

Computational investigation, ADMET profiles, Electrical and electronic parameters and NLO behavior of Imidazolidine derivative

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Abstract

We have examined in detail an Imidazolidine derivative entitled with 3a,8a-Dihydroxy-1,3,3a,8a-tetrahydro indeno[1,2-d]imidazole-2,8-dione $C_{10}H_{18}N_2O_4$ [NIOPDA]. 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: Imidazolidine derivative $C_{10}H_{18}N_2O_4$ [NIOPDA], ADMET; DFT; HOMO-LUMO, MESP.

I. Introduction

Imidazolidines represent a significant class of nitrogen-containing heterocyclic compounds because of their diverse biological and pharmacological properties. Various imidazolidine derivatives have demonstrated a broad spectrum of biological activities, including antimicrobial[1] analgesic, [2] anti-inflammatory[3], oral hypoglycemic [4], and anticonvulsant activity [4]. These diverse biological properties establish imidazolidines as promising structural frameworks for the design and development of novel therapeutic agents. 3a,8a-Dihydroxy-1,3,3a,8a-tetrahydro indeno[1,2-d]imidazole-2,8-dione is the compound's title. Our research team synthesized [NIOPDA] and detailed both its synthesis and supramolecular chemistry [5]. The present study produced various structural and biological properties of the title molecule using Gaussian 09 software and the DFT B3LYP/LANL2DZ technique. To examine the chemical reactivity and reactive sites of the molecule, electronic characteristics such as HOMO, LUMO, frontier orbital energy difference, and molecular electrostatic potential surface (MESP) have been demonstrated. Electrical metrics such as dipole moment, molecular polarizability, and initial static hyperpolarizability have been used to predict the biological properties of the molecule. To assess the pharmacological efficacy, the pharmacokinetic and ADMET properties have also been calculated.

II. Material and Methods

Gaussian 09 software was used to perform quantum chemical calculations for the molecule NIOPDA [6]. 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 [7-9]. 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 [10]. VEDA 4.0 software was used to calculate the potential energy (PED) distribution for these modes [11]. SWISSADME online program was used to evaluate ADMET and pharmacokinetic properties [12].

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), a cyclopentanone ring (R2), and a Imidazolidine-2,4-dione (R3). Energy minimization has been used to optimize the equilibrium geometry for the lowest energy conformer. The optimized geometry of the molecule NIOPDA 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.

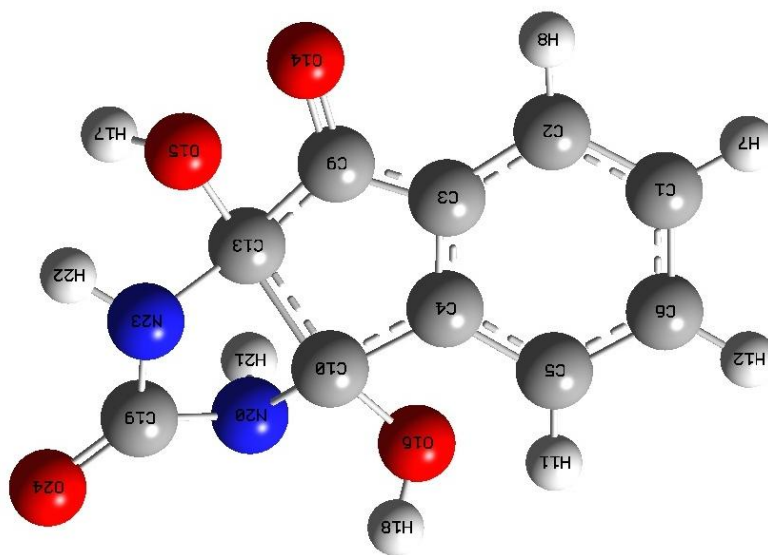


Fig. 1: Optimized geometrical structure of NIOPDA

The optimized bond lengths of (C=O) are computed within the range of 1.21-1.24 Å. The optimized bond lengths of (C-N) are computed within the range of 1.44-1.45 Å and bond lengths of (C-H) are determined to be 0.96 to 1.01 Å. The (C-C) stretching is found to be in the range of 1.46 Å-1.58 Å for cyclopentane ring. The (C=O) stretching exhibited a lower value of 1.24 Å in comparison to the (C-O) stretching, which was determined at 1.39 Å. The optimized (O-H) stretching modes were determined at 0.89-0.94 Å. These optimized bond lengths are consistent with the experimental X-ray values [5] 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.

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

S. No.	Parameter	Method	DFT	S. No.	Parameter	Method	DFT
		X ray	B3LYP			X ray	B3LYP
	Stretching (Å)				Bond Angle (Deg)		
1.	R(1,2)	1.38	1.3883	41.	A(4,10,13)	74.854	103.71
2.	R(1,6)	1.39	1.4288	42.	A(4,10,20)	126.0605	113.22
3.	R(1,7)	0.97	1.087	43.	A(13,10,16)	166.4114	115.83
4.	R(2,3)	1.39	1.4306	44.	A(13,10,20)	51.88	102.17
5.	R(2,8)	0.96	1.0848	45.	A(16,10,20)	116.2951	112.93
6.	R(3,4)	1.39	1.4547	46.	A(9,13,23)	133.1486	111.16
7.	R(3,9)	1.46	1.458	47.	A(9,13,10)	69.69	104.99
8.	R(4,5)	1.39	1.4494	48.	A(10,13,15)	164.414	116.95
9.	R(4,10)	1.51	1.4063	49.	A(10,13,23)	67.7436	102
10.	R(4,16)	-	2.3965	50.	A(15,13,23)	113.0253	113.44
11.	R(5,6)	1.39	1.3799	51.	A(9,15,17)	68.364	-
12.	R(5,11)	1.01	1.084	52.	A(13,15,14)	65.8517	-
13.	R(6,12)	0.96	1.0868	53.	A(13,15,17)	102.6595	107.1
14.	R(9,13)	1.54	1.4379	54.	A(14,15,17)	36.8082	-
15.	R(9,14)	1.21	1.3195	55.	A(10,13,23)	67.7436	102
16.	R(9,15)	-	2.342	56.	A(15,13,23)	113.0253	113.44
17.	R(10,13)	1.58	3.3697	57.	A(9,15,17)	68.364	-
18.	R(10,16)	1.39	1.3957	58.	A(13,15,14)	65.8517	-
19.	R(10,20)	1.45	1.3943	59.	A(13,15,17)	102.6595	107.1
20.	R(11,16)	-	2.3232	60.	A(14,15,17)	36.8082	-
21.	R(13,15)	1.39	1.3657	61.	A(4,16,18)	139.9413	-
22.	R(13,23)	1.44	1.3918	62.	A(10,16,18)	112.6374	108
23.	R(14,15)	-	2.4809	63.	A(20,19,23)	112.0	108.47
24.	R(15,17)	0.94	1.02	64.	A(20,19,24)	122.3921	126.05

25.	R(16,18)	0.89	0.982	65.	A(23,19,24)	125.6043	125.48
26.	R(19,20)	1.35	1.4625	66.	A(10,20,19)	115.3859	113.31
27.	R(19,23)	1.36	1.3729	67.	A(10,20,21)	116.3628	122.7
28.	R(19,24)	1.24	1.2457	68.	A(19,20,21)	112.7061	122.8
29.	R(20,21)	0.86	1.0209	69.	A(13,23,19)	124.8886	112.65
30.	R(22,23)	0.83	1.019	70.	A(13,23,22)	116.594	122.8
31.	Angle bending (deg)			71.	A(19,23,22)	116.1168	119.6
32.	A(2,1,6)	120.11	120.68	72.	A(3,4,5)	118.6215	-
33.	A(2,1,7)	119.9373	119.2	73.	A(3,4,10)	124.1687	112.3
34.	A(6,1,7)	119.9433	120.1	74.	A(3,4,16)	152.788	-
35.	A(1,2,3)	122.2949	118.12	75.	A(5,4,10)	116.7533	127.23
36.	A(1,2,8)	121.1786	121.2	76.	A(5,4,16)	86.0158	-
37.	A(3,2,8)	116.5123	120.6	77.	A(4,5,6)	121.4627	117.9
38.	A(2,3,4)	117.3639	121.22	78.	A(4,5,11)	117.7914	119.6
39.	(2,3,9)	113.7345	128.63	79.	A(6,5,11)	120.7215	122.5
40.	A(4,3,9)	128.8844	110.13	80.	A(1,6,5)	119.781	121.62
81.	A(1,6,12)	120.074	120.9				
82.	A(5,6,12)	120.1415	117.3				
83.	(3,9,13)	125.3817	108.32				
84.	A(3,9,14)	121.2247	128.27				
85.	A(3,9,15)	154.954	-				
86.	A(13,9,14)	112.2875	123.41				

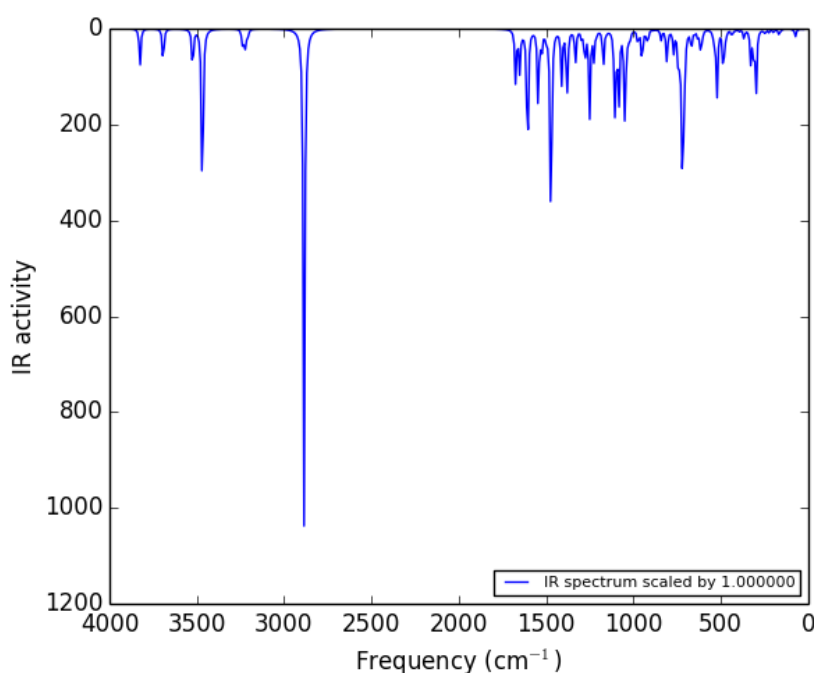


Fig.2: Simulated IR spectrum of NIOPDA

3.2 Assignments of Vibrational Modes

The analyzed compound, NIOPDA 24 atoms, thus exhibits 66 vibrational modes. The electron-electron interaction and the an-harmonicity were ignored [13]. The calculated frequencies are at a higher level compared to the experimental values [5] 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 [14]. 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, Fig 2.

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

S.No.	Calc Freq		Exp freq	Assignment Modes [PED %]
	Unscaled	Scaled	FTIR	
1	3666	3519	3556	$\nu(\text{O16-H18})[100]$

2	3575	3432		v(N23-H22)[100]
3	3532	3391	3312	v(N20-H21)[100]
4	3254	3124	3175	v(C5-H11)[79]+v(C6-H12)[11]
5	3246	3116		v(C1-H7)[80]+v(C2-H8)s-R2[10]
6	3222	3093		v(C6-H12)[43]+v(C1-H7)[38]+v(C2-H8)[11]
7	3204	3076		v(C6-H12)[49]+v(C1-H7)[45]
8	3067	2944		v(O16-H18)[96]
9	1702	1634	1682	v(C24=O19)[62] {char}+v(N23=C19)[17]+φ(H22-N23-C19)[13]
10	1652	1586	1605	v(C6=C5)[31]+v(C2=C1)[18] {char}
11	1604	1540		v(C10-C4)[39]
12	1551	1489		v(C13-C19)[18]+v(N23-C13)[15]+φ(H17-O15-C13)[23]
13	1505	1445		v(N23-C13)[18]+φ(H22-N23-C19)[46]
14	1492	1432	1429	φ(H21-N20-C19)[42]+φ(H7-C1-C2)[11]+φ(H8-C2-C1)[27]
15	1469	1410		φ(H22-N23-C19)[46]+φ(H12-C6-C1)[13]
16	1443	1385	1340	φ(H21-N20-C19)[15]
17	1349	1295	1296	φ(H22-N23-C19)[22]
18	1296	1244		φ(H8-C2-C1)[25]
19	1263	1212	1218	φ(H11-C5-C6)[12]
20	1208	1160	1179	φ(H12-C6-C1)[27]+φ(H7-C1-C2)[20]
21	1203	1155		v(N13-C13)[18]+φ(H17-O5-C13)[10]+φ(H7-C1-C2)[11]
22	1192	1144	1113	v(O14-C9)[14]+φ(H18-O16-C10)[10]+φ(H17-O15-C13)R3[14]
23	1136	1091		v(C4-C5)[10]+φ(H34-O4-C15)[29]
24	1045	1003		τ(H7-C1-C2-C3)[27] +τ(H8-C2-C1-C6)[21]+τ(H12-C6-C1-C2)[15]
25	1040	998		v(O16-C10)[24]+φ(C4-C5-C6)[11]
26	1026	985	933	τ(H11-C5-C6-C1)[27]+τ(H12-C6-C1-C2)[33]+τ(H8-C2-C1-C6)[26]
27	915	878		τ(H7-C1-C2-C3)[23] +τ(H11-C5-C6-C1)[27]+τ(H8-C2-C1-C6)[26]
28	892	856		τ(H17-O15-C13-N23)[93] {CHAR}
29	807	775		τ(H12-C6-C1-C2)[30]+τ(H7-C1-C2-C3)[28]+τ(H11-C5-C6-C1)[10]+
30	779	748	742	τ(H11-C5-C6-C1)[10] +ω(O14=C9-C3-C13)[11]+ω(C10-C3-C5-C4)[24]
31	762	732		τ(H22-N23-C19-N20)[43]+τ(H7-C1-C2-C3)[28]
32	710	682		τ(H21-N20-C19-N23)[19]+τ(H7-C1-C2-C3)[14]
33	707	679		τ(H22-N23-C19-N20)[22]
34	684	657	659	ω(O14=C9-C3-C13)[32]+ω(C10-C3-C5-C4)[24]
35	654	628		φ(C2-C1-C6)[12]+φ(C1-C6-C5)[19]+φ(C3-C2-C1)[12]
36	583	560		φ(C13-C9-C3)[10]+φ(C1-C6-C5)[11]
37	567	544		φ(C4-C5-C6)[15]+φ(C19-N23-C13)[14]+φ(C3-C2-C1)[12]
38	519	498		τ(C4-C5-C6-C1)[16] +ω(C15-N23-C9-C13)[13]
39	494	474		φ(N23-C13-C9)[17]+ +ω(C9-C4-C2-C3)[13]
40	455	437		φ(O24-C19-C23)[12]+τ(C3-C2-C1-C6)[12] +ω(C15-N23-C9-C13)[13]
41	436	419		φ(O24-C23-N19)[17]+φ(O16-C10-N20)[11]
42	400	384		φ(O14-C9-C13)[12]+φ(O24-C19-C23)[16]
43	371	356		φ(O14-C9-C13)[12]+φ(O24-C19-C23)[11]
44	347	333		φ(O14-C9-C13)[10]+φ(O16-C10-N20)[14]
45	308	296		v(C9-C3)[17]+φ(O15-C13-C9)[13]
46	290	278		φ(N23-C13-C9)R2[13]
47	520	500		τ(H9-N8-C10-N7)[16]
48	487	467		τ(H9-N8-C10-N7)[20]+τ(H34-O4-C15-C7)[34]
49	479	459		τ(O23-H33-O3-C7)[23]+τ(H34-O4-C15-C7)[14]
50	468	449		φ(N5-C17-C18)[11]
51	437	419		φ(N5-C17-C22)[14]+τ(C-C-C-C)R3[11]
52	426	408		τ(C-C-C-C)R4[68]
53	421	405		v(S1-C16)[13]
54	419	403		φ(S1-C16-N5)[14]+φ(C-C-C)R2[10]
55	385	369		v(O3-H33)[26]+φ(O3-C7-C8)[10]

56	371	356	$\phi(\text{O4-C15-N6})[15] + \phi(\text{O=C8-C9})[13] + \phi(\text{C-C-C})\text{R2}[12]$
57	347	334	$\phi(\text{O3-C7-N5})[14] + \phi(\text{O=C8-C9})[10] + \phi(\text{C-C-C})\text{R2}[12]$
58	308	296	$\tau(\text{H36-O23-H33-O3})[56]$
59	290	278	$\phi(\text{N5-C16-C6})[11] + \omega(\text{O3-C7-C8-C15})[11]$
60	250	240	$\nu(\text{N6-C16})[10]$
61	167	161	$\phi(\text{C13-C14-C15})[15]$
62	155	149	$\nu(\text{O4-H34})[11] + \phi(\text{S1-C16-N6})[16]$
63	128	123	$\nu(\text{O23-H36})\nu(\text{O23-H37})[24] + \phi(\text{S1-C16-N5})[14]$
64	102	98	$\phi(\text{O2-H36-O23})[11] + \omega(\text{C8-C9-C10-C14})[11]$
65	89	85	$\phi(\text{S1-C16-N5})[19] + \omega(\text{C8-C9-C10-C14})[11]$
66	25	24	$\tau(\text{C15-N6-C16-N5})[11] + \tau(\text{C-C-C-C})\text{R3}[11]$

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 3519 cm^{-1} with 100% potential energy distribution [PED]. These vibrations manifest as a singular weak absorption peak at 3556 cm^{-1} in the experimental FTIR spectra [5A].

3.2.2 N-H stretching

The -N-H stretching vibrations of NIOPDA is computed at a frequency of $3432\text{--}3391\text{ cm}^{-1}$ with a 100% PED while the experimental value shows peaks at 3312 cm^{-1} .

3.2.3 C-H vibrational modes

Aromatic C-H stretching are predicted to occur within the frequency range of $3116\text{--}3076\text{ cm}^{-1}$. These vibrations manifest as a slight absorption peak seen at 3175 cm^{-1} in the FTIR spectra, all exhibiting high PED values. The C-H in-plane bending frequencies are extremely useful for characterization and are found in the frequency range of $1300\text{--}1000\text{ cm}^{-1}$ [15]. The calculated frequencies within the range of $1295\text{--}1003\text{ cm}^{-1}$ correspond precisely to the C-H in-plane bending vibrations, appearing as a significant band in the FTIR spectra between 1296 and 1179 cm^{-1} .

3.2.4 C=O stretching

The $\nu(\text{C=O})$ stretching is estimated at 1634 cm^{-1} , corresponding to a very intense peak at 1682 cm^{-1} in the FTIR spectrum, with high PED value.

3.2.5 C-C vibrational modes

The $\nu(\text{C-C})$ aromatic stretch produces the typical bands in the spectral region of $1600\text{--}1000\text{ cm}^{-1}$ [17]. In the current molecule investigation, $\nu(\text{C-C})$ stretching vibrations are detected in FTIR spectra at frequencies 1605 cm^{-1} , which are computed by DFT within the frequency range of 1489 and 1586 cm^{-1} , these modes are combined with the in-plane bending modes.

3.2.6 C-N vibrations

The investigation about (C-N) vibrational modes is challenging because they mix with other vibrational modes in the frequency range $1200\text{--}1000\text{ cm}^{-1}$. For NIOPDA, these are assigned to the experimental frequency peaks in the spectrum at 1155 cm^{-1} and are estimated within the frequency range of $1245\text{--}1040\text{ cm}^{-1}$.

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 [16]. 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 [5] and are well matched with the computed values. The table includes the list of each of these modes comprising several peaks in the experimental spectra at frequencies 742 and 659 cm^{-1} and are optimized in the range 748 and 755 cm^{-1} respectively. These seems to be the characteristics modes for the title compound NIOPDA.

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 [18, 19].

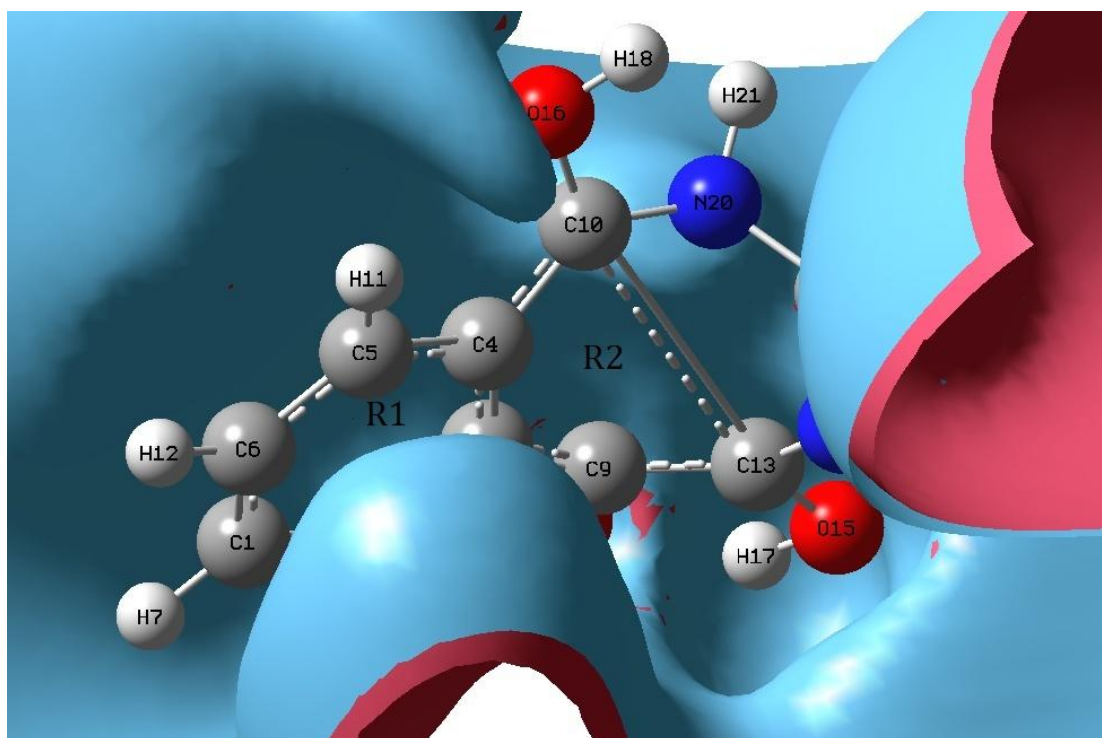


Fig. 4 2D MESP plot of NIOPDA

Additionally, the area surrounding the Ring R1 is deficient in electrons (represented by the minimum electrostatic potential in blue), providing binding sites for nucleophilic attack.

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 5.61 eV, the electron affinity as 2.801 eV, the electronegativity as 4.2055 eV, and the chemical hardness as 1.4045 eV. Therefore, the title molecule should have sufficient biological activity, according to these criteria and the electrophilicity levels (6.29 eV).

Table 3 Electronic parameters of NIOPDA

Parameters	DFT Values
E_{HOMO} (eV)	-5.61
E_{LUMO} (eV)	-2.801
ΔE (eV)	2.805
Ionization potential (I)	5.61
Electron affinity(A)	2.801
Electronegativity(χ)	4.2055
Chemical potential(μ)	-4.2055
Chemical hardness(η)	1.4045
Global softness(S)	0.356
Electrophilicity index (ω)	6.29

3.4 Electrical parameters

The dipole moment of the NIOPDA molecule is aligned in the Y-Z plane, with calculated values of 3.93 D (Table 4). The α_{YY} and α_{ZZ} components has a greater contribution to the mean polarizability $\langle\alpha\rangle$ than the α_{XX} component, which accounts for their greater elongation along the Y-Z-axes. The average polarizability $\langle\alpha\rangle$ was recorded at -91.72 a.u., 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. Organic compounds with an (N-H) group exhibit increased molecular hyperpolarizability and mechanical stability because of the presence of hydrogen bond interactions. Furthermore, the first-order hyperpolarizability correlates with the energy band gap that exists between the HOMO and LUMO. Consequently, a wider band gap is associated with a reduced first hyperpolarizability. The calculated first-order

hyperpolarizability β_{total} is 0.046×10^{-30} e.s.u., which is less than the benchmark compound Urea ($\beta_{\text{total}} = 0.3728 \times 10^{-30}$ e.s.u.), suggesting that it is not appropriate for nonlinear optical (NLO) purposes [22, 23].

Table 4: Electric parameters for NIOPDA by DFT

Table 2: Electric parameters for NPTU by DFT

Components	NPTU	Components	Hyperpolarizability (e.s.u. *10 ⁻³³)
α_{xx}	-107.36	β_{XXX}	12.36
α_{xy}	14.37	β_{XXY}	-44.74
α_{yy}	-152.46	β_{XYX}	29.48
α_{xz}	-11.93	β_{YYX}	-42.86
α_{yz}	9.92	β_{xzx}	-25.37
α_{zz}	-141.00	β_{XYZ}	0.88
$\langle \alpha \rangle$	-133.61	β_{YYZ}	12.00
		β_{XZZ}	-20.37
Electric Dipole	4.47	β_{YZZ}	-17.75
moment (μ) (D)		β_{ZZZ}	7.22
		β_1	460.53
		β_2	11098.71
		β_3	37.85
		β_{total}	107.69

3.5 Characteristics of Drug Likeness and ADME Profiles

ADME profiles and drug likeness metrics were assessed utilizing PreADME and SWISSADME online tools for the compound under investigation and are shown in Table 5. The Lipinski rule of 5 (LiR of 5) helps to distinguish between drug-like and non-drug-like molecules. The calculated values for drug likeness parameters of the title compound are: (i) HBD is 4 (≤ 5), (ii) HBA is 4 (≤ 10), (iii) MW is 220.18 g/mol (≤ 500 g/mol), (iv) MR is 59.4 ($40\text{--}130 \text{ cm}^3 \text{ mol}^{-1}$) and (v) log P is 0.35 (0-5), suggesting excellent permeability through biological membranes and advantageous binding to plasma proteins [24-26].

Table 5 ADME Prediction of DTIID from SwissAdDME software

Molecule	Molecule 1
Canonical SMILES	<chem>O=C1NC(=C([O])c2c([C](N1)O)cccc2)O</chem>
Formula	C10H8N2O4
MW	220.18
#Heavy atoms	16
#Aromatic heavy atoms	6
Fraction Csp3	0.1
#Rotatable bonds	0
#H-bond acceptors	4
#H-bond donors	4
MR	59.4
TPSA	81.59
iLOGP	0
XLOGP3	-0.34
WLOGP	-0.6

MLOGP	-0.08
Silicos-IT Log P	-0.71
Consensus Log P	0.35
ESOL Log S	-1.27
ESOL Solubility (mg/ml)	1.19E+01
ESOL Solubility (mol/l)	5.39E-02
ESOL Class	Very soluble
Ali Log S	-0.91
Ali Solubility (mg/ml)	2.70E+01
Ali Solubility (mol/l)	1.23E-01
Ali Class	Very soluble
Silicos-IT LogSw	-1.52
Silicos-IT Solubility (mg/ml)	6.63E+00
Silicos-IT Solubility (mol/l)	3.01E-02
Silicos-IT class	Soluble
GI absorption	High
BBB permeant	No
Pgp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
log Kp (cm/s)	-7.88
Lipinski #violations	0
Ghose #violations	1
Veber #violations	0
Egan #violations	0
Muegge #violations	0
Bioavailability Score	0.55
PAINS #alerts	0
Brenk #alerts	0
Leadlikeness #violations	1
Synthetic Accessibility	3.01
Caco-2 cell permeability (nm/s)	0.15
Plasma_Protein_Binding	86.3566
Skin_Permability (log Kp)	-4.16788
HIA (%)	67.312
MDCK cell permeability (nm/s)	41.2356

The van der Waals topological polar surface area (TPSA) of the compound is 81.59 Å², which is less than 120 Å². The partition coefficient (Milog P) is -0.08, which is within the range of ≤ 5 . Based on these values, it is evident that the compound NIOPDA surpasses the LiR of 5 and is therefore considered suitable for in vivo testing. In terms of ADME parameters, the human intestinal absorption (HIA) value represents the combined absorption and bioavailability derived from the excretion through urine, bile, and feces, with a calculated value of 71.217% [27, 28]. CaCo-2 is a cell line derived from human colon epithelial tissue and is frequently used as a model to evaluate drug absorption in the human digestive system. The calculated value of 3.29 nm/s falls outside the acceptable range of [13.0–76.7 nm/s], indicating low permeability intestinal absorption. Madin Darby Canine Kidney (MDCK) cells are commonly used in vitro to determine the permeability of drug candidates, offering insights into their potential absorption in the gastrointestinal tract and across the blood-brain barrier. Drug

permeability through MDCK cell monolayers is typically measured in nm/s and is used to classify the drug's absorption capacity, as MDCK cells grow faster than CaCo-2 cells [29]. The permeability measurement for MDCK cells was found to be 41.2356 nm/s [25–500 nm/s], which is suitable for elimination by renal cells. The computed skin permeability value for NIOPDA is -2.771 ($\log K_p < -4$), indicating that the compound does not penetrate the skin. The plasma protein binding value is 86.35, which is within the range of <80% PPB <99, suggesting strong binding with blood plasma. The inability of NIOPDA to inhibit CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 indicates that the molecule requires xenobiotic metabolism in the body. Typically, a molecule with 10 or fewer rotatable bonds (RBs) is considered to have favorable drug-like properties. NIOPDA has no rotatable bond. In both in vitro and in silico evaluations of drug-like properties, the expected pharmacokinetic parameters and physicochemical characteristics known as Lipinski's rules are important [30, 31].

3.6. Toxicity predictions

Assessing toxicity is crucial in drug development and aids in recognizing harmful effects of new medications on the body. The toxicity of the compound NIOPDA was assessed using the ProTox-II online software [32]. The findings of organ toxicity indicated that NIOPDA was forecasted to be hepatotoxic, respiratory, and clinical toxic (Table 6).

Table 6 Prediction of Toxicity of NIOPDA using ProTox-3.0 software

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Active	0.52
Organ toxicity	Neurotoxicity	neuro	Inactive	0.54
Organ toxicity	Nephrotoxicity	nephro	Active	0.54
Organ toxicity	Respiratory toxicity	respi	Active	0.53
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.78
Toxicity end points	Carcinogenicity	carcino	Active	0.50
Toxicity end points	Immunotoxicity	immuno	Inactive	0.95
Toxicity end points	Mutagenicity	mutagen	Inactive	0.59
Toxicity end points	Cytotoxicity	cyto	Inactive	0.70
Toxicity end points	BBB-barrier	bbb	Inactive	0.53
Toxicity end points	Ecotoxicity	eco	Inactive	0.68
Toxicity end points	Clinical toxicity	clinical	Active	0.59
Toxicity end points	Nutritional toxicity	nutri	Inactive	0.54
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.74
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.96

Classification	Target	Shorthand	Prediction	Probability
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.95
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.92
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.94
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.96
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.93
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.93
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.73
Tox21-Stress response pathways	Phosphoprotein (Tumor Suppressor) p53	sr_p53	Inactive	0.77
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.93
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.82
Molecular Initiating Events	Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.85
Molecular Initiating Events	Transthyretin (TTR)	mie_ttr	Inactive	0.53
Molecular Initiating Events	Ryanodine receptor (RYR)	mie_ryr	Inactive	0.81
Molecular Initiating Events	GABA receptor (GABAR)	mie_gabar	Inactive	0.81

Classification	Target	Shorthand	Prediction	Probability
Molecular Initiating Events	Glutamate N-methyl-D-aspartate receptor (NMDAR)	mie_nmdar	Inactive	0.89
Molecular Initiating Events	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPA)	mie_ampar	Inactive	0.97
Molecular Initiating Events	Kainate receptor (KAR)	mie_kar	Inactive	0.99
Molecular Initiating Events	AChE	mie_ache	Inactive	0.87
Molecular Initiating Events	Constitutive androstane receptor (CAR)	mie_car	Inactive	0.99
Molecular Initiating Events	Pregnane X receptor (PXR)	mie_pxr	Inactive	0.62
Molecular Initiating Events	NADH-quinone oxidoreductase (NADHox)	mie_nadhox	Inactive	0.85
Molecular Initiating Events	Voltage gated sodium channel (VGSC)	mie_vgsc	Inactive	0.67
Molecular Initiating Events	Na⁺/I⁻ symporter (NIS)	mie_nis	Inactive	0.65
Metabolism	Cytochrome CYP1A2	CYP1A2	Inactive	0.84
Metabolism	Cytochrome CYP2C19	CYP2C19	Inactive	0.88
Metabolism	Cytochrome CYP2C9	CYP2C9	Inactive	0.61
Metabolism	Cytochrome CYP2D6	CYP2D6	Inactive	0.78
Metabolism	Cytochrome CYP3A4	CYP3A4	Inactive	0.90
Metabolism	Cytochrome CYP2E1	CYP2E1	Inactive	1.0

The results for toxicity endpoints indicated that NIOPDA shows activity against Hepatotoxicity, Neurotoxicity, Nephrotoxicity, Respiratory toxicity, Carcinogenicity and Clinical toxicity. The predicted probabilities ranged from 0.50 to 0.59, with clinical toxicity showing the highest probability (0.59). Among the evaluated endpoints, clinical toxicity showed the highest predicted probability (0.59), whereas carcinogenicity showed the lowest (0.50). The title compound demonstrated inactivity for molecular initiation events across all parameters, including the GABA receptor. Further in-vitro and in-vivo toxicological studies are required to validate these predictions and establish the actual safety profile of the compound.

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 [NIOPDA] 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 (2.805 eV) indicate its high polarizability and chemical reactivity. Based on the calculated electronic parameters, particularly the electrophilicity levels (6.29 eV), the compound in question is expected to exhibit adequate biological activity. The title compound exhibited promising ADMET characteristics and met Lipinski's drug likeness criteria. These findings may lead to the development of additional new biologically active compounds that contain imidazole rings.

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