Norleucine

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summary

Norleucine, also known as 2-aminohexanoic acid, is a non-proteinogenic amino acid with the chemical formula $C6H13NO2$, notable for its structural similarity to the

essential amino acid leucine. This amino acid is characterized by a shorter side chain and the absence of sulfur, setting it apart from its homologs. With a molecular weight of approximately 131.18 g/mol, norleucine exists in two enantiomeric forms: L-norleucine, which occurs naturally, and D-norleucine. Its significance extends beyond basic biochemistry, as it plays critical roles in various metabolic pathways and has garnered attention in nutritional and therapeutic contexts, particularly concerning cancer treatment and age-related disorders[1][2][3][4].

The biosynthesis of norleucine occurs through a series of enzymatic reactions involving precursors from the tricarboxylic acid (TCA) cycle, and its production has been optimized in engineered host strains for industrial applications. Norleucine's involvement in amino acid metabolism is pivotal, as it contributes to energy production and the synthesis of other biomolecules. Recent studies have indicated its potential impact on cancer metabolism, particularly in the context of glutamine utilization, which could influence therapeutic strategies targeting tumor metabolism[5][4][6].

In addition to its metabolic functions, norleucine's physiological importance includes its role in protein synthesis and as a signaling molecule that regulates cellular processes, particularly in immune cell function. Its implications in cancer immunotherapy and age-related disorders have sparked research into its therapeutic potential, with ongoing studies examining its efficacy in enhancing anti-tumor immunity and addressing metabolic dysregulations associated with aging[6][7][4].

Despite its beneficial roles, safety concerns have emerged regarding norleucine's toxicity, particularly due to its structural similarity to branched-chain amino acids (BCAAs). Research has indicated potential neurotoxic effects linked to elevated levels of BCAAs, raising caution for norleucine's application in dietary and therapeutic contexts. Regulatory oversight regarding its use in food and supplements remains limited, emphasizing the need for further investigation into its safety profile and long-term effects on health[8][9]. As research continues to evolve, norleucine is positioned at the forefront of studies exploring novel therapeutic approaches in metabolic diseases and cancer treatment.

Chemical Structure

Norleucine, also known as 2-aminohexanoic acid, has the chemical formula C6H13NO2 and a molecular weight of approximately 131.18 g/mol[1][2]. It is characterized by its structure, which can be represented linearly as CH3(CH2)3CH(NH2)CO2H[1][10]. As a non-proteinogenic amino acid, norleucine features a shorter side chain compared to its homolog, leucine, making it structurally similar to this essential amino acid but without the sulfur found in methionine[3][11][12].

Norleucine exists as both L-norleucine and D-norleucine, with the former being the naturally occurring enantiomer[13][14]. The CAS number for L-norleucine is 327-57-1, while the D-enantiomer has the CAS number 327-56-0[2][15]. Its stereoisomers include both the DL-alpha-amino-n-caproic acid and L-norleucine[16]. The molecule can be visualized in various formats, including 2D and 3D representations[17][18].

In terms of physical properties, norleucine exhibits a range of behaviors useful in biochemical research, owing to its unique structural characteristics that allow for interactions similar to leucine in protein synthesis and structure[19].

Biosynthesis

Norleucine, a methionine analog, is synthesized through a series of enzymatic reactions involving precursor compounds. The biosynthesis of norleucine begins with the action of 2-isopropylmalate synthase on ±-ketobutyrate, leading to its formation in a metabolic pathway that also engages various intermediates of the tricarboxylic acid (TCA) cycle[20][5].

In engineered host strains, scalable bioprocesses have been developed to achieve appropriate titers for norleucine production, demonstrating the potential for industrial applications[5]. Notably, during its biosynthesis, norleucine's structural characteristics are comparable to those of methionine, yet it notably lacks sulfur in its structure[3]. This difference plays a crucial role in the function and application of norleucine in biochemical contexts.

Furthermore, the biosynthetic pathway of norleucine highlights the significance of lipid metabolism and post-translational modifications of proteins. Lipids serve as critical substrates for protein modifications, influencing various cellular functions, including the modulation of signaling pathways that are vital for the proliferation and differentiation of immune cells[21][22].

Biological Role

Norleucine, a noncanonical amino acid, plays significant physiological roles similar to those of standard amino acids. It serves as a building block for proteins and is involved in various metabolic pathways within the body. Norleucine, like other amino acids, is crucial for the synthesis of proteins, which are essential for cell structure, function, and regulation[23][24].

Metabolic Functions

Amino Acid Metabolism

Norleucine is metabolized alongside other amino acids, contributing to energy production and serving as substrates for the synthesis of other biomolecules. Amino acids, including norleucine, are vital for the normal growth, differentiation, and functioning of cells[25]. They can act as precursors for low-molecular-weight compounds and are involved in various biochemical reactions essential for maintaining cellular homeostasis[23][26].

Role in Cancer Metabolism

Recent studies have highlighted the potential role of norleucine in cancer metabolism. The enzyme glutaminase (GLS), which is involved in the metabolism of glutamine, can influence the utilization of norleucine as part of broader metabolic pathways in cancer cells. Inhibition of GLS has shown to impact the metabolic landscape of tumors, suggesting that norleucine may have implications in therapeutic strategies targeting cancer metabolism[4][27].

Physiological Importance

Cellular Functions

Norleucine and other amino acids function as signaling molecules that can affect various cellular processes, including growth and proliferation. They serve as metabolic regulators that help modulate cell function in response to changes in the external microenvironment, such as nutrient availability[6]. This ability to sense and adapt to environmental changes is critical for the activation and differentiation of immune cells within the tumor microenvironment[6][4].

Nutritional Aspects

In human nutrition, norleucine can be obtained through dietary sources, particularly from protein-rich foods. While the body can synthesize certain amino acids, dietary intake of amino acids, including norleucine, remains important for optimal physiological functions and metabolic balance[24].

Applications

Cancer Therapy

Norleucine has garnered attention in the context of cancer therapy due to its role in glutamine metabolism. The inhibition of glutamine metabolism, where norleucine acts as a relevant metabolite, has emerged as a promising strategy to combat cancer. Clinical trials are investigating several new drugs, including CB-839, IPN60090, and DRP-104, which target glutaminolysis to improve patient outcomes and advance precision medicine[4]. Ongoing research aims to explore the precise mechanisms of action of these compounds and identify patient populations that may benefit most from these therapies[4].

Age-Related Disorders

Emerging studies suggest that norleucine may play a role in addressing age-related disorders by targeting glutaminolysis. Research has shown that inhibiting glutaminolysis can selectively eliminate senescent cells, leading to improvements in tissue function and mitigating disorders associated with aging, such as frailty and cardiovascular dysfunction[7]. These findings propose that targeting glutaminolysis holds therapeutic promise for enhancing health outcomes in various age-associated disorders[7].

Immunotherapy

The interplay between glutamine metabolism and the immune landscape of cancer has become a focal point of research, highlighting the potential of norleucine in immunotherapeutic approaches. Investigations into the molecular mechanisms of glutamine metabolism suggest that it may enhance anti-tumor immunity, thereby revolutionizing cancer treatment strategies[4]. This ongoing inquiry into the immunogenic characteristics of glutaminase inhibitors aims to develop innovative interventions that can significantly impact cancer therapy[4].

Nutritional Applications

Norleucine's amino acid profile contributes to its significance in nutritional formulations. As part of specialized diets, it may assist in protein synthesis and overall metabolic health, although its specific role in dietary supplementation is still under investigation. Its hypoallergenic properties make it a suitable candidate for inclusion in infant food products, ensuring safe nutritional options[28].

Safety and Toxicology

Norleucine, an amino acid analog, has been studied for its safety profile and potential toxicological effects. It is essential to understand its impact on various biological systems, particularly given its structural similarity to leucine.

Toxicity Mechanisms

Research indicates that norleucine may exhibit toxicity through mechanisms similar to those of branched-chain amino acids (BCAAs). Elevated levels of BCAAs, particularly leucine, have been shown to have neurotoxic effects in certain metabolic disorders, leading to concerns about norleucine's safety in similar contexts[8][28]. While norleucine itself has not been directly linked to severe neurotoxicity, caution is advised due to its competitive interaction with neurotransmitter systems.

Dietary Implications

The dietary implications of norleucine must also be considered. In some animal models, high levels of dietary norleucine have been associated with negative health outcomes, such as impaired growth and metabolic dysfunctions[9]. For instance, dietary restrictions and management strategies in conditions like Maple Syrup Urine Disease (MSUD) highlight the importance of monitoring amino acid profiles to avoid toxic accumulation of specific substrates, suggesting that similar attention should be applied when considering norleucine in diet formulations[8].

Regulatory Perspectives

Regulatory bodies have set guidelines regarding amino acid supplementation in animal feeds, yet comprehensive regulations concerning norleucine specifically are lacking. For instance, the Food and Drug Administration (FDA) in the United States mandates that all food additives, including amino acids, must be proven safe before market approval, which implies that any use of norleucine in food products would require thorough safety assessments[9]. Moreover, the European Union emphasizes safety and proper labeling of feed additives, indicating a need for research on the long-term effects of compounds like norleucine in livestock diets[9].

Recent Developments

Recent research has highlighted the potential of amino acid transporters and metabolic interventions as therapeutic strategies in cancer treatment. One of the promising avenues involves the utilization of the glutamine antagonist 6-Diazo-5-oxo-L-norleucine (DON), which has garnered significant attention for its anticancer efficacy. While DON exhibits remarkable therapeutic potential, challenges such as toxicity, particularly gastrointestinal side effects, have limited its clinical application[6][29].

Innovative approaches have been developed to enhance anti-tumor immune responses by combining therapies targeting amino acid metabolism. A groundbreaking strategy involves using molybdenum disulfide (MoS2) as a carrier for the delivery of anti-PD-L1 antibodies alongside V9302, a competitive transmembrane antagonist targeting the amino acid transporter ASCT2. This combination therapy has shown the capability to improve antitumor immunity in syngeneic mouse models, facilitating the migration of CD8+ T cells into tumor cores and significantly impeding tumor growth in triple-negative breast cancer (TNBC) models[4][7]. Following treatment, a notable increase in glutamine levels within tumor interstitial fluid was observed, leading to an augmentation of activated T cells, which underscores the interplay between glutamine metabolism and immune function[4].

Furthermore, investigations into the role of cellular metabolism in immune cell activity reveal that metabolic regulators play a crucial role in modulating immune responses. These regulators, which can be influenced by the tumor microenvironment, help direct the differentiation and proliferation of immune cells, potentially providing new insights into combinatorial therapies aimed at both tumor cells and the immune system[7][6].

As research progresses, there is a growing emphasis on unraveling novel therapeutic strategies that leverage glutamine metabolism to combat cancer, thus expanding the potential applications of compounds like norleucine and its derivatives in precision medicine[7][30].

History

Norleucine, an amino acid analog of leucine, has been the subject of scientific research since its initial identification. The compound is notable for its unique structural properties and implications in both nutrition and metabolic studies. Early investigations into norleucine focused on its role in protein synthesis and its potential effects on metabolic pathways in various organisms.

In the late 20th century, significant advancements in amino acid research led to a deeper understanding of norleucine's physiological effects. Studies revealed its potential as a tool for exploring metabolic dependencies in cancer cells, particularly in relation to glutamine metabolism. Researchers began to investigate the intricate interactions between norleucine and other metabolic pathways, including those of glucose and lipids, prompting a renewed interest in its applications in cancer therapy and metabolic research[4][7].

More recently, the integration of multi-omics data has facilitated a comprehensive approach to studying norleucine. This advancement allows scientists to unravel the complex networks involving norleucine and other metabolites, paving the way for innovative treatment strategies and potential therapeutic applications[4]. The ongoing exploration of norleucine in relation to cancer metabolism highlights its significance in the development of targeted therapies, especially as researchers continue to decipher its interplay with the immune landscape of tumors[4][7].

As the field progresses, norleucine remains a focal point in metabolic research, underscoring its importance in understanding the biochemical underpinnings of diseases and potential therapeutic interventions.

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