Pentafluorophenylalanine

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summary

Pentafluorophenylalanine (PFPA) is a fluorinated amino acid derivative of alanine that has gained prominence in peptide synthesis and medicinal chemistry due to its unique properties and versatility. Its molecular structure, characterized by five fluorine atoms, enhances the stability, solubility, and overall yield of synthesized peptides, making PFPA an invaluable tool in the development of novel therapeutic agents and complex biomolecules. The interest in PFPA dates back to the 1970s, when initial studies began exploring the potential of fluorinated amino acids, with further significant advancements occurring in the 1990s as researchers recognized its advantages in solid-phase peptide synthesis (SPPS) and other chemical reactions.[1][2]

The applications of PFPA extend beyond peptide synthesis to fields such as bioconjugation, analytical chemistry, and material science, where it contributes to the development of functional materials and targeted drug delivery systems. This compound has been instrumental in enhancing peptide stability and bioactivity, as evidenced by recent studies highlighting its use in the synthesis of hormone analogs and other biologically active peptides.[1][3][4] Additionally, PFPA's incorporation into various synthetic methodologies underscores its growing importance in the ongoing evolution of sustainable chemistry practices, where the efficiency of peptide synthesis is increasingly emphasized.[5]

Despite its advantages, pentafluorophenylalanine raises notable toxicological and safety concerns that are critical for its handling and use. Reports indicate that PFPA can cause skin irritation, and its full toxicological profile remains under investigation. Furthermore, it poses environmental risks if improperly managed, necessitating stringent safety protocols during storage and handling to mitigate exposure and contamination risks.[6][7] As research into PFPA continues to evolve, its role in both pharmaceutical applications and biological interactions highlights the compound's significance in advancing peptide-based therapeutics and our understanding of protein dynamics.[8][9]

History

Pentafluorophenylalanine (PFPA) has garnered attention due to its unique properties and applications in peptide synthesis. The exploration of fluorinated amino acids began in the 1970s, with significant contributions made by researchers such as Patchornik et al., who published a notable study on amino acid derivatives in 1970[1]. This early work paved the way for subsequent investigations into the utility of fluorinated amino acids in various chemical reactions.

In the 1990s, several studies highlighted the advantages of using PFPA in solid-phase peptide synthesis (SPPS). Bycroft et al. (1993) and Matysiak et al. (1998) noted that the incorporation of fluorinated amino acids could enhance the stability and solubility of peptides, leading to improved yields and purity[2][1]. These findings have positioned PFPA as a valuable tool in the field of medicinal chemistry, particularly in the design of novel therapeutic agents.

As the demand for efficient peptide synthesis techniques grew, researchers began to focus on sustainable methods. The integration of green chemistry principles into peptide synthesis has been discussed in various reviews, including the comprehensive overview by Isidro-Llobet et al. (2009), which outlines advancements in the field and the importance of sustainable practices[1][5]. The ongoing evolution of these methods continues to be influenced by the foundational research on compounds like pentafluorophenylalanine, demonstrating its lasting impact on drug development.

Looking forward, the role of PFPA in peptide synthesis is expected to expand, particularly as automation and computational modeling become more prevalent in the field. These technological advancements, alongside the historical groundwork laid by earlier studies, position PFPA as a crucial element in the future of peptide-based pharmaceuticals[10].

Properties

Physical and Chemical Properties

Pentafluorophenylalanine is a solid compound characterized by its unique molecular structure. Its molecular formula is C9H6F5NO2, with a molecular weight of 227.15 g/mol[11]. The compound appears as a white powder and exhibits a melting point range of 170 to 185 ºC[11][12].

Spectroscopic Characteristics

The interactions of pentafluorophenylalanine with lipids have been studied using Fourier transform-infrared spectroscopy (FT-IR), which demonstrated significant shifts in absorbance wavenumbers. These shifts indicate the involvement of the polar heads of lipids in the interactions with pentafluorophenylalanine and peptides, suggesting a strong relationship between the compound and lipid structures[13].

Molecular Dynamics

Pentafluorophenylalanine's behavior in solution has been analyzed through molecular dynamics simulations. These simulations were conducted under NPT conditions (constant number of particles, pressure, and temperature), maintaining a temperature of 300 K and a pressure of 1 bar. The methods used for these simulations included the v-rescale method for temperature control and the Berendsen barostat for pressure maintenance, with the Particle Mesh Ewald method employed for treating electrostatic interactions[8].

Synthesis

Pentafluorophenylalanine, a fluorinated derivative of alanine, can be synthesized using various methods, primarily focusing on the formation of pentafluorophenyl esters from N-protected amino acids. One common approach involves the reaction of an N-protected amino acid with a condensing agent such as dicyclohexylcarbodiimide (DCC) in the presence of pentafluorophenol, typically carried out in solvents like tetrahydrofuran or ethyl acetate at low temperatures ranging from -10°C to 0°C[14][15].

Automated Peptide Synthesis

In automated peptide synthesis, the use of preformed Fmoc-amino acid pentafluorophenyl esters has demonstrated significant utility. These esters enable the synthesis of complex peptide sequences in a polar reaction medium[16][17]. The Fmoc (9-fluorenylmethoxycarbonyl) group acts as a protective group, which can be selectively removed during synthesis to facilitate further coupling reactions.

Activation Methods

The first step in the coupling reaction during the synthesis of pentafluorophenylalanine typically involves the activation of the carboxyl moiety. This can be achieved using various activating reagents, which lead to the formation of reactive intermediates capable of undergoing nucleophilic attack by the ±-amino group of a protected amino acid[18][19]. Notably, the generation of carboxylic anhydrides or the use of carbodiimides with additives are common strategies employed to enhance the efficiency of this activation step[20][19].

Recent Advances

Recent advancements in the asymmetric synthesis of ±-(trifluoromethyl)-containing ±-amino acids highlight the evolving methodologies in producing fluorinated amino acids, including pentafluorophenylalanine. These developments contribute to improved enantiopurity and yield in the synthesis process, thereby expanding the potential applications of fluorinated amino acids in peptide therapeutics[21][22].

The combination of these techniques and methodologies demonstrates the versatility and effectiveness of the synthetic routes available for producing pentafluorophenylalanine and similar fluorinated amino acids.

Applications

Pentafluorophenylalanine (Pfp) is a versatile compound with several significant applications across various fields, particularly in peptide synthesis, bioconjugation, analytical chemistry, and material science.

Material Science

In the field of material science, Pfp can be utilized in the development of functional materials, such as hydrogels. These materials have applications in tissue engineering and regenerative medicine, highlighting the compound's versatility beyond traditional peptide chemistry[23][11].

Peptide Synthesis

Pfp serves as a key building block in the synthesis of peptides, facilitating the creation of complex peptide structures efficiently. This compound is particularly valuable in solid-phase peptide synthesis (SPPS) due to its unique chemical properties, which enhance the yield and purity of the final peptide products[1][14].

Bioconjugation

In bioconjugation techniques, pentafluorophenylalanine plays a crucial role by enabling the attachment of biomolecules to surfaces or other molecules. This application is essential for developing targeted drug delivery systems, as it allows for precise control over the interaction between therapeutic agents and their intended targets[4][3].

Analytical Chemistry

Pentafluorophenylalanine is employed in various analytical methods aimed at studying protein interactions and modifications. Its use provides insights into biological processes and disease mechanisms, making it an important tool for researchers investigating protein dynamics and functionality[24][25].

Toxicology and Safety

Pentafluorophenylalanine has been associated with various toxicological and safety concerns that are critical for handling and usage. The ATSDR toxicological profile provides a summary of the toxicologic and adverse health effects related to this compound, although the full extent of its toxicological properties has not been thoroughly investigated[6][7].

Health Effects

Skin contact with pentafluorophenylalanine can lead to irritation, categorizing it as hazardous under such conditions[26]. The compound has not been adequately assessed for acute and chronic toxicity, and there is limited information on its other potential adverse effects on humans[26][27]. Personal precautions are advised when handling the substance, including the avoidance of dust formation and inhalation of vapors[28].

Environmental Safety

Pentafluorophenylalanine should be handled with care to prevent environmental contamination. It is essential to avoid discharging this substance into drains, as it may pose ecotoxicity risks[7][29]. Moreover, safety measures dictate that it must be kept away from food, drink, and animal feeding areas to mitigate any potential risks of ingestion or exposure[29][28].

Storage and Handling

Due to its hazardous nature, pentafluorophenylalanine should be stored in compliance with safety regulations, specifically categorized as a combustible solid[30]. Proper protective equipment is essential during handling to minimize the risk of exposure and to ensure safe working conditions[28][30].

Regulatory Status

Certificates of Origin

The Certificates of Origin (COO) for Pentafluorophenylalanine confirm the country of manufacture and provide details about the materials and components used in the synthesis of the compound. This certificate is crucial for customs, trade, and regulatory compliance, as it indicates whether the product is derived from natural, synthetic, or other specific sources[31][32].

Safety Data Sheets

Safety Data Sheets (SDS) are provided to offer comprehensive safety information regarding the handling, storage, and disposal of Pentafluorophenylalanine. The SDS outlines potential hazards associated with the substance and includes guidelines to ensure safe usage[31][8].

Product Specifications

Product Specifications (PS) provide an in-depth breakdown of Pentafluorophenylalanine's properties, including its chemical composition, physical state, purity, and storage requirements. Additionally, the PS details acceptable quality ranges and the intended applications of the product, ensuring that users are informed about the necessary handling procedures[31][32].

Certificates of Analysis

Certificates of Analysis (COA) can be obtained by searching with the product's Lot Number. This document confirms the quality and consistency of Pentafluorophenylalanine, detailing results from batch testing, which can include assessments of purity and concentration[8][4].

Biological Interactions

Pentafluorophenylalanine (PFPhe) plays a notable role in biological interactions, particularly in the study of protein dynamics and functionality. The intrinsic dynamics of proteins, including those incorporating PFPhe, are essential for their biological roles, as these dynamics facilitate complex and diverse functions through controlled atomic motions of their structures[33].

Mechanisms of Action

The interaction of PFPhe within protein structures can influence enzyme catalysis, channel gating, and other crucial biological processes. The amino acid's unique chemical properties, including its electron-withdrawing fluorine substituents, may enhance the stability and functionality of the proteins it is integrated into, thereby affecting the overall protein dynamics and their associated biological activities[2][9].

Structural and Environmental Influences

Various environmental factors, such as pH conditions and ionic strength, can modulate the effectiveness of PFPhe in protein activities. Studies indicate that even moderate changes in the bulkiness of amino acids, including PFPhe, can significantly affect protein activity, suggesting a nuanced relationship between protein structure and function that is highly sensitive to environmental contexts[2][9].

Moreover, understanding how PFPhe interacts with the dynamic conformational ensembles of proteins is essential for unraveling the mechanisms by which proteins fold and function. This insight could be crucial for elucidating misfolding pathways that lead to amyloid aggregates and related diseases, highlighting the importance of PFPhe in both functional and pathological protein interactions[8][34].

Technological Advancements

Recent advancements in structural biology, such as mass spectrometry and chemical crosslinking, have improved the ability to study protein interactions involving PFPhe at a cellular level[35][36]. These technologies facilitate the tracking of protein movements and their effects across tissues, thus bridging gaps in our understanding of cellular functions and the roles of specific amino acids like PFPhe in various biological contexts[36].

Metabolism

Pentafluorophenylalanine (PFPhe) is a modified form of the standard amino acid phenylalanine, which plays a crucial role in various metabolic processes within the body. As a precursor in the biosynthesis of several important biomolecules, PFPhe's metabolic pathway closely resembles that of phenylalanine itself.

Conversion to Tyrosine

In biological systems, L-phenylalanine is metabolically converted into L-tyrosine through the action of the enzyme phenylalanine hydroxylase. This reaction is critical as L-tyrosine serves as a substrate for the synthesis of several neurotransmitters, including dopamine, norepinephrine, and epinephrine, collectively known as catecholamines[37][38]. Although the specific metabolic fate of PFPhe is not fully elucidated, it is hypothesized that it may also undergo similar enzymatic conversion processes, potentially influencing catecholamine production.

Dietary Recommendations

The metabolism of phenylalanine and its derivatives, such as PFPhe, is regulated by dietary intake. The Recommended Dietary Allowance (RDA) for phenylalanine, which is directly applicable to its derivatives, is established at 33 mg/kg body weight per day for adults[37]. Understanding these guidelines is essential for evaluating the metabolic impact of PFPhe, particularly in individuals with phenylketonuria (PKU), where the metabolism of phenylalanine is impaired.

Biological Activity and Safety

Recent studies indicate that modifications of amino acids like PFPhe can influence their biological activities. For instance, aminoglycerol-functionalized small carboxylate nanoparticles (SCNP-F2), which include phenylalanine derivatives, have shown no significant decrease in metabolic activity in brain endothelial cell lines, suggesting a favorable profile for biological applications[39]. These findings highlight the potential of modified amino acids, such as PFPhe, in various biomedical contexts while emphasizing the need for further investigations into their metabolic pathways and cellular compatibility.

Notable Studies

Introduction to Pentafluorophenylalanine in Peptide Synthesis

Pentafluorophenylalanine (Pfp) has emerged as a significant building block in peptide synthesis due to its unique chemical properties. This amino acid allows researchers to explore various modifications and functionalizations of peptides, enhancing their stability and bioactivity[3]. The versatility of Pfp has been highlighted in several notable studies focusing on peptide design and synthesis methodologies.

Applications in Solid-Phase Peptide Synthesis

Recent advancements in automated solid-phase peptide synthesis (SPPS) have underscored the importance of Pfp in creating complex peptide structures. The integration of Pfp into peptide sequences has enabled the synthesis of peptides with improved chemical and biological properties. For example, the Fmoc/t-Bu-based SPPS technique, which incorporates Pfp, has demonstrated effectiveness in synthesizing larger peptides and proteins, expanding the potential for therapeutic applications[1][40].

Enhancing Peptide Stability

Studies have shown that incorporating pentafluorophenylalanine into peptide sequences can significantly enhance their stability. Modifications such as lipidation and PEGylation have been evaluated in conjunction with Pfp, yielding peptides that resist degradation while maintaining biological activity. These modifications are particularly relevant in developing peptide therapeutics where stability and bioavailability are critical factors[1].

Exploration of Peptide Hormones

Pfp has also been utilized in the synthesis of selected peptide hormones, which illustrates its applicability in the field of endocrinology. The ability to engineer peptides with precise modifications using Pfp enables researchers to create hormone analogs with tailored pharmacological profiles. Such studies contribute to a deeper understanding of peptide hormone functions and their interactions within biological systems[1].

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