Synthesis And Biological Activity Of Aminopyrimidine Derivatives

Pravinsinh Bhupatsinh Dodia[1*], Prof. Rameshwar Ameta[2], Dr. Kartik B. Vyas[3]

[1&2]Department of Chemistry, Pacific Academy of Higher Education & Research University, Udaipur, Rajasthan, India.
[3]Department of Chemistry Sheth L.H. Science College, Mansa, Gujarat (India).
Email: dodiapravinsinhbhu@gmail.com

Abstract

Heterocyclic compounds are useful in medicinal field. Heterocyclic compound with pyrimidine, pyrazole, quinine etc. nucleus is very importance for the biological activity. In presence study, we have synthesized various pyrimidines by reaction between chalcones and Guanidine in the presence of sodium hydroxide as the base. Antimicrobial activity of all the synthesized compounds were perform against gram +ve and gram -ve bacteria. All synthesized compounds were done by ^{1}H NMR, ^{13}C NMR, IR, MASS techniques.

Keywords: Guanidine, Pyrimidine, Aldehydes, Antimicrobial Activity and Spectroscopy.

1. Introduction

Heterocyclic compounds are the largest and most diverse group of organic chemicals. After all, any carbocyclic compound, regardless of structure or usefulness, can theoretically be transformed into a collection of heterocyclic analogues by substituting a different element for one or more of the carbon atoms in the ring. Even if we limit ourselves to the most frequent heterocyclic constituents of oxygen, nitrogen, and sulphur, the permutations and combinations of such a replacement are vast. Heterocyclic compounds can be used in a variety of ways. They are the most common sorts of compounds used as medications, agrochemicals, veterinary products, antioxidants, corrosion inhibitors, and other forms of additives. Heterocyclic structures can be found in a variety of dyes and pigments.

In medicinal chemistry, analogues of nitrogen-based heterocycles occupy a special position as a valuable source of pharmaceuticals. More than 75% of drugs that have been FDA-

approved and are currently on the market contain heterocyclic moieties that are nitrogen-containing. New pharmaceuticals with nitrogen as an active ingredient are likely to make up a much larger portion of the market in the following decade. There have been numerous new nitrogen-based heterocycles made. There are increasingly more novel N-heterocyclic molecules with important physiological traits and potential medicinal chemistry uses. This article emphasizes the use of nitrogen-based moieties in drug design and the creation of a number of effective and capable candidates against a variety of diseases **[1].**

The most prevalent pharmacophore system among nitrogen-based compounds is the 1,2,3-triazole moiety, and it is essential for the creation of new biological targets **[2]**. These three nitrogen heteroatoms can be used to easily assemble these five-membered heterocyclic motives thanks to "click" chemistry. These substances can interact with a range of biological targets through hydrogen bonding, noncovalent and van der Waals interactions, as well as dipole-dipole bonding interactions **[3-6]**. Triazoles are weakly acidic and basic, making them more vulnerable to reducing agents. Additionally, the 1,2,3-triazole-based compound carboxyamidotriazole has been successfully used in clinical studies to treat cancer **[7]**. The triazole unit's strong dipole properties have also increased its value in medicinal chemistry because they allow for highly specific binding to biological targets **[8]**.

One of the most adaptable and frequently used nitrogen-based heterocyclic similar fragments in the creation of drugs for typical clinical disorders are indoles and their derivatives, for instance **[9]**. There has been an emphasis on the synthesis of indole derivatives recently because there are practically endless possibilities for architectural design of polycyclic structures by incorporating multiple fused heterocyclic scaffolds in an effort to achieve promising new heterocycles with chemical and biomedical relevance. Due to physicochemical characteristics like hydrogen bond donor-acceptor capability, stacking interactions, coordination bonds with metals as a ligand, van der Waals, polarization, and hydrophobic forces, these fragments are gaining more and more attention. Derivatives can readily bind to a variety of biomolecules, including enzymes and nucleic acids, due to the properties that cause their reactivity **[10-13]**.

Pyrimidines and pyrimidinones have drawn a lot of attention in organic synthesis due to the variety of biological activities they exhibit **[14]**. The pyrimidine nucleus is a six-

membered 1,3-diazine ring with a ketone unit. Natural products and nucleic acids, among other biologically active substances, contain pyrimidine analogues. Additionally, this type of heterocyclic molecule has several therapeutic uses in medicinal chemistry as a crucial building block of a wide range of drug candidates and nucleic acids due to its structural resemblance to purines. pyrimidine and pyrimidinone derivative-based anticancer medications (ibrutinib, capecitabine, folinic acid, and monastrol). These pyrimidines and their scaffolds are frequently used in drug development studies because of the wide range of bioactivity they exhibit **[15-17]**.

Literature survey reveals that, there has been lot of scope for the synthesis of novel aminopyrimidines and its application in pharmaceutical field. Here in presence paper, we have planned to synthesize novel aminopyrimidine from novel chalcone and guanidine as basic starting material and screened the synthesized compounds for biological activity.

2. Methods and Materials

2.1 Chemicals and Reagents

All chemicals used were of laboratory reagent grade and used without further purification. Various aldehydes, 1-(5-hydroxynaphthalen-1-yl) ethan-1-one, 1-chloro-5-fluoro-2-methyl-4-nitrobenzene, NaOH, Guanidine and ethanol were used as received from Merck, Mumbai, India.

2.2 Experimental

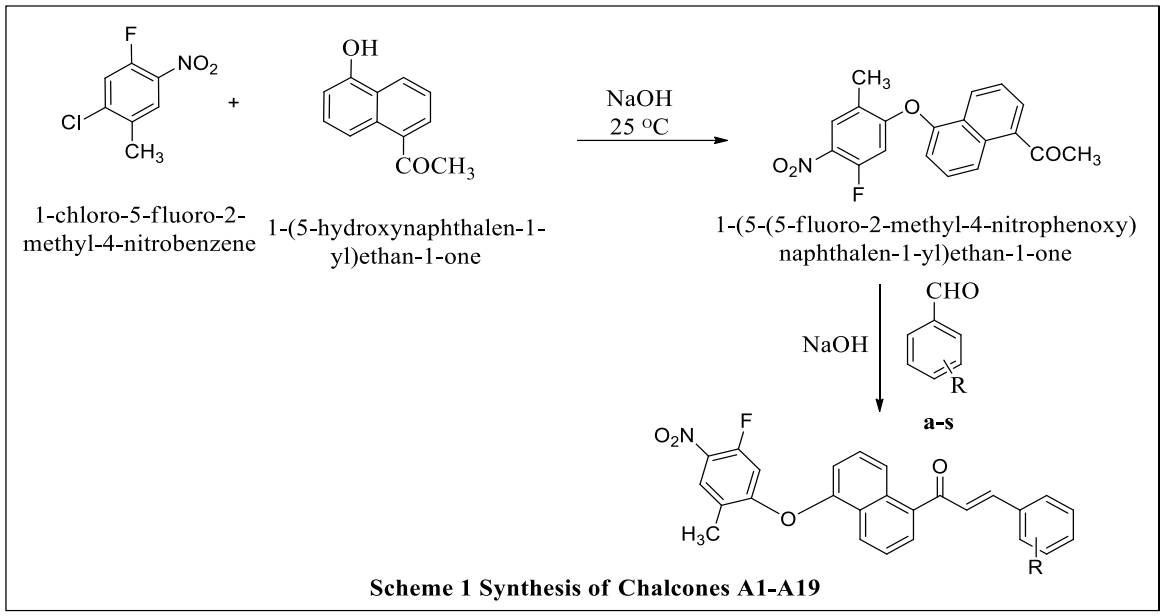
Bruker Avance-400 instrument was used for Proton NMR study and 100 MHz frequency instrument was used for ^{13}C NMR. Parts per million unit was used to expressed chemical shift value. ABB Bomem Inc. FT-IR 3000 Spectrophotometer was used for Infrared Spectral study. Data obtained was expressed in cm^{-1} 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 various chalcones A1-A19

In a 250 ml round bottom flask, a well stirred solution of 1-(5-hydroxynaphthalen-1-yl)ethan-1-one (0.01 mol) and 1-chloro-5-fluoro-2-methyl-4-nitrobenzene (0.01 mol) in ethanol (40 ml) was taken. Add 40% sodium hydroxide (40 ml) followed by

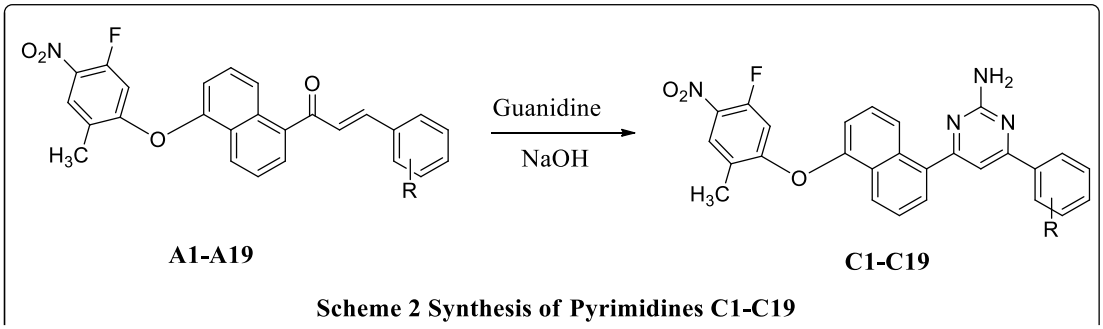
drop wise addition of aromatic aldehyde (0.01 mol) at 0°C. After the completion of addition, the mixture was stirred for further1-2 hours and left overnight. The contents were poured into ice water and crystallized from ethanol (**Scheme 1**).



Scheme 1 Synthesis of Chalcones A1-A19

2.3.2 Synthesis of Thiopyrimidines

Chalcone (0.01 mol) was taken in 250 ml RBF, added 0.01 mol Guanidine, 40 ml ethanol and 40 ml 40% NaOH. Refluxed the entire mixture for 1-2 hour to produced Primidone**.** Completion of reaction was monitored by TLC. Completion of reaction was checked by TLC. The novel pyrimidine obtained called **C1** (**Scheme 2)**.



Scheme 2 Synthesis of Pyrimidines C1-C19

3. Result and Discussion

Table 1 Data showing synthesis of Pyrimidine C1-C19.

Sr. No.	Compounds Code	R	Reaction Time (hr)	% Yield[b]
1	**C1**	-H	4	80
2	**C2**	4-OH	4	75
3	**C3**	3-OH	4	83

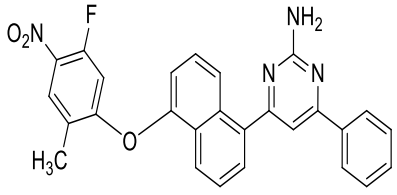
4	**C4**	2-OH	4	83
5	**C5**	2- OCH_3	4.5	82
6	**C6**	4-OCH_3	4.5	78
7	**C7**	2-Cl	3.5	72
8	**C8**	4-Cl	3.5	72
9	**C9**	3-Cl	3.5	68
10	**C10**	2-NO_2	3.5	75
11	**C11**	4-NO_2	3.5	68
12	**C12**	3-NO_2	3.5	67
13	**C13**	3-Br	4	80
14	**C14**	2- Br	4	72
15	**C15**	4- Br	4	82
16	**C16**	3, 4-$(OCH_3)_2$	4.5	80
17	**C17**	3,4,5-$(OCH_3)_3$	4.5	75
18	**C18**	2-furfuryl[c]	3.5	78
19	**C19**	2-Thineyl[c]	3.5	72

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

Table 1 shows the various condensation product of reaction between various chalcones and guanidine. 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 **C7-C15** bearing electron withdrawing were synthesized in **3.5 to 4 hr** as compared to compounds bearing electron donating group. Compounds **C5, C6, C16** and **C17** having electron donating group synthesized in **4.5 hr**.

4. Characterization

For characterization, **compound C1** was taken as the model compound from the series and it was characterized by various spectroscopic methods such as ^{1}H NMR, ^{13}C NMR, MASS and IR spectroscopy.

Compound code: C1	
$C_{27}H_{19}FN_4O_3$	
M. P. (°C): 236	4-(5-(5-fluoro-2-methyl-4-nitrophenoxy)naphthalen-1-yl)-6-phenylpyrimidin-2-amine

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	2.5 (s, 3H, -CH_3 group), 6.8-8.3 (14H, Ar-H, complex). 4.5 (s, NH_2, singlet).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.0, 62.2, 129.4, 131.6, 140.2, 146.6, 151.8, 153.6, 155.1 and 160.2.
IR cm^{-1} (KBr):	3415, 3311, 3120, 2950, 1612, 1592, 1569, 1480, 744.
Mass (M+1):	466.1
Elemental analysis:	**Calculated (%):** C: 69.60; H: 3.88; N:8.99. **Found (%) :** C: 69.30; H: 3.80; N: 8.85

5. Antimicrobial Activity

5.1 Preparation of Media:

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

5 gm Peptone, 3 gm Meat Extract, 5 gm NaCl and 15 gm 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.

5.3. Experimental Data of Antimicrobial Study.

Table 2 Experimental data of Compounds C1-C19

Samples	S.aureus (+Ve)	B.megaterium (+Ve)	E.coli (-Ve)	P.vulgaris (-Ve)
C1	9	4	5	4
C2	9	9	12	8
C3	7	12	10	10
C4	9	8	8	6
C5	7	6	8	7
C6	8	9	9	6
C7	8	12	12	5
C8	10	12	10	10
C9	12	12	10	12
C10	12	6	4	7
C11	7	7	7	6
C12	6	8	6	8
C13	8	6	3	10
C14	3	6	11	4
C15	10	9	6	7
C16	9	4	6	6
C17	8	9	9	10
C18	9	12	11	4
C19	11	11	4	6
Ampicillin	**15**	**14**	**17**	**19**
Gentamycin	**16**	**15**	**14**	**16**

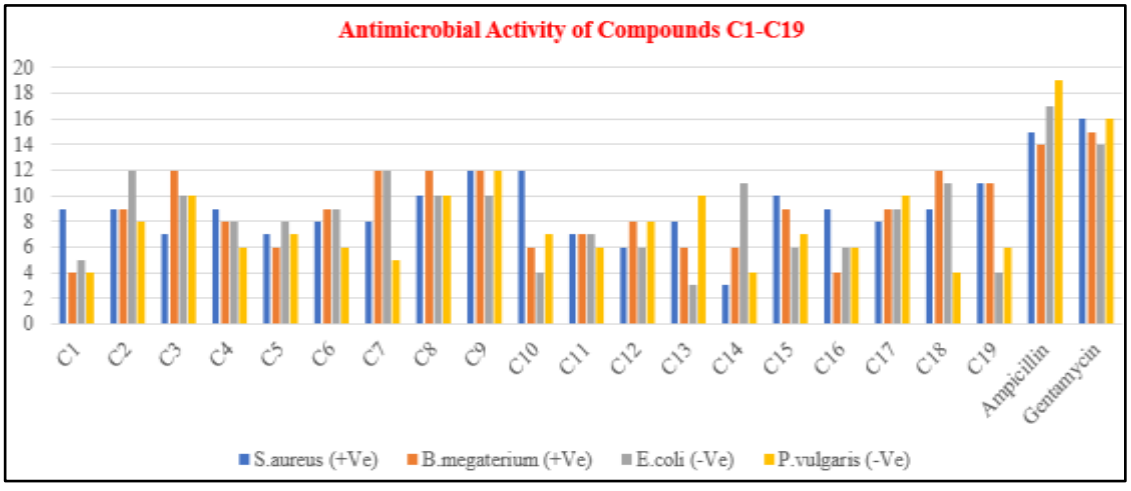


Figure 1 Antibacterial Activities of COMPOUNDS C1-C19

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

(I) **Against Staphylococcus aureus:** Maximum activity were found in compounds (C9 and C10) zone of inhibition -12.0 m.m whereas minimum activity was found in compound (C14) zone of inhibition -3.0 m.m.

(II) **Against Bacillus megaterium:** Maximum activity was found in compound (C3, C7-C10 and C18) zone of inhibition -12.0 m.m (near to standard drug) and minimum activity were found in compounds (C1 and C16) zone of inhibition -4.0 m.m.

(III) **Against Escherichia coli:** Maximum activity was found in compounds (C2 and C7) zone of inhibition-12.0 m.m. and minimum activity was found in compound (C13) zone of inhibition -3.0 m.m.

(IV) **Against Proteus vulgaris:** Maximum activity was found in compound (C9) zone of inhibition -12.0 m.m and minimum activity were found in compounds (C1, C14 and C17) zone of inhibition -4.0 m.m.

6. Conclusion

In conclusion the highly functionalized Pyrimidine were synthesized from readily available starting materials. We have synthesized library of pyrimidines compound possesses reactive functional group. All prepared pyrimidines were characterized by spectroscopic techniques. All the synthesized compounds were 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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