Synthesis And Biological Evaluation of Various Pyrimidones

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***Abstract*—Heterocyclic compounds such as such as pyrimidine, benzimidazole, benzoxazole etc. are aromatic in nature and present in various medicinal compounds. Triazoles is five membered ring based heterocyclic compound with three nitrogen atom presence in it. Chemistry of heterocyclic compounds plays an important role in our daily lives. Food and drink have been made safe to consume; the whole area of pharmaceuticals has allowed the development and synthesis of new medicines for illnesses and diseases. In the present study, we have synthesized a series of novel chalcones from 2-chloro-7H-pyrrolo[2,3-d] pyrimidine and 1-(4-aminophenyl) ethenone followed by reaction with aldehyde. Further these prepared chalcones were react with urea to produced various Pyrimidones C1-C15. All prepared compounds were characterized by ^{1}HNMR, ^{13}CNMR, IR and Mass spectroscopy and screened for their antimicrobial activity.**

***Index Terms*—Antimicrobial activity, Urea, Heterocyclic compounds, Chalcones, Pyrimidones Spectroscopy**

I. INTRODUCTION

A heterocyclic compound is one in which the ring structure contains at least one atom other than carbon [1, 2]. Due to their enormous potential for processing and synthesizing a broad range of pharmacological actions, heterocyclic compounds have a significant role to play in medicinal chemistry and are currently the focus of a lot of research. Heterocyclic compounds are often found in natural products and play a significant role in the synthesis of biological molecules including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). In fact, DNA is the most important macromolecule in existence, and nucleotides, the units that make up our genes, are derivatives of the purine and pyrimidine bases. Both hemes, the non-protein component of haemoglobin, which is generated from enormous porphyrin rings, and chlorophyll, a green pigment that helps plants create oxygen by absorbing carbon dioxide, are responsible for carrying oxygen in animals. Contrarily, synthetic heterocyclic compounds have a variety of therapeutic uses, such as antibacterial [3], antifungal [4], analgesic [5], anti-inflammatory [6], antimycobacterial [7], antitubercular [8], antimalarial [9], trypanocidal [10], anti-HIV activity [11], anticonvulsant [12], antitumoural [13], antileishmanial agents, and genotoxic [14]. They are also a key structural component of many synthetic drugs and compounds derived from agriculture. For example, fluorescent sensors and dyes, brighteners, polymers, information storage, and analytical reagents are only a few of the several crucial material science uses of most heterocyclic compounds [15].

Chalcones are one of the most important classes of natural products existing in many plant species. In nature, they serve as precursors for flavonoids and isoflavonoids biosynthesis. They are 1,3-diphenyl-2-propen- 1-ones (two aromatic rings connected with a carbonyl moiety). According to Harborne and Mabry (1982), chalcones are crucial flavonoid and isoflavonoid precursors. The preparation of many chalcones by Claisen- Schmidt condensation of methyl ketones with aldehydes in a basic environment Claisen and others, 1881. These substances exhibit antimalarial action in vitro. against variants of Plasmodium that are both chloroquine-sensitive and chloroquine-resistant falciparum [16]. Authors recently reported on the synthesis of chalcones. utilizing acetic acid and perchloric acid as well under acidic conditions [17]. Numerous chalcones have been identified as potent tyrosinases as new depigmenting agents since they act as antioxidants and inhibitors [18].

The creation of organic conductors, semiconductors, photovoltaic cells, molecular wires, organic light-emitting diodes (LED), light harvesting systems, optical data carriers, chemically programmable switches, and liquid crystalline compounds can also make use of a variety of heterocyclic compounds [19-22].

The chemistry of pyrimidine and its derivatives have been studied since the past century due to their diverse pharmacological properties. Both pyrimidine and purine are planar and this flat shape is very important when we consider the structure of nucleic acids. In the presence paper, we have synthesized novel Pyrimidones C1-C15 from novel chalcones and urea by condensation reaction in the presence of alkali under ethanol as the solvent.

II. METHODS AND MATERIALS

2.1 Chemicals and Reagents

All chemicals used were of laboratory reagent grade and used without further purification. Various aldehydes, 1-(4-aminophenyl) ethenone, 2-chloro-7H-pyrrolo[2,3-d] pyrimidine, urea, KOH and ethanol were used as received from Merck, Mumbai, India.

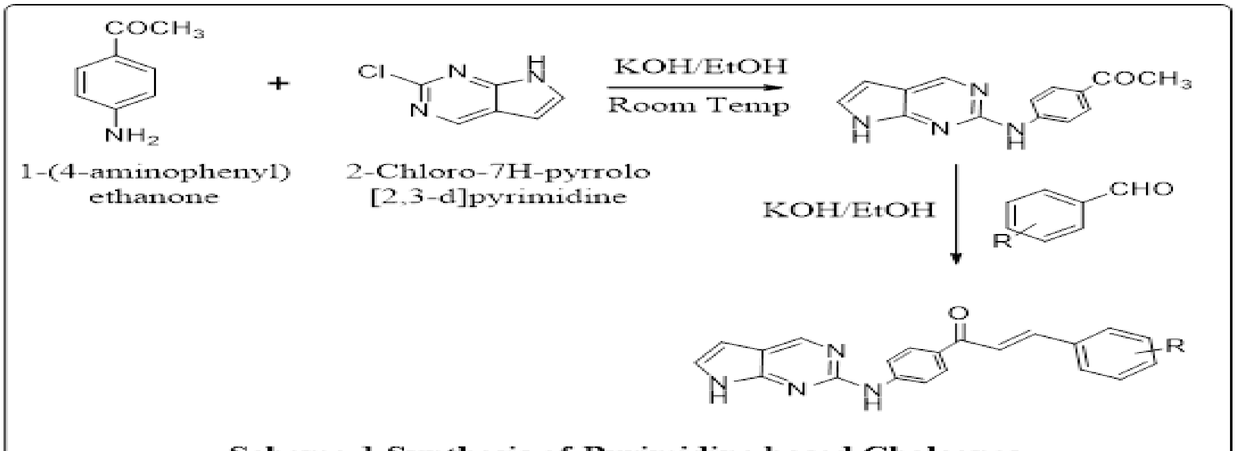
2.2 Experimental

Bruker Avance-400 instrument was used for Proton NMR study and 100MHZ frequency instrument was used for ^{13}C NMR. Parts per million unit was used to expressed chemical shift value. ABB Bomem Inc. FT-IR 3000 Spectrophotometer was used for Infrared Spectral study. Data obtained was expressed in cm^{-1} unit. Shimadzu LCMS-2010 was used for MASS spectral analysis. Perkin Elmer-2400 Series II CHNS/O Elemental Analyzer was used for Composition measurement.

2.3 Method of Synthesis

2.3.1 Synthesis of various chalcones A1-A15

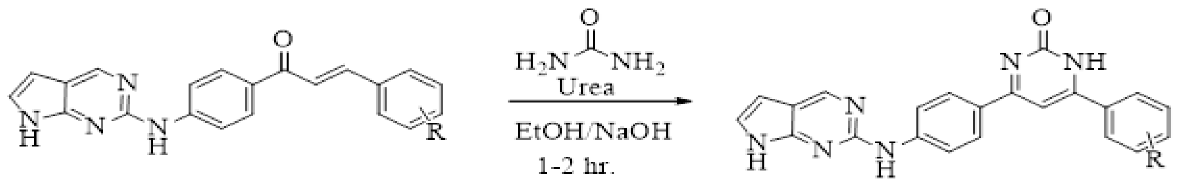
In a 250 ml round bottom flask, 2-chloro-7H-pyrrolo[2,3-d] pyrimidine (0.1 mol) and 1-(4-aminophenyl) ethenone (0.1 mol) dissolved in ethannol (50 ml) with constant shaking maintaining the temperature below 25°C. After the completion of dissolution, the mixture was refluxed for 1.5 hr. then it was cooled and poured into crushed ice. Solid was separated by filtration and crystalline from ethanol. To a well stirred solution, add 40% potassium hydroxide (40 ml) followed by addition of aromatic aldehyde (0.01 mol) drop wise at 0ºC). After the completion of addition, the mixture was stirred for further 1-1.5 hours and left overnight. The contents were poured into ice water and crystallized from ethanol (Scheme 1).



Scheme-1 Synthesis of Pyrimidine based Chalcones

2.3.2 Synthesis of Pyrimidones

Take chalcones (0.01 mol) in 250 ml RBF, add 0.01 mol urea, 40 ml ethanol and 40 ml 40% KOH to this mixture solution. Reflux the entire mixture for 1-2 hr to produced pyrimidine. Completion of reaction was monitored by TLC (Scheme 2).



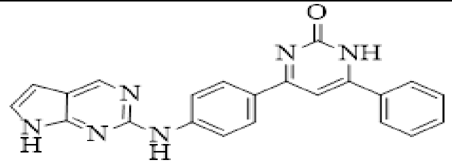
A1-A15

C1-C15

Scheme-2 Synthesis of Pyrimidones C1-C15

III. CHARACTERIZATION

C1 compound of the series is taken as the representative compound. In the ^{1}HNMR spectrum the characteristic signals due to each proton and functional groups with protons are well described on the basis of shielding and deshielding effects. The signal due to aromatic proton of compound was observed in more downfield region at chemical shift value around 6 to 8 ppm. ^{1}HNMR, ^{13}CNMR, IR, MASS spectroscopic data of C1 compound shown below.

Compound code: C1	
Molecular formula: $C_{22}H_{16}N_6O$	
M. P. (°C): 240	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	9.1 (1H, s, NH of amide linkage), 6.5-8.5 (13H, Ar-H, complex), 4.3 (1H, s, -NH of ring), 3.7 (1H, s, -NH of non-ring part).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	127.2, 128.4, 130.4, 131.2, 138.3, 142.4, 150.8, 152.4, 154.1, 157.8.
IR cm^{-1} (KBr):	3515, 3445, 3340, 3051, 3015, 1670, 1593, 1562, 741.
Mass (M+1):	380.1
Elemental analysis:	Calculated (%): C: 69.46; H: 4.24; N:22.09. Found (%): C: 69.51; H: 4.30; N: 22.15

IV. RESULT AND DISCUSSION

Table 1 Data showing synthesis of Pyrimidones C1-C15.

Sr. No.	Compounds Code	R	Reaction Time^a hr	% Yiled^b
1	C1	-H	3.0	77
2	C2	4-OH	3.5	75
3	C3	3-OH	3.5	72
4	C4	2-OH	3.5	72
5	C5	2- OCH_3	4.0	72
6	C6	4-OCH_3	4.0	71
7	C7	2-Cl	3.0	81
8	C8	4-Cl	3.0	82
9	C9	3-Cl	3.0	83
10	C10	2-NO_2	3.0	85
11	C11	4-NO_2	3.0	85
12	C12	3-NO_2	3.0	85
13	C13	3-Br	3.0	78
14	C14	2- Br	3.0	78
15	C15	4- Br	3.0	78

From the Table 1 show the various condensation product of condensation reaction between compounds A1-A15 and urea. It clearly indicates that the compounds bearing electron withdrawing group are synthesized in shorter reaction time as compared to compounds bearing electron donating group. Compounds C10-C12 bearing electron withdrawing were synthesized in 3.5 hr as shorter time as compared to compound B5 and B6 bearing electron donating group in 4.5 hr.

V. ANTIMICROBIAL STUDY

5.1 Experimental Method

The antimicrobial activity of the synthesized compounds was evaluated using the disc diffusion method. Sterile paper discs were impregnated with 50 mg of each test compound and assessed for their inhibitory effects against selected microbial strains. The antibacterial efficacy was examined against Gram-positive organisms, namely Bacillus megaterium [MTCC 121] and Staphylococcus aureus [MTCC 96], as well as Gram-negative bacteria including Proteus vulgaris [MTCC 1771] and Escherichia coli [MTCC 443].

5.1.1 Preparation of Culture Medium

Nutrient agar was employed as the growth medium for bacterial cultures. The medium was prepared by dissolving 5 g of peptone, 3 g of meat extract, 5 g of sodium chloride, and 15 g of agar-agar in 1 liter of distilled water. The solution was sterilized in an autoclave at 125°C under 15 psi pressure for 25 minutes. After sterilization, the medium was allowed to cool to approximately 45°C and then dispensed into sterile Petri plates at a volume of 20 ml per plate. The pH of the medium was maintained between 7.0 and 7.5.

5.1.2 Preparation of Bacterial Inoculum

Bacterial strains were cultured in nutrient broth composed of 10 g beef extract, 5 g sodium chloride, and 10 g peptone per liter of distilled water. The cultures were incubated at 37°C to achieve optimal growth. For the disc diffusion assay, paper discs measuring 5 mm in diameter were sterilized by autoclaving and subsequently dried to eliminate residual moisture. The sterile discs were then impregnated with the test compounds and carefully placed onto the agar plates previously inoculated with the respective bacterial cultures.

5.2 Experimental results

Table 2 Experimental data of antimicrobial activity of compounds C1-C15

Samples	S.aureus (+Ve)	B.megaterium (+Ve)	E. coli (-Ve)	P.vulgaris (-Ve)
C1	7	4	5	5
C2	8	10	10	8
C3	11	12	12	12
C4	8	9	7	6
C5	6	8	7	8
C6	7	11	6	6
C7	8	11	12	9
C8	10	10	8	10
C9	11	12	9	13
C10	12	7	6	7
C11	8	9	6	7
C12	6	7	7	8
C13	8	5	4	11
C14	5	7	10	5
C15	9	9	7	8
Ampicillin	15	14	17	19
Gentamycin	16	15	14	16

(I) Activity against Staphylococcus aureus:

The highest antibacterial effect was observed for compound C12, which exhibited a zone of inhibition of 12.0 mm, while the lowest activity was recorded for compound C14, with a zone of inhibition of 5.0 mm.

(II) Activity against Bacillus megaterium:

Compounds C3 and C9 demonstrated the strongest activity, each showing an inhibition zone of 12.0 mm, comparable to the standard drug. In contrast, compound C1 displayed the lowest activity, with inhibition zones of 4.0 mm.

(III) Activity against Escherichia coli:

Maximum antibacterial activity against this strain was noted for compound C3 and C7, with a zone of inhibition of 12.0 mm. Compound C13 exhibited the least activity, producing a zone of 4.0 mm.

(IV) Activity against Proteus vulgaris:

The highest activity was observed for compound C9, showing a 13.0 mm zone of inhibition. The lowest activity was seen for compounds C1 and C14, each producing an inhibition zone of 5.0 mm.

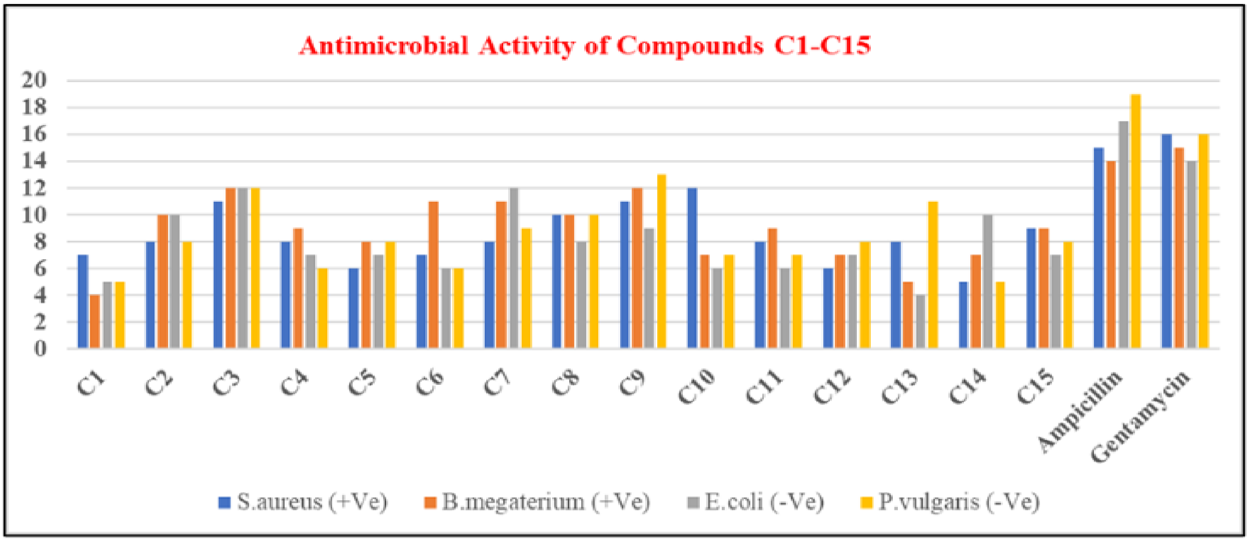


Figure 1 Antimicrobial activity of Compounds C1-C15

VI. CONCLUSION

In conclusion the highly functionalized Pyrimidones C1-C15 were synthesized from various chalcones and urea by condensation reaction. Chalcones used in the pyrimidine synthesis are synthesized from various aromatic aldehydes, 1-(4-aminophenyl) ethenone and 2-chloro-7H-pyrrolo[2,3-d] pyrimidine. All the compounds are well characterized by different spectroscopic techniques.

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