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Hirshfeld analysis, anticancer efficacy and molecular docking studies for ferrocenecarboxaldehyde oxime and ferrocene-based aldimine

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Ferrocenecarboxaldehyde oxime **1** and ferrocene-based aldimine **2** have been evaluated for their anticancer potentials against MCF-7 and T47D cell lines supported with molecular docking studies. Aldoxime **1** demonstrates an IC_{50} that is 2.4 to 1.5 times more potent than aldimine **2** against MCF-7 and T47D cancer cell lines, indicating its superior anticancer activity. Molecular docking analyses show that both compounds exhibit strong binding affinities to the EGFR receptor, a well-known cancer receptor. These findings highlight the significant potential of these compounds as effective anticancer agents. In addition, Hirshfeld analysis for molecular packing has been used to inspect the possible contacts which control the molecular packing of both compounds. For aldoxime **1**, the important N…H interactions contribute upto 10.1% while for aldimine **2**, the C...H (25.7%) and O...H (7.0%) contacts are the most significant.

Keywords: (*Z*)-Ferrocenecarboxaldehyde aldoxime, (*E*)-Ferrocene-based aldimine, Hirshfeld, Anticancer, Molecular docking

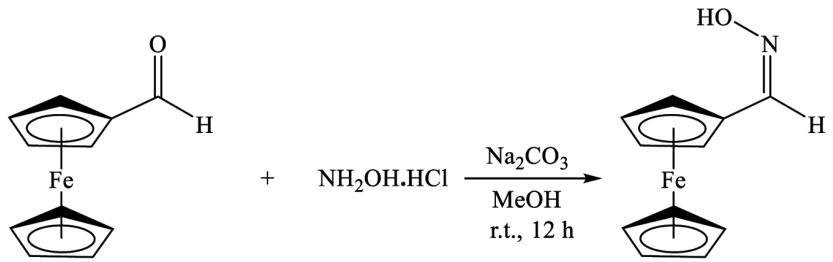
The conversion of carbonyl functionality into derived oximes is a known transformation in synthetic organic chemistry[1,2]. Oximes are organic compounds having the chemical formula, HO–N=CR^1R^2, which are reported as a potent class of organic compounds with various chemical applications[1,2]. Oximes are valuable and simple compounds bearing O–N=C functional group[3-5], which for instance, can be added to different coordinated-nitrile ligands, to furnish a number of nitrogen-containing complexes *e.g.* iminoacylate[6,7] or 1,3,5-triazapentadiene complexes[8]. Imines which are represented by the general formula, $R^3R^2C=NR^1$, are very important compounds due to their different applications in the field biology, pharmacy and medicine including antimicrobial, antifungal and anticancer applications[9-12]. On the other hand, materials containing ferrocene (Fc) moiety have been of considerable interest for their application in environmental remediation[13,14]. The synthesis of ferrocenecarboxaldehyde oxime and ferrocene-based imine and their use for the elimination of anionic methyl blue dye from wastewater have been reported by us[15]. Furthermore, Fc is a potent organometallic compound which have been combined with other reagents resulting in products with enhanced medicinal activity such as antimalarial and anticancer applications[16]. Drugs such as ferroquine were developed from Fc and chloroquine and tested as an antimalarial agent[17]. In the last years, many research groups have reported Fc and their related organometallic compounds as useful anticancer drugs when functionalized with other pharmaceutical scaffolds[18-22].

This current work attempts to assess the Hirshfeld surface analysis and the effects of (*Z*)-ferrocenecarboxaldehyde oxime **1** and (*E*)-ferrocene-based aldimine **2** on the anticancer impact on both MCF-7 and T47D cell lines with the aid of molecular docking studies.

Experimental Section

General methods

Solvents, reagents and instrumentation used in this work as well as synthesis, NMR and ESI-MS description and spectra of compounds **1** and **2** are indicated in Method S1 and Figs. S1-S4, respectively (Supplementary Information).



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Scheme 1 — Synthesis of (*Z*)-ferrocenecarboxaldehyde oxime **1**

Hirshfeld analysis

The topology analyses were performed using Crystal Explorer 17.5 program[23].

Assessment of IC_{50} of compounds 1 and 2 against human breast cancer cell lines

King Abdulaziz University's Tissue Culture Unit in the Department of Biochemistry provided two human breast cell lines, MCF-7 and T47D. These cell lines were cultured in T75 flasks with DMEM complete media (purchased from Gibco Life Technologies) for 24 h. The media included 10% fetal bovine serum (FBS) and 1% antibiotic. The flasks were then incubated at 37 °C with 5% CO_2 and 95% humidity. Once the cells reached 90% confluency, 4 mL of 0.25% Trypsin was added to detach the adherent cells, followed by a 5 min incubation at 37 °C. The cell pellets were resuspended in complete media and counted using a hemacytometer after staining with 0.4% trypan blue. Each well of a 96-well microplate was seeded with 7000 cells in 0.1 mL of complete media and incubated for 24 h. Attached cells in each well were treated with varying concentrations of compounds **1** or **2** (ranging from 6.25 to 200 µg/mL) dissolved in complete DMEM medium. Each concentration was tested in triplicate wells and incubated in a CO_2 incubator for 48 h. Subsequently, 100 µL of MTT medium was added to each well and incubated in the dark for 3 h, followed by the addition of 100 µL of DMSO and a 15 min incubation. The absorbance was measured using a Japanese Bio-RAD microplate reader set to 595 nm. The IC_{50} values, representing the concentrations of compounds **1** and **2** that inhibited 50% of cell growth, were determined using GraphPad Prism 9 software by plotting the percentage of viable cells against the compound concentrations[24,25].

Molecular docking

Protein Preparation

Chemical compounds were designed using ChemDraw and saved in SDF format. The target protein, Epidermal Growth Factor Receptor (EGFR) (PDB ID: 1M17), which is known for its expression in various cancers, was obtained from the Protein Data Bank in PDB format. Protein preparation was performed using BIOVIA Discovery Studio, which involved the removal of water molecules, ligands, and unwanted atoms. Molecular docking studies were performed using PyRx 0.8 software. The docking results were visualized and analyzed using BIOVIA Discovery Studio.

Molecular docking

Studies were performed to evaluate the interaction between the chemical compounds and the IAP protein using CB-Dock2 server. Visualization of the docking results was conducted using Biovia Discovery Studio.

Results and Discussion

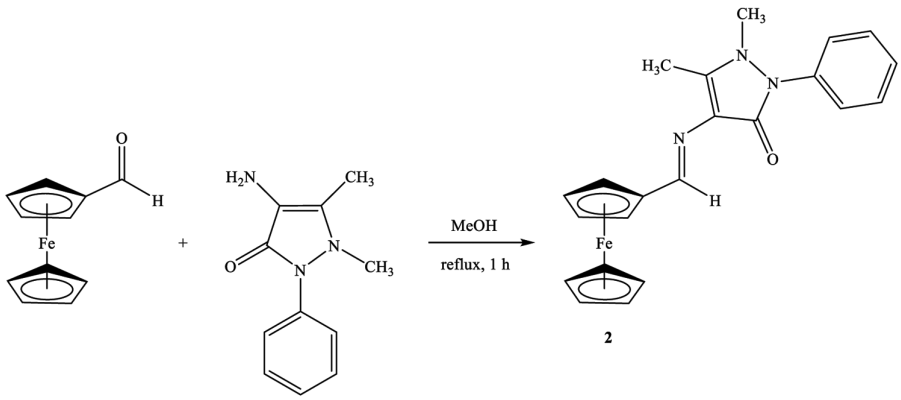
Synthesis of (*Z*)-ferrocenecarboxaldehyde oxime 1 and (*E*)-ferrocene-based aldimine 2

Treatment of ferrocenecarboxaldehyde with $NH_2OH.HCl$ in the presence of Na_2CO_3 in MeOH furnishes (*Z*)-ferrocenecarboxaldehyde oxime **1** (Scheme 1). Aldoxime **1** was characterized by IR, ^1H, ^{13}C and DEPT-135 NMR spectroscopy and also by single crystal X-ray [15]. Additionally, the structure of **1** was also confirmed by High resolution ESI^+-MS; the peak at *m/z*: 230.02 $[M+1]^+$ was detected and confirmed the molecular structure of **1**.

Treatment of ferrocenecarboxaldehyde with 4-aminoantipyrine in refluxing MeOH furnishes (*E*)-ferrocene-based aldimine **2** (Scheme 2). Aldimine **2** was characterized by IR, ^1H and ^{13}C NMR spectroscopy and also by single crystal X-ray [15]. Furthermore, the structure of **2** was also confirmed by High resolution ESI^+-MS; the peak at *m/z*: 400.11 $[M+1]^+$ was detected and confirmed the molecular structure of **2**.

Hirshfeld surface analysis

Exploration of the different intermolecular contacts which occur in the crystal structure is important for understanding the molecular packing in the crystal



Scheme 2 — Synthesis of (*E*)-ferrocene-based aldimine **2**

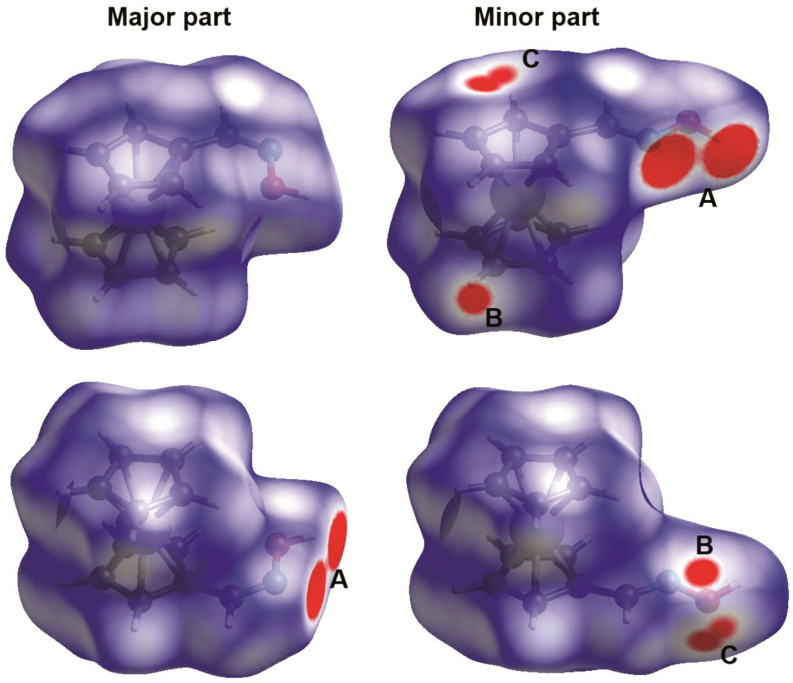


Fig. 1 — Hirshfeld d_{norm} maps for aldoxime **1**

structure. In this regard, Hirshfeld surfaces of the major and minor parts of aldoxime **1** are presented in Fig. 1. In the major part, there is only important N…H interactions which have short interaction distances of 1.961 Å (N1…H7). The percentage of the N…H contacts is 10.1% while the other contacts such as H…H (64.7%), C…H (19.4%) and O…H (4.9%) have less significance. The N…H contacts appeared as red spots in the d_{norm} map while all other contacts appeared as either blue or white colored regions indicating less significant interactions.

On the other hand, the minor part showed greater number of important interactions. In this part, there are important N…H, O…H and C…O contacts which are labelled as A to C, respectively in Fig. 1. Their percentages are calculated to be 9.2, 5.9 and 4.1%, respectively (Fig. 2). Also, these contacts appeared as red spots in the dnorm map and also sharp spikes in the fingerprint plot revealing their significance. The contacts N1…H7B (1.910 Å), O7B…H8 (2.356 Å), C3…O7B (3.009 Å) and C4…O7B (3.056 Å) are the most significant.

For aldimine **2**, the red spots in d_{norm} map are related to C...H (A) and O...H (B) contacts (Fig. 3). Both appeared as sharp spikes in the fingerprint plots revealing their importance. The H5A…H16C (2.163 Å), O1…H15C (2.418 Å), O1…H8A (2.463 Å), C11…H18A (2.633 Å) and C10…H18A (2.786 Å)

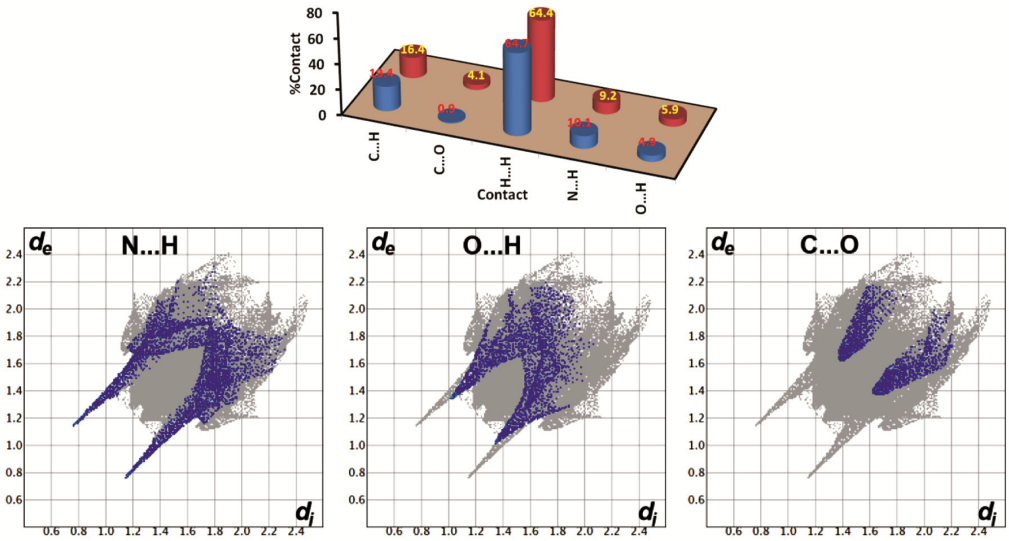


Fig. 2 — Fingerprint plots for the important contacts and their percentages in aldoxime **1**

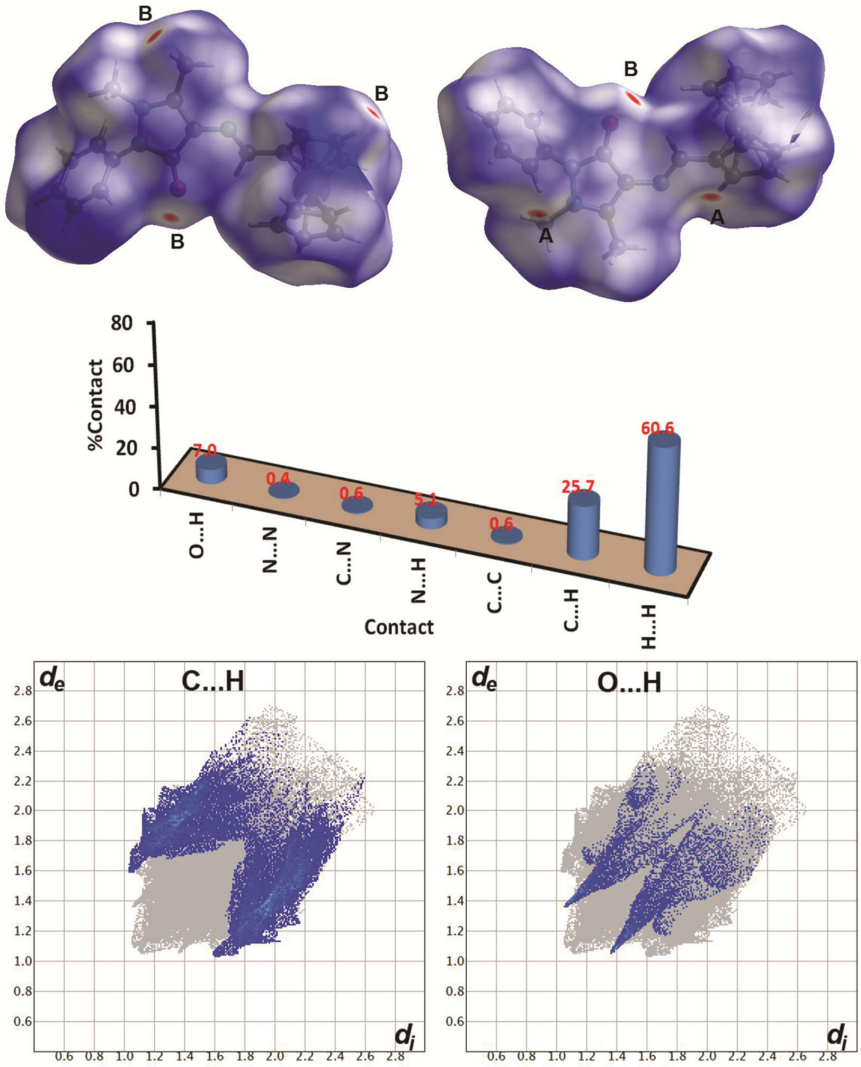


Fig. 3 — Hirshfeld analysis of aldimine **2**; C...H (**A**) and O...H (**B**)

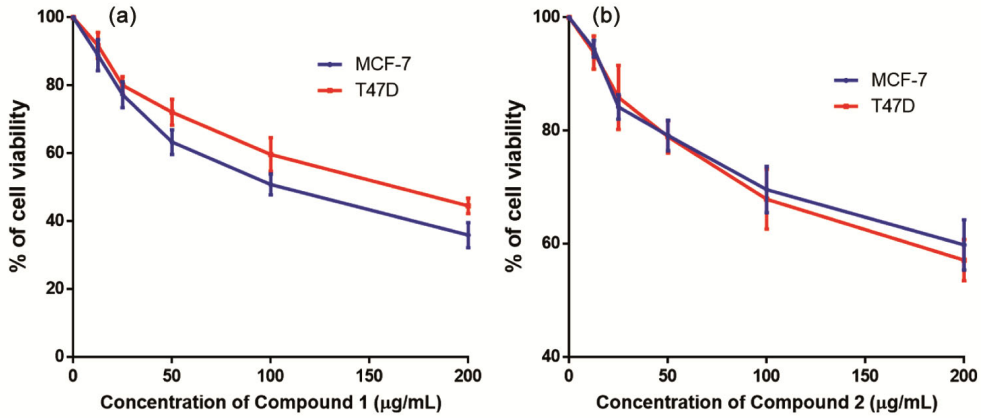


Fig. 4 — percentage of cell viability of compounds **1** and **2** against MCF-7 and T47D

Table 1 — IC_{50} of compounds **1** and **2** against MCF-7 and T47D

Compd	MCF-7		T47D	
1		428.053785		602.8351032
Range	87.82 - 109.5	383.3929975	125.5 - 160.7	509.4169505
IC_{50}	98.05	478.040688	142.1	713.7848127
2				
Range	203.4 - 285.0		191.3 - 261.8	
IC_{50}	240.7		223.8	

Table 2 — Docking scores of the tested compounds **1** and **2** against EGFR

Compd	Binding Affinity (kcal/mol)
1	–5.6
2	–8.4

are the most short intermolecular interactions in this case. The %C...H and O...H interactions are 25.7 and 7.0, respectively, while the most abundant interaction is the H...H contacts (60.6%). In both compounds no characteristic red/blue triangles in the shape index and no flat green area in curvedness indicating insignificant π-π interactions (Figs. S5-S6, Supplementary Information).

Anti-tumor effects of compounds 1 and 2 against MCF-7 and T47D cancer cell lines

MCF-7 and T47D human breast cancer cell lines were exposed to various concentrations (6.25-200 µg/mL) of compounds **1** and **2** for 48 h to evaluate cell viability. Although both cell lines are positive for estrogen receptors, MCF-7 primarily represents breast cancer of epithelial origin, while T47D consists of luminal breast cancer cells. The IC_{50} values, which represent the concentration needed for 50% inhibition, were found to be 98 µg/mL for MCF-7 and 240 µg/mL for T47D with aldoxime **1**, and 142 µg/mL for MCF-7 and 223.8 µg/mL for T47D with aldimine **2**. These results indicate that both compounds are more effective against MCF-7 compared to T47D, with compound **1** being 2.4 times and 1.5 times more effective against MCF-7 and T47D than compound **2**, respectively (Table 1 and Fig. 4).

Molecular docking

The molecular docking studies indicated that the tested compounds **1** and **2** exhibited significant binding affinities towards the Epidermal Growth Factor Receptor (EGFR) (Table 2). Notably, aldimine **2** showed the highest binding affinity with a binding energy of -8.4 kcal/mol, followed by aldoxime **1** with a binding energy of -5.6 kcal/mol. These findings suggest a strong interaction between the compounds and the target protein, indicating their potential as potent anticancer agents. Aldoxime **1** primarily formed Van der Waals, π-alkyl and salt bridge interactions (Fig. 5). In contrast, aldimine **2** formed various chemical bonds with the target protein with Van der Waals, π-sulfur, and π-alkyl interactions being the most prominent (Fig. 6).

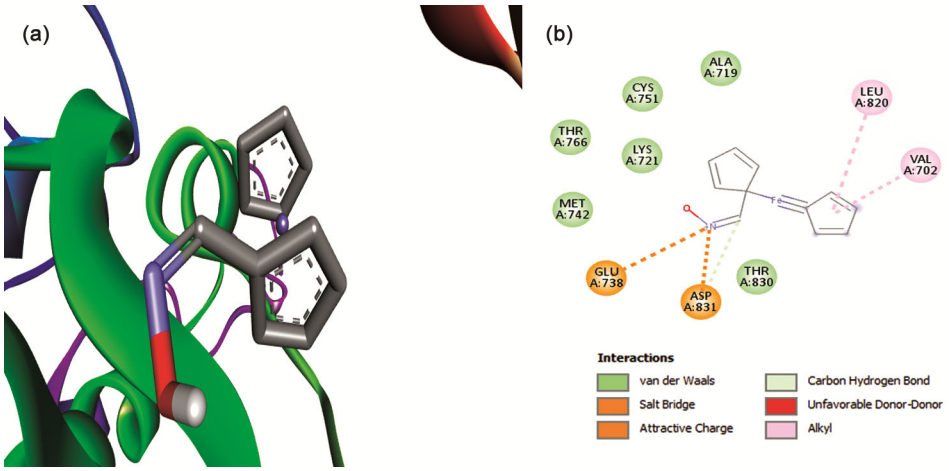


Fig. 5 — (**A**) shows the 3D interaction between the ligand **1** and the receptor EGFR. (**B**) shows the interacting atoms, and the bonds between the ligand and the receptor

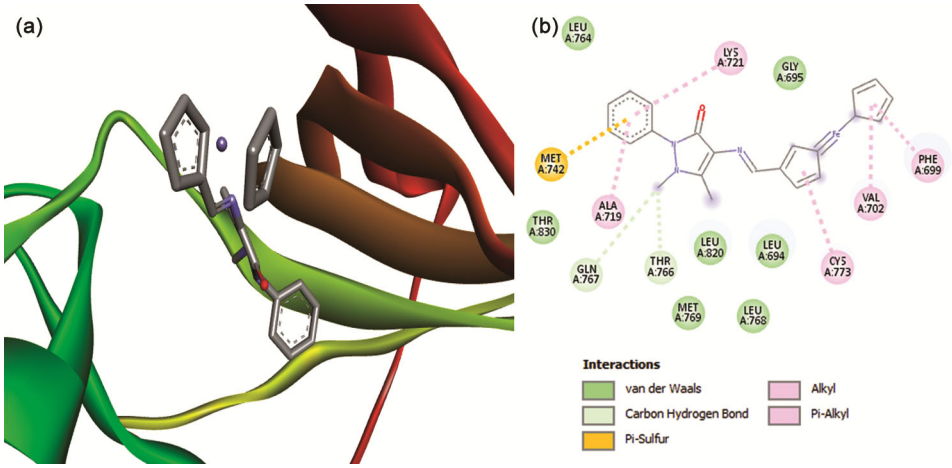


Fig. 6 — (**A**) shows the 3D interaction between the ligand **2** and the receptor EGFR. (**B**) shows the interacting atoms and the bonds formed between the ligand and the receptor

Conclusions

The supramolecular structure aspects of aldoxime **1** and aldimine **2** were described using Hirshfeld surface analysis. In the latter, the C...H (25.7%) and O...H (7.0%) contacts were the most significant. For aldoxime **1**, the N…H was the most important and contributed by 10.1% from the whole interactions occurred in this crystal structure. Compounds **1** and **2** showed potential *in vitro* for inhibiting tumor growth, with aldoxime **1** displaying greater antitumor efficacy against MCF-7 and T47D cell lines, being 2.4 and 1.5 times more effective than aldimine **2**, respectively. Molecular docking studies confirmed that both compounds strongly bind to the EGFR receptor, suggesting significant potential as anticancer agents. However, further *in vivo* studies are needed for preclinical testing to explore the drug's mechanisms of action or possible combinations with chemotherapy.

Supplementary Information

Supplementary information is available in the website https://nopr.niscpr.res.in/handle/123456789/58776.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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