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Synthesis, Crystal Structure and Anti-Leukemic Activity of (*E*)-Pyrrolo[1,2-*a*]quinoxalin-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

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Abstract: (*E*)-Pyrrolo[1,2-*a*]quinoxalin-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one was designed then synthesized using a multi-step pathway starting from commercially available 2-nitroaniline. Structure characterization of this original substituted pyrrolo[1,2-*a*]quinoxaline compound was achieved by using FT-IR, ^{1}H-NMR, ^{13}C-NMR, X-Ray and HRMS spectral analysis. This new pyrroloquinoxaline shows interesting cytotoxic potential against different human leukemia cell lines (MV4-11, K562, MOLM14 and Jurkat cells).

Keywords: pyrrolo[1,2-*a*]quinoxaline derivative; leukemia; antiproliferative activity

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1. Introduction

Among heterocyclic nitrogen derivatives that have attracted attention due to their broad profile of biological activities, the pyrrolo[1,2-*a*]quinoxaline moiety has shown wide interest for its various biological properties. [1,2]. Thus, many pyrrolo[1,2-*a*]quinoxaline compounds have been designed, synthesized and described as antipsychotic agents [3], antiviral agents [4], adenosine receptor modulators [5], antituberculosis agents [6,7], antiparasitic [8–15] and anticancer compounds [16–22]. However, despite the recent and promising development of targeted therapies, there is still a need to discover new cytotoxic molecules for the treatment of human cancers.

We previously published a series of new pyrrolo[1,2-*a*]quinoxaline derivatives endowed with promising pharmacological activity towards human leukemia cells [16–21]. In this context, and as an extension of our research work on the development and assessment of new antiproliferative heterocyclic derivatives, we decided to further modulate and substitute our heterocyclic pyrrolo[1,2-a]quinoxaline pharmacophore. DYT-1, a substituted quinoline, was recently screened from a chemical library and identified as a hit compound active against several leukemia [23,24]. Consequently, taking into account the experience of our lab in the domain of the synthesis of new bioactive nitrogen heterocyclic compounds based on this pyrrolo[1,2-a]quinoxaline heterocyclic scaffold, we report herein the design, synthesis and structural identification of (*E*)-pyrrolo[1,2-*a*]quinoxalin-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (JG1679) that could be considered a new structural

bioisostere analogue of the previously described bioactive quinoline DYT-1 compound (Figure 1). This novel substituted pyrrolo[1,2-*a*]quinoxaline derivative JG1679 is then tested against four leukemia cell lines, namely, MV4-11, K562, Jurkat and MOLM14.

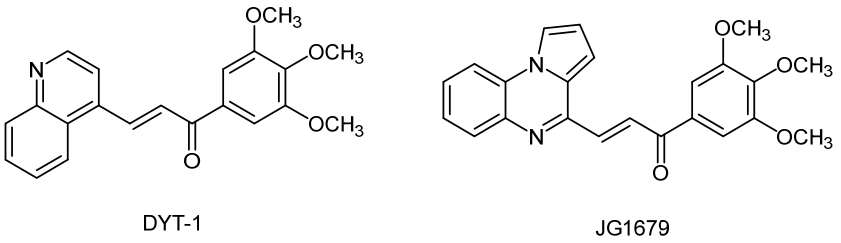
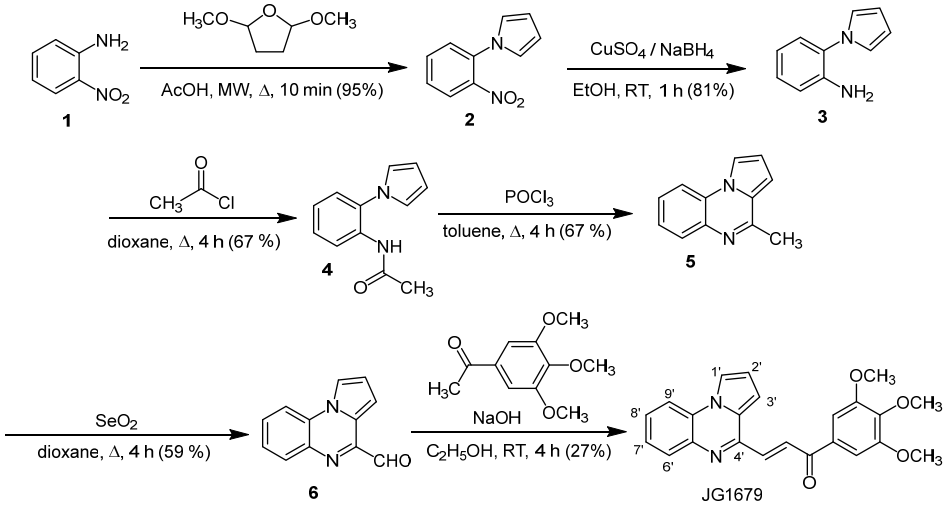


Figure 1. Chemical structures of compounds DYT-1 and JG1679.

2. Results and Discussion

2.1. Synthesis of (E)-Pyrrolo[1,2-a]quinoxalin-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (JG1679)

The preparation of (*E*)-pyrrolo[1,2-*a*]quinoxalin-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (JG1679) has been accomplished in six steps starting from the commercially available 2-nitroaniline **1** according to the sequence depicted in Scheme 1. The Clauson-Kaas reaction of commercially available 2-nitroaniline **1** with 2,5-dimethoxytetrahydrofuran (DMTHF) in refluxing acetic acid under microwave conditions gave phenylpyrrole **2**, which was then reduced using a $NaBH_4$-$CuSO_4$ treatment to provide 1-(2-aminophenyl)pyrrole **3**. The reaction of acetyl chloride with **3** led to acetamide **4**. 4-methylpyrrolo[1,2-*a*]quinoxaline **5** was prepared via the cyclisation of this amide **4** in refluxing phosphorus oxychloride according to the Bischler–Napieralski reaction. Then, we synthesized pyrrolo[1,2-*a*]quinoxaline-4-carboxaldehyde **6** via the oxidation of **5** with SeO_2 in refluxing dioxane. Finally, aldehyde **6** reacted with 3′,4′,5′-trimethoxyacetophenone under the presence of an aqueous NaOH solution, resulting in the synthesis of compound JG1679 as a single *E* isomer [23]. Thus, a coupling constant value of 15.15 Hz was in favor of a *trans* configuration in the double bond. The structure of this original synthesized pyrroloquinoxaline derivative JG1679 was then corroborated by FTIR, $^1H/^{13}C$-NMR, X-ray and ESI-MS experiments (see Supplementary Materials, Figures S1–S4). The 3D structural determination of this new substituted pyrrolo[1,2-*a*]quinoxaline JG1679 was established by X-ray crystallography (Figure 2) [25], and the confirmation of the structure being in the solid state was anticipated on the basis of NMR analysis.



Scheme 1. Synthesis of (*E*)-Pyrrolo[1,2-*a*]quinoxalin-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (JG1679).

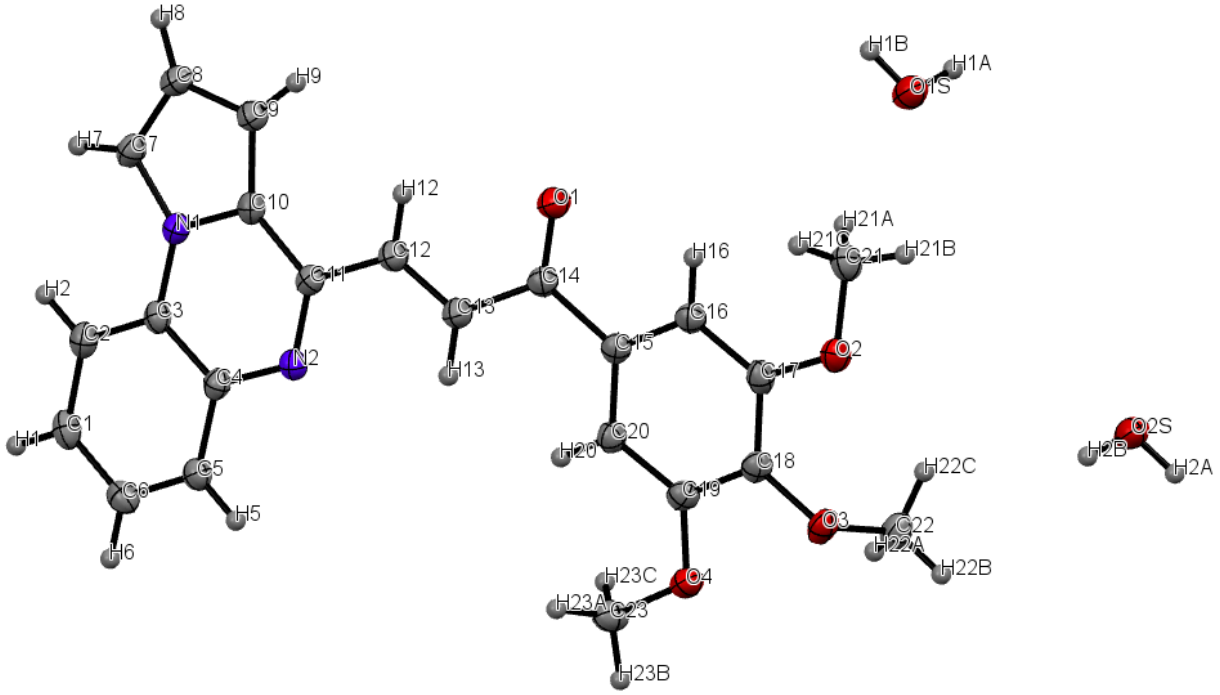


Figure 2. The ORTEP (Oak Ridge Thermal Ellipsoid Plot) drawing of the 1(*E*)-Pyrrolo[1,2-*a*]quinoxalin-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (JG1679) with thermal ellipsoids at 30% level.

2.2. Cytotoxic Activity

The cytotoxic activity of this new (*E*)-pyrrolo[1,2-*a*]quinoxalin-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one JG1679 was evaluated against the following human leukemia K562, MV4-11, Jurkat and MOLM14 cell lines with the MTS assay [16,17] (Table 1). The IC_{50} values of quinoline DYT-1, used as reference a drug, are reported in Table 1 as previously described [23,24]. Against the human myeloid leukemia cell line K562, our new pyrroloquinoxaline derivative JG1679 displayed none antiproliferative activity (IC_{50} > 50 µM), while this new compound inhibited the growth of MV4-11 human myeloid leukemia cells with an IC_{50} value of 1.7 µM. Moreover, the IC_{50} of JG1679 was noticed to be superior to 2 µM against the human MOLM14 acute myeloid leukemia cell line. Against the T-acute lymphoblastic leukemia Jurkat cell line, the biological result of compound JG1679 exhibited potent cytotoxicity with an IC_{50} value of 3.0 µM.

Table 1. In vitro activity of compounds JG1679 and DYT-1 on K562, MV4-11, Jurkat, MOLM14 and HEK293 cells.

Compound	IC_{50} Values (µM) [a]				
	K562	**MV4-11**	**Jurkat**	**MOLM14**	**HEK293**
JG1679	>50	1.7 ± 0.3	3.0 ± 0.5	>2	31.2 ± 0.3
DYT-1	6.2 ± 0.5 [23,24]	n.d. [b]	7.9 ± 0.4 [23,24]	n.d. [b]	n.d. [b]

[a] The IC_{50} (µM) values correspond to the mean ± standard deviation from 3 independent experiments. [b] n.d.: not done.

In addition, (*E*)-pyrrolo[1,2-*a*]quinoxalin-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one JG1679 was also tested against human epithelial cell line HEK293 to evaluate its cytotoxicity on normal cells. Thus, compound JG1679 showed a low cytotoxicity against this HEK293 cell line (IC_{50} = 31.2 µM). Index of selectivity (IS) was defined as the ratio of the IC_{50} value on normal cell line HEK293 to the IC_{50} value on the different leukemia cell lines. Derivative JG1679 showed a promising selectivity towards the MV4-11 cell line

(IS = 18.35) and also towards the lymphoblastic leukemia Jurkat cell line with a calculated index of selectivity of 10.4.

3. Materials and Methods

Commercial reagents were used as received without additional purification. Melting points were determined with an SM-LUX-POL Leitz hot-stage microscope (Leitz GMBH, Midland, ON, USA) and are uncorrected. IR spectra were recorded on a NICOLET 380FT-IR spectrophotometer (Thermo Electron Scientific Instruments LLC, Madison, WI, USA). NMR spectra were recorded with tetramethylsilane as an internal standard using a BRUKER AVANCE 300 spectrometer (Bruker BioSpin, Wissembourg, France). Splitting patterns were reported as follows: s = singlet; bs = broad singlet; d = doublet; t = triplet; q = quartet; dd = double doublet; ddd = double double doublet; dt = double triplet; m = multiplet. 2D-NMR experiments were used for resonance assignments. Analytical TLC was carried out on 0.25 precoated silica gel plates (POLYGRAM SIL G/UV254) and the 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 (Bruker Daltonics, Bremen, Germany) [13,14].

3.1. (E)-Pyrrolo[1,2-a]quinoxalin-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (JG1679)

To a solution of pyrrolo[1,2-*a*]quinoxaline-4-carboxaldehyde **5** (1.7 mmol) and 3′,4′,5′-trimethoxyacetophenone (1.7 mmol) in ethanol (7 mL) at 0 °C, a 40% aqueous solution of NaOH (0.8 mL) was added dropwise and stirred at this temperature for 30 min. The reaction mixture was then stirred at room temperature for 4 h, the formed solid was filtered, washed with water and then ethanol and dried to give the crude product. Column chromatography of this precipitate on silica gel using ethyl acetate-cyclohexane (3/7) as an eluent gave the pure product JG1679 (27%). Yellow crystals, m.p. 196–198 °C; IR (KBr) 1656 (CO), 1607 (C=N). ^{1}H-NMR (δ, ppm, $CDCl_3$, 300 MHz): 8.38 (d, 1H, *J* = 15.15 Hz, HC=), 8.18 (d, 1H, *J* = 15.15 Hz, =CH), 8.07 (dd, 1H, *J* = 8.05 and 1.30 Hz, H-9′), 8.03 (dd, 1H, *J* = 2.80 and 1.10 Hz, H-1′), 7.92 (dd, 1H, *J* = 8.05 and 1.30 Hz, H-6′), 7.59 (ddd, 1H, *J* = 8.05, 7.60 and 1.30 Hz, H-8′), 7.47 (ddd, 1H, *J* = 8.05, 7.60 and 1.30 Hz, H-7′), 7.44 (s, 2H, 2 CH_{phenyl}), 7.20 (dd, 1H, *J* = 4.05 and 1.10 Hz, H-3′), 6.99 (dd, 1H, *J* = 4.05 and 2.80 Hz, H-2′), 4.00 (s, 6H, $2OCH_3$), 3.98 (s, 3H, OCH_3). ^{13}C-NMR (δ, ppm, $CDCl_3$, 75 MHz): 188.7 (C=O), 153.2 (C-3_{phenyl} and C-5_{phenyl}), 147.8 (C-4′), 143.1 (C-4_{phenyl}), 137.9 (HC=), 135.9 (C-5a), 133.0 (C-7′), 130.4 (C-8′), 128.3 (C-6′), 128.0 (C-9′), 127.6 (C-3a), 126.4 (C-1_{phenyl}), 125.5 (C-9a), 114.8 (=CH), 114.3 (C-1′), 113.8 (C-2′), 106.5 (C-2_{phenyl} and C-6_{phenyl}), 106.2 (C-3′), 61.0 (OCH_3), 56.5 ($2OCH_3$). HR-MS *m*/*z* $[M+H]^+$ Calcd for $C_{23}H_{21}N_2O_4$: 389.1501, Found: 389.1498.

3.2. X-ray Data

The structure of compound JG1679 was established using X-ray crystallography (Figure 2). The yellow single crystal of JG1679 was obtained by slow evaporation from a methanol/chloroform solution (*v*/*v*: 15/85): monoclinic, space group C c, a = 30.4488(6) Å, b = 4.8817(1) Å, c = 14.3011(3) Å, α = 90°, β = 109.613(1)°, γ = 90°, V = 2002.41(7)Å^3, Z = 4, δ(calcd) = 1.408 Mg.m^{-3}, FW = 424.44 for $C_{23}H_{20}N_2O_4.2H_2O$, F(000) = 896.0. Full crystallographic results were deposited at the Cambridge Crystallographic Data Centre (CCDC-2237246), UK, as shown in the Supplementary X-ray Crystallographic Data [25]. The data were corrected for Lorentz and polarization effects and for empirical absorption correction [26]. The structure was solved by direct methods Shelx 2013 [26] and refined using Shelx 2013 [27] suite of programs.

3.3. Cell Culture

All leukemic cell lines (MV4-11, Jurkat, MOLM-14, K562) were cultured in Roswell Park Memorial Institute (RPMI) 1640 1X Glutamax (Gibco™, Thermo Fisher Scientific,

Villebon-sur-yvette, France), supplemented with 10% fetal calf serum (FCS), 50 U/mL penicillin and 50 µg/mL streptomycin (Gibco™, Thermo Fisher Scientific, Villebon-sur-yvette, France). Cells were cultured with vehicle or the different compounds dissolved in dimethyl sulfoxide (0.1%) at 37 °C in a fully humidified atmosphere (37 °C, 5% CO_2) in a CO_2-regulated incubator (Jouan, Saint-Nazaire, France).

3.4. Cytotoxic Activity

Cell proliferation assays were performed using MTS tetrazolium (Cell Titer96 Aqueous; Promega, Charbonnières-les-Bains, France) on the human leukemic cell lines K562, MV4-11, Jurkat and MOLM14 as previously described by our team [16,17,21]. Cells (10^5) were plated in quadruplicate into microtiter-plate wells in 100 µL of culture medium with various doses of compounds (1; 5; 10; 20; 50 µM). After 3 h of incubation of 20 µL of MTS, plates were read in a microplate autoreader (Imark Biorad, Marnes-la-Coquette, France) at a wavelength of 490 nm. The MTT proliferation test on the epithelial cell line HEK293 was performed as previously described [28]. The 50% inhibiting concentrations (IC_{50}) were determined by linear regression analysis.

4. Conclusions

By taking into account our previous research using the valuable and biological active pyrrolo[1,2-*a*]quinoxaline scaffold, we synthesized here a new (*E*)-pyrrolo[1,2-*a*]quinoxalin-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one JG1679 and then evaluated its antileukemic activity on different human leukemic cell lines, such as MV4-11, K562, Jurkat and MOLM14. This novel pyrrolo[1,2-*a*]quinoxaline JG1679 exhibited promising antileukemia properties on the MV4-11 and Jurkat human leukemia cell lines, meaning it could become an interesting candidate for further pharmacomodulations and biological investigations.

Supplementary Materials: FTIR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of title compound **9** are available online. Figure S1: ^{1}H-NMR spectrum of compound JG1679. Figure S2: ^{13}C-NMR spectrum of compound JG1679. Figure S3: FT-IR spectrum of compound JG1679. Figure S4: HRMS data for compound JG1679.

Author Contributions: J.G. and S.M. conducted the synthesis and prepared and revised the manuscript; S.S. and N.F. carried out the experiments; S.A.-R. helped in the analysis of the compounds; V.B. and V.D. conducted the in vitro tests; N.P. carried out the crystallographic experiments. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article [and/or] its Supplementary Materials.

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