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Crystal Structure of 6,7-Dihydro-5a,7a,13,14-tetraaza-pentaphene-5,8-dione

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The X-ray crystal structure of 6,7-dihydro-5a,7a,13,14-tetraaza-pentaphene-5,8-dione, a potential antiproliferative agent on A2058 melanoma cells, was established. It crystallizes in the monoclinic space group $P2_1/c$ with cell parameters $a = 24.879(3)\text{Å}$, $b = 6.868(2)\text{Å}$, $c = 26.068(4)\text{Å}$, $\alpha = 90$, $\beta = 110.49(2)$, $\gamma = 90$, $V = 4172.4(15)\text{Å}^3$ and $Z = 12$. The crystal structure was refined to final values of $R1 = 0.1353$ and $wR2 = 0.1936$. An X-ray crystal structure analysis revealed that each molecule features intermolecular $C_{\text{Arom.}}-H\cdots O$ hydrogen bonds to form trimers.

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Condensed heterocycles of quinazolines have become attractive targets in synthetic and medicinal chemistry due to their useful and significant pharmacological activities. Thus, the occurrence of the quinazoline skeleton in various natural and synthetic products has generated the interest of many groups on account of its useful biological properties such as analgesic, anti-inflammatory, anti-convulsant, sedative-hypnotic, anti-histaminic, anti-hypertensive, anti-cancer, anti-microbial, anti-tubercular and anti-viral activities.¹⁻³ As a part of our ongoing research activity, we launched a research program dealing with the preparation and pharmacological evaluation of some original quinazoline derivatives structurally related to well-studied terrestrial alkaloids (*e.g.* Rutacarpine and Luotonine A), which possess a quinazolin-4-one moiety fused with indolopyrido and pyrroloquinoline ring systems,⁴ respectively. Thus, exploring the potential synthetic applications of the Niementowski reaction and in association with our work on the application of microwaves in organic chemistry, we planned to prepare novel pentacyclic tetraaza-pentaphene-5,8-diones, from various anthranilic acids and 2,3-condensed (3*H*)-quinazolin-4-ones.⁴ In particular, this kind of pentacyclic fused bisquinazolinones has been described as being antibacterial, antifungal, antitubercular and antiproliferative agents.⁴⁻⁶

We report herein on the structural characterization of the 6,7-dihydro-5a,7a,13,14-tetraaza-pentaphene-5,8-dione (Fig. 1), a fused bis-quinazolin-4-one derivative that has been synthesized *via* a modified Niementowski condensation.⁴ This new pentacyclic bisquinazolinone induced $40.2 \pm 3.3\%$ and $6.9 \pm 3.5\%$ growth inhibition at 10 and 1 μM , respectively, which can be considered to be a high antiproliferative activity, in the range of growth inhibition obtained with control antimelanoma drugs (Vemurafenib, BRAF inhibitor, $\text{IC}_{50} = 11.71 \mu\text{M}$).

Colorless crystals having dimensions of $0.25 \times 0.10 \times 0.10 \text{ mm}^3$ suitable for X-ray diffraction analysis were obtained by slow crystallization from a dichloromethane-methanol solution at $+20^\circ\text{C}$. The molecular structure of the pentacyclic title compound is depicted in Fig. 2. Crystal and experimental data are given in Table 1.

Crystallographic data of this pentacyclic compound were collected at 296 K with an Enraf-Nonius CAD-4 diffractometer using the $\text{Cu K}\alpha$ radiation ($\lambda = 1.5418 \text{ Å}$). The collected data were reduced using NONIUS CAD4 software, and all reflections were used for unit-cell refinement. The crystal structure was solved by direct methods and successive Fourier difference syntheses with the SHELXS program.⁷ Refinement of the crystal structure was performed on F^2 by weighted anisotropic full-matrix least-squares methods using the SHELXL program.⁷ An absorption correction was performed using the psi-scan method.⁸ All non-H atoms were refined anisotropically, and the positions of the H atoms were deduced from the coordinates of the non-H atoms to which they are linked, confirmed by Fourier

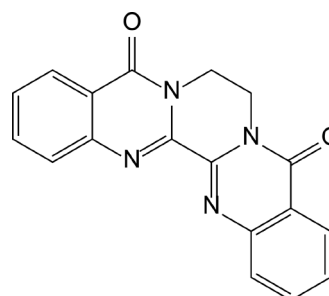


Fig. 1 Chemical structure of 6,7-dihydro-5a,7a,13,14-tetraaza-pentaphene-5,8-dione.

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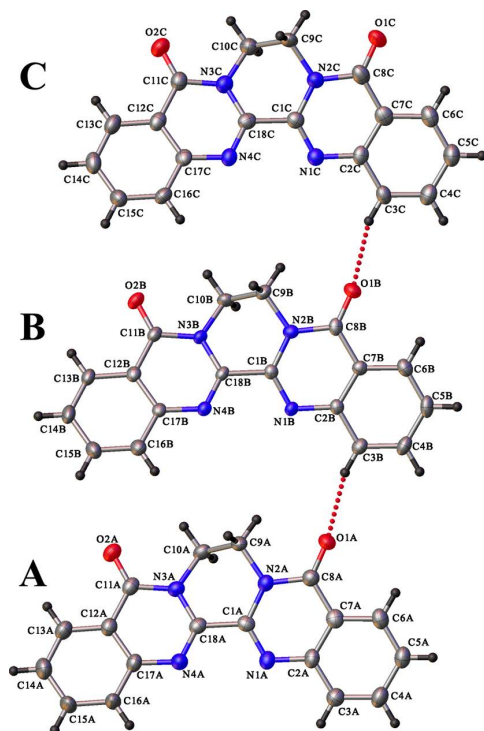


Fig. 2 Asymmetric unit ORTEP view of the crystal structure of the title compound {molecules A [label suffixes A], B [label suffixes B] and C [label suffixes C]} with our numbering scheme. Displacement thermal ellipsoids are drawn at the 50% probability level.

Table 1 Crystal and experimental data for the title compound

Empirical formula: $C_{18}H_{12}N_4O_2$	
Formula weight = 316.32	
$T = 296$ K	
Crystal system: monoclinic	Space group $P2_1/c$
$a = 24.879(3)$ Å	
$b = 6.868(2)$ Å	
$c = 26.068(4)$ Å	
$\beta = 110.49(2)^\circ$	
$V = 4172.4(15)$ Å ³	
$Z = 12$	$Z' = 12, 3$
$\rho_{\text{calc}} = 1.511$ cm ⁻³	
$\mu = 0.842$ mm ⁻¹	
$F(0\ 0\ 0) = 1968$	
Crystal size = $0.25 \times 0.1 \times 0.1$ mm ³	
Radiation: Cu $K\alpha$ ($\lambda = 1.5418$ Å)	
2θ range for data collection: 6.898 to 135.31°	
Index ranges $-29 \leq h \leq 27$, $-8 \leq k \leq 6$, $-31 \leq l \leq 31$	
Reflections collected: 49888	
Independent reflections: 7408 [$R_{\text{int}} = 0.0526$, $R_{\text{sigma}} = 0.0378$]	
Data/restraints/parameters: 7408/0/649	
Goodness-of-fit on $F^2 = 1.056$	
Final R indexes [$I > 2\sigma(I)$]: $R1 = 0.1353$, $wR2 = 0.1898$	
Final R indexes [all data]: $R1 = 0.1420$, $wR2 = 0.1936$	
Largest diff. peak/hole $1.12/-0.34$ eÅ ⁻³	
CCDC deposition number: 267198	

synthesis and treated according to the riding model during refinement. H atoms were included for structure factor calculations, but not refined. Some measured intensities presented unexpected bias. Then, deviations, $|F_o^2 - F_c^2|$, do not follow a statistical normal distribution, which is probably due to unresolved twinning of the crystal. The most affected intensities

were thus omitted from refinement, and weights have been manually adjusted at the final stage to reach a goodness of fit close to 1.

Crystallographic data have been deposited in the Cambridge Crystallographic Data Centre (CCDC 267198). Copies of these data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/data_request/cif).

The title compound crystallizes in the monoclinic $P2_1/c$ space group, and the asymmetric unit is constituted by three independent molecules of 6,7-dihydro-5a,7a,13,14-tetraaza-pentaphene-5,8-dione (designated as A, B and C). The three independent molecules develop intermolecular $C_{\text{Arom}}\text{-H}\cdots\text{O}$ hydrogen bonds to form supramolecular trimers (Fig. 2). In the title compound, all bond lengths and angles of the fused heterocyclic rings were found to be within the normal ranges by comparing with the earlier substituted fused quinazolin-4-one derivatives.^{4,9}

X-ray data confirmed the pentacyclic 6,7-dihydro-5a,7a,13,14-tetraaza-pentaphene-5,8-dione structure in the solid state. The C1a-N1a, C18a-N4a, C1b-N1b, C18b-N4b, C1c-N1c, C18c-N4c bonds in this bis-quinazolin-4-one derivative were found in the range of 1.293(5) to 1.318(5) Å, as typically observed for the C=N double bonds,¹⁰ while the various C-N single bonds were noticed at 1.379(5) – 1.488(5) Å. The various quinazolinone systems of the title compound were also found to be quite planar with a maximum displacement from the mean plane of 0.067(3) Å for N3a. The interplanar dihedral angles between the quinazolinone least-squares planes in each independent molecule were found at 18.15(8), 21.02(7) and 20.69(7) for molecules A, B and C respectively. In addition, the torsion angles of the conjugated N1-C1-C18-N4, were observed at 19.9(6), 22.7(5) and 21.5(6)°, for molecule A, B and C respectively. Moreover, the torsion angle N2-C9-C10-N3 was found at 58.4(4)° for A, and their homologous torsion angles were noticed in the same range at 60.7(4)° and 61.7(5)°, for B and C respectively. The C=O bonds were noticed in the range of 1.222(5) to 1.231(5) Å, as typically observed for $C_{\text{sp}2}=\text{O}$ bonds in lactams.

The crystal-structure cohesion is then ensured by several H-bond like interactions between the carbonyl and aromatic hydrogen that form trimers that are linked together by weaker H-bond like interactions (Table S1) within approximately the **a** direction and by π -stacking within the **b** direction (Table S2 and Fig. S1). Weaker Van der Waals contacts complete the intermolecular interactions in the crystal structure approximately in the **c** direction.

Supporting Information

A CIF format file and Tables S1 and S2, and Fig. S1. These materials are available free of charge on the Web at <http://www.jsac.or.jp/xraystruct/>.

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