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Design, Synthesis, And Spectral Characterization Of Chalcone-Based Pyrimidines

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Abstract
Heterocyclic compounds such as pyrimidine, benzimidazole, and benzoxazole are aromatic in nature and are commonly found in a wide range of medicinal agents. Triazoles, which are five-membered heterocyclic rings containing three nitrogen atoms, are another important class of these compounds. The chemistry of heterocycles plays a vital role in everyday life—contributing significantly to the safety of food and beverages, and especially to the advancement of pharmaceutical science through the development of new therapeutic agents.

In the present study, a series of novel chalcones were synthesized using 2-chloro-7H-pyrrolo[2,3-d]pyrimidine and 1-(4-aminophenyl)ethenone, followed by condensation with various aldehydes. These chalcones were subsequently reacted with guanidine to yield a range of pyrimidine derivatives, labeled B1–B15. The synthesized compounds were characterized using techniques such as ^{1}H NMR, ^{13}C NMR, IR and MASS spectrometry. Furthermore, all compounds were evaluated for their antimicrobial activity.

Keywords: *Guanidine, Antimicrobial activity, Chalcones, Heterocyclic* compounds, pyrimidines and Spectroscopy.

INTRODUCTION

Chalcones represent a significant class of naturally occurring compounds found in a wide variety of plant species. They serve as key intermediates in the biosynthesis of flavonoids and isoflavonoids in nature. Structurally, chalcones are characterized as 1,3-diphenyl-2-propen-1-ones, consisting of two aromatic rings linked via a three-carbon α,β-unsaturated carbonyl system. As noted by Harborne and Mabry (1982), chalcones are essential precursors in the biosynthetic pathways of flavonoids and isoflavonoids.

Traditionally, chalcones are synthesized through Claisen-Schmidt condensation, which involves the base-catalyzed reaction of methyl ketones with aromatic aldehydes—a method dating back to Claisen and colleagues in 1881. These compounds have demonstrated in vitro antimalarial properties against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* [1]. Recent advancements in chalcone synthesis also include methodologies utilizing acidic conditions, such as reactions catalyzed by acetic acid and perchloric acid [2]. Additionally, numerous chalcone derivatives have emerged as potent tyrosinase inhibitors, positioning them as promising antioxidant and depigmenting agents [3].

Heterocyclic compounds, defined by the inclusion of at least one non-carbon atom (commonly nitrogen, oxygen, or sulfur) within their ring structure [4,5], occupy a central role in modern medicinal chemistry. Their structural diversity and reactivity offer vast potential for the development of bioactive molecules. These compounds are prevalent in nature, forming integral components of essential biomolecules such as DNA and RNA, which are constructed from purine and pyrimidine heterocycles. Furthermore, critical biological molecules like heme and chlorophyll—responsible for oxygen transport in animals and photosynthesis in plants, respectively—are derived from complex heterocyclic systems like porphyrins.

Beyond natural systems, synthetic heterocyclic compounds have been extensively investigated for their pharmacological applications. They exhibit a broad spectrum of biological activities, including antibacterial [6], antifungal [7], analgesic [8], anti-inflammatory [9], antimycobacterial [10], antitubercular [11], antimalarial [12], trypanocidal [13], anti-HIV [14], anticonvulsant [15], antitumor [16], antileishmanial, and genotoxic properties [17]. Their significance extends into agricultural chemistry and materials science as well. Heterocycles are essential components in the development of dyes, fluorescent probes, brighteners, polymers, and analytical reagents. Moreover, they contribute to the design of organic electronic devices, such as light-emitting diodes (OLEDs), photovoltaic cells, molecular wires, optical data storage systems, and liquid crystal materials [18–22].

Pyrimidine was first synthesized by Gabriel and Colman in 1899, and since then, its chemistry and that of its derivatives have been extensively explored due to their wide range of pharmacological activities. Although pyrimidine itself is not naturally occurring, it serves as the core structure for several biologically significant compounds. Along with purine, pyrimidine forms the foundational nitrogen-containing heterocyclic frameworks of the nucleic acid bases, which are critical components of DNA and RNA. Both purine and pyrimidine rings are planar structures—a feature essential to the stability and stacking interactions within nucleic acid helices.
In the present study, we report the synthesis of a series of novel pyrimidine derivatives (B1–B15) obtained through the reaction of newly prepared chalcones with guanidine.

METHODS AND MATERIALS

Chemicals and Reagents

All chemicals used were of laboratory reagent grade and used without further purification. Various aldehydes, 1-(4-aminophenyl)ethenone, 2-chloro-7H-pyrrolo[2,3-d]pyrimidine, guanidine, KOH and ethanol were used as received from Merck, Mumbai, India.

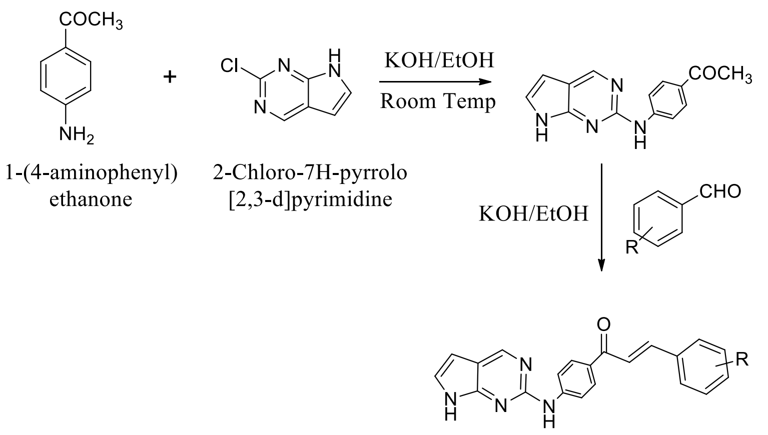
Experimental

Bruker Avance-400 instrument was used for Proton NMR study and 100MHZ 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.

Method of Synthesis

Synthesis of Various Chalcones A1-A15

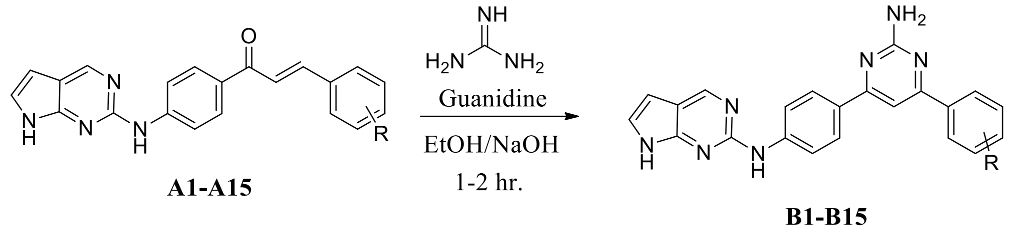
In a 250 ml round bottom flask, 2-chloro-7H-pyrrolo[2,3-d] pyrimidine (0.1 mol) and 1-(4-aminophenyl) ethenone (0.1 mol) dissolved in ethannol (50 ml) with constant shaking maintaining the temperature below 25°C. After the completion of dissolution, the mixture was refluxed for 1.5 hr. then it was cooled and poured into crushed ice. Solid was separated by filtration and crystalline from ethanol. To a well stirred solution, add 40% potassium hydroxide (40 ml) followed by addition of aromatic aldehyde (0.01 mol) drop wise at 0°C). After the completion of addition, the mixture was stirred for further 1-1.5 hours and left overnight. The contents were poured into ice water and crystallized from ethanol (**Scheme 1**).



Scheme-1 Synthesis of Pyrimidine based Chalcones

Synthesis Of 2-Aminopyrimidines

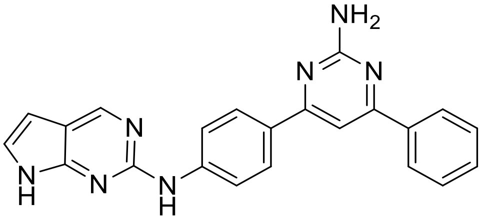
Take chalcones (0.01 mol) in 250 ml RBF, add 0.01 mol guanidine, 40 ml ethanol and 40 ml 40% KOH to this mixture solution. Reflux the entire mixture for 1-2 hr to produced pyrimidine. Completion of reaction was monitored by TLC (**Scheme 2**).



Scheme-2 Synthesis of Pyrimidines B1-B15

Characterization

Compound B1 was selected as the representative example for detailed spectroscopic analysis. In the ^{1}H NMR spectrum, all proton signals were identified and assigned based on their chemical environment, influenced by shielding and deshielding effects. Aromatic protons appeared in the downfield region, typically between δ 6.0 and 8.0 ppm, indicating the presence of conjugated aromatic systems. The NH and NH_2 signals were observed as singlets in the higher δ region, confirming the expected substitution pattern.

Compound code: B1	
Molecular formula: $C_{22}H_{17}N_7$	
M. P. (°C): 232	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	9.2 (NH_2, s), 6.6-8.4 (13H, Ar-H, complex), 4.2 (1H, s, -NH), 3.8 (1H, s, -NH).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	128.2, 129.4, 130.3, 131.6, 139.2, 143.6, 151.8, 153.6, 155.1, 156.8.
IR cm^{-1} (KBr):	3510, 3442, 3320, 3029, 1660, 1592, 1569, 744.
Mass (M+1):	379.10
Elemental analysis:	**Calculated (%):** C: 69.64; H: 4.52; N:25.84. **Found (%)** : C: 69.32; H: 4.64; N: 25.72

RESULT AND DISCUSSION

Table 1.1 Data Showing Synthesis Of Pyrimidnes B1-B15.

Sr. No.	Compounds Code	R	Reaction Time^a hr	% Yiled^b
1	B1	-H	3.5	75
2	B2	4-OH	4	73
3	B3	3-OH	4	70
4	B4	2-OH	4	70
5	B5	2- OCH_3	4.5	70
6	B6	4-OCH_3	4.5	69
7	B7	2-Cl	3.5	80
8	B8	4-Cl	3.5	81
9	B9	3-Cl	3.5	82
10	B10	2-NO_2	3.5	83
11	B11	4-NO_2	3.5	82
12	B12	3-NO_2	3.5	83
13	B13	3-Br	3.5	78
14	B14	2- Br	3.5	80
15	B15	4- Br	3.5	80

The data clearly illustrate that the nature of substituents on the aromatic ring significantly affects the reaction time. Chalcones bearing electron-withdrawing groups (e.g., $-NO_2$, –Cl, –Br) resulted in faster reactions, typically completing in 3.5 hours, and yielded products with relatively higher efficiency (B7–B15). In contrast, chalcones with electron-donating groups (e.g., –OH, $-OCH_3$) required longer reaction times (4.0 to 4.5 hours) and generally afforded slightly lower yields (B2–B6). This trend suggests that electron-withdrawing substituents enhance the electrophilic character of the carbonyl group in chalcones, thereby facilitating nucleophilic attack by guanidine and accelerating the formation of the pyrimidine ring.

CONCLUSION

In summary, a series of highly functionalized 2-aminopyrimidine derivatives (B1–B15) were successfully synthesized via a condensation reaction between guanidine and various chalcones. The chalcones themselves were prepared using different aromatic aldehydes, 1-(4-aminophenyl)ethenone, and 2-chloro-7H-pyrrolo[2,3-d]pyrimidine. All synthesized compounds were thoroughly characterized using a range of spectroscopic techniques to confirm their structures.

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