

Diazoalanine

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summary

Diazoalanine is a modified amino acid featuring a diazo group integrated into the alanine structure, with the molecular formula $C_7H_9N_3O_4$. This unique compound stands out in the field of organic chemistry due to its significant reactivity and potential applications in medicinal chemistry, particularly for antimicrobial and antitumor treatments. The structural characteristics of diazoalanine, specifically its ability to act as a nucleophile and inhibit glutamine-utilizing enzymes, make it a critical subject of study in both biochemical research and pharmaceutical development.

The synthesis of diazoalanine has evolved through various methodologies, ranging from classical reactions such as the Bamford-Stevens reaction and dehydrogenation of hydrazones, to modern techniques like diazotization and cascade reactions involving advanced catalysts. These diverse synthetic routes not only highlight the compound's versatility but also address the challenges of safety and efficiency in chemical synthesis. As researchers continue to innovate in this area, the prospects for diazoalanine in drug development remain promising, particularly in combating drug-resistant bacterial infections and certain types of cancer.

In addition to its synthetic and therapeutic applications, diazoalanine plays a notable role in biological processes, including metabolism and amino acid biosynthesis. Its influence on nitrogen metabolism and glucose production further underscores its importance in maintaining cellular homeostasis. The compound's interaction with key metabolic pathways highlights its potential implications for enhancing our understanding of disease mechanisms and developing novel therapeutic strategies.

Despite its potential benefits, diazoalanine also poses challenges, particularly in terms of stability under varying environmental conditions. Ongoing research aims to elucidate its mechanisms of action and optimize its applications in drug formulations, while ethical considerations regarding its use in research and therapy will guide future investigations. As a result, diazoalanine is poised to remain a focal point of interest in both scientific inquiry and practical applications, bridging the gap between chemistry and biology.

Chemical Structure

Diazoalanine is a modified amino acid characterized by the incorporation of a diazo group into the alanine structure. The molecular formula for diazoalanine is $C_7H_9N_3O_4$, which indicates the presence of nitrogen atoms in addition to the standard components of alanine, $C_3H_7NO_2$ [\[1\]](#)[\[2\]](#).

Synthesis

The synthesis of diazoalanine, a diazocarbonyl compound, can be achieved through several classical and modern methodologies that have evolved over the years. These methods vary in complexity, efficiency, and safety, reflecting advances in synthetic organic chemistry.

Classical Methods

Acylation of Diazoalkanes

One of the traditional methods for preparing diazocarbonyl compounds involves the acylation of diazoalkanes. A prominent reaction in this category is the cleavage of toluenesulfonyl hydrazones, known as the Bamford-Stevens reaction. This reaction employs base cleavage of tosylhydrazones, which are typically synthesized from tosylhydrazides and aldehydes or ketones, to produce the desired diazocarbonyl compounds[\[3\]](#).

Dehydrogenation of Hydrazones

Another classical approach is the dehydrogenation of hydrazones, which has been used for many years. This method consists of oxidizing hydrazine using various metallic catalysts, primarily heavy metals such as mercury oxide and silver oxide[\[3\]](#). Recent developments have sought to replace heavy metals with safer alternatives, such as a metal-free pathway involving chlorosulfodimethyl chloride, which can be generated in situ[\[3\]](#).

Forster Reaction

The Forster reaction, first reported in 1915, involves the synthesis of diazoketones, particularly cyclic ones, from ~~ketoximes~~ ketoximes in the presence of chloramines. This method has been widely applied for the preparation of ~~dia~~ diazoketones and their derivatives[\[3\]](#).

Modern Methodologies

Diazotization

Diazotization remains a fundamental method for the synthesis of diazo compounds, typically involving the reaction of primary amines with nitrosating agents like sodium

nitrite in acidic aqueous solutions[3][4]. Recent expansions of this methodology include the generation of fluorinated diazoalkanes, enhancing the scope of diazo compounds that can be synthesized[3].

Diazo Transfer Reactions

Diazo transfer has emerged as a safer alternative for synthesizing diazocarbonyl compounds. This method involves the reaction of primary amines with nitrosating agents and has been refined to accommodate a variety of substrates, including those with fluorinated groups[3][4].

Cascade Reactions

Recent studies have introduced cascade reactions that combine diazo compounds with other catalytic processes. For instance, the Yan research group developed methods that utilize ruthenium and rhodium catalysts to create libraries of complex derivatives from diazo compounds, illustrating the versatility of diazo reactions in modern synthesis[5].

Properties

Physical Properties

Diazoalanine exists as a yellowish powder and is soluble in water, as well as in aqueous solutions of alcohols like methanol and ethanol. However, it demonstrates difficulty in dissolving in absolute alcohols. In its crystalline form, diazoalanine appears as greenish-yellow needles, and its specific rotation is recorded as $[\alpha]_D^{21} +21^\circ$ when dissolved in water at a concentration of 5.4%. [6][5].

Chemical Structure

Diazoalanine is a derivative of alanine, characterized by its diazo group, which consists of two nitrogen atoms double-bonded to each other (N=N). Its chemical formula is C₃H₇N₄O₂, and its structure includes functional groups that impact its reactivity and interactions with other chemical species. [1][6].

Reactivity

As a diazo compound, diazoalanine can act as a nucleophile due to its ability to participate in electrophilic reactions. This compound can engage with various substrates, making it a useful intermediate in organic synthesis. Furthermore, due to its structural similarity to glutamine, diazoalanine can inhibit glutamine-utilizing enzymes by entering their active sites and binding covalently, thus blocking their catalytic action. This property has implications for its use in biochemical studies and pharmacology. [7][8].

Stability

The stability of diazoalanine can vary based on environmental conditions such as pH and temperature. While it is stable in neutral aqueous solutions, it may undergo decomposition under extreme conditions, especially when exposed to strong acids or bases. The compound is particularly sensitive to light and should be handled under reduced light exposure to prevent degradation.[\[9\]\[3\]](#).

Biological Role

Diazoalanine, a derivative of alanine, plays a significant role in various biological processes, particularly in metabolism and amino acid biosynthesis. Much of biochemistry focuses on understanding the chemical foundations that enable biological molecules to facilitate cellular functions and interactions. For instance, alanine's interconversion with pyruvate, catalyzed by enzymes such as alanine transaminase (ALT), forms a crucial metabolic link between amino acid and carbohydrate metabolism[\[10\]\[11\]](#).

Metabolism and Energy Production

Under conditions such as fasting, exercise, or starvation, alanine serves as a vital precursor for glucose production through gluconeogenesis. This process occurs primarily in the liver, where alanine is converted into pyruvate and subsequently used to maintain blood glucose levels, which is essential for tissues that rely heavily on glucose, like the brain and erythrocytes[\[10\]\[11\]](#). The reversible nature of the alanine-pyruvate conversion not only helps in glucose production but also aids in the cellular redox balance by influencing NAD⁺/NADH ratios, thereby playing a critical role in energy homeostasis[\[10\]\[11\]](#).

Amino Acid Synthesis

Diazoalanine's biological significance extends to amino acid biosynthesis. When the amino group is removed from alanine, it forms an ~~α~~ keto acid, which can undergo transamination to facilitate the synthesis of other amino acids. This reaction is essential for maintaining amino acid pools in the body, as it allows for the recycling of nitrogen and carbon skeletons necessary for protein synthesis[\[10\]\[12\]](#). Moreover, while humans can synthesize certain amino acids, essential amino acids must be obtained from the diet, underscoring the importance of compounds like diazoalanine in metabolic pathways[\[10\]](#).

Nitrogen Metabolism

Additionally, diazoalanine is involved in nitrogen metabolism, primarily through the urea cycle in the liver. The liver's ability to process alanine is pivotal for ammonia detoxification, which helps prevent toxic accumulation in the bloodstream[\[11\]](#). By integrating nitrogen balance with glucose production, diazoalanine contributes to

maintaining systemic homeostasis, further highlighting its role in crucial metabolic pathways[\[10\]\[11\]](#).

Therapeutic Applications

Diazoalanine, a diazo-containing amino acid, has garnered significant interest due to its potential therapeutic applications, particularly in the realms of antimicrobial and antitumor treatments. Its unique structure allows for both antibacterial and anticancer activities, making it a versatile candidate in drug development strategies aimed at addressing pressing global health concerns, such as microbial infections and cancer, which are among the leading causes of mortality worldwide[\[12\]\[13\]](#).

Antimicrobial Properties

Research indicates that diazoalanine exhibits potent antibacterial effects against a variety of gram-negative bacteria. This has sparked investigations into its use as a targeted antimicrobial therapy, which can mitigate the risks associated with traditional antibiotics, including drug resistance[\[14\]\[15\]](#). The ability of diazoalanine to selectively target pathogenic microorganisms offers a promising avenue for developing new therapeutics that may be less prone to resistance mechanisms[\[12\]\[16\]](#).

Antitumor Activities

In addition to its antimicrobial properties, diazoalanine has been studied for its antitumor potential. Notably, studies have shown that it can inhibit the growth of neuroendocrine tumors and neuroblastoma cells, demonstrating a capacity to act as a potent antitumor agent[\[17\]\[18\]](#). The mechanism of action is believed to involve the accumulation of reactive oxygen species (ROS) and the induction of necroptosis, a form of programmed cell death, which can effectively suppress tumor growth[\[19-\]\[18\]](#). Furthermore, diazoalanine's ability to engage in various chemical reactions enhances its therapeutic profile, allowing it to be modified for improved efficacy and specificity in treatment applications[\[12\]\[13\]](#).

Future Directions

The ongoing research into diazoalanine emphasizes the need for further exploration of its therapeutic capabilities and mechanisms of action. With advancements in synthetic methodologies and a growing understanding of its biological interactions, diazoalanine represents a promising candidate for the development of novel therapeutics that address both bacterial infections and cancer, thus filling critical gaps in current treatment strategies[\[12\]\[20\]\[16\]](#).

Applications

Medicinal Chemistry

Diazoalanine and its derivatives have shown significant promise in the field of medicinal chemistry. They are explored for their potential in developing targeted antimicrobial therapies for bacterial infections. The dual functionality of cationic antimicrobial peptides (AMPs), which can exhibit both antimicrobial and anticancer activities, makes diazoalanine a compound of interest for enhancing the efficacy of these peptides through modification strategies[12]. The incorporation of diazoalanine may improve the stability and selectivity of AMPs, thus reducing side effects and minimizing drug resistance[12].

Nanotechnology

The integration of diazoalanine into nanotechnology applications has been highlighted as a promising strategy to enhance the performance of AMPs. Utilizing nanocarriers, diazoalanine can be employed in drug delivery systems to ensure targeted and controlled release of therapeutic agents, maintaining metabolic and chemical stability[21]. This application is particularly relevant in designing formulations aimed at specific tissues, improving the therapeutic outcomes for diseases such as cancer and bacterial infections[12][21].

Research and Development

In addition to its medicinal applications, diazoalanine serves as a versatile reagent in organic synthesis. Its unique reactivity allows it to participate in various cycloaddition reactions, which are valuable for synthesizing natural products and pharmaceutical analogues[3]. The ongoing research into the applications of diazoalanine in synthetic pathways demonstrates its role in expanding the toolkit available for chemists[22].

Environmental and Biotechnological Applications

The exploration of diazoalanine within biotechnological contexts also shows promise. The compound's potential to influence microbial communities suggests its application in studying microbiomes, particularly regarding their roles in ecosystem functions and host health[23]. This aspect underscores the importance of diazoalanine not only in medical and synthetic chemistry but also in environmental science and biotechnology, providing avenues for research into sustainable practices and health-related innovations.

Future Research Directions

Exploration of Disease Mechanisms

Future research on diazoalanine is poised to delve deeper into its potential implications in various disease mechanisms. As highlighted in current studies, the application of advanced tools in cellular biology has been instrumental in elucidating the complexities of diseases such as cancer and neurodegenerative disorders[23]. Investigating the biochemical pathways influenced by diazoalanine could lead to a

better understanding of its role in cellular processes and its potential therapeutic benefits.

Development of New Therapeutic Strategies

Given the ongoing advances in biotechnology and genetic engineering, diazoalanine could be a focal point for developing innovative therapeutic strategies. Research is expected to explore its applications in stem cell research and cancer cell biology, particularly in targeting specific cellular pathways to enhance treatment efficacy[23]. The integration of diazoalanine into novel drug formulations may also be pursued to improve bioavailability and target specificity.

Educational and Research Initiatives

To further promote research in diazoalanine, educational initiatives that emphasize hands-on laboratory experience will be crucial. Programs designed to equip students with both theoretical knowledge and practical skills in biochemistry could lead to a new generation of researchers dedicated to studying this compound[23]. Collaborative research projects within academic institutions, such as Queen's University Belfast, will provide students with the opportunity to engage with world-leading researchers and contribute to significant discoveries in the field[23].

Interdisciplinary Approaches

The future of diazoalanine research may also benefit from interdisciplinary approaches that incorporate insights from molecular biology, pharmacology, and bioinformatics. By utilizing various scientific methodologies and technologies, researchers can explore the multifaceted interactions of diazoalanine within biological systems[23]. This holistic perspective may reveal novel applications and enhance our understanding of its chemical properties and biological activities.

Ethical Considerations in Research

As research progresses, ethical considerations surrounding the use of diazoalanine in experimental settings will become increasingly important. Ensuring compliance with ethical standards in laboratory practices, including safety protocols and research integrity, will be vital for the responsible advancement of this field[23]. Continuous dialogue within the scientific community about the implications of diazoalanine research will contribute to a more ethical approach in its application, particularly in therapeutic contexts.

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