Fluoroalanine

Table of Contents

Check https://storm.genie.stanford.edu/article/1186973 for more details

Stanford University Open Virtual Assistant Lab

summary

Fluoroalanine is a fluorinated analogue of the amino acid alanine, notable for its unique chemical structure and potential applications in pharmaceuticals and biochemical research. Specifically, 3-fluoro-D-alanine and 3-fluoro-L-alanine are two prominent isomers of fluoroalanine, both of which contain a fluorine atom that significantly alters their properties compared to standard alanine. The presence of fluorine enhances the stability and binding interactions of these compounds with biological targets, making them subjects of interest in drug design, particularly in the development of antibacterial agents and cancer therapeutics[1][2][3].

The synthesis of fluoroalanine involves several methods, including photofluorination, asymmetric synthesis via ketimine intermediates, and enzymatic systems. These techniques facilitate the production of specific isomers with desired biological activities, which is critical for their application in medicinal chemistry[4][5]. The unique properties of 3-fluoro-D-alanine, such as its conformational stability and optically active nature, have further spurred research into its effectiveness as an enzyme inhibitor, particularly against alanine racemase, thereby influencing metabolic pathways essential for bacterial growth and drug resistance mechanisms[6][7].

Fluoroalanine's role in cancer treatment and metabolic research has garnered considerable attention. Its structural similarity to alanine allows it to disrupt metabolic pathways associated with cancer cell proliferation and drug resistance, positioning it as a promising candidate for combination therapies with existing chemotherapeutic agents[8][9]. However, the potential toxicity of fluoroalanine and its fluorinated nature raises safety concerns that necessitate thorough evaluation, including adherence to regulatory standards for drug development[10][11].

Overall, fluoroalanine represents a significant area of research in the fields of biochemistry and pharmacology, with its applications extending to enzyme inhibition, cancer treatment, and the study of metabolic adaptations. Continued exploration of its properties and effects may lead to innovative therapeutic strategies aimed at overcoming challenges in drug resistance and improving treatment efficacy[10][12].

Chemical Structure

Fluoroalanine refers to a series of amino acids that contain a fluorine atom in their structure, with 3-fluoro-D-alanine and 3-fluoro-L-alanine being two prominent isomers. The molecular formula for 3-fluoro-D-alanine is C3H6FNO2, indicating the presence of carbon, hydrogen, fluorine, nitrogen, and oxygen atoms in its composition[1][2][13]. The compound features an amine group and a carboxylic acid group, both attached to the central carbon atom, which also carries a methyl group side chain[14].

Physical Properties

3-fluoro-D-alanine exhibits a molecular weight of approximately 107.084 g/mol and has a melting point ranging from 143 to 149 °C[1][15]. Its density is reported at 1.302 g/cm³ at standard pressure[1]. The introduction of fluorine into its structure significantly affects the compound's stability and its interactions within biological systems, making it an important subject in drug design and development[2][16].

Conformational Stability

Recent studies have explored the conformational stability and molecular structure of 3-fluoro-D-alanine through both experimental and theoretical methods[17]. The fluorine atom enhances binding interactions with biological targets, which can lead to increased metabolic stability and improved potency of the compound as an antibacterial agent[3][16][18][19].

Stereochemistry

3-fluoro-D-alanine is classified as an optically active compound, which can be designated as R or S according to IUPAC nomenclature rules. The distinction between the D and L isomers is crucial, as the D-isomer is noted for its antibacterial properties, while the L-isomer, despite also having antibacterial activity, is often regarded as less desirable in pharmaceutical applications[3][20]. The synthesis of 3-fluoro-D-alanine can be accomplished via asymmetric rearrangement techniques involving precursor compounds, which underscores its significance in organic synthesis[3][13].

Synthesis

Fluoroalanine, specifically 3-fluoroalanine, can be synthesized using various methods, which predominantly focus on photofluorination and asymmetric synthesis techniques.

Photofluorination

One of the earliest methods for synthesizing 3-fluoro-D-alanine involved photofluorination, where D-alanine is irradiated with fluorine gas under controlled conditions. This method, demonstrated by Kollonitsch and Kahan, allows for the direct fluorination of D-alanine while retaining its configuration. Although this approach is efficient, it necessitates specialized equipment for handling gaseous fluorine, which can limit its scalability and practical application in larger syntheses[4].

Asymmetric Synthesis via Ketimine Intermediates

Another significant method for producing 3-fluoroalanine involves asymmetric synthesis through the use of ketimine intermediates. This technique offers a more versatile approach to achieve the desired stereochemistry of the product, which is critical for its biological function[21][4].

Enzymatic Systems

Recent advancements have introduced coupled enzymatic systems that facilitate the simultaneous synthesis of both (S)-3-fluoroalanine and (R)-3-fluorolactic acid using l-alanine dehydrogenase (l-AlaDH) [5]. These methods provide a more selective and potentially more efficient pathway to synthesize the desired enantiomers, which are important for various applications in pharmaceuticals and biochemistry[21].

Total and Semi-synthesis

Additionally, while the focus on 3-fluoroalanine synthesis primarily involves direct fluorination and asymmetric methods, other compounds related to the synthesis of ±monofluoroalkyl-±amino acids often utilize total and semi-synthetic approaches. Total synthesis is considered the most challenging method of bioactivity optimization, but can yield effective results, as seen in compounds like shikonin, which has been fully synthesized for therapeutic use[10]. Semi-synthesis, on the other hand, utilizes chemical reactions to enhance the pharmacological properties of naturally occurring compounds, demonstrating versatility in the optimization of compounds with significant bioactivity[10].

Properties

Chemical and Physical Properties

Fluoroalanine, specifically 3-fluoro-D-alanine, is characterized by the molecular formula C3H6FNO2 and has a molecular weight of approximately 107.084 g/mol[1][15]. Its density is measured at 1.302 g/cm³, with a melting point range of 143 to 149 °C[1][15]. The compound exhibits a boiling point of 266.9 °C at 760 mmHg[1].

Analytical Applications

3-Fluoro-D-alanine is utilized as a standard in analytical chemistry, particularly for quantifying amino acids in biological samples. Its accurate properties allow researchers to gather reliable data for various research applications[11].

Safety and Handling

Comprehensive safety information regarding 3-fluoro-D-alanine is provided in Safety Data Sheets (SDS), which detail the procedures for handling, storage, and disposal of the product[11]. Additionally, product specifications (PS) include a breakdown of the compound's properties, physical state, purity, and storage requirements, ensuring proper use in laboratories[11].

Certificates of Analysis

Certificates of Analysis (COA) are available for 3-fluoro-D-alanine, allowing users to verify its quality and composition based on the specific lot number. These documents ensure that the product meets the necessary quality standards for research and industrial applications[11][15].

Molecular Characteristics

The molecular structure of 3-fluoro-D-alanine is influenced by the atomic charges of its amino group and carboxyl function, which remain relatively stable compared to alanine[17]. This characteristic contributes to its conformational stability and makes it a subject of interest in both experimental and theoretical studies[17].

Biological Role

Fluoroalanine, an analog of the amino acid alanine, plays a significant role in biochemical processes primarily through its function as an enzyme inhibitor. It exerts its inhibitory effects on specific enzymes by utilizing a mechanism of competitive inhibition. This occurs when fluoroalanine competes with alanine for the active site of alanine racemase, effectively disrupting the enzyme's ability to catalyze the conversion of L-alanine to D-alanine[6]. Such inhibition can impact various metabolic pathways where D-alanine is a crucial component, particularly in bacterial cell wall synthesis and maintenance.

In a broader context, enzyme inhibitors like fluoroalanine are critical for regulating metabolic processes. They can modulate the activity of metabolic enzymes, thereby influencing the concentrations of metabolites in cellular environments. For instance, the inhibition of alanine racemase by fluoroalanine can lead to a decrease in D-alanine levels, which may have downstream effects on cellular functions and growth[10].

Furthermore, the biological implications of fluoroalanine extend beyond enzymatic inhibition; its interaction with metabolic pathways has been leveraged in research aimed at understanding drug resistance mechanisms. The presence of fluoroalanine can mimic the effects of certain drugs, allowing scientists to explore how competitive inhibition influences therapeutic outcomes in various cell types, including those resistant to standard treatments[7]. Such studies underscore the potential of fluoroalanine as a valuable tool in biochemical research and drug development.

Applications

Fluoroalanine, an amino acid analogue, has garnered attention for its potential applications in cancer treatment and metabolic research. Its structural similarity to alanine allows it to interfere with various metabolic pathways, particularly those involved in cancer cell proliferation and resistance mechanisms.

Cancer Treatment

Fluoroalanine has been studied for its role as a selective agent against certain cancer cells. The incorporation of fluoroalanine into cellular metabolism can disrupt the normal function of proteins and enzymes that rely on alanine, thereby affecting cancer cell viability. This is particularly relevant in the context of drug resistance, where cancer cells often adapt to conventional therapies, leading to treatment failure. By targeting metabolic pathways that are often altered in cancer cells, fluoroalanine may provide a novel strategy to enhance the effectiveness of existing treatments and counteract drug resistance [8][22].

Metabolic Research

In metabolic studies, fluoroalanine serves as a valuable tool for probing amino acid metabolism and the Warburg effect, which describes the tendency of cancer cells to favor glycolysis over oxidative phosphorylation. Its ability to act as a competitive inhibitor of certain metabolic enzymes allows researchers to better understand the metabolic adaptations that occur in cancerous tissues. By analyzing the effects of fluoroalanine on cellular metabolism, scientists can gain insights into the mechanisms driving cancer progression and identify potential therapeutic targets [23][10].

Combination Therapies

Recent investigations have explored the use of fluoroalanine in combination with other anti-cancer agents. This approach aims to exploit the synergistic effects of multiple drugs to enhance therapeutic outcomes while potentially mitigating the side effects commonly associated with monotherapies. For instance, pairing fluoroalanine with established chemotherapeutic agents could enhance the sensitivity of resistant cancer cells, leading to improved patient responses [9][24].

Safety and Toxicology

Fluoroalanine, like many natural and synthetic compounds, presents safety and toxicity considerations that must be thoroughly evaluated. The compound can exhibit both beneficial and adverse effects depending on its concentration and the biological context in which it is applied.

Toxicological Profile

The toxicity of fluoroalanine is a critical area of concern, as it is a fluorinated amino acid which may impact cellular processes. Some studies have indicated that fluorinated compounds can have detrimental effects on cellular metabolism, potentially leading to cytotoxicity in certain concentrations[10]. It is essential to determine the therapeutic window where fluoroalanine can exert beneficial effects without posing risks to healthy cells.

Natural compounds, including fluoroalanine, may have undesirable side effects or interact with other medications, necessitating careful safety evaluations before clinical application[7]. As with many naturally derived substances, there is a risk of adverse reactions, highlighting the importance of preclinical and clinical studies to establish safety profiles.

Strategies to Mitigate Toxicity

To reduce the risk of toxicity, researchers have explored various strategies. One such method involves the use of prodrugs and appropriate drug delivery systems. These approaches aim to enhance the selectivity of fluoroalanine for target cells while minimizing harm to healthy tissues. Techniques such as conjugation can refine pharmacokinetic properties, improving the targeting of disease cells and reducing overall toxicity[10][6].

Regulatory Considerations

Given the potential toxicity of fluoroalanine, it is imperative for developers to adhere to rigorous regulatory standards during the drug development process. This includes comprehensive toxicity testing and the provision of safety data, such as Safety Data Sheets (SDS), which offer critical information on handling and potential hazards[15][11]. The regulatory framework requires that all compounds, especially those derived from natural sources, undergo thorough scrutiny to ensure they meet safety requirements for human use.

Future Directions

The exploration of fluoroalanine and its derivatives presents a promising frontier in therapeutic development, particularly in the context of overcoming challenges associated with drug resistance and enhancing treatment efficacy. Current research indicates that fluoroalanine may play a significant role in combination therapies, where it can complement other therapeutic agents by targeting distinct biological pathways relevant to disease progression[10][9]. This approach is particularly valuable in oncology and antimicrobial treatment, where the use of multi-modal strategies could mitigate the risk of resistance development and improve patient outcomes[12][10].

Future investigations should focus on the optimization of fluoroalanine's pharmacokinetic properties to enhance bioavailability and reduce potential toxicity. Advances in drug delivery systems could facilitate the clinical application of fluoroalanine, allowing for better therapeutic results[9][25]. Moreover, ongoing studies should aim to evaluate the efficacy of fluoroalanine in various disease models, particularly its potential to act synergistically with other natural compounds and synthetic drugs[10][9].

Furthermore, research should also consider the long-term effects and mechanisms of fluoroalanine in vivo to fully understand its therapeutic potential and to establish guidelines for clinical use[12][9]. As part of this effort, collaborative research efforts across different institutions will be essential in validating findings and advancing fluoroalanine's application in modern medicine. The integration of data from diverse studies could pave the way for innovative treatment protocols that leverage the unique properties of fluoroalanine and its derivatives in combating prevalent health issues.

References

[1]: 2-FLUORO-DL-ALANINE | CAS#:43163-93-5 | Chemsrc
[2]: CAS 16652-37-2: Alanine, 3-fluoro- | CymitQuimica
[3]: alpha-Fluoro-beta-alanine | C3H6FNO2 | CID 13351 - PubChem
[4]: Alanine - Wikipedia
[5]: 2-Fluoro-DL-alanine - Chem-Impex
[6]: The Many Roles for Fluorine in Medicinal Chemistry
[7]: (PDF) The Conformers of 3-Fluoroalanine. A Theoretical Study
[8]: US3880922A - Process for preparing 3-fluoro-D-alanine by ...
[9]: 3-fluoroalanine and (R)-3-fluorolactic acid - ScienceDirect
[10]: Synthesis and use of N-Fmoc-l-fluoroalanine - ScienceDirect.com
[11]: 7.9: Effects of enzyme microenvironment on acidity and basicity
[12]: 3-Fluoro-D-alanine (35455-20-0) for sale - Vulcanchem
[13]: Amino Acid Based Antimicrobial Agents – Synthesis and Properties
[14]: Simultaneous enzymatic synthesis of (S)-3-fluoroalanine and (R)
[15]: Natural compounds as lactate dehydrogenase inhibitors - Frontiers
[16]: 2-Fluoro-DL-alanine - Chem-Impex
[17]: Enzyme Inhibitors and Activators - IntechOpen
[18]: Enzyme inhibitor - Wikipedia
[19]: Unveiling the mechanisms and challenges of cancer drug resistance
[20]: Multidrug Resistance in Cancer: Understanding Molecular ...
[21]: Window of opportunity clinical trial designs to study cancer metabolism
[22]: Exploring treatment options in cancer: tumor treatment strategies
[23]: Anti-Cancer Drugs - LWW.com
[24]: Future Antibacterial Strategies: From Basic Concepts to Clinical ...
[25]: Relationship between the appropriateness of antibiotic treatment ...