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Synthesis and Characterization of Novel 4-(4-(4-(4-Methoxyphenoxy) Phenoxy) Phenyl)-6-Phenylpyrimidine 2-Amine and their Biological Evaluation

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ABSTRACT:

The synthesis of chalcones was carried out by one pot condensation of 1-chloro-(4-tolyloxy) benzene with 1-(4-hydroxylphenyl) ethanone followed by condensation with various aromatic aldehydes. Prepared chalcones were refluxing with guanidine to yields various pyrimidine derivatives. All the prepared compounds were characterized in by 1H NMR, 13C NMR, IR, MASS spectroscopic techniques. Biological evaluation of mention compounds was also made in terms of gram positive bacteria such as Staphylococcus aureus, Bacillus megaterium and gram negative bacteria Escherichia coli, Proteus vulgaris.

KEYWORDS: Pyrimidine, Chalcone, Aldehydes, Antimicrobialactivity, Guanidine, Spectroscopy.

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1 INTRODUCTION:

Nitrogen containing heterocycles have always played a major role in the pharmaceutical and agrochemical industries because of their potent physiological properties, which have resulted in numerous applications [1]. Quinazolinone and their derivatives are building block for around more than 150 naturally occurring alkaloid isolated from plant kingdom, microorganisms and animals. There has been enomous increase in the interest among biologist and chemist in their synthesis and bioactivity of quinazolinone derivatives. Compound having 4(3H)-quinazolinone ring system is known to possess antitumor, antimicrobial and anticoagulant activities [2-6]. Quinazolinone have been frequently used in medicines [7-9].

Diseases of the arterial tree cause more premature deaths than all other diseases such as cancer. Among the major risk factors for arterial diseases, high blood pressure is the most important one [10]. Following the observation made in the late 1940's that some 2-4 diaminopyrimidines were capable of interfering with the utilization of folic acid Lactobacillus casei, a property also shown by proguanil, these received intensive study as potential anti malarial .It is noted that certain 2,4-diamino -5-phenoxy pyrimidines possessed a structural resemblance to proguanil, a large series of 2,4-diamino-5-phenyl pyrimidines is prepared tested for activity. Maximum activity is present in the 6th position of pyrimidine ring and when chlorine atom is present in the Para position of the phenyl ring. The best in the series of compound is one that became known as pyrimethamine.

Objectives of present work To synthesized various chalcones **3a-3s** by condensation reaction of 1-chloro-(4-tolyloxy) benzene with 1-(4-hydroxylphenyl) ethanone to yields product which upon condensation with various aromatic aldehyde. Prepared chalcones on condensation reactions with guanidine to afford various condensation products **A1-A19**. All the synthesized compounds by ^{1}HNMR, ^{13}CNMR, IR, MASS spectroscopic techniques.

2. METHODS AND MATERIALS

2.1 Chemicals and Reagents

All chemicals used were of laboratory reagent grade and used without further purification**.** Various aldehydes, guanidine, ethanol and sodium hydroxides were used as received from Merck, Mumbai, India. All the solvent were used as received from Merck, Mumbai, India.

2.2 Experimental

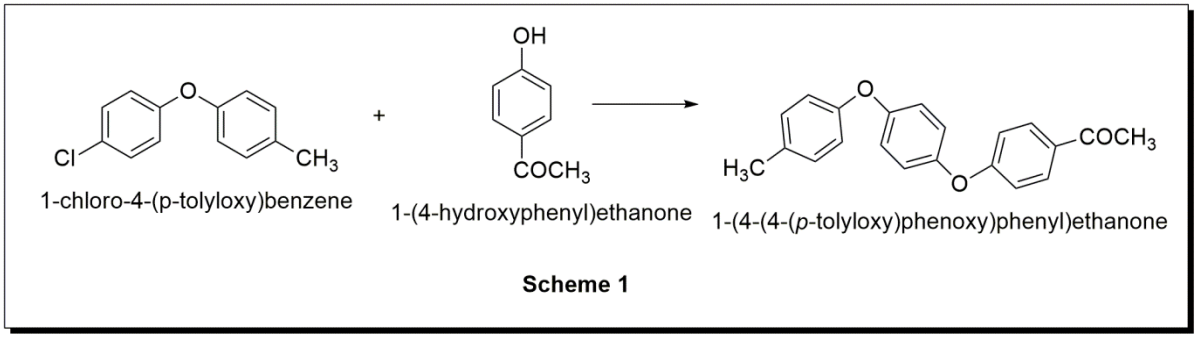
Melting points were determined by open capillary method and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR, as solutions in DMSO-d6. Chemical shifts (d) are expressed in parts per million (ppm) and referenced to the residual protic solvent. FT-IR spectra were recorded on Shimadzu FT-IR 8401 spectrometer using KBr disc, and are expressed in wavenumbers (cm^{-1}). The mass spectra (ESI-MS) were recorded on Shimadzu LCMS-2010 spectrometer. Carbon, Hydrogen and Nitrogen were estimated on a PerkinElmer

2400 Series II CHNS/O Elemental Analyzer. All the reactions were monitored by thin-layer chromatography (TLC).

2.3 Method of Synthesis

2.3.1 Synthesis of 1-(4-(4-(p-tolyloxy) phenoxy) phenyl) ethanone

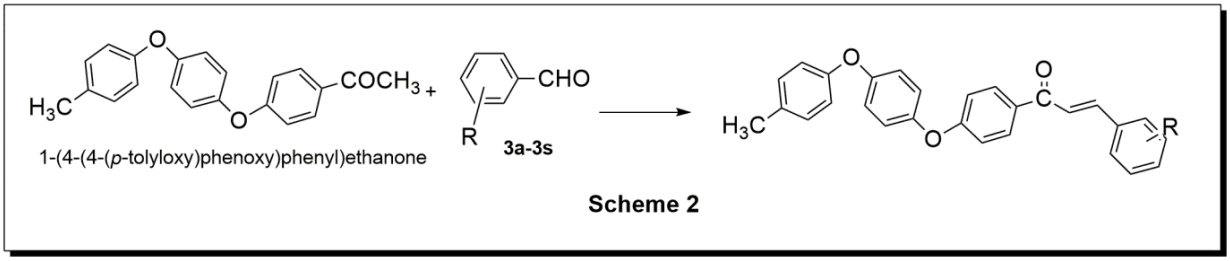
In a 250 ml round bottom flask, 1-chloro-(4-tolyloxy) benzene (0.1mol) was) and 1-(4-hydroxylphenyl) ethanone (0.1 mol) dissolved in pyridine (75 ml) with constant stirring maintaining the temperature below 25°C. After the completion of dissolution the mixture was refluxed for 2 hr. then it was cooled and poured into crushed ice. Solid was separated by filtration and crystalline from ethanol (**Scheme 1)**.



Scheme 1

2.3.2 Synthesis of various chalcones

To a well stirred solution of 1-(4-(4-(p-tolyloxy) phenoxy) phenyl) ethanone (0.01 mol)in ethanol (40 ml) and 40% sodium hydroxide (40 ml), various aldehyde **3a-3s** (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. Completion of reaction was monitored by TLC (**Scheme 2)**.

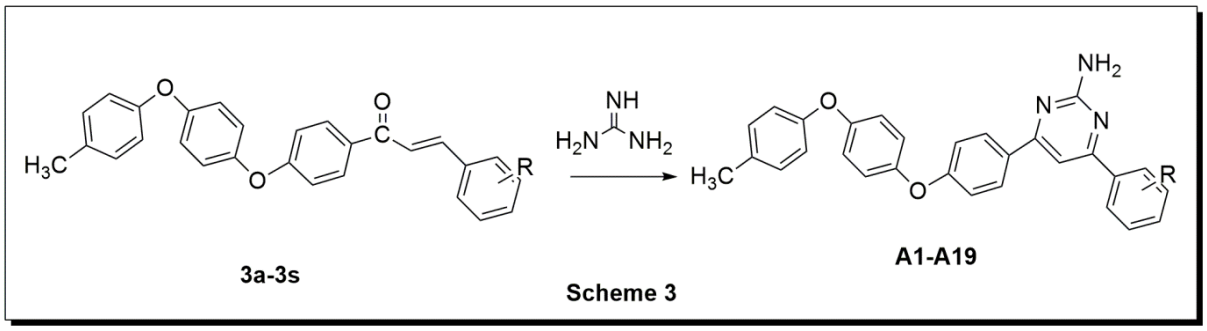


Scheme 2

2.3.4 Condensation of chalcones with guanidine

Various chalcones were synthesized in above section were reflux with guanidine nitrate in the

presence of sodium hydroxide under ethanol to produced compounds **A1-A19** within time period of 25-40 min. completion of reaction was monitored by TLC (**Scheme 3)**.

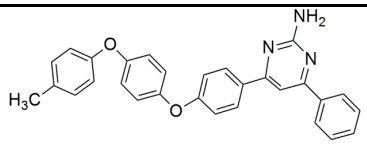


Scheme 3

2.3.5 Characterization

A1 compound 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 8 ppm. ^{1}HNMR, ^{13}CNMR, IR, MASS spectroscopic data of **A1** shown below Table 1.

Table 1 Characterization of Sample compound A1

Compound code: A1	
Molecular formula: $C_{29}H_{23}N_3O_2$	
M. P. (°C):	**>**250
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	2.34 (3H, s), 4.9 (2H, s), 6.86-7.40 (18H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	20.5, 39.2, 52.6, 117.5, 118.8, 120.9, 121.2, 127.5, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 151.8.
IR cm^{-1} (KBr):	3545, 3049, 1644, 1614, 1592, 1569, 744.
Mass (M+1):	446.0
Elemental analysis:	**Calculated (%):** C: 78.18; H: 5.20; N:9.43 **Found (%) :** C: 77.66; H: 5.39; N: 9.25

3. RESULT AND DISCUSSION

3.1 Characteristics data showing the synthesis compounds A1-A19

Table 2 Characteristic data showing synthesis of compounds A1-A19 from various chalcones (3a-3s)

Sr. No.	Compounds Code	R	Reaction Time[a] (min)	% Yiled[b]
1	A1	-H	30	74
2	A2	4-OH	35	75
3	A3	3-OH	35	76
4	A4	2-OH	35	77
5	A5	2- OCH_3	40	81
6	A6	4-OCH_3	40	80
7	A7	2-Cl	35	84
8	A8	4-Cl	35	84
9	A9	3-Cl	35	84
10	A10	2-NO_2	25	92
11	A11	4-NO_2	25	95
12	A12	3-NO_2	25	90
13	A13	3-Br	35	82
14	A14	2- Br	35	82
15	A15	4- Br	35	84
16	A16	3, 4-$(OCH_3)_2$	45	75
17	A17	3,4,5-$(OCH_3)_3$	45	75
18	A18	2-furfuryl[c]	30	85
19	A19	2-Thineyl[c]	30	88

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

From the **Table 2** show the various condensation product of condensation reaction between chalcones 3a-3s with various aromatic aldehydes. 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 **A10-A12** bearing electron withdrawing were synthesized in 25 min as shorter time as compared to compound **A16** and **A17** bearing electron donating group in 45 min. Very good yield was obtained in case of aldehyde bearing electron withdrawing group especially nitro group.

4. ANTIMICROBIAL ACTIVITY

The antibacterial activity of the compounds was screened by disc plate method. The test discs were containing 50 microgram per disc of the test compound. The activity was shown against gram positive bacteria are *Staphylococcus aureus* [MTCC (96)], *Bacillus megaterium* [MTCC (121)] and gram negative bacteria *Escherichia coli* [MTCC (443)], *Proteus vulgaris* [MTCC (1771)].

2.5.1 Preparation of Media

For bacterial activity nutrient agar is used. Nutrient agar is prepared as follows:

1) Peptone : 5 gm
2) Meat Extract : 3 gm
3) Sodium chloride : 5 gm
4) Agar Agar : 15 gm

All the above ingredients 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^{o}C for 20 minutes. The medium was cooled down to 45^{o}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^{o}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^{o}C. After the incubations the zone of inhibition was measured.

A short review of results of antibacterial screening of the compounds of this section is mentioned here:

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

Maximum activity were found in compounds (A18, A19) zone of inhibition-13.0 m.m. and minimum activity were found in compounds (A7, A11) zone of inhibition -6.0 m.m.

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

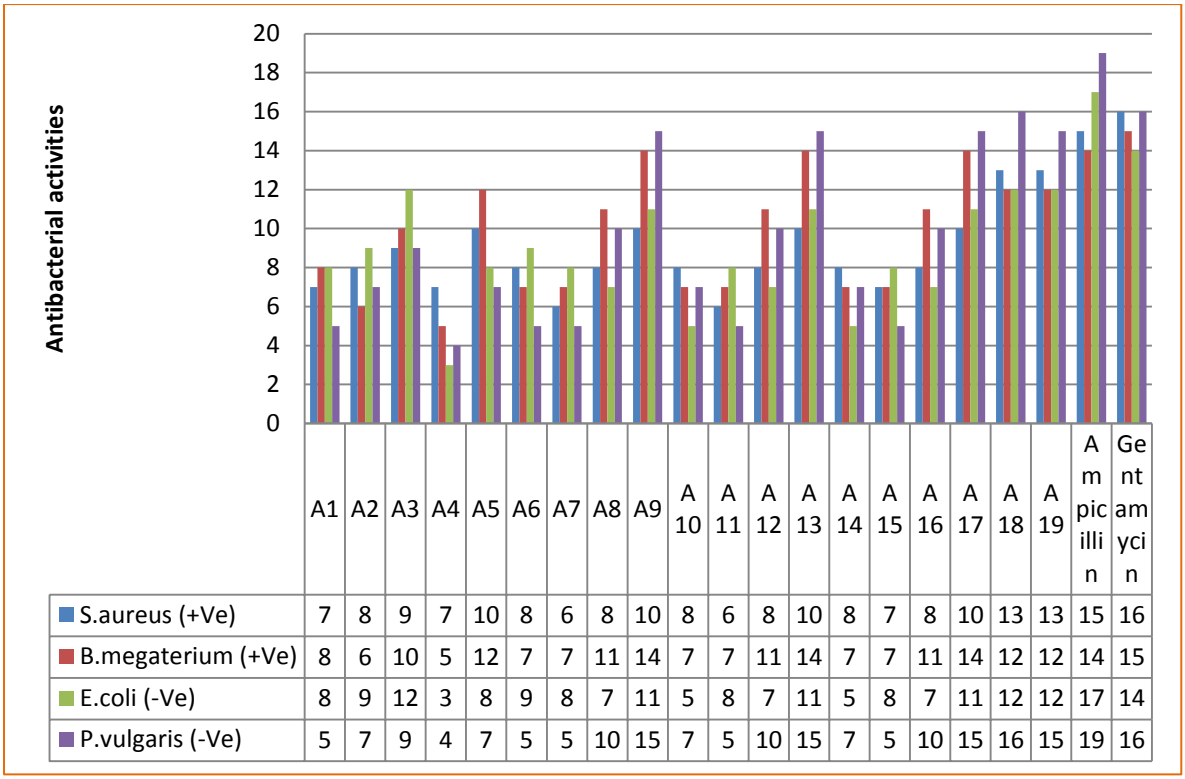
Maximum activity were found in compounds (A13, A17) zone of inhibition -14.0 m.m whereas minimum activity were found in compound (A5) zone of inhibition -5.0 m.m.

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

Maximum activity were found in compounds (A3, A18, A19) zone of inhibition -12.0 m.m and minimum activity were found in compounds (A4) zone of inhibition -3.0 m.m.

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

Maximum activity were found in compound (A9, A3, A18, A19) zone of inhibition -16.0 m.m (near to standard drug) and minimum activity were found in compounds (A4) zone of inhibition -4.0 m.m.



	A1	A2	A3	A4	A5	A6	A7	A8	A9	A 10	A 11	A 12	A 13	A 14	A 15	A 16	A 17	A 18	A 19	Ampicillin	Gentamycin
S.aureus (+Ve)	7	8	9	7	10	8	6	8	10	8	6	8	10	8	7	8	10	13	13	15	16
B.megaterium (+Ve)	8	6	10	5	12	7	7	11	14	7	7	11	14	7	7	11	14	12	12	14	15
E.coli (-Ve)	8	9	12	3	8	9	8	7	11	5	8	7	11	5	8	7	11	12	12	17	14
P.vulgaris (-Ve)	5	7	9	4	7	5	5	10	15	7	5	10	15	7	5	10	15	16	15	19	16

Figure 1 Antibacterial Activities of *COMPOUND A1-A19*

5. CONCLUSION

In conclusion the highly functionalized pyrimidine derivatives (**A1-A19)** 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. In this study, the synthesized compounds may be used as lead compounds for anti-inflammatory activity and may further be evaluated for toxicological contour in approaching research.

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