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Proximicin A-C as Prospective HER2-Positive and Negative Breast Cancer Drugs: Molecular Docking and In silico ADME Modeling

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Abstract

Breast cancer is the second leading cause of cancer-related death among women worldwide. Proximicin A-C are bioactive chemicals produced by the marine *Verrucosispora* strain, which have been shown to have a potent cytostatic effect against human breast cancer [MCF 7]. HER2 (Human epidermal growth factor receptor 2) is a gene that has been linked to breast cancer development. The study's goals are to (1) forecast the intensity of binding affinity and interactions between HER2 and proximicin A-C, and (2) analyze ADME characteristics of proximicin A-C (Absorption, Distribution, Metabolism, and Excretion). The CB-Dock web service was used to dock proximicin A-C and commonly used breast cancer medicines Neratinib (Nerlynx) and Talazoparib against HER2, and protein-ligand interaction findings were collected via the protein-ligand interaction profiler (PLP) web server. The SwissADME web server was used to investigate ADME properties of the substances. In terms of docking, proximicin A has a vina score of -8.6, proximicin B and C has a score of -10, Talazoparib has a vina score of -8.5, and Neratinib (Nerlynx) has a vina score of -10.2 on CB-Dock. This means that proximicin B and C bind to HER2 more strongly than proximicin A and Talazoparib. Furthermore, their high binding affinity is nearly equivalent to Neratinibs (Nerlynx). Talazoparib has a lower binding affinity for HER2 than proximicin A. With HER2, all three chemicals have a strong hydrogen bond and hydrophobic contact. SwissADME estimated that all three substances follow the Lipinski rule (RO5) and have a bioavailability score of 0.55. They don't have any structural issue in medicinal chemistry (no alerts in PAINS and Brenk forecasts), and their synthetic accessibility scales range from 3 to 3.5. Only proximicin A, on the other hand, has the leadlikeness feature. All three drugs failed to cross the blood-brain barrier (BBB) in terms of pharmacokinetics. Proximicin A has a high absorption rate in the GI tract, whereas proximicin B-C has a low absorption rate in the GI tract (GI). Similarly, proximicin A is neither a P-gp substrate nor a CYP1A2, CYP2C19, CYP2C9, CYP2D6, or CYP3A4 inhibitor. Proximicin B-C, on the other hand, are P-gp substrates, and proximicin C is an inhibitor of all provided CYP enzymes, whilst proximicin B inhibits only three. Overall, proximicin A-C could be used as a possible breast cancer therapeutic candidate. Proximicin B-C will outperform proximicin A in terms of therapeutic efficacy. Proximicin A, on the other hand, will have better ADME qualities than Proximicin B-C. This study will provide the lead information for developing a new breast cancer medication with a good pharmacological profile.

Keywords: *Proximicin, binding affinity, ADME properties, breast cancer, HER2*

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Introduction

The uncontrolled development and duplication of tissue cells in the breast causes breast cancer. Breast cancer is still the main cause of cancer death in women around the world today. One in every eight women will be diagnosed with breast cancer at some point in their lives, and one in every 38 will succumb to the disease. [1] Breast cancer is classified into two categories based on the type of proteins found in breast cells that cause it: (1) Human epidermal growth factor receptor 2 (HER2)-positive and HER2-negative breast cancers, as well as hormone-receptive breast cancers (either estrogen-receptive or progesterone receptive cancer). [2]

HER2-positive is a breast cancer that tests positive for the protein human epidermal growth factor receptor known as human epidermal growth factor receptor 2 breast cancer (HER2). This protein encourages cancer cell proliferation. Extra copies of the gene that produces the HER2 protein are found in around one out of every five breast tumors. Breast cancers that are HER2-positive are more aggressive than other kinds of breast cancer. [3] HER2-negative breast cancer suggests that the malignant cells do not have high amounts of the protein HER2. There are a variety of therapy options for this form of breast cancer, however the prognosis varies. [4] Over the last two decades, medical advancements have resulted in the development of new, effective treatments. Trastuzumab (Herceptin) was the first FDA-approved targeted therapy for HER2-positive breast cancer. Trastuzumab is administered intravenously (via an IV) once a week or once every three weeks. [5]

A marine *Verrucosispora* strain produces a family of three novel aminofuran antibiotics known as proximicin. Proximicins B, which has a molecular mass of about 413 kDa, can inhibit the growth of gram-positive bacteria, whereas proximicins C, which has a molecular mass of about 436 kDa, can only inhibit the growth of *Brevibaccillus brevis*. Surprisingly, gram-negative bacteria like *E. coli* K12, *Pseudomonas fluorescens*, and *Proteus mirabilis*, as well as yeasts like *Saccharomyces cerevisiae*, are all resistant to proximicins. Proximicins have a molecular structure that includes 4-amino-furan-2-carboxylic acid, a previously discovered -amino acid. Although they are mild bactericidal peptides, they have a strong cytostatic effect on human breast cancer (MCF 7). Proximicin C can produce cell cycle arrest at the G0/G1 phase after 24

hours and enhance the number of apoptotic cells after 40 hours, according to an in vivo study on gastric adenocarcinoma (AGS) cells. In AGS cells, it can also increase intracellular levels of p53 and the cyclin kinase inhibitor p21. [6] The molecular docking analysis of proximicin A-C against human epidermal growth factor receptor 2 (HER2) and the computational assessment of pharmacokinetic or ADME features for proximicin A-C are both part of this research project. The most promising route for drug design and discovery is through computational molecular docking and scoring. As a result, this research could lead to the development of a novel breast cancer treatment.

Materials and Methods

Selection of ligands and protein

Three bioactive compounds, proximicin A-C from the *Verrucosispora* strain were retrieved in SDF format from pubChem (http://pubchem.ncbi.nlm.nib.gov/) based on public databases and published research articles. In addition, two standard medicines, Neratinib (Nerlynx) and Talazoparib, were downloaded in 3D SDF format for comparison with the phytochemicals, having Pubmed IDCID 135565082 and CID 9915743, respectively. PDB ID 3PP0 was used to get the 3D structure of the human endothelium receptor HER-2 from the RCSB protein data bank.

Molecular Docking study

The CB-Dock web server (http://cao.labshare.cn/cb-dock/) was used to analyze the docking of the compounds. The CB-Dock online server simply requires a protein file in PDB format and a ligand file in MOL2, MOL, or SDF format as input. Following submission, the CB-Dock examines the input files and uses OpenBabel and MG Tools to convert them to pdbqt formatted files. CB-Dock then predicts the protein's cavities and determines the centres and sizes of the top N (by default, n=5) cavities. AutoDock Vina is used to dock the centres and sizes, as well as the pdbqt files. After computing, the final findings are displayed. In the table, users can look up binding scores, cavity size, and docking parameters for projected binding modes. Users can also examine the 3D structures of any binding modes on the web page by clicking on the structures in the associated table. [7] Only the best pose of binding modes for each molecule was evaluated in this investigation, as shown in the Table 1.

Protein-ligand interaction

For protein-ligand interaction, the best poses of protein-ligand complex pdb file obtained from CB-Dock web server were submitted to protein- ligand interaction profiler (PLP) web server (http:plip-tool.biotec.tu-dresden.de) for each molecule. Protein- ligand interaction profiler (PLP) is a novel web service for fully automated detection and visualization of relevant non-covalent protein- ligand contacts in 3D structures, freely available at projects.biotec.tu-dresden.de/plip-web. It returns a list of detected interactions on single atom level, covering seven interaction types (hydrogen bonds, hydrophobic contacts, pi-stacking, pi-cation interactions, salt bridges, water bridges and halogen bonds. [8]

In silico ADME Study

SwissADME (http:// www. swiss adme. ch/ index. php) was used to investigate pharmacokinetics parameters in the ligands, such as absorption, distribution, metabolism, and excretion. Lipinski's rule of five (RO5), Ghose's, Egan's, Veber's, and Muegee's criteria were used to assess the drug-likeness of compounds. The PAINS and Brenk filters were used to determine whether chemicals were promiscuous. The leadlikeness approach was designed because it is critical to determine whether a given molecule is suitable for the start of lead optimization. The SwissADME online programme also generated in silico data for the key human cytochrome P450 (CYP) isoforms involved in drug metabolism, such as CYP2C9, CYP2D6, and CYP3A4. SwissADME can additionally provide the BOILED-Egg model, a synthetic accessibility score, and computational filters like Ghose, Egan, Veber, and Muegee PAINS, as well as Brenk. The SwissADME online tool was also used to determine molecular parameters like MW (molecular weight), HBD (hydrogen bond donor), HBA (hydrogen bond acceptor), log P (lipophilicity log), log S (aqueous solubility), TPSA (topological polar surface area), MW, nRot (number of rotatable bonds), and MR (molar refractivity). [9-10]

Results and Discussion

Molecular docking study

Molecular docking is a method for predicting a ligand's optimal orientation, affinity, and interaction in a protein's binding site. Using scoring functions, the preferred orientation can be utilized to predict the strength of binding affinity between the therapeutic target and the ligand molecule. Because of its medical uses, the protein-ligand interaction is the most intriguing instance. [11]

The three bioactive molecules, proximicin A-C, were tested against the human epidermal growth factor receptor 2 in molecular docking studies (HER2). HER2 proteins aid in the rapid growth of breast cancer cells. Neratinib (Nerlynx) and Talazoparib, two commonly used breast cancer medicines, were also docked against the target receptor to compare their binding affinity to that of proximicin A-C.

Neratinib (Nerlynx) is a kinase inhibitor that prevents cancer cells from growing by blocking the action of HER2 and other kinase proteins. After a year of trastuzumab, it's utilised to treat HER2 positive early breast cancer. It is a tablet that must be taken on a daily basis. Talazoparib is a drug that is used to treat advanced or metastatic HER2-negative breast cancer in women who have had chemotherapy and have a BRCA gene mutation. [5]

The CB-Dock web server calculates vina ratings for binding affinity and binding modes for each chemical ligand. Only the best position of each molecule was taken into account, as shown in the table. Vina score is a quantitative criterion for determining the affinity, or efficiency, of protein-ligand interactions. [12]

The vina scores of proximicin B and C are the same [-10], and they are much lower than those of proximicin A [-8.6] (Table 1). Proximicin A-C has a lower score than Talazoparib [-8.5], and Neratinib (Nerlynx) has a poorer score than all three substances when compared to the conventional medications. A strong binding affinity between protein and ligand is indicated by a low vina score. [13] As a result of their vina score, it may be deduced that proximicin A-C have a high binding affinity for HER2. Furthermore, when compared to proximicin A and Talazoparib, Proximicin B and C show a greater binding affinity for HER 2. The strength of the connection between the drug and its receptor is defined by affinity. The stronger the connections, the more the ligand will alter the physiological function of the target proteins; thus, drug candidates are chosen from ligands that bind strongly to the target protein. Because the anticipated binding affinity of ligands in a library can be used for virtual screening or lead optimization, precise binding affinity prediction can lower the cost of a de novo drug design. A low dosage required is usually accompanied with a high affinity (compared with low affinity for the same receptor). [14]

Table 1: The vina scores and cavity information of proximicin A-C and Neratinib (Nerlynx) and Talazoparib against HER2

Compounds	Vina Score	Cavity Size	Center			Size		
			x	y	z	x	y	z
Proximicin A	-8.6	4513	9	18	23	32	30	24
Proximicin B	-10	4513	9	18	23	27	27	27
Proximicin C	-10	4513	9	18	23	27	27	27
Neratinib (Nerlynx)	-10.2	1755	36	40	-13	26	26	26
Talazoparib	-8.5	380	23	36	27	21	21	21

Protein-ligand interaction

Characterizing interactions in protein-ligand complexes is critical for structural bioinformatics, drug development, and biology research. Proximicin A-C was discovered to bind efficiently with the human epidermal growth factor receptor 2 (Figures 1-2 and Table 2-4) (HER2). Proximicin A has four hydrogen bond contacts with GLU-770A [2.42], SER-783A [3.20], THR-862A [1.86], and ASP-863A [2.73], as well as two hydrophobic interactions with VAL-734A [3.61], and LYS-753A [3.88]. Only proximicin A [5.07] has π stacking (perpendicular) with the PHE-864A residue.

Proximicin B contains four hydrogen bond contacts with the residues of LEU -726A [2.54], VAL -734A [3.87], MET -774A [3.39], LEU -785A [3.59], LEU -796A [3.46], LEU -788A [3.13], and THR-798A [3.99] and eight hydrophobic interactions with the residues of LEU -726A [3.54], VAL -734A Proximicin C forms three hydrogen bond contacts with the residues of ASP -808A [2.09], ARG -849A [2.43], and ASP - 863A [3.28], as well as six hydrophobic interactions with the residues of LYS -753A [3.95], MET -774A [3.58], LEU -785A [3.71], THR -798A [3.71], LEU -852A [3.75], and and PHE -864A [3.67 Å].

If ligands can make hydrophobic interactions with the binding site's hydrophobic amino acids, the binding affinity will be higher. This is why, in comparison to proximicin B and C, proximicin A has a lesser affinity. [15] Proximicin B and C will have a higher therapeutic efficacy than proximicin A, according to the findings of this study. However, because their binding affinity is comparable to that of typical medications, proximicin A-C have the potential to act as breast cancer treatments.

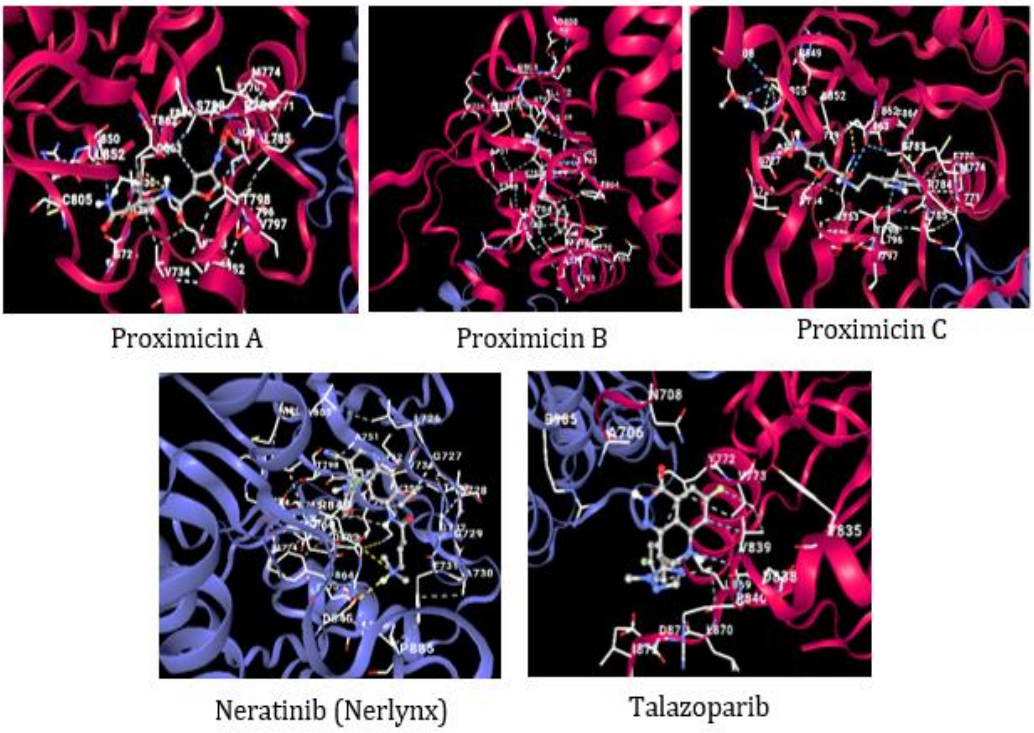

Figure 1: The 3D binding interactions of the best-docked proximicin A-C and Neratinib (Nerlynx) and Talazoparib within HER2

Table 2: Hydrogen bond interactions between proximicin A-C and HER2

	Residue	AA	Distance		Donor Angle	Donor Atom	Acceptor Atom
			H-A	D-A			
Proximicin A	770A	GLU	2.42	3.16	128.80	4681 [Nam]	500 [O2]
	783A	SER	3.20	3.92	132.60	595 [O3]	4660 [Nam]
	862A	THR	1.86	2.83	160.13	4660 [Nam]	1219 [O3]
	863A	ASP	2.73	3.52	137.67	1221 [Nam]	4660 [Nam]
Proximicin B	726A	LEU	2.45	3.08	121.92	4673 [Nam]	166 [O2]
	783A	SER	3.18	3.85	127.86	595 [O3]	4681 [Nam]
	783A	SER	3.12	3.85	131.83	4681 [Nam]	595 [O3]
	805A	CYS	2.02	2.97	160.66	755 [Nam]	4675 [O2]
Proximicin C	808A	ASP	2.09	3.07	172.05	425 [O3]	4679 [O3]
	849A	ARG	2.43	3.37	160.02	441 [N3]	4672 [N3]
	863A	ASP	3.28	4.02	133.47	4672 [N3]	441 [N3]

Table 3: Hydrophobic interactions between proximicin A-C and HER2

Compounds	Residue	AA	Distance	Ligand Atom	Protein Atom
Proximicin A	734A	VAL	3.61	4667	218
	753A	LYS	3.88	4667	367
Proximicin B	726A	LEU	3.54	4672	167
	734A	VAL	3.87	4662	217
	774A	MET	3.39	4690	534
	785A	LEU	3.59	4689	614
	785A	LEU	3.46	4690	611
	796A	LEU	3.13	4687	691
	798A	THR	3.99	4662	706
	864A	PHE	3.53	4684	1236
Proximicin C	753A	LYS	3.95	4669	365
	774A	MET	3.58	4678	534
	785A	LEU	3.71	4678	611
	798A	THR	3.71	4669	706
	852A	LEU	3.75	4661	1142
	864A	PHE	3.67	4675	1236

Table 4: π stacking interaction between proximicin A-C and HER2

Compounds	Residue	AA	Distance	Angle	Offset	Stacking Type	Ligand Atoms
Proximicin A	864A	PHE	5.07	57.64	0.90	T	4674, 4675, 4676, 4678

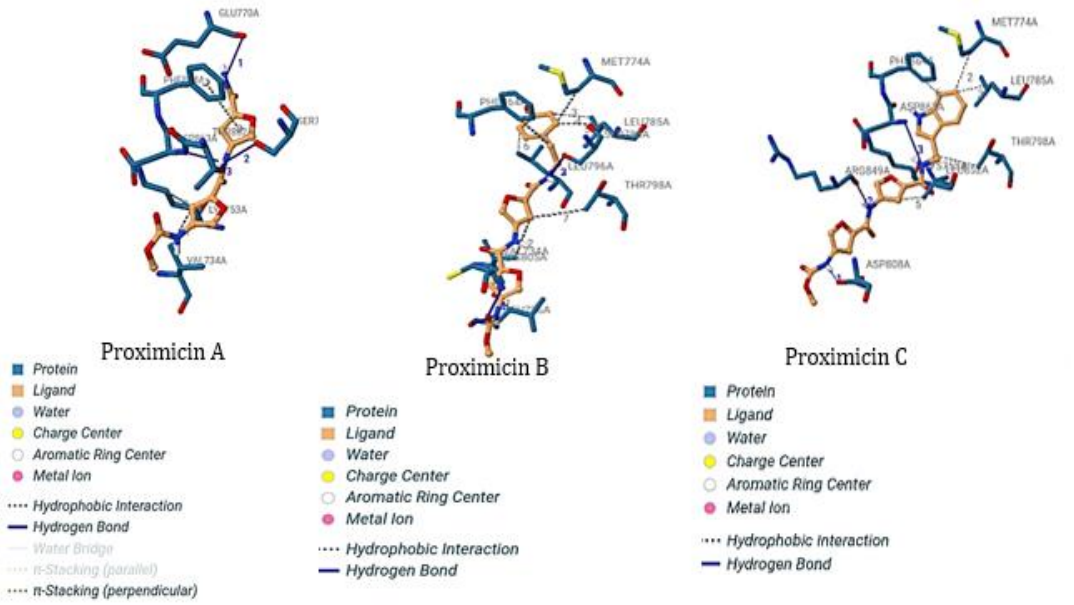

Figure 2: Docking pose and binding modes of proximicin A-C.

In silico ADME Study

The flow of a medicine through the body's biological systems is referred to as pharmacokinetics. Absorption, distribution, metabolism, and excretion (ADME) are the four processes of the pharmacokinetic phase [1]. The ADME study has recently been added to incorporate the toxicological evaluation of new medication candidates. The distribution and fate of pharmacological chemicals within an organism, particularly in the human body, is described by ADME. The biggest cause of failure during the drug development phase is the candidate compound's poor pharmacokinetics (PK) and toxicity in compared to its efficacy. [16]

Many bioactive chemicals, for example, have demonstrated substantial anticancer activity, but their use is restricted because to their harmful and life-threatening side effects and toxic consequences. [17] Both high-throughput experimental and computational (in silico) directions are now available. Drug-transporter interactions involving P- glycoprotein transporters in the intestines frequently result in poor absorption and low oral bioavailability because the drug is easily effluxed backed into methods have become well-known for obtaining ADME or PK properties of a large number of compounds during the early stages of drug discovery. [18]

In the gastrointestinal system, proximicin A was found to have a high absorption rate. Given the advantages of the oral mode of administration, this means that Proximicin A has a highly favourable feature of a medication candidate. The microvascular endothelial cell layer of the brain that separates the brain from the blood is known as the blood brain barrier (BBB). Only chemicals that target the central nervous system are required to penetrate the BBB (CNS). [19] The target chemicals do not appear to be capable of bridging the BBB based on the computational findings. Because none of the chemicals showed the ability to cross the BBB, this may be a benefit because they are less likely to cause deleterious effects in the CNS (Table 5).

P-glycoprotein (P-gp) is a type of membrane transporter that transports chemicals in the intracellular or extracellular lumen of the intestine and excretes them. Furthermore, P- glycoprotein inhibits the uptake of a wide range of structurally and functionally varied drugs, including the majority of cancer treatments, resulting in multidrug resistance. P-glycoprotein is also overexpressed in cancer cells, posing a substantial treatment hurdle by causing drug efflux and rendering chemotherapy ineffective. [20] Compound 1 was determined to be P-gp non-substrates. This means that the compounds would be unaffected by P-efflux gp's action, which causes compounds to be eliminated from cells, resulting in therapeutic failure due to lower concentrations than expected. Proximicin B and C are thought to be P-gp substrates. This means that they may have poor absorption and oral bioavailability, resulting in multidrug resistance as a result of their potency. Because it is not a P-gp substrate, proximicin A is the best candidate for cancer treatment against multidrug-resistant cancer cells (Table 5).

The basic enzymes for drug biotransformation are the cytochrome P450 (CYP) enzymes. CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, and CYP3A4 inhibitor are the most important inhibitors in biotransformation. CYP isoenzymes are involved in xenobiotic detoxification, cellular metabolism, and homeostasis. As a result, drug metabolism via CYP isoenzymes is a key determinant of drug interactions, which can result in drug toxicity and a reduction in pharmacological activity [21-22]. CYP3A4 is not only the most common CYP enzyme in the liver, but it is also utilised by more than half of all drugs on the market for metabolism and elimination from the body. Both proximicin B and C are predicted to inhibit CYP3A4, which could be a disadvantage because this CYP isoform is involved in the metabolism and elimination of the majority of clinically used drugs, including calcium channel blockers, some stains, immunosuppressors, macrolides, and atypical antipsychotics, among others. [23] Proximicin A would have no effect on CYP1A2, CYP2C19, CYP2C9, CYP2D6, or CYP3A4, however proximicin C would inhibit all of the CYP enzymes. CYP1A2 and CYP2C19 were not inhibited by proximicin B, although it did inhibit CYP2C9, CYP2D6, and CYP3A4. Because proximicin A has no inhibitory effect on these enzymes, the chemicals have a high chance of being converted and hence accessible after oral treatment (Table 5).

Inhibition of the CYP isomers by proximicin B and C, on the other hand, can result in poor bioavailability due to failure to be metabolised and hazardous side effects due to their buildup. Proximicin B, on the other hand, may be processed by more than one enzyme, lowering the probability of a drug-drug interaction. The skin acts as a selective barrier, allowing various chemicals to enter at different rates based on their physicochemical qualities. As a result, skin permeability (LogKp) is an important characteristic to consider when evaluating medicines that may require transdermal delivery. [23] Table 5 shows the LogKp of the various compounds. Because they had negative values between -8.7 and -6.2 cm/s, all of the chemicals should be accessible. This means that none of the three chemicals could be delivered efficiently through the skin.

The term "drug-likeness" refers to how likely a molecule is to become an oral drug in terms of bioavailability. Structure or physicochemical inspections of research compounds progressed enough to be deemed oral drug candidates were used to determine drug-likeness. [22] As a result, swissADME was used to assess the physiochemical characteristics and lipophilicity of compounds in Tables 7 and 8. The Lipinski (Pfizer) filter was the first of its kind in terms of predicting oral medication candidates. Many extensions have been provided to improve the predictions of drug candidates for oral administrations, such as The Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer) guidelines.

Table 5: Pharmacokinetic evalution of the compounds (GI; gastro-intestinal absorption, BBB; blood brain barrier, CYP; cytochromes, P-gp; P-glycoprotein; Log K_p - skin permeation

Compound	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
Proximicin A	High	No	No	No	No	No	No	No	-8.08
Proximicin B	Low	No	Yes	No	No	Yes	Yes	Yes	-7.39
Proximicin C	Low	No	Yes	Yes	Yes	Yes	Yes	Yes	-7.19

There are five different types of rule-based filters, as follows: 1. Molecular weight 500, MLOGP (lipophilicity) 4.15, hydrogen bond acceptors 10, and hydrogen bond donors 5 are all included in Lipinski's filter. [24] 2. Ghose's filter has a molecular weight of 480, a lipophilicity of 0.4 WLOGP (5.6), a molar refractivity of 40, and a number of atoms of 20. [25] 3. The number of rotatable bonds is 10 and the total polar surface area is 140 in Veber's filter. [26] 4. WLOGP (Lipophilicity) 5.88 and total polar surface area 131.6 are included in Egan's filter. [27] 5. Muegge's filter includes the following parameters: 200 molecular weight 600, 2 XLOGP3 (lipophilicity) 5, total polar surface area 150, number of rings 7, number of carbon > 4, number of heteroatoms > 1, number of rotatable bonds 15, hydrogen bond acceptors 10, and hydrogen bond donors 5. [28]

The Lipinski's rule, Ghose's rule, and Muegge's rule are all in agreement with proximicin A-C. Proximicin A met Veber's qualifying conditions, however proximicin B broke two regulations (Rotors>10 and TPSA>140) and proximicin C broke one rule (Rotors>10), according to Veber's rule. All of the compounds in the Egan's rule cases had one violation (TPSA>131.6) (Table 6). If a substance violates more than one of Ro5, poor oral absorption of medicinal molecules is found. A compound is predicted to be a non-orally accessible medication if two or more of these conditions are violated. [23]

All of the compounds were orally bioavailable, meeting the requirements of the Lipinski's, Ghose's, Egan's, and Muegge's filters. According to Veber's filter, proximicin B is expected to have some oral bioavailability issues, whereas proximicin A and C are expected to have acceptable oral bioavailability. Proximicin A-C, on the other hand, has a bioavailability of 0.55. This indicates that the chemicals have a 55% chance of being bioavailable. The bioavailability score is an indicator of drug material oral absorption. Any medication molecule with a BA score of 0.55 that meets the rule of five is regarded suitably absorbable via oral route. [23] Proximicin A-C had a score of 0.55, indicating that it has good oral bioavailability (Table 6).

There are some basic guidelines for determining the medicinal chemistry of produced substances. The physicochemical filters PAINS and Brenk are used to anticipate the compounds that have poor pharmacokinetic properties. PAINS is a filter that helps to identify a molecule by determining if it is a reaction to biological assays or not, and Brenk is a filter that helps to identify compounds with the acceptable hazardous level, chemical reactivity, and metabolic instability. [29-30] Proximicin A-C are structurally sound and unlikely to be reactive or hazardous.

The synthetic accessibility value is a number based on fragmental structural research; the more molecular fragments there are, the easier the molecule is to produce. Descriptors for molecule size and complexity correct this fragmental contribution approach. The score ranges from 1 (easy synthesis) to 10 (very difficult synthesis). [22-31] Smaller synthetic accessibility numbers are often easier to synthesise than bigger values between 1 and 10. Proximicin A-C may be produced with synthetic accessibility scales of 3.01, 3.31, and 3.42, according to the findings (Table 6).

The concept of leadlikeness is comparable to that of druglikeness. Leads are subjected to chemical changes in order to improve their size and lipophilicity. As a result, leads must be less hydrophobic and smaller than drug-like compounds. The following are the qualifying rules for the lead likeness property: 250 = molecular weight=350, XLOGP=3.5, and number of rotatable bonds=7. [22] Only Proximicin A has no violations in the lead likeness property, indicating that it meets the standards for a lead compound, but Proximicin B-C have two violations in the lead likeness parameter (MW>350 and Rotors>7).

Table 6: Druglikeness and medicinal chemistry of proximicin A-C.

Compound	Lipinski violations	Ghose violations	Veber violations	Egan violations	Muegge violations	Bioavailability score	PAINS alerts	Brenk alerts	Leadlikeness violations	Synthetic Accessibility
Proximicin A	0	0	0	1	0	0.5	0	0	0	3.01
Proximicin B	0	0	2	1	0	0.5	0	0	2	3.31
Proximicin C	0	0	1	1	0	0.5	0	0	2	3.42

Table 7: Physiochemical properties of proximicin A-C (MW; molecular weight, MR; molar refracitivity; TPA; total surface area.

Compound	MW	Heavy atoms	Aromatic heavy atoms	Fraction Csp3	Rotatable bonds	H-bond acceptors	H-bond donors	MR	TPSA
Proximicin A	293.23	21	10	0.08	7	6	3	69.07	136.8
Proximicin B	413.38	30	16	0.15	11	7	4	105.29	143.04
Proximicin C	436.42	32	19	0.14	11	6	4	115.12	138.6

Table 8: Lipophilicity evaluation of proximicin A-C.

Compound	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P
Proximicin A	1.74	0.01	1.02	-1.31	-0.23	0.25
Proximicin B	2.79	2.01	2.6	-0.05	1.62	1.79
Proximicin C	2.8	2.5	3.38	0.25	2.64	2.31

Conclusion

In this study, when compared to standard medications (Neratinib (Nerlynx) and Talazoparib), docking studies demonstrated that proximicin A-C have a decent ability to operate as possible breast cancer drugs since they all have a comparable high binding affinity with human epidermal growth factor receptor 2 (HER2). Proximicin B and C, on the other hand, will have a stronger therapeutic efficacy than proximicin A since they have a higher binding affinity for HER 2. All three compounds, proximicin A-C, had good oral bioavailability and they all met Lipinski's rule of five for oral drugability (RO5). However, none of the compounds were able to cross the blood-brain barrier (BBI). Because proximicin A is the only one of these three compounds that isn't a P-gp substrate and doesn't inhibit any cytochrome P450 (CYP) enzymes, it will be the most suitable oral medication choice. It also has a high gastrointestinal absorption rate and follows the druglikeness and leadlikeness principles. This research can be used to develop a new breast cancer medication with a favourable pharmacological profile.

References

1. Yaghoubi A, Khazaei M, Hasanian SM, Avan A, Cho WC, Soleimanpour S. Bacteriotherapy in Breast Cancer. Int. J. Mol. Sci. 2019 November 23;20(23)5880. [doi: 10.3390/ijms20235880]
2. Shoemake MD B. The importance of breast cancer awareness. 1-888-781-WELL (9355). www.wellmedhealthcare.com/the-importance-of-breast-cancer awareness/#
3. Callahan MD R, Hurvitz MD S. HER2 positive breast cancer: Management of early, Advanced, and Recurrent Disease. 2015 Jan 27. Curr Opin Obstet Gynecol. 2011 Feb. 23(1): 37–43. [doi: 10.1097/gco.0b013e3283414e87]
4. Lillis C. What to know about Her2-negative breast cancer. 2021 November. MedicalNewsToday. www.medicalnewstoday.com/article/326099#type
5. American cancer society. Treating breast cancer. Cancer.org. 1.800.227.2345.
6. Yaghoubi A, Khazaei M, Hasanian SM, Avan A, Cho WC, Soleimanpour S. Bacteriotherapy in Breast Cancer. Int. J. Mol. Sci. 2019 November 23;20(23)5880. [doi: 10.3390/ijms20235880]
7. Liu Y, Grimm M, Dai Wt et al. CB-Dock: a webserver for cavity detection-guided protein-ligand blind docking. Acta Pharmacol Sin 2019 July 01;41.138-144. [doi.org/10.1038/s4140-019-0228-6]
8. Salentin S, Schreliber S, Haupt VJ, Adasme, MF, Schroeder M. PLIP: fully automated protein-ligand interaction profiler. Nucleic acid research. 2015 April 14;43. 443-447. [doi: 10.1093/nar/gkv315]
9. Daina, A., Michielin, O. & Zoete, V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep* **7,** 42717 (2017). [https://doi.org/10.1038/srep42717]
10. Daina A, Michielin O and Zoete V. Scientific pharmacokinetics, druglikeness and medicinal chemistry friendliness of small molecules. Scientific Reports. 2017.7.42717. [doi: 10.1038/srep42717]
11. Tiwari A, Singh S. Chapter 13 – Computational approaches in drug designing. Bioinformatics, Academic Press. 2022. 201-217. [http//:doi.org/10.1016/B978-0-323-89775-4.00010-9]
12. Liu J, Wang R. Classification of current scoring functions. J. Chem. Inform. Model. 2015.55.475-482. [http//:doi: 10.1021/ci500081m].
13. Wojcikowski M, Ballester PJ, Sie P. Performance of machine-learning scoring functions in structure-based virtual screening. Scientific report. 2017 April 25; 7. 46710. [doi: 10.1038/srep46710(2017)]
14. Currie GM. Pharmacology, part 1: Introduction to pharmacology and pharmacodynamics. Continuing Education. Journal of Nuclear Technology. 2018 June. 46(2)81-85
15. Mohapatra S, Prasad A, Haque F, Ray S, De B, Ray SS. In silico investigation of black tea components on α-amylase, α-glucosidase and lipase. Journal of Applied Pharmaceutical Science 2015 December. 5(12). 042-047. [doi:10.7324/JAPS.2015.501207]
16. Smith DA, Van de Waterbeemd H, Walker DK. Pharmacokinetics and Metabolism in Drug Design, (Wiley–VCH, Weinheim, Germany, 2001).
17. Yeni, Supandi, Merdekawati F. In silico toxicity prediction of 1-phenyl-1-(quinazolin-4-yl) ethanol compounds by using Toxtree, pkCSM and preaADEMET. 2018;8(2).205-216. doi: 10.12928/pharmaciana.v8i2.9508
18. Shin HK, Kang Y-M, No KT. Predicting ADME Properties of Chemicals. Springer International Publishing Switzerland. J. Leszczynski et al. (eds.), Handbook of Computational Chemistry. 2017.p. 2265-2305 doi: 10.1007/978-3-319-27282-5_59
19. Holguin NF, Frau J, Mitnik GM. Chemical-reactivity Properties, Drug Likeness, and Bioactivity Scores of Seragamides A-F anticancer Marine Peptides: Conceptual Density Functional Theory Viewpoint. Computation. 2019 September. 7. 52. [doi:10.3390/computation7030052]
20. Finch A, Pillans P. P-glycoprotein and its role in drug-drug interactions. Australian Prescriber. 2014 August 4; 37(4). 137-139
21. Ogu CC, PharmD, Maxa JL, Rph. Drug interactions due to cytochrome P450. Proc (Bayl Univ Med cent). 2000 October. 13(14): 421-423. [doi: 10.1080/08998280.2000.11927719]
22. Daina A, Michielin O and Zoete V. Scientific pharmacokinetics, druglikeness and medicinal chemistry friendliness of small molecules. Scientific Reports. 2017;7:42717.doi: 10.1038/srep42717
23. Khalfaoui A, Noumi E, Belaabed S, Aouadi K et al. LC-ESI/MS-phytochemical profiling with antioxidant, antibacterial, antifungal, antiviral and in silico pharmacological properties of Algerian Asphodelus tenuifolius (Cav.) organic extracts. Antioxidant. 2021 April. 10. 628. [doi.org/10.3390/antiox10040628]
24. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev. 2001 March. 46 (1–3): 3–26. [doi:10.1016/S0169-409X(00)00129-0. PMID 11259830]
25. Ghose AK, Viswanadhan VN, Wendoloski JJ. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. J Comb Chem. 1999 January. 1 (1): 55–68. [doi:10.1021/cc9800071. PMID 10746014]
26. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J. Med. Chem. 2002 June.45 (12): 2615–23. [doi:10.1021/jm020017n. PMID 12036371]
27. Egan WJ, Merz KM Jr, Baldwin JJ. Prediction of drug absorption using multivariate statistics. J Med Chem. 2000 Oct 19;43(21):3867-77. [doi: 10.1021/jm000292e]
28. Muegge I, Heald SL, Brittelli D. Simple selection criteria for drug-like chemical matter. J Med Chem. 2001 Jun 7;44(12):1841-6. [doi: 10.1021/jm015507e] PMID: 11384230
29. Brenk R, Schipani A, James D, Krasowski A, Gilbert IH, Frearson J, et al. Lessons learnt from assembling screening libraries for drug discovery for neglected diseases. ChemMedChem. 2008;3(3):435-444. 2008 Mar;3(3):435-44. [doi: 10.1002/cmdc.200700139]
30. Baell JB, Holloway GA, New substructure filters for removal of pan assay interference compounds (PAINS) from screening libraries and for their exclusion in bioassays. J Med Chem. 2010;53 (7):2719-2740. 2010 Apr 8;53(7):2719-40. [doi: 10.1021/jm901137j]
31. Prabba B, Ezhilarasi MR. Syntesis, spectral Characterization, in Vitro and in Silico studies of Benzodioxin Pyrazoline derivatives. Biointerface Research in applied chemistry. 2021 September. 11(2). 9126-9138. [doi.org/10.33262/BRIAC112.91269138].

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