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Molecular docking study for binding affinity of indole derivatives against solution structure of the antimicrobial peptide Btd-2[3,4]

Shivangi Sharma

Department of Applied Chemistry, Amity School of Applied Sciences, Amity University Madhya Pradesh, Gwalior, Madhya Pradesh. India

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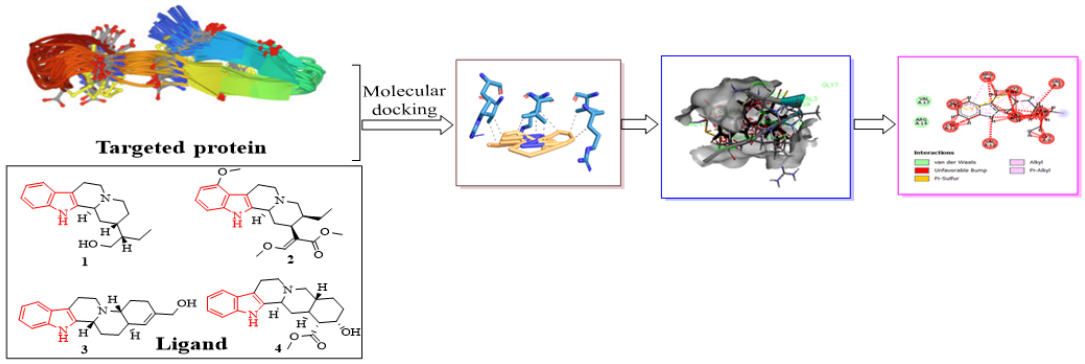
Article

ABSTRACT



Indole based drugs are major constituents in natural products, active pharmacophores, and have excellent biological activities. The molecular docking analysis of indoloquinolizidine derivatives and solution structure of the antimicrobial peptide Btd-2[3,4] (PDB ID: 2M2Y) have been revealed in this article. The study of in silico molecular docking analysis of such indoloquinolizidine derivatives helps to determine the residual interaction, binding affinity, and hydrogen bonding of several indoloquinolizidine-based derivatives against solution structure of the antimicrobial peptide Btd-2[3,4]. The current work demonstrated that indoloquinolizidine derivatives could be very effective antibacterial agents to produce potent antibiotic medicines.

Keywords: Docking, Interaction, Indole, Amino acid, Residues, Bioactivity, Antibacterial.

INTRODUCTION

Indoles are abundant in nature and many of them exhibit significant biological functions. Additionally, both natural and synthetic indoles have been used in the pharmaceuticals and agricultural chemicals. As a result, the synthesis and functionalization of indoles has been ongoing for more than 150 years. Since many natural compounds have indole fundamental ring that found to be a therapeutic drug, the indole core has been very active core in the field of pharmacy.[1] Indole derivatives have been shown to possess antiviral,[2,3] antifungal,[4-6] antibacterial,[7-9] anti-inflammatory,[10] analgesic,[11,12] chemotherapeutic,[13,14] anti-TB,[15-17] antimalarial,[18-20] and antioxidant properties.[21,22] Organic and Medicinal chemists faces a formidable challenge in the developing of potent and novel antibacterial drugs due to emergence of drug-resistant bacterial infections that cause high mortality rates.[23] In contrast to other medical specialties, the potential of indoloquinolizidine derivatives as antibacterial agents has not received as much attention. Based on the previous discoveries, unique bioactive hybrid compounds based on indoloquinolizidine derivatives having better antibacterial efficacy has been developed nowadays. For example- Dihydroantirhine **1**, Mitragynine **2**, Tangutorine **3** & Yohimbine **4** are shown in **figure 1**.[24]

The atom count of this antibacterial protein is **139**. The chains in this protein (Solution structure of the antimicrobial peptide Btd-2[3,4]) is **1** but the different model of deposited residue is **18**. And the total structural weight of protein is **2.09 kDa**.

In this article, we have reported the binding affinity and the several interactions of indoloquinolizidine derivatives[25] (1-4) against the solution structure of the microbial peptide Btd-2[3,4] (**PDB ID: 2M2Y**). This is an antibacterial based protein. The binding energy of compound **1-4** is **-5.1** to **-6.1 kcal/mol**. This interaction shows that compound 3 shows highest binding affinity (**-6.1 Kcal/mol**) as compared to other derivatives of indoloquinolizidine. We used a variety of software programmes for this docking study, including Auto Dock vina 4,[26a] discovery studio,[26b] and protein-ligand interaction profiler. The study and analysis of docking position, docking size, binding affinity, energy range, and exhaustiveness are made easier with the aid of

*Corresponding Author: Shivangi Sharma, AMITY University, Gwalior, India.
Email: shivangiksharma1997@gmail.com

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these software programmes. The ligands (indoloquinolizidine derivatives) are attached to a number of amino acids, and its analogues exhibit a variety of interactions, some of which are as follows: ARG A:1, ARG A:10, ARG A:14, CYS A:2, CYS A:4, CYS A:9, CYS A:11, CYS A:13, CYS A:18, VAL A:3, VAL A:12, VAL A:17, and GLY A:7. The docking result is given in **Table 1**.

A small subset of the indole monoterpene alkaloids called Dihydroantirhine **1**[27] has some remarkably distinctive structural features. Vinyl (or ethyl) group in the antirhine[28] family is connected to the side chain which opposed to the meta carbon of the piperidine ring. Several synthetic chemists have paid close attention to the antirhine family's distinctive physical features. Traditionally, the antirhine family's natural product has been synthesized from a particular starting material that has the essential fragment and the desired stereochemistry at C-15 and C-20. Then the desired natural product is produced by adding tryptamine to the C and D rings afterward. Numerous total synthesis of antirhine[29] and 18,19-dihydroantirhine have been reported using different methods.[30]

Mitragynine **2** is the most abundant active alkaloid in the Southeast Asian plant Mitragyna speciosa, also known as kratom.[31] It is an indole-based alkaloid. In dried leaves, the total alkaloid concentration ranges from 0.5 to 1.5%.[32] Mitragynine is the most abundant component in Thai varieties, while 7-hydroxymitragynine is a minor constituent. Mitragynine is present in lower concentrations in Malaysian kratom varieties.[32,33] Mitragynine use as a recreational and medicinal drug has recently spread throughout Europe and the Americas.[34]

Tangutorine **3** alkaloids are isolated from Nitraria species (Nitraria schoberi[35] as well as Nitraria tangutorum,[36] respectively), which belong to the Nitrariaceae family, whereas yohimbine-type alkaloids are found in plants of the Loganiaceae, Rubiaceae, & Apocinaceae families. This proposal was based on biosynthetic considerations as well as a comparison of the physical and spectroscopic data reported for these alkaloids with tangutorine[37] and its O-acetyl and dihydro derivatives. Furthermore, the specific rotation for alkaloids has been reported to be zero, which could be attributed to similar biosynthetic pathways that do not involve the monoterpene secologanin.[38,39]

Yohimbine **4**, also known as quebrachine, is an indole alkaloid derived from the bark of the African tree Pausinystalia johimbe[40] and the unrelated South American tree Aspidosperma quebracho-blanco.[41] Yohimbine is a 2-adrenergic receptor antagonist that has been used in a number of studies. It is a veterinary medication used to treat sedation in dogs and deer. While yohimbine is an aphrodisiac in some mammals, it is not in humans. It has been used to treat erectile dysfunction, though its reported clinical benefits were modest, and it has been largely replaced by the PDE-5 inhibitor class of drugs. Substances claiming to be yohimbe tree extracts have been marketed as dietary supplements for a variety of purposes, but they contain varying amounts of yohimbine, if any at all, and no published scientific evidence supports their efficacy. Yohimbine is a veterinary drug used to reverse the effects of xylazine in dogs and deer.[42] It is used in research as a reagent. In the United States, it is occasionally prescribed for male erectile dysfunction.[43]

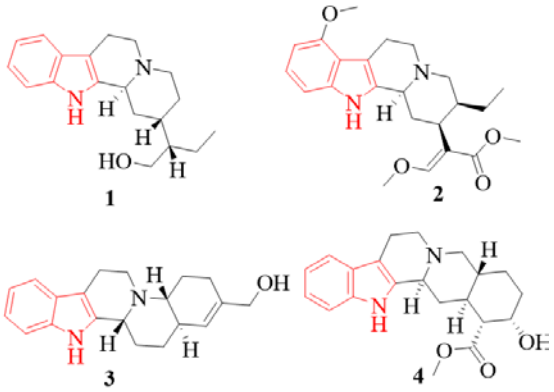


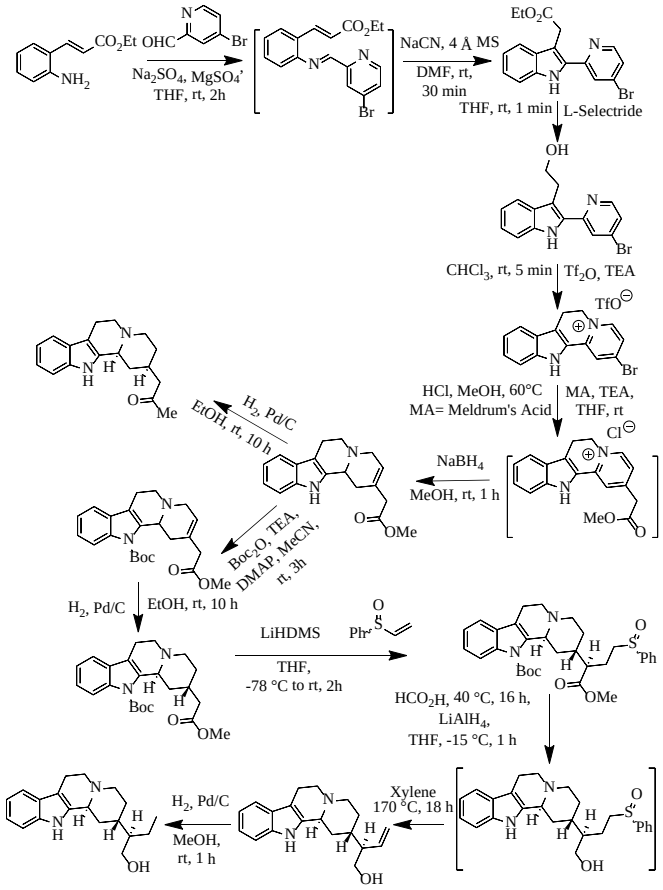
Figure 1. Structure of indoloquinolizidine derivatives.

MATERIALS & METHODS

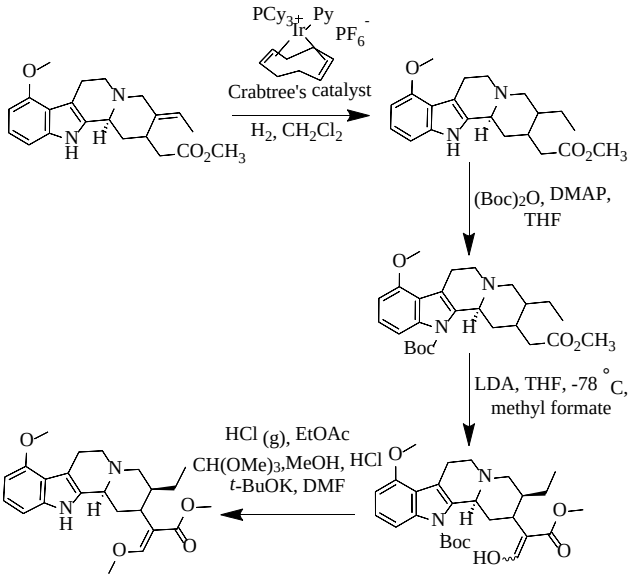
Dihydroantirhine - This study developed a general synthetic strategy for antirhine alkaloids. The imino-Stetter reaction of ethyl 2-aminocinnamate & 4-bromopyridine-2-carboxaldehyde catalyzed by the cyanide that produce the corresponding derivatives of indole-3-acetic acid. The formation of the following six-membered carbon ring, trans-selective installation of the two-carbon unit at C-15 allowed for quick access to the key intermediate. The total synthesis of 18,19-dihydroantirhine and its several epimers, all of which are known natural products in the antirhine family, was enabled by the stereoselective installation of substituents at C-20 (**Scheme 1**).[44]

Mitragynine - In this, authors describe the synthesis of Mitragynine. Initially, an indole synthesis was used to develop an efficient multigram scale synthetic route to the optically active 4-methoxytryptophan ethyl ester. A bromination of radical-mediated regioselective of indoline that served as a key step in obtaining the ethyl ester of 4-methoxytryptophan. 4-methoxytryptophan is an intermediate that also formed by the Larock heteroannulation of aryl iodide with the internal alkyne. The Boc used to protect aniline was critical to the successful completion of this hetero annulation. The Pictet-Spengler reaction was used to synthesize the α, β-unsaturated ester. This was followed by the cyclization mediated of $Ni(COD)_2$ that helps to establish the stereocenter at C-15. This chiral tetracyclic ester was used in the complete synthesis of the opioid agonistic indole alkaloid, mitragynine. (**Scheme 2**). [45]

Tangutorine - The cyclo-condensation reaction of (*S*)-tryptophanol with keto ester yielded tricyclic lactam. Starting with tricyclic lactam, the central C ring was successfully closed under classic *Bischler Napieralski* reaction conditions. Treatment of the hexacyclic derivative with $LiAlH_4$ without purification resulted in both the reductive opening of the oxazolidine ring to stereo selectively give the required *cis*-decahydroquinoline ring junction and the reduction of the ester function, yielding the pentacyclic diol derivative in 60% overall yield. A similar sequence from tricyclic lactam resulted in the indoloquinolizidine derivative, which resulted from an initial amido alkylation reaction on the indole ring.



Scheme 1 Synthesis of Dihydroantirhine.



Scheme 2 Synthesis of Mitragynine.

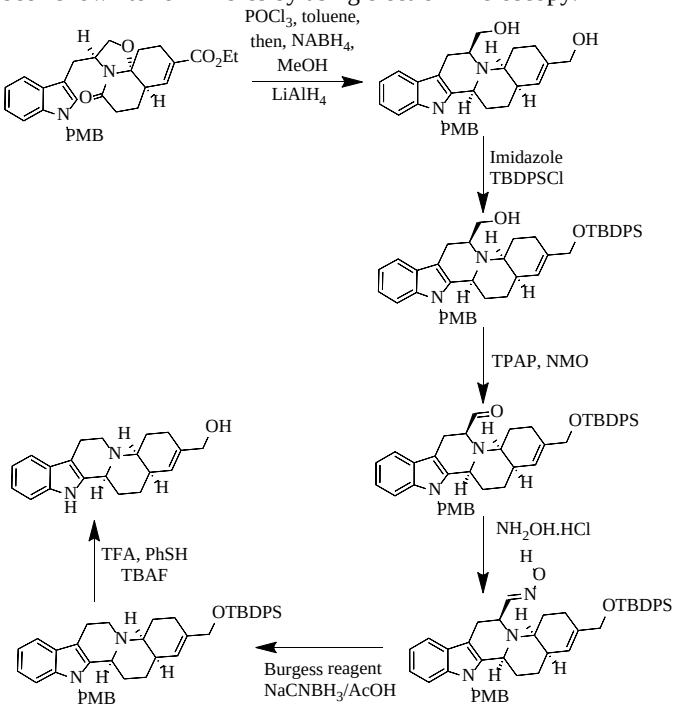
A similar sequence from tricyclic lactam resulted in the indoloquinolizidine derivative, which resulted from an initial amidoalkylation reaction on the indole ring. The removal of the hydroxymethyl substituent derived from tryptophanol required the selective protection of the allylic hydroxy group, but unfortunately, the insolubility of diol prevented its manipulation. As a result, the tricyclic lactam's indole nitrogen was protected as a *p*-methoxybenzyl derivative, and the resulting lactam was converted to the product in 68% overall yield using the above Bischler-Napieralski cyclization $LiAlH_4$ reduction sequence. Once the allylic hydroxyl group was selectively protected with the bulky *tert*-butyldiphenylsilyl group, the removal of the hydroxymethyl substituent of intermediate was performed in four steps: oxidation to aldehyde using tetrapropylammonium perruthenate in the presence of *N*-methylmorpholine *N*-oxide as the co-oxidant (TPAP/NMO), subsequent dehydration of the corresponding oxime with Burgess reagent, and reductive de-cyanation of the resulting α-amino nitrile. Finally, the target pentacyclic alcohol was obtained by deprotecting the indole nitrogen of the pentacycle with TFA in the presence of PhSH as a carbocation scavenger, followed by de-silylation of the alcohol function (**Scheme 3**).[46] **Yohimbine-** The total synthesis of (+)-yohimbine was accomplished in several steps. The absolute configuration was established using a highly enantioselective thiourea-catalyzed acyl-Pictet Spengler reaction, and the remaining stereocenters were set concurrently using a substrate-controlled intramolecular Diel's-Alder reaction (**Scheme 4**). [47]

DIFFERENT MODELS OF PROTEIN (SOLUTION STRUCTURE OF THE ANTIMICROBIAL PEPTIDE BTD-2[3,4])-

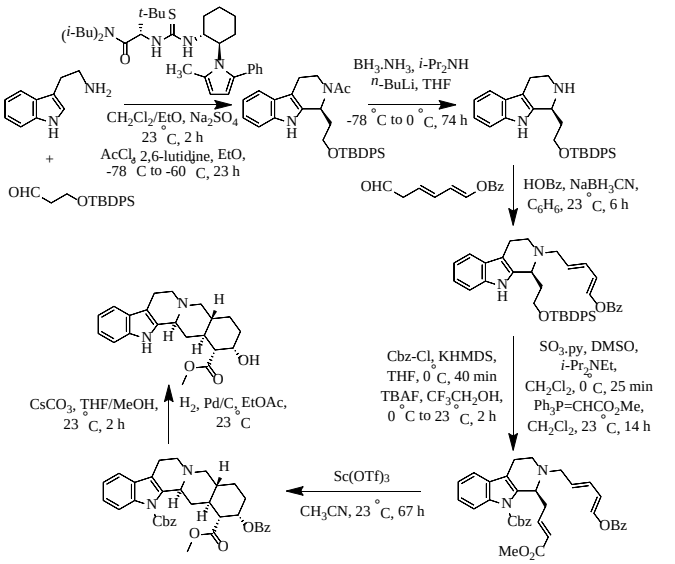
θ-Defensins are cyclic peptides that are ribosomal synthesized and found in the leukocytes of some primate species. They have promising applications as antimicrobial agents and scaffolds for peptide drugs. The cyclic cystine ladder motif, which consists of a cyclic peptide backbone and three parallel disulfide bonds, is unique to θ-defensins. In this, author investigate the role of the cyclic peptide backbone and cystine ladder in the structure, stability, and activity of θ-defensins in this study. θ-Defensin analogues with various numbers and combinations of disulfide bonds were synthesized and tested for serum and thermal stability, as well as antibacterial and membrane-binding activity. Whereas the peptides' structures and stabilities were primarily determined by the number and position of disulfide bonds, their antibacterial and membrane-binding properties were determined by the cyclic backbone. The findings shed light on the mechanism of action of θ-defensins and demonstrate the utility of θ-defensin analogues as scaffolds for peptide drug design.[48]

The antimicrobial protein the Solution structure of the antimicrobial peptide Btd-2[3,4] (**Figure. 2**) are fluorescently labelled cationic peptide LAH4 when it attached to the membranes, it was used in one of the first studies describes the formation of fibre *via* end-to-end alignment. Furthermore, supramolecular structures were deduced from the antimicrobial peptide BTD-2 or the membrane-disruptive phenol-soluble modulin alpha 3 (PSMα3) based on their higher oligomeric state in crystal lattices. [49-51] BTD-2 peptides organize within the crystal lattice in a fibril-like state, similar to PSMα3 fibrils, both of which appear to form amyloid-like states *via* zipper motifs, providing structural evidence linking antimicrobial and amyloid

peptides. When incubated with lipid vesicles, LL-37 has also been shown to form fibres by using electron microscopy.



Scheme 3 Synthesis of Tangutorine.



Scheme 4 Synthesis of Yohimbine.

In our research, we demonstrated the supramolecular formation of LL-37 fibres in crystal lattices via a head-to-tail dimer arrangement. Using gold-labeled peptides incubated with lipid vesicles, we confirmed these fibres using electron microscopy. Fibril structures were only formed as a result of LL-37/detergent or LL-37/lipid interactions[52,53], followed by termini structural reorganization and polymerization. Peptides with antimicrobial activity that form fibril structures include phenol-soluble modulins (PSMαs), BTD-2, the cationic peptide $LiAlH_4$, and amyloid peptides.[54,55]

This antimicrobial protein (Solution structure of the antimicrobial peptide Btd-2[3,4]) having 18 models of protein. The binding of all the models vary from **-4.2 kcal/mol** to **-5.2 kcal/mol**. But the best binding energy is **-5.2 kcal/mol** for protein model 17. So, we study all the docking for these four compounds (indoloquinolizidine derivatives) against the protein model **17**.

***Molecular docking studies*:** The preliminary interpretation of structure activity relationship has been carried out by using a variety of methods, including molecular docking modelling and docking studies, where the interpretability is significantly improved. Pharmacophore techniques can provide a significant benefit and a clearer look at the structural elements that contribute to the structure-activity relationship (SAR) in this approach.[56-65] Pharmacophore generation was discovered in this study using Auto Dock vina 4 (The Scripps Research Institute) and discovery studio. In the result and discussion section, the scoring of ligands (ligand internal energy, binding affinity, and distance) is described. The "protein ligand interaction profiler" calculated the binding affinity of ligands in stable ligand-protein complexes required for ligand binding with the receptor using the default settings. According to the molecular docking study, the dielectric constant is **0.1465** and the binding spacing is **0.308**. The exhaustiveness setting is set to **10**, and the RMSD values are calculated relative to the best mode using only movable heavy atoms. There are two RMSD metrics provided: rmsd/lb (RMSD lower bound) and rmsd/ub (RMSD upper bound). Furthermore, the energy of binding modes in the output is **5**. To calculate the interaction of protein and ligands in the stable ligand-protein complex required for ligand binding to the receptor, the "protein-ligand interaction profiler" (PLIP) was used. The hydrogen bond, residual interaction, and pi-interaction of the four compounds were summarized in **Table 1**.

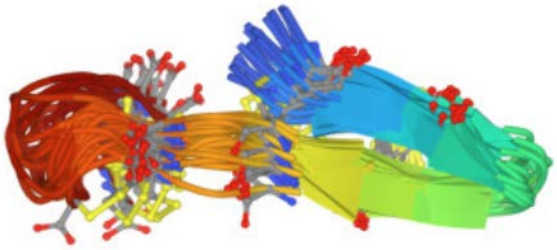


Figure 2 Structure of the antimicrobial protein.

Dihyroantirhine **1** shows the similar residual interaction with the several amino acid residues ARG A:1, ARG A:10, ARG A:14, CYS A:2, CYS A:9, CYS A:11, CYS A:13, CYS A:18, VAL A:3, VAL A:12, VAL A:17 as shown in **figure 3**. The *in-silico* interaction results of the synthesized compound against the solution structure of the antimicrobial peptide Btd-2[3,4]. Among which this compound **1** shows moderate binding affinity as compared to other indoloquinolizidine derivatives with the value **-5.2 kcal/mol.** Mitragynine **2** shows the similar residual interaction with the several amino acid residues ARG :10, CYS A:2, CYS A:9, CYS A:11, CYS A:13, CYS A:18, VAL A:8, VAL A:13, as shown in **figure 4**. The *in-silico* interaction results

of the synthesized compound against the solution structure of the antimicrobial peptide Btd-2[3,4]. Among which this compound **2** shows lower binding affinity as compared to other indoloquinolizidine derivatives with the value **-5.1 kcal/mol.**

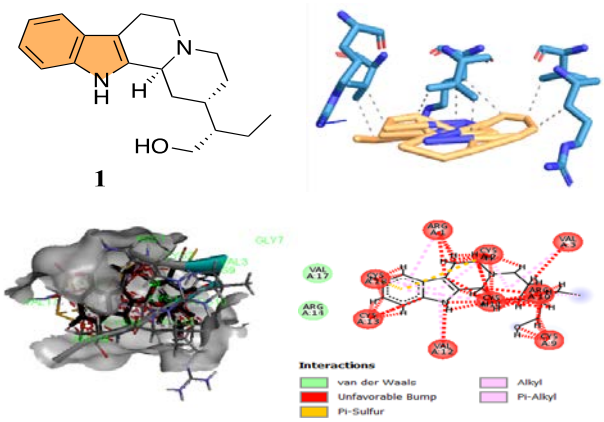


Figure 3. Binding interaction of Dihyroantirhine **1** against Solution structure of the antimicrobial peptide Btd-2[3,4] (**PDB ID: 2M2Y**). (a) Structure of Dihyroantirhine **1**, (b) interaction of protein and ligand, (c) receptor cavities present during interaction and (d) 2D-structure.

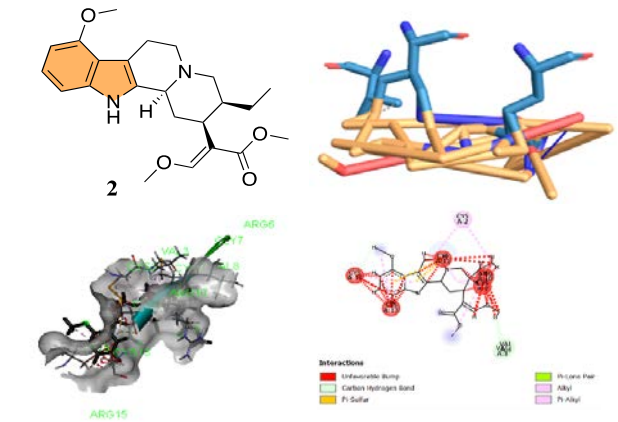


Figure 4 Binding interaction of Mitragynine **2** against Solution structure of the antimicrobial peptide Btd-2[3,4] (**PDB ID: 2M2Y**). (a) Structure of Mitragynine **2**, (b) interaction of protein and ligand, (c) receptor cavities present during interaction and (d) 2D-structure.

Tangutorine **3** shows the similar residual interaction with the several amino acid residues ARG :10, ARG :14, CYS A:2, CYS A:4, CYS A:9, CYS A:11, CYS A:13, CYS A:18, VAL A:12, VAL A:17, GLY A:7, as shown in **figure 5**. The *in-silico* interaction results of the synthesized compound against the solution structure of the antimicrobial peptide Btd-2[3,4]. Among which this compound **3** shows higher binding affinity as compared to other indoloquinolizidine derivatives with the value **-6.1 kcal/mol.**

Yohimbine **4** shows the similar residual interaction with the several amino acid residues ARG :10, CYS A:2, CYS A:4, CYS A:9, CYS A:11, CYS A:13, CYS A:18, VAL A:17, as shown in **figure 6**. The *in-silico* interaction results of the synthesized compound against the solution structure of the antimicrobial peptide Btd-2[3,4]. Among which this compound **4** shows moderate binding affinity as compared to other indoloquinolizidine derivatives with the value **-5.7 kcal/mol.**

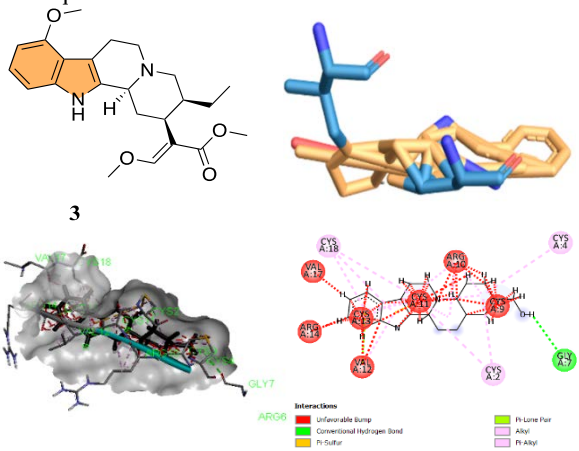


Figure 5 Binding interaction of Tangutorine **3** against Solution structure of the antimicrobial peptide Btd-2[3,4] (**PDB ID: 2M2Y**). (a) Structure of Tangutorine **3**, (b) interaction of protein and ligand, (c) receptor cavities present during interaction and (d) 2D-structure.

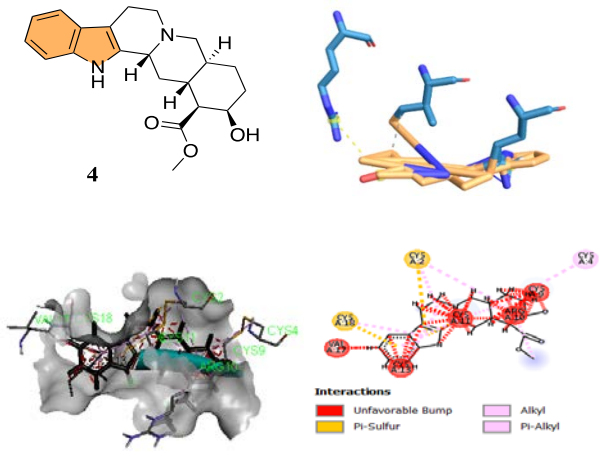


Figure 6 Binding interaction of Yohimbine **4** against Solution structure of the antimicrobial peptide Btd-2[3,4] (**PDB ID: 2M2Y**). (a) Structure of Yohimbine **4**, (b) interaction of protein and ligand, (c) receptor cavities present during interaction and (d) 2D-structure.

Result & Discussion

In this article, we have reported the binding affinity and the several interactions of indoloquinolizidine derivatives [25] (**1-4**) against the solution structure of the microbial peptide Btd-2[3,4] (**PDB ID: 2M2Y**). This is antibacterial based protein. The binding energy of compound **1-4** is **-5.1 to -6.1 kcal/mol**. This interaction shows that compound **3** shows highest binding affinity (**-6.1 Kcal/mol**) as compared to other derivatives of indoloquinolizidine. We used a variety of software programmes for this docking study, including Auto Dock vina 4 [26], discovery studio, and protein-ligand interaction profiler. The study and analysis of docking position, docking size, binding

affinity, energy range, and exhaustiveness are made easier with the aid of these software programmes.

Table 1: Value of molecular docking of the compounds (**1-4**) against solution structure of the antimicrobial peptide Btd-2[3,4].

Compound	Binding Affinity (kcal/mol)	r.m.s.d Lower bound	r.m.s.d Upper bound	Hydrogen bonding	Hydrophobic Interaction	Pi-alkyl	Salt bridges	Pi-cation	Pi-sulfur
Dihyroantirhine 1	-5.2	3.21	6.898	ARG A:1 (3.01)	ARG A:10 (3.78), VAL A:3 (3.55), VAL A:12 (3.80)	-	ARG A:1 (4.96)	ARG A:1 (4.96)	-
Mitragynine 2	-5.1	2.719	6.898	ARG A:10, VAL A:8 VAL A:13	VAL A:3 (1.89), VAL A:12 (3.35)	CYS A:2	-	-	-
Tangutorine 3	-6.1	3.03	6.898	ARG A:10, ARG A:14, VAL A:12	VAL A:3 (1.81)	CYS A:2, CYS A:4, CYS A:18	-	-	CYS A:2, CYS A:18
Yohimbine 4	-5.7	3.227	6.898	ARG A:10	VAL A:3 (3.05), VAL A:17	CYS A:4	-	-	-

The ligands (indoloquinolizidine derivatives) are attached to a number of amino acids, and its analogues exhibit a variety of interactions, some of which are as follows: ARG A:1, ARG A:10, ARG A:14, CYS A:2, CYS A:4, CYS A:9, CYS A:11, CYS A:13, CYS A:18, VAL A:3, VAL A:12, VAL A:17, and GLY A:7. The docking result is given in Table 1.

CONCLUSION

Current research demonstrates how critical it is to conduct research to identify potential indoloquinolizidine derivative-containing antibacterial agents that could one day lead to the development of powerful antibiotics. In this work, a number of software programs, including AutoDock Vina 4, Discovery Studio, and protein-ligand interaction Profler, were used to study the interaction of ligand and protein (PLIP). This article investigated the molecular docking of compounds with an indoloquinolizidine derivatives against the solution structure of the antimicrobial peptide Btd-2[3,4]. The antimicrobial peptide Btd-2 has a solution structure that has high binding affinities, adequate residual interactions, and hydrogen bonding interactions against the protein, according to an in silico molecular docking study of these compounds (**PDB ID: 2M2Y**). For indoloquinolizidine and its derivatives **1-4**, the binding affinity ranges from 5.1 to 6.1 Kcal/mol. The study also showed that several amino acids interact with ligands that are derivatives of indoloquinolizidine and their analogues. ARG A:1, ARG A:10, ARG A:14, CYS A:2, CYS A:4, CYS A:9, CYS A:11, CYS A:13, CYS A:18, VAL A:3, VAL A:12, VAL A:17, and GLY A:7 is a few of the identified amino acids. The reported core generally demonstrates antibacterial activity already and may be further refined to act as antibacterial compounds in the close future.

ABBREVIATION

PSMαs:Phenol-soluble modulins alpha 3**;** THF:Tetra Hydro Furan**;** TEA:Triethylamine**;** MA:Meldrum's Acid**;** RMSD:Root Mean Square Deviation**;** PDB:Protein Data Bank**;** SAR:Structure Activity Relationship**;** PLIP:Protein Ligand Interaction Profiler

COMPETING INTERESTS

The authors declare that they have no competing financial interests.

FUNDING: Not applicable.

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