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Synthesis of Isatin Monohydrazone, Spectroscopic Analysis, DFT Studies, and Molecular Docking Applications to MCF-7 Cell Line

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ABSTRACT

In this study, 3-hydrazinoindolin-2-one (S), an isatin monohydrazone compound, was synthesized. Spectroscopic (IR and ^{1}H-NMR) analyses were performed for the synthesized isatin monohydrazone compound. To compare the experimental spectroscopic data obtained, isatin was optimized at B3LYP/6-31G(d,p). The calculated data were found to be compatible with the experimental data obtained for structural analysis. Contour diagrams and MEP maps were also obtained to identify the electrophilic and nucleophilic attack sites of the synthesis compound. To evaluate their compatibility with biomolecular system, the synthesized compounds were fused with target protein representing MCF-7 cell line. The PDB ID of the synthesized compound: 1M17 and 3HY3 were calculated as -5.70 and -5.73 kcal/mol with the target proteins, respectively. Based on the obtained molecular docking parameters, it was determined to be suitable for anti-cancer applications.

Keywords: Synthesis, Computational chemistry, Molecular docking

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Introduction

The closed formula for the indole chemical, which has an abundance in nature and is found in the heterocyclic ring structure, is C_8H_7N. 2,3-Benzopyrrole, sometimes known as 1-H indole or simply benzopyrrole, is the indole ring. The closed formula for isatin, an organic molecule produced from indole, is C8H5NO2. It is also known as tribulin, 2,3-dioxindole or 1H-indole-2,3-dione. Isatins serve as building blocks for the production of indole compounds, which have significant biological functions [1]. It is a heterocyclic molecule with two carbonyl groups attached to the polyfunctional indole nucleus are given Figure 1.

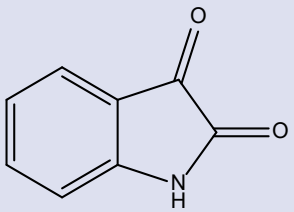


Figure 1. Molecular structure of isatin.

Structurally, isatin consists of two rings with six-membered aromatic and five-membered anti-aromatic characters. Many species replace certain regions in the structure of the isatin skeleton. Therefore, isatin is an important starting material in the synthesis studies of new isatin derivatives [2,4]. Isatin and its derivatives are also used as precursors in drug synthesis. These molecules are used in drug treatment such as anticancer, antibiotics, and antidepressant drugs and have many more clinical applications [3,5]. As an anticancer efficacy study of isatin, Vine et al synthesized a series of substituted 1H-indole-2,3-diones (isatins) and examined there in vitro cytotoxicity against the human monocyte-like histiocytic lymphoma (U937) cell line. Studies have been developed on the structure-activity relationships of di- and tri-halogenated isatins. These compounds showed greater selectivity against leukemia and lymphoma cells over breast, prostate and colorectal carcinoma cell lines. Of the most active compounds, 5, 6, 7-tribromoisatin was found to be antiproliferative at low micromolar concentrations. These results suggest that di- and tri-substituted isatins may be useful guides for future anticancer drug development [6]. When isatin and its derivatives are examined in the literature, it is noteworthy that it has been studied in a broad perspective and there are many noteworthy findings.

Murukan et al. synthesized iron (III), cobalt (III), and manganese (III) complexes of bishydrazone and investigated their antibacterial activity. They found that the 2-hydroxy-1-naphthaldehyde-3-isatin-bishydrazone ligand exhibited enhanced antibacterial properties upon metal complexation [7]. Pandeya et al. synthesized Schiff bases by reacting isatin and its derivatives with 4-(4'-chlorophenyl)-6-(4"-methyl phenyl)-2-aminopyrimidine and evaluated their anti-HIV activity [8]. In a recent study, Sindhu Kumari et al. synthesized coumarin-isatin monohydrazone and their cobalt(II), nickel(II), copper(II) and zinc(II) metal complexes. They used human cancer cell lines such as breast cancer cell (MCF-7) and leukemia

cancer cell (K-562) for in vitro anticancer activity. The results showed moderate activity compared to the standard drug [9]. The DFT (Density Functional Theory) approach is based on modeling electron correlation through electron density functions. This method, rooted in the Hohenberg-Kohn theorem, provides a computational framework for analyzing the electronic structure of molecules, making it essential in chemistry, biology, and physics [10].

In this study, isatinmonohydrazone (S) was synthesized and structurally characterized using spectroscopic methods. The B3LYP/6-31G(d,p) level of theory was employed to compute and compare its spectroscopic data with experimental results. Furthermore, contour diagrams, molecular electrostatic potential (MEP) maps, and frontier molecular orbitals (FMOs) were analyzed to gain insights into its electronic properties. A key objective of this study is to assess the anti-cancer potential of isatinmonohydrazone through molecular docking. To achieve this, molecular docking studies were conducted against target proteins associated with the MCF-7 breast cancer cell line. The docking simulations were performed using PDB IDs: 1M17 [11] and 3HY3 [12], providing insights into the binding interactions that could contribute to the compound's potential as an anti-cancer agent.

Calculation Techniques

Input files of the synthesized isatin monohydrazone were prepared with GaussView 6.0 [13]. All calculations were performed via TR-Grid [14]. With Gaussian 16 Linux version. The molecules were fully optimized using the DFT/B3LYP/6-31G(d,p) level [15,16]. Leading molecular orbitals such as high-energy occupied molecular orbital (E_{HOMO}) and low-energy unoccupied molecular orbital (E_{LUMO}) were calculated according to Koopmans theorem [17].

$$I = -E_{HOMO}$$
$$A = -E_{LUMO}$$

Molecular electrostatic potential (MEP) is related to electronic density and is a very useful descriptor for identifying active sites for electrophilic attacks and nucleophilic attack. Electron-withdrawing and electron-donating parts of the synthesized compounds will be determined with MEP maps.

Docking process DockingServer also MOPAC2009 [18]. Ligands and proteins were optimized using the PM6 method. The parameters of torsion step (0.2 Å), rigid body orientation step (5°), dihedral angle step (5°) and square root of deviation tolerance (2.0 Å) were used in the calculation [19]. All docking calculations are based on AutoDock connection parameters [20]. The binding affinity was measured in kcal/mol, with lower values indicating stronger binding interactions. The docking simulations targeted the active binding pockets of the respective proteins, ensuring alignment with previously reported binding sites. Validation Procedures: The docking protocol was validated using a re-docking approach, and RMSD calculations were performed to assess the accuracy of ligand placement.

Materials and Methods

Chemicals and Solvents Used

Isatin, Hydrazine monohydrate, ethanol are the chemicals and solvents used. Bought from BLDpharm and Sigma-Aldrich brands.

Devices and Computer Programs Used

NMR measurements were taken by dissolving isatin monohydrazone ^{1}H-NMR spectra in DMSO (Dimethyl sulfoxide) -D6, which was synthesized in two stages. Recorded on JEOL (400 MHz) JNM-ECZ400S/L1 NMR Device. Synthesis compound rod models were drawn and added in ChemDraw Professional 15.1. Optimized, MEP, HOMO and LUMO views of the compounds were obtained with GaussView 6.0 computer programs.

Synthesis of Isatine Monohydrazone

It was synthesized according to the reported procedure [21] with minor modifications. Isatin (1g, approximately 7mmol) was dissolved in some ethanol (25ml) and 0.4g of hydrazine hydrate solution was added by dissolving in a small amount of ethanol (2ml). The prepared solution was taken on a heating tablet and left to the reflux system for 3 hours with mixing and temperature. After 3 hours, the reaction was terminated and TLC (thin layer chromatography) was performed to observe the formation of a new product. Then, the newly formed reaction was kept in the fume hood with its mouth open for crystal formation. Crystal formation was observed during the day. The resulting product was washed with ether and filtered on filter paper. A yellow solid was obtained. After the product dried, it was dissolved with ethanol again and excess solvent was removed by Rotary. It was allowed to recrystallize. Yield: 72%.

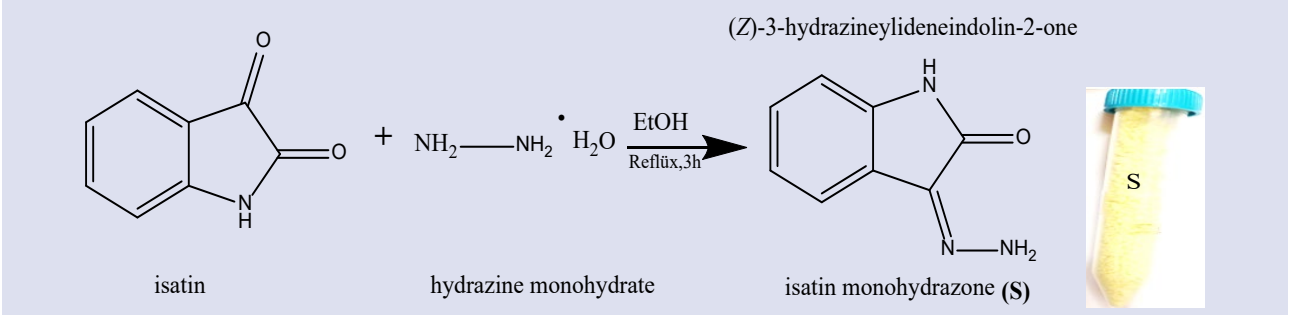
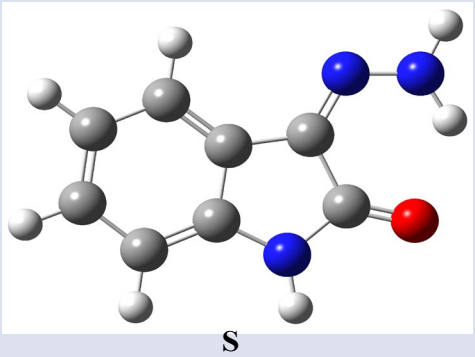


Figure 2. General step synthesis of isatin monohydrazone.

Result and Discussion

Optimized Structure

The molecular structure of synthesized S compound is shown in GaussView 6.0.16 program. Calculations at the B3LYP/6-31G(d,p) level were created using Gaussian16 IA32W-G16RevB.01, Gaussian09 AS64L-G09RevD.01. Figure 3 shows the optimized structure of S compound.



S

Figure 3. Calculated optimized structure of synthesized S compound at the B3LYP/6-31G(d,p) level.

^{1}H-NMR Calculation-Experimental

Chemical shifts of the ^{1}HNMR spectrum are calculated based on TMS (tetramethylsilane). Structural characterization and ^{1}HNMR spectrum of the synthesized isatin monohydrazone (S) were calculated and the peaks were labeled. TMS proton is calculated as 31.6412 ppm. ^{1}HNMR spectra were calculated at the B3LYP/6-31G(d,p) level and are given in Figure 4.

Table 1. Calculated proton chemical shifts for S.

^{1}H-NMR (ppm)	H9	H10	H11	H12	H18	H19
S	7.42	6.90	7.02	6.50	6.57	5.98

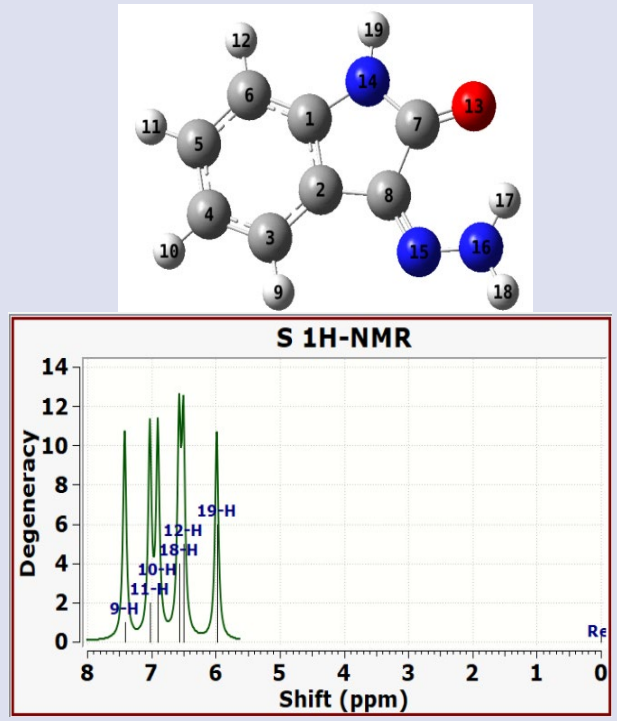


Figure 4. The calculated ^{1}H-NMR spectrum of the compound S.

(Z)-3-hydrazineylideneindolin-2-one (isatin monohydrazone, S)

Yellow powdery substance, Yield %72. ^{1}H NMR (400 MHz, DMSO-D6) δ 10.63, 10.49 (d, J = 14.6 Hz, 1H), 9.49 (d, J = 14.7 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.10 (td, J = 7.7, 1.3 Hz, 1H), 6.92 (td, J = 7.6, 1.1 Hz, 1H), 6.81 (d, J = 7.7 Hz, 1H).

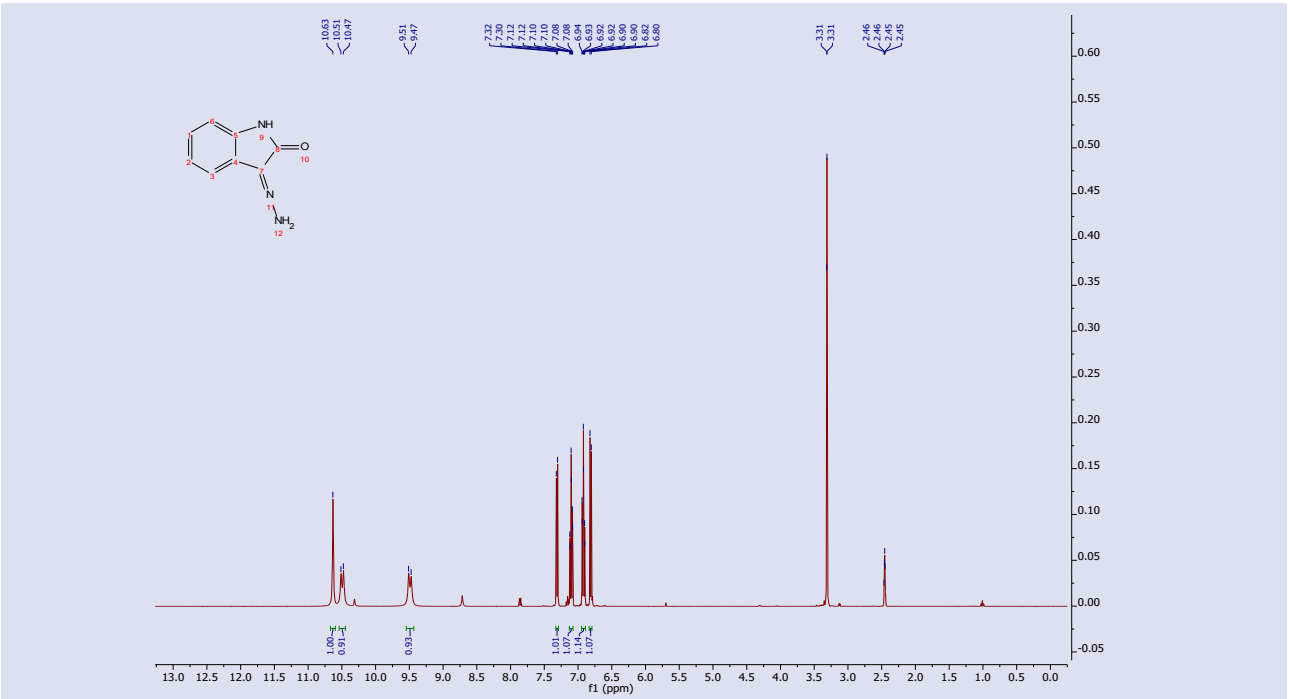


Figure 5. Experimental ^{1}H-NMR spectrum of the S compound.

IR Calculation

The IR spectra of compound S were calculated with the B3LYP/6-31G(d,p) level. The calculated IR spectrum is given in Figure 6. The frequencies obtained by calculation methods are the harmonic frequencies. A measurement factor of 0.967 was used to convert harmonic frequencies into anharmonic frequencies. The calculated anharmonic frequencies of S compounds and their labelling are given in Table 2.

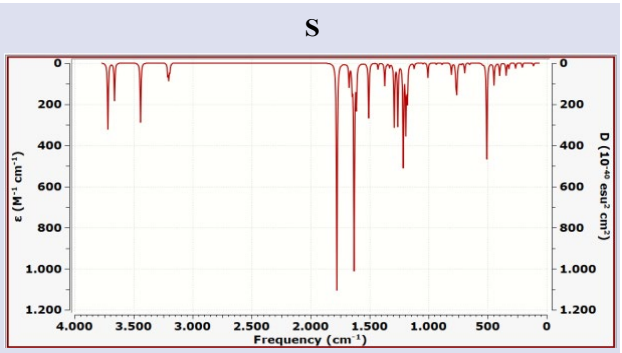


Figure 6. Calculated IR spectrum of the synthesized compound S.

Isatin is a chemical structure containing -C=N-N2, -NH and =O functionals in its monohydrazone structure. νN-H (3541.3 cm^{-1}) vibration refers to the stretching vibration of the N-H bond. Amine (N-H) and amide (N-H) groups are usually seen between 3500-3300 cm^{-1}. This frequency indicates the presence of hydrazone (-NH-N=) or amide structure in the compound. νCaro-H (3087.7 cm^{-1}), the stretching vibration of the C-H bonds in the aromatic ring is seen in this region. C-H vibrations of aromatic compounds usually occur between 3100-3000 cm^{-1}. νC=O (1719.1 cm^{-1}) is defined as the stretching vibration of the carbonyl (C=O) bond.

Table 2. Calculated frequencies (cm^{-1}) and their labelling for compound S.

Modes	Calc.
νN-H	3541.3
νC-H(aro)	3087.7
νC=O	1719.1
νC=C	1594.0
νC=N	1577.8
νC=C+ωCH	1458.2
νCN+ωNH+ ωCH	1381.6
νCN	1310.8
νNN	1248.9
ωCH +ωCH	1175.0
ωCH	1085.5

ν: stretching, δ: Scissoring, ω; Wagging

It is usually seen between 1700-1750 cm^{-1} and indicates the presence of ketone, amide or acid carbonyl group in the compound. Here, the value of 1719.1 cm^{-1} shows the typical vibration of the carbonyl group in the isatin structure. νC=C (1594.0 cm^{-1}) is defined as the stretching vibration of the double bonds (C=C) in the aromatic ring. C=C vibrations of aromatic systems are found between 1600-1450 cm^{-1}. This value confirms that the compound has aromatic character. νC=N (1577.8 cm^{-1}), the stretching vibration of the C=N bond is seen in this region. Values between 1600-1550 cm^{-1} indicate the presence of hydrazone (-C=N-NH2) or imine (-C=N) groups. The vibration of the hydrazone (C=N) group in the isatin monohydrazone structure is observed here. νC=C + ωCH (1458.2 cm^{-1}), CH bending (wagging) vibrations are observed together with the stretching of the C=C bond. It is a frequently encountered mode in aromatic systems. νCN + ωNH + ωCH (1381.6 cm^{-1}), NH and CH bending (wagging) vibrations are observed together with C-N stretching vibrations. This supports the presence of hydrazone (-C=N-NH2) or amine (-NH2) functional groups in the compound. νCN (1310.8 cm^{-1}), C-N stretching vibration is generally observed between 1300-1200 cm^{-1}. This value represents the C-N bonds found in the hydrazone (C=N-NH2) structure. νNN (1248.9 cm^{-1}), stretching vibration of N-N bond, especially seen in hydrazone and azine (N-N) structures. This value is a strong indicator of hydrazone structure. ωCH + ωCH (1175.0 cm^{-1}), CH bending (wagging) vibrations in aromatic ring are seen in this region. CH bending vibrations are common between 1200-1100 cm^{-1}. ωCH (1085.5 cm^{-1}), aromatic CH bending (wagging) vibration is observed as a lower frequency mode.

Frontier Molecular Orbitals

HOMO and LUMO orbitals, also known as boundary molecular orbitals, are when a molecule interacts with another molecule. HOMO, the highest occupied molecular orbital and LUMO, the lowest unoccupied molecular orbitals are used in quantum chemical parameters studies. These orbitals are comparable in their ability to donate and gain electrons. The HOMO orbital represents the electron donating potential. The data show that electron exchange is easy by donating electrons, and the energy gap between the LUMO orbital energy and the HOMO and LUMO orbitals. To indicate the chemical state of a molecule, the energy difference between the HOMO and LUMO orbitals is looked at. When this difference is calculated, information about the stability of the molecule is obtained. It is a pioneer in experimental studies by obtaining theoretical ideas with quantum mechanical studies. With HOMO and LUMO molecular orbitals, inferences can be made about inhibitory reactive sites. B3LYP/6-31G(d,p) level in Figure 7 shows the boundary molecular orbitals of S [22,23].

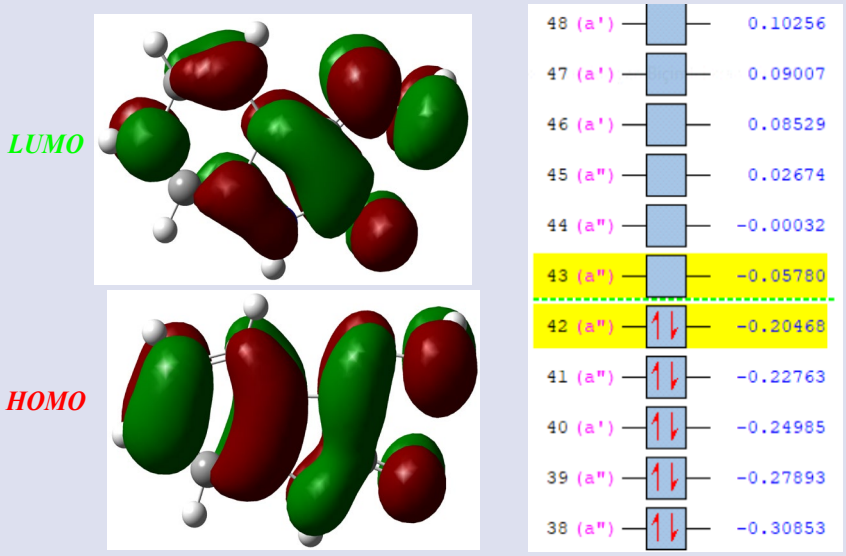


Figure 7. Frontier molecular orbital contour diagrams of S.

As seen in Figure 7, the regions shown in green and red indicate that the electron is localized. LUMO vacant orbitals gain electrons in the red and green portions of the molecule. The HOMO filled orbitals define the electron donating sites in the molecule.

Molecular electrostatic potential (MEP) maps

It provides information about the reactivity of that molecule by showing the same or different colors in each region of the molecule. Electrophilic and nucleophilic attack regions of molecules can also be viewed from MEP maps. In addition, MEP maps are used about the electrostatic potential data of the molecule, the shape of the molecule and the size of the molecule. The colors used to define electrostatic potentials and the order of their potentials are from small to large; red-orange-yellow-green-blue [24,25].

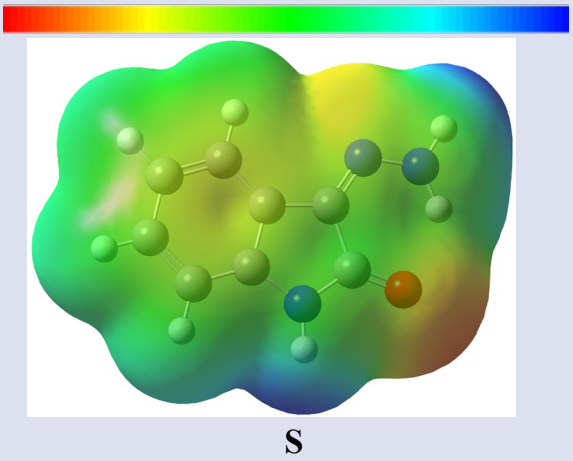


Figure 8. MEP map of synthesized S.

The green areas on the MEP map are neutral regions. Electron donating groups such as -C=N-NH_2, NH in the S compound, for example =NH-N=, NH are positively charged and their presence makes that region poor in terms of electrons. Also shown in blue. These synthesized compounds are shown in yellow and red when looking at the MEP map. The presence of oxygen in the -C=O group is negatively charged and electron rich regions. Therefore, red regions are active regions. MEP maps gave results consistent with contour diagrams of HOMO and LUMO boundary molecular orbitals.

Molecular Docking Studies

The molecular docking method is used in many fields of chemistry and cancer research. Computational studies are a priority in drug design. The molecular docking method is used to understand binding energies and ligand-receptor interaction between proteins. For many types of cancer, the selected target protein can be bound by the binding energy between the selected protein and the compounds studied by molecular docking. The selected cancer cell matches the target protein derived from the protein database [26]. The effect and biological activities of different substituents will be determined by docing studies. The synthesized S is isatin, an organic compound derived from indole. A molecular docking study was performed with target proteins PDB ID= 1M17 [27] and PDB ID= 3HY3 [28] corresponding to the MCF-7 cell line. Docking calculations were performed with DockingServer [29]. Est. between the studied isatin monohydrazone and target proteins. Free Energy of Binding, Est. Inhibition Constant, Ki, vdW + Hbond + desolv Energy, Total Intermolec. Energy and Interact. Surface is given in Table 3.

Additionally, the interaction poses between the synthesis compound and target proteins are given in Figure 9.

Table 3. Docking results between isatin monohydrazone compound and target proteins.

Docking results	1M17	3HY3
Est. Free Energy of Binding (kcal/mol)	-5.70	-5.76
Est. Inhibition Constant, Ki (µM)	65.97	59.50
vdW + Hbond + desolv Energy (kcal/mol)	-5.65	-5.83
Total Intermolec. Energy	-6.00	-6.06
Interact. Surface	458.004	494.986

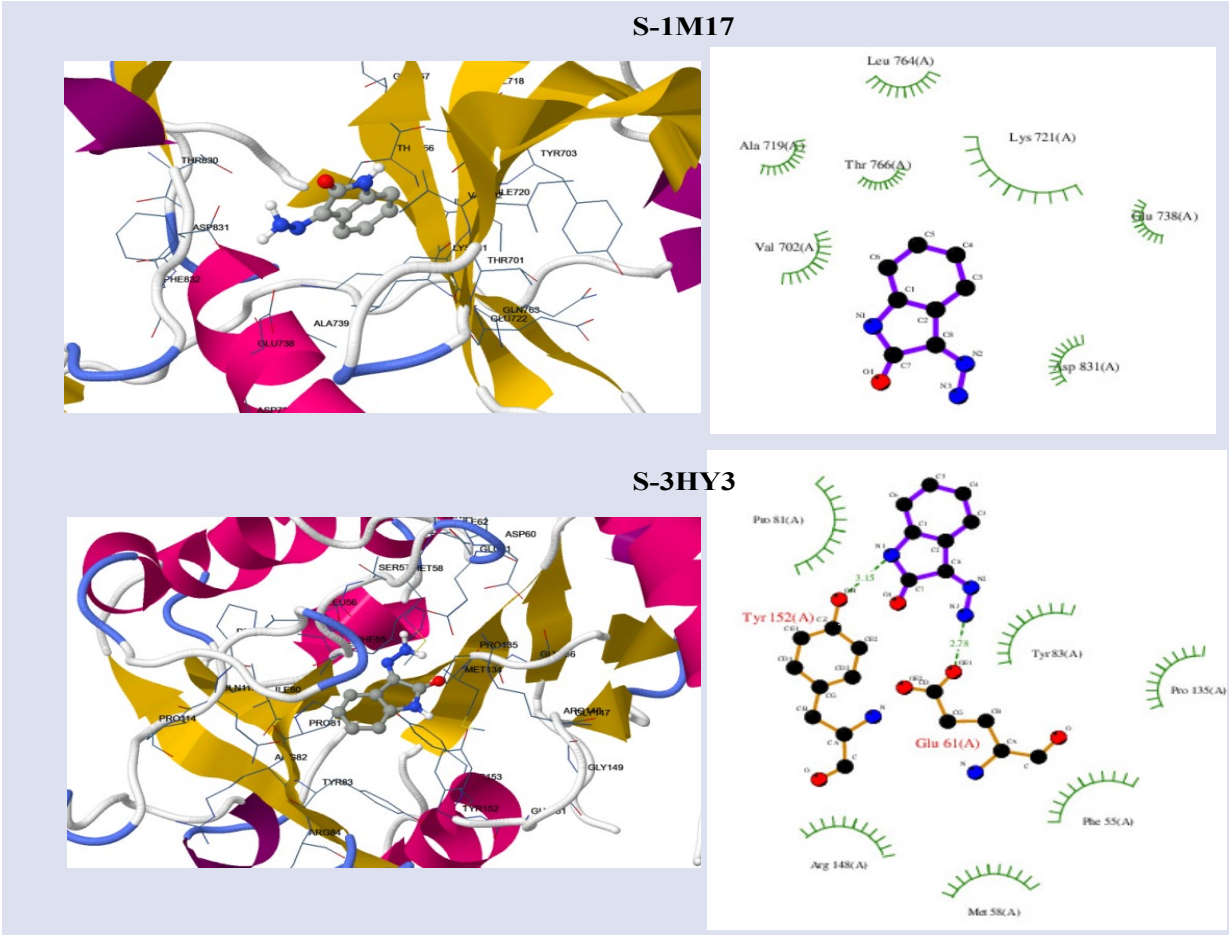


Figure 9. Interaction modes between ligand and protein.

According to the docking results given in Table 3, compound S shows that it is active against breast cancer. The greater the binding energy in absolute value, the higher its anticancer activity. Similar trends are vdW + Hbond + desolv Energy (kcal/mol) and Total Intermolec. It is the same for energy values. When examined in general, large differences in the activity of molecules with small volumes that do not contain functional groups may not be expected. The binding energy between the S molecule and the 1M17 target protein is -5.70 kcal/mol, and the binding energy between the 3HY3 target protein is -5.76 kcal/mol. Although there is not much difference between the activities against different protein sequences of the cancer cell, the activity against the 3HY3 target protein is higher. Considering the interaction poses given in Figure 6, the H-bond between the S molecule and the 3HY3 target protein is noteworthy. The binding energy of 3HY3 with the target protein may have increased due to the energy of the H-bond. The S molecule interacts polarly with amino acid residues LYS721, GLU738 and ASP831 of the 1M17 target protein. It makes hydrophobic interactions with amino acid residues VAL702, ALA719 and LEU764. The nitrogen atom of the S molecule formed an H-bond with the GLU61 and TYR152 amino acid residues of the 3HY3 target protein. In addition, it interacts polarly with GLU61, ARG148 and TYR152, and hydrophobicly with MET58 and PRO81. As a result, compounds that can be synthesized with the S molecule can be evaluated biochemically.

Conclusion

The synthesized isatin monohydrazone (S) was synthesized and examined by computational chemistry method. Starting from the widespread use of Density functional theory (DFT), which is a computational chemistry method, to support experimental data and correlate the biological activities of the molecule, its relationship with experimental data was also examined by applying the quantum chemical calculation method. Contour diagrams and molecular electrostatic potential maps (MEP) of the synthesized S were visualized. In the MEP map, it was determined that oxygen atoms were electron withdrawing regions. Nitrogen regions were determined to be electron donor regions. Structural characterization of compound S was determined by both experimental and computational ^{1}H-NMR chemical shift. Their activities against different protein sequences of breast cancer were examined by molecular docking. The results obtained showed that it has activity and can be used as a starting material for new molecules.

Conflicts of interest

The authors have made the following contributions to this article. Ceylan Alkaya Yıldız: Methodology, Investigation. Sultan Erkan: Writing, Methodology, Investigation.

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