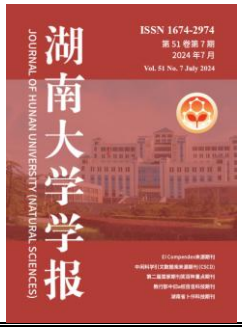

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Biochemical Evaluation of Potential Antibacterial Activities of (2,6-Diethylphenyl)-5-Oxopyrrolidine Derivatives via In-Silico Study

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Abstract: The focus of several researchers has been drawn to the surge in bacterial activity among humans and the resistance to antibacterial agents. The increasing interest in developing long-lasting antibacterial agents has been observed. Therefore, the purpose of this study was to use an in-silico approach to examine the specific inhibitory activity of pyrrolidine derivatives against the investigated receptor. Therefore, the inhibitory activities of the (2,6-diethylphenyl)-5-oxopyrrolidine derivatives were investigated using *insilico* approach. In this study, various software programs were employed, including Spartan 14, AutoDock Tools, AutoDock Vina, and Discovery Studio. Compound 9 exhibits the greatest propensity to yield electrons, as indicated by the calculated HOMO, and according to LUMO and band gap, Compound 5 demonstrates the highest potential to accept electrons and exhibit superior reactivity among the other compounds studied. Compounds 8 to 12 displayed the most potent ability to inhibit the Bacillus cereus spor-lytic enzyme (PDB ID: 4PHQ) and Cytolysin A (ClyA) CC6/264 ox (6-303) SleL (PDB ID: 4S3J) compared to other studied ligands. Our findings may open the door for the design of a collection of proficient pyrrolidine-based drug-like molecules as potential antibacterial agents.

Keywords: 2-oxopyrrolidine, antibacterial agent, protein, inhibitors, docking.

通过计算机模拟研究对 (2,6-二乙基苯基)-5-氧代吡咯烷衍生物的潜在抗菌活性进行生化评估

摘要：一些研究人员的注意力已经集中在人类细菌活性的激增和对抗菌剂的耐药性上。人们发现，人们对开发长效抗菌剂的兴趣日益浓厚。因此，本研究的目的是使用计算机模拟方法来检查吡咯烷衍生物对所研究受体的特定抑制活性。因此，使用计算机模拟方法研究了(2,6-二乙基苯基)-5-
氧代吡咯烷衍生物的抑制活性。在本研究中，使用了各种软件程序，包括斯巴达14、自动对接工具、维纳自动对接和探索工作室。化合物9表现出最大的产生电子的倾向，如计算出的HOMO所示，根据LUMO和带隙，化合物5表现出接受电子的潜力最高，并且在所研究的其他

化合物中表现出优异的反应性。与其他研究的配体相比，化合物8至12显示出最强的抑制蜡状芽孢杆菌孢子溶解酶(PDB ID：4PHQ)和溶细胞素A (ClyA) CC6/264 ox (6-303) SleL (PDB ID：4S3J)的能力。我们的研究结果可能为设计一系列高效的吡咯烷类药物分子作为潜在的抗菌剂打开大门。

关键词：2-氧代吡咯烷，抗菌剂，蛋白质，抑制剂，对接。

1. Introduction

Bacteria have existed for centuries and are responsible for various types of infectious diseases that are harmful to human health [1]. Bacteria present a significant challenge in the realm of treatment, primarily as a result of the indiscriminate use of antibiotics. This issue has become one of the most pressing concerns in the field of healthcare as the widespread application of antibiotics significantly increases the risk of multidrug-resistant bacteria [2, 3]. Consequently, there is a pressing need for the discovery and development of powerful and effective antibacterial agents among researchers worldwide. As a result of extensive research conducted by scientists worldwide, there is an increasing demand for safe, effective, and non-resistant medications [4].

The development of therapeutically effective drugs relies heavily on the incorporation of heterocyclic scaffolds, several of which contain nitrogen as the active component. The presence of a substantial number of bioactive compounds serves as evidence of the significance of this approach [5-7]. Moreover, statistical analysis by Tajabadi et al. [8] indicated that approximately 70% of 15,822 scaffolds that belong to natural products possess non-flat properties, thereby representing a resourceful compendium for designing a new set of synthetic compounds [9].

The pyrrolidine moiety can be found in non-synthetic goods, and most phytochemicals can be sequestered from microbes and plants [10, 11]. Pyrrolidine, a scaffold, plays a crucial role in drug design and pharmaceutical research [12]. It appears 37 times in the United States Food and Drug Administration and has been reported to be among the usual five-membered ring compounds used in drug design and discovery [13]. According to Kairytė et al. [14], 2-pyrrolidinones are heterocycles with various bioactivities. As for 5-oxopyrrolidine, the bio-potential of hydrazones has attracted the interest of researchers in the field of drug discovery, drug design, and development [14]. Compounds of this nature have been found to exhibit analgesic, anti-inflammatory [15], antiviral [16], antimicrobial [15, 17], antitumor [15], anticonvulsant [19], and cardioprotective properties [20]. Additionally, these compounds have been shown to be effective antifungal agents [21].

Therefore, this study aimed to examine the inhibitory activity of pyrrolidine derivatives against the studied receptors using an in-silico method.

2. Materials and Methods

2.1. Optimization of the Studied Compounds

Twelve 2-pyrrolidine derivatives, which were synthesized by Žukauskas et al. [22], were modeled using ChemDraw Ultra12.0, and the studied compounds were optimized using the Spartan 14 software. These compounds were selected because of their high biological impact in the medicinal world, which has drawn the attention of many researchers globally.

Energy calculations and optimization were performed on the studied compounds using density functional theory with 6-31G* as the basis set [22]. In this study, a series of descriptors was obtained from the optimized molecules and reported appropriately (Fig. 1).

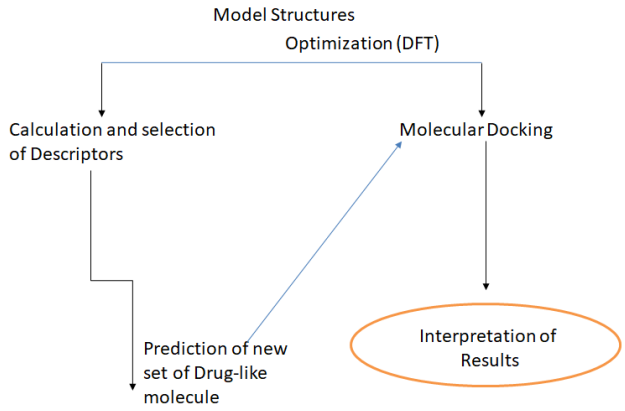
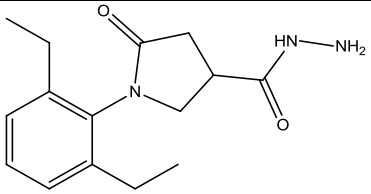
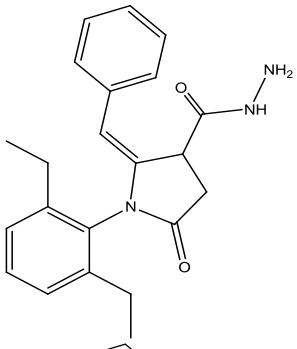
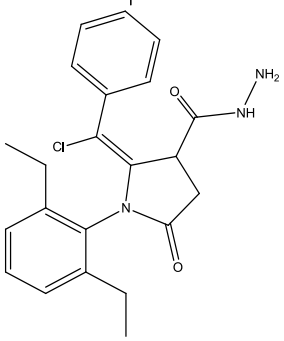
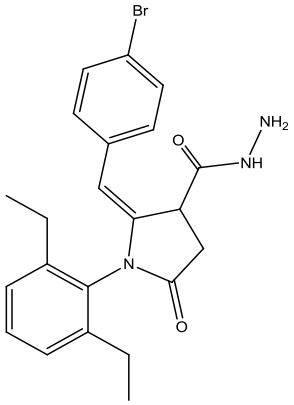
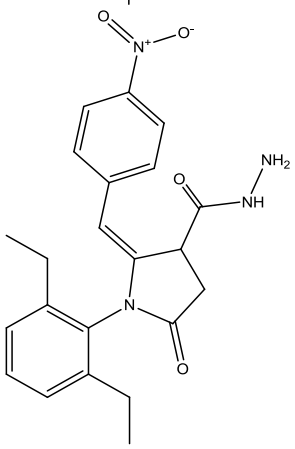
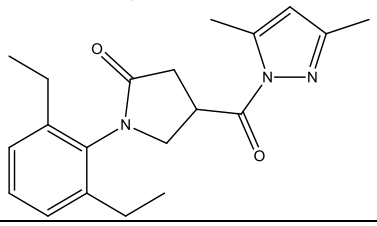
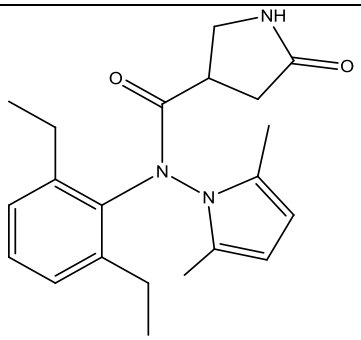
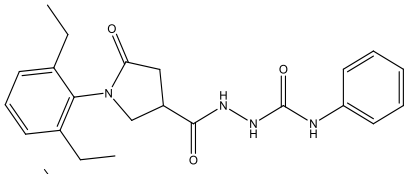
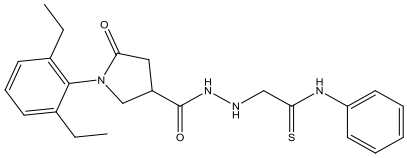
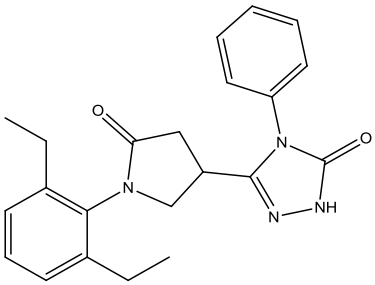
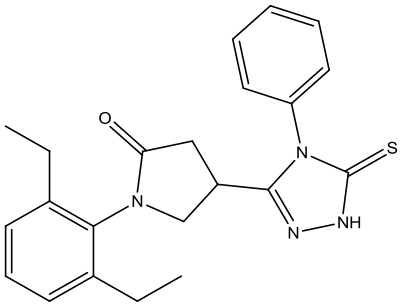
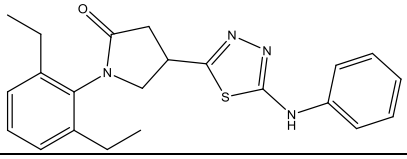


Fig. 1 Schematic structure of the method used (Developed by the authors)

Table 1 Two-dimensional structure of the 2-oxopyrrolidine derivative (Developed by the authors)

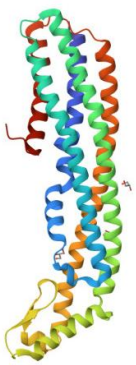
S/N	Structure	IUPAC Name
1		1-(2,6-diethylphenyl)-5-oxopyrrolidine derivatives
2		1-(2,6-Diethylphenyl)-5-oxopyrrolidine-3-carbohydrazide
3		N'-Benzylidene-1-(2,6-diethylphenyl)-5-oxopyrrolidine-3-carbohydrazide
4		N'-Benzylidene-1-(2,6-diethylphenyl)-5-oxopyrrolidine-3-carbohydrazide
5		N'-(4-Bromobenzylidene)-1-(2,6-diethylphenyl)-5-oxopyrrolidine-3-carbohydrazide
6		N'-(4-Nitrobenzilidene)-1-(2,6-diethylphenyl)-5-oxopyrrolidine-3-carbohydrazide

Continuation of Table 1

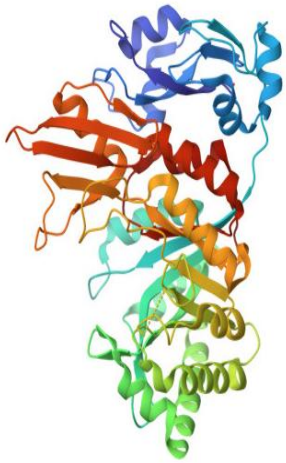
7		1-(2,6-Diethylphenyl)-N-(2,5-dimethyl-1Hpyrrol-1-yl)-5-oxopyrrolidine-3-carboxamide
8		2-(1-(2,6-Diethylphenyl)-5-oxopyrrolidine3-carbonyl)-N-phenylhydrazine-1-carboxamide
9		2-(2-(1-(2,6-Diethylphenyl)-5-oxopyrrolidine-3-carbonyl) hydrazinyl)-N-phenylethane thioamide
10		5--(1-(2,6-Diethylphenyl)-5-oxopyrrolidin3-yl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazol3-one
11		5-(1-(2,6-Diethylphenyl)-5-oxopyrrolidin3-yl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazol3-thione
12		1-(2,6-Diethylphenyl)-4-(5-(phenylamino)-1,3,4-thiadiazol-2-yl)pyrrolidin-2-one

2.2. Molecular Docking Study

Two receptors, ClyA CC6/264 ox (6-303) (PDB ID: 4PHQ) and Bacillus cereus spore cortex-lytic enzyme SleL (PDB ID: 4S3J), were retrieved from protein data bank. The two targets were subjected to Discovery Studio for cleaning and preparing them for docking. In addition, the binding sites in the two receptors were identified using the AutoDock Tools software, and the predicted values that describe the site where bioactivity could occur were as follows: center x -42.349625 y = 76.736500, z = 216.350750 for PDB ID: 4PHQ and center x = -30.844000 y = -2.772900 z = 111.132800 for PDB ID 4S3J. Docking calculations were executed on the studied complexes using the AutoDock Vina software [22], and the predicted results were reported.



A



B

Fig. 2 A - ClyA CC6/264 ox (6-303) SleL (PDB ID: 4S3J); B - Bacillus cereus spore-lytic enzyme (PDB ID: 4PHQ) (The authors)

3. Results and Discussion

3.1. Calculated Descriptors from (2,6-Diethylphenyl)- 5-Oxopyrrolidine Derivatives

Table 2 shows the calculated molecular descriptors of the studied compounds derived from the optimization using Spartan'14. The descriptors included the highest occupied molecular orbital energy (EHOMO), lowest unoccupied molecular orbital energy (ELUMO), band gap (BG), molecular weight (MW), Log P, volume, polar surface area (PSA), polarizability, dipole moment, hydrogen bond acceptor, energy band gap, area, and hydrogen bond donor. These molecular descriptors revealed some antibacterial activities of 1-(2,6-dimethylphenyl)-5-oxopyrrolidine derivatives.

Table 2 Calculated molecular descriptors for optimized compounds (Developed by the authors)

Mol	EHOMO	ELUMO	BG	MW	LogP	Volume	PSA	Pol	HBD	HBA
1	-6.13	-0.19	-5.94	275.352	-0.27	291.62	70.17	63.63	2	5
2	-5.89	-0.41	-5.48	363.461	0.36	389.99	68.584	71.71	2	5
3	-5.89	-0.71	-5.18	397.906	0.22	403.4	70.211	72.87	2	5
4	-6.04	-0.74	-5.3	442.357	0.49	408.34	69.15	73.24	2	5
5	-6.29	-3.25	-3.04	408.458	-2.08	412.34	111.108	74.1	2	8
6	-6.1	-1.38	-4.72	339.439	1.01	364.92	39.947	69.86	0	5
7	-5.54	-0.74	-4.8	353.466	0.23	382.72	39.695	71.28	1	5
8	-6.02	-0.31	-5.71	394.475	-0.17	410.53	74.897	73.33	3	7
9	-5.75	-1.5	-4.25	424.569	0.21	440.01	60.354	76.06	3	7
10	-6.14	-0.68	-5.46	374.46	0.96	394.65	54.474	1.59	1	5
11	-5.58	-1.07	-4.51	392.527	2.24	401.35	40.024	72.86	1	5
12	-5.79	-0.99	-4.8	392.527	2.72	404.66	43.556	73.06	0	5
STD	-6.34	-0.44	-5.9	349.411	-0.2	331.9	98.344	66.9	2	7

EHOMO indicates the strength to donate electrons, while ELUMO indicates the strength to accept electrons [23, 24], and these have been observed to have a high impact on the reactivity of any compound. Therefore, Compound 9 possesses the highest electron-accepting strength. In addition, the compound with the lowest LUMO value, namely Compound 5, is expected to exhibit higher reactivity compared to the other compounds in the study. The lower the band gap, the higher the reactivity of any compound; thus, Compound 5 displays a greater propensity for reactivity than all other ligands.

Moreover, Lipinski's rule of five was observed for the studied compounds, and the descriptors considered were molecular weight $\leq$ 500, HBD $\leq$ 5, HBA $\leq$ 10, and Log P $\leq$ 5 [18]. As shown in Table 2, all the studied molecules had a tendency to act as drugs since they passed the Lipinski rule of five.

3.2. Calculated Binding Affinity

The predicted scoring for individual studied compounds is reported in Tables 3 and 4. As shown in Tables 3 and 4, the calculated scoring for the two targets were -4.9 kcal/mol, -5.5 kcal/mol, -5.6 kcal/mol, -5.5 kcal/mol, -5.6 kcal/mol, -5.6 kcal/mol, -4.9 kcal/mol, -6 kcal/mol, -5.5 kcal/mol, -6.1 kcal/mol, -5.5 kcal/mol, and -6.1 kcal/mol (4PHQ) and -5.2 kcal/mol, -5.3 kcal/mol, -5.2 kcal/mol, -5.3 kcal/mol, -5.3 kcal/mol, -5.3 kcal/mol, -5.1 kcal/mol, -6.1 kcal/mol, -6.5 kcal/mol, -5.6 kcal/mol, -5.8 kcal/mol,

and -6 kcal/mol (4S3J). The results displayed in the tables reveal the inhibitory activity of the studied ligands against the two targets. In Tables 3 and 4, it is evident that Compounds 8, 10, and 12 displayed a more potent inhibitory effect against Bacillus cereus spore-lytic enzyme (PDB ID: 4PHQ) than the referenced compound, while Compounds 8 to 12 exhibited a stronger inhibitory effect on the activity of ClyA CC6/264 ox (6-303) SleL (PDB ID: 4S3J) than the referenced compound (ampicillin).

Table 3 Binding affinity, residues, and non-bonding interaction of molecular compounds interacting with 4PHQ (Developed by the authors)

Compounds	Binding affinity	Amino acid residue	Non-bonding interaction
1	-4.9	LYS113, ARG261, ASP114, PHE262	Conventional Hydrogen Bond, Alkyl, Pi-Cation, Pi-Alkyl
2	-5.5	ILE115, LYS118, ILE117	Alkyl Pi-Alkyl
3	-5.6	GU106, PHE262, LYS113	Conventional Hydrogen Bond, Pi-Cation, Pi-Alkyl, Pi-Anion
4	-5.5		
5	-5.6	LYS118, LYS117, LYS115	Alkyl Pi-Alkyl
6	-5.6	ASP 114, ILE115, ILE117, LEU93, LYS118	Carbon Hydrogen Bond, Pi-Alkyl, Alkyl
7	-4.9	LYS113, PHE262, TYR263	Conventional Hydrogen Bond, Alkyl, Pi-Cation
8	-6.0	ALA111, ASP114, ILE117, LYS107, LYS118	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Amide-Pi Stacked, Alkyl, Pi-Alkyl
9	-5.5	ALA96, GLN92, LEU93, LEU100, ILE115, VAL89	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Alkyl, Pi-Alkyl, Pi-Sigma
10	-6.1	ALA96, ALA111, GLN92, ILE115, LEU93, LEU100, LYS118, VAL89	Conventional Hydrogen Bond, Alkyl, Pi-Alkyl, Pi-Sigma
11	-5.5	ALA96, ALA111, ASP102, LEU99, LEU100, LYS107, LYS108	Conventional Hydrogen Bond, Alkyl, Pi-Akyl, Pi-Alkyl, Pi-Cation, Pi-Sigma
12	-6.1	ALA108, ILE117, LYS113	Conventional Hydrogen Bond, Alkyl, Pi-Alkyl
STD	-6.3	ARG261, GLU106, LYS107, LYS113, PHE262	Conventional Hydrogen Bond, Alkyl, Pi-Alkyl, Pi-Anion Unfavourable Donor

Table 4 Binding affinity, residues, and non-bonding interaction of molecular compounds interacting with 4S3J (Developed by the authors)

Compounds	Binding affinity	Amino acid residue	Non-bonding interaction
1	-5.2	GLY91, TYR20, TYR55	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Alkyl, Pi-Pi Stacked
2	-5.3	LYS19, TYR55	Conventional Hydrogen Bond, Pi-Alkyl
3	-5.2	LYS19, TYR55	Conventional Hydrogen Bond, Pi-Alkyl
4	-5.3		
5	-5.3	LYS98, LYS101, PHE0	Alkyl, Pi-Alkyl, Pi-Sigma, Pi-Donor Hydrogen Bond, Unfavorable Positive
6	-5.3	TYR 95	Pi-Pi T-Shaped, Pi-Alkyl
7	-5.1	GLN93, LYS19, TYR20, TYR55	Conventional Hydrogen Bond, Alkyl, Pi-Aalkyl, Pi-Pi Stacked, Pi-Cation, Pi-Sigma
8	-6.1	ASN58, GUN93, LEU94, LYS50, LYS94, TYR55, TYR95	Conventional Hydrogen Bond, Alkyl, Pi-Alkyl, Pi-Sigma, Amide Pi-Stacked
9	-6.5	LYS101, GLU422, PHE0, TYR69	Conventional Hydrogen Bond, Attractive Charge, Pi-Cation, Pi-Sulphur, Salt Bridge
10	-5.6	GLN93, LYS50, TYR95	Conventional Hydrogen Bond, Pi-Alkyl, Pi-Pi T-Shaped
11	-5.8	GLN93, LYS50, TYR95	Conventional Hydrogen Bond, Pi-Alkyl, Pi-Pi T-Shaped
12	-6	ASN52, LYS98, PRO97, TYR95, VAL79	Conventional Hydrogen Bond, Alkyl, Pi-Alkyl, Pi-Sigma, Pi-Pi T-Shaped
STD	-5.5	ASN53, TYR55	Conventional Hydrogen Bond, Pi-Pi Stacked

The atom/compound attached to the parent compound was observed to enhance the biological ability of Compounds 8-12, and these made the selected compounds having the greatest strength compared to the others. Tables 3 and 4 show the non-bonding interactions and amino acids involved in the interactions after the docking study.

4. Conclusion

Twelve 2-pyrrolidine derivatives were examined using an in-silico approach. In this study, molecular descriptors were obtained using a quantum chemical study, and they proved to be reactive based on the calculated descriptors obtained from the compounds. In addition, all the studied compounds proved to be weak against ClyA and exhibited strong inhibition against the cortex-lytic enzyme SleL. This revealed that the derivatives of 2-pyrrolidine exhibited anti-gram-positive activity, which could be explored to design a range of efficient pyrrolidine-based drug-like molecules as potential anti-gram-negative bacterial agents.

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