

Computational Study of ADMET Properties, Electronic Structure, Electrical Parameters, and Nonlinear Optical Response of Indane 1, 3 dione derivative

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Abstract

Indane-1,3 dione derivative entitled 2-Hydroxy-2-(3-oxobutan-2-yl)indan-1,3 dione $C_{13}H_{12}O_4$ [NIAC] was examined. The compound's equilibrium geometry has been derived and examined using the DFT-B3LYP/LANL2DZ approach. FT-IR analysis was employed to recognize the different functional groups, and the results are compared with the experimental and simulated spectra. Theoretical examination was performed employing the oscillation modes. The electronic characteristics, including HOMO and LUMO energies and the corresponding frontier energy band gap, were determined. Predictions of molecular electrostatic potential surface was carried out to examine the electrophilic and nucleophilic sites. Electrical properties viz. dipole moment, molecular polarizability, and first static hyperpolarizability have been employed to predict the biological characteristics of the molecule. The drug-likeness and ADMET factors were calculated to examine their medicinal properties.

Keywords: Indane-1,3 dione $C_{13}H_{12}O_4$ [NIAC], ADMET; DFT; HOMO-LUMO, MESP.

I. Introduction

Indanedione derivatives comprise a versatile class of oxygen-containing cyclic compounds that have received significant attention owing to their diverse chemical reactivity and potential applications in organic and medicinal chemistry. The indane nucleus consists of a benzene ring fused to a five-membered saturated ring, and the incorporation of carbonyl functionalities within this framework generates a versatile class of indane-dione derivatives. Many indane dione derivatives have demonstrated a broad spectrum of biological activities, including antimicrobial, antitumor, anti-inflammatory and Anticoagulant Activities [1-2]. 2-Hydroxy-2-(3-oxobutan-2-yl)indan-1,3 dione $C_{13}H_{12}O_4$ [NIAC] was synthesized by our research team and its structure was determined by different spectral analysis and by X ray crystallography [3-4]. The present study produced various structural and biological properties of the title molecule using Gaussian 09 software and the DFT B3LYP/LANL2DZ technique. To elucidate the chemical reactivity and identify the reactive sites of the molecule, key electronic properties, such as the highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), frontier molecular orbital energy gap, and molecular electrostatic potential (MESP) surface, were investigated. The dipole moment, molecular polarizability, and static first-order hyperpolarizability were investigated to gain insights into the electronic characteristics and potential biological properties of the molecule. The pharmacological potential of the molecule was further evaluated by assessing its pharmacokinetic and ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties.

II. Material and Methods

Gaussian 09 software was used to perform quantum chemical calculations for the molecule NIAC[5]. In this work, DFT is used in conjunction with the Lee, Yang, and Parr correlation functional and Becke's three-parameter hybrid exchange functional B3LYP [6-8]. In order to calculate vibrational frequencies, electric and electronic parameters, Fukui functions, etc., the optimal geometry has been obtained. The GaussView 6.0 software application was used to create the model molecular structures, HOMO-LUMO, and MESP surfaces for the chemical in question [9]. VEDA 4.0 software was used to calculate the potential energy (PED) distribution for these modes [10]. ADME, drug likeness and pharmacokinetic properties were calculated incorporating SwissADME and pkCSM online software [11, 12]. Various toxicity parameters for the title compound were calculated employing the PreADMET online software tool [13].

III. Results and Discussion

3.1 Optimized Molecular Geometry

Molecular geometry usually shows a compound's physical parameters along with its constituent parts, making it possible to investigate these physical parameters. The chemical in question has one benzene rings (R1), and a cyclopentanone ring (R2). Energy minimization has been used to optimize the equilibrium geometry for the

lowest energy conformer. The optimized geometry of the molecule NIAC is at a minimum on the potential energy surface, as indicated by the computed vibration spectrum's lack of imaginary wave number. Figure 1 shows the compound's optimal configuration, which is comparable to that obtained by X-ray diffraction study [3].

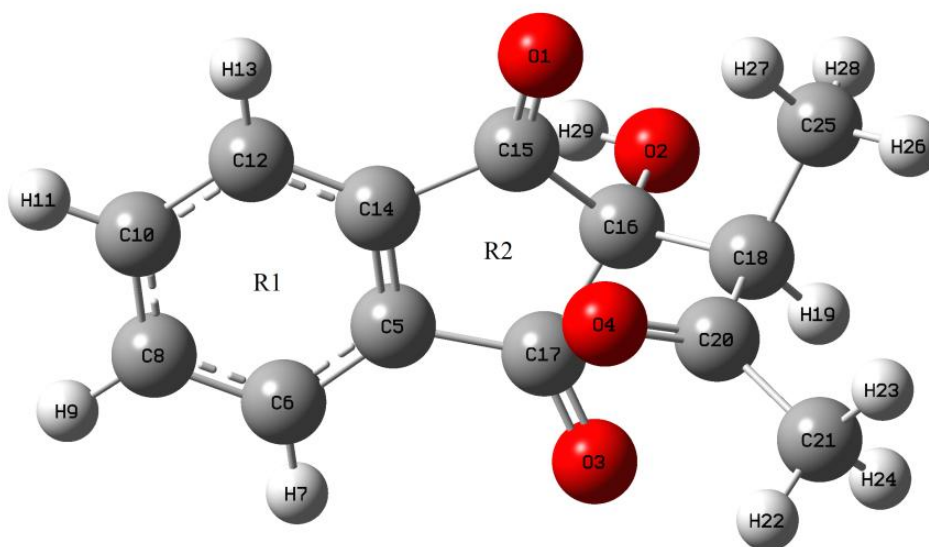


Fig. 1: Optimized geometrical structure of NIAC

Table 1: Optimized ground state structural parameters of NIAC at B3LYP method

S. No.	Parameter <i>Stretching</i> (Å)	Method X ray	DFT B3LYP	S. No.	Parameter <i>Bond Angle (Deg)</i>	Method X ray	DFT B3LYP
1.	R(1,15)	1.21	1.25	42.	A(16,2,29)	108.3	111.5
2.	R(2,16)	1.42	1.47	43.	A(6,5,14)	121.2	121.2
3.	R(2,29)	0.89	0.98	44.	A(6,5,17)	128.5	128.7
4.	R(3,17)	1.21	1.25	45.	A(14,5,17)	110.2	110.1
5.	R(4,20)	1.22	1.25	46.	A(5,6,7)	121.1	120.5
6.	R(5,6)	1.39	1.40	47.	A(5,6,8)	117.7	117.9
7.	R(5,14)	1.39	1.41	48.	A(7,6,8)	121.1	121.5
8.	R(5,17)	1.48	1.49	49.	A(6,8,9)	119.5	119.8
9.	R(6,7)	0.93	1.09	50.	A(6,8,10)	120.9	120.9
10.	R(6,8)	1.39	1.41	51.	A(9,8,10)	119.5	119.3
11.	R(8,9)	0.93	1.09	52.	A(8,10,11)	119.3	119.3
12.	R(8,10)	1.39	1.42	53.	A(8,10,12)	121.3	120.9
13.	R(10,11)	0.93	1.09	54.	A(11,10,12)	119.3	119.8
14.	R(10,12)	1.39	1.41	55.	A(10,12,13)	121.3	121.6
15.	R(12,13)	0.93	1.09	56.	A(10,12,14)	117.4	118.0
16.	R(12,14)	1.39	1.40	57.	A(13,12,14)	121.4	120.5
17.	R(14,15)	1.48	1.49	58.	A(5,14,12)	121.3	121.1
18.	R(15,16)	1.54	1.56	59.	A(5,14,15)	109.7	110.4
19.	R(16,17)	1.54	1.56	60.	A(12,14,15)	129.0	128.5
20.	R(16,18)	1.52	1.54	61.	A(1,15,14)	127.0	126.4
21.	R(18,19)	0.98	1.10	62.	A(1,15,16)	124.5	125.9
22.	R(18,20)	1.52	1.53	63.	A(14,15,16)	108.5	107.7

23.	R(18,25)	1.51	1.55	64.	A(2,16,15)	124.5	109.9
24.	(20,21)	1.49	1.52	65.	A(2,16,17)	110.0	109.2
25.	R(21,22)	0.96	1.09	66.	A(2,16,18)	107.2	104.7
26.	R(21,23)	0.96	1.10	67.	A(15,16,17)	102.3	103.1
27.	R(21,24)	0.96	1.10	68.	A(15,16,18)	110.7	116.8
28.	R(25,26)	0.96	1.10	69.	A(17,16,18)	116.9	113.0
29.	(25,27)	0.96	1.09	70.	A(3,17,5)	126.6	127.3
30.	R(25,28)	0.96	1.09	71.	A(3,17,16)	124.9	124.7
				72.	A(5,17,16)	108.3	108.0
	Angle bending (deg)			73.	A(20,21,23)	109.5	109.7
31.	A(16,18,19)	107.2	105.5	74.	A(20,21,24)	109.5	111.4
32.	A(16,18,20)	110.6	110.7	75.	A(22,21,23)	107.2	108.4
33.	A(16,18,25)	113.7	113.1	76.	A(22,21,24)	107.2	110.1
34.	A(19,18,20)	107.2	107.1	77.	A(23,21,24)	109.5	107.4
35.	A(19,18,25)	110.6	107.9	78.	A(18,25,26)	109.5	110.5
36.	A(20,18,25)	110.6	112.0	79.	A(18,25,27)	109.5	111.4
37.	A(4,20,18)	120.8	120.7	80.	A(18,25,28)	109.5	109.1
38.	A(4,20,21)	121.4	121.2	81.	A(26,25,27)	109.5	109.3
39.	A(18,20,21)	117.7	118.1	82.	A(26,25,28)	109.5	108.4
40.	A(20,21,22)	109.5	109.7				
41.	A(27,25,28)	109.5	108.2				

The optimized bond lengths of (C=O) are computed within the range of 1.21-1.42 Å. The optimized bond lengths of (C-O) for 30 alcohols are computed at 1.42 Å. The –C-H bond length of benzene ring are determined to be 0.93 Å. The (C-C) bond lengths of all the carbon of benzene ring is found to be equal at 1.39 Å. The optimized (O-H) stretching modes were determined at 0.98 Å. These optimized bond lengths are consistent with the experimental X-ray values [3,4] presented in supplementary Table 1. All the optimized bond angles and dihedral angles aligned well with the experimental data. Consequently, this geometrical data provides a dependable estimate when integrated with experimental crystal data, making the outcomes suitable for calculations of vibrational frequencies.

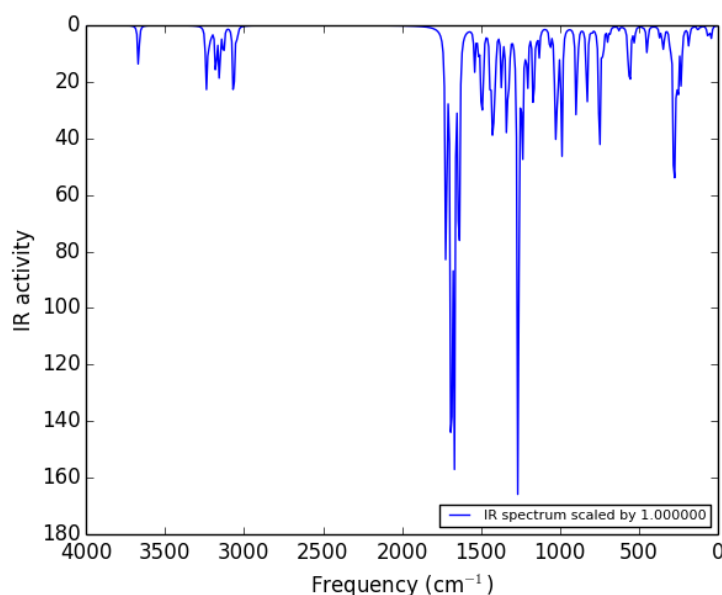


Fig.2 : IR simulated spectra of NIAC

3.2 Assignments of Vibrational Modes

The analyzed compound, NIAC contains 29 atoms, thus exhibits 81 vibrational modes. The electron-electron interaction and the an-harmonicity were ignored [14]. The calculated frequencies are at a higher level compared to the experimental values [4] due to these approximations. Consequently, we applied 0.958 to adjust the estimated frequencies to 1700 cm^{-1} and used 0.9688 for frequencies that are lower [15]. The simulated IR spectra generated using Gausssum 3.0 software is presented in Figure 2. All the assignments for vibrational modes are shown in Table 2.

Table 2 Frequency assignments for NIAC at B3LYP/6-311G(d,p) in cm^{-1} , with PED[%]

S.No.	Calc Freq		Exp freq	Assignment Modes [PED %]
	Unscaled	Scaled	FTIR	
1	3699	3,544	3384	$\nu(\text{O2-H29})$ [94]
2	3240	3,104		$\nu(\text{C-H})_{\text{sym-R1}}$ [95]
3	3231	3,095		$\nu(\text{C-H})_{\text{asym-R1}}$ [94]
4	3219	3,084		$\nu(\text{C-H})_{\text{asym-R1}}$ [100]
5	3204	3,069	3064	$\nu(\text{C-H})_{\text{asym-R1}}$ [96]
6	3181	3,047		$\nu(\text{C25-H26H27H28})_{\text{asym}}$ [91]
7	3178	3,045		$\nu(\text{C21-H22H23H24})_{\text{asym}}$ [95]
8	3155	3,022		$\nu(\text{C25-H26H27H28})_{\text{asym}}$ [94]
9	3129	2,998	2963	$\nu(\text{C21-H22H23H24})_{\text{asym}}$ [95]
10	3066	2,937	2944	$\nu(\text{C25-H26H27H28})_{\text{sym}}$ [90]
11	3049	2,921		$\nu(\text{C21-H22H23H24})_{\text{sym}}$ [93]
12	3041	2,913	2908	$\nu(\text{C21-H22H23H24})_{\text{sym}}$ [36]+ $\nu(\text{C18-H19})_{\text{sym}}$ [56]
13	1720	1,648		$\nu(\text{C15=O1})_{\text{sym}}$ [42]+ $\nu(\text{C15=O1})_{\text{sym}}$ [48]
14	1687	1,634		$\nu(\text{C15=O1})_{\text{sym}}$ [47]+ $\nu(\text{C15=O1})_{\text{sym}}$ [42]
15	1668	1,616		$\nu(\text{C29=O4})_{\text{sym}}$ [59]
16	1639	1,588	1593	$\nu(\text{C-C})_{\text{R1}}$ [38] + $\phi(\text{C-C-C})_{\text{R1}}$ [10]+ $\phi(\text{H-C-C})_{\text{R1}}$ [10]
17	1638	1,587		$\nu(\text{C-C})_{\text{R1}}$ [29] + $\phi(\text{C-C-C})_{\text{R1}}$ [22]+ $\phi(\text{H-C-C})_{\text{R1}}$ [18]
18	1539	1,491		$\nu(\text{C25-H27})$ [69]+ $\nu(\text{C25-H28})$ [21]
19	1516	1,469		$\nu(\text{C25-H26})$ [36]+ $\nu(\text{C25-H27})$ [49]+ $\nu(\text{C25-H28})$ [21]
20	1499	1,452	1452	$\nu(\text{C21-H22})$ [36]+ $\nu(\text{C21-H23})$ [49]+ $\nu(\text{C21-H24})$ [21]
21	1498	1,451		$\nu(\text{C-C})_{\text{R1}}$ [49] + $\phi(\text{C-C-C})_{\text{R1}}$ [20]+ $\phi(\text{H-C-C})_{\text{R1}}$ [14]
22	1495	1,448		$\nu(\text{C21-H22})$ [22]+ $\nu(\text{C21-H23})$ [32]+ $\nu(\text{C21-H24})$ [20]
23	1488	1,442		$\nu(\text{C25-H26})$ [28]+ $\nu(\text{C25-H27})$ [26]+ $\nu(\text{C25-H28})$ [24]
24	1439	1,394	1403	$\nu(\text{C21-H22})$ [18]+ $\nu(\text{C21-H23})$ [29]+ $\nu(\text{C21-H24})$ [17]
25	1423	1,379		$\nu(\text{C-C})_{\text{R1}}$ [21] + $\phi(\text{C-C-C})_{\text{R1}}$ [19]+ $\phi(\text{H-C-C})_{\text{R1}}$ [20]
26	1408	1,364	1355	$\phi(\text{C25-C28-H19})$ [21]+ $\phi(\text{C20-C28-H19})$ [44]
27	1368	1,325		$\nu(\text{O2-H38})$ [45] + $\phi(\text{C-C-C})_{\text{R2}}$ [34]
28	1338	1,296		$\phi(\text{C25-C28-H19})$ [24]+ $\phi(\text{C20-C28-H19})$ [25]
29	1328	1,287		$\phi(\text{C25-C28-H19})$ [27]+ $\phi(\text{C20-C28-H19})$ [35]
30	1320	1,279	1264	$\nu(\text{C18-H19})$ [47] + $\phi(\text{C-C-C})_{\text{Rock}}$ [33]
31	1264	1,225		$\nu(\text{C-C})_{\text{R1}}$ [41] + $\phi(\text{C-C-C})_{\text{R1-breath}}$ [32]+ $\phi(\text{C-C-C})_{\text{R2-breath}}$ [12]
32	1236	1,197	1194	$\nu(\text{C-C})_{\text{R1}}$ [28] + $\phi(\text{C-C-C})_{\text{R1-breath}}$ [29]+ $\phi(\text{C-C-C})_{\text{R2-breath}}$ [11]
33	1216	1,178		$\nu(\text{C-C})_{\text{R1}}$ [28] + $\phi(\text{H-C-C})_{\text{R1-breath}}$ [39]+ $\phi(\text{H-C-C})_{\text{R2-breath}}$ [11]
34	1204	1,166		$\nu(\text{C-C})_{\text{R1,R2}}$ [28] + $\phi(\text{H-C-C})_{\text{R1-breath}}$ [49]+ $\phi(\text{H-C-C})_{\text{R2-breath}}$ [11]
35	1166	1,130	1125	$\nu(\text{H29-O2})$ [29] + $\phi(\text{H29-O2-C16})$ [31]+ $\phi(\text{C18-C20-C21})$ [16]
36	1149	1,113		$\nu(\text{C-C})_{\text{R1,R2}}$ [27] + $\phi(\text{C18-C20-C25})$ [16]
37	1130	1,095		$\phi(\text{H-C-C})_{\text{R1}}$ [33]+ $\phi(\text{C-C-C})_{\text{R2}}$ [22]
38	1112	1,077		$\phi(\text{H-C-C})_{\text{R1}}$ [41]+ $\phi(\text{C-C-C})_{\text{R1}}$ [20]
39	1061	1,028	1048	$\nu(\text{C18-C25})$ [41] + $\phi(\text{C20-C18-C25})$ [20]
40	1054	1,021		$\tau(\text{H-C-C-C})_{\text{R1}}$ [32]+ $\omega(\text{H-C-C-C})$ [24]
41	1032	1,000		$\tau(\text{H-C-C-C})_{\text{R1}}$ [47]+ $\tau(\text{C-C-C-C})_{\text{R2}}$ [24]

42	1027	995		$\tau[\text{C-C-C-C})\text{R2}[42] + \omega(\text{H-C-C-C})\text{R1}[36]$
43	1014	982		$\tau[\text{C-C-C-C})\text{R2}[22] + \omega(\text{H-C-C-C})\text{R1}[44]$
44	1007	976		$\tau[\text{C20-C21-H22-H24})[28] + \tau[\text{C20-C21-H23-H24})[12] + \tau[\text{C20-C21-H22-H23})[12]$
45	993	962	966	$\tau[\text{C20-C21-H22-H24})[21] + \tau[\text{C20-C21-H23-H24})[17] + \tau[\text{C20-C21-H22-H23})[13]$
46	987	956		$\phi(\text{H16-C18-C29})\text{R1}[41] + \tau[\text{C20-C21-H22-H24})[20] + \tau[\text{C20-C21-H23-H24})[15]$
47	945	916		$\tau[\text{C20-C21-H22-H24})[25] + \tau[\text{C20-C21-H23-H24})[18]$
48	895	867	891	$\tau[\text{C20-C21-H22-H24})[27] + \tau[\text{C20-C21-H23-H24})[15]$
49	883	855		$\phi(\text{C-C-C})\text{R1-breath}[33] + \phi(\text{C-C-C})\text{R2-breath}[22]$
50	828	802		$\phi(\text{C-C-C})\text{R1}[38] + \phi(\text{C-C-C})\text{R2}[26]$
51	822	796	799	$\omega(\text{H-C-C-C})\text{R1}[44] + \tau[\text{C20-C21-H22-H23})[15]$
52	796	771		$\omega(\text{C-C-C-C})\text{R1}[34] + \omega(\text{C-C-C-C})\text{R2}[28]$
53	748	725	735	$\phi(\text{C25-C18-H26})[23] + \phi(\text{C25-C18-H27})[27] + \phi(\text{C25-C18-H28})[19]$
54	725	702		$\omega(\text{H-C-C-C})\text{R1}[24] + \tau[\text{C20-C21-H22-H23})[25]$
55	696	674	679	$\omega(\text{H-C-C-C})\text{R1}[32] + \tau[\text{C20-C21-H22-H23})[25]$
56	681	660		$\phi(\text{C-C-C})\text{R1}[31] + \phi(\text{C-C-C})\text{R2}[21]$
57	625	606	616	$\phi(\text{C-C-C})\text{R1}[26] + \phi(\text{C-C-C})\text{R2}[25]$
58	568	550	561	$\nu(\text{C-C})\text{R1}[31] + \phi(\text{C-C-C})\text{R1}[28]$
59	556	539		$\phi(\text{H16-C18-C29})\text{R1}[35] + \tau[\text{C20-C21-H22-H24})[20] + \tau[\text{C20-C21-H23-H24})[11]$
60	538	521		$\phi(\text{H16-C18-C29})\text{R1}[30] + \tau[\text{C20-C21-H22-H24})[20] + \tau[\text{C20-C21-H23-H24})[10]$
61	527	511		$\phi(\text{H16-C18-C29})\text{R1}[33] + \tau[\text{C20-C21-H22-H24})[22]$
62	469	454		$\phi(\text{C-C-C})\text{R1}[28] + \phi(\text{C-C-C})\text{R2}[14]$
63	446	432		$\phi(\text{C18-C20-O4})[23] + \phi(\text{O2-C16-C18})\text{R2}[17] + (\text{H16-C18-C29})\text{R1}[33]$
64	367	356		$\omega(\text{H-C-C-C})\text{R1}[22] + \tau[\text{C20-C21-H22-H23})[15]$
65	347	336		$\omega(\text{H-C-C-C})\text{R1}[18] + \tau[\text{C20-C21-H22-H23})[18]$
66	340	329		$\tau[\text{C15-C16-H17=O3})[20] + \tau[\text{C18-C16-H15=O1})[20]$
67	300	291		$\phi(\text{C18-C20-O4})[23] + \phi(\text{O2-C16-C18})\text{R2}[17] + (\text{H16-C18-C29})[33]$
68	278	269		$\omega(\text{H-C-C-C})\text{R1}[18] + \tau[\text{C20-C21-H22-H23})[18]$
69	275	266		$\tau[\text{C15-C16-H17=O3})[20] + \tau[\text{C18-C16-H15=O1})[20]$
70	267	259		$\phi(\text{C18-C20-O4})[21] + \phi(\text{O2-C16-C18})\text{R2}[17] + (\text{H16-C18-C29})[33]$
71	251	243		$\omega(\text{H-C-C-C})\text{R1}[20] + \tau[\text{C20-C21-H22-H23})[18]$
72	230	223		$\tau[\text{C15-C16-H17=O3})[21] + \tau[\text{C18-C16-H15=O1})[20]$
73	213	206		$\phi(\text{C18-C20-O4})[23] + \phi(\text{O2-C16-C18})\text{R2}[17] + (\text{H16-C18-C29})[33]$
74	182	176		$\omega(\text{H-C-C-C})\text{R1}[18] + \tau[\text{C20-C21-H22-H23})[18]$
75	140	136		$\phi(\text{C18-C20-O4})[23] + \phi(\text{O2-C16-C18})\text{R2}[17] + \tau(\text{H16-C18-C29})[33]$
76	126	122		$\omega(\text{H-C-C-C})\text{R1}[16] + \tau[\text{C20-C21-H22-H23})[18]$
77	120	116		$\omega(\text{H-C-C-C})\text{R1}[14] + \tau[\text{C-C-C-H})\text{R1}[17]$
78	105	102		$\omega(\text{H-C-C-C})\text{R1}[18] + \tau[\text{C-C-C-H})\text{R1}[11]$
79	65	63		$\omega(\text{H-C-C-C})\text{R1}[18] + \tau[\text{C-C-C-H})\text{R1}[11]$
80	53	51		$\phi(\text{C-C-O})[25] + \phi(\text{O-C-C})[17] + \tau(\text{H-C-C-H})[13]$
81	40	39		$\omega(\text{H-C-C-C})\text{R1}[18] + \tau[\text{C-C-C-H})\text{R1}[11]$
Abbreviations:- ν ->stretching mode, ϕ -> in-plane bending mode, τ -> torsional mode, ω -> out of plane wagging, s ->symmetric stretch, a ->asymmetric stretch, $char$ ->characteristic mode				

3.2.1 O-H stretching The (O-H) vibrations for the title compound are calculated within the frequency range of 3544cm^{-1} with 94% potential energy distribution [PED]. These vibrations manifest as a singular weak absorption peak at 3384cm^{-1} in the experimental FTIR spectra [4].

3.2.2 C-O stretching

The C-O stretching vibrations of 3^o alcoholic group of NIAC is computed at a frequency of 1130cm^{-1} with a 46% PED while the experimental value shows peaks at 1125cm^{-1} .

3.2.3 C-H vibrational modes

Aromatic -C-H stretching are predicted to occur within the frequency range of 3104-3045 cm^{-1} . These vibrations manifest as a slight absorption peak seen at 3064 cm^{-1} in the FTIR spectra, all exhibiting high PED values. The aromatic C-H bending frequencies are found in the frequency range of 916-702 cm^{-1} [16] correspond precisely to the C-H bending vibrations, appearing as a significant band in the FTIR spectra between 891 and 735 cm^{-1} .

3.2.4 C=O stretching

The ν (C=O) stretching is estimated at 1634 cm^{-1} for indane dione carbonyl group corresponding to peak at 1704 cm^{-1} in the FTIR spectrum, with high PED value.

3.2.5 C-C vibrational modes

The ν C-C aromatic stretch produces the typical bands in the spectral region of 1600-1450 cm^{-1} [17]. In the current molecule investigation, ν (C-C) stretching vibrations are detected in FTIR spectra at frequencies 1403-1593 cm^{-1} , which are computed by DFT within the frequency range of 1616-1442 cm^{-1} , these modes are combined with the in-plane bending modes.

3.2.7 Modes in the lower spectral region

Investigation of low-frequency vibrational modes is crucial because it sheds light on the weak intermolecular interactions that occur during enzyme activities [18]. The interpretation of the impact of electromagnetic radiation on biological systems can also benefit from the knowledge of low frequency modes [17]. Several torsional modes are obtained in the lower-middle region of the experimental FTIR spectrum [4] and are well matched with the computed values. The table 2 includes the list of each of these modes comprising several peaks in the experimental spectra at frequencies 735 and 679 cm^{-1} and are optimized in the range 725 and 674 cm^{-1} respectively. These seems to be the characteristics modes for the title compound NIAC.

3.3 Frontier molecular orbital analysis and electronic parameters

HOMO and LUMO have been extensively employed to understand the reactivity and area selectivity of various chemical compounds. A narrower HOMO and LUMO gap suggest a more unstable and softer molecular structure, whereas a wider energy gap signifies a more stable and harder molecular structure. The soft molecules are typically unstable and relatively prone to chemical reactions [19, 20]. The relatively substantial energy gap between HOMO and LUMO suggests that the molecule possesses appreciable electronic stability and requires considerable energy for frontier-orbital excitation. The chemical hardness and the corresponding global softness values indicate a moderate resistance of the molecular electronic distribution toward external perturbation. Figure 3 illustrates the 2D representations of the HOMO and LUMO for the title compound NIAC. It shows that the major part of HOMO is concentrated on the cyclopentene ring R2 and at some portion of benzene ring R1, while the LUMO is distributed equally on benzene ring R1 and cyclopentene ring R2. Consequently, most of the charge transfer should take place from the ring R2 to the ring R1. The calculated HOMO-LUMO energy gap of 4.2 eV indicates that the title compound NIAC has a high degree of polarizability and chemical reactivity, thus categorizing it as a soft molecule [21, 22].

Table 3 : Electronic parameters of NIAC

Parameters	Symbolic Formula	DFT Value
E_{HOMO} (eV)		-6.84
E_{LUMO} (eV)		-2.64
ΔE (eV)		4.02
Ionization potential (I)	NEG(HOMO)	6.84
Electron affinity(A)	NEG(LUMO)	2.64
Electronegativity(χ)	(I+A)/2	4.74
Chemical potential(μ)	[-(I+A)]/2	-4.74
Chemical hardness(η)	(I-A)/2	2.1
Global softness(S)	1/2 η	0.23
Electrophilicity index (ω)	$\chi^2/2\eta$	5.34

A number of calculated electronic characteristics that characterize the overall reactivity of the molecule are shown in table 3. The results showed that the ionization potential was estimated as 6.84 eV, the electron affinity as 2.64 eV, the electronegativity as 4.74 eV, and the chemical hardness as 2.1 eV. Therefore, the title molecule should have sufficient biological activity, according to these criteria and the electrophilicity levels (5.34 eV).

The molecular electrostatic plot (MESP) for the title compound NIAC is shown in figure 4. It is evident from the figure 4, that R1 is the most inert site in the compound, as it possesses the smallest covered area with

MESP. The region with high electron density (maximum electrostatic potential represented in pink color) is primarily located over the oxygen atom O1 and O3, making it a potential active site for electrophilic attack.

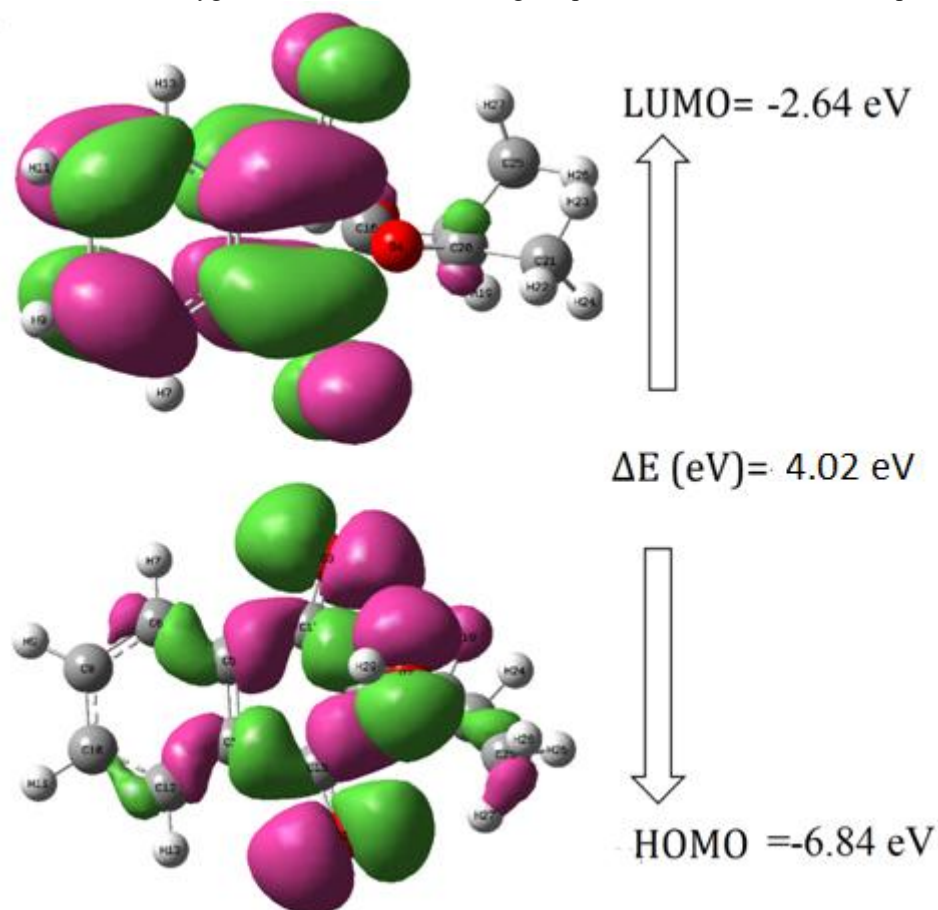


Fig.3: 2D-HOMO-LUMO plot of NIAC

3.4 Electrical parameters

The dipole moment of the NIAC molecule is aligned in the Y-Z plane, with calculated values of 4.02 D (Table 4) indicating appreciable charge separation and molecular polarity. The average polarizability $\langle\alpha\rangle$ was recorded at -93.54 suggesting that it is likely to show adequate biological activity. Table 4 outlines various relevant electric parameters, such as dipole moment, polarizability, and first-order hyperpolarizability for the molecule. The first-order hyperpolarizability tensor components exhibit both positive and negative values, reflecting the direction-dependent nature of the molecular nonlinear optical response. Among the calculated components, β_{XXZ} and β_{XZZ} show comparatively high magnitudes of 31.5604×10^{-33} e.s.u., suggesting a significant contribution from the corresponding molecular directions.

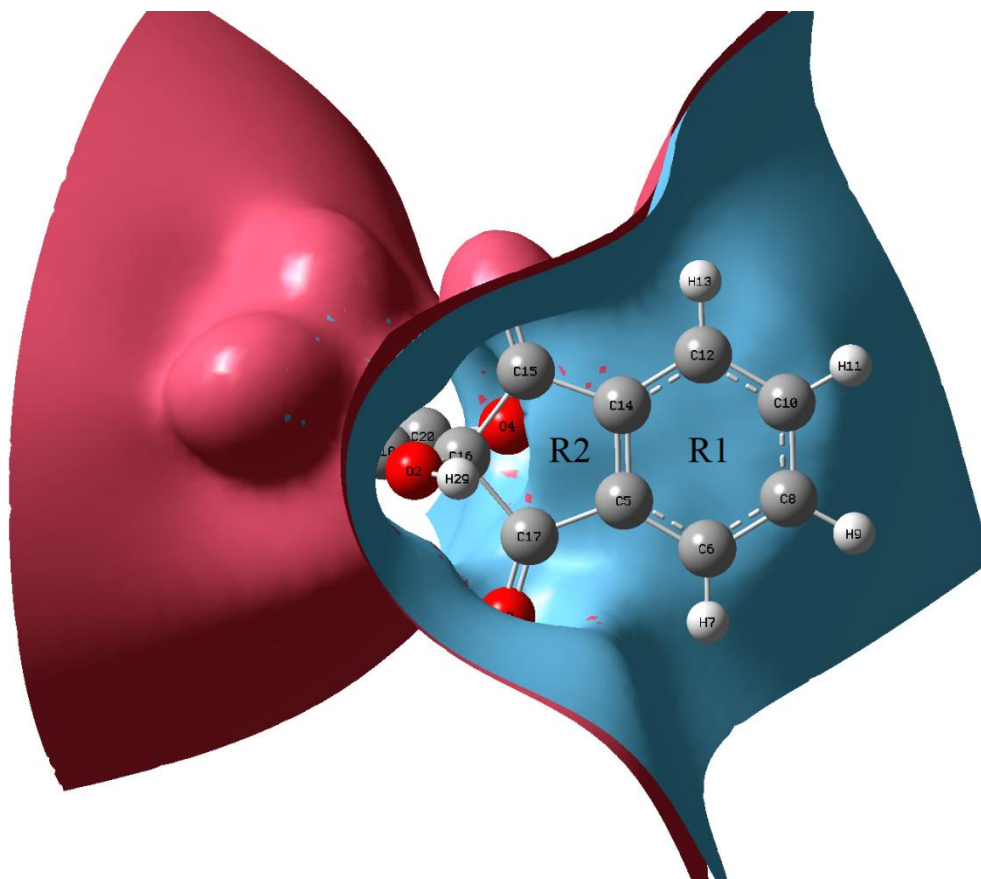


Fig. 4 2D MESP plot of NIAC

The calculated hyperpolarizability parameters therefore indicate that NIAC possesses a measurable nonlinear optical response. The observed electronic response may be associated with charge-transfer interactions within the molecular framework, which can enhance molecular polarizability and hyperpolarizability. The calculated first-order hyperpolarizability (β_{total}) of the investigated compound is 0.029×10^{-30} e.s.u., which is considerably lower than the β_{total} value of 0.3728×10^{-30} e.s.u. reported for urea, a commonly used reference compound in nonlinear optical (NLO) studies. Therefore, the relatively low β_{total} value of the NIAC indicates that it exhibits a comparatively weaker second-order nonlinear optical response than urea [23,24].

Table 4: Electric parameters for NIAC by DFT

Components	NIOPDA	Components	Hyperpolarizability (e.s.u. * 10^{-33})
α_{xx}	-70.8664	β_{xxx}	9.4407
α_{xy}	3.3265	β_{xxy}	-17.1474
α_{yy}	-107.2364	β_{xyy}	10.8627
α_{xz}	3.4661	β_{yyy}	-8.7053
α_{yz}	3.5684	β_{xxz}	-31.5604
α_{zz}	-8.9822	β_{xyz}	-8.9822
$\langle \alpha \rangle$		β_{yyz}	-5.4116
		β_{xzz}	-31.5604
Electric Dipole moment (μ) (D)	4.02	β_{yzz}	16.071
		β_{zzz}	11.2511
		β_1	126.72

β_2	95.68
β_3	661.56
β_{total}	29.73

3.5 Characteristics of Drug Likeness and ADME Profiles

ADME profiles and drug likeness metrics were determined using SWISSADME and pkCSM online tools for the compound in question and are presented in Table 5. The Lipinski rule of 5 (LiR of 5) assists in differentiating drug-like molecules from non-drug-like ones. The computed values for drug likeness parameters of title compound are; (i) HBD equals 1 (≤ 5), (ii) HBA is 4 (≤ 10), (iii) MW is 232.23 g/mol (≤ 500 g/mol), (iv) MR is 60.54 ($40 < MR < 130$), (v) log P as 1.22 suggesting high permeability through biological membranes and favorable binding to plasma proteins [27-29]. The value of van der Waals topological polar surface area (TPSA) is calculated as 71.44 Å² (< 120 Å²), partition coefficient (Milog P) is calculated as 0.03 (≤ 5) respectively. Therefore, it is evident that the title molecule had passed the LiR of 5 and thus are qualified to be tested in vivo. In ADME parameters, the outcomes of human intestinal absorption (HIA) are the total of absorption and bioavailability established from the combined excretion in urine, bile, and feces and its value was determined to be 92.312 %, suggesting excellent oral bioavailability due to favorable lipophilicity and low molecular size [30, 31]. CaCo-2 is a cell line derived from human colon epithelial tissue, commonly employed as a model to evaluate drug absorption in the human digestive system.

Table 5: Drug Likeness, ADME parameters of NIAC

S.No	Drug Likeness parameters		S.No.	ADME parameters	
	Parameters	NIAC		Parameters	NIAC
1	Formula	C13H12O4	16	GI absorption	High
2	MW	232.23 g/mol	17	BBB permeant penetration (c.brain/ c.blood) /log(BB)	-0.18/(-0.78) (yes)
3	Bioavailability Score	0.55	18	Lipinski Violations(LiR5)	0
4	Rotatable bonds(RBs)	2	19	Caco-2 cell permeability (nm/s)	2.893
5	Heavy atoms	17	20	CYP1A2 inhibitor	Yes
6	Aromatic heavy atoms	6	21	CYP2C19 inhibitor	No
7	Fraction Csp3	0.12	22	CYP2C9 inhibitor	No
8	H-bond acceptors(HBA)	4	23	CYP2D6 inhibitor	No
9	H-bond donors(HBD)	1	24	CYP3A4 inhibitor	No
10	MR	60.54	25	HIA (%)	80.312
11	TPSA	71.44	26	CNS permeability (log PS)	-2.554
12	CNS permeability	-2.554	27	Pgp_inhibition	No
13	MLOGP	0.03	28	Plasma_Protein_Binding	72.235
14	Drug-Induced Liver Injury (DILI)	Low Risk	29	Pure_water_solubility_mg/L	-1.704
15	Ali Log S	-3.16	30	Skin_Permability (log Kp)	-6.28

The calculated values 250 nm/s of CaCo-2 fall within the acceptable range [> 100 nm/s], indicating high-permeability. In central nervous system (CNS) pharmacology, a log(BB) > -1.0 indicates that a molecule successfully crosses the blood-brain barrier and achieves meaningful therapeutic exposure in brain tissue. While it is not highly concentrated in the brain compared to plasma, it easily crosses the threshold required to be classified as BBB permeable (BBB+). The calculated skin permeability value is -3.512 (log Kp < -4) for NIAC indicate that it is free from any skin penetration effect. The plasma protein binding values are calculated to be 72.2326 ($< 80\%$ PPB < 99], indicating moderate binding with blood plasma. The title molecule NIAC to inhibit Cytochrome P450

1A2 (CYP1A2) preferentially targets planar, neutral, or slightly basic lipophilic molecules containing aromatic rings. The rigid, planar benzene-fused dione ring of the indan-1,3-dione core acts as a high-affinity binding feature for the CYP1A2 active site geometry. The title molecule is an active CYP1A2 substrate but not an inhibitor, its systemic clearance will depend significantly on hepatic CYP1A2 enzyme expression levels. For instance, its metabolic rate could *increase* in the presence of strong CYP1A2 inducers (like tobacco smoke or omeprazole) or *decrease* if co-administered with a potent CYP1A2 inhibitor like fluvoxamine. A molecule with 10 or fewer rotatable bonds (RBs) is considered to have good drug-like properties and for NIAC it was calculated as only 2 rotatable bonds. In the evaluations of drug-like properties conducted both *in vitro* and *in silico*, the anticipated pharmacokinetic parameters and physicochemical characteristics referred to as Lipinski's filters are crucial [32, 33]. This molecule exhibits a highly optimal drug-like profile suitable for CNS-targeted small molecule discovery. It balances strong passive intestinal absorption, a clear avoidance of P-gp mediated brain efflux, and a log(BB) score that guarantees adequate blood-brain barrier penetration.

3.6. Toxicity predictions

Analysis of toxicity plays an important role in drug development and helps identify adverse effects of new drugs on the body. The toxicity of the title compound NIAC was calculated using ProTox-II online software [34]. Organ toxicity results suggested that the NIAC bears to be respiratory toxicity and clinical toxicity. The compound exhibits an exceptionally clean secondary toxicity profile. It shows no alarming indicators for mutagenicity, cardiotoxicity, or hepatotoxicity, rendering it a highly viable chemical framework for further lead optimization. Various toxicity parameters along with their calculated values by pkCSM online software tool are given in Table 6.

Table 6: Toxicity parameters by pkCSM online software

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	<u>Hepatotoxicity</u>	dili	Inactive	0.69
Organ toxicity	<u>Neurotoxicity</u>	neuro	Inactive	0.89
Organ toxicity	<u>Nephrotoxicity</u>	nephro	Inactive	0.67
Organ toxicity	<u>Respiratory toxicity</u>	respi	Active	0.56
Organ toxicity	<u>Cardiotoxicity</u>	cardio	Inactive	0.78
Toxicity end points	<u>Carcinogenicity</u>	carcino	Inactive	0.50
Toxicity end points	<u>Immunotoxicity</u>	immuno	Inactive	0.89
Toxicity end points	<u>Mutagenicity</u>	mutagen	Inactive	0.77
Toxicity end points	<u>Cytotoxicity</u>	cyto	Inactive	0.78
Toxicity end points	<u>BBB-barrier</u>	bbb	Active	0.83
Toxicity end points	<u>Ecotoxicity</u>	eco	Inactive	0.54
Toxicity end points	<u>Clinical toxicity</u>	clinical	Active	0.58
Toxicity end points	<u>Nutritional toxicity</u>	nutri	Inactive	0.56
Tox21-Nuclear receptor signalling pathways	<u>Aryl hydrocarbon Receptor (AhR)</u>	nr_ahr	Active	0.66

Classification	Target	Shorthand	Prediction	Probability
Tox21-Nuclear receptor signalling pathways	<u>Androgen Receptor (AR)</u>	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	<u>Androgen Receptor Ligand Binding Domain (AR-LBD)</u>	nr_ar_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	<u>Aromatase</u>	nr_aromatase	Inactive	0.95
Tox21-Nuclear receptor signalling pathways	<u>Estrogen Receptor Alpha (ER)</u>	nr_er	Inactive	0.91
Tox21-Nuclear receptor signalling pathways	<u>Estrogen Receptor Ligand Binding Domain (ER-LBD)</u>	nr_er_lbd	Inactive	0.93
Tox21-Nuclear receptor signalling pathways	<u>Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)</u>	nr_ppar_gamma	Inactive	0.96
Tox21-Stress response pathways	<u>Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)</u>	sr_are	Inactive	0.96
Tox21-Stress response pathways	<u>Heat shock factor response element (HSE)</u>	sr_hse	Inactive	0.96
Tox21-Stress response pathways	<u>Mitochondrial Membrane Potential (MMP)</u>	sr_mmp	Active	0.69
Tox21-Stress response pathways	<u>Phosphoprotein (Tumor Suppressor) p53</u>	sr_p53	Inactive	0.59
Tox21-Stress response pathways	<u>ATPase family AAA domain-containing protein 5 (ATAD5)</u>	sr_atad5	Inactive	0.91
Molecular Initiating Events	<u>Thyroid hormone receptor alpha (THRα)</u>	mie_thr_alpha	Inactive	0.74
Molecular Initiating Events	<u>Thyroid hormone receptor beta (THRβ)</u>	mie_thr_beta	Inactive	0.80
Molecular Initiating Events	<u>Transthyretin (TTR)</u>	mie_ttr	Active	0.70

Classification	Target	Shorthand	Prediction	Probability
Molecular Initiating Events	<u>Ryanodine receptor (RYP)</u>	mie_ryr	Inactive	0.93
Molecular Initiating Events	<u>GABA receptor (GABAR)</u>	mie_gabar	Active	0.50
Molecular Initiating Events	<u>Glutamate N-methyl-D-aspartate receptor (NMDAR)</u>	mie_nmdar	Inactive	0.99
Molecular Initiating Events	<u>alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPA)</u>	mie_ampar	Inactive	1.0
Molecular Initiating Events	<u>Kainate receptor (KAR)</u>	mie_kar	Inactive	1.0
Molecular Initiating Events	<u>Achetylcholinesterase (AChE)</u>	mie_ache	Inactive	0.72
Molecular Initiating Events	<u>Constitutive androstane receptor (CAR)</u>	mie_car	Inactive	0.99
Molecular Initiating Events	<u>Pregnane X receptor (PXR)</u>	mie_pxr	Active	0.61
Molecular Initiating Events	<u>NADH-quinone oxidoreductase (NADHox)</u>	mie_nadhox	Inactive	0.76
Molecular Initiating Events	<u>Voltage gated sodium channel (VGSC)</u>	mie_vgsc	Inactive	0.96
Molecular Initiating Events	<u>Na⁺/I⁻ symporter (NIS)</u>	mie_nis	Inactive	0.98
Metabolism	<u>Cytochrome CYP1A2</u>	CYP1A2	Inactive	0.77
Metabolism	<u>Cytochrome CYP2C19</u>	CYP2C19	Inactive	0.78
Metabolism	<u>Cytochrome CYP2C9</u>	CYP2C9	Inactive	0.51
Metabolism	<u>Cytochrome CYP2D6</u>	CYP2D6	Inactive	0.79
Metabolism	<u>Cytochrome CYP3A4</u>	CYP3A4	Inactive	0.85
Metabolism	<u>Cytochrome CYP2E1</u>	CYP2E1	Inactive	0.99

IV. Conclusions

A theoretical quantum chemical investigation of 3a,8a-Dihydroxy-1,3,3a,8a-tetrahydro indeno[1,2-d]imidazole-2,8-dione C₁₀H₁₈N₂O₄ [NIAC] was conducted using the DFT-B3LYP/LANL2DZ approach. An excellent correlation between the experimental and computed normal modes of vibrations was obtained. The electric descriptors had revealed the biological properties of the molecule. The HOMO LUMO plot and the narrow frontier energy gap of the title compound (4.2 eV) indicate its high polarizability and chemical reactivity. Based on the calculated electronic parameters, particularly the electrophilicity levels (5.34 eV), the compound in question is expected to exhibit adequate biological activity. This molecule exhibits a highly optimal drug-like profile suitable for CNS-targeted small molecule discovery, exhibited promising ADME characteristics and met Lipinski's drug likeness criteria. The compound exhibits an exceptionally clean secondary toxicity profile and exhibited no alarming indicators for mutagenicity, cardiotoxicity, or hepatotoxicity, rendering it a highly viable chemical framework for further lead optimization. These findings may lead to the development of additional new biologically active compounds that contain imidazole rings.

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