IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
January 2022 Vol.:23, Issue:2

Synthesis, Characterization, and Pharmacological Evaluation of Some New Pyrimidine Schiff Bases and Their Amines as Possible Antibacterial Agents

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ISSN 2349-7203
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Submitted: 21 December 2021
Accepted: 26 December 2021
Published: 30 January 2022

Keywords: Tetraamino pyrimidine, Benzaldehyde, Schiff base, Antibacterial activity

ABSTRACT

A series of (1Z,1'Z)-N, N'-(5,6-bis(((E)-benzylidene)amino)pyrimidine-2,4-diyl)bis(1-phenylmethanamine) derivatives were prepared by the reaction of tetraamino pyrimidine using various substituted aldehydes. The synthesized tetraamino pyrimidine-Schiff bases were evaluated for their possible antibacterial activity using the nutrient agar cup-plate method and their minimum inhibitory concentration (MIC)values were calculated using the broth dilution method against four different strains of bacteria i.e., *S. aureus, B. subsites, E. coli,* and *P. aeruginosa.* Compounds III_c &IV_c exhibited the highest antibacterial activity. All the synthesized compounds were characterized by IR,^{1}H NMR, and Mass spectral data.

INTRODUCTION

Pyrimidines are 6-membered heterocyclics composed of nitrogen and carbon[1-3]. Pyrimidine derivatives have remarkable pharmacological activities. They were found to possess anticonvulsant, antihypertensive, anticancer, antimalarial, anti-inflammatory, and antibacterial activities. Hence pyrimidine nucleus is of great pharmaceutical importance. In this regard, some new benzyl substituted tetraamino pyrimidines were designed and their molecular properties were predicted by using Lipinski's rule of 5, PASS, OSIRIS molecular property explorer, Molsoft, and Docking softwares[4-7]. All the compounds were synthesized by a conventional method. The synthesized compounds were evaluated for their possible antibacterial activity against *Bacillus subtilis, Staphylococusarues*(*Gram* +ve) and *Escherichia coli, and Pseudomonas aeruginosa (Gram* –ve)by using the cup plate method, and the MICvalues were determined by broth-dilution method using Trimethoprim as standard[8-10].

MATERIALS AND METHODS

Reagents and various solvents are used for synthetic work. All the reactions were performed in dried Borosil glass beakers, round bottom flasks, conical flasks. Precoated silica gel plates(MERK) were used for TLC. Compounds melting points were determined by the open capillary method. JASCO UV Chamber was used for the detection of spots in TLC.IR spectra were recorded on the BRUKER FTIR spectrometer.

^{1}H NMR spectra were recorded on a BRUKER-400MHZ spectrometer using DMSO as solvent. The chemical shift data were expressed as values relative to TMS in δ ppm.

In silico screening

Lipinski rule

Designed molecules (6) were subjected to Lipinski filtration to predict their molecular properties. Online software (supercomputer IIT Delhi) site was used. Molecules that satisfied Lipinski's rule of five were selected for further investigation.

Prediction of activity spectra for substances (PASS)

Molecules that have been filtered through the Lipinski rule were subjected to online software to predict their biological activities.

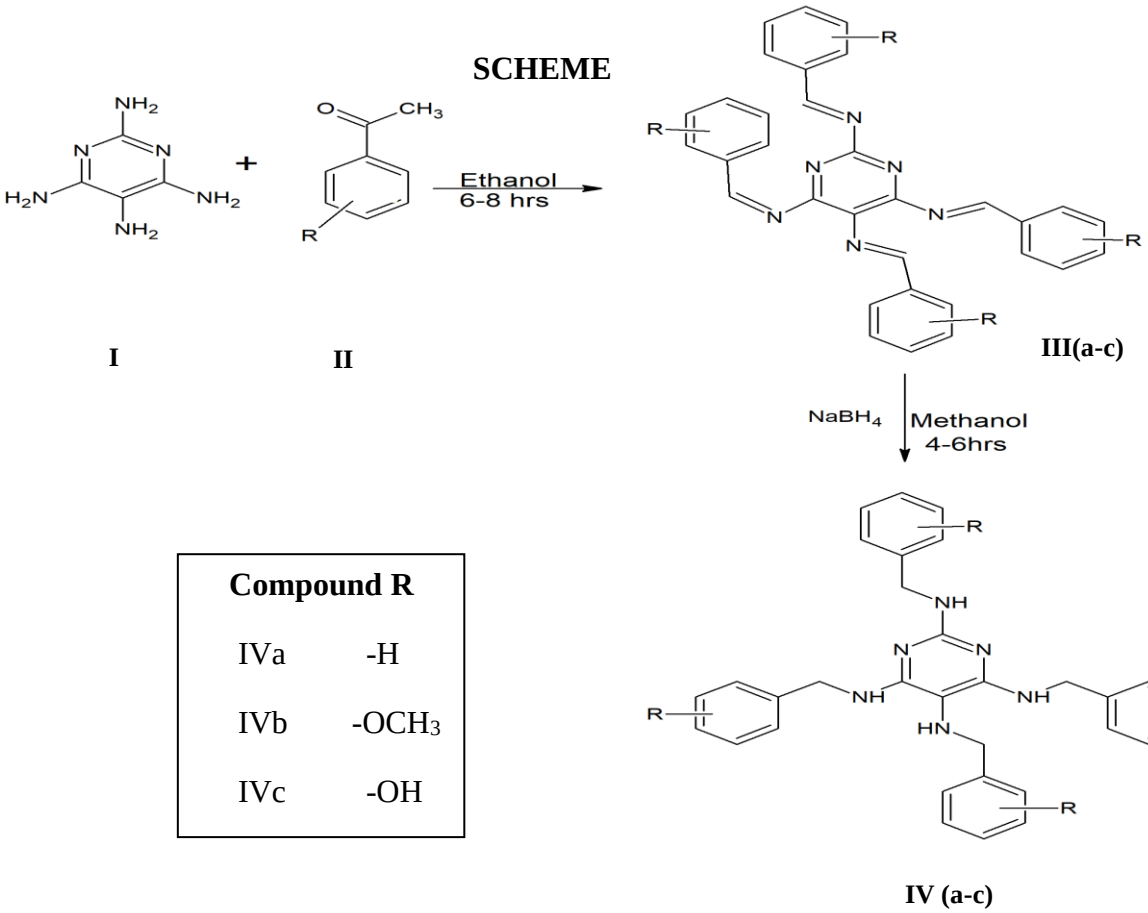
Osiris Molecular Property Explorer (version 2)

Molecules that have been selected from rigid docking are subjected to Osiris Molecular Property Explorer to predict toxicity risk. Non-toxic, safe molecules were selected for further investigation.

Docking

Molecular docking studies were performed by using auto dock 1.5.6 on the filtered non-toxic, safe molecules at the active site of the crystal structure of folic acid reductase inhibitor PDF (PDB ID:2W9S) to predict the affinity, activity, binding orientation of each ligand with the target proteins and to analyze the best conformations.

SCHEME



I **II** **III(a-c)**

Compound	R
IVa	-H
IVb	-OCH_3
IVc	-OH

IV (a-c)

Experimental section:

General procedure for the synthesis of Schiff bases $III_{(a-c)}$:

A solution of 1.19g of Tetra amino pyrimidine is treated with 2mL of aldehyde (Benzaldehyde, Anisaldehyde, Salicylaldehyde) in 10-12mL of ethanol and glacial acetic acid

in a round bottom flask under reflux for 6-8hrs. Now the temperature is maintained in the mixture at about 160˚C(the limits are 160-180˚C). The mixture is stirred frequently. The progress of the reaction is monitored by TLC. The reaction mixture is recrystallized from ethanol to give pure (by removing excess aldehyde) compound.

General procedure for the synthesis of amine compounds IV$_{(a-c)}$:

To the Schiff bases, 0.076g of Sodium borohydride (0.05mol) is added in methanol and the solution is heated under reflux for 4-6hrs. Temperature maintained at about 180˚C. The progress of the reaction is monitored by TLC. The reaction mixture is recrystallized from ethanol to give pure (by removing excess Schiff base) compound.

(1Z,1'Z)-N,N'-(5,6-bis(((E)-benzylidene)amino)pyrimidine-2,4-diyl)bis(1-phenylmethanmine) (III$_a$):FTIR (KBr cm^{-1}): 2851.83(C-H Aliphatic str), 1695.13(C=N str), 1461.53(C=C str), 1219.52(C-N str), 772.35 (C-H mono sub CH str).^{1}H NMR (δ ppm, DMSO): 7.52-7.54(m, 12H, Ar -H), 7.83-7.84(m, 8H, Ar -H), 8.36-8.37(s, 4H,-(CH)$_4$). EI-MS:m/z 493 (M+1 peak).Analysis Calculated for C_{32} H_{24} N_6: C, 78.05; H, 4.89; N, 17.04. Found: C, 78.03; H, 4.91; N, 17.06.

5-methoxy-2-((E)-((2,4,6-tris(((E)-4-methoxybenzylidene)amino)pyrimidin-5-yl)imino)methyl)phenol(III$_b$):FTIR (KBr cm^{-1}): 2921.11(C-H Aliphatic str), 1550.22(C=N str), 1361.64(C=C str), 1284.30(C-N str), 772.58 (C-H mono sub CH str). ^{1}H NMR (δ ppm, DMSO): 3.83-3.84(s, 12H,-(CH_3)$_4$),7.06-7.07(m, 8H,Ar -H), 7.84-7.85(m, 8H,Ar -H), 8.36-8.37(s, 2H,-(CH)$_2$), 8.38-8.39(s, 1H, -CH), 8.59-8.60(s, 1H, -CH).EI-MS:m/z 613(M+1 peak).Analysis Calculated for C_{32} H_{32} N_6 O_4: C, 68.05; H, 5.70; N, 14.86; O, 11.31. Found: C, 68.07; H, 5.71; N, 14.88; O, 11.33.

2,2',2'',2'''-((1E,1'E,1''E,1'''E)-(pyrimidine-2,4,5,6-tetrayltetrakis(azaneylylidene))tetrakis(methaneylylidene))tetraphenol(III$_c$):FTIR (KBr cm^{-1}): 2957.06(C-H Aliphatic str), 1361.64(C=N str), 1284.30(C=C str), 1217.93(C-N str), 773.56 (C-H mono sub CH str). ^{1}H NMR (δ ppm, DMSO): 5.35-5.36(s, 4H, -(OH)$_4$), 7.02-7.52(m, 8H,Ar -H), 7.08-7.66(m, 8H,Ar -H), 8.36-8.37(s, 1H, -CH), 8.59-8.60(s, 2H, -(CH)$_2$), 9.35-9.36(s, 1H, -CH).EI-MS:m/z 557(M+1 peak).Analysis Calculated for C_{24} H_{32} N_6 O_4: C, 61.50; H, 6.86; N, 17.96; O, 13.65. Found: C, 61.52; H, 6.88; N, 17.94; O, 13.66.

5-methoxy-2-((E)-((2,4,6-tris(((E)-4-methoxybenzylidene)amino)pyrimidin-5-yl)imino)methyl)phenol (IV$_a$):FTIR (KBr cm^{-1}): 2753.21(C-H Aliphatic str), 1694.13(

C=N str), 1463.53(C=C str), 1217.52(C-N str), 773.32 (C-H mono sub CH str). ^{1}H NMR (δ ppm, DMSO): 4.0-4.1(s, 4H, -$(NH)_4$), 4.35-4.36(s, 8H, -$(CH_2)_4$), 7.23-7.33(m, 20H,Ar -H).EI-MS:m/z 501(M+1 peak).Analysis Calculated for C_{32} $H_{32}N_6$: C, 76.75; H, 6.42; N, 16.76. Found: C, 76.77; H, 6.44; N, 16.79.

5-methoxy-2-(((2,4,6-tris((4-methoxybenzyl)amino)pyrimidin-5-yl)amino)methyl)phenol(IV_b):FTIR (KBr cm^{-1}): 2756.91(C-H Aliphatic str), 1692.13(C=N str), 1469.53(C=C str), 1220.52(C-N str), 774.35 (C-H mono sub CH str). ^{1}H NMR (δ ppm, DMSO): 3.83-3.84(s, 12H,-$(CH_3)_4$), 4.35-4.36(s, 8H, -$(CH_2)_4$), 6.87-6.88(m, 8H,Ar -H), 7.25-7.27(m, 8H, Ar-CH).EI-MS:m/z 621(M+1 peak).Analysis Calculated for C_{32} H_{24} N_6 O_4: C, 69.05; H, 4.31; N, 15.06; O, 11.49. Found: C, 69.06; H, 4.35; N, 15.10; O, 11.50.

2,2',2'',2'''-((1E,1'E,1''E,1'''E)-(pyrimidine-2,4,5,6-tetrayltetrakis(azaneylylidene))tetrakis(methaneylylidene))tetraphenol (IV_c):FTIR (KBr cm^{-1}): 2853.93(C-H Aliphatic str), 1690.13(C=N str), 1465.53(C=C str), 1218.52(C-N str), 770.33 (C-H mono sub CH str). ^{1}H NMR (δ ppm, DMSO): 4.0-4.1(s, 4H, -$(NH)_4$), 4.35-4.36(s, 8H, -$(CH_2)_4$), 5.35-5.36(s, 4H,-$(OH)_4$), 6.83-6.89(m, 8H, Ar-CH), 7.06-7.09(m, 8H, Ar-H).EI-MS:m/z 565(M+1 peak).Analysis Calculated forC_{32} H_{32} N_6 O_4: C, 68.11; H, 5.71; N, 14.86; O, 11.31. Found: C, 68.07; H, 5.71; N, 14.88; O, 11.33.

Evaluation of Antibacterial activity

The antibacterial activity of the test compounds was assayed systematically against four non-pathogenic strains of bacteria *i.e. S.aureus, E.coli, P.aeruginosa, and B.substilis.*

The antibacterial activity of a compound is its ability to inhibit the growth of bacteria in nutrient broth or agar. The method used in this present investigation was the cup plate method.

Cup-Plate Method

The test compounds $III_{(a-c)}$ &$IV_{(a-c)}$ in the concentration of 50,100µg/ml were prepared by dissolving in DMSO. Sterilized media was cooled to 40˚C, inoculated with respective bacteria, and poured into Petri plates. After solidification of the medium at room temperature, cups of 4mm diameter were made on each plate with a sterile borer. Accurately 0.01ml of test solution was transferred to cups and labeled accordingly. The plates were kept undistributed for at least two hours at room temperature to allow diffusion properly. Incubation of the Petri

plates was done at 37±1˚C for 24h. The growth/inhibition of bacteria was observed after 24hrs. Simultaneously controls were maintained employing DMSO to observe the solvent effects. The diameter of the zone of inhibition was read and results were calculated. Trimethoprim is chosen as the standard.

Minimum inhibitory concentration-broth dilution method

The Minimum Inhibitory Concentration Assay is a technique used to determine the lowest concentration of a particular antibiotic needed to kill bacteria. This assay is typically performed on planktonic (free-floating) bacteria cells. Take clean and dry test tubes, sterilize and label them.Prepare dilutions for different concentrations (6.25,12.5,25,50,75,100,125 µg/ml) of test compounds III_c &IV_c.Then nutrient broth was prepared, sterilized, and allowed to cool to room temperature. It was transferred to test tubes, 10-15ml in each tube. The bacterial culture was inoculated into the tubes in the laminar chamber at aseptic conditions to avoid contamination. The test tubes were shaken to allow proper mixing. Various concentrations of test compounds were added to the test tubes. The test tubes were shaken well and tightly closed with a cotton plug. The tubes were allowed to incubate overnight (18-24hrs). Broth tubes that appeared turbid are indicative of bacterial growth while tubes that remained clear indicate no growth.MIC was calculated by using the following formula.

$$MIC=\frac{\text{Highest conc. that inhibit growth + Lowest conc.that allow growth of M.O's}}{2}$$

RESULTS AND DISCUSSION

***In silico* screening**

Lipinski filters: The molecules which are colored red did not satisfy Lipinski's rule of 5 whereas green colored molecules have satisfied the rule. Out of 5 molecules, 5 molecules displayed green and satisfied Lipinski's rule (Table 1).

Table 1: Results of Lipinski's Filtration

Compound	Molecular weight	Hydrogen bond donors	Hydrogen bond acceptors	Log P	Molar Refractivity
III_a	492.00	0	6	6.64	77.145
III_b	612.25	0	10	7.00	82.51
III_c	556.19	4	10	5.12	118.53
IV_a	500.23	2	4	7.07	60.77
IV_b	620.31	4	6	7.43	90.94
IV_c	564.25	8	6	5.55	126.96

By the above values, the synthesized pyrimidine derivatives obey the Lipinski rule of 5.

Prediction of activity spectra for substances (PASS)

The Pa and Pi values vary from 0.000 to 1.000. To define the threshold for selecting types of activity to be predicted, the cutoff value of Pa should be chosen. Pa of 0.3- 0.7 was selected. Only activities with a Pa value greater than the chosen threshold will be given in predicted activity spectra (Table 2).

Table 2: PASS prediction study results

Compound No	P_a	P_i
III_a	0.164	0.039
III_b	0.136	0.120
III_c	0.182	0.135
IV_a	0.346	0.056
IV_b	0.147	0.061
IV_c	0.378	0.045

All Pa>Pi Pa>0.3 Pa>0.7

OSIRIS MOLECULAR PROPERTY EXPLORER: The molecules that have been subjected to OSIRIS property explorer, molecules have shown green color with represents, non-toxic, safe, drug-conform behavior (Table 3).

Table 3: Molecular property prediction by OSIRIS property Explorer (version 2)

Comp.NO	Properties	clogP	Solubility	MW	TPSA	Drug likeness	Drug score
III_a	Nill	6.66	-8.1	492	75.22	-0.29	0.16
III_b	Nill	6.38	-8.17	612	112.1	0.08	0.14
III_c	Nill	5.2	-8.92	556	156	-0.35	0.19
IV_a	Nill	5.43	-7.46	500	73.6	-0.16	0.21
IV_b	Nill	5.15	-7.54	620	110.6	1.29	0.17
IV_c	Nill	4.05	-8.28	584	154.8	-0.19	0.25

clogP- calculated log P, TPSA-Topological polar surface area, MW-molecular weight

Docking results

Name of the Protein: 2W9S

Docking is used to find the exact binding conformation and orientation of the ligand molecule into the active site of the protein. The synthesized five thiazole compounds and standard (Trimethoprim) were docked against beta-tubulin using Auto-Dock Tool 4.0, an automated docking tool.

The docking process involves four main steps,

(i) Protein preparation

(ii) Ligand preparation

(iii) Grid preparation and

(iv) Docking.

The Lamarckian genetic algorithm has been used as the search algorithm to search for the best conformers. The initial population size was set randomly as 150 individuals and ten generations were set for each genetic algorithm run and the maximum number of energy evaluations was set to 2,500,000. The grid box was centered at x-46A˚, x-52A˚, x-70A˚, and

the dimensions of the grid box have been set as 65, 70, 40 (X, Y, Z coordinates) to include all the active site residues.

Docking studies have shown that all ligands chosen for analysis possessed the least binding affinity with the target protein *dihydrofolate reductase*. The protein-ligand interactions were studied in terms of protein binding energy (Kcal/mol) and the number of hydrogen bonds formed with active site residues. The interactions of six ligands and the protein dihydrofolate reductase were visualized using Chimera 1.13.1 and shown in Fig. 1, 2 & 3. The final docked conformation obtained for the different ligands based on binding energy, number of hydrogen bonds formed, bond distance, and the interacting residues were shown in Tables 4 & 5. $IV_c$and Trimethoprim shows the least binding energy with the docking score -14.10Kcal/mol (forms hydrogen bonds with LEU, SER, THR) and -7.61 10Kcal/mol (forms hydrogen bonds with LEU, SER, THR, VAL, TYR, GLY) respectively against dihydrofolate reductase.

The length of the hydrogen bonds formed with interacting residues for all the ligands shows the bonding was good. Most of the key residues shown in Table 7,8 are the active site residues of the target protein predicted by PDB. Based on the docking score all the ligands have docking interactions with the protein dihydrofolate reductase. The antibacterial activity was chosen ass ligands in this study have different modes of action.

Table 4: Docking results of all synthesized compounds & standard

Compound	No.of hydrogens	Docking Score (Kcal/Mol)	Ranking
III_a	3	-12.55	III
III_b	4	-11.69	V
III_c	5	-13.54	II
IV_a	6	-12.05	IV
IV_b	10	-10.68	VI
IV_c	11	-14.10	I
Trimethoprim	15	-7.61	VII

Table 5: Amino acids binding to the docking molecule

S.No	Compound No	Amino acids	No. of hydrogen bonds
1	Trimethoprim	THR,VAL,LEU,SER,TYR,GLY	15
2	III_c	ASN,ASP	5
3	IV_c	LEU,SER,THR	11

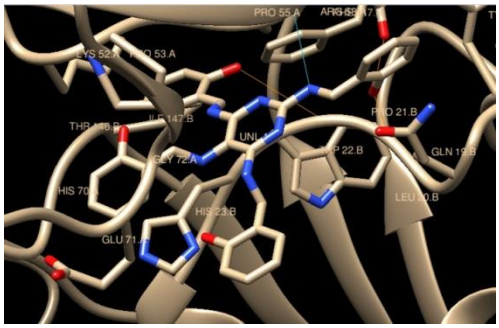


Fig. 1: Docking of III_c with 2W9S

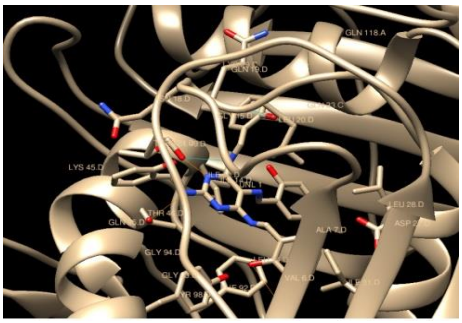


Fig. 2: Docking of IV_c with 2W9S

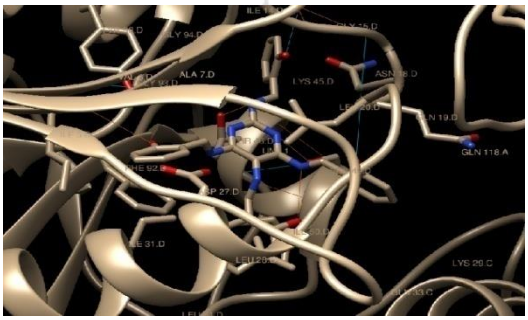


Fig. 3: Docking of Trimethoprim to 2W9S

Chemistry:

The filtered non-toxic molecules were synthesized as shown in scheme-I. The Schiff bases (III_{a-c}) were prepared by the addition of aldehydes in ethanolic glacial acetic acid by a conventional method. Compounds $III_{(a-c)}$ were obtained in 85-90% yield. The amines $IV_{(a-c)}$ are formed by the reduction of the Schiff bases in the presence of Sodium boro hydrate. All the newly synthesized final products were characterized based on their physical data (Table 6).

Table 6: Physical data of the synthesized compounds

Compound	Molecular formula	R	Mol Wt	R_f value	%Yield	Melting point (^{0}C)
III_a	$C_{32}H_{24}N_6$	-H	492.21	0.68	70	220-221
III_b	$C_{32}H_{32}N_6O_4$	$-OCH_3$	612.19	0.55	75	222-223
III_c	$C_{24}H_{32}N_6O_4$	-OH	556.19	0.51	82	225-227
IV_a	$C_{32}H_{32}N_6$	-H	500.23	0.59	70	228-230
IV_b	$C_{32}H_{36}N_6O_4$	$-OCH_3$	620.31	0.82	75	235-237
IV_c	$C_{32}H_{36}N_6O_4$	-OH	564.25	0.71	78	232-234

Antibacterial studies: The synthesized compounds are evaluated for their *in-Vitro* antibacterial activity against *Staphylococcus aureus*, *Bacillus substilis* Gram +ve bacteria, and *Escherichia coli*, *Pseudomonas aeruginosa* Gram –ve bacteria by cup plate method. The compounds are dissolved in DMSO to get solutions of concentrations(6.25,12,25,50,100,125µg/ml) and are incubated for 18-24hrs and the zone of inhibition is measured in millimetres (Table 7) and (Fig. 4,5,6,7).

Trimethoprim is taken as the reference drug to the compounds. The investigation revealed that the III_c&IV_ccompounds show good inhibition compared to standard whereas other compounds showed moderate inhibition compared to the standard. Thus, these compounds may be used for biological activities.

Table 7: Zone of inhibition (mm) of compounds $III_{(a-c)}$ & $IV_{(a-c)}$

	S. aureus		*B. substilis*		*E. coli*		*P.aeruginosa*	
	100µg/ml	50µg/ml	100µg/ml	50µg/ml	100µg/ml	50µg/ml	100µg/ml	50µg/ml
Trimethoprim	20	18	18	16	16	14	18	16
III_a	13	10	14	10	14	13	14	10
III_b	14	11	15	13	-	-	13	12
III_c	19	17	20	14	16	13	18	16
IV_a	14	11	12	11	12	10	14	12
IV_b	12	10	14	10	-	-	16	12
IV_c	22	18	16	13	20	16	18	14

n=3, *p<0.05,**p<0.1, ***p<0.0.1 and ****p<0.001 when compared to control data was analyzed by one way ANOVA followed by Dunnet's test for multiple comparisons.

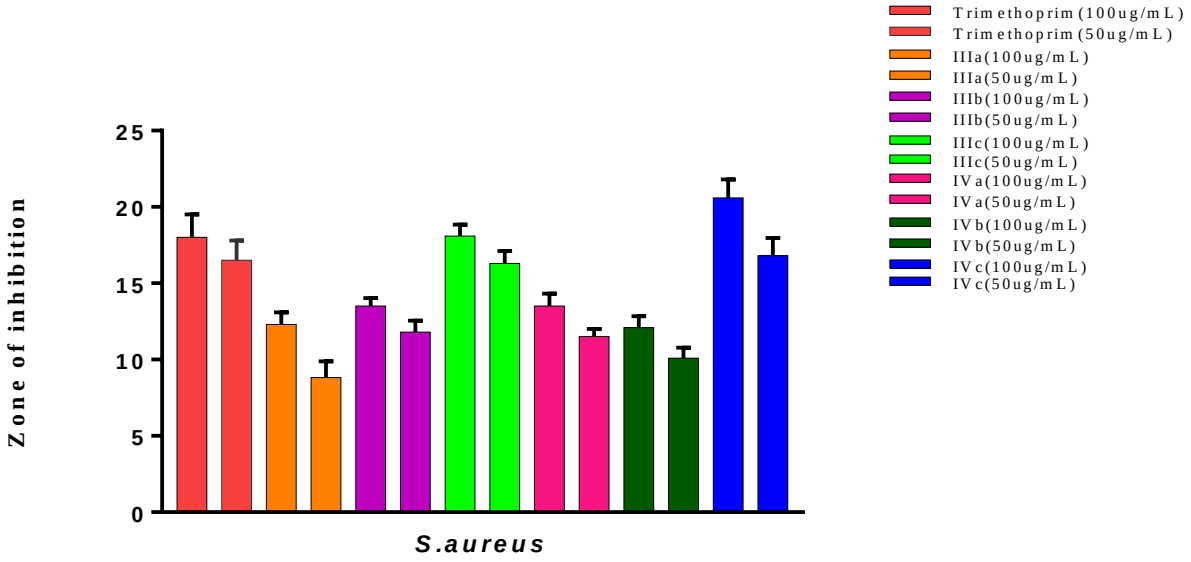


Fig. 4: Antibacterial activity (concentration(µg/mL)VS Zone of Inhihibition) for *S.aureus*

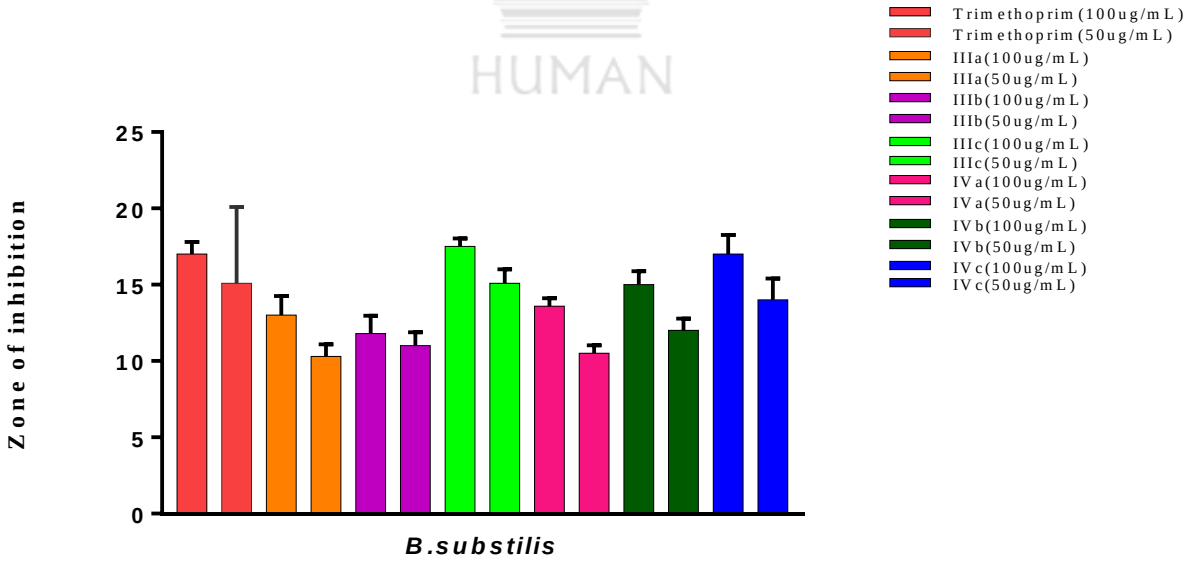


Fig. 5: Antibacterial activity (concentration(µg/mL)VS Zone of Inhihibition) for *B.substilis*

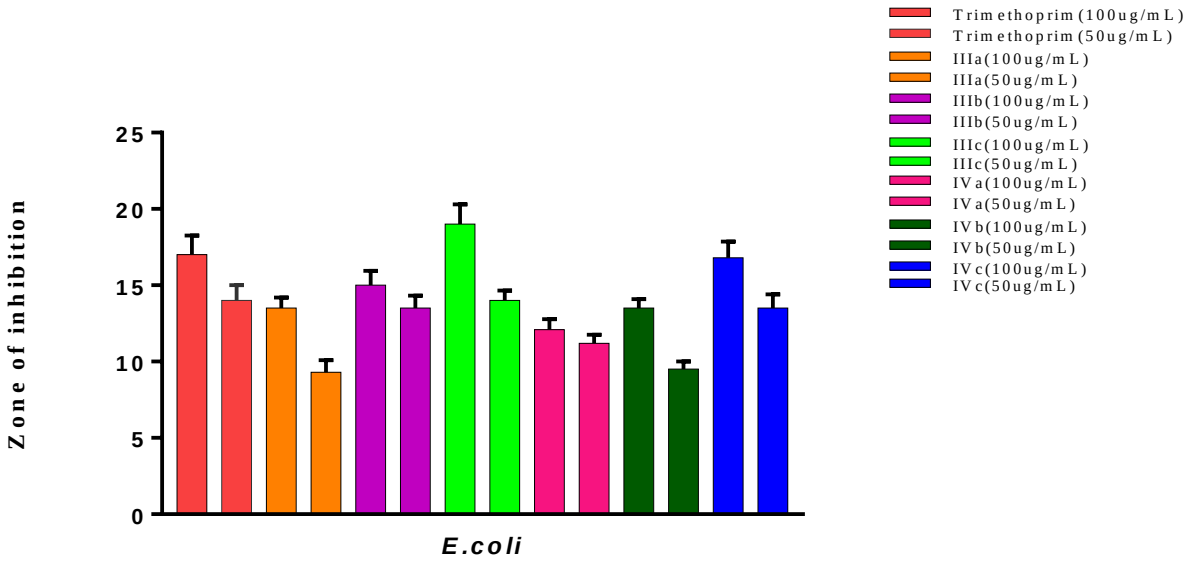


Fig. 6: Antibacterial activity (concentration(µg/mL)VS Zone of Inhihibition) for *E.coli*

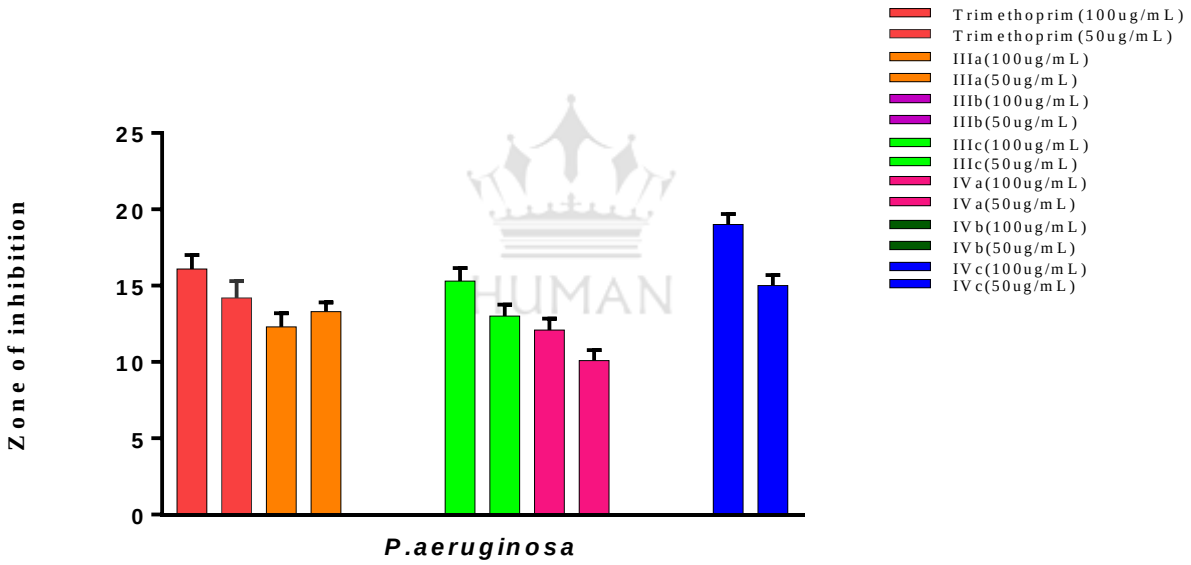


Fig. 7: Antibacterial activity (concentration(µg/mL)VS Zone of Inhihibition) for *P.aeruginosa*

These potent compounds are also evaluated for their minimum inhibitory concentration and found that all the compounds show minimum inhibition at 25µg/ml i.e, the equal concentration of the standard (Table 8).

Table 8: Minimum inhibitory concentration of the compound III_c &IV_c

	MIC(µg/ml)			
	S. aureus	*B.substilis*	*E. coli*	*P. aeruginosa*
Trimethoprim	68.75	56.25	68.75	65.62
III_c	53.12	62.50	68.75	56.25
IV_c	53.12	56.25	75.00	43.75

CONCLUSION

The present work entitled "Pyrimidines Schiff Bases And Their Amines As Antibacterial Agents" is carried out. From the literature survey and Insilco studies, we found that the pyrimidine derivatives have pronounced antibacterial activity, antimycobacterial activity, etc., Compound III_c &IV_cshown good binding energies with the protein 2W9S in docking it may be due to the presence of amine group and hydroxyl group in the ring system. Among all the compounds tested shows good antibacterial activity with bacteria. Compound III_c shows equipotent activity where IV_cshows more potent activity than the standard drug (Trimethoprim). The title compounds were synthesized as per the scheme which consists of 2 steps. In the first step tetra, amino pyrimidine treated with substituted benzaldehydes gave Schiff bases. In the second step, Schiff bases are reacted with Sodiumborohydrate in the presence of methanol to produce amine compounds. The synthesized Tetra amino pyrimidine-Schiff bases were evaluated for their antibacterial activity using the nutrient agar cup-plate method and their MIC values were calculated using the broth dilution method against four different strains of bacteria i.e., *S. aureus, B. substilis, E. coli, P. aeruginosa*. Compounds III_c & IV_c exhibited the highest antibacterial activity. It can be studied further for any other activity.

ACKNOWLEDGEMENT

The authors are grateful to the Management and Principal of Vaagdevi College of Pharmacy, Ramnagar, Hanamkonda, Warangal (U) -506001, and Telangana, India for providing the necessary research facilities.

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Conflict of Interest	No Conflict of Interest
Funding Information	No funding from external source
Authors contribution	All Authors contributed in the research work.
Acknowledgement	The authors are grateful to the Management and Principal of Vaagdevi College of Pharmacy, Ramnagar, Hanamkonda, Warangal (U) -506001, and Telangana, India for providing the necessary research facilities.