b-Methylalanine

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summary

²-Methylalanine, also known as N-methylalanine or ²-MAA, is an ±-amino acid with the chemical formula C4H9NO2, notable for its potential neurotoxic effects and implications in various biological processes. As a substituted derivative of alanine, ²-methylalanine features a methyl group attached to its nitrogen atom, which distinguishes it from standard amino acids and plays a crucial role in its chemical behavior and biological activity. It has gained attention within the fields of neurobiology, pharmacology, and biochemistry due to its interactions with neurotransmitter systems and its involvement in metabolic pathways, highlighting its significance in health and disease contexts.

The compound has garnered considerable research interest owing to its associations with neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Studies have shown that exposure to ²-methylalanine may disrupt synaptic function and induce oxidative stress, potentially leading to long-lasting neurological deficits and behavioral changes in model organisms. Furthermore, it has been linked to protein misincorporation and aggregation, mechanisms that are particularly concerning in the context of neurodegeneration.[1][2][3]

In addition to its neurotoxicological profile, ²-methylalanine is being explored for its therapeutic potential, particularly as a neuroprotective agent. Its incorporation into peptide sequences and natural products is under investigation, with researchers aiming to improve solubility and biological activity for drug development. Moreover, the amino acid is also being evaluated for dietary supplement applications, particularly in enhancing muscle growth and recovery, and for its potential role in agricultural biostimulants to promote plant growth and resilience.[4][5][6]

Overall, the multifaceted role of ²-methylalanine in biological systems—ranging from its impact on neurological health to its applications in medicine and agriculture—highlights both its promise and the urgent need for continued research into its safety and efficacy. The compound's controversial neurotoxic effects further underscore the importance of understanding its mechanisms of action and potential implications for human health.[3][7]

Chemical Structure

N-Methylalanine, or b-Methylalanine, is an ±-amino acid with the chemical formula C4H9NO2, and it possesses a molecular weight of 103.12 g/mol[8][9]. Its structure consists of a central carbon atom bonded to an amino group (–NH2), a carboxyl group (–COOH), a methyl group (–CH3), and a hydrogen atom, making it a substituted version of alanine[10][9]. The presence of the methyl group on the nitrogen distinguishes N-methylalanine from standard alanine and is critical in determining its chemical properties and reactivity.

The empirical formula for N-Methylalanine, as represented by Hill notation, is C4H9NO2, which indicates that it contains four carbon atoms, nine hydrogen atoms, one nitrogen atom, and two oxygen atoms[11]. The structural configuration can be visualized as follows: the amino group is attached to the ±-carbon, which is also connected to the carboxyl group and the side chain, which, in this case, is a methyl group. This arrangement forms the basis of its classification as an amino acid.

In terms of stereochemistry, N-Methylalanine exists primarily in the L-configuration, which is biologically relevant. The chiral nature of the ±carbon allows for the existence of stereoisomers, although N-methylalanine is predominantly encountered in its L-form in biological systems[12]. This stereochemistry plays a vital role in its interactions within proteins and its incorporation into peptides.

N-Methylalanine can also participate in various chemical reactions typical of amino acids, such as amide formation through condensation with carboxylic acids[13][14]. This reactivity underlines its significance in both synthetic and natural biochemical processes.

Physical Properties

Solubility

The solubility characteristics of N-methylalanine are influenced by its molecular structure. While specific solubility data for this compound are limited, similar amino acids typically exhibit varying degrees of water solubility, with some exhibiting high solubility due to their polar functional groups. However, certain derivatives and prodrugs of amino acids, such as those incorporating N-methylalanine, have been reported to enhance solubility in biological environments, indicating potential modifications that could improve its pharmacological properties[15].

General Characteristics

N-Methyl-L-alanine, also known as b-methylalanine, exhibits several notable physical and chemical properties. Its density is approximately 1.048 g/cm^3, indicating a relatively high mass for its volume compared to many other amino acids[16][8]. The compound has a melting point of around 317 °C, where it decomposes, and a boiling point predicted to be approximately 190.1 °C[16][8].

Acidity

N-Methyl-L-alanine possesses distinct acidic properties, with pKa values of approximately 2.36 for the carboxyl group and 10.21 for the amino group in aqueous solution[17]. These values suggest that the amino acid can exist in both protonated and deprotonated forms depending on the pH of the environment, which is a common trait among amino acids that influences their interactions in biological systems.

Structural Features

The molecular structure of N-methylalanine includes a methyl group attached to the nitrogen atom of the amine group. This modification impacts the sterics and electronic properties of the molecule, which can affect its biological activity and interaction with other biomolecules[8]. The hydrogen bonds formed between the carbonyl oxygen of one monomer and the N–H bonds of adjacent monomers also contribute to the stability of polymers derived from this amino acid[14].

Synthesis

Overview of Synthesis Methods

The synthesis of ²-methylalanine (BMAA) has been explored through various methods, including both solution-phase and solid-phase techniques. These methodologies have been crucial for incorporating ²-methylalanine into peptide sequences, thereby enhancing the understanding of its role and functionality in biological systems[18].

Solution-phase Synthesis

In solution-phase synthesis, ²-methylalanine can be derived from amino acid precursors through established chemical reactions. Researchers have developed efficient protocols to convert readily available substrates into BMAA, which can then be utilized in further peptide synthesis or modification. Notably, the incorporation of ²-methylalanine into peptide sequences is facilitated by its compatibility with existing amino acid coupling methods, enabling the generation of complex structures that may exhibit improved biological activities[18].

Solid-phase Synthesis

Solid-phase synthesis is another effective approach for the production of ²-methylalanine-containing peptides. This method allows for the stepwise assembly of peptide chains on a solid support, where ²-methylalanine can be strategically introduced. This technique not only enhances the efficiency of synthesis but also enables the easy purification of the resulting peptides, making it a preferred method in peptide chemistry[18].

Structural Modifications and Applications

The structural modification of natural products using ²-methylalanine has garnered significant interest due to its potential to improve the physicochemical properties and biological activities of these compounds. By introducing ²-methylalanine into natural product scaffolds, researchers have reported enhanced solubility and bioavailability, which are critical factors in drug development[18]. Furthermore, the incorporation of this amino acid has been linked to the development of novel therapeutic agents, particularly in the field of medicinal chemistry, highlighting its importance as a building block in drug design and development[19].

Biological Role

^{2}Methylalanine (BMAA) is an amino acid that has garnered attention due to its potential neurotoxic effects and its involvement in various biological processes. Research indicates that BMAA interacts with neurotransmitter systems, particularly acetylcholine, which is crucial for cognitive function and may contribute to neurodegenerative diseases[1][2].

Neurotoxicity and Behavioral Effects

Studies have demonstrated that exposure to BMAA leads to synaptic disturbances that can result in neurological deficits. For instance, perinatal exposure to BMAA in animal models has been shown to produce long-lasting behavioral changes, potentially linked to DNA damage and oxidative stress[2]. In larval zebrafish, BMAA has been found to modulate behavior and exacerbate molecular changes associated with neurodegeneration[1][2].

Role in Metabolism

Beyond its neurotoxic effects, BMAA appears to influence metabolic health. A low isoleucine diet, which includes considerations of amino acid metabolism, has been linked to increased hepatic insulin sensitivity and enhanced ketogenesis, thereby promoting energy expenditure and altering metabolic pathways[20]. This highlights BMAA's potential role in metabolic reprogramming and its implications for conditions such as type 2 diabetes and obesity[21].

Implications for Health

The biological roles of BMAA underline the importance of understanding its impact on both neurological health and metabolic processes. Given its widespread presence in various biological sources, including algae and marine organisms, further research is warranted to elucidate the comprehensive effects of BMAA on human health and disease mechanisms[7].

Applications

Therapeutic Uses

^{2}Methylalanine (BMAA) has garnered interest for its potential therapeutic applications, particularly in addressing neurodegenerative diseases. Current research indicates that BMAA may influence motor neuron dysfunction through multiple mechanisms, including excitotoxicity and protein misincorporation, which could contribute to conditions such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS)[22][3]. The substance's ability to interact with glutamate receptors has prompted investigations into its role as a neuroprotective agent, although the precise mechanisms remain to be fully elucidated.

Dietary Supplements

BMAA has also been explored as a component in dietary supplements, particularly for its proposed benefits in muscle building and enhancing physical performance. For instance, ²-hydroxy ²-methylbutyrate (HMB), which is related to BMAA, is noted for its positive effects on muscle growth and recovery in human subjects[4]. Research into incorporating BMAA into dietary formulations aims to leverage its biochemical properties to improve overall health and athletic performance.

Agricultural Applications

In addition to its health-related uses, BMAA is being studied for its applications in agriculture. Its properties may enhance plant growth and stress resistance, making it a potential candidate for use in agricultural biostimulants[5]. By improving the resilience of crops, BMAA could play a significant role in sustainable farming practices, contributing to food security and environmental health.

Natural Products and Drug Development

Natural products have long been a source of effective therapeutic drugs, and BMAA's structural attributes allow for modifications that may enhance its bioactivity. Research indicates that integrating amino acids like BMAA into natural compounds can improve their solubility and pharmacological effects, which could lead to the development of novel drugs[15][6]. As scientists continue to explore these avenues, BMAA may become a vital component in the next generation of pharmaceuticals targeting various ailments.

Safety and Toxicology

²-Methylamino-L-alanine (BMAA) is a non-protein amino acid that has been identified as a potential neurotoxin, linked to various neurodegenerative diseases. The toxicological effects of BMAA stem from multiple mechanisms, which can lead to neuronal dysfunction and cell death. BMAA can act as an excitotoxin by interacting with glutamate receptors, including NMDA, AMPA, and kainate receptors, which may lead to increased oxidative stress through glutathione depletion[3].

In addition to its excitotoxic properties, BMAA has been shown to be misincorporated into proteins in place of L-serine. This misincorporation can result in protein misfolding and aggregation, which are associated with neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) [3]. In vitro studies suggest that excess L-serine can inhibit the association of BMAA with proteins, potentially mitigating its toxic effects[3].

Research indicates that BMAA can enhance neurotoxicity through various mechanisms, including the activation of metabotropic glutamate receptors, which can further induce oxidative stress in neurons[3]. Additionally, exposure to BMAA may interact synergistically with other environmental neurotoxins, compounding its neurotoxic effects[3][7].

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