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Synthesis, in-vitro and in-silico investigation of oxindole-containing Schiff base derivative as potential anticancer agents

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ABSTRACT

Herein, the transformation of oxindole into oxindole-containing Schiff base using diaminohexane as a linker for the development of drug-like molecules and their cytotoxicity against sixty human cancer cell lines are reported. However, synthesized compound 3a was successfully validated using analytical tools like FT-IR and ^{1}H and ^{13}C NMR. Moreover, the National Cancer Institute from the United States of America biologically tested against sixty selected human cancer cell lines. This synthesized compound 3a was found to be a strong drug against SNB-75 of central nervous system (CNS) cancer and UO-31 of renal cancer at 10 µM concentrations. After that, synthesized compound 3a was further analyzed to find out their pathway inhibition, which was conducted through the in-silico-based analysis as well. Consequently, docked complexes named HIF-1α-3a and HIF-1α-sunitinib showed the binding affinities of 5.5 kcal/mol and 4.9 kcal/mol, respectively. The aim of the proposed work is the discovery of anticancer drugs; such investigation was done as preliminary analyses.

KEYWORDS: *Oxindole, Schiff base, anticancer, molecular docking, NCI.*

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1. INTRODUCTION

Oxindole, a heterocyclic compound also known as isatin, features an indol-2,3-dione core that has garnered significant interest in medicinal chemistry due to its diverse pharmacological properties[1–3]. It is a ubiquitous heterocyclic scaffold present in numerous natural products and synthetic compounds exhibiting a broad spectrum of biological activities, including significant anticancer properties [4]. The structural motif of oxindole comprises a benzene ring fused to a five-membered pyrrole ring, with a carbonyl group at the C-2 position, and it is known for its tautomeric hydroxyl isomers[5]. This structural flexibility contributes to its diverse pharmacological profile, making it a promising core for the development of novel therapeutic agents. Specifically, the incorporation of oxindole into Schiff base derivatives, formed via the condensation of amines and carbonyl compounds, has garnered considerable attention due to the enhanced stability and tunable biological activities of the resulting imine linkage [6,7]. The strategic design of these oxindole-Schiff base conjugates often leverages the inherent reactivity of aldehyde compounds over ketones in condensation reactions, yielding less sterically hindered and more readily polymerizable products[8–11].This structural motif makes them versatile pharmacophores, widely investigated for their diverse biological activities including antimicrobial, antiviral, and anticancer properties [12,13].This versatility stems from their structural flexibility, allowing for facile modification and coordination with metal ions, which can significantly influence their physicochemical and pharmacological profiles. Moreover, the incorporation of heterocyclic and/or aromatic rings within the Schiff base scaffold, particularly when complexed with metals, has been shown to enhance their therapeutic potential, rendering them attractive candidates for novel drug development [14]. The nitrogen, oxygen, and sulfur donor atoms prevalent in these compounds facilitate their involvement

in crucial biochemical processes such as haloperoxidation, nitrogen fixation, and anticancer mechanisms [15]. Their broad spectrum of biological applications encompasses roles in the food and dye industry, agrochemicals, polymer science, catalysis, and analytical chemistry. However, oxindole is a bicyclic compound featuring a fused indole and lactam ring, serving as a core structure in various bioactive molecules. Several FDA-approved drugs incorporate the oxindole scaffold, notably likes “Sunitinib, toceranib and nintedanib”which are multitargeted receptor tyrosine kinase (RTK) inhibitor used in the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumors (GISTs) and an adjunctive treatment for Parkinson's disease, functioning as a selective, reversible monoamine oxidase B inhibitor, and an atypical antipsychotic and antidepressant used in the treatment of schizophrenia, bipolar disorder, and clinical depression, respectively (**Figure 1**)[16–20]. These drugs exemplify the therapeutic potential of the oxindole scaffold in developing treatments for various medical conditions.

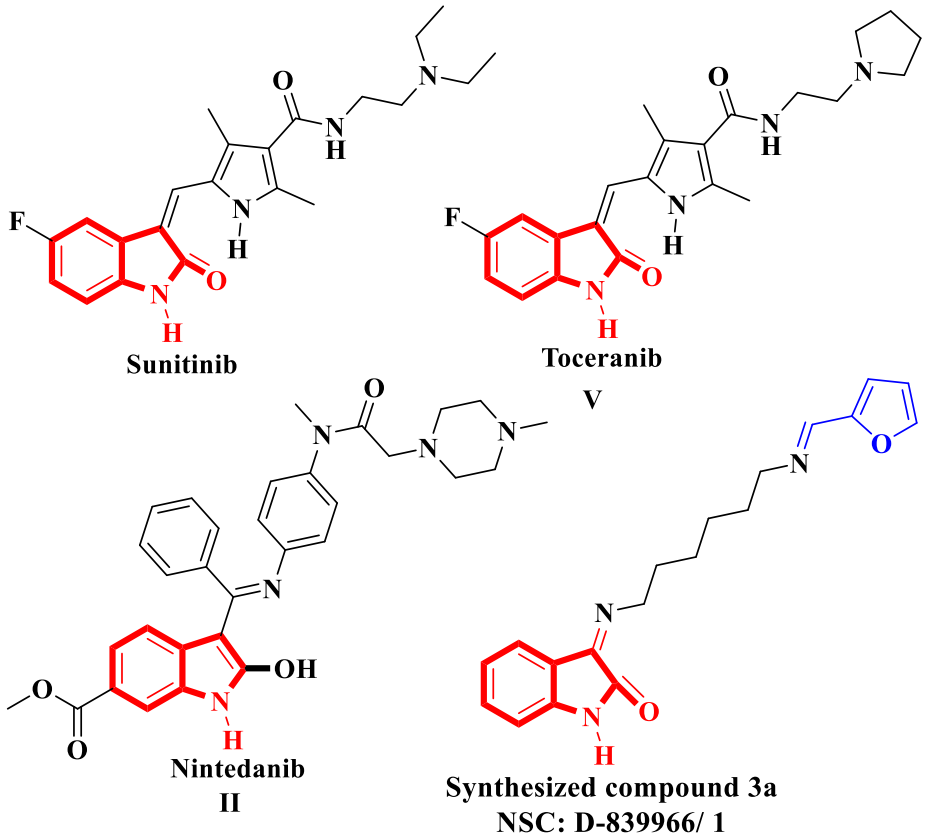
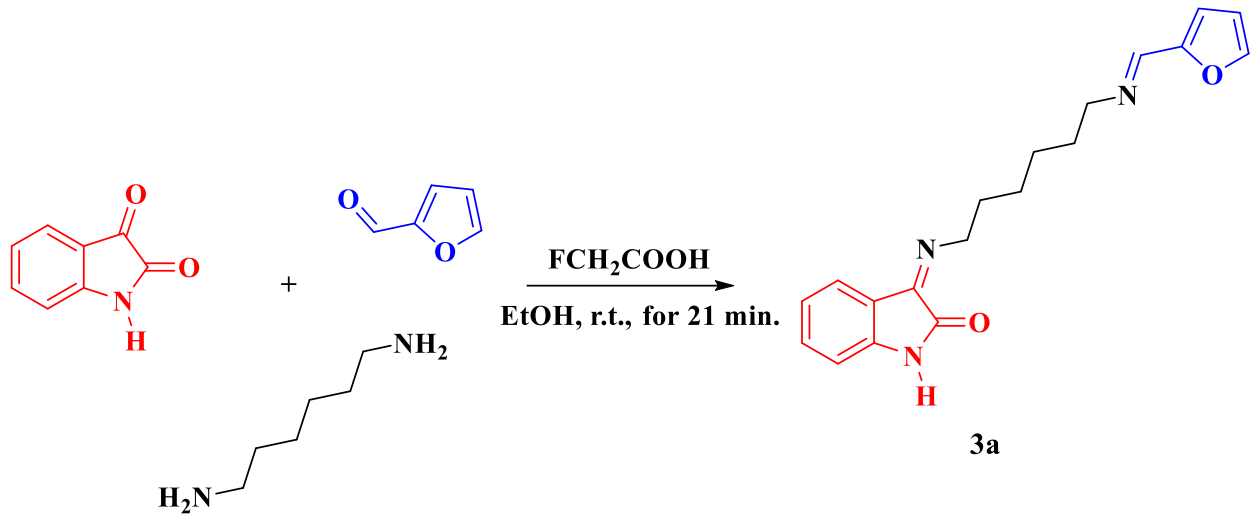


Figure 1.Functionalized C-3 oxindole-containing drugs

The synthesis of oxindole-containing Schiff base derivatives has garnered attention due to their promising anticancer potential, warranting further exploration of their biological activities.Furthermore, the identification of key structural features responsible for their activity could facilitate the design of more potent derivatives, ultimately improving therapeutic outcomes in cancer treatment. Therefore, we decided to the synthesis of 3-((6-(((E)-furan-2-ylmethylene)amino)hexyl)imino)indolin-2-one derivative (**3a**) and the anticancer activity was successfully evaluated by the National Cancer Institute from the United States of America, against sixty human tumor cells at the 10 M concentration. As per such screening result, those tumor cells showed the greater inhibition by dosing compound was further evaluated by the molecular docking analysis as preliminary investigation.

2. SYNTHESIS

In synthesis, participating active reactants named dioxindole, diaminohexane and furan-2-carbaldehyde were reacted in the presence of ethanol solvent at room temperature for approximately 21 minutes. Such reaction was catalyzed by fluoroacetic acid and formed 3-((6-(((E)-furan-2-ylmethylene)amino)hexyl)imino)indolin-2-one under nucleophilic elimination reaction (**Scheme 1**). The C-3 carbonyl group of oxindole has more activity than C-2 owing to tautomerization, while diaminohexane has two terminals primary amino groups which act nucleophile. Consequently, such nucleophiles (primary amines) attack on nucleus of carbonyl carbon in presence of acidic medium and getting bis-Schiff base oxindole compound. These reactivity of reactants were judge to compilation by the thin layer chromatography (TLC) using polar and non-polar (ethyl acetate and n-hexane) solvents and getting product was purified using column chromatography as well.



Scheme 1.Proposed reaction for the synthesis of oxindole-containing Schiff base derivative 3a

For characterization of this synthesized compound were done by the modern analytical techniques like FT-IR, ^{1}H NMR and ^{13}C NMR.Firstly, FT-IR (Fourier transform-infrared) was recorded with a KBr plate in the range between 500 and 3500 cm^{-1} to distinguish the characteristic frequencies for specific functional groups that were present in the synthesized compound. As per the FT-IR spectrum, stretching of secondary amine (>N-H) was considered at 3250 cm^{-1}, sp^{2} hybridized C-H stretching at 3110, sp^{3} hybridized C-H stretching at 2890 cm^{-1}, and 1730 cm^{-1} was considered for the carbonyl group, respectively (**Figure 2**).

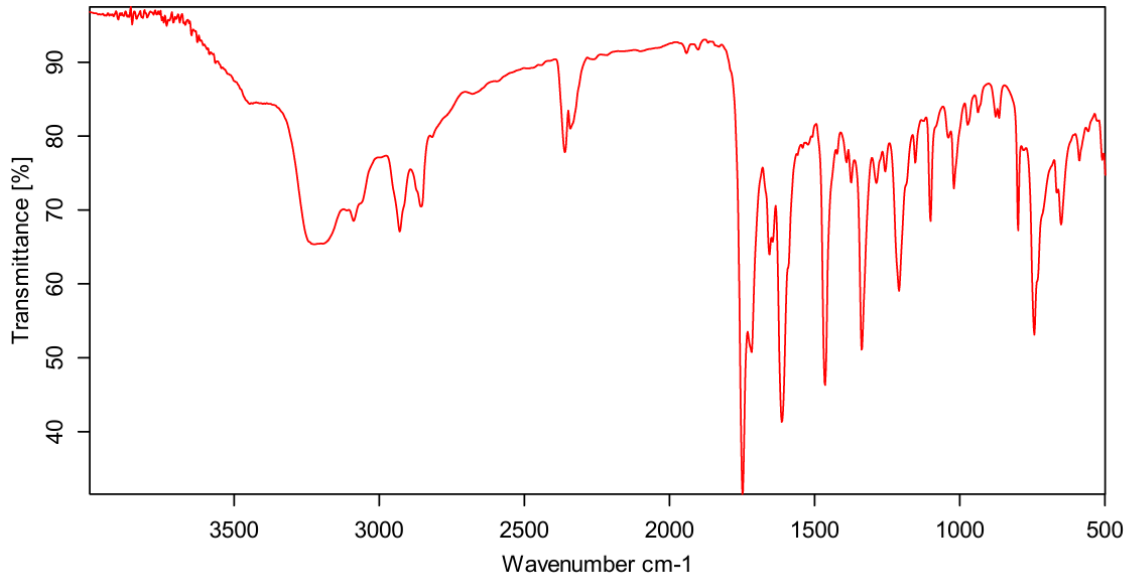


Figure 2.FT-IR spectrum recorded for synthesized compound 3a

After that, ^{1}H NMR was recorded in DMSO-d6 solvent at 400 MHz for finding the number of hydrogens present in the synthesized compound. The chemical shift value of 10.90 ppm corresponded to the secondary amine (>N-H) hydrogen, 6.59 to 7.73 ppm for aromatic hydrogens, and 1.43 to 4.32 ppm for aliphatic hydrogens (**Figure 3**). Furthermore, ^{13}C NMR analysis was also conducted in DMSO-d6 solvent at 100 MHz to confirm the carbons in the synthesized compound. As per spectrum, 160.10 and 164.16 ppm chemical shifting values were considered carbonyl groups in the synthesized compound. Moreover, the chemical shift values of 110.96 to 154.92 ppm were confirming the aromatic nature of the carbons; similarly, 27.32 to 54.00 ppm peaks were noted for six aliphatic carbons. 39.4 to 40.49 ppm for DMSO-d_6 solvent (**Figure 4**). Consequently, the synthesized compound was successfully characterized by these respective analytical techniques.

3. CHARACTERIZATION DETAILS

FT-IR (KBr: 500 to 3500 cm^{-1}) = 3250 secondary amine (>N-H) stretching, 3110 sp^{2} hybridized C-H stretching, 2890 sp^{3}

hybridized C-H stretching and 1730 (>C=O) cm^{-1}.**^{1}H NMR (DMSO-d_6, 400 MHz)** δ = 10.90 (s, 1H, >NH), 7.73 to 6.59 (m, 7H, Aromatic-H), 4.32 to 1.43 (m, 6H, Aliphatic-H) ppm. **^{13}C NMR (DMSO-d_6, 100 MHz)** δ = 164.16, 160.10, 154.92, 153.89, 146.23, 144.71, 138.88, 133.79, 133.28, 127.61, 125.17, 123.28, 122.66, 122.03, 117.11, 112.68, 111.53, 110.96, 54.00, 51.59, 31.23, 30.98, 30.93, 27.32 ppm.

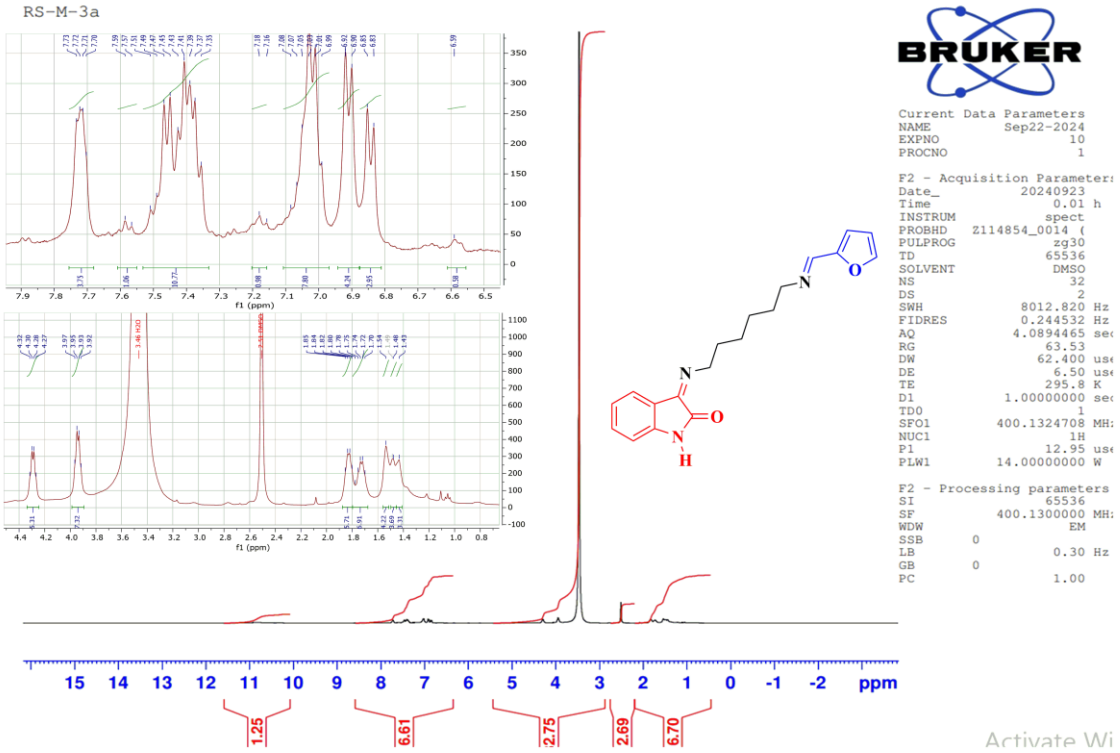


Figure 3.^{1}H NMR spectrum for synthesized compound 3a

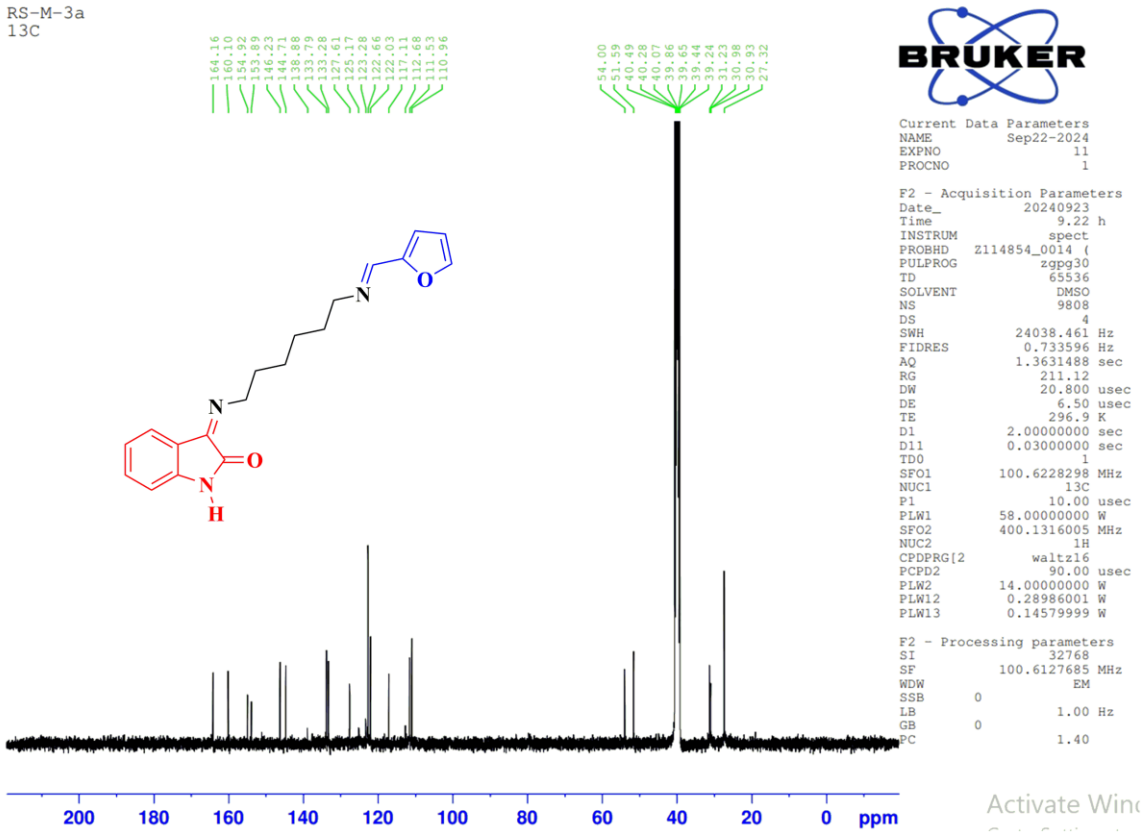


Figure 4.^{13}C NMR spectrum for synthesized compound 3a

National Cancer Institute's report of oxindole-containing Schiff base effects on human cancer cells

The synthesized compound was submitted to the National Cancer Institute for testing to find out the cytotoxicity nature against the sixty human cancer cell lines at 10 µM concentrations under in-vitro analysis (**Figure 5**). Cancer property of the synthesized compound was found to be an active anti cancer drug against multi-targeted panel. As per screening report that was provided one-dose test and their inhibition effect displayed in % inhibition growth (%IG), individually. Compound's anticancer effect was illustrated as following types (**Table1**)[21].

Table 1.Used human cancer cell lines against synthesized compound

Panel	% growth of human cancer cells against 3a at 10 µM concentrations
Leukemia	CCRF-CEM 114.40 (%G) HL-60(TB) 126.23 (%G) K-562 110.89 (%G) MOLT-4 117.81(%G) RPMI-8226 (%G) 106.48 SR 117.14 (%G).
Non-Small Cell Lung Cancer	A549/ATCC 93.79 (%G) EKVX 91.37 (%G) HOP-62 90.03 (%G) NCI-H226 97.45 (%G) NCI-H23 95.32 (%G) NCI-H322M 100.19 (%G) NCI-H460 108.53 (%G) NCI-H522 110.28 (%G).
Colon Cancer	COLO 205 109.77 (%G) HCC-2998 104.23 (%G) HCT-116 101.30 (%G) HCT-15 97.47 (%G) HT29 102.85 (%G) KM12 104.82 (%G) SW-620 96.02 (%G)
CNS Cancer	SF-268 95.39 (%G) SF-295 94.29 (%G) SF-539 90.17 (%G) SNB-19 95.15 (%G) SNB-75 73.66 (%G) U251 91.39 (%G).
Melanoma	LOX IMVI 93.21 (%G) MALME-3M 93.40 (%G) M14 94.86 (%G) MDA-MB-435 100.24 (%G) SK-MEL-2 115.17 (%G) SK-MEL-28 101.36 (%G) SK-MEL-5 101.36 (%G) UACC-257 95.83 (%G) UACC-62 92.05 (%G).
Ovarian Cancer	IGROV1 98.44 (%G) OVCAR-3 111.97 (%G) OVCAR-4 107.61 (%G) OVCAR-5 98.71 (%G) OVCAR-8 98.07 (%G) SK-OV-3 96.38 (%G)
Renal Cancer	786-0 103.88 (%G) A498 118.70 (%G) ACHN 96.07 (%G) CAKI-1 81.07 (%G) RXF 393 106.31 (%G) SN12C 98.28 (%G) TK-10 108.35 (%G) UO-31 67.03 (%G).
Prostate Cancer	PC-3 110.12 (%G) DU-145 111.24 (%G).
Breast Cancer	MCF7 95.35 (%G) MDA-MB-231/ATCC 91.25 (%G) HS 578T 94.50 (%G) BT-549 99.77 (%G) T-47D 94.96 (%G) MDA-MB-468 114.16 (%G)

The anticancer activity of the synthesized compound was calculated in the form of % growth inhibition (%IG), and then the results are discussed. For the leukemia panel, all used tumor cells showed 0% IG against the compound; therefore, these cells were not affected by the dosing of the compound. For non-small cell lung cancer cells, those cells were affected by the compounds A549/ATCC 6.21 (%IG), EKVX 8.63 (%IG), HOP-62 9.07 (%IG), NCI-H226 2.55 (%IG), and NCI-H23 4.68 (%IG), respectively.In the same context for colon cancer cells, two cells were affected by compound HCT-15 2.53 (%IG) and SW-620 3.98 (%IG). For CNS cancer, this compound showed good activity against these cells named SF-268 (4.61% IG), SF-295 (5.71% IG), SF-539 (9.83% IG), SNB-19 4.85 (%IG), SNB-75 26.44 (%IG), and U251 8.41 (%IG), respectively, as well. Moreover, the tumor cells under melanoma showed the % IG-like LOX IMVI 6.79 (%G) MALME-3M 6.60 (%IG), M14 5.14 (%IG), UACC-257 4.17 (%IG), and UACC-62 7.98 (%IG), respectively, as well. Despite the OVCAR-3/4 cells of ovarian cancer cells, others were inhibited by the dosing of compound-like IGROV1 1.66 (%IG) OVCAR-5 1.29 (%IG) OVCAR-8 1.93 (%IG) and SK-OV-3 3.62 (%IG), respectively.

As per the results, it was noted that two renal cancer cells named 786-0 103.88 (%IG) and A498 118.70 (%IG) were not inhibited by the compound, while others were inhibited, such as ACHN 3.93 (%IG) CAKI-1 18.93 (%IG), SN12C 1.72 (%IG), and UO-31 32.93 (%IG), respectively. In the last panel of cancerous cells under breast cancer cells, despite the MDA-MB-468 cell, the %IG, which are MCF7 4.65 (%IG), MDA-MB-231/ATCC 8.75 (%IG), HS 578T 5.50 (%IG), BT-549 0.33 (%IG), and T-47D 5.04 (%IG), respectively.It was concluded that the best activity was found to be against SNB-75 of central nervous system (CNS) cancer and UO-31 of renal cancer at 10 µM concentrations (**Figure 5**).

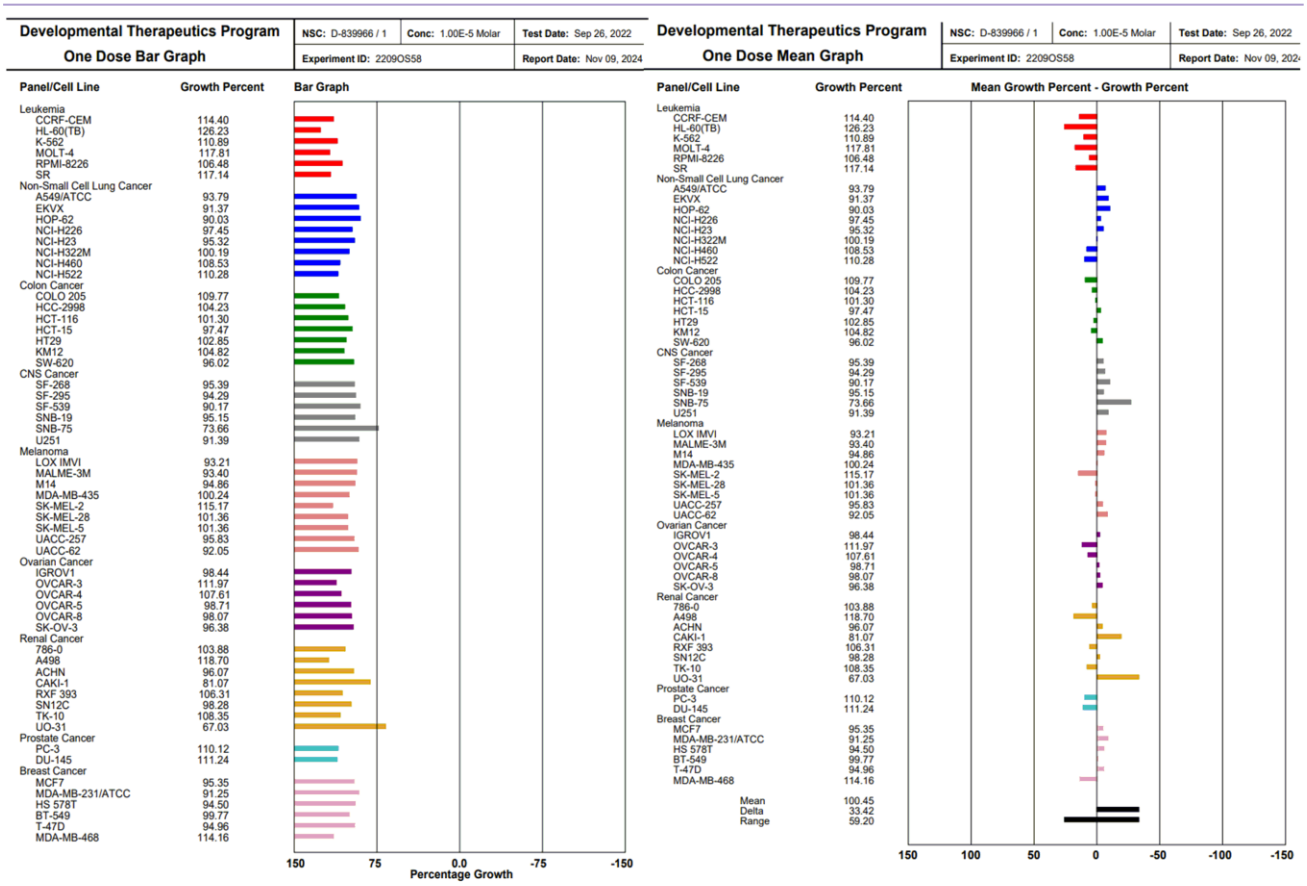


Figure 5.One-dose mean screening graph for synthesized compound 3a against sixty human cancer cells

4. MOLECULAR DOCKING ANALYSIS

According to an in vitro study, the compound demonstrated significant anticancer activity against SNB-75 cancer cells of the central nervous system and UO-31 cancer cells of the renal system. As a preliminary investigation, the pathway of inhibition to these cells by the compound's active sites has been identified by selected proteins for the conduction of the docked complex in order to identify binding affinities by their potential interactions. Therefore, we demonstrated anticancer effects of the synthesized compound **3a** under in-silico analysis for further evaluation. For that, hypoxia-inducible factor 1-alpha (HIF-1α)(**PDB ID: 1L8C**)-related protein was chosen for the development of a docked complex with the synthesized compound as a ligand to find the interactions in terms of binding affinities through the active sites of them.HIF-1α plays a crucial role in the development and progression of CNS malignancies, including glioblastoma. The protein's residues also impact tumor growth and resistance to therapies. Furthermore, it stimulates this by activating genes involved in angiogenesis (new blood vessel construction), metabolic reprogramming (e.g., glycolysis), and immunological evasion. HIF-1α is a key target for cancer medicines that aim to interrupt tumor-promoting pathways.

As per docking results, synthesized compound 3a and FDA-approved sunitinib as a control were taken for the formation of docked complexes with HIF-1α-containing protein. Consequently, docked complexes named HIF-1α-3a and HIF-1α-sunitinib showed the binding affinities of 5.5 kcal/mol and 4.9 kcal/mol, respectively. For the HIF-1α-3a complex, the solvent accessible surface (SAS) and hydrophobicity, ionizability, aromaticity, interpolated charge, and H-bonds were also analyzed for conveying their properties (**Figures 6-7**). For the HIF-1α-sunitinib complex, such properties were also analyzed, which demonstrated as well. (**Figure 8-9**) as well.

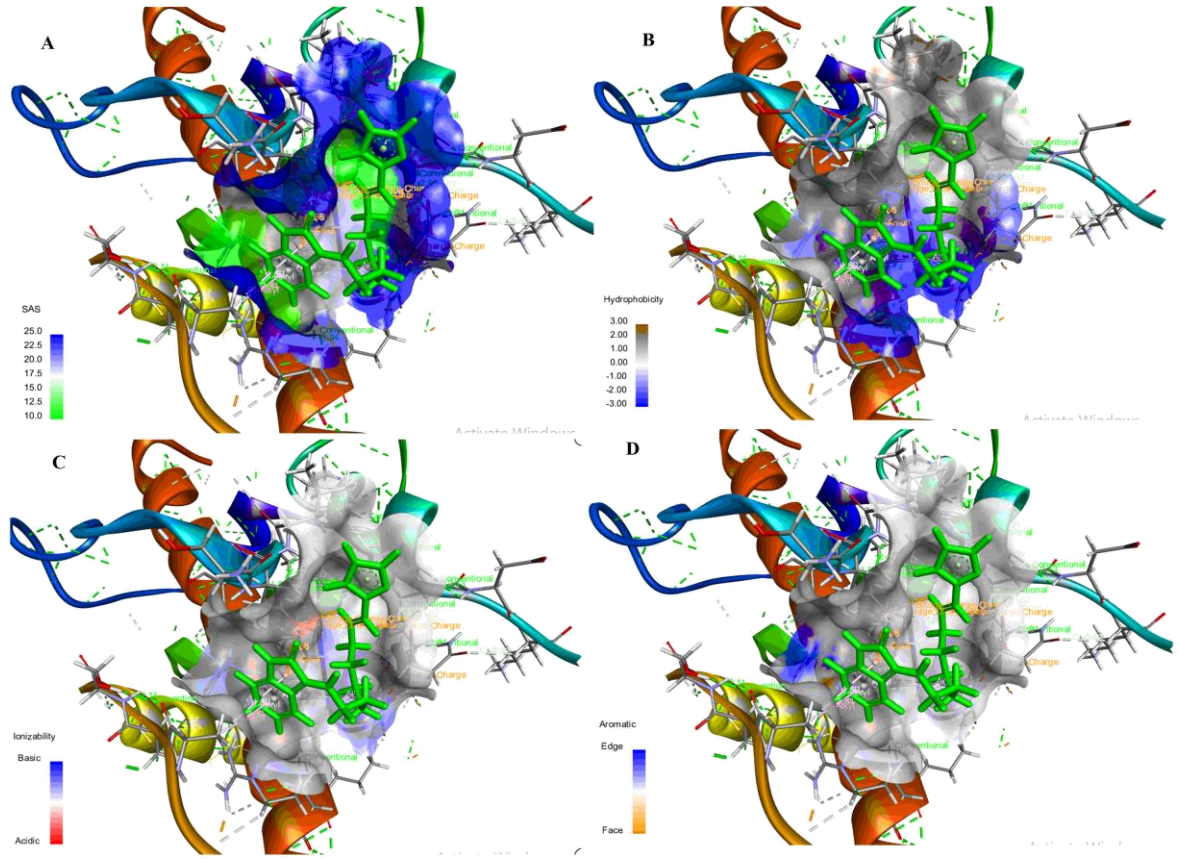


Figure 6.HIF-1α-3a docked complexes, which showed their properties like A: solvent accessible surface (SAS), B: hydrophobicity, C: ionizability, D: aromatic

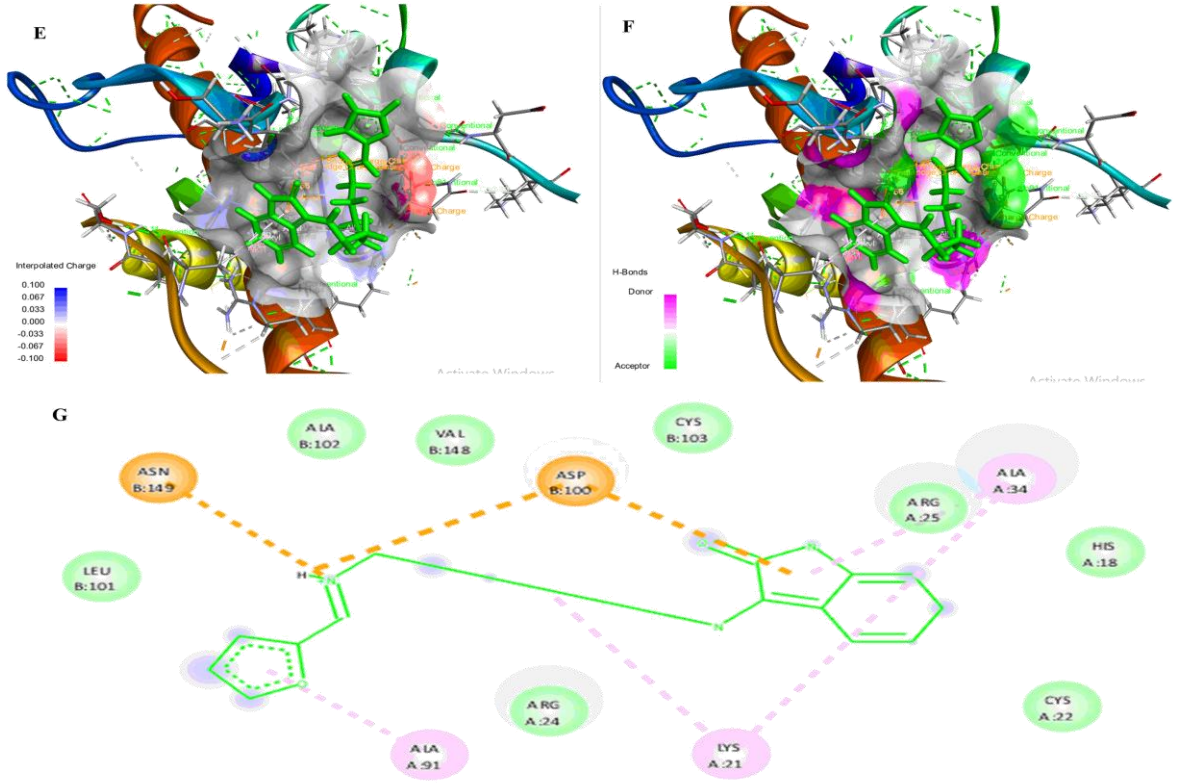


Figure 7.HIF-1α-3a docked complexes, which showed their properties like E: interpolated charge, F: H-bonds, G: 2D complex

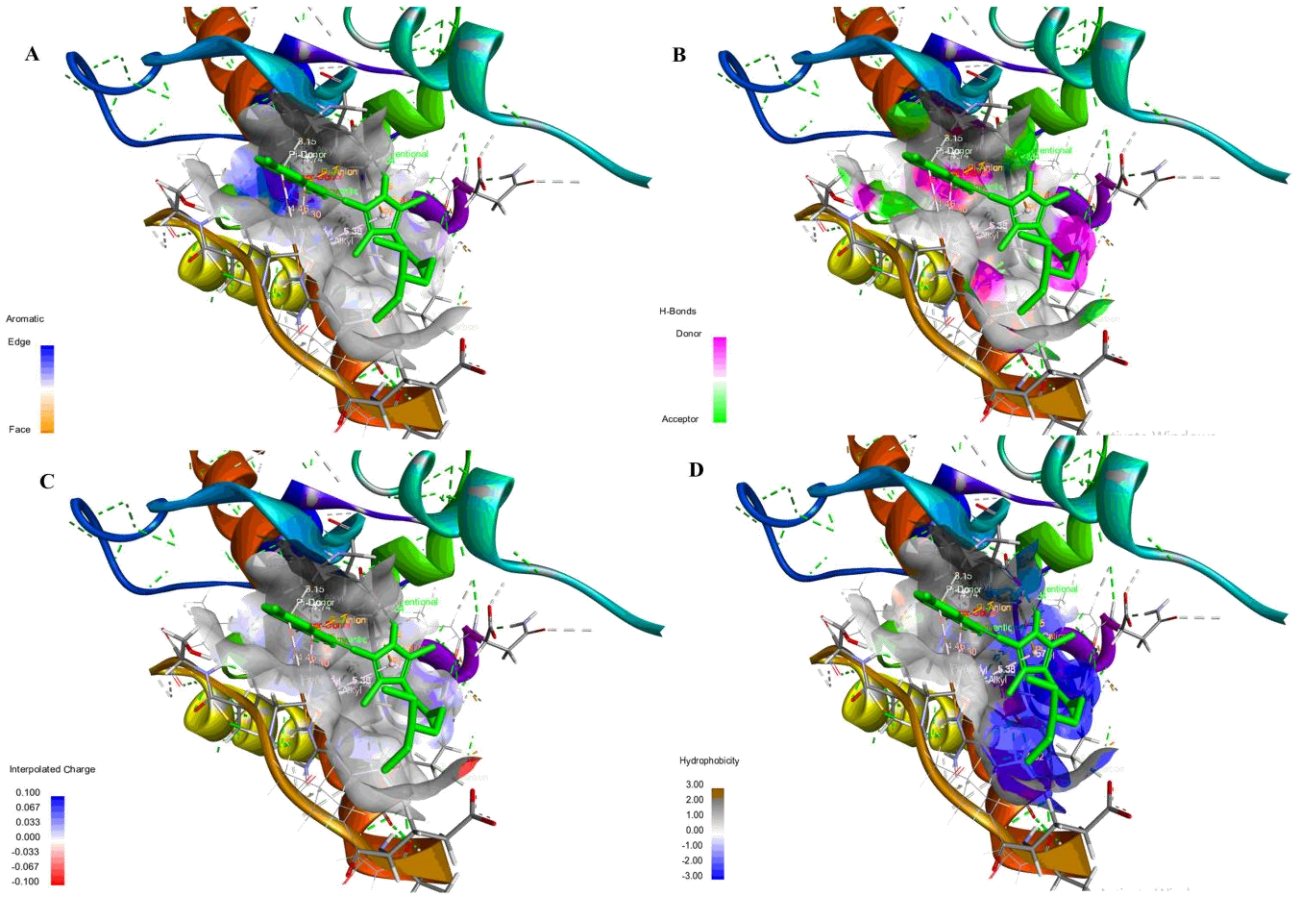


Figure 8.HIF-1α-sunitinib docked complexes, which showed their properties like A: solvent accessible surface (SAS), B: hydrophobicity, C: ionizability, D: aromatic

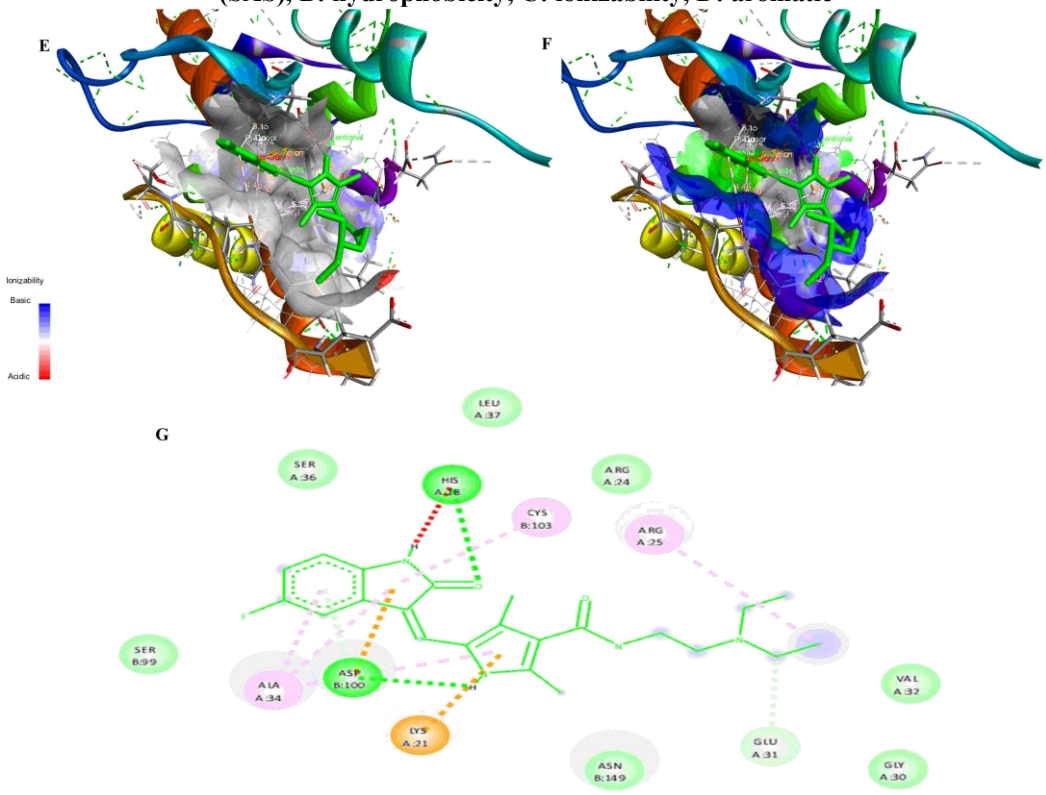


Figure 9.HIF-1α-sunitinib docked complexes, which showed their properties like E: interpolated charge, F: H-bonds, G: 2D complex

5. CONCLUSION

The synthesis of oxindole-containing Schiff base 3a was reported as anti-CNS cancer drug. Actually, the transformation of oxindole into an oxindole-containing Schiff base employing diaminohexane as a linker for the synthesis of drug-like compounds and their cytotoxicity against sixty human cancer cell lines has been described. Compound 3a was verified using FT-IR, ^{1}H, and ^{13}C NMR. Furthermore, the National Cancer Institute of the United States of America conducted biological tests against sixty different human cancer cell lines.At 10 µM doses, compound 3a effectively treated SNB-75 (%IG = 26.44) of CNS cancer and UO-31 (%IG = 32.93) of renal cancer. Following that, the synthesized chemical 3a was further evaluated to determine pathway inhibition, which was also done using an in-silico approach. The docked complexes HIF-1α-3a and HIF-1α-sunitinib have binding affinities of 5.5 and 4.9 kcal/mol,respectively. The aim of proposed work is that to development of anticancer drug, which was done as preliminary investigation.

Methods and materials

Synthesis

For synthesis, the reactants used were purchased from the Sigma-Aldrich agency with 97% purity. Moreover, thin-layer chromatography silica gels and solvents were also from Scientific Fine (SDF) Company. The FT-IR analysis was conducted with KBr pate and used a range between 500 and 3500 cm^{-1}, which was analyzed by the CIF at Integral University, Lucknow, India. Similarly, NMR analyses were done by the Bruker NMR tool at SGPGIMS, Lucknow, India.

Anticancer evaluation

The synthesized compound was then evaluated by the National Cancer Institute of the United States of America against sixty human cancer cells at 10 µM concentrations, as per NCI guidelines[22,23].

Molecular docking

The molecular docking was conducted to find out their anticancer effects that were conducted by PyRx software. Demonstration of the anticancer effects of the synthesized compound 3a under in-silico analysis for further evaluation, respectively[24,25]. For that, hypoxia-inducible factor 1-alpha (HIF-1α)(PDB ID: 1L8C)-related protein was chosen for the development of a docked complex with the synthesized compound as a ligand to find the interactions in terms of binding affinities through the active sites of them.

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