Original Article: Anti-microbial evaluation, Experimental and Theoretical Insights into Molecular Structure, Electronic Properties, and Chemical Reactivity of (*E*)-2-((1*H*-indol-3-yl)methylene)-2,3-dihydro-1*H*-inden-1-one

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ABSTRACT

The present investigation dealt with antimicrobial computational study of (*E*)-2-((1*H*-indol-3-yl) methylene)-2,3-dihydro-1*H*-inden-1-one (IMDHI) molecule. The spectroscopic characterization methods such ^{1}H NMR, and ^{13}C NMR techniques were used to confirm the structure of the (IMDHI) molecule. Antimicrobial activity of the IMDHI molecule was evaluated against two Gram-negative (*E. coli*&*P.Vulgaris*) and two Gram-positive (*S. aureus*&*B. subtilis*) bacteria whereas antifungal investigation was performed against A. Niger and C. albicans fungal species. The IMDHI molecule is found to display a strong activity against *E. coli*, *P. Vulgaris*, and, *B. subtilis* bacterial strains. The density functional theory (DFT) calculations were performed using the Gaussian-03 package. The B3LYP/6-31G (d, p) basis set was used for the evaluation of the molecular structure, electronic properties, and chemical reactivity properties. Ionization potential, electron affinity, electronegativity, chemical hardness and softness, global electrophilicity, and chemical potential were calculated using HOMO and LUMO energy values. To investigate the electron distribution, Mulliken atomic charges and molecular electrostatic potential surfaces were discussed.

Introduction

Chalcones, both naturally occurring and synthetic analogs, have a broad range of biological activities. The chalcone nucleus is one of the most common and well-known intermediates, found in a wide range of flavonoids and medicinal agents. This component is used to biosynthesize naturally occurring secondary metabolites including flavonoids and isoflavonoids [1-5]. Naturally occurring and synthetic chalcone compounds

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have proven to have potential biological activity and harmless profiles. Chalcones are the versatile materials for the development of various heterocyclic frameworks such as pyrazoline [6], oxazoline [7], thiazine [8], oxazine [9], pyrimidine [10], etc. Chalcones, widely recognized as 1,3-diaryl-2-propen-1-ones, are open-chain flavonoids that have a three-carbon, α, β-unsaturated carbonyl system appending the two aromatic rings [11]. Furthermore, Chalcones containing indanone moiety are likely to be the most pondered molecules in therapeutic science in view of their broad scope of pharmacologically exercises [12]. 1-indanone and its structural analogs have been thought to play a significant role in the field of medicinal chemistry [13]. The presence of active methylene hydrogens contiguous to the carbonyl gathering of indanone makes it significant in various organic transformations. Lately, indanone derivatives with anticancer [14], antibacterial [15], antiviral [16], antifungal [17], antimalarial [18], anti-inflammatory [19] exercises have been accounted for. Indole is a potent supporting molecule that aids in the broadening of the main pharmacophore by transforming its functional groups [20]. It's worth noting that the indole moiety is an essential pharmacophoric fragment for drug design and production, according to the literature. Indole is a notable heterocyclic compound containing a pyrrole ring with a benzene ring fused to α, β position. Indole bearing compounds possess various types of biological activities such as antibacterial [21], antifungal [22], antiviral [23], antimalarial [24], and anti-HIV [25]. Some of the indole compounds are quite effective antioxidants, protecting both lipids and proteins from peroxidation and influence the antioxidant efficacy in biological systems [26, 27]. Similarly, chalcone (1,3-diaryl-2-propen-1-one) moiety frames the focal center for an assortment of biologically active compounds with various medicinal properties. From the perspective of molecular design, the combination of two pharmacophores into a single molecule has been found to enhance the biological properties of the resultant hybrid molecule. The remarkable bioactivity of indole-based chalcones, as well as their unusual structural variety, makes them appealing targets for drug development. Green chemistry principles have been found to be utilized for the synthesis of various organic compounds [28-32].

Over the past few years, theoretical calculations based on DFT have been effectively used to assess various structural aspects of synthetically and pharmacologically important organic motifs [33, 34]. The DFT/B3LYP method using various basis sets has been found to be extremely useful in studying the structural, chemical, and spectroscopic properties of molecules [35-38]. The Quantum chemical method allows the prediction of different properties based on knowledge of a few quantum superpositions and the use of standard programming for electronic structure calculations [39-50]. DFT has received a lot of attention in the last two decades because it is less computationally expensive. B3LYP stands for "Becke, 3-parameter, Lee-Yang-Parr". The density functional theory based on theoretical quantum calculations has been effectively used to explore the structural and chemical properties of organic molecules [51-56] The importance of spectroscopic and quantum calculations in predicting various quantum chemical parameters and thermodynamic aspects has been discovered [57-59]. Taking into consideration of entire mentioned properties and the future province of the chalcone derivatives, we have designed (*E*)-2-((1*H*-indol-3-yl)methylene)-2,3-dihydro-1*H*-inden-1-one molecule and explored for the investigation of their structural, chemical, electronic, thermodynamic, and quantum chemical parameters.

Materials and Methods

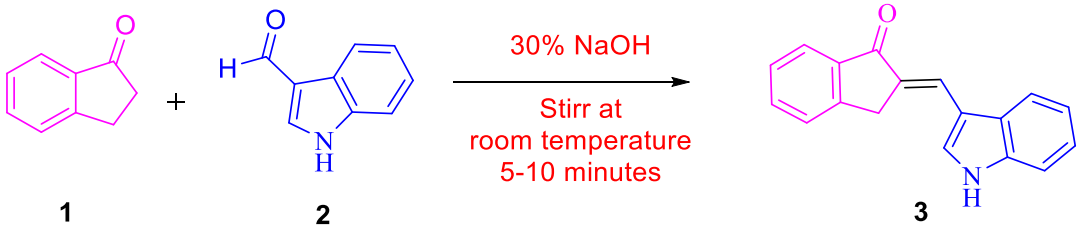
General remarks

All chemicals and solvents (Make- Sigma Aldrich and SD Fine) were purchased and used as received. The ^{1}HNMR and ^{13}C NMR experiments were carried out on sophisticated multinuclear FT-NMR Spectrometer (500 MHz) model Advance-II (Bruker). The compound was dissolved in $CDCl_3$ and the chemical shifts were reported in ppm using TMS as an internal

standard reference. The reactions were monitored by using thin-layer chromatography on Merck Aluminium TLC plate, silica gel coated with fluorescent indicator F254. All of the glassware was cleaned and dried in the oven before use.

Experimental procedure for the synthesis of (E)-2-((1H-indol-3-yl) methylene)-2,3-dihydro-1H-inden-1-one (IMDHI)

The compound **IMDHI** was synthesized using the Claisen-Schmidt condensation reaction. In a typical synthesis scheme, 2,3-dihydro-1*H*-inden-1-one (**1**, 10 mmol) and 1*H*-indole-3-carbaldehyde(**2**, 10 mmol) were mixed in 10 mL ethyl alcohol. 5 mL 30 percent NaOH was added to this. Then, the alkaline mixture was stirred at room temperature for 5-10 minutes until the formation of the product. The reaction was smothered by pouring onto crushed ice after it was completed (as determined by TLC). It was then acidified with dilute HCl, and the crude product obtained was filtered, dried, and recrystallized with hot ethanol to get crystals of the pure product (**3**). The reaction is presented in **Scheme 1**.



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Scheme 1. Synthesis of the **IMDHI** molecule

Spectral data

(*E*)-2-((1*H*-indol-3-yl)methylene)-2,3-dihydro-1*H*-inden-1-one*:* Dark Yellow colour; Yield; m.p.: 158-160 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 2H), 7.33 – 7.30 (m, 2H), 7.68 (s, 2H), 7.84 (s, 1H), 7.92 (m, 2H), 7.97 (m, 2H), 8.12 (m, 1H), 8.75 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.73, 111.47, 119.52, 121.42, 123.57, 123.73, 123.80, 124.18, 126.04, 126.24, 126.41, 126.53, 127.41, 132.57, 134.79, 137.19, 153.84, 208.21.

Computational details

The Gaussian 03 package was used to perform all calculations [60]. DFT with the B3LYP (Becke three-parameter Lee–Yang–Parr) exchange-correlation functional was used for all computational calculations. The molecular structure of **IMDHI** was optimized by employing the 6-31G(d,p) basis set. On fully DFT optimized geometry, the geometrical parameters, frontier molecular orbitals, global reactivity parameters, and MESP surfaces were all predicted using the same basis set. Ionization potential, electron affinity, electronegativity, chemical hardness and softness, global electrophilicity, and chemical potential were also calculated using HOMO and LUMO energy values.

Antimicrobial screening

The antimicrobial activities of the **IMDHI** molecule were determined using the Agar diffusion assay (Disc diffusion process, Disc size 6 mm) [61, 62]. Compound concentration was determined by making a stock solution [1000 microgram per mL] of each compound in distilled water. The concentration of 100 micrograms per disc was used in the assay. Microbiological media used for bacteria was Nutrient agar (Hi-media); composition (gL^{-1}): sodium chloride, 5.0; beef extract 10.0; peptone 10.0 (pH 7.2). Microbiological media for fungi was potato dextrose agar (all ingredients of Hi media); composition (gL^{-1}): potatoes infusion, 200; dextrose, 20; Agar, 15; final pH (at 25°C) 5.6±0.2. For antibacterial evaluation, Chloramphenicol was used as a standard and, Amphotericin-B for antifungal screening. Antibacterial screening was observed against *Escherichia coli* [2109] *Staphylococcus aureus*(NCIM 2079) *Proteus vulgaris* (NCIM

2172)and*Bacillussubtilis* [2063] while the antifungal screening was observed against *Aspergillus niger* (NCIM 545) and *Candida albicans* (NCIM 3471). [NCIM stands for National Collection of Industrial Microorganisms, and NCL is National Chemical Laboratory, Pune, India].

Results and Discussion

Chemistry

The title compound **IMDHI** was synthesized by the well-known Claisen-Schmidt reaction at room temperature. Solution of 30 percent NaOH was used to accomplish the transformation. This synthetic strategy is dependent on high product yields. The synthesized compound was examined using ^{1}H NMR and ^{13}C NMR spectroscopic methods. The ^{1}H NMR and ^{13}C NMR examination of the title compound have shown a great connection with their structures. In ^{1}H NMR spectra ofthe **IMDHI** molecule, the peak at 3.90 ppm (m, 2H) affirms the presence of saturated -CH_2 group of indanone counterpart in the synthesized compound. In ^{13}C NMR spectra, the same –CH_2 group can be confirmed by observing a peak at 35.73 ppm. The aromatic protons were observed in the 7.30 to 8.75 ppm range in ^{1}H NMR. The presence of carbonyl function in the synthesized compound can be confirmed by observing a peak at 208.21 ppm in ^{13}C NMR.

Computational study

Molecular structure, bond length, bond angle study

The optimized molecular structures of the **IMDHI** molecule at B3LYP/6-31G(d,p) basis set is presented in **Figure 1**. The DFT study uncovered that the **IMDHI** molecule had C1 point group symmetry, demonstrating that the molecule was overall asymmetric. **IMDHI** molecule with dipole moment 5.9583 Debye indicated that molecule had appreciable polarity. The total energy of the **IMDHI** molecule was −1029.21 **(Table 3)**.The bond length and bond angle data of the title molecule are given in **Table 1** and **Table 2**. The olefinic bond length in the **IMDHI** molecule was 1.3521 Å. The C20-C21 bond is the longest aromatic double bond and C17-C18 is the shortest aromatic double. The carbonyl bond (C9-O13) length is nearly 1.2252 Å. All-inclusive C3-C10 bond is the longest bond while N28-H29 shortest bond. All other bond length values are showing good agreement with the structures of the title molecule. The C4-C9-C14 bond angle is 106.1648°. Likewise, other bond angle data are rightly matching with the various bond angles of the **IMDHI** molecule.

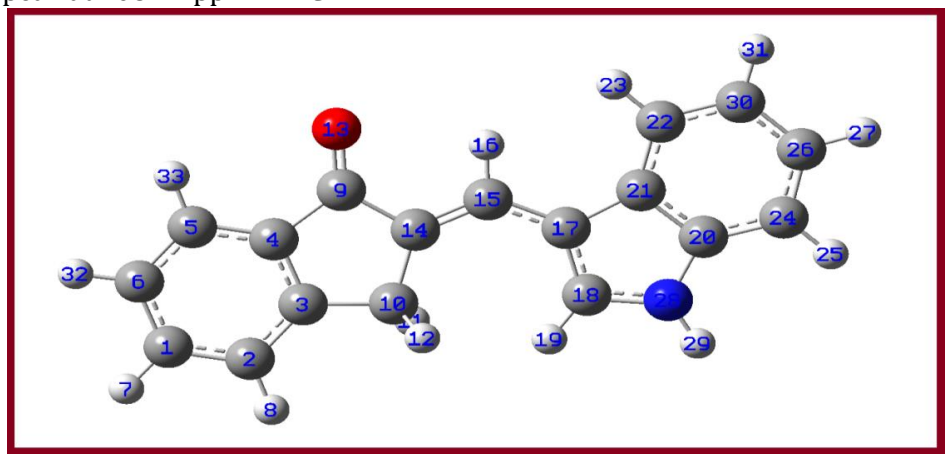

Figure 1. The optimized molecular structures of IMDHI molecule at DFT B3LYP/6-31G (d, p) basis set

Table 1. Optimized geometrical parameters of IMDHI molecule by DFT/ B3LYP with 6-31G (d, p) basis set

Bond lengths (Å)			
C1-C2	1.3981	C15-H16	1.0897
C1-C6	1.4027	C15-C17	1.4412
C1-H7	1.0865	C17-C18	1.3882
C2-C3	1.3931	C17-C21	1.4534
C2-H8	1.087	C18-H19	1.0788
C3-C4	1.4	C18-N28	1.3711
C3-C10	1.5187	C20-C21	1.4171
C4-C5	1.3953	C20-C24	1.3976
C4-C9	1.4874	C20-N28	1.3849
C5-C6	1.3933	C21-C22	1.4039
C5-H33	1.0858	C22-H23	1.0858
C6-H32	1.086	C22-C30	1.3894
C9-O13	1.2252	C24-H25	1.0861
C9-C14	1.4904	C24-C26	1.3899
C10-H11	1.0999	C26-H27	1.0857
C10-H12	1.0999	C26-C30	1.4092
C10-C14	1.5131	N28-H29	1.0073
C14-C15	1.3521	C30-H31	1.0857

Table 2. Optimized geometrical parameters of IMDHI molecule by DFT/ B3LYP with 6-31G (d, p) basis set

Bond Angles (°)			
C2-C1-C6	121.1409	C14-C15-H16	114.3157
C2-C1-H7	119.4537	C14-C15-C17	129.6292
C6-C1-H7	119.4055	H16-C15-C17	116.0551
C1-C2-C3	118.7164	C15-C17-C18	129.0974
C1-C2-H8	120.2241	C15-C17-C21	125.1407
C3-C2-H8	121.0595	C18-C17-C21	105.7619
C2-C3-C4	119.8658	C17-C18-H19	129.8823
C2-C3-C10	129.1601	C17-C18-N28	109.9346
C4-C3-C10	110.9741	H19-C18-N28	120.183
C3-C4-C5	121.7019	C21-C20-C24	122.7146
C3-C4-C9	109.9273	C21-C20-N28	107.0457
C5-C4-C9	128.3708	C24-C20-N28	130.2397
C4-C5-C6	118.3544	C17-C21-C20	107.4354
C4-C5-H33	119.7321	C17-C21-C22	133.8175
C6-C5-H33	121.9135	C20-C21-C22	118.7472
C1-C6-C5	120.2206	C21-C22-H23	120.6675
C1-C6-H32	119.5969	C21-C22-C30	118.954
C5-C6-H32	120.1824	H23-C22-C30	120.3784
C4-C9-O13	126.7432	C20-C24-H25	121.4754
C4-C9-C14	106.1648	C20-C24-C26	117.2253
O13-C9-C14	127.092	H25-C24-C26	121.2993
C3-C10-H11	111.3462	C24-C26-H27	119.4051
C3-C10-H12	111.3478	C24-C26-C30	121.1368
C3-C10-C14	103.5833	H27-C26-C30	119.4581
H11-C10-H12	106.4321	C18-N28-C20	109.8224
H11-C10-C14	112.1266	C18-N28-H29	124.9103

H12-C10-C14	112.1273	C20-N28-H29	125.2672
C9-C14-C10	109.3506	C22-C30-C26	121.2221
C9-C14-C15	120.8409	C22-C30-H31	119.5553
C10-C14-C15	129.8085	C26-C30-H31	119.2226

HOMO-LUMO and reactivity descriptors

The HOMO-LUMO orbitals of the molecule under investigation were obtained by using the TD-DFT method at CAM-B3LYP basis set. The HOMO-LUMO orbitals are called frontier molecular orbitals (FMOs) put together. The FMOs provides lots of information about the molecules' stability and reactivity. The energy gap between FMOs is very crucial to comprehend numerous significant electronic aspects of the molecules. The HOMO-LUMO of the title molecule with energy difference is given in **Figure 2**. The electronic parameters are given in **Table 3**. The **IMDHI** molecule is found to possess 6.59 eV electron ionization potential and 2.39 eV electron affinity value. Using Koopman's theorem, various global reactivity parameters such as chemical hardness (η), chemical softness (σ), global electrophilicity (ω), electronegativity (χ) and chemical potential (μ) were calculated from HOMO-LUMO energy values [63]. The chemical hardness and softness values were found for the **IMDHI** molecule 2.10 eV and 0.48 eV^{-1}, respectively.

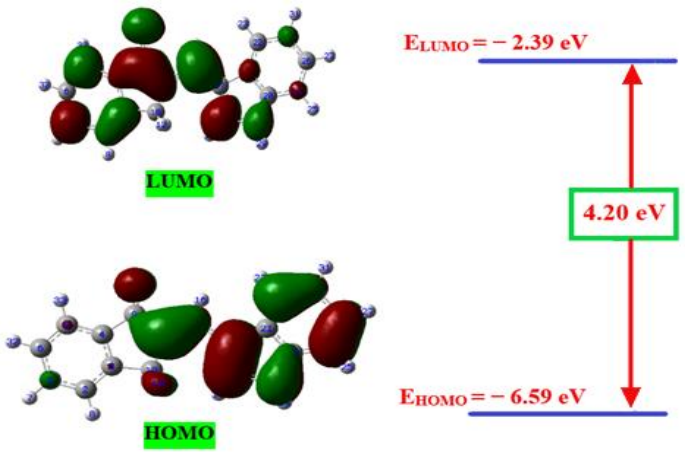

Figure 2.HOMO-LUMO representation of **IMDHI** molecule at TD-DFT CAM-B3LYP/6-31G (d, p) basis set

Table 3. Electronic parameters of IMDHI molecule

Electronic parameters	Value
E_{Total}(a.u.)	–1029.21
E_{HOMO} (eV)	–6.59
E_{LUMO} (eV)	– 2.39
I (eV)	6.59
A (eV)	2.39
ΔE (eV)	4.20

Table 4. Global reactivity parameters of IMDHI molecule

Global reactivity parameters	Value
η (eV)	2.10
σ (eV^{-1})	0.48
ω (eV)	4.80
X (eV)	4.49
μ (eV)	-4.49
ΔNmax (eV)	2.14

Mulliken atomic charges and MESP analysis

Mulliken charges emerge from Mulliken population analysis [64]. It gives a way to calculate partial atomic charges from computational simulations. The Mulliken charges are charges dependent on the charge density. The Mulliken atomic charges of the **IMDHI** molecule are given in **Table 5**. The investigation on Mulliken atomic charges revealed that all hydrogen atoms of the **IMDHI** molecule are having a positive character. In view of Mulliken population analysis, the most negative and positive carbon atoms in the **IMDHI** molecule are C10 (-0.290093) and C9 (0.339950), respectively. **Figure 3** portrays the MESP of the **IMDHI** molecule. MESP correlates the total charge distribution with dipole moment, electronegativity, and partial charges, and site of chemical reactivity of a molecule. It gives a visual strategy to understand the relative polarity of a molecule and serves as a useful quantity to explain the hydrogen bonding, reactivity, and structure-activity relationship of molecules. It is the potential energy of a proton at a particular location near a molecule. Different values of the electrostatic potential at the surface of a molecule appear with different colors. In general, the attractive potential appears in red color regions and those of repulsive potential appear in blue.

Table 5. Mulliken atomic charges of IMDHI molecule

Atom	Charge	Atom	Charge
1 C	-0.079168	18 C	0.080355
2 C	-0.138690	19 H	0.115236
3 C	0.058169	20 C	0.280635
4 C	0.065337	21 C	0.052873
5 C	-0.113200	22 C	-0.138053
6 C	-0.093658	23 H	0.097535
7 H	0.088564	24 C	-0.094665
8 H	0.080898	25 H	0.081029
9 C	0.339950	26 C	-0.104430
10 C	-0.290093	27 H	0.084462
11 H	0.124809	28 N	-0.620841
12 H	0.124801	29 H	0.265199
13 O	-0.506235	30 C	-0.095415
14 C	0.034535	31 H	0.084546
15 C	-0.132225	32 H	0.089738
16 H	0.112344	33 H	0.109376
17 C	0.036283	-	-

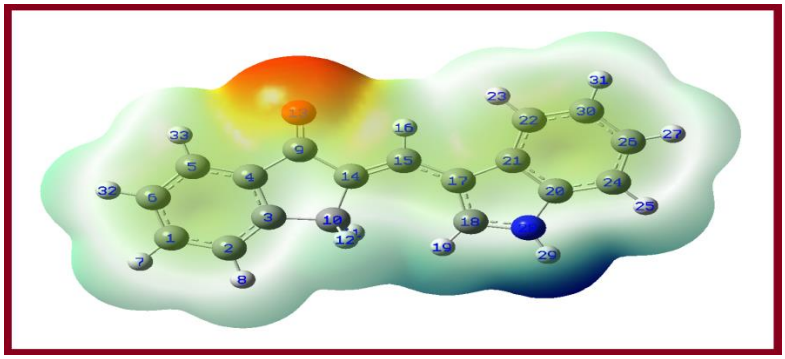

Figure 3. The Molecular electrostatic surface potential plot of **IMDHI** molecule

Antimicrobial Study

The antimicrobial examination of the synthesized **IMDHI** molecule was performed against two Gram-negative (*E. coli*&*P.Vulgaris*) and two Gram-positive (*S. aureus*&*B. subtilis*) bacteria whereas antifungal examination was performed against *A.Niger* and *C.albicans* fungal species. The posteffects of the antimicrobial evaluation are presented in **Table 6**. The outcomes imply that the **IMDHI** molecule is a very good antimicrobial agent against some of the tested strains. The **IMDHI** molecule has shown strong activity against *E. coli*, *P.Vulgaris,*and, *B. subtilis* bacterial strains but has not shown antibacterial action against the *S. aureus*and antifungal action against *A.Niger* and *C.albicans*. The antimicrobial data presented here could give a great stage to extra advancement of the antimicrobial agent. The minimum inhibitory concentration (MIC) was studied using the previously reported method [65].The MIC values of the synthesized compound were evaluated and the results are depicted in **Table 7,** which stresses the differential of sensitivity pathogens toward the title compound.

Table 6. Antibacterial and antifungal activity of IMDHI molecule

Entry	E. Coli	P. vulgaris	S. aureus	B. subtilis	A. Niger	C. Albicans
IMDHI	+++	++++	-	+++	-	-
Chloramphenicol	+++++	+++++	+++++	+++++	NA	NA
Amphotericin-B	NA	NA	NA	NA	++++	++++

+ = < 5 mm zone, ++ = 5-10 mm zone, +++ = >10-15 mm zone, ++++ = >15-20 mm, +++++ = > 20 mm, - = No inhibition, NA = Not applicable

Table 7. Minimum inhibitory concentration (MIC) of IMDHImolecule

Compound	*E.coli*	*P. vulgaris*	*S. aureus*	*B.subtilis*	*A.Niger*	*C.Albicans*
IMDHI	62.5	31.25	>250	31.25	>250	>250
Chloramphenicol	1.95	1.95	1.95	3.9	NA	NA
Amphotericin-B	NA	NA	NA	NA	1.95	1.95

Conclusion

In the current progression of investigation work, we have analyzed the geometrical parameters, frontier molecular orbitals, global reactivity parameters, MESP surfaces of the title molecule, and found that these computed outcomes are in worthy conformity with the experimental data. The synthesized chalcone was characterized by instrumental methods like PMR and CMR. **IMDHI** molecule with dipole moment 5.9583 Debye showed that molecule had appreciable polarity. The MESP plot showed the negative potential location for oxygen atom and the positive potential locations for hydrogen atoms. Our present study shows that **IMDHI** molecule pharmacological significant may be due to the combination of two pharmacophores; indole and indanone into a single molecule; yet, further intensive investigations are expected to affirm this prediction toward this path. The current quantum chemical examination may add a perception of properties of title the molecule and may similarly help its usage for additional created applications.

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Conflict of Interest

The authors declared that they do not have any conflict of interest regarding this research article.

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