"Synthesis, characterization, and antimicrobial activities of novel Schiff base moieties of pyrimidine nucleus"

THESIS SUBMITTED IN THE PARTIAL FULFILLMENT FOR THE DEGREE OF

MASTER OF PHARMACY
(PHARMACEUTICAL CHEMISTRY)

In the Faculty of Pharmaceutical Sciences,

BHARATI VIDYAPEETH (DEEMED TO BE UNIVERSITY)

BY

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Under the guidance of

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And

Dr. Dileep Kumar

(Research Co-Guide)

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Erandwane, Pune – 411038, India, 2020-2021

CERTIFICATE

This is to certify that the work presented in the dissertation entitled ***"Synthesis, characterization, and antimicrobial activities of novel Schiff base moieties of pyrimidine nucleus"*** for the degree of **Master of Pharmacy (Pharmaceutical Chemistry)** in the faculty of **Pharmaceutical Sciences** has been carried out by **Mr. Dipanjan Karati,** in the laboratories of **Bharati Vidyapeeth (Deemed To Be University), Poona College of Pharmacy, Erandwane, Pune** under the guidance of **Dr. K. R. Mahadik** (Research Guide) and **Dr. Dileep Kumar** (Research Co-Guide).

Date: September 2021

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DECLARATION BY THE CANDIDATE

This is to state that the research work entitled ***"Synthesis, characterization, and antimicrobial activities of novel Schiff base moieties of pyrimidine nucleus"*** for the degree of **Master of Pharmacy (Pharmaceutical Chemistry)** has not been submitted in parts or full to any other university by me. This is the original work undertaken by me under the guidance of **Dr. K. R. Mahadik** (Research Guide) and **Dr. Dileep Kumar** (Research Co-Guide). Department of Pharmaceutical Chemistry, Bharati Vidyapeeth (Deemed to be University), Poona College of Pharmacy, Pune. Such materials, as obtained from other sources, have been duly acknowledged in this thesis.

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Date: Mr. Dipanjan Karati

Place: Pune

INDEX

List of Tables

List of Figures

CHAPTER 1

INTRODUCTION

1.1Introduction to Antimicrobial agents

Antimicrobial medicines are the biggest therapeutic contribution of the twentieth century. Their introduction altered physicians' perceptions of the impact that medicines may have on illnesses. They are one of the few medicines that can cure rather than simply relieve symptoms. In underdeveloped nations, when ineffective illnesses are prevalent, their significance is amplified. They are one of the most commonly used and misunderstood drug classes. This class of drugs is distinct from all others in that they are intended to suppress or kill the infecting organism while having no or little effect on the receiver. Chemotherapy refers to the treatment of systemic infections using medicines that selectively inhibit the infecting bacteria without having a major impact on the host. In the late 1960s and early 1970s, the amazing success of antimicrobial medicines led to the mistaken belief that infectious illnesses had been eradicated. Infectious illnesses are still the third greatest cause of mortality in the United States and the second major cause of death worldwide, 40 years later. Furthermore, the rise of multidrug-resistant bacteria has resulted in a scenario where infection with some germs has few or no therapeutic choices. Despite the growing demand for novel antimicrobials, their development confronts considerable challenges. Because of the rise of multidrug resistance in common diseases, the rapid appearance of novel illnesses, and the possibility for using multidrug-resistant organisms in bioweapons, the need for new antimicrobial drugs is higher than ever. [1-5]

1.2 Classification of Antimicrobial agents

Antimicrobial drugs can be classified in many ways like based on structure, mechanism of action, organism against which primarily active, spectrum of activity.

a. **Chemical structure**-

Sulphonamides- sulfadiazine, dapsone, para-amino salicylic acid.

Diaminopyrimidine- trimethoprim, pyrimethamine.

Quinolones- nalidixic acid, norfloxacin, ciprofloxacin.

Beta lactam antibiotics- penicillin, cephalosporin.

Tetracyclines- oxytetracyclines, doxycycline.

Macrolides- erythromycin, azithromycin.

Azole derivatives- miconazole, ketoconazole.

b. **Mechanism of action**-

Inhibit cell wall synthesis- penicillin, cephalosporin, vancomycin etc.

Cause leakage from cell membrane- nystatin, Amphotericin B, colistin etc.

Inhibit protein synthesis- oxytetracyclines, doxycycline, erythromycin, azithromycin etc.

Inhibit DNA gyrase- nalidixic acid, norfloxacin, ciprofloxacin etc.

Interfere with DNA function- rifampicin.

Interfere with DNA synthesis- acyclovir, zidovudine.

c. **Spectrum of activity**-

Narrow spectrum- pen G, erythromycin etc.

Broad spectrum- Tetracyclines, chloramphenicol.

d. Types of organism against which active-

Antibacterial- pen G, Quinolones, erythromycin etc.

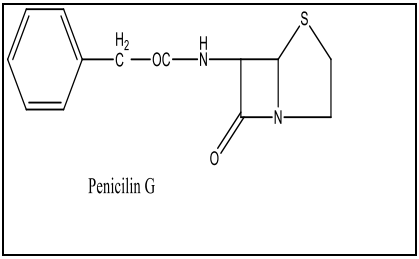
Antifungal- ketoconazole, griseofulvin.

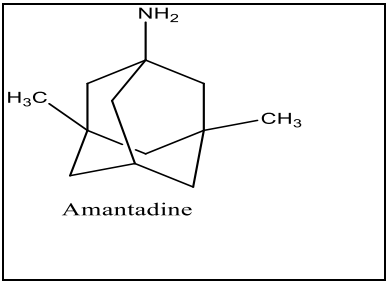
Antiviral- acyclovir, amantadine etc.

Antiprotozoal- chloroquine, metronidazole etc.

Anthelmintic- mebendazole, diethyl carbamazepine etc.

1.3 Some Structures of Above Class of Antimicrobial Drugs are Given Here.


Penicilin G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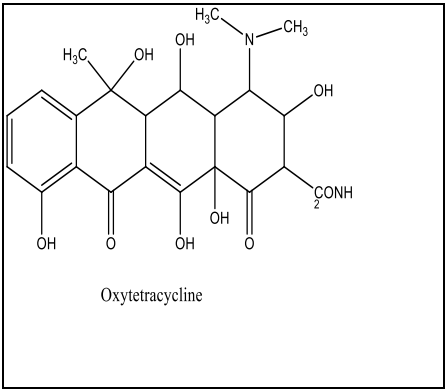
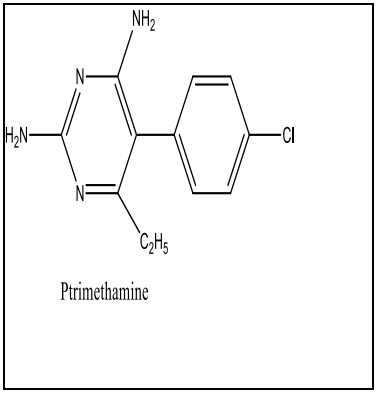
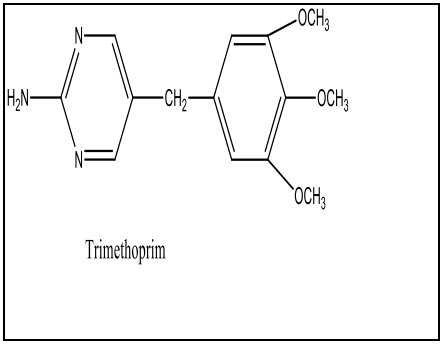
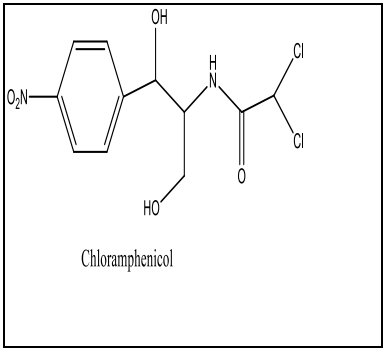
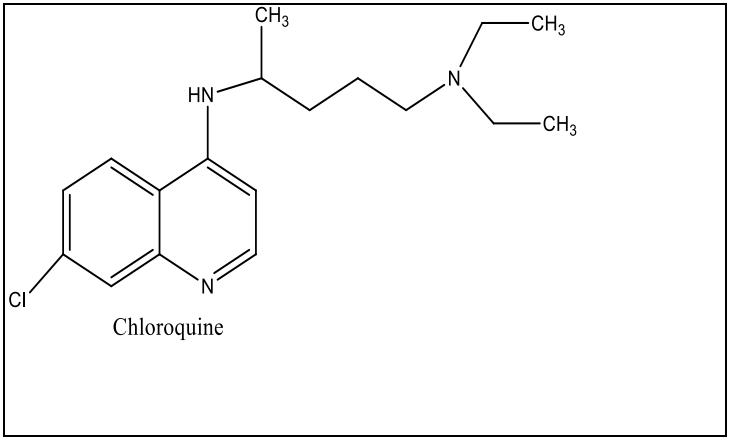

Oxytetracycline


Ptrimethamine


Trimethoprim


Chloramphenicol

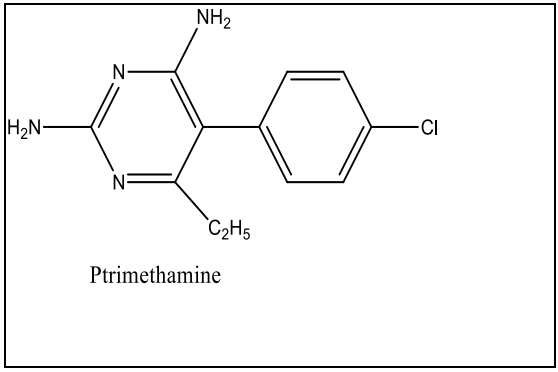


Chloroquine

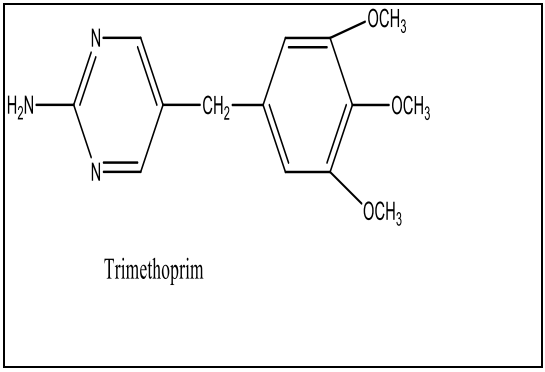
Compounds based on the pyrimidine scaffold have been shown to have a wide range of biological effects, including antibacterial, antifungal, anti-inflammatory, and anticancer properties. Many amino pyrimidine-based derivatives have been shown to block dihydrofolate reductase, resulting in antibacterial activity (DHFR) [6-7]. SAR points of dihydrofolate reductase inhibitors are as following-

1. Electron donating group must be present at C_6 position.
2. Cl at para position is important for activity.
3. Two rings are not separated by carbon atom.

Example of this group of drugs are pyrimethamine, trimethoprim.



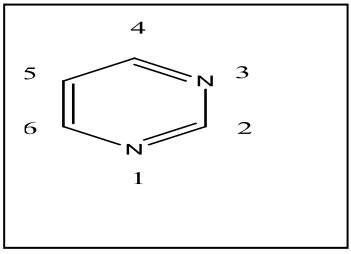
Ptrimethamine



Trimethoprim

Pyrimidine is a heterocyclic ring system having two nitrogen atoms at positions 1 and 3 in the ring [8]. Pyrimidine derivatives are an essential part of today's therapies, since they are among a large range of heterocycles that have been investigated for creating medicinally relevant compounds. They are known to have a wide range of pharmacological actions, including antibacterial, antitubercular, anti-inflammatory, anticancer, antiviral, and antimalarial effects, highlighting the heterocyclic nucleus' importance in modern medicinal chemistry [9].

1.4 Structure Activity Relationship of Pyrimidine Derivatives-



1. The insertion of five membered saturated heterocycle rings at the 1st position leads to anti-cancer and anti-viral operations.

2. If Keto group replacement or Amino substitution or combined substitution will be occurred at the 2nd and 4th positions of pyrimidine nucleus, then it leads to anti-cancer, anti-viral, anti-fungal activities.

3. Halogen groups, substituted amine group or heterocycles ring if will be placed at 5^{th} position of pyrimidine ring it will give anticancer, anti-bacterial activity.

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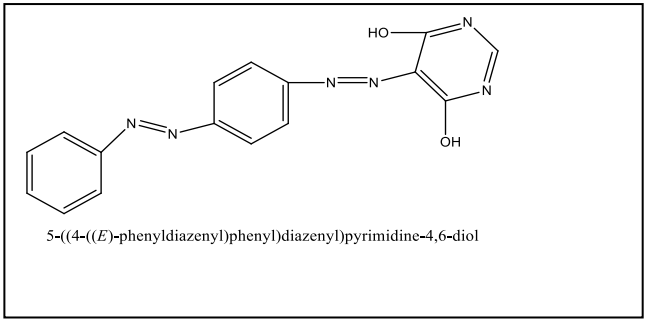
CHAPTER 2

LITERATURE REVIEW

2 Literature Review

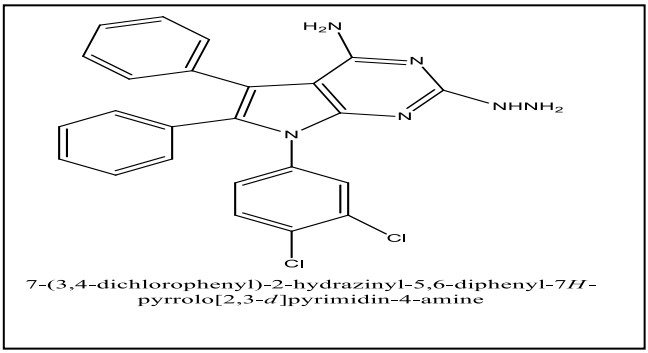
A survey was conducted to learn more about pyrimidine antibacterial medicines with less side effects and toxicity. The brief review of the literature is mentioned below:

Yazdanbakhsh *et al*., reported the synthesis of 4, 6-dihydroxypyrimidines and evaluated for their antibacterial activity against Salmonella typhimurium, Micrococcus luteus, Bacillus subtilis and Pseudomonas aeruginosa at concentration of 125µg/ml by using Tetracycline and Erythromycin as standard drugs. One compound showed good antibacterial activity against B. subtilis and P. aeruginosa when compared with standard drugs. [10].



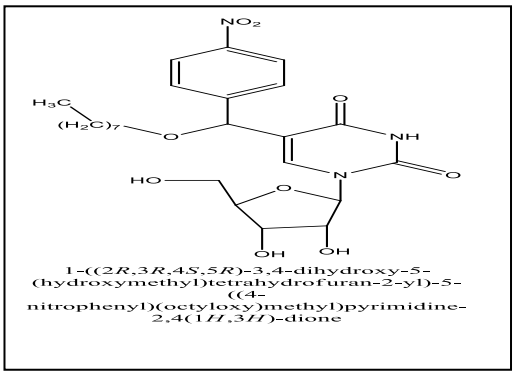
5-((4-((*E*)-phenyldiazenyl)phenyl)diazenyl)pyrimidine-4,6-diol

A series of 8-Aryl-pyrrolo, thiazolo pyrimidine derivatives prepared by Mohameda *et al*., All newly synthesized compounds were examined for their antibacterial activity against Staphylococcus pyrogens and antifungal activity against *Candida albicans* and *Aspergillus flavus* according to cup plate method at a concentration of 0.035mg/ml by using Chloramphenicol and Flucanazole as standards for antibacterial and antifungal activities respectively. Some compounds showed promising antimicrobial activities when compared with their respective standard drugs [11].



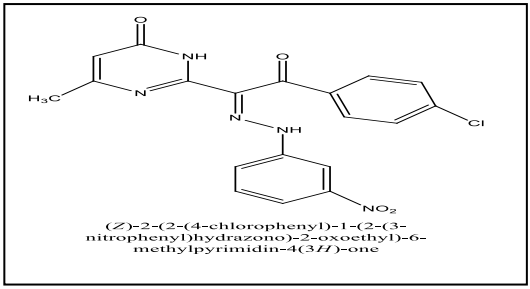
7-(3,4-dichlorophenyl)-2-hydrazinyl-5,6-diphenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

A series of uridine analogues was synthesized by Brulikova *et al.*, and tested for their antibacterial activity against *Pseudomonas aerugenosa* and Staphylococcus aureus and antifungal activity against *Aspergillus niger* and *Candida albicans*. For comparison of antibacterial and antifungal properties, chloramphenicol and flucanazole were utilized as standards. Some compounds demonstrated significant antibacterial activity against *P. aerugenosa* and *S. aureus* whereas other scaffolds revealed appreciable antifungal action in contrast to *A. niger* and *C. albicans* when compared with their respective standard drugs [12].



1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-((4-nitrophenyl)(octyloxy)methyl)pyrimidine-2,4(1*H*,3*H*)-dione

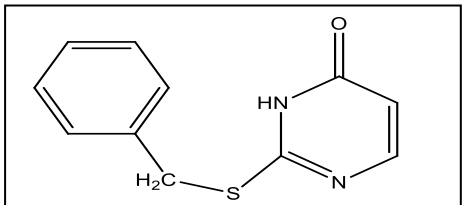
Edrees *et al*., prepared a series of 2-[N-aryl-2-oxo-2-(4-chlorophenyl) ethanehydrazonoyl]-6-methyl-4(3H) pyrimidinones derivatives. All newly synthesized compounds were screened for their potent antibacterial activity against *Pseudomonas aerugenosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Candida albicans*. Chloramphenicol and Flucanazole were used as standards. Some compounds showed promising antibacterial activity against *P. aerugenosa* and *S. aureus* whereas other compounds exhibited significant antifungal activity against *A. niger* and *C. albicans*. One compound showed good antimicrobial activity at minimum inhibitory concentration of 15.10µg/mL against the bacterial stains [13].



(*Z*)-2-(2-(4-chlorophenyl)-1-(2-(3-nitrophenyl)hydrazono)-2-oxoethyl)-6-methylpyrimidin-4(3*H*)-one

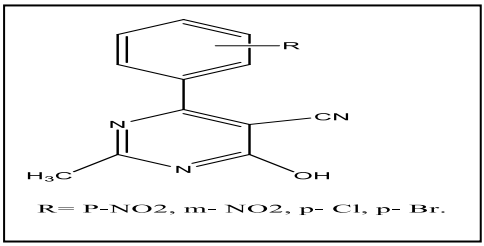
Prachayasittikul *et al*., reported thiopyrimidines derivatives (6) as potential therapeutics achieved novel analogs of bioactive thiopyrimidines-4-(3H)-ones and investigated their antibacterial activity against *Pseudomonas aerugenosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Candida albicans*. Chloramphenicol and Flucanazole were used as standards for comparison of antibacterial and antifungal activities respectively. Some compounds showed promising antibacterial activity against *P. aerugenosa* and *S. aureus* and antifungal activity against *A. niger* and *C. albicans* and exhibited potent antimicrobial activity. One compound showed complete inhibition against *Streptococcus pyogenes* and

Branhamella catarrhalis as well as antifungal action against *Candida albicans* and it was found to be the most potent antimicrobial compound when compared with standard drugs [14].



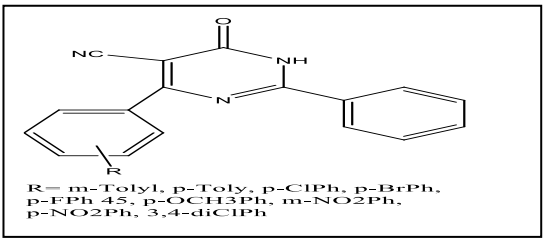
2-(benzylthio)pyrimidin-4(3*H*)-one

Santosh S. Undare *et al*., reported '' One-pot synthesis and in vivo biological evaluation of new pyrimidine privileged scaffolds as potent anti-inflammatory agents'' [15].



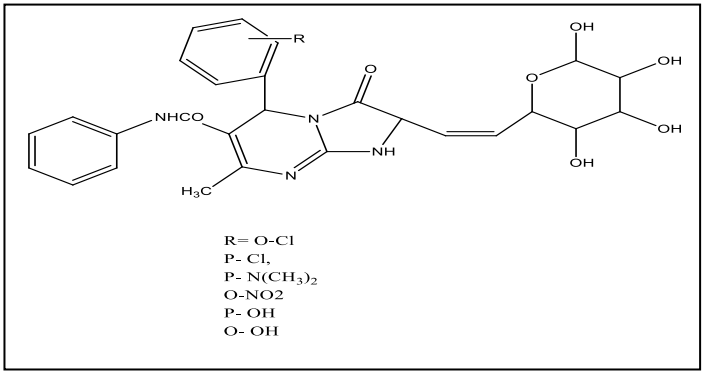
R= P-NO2, m- NO2, p- Cl, p- Br.

A. L. Xavier *et al*., reported "Antinociceptive pyrimidine derivatives: aqueous multicomponent microwave assisted synthesis" [16].



R= m-Tolyl, p-Toly, p-ClPh, p-BrPh, p-FPh 45, p-OCH3Ph, m-NO2Ph, p-NO2Ph, 3,4-diClPh

J. Rani, M Saini *et al*., reported “Design, synthesis and biological potentials of novel tetrahydroimidazo[1,2-a] pyrimidine derivatives” [17].



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CHAPTER 3

AIM AND OBJECTIVE, NEED OF WORK, PLAN OF WORK

3.1 Aim and Objective.

Aim: Synthesis, characterize and testing the antimicrobial activity of several pyrimidine derivatives containing Schiff base.

Objective: The objective of the present research work has been to characterise the synthesized compounds by several analytical methods like IR, NMR, MASS spectroscopy and to evaluate the biological activities of the synthesized drugs.

3.2 Need of Research Work:

Because of their anti-inflammatory, analgesic, antibacterial, antiviral properties, pyridines and their oxo-derivatives have been extensively studied. As a result, new pyrimidine derivatives are regularly produced in order to develop small molecule libraries for drug discovery. The synthesis of 2,6-diaryl-4-aminopyrimidines is generally a two-day laboratory endeavor with ethanol as the solvent and triethylamine as the base. In this Letter, we have presented a one-step alternative synthesis approach that uses a microwave reactor in an aqueous media with potassium carbonate as the base and takes 40 minutes to complete. The average yields were also somewhat improved. This new method thus emerges as more eco-friendly, not only because it does not employ triethylamine as base, but also due to a much-reduced usage of organic solvents, leading to less harmful residues. Using this method, we synthesized twenty pyrimidine derivatives with antinociceptive activities in satisfactory chemical yields.

3.3 Plan of Work

The work is carried out as given below:

3.3.1 Synthesis and Purification.

Synthesis of pyrimidine analogues containing Schiff base and its analogous and to confirm purity and characterize structure. characterization of the synthesized analogous by spectral and chromatographic methods such as:

Thin Layer Chromatography.

Melting Point.

Infra-Red Spectral Analysis.

Proton NMR (H1 NMR).

Mass Spectrometry

CHAPTER 4

EXPERIMENTAL WORK

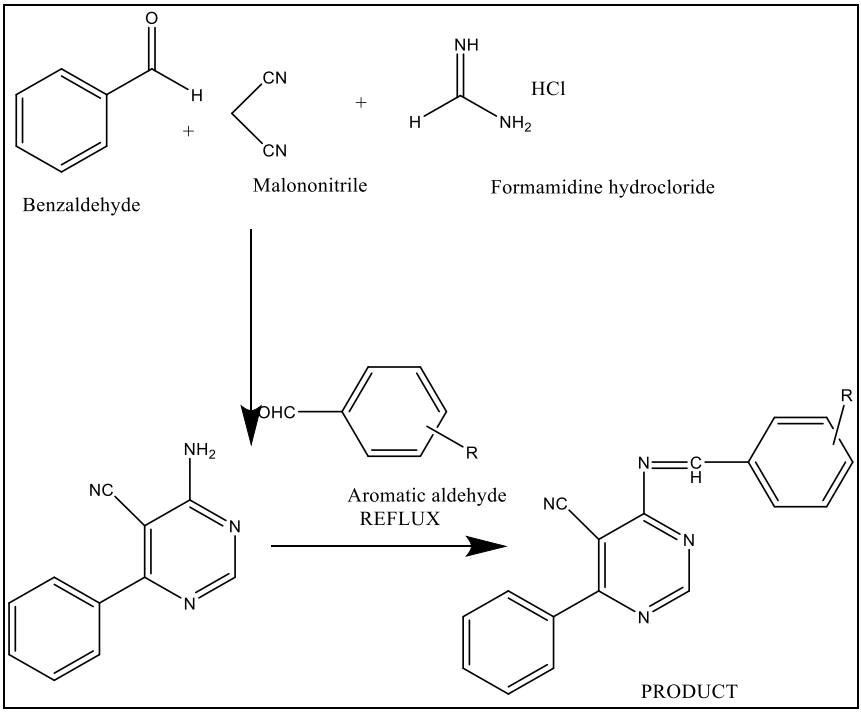
4. Experimental Work

4.1General protocols

All the chemicals used were procured from commercial sources such as Sigma-Aldrich, Merck and Loba Chemie and purified prior to use. Melting points were recorded on open capillary tube on Campbell Melting-point Apparatus and are uncorrected. The purity of all the final compounds was assessed by thin layer chromatography (TLC). The silica gel used for TLC was Silica Gel G procured from Merck and was coated on laboratory glass slides. TLC plates were visualized using iodine chamber or observed under UV light.

Fourier transform infrared (FT-IR) spectra were recorded in potassium bromide (KBr) disk on "Jasco FTIR 4100" and are reported in cm-1. Proton nuclear magnetic resonance (1HNMR) spectra were recorded in CDCl3/ DMSO-d6 using "Bruker Avance (400 MHz) with tetra methyl silane (TMS) as an internal standard. The mass spectra of compounds were recorded on Agilent 6460 Triple Quadrupole LC/MS System with Jet stream ESI ion source.

4.2Synthetic Scheme



4.2.1 General method of synthesis

To a sealed vessel appropriated for reactions in microwave reactors (capacity: 30 mL), were added 1.13 mmol (176 mg, 1.2 equivalent) of acetamidine hydrochloride and 1.88 mmol (249 mg, 2.0 equivalent) of potassium carbonate dissolved in 10 mL of distilled water. This mixture was stirred at room temperature until the neutralization of the acetamidine salt. To the clear basic solution, 0.94 mmol of the corresponding aromatic aldehyde (1.0 equivalent) malononitrile were added. The

mixture was placed in a microwave reactor under the following conditions: temperature 100 C and 300 W of initial power for 40 min. After this time, the consumption of the starting aldehyde was verified by TLC (hexane/ethyl acetate, 8:2 v/v). Allowing the reaction to cool to normal temperature, it was poured over ice. The formed precipitate was then vacuum filtered, washed with distilled water (50 mL), and recrystallized from ethanol to provide the pure pyrimidinones or pyrimidines.

4.3Physicochemical properties of synthesized analogous-

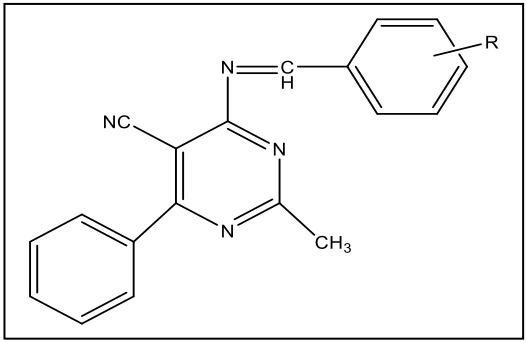


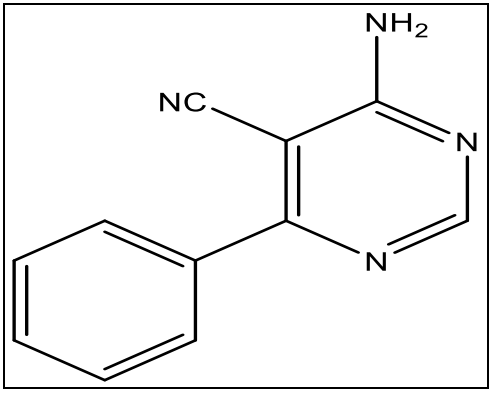
Table 4.1: Physicochemical properties of synthesized analogous.

Compound	R	Melting Point (ºC)	Rf value	%Yield
1	H	254-258	0.75	75
2	p-OCH_3	260-262	0.78	72
3	m-NO_2	246-251	0.65	60

4	p-NO_2	248-250	0.62	65
5	3,4-NO_2	245-247	0.69	68

4.4Spectral data of synthesized analogous

4.4.1 4-amino-6-phenylpyrimidine-5-carbonitrile (intermediate)



4-amino-6-phenylpyrimidine-5-carbonitrile

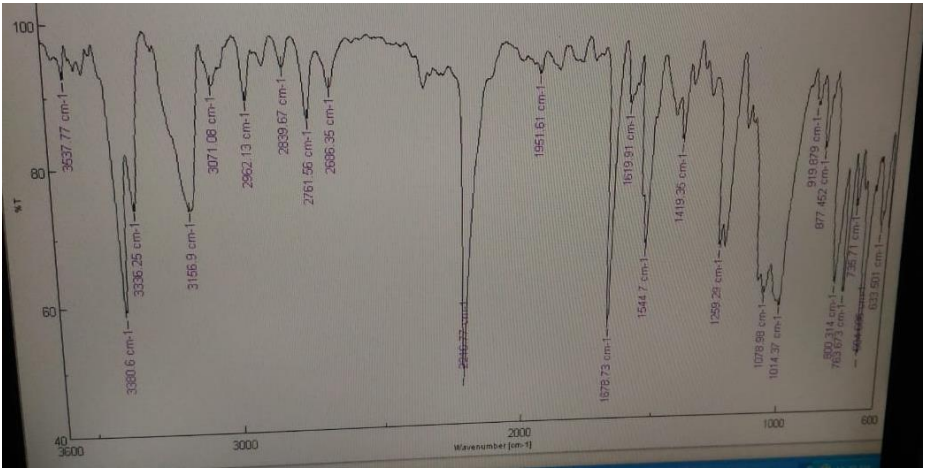


Figure 4.1 IR spectra of intermediate compound.

Table 4.2 IR data of intermediate compound.

Functional group	IR ranges (cm^{-1})
Primary amine group	3368, 3340
Cyano group	2198
C-H(alkane)	2962 cm-1

Mass peak 196.05 M/z

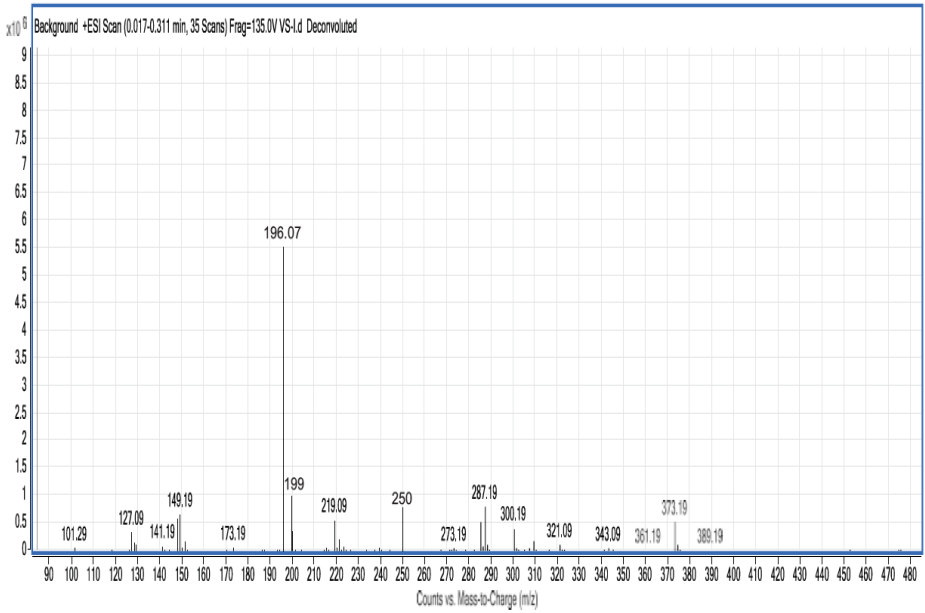
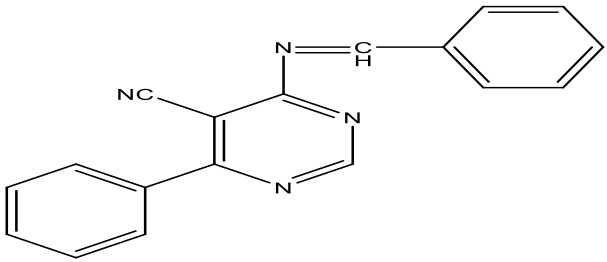


Figure 4.2 Mass spectra of intermediate compound.

4.4.2 4-(benzylidene-amino)-6-phenyl-pyrimidine-5-carbonitrile (Derivative 1)



4-(benzylidene-amino)-6-phenyl-pyrimidine-5-carbonitrile

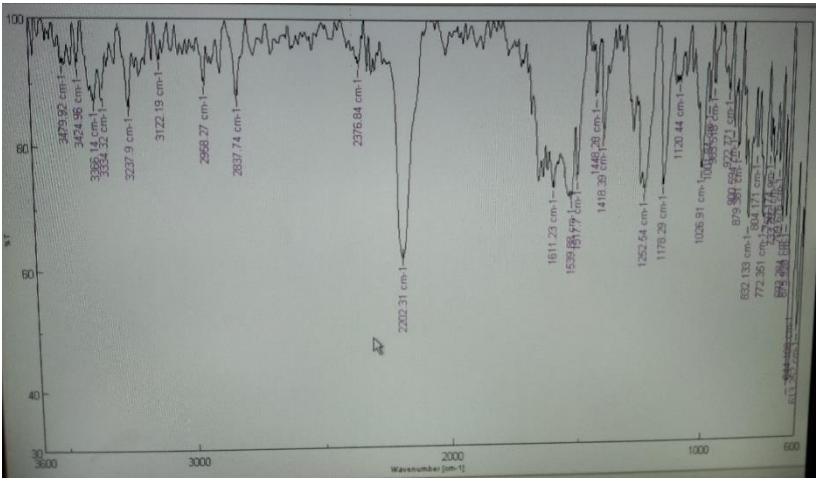


Figure 4.3 IR spectra of derivative 1 compound.

Table 4.3 IR data of derivative 1.

Functional group	IR ranges (cm^{-1})
N=CH	1611
Cyano group	2198
Aromatic (C=C)	1539

Mass peak 284.11 M/z

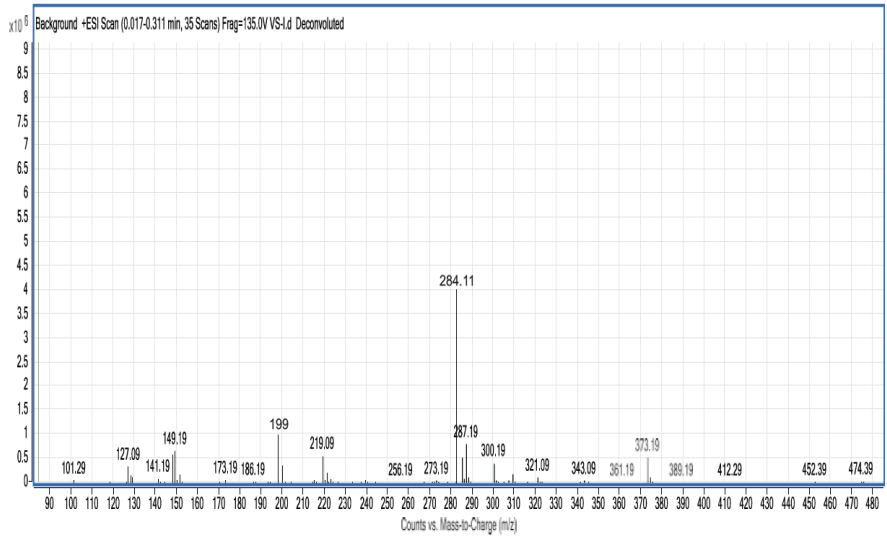


Figure 4.4 Mass spectra of derivative 1.

NMR Spectra of Derivative 1

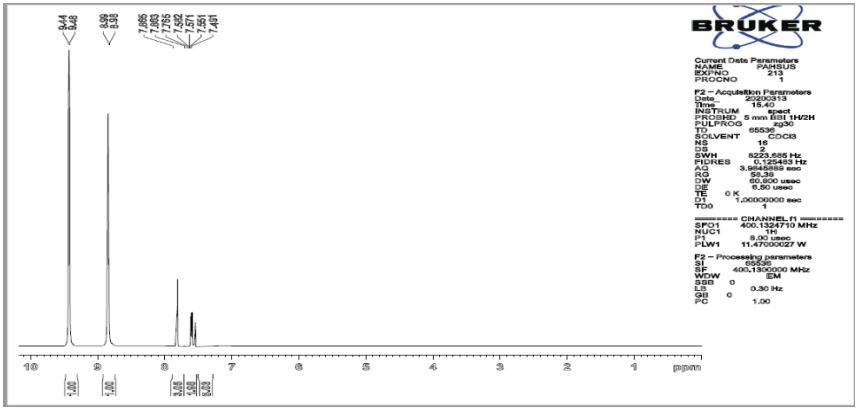
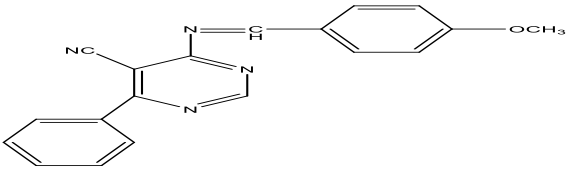


Figure 4.5 NMR spectra of derivative 1

Table 4.4 NMR data of Derivative 1

Sr. No.	Type of H	No. of H	δ Value(ppm)
1.	H of Schiff base	1	8.99
2.	Aromatic H	10	7.3-7.5

4.4.3. 4-((4-methoxybenzylidene) amino)-6 phenylpyrimidine-5-carbonitrile (Derivative 2)



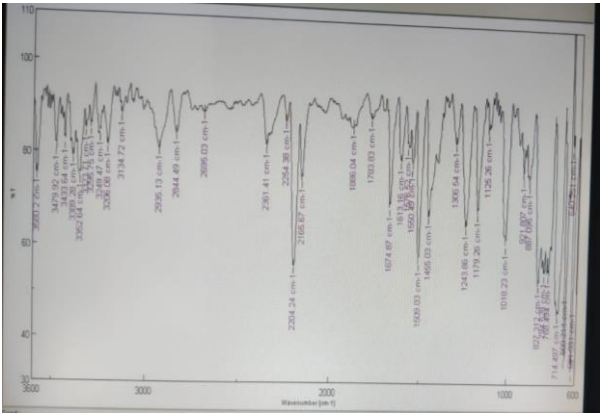


Figure 4.6 IR spectra of derivative 2 compound

Table 4.5 IR data of derivative 2

Functional group	IR ranges (cm^{-1})
N=CH	1613
Cyano group	2198
C-H(alkane)	2962 cm-1
Aromatic (C=C)	1509

Mass Peak 314.12 M/Z

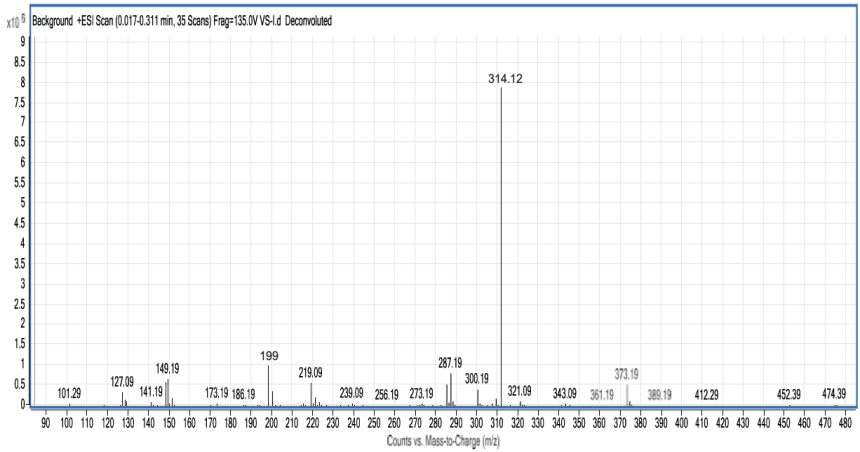
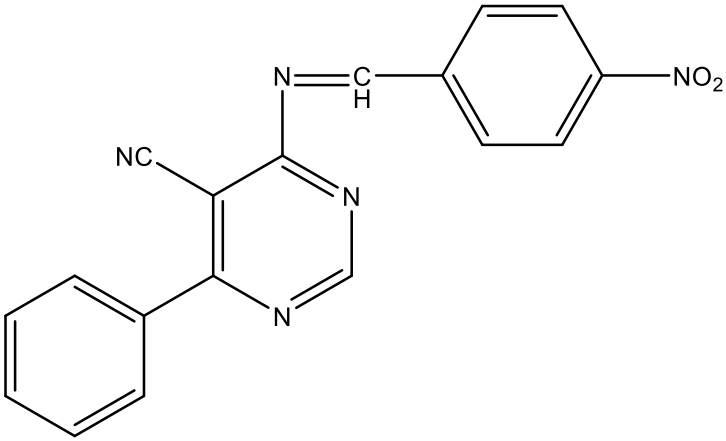


Figure 4.7 Mass spectra of derivative 2.

4.4.4 4-((4-nitrobenzylidine) amino)-6-phenylpyrimidine-5-carbonitrile. (Derivative 3)



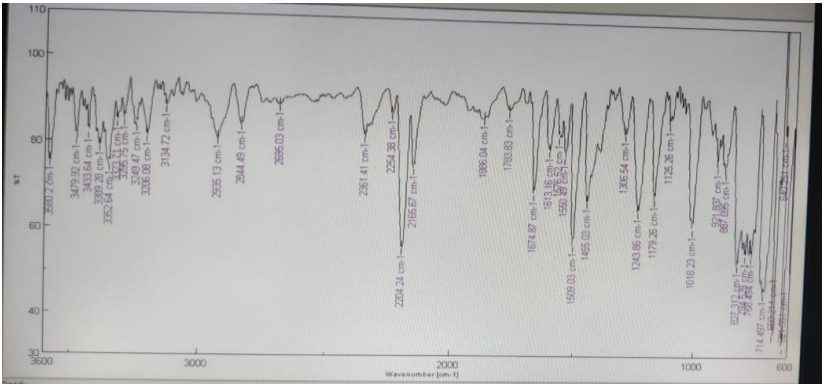


Figure 4.8 IR spectra of derivative 3 compound

Table 4.6 IR data of derivative 3

Functional group	IR ranges (cm^{-1})
N=CH	1611
Cyano group (CN)	2198

Aromatic NO_2	1509, 1306

Mass Peak 329.06 M/Z

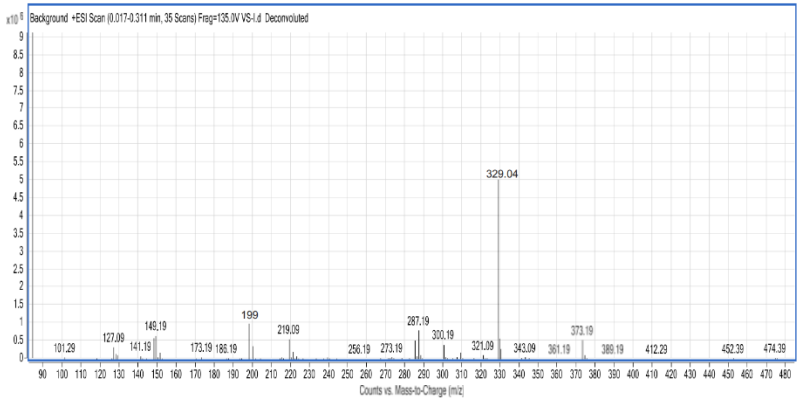
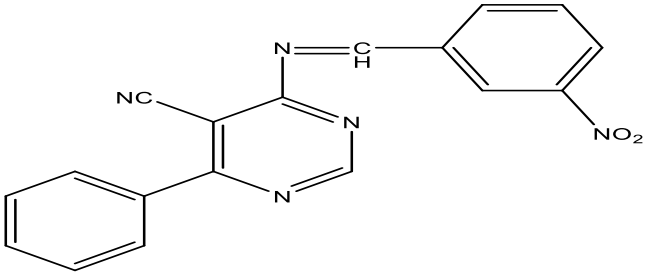


Figure 4.9 Mass spectra of derivative 3.

4.4.5 4-((3-nitro benzylidene) amino) -6-phenylpyrimidine-5-carbonitrile (derivative 4)



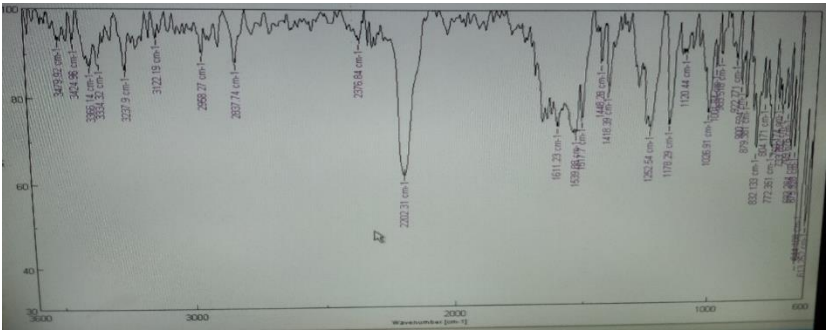


Figure 4.10 IR spectra of derivative 4 compound

Table 4.7 IR data of derivative 4

Functional group	**IR ranges (cm^{-1})**
N=CH	1611
Cyano group	2198
Aromatic NO_2	1550

CHAPTER 5

ANTIMICROBIAL ACTIVITY

5.1 Antimicrobial activity

Antimicrobial activities of newly synthesized Schiff base scaffolds have been performed by taking *S. Aureus, E. coli, and K. pneumoniae* bacterial species. The diameters of inhibition zones (Table 5.1) indicate that all three compounds (4.4.2-4.4.4) exhibited various degrees of antimicrobial activity against the tested microbial species. Among the tested microorganisms, the inhibition of bacterial growth was more pronounced in Gram-positive bacteria S. aureus. A significant inhibitory effect was observed for all compounds against K. pneumoniae. Conversely, the compounds were found to be relatively less effective against E. coli as compared to the other two bacterial species.

Table 5.1 Zone inhibition (mm) showed by novel Schiff bases and the references antibiotic.

Sample	S. aureus (Gm positive)	K. pneumoniae (Gm negative)	E. coli (Gm negative)
4.4.2	7	9	8
4.4.3	14	12	9
4.4.4	11	10	5
Ofloxacin	21	30	15

Figure 5.1 Klebsiella pneumonia

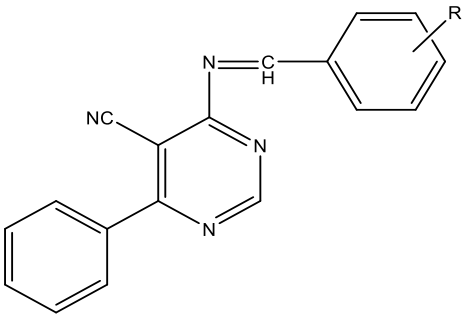
CHAPTER 6

RESULTS, DISCUSSION AND CONCLUSION

6.1 Result, Discussion and Conclusion-

Novel Schiff base moieties of pyrimidine nucleus have been successfully synthesized and characterized by several spectroscopic methods (IR, NMR, MASS).

The general structure of the synthesized drug is as following



From the compounds given in table 4.1 and their activity data given in table 5.1, a simple structure activity relationship can be suggested. **4.4.3** compound having 4-methoxy group [positive resonance effect (+R)] was found to exhibit more potent activity compared to compound **4.4.2 and 4.4.4** containing hydrogen and electron withdrawing 4-Nitro group respectively.

Conclusion-

In our research project we carried out the synthesis of novel Schiff bases of pyrimidine nucleus. The microwave method of synthesis was performed. The physical chemical properties and spectral data of all compounds (4.4.1-4.4.5) have been mentioned in determined are presented in tables 4.1 to 4.14 and in figures 4.1 to 5.1. After confirming their purity and structure we subjected these compounds for antimicrobial activity using. The work can be extended further from the present research results to obtain better compounds.