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Crystal Structure of *N*-(7-[[2-(Dimethylamino)ethyl]amino]-1-methyl-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl)-3,4,5-trimethoxybenzamide

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The X-ray crystal structure of *N*-(7-[[2-(dimethylamino)ethyl]amino]-1-methyl-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl)-3,4,5-trimethoxybenzamide, a potential anticancer agent targeting Hsp90, was established. It crystallizes in the triclinic space group *P*-1 with cell parameters $a = 9.3554(4)\text{Å}$, $b = 11.4450(5)\text{Å}$, $c = 11.5629(4)\text{Å}$, $\alpha = 87.140(2)$, $\beta = 78.8070(19)$, $\gamma = 69.2119(19)$, $V = 1135.21(8)\text{Å}^3$ and $Z = 2$. The crystal structure was refined to final values of $R1 = 0.0492$ and $wR2 = 0.1386$. An X-ray crystal structure analysis revealed that each molecule features intermolecular N-H...N hydrogen bonds to form dimers.

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Naphthyridones are well-known heterocyclic building-blocks that have been attracting considerable attention due to their potential pharmaceutical interests. Especially, 1,8-naphthyridin-4(1*H*)-ones have been widely investigated as aza-heterocycles with a large family of fluoroquinolones antibiotics.¹ Moreover, substituted 1,6-naphthyridin-2(1*H*)-one compounds have shown many interesting biological activities as, for example, cardiotoxic drugs,² protein kinases inhibitors³ or neuroprotective agents.⁴

Furthermore, due to this large range of biological applications we undertook to investigate the synthesis of functionalized 1,6-naphthyridin-2(1*H*)-ones⁵ in order to propose a practical access to these heterocycles and find potential biological activities.

We report herein on the structural characterization of the *N*-(7-[[2-(dimethylamino)ethyl]amino]-1-methyl-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl)-3,4,5-trimethoxybenzamide (Fig. 1), a 1,6-naphthyridin-2(1*H*)-one derivative that has been described to display antiproliferative activity towards breast cancer cell lines.⁵

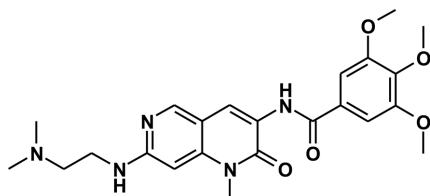


Fig. 1 Chemical structure of *N*-(7-[[2-(dimethylamino)ethyl]amino]-1-methyl-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl)-3,4,5-trimethoxybenzamide.

The title compound was synthesized by through regioselective palladium-catalyzed cross-coupling reactions. Pale-yellow crystals having dimensions of $0.24 \times 0.13 \times 0.04\text{ mm}^3$ suitable for X-ray diffraction analysis were obtained by the slow crystallization from a dichloromethane-ethyl acetate solution at $+20^\circ\text{C}$. The molecular structure of the title compound is depicted in Fig. 2. Crystal and experimental data are given in Table 1.

Crystallographic data of this compound were collected at 200 K with a Bruker APEX II diffractometer using monochromatic Mo- $K\alpha$ radiation ($\lambda = 0.71073\text{ Å}$). The collected data were reduced using SAINT software (SAINT, Bruker AXS Inc., Madison, Wisconsin, USA), 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.⁶ Refinement of the crystal structure was performed on F^2 by weighted anisotropic full-matrix least-squares methods using the SHELXL program.⁶ An absorption correction was performed by semi-empirical methods using the

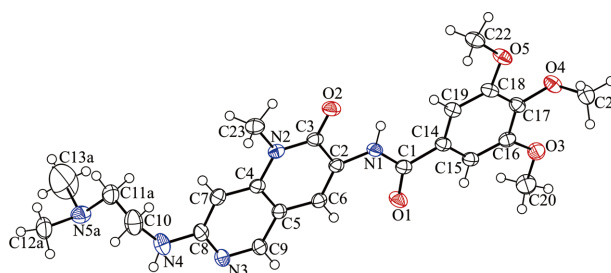


Fig. 2 Asymmetric unit ORTEP view of the crystal structure of the title compound with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

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SADABS program.⁷ All parts of program were used within the OLEX2 package.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 synthesis and treated according to the riding model during refinement. H atoms were included for structure factor calculations, but not refined.

The title compound crystallizes in the triclinic *P*-1 space group, and the asymmetric unit is constituted by one molecule of *N*-(7-[[2-(dimethylamino)ethyl]amino]-1-methyl-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl)-3,4,5-trimethoxybenzamide. 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 naphthyridones.^{9,10}

Table 1 Crystal and experimental data for the title compound

Chemical formula: C ₂₃ H ₂₉ N ₅ O ₅
Formula weight: 455.51
<i>T</i> = 200(2)K
Crystal system: triclinic
Space group: <i>P</i> -1
<i>a</i> = 9.3554(4)Å
<i>b</i> = 11.4450(5)Å
<i>c</i> = 11.5629(4)Å
α = 87.140(2)
β = 78.8070(19)
γ = 69.2119(19)
<i>V</i> = 1135.21(8)Å ³
<i>Z</i> = 2
<i>D</i> _x = 1.333 Mg/m ³
Radiation: Mo <i>K</i> α (λ = 0.71073 Å)
<i>F</i> (0 0 0) = 484
Crystal size = 0.24 × 0.13 × 0.04 mm ³
No. of reflections collected = 27362
No. of independent reflections = 4641
No. of reflections used [<i>I</i> > 2σ(<i>I</i>)] = 2859
2θ range for data collection: 5.594 to 52.742°
Data/Restraints/Parameters = 4641/0/343
Goodness-of-fit = 1.012
<i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]: <i>R</i> 1 = 0.0492, <i>wR</i> 2 = 0.1175
<i>R</i> indices (all data): <i>R</i> 1 = 0.0915, <i>wR</i> 2 = 0.1386
(Δ/σ) _{max} = 0.000
(Δρ) _{max} = 0.276 Å ⁻³
(Δρ) _{min} = -0.207 Å ⁻³
Structure determination: SHELXS ⁶
Refinement: SHELXL ⁶
CCDC deposition number: 1511241

The dimethylamino-ethyl group is disordered on two positions with 43 and 57% respective proportions.

Thus, the torsion angle N(4)–C(10)–C(11a)–N(5a) was found at 71.7(4)°, and the homologous torsion angle N(4)–C(10)–C(11b)–N(5b) was –82.5(8)° showing that the 2-(dimethylamino)-ethyl]amino chain is not fully extended.

The naphthyridine ring atoms (N2–C4) have a root-mean-square deviation of only 0.026 Å from their least-squares plane, and thus are approximately coplanar. The interplanar dihedral angle between the naphthyridine least-squares plane and that through the trimethoxyphenyl ring atoms (C14–C19) is 6.61(5)°. The torsion angle involving the N(2)–C(3) bond in the pyridine ring [C(3)–N(2)–C(4)–C(5)] is noticed at 2.9(3)°, while the torsion angle of the conjugated C(6)–C(2)–C(3)–O(2) is found at 176.76(18)°. In addition, the conjugated C(2)–C(6) double bond was noticed at 1.350(3)Å, in the same range as that observed at 1.363(4)Å in the molecule 7-amino-1,8-naphthyridin-2(1*H*)-one.¹⁰

Two of the three methoxy groups, O(3)–C(20) and O(5)–C(22), were also found in-plane of the benzene system, as usually observed in methoxy functionalized aromatic systems. Hence, the torsion angles, C_{arom}–C_{arom}–O–C_{methoxy}, bearing these two methoxy group are noticed between –1.6(3) to 4.6(3)°, and between –174.51(19) to 178.51(17)°. These two methoxy groups lie close to the aromatic plane, while the third one is out of the aromatic plane (C18–C17–O4–C21 torsion angle = 87.8(3)°) probably due to steric reasons as already observed in

Table 2 Hydrogen-bonding geometry (Å, °)

D–H...A	H–A	D–A	D–H...A
N(4)–H(4)–N(3) ^a	2.155	3.033(3)	175.4

Symmetry code: *a* = (–*x*, 2–*y*, –*z*).

Table 3 π–π interactions (Å, °)

Plane 1	Plane 2	Angle ^a	Distance ^b	Shift ^c
C14–C15–C16–C17–C18–C19	(N2–C4–C5–C6–C2–C3) ^a	5.64(8)	3.967(1)	1.920(4)
N2–C4–C5–C6–C2–C3	(N2–C4–C5–C6–C2–C3) ^b	0.0	3.439(2)	0.898(3)

a. Angle between planes.

b. Centroid to centroid distance.

c. Shift distance.

Symmetry codes: *a* = (2–*x*, 1–*y*, –*z*); *b* = (1–*x*, 1–*y*, –*z*).

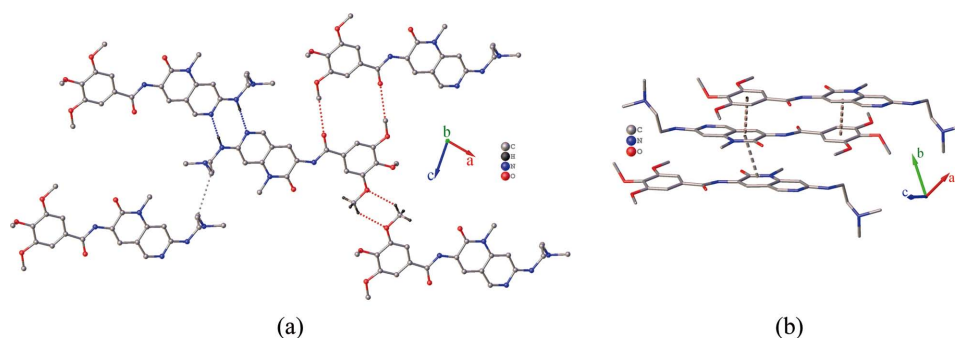


Fig. 3 View of the crystal packing of the title compound (a) along the *b* direction showing the hydrogen bonds and Van der Waals interactions network, and (b) along the 102 lattice direction showing the π-stacking interactions.

other aromatic systems functionalized with 3 methoxy groups. Moreover, the N-C and C-C distances within this six-membered pyridine ring of the naphthyridine are in the range of 1.319(3) to 1.351(3)Å, and of 1.386(3) to 1.403(3)Å, respectively; consistent with the aromatic character of the ring system.

In common with other naphthyridone-based molecules, the title compound contains a double bond, C(2)-C(6), which was noticed at 1.350(3)Å, in the same range as those observed in various naphthyridones.^{9,10} The C(3)=O(2) bond was noticed at 1.230(2)Å, as typically observed for C_{sp2}=O bonds in lactams.

Significant intermolecular N-H...N hydrogen bonds occur between the amino N(4) and N(3) of the pyridine moiety, leading to the formation of a supramolecular dimer (Table 2). The crystal-structure cohesion is then ensured by several Van der Waals interactions and π -stacking that connect the dimers together (Table 3). Van der Waals interactions involving the dimethylamino, the methoxy and the carbonyl moieties connect the dimers approximately in the *a* and *c* direction while π -stacking interaction between the *N*-methyl pyridine of the double aromatic ring and the trimethoxy-benzene system complete the intermolecular interactions in the crystal structure approximately in the *b* direction (Fig. 3).

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