ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2014; 5(1): 94 - 102

ORIGINAL RESEARCH ARTICLE

# Computational Estimation of Some New Diarylsulfonylurea-Chalcone Hybrids as Potential Cytotoxic Agents by Using Molecular Docking Studies

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## ABSTRACT

Ligand–protein inverse induced fir docking (LPIIFD) approach has been used as a useful tool in facilitating drug design. In this approach, docking single or multiple small molecules in single or multiple conformations to a receptor site is attempted to find putative ligands. A number of flexible docking algorithms have been introduced. These include multiple-conformer shape matching, genetic algorithm, evolutionary programming, simulated annealing, fragment-based docking, and other novel algorithms. Testing results have shown that these algorithms are capable of finding ligands and binding conformations at a receptor site close to experimentally determined structures. Because of their capability in identifying potential ligands and binding conformations, these algorithms are expected to be equally applicable to an inverse-docking process for finding multiple putative protein targets to which a small molecule can bind or weakly bind. This may be applied to the identification of unknown and secondary therapeutic targets of drugs, drug leads, natural products and other ligands. In the present investigation we proposed to carry out molecular docking studies on a set of diarylsulfonylurea-chalcone hybrid molecules which earlier reported from our research laboratories against selected anticancer drug targets to identify the putative binding mode, binding energy and binding orientation within the active binding site region of selected target binding proteins.

**Key words:** Ligand–protein inverse induced fir docking (LPIIFD), Diarylsulfonylurea-chalcone hybrid molecules, ligands, molecular docking studies.

## INTRODUCTION

Drug discovery and development is an interdisciplinary, expensive and time consuming process. Scientific technology advancements during the past two decades have changed the approach of the pharmaceutical research to generate novel bioactive molecules. Advances in computational techniques and in parallel hardware support have enabled *in silico* methods, and in particular structure-based drug design method, to speed up new target selection through the identification of hits to the optimization of lead compounds in the drug discovery process. Genomics, proteomics, bioinformatics and chemoinformatics have gained immense popularity and have become an integral part of the industrial and academic research, directing drug design and discovery. Virtual screening emerged as an important tool in our quest to access novel drug like compounds [1]. The LPIIFD approach is now applied to the database of compounds synthesized in the present study for finding 'best fit' (hit identification) against selected anticancer protein drug targets. The compound with least binding energy against each individual target protein is considered for further study. By these means, it is possible to understand how the compounds interact with the target protein. The results emerging out of these studies can be used to identify new active ligands by using the knowledge obtained from the *in silico* established secondary protein targets [2-16].

## MATERIALS AND METHODS

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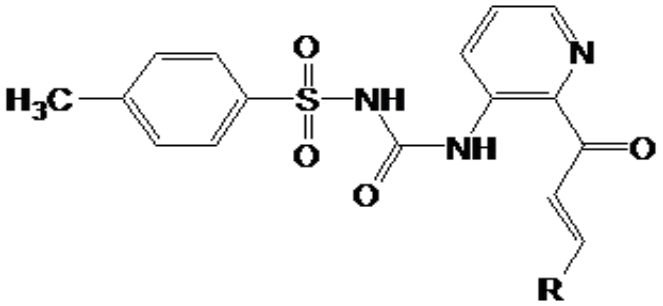
## CHEMICAL SYNTHESIS

The molecules subjected for docking studies which earlier reported their synthesis, characterization and cytotoxicity studies from our research laboratories. The compounds were shown in the following (**Table 1)** [17].

**Table 1: List of diarylsulfonylurea-chalcone hybrids II.1-28 selected for the molecular docking study**



**(II.1-28)**

| Compound | R | RMM | Compound | R | RMM |
|---|---|---|---|---|---|
| **II.1** | $C_6H_5$ | 421 | **II.15** | 3-$NO_2C_6H_4$ | 466 |
| **II.2** | 4-$MeC_6H_4$ | 435 | **II.16** | 5-OH,2-$NO_2C_6H_3$ | 482 |
| **II. 3** | 4-$NMe_2C_6H_4$ | 464 | **II.17** | 3-$FC_6H_4$ | 439 |
| **II.4** | 3-$OMeC_6H_4$ | 451 | **II.18** | 4-$FC_6H_4$ | 439 |
| **II. 5** | 4-$OMeC_6H_4$ | 451 | **II.19** | 2-$ClC_6H_4$ | 455 |
| **II.6** | 3,4-di$OMeC_6H_3$ | 481 | **II.20** | 4-$ClC_6H_4$ | 455 |
| **II.7** | 2,4-di$OMeC_6H_3$ | 481 | **II.21** | 2,4-di$ClC_6H_3$ | 490 |
| **II.8** | 3,4, 5-tri$OMeC_6H_2$ | 511 | **II.22** | 3-$BrC_6H_4$ | 500 |
| **II.9** | 2-$OHC_6H_4$ | 437 | **II.23** | 4-Allyl-$OC_6H_4$ | 477 |
| **II.10** | 3-$OHC_6H_4$ | 437 | **II.24** | Phenylethene-yl | 447 |
| **II.11** | 4-$OHC_6H_4$ | 437 | **II.25** | Pyrrol-2-yl | 410 |
| **II.12** | 3-OEt,4-$OHC_6H_3$ | 481 | **II.26** | Pyridin-3-yl | 422 |
| **II.13** | 3-OMe,4-$OHC_6H_3$ | 467 | **II.27** | Pyridin-4-yl | 422 |
| **II.14** | 2-$NO_2C_6H_4$ | 466 | **II.28** | Anthracen-9-yl | 521 |

**RMM:** Relative Molecular Mass

## COMPUTATIONAL SOFTWARE

In the present molecular docking study, software Molegro Virtual Docker (MVD) v 5.0 (www.molegro.com) along with Graphical User Interface (GUI), MVD tools was utilized to generate grid, calculate dock score and evaluate conformers. Molecular docking was performed using MolDock docking engine of software. The scoring function used by MolDock is derived from the Piecewise Linear Potential (PLP) scoring functions. The active binding site region was defined as a spherical region which encompasses all protein within 15.0 $A^o$ of bound crystallographic ligand atom with selected co-ordinates of X, Y and Z axes, respectively. Default settings were used for all the calculations. Docking was performed using a grid resolution of 0.30 $A^o$ and for each of the 10 independent runs; a maximum number of 1500 iterations were executed on a single population of 50 individuals. The active binding site was considered as a rigid molecule, whereas the ligands were treated as being flexible, i.e. all non-ring torsions were allowed [18].

## LIGAND PREPRATION

The chemical structures of the diarylsulfonylurea-chalcone hybrid molecules **II.1-28** were drawn using Chemdraw ultra v 10.0 (Chemical Structure Drawing Standard; Cambridge Soft corporation, USA), copied to Chem3D ultra v 10.0 to create a 3D model and, finally subjected to energy minimization using molecular mechanics ($MM_2$). The minimization was executed until the root mean square gradient value reached a value smaller than 0.001kcal/mol. Such energy minimized structures are considered for molecular docking studies. However, corresponding pdb files were prepared using Chem3D ultra v 10.0 integral option (save as /Protein Data Bank (pdb)) [19].

## PROTEIN SELECTION AND PREPARATION

The selection of protein target for molecular docking studies is based upon several factors i.e. structure should be determined by X-ray diffraction, and resolution should be between 2.5-3.0 $A^o$, it should contain a co-crystallized ligand; the selected protein should not have any protein

breaks in their 3D structure. On the other hand, we considered Ramachandran plot statistics as the important filter for protein selection with none of the residues present in disallowed region. Finally the resultant protein target was prepared for molecular docking simulation in such a way that all heteroatoms (i.e., nonreceptor atoms such as water, ions, etc.) were removed. Kollmann charges were assigned [20].

## SOFTWARE VALIDATION

Before initiating molecular docking, the docking protocol of Molegro Virtual Docker (MVD) was validated by predicting the binding mode of the crystallographic ligand, of 3CS8. The (**Fig 1)** shows a comparison between binding mode of the crystallographic ligand and the binding mode predicted by MVD. (**Fig 1)** clearly shows that MVD successfully predicted the binding mode of crystallographic mode with a root-mean square (RMS) deviation of 1.25 A$^{o}$ [21].

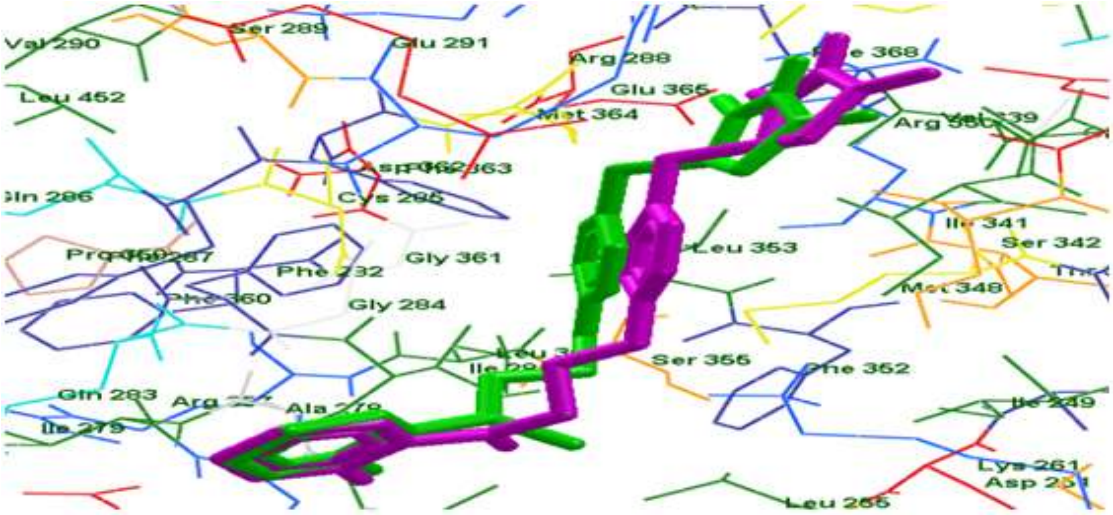



**Fig 1: Superimposed binding orientation of the crystallographic ligand (pink) and docked conformer (green) predicted by MVD in the 3CS8 active binding site.**

## ANTICANCER TARGET PROTEINS

The knowledge of the molecular basis of carcinogenesis has provided for the discovery of new, more selective and less toxic chemopreventive agents. In the present research, considerable attention has been focused on identifying some novel diarylsulfonylurea-chalcone hybrid molecules **II.1-28 (Table 1)** capable of showing significant cytotoxicity. The docking simulation was performed using ten different anticancer target proteins involved with cell cycle, cell growth, and DNA replication. The importance of every individual anticancer target protein selected for molecular docking studies is given below.

### EPIDERMAL GROWTH FACTOR (EGF)

The X-ray crystal structure was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb) (PDB.ID: 1M17).

### VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

The X-ray crystal structure was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb) (PDB.ID: 3C7Q).

### CYCLIN-DEPENDENT KINASE-2 (CDK-2)

The X-ray crystal structure was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb) (PDB.ID: 3PY1).

### CASEIN KINASE II (CK2)

The X-ray crystal structure was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb) (PDB.ID: 1RQF).

### AURORA KINASE-A (AUR-A)

The X-ray crystal structure was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb) (PDB.ID: 3H10).

### VRAF MURINE SARCOMA VIRAL ONCOGENE HOMOLOGUE B1 (BRAF)

The X-ray crystal structure was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb) (PDB.ID: 3PRI).

### HISTONE DEACETYLASE (HDAC)

The X-ray crystal structure was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb) (PDB.ID: 3MAX).

### B-CELL LYMPHOMA-2 (Bcl-2)

The X-ray crystal structure was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb) (PDB.ID: 2W3L).

## FARNESYL TRANSFERASE (FT)

The X-ray crystal structure was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb) (PDB.ID: 1SA4).

## CATHEPSIN B (CAT B)

The X-ray crystal structure was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb) (PDB.ID: 1GMY).

## RESULTS AND DISCUSSION

**Table 2: Diarylsulfonylurea-chalcone hybrid molecules (II.1-28) with their MolDock scores against selected anticancer target proteins**

| Compound | R | MolDock score (kcal/mol) | | | | |
|---|---|---|---|---|---|---|
| | | EGF | VEGF | CDK-2 | CK-2 | AUR-A |
| **II.1** | $C_6H_5$ | -118.671 | -115.777 | -142.793 | -122.827 | -113.129 |
| **II.2** | 4-$MeC_6H_4$ | -117.539 | -113.481 | -148.509 | -159.819 | -113.107 |
| **II.3** | 4-$NMe_2C_6H_4$ | -117.41 | -136.385 | -147.976 | -146.82 | -126.371 |
| **II.4** | 3-$OMeC_6H_4$ | -119.601 | -130.394 | -154.771 | -145.416 | -119.445 |
| **II.5** | 4-$OMeC_6H_4$ | -106.705 | -112.153 | -146.259 | -147.528 | -117.345 |
| **II.6** | 3,4-di$OMeC_6H_3$ | -121.018 | -120.133 | -154.008 | -154.589 | -121.18 |
| **II.7** | 2,4-di$OMeC_6H_3$ | -112.896 | -128.48 | -156.88 | -134.621 | -121.509 |
| **II.8** | 3,4,5-tri$OMeC_6H_2$ | -124.946 | -118.569 | -152.219 | -134.089 | -125.565 |
| **II.9** | 2-$OHC_6H_4$ | -113.389 | -125.783 | -144.888 | -165.013 | -126.082 |
| **II.10** | 3-$OHC_6H_4$ | -104.646 | -107.414 | -151.099 | -130.946 | -119.948 |
| **II.11** | 4-$OHC_6H_4$ | -107.724 | -103.584 | -147.838 | -146.267 | -121.01 |
| **II.12** | 3-OEt,4-$OHC_6H_3$ | -114.705 | -107.131 | -147.356 | -127.779 | -128.638 |
| **II.13** | 3-OMe,4-$OHC_6H_3$ | -114.957 | -92.541 | -141.17 | -131.669 | -105.985 |
| **II.14** | 2-$NO_2C_6H_4$ | -93.8722 | -99.8256 | -131.464 | -135.457 | -106.873 |
| **II.15** | 3-$NO_2C_6H_4$ | -103.585 | -123.656 | -148.493 | -138.231 | -127.826 |
| **II.16** | 5-OH,2-$NO_2C_6H_3$ | -111.128 | -116.125 | -148.088 | -149.673 | -112.891 |
| **II.17** | 3-$FC_6H_4$ | -111.604 | -118.677 | -154.175 | -157.649 | -125.818 |
| **II.18** | 4-$FC_6H_4$ | -112.328 | -111.307 | -151.071 | -126.665 | -123.448 |
| **II.19** | 2-$ClC_6H_4$ | **-144.72** | -145.909 | **-214.426** | **-184.914** | **-155.839** |
| **II.20** | 4-$ClC_6H_4$ | -116.135 | -113.249 | -151.658 | -126.179 | -130.028 |
| **II.21** | 2,4-di$ClC_6H_3$ | -117.286 | -112.718 | -141.447 | -143.981 | -115.311 |
| **II.22** | 3-$BrC_6H_4$ | -112.453 | -107.146 | -146.84 | -161.187 | -116.089 |
| **II.23** | 4-Allyl-$OC_6H_4$ | -109.065 | -143.589 | -160.316 | -137.844 | -130.663 |
| **II.24** | Phenylethene-yl | -123.463 | **-160.11** | -184.534 | -157.755 | -138.757 |
| **II.25** | Pyrrol-2-yl | -104.911 | -109.138 | -156.15 | -144.459 | -117.011 |
| **II.26** | Pyridin-3-yl | -96.2835 | -121.528 | -139.734 | -109.109 | -105.454 |
| **II.27** | Pyridin-4-yl | -98.694 | -107.147 | -141.422 | -117.919 | -114.187 |
| **II.28** | Anthracen-9-yl | -106.946 | -113.707 | -165.854 | -141.152 | -125.42 |

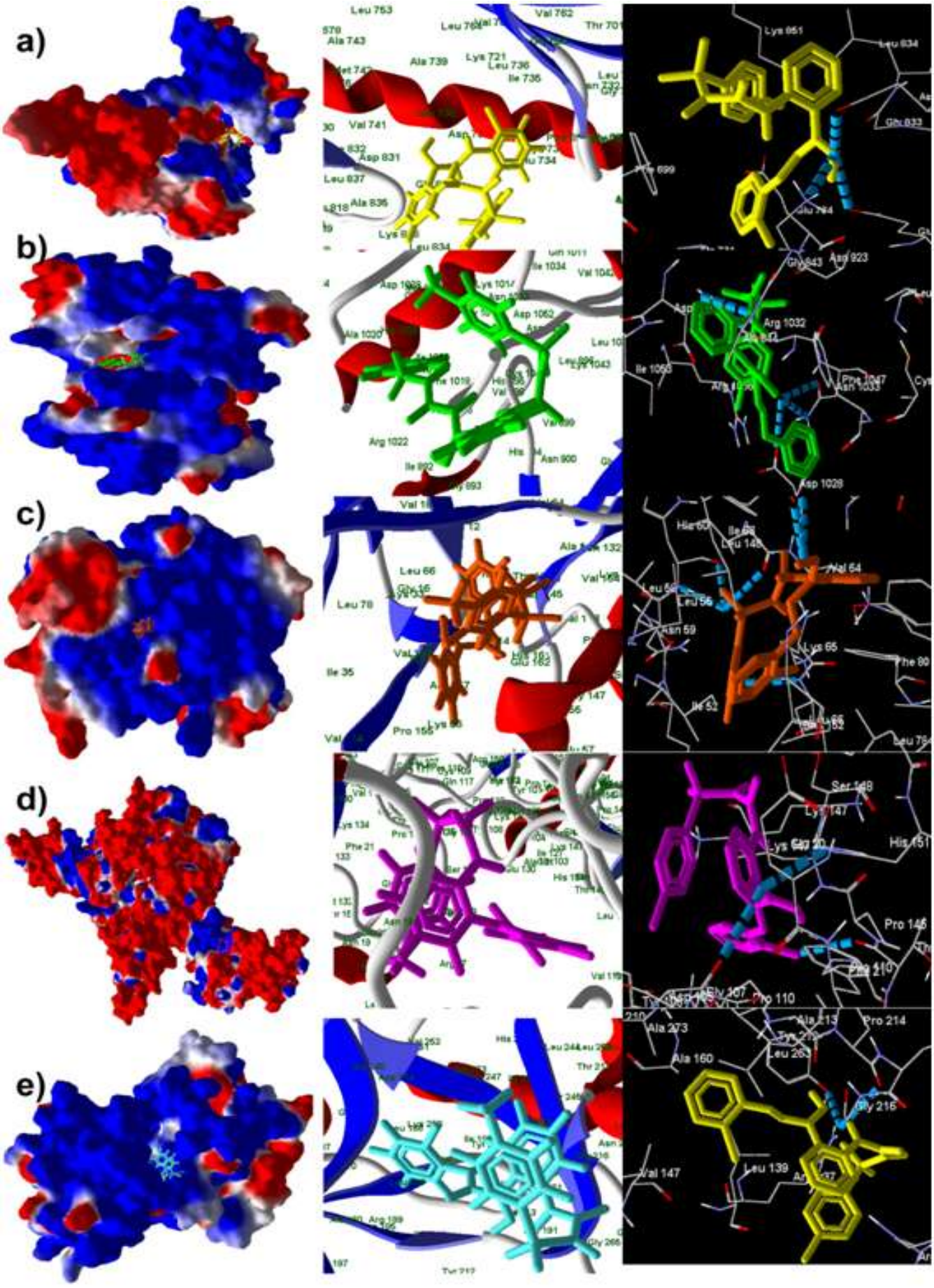



**Fig 2:** a) Active binding site, binding mode and H-bond interactions of **II.19** against **EGF** b) Active binding site, binding mode and H-bond interactions of **II.24** against **VEGF** c) Active binding site, binding mode and H-bond interactions of **II.19** against **CDK-2** d) Active binding site, binding mode and H-bond interactions of **II.19** against **CK-2** e) Active binding site, binding mode and H-bond interactions of **II.19** against **AUR-A**

**Table 3: Diarylsulfonylurea-chalcone hybrid molecules (II.1-28) with their MolDock scores against selected anticancer target proteins**

| Compound | R | MolDock score (kcal/mol) | | | | |
|---|---|---|---|---|---|---|
| | | **BRAF** | **HDAC** | **Bcl-2** | **FT** | **CAT B** |
| **II.1** | $C_6H_5$ | -124.779 | -159.135 | -92.8475 | -115.647 | -132.621 |
| **II.2** | 4-$MeC_6H_4$ | -133.027 | -175.11 | -108.781 | -132.599 | -138.644 |
| **II.3** | 4-$NMe_2C_6H_4$ | -141.499 | -171.404 | -96.9909 | -131.418 | -140.27 |
| **II.4** | 3-$OMeC_6H_4$ | -144.419 | -170.073 | -105.444 | -113.752 | -131.464 |
| **II.5** | 4-$OMeC_6H_4$ | -137.651 | -162.485 | -93.5794 | -104.131 | -136.415 |
| **II.6** | 3,4-di$OMeC_6H_3$ | -137.662 | -167.16 | -104.737 | -132.997 | -137.094 |
| **II.7** | 2,4-di$OMeC_6H_3$ | -139.15 | -168.859 | -100.511 | -112.552 | -144.649 |
| **II.8** | 3,4,5-tri$OMeC_6H_2$ | -139.24 | -171.886 | -90.2969 | -117.25 | -132.754 |
| **II.9** | 2-$OHC_6H_4$ | -137.633 | -155.847 | -101.622 | -118.381 | -133.461 |
| **II.10** | 3-$OHC_6H_4$ | -145.491 | -159.937 | -103.24 | -110.309 | -133.659 |
| **II.11** | 4-$OHC_6H_4$ | -132.808 | -160.973 | -100.894 | -118.792 | -130.555 |
| **II.12** | 3-OEt,4-$OHC_6H_3$ | -137.721 | -162.306 | -108.092 | -112.948 | -136.946 |
| **II.13** | 3-OMe,4-$OHC_6H_3$ | -113.846 | -168.554 | -95.5049 | -101.695 | -104.645 |
| **II.14** | 2-$NO_2C_6H_4$ | -125.264 | -154.284 | -89.9215 | -107.469 | -117.543 |
| **II.15** | 3-$NO_2C_6H_4$ | -135.665 | -165.593 | -107.653 | -111.533 | -130.787 |
| **II.16** | 5-OH,2-$NO_2C_6H_3$ | -122.347 | -161.119 | -101.34 | -121.578 | -134.2 |
| **II.17** | 3-$FC_6H_4$ | -131.623 | -162.695 | -106.713 | -124.648 | -136.469 |
| **II.18** | 4-$FC_6H_4$ | -130.408 | -166.494 | -104.267 | -113.323 | -136.427 |
| **II.19** | 2-$ClC_6H_4$ | -151.155 | **-209.731** | **-144.312** | **-150.059** | **-196.138** |
| **II.20** | 4-$ClC_6H_4$ | -132.101 | -164.054 | -114.262 | -110.891 | -134.275 |
| **II.21** | 2,4-di$ClC_6H_3$ | -124.372 | -162.15 | -101.303 | -112.984 | -119.755 |
| **II.22** | 3-$BrC_6H_4$ | -120.937 | -157.708 | -104.122 | -110.743 | -125.734 |
| **II.23** | 4-Allyl-$OC_6H_4$ | -137.379 | -178.148 | -110.504 | -126.359 | -148.973 |
| **II.24** | Phenylethene-yl | **-162.62** | -193.197 | -114.081 | -139.282 | -154.48 |
| **II.25** | Pyrrol-2-yl | -121.015 | -135.587 | -104.797 | -117.823 | -142.373 |
| **II.26** | Pyridin-3-yl | -107.467 | -134.921 | -104.578 | -98.4266 | -130.294 |
| **II.27** | Pyridin-4-yl | -111.242 | -138.905 | -96.5011 | -123.599 | -131.635 |
| **II.28** | Anthracen-9-yl | -129.561 | -98.6285 | -107.286 | -112.466 | -112.579 |

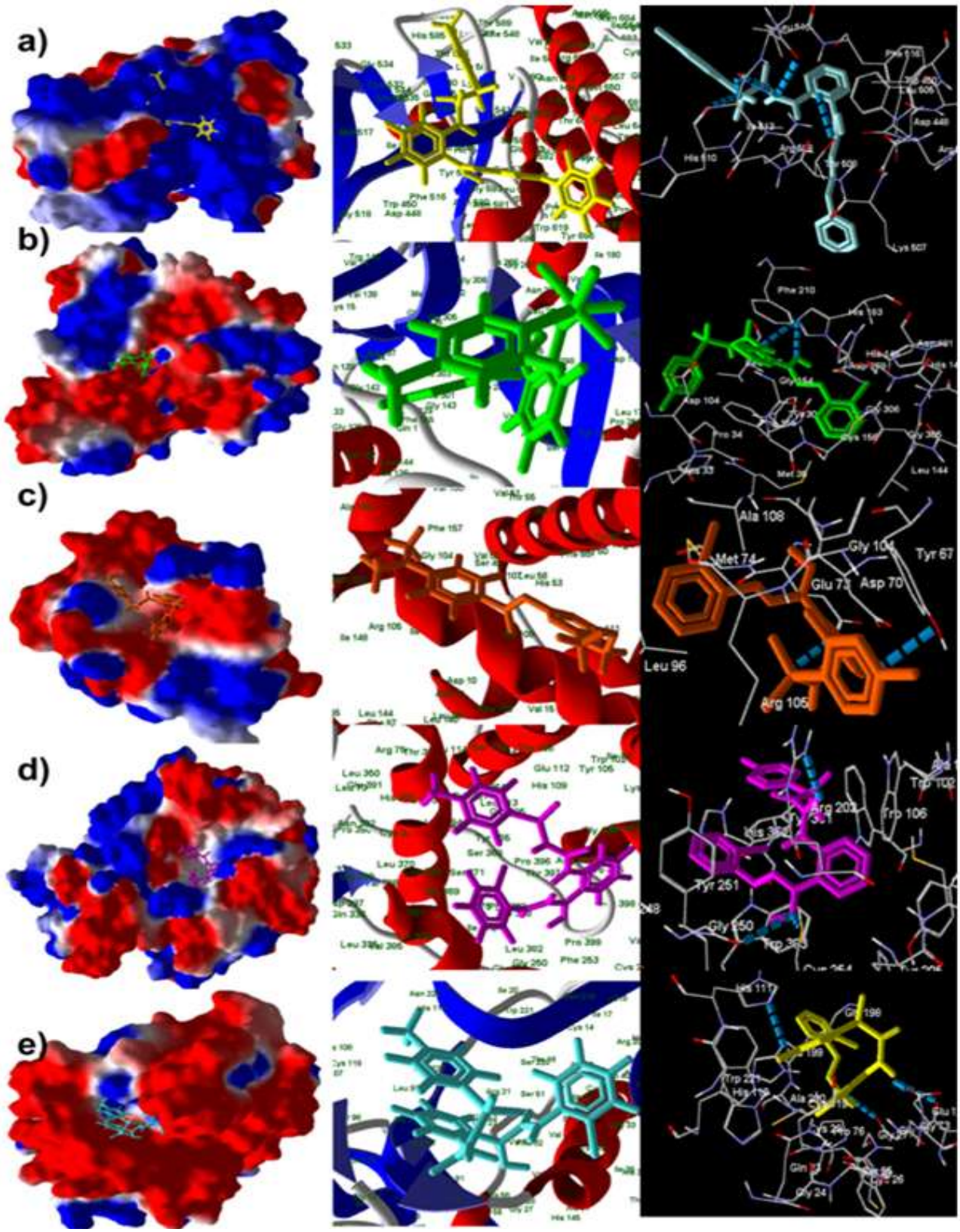



**Fig 4: a) Active binding site, binding mode and H-bond interactions of II.24 against BRAF b) Active binding site, binding mode and H-bond interactions of II.19 against HDAC c) Active binding site, binding mode and H-bond interactions of II.19 against Bcl-2 d) Active binding site, binding mode and H-bond interactions of II.19 against FT e) Active binding site, binding mode and H-bond interactions of II.19 against CAT B**

## DISCUSSIONS

A set of 28 diarylsulfonylurea-chalcone hybrid molecules **II.1-28** were subjected to ligand-protein inverse induced fit docking simulation using software Molegro Virtual Docker v 5.0. These compounds were docked against selected anticancer and antidiabetic drug targets. The results **(Table 2 and 3)** of these studies could help in preliminary identification of potential target

based hit (best fit) with respect to the observed activities (i.e. cytotoxicity activity). The hit (best fit molecule) identified against each target and its binding energy, hydrogen bond forming residues are specified as follows [22]. From the results of LPIIF docking studies on 28 diarylsulfonylurea-chalcone hybrid molecules **II.1-28** against ten different anticancer target proteins **(Table 2 and 3)**, the compounds **II.19** (-144.72)**, II.24** (-160.11)**, II.19** (-214.426)**, II.19** (-184.914)**, II.19** (-155.839)**, II.24** (-162.62)**, II.19** (-209.731)**, II.19** (-144.312)**, II.19** (-150.059) and **II.19** (-196.138) exhibited least binding energies and most stable binding orientation within the active binding site region of protein targets **EGF, VEGF, CDK-2, CK-2, AUR-A, BRAF, HDAC, Bcl-2, FT** and **CAT B**, with hydrogen bonds and corresponding hydrogen bond interacting residues (4/Lys 721, Asp 831), (1/Arg 1032), (3/Phe 146, Val 64), (5/Ser 148, Lys 147), (6/Ala 213, Tyr 212, Arg 137), (3/Pro 214), (2/Thr 508, His 510), (1/His 183), (3/Tyr 67) and (1/Gly 250, Cys 254, Arg 202, Glu 122) respectively.

## CONCLUSION

In this study the ligand-protein inverse induced fit docking (LPIIFD) simulation technique was used to preliminarily investigate the potential molecular target(s) for the diarylsulfonylurea-chalcone hybrid molecules **II.1-28** with observed cytotoxicity. The analysis of the best docked ligands against selected targets revealed the binding mode of compounds involved in this study and confirm the role as potential cytotoxic drugs. Binding energies of the drug–enzyme (receptor) interactions are important to describe how fit the drug binds to the target macromolecule. The residues participated in the hydrogen bond formation within the active binding site region revealed the importance of these residues towards the observed activity with respect to the hit identified under each class of compounds tested against cancer. The obtained results are useful to understand the structural features required to enhance the affinity as well as intrinsic activity.

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