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Experimental investigation of the structure of compound 7-methoxy-8-(3-methylbut-2-en-1-yl)-2H-chromen-2-one

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Abstract – This study includes elucidating the structure of a coumarin derivative compound obtained from the imperatoria ostruthium plant and investigating the usage areas of this compound. For this porpose, the liquid from this plant was used to prepare single crstals. The prepared single crystal sample was placed against the X-Ray. Masterwort is used as a flavouring for various liqueurs and bitters. Its roots and leaves have been used in the traditional Austrian medicine internally (as tea, liqueurs and wine) and externally (as fumigation, tincture or incense) for treatment of disorders of the gastrointestinal tract, skin, respiratory tract, cardiovascular system, infections, fever, flu and colds. The plant is a source of coumarin, including oxypucedanin, ostruthol, imperatorin, osthole, isoimperatorin, and ostruthin. In this study, some biological properties of the title compound obtained from the plant, which is widely used in the pharmaceutical industry, are mentioned. Structure solution and refinement were carried out with the help of the data obtained from the diffraction pattern. After the completion of the structure, the geometric parameters of the structure are released with various software programs. The cif (crystalographic information file) input file prepared for the surface analysis of the structure was also used in the CrsytalExplorer program. XRD analysis and analysis of Hirshfeld surfaces showed that this structure crystalizes in triclinic crystal system and P-1 space group. The structure data prepared with a colourless prism single crystal sapmle. The ADME scores revealed that the title molecule has a high gastrointestinal absorption (GI) and that it is not a substrate for P-glycoprotein (Pgp).

Keywords – Experimental Investigation, Coumarin Derivative

I. INTRODUCTION

Similar to flavonoids, cumarin chemicals are widely found in nature and contribute to the daily nutrition of edible plants. It is known that coumarin compounds have a wide range of biological activity, including antithrombotic effect, vas dilating effect on coronary vessels, tonic influence on capillary blood vessels, reduction in blood pressure, antispastic and photosensitizing effect [1]. This study includes elucidating the structure of a coumarin derivative compound obtained from the imperatoria ostruthium plant and investigating the usage areas of this compound. The title compound, synthesized and published in 1989 [1], is here elucidated and Hirshfeld Analyzes of the compound have been performed, which have not been studied before. And some biological properties of the title compound obtained from the plant, which is widely used in the pharmaceutical industry, are mentioned.

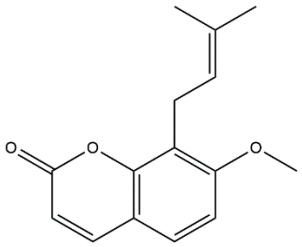
Fig. 1 Imperatoria ostruthium plant

II. Materials and Method

The data obtained from the diffractometer were solved using the following programs and visuals were obtained. X-AREA [2] X-AREA, X-RED32 [2], SHELXT2018/3[3]SHELXL2018/3 [4] OLEX2 [5] and Mercury [6], WinGX [7], SHELXL2018/[4], PLATON [8] and publCIF [9]. The positions and bond lengths, bond angles, and torsion angles of the atoms in the molecule were calculated. In addition, Hirshfeld surface analysis of the molecule was performed using the Crystal Explorer program 17.5 [10].

III. STRUCTURAL COMMENTARY

A. SXCRD Analysis



7-methoxy-8-(3-methylbut-2-en-1-yl)-2*H*-chromen-2-one

Fig. 2 Crystal Scheme

Crystal data, data collection, and structure refinement details are summarized in Table 1.

Table 1. Experimental details

Empirical formula	$C_{14}H_{16}O_3$
Formula weight	232.27
Temperature/K	293(2)
Crystal system	triclinic
Space group	P-1
a/Å	7.5137(14)
b/Å	9.6824(18)
c/Å	10.768(2)
α/°	64.320(14)
β/°	75.774(15)
γ/°	71.918(15)
Volume/Å^3	665.5(2)
Z	2
ρ_{calc}g/cm^3	1.159
μ/mm^{-1}	0.081
F(000)	248.0
Crystal size/mm^3	0.04 × 0.50 × 0.35
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.232 to 58.746
Index ranges	-10 ≤ h ≤ 10, -13 ≤ k ≤ 13, -14 ≤ l ≤ 14
Reflections collected	6595
Independent reflections	3337 [R_{int} = 0.0530, R_{sigma} = 0.0461]
Data/restraints/parameters	3337/0/166
Goodness-of-fit on F^2	1.155
Final R indexes [I>=2σ (I)]	R_1 = 0.1034, wR_2 = 0.2112
Final R indexes [all data]	R_1 = 0.1310, wR_2 = 0.2306
Largest diff. peak/hole / e Å^{-3}	0.37/-0.22

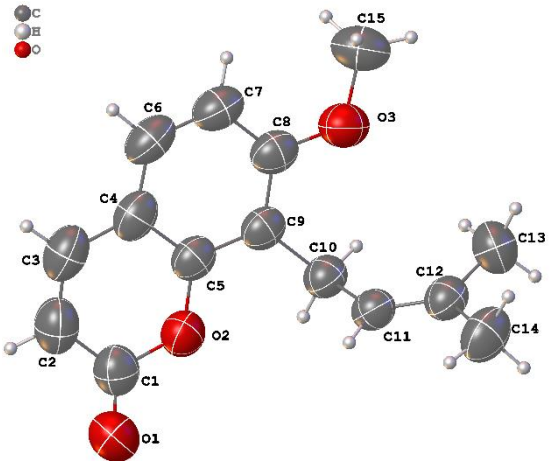


Fig. 3 The molecular structure of the title compound, showing the atom labeling. Displacement ellipsoids are drawn at the 40% probability level.

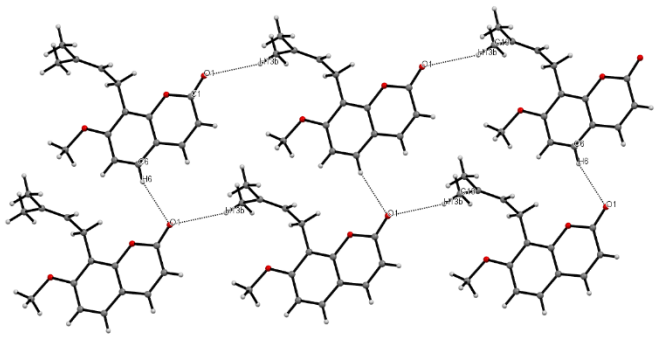


Fig. 4 H bonds

Table 2. H-Bonds

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H6···O1^{i}	0.93	2.76	3.65 (4)	161.7
C13—H13B···O1	0.96	2.91	3.83(4)	161.4
Symmetry code: (i) x-1,+y,+z. (ii) x,+y,+z-1				

Table 3. Selected geometric parameters

No intramolecular contacts are observed in the title structure. Fig.5 shows the packing and two pyran ring have 4.914 Å distance.

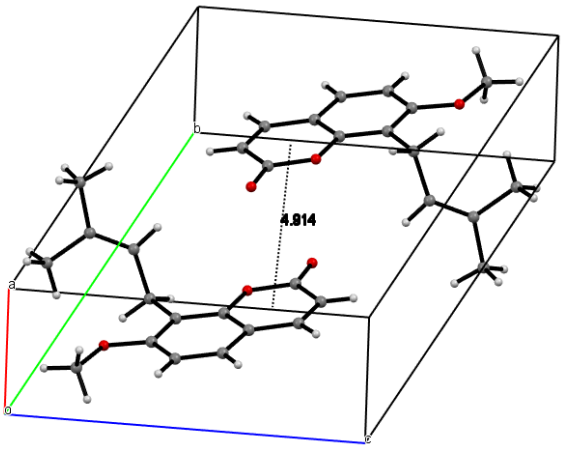


Fig. 5 Crystal packing diagram

B. Hirshfeld Surface Analysis

The Hirshfeld surface analysis was performed and the two-dimensional fingerprint plots were generated with *Crystal Explorer17* [9,10] to quantify the intermolecular contacts present within the crystal structure. Fig. 4 shows that the most important contribution for the crystal packing is from H···H (55.8% contribution). Atomic distance in closest H ···H interaction is 2.15 Å. The another important interaction is C···H/H···C, contributing 22.5% to the overall crystal packing has a pair of spikes with the tips at $d_e + d_i = 2.82$Å. The last important interaction is O···H/H···O interactions arising from the C—H···O hydrogen bonds (Table 2). The symmetrical pair of spikes in Fig. 6 (O···H/H···O interactions that contribute 15.4% to the HS) has tips at $d_e + d_i = 2.62$ Å.

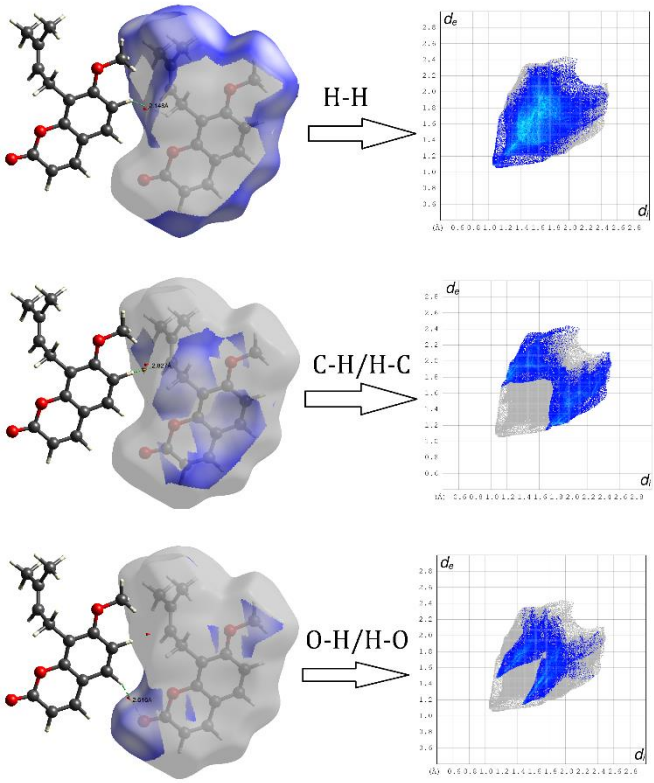


Fig. 6. Two-dimensional fingerprint plots delineated into H ···H, H···C/C···H and H···O/O···H contacts and the left side the dnorm surfaces.

C. Energy Frame-Work

Interaction energies for the title compound were calculated using the CE-B3LYP/6-31G(d,p) quantum level of theory, as available in *CrystalExplorer* [10]. The total intermolecular interaction energy (E_{tot}) is the sum of four energy terms: electrostatic (E_{ele}), polarization (E_{pol}), dispersion (E_{disp}) and exchange-repulsion (E_{rep}) with scale factors of 1.057, 0.740, 0.871 and 0.618, respectively. The relative strengths of the interaction energies in individual directions are represented by cylinder-shaped energy frameworks. The energy-framework calculations were analysed to understand the topologies of the pair-wise intermolecular interaction energies. The energy framework is constructed to compare the different energy components, *i.e.* repulsion (E_{rep}),

electrostatic (E_{ele}), dispersion (E_{dis}), polarization (E_{pol}) and total (E_{tot}) energy [12]. The energies between molecular pairs are indicated as cylinders joining the centroids of pairs of molecules with the thickness of the cylinder radius being directly proportional to the amount of interaction energy between the pair of molecules. As seen in Fig. 7.. The dispersion energy is dominant (Fig. 8.).

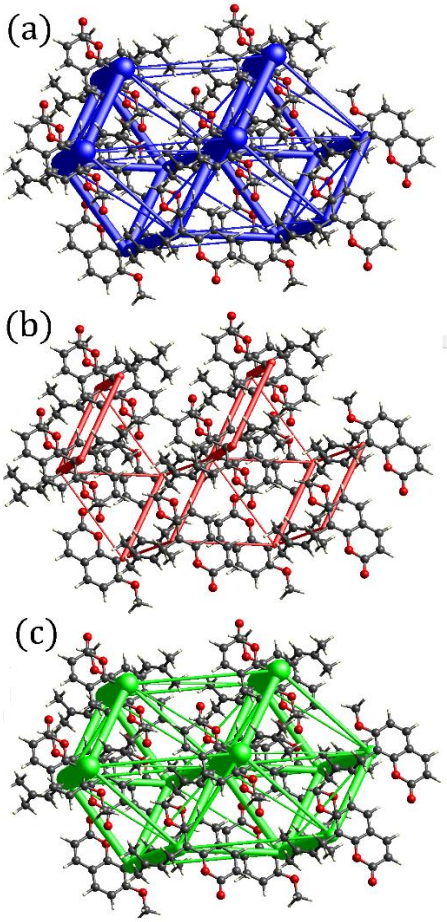


Fig. 7. .Intermolecular interaction energies: (a) total interaction energy for the title compound, (b) Coulombic and (c) dispersion energy for the title compound

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	1	-x, -y, -z	8.48	B3LYP/6-31G(d,p)	0.3	-1.0	-12.1	3.0	-9.1
	2	x, y, z	7.51	B3LYP/6-31G(d,p)	-13.6	-4.1	-25.7	17.8	-28.8
	1	-x, -y, -z	7.63	B3LYP/6-31G(d,p)	-5.8	-1.0	-19.7	8.3	-18.9
	2	x, y, z	11.52	B3LYP/6-31G(d,p)	1.0	-0.5	-8.7	3.9	-4.4
	1	-x, -y, -z	10.53	B3LYP/6-31G(d,p)	-2.3	-1.1	-12.1	6.9	-9.5
	1	-x, -y, -z	4.36	B3LYP/6-31G(d,p)	-18.4	-2.6	-60.1	29.0	-55.8
	1	-x, -y, -z	7.21	B3LYP/6-31G(d,p)	-6.5	-1.2	-38.9	21.1	-28.6
	2	x, y, z	10.77	B3LYP/6-31G(d,p)	-0.3	-1.8	-5.5	1.9	-5.3
	1	-x, -y, -z	7.11	B3LYP/6-31G(d,p)	-4.1	-5.3	-24.7	9.7	-23.8
	1	-x, -y, -z	11.45	B3LYP/6-31G(d,p)	-1.4	-0.1	-4.8	1.8	-4.6
	1	-x, -y, -z	10.84	B3LYP/6-31G(d,p)	-1.3	-0.2	-6.4	1.7	-6.1

Scale factors for benchmarked energy models
See Mackenzie et al. IUCrJ (2017)

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF ... HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

Fig. 8. Energy calculation results

D. ADME Properties

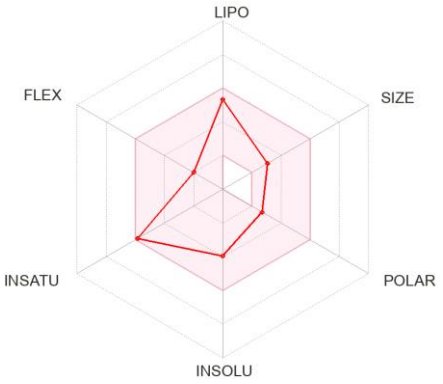


Fig. 9. Radar

In this work, computational online tools were used to determine the title compound ADME features. Using six physicochemical factors; saturation, lipophilicity, polarity, size, solubility, and flexibility the bioavailability radar assesses this compound drug-likeness [13]. Fig. 9 clearly depicted the ideal range for each property, with the exception of insaturation scales, by highlighting it in pink within the hexagon. The ADME scores revealed that the title molecule has a high gastrointestinal absorption (GI) and that it is not a substrate for P-glycoprotein (Pgp).

Table 4. Water Solubility and Lipophilicity

Water Solubility		Lipophilicity	
Log *S* (ESOL)	-3.97	Log $P_{o/w}$ (iLOGP)	2.93
Solubility	2.63e-02 mg/ml ; 1.08e-04 mol/l	Log $P_{o/w}$ (XLOGP3)	3.81
Class	Soluble	Log $P_{o/w}$ (WLOGP)	3.31
Log *S* (Ali)	-4.33	Log $P_{o/w}$ (MLOGP)	2.63
Solubility	1.13e-02 mg/ml ; 4.64e-05 mol/l	Log $P_{o/w}$ (SILICOS-IT)	4.03
Class	Moderately soluble	Consensus Log $P_{o/w}$ x	3.34
Log *S* (SILICOS-IT)	-5.01		
Solubility	2.37e-03 mg/ml ; 9.68e-06 mol/l		
Class	Moderately soluble		
Pharmacokinetics		**Physicochemical Properties**	
GI absorption	High	Formula	C15H16O3
BBB permeant	Yes	Molecular weight	244.29 g/mol

P-gp substrate	No	Num. heavy atoms	18
CYP1A2 inhibitor	Yes	Num. arom. heavy atoms	10
CYP2C19 inhibitor	Yes	Fraction Csp3	0.27
CYP2C9 inhibitor	Yes	Num. rotatable bonds	3
CYP2D6 inhibitor	No	Num. H-bond acceptors	3
CYP3A4 inhibitor	No	Num. H-bond donors	0
Log K_p (skin permeation)	-5.09 cm/s	Molar Refractivity	72.70
		TPSA	39.44 Å²
Druglikeness		Medicinal Chemistry	
Lipinski	Yes; 0 violation	PAINS	0 alert
Ghose	Yes	Brenk	2 alerts: cumarine, isolated_alkene
Veber	Yes	Leadlikeness	No; 2 violations: MW<250, XLOGP3>3.5
Egan	Yes	Synthetic accessibility	3.13
Muegge	Yes		
Bioavailability Score	0.55		
Num. H-bond donors	0		
Molar Refractivity	72.70		
TPSA	39.44 Å²		

IV. RESULTS AND DISCUSSION

The molecule crystalize in triclinic system. The structure provides the package structure with two hydrogen bonds. Atomic distance in closest H ⋯H interaction is 2.15 Å. The net interaction energies for the title compound are electrostatic (E_{ele}) = −52.3 kJ mol^{-1}, polarization (E_{pol}) = +18.9 kJ mol^{-1}, dispersion (E_{dis}) = −218.7 kJ mol^{-1}, repulsion (E_{rep}) = 105.1 kJ mol^{-1} total interaction energy (E_{tot}) = −86.2 kJ mol^{-1} The ADME scores revealed that the title molecule has a high gastrointestinal absorption (GI) and that it is not a substrate for P-glycoprotein (Pgp).

V. CONCLUSION

According to the X-ray structural results, the crystal structure is governed by hydrogen bonding and intermolecular interactions, resulting infnite corrugated sheet network. The dispersion energy is dominant.

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