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Review Article

Synthesis of Benzoyl glycine and Anti-bacterial screening

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Abstract

Because of their promising biological properties and structural versatility, benzoyl glycine, also referred to as hippuric acid, and its derivatives have garnered a lot of interest in medicinal chemistry. Novel pharmacopoeias can be created by conjugating glycine with benzoyl groups to create compounds that are easily modified at the aromatic ring and amino acid moiety. Benzoyl glycine derivatives have been synthesized using a variety of methods, such as the traditional Schotten–Baumann reaction (benzoyl chloride with glycine in an alkaline environment), direct acylation, and more recent environmentally friendly methods that use solvent-free or enzymatic catalysis. It has been demonstrated that structural alterations to the benzoyl ring, especially those involving electron-withdrawing substituents like nitro, halogen, and chloro groups, greatly increase antibacterial activity. These derivatives have been shown to be effective against both Gram-positive and Gram-negative strains, including Staphylococcus aureus and Escherichia coli, when screened for bacteria using common assays like agar well diffusion and minimum inhibitory concentration (MIC) tests. All things considered, benzoyl glycine derivatives are a useful scaffold for designing antibacterial drugs, and additional refinement through sensible substitution might yield promising leads for the fight against antibiotic resistance.

Keywords: Benzoyl glycine derivatives, Hippuric acid, Enzymatic catalysis, Green chemistry synthesis, Structure–activity relationship (SAR), Antibacterial activity, Gram-positive and Gram-negative bacteria, Staphylococcus aureus, Escherichia coli, Electron-withdrawing substituents

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1. Introduction

Hippuric acid, also referred to as benzoyl glycine, is an amide that is created when glycine is conjugated with a benzoyl moiety.[1] In order to create derivatives with a variety of pharmacological characteristics, benzoyl glycine can be altered at both the aromatic ring and the amino acid moiety. Because of their possible antimicrobial, anti-inflammatory, and anticancer properties, benzoyl glycine derivatives have garnered a lot of interest in medicinal chemistry. Benzoyl glycine derivatives' structural variety permits sensible modification, which may affect biological activity.[2] It has been demonstrated that adding electron-withdrawing substituents to the benzoyl ring, like nitro or halogen groups, increases its antibacterial activity.[2] Glycine moiety modifications can enhance solubility, bioavailability, and biological target interaction.[3] Benzoyl glycine derivatives are frequently synthesized using the direct acylation and classical Schotten–Baumann acylation techniques.[4] Eco-friendly substitutes for the synthesis of benzoyl glycine derivatives are provided by enzymatic catalysis and recent green chemistry techniques.[5] To maximize biological activity, functional groups can be introduced selectively using the synthesis techniques.[5] Significant antibacterial activity against both Gram-positive and Gram-negative strains has been shown by some benzoyl glycine derivatives.[6]

Derivatives thiourea- and azo-linked have demonstrated strong antibacterial activity against Escherichia coli and Staphylococcus aureus.[6,7] The type and location of substituents on the benzoyl ring have a significant impact on the antibacterial activity of benzoyl glycine derivatives, underscoring significant structure–activity relationships.[7] Prolonged infections and increased mortality are the results of antimicrobial resistance (AMR), which happens when microorganisms develop defense mechanisms against

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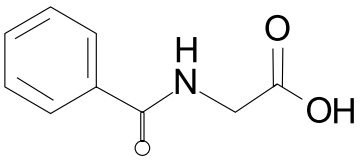
medications that once stopped their growth.[8] AMR is one of the biggest threats to global health, according to the WHO, which highlights the urgent need for new antibacterial agents.[8] Because of their structural tunability, synthetic accessibility, and proven antibacterial potential, benzoyl glycine derivatives offer a promising platform for the development of novel antibacterial agents.[6,9]

Strong compounds that can fight resistant bacterial strains may be produced by rationally designing and further optimizing the structure of these derivatives.[9]



N-benzoylglycine (Hippuric acid)

2. Synthesis

The Schotten–Baumann reaction, which combines benzoyl chloride and glycine with a base, usually sodium hydroxide or sodium carbonate, can be used to create benzoyl glycine.[10] Using this technique, benzoyl glycine is created when the amino group of glycine attacks the carbonyl carbon of benzoyl chloride, creating an amide bond.[11] Another popular method that introduces a variety of substituents on the aromatic ring is the direct acylation of glycine with substituted benzoic acids using coupling agents such as dicyclohexylcarbodiimide (DCC) or N,N'-carbonyldiimidazole (CDI).[12] In order to reduce the need for harsh chemicals, enzymatic catalysis has also been investigated for the synthesis of benzoyl glycine. This method uses lipases or proteases to catalyze the formation of amide bonds under mild conditions.[13] In order to increase yield, decrease reaction time, and lessen their negative effects on the environment, green chemistry techniques such as solvent-free synthesis, microwave-assisted reactions, and mechanochemical methods have been developed.[12,14] By reacting glycine with substituted benzoyl chlorides, one can create substituted benzoyl glycine derivatives, which allow for the addition of electron-donating or electron-withdrawing groups to the benzoyl ring to improve biological activity.[15] Benzoyl glycine is first transformed into the corresponding isothiocyanate for thiourea-linked derivatives. This isothiocyanate then reacts with the right amines to produce the thiourea moiety, which results in derivatives with improved antibacterial potential.[16] By diazotizing aromatic amines and then coupling them with benzoyl glycine at a regulated pH, azo-linked benzoyl glycine derivatives can be created, adding azo functionality that supports antimicrobial activity. The yield, purity, and biological activity of the final derivatives are strongly influenced by the synthetic method selected and the type of substituents present on the glycine moiety or benzoyl ring. Overall, these synthetic strategies provide flexibility for structural modification, enabling rational design of benzoyl glycine derivatives with optimized antibacterial properties.[15]

3. Antibacterial Screening of Benzoyl Glycine Derivatives

Benzoyl glycine derivatives are frequently screened for antibacterial activity using the agar well diffusion and disc diffusion methods, where inhibition zones show antibacterial potential. The lowest concentration of a derivative needed to prevent visible bacterial growth is often ascertained using Minimum Inhibitory Concentration (MIC) assays. Derivatives of benzoyl glycine have been tested against both Gram-negative (Escherichia coli, Pseudomonas aeruginosa) and Gram-positive (Staphylococcus aureus, Bacillus subtilis) bacteria. Antibacterial activity is greatly impacted by substitution on the benzoyl ring, with electron-withdrawing groups (like -Cl, -NO_2, and -Br) strengthening inhibitory effects against Gram-positive strains. Strong antibacterial activity was demonstrated by derivatives with thiourea linkages; compounds like 2-(4-(3-(3-bromophenyl)thioureido) benzamido)acetic acid demonstrated significant inhibition against S. aureus and E. coli. Because they can interfere with microbial enzyme systems and protein synthesis, azo-linked benzoyl glycine derivatives have also demonstrated broad-spectrum antibacterial activity.[17] According to screening studies, the antibacterial activity of derivatives with halogen substitutions on the benzoyl ring is stronger than that of derivatives with electron-donating substituents like -OH or -OCH_3. In tests against multi-drug resistant (MDR) strains, certain benzoyl glycine derivatives demonstrated moderate to good activity, indicating the possibility of development against resistant pathogens. Comparative research showed that in early in vitro models, the activity of benzoyl glycine derivatives is frequently on par with or better than that of common antibiotics like ampicilline. All things considered, benzoyl glycine derivatives' antibacterial screening shows promise as lead scaffolds for antibacterial drug development, especially when sensible structural changes are made.[18]

4. Discussion

The classic Schotten-Baumann reaction, enzymatic catalysis, and green chemistry techniques are among the synthetic methods for producing these derivatives that are described in the text. This flexibility in synthesis makes it possible to create a variety of structures. The capacity to strategically alter the glycine moiety and benzoyl ring is the most important factor. The addition of electron-withdrawing groups, such as nitro or halogen groups, improves antibacterial activity, according to the text. Additionally, it lists particular, very potent derivatives that exhibit potent activity against common bacterial strains like Staphylococcus aureus and Escherichia coli, such as those with thiourea- and azo-linkages.The text presents positive results from antibacterial screening. Both Gram-positive and Gram-negative bacteria are susceptible to the compounds' broad range of activity, with some derivatives outperforming or surpassing current antibiotics like ampicillin. The structure-activity relationship (SAR), which is essential to comprehending how these alterations affect biological effects, is emphasized in the conversation. Even though these results are encouraging, more research

is required, the conclusion emphasizes. To make these promising scaffolds into antibacterial medications that are clinically viable, this entails toxicity profiling, in vivo studies, and property optimization.

5. Conclusion

Benzoyl glycine, another name for hippuric acid, and its derivatives comprise a noteworthy class of compounds with significant pharmacological and medicinal uses . Their structural simplicity and synthetic accessibility make them an excellent scaffold for logical drug design and chemical modification. Numerous synthetic methods, including direct acylation, enzymatic catalysis, classical Schotten–Baumann acylation, and green chemistry approaches, provide flexibility in the preparation of structurally diverse derivatives. Adding electron-withdrawing groups (-Cl, -NO_2, -Br) to the benzoyl ring specifically has been shown to increase its antibacterial activity. Derivatives such as thiourea-linked and azo-linked benzoyl glycine analogues have been demonstrated to significantly inhibit both Gram-positive and Gram-negative bacteria, including Staphylococcus aureus and Escherichia coli .Future studies should focus on a few crucial areas in order to fully realize their therapeutic potential. First, to comprehend how these compounds' chemical structure affects their antibacterial qualities, a comprehensive structure–activity relationship (SAR) analysis is required. This information is essential for creating medications that are more effective and selective. Second, to make sure these derivativBes are properly absorbed, distributed, metabolized, and eliminated by the body, researchers need to maximize their pharmacokinetic characteristics. Finally, before they can be considered for clinical use, in vivo evaluation in living organisms is necessary to confirm their safety and efficacy.

The need for new drug scaffolds is urgent due to the growing threat of antimicrobial resistance (AMR). Benzoyl glycine derivatives are a good place to start in this crucial endeavor because of their demonstrated efficacy and structural adaptability.

6. Source of Funding

None.

7. Conflict of Interest

None.

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