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Original Research Article

Design, Synthesis and Pharmacological evaluation of Novel Pyrrolidine analogues as potent Antibacterial agents: Experimental and Molecular docking approach

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Abstract

Background: Pyrrolidine and its derivatives are extremely important in medicinal chemistry due to their enormous variety and possible pharmacological activity. Synthesis of various pyrrolidine derivatives of biological interest, which have been reported in a wide spectrum of pharmacological activities

Material and methods: According to a synthetic approach, a number of acetyl pyrrolidine 2-carboxamide compounds have been synthesized. Mass spectrum analysis, infrared, and proton nuclear magnetic resonance were used to analyze the synthesized compounds. These substances were examined for their antibacterial properties against a range of bacterial strains in order to determine their biological activity. Additionally, the molecular docking investigation confirmed the experimental conclusions.

Results: A variety of new pyrrolidine-2-carboxamide derivatives have been synthesized with good yield, successfully characterized by TLC, IR, NMR and Mass Spectra and evaluated for their antibacterial activity. Compound 1 with the pyrrolidine group (-7.4 kcal/mol) shown a strong binding affinity with compared to Streptomycin (-7.1 kcal/mol) with 3uzu binding protein in the docking.

Conclusion: All of the newly synthesized compounds showed moderate to good antibacterial activity against both Gram positive and Gram negative strains. When compared to Streptomycin, compounds with the pyrrolidine and piperazine groups exhibit the largest zone of inhibitions against three bacterial strains.

Keywords: Pyrrolidine, Antibacterial**,** Antimicrobial, Molecular docking, Streptomycin.

1. Introduction

Antimicrobial substances are used to treat and prevent infections. Antimicrobial agents include things like antibiotics, which kill bacteria, antifungals, which kill fungus, antivirals, which kill viruses, and antiparasitics, which kill parasites [1-6]. Bacterial resistance to widely used antibiotics has long been a global health epidemic and could pose a major threat to public health.

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Over the past ten years, antibiotics have been used extensively to treat a wide range of infectious diseases, which continue to rank among the world's top causes of death and morbidity. However, because of the widespread use of these antibiotics, bacteria that are resistant to many conventional antibiotics have emerged. Methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus are examples of such resistant bacteria, which place restrictions on the available therapeutic therapies. Creating new molecules is one potential strategy to combat this issue [7-8].

Piper nigrum, Vitis vinifera, and Cannabis sativa are natural sources of pyrrolidine, frequently referred to as azolidines. Four carbon atoms and one nitrogen atom makes up the five-membered ring of pyrrolidine, a cyclic amine.

The succinimid, which has the formula $C_4H_5NO_2$, is the parent chemical of the pyrrolidine family. It is an azacycloalkane, a saturated organic heteromonocyclic parent, and a pyrrolidine. Finding structurally new derivatives using a pyrrolidine ring as a core moiety is greatly aided by the scaffold's three-dimensional structure, which aids in binding with the target locations [9-13].
Synthesis of various pyrrolidine derivatives of biological interest, which have been reported in a wide spectrum of pharmacological activities such as antimicrobial, antitumor, anticonvulsant, antitubercular, analgesic activity, etc... The pyrrolidine ring is the essential feature of many biologically activecompounds [14-18]. Docking is a computational technique used in molecular modeling that determines the ligand's preferred orientation with respect to the receptor and confirms that the ligand and receptor are bonded together [19-22].

The present research work deals with the synthesis of the title parent compounds starting from substituted 1-(2-aminoacetyl)-N-(4-methoxyphenyl)pyrrolidine-2-carboxamide, followed by their molecular docking study and antibacterial screening.

2. METHODOLOGY

Materials and Methods

Chemicals and reagents:
All of the compounds were purchased from Vijay compounds, Merck, and Aldrich and were commercially accessible. All of the solvents and reactants were analytically pure and didn't require additional purification. The starting compounds, 1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (I) and 4-methoxybenzenamine (II) were purchased from Vijay chemicals, Mehsana. Streptomycin was purchased from National institutes of Food and drug control.

Instrumentation:
Thin layer chromatography (TLC) was performed on silica gel plates (silica gel GF254) visualized at 254 nm. Infrared (IR) spectra were measured on Bruker, Alpha- II. On a Bruker biospin AV400 device, 1H nuclear magnetic resonance (NMR) spectra were obtained at 400 MHz. A Q-TOF mass spectrometer (Impact II, Bruker) was used to get the high resolution mass spectra.

Molecular Docking study:
Software Used: AutoDock Vina 4.2.6
Procedure:Protein-ligandDocking

Study period:

The research study was conducted between October 2023 and April 2024, spanning duration of 7 months.

Study place:

Research study was conducted in Department of Pharmaceutical chemistry, Faculty of Pharmacy. The college is located in SRI campus of Vadasma, Mehsana, Gujarat.

Procedure for AutoDock Vinasoftware:
Firstly, choose the receptor protein target and ligand molecule file.

1. Prepare the receptor (protein) target file:

Download the protein structure in DBP format form Protein Data Bank (DBP). Remove unnecessary water atoms. Save as PDBQT file.

2. Preapre the Ligand file:

Draw the ligand structure using ChemDraw. Save as PDBQT file.
Both Protein and Ligand was saved in Docking Folder.

3. Running AutoDock Vina:
Lunch Autodock Vina:

Download and install AutoDock Vina 4.2.6. Lunch the software.
Load the PDBQT file of receptor and then ligand. Set the binding site coordinates. Choose the Docking algorithm (Vina) and set the parameters. Run the docking stimulation with click the “DOCK” button to start the stimulation. Wait for the stimulation to complete.

4.------ Analyzing the Results:

Evaluate the binding affinity (score) of each pose. Use PyMOL to visualize interactions.

Determination of Antibacterial activity

Microbial screening
The antibacterial activity of the above developed compounds was assessed and tested against Gram-positive bacteria, Bacillus substillis, and Staphylococcus aureus, and Gram-negative bacteria, Escherichia coli. The preliminary antibacterial activity was determined using the widely utilized Agar well diffusion method. The standard medication was streptomycin. The efficiency of antibiotics depends on a number of factors, such as the host's features, inoculum size, antimicrobial concentrations, and the bacterial condition (susceptibility and resistance, tolerance, persistence, and biofilm). The average diameter of the zone of inhibition of bacterial growth surrounding the discs, measured in millimeters, was

used to record the results for each tested substance (23-24).

Antibacterial activity measurement using Agar Well Diffusion Method:

Composition of Agar media:

- Nutrient Agar: 15%
- Peptone: 5%
- Sodium chloride: 5%
- Meat extract: 1.5%
- Yeast extract: 1.5%
- Final pH (after sterilization): 7.2 to 7.5 ±0.2
- Distilled water: up to 1000ml

Micro-organisms used:

Table 1: Micro-organisms used in Agar Well Diffusion

Micro-organism	Type
Escherichia coli	Gram negative
Bacillus substillis	Gram positive
Staphylococcus aureus	Gram positive

Standard Drug used:

Streptomycin was used as standard drug used in Agar Well Diffusion Method.

Preparation of synthetic compounds for microbiological assay:

Ten milligrams of each produced chemical were diluted in one milliliter of dimethyl sulfoxide (DMSO) as a solvent to create a stock solution. The Agar well diffusion method was used to assess the synthetic compounds' antibacterial properties.

Procedure of Agar Well Diffusion Method:

Using the standard precautions to prevent contamination, a suitable amount of the liquid agar media roughly 15 to 20 milliliters of melted agar was spread onto each sanitized Petri dish. The test organism was spread out on the solidified agar media once the liquid media had solidified. Every Petri dish was labeled in a particular manner. To make well, a sterile cork borer was utilized. The spread plate approach was used to inoculate the agar plates with the specific organism's suspension. Lastly, the test solution was added to the agar well plates. The plates were placed in a freezer for diffusion and then incubated for 24 hours at 37°C for bacteria in a B.O.D. incubator after the tested samples were added. The zone of inhibition, if any, for the given drug and organism was then measured in millimeters. Since every microbial strain utilized belonged to a non-invasive species within its genus, it was suitable for use in analytical studies. Gram-positive bacteria include *S. aureus* and *B. substillis*, while Gram-negative bacteria include *E. coli*.

Results

Chemistry:

Acetyl pyrrolidine 2-carboxamide derivatives were synthesized according to **Scheme 1**. According to designed scheme, six derivatives were prepared. All the intermediate and target molecules were confirmed by TLC, IR, NMR and Mass Spectra.

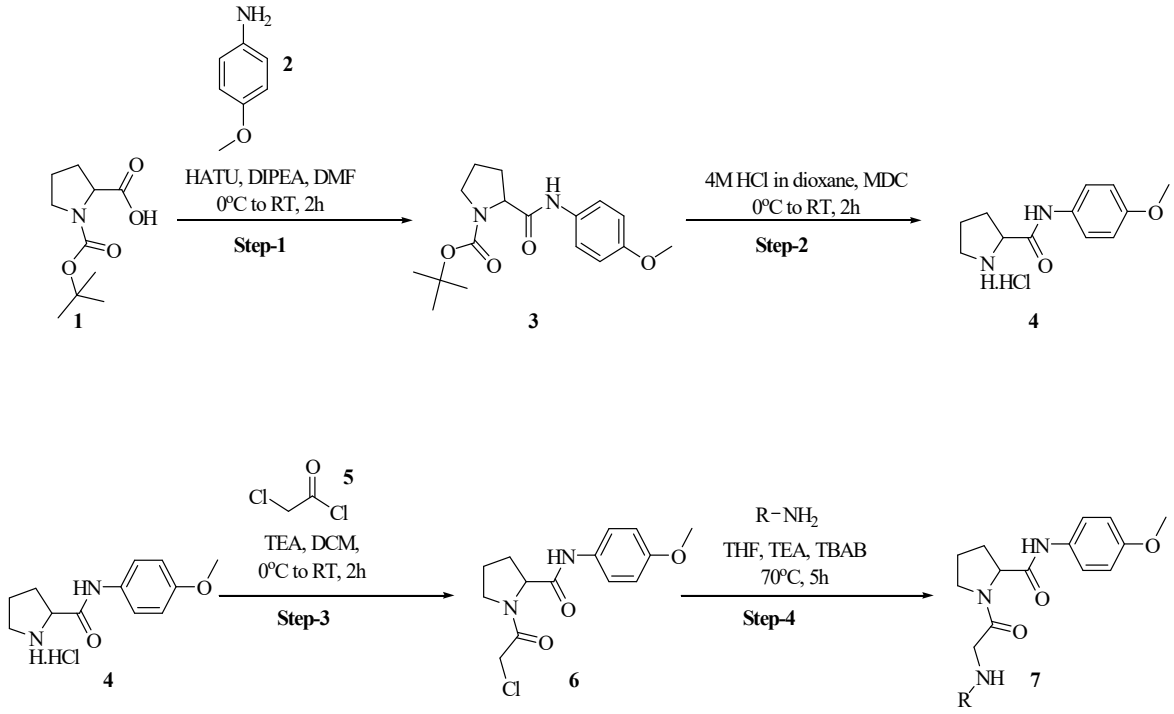
General procedure for synthesis of newer compounds:

Synthesis of tert-butyl 2-(4-methoxyphenylcarbamoyl)pyrrolidine-1-carboxylate(3) [step- 1]:

Assemble 100 ml three neck round bottom flask on magnetic stirrer, under nitrogen atmosphere Compound 1 (5 g, 0.023 mol, 1.0 eq.) in N,N-Dimethyl formamide (50 ml) was cooled to 0 ˚C and added HATU (9.82 g, 0.030 mol, 1.3eq.) and stirred at 0 ºC for 20min. Compound 2 (2.86 g, 0.023 mol, 1.0 eq.) was added followed by N,N-Diisopropylethylamine (9 g, 0.069 mol, 3 eq.) at 0˚C and reaction mixture was allowed to warmed at RT and stirred at RT for 2hrs. TLC tracked the reaction's progression. Following the completion of the reaction, the reaction mixture was extracted using ethyl acetate and put into ice-cold water. Step 1 product (3) (4g) was obtained by eluting the organic layer in 10% ethyl acetate in hexane after it had been cleaned with brine, dried over sodium sulphate, and concentrated under reduced pressure. The crude was then refined using silica gel chromatography.

Synthesis of N-(4-methoxyphenyl)pyrrolidine-2-carboxamide hydrochloride (4) [step- 2]:Assemble a 250 ml three neck round bottom flask with calcium chloride guard tube on magnetic stirrer, under nitrogen atmosphere Compound 3 (4 g, 0.0125 mol, 1.0 eq.) was dissolved in dichloromethane (40 ml). Reaction mixture was cooled to 0˚C and 4M HCl in dioxane (20 ml) was added drop wise using dropping funnel and reaction mixture was allowed to warm at RT and stirred at RT for 2hrs. TLC monitored the reaction's progression. The reaction mixture was concentrated under low pressure once the reaction was finished, yielding a crude product. This product was then refined using diethyl ether trituration to yield step 2 product (4), which is an HCl salt (2g).

Synthesis of 1-(2-chloroacetyl)-N-(4-methoxyphenyl)pyrrolidine-2-carboxamide(6) [step-3]: Assemble 100 ml three neck round bottom flask on magnetic stirrer, under nitrogen atmosphere Compound 4 (2 g, 0.0078 mol, 1.0 eq.) in dichloromethane (30 ml) was cooled to 0 ˚C and added triethylamine (3.94 g, 0.039 mol, 5 eq.) Compound 5 (2 g, 0.010 mol, 1.3 eq.) was added drop wise at 0 ˚C and reaction mixture was allowed to warm at RT and stirred at same temperature for 2 hrs.



Scheme 1: Synthetic Scheme of Target compounds

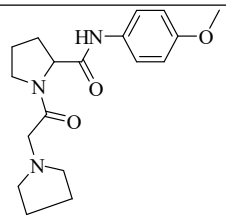
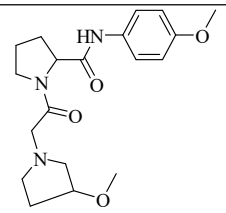
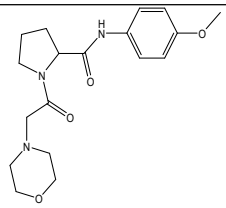
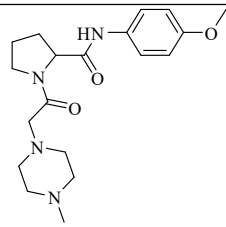
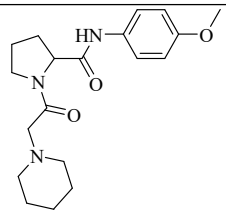
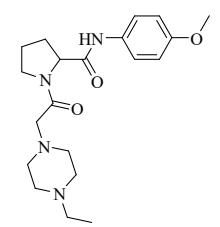
Physical and Spectral characterization of newer compounds:

Table 2: Physical characterization data of Intermediates

Intermediates	Molecular Formula	IUPAC name	Mol. Wt. (g/mol)	Melting Point (°C)	Yield %	*Rf
Step 1 product- **(3)**	$C_{17}H_{24}N_2O_4$	tert-butyl 2-(4-methoxyphenylcarbamoyl) pyrolidine-1-carboxylate	320.17	172-176	80.12	0.61
Step 2 product- **(4)**	$C_{12}H_{17}ClN_2O_2$	N-(4-methoxyphenyl)pyrrolidine-2- carboxamide hydrochloride	256.10	184-188	52.17	0.71
Step 3 product- **(6)**	$C_{14}H_{17}ClN_2O_3$	1-(2-chloroacetyl)-N-(4 methoxyphenyl)pyrrolidine-2- carboxamide	296.09	164-168	75.56	0.38

Mobile phase combination used for TLC:*Chloroform: methanol (9.5: 0.5)

Table 3: Physical characterization data of synthesized compounds

Comp.	Structure of compound	Molecular formula	IUPAC name	Mol. Wt. (g/mol)	Melting Point (°C)	Yield %	*Rf
1		$C_{18}H_{25}N_3O_3$	N-(4-methoxyphenyl)-1-(2- (pyrrolidin-1-yl)acetyl)pyrrolidine-2- carboxamide	331.19	189-192	60.23	0.52
2		$C_{19}H_{27}N_3O_4$	N-(4-methoxyphenyl)-1-(2-(3-methoxypyrrolidin-1-yl) acetyl)pyrrolidine-2- carboxamide	361.20	193-196	64.78	0.60
3		$C_{18}H_{25}N_3O_4$	N-(4-methoxyphenyl)-1-(2-morpholinoacetyl)pyrrolidine-2-carboxamide	347.18	158-162	71.16	0.49
4		$C_{18}H_{26}N_4O_3$	N-(4-methoxyphenyl) -1-(2- (piperazin-1-yl)acetyl)pyrrolidine-2-carboxamide	346.20	163-167	74.89	0.76
5		$C_{19}H_{27}N_3O_3$	N-(4-methoxyphenyl)-1-(2- (piperidin-1-yl)acetyl)pyrrolidine-2-carboxamide	345.21	171-174	67.89	0.47
6		$C_{19}H_{24}N_4O_3$	N-(4-methoxyphenyl)-1-(2-(4-methylpiperazin-1-yl)acetyl)pyrrolidine-2- carboxamide	360.22	178-180	66.34	0.58

Mobile phase combination used for TLC: *Chloroform: methanol (9:1)

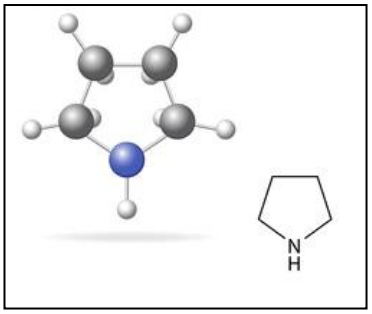
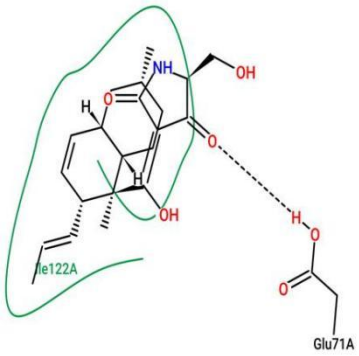
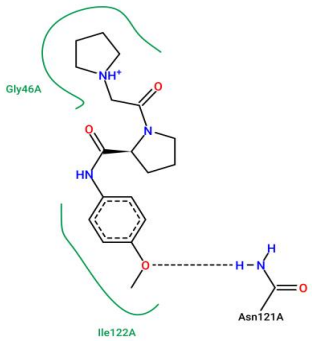


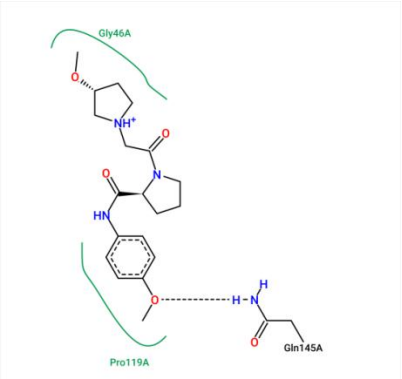
Fig. 1: 3D structure of Pyrrolidine



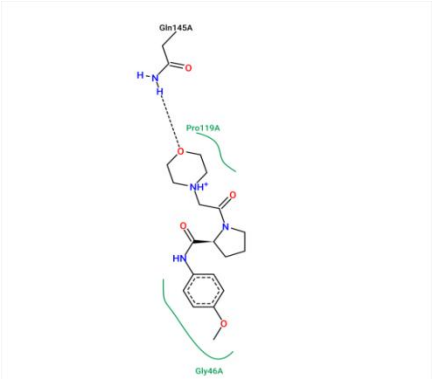
Standard drug



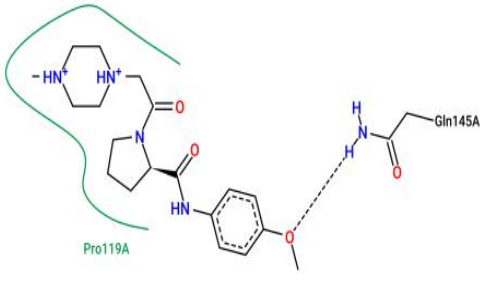
Compound 1



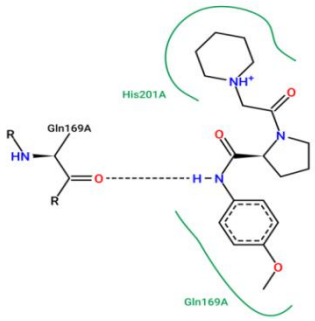
Compound 2



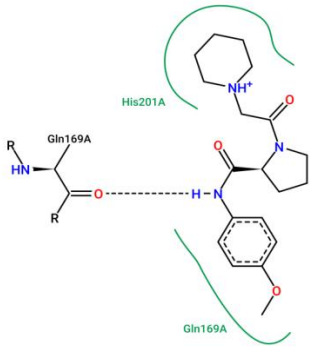
Compound 3



Compound 4

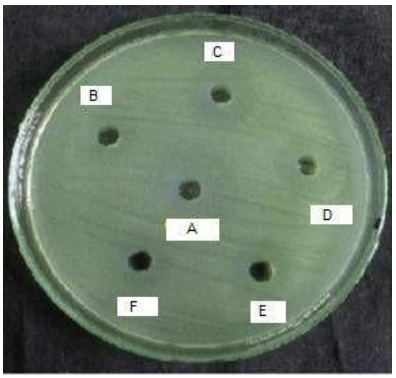


Compound 5

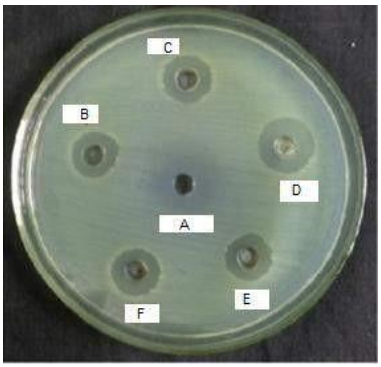


Compound 6

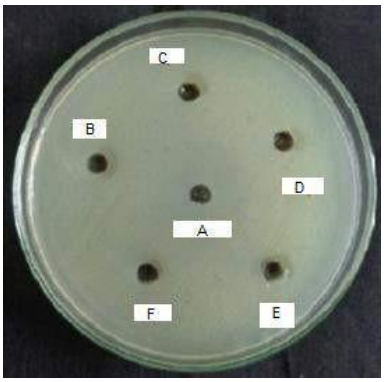
Fig. 2: 2D interaction image Molecular docking study of derivatives



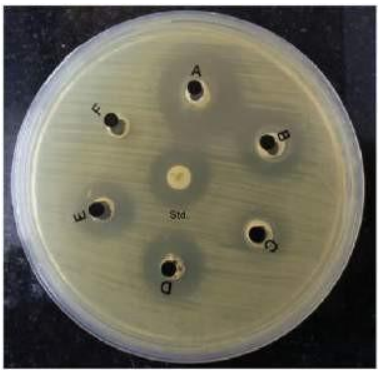
(a) Grampositive (*S.aureus)*



(b) Gram positive (*B.substillis)*



(c) Gramnegative(*E.coli)*



(d) Standard drug (Streptomycin)

Fi

Fig. 3: Observed Petri- plates for Anti bacterialactivity

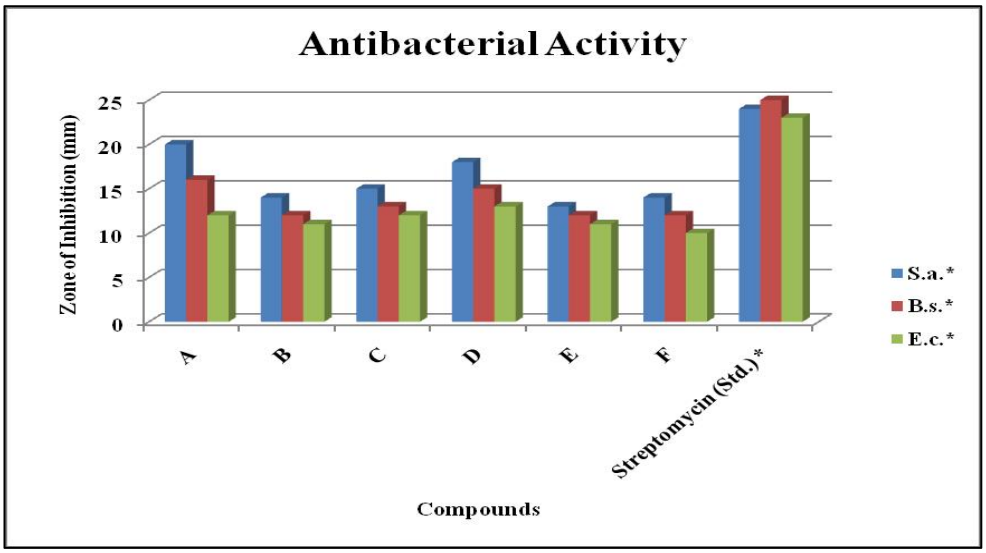


Fig. 4: Comparison graph of zone of inhibition of compounds and standard drugs

TLC tracked the reaction's progression. The reaction mixture was put into water and extracted using dichloromethane once the reaction was complete. Step 3 product-(6) (1.5g) was obtained by eluting the organic layer in 55% ethyl acetate in hexane after it had been cleaned with brine, dried over sodium sulphate, and concentrated under low pressure. The crude was then refined using silica gel chromatography.

Synthesis of substituted Acetyl pyrrolidine 2-carboxamide derivatives(7) [step- 4]:

In 30 ml seal tube, to a solution of Compound 6 (0.25 g, 0.00084 mol, 1.0 eq.) in tetrahydrofuran (10 ml) was added different heterocyclic compound (1.5 eq.) followed by triethylamine (0.255g, 0.0025mol, 3eq.) and tetrabutyl ammonium bromide (0.135g, 0.00042 mol, 0.5 eq.). Reaction mixture was heated at 70°C and stirred at same temperature for 5 hrs. Progression of reaction was monitored by TLC. After completion of reaction, reaction mixture was poured into water and extracted with ethyl acetate. Organic layer was washed with brine and dried over sodium sulphate and concentrated under reduced pressure to afforded crude which was purified by silica gel chromatography and product was eluted in 2-7% methanol in dichloromethane to afford substituted Acetyl pyrrolidine 2-carboxamide- **(7)**.

Spectral characteristics of synthesized compounds:

N-(4-methoxyphenyl)-1-(2-(pyrrolidin-1-yl)acetyl)pyrrolidine-2-carboxamide:

IR in cm^{-1} (KBr**)** 3056, 3027 (Aromatic CH), 2924 (Aliphatic CH), 3261, 3358 (NH- amine), 1701 (C=O Amide), 1158 (C=O), 1410(C≡N);

Mass M^+peak (m/z) 332.2 $(M+H)^+$

^{1}H NMR in δ ppm (DMSO, 400 MHz) 6.75-7.53 (Aromatic- H, Benzene), 8.00 (Aliphatic- H, 2^O NH^+), 1.59- 4.40 (Heterocyclic- H, Pyrrolidine), 3.73 (Aliphatic- H, Methyl), 3.25 (Aliphatic- H, Methylene)

N-(4-methoxyphenyl)-1-(2-(3-methoxypyrrolidin-1-yl)acetyl)pyrrolidine-2-carboxamide:

IR in cm^{-1} (KBr**)** 3056, 3027 (Aromatic CH), 2925 (Aliphatic CH), 3365, 3261 (NH- Amine), 1701 (C=O Amide), 1159 (C=O), 1410(C≡N);

Mass M^+peak (m/z) 362.4 $(M+H)^+$

^{1}H NMR in δ ppm (DMSO, 400 MHz) 6.75-7.53 (Aromatic- H, Benzene), 8.00 (Aliphatic- H, 2^O NH^+), 1.60- 4.40 (Heterocyclic- H, Pyrrolidine), 3.23- 3.73 (Aliphatic- H, Methyl), 3.25 (Aliphatic- H, Methylene)

N-(4-methoxyphenyl)-1-(2-morpholinoacetyl)pyrrolidine-2-carboxamide:

IR in cm^{-1} (KBr**)** 3058, 3027 (Aromatic CH), 2925 (Aliphatic CH), 3398, 3308 (NH- Amine), 1627 (C=O Amide), 1068 (C=O), 1410(C≡N);

Mass M^+ peak (m/z) 348.4 $(M+H)^+$

^{1}H NMR in δ ppm (DMSO, 400 MHz) 6.75-7.53 (Aromatic- H, Benzene), 8.00 (Aliphatic- H, 2^O NH^+), 1.92- 4.40 (Heterocyclic- H, Pyrrolidine), 2.37-3.56 (Heterocyclic- H, tetrahydro- 1,4- oxazine), 3.73 (Aliphatic- H, Methyl), 3.25 (Aliphatic- H, Methylene)

N-(4-methoxyphenyl)-1-(2-(piperazin-1-yl)acetyl)pyrrolidine-2-carboxamide:

IR in cm^{-1} (KBr**)** 3072, 3025 (Aromatic CH), 2833 (Aliphatic CH), 3369 (NH- Amine), 1701 (C=O Amide), 1187 (C=O), 1451 (C≡N);

Mass M^+ peak (m/z) 361.3 $(M+H)^+$

^{1}H NMR in δ ppm (DMSO, 400 MHz) 6.75-7.53

(Aromatic- H, Benzene), 8.00 (Aliphatic- H, 2^{O} NH^{+}), 1.92- 4.40 (Heterocyclic- H, Pyrrolidine), 2.27-3.73 (Aliphatic- H, Methyl), 2.46- 3.25 (-CH_2, Methylene)

N-(4-methoxyphenyl)-1-(2-(piperidin-1-yl)acetyl)pyrrolidine-2-carboxamide:
IR in cm^{-1} (KBr**)** 3074 (Aromatic CH), 2895 (Aliphatic CH), 3355, 3292 (NH- Amine), 1706, 1646 (C=O Amide), 1147 (C=O), 1447(C≡N);

Mass M^{+}peak (m/z) 346.4 $(M+H)^{+}$

^{1}H NMR in δ ppm (DMSO, 400 MHz) 6.75-7.53 (Aromatic- H, Benzene), 8.00 (Aliphatic- H, 2^{O} NH^{+}), 1.92- 4.40 (Heterocyclic- H, Pyrrolidine), 1.50-2.24 (Heterocyclic- H, Piperidine), 3.73 (Aliphatic- H, Methyl), 3.25 (Aliphatic- H, Methylene)

N-(4-methoxyphenyl)-1-(2-(4-methylpiperazin-1-yl)acetyl)pyrrolidine-2-carboxamide:
IR in cm^{-1} (KBr**)** 3062, 2988 (Aromatic CH), 2933 (Aliphatic CH), 1653 (C=O Amide), 1142 (C=O), 1425 (C≡N);

Mass M^{+} peak (m/z) 375.3 $(M+H)^{+}$

^{1}H NMR in δ ppm (DMSO, 400 MHz) 6.75-7.53 (Aromatic- H, Benzene), 8.00 (Aliphatic- H, 2^{O} NH^{+}), 1.92- 4.40 (Heterocyclic- H, Pyrrolidine), 1.00-3.73 (Aliphatic- H, Methyl), 2.40-3.25 (-CH_2, Methylene)

Molecular Docking study:

Table 4: Docking score of derivatives

Compounds	Docking Binding energy(kcal/mol)
Standard	**-7.1**
Compound- 1 (A)	**-7.4**
Compound- 2 (B)	-8.0
Compound- 3 (C)	-7.5
Compound- 4 (D)	-7.8
Compound- 5 (E)	-8.1
Compound- 6 (F)	-7.5

From the docking binding energy, we conclude that compound 1, compound 3, compound 4 and compound 6 may give antibacterial activity. Among all these compounds, **compound 1 may give better antibacterial activity**.

Antibacterial activity:
All of the newly synthesized compounds displayed modest antibacterial activity against both Gram positive and Gram negative bacteria, according to the results. Compared to other produced compounds, compounds 1 and 4 were the most effective against three bacterial strains, but they were not as effective as the reference medication.

Table 5: The zone of inhibition values (mm) of compounds

Compounds*	Zone of Inhibition (mm)		
	Gram positive		Gram negative
	S.a.*	B.s.*	E.c.*
Compound- 1 (A)	**20**	**16**	**12**
Compound- 2 (B)	14	12	11
Compound- 3 (C)	15	13	12
Compound- 4 (D)	**18**	**15**	**13**
Compound- 5 (E)	13	12	11
Compound- 6 (F)	14	12	10
Streptomycin (Std.) *	24	25	23
DMSO	---	---	---

*E.c. - *Escherichia coli* *B.s.-*Bacillus substillis*

*S.a.- *Staphylococcus aureus*

DMSO - No activity

*std. drug concentration: 0.1 mmol & Test compound concentration: 1 mmol

Discussion:

A variety of new pyrrolidine-2-carboxamide derivatives have been synthesized with good yield, successfully characterized by TLC, IR, NMR and Mass Spectra and evaluated for their antibacterial activity. Compared to the other produced compounds in the series, the compounds 1 and 4 with the pyrrolidine and piperazine groups, respectively exhibited good antibacterial action. Furthermore, the outcomes of molecular docking and their interactions are supported by these in-vitro assessments in various biological models and thorough investigations.

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3. CONFLICT OF INTEREST:

The authors had no conflict of interest with respect to conduct, authorship, or publication of this research work.

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