.21. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Tsuzuki, S., Honda, K., Uchimaru, T., Mikami, M. & Tanabe, K. (2002). *J. Am. Chem. Soc.* **124**, 104–112.