

## A NEW ORGANIC COMPOUND WITH MEDICINAL AND COMPUTATIONAL APPROACHES: 2-(((2-BROMOPHENYL)IMINO)METHYL)-4-NITROPHENOL

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### Abstract

*In this study, a Schiff base compound named 2-(((2 bromophenyl)imino)methyl)-4-nitrophenol was synthesized and characterized by X-ray diffraction spectroscopy. The synthesized compound was studied to reveal its molecular structure and interactions, electronic properties, physicochemical, pharmacokinetic and medicinal properties. Potential biological targets for bimolecular activity were also determined, and docking studies were performed on the identified targets. The title compound showed high binding efficacy to tankyrase-2, a transferase enzyme. The calculated docking score of the complex with the title compound was found to be -9.158 kcal.mol<sup>-1</sup>. In addition, the title compound was found to be a potent ligand for several targets, including secretase, hydrolase, kinase, transferase, HCV, influenza, and tuberculosis.*

**Keywords:** brominated Schiff base, DFT, docking, ADME, FMOs

### 1. INTRODUCTION

Schiff bases were first synthesized in 1864 by the German chemist Hugo Schiff through the reaction between primary amines and carbonyl compounds. Thus, these compounds are named after him and are also known as imines or azomethine compounds. Schiff bases have the general formula R<sup>2</sup>C=NR', where R' must differ from a hydrogen atom [1]. Schiff base compounds are known for their biological and therapeutic activities. They show anticancer, antibacterial, antiviral, and antifungal properties [2]. To rapidly predict outcomes, reduce costs and time, and assess risks, in silico drug design is an effective method. The most critical issue of an in silico method is high predictability, especially when used at the beginning of drug development [3]. A variety of tools have been developed for ADME [4-6], and toxicity prediction [7], and target identification [8-10]. Scientists use density functional theory (DFT) in many fields to determine and predict molecular properties. It can be used for independent studies and comparative studies of experimental results. DFT techniques can be used with high accuracy to determine the studied compounds' geometrical, electrostatic, and spectroscopic properties [11].

### 2. MATERIALS AND METHODS

#### 2.1 Chemicals

The chemicals used for the synthesis reaction were supplied by commercial vendors.

#### 2.2 Software and web tools

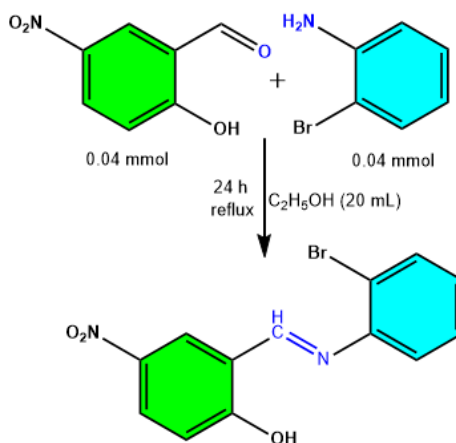
**X-ray diffraction:** A STOE IPDS 2 instrument was used for X-ray data collection. SHELX program [12] was used to solve and refine the structure. The CIF file of the title compound was prepared using PubCIF.

**DFT studies:** Optimized structure, MEP surface, and FMOs of the title compound were obtained using the DFT method [13] at the B3LYP- 6-311 G (d, p) level of theory.

**ADME and target identification:** ADME predictions were performed using the SwissADME tool [4]. LigTMap was used for target identification and docking studies [14].

### 3. EXPERIMENTAL PROCEDURE

The synthesis study of the title compound was carried out using the synthesis method described in [15]. The synthesis reaction is shown in **Fig. 1**.  $C_{13}H_9BrN_2O_3$ . Yield: 55%. SMILES: OC1=C(C=N\C2=CC=CC=C2Br)C=C(C=C1)[N+][O-]

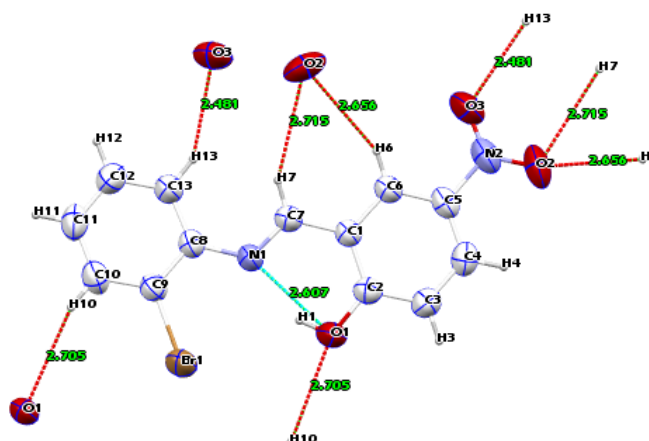


**Fig. 1.** Synthesis reaction of title compound

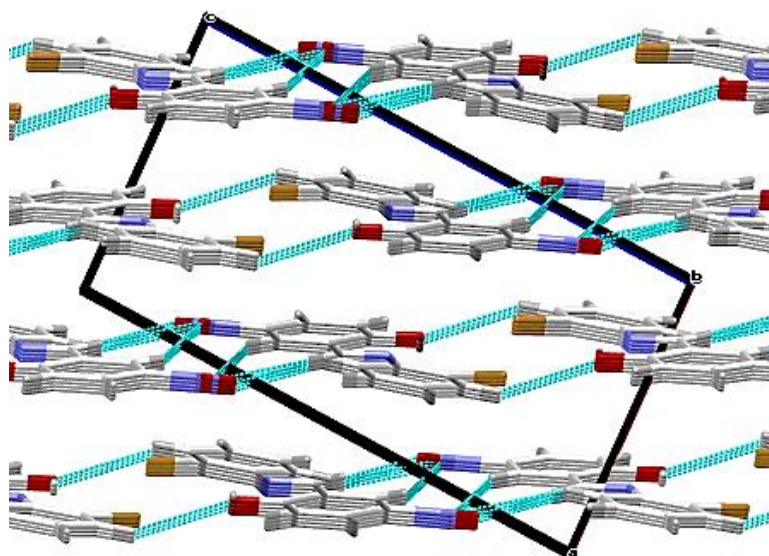
### 4. RESULTS AND DISCUSSION

#### 4.1 X-ray analysis and structural properties

X-ray solution of the title compound was performed using STOE IPDS 2 diffractometer. Orange and prism-shaped crystal with the dimensions of  $0.67 \times 0.42 \times 0.18$  mm<sup>3</sup> were selected for structure elucidation. SHELXT [16] and SHELXL [17] programs were used for structure solving, and refinement, respectively. All non-hydrogen atoms were refined anisotropically. The CIF file of the title compound was created with WinG [18] and finished using PubCIF. The other crystallographic parameters for further crystallographic data can be found at CCDC 2211898. Crystal data, data collection, and refinement parameters are listed in **Table 1**. An intramolecular hydrogen bond (**Table 2**) was determined between H1 and N1 atoms (see **Fig. 2** for the numbered model). The bond length was measured to be 1.86 Å. **Fig. 2** displays intermolecular hydrogen bonds and interacted atoms, together with bond lengths. An arrangement section from the crystal lattice, including the unit cell, is shown in **Fig. 3**.



**Fig. 2.** Molecular representation of title compound with the numbered and ellipsoid scheme (50% probability level), and intra/intermolecular interaction points



**Fig. 3.** View of molecular self-assembly with the capped stick model in crystal lattice and unit cell.

| Crystal Data                            |                                                                | Data Collection                                    |                       |
|-----------------------------------------|----------------------------------------------------------------|----------------------------------------------------|-----------------------|
| CCDC deposition number                  | 2211898                                                        | Diffractometer                                     | STOE IPDS 2           |
| Chemical formula                        | C <sub>13</sub> H <sub>9</sub> BrN <sub>2</sub> O <sub>3</sub> | $\theta$ min-max for data collection (°)           | 2.3-26.5              |
| Formula weight                          | 321.13                                                         | Index ranges; h, k, l                              | -9/9, -14/14, -17/17  |
| Temperature (K)                         | 296                                                            | Measurement method                                 | Rotation method scans |
| Wavelength (Å)                          | 0.71073                                                        | Measured reflections                               | 18894                 |
| Crystal system                          | monoclinic                                                     | Independent reflections                            | 2566                  |
| Space group                             | P2 <sub>1</sub> /c                                             | Reflections with I > 2 $\sigma$ (I)                | 2202                  |
| $a \neq b \neq c$ (Å)                   | 7.60, 11.58, 14.05                                             | Absorption correction                              | X-RED32 [19]          |
| $\alpha = \gamma \neq \beta$ (°)        | 90, 90, 94.21                                                  | $T_{\text{min-max}}$                               | 0.234-0.596           |
| Crystal size (mm)                       | 0.67 x 0.42 x 0.18                                             | $R_{\text{int}}$                                   | 0.061                 |
| Z                                       | 4                                                              | Refinement method                                  |                       |
| Volume, V (Å <sup>3</sup> )             | 1235.37                                                        | Refinement method                                  | on F <sup>2</sup>     |
| $\mu$ (mm <sup>-1</sup> )               | 3.33                                                           | No of parameters                                   | 176                   |
| F (000)                                 | 639.61                                                         | $R [F^2 > 2\sigma(F^2)]$                           | 0.043                 |
| $\theta$ (°)                            | 2.3-27.4                                                       | $wR(F^2)$                                          | 0.091                 |
| Calculated density (Mgm <sup>-3</sup> ) | 1.727                                                          | GooF=S                                             | 1.12                  |
| Color and shape                         | Orange, prism                                                  | $\Delta\rho_{\text{min-max}}$ (e Å <sup>-3</sup> ) | -0.41/0.55            |

**Table 1.** Crystallographic data obtained by the CIF file of title compound

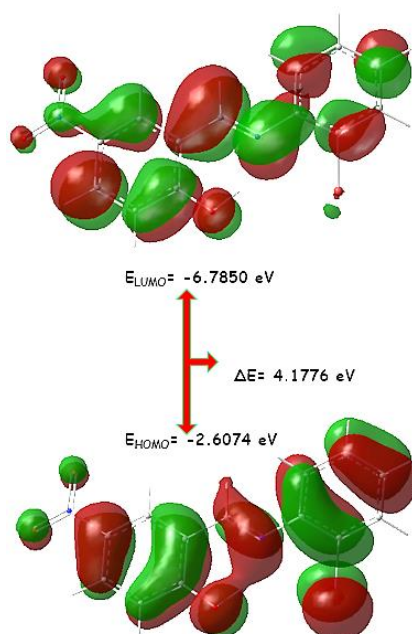
|                   |          |              |              |                |
|-------------------|----------|--------------|--------------|----------------|
| D—H $\cdots$ A    | D—H      | H $\cdots$ A | D $\cdots$ A | D—H $\cdots$ A |
| O1—H1 $\cdots$ N1 | 0.82 (4) | 1.86 (5)     | 2.607 (4)    | 152 ( )        |

**Table 2.** Hydrogen bond geometry list for title compound (Å, °)

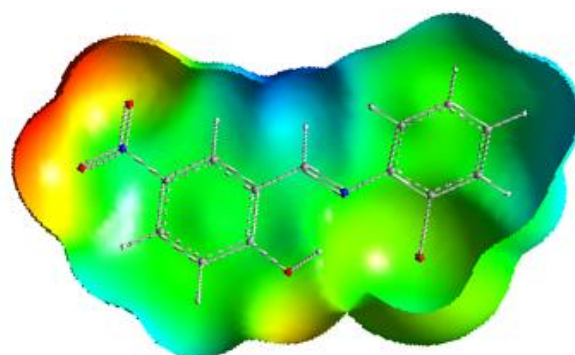
#### 4.2 Frontier molecular orbitals (FMOs) and molecular electrostatic potential (MEP)

The electronic and surface properties of the title compound were examined using FMOs and MEP surface. Both pictograms and calculations were performed by the DFT method at B3LYP 6-311 G (d, p) level. **Fig. 4** shows HOMO and LUMO orbitals, and **Fig. 5** shows the MEP surface of the title compound. As important factors in the determination of molecular reactivity, the energies of HOMO, LUMO, and HOMO-LUMO band gap ( $\Delta E$ ) were calculated to be -2.6074, -6.7850, and 4.1776, respectively. The high band gap value (4.1776) shows the title compound's hard, chemically, and kinetically stable nature. The positional changes in the HOMO and LUMO lobes are related to electronic transitions within the title molecule.

The MEP surface's red, blue, and green regions show negative, zero, and positive electrostatic potentials. These areas are determining factors for molecular interaction points and the electrophilic and nucleophilic properties of the investigated molecules. The regions with the highest (red) and lowest (blue) electron density are related to the molecules' high electrophilic and nucleophilic reactivity. For the title compound, oxygen atoms (O1, O2, and O3) are colored red, which means these atoms behave as electrophilic reactivity centers. The hydrogen atom belonging to the azomethine group (H7) is colored dark blue and acts as a nucleophilic reactivity center.



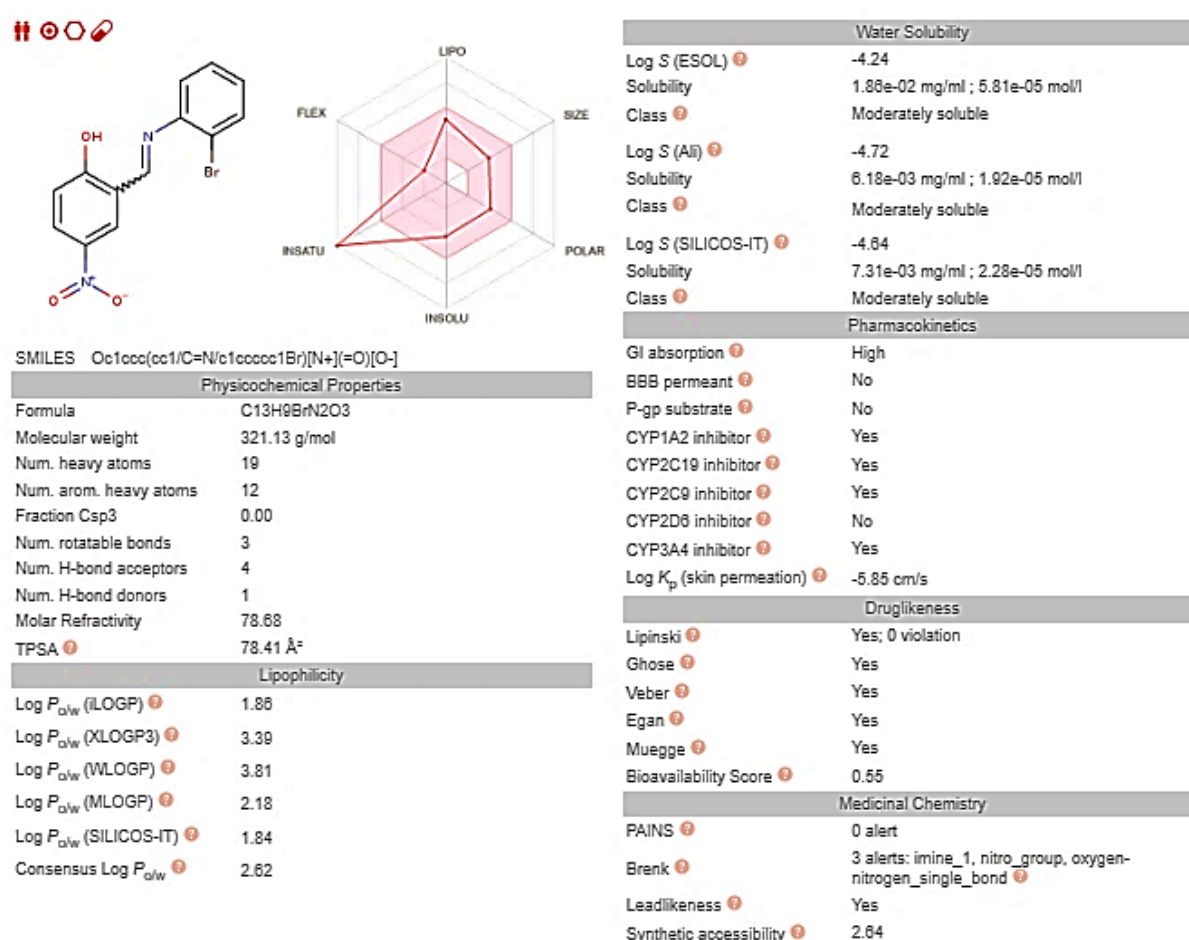
**Fig. 4.** HOMO and LUMO orbitals of title compound



**Fig. 5.** MEP surface of title compound.

#### 4.3 Physicochemical descriptors and pharmacokinetics properties for medicinal chemistry

Physicochemical descriptors, ADME parameters, pharmacokinetics, drug-likeness, and medicinal chemistry properties of the title compound were summarized in **Table 3**. These calculations and predictions were performed using the SwissADME server. A radar chart of physicochemical properties was shown in **Table 3**. As can be seen on this hexagon, the INSATU value of the title compound showed a positive deviation from the domain because the sp<sup>3</sup> fraction value is zero. The other physicochemical parameters remained in the optimal range. Water solubility (logS) was determined in the range of -4.24 to -4.72 mol/L. High gastrointestinal absorption was predicted, while BBB permeation remained negative. For 5CYPs, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP2D6, the title compound showed inhibitory efficacy apart from CYP2D6. The title compound obeyed all the drug-likeness rules. PAINS [20] alerts were not detected, while Brenk [21] reported three structural alerts. The title compound was classified as a potential lead molecule.



**Table 3.** Physicochemical and pharmacokinetics properties of the title compound.

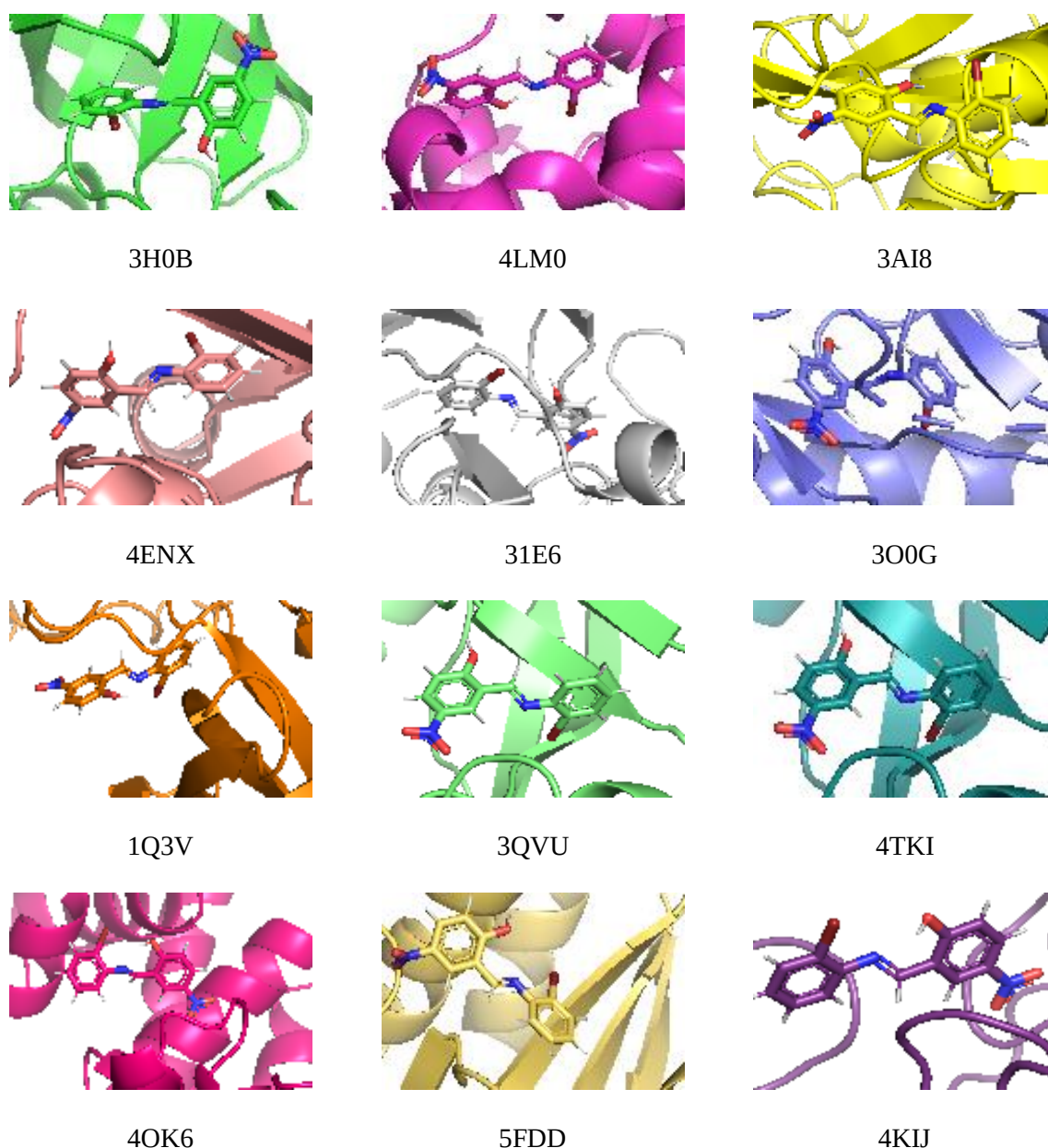
#### 4.4 Molecular docking experiments

Molecular target prediction and molecular docking experiments were performed using an online server, LigTMap. LigTMap computes putative targets for the studied ligands in 17 target classes, including human and disease targets. According to the structure-based drug design model, 12 potential targets were identified for our compound. These targets, their PDB IDs, ligand and binding similarity scores, and docking scores are listed in **Table 4**. **Fig. 6** shows the binding pose of the title compound with the indicated targets. By the obtained results, the title compound has been found functional for secretase, hydrolase, kinase, transferase, HIV, influenza, and tuberculosis targets. The lowest activity among the

investigated targets was observed for cathepsin B (docking score/DS: -4.133 kcal/mol) which belongs to the hydrolase class, whereas the highest activity was determined for tankyrase 2 with a docking score -9.158 kcal/mol. This order is followed by cell division protein kinase 5 (DS: -8.019 kcal/mol), a serine/threonine kinase (PIM1) (DS: -7.634 kcal/mol), sulfotransferase 1A1 (DS: -7.463 kcal/mol), cell division protein kinase 2 (DS: -7.325 kcal/mol), cAMP and cAMP-inhibited cGMP 3',5'-cyclic phosphodiesterase 10A (DS: -7.085 kcal/mol). The targets mentioned above are related to the various disease including cancer [22], neurotoxicity and neurodegeneration [23]. As a result, the title compound can be recommended for further laboratory test on the related targets.

|    | Target Name                                                     | PDB ID | Target class   | Ligand name | Ligand similarity score | Binding similarity score | LigTMap score | Predicted affinity (-logM) | Docking score (PSOVina2, kcal/mol) |
|----|-----------------------------------------------------------------|--------|----------------|-------------|-------------------------|--------------------------|---------------|----------------------------|------------------------------------|
| 1  | Beta-secretase 1                                                | 3H0B   | Beta secretase | B35         | 0.431                   | 0.188                    | 0.358         | 5.265                      | -6.749                             |
| 2  | cAMP and cAMP-inhibited cGMP 3',5'-cyclic phosphodiesterase 10A | 4LM0   | Hydrolase      | 5NI         | 0.418                   | 0.2                      | 0.352         | 4.99                       | -7.085                             |
| 3  | Cathepsin B                                                     | 3AI8   | Hydrolase      | HNQ         | 0.472                   | 0                        | 0.331         | 4.99                       | -4.133                             |
| 4  | Serine/threonine-protein kinase pim-1                           | 4ENX   | Kinase         | Z20         | 0.489                   | 0.4                      | 0.462         | 5.927                      | -7.634                             |
| 5  | Cell division protein kinase 2                                  | 31E6   | Kinase         | 2BZ         | 0.422                   | 0.25                     | 0.37          | 5.927                      | -7.325                             |
| 6  | Cell division protein kinase 5                                  | 3O0G   | Kinase         | 3O0         | 0.41                    | 0.273                    | 0.369         | 5.927                      | -8.019                             |
| 7  | Glycogen synthase kinase-3 beta                                 | 1Q3V   | Kinase         | ATU         | 0.414                   | 0.1                      | 0.32          | 5.927                      | -6.327                             |
| 8  | Sulfotransferase 1A1                                            | 3QVU   | Transferase    | NPO         | 0.54                    | 0.231                    | 0.447         | 6.208                      | -7.463                             |
| 9  | Tankyrase-2                                                     | 4TKI   | Transferase    | 33E         | 0.407                   | 0.158                    | 0.333         | 6.208                      | -9.158                             |
| 10 | Serine protease NS3                                             | 4OK6   | HCV            | 2T7         | 0.443                   | 0                        | 0.31          | 4.869                      | -6.084                             |
| 11 | Polymerase acidic protein                                       | 5FDD   | Influenza      | 4P8         | 0.521                   | 0.1                      | 0.394         | 5.065                      | -6.237                             |
| 12 | 3-dehydroquinate dehydratase                                    | 4KIJ   | Tuberculosis   | KIJ         | 0.475                   | 0.2                      | 0.392         | 4.819                      | -6.848                             |

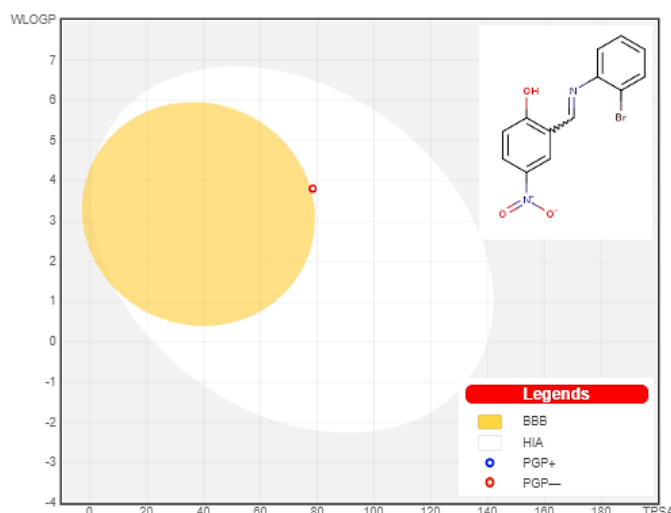
**Table 4.** Docking scores and other parameters of title compound with the predicted targets.



**Fig. 6.** The docking poses the title compound with its potential targets.

#### 4.5 BOILED-Egg

The BOILED-egg model belonging to the title compound is shown in **Fig.7**. Daina and Zoete [24] developed this model to understand BBB permeability and intestinal absorption of molecules. It works by calculating two physicochemical parameters, lipophilicity (WLOGP) and polarity (TPSA). The red cycle in **Fig. 7** indicates the location of the compound under study and provides information about the BBB permeability and GI absorption based on its place. The yolk area indicates a positive result for intestinal absorption and blood-brain barrier permeability, while albumin indicates a positive result only for GI absorption. If the red cycle places on the grey area, it means the investigated substance does not cross the blood-brain barrier and is not absorbed by the human intestine. The red cycle in **Fig. 7** is placed on the white area of the egg. The title compound does not pass the blood-brain barrier but can be absorbed by the human intestine.



**Fig. 7.** BOILED-Egg model of the title compound for BBB permeation and GI absorption.

## 5. CONCLUSIONS

In the current study, we reported the structure of a newly synthesized Schiff base ligand by X-ray analysis. We investigated its molecular and medicinal properties using computational approaches. At the end of our study, we determined its unit cell content ( $Z=4$ ), crystal system (monoclinic), and space group (P21/c). This structure has an intramolecular hydrogen bond between H1 and N1 atoms with a bond length of 1.86 Å. The title compound has electrophilic and nucleophilic centers, which play an important role in secondary interactions in molecular self-assembly and interactions with biological structures. The oxygen atoms in the nitro substituent have high electron density, and they behave as electron donors (nucleophile). The hydrogen atom in the imine carbon has low electron density, and it behaves as an electron acceptor (electrophile). The title compound was relatively found as hard and chemically stable molecule because its energy band gap is high. Medicinal properties of the title compound were found at the domain region regarding drug-likeness rules, physicochemical properties (except for INSATU), and GI absorption. However, this compound cannot cross the BBB, so it is not a useful molecule for neurodegenerative disease for future perspective. Many biological targets were determined for the title compound, and docking experiments were done with these targets. The title compound has shown highest efficacy for tankyrase-2 among the studied targets, and it has a docking score of  $-9.158 \text{ kcal.mol}^{-1}$ .

## SUPPLEMENTARY DATA

CCDC 2211898 deposits a supplementary information for the crystallographic details of title compound.

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