Structural and Theoretical Investigations, Hirshfeld Surface Analyses, and Cytotoxicity of a Naphthalene-Based Chiral Compound

Saud I. Al-Resayes, Mohammad Azam, Agata Trzesowska-Kruszynska, Rafal Kruszynski, Saied M. Soliman, Ranjan K. Mohapatra, and Zahid Khan

ABSTRACT: A novel Schiff base compound derived from the condensation of 2-hydroxy-1-naphthaldehyde with (1S,2S)-(−)-1,2-diphenylethylenediamine in 2:1 M ratio was reported and investigated by elemental analyses, Fourier transform infrared and NMR spectroscopic studies, and single-crystal X-ray crystallography. Hirshfeld surface analyses were also carried out to measure the various intermolecular contacts controlling the supramolecular topology, suggesting the H⋯O (7.6%) contacts to be the most significant interactions, whereas the H⋯H (48.9%) and C⋯H (40.2%) interactions are less-significant. The data obtained from the energy calculations revealed the structure observed experimentally to be the most stable isomer and its energy being lower than 18.0441 kcal/mol than the less stable one. Density functional theory calculations were also carried out to analyze the natural charges, reactivity descriptors, and different intramolecular charge transfer interactions. The in vitro anticancer activity of the compound was evaluated by MTT assays against human colorectal cancer cells, HT-29 and SW620. The results showed that the compound has potential anticancer activity against these cells lines.

INTRODUCTION

Despite the significant advances, cancer, which is caused by the unregulated proliferation of abnormal cells, remains one of the leading causes of death worldwide. Over the years, the clinical success of cisplatin and its second-generation analogues encouraged researchers to discover new drugs with minimal side effects and maximal curative potential. However, the use of cisplatin is limited because of severe toxic side effects including nephrotoxicity, neurotoxicity, and ototoxicity. Low water solubility, instinct, and acquired resistance exhibited in various types of cancers are also valid problems prohibiting the usage of cisplatin. For these reasons, the development of new potential chemotherapeutic drugs with high efficacy and low toxicity is a great challenge in modern cancer research.

Over the years, Schiff bases have received enormous significance in medicinal chemistry because of their biological, pharmacological, and antitumor properties, chelating behavior, preparative accessibilities, structural varieties, and varied denticities. It is shown that the presence of the >C=NH functional group is supposed to be responsible for medicinal properties exhibited by Schiff bases. Furthermore, there are several reports that Schiff bases have the capability of stabilizing oxidation states of various metal ions and therefore play an extensive role in various catalytic reactions. However, the geometry of Schiff bases largely depends on the diamine structural unit, nature of the ancillary ligand, and central metal ion.

RESULTS AND DISCUSSION

All atoms of the studied Schiff base compound occupy general positions, but the 2-fold rotation axis going through the midpoint of the ethylenediamine C—C bond causes one molecule to be located in two asymmetric units.

We are reporting here a novel Schiff base compound derived from 2-hydroxy-1-naphthaldehyde and (1S,2S)-(−)-1,2-diphenylethylenediamine in 2:1 M ratio. There are several reports published on the synthesis of the studied compound in the literature. In our work, we discuss the never previously reported crystal structure of the compound, enriched by elemental analyses and spectroscopic studies [Fourier transform infrared (FT-IR) and NMR]. However, we used the methods of quantum crystallography [density functional theory (DFT) calculations and Hirshfeld surface analyses] to provide even better insights into the properties of the structure. We conclude our investigation with an analysis of potential anticancer activity against the colorectal cancer cells HT-29 and SW620. Results suggest potential activity against both types of the studied cancer cells.

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The (2-hydroxy-1-naphthylmethylene)amine moieties are close to planarity (Table 1) and the twist of the molecule occurs only within ethylenediamine linkage (about its three bonds, two C–N, and one C–C; Table 1). The analysis of dihedral angles (Table 1) shows that the molecule adopts the anticlinal–synclinal–anticlinal conformation of the methylene–ethylenediamine bridge. The comparison of C–N bond lengths shows that the double bonds are fully localized within naphthylmethyleneamine moieties. Both chiral centers possess S configuration. The terminal naphthalamine ring systems are inclined at 40.21(4)°, which originates from the twist of the above-described central C=N–C=C=N=C linkages. The least squares planes calculated through all atoms of naphthyl moieties show that some of their atoms slightly deviate from the substituent plane. Observed deviations are not larger than 0.0371(12) Å (this value was registered for the C1 atom) and 0.0370(12) Å (this value was registered for the C1 atom) and such deviations are typical for similar compounds.17 Each molecule is internally linked by two types of hydrogen bonds (Table 2), that is, O molecule is internally linked by two types of hydrogen bonds. Additionally, the molecules are assembled by the intermolecular C–H···O hydrogen bond (Table 2) to a supramolecular chain extending along the crystallographic [0 1 0] axis and described by the C(10) motif of unitary graph of the lowest degree [Figure 2]. Because of the presence of the above-described 2-fold rotation axis (going through the midpoint of the ethylenediamine C=C bond), the intermolecular C–H···O hydrogen bond forms also a $R_2^2(20)$ motif of unitary graph of lowest degree. The formed hydrogen-bonded chains are well separated and do not assemble in a larger supramolecular structure even via the π···π interactions (neighboring crystal net aromatic rings are distinctly nonparallel).

The 1H NMR spectral results further confirm the 1H NMR findings. The most important and characteristic signal due to azomethine appears at 168.0 ppm, whereas the signals due to aromatic protons appear at 118.9–138.7 ppm. However, the carbon signal due to C–O appears at 161.3 ppm. The signal due to –CH=N=N–CH– appears at 107.0 ppm [Figure S2].

The characteristic azomethine vibration due to $\nu_{\text{C}=(\text{CH} = N)}$ is located at 1621 cm$^{-1}$. A strong band due to the phenolic (C–O) vibration appears at 1190 cm$^{-1}$. Furthermore, vibrations due to the aromatic ring appear at 648, 1030, and 1480 cm$^{-1}$ [Figure S3].

**Hirshfeld Analysis of Molecular Packing.** Various observed contacts and their percentages in the crystal structure of the studied compound based on Hirshfeld calculations are displayed in Figure 3. The packing of molecules is mainly dependent on H···H (48.9%) and C···H (40.2%) interactions and the significant C–H···O interactions (7.6%). All intermolecular contacts appearing as blue regions in the $d_{\text{norm}}$ map indicate interactions with longer distances than vdW radius sum of the interacting elements [Figure 4]. The only exception are the C···H···O interactions, which appear as red spots in the $d_{\text{norm}}$ map and sharp spikes in the fingerprint plot, indicating that these intermolecular interactions have contact distances shorter (2.347 Å; O1···H14) than the sum of the van der Waals radii of the oxygen and hydrogen atoms [Figure 4]. As can be seen from this figure, the $d_{\text{norm}}$ maps indicate interaction distances longer than the vdW radius sum of the interacting atoms for the H···H and C···H interactions.

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### Table 1. Selected Structural Data of the Compound [Å, °](a)

| Bond          | D–H–A   | d(D–H)   | d(H–A)   | $d$(A–D)   | $\angle$(DHA) |
|---------------|---------|----------|----------|------------|---------------|
| O1–H11–N1    | 0.86    | 1.71     | 2.5328(17)| 157.6      |
| C14–H14–O1†  | 0.95    | 2.48     | 3.315(2) | 146.2      |
| C18–H18–N1   | 0.95    | 2.51     | 3.836(2) | 100.3      |

(a) Symmetry transformations used to generate equivalent atoms: (i) $-x + 2, y - 1, z$.

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Figure 1. Molecular structure of the compound with 50% probability of displacement ellipsoids.
DFT Studies. The optimized geometry of the compound together with the structure matching between the experimental and calculated structures is presented in Figure 5. The calculated bond distances and angles compared to the experimental results are listed in Table S1 and Figure S4. However, in contrary to the X-ray structure, slight deviations in the calculated structure are likely due to the calculation in the gas phase and therefore free from the environmental effects causing the interactions with the neighboring molecules. Figure 6 reveals that the correlation coefficients between the calculated and experimental geometric parameters are high (0.9844−0.9748). The molecular structure is stabilized by two equidistance intramolecular O–H···N hydrogen bonds with hydrogen-acceptor distances of 1.631 Å (exp. 1.714 Å).

The calculated charges at the different atomic sites are listed in Table S2. Distribution of molecular electrostatic potential (MEP) mapped over electron density revealed that the N (−0.537e) and O (−0.687e) sites and most of the carbon atoms have negative partial charges. However, only the C atoms attached to N or O are electropositive, whereas the O–H protons have the most positive partial charges (+0.517e) [Figure 7]. The calculations predicted that the studied compound is a polar molecule with a net dipole moment of 2.641 debye.

The frontier molecular orbitals, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), are important for the molecular reactivity. However, the patterns of both molecular orbitals are very similar [Figure 7] and distributed over the fused ring π-system, suggesting the HOMO → LUMO excitation of the π−π* transition type. The energy calculated for both the HOMO and LUMO is −5.510 and −1.564 eV, respectively, and the energy of this transition is 3.946 eV. In this regard, the reactivity descriptors23−27 such as the ionization potential (I), electron affinity (A), hardness (η), electrophilicity index (ω), and chemical potential (μ) are calculated to be 5.510, 1.564, 3.946, 1.585, and −3.537 eV, respectively.

Natural Bond Orbital Analysis. Various intramolecular charge transfer (IMCT) processes arising in the studied compound with the help of second-order perturbation theory and natural bond orbital (NBO) calculations are listed in Table S3.28,29 The σ−σ* IMCT has stabilization energies (E(2)) not exceeding 5 kcal/mol; therefore, these IMCT interactions are not included in this discussion. The system is stabilized by many significant π → π* IMCT interactions with energy values up to 24.62 kcal/mol for the π(C−C) → π*(C−N) IMCT interaction. The net E(2) value for all π → π* IMCT interactions is the highest (701.74 kcal/mol). On the other hand, the system is stabilized by few number of n → σ* and n → π* IMCT with a net stabilization energy of 18.49 and 85.68 kcal/mol, respectively (Table S3).

Energetics and Relative Stability. The studied compound possesses two stereogenic centers, leading to a maximum of four possible isomers. However, the optimized structures of the two energetically distinguishable isomers A and B are shown in Figure 8. The energies and thermodynamic parameters of these isomers, listed in Table 4, suggest that the isomer A is more stable than B by 18.0441 kcal/mol and the conversion from B to A is a thermodynamically favored process.
with a net Gibbs free energy change of −19.1008 kcal/mol. The extra stability of A is in good agreement with the reported X-ray structure of the studied compound.

**In Vitro Antitumorigenic Activity.** The antitumorigenic activity of the compound was examined using MTT assay on colorectal cancer cell lines. The cytotoxic effect on HT29 and SW620 colorectal cancer cells was monitored after exposing them to a wide range of different concentrations from 1.25 to 20 μM of the compound for 24 h. A significant decrease in cell viability was observed with increase in drug dosage in both the cancer cell lines [Figure 9]. The cell viability at the maximum tested drug concentration of 20 μM for HT29 cells relative to
the untreated control cells decreased to 13.6% and that for SW620 cells reduced to 14.3%. The IC50 for the HT29 and SW620 colorectal cancer cell lines was calculated to be 6.2 and 7.1 μM, respectively. These findings suggest that the compound is significantly cytotoxic and has the potential to be utilized as an antitumorigenic agent in colorectal cancer treatment.

**CONCLUSIONS**

We have successfully synthesized and crystallized a naphthalene-based Schiff base compound and investigated it by single-crystal X-ray crystallography and spectroscopic studies. DFT calculations were also carried out to describe electronic aspects of the compound, whereas the Hirshfeld surface analysis revealed various interactions. The compound exhibited potential anticancer activity when tested against human colorectal cancer cells, HT-29 and SW620.

**EXPERIMENTAL SECTION**

**Materials and Methods.** (1S,2S)-(−)-1,2-Diphenylethenediamine, 2-hydroxy-1-naphthaldehyde, and other reagents were purchased from Sigma. C, H, N analyses and FT-IR and NMR studies were performed using an Elementar Varrio EL analyzer, PerkinElmer 621 spectrophotometer, and JEOL spectrometer at 400 and 100 MHz in CDCl3, respectively.

**Synthesis of the Naphthalene-Based Schiff Base Compound, (1S,2S)-(−)-1,2-Diphenyl-N,N′-bis[(E)-2-hydroxy-1-naphthalen-1-ylmethylidene]ethane-1,2-diamine.** A methanolic solution of (1S,2S)-(−)-1,2-diphenylethenediamine (100 mg, 0.471 mmol) was added in a solution of 2-hydroxy-1-naphthaldehyde (162.2 mg) in 1:2 molar ratio in the same solvent followed by stirring for 10 h at room temperature. A yellow-colored product was formed, which was filtered off and dried. The product was dissolved in dichloromethane and produced beautiful crystals upon diffusion in n-pentane.

**Color:** yellow; **Analytical Calcd** for C36H28N2O2 (calcd): C, 83.05; H, 5.42; N, 5.38; (Found): C, 83.00; H, 5.38; N, 5.35; 1H NMR (CDCl3): δ (ppm) 8.97 (s, 2H, −CH=N), 6.36–
Crystal Explorer 17.5,36 whereas all DFT calculations were recorded on the Gaussian 09 software package37,38 by the B3LYP/6-31G(d,p) method. NBO analyses were recorded on the NBO 3.1 program.39

**Cell Culture.** The HT-29 and SW620 human colorectal cancer cells were grown in RPMI medium (Thermo Fisher Scientific) supplemented with 10% heat-inactivated fetal bovine serum, 100 μg/mL streptomycin, 100 units/mL penicillin, and 2 mmol/L L-glutamine. Cells were cultured in a humidified 5% CO₂ incubator at 37 °C. A cell confluence of 70–80% was achieved before their use for experiments.

**Cell Viability Assay.** The human colorectal cancer cells HT-29 and SW620 were grown in 96 well plates. After a period of 24 h, cells were exposed to increasing concentrations from 1.25 to 20 μM of the compound for 24 h. Cells treated with an equal volume of dimethyl sulfoxide (DMSO) as the vehicle was used as control. Cell viability was assessed using tetrazolium dye MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide as described earlier.40 Briefly, after 24 h of incubation of the cells with the tested compound, freshly prepared 10 μL of MTT (5 mM) solution was added and incubated further for 2 h at 37 °C in 5% CO₂. Finally, to dissolve the formazan crystals formed during MTT incubation, 100 μL of DMSO was added and mixed well by pipetting. Absorbance of the solution was recorded at 540 nm in a microplate reader, whereas experiments were performed in triplicate for every concentration of the compound.

**Figure 9.** Cytotoxic activity of the compound. HT-29 (a) and SW620 (b) colorectal cancer cell lines were exposed to the indicated concentration of the compound for 24 h. Cell viability was evaluated by MTT assay and results are expressed from experiments performed in triplicate as mean ± SD.

**Table 3.** Crystal and Structure Refinement Data of the Studied Compound

| Parameter                        | Value            |
|----------------------------------|------------------|
| compound                         | Schiff base compound |
| empirical formula                | C₁₅H₁₄N₂O₃       |
| formula weight                   | 520.60           |
| crystal system, space group      | monoclinic, C2 (no. S) |
| unit cell dimensions [Å, deg]    | a = 20.8290(S)   |
| volume [Å³]                      | 1341.95(7)       |
| Z, calculated density [mg/m³]    | 2, 1.288         |
| F(000)                           | 548              |
| crystal size [mm]                | 0.119, 0.113, 0.098 |
| θ range for data collection [deg] | 4.597 to 70.205  |
| index ranges                     | -24 ≤ h ≤ 25, -8 ≤ k ≤ 8, -12 ≤ l ≤ 12 |
| reflections collected/unique     | 7396/2457 [R(int) = 0.0861] |
| completeness [%]                 | 99.9 (to θ = 70°) |
| data/restraints/parameters       | 24571/1/181      |
| Friedel reflections coverage     | 0.760            |
| Friedel reflections fraction     | 0.917            |
| Flack parameter                  | 0.02(5)          |
| goodness-of-fit on R²            | 1.047            |
| final R indices [I > 2σ(I)]      | R₁ = 0.0259, wR₂ = 0.0701 |
| R indices (all data)             | R₁ = 0.0263, wR₂ = 0.0706 |
| largest diff. peak and hole [e/Å³] | 0.173, -0.141 |

*Floating origin restraint.*

**Table 4.** Energies and Thermodynamic Parameters in au of the Isomers A and B

| Parameter       | A                | B                |
|-----------------|------------------|------------------|
| E               | -1648.7165       | -1648.6878       |
| ZPVE            | 0.5466           | 0.5466           |
| E_{tot}         | -1648.1699       | -1648.1412       |
| H               | -1648.1372       | -1648.1083       |
| S (cal mol⁻¹ K⁻¹) | 211.890           | 208.613          |
| G               | -1648.2378       | -1648.2074       |

*Zero point energy correction.*
ASSOCIATED CONTENT

+ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c03376.

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AUTHOR INFORMATION

Corresponding Author
Mohammad Azam — Department of Chemistry, College of Science, King Saud University, Riyadh 11451, Saudi Arabia; orcid.org/0000-0002-4274-2796; Email: azam_res@yahoo.com, mhashim@ksu.edu.sa

Authors
Saud I. Al-Resayes — Department of Chemistry, College of Science, King Saud University, Riyadh 11451, Saudi Arabia
Agata Trzesowska-Kruszynska — Institute of General and Ecological Chemistry, Lodz University of Technology, Lodz 90-924, Poland
Rafal Kruszynski — Institute of General and Ecological Chemistry, Lodz University of Technology, Lodz 90-924, Poland; orcid.org/0000-0003-1667-4379
Saied M. Soliman — Department of Chemistry, Faculty of Science, Alexandria University, Alexandria 21321, Egypt; orcid.org/0000-0001-8405-8370
Ranjan K. Mohapatra — Department of Chemistry, Government College of Engineering, Keonjhar, Odisha 758002, India
Zahid Khan — Genome Research Chair, Department of Biochemistry, College of Science, King Saud University, Riyadh 11451, Saudi Arabia

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acsomega.0c03376

Notes
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