



# Synthesis, Crystal Structure and Anti-leukemic Activity of 4-{4-[(4-(2-Oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-3-phenyl-3*H*-pyrrolo[2,3-*c*]quinoline

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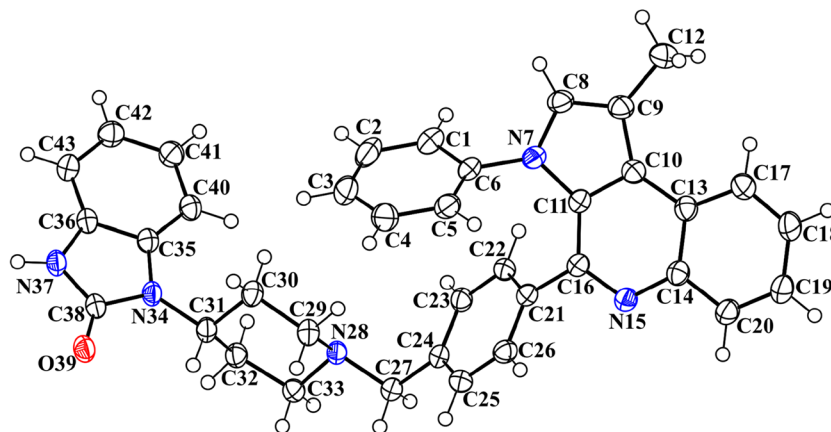
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## Abstract

The title compound 4-{4-[(4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-3-phenyl-3*H*-pyrrolo[2,3-*c*]quinoline **1**, a compound that showed cytotoxic potential against two leukemia cell lines, has been synthesized via a multi-step pathway. This compound was characterized by single-crystal X-ray diffraction, IR, MS, elemental analysis, <sup>1</sup>H and <sup>13</sup>C NMR. The crystal (C<sub>37</sub>H<sub>33</sub>N<sub>5</sub>O, *M<sub>r</sub>* = 563.68) belongs to orthorhombic, space group *Pbcn* with cell parameters *a* = 30.198(2) Å, *b* = 12.5097(11) Å, *c* = 15.6648(13) Å, *V* = 5917.7(8) Å<sup>3</sup>, *Z* = 8, *D<sub>c</sub>* = 1.265 g/cm<sup>3</sup>, CuKα radiation, λ = 1.54180 Å, μ = 0.611 mm<sup>-1</sup>, *F*(000) = 2384, the final *R* = 0.0491 and *wR* = 0.1585 for 5698 observed reflections with *I* > 2σ(*I*).

## Graphical Abstract

The antileukemial 4-{4-[(4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-3-phenyl-3*H*-pyrrolo[2,3-*c*]quinoline was synthesized and characterized by X-ray crystallography.



**Keywords** Antileukemial · Pyrrolo[2,3-*c*]quinoline · Heterocycle

## Introduction

Acute leukemia is one of the most aggressive hematopoietic malignancies and is characterized by abnormal proliferation of the immature cells of the hematopoietic system. Acute myeloblastic leukemia (AML) is a heterogeneous group of

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hematological malignancies whose prognosis remains poor due to a large number of relapses. Thus, identifying and understanding the treatment-related resistance mechanisms is of major interest to improve the therapeutic strategy [1]. Therefore, there is an urgent need for new therapeutics, which could act as anti-leukemic agents with less or minimal side effects.

Heterocyclic compounds attracted a lot of attention because of its wide spread biological activities. Among them, the pyrrolo[2,3-*c*]quinoline heterocyclic framework constitutes the basis of an important class of compounds possessing interesting biological activities. These compounds have been reported to serve as key intermediates for the assembly of several heterocycles including antiparasitic agents [2–5], antitubercular agents [6], and PDE4 inhibitors [7], a target for numerous CNS disorders.

In the course of our work devoted to discover new compounds employed in the cancer chemotherapy, we previously identified several series of substituted heterocyclic derivatives endowed with good activity towards the human leukemia cells [8–12]. In this context, and as an extension of our work on the development of new anticancer heterocyclic drugs, we decided to substitute our previous heterocyclic pharmacophores by a new bio-isostere heterocyclic analogue, i.e. the bioactive pyrrolo[2,3-*c*]quinoline moiety. Thus, we report herein on the synthesis and structural characterization of one of them, i.e. the 4-{4-[(4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-3-phenyl-3*H*-pyrrolo[2,3-*c*]quinoline **1**. The cytotoxicity of this new pyrrolo[2,3-*c*]quinoline derivative was then evaluated against two myeloid leukemia cell lines (K562 and HL60). The preliminary biological results exhibited inhibitory activity in a submicromolar range against these two different leukemia cell lines, including K562 and HL60 with IC<sub>50</sub> of 16 and 1 μM, respectively. 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 pyrrolo[2,3-*c*]quinoline skeleton. Moreover, solid-state data could be used to clarify further the mechanism of action implicating this anti-proliferative pyrrolo[2,3-*c*]quinoline derivative through a possible interaction with different kinases targets.

## Experimental

### Reagents and Measurements

Reagents were used as received without additional purification. Melting points were determined with an SM-LUX-POL Leitz hot-stage microscope and are uncorrected. IR spectra

were recorded on a NICOLET 380FT-IR spectrophotometer. NMR spectra were recorded with tetramethylsilane as an internal standard using a BRUKER AVANCE 300 spectrometer. Splitting patterns have been reported as follows: s = singlet; d = doublet; dd = double doublet; ddd = double double doublet; m = multiplet. Analytical TLC were carried out on 0.25 precoated silica gel plates (POLYGRAM SIL G/UV254) and visualization of compounds after UV light irradiation. Silica gel 60 (70–230 mesh) was used for column chromatography. High resolution mass spectra (electrospray in positive mode, ESI+) were recorded on a Waters Q-TOF Ultima apparatus. Mass spectra were recorded on an Ultraflex III TOF/TOF system (Bruker Daltonics, Bremen, Germany), equipped with 200 Hz smartbeam laser (355 nm) and operating in reflectron positive ion mode. Mass spectra were acquired over the *m/z* range 300–5000 by accumulating data from 1000 laser shots for each spectrum. The instrumental conditions employed to analyze molecular species were the following: ion source 1: 25.08 kV; ion source 2: 21.98 kV, lens: 11.03 kV, pulsed ion extraction: 30 ns, reflector: 26.39 kV, reflector 2: 13.79 kV. Matrix suppression was activated by deflection mode: suppression up to 450 Da. Mass calibration was performed for each sample with a peptide calibration mixture (8,206,195, Peptide Calibration Standard, Bruker Daltonics). The instrument was controlled using Bruker's flexControl 3.4 software and mass spectra were analyzed in Bruker's FlexAnalysis 3.4 software (Bruker Daltonics, Billerica, MA, USA).

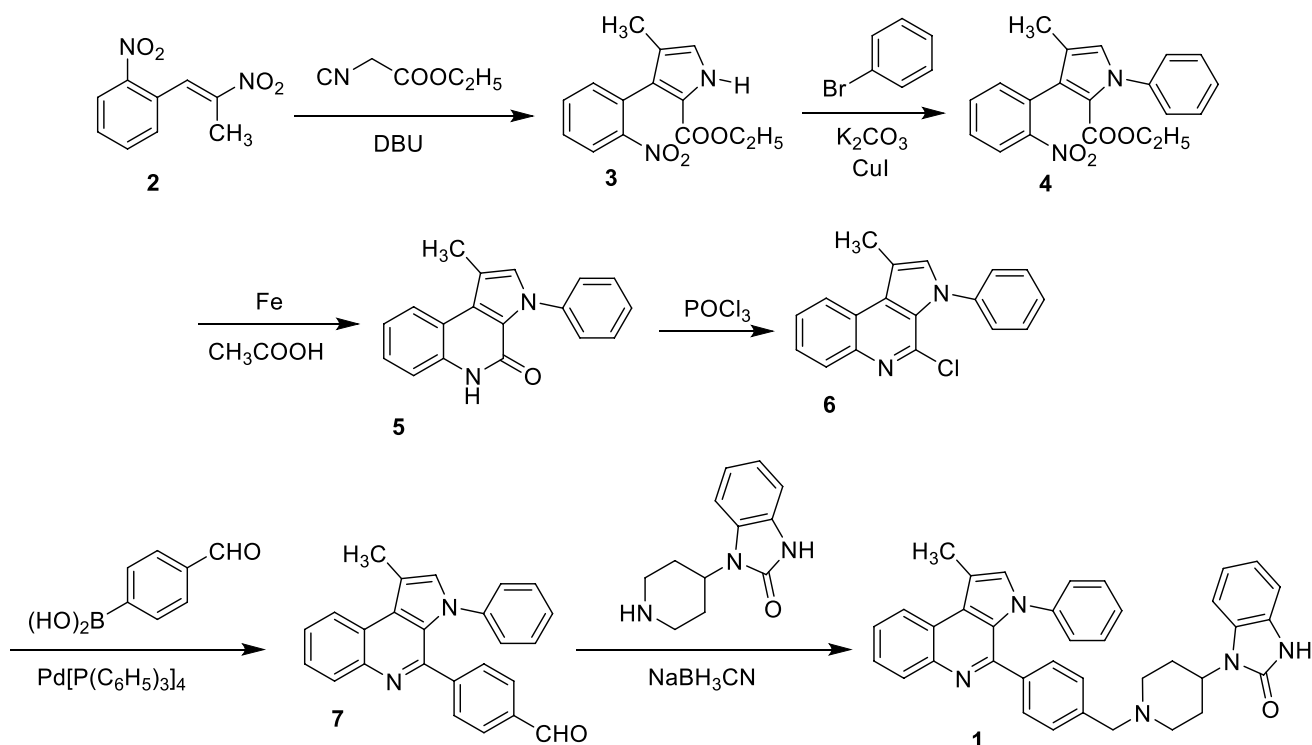
### Synthesis

The ethyl 4-methyl-3-(2-nitrophenyl)pyrrole-2-carboxylate **3** was synthesized starting from styrene **2** using a Barton–Zard reaction [13] according to the procedure reported before [14], which was further treated as depicted in Scheme 1 to afford the title compound **1**.

### Ethyl

#### 4-methyl-3-(2-nitrophenyl)-1-phenylpyrrole-2-carboxylate (**4**)

A mixture of the ester **3** (0.95 g, 3.46 mmol), anhydrous K<sub>2</sub>CO<sub>3</sub> (0.82 g, 5.96 mmol), 12 mL of bromobenzene and cuprous iodide (0.11 g, 0.6 mmol) was heated under reflux for 4 h. The reaction mixture was cooled and filtered, and the residue was washed with toluene. The filtrate and washing were combined, and the solvent was removed. The residue was chromatographed on silica gel using CH<sub>2</sub>Cl<sub>2</sub> as eluent to give the ethyl 4-methyl-3-(2-nitrophenyl)-1-phenylpyrrole-2-carboxylate **4** as a yellow oil (0.98 g, 81%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.76 (t, 3H, *J* = 7.20 Hz, CH<sub>3</sub>), 1.97 (s, 3H, CH<sub>3</sub>), 3.84 (q, 2H, *J* = 7.20 Hz, OCH<sub>2</sub>), 6.85 (s, 1H, H-5), 7.28–7.47 (m, 6H, C<sub>6</sub>H<sub>5</sub> and H-6'), 7.52 (ddd, 1H,



**Scheme 1** Synthetic route of compound **1**

$J=8.10$ ,  $7.50$  and  $0.9$  Hz, H-4'),  $7.64$  (ddd,  $1H$ ,  $J=8.10$ ,  $7.50$  and  $0.9$  Hz, H-5'),  $8.03$  (dd,  $1H$ ,  $J=8.10$  and  $0.9$  Hz, H-3'). Anal. Calcd. for  $C_{20}H_{18}N_2O_4$ : C, 68.56; H, 5.18; N, 8.00%. Found: C, 68.72; H, 5.26; N, 7.89%.

#### 1-Methyl-3-phenyl 5*H*-pyrrolo[2,3-*c*]quinolin-4-one (**5**)

A suspension of **4** (0.98 g, 2.8 mmol) and iron powder (0.63 g, 11.2 mmol) in 14 mL of acetic acid was heated under reflux for 1.5 h. The reaction mixture was cooled, suspended in 200 mL of a 1 M aqueous solution of HCl, agitated, then filtered off, washed with HCl 1 M (10 mL), water, Et<sub>2</sub>O and dried to give lactam **5** as a fluffy white solid (0.50 g, 65%). m.p. > 260 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  2.53 (s, 3H, CH<sub>3</sub>), 7.22–7.45 (m, 9H, H-2, C<sub>6</sub>H<sub>5</sub>, H-7, H-8 and H-9), 8.07 (dd,  $1H$ ,  $J=8.10$  and  $1.0$  Hz, H-6), 11.37 (s,  $1H$ , NH). Anal. Calcd. for  $C_{18}H_{14}N_2O$ : C, 78.81; H, 5.14; N, 10.21%. Found: C, 79.05; H, 5.18; N, 10.34%.

#### 4-Chloro-1-methyl-3-phenylpyrrolo[2,3-*c*]quinoline (**6**)

A solution of 5*H*-pyrrolo[2,3-*c*]quinolin-4-one **5** (0.48 g, 1.75 mmol) in POCl<sub>3</sub> (5 mL) was refluxed for 4 h. After removing excess of reactive under vacuum, the residue was carefully dissolved in water at 0 °C and the resulting solution was made basic with sodium carbonate. The precipitate was filtered, washed with water, and solubilized in

CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried, filtered and evaporated to dryness. The residue was chromatographed on silica gel using CH<sub>2</sub>Cl<sub>2</sub> as eluent to give the 4-chloro-1-methyl-3-phenylpyrrolo[2,3-*c*]quinoline **6** as a white crystals (0.45 g, 88%). m.p. 165–167 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  2.71 (s, 3H, CH<sub>3</sub>), 7.23 (s,  $1H$ , H-2), 7.41–7.52 (m, 2H, C<sub>6</sub>H<sub>5</sub>), 7.49–7.65 (m, 3H, C<sub>6</sub>H<sub>5</sub>), 7.61–7.65 (m, 2H, H-7 and H-8), 8.15 (dd,  $J=8.00$  and  $1.10$  Hz, H-9), 8.43 (dd,  $J=8.00$  and  $1.10$  Hz, H-6). Anal. Calcd. for  $C_{18}H_{13}ClN_2$ : C, 73.85; H, 4.48; N, 9.57%. Found: C, 74.03; H, 4.55; N, 9.67%.

#### 4-(4-Formylphenyl)-1-methyl-3-phenylpyrrolo[2,3-*c*]quinoline (**7**)

To suspension of 4-chloro-1-methyl-3-phenylpyrrolo[2,3-*c*]quinoline **6** (0.45 g, 1.54 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.09 g, 0.077 mmol) in a mixture of toluene/EtOH (21/2 mL) under nitrogen were added K<sub>2</sub>CO<sub>3</sub> (0.23 g, 1.69 mmol) and phenylboronic acid (0.26 g, 1.7 mmol). The reaction mixture was refluxed for 24 h, and the cooled suspension was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL). The organic layer was washed with a saturated solution of NaCl (35 mL), and the combined organic extracts were dried over sodium sulfate, filtered, and evaporated under reduced pressure. The crude residue was triturated in ethanol. The resulting precipitate was filtered, washed with ethanol, and purified by column

chromatography on silica gel using dichloromethane as eluent gave the pure product **7** as white solid (0.30 g, 54%). m.p. 211–213 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.83 (s, 3H, CH<sub>3</sub>), 6.95–6.99 (m, 2H, C<sub>6</sub>H<sub>5</sub>), 7.05–7.09 (m, 3H, C<sub>6</sub>H<sub>5</sub>), 7.32 (s, 1H, H-2'), 7.48 (d, 2H, *J* = 8.10 Hz, H-3 and H-5), 7.59 (d, 2H, *J* = 8.10 Hz, H-2 and H-6), 7.67–7.71 (m, 2H, H-7' and H-8'), 8.29 (dd, *J* = 8.10 and 1.20 Hz, H-9), 8.57 (dd, *J* = 8.10 and 1.20 Hz, H-6). Anal. Calcd. for C<sub>25</sub>H<sub>18</sub>N<sub>2</sub>O: C, 82.85; H, 5.01; N, 7.73%. Found: C, 83.06; H, 4.88; N, 7.79%.

#### 4-{4-[(4-(2-Oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-3-phenyl-3*H*-pyrrolo[2,3-*c*]quinoline (1)

The pH of a solution of the aldehyde **7** (0.30 g, 0.83 mmol) and 4-(2-ketobenzimidazolin-1-yl)piperidine (0.22 g, 0.99 mmol) in 21 mL methanol was adjusted to 6 by the dropwise addition of acetic acid. Powered sodium cyanoborohydride (0.14 g, 2.28 mmol) was then added, and the resultant mixture was refluxed for 5 h. 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 methanol-chloroform (1/9) as eluent gave the crude product. This solid was then triturated with diethyl ether, filtered, washed with diethyl ether and dried under reduced pressure to give the compound **1** (0.40 g, 85%). Colourless prisms suitable for X-ray analysis were obtained by slow evaporation of the compound from a methanol-dichloromethane solution (2/8—v/v) at +20 °C. m.p. > 300 °C; IR  $\nu_{\max}$  (KBr)/cm<sup>-1</sup> 3131 (NH), 1697 (C=O), 1624 (C=N); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.83–1.88 (m, 2H, CH<sub>2</sub> pip.), 2.07–2.20 (m, 2H, CH<sub>2</sub> pip.), 2.43–2.58 (m, 2H, CH<sub>2</sub> pip.), 2.82 (s, 3H, CH<sub>3</sub>), 2.95–3.00 (m, 2H, CH<sub>2</sub> pip.), 3.49 (s, 2H, CH<sub>2</sub>N), 4.38–4.50 (m, 1H, CH pip.), 6.98–7.13 (m, 9H, C<sub>6</sub>H<sub>5</sub>, 3H benzimid. and H-2), 7.28–7.35 (m, 5H, H benzimid., H-2', H-3', H-5' and H-6'), 7.62–7.70 (m, 2H, H-7 and H-8), 8.32 (dd, *J* = 8.10 and 1.20 Hz, H-9), 8.56 (dd, *J* = 8.10 and 1.20 Hz, H-6), 10.07 (s, 1H, NH). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 13.9 (CH<sub>3</sub>), 27.2 (CH<sub>2</sub>), 48.7 (CH), 52.9 (NCH<sub>2</sub>), 60.0 (NCH<sub>2</sub>), 110.3 (C-2), 110.9 (C-2 and C-6 phenyl), 111.2 (C-1), 115.1 (C-3a), 117.7 (C-9a), 118.9 (C-3a benzimid), 122.1 (C-4 and C-7 benzimid), 122.2 (C-5 and C-6 benzimid), 122.6 (C-8), 124.5 (C-7a benzimid), 126.0 (C-4 phenyl), 127.5 (C-4 benzyl), 128.6 (C-2 and C-6 benzyl), 129.9 (C-9), 130.5 (C-3 and C-5 benzyl), 131.4 (C-6), 132.3 (C-3 and C-5 phenyl), 133.4 (C-1 benzyl), 134.1 (C-9b), 134.7 (C-1 phenyl), 139.3 (C-5a), 143.9 (C-7), 145.2 (CO), 155.5 (C-4); MALDI-TOF MS *m/z* [M+H]<sup>+</sup> Calcd for C<sub>37</sub>H<sub>34</sub>N<sub>5</sub>O: 564.276, Found:

564.284. Anal. Calcd. for C<sub>37</sub>H<sub>33</sub>N<sub>5</sub>O: C, 78.84; H, 5.90; N, 12.42%. Found: C, 79.08; H, 6.03; N, 5.97%.

#### X-ray Crystallographic Analysis

A colourless single crystal of the title compound **1** with dimensions of 0.12 mm × 0.10 mm × 0.08 mm was mounted on the top of a glass fiber. All of the data were collected with a R-Axis Rapid Rigaku MSC diffractometer using Cu K $\alpha$  radiation and a graphite monochromator. The cell parameters were then refined using the full set of collected reflections in the range 6.83° <  $\theta$  < 72.16°. All reflections were used for unit-cell refinement. A total of 74,565 reflections were collected, of which 5698 were independent ( $R_{\text{int}} = 0.0406$ ) and 4473 were observed with  $I > 2\sigma(I)$ . The structure was solved by direct methods and successive Fourier difference syntheses and refined on ( $F^2$ ) by full-matrix least-squares methods respectively with the SHELXS-97 and SHELXL-97 programs [15]. 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. All graphical contents have been performed using the OLEX2 interface [16].

The final refinement gave  $R = 0.0491$ ,  $wR = 0.1585$  ( $w = 1/[\sigma^2(F_o^2) + (0.1256P)^2 + 0.3505P]$ , where  $P = (F_o^2 + 2F_c^2)/3$ ),  $S = 1.010$ ,  $(\Delta/\sigma)_{\max} = 0.001$ ,  $(\Delta\rho)_{\max} = 0.307$  and  $(\Delta\rho)_{\min} = -0.215$  e/Å<sup>3</sup>. Crystallographic data (excluding structure factors) for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, No. CCDC-888296. 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: <http://www.ccdc.cam.ac.uk>.

Crystal data and structure refinement details are listed in Table 1. The selected bond lengths and bond angles are given in Table 2.

## Results and Discussion

### Synthesis

The synthesis of this new pyrrolo[2,3-*c*]quinoline derivative **1** is depicted in Scheme 1. The ethyl 4-methyl-3-(2-nitrophenyl)pyrrole-2-carboxylate **3** was synthesized using a Barton-Zard reaction [13]; the (*E*)-1-(2-nitrophenyl)-2-nitropropene **2** reacted with one equivalent of ethyl isocyanide previously anionized with one equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) leading to pyrrole **3** (Scheme 1) [14]. The preparation of *N*-aryl pyrrole **4** was obtained by

**Table 1** Crystal data and structure refinement

Empirical formula	C <sub>37</sub> H <sub>33</sub> N <sub>5</sub> O
Formula weight	563.68
Crystal system, space group	Orthorhombic, <i>Pbcn</i>
Unit cell dimensions	
<i>a</i> (Å)	30.198(2)
<i>b</i> (Å)	12.5097(11)
<i>c</i> (Å)	15.6648(13)
$\alpha$ (°)	90
$\beta$ (°)	90
$\gamma$ (°)	90
Volume (Å <sup>3</sup> )	5917.7(8)
<i>Z</i>	8
Density (Mg/m <sup>3</sup> )	1.265
Absorption coefficient (mm <sup>-1</sup> )	0.611
<i>F</i> (000)	2384
Crystal size (mm <sup>3</sup> )	0.12 × 0.10 × 0.08
Theta range for data collection (°)	6.83 to 72.16
Index ranges	−37 ≤ <i>h</i> ≤ 37 −13 ≤ <i>k</i> ≤ 15 −18 ≤ <i>l</i> ≤ 19
Reflections collected	74,565
Reflections unique	5698 [R (int) = 0.0406]
Completeness to theta = 72.16	97.5%
Data/restraints/parameters	5698/0/389
Max. and min. transmission	0.9528 and 0.9303
Refinement method	Full-matrix least-squares on <i>F</i> <sup>2</sup>
Goodness-of-fit on <i>F</i> <sup>2</sup>	1.010
Final <i>R</i> indices [ <i>I</i> > 2σ( <i>I</i> )]	<i>R</i> <sub>1</sub> = 0.0491 <i>wR</i> <sub>2</sub> = 0.1585
<i>R</i> indices (all data)	<i>R</i> <sub>1</sub> = 0.0607 <i>wR</i> <sub>2</sub> = 0.1709
Largest diff. peak and hole (e/Å <sup>-3</sup> )	0.307 and −0.215
CCDC No	888296

nucleophilic substitution of the ethyl pyrrole-2-carboxylate **3** with bromobenzene using potassium carbonate as the base and copper iodide as catalyst [17]. Reduction of the nitro moiety of **4** with iron in hot glacial acetic acid produced

the spontaneous ring closure onto the ester to afford the desired tricyclic pyrrolo[2,3-*c*]quinoline **5** through a one-pot reduction-cyclization step [8]. The lactam **5** was subsequently chlorodehydroxylated with phosphorous oxychloride, leading to the 4-chloroquinoline **6**. 4-(Pyrrolo[2,3-*c*]quinolin-4-yl)benzaldehyde **7** was easily prepared by a direct Suzuki–Miyaura cross-coupling reaction of 4-chloroquinoline **6** with 4-formylphenylboronic acid performed in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> as a catalyst, and in the presence of potassium carbonate used as the base [8–12]. The aldehyde **7** was then engaged in a reductive amination with NaBH<sub>3</sub>CN and the 4-(2-ketobenzimidazolin-1-yl)piperidine to give the substituted pyrroloquinoline **1**.

## Crystal Structure

The 3D spatial determination established by X-ray crystallography confirmed the structure of the title compound **1** in the solid state as anticipated on the basis of IR, MS, elemental analysis, <sup>1</sup>H and <sup>13</sup>C NMR data. The structure elucidation of compound **1**, unambiguously established by X-ray crystallography, makes it possible to validate the structures of our first three key intermediates in the synthesis of **1**; *i.e.*: the substituted pyrrole **3** through a Barton–Zard reaction, its *N*-arylation leading to compound **4**, and the key intermediate lactam **5**. The collection of crystallographic data on this pyrrolo[2,3-*c*]quinoline structure **1**, which shows promising antitumoral activities, should bring new interesting clues that will help in the step-by-step comprehension of the mechanism of action of this new class of cytotoxic agent. These crystallographic data could also be an interesting starting point in a future molecular modelling study.

The final compound crystallizes in the orthorhombic space group *Pbcn* with cell parameters *a* = 30.198(2) Å, *b* = 12.5097(11) Å, *c* = 15.6648(13) Å,  $\alpha$  = 90,  $\beta$  = 90,  $\gamma$  = 90, *V* = 5917.7(8) Å<sup>3</sup>, *Z* = 8, *M<sub>r</sub>* = 563.68, *D<sub>c</sub>* = 1.265 Mg/m<sup>3</sup>, *S* = 1.010,  $\mu$  = 0.611 mm<sup>-1</sup>, *F*(000) = 2384, the final *R* = 0.0491 and *wR*<sub>2</sub> = 0.1585 for 5698 observed reflections with (*I* > 2σ(*I*)). The molecular structure of the 4-[(4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)]

**Table 2** Selected bond lengths (Å), and bond angles (°)

Bond	Dist.	Bond	Dist.	Bond	Dist.
N(15)–C(16)	1.322(2)	N(7)–C(6)	1.436(2)	C(38)–O(39)	1.2336(19)
C(8)–N(7)	1.377(2)	C(31)–N(34)	1.466(2)	C(16)–C(21)	1.485(2)
C(11)–N(7)	1.387(2)	N(34)–C(38)	1.3836(19)	N(28)–C(29)	1.464(2)
C(9)–C(10)	1.434(2)	N(37)–C(38)	1.360(2)	N(28)–C(33)	1.4636(19)
Angle	(°)	Angle	(°)	Angle	(°)
N(28)–C(29)–C(30)	110.49(14)	C(11)–C(16)–C(21)–C(22)	47.1(2)	C(29)–C(30)–C(31)	110.14(14)
N(28)–C(33)–C(32)	111.64(13)	C(11)–N(7)–C(6)–C(5)	44.6(2)	C(33)–C(32)–C(31)	110.44(14)

piperidin-1-yl)benzyl]}-3-phenyl-3*H*-pyrrolo[2,3-*c*]quinoline **1** is depicted in Fig. 1, and the selected bond lengths and bond angles are listed in Table 2.

The fused pyrrolo[2,3-*c*]quinoline moiety is almost planar, and the maximum deviation from planarity is found for N(7) lying 0.102(2) Å from the plane defined by the heterotricyclic system. All atoms that constitute this system have a planar-trigonal configuration, i.e., they are  $sp^2$ -hybridized. The tricyclic system can be regarded as heteroaromatic: it contains 14  $p$ -electrons. In the pyrrole five-membered ring containing atom N(7), the intra-ring bond angles range from 105.85(15)° to 111.32(15)°; the N(7)–C(8) and N(7)–C(11) bond lengths are 1.377(2) and 1.387(3) Å, respectively, which indicates that the geometry around N(7) is normal for  $sp^2$  hybridization. Moreover, the C(9)–C(10) bond, noticed at 1.434(2) Å, is longer than the standard aromatic C–C bond [18] and is in agreement with the values observed in the 4-methyl-3*H*-pyrrolo[2,3-*c*]quinoline [19]. The C(1)–C(6) phenyl ring makes a dihedral angle of 57.93(5)° with the mean plane of the pyrrolo[2,3-*c*]quinoline moiety, and the C(21)–C(26) phenyl group at 4-position makes a dihedral angle of 49.15(4)° with the plane of the pyrroloquinoline ring. The torsion angles C(11)–C(16)–C(21)–C(22) and C(11)–N(7)–C(6)–C(5) are  $\pm 47.1(2)^\circ$  and  $\pm 44.6(2)^\circ$ , respectively. Presumably, the substituents on C(16) and N(7) in this derivative are turned apart for steric reasons.

The C(16)–N(15) double bond in the quinoline ring was noticed at 1.322(2) Å, as typically observed for  $C_{ar}=N$  bonds [17].

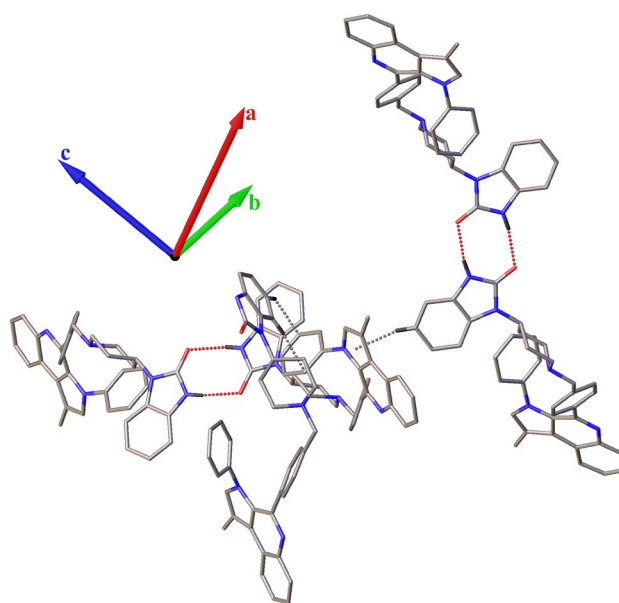
The piperidine ring has the chair conformation; the nitrogen atom N(28) and the carbon C(31) are displaced on either side from the least-squares plane C29–C30–C32–C33 by 0.691(2) and 0.651(2) Å, respectively. Moreover, the angles N(28)–C(29)–C(30) and N(28)–C(33)–C(32) are found in the same range 110.49(14) and 111.64(13)°. The 1,3-dihydrobenzimidazol-2-one ring system is almost planar, with the largest deviation being for atom O(39) [0.059(1) 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-1*H*-benzimidazol-1-yl compounds in the literature [10, 11].

Molecules of the title compound are linked by a double H-bonds between the O(39) and N(37) atoms of the imidazole rings to form dimers. The crystal cohesion is ensured by short Van der Waals contacts and C–H $\cdots\pi$  interactions in the others directions (Fig. 2).

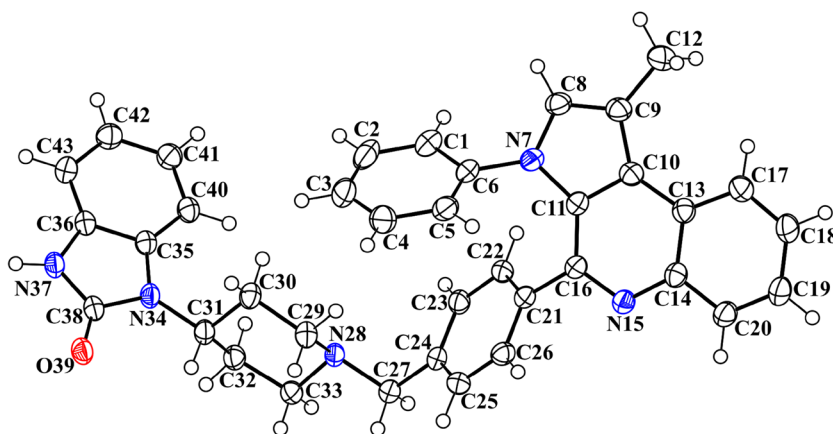
### Cytotoxicity in Leukemia Cell Lines

This new 4-{4-[(4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-3-phenyl-3*H*-pyrrolo[2,3-*c*]quinoline **1** was then tested in MTS assay for its *in vitro* anti-proliferative activity against two human myeloid leukaemia



**Fig. 2** Perspective view of the molecular packing of compound **1**. H atoms have been omitted for clarity except when they were involved in an intermolecular interaction

**Fig. 1** X-ray crystal structure of compound **1** with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level



cell lines (K562 and HL60). Against the HL60 human acute myeloblastic leukemia cell line, compound **1** exhibited potent cytotoxicity with an  $IC_{50}$  value of 1  $\mu$ M, while this quinoline **1** showed moderate antiproliferative activity against the K562 chronic myeloid leukemia cell line, i.e.  $IC_{50} = 16 \mu$ M.

## Conclusion

In this work, we have synthesized the new 4-{4-[(4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl)benzyl]}-3-phenyl-3*H*-pyrrolo[2,3-*c*]quinoline, an original compound which showed antileukemic activity in a submicromolar range on the human leukemic cell lines K562 and HL60 (myeloid cell lines). We report herein on the structural characterization of this new pyrrolo[2,3-*c*]quinoline 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 substituted pyrrolo[2,3-*c*]quinoline of medicinal interest. Moreover, solid-state data could be used to clarify the mechanism of action implicating this anti-leukemic compound through a possible interaction with different kinases targets.

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