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Synthesis, Structure, Hirshfeld Surface Analysis, Non-Covalent Interaction, and In Silico Studies of 4-Hydroxy-1-[(4-Nitrophenyl) Sulfonyl]Pyrrolidine-2-Carboxyllic Acid

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Abstract

The new compound 4-hydroxy-1-[(4-nitrophenyl)sulfonyl]pyrrolidine-2-carboxyllic acid was obtained by the reaction of 4-hydroxyproline with 4-nitrobenzenesulfonyl chloride. The compound was characterized using single crystal X-ray diffraction studies. Spectroscopic methods including NMR, FTIR, ES-MS, and UV were employed for further structural analysis of the synthesized compound. The title compound was found to have crystallized in an orthorhombic crystal system with space group P2₁2₁2₁. The S1-N1 bond length of 1.628 (2) Å was a strong indication of the formation of the title compound. The absence of characteristic downfield ¹H NMR peak of pyrrolidine ring and the presence of S–N stretching vibration at 857.82 cm⁻¹ on the FTIR are strong indications for the formation of the sulfonamide. The experimental study was complemented with computations at the B3LYP/6-311G + + (d,p) level of theory to gain more understanding of interactions in the compound at the molecular level. Noncovalent interaction, Hirsfeld surface analysis and interaction energy calculations were employed in the analysis of the supramolecular architecture of the compound. Predicted ADMET parameters, awarded suitable bioavailability credentials, while the molecular docking study indicated that the compound enchants promising inhibition prospects against dihydropteroate synthase, DNA topoisomerase, and SARS-CoV-2 spike.

Graphical Abstract

Herein we present the solid state structure, noncovalent interaction and spectroscopic analysis of a prospective bioactive compound 4-hydroxy-1-[(4-nitrophenyl)sulphonyl]pyrrolidine-2-carboxyllic acid.



Keywords Synthesis \cdot Supramolecular structure \cdot Non-covalent interaction \cdot Hirshfeld surface \cdot Interaction energy \cdot In silico

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The relevance of sulfonamides or sulfa drugs in medicine can never be overemphasized [1] They have played significant roles in the medical revolution as they are very effective over a wide range of bacterial infections and thus were the first real success in the fight against bacteria [2, 3]. In asymmetric synthesis, the aryl sulfonyl group of aryl sulfonamides has been applied to protect nitrogen and oxygen functional groups as well as amino acids during conditions that involve the reaction of the carbonyl group with organometallic reagents [4, 5]. In addition, the presence of sulfonamide moiety in azo dyes has improved light stability, fixation to fiber, and water solubility [6, 7]. A lot of research on the activities of sulfonamides has uncovered their pharmacological applications not only as antibacterial [8, 9] but also as potent anticancer [10, 11], anti-influenza [12], anti-inflammatory[13], antitrypanosomal [14], antimalarial [15], anti-HIV [16], and antitumor [17] agents. The versatility of sulfonamides has led to the search for more active derivatives while applying different synthetic methodologies. Conventionally, sulfonamides are prepared by reacting either a primary or secondary amine with sulfonyl chloride in the presence of a base that assists to scavenge the HCl produced in the reaction [18]. Other methods also exist, some of which involve the use of transition metals as catalysts [19], N-chlorosulfonyl carbamate as a sulfonating agent at 0 °C [20–22], conversion of methyl sulfinates into sulfinamides, and subsequent oxidation to sulfonamides [23]. Milder synthetic conditions including the use of water as solvents for sulfonation of amines have been explored [24]. Recent reports on the beneficial properties of ionic liquids have also led to their use as an alternative solvent for sulfonamide synthesis [25-27]. These methods do however suffer some setbacks ranging from low reactivity, use of more catalysts to increase yield, metal contamination, and difficulty in catalyst recovery to complex purification steps. The use of amine as a nitrogen source and sulfonyl chloride to create the N-S bond is still preferred [28] due to its simplicity, good reactivity even at room temperature, and simple filtration process to obtain pure compounds [29]. Recently our group has been working on the synthesis and characterization of a number of sulfonyl and



sulfonamide derivatives for various applications [30–36]. In continuation of this project, we report herein the synthesis and structural characterization of a novel sulfonamide derivative 4-hydroxy-1-[(4-nitrophenyl)sulfonyl]pyrrolidine-2-carboxyllic acid (HNPCA) from the coupling of 4-nitrobenzene sulfony chloride with the amino acid 4-hydroxyproline at room temperature using sodium carbonate in the presence of water, *in-silico* studies were used to understand the drug-likeness of the title compound.

Experimental

Materials

Na₂CO₃, NaCl, and 20% HCl were obtained from Fluka, while 4-nitrobenzene sulfonyl chloride and 4-hydroxyproline were obtained from Sigma Aldrich (Bristol Scientific Nigeria). IR spectra were recorded on Bruker FT-IR spectrophotometer. The NMR peaks were recorded on Bruker DPX 300 spectrophotometer with ¹H at 400 MHz and 13 °C at 100 MHz. Chemical shifts δ are given in ppm and referenced to tetramethylsilane. Methanol was used as a solvent for crystallization. X-ray data of the single crystal were collected on an XtaLAB Synergy, Dualflex, Pilatus 200 K diffractometer using CuK α radiation at 105.4 (7)K. The pharmacokinetic properties were studied using SwissADME free online tool (https://www.swissadme.ch), while the Molecular docking was carried out using the Molecular operating environment (MOE) (AutoDock Vina, BIOVIA).

Synthesis of 4-Hydroxy-1-[(4-Nitrophenyl)Sulfonyl] Pyrrolidine-2-Carboxyllic Acid

Sodium carbonate (Na₂CO₃, 5 mmol) was added to a solution of 4-hydroxyproline (5 mmol) in water (15 mL) with continuous stirring until all the solutes dissolved. The solution was cooled to -5 °C and 4-nitrobenzenesulfonyl chloride (5 mmol) was added in four portions over a period of 1 h. The reaction mixture was further stirred at room temperature for 4 h(Scheme 1). The mixture was acidified using 20% HCl until a pH of 2 was obtained. The white product

obtained was filtered, washed, and dried in the open air. Yield (1.12 g, 71.34%), MP = 190–192 °(O), 1004 (C–N), 685 (S–N). ¹H-NMR (DMSO, 400 MHz) δ : 8.40 (m, 2H, ArH), 8.10 (m, 2H, ArH), 4.87 (s, 1H, OH exchangeable with HDO), 4.31 (m, 2H, CH-CO₂H and CH-OH), 3.59 (dd, 1H, CH_a of CH₂-CH-CO₂H, J = 8.00, 4.00 Hz) 3.41 (dt, 1H, CH_b of CH₂-CH-CO₂H, J = 8.00, 4.00 Hz), 2.19 (ddt, 1H, CH_b of CH₂-CH-CO₂H, J = 8.00, 4.00 Hz), 2.06 (ddd, 1H, CH_b of CH₂-N, J = 12.00, 8.00, 4.00 Hz), 2.06 (ddd, 1H, CH_b of CH₂-N, J = 12.00, 8.00, 4.00 Hz). ¹³C NMR (DMSO, 100 MHz) δ : 174.19 (C=O), 150.28, 143.40, 128.81, 123.79 (4 aromatic carbons), 69.21, 59.94, 56.51, 39.00 (4 aliphatic carbon). DEPT (100 MHz) δ : 174.19, 150.28, 143. 40 (tertiary C), 128.81, 123.79, 69.21, 59.94 (CH carbons), 56.51 and 39.00 (CH₂ carbons).

X-Ray Determination of HNPCA

Dark green crystals of the titled compound were obtained from methanol under slow evaporation at room temperature. A single crystal suitable for X-ray diffraction measurement was mounted on a goniometer of an XtaLabSnergy, Dualflex Pilatus 200 K diffractometer. The crystal data were collected at 105.4 (7) K using graphite monochromated CuKa radiation ($\lambda = 1,54,184$) Table 1. Data reduction and empirical absorption correction were implemented in Crysallispro [37]. The structure was solved, with ShelXT [38], structure solution program using the intrinsic phasing solution method and Olex2 as the graphical interface. The structure was refined in ShelXL by full-matrix least-squares analysis of F2 against all reflections [39]. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Unless otherwise noted, hydrogens were included in calculated positions. Atomic displacement parameters for the hydrogens were tied to the Ueq parameter of the atom to which they are bonded (1.5), for methyl, 1.2. for all others). N-H protons refined freely without any restraints. The molecular structural diagram was drawn in Olex2 Software Package [40]

Computational Method

The compound HNPCA was fully optimized in the gas phase using the DFT method. The functional used was B3LYP [41, 42] with the 6-311 + + G(d,p) basis set. HNPCA was also optimized in methanol using the same theoretical method within the PCM solvation model [43, 44] The ground-state structure was confirmed by frequency computations with the absence of imaginary frequency in both the gas phase and methanol. The optimized structure of HNPCA in methanol was used for computing chemical shifts with the Gauge-Including Atomic Orbital method [45] using isotropic shieldings of tetramethylsilane (TMS) computed using the

Table 1	Crystal	data and	structure	refinement	for	HNPC	A
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Identification code	HNPCA
Empirical formula	$C_{11}H_{13}N_2O_7S$
Formula weight	317.29
Temperature/K	105.4(7)
Crystal system	Orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	7.5390(3)
b/Å	10.5933(4)
c/Å	15.7850(6)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	1260.64(8)
Z	4
$\rho_{calc}g/cm^3$	1.666
μ/mm^{-1}	2.678
F(000)	656.0
Crystal size/mm ³	$0.1 \times 0.05 \times 0.05$
Radiation	CuKa ($\lambda = 1.54184$)
2Θ range for data collection/°	10.056 to 149.192
Index ranges	$-9 \le h \le 9, -12 \le k \le 9, -19 \le l \le 18$
Reflections collected	5075
Independent reflections	2216 [R _{int} =0.0324, R _{sigma} =0.0407]
Data/restraints/parameters	2216/0/192
Goodness-of-fit on F ²	0.978
Final R indexes $[I > = 2\sigma (I)]$	$R_1 = 0.0301, wR_2 = 0.0776$
Final R indexes [all data]	$R_1 = 0.0332, wR_2 = 0.0793$
Largest diff. peak/hole/e \AA^{-3}	0.31/- 0.31
Flack parameter	- 0.006(13)

same method. The non-covalent interaction (NCI), based on the reports of Johnson et al. [46], was explored by the noncovalent interaction-reduced density gradient (NCI-RDG) analysis using the Multiwfn program [47]. The isosurfaces were plotted using the Visual Molecular Dynamic (VMD) software [48] and The Gnuplot 4.2 program [49] and Ghostscript interpreter were employed to generate the 2D plots. All computations were carried out at 1 atm and 298.15 K using Gaussian 16 [50]. Visualization of the output files was done using GaussView 6 [51] and Chemcraft [52]. The coordinates of the optimized structure of HNPCA in the gas phase and methanol are provided in Table S1 of the supplementary information.

The interactions in the crystal structure of HNPCA were investigated by the Hirshfeld surface analysis [53] along with their 2D fingerprint plots [54] which were generated using the CrystalExplorer17.5 software [55]. Hirshfeld surface is represented by d_e and d_i , denoting the distance from the nearest atom outside and inside of the surface, respectively, and both are used to define the normalized contact distance (d_{norm}) with respect to the Van der Waals (vdW) radii as per Eq. 1.

$$d_{norm} = \frac{(d_i - r_i^{vdW})}{r_i^{vdW}} + \frac{(d_e - r_e^{vdW})}{r_e^{vdW}}$$
(1)

For the visualization of d_{norm} , a red-blue-white color scale was selected. The red color denotes a negative value of the d_{norm} whereas the blue color denotes a positive value of the d_{norm} . The positive and negative values of the d_{norm} denote whether intermolecular interactions are larger or smaller than the vdW separation respectively. Therefore, the mapping of d_{norm} on the Hirshfeld surface illustrates the donor and acceptor properties and helps in the analysis of the intermolecular interactions.

ADMET Prediction

The drug-likeness of HNPCA was predicted using Swiss free online ADMET tool (SwissADME; https://www. swissadme.ch). Calculated parameters include molecular weight, H-bond donor, H-bond acceptor, number of rotatable bonds, water partition coefficient (MlogP), and total polar surface area (TPSA).

Ligand and Protein Preparation

The compound was designed using ChembioDraw Professional 13.0 [56] and was converted to 2D by using BIOVIA Discover Studio Visualizer 17.2.0.16349 [57]. Structure optimization was achieved by applying the Hahn forcefield [58]. Optimized structures were used for the docking study. Crystal structure of dihydropteroate synthase, 5uoy [59], DNA topoisomerase II gyrase; 5mmn [60], and SARS-CoV-2 spike; 6vsb [61] were retrieved from protein data bank with resolutions 1.82 Å, 1.90 Å and 3.46 A respectively. Protein editing was done by means of Discovery Studio[57] which included the deletion of co-crystallized ligands, multiple chains, hetero atoms, the water of crystallization, the addition of polar hydrogens, energy minimization, and structure optimization [58]. Enhanced proteins were used for molecular docking.

Ligand–Protein Docking Protocol Validation

The reliability of the docking protocol was corroborated by re-docking. Initially, the native ligand was withdrawn from protein binding site cavity and the binding site was defined by applying current ligand selection to obtain the ligand attributes; X = -26.1303, Y = 11.7748, Z = -17.6060,

radius = 9.1985 for 5uoy, X = -47.8198, Y = 3.2066, Z = 4.8274, radius = 8.6011 for 5mm, and X = 190.2069, Y = 233.0658, Z = 210.6196, radius = 5.2447 for 6vsb. Docking was performed using Autodock Vina PyRx [62]. The native ligand was re-docked into the defined binding site and desired site attributes were carefully adjusted to fit the obtained Grid center. PyRx nonspecific algorithm was used to generate protein–ligand docked pose by applying Vina Wizard script. The lowest binding energy was used to select the best-docked model, while a comparison of H-bond and other key interactions selected the best-docked pose. The lower the binding energy, the higher the binding affinity. The RMSD of > 2 Å obtained for the superimposing of native crystal with the best-docked pose confirms the acceptability of the docking.

Results and Discussions

X-Ray Crystallography

The molecular structure of the titled compound is shown in Fig. 1 The compound consists of a sulfonamide moiety sandwiched between a para-nitro phenyl moiety and hydroxy pyrrolidone carboxylic acid in a slightly distorted tetrahedral. The S1-N1 [1.628 (2) Å] bond length indicates the formation of the titled compound. This is similar to the reported value of 1.636 in the work of Murthy et al. [63]. The phenyl ring is planar to a rmsd 0.013 Å and disubstituted at *para* positions with *nitro* and sulfonyl groups. The N2-C4 and S1–C1 bonds are 1.472 (4) and 1.774 (3) Å respectively. These values are similar to the values reported for a related sulfonyl compound [64]. The pyrrolidine ring on the other hand is puckered to a rmsd of 0.182 Å and trisubstituted by carboxylic acid, hydroxyl, and sulfonyl groups. The dihedral angles between the sulfonyl groups



Fig. 1 The ORTEP structure of 4-hydroxy-1-((4-nitrophenyl)sulfonyl) pyrrolidine-2-carboxylic acid

Fig. 2 Molecular aggregation in the crystal structure of the title compound showing O4-H4 … O5 and O7-H4 … O3 hydrogen bonding interactions



Table 2 Hydrogen bond geometry of the title compound (Å, °)

$D - H \cdots A$	D - H	$H \cdots A$	$D \cdots A$	$D - H \cdots A$
$O4 - H4 \cdots 05^{a}$	0.80 (5)	1.88 (5)	2.668 (3)	168 (5)
$O5 - H5 \cdots O7^{a}$	0.88 (5)	2.03 (5)	2.888 (3)	163 (5)

Symmetry codes: (i) 1-x, 1-y, -z (ii) -1 + x, y, z (iii) 1-x, -y, 1-z (iv) 1-x, 1-y, 1-z (v)



Fig.3 The three-dimensional NCI surface of HNPCA. The surfaces are coloured according to the blue-green–red scale based on the sign(λ_2) ρ (r) values ranging from – 0.05 to 0.05 a.u (Color figure online)

and the paranitrophenyl and the five membered pyrrolidone rings respectively are 47.16 and 27.90°. The bond lengths of O4-C11 and O3-C11 are 1.331 and 1.200 Å respectively. The sulfonyl bonds S1-O1 and S1-O2 with lengths 1.431(5) and 1.427(3) are similar to the values reported for related benzene sulfonyl compounds.[64, 65] As expected, the length of C=O (O3-C11) is shorter than that of C-OH (O4-C11). The angles around the slightly distorted tetrahedron range from a narrower O1-S1-N1 (106.21 (13)) to a slightly larger O1-S1-C1 [107.57 (13)]. The sulfonamide is stabilized by the torsion angles of O2-S1-N1-C10 $[-51.5 (2)^{\circ}]$ and O1-S1-NI-C7 [39.9 (2)°]. The molecular



Fig. 4 Plots of reduced density gradient (RDG) against $\text{sign}(\lambda_2)\rho(r)$ of HNPCA

aggregation structure of the solid-state structure of the compound in Fig. 2 consists of a 9-molecule aggregate synthon linked by a chain of O–H … O hydrogen bonding interactions and stabilized by both intramolecular and bifurcated intermolecular C-H … H short contacts in a 2-D supramolecular architecture. There are predominantly two types of O–H … O intermolecular hydrogen bonding interactions, the carboxyl-O4-H4-O5(hydroxyl) and hydroxyl-O5-H5-O7(nitrophenyl). The hydrogen bond geometries are presented in Table 2.

Non Covalent Index NCI

The stability of HNPCA can be determined based on its molecular interactions which can be analyzed using the RDG based on NCI. The NCI isosurface was generated using the B3LYP optimized geometry and this is illustrated in Fig. 3. The blue-green–red isosurfaces color are classified according to the strength and type of interaction whereby blue indicates strong attractive interactions, green indicates Van der Waals interaction and red indicates a strong repulsion[66]. Therefore, the presence of the green and red isosurfaces in Fig. 3 indicates the presence of Van der Waals interaction as well as steric interactions [67]. In addition to the NCI



Fig. 5 Hirshfeld surface of HNPCA a mapped over d_{norm} in the range -0.7104 to 1.0921 Å. b Intermolecular interactions on the d_{norm} surface

isosurface, the 2D NCI scatter plot is displayed in Fig. 4. The spikes in the RDG region where $\lambda_2 \approx 0$ and $\rho \approx 0$, suggest that HPNCA consists of Van der Waals interactions (- 0.02 to 0 a. u.) mainly corresponding to the intramolecular O···H interactions. Spikes are also observed in the positive region (0 to 0.04 a. u.) indicating steric hindrance arising from the aromatic ring as well as the pyrrolidine ring. The absence of blue coloured spikes confirms that HNPCA does not exhibit any conventional intramolecular hydrogen bond within the structure but engages in intermolecular hydrogen bond.

Hirshfeld Surface Analysis

The Hirshfeld surface contacts were mapped over d_{norm} using the method described in [68–70] and presented in Fig. 5a. The red regions are located mainly on the oxygen atoms and one of the H atoms of the aromatic ring of the compound, indicating stronger intermolecular hydrogen bonds with neighboring atoms. However, the light-colored regions indicate weaker and longer contacts other than hydrogen bonds [34, 71, 72]. Some of the significant intermolecular interactions within the crystal structure of HNPCA are shown in Fig. 5b and these include phenyl-C-H···O(sulfonyl) in green dotted lines, pyrrolidone-C-H···O(nitro) in red dotted lines and phenyl-C...O interactions in magenta^[73]. The fingerprint plots in Fig. 6, have been decomposed to analyze individual contributions and corroborate the results of the Hirshfeld surface analysis [54, 74]. The fingerprint plots indicate that the most dominant interaction is the O···H interactions (58.9%). The two sharp spikes correspond to the -OH group (O4-H) of the carboxylic group and the hydroxyl group (O5–H) of the pyrrolidone ring. The H···H interaction contributes to 19.9% of the surface area of the fingerprint plot. All other interactions observed are less than 8.0% [C···H $(7.1\%) > S \cdots H (0.2\%) > O \cdots C (5.6\%) > O \cdots O (4.1\%) > O \cdots N$ $(2.1\%) > N \cdots H (2.0\%) > C \cdots C (0.1\%)].$

Interaction Energy Calculations

The strength of intermolecular interactions can be estimated by calculating the interaction energies between pairs of molecules within the crystal of HNPCA and adding up the resulting four energy components comprising of the electrostatic (E_{ele}), polarization (E_{pol}), dispersion(E_{dis}), and exchange repulsion (E_{rep}) energies [75]. The energies were obtained by calculating the wave function of each pair of molecules or atoms at the B3LYP/6-31G(d,p) level of theory [69, 75]. Quantitative estimation of the strength and nature of the intermolecular interactions in HNPCA crystal with individual energy components (E_{ele}, E_{pol}, E_{dis}, and E_{rep}) as well as the sum of the energy components, E_{tot} are presented in Table 3. The energy values show that the electrostatic component of the energy makes the most significant contribution to the total interaction energy profile in the crystal structure probably due to the intermolecular Van der Waals interactions resulting from the high level of H ... O/H ... O and H ... H intermolecular interactions. The dispersive interaction energy component of the total interaction energy is the second highest contributor to the total interaction energy and these probably result from the $\pi \cdots \pi$ interaction of successive pairwise phenyl and pyrrolidone rings in the crystal lattice [70, 76]. A graphical representation of the magnitude of the interaction energies is presented in Fig. 7a-d in the form of energy frameworks to show the supramolecular architecture using cylindrical poles joining the centroids of molecular pairs. The red, green, and blue color-coded frameworks in 7a, 7b, and 7c respectively represent E_{ele}, E_{dis} and E_{tot} energy components for intermolecular interactions HNPCA crystal, while 7d is the annotated E_{tot} energy. The magnitude of the cylindrical poles corroborates the results from the fingerprint plots indicating that the E_{ele} energy component to the total interaction energy is significant and



Fig. 6 Fingerprint plots of HNPCA showing O…H and H…H interactions

Table 3 A summary ofinteraction energies (kJmol ⁻¹)	N	Symop	R	Electron Density	Eele	E_pol	E_dis	E_rep	E_tot
calculated for HNPCA	1	-x, y+1/2, -z+1/2	8.40	B3LYP/6-31G(d,p)	- 21.9	- 5.7	- 22.8	17.9	- 36.2
	1	x, y, z	7.54	B3LYP/6-31G(d,p)	- 82.5	- 18.5	- 33.8	97.3	- 70.3
	1	-x + 1/2, -y, z + 1/2	7.96	B3LYP/6-31G(d,p)	1.6	- 4.0	- 24.6	14.4	- 13.8
	0	x + 1/2, -y + 1/2, -z	7.47	B3LYP/6-31G(d,p)	- 36.8	- 8.3	- 24.0	49.9	- 35.1
	1	x + 1/2, -y + 1/2, -z	7.24	B3LYP/6-31G(d,p)	- 4.6	- 3.2	- 18.3	11.4	- 16.1
	1	-x, y+1/2, -z+1/2	7.46	B3LYP/6-31G(d,p)	3.9	- 3.0	- 16.3	7.8	- 7.5
	0	-x + 1/2, -y, z + 1/2	10.25	B3LYP/6-31G(d,p)	- 5.5	- 1.3	- 7.7	4.5	- 10.6

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Fig. 7 Perspective views of the energy frameworks of the title compound showing \mathbf{a} electrostatic, \mathbf{b} dispersion, \mathbf{c} total energy, and \mathbf{d} annotated total energy. The cylindrical radius is proportional to the

contributes substantially to the molecular packing in the crystal lattice.

Spectroscopic Studies

IR Spectra

The Infrared spectrum of the compound being investigated was recorded in the 4000–600 region using Bruker FT-IR spectrophotometer. The spectra of the compound (Figure S1) shows an S–N stretching prevalent for benzenesul-fonamide derivatives at 857 cm⁻¹(usually in the range of 947–836 cm⁻¹) [77], and the band at 1355 cm⁻¹ was assigned to S=O indicating the formation of the benzenesulfonamide. Other characteristics bands present are; the C=O stretching of a carboxylic at 1745.19 cm⁻¹, N–O stretching for a nitro

relative strength of the corresponding energies and they were adjusted to the same scale factor of 100 with a cut-off value of 5 kJmol⁻¹ within a $2 \times 2 \times 2$ unit cells

compound at 1524.70 cm⁻¹, O–H stretching at 3450 and 2700 cm⁻¹assigned to the OH of the alcohol and carboxylic acid respectively, C–H stretching at 2950 and 3100 cm⁻¹ for the aliphatic and aromatic carbons respectively. The simulated IR spectrum is provided in Figure S2 and describes a detailed vibrational analysis of HNPCA in the gas phase as performed based on potential energy distribution using VEDA 4 program.

¹H NMR,¹³C NMR, and DEPT

The ¹H and 13C NMR of the named compound are presented in Figures S4 and S5 of the supplementary information. ¹H NMR chemical shift at 8.38–8.41 were assigned to the protons present in the aromatic ring. The chemical shift at 8.08–8.11 were assigned to the protons of the Table 4ADMET calculationfor HNPCA

	MW	Donor HB	Accept HB	log P	RBC	Rule of five	TPSA [Å ²]	Bioavail- ability score
Recom- mended values	316.29 ≤500	2 ≤5	8 ≤10	- 0.61 ≤5	4 ≤10	0 Max 2	149.11 ≤140	0.56

MW Molecular weight of the molecule, *donorHB* approximated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution, *acceptHB* approximated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution, *Rule of five* Number of violations of Lipinski rule, *Log P* water partition coefficient, *RBC* approximated number of rotatable bonds, *TPSA* topological polar surface area

pyrrolidine ring. Also, the absence of a chemical shift for N-H at the upper field confirms the formation of the desired compounds. The ¹³C NMR like the ¹H NMR agrees with the crystal structure of the compound gotten via X-ray diffraction studies of the compound's crystal. The signal at 174.19 was assigned to C=O, signals between 150.28 and 123.79 were assigned to the six aromatic carbon atoms, while the signals from 69.21 to 39.00 were assigned to the four aliphatic carbons of the compound. The NMR values are corroborated by the calculated NMR values presented in Table S1 of the supplementary information. The DEPT analysis (Figure S6) showed that the compound had three tertiary carbons, six CH carbons, and two CH₂ carbons. Although only four carbons appeared among the CH carbons, this was expected due to chemical equivalence in the para-substituted benzene ring. There was also no appearance of methyl carbon in the DEPT results. These observations are in agreement with the structure obtained from XRD analysis.

ADMET

Due to poor bioavailability, most orally administered drugs are unable to reach the target therapeutic site, resulting in failed clinical trials despite promising *in vitro* and *in vivo* efficacy [78]. lipniski rule of five (MW \leq 500, HBD \leq 5, HBA \leq 10, log p \leq 5, RBC \leq 10) is a valid assessment of the oral bioavailability of a drug candidate [79]. A molecule that violates more than two categories is adjudged to elicit poor bioavailability. HNPCA was studied for lipinski rule compliance and other properties that influence drug absorption, and the result is presented in Table 4. HNPCA showed total compliance in all calculated parameters except for TPSA (Veber rule: TPSA \leq 140 Å²)[80], signaling a good bioavailability potential.

Molecular Docking Study

Molecular docking permits the prediction of molecular interaction between ligand-protein and has become

Table 5 The binding energy of HNPCA with protein targets

Ligands	Protein	Binding energy (kcal/ mol)
HNPCA	6vsb	- 5.90
Dexamethasone		- 6.90
Remdesivir		- 7.40
Native ligand		- 8.80
HNPCA	5uoy	- 7.20
Ciprofloxacin		- 7.10
Gentamicin		- 6.80
Native ligand		- 7.60
HNPCA	5mmn	- 7.30
Ciprofloxacin		- 7.40
Gentamicin		- 7.20
Native ligand		- 7.80

a reliable tool in drug discovery. A docking study on HNPCA was done with selected protein targets; dihydropteroate synthase (5uoy), topoisomerase II DNA gyrase (5mmn), and a 2019-nCoV spike (6vsb) Fig 8. Dihydropteroate synthase (DHPS) catalyzes the transformation of 6-hydroxymethyl-7,8-dihydropterin pyrophosphate (DHPP) plus p-aminobenzoic acid (PABA) to 7,8-dihydropteroate, important folate intermediate in the folate biosynthetic pathway [81]. As a result, DHPS is an important antibacterial drug target and research on new inhibitors has intensified in recent times [82–84]. DNA gyrase is a type II topoisomerase that functions in DNA supercoils and replication, hence is investigated as a drug target for many agents, including antitumor and antibacterial [85]. The CoV spike (S) glycoprotein is a vital target for vaccines, and therapeutic antibodies [61]. HNPCA was docked in the active site of augmented protein targets using the intrinsic PyRx algorithm and obtained ligand-protein docked poses were visualized with Discovery Studio.







Fig. 9 Molecular overlay of HNPCA (blue) with native ligand (yellow) against 5uoy, depicting close connectivity (Color figure online)

Binding Affinity of HNPCA with the Protein Target

The binding energy of HNPCA with protein targets had been shown in Table 5. In the case of 5uoy and 5mmn, HNPCA interacted significantly with receptor site residues, thereby eliciting higher or comparable binding affinity with the native ligand, ciprofloxacin or gentamicin. This suggests that the compound could intercalate well with the studied antibacterial targets to demonstrate promising efficacy. A lower binding affinity was recorded with 6vsb, compared to the crystal ligand, remdesivir or dexamethasone, which have been indicated to reduce mortality in people with severe COVID-19 [86].

Bonding Model HNPCA with Protein Target

H-bond is an important interaction stabilizing ligands with receptors. In the binding pocket of 5uoy, Fig 9, HNPCA demonstrated extensive H-bond between the COOH, OH, NO₂, SO₂-NR₂ moieties and Thr62, Arg63, Glu60, Asn22, Arg255, His257, and Lys221 residues, Fig. 8. In addition, a closer look showed a pi-bonding between the O = S = O group with His257. The extensive H-bonding may have conferred a higher binding affinity, indicating a reliable stability with protein target active site residues to impact promising antibacterial activity.

In the case of 5mmn, the NO₂ group of HNPCA engaged in H-bond with Arg76, Gly77, Thr165, while the COOH group approached Asn46 in H-bond. Additional stability was supported by the phenyl ring, which had invested in Ile78 and Glu50 via pi-alkyl and pi-anion interactions. These key interactions providing stability encourage potential strong inhibitory efficacy against microbial strains, Fig. 8.

On the other hand, the COOH, SO_2 , and NO_2 groups established H-bond with Glu619, Thr618, Ser591, Thr553, and Asn536 amino acid residues in the binding cavity of 6vsb, while the phenyl group added stability by engaging in hydrophobic interaction with Val558, Fig. 8.

Conclusion

A novel compound 4-hydroxy-1-[(4-nitrophenyl)sulfonyl] pyrrolidine-2-carboxyllic has been synthesized and characterized using XRD and spectroscopic techniques. Intermolecular O4-H4 ··· O5 interaction in the crystal structure of the compound connects different molecules of the compound in a continuous chain and is stabilized by N4-H4 ... O3 intermolecular hydrogen bonding interaction. Hirshfeld surface analysis of the intermolecular interactions suggests that O ... H/H ... O interactions contributed more than half of the total intermolecular contacts in the compound. The NCI analysis of the compound did not reveal any intermolecular hydrogen bonding interactions in the compounds. There was however evidence of the presence of some Van der waals and steric interactions, corroborated by the results of the interaction energy calculations which showed higher electrostatic interactions than dispersive forces. The results of the molecular docking studies showed that the compound had a high binding affinity and is well stabilized in the active pocket of dihydropteroate synthase, DNAtopoisomerase II gyrase, and SARS-CoV-2 spike via extensive H-bond network, which suggests that the compound may be a starting point for a rational drug design.

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Code Availability All softwares and codes used are open source and can be obtained freely online.

Declarations

Competing interests The authors declare no competing interests.

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