Second Polymorph of 7-Methoxy-4-[(*E*)-oct-1-enyl]pyrrolo[1,2-*a*]quinoxaline

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A second polymorphic form of the antileishmanial 7-methoxy-4-[(*E*)-oct-1-enyl]pyrrolo[1,2-*a*]quinoxaline was established. This second form crystallizes in the triclinic space group $P\bar{1}$. In addition to the previous results, these new data could be further used to clarify the mechanism of action, implicating this antileishmanial synthetic compound.

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Leishmaniasis is a parasitic disease caused by hemoflagellate, *Leishmania* spp. The parasite is transmitted by the bite of an infected female phlebotomine sandfly. The disease currently threatens about 350 million women, men and children in 88 countries around the world, with about 2 million affected annually. The current treatment of the disease is based on a limited number of chemotherapeutic agents, which are rapidly becoming ineffective, and are characterized by high toxicity and cost.¹

Following our search for antileishmanial compounds, we previously identified a series of 4-(*E*)-alkenyl-pyrrolo[1,2-*a*]quinoxaline derivatives presenting antiparasitic activity *in vitro* upon the *Leishmania amazonensis* and *Leishmania infantum* strains.^{2,3} Concerning these bioactive series, we recently reported a first polymorph of 7-methoxy-4-[(*E*)-oct-1-enyl]pyrrolo[1,2-*a*]quinoxaline ($IC_{50} = 2$ and $1.2 \mu M$ on *Leishmania amazonensis*, and *Leishmania infantum*, respectively), which crystallizes in space group $P2_1/c$.⁴

We report herein a second polymorphic form of this 7-methoxy-4-[(*E*)-oct-1-enyl]pyrrolo[1,2-*a*]quinoxaline (Fig. 1). In addition to previous crystallographic data, the present crystal structure determination could now be used to clarify the mechanism of the action implicating this antileishmanial synthetic compound, and could also be useful for designing new derivatives through further pharmacomodulations.

Pale-yellow crystals suitable for X-ray analysis were obtained by slow crystallization from ethanol at +4°C. The molecular

structure of 7-methoxy-4-[(*E*)-oct-1-enyl]pyrrolo[1,2-*a*]quinoxaline is depicted in Fig. 2. This second form crystallizes in the triclinic space group $P\bar{1}$. Crystal and experimental data are given in Table 1. Due to the small crystal size of our compound, the structure data were collected with a theta maximum of 50.42°.

Table 1 Crystal and experimental data

Chemical formula: C ₂₀ H ₂₄ N ₂ O
Formula weight: 308.41
<i>T</i> = 193(2)K
Crystal system: triclinic
Space group: $P\bar{1}$
<i>a</i> = 4.1683(4) Å
<i>b</i> = 16.7997(14) Å
<i>c</i> = 14.350(3) Å
α = 81.776(6)°
β = 85.879(7)°
γ = 83.021(6)°
<i>V</i> = 985.6(2) Å ³
<i>Z</i> = 2
<i>D_x</i> = 1.039 Mg/m ³
Radiation: Cu K α (λ = 1.54180 Å)
<i>F</i> (0 0 0) = 332
Crystal size = 0.15 × 0.02 × 0.02 mm ³
No. of reflections collected = 6945
No. of independent reflections = 1956
No. of reflections used [<i>I</i> > 2σ(<i>I</i>)] = 1405
θ range for data collection: 7.66 to 50.42°
Data/Restraints/Parameters = 1956/0/211
Goodness-of-fit = 1.097
<i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)] : <i>R</i> 1 = 0.0988, <i>wR</i> 2 = 0.2688
<i>R</i> indices (all data) : <i>R</i> 1 = 0.1247, <i>wR</i> 2 = 0.2848
(Δσ) _{max} = 0.002
(Δρ) _{max} = 0.465 Å ⁻³
(Δρ) _{min} = -0.254 Å ⁻³
Measurement: R-Axis Rapid ⁵
Structure determination: SHELXS-97 ⁶
Refinement: SHELXL-97 ⁷
CCDC deposition number: 711851

Fig. 1 Chemical structure of 7-methoxy-4-[(*E*)-oct-1-enyl]pyrrolo[1,2-*a*]quinoxaline.

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Fig. 2 View of the crystal structure of 7-methoxy-4-[(*E*)-oct-1-enyl]pyrrolo[1,2-*a*]quinoxaline with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

The 3D structure of the 4-octenylpyrrolo[1,2-*a*]quinoxaline confirmed the (*E*)-configuration of the α -unsaturated octenyl chain in the solid state. The (*E*) C(7)–C(8) double bond was noticed at 1.320(9) Å in the same range as that observed at 1.308(3) Å in the first polymorph.

The pyrroloquinoxaline moiety is almost planar; a derivation of the C(17) atom was noticed at $-0.0265(6)$ Å from the plane defined by the tricyclic system. The C(8) atom was also found in the same plane as the pyrrolo[1,2-*a*]quinoxaline nucleus. Compared with the monoclinic form, the (*E*)-octenyl chain in this triclinic form was not found to be planar; only the C(1)–C(7) length was planar with a derivation of the C(5) atom noticed at $0.0670(6)$ Å from the least-squares plane defined by the other atoms. The angle between the least-squares planes, defined by the C(8)–pyrroloquinoxaline plane and the C(1)–C(7) chain length, was approximatively $31.13(3)^\circ$.

Moreover, the C(1)–C(7) length of the octenyl chain adopts a quite regular conformation, described by the torsion angles C(1)–C(2)–C(3)–C(4), C(2)–C(3)–C(4)–C(5), C(3)–C(4)–C(5)–C(6), C(4)–C(5)–C(6)–C(7) and C(6)–C(7)–C(8)–C(9), which are $177.9(7)$, $-177.5(6)$, $176.0(6)$, $-178.4(6)$ and $178.2(7)^\circ$, respectively. However, the C(5)–C(6)–C(7)–C(8) angle was noticed at $-125.7(8)^\circ$.

The C_{sp^3} – C_{sp^3} bond lengths in the octenyl chain range from 1.507(9) to 1.527(11) Å, while the C_{sp^3} – C_{sp^2} bond distance was observed at 1.495(9) Å.

Molecular packing inspections have shown that the structure contains a channel shape void along the *a*-axis and around 0.15, 0.5, 0.0 (fractional coordinates) with a volume of about 173 Å³. We could suppose that some solvent was occupying the area before solvent removal.

The crystal-structure cohesion is partially ensured by the

Fig. 3 Ring-stacking interactions in the crystal of 7-methoxy-4-[(*E*)-oct-1-enyl]pyrrolo[1,2-*a*]quinoxaline.

formation of π -stacked polymeric units in the crystal packing. Hence, the distances of these intermolecular π – π interactions (ring A...ring B', then ring A'...ring B'') were observed with values ranging from 3.55 to 3.58 Å (Fig. 3). For the interactions shown, rings A, B and C belong to the molecule at $x-1, y, z$, rings A', B' and C' to the molecule at x, y, z , and rings A'', B'' and C'' to the one at $x+1, y, z$.

Moreover, the inter-pyrrolo[1,2-*a*]quinoxaline contacts are of the van der Waals variety.

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