Rank The Labeled N Atoms In The Anticancer Drug Imatinib (trade Name Gleevec) In Order Of Increasing

Rank The Labeled N Atoms In The Anticancer Drug Imatinib (trade Name Gleevec) In Order Of Increasing is a question that delves into understanding the molecular structure of this groundbreaking medication. Imatinib, commonly known by its trade name Gleevec, revolutionized cancer treatment by targeting specific enzymes involved in disease progression. Central to its molecular architecture are nitrogen atoms, some of which are labeled with isotopic markers for research and analytical purposes. Properly ranking these labeled nitrogen atoms in order of increasing value or property requires a detailed understanding of their placement, labeling techniques, and the chemical environment within the molecule. This article aims to clarify this ranking process, explore the significance of labeled nitrogen atoms, and provide a comprehensive overview of Imatinib's structure, all within an SEO-optimized framework.

Understanding Imatinib (Gleevec) and Its Molecular Structure

What is Imatinib?

Imatinib is a targeted anticancer drug primarily used to treat chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST). Its mechanism involves inhibiting the BCR-ABL tyrosine kinase, preventing the proliferation of malignant cells. The chemical formula of Imatinib is $C25H25N3O$, and its structure consists of multiple aromatic rings, heterocycles, and nitrogen atoms that are critical for its activity.

Structural Features of Imatinib

Imatinib's molecular architecture includes:
- A pyrimidine ring
- An imidazole ring
- Aromatic phenyl groups
- Amide and amino groups
These features contribute to its binding affinity and specificity for the BCR-ABL kinase.

Importance of Labeled N Atoms in Chemical and Pharmacological Studies

Why Label Nitrogen Atoms?

Labeling nitrogen atoms with isotopes such as nitrogen-15 (^15N) allows researchers to:
- Trace the metabolic pathways of the drug
- Study binding interactions at the molecular level
- Perform nuclear magnetic resonance (NMR) spectroscopy for structural elucidation
- Investigate pharmacokinetics and bioavailability

Methods of Nitrogen Labeling

Common techniques include:
- Incorporation of ^15N during synthesis
- Isotope exchange reactions
- Selective labeling of specific nitrogen atoms within functional groups

Identifying and Ranking Labeled N Atoms in Imatinib

Step 1: Structural Analysis of Imatinib's Nitrogen Atoms

In the molecular structure of Imatinib, nitrogen atoms are located primarily in:
- The pyrimidine ring (two nitrogen atoms)
- The imidazole ring (two nitrogen atoms)
- The amino groups attached to aromatic rings
- The amide linkage nitrogen

Each nitrogen atom's chemical environment influences its properties and labeling behavior.

Step 2: Determining Labeling Sites

Researchers typically label specific nitrogen atoms based on:
- Their position within heterocyclic rings
- Their involvement in hydrogen bonding
- Their accessibility during synthesis

In Imatinib, the typical labeled N atoms are:
1. Pyrimidine nitrogen (N1 and N3 positions)
2. Imidazole nitrogen (N1 and N3 positions)
3. Amide nitrogen
4. Aromatic amino nitrogen

Step 3: Ranking the Labeled N Atoms

The ranking of labeled nitrogen atoms can be based on:
- Their chemical environment (electron density)

- Their role in binding interactions
- The ease of isotope incorporation
- The stability of the labeled isotope within the molecule

Assuming the goal is to rank the N atoms in order of increasing chemical shift or reactivity in NMR studies or in terms of labeling efficiency, the following order is often observed:

1. Amide nitrogen (least shielded and often with the lowest chemical shift)

2. Aromatic amino nitrogen

3. Pyrimidine N1

4. Imidazole N3

5. Pyrimidine N3

6. Imidazole N1 (most shielded or with the highest chemical shift)

This order reflects the typical chemical environment and experimental data from NMR spectroscopy.

Significance of Proper Labeling and Ranking

Implications for Drug Development and Research

Accurate labeling and ranking of nitrogen atoms in Imatinib facilitate:
- Precise tracking of metabolic transformations
- Better understanding of drug-receptor interactions
- Optimization of labeling strategies for analytical techniques

Analytical Techniques

The primary method for detecting and analyzing labeled N atoms is NMR spectroscopy, which provides information about:
- Chemical shifts
- Coupling constants
- Molecular dynamics

Proper ranking guides researchers in selecting which nitrogen positions to label for specific studies.

Conclusion

The process of ranking labeled nitrogen atoms in Imatinib involves understanding its molecular structure, the environment of each nitrogen atom, and their roles in biological activity and analytical detection. By analyzing the chemical environment and experimental data, researchers can determine an order of increasing significance or reactivity. Such insights are crucial for advancing pharmacological research, improving drug design, and enhancing analytical techniques. Whether for metabolic tracking, structural elucidation, or binding studies, the precise labeling and ranking of nitrogen atoms form an essential part of modern medicinal chemistry and drug development.

Meta Description: Discover how to rank the labeled nitrogen atoms in the anticancer drug Imatinib (Gleevec) in order of increasing significance. Learn about its structure, labeling techniques, and research applications.

Frequently Asked Questions

What are the labeled nitrogen atoms in imatinib, and how are they identified?

The labeled nitrogen atoms in imatinib are specific nitrogen atoms within its molecular structure that are isotopically labeled (commonly with nitrogen-15) to facilitate studies like NMR spectroscopy. They are identified based on their position within the molecular scaffolds, such as the pyrimidine ring, the amino group, or other heterocyclic components.

Why is ranking the nitrogen atoms in imatinib important for anticancer research?

Ranking the nitrogen atoms helps understand their individual contributions to the drug's binding affinity, pharmacokinetics, and mechanism of action, thereby aiding in the design of more effective analogs and understanding resistance mechanisms.

What does the order of increasing nitrogen atom rank in imatinib indicate?

It indicates the sequence of nitrogen atoms based on specific properties such as electron density, reactivity, or their contribution to binding affinity, with the lowest rank representing the most reactive or most influential nitrogen in the drug's activity.

How are the labeled nitrogen atoms in imatinib experimentally determined and ranked?

They are identified through spectroscopic techniques like NMR, where the chemical shifts and coupling constants help assign each nitrogen's position. The ranking is then based on properties such as chemical shift values or their impact on biological activity.

Can the ranking of nitrogen atoms influence the synthesis of imatinib derivatives?

Yes, understanding which nitrogen atoms are most reactive or critical allows chemists to target specific sites for modification, leading to the development of derivatives with improved efficacy or reduced side effects.

Are there computational methods used to rank the labeled nitrogen atoms in imatinib?

Yes, computational techniques like quantum chemical calculations and molecular docking can predict the electronic properties of nitrogen atoms, helping to rank them based on their potential reactivity and contribution to binding.

What role does the ranking of nitrogen atoms play in understanding imatinib’s mechanism of action?

It helps identify which nitrogen atoms are involved in key interactions with the BCR-ABL kinase or other targets, thereby elucidating the binding mode and informing drug design.

Is the ranking of labeled nitrogen atoms specific to imatinib, or is it applicable to other anticancer drugs?

While this ranking process is specific to the molecular structure of imatinib, similar approaches can be applied to other labeled compounds to understand their electronic and reactive properties.

How does the order of increasing nitrogen atom rank impact the understanding of imatinib’s pharmacodynamics?

It provides insights into which nitrogen atoms are most likely to participate in interactions with the biological target, influencing the drug’s potency, selectivity, and overall pharmacodynamic profile.

What are the practical applications of ranking labeled nitrogen atoms in imatinib for clinical development?

This ranking can guide the design of improved analogs, help predict resistance mutations, and optimize drug delivery strategies, ultimately enhancing therapeutic outcomes in cancer treatment.

Additional Resources

Ranking the Labeled N Atoms in the Anticancer Drug Imatinib (Trade Name Gleevec) in Order of Increasing Significance

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Introduction

Imatinib, marketed under the trade name Gleevec, represents a milestone in targeted cancer therapy. Its design as a tyrosine kinase inhibitor revolutionized the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GISTs). Central to its molecular architecture is a carefully crafted structure featuring multiple nitrogen atoms, each playing distinct roles in binding affinity, pharmacokinetics, and overall biological activity. Understanding the significance of these labeled nitrogen atoms (denoted as N1, N2, N3, etc.) provides key insights into the molecule's mechanism of action and guides future drug design efforts.

This review aims to rank the labeled nitrogen atoms in Imatinib according to their importance, starting from the least impactful to the most crucial. Such an analysis sheds light on the molecular intricacies that enable Imatinib’s efficacy and specificity.

Structural Overview of Imatinib

Before delving into the ranking, it is essential to understand the core structure of Imatinib. The molecule features:

- An aromatic pyrimidine ring, crucial for kinase binding.
- An aniline moiety attached via a flexible linker.
- A methylpiperazine group influencing solubility and pharmacokinetics.
- Multiple nitrogen atoms embedded within aromatic and heteroaromatic rings.

The labeled nitrogen atoms are typically identified based on the molecular structure during synthesis and analysis, often designated as N1, N2, N3, etc., depending on the context.

Cataloging the Labeled Nitrogen Atoms in Imatinib

For clarity, let's define the labeled nitrogen atoms in Imatinib:

- N1: The nitrogen atom in the pyrimidine ring positioned at the 1-position.
- N2: The nitrogen atom in the pyrimidine ring at the 3-position.
- N3: The nitrogen atom in the amino group attached to the aromatic ring.
- N4: The nitrogen in the methylpiperazine moiety.
- N5: The nitrogen in the aniline ring (attached to the phenyl group).
- N6: The nitrogen involved in the linker connecting the aromatic rings.

Note: The exact labeling may vary depending on the structural diagrams, but for this review, these designations are used as a working framework.

Criteria for Ranking Significance

To evaluate the importance of each nitrogen atom, consider the following aspects:

- Role in binding affinity: How essential is the nitrogen in facilitating interactions with the kinase active site?
- Contribution to molecular stability: Does the nitrogen stabilize the conformation or the overall structure?
- Impact on pharmacokinetics: Does modification or mutation of the nitrogen influence absorption, distribution, metabolism, or excretion?
- Participation in key interactions: Is the nitrogen involved in hydrogen bonding, pi-stacking, or other non-covalent interactions critical for activity?
- Synthetic and chemical reactivity: How critical is the nitrogen for the synthesis and chemical stability of Imatinib?

Based on these criteria, the ranking will reflect the relative importance of each nitrogen atom.

Ranking of Labeled N Atoms in Imatinib

6. N4 — The Nitrogen in the Methylpiperazine Group

Overview:
The N4 atom resides within the methylpiperazine ring, a heterocyclic amine attached to the core structure. It primarily influences pharmacokinetic properties such as solubility and bioavailability rather than direct binding to the kinase.

Significance:

- Role in pharmacokinetics:
The piperazine moiety enhances aqueous solubility and facilitates membrane permeability.

- Impact on binding affinity:
Indirect; it does not participate directly in kinase interactions.
- Chemical stability:
The nitrogen's basicity can influence metabolic stability but is not critical for the core activity.

Conclusion:
While important for drug delivery and formulation, N4's role in binding and activity is minimal, making it the least critical among the labeled N atoms.

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5. N5 — The Nitrogen in the Aniline Ring

Overview:
This nitrogen is part of the phenyl ring connected via an amino linkage. It can be involved in hydrogen bonding but generally plays a secondary role.

Significance:

- Binding interactions:
May participate in weak hydrogen bonds or pi-stacking interactions with the kinase's active site residues.
- Electronic effects:
Electron donation from this nitrogen can influence the electronic properties of the aromatic ring.
- Metabolic considerations:
Can be sites for oxidative metabolism, affecting drug half-life.

Conclusion:
N5 contributes modestly to binding affinity, mainly through electronic effects, but is not essential for the core inhibitory activity.

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4. N3 — The Nitrogen in the Amino Group Attached to the Aromatic Ring

Overview:
N3 is part of the amino substituent on the aromatic ring, which can influence molecular polarity and hydrogen bonding capabilities.

Significance:

- Hydrogen bonding:
Can act as a donor or acceptor, facilitating interactions within the kinase binding pocket.
- Structural influence:

The amino group helps orient the aromatic system for optimal binding.
- Metabolic implications:
Potential site for conjugation or oxidation.

Conclusion:
While contributing to binding and orientation, N3's role is supportive rather than central.

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3. N2 — The Nitrogen in the Pyrimidine Ring at the 3-Position

Overview:
N2 resides within the pyrimidine core, a critical component for kinase binding.

Significance:

- Direct binding interactions:
Acts as a hydrogen bond acceptor with amino acid residues in the kinase active site.
- Structural role:
Maintains the integrity of the heteroaromatic system, essential for proper orientation.
- Electronic contribution:
The nitrogen's lone pair influences the electron density of the pyrimidine ring, affecting binding affinity.

Conclusion:
N2 is more significant than the previous atoms due to its direct involvement in key hydrogen bonding interactions with the kinase.

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2. N1 — The Nitrogen in the Pyrimidine Ring at the 1-Position

Overview:
N1 is also part of the pyrimidine ring but occupies a different position than N2.

Significance:

- Essential for binding:
It forms critical hydrogen bonds with residues in the kinase active site, stabilizing the drug-protein complex.
- Electronic properties:
Contributes to the electron-deficient nature of the pyrimidine ring, which is vital for recognition.
- Structural importance:

Maintains the planarity and aromaticity of the core, necessary for optimal binding.

Conclusion:
N1 is a key contributor to Imatinib’s binding efficacy, making it the second most important N atom after N6.

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1. N6 — The Nitrogen in the Linker Connecting Aromatic Rings

Overview:
N6 is involved in the linker region connecting the aromatic pyrimidine core to other functional groups.

Significance:

- Critical for molecular conformation:
The nitrogen atom participates in hydrogen bonding and conformational stabilization, ensuring the molecule adopts the bioactive conformation.
- Direct involvement in binding:
Often forms hydrogen bonds or electrostatic interactions with amino acids in the kinase's ATP-binding pocket.
- Influence on activity:
Any modification or mutation at this position dramatically affects binding affinity and selectivity.

Supporting Evidence:

- Structural studies, including X-ray crystallography, demonstrate N6's role in forming key interactions.
- SAR (structure-activity relationship) analyses show that alterations here reduce inhibitory potency.

Conclusion:
N6 is unequivocally the most significant labeled nitrogen atom in Imatinib, central to its activity and efficacy.

Summary of the Ranking

Rank	Nitrogen Atom	Significance Level	Primary Role
1	N6	Most critical	Central to binding and molecular conformation
2	N1	Highly important	Key in hydrogen bonding within the kinase pocket

3	N2	Significant	Contributes to electronic properties and binding
4	N3	Moderate	Supports hydrogen bonding and orientation
5	N5	Less	Influences electronic effects and metabolism
6	N4	Least	Affects pharmacokinetics but not binding directly

Implications for Drug Design and Future Research

Understanding the hierarchy of nitrogen atom importance in Imatinib informs rational modifications. For instance:

- Targeted modifications at N6:
Could enhance binding affinity or selectivity, but must preserve the hydrogen bonding capacity.
- Alterations at N1 or N2:
Risk compromising the core binding interactions, potentially reducing efficacy.
- Modifications at N4 or N5:
Primarily influence pharmacokinetics or metabolic stability rather than activity.

Future research could explore:

- Biois

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