DESIGN OF PUTATIVE LIGANDS AGAINST CANCER TAKING VINBLASTINE AS REFERENCE LIGAND AND TUBULIN AS TARGET PROTEIN

BY

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IN
BIOINFORMATICS

DEPARTMENT OF
BIOIFORMATICS & BIOTECHNOLOGY
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TECHNOLOGY-WAKNAGHAT
MAY-2008

CERTIFICATE

This is to certify that the work entitled, "Design of Putative Ligands against cancer taking Vinblastine as reference ligand and Tubulin as target protein" submitted by "Ashutosh Kumar (041549) and Abhishek Dixit (041556)" in fulfillment of the requirements for the award of degree of Bachelor of Technology in ---7th & 8th semester-------- of Jaypee University of Information Technology has been carried out under my supervision. This work has not been submitted partially or wholly to any other University or Institute for the award of this or any other degree or diploma.

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ACKNOWLEDGEMENT

Ashutosh Kumar (041549)
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LIST OF ABBREVIATIONS

VBL –Vinblastine

VCR –Vincristine

VDS – Vindesine

VLRB-Vinorelbine

COL-Colchicine

TXL-Taxol

ABSTRACT

Protein tubulin plays a very pivotal role in cell division, by virtue of this very property it has been targeted by various drugs designed to cure cancer, lymphoma. Many of the existing antineoplastic drug categories comprises mainly of vinca alkaloids, taxanes and colchicines. All these drugs basically inhibit microtubule assembly to curb the unregulated cell division, leading to cancer.

In this project with the help of comparative analysis and molecular modeling ,our aim is to develop such a ligand molecule which shows high affinity for the protein tubulin and has minimal side effects. Using comparative analyisis as our first step in this project we have come to know that out of the three existing drug categories, the vinca alkaloids ,taxanes and colchicines, vinca alkaloids show much efficient binding to tubulin and also have less number of side effects. The most prominent of vinca alkaloid available today in clinical trials are VBL,VCR,VLRB.Comparitive analysis among the three vinca drugs VBL,VCR,VLRB ,projected VBL as the best ligand,this is attributed to its high binding affinity with the protein tubulin.We have taken VBL as our reference ligand for the synthesis of putative ligand molecules. Owing to the ubiquitous nature of protein tubulin it becomes quite difficult to control side effects arising by the ligand-tubulin interaction, thus we are aiming to come up with such a ligand molecule which shows least number of side effects as compared to the already exisiting drugs. It will be ensured that the ligands do not show any Central Nervous System Activity ,don't contain any toxic moieties and are the unpatent ones.

It has been found that calcium can also be used as an antineoplastic agent.

METHODOLOGY

Comparative analysis with reference to interaction with tubulin among the exisiting drug categories, the vinca alkaloids ,taxanes and colchicines, showed vinca as the best drug category. Comparative analysis among different vinca alkaloid drugs projected VBL as the best drug; consequently it became the reference ligand in the ligand designing process. Results of the comparative analysis are summarized in Table -I

Table - I

Characteristics	VBL	VCR	VLRB	VDS
Disease	Leukaemia,Lymphoma,Breast & Lung Cancer	Leukaemia,Lymphoma,Breast & Lung Cancer	Breast & Lung Cancer	Leukaemia,Lymphoma,Melanoma Breast & Lung Cancer
Efficacy	GTP (25c) G☐ - 14.6 GDP(25c) G☐ - 15.1	GTP (25c) G☐ - 14.1 GDP(25c) G☐ - 14.7	GTP (25c) G☐ - 14.1 GDP(25c) G☐ - 14.7	------------------
Side effects	Abdominal cramps and constipation, Numbness and Tingling in hands or feet	Lowered resistance to infection,Bleeding,Anaemia,Nausea	Lowered resistance to infection,Bleeding,Anaemia,Nausea, Numbness	Lowered resistance to infection,Bleeding,Anaemia,Hair loss
Binding affinity	Highest overall affinity for tubulin	Lowest overall affinity	Lower than Vincristine	Lower than Vinorelbine
Remarks	Stated as best drug as due to high affinity and better efficacy.	--------	----------	------------

Literature studies and docking of protein tubulin with the ligand VBL has suggested that the binding site of protein tubulin lies on the junction of two heterodimer(Tubulin

comprises of alpha and beta monomers, these monomers join together to form a tubulin heterodimer)

Localization of VBL binding site on tubulin has yielded a chain of residues from 177-215 in beta monomer to which VBL binds in part.

VBL binding site sequences from *Homo sapiens, Rattus norvegicus* and *Sus scrofa* were taken and their multiple sequence alignment was done to see if some conservative nature can be associated with the VBL,COLand TXL binding site or not.
The results obtained are shown in the Table- II below.

Table -II

CONSENSOS SEQ COMING FOR VINCA (176 TO 215)AFTER MSA	SEQ COMING FOR VINCA(REF- DONNER Laboratory BY Kenneth H. Downing)
VSDTVVEPYNATLSVHQLVENTDETY CIDNEALYDICSRTL	VSDTVVEPYNATLSVHQLVENTDETYCIDNEALYD ICFRTL
CONSENSOS SEQ COMING FOR TAXOL (219 TO 233)AFTER MSA	SEQ COMING FORTAXOL(REF-journal "JBC" by SRINIVASA RAO & DONNER Laboratory BY Kenneth H. Downing)
TPTYGDLNHLVSATM	TPTYGDLNHLVSATM
CONSENSOS SEQ COMING FOR COLCHICINE (216 TO 243)AFTER MSA	SEQ COMING FOR COLCHICINE (REF- DONNER Laboratory BY Kenneth H. Downing)
KLPTPTYGDLNHLVSATVSGVTTCLRF P	KLTTPTYGDLNHLVSATMSGVTTCLRFP

Remarks on the MSA are given below,

Change in the sequence pattern is indicated by black color .

None of the sequence of amino acid is undefined after doing MSA .

MSA result showed that there is 95 to 99 percent homology in VBL binding site in beta tubulin

Literature study pertaining to VBL crystal structure suggested that COOCH3 group on the C18' position is vital for antitumour activity. The above fact was taken into the consideration when ligand designing was performed.
Software LigBuilderv1.2 was used for the ligand synthesis.
LigBuilderv1.2 utilized "grow" method to develop new ligands.
Prerequisites for LigBuilderv1.2
Receptor file – 1TUB.pdb (Protein Data Bank)
Ligand file – vbl.mol2(Extracted from 1z2b.pdb-Protein Data Bank)
Seed file – seed.mol2

Methyl ethanoate structure was taken as the seed structure, as this ensures the presence of COOCH3 moiety in new ligands, responsible for antitumour action. The 3d coordinates of Methyl ethanoate (seed.mol2) were correspondingly changed so that it can be accommodated into the binding pocket of protein tubulin, the seed molecule was allowed to grow and 100 new ligands were synthesized.
As out of the 100 new ligands some might be showing Central Nervous System(CNS) activity thus to screen these ligands the incorporation of " Lipinski rule of 2" was done. Utilization of the "Lipinski rule of 2" yielded 53 ligands free from any neurological side effects. A further screening on the basis of ligand's current patent status was done using online patent databases like USPTO, Australian patents etc, this yielded 32 non patent ligands .At this stage we would like to tell that the antitumour moiety CH3COO wasn't found in any of the these 32 ligands. A probable explanation for this might be:
1) those ligands which contain the seed moiety might have been left out in the two rounds of screening; and,
2) the Ligbuilder v1.2 might have modified the seed moiety to yield the best fit. If the second explanation were to be true; then in this regard, we should also like to add that the basis for CH3COO moiety being identified to confer anticancer properties to vinblastine is based on an earlier publication where the chemical reactions formed the basis of moiety's identification. Nonetheless, upon visualizing the 1z2b.pdb (vinblastine-tubulin complex structure) one would find that, the CH3COO moiety is not in contact to any atom on Tubulin. However, the CH3COO moiety may, in part, be essential to retain the structural integrity of vinblastine, thereby indirectly contributing to its anticancer properties.

These 32 Ligands generated by Ligbuilder were then taken for Docking with tubulin in Schrödinger Maestro 8.0The module used for docking is Glide (Grid-based Ligand Docking with Energetics). Initially the 32 selected ligands were converted to mae format (Maestro, Schrödinger, Inc.).Tubulin protein (PDB ID -1z2b, only B&C chain) taken from the Protein Data Bank was used as the target for docking studies.

Protein preparation wizard module by applying an OPLS-AA force field was used to identify any errors in the target protein i.e. tubulin. This refinement procedure is recommended by Schrödinger because Glide uses the full OPLS-AA force field at an

intermediate docking stage and is claimed to be more sensitive to geometrical details than other docking tools. An atom was found to be defragmented at position 3532(N), 5331 (Cg) which was rectified using Build panel that place bond at that position. Energy minimization of all 32 Ligands was done initially and optimized by means of the MMFF94 force field using a default setting .

Ligprep module of Maestro 8.0 was run by taking the constraints like – retain original conformation, produce stereoisomer, no Ionization, no Tautomers. It generated about 114 conformers overall for all the 32 ligands.

After ensuring that the protein and ligands were in the correct form for docking, the receptor-grid files were generated using a grid-receptor generation program. A Grid was generated by selecting Receptor Grid generation module by taking the active site residue number 177 to 215 of the target protein.The Grid box thus formed was further increased in dimension from its default dimension of 4 Å to about 48 Å along all corners in order to have better binding. Grid was generated at the centroid of the active site consisting of residues Pro-175(B), Val-177(B), Phe-214(B), Thr-220(B),Tyr-224(B), Asp-179(B), Val-353(C), Phe-351(C), Ile-355(C) and Asn-329(C) (from PDBSum-Ligplot) and the size of ligands to be docked was selected from the workspace.

Docking was then performed by selecting the Glide module and docking performed was Flexible docking.

Flexible docking is done because it automatically generates conformations for each input ligand.

Subsequently Docking was done through Glide SP (standard precision) and Glide XP (extra precision) module. Glide calculations were performed with Impact version v18007 (Schrödinger, Inc.) Finally LSBD module was run that yielded Lipinski rule of 5 score and other parameters.

The final energy evaluation is done with Glide Score and a single best pose is generated as the output for a particular ligand. In addition to the ligand docking a docking step called "control" was also allowed to be run in Schrodinger Maestro 8.0 The "control" step was all about the vinblastine –tubulin docking .The essentials of "control" are given in subsequent section.

CONTROL

The coordinates of vinblastine were obtained from the Protein data bank (PDB ID :1z2b) and converted to mae format (Maestro, Schrödinger, Inc.).

Similar steps were followed for Vinblastine, energy minimization step was run and in Ligprep module by selecting the constraints like retain original conformation, produce stereoisomer, no Ionization & no Tautomers. Atmost 32 conformers were allowed to generate and generated conformers were docked with the grid file of target protein in Glide and Docking was achieved.

The docking results as obtained are presented as Table III and Table IV in the Results section.

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RESULTS

Table –III

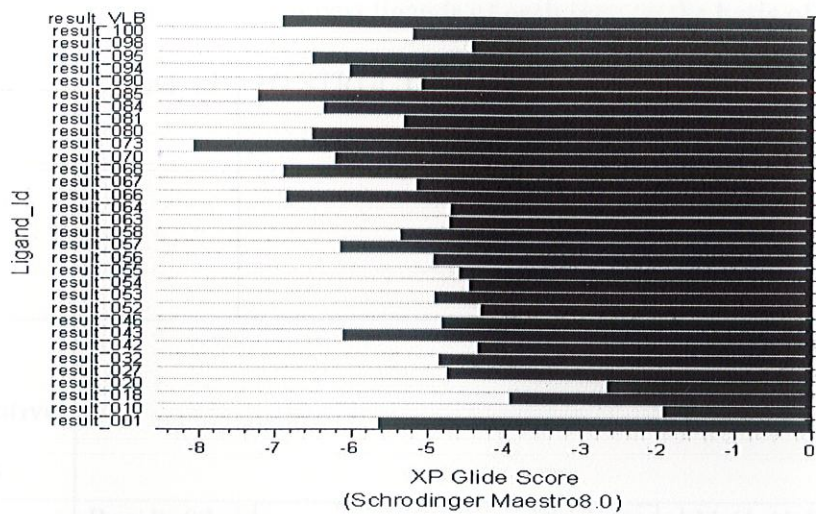| Ligand type	Ligand IUPAC	RANK*	XP Glide Score	XP Glide energy (Kcal/mol)
I. UREA DERIVATIVES				
1. result_073 (4)	N-(4-{1-[2-hydroxy-4-(hydroxymethyl)-1H-indol-7-yl]vinyl}-3-{(2Z)-3-[(1S,2S)-2-m ethylcyclohex-3-en-1-yl]-5-oxo-2-vinylhept-2-en-1-yl}phenyl)urea	1	-8.07	-63.65
2. result_085 (4)	N-{4-(1-{2-[(S)-(formylamino)(1H-pyrrol-2-yl)methyl]-1H-indol-7-yl}vinyl)-3-hydr oxy-5-[(2E,4R)-4-propionyl-2-vinylhepta-2,6-dien-1-yl]phenyl}urea	2	-7.22	-70.05
3. result_068 (2)	N-(4-{1-[5-(2-oxoethyl)-1H-pyrrol-3-yl]vinyl}-3-{(2E,4S)-5-oxo-2-[(1Z)-1-propylp ent-1-en-1-yl]-4-vinylhept-2-en-1-yl}phenyl)urea	3	-6.89	-53.36
4. result_066 (2)	N-[3-{(2E,3Z)-2-[(2R)-2-ethyl-3-oxopentylidene]hepta-3,6-dien-1-yl}-5-hydroxy-4-(1-{5-[(1R)-1-methylbut-3-en-1-yl]-1H-pyrrol-3-yl}vinyl)phenyl]urea	4	-6.86	-59.28
5. result_080 (2)	N-(4-[1-(4-acetyl-1H-indol-7-yl)vinyl]-3-{(2Z)-3-[(1R)-cyclohex-3-en-1-yl]-5-oxo-2-vinylhept-2-en-1-yl}phenyl)urea	5	-6.52	-59.67
6. result_095 (4)	N-(4-[1-(4-amino-1H-indol-2-yl)vinyl]-3-{(2E)-3-methylene-2-[(2S,3R)-3-methyl-2-propionylcyclohexylidene]hexyl}phenyl)urea	6	-6.51	-61.81
7. result_084 (4)	N-{3-{(2Z)-3-[(1R)-cyclohex-3-en-1-yl]-5-oxo-2-vinylhept-2-en-1-yl}-4-[(4R)-10-(hydroxymethyl)-4-methyl-4,5-dihydroazepino[3,2,1-hi]indol-7-yl]phenyl}urea	7	-6.36	-47.60
8. result_070 (2)	N-{3-{(2E,4S)-4-ethyl-2-[(1Z)-1-ethylpent-1-en-1-yl]-5-oxohept-2-en-1-yl}-4-[1-(5-ethyl-1H-pyrrol-3-yl)vinyl]-5-methoxyphenyl}urea	8	-6.21	-53.31

9. result_057 (8)	N-(3-{(2E,4R)-4-ethyl-5-oxo-2-[(1Z)-prop-1-en-1-yl]hept-2-en-1-yl}-4-{1-[(7R,8R)-7-formyl-8-methyl-5,6,7,8-tetrahydroindolizin-2-yl]vinyl}phenyl)urea	9	-6.14	-56.60
10. result_043 (4)	N-{3-{(2E,3Z)-2-[(2R)-2-(formylamino)-3-oxopentylidene]octa-3,7-dien-1-yl}-4-[(2S,4E)-2-formyl-1-methyleneoct-4-en-1-yl]phenyl}urea	10	-6.11	-62.19
11. result_094 (2)	N-{3-[(2E,4S)-3-ethyl-4-hydroxy-2-(1-methylenebutyl)-5-oxohept-2-en-1-yl]-4-[1-(6-isopropyl-1H-indol-2-yl)vinyl]phenyl}urea	11	-6.03	-57.57
12. result_001 (2)	N-({7-[(3E,5E)-3-ethyl-1-methylene-4-(2-oxobutyl)octa-3,5-dien-1-yl]-3-formyl-4-[(1S)-1-formylbutyl]-6-methyl-1H-indol-2-yl}methyl)urea	12	-5.64	-54.16
13.result_058 (2)	N-{3-{(2E,4S)-2-[(1Z)-1-ethylpent-1-en-1-yl]-5-oxo-4-vinylhept-2-en-1-yl}-4-[1-(5-ethyl-1H-pyrrol-3-yl)vinyl]-5-hydroxyphenyl}urea	13	-5.37	-54.02
14 . result_100 (16)	Ionic form (IUPAC Name Not available)	15	-5.20	-58.54
15. result_067 (2)	N-(4-[1-(5-ethyl-1H-pyrrol-3-yl)vinyl]-3-hydroxy-5-{(2E,4R)-4-isopropyl-5-oxo-2-[(1Z)-1-vinylpent-1-en-1-yl]hept-2-en-1-yl}phenyl)urea	16	-5.16	-55.34
16. result_090 (2)	N-{4-[1-(4-acetyl-1H-indol-7-yl)vinyl]-3-[(2E,4R)-5-oxo-2,4-divinylhept-2-en-1-yl]phenyl}urea	17	-5.10	-58.23
17. result_056 (4)	N-[3-{(2E,3Z)-3-ethyl-2-[(2R)-2-methyl-3-oxopentylidene]oct-3-en-1-yl}-4-(1-{5-[(1R)-1-methyl-3-oxopropyl]-1H-pyrrol-3-yl}vinyl)phenyl]urea	18	-4.93	-52.66
18. result_053 (4)	N-{3-{(2E,3Z)-2-[(2R)-2-(aminomethyl)-3-oxopentylidene]octa-3,7-dien-1-yl}-4-[(2R,4E)-2-formyl-1-methylenehex-4-en-1-yl]phenyl}urea	19	-4.91	-49.47
19. result_032 (8)	N-((3aS,9bS)-6-{(2E,4S)-2-[(1Z)-1-ethylprop-1-en-1-yl]-4-propionylhepta-2,6-dien-1-yl}-5-methylene-3a,4,5,9b-tetrahydro-1H-benzo[g]indol-8-yl)urea	20	-4.87	-56.14
20. result_046 (4)	N-{3-{(2Z,3E)-2-[(2S)-2-ethyl-3-oxopentylidene]-3-formylocta-3,7-dien-1-yl}-4-[(2R,4E)-2-formyl-1-methylenehept-4-en-1-yl]phenyl}urea	21	-4.80	-51.79

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21. result_027 (4)	N-{3-{(2E,3Z)-2-[(2R)-2-ethyl-3-oxopentylidene]octa-3,7-dien-1-yl}-4-[(2R)-2-formyl-1-methylenepent-4-en-1-yl]phenyl}urea	22	-4.76	-56.39
22. result_063 (2)	N-(3-{(2E,4R)-4-ethyl-5-oxo-2-[(1Z)-1-propylpent-1-en-1-yl]hept-2-en-1-yl}-4-{1-[5-(2-oxoethyl)-1H-pyrrol-3-yl]vinyl}phenyl)urea	23	-4.74	-59.72
23. result_064 (2)	N-(3-{(2E,4R)-4-ethyl-2-[(1Z)-1-ethylpent-1-en-1-yl]-5-oxohept-2-en-1-yl}-4-{1-[5-ethyl-1-(2-oxopropyl)-1H-pyrrol-3-yl]vinyl}-5-methoxyphenyl)urea	24	-4.70	-56.15
24. result_055 (2)	N-{3-{(2E,3Z)-2-[(2R)-2-ethyl-3-oxopentylidene]-3-[(1Z)-prop-1-en-1-yl]hepta-3,6-dien-1-yl}-4-[1-(5-ethyl-1H-pyrrol-3-yl)vinyl]-5-hydroxyphenyl}urea	25	-4.59	-55.63
25. result_054 (2)	N-{3-{(2E,3Z)-3-ethyl-2-[(2R)-3-oxo-2-vinylpentylidene]hepta-3,6-dien-1-yl}-4-[1-(5-ethyl-1H-pyrrol-3-yl)vinyl]-5-hydroxyphenyl}urea	26	-4.46	-53.90
26. result_052 (2)	N-(4-(1-methylene-3-oxopropyl)-3-{(2E,3Z)-2-[(2S)-3-oxo-2-vinylpentylidene]-3-propylocta-3,7-dien-1-yl}phenyl)urea	29	-4.33	-54.83
27. result_018 (4)	N-(4-[(2R,4E)-2-formyl-1-methylenehept-4-en-1-yl]-3-{(2E,3Z)-2-[(2S)-2-formyl-3-oxopentylidene]octa-3,7-dien-1-yl}phenyl)urea	30	-3.93	-53.87
28. result_020 (2)	N-{3-{(2E,3Z)-2-[(2R)-2-(aminomethyl)-3-oxopentylidene]-3-ethylocta-3,7-dien-1-yl}-4-[(4E)-1-methylenehex-4-en-1-yl]phenyl}urea	31	-2.66	-59.72
II OTHER DERIVATIVES				
29. result_081 (4)	(2R)-2-{4-[1-(4-[(aminocarbonyl)amino]-2-{(2E,4S)-4-methyl-5-oxo-2-[(1Z)-prop-1-en-1-yl]hept-2-en-1-yl}phenyl)vinyl]phenyl}-2-cyclohex-1-en-1-ylacetamide	14	-5.31	-56.58
30. result_098 (2)	5-[(aminocarbonyl)amino]-2-(2-cyclopentyl-1-methyleneprop-2-en-1-yl)-3-{(2E,3Z)-2-[(2S)-3-oxo-2-vinylpentylidene]hepta-3,6-dien-1-yl}phenyl formate	27	-4.44	-55.62

31. result_042 (2)	3-{2-{(2E,3Z)-3-allyl-2-[(2R)-2-ethyl-3-oxopentylidene]octa-3,7-dien-1-yl}-4-[(aminocarbonyl)amino]phenyl}but-3-enoic acid	28	-4.34	-55.52
32. result_010 (1)	N-{[7-[(3E,5E)-3-butyl-1-methylene-4-(2-oxobutyl)octa-3,5-dien-1-yl]-2-(hydroxymethyl)-6-vinyl-1H-indol-4-yl]carbonyl}-beta-alanine	32	-1.93	-59.61
III VINBLASTINE (Best conformer)				
result_VLB (32)	(2alpha,2'beta,3alpha,5beta,19beta)-vincaleukoblastine (as given in PDB) (2b,3b,4b,5a,12b,13b,15b,16a,18a,19a)-15-{(5R,7R,9S,9aS,10aR,14aR,14bS)-5-ethyl-5-hydroxy-9-[(R)-hydroxy(methoxy)methyl]hexadecahydro-2H-3,7-methanoazacyclounde cino[5,4-b]indol-9-yl}-4-[(1R)-1-hydroxyethoxy]-3-[(R)-hydroxy(methoxy)methyl]-1 6-methoxy-1-methyl-13,14,15,16,17,18-hexahydroaspidospermidin-3-ol		-6.91	-55.28

*   Ranking by authors on the basis of XP Glide score

( )   In the parenthesis ( ) are the numbers of stereoisomers generated by the Liqprep module of Schrodinger keeping the original conformation retained
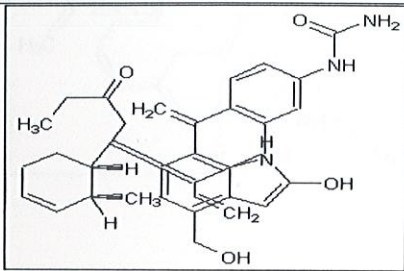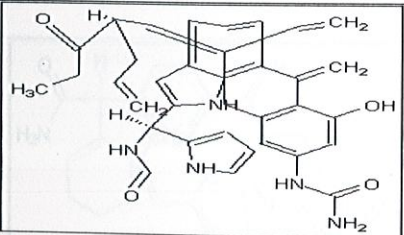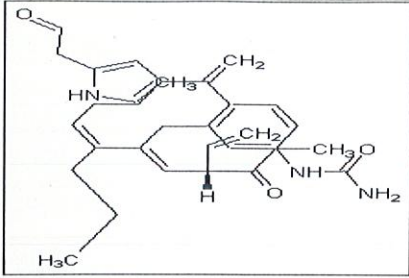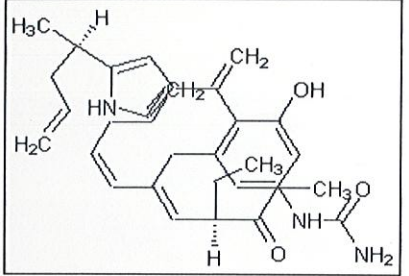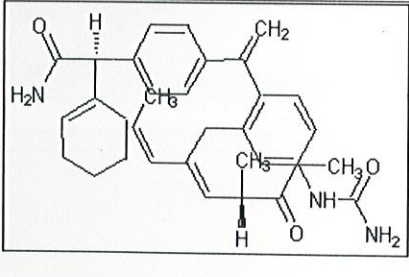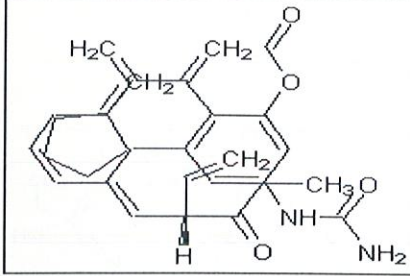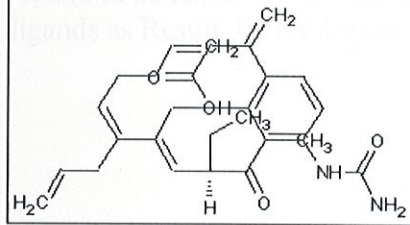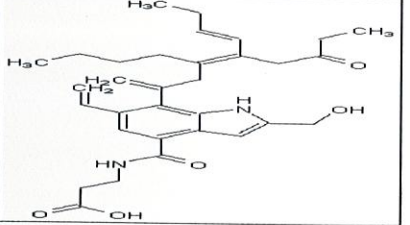
11

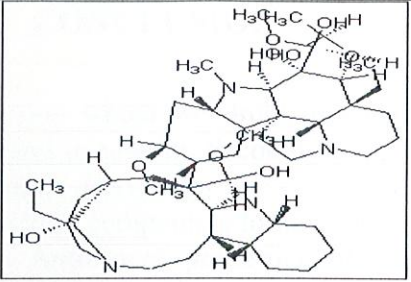Bar diagram showing the variation of XPGlide score in the generated Ligands

Table –IV

Table showing 4 best ligands of each type on the basis of GlideXP score.

Ligand type	Ligand_Id *	2D STRUCTURE	IUPAC #	XP Glide score	XP Glide Energy (kcal/mol)
I Urea derivatives (102)$					
1. #	Result_073 (4)		N-(4-{1-[2-hydroxy-4-(hydroxymethyl)-1H-indol-7-yl]vinyl}-3-{(2Z)-3-[(1S,2S)-2-methylcyclohex-3-en-1-yl]-5-oxo-2-vinylhept-2-en-1-yl}phenyl)urea	-8.07	-63.65
2 #	Result_085 (4)		N-{4-(1-{2-[(S)-(formylamino)(1H-pyrrol-2-yl)methyl]-1H-indol-7-yl}vinyl)-3-hydroxy-5-[(2E,4R)-4-propionyl-2-vinylhepta-2,6-dien-1-yl]phenyl}urea	-7.22	-70.05

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3.	Result_06 8 (2)		N-(4-{1-[5-(2-oxoethyl)-1H-pyrrol-3-yl]vinyl}-3-{(2E,4S)-5-oxo-2-[(1Z)-1-propylp ent-1-en-1-yl]-4-vinylhept-2-en-1-yl}phenyl)ure a	-6.89	-53.36
4.	Result_06 6 (2)		*N*-[3-{(2E,3Z)-2-[(2R)-2-ethyl-3-oxopentylide ne]hepta-3,6-dien-1-yl}-5-hydroxy-4-(1-{5-[(1R)-1-methylbut-3-en-1-yl]-1H-pyrrol-3-yl}vinyl)phen yl]urea	-6.86	-59.27
II Other Derivativ es (9)					
1.	Result_08 1 (4)		(2R)-2-{4-[1-(4-[(aminocarbo nyl)amino]-2-{(2E,4S)-4-methyl-5-oxo-2-[(1Z)-prop-1-en-1-yl]hept-2-en-1-yl}phenyl)vin yl]phenyl}-2-cyclohex-1-enylacetamie	-5.31	-56.58

2.	Result_098 (2)		5-[(aminocarbonyl)amino]-2-(2-cyclopentyl-1-methylenepropp-2-en-1-yl)-3-{(2E,3Z)-2-[(2S)-3-oxo-2-vinylpentylidene]hepta-3,6-dien-1-yl}phenyl formate	-4.44	-55.61
3.	Result_042 (2)		3-{2-{(2E,3Z)-3-allyl-2-[(2R)-2-ethyl-3-oxopentylidene]octa-3,7-dien-1-yl}-4-[(aminocarbonyl)amino]phenyl}but-3-enoic acid	-4.34	-55.51
4.	Result_010 (1)		N-{[7-[(3E,5E)-3-butyl-1-methylene-4-(2-oxobutyl)octa-3,5-dien-1-yl]-2-(hydroxymethyl)-6-vinyl-1H-indol-4-yl]carbonyl}-beta-alanine	-1.93	-59.60

III Vinblastine (32)	Result_VLB (32)		(2alpha,2'beta,3alpha,5beta,19beta)-vincaleukoblastine	-6.90	-55.27

ABSORPTION, DISTRIBUTION, METABOLISM, ELIMINATION or TOXICITY (ADMET) for the top 4 ligands of t each types were checked using the online server ADMETox, this projected that Result_073 & Result_066 as non toxic other ligands including vinblastine were found to be toxic.

Thus, we project the best ligands as Result_073 & Result_066

CONCLUSION

The first notable conclusion which we drew was that the moiety CH3C00 was not essential in binding of ligand to tubulin. Secondly ,urea derivatives showed much better binding in comparison to other derivatives.

Urea is one of the first organic compounds to have been synthesized artificially and has multiple uses, including. Anticancer properties of urea derivatives have also been documented.Thus, taking into account our results ,the Best ligands [Result_073 & Result_066], it is possible that urea derivatives, inpart, although premature, may represent a better alternative to the existing vinca alkaloid class of drugs. Nevertheless, more amount of work would be required in the mentioned direction which is presently beyond the scope of this project.

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