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Synthesis, Antibacterial Evaluation, Crystal Structure, Molecular Interaction Analysis and DFT Calculations of Novel N-hydroxy-2-(4-methylbenzamido)benzamide

Elmutasim O.Ibnouf,^{1,7} Abdellah Kaiba,² Mohammed H. Geesi,³ Abdullah M. Alghamdi,⁴ Ziyad S. Aldajani,⁴ Oussama Dehbi,⁵ Philippe Guionneau,⁶ Rachid Azzallou,⁸ Yassine Riadi,^{4*}

¹Department of Pharmaceutics, College of Pharmacy, Prince Sattam bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia.

²Department of physic, College of science and humanities in Al-Kharj, Prince Sattam bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia.

³Department of Chemistry, College of science and humanities in Al-Kharj, Prince Sattam bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia.

⁴Department of Pharmaceutical Chemistry, College of Pharmacy, Prince Sattam bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia.

⁵Department of Chemistry, College of Science and Arts of Al Qurayyat, Jouf University, Saudi Arabia.

⁶CNRS, Univ. Bordeaux, Bordeaux INP, ICMCB, UMR 5026, 87 av. Dr A. Schweitzer, F-33600 Pessac (France).

⁷Department of Medical Microbiology, Faculty of Medical Laboratory Sciences, Omdurman Islamic University, Sudan.

⁸Laboratoire de Biochimie, Environnement & Agroalimentaire, URAC 36, Faculté des Sciences et techniques de Mohammedia Université Hassan II-Casablanca, Mohammedia, Maroc.

* Corresponding author. Tel.: +966 5 374 931 75; e-mail: y.riadi@psau.edu.sa/yassinriadi@yahoo.fr

Abstract

In this study, an efficient strategy for the synthesis of a new benzamide derivative N-hydroxy-2-(4-methylbenzamido)benzamide was reported by using readily available reagents, and its antibacterial activity against bacterial strains was investigated. This new compound crystallized in a monoclinic system with the P21/n space group. Its unit-cell parameters were $a = 7.5103(2) \text{ \AA}$, $b = 11.7991(3) \text{ \AA}$, $c = 15.2645(4) \text{ \AA}$, $\beta = 91.907(2)^\circ$ and $Z = 4$. Crystal packing was stabilized by hydrogen bonds and π -stacking interactions and van der Waals interactions. Hirshfeld surfaces and their associated two-dimensional fingerprint plots were utilized to analyze the intermolecular interactions in the crystal structure. In addition, electrostatic surface potential (ESP) was generated by the density functional theory.

Keywords: Benzamide, Antibacterial activity, Crystal structure, Hirshfeld surface analysis.

1. Introduction

Benzamide scaffolds are useful molecules in organic synthesis, and these scaffolds are sub-structures in various pharmaceutical compounds [1, 2]. Benzamides have been synthesized by the hydrolysis of aromatic nitriles, interconversion of carboxylic acid derivatives, aminocarbonylation, oxime rearrangement and other routes. In addition, aromatic amides

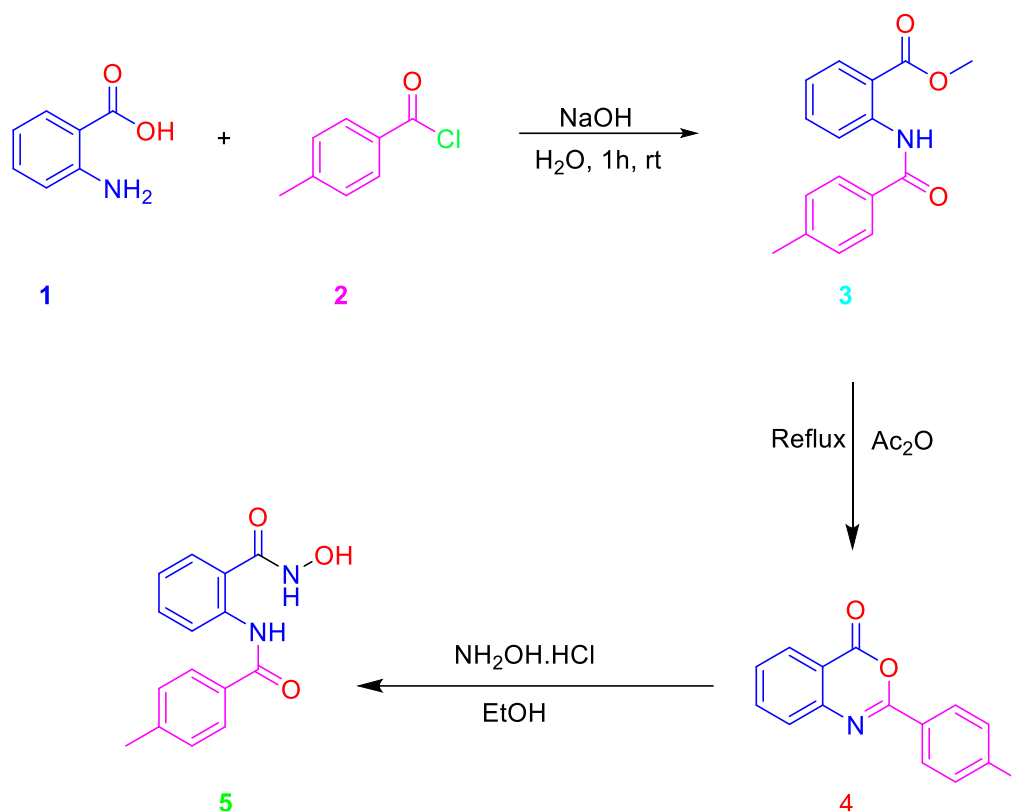
have been prepared by Friedel–Crafts-type reactions of isocyanates, in particular secondary amides [3, 4]. Previously, primary benzamides have been synthesized using trimethylsilylisocyanate and chlorosulfonylisocyanate—two reagents that are not easily accessible and exhibit high toxicity.

Derivatives of this scaffold have demonstrated potential antimicrobial activity [5]. In fact, they are utilized as anthelmintics [6], antitumour [7] antiproliferative [8], analgesic and anti-pyretic agents [9], as well as antiviral [10], anti-tuberculosis [11], anti-cytotoxin [12], anti-oxidant [13], anti-hypertension [14] and anti-diabetes agents [15]. Medicinal chemists synthesized different benzamide moieties have exhibited versatile biological activities, such as efficient antibacterial [16], anti-allergic [17] and anti-inflammatory drugs [18]. In addition, several examples of drugs have been reported, such as metoclopramide and tiapride [19].

Therefore, as continuation of our research into the development of a new process to prepare new heterocyclic and pharmaceutical compounds [20-31], in this study, the synthesis of a new benzamide derivative N-hydroxy-2-(4-methylbenzamido)benzamide (**5**) with excellent yield and the investigation of its antibacterial activity were reported (Scheme 1). A crystallographic study of derivative **5** was conducted, in addition to the description of its molecular interactions, electrostatic surface potential (ESP) and fingerprint plots.

2. Synthesis

The benzamide derivative was synthesized according to a previous study (Scheme 1). First, a mixture of anthranilic acid (1 mmol) and substituted 4-methylbenzoyl chloride (1.1 mmol) was stirred at room temperature in the presence of 10% sodium hydroxide (10 mL) for 1 h to obtain intermediate **3** (Mp = 113-115 [32]). Second, intermediate **3** was heated under reflux in acetic anhydride (10 mL) for 2 h. After cooling by pouring the reaction mixture onto crushed ice, the resultant solid was filtered to obtain compound **4** (Mp = 154-155 [33]). Then, the obtained intermediate **4** was refluxed in the presence of an equimolar quantity of hydroxylamine hydrochloride in ethanol (10 mL) overnight, followed by the cooling of the reaction and subsequent filtration and recrystallization of the resultant solid from ethanol to obtain the final product as a yellow crystal (87% yield).



Scheme 1. Strategy for the preparation of N-hydroxy-2-(4-methylbenzamido)benzamide (**5**)

3. Antibacterial activity

The antibacterial activity of prepared derivative **5** was assessed against two Gram-positive bacteria (i.e. *Bacillus subtilis* and *Methicillin-resistant Staphylococcus aureus* [MRSA], respectively) and two gram-negative bacteria (i.e. *Escherichia coli* and *Pseudomonas aeruginosa*, , respectively) using a standard method reported in reference [32] and also described in detail in a previous article reported by our group [31]

Table 1 lists the results obtained for the biological activity of compound **5**. Benzamide derivative **5** was active against all bacterial strains.

Table 1: Activity of derivative **5** against bacterial strains.

	Bacterial Strains				
	MRSA	Bs	Pa	Ec	
Compound 5	MIC ($\mu\text{g/mL}$)	25	38.5	25	12.5
	MBC ($\mu\text{g/mL}$)	18.75	25	18.75	9.37
	Inhibition zone in mm (100 $\mu\text{g/mL}$)	21	14	19	24
Ciprofloxacin	MIC ($\mu\text{g/mL}$)	18.75	12.5	12.5	12.5

^aMIC: Minimum inhibitory concentration in $\mu\text{g/mL}$. MBC: Minimum bactericidal concentration ^b: No inhibition zone, no activity.

4. Crystal structure

4-1 Single-crystal data collection and structure determination

Single-crystal data for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_3$ were collected on a Bruker Apex II diffractometer, which was equipped with a molybdenum anticathode and graphite monochromator. Table 2 lists details of experimental data and structure refinement parameters. A structural hypothesis was provided by the SIR97 program [35]. The structure solution was solved by direct methods using the SHELX97 program, and refinement was performed on F^2 by the full-matrix least squares techniques using SHELXL [36]. The non-hydrogen atoms were refined anisotropically, but the hydrogen atoms were located theoretically. For visualization, the MERCURY program for Windows was used [37]. All of the crystallography programs were used within the WINGX package [38]. CCDC2048823 contains crystallographic data for the titled molecule. These data can be obtained free of charge by the following link: www.ccdc.cam.ac.uk/data_request/cif.

Table 2: Crystallographic and structure refinement data

Empirical formula	C ₁₅ H ₁₃ N ₂ O ₃	
Formula weight	269.27	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 7.5103(2) Å b = 11.7991(3) Å c = 15.2645(4) Å	α = 90°. β = 91.907(2)° γ = 90°.
Volume	1351.91(6) Å ³	
Z	4	
Density (calculated)	1.323 Mg/m ³	
Absorption coefficient	0.094 mm ⁻¹	
F(000)	564	
Theta range for data collection	2.182 to 27.486°.	
Index ranges	-9 ≤ h ≤ 9, -14 ≤ k ≤ 15, -	
Reflections collected	17 ≤ l ≤ 19	
Independent reflections	9661	
Completeness to theta = 25.242°	3097 [R(int) = 0.0326]	
Refinement method	100.0 %	
Data / restraints / parameters	Full-matrix least-squares on F ²	
Goodness-of-fit on F ²	3097 / 0 / 186	
Final R indices [I > 2σ(I)]	1.011	
R indices (all data)	R1 = 0.0967, wR2 = 0.2247	
Extinction coefficient	R1 = 0.1565, wR2 = 0.2894	
Largest diff. peak and hole	0.18(2) 0.859 and -0.868 e. Å ⁻³	

4-2 Crystal structure

The crystallographic analysis of the title compound revealed that the asymmetric unit contains one molecule of C₁₅H₁₃N₂O₃. It crystallizes at room temperature in the monoclinic symmetry with the P21/n space group, and dimensions for the unit-cell parameters: *a* = 7.5103(2) Å, *b* = 11.7991(3) Å, *c* = 15.2645(4) Å, β = 91.907(2) and *Z* = 4 parameters. Figure 1 shows the molecular structure of the title compound.

Table 3 lists the atomic positions (*x*, *y*, *z*) (×10⁴) and equivalent isotropic displacement parameters *U*_{eq} (Å²×10³).

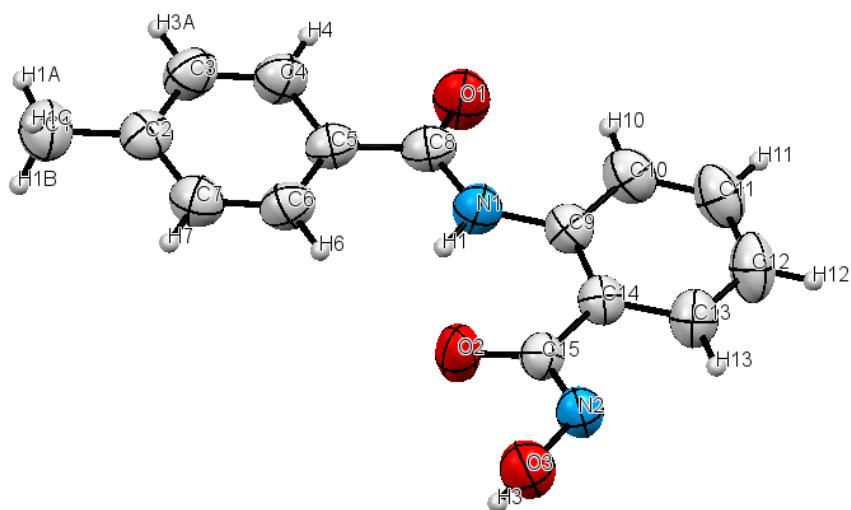


Figure 1: View along b axis of asymmetric unit cell of $C_{15}H_{13}N_2O_3$.

Table 3: Atomic positions ($\times 10^4$) and equivalent isotropic displacement parameter $U(\text{eq}) \text{ \AA}^2 \times 10^3$ for $C_{15}H_{13}N_2O_3$

	x	y	z	U(eq)
O(1)	8768(3)	1405(2)	8106(1)	83(1)
O(2)	10557(3)	3783(2)	5692(1)	76(1)
O(3)	12880(3)	4881(2)	4677(1)	79(1)
N(1)	9988(3)	2405(2)	7012(2)	59(1)
N(2)	13318(3)	4448(2)	5529(1)	57(1)
C(15)	12109(3)	3917(2)	6006(2)	49(1)
C(14)	12678(3)	3509(2)	6892(2)	51(1)
C(9)	11621(4)	2771(2)	7378(2)	52(1)
C(8)	8687(4)	1760(2)	7353(2)	57(1)
C(13)	14324(4)	3865(3)	7265(2)	62(1)
C(4)	5850(4)	772(3)	7044(2)	64(1)
C(5)	7128(4)	1523(2)	6756(2)	54(1)
C(11)	13886(4)	2752(3)	8536(2)	74(1)
C(7)	5326(4)	1773(3)	5439(2)	64(1)
C(12)	14927(4)	3496(3)	8072(2)	76(1)
C(6)	6840(4)	2004(2)	5934(2)	61(1)
C(2)	4044(4)	1040(2)	5729(2)	59(1)
C(1)	2352(5)	806(3)	5197(2)	79(1)
C(10)	12266(4)	2386(3)	8200(2)	66(1)
C(3)	4349(4)	545(3)	6544(2)	70(1)

Cohesion is ensured by intermolecular hydrogen bonds and π -stacking interactions. In addition, an intermolecular hydrogen-bond interaction exists between hydroxamic acid and C=O (C=O \cdots OHNC=O), with a distance of ~ 2.634 Å. The hydrogen-bond distances of O \cdots O, O \cdots H and O \cdots N are 2.933 Å, 2.296 Å and 2.991 Å, respectively. The H \cdots O=C π -stacking distance is ~ 2.575 Å (Figure 2). The C–C bond length is between 1.370 and 1.510 Å. The C–N bond length is between 1.338 Å and 1.399 Å. The bond lengths of the ketone C=O and hydroxamic acid group C=O are ~ 1.224 Å and 1.255 Å, respectively. The angle between the plane of hydroxamic acid and that of the molecule is $\sim 12.04^\circ$ (Figure 3).

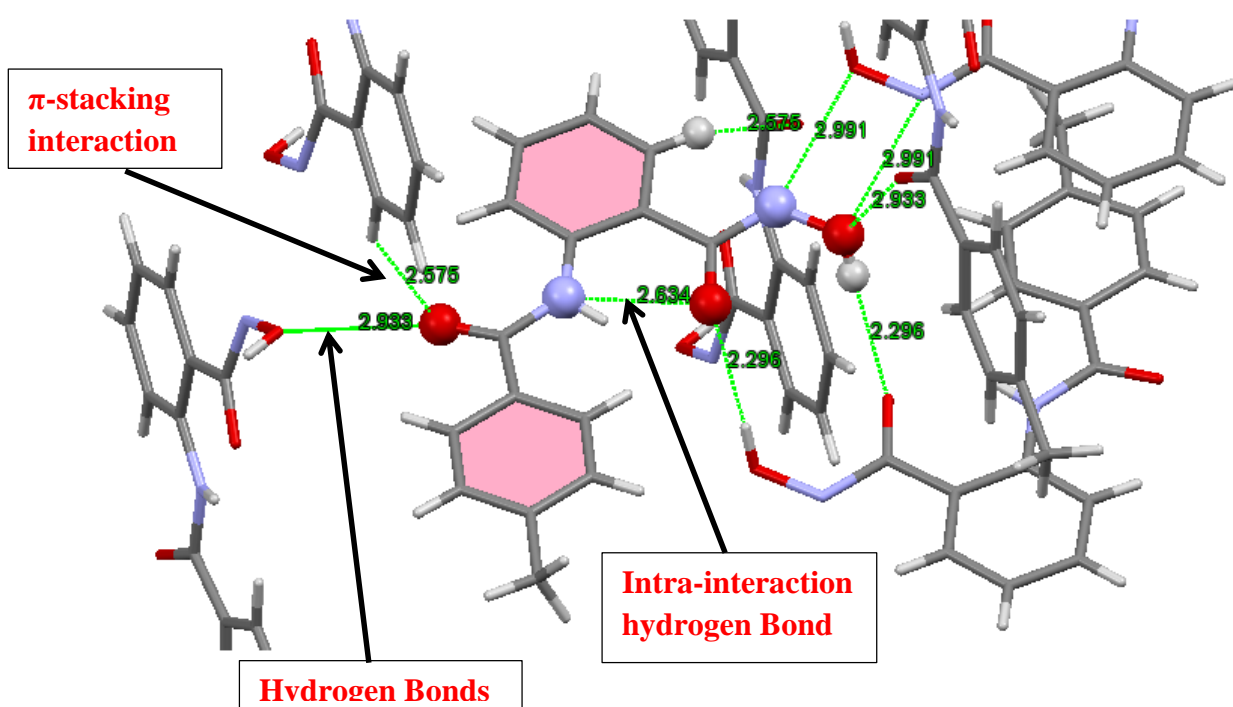


Figure 2: View showing the connection between the molecules by hydrogen bonds and π -stacking interactions (dashed lines).

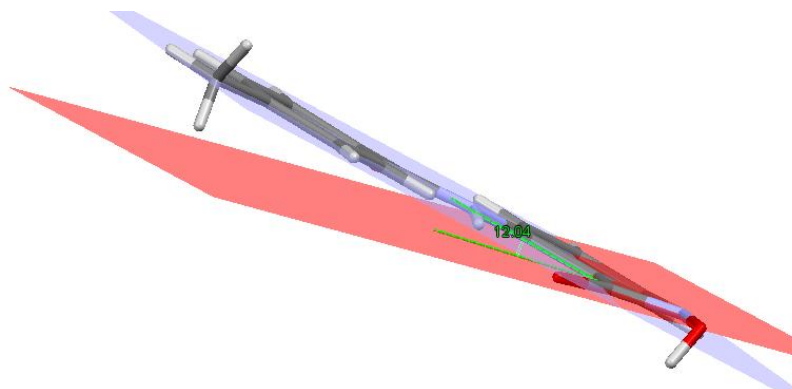


Figure 3: View showing the angle between the plane of the molecule and the plane of hydroxamic acid group.

The crystal structure comprised hydrogen bonds and π -stacking interactions between neighboring molecules. Crystal packing involved intermolecular interactions between molecules (Figure 4). Indeed, each molecule is connected to five other neighboring molecules through oxygen, nitrogen and hydrogen atoms, as well as benzene via hydrogen bonds and π -stacking interactions.

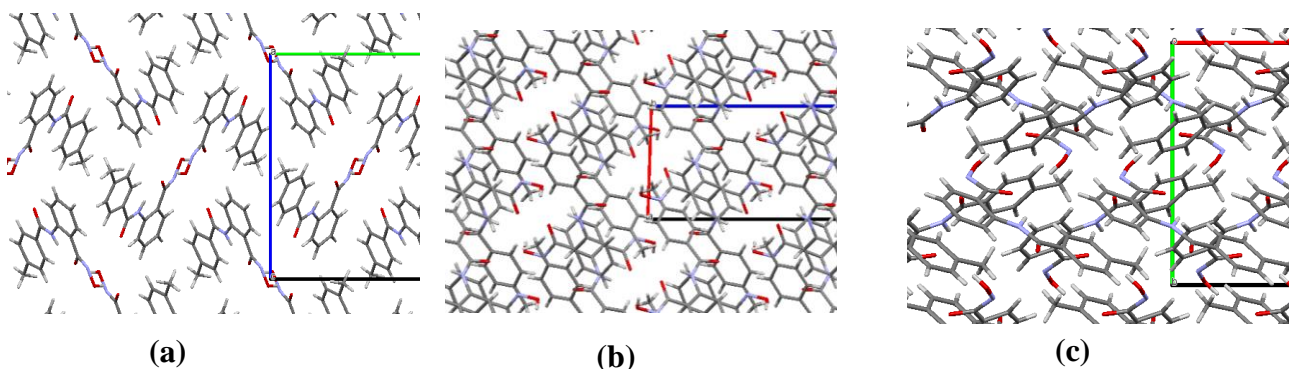


Figure 4: Packing of molecules in the crystal. a- Projection along a axis, b- Projection along b axis, c- Projection along c axis.

5. Computational details

The analysis of intermolecular interactions using the Hirshfeld surface permitted the knowledge regarding the behavior of intermolecular interactions in the crystal. The Hirshfeld surface of the title compound was generated using Crystal Explorer [39]. The intermolecular contacts analyzed around the asymmetric unit in Figure 5 revealed the different intermolecular interactions around the molecule computed by the Hirshfeld surface d_{norm} mapping. Figure 5a shows the contributor contacts on the Hirshfeld surface. Red spots represent the shorter hydrogen-bond $\text{O}\cdots\text{H}$ interactions, whereas the blue and white areas represent the $\text{H}\cdots\text{H}$, $\text{C}\cdots\text{H}$, $\text{O}\cdots\text{O}$, $\text{O}\cdots\text{N}$ and $\text{N}\cdots\text{H}$ contacts. Clearly, the red regions rich in hydrogen bonds on the d_{norm} surface are in agreement with the results obtained by X-ray diffraction.

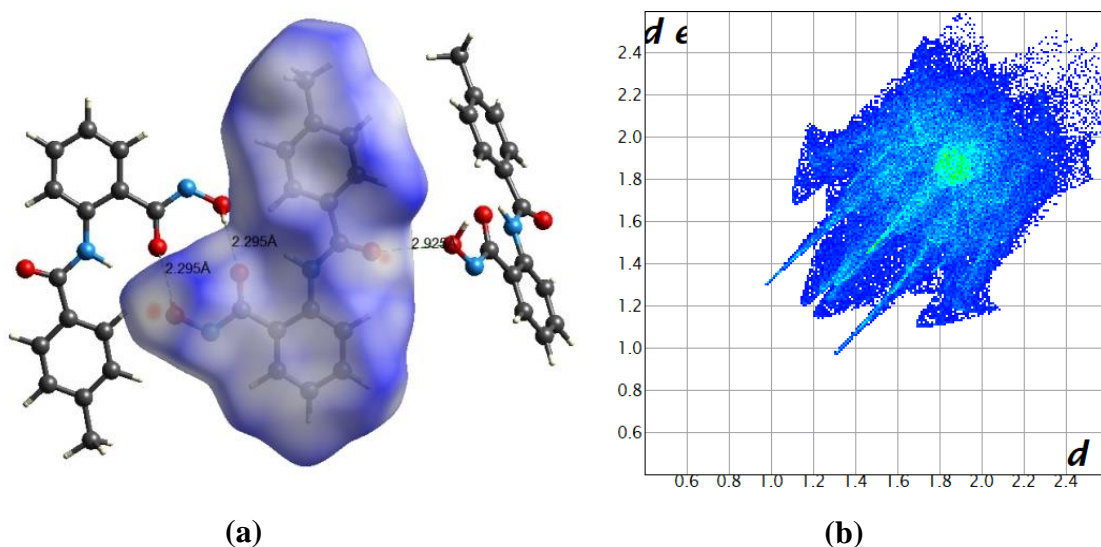


Figure 5: d_{norm} mapped on the Hirshfeld surface for visualizing intermolecular interactions of $C_{15}H_{13}N_2O_3$.

Figure 6 shows the 2D fingerprint plots of the intermolecular contacts of $C_{15}H_{13}N_2O_3$, and Table 4 lists the ratio of their contributions. Overall, $H\cdots H$ contacts are the most favorable (38.3%) in crystal packing, while $C\cdots H/H\cdots C$ contacts represent 25.1% of the total Hirshfeld surface (aromatic ring), corresponding to the second-most frequent interactions due to the abundance of hydrogen atoms on the molecular surface. The $O\cdots H/H\cdots O$ contacts (18.1%) and $N\cdots H/H\cdots N$ and $O\cdots O$ contacts represent 6.7% and 2.8% of the total Hirshfeld surface, respectively.

Quantitative analysis revealed that the $H\cdots H$ intermolecular contacts are the most abundant contacts, which constitute the driving force in this crystal packing. The Hirshfeld surfaces permits the quantitative and qualitative analysis by displaying all of the intermolecular interactions; hence, this method demonstrates immense promise in crystal engineering.

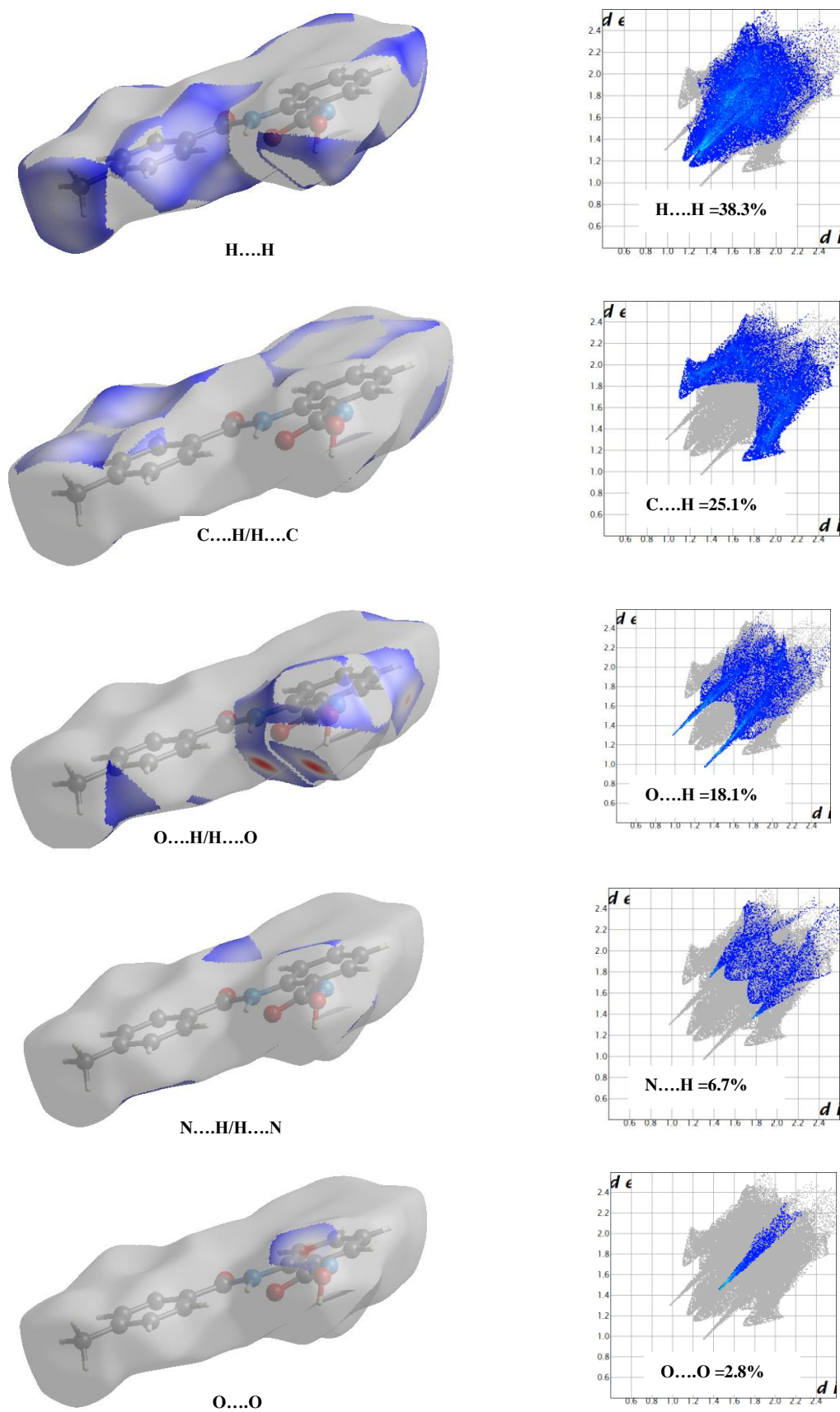


Figure 6: The two-dimensional fingerprint plot (97.7%) of $C_{15}H_{13}N_2O_3$, showing contributions from different contacts

Table 4: Summary of the major closest contacts and their percentage contributions to the Hirshfeld surface.

Type of contact	Contribution (%)
H···H	38.6
C···H/ H···C	25.1
O···H/ H···O	18.1
N···H/ H···N	6.7
O···O	2.8

DFT calculations were performed using the Gaussian 16w package [40]. The electrostatic surface potentials (ESP) of $C_{15}H_{13}N_2O_3$ are calculated to locate the positively and negatively charged electrostatic potential in the molecule (Figure 7). In ESP, the red color with negative indicates the minimum electrostatic potential and act as an electrophilic attack. Blue indicates the maximum of electrostatic potential, and it acts opposite. The pair of oxygen atoms of the ketone moiety and hydroxamic acid is a hydrogen-bond acceptor. This result is in agreement with the Hirshfeld surface analysis, indicating that the formation of a strong intermolecular hydrogen bond between the pair of oxygen atom of the ketone moiety with the hydrogen atom of C···H of the aromatic ring and hydroxamic acid, also the strong intermolecular hydrogen bond via the hydroxamic acid group (Figure 5).

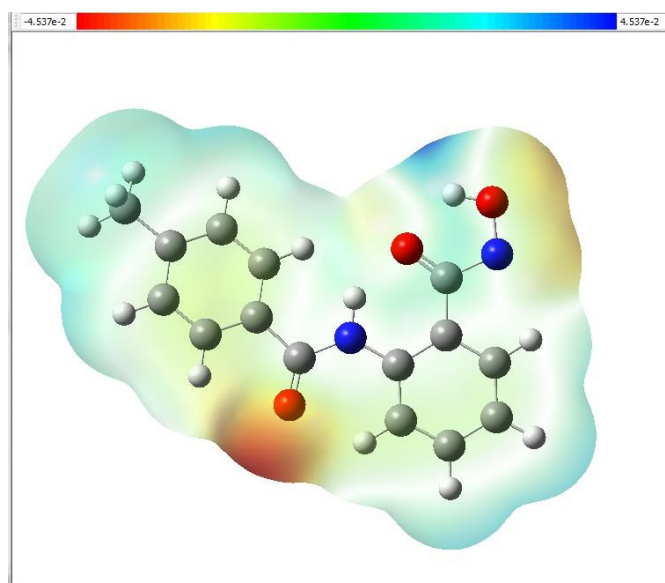


Figure 7: Electrostatic surface potential of $C_{15}H_{13}N_2O_3$ obtained at the B3LYP/6-311++G(d,p) level of theory.

Conclusion

In this study, the synthesis of novel n-hydroxy-2-(4-methylbenzamido)benzamide (**5**) was reported. The antibacterial efficiency of **5** was examined against four bacterial strains. The compound crystallized in a monoclinic system with the P21/n space group. It exhibited hydrogen-bond interaction and π -stacking interactions and van der Waals interactions that assure the connection between molecules and stabilize the crystal. Moreover, the contribution of these interactions was analyzed by visualizing the Hirshfeld surface. In addition, the electrostatic surface potential was obtained using the DFT method to locate the positively and negatively charged electrostatic potentials in the molecule.

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