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-diamino-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 checkpoint 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:...
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117 K), a mutant protein showed 99% sequence similarity and it was chosen as template for modeling UBE2C [15-17]. Prime tool (Schrödinger) was employed to construct 3D structure of UBE2C using 117 K as template [18,19]. Compound libraries such as Drug-likeliness 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 117 K), 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 SCHRODINGER 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 0.3Å 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 (Schrödinger 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.

Ligands 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-likeliness 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 1.0Å with partial atomic charge less than 0.25Å, gird was generated around active sites detected by QsiteFinder and by SiteMap (Schrödinger) and enclosed by a box at the centroid 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 (Schrödinger 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 + site + 0.130 Coul + 0.065 vDW – Burry 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: 117 K), with a resolution of 1.95 Å can be used as suitable template.
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 SCHRODINGER Prime module (Schrodinger, 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 0.3Å and the resulting optimized structure was used for further studies. The stereochemical properties of UBE2C model was evaluated by Ramachandran 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].

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, Asp145, Ser146, Pro147, Leu148, Ala152, Ala153, Glu154, Trp156; **Pocket 3:** Phe98, Cys102, Tyr103, His104, Pro105, Asn106, Val107, Asp108, Gly111, Ile113, Cys114, Leu138, Leu148, Asn106, Val107, Asp108, Gly111, Ile113, Cys114, Leu138, Leu148, Asn106, Val107.

Figure 3: SiteMap Binding pocket

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 site score 0.928 (Figure 3).

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-triies (3(4-methyl-1-piperaziny1)propyl)-1,3,5-triazinan; c) 2-amino-5-hydroxy-1-indanone; d) 1,4-di(1H-benzimidazol-2-yl)-1,2,3,4-butane-tetrol
Figure 5: Binding modes of Not annotated NCI subset ligands with UBE2C a) Sulfuric acid compound with 5,6-diamino-2,4-pyrimidinediol (1:1); b) 1,6-dihydro-3-pyridinecarboxamide 1-oxide; c) nicotinic acid compound with 8-quinolinol (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 Cys112 of active site with binding score of -6.206891 and -7.05162 respectively (Figure 4 a,b,c,d).

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 a 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 & 5. Ttdac-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 (QlogMDCK), logKp (Skin permeability), QikProp predicted log IC50 value for blockage of K+ channels (QlogHERG), 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.

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. 

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 stereochemical 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)       | -6.43595    |
| sulfuric acid compound with 2-methyl-1,4-benzenediamine (1:1)          | -6.21697    |
| 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-dihydrosoquinoline                                        | -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-diethylcyloparanol                                                 | -5.8812     |
| 2,5,6-triamino-4-pyrimidindiol                                         | -5.86902    |
| 4-(methylthio)-2-pyrindimamine                                         | -5.82       |
| 2-(hydroxyimino)malononitrile compound with 2,5-pyrrlidenimine (1:1)  | -5.79534    |
| 1-aminocyclopentanehydrorazide                                         | -5.79113    |
| N-(3-methyl-1H-1,2,4-triazol-5-yl)urea                                  | -5.78429    |
| SITE 10                                                                |
| 5-(1-proply)-2(5H)-furanone                                            | -6.17532    |
| 4-methyl-2,5-pyrimidindiamine                                          | -6.08242    |
| 2-acetylcylohexanone                                                   | -6.0347     |
| 2-hydrazone-3-methylbutanoic acid                                      | -5.95696    |
| formic acid compound with 5-(amiomethyl)-2,4-pyrimidinediamine (1:1)   | -5.87822    |
| 2-amino-6-(fluoromethyl)-4-pyrindinol                                   | -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-hydradine-1-methylpyrrolene-2-butenedioate                           | -5.69524    |
| 5,5-dimethyl-1,3-cyclohexadiene-1,3-diol                               | -5.69249    |
| SITE MAP                                                               |
| 1H-imidazole-1-sulfonic acid compound with 1H-imidazole (1:1)          | -6.24876    |
| 6-methyl-1,6-dihydroprazol(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-pyrimidinediol                                            | -6.09415    |
| acrylic acid compound with 2-vinyl-1H-benzimidazole (1:1)              | -5.9994     |
| 2-amino-6-(fluoromethyl)-4-pyrindinol                                   | -5.95652    |
| 6-(fluoromethyl)-2-methyl-4-pyrindinol                                  | -5.94646    |
| 2-amino-6-mercapto-4-pyrindinol                                        | -5.89122    |
| 1-ethylcyclohexanone                                                   | -5.82026    |
| (1-tert-butyl-2-acetidinyl)methamine                                   | -5.77451    |
| sulfuric acid compound with 4-(dimethylamino)phenol (1:1)              | -5.76117    |
| phosphoric acid compound with 5-aminophenol-2-methyl-1H-imidazole-4-carboxamide (1:1) | -5.71379 |
| N-(5-oxo-2,5-dihydro-2-furany)lcarbamad                               | -5.69788    |
| 2,2,5-trimethyl-1,3-oxazolidin-4-one                                   | -5.68023    |
| formaldehyde compound with methylsilanetiol (1:1)                      | -5.67743    |
| 1-methyl-1,2-dihydro-3H-1-pyrazol(3,4-bpyridin-3-ime)                   | -5.66826    |
| 6-(hydroxy)imidazol(1,2,1)heptan-2-one                                  | -5.66523    |
| 6-hydrazino-2,4(3H,5H)-pyrimidinedione                                 | -5.62762    |
| 2-amino-5-fluoro-6-methyl-4-pyrindinol                                 | -5.62166    |
| 5-ethyl-2-hydroxynicotinonitrile                                      | -5.58859    |
| 2-(1-hydroxyethyl)cyclopentanol                                       | -5.56349    |
| 1-aminocyclopentanehydrorazide                                        | -5.57548    |
| 2,5-dihydro-1,3-oxazol-2-yl methyl sulfide                             | -5.57338    |
| 2,2-dimethyl-3-oxyclobutanecarboxylic acid                            | -5.56372    |
| ethanesulfonic acid compound with 3-aminoazobenzenitrile (1:1)         | -5.55996    |
| 3,3-dimethyl-5-methylene-2-pyrrolidinone                               | -5.55365    |
| N-phenylcyanic hydradizine                                             | -5.551      |
| 2-mercapto-6-methyl-4-pyrindinol                                       | -5.54768    |
| 5-fluoro-2,6-dimethyl-4-pyrindinol                                     | -5.54645    |
| 1-chloro-1,1-difluoro-2-butanol                                       | -5.53501    |
| ethyl cyanoacetate compound with 2,3-pyrrlidenimine (1:1)              | -5.52843    |
Table 2: Drug-likeness NCI subset Glide Score

| Ligand | Glide Score |
|--------|-------------|
| Site 1 |             |
| 2,4-diamo-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-dimino-1,3,5-thiadiazinan-2-thione | -6.190071 |
| 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- | -5.939981 |
| 2-(methylsulfonyl)-9H-purin-6-ol | -5.882179 |
| 3,4-dihydroxyphenyl thioyanate | -5.851408 |
| 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 | -5.777527 |
| 2-chloro-N,7-dimethyl-7H-purin-6-amine | -5.775423 |
| 5-ethyl-1,5-dimethyl-2,4(1H,3H,5H)-pyrimidinetriene | -5.76751 |
| 2-amino-5-hydroxy-1-indanone | -5.766126 |
| Site 8 |             |
| 1,3,5-tris[(4-methyl-1-piperazinyl)propyl]-1,3,5-triazinan | -6.30476 |
| 3-[1-(2-hydroxyethyl)amino)methyl][1,1-biphenyl]-2-ol | -6.03167 |
| 3-(4-O-4-O-(3-O-acetyl-2,6-dideoxy-4-O-hepxyranosylhexpyranosyl)-2,6-dideoxyhexyranosyl)oxy)-14-hydroxyocard-20(22)-enolide | -6.0037 |
| 2-[(3,5-dimethoxybenzyl)amino]ethanol | -5.99681 |
| 1-fluoro-2-oxo-2-phenylethanesulfonic acid | -5.956 |
| 2,3,4,5,6-pentahydroxycyclohexanone thiosemicarbazone | -5.89372 |
| 5-(aminosulfonil)-2-furanide | -5.87876 |
| 4-tert-butyl-2,5-dihydroxybenzoic acid | -5.83596 |
| N-(4-[4-(4-acetylaminophenyl)isoufonyl]amino)-5,6-dimethyl-2-pyrazinylamino)sulfonyl)phenyl)acetamide | -5.80498 |
| (2,4-dihydroxyphenyl)acetic acid | -5.639317 |
| 4-(2,4,6-triamino-1,3,5-triazan-1-yl)benzenesulfonic acid | -5.64389 |
| N-hydroxy-2-(1H-indol-3-ylmethyl)-3-oxo-beta-alanine | -5.63774 |
| 6-O-hexopyranosylexose | -5.62172 |
| 2,6-dihydrazino-9H-purine | -5.6147 |
| 9,10-dihydroxy-2-anthracencarboxylic acid | -5.61235 |
| 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 | -6.206981 |
| 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 | -5.993351 |
| 7,10-dihydroxy-3H-10-benzo-a-phenoxazin-3-one | -6.335365 |
| 2-(3-chlorobenzyl)-6-methylphenol | -6.675156 |
| 2-(2-chlorobenzyl)-6-methylphenol | -6.005913 |
| 1,4-dihydroxy-2-naphthyl imidothiocarbamate | -7.044107 |
| 4-(3-benzilidene) | -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-anthracencarboxylic acid | -6.418103 |
| diethyl 5-(hydroxyethyl)-3-methyl-1H-pyrrole-2,4-dicarboxylate | -6.06098 |
| 5-(hydroxy(oxido)amino)-2-furaldehyde N'-(2-hydroxypropyl)semicarbazone | -6.160962 |
| 2-hydroxy-N-(4-methoxyphenyl)-2-phenylacetamide | -6.281176 |
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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
4-amino-N-(6-methyl-3-pyridazinyl)benzenesulfonamide - 6.596866
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)penitil - 6.733362
1-(5-chloro-2-hydroxophenyl)-3,5,5-trimethyl-1-hexanone - 6.120757
4-(2-hydroxy-4-dimethylphenyl)diacylenbenzoic acid - 6.466418
1-(2-quinolylmethyl)-1-lambd-5-quinoline - 6.040228
5-cinnamyl-5-ethyl-4,6(1H,3H,5H)-pyrimidinetrione - 6.190824
4-(2,4-diamino-6-hydroxy-5-pyrimidinyl)diacylenbenzoic 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 - 7.386005
4-amino-N-(4,5,6-trimethyl-2-pyridinyl)benzenesulfonamide - 6.595716
N-(4-aminosulfonyl)phenyl)-2-bromoacetamide - 5.909888

Gallamine Blue
2-hydroxy-3-(2-methylcrotyl)napthoquinone - 5.955845
N-(2-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-4-yl)-4-methylbenzenesulfonamide - 6.057604
2-hydroxy-3-(2-methylcrotyl)napthoquinone - 6.06432
2-hydroxy-N-(2-(2-(2-hydroxyethyl)amino)ethyl)-3,5-bis(hydroxy(oxido)aminobenzamide - 5.999864
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 - 6.398936

Site Map
1,4-di(1H-benzimidazol-2-yl)-1,2,3,4-butane tetrol - 7.05162
Xylol A - 6.79132
4-amino-N-(4-((diethylamino)methyl)-4,5,6,7-tetrahydro-1,3-benzo1azol-2-yl)benzenesulfonamide - 6.4404
2-(dibutylamino)-1-(4-fluoro-1-naphthyl)ethanol - 6.4223
Dextrose - 6.40425
3-hydroxy-4-(4-(4-methyl-2-sulfophenyl)diacylen)-1-naphthoic acid - 6.39124
2-amino-1-dibenz[b,d]furane-2-ylthelone - 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-dichlophenyl)ethanol - 6.34294
1,3-bis(7-chloro-4-quinolinyl)amino)-2-propanol - 6.28573
5-(2-(1-pyrrolidinyl)ethyl) diphenylethanethioate - 6.23874
2-(1-(2-(2,4-dichlorobenzyl)amino)hexyl)ethanol - 6.22667
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-furamid - 6.21882
2,5-diisopropylbenzenesulfonamide - 6.2105
N-(1,3-benzodiox-5-ylmethyl)-N-benzyl-2-chlorothanamine - 6.19607
2,2-dihydroxy-N'-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazincarboximido hydrazide - 6.17785
6-methyl-1,2,8-anthracenetriol - 6.16791
4-(lmino(4-methoxyphenyl)methy)-1,N-N-dimethylaniline - 6.10817
2-(4-chlorophenyl)-N-1,7-(chloro-4-quinolinyl) -N-5~5~N-5~5~diethy1-1,5-pentanediamine - 6.09046
6-methoxy-N-(2-(2-pyrrolidinyl)ethyl)-8-quinolinamino - 6.07115
3-(2-diethylamino)(ethyl)-4(3H)-quinazolinone - 6.05773
2,4-dihydrobenzaldehde semicarbazon - 6.05454
5-ethyl-5-pentyl-4,6(1H,3H,5H)-pyrimidinetrione - 6.03397
3-(l(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-methylhydrazinio)9H-purine - 6.012277
8-(dibutylamino)-1-(6-methoxy-4-quinolynyl)-1-octanol - 6.01042
N-(4-(2,4-diamino-6-hydroxy-5-pyrimidinyl)diacylenbenzyl)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-(diethylamino)-1-methylbutyl)-N-6-N-6'-(4-dimethyl-4-quinolinediamine - 5.95746
2-(6-fluoro-1-4H-pyrazolo[3,4-d]pyrimidin-4-yl)-1-ethyl)ethanol - 5.95354
4-(4-bromobenzyl)methylamino)-1,N,N-diethylanilin - 5.94406
N-(2-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-4-yl)-4-methylbenzenesulfonamide - 5.94064
5-(3-methylcyclohekyldiene)-2-thiooxo-4-midazolidindine - 5.92223
3-(6-methoxy-8-quinolynil)amino)-1,2-propanediol - 5.9211
2-(2-hydroxy-7-quinolynil)phenyl)methylamino)-benzoic acid - 5.918
3-(diethylamino)-2-(2-methoxyphenoxy)-1-phenyl-1-propanone - 5.91291

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Table 3: ChemBank subset Glide score

| Ligand               | Glide Score |
|----------------------|-------------|
| Site 1               |             |
| cdk2/ 5 inhibitor    | -7.10332    |
| itdac-6              | -5.93705    |
| ZM226600             | -5.152617   |
| fosphotymcin         | -5.83738    |
| Z-2-iminobiotin      | -5.572837   |
| cpd 5                | -5.50081    |
| remiszewski_008      | -5.48895    |
| ZM336372             | -5.47394    |
| Site 8               |             |
| Lavedustin A         | -6.1414     |
| agl1433              | -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-aminobacteric acid | -5.07492 |
| chap-31              | -4.95615    |
| remiszewski_013      | -4.87124    |
| massa_2              | -4.85814    |
| 14,15-DEHYDRO-LEUKOTRIENE B4| -4.83981 |
| Bromo-CA MP [8-Bromo-ca MP] | -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-6              | -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-PE2  | -4.963183   |
Table 4: ChemPDB subset Glide score

| Ligand                                                                 | Glide Score |
|------------------------------------------------------------------------|-------------|
| Site1                                                                  |             |
| 5-(5'-THIOPYRIDOXAMINYL)CYSTEINE                                       | 5.9942      |
| 3,4,3'-TRIDEOXY-2,6-DIAMINO GLUCOSE                                     | -6.9702     |
| 1-[2-(5'-AMINO(MINO)METHYL)-2-HYDROXYPHENOXY]-6-[3-(4,5-DIHYDRO-1-METHYL-1H-IMIDAZOL-2-YL)PHENOX Y] | -6.6713     |
| PYRIDIN-4-YLPIPERIDINE-3-CARBOXYLIC ACID                              |             |
| (1-METHYL-1H-IMIDAZOL-2-YL)-(3-METHYL-4-β-(PYRIDIN-3-YLMETHYL)-AMINO)-PROPOXY)-BENZOFURAN-2-YL)-METHANONE | -5.93876    |
| Site 8                                                                 |             |
| 3'-AMINOPOYRIDINE-ADENINE DINUCLEOTIDE PHOSPHATE                        | -7.3259     |
| 1-[2-(5'-AMINO(MINO)METHYL)-2-HYDROXYPHENOXY]-6-[3-(4,5-DIHYDRO-1-METHYL-1H-IMIDAZOL-2-YL)PHENOX Y] | -6.9702     |
| PYRIDIN-4-YLPIPERIDINE-3-CARBOXYLIC ACID                              |             |
| 6-[(ADENESINE TETRAHYDROXY)-METHYL]-7,8-DIHYDROPTERIN                  | -6.727154   |
| 1'-5'-ANHYDRO-2,3'-DIDEOXY-Z'-[GUANIN-9-YL]-6-O-PHOSPHORYL-DARABINO-HEXITOL | -6.150197   |
| [4R-(4ALPHA,SEPHRA,SEPHA,7ALPHA)];3,3-[(TETRAHYDRO-5,6-DIHYDROXY-2-OXO-4,7-BIS(PHENYL METHYL)-1H-1,3-DIAZEPINE-1,2H)-DIYLI][BIS(METHYLENE)][BIS(N-1H-BENZIMIDAZOL-2-YL)BENZAMIDE] | -6.098701   |
| THIOPHOSPHORIC ACID 0-(AENOSYLYL-PHOSPHO)-PHOSPHO)-SACETAMIDYL-DIESTER  | -6.010479   |
| 5,2-3-DIHYDRO-5GLYCIN-2YLISOXAZOL-3YL-CYSTEINE                          | -5.96573    |
| N-[1-METHYL-3-HYDROXY-4-(3-METHYL-2-(3-METHYL-3-PYRIDIN-2-YLMETHYL-UREIDO)-BUTYRLAMINO)-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-PHOSPHOXY-5'-DEOXY-RIBOFURANOSYL)-1H-IMIDAZOL-4-YLAMINO)-METHYL]AMINO]-2,3,4-TRIHYDROXY-PENTYL) ESTER | -5.797348   |
| GUANYLATE-O'-PHOSPHORIC ACID MONO-(2AMINO-5,6-DIMERCAPTO-4-OXO-3,5,6,7,8A,9,10,10A-OCTAHYDRO-4H-8- OXA-1,3,9,10TETRAAZA-ANTHRACEN-7-YLMETHYL) ESTER                      | -5.758999   |
| 2-METHYLADENOSINE-5'MONOPHOSPHATE                                       | -5.734126   |
| 2'(AMINO(MINO)METHYL)-2'HYDROXYPHENOXY]-6-[3-(4,5-DIHYDRO-1H-IMIDAZOL-2-YL)PHENOXYPYRIDINE-4-CARBOXYLIC ACID | -5.649238   |
| METHYLPHOSPHONIC ACID ADENOSINE ESTER                                   | -5.629544   |
| 2,6-DIAMINO-2,3,6-TRIDEOXY-ALPHA-RIBO-HEXOPRANOSYL                      | -5.618363   |
| AERUGINOSIN 98-B                                                         | -5.536799   |
| 7-ALPHA-D-RIBOFURANOSYL-2AMINOPURINE-5'PHOSPHATE                        | -5.535039   |
| 5-(2-MORPHOLIN-4-YLTHOXY)BENZOFURAN-2-CARBOXYLIC ACID ([S]-3-METHYL-1-[S]-3-OXO-1-[2-(3-PYRIDIN-2-YLPHENYLACETYL]JEPAN-4-YLCARBOXYL]BUTYLAMIDE | -5.513364   |
| 5'HYDROXY-THYMINE-5'MONOPHOSPHATE                                       |             |
| 2-[5'-(AMINO(MINO)METHYL)-6-FLUORO-1H-BENZIMIDAZOL-2-YL]-6ISOBUTOXYBENZENOLATE | -5.462337   |
| [HISTIDIN-1-YL-4H-1,2,4TRIAZOL-5-YL)-AMINE                               | -5.436131   |
| PHOSPHORIC ACID MONO-[5-HYDROXYMETHYL-2-METHYL-3-THYMINE-5-CYCLOPENTYL-5'METHYL)] ESTER GROUP | -5.429371   |
| 4THIOURIDINE-5'MONOPHOSPHATE                                            | -5.383348   |
| 1-ALPHA-D-RIBOFURANOSYL-BENZIMIDAZOLE-5'PHOSPHATE                       | -5.378021   |
| Site10                                                                  |             |
| 7-ALPHA-D-RIBOFURANOSYL-2AMINOPURINE-5'PHOSPHATE                        | -7.1027     |
| 2'-DEOXYRISTEROMYCIN-5'PHOSPHATE                                        | -6.5625     |
| 2,6-DIAMINO-2,3,6-TRIDEOXY-ALPHA-RIBO-HEXOPRANOSYL                     | -6.44879    |
| 2-(5'CARBAMIDOMYL-2-HYDROXY-BENZYLAMINO)-PROPIONIC ACID                 | -6.44679    |
| [HISTIDIN-1-YL-4H-1,2,4TRIAZOL-5-YL)-AMINE                               | -6.30433    |
| PHOSPHORIC ACID MONO-[5-HYDROXYMETHYL-2-METHYL-3-THYMINE-5-CYCLOPENTYL-5'METHYL)] ESTER GROUP | -6.13677   |
| 7-ALPHA-D-RIBOFURANOSYL-PURINE-5'PHOSPHATE                              | -6.08081    |
| 3'-DEOXY-3'-ACETAMIDYL-URIDINE                                         | -5.92804    |
| 4THIOURIDINE-5'MONOPHOSPHATE                                            | -5.79657    |
SITEMAP

Table 5: KEGG Ligand subset Glide score

| Ligand                                                                 | Glide Score |
|----------------------------------------------------------------------|-------------|
| Site 1                                                                |             |
| 3-Dehydroshikimate                                                   | -6.9362     |
| 3-Dehydroquininate                                                   | -6.8241     |
| 1,3-beta-D-Xylan                                                      | -6.73308    |
| (15,3R,4S)-3,4-Dihydroxyxyclohexane-1-carboxylate                    | -6.71847    |
| Phthalylamide                                                        | -6.692      |
| 3,5-Dihydroxyantranilate                                             | -6.53602    |
| 1-(5-Phosphoribosyl)-4-(N-succinocarboxamido)-5-aminimidazole        | -6.53445    |
| Gentianamine                                                         | -6.49381    |
| (1,4-alpha-D-Galacturonicid)                                         | -6.31073    |
| Site 8                                                                |             |
| N5-Formyl-5,6,7,8-tetrahydroxymethanopterin                         | -6.5011     |
| Anthranil-CoA                                                        | -6.3501     |
| Arabinoxylan                                                         | -6.24471    |
| Farnesoyl-CoA                                                        | -6.15049    |
| Site10                                                               |             |
| Lupinate                                                             | -6.0058     |

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