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### Structural, spectroscopic, Hirshfeld surface and charge distribution analysis of 3-(1*H*imidazol-1-yl)-1-phenylpropan-1-ol complemented by molecular docking predictions: an integrated experimental and computational approach

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#### Abstract

The optimized structure of title compound 3-(1*H*-imidazol-1-yl)-1-phenylpropan-1-ol (3HIP) was predicted according to the density functional theory (DFT) using the B3LYP method with 6-311G(d,p) basis set. Computed structural parameters of 3HIP were compared with X-ray diffraction data. Recorded and computed wavenumbers were assigned according to the total energy distribution (TED) using VEDA software. The natural bond orbital (NBO) analysis was used to characterize intramolecular rehybridization and delocalization of the electron density within the title molecule. Predictions of the NMR (<sup>1</sup>H and <sup>13</sup>C) chemical shift assignments obtained by applying the gauge including atomic orbital (GIAO) approach were consistent with the corresponding experimental values. Ultraviolet-visible spectra of the title compound were simulated and validated experimentally. A molecular electrostatic potential (MEP) diagram visualized the electrophilic and nucleophilic sites of the 3HIP molecule. Hirshfeld surface analysis assessed the potential interactions of each atom inside the 3HIP molecule. Moreover, molecular docking analysis simulated the potential binding site pose of 3HIP within the active site of its target protein. The resulting 3HIP-target protein model can provide guidance for the development of new potent antifungal treatments.

#### 1. Introduction

A significant increase in the use of antifungal agents in recent years led to the emergence of resistance to the currently available antifungal drugs [1], which necessitates the search for new antifungal agents that act on novel targets and have a broad spectrum, high potency, and few side effects. Computational chemistry has become a source for critical tools that are used not only in organic chemistry but also in other areas of chemical research, as well as in biology or material science. It improves our understanding of the molecular structure of bioactive organic compounds and provides predictions for their potential reaction mechanisms, as well as their geometrical and electronic properties. Moreover, combining computational and experimental chemistry has already solved an array of organic problems. In addition, the development of the density functional theory (DFT) has contributed significantly to the advances in organic synthesis and has been extensively utilized for computing the geometrical and electronic properties of bioactive organic compounds [2-4].

The azole moiety (imidazole or triazole) is the pharmacophore fragment in azolecontaining antifungal lead compounds that inhibit cytochrome P450-dependent  $14\alpha$ -lanosterol demethylase, which subsequently suppresses sterol synthesis in fungi [5]. A literature survey indicated that available azole antifungal candidate compounds often have an aromatic moiety linked to the azole nitrogen via an ethyl group [6], whereas a limited number have a propyl group instead of the ethyl group. Hence, we were interested in synthesizing the title compound using a propyl group to link the imidazole and phenyl moieties, which created a precursor for the synthesis of new imidazole-containing antifungal agents.

Considering the potential pharmaceutical properties of the title compound, 3-(1*H*imidazol-1-yl)-1-phenylpropan-1-ol (3HIP), we performed vibrational analyses using DFT computations that have not been reported previously. Spectroscopic (FT-IR, FT-Raman, UV, <sup>1</sup>H and <sup>13</sup>C NMR) analyses were recorded and compared with simulated results. In addition, we examined intermolecular and intramolecular interactions, molecular geometry, and orbital energy levels of the 3HIP molecule. A natural bond orbital (NBO) analysis explored potential hyperconjugation or intermolecular delocalization of the title molecule. Studies on molecular orbitals, i.e., HOMO and LUMO, were performed to characterize potential intermolecular interactions of the 3HIP molecule. Furthermore, the Hirshfeld analysis generated a graphical image for in-depth exploration of the intermolecular interactions of the title molecule, while reduced density gradient (RDG) analysis and color-filled electron density diagrams assessed its non-covalent interactions. We also used a molecular docking tool to predict the binding pose of the title compound in the target protein.

#### 2. Experimental details

#### 2.1. Synthesis

A reaction mixture containing dimethylamine hydrochloride (2.2 g, 27 mmol), paraformaldehyde (0.81 g, 9 mmol), acetophenone (2.4 g, 20 mmol), and a catalytic amount of concentrated hydrochloric acid (0.1 mL) in absolute ethanol was stirred under reflux for two hours. Acetone (30 mL) was added to the cooled reaction mixture to precipitate the Mannich base hydrochloride **1** as a white powder, which was filtered off, washed with cold acetone (10 mL), and dried. Compound **1** (2.1 g, 10 mmol) was dissolved in water and imidazole (1.4 g, 20 mmol) was added under stirring; the resulting solution was heated under reflux for five hours. The reaction mixture was cooled, and the precipitated solid was recovered by filtration to obtain compound **2** (2.0 g, 10 mmol) dissolved in methanol (100 mL). The reaction mixture was stirred

at room temperature (RT) for 18 hours and concentrated under vacuum before adding water (50 mL) to the residue. The aqueous solution was extracted with ethyl acetate (3 x 50 mL), and the organic phases were collected, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated under reduced pressure, generating the title compound 3HIP at an almost quantitative yield as a white powder, m.p. 107–109 °C [7, 8].

#### 2.2. Spectral characterization

The FT-IR spectrum of 3HIP was recorded with the IFS66V spectrophotometer in the range of 4000-400 cm<sup>-1</sup> using the KBr pellet technique. The Nerus 670 spectrophotometer (Thermo Electron Corporation, Waltham, MA) was used to measure the FT-Raman spectrum of the title compound with the Nd-YAG laser as excitation source in the range of 3500-50 cm<sup>-1</sup>. The NMR (<sup>13</sup>C and <sup>1</sup>H) spectra of the 3HIP molecule were measured in CDCl<sub>3</sub> using the Bruker NMR spectrometer (Bruker, Billerica, MA) at 500 MHz for <sup>1</sup>H and 125.76 MHz for <sup>13</sup>C at the Research Center, College of Pharmacy, King Saud University, Saudi Arabia. The ultraviolet absorption spectrum of the 3HIP molecule was measured in chloroform in the range of 200-600 nm using the UV-1650 PC spectrophotometer (Shimadzu, Kyoto, Japan). Single crystal data collection of the 3HIP molecule was carried out at 100 K on an APEX-II D8 Venture area diffractometer (Bruker) equipped with a graphite monochromatic Mo K $\alpha$  radiation source,  $\lambda = 0.71073$  Å. Data reduction and cell refinement were executed using the SAINT software (Bruker). The 3HIP structure was solved with the aid of the SHELXT program [9].

#### 2.3. Computational data processing

The optimized geometry of the 3HIP molecule and its vibrational wavenumbers were calculated using the Gaussian 09W program package with the 6-311G(d,p) basis set [10]. Total energy distribution (TED) calculations with the VEDA 4 program [11] were used for vibrational assignments of the normal modes for the title compound. The calculated vibrational wavenumbers were scaled down by the scale factor 0.967 [12] to offset the systematic error caused by negating electron density and anharmonicity, which allowed the comparison between the calculated data and the experimental results. The NBO calculations were carried out using the NBO 3.1 program [13] as implemented in the Gaussian 09W [10] package at the B3LYP/6-311G(d,p) level of the basis set. The UV-Vis spectrum, vertical excitation, electron transition energies, and oscillator strength were computed by applying the time-dependent density functional theory (TD-DFT) method, and the electronic properties were specified by the TD-

DFT approach [14]. The reduced density gradients (RDG) and the electrostatic potential (EPS) were plotted using the Multiwfn software [15] and the VMD 1.9.1 program [16], respectively.

#### 3. Results and discussion

#### 3.1. Synthesis

The synthesis of title compound 3HIP was initiated using commercially available acetophenone as a substrate in the Mannich reaction as illustrated in Scheme 1. The Mannich base hydrochloride 1 was converted to imidazole derivative 2, which was subsequently reduced by sodium borohydride to generate 3HIP.



*Reagents and conditions*: i) HN(CH<sub>3</sub>)<sub>2</sub>.HCl, (CH<sub>2</sub>O)<sub>n</sub>, conc. HCl, ethanol, reflux, 2 h; ii) imidazole, water, reflux, 5 h; iii) NaBH<sub>4</sub>, methanol, RT, 18 h.

Scheme 1: Synthesis of title compound 3HIP.

#### 3.2. Optimized structure

The 3HIP molecule crystallizes as P21/c space group with the following cell constants: a = 9.0352(5) Å, b = 11.8521(7) Å, c = 10.3462(6) Å, a = 90.00°, b = 109.6880(10)°, c = 90.00°, V = 1043.17(10) Å<sup>3</sup>, and Z = 4 as reported previously [9]. The optimized molecular structure is shown in Fig. 1. The 3HIP molecule was optimized using the B3LYP/6-311G(d,p) method; the optimized parameters (bond lengths, bond angles, and dihedral angles) are summarized in Table 1. The presence of an O-H group in a small molecule affects its structural and vibrational

properties. The 3HIP molecule contains two rings, i.e., the phenyl and imidazole rings, and possesses a total of four C-N bonds, thirteen C-H bonds, and one O-H bond.

The propane chain substitution linking the phenyl and imidazole rings distorted the phenyl ring as indicated by the bond angle C1-C6-C5 =  $118.937^{\circ}$ , which deviated from the normal value of  $120^{\circ}$ . However, the bond angle C23-N22-C24 =  $106.253^{\circ}$  in the imidazole ring indicated that it was not much affected by the propane chain. In the phenyl ring, the C-C bond lengths were C1-C2 = 1.393 Å, C1-C6 = 1.398, C2-C3 = 1.394 Å, C3-C4 = 1.393 Å, C4-C5 = 1.393 Å, and C5-C6 = 1.397 Å according to the B3LYP/6-311G(d,p) method, and the corresponding X-ray diffraction (XRD) values were 1.391, 1.399, 1.398, 1.388, 1.394, and 1.393 Å, respectively.

The C-O (C12-O14) bond length of 1.431 Å was in a good agreement with the standard literature value of 1.400 Å [17]. The bond lengths of C6-C12 = 1.519 Å, C12-C16 = 1.532 Å, C16-C19 = 1.534 Å, and C19-N22 =1.459 Å indicated a large repulsion in the propane chain, which might lead to a push-pull electron effect in this title compound region.

As reported previously, deviations in the aromatic C-H bond lengths upon substitution may be caused by changes in the charge distribution on the carbon atoms of the benzene ring [18]. In addition, the substitution of hydrogen atoms can increase the electron density of aromatic ring carbons, which decreases the C-H force constants will occur and increases the bond lengths. The title compound C-H bond length was 1.084 Å for C1-H7, C2-H8, C3-H9, and C4-H10 and 1.086 Å for C5-H11 according to the B3LYP/6-311G(d,p) method. These values differed slightly from the XRD values, which might be related to the low scattering factor of hydrogen atoms involved in the X-ray diffraction experiment [18].

Table 1: Molecular geometry [bond length (Å), bond angle ( $^{\circ}$ ) and dihedral angle ( $^{\circ}$ )] of 3HIP by B3LYP/6-311G(d,p).

Parameter	Calculated	<b>XRD</b> <sup>a</sup>
Bond length(Å)		
C1-C2	1.393	1.391
C1-C6	1.398	1.399
C1-H7	1.084	0.950
C2-C3	1.394	1.398
C2-H8	1.084	0.950
C3-C4	1.393	1.388

	С3-Н9	1.084	0.950	
	C4-C5	1.393	1.394	
	C4-H10	1.084	0.950	
	C5-C6	1.397	1.393	
	C5-H11	1.086	0.950	
	C6-C12	1.519	1.518	
	С12-Н13	1.101	1.001	Ý
	C12-O14	1.431	1.417	
	C12-C16	1.532	1.527	
	014-H15	0.963	0.964	
	C16-H17	1 094	0.990	
	C16-H18	1.094	0.990	
	C16-C19	1.534	1 526	
	C10-C17	1.00	0.990	
	С19-1120	1.090	0.000	
	C19-FI21	1.094	1.464	
	N22 C22	1.439	1.404	
	N22-C23	1.380	1.377	
	C23-C25	1.30/	1.357	
	C23-H26	1.078	0.950	
	C24-H27	1.080	0.950	
	C24-N29	1.314	1.322	
	C25-H28	1.079	0.950	
	C25-N29	1.375	1.380	
	Bond angle (°)	100.450	100.40	
	C2-C1-C6	120.462	120.42	
	С2-С1-Н7	120.421	119.80	
	С6-С1-Н7	119.114	119.79	
	C1-C2-C3	120.225	120.16	
	С1-С2-Н8	119.764	119.91	
(	С3-С2-Н8	120.011	119.93	
	C2-C3-C4	119.670	119.55	
C	С2-С3-Н9	120.189	120.19	
	С4-С3-Н9	120.141	120.26	
	C3-C4-C5	120.036	120.22	
Y	C3-C4-H10	120.107	119.90	
	C5-C4-H10	119.856	119.88	
	C4-C5-C6	120.668	120.59	
	C4-C5-H11	119.713	119.71	
	C6-C5-H11	119.619	119.70	
	C1-C6-C5	118.937	119.04	
			1	

	C1-C6-C12	120.534	120.64	
	C5-C6-C12	120.516	120.32	
	C6-C12-H13	108.187	108.70	
	C6-C12-O14	112.295	112.56	
	C6-C12-C16	112.059	110.39	
	H13-C12-O14	109.577	108.68	
	H13-C12-C16	108.462	108.71	<b>Y</b>
	O14-C12-C16	106.185	107.72	
	C12-O14-H15	108.039	107.68	
	C12-C16-H17	109.148	108.83	
	C12-C16-H18	108.581	108.76	
	C12-C16-C19	112.277	113.82	
	H17-C16-H18	107.181	107.70	
	H17-C16-C19	109.833	108.75	
	H18-C16-C19	109.679	108.81	
	C16-C19-H20	109.859	109.04	
	C16-C19-H21	110.290	109.02	
	C16-C19-N22	112.832	112.79	
	H20-C19-H21	107.287	107.78	
	H20-C19-N22	108.849	109.03	
	H21-C19-N22	107.544	109.06	
	C19-N22-C23	126.728	126.59	
	C19-N22-C24	126.941	126.45	
	C23-N22-C24	106.253	106.94	
	N22-C23-C25	105.699	105.80	
	N22-C23-H26	121.778	127.14	
	С25-С23-Н26	132.521	127.06	
	N22-C24-H27	121.743	123.99	
	N22-C24-N29	112.427	111.96	
	H27-C24-N29	125.826	124.06	
	С23-С25-Н28	127.979	124.89	
	C23-C25-N29	110.569	110.28	
	H28-C25-N29	121.450	124.83	
Y	C24-N29-C25	105.052	105.02	
	Dihedral angle (°)			
	C6-C1-C2-C3	-0.136	-1.16	
	С6-С1-С2-Н8	179.913	178.81	
	H7-C1-C2-C3	-179.485	178.86	
	H7-C1-C2-H8	0.564	-1.17	

C2-C1-C6-C5	-0.218	1.20	
C2-C1-C6-C12	178.520	-178.30	
H7-C1-C6-C5	179.139	-178.82	
H7-C1-C6-C12	-2.124	1.68	
C1-C2-C3-C4	0.277	-0.15	
С1-С2-С3-Н9	179.986	179.89	
Н8-С2-С3-С4	-179.772	179.88	<b>A</b>
Н8-С2-С3-Н9	-0.063	-0.08	
C2-C3-C4-C5	-0.061	1.41	
C2-C3-C4-H10	179.511	-178.56	
Н9-С3-С4-С5	-179.770	-178.63	
H9-C3-C4-H10	-0.198	1.41	
C3-C4-C5-C6	-0.299	-1.37	
C3-C4-C5-H11	179.396	178.59	
H10-C4-C5-C6	-179.871	178.60	
H10-C4-C5-H11	-0.177	-1.44	
C4-C5-C6-C1	0.436	0.06	
C4-C5-C6-C12	-178.302	179.56	
H11-C5-C6-C1	-179.259	-179.91	
H11-C5-C6-C12	2.003	-0.40	
C1-C6-C12-H13	155.861	170.33	
C1-C6-C12-O14	34.805	49.88	
C1-C6-C12-C16	-84.616	-70.52	
C5-C6-C12-H13	-25.421	-9.17	
C5-C6-C12-O14	-146.478	-129.62	
C5-C6-C12-C16	94.102	109.99	
C6-C12-O14-H15	55.923	39.65	
H13-C12-O14-H15	-64.332	-80.81	
C16-C12-O14-H15	178.720	161.57	
C6-C12-C16-H17	-55.779	-62.48	
С6-С12-С16-Н18	60.747	54.59	
C6-C12-C16-C19	-177.810	176.07	
H13-C12-C16-H17	63.583	56.67	
H13-C12-C16-H18	-179.891	173.74	
H13-C12-C16-C19	-58.448	-64.78	
O14-C12-C16-H17	-178.725	174.27	
O14-C12-C16-H18	-62.199	-68.67	
O14-C12-C16-C19	59.245	52.81	
С12-С16-С19-Н20	-57.362	-62.23	

C12-C16-C19-H21	60.697	-179.66
C12-C16-C19-N22	-179.014	59.04
H17-C16-C19-H20	-179.002	176.28
H17-C16-C19-H21	-60.943	58.84
H17-C16-C19-N22	59.346	-62.45
H18-C16-C19-H20	63.451	-58.21
H18-C16-C19-H21	-178.491	59.22
H18-C16-C19-N22	-58.202	-179.51
C16-C19-N22-C23	80.793	71.41
C16-C19-N22-C24	-95.531	-107.01
H20-C19-N22-C23	-41.429	-49.86
H20-C19-N22-C24	142.247	131.71
H21-C19-N22-C23	-157.356	167.31
H21-C19-N22-C24	26.320	14.27
C19-N22-C23-C25	-177.220	-179.01
C19-N22-C23-H26	3.278	1.00
C19-N22-C23-H26 C24-N22-C23-C25	3.278 -0.280	1.00 -0.34
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26	3.278 -0.280 -179.782	1.00 -0.34 179.68
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27	3.278 -0.280 -179.782 -3.360	1.00 -0.34 179.68 -1.02
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27 C19-N22-C24-N29	3.278 -0.280 -179.782 -3.360 177.302	1.00 -0.34 179.68 -1.02 178.99
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27 C19-N22-C24-N29 C23-N22-C24-H27	3.278 -0.280 -179.782 -3.360 177.302 179.709	1.00 -0.34 179.68 -1.02 178.99 -179.69
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27 C19-N22-C24-N29 C23-N22-C24-H27 C23-N22-C24-N29	3.278 -0.280 -179.782 -3.360 177.302 179.709 0.370	1.00 -0.34 179.68 -1.02 178.99 -179.69 0.31
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27 C19-N22-C24-N29 C23-N22-C24-H27 C23-N22-C24-H27 N22-C23-C25-H28	3.278 -0.280 -179.782 -3.360 177.302 179.709 0.370 -179.377	1.00 -0.34 179.68 -1.02 178.99 -179.69 0.31 -179.71
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27 C19-N22-C24-N29 C23-N22-C24-H27 C23-N22-C24-H27 N22-C23-C25-H28 N22-C23-C25-N29	3.278 -0.280 -179.782 -3.360 177.302 179.709 0.370 -179.377 0.115	1.00 -0.34 179.68 -1.02 178.99 -179.69 0.31 -179.71 0.26
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27 C19-N22-C24-N29 C23-N22-C24-H27 C23-N22-C24-H27 C23-N22-C24-N29 N22-C23-C25-H28 N22-C23-C25-H28	3.278 -0.280 -179.782 -3.360 177.302 179.709 0.370 -179.377 0.115 0.049	1.00 -0.34 179.68 -1.02 178.99 -179.69 0.31 -179.71 0.26 0.28
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27 C19-N22-C24-N29 C23-N22-C24-N29 N22-C23-N22-C24-N29 N22-C23-C25-H28 N22-C23-C25-N29 H26-C23-C25-N29	3.278 -0.280 -179.782 -3.360 177.302 179.709 0.370 -179.377 0.115 0.049 179.540	1.00 -0.34 179.68 -1.02 178.99 -179.69 0.31 -179.71 0.26 0.28 -179.76
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27 C19-N22-C24-N29 C23-N22-C24-N29 N22-C23-C25-H28 N22-C23-C25-H28 H26-C23-C25-H28 H26-C23-C25-N29 N22-C24-N29-C25	3.278 -0.280 -179.782 -3.360 177.302 179.709 0.370 -179.377 0.115 0.049 179.540 -0.294	1.00 -0.34 179.68 -1.02 178.99 -179.69 0.31 -179.71 0.26 0.28 -179.76 -0.15
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27 C19-N22-C24-H27 C23-N22-C24-N29 N22-C23-C25-H28 N22-C23-C25-H28 H26-C23-C25-H28 H26-C23-C25-N29 N22-C24-N29-C25 H27-C24-N29-C25	3.278         -0.280         -179.782         -3.360         177.302         179.709         0.370         -179.377         0.115         0.049         179.540         -0.294	1.00         -0.34         179.68         -1.02         178.99         -179.69         0.31         -179.71         0.26         0.28         -179.76         -0.15         179.85
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27 C19-N22-C24-H27 C23-N22-C24-N29 N22-C23-C24-N29 N22-C23-C25-H28 H26-C23-C25-N29 N22-C24-N29-C25 H27-C24-N29-C25 C23-C25-N29-C24	3.278         -0.280         -179.782         -3.360         177.302         179.709         0.370         -179.377         0.115         0.049         179.540         -0.294         -179.600         0.104	$     1.00 \\     -0.34 \\     179.68 \\     -1.02 \\     178.99 \\     -179.69 \\     0.31 \\     -179.71 \\     0.26 \\     0.28 \\     -179.76 \\     -0.15 \\     179.85 \\     -0.07 \\     $
C19-N22-C23-H26 C24-N22-C23-C25 C24-N22-C23-H26 C19-N22-C24-H27 C19-N22-C24-H27 C23-N22-C24-N29 N22-C23-N22-C24-H27 N22-C23-C25-H28 N22-C23-C25-H28 H26-C23-C25-N29 N22-C24-N29-C25 H27-C24-N29-C25 C23-C25-N29-C24 H28-C25-N29-C24	3.278         -0.280         -179.782         -3.360         177.302         179.709         0.370         -179.377         0.115         0.049         179.540         -0.294         -179.600         0.104	1.00 -0.34 179.68 -1.02 178.99 -179.69 0.31 -179.71 0.26 0.28 -179.76 -0.15 179.85 -0.07 179.89

<sup>a</sup>Taken from reference [16].

#### 3.3. Hirshfeld surface analysis

Intermolecular interactions of 3HIP molecules were characterized using the Hirshfeld surface analysis, which simulates the surface character of the molecule [19, 20]. The Hirshfeld surfaces are associated with the 2D fingerprint plot as a quantitative measure of intermolecular interactions on the molecule surface [21, 22]. There are two critical distances in the Hirshfeld surfaces, de as the distance from the nearest nucleus exterior to the surface, and di as the distance

from the nearest nucleus interior to the surface. The normalized contact distance  $(d_{norm})$  is based on de and di as written below:

$$d_{norm} = \frac{(di - ri^{vdW})}{ri^{vdW}} + \frac{(de - re^{vdW})}{re^{vdW}}$$
(1)

where ri<sup>vdW</sup> and re<sup>vdW</sup> represent the van der Waals radii of the atoms. Negative d<sub>norm</sub> values are indicated in red, denoting a shorter distance than the sum of the van der Waals radii. White marks intermolecular distances close to the van der Waals radii and a d<sub>norm</sub> value of zero. Positive d<sub>norm</sub> values are marked in blue, indicating a longer distance than the sum of the van der Waals radii. The Hirshfeld surface was generated with Crystal Explorer 3.0 [23] as shown in Figs. 2 and 3. The surface maps d<sub>norm</sub> (A), shape index (B), curvedness (C), di, and de are presented in the range of -0.593-1.159 Å, -1.000-1.000 Å, -4.000-0.400 Å, 0.741-2.375 Å, and 0.740-2.452 Å, respectively. Deep red (circular depression) on the Hirshfeld surface indicates the presence of O...H hydrogen bond contacts; specifically, the concave regions around the acceptor hydrogens are labeled in red, and the convex regions around the oxygen are marked in blue. The  $\pi$ .... $\pi$  interactions are absent in the 3HIP crystal as supported by the shape index, which does not have adjacent red and blue triangle patterns [24]. In the 2D fingerprint, the C-H, C-O, N-H, and H-O interactions are indicated by spikes at the bottom, and the H-C, O-C, N-H, and O-H interactions are represented as spikes in the top left region. Two sharp peaks close to the lower left of the plot represent H...H hydrogen bonding. The short distance minimum value (di + de) = 1.0 Å indicates the importance of hydrogen bond interactions. The proportions of H...H, C...H, and N...H are 59.5%, 23.7%, and 12.0% in the 2D fingerprint plot. The characteristic wing of  $(di + de) \sim 1.2$  Å corresponds to C...H/H...C bonds as shown in Fig. 2.

#### 3.4. Mulliken charge analysis

Mulliken charge analysis predicts the characteristics of molecules based on atomic charges that affect their molecular properties, including dipole moment, electronic structure, and molecular polarizability. The Mulliken charges of the 3HIP molecule were computed using the B3LYP/6-311G(d,p) method as shown in Fig. 4. All phenyl ring carbon atoms have negative charges (C1 = -0.052 e, C2 = -0.090 e, C3 = -0.087 e, C4 = -0.090 e, C5 = -0.065 e and C6 = -0.157 e). The atom C6 has the strongest negative charge, which could be attributed to its direct bond to the propane group. The atom H15 has the highest positive charge among all hydrogen

atoms because of its bond to the electronegative oxygen atom. The atom O14 shows the strongest negative charge (-0.408 e) due to its high inherent electronegativity. In the imidazole ring, the atom C24 has the highest positive charge (0.158 e) because of its covalent bonds to the electronegative atoms N22 and N29. All hydrogen atoms are inherently positive as shown in Fig. 4.

#### 3.5. Natural bond orbital (NBO) analysis

NBO analysis assesses intramolecular and intermolecular bonding and the interactions among bonds. It is also a tool for investigating charge transfer or conjugative interactions in molecular systems. The larger the  $E^{(2)}$  value, the stronger is the interaction between electron donors and acceptors, i.e., the higher the donating tendency from electron donors to electron acceptors, the stronger the covalent bonds of the whole system. Delocalization of electron density between occupied Lewis-type (bond or lone pair) NBOs and formally unoccupied (antibond or Rydgberg) non-Lewis NBOs stabilizes donor–acceptor interactions [25]. The NBO analysis of the title molecule at the DFT/B3LYP/6-311+G (d,p) level assessed the molecule's intramolecular rehybridization and electron density delocalization within the molecule. The second order Fock matrix was performed to evaluate the donor–acceptor interactions of the NBOs. These interactions can cause a loss of occupancy converting the localized NBO of an idealized Lewis structure of a molecule into an empty non-Lewis orbital. For each donor (i) and acceptor (j), the stabilization energy  $E^{(2)}$  associated with delocalization i—j is estimated as:

$$E_2 = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i}$$
<sup>(2)</sup>

where  $q_i$  is the donor orbital occupancy,  $\varepsilon_i$  and  $\varepsilon_j$  are diagonal elements, and F (i, j) is the offdiagonal NBO Fock matrix element. Intramolecular hyperconjugative interactions occur during overlaps between bonding and antibonding orbitals, i.e., (C-C), (C-N), (C-H), (C-O), and (O-H), which results in an intramolecular charge transfer (ICT) that stabilizes the molecular system. These interactions are indicated by an increase in electron density (ED) in the bonding orbitals (C-C) and (C-N) and the antibonding orbital (C-C) that weakens the respective bonds. The electron density (~1.9 e) of the conjugated bonds in the 3HIP molecule is an indicator of strong delocalization.

The strong intramolecular hyperconjugative interactions between the  $\sigma$  and  $\pi$  electrons of C-C bonding and antibonding orbitals of the aromatic ring in the 3HIP molecule partially stabilizes the ring structure as shown in Table 2. For example, the intramolecular hyperconjugative interactions of  $\sigma$ (C1-C2) distributed to  $\sigma$ \*((C1-C6), (C2-C3), (C3-H9), and (C6-C12)) were stable at 3.96, 3.07, 2.38, and 3.79 KJ/mol, respectively. This stability promoted further conjugation with the antibonding orbital  $\pi$ (C1-C2), which caused strong delocalization of  $\pi^*((C3-C4)$  and (C5-C6)) at 20.31 and 21.71 KJ/mol, respectively, as shown in Table 2. The same type of interaction was observed for the C3-C4 bond that distributed energy to  $\sigma^*((C2-C3))$ , (C2-H8), (C4- C5) and (C5-H11)) with stabilization energy values of 3.00, 2.45, 3.12 and 2.53 KJ/mol, respectively, as shown in Table 2. This stimulated conjugation with antibonding orbital  $\pi$ (C3-C4), leading to strong delocalization to  $\pi^*$ ((C1-C2) and (C5-C6)) with a stabilization energy of 20.67 and 20.33 KJ/mol, respectively, as presented in Table 2. Similar behavior was computed for the C5-C6 and C23-C25 bonds. Moreover, the charges transferred from lone pairs LP(2)O14, LP(1)N22, and LP(1)N29 had stabilization energy values of 5.44, 6.98, 5.83, 2.46, 31.27, 46.55, 8.32, 5.51, 2.23, and 2.19 KJ/mol for (C6-C12), (C12-H13), (C16-C19), (C19-H20), (C23-C25), (C24-N29), (N22-C24), (C23-C25), (C24-H27), and (C25-H28), respectively.

CEP CE

Donor (i)	Туре	ED/e	Acceptor (j)	Туре	ED/e	E(2) (Kj/Mol)	E(j)-E(i) (a.u)	<b>F</b> ( <b>i</b> , <b>j</b> ) ( <b>a.u</b> )
C1-C2	σ	1.97708	C1-C6	σ*	0.02635	3.96	1.27	0.063
C1-C2	σ	1.97708	C2-C3	σ*	0.01708	3.07	1.27	0.056
C1-C2	σ	1.97708	С3-Н9	σ*	0.01462	2.38	1.14	0.047
C1-C2	σ	1.97708	C6-C12	σ*	0.03918	3.79	1.10	0.058
C1-C2	π	1.66191	C3-C4	$\pi^*$	0.33025	20.31	0.28	0.068
C1-C2	π	1.66191	C5-C6	π*	0.35496	21.71	0.28	0.070
C1-C6	σ	1.97172	C1-C2	σ*	0.01639	3.50	1.27	0.060
C1-C6	σ	1.97172	C2-H8	σ*	0.01466	2.20	1.14	0.045
C1-C6	σ	1.97172	C5-C6	σ*	0.02438	4.22	1.27	0.065
C1-C6	σ	1.97172	C5-H11	σ*	0.01595	2.54	1.13	0.048
C1-C6	σ	1.97172	C6-C12	σ*	0.03918	2.23	1.10	0.044
C1-H7	σ	1.97851	C2-C3	σ*	0.01708	3.75	1.09	0.057
C1-H7	σ	1.97851	C5-C6	σ*	0.02438	4.76	1.09	0.064
C2-C3	σ	1.97914	C1-C2	σ*	0.01639	3.13	1.28	0.056
C2-C3	σ	1.97914	C1-H7	σ*	0.01596	2.48	1.15	0.048
C2-C3	σ	1.97914	C3-C4	σ*	0.01691	3.01	1.27	0.055
C2-C3	σ	1.97914	C4-H10	$\sigma^*$	0.01446	2.47	1.14	0.047
C2-H8	σ	1.97956	C1-C6	$\sigma^*$	0.02635	4.10	1.09	0.060
C2-H8	σ	1.97956	C3-C4	σ*	0.01691	3.81	1.09	0.058
C3-C4	σ	1.97889	C2-C3	σ*	0.01708	3.00	1.27	0.055
C3-C4	σ	1.97889	С2-Н8	$\sigma^*$	0.01466	2.45	1.14	0.047
C3-C4	σ	1.97889	C4-C5	σ*	0.01628	3.12	1.27	0.056
C3-C4	σ	1.97889	C5-H11	σ*	0.01595	2.53	1.13	0.048
C3-C4	π	1.66013	C1-C2	π*	0.32468	20.67	0.28	0.069
C3-C4	π	1.66013	C5-C6	π*	0.35496	20.33	0.28	0.068

## Table 2: Second order perturbation theory analysis of Fock matrix on NBO of 3HIP using the B3LYP/6-311G(d,p) method.

С3-Н9	σ	1.97954	C1-C2	$\sigma^*$	0.01639	3.86	1.10	0.058
C3-H9	σ	1.97954	C4-C5	$\sigma^*$	0.01628	3.87	1.09	0.058
C4-C5	σ	1.97716	C3-C4	σ*	0.01691	3.04	1.27	0.063
C4-C5	σ	1.97716	С3-Н9	$\sigma^*$	0.01462	2.39	1.14	0.047
C4-C5	σ	1.97716	C5-C6	σ*	0.02438	3.97	1.27	0.063
C4-C5	σ	1.97716	C6-C12	σ*	0.03918	3.83	1.10	0.058
C4-H10	σ	1.97952	C2-C3	σ*	0.01708	3.79	1.09	0.058
C4-H10	σ	1.97952	C5-C6	σ*	0.02438	4.08	1.09	0.060
C5-C6	σ	1.97220	C1-C6	σ*	0.02635	4.26	1.27	0.066
C5-C6	σ	1.97220	C1-H7	σ*	0.01596	2.44	1.15	0.047
C5-C6	σ	1.97220	C4-C5	σ*	0.01628	3.57	1.27	0.060
C5-C6	σ	1.97220	C4-H10	σ*	0.01446	2.16	1.14	0.044
C5-C6	σ	1.97220	C6-C12	σ*	0.03918	2.14	1.10	0.043
C5-C6	π	1.66000	C1-C2	π*	0.32468	19.77	0.29	0.067
C5-C6	π	1.66000	C3-C4	$\pi^*$	0.33025	20.73	0.29	0.069
C5-C6	π	1.66000	C12-O14	σ*	0.02735	2.28	0.53	0.034
C5-C6	π	1.66000	C12-C16	σ*	0.02512	2.90	0.62	0.041
C5-H11	σ	1.97910	C1-C6	σ*	0.02635	4.66	1.09	0.064
C5-H11	σ	1.97910	C3-C4	σ*	0.01691	3.69	1.10	0.025
C6-C12	σ	1.97018	C1-C2	σ*	0.01639	2.54	1.21	0.050
C6-C12	σ	1.97018	C1-C6	$\sigma^*$	0.02635	2.40	1.20	0.048
C6-C12	σ	1.97018	C4-C5	$\sigma^*$	0.01628	2.45	1.21	0.049
C6-C12	σ	1.97018	C5-C6	$\sigma^*$	0.02438	2.40	1.21	0.048
C12-H13	σ	1.97601	C1-C6	σ*	0.02635	3.81	1.08	0.057
C12-H13	σ	1.97601	C16-H18	$\sigma^*$	0.01595	2.66	0.92	0.044
C12-C16	σ	1.96474	C5-C6	$\pi^*$	0.35496	2.53	0.65	0.039
C12-C16	σ	1.96474	C19-N22	σ*	0.02790	2.33	0.96	0.042
O14-H15	σ	1.98847	C12-C16	$\sigma^*$	0.02512	2.53	1.09	0.047

C16-H17	σ	1.97475	C12-O14	σ*	0.02735	3.83	0.77	0.049
C16-H17	σ	1.97475	C19-H20	σ*	0.01635	2.53	0.91	0.043
C16-H18	σ	1.97600	C12-H13	σ*	0.03607	2.74	0.88	0.444
C16-H18	σ	1.97600	C19-H21	σ*	0.01485	2.64	0.89	0.043
C16-C19	σ	1.97528	C6-C12	σ*	0.03918	2.07	1.02	0.041
C19-H20	σ	1.98004	C16-H17	σ*	0.01156	2.62	0.92	0.044
C19-H20	σ	1.98004	N22-C24	σ*	0.04255	3.81	0.98	0.055
C19-H21	σ	1.98064	C16-H18	σ*	0.01595	2.59	0.93	0.044
C19-H21	σ	1.98064	N22-C23	σ*	0.02372	4.51	0.98	0.059
N22-C23	σ	1.98140	N22-C24	σ*	0.04255	2.19	1.25	0.047
N22-C23	σ	1.98140	C24-H27	σ*	0.02243	2.67	1.21	0.051
N22-C23	σ	1.98140	C25-H28	σ*	0.01815	3.06	1.24	0.055
N22-C24	σ	1.98605	N22-C23	σ*	0.02372	2.12	1.25	0.046
N22-C24	σ	1.98605	C23-H26	σ*	0.01277	2.70	1.24	0.052
C23-C25	σ	1.98381	C19-N22	σ*	0.02790	5.85	1.04	0.070
C23-C25	π	1.85770	C24-N29	π*	0.38194	15.12	0.28	0.062
C23-H26	σ	1.98543	N22-C24	σ*	0.04255	3.12	1.01	0.051
C24-H27	σ	1.98380	N22-C23	σ*	0.02372	3.29	1.00	0.051
C24-H27	σ	1.98380	C25-N29	σ*	0.01136	3.18	1.05	0.052
C24-N29	σ	1.98501	C19-N22	σ*	0.02790	3.78	1.15	0.059
C24-C29	σ	1.98501	C25-H28	σ*	0.01815	3.27	1.27	0.058
C24-C29	π	1.86725	C23-C25	π*	0.30719	21.55	0.33	0.078
C25-H28	σ	1.98550	C24-N29	σ*	0.38194	2.86	1.10	0.050
C25-N29	σ	1.97835	C23-H26	σ*	0.01277	3.43	1.18	0.057
C25-N29	σ	1.97835	C24-H27	σ*	0.02243	5.19	1.17	0.069
LP(2)O14	n	1.95456	C6-C12	σ*	0.03918	5.44	0.72	0.056
LP(2)O14	n	1.95456	C12-H13	σ*	0.03607	6.98	0.70	0.062
LP(1)N22	n	1.55711	C16-C19	σ*	0.01988	5.83	0.62	0.060

LP(1)N22	n	1.55711	C19-H20	σ*	0.01635	2.46	0.66	0.041
LP(1)N22	n	1.55711	C23-C25	π*	0.30719	31.27	0.29	0.088
LP(1)N22	n	1.55711	C24-N29	π*	0.38194	46.55	0.28	0.103
LP(1)N29	n	1.92411	N22-C24	$\sigma^*$	0.04255	8.32	0.81	0.074
LP(1)N29	n	1.92411	C23-C25	σ*	0.01884	5.51	0.94	0.065
LP(1)N29	n	1.92411	C24-H27	$\sigma^*$	0.02243	2.23	0.77	0.037
LP(1)N29	n	1.92411	C25-H28	σ*	0.01815	2.19	0.80	0.038
			CER					

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#### 3.6. Vibrational analysis

The maximum number of potentially active fundamental vibrations of a non-linear molecule consisting of N atoms is 3N - 6, apart from three translational and three rotational degrees of freedom. The title molecule has 29 atoms with 81 normal vibrations and displays C<sub>1</sub> point group symmetry. The simulated and experimental FT-IR and FT-Raman spectra of the 3HIP molecule are shown in Figs. S1 and S2. The observed and scaled theoretical frequencies of 6-311+G(d,p) basis sets and the respective TEDs are listed in Table 3. The 3HIP molecule was subjected to vibrational analyses using the B3LYP/6-311G(d,p) method. The computed wavenumbers were generally higher than the recorded (FT-IR and FT-Raman) wavenumbers, which might be related to the neglect of the anharmonicity in the built-in real calculation system of the software. These discrepancies can be corrected by either computing anharmonicity corrections explicitly or introducing a scaled field or directly scaling the wavenumbers using a proper scale factor [12]. However, tentative assignments are often made using the non-scaled frequencies by assuming that the observed frequencies are in the same magnitude as the calculated values.

#### 3.6.1. C-H vibrations

Carbon-hydrogen stretching vibrations are assigned on the basis of scaled *ab initio* predicted frequencies and known "group frequencies." The 3HIP molecule has one imidazole substructure and one phenyl ring linked by a propane bridge as shown in Fig. 1. The imidazole moiety has three C-H bonds, and the phenyl ring has five. The heterocyclic aromatic substructures have C-H stretching vibrations in the range of 3100–3000 cm<sup>-1</sup> [26]. In this range, the substituents do not significantly affect the vibration bands. The scaled vibrations (mode nos.: 2-9) correspond to the stretching modes of the C-H bonds in the imidazole and phenyl rings. Computing of these vibrations for the title compound by using the B3LYP/6-311G(d,p) method generated the following values, 3155, 3126, 3121, 3087, 3080, 3069, 3060, and 3047 cm<sup>-1</sup>, which were in good agreement with the recorded FT-IR spectrum band at 3166 cm<sup>-1</sup> and the FT-Raman spectrum bands at 3135, 3117, and 3074 cm<sup>-1</sup>. The computed TED contribution for the C-H vibration was 100% as shown in Table 3. The aromatic C-H stretching bands were weak because of the low dipole moment based on the weak negative charge on the carbon atoms, which is caused by increasing the chain length of the substituent [27].

Substitution-sensitive C-H in-plane-bending vibrations are in the range of 1300–1000 cm<sup>-1</sup> [26]. For the title compound, the medium and strong bands at 1292, 1255, and 1147 cm<sup>-1</sup> in the FT-IR spectrum and at 1280, 1210, 1109, and 1076 cm<sup>-1</sup> in the FT-Raman spectrum were assigned as C-H in-plane-bending vibrations. The theoretically computed wavenumbers for this mode were 1282, 1277, 1264, 1243, 1236, 1216, 1174, 1158, 1144, 1129, 1102, 1074, and 1058 cm<sup>-1</sup> using B3LYP/6-311G (d,p) method. The computed C-H out-of-plane bending vibrations for both rings of the 3HIP molecule are in good agreement with recorded wavenumbers as shown in Table 3.

#### 3.6.2. CH<sub>2</sub> vibrations

Assigning of methylene group vibrations is based on spectral similarity to amino acids, which have expected CH<sub>2</sub> symmetric and antisymmetric vibrations of  $\sim 3100-2900$  cm<sup>-1</sup> [28]. The calculated CH<sub>2</sub> symmetric and antisymmetric stretching modes of the title compound were 3015, 2983, 2954, 2943, and 2863 cm<sup>-1</sup> (mode nos. 10–14, respectively) with TED contributions of ~95% indicating a pure mode. The wavenumbers of the recorded FT-IR and FT-Raman spectra of the 3HIP molecule show bands near 2981, 2927, and 2943 cm<sup>-1</sup>, which were assigned to CH<sub>2</sub> antisymmetric and symmetric stretching vibrations. Position shift and changes in the intensity of the C-H stretching and bending modes can be caused by electronic effects including back donation due to a nitrogen atom adjacent to the methylene group. The CH<sub>2</sub> bending (scissoring) mode is in the range of 1450–875 cm<sup>-1</sup>, and its wagging mode is approximately 1340  $\pm$  25 cm<sup>-1</sup> [28, 29]. The CH<sub>2</sub> wagging mode calculated for the 3HIP molecule was at 1350 cm<sup>-1</sup> with a TED contribution of ~35% using the B3LYP/6-311+G(d,p) method. A weak band recorded at 1352 cm<sup>-1</sup> of the 3HIP FT-Raman spectrum of the title compound was assigned as CH<sub>2</sub> wagging mode. The band recorded at 1456 cm<sup>-1</sup> of the 3HIP FT-Raman spectrum was categorized as CH<sub>2</sub> scissoring mode, and its computed TED indicated a pure mode with a contribution of ~60% as shown in Table 3.

#### 3.6.3. O-H vibrations

The O-H group induces vibrations in stretching, in-plane bending, and out-of-plane bending modes. Vibrations of the O-H group are most sensitive to the surrounding environment; they show pronounced shifts in the spectra of hydrogen-bonded molecule species. The frequencies of O-H stretching vibrations are approximately 3500 cm<sup>-1</sup> [30]; however, in unsubstituted phenol derivatives, they appear in the gas phase at approximately 3657 cm<sup>-1</sup> [31]. The

3HIP molecule analysis detected a strong FT-IR band at 3166 cm<sup>-1</sup>, which was categorized as O-H stretching vibration. The measured O-H stretching band value had a negative deviation of approximately 500 cm<sup>-1</sup> from the literature values, which could be related to the absence of the harmonic approximation as a vibration parameter of atomic groups involved in intramolecular hydrogen bonds as shown in Table 3. The computed wavenumber of this vibration was 3698 cm<sup>-1</sup> (mode no. 1) with a 100% TED contribution.

The O-H in-plane-bending vibration of phenols is in the range of 1250–1150 cm<sup>-1</sup>, and it is not significantly affected by intramolecular hydrogen bonding unlike the stretching and out-ofplane bending vibrations [30]. The observed bands at 1292 and 1280 cm<sup>-1</sup> in the FT-IR and FT-Raman spectra, respectively, of the 3HIP molecule were classified as O-H in-plane-bending vibrations. The corresponding computed wavenumber was 1282 cm<sup>-1</sup> with a TED contribution of approximately 35%.

The free O-H group has vibrations in out-of-plane bending mode at 300 cm<sup>-1</sup>, which was beyond the infrared spectral range of this investigation. However, in compounds, the O-H out-of-plane bending vibrations are in the range of 517-710 cm<sup>-1</sup> in intermolecular and intramolecular interactions. For the title compound, the O-H out-of-plane bending vibrations computed using the B3LYP/6-311+G(d,p) method were in good agreement with the recorded spectral data.

#### 3.6.4. Ring vibrations

Ring mode vibrations are affected by substitutions in the ring system. Due to different substituents, the imidazole ring absorbs strongly in the range of  $1630-1300 \text{ cm}^{-1}$  [30]. Typically, the indole ring has several bands of variable intensities in the range of  $1530-1013 \text{ cm}^{-1}$  due to ring stretching vibrations [31]. The bands at 958 and 889 cm<sup>-1</sup> in the FT-IR spectrum of the title compound and at 1000, 978, 779, 750 cm<sup>-1</sup> in its FT-Raman spectrum were categorized as C-C stretching vibrations, which were in good agreement with the following wavenumber values computed using the B3LYP/6-311+G(d,p) method, 1048, 1017, 1014, 1012, 1005, 983, 973, 954, 912, 899, 889, and 835 cm<sup>-1</sup>. The computed C-C-C in-plane and out-of-plane bending vibration wavenumbers were in a good agreement with recorded spectra data as shown in Table 3.

#### 3.7. UV-Vis and Frontier molecular orbital (FMO) analysis

The UV-Vis spectral data of the 3HIP molecule in the gas and chloroform phases were computed according to the time-dependent density functional theory (TD-DFT) using the B3LYP/6-311G (d,p) method. Fig. S3 shows the UV-Vis absorption spectrum of 3HIP in

chloroform. The computed electronic properties such as absorption wavelength, excitation energy, oscillator strength, and the major contribution of each transition along with its assignment are shown in Table 4. Single peaks were calculated for the title compound in the gas and chloroform phases at 245.49 and 232.29 nm, respectively. The recorded UV-Vis spectrum peak of the title compound in chloroform at 258 nm was attributed to the hyperconjugation interactions in the ring substructures and assigned to  $n\rightarrow\pi^*$  electronic transition, i.e., the lone pair electrons of the electronegative phenyl ring in the 3HIP molecule underwent the transition to the  $\pi$  electrons of this ring. The computed UV-Vis spectrum of the title compound is presented in Fig. 5.

Among the two frontier orbitals, the HOMO is the outermost orbital occupied by electrons that tends to donate them, whereas the LUMO represents the free, unoccupied space that tends to accept electrons [32, 33]. The interaction between the frontier orbitals of 3HIP was based on the  $n \rightarrow \pi^*$  transition. The energy difference between HOMO and LUMO orbitals determines critical electronic parameters such as ionization potential, electron affinity, global hardness, chemical potential, electrophilic index, and chemical softness. The respective electronic parameters of 3HIP in the gas and chloroform phases were computed using the B3LYP/6-311G(d,p) method as shown in Table 5. The computed parameters indicated that the 3HIP molecule is chemically soft and may possess certain biological activities.

Mode nos.	Expe Wavenu	rimental mber (cm <sup>-1</sup> )	V	Theoretica Vavenumber (	l cm <sup>-1</sup> )	TED (≥10%) Assignments
	FT-IR	FT-Raman	Wavenumber	IR <sub>Intinisty</sub>	Raman <sub>Activity</sub>	
1			3698	29.2539	110.465	vOH(100)
2	3166 s		3155	2.4972	97.0936	vCH(99)
3		3135 s	3126	5.2045	115.062	vCH(82)
4		3117 s	3121	4.107	46.2067	vCH(96)
5			3087	13.4354	301.6916	vCH(98)
6		3074 ms	3080	20.0083	38.807	vCH(95)
7			3069	16.6743	102.9361	vCH(93)
8			3060	0.1181	84.8434	vCH(80)
9		3052 s	3047	8.9797	45.1221	vCH(97)
10			3015	11.3894	24.4454	vCH(88)
11	2981 s		2983	7.942	45.95	vCH(99)
12			2954	32.7296	37.3686	vCH(96)
13	2927 ms	2943 ms	2943	1.8283	90.3903	vCH(97)
14			2863	41.1782	78.9794	vCH(98)
15		1599 s	1592	2.7215	39.2626	vCH(55)
16	1567 w		1573	0.7586	6.6279	vCH(68)
17	1499 m		1486	24.7969	2.7773	$\nu NC(24) + \nu CC(30) + \beta HCC(14)$
18			1480	40.5059	8.0339	$vCC(21)+\beta CNC(16)+\beta HCC(16)+\beta HCH(11)$

## **Table 3:** Vibrational wavenumbers obtained for the 3HIP molecule at B3LYP /6-311G(d,p) method.

19	1473 s		1476	12.0087	1.2192	βHCC(61)
20		14560 vw	1450	21.8502	3.0912	βHCH(60)
21			1436	10.5121	0.5984	vCC(22)+βHCC(38)
22			1429	8.2081	21.2675	βHCH(87)
23	1379 ms		1367	15.2077	5.4671	$\nu$ NC(17)+ $\gamma$ CCNH(11)+ $\tau$ HCCC(23)
24			1364	25.1505	8.668	$\beta$ HOC(16)+ $\beta$ HCN(10)+ $\beta$ HCC(12)+ $\tau$ HCCN(22)+ γCCCH(13)
25		1352 w	1350	3.0391	19.882	βHCN(19)+τCCCH(35)
26			1339	9.0834	17.8578	vNC(25)+βHCC(19)
27			1334	4.2829	15.36	vNC(26)+βHCN(13)+βHCC(15)
28			1305	2.9689	0.8004	βHCC(57)
29	1292 s	1280 m	1282	23.6727	5.9097	βHOC(11)+βHCC(35)
30			1277	1.6797	2.73	vCC(20)
31	1255 ms		1264	27.9995	16.0403	vNC(11)+βHCC(43)
32			1243	25.1309	1.6211	$\beta$ HOC(18)+ $\beta$ HCC(18)+ $\tau$ HCCN(12)
33			1236	15.0415	0.7916	$\beta$ HCC(19)+ $\tau$ HCCN(16)
34		1210 w	1216	32.8976	4.9564	vNC(23)+βHCN(57)
35			1174	1.4703	16.7514	$\nu CC(41) + \beta HCC(10)$
36			1158	1.0541	6.1533	βHCC(73)
37	1147 vs		1144	0.0744	3.9517	vCC(10)+βHCC(73)
38			1129	1.652	3.6986	$\nu$ NC(11)+ $\beta$ HCN(12)+ $\tau$ HCCC(11)
39		1109 w	1102	17.1502	6.7934	vNC(58)+βHCC(22)
40		1076 m	1074	8.755	1.6161	vCC(24)+vOC(10)
41			1058	24.6236	9.7708	vCC(20)+βHCC(49)
42			1048	37.4455	6.8649	vOC(21)
43			1017	41.6054	14.3775	vCC(34)+βHOC(10)
44			1014	6.3276	11.2528	vCC(57)
45			1012	6.4814	4.5923	vCC(12)+βCCN(36)

46	1000 vs	1005	36.515	13.0964	$vCC(52)+\beta CCN(14)$
47		983	0.5324	35.3427	νCC(21)+βCCC(66)
48	978 m	973	0.4591	0.0314	τHCCH(70)
49	958 s	954	0.025	0.0318	τHCCC(24)+τHCCH(40)
50		912	10.4503	2.6857	vCC(15)+vOC(28)
51		899	1.0808	2.1793	$\tau$ HCCC(17)+ $\tau$ HCCH(45)
52	889 vs	889	11.8444	3.2132	$\nu NC(10) + \beta CNC(72)$
53		835	1.5913	0.349	$\tau$ HCNC(14)+ $\tau$ HCCH(80)
54		835	0.0468	1.0064	τHCCC(21)+τHCCH(71)
55		817	3.3625	5.6934	νCC(27)+βCCC(19)
56	779 w	787	30.0652	0.8395	γCNNH(88)
57		758	1.6371	0.53	$\beta$ HCC(15)+ $\gamma$ CCNH(25)+ $\tau$ HCCN(16)
58	750 vw	748	26.8554	1.05	τHCCC(28)+τCCCC(42)
59	712 vw	709	28.2746	0.6865	τHCNC(76)+τHCCH(14)
60		706	4.5605	1.4101	νNC(21)+βCNC(23)
61		694	37.8496	0.4733	τHCCC(64)+τCCCC(20)
62	639 ms	656	16.4995	0.1766	τCNCN(93)
63		622	1.4825	1.9923	τCNCC(63)
64		614	0.5227	4.962	βCCC(74)
65		608	14.4752	1.9587	$\beta CCC(19) + \beta CCO(14) + \tau CNCC(17)$
66	562 m	535	27.6639	0.6824	τCCCC(45)
67		495	4.8639	0.3753	$\beta CCC(10) + \gamma OCCC(32)$
68		403	1.7212	0.0716	τCCCC(85)
69	377 w	378	26.8244	2.3942	$\beta$ CCO(11)+ $\beta$ CCN(14)+ $\tau$ HCOH(12)+ $\tau$ CCCC(21)
70	362 vw	354	48.702	2.4366	βCCN(13)+τHCOH(39)
71		333	38.8219	0.4046	$\beta CNC(45) + \tau HCOH(25)$
72		326	29.5431	0.9495	$\beta CNC(31) + \beta CCO(13) + \tau HCOH(19)$
73		237	1.1241	3.5421	$\beta$ CCC(25)+ $\tau$ CCCC(26)+ $\tau$ CNCN(11)

74	225 w	226	0.6517	1.19	$\beta CCC(40) + \gamma OCCC(11)$
75		202	0.5978	0.7708	$\beta CCC(50) + \beta CCO(14)$
76		116	0.3341	1.1871	$\tau CCCC(39) + \tau CNCN(39)$
77		99	1.2795	0.303	$\tau CCCC(52) + \tau CCNC(11)$
78		61	1.622	1.6069	$\tau CCCC(33) + \tau CCCN(38)$
79		44	0.6167	6.9525	$\beta$ CCC(37)+ $\beta$ CCN(15)+ $\tau$ CCCC(20)+ $\tau$ CNCN(20)
80		35	1.6557	6.62	$\tau CCCC(49) + \tau CCNC(35)$
81		23	0.6654	4.3419	τCCCC(21)

w-weak; vw-very weak; s-strong; vs-very strong; m-medium; br, sh-broad, shoulder; v-stretching; v<sub>sym</sub>-symmetric stretching; v<sub>asy</sub>antisymmetric stretching;  $\beta$ - in-plane bending;  $\gamma$ -out-of -plane bending;  $\omega$ -wagging; t-twisting;  $\delta$ -scissoring;  $\tau$ -torsion.

Table 4: Experimental and calculated absorption wavelengths, energies, and oscillator strengths of the 3HIP molecule according to the TD-DFT method using the B3LYP/6-311G(d,p) method.

$\lambda$ (nm)	E(eV)	( <b>f</b> )	Experimental	Major contributions <sup>a</sup>	Assignment				
Gas				7					
245.49	5.0505	0.0043		H→L (100%)	n→π*				
241.98	5.1238	0.0001		H→L+1 (99%)	$\pi \rightarrow \pi^*$				
232.22	5.3391	0.0007		H-3→ $L$ (39%), $H$ -1→ $L$ +1(44%)	$\pi \rightarrow \pi^*$				
Chloroform			Y						
232.29	5.3376	0.0012	258	H-2→ $L$ (39%), $H$ -1→ $L$ +1(48%)	n→π*				
230.22	5.3854	0.0083	230	H→L (97%)	$\pi \rightarrow \pi^*$				
226.90	5.4643	0.0001		H→L+1 (94%)	$\pi \rightarrow \pi^*$				
<sup>a</sup> H: HOMO; L	: LUMO								

Parameter	eterEnergyGas PhaseChloroform-6.13-6.3-0.65-0.5(eV)5.485.485.80-7.0-6.9-0.6-0.4gap (eV)6.4-7.11-7.110.590.5s $\eta$ (eV)2.742.742.90 $\chi$ (eV)3.393.4		
	Gas Phase	Chloroform Phase	
E (eV) HOMO	-6.13	-6.33	
E LUMO	-0.65	-0.53	
$E_{HOMO} - E_{LUMO} gap^{(eV)}$	5.48	5.80	
E HOMO-1	-7.0	-6.93	
E LUMO+1	-0.6	-0.47	
$E_{HOMO-1} - E_{LUMO+1} gap^{(eV)}$	6.4	6.46	
E HOMO-2	-7.11	-7.16	
E LUMO+2	0.59	0.5	
Chemical hardness η (eV)	2.74	2.90	
Electronegativity $\chi$ (eV)	3.39	3.43	
Chemical softness $\xi$ (eV )	1.37	1.45	
Electrophilicity index ((eV))	2.0970	2.028	
Dipole moment (Debye)	5.3521	6.1333	

**Table 5:** Calculated energy values of HOMOs and LUMOs in the 3HIP molecule in the gas and chloroform phases using the B3LYP/6-311G(d,p) method.

The density of state (DOS) spectra of the 3HIP molecule in the gas and chloroform phases were predicted using the GaussSum [34] software for calculating the Gaussian curves including their heights as shown in Fig. 5. The energy gap value between HOMO and LUMO of the title compound was 5.48 and 5.80 eV in the gas and chloroform phases, respectively. An increase in the electron donating properties caused by substituents on ring substructure leads typically to an increase in the HOMO-LUMO energy and a decrease in the HOMO-LUMO energy gap [35]. The energy gap between the HOMO-LUMO indicates the eventual charge transfer within the molecule. The marginal lowering of the HOMO-LUMO energy gap in the title compound could be attributed to the propane group substitution connecting the two ring substructures. The frontier molecular orbitals of 3HIP are displayed in Fig. 6. Positively charged regions are marked in green and negatively charged regions in red. The HOMO $\rightarrow$ LUMO transitions indicated the occurrence of an electron density transfer from the imidazole ring to the phenyl moiety.

#### 3.8. Molecular electrostatic potential

The molecular electrostatic potential (MEP), also called the molecular electrical potential surface, represents the 3D charge distribution in the molecule by visualizing the electrophilic and nucleophilic charged regions. The MEP surface of 3HIP was generated using the B3LYP/6-

311G(d,p) method as shown in Fig. 7. Electron-rich regions with the lowest electrostatic potential are marked in red, and areas with the lowest electron concentration and the highest electrostatic potential are marked in blue. An intermediate color represents an intermediary electrostatic potential. In the 3HIP molecule, all hydrogen atoms have an electrophilic site whereas the imidazole ring represents a nucleophilic site.

#### 3.9. NMR analysis

Nuclear magnetic resonance (NMR) spectroscopic technique is used to investigate the chemical structure of organic compounds. The molecular structure of the 3HIP molecule was optimized using B3LYP/6-311G(d,p) method; then, the gauge including atomic orbital (GIAO) method was adopted to determine <sup>1</sup>H and <sup>13</sup>C chemical shift values. The recorded and computed (gas and chloroform phase) chemical shift values are presented in Table 6. In <sup>13</sup>C NMR spectrum of the 3HIP molecule, the signal peak observed at 78.54 ppm was assigned to the C12 atom, and its computed value was 77.96 ppm in the chloroform phase using the B3LYP/6-311G(d,p) method. The chemical shifts of the shielded C16 and C19 atoms were observed at 38.9 and 42.7 ppm, and their computed values were 47.43 and 47.71 ppm, respectively. The <sup>13</sup>C chemical shift values for aromatic carbons are typically around 120–140 ppm [35]. The computed <sup>13</sup>C NMR chemical shifts of the phenyl ring carbons C1, C2, C3, C4, C5, and C6 were 128.28, 132.78, 131.74, 132.09, 129.49, and 151.35 ppm in chloroform, respectively. The chemical shift values of the imidazole ring carbons C23, C24, and C25 in chloroform were calculated as 122.39, 139.21, and 132.84 ppm, respectively. The computed <sup>1</sup>H chemical shift values of the methylene protons were 1.67, 1.90, 4.37 and 3.90 ppm for the hydrogens H17, H18, H20, H21, respectively. The recorded spectra peaked at 1.93 and 3.92 ppm corresponding to the methylene protons in chloroform. The calculated <sup>1</sup>H chemical shift values of the phenyl ring hydrogens were in the range of 7.28–7.82 ppm using the B3LYP/6-311G(d,p) method.

Atom	B3LYP/	Exp.	
Number	Gas Phase	Chloroform Phase	_
C1	128.09	128.28	126.5
C2	132.94	132.78	127.8
C3	131.88	131.74	124.7
C4	132.06	132.09	127.8
C5	128.99	129.49	126.5

**Table 6:** Computed NMR parameters of the 3HIP molecule using the B3LYP/6-311G(d,p) method.

C6	150.80	151.35	143.6
C12	78.54	77.96	68.9
C16	47.75	47.43	38.9
C19	47.67	47.71	42.7
C23	120.35	122.39	117.8
C24	137.95	139.21	136.2
C25	134.64	132.84	127.5
H7	7.79	7.82	7.14
H8	7.48	7.55	7.19
H9	7.34	7.42	7.20
H10	7.35	7.44	7.19
H11	7.15	7.28	7.14
H13	4.67	4.82	4.41
H17	1.61	1.67	1.93
H18	1.93	1.90	1.93
H20	4.37	4.37	3.92
H21	3.69	3.90	3.92
H26	6.78	7.01	6.79
H27	7.18	7.33	7.25
H28	7.03	6.98	6.79

#### 3.10. Reduced density gradient (RDG)

Johnson *et al.* [36] were the first to develop the methodology for calculating the reduced density gradient (RDG) from the electron density as a dimensionless quantity.

$$RDG = (r) = \frac{1}{2(3\pi r^2)^{\frac{1}{3}}} \frac{\left|\Delta^2 \rho(r)\right|}{\rho(r)^{\frac{4}{3}}}$$
(3)

The plot of  $\rho(r)$  versus the sign of  $\lambda_2$  helps to characterize the nature and strength of the interactions. The sign of  $\lambda_2$ , the second largest value of the Hessian matrix of electron density, is used to define the interaction type;  $\lambda_2 > 0$  for non-bonded species and  $\lambda_2 < 0$  for bonded species. The RDG isosurface of the 3HIP molecule was drawn using an isosurface value of 0.5 as shown in Fig. 8. The software used for plotting the RDG surface was Multiwfn software supported by the VMD program [16]. In Fig. 8, red indicates a strong repulsion that appears at the centers of the phenyl and imidazole ring systems. As shown in the same figure, a strong van der Waals interaction happened between the O-H group and phenyl ring hydrogens.

#### 3.11. Molecular docking

A docking analysis simulates potential ligand-target interactions that can be used to predict the biological activities of compounds. The structure of Candida albicans Nmyristoyltransferase (PDB ID: 1IYL) as target receptor with a bound non-peptidic inhibitor was obtained from the RCSB protein data bank [37]. The Autodock 2 docking [38] software tool was used for the docking study. The protein structure was processed using the Autodock tools graphical user interface. Polar hydrogens were added to the protein, and atomic charges were calculated by the Kollman method. Water molecules and co-crystalline solvents were removed. The 3HIP molecule was prepared for docking by minimizing its energy status using the B3LYP/6-311G(d,p) method. The active site of the target protein was defined by applying a grid size of 90×90×90 Å using Autogrid [39]. The docking study was performed by implementing the Lamarckian Genetic Algorithm with Autodock [40]. The estimated binding energy of the 3HIP molecule to the target protein was -5.41 kcal/mol at an inhibition constant of 107.97 µM. The simulated binding pose of the title compound indicates the engagement of its O-H group with the LEU419 and TYR422 residues whereas its N-H moiety interacts with the TYR210 residue via hydrogen bonding as illustrated in Fig. 9. The predicted interactions could significantly enhance the bioactivity of the 3HIP molecule.

#### Conclusion

A comprehensive vibrational analysis of 3-(1*H*-imidazol-1-yl)-1-phenylpropan-1-ol (3HIP) was conducted using different DFT methods with the 6-311G(d,p) basis set. The experimental FT-Raman and FT-IR spectra of 3HIP were in good agreement with the computed data. The computed structural parameters of the 3HIP molecule were compared and further assessed using experimental XRD data. The experimental NMR (<sup>1</sup>H and <sup>13</sup>C) chemical shifts values of 3HIP were consistent with the corresponding computed values derived using the GIAO approach. The MEP diagram of the title molecule visualized its electrophilic and nucleophilic regions. The possible intermolecular and intramolecular transitions inside the 3HIP molecule were studied by NBO analysis. Hirshfeld surface analysis assessed the potential interaction of each atom inside the 3HIP molecule. Molecular docking of 3HIP illustrated its possible binding pose within the active site of its target protein. The resulting model of the 3HIP–target protein interaction derived from our integrated experimental and computational study will provide

critical information for the development of new potent antifungal candidates for the treatment of drug-resistant fungal infections.

#### **Supplementary Information**

Figures S1-S3 are provided in the supporting information.

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**Figures captions** 

Scheme 1: Synthesis of the title compound 3HIP.

Fig. 1: Molecular structure and atom numbering scheme of the 3HIP molecule.

Fig. 2: Hirshfeld surfaces of di, shape index,  $d_{norm}$ , and curvedness simulations of the title compound.

Fig. 2: 2D fingerprint diagram of the title compound.

Fig. 4: Mullikan charges of the 3HIP molecule.

**Fig. 5:** Density state and theoretical UV-Vis spectrum of the title compound in the gas (left) and the chloroform (right) phases.

Fig. 6: The atomic orbital compositions of the frontier molecular orbital of the 3HIP molecule.

Fig. 7: Molecular electrostatic potential diagram of the 3HIP molecule.

Fig. 8: Reduced density gradient diagram (RDG) of the 3HIP molecule.

**Fig. 9:** The hydrogen bond diagram of *Candida albicans N*-myristoyltransferase with bound 3HIP molecule.

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# Table 1. Molecular geometry [bond length (Å), bond angle ( $\circ$ ) and dihedral angle ( $\circ$ )] of 3HIP by B3LYP/6-311G(d,p).

Parameter	Calculated	<b>XRD</b> <sup>a</sup>	
Bond length(Å)			
C1-C2	1.393	1.391	-
C1-C6	1.398	1.399	-
C1-H7	1.084	0.950	-
C2-C3	1.394	1.398	
C2-H8	1.084	0.950	
C3-C4	1.393	1.388	
С3-Н9	1.084	0.950	
C4-C5	1.393	1.394	
C4-H10	1.084	0.950	
C5-C6	1 397	1 393	
C5-H11	1.097	0.950	
C6-C12	1.000	1 518	
C12 H13	1.517	1.001	-
C12-III3	1.101	1.001	-
C12-014	1.431	1.417	-
014 U15	1.332	1.327	-
014-П15	0.903	0.904	
C16-H1/	1.094	0.990	-
C16-H18	1.094	0.990	-
C16-C19	1.534	1.526	-
C19-H20	1.090	0.990	-
С19-Н21	1.094	0.990	-
C19-N22	1.459	1.464	-
N22-C23	1.380	1.377	-
N22-C24	1.367	$\frac{1.357}{1.367}$	-
C23-H26	1.571	1.507	-
C24-H27	1.078	0.950	-
C24-N29	1.314	1.322	-
C25-H28	1.079	0.950	
C25-N29	1.375	1.380	
Bond angle (°)	1 1		-
C2-C1-C6	120.462	120.42	
С2-С1-Н7	120.421	119.80	
С6-С1-Н7	119.114	119.79	
C1-C2-C3	120.225	120.16	
С1-С2-Н8	119.764	119.91	]
С3-С2-Н8	120.011	119.93	]
C2-C3-C4	119.670	119.55	1
С2-С3-Н9	120.189	120.19	
С4-С3-Н9	120.141	120.26	
C3-C4-C5	120.036	120.22	1

	C3-C4-H10TED	M120.1107 CI	RIP[19.90	
	C5-C4-H10	119.856	119.88	
	C4-C5-C6	120.668	120.59	
	C4-C5-H11	119.713	119.71	
	C6-C5-H11	119.619	119.70	
	C1-C6-C5	118.937	119.04	
	C1-C6-C12	120.534	120.64	
	C5-C6-C12	120.516	120.32	
	C6-C12-H13	108.187	108.70	
	C6-C12-O14	112.295	112.56	
	C6-C12-C16	112.059	110.39	
	H13-C12-O14	109.577	108.68	
	H13-C12-C16	108.462	108.71	OL'
	O14-C12-C16	106.185	107.72	
	С12-О14-Н15	108.039	107.68	
	С12-С16-Н17	109.148	108.83	
	С12-С16-Н18	108.581	108.76	
	C12-C16-C19	112.277	113.82	
	H17-C16-H18	107.181	107.70	
	H17-C16-C19	109.833	108.75	
	H18-C16-C19	109.679	108.81	
	С16-С19-Н20	109.859	109.04	
	С16-С19-Н21	110.290	109.02	
	C16-C19-N22	112.832	112.79	
	H20-C19-H21	107.287	107.78	
	H20-C19-N22	108.849	109.03	
	H21-C19-N22	107.544	109.06	
	C19-N22-C23	126.728	126.59	
	C19-N22-C24	126.941	126.45	
	C23-N22-C24	106.253	106.94	
	N22-C23-C25	105.699	105.80	
(	N22-C23-H26	121.778	127.14	
	С25-С23-Н26	132.521	127.06	
	N22-C24-H27	121.743	123.99	
	N22-C24-N29	112.427	111.96	
	H27-C24-N29	125.826	124.06	
	С23-С25-Н28	127.979	124.89	
	C23-C25-N29	110.569	110.28	
	H28-C25-N29	121.450	124.83	
	C24-N29-C25	105.052	105.02	
	Dihedral angle (°)		1	
	C6-C1-C2-C3	-0.136	-1.16	
	С6-С1-С2-Н8	179.913	178.81	
	Н7-С1-С2-С3	-179.485	178.86	

	H7-C1-C2-H8 ED	M.0.564SC	RIPT1.17	
	C2-C1-C6-C5	-0.218	1.20	
	C2-C1-C6-C12	178.520	-178.30	
	H7-C1-C6-C5	179.139	-178.82	
	H7-C1-C6-C12	-2.124	1.68	
	C1-C2-C3-C4	0.277	-0.15	
	С1-С2-С3-Н9	179.986	179.89	
	H8-C2-C3-C4	-179.772	179.88	
	Н8-С2-С3-Н9	-0.063	-0.08	
	C2-C3-C4-C5	-0.061	1.41	
	C2-C3-C4-H10	179.511	-178.56	
	H9-C3-C4-C5	-179.770	-178.63	
	H9-C3-C4-H10	-0.198	1.41	
	C3-C4-C5-C6	-0.299	-1.37	
	C3-C4-C5-H11	179.396	178.59	
	H10-C4-C5-C6	-179.871	178.60	
	H10-C4-C5-H11	-0.177	-1.44	
	C4-C5-C6-C1	0.436	0.06	
	C4-C5-C6-C12	-178.302	179.56	
	H11-C5-C6-C1	-179.259	-179.91	
	H11-C5-C6-C12	2.003	-0.40	
	C1-C6-C12-H13	155.861	170.33	
	C1-C6-C12-O14	34.805	49.88	
	C1-C6-C12-C16	-84.616	-70.52	
	С5-С6-С12-Н13	-25.421	-9.17	
	C5-C6-C12-O14	-146.478	-129.62	
	C5-C6-C12-C16	94.102	109.99	
	C6-C12-O14-H15	55.923	39.65	
	H13-C12-O14-H15	-64.332	-80.81	
	C16-C12-O14-H15	178.720	161.57	
	С6-С12-С16-Н17	-55.779	-62.48	
(	C6-C12-C16-H18	60.747	54.59	
	C6-C12-C16-C19	-177.810	176.07	
	H13-C12-C16-H17	63.583	56.67	
	H13-C12-C16-H18	-179.891	173.74	
	H13-C12-C16-C19	-58.448	-64.78	
× ×	O14-C12-C16-H17	-178.725	174.27	
	O14-C12-C16-H18	-62.199	-68.67	
	O14-C12-C16-C19	59.245	52.81	
	С12-С16-С19-Н20	-57.362	-62.23	
	С12-С16-С19-Н21	60.697	-179.66	
	C12-C16-C19-N22	-179.014	59.04	
	H17-C16-C19-H20	-179.002	176.28	

	H17-C16-C19-H21D	M-60.943 CI	RIP <b>5</b> 8.84	
	H17-C16-C19-N22	59.346	-62.45	
	H18-C16-C19-H20	63.451	-58.21	
	H18-C16-C19-H21	-178.491	59.22	
	H18-C16-C19-N22	-58.202	-179.51	
	C16-C19-N22-C23	80.793	71.41	
	C16-C19-N22-C24	-95.531	-107.01	
	H20-C19-N22-C23	-41.429	-49.86	
	H20-C19-N22-C24	142.247	131.71	
	H21-C19-N22-C23	-157.356	167.31	
	H21-C19-N22-C24	26.320	14.27	
	C19-N22-C23-C25	-177.220	-179.01	
	C19-N22-C23-H26	3.278	1.00	
	C24-N22-C23-C25	-0.280	-0.34	
	C24-N22-C23-H26	-179.782	179.68	
	C19-N22-C24-H27	-3.360	-1.02	
	C19-N22-C24-N29	177.302	178.99	
	C23-N22-C24-H27	179.709	-179.69	
	C23-N22-C24-N29	0.370	0.31	
	N22-C23-C25-H28	-179.377	-179.71	
	N22-C23-C25-N29	0.115	0.26	
	H26-C23-C25-H28	0.049	0.28	
	H26-C23-C25-N29	179.540	-179.76	
	N22-C24-N29-C25	-0.294	-0.15	
	H27-C24-N29-C25	-179.600	179.85	
	C23-C25-N29-C24	0.104	-0.07	
	H28-C25-N29-C24	179.634	179.89	
: :	Takan from reference	[16]		

<sup>a</sup>Taken from reference [16].

Y

Donor (i)	Туре	ED/e	Acceptor (j)	Туре	ED/e	E(2) (Kj/Mol)	E(j)-E(i) (a.u)	F(i,j) (a.u)
C1-C2	σ	1.97708	C1-C6	σ*	0.02635	3.96	1.27	0.063
C1-C2	σ	1.97708	C2-C3	σ*	0.01708	3.07	1.27	0.056
C1-C2	σ	1.97708	С3-Н9	σ*	0.01462	2.38	1.14	0.047
C1-C2	σ	1.97708	C6-C12	σ*	0.03918	3.79	1.10	0.058
C1-C2	π	1.66191	C3-C4	$\pi^*$	0.33025	20.31	0.28	0.068
C1-C2	π	1.66191	C5-C6	$\pi^*$	0.35496	21.71	0.28	0.070
C1-C6	σ	1.97172	C1-C2	σ*	0.01639	3.50	1.27	0.060
C1-C6	σ	1.97172	C2-H8	σ*	0.01466	2.20	1.14	0.045
C1-C6	σ	1.97172	C5-C6	σ*	0.02438	4.22	1.27	0.065
C1-C6	σ	1.97172	C5-H11	σ*	0.01595	2.54	1.13	0.048
C1-C6	σ	1.97172	C6-C12	σ*	0.03918	2.23	1.10	0.044
C1-H7	σ	1.97851	C2-C3	σ*	0.01708	3.75	1.09	0.057
C1-H7	σ	1.97851	C5-C6	σ*	0.02438	4.76	1.09	0.064
C2-C3	σ	1.97914	C1-C2	σ*	0.01639	3.13	1.28	0.056
C2-C3	σ	1.97914	C1-H7	σ*	0.01596	2.48	1.15	0.048
C2-C3	σ	1.97914	C3-C4	σ*	0.01691	3.01	1.27	0.055
C2-C3	σ	1.97914	C4-H10	σ*	0.01446	2.47	1.14	0.047
C2-H8	σ	1.97956	C1-C6	σ*	0.02635	4.10	1.09	0.060
C2-H8	σ	1.97956	C3-C4	σ*	0.01691	3.81	1.09	0.058
C3-C4	σ	1.97889	C2-C3	σ*	0.01708	3.00	1.27	0.055
C3-C4	σ	1.97889	С2-Н8	σ*	0.01466	2.45	1.14	0.047
C3-C4	σ	1.97889	C4-C5	σ*	0.01628	3.12	1.27	0.056
C3-C4	σ	1.97889	C5-H11	σ*	0.01595	2.53	1.13	0.048
C3-C4	π	1.66013	C1-C2	$\pi^*$	0.32468	20.67	0.28	0.069

Table 2. Second Order perturbation theory analysis of Poek matrix in NDO basis for the STIT inforeate by DSE 11/0-5110(a,p) method.
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C3-C4	π	1.66013	C5-C6	$\pi^*$	0.35496	20.33	0.28	0.068
С3-Н9	σ	1.97954	C1-C2	σ*	0.01639	3.86	1.10	0.058
С3-Н9	σ	1.97954	C4-C5	σ*	0.01628	3.87	1.09	0.058
C4-C5	σ	1.97716	C3-C4	σ*	0.01691	3.04	1.27	0.063
C4-C5	σ	1.97716	C3-H9	σ*	0.01462	2.39	1.14	0.047
C4-C5	σ	1.97716	C5-C6	σ*	0.02438	3.97	1.27	0.063
C4-C5	σ	1.97716	C6-C12	σ*	0.03918	3.83	1.10	0.058
C4-H10	σ	1.97952	C2-C3	σ*	0.01708	3.79	1.09	0.058
C4-H10	σ	1.97952	C5-C6	σ*	0.02438	4.08	1.09	0.060
C5-C6	σ	1.97220	C1-C6	σ*	0.02635	4.26	1.27	0.066
C5-C6	σ	1.97220	C1-H7	σ*	0.01596	2.44	1.15	0.047
C5-C6	σ	1.97220	C4-C5	σ*	0.01628	3.57	1.27	0.060
C5-C6	σ	1.97220	C4-H10	σ*	0.01446	2.16	1.14	0.044
C5-C6	σ	1.97220	C6-C12	σ*	0.03918	2.14	1.10	0.043
C5-C6	π	1.66000	C1-C2	π*	0.32468	19.77	0.29	0.067
C5-C6	π	1.66000	C3-C4	π*	0.33025	20.73	0.29	0.069
C5-C6	π	1.66000	C12-O14	σ*	0.02735	2.28	0.53	0.034
C5-C6	π	1.66000	C12-C16	σ*	0.02512	2.90	0.62	0.041
C5-H11	σ	1.97910	C1-C6	σ*	0.02635	4.66	1.09	0.064
C5-H11	σ	1.97910	C3-C4	σ*	0.01691	3.69	1.10	0.025
C6-C12	σ	1.97018	C1-C2	σ*	0.01639	2.54	1.21	0.050
C6-C12	σ	1.97018	C1-C6	σ*	0.02635	2.40	1.20	0.048
C6-C12	σ	1.97018	C4-C5	σ*	0.01628	2.45	1.21	0.049
C6-C12	σ	1.97018	C5-C6	σ*	0.02438	2.40	1.21	0.048
C12-H13	σ	1.97601	Č1-C6	σ*	0.02635	3.81	1.08	0.057
C12-H13	σ	1.97601	C16-H18	σ*	0.01595	2.66	0.92	0.044
C12-C16	σ	1.96474	C5-C6	$\pi^*$	0.35496	2.53	0.65	0.039
C12-C16	σ	1.96474	C19-N22	σ*	0.02790	2.33	0.96	0.042

O14-H15	σ	1.98847	C12-C16	σ*	0.02512	2.53	1.09	0.047
C16-H17	σ	1.97475	C12-O14	σ*	0.02735	3.83	0.77	0.049
C16-H17	σ	1.97475	C19-H20	σ*	0.01635	2.53	0.91	0.043
C16-H18	σ	1.97600	C12-H13	σ*	0.03607	2.74	0.88	0.444
C16-H18	σ	1.97600	C19-H21	σ*	0.01485	2.64	0.89	0.043
C16-C19	σ	1.97528	C6-C12	σ*	0.03918	2.07	1.02	0.041
C19-H20	σ	1.98004	C16-H17	σ*	0.01156	2.62	0.92	0.044
C19-H20	σ	1.98004	N22-C24	σ*	0.04255	3.81	0.98	0.055
C19-H21	σ	1.98064	C16-H18	σ*	0.01595	2.59	0.93	0.044
C19-H21	σ	1.98064	N22-C23	σ*	0.02372	4.51	0.98	0.059
N22-C23	σ	1.98140	N22-C24	σ*	0.04255	2.19	1.25	0.047
N22-C23	σ	1.98140	C24-H27	σ*	0.02243	2.67	1.21	0.051
N22-C23	σ	1.98140	C25-H28	σ*	0.01815	3.06	1.24	0.055
N22-C24	σ	1.98605	N22-C23	σ*	0.02372	2.12	1.25	0.046
N22-C24	σ	1.98605	C23-H26	σ*	0.01277	2.70	1.24	0.052
C23-C25	σ	1.98381	C19-N22	σ*	0.02790	5.85	1.04	0.070
C23-C25	π	1.85770	C24-N29	π*	0.38194	15.12	0.28	0.062
C23-H26	σ	1.98543	N22-C24	σ*	0.04255	3.12	1.01	0.051
C24-H27	σ	1.98380	N22-C23	σ*	0.02372	3.29	1.00	0.051
C24-H27	σ	1.98380	C25-N29	σ*	0.01136	3.18	1.05	0.052
C24-N29	σ	1.98501	C19-N22	σ*	0.02790	3.78	1.15	0.059
C24-C29	σ	1.98501	C25-H28	σ*	0.01815	3.27	1.27	0.058
C24-C29	π	1.86725	C23-C25	$\pi^*$	0.30719	21.55	0.33	0.078
C25-H28	σ	1.98550	C24-N29	σ*	0.38194	2.86	1.10	0.050
C25-N29	σ	1.97835	C23-H26	σ*	0.01277	3.43	1.18	0.057
C25-N29	σ	1.97835	C24-H27	σ*	0.02243	5.19	1.17	0.069
LP(2)O14	n	1.95456	C6-C12	σ*	0.03918	5.44	0.72	0.056
LP(2)O14	n	1.95456	C12-H13	σ*	0.03607	6.98	0.70	0.062
				3				

LP(1)N22	n	1.55711	C16-C19	σ*	0.01988	5.83	0.62	0.060
LP(1)N22	n	1.55711	C19-H20	σ*	0.01635	2.46	0.66	0.041
LP(1)N22	n	1.55711	C23-C25	π*	0.30719	31.27	0.29	0.088
LP(1)N22	n	1.55711	C24-N29	π*	0.38194	46.55	0.28	0.103
LP(1)N29	n	1.92411	N22-C24	σ*	0.04255	8.32	0.81	0.074
LP(1)N29	n	1.92411	C23-C25	σ*	0.01884	5.51	0.94	0.065
LP(1)N29	n	1.92411	C24-H27	σ*	0.02243	2.23	0.77	0.037
LP(1)N29	n	1.92411	C25-H28	σ*	0.01815	2.19	0.80	0.038

C25-H28 σ\* 0.01815 2.19

**Table 3:** Vibrational wavenumbers obtained for the 3HIP molecule at B3LYP /6-311G(d,p) method.

Mode nos.	Expe Wavenui	rimental mber (cm <sup>-1</sup> )	v	Theoretica Vavenumber (	l cm <sup>-1</sup> )	TED (≥10%) Assignments
			E	<u>33LYP/6-3110</u>	<b>d,p</b>	Q_'
	FT-IR	FT-Raman	Wavenumber	<b>IR</b> Intinisty	Raman <sub>Activity</sub>	
1			3698	29.2539	110.465	vOH(100)
2	3166 s		3155	2.4972	97.0936	vCH(99)
3		3135 s	3126	5.2045	115.062	vCH(82)
4		3117 s	3121	4.107	46.2067	vCH(96)
5			3087	13.4354	301.6916	vCH(98)
6		3074 ms	3080	20.0083	38.807	vCH(95)
7			3069	16.6743	102.9361	vCH(93)
8			3060	0.1181	84.8434	vCH(80)
9		3052 s	3047	8.9797	45.1221	vCH(97)
10			3015	11.3894	24.4454	vCH(88)
11	2981 s		2983	7.942	45.95	vCH(99)
12			2954	32.7296	37.3686	vCH(96)
13	2927 ms	2943 ms	2943	1.8283	90.3903	vCH(97)
14			2863	41.1782	78.9794	vCH(98)
15		1599 s	1592	2.7215	39.2626	vCH(55)
16	1567 w		1573	0.7586	6.6279	vCH(68)
17	1499 m		1486	24.7969	2.7773	$\nu NC(24) + \nu CC(30) + \beta HCC(14)$
18			1480	40.5059	8.0339	$vCC(21)+\beta CNC(16)+\beta HCC(16)+\beta HCH(11)$

19	1473 s		1476	12.0087	1.2192	βHCC(61)
20		14560 vw	1450	21.8502	3.0912	βHCH(60)
21			1436	10.5121	0.5984	$\nu CC(22) + \beta HCC(38)$
22			1429	8.2081	21.2675	βHCH(87)
23	1379 ms		1367	15.2077	5.4671	$vNC(17)+\gamma CCNH(11)+\tau HCCC(23)$
24			1364	25.1505	8.668	$\beta$ HOC(16)+ $\beta$ HCN(10)+ $\beta$ HCC(12)+ $\tau$ HCCN(22)+ $\gamma$ CCCH(13)
25		1352 w	1350	3.0391	19.882	βHCN(19)+τCCCH(35)
26			1339	9.0834	17.8578	vNC(25)+βHCC(19)
27			1334	4.2829	15.36	vNC(26)+βHCN(13)+βHCC(15)
28			1305	2.9689	0.8004	βHCC(57)
29	1292 s	1280 m	1282	23.6727	5.9097	$\beta$ HOC(11)+ $\beta$ HCC(35)
30			1277	1.6797	2.73	vCC(20)
31	1255 ms		1264	27.9995	16.0403	$\nu NC(11) + \beta HCC(43)$
32			1243	25.1309	1.6211	$\beta$ HOC(18)+ $\beta$ HCC(18)+ $\tau$ HCCN(12)
33			1236	15.0415	0.7916	$\beta$ HCC(19)+ $\tau$ HCCN(16)
34		1210 w	1216	32.8976	4.9564	vNC(23)+βHCN(57)
35			1174	1.4703	16.7514	$vCC(41)+\beta HCC(10)$
36			1158	1.0541	6.1533	βHCC(73)
37	1147 vs		1144	0.0744	3.9517	vCC(10)+βHCC(73)
38			1129	1.652	3.6986	$\nu$ NC(11)+ $\beta$ HCN(12)+ $\tau$ HCCC(11)
39		1109 w	1102	17.1502	6.7934	$vNC(58)+\beta HCC(22)$
40		1076 m	1074	8.755	1.6161	vCC(24)+vOC(10)
41			1058	24.6236	9.7708	vCC(20)+βHCC(49)
42			1048	37.4455	6.8649	vOC(21)
43			1017	41.6054	14.3775	$vCC(34)+\beta HOC(10)$
44			1014	6.3276	11.2528	vCC(57)
45			1012	6.4814	4.5923	vCC(12)+βCCN(36)

46		1000 vs	1005	36.515	13.0964	$vCC(52)+\beta CCN(14)$
47			983	0.5324	35.3427	$vCC(21)+\beta CCC(66)$
48		978 m	973	0.4591	0.0314	τHCCH(70)
49	958 s		954	0.025	0.0318	$\tau$ HCCC(24)+ $\tau$ HCCH(40)
50			912	10.4503	2.6857	vCC(15)+vOC(28)
51			899	1.0808	2.1793	$\tau$ HCCC(17)+ $\tau$ HCCH(45)
52	889 vs		889	11.8444	3.2132	vNC(10)+βCNC(72)
53			835	1.5913	0.349	τHCNC(14)+τHCCH(80)
54			835	0.0468	1.0064	τHCCC(21)+τHCCH(71)
55			817	3.3625	5.6934	vCC(27)+βCCC(19)
56		779 w	787	30.0652	0.8395	γCNNH(88)
57			758	1.6371	0.53	$\beta$ HCC(15)+ $\gamma$ CCNH(25)+ $\tau$ HCCN(16)
58		750 vw	748	26.8554	1.05	τHCCC(28)+τCCCC(42)
59	712 vw		709	28.2746	0.6865	τHCNC(76)+τHCCH(14)
60			706	4.5605	1.4101	vNC(21)+βCNC(23)
61			694	37.8496	0.4733	τHCCC(64)+τCCCC(20)
62	639 ms		656	16.4995	0.1766	τCNCN(93)
63			622	1.4825	1.9923	τCNCC(63)
64			614	0.5227	4.962	βCCC(74)
65			608	14.4752	1.9587	$\beta CCC(19) + \beta CCO(14) + \tau CNCC(17)$
66	562 m		535	27.6639	0.6824	τCCCC(45)
67			495	4.8639	0.3753	$\beta$ CCC(10)+ $\gamma$ OCCC(32)
68			403	1.7212	0.0716	τCCCC(85)
69		377 w	378	26.8244	2.3942	$\beta$ CCO(11)+ $\beta$ CCN(14)+ $\tau$ HCOH(12)+ $\tau$ CCCC(21)
70		362 vw	354	48.702	2.4366	$\beta CCN(13) + \tau HCOH(39)$
71			333	38.8219	0.4046	$\beta$ CNC(45)+ $\tau$ HCOH(25)
72			326	29.5431	0.9495	$\beta$ CNC(31)+ $\beta$ CCO(13)+ $\tau$ HCOH(19)
73			237	1.1241	3.5421	$\beta$ CCC(25)+ $\tau$ CCCC(26)+ $\tau$ CNCN(11)

74	225 w	226	0.6517	1.19	$\beta CCC(40) + \gamma OCCC(11)$
75		202	0.5978	0.7708	$\beta CCC(50) + \beta CCO(14)$
76		116	0.3341	1.1871	τCCCC(39)+τCNCN(39)
77		99	1.2795	0.303	$\tau CCCC(52) + \tau CCNC(11)$
78		61	1.622	1.6069	τCCCC(33)+τCCCN(38)
79		44	0.6167	6.9525	$\beta$ CCC(37)+ $\beta$ CCN(15)+ $\tau$ CCCC(20)+ $\tau$ CNCN(20)
80		35	1.6557	6.62	τCCCC(49)+τCCNC(35)
81		23	0.6654	4.3419	τCCCC(21)

rioad, . .ig; ω – waggin<sub>b</sub> w-weak; vw- very weak; s-strong; vs-very strong; m-medium; br, sh- broad, shoulder,  $\upsilon$  - stretching;  $\upsilon_{sym}$  - symmetric stretching;  $\upsilon_{asy}$ asymmetric stretching;  $\beta$ - in plane bending;  $\gamma$ - out-of –plane bending;  $\omega$  – wagging; t- twisting;  $\delta$  –scissoring;  $\tau$ - torsion.

Table 4: Experimental and calculated absorption wavelengths, energies and oscillator strengths of the 3HIP molecule by TD-DFT method at B3LYP/6-311G(d,p) method.

$\lambda$ (nm)	E(eV)	( <b>f</b> )	Experimental	Major contributions <sup>a</sup>	assignment
Gas					
245.49	5.0505	0.0043		H→L (100%)	n→π*
241.98	5.1238	0.0001		H→L+1 (99%)	n→π*
232.22	5.3391	0.0007		H-3→L(39%), H-1→L+1(44%)	n→π*
Chloroform					
232.29	5.3376	0.0012	258	H-2→L (39%), H-1→L+1(48%)	n→π*
230.22	5.3854	0.0083	230	H→L (97%)	n→π*
226.90	5.4643	0.0001		H→L+1 (94%)	n→π*
$H \cdot H \cap M \cap I \cdot I$	UMO				

"H: HOMO; L: LUMO

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Table 5: HOMO and LUMO calculated energy values of the 3HIP molecule in the gas and	ł
chloroform phases using B3LYP/6-311G(d,p) method.	

Parameter		Energy
	Gas Phase	Chloroform Phas
E (eV) HOMO	-6.13	-6.33
E LUMO	-0.65	-0.53
$E_{HOMO} - E_{LUMO} gap^{(eV)}$	5.48	5.80
E HOMO-1	-7.0	-6.93
E LUMO+1	-0.6	-0.47
$E_{HOMO-1} - E_{LUMO+1} gap^{(eV)}$	6.4	6.46
E HOMO-2	-7.11	-7.16
E LUMO+2	0.59	0.5
Chemical hardness $\eta$ (eV)	2.74	2.90
Electronegativity $\chi$ (eV)	3.39	3.43
Chemical Softness $\xi$ (eV)	1.37	1.45
Electrophilicity index $\omega$ (eV )	2.0970	2.028
Dipole moment (Debye)	5.3521	6.1333
	Ar'	

Atom	B3LYP/6-311G(d,p)		Exp.
Number	Gas Phase	Chloroform Phase	
C1	128.09	128.28	126.5
C2	132.94	132.78	127.8
C3	131.88	131.74	124.7
C4	132.06	132.09	127.8
C5	128.99	129.49	126.5
C6	150.80	151.35	143.6
C12	78.54	77.96	68.9
C16	47.75	47.43	38.9
C19	47.67	47.71	42.7
C23	120.35	122.39	117.8
C24	137.95	139.21	136.2
C25	134.64	132.84	127.5
H7	7.79	7.82	7.14
H8	7.48	7.55	7.19
H9	7.34	7.42	7.20
H10	7.35	7.44	7.19
H11	7.15	7.28	7.14
H13	4.67	4.82	4.41
H17	1.61	1.67	1.93
H18	1.93	1.90	1.93
H20	4.37	4.37	3.92
H21	3.69	3.90	3.92
H26	6.78	7.01	6.79
H27	7.18	7.33	7.25
H28	7.03	6.98	6.79

 Table 6: Computed NMR parameters of the 3HIP molecule by B3LYP/6-311G(d,p) method.



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Fig. 6: The atomic orbital compositions of the frontier molecular orbital of the 3HIP molecule.









• Spectroscopic analysis of  $C_{12}$   $H_{14}N_2O$ , a potential precursor to antifungal agents.

- FT-IR, FT-Raman, <sup>1</sup>H and <sup>13</sup>C NMR spectral analyses are reported.
- The geometrical parameters are in agreement with XRD data.
- Molecular docking and Hirshfeld surface analysis were carried out.