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RESEARCH ARTICLE

Study of Synthesis And Antimicrobial Activity of Novel Pyrimidones From Chalcones and Urea

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ABSTRACT

The Various chalcones A1-A19 were obtained by one pot condensation of 1-chloro-4-methyl benzene with 1-(4-aminophenyl) ethanone followed by condensation with various aromatic aldehydes. All prepared chalcones were further reflux with urea to give pyrimidines B1-B19. All the synthesized pyrimidines were characterized in by 1HNMR, 13CNMR, IR, MASS spectroscopic techniques. Biological evaluation of all synthesized pyrimidines were done using f gram positive bacteria such as Staphylococcus aureus, Bacillus megaterium and gram negative bacteria Escherichia coli, Proteus vulgaris. Most of the prepared compounds shows moderate to good activity against bacteria as compared to standard drugs.

KEYWORDS

Pyrimidone, Chalcone, Aldehydes, Antimicrobial activity, Urea, Spectroscopy

INTRODUCTION

The heterocyclic study for both the preparation & the degradation of pyrimidines result to ring opening or closing these reactions are known amido hydrolases & they are fraction of a super family bearing a varied set of enzymes that catalyze mainly hydrolysis procedure & few isomerization method. They occupation on a several of moiety like as nucleic acid, amino acids and ester of organophosphate of the recognizable amidohydrolases, various enclose been exposed to be necessary for the synthesis or scarcity of pyrimidines.

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This member of biocatalyst has a mono or binuclear metal. At the time of synthesis of the amidohydrolase, dihydrotase catalyzes the ring formation of carbamoyl-L-aspartate.

Organisms that applied the reduction way for pyrimidine dilapidation uses dihydopyrimidases to open pyrimidine nucleus. Organisms that utilize the oxidative pathway use barbituases. All of these enzymes share a seemingly common mechanism, using a metal hydroxide as an acid/base. These reactions are generally reversible. One of the best studied enzymes is dihydroorotase from Escherichia coli. A less studied pyrimidine utilizing-amidohydrolase, which has recently been found, is barbiturase. This enzyme carries out a function similar to that of the dihydropyrimidases. Preliminary biochemical studies of this enzyme show that the enzyme carries out the conversion of barbiturate to uriedo malonic acid, a necessary step in the oxidative catabolism of pyrimidines. This enzyme shows that it has

relatively low homology to the dihydropyrimidases and dihydroorotases. Barbiturase has been shown to be a tetramer with 4.4 mols of zinc per enzyme, likely a mononuclear zinc aminohydrolase. This property indicates a slight difference between the mechanism of this amidohydrolase and those of dihydroorotates and dihydropyrimidases, both of which use a binuclear metal center. Lower metal content for dihydropyrimidase led early researchers to also conclude that it was a mononuclear zinc enzyme. This phenomenon is due to pH playing an important part in the metal binding to amidohydrolases. Both dihydroorotases and dihydropyrimidases require a posttranslational carboxylation of an active site lysine to function properly and bind the second metal effectively. This modification and the increase in metal affinity it provides are highly dependent upon pH. Further structural studies or pH-dependent metal titrations of this enzyme should provide better insight as to whether this new amidohydrolase family does indeed use a different mechanism than that found for the dihydroorotases and dihydropyrimidases. The ring opening of pyrimidines is also seen in nature without the aid of enzymes. At high temperatures, the pyrimidine dihydrouridine, found in modified t-RNA, has been shown to undergo ring opening through hydrolysis. This reaction is accelerated by both heat as well as basic pH, one reason dihydrouracil is thought to be absent in the RNA of thermophiles.

Pyrimidine was first isolated by Gabriel and Colman in 1899. The chemistry of pyrimidine1 and its derivatives have been studied since the past century due to their diverse pharmacological properties. Pyrimidine and purine, the two nitrogen containing heterocyclic aromatic compounds are the parents of the “bases” that constitute a key structural unit of nucleic acids, even though pyrimidine itself does not exist in nature. Both pyrimidine and purine are planar and this flat shape is very important when we consider the structure of nucleic acids.

Methods and Materials

Chemicals and Reagents

All chemicals used were of laboratory reagent grade and used without further purification**.** Various aldehydes, pyridine, 1-chloro-4-methyl benzene, 1-(4-aminophenyl)ethanone urea, NaOH and ethanol were used as received from Merck, Mumbai, India.

Experimental

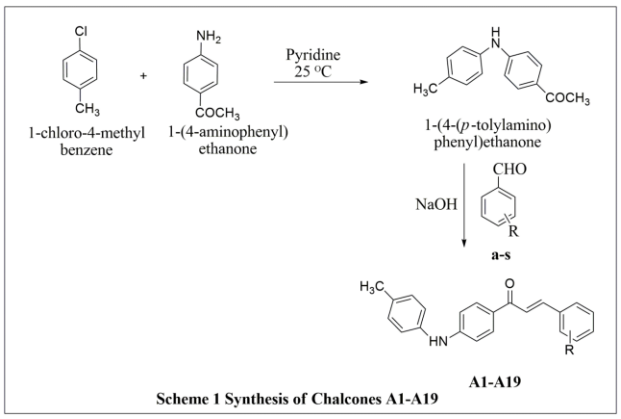
Bruker Avance-400 instrument was used for Proton NMR study and 100MHZ frequency instrument was used for 13C NMR. Parts per million unit was used to expressed chemical shift value. ABB Bomem Inc. FT-IR 3000 Spectrophotometer was used for Infrared Spectral study. Data obtained was expressed in cm-1 unit.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

Method of Synthesis

Synthesis of various chalcones A1-A19

In a 250 ml round bottom flask, 1-chloro-4-methyl benzene (0.1 mol) and1-(4-aminophenyl)ethanone (0.1 mol) dissolved in pyridine (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.

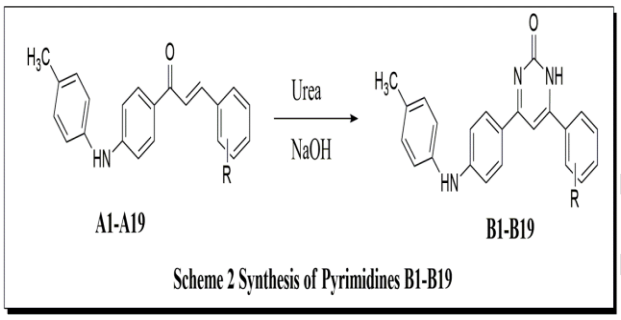
Solid was separated by filtration and crystalline from ethanol. To a well stirred solution of 1-(4-(p-tolylamino)phenyl)ethenone (0.01 mol) in ethanol (40 ml), 40% sodium hydroxide (40 ml) and aromatic aldehyde (0.01 mol) was added drop wise at 0oC). After the completion of addition, the mixture was stirred for further 2-3 hours and left overnight. The contents were poured into ice water and crystallized from ethanol (Scheme 1).



Scheme 1 Synthesis of Chalcones A1-A19

Synthesis of Pyrimidones

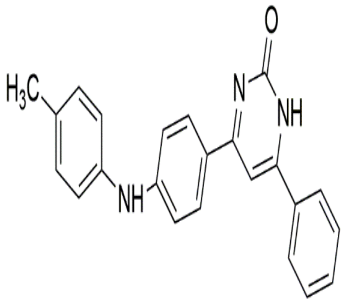
Take chalcones (0.01 mol) in 250 ml RBF, add 0.01 mol urea, 40 ml ethanol and 40 ml 40% NaOH to this mixture solution. Reflux the entire mixture for 30-50 minutes to produced Primidone. Completion of reaction was monitored by TLC (Scheme 2).



Scheme 2 Synthesis of Pyrimidines B1-B19

Characterization

B1 compound of the series is taken as the representative compound. In the ^{1}HNMR spectrum the characteristic signals due to each protons 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 B**1** compound shown below.

Compound code: B1	
Molecular formula: $C_{23}H_{19}N_3O$	
M. P. (°C): 215	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	9.2 (NH, s), 8.3 (NH, s), 6.86-8.40 (14H, Ar-H, complex), 2.5 (3H, s)
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	39.2, 128.2, 129.4, 130.3, 131.6, 139.2, 143.6, 151.8, 153.6, 155.1, 156.8, 170.1.
IR cm^{-1} (KBr):	3441, 3320, 3029, 2950, 1660, 1592, 1569, 744.
Mass (M+1):	353.10
Elemental analysis:	**Calculated (%):** C: 78.16; H: 5.42; N:11.89. **Found (%) :** C: 79.62; H: 5.84; N: 12.02

Result and Discussion

Table 1.1 Data showing synthesis of Pyrimidone B1-B19

Sr. No.	**Compounds Code**	**R**	**Reaction**	**% Yield**

			Time[a] (min)	
1	**B1**	-H	32	74
2	**B2**	4-OH	36	74
3	**B3**	3-OH	36	70
4	**B4**	2-OH	36	78
5	**B5**	2-OCH_3	42	70
6	**B6**	4-OCH_3	42	69
7	**B7**	2-Cl	37	82
8	**B8**	4-Cl	37	82
9	**B9**	3-Cl	37	78
10	**B10**	2-NO_2	27	85
11	**B11**	4-NO_2	27	85
12	**B12**	3-NO_2	27	84
13	**B13**	3-Br	38	80
14	**B14**	2- Br	38	78
15	**B15**	4- Br	38	78
16	**B16**	3, 4-(OCH_3)$_2$	47	74
17	**B17**	3,4,5-(OCH_3)$_3$	47	74
18	**B18**	2-furfuryl[c]	32	84
19	**B19**	2-Thineyl[c]	32	84

[a]Reaction is monitored by TLC, [b]Isolated yield & [c]Names of aldehyde groups

From the Table 1.1 show the various condensation product of condensation reaction between compounds A1-A19 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 B10-B12 bearing electron withdrawing were synthesized in 27 min as shorter time as compared to compound B16 and B17 bearing electron donating group in 47 min.

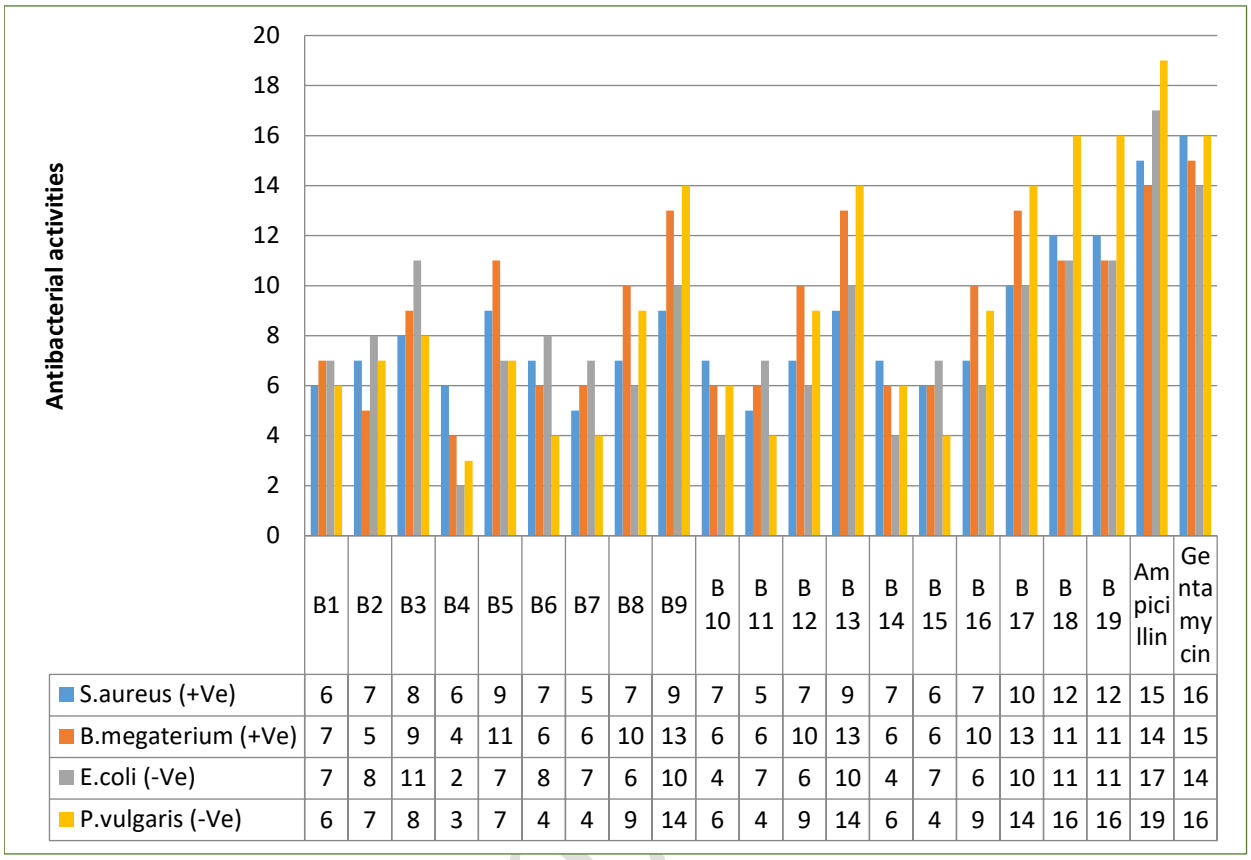
Antimicrobial Activity
Preparation of Media:

For bacterial activity nutrient agar is used. Nutrient agar is prepared as follows:
5gm Peptone, 3gm Metal Extract, 5gm NaCl and 15gm Agar-Agar Peptone were mixed in one liter distilled water and heated to dissolve all the ingredients. The medium was stabilized in autoclave at 15 pound pressure at 125oC for 20 minutes. The medium was cooled down to 45oC and 20 ml poured in sterilized Petri-dish. The pH of the medium was adjusted between 7.0 to 7.5. The culture of the above organism was prepared in nutrient broth dissolved in distilled water. The content of nutrient broth is:

Beef extract : 10 gm
Peptone : 10 gm
Sodium chloride : 5 gm

After sterilizing the above media, it was used for the culture purpose. The culture was ground at 37oC in incubator. With the help of swab, the culture was spread over the agar plates, under specific condition 5 mm diameter paper discs were prepared and were sterilized in autoclave. The solution of the test compound was kept over these paper discs with the help of micropipette. These discs were dried to remove the solvent. Sterile test compound coated by discs were kept in Petri dish containing culture media. The

Figure 1 Antibacterial Activities of *COMPOUNDS B1-B19*



	B1	B2	B3	B4	B5	B6	B7	B8	B9	B 10	B 11	B 12	B 13	B 14	B 15	B 16	B 17	B 18	B 19	Ampicillin	Gentamycin
S.aureus (+Ve)	6	7	8	6	9	7	5	7	9	7	5	7	9	7	6	7	10	12	12	15	16
B.megaterium (+Ve)	7	5	9	4	11	6	6	10	13	6	6	10	13	6	6	10	13	11	11	14	15
E.coli (-Ve)	7	8	11	2	7	8	7	6	10	4	7	6	10	4	7	6	10	11	11	17	14
P.vulgaris (-Ve)	6	7	8	3	7	4	4	9	14	6	4	9	14	6	4	9	14	16	16	19	16

discus was pressed to sterile on media and Petri dishes were incubated for 24 hours at 37oC. After the incubations the zone of inhibition was measured.

Experimental Data of Antimicrobial Study

(I) **Against *Staphylococcus aureus*:**

Maximum activity were found in compounds (B18, B19) zone of inhibition-13.0 m.m. and minimum activity were found in compounds (B7, B11) zone of inhibition -6.0 m.m

(II) **Against *Bacillus megaterium*:**

Maximum activity were found in compounds (B13, B17) zone of inhibition -14.0 m.m where as minimum activity were found in compound (B4) zone of inhibition -5.0 m.m.

(III) **Against *Escherichia coli*:**

Maximum activity were found in compounds (B13, B9, B13, B17, B18, B19) zone of inhibition -12.0 m.m and minimum activity were found in compounds (B4) zone of inhibition -3.0 m.m

(IV) **Against *Proteus vulgaris*:**

Maximum activity were found in compound (B9, B13, B17, B18, B19) zone of inhibition -16.0 m.m (near to standard drug) and minimum activity were found in compounds (B4) zone of inhibition 3.0 mm.

CONCLUSION

In conclusion the highly functionalized pyrimidones derivatives (**B1-B19)** were

synthesized from various chalcones which is insitu formed from different aromatic aldehydes. All the compounds are well characterized by different spectroscopic techniques and screened for antimicrobial activity against gram positive and gram-negative bacteria. Satisfactory results of antimicrobial activity were obtained with most of the compounds.

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