

Molecular and crystal structure of 2-amino-6-dimethylamino-4-(tricyclo[3.3.1.1^{3,7}]dec-1-yl) methyl-1,3,5-triazine

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The crystal and molecular structure of the title compound has been determined by X-ray crystallographic studies. The compound crystallizes in the triclinic space group $P\bar{1}$ with $a = 10.777(8)$ Å, $b = 13.003(9)$ Å, $c = 13.045(8)$ Å, $\alpha = 72.26^\circ(4)$, $\beta = 104.25^\circ(5)$, $\gamma = 108.87^\circ(5)$ and $Z = 4$. The structure was solved by direct methods and full-matrix least-squares refinement converged to a final $R = 0.083$ for 2656 observed reflections. The two independent molecules differ only in orientation of the adamantyl moiety. Both of them utilize the two hydrogens of the amine nitrogen N(7) to make hydrogen bonds linking the molecules into infinite chains which are held together by van der Waals interactions. The conformation of the substituents at position 6 of the triazine ring is such that the torsion angle is close to 0° for both independent molecules of the asymmetric unit.

Introduction

Dihydrofolate reductase [5,6,7,8-tetrahydrofolate:NADP+ oxidoreductase (E.C. 1.5.1.3)] (DHFR) is an NADPH-linked enzyme responsible for maintaining intracellular pools of tetrahydrofolate. The latter is an essential cofactor in the synthesis of thymidylate, inosinate, methionine, and other important metabolites (Blakley, 1969). Blockade of DHFR has been achieved with a number of clinically useful drugs such as the antineoplastic (antitumor) agent methotrexate and the antibiotic trimethoprim. The activity of these drugs is due to selective inhibition of the enzyme from species to species (Baccarani *et al.*, 1982; Hitchings and Smith, 1980). Despite extensive efforts, the exact molecular

mechanism of selective inhibition remains largely unknown.

Diamino-s-triazines are a class of compounds that act as inhibitors of DHFR and, as such, have shown promise for use as antineoplastic agents (Modest *et al.*, 1952). It has been demonstrated that the lipophilicity of these compounds is a principal structural characteristic necessary for binding to DHFR (Greco and Hakala, 1980).

In the course of investigations on adamantyl ring bearing compounds (Antoniadou-Vyzas and Foscolos, 1986; Garoufalas *et al.*, 1988) it was considered likely that this group attached on a triazine ring would increase the lipophilicity of the resulting s-triazines and may result in better DHFR inhibition. In addition, the absence of any information on amino-substituted analogs acting as antifolates, in contrast to considerable information on the diamino-derivatives, has led to attempts of substitution on the 6-amino nitrogen of the triazine molecule (Tsitsa *et al.*, 1992). Therefore, possible DHFR inhibitors of the general types I and II, have been synthesized as a potential antitumor, antibacterial and antifungal agents. Currently these compounds are being tested for DHFR-binding affinity and pharmacological properties (Tsitsa *et al.*, 1993).

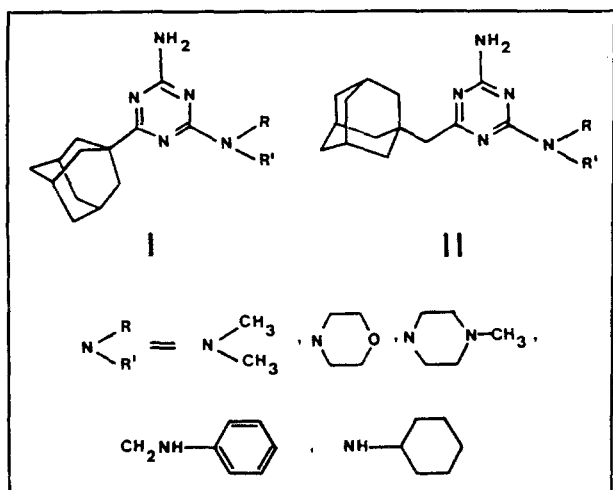
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Crystal structure determinations and conformational analysis of both active and inactive lipophilic compounds of types I and II are underway. As well, modelling studies of binding of these compounds on bacterial and mammalian DHFR's and co-crystallization attempts involving active compounds with DHFR are being tried, in order to understand the observed variation in biological activity and to compare structure and binding with other antifolate ligands (Hamodrakas *et al.*, 1992; Gessman *et al.*, 1992; Tsitsa *et al.*, 1992). The title compound is a member of the type II series.



Experimental

Crystals were obtained as thin needles by evaporation from methanol. A precession camera was used to establish the space group and cell parameters. The refined cell parameters were obtained by measurement of the angular parameters of 12 high angle reflections ($40^\circ < 2\theta < 60^\circ$) on a diffractometer and application of the least-squares method.

Crystal data are: $P\bar{1}$ space group, $a = 10.777(8)$, $b = 13.003(9)$, $c = 13.045(8)$ Å; $\alpha = 72.26(4)$, $\beta = 104.25(5)$, $\gamma = 108.87(5)$; $V = 1625.29$ Å³, $Z = 4$.

A crystal of dimensions $0.2 \times 0.5 \times 0.8$ mm was chosen for data collection. Intensities were collected on an automated four-circle diffractometer. $\text{CuK}\alpha$ radiation and $\theta/2\theta$ scan mode with a scan speed of 2 deg/min was utilized. Three standard reflections monitored every 100 reflections showed only random variations within 5%. A total of 5541 unique reflections were recorded ($3^\circ < 2\theta < 132^\circ$) of which 2656 were considered observed using $I > 3\sigma(I)$ discrimination. Space group $P\bar{1}$ was chosen, with two independent molecules of the title compound in the asymmetric unit. The intensities were corrected for Lorentz and polarization factors. No absorption corrections were applied.

The molecular structure was determined by direct methods using SHELXS-86 (Sheldrick, 1985). The E-map with the best figure of merit revealed the entire structure consisting of the two independent molecules. Subsequent refinement and difference maps showed all the triazine hydrogen atom positions in both molecules, but not the hydrogens on the adamantyls; their positions were calculated to fit the geometry. After several more cycles of refinement, difference electron density calculations revealed no significant residual electron density. The positional parameters of all the atoms including hydrogens were refined and anisotropic temperature factors for atoms other than hydrogen were used and allowed to vary. The isotropic temperature factors for hydrogen atoms were kept constant at $U = 0.07$ Å². The final R factor converged at 8.3%; this rather high R value was due to poor quality of the crystals used in the investigation. Several attempts to produce better crystals were not successful. SHELX-76 (Sheldrick, 1976) and a Cray computer were used for all refinement calculations.

Results and Discussion

Positional and isotropic thermal parameters of non-hydrogen atoms are listed in Table 1, bond lengths in Table 2 and bond angles in Table 3. A perspective view, showing the atomic numbering scheme used for the two independent molecules of the asymmetric unit is given in Fig. 1.

The triazine ring with the following additional atoms N7, N8, C19, C20 and C21 is virtually flat in both molecules of the asymmetric unit, the maximum deviation from planarity being 0.03 Å and 0.04 Å in molecules A and B, respectively, when all 11 atoms are included in the calculation of the plane. The only significant difference between the two molecules is in the conformational relationship of the adamantyl moiety to the triazine ring. This is quantified by dihedral angles such as N3-C4-C21-C9 (97.8° and -90.7° in A and B), N5-C4-C21-C9 (-82.3° and 87.0°) and C10-C9-C21-C4 (-168.5° and 172.5°). Averaging the differences shows that the two adamantyl orientations differ by a rotation of approximately 170.5° about the C4-C21 bond. In a related structure, but of the type I series, conformational analysis utilizing semi-empirical INDO energy calculations indicated that rotation of the adamantyl group did not significantly affect the total molecular energy (Hamodrakas *et al.*, 1992). With the greater flexibility inherent in the type II series it is reasonable to expect a similar result here. The two conformations observed (A and B) may be of marginally lower energies than other possibilities.

Table 1. Fractional atom coordinates ($\times 10^4$) for non-H-atoms and equivalent isotropic temperature factors ($\text{Å}^2 \times 10^4$)

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}^a
N1A	8159(6)	6751(3)	3066(3)	538(43)
C2A	8769(6)	6007(5)	3786(5)	526(50)
N3A	9358(5)	5371(3)	3531(3)	461(40)
C4A	9300(6)	5508(5)	2466(5)	443(48)
N5A	8722(6)	6212(5)	1669(5)	556(43)
C6A	8169(6)	6812(5)	2013(6)	533(53)
N7A	8806(7)	5914(6)	4839(5)	701(57)
N8A	7594(6)	7548(5)	1243(5)	762(53)
C9A	8996(6)	3750(5)	1806(5)	402(44)
C10A	9866(7)	3046(6)	1720(6)	649(65)
C11A	8094(7)	4013(6)	707(6)	616(59)
C12A	8133(7)	3039(6)	2680(6)	611(57)
C13A	8971(7)	1957(6)	1392(6)	749(68)
C14A	8089(8)	2239(6)	300(6)	791(73)
C15A	7224(8)	2906(6)	399(6)	753(65)
C16A	6363(8)	2211(7)	1284(8)	955(92)
C17A	7258(8)	1949(6)	2368(6)	771(69)
C18A	8133(10)	1270(6)	2275(7)	885(75)
C19A	7014(10)	8289(8)	1501(6)	1178(95)
C20A	7619(12)	7709(10)	86(6)	1295(99)
C21A	9933(6)	4819(6)	2128(6)	495(53)
N1B	2416(5)	2594(3)	4336(3)	488(42)
C2B	1596(6)	1582(6)	4623(6)	549(56)
N3B	1247(6)	746(3)	4101(5)	548(44)
C4B	1844(6)	986(5)	3242(5)	497(51)
N5B	2723(6)	1943(5)	2897(5)	589(46)
C6B	2953(6)	2730(6)	3458(6)	572(56)
N7B	1061(6)	1335(6)	5526(6)	708(57)
N8B	3822(6)	3731(5)	3129(5)	648(48)
C9B	2433(6)	-722(5)	3079(5)	424(45)
C10B	1836(8)	-1687(7)	2506(7)	960(78)
C11B	3819(10)	-138(6)	2809(10)	1137(94)
C12B	2531(10)	-1231(7)	4298(6)	987(81)
C13B	2712(8)	-2518(7)	2903(8)	939(84)
C14B	4018(12)	-1934(8)	2603(7)	1036(88)
C15B	4659(8)	-975(7)	3145(13)	1261(98)
C16B	4785(10)	-1403(10)	4350(10)	1251(99)
C17B	3436(13)	-2025(10)	4657(6)	1206(96)
C18B	2829(10)	-2978(6)	4092(10)	1165(97)
C19B	4140(8)	4623(6)	3682(7)	1019(79)
C20B	4442(10)	3984(6)	2181(7)	1118(89)
C21B	1518(6)	71(5)	2667(5)	481(46)

$$^a U_{\text{eq}} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* \cdot a_i \cdot a_j$$

Table 2. Bond lengths (Å)

C2A—N1A	= 1.343(9)	C2B—N1B	= 1.328(8)
C6A—N1A	= 1.354(10)	C6B—N1B	= 1.346(11)
N3A—C2A	= 1.344(11)	N3B—C2B	= 1.360(11)
N7A—C2A	= 1.334(10)	N7B—C2B	= 1.345(12)
C4A—N3A	= 1.336(9)	C4B—N3B	= 1.333(10)
N5A—C4A	= 1.333(8)	N5B—C4B	= 1.325(8)
C21A—C4A	= 1.496(13)	C21B—C4B	= 1.499(11)
C6A—N5A	= 1.346(12)	C6B—N5B	= 1.359(11)
N8A—C6A	= 1.341(9)	N8B—C6B	= 1.351(8)

Table 2. Continued

C19A—N8A	= 1.456(17)	C19B—N8B	= 1.454(12)
C20A—N8A	= 1.467(11)	C20B—N8B	= 1.449(13)
C10A—C9A	= 1.549(13)	C10B—C9B	= 1.538(13)
C11A—C9A	= 1.531(9)	C11B—C9B	= 1.515(12)
C12A—C9A	= 1.530(10)	C12B—C9B	= 1.516(10)
C21A—C9A	= 1.540(9)	C21B—C9B	= 1.544(10)
C10A—C13A	= 1.550(12)	C10B—C13B	= 1.549(15)
C14A—C13A	= 1.514(11)	C14B—C13B	= 1.453(15)
C18A—C13A	= 1.519(13)	C18B—C13B	= 1.472(17)
C15A—C14A	= 1.521(16)	C15B—C14B	= 1.507(18)
C11A—C15A	= 1.550(11)	C11B—C15B	= 1.532(16)
C15A—C16A	= 1.536(14)	C15B—C16B	= 1.486(21)
C17A—C16A	= 1.513(13)	C17B—C16B	= 1.504(17)
C12A—C17A	= 1.537(11)	C12B—C17B	= 1.538(20)
C18A—C17A	= 1.531(17)	C18B—C17B	= 1.516(17)

Table 3. Bond angles ($^\circ$)

C6A—N1A—C2A	= 113.6(7)	C6B—N1B—C2B	= 113.1(7)
N3A—C2A—N1A	= 125.5(7)	N3B—C2B—N1B	= 126.3(7)
N7A—C2A—N1A	= 116.6(8)	N7B—C2B—N1B	= 118(7)
N7A—C2A—N3A	= 117.9(6)	N7B—C2B—N3B	= 115.7(6)
C4A—N3A—C2A	= 115.3(5)	C4B—N3B—C2B	= 114.7(5)
N5A—C4A—N3A	= 125.2(8)	N5B—C4B—N3B	= 125(7)
C21A—C4A—N3A	= 117.9(6)	C12B—C4B—N3B	= 116.2(5)
C21A—C4A—N5A	= 116.9(7)	C21B—C4B—N5B	= 118.8(7)
C6A—N5A—C4A	= 114.7(6)	C6B—N5B—C4B	= 114.9(7)
N5A—C6A—N1A	= 125.7(8)	N5B—C6B—N1B	= 125.8(6)
N8A—C6A—N1A	= 117.2(8)	N8B—C6B—N1B	= 116.6(7)
N8A—C6A—N5A	= 117(7)	N8B—C6B—N5B	= 117.6(7)
C19A—N8A—C6A	= 122.8(7)	C19B—N8B—C6B	= 121.6(7)
C20A—N8A—C6A	= 120.7(9)	C20B—N8B—C6B	= 121.6(7)
C20A—N8A—C19A	= 116.4(8)	C20B—N8B—C19B	= 116.7(6)
C11A—C9A—C10A	= 108.7(7)	C11B—C9B—C10B	= 107.5(8)
C12A—C9A—C10A	= 107.8(6)	C12B—C9B—C10B	= 107.7(6)
C12A—C9A—C11A	= 109.1(6)	C12B—C9B—C11B	= 109(7)
C21A—C9A—C10A	= 107.9(6)	C21B—C9B—C10B	= 108.2(6)
C21A—C9A—C11A	= 112.2(5)	C21B—C9B—C11B	= 112.1(5)
C21A—C9A—C12A	= 111.1(6)	C21B—C9B—C12B	= 112.1(8)
C13A—C10A—C9A	= 110.1(6)	C13B—C10B—C9B	= 110.2(7)
C15A—C11A—C9A	= 109.9(6)	C15B—C11B—C9B	= 110.5(7)
C17A—C12A—C9A	= 110.1(7)	C17B—C12B—C9B	= 109.7(9)
C14A—C13A—C10A	= 110.2(6)	C14B—C13B—C10B	= 108.8(8)
C18A—C13A—C10A	= 108.5(8)	C18B—C13B—C10B	= 110.9(10)
C18A—C13A—C14A	= 110.7(7)	C18B—C13B—C14B	= 110.2(8)
C15A—C14A—C13A	= 108.7(8)	C15B—C14B—C13B	= 109.7(11)
C14A—C15A—C11A	= 110.2(7)	C14B—C15B—C11B	= 111.5(9)
C16A—C15A—C11A	= 109.1(8)	C16B—C15B—C11B	= 107(13)
C16A—C15A—C14A	= 109.7(7)	C16B—C15B—C14B	= 110.1(9)
C17A—C16A—C15A	= 109.3(7)	C17B—C16B—C15B	= 109.6(8)
C16A—C17A—C12A	= 110.2(7)	C16B—C17B—C12B	= 110.1(9)
C18A—C17A—C12A	= 110(7)	C18B—C17B—C12B	= 109.4(9)
C18A—C17A—C16A	= 108.9(9)	C18B—C17B—C16B	= 108.8(12)
C17A—C18A—C13A	= 109.1(7)	C17B—C18B—C13B	= 109.4(7)
C9A—C21A—C4A	= 116.2(6)	C9B—C21B—C4B	= 115.9(5)

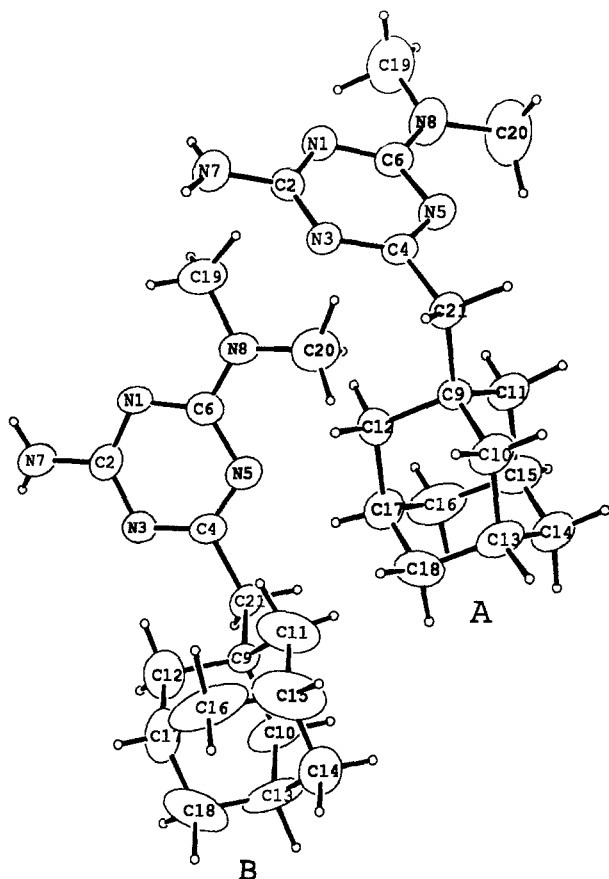


Fig. 1. A perspective view of molecules A and B showing the atomic numbering scheme.

The two hydrogens at N7 are utilized in the crystal packing to make ribbons of hydrogen bonded molecules. The geometries of the hydrogen bonds are:

D—H···A	D···A	H···A	<D—H···A
N7A—H71···N1B	3.21 Å	2.41 Å	164°
N7A—H72···N3A	3.02	2.24	165
N7B—H71···N1A	3.30	2.47	176
N7B—H72···N3B	3.03	2.22	166

Due to this type of hydrogen bonding the molecules constitute infinite chains throughout the crystal with primarily hydrophobic van der Waals interactions between them. This hydrogen bonding pattern is somewhat different from other triazine structures of the series that were solved previously (Hamodrakas *et al.*, 1992; Gessman *et al.*, 1992; Tsitsa *et al.*, 1993).

The conformation of the substituents at position 6 of the triazine ring is determined by the torsion angle N(1)—C(6)—N(8)—C(19). In all triazine crystal structures solved this angle is always close to 0°; the same holds for both molecules of the asymmetric unit of the title compound, with values of 2.0° and 1.2°, respectively.

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