3910 measured reflections
3906 independent reflections

3 standard reflections every 150 reflections
intensity decay: 2.43%

Refinement

Refinement on F
$R = 0.038$
$wR = 0.052$
$S = 1.282$
2228 reflections
218 parameters
H atoms included but not refined
$w = 1/[\sigma^2(F_o) + 0.00063|F_o|^2]$
$(\Delta/\sigma)_{max} = 0.006$

$\Delta\rho_{max} = 0.150$ e Å^{-3}
$\Delta\rho_{min} = -0.180$ e Å^{-3}
Extinction correction: Zachariasen (1967) type 2 Gaussian isotropic
Extinction coefficient: 0.039 (6)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

Cl(1)—C(16)	1.737 (2)	N(3)—N(4)	1.378 (3)
N(2)—C(6)	1.372 (2)	N(3)—C(6)	1.311 (3)
N(2)—C(7)	1.371 (3)	N(4)—C(7)	1.316 (3)
N(2)—C(13)	1.444 (2)		
C(6)—N(2)—C(7)	104.7 (2)	N(3)—C(6)—C(5)	123.6 (2)
N(4)—N(3)—C(6)	107.9 (2)	N(2)—C(7)—N(4)	110.1 (2)
N(3)—N(4)—C(7)	107.3 (2)	N(2)—C(7)—C(8)	127.1 (2)
N(2)—C(6)—N(3)	109.9 (2)	N(4)—C(7)—C(8)	122.7 (2)
N(2)—C(6)—C(5)	126.4 (2)		

Data collection: *Rigaku/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1995*a*). Cell refinement: *Rigaku/AFC Diffractometer Control Software*. Data reduction: *TEXSAN* (Molecular Structure Corporation, 1995*b*). Program(s) used to solve structure: *DIRDIF*92 (Beuskens *et al.*, 1992). Program(s) used to refine structure: *TEXSAN*. Molecular graphics: *SHELXTL* (Sheldrick, 1994). Software used to prepare material for publication: *TEXSAN*.

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Anticancer Agents. III. 4,4′-(Hexane-1,6-diyl)bis(piperazine-2,6-dione)

Q. Liu, S.-W. Zhang and M.-C. Shao

Department of Chemistry, Peking University, Beijing 100871, People's Republic of China. E-mail: zsw@ipc.pku.edu.cn

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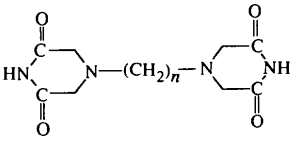
Abstract

In the crystals of $C_{14}H_{22}N_4O_4$, the molecule has a crystallographic inversion centre and the methylene chain is fully extended.

Comment

Compound (I) with $n = 2$ (ICRF-154) has been shown to have anticancer activity against a variety of cancer cells (Creighton, 1971; Cai *et al.*, 1989).



(I)

In a previous study, it was found that bifunctionalized compounds with six methylenes in the bridging group were usually more effective against cancer cells and less toxic than those with bridging groups of other lengths; examples include hexamethylenebis(acetamide) (Reuben *et al.*, 1976) and a suberic acid bis(methylamide) series (Breslow *et al.*, 1991). In order to discover new and more effective anticancer agents, we synthesized the title compound, which is an analogue of ICRF-154 with $n = 6$. Its activity against human erythroleukemia K562 cells was found to be greater than that of ICRF-154. This result suggests that six methylene groups may provide a suitable spacer distance between functional groups to match receptors or binding groups on the target.

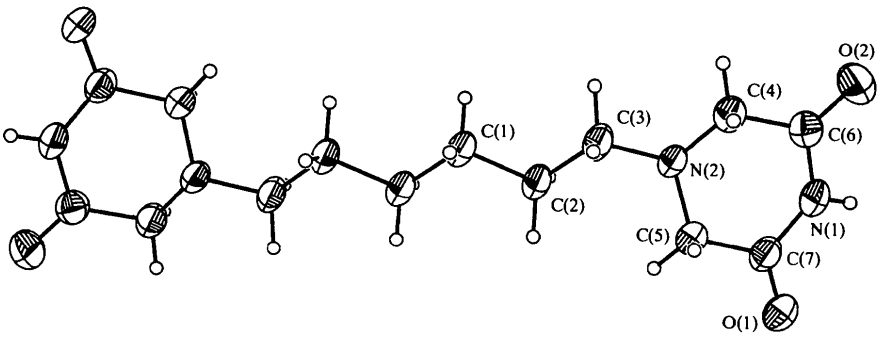


Fig. 1. View of $C_{14}H_{22}N_4O_4$ showing the atomic labelling. Displacement ellipsoids are shown at 50% probability levels and H atoms are drawn as small circles of arbitrary radii.

Experimental

The title compound was prepared by condensation of hexamethylenetetraacetic acid and formamide using Schlenk procedures. Recrystallization was from *N,N*-dimethylformamide–methanol solution.

Crystal data

$C_{14}H_{22}N_4O_4$
$M_r = 310.4$
Monoclinic
$P2_1/c$
$a = 10.756\,(2)$ Å
$b = 7.0690\,(10)$ Å
$c = 10.160\,(2)$ Å
$\beta = 91.90\,(3)°$
$V = 772.1\,(2)$ Å^3
$Z = 2$
$D_x = 1.335$ Mg m^{-3}
$D_m = 1.329\,(1)$ Mg m^{-3}
D_m measured by flotation in $CHCl_3$ and $Cl(CH_2)_3Cl$

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 25 reflections
$\theta = 5.0$–$12.5°$
$\mu = 0.093$ mm^{-1}
$T = 295.0\,(1)$ K
Block
0.30 × 0.30 × 0.20 mm
Colourless

Data collection

Rigaku AFC-6*S* diffractometer
2θ scans
Absorption correction: none
2007 measured reflections
1769 independent reflections
1210 reflections with $F \geq 4\sigma(F)$

$R_{int} = 0.018$
$\theta_{max} = 27.5°$
$h = -13 \rightarrow 13$
$k = -9 \rightarrow 0$
$l = 0 \rightarrow 13$
3 standard reflections
every 150 reflections
intensity decay: 3%

Refinement

Refinement on F
$R = 0.058$
$wR = 0.053$
$S = 0.62$
1210 reflections
144 parameters
All H atoms refined
$w = 1/[\sigma^2(F) + 0.001F^2]$

$(\Delta/\sigma)_{max} = 0.0013$
$\Delta\rho_{max} = 0.22$ e Å^{-3}
$\Delta\rho_{min} = -0.25$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)

Table 1. *Selected geometric parameters (Å, °)*

N(1)—C(6)	1.376 (4)	O(2)—C(6)	1.205 (4)
N(1)—C(7)	1.363 (4)	C(1)—C(2)	1.540 (4)
N(2)—C(3)	1.478 (4)	C(1)—C(1^i)	1.512 (6)
N(2)—C(4)	1.445 (4)	C(2)—C(3)	1.510 (5)
N(2)—C(5)	1.458 (4)	C(4)—C(6)	1.502 (5)
O(1)—C(7)	1.217 (4)	C(5)—C(7)	1.508 (4)
C(6)—N(1)—C(7)	125.5 (3)	N(2)—C(5)—C(7)	110.5 (2)
C(3)—N(2)—C(4)	109.8 (2)	N(1)—C(6)—O(2)	121.3 (3)
C(3)—N(2)—C(5)	112.6 (2)	N(1)—C(6)—C(4)	115.7 (3)
C(4)—N(2)—C(5)	109.8 (2)	O(2)—C(6)—C(4)	123.0 (3)
C(2)—C(1)—C(1^i)	112.7 (3)	N(1)—C(7)—O(1)	121.4 (3)
C(1)—C(2)—C(3)	110.3 (3)	N(1)—C(7)—C(5)	116.3 (3)
N(2)—C(3)—C(2)	114.1 (3)	O(1)—C(7)—C(5)	122.2 (3)
N(2)—C(4)—C(6)	112.2 (3)		

Symmetry code: (i) $1-x, -1-y, 1-z$.

Data collection: Rigaku PC/AFS software. Cell refinement: *LSQUARE* in *SHELXTL-Plus* (Sheldrick, 1991). Data reduction: *XS* in *SHELXTL-Plus*. Program(s) used to solve structure: *XS* in *SHELXTL-Plus*. Program(s) used to refine structure: *XLS* in *SHELXTL-Plus*. Molecular graphics: *XP* in *SHELXTL-Plus*. Software used to prepare material for publication: *XPBL* and *XTEXT* in *SHELXTL-Plus*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: HA1201). Services for accessing these data are described at the back of the journal.

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