



*Dedicated to Prof. Ion Grosu
on the occasion of his 70th anniversary*

CRYSTAL STRUCTURE AND HIRSHFELD SURFACE ANALYSIS OF (Z)-4-((5-ISOPROPYL-3,8-DIMETHYLAZULEN-1-YL)METHYLENE)-2-PHENYLOXAZOL-5(4H)-ONE^{**/**}

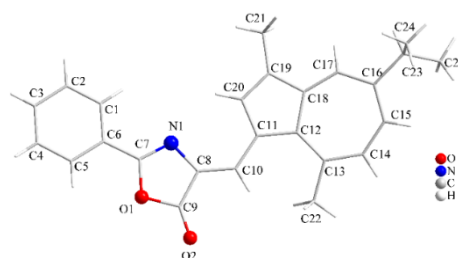
Mihai RĂDUCĂ,^{a,b} Marcel Mirel POPA,^a Mihaela CRISTEA,^{a,*} Alexandru C. RAZUS^a and Florea DUMITRASCU^a

^a“C. D. Nenitescu” Institute of Organic and Supramolecular Chemistry, Roumanian Academy, 202 B, Splaiul Independentei, 060023 Bucharest, Roumania

^bInorganic Chemistry Department, Faculty of Chemistry, University of Bucharest, Regina Elisabeta Blvd., 4-12, 030018 Bucharest, Roumania

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The structure of the title compound, *i.e.*, (Z)-4-((5-isopropyl-3,8-dimethylazulen-1-yl)methylene)-2-phenyloxazol-5(4H)-one (**1**) has been solved by single-crystal X-ray diffraction. Compound **1** was obtained in good yield (66%) following the Erlenmeyer—Plöchl synthesis, by the condensation of 5-isopropyl-3,8-dimethylazulene-1-carbaldehyde (**a**) with hippuric acid (**b**). The packing diagram of the pseudo planar compound **1** exhibits π - π interactions between neighboring molecules with distances in the range 3.337–3.351 Å. Hirshfeld surface analysis and energy frameworks was performed to determine the relevant interactions and their nature within the crystal network which is dominated by dispersive forces.



INTRODUCTION

Due to their promising applications as chemically modified electrodes with complexation properties^{1–3} and chemosensors for detection of heavy metal ions,^{4–8} the interest for the study of the 1-vinylazulenes with different substituents at the C=C double bond is legitimate.^{9,10} The synthesis and the properties of this class of push-pull compounds

were described by our research group in previously published papers.^{11–15}

Although the naturally occurring guaiazulene¹⁶ (*i.e.* 7-isopropyl-1,4-dimethylazulene) has been clinically used as an anti-inflammatory and anti-ulcer agent, its applications in other fields are limited.

In the previous papers^{17–21} there have been reported the syntheses, the molecular and crystal structures, the

* Corresponding author: mihcris2012@yahoo.ro

** This paper is dedicated to the memory of Dr. Liviu Birzan.

*** Supplementary information on <https://www.icf.ro/rrch/> or <https://revroum.lew.ro>

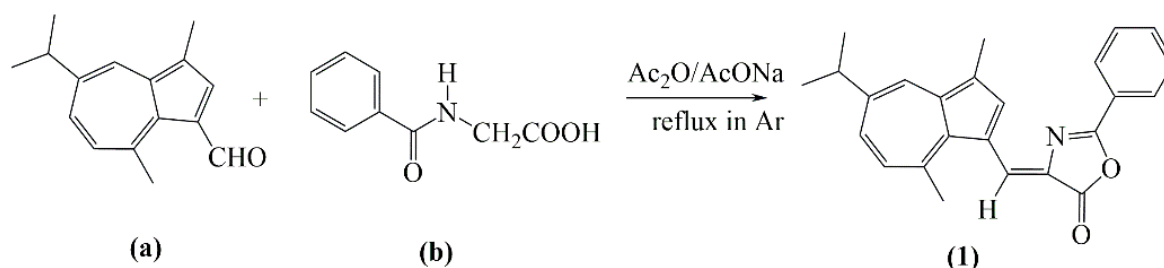
spectroscopic and characteristic chemical properties, as well as the electrochemical behavior of the conjugated π -electron systems with large dipole moment, which possess an azulene-1-yl,^{22–24} a 3-(methoxycarbonyl)azulene-1-yl,²⁵ or a 3-guaiazulene-1-yl (*i.e.* 5-isopropyl-3,8-dimethylazulene-1-yl)^{26–30} group.

Hence, we continue the investigation of the molecular structure of the previously synthesized 1-vinylazulene with oxazolonic ring, *i.e.* (*Z*)-4-((5-isopropyl-3,8-dimethylazulene-1-yl)methylene)-2-phenyloxazol-5(*H*)-one (**1**). In this paper the features of the crystal structure of the title compound are described and Hirshfeld analysis is carried out by comparing the features of compound **1** with its analogue *ZIFSEQ* structure previously reported.³¹

RESULTS AND DISCUSSION

The synthesis of compound **1** (Scheme 1) and the proposed reaction mechanism were previously described in literature.¹⁵

The compound **1** was obtained in good yield (66%) by the condensation of 5-isopropyl-3,8-dimethylazulene-1-carbaldehyde (**a**) with hippuric acid (**b**), at reflux, under inert atmosphere (Ar), in Erlenmeyer–Plöchl reaction conditions.³² The raw material, 5-isopropyl-3,8-dimethylazulene-1-carbaldehyde (**a**), was synthesized using the Vilsmeier procedure.^{33,34} Acetic anhydride was used as solvent and dehydrating agent and the AcONa as catalyst. Suitable crystals of **1** for single crystal X-ray diffraction measurement have been obtained by slow evaporation of the solvent from a solution with chloroform (Fig. 1).



Scheme 1 – Reaction scheme of compound **1** obtained from 5-isopropyl-3,8-dimethylazulene-1-carbaldehyde (**a**) and hippuric acid (**b**).

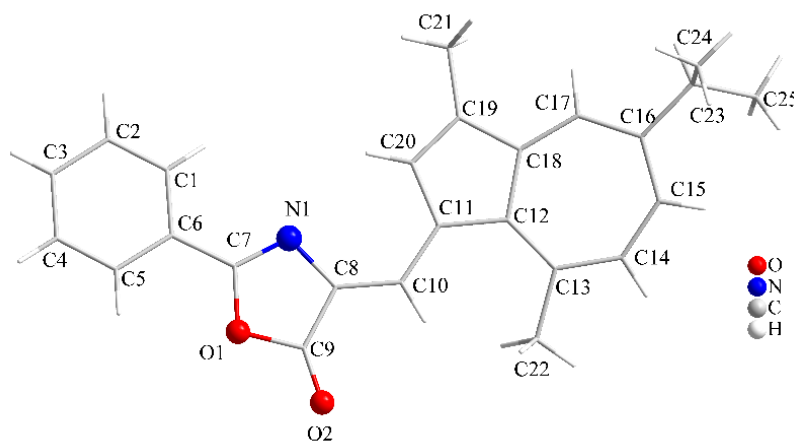


Fig. 1 – Crystal structure of compound **1** with the numbering scheme.

Compound **1** crystallizes in triclinic crystal system, *P-1* space group (Table 1). The alkene bond length is C8–C10 = 1.357(2) Å.³⁵ In the crystal packing, between adjacent molecules, π - π interactions are established between fivefold heterocycle and azulene moieties having the average distances 3.337–3.351 Å and 3.403 Å between centroids, respectively (Fig. 2).^{36,37} Similar interactions have been observed and described

previously for a related compound, *i.e.* *ZIFSEQ*, featuring methyl groups instead of isopropyl.³¹ The dihedral angle between the terminal cycles is influenced by the substituent present to C16 position. In this case the substituent is isopropyl and the angle is 20.8°, four times bigger compared to the similar compound with methyl moiety, 4.2°. ³¹ This arrangement generates a slightly bended, pseudo planar molecule.

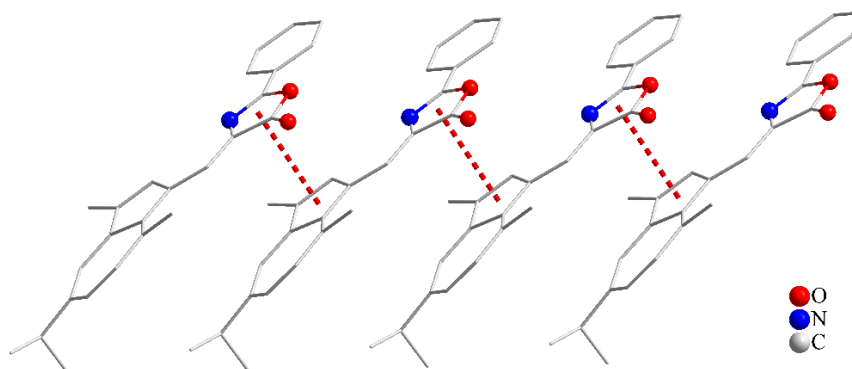


Fig. 2 – View of the π - π interactions established between subsequent molecules of **1**. Hydrogen atoms are not depicted.

MATERIALS AND METHODS

X-ray diffraction measurement was performed on a Rigaku XtaLAB Synergy-S diffractometer operating with Mo-K α ($\lambda = 0.71073$ Å) micro-focus sealed X-ray tube. The crystal was kept at 293(2) K during data collection. Using Olex2,³⁸ the structure was solved with the SHELXS³⁹ structure solution program using Direct Methods and refined with the SHELXL⁴⁰ refinement package using Least Squares

minimization. The non-H atoms were refined with anisotropic displacement parameters. A summary of the crystallographic data and the structure refinement are given in Table 1. Deposition number for **1** (2367271) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Table 1

Crystallographic data and structure refinement for compound **1**.

Compound	1
Chemical formula	C ₂₅ H ₂₃ NO ₂
M (g mol ⁻¹)	369.44
Temperature, (K)	293(2)
Wavelength, (Å)	0.71073
Crystal system	<i>Triclinic</i>
Space group	<i>P-1</i>
<i>a</i> (Å)	5.5365(2)
<i>b</i> (Å)	13.2732(5)
<i>c</i> (Å)	14.8476(6)
<i>a</i> (°)	65.453(4)
<i>b</i> (°)	79.559(3)
<i>g</i> (°)	83.058(3)
<i>V</i> (Å ³)	974.80(7)
<i>Z</i>	2
ρ_c (g cm ⁻³)	1.259
μ (mm ⁻¹)	0.079
<i>F</i> (000)	392
GOF	1.095
Final <i>R</i> ₁ , <i>wR</i> ₂ [<i>I</i> > 2 σ (<i>I</i>)]	0.0526, 0.1546
<i>R</i> ₁ , <i>wR</i> ₂ (all data)	0.0716, 0.1680
<i>D</i> _{Tmin} / <i>D</i> _{Tmax} (e Å ⁻³)	0.26, -0.26

Hirshfeld Surface (HF) was generated for compound **1** (Fig. 3) using CrystalExplorer v.21.^{41,42}

The HF presents red spots for the O \cdots H contacts implied in the formation of the corrugated layers formed by anti-parallel bonded molecules held together by H \cdots H contacts (Figs. 4a, b). These layers are bonded by CH₃ \cdots C=O (white spots on the face of

the HF) and by π \cdots π interactions represented as complementarity zones in shapeindex mode⁴² (Fig. 4c) between the oxazolone ring and the 5-membered ring in the azulene moiety (*d*_{cg \cdots cg}, 3.403 Å) leading to the 3D supramolecular network. Also, the compound **1** presents π \cdots π contacts (Fig. 4c) between two antiparallel phenyl-oxazolones (*d*_{cg \cdots cg}, 3.885 Å).

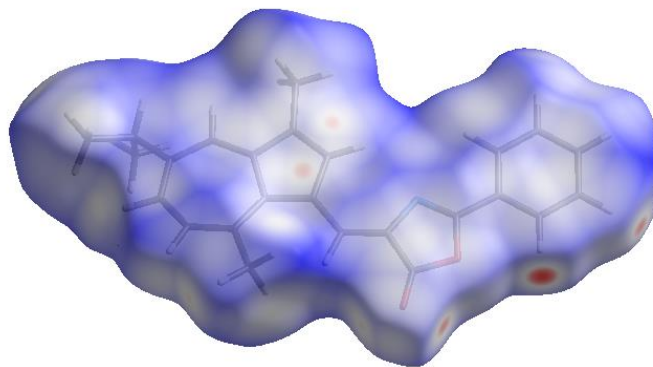


Fig. 3 – Hirshfeld Surface of compound **1** represented in d_{norm} mode⁴¹ (contacts are presented as a function of the sum of the van der Waals radii of the implied atoms: red-shorter, white – sum of the vdW radii, blue – greater than the sum of the vdW radii).

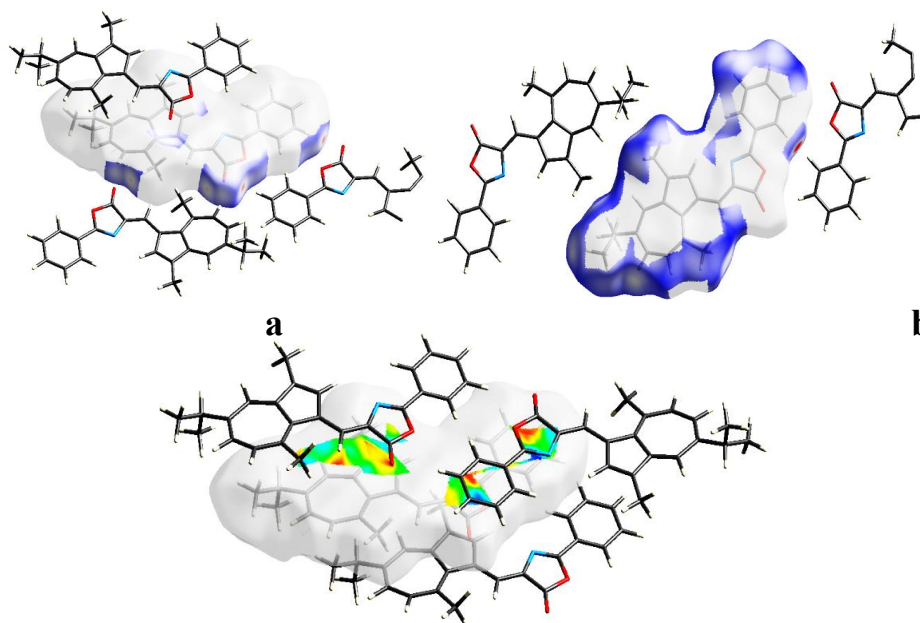


Fig. 4 – Hirshfeld Surface of compound **1** presenting: (a) O \cdots H contacts in d_{norm} (b) H \cdots H contacts in d_{norm} mode (c) C \cdots C contacts in shapeindex mode.

As a difference, the analogue compound **ZIFSEQ**³¹ forms corrugated layers in a similar way, but with only one O \cdots H (depicted in the corresponding HF-See Supplementary Material) and the hydrophobic part of the azulene oriented in similar manner but with weaker H \cdots H contacts. The H \cdots H contacts are formed in **ZIFSEQ** between the layers together with $\pi\cdots\pi$

interactions. This is nicely observed from the fingerprint plots of **1** and **ZIFSEQ** (56.2% vs. 52.3% H \cdots H contacts). The contributions of the supramolecular interactions are similar in the two compounds inferring their structural similarity (Fig. 5). (For direct comparison between the two compounds see Supplementary Material).

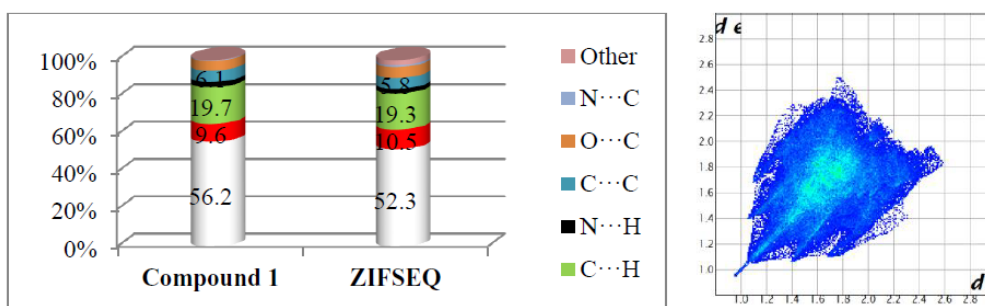


Fig. 5 – Percentage interactions in compounds **1** and **ZIFSEQ** extracted from the fingerprint plot (right: finger print plot of **1**).

One interesting thing is that Fingerprint of **ZIFSEQ** presents $N\cdots C$ contacts compared to **1** and a larger percentage of $C\cdots C$ bonds these two might suggest a stronger π -interaction between the oxazolone ring and the azulene 7-membered ring on

both faces of the molecule (3.5 to 3.7 Å).

The energy frameworks^{43,44} for **1** (Fig. 6) present the electrostatic forces within the layer which are higher than for **ZIFSEQ** due to more $O\cdots H$ contacts (see Supplementary Material).

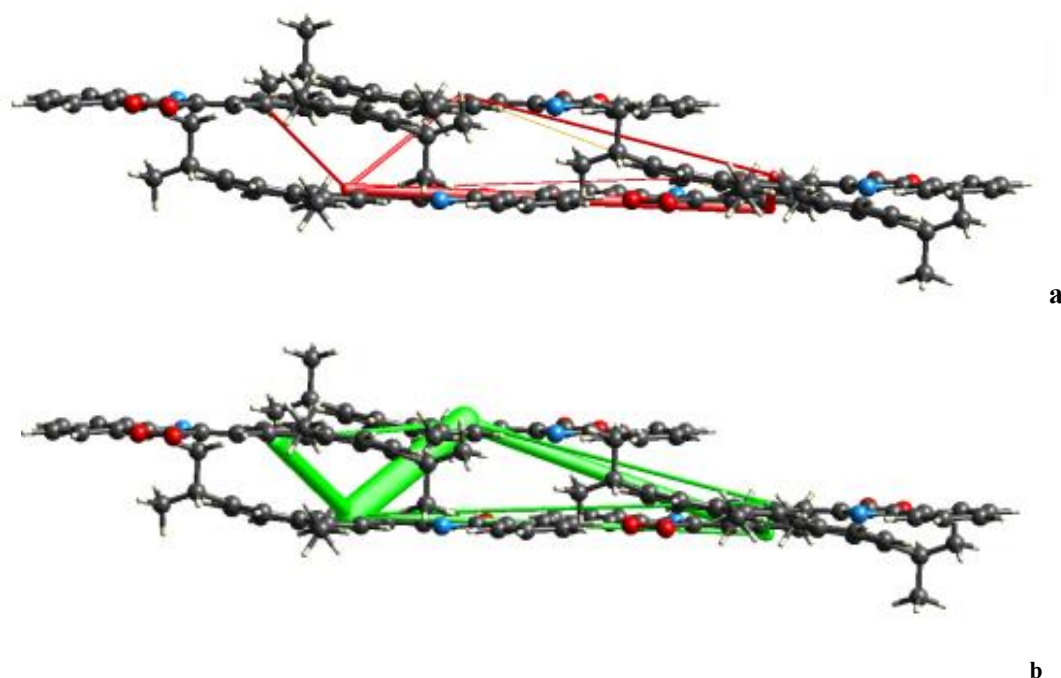


Fig. 6 – Depiction of molecules of **1** in two adjacent layers and the relevant energy frameworks. The thickness of the bars represents the magnitude of the interaction energy. (Red: electrostatic energy, green: dispersion energy).

At the same time within the layer **ZIFSEQ** presents strong dispersive forces due to $H\cdots H$ contacts. However, both **1** and **ZIFSEQ** present strong dispersive forces induced by the $\pi\cdots\pi$ interactions which are directed perpendicular to the corrugated layers (See Supplementary Material for comparative data between the two compounds). For **1** the green bars have a continuous aspect while for **ZIFSEQ** present a zig-zag aspect due to different π -interactions on each face of the molecule (See Supplementary Material for Energy frameworks comparison). Compared to **ZIFSEQ**, compound **1** presents stronger electrostatic forces within the layer but weaker dispersive forces between the layers. Even in this situation the electrostatic forces are weak in compound **1**.

CONCLUSIONS

The crystals structure of (Z)-4-((5-isopropyl-3,8-dimethylazulen-1-yl)methylene)-2-phenyloxazol-5(4H)-one (**1**) has been solved. The packing in the crystal is governed by π - π interactions between adjacent molecules. While the crystal supra-molecular structure presents important H-bonding, the cohesive forces within the network are mainly of dispersive nature.

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