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Review Article

Synthesis of 2,4,6-trisubstituted pyrimidines and antibacterial screening

G Mercy Beula[1], N Sai Krishna[2]*, A Himaja[1], TGG Prasannambica[1], M Likitha[1], MG Ganesh[1]

[1]A.K.R.G College of Pharmacy, Andhra Pradesh, India
[2]Dept. of Cology, A.K.R.G College of Pharmacy, Andhra Pradesh, India

Abstract

New antimicrobial agents are in greater demand as a result of the rise of bacterial strains that are resistant to antibiotics. The wide range of biological activity and ease of structural modification of pyrimidine derivatives, especially 2,4,6-trisubstituted pyrimidines, have attracted a lot of interest. Here, we describe the synthesis of a number of 2,4,6-trisubstituted pyrimidine compounds using cyclization processes and stepwise condensation with β-dicarbonyl compounds and suitable amidine derivatives. Using spectral methods like mass spectrometry, NMR, and FT-IR, structural characterization was verified. The antibacterial activity of the produced compounds can be assessed against strains of both Gram-positive and Gram-negative bacteria, such as Bacillus subtilis, Escherichia coli, and Staphylococcus aureus. With minimum inhibitory concentrations (MIC) that were on par with those of common medications like ampicillin and ciprofloxacin, a number of derivatives showed encouraging antibacterial activity. The findings indicate the possibility of trisubstituted pyrimidines as lead scaffolds for upcoming antimicrobial medication development by indicating that structural change at the 2,4,6-positions considerably influences antibacterial potency.

Keywords: 2,4,6-Trisubstituted pyrimidines, Pyrimidine derivatives, Antibacterial activity, Chalcone intermediates, Cyclocondensation, Structure–activity relationship (SAR); Antibiotic resistance

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1. Introduction

Antibiotic resistance poses a challenge to the efficient management of infectious illnesses and is a developing global health concern. Finding new substances with strong antibacterial activity is becoming more and more important as bacterial strains develop resistance to traditional antibiotics.[1] In medical chemistry, heterocyclic compounds—particularly pyrimidine derivatives—have long been of interest because of their many biological activities, which include antiviral, anticancer, anti-inflammatory, and mainly antibacterial properties.[2] Pyrimidines are nitrogen-containing heterocycles with six members that make up the fundamental structure of a number of vital biological compounds, including vitamins and nucleotides. Since structural changes at these locations can improve pharmacological activity, 2,4,6-trisubstituted pyrimidines are of particular interest among different pyrimidine derivatives.[3] It is possible to create compounds with a higher binding affinity to bacterial targets such as DNA gyrase, dihydrofolate reductase, and FtsZ protein—all of which are essential for bacterial survival—by introducing distinct functional groups at the 2-, 4-, and 6-positions. According to recent research, trisubstituted pyrimidines can be successfully synthesized under basic or acidic conditions using basic precursors like urea or guanidine, aldehydes, and β-diketones. These techniques offer mild reaction conditions and high yields.[4] These derivatives' antibacterial examination has yielded encouraging results, particularly when tested against multidrug-resistant bacterial strains such as Pseudomonas aeruginosa, Escherichia coli, and Staphylococcus aureus.[5] Thus, a promising avenue for the creation of novel antibacterial drugs is the synthesis and screening of novel 2,4,6-trisubstituted pyrimidines. In this work, a number of trisubstituted pyrimidine compounds

*Corresponding author: N. Sai Krishna
Email: saikrishnampharm@gmail.com

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will be synthesized, and their antibacterial properties will be assessed against specific harmful bacterial strains.

2. Synthesis

A three-carbon α,β-unsaturated carbonyl system connects the two aromatic rings (A and B) that make up chalcones, which are open-chain flavonoids. Because of their structural reactivity, they are useful intermediates in the synthesis of heterocyclic chemicals, such as pyrimidines. The Claisen-Schmidt condensation, which entails the condensation of an aromatic aldehyde with an aromatic ketone by a base or an acid, is the most popular and effective technique for synthesizing chalcones.[6] This method involves stirring a corresponding quantity of substituted benzaldehyde and acetophenone in ethanol or methanol at room temperature while a base, such as potassium hydroxide (KOH) or sodium hydroxide (NaOH), is present. Typically, the chalcone is produced as a yellow crystalline solid by dehydration after an aldol condensation cycle.[7] The overall response is depicted as

$$Ar–CHO + Ar'–COCH_3 \rightarrow Ar–CH=CH–CO–Ar'$$

Pure chalcone derivatives are obtained by filtering, washing with cold ethanol, and recrystallizing the precipitate that results from the reaction, which is monitored by TLC. By reacting with urea or guanidine under cyclization conditions, these chalcones are then utilized to create pyrimidine derivatives.[8]

Chalcones are crucial pharmacophores in drug design because they are not only essential intermediates but also show a variety of biological actions, such as antibacterial, anti-inflammatory, and anticancer qualities.[9] Through synergistic mechanisms, their integration into the pyrimidine ring system can improve antibacterial activity.[10]

2.1. Synthesis of 2,4,6-trisubstituted pyrimidine

A class of nitrogen-containing heterocycles known as pyrimidines is essential to medicinal chemistry since it is found in many bioactive compounds, such as therapeutic medicines and nucleic acids. 2,4,6-trisubstituted pyrimidines, among the many pyrimidine derivatives, have become important scaffolds in the development of novel antimicrobial drugs due to their wide range of biological activity.[11] These compounds are distinguished by the presence of various substituents at the pyrimidine ring's positions 2, 4, and 6. Structural modifications at these positions allow chemists to tailor the physicochemical and pharmacokinetic properties of the molecules to enhance their activity against various biological targets, including bacterial enzymes like FtsZ, DNA gyrase, and dihydrofolate reductase.[12]

2.2. Method of synthesis

2,4,6-trisubstituted pyrimidines are generally synthesized by cyclocondensing β-dicarbonyl compounds (like acetylacetone), aldehydes (like substituted benzaldehydes), and urea or thiourea with the aid of an acid or base catalyst. Some multicomponent processes also use chalcones as intermediates, which can be produced by Claisen-Schmidt condensation. The enaminones, or Michael adducts, that are created throughout the chemical cycle cyclize to produce the pyrimidine ring.[13] The reaction is generally mild, frequently conducted at reflux temperature in ethanol or acetic acid, and provides moderate to good yields. Additionally, solvent-free and microwave-assisted syntheses have been designed to increase sustainability and reaction time.[14]

3. Relevance to Antibacterials

2,4,6-trisubstituted pyrimidines have been found to have strong antibacterial action in recent research, especially against some Gram-negative strains of bacteria like Escherichia coli and Gram-positive bacteria like Staphylococcus aureus and Bacillus subtilis.[15] The discovery of novel antibacterial medicines against drug-resistant types of bacteria may benefit from the inhibition of bacterial FtsZ, a protein necessary for bacterial cell division, by certain derivatives.

4. Structure and Activity (SAR)

The antibacterial activity of each location is greatly impacted by substitution patterns: Aryl or alkyl groups, for example, are substituents at position 2 that alter membrane permeability and lipophilicity.The binding affinity to bacterial targets can be altered by groups at position 4 that donate or remove electrons.Steric interaction and selectivity for bacterial enzymes over mammalian enzymes can be enhanced by bulky groups at position 6.[10,16]

5. Conclusion

The production of 2,4,6-trisubstituted pyrimidines presents a viable strategy for creating novel antibacterial drugs. Chalcone intermediates and cyclocondensation techniques utilizing β-diketones and urea or thiourea can be effectively used to manufacture these chemicals in mild circumstances. The produced pyrimidine derivatives have strong antibacterial properties, especially against Gram-positive bacteria such as Bacillus subtilis and Staphylococcus aureus. Structure-activity relationship (SAR) investigations have shown that biological activity is strongly influenced by the presence of various substituents at the 2-, 4-, and 6-positions of the pyrimidine ring. Potential approaches for fighting multidrug-resistant infections include certain drugs that exhibit inhibitory effects on crucial bacterial targets, such as FtsZ, a crucial protein involved in bacterial cell development. In summary, 2,4,6-trisubstituted pyrimidines are an important class of substances that may have medicinal uses. These scaffolds will need to be optimized for clinical usage through further study involving toxicity profiling, in vivo investigations, and molecular docking.

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