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Synthesis and Characterization of N-(4-(N-(4-(4-(4-(4-Methoxy Phenoxy) Phenoxy) Phenyl)-6-Phenylpyrimidin-2-YL-(Salfamoyl) Phenyl) Acetamide Derivative

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ABSTRACT:

Chalcones was synthesized by one pot condensation of 1-chloro-(4-tolyloxy) benzene with 1-(4-hydroxylphenyl) ethanone followed by condensation with various aromatic aldehydes. Synthesized chalcones (3a-3s) were refluxing with guanidine to yields various pyrimidine derivatives. Synthesized pyrimidine on treatment with 4-acetamidobenzene sulfonyl chloride produced N-(4-(N-(4-(4-(4-(4-methoxy phenoxy) phenoxy) phenyl)-6-phenylpyrimidin-2-yl (salfamoyl) phenyl) acetamide derivatives (B1-B19). All the prepared compounds were characterized in by 1HNMR, 13CNMR, 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: Acetamidobenzenesulfonyl chloride, Pyrimidine, Aldehydes, Chalcones, Antimicrobial activity, Guanidine.

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1 INTRODUCTION:

Pyrimidines[1] are common heterocyclic aromatic moiety resemble to benzene and pyridine having two N atoms at 1 and 3 positions of the six membered rings. Heterocycles having pyrimidine moiety are of great significant because they construct significant class of natural and non-natural products, many of which shows applicable biological potency and clinical uses[2,3]. Substituted pyrimidines and purines occur very widely in living organisms and were some of the first compounds studied by researcher[4]. Pyrimidines are biologically very significant heterocycles and shows by far the most prominent of the diazine class with uracil[5] and thymine[6] being constituents of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) and with cytosine[7]. In addition to this, pyrimidines moiety is also present in many natural vitamin B1 (thiamine) and many synthetic compounds, such as barbituric acid[8] and Veranal[9] which are used as hypnotics[10].

The presence of Pyrimidine base in cytosine, thymine and uracil, which are the important building units of DNA and RNA, is one possible explanation for their widespread therapeutic uses. The Pyrimidines shows one of the most active classes of compounds possessing wide spectrum of biological activities like significant in vitroactivity against unrelated DNA and RNA, viruses including polio herpes viruses, diuretic, antitumor, anti-HIV, and cardiovascular[11]. The literature survey reveals that a broad range of pharmacological potency are exhibited by the heterocycles possess

pyrimidines moiety. In addition to this, differents analogs of pyrimidines have been detected to possesantibacterial[12-13], antifungal[14], antileishmanial[15], anti-inflammatory[16,], analgesic[17], antihypertensive[18], antipyretic[19], antiviral[20], antidiabetic[21], antiallerggic[22], anticonvulsant[23], antioxidant[24,], antihistaminic[25], herbicidal[26] and anticancer activities[27] and many of pyrimidines derivatives are cited to possess potential central nervous system (CNS) depressant properties[28] and also act as Ca channel blockers[29]. Because of wide range of application we have plane to synthesized chalcone based pyrimidine moiety N-(4-(N-(4-(4-(4-(4-methoxy phenoxy) phenoxy) phenyl)-6-phenylpyrimidin-2-yl (salfamoyl) phenyl) acetamide derivative.

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.

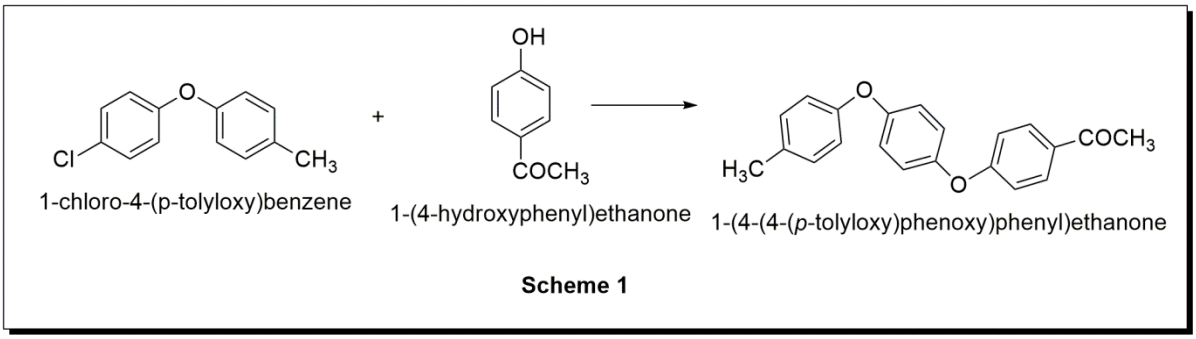
2.2 Experimental

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

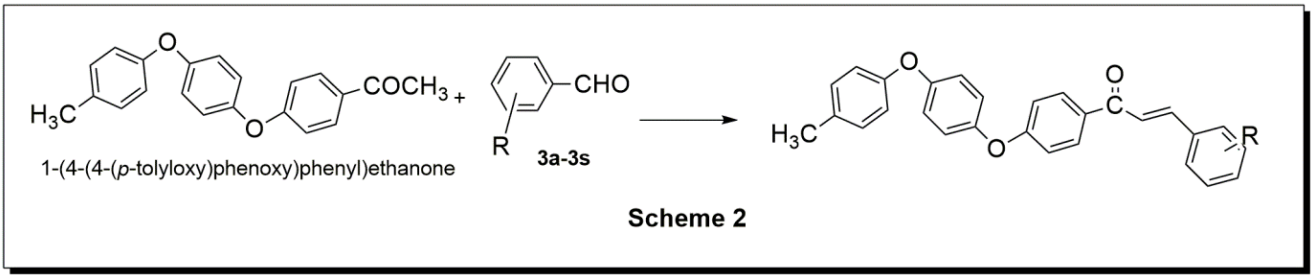
In a 250 ml round bottom flask, 1-chloro-(4-tolyloxy) benzene (0.1mol) was) and 1-(4-hydroxylphenyl) ethanone (0.1 mol) dissolved in pyridine (75 ml) with constant stirring maintaining the temperature below 25°C. After the completion of dissolution the mixture was refluxed for 2 hr. then it was cooled 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

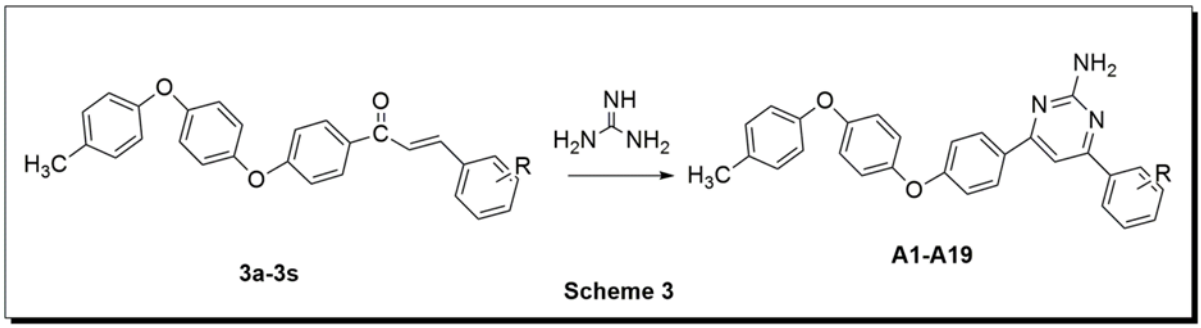
To a well stirred solution of 1-(4-(4-(p-tolyloxy) phenoxy) phenyl) ethanone (0.01 mol)in ethanol (40 ml) and 40% sodium hydroxide (40 ml), various aldehyde **3a-3s** (0.01 mol) was added drop wise at 0^{o}C. After the completion of addition, the mixture was stirred for further 2-3 hours and left overnight. 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

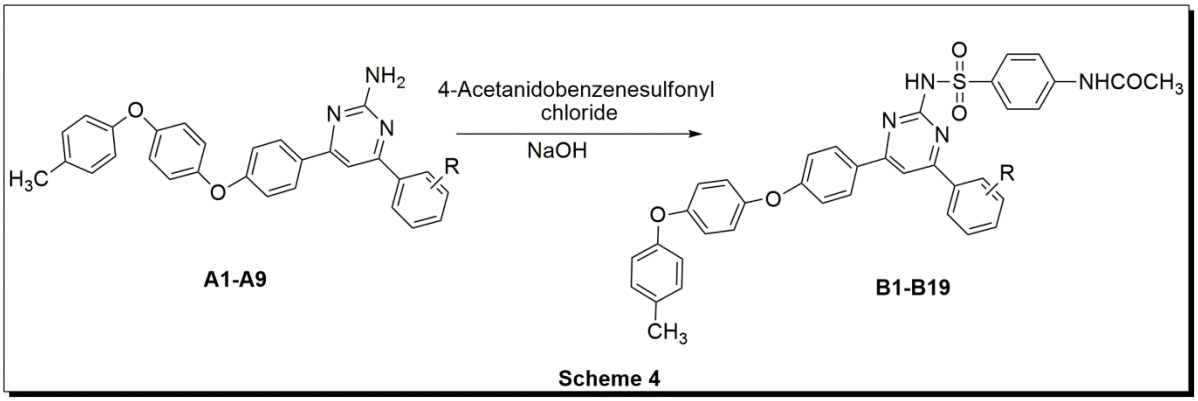
Various chalcones were synthesized in above section were reflux with guanidine nitrate in the presence of sodium hydroxide under ethanol to produced compounds **A1-A19** within time period of 25-40 min. completion of reaction was monitored by TLC (**Scheme 3)**.



Scheme 3

2.3.5 Synthesis of N-(4-(N-(4-(4-(4-(4-methoxy phenoxy) phenoxy) phenyl)-6-phenylpyrimidin-2-yl (salfamoyl) phenyl) acetamides B1-B19

Various pyrimidines **A1-A19** were synthesized in above section were reflux with 4-acetamidobenzenesulfonyl chloride in the presence of sodium hydroxide under ethanol to produced compounds **B1-B19** within time period of 25-30 min. completion of reaction was monitored by TLC (**Scheme 4)**.



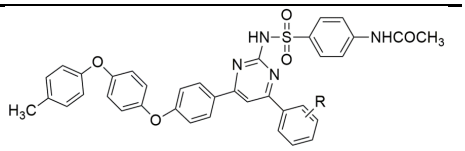
Scheme 4

2.3.5 Characterization

B1 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 **B1** shown below.

3.1 Characteristics data showing the synthesis compounds B1-B19

From the **Table 1** show the various condensation product of condensation reaction between pyrimidines **A1-A19** with 4-acetamidobenzenesulfonyl chloride. 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 20 min as shorter time as compared to compound **B16** and **B17** bearing electron donating group in 30 min. very good yield was obtained in case of aldehyde bearing electron withdrawing group especially nitro group.

Compound code: B1	
Molecular formula: $C_{37}H_{30}N_4O_5S$	
M. P. (°C):	>250
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	2.30 (3H, s), 2.34 (3H, s), 4.9 (1H, s), 5.2(1H, s) 6.86-7.40 (22H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	20.5, 35.0, 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. 205.
IR cm^{-1} (KBr):	3545, 3049, 1710, 1644, 1614, 1592, 1569, 744.
Mass (M+1):	643.0
Elemental analysis:	**Calculated (%):** C: 59.14; H: 4.70; N:8.72 **Found (%) :** C: 60.10; H: 5.10; N: 9.25

3. RESULT AND DISCUSSION

Table 1 Characteristic data showing synthesis of compounds **B1-B19** from various pyrimidines (**A1-A19**).

Sr. No.	Compounds Code	R	Reaction Time[a] (min)	% Yiled[b]
1	B1	-H	25	79
2	B2	4-OH	28	78
3	B3	3-OH	25	78
4	B4	2-OH	25	76
5	B5	2- OCH_3	30	81
6	B6	4-OCH_3	30	81
7	B7	2-Cl	28	84
8	B8	4-Cl	28	85
9	B9	3-Cl	28	84
10	B10	2-NO_2	20	90
11	B11	4-NO_2	20	90
12	B12	3-NO_2	20	88
13	B13	3-Br	30	86
14	B14	2- Br	28	86
15	B15	4- Br	28	85
16	B16	3, 4-$(OCH_3)_2$	30	78
17	B17	3,4,5-$(OCH_3)_3$	30	78
18	B18	2-furfuryl[c]	30	87
19	B19	2-Thineyl[c]	30	88

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

4. Antimicrobial Activity

4.1 Preparation of Media

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

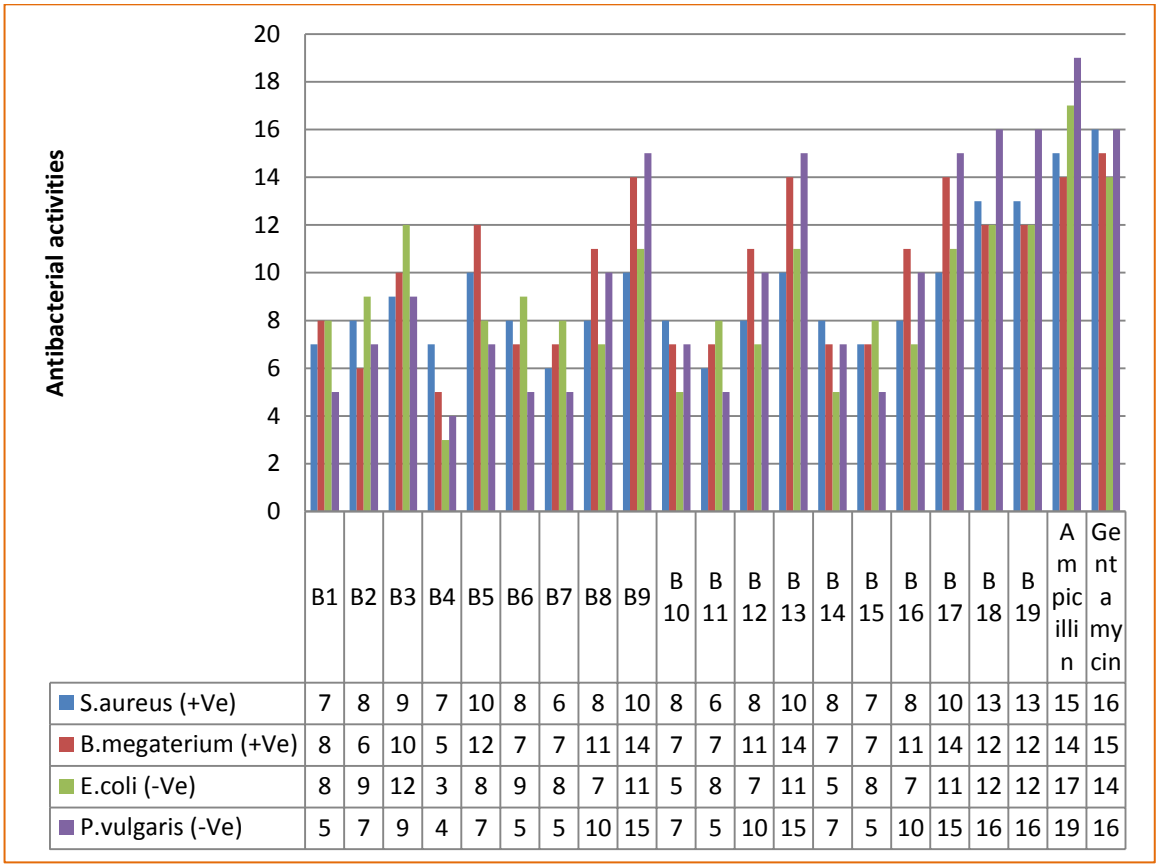
1) Peptone : 5 gm
2) Meat Extract : 3 gm
3) Sodium chloride : 5 gm
4) Agar Agar : 15 gm

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 are:

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°C. After the incubations the zone of inhibition was measured.



	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)	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	16	19	16

Figure 1 Antibacterial Activities of *COMPOUND B1-B19*

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 (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 (B5) zone of inhibition -5.0 m.m.

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

Maximum activity were found in compounds (B3, 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, B3, B18, B19) zone of inhibition -16.0 m.m (near to standard drug) and minimum activity were found in compounds (B4) zone of inhibition -4.0 m.m.

5. CONCLUSION

In conclusion the highly functionalized N-(4-(N-(4-(4-(4-(4-methoxy phenoxy) phenoxy) phenyl)-6-phenylpyrimidin-2-yl (salfamoyl) phenyl) acetamides **B1-B19** were synthesized from various pyrimidines **A1-A19**, which is in situ formed from different chalcones **3a-3s**. 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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