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Virtual Screening of compounds from *Tabernaemontana divaricata* for potential anti-bacterial activity

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Abstract:
Virtual Screening and Molecular Docking analysis for *Tabernaemontana divaricata* derived 66 Law Molecular Weight Compounds (LMW) was conducted and to identified and predicted novel molecules as a inhibitor of *Streptococcus pneumonia.* The investigation has revealed several compounds with optimum binding towards Penicillin-binding proteins, Sialidases, Aspartate beta-semialdehide dehydrogenase cell membrane protein of *Streptococcus pneumonia.* Docking results were computed in term of binding energy, ligand efficiency and number of hydrogen bonding. Apparicine (-5.14), 5-Hydroxyvoaphylline (-4.78), Voacangine (-4.7), 19-Hydroxycoronaridine (-4.44) and Coronaridine (-4.72) are identified as most suitable to bind with N-acetylglucosamine-1-phosphate uridyltransferase receptor. Ervaticine (-6.33), Ibogamine (-6.15), Methylvoaphylline (-5.74) and Coronaridine hydroxyindolenine (-5.32) has showed novel binding against the penicillin-binding proteins. Ervaticine (-6.42), 5-oxo-11-hydroxy voaphylline (-6.18), Conolobine B (-6.02) has found optimum binding against the active site of NanB sialidase of *Streptococcus pneumonia*. The compounds 3S-Cyanocoronaridine (-6.71), 19-Epivoacristine (-5.48) and Ervaticine(-5.45) interacting with aspartate beta-semialdehide and found suitable with least docking score.

Key words: Virtual Screening, Docking, Hydrogen bonding, *Streptococcus pneumonia.*

Background:
Tabernaemontana divaricata is a glabrous, evergreen, dichotomously branched shrub, belonging to the family Apocynaceae. This plant is known as Crepe jasmine in India, Togor, Dudhphul in Bangladesh. *T. divaricata* is common garden plant and widely distributed in the northern part of Thailand and used as Thai folk medicine for treatment of inflammation, pneumonia and fever etc **[1].** The growing scientific evidence has establishing this plant for its medicinal importance and possibility of this plant as pharmaceutical purposes **[2].** During last few decades, investigation to characterized chemical constituents from the leaves, stems and roots of this plant was carried out across the world , and more than 100 Law Molecular Weight Compound has been reported till date **[3-6].** The beneficial properties of *T. divaricata* are antioxidant, anti-infection, anti-tumour action, anti-bacterial, analgesia and the enhancement of cholinergic activity in both peripheral and central nervous systems **[3].** In North-East India region, the leaves stem and root part of this plant is traditionally used for the treatment of Pneumonia related infection by Local healer. Therefore, there is great demand to study the molecular interaction of these compounds against bacterial protein for designing anti-bacterial lead compound **[7].** In this present investigation, we have studied 66 Low Molecular Weight (LMW) compound reported from *T. divaricata* in their structural level. We predicted few structural properties of these compounds necessary for a novel candidate drug and performed Molecular Docking analysis against few established drug target of *Streptococcus pneumonia. Streptococcus pneumonia is* a causative organism *of pneumoniae*, also called *pneumococcus*, can infect the upper respiratory tracts of adults and children and can spread to the blood, lungs, middle ear, or nervous

system **[8].** Presently antibiotic such as Amoxicillin, Cefazolin, Dicloxacillin, Levofloxacin, Ciprofloxacin etc are suggested for the treatment of Bacterial pneumonia, but due to adverse side effect and law efficacy , these drugs fails to inhibit bacterial pathogen especially *Streptococcus pneumonia* **[9-13].** Bacterial membrane protein plays an important role in growth, cell division and maintaining the cellular structure in bacteria. Therefore, inhibition of these proteins is important for controlling the pathogen.

Penicillin-binding proteins (PBPs) are a group of proteins that are characterized by their affinity for and binding of penicillin. They are a normal constituent of many bacteria as well as *S. pneumonia* **[14].** The enzyme has a penicillin-insensitive transglycosylase N-terminal domain (involved in formation of linear glycan strands) and a penicillin-sensitive transpeptidase C-terminal domain (involved in cross-linking of the peptide subunits) and the serine at the active site is conserved in all members of the PBP family **[15].** Another important receptor sialidases (or neuraminidases) are believed to be involved in removing sialic acid from host cell surface glycans, thereby promoting colonization of the upper respiratory tract. The biosynthesis of UDP-GlcNAc in bacteria is carried out by GlmU, an essential bifunctional uridyltransferase that catalyzes the CoA-dependent acetylation of GlcN-1-PO_4 to form GlcNAc-1-PO_4 and its subsequent condensation with UTP. GlmU is an essential enzyme in both Gram-positive and Gram-negative bacteria, and is viewed as an attractive target for the development of antimicrobial compounds peptidoglycan, lipopolysaccharide and techoic acid synthesis has been identified as an novel drug target. Plants are the major source of anti-bacterial agent without side effect. Therefore, herein an attempt was made to identify potential photochemical from this plant as a selective anti-bacterial agent.

Methodology:

Compound Library Creation and protein preparation

Literature study was conducted and a data set of 66 *Tabernaemontana divaricata* derived compounds was prepared **[13].** The name and compound ID of few top ranking compounds are presented at **Table 1 & 2 (see supplementary material).** ChemBio Office Ultra **[16]** and Marvin Sketch software was used to draw their structure. Open Bable software was used for file conversion purpose. Crystal structures of *Streptococcus pneumonia* membrane protein receptor namely Penicillin-binding proteins **[15],** NanB sialidase **[17]** and acetylglucosamine-1-phosphate uridyltransferase **[18]** and aspartate beta-semialdehide dehydrogenase **[19]** was retrieved from Protein Data Bank along with their co-crystallized ligand. The lists of receptor model with resolution are presented in the **Table 3 (see supplementary material).**

Physiochemical Property and Force field Calculation

Prediction of physiochemical property of retrieved compounds is performed by using Molesoft Browser and optimized their structure in ChemBio Office 3D tool using MM2 force field. Prediction of drug likeness properties of these optimized compounds were performed using Mol-Soft ICM Browser and ChemBioOffice. PASS (Prediction of Activity Spectra for Substance) software was used to predict the drug-likeness and toxicity properties of these ligands as shown in the **Table 4 (see supplementary material) [20].** The force field values of lignads are presented in the **Table 5 (see supplementary material).** Drug-likeness of all those compounds were also studied and given in the **Table 6 (see supplementary material).**

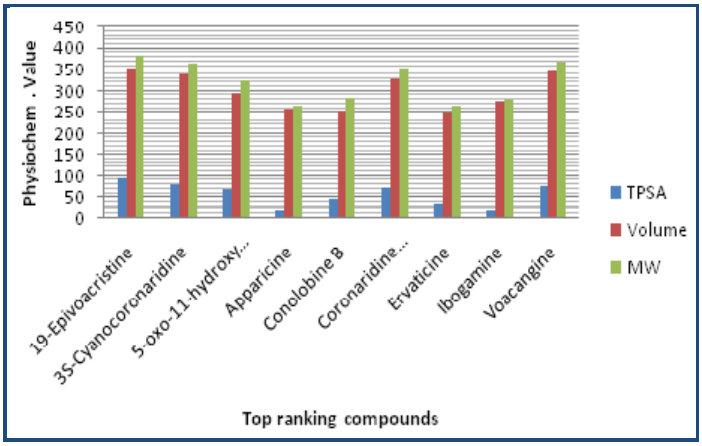

Figure 1: Ligands physiochemical properties in acceptable range.

Drug-likeness study of Ligand

The proposed ligands were predicted for the non violation of CMC like, Lead like. Identification and optimization of lead compounds as a chemical staring points are very important in combinatorial chemistry. MDDR like and Lipinski's rule of five necessary for a ideal drug compound. The drug-likeness values of these compounds are presented in the **Table 7 (see supplementary material).** The PreADMET server was employed to predict drug like rule for these entire compound **[21].**

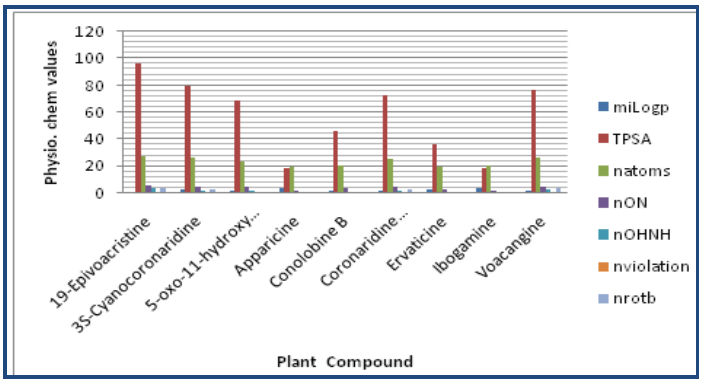

Figure 2: Physiochemical Properties predicted in accepted limit.

Molecular Docking Study

Molecular interactions study of the *Streptococcus pneumonia* membrane protein receptor models with these phytochemical was carried out using Autodock 4.0 tools. Energy grid was built within a cubic box of dimensions 60 × 60 × 60A grid points and 0.375 A° spacing using the Autogrid program. Docking was performed based on Lamarckian Genetic Algorithm. Grid points were generated around the catalytic pocket to cover the entire ligand binding site, such that the compound to be docked can move freely within it. Docking simulations were performed using Lamarckian Genetic Algorithm (LGA). The docking parameters set to perform each docking experiment were derived from 100 different runs that were set to terminate after a maximum of 2,500,000 energy evaluations, elitism of 1, mutation rate of 0.02, cross-over rate of 0.8, and local search rate

of 0.06. The population size was set to 150 **[22].** The receptor wise results of docking are presented in the **Table 7 (see supplementary material).**

Result & Discussion:

Tabernaemontana divaricata is a widely used medical plant used for the treatment of inflammation, pneumonia, fever etc. Anti-bacterial and anti-fungal properties of this plant have been reported and more than 100 compounds are characterized till date by many workers across the worldwide. The Virtual Screening and Molecular Docking is standard protocol to find out the molecular interaction of small compounds with the receptor models of pathogen. In this study, we employed the Virtual Screening of 66 compounds reported from *T. divaricata*. The physiochemical properties and drug-likeness prediction of these compounds has clearly reflecting the importance of these compounds as a drug candidate **(Table 4, Figure 1 & Figure 2).** Herein, we found 70% compounds following lipinki's rule of five and 50 compounds not violating other drug-like rules such as CMC, MDDR etc necessary for a novel lead compound. In this present work, the docking was performed against three membrane protein namely *Streptococcus pneumonia* Penicillin-binding proteins, sialidases, GlmU and aspartate beta-semialdehide dehydrogenase. These receptors are selected because they are present in most of the bacterial community and established targets of many existing anti-biotics. The Molecular Docking of these compounds with receptor model was conducted in autodock 4.0 tool using the parameter as described in the methodology part after calculating their forcefield **(Table 5).** Docking results are computed in term of binding energy, ligand efficiency and Number of hydrogen bonding. Apparicine (-5.14), 5-Hydroxyvoaphylline (-4.78), Voacangine (-4.7), 19-Hydroxycoronaridine (-4.44) and Coronaridine (-4.72) are identified as most suitable to bind with N-acetylglucosamine-1-phosphate uridyltransferase receptor. Ervaticine (-6.33),Ibogamine(-6.15),Methylvoaphylline(-5.74) and Coronaridine hydroxyindolenine (-5.32) has shown novel binding against the penicillin-binding proteins. Ervaticine(-6.42), 5-oxo-11-hydroxy voaphylline(-6.18), Conolobine B(-6.02) has found optimum binding against the active site of NanB sialidase from *Streptococcus pneumonia*. The compounds 3S-Cyanocoronaridine (-6.71), 19-Epivoacristine (-5.48) and Ervaticine(-5.45) interacting with aspartate beta-semialdehide. Interestingly few derivatives of Coronaridine has showed good binding against receptor models. This compound is already reported for strong antibacterial activity against *K. pneumonia*. However, there is no report of molecular interaction of these compounds with bacterial membrane protein targets. Therefore, the present study may be a useful starting point to design novel anti-bacterial compounds from these 66 Low Molecular Weight drug-like compounds derived from *Tabernaemontana divaricata*. In the study, it was also observed that the most of suitable compounds interacting with receptor models are characterized from leaves and study was significant in this aspect.

Conclusion:

Virtual Screening and Docking of 66 Law Molecular Weight compounds of *Tabernaemontana divaricata* has clearly reflecting their drug-likeness as promising inhibitors of bacterial cell membrane protein. Experiment study on compounds such as Voacangine, Ibogamine, Methylvoaphylline may be carried out to confirm the novelty of their bacterial inhibition. More importantly the few derivatives of Coronaridine with least binding energy (Kcal/mol) may be useful as lead molecule to design and development of future anti-biotic for the treatment of bacterial pneumonia and other bacterial infection by inhibiting their cell membrane proteins.

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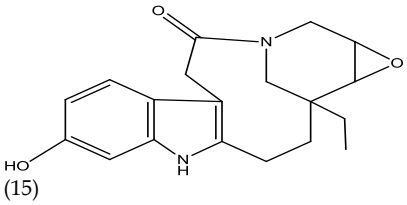
Supplementary material:

Table 1: Potential T.divaricata compounds.

Compound name	Plant part	Formula	IUPAC Name
5-oxo-11-hydroxy voaphylline	leaves	$C_{19}H_{22}N_2O_3$	13-ethyl-8-hydroxy-5,10,11,12,13,13a-hexahydro-1aH 3,13methanooxireno[2',3':9,10][1]azacycloundecino[5,4-b]indol-4(2H)-one
Apparicine	cell suspension culture	$C_{18}H_{20}N2$	(5R,E)-4-ethylidene-6-methylene-1,3,4,5,6,7-hexahydro-2,5-ethanoazocino[4,3-b]indole
Conolobine B	stems, barks	$C_{17}H_{18}N_2O_2$	(2S,2'R,3'S,5S)-3'-methyl-5,7-dihydro-1H-spiro[2,5-ethanoazocino[4,3-b]indole-4,2'-oxiran]-6(3H)-one
Ervaticine	leaves	$C_{21}H_{26}N_2O_3$	(E)-4-ethylidene-3,4,5,7-tetrahydro-2,5-ethanoazocino[4,3-b]indol-6(1H)-one
Ibogamine	root bark	$C_{19}H_{24}N_2$	(6R,6aS,7S,9R,11S)-7-ethyl-6,6a,7,8,9,10,12,13-octahydro-5H-6,9-methanopyrido[1',2':1,2]azepino[4,5-b]indole
Voacangin	leaves	$C_{22}H_{28}N_2O_3$	1-((6S,6aS,7S,9R,11S)-7-ethyl-2-(hydroxymethyl)-6,6a,7,8,9,10,12,13-octahydro-5H-6,9-methanopyrido[1',2':1,2]azepino[4,5-b]indol-6-yl)-2-hydroxyethanone

Table 2: Structures of *T.divaricata* compound



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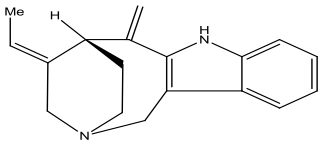

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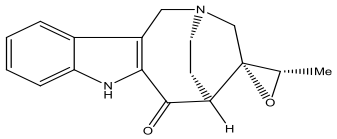

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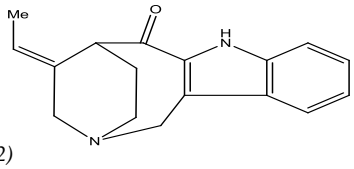

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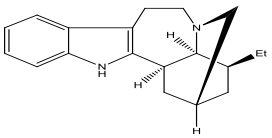

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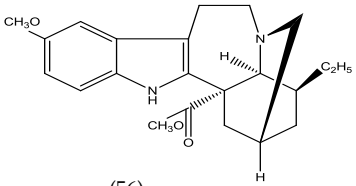

(56)

Table 3: The receptor model considered for docking study.

PDB ID	Primary Citation	Resolution (Å)	Co-crystallized ligand
1HM8	Crystal structure of Streptococcus pneumoniae N-acetylglucosamine-1-phosphate uridyltransferasebound to acetyl-coenzyme A reveals novel active site architecture.	2.50	Acetyl Coenzyme A
2ZC5	Crystal structures of biapenem and tebipenem complexed with penicillin-binding proteins 2X and 1Afrom Streptococcus pneumonia.	3.00	(4R,5S)-3-(6,7-dihydro-5H-pyrazolo[1,2-a][1,2,4]triazol-4-ium-6-ylsulfanyl)-5-[(1S,2R)-1-formyl-2-hydroxypropyl]-4-methyl-4,5-dihydro-1H-pyrrole-2-carboxylate
2VW1	Crystal structure of the NanB sialidase from Streptococcus pneumoniae.	2.39	2-Deoxy-2,3-Dehydro-N-Acetyl-Neuraminic Acid and Glycerol
3PYL	Crystal structure of aspartate beta-semialdehide dehydrogenase from Streptococcus pneumoniae with D-2,3-diaminopropionat	2.20	3-amino-D-alanine

Table 4: Result of physiochemical property calculation of *T. divaricata* compounds.

SN	Compound Name	miLogp	TPSA	natoms	MW	nON	nOHNH	nviolation	nrotb	Volume
6	19-Epivoacristine	1.012	96.784	28	384.476	6	4	0	4	354.304
1	3S-Cyanocoronaridine	2.618	80.12	27	363.45	5	2	0	3	338.326
2	5-oxo-11-hydroxy voaphylline	2.296	68.856	24	326.16	5	2	0	1	296.796
3	Apparicine	3.683	19.029	20	264.36	2	1	0	0	259.865
4	Conolobine B	2.284	46.628	21	282.34	4	1	0	0	255.175
5	Coronaridine hydroxyindolenine	1.795	73.129	26	354.44	5	2	0	3	329.404
6	Ervaticine	2.85	36.1	20	266.34	3	1	0	0	251.117
7	Ibogamine	4.238	19.029	21	280.41	2	1	0	1	277.962

Table 5: Result of optimization of T. divaricata compound

No	Compound name	Stretch	Bend	Stretch-Bend	Torsion	Non-1,4 VDW	1,4 VDW	Dipole /Dipole	Total Energy
3	Apparicine	2.800	56.605	0.546	-0.244	-0.195	21.349	0.176	81.037
4	Conolobine B	13.12	108.54	-0.25	10.112	-2.142	24.257	1.774	155.415
5	Coronaridine	2.551	19.873	0.469	7.922	-5.903	20.990	2.524	48.427
6	Ervaticine	2.871	54.941	0.753	1.090	0.572	21.013	2.666	83.908
7	Ibogamine	1.967	17.830	0.272	7.576	-4.783	19.644	0.596	43.104
8	Voacangine	2.684	20.46	0.477	7.450	-6.519	21.731	2.781	49.074

Table 6: Result of Druglikeness Prediction of T.divaricata compound

N	Compound Name	CMC like Rule	Lead like Rule	MDDR like Rule	Rule of 5 Violations	WDI like Rule
1	19-Epivoacristine	+	-(2)	-(1)	+	+
2	19-Hydroxycoronaridine	+	-(1)	-(1)	+	+
3	5-oxo-11-hydroxy voaphylline	+	+	-(1)	+	+
4	Apparicine	+	+	-(1)	+	+
5	Conolobine B	+	-(1)	-(1)	+	+
6	Coronaridine	+	+	-(1)	+	+
7	Coronaridine hydroxyindolenine	+	-(2)	-(1)	+	+
8	Ervaticine	+	+	-(1)	+	+
9	Ibogamine	+	+	-(1)	+	+
10	Voacangine	+	-(2)	-(1)	+	+

N.B: The number in the braces indicating numbers of rule violating and "+" sign indicate the non violation of drug like rules.

Table 7: Receptor wise Docking of the *T. divaricata* compound

SN	Compound-ID	Binding Energy (Kcal/mol)	Ligand Efficiency	No. of H Bond
1HM8 Protein				
8	5-oxo-11-hydroxy voaphylline	-3.7	-0.15	2
9	5-Oxocoronaridine	-2.7	-0.1	2
10	Apparicine	-5.14	-0.26	1
18	Voacangine	-4.7	-0.17	1
19	Voafinine	-4.15	-0.18	1
2ZC5 Protein				
5	5-oxo-11-hydroxy voaphylline	-4.32	-0.01	2
10	Conolobine B	-5.22	-0.25	1
13	Ervaticine	-6.35	-0.32	1
14	Heyneanine	-4.72	-0.18	2
15	Ibogamine	-6.15	-0.29	1
2VW1 Protein				
8	5-oxo-11-hydroxy voaphylline	-6.18	-0.26	2
13	Dregamine	-4.93	-0.19	1
14	Ervaticine	-6.42	-0.32	1
23	Voacangine	-5.22	-0.19	2
3PYL Protein				
8	5-oxo-11-hydroxy voaphylline	-6.18	-0.26	2
13	Dregamine	-4.93	-0.19	1
14	Ervaticine	-6.42	-0.32	1
23	Voacangine	-5.22	-0.19	2
3PYL Protein				
5	3S-Cyanocoronaridine	-6.71	-0.25	2
6	3S-Cyanoisovoacangine	-5.38	-0.19	1
7	5-oxo-11-hydroxy voaphylline	-5.19	-0.22	2
8	Conolobine A	-5.28	-0.25	1
9	Ervaticine	-5.45	-0.27	1
10	Ibogamine	-5.16	-0.25	1
14	Voacangine	-2.74	-0.1	2