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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Identification of new insulin growth factor receptor-1 (IGF-1R) inhibitors via exploring ATPas kinase domain of IGF-1R through virtual screening

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Abstract Insulin growth factor receptor-1 is a transmembrane tyrosine kinase receptor that mediates the polypeptide protein hormone insulin growth factor-1, responsible for normal function and growth of human cells. The overexpression of insulin growth factor receptor-1 has been associated with a variety of cancers. A number of small molecule inhibitors of insulin growth factor receptor-1 are discovered by various researchers but all of them get failed in preclinical trials due to less potency and resistance. In the present paper, we have identified new insulin growth factor receptor-1 inhibitors through virtual screening based on ATPase kinase domain having phosphate, sugar and hydrophobic regions lined with amino acid residues such as Asp 1150, Lys 1003, Phe 1124 and Lys 1033. A total of 7659 compounds were selected from PubChem database. Then on applying, the rule of five, 4482 compounds were enlisted and downloaded. Further on performing high throughput virtual screening, standard precision and extra precision three best scoring compounds were identified, which could be taken further for drug development.

Keywords IGF-1R · IGF-1R inhibitors · Virtual Screening · Molecular docking · Anticancer activity

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Introduction

The insulin-like growth factor system consists of insulin receptors (IRs), insulin-like growth factor-1 receptor (IGF-1R), insulin-like growth factor-2 receptor (IGF-2R); their ligands i.e., insulin, IGF-1, IGF-2; and six IGF-binding proteins (Negi et al. 2013). IGF-1R plays a role in cell survival and prevention of programmed cell death, while IGF-2R doesn't appear to be involved in the regulation of apoptosis (Delafontaine et al. 2004). Both IGF-1 and IGF-2 show high affinity towards IGF-1R. The IGF-1R is a tyrosine kinase receptor that is homologous to the IR, but both have distinct functions. IR plays a role in metabolic homeostasis, while IGF-1R plays a role in cell development and proliferation process. IGF-1R consists of two α-subunits and two β-subunits covalently linked by three disulfide bridges. The two α-subunits are extracellular while β-subunits span the membrane and are responsible for intracellular signal transduction upon ligand stimulation. Each α-subunit has molecular weight of ~ 130 kDa, contains ligand binding site on the cysteine-rich region, whereas each β-subunit is having molecular weight of ~ 90–95 kDa and contains the tyrosine kinase domain. The mature IGF-1R has a molecular weight of approximately 320 kDa (Adams et al. 2000; Bahr and Groner 2004). The IGF-1R is recognized as a druggable target as it has been overexpressed in a number of cancer including lung, breast, prostate, neuroendocrine, head and neck cancer, GIT cancer (Lawrence et al. 2007; Sarzehi and Chamani 2010). Many IGF-1R inhibitors or protein-protein interaction inhibitors (Meena et al. 2014) acting as anticancer agents are reported in literature that contain a heterocyclic (Garg et al. 2014) scaffold such as imidazopyrazine (Mulvihill et al. 2008), pyrrolopyrimidine (García-Echeverría et al. 2004; Grotzfeld et al. 2005), pyrimidine/triazine-quinolines(Iranfar et al.

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2012) naphthalene (Buchanan et al. 2011), isoquinolinedione (Mayer et al. 2008), hydantoin-quinoline (Lesuisse et al. 2011), cyanoquinolines (Miller et al. 2009), benzimidazolepyridone (Wittman et al. 2005), thiazolidinediones (Geissler et al. 1992) (Liu et al. 2010), pyrrolo[1,2-*f*][1,2,4]triazines (Wittman et al. 2009), pyrrolo[2,3-*b*] pyridine (Patnaik et al. 2009) etc. in their basic skeleton (Chauhan et al. 2005).

In recent past, some IGF-1R inhibitors have been identified through in silico methods also. Though many IGF-1R inhibitors are discovered, the majority of them failed in preclinical trials due to their less potency.

In our continuing research on drug discovery (Alex et al. 2014) and development of anticancer agents (Joshi et al. 2016, 2015; Negi et al. 2015a, b) (Chauhan et al. 2015), we herein present computational approaches for identification of the small molecules as the IGF-1R inhibitor. For the identification of IGF-1R inhibitors, virtual screening has been utilized on the freely available database PubChem using Schrodinger (Kellenberger et al. 2004). The basic moiety was selected on the basis of the structure of the IGF-1R inhibitors reported in the literature. Schrodinger helps in calculation of the docking score or glide score that is calculated according to the following equation

$$\Delta G_{\text{Bind}} = G(PL)_{\text{Aq}} - G(P)_{\text{Aq}} + G(L)_{\text{Aq}}$$

$$\text{Glide score} = 0.065 * E_{\text{vdW}} + 0.130 * E_{\text{Coul}} + E_{\text{Lipo}} + E_{\text{HBond}} + E_{\text{Metal}} + E_{\text{BuryP}} + E_{\text{RotB}} + E_{\text{Site}}$$

Thus, binding energy (ΔG_{Bind}) can be calculated as the difference between the free energies of the complex and ligand/protein in aqueous solution. Glide score describes the interactions between the atoms of the protein and ligand. Each term designates different types of interactions that are probably between a ligand and a protein. The terminologies used in the above equation are van der Waals (vdW) energy (contact term), a Coulomb (Coul) interaction energy that describes electrostatic interactions, the H Bond term governing hydrogen bond interactions, the Lipo term

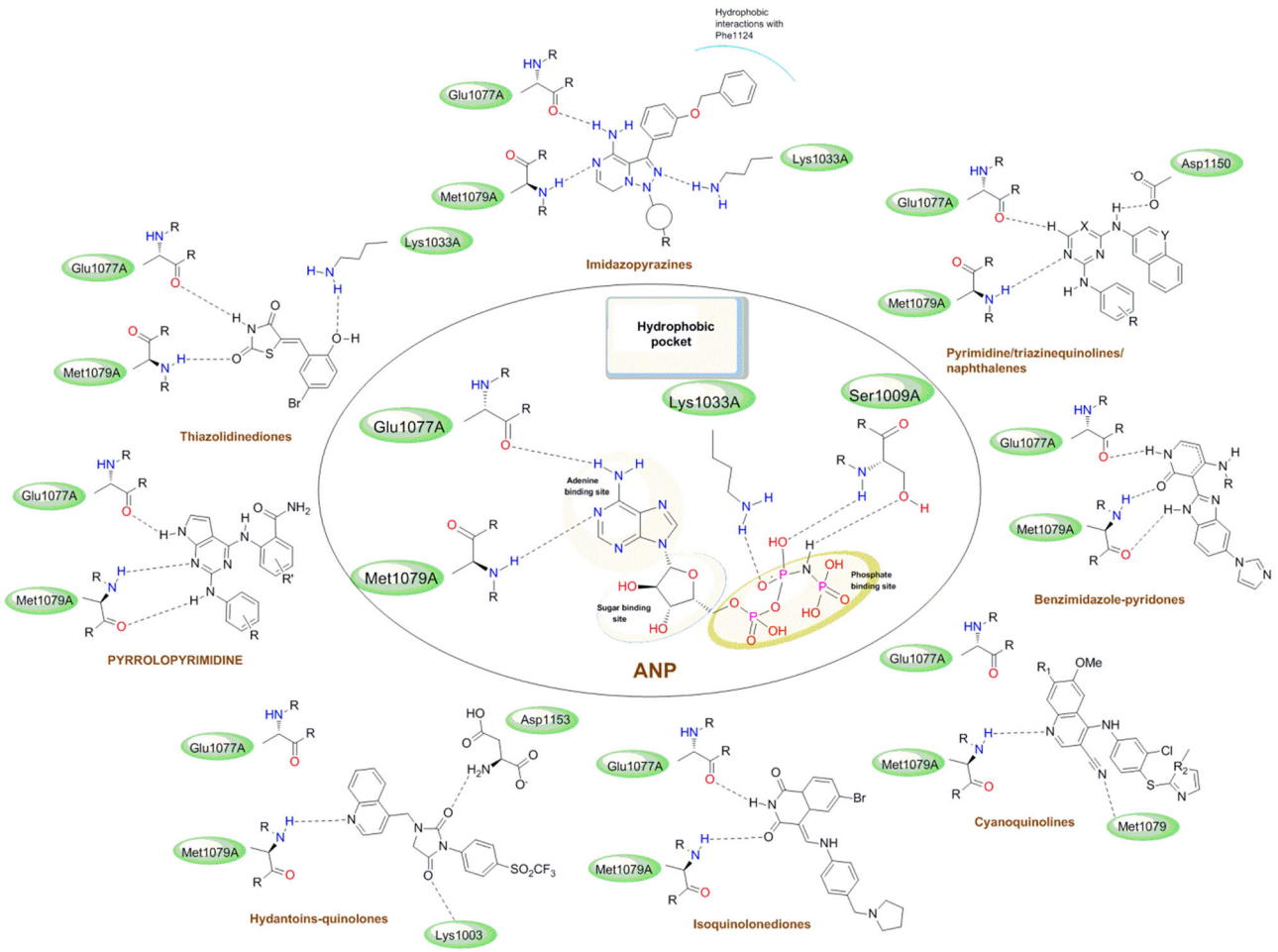


Fig 1 Interactions of various inhibitors and ANP (PDB code: 1jqh) with IGF1R kinase binding site (color figure online)

accounting for lipophilic interactions, the Metal term that governs ligand metal interactions, the RotB term giving a penalty for freezing rotatable bonds, the BuryP term that penalizes buried polar groups and finally Site term that takes care of polar interactions in the active site, respectively. These scores represent the best-fit compound conformations and help in the identification of hits and lead compounds that may provide new insight into the design as well as identification of IGF-1R inhibitors.

From X-ray co-crystal structures of IGF-1R with ANP (Phosphoaminophosphonic acid-adenylate ester); PDB code: 1jqh (Pautsch et al. 2001), it was found that hinge amino acids residues Glu 1080 and Met 1082 of the ATP-binding cavity of kinase domain remain conserved and form hydrogen bonds with adenine or other heterocyclic compounds. Some of the inhibitors show extra interactions with other amino acids present in phosphate, sugar and hydrophobic regions like Asp 1150, Lys 1003, Phe 1124, and Lys 1033 etc. (Fig. 1).

Methodology

Schrödinger Maestro, version 9.6 (Release 2013) was used for performing all the computational analysis. A number of steps were performed for virtual screenings that are as follows:

Selection of basic moiety

From literature search, it was observed that all most all reported IGF-1R inhibitors are heterocyclic in nature and contain adenosine or heterocyclic moiety in their structure. Since there is a need of heterocyclic scaffold that contains one hydrogen bond acceptor and one hydrogen bond donor to show IGF1R kinase activity that may inhibit the phosphorylation by ATP molecule. So we choose adenosine as basic moiety (Fig. 2).

Selection of compound database

PubChem database is freely and easily assessable that contains almost 54 million compounds (Wang et al. 2009). The compounds with substructure adenosine were searched. Almost around 7659 compounds were obtained. Then to evaluate drug-likeness these compounds were subjected to the Lipinski's rule of five, which states that for a drug, molecular mass should be less than 500 Dalton, lipophilicity log*P* should be less than 5, number of hydrogen bond acceptors should be less than 10 and number of hydrogen bond donors should be less than 5. After applying rule of five, a number of compounds were filtered out and only 4482 compounds were remained.

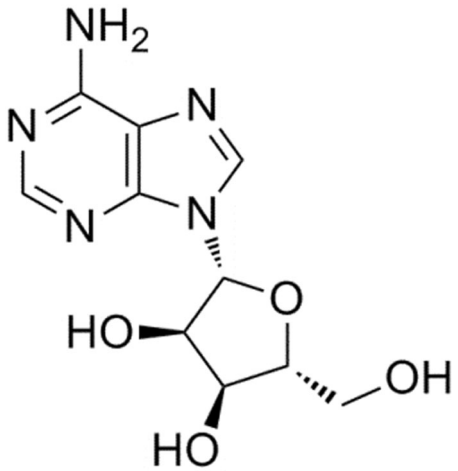


Fig 2 Basic moiety adenosine

Obtaining protein from RCSB

A number of IGF-1R X-ray crystal structures are available in Protein Data Bank. Some of them are given in Table 1. There are two criteria for the selection of PDB ID (1) Better resolution (2) Ligand bound protein. Thus keeping in mind these criteria, 3EKK (resolution 2.10 Å) was retrieved from Protein Data Bank for the experimental studies.

Protein preparation wizard in Schrödinger 2013 was used for protein preparation. Hydrogen atoms were added to analyze the structure and the bond order assigned. All the missing side chains and loops were filled using prime.

Receptor grid preparation

Grid generation at a particular site in the protein after analyzing the receptor; is the key step to perform Molecular Docking and the Molecular Mechanics Generalized Born Surface Area (MGBSA) studies (Knegtel et al. 1997). It helps to specify the receptor pocket; where docking is performed. By adjusting the different parameters, an environment virtually similar to in vivo conditions; favorable interactions between ligands and receptors can be observed. The receptor grid generation panel was used to generate a grid. The grid generated was excluding the structure of receptor containing other ligands. The grid was generated at the place of preexisting ligand using default settings. The grid was generated with vdW scaling 1.0 and with partial atomic charge cut-off of 0.25. The *X*, *Y*, *Z*-ranges for receptor setup was 20, 20 and 20.

Validation

To validate the molecular docking protocol, bound ligand i.e., (2-[(2-[1-(*N*, *N*-dimethylglycyl)-5-methoxy-1*H*-indol-6-yl]

Table 1 Some reported X-ray co-crystal structures of IGF-1R with the inhibitors and their resolution values

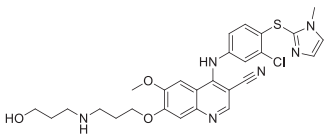
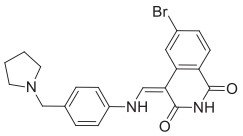
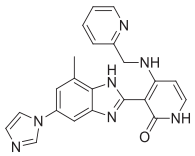
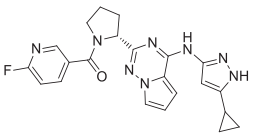
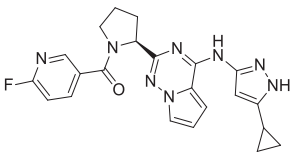
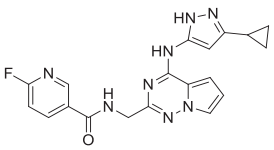
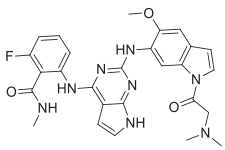
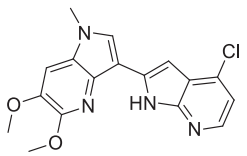
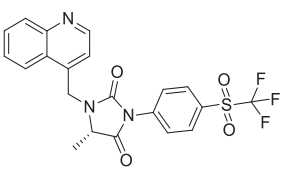
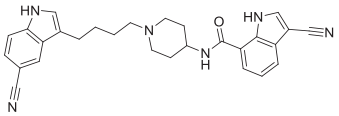
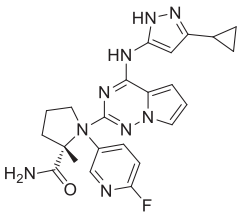
S.No.	PDB Id	Inhibitor	Resolution (Å)
1	3F5P		2.90
2	2ZM3		2.50
3	20J9		2.00
4	3NW5		2.14
5	3NW6		2.20
6	3NW7		2.11
7	3EKK		2.10
8	3LVP		3.00
9	3O23		2.10

Table 1 continued

S.No.	PDB Id	Inhibitor	Resolution (Å)
10	3LW0		1.79
11	3I81		2.08

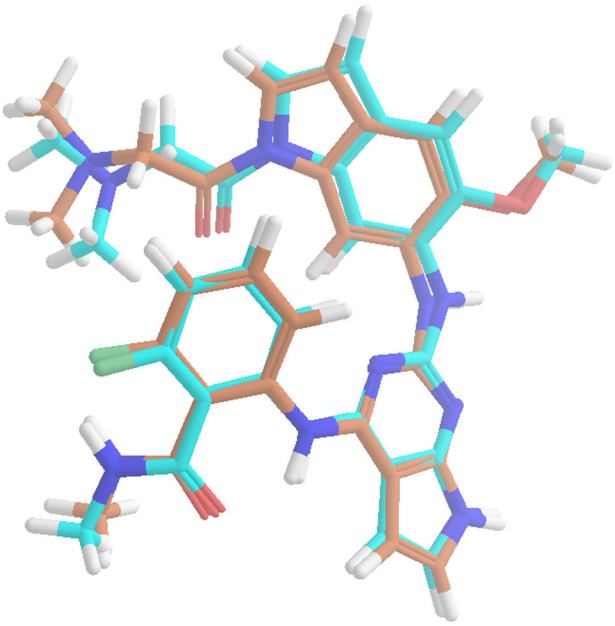


Fig 3 Superimposition of co-crystallized ligand (brown) and re-docked ligand with RMSD 0.4975 at the binding site of the protein (PDB ID—3EKK) (color figure online)

amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-6-fluoro-*N*-methyl benzamide) was initially re-docked into the crystal structure of the protein (PDB—3EKK). The re-docked ligand (IGFR-1 inhibitor) was found to have similar binding pose as compared to the co-crystallized ligand with a root mean square deviation (RMSD) of about 0.4795 and docking score—12.1398. Moreover, the superimposition of re-docked and co-crystallized ligand (2-[(2-[1-(*N, N*-dimethylglycyl)-5-methoxy-1*H*-indol-6-yl]amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-6-fluoro-*N*-methyl benzamide) suggested that it occupies the binding pocket in a similar fashion. Thus, validation of the adopted docking methodology suggested that docking protocol is reliable enough to carry out further binding mode analysis of investigational ligands (Fig. 3).

Virtual screening

Virtual screening is the easiest way for the compounds from the database to be identified and rank potential drug candidates (Lyne 2002). Based on the ATP-binding site of IGF-1R, high throughput virtual screening (HTVS) was performed using compounds from PubChem database. During the performance of this step, chiralities were determined from 3D structure and original states of ionization were retained. "Ligprep" application of the Maestro 9.6 utilizes OPLS-2005 force field. The glide based three-tiered docking strategy was adopted (Dunna et al. 2015). In this strategy, all the compounds are docked by three stages of the docking protocol: HTVS, standard precision (SP) and extra precision (XP). First stage HTVS reduces the intermediate conformations of the compounds. HTVS screens a large number of compounds rapidly. The speed of HTVS is highest i.e., 3–5 s/lig. While the speeds for SP and XP are 30–50 s/lig and 3–5 min/lig, respectively. After screening by HTVS, the compounds were subjected to the second stage of the SP docking. After SP docking, the compounds were subjected to XP docking. The glide includes ligand–protein interaction energies, hydrogen bonds, hydrophobic interactions, π-π stacking interactions, internal energy and RMSD (Kitchen et al. 2004).

Protein–ligand binding studies

The Prime MM-GBSA is used for binding energy estimation by uploading Maestro pose viewer file. MMGBSA Dg bind as a major descriptor was taken into consideration,

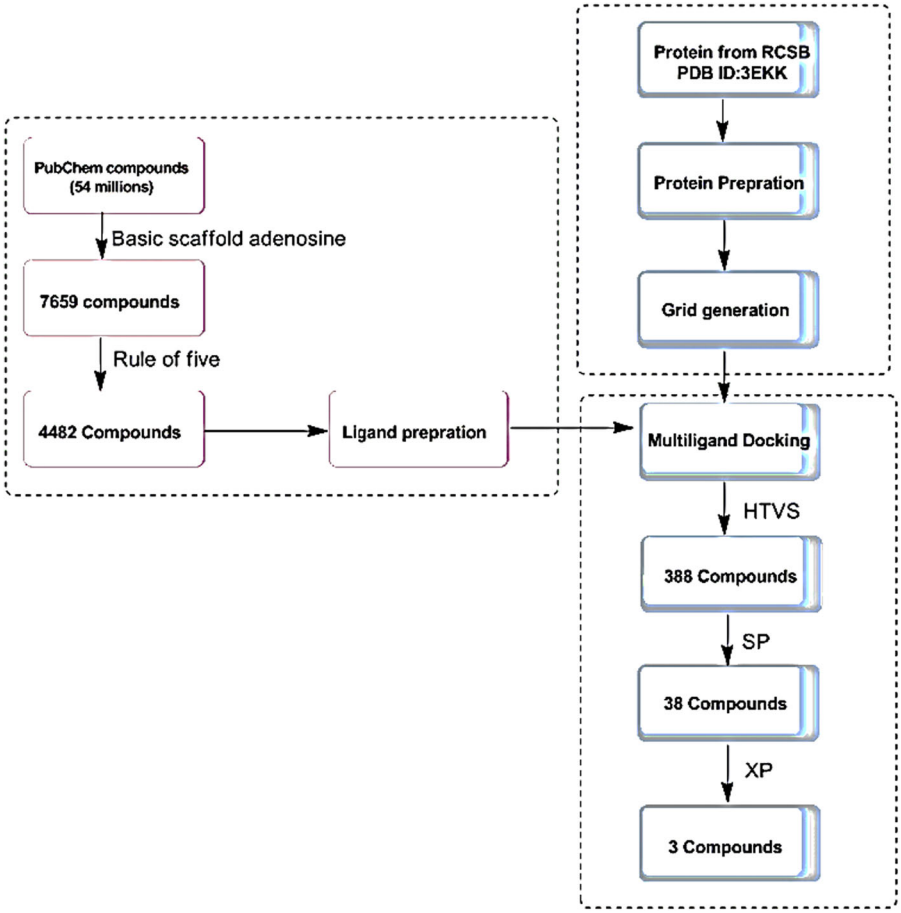


Fig 4 Flow chart for virtual screening (color figure online)

which depicts the binding energy of the receptor and ligand as calculated by, Prime energy, a molecular mechanics and implicit solvent energy functions (kcals/mol) = Prime energy (optimized complex)—Prime energy (optimized free ligand)—Prime energy (optimized free receptor) (Greenidge et al. 2012). Ligand strain energy is a prediction of the energetic penalty due to strain between the ligand in the complex and the ligand in the free state based on the difference in Prime energy (kcals/mol) = Prime energy (ligand geometry from optimized complex)—Prime energy (optimized free ligand). Rec (receptor) Strain Energy that is a prediction of the energetic penalty due to strain between the receptor in the complex and the receptor in the free state based on the difference in Prime Energy (kcals/mol) = Prime energy (receptor geometry from optimized complex)—Prime energy (optimized free receptor). The prepared ligands were docked on the respective protein to study their binding interactions. Binding energy was calculated using MM-GBSA, which is a thermodynamic statistics for bimolecular systems. MM-GBSA can be stated as molecular mechanics—the generalized born model and solvent accessibility method (Jacobson et al. 2004; Mobley and Dill 2009).

Results and discussion

It has been learned that there are two residues that are essential for ATP-binding with IGF-1R namely, Glu 1080 and Met 1082. We used three different stages of docking and scoring processes for this study, starting from HTVS, followed by SP and finally with XP. IGF-1R protein target was docked with compounds from PubChem database using glide. A total of 4482 compounds were selected for HTVS. Then after removing reactive functional groups and performing HTVS, 388 compounds were remained. These 388 compounds were subjected to SP docking that lead 38 compounds. The final docking with XP ranked the 38 best-scored compounds, and 3 were selected by keeping 10 % best scoring compounds (Fig. 4). The ID's and docking score of best scoring compounds and some reported inhibitors are as shown in Table 2.

The final compounds are having better docking score than that of the reported inhibitors. Some reported inhibitors i.e., BMI (PubChem ID 16058649), ANP (PubChem ID 36735) and LGX (PubChem ID 46829319) were docked into 3EKK. The docking scores of these inhibitors were −8.400, −8.030 and −7.15165 Kcal/mol, and binding

Table 2 Docking score of best scoring compounds and some reported inhibitors

	Pub Chem id	Compound/inhibitor	Docking score	MMGBSA-dG-Bind	RMSD	Molecular weight	H Bond acceptor	H Bond donor
Compounds	13195423	2-[6-(3-aminopropylamino)purin-9-yl]-5-(hydroxymethyl) oxolane-3,4-diol	−11.6447	−54.6625	0.032409	324.339	9	5
	49786975	2-amino-N-[(2S,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hydroxy-2-(hydroxymethyl)oxolan-3-yl]acetamide	−11.1127	−65.9886	0.014916	323.311	9	5
	69548358	(2R,5R)-2-[6-amino-2-(6-aminohex-1-ynl)purin-9-yl]-5-(hydroxymethyl) oxolane-3,4-diol	−10.9901	−74.4848	0.047884	362.388	9	5
Inhibitors	16058649	BMI	−8.40023	−59.5559	0.038281	397.43256	6	3
	36735	ANP	−8.0304	−20.2767	0.031173	522.19566	15	9
	46829319	LGX	−7.15165	−74.9273	0.037745	433.46148	6	3

energies of these inhibitors were −59.5559, −20.2767 and −74.9273 Kcal/mol, respectively.

Docking results showed that 13195423, 49786975 and 69548358 from PubChem database occupy the ATP-binding region of IGF-1R with a docking score of −11.6447, −11.1127 and −10.9901 Kcal/mol, and binding energy of −54.6625, −65.9886 and −74.4848 Kcal/mol, respectively. Maestro ligand interaction 2D diagram was used to understand the in-depth interaction pattern of the ligands and IGF-1R.

On superimposition, the binding pose of compounds 131955423 and 49786975 overlaps with the binding pose of ANP (analog of ATP) with 3EKK (Fig. 5).

The third compound, 69548358 shows a different pose from other two compounds due to the presence of a side chain at position 2 (Fig. 6).

Binding mode of 13195423 with ATP-binding region of IGF-1R

The ligand 13195423 occupies the ATP-binding region of IGF-1R with a docking score −11.6447 and the binding energy (MMGBSA-dG-Bind) −54.6625 Kcal/mol. H-bond interactions were identified with the backbone of amino acid residues Glu 1077 and Met 1079, and side chain of amino acid residues Asp 1150 and Asp 1083 (Fig. 7).

The 2D and 3D interaction poses of compound 13195423 with ATP-binding site of IGF-1R were taken. The 2D pose is shown in Fig. 7 and 3D pose is shown in Fig. 8.

Fig. 9 shows that the compound 13195423, represented by green color, binds in the cavity in similar pose as that of ANP, represented by pink color.

Binding mode of 49786975 with ATP-binding region of IGF-1R

The ligand 49786975 occupies the ATP-binding region of IGF-1R with a glide score −11.1127 and the binding energy (MMGBSA-dG-Bind) is −65.9886 Kcal/mol. H-bond interactions were identified with the backbone of amino acid residue Glu 1077, Met 1079, Asp 1083 and Gln 1004 and side chain of amino acid residue Asp 1083 (Fig. 10).

The 2D and 3D interaction poses of compound 49786975 with ATP-binding site of IGF-1R were taken. The 2D pose is shown in Fig. 10 and 3D pose is shown in Fig. 11.

Fig. 12 shows that the compound 49786975, represented by green color, binds in the cavity in similar pose as that of ANP, represented by pink color.

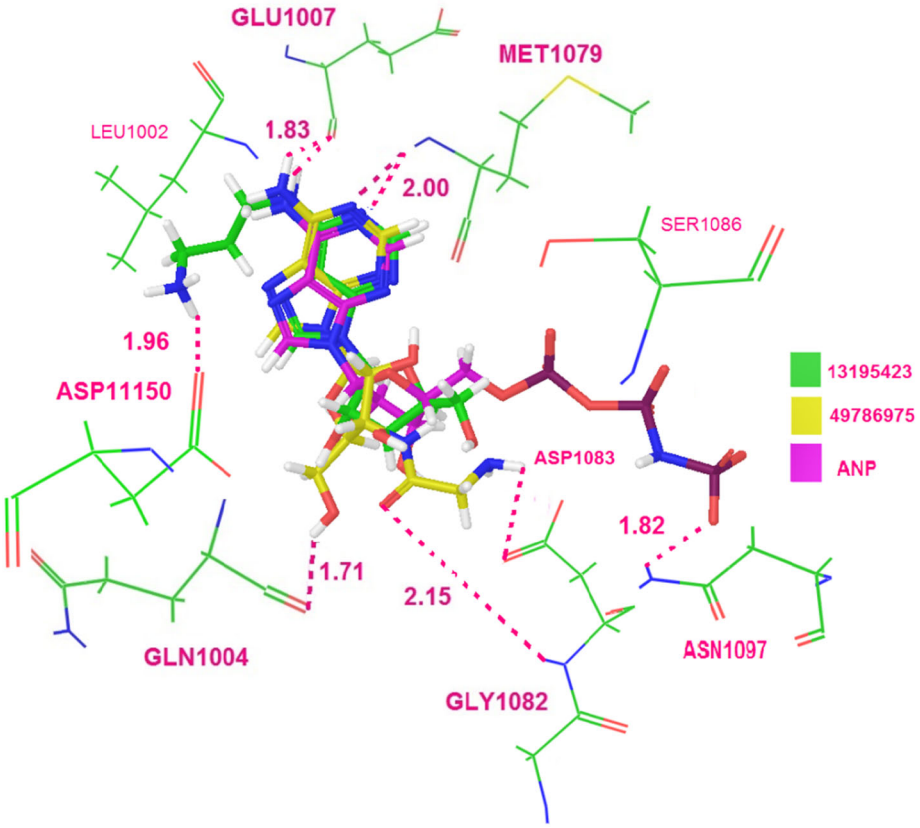


Fig 5 Superimposition of 13195423 and 49786975 with ANP (color figure online)

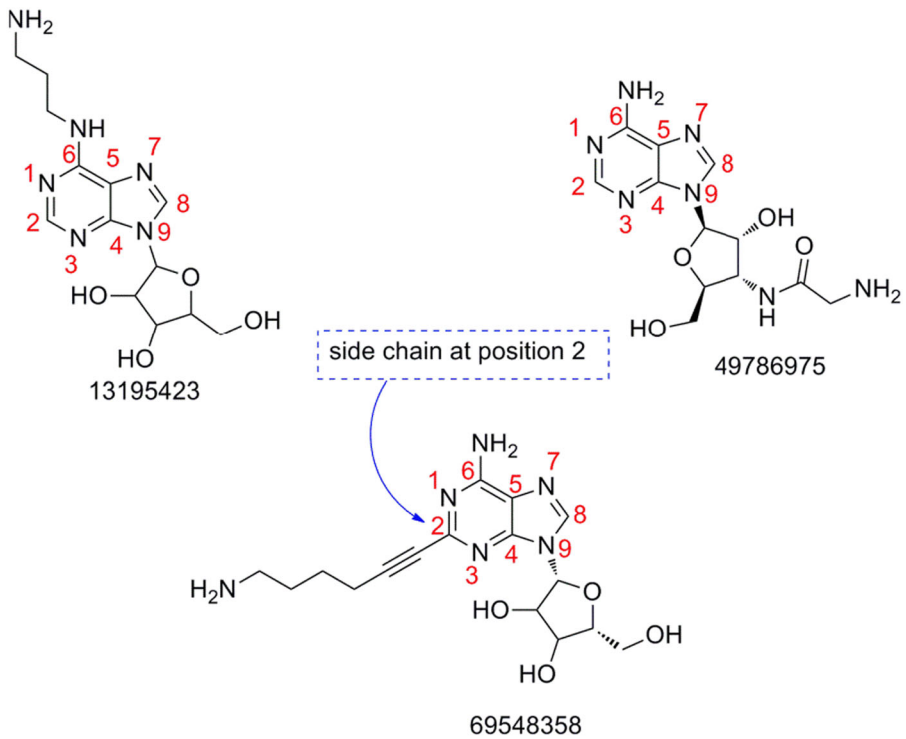


Fig 6 Three best scoring compound (color figure online)

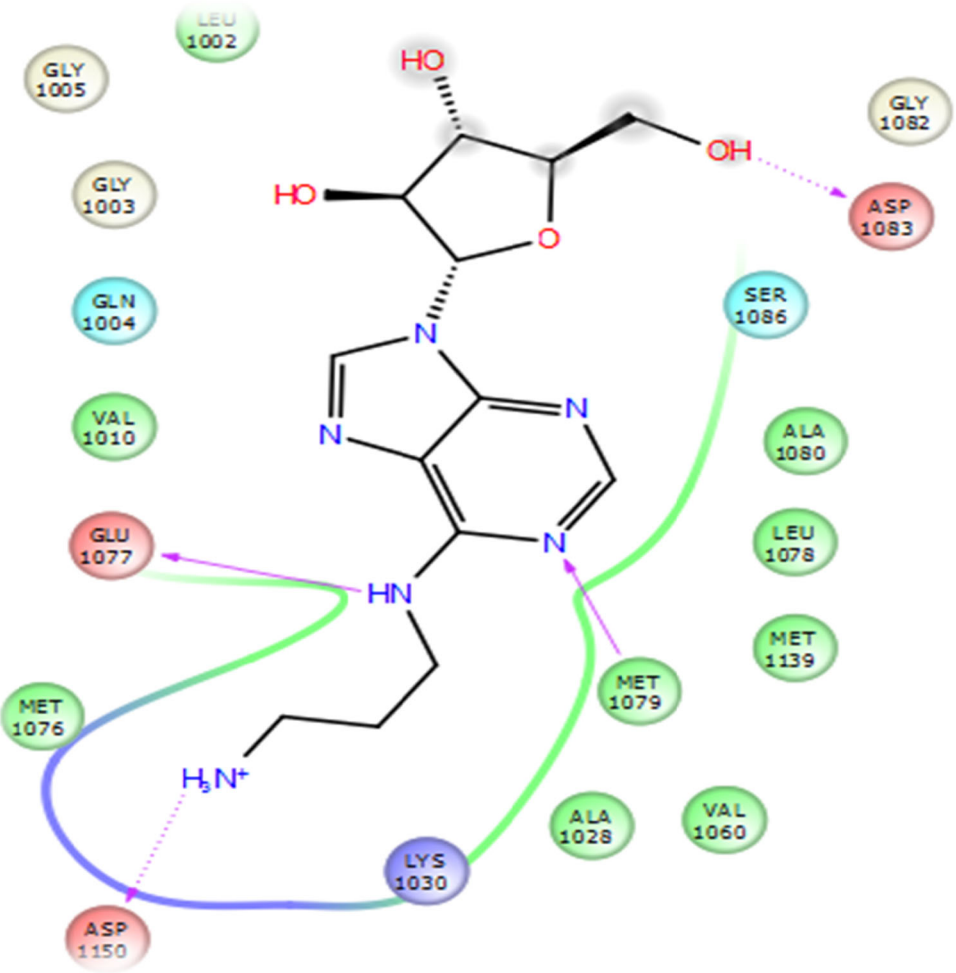


Fig 7 2D Interactions of compound 13195423 with ATP-binding site of IGF-1R (color figure online)

Binding mode of 69548358 with ATP-binding region of IGF-1R

The ligand 69548358 occupies the ATP-binding region of IGF-1R with a docking score −10.9901 and the binding energy (MMGBSA-dG-Bind) is −74.4848 Kcal/mol. H-bond interactions were identified with the backbone of amino acid residue Gln 1004 and side chain of amino acid residues Asp 1150 and Asp 1083 (Fig. 13).

The 2D and 3D interaction poses of compound 69548358 with ATP-binding site of IGF-1R were taken. The 2D pose is shown in Fig. 13 and 3D pose is shown in Fig. 14.

Fig. 15 shows that the compound 69548358, represented by green color binds in the cavity in similar pose as that of ANP, represented by pink color.

Conclusions

Currently due to non-availability of drug in the market acting against IGF-1R for the treatment of cancer, we performed Molecular docking studies to identify small molecule inhibitors binding to ATP active domain of IGF-1R. HTVS screened compounds from PubChem database were subjected to SP docking that resulted in 38 compounds. These compounds were further taken for XP docking. Based on the glide score, glide energy and H-bond interactions with the amino acid residue of the ATP-binding site, 3 compounds among them were shortlisted. Out of these three compounds, the compounds 13195423 and 49786975 have an excellent glide score and binding energy. Moreover, ligands have a worthy interaction with the specific amino acid residues Glu 1077 and Met 1079 and other residues like Asp 1150, Asp 1083, Gln 1004 and GLY 1082 (Fig. 16).

Thus we conclude based upon in silico results, compounds show favorable interaction and have shown potential scope to be developed as IGF-1R inhibitors in future. These ligands may be further synthesized and subjected to detailed biology for 1GF-1R inhibition, which will surely help in finding new leads and establish a new target to overcome one of major health problems i.e., cancer.

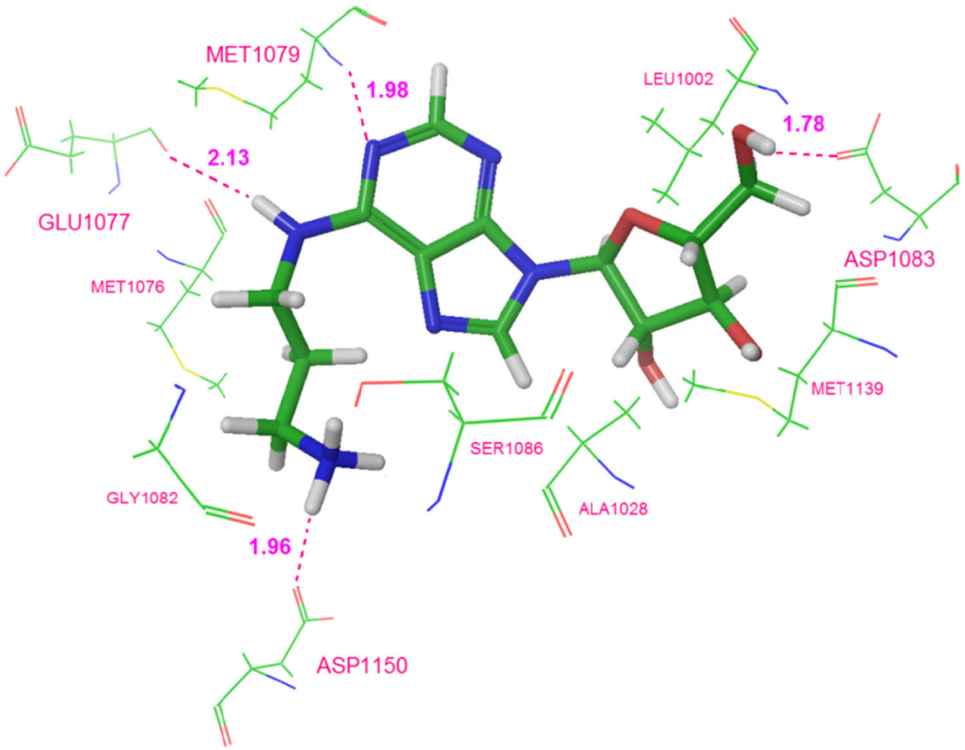


Fig 8 3D Interactions of compound 13195423 with ATP-binding site of IGF-1R (color figure online)

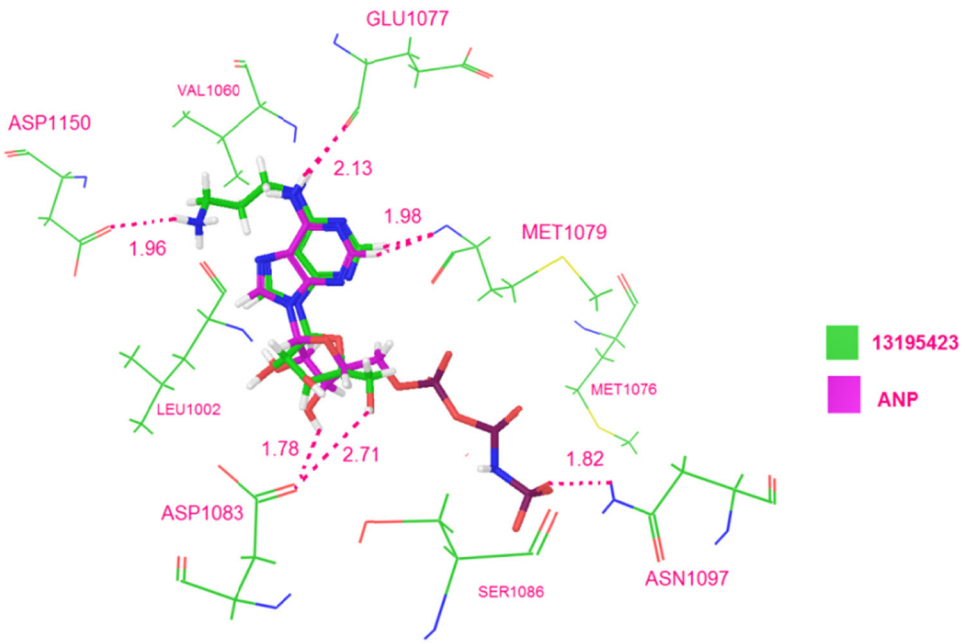


Fig 9 Binding pose of compound 13195423 (*Green*) and ANP (*Pink*) (color figure online)

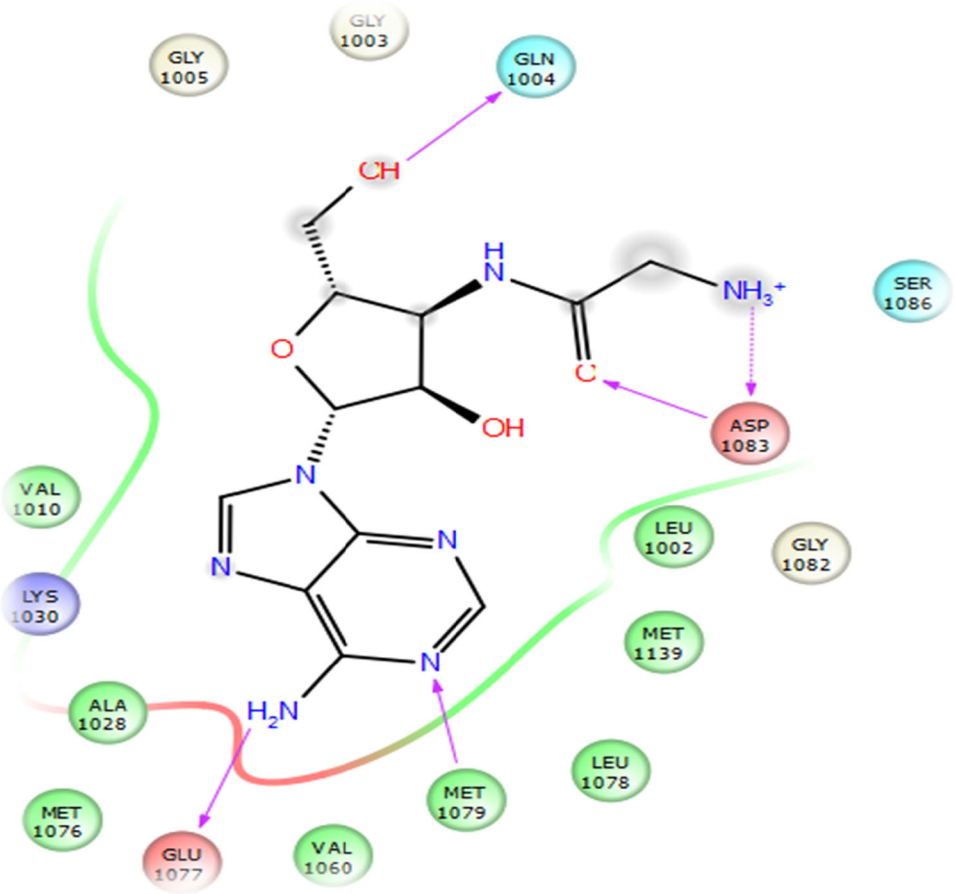


Fig 10 2D Interactions of compound 49786975 with ATP-binding site of IGF-1R (color figure online)

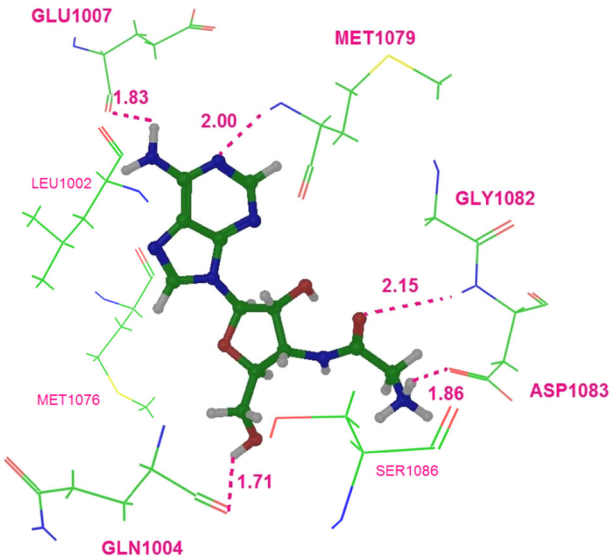


Fig 11 3D Interactions of compound 49786975 with ATP-binding site of IGF-1R (color figure online)

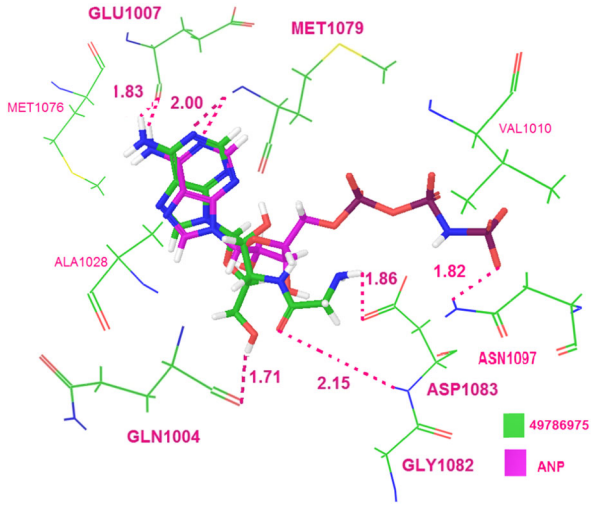


Fig 12 Binding pose of compound 49786975 (*Green*) and ANP (*Pink*) (color figure online)

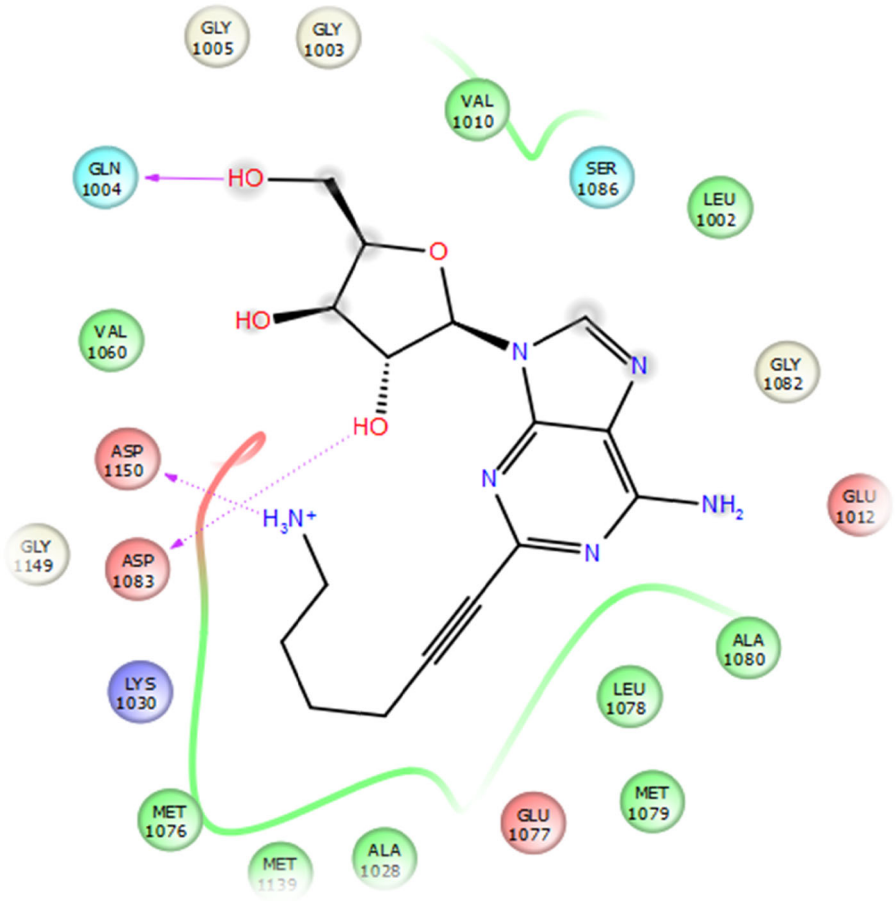


Fig 13 2DInteractions of compound 69548358 with ATP-binding site of IGF-1R (color figure online)

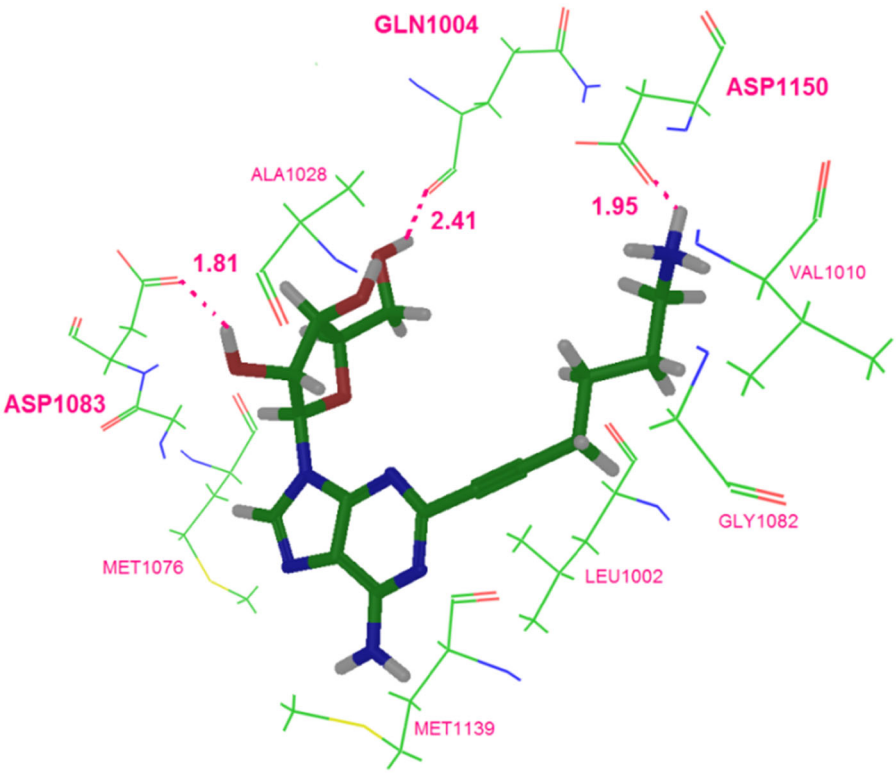


Fig 14 3D Interactions of compound 69548358 with ATP-binding site of IGF-1R (color figure online)

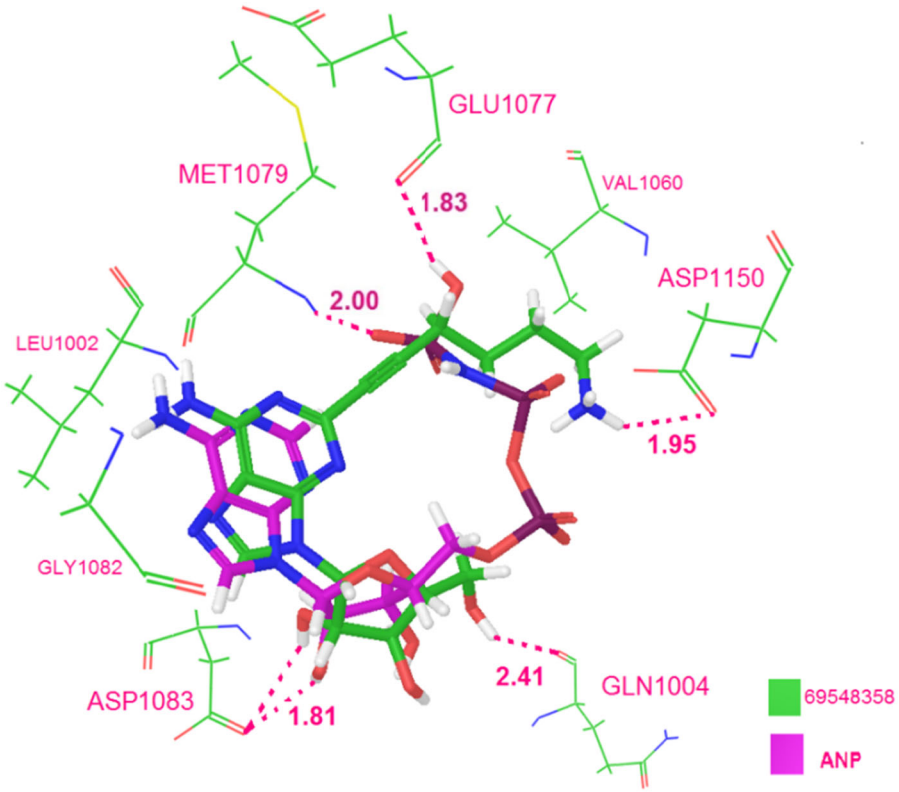


Fig 15 Binding pose of compound 69548358 (*Green*) and ANP (*Pink*) (color figure online)

REIDUES INTERACTING	COMPOUND 13195423	COMPOUND 49786975	COMPOUND 69548358
GLU1077	+	+	−
MET1079	+	+	−
ASP1083	+	+	+
ASP1150	+	−	+
GLN1004	−	+	+
GLY1082	−	+	−

Fig 16 Various residues interacting with three best scoring compounds (color figure online)

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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