Cyclohexylalanine

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summary

Cyclohexylalanine is a non-canonical amino acid characterized by the presence of a cyclohexyl side chain, which imparts unique biochemical properties and functions. With a general molecular formula of C9H17NO2, cyclohexylalanine contains an amino group, a carboxylic acid group, and exhibits zwitterionic behavior in solution.[1][2] This compound is notable not only for its role as a building block in protein synthesis but also for its significant implications in pharmaceutical development, particularly in the treatment of neurological disorders and enhancing drug delivery across the blood-brain barrier.[3]

There are several notable derivatives of cyclohexylalanine, including N-Cyclohexyl-DL-alanine and 3-Cyclohexyl-L-alanine, each exhibiting distinct structural configurations that influence their biochemical interactions and applications.[1][4][5] Cyclohexylalanine's hydrophobic characteristics and its impact on protein structure and stability underscore its importance in various biological processes, such as protein-protein interactions and enzyme activity.[6][7] Moreover, its nonpolar nature aligns it with other aliphatic amino acids, affecting the folding and stability of proteins in which it is incorporated.[8]

The synthesis of cyclohexylalanine involves advanced methods that utilize chiral catalysts, allowing for high yield and enantioselectivity, which are critical in pharmaceutical applications.[9][10] This compound not only serves as a valuable tool in biochemical research but also holds promise for innovative drug formulations, particularly in enhancing therapeutic efficacy for conditions like Alzheimer’s and Parkinson’s disease.[3][11] Furthermore, cyclohexylalanine is being explored for its potential benefits in the cosmetic and food industries, indicating its versatile applications beyond traditional biochemical roles.[12]

Despite its numerous advantages, the incorporation of cyclohexylalanine into therapeutic formulations presents challenges, particularly concerning its solubility and interaction with polar biological systems. Ongoing research aims to elucidate these complexities and optimize its use in targeted therapies, highlighting the need for further investigation into its mechanistic roles and therapeutic potentials.[13][14][15]

Chemical Structure

Cyclohexylalanine refers to a group of amino acids that share a common structural feature characterized by the presence of a cyclohexyl group. The general molecular formula for cyclohexylalanine is C9H17NO2, indicating the presence of an amino group (-NH2), a carboxylic acid group (-COOH), and a cyclohexyl side chain[1][2].

Types of Cyclohexylalanine

There are several notable derivatives of cyclohexylalanine, including:

N-Cyclohexyl-DL-alanine

N-Cyclohexyl-DL-alanine, with the same molecular formula (C9H17NO2), exhibits unique chemical properties and can be used in various biochemical applications[1].

3-Cyclohexyl-L-alanine

Another variant is 3-Cyclohexyl-L-alanine, which also maintains the formula C9H17NO2. This compound is of interest due to its distinct structural configuration that impacts its interactions in biological systems[4][5][2].

L-Cyclohexylalanine

L-Cyclohexylalanine (CAS 27527-05-5) presents yet another structural variation. It is characterized by specific melting and boiling points, which further delineate its physical properties within the category of amino acids[2][16].

Structural Characteristics

The core structural characteristics of cyclohexylalanine derivatives include the following:

Zwitterionic Nature: Cyclohexylalanine exists predominantly as zwitterions in solution, reflecting its dual charge state that balances the positive charge of the ammonium group and the negative charge of the carboxylate group[17][18].

Stereochemistry: These compounds can exhibit specific stereochemistry, which is essential for their biological function and interaction with proteins[19][20].

The arrangement of atoms and functional groups in cyclohexylalanine contributes to its classification as a nonpolar amino acid due to the hydrophobic cyclohexyl side chain. This property influences its solubility and the structural conformations of proteins that incorporate cyclohexylalanine residues[13][18].

Synthesis

The synthesis of cyclohexylalanine can be accomplished through a specific method that also allows for the production of L-tert-leucine. This process is particularly significant in the technical field of amino acid preparation, highlighting the versatility and application of chiral catalysts in organic synthesis.

Method Overview

The synthesis method involves two primary steps. The first step utilizes pentafluorophenol-(dibenzyl ammonia) ester and benzhydrol as starting materials. These are

reacted in an organic solvent—preferably a mixed solvent of benzotrifluoride and dichloroethane (1:1 volume ratio)—at low temperatures ranging from -20°C to 0°C. The reaction is facilitated by the presence of a chiral catalyst and an inorganic base, leading to the formation of an intermediate compound[9][10].

In the second step, the intermediate compound undergoes catalytic hydrogenation using palladium carbon as a catalyst, resulting in the formation of L-tert-leucine and L-cyclohexylalanine[9].

Catalytic Mechanism

The reaction employs dynamic kinetic resolution, wherein the oxygen atoms in the chiral catalyst function as nucleophilic sites. This method is noted for its high yield and enantioselectivity, with the enantiomeric excess (ee) of the resulting product exceeding 99.5%[9][18]. This demonstrates the efficacy of the chosen synthetic route, as it provides a novel pathway for the preparation of chiral amino acids.

Advantages of the Method

The described synthesis method has several advantages, including:

High yield of target compounds.

Excellent enantioselectivity, critical for the production of pharmaceuticals and biochemically active compounds.

The ability to incorporate various functional groups through the chemical reactions that can occur post-synthesis, such as oxidation and substitution reactions, thereby enhancing the versatility of the resulting amino acids[21][22].

Biological Role

Cyclohexylalanine, an amino acid derivative, plays a significant role in various biological processes due to its structural and functional properties. As an amino acid, it serves as a building block for proteins, which are essential for numerous cellular functions including enzyme activity, structural support, and signaling pathways[6][-18].

Protein Synthesis and Structure

In the context of protein synthesis, cyclohexylalanine can be incorporated into polypeptide chains, influencing protein conformation and stability. The unique cyclic structure of cyclohexylalanine may enhance the hydrophobic interactions within proteins, contributing to their three-dimensional structures. These noncovalent interactions are crucial for maintaining protein integrity and facilitating proper folding[23][18].

Role in Protein–Protein Interactions

Cyclohexylalanine also plays a role in modulating protein–protein interactions (PPIs). PPIs are vital for many biological processes, and the presence of cyclohexylalanine

can impact the affinity and specificity of these interactions[7]. Dysregulation of such interactions may lead to aberrant biological functions, highlighting the importance of cyclohexylalanine in cellular signaling and metabolic pathways[7].

Therapeutic Potential

Due to its properties, cyclohexylalanine has potential applications in therapeutic formulations. It can be utilized in designing peptides that promote biodistribution across biological barriers, such as the blood-brain barrier (BBB)[3]. This capability is particularly valuable in developing treatments for neurological disorders where targeted delivery of therapeutic agents is critical.

Nutritional Considerations

From a nutritional standpoint, cyclohexylalanine, like other amino acids, contributes to overall health and well-being. Adequate intake of amino acids is essential for muscle repair, mood regulation, and immune function. As a building block for proteins, cyclohexylalanine supports the synthesis of hormones and neurotransmitters, thereby playing a role in mood and cognitive function[11][8].

Applications

Pharmaceutical Development

Cyclohexylalanine serves as a critical building block in the synthesis of various pharmaceuticals, particularly those targeting neurological disorders. The compound is instrumental in developing drugs that aim to treat, image, and diagnose a range of neurodegenerative and neurological pathologies, including Alzheimer's disease, Parkinson's disease, epilepsy, and multiple sclerosis, among others[3].

Drug Delivery Systems

One of the significant challenges in CNS drug development is the blood-brain barrier (BBB), which restricts the passage of therapeutic molecules into the brain. Cyclohexylalanine can be utilized to enhance the transport of drug candidates across the BBB by coupling with peptide or pseudo-peptide vectors. These vectors can bind to low-density lipoprotein receptors (LDLR) on pathological cells, facilitating the delivery of both small and macromolecular therapeutics[3]. This method improves the bioavailability of drugs for treating conditions such as brain tumors and other neurological disorders.

Biochemical Research

In biochemical research, cyclohexylalanine is employed to study protein interactions and enzyme functions, thereby providing insights into metabolic pathways. Its unique

structural properties make it valuable in the synthesis of peptides, enhancing their stability and bioactivity, which is crucial for therapeutic applications[24].

Cosmetic and Food Industries

Beyond its pharmaceutical applications, cyclohexylalanine is explored in cosmetic formulations for its potential benefits in skincare, offering moisturizing and protective properties. Additionally, it can be used as a flavor enhancer or food additive, improving the sensory properties of various products[12].

Hydrophobicity and Interaction with Biological Systems

Cyclohexylalanine, a non-canonical amino acid, exhibits unique hydrophobic properties due to the presence of the cyclohexyl moiety. This moiety influences the conformation and stability of peptides, enhancing their interactions within biological systems[25]. The hydrophobicity of amino acids plays a crucial role in protein stability and protein–protein interactions, particularly for residues like phenylalanine[26]. The hydrophobicity index quantifies the relative hydrophobicity of amino acids, which is pivotal in understanding their solubility and interactions in aqueous environments[-27].

Hydrophobic interactions significantly control many aspects of protein and enzyme function, with non-canonical amino acids like cyclohexylalanine allowing for advanced hydrophobic tuning in protein engineering. This tuning can enhance the functionality of enzymes, as demonstrated in the engineering of bacterial laccases, where the incorporation of bulky, hydrophobic amino acids led to notable improvements in catalytic activity, including increased kcat and turnover numbers[28]. Such modifications are particularly important in industrial applications where enzyme efficiency is critical.

Moreover, non-covalent interactions, such as C H–π and N H–π interactions, contribute to protein stability and specificity, underscoring the importance of hydrophobicity in biological systems[29][23]. The interplay between hydrophobicity and molecular recognition processes further emphasizes the necessity of understanding these properties in the context of protein interactions and the development of therapeutic agents. Overall, the hydrophobic nature of cyclohexylalanine not only influences peptide stability but also enhances the versatility of proteins in various biological functions[6][7].

Comparison with Related Amino Acids

Cyclohexylalanine, a derivative of the common amino acid alanine, exhibits distinct structural characteristics due to the incorporation of a cyclohexyl group in its side chain. This modification influences its biochemical behavior and interaction with other molecules, particularly proteins.

Structural Characteristics

Cyclohexylalanine shares the fundamental structure of amino acids, featuring both amino and carboxylic acid functional groups. However, the presence of the cyclohexyl side chain contributes to its nonpolar nature, positioning it among the Group I nonpolar amino acids. Similar nonpolar amino acids include valine, leucine, and isoleucine, all of which also possess hydrophobic side chains that are aliphatic or aromatic in structure.[8][18][30].

The uniqueness of cyclohexylalanine's side chain compared to other nonpolar amino acids lies in its cyclic structure, which may affect the folding and stability of proteins in which it is incorporated. Nonpolar amino acids generally promote hydrophobic interactions that drive the tertiary structure of proteins, and cyclohexylalanine's bulky side chain could play a significant role in these interactions[8][18].

Functional Implications

The distinctive properties of cyclohexylalanine also enable it to participate in unique biochemical processes. While many amino acids engage in hydrogen bonding or ionic interactions, cyclohexylalanine’s nonpolar characteristics limit such interactions, rendering it more compatible with hydrophobic environments. This trait is essential in the context of membrane proteins and protein-protein interactions, where the hydrophobic regions need to be shielded from aqueous surroundings[23][29].

Furthermore, the cyclohexyl group can influence the conformational flexibility of peptides, potentially affecting their binding affinity to various targets. For instance, when compared to alanine, which serves as a basic building block in protein synthesis, cyclohexylalanine may provide enhanced stability in certain structural contexts due to its unique steric properties[3][31].

Comparison with Polar Amino Acids

In contrast to Group II amino acids, such as serine, cysteine, and glutamine, which possess functional groups capable of hydrogen bonding, cyclohexylalanine's nonpolar characteristics render it less interactive with polar solvents[13][18]. The lack of polar functional groups in cyclohexylalanine may limit its solubility in aqueous solutions compared to polar amino acids, which are critical for interactions in biological systems. This delineation further underscores the importance of cyclohexylalanine's structural and functional properties in the realm of amino acid functionality and protein design[8][13][14].

Health Benefits and Therapeutic Potential

Cyclohexylalanine, a non-standard amino acid, has shown promise in various therapeutic applications, particularly in the context of neurological diseases and tissue injuries. The treatment modalities involving cyclohexylalanine focus on its ability to enhance biological activity when used in conjunction with therapeutic molecules,

diagnostic agents, or molecular probes[3]. This capability is crucial for developing effective therapies aimed at improving patient outcomes in various medical conditions.

Mechanism of Action

The treatment employing cyclohexylalanine aims to achieve pharmacological and physiological effects, such as inhibiting cancer cell growth and promoting cell death-[3]. These effects can be prophylactic, aimed at preventing disease progression in at-risk individuals, or therapeutic, focusing on treating existing conditions and alleviating associated symptoms. Specifically, cyclohexylalanine may assist in the prevention of diseases like cancer or mitigate symptoms in patients already diagnosed with neurological disorders[3].

Applications in Disease Management

Recent studies highlight the potential of D-amino acids, including cyclohexylalanine, as therapeutic agents for various neurological diseases[15]. The compound's unique structural properties allow it to interact favorably with biological systems, potentially offering new avenues for treating conditions previously deemed "undruggable"[32]. Moreover, cyclohexylalanine's versatility extends to applications in the development of small molecule drugs, which have been instrumental in advancing treatment options for complex human diseases[32].

In addition to its role in treating neurological disorders, the therapeutic utility of cyclohexylalanine encompasses strategies to prevent or alleviate conditions such as cancer through targeted pharmacological interventions[3]. By formulating effective dosing regimens, researchers aim to optimize the benefits of this amino acid in clinical settings, improving patient responses and outcomes across a spectrum of diseases.

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