Computational Screening and Docking of Small Molecules Targeting IGF-1R to Inhibit its Biological Activity

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Abstract

IGF-signaling pathways plays crucial role in tumor development. The intricate interactions between IGF-1 and important signaling pathways like PI3K/AKT and MAPK, which enhance the carcinogenic potential of cancer cells, are also the subject of this research.

Insulin-like Growth Factor-1 Receptor (IGF-1R) are receptor tyrosine kinases, Insulin-like growth factor-binding protein 7 (IGFBP-7) are secretory protein that binds to IGF-1R. Inhibition of IGF-1R will inactivate the cancer cell proliferation. Therefore, small molecules were targeted against IGF-1R. It is a computationally screened and docked to block their biological action. The work comprised energy reduction during ligand production, which resulted in 10,653 ligand conformations for molecular docking. Protein preparation was also performed to guarantee that the protein structure was appropriate for docking investigations. To analyze protein structure and ligand interactions, were performed on Desmond.

The references emphasize the role of IGF-1R in cancer therapeutic resistance and poor prognosis in specific malignancies. Research on IGF-binding proteins (IGFBPs) has provided information on their involvement in regulating IGF-receptor binding and downstream signalling pathways. The study sheds light on the molecular processes of IGF-1R signalling, the efficacy of small compounds in targeting IGF-1R, and the implications for cancer treatment.

Keywords: IGF-signaling pathways, IGFBP-7, IGF-1R, Docking, Cancer Cell Therapeutic

1.0 Introduction

Insulin-Like Growth Factor (IGF) signaling pathways which regulates cell proliferation and survival [1]. There are three receptor tyrosine kinases- Insulin-like growth factor-1 receptor (IGF-1R), Insulin-lie growth factor-2 receptor (IGF-2R) and Insulin Receptor (INSR) [2,3]. It consists of six serum which has high-low affinity with Insulin-like growth factor binding protein (IGF-BP's) that regulates and determine ligand bioavailability [4] these are well organized to prevent the degradation with proteases.

The malignancy formation due to numerous cancer and normal growth development which are mediated with IGF signaling pathways. The IGF-BP are carrier protein that increases half-life of IGFs and controls the binding affinity with the IGF-receptors.

There are sixteen proteins that make up the IGFBP superfamily, including IGFBP7, it has high affinity with IGFs [5]. Insulin-like growth factor-binding protein 7 (IGFBP7), also known as IGFBP-rP1 or mac25, is a multifunctional protein that plays a role in a variety of physiological and pathological processes. IGFBP-7 is a 26.4 KDa protein encoded by a gene on chromosome 4q and has an amino acid sequence with high similarity to the other human IGFBPs. It regulates activity of insulin-like growth factors (IGFs), primarily IGF-1 and IGF-2 [6]. IGFBP7 is widely expressed in numerous tissues, including the kidney, liver, heart, and reproductive organs, and it serves a range of functions throughout the body. It is involved in cellular processes such as cell proliferation, differentiation, senescence, and apoptosis, highlighting its significance in development, tissue homeostasis, and disease [7].

IGFBP7 has a promising role in cellular environment and cancer type, it has positive and negative inhibition i.e., tumor suppressor and tumor promoter. IGFBP inhibits proliferation by inducing apoptosis and suppresses metastasis through many signaling pathways which includes TGF-β and p53. In some cases, IGFBP7 may increase tumor growth by enhancing angiogenesis, epithelial-to-mesenchymal transition (EMT), and cancer cell migration [8].

Despite the involvement of IGFBP7 in cancer, therapeutic techniques targeting its interactions with specific ligands remain unexplored. The purpose of this study is to analyze the docking of IGFBP7 with ligands to further understand the possible therapeutic uses for cancer treatment. By discovering small compounds or peptides that affect IGFBP7 activity, this study hopes to discover new targeted medicines capable of slowing cancer growth and improving patient outcomes.

The investigation of IGFBP7 docking with ligands for cancer therapies is a promising method in oncology. This work intends to modulate IGFBP7 activity and downstream signaling pathways associated with cancer progression by focusing on the interaction of IGFBP7 with specific ligands, such as small compounds or peptides. This method offers various advantages, including the possibility to improve IGFBP7's tumor-suppressive actions or decrease its oncogenic effects.

Furthermore, addressing protein-ligand interactions allows for a more targeted and personalized approach to cancer treatment. Studying IGFBP7 docking with ligands for cancer treatments is a novel approach that has the potential to provide targeted therapy methods for a variety of cancer types.

Exploring IGFBP7-ligand interactions and taking advantage of its diverse roles may provide a possible path towards specific cancer therapies. Through the process of understanding the molecular mechanisms that cause these interactions, new therapeutic potential may be found, providing specialized methods to stop the spread of cancer and enhance patient outcomes.

Insulin-Like Growth Factor-1 Receptor (IGF-1R) are tyrosine kinases with disulfide linked homodimer structure. The autophosphorylation of tyrosine residues within the cytoplasmic domain of receptor it triggers downstream signaling cascades essential for cellular responses of IGF-stimulation [9].

IGFBP7 protein binds to IGF1R which inhibits the activity and downstream signaling. It interacts IGF-1 and insulin with low affinity. IGFBP7 inhibits IGF1R internalization despite insulin stimulation which has a prolonged effect on IGF-1R activation [10,11].

IGFBP7 reduces IGF signalling via binding to and blocking IGF1R, rather than sequestering IGF ligands. This renders IGFBP7 a strong tumor suppressor, capable of overcoming IGF1R-mediated cancer cell survival and medication resistance [12].

Some case studies show increases IGF-1R expression are associated with poor prognosis in colorectal cancer. It inhibits IGF-1R can sensitize breast cancer cells for cancer treatment such as chemotherapy and radiosensitivity [13].

Therefore IGF-1R act as the best inhibitor complex for cancer cell proliferation. IGF-1R inhibition decreases immunosuppression in tumor microenvironment. Thus essential in drug discovery.

2.0 Material and Method

2.1 Selection of Protein

The target protein was IGF-1-Receptor Kinase Domain (IGF-1R), which was taken from Protein Data Bank (PDB) database [14]. The target protein is 1JQH from PDB. The target protein are generally attacked by IGFBP7 secreted protein which inhibits the downstream signaling pathway. Inhibiting IGF-1R significantly reduces the cancer cell growth and sensitize them from cancer treatments like chemotherapy and radiation [15].

2.2 Selection of Ligands

The ligands were obtained from ChemDiv (https://www.chemdiv.com/)-Immunological Library which consist of 6531 compounds [16]. It is specially designed for drug discovery with strong immunological targets. It is highly therapeutics specific, chemokine receptors which has pivotal role in immune cell migration. These are used as the essential small molecules to inhibit the IGF-1R process which initiate cancer progression.

2.3 Validation of Protein Structure

A web-based platform called SAVES-v6.0 (Structural Analysis and Verification Server) provides numerous information [17], it also generates confirmation of structure proteins. It provides various modules to evaluate elements of protein structure such as energetics, stereochemistry, and geometry. Using this tool Ramachandran plots were generated and analyzed. It provides information on the basic configuration of protein structures. This analysis helps in locating structural sections that might have incorrect backbone torsion angles.

2.4 Virtual Screening of Molecules

Analyzing the interaction of ligands against target protein using Schrodinger [18,19]. Initially the ligands were prepared using Lig-Prep module. It is an application which consist of series of steps that perform conversion of 2D structures to 3D structure. This step utilizes the structure for minimizing the bond angles and distances which optimize the energy [20].

Protein Preparation is performed to analyze the high-confidence structure ideal use with wide variety of modeling applications. It is an essential step is an essential step and it is necessary to

minimize the energy of protein molecule prior to docking studies with ligands. Both the Protein for ligand docking study was prepared by using protein preparation wizard tool in which was used to import proteins for the protein data bank (PDB). In this pre-processing of protein several parameters can be initiated such as adding hydrogen, creating zero order bonds to metals and di-sulphide bonds and remover waters [21]. Followed by Receptor-Grid Generation are performed prior to running a virtual screening glide. The shape and properties of the receptor are represented in a grid by field that provides progressively more accurate scoring of the ligand poses. For receptors that adopt more than one conformation on binding, Glide prepares grids for each conformation, to ensure that possible actives are not missed which includes receptor, site and constraints. The ligand docking process helps to predict ligand conformation and orientation (posing) within a targeted binding site and thus helps to interpret interactions of ligand atoms with amino acids of proteins, and to understand the binding affinity. The ligand docking was performed using ligand docking panel where the receptor grid output was selected along with the prepared ligand. This provides information about geometric complementarity, interaction complementarity, docking score, correlation with experimental data, ligand interaction diagrams, and more. The detailed examination of the ligands alongside of amino acid within binding pockets with the protein.

2.5 Toxicity Prediction

Toxicity prediction is crucial in drug discovery as it identify the potential safety issues related in the drugs. It helps to prioritize compounds with lower toxicity profiles and reduce the risk in later stages. ADMET-AI is a machine learning platform that execute toxicity prediction [22].

3.0 Results and Discussion

3.1 Validation of Protein

The study was targeting IGF-1R protein which was collected from PDB-1JQH. Before starting the analysis, the protein was validated using SAVES6.0 tool where Ramachandran plot was examined. The protein 87.8% falls under flavored regions, 11.4% falls under allowed regions, 0.5% falls under general region and 0.3% falls under disallowed regions. Figure:1 represents the protein’s Ramachandran plot.

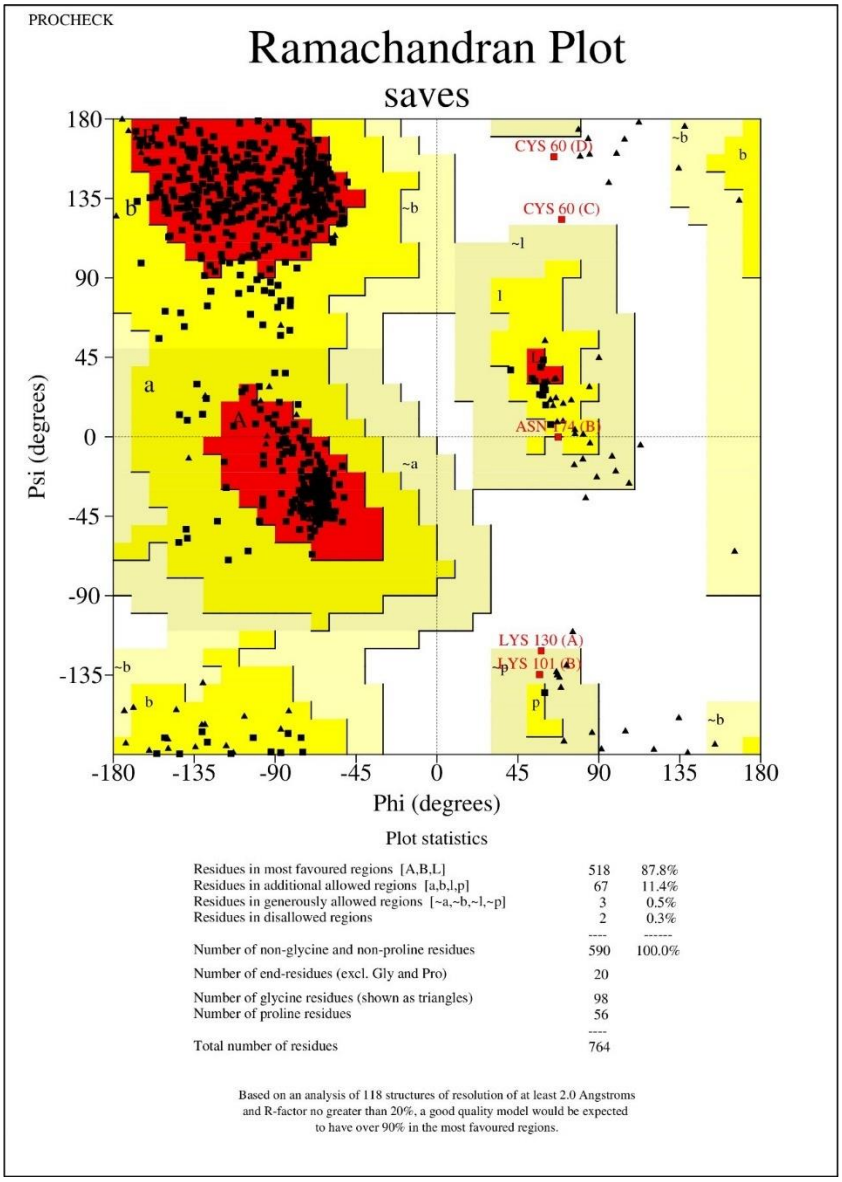

Figure:1- Represents Ramachandran Plot for Target Protein obtained from 1JQH

3.2 Virtual Screening of Ligand and Protein

The energy minimization was executed during ligands preparation. After performing lig-prep 10,653 compounds was generated. All this conformation ligands were used in molecular docking study. Followed by protein-preparation of the protein which was performed to ensure the protein structure is suitable for molecular docking it is given in Figure:2.

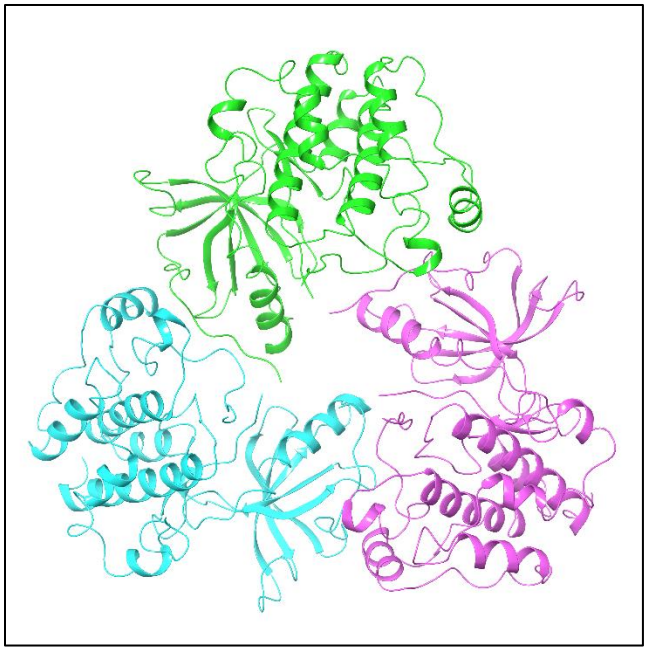

Figure:2- Representation of Protein

3.3 Molecular Docking

Receptor grid was generated for the protein which was used for input for ligand docking, along with all the ligands that was generated. All the lig-prep compounds (10,653) were docked against the target protein. The top-50 compounds were taken further for validation. The list of ligands and their docking scores are given in Table-1. The top ligands had the best docking score. N-(1-benzyl-4-piperidyl)-3-(3-thienyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxamide with -8.0228 kcal/mol. The protein consists of three chains. The binding pocket for each chain is given below:

Chain A Ala984, Asp985, Arg1042, Thr 1157, Asp1159

Chain B Ala 984, Glu1046, Asn1049, Gly1155, Met1156, Thr1157, Arg1158, Asp1159, Ile1160, Tyr1161

Chain C Ala984, Glu1050, Asp1159, Ile1160, Tyr1161, Glu1162

The hydrogen bonds are significantly important for binding affinity. The interaction of protein Chain-A is at Asp1159 and chain-B is at Arg1158. The same is given in Figure:3.

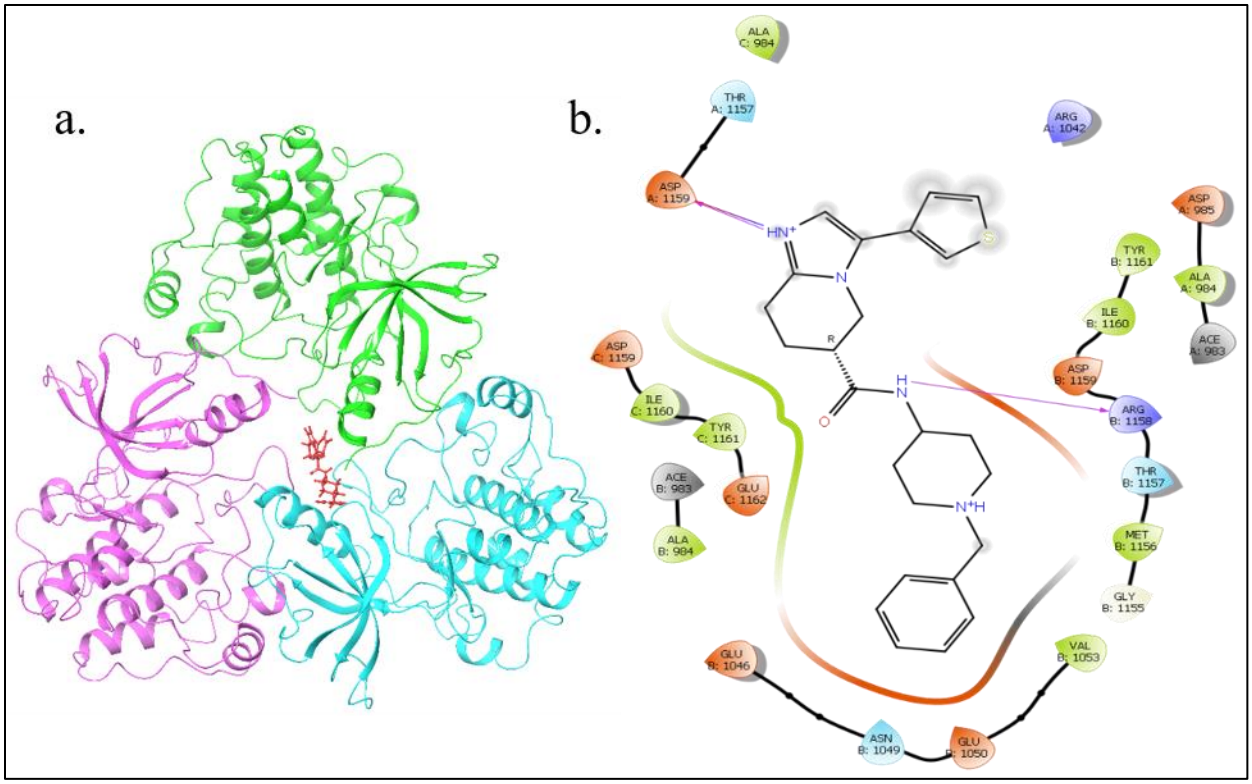

Figure:3- Molecular Docking for IGF-1R and Anti-Cancer Drug, a. represents the ligand and protein and b. represents the interaction profile.

Table-1 Illustartes top 50 ligands along with their docking scores

LIGAND NAMES	**DOCKING SCORE (kcal/mol)**
N-(1-benzyl-4-piperidyl)-3-(3-thienyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxamide	-8.0228
N-(4-acetylphenyl)-2-({5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4-phenyl-4H-1,2,4-triazol-3-yl}sulfanyl)acetamide	-7.5514
2-({[(2,4-dimethoxyphenyl)methyl][2-(1H-indol-3-yl)ethyl]amino}methyl)-N-[(4-fluorophenyl)methyl]-1,3-oxazole-4-carboxamide	-7.529
2-fluoro-4-[(3-{[2-(piperidine-1-carbonyl)phenoxy]methyl}piperidin-1-yl)methyl]phenol	-7.4148
2-(4-{[(4-fluorophenyl)carbamoyl]methyl}piperazin-1-yl)-N-(4-	-7.4106

phenoxyphenyl)acetamide	
N~1~-[3-(2-ethylpiperidino)propyl]-2-[4-methyl-1-oxo[1]benzothieno[2,3-d]pyridazin-2(1H)-yl]propanamide	-7.2538
1-(3-chloro-4-methylphenyl)-3-[2-(2-phenyl-1H-1,3-benzodiazol-1-yl)ethyl]urea	-7.2219
6-({4-[(4-fluorophenyl)methyl]piperazin-1-yl}methyl)-2-(4-{[4-(propan-2-yl)phenyl]methyl}piperazin-1-yl)-3,4-dihydropyrimidin-4-one	-7.2183
3-[1-(3-chlorophenyl)-5-methyl-1H-pyrazol-3-yl]-9-[(3,4-difluorophenyl)methoxy]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	-7.2146
N-(2,4-dimethoxyphenyl)-2-{[4-(4-fluorophenyl)-5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4H-1,2,4-triazol-3-yl]sulfanyl}acetamide	-7.1724
N-[(4-fluorophenyl)methyl]-2-({[2-(1H-indol-3-yl)ethyl][(2-methoxyphenyl)methyl]amino}methyl)-1,3-oxazole-4-carboxamide	-7.1704
2-(dimethylamino)-1-[3-(4-fluorophenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-5-yl]ethan-1-one	-7.1472
2-{1-[(furan-2-yl)methyl]piperidin-4-yl}-6-methyl-3-(piperidine-1-carbonyl)pyridine	-7.0977
2-{[4-(4-fluorophenyl)-5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4H-1,2,4-triazol-3-yl]sulfanyl}-N-[(furan-2-yl)methyl]acetamide	-7.0633
9-[(3,4-difluorophenyl)methoxy]-3-[1-(2,4-dimethylphenyl)-5-methyl-1H-pyrazol-3-yl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	-7.0526
9-[(3,4-difluorophenyl)methoxy]-2-methyl-3-[5-methyl-1-(3-methylphenyl)-1H-pyrazol-3-yl]-4H-pyrido[1,2-a]pyrimidin-4-one	-7.0358
1-(4-fluorophenyl)-N-{3-oxo-2H,3H,5H,6H,7H,8H,9H-[1,2,4]triazolo[4,3-a]azepin-7-yl}methanesulfonamide	-7.032
N-[1-benzyl-4-(hydroxymethyl)pyrrolidin-3-yl]-4-fluorobenzamide	-7.0268
N-(3-acetamidophenyl)-2-({5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4-phenyl-4H-1,2,4-triazol-3-yl}sulfanyl)acetamide	-6.9923
N~1~-{3-[benzyl(methyl)amino]propyl}-2-[6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl]acetamide	-6.9866

3-[(4-acetyl-4-phenylpiperidino)methyl]-N~1~-(2-pyridylmethyl)benzamide	-6.9438
1-[4-(2-fluorophenyl)piperazin-1-yl]-3-{[2-(4-methoxyphenyl)quinazolin-4-yl][3-(morpholin-4-yl)propyl]amino}propan-1-one	-6.8575
N-(4-acetylphenyl)-2-{[4-(4-chlorophenyl)-5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4H-1,2,4-triazol-3-yl]sulfanyl}acetamide	-6.8324
N-[(2,4-difluorophenyl)methyl]-4-methyl-1-[2-(3-methylphenyl)acetyl]piperidine-4-carboxamide	-6.8291
2-{7-methyl-2-oxo-3-[(phenylamino)methyl]-1,2-dihydroquinolin-1-yl}-N-(4-methylphenyl)acetamide	-6.8265
N~1~-(2,4-dimethylphenyl)-2-{[4-(2-furylmethyl)-5-oxo-4,5-dihydrothieno[2,3-e][1,2,4]triazolo[4,3-a]pyrimidin-1-yl]sulfanyl}acetamide	-6.7842
9-[(3,4-difluorophenyl)methoxy]-2-methyl-3-[5-methyl-1-(4-methylphenyl)-1H-pyrazol-3-yl]-4H-pyrido[1,2-a]pyrimidin-4-one	-6.7728
N-{3-[cyclohexyl(methyl)amino]propyl}-2-(3,6,7-trimethyl-2-oxo-1,2-dihydroquinoxalin-1-yl)acetamide	-6.7707
3-[1-(2-chlorophenyl)-5-methyl-1H-pyrazol-3-yl]-9-[(3,4-difluorophenyl)methoxy]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	-6.7642
N-[2-(4-benzylpiperidin-1-yl)ethyl]-3-[2-(3-fluorophenyl)-5,7-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]propanamide	-6.7591
9-[(3,4-difluorophenyl)methoxy]-3-[1-(2-methoxyphenyl)-5-methyl-1H-pyrazol-3-yl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	-6.7354
2-(4-methoxyphenoxy)-N-{1-methyl-2-[(4-methylpiperidin-1-yl)methyl]-1H-1,3-benzodiazol-5-yl}acetamide	-6.7302
3-[1-(4-chlorophenyl)-5-methyl-1H-pyrazol-3-yl]-9-[(3,4-difluorophenyl)methoxy]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	-6.7252
1-{4-[(4-fluorophenyl)methyl]piperazin-1-yl}-2,2-diphenylethan-1-one	-6.7178
N-benzyl-N-methyl-1'-(3-methylbutanoyl)-[1,4'-bipiperidine]-4-carboxamide	-6.7162
N-(4-chlorophenyl)-2-({4-[(4-methoxyphenyl)methyl]piperazin-1-yl}methyl)-1,3-oxazole-4-carboxamide	-6.7132
N-(2-{[(furan-2-yl)methyl](2-phenylethyl)amino}ethyl)-2-(pyridin-3-	-6.702

yl)quinoline-4-carboxamide	
1-[2-({7-chloro-4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl}methoxy)phenyl]-3-(2,4-dimethoxyphenyl)urea	-6.6922
2-({4-[(2,5-dimethoxyphenyl)methyl]piperazin-1-yl}methyl)-N-(3-fluoro-4-methylphenyl)-1,3-oxazole-4-carboxamide	-6.6719
N-[(2-ethoxyphenyl)methyl]-1-{pyrrolo[1,2-a]quinoxalin-4-yl}piperidine-3-carboxamide	-6.6164
N-(1-benzylpiperidin-4-yl)-1-(3-fluorophenyl)-3,6-dimethyl-1H-pyrazolo[3,4-b]pyridine-4-carboxamide	-6.6073
2-{2-[4-(4-methylphenyl)-1,3-thiazol-2-yl]-1H-pyrrol-1-yl}-N-[2-(4-methylpiperidin-1-yl)ethyl]acetamide	-6.5968
N-(3-{[1,4'-bipiperidin]-1'-yl}propyl)-2-(2-phenylethyl)-1,3-benzoxazole-6-carboxamide	-6.5682
3-(3,4-dimethoxyphenyl)-1-[(4-fluorophenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]urea	-6.5519
N-{1-[(4-fluorophenyl)methyl]-4-(hydroxymethyl)pyrrolidin-3-yl}benzamide	-6.5499
4-{cyclopentyl[(2-methylbutyl)carbamoyl]methyl}-N-phenylpiperazine-1-carboxamide	-6.5357
N-[1-benzyl-4-(hydroxymethyl)pyrrolidin-3-yl]-2-(4-methoxyphenyl)acetamide	-6.5255
1-benzyl-4-{4-[(piperidin-1-yl)methyl]benzoyl}piperazine	-6.4997
{2-benzyl-8-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]-2,8-diazaspiro[4.5]dec-4-yl}methanol	-6.4974
N-{2-[cyclohexyl(methyl)amino]ethyl}-2-{4-oxo-3H,4H,5H-pyridazino[4,5-b]indol-3-yl}acetamide	-6.4965

3.4 Toxicity Prediction

Machine learning is a crucial technique in predicting toxicity during drug discovery which has high efficiency and accuracy in screening the drug candidates. The safety profile which reduces the risk of adverse effects the computational significance in toxicity resource and minimizing the animal model testing.

The ligands which was used for the prediction had anti-cancer effect which plays essential role in inhibition of IGF production due to which cancer cells proliferate. The toxicity predicted value using ADMET-AI is given in Table-2. Based on this compound N-(1-benzyl-4-piperidyl)-3-(3-thienyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxamide has BBB percentile of 72.27% which means there is higher probability of the molecules does not cross blood-brain barrier. Bioavailability percentile of 24.81% is moderately absorbed in the body. And carcinogenity percentile are 26.94% are less carcinogenic in nature and does not harm the body given in Figure:4. Although it has favorable LogP value which is at the range of 3.9548 and CaCo2 of -5.6682 which indicates ligands having good drug-likeness and bioavailability it is given in Figure:6

These compounds have anti-cancer therapeutic properties. N-(1-benzyl-4-piperidyl)-3-(3-thienyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxamide in pharmaceuticals are potential anti-cancer agent. This inhibits cell growth, induce apoptosis or interfere with specific pathways essential for cancer cell survival proliferation [23]. N-(4-acetylphenyl)-2-({5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4-phenyl-4H-1,2,4-triazol-3-yl}sulfanyl)acetamide which exhibit potential anti-cancer effects against cancer by inhibiting cell proliferation, inducing G2/M phase arrest and promoting apoptosis in cancer cells. It also suppresses the Notch-AKT signalling pathways associated with oxidative stress, indicating that it is effective in targeting cancer cells [24].

2-({[(2,4-dimethoxyphenyl)methyl][2-(1H-indol-3-yl)ethyl]amino}methyl)-N-[(4-fluorophenyl)methyl]-1,3-oxazole-4-carboxamide inhibits cell growth, induces cell cycle arrest, and promotes apoptosis, all of which have anticancer properties against breast cancer cells [25].

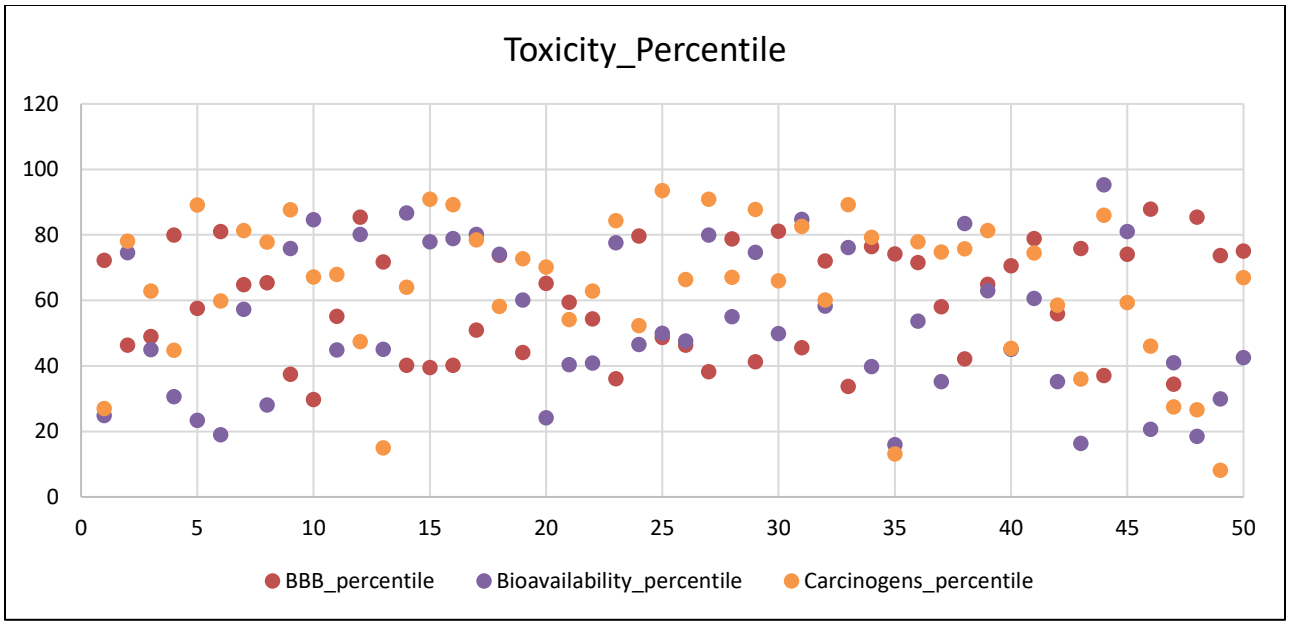

Figure:4- Representation of BBB, Bioavailability and Carcinogenic Percentile Plot for top-50 ligands

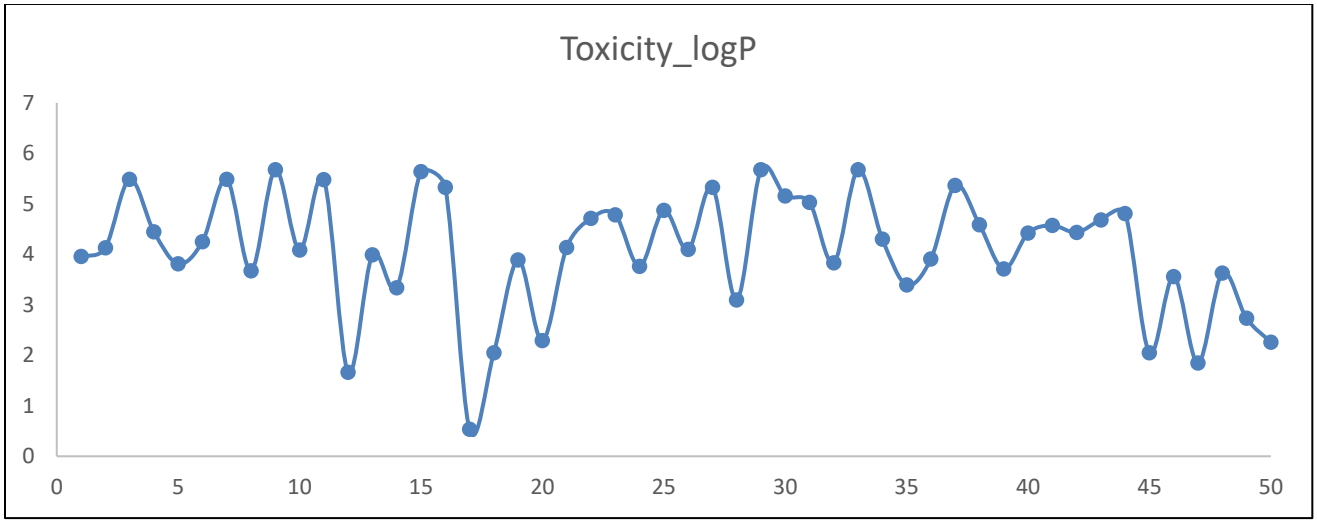

Figure:5- Represents LogP toxicity value for all top-50 ligands

Table-2 Represents the toxicity prediction for top-50 ligands

Names	logP	Caco2	BBB_percentile	Bioavailability_percentile	Carcinogens_percentile
N-(1-benzyl-4-piperidyl)-3-(3-thienyl)-5,6,7,8-	3.9548	-5.66	72.2761	24.8158	26.9484

tetrahydroimidazo[1,2-a]pyridine-6-carboxamide		82			
N-(4-acetylphenyl)-2-({5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4-phenyl-4H-1,2,4-triazol-3-yl}sulfanyl)acetamide	4.13	-5.6345	46.3358	74.6026	78.0923
2-({[(2,4-dimethoxyphenyl)methyl][2-(1H-indol-3-yl)ethyl]amino}methyl)-N-[(4-fluorophenyl)methyl]-1,3-oxazole-4-carboxamide	5.4871	-5.5356	49.0112	44.9399	62.8538
2-fluoro-4-[(3-{[2-(piperidine-1-carbonyl)phenoxy]methyl}piperidin-1-yl)methyl]phenol	4.4484	-5.0144	79.9922	30.5933	44.7848
2-(4-{[(4-fluorophenyl)carbamoyl]methyl}piperazin-1-yl)-N-(4-phenoxyphenyl)acetamide	3.8128	-5.1071	57.5417	23.3812	89.1819
N~1~-[3-(2-ethylpiperidino)propyl]-2-[4-methyl-1-oxo[1]benzothieno[2,3-d]pyridazin-2(1H)-yl]propanamide	4.25142	-5.6278	81.0004	18.9608	59.8682
1-(3-chloro-4-methylphenyl)-3-[2-(2-phenyl-1H-1,3-benzodiazol-1-yl)ethyl]urea	5.48682	-4.9562	64.8313	57.309	81.2718
6-({4-[(4-	3.672	-	65.413	28.1117	77.7821

fluorophenyl)methyl]piperazin-1-yl}methyl)-2-(4-{[4-(propan-2-yl)phenyl]methyl}piperazin-1-yl)-3,4-dihydropyrimidin-4-one	4	5.4285			
3-[1-(3-chlorophenyl)-5-methyl-1H-pyrazol-3-yl]-9-[(3,4-difluorophenyl)methoxy]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	5.67464	-4.8323	37.4564	75.8434	87.6309
N-(2,4-dimethoxyphenyl)-2-{[4-(4-fluorophenyl)-5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4H-1,2,4-triazol-3-yl]sulfanyl}acetamide	4.0837	-5.4224	29.7402	84.684	67.119
N-[(4-fluorophenyl)methyl]-2-({[2-(1H-indol-3-yl)ethyl][(2-methoxyphenyl)methyl]amino}methyl)-1,3-oxazole-4-carboxamide	5.4785	-5.5743	55.1377	44.8623	67.9721
2-(dimethylamino)-1-[3-(4-fluorophenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-5-yl]ethan-1-one	1.6621	-4.5721	85.4595	80.1861	47.3827
2-{1-[(furan-2-yl)methyl]piperidin-4-yl}-6-methyl-3-(piperidine-1-	3.98872	-5.0094	71.7332	45.0562	15.0058

carbonyl)pyridine					
2-{[4-(4-fluorophenyl)-5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4H-1,2,4-triazol-3-yl]sulfanyl}-N-[(furan-2-yl)methyl]acetamide	3.3372	-5.6034	40.1706	86.739	63.9783
9-[(3,4-difluorophenyl)methoxy]-3-[1-(2,4-dimethylphenyl)-5-methyl-1H-pyrazol-3-yl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	5.63808	-4.7507	39.5502	77.9372	90.8879
9-[(3,4-difluorophenyl)methoxy]-2-methyl-3-[5-methyl-1-(3-methylphenyl)-1H-pyrazol-3-yl]-4H-pyrido[1,2-a]pyrimidin-4-one	5.32966	-4.7442	40.1706	78.8678	89.2206
1-(4-fluorophenyl)-N-{3-oxo-2H,3H,5H,6H,7H,8H,9H-[1,2,4]triazolo[4,3-a]azepin-7-yl}methanesulfonamide	0.535	-5.342	50.9112	80.1473	78.5188
N-[1-benzyl-4-(hydroxymethyl)pyrrolidin-3-yl]-4-fluorobenzamide	2.0484	-4.7685	73.8271	74.0597	58.2009
N-(3-acetamidophenyl)-2-({5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4-phenyl-4H-1,2,4-triazol-3-yl}sulfanyl)acetamide	3.8858	-5.8063	44.0481	60.1396	72.7414
N~1~-{3-	2.287	-	65.1803	24.1954	70.221

[benzyl(methyl)amino]propyl }-2-[6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl]acetamide	5	5.7768			
3-[(4-acetyl-4-phenylpiperidino)methyl]-N~1~-(2-pyridylmethyl)benzamide	4.1344	-5.3683	59.4029	40.4033	54.1295
1-[4-(2-fluorophenyl)piperazin-1-yl]-3-{[2-(4-methoxyphenyl)quinazolin-4-yl][3-(morpholin-4-yl)propyl]amino}propan-1-one	4.7121	-4.7683	54.3622	40.9073	62.8926
N-(4-acetylphenyl)-2-{[4-(4-chlorophenyl)-5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4H-1,2,4-triazol-3-yl]sulfanyl}acetamide	4.7834	-5.4706	36.0605	77.5882	84.335
N-[(2,4-difluorophenyl)methyl]-4-methyl-1-[2-(3-methylphenyl)acetyl]piperidine-4-carboxamide	3.76082	-4.7962	79.682	46.4909	52.3459
2-{7-methyl-2-oxo-3-[(phenylamino)methyl]-1,2-dihydroquinolin-1-yl}-N-(4-methylphenyl)acetamide	4.86914	-5.1661	48.701	49.9806	93.5634
N~1~-(2,4-dimethylphenyl)-2-{[4-(2-furylmethyl)-5-oxo-	4.09464	-5.64	46.3358	47.5766	66.3435

4,5-dihydrothieno[2,3-e][1,2,4]triazolo[4,3-a]pyrimidin-1-yl]sulfanyl}acetamide		87			
9-[(3,4-difluorophenyl)methoxy]-2-methyl-3-[5-methyl-1-(4-methylphenyl)-1H-pyrazol-3-yl]-4H-pyrido[1,2-a]pyrimidin-4-one	5.32966	-4.7665	38.2706	79.9922	90.8879
N-{3-[cyclohexyl(methyl)amino]propyl}-2-(3,6,7-trimethyl-2-oxo-1,2-dihydroquinoxalin-1-yl)acetamide	3.09256	-5.1673	78.7902	55.0601	67.0803
3-[1-(2-chlorophenyl)-5-methyl-1H-pyrazol-3-yl]-9-[(3,4-difluorophenyl)methoxy]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	5.67464	-4.8755	41.2175	74.6801	87.786
N-[2-(4-benzylpiperidin-1-yl)ethyl]-3-[2-(3-fluorophenyl)-5,7-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]propanamide	5.15574	-5.409	81.0779	49.8643	65.9558
9-[(3,4-difluorophenyl)methoxy]-3-[1-(2-methoxyphenyl)-5-methyl-1H-pyrazol-3-yl]-2-	5.02984	-4.7482	45.5603	84.7615	82.6289

methyl-4H-pyrido[1,2-a]pyrimidin-4-one					
2-(4-methoxyphenoxy)-N-{1-methyl-2-[(4-methylpiperidin-1-yl)methyl]-1H-1,3-benzodiazol-5-yl}acetamide	3.8313	-4.9638	72.0434	58.2784	60.1008
3-[1-(4-chlorophenyl)-5-methyl-1H-pyrazol-3-yl]-9-[(3,4-difluorophenyl)methoxy]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	5.67464	-4.8358	33.6952	76.1148	89.2594
1-{4-[(4-fluorophenyl)methyl]piperazin-1-yl}-2,2-diphenylethan-1-one	4.302	-4.9713	76.425	39.8216	79.2555
N-benzyl-N-methyl-1'-(3-methylbutanoyl)-[1,4'-bipiperidine]-4-carboxamide	3.3941	-4.8836	74.176	15.9364	13.1446
N-(4-chlorophenyl)-2-({4-[(4-methoxyphenyl)methyl]piperazin-1-yl}methyl)-1,3-oxazole-4-carboxamide	3.9067	-5.1207	71.5006	53.6254	77.8984
N-(2-{[(furan-2-yl)methyl](2-phenylethyl)amino}ethyl)-2-(pyridin-3-yl)quinoline-4-carboxamide	5.3645	-5.44	58.0845	35.2462	74.7577
1-[2-({7-chloro-4-oxo-4H-pyrido[1,2-a]pyrimidin-2-	4.5881	-5.02	42.1869	83.482	75.7658

yl}methoxy)phenyl]-3-(2,4-dimethoxyphenyl)urea		25			
2-({4-[(2,5-dimethoxyphenyl)methyl]piperazin-1-yl}methyl)-N-(3-fluoro-4-methylphenyl)-1,3-oxazole-4-carboxamide	3.70942	-4.9442	64.9477	62.9701	81.2718
N-[(2-ethoxyphenyl)methyl]-1-{pyrrolo[1,2-a]quinoxalin-4-yl}piperidine-3-carboxamide	4.419	-5.1508	70.5312	45.0562	45.3664
N-(1-benzylpiperidin-4-yl)-1-(3-fluorophenyl)-3,6-dimethyl-1H-pyrazolo[3,4-b]pyridine-4-carboxamide	4.57084	-5.3268	78.9066	60.6437	74.4862
2-{2-[4-(4-methylphenyl)-1,3-thiazol-2-yl]-1H-pyrrol-1-yl}-N-[2-(4-methylpiperidin-1-yl)ethyl]acetamide	4.43512	-5.3845	55.9131	35.2074	58.5498
N-(3-{[1,4'-bipiperidin]-1'-yl}propyl)-2-(2-phenylethyl)-1,3-benzoxazole-6-carboxamide	4.6832	-5.6796	75.8046	16.3629	36.0217
3-(3,4-dimethoxyphenyl)-1-[(4-fluorophenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]urea	4.804	-4.9523	37.0686	95.2695	85.9636
N-{1-[(4-fluorophenyl)methyl]-4-(hydroxymethyl)pyrrolidin-3-	2.0484	-4.7629	74.0597	81.0004	59.3641

yl}benzamide					
4-{cyclopentyl[(2-methylbutyl)carbamoyl]methyl}-N-phenylpiperazine-1-carboxamide	3.5572	-4.7926	87.9023	20.6669	46.0256
N-[1-benzyl-4-(hydroxymethyl)pyrrolidin-3-yl]-2-(4-methoxyphenyl)acetamide	1.8468	-4.8733	34.432	40.9849	27.4525
1-benzyl-4-{4-[(piperidin-1-yl)methyl]benzoyl}piperazine	3.6305	-4.8308	85.4595	18.4568	26.6382
{2-benzyl-8-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]-2,8-diazaspiro[4.5]dec-4-yl}methanol	2.733 04	-5.4674	73.7107	29.9341	8.14269
N-{2-[cyclohexyl(methyl)amino]ethyl}-2-{4-oxo-3H,4H,5H-pyridazino[4,5-b]indol-3-yl}acetamide	2.2585	-5.496	75.1066	42.5746	66.9639

4.0 Conclusion

IGF-signaling pathways are involved in activating cancer cells. IGFBP-7 are secretory proteins which binds to the IGF-1R that activates and trigger enormous amount of cell proliferation Therefore, small molecules were collected from Chem-Div to inhibit IGF-1R process. Using Desmond all the molecules were docked against the target protein to which toxicity was predicted using AMET-AI. Toxicity prediction is effect in identifying the safety profile, highly cost effect and reduces the animal test risk. This shift computational toxicity prediction which contributes to the 3R principle which is replacement, reduction and refinement.

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6.0 Reference

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