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Identification of small molecule inhibitors against UBE2C by using docking studies

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Abstract:
An increased expression of UBE2C (Ubiquitin-conjugating enzyme E2C) has been associated with high tumor grade and cancer progression. It is an essential indicator of the mitotic destruction events. Our microarray study on cervical cancers showed UBE2C to be over expressed in cervical cancer. Subsequent studies from our laboratory, showed that inhibition of UBE2C can enhance radiation and chemosensitivity. Therefore it can be an appropriate target for drug development to identify potential and specific inhibitor of cancer. To identify small molecule inhibitors, a computational approach was used to model UBE2C and further docking studies were carried out. Different ligand subsets such as ChemBank, PDB, KEGG, Drug-likeness NCI, Not annotated NCI of ligand library ligands were downloaded and docked with UBE2C. Schrodinger tools were used for identifying active sites and docking studies of ligands with UBE2C. Based on glide score, the potential ligands were screened and its interaction with UBE2C was identified. We also analyzed the drug like properties such as absorption, distribution, metabolism, excretion and toxicity (ADME/T) of docked compounds. Our results suggest that 2,4-diimino-1-methyl-1,3,5-triazepan-6-one, sulfuric acid compound with 5,6-diamino-2,4-pyrimidinediol (1:1) and 7-alpha-d-ribofuranosyl-2-aminopurine-5'-phosphate may act as best inhibitors and further in vitro studies, may lead to development of novel and best inhibitor of UBE2C.

Key words: Glide, UBE2C, ADME/T and Docking.

Background:
The ubiquitin conjugating enzyme 2C (UBE2C) protein is an anaphase promoting complex and cyclosome (APC/C)-specific ubiquitin-conjugating enzyme. It has a critical role in APC/C-dependent M-phase cell-cycle progression by inactivating the M-phase check point by targeted degradation of short lived proteins **[1, 2].** It also plays a role in mitotic spindle checkpoint control **[3].**Cells which are over expressing UBE2C ignore the mitotic spindle checkpoint signals and lose genomic stability accelerating cell proliferation**[4-6].** Over expression of UBE2C at the mRNA level is reported in a number of cancer cell lines and primary tumors, including lung, gastric, breast, bladder, and uterine cancers, whereas only low levels were found in normal tissues **[7].** Our studies on gene expression profiling, showed UBE2C to be upregulated in cervical cancer when compared with normal cervix and dysplasia **[8].** We have also shown that a 7 gene signature which includes UBE2C could be useful to identify patients who can be treated with radiotherapy alone **[9].** Functional studies inhibiting UBE2C was found to enhance radiation and chemo-sensitivity in cervical cancer cell lines **[10].** UBE2C has been shown to be preferentially over expressed in cancers compared to 17 other E2 genes **[7].** In this manuscript we describe computational studies to design specific inhibitors for UBE2C. Computational techniques have become crucial components of many drug discovery programmers, such as hit identification to lead optimization and structure based virtual screening **[11-13].**

Virtual screening is a process of screening small molecule libraries for a subset of compounds enriched for interacting with a therapeutic protein target of interest **[14].** The knowledge of 3D structure of UBE2C can help in understanding its function and role in cell in order to study the molecular interaction with other proteins as well as to design new molecules to inhibit its activity. To build the 3D structure of UBE2C, homology modeling using NCBI BLAST algorithm was used to identify the template. Crystal structure of Human Mitotic-specific Ubiquitin Conjugating Enzyme (PDB code:

1I7K), a mutant protein showed 99% sequence similarity and it was chosen as template for modeling UBE2C **[15-17].**Prime tool (Schrodinger 2009) was employed to construct 3D structure of UBE2C using 1I7K as template **[18,19].** Compound libraries such as Drug-likeness NCI, Not annotated NCI , ChemBank, ChemPDB and KEGG **[20]** were virtually docked into the target binding site through GLIDE a docking program **[21-23],** which computationally models the ligand–target interaction to achieve an optimal complementarity of steric and physicochemical properties. The compounds which showed minimum docking score can be further subjected to experimental validation and clinical trials to establish a more potent drug for treatment of different cancers.

Methodology:

Homology modeling of UBE2C

The sequence of UBE2C was obtained from UniProtKB/Swiss-Prot **[24].** NCBI BLAST programme was used to identify the template for modeling. The results yielded by NCBI BLAST against the PDB database revealed that crystal structure of Human Mitotic-Specific Ubiquitin- Conjugating Enzyme (PDB code: 1I7K), with a resolution of 1.95 Å as a suitable template. The template and the target have 99% of residues identical with an *E*-value of 1e-103. The structure was modeled with the help of commercial software SCHRÖDINGER Prime module (Schrödinger, 2009). The modeled structure was imported and corrections were carried out by Protein Preparation wizard, where hydrogen's were added automatically and refinement of the structure was also done. Energy minimization was done by using OPLS_AA force field and refinement was carried out until average mean square deviation of the non hydrogen atoms reached 0.3A^0 and the resulting optimized structure was used for further studies

Active site prediction

After obtaining the final model, the possible binding sites of UBE2C were searched using Qsite Finder (http://bmbpcu36.leeds.ac.uk/qsitefinder/) **[25, 26]** and SiteMap (Schrodinger 2009) **[27, 28].** Out of ten binding pockets predicted by QsiteFinder and four pockets by sitemap, we selected three pockets of QsiteFinder and one pocket of sitemap which possess cystine at 114 for further docking studies. SiteMap assigns numerical descriptors to evaluate predicted binding sites by a series of physical parameters such as size, degree of enclosure/exposure, tightness, hydrophobic/hydrophilic character, and hydrogen bonding possibilities. A weighted average of these measurements is then assigned to prioritize possible binding sites.

Ligand selection and preparation

Ligands were downloaded from Ligand Info (http://ligand.info/). Ligand .Info is a compilation of various publicly available databases of small molecules such as ChemBank, ChemPDB, KEGG, Drug-likeness NCI subset and Not annotated NCI subset. Small molecules can be downloaded in SDF format and used for high throughput screening of new potential drugs for UBE2C. The ligands did not have correct bond orders and bond angles; they were subjected to full minimization with OPLS_2005, followed by assigning appropriate ionization state of each ligand by using the "ionizer" option.

Grid Generation

Residues of each active site in UBE2C was scaled by vander waal's radii of 1.0A^0 with partial atomic charge less than 0.25A^0 ,gird was generated around active sites detected by QsiteFinder and by SiteMap (Schrodinger) and enclosed by a box at the centeroid of selected residues. Ligand docking jobs cannot be performed until the receptor grids have been generated. Receptor grid generation requires a "prepared" structure: an all atom structure with appropriate bond orders and formal charges (Schrodinger 2009).

Docking Studies

We have applied the GLIDE docking method to build a binding affinity model for UBE2C with ligands. Docking procedures basically aim to identify the correct conformation of ligands in the binding pocket of a protein and to predict the affinity between the ligand and the protein. It is a process by which two molecules fit together in a 3-dimensional space. Glide score was based on Chemscore, but includes a steric clash term and adds buried polar terms devised by Schrodinger to penalize electrostatic mismatches. Glide score takes into account a number of parameters such as Hydrogen bond (H bond), hydrophobic (Lipo), Vander-Waals (vdW), columbic (Coul), polar interactions in the binding site (site), metal binding term (metal) and penalty for buried polar group (Burry P) and freezing rotatable bonds (RotB).

G-Score = H bond + Lipo +Metal + site + 0.130 Coul + 0.065 vdW – Bury P – RotB

ADME/T properties prediction

Absorption, Distribution, Metabolism, Excretion and Toxicity (ADME/T) properties of glide docked molecules were predicted using QikProp tool of Schrodinger. It predicts properties such as octanol/water partition, log BB, overall CNS activity, Caco-2 and MDCK cell permeability, logKhsa for human serum albumin binding and log IC50 for HERG K+ channel blockage **[29-32].**

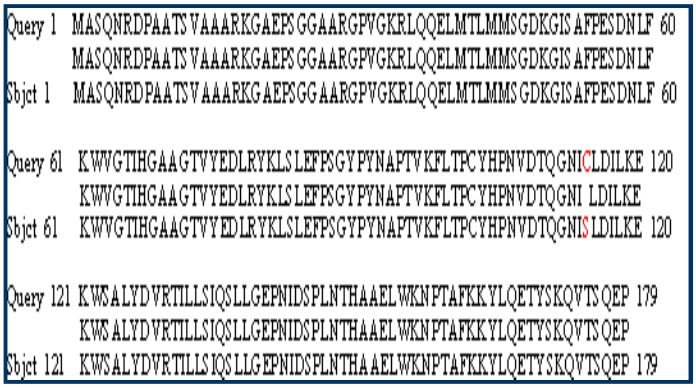

Figure 1: Amino acid sequence alignment of UBE2C

Results:

Structure prediction and evaluation

The sequence of UBE2C was obtained from UniProtKB/Swiss-Prot. We used NCBI BLAST programme to identify the template for modeling. The results yielded by NCBI BLAST against the PDB database revealed that crystal structure of Human Mitotic-Specific Ubiquitin- Conjugating Enzyme (PDB code: 1I7K), with a resolution of 1.95 Å can be used as suitable

template because the template and the target having 99% similarity with an *E*-value of 1e-103 **(Figure 1).** The structure of UBE2C was modeled with the help of commercial software SCHRÖDINGER Prime module (Schrödinger, 2009). The modeled structure was imported and corrections were carried out by Protein Preparation wizard, hydrogens were added automatically and refinement of the structure was also done. Energy minimization was done by using OPLS_AA force field and refinement was carried out until average mean square deviation of the non hydrogen atoms reached 0.3A^0 and the resulting optimized structure was used for further studies. The stereochemical properties of UBE2C model was evaluated by Ramachnadran plot after protein preparation script of Schrodinger. 96.5% of the residues were in the favored region, 2.8% were in the allowed region and only 0.7% was in the disfavored region .These results indicate that the phi and psi back-bone dihedral angles in the UBE2C model are accurate **[33,34].**

Figure 2: Ten binding pockets predicted by Q-SiteFinder

Binding pocket prediction

The binding pockets of UBE2C model was predicted by Q-SiteFinder and SiteMap (Schrodinger, 2009). QsiteFinder detects by binding hydrophobic probes to the protein and finding clusters of probes with the most favorable binding energy. These clusters are placed in rank order of the likelihood of being a binding site according to the sum total binding energies for each cluster. (**Figure 2)** shows ten different binding pockets predicted by Q-SiteFinder**.** Binding site prediction of UBE2C was also performed in Maestro using SiteMap (Schrodinger, 2009) package, it identifies one potential binding site with site score of >0.9. SiteMap highlights regions within the binding site suitable for occupancy by hydrophobic groups or by ligand hydrogen-bond donors, acceptors, or metal-binding functionality. SiteScore, the scoring function of sitemap used to assess a site's propensity for ligand binding, accurately ranks possible binding sites to eliminate those not likely to be pharmaceutically relevant. The following residues are predicted as best binding sites for UBE2C Ser51, Ala52, Phe53, Val63, Gly64, Thr65, Tyr74, Leu77, Lys80, Phe98, Leu99, Thr100, Pro101, Cys102, His104, Pro105, Val107, Asp108, Thr109, Gln110, Gly111, Asn149, Ala152, Tyr165,Leu166,Thr169, Tyr170, Gln173,Val174 with sitescore **0.928 (Figure 3).**

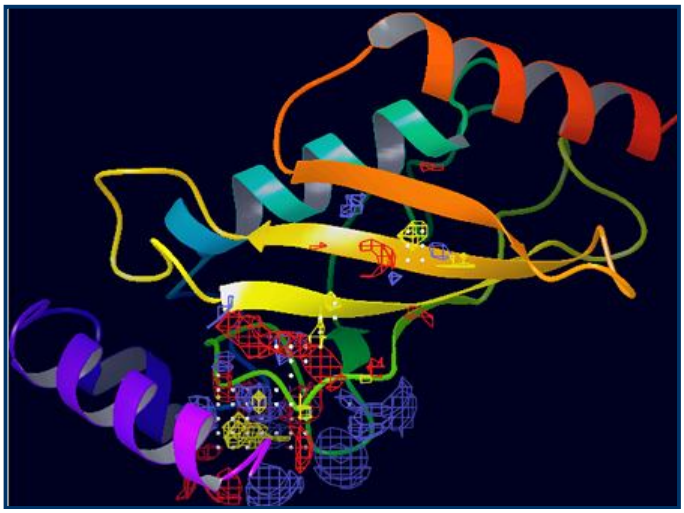

Figure 3: SiteMap Binding pocket

Docking Studies

For docking studies we selected three binding pockets of QsiteFinder which posses CYS114 in its pocket and sitemap pocket. **Pocket 1:** Tyr103, His104, Pro105, Asn106, Val107, Asp108, Thr109, Gln110, Gly111, Asn112, Ile113, cys114, Leu115, Asp116, Ile117, Leu118; **Pocket 2:** His104, Pro105, Asn106, Cys114, Leu138, Pro142, Asn143, Ile144, Asp145, Ser146, Pro147, Leu148, Ala152, Ala153, Glu154, Trp156; **Pocket 3:**Phe98,Cys102,Tyr103,His104,Pro105,Asn106,Val107,Asp108,Gly111,Ile113,Cys114,Leu138, Leu148,Asn149.

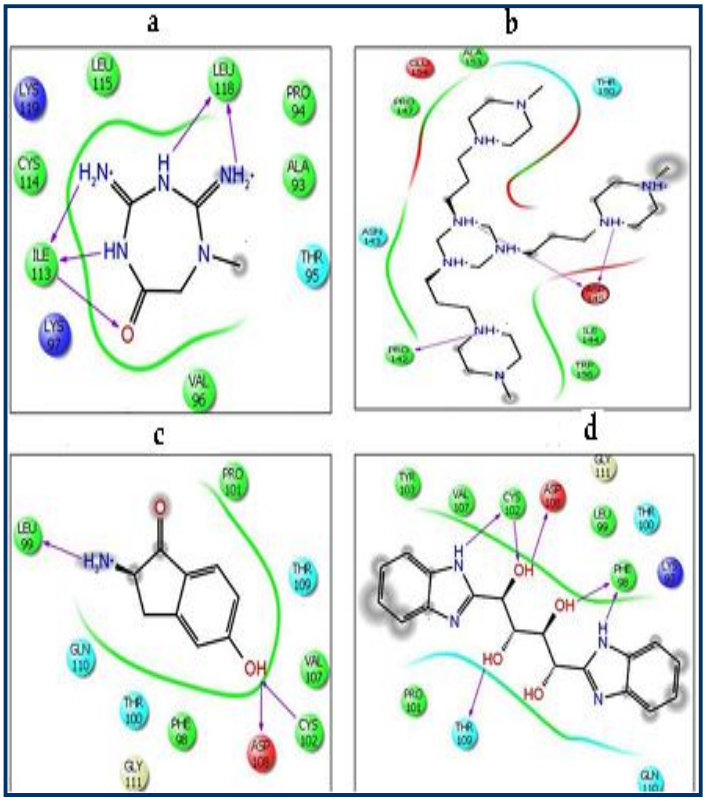

Figure 4: Structure of different ligands (Drug likeness NCI subset) bound to UBE2C; **a)** 2, 4-diimino-1 methyo-1,3,5-triazepan-6-one; **b)** 1,3,5-tries (3(4-methyl-1-piperazinyl)probyl)-1,3,5-triazinane; **c)** 2-amino-5-hydroxy-1-indanone; **d)** 1,4-di(1H-benzimidazol-2-yl)-1,2,3,4-butanetetrol

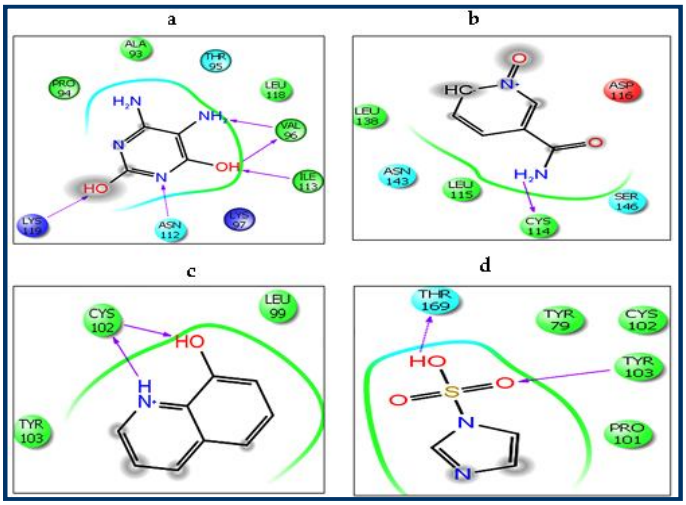

Figure 5: Bindning modes of Not annotated NCI subset ligands with UBE2C **a)** Sulfuric acid compund with 5,6-diamino-2,4-pyrimidinedio (1:1); **b)** 1,6-dihydro-3-pyridinecarboxamide 1-oxide; **c)** nicotinic acid compound with 8-quinolino (1:1); **d)** 1H-imidazole- 1-sulfonic acid compound with 1H-imidazole (1:1)

Compounds from different ligand database (ligand.info) such as Druglikeness, NCI annotated, ChemBank, KEGG and PDB were downloaded and we generated 3D structures using ligand preparation tool. The prepared compounds from different datasets were docked into different binding pockets and compounds which showed high binding affinities were filtered using ADME properties. The compounds were docked into UBE2C considering ligands as flexible and protein as rigid. We used standard precision mode of Glide for all docking calculations. The docking scores of most potent ligands of different datasets are listed in **Table (1, 2, 3, 4 & 5 see supplementary materials)**. The compounds of Not annotated NCI subset such as 2,4-diimino-1-methyl-1,3,5-triazepan-6-one forms three hydrogen bonds with Ile113 and two hydrogen bonds with Leu118 and shows a docking score of -6.401379, 2,4-diimino-1-methyl-1,3,5-triazepan-6-one and 1,4-di(1H-benzimidazol-2-yl)-1,2,3,4-butanetetrol binds with Asp108 and Cys102 of active site with binding score of -6.206891 and -7.05162 respectively **(Figure 4 a,b,c,d).**

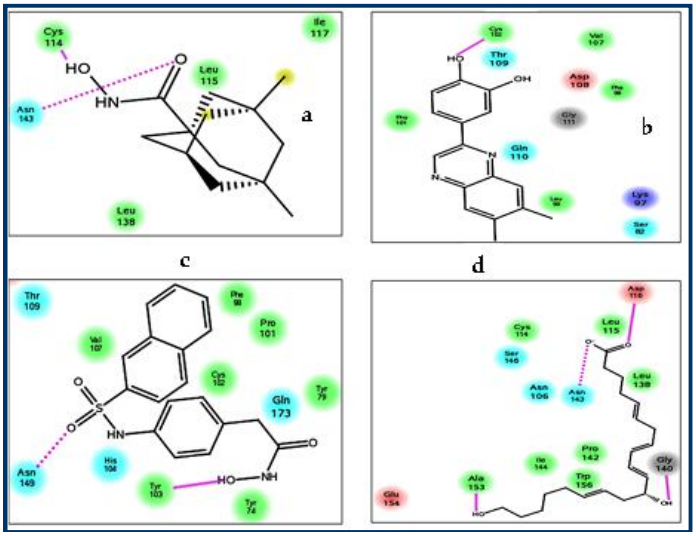

Figure 6: Interaction of ChemBank subset compounds with UBE2C: **a)** Itdac-6; **b)** ag1433; **c)** Methylene; **d)** (s),20-DIHETE

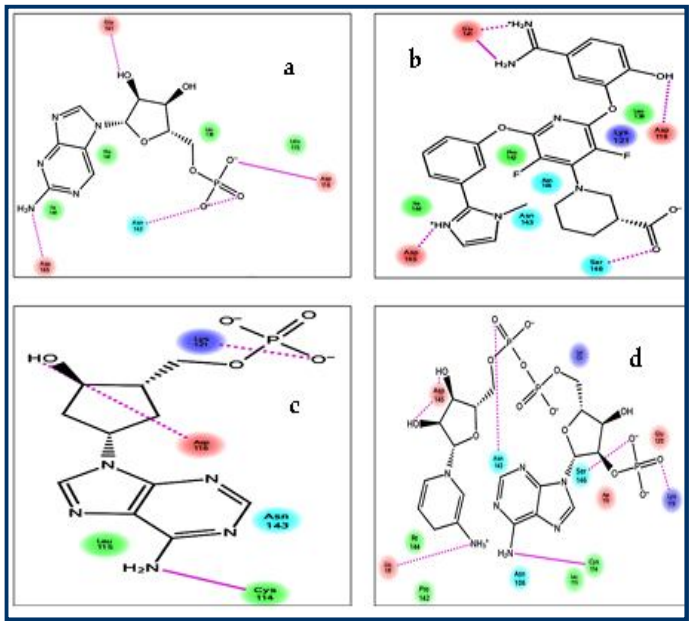

Figure 7: Binding of Chem PDB subset with UBE2C: **a)** 7-alpha-ribofuranosyl-2 aminopurinephospahte**; b)** 1, 2, 3-amino imino methyl; **c)** 2'deoxyaristeromycin; **d)** 3 Aminopyridine adenine

The compounds of Drug-likeness NCI subset sulfuric acid compound with 5,6-diamino-2,4-pyrimidinediol (1:1) , 1,6-dihydro-3-pyridinecarboxamide 1-oxide, nicotinic acid compound with 8-quinolinol (1:1) , 1H-imidazole-1-sulfonic acid compound with 1H-imidazole (1:1) **(Figure 5 a,b,c,d)** were binding with docking score of above -6 **(Table 2)**. 1, 6-dihydro-3-pyridinecarboxamide 1-oxide forms an hydrogen bond with Cys114 of active site (**Figure 5 b**). The compounds of different subsets such ChemBank (**Figure 6**), ChemPDB (**Figure 7**) and KEGG (**Figure 8**) which showed good binding score with UBE2C are listed in **Table 3,4 & 5.** Itdac-6 (N- hydroxy- 3, 5-dimethyladamantane- 1- carboxamide) chembank compound binds with UBE2C and forms hydrogen bond with Cys 114 and Asn143. 12(s), 20-DIHETE forms four hydrogen bonds with residues Asp116, Asn143, Gly140 and Ala 153 and have very less docking score -6.28781. The binding mode of ChemPDB compounds are shown in (**Figure 8**). 3-Aminopyridine adenine forms seven hydrogen bonds with Cys114, Lys119, Glu141, Asn143, Asp145 and Ser146. 2-deoxy steromycin shows interaction with Cys114, Asp116 and Lys121.

The ADME properties of these compounds were analyzed using QikProp tool of Schrodinder software. QikProp settings determine which molecules are flagged as being dissimilar to other 95% of the known drugs. The ADME/T properties such as permeability through MDCK cells (QPlogMDCK), logKp (Skin permeability),QikProp predicted log IC50 value for blockage of K^+ channels (QPlogHERG), percentage of human oral absorption of compounds were reported in Supplementary **Table 1 (see supplementary material)**. The number of stars of most of the compounds was within acceptable range. A large number of stars suggest that a molecule is less drug like than molecules with few stars.QikProp also evaluated physiochemical properties of compounds such as their molecular weights, hydrogen bond donors, hydrogen bond acceptors and solubility **Table 2 (see supplementary material),** and these properties were well

within acceptable range of the Lipinski rule for drug like molecules. These molecules were further evaluated for their pharmacokinetic properties such as octanol/water partition coefficient, cell permeability of Caco-2 cells and blood/brain partition coefficient. All these pharmacokinetic properties were within acceptable range for most of the compounds, the compounds which showed very high docking score and within the acceptable range of ADME/T properties would be taken for further studies.

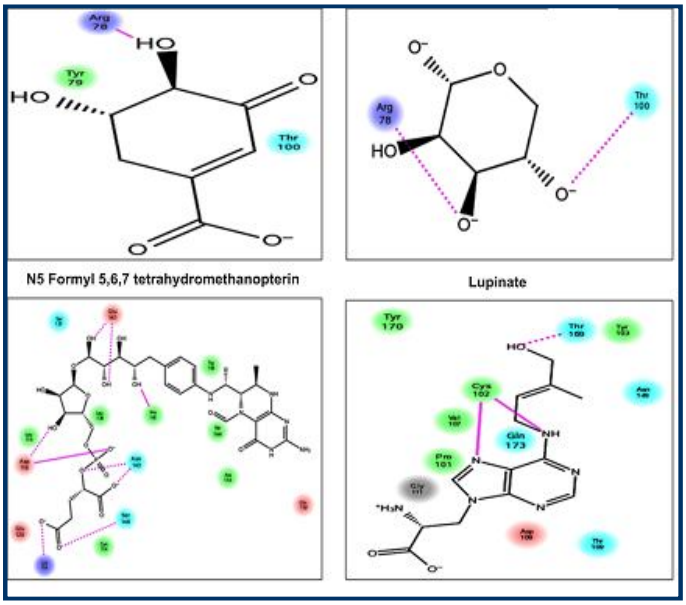

Figure 8: Interaction of KEGG subset compounds with UBE2C: **a)** 3-Dehydroshikimate; **b)** Arabinoxylan; **c)** N5 Formyl 5, 6,7 tetrahydromethanopterin; **d)** Lupinate

Discussion:

Ubiquitin-conjugating enzyme 2C (UBE2C) participates in cell cycle progression and checkpoint control by targeted degradation of short-lived proteins **[35].** As a conjugating enzyme, it directs polyubiquitination and in addition to its role in cyclin B destruction that is essential for exit from mitosis, UBE2C also plays an important role in mitotic spindle checkpoint control. Cells overexpressing UBE2C ignore the mitotic spindle checkpoint signals and lose genomic stability, which leads to cancer and poor prognosis in many cancers. Our previous studies have shown UBE2C to be a potential target for treatment in cervical cancer **[8-10].**

In the present study we modeled UBE2C using Prime homology modeling and corrections were carried out using protein preparation wizard and its sterochemical properties were checked by Ramachandran plot. Based on Ramachandran plot analysis, a good quality model would be expected to have above 90% in the most favoured region , the modeled structure of UBE2C in our study have 96.5% residues in most favoured region and the distribution of the main chain bond lengths and bond angles found to be within the limits. The PDB structure 1I7K was compared with modeled UBE2C (Ser114 → Cys114) to find structural alignment using the RMSD value, the RMSD score for 3D structure of UBE2C was below 2.00A^{o} and the structure could be taken for further analysis. Missing hydrogen atoms and unfilled valence atoms were corrected using protein preparation and the protein was subjected to energy minimization using the OPLS 2009 force field.

The active sites predicted by Q-Site Finder and SiteMap were used for further screening and docking studies. The ligand database was used for virtual screening against UBE2C using Glide docking tool of Schrodinger using standard precision mode. To identify compounds which were having good binding affinity four parameters are considered: G-Score, Glide Energy, H-bonds and Good Van-der-walls interactions. The more negative value of Glide score indicates that good binding affinity of ligand with receptor. 1,4-di(1H-benzimidazol-2-yl)-1,2,3,4-butanetetrol binds with UBE2C with a high G-Score of -7.05162 and it forms six hydrogen bonds via residues Asp108,Cys102,Phe98 and with Thr109. The compounds which showed very high scores and its interaction through hydrogen bonds with UBE2C are shown in Fig 6. The top scored compounds forms hydrogen bonds with residues such as Asp108, Cys102, and Ile113. This allows us to conclude that the compounds which have high binding score, high binding energy and have more hydrogen bonds are best inhibitors of UBE2C. In order to confirm the drug like properties of the docked compounds, prediction of ADME/T properties was performed. According to Lipinski's rule of five, the lead molecules molecular weights are below <500 Daltons with <5 hydrogen bond donors, < 10 hydrogen bond acceptors and a log p value within acceptable range. These compounds are further evaluated for their drug-like behavior through analysis of pharmacokinetic parameters required for absorption, distribution, metabolism, excretion and toxicity (ADMET) by use of QikProp. For most of the compounds, the partition coefficient (QPlogPo/w) and water solubility (QPlogS) shows good results with least number of stars and least number of violations. We also analyzed cell permeability (QPPCaco), a key factor governing drug metabolism and its access to biological membranes, ranged from 0 to 9906.Overall, the percentage human oral absorption for the compounds ranged from 0 to 100 %. The compounds which are not within the acceptable range will not be taken for further drug screening analysis. Compounds which pass all filter levels will be considered as possible drug candidates for UBE2C.

Conclusion:

Three dimensional structure of UBE2C was predicted with good sterochemical properties. The structure was used for further docking studies and for structure based drug discovery. The high scoring docking molecules were analyzed further for their binding affinity and ADME/T properties. Compounds which show good binding affinity and pass Lipinski's rule and ADME/T properties within acceptable range can be evaluated in vivo and in vitro and may be developed as inhibitor of UBE2C.

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Supplementary material:

Table 1: Not annotated NCI subset Glide score

Ligand	Glide score
SITE 1	
sulfuric acid compound with 5,6-diamino-2,4-pyrimidinediol (1:1)	-6.435095
sulfuric acid compound with 2-methyl-1,4-benzenediamine (1:1)	-6.216972
sulfuric acid compound with 2,6-diamino-4,5-pyrimidinediol (1:1)	-5.645991
sulfuric acid compound with 2,4,5,6-pyrimidinetetramine (1:1)	-5.628549
sulfuric acid compound with 2,5-diamino-4,6-pyrimidinediol (1:1)	-5.536239
nicotinic acid compound with 8-quinolinol (1:1)	-5.528486
1-methyl-2,3-dihydroisoquinoline	-5.253107
5,5-dimethyl-1,3-cyclohexadiene-1,3-diol	-5.248514
SITE 8	
1,6-dihydro-3-pyridinecarboxamide 1-oxide	-6.24917
3,4-dihydro-2H-pyran-4-yl acetate	-5.99422
3-(hydroxy(oxido)amino)phenol	-5.98762
2,5-diethylcyclopentanol	-5.8812
2,5,6-triamino-4-pyrimidinol	-5.86902
4-(methylthio)-2-pyrimidinamine	-5.82
2-(hydroxyimino)malononitrile compound with 2,5-pyrrolidinediimine (1:1)	-5.79534
1-aminocyclopentanecarbohydrazide	-5.79113
N-(3-methyl-1H-1,2,4-triazol-5-yl)urea	-5.78429
SITE 10	
5-(1-propenyl)-2(5H)-furanone	-6.17532
4-methyl-2,5-pyrimidinediamine	-6.04824
2-acetylcyclohexanone	-6.0347
2-hydrazino-3-methylbutanoic acid	-5.95696
formic acid compound with 5-(aminomethyl)-2,4-pyrimidinediamine (1:1)	-5.87822
2-amino-6-(fluoromethyl)-4-pyrimidinol	-5.87696
3-(1-aminoethylidene)-2,4(3H,5H)-furandione	-5.79747
2,5-dihydro-1,3-oxazol-2-yl methyl sulfide	-5.79622
2-isopropyl-1,3-dioxepane	-5.70699
3-hydrazino-1-methylpiperidine 2-butenedioate	-5.69524
5,5-dimethyl-1,3-cyclohexadiene-1,3-diol	-5.69349
SITE MAP	
1H-imidazole-1-sulfonic acid compound with 1H-imidazole (1:1)	-6.24876
6-methyl-1,6-dihydropyrazolo[3,4-c]pyrazol-3(2H)-imine	-6.20073
5-hydroxy-3,3,5-trimethyl-2-pyrrolidinone	-6.1055
sulfuric acid compound with 5,6-diamino-2,4-pyrimidinediol (1:1)	-6.10307
6-chloro-2,4-pyridinediol	-6.09415
acrylic acid compound with 2-vinyl-1H-benzimidazole (1:1)	-5.9984
2-amino-6-(fluoromethyl)-4-pyrimidinol	-5.95582
6-(fluoromethyl)-2-methyl-4-pyrimidinol	-5.94646
2-amino-6-mercapto-4-pyrimidinol	-5.89122
1-ethynylcyclopentanol	-5.82026
(1-tert-butyl-2-azetidinyl)methanamine	-5.77451
sulfuric acid compound with 4-(dimethylamino)phenol (1:1)	-5.76117
phosphoric acid compound with 5-amino-2-methyl-1H-imidazole-4-carboxamide (1:1)	-5.71379
N-(5-oxo-2,5-dihydro-2-furanyl)acetamide	-5.69788
2,2,5-trimethyl-1,3-oxazolidin-4-one	-5.68623
formaldehyde compound with methylsilanetriol (1:1)	-5.67743
1-methyl-1,2-dihydro-3H-pyrazolo[3,4-b]pyridin-3-imine	-5.66826
6-(hydroxymethyl)bicyclo[2.2.1]heptan-2-one	-5.66523
6-hydrazino-2,4(3H,5H)-pyrimidinedione	-5.62762
2-amino-5-fluoro-6-methyl-4-pyrimidinol	-5.62166
5-ethyl-2-hydroxynicotinonitrile	-5.58589
2-(1-hydroxyethyl)cyclopentanol	-5.58349
1-aminocyclopentanecarbohydrazide	-5.57548
2,5-dihydro-1,3-oxazol-2-yl methyl sulfide	-5.57338
2,2-dimethyl-3-oxocyclobutanecarboxylic acid	-5.56372
ethanesulfonic acid compound with 3-aminobenzonitrile (1:1)	-5.55996
3,3-dimethyl-5-methylene-2-pyrrolidinone	-5.55365
N-phenylcyanic hydrazide	-5.551
2-mercapto-6-methyl-4-pyridinol	-5.54768
5-fluoro-2,6-dimethyl-4-pyrimidinol	-5.54645
1-chloro-1,1-difluoro-2-butanol	-5.53501
ethyl cyanocarbamate compound with 2,3-pyridinediamine (1:1)	-5.52843

sulfuric acid compound with 2-anilinoethanol (1:1)	-5.47473
N-(3-methyl-1H-1,2,4-triazol-5-yl)urea	-5.45848
5-propyl-1,3-oxazolidine-2,4-dione	-5.45666
O-(2-pyrazinylmethyl)hydroxylamine	-5.45615
1-methyl-1,4-dihydropyrimido[5,4-e][1,2,4]triazine	-5.45552

Table 2: Drug-likeness NCI subset Glide Score

Ligand	Glide Score
Site 1	
2,4-diimino-1-methyl-1,3,5-triazepan-6-one	-6.401379
6-hydroxy-7,9-dihydro-8H-purine-8-thione	-6.377613
3-(2,4-dihydroxyphenyl)-1-(3-hydroxyphenyl)-2-propen-1-one	-6.238807
5-amino-1,3-dimethyl-6-thioxodihydro-2,4(1H,3H)-pyrimidinedione	-6.230218
4,6-diimino-1,3,5-thiadiazinane-2-thione	-6.149071
2-amino-6-(hydroxymethyl)-5,6,7,8-tetrahydro-4-quinazolinol	-6.013277
hexopyranosylamine	-5.996869
6-hydrazino-7-methyl-7H-purine	-5.991705
Crotonosid	-5.9905
4-(hydroxy(oxido)amino)-1-methyl-1H-imidazole-5-carboxamide	-5.937669
9H-Purine, 6-hydrazino-9-.beta.-D-ribofuranosyl-	-5.930981
2-(methylsulfonyl)-9H-purin-6-ol	-5.882179
3,4-dihydroxyphenyl thiocyanate	-5.851418
N-(4-carboxyphenyl)pentopyranosylamine	-5.809665
N,7-dimethyl-7H-purin-6-amine	-5.809191
2-((5-amino-6-chloro-4-pyrimidinyl)amino)cyclopentanol	-5.789705
2,7-dihydroxy-4-isopropyl-2,4,6-cycloheptatrien-1-one	-5.777257
2-chloro-N,7-dimethyl-7H-purin-6-amine	-5.775423
5-ethyl-1,5-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione	-5.76751
2-amino-5-hydroxy-1-indanone	-5.766126
Site 8	
1,3,5-tris(3-(4-methyl-1-piperazinyl)propyl)-1,3,5-triazinane	-6.30476
3-(((2-hydroxyethyl)amino)methyl)[1,1'-biphenyl]-2-ol	-6.03167
3-((4-O-(4-O-(3-O-acetyl-2,6-dideoxy-4-O-hexopyranosylhexopyranosyl)-2,6-dideoxyhexopyranosyl)-2,6-dideoxyhexopyranosyl)oxy)-14-hydroxycard-20(22)-enolide	-6.0037
2-((3,5-dimethoxybenzyl)amino)ethanol	-5.96681
1-fluoro-2-oxo-2-phenylethanesulfonic acid	-5.956
2,3,4,5,6-pentahydroxycyclohexanone thiosemicarbazone	-5.89372
5-(aminosulfonyl)-2-furamide	-5.87376
4-tert-butyl-2,5-dihydroxybenzoic acid	-5.83596
N-(4-(((3-(((4-(acetylamino)phenyl)sulfonyl)amino)-5,6-dimethyl-2-pyrazinyl)amino)sulfonyl)phenyl)acetamide	-5.80498
(2,4-dihydroxyphenyl)(oxo)acetic acid	-5.69317
4-(2,4,6-triimino-1,3,5-triazinan-1-yl)benzenesulfonic acid	-5.64389
N-hydroxy-2-(1H-indol-3-ylmethyl)-3-oxo-beta-alanine	-5.63774
6-O-hexopyranosylhexose	-5.62172
2,6-dihydrazino-9H-purine	-5.6147
9,10-dihydroxy-2-anthracenecarboxylic acid	-5.61135
11,17-dihydroxyestr-4-en-3-one	-5.56074
3-tert-butyl-2,5-dihydroxybenzoic acid	-5.53963
1-ethyl-3-hydroxy-5,6-indolinedione 5-semicarbazone	-5.48471
SITE 10	
2-amino-5-hydroxy-1-indanone	-6.206891
1-(2-hydroxyethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol	-5.905926
5-ethyl-5-(2-pyridinyl)-2,4-imidazolidinedione	-6.073291
3-tert-butyl-2,5-dihydroxybenzoic acid	-5.941977
5-(4-methylcyclohexylidene)-2-thioxo-4-imidazolidinone	-5.987524
2-((6-chloro-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)ethanol	-6.226296
3-hydroxy-1-phenyl-3-(4-pyridinyl)-1-propanone	-6.656043
N-(2-(hydroxymethyl)phenyl)benzamide	-5.993551
7,10-dihydroxy-3H-10lambda~5~-phenoxazin-3-one	-6.335365
2-(3-chlorobenzyl)-6-methylphenol	-6.675546
2-(2-chlorobenzyl)-6-methylphenol	-6.005913
1,4-dihydroxy-2-naphthyl imidothiocarbamate	-7.044107
4-(3-chlorobenzyl)-1,3-benzenediol	-6.626621
N-(5-hydroxy-9H-fluoren-2-yl)acetamide	-6.141409
5-(hydroxy(oxido)amino)-2-furaldehyde N'-(2-hydroxyethyl)semicarbazone	-5.984431
9,10-dihydroxy-2-anthracenecarboxylic acid	-6.418103
diethyl 5-(hydroxymethyl)-3-methyl-1H-pyrrole-2,4-dicarboxylate	-6.060589
5-(hydroxy(oxido)amino)-2-furaldehyde N'-(2-hydroxypropyl)semicarbazone	-6.160962
2-hydroxy-N-(4-methoxyphenyl)-2-phenylacetamide	-6.281176

2-(5-ethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)ethyl imidothiocarbamate	-5.997487
1-(4-(4-(1-hydroxyethyl)phenoxy)phenyl)ethanol	-6.112397
5-hexyl-5-(4-pyridinyl)-2,4-imidazolidinedione	-6.652477
2-(diethylamino)-1-(4-fluoro-1-naphthyl)ethanol	-5.957384
Leucoindigo	-6.535327
4-amino-N-(6-methyl-3-pyridazinyl)benzenesulfonamide	-6.598686
3-(1H-benzimidazol-2-ylthio)propyl imidothiocarbamate	-7.029526
5-benzyl-5-(3-pyridinyl)-2,4-imidazolidinedione	-6.0558
1-C-(1H-benzimidazol-2-yl)pentitol	-6.733362
1-(5-chloro-2-hydroxyphenyl)-3,5,5-trimethyl-1-hexanone	-6.135517
4-((2-hydroxy-4,5-dimethylphenyl)diazenyl)benzoic acid	-6.466418
1-(2-quinolinylmethyl)-1lambda~5~-quinoline	-6.040228
5-cinnamyl-5-ethyl-2,4,6(1H,3H,5H)-pyrimidinetrione	-6.190824
4-((2,4-diamino-6-hydroxy-5-pyrimidinyl)diazenyl)benzoic acid	-6.131668
4-(3-bromobenzyl)-1,3-benzenediol	-6.273388
N-(2,6-diethylphenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine	-7.388605
4-amino-N-(4,5,6-trimethyl-2-pyrimidinyl)benzenesulfonamide	-6.595716
N-(4-(aminosulfonyl)phenyl)-2-bromoacetamide	-5.908888
Gallamine Blue	-6.662291
2-hydroxy-3-(2-methyloctyl)naphthoquinone	-5.955845
N-(2-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-4-yl)-4-methylbenzenesulfonamide	-6.057604
2-hydroxy-3-(2-methyloctyl)naphthoquinone	-6.06432
2-hydroxy-N-(2-((2-hydroxyethyl)amino)ethyl)-3,5-bis(hydroxy(oxido)amino)benzamide	-5.998644
3,4,5-trihydroxybenzoic acid compound with 8-quinolinol (1:1)	-6.32075
2-(1-pyrrolidinyl)propyl diphenylacetate	-6.054506
2-(2-ethyl-1-pyrrolidinyl)ethyl 2-cyclopenten-1-yl(phenyl)acetate	-6.039924
Celestin Blue	-6.388936
Site Map	
1,4-di(1H-benzimidazol-2-yl)-1,2,3,4-butanetetrol	-7.05162
Xylosyl A	-6.79132
4-amino-N-(4-((dimethylamino)methyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)benzenesulfonamide	-6.4404
2-(dibutylamino)-1-(4-fluoro-1-naphthyl)ethanol	-6.4223
Dextrosazone	-6.40425
3-hydroxy-4-((4-methyl-2-sulfophenyl)diazenyl)-2-naphthoic acid	-6.39124
2-amino-1-dibenzo[b,d]furan-2-ylethanone	-6.38145
3-(diethylamino)-1-(3-phenanthryl)-1-propanone	-6.37403
2,6,7-trihydroxy-9-(2-hydroxyphenyl)-3H-xanthen-3-one	-6.36837
2-(benzyl(4-(diethylamino)benzyl)amino)-1-(3,4-dichlorophenyl)ethanone	-6.34294
1,3-bis((7-chloro-4-quinolinyl)amino)-2-propanol	-6.28573
S-(2-(1-pyrrolidinyl)ethyl) diphenylethanethioate	-6.23874
2-((3-((7-chloro-4-quinolinyl)amino)propyl)(ethyl)amino)ethanol	-6.23113
1-deoxy-1-((2,4-dichlorobenzyl)(methyl)amino)hexitol	-6.22857
2-oxopropyl 3,3-dimethyl-7-oxo-6-((phenylacetyl)amino)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate	-6.22795
4-tert-butyl-2-(((2-hydroxyethyl)amino)methyl)phenol	-6.22035
5-(hydroxy(oxido)amino)-2-furamide	-6.21882
2,5-diisopropylbenzenesulfonamide	-6.2105
N-(1,3-benzodioxol-5-ylmethyl)-N-benzyl-2-chloroethanamine	-6.19607
2,2-dihydroxy-N'-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazinecarboximidohydrazide	-6.17785
6-methyl-1,2,8-anthracenetriol	-6.16791
4-(imino(4-methoxyphenyl)methyl)-N,N-dimethylaniline	-6.10817
2-(4-chlorophenyl)-N~1~-(7-chloro-4-quinolinyl) -N~5~,N~5~-diethyl-1,5-pentanediamine	-6.09046
6-methoxy-N-(2-(2-pyridinyl)ethyl)-8-quinolinamine	-6.07115
3-(2-(diethylamino)ethyl)-4(3H)-quinazolinone	-6.05773
2,4-dihydroxybenzaldehyde semicarbazone	-6.05454
5-ethyl-5-pentyl-2,4,6(1H,3H,5H)-pyrimidinetrione	-6.03339
3-(((5-(hydroxy(oxido)amino)-2-furyl)methylene)amino) -5-methyl-1,3-oxazolidine-2-thione	-6.03196
3-phenyl-1,2-propanediol	-6.01433
6-(2-methylhydrazino)-9H-purine	-6.01227
8-(dibutylamino)-1-(6-methoxy-4-quinolinyl)-1-octanol	-6.01042
N-(4-((2,4-diamino-6-hydroxy-5-pyrimidinyl)diazenyl)benzoyl)glutamic acid	-6.0004
5-amino-1-(2-hydroxyethyl)-3-methyl-1H-pyrazole-4-carboxamide	-5.9628
1-(benzylamino)-2-indanol	-5.96208
N~4~-(4-(diethylamino)-1-methylbutyl) -N~6~,N~6~-dimethyl-4,6-quinolinediamine	-5.95746
2-((6-chloro-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)ethanol	-5.95354
4-(((4-bromobenzyl)(methyl)amino)methyl)-N,N-diethylaniline	-5.94406
N-(2-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-4-yl)-4-methylbenzenesulfonamide	-5.94064
5-(3-methylcyclohexylidene)-2-thioxo-4-imidazolidinone	-5.92223
3-((6-methoxy-8-quinolinyl)amino)-1,2-propanediol	-5.9211
2-(((8-hydroxy-7-quinolinyl)(phenyl)methyl)amino)benzoic acid	-5.918
3-(diethylamino)-2-(2-methoxyphenoxy)-1-phenyl-1-propanone	-5.91291

2-(benzyl(4-(diethylamino)benzyl)amino)-1-(4-chlorophenyl)ethanone	-5.90167
N-benzyl-3-methyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine	-5.89183
1-(4-chlorophenyl)-2-((4-methoxybenzyl)(methyl)amino)ethanol	-5.88661
1-isopentyl-3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione	-5.8465
1-(4-chloro-1-naphthyl)-3-(diethylamino)-1-propanol	-5.827
octyl 5-chloro-2-hydroxy[1,1'-biphenyl]-3-carboxylate	-5.82584
N-(2,4-dihydroxyphenyl)benzamide	-5.82424
1-(4-chlorophenyl)-2-(methyl(1-phenylpentyl)amino)ethanol	-5.82389
1,2-bis(4-chlorophenyl)-2-(ethyl(2-hydroxyethyl)amino)ethanone	-5.81364
1-(2-hydroxyethyl)-6-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-ol	-5.80508
1-methyl-2-(1-pyrrolidinyl)ethyl 2-cyclopenten-1-yl(phenyl)acetate	-5.80311
2,6-dimethoxy-9H-purine	-5.78661
4-amino-N-(4-(1-piperidinylmethyl)-1,3-thiazol-2-yl)benzenesulfonamide	-5.76745
9-(3-pyridinyl)-9H-xanthen-9-ol	-5.74865
9-methyl-9H-purine-6-thiol	-5.74305
2-(5-ethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)ethyl imidothiocarbamate	-5.7181

Table 3: ChemBank subset Glide score

Ligand	Glide Score
Site 1	
cdk2/5 inhibitor	-7.10332
itdac-6	-5.93785
ZM226600	-5.152617
fosphomycin	-5.83738
2-iminobiotin	-5.572837
cpd 5	-5.50081
remiszewski_008	-5.48895
ZM336372	-5.47394
Site 8	
Lavedustin A	-6.1414
ag1433	-5.88394
AM 92016	-5.64615
enantiotubacin	-5.62534
Bromo-cGMP [8-Bromo-cGMP]	-5.62262
schreiber_2	-5.29718
A-3	-5.28176
colletti_10	-5.09418
chap-l-aminosuberic acid	-5.07492
chap-31	-4.95615
remiszewski_013	-4.87124
massa_2	-4.85814
14,15-DEHYDRO-LEUKOTRIENE B4	-4.83981
Bromo-cAMP [8-Bromo-cAMP]	-4.82203
Site 10	
methylgene_02	-6.950566
methylgene_11	-6.90497
depudecin	-6.853724
1-(3'-carboxy-4'-hydroxyphenyl)-2-(2,5-dihydroxyphenyl) ethane	-6.306385
blebbistatin-CP	-6.210956
remiszewski_010	-6.002783
5-iodotubericidin	-5.98964
SQ22536	-5.884746
methylgene_10	-5.85437
itdac-8	-5.738741
itdac-1	-5.670952
manumycinA	-5.631559
methylgene_12	-5.601467
methylgene_01	-5.581606
MCI186	-5.540619
cimaterol	-5.459046
massa_1	-5.439284
methylgene_04	-5.389579
remiszewski_007	-5.290729
methylgene_13	-5.279326
blebbistatin	-6.210956
decoyinine	-5.088611
Cyclopiazonic Acid	-5.047267
N-Phenylanthranilic (CL)	-5.007092
17-PHENYL-TRINOR-PGE2	-4.963183

methylgene_05	-4.962501
tyrphostin [bis-tyrphostin] B42 270-168	-4.953311
ag112	-4.882607
methylgene_08	-4.862447
D609	-4.819564
SITE MAP	
12(s),20-DIHETE	-6.28781
methylgene_07	-5.870312
2,3-DINOR-6-KETO-PGF1a	-5.807333
9(s)-HETE	-5.806883
1400W	-5.411402
clonidine	-5.369437
Dihydrosphingosine-1-phosphate	-5.363779
VAD-FMK	-5.343214
EICOSATRIENOIC ACID (20:3 n-3)	-5.312881
methylgene_03	-5.297444
colletti_16	-5.207081

Table 4: ChemPDB subset Glide score

Ligand	Glide Score
Site1	
S-[S-THIOPYRIDOXAMINYL]CYSTEINE	-6.6713
2,3,6-TRIDEOXY-2,6-DIAMINO GLUCOSE	-6.03281
1-[2-[5-[AMINO(IMINO)METHYL]-2-HYDROXYPHENOXY]-6-[3-(4,5-DIHYDRO-1-METHYL-1H-IMIDAZOL-2-YL)PHENOXY] PYRIDIN-4-YL]PIPERIDINE-3-CARBOXYLIC ACID	-5.9942
(1-METHYL-1H-IMIDAZOL-2-YL)-(3-METHYL-4-{3-[(PYRIDIN-3-YLMETHYL)-AMINO]-PROPOXY}-BENZOFURAN-2-YL)-METHANONE	-5.93876
Site 8	
3-AMINOPYRIDINE-ADENINE DINUCLEOTIDE PHOSPHATE	-7.3259
1-[2-[5-[AMINO(IMINO)METHYL]-2-HYDROXYPHENOXY]-6-[3-(4,5-DIHYDRO-1-METHYL-1H-IMIDAZOL-2-YL)PHENOXY] PYRIDIN-4-YL]PIPERIDINE-3-CARBOXYLIC ACID	-6.9702
6-(ADENOSINE TETRAPHOSPHATE-METHYL)-7,8-DIHYDROPTERIN	-6.727154
1',5'-ANHYDRO-2',3'-DIDEOXY-2'-(GUANIN-9-YL)-6'-O-PHOSPHORYL-D-ARABINO-HEXITOL	-6.150197
[4R-(4ALPHA,5ALPHA,6ALPHA,7ALPHA)]-3,3'-{{TETRAHYDRO-5,6-DIHYDROXY-2-OXO-4,7-BIS(PHENYLMETHYL)-1H-1,3-DIAZEPINE-1,3(2H)-DIYL]BIS(METHYLENE)]BIS[N-1H-BENZIMIDAZOL-2-YLBENZAMIDE]	-6.098701
THIOPHOSPHORIC ACID O-((ADENOSYL-PHOSPHO)PHOSPHO)-S-ACETAMIDYL-DIESTER	-6.010479
S-2,3-DIHYDRO-5-GLYCIN-2-YL-ISOXAZOL-3-YL-CYSTEINE	-5.96573
N-{1-BENZYL-3-HYDROXY-4-[3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRYLAMINO]-5-PHENYL-PENTYL}-3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRAMIDE	-5.808388
DIPHOSPHOMETHYLPHOSPHONIC ACID ADENYLATE ESTER	-5.801628
PHOSPHORIC ACID MONO-[5-({[5-CARBAMOYL-3-(5-PHOSPHONOOXY-5-DEOXY-RIBOFURANOSYL)- 3H-IMIDAZOL-4-YLAMINO]-METHYL}-AMINO)-2,3,4-TRIHYDROXY-PENTYL] ESTER	-5.797348
GUANYLATE-O'-PHOSPHORIC ACID MONO-(2-AMINO-5,6-DIMERCAPTO-4-OXO-3,5,6,7,8A,9,10,10A-OCTAHYDRO-4H-8-OXA-1,3,9,10-TETRAAZA-ANTHRACEN-7-YLMETHYL) ESTER	-5.758999
2-METHYLADENOSINE-5'-MONOPHOSPHATE	-5.734126
2-[AMINO(IMINO)METHYL]-2-HYDROXYPHENOXY]-6-[3-(4,5-DIHYDRO-1H-IMIDAZOL-2-YL) PHENOXY]PYRIDINE-4-CARBOXYLIC ACID	-5.649238
METHYL PHOSPHONIC ACID ADENOSINE ESTER	-5.629544
2,6-DIAMINO-2,3,6-TRIDEOXY-ALPHA-D-RIBO-HEXOPYRANOSYL	-5.618363
AERUGINOSIN 98-B	-5.536799
7-ALPHA-D-RIBOFURANOSYL-2-AMINOPURINE-5'-PHOSPHATE	-5.535039
5-(2-MORPHOLIN-4-YLETHOXY)BENZOFURAN-2-CARBOXYLIC ACID ((S)-3-METHYL-1-{(S)-3-OXO-1-[2-(3-PYRIDIN-2-YLPHENYL)ACETYL]AZEPAN-4-YLCARBAMOYL}BUTYL)AMIDE	-5.513364
5-HYDROXY-THYMIDINE-5'-MONOPHOSPHATE	-5.462337
2-{5-[AMINO(IMINIO)METHYL]-6-FLUORO-1H-BENZIMIDAZOL-2-YL}-6-ISOBUTOXYBENZENOLATE	-5.436131
[HISTIDIN-1-YL-4H-[1,2,4]TRIAZOL-5-YL]-AMINE	-5.429371
PHOSPHORIC ACID MONO-[5-HYDROXYMETHYL-2-METHYL-3-THYMINYL-CYCLOPENTYLMETHYL] ESTER GROUP	
4-THIOURIDINE-5'-MONOPHOSPHATE	-5.383348
1-ALPHA-D-RIBOFURANOSYL-BENZIMIAZOLE-5'-PHOSPHATE	-5.378021
Site10	
7-ALPHA-D-RIBOFURANOSYL-2-AMINOPURINE-5'-PHOSPHATE	-7.1027
2'-DEOXYARISTEROMYCIN-5'-PHOSPHATE	-6.5625
2,6-DIAMINO-2,3,6-TRIDEOXY-ALPHA-D-RIBO-HEXOPYRANOSYL	-6.44879
2-(5-CARBAMIMIDOYL-2-HYDROXY-BENZYLAMINO)-PROPIONIC ACID	-6.44679
[HISTIDIN-1-YL-4H-[1,2,4]TRIAZOL-5-YL]-AMINE	-6.30433
PHOSPHORIC ACID MONO-[5-HYDROXYMETHYL-2-METHYL-3-THYMINYL-CYCLOPENTYLMETHYL]ESTER GROUP	-6.13677
7-ALPHA-D-RIBOFURANOSYL-PURINE-5'-PHOSPHATE	-6.08081
3'-DEOXY-3'-ACETAMIDO-URIDINE	-5.92804
4-THIOURIDINE-5'-MONOPHOSPHATE	-5.79637

S-2,3-DIHYDRO-5-GLYCIN-2-YL-ISOXAZOL-3-YL-CYSTEINE	-5.64072
(1'R,2'S)-9-(2-HYDROXY-3'-KETO-CYCLOPENTEN-1-YL)ADENINE	-5.52069
SITEMAP SITE	
AMIDOCARBOXYMETHYLDETHIA COENZYME *A	-6.7979
2-AMINO-6-[(4-CARBOXY-PHENYLAMINO)-METHYL]-4-HYDROXY-PTERIDIN-1-IUM	-6.6255
2-(3-METHOXYPHENYL)-2H-THIENO-[3,2-E]-1,2-THIAZINE-6-SULFINAMIDE-1,1-DIOXIDE	-6.360391
2,4-DIAMINO-6-PHENYL-5,6,7,8,-TETRAHYDROPTERIDINE	-6.053033
2'-MONOPHOSPHOADENOSINE-5'-DIPHOSPHORIBOSE	-5.772513
THIOALANINE	-5.728678
6-(5-AMINO-5-CARBOXY-PENTANOYLAMINO)-3-HYDROXYMETHYL-7-OXO-4-THIA-1-AZA-BICYCLO[3.2.0]HEPTANE-2-CARBOXYLIC ACID	-5.587483
7-AMINO-3,3A,4,5-TETRAHYDRO-8H-2-OXA-5,6,8,9B-TETRAAZA-CYCLOPENTA[A]NAPHTHALENE-1,9-DIONE	-5.587483
PHOSPHOAMINOPHOSPHONIC ACID-ADENYLATE ESTER	-5.415326
ALLOSAMIZOLINE	-5.05633
2-AMINO-3-OXO-4-SULFO-BUTYRIC ACID	-5.044742
2-[(3-HYDROXY-2-METHYL-5-PHOSPHONOOXYMETHYL-PYRIDIN-4-YLMETHYL)-AMINO]-2-METHYL-SUCCINIC ACID	-4.85522
4-(4-AMINO-CYCLOHEXYLIDENE)-4H-IMIDAZOL-2-YLAMINE	-4.847446
ADENYLYL-3'-5'-PHOSPHO-URIDINE-3'-MONOPHOSPHATE	-4.828918
2-AMINOETHYLGLYCINE-CARBONYLMETHYLENE-ADENINE	-4.819122
3,4-DIHYDRO-4-HYDROXY-2-(2-THIENYMETHYL)-2H-THIENO[3,2-E]-1,2-THIAZINE-6-SULFONAMIDE-1,1-DIOXIDE	-4.674181
THIOPHENE-2,5-DISULFONIC ACID 2-AMIDE-5-(4-METHYL-BENZYLAMIDE)	-4.639597
3-(10-METHYL-ANTHRACEN-9-YL)-PROPIONIC ACID	-4.610169
(2-{[4-({4-[(4-FORMYLAMINO-1-METHYL-1H-IMIDAZOLE-2-CARBONYL)-AMINO]-1-METHYL-1H-IMIDAZOLE-2-CARBONYL}-AMINO)-1-METHYL-1H-IMIDAZOLE-2-CARBONYL]-AMINO}-ETHYL)-DIMETHYL-AMMONIUM	-4.605567
(S)-3,4-DIHYDRO-2-(3-METHOXYPHENYL)-4-METHYLAMINO-2H-THIENO[3,2-E]-1,2-THIAZINE-6-SULFONAMIDE-1,1-DIOXIDE	-4.500853
(1-AMINO-2-PHENYL-ETHYL)-CARBAMIC ACID	-4.338817
{3-[3-(3,4-DIMETHOXY-PHENYL)-1-(1-{1-[2-(3,4,5-TRIMETHOXY-PHENYL)-BUTYRYL]-PIPERIDIN-2YL}-VINYLOXY)-PROPYL]-PHENOXY}-ACETIC ACID	-4.249909
9-DEOXY-9-AMINO-2-O-METHYL-5-N-ACETYL-ALPHA-D-NEURAMINIC ACID	-4.204528
2-(1-CARBOXY-2-HYDROXY-2-METHYL-PROPYL)-5,5-DIMETHYL-THIAZOLIDINE-4-CARBOXYLIC ACID	-4.201616
2-[N'-(4-AMINO-BUTYL)-HYDRAZINOCARBONYL]-PYRROLIDINE-1-CARBOXYLIC ACID BENZYL ESTER	-4.136994
CARBOBENZYLOXYLEUCINYL-LEUCINYL-LEUCINAL	-3.73145
ASPARTYL-2'-DEOXY-ADENOSINE-5'-MONOPHOSPHATE	-3.643039
ASPARTYL-ADENOSINE-5'-MONOPHOSPHATE	-3.643039

Table 5: KEGG Ligand subset Glide score

Ligand	Glide Score
Site 1	
3-Dehydroshikimate	-6.9362
3-Dehydroquinate	-6.8241
1,3-beta-D-Xylan	-6.73308
(1S,3R,4S)-3,4-Dihydroxycyclohexane-1-carboxylate	-6.71847
Phthalylamide	-6.692
3,5-Dihydroxyanthranilate	-6.53602
1-(5-Phosphoribosyl)-4-(N-succinocarboxamide)-5-aminoimidazole	-6.53445
Gentianamine	-6.49381
(1,4-alpha-D-Galacturonide)n	-6.31073
Site 8	
N5-Formyl-5,6,7,8-tetrahydromethanopterin	-6.5011
Anthranilyl-CoA	-6.3501
Arabinoxylan	-6.24471
Farnesoyl-CoA	-6.15049
Site10	
Lupinate	-6.0058
SITEMAP	
1,4-beta-D-Galactosyl-(alpha-1,3-L-fucosyl)-N-acetyl-D-glucosaminyl-	-6.4972
Aspulvinone G	-6.0868