

Synthesis and Crystal Structure of 3-{4-[(4-(2-Oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-2-phenylindole

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Abstract

The X-ray crystal structure of 3-{4-[(4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-2-phenylindole, a compound that showed high cytotoxic potential against various leukemia cell lines, was established. The 3D spatial determination confirmed the structure in the solid state. It crystallizes in the triclinic space group P-1 with cell parameters $a=9.572(7)$ Å, $b=11.091(2)$ Å, $c=15.976(4)$ Å, $\alpha=92.53(2)$, $\beta=105.45(3)$, $\gamma=94.65(3)$, $V=1625.6(13)$ Å³ and $Z=2$. The crystal structure was refined to final values of $R1=0.0638$ and $wR2=0.1800$. The crystal packing is controlled by intermolecular hydrogen bonding and C-H π interactions. In addition, these new data could be further used to clarify the mechanism of action, implicating the antiproliferative effect of this new synthetic indole derivative on human leukemic cells.

Keywords: Single-crystal x-ray study; Indole derivative; Antiproliferative activity; R factor

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Introduction

Acute leukemia is one of the most aggressive hematopoietic malignancies and is characterized by the abnormal proliferation of the immature cells and a premature block in lymphoid or myeloid differentiation. Adult acute leukemia has a poor prognosis due to a large number of relapses, because of treatment-related resistance mechanisms [1]. Therefore, there is an urgent need to find new therapeutics, which could lead to the development of novel treatment strategies with less or minimal side effects. Heterocyclic compounds attracted a lot of attention because of its wide spread biological activities. Among them, the indole heterocyclic framework constitutes the basis of an important class of compounds possessing interesting biological activities [2-7]. These compounds have been reported to serve as key intermediates for the assembly of several heterocycles including anti-migraine agents, antiviral agents, antiparasitic agents, and antitumor agents [8-13]. In this last field, the discovery and development of novel therapeutic agents are one of the most important goals in medicinal chemistry. In the course of our work devoted to discover new compounds employed in the cancer chemotherapy, we previously identified four series of substituted heterocyclic pyrrolo[1,2-*a*]quinoxaline derivatives endowed with good activity towards the human leukemia cells [14-17]. In this context, and as an extension of our work on the development of new anticancer heterocyclic drugs, we decided to substitute our pyrrolo[1,2-*a*]quinoxaline pharmacophore by

a bio-isostere heterocyclic analogue, i.e., the bioactive indole moiety. Thus, we report herein on the synthesis and structural characterization of a new analogue of these previously described compounds based on an indole scaffold, i.e., the 3-{4-[(4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-2-phenylindole. The synthesis of this new indole derivative is depicted in **Scheme 1**. Its preparation involved a reductive

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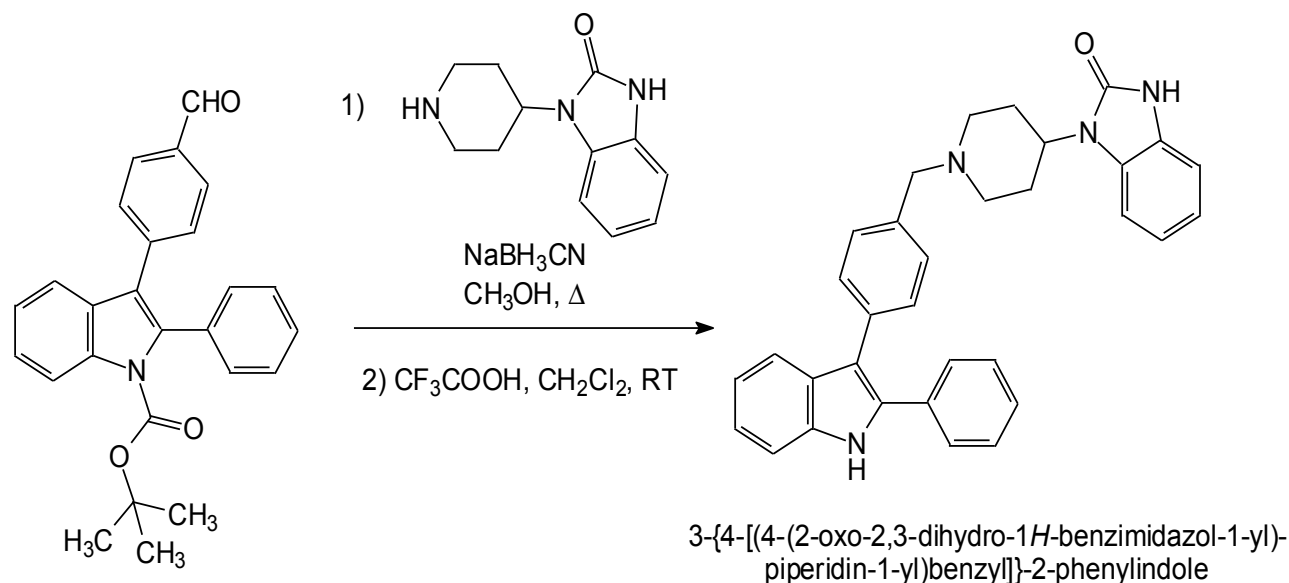
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Scheme 1 Schematic representation of synthesis of 3-{4-[(4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-2-phenylindole.

amination of tert-butyl 3-(4-formylphenyl)-2-phenyl-indole-1-carboxylate with 4-(2-ketobenzimidazol-1-yl)piperidine using sodium cyanoborohydride (NaBH_3CN), then followed by the cleavage of the Boc-protecting group of indole achieved using a trifluoroacetic acid solution in dichloromethane leading to the title compound. The cytotoxicity of this new compound was then evaluated against five different leukemia cell lines, including Jurkat and U266 (lymphoid cell lines), and K562, U937, HL60 (myeloid cell lines), as well as normal human peripheral blood mononuclear cells (PBMNCs) [14-17]. The preliminary biological results exhibited inhibitory activity in a submicromolar range against different leukemia cell lines, including Jurkat (lymphoid cell line), K562 and HL60 (myeloid cell lines) with IC_{50} of 8, 5 and 12 μM , respectively. This compound was also tested on activated (PBMNC + PHA) human peripheral blood mononuclear cells to evaluate its cytotoxicity on normal cells ($\text{IC}_{50} > 50 \mu\text{M}$). Indexes of selectivity (IS) were defined as the ratio of the IC_{50} value on the human mononuclear cells to the IC_{50} value on the different leukemia cell lines. Thus, the title compound shows an interesting index of selectivity > 10 on the human myeloid leukemia cell lines K562. The present crystal structure determination will not only help us understand the detailed three-dimensional arrangement of the compound, which could be useful for designing new derivatives, but will also contribute to the structural database in which there are very few structures containing the indole skeleton. Moreover, solid-state data could be used to clarify the mechanism of action implicating this anti-proliferative derivative.

Experimental

The pH of a solution of tert-butyl 3-(4-formylphenyl)-2-phenyl-indole-1-carboxylate (0.756 mmol) and 4-(2-ketobenzimidazol-1-yl)piperidine (0.907 mmol) in 20 mL methanol was adjusted to 6 by the dropwise addition of acetic acid. Powered sodium cyanoborohydride (2.08 mmol) was then added, and the resultant mixture was refluxed for 5 hrs. After removal of the methanol by rotary evaporation, the residue was triturated in

water and extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate and evaporated to dryness. Column chromatography of the residue on silica gel using ethyl acetate - cyclohexane (1/1) as eluents gave a white powder. To a cooled solution of this latter solid (0.5 mmol) in 5 mL of dichloromethane was added 10 mL of a 15% trifluoroacetic acid solution in dichloromethane. The mixture was stirred at room temperature for 24 h, then neutralized with 15 mL of a saturated aqueous solution of potassium carbonate and extracted with 3×10 mL of dichloromethane. The organic layer was washed with brine and dried with anhydrous sodium sulphate. The solvent was removed under reduced pressure. The crude residue was then purified by column chromatography using ethyl acetate - cyclohexane (1/1) as eluents gave a white powder of the title compound with melting point 169°C and yield 64%. Single crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of the compound under a methanol-dichloromethane solution (3/7 - v/v) at $+20^\circ\text{C}$. IR (KBr) 3403 and 3221 (NH), 1692 (CO). ^1H NMR (CDCl_3) δ : 9.36 (s, 1H, NH indole), 8.39 (s, 1H, NH benzimid.), 7.74 (d, 1H, $J=7.80$ Hz, H indole), 7.49-7.18 (m, 11H, H indole, H phenyl and H benzimid.), 7.13 (t, 1H, $J=7.80$ Hz, H indole), 7.12-7.05 (m, 4H, H phenyl and H benzimid.), 4.49-4.37 (m, 1H, CH pip.), 3.65 (s, 2H, CH_2N), 3.17-3.13 (m, 2H, CH_2 pip.), 2.59-2.47 (m, 2H, CH_2 pip.), 2.29-2.21 (m, 2H, CH_2 pip.), 1.88-1.83 (m Hz, 2H, CH_2 pip.). ^{13}C NMR (CDCl_3) δ : 156.71 (C=O benzimid.), 137.41 (C-7a), 137.05 (C-4'), 135.62 (C-2), 135.51 (C-1'), 134.24 (C-3 and C-7a benzimid.), 131.45 (C-3' and C-5'), 130.88 (C-3'' and C-5''), 130.42 (C-1''), 130.06 (C-2'' and C-6''), 129.70 (C-2' and C-6'), 129.48 (C-3a benzimid.), 129.06 (C-4''), 124.06 (C-6 benzimid.), 122.59 (C-5 benzimid.), 122.47 (C-5), 121.77 (C-7 benzimid.), 121.13 (C-4 benzimid.), 116.08 (C-3a), 112.39 (C-6), 111.31 (C-4), 111.19 (C-7), 64.20 (NCH_2), 54.54 (NCH_2 pip.), 52.16 (CH pip.), 30.52 (CH_2 pip.). MALDI-TOF MS m/z $[\text{M}+\text{H}]^+$ Calculated for $\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}$: 499.250, Found: 499.216. Anal. Calculated for $\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}$: C, 79.49; H, 6.06; N, 11.24. Found: C, 79.53; H, 5.97; N, 11.13.

X-ray structure determination

Single crystal X-ray diffraction data for the compound at room temperature was collected on a CAD-4 Enraf-Nonius diffractometer equipped with graphite monochromated CuK α radiation ($\lambda=1.54180$ Å). Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections. The cell parameters were then refined using the full set of collected reflections in the range $2.88^\circ < 2\theta < 68.92^\circ$. The half sphere of data was collected at 293 K giving rise to 6004 unique reflections, of which 4040 were observed with $I/\sigma(I) > 2$. The linear absorption coefficient for CuK α is 6.36 cm^{-1} . An empirical absorption correction, based on azimuthal scans of two reflections [18], was applied which resulted in transmission factors ranging from 0.89 to 0.94. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 49×10^{-4}). The structure was solved by direct methods and successive Fourier difference syntheses and refined on (F²) by full-matrix least-squares methods respectively with the SHELXS-97 and SHELXL-97 programs [19]. All non-H atoms were refined anisotropically and the positions of the H atoms were deduced from coordinates of the non-H atoms they are linked to, 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 final cycle of full-matrix least-squares refinement was based on 4040 observed reflections [$I > 2.00\sigma(I)$] and 404 variable parameters and converged with agreement factors of $R_1=0.064$ and $wR_2=0.180$ (All data). All graphical contents have been performed using the OLEX2 interface [20].

The crystal data and refinement details are summarized in **Table 1**. Crystallographic data (excluding structure factors) for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, No. CCDC-888295. Copies of this information may 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 web: www.ccdc.cam.ac.uk.

Results and Discussion

The molecular structure of 3-{4-[(4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-2-phenylindole is depicted in **Figure 1**. The 3D spatial determination established by X-ray crystallography confirmed the structure in the solid state as anticipated on the basis of IR, ¹H and ¹³C NMR data. The asymmetric unit of the crystal structure consists in one molecule of the title compound co-crystallized with three methanol molecules. The selected bond distances and torsion angles are collected in **Table 2**. The indole system is nearly planar; the maximum deviations from the least-squares plane are found for C(10) lying 0.006(2) Å from the benzene ring and for C(11) lying -0.010(2) Å from the pyrrole ring, the dihedral angle between the two ring planes being $0.62(13)^\circ$. In the five-membered ring containing atom N(8), the intra-ring bond angles range from $106.5(2)^\circ$ to $110.0(2)^\circ$; the N(8)-C(7) and N(8)-C(9) bond lengths are 1.386(3) and 1.365(3) Å, respectively, which indicates that the geometry around N(8)

is normal for sp^2 hybridization, as expected for π -conjugation of indole rings previously described [21]. Thus, all atoms that constitute this system have a planar-trigonal configuration, i.e., they are sp^2 -hybridized. Moreover, the C(10)-C(11) bond, noticed at 1.440(4) Å, is longer than the standard aromatic C-C bond [22] and is in agreement with the values observed in various other indole derivatives [23-25]. The C(1)-C(6) phenyl ring makes a dihedral angle of $32.3(1)^\circ$ with the mean plane of the indole moiety, and the C(16)-C(21) phenyl group at 3-position makes a dihedral angle of $49.4(1)^\circ$ with the plane of the indole ring. The torsion angles C(11)-C(7)-C(6)-C(5) and C(7)-C(11)-C(16)-C(17) are $\pm 31.4(5)^\circ$ and $\pm 46.6(4)^\circ$, respectively. Presumably, the substituents on C(11) and C(7) in this molecule are turned apart for steric reasons: fairly bulky groups are attached to contiguous carbon atoms of the five-membered ring, in accordance with previously described 2,3-diphenylindole derivatives [25]. The piperidine ring has the chair conformation; the nitrogen atom N(23) and the carbon C(26) are displaced on either side from the least-squares plane C24-C25-C27-C28 by 0.691(4) and 0.656(4) Å, respectively. Moreover, the angles N(23)-C(28)-C(27) and N(23)-C(24)-C(25) are found in the same range $110.8(2)$ and $111.4(2)^\circ$. The 1,3-dihydrobenzimidazol-2-one ring system is almost planar, with the largest deviation being for atom O(38) [0.019(2) Å]. The average bond distances and angles for this 1,3-dihydrobenzimidazol-2-one system are in agreement with those of previous studies on 2-oxo-2,3-dihydro-1H-benzimidazol-1-yl compounds in the literature [14-17]. Molecules of the title compound are linked by a double H-bonds between the O(38) and

Table 1 Crystal data, data collection and structure refinement.

Parameter	Value
Chemical formula	C ₃₃ H ₃₀ N ₄ O, 3(CH ₃ OH)
Formula weight	594.74
T (K)	293(2) K
Wavelength	1.54180 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a=9.572(7) Å b=11.091(2) Å c=15.976(4) Å
	$\alpha = 92.53(2)$ $\beta = 105.45(3)$ $\gamma = 94.65(3)$
Volume	1625.6(13) Å ³
Z, Calculated density	2, 1.215 Mg/m ³
Absorption coefficient	0.636 mm ⁻¹
F (000)	636
Crystal size	0.18 × 0.15 × 0.10 mm
Theta range for data collection	2.88 to 68.92°
Limiting indices	-11 ≤ h ≤ 11, -13 ≤ k ≤ 13, 0 ≤ l ≤ 19
Reflections collected/unique	6004/6004 [R(int)=0.0000]
Completeness to theta=68.92	99.4%
Refinement method	Full-matrix least-squares on
Data/restraints/parameters	6004/0/404
Goodness-of-fit on F ²	1.019
Final R indices [I > 2σ(I)]	R1=0.0638, wR2=0.1528
R indices (all data)	R1=0.0973, wR2=0.1800
Largest diff. peak and hole	0.351 and -0.279 e.Å ⁻³

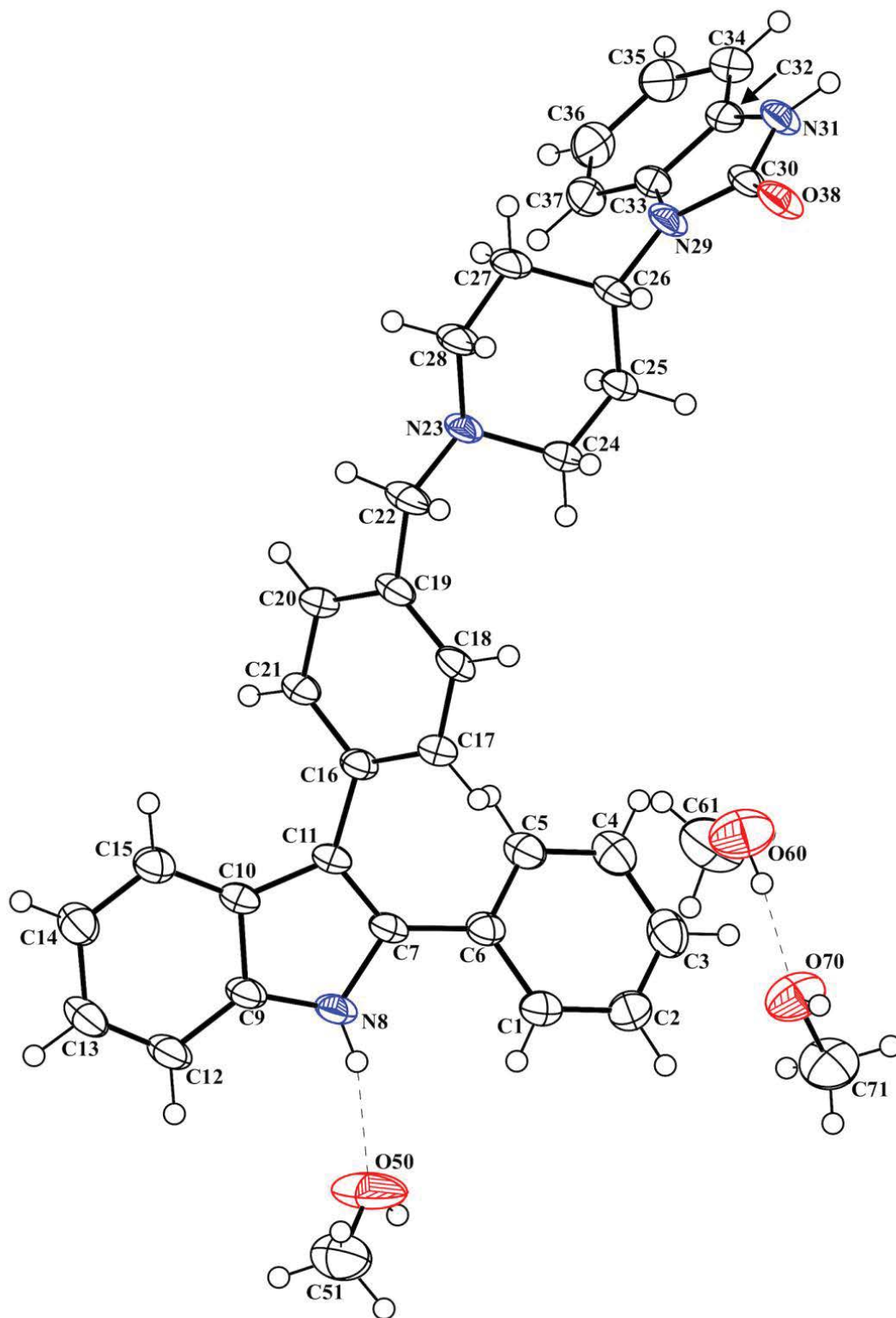


Figure 1 ORTEP view of the crystal structure of 3-[4-[(4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl)benzyl]]-2-phenylindole with our numbering scheme at 293 K. Displacement ellipsoids are drawn at the 30% probability level.

N(31) atoms of the imidazole rings to form dimers and H-bonding interactions through the three methanol molecules that connect

Table 2 Selected bond distances, angles and torsion angles (Å, °) with su's in parentheses.

Bond Distances	Value
N(8)-C(7)	1.386(3)
N(8)-C(9)	1.365(3)
C(10)-C(11)	1.440(4)
C(30)-O(38)	1.229(3)
N(31)-C(30)	1.367(3)
N(29)-C(30)	1.369(3)
N(23)-C(24)	1.467(3)
N(23)-C(28)	1.472(3)
N(23)-C(22)	1.477(3)
Bond Angles	Value
N(8)-C(7)-C(11)	108.2(2)
C(7)-C(11)-C(10)	107.5(2)
C(11)-C(10)-C(9)	106.5(2)
C(10)-C(9)-N(8)	107.8(2)
C(9)-N(8)-C(7)	110.0(2)
N(23)-C(28)-C(27)	110.8(2)
N(23)-C(24)-C(25)	111.4(2)
Torsion Angles	Value
C(11)-C(7)-C(6)-C(5)	± 31.4(5)
C(7)-C(11)-C(16)-C(17)	± 46.6(4)

the dimers together to form chains in the (1 -1 0) direction (**Table 3**) (**Figure 2**). The crystal cohesion is ensured by short Van der Waals contacts and C-H π interactions in the others directions.

Conclusion

In the present work, we synthesized the new 3-{4-[(4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-2-phenylindole which showed antileukemic activity in a submicromolar range on the human leukemic cell lines Jurkat (lymphoid cell line), K562 and HL60 (myeloid cell lines). We report herein on the structural characterization of this new indole scaffold. The present crystal structure determination could now help us to understand the detailed three-dimensional arrangement of this compound, which could be used to generate a broad variety of 3-substituted 2-phenylindoles of interest to medicinal chemists, but will also contribute to the structural database in which there are very few structures containing the indole skeleton. Moreover, solid-state data could be used to clarify the mechanism of action implicating this anti-proliferative derivative.

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Table 3 Hydrogen-bonding geometry (Å, °). Symmetry codes: (i) -1-x, 2-y, 1-z, (ii) 1+x, +y, +z, (iii) +x, -1+y, +z.

D-H...A	D-H	H...A	D...A	D-H...A
N(8)-H(8)---O(50)	0.86	1.97	2.814(4)	165.1
N(31)-H(31)---O(38) ⁱ	0.86	1.92	2.771(3)	169.4
O(50)-H(50)---O(60) ⁱⁱ	0.82	1.83	2.646(4)	170.4
O(60)-H(60)---O(70)	0.82	1.78	2.602(4)	174.2
O(70)-H(70)---N(23) ⁱⁱⁱ	0.82	1.94	2.758(4)	175.4

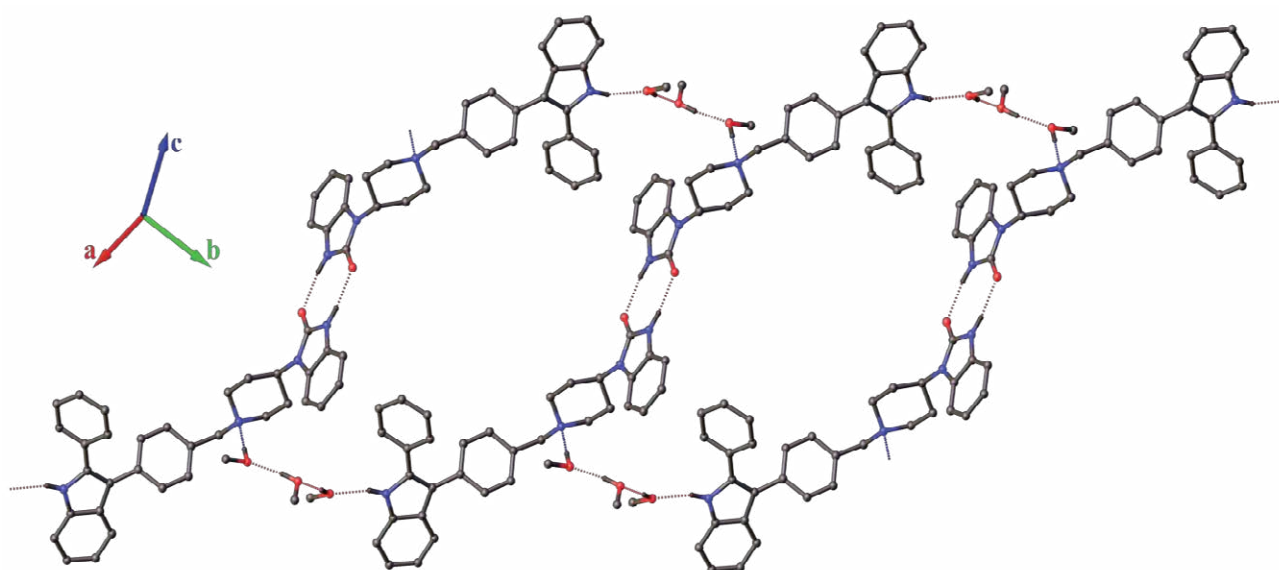


Figure 2 Packing of the compound with viewing direction (2 1 2). Hydrogen bonds are shown as dashed lines.

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