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Pharmacophore based Identification of Tubulin Inhibitors

C. ELAKKIYAH[1], A. MOULINAMARY[1] AND A. NAGARAJAN*[2]

[1] School of Chemical and Biotechnology, SASTRA University Thanjavur District, Tamil Nadu, India,
[2]Centre for Advanced Research in Indian System of Medicine (CARISM), SASTRA University, Thanjavur District, Tamil Nadu, India.

ABSTRACT

Cancer is the most commonly found disease nowadays and treatment for cancer involves targeting many biological pathways. Attempts to use biological agents to target Tubulin system has gained importance over other mechanisms attacking DNA, thus making Tubulin has been in the centre stage for cancer chemotherapy. Tubulin is a protein that forms microtubules which are involved in cell proliferation. The compounds that bind to the β-tubulin can inhibit the formation of microtubule through which cancer cell proliferation can be stopped. To find the structure of the β-tubulin of homosapiens, homology modeling has been done. Pharmacophore modeling has been carried out with nearly 49 compounds obtained from literature study. Molecules having similar pharmacophoric features have been searched through the use of zinc database. The obtained ligand molecules were properly validated using Lipinski rule based on which some of the molecule were filtered out. The binding efficiency of each drug is analysed using docking and finally the best drug molecules were selected.

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Key word: Tubulin polymerization, inhibitors, pharmacophore

A. NAGARAJAN
Centre for Advanced Research in Indian System of Medicine (CARISM), SASTRA University, Thanjavur District, Tamil Nadu, India.

INTRODUCTION

Cancer is a life threatening disease nowadays and drugs used for cancer treatment follow various mechanisms. Cancer is characterized by unregulated cell growth spans across a broad group of various diseases [1]. In cancer abnormal growth and division of cells occur leading to formation of malignant tumors and in metastasis they invade nearby organs of the body through the lymphatic system or bloodstream. Observed symptoms of cancer are, weight loss, fever, fatigue and pain. β-tubulin inhibitors are drugs that target microtubule dis-assembly [2]. α-tubulin and β-tubulin comprise tubulin, a small family of globular proteins that constitute microtubules. Molecular weights of tubulins are in the range approximately 55 kDa and the subunits are slightly acidic

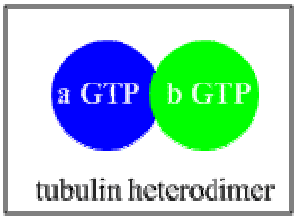

Figure 1 : *Tubulin heterodimer*

The dimers of α- and β-tubulin bind to GTP and assemble onto the (+) ends of microtubules while in the GTP-bound state the β (-) side of dimers connect to the plus end while the α sides (+) point externally to connect the incoming minus ends. Assembly of dimers bound to GTP tend to form microtubules, while those bound to GDP tend to fall apart, making this GTP cycle an essential component for the dynamic instability of the microtubule [3]. Microtubules, components of the cytoskeleton play a major role in maintaining cell integrity, facilitate intracellular transport and also assist in spindle formation during mitosis. [4]. Microtubules extend in length indefinitely through addition of more protofilaments in addition to the 13 protofilaments that form structure of microtubule and an imperfect helical structure results from their lateral association.

Microtubules are observed nucleated through dedicated microtubule-organizing center (MTOC) and form a circular "γ-tubulin ring complex" (γ-TuRC) which acts as a scaffold in the initiation of polymerization of α/β tubulin dimers.

Need for targeting tubulin

Tubulin is a crucial protein for cellular replication since microtubules formed by the polymerization between alpha and beta tubulin and helps separate daughter chromosomes in mitosis. Hence interaction with the protein tubulin is considered important as microtubules represent the best cancer target identified to date [5].

Objective

From the literature study it has been shown that β-tubulin is an important target for the cancer, but the inhibitors that targets the tubulin are less effective. So there is a need to search for identifying new inhibitors targeting the β-tubulin [1]. Recently chemo preventive agent phenethyl isothiocyanate (peitc) present in watercress (*nasturtium officinale*) has been shown to inhibit the metabolism of a nitrosamino compound present in tobacco that cause cancer through its metabolite employing docking and prediction of binding affinity of peitc to cytochrome p450 [6]. Several natural products have been evaluated for cancer treatment through inhibition of tubulin polymerization [7, 8]. Reviews on Tubulin inhibitors centre around the mechanism and

clinical efficacy [9, 10]. Several studies have been directed toward finding novel tubulin polymerization inhibitors and characterized as anti-mitotic agents [11].

MATERIALS AND METHODS

Generation of 3D structure through homology modeling

Homology modeling was done using modeller 9v8.The target sequence was obtained from uniprot and the blast search was done to find the template sequence. The alignment between the target and template sequence were identified and the models were generated.

Use of phase for the generation of pharmacophore model

Phase is employed for building a pharmacophore model, building a pharmacophore hypothesis from a single ligand, preparing a 3D database including pharmacophore information and searching a database for the structural matches for a pharmacophore hypothesis.

Softwares used

Modeller-mod9v8, Schrodinger-Maestro, Visualisation tools such as PyMOL and Chimera.

Database used

Protein data Bank, Zinc database, Pubchem, BLASTp, MUSCLE, SAVES

Data collection

49 compounds from the literature were collected [12] which show efficient interaction with the β-tubulin (Table 1). The Ic_{50} value of those compounds is collected to find the PIC_{50} value which is the anti logarithm of IC50 value that is used to give the appropriate predicted activity.The 3D structure of all the collected ligands have been drawn using YASARA tool and used for the study.

Table 1
Inhibitors of tubulin polymerization with its Ic50 values.

S.No	*Compounds*	*PIC50 value*	*Molecular properties*
1	Anasmitocins	3.222	ALogP:4.5383 H Donor Count:2/H Acceptor Count:9 Formula Weight:649.17
2	10-Deacetyl baccatin	5.25	ALogP:2.3254 H Donor Count:3/H Acceptor Count:9 Formula Weight:528.59
3	(5-methoxy-1H-indol-2-yl)-phenyl-methanone	7.0060	ALogP:2.5527 H Donor Count:1/H Acceptor Count: 3 Formula Weight:251.28
4	E-7070 (N1-(3-chloro-2,3,3a,7a-tetrahydro-1H-indol-7)benzene-1,4-disulfonamide dihydrochloride	6.25	ALogP:-1.0802 H Donor Count:5/ H Acceptor Count: 7 Formula Weight:462.8
5	2-[1-[(4-chlorophenyl)methyl]indol-3-yl]-2-oxo-N-(4-	5.09691	ALogP:3.3478 H Donor Count:1/ H Acceptor Count: 4

	pyridyl)acetamide		Formula Weight:389.83
6	A-289099	5.6777	ALogP:3.1257 H Donor Count:0/H Acceptor Count: 6 Formula Weight:366.41
7	Cabazitaxel	8.3010	ALogP:3.1985 H Donor Count:3/H Acceptor Count: 14 Formula Weight:779.83
8	Cisplatin	8.0809	Formula Weight:316.472(6) Formula:CH_3Cl_3Pt
9	Colcemid	8.3979	ALogP:1.2516 H Donor Count:1/H Acceptor Count: 6 Formula Weight:371.43
10	Cyclostreptin	7.0457	ALogP:0.8703 H Donor Count:2/H Acceptor Count: 5 FormulaWeight:388.50
11	Cytarbine	8.0132	ALogP:-1.4211 H Donor Count:4/H Acceptor Count: 6 Formula Weight:243.217
12	Discodermolide	7.9208	ALogP:5.0502 H Donor Count:5/H Acceptor Count:8 Formula Weight:593.79
13	Docetaxel	8.3306	ALogP:3.7471 H Donor Count:4/ H Acceptor Count:14 Formula Weight:806.89
14	Dolastatin 10	5.6989	ALogP:5.0241 H Donor Count:4/ H Acceptor Count:8 Formula Weight:773.08
15	Dolastatin 15	5.6989	ALogP:4.006 H Donor Count:1/ H Acceptor Count:10 Formula Weight:837.06
16	Eleutherobin	6.89	ALogP:3.6374 H Donor Count:3/ H Acceptor Count:12 Formula Weight:644.75
17	Epothilone B	8.3979	ALogP:3.5783 H Donor Count:2/ H Acceptor Count:7

			Formula Weight:507.68
18	Epothilone D	8.3979	ALogP:4.7315 H Donor Count:2/ H Acceptor Count:6 Formula Weight:491.68
19	Eribulin	5.000	ALogP:2.8687 H Donor Count:3/ H Acceptor Count:11 Formula Weight:729.94
20	Methoxy estradiol	5.2228	ALogP:4.0079 H Donor Count:2/ H Acceptor Count:2 Formula Weight:272.3
22	Halichondrin	5.26	ALogP:4.2538 H Donor Count:3/ H Acceptor Count:19 Formula Weight:1111.31
23	Colchicine	8.5376	ALogP:1.1124 H Donor Count:1/ H Acceptor Count:5 Formula Weight:415.50
24	Hemiasterilin	7.1674	ALogP:2.1352 H Donor Count:5/ H Acceptor Count:7 Formula Weight:475.62
25	Ixabepilone	8.5850	ALogP:2.4799 H Donor Count:3/ H Acceptor Count:6 FormulaWeight:480.66
26	Lamiudine	5.5686	ALogP:-0.1314 H Donor Count:2/ H Acceptor Count:4 Formula Weight:229.256
27	Larotaxel	7.1366	ALogP:1.9976 H Donor Count:3/ H Acceptor Count:14 Formula Weight:789.82
28	Laulumalide	8.2441	ALogP:3.0456 H Donor Count:2/ H Acceptor Count:8 Formula Weight:528.63
29	Lophocladine A	8.3767	ALogP:1.2996

			H Donor Count:1/ H Acceptor Count:2Formula Weight:222.24
30	Lophocladine B	8.3767	ALogP:2.0248 H Donor Count:1/ H Acceptor Count:3 Formula Weight:221.26
31	Maytansine	5.4559	ALogP:1.4351 H Donor Count:2/ H Acceptor Count:10 Formula Weight:715.23
32	Thio colchicine	8.5376	ALogP:1.1124 H Donor Count:1/ H Acceptor Count:5Formula Weight:415.50
33	Mivudine	4.2261	ALogP:2.5191 H Donor Count:3/ H Acceptor Count:6 Formula Weight:325.36
34	N-4-iodophenyl-N(2-chloro ethyl urea)	5.09691	ALogP:3.3785 H Donor Count:1/ H Acceptor Count:3 Formula Weight:353.544
35	Noscapine	7.2567	ALogP:2.3115 H Donor Count:2/ H Acceptor Count:8 Formula Weight:413.42
36	Paclitaxel	6.4089	ALogP:4.5337 H Donor Count:3/ H Acceptor Count:14 Formula Weight:852.92
37	Peloruside	7.744	ALogP:1.3553 H Donor Count:5/ H Acceptor Count:11 Formula Weight:548.66
38	Phomopsin	5.6197	ALogP:0.907 H Donor Count:9/ H Acceptor Count:13 Formula Weight:775.20
39	Rhizoxin	7.2839	ALogP:2.8298 H Donor Count:1/ H Acceptor Count:10 Formula Weight:625.75

40	Spongistatin	5.4436	ALogP:6.0594 H Donor Count:8/ H Acceptor Count:20 FormulaWeight:1147.39
41	Taxoprexin	8.5228	ALogP:10.8087 H Donor Count:4 /H Acceptor Count:14 Formula Weight:1122.34
42	Nocadazole	6.5228	ALogP:1.8148 H Donor Count:24 /H Acceptor Count:5 Formula Weight:301.32
43	Topotecan	3.25	ALogP:-0.528 H Donor Count:0/H Acceptor Count:6 FormulaWeight:232.230
44	Ustiloxin	4.9871	ALogP:-2.7208 H Donor Count:10/H Acceptor Count:14 Formula Weight:633.67
45	Vinblastine	5.0506	ALogP:3.9252 H Donor Count:3/H Acceptor Count:13 Formula Weight:810.97
46	Vincristine	7.231	ALogP:1.0469 H Donor Count:3/ H Acceptor Count:13 Formula Weight:841.00
47	Vinorelbine	7	ALogP:4.3296 H Donor Count:2/ H Acceptor Count:12 Formula Weight:778.93
48	Vindesine	7.9355	ALogP:2.8996 H Donor Count:5/ H Acceptor Count:11 Formula Weight:753.93
49	Vinfluinine	7.5228	ALogP:4.402 H Donor Count:3/ H Acceptor Count:13 Formula Weight:14.0266

Methodology

Homology Modeling

We have done modeling with the use of Modeller 9v8. The Target sequence obtained from SWISSPROT is searched again BLAST (Basic Local Alignment Tool). The structure of β-tubulin (Fig. 2) and the structural alignment of β-tubulin and 1SA0 (Fig. 3) are shown below.

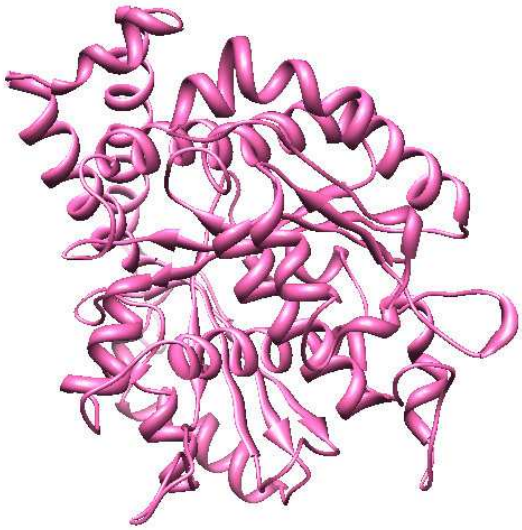

Figure 2
Structure of β-tubulin

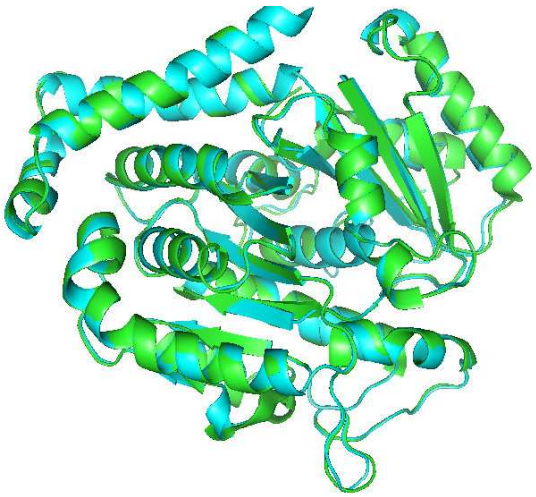

Figure 3
Structural alignment of β-tubulin and 1SA0

In general Rmsd value should be less than 1and for our predicted model, the low Rmsd value states that, the modeled structure has better alignment with the template structure.

Template selection

Template selection is the most important and critical step in modeling technique, because this step only will decide to give the template which is highly used to generate the model for the Target sequence. If the percentage sequence identity between the sequence of interest and a protein with known structure is high enough (more than 25 or 30 %) simple database search programs like BLAST is clearly adequate to detect the homology.

Developing pharmacophore model

The first step in developing a pharmacophore model is to prepare ligands and for this step possible conformation of

the selected molecules have been generated. This step is performed in the Prepare Ligands step of the Develop Pharmacophore Model panel. Then the molecules will be selected as active, inactive and neutral. Developing a pharmacophore model requires all-atom 3D structures that are realistic representations of the experimental molecular structure. Most ligands are flexible, so it is important to consider a range of conformations in order to increase the chances of finding something close to the bound structure. The second step in developing a pharmacophore model is to use a set of pharmacophore features to create pharmacophore sites for all the ligands. This step is performed in the Create Sites step of the Develop Pharmacophore Model panel. In this step, the sites will be created for each pharmacophore features. In the next step, pharmacophores from all conformations of the ligands in the active set are examined, and those pharmacophores that contain identical sets of features with very similar spatial arrangements are grouped together. If a given group is found to contain at least one pharmacophore from each ligand, then this group gives rise to a common pharmacophore. Any single pharmacophore in the group could ultimately become a common pharmacophore hypothesis-an explanation of how ligands bind to the receptor. Then in the Score Hypotheses step, common pharmacophores are examined, and a scoring procedure is applied to identify the pharmacophore from each surviving n-dimensional box that yields the best alignment of the chosen actives. This pharmacophore provides a hypothesis to explain how the active molecules bind to the receptor. There will of course be many hypotheses, because there are many boxes. The scoring procedure provides a ranking of the different hypotheses, allowing us to make rational choices about which hypotheses are most appropriate for further investigation. In the Build QSAR Model step, we build QSAR models for the hypotheses selected in the Score Hypotheses step, using the activity data for all the available ligands. The obtained pharmacophore model has the three Acceptors and one Hydrophic group. This feature has been searched against the zinc database using Schrodinger. The generated output was subjected to docking. In the Glide docking, optimization of the Protein structure was done by keeping the chain structure deleting water molecule which does not have any interaction. Minimized structure was generated and proteinprep.mae file was generated. Ligand preparation was executed using LigPrep which produces a single low-energy 3D structure with correct chiralities for each successfully processed input structure. It was used for removing unwanted molecules, adding hydrogens, and minimizeing the ligand structure. Grid preparation is employed to locate where the ligand should have its binding with the receptor. In order to run the docking, the output from the ligand preparation step and the grid preparation step will be given. It will dock the given ligands with the receptor and it will give the G score, energy and H-bond interactions. The output will be in the format of xp based on the H-bond interactions, G score the best docked ligand will be selected.

RESULTS AND DISCUSSION

The aligned sequence of the target and the template are shown in Fig 4.

```
sp|P07437|TBB5_HUMAN          MREIVHIQAGQCGNQIGAKFWEVISDEHGIDPTGTYHGDSDLQLDRISVYYNEATGGKYV
1SA0:B|PDBID|CHAIN|SEQUENCE   MREIVHIQAGQCGNQIGAKFWEVISDEHGIDPTGSYHGDSDLQLERINVYYNEAAGNKYV
                              ********************************:*********:**.******:*.***

sp|P07437|TBB5_HUMAN          PRAILVDLEPGTMDSVRSGPFGQIFRPDNFVFGQSGAGNNWAKGHYTEGAELVDSVLDVV
1SA0:B|PDBID|CHAIN|SEQUENCE   PRAILVDLEPGTMDSVRSGPFGQIFRPDNFVFGQSGAGNNWAKGHYTEGAELVDSVLDVV
                              ************************************************************

sp|P07437|TBB5_HUMAN          RKEAESCDCLQGFQLTHSLGGGTGSGMGTLLISKIREEYPDRIMNTFSVVPSPKVSDTVV
1SA0:B|PDBID|CHAIN|SEQUENCE   RKESESCDCLQGFQLTHSLGGGTGSGMGTLLISKIREEYPDRIMNTFSVVPSPKVSDTVV
                              ***:********************************************************

sp|P07437|TBB5_HUMAN          EPYNATLSVHQLVENTDETYCIDNEALYDICFRTLKLTTPTYGDLNHLVSATMSGVTTCL
1SA0:B|PDBID|CHAIN|SEQUENCE   EPYNATLSVHQLVENTDETYCIDNEALYDICFRTLKLTTPTYGDLNHLVSATMSGVTTCL
                              ************************************************************

sp|P07437|TBB5_HUMAN          RFPGQLNADLRKLAVNMVPFPRLHFFMPGFAPLTSRGSQQYRALTVPELTQQVFDAKNMM
1SA0:B|PDBID|CHAIN|SEQUENCE   RFPGQLNADLRKLAVNMVPFPRLHFFMPGFAPLTSRGSQQYRALTVPELTQQMFDAKNMM
                              ********************************************************:*******

sp|P07437|TBB5_HUMAN          AACDPRHGRYLTVAAVFRGRMSMKEVDEQMLNVQNKNSSYFVEWIPNNVKTAVCDIPPRG
1SA0:B|PDBID|CHAIN|SEQUENCE   AACDPRHGRYLTVAAVFRGRMSMKEVDEQMLNVQNKNSSYFVEWIPNNVKTAVCDIPPRG
                              ************************************************************

sp|P07437|TBB5_HUMAN          LKMAVTFIGNSTAIQELFKRISEQFTAMFRRKAFLHWYTGEGMDEMEFTEAESNMNDLVS
1SA0:B|PDBID|CHAIN|SEQUENCE   LKMSATFIGNSTAIQELFKRISEQFTAMFRRKAFLHWYTGEGMDEMEFTEAESNMNDLVS
                              ***:.************************************************************

sp|P07437|TBB5_HUMAN          EYQQYQDATAEEEEDFGEEAEEEA-
1SA0:B|PDBID|CHAIN|SEQUENCE   EYQQYQDATADEQGEFEEEGEEDEA
                              **********:*: :* **.**:
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Figure 4
Sequence Alignment

Amino acids in Red: small, hydrophobic, aromatic, amino acids in Blue: acidic,amino acids in Magenta: basic, amino acids in Green: hydroxyl, amine, amide, basic, If "*": identical, If ":": conserved substitutions (same colour group).,If".": semi-conserved substitution (similar shapes).

Structure validation was done using Ramachandran plot of β-Tubulin protein (Fig. 5). For our generated target protein β-tubulin has 0 residues in the disallowed region. More than 87% of the residues present in the allowed region of the plot. Disallowed region has o residues. From this it is been concluded that the generated model is valid to proceed further steps.

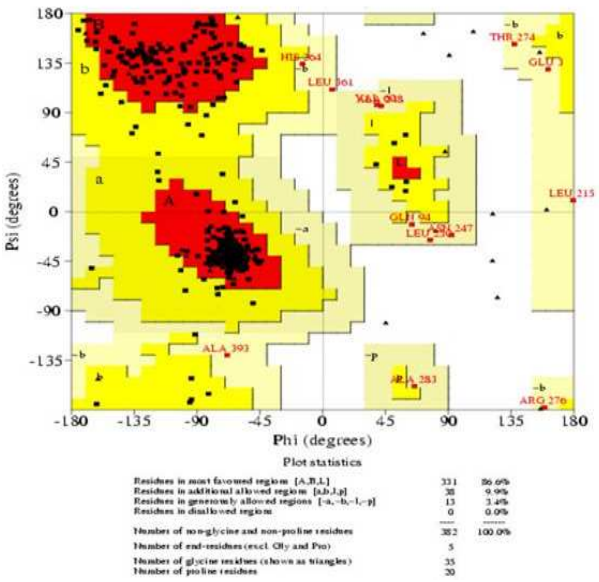


Figure 5
Ramachandran plot of β-Tubulin protein

Pharmacophore model generation

Thirty five molecules forming the training set were used to develop the pharmacophore model. The pharmacophoric features selected for creating sites were hydrogen bond acceptor (A) and Hydrophobic group (H). Pharmacophore models containing four to five features were generated. The five featured pharmacophore hypothesis was rejected due to low value of survival score, as they were unable to define the complete binding space of the selected molecules. The four featured pharmacophore hypothesis was selected and subjected to stringent scoring function analysis.

Pharmacophore model generated using three point pharmacophore is shown in Fig. 6. The above model has four features(AAAH).

A->Acceptor(pink)
H->Hydrophobic(Green)

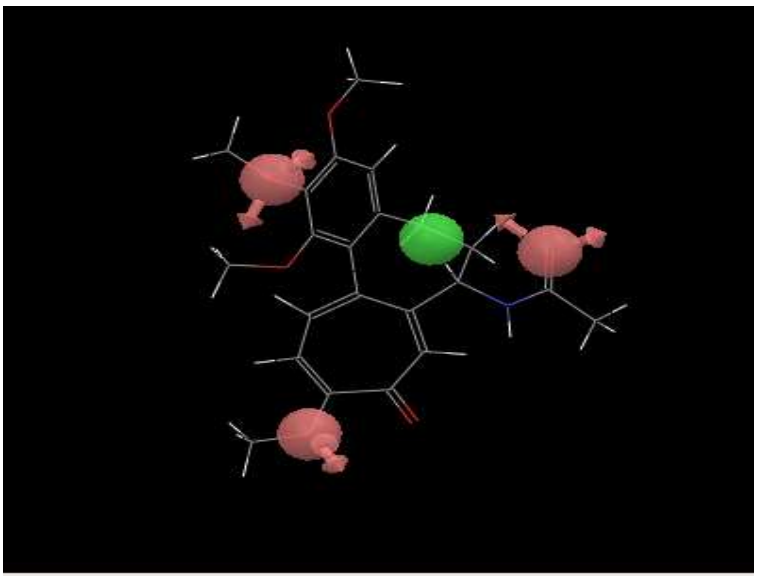


Figure 6
Pharmacophore model

For each ligand, one aligned conformer from those of the corresponding reference feature was superimposed on best hypothesis AAAH- 1. Then fitness scores for all ligands were observed on the best scored pharmacophore model AAAH-1. A greater fitness score predicts a greater activity of the compound. The fit function apart from checking whether the feature is mapped or not, measures the distance that separates the feature on the molecule from the centroid of the hypothesis feature. Scatter plot of training set Fig. 7 and test set Fig. 8 are shown below which indicates a R^2 value of 0.61 for the test set.

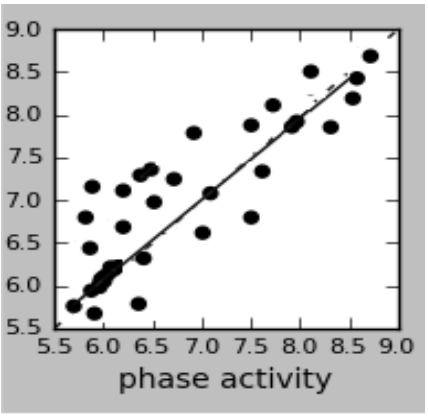


Figure 7
Scatter plot of Training set

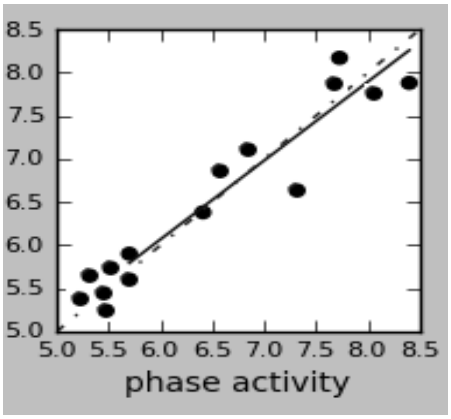


Figure 8
Scatter plot of test set

The generated pharmacophore model is searched against ZINC database having more than 18,000 compounds in it. That is, the best pharmacophore model derived is used to perform 3D search of ZINC database to identify compounds that matches pharmacophore features. This process helps to find the similar compounds that fit with our generated 3D pharmacophore model. Finally, 900 compounds were obtained from the search which fits into the model. These compounds were separated and docking was done for all the separated compounds. Based on the glide score and hydrogen bond interactions the top 20 compounds were selected. These final compounds obtained have the similar features and best fitness value and the structures are shown (Table 2).

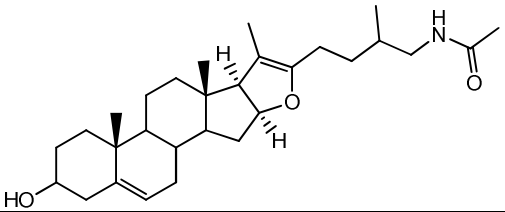
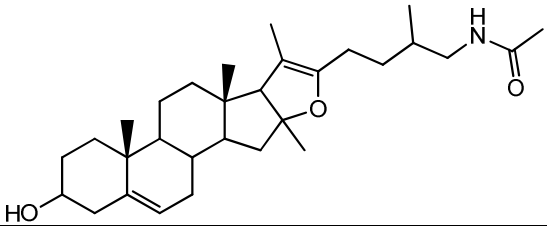
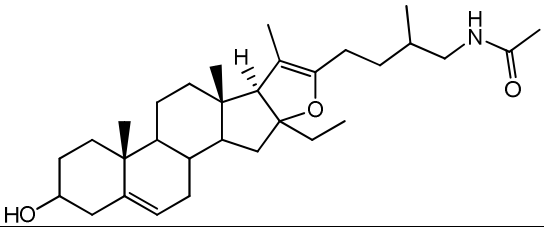
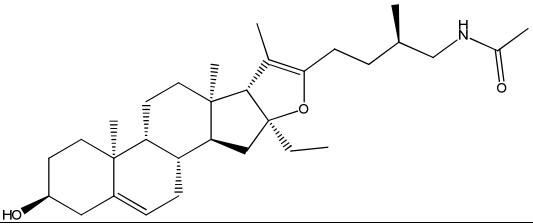
Table 2
Glide scores for the best 20 compounds

S.No	Zinc-Compound ID	G-Score
1	ZINC_4014843	-8.98
2	ZINC_35361059	-8.65
3	ZINC_4014841	-8.53
4	ZINC_16101925	-8.51
5	ZINC_4014875	-8.08
6	ZINC_4064733	-8.01
7	ZINC_8740057	-7.91
8	ZINC_4014874	-7.53
9	ZINC_8740137	-7.15
10	ZINC_16028404	-6.91
11	ZINC_16028406	-6.89
12	ZINC_16101923	-6.89
13	ZINC_35867983	-6.25
14	ZINC_3838174	-6.13

15	ZINC_4014841	-5.98
16	ZINC_4014843	-5.95
17	ZINC_4014875	-5.91
18	ZINC_174787	-5.91
19	ZINC_1610925	-5.25
20	ZINC_35361059	-5.31

From this the top 4 compounds have been selected and used for calculating the molecular properties. All these four compounds satisfy the Lipinski's rule of five and have high glide score indicating that there is a higher binding affinity with tubulin (Table 3).

Table 3
Glide scores for the best 4 compounds

Compound Number	***ZINC-ID***	***Glide Score***	***Properties***
1	4014843 	-8.98	H bond Acceptor : 4; H bond donor : 2 AlogP : 5.81; Molecular weight :455.683
2	35361059 	-8.65	H bond Acceptor : 4; H bond donor : 2 AlogP : 6.25; Molecular weight : 469.71
3	4014875 	-8.51	H bond Acceptor : 4; H bond donor : 1 AlogP : 6.75; Molecular weight : 483.737
4	16101925 	-8.08	H bond Acceptor : 4; H bond donor : 2 AlogP : 6.76; Molecular weight : 483.737

The docking postures for all these four compounds have been visualized using chimera and shown in Fig. 9.

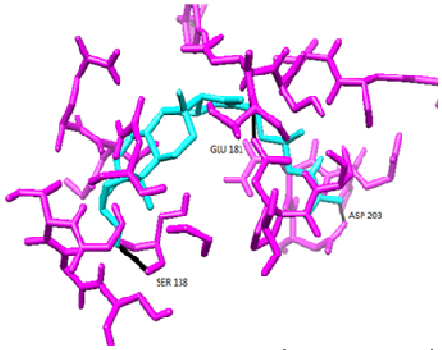


Figure 9 a: Compound 4014843 and its interacting with tubulin residues

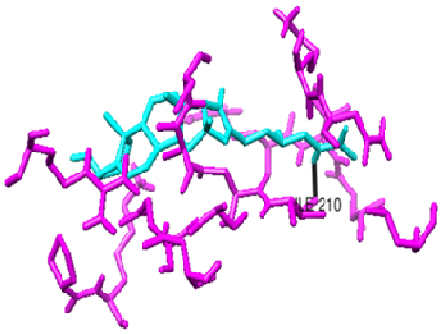


Figure 9 b: Compound 35361059 and its interacting with tubulin residues

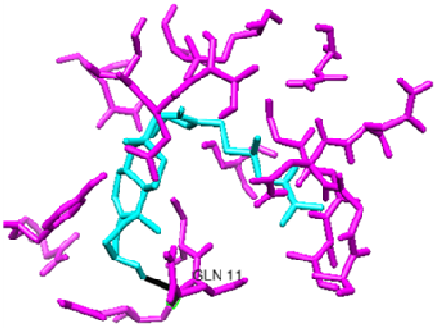


Figure 9 c: Compound 4014875 and its interacting with tubulin residues

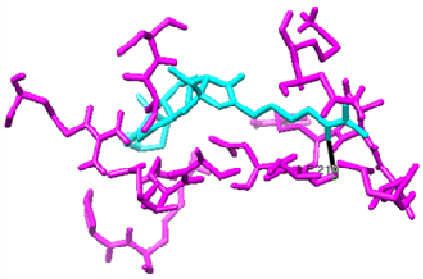


Figure 9 d: Compound 16101925 and its interacting with tubulin residues

Figure 8
Best four compounds and their interacting with tubulin residues

It has been documented that the interaction of tubulin inhibitor around this region is an important contributor for tubulin polymerization inhibition. For example, Kim et.al., [11] using docking model, identified hydrogen bond interaction between one inhibitor and Thr 179 in the backbone of a-tubulin and Ala 250 in the main chain of b-tubulin and interactions with Val 181, Lys 352 side chain and Asn 258 side chain in b-tubulin for another inhibitor. From a study involving mutations, residues Lys-19, Val-23, Asp-26, His-227, and Phe-270 have been identified as important for inhibiting tubulin polymerization, especially on the taxol binding domain using structure PDB 1JFF [13]. Through a study involving colchicines binding site, three hydrogen bond acceptors, namely, with Valb181, Cysb241 and Alab250, Aspb251, and Leub252 were observed while a hydrogen bond donor, involving Thrb179 has also been identified [14].

In our present study, we have used the structures related to colchicines binding domain. The hits identified, 4014843 showed an interaction with Glu 181 and Asp 203 while these interactions are absent with other three ligands identified through docking which have comparable dock score. This could presumably be due to the presence of an extra alkyl group at the dihydrofuran bridge in the other three molecules compared to the first one 4014843. These interactions are essentially similar to those observed for colchicines and podophyllotoxin interaction. In yet another study employing the same structure as the one used in the present study, namely, Hypo1, comparison of docking position of several compounds in the colchicine-binding site of tubulin H-bond between Thr179, Asn101 and the inhibitor with distances are 2.89 and 3.05A°, respectively, have been reported [15]. Thus the new hits

identified through the present study are occupying the colchicine binding domain and owing to the structural difference of these compounds compared to other known inhibitors of tubulin polymerization, they could offer a new series of potential tubulin inhibitors.

CONCLUSION

The β-tubulin structure was identified using homology modeling and the structure was validated and the properties of many molecules that act as tubulin inhibitors were studied. These molecules were used to generate pharmacophore model and the best feature that has best R^2 value have been identified. The best model was searched against the zinc database and nearly 900 compounds were filtered out which has best fit. Using these compounds, glide docking were done and based on many parameters like many parameters like binding energy, glide score and distance of hydrogen bond interactions were considered and best 20 compounds were filtered out. Out of these 20 compounds, top 4 compounds were rendered with the tubulin and shown. These compounds having higher G score and the feature (AAAH) can be used for further studies and also new compounds can be identified by using this feature as reference.

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