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SYNTHESIS OF VARIOUS PYRIMIDINE DERIVATIVES FROM UREA AND CHALCONES.

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Abstract: The Chalcones are intermediate compounds useful for the synthesis of full various heterocyclic compounds such as flavones, flavanols, pyrimidines, pyrazolines, anthocyanins, benzal coumarones as well as certain compounds like deoxybenzoins and hydantoins which are of some therapeutic value. Condensation reaction of p-cresol with 1-(3-chlorophenyl)ethanone gives product 1-(3-(p-tolyloxy)phenyl) ethanone. which upon condensation with various aromatic aldehyde yield novel chalcones **A1-A15.** All prepared chalcones **A1-A15** werefurther reflux with urea to give pyrimidones **B1-B15**. Characterizationsof all synthesized pyrimidones were done using various spectroscopic techniques such as ^{1}HNMR, ^{13}C NMR, IR, MASS.

Keywords: Pyrimidone, p-cresol, Chalcone, Aldehydes, Urea, Spectroscopy.

Introduction

Chalcones are one of full 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 falsciparum [1].

Authors recently reported on the synthesis of chalcones. utilising acetic acid and perchloric acid as well under acidic conditions [2].

Numerous chalcones have been identified as potent tyrosinases as new depigmenting agents since they act as antioxidants and inhibitors [3].

Herpes simplex virus type 1 (HSV-1)

and human immunodeficiency virus type 1 (HIV-1) have been shown to be sensitive to nitrogen heterocycles with chalcone moiety [4].

Additionally, this group of substances has cytotoxic effects on leukaemia cell lines [5].

We were inspired to synthesise chalcones and convert them to other heterocycles in order to obtain other heterocycles with potentially different or superior physiological activity in light of the variety of pharmacological properties demonstrated by chalcones. The synthesis of chalcone and its transformation into bipyrazoles with nitrogen bases are reported here as a continuation of our work on 3-formyl-4-hydroxycoumarin[6] and 3-formylchromone [7].

It's important to note that bipyrazoles have been claimed to exhibit anti-inflammatory[8],cytotoxic[9], insecticidal[10], herbicidal, and fungicidal[11]; Nayak It has been reported that a number of different chalcones have insecticidal, antichinoviral, and antipicorniviral activities. Chalcone derivatives display a wide variety of attractive biological activities, such as anti-inflammatory, anticancer, antidiabetic, antiprotozoal, antibacterial, antiviral and antioxidant. They have also been reported to show antihypertension and antitumor effects. Their fascinating properties has made them a main target for the development of novel drugs.

Due to their intriguing potential as bioactive molecules, heterocyclic compounds containing nitrogen, oxygen, and sulphur have recently received a lot of attention. Examples of substances with these qualities include pyrazole, benzimidazole, and triazole, which have been shown to have antiproliferative, anti-inflammatory, kinase inhibitory, antibacterial, and anticancer effects. Meanwhile, because of their potential for use as antitubercular, antibacterial, antioxidant, cytotoxic, and anticancer medications. heterocycles containing oxygen as well as sulphur, such benzofuran, benzopyran, and benzothiophene derivatives, have caught the attention of medicinal chemists. Numerous researchers have concentrated their research on the synthesis of chalcone derivatives using heterocyclic scaffolds due to the broad benefits of organic molecules containing heterocyclic moieties.

With the presence of a heterocyclic ring in the structure, several bioactive chalcones are produced. Due to their remarkable biological activities, these compounds have recently undergone significant development that is the topic of this review in the area of medicinal chemistry.

In the field of naturally occurring, vibrant compounds known as "chalcone," Kotahecki and Tambor presented groundbreaking findings. [12].

The Greek word "chalcos," which means "bronze," is where the term "Chalcone" originates. A group of naturally occurring compounds known as chalcones has a wide range of characteristics and biological activity [13].

This molecule contains a carbon-oxygen double bond as well as a carbon-carbon double bond. Unsaturated carbonyl compounds[14]. which are ones in which the double bond between oxygen and carbon is not broken, have bonding characteristics that are comparable to those of both functional groups.

Two carbon-carbon double bonds are separated by a single carbon-carbon bond, and both double bonds are conjugated.

2. Methods and Materials

2.1 Chemicals and Reagents

All chemicals used were of laboratory reagent grade and used without further purification**.** Various aldehydes, p-cresol, 1-(3-chlorophenyl)ethenone, urea, NaOH 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 (E)-3-phenyl-1-(3-(p-tolyloxy)phenyl)prop-2-en-1-one A1-A15.

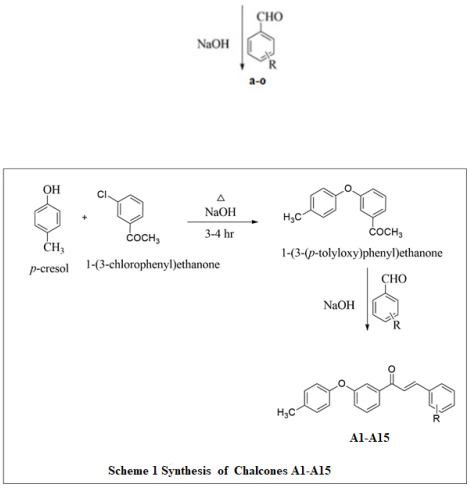
In a 250 ml round bottom flask, p-cresol (0.1 mol) and 1-(3-chlorophenyl)ethenone in the presence of sodium hydroxide (30 ml) with constant shaking maintaining the temperature below 25°C.

After the completion of dissolution, the mixture was refluxed for 3-4 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 this prepared product **1-(3-(p-tolyloxy)phenyl)ethanone**(0.01 mol)in ethanol (40 ml), 40% sodium hydroxide (40 ml) and aromatic aldehyde (0.01 mol) was added drop wise at 0°C).

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 to produced chalcone **A1-A15**

(**Scheme 1**).

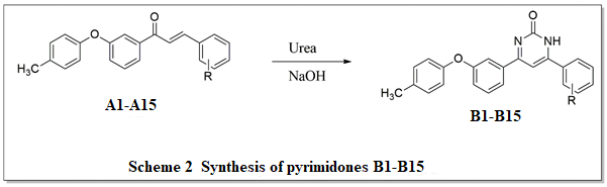
Add label (a-o) for aldehyde in step 2 upon reaction arrow. given as below:



Scheme 1 Synthesis of Chalcones A1-A15

2.3.2 Synthesis of Pyrimidones B1-B15.

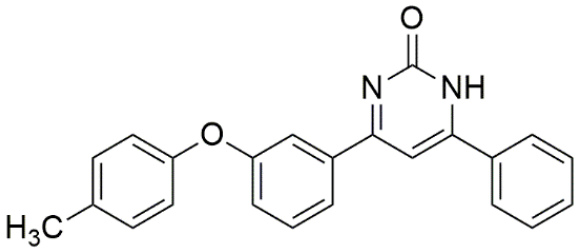
Take chalcones (0.01 mol) in 250 ml round bottom flask, add 0.01 mol urea, 40 ml ethanol and 40 ml 40% NaOH to this mixture solution. Reflux the entire mixture for 30-50 minutes toproduced Pyrimidone **B1-B15.** Completion of reaction was monitored by TLC **(Scheme 2)**.

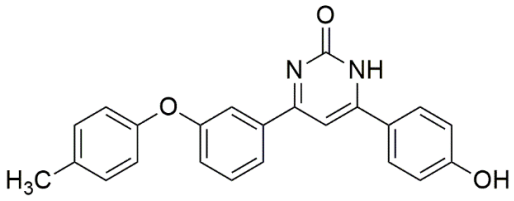


Scheme 2 Synthesis of pyrimidones B1-B15

3. Characterization

B1 &B2 compounds of the series is taken as the representative compound. In the ^{1}H NMR 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 8ppm.^{1}HNMR, ^{13}CNMR, IR, MASS spectroscopic data of **B1 & B2** compounds shown below.

Compound Code : B1	
Molecular Formula $C_{23}H_{18}N_2O_2$	
M.P. (°C):236	
^{1}H NMR (400 MHz, $CDCl_3$) **δ ppm:**	δ 2.23 (3H, s), 6.77 (1H, s), 6.90 (2H, ddd, J = 8.2, 1.8, 0.6 Hz), 6.96-7.10 (3H, 7.03 (ddd, J = 8.2, 1.0, 0.6 Hz), 7.04 (dt, J = 8.2, 1.4 Hz)), 7.36 (1H, ddd, J = 8.2, 7.9, 0.5 Hz), 7.48-7.65 (4H, 7.55 (dddd, J = 8.0, 7.3, 1.3, 0.4 Hz), 7.58 (dddd, J = 8.0, 1.6, 1.5, 0.4 Hz)), 7.66-7.78 (2H, 7.72 (tt, J = 7.3, 1.6 Hz), 7.73 (ddd, J = 1.5, 1.3, 0.5 Hz)), 8.09 (1H, dt, J = 7.9, 1.4 Hz).
^{13}C NMR (100 MHz, $CDCl_3$) **δ ppm:**	32.4, 126.2, 129.4, 130.3, 138.6, 139.2, 143.6,151.8, 153.6, 155.1, 160.8, 170.1.
IR cm^{-1}(KBr) :	3356, 3020, 2970, 1640, 1592, 1569, 744
Mass (M+1):	354.0
Elemental analysis:	**Calculated (%):**C: 77.95, H: 5.12, N: 7.90 .**Found (%):** C: 77.92, H: 5.30, N: 7.93

Compound Code : B2	
Molecular Formula $C_{23}H_{18}N_2O_3$	
M.P. (°C):242	
^{1}H NMR (400 MHz, $CDCl_3$) **δ ppm:**	δ 2.23 (3H, s), 6.66 (1H, s), 6.81-6.96 (4H, 6.87 (ddd, J = 8.0, 1.0, 0.4 Hz), 6.90 (ddd, J = 8.2, 1.8, 0.6 Hz)), 6.96-7.09 (3H, 7.03 (ddd, J = 8.2, 1.0, 0.6 Hz), 7.03 (dt, J = 8.2, 1.4 Hz)), 7.35-7.60 (3H, 7.42 (ddd, J = 8.2, 7.9, 0.5 Hz), 7.54 (ddd, J = 8.0, 1.6, 0.4 Hz)), 7.72 (1H, ddd, J = 1.5, 1.3, 0.5 Hz), 8.08 (1H, dt, J = 7.9, 1.4 Hz).
^{13}C NMR (100 MHz, $CDCl_3$) **δ ppm:**	32.6, 125.2, 127.4, 130.3, 138.6, 139.4, 143.6, 151.8, 153.6, 155.1, 160.8, 170.1.
IR cm^{-1}(KBr) :	3437, 3356, 3020, 2970, 1640, 1592, 1569, 744.
Mass (M+1):	370.0
Elemental analysis:	**Calculated (%):**C: 74.58, H: 4.90; N:7.56. .**Found (%):** C: 74.80; H: 4.92;N: 7.60

4. Result and Discussion

Table1 Data showing synthesis of Pyrimidone B1-B15.

Sr. No.	Compounds Code	R	Reaction Time[a] (hr)	% Yiled[b]
1	**B1**	-H	3	73
2	**B2**	4-OH	3.5	73
3	**B3**	3-OH	3.5	69
4	**B4**	2-OH	3.5	76
5	**B5**	2- OCH_3	4	69
6	**B6**	4-OCH_3	4	68
7	**B7**	2-Cl	3.5	81
8	**B8**	4-Cl	3.5	81
9	**B9**	3-Cl	3.5	76
10	**B10**	2-NO_2	2.5	84
11	**B11**	4-NO_2	2.5	84
12	**B12**	3-NO_2	2.5	83
13	**B13**	3-Br	3.5	79
14	**B14**	2- Br	3.5	76
15	**B15**	4- Br	3.5	79

[a]Reaction is monitored by TLC, [b]Isolated yield .

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 **B10-B12** bearing electron withdrawing were synthesized in **2.5 hr**as shorter time as compared to compound **B5** and **B6** bearing electron donating group in **4.0**hr.

5. Antimicrobial Activity

5.1 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 125°C for 20 minutes. The medium was cooled down to 45°C 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:

1) Beef extract : 10 gm
2) Peptone : 10 gm
3) Sodium chloride : 5 gm

After sterilizing the above media, it was used for the culture purpose. The culture was ground at 37°C 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 discus was pressed to sterile on media and Petri dishes were incubated for 24 hours at 37°C. After the incubations the zone of inhibition was measured.

5.2 Experimental Data of Antimicrobial Study.

Table 2 Antibacterial Activities of *COMPOUND B1-B15*

Samples	S.aureus (+Ve)	B.megaterium (+Ve)	E.coli (-Ve)	P.vulgaris (-Ve)
B1	9	8	4	9
B2	7	9	8	8
B3	8	4	10	12
B4	4	5	6	4
B5	11	11	7	7
B6	9	6	5	6
B7	8	7	5	10
B8	10	9	10	5
B9	12	12	12	6
B10	9	5	7	6
B11	9	5	4	7
B12	10	9	9	8
B13	12	7	13	6
B14	8	8	9	6
B15	8	8	6	10
Ampicillin	15	14	17	19
Gentamycin	16	15	14	16

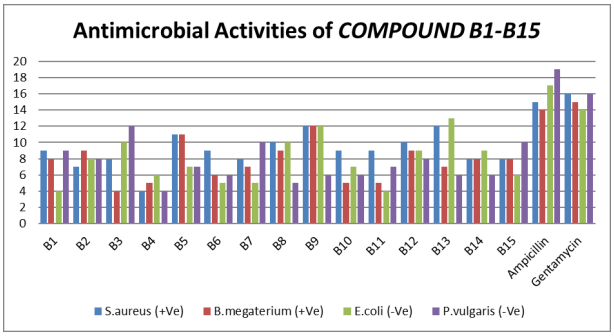


Figure 1 Antimicrobial Activities of COMPOUND B1-B15

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

Maximum activity were found in compounds (B9, B13) zone of inhibition 12.0 mm whereas minimum activity were found in compound (B4) zone of inhibition 4.0 mm.

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

Maximum activity was found in compounds (B9) zone of inhibition 12.0 mm. and minimum activity were found in compounds (B3) zone of inhibition 4.0 mm.

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

Maximum activity were found in compound (B13) zone of inhibition 13.0 mm (near to standard drug) and minimum activity were found in compounds (B1 and B11) zone of inhibition 4.0 mm

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

Maximum activity were found in compounds (B3) zone of inhibition 12.0 mm and minimum activity were found in compounds (B4) zone of inhibition 4.0 mm

6. Conclusion

In conclusion the highly functionalized pyrimidones derivatives (**B1-B15)** were synthesized from various chalcones which is insituformed 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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