Green Synthesis, SC-XRD, Non-Covalent Interactive Potential and Electronic Communication via DFT Exploration of Pyridine-Based Hydrazone

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Abstract: Ultrasound-based synthesis at room temperature produces valuable compounds greener and safer than most other methods. This study presents the sonochemical fabrication and characterization of a pyridine-based halogenated hydrazone, (E)-2-((6-chloropyridin-2-yl)oxy)-N′-(2-hydroxybenzylidene) acetohydrazide (HBPAH). The NMR spectroscopic technique was used to determine the structure, while SC-XRD confirmed its crystalline nature. Our structural studies revealed that strong, inter-molecular attractive forces stabilize this crystalline organic compound. Moreover, the compound was optimized at the B3LYP/6-311G(d,p) level using the Crystallographic Information File (CIF). Natural bonding orbital (NBO) and natural population analysis (NPA) were performed at the same level using optimized geometry. Time-dependent density functional theory (DFT) was performed at the B3LYP/6-311G (d,p) method to calculate the frontier molecular orbitals (FMOs) and molecular electrostatic potential (MEP). The global reactivity descriptors were determined using HOMO and LUMO energy gaps. Theoretical calculations based on the Quantum Theory of Atoms in Molecules (QT-AIM) and Hirshfeld analyses identified the non-covalent and covalent interactions of the HBPAH compound. Consequently, QT-AIM and Hirshfeld analyses agree with experimental results.

Keywords: hydrazones; sonochemical-based synthesis; single-crystal analysis; non-covalent interaction; Hirshfeld surface study

1. Introduction

Humanity faces increasing health, shelter, and economic problems as we consume more resources to pollute, urbanize, and deforest our environment. Fatal diseases have not only taken many lives
but also severely harmed the global economy. To combat global pandemics and other diseases, synthetic organic chemists need to synthesize novel and potent chemicals by safe and green methods. One such chemical, hydrazones, plays a substantial role in the bio-medicinal applications due to its versatility [1–3]. It has many effortlessly reachable binding sites for the medicinal applications [4], such as antimicrobial [5], cardioprotective [6], anti-HIV [7], anti-inflammatory [8], anticancer [9], antihypertensive [10], antitubercular [11], antimalarial [12], antidepressant [13], antioxidant [14], and anticonvulsant [15]. For example, pyridine-based hydrazone derivatives ubiquitously displayed antifungal properties [16–18]. Acylpyridine derivative, 2-benzoxazolylhydrazon, suppresses leukemia, colon and ovarian cancer cell lines [19]. Acylhydrazide introduction in 1, 2, 4-triazolo [4, 3-a] pyridine derivatives by a microwave-assisted method leads to herbicidal and pesticidal lead compounds [1]. Hydrazone derivatives also possess unique physical and chemical properties including fluorescence emission [20], corrosion inhibitory properties and passivation [21], and iron chelation in iron toxicity [22]. In addition, lone electron pairs and pi-electrons play a key role in medicinal applications due to their ability of non-covalent interaction, such as van der Waals interactions, hydrophobic bonds, ionic bonds, and hydrogen bonds [23–26]. In particular, these non-covalent interactions facilitate crystals packing, proton transfer reactions, the stability of molecules, enzymatic catalysis [25,27–29]. Several molecules with hydrogen bonding capacity are important for catalysis in organic transformation such as diols, bisphenols, hydroxy acids, urea, guanidinium and amidinium ions, thioureas, lactams, thioureas, cinchona alkaloids, and phosphoric acids [30–34]. Amongst them, hydrazones have a unique chemical architecture (Figure 1), allowing its significant ability to form non-covalent interactions [35].

Studies show that microwave-assisted synthesis accelerates chemical synthesis with a better yield and higher purity in comparison to conventional methods [18,36,37]. Microwave (MW) radiations assist in non-thermal polarizing radiation, dipolar polarization, ionic conduction reactions [38]. This study reports the ultrasound-based synthesis, SC-XRD exploration, and density functional theory (DFT) analysis of the pyridine-based novel crystalline hydrazones, i.e., (E)-2-((6-chloropyridin-2-yl)oxy)-N’-(2-hydroxybenzylidene) acetohydrazide.

2. Materials and Methods

2.1. General

Analytical grade solvents and pure reagents were used without any further purification. TLC (Thin layer chromatography) cards, coated with silica gel (0.25 mm thickness), were used to monitor the reaction progress. For the NMR spectra measurement, Bruker-Avance, A-V spectrometer, was used. For the single crystal analysis, Bruker Kappa APEX-II diffractometer was used where the data correction and data reduction were made by APEX-II and SAINT, respectively [39]. For the structure solution, SHELXS97 software [40,41] and for refinement, SHELXL2014/6 was used to minimize the structural errors [42]. For the graphical representation of the asymmetric unit, ORTEP was used while for the hydrogen bonding, PLATON was used [43].

2.2. Synthesis of 2-(6′-Chloroazin-2′-yl) oxy-aceto-hydrazide (A)

The precursor A was manufactured according to the procedure described elsewhere [35,44]. Accordingly, a mixture of ethyl 2-(6′-chloroazin-2-yl)-ox-ethanoate (131 mg, 0.61 mmol) and N2H4.H2O (0.09 mL, 1.83 mmol) in ethanol was refluxed for 3 h. The reaction on completion (monitored by TLC)
was cooled to room temperature and concentrated under reduced pressure. The targeted hydrazide was purified by column chromatography yielding 89 mg of the isolated A (73%).

2.3. General Procedure for the Synthesis of (E)-2-((6-chloropyridin-2-yl)oxy)-N’-(2-hydroxybenzylidene)acetohydrazide

A mixture of A (2-(6′-chloroazin-2′-yl) oxy-aceto-hydrazide) (0.48 mmol) and Salicylaldehyde (0.54 mmol) was dissolved in ethanol separately to make clear solutions. The solutions were mixed at room temperature, and the mixture was sonicated for 5 to 10 min. The targeted compound was precipitated that was filtered through standard filtration and recrystallized in ethanol (Scheme 1).

\[ \text{A} + \text{EtOH (5-10 min)} \rightarrow \text{85%} \]

\[ \text{Scheme 1. Ultrasonic-based Synthesis of (E)-2-((6-chloropyridin-2-yl)oxy)-N’-(2-hydroxybenzylidene) acetohydrazide.} \]

\[ ^1\text{H NMR (400 MHz, DMSO)} \delta 11.84 (s, 1H), 10.99 (s, 1H), 8.48 (s, 1H), 7.81 (dt, J = 15.3, 7.8 Hz, 2H), 7.72–7.67 (m, 1H), 7.32–7.21 (m, 2H), 7.15 (d, J = 7.5 Hz, 1H), 7.00–6.94 (m, 1H), 5.31 (s, 2H). \]

\[ ^{13}\text{C NMR (100 MHz, DMSO)} \delta 168.2, 163.8, 162.4, 156.4, 147.6, 142.1, 141.3, 131.2, 126.2, 119.3, 116.8, 116.1, 109.6, 62.9 (Figure S1). \]

2.4. Computational Studies

The simulation study for the entitled compound, (E)-2-((6-chloropyridin-2-yl)oxy)-N’-(2-hydroxybenzylidene) acetohydrazide (HBPAH), was performed through DFT [45–47] employing Gaussian 09 program package [48]. By the use of GaussView 5.0. [49] all input files were organized. Finally, Chem craft [50], Avogadro [51] and Gauss Sum [52], AIM-All Professional [53], and Crystal Explorer [54] programs were used for the interpretation of output files. The Structure of HBPAH was optimized using SC-XRD-based geometry at the B3LYP/6-311G(d,p) level [57,58]. Moreover, the Hirshfield surface (HS) analysis [59,60] was carried out to determine the non-covalent interactions. The Quantum Theory of Atoms in Molecules (QT-AIM) [61] analysis was employed to explore the non-covalent interactions. The electron affinity (EA), electronegativity (X) [62], global electrophilicity index (ω) [62–64], ionization potential (IP) [65], global hardness (η) [66,67], global softness (S) [68] and chemical potential (μ) [69] were known as global reactivity parameters, and their values can be calculated by HOMO-LUMO energies. These parameters were also reported as biological activity descriptors having numerous optoelectronic applications and are helpful in determining stability, reactivity, and selectivity of the molecules [62,70–72]. They were calculated through Equations (1)–(7):

\[ \text{IP} = -E_{\text{HOMO}} \]  
\[ \text{EA} = -E_{\text{LUMO}} \]

where IP = ionization potential (eV), EA = electron affinity (eV).

Koopmans’s theorem [73] was usually used to calculate the chemical potential (μ), electronegativity (x) and chemical hardness (η) and was equated as:

\[ \mu = \frac{E_{\text{HOMO}} + E_{\text{LUMO}}}{2} \]
\[ x = \frac{[\text{IP} + \text{EA}]}{2} = -\frac{[\text{E}_{\text{LUMO}} + \text{E}_{\text{HOMO}}]}{2} \]  
\[ \eta = \frac{[\text{IP} - \text{EA}]}{2} = -\frac{[\text{E}_{\text{LUMO}} - \text{E}_{\text{HOMO}}]}{2} \]  
(4)  
(5)  

The following equation was used for global softness (\(\sigma\)):

\[ \sigma = \frac{1}{2\eta} \]  
(6)  

The calculation of electrophilicity index (\(\omega\)) was reported by Parr et al. as:

\[ \omega = \frac{\mu^2}{2\eta} \]  
(7)  

3. Results and Discussion

The hydrazone, (E)-2-((6-chloropyridin-2-yl)oxy)-N'-(2-hydroxybenzylidene) acetohydrazide (HBPAH), was synthesized with a yield of 85% and its structures were determined by NMR spectroscopy and SC-XRD analysis. The \(^1\)H- and \(^13\)C-NMR of the title compound showed the presence of each signal in duplication that indicates that the title compound exists in two isomeric forms; a minor isomer A (E) that is 45.87% and a major isomer B (Z) that is 54.12% (Scheme 2). The ratio of the E and Z isomers was calculated from the \(^1\)H-NMR analysis, where the methylenic signals of both isomers were integrated into the \(^1\)H NMR spectra (Figure S2 in Supplementary Materials).

\[ \text{Scheme 2. Isomeric existence of the title compound. The highlighted region shows the double-bond conferring E and Z isomers.} \]

The DFT calculation of HBPAH was performed by DFT/B3LYP/6-311G (d, p). Table 1 shows the single-crystal analysis details, Hirshfeld surface, and computational details.

\[ \text{Table 1. Experimental details of the compound (E)-2-((6-chloropyridin-2-yl)oxy)-N'-(2-hydroxybenzylidene) acetohydrazide (HBPAH).} \]

| Crystal Data                  | HBPAH                                      |
|-------------------------------|--------------------------------------------|
| CCDC* number                  | 2012169                                    |
| Chemical formula              | 2(C\(_{14}\)H\(_{12}\)ClN\(_3\)O\(_3\))·H\(_2\)O |
| \( M_r \)                     | 629.45                                     |
| Crystal system, space group   | Triclinic, \(P\bar{1}\)                     |
| Temperature (K)               | 296                                        |
| \( a, b, c \) (Å)             | 6.6987 (8), 7.3628 (9), 31.513 (4)         |
| \( \alpha, \beta, \gamma \) (°) | 90.978 (7), 93.508 (6), 113.954 (7)        |
| \( V \) (Å\(^3\))            | 1416.2 (3)                                 |
| \( Z \)                      | 2                                          |
| Density (calculated)          | 1.476 Mg/m\(^3\)                          |
| \( F(000) \)                 | 652                                        |
Table 1. Cont.

| Crystal Data                  | HBPAH       |
|-------------------------------|-------------|
| Radiation type                | Mo Kα       |
| Wavelength (λ)                | 0.71073 Å   |
| μ (mm⁻¹)                      | 0.288       |
| Crystal shape                 | Needle      |
| Crystal Color                 | Colorless   |
| Crystal size (mm)             | 0.38 × 0.22 × 0.18 |

| Data Collection               | HBPAH       |
|-------------------------------|-------------|
| Diffractometer                | Bruker APEX II CCD diffractometer |
| Absorption correction         | multi-scan (SADABS; Bruker, 2007) |
| No. of measured, independent and observed reflections | 15,051, 5452, 2920 |
| Rint                          | 0.070       |
| Theta range for data collection | 0.648 to 26.000° |
| Index ranges                  | −8 ≤ h ≤ 7, −9 ≤ k ≤ 9, −37 ≤ l ≤ 38 |
| (sin θ/λ)max (Å⁻¹)            | 0.617       |

| Refinement                    | HBPAH       |
|-------------------------------|-------------|
| R[F² > 2σ(F²)], wR(F²), S     | 0.083, 0.195, 1.05 |
| No. of reflections            | 5452        |
| No. of parameters             | 396         |
| H-atom treatment              | H atoms treated by a mixture of independent and constrained refinement |
| ∆ρmax, ∆ρmin (e Å⁻³)          | 0.24, −0.30 |

*CCDC (Cambridge Crystallographic Data Centre).

HBPAH (Table 1, Figure 2) crystals contain two crystallographically independent molecules of (E)-2-((6-chloropyridin-2-yl)oxy)-N′-(2-hydroxybenzylidene)acetohydrazide and one water molecule. In the first molecule (C1-C14/N1-N3/O1-O3/CL1) (red in overlay plot), the 6-chloropyridin-2-ol moiety A (C1-C5/N1/CL1), acetohydrazide group B (C6/C7/N2/O2) and O-cresol moiety C (C8-C14/O3) are planar with an r.m.s deviation of 0.0058, 0.0067 and 0.0133 Å, respectively, whereas, in the second molecule (C15-C28/N4-N6/O4-O6/CL2) (blue in overlay plot), the similar moieties D (C15-C19/N4/O4/CL2), E (C20/C21/N5/O5) an F (C22-C28/O6) are planar with r.m.s deviation of 0.0065, 0.0034, and 0.0108 Å, respectively. The dihedral angles between moieties in the first molecule A/B, A/C, and B/C are 14.15 (1)°, 9.82 (1)°, and 23.13 (1)°, respectively whereas the dihedral angle between similar moieties in second molecule D/E, D/F, and E/F is 12.37 (1)°, 11.87 (1)° and 3.7 (1)°, respectively. The two crystallographic independent molecules differ in terms of geometric parameters, as shown in Figure 3. The second molecule is inverted and then made to overlap with the first molecule. This analysis shows that the root mean square deviation between the first molecule and the second molecule is 0.2376 Å.

In both molecules within the lattice, the NH of acetohydrazide group interacts with the O-atom of 6-chloropyridin-2-ol moiety through intra N-H···O bonding to form S(5) loop, and the hydroxyl group of o-cresol moiety interacts with N-atom of acetohydrazide group through intra O-H···N bonding to form S(6) loop. The first molecule connects with the second molecule through N-H···O bonding, where NH is from acetohydrazide group E, and O-atom is from the acetohydrazide group B. Water molecule is engaged in two types of classical H-bonding named as O-H···O and N-H···O. Water acts as a donor in O-H···O (carbonyl O-atom of acetohydrazide group B) and O-H···O (carbonyl O-atom of acetohydrazide group E) to connect molecule of the first type with a molecule of the second type whereas it acts as an acceptor in N-H···O bonding where NH is from acetohydrazide group E. Water molecule is also engaged in one weak non-classical C-H···O (CH is from O-cresol moiety C) bonding with C-O distance of 3.271 Å and angle of 139.06° [74,75]. R²(6) loop is formed through classical N-H···O and non-classical C-H···O bonding in which water acts as an acceptor. The carbonyl O-atom

*CCDC (Cambridge Crystallographic Data Centre).*
of acetoxydrazide group E is also engaged in weak non-classical C-H···O (CH is from o-cresol moiety F) bonding to connect molecules of the second type with each other with a C-O distance of 3.433 Å and angle of 162.40° [76].

![Figure 2. ORTEP diagram of HBPAH drawn at a probability level of 30% with H-atoms are displayed by tiny circles of arbitrary radii. Red color shows oxygens, blue nitrogen, green chlorine, white is for hydrogen, and black/white contours show carbon atoms.](image)

![Figure 3. Molecular overlay of two crystallographically independent molecules: first molecule (red) and second molecule (blue).](image)

All the above-mentioned loops and H-bonding are shown in Figure 4, Figure S3 and Table 2. Both molecules and water are connected to form an infinite 2-D network in the crystallographic plane (0 0 1) with base vector (1 0 0) and (0 1 0). Along with the intra and intermolecular H-bonding, a cyclic face-to-face stacking between different rings assists in further strengthening crystal packing.
The pyridine ring (C1-C5/N1) at the asymmetric position stacks with two symmetry mates’ phenyl rings (C23-C28) located at (x, 1 + y, z) and (1 + x, 1 + y, 1 + z) with inter-centroid separation of 3.671 Å and 3.810 Å as displayed in Figure 5 and Table 3. Similarly, the phenyl ring (C9-C14) at the asymmetric position stacks with two symmetry-related pyridine rings (C15-C19/N4) located at (1 + x, 1 + y, 1 + z) and (1 + x, 1 + y, z) with inter-centroid separation of 3.874 Å and 3.876 Å, respectively. Cg(1), Cg(2), Cg(3), and Cg(4) are the centroids of pyridine ring (C1-C5/N1), phenyl ring (C9-C14), pyridine ring (C15-C19/N4), phenyl ring (C23-C28), respectively. Dde, DAde, De (f) and Df (e), respectively, show the distance between centroids of rings, the dihedral angle between the planes of rings, perpendicular distance of Cg(e) to Cg(f), perpendicular distance of Cg(f) to Cg(e).

Figure 4. Packing diagram of HBPAH showing H-bonded connection of first, 2nd type of molecules and water with H-atoms not engaged in H-bonding are omitted for clearness. Red color shows oxygens, blue nitrogen, green chlorine, and black/white contours shows carbon atoms.

Table 2. Geometrical parameters of potential Hydrogen-bonds (Å, º) for HBPAH.

| D–H···A | D–H | H···A | D···A | D–H···A |
|---------|-----|-------|-------|--------|
| O3–H3A···N3 | 0.82 | 1.95 | 2.659 (5) | 145 |
| N2–H2A···O1 | 0.86 | 2.235 | 2.655 | 105.34 |
| N2–H2A···O7 | 0.86 | 2.08 | 2.902 (5) | 160 |
| O6–H6···N6 | 0.82 | 1.88 | 2.587 (5) | 145 |
| N5–H5···O4 | 0.86 | 2.170 | 2.571 | 108.18 |
| N5–H5···O2i | 0.86 | 2.48 | 3.029 (5) | 122 |
| O7–H7A···O5ii | 0.91 (6) | 2.03 (6) | 2.877 (5) | 155 (6) |
| O7–H7B···O2ii | 0.89 (6) | 1.95 (7) | 2.826 (6) | 168 (6) |

Symmetry codes: i x – 1, y – 1, z; ii x – 1, y, z.
Figure 4. Packing diagram of HBPAH showing H-bonded connection of first, 2nd type of molecules and water with H-atoms not engaged in H-bonding are omitted for clearness. Red color shows oxygens, blue nitrogen, green chlorine, and black/white contours shows carbon atoms.

Figure 5. Cyclic Face-to-face stacking interaction between various rings in the crystal packing. Distances shown are in Å with H-atoms omitted for clarity.

Table 2. Geometrical parameters of potential Hydrogen-bonds (Å, º) for HBPAH.

| D—H···A | D—H | H···A | D···A | D—H···A |
|---------|------|-------|-------|---------|
| O3—H3A | 0.82 | 1.95  | 2.659 (5) | 145 |
| N2—H2A | 0.86 | 2.235 | 2.655  | 105.34  |
| N2—H2A | 0.86 | 2.08  | 2.902 (5) | 160 |
| O6—H6···N6 | 0.82 | 1.88  | 2.587 (5) | 145 |
| N5—H5···O4 | 0.86 | 2.170 | 2.571  | 108.18  |
| N5—H5···O2 i | 0.86 | 2.48  | 3.029 (5) | 122 |
| O7—H7A···O5ii | 0.91 (6) | 2.03 (6) | 2.877 (5) | 155 (6) |
| O7—H7B···O2ii | 0.89 (6) | 1.95 (7) | 2.826 (6) | 168 (6) |

Symmetry codes: (i) x, 1 + y, z; (ii) 1 + x, 1 + y, z.

Table 3. Geometry-related parameters of cyclic face-to-face stacking interactions for HBPAH with distance given in Å.

| Cg(e)–Cg(f) | D_{ef} | D_{Aef} | D_{e} (f) | D_{f} (e) | Ring Off-Set |
|-------------|--------|---------|-----------|-----------|--------------|
| Cg(1)–Cg(4) iii | 3.671  | 1.2(2)  | 3.4556(19) | 3.460(2) | - |
| Cg(1)–Cg(4) iv | 3.810  | 1.2(2)  | 3.4495(19) | 3.479(2) | - |
| Cg(2)–Cg(3) iv | 3.874  | 2.7(2)  | 3.4350(19) | 3.3581(19) | - |
| Cg(2)–Cg(3) v | 3.876  | 2.7(2)  | 3.4495(19) | 3.4066(19) | - |

Symmetry codes: iii x, 1 + y, z; iv 1 + x, 1 + y, 1 + z; v 1 + x, 1 + y, z.

3.1. Comparative Structural Study

The SC-XRD-based structure of HBPAH was used for geometry optimization in bond length and bond angle calculations. For HBPAH, an atom numbering scheme was presented in Figure S4 (Supplementary Information), and the aforementioned geometrical parameter results were shown in Table S1 (Supplementary Information). DFT-calculated and SC-XRD-driven parameters agree with each other with an overall variation of 0.039 ± 0.028 Å. Similarly, bond angles in HBPAH deviate around 3.0 ± 3.3°.

3.1.1. Hirshfeld Surface Analysis

The crystal structure of HBPAH contains many N-H/O, C-H/O, O-H/O, C-O···π, C-H···π, and π···π interactions. The HS analysis calculates the percentage of significant non-covalent interactions contributions [77–82]. The HS mapped with properties like $d_{\text{norm}}$, $d_e$, $d_i$, shape index, curvedness, and the 2D fingerprint plots of HBPAH are shown in Figure 5, Figures S5 and S6 (Supplementary Information). Red and white in the HS analysis represent the strongest and intermediate interactions, whereas blue illustrates weaker intermolecular interactions. As $d_e$ and $d_i$ are external and internal distance from a surface to the nearest nuclei, respectively, $d_{\text{norm}}$ can be defined by Equation (8) [83]:

$$d_{\text{norm}} = \frac{d_i - r_{i}^{vdw}}{r_{i}^{vdw}} + \frac{d_e + r_{e}^{vdw}}{r_{e}^{vdw}}$$

In HBPAH, the $d_{\text{norm}}$ surfaces with dark red spots demonstrate hydrogen bonding interactions [84,85]. The oxygen of –C=O aceto group, the nitrogen of hydrazide -NH, the hydroxyl group of $N'$-(2-hydroxybenzildene), and other hydrazide nitrogen near the $N'$-(2-hydroxybenzildene)
participate the strong interactions as shown in Figure 6. The HS analysis of HBPAH has mapped the distances $d_{\text{norm}}$ (−0.5807 to 1.0525 a.u.), shape index (−1.000 to 1.000 a.u.), and curvedness (−4.000 to 0.4000 a.u.), as shown in Figure 6.

(a) $d_{\text{norm}}$ (HBPAH)

(b) Shape Index (HBPAH)

(c) Curvedness (HBPAH)

Figure 6. Hirshfeld surfaces of the entitled compound mapped over (a) $d_{\text{norm}}$, (b) shape index, and (c) curvedness, respectively, for HBPAH (1 a.u. of electron density = 6.748 e Å$^{-3}$).

In the curvedness diagram, the broader green areas separated by blue outlines show the stacking interactions. Figure 6 shows the shape index that explains the $\pi$-$\pi$ stacking interactions with blue humps and red hollows.

We then used two-dimensional fingerprint plots to explain the intermolecular interactions within the molecular structure [86–88]. The strongest interaction among hydrogen atoms in the compound is 33.2%, as shown in Figure 7, alongside percentage contribution for all interatomic contacts. Figure S5 shows the two-dimensional fingerprint plots. The most dominant contributions within the crystal packing are as follows: H-H (33.20%), C-H (13.00%), O-H (17.20%), Cl-H (15.60%), C-C (7.50%) and C-N (7.50%).
(2.70%). Our HS analysis shows that C-H⋅π interactions dominate the stability within the molecular structure of HBPAH.

**Figure 7.** Percentage contributions of all interatomic contacts for an entitled compound.

Our HS analysis also reports secondary interactions between molecules [78,87,89], such as carbon atom attached with −NH of hydrazide part bonded with the hydrogen atom of the O=C-H group [90]. Figure 8 shows the intermolecular hydrogen bonds (dashed green lines between the hydrazide −NH and the hydroxybenzylide O-H) and intermolecular hydrogen bond with the water molecule (solvent interaction).

**Figure 8.** Hydrogen bonds in HBPAH.
3.1.2. QT-AIM Analysis

Next, we used the Quantum Theory of Atoms in Molecules (QT-AIM) \[61,91,92\] to analyze non-covalent inter and intramolecular interactions, such as hydrogen bonding (HBs) (Table S2, Supplementary Information). The AIM analysis revealed that the crystal is stabilized through intra- and inter-molecular interactions \[93,94\], as shown by the dashed bond paths (BPs) (Figure 9). We calculated the non-covalent interactions (NCI) by calculating real-space regions where non-covalent interactions are essential and based entirely on $\rho$ and its gradient \[94\]. HBPAH displayed intermolecular interactions that stabilized the molecules within the crystal. The O-H $\rho$ values at BCPs (Bond critical points), H16-O36, H8-O36, H23-O36 and H19-O37 were $+0.0029 \text{ e}/\text{a}^3$, $+0.0127 \text{ e}/\text{a}^3$, $+0.0091 \text{ e}/\text{a}^3$ and $+0.0073 \text{ e}/\text{a}^3$, respectively. The N-H $\rho$ values at BCPs, H5-N9, and H38-N42 were $+0.0436 \text{ e}/\text{a}^3$ and $+0.0421 \text{ e}/\text{a}^3$, respectively (Table 4). Other intermolecular interactions, O2-O37 and H33-H53 were $+0.0066 \text{ e}/\text{a}^3$ and $+0.0016 \text{ e}/\text{a}^3$.

Figure 9. AIM based Schematic structure of HBPAH.
HBPAH shows two different sets of HBs, intramolecular and intermolecular, with the water molecule (solvent interaction). The intramolecular HB was displayed between oxygen next to pyridine moiety and the hydrazide hydrogen, with the O-H \( ρ \) value (O2-H8 = +0.0181 e/Å\(^3\) and O35-H41 = +0.0179 e/Å\(^3\)). The solvent-based HBs measure weaker than the intramolecular HB with O-H \( ρ \) values at BCPs, H49-O67, H56-O67, and H41-O67 were +0.0062 e/Å\(^3\), +0.0114 e/Å\(^3\), and +0.0148 e/Å\(^3\), respectively (Table 4 and Table S2).

### 3.1.3. Natural Bonding Orbital (NBO) Analysis

We next used NBO analysis to interpret charge transformation, different types of HB (inter- and intra-molecular), and hyper conjugative interactions [95–97]. For all orbitals, second-order perturbation energy \( E^{(2)} \) could be calculated from Equation (9).

\[
E^{(2)} = q_i \left( F_{ij} \right)^2 / (\epsilon_j - \epsilon_i)
\]

\( q_i \) is donor orbital occupancy, \( \epsilon_j \) and \( \epsilon_i \) are diagonal elements, and \( F_{ij} \) is off-diagonal NBO Fock matrix element. For HBPAH, all \( E^{(2)} \) values are displayed in Table S3, while the imperative \( E^{(2)} \) values are arranged in Table 5.

Among probable electronic \( π→π^* \) transitions of the highest magnitude, \( π(C46-C48)→π^*(N39-C50) \) corresponds to stabilization energy of 30.35, kcal/mol in HBPAH. The transitions such as \( δ(C13-H14)→δ^*(C11-C13) \) show the lowest stabilization energy of 0.51 kcal/mol for HBPAH, corresponding to weak interactions between the electron donor and acceptor. Other \( π→π^* \) interactions, such as \( π(C13-C15)→π^*(N6-C17), π(N39-C50)→π^*(C43-C44), π(C43-C44)→π^*(C45-C48), \) and \( π(C46-C48)→π^*(N39-C50) \), yield 29.62, 28.32, 22.45 and 30.35 kcal/mol stabilization energies, respectively (Table 5).

Moreover, the most prominent interactions in LP→π\(^*\) manifested as LP1(N40)→π\(^*\)(O36-C54), LP1(N7)→π\(^*\)(O3-C21), LP2(O35)→π\(^*\)(N39-C50), and LP2(C11)→π\(^*\)(N6-C10) showed stabilization energies of 62.83, 56.48, 35.80, and 5.79 kcal/mol, respectively (Table 5).

For HBPAH, two additional interactions, i.e., LP1(N40)→π\(^*\)(O36-C54) and LP1(N7)→π\(^*\)(O3-C21) with respective high stabilization energies of 62.83 and 56.48 kcal/mol, indicated the strong HB between lone-pair to anti-bonding orbitals in our HS and QT-AIM analyses. We conclude that these interactions directly stabilize HBPAH in its solid-state.
Table 5. Natural bonding orbital (NBO) analysis for HBPAH using the B3LYP/6-311G(d,p) level.

| Compound | Donor(i) | Type | Acceptor(j) | Type | $E_a$(2) | $E(j)E(i)_{b(a.u)}$ | $F(i,j)_{c(a.u)}$ |
|----------|----------|------|-------------|------|----------|----------------------|------------------|
| C13-H14  | $\partial$ |     | C11-C13     | $\partial$ | 0.51     | 1.09                 | 0.021            |
| C46-C48  | $\pi$    |     | N39-C50     | $\pi$  | 30.35    | 0.26                 | 0.082            |
| C13-C15  | $\pi$    |     | N6-C17      | $\pi$  | 29.62    | 0.26                 | 0.082            |
| N39-C50  | $\pi$    |     | C43-C44     | $\pi$  | 28.32    | 0.33                 | 0.088            |
| C43-C44  | $\pi$    |     | C45-C48     | $\pi$  | 22.45    | 0.30                 | 0.074            |
| C30-C32  | $\pi$    |     | C26-C28     | $\pi$  | 21.46    | 0.29                 | 0.071            |
| C13-C15  | $\pi$    |     | C10-C11     | $\pi$  | 16.09    | 0.27                 | 0.060            |
| C43-C44  | $\pi$    |     | N39-C50     | $\pi$  | 14.78    | 0.27                 | 0.058            |
| O40      | LP(1)    |     | O36-C54     | $\pi$  | 62.83    | 0.29                 | 0.121            |
| N7       | LP(1)    |     | O3-C21      | $\pi$  | 56.48    | 0.29                 | 0.117            |
| O35      | LP(2)    |     | N39-C50     | $\pi$  | 35.80    | 0.32                 | 0.103            |
| C11      | LP(2)    |     | N6-C10      | $\partial$ | 5.79  | 0.85                 | 0.063            |
| N9       | LP(1)    |     | N7-H8       | $\partial$ | 7.04  | 0.81                 | 0.069            |
| O2       | LP(1)    |     | N6-C17      | $\partial$ | 6.61  | 1.08                 | 0.076            |
| O36      | LP(1)    |     | N7-H8       | $\partial$ | 2.22  | 1.13                 | 0.045            |

* antibonding energetic orbitals; $^aE_a$(2) is the energy of hyper conjugative interaction (stabilization energy in kcal mol$^{-1}$); $^bE(j)E(i)$ is the energy difference between donor and acceptor $i$ and $j$ NBO orbitals; $^cF(i,j)$ is the Fock matrix element between $i$ and $j$ NBO orbitals.

3.1.4. Natural Population Analysis (NPA)

For HBPAH, the natural population-based analysis on NBO was determined by B3LYP/6-311G(d,p) (Figure S7). The phenomenon correlates to charge transformation, and the electronegativity equalization process occurs in reaction to access the electrostatic ability on the external surfaces of the structure [66,98,99]. The charges of atoms play a crucial role within the molecular conformation and bonding capability in HBPAH. The electronegative atoms such as Cl, O, and N made unequal redistribution of the electron density over the pyridine or aromatic rings. Atomic charge of oxygen atoms was O2 ($-0.38655e$) and O36 ($-0.39665e$), and for hydrogen atoms, charges were H8($0.28089e$) and H38($0.281296e$), respectively, due to the involvement of these atoms in the intermolecular hydrogen bonding interactions.

Furthermore, the NPA of HBPAH showed that carbon atoms, namely C10, C17, C18, C22, C25, C43, C50, C51, C54, C55, and C58, were positively charged, while C11, C13, C15, C24, C25, C28, C30, C44, C46, C48, C57, C59, C61, C63, and C65 were negatively charged (Figure S7). Moreover, all oxygen, nitrogen, and chlorine atoms were negatively charged. All hydrogens are positively charged in HBPAH.

3.1.5. Frontier Molecular Orbital (FMO) Analysis

The FMOs evaluate chemical bond strength and molecule stability [100]. In HBPAH, the energy of HOMO, LUMO, and its two upper and lower orbitals (HOMO-1, HOMO-2, LUMO+1, LUMO+2) were calculated by the TD-DFT/B3LYP/6-311G (d, p) and displayed in Figure 10. The energy difference between HOMO-LUMO is assumed to be a significant key factor to illustrate the chemical reactivity, optical properties, kinetic stability, and electronic character of the compounds [101,102]. Table 6 shows the energy data with their energy gap ($\Delta E$) for six MO (molecular orbitals).
was chemically hard with the affective electron-donating ability and highest electron gain capacity were defined by the ionization potential and the electron affinity values, which correlate to the HOMO-LUMO energy difference. Consequently, the $\Delta E$ value shows a lower magnitude than the $E_{\text{HOMO}}$ value, indicating that HBPAH contained excellent electron-donating capability. This supports the findings of global electrophilicity ($\omega$) (Table S4). In HBPAH, the calculated global softness ($\epsilon$) values obtained were lower than the global hardness ($\eta$) values, making HBPAH stable and relatively unreactive. Additionally, the chemical potential ($\mu$) value (−3.783 (eV)) revealed that HBPAH was chemically hard with the affective electron-donating ability and highest kinetic stability (Table S4).

3.1.6. Molecular Electrostatic Potential (MEP)

The MEP significance shows the size and configuration of the molecule, along with neutral (white), negative (red), and positive (blue) electrostatic potential regions comparable to shading assessing scheme. MEP explores the connection between molecular structural insights and physiochemical properties [103]. We Analyzed HBPAH’s MEP surface through the B3LYP/6-311G(d,p) level of theory, as shown in Figure 11. The negative red indicates the electrophilic sites at the oxygen atoms. Therefore, Figure 10 shows that HBPAH contained an energy gap of 3.634 eV, which exposed the effective intra-molecular charge transfer (ICT) within the compound. For HBPAH, the HOMO was populated on the first part of molecule (Z)-N′-(2-hydroxybenzylidene) acetohydrazide moiety and a small effect exists on the hydroxyl group. LUMO was populated on the second part of the molecule, i.e., (Z)-N′-(2-hydroxybenzylidene) propionohydrazide moiety (Figure 10). HOMO and LUMO energy gap values for two antifungal 1,2,4-triazolo[4,3-a]pyridine derivatives were found to be 4.318 and 3.705 eV, where high energy gap was associated with the more potent antifungal compound [16].

HBPAH contained an $IP$ value of 5.6 eV and an $EA$ value of 1.966 eV. Its electron loss and the electron gain capacity were defined by the ionization potential and the electron affinity values, which correlate to the HOMO-LUMO energy difference. Consequently, the $IP$ value shows a lower magnitude than the $EA$ value, indicating that HBPAH contained excellent electron-donating capability. This supports the findings of global electrophilicity ($\omega$) (Table S4). In HBPAH, the calculated global softness ($\epsilon$) values obtained were lower than the global hardness ($\eta$) values, making HBPAH stable and relatively unreactive. Additionally, the chemical potential ($\mu$) value (−3.783 (eV)) revealed that HBPAH was chemically hard with the affective electron-donating ability and highest kinetic stability (Table S4).

Table 6. The $E_{\text{HOMO}}$, $E_{\text{LUMO}}$, $E_{\text{HOMO}-1}$, $E_{\text{LUMO}+1}$, $E_{\text{HOMO}-2}$, $E_{\text{LUMO}+2}$, and energy gap ($\Delta E$) in eV of the entitled compound at the DFT/B3LYP/6-311G(d,p) level of theory.

| MO(s)  | Energy | $\Delta E$(eV) |
|-------|--------|----------------|
| HOMO  | −5.600 | 3.634          |
| LUMO  | −1.966 |                |
| HOMO-1| −6.266 | 4.65           |
| LUMO+1| −1.616 |                |
| HOMO-2| −6.274 |                |
| LUMO+2| −1.240 | 5.034          |

HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital, MO = molecular orbital.

Figure 10 shows that HBPAH contained an energy gap of 3.634 eV, which exposed the effective intra-molecular charge transfer (ICT) within the compound. For HBPAH, the HOMO was populated on the first part of molecule (Z)-N′-(2-hydroxybenzylidene) acetohydrazide moiety and a small effect exists on the hydroxyl group. LUMO was populated on the second part of the molecule, i.e., (Z)-N′-(2-hydroxybenzylidene) propionohydrazide moiety (Figure 10). HOMO and LUMO energy gap values for two antifungal 1,2,4-triazolo[4,3-a]pyridine derivatives were found to be 4.318 and 3.705 eV, where high energy gap was associated with the more potent antifungal compound [16].

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3.1.6. Molecular Electrostatic Potential (MEP)

The MEP significance shows the size and configuration of the molecule, along with neutral (white), negative (red), and positive (blue) electrostatic potential regions comparable to shading assessing scheme. MEP explores the connection between molecular structural insights and physiochemical properties [103]. We Analyzed HBPAH’s MEP surface through the B3LYP/6-311G(d,p) level of theory, as shown in Figure 11. The negative red indicates the electrophilic sites at the oxygen atoms. Therefore,
the oxygen atoms are the most effective target for nucleophilic attack, along with the most suitable sphere to attack the molecules’ positive zones. The negative potential magnitude of HBPAH is $-1.00 \times 10^{-2}$ to $1.00 \times 10^{-2}$ a.u. Green areas represent the region of zero potential. The blue areas of the HBPAH molecule situate over the hydrogen atoms. They show a combination of positive charges, demonstrating the nucleophilic localities.

![Molecular electrostatic potential and color scheme of HBPAH.](image)

**Figure 11.** Molecular electrostatic potential and color scheme of HBPAH.

4. Conclusions

In conclusion, we used a room-temperature sonochemical approach to synthesize crystalline $(E)$-2-((6-chloropyridin-2-yl)oxy)-N’-(2-hydroxybenzylidene)acetohydrazide. The SC-XRD study revealed the presence of attractive intermolecular forces for the structural stabilization in this Triclinic crystal system with $P\bar{T}$ space group. The QT-AIM and Hirshfeld analysis revealed the presence of non-covalent interactions (NCIs); Scheme H5-N9, H38-N42, H16-O36, H8-O36, H19-O37, and H33-H53 that stabilize the structure of the compound. The NBO study showed that HBPAH has molecular stability of hyper-conjugation due to the intramolecular charge transfer (62.83, kcal/mol for LP1(N40) $\rightarrow \pi^*$(O36-C54)). The HOMO/LUMO energy band gap value describes the possible charge-transfer interactions, which occur inside the molecule. The calculated FMO energy bandgap of HBPAH is 3.634 eV, which illustrates it has intra-molecular charge-transferability and good NLO properties. The global reactivity descriptors calculation illustrates less reactivity and good stability. The MEP map displayed the negative red areas indicating the electrophilic sites at the oxygen atoms. All computational and experimental findings determined that HBPAH exists in stabilized crystal form because of non-covalent interactions (NCIs) and intra- and inter-molecular H-bonding interactions.

**Supplementary Materials:** The following are available online at http://www.mdpi.com/2073-4352/10/9/778/s1, Figure S1: 1H and 13C NMR spectra of HBPAH, Figure S2: The 1H-NMR of the title compound in (CD3)2SO-d6 showing the integration of methylenic (CH2) 1Hs, which has been used as a tool to calculate the ratio of two isomers (A and B), Figure S3: The geometrical parameters (bond lengths (Å) and bond angles (°) of entitled compound calculated through XRD and at DFT/B3LYP/6-311G (d,p) level of theory, Figure S4: ORTEP diagram of HBPAH compound, Figure S5: Hirshfeld surfaces of the entitled compound mapped over, de and di for HBPAH (1 a.u. of electron density = 6.748 eÅ$^{-3}$), Figure S6: 2-D Fingerprint plots for individual contributions in HBPAH, Figure S7: Natural population analysis (NPA) of entitled compound, Table S1: Comparison of XRD and DFT values of bond length, bond angle, ellipticity, and density of potential energy (V), Table S2: AIM properties of HBPAH; Electronic density ($\rho$), Laplacian of density ($\nabla^2 \rho$), ellipticity ($\epsilon$) and density of potential energy (V), Table S3: NBO analysis of HBPAH at DFT/B3LYP/6-311G (d,p) level of theory, Table S4: Ionization potential (IP), electron affinity (EA), electronegativity (X), global hardness ($\eta$), chemical potential ($\mu$), global electrophilicity index ($\omega$) and global softness ($\sigma$).
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