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SYNTHESIS OF VARIOUS PYRIMIDINE DERIVATIVES FROM THIOUREA AND CHALCONES.

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Abstract: Chalcones are kin moieties for synthesizing various heterocyclic compounds having medicinal value. Such medicinally importance compounds are Chalcones are flavones, flavanols, pyrimidines, pyrazolines, anthocyanins, thiopyrimidine, benzal coumarones as well as certain compounds like deoxybenzoins and hydantoins which are of some medicinal value.

Reaction between p-cresol with 1-(3-chlorophenyl)ethanone gives product 1-(3-(p-tolyloxy)phenyl)ethanone. This product upon condensation with various aromatic aldehyde produced novel chalcones **A1-A15.** All prepared chalcones **A1-A15** were further reflux with Thiourea to give Thiopyrimidones **C1-C15**. characterizations of all synthesized Thiopyrimidones were done using various spectroscopic techniques such as ^{1}HNMR & ^{13}CNMR. IR, MASS.

Keywords: Thiopyrimidone, p-cresol, Chalcone, Aldehydes, Thiourea, Spectroscopy.

1. 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.

In the field of drugs invention heterocyclic chemistry plays important role. Heterocycles are common in marketed drugs both as flat heteroaromatics and as saturated, fused or spirocy clicmoiety[1].

The functionalized heterocyclic compounds is censorious for drug

invention and expansion. Accessibility of various newly synthetic approach, the most popular helping reaction in medicinal chemistry was invented 20 year ago. Very useful methodology is SNAr Substitution[2].

synthesized, characterized, and evaluated heterocyclic compounds with various heterocycles component such as benzoxazinone, benzimidazole, quinazolinone, and benzofuranone heterocyclic ring useful for anticancer activity in human against human hepatocellular carcinoma cell line (HepG2) using sulforhodamine B (SRB) and dimethylthiazol-diphenyltetrazolium bromide (MTT) assays[3].

For the treatment of cancer platinum base compounds were used such as cisplatin it is useful for fight against cancer. N- heterocycliccarbene (NHCs) have invent for flexible class of ligands which can be easily redesign. Metal-NHCs is popular for their catalysts use such as antimicrobial agents and anti canceragents[4].

Heterocyclic compounds are compounds that possess complex toroidal component containing atoms in addition to carbon atom. The more common heterogeneous atoms are nitrogen, oxygen and sulfur. The importance of these compounds are involved in the installation of chlorophyll in the plant, and the Hemoglobin contain four rings of Pyrrole is widespread compounds in Nature. Many antibiotics with penicillin-containing ring systems are homogenous, and this allows for the synthesis of a large number of heterocyclic compounds in vitro. Another benefit of having biological activity is that these compounds may be used as dyes, insecticides, and polymers.In organic synthesis methods, heterocycles are easily controlled; compound modifications are simple to do and can improve or reduce reactivity[5].

The broadest and most varied collection of organic natural or manufactured chemicals that lacks clear boundaries is comprised of heterocyclic compounds. In addition to making up the great majority of commercially available compounds, heterocycles are crucial in the design and discovery of contemporary drugs because they enable the manufacture of a large range of scaffolds and compounds using reliable synthetic research techniques.

Modern improvements in synthetic techniques enable quick access to a variety of functionalized heterocyclic compounds, expanding the class of chemical compounds that are similar to drugs and aiding in the process of drug discovery. Heterocyclic compounds provide a number of benefits, including the optimisation of lipophilicity, solubility, polarity, H-bonding capacity, etc., which may improve the ADMET profile, physicochemical properties, and pharmacological characteristics of drug-like candidates[6].

One of the most significant medical advances of the past century was the creation of antimicrobial agents (antibacterials and antifungals) to treat infections. The improvements in medical field.

However, a condition known as "antimicrobial resistance" poses a hazard to health care. Resistance to these medications has emerged as a result of the growing usage of antibacterial and antifungal treatments in recent years, with significant implications for morbidity, mortality, and healthcare expenditures. Despite the abundance of antibiotics and chemotherapeutics that are now used in medicine, antimicrobial resistance has significantly increased the demand for new classes of antimicrobial drugs in recent decades[7].

A growing number of immunocompromised hosts, including as those with HIV infection, transplant recipients, and cancer patients, has enhanced the clinical importance of fungi illnesses significantly in the latter part of the 20th century.The presence of aspergillosis in severe acute respiratory syndrome (SARS) and the inclusion of Coccidioidesimmitis as a strong agent of bioterrorism are examples of the growing fungal danger. Most human investigations show that the crude death rate from opportunistic fungal infections still surpasses 50%, and Aspergillus spp.-infected bone marrow transplant patients have reported a crude mortality rate as high as 95%[8].

These substances exhibit antimalarial action in vitro. against variants of Plasmodium that are both chloroquine-sensitive and chloroquine-resistant falsciparum [9].

Authors recently reported on the synthesis of chalcones. utilising acetic acid and perchloric acid as well under acidic conditions [10]. Numerous chalcones have been identified as potent tyrosinases as new depigmenting agents since they act as antioxidants and inhibitors [11].

Chalcone is very important class of intermediate found in the natural product and plant occurring. 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. chalcone derivative 2 -hydroxyl-4-dimethylamino-chalcone shows highly florescence[12].

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.

In the presence paper we have synthesized various chalcones and then carried out condensation reaction with Thiourea to produced Thiopyrimidine derivatives.

2. Methods and Materials

2.1 Chemicals and Reagents

All of the chemicals were of the reagent-grade variety and were used directly. As acquired from Merck, Mumbai, India, various aldehydes, p-cresol, 1-(3-chlorophenyl)ethenone, Thiourea, NaOH, and ethanol were utilised.

2.2 Experimental

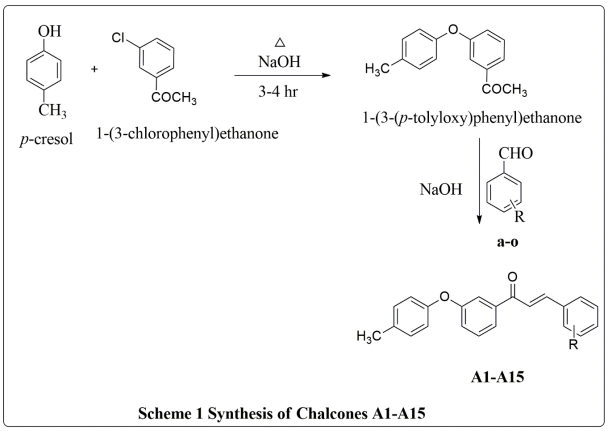
For the Proton NMR investigation, a Bruker Avance-400 instrument was employed, and for the ^{13}CNMR study, a 100MHZ frequency equipment. Chemical shift value was reported in parts per million. The infrared spectrum analysis was conducted using an FT-IR 3000 Spectrophotometer from ABB Bomem Inc. The measured data were represented in cm-1 units. For MASS spectrum analysis, a Shimadzu LCMS-2010 was employed. For measuring composition, a Perkin Elmer-2400 Series II CHNS/O Elemental Analyzer was employed.

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) ethanone 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^{o}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**

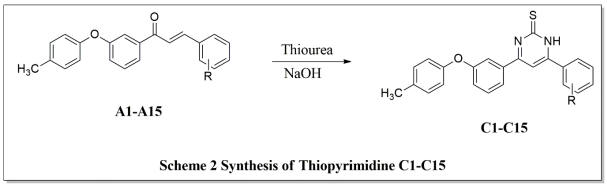
(**Scheme 1**).



Scheme 1 Synthesis of Chalcones A1-A15

2.3.2 Synthesis of Thiopyrimidones C1-C15.

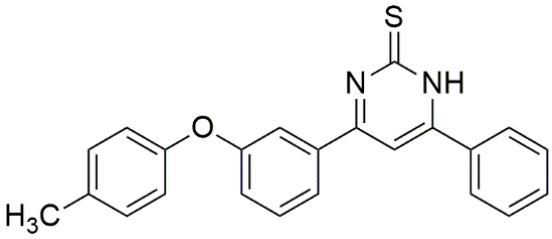
Take chalcones (0.01 mol) in 250 ml round bottom flask, add 0.01 mol Thiourea, 40 ml ethanol and 40 ml 40% NaOH to this mixture solution. Reflux the entire mixture for 30-50 minutes to produced Primidone**.** Completion of reaction was monitored by TLC (**Scheme 2)**.

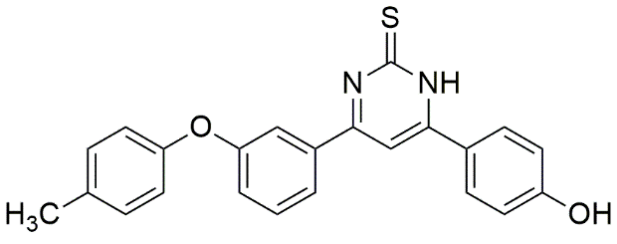


Scheme 2 Synthesis of Thiopyrimidine C1-C15

3. Characterization

C1 & C2 compounds 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 8ppm. ^{1}HNMR, ^{13}CNMR, IR, MASS spectroscopic data of **C1 & C2** compounds shown below.From the

Compound Code : C1	
Molecular Formula $C_{23}H_{18}N_2OS$	
M.P. (°C):242	
^{1}H NMR (400 MHz, $CDCl_3$) **δ ppm:**	δ 2.23 (3H, s), 6.57 (1H, s), 6.84-7.09 (5H, 6.90 (ddd, J = 8.2, 1.8, 0.6 Hz), 6.98 (dt, J = 8.2, 1.4 Hz), 7.03 (ddd, J = 8.2, 1.0, 0.6 Hz)), 7.33-7.59 (6H, 7.40 (ddd, J = 8.2, 7.9, 0.5 Hz), 7.48 (dddd, J = 7.8, 1.7, 1.4, 0.4 Hz), 7.52 (dddd, J = 7.8, 7.4, 1.5, 0.4 Hz), 7.52 (tt, J = 7.4, 1.7 Hz)), 7.66 (1H, ddd, J = 1.5, 1.3, 0.5 Hz), 8.02 (1H, dt, J = 7.9, 1.4 Hz).
^{13}C NMR (100 MHz, $CDCl_3$) **δ ppm:**	33.4, 127.2, 129.4, 131.3, 138.6, 132.2, 143.6, 151.8, 153.6, 155.1, 161.8, 165.1.
IR cm^{-1}(KBr) :	3345, 3021, 2978, 1640, 1592, 1564, 742.
Mass (M+1):	370.0
Elemental analysis:	**Calculated (%):**C: 74.57, H: 4.90; N:7.56. .**Found (%):** C: 74.92; H: 4.30;N: 7.93

Compound Code : C2	
Molecular Formula $C_{23}H_{18}N_2O_2S$	
M.P. (°C):256	

^{1}H NMR (400 MHz, $CDCl_3$) **δ ppm:**	δ 2.23 (3H, s), 6.47 (1H, s), 6.84-7.09 (7H, 6.90 (ddd, J = 8.2, 1.8, 0.6 Hz), 6.90 (ddd, J = 8.4, 1.1, 0.4 Hz), 6.97 (dt, J = 8.2, 1.4 Hz), 7.03 (ddd, J = 8.2, 1.0, 0.6 Hz)), 7.39 (1H, ddd, J = 8.2, 7.9, 0.5 Hz), 7.51-7.71 (3H, 7.57 (ddd, J = 8.4, 1.9, 0.4 Hz), 7.66 (td, J = 1.4, 0.5 Hz)), 8.01 (1H, dt, J = 7.9, 1.4 Hz).
^{13}C NMR (100 MHz, $CDCl_3$) **δ ppm:**	33.6, 126.2, 127.4, 131.3, 138.6, 140.4, 143.6, 151.8, 153.6, 155.1, 160.8, 160.1
IR cm^{-1}(KBr) :	3432, 3346, 3020, 2971, 1640, 1590, 1569, 744.
Mass (M+1):	386.0
Elemental analysis:	**Calculated (%):**C: 71.48, H: 4.69; N:7.25. .**Found (%):** C: 71.47; H: 4.92;N: 7.30.

4. Result and Discussion

Table 1 Data showing synthesis of ThioPyrimidone C1-C15.

Sr. No.	Compounds Code	R	Reaction Time[a] (hr)	% Yiled[b]
1	**C1**	-H	2.5	74
2	**C2**	4-OH	3.0	74
3	**C3**	3-OH	3.0	68
4	**C4**	2-OH	3.0	75
5	**C5**	2- OCH_3	3.5	68
6	**C6**	4-OCH_3	3.5	67
7	**C7**	2-Cl	2.3	80
8	**C8**	4-Cl	2.3	80
9	**C9**	3-Cl	2.3	75
10	**C10**	2-NO_2	2.0	83
11	**C11**	4-NO_2	2.0	83
12	**C12**	3-NO_2	2.0	82
13	**C13**	3-Br	3.0	78
14	**C14**	2- Br	3.0	75
15	**C15**	4- Br	3.0	75

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

Table 1 show the various condensation product of condensation reaction between compounds **A1-A15** and Thiourea. It clearly indicates that the compounds bearing electron with drawing group are synthesized in shorter reaction time as compared to compounds bearing electron donating group. Compounds

C10-C12 bearing electron with drawing were synthesized in **2.0hr** as shorter time as compared to compound **C5** and **C6** bearing electron donating group in **3.5 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 C1-C15*

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

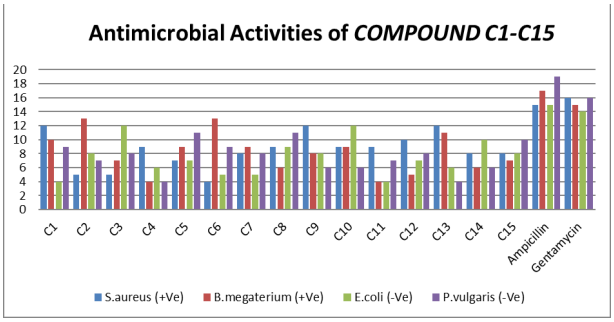


Figure 1 Antimicrobial Activities of COMPOUND C1-C15

(I) Against *Staphylococcus aureus*:

Maximum activity were found in compounds (C1, C9 and C13) zone of inhibition -12.0 m.m where as minimum activity were found in compound (C6) zone of inhibition -4.0 m.m.

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

Maximum activity was found in compounds (C2 and C6) zone of inhibition-13.0 mm. and minimum activity were found in compounds (C4 and C11) zone of inhibition -4.0 mm

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

Maximum activity were found in compound (C3 and C10) zone of inhibition -12.0 mm (near to standard drug) and minimum activity were found in compounds (C1 and C11) zone of inhibition -4.0 mm

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

Maximum activity were found in compounds (C5 and C8) zone of inhibition -11.0 mm and minimum activity were found in compounds (C4 and C13) zone of inhibition -4.0 mm.

6. Conclusion

In conclusion the highly functionalized Thiopyrimidones derivatives (**C1-C15)** were synthesized from various chalcones which is in situ 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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