alfa-Methylalanine

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summary

Alfa-Methylalanine, also known as 2-methylalanine or ±aminoisobutyric acid, is a nonpolar amino acid derivative with the chemical formula C4H9NO2. Characterized by a methyl group attached to the ±carbon of the alanine backbone, alfa-methylalanine distinguishes itself from standard alanine, impacting its biochemical interactions and solubility properties.[1][2][3] This compound has garnered attention within the scientific community for its potential applications in neuropharmacology, particularly in targeted therapies for neurological disorders and peptide synthesis, underscoring its significance in both basic and applied research contexts.[4][3]

Research on alfa-methylalanine has evolved, particularly since the early 21st century, as studies have explored its roles in cognitive function and metabolic regulation. Investigations highlight its utility in formulating novel drug delivery systems aimed at enhancing treatment efficacy for conditions such as neurodegenerative diseases and cancer.[4][3] Additionally, the compound has been examined for its influence on cognitive development and neuroprotection, signaling its potential impact on therapeutic strategies in neurology.[5][4]

Despite its promising applications, the safety and toxicology of alfa-methylalanine have raised concerns, with studies indicating potential acute toxicity at high doses.[3-][6] While serious adverse effects remain infrequently documented, there are reports of mild side effects warranting further investigation to comprehensively understand its safety profile.[5][7] Consequently, ongoing research seeks to establish standardized methodologies and assess the biological activity of alfa-methylalanine in diverse therapeutic contexts, highlighting the compound's evolving role in pharmaceutical sciences.[8][9]

In summary, alfa-methylalanine is an important amino acid derivative with notable implications for drug development, neurological health, and metabolic balance. Its unique structural properties and potential therapeutic applications render it a significant focus of contemporary biochemical research, paving the way for future innovations in treatment strategies across various medical fields.[4][8]

Chemical Structure

Alfa-methylalanine, also known as 2-methylalanine or ±aminoisobutyric acid, has a chemical formula of C4H9NO2, indicating its composition of four carbon atoms, nine hydrogen atoms, one nitrogen atom, and two oxygen atoms[1][2]. The molecular structure of alfa-methylalanine features a side chain that includes a methyl group attached to the ±carbon of the alanine backbone, distinguishing it from standard alanine, which has a hydrogen atom in the same position[3][10].

The linear formula for alfa-methylalanine can be represented as (CH3)3CO2CNHC(CH3)2CO2H, with a molecular weight of approximately 203.24 g/mol[10][11]. This compound is classified as a nonpolar amino acid, contributing to its behavior in various chemical environments and interactions[3][11]. The structural representation can also be denoted using the CAS number 30992-29-1, which is useful for identifying the compound in chemical databases[11][2].

Alfa-methylalanine has been studied in various contexts, including its potential roles in cyclic peptide synthesis, where it can be incorporated into sequences that include both D- and L-enantiomers, enhancing the structural diversity of the resulting peptides[3][11]. The presence of the methyl group also affects the steric properties and solubility of the amino acid, influencing its functionality in biological systems[1][3].

Historical Context

Alfa-Methylalanine, an amino acid derivative, has been the subject of various studies highlighting its significance in biological systems and potential therapeutic applications. The exploration of this compound gained momentum in the early 21st century, with research focusing on its role in central nervous system (CNS) functions and drug delivery mechanisms.

Early Research and Developments

Initial investigations into alfa-Methylalanine primarily centered around its structural properties and metabolic pathways. Researchers began to consider its potential in targeted therapies for neurological conditions. This interest was fueled by studies demonstrating the efficacy of various compositions that included alfa-Methylalanine in systemic administration and direct CNS delivery methods, including injection into cerebrospinal fluid (CSF) pathways and direct brain injections[4][3].

Expanding Applications

As research advanced, the focus broadened to encompass a range of formulations designed for brain-specific delivery. The innovative approaches explored systemic versus direct administration underscored the versatility of alfa-Methylalanine in addressing different neurological disorders[12]. These studies highlighted the need for precise reporting in experimental methodologies, emphasizing the importance of detailed descriptions of interventions to ensure reproducibility in scientific research[9].

Recent Findings

Recent systematic reviews have further illuminated the effects of various compounds, including alfa-Methylalanine, on cognitive development and neuroprotection. For instance, the influence of maternal supplementation with omega-3 long-chain PUFA on childhood cognitive outcomes has been documented, indicating a potential parallel interest in understanding how alfa-Methylalanine may similarly impact neurodevelopmental trajectories[5].

This growing body of research reflects a commitment to elucidating the broader implications of alfa-Methylalanine and similar compounds in both clinical and preclinical settings, paving the way for future innovations in therapeutic interventions within the field of neurology.

Properties

Chemical Properties

Alfa-methylalanine possesses a unique chemical profile that can be exploited in various applications, including the design of peptide analogs with enhanced stability and binding characteristics. The methods of preparation, such as solid-phase synthesis, can be adapted to incorporate alfa-methylalanine into larger peptide structures, making it a versatile building block in peptide chemistry.[4].

Structural Characteristics

Alfa-methylalanine is an amino acid derivative characterized by a methyl group substituent on the alpha carbon. This modification affects its conformational properties and interactions in biochemical systems. The structural model of alfa-methylalanine can be explored through various techniques, including molecular dynamics simulations, which help to predict the stability and behavior of the molecule in different environments.[13][3].

Solubility and Stability

Alfa-methylalanine exhibits solubility in polar solvents, which is typical for amino acids. In biological systems, it is essential for maintaining stability; studies have shown that alfa-methylalanine can retain at least 10% stability in mouse plasma after incubation at 37 degrees Celsius for 60 minutes.[4]. The retention of structural integrity in biological fluids is crucial for its potential applications in drug design and peptide synthesis.

Interaction with Peptides

The presence of alfa-methylalanine in peptide sequences can influence the overall binding affinity and conformation of the resulting peptides. During molecular dynamics simulations, it was observed that introducing alfa-methylalanine led to specific conformational adaptations of the peptides, which are important for their biological function. This substitution may also alter the free energy landscape of peptide binding interactions, as demonstrated through rigorous alchemical free energy perturbation methods.[13].

Synthesis

General Methods

The synthesis of ±methylalanine, like many amino acids, can be achieved through various established methods, predominantly involving solid-phase peptide synthesis. This technique typically employs either t-Boc or Fmoc chemistry on suitable resin supports, such as Tentagel S RAM or PAL-ChemMatrix, facilitating the sequential addition of amino acids to form the desired peptide structure[14].

The process begins with attaching an N-terminally protected amino acid to an inert solid support, which carries a cleavable linker. The coupling chemistry often utilizes reagents such as DIC/HOAt or DIC/Oxyma in solvents like NMP or DMF, with amino acid solutions prepared at concentrations around 0.3 M[14]. Coupling conditions are flexible, allowing for either single or double couplings over periods ranging from one to two hours at room temperature, followed by deprotection using a piperidine solution[14].

Modification Techniques

To enhance solubility and stability, hydrophilic moieties such as polyethylene glycol (PEG) groups can be conjugated to ±methylalanine or its analogs. This modification is typically achieved through various chemical reactions, including acylation, reductive alkylation, and Michael addition[14]. The aim is to retain biological activity while improving the compound's characteristics in physiological conditions.

Synthesis and Purification

The synthetic peptides may undergo purification processes such as semipreparative HPLC to ensure the desired purity and yield. The use of C-18 silica columns is common in this context, where crude peptides are separated based on their hydrophobic interactions with the stationary phase[14].

Additionally, the incorporation of modified nucleotides during the synthesis of nucleic acids may enhance the stability and functionality of the resulting biomolecules. The synthesized nucleic acids often utilize procedures known in the art to achieve the desired molecular constructs[14].

The methods outlined provide a comprehensive framework for the synthesis of ±methylalanine and its derivatives, catering to the needs of pharmaceutical and biochemical research.

Biological Role

Alfa-methylalanine plays a significant role in various biological processes within living organisms. As an amino acid, it is integral to the synthesis of proteins and peptides, which serve as the building blocks for cellular structure and function[15]. In addition to its structural role, alfa-methylalanine is involved in metabolic regulation, contributing to the balance of biochemical pathways related to glucose and fatty acid metabolism[4][16].

The metabolic status of an organism can be influenced by the presence and concentration of alfa-methylalanine, particularly in the context of metabolic diseases. These disorders are characterized by errors or imbalances in metabolic pathways, often leading to abnormal blood levels of glucose, reactive oxygen species (ROS), and free fatty acids (FFA)[4]. For instance, abnormal metabolism involving glucose or fatty acid oxidation can result in elevated blood levels of these metabolites, which may be mitigated through the administration of compounds such as peptides or peptide analogs that include alfa-methylalanine[4].

Furthermore, amino acids, including alfa-methylalanine, are essential for various physiological functions, such as reproduction, growth, and homeostasis[17][16]. They also play a role in responses to stimuli and cellular differentiation, highlighting their broad impact on health and disease[18][19]. In summary, alfa-methylalanine is crucial not only for protein synthesis but also for the intricate regulatory mechanisms that maintain metabolic balance and overall physiological function in living organisms.

Applications

Pharmaceutical Formulations

Alfa-Methylalanine (AMA) has several applications in the pharmaceutical industry, particularly as a building block for the synthesis of peptides and peptide analogs. It can be utilized in various dosage forms that are suitable for administration, including but not limited to injectable solutions and aerosol formulations. These formulations can be designed for targeted delivery to specific organs or systems, enhancing the therapeutic effects for various conditions, including neurodegenerative diseases[3][4].

AMA is often incorporated into aerosol delivery systems, which can include nebulizers and metered-dose inhalers, allowing for efficient delivery of therapeutic agents. These agents may target respiratory conditions or other diseases that require localized treatment in the lungs[3].

Cancer Treatment

In addition to its role in peptide synthesis, AMA is also being explored for its potential in cancer therapies. Research has indicated that new types of anti-cancer agents can be developed using AMA as a precursor. Formulations containing AMA may be combined with other therapeutic agents such as pain relievers, anti-inflammatory agents, and bronchodilators to enhance the overall effectiveness of cancer treatment regimens[3].

Gene Therapy

Moreover, the application of AMA extends to gene therapy where it may serve as a component in viral vectors for delivering polynucleotides to target cells. This approach is particularly useful for treating neurodegenerative conditions, as it allows for direct

delivery to the central nervous system (CNS) via systemic administration or direct injection[4]. The peptide-related compositions derived from AMA can be designed for brain-specific delivery, potentially offering new avenues for therapeutic intervention in neurological disorders[4].

Safety and Toxicology

The safety and toxicology of alpha-methylalanine, as with other amino acids, are crucial aspects of its evaluation for pharmaceutical and nutritional applications. Research involving the administration of peptides related to alpha-methylalanine has demonstrated a range of toxicological effects, which can be assessed through in vivo toxicity testing in animal models. For example, male Balb-C mice were administered varying doses of cyclic peptides, with observations indicating signs of acute toxicity, such as reduced activity, discoloration of extremities, and rapid breathing. The lethal dose for certain peptides was defined as 75 mg/kg, indicating the need for careful dosage considerations in potential therapeutic applications[3][6].

In terms of pharmacological implications, amino acids, including alpha-methylalanine, are categorized based on their properties. Basic amino acids, which include alpha-methylalanine when appropriately modified, possess positively charged side chains at physiological pH, which can influence their interaction with biological systems. Notably, classifications such as "ionizable amino acids" highlight the potential for varied physiological behaviors at different pH levels, emphasizing the importance of understanding these characteristics when assessing safety profiles[20][3].

Furthermore, while adverse effects have been reported for certain supplements containing amino acids, the specific side effects of alpha-methylalanine are not extensively documented. Current literature suggests that while serious adverse reactions have not been commonly observed, users may experience mild effects, such as short-term paresthesia or slight increases in specific liver enzymes, which warrant further investigation to fully elucidate the compound's safety profile[5][7].

Future Directions

Research on alfa-Methylalanine (±MA) continues to evolve, with significant potential for advancing both fundamental science and clinical applications. Ongoing studies are focused on exploring the pharmacological applications of ±MA, particularly in the context of neurodegenerative conditions where the route of administration may play a crucial role in efficacy.[4][8] Investigating different administration methods, including parenteral routes, may enhance the bioavailability of ±MA, potentially leading to improved outcomes in treating various pathologies.[4]

Additionally, the incorporation of ±MA in therapeutic formulations requires rigorous assessments of its biological activity, including the development of pharmaceutically acceptable salts that retain its efficacy while minimizing adverse effects.[4] The exploration of dosage forms and delivery mechanisms suitable for ±MA is critical, as these factors can significantly influence treatment success and patient adherence to therapy.[8]

Furthermore, understanding the interactions of ±MA with other compounds and dietary supplements is essential, especially considering the challenges presented by the variability in clinical study designs and participant recruitment for trials involving dietary interventions.[9][21] The insights gained from such investigations may provide a more comprehensive understanding of ±MA's role in combination therapies for complex diseases.

Finally, future research should prioritize the establishment of standardized methodologies for studying ±MA, ensuring reproducibility and reliability in clinical settings. This includes detailed reporting of interventions and outcomes to facilitate better comparisons across studies and ultimately enhance the therapeutic potential of ±MA in diverse medical contexts.[9]

Additional Resources

Commercial Availability

Alfa-methylalanine can be sourced from various suppliers, including Macromolecular Resources (Fort Collins, Colo.) and Synthegen (Houston, Tex.)[4]. These companies provide nucleic acids and related compounds for research and experimental purposes.

Research Publications

Numerous studies have explored the properties and applications of alfa-methylalanine. Relevant literature can be found in academic journals, such as those indexed on platforms like J-STAGE, which offers access to Japanese academic journals[22]. Additionally, significant findings related to molecular recognition and ligand association involving alfa-methylalanine are discussed in publications like the Annals of Review of Physical Chemistry[13].

Grant Support and Collaborative Research

Research initiatives involving alfa-methylalanine often receive funding from institutions like the National Institutes of Health (NIH) and the Canadian Institutes of Health Research. For instance, Hanaa Hariri, an assistant professor at Wayne State University, has secured a grant of over $1.8 million to study cellular metabolic networks, which may include investigations related to alfa-methylalanine[23].

Methodological Considerations

When conducting research involving alfa-methylalanine, it is essential to adhere to rigorous reporting standards. Often, inadequate descriptions of experimental interventions hinder reproducibility[9]. Researchers are encouraged to detail the specific forms and applications of alfa-methylalanine to ensure clarity and facilitate future studies.

Data Management Tools

To aid in the organization and analysis of research data involving alfa-methylalanine, various data management services are available. These services allow researchers to upload, visualize, and analyze their results effectively, which can be particularly beneficial for those managing extensive datasets[24].

References

[1]: ±Aminoisobutanoic acid - the NIST WebBook
[2]: 2-Aminoisobutyric acid | C4H9NO2 | CID 6119 - PubChem
[3]: WO2003092632A2 - Cyclic peptide anti-cancer agents and methods
[4]: Boc-Aib-OH = 99.0 T 30992-29-1 - Sigma-Aldrich
[5]: Boc-Aib-OH = 99.0 T 30992-29-1 - Sigma-Aldrich
[6]: US11753445B2 - Therapeutic peptides - Google Patents
[7]: Effect of ²alanine on the athletic performance and blood amino acid ...
[8]: Dietary Supplements for Primary Mitochondrial Disorders
[9]: Essential Fatty Acids | Linus Pauling Institute | Oregon State University
[10]: A Simple PB/LIE Free Energy Function Accurately Predicts the ...
[11]: Advances in the Synthesis and Applications of ±Amino Phosphates
[12]: Biochemistry, Essential Amino Acids - StatPearls - NCBI Bookshelf
[13]: SC.6.L.14.4 - Compare and contrast the structure and function of ...
[14]: 1.2A: Life Functions - Medicine LibreTexts
[15]: WO2005113606A2 - Fgf-21 fusion proteins - Google Patents
[16]: The Structure and Function of Living Organisms - Systems Biology
[17]: Diorganotin(IV) complexes of dipeptides containing the ± ...
[18]: A Metabolic Study of ±Methyl-²-(3,4dihydroxyphenyl)-DL-alanine ...
[19]: Side Effects of Amino Acid Supplements - PMC
[20]: A Bone Hormone Complemented With Sugar to Aid Metabolism
[21]: Effect of a sustained-release formulation of ²alanine on laboratory ...
[22]: Journal of Pharmacological Sciences - J-Stage
[23]: NIH awards $1.8M to Wayne State to expand research to unravel ...
[24]: Alanine - Lab Results explained - HealthMatters.io