SYNTHESIS AND BIOLOGICAL EVALUATION OF VARIOUS CHALCONE BASED NOVEL PYRIMIDINES

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ABSTRACT

Chalcones was carried out by one pot condensation of 1-chloro-4-(4-methoxyphenoxy) benzene with 1-(5-hydroxynaphthalen1-yl)ethanone followed by condensation with various aromatic aldehydes. Synthesized chalcones were refluxing with guanidine to yields various pyrimidine derivatives. Spectroscopic characterization of all synthesized compounds were done by ^{1}H NMR, ^{13}C NMR, IR, MASS techniques. Antimicrobial activities of synthesized compounds were done by open disc method. Gram positive bacteria such as *Staphylococcus aureus*, *Bacillus megaterium* and gram negative bacteria *Escherichia coli*, *Proteus vulgaris* were taken for study.

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

1. Introduction

In the preparation of chalcones from aromatic carbonyl compound by condensation with aldehydes, in the presence of dry hydrochloric acid gas as a condensing agent is not unbeaten in all the cases. However, it was widely utilized by Russell and Todd **[1]** to synthesized chalcones necessary in association with synthetic preparation of compound related to natural paleobotanies. In order to avoid impediment arising due to presence of free hydroxyl group, they applied benzylated ketones and aldehydes as the precursor materials and obtained benzoyloxy chalcones which produced the resultant hydroxyl chalcones on debenzylation. They synthesize 2',4',3,4-tetrahydroxy- chalcone from resacetophenone dibenzoate and protocatechuic aldehyde dibenzoate to get tetrabenzoyl chalcone from which from which free chalcone was synthesized on debenzoylation.

Dandega, Ambekar, Jalod and Rajgopal **[2]** prepared 2-hydroxy-4-methoxy Chalcone. Timoney and Vickars **[3]** condensed 2'-hydroxyacetophenone with heterocyclic aldehydes in occurrence of the base and found 2-heterocyclic substituted chromones and related Chalcones. Kushwaha, Dinkar and Lal **[4]** synthesized Chalcones having a heterocyclic nucleus.

Shah **[5]** applied 40-50% alkali to derive the chalcones from 5-hydroxy-6- acetyl-4-methylcoumarin. Chalcones having pyrrole **[6]**, thiophene **[7, 8]** pyridine **[9, 10]** and quinoline nuclei **[11]** have also been reported.

Lyle, Paradis **[12]** and Marathey **[13]** applied methanol solution of dry hydrochloric acid gas at 0 °C Sipos, Dobo and Czukor **[14]** also fruitfully applied ethanol solution soaked with dry hydrogen fluoride & finished that electron donating groups in the aldehyde favour compression by dry HF & electron withdrawing substituent's support condensation by sodium hydroxide.

Tsukerman **[15]** also applied this condensing agent in the synthesis of chalcones having a selenophene nucleus. Caussac and Boucherie **[16]** cited chalcones from 3-acetylpyridine with various aldehydes utilizing dilute (1:1) hydrochloric acid while Hermes **[17]** applied conc. hydrochloric acid & compressed p-methylacetophenone with vanillin. Onoda and Tetsuko **[18]** utilizing hydrochloric acid as condensing agent for synthesized of chalcone.

Objectives of present work to synthesized various chalcones by condensation reaction of 1-chloro-4-(4-methoxyphenoxy) benzene (0.1 mol) and 1-(5-hydroxynaphthalen1-yl)ethanone (0.1 mol) to yields product which upon condensation with various aromatic aldehyde. Prepared chalcones on condensation reactions with guanidine to afford various condensation products **C1-C19**. 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 was 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-(5-(4-(-4-methoxyphenoxy)phenoxy)naphthalene-1-yl) ethanone

In a 250 ml round bottom flask, 1-chloro-4-(4-methoxyphenoxy) benzene (0.1 mol) and 1-(5-hydroxynaphthalen1-yl)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.

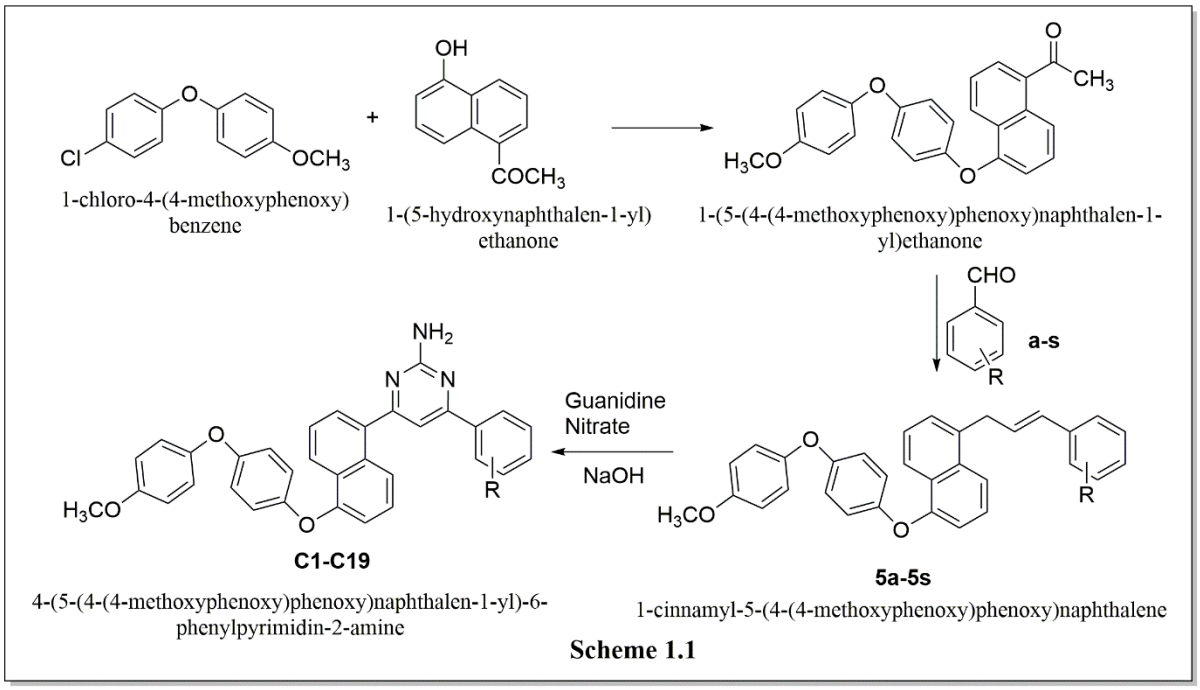
2.3.2 Synthesis of various chalcones

To a well stirred solution of 1-(5-(4-(-4-methoxyphenoxy)phenoxy)naphthalene-1-yl)ethanone (0.01 mol) in ethanol (40 ml) and 40% sodium hydroxide (40 ml), various aldehyde **a-s** (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. Completion of reaction was monitored by TLC.

2.3.3 Synthesis of pyrimidine

Various chalcones **5a-5s** were synthesized in above section were reflux with guanidine in the presence of ethanol to produced compounds **C1-C19** within time period of 25-40 min. completion of reaction was monitored by TLC (**Scheme 1.1)**.

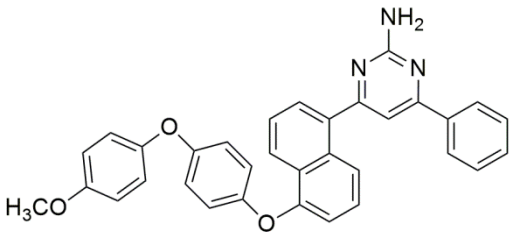


Scheme 1.1

3. Characterization

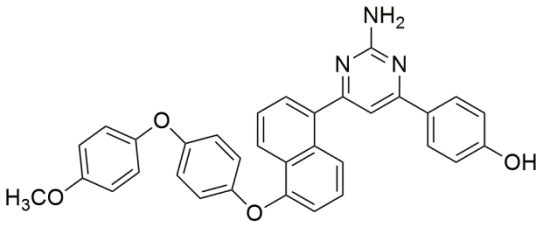
C1 & C2 compounds of the series is taken as the representative compound. In the ^{1}H NMR spectrum the characteristic signals due to each protons and functional groups with protons are well described on the basis of shielding and deshielding effects. The signal due to aromatic proton of compound was observed in more downfield region at chemical shift value around 6 to 8 ppm. ^{1}HNMR, ^{13}CNMR, IR, MASS spectroscopic data of **C1 & C2** compounds shown below.

Compound code: C1
Molecular formula: $C_{33}H_{25}N_3O_3$
M. P. (°C): >250



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.6 (3H, s), 5.3 (2H, s), 6.86-7.40 (20H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	21.5, 39.2, 52.6, 117.5, 118.8, 120.9, 121.2, 127.5, 128.1, 129.3, 130.1, 131.4, 132.9, 143.6, 151.8, 153.6, 155.1, 158.8.
IR cm^{-1} (KBr):	3332, 3049, 1600, 1614, 1542, 1569, 840.
Mass (M+1):	512.0
Elemental analysis:	**Calculated (%):** C: 77.48; H: 4.93; N:8.21
	Found (%) : C: 77.66; H: 4.98; N: 8.30

Compound code: C2
Molecular formula: $C_{33}H_{25}N_3O_4$
M. P. (°C): >250



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.6 (3H, s), 4.9 (2H, s), 2.1 (1H, s), 6.86-7.40 (19H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 30.5, 40.2, 52.6, 116.5, 118.8, 120.9, 121.2, 127.5, 128.1, 129.3, 130.1, 135.4, 136.9, 143.6, 151.8, 153.6, 155.1, 158.8.
IR cm^{-1} (KBr): 3350, 3302, 3049, 1650, 1614, 1592, 1569, 840.
Mass (M+1): 528.0
Elemental analysis: **Calculated (%):** C: 75.13; H: 4.78; N:7.96
Found (%) : C: 75.66; H: 4.85; N: 7.98

4. Result and Discussion

Table 1.1 Characteristic data showing synthesis of compounds C1-C19 from various chalcones.

Sr. No.	Compounds Code	R	Reaction Time[a] (min)	% Yiled[b]
1	C1	-H	30	78
2	C2	4-OH	35	78
3	C3	3-OH	35	78
4	C4	2-OH	35	75
5	C5	2- OCH_3	40	80
6	C6	4-OCH_3	40	80
7	C7	2-Cl	35	85
8	C8	4-Cl	35	85
9	C9	3-Cl	35	85
10	C10	2-NO_2	25	90
11	C11	4-NO_2	25	95
12	C12	3-NO_2	25	90
13	C13	3-Br	35	82
14	C14	2- Br	35	82
15	C15	4- Br	35	84
16	C16	3, 4-$(OCH_3)_2$	45	75
17	C17	3,4,5-$(OCH_3)_3$	45	75
18	C18	2-furfuryl[c]	30	85
19	C19	2-Thineyl[c]	30	88

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

From the **Table 1.1** 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 **C10-C12** bearing electron withdrawing were synthesized in 25 min as shorter time as compared to compound **C16** and **C17** bearing electron donating group in 35 min.

5. Biological Activity

5.1 Preparation of Media:

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

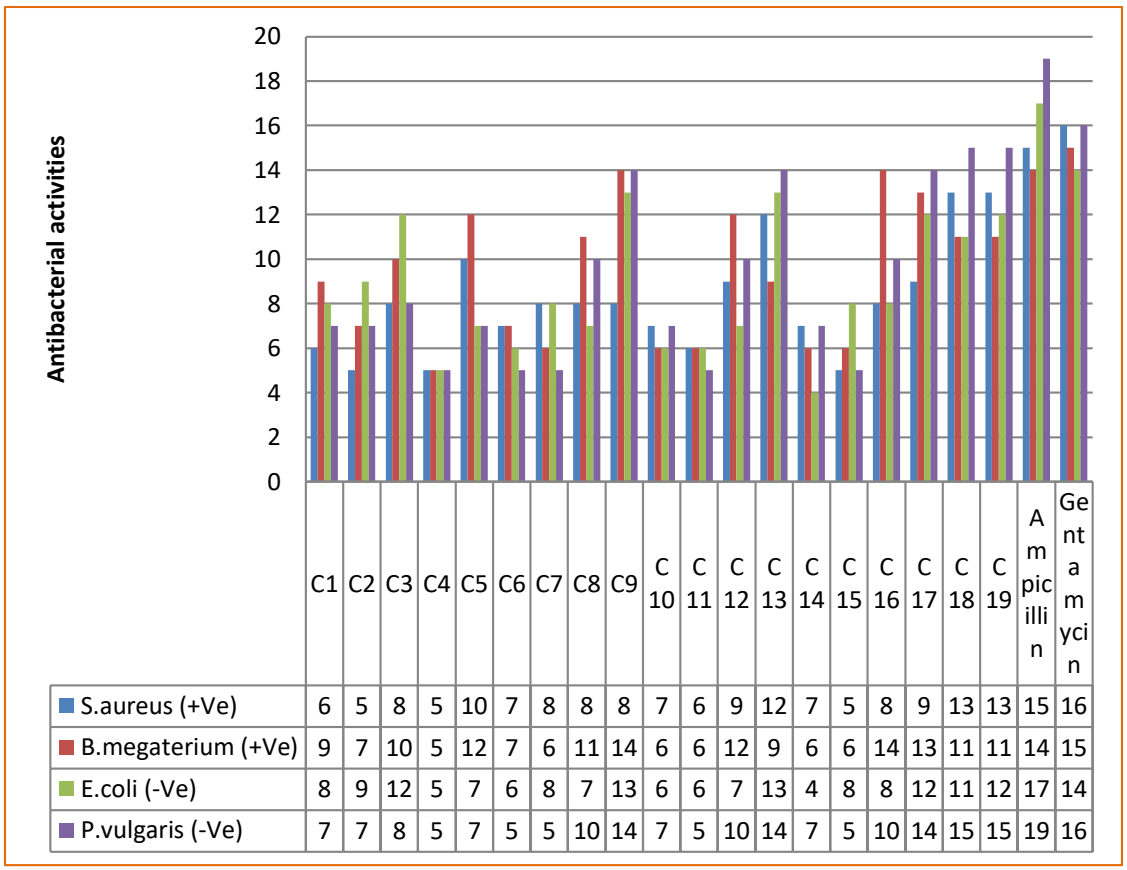
1) Peptone : 5 gm
2) Meat Extract : 3 gm
3) Sodium chloride : 5 gm
4) Agar Agar : 15 gm

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.

5.2 Antimicrobial activity of Compounds C1-C19



	C1	C2	C3	C4	C5	C6	C7	C8	C9	C 10	C 11	C 12	C 13	C 14	C 15	C 16	C 17	C 18	C 19	Ampicillin	Gentamycin
S.aureus (+Ve)	6	5	8	5	10	7	8	8	8	7	6	9	12	7	5	8	9	13	13	15	16
B.megaterium (+Ve)	9	7	10	5	12	7	6	11	14	6	6	12	9	6	6	14	13	11	11	14	15
E.coli (-Ve)	8	9	12	5	7	6	8	7	13	6	6	7	13	4	8	8	12	11	12	17	14
P.vulgaris (-Ve)	7	7	8	5	7	5	5	10	14	7	5	10	14	7	5	10	14	15	15	19	16

Figure 1.1 Antibacterial Activities of *COMPOUND C1-C19*

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

Maximum activity were found in compounds (C5, C13, C18, C19) zone of inhibition-13.0 m.m. and minimum activity were found in compounds (C2, C15) zone of inhibition -6.0 m.m

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

Maximum activity were found in compounds (C5, C9, C12, C16, C17) zone of inhibition -14.0 m.m where as minimum activity were found in compound (C4) zone of inhibition -5.0 m.m.

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

Maximum activity were found in compounds (C3, C9, C13, C17, C19) zone of inhibition -12.0 m.m and minimum activity were found in compounds (C4, C14) zone of inhibition -3.0 m.m

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

Maximum activity were found in compound (C9, C13, C17, C18, C19) zone of inhibition -16.0 m.m (near to standard drug) and minimum activity were found in compounds (C4, C6, C7, C11, C15) zone of inhibition -4.0 m.m

6. Conclusion

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. In conclusion the highly functionalized pyrimidine derivatives (**C1-C19)** 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.

7. References

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