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Research article

# *In-silico* studies and docking of n-substituted isoindoline-1, 3-dioine analogues as anti-proliferative agents

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## ABSTRACT

Recently,isoindoline-1,3-dione compounds based folpet, phosmet, captonand thalidomide were developed because they have a comparable degree of anti-proliferative efficacy owing to their diverse mechanisms such as HDAC inhibitors, tryptase inhibitors, inhibits the mode of tnf-α, and angiogenesis inhibitors. It was investigated how the phthalimide pharmacophore interacted with molecules such tnf-α, HDAC, VEGF, EGF, and Tyrosine Kinase Angiogenesis. In order to assess the inhibitory activity against enzyme assay, a series of phthalimidepharmacophores with various substituent's (Schiff's base) at the N-phenyl ring were submitted to protein-ligand docking investigations using the lib-dock method in the current work. All of the compounds' chemical structures were designed using Cambridge software, ChemBioOffice Ultra 12.0, and their molecular characteristics were determined using the online molecular modelling tool Molinspiration. Utilizing the Discovery Studio Client version 4.1, ADMETlab 2.0, and Lazar 1.4.2 softwares, ADME, Toxicity, and Molecular Docking investigations using the lib-dock method were carried out to evaluate the binding mode and interactions of synthetic hits at the binding site of receptors. Docking studies demonstrated that these sorts of ligands interacted mostly with TNF-α, HDAC, VEGF, EGF, Tyrosine kinase, and angiogenesis reports, among others, by forming hydrogen bonds and interacting hydrophobically with the domain. Our docking results indicate that compounds A1, A10, A11, A22, A26, and A28 demonstrated the greatest binding affinity with the corresponding proteins based on the predicted binding energy. These computer simulations have shown that phthalimide compounds with N-phenyl rings replaced can effectively suppress enzymatic assay.

**Keywords**:Phthalimide, ADME, Discovery Studio Client, Molecular Docking, Enzymatic assay.

## INTRODUCTION

Cancer is a condition characterized by aberrant cell development that has the ability to infiltrate and spread to other bodily regions [1]. This article basically deals with cancer and phthalimide derivatives which have potential in treating cancer and for their anti-proliferative property, but this compound has the severe disadvantage of teratogenicity. But in this study the modifications made in this molecule help us to overcome this big severe adverse effect of this compound.

Cancer is basically associated with a genetic defect where the cells multiply vigorously without undergoing cell cycle, some of the receptors responsible whose activation can significantly show the onset of carcinogenic properties in cell-like tumor necrosis factor-α, vascular endothelial growth factor, tyrosine kinase, advanced glycation end-products. [2] The genesis of cancer involves a series of genetic and epigenetic alterations that give cells the ability to avoid homeostatic regulators, which generally inhibit improper

proliferation and prohibit the survival of aberrantly proliferating cells beyond their normal habitats.[3]Once a tumor begins to grow, the centre begins to lose access to nutrients and oxygen, which commonly leads to the formation of new blood vessels (angiogenesis), which restores the centre of the tumor's access to those substances.[4]The hallmark of malignancy, metastasis, occurs when tumour cells acquire the capacity to penetrate tissue beyond their usual borders, enter the bloodstream, and seed new cancers in other areas.[5]

Recently, due to their diverse mechanisms, such as HDAC inhibitors, tryptase inhibitors, inhibits the mode of tnf-, and angiogenesis inhibitors, N-amino phthalimide derivatives were developed based on folpet, caption, and thalidomide. These drugs all have a comparable degree of anti-proliferative efficacy. [6, 7]It was investigated how phthalimide interacted with several anti-proliferative mechanisms. Indeed, the phthalimide moiety is a rigid form and having the imide derivative of phthalic anhydride. [8]

The anti-proliferation and recognised effects of isoindoline-1, 3-dione derivatives are mostly due to the hydrophobic interactions of different amino compounds. Therefore, we explored it further with the docking studies, ADME and their toxicity investigation.

## MATERIAL AND METHODS

### *In-silico* studies

### ChemBio office ultra 12.0/acd

ChemBio Office Ultra 12.0, a piece of software from Cambridge, was used to design the chemical structure of each compound. Additionally, there is software that enables the display of molecules and molecular models in two and three dimensions, allowing users to better comprehend the makeup of functional groups and the structure of chemical bonds. ACD labs/ChemSketch version 12.0 was used to determine the chemical structures and SMILE notations of the compounds. [9]

### Pharmacokinetics properties

To forecast the oral bioavailability of possible lead or therapeutic compounds, Lipinski's rule of five is employed in drug design and development. The term ADME describes a molecule's intake, circulation, metabolism, and excretion inside an organism. For each medicine, each of these qualities is crucial. One of the most difficult challenges in medication development is having favourable ADME properties. As a result, early optimization is crucial in this process. Through early optimization, a time and money wastage in the latter phases of medication development may be avoided. The research process becomes more efficient and cost-effective through the detection and removal of undesirable substances. [10]Due to this, it is crucial to evaluate the pharmacokinetic characteristics of novel drug candidates as early as feasible in the drug development process. [11]In this work, ADME experiments were conducted using Discovery Studio Client 4.5, and ADMET lab 2.0 predicts a range of ADME features from an input chemical structure. Predictions are computed automatically and reproducibly using DSC 4.5 and ADMET lab 2.0. For the critical review by pharmacokinetic specialists, rationales for predictions, applicability domain estimations, and validation results are displayed in a simple graphical interface.

### Toxicity

We cover a few of *in-silico* toxicity prediction methods.[12] Using Lazar 1.4.2 software, which uses a chemical structure as input and makes predictions for a range of hazardous characteristics, the toxicity experiments in this study were carried out. Lazar 1.4.2 Programme makes predictions using an automated, repeatable read through process. For the critical review by toxicological specialists, rationales for predictions, applicability domain estimations, and validation findings are given in a simple graphical interface. [13]

### Molecular docking

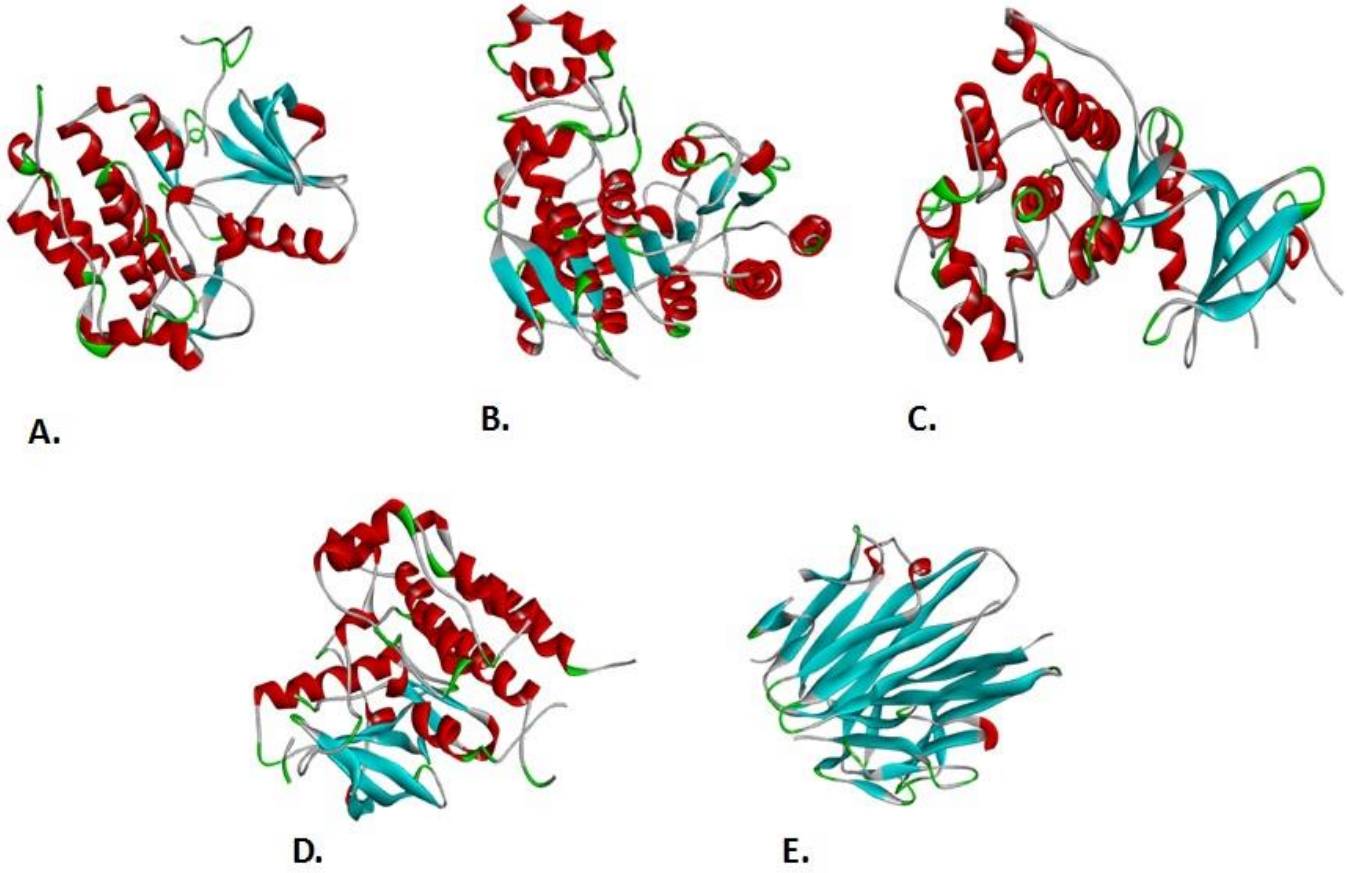
In the Research Collaborator for Structural Bioinformatics, Protein Data Bank (RSCB, PDB), there exist a variety of protein crystal structures targeting cancer targets. [14]Resolution and other factors, including crystal structure determination method, Ramachandran outlier, several R-values (R-value working, R-value free, and R-value observed), and diverse literatures (most-cited crystal structure) were assessed for the selection of protein crystal structures. The X-ray crystallographic structure of analysis is based on the above-mentioned factors. Protein kinase (PDB ID: 3MY1,[15] resolution of 2.8 Å, Vascular endothelial growth factor receptor (PDB ID: 2OH4, resolution of 2.05 Å, Histone deacetylase (PDB ID: 4LXZ, resolution of 1.85 Å, Tumor necrosis factor-α (PDB ID: 2AZ5), resolution of 2.10 Å, Epithelial growth factor (PDB ID: 6S89), resolution of 2.701 Å complexes containing a co-crystal ligand were chosen and employed in the following experiments. [16]

### Protein preparation

In order to prepare proteins, following processes were taken: Initially, the protein complex's co-crystal (bound ligand molecules) was removed, followed by the removal of water molecules. Clean up the protein by adding missing amino acid residues and removing those that aren't needed, Adding hydrogen atoms to a mixture, Loop insertion, Utilizing the define and modify binding site methods in the receptor-ligand interaction tool, the spare binding site was produced. The PDB site information was automatically used to select the binding site. Togther stable protein, the last stage of minimization and pKa calculation was conducted using the CHARMm based Force field and Smart Minimizer algorithm, as well as other default parameters. The Macromolecules

tool panel in Discovery Studio Client (DSC) 4.5 Software were used to complete these processes individually for each proteins. [17]

**Figure 1:** 3D-Structures of prepared protein, A. 6S89, B. 4LXZ, C. 3MY1, D. 2OH4, E. 2AZ5




**Ligand preparation**

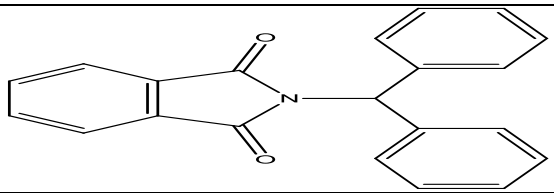
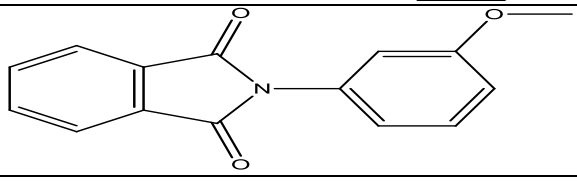
All 30 compounds' structures were sketched independently in ChemBio Draw Ultra 12.0 and saved as .mol files (because they are frequently used for sharing libraries of compound structure data). Small molecule tools included in DSC 4.5 were used to convert ligands to 3D orientation and prepare them. The conformations were produced with CAESAR (Conformer Algorithm based on Energy Screening and Recursive Build-up) as the conformation technique and the generate conformations protocol with a maximum conformer hundred. The CHARMm Force field (because it is one of the best force fields used in the computational simulation for the properties of DNA, Protein, etc.)Via Smart Minimizer algorithm and the Momany-Rone technique for Partial Charge Estimation were used to minimize energy for all of the compounds.

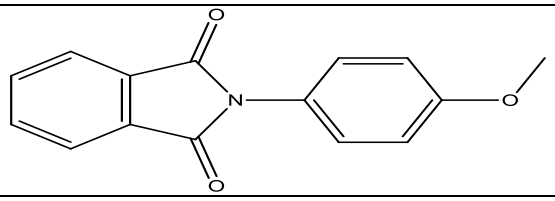
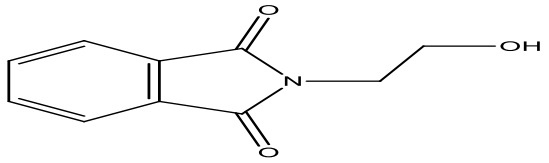
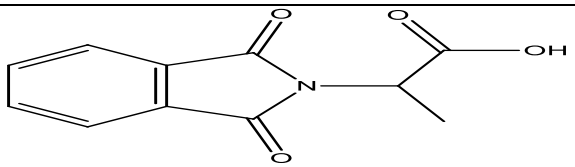
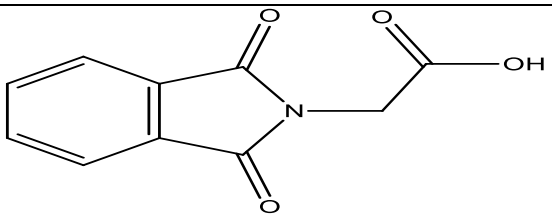
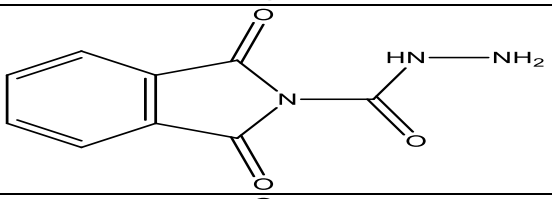
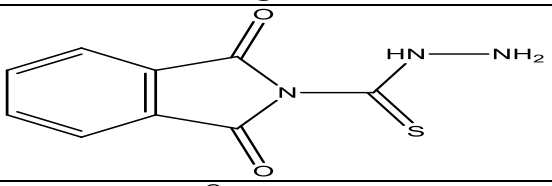
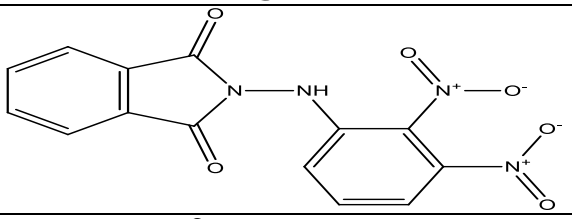
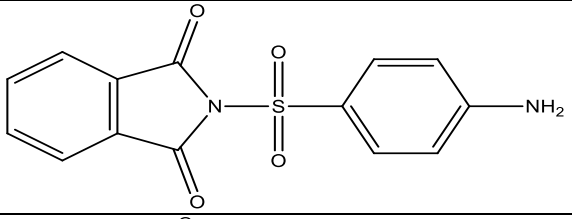
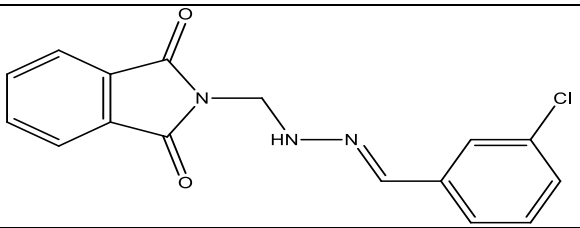
**Docking process validation**

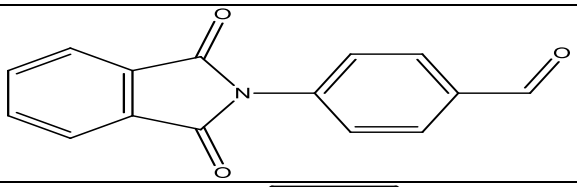
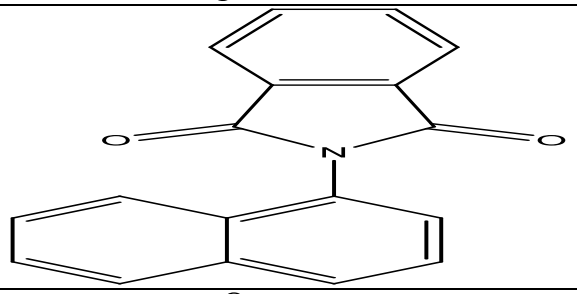
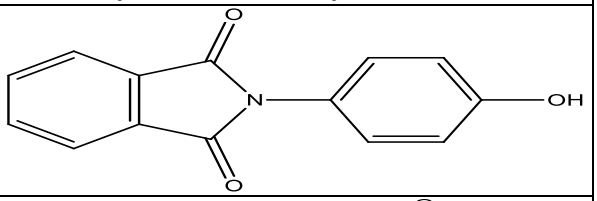
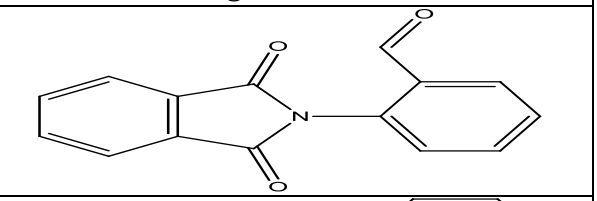
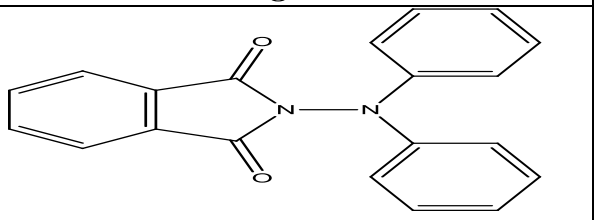
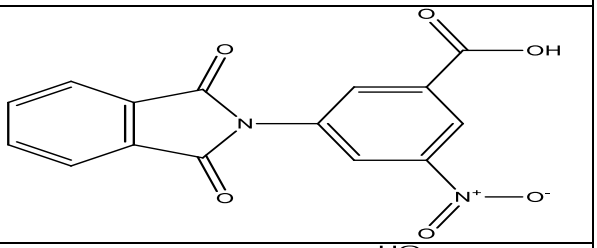
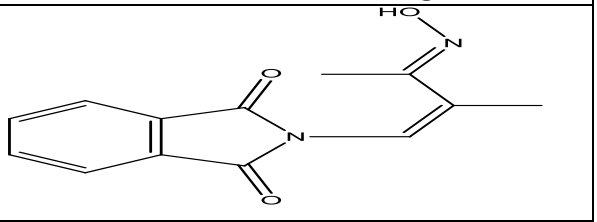
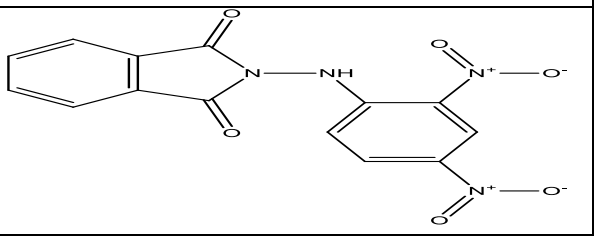
The validation of the docking procedure is the first step in docking analysis. In the literature, several different validation processes have been described. The current research project entails the posture selection approach was employed in this study to validate the docking procedure by re-docking the bound ligand and comparing the root mean square deviation (RMSD) value (≤ 2 Å Standard) between the bound and re-docked ligand.

The Lib Dock algorithm was used for the docking investigation. During the docking investigation, the following parameters were used: a) the number of hotspots is 100. b) High Quality Docking Preference, c) CAESAR Confirmation Method, d) Smart Minimizer Minimization Algorithm, as well as other default settings. In each protein, all of the ligand molecules were docked independently. The Lib Dock score was used to evaluate various postures of all docked ligands. Finally, the Analyze Ligand Poses Programme was used to examine the interactions of docked ligand-protein complexes. All of these tasks were completed with DSC 4.5 on a Windows operating system. [18]

**Table 1:** Chemical Structure of the 30 Selected Isoindoline-1, 3-Dione Derivatives

| Sample Codes | Molecular Structure |
|---|---|
| $A_1$ |  |
| $A_2$ |  |

| | |
|---|---|
| $A_3$ |  |
| $A_4$ |  |
| $A_5$ |  |
| $A_6$ |  |
| $A_7$ |  |
| $A_8$ |  |
| $A_9$ |  |
| $A_{10}$ |  |
| $A_{11}$ |  |

| | |
|---|---|
| $A_{12}$ |  |
| $A_{13}$ |  |
| $A_{14}$ |  |
| $A_{15}$ |  |
| $A_{16}$ |  |
| $A_{17}$ |  |
| $A_{18}$ |  |
| $A_{19}$ |  |

| | |
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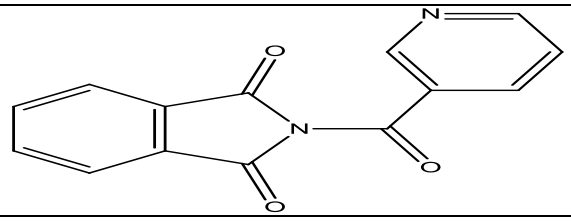
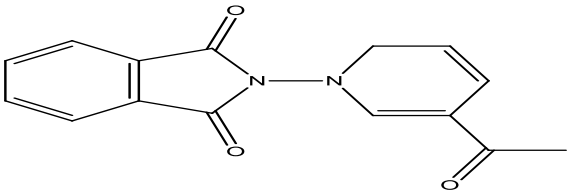
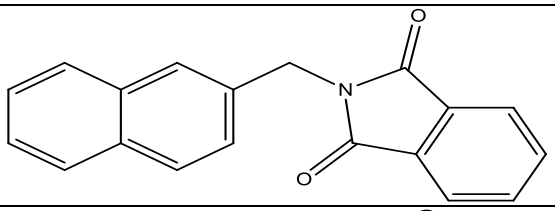
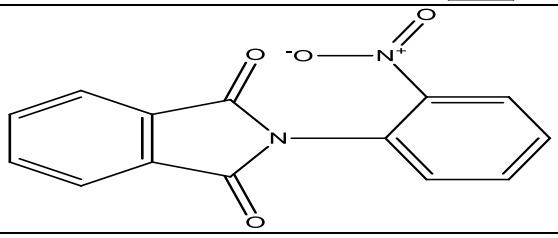
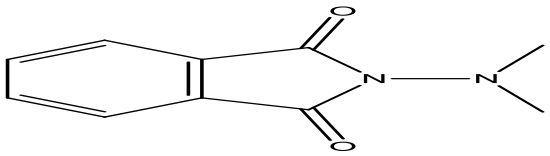
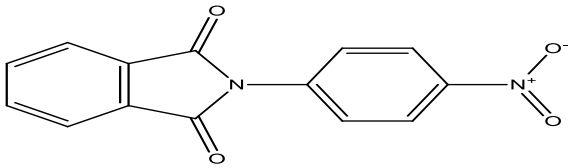
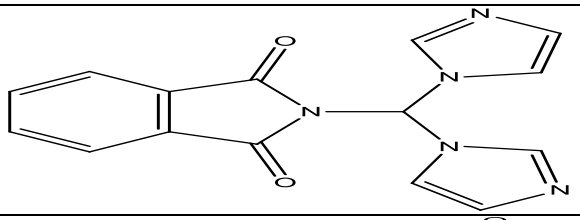
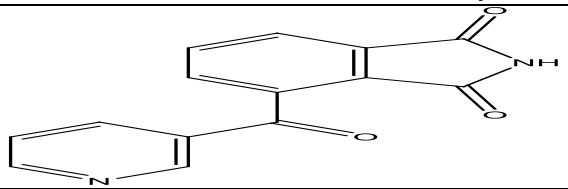
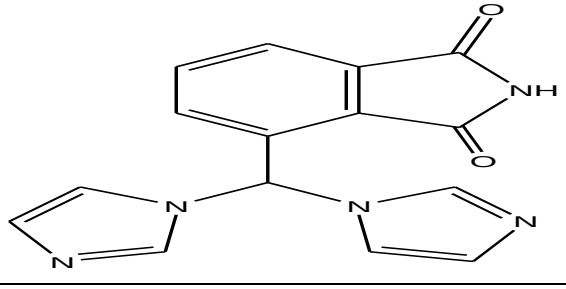
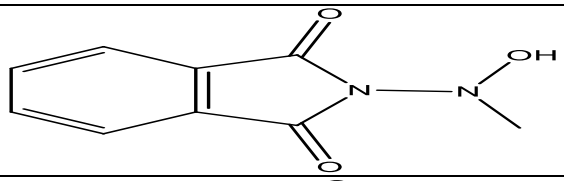
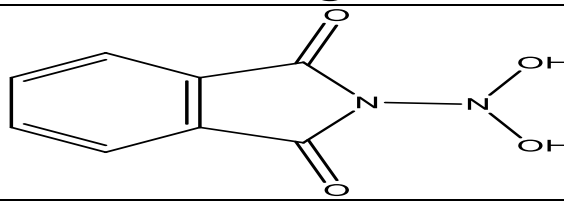
| $A_{20}$ |  |
| $A_{21}$ |  |
| $A_{22}$ |  |
| $A_{23}$ |  |
| $A_{24}$ |  |
| $A_{25}$ |  |
| $A_{26}$ |  |
| $A_{27}$ |  |
| $A_{28}$ |  |

| | |
|---|---|
| $A_{29}$ |  |
| $A_{30}$ |  |

**Docking calculations**

Docking Calculations are performed by using Discovery Studio Client ver. 4.1 software with the following PDB's were downloaded from RCSB i.e. Protein data Bank which is being modelled with help of homology modelling following multiple and single alignments strands. Based on the binding energy, the docked conformations of each ligand were grouped into clusters, and the top-ranked conformations underwent visual inspection. Between docked powerful agents and macromolecules, hydrogen bonding and hydrophobic interactions were examined.

## RESULTS

All the data sets utilized for the computational investigation underwent flexible docking on the protein's active site. The anticipated binding energy, docking energy, and inhibition-constant (Ki) of various inhibitors into the active site are presented in Table 2 based on the technique described in the experimental section. The intermolecular energy, the torsional free-energy penalty, and the internal energy of docking the ligand are added together to generate the projected binding and docked energies, the inhibition-constant (Ki), respectively is determined by the DSC 4.5 Programme in the form of a Libdosck score. Based on the projected binding energy, our docking results show that compounds A1, A10, A11, A22, A26 and A28 showed best binding affinity with the Protein kinase (PDB ID: 3MY1),[15] Vascular endothelial growth factor receptor (PDB ID: 2OH4),[16]Histone deacetylase (PDB ID: 4LXZ),[17]Tumor necrosis factor-α (PDB ID: 2AZ5),[18] Epithelial growth factor (PDB ID: 6S89).

Proposed compounds were designed and evaluated by various in-silico tools such as ChemBio Office Ultra 12.0, Molinspiration, Discovery studio client 4.5, ADMETlab 2.0 and Lazar 4.2 softwares.

**Determination of drug likeness properties**

In accordance with Lipinski's rule of five, novel molecules intended for oral administration should have a MW of at least 500, a log Po/w of at most 5, a maximum of five hydrogen bond donors, and a maximum of ten hydrogen bond acceptors. Table 2 presents the outcomes.

**Table 2:** Lipinski Rule Analysis of Proposed Derivatives

| Compound Code | Molecular Weight (a.m.u.) | Log P | nON | nOHNH | Nrotb | No. of Violations |
|---|---|---|---|---|---|---|
| $A_1$ | 314 | 4.70 | 3 | 0 | 3 | 0 |
| $A_2$ | 253 | 3.04 | 4 | 0 | 2 | 0 |
| $A_3$ | 253 | 2.86 | 4 | 0 | 2 | 0 |
| $A_4$ | 191 | 0.89 | 4 | 1 | 2 | 0 |
| $A_5$ | 219 | 1.13 | 5 | 1 | 2 | 0 |
| $A_6$ | 205 | 0.77 | 5 | 1 | 2 | 0 |
| $A_7$ | 205 | -0.27 | 6 | 3 | 0 | 0 |
| $A_8$ | 221 | 0.27 | 5 | 3 | 2 | 0 |
| $A_9$ | 328 | 2.80 | 10 | 1 | 4 | 0 |
| $A_{10}$ | 287 | 1.51 | 6 | 2 | 2 | 0 |
| $A_{11}$ | 325 | 3.92 | 5 | 1 | 4 | 0 |
| $A_{12}$ | 251 | 2.59 | 4 | 0 | 2 | 0 |
| $A_{13}$ | 273 | 4.17 | 3 | 0 | 1 | 0 |
| $A_{14}$ | 239 | 2.32 | 4 | 1 | 1 | 0 |
| $A_{15}$ | 251 | 2.75 | 4 | 0 | 2 | 0 |
| $A_{16}$ | 314 | 4.92 | 4 | 0 | 3 | 0 |
| $A_{17}$ | 312 | 3.02 | 8 | 1 | 3 | 0 |
| $A_{18}$ | 244 | 2.25 | 5 | 1 | 2 | 0 |
| $A_{19}$ | 328 | 2.83 | 10 | 1 | 4 | 0 |
| $A_{20}$ | 252 | 1.76 | 5 | 0 | 1 | 0 |
| $A_{21}$ | 268 | 1.575 | 5 | 0 | 2 | 0 |
| $A_{22}$ | 287 | 4.30 | 3 | 0 | 2 | 0 |
| $A_{23}$ | 268 | 2.92 | 6 | 0 | 2 | 0 |
| $A_{24}$ | 190 | 1.53 | 4 | 0 | 1 | 0 |
| $A_{25}$ | 268 | 2.76 | 6 | 0 | 2 | 0 |
| $A_{26}$ | 293 | 0.85 | 7 | 0 | 3 | 0 |
| $A_{27}$ | 252 | 1.31 | 5 | 1 | 2 | 0 |
| $A_{28}$ | 293 | 0.40 | 7 | 1 | 3 | 0 |
| $A_{29}$ | 192 | 1.21 | 5 | 1 | 1 | 0 |
| $A_{30}$ | 194 | 1.28 | 6 | 0 | 1 | 0 |

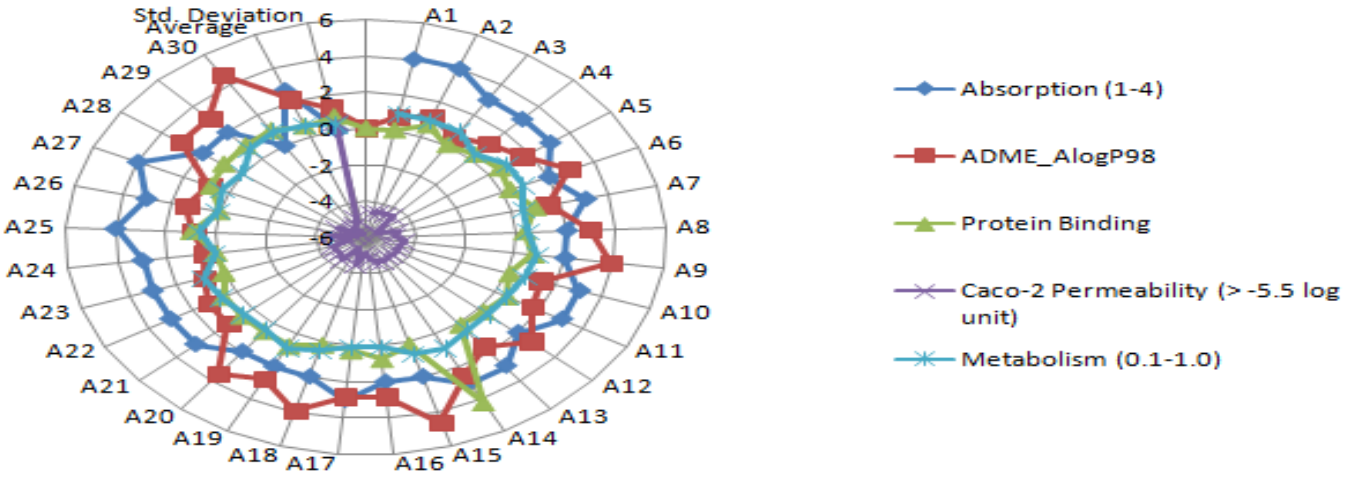
**Table 3:** ADME prediction by Discovery Studio Client 4.5 software and ADMETlab 2.0

| Compound Code | Absorption (1-4) | ADME_AlogP98 (>5) | Protein Binding (-1.5 – 1.5) | Caco-2 Permeability (> -5.5 log unit) | Metabolism (0.1-1.0) |
|---|---|---|---|---|---|
| $A_1$ | 4 | 0.755 | 0.0023129 | -4.665 | 0.9-1.0 |
| $A_2$ | 4 | 1.115 | 0.650879 | -4.589 | 0.9-1.0 |
| $A_3$ | 3 | 0.469 | 0.0464774 | -4.558 | 0.9-1.0 |
| $A_4$ | 3 | 1.104 | 0.304915 | -4.409 | 0.3-0.5 |
| $A_5$ | 3 | 1.644 | 0.552483 | -5.495 | 0.9-1.0 |
| $A_6$ | 2 | 2.953 | 0.341335 | -5.549 | 0.9-1.0 |
| $A_7$ | 3 | 1.475 | 0.939732 | -4.720 | 0.5-0.7 |
| $A_8$ | 2 | 2.953 | 0.341335 | -4.824 | 0.5-0.7 |
| $A_9$ | 2 | 3.878 | 0.732071 | -4.456 | 0.9-1.0 |
| $A_{10}$ | 3 | 1.388 | 0.0699466 | -4.624 | 0.7-0.9 |
| $A_{11}$ | 3 | 1.684 | 0.504531 | -4.558 | 0.5-0.7 |
| $A_{12}$ | 2 | 2.761 | 0.207826 | -4.578 | 0.5-0.7 |
| $A_{13}$ | 3 | 1.65 | 0.115187 | -4.614 | 0.5-0.7 |
| $A_{14}$ | 3 | 2.583 | 4.21249 | -4.541 | 0.9-1.0 |
| $A_{15}$ | 2 | 4.629 | 0.147584 | -4.570 | 0.7-0.9 |
| $A_{16}$ | 2 | 2.818 | 0.724854 | -4.793 | 0.1-0.3 |
| $A_{17}$ | 3 | 2.817 | 0.251859 | -5.126 | 0.1-0.3 |
| $A_{18}$ | 2 | 3.967 | 0.155147 | -4.425 | 0.5-0.7 |
| $A_{19}$ | 2 | 2.818 | 0.724854 | -5.346 | 0.9-1.0 |
| $A_{20}$ | 2 | 3.598 | 0.564927 | -4.410 | 0.5-0.7 |
| $A_{21}$ | 3 | 1.267 | 0.585409 | -4.647 | 0.5-0.7 |
| $A_{22}$ | 3 | 1.267 | 0.585409 | -4.571 | 0.7-0.9 |
| $A_{23}$ | 3 | 0.843 | 0.00154204 | -4.531 | 0.9-1.0 |
| $A_{24}$ | 3 | 0.469 | 0.0472875 | -5.271 | 0.1-0.3 |
| $A_{25}$ | 4 | 0.868 | 0.963771 | -4.561 | 0.7-0.9 |
| $A_{26}$ | 3 | 1.352 | 0.0314217 | -5.600 | 0.1-0.3 |
| $A_{27}$ | 4 | 0.847 | 0.799991 | -4.733 | 0.3-0.5 |
| $A_{28}$ | 2 | 3.042 | 0.970975 | -5.789 | 0-0.1 |
| $A_{29}$ | 2 | 3.042 | 0.970975 | -5.284 | 0.7-0.9 |
| $A_{30}$ | 2 | 4.582 | 0.999891 | -5.187 | 0.9-1.0 |

**Determination of ADME properties**

DSC 4.5 and ADMETlab 2.0 were used to calculate the ADME parameters of the produced compounds (A1-A30). Predicted ADME characteristics for all drugs are shown in Table 3, which includes the following metrics: metabolism, Caco-2 permeability, protein binding, absorption, and % oral absorption. Consequently, it may be inferred that the final molecules might have a favourable pharmacokinetic profile based on predictions of the ADME features.

**Figure 2:** Graphical interpretation of ADME study.




**Molecular docking studies**

Molecular docking studies of 30 derivatives of isoindoline-1, 3-dione compounds were done by using Discovery Studio Client 4.5 software. Docking studies were conducted on Protein kinase (PDB ID: 3MY1), resolution of 2.8 Å, Vascular endothelial growth factor receptor (PDB ID: 2OH4) resolution of 2.05 Å, Histone deacetylase (PDB ID: 4LXZ),[17] resolution of 1.85 Å, Tumor necrosis factor-α (PDB ID: 2AZ5),[18] resolution of 2.10 Å, Epithelial growth factor (PDB ID: 6S89), resolution of 2.701 Å. Most of the designed compounds show potent anticancer activity. The docking scores of the derivatives are given in Table 4.

**Table 4:** Lib-dock Scores of proposed derivatives

| Compound code | Protein Kinase (PDB I.D. 3MY1) | Vascular Endothelial Growth Factor (PDB I.D. 2OH4) | Histone Deacetylase (PDB I.D. 4LXZ) | Tumor Necrosis Factor-α (PDB I.D. 2AZ5) | Epithelial Growth Factor (PDB I.D. 6S89) |
|---|---|---|---|---|---|
| $A_1$ | 100.165 | 92.1485 | 101.15 | 101.656 | 97.2207 |
| A2 | 82.9882 | 88.2249 | 78.1294 | NA | NA |
| A3 | 80.9778 | 87.9161 | 73.0407 | 75.6945 | NA |
| A4 | 73.5515 | 72.809 | 51.298 | 71.8593 | 67.1838 |
| A5 | 78.2647 | 81.0761 | 52.0731 | 77.1375 | 69.334 |
| A6 | 75.6634 | 77.5403 | 77.8654 | 72.4992 | NA |
| A7 | 76.6777 | 77.4726 | 48.4578 | NA | NA |
| A8 | 72.8148 | 76.4092 | 49.2939 | 58.6484 | NA |
| A9 | NA | NA | NA | NA | NA |
| A10 | 101.199 | 97.7863 | 90.4141 | 86.7635 | 84.6625 |
| A11 | 101.198 | 109.347 | 104.563 | 92.7347 | 116.207 |
| A12 | 83.6768 | 88.4349 | 74.8684 | NA | NA |
| A13 | 81.1417 | 81.566 | 58.8389 | 87.8478 | 64.0805 |
| A14 | 81.9303 | 83.3648 | 60.6702 | NA | NA |
| $A_{15}$ | 73.5354 | 73.8747 | 47.7082 | 69.7707 | NA |
| $A_{16}$ | 79.2194 | 108.201 | 34.8954 | 74.0566 | NA |
| $A_{17}$ | 98.5826 | 78.1581 | 51.4954 | 84.0027 | NA |
| $A_{18}$ | 61.309 | 49.4151 | 38.4905 | NA | NA |
| $A_{19}$ | 81.5172 | 66.3665 | 62.1097 | 64.2233 | 47.746 |
| $A_{20}$ | 76.5235 | 83.0393 | 65.7119 | NA | 63.3488 |
| $A_{21}$ | 82.3065 | 85.2128 | 51.1796 | 74.2676 | 57.6806 |
| $A_{22}$ | 100.407 | NA | 96.6263 | NA | 97.523 |
| $A_{23}$ | 68.1548 | 63.0139 | 30.2115 | NA | 24.8073 |
| $A_{24}$ | 66.7625 | 71.2453 | 50.6357 | NA | NA |
| $A_{25}$ | 85.466 | 91.0376 | 76.9202 | 59.8671 | NA |
| $A_{26}$ | 93.493 | 97.9179 | 87.7662 | 95.3993 | 99.6607 |
| $A_{27}$ | 77.1553 | 81.3313 | 71.0007 | 74.2153 | 83.4209 |
| $A_{28}$ | 97.1761 | 98.0791 | 80.9728 | 106.611 | NA |
| $A_{29}$ | 68.1547 | 68.2511 | 48.0653 | 62.5522 | NA |
| $A_{30}$ | 71.6292 | 67.4148 | 47.8832 | 62.4968 | NA |

*NA- it means respective structure doesn't show any binding affinity towards the active site of respective protein.

All the designed derivatives are docked with receptors Protein kinase (PDB ID: 3MY1), [15] resolution of 2.8 Å, Vascular endothelial growth factor receptor (PDB ID: 2OH4), [16] resolution of 2.05 Å, Histone deacetylase (PDB ID: 4LXZ), [17]resolution of 1.85 Å, Tumor necrosis factor-α (PDB ID: 2AZ5), [18] resolution of 2.10 Å, Epithelial growth factor (PDB ID: 6S89), resolution of 2.701 Å for anti-proliferative activity. Docking interaction of various compounds with different proteins were shown in following figures.

**Figure 3:** 3D and 2D binding interaction of Compound A1 in the active site of Protein Kinase (PDB ID: 3MY1

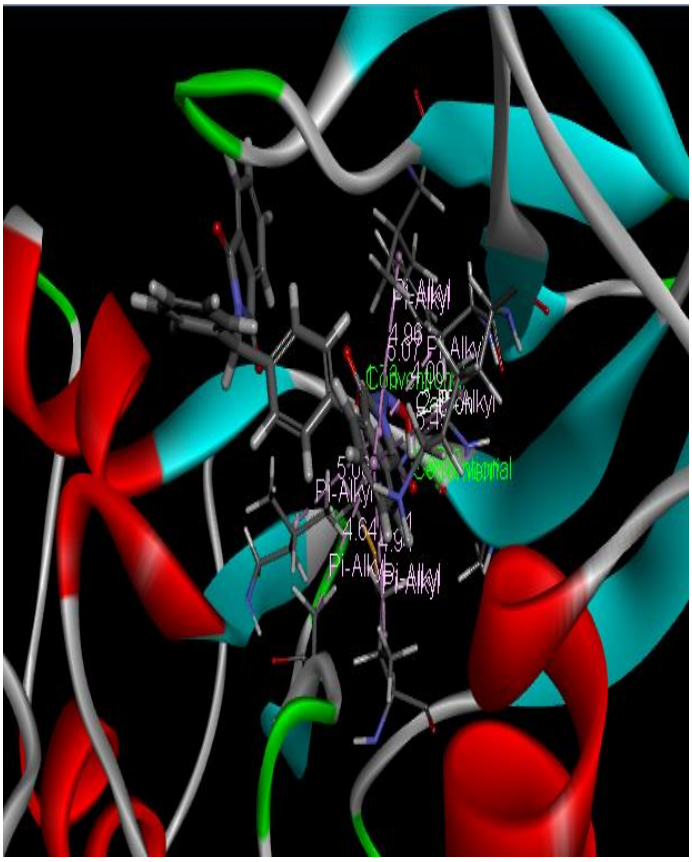



**Figure 4:** 3D and 2D binding interaction of Compound A11 in the active site of Vascular Endothelial Growth Factor (PDB ID: 2OH4)

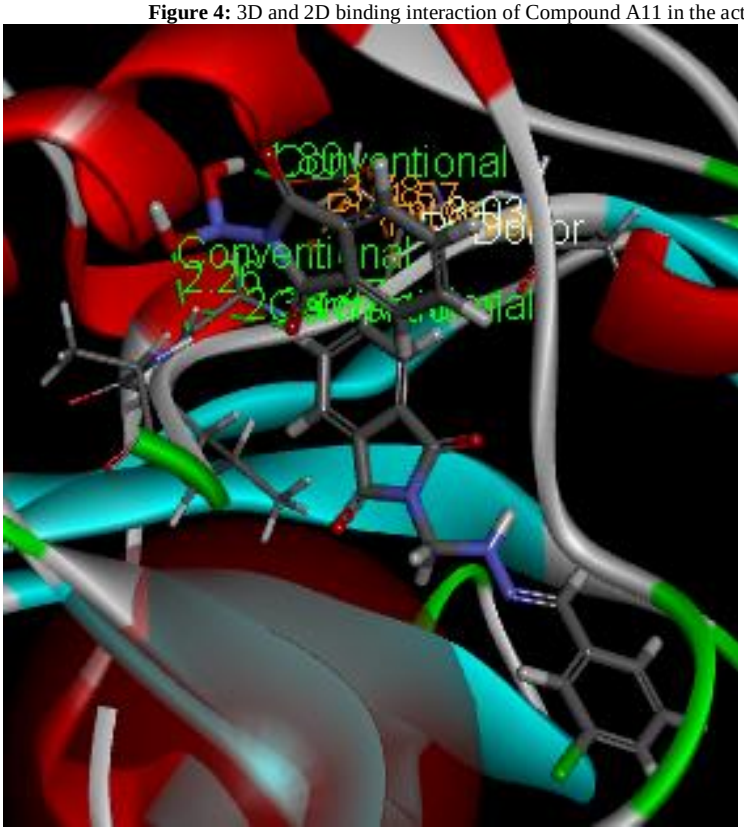
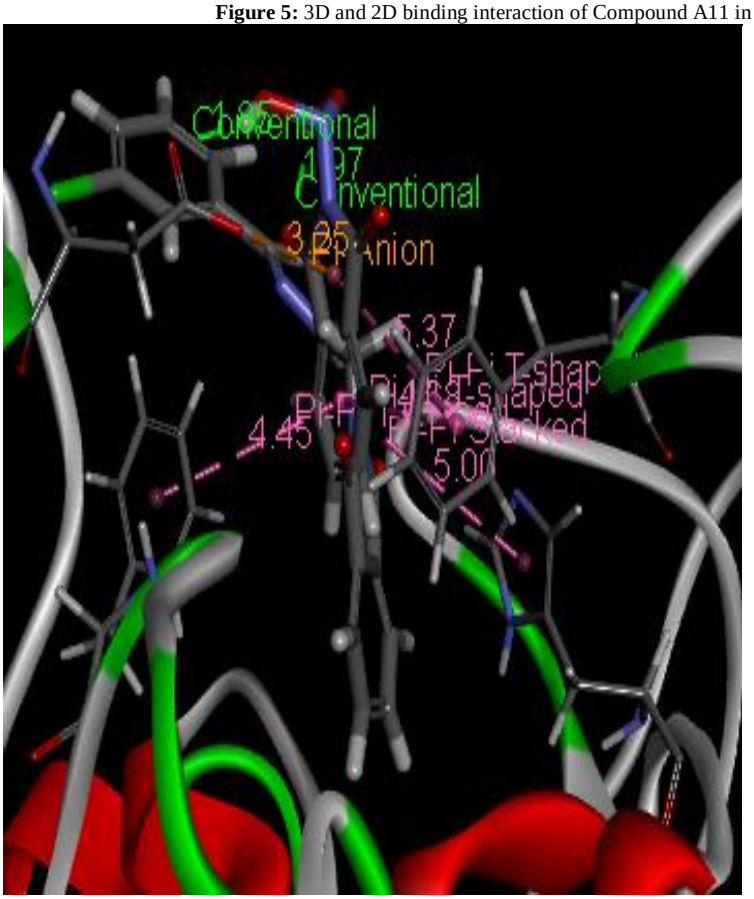


**Figure 5:** 3D and 2D binding interaction of Compound A11 in the active site of Histone Deacetylase (PDB ID: 4LXZ)



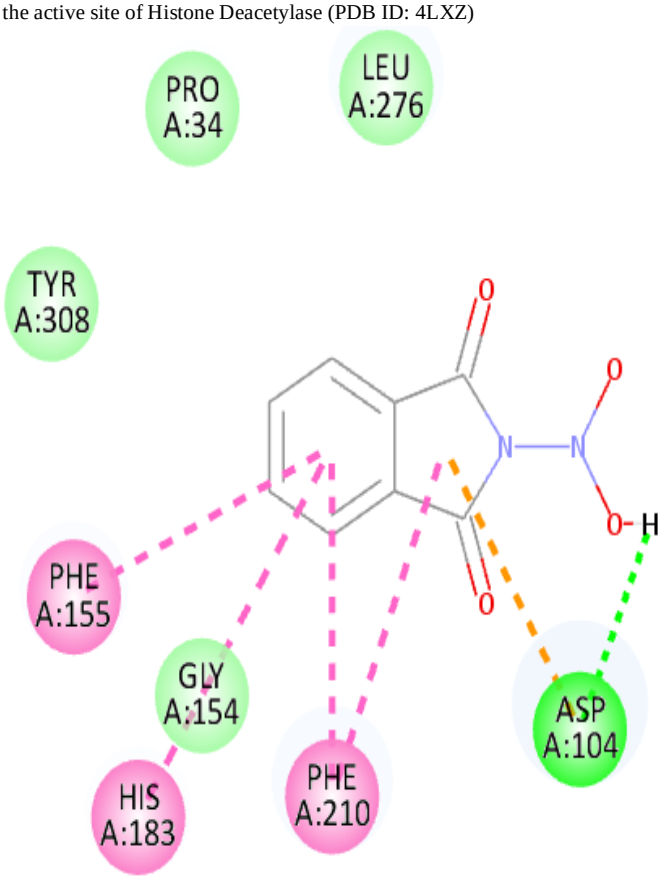
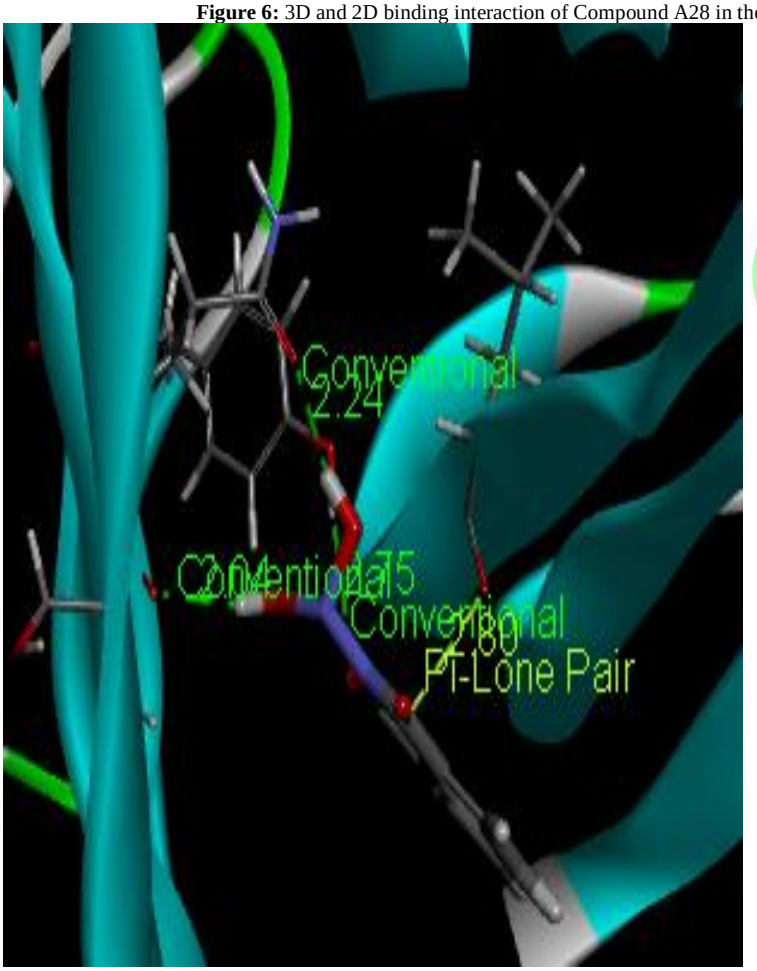




**Figure 6:** 3D and 2D binding interaction of Compound A28 in the active site of Tumor Necrosis Factor-α (PDB ID: 2AZ5)



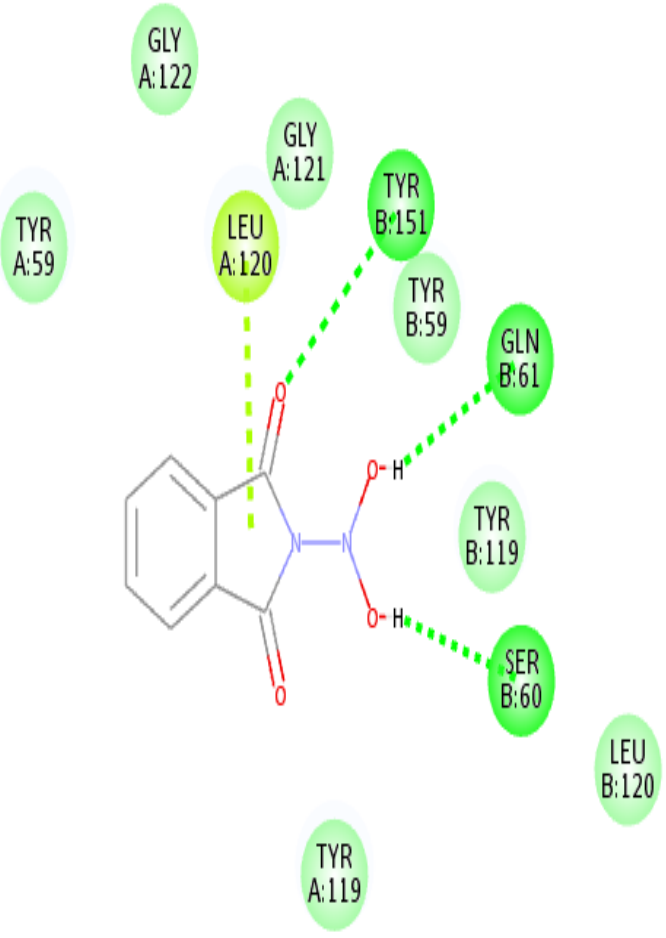
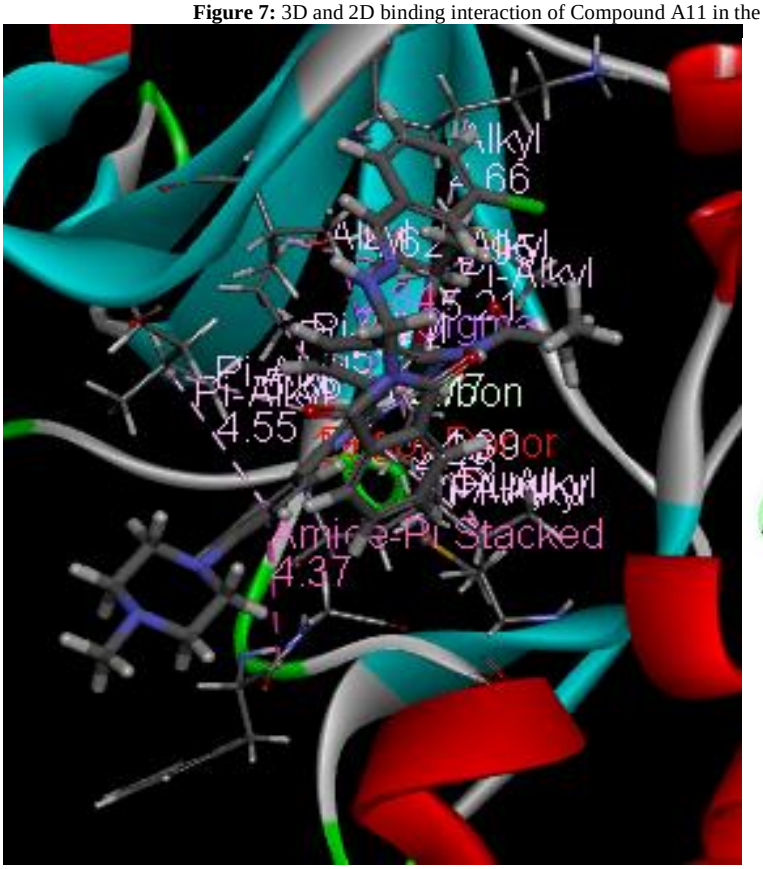
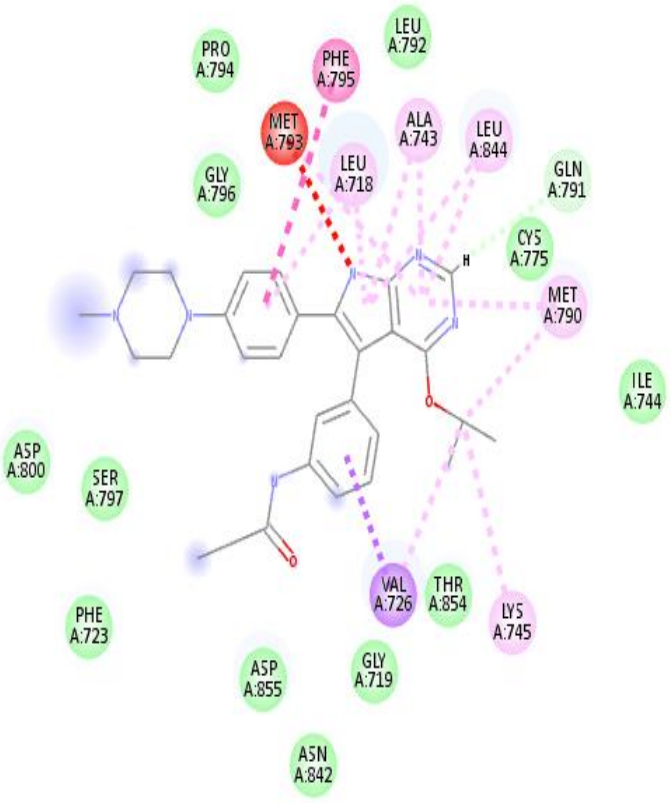



**Figure 7:** 3D and 2D binding interaction of Compound A11 in the active site of Endothelial Growth Factor (PDB ID: 6S89)




## Toxicity prediction

**Table 5:** Toxicity Prediction by Lazar 1.4.2 software

| Compound Code | Carcinogenecity | Mutagenecity |
|---|---|---|
| $A_1$ | Non-Carcinogenic | Non-Mutagenic |
| $A_2$ | Non-Carcinogenic | Non-Mutagenic |
| $A_3$ | Non-Carcinogenic | Non-Mutagenic |
| $A_4$ | Non-Carcinogenic | Non-Mutagenic |
| $A_5$ | Non-Carcinogenic | Non-Mutagenic |
| $A_6$ | Non-Carcinogenic | Non-Mutagenic |
| $A_7$ | Non-Carcinogenic | Non-Mutagenic |
| $A_8$ | Non-Carcinogenic | Non-Mutagenic |
| $A_9$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{10}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{11}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{12}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{13}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{14}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{15}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{16}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{17}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{18}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{19}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{20}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{21}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{22}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{23}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{24}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{25}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{26}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{27}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{28}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{29}$ | Non-Carcinogenic | Non-Mutagenic |
| $A_{30}$ | Non-Carcinogenic | Non-Mutagenic |

Toxicity prediction of compounds which is selected on the basis of molecular docking studies. All 30 compounds were evaluated by using Lazar 1.4.2 software and evaluated their carcinogenicity and mutagenicity characteristics of selected compounds. Selected 30 compounds shows non-carcinogenic and non-mutagenic in nature (Table 5).

## CONCLUSION

In this research work, we designed 30 different derivatives of isoindoline-1, 3-dione scaffold and elevated their molecular docking studies with the receptors for the anti-proliferative activity through *in-silico studies*. All of the compounds in the series had a favourable expected pharmacokinetics profile. Molecular docking study reveals that, compounds A1, A10, A11, A17 and A22 with the receptor Protein kinase (3MY1), compounds A10, A11,A16, A26, A28 with the receptor Vascular endothelial growth factor receptor (2OH4), compounds A1, A11, A22with the receptor Histone deacetylase (4LXZ), compounds A1, A26, A28with the receptor Tumor necrosis factor-α (2AZ5) and compounds A1, A11, A22, A27with the receptor Epithelial growth factor (6S89) are having best Lib-docscore among the compound A1 to A30 respectively, whereas compound A9 unable to show any binding affinity to any of the proteins. Consequently, based on the computational studies, introduced several isoindoline-1, 3-dione derivatives as potent anti-proliferative agents.

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**Declarations**

**Ethical approval**

The manuscript is original and have not been published elsewhere in any form or language.

**Consent to participate**

All authors agreed with the content and that all gave explicit consent to submit and that they obtained consent from the responsible authorities at the institute/organization where the work has been carried out, before the work is submitted.

**Consent to publish**

All authors have given their consent for publishing this manuscript in Journal of medical pharmaceutical and allied sciences.

**Author contributions**

Authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ajay Singh Sarthi, under the guidance of Prof. Shailendra Saraf and Prof. Swarnlata Saraf. All authors read and approved the final manuscript.

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**Competing interests**

The authors have no competing interests to declare that are relevant to the content of this article.

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