

Azaalanine

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summary

Azaalanine is a non-classical amino acid and a derivative of alanine characterized by a unique molecular structure that features a nitrogen atom replacing the ~~α~~carbon. This distinctive configuration enables azaalanine to engage in novel noncovalent interactions that stabilize its conformation, setting it apart from traditional amino acids. It has garnered attention within the scientific community for its potential applications in drug design and metabolic pathways, particularly due to its ability to participate in

crucial biochemical processes such as gluconeogenesis and nitrogen regulation in the liver and skeletal muscle. [\[1\]\[2\]\[3\]](#).

The biological relevance of azaalanine extends to its roles as a metabolite and enzymatic inhibitor, implicating it in significant metabolic pathways. Its transformation into intermediates like glutamate and pyruvate highlights its contribution to energy production and metabolic flexibility. Moreover, azaalanine's unique chemical properties enable it to form structured motifs within peptide chains, thereby enhancing the stability and efficacy of peptidomimetics used in therapeutic contexts. [\[4\]\[5\]\[3\]](#).

Research on azaalanine has opened avenues for its application in various therapeutic strategies, particularly in cancer treatment and neurological disorders. Its influence on metabolic pathways and regulatory interactions has positioned azaalanine as a candidate for enhancing the effectiveness of treatments, including combination therapies for leukemia and potential neuroprotective agents for diseases such as Alzheimer's. [\[6\]\[7\]\[3\]](#).

Despite its promise, the exploration of azaalanine is not without challenges, as its metabolic roles and interactions with other biomolecules continue to be areas of active investigation. Ongoing research aims to elucidate the comprehensive functions of azaalanine within biological systems and its implications for metabolic engineering and sustainable bioprocesses. [\[8\]\[9\]](#).

Chemical Properties

Azaalanine, a non-classical amino acid, exhibits unique chemical properties that distinguish it from traditional amino acids. Its structure includes a nitrogen atom replacing the α -carbon in the backbone, resulting in novel noncovalent interactions that can stabilize its conformation. This is highlighted by the presence of an unusual C8 CO...HN hydrogen bond that stabilizes proline amides in a trans conformation, as confirmed by computational studies using Density Functional Theory (DFT) and spectroscopic methods such as NMR and circular dichroism (CD) [\[1\]\[4\]](#).

Interaction Dynamics

The interactions of azaalanine within peptide chains can lead to the formation of structured turn motifs, particularly in environments such as aqueous solutions and solid-state forms. Such properties make azaalanine a subject of interest for drug design and the development of peptidomimetics, which can benefit from enhanced stability and rigidity imparted by these unique interactions [\[4\]\[10\]](#).

Metabolic Role

As a glucogenic amino acid, azaalanine can be metabolically transformed into intermediates such as glutamate and pyruvate in the liver. This transformation facilitates its incorporation into energy-producing pathways, thereby linking its chemical properties to physiological roles in metabolism [\[2\]](#). Azaalanine's ability to be synthesized

from other branched-chain amino acids further emphasizes its relevance in metabolic networks [\[11\]](#).

Resilience to Perturbations

Studies on the metabolic network involving azaalanine suggest a high degree of modularity and resilience. Percolation analysis of the human metabolic network indicates that disruptions, whether by the removal of edges or nodes, do not drastically affect the interconnected pathways involving azaalanine. This characteristic demonstrates the robustness of metabolic interactions, underscoring the importance of azaalanine in sustaining metabolic integrity amid environmental challenges [\[8\]](#).

Biosynthesis

Azaalanine, a derivative of alanine, is synthesized through various metabolic pathways within biological organisms. The biosynthesis of azaalanine is intricately linked to the metabolism of other amino acids and metabolites, particularly within the context of nitrogen transport and energy metabolism.

Amino Acid Precursor Utilization

The production of azaalanine can be influenced by the availability and interconversion of precursor amino acids, particularly those involved in the urea cycle and amino acid catabolism. For instance, ornithine and citrulline play significant roles in this metabolic process, providing substrates that can lead to the formation of azaalanine under specific physiological conditions [\[12\]](#)[\[3\]](#).

Enzymatic Pathways

The enzymatic reactions involved in the synthesis of azaalanine typically require specific enzymes that facilitate the modification of existing amino acids. These pathways may share similarities with those utilized in the synthesis of other non-essential amino acids. For example, the action of enzymes such as transaminases and decarboxylases can lead to the conversion of alanine and related compounds into azaalanine through a series of sequential reactions [\[11\]](#)[\[13\]](#).

Metabolic Context

The synthesis of azaalanine is not only a standalone process but also integrates with broader metabolic networks. It participates in the dynamic interrelationships among amino acids, where the product of one enzymatic reaction can serve as a substrate for subsequent reactions, thereby influencing overall metabolic flux. This interconnectedness is particularly evident in tissues such as the liver and muscle, where alanine metabolism is tightly regulated to meet various metabolic demands [\[3\]](#)[\[14\]](#).

Biological Functions

Azaalanine, a derivative of alanine, plays significant roles in various biological processes, particularly in metabolism. It is involved in critical metabolic pathways, acting both as a fundamental metabolite and as an inhibitor of specific enzymatic reactions, notably as an inhibitor of EC 4.3.1.15 (diaminopropionate ammonia-lyase) [5]. This positioning highlights its relevance in biochemical processes associated with amino acid metabolism.

Metabolic Pathways

Azaalanine participates in key metabolic pathways, contributing to the regulation of nitrogen and glucose levels in the body. The liver serves as a central hub for these metabolic processes, where azaalanine's contributions are significant in maintaining systemic homeostasis through nitrogen balance and glucose production [3]. In skeletal muscle, azaalanine is produced during periods of increased protein catabolism, such as during exercise or fasting, where amino acids undergo degradation to generate intermediates that are converted into azaalanine via transamination reactions. This produced azaalanine is then transported to the liver for conversion to glucose through gluconeogenesis, thus playing a pivotal role in blood sugar regulation [3].

Interactions and Signaling

The biological functions of azaalanine extend to its interactions within broader molecular networks. It influences metabolic pathways through its role in protein-protein interactions and regulatory interactions with enzymes. Such interactions can dictate various biochemical responses crucial for maintaining cellular functions and overall metabolic stability [8][11]. Furthermore, these integrated approaches to studying biological functions underscore the importance of understanding how azaalanine interacts with other biomolecules, which can impact health and disease states [14].

Applications

Therapeutic Potential

Azaalanine, a modified form of alanine, has shown promise in various therapeutic applications due to its unique structural properties. Its incorporation into peptide drugs has been found to enhance stability and bioavailability, making it an attractive candidate for drug development [15][16]. The potential uses of azaalanine extend to treating metabolic disorders, cancer, and infectious diseases, where its effects on metabolic pathways can be particularly beneficial [6][3].

In Cancer Therapy

Recent studies have highlighted azaalanine's role in cancer treatment strategies. Its interaction with enzymes involved in metabolic processes has led to its exploration in combination therapies, especially where synthetic lethality plays a crucial role. For instance, azaalanine can influence the activity of glycogen synthase kinase 3

(GSK3), which is implicated in the regulation of cancer cell growth and apoptosis. When combined with agents like ASNase, azaalanine may enhance therapeutic efficacy in leukemia treatment by maintaining asparagine levels through the modulation of proteasomal degradation[7][17].

Neurological Applications

Research into azaalanine's influence on neurotransmitter regulation suggests potential applications in neurodegenerative disease treatment. Its ability to affect synaptic transmission presents avenues for developing drugs aimed at conditions such as Alzheimer's and Parkinson's disease, where neuroprotection is a critical factor[3].

Metabolic Engineering

Azaalanine is also being investigated in the context of metabolic engineering. Its unique properties allow for the modification of microbial or yeast strains to produce amino acids in high yields. This application is particularly relevant in the production of biofuels, chemicals, and specialty metabolites, making azaalanine a key component in the advancement of sustainable bioprocesses[3][8].

Research and Development

Research on azaalanine, an amino acid analog, has gained traction due to its potential implications in metabolic processes and cancer therapy. Recent studies have highlighted the role of asparagine, another amino acid, in modulating immune responses, particularly in the activation and metabolic fitness of CD8 + T lymphocytes, which are crucial for antitumor immunity[7]. Understanding these interactions opens avenues for integrating azaalanine into therapeutic strategies aimed at enhancing immune responses against tumors.

In the realm of cancer treatment, immunotherapy has emerged as a leading approach, with immune checkpoint blockade (ICB) and adoptive cell transfer (ACT) being the foremost strategies[7]. The relationship between amino acids and immune modulation, particularly in the context of cancer, presents a promising area for exploration. Azaalanine, through its structural similarity to other amino acids, could potentially influence metabolic pathways involved in lymphocyte activation and function.

The significance of amino acids in cellular metabolism is also emphasized through their roles in various biochemical reactions that affect physiological activities, such as growth and metabolism[9]. As research progresses, the integration of comprehensive databases like the Kyoto Encyclopedia of Genes and Genomes (KEGG) aids in elucidating the metabolic networks involving azaalanine and its analogs, thereby facilitating a better understanding of their functional roles within biological systems[8].

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