RESEARCH ARTICLE

In silico Design of Novel Amino Indole – Piperazine Derivativesas Antibacterial Agents

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ABSTRACT
Over the past few decades, the use of antibiotics has highly improved public health worldwide. However, due to the improper use of antibiotics, bacteria develop drug resistance rapidly to most antibiotics. Nowadays, the issue of antibacterail resistance is critical and is a global problem. Indole-Piperazine based derivatives have been used to treat and develop antibiotics against Gram-positive, Gram-negative, and multidrug-resistant microorganisms. The results of the antimicrobial assay showed that most of the products exhibited promising activity against the tested bacterial strains, especiallyS. aureu, B. subtilis, P. aeruginosaand E. coli. The molecular docking results illustrate superior binding affinity of RIPA 1-10 titled compounds, RIPA 6 & RIPA7 are forming stable molecular interactions within the active site compared to the standard antibacterial agent and showing potent zone of inhibition.
Keywords: Indole-piperazine, antimicrobial resistance, antibiotics.
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INTRODUCTION

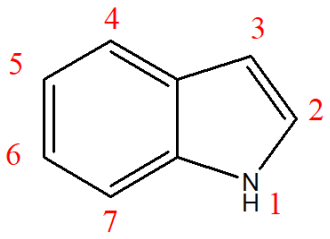
Indole was initially discovered in the 1860s by Baeyer and associates while examining the structure of indigo. It is now widely used as a pharmacophore in many pharmacological applications[1]. Indole is an aromatic fused heterocyclic organic compound with a bicyclic structure, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery[1].

The Indole basic structure composed of a six membered benzene ring fused with a five-membered pyrrole ring. The two rings fused together to constitute the basic nucleus 1H-indole.The indole nucleus is a cyclic, planar and conjugated fused aromatic heterocyclic molecule with delocalization of 10π electrons (8π electrons from 4 double bonds and 2π electrons from nitrogen), making it aromatic according to Huckel's rule. Indole molecule act as a weak base, protonates only in the presence of strong acid. The 3-position of the nucleus has the high electron density and is most reactive for electrophilic substitution. However, the somewhat acidic character of the NH makes it weak to N-substitution reactions under basic conditions. Here showed graphical structure of indole moiety[2]figure 1.

Physical Properties of Indole Nucleus

Chemical Formula: C_8H_7N
IUPAC Name: 1H- indole
Molecular Weight(Molar mass): 117.15 g/mol
Appearance: Colorless crystalline Solid
Odour: Pleasant and flowery smell
Density: 1.1747 g/cm³
Melting Point: 52-55 °C
Boiling Point: 253 to 254 °C:Sparingly soluble in cold water, but soluble in hot water and most organic solvents like chloroform, methanol, and DMSO
Hydrogen Bond Acceptor: 0
Hydrogen Bond Donor: 1
Lipinski Rules (drug-likeness): Yes, Zero violations
Xlogp3 (cLogP):2.05 (Moderately lipophilic)
Molecular Shape: Planar

Indole exhibits diverse biological activities, making it a significant scaffold in medicinal chemistry for developing pharmaceuticals with anticancer, anti-inflammatory, antimicrobial, antiviral, and antidiabetic properties, among others. Its core structure is found in various natural compounds, including neurotransmitters like serotonin and hormones like indole-3-acetic acid (IAA). Indole derivatives are actively researched for their efficacy against cancer cells, infectious agents, and metabolic



1*H*-indole

Figure 1: Structure of Indole Scaffold

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disorders, with ongoing efforts to optimize their therapeutic potential through structural modification and computational modeling[3].

Piperazines, especially disubstituted heterocyclic scaffold, exhibit a broad range of biological properties, as reported in the literature. In the last decade, a series of piperazine derivatives have been synthesized and reported for their antibacterial activity demonstrated that these targets had the ability to suppress the bacterial growth. As a result of the study for the lead compounds, it has been reported that inhibitory action was observed against gram positive and gram negative in many indole-carrying small molecules. Thus, based on these observations in the literature, the present study was initiated with the aim of identifying the structural requirements of the indole-based piperazines in terms of antibacterial activity. The versatile utility of Mannich bases on the effectiveness and inhibitory of the parent compounds RIPA 1-10 prompted us to prepare a series of piperazinopropanamide derivatives of indole structure and evaluate their antibacterial activity against different bacterial strains[4]. Here graphical representation of biological activities of indole scaffold in figure 2.

EXPERIMENTAL METHOD

Synthesis of Indole – Piperazine Derivatives

Step-I: Synthesis of N-(1H-indol-3-yl)acetamide

Acetyl chloride (0.055 mol) was added to a solution of the appropriate 3-amino indole (0.01 mol) in glacial acetic acid (10 ml) in the presence of dimethylaluminium chloride or diethylaluminium chloride. The reaction proceeds under mild conditions at room temperature, which was purified by column chromatography on silica gel (toluene: ethyl acetate: formic acid) to give the required 3-indole-3-acetamide[4].

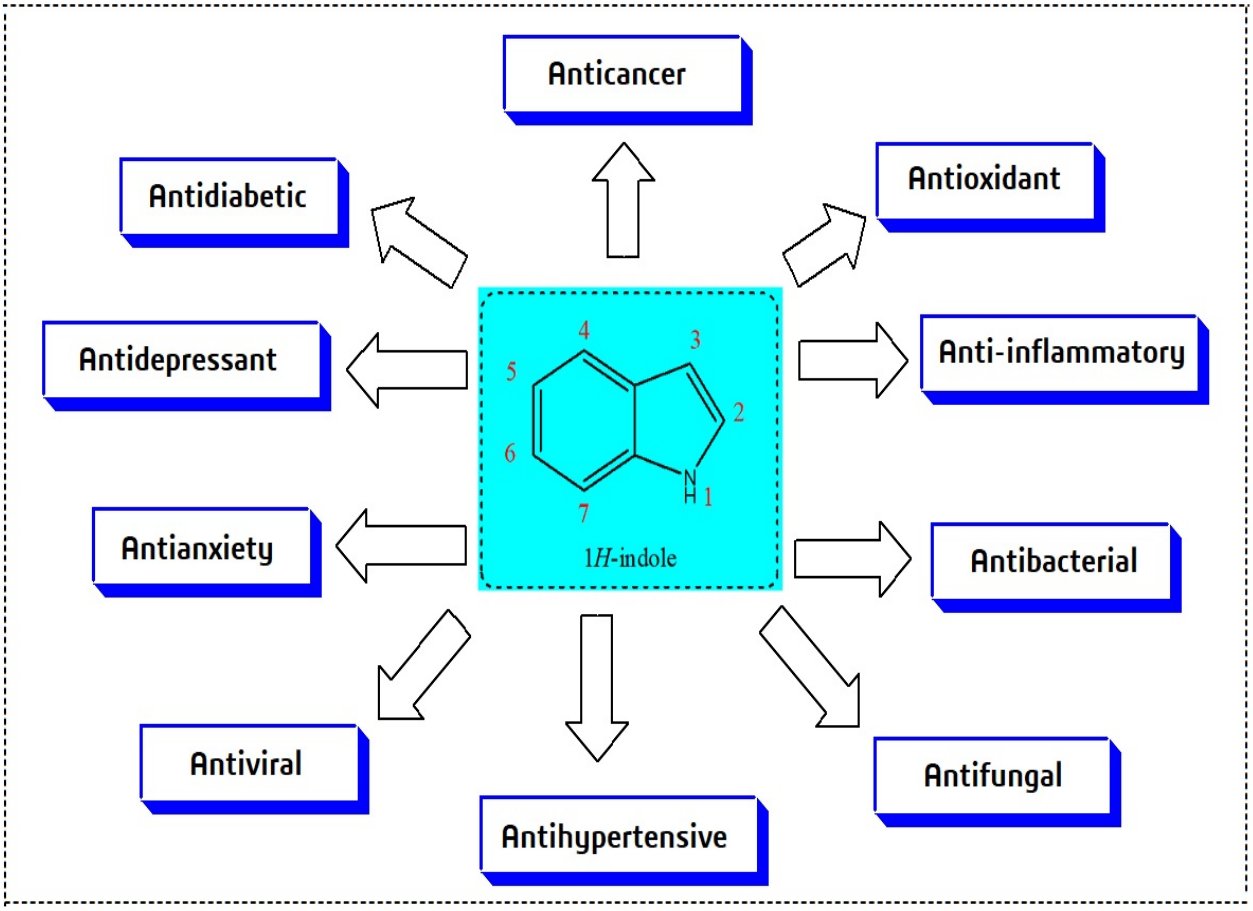


Figure 2: Graphitic representation of Biological Activities of Indole Scaffold

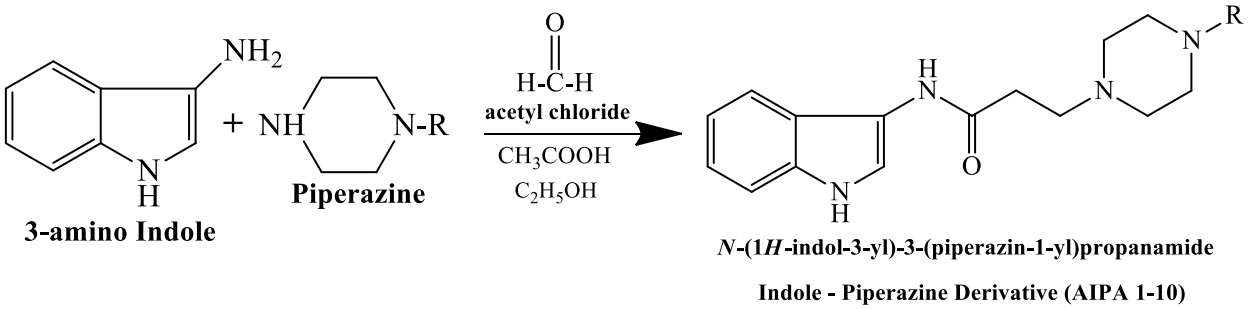


Figure 2: Scheme of Preparation of Indole – Piperazine Derivatives

Table 1: Substituents of synthesized compounds of Scheme – I (RIPA 1-10)

S.No.	Compounds name	Substituents
		R
1	RIPA-1	4-hydroxyphenly
2	RIPA-2	4-chlorophenyl
3	RIPA-3	4-bromophenyl
4	RIPA-4	4-fluorophenyl
5	RIPA-5	4-methoxyphenyl
6	RIPA-6	4-nitrophenyl
7	RIPA-7	4-aminophenyl
8	RIPA-8	benzoic acid
9	RIPA-9	benzene sulphonic acid
10	RIPA-10	3-chloro-4-nitrophenyl

Step-II: Synthesis of N-(1H-indol-3-yl)-3-(piperazin-1-yl)propanamideCompounds (RIPA 1-10)

The target N-(1H-indol-3-yl)-3-(piperazin-1-yl)propanamide compounds (RIPA 1-10) were prepared by Mannich reaction between indole-3-acetamide (1) and appropriate piperazines (2) with formaldehyde in the presence of ethanol at room temperature (Scheme-2).

Although a group of compounds were reported in the table-1, RIPA 1-10 all the compounds of the series were synthesized with a view to structural elucidation, and evaluation of the structure activity relationship[4]. The schematic preparation route showed in figure 2.

List of Compounds to be Synthesized (Table 2)

Table 2: structures of synthesized titled compounds RIPA 1-10

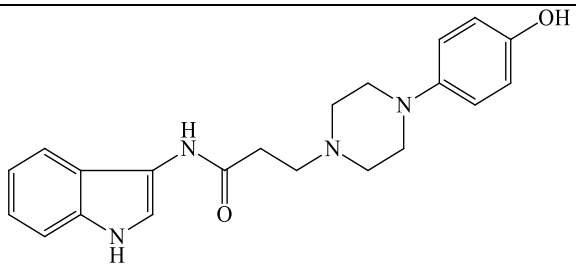
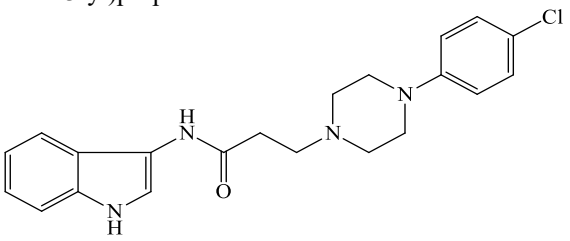
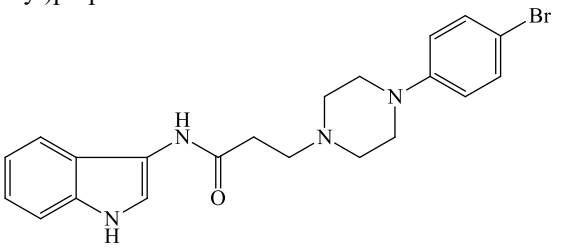
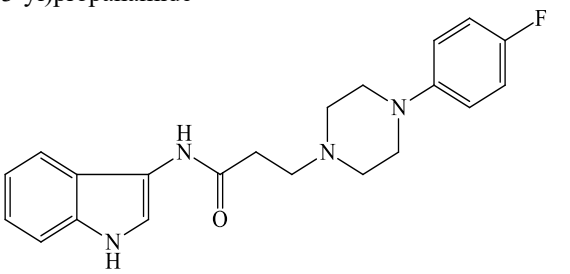
S. No.	Compound ID	Structure and its IUPAC name	Smile
1	RIPA-1	 3-(4-(4-hydroxyphenyl)piperazin-1-yl)-N-(1H-indol-3-yl)propanamide	O=C(CCN1CCN(C2=CC=C(O)C=C2)CC1)NC3=CNC4=CC=CC=C43
2	RIPA-2	 3-(4-(4-chlorophenyl)piperazin-1-yl)-N-(1H-indol-3-yl)propanamide	O=C(CCN1CCN(C2=CC=C(Cl)C=C2)CC1)NC3=CNC4=CC=CC=C43
3	RIPA-3	 3-(4-(4-bromophenyl)piperazin-1-yl)-N-(1H-indol-3-yl)propanamide	O=C(CCN1CCN(C2=CC=C(Br)C=C2)CC1)NC3=CNC4=CC=CC=C43
4	RIPA-4	 3-(4-(4-fluorophenyl)piperazin-1-yl)-N-(1H-indol-3-yl)propanamide	O=C(CCN1CCN(C2=CC=C(F)C=C2)CC1)NC3=CNC4=CC=CC=C43

Table 2: structures of synthesized titled compounds RIPA 1-10

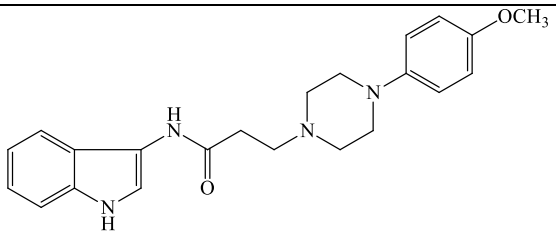
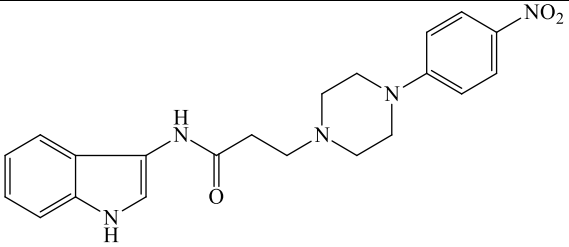
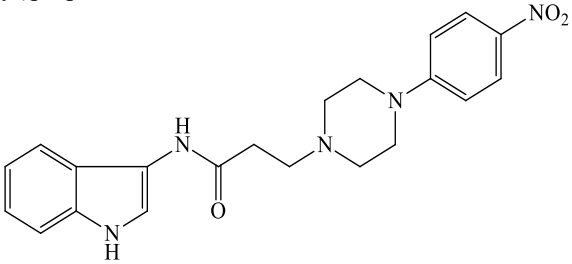
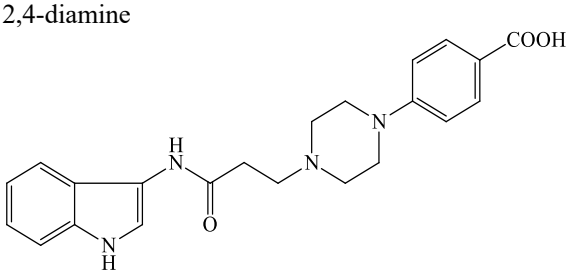
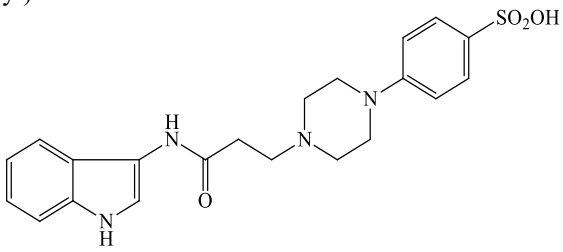
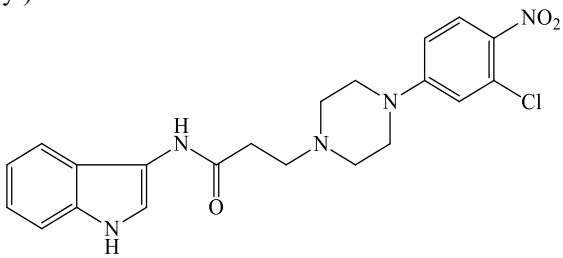
S. No.	Compound ID	Structure and its IUPAC name	Smile
5	RIPA-5	 N-(1H-indol-3-yl)-3-(4-(4-methoxyphenyl)piperazin-1-yl)propanamide	O=C(CCN1CCN(C2=CC=C(OC)C=C2)CC1)NC3=CNC4=CC=CC=C43
6	RIPA-6	 N-(1H-indol-3-yl)-3-(4-(4-nitrophenyl)piperazin-1-yl)propanamide	O=C(CCN1CCN(C2=CC=C([N+]([O-])=O)C=C2)CC1)NC3=CNC4=CC=CC=C43
7	RIPA-7	 6-(4-aminophenyl)-N4-(1H-indol-3-yl)pyrimidine-2,4-diamine	O=C(CCN1CCN(C2=CC=C([N+]([O-])=O)C=C2)CC1)NC3=CNC4=CC=CC=C43
8	RIPA-8	 4-(6-(1H-indol-3-ylamino)-2-aminopyrimidin-4-yl)benzoic acid	O=C(CCN1CCN(C2=CC=C(C(O)=O)C=C2)CC1)NC3=CNC4=CC=CC=C43
9	RIPA-9	 4-(6-(1H-indol-3-ylamino)-2-aminopyrimidin-4-yl)benzenesulfonic acid	NC1=NC(C4=CC=C(S(=O)(O)=O)C=C4)=CC(NC2=CNC3=C2C=CC=C3)=N1
10	RIPA-10		NC1=NC(C4=CC(Cl)=C([N+]([O-])=O)C=C4)=CC(NC2=CNC3=C2C=CC=C3)=N1

Table 2: structures of synthesized titled compounds RIPA 1-10

S. No.	Compound ID	Structure and its IUPAC name	Smile
		3-(4-(3-chloro-4-nitrophenyl)piperazin-1-yl)-N-(1H-indol-3-yl)propanamide	

Table 3: -CDOCKER Interaction Energies of synthesized titled compounds RIPA 1-10

S. No.	CID	-CDOCKER INTERACTION ENERGY (PDB: 2OLV)	-CDOCKER INTERACTION ENERGY (PDB:5M18)
1	RIPA-1	44.7004	47.3623
2	RIPA-2	37.5121	39.9467
3	RIPA-3	39.3512	33.1564
4	RIPA-4	38.5323	48.2571
5	RIPA-5	39.9332	29.1351
6	RIPA-6	35.5427	37.6103
7	RIPA-7	38.9753	35.1592
8	RIPA-8	42.6779	40.3270
9	RIPA-9	36.2367	39.8817
10	RIPA-10	43.3352	32.7323
11	Lenezolid	48.6962	46.5583
12	Ciprofloxacin	58.7021	53.2901

*CID – Compound ID

Insilico Studies (Table 3)

Molecular docking is a computational method in drug discovery and development that predicts the optimal interaction between a protein and a ligand while evaluating their binding energy, helping in the identification of potential drug candidates by analyzing their binding efficiency and stability by using Biovia discovery studio software[6]. In the present study, the binding energies (-CDOCKER Interaction Energy) of the all synthesized (RIPA 1-10) target mannich basesshowed in bellowed table3.

Analysis of Drug-likeness Properties (Table 4)

The compounds make use of better antimicrobial activity with E. coli and S. aureus were analyzed for their drug-likeness properties[7]. ADMET of RIPA 1-10 was also analyzed since it is involved in protein ligand interaction with the mannich bases. SwissADME webserver was used for the analysis of Lipinski's rule of five (RO5), Ghose, Veber, Egan, and Muegge rules[6]. The all titled target compound ADMET details are showedbellow table 4.

Antibacterial Activity (Table 5)

The antibacterial activities of newly synthesized compounds (RIPA 1-10) were studied against S. aureu, B. subtilis, P. aeruginosaand E. coli on paper disc diffusion method[5]. The results of antibacterial activity (inhibition zone of discs) against all bacterial strainsare given in table 5.

RESULTS AND DISCUSSION

The synthetic route to the target compounds (RIPA 1-10) is presented in Scheme 1. The key intermediate, N-(1H-indol-3-yl)acetamide was synthesized from 3-amino indole (3AI). Initially, 3-aminoindole acetylation with acetyl chloride in the presence of g. acetic acid[7]. The **final mannich base** wascarried out by reacting it with Piperazine and formaldehyde inethanol at room temperature.The compositions and structures of

Table 4: ADMET analysis and drug-likeness properties of synthesized titled compounds

Compound ID	Molecular Formula	Mol. Wt. (g/mol)	No.of Rotatable bonds	No of H-bond acceptors	No of H-bond donors	ClogP	PSA	Solubility	Druglikeness (Lipinski/Ghose/Veber)Follow /Violations	Bio-availability
RIPA-1	$C_{21}H_{24}N_4O_2$	364.44	6	3	3	2.19	71.60	Poorly Soluble	Yes / 0	0.55
RIPA-2	$C_{21}H_{23}ClN_4O$	382.89	6	2	2	3.16	51.37	Poorly Soluble	Yes / 0	0.55
RIPA-3	$C_{21}H_{23}BrN_4O$	427.34	6	2	2	3.60	51.37	Poorly Soluble	Yes / 0	0.55
RIPA-4	$C_{21}H_{23}BrN_4O$	366.43	6	3	2	2.92	51.37	Poorly Soluble	Yes / 0	0.55
RIPA-5	$C_{22}H_{26}N_4O_2$	378.47	7	3	2	2.57	60.60	Poorly Soluble	Yes / 0	0.55
RIPA-6	$C_{22}H_{26}N_4O_2$	378.47	7	2	2	2.56	60.45	Poorly Soluble	Yes / 0	0.55
RIPA-7	$C_{21}H_{23}N_5O_3$	393.44	7	3	2	1.89	97.17	Poorly Soluble	Yes / 0	0.55
RIPA-8	$C_{22}H_{24}N_4O_3$	392.45	7	4	3	1.75	88.043	Poorly Soluble	Yes / 0	0.55
RIPA-9	$C_{21}H_{24}N_4O_4S$	428.50	7	5	3	1.74	132.344	Poorly Soluble	Yes / 0	0.55
RIPA-10	$C_{21}H_{122}ClN_5O_3$	242.88	7	4	2	2.72	119.75	Poorly Soluble	Yes / 0	0.55
CIPROFLOXACIN	$C_{17}H_{18}FN_3O_3$	331.34	3	5	2	0.182	74.57	Soluble	Yes / 0	0.55

Table 5: Antibacterial activities of N-(1H-indol-3-yl)-3-(piperazin-1-yl)propanamide compounds (RIPA 1-10)

S.No.	CID	Conc. in µg/ml	Zone of Inhibition (in mm)			
			B. subtilis	S. aureus	E. coli	P. aeruginosa
1	RIPA 1	100	8	10	8	9
		150	10	12	10	10
		200	13	13	11	12
2	RIPA 2	100	9	8	7	8
		150	11	10	9	9
		200	12	11	10	11
3	RIPA 3	100	11	10	9	8
		150	13	12	12	11
		200	16	14	14	13
4	RIPA 4	100	7	8	8	9
		150	9	10	10	11
		200	11	12	11	14
5	RIPA 5	100	8	10	9	10
		150	10	12	11	13
		200	12	14	12	15
6	RIPA 6	100	12	11	10	10
		150	14	13	12	12
		200	18	18	16	16
7	RIPA 7	100	11	11	9	9
		150	13	12	10	10
		200	16	16	18	16
8	RIPA 8	100	11	10	10	9
		150	14	13	14	12
		200	16	15	15	14
9	RIPA 9	100	10	11	10	9
		150	13	14	13	11
		200	15	16	15	14
10	RIPA 10	100	8	9	10	8
		150	9	11	11	10
		200	11	13	12	11

Standard drug: Ciprofloxacin (10µg/ml) shows 20mm Zone of inhibition

compounds **RIPA 1-10** were confirmed by elemental analysis, IR and 1HNMR spectroscopy, and mass spectrometry. The structures of synthesized titled compounds **RIPA 1-10** are showed in Table 2.

ADME/T Analysis and Drug-likeness Properties

Drug-likeness properties i.e., absorption, distribution, metabolism, excretion and toxicity (ADMET) and their analysis are significant parameters for evaluate a compound's potential as a drug candidate[6]. These properties can be evaluated using online tools such as SwissADME. The drug-likeness characteristics of Ciprofloxacin, Mannich bases are illustrated in futher information Table 4.For a compound to be considered ideal, its physicochemical properties should fall within the range. Streptomycin exhibits favourable drug-like properties for most parameters. One of the key criteria for determining oral bioavailability is Lipinski's Rule of Five (RO5). The title target compounds (RIPA 1-10) are passed RO5 without any violations. Additionally, the compounds were evaluated against Ghose, Veber, Egan, and Muegge rules, as summarized in supplementary information Table 4. Overall, all targeted title compounds (RIPA 1-10), and the standard antibiotic streptomycin exhibit drug-likeness characteristics, were indicating their potential as drug candidates[8].

CONCLUSIONS

In conclusion, a series of new indole Piperazine derivatives, N-(1H-indol-3-yl)-3-(piperazin-1-yl)propanamide compounds **(RIPA 1-10)**, were synthesized as potential biologically active compounds. All the products were evaluated for their antibacterial activity. The results of the antibacterial activity assay showed that most of the test compounds show remarkable antibacterial activity against all the test bacterial strains with the zones of inhibition (ZOI) range. Compounds **RIPA 6**and **RIPA 7**containing a 4-nitro substituted phenyl ring and a 4-aminophenyl ringproved to be the most potent antibacterial agents compared to the other test compounds and closer in activity to the standard drugs shown in table 5.

The effect of combination of indole-piperazine and its protein-ligand interactions on antibacterial activity has been studied against S. aureu, B. subtilis, P. aeruginosaand E. coli by in vitro and in silico techniques. The ADMET studies reveal that the all targeted titled compounds (RIPA 1-10) have been passed Lipinski's rule of five without any violations and they have drug-likeness properties. Interestingly, the position of piperazine nitrogen significantly influenced on antibacterial activity. The

piperazine nitrogen atom at the 1st& 4thposition (RIPA 6) of the mannich base showed more inhibition towards all bacterial Strains showed in table 5. These observations are also supported by molecular docking and ADMET analysis.

The in silico analysis of mannich bases (RIPA 6 and RIPA 7) and E. coli and S. aureus protein targets demonstrates a strong correlation with the experimental results, supporting the potential of these compounds as effective antimicrobial agents. This correlation between computational and experimental results may reinforce the design of novel antimicrobial agents, in future. Moreover, these findings emphasize the critical need to explore novel antimicrobial compounds in the ongoing effort to combat antimicrobial resistance, which remains a significant global health challenge.

Author Contributions

SeetaramswamySeepana contributed to data collection, analysis, and manuscript preparation. Dr. Vikas Verma. Dr. Pankaj Sharma, Dr. Jaya Sharma and Dr. N.Ravindra conceptualized, supervised, and finalized the manuscript.

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