Medvolt's

AI-powered module for hit to lead

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Introduction

The Drug Discovery process naturally flows from target validation to clinical development, passing through the Hit-To-Lead stage. A hit is a term that describes a chemical compound that has a desired therapeutic effect at a known target molecule. The lead is the product of the screening process, which can be used in advanced stages.

Hit-to-Lead (H2L) is a critical phase in drug discovery that bridges the identification of potential drug candidates, known as hits, to the selection and optimization of lead compounds. This iterative process aims to transform early-stage discoveries into promising leads with the desired pharmacological properties, setting the stage for further development. Hit-to-Lead serves as a pivotal stage where the initial hits are evaluated and refined to enhance their drug-like characteristics and increase the likelihood of successful development into a viable drug candidate.

In the expansive realm of drug discovery, where the pursuit of novel therapeutic agents is akin to a scientific odyssey, Hit-to-Lead takes center stage. It is the linchpin that propels molecular entities from the realm of intriguing hits towards the zenith of lead compounds, endowed with the optimal blend of pharmacological prowess and druggability. This transformative process is a delicate dance of scientific acumen and strategic refinement, where hits undergo a metamorphosis, shedding their nascent identities to emerge as promising leads.

Various Approaches for H2L

Here are the key approaches for Hit To Lead :

1. **High-Throughput Screening (HTS):**
    - HTS is a cornerstone in the early stages of drug discovery, where large libraries of compounds are rapidly screened against biological targets to identify hits
2. **Structure-Based Drug Design (SBDD):**
    - SBDD leverages structural information about the target protein to guide the design and optimization of compounds for enhanced binding affinity and selectivity

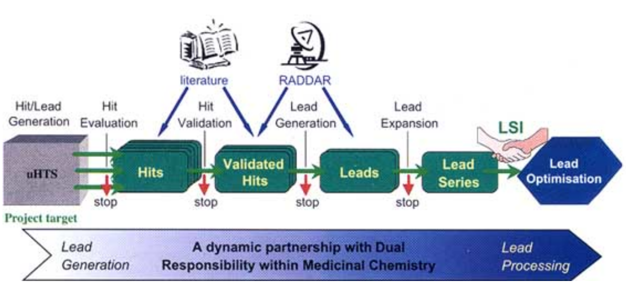


Figure 1. Hit To Lead Process

3. **Fragment-Based Drug Design (FBDD):**
    - FBDD involves screening smaller, fragment-sized molecules for binding to the target, with subsequent assembly and optimization of fragments to generate lead-like compounds

Advantage of H2L

- Hit-to-Lead meticulously sifts through a pool of hits, allowing for the discerning identification and selection of compounds with the utmost precision. This strategic approach ensures that only the most promising candidates advance to the lead optimization phase
- Hit-to-Lead functions as a sentinel against potential pitfalls, offering a comprehensive evaluation of hits
- At its core, Hit-to-Lead is an art of optimization. This phase enables the fine-tuning of key pharmacological properties, including bioavailability, metabolic stability, and target engagement

Disadvantage of H2L

- The journey from hit to lead demands a substantial investment of time and resources. The resource-intensive nature of Hit-to-Lead, coupled with the intricate optimization processes, underscores the commitment required for successful progression
- Hit-to-Lead is not immune to the unpredictable challenges inherent in drug development. Researchers must navigate uncharted territories, addressing unforeseen issues such as unexpected toxicity or difficulties in achieving desired pharmacokinetic properties, adding an element of uncertainty to the process
- Despite advancements in predictive tools, accurately forecasting which hits will successfully evolve into lead compounds remains a complex task

Applications of H2L in Drug Discovery

1. **Lead Identification as Scientific Revelation:**
    - Hit-to-Lead serves as the revelation in the scientific scripture, identifying and revealing the potential leads hidden within the realm of hits
2. **Sculpting SAR Landscapes:**
    - The canvas of SAR exploration is painted during Hit-to-Lead, where the brushstrokes of molecular design transform hits into works of art
3. **Structural-Based Symphony:**
    - Hit-to-Lead orchestrates a structural symphony, leveraging insights into molecular architectures to compose compounds that resonate harmoniously with target proteins. It is the fusion of structural insight and rational design

Hit Identification Strategies

Hit identification is the pivotal first step in drug discovery, where researchers sift through vast chemical landscapes to uncover potential candidates for further development. This section delves into diverse strategies employed to identify hits and initiate the journey toward lead optimization.

The quest for hits initiates with the recognition that promising drug candidates may exist within vast chemical libraries or even in silico landscapes. Identifying these hits is a strategic art, combining innovation, technology, and a deep understanding of the target biology. Researchers embark on this journey armed with diverse methodologies, each designed to unearth compounds that demonstrate specific biological activities against a given target.

Hit identification is not a one-size-fits-all endeavor. Instead, it involves a palette of strategies, each tailored to address the unique challenges posed by different targets, pathways, and diseases. From the high-throughput screening of large compound libraries to the meticulous scrutiny of molecular fragments, the strategies encompass both experimental and computational approaches, forming a symbiotic relationship to cast a wide net in the pursuit of promising hits.

Various Strategies for Hit Identification

1. High-Throughput Screening (HTS):

- HTS involves rapidly testing large libraries of compounds against a target to identify those with biological activity
- **Advantage:**

a. Enables the screening of thousands to millions of compounds

b. Accelerates the identification of hits with desired biological activity

- **Challenges:**

a. Requires robust assay development and automation

b. May yield false positives or false negatives

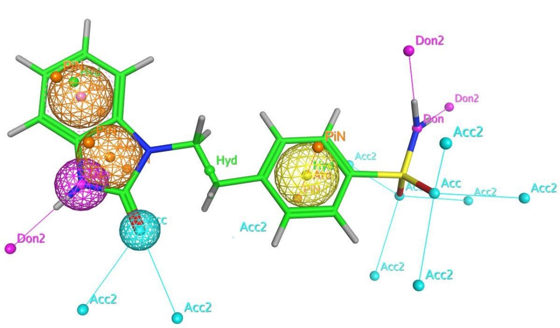


Figure 2. Ligand Based Approach

2. Virtual Screening:

- Virtual screening employs computational methods to predict the likelihood of a compound binding to a target
- **Advantage:**

a. Cost-effective and time-efficient compared to experimental screening

b. Facilitates screening of virtual compound libraries

- **Challenges:**

a. Limited accuracy and reliability, necessitating experimental validation

b. Highly dependent on the quality of the target structure

3. Fragment-Based Screening:

- Fragment-based drug design involves screening small, low-molecular-weight compounds (fragments) for binding to a target
- **Advantage:**

a. Identifies smaller, more ligand-efficient compounds

b. Enhances the probability of identifying hits with high binding affinity

- **Challenges:**

a. Requires efficient fragment screening methods

b. May necessitate merging and elaboration of fragments for lead optimization

4. Computational Approaches:

- Computational methods, such as ligand-based and structure-based approaches, aid in predicting potential hits
- **Advantage:**

a. Expedites hit identification through in silico analysis

b. Complements experimental method

- **Challenges:**

a. Relies on accurate target information

b. Requires validation through experimental screening

5. Phenotypic Screening:

- Phenotypic screening evaluates the effects of compounds on whole cells or organisms, aiming to identify hits based on observable phenotypic changes
- **Advantage:**

a. Captures complex biological responses

b. May reveal unexpected targets and mechanisms

- **Challenges:**

a. Requires appropriate phenotypic assays

b. Interpretation of hits may be challenging

Hit Validation in Drug Discovery

Hit Validation is a pivotal phase in drug discovery that ensures the reliability and relevance of identified hits. By employing a combination of experimental assays, computational methods, and chemical verification, researchers can confidently select hits for further development. This rigorous validation process is fundamental to building a strong foundation for successful drug development campaigns.

1. Importance of Hit Validation:

- **Eliminating False Positives:**

a. Hit validation helps distinguish true hits from false positives that may arise during high-throughput screening or virtual screening

- **Minimizing False Negatives:**

a. Ensures that potentially valuable compounds are not overlooked due to experimental artifacts

2. Hit Validation Approaches:

- **Biological Assays:**

a. Experimental assays are conducted to confirm the biological activity of hits against the target

b. Assays may include enzymatic assays, cellular assays, or other relevant biological models

- **Dose-Response Studies:**

a. Determining the dose-dependent effect of hits to assess potency and specificity

b. Helps identify compounds with suitable activity for further development

3. Considerations in Hit Validation:

- **Selectivity Against Off-Targets:**

a. Evaluating the selectivity of hits against other targets to minimize off-target effects

- **Reproducibility:**

a. Replicating experiments to ensure consistent and reproducible results

b. Confirmation of hit activity across multiple assays or laboratories

Figure 3. Target Validation

4. Integration with Computational Methods:

- **Docking Studies:**

a. Computational docking studies may be employed to predict and validate the binding mode of hits

b. Provides structural insights into the interaction between hits and the target

- **Quantitative Structure-Activity Relationship Analysis:**

a. Correlating the structure of hits with their biological activity to validate and predict activity against the target

6. Confirmation of Chemical Identity:

- **Chemical Verification:**

a. Ensuring that the chemical identity of hits is confirmed through analytical techniques

b. Techniques may include mass spectrometry, NMR spectroscopy, or other analytical methods

7. Hit Triage and Prioritization:

- **Lead-Likeness Criteria:**

a. Applying lead-likeness criteria to assess hits for their potential to become lead compounds

b. Considering factors such as molecular weight, chemical structure, and drug-likeness

8. Hit Confirmation in Disease-Relevant Models:

- **Cellular Models or Animal Studies:**

a. Verifying hits in disease-relevant cellular models or animal studies to assess their potential therapeutic relevance

b. Integration with pharmacodynamic endpoints

9. Hit Validation Challenges:

- **False Positives/Negatives:**

a. Addressing the challenges associated with false positives or negatives, which may arise due to experimental variability or assay artifacts

b. Implementing robust statistical analyses

10. Decision-Making for Hit Progression:

- **Iterative Optimization:**

a. Hit validation informs decisions on whether to progress hits to lead optimization

b. The iterative process involves refining hit structures based on validation results

Lead Optimization Approaches

As promising hits emerge from the expansive landscape of drug discovery, the focus shifts to the intricate art of lead optimization. This crucial phase entails transforming initial hits into lead compounds with enhanced pharmacological properties, setting the stage for the development of efficacious and safe therapeutic agents. This section delves into the multifaceted approaches employed in lead optimization, navigating the delicate balance between potency, selectivity, and drug-like properties.

Various Strategies for Lead Optimization

1. Structure-Activity Relationship (SAR) Studies:

- SAR studies involve systematic exploration of chemical modifications to understand the relationship between a compound's structure and its biological activity
- **Objective:**

a. Uncover key structural features influencing potency and selectivity

b. Guide the design of analogs with improved properties

- **Methods:**

a. Iterative synthesis and testing of compound analogs

b. Utilization of computational tools for SAR analysis

2. Medicinal Chemistry Optimization:

- Medicinal chemistry optimization focuses on refining chemical structures to improve a lead compound's drug-like properties
- **Priorities:**

a. Enhance solubility, bioavailability, and metabolic stability

b. Minimize toxicity and off-target effects

- **Strategies:**

a. Introduction of functional groups

b. Modification of side chains

c. Optimization of physicochemical properties

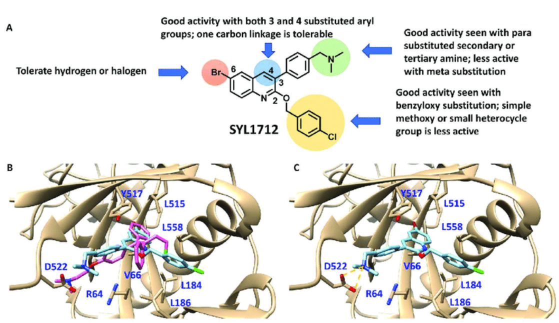


Figure 4. Structure Activity Relationship (SAR)

3. Computational Methods in Lead Optimization:

- Computational tools play a pivotal role in predicting the impact of chemical modifications on lead compounds
- **Applications:**

a. Molecular docking for predicting binding affinities

b. Quantitative structure-activity relationship (QSAR) modeling

- **Advantages:**

a. Accelerates lead optimization through virtual screening

b. Provides insights into potential off-target effects

4. ADME-Tox Profiling:

- Absorption, distribution, metabolism, excretion, and toxicity (ADME-Tox) profiling assesses the pharmacokinetic and safety profiles of lead compounds
- **Goals:**

a. Predict bioavailability and distribution in the body

b. Identify potential metabolic liabilities and toxicity

- **Methods:**

a. In vitro assays for metabolic stability

b. In silico predictions of pharmacokinetic parameters

4. Bioisosterism and Analog Design:

- Bioisosteres are chemical substitutes with similar biological properties. Analog design explores the replacement of functional groups to optimize lead compounds
- **Rationale:**

a. Maintain or improve potency

b. Address unfavorable pharmacokinetic properties

- **Examples:**

a. Replacement of a functional group with a bioisostere

b. Introduction of non-classical isosteres

5. Target Engagement and Selectivity:

- Target engagement and selectivity studies ensure lead compounds interact specifically with the intended target
- **Approaches:**

a. Use of biochemical and cellular assays

b. Structural biology techniques (X-ray crystallography, NMR)

- **Significance:**

a. Minimize off-target effects

b. Optimize lead compounds for specific indications

Scaffold Hopping in Hit To Lead

Scaffold hopping in the context of Hit to Lead optimization is a strategy employed to explore different core structures while maintaining the key pharmacophoric elements of a molecule. This approach allows researchers to modify the central framework or scaffold of a hit or lead compound to generate diverse analogs with the potential for improved biological activity, selectivity, or other desired properties.

Key Concepts of Scaffold Hopping:

1. Diversity Enhancement:

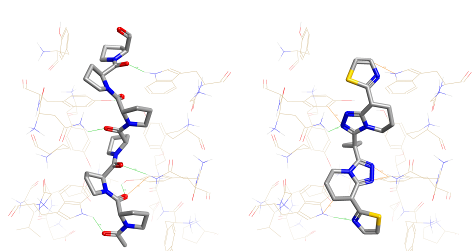
- **Objective:**
  a. The primary goal of core scaffold hopping is to introduce structural diversity into a chemical series
- **Rationale:**
  a. By changing the central scaffold, researchers can access different chemical space, potentially discovering compounds with enhanced properties.

2. Maintaining Pharmacophores:

- **Priorities:**
  a. Core scaffold hopping is performed while preserving essential pharmacophoric features
- **Conserved Binding Interactions:**
  a. Critical interactions with the target, such as hydrogen bonding or hydrophobic contacts, are retained to ensure the new scaffold maintains binding affinity

3. Addressing Limitations:

- **Optimizing Deficiencies:**
  a. If the original scaffold has limitations, such as poor bioavailability or metabolic instability, core scaffold hopping provides an opportunity to address these deficiencies
- **Structure-Activity Relationship (SAR):**
  a. Understanding SAR is crucial to guide scaffold modifications while maintaining or improving activity



Cortactin SH3 interacting peptide derived from AMP1 from PDB: 2D1X is a potential breast cancer therapeutic blocking cortactin—ARF6 mediated metastasis

Example de-novo design / scaffold hop using field-based software

Figure 5. Scaffold Hopping in Hit To Lead

4. Bioisosterism:

- **Definition:**
  a. Bioisosteres are atoms or groups that, when substituted in a molecule, retain its biological activity
- **Integration with Core Hopping:**
  a. Bioisosterism is often utilized during core scaffold hopping to replace elements while preserving or enhancing biological activity

5. Exploration of New Chemical Space:

- **Chemical Diversity:**
  a. Changing the core scaffold introduces the potential for exploring new chemical space
- **Diverse Analog Library:**
  a. Researchers can generate a library of analogs with different central scaffolds to assess a broader range of chemical structures

6. Synthetic Feasibility:

- **Practical Considerations:**
  a. The feasibility of synthesizing the new core scaffolds is a crucial aspect of this strategy
  b. Address unfavorable pharmacokinetic properties
- **Medicinal Chemistry Expertise:**
  a. Medicinal chemists play a key role in designing synthetic routes that are practical and efficient

Application in Hit To Lead Optimization:

1. Hit Expansion:

- **From Hit to Lead:**
  a. Core scaffold hopping is often employed during the transition from hit to lead optimization
- **Diversifying Hit Series:**
  a. It allows for the exploration of multiple core scaffolds derived from a successful hit, potentially identifying more advanced lead candidates

2. Lead Optimization Iterations:

- **Iterative Process:**
  a. Core scaffold hopping is part of the iterative optimization process where feedback from biological assays guides further modifications
- **Balancing Properties:**
  a. Optimization involves balancing improvements in potency, selectivity, and other relevant properties

Navigating Novel Frontiers: The Art of Scaffold Hopping in Drug Discovery

Scaffold hopping, a formidable strategy in drug discovery, involves venturing into uncharted chemical territories beyond the foundational structure (scaffold) of a known active compound. This approach aims to unveil innovative, structurally distinct molecules that exhibit similar or enhanced biological activity—a journey akin to leaping from one island of activity to another in the vast chemical sea, where new treasures await while preserving valuable properties.

Illustrative Example:

Consider a group of COX-2 inhibitors, each honing in on the same enzyme but employing different scaffolds intricately connected to the central phenyl rings. This vivid example underscores the remarkable versatility of scaffold hopping, demonstrating its prowess in optimizing drug properties while upholding crucial activity levels. In this dynamic exploration, researchers embark on a quest to discover promising compounds by strategically navigating the diverse landscapes of chemical space.

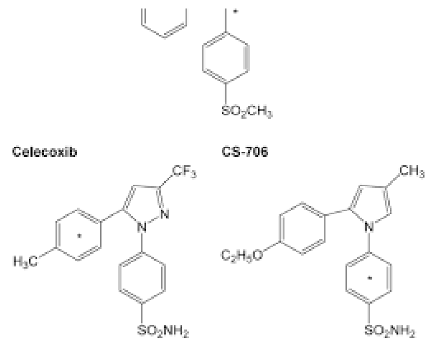


Figure 6. Diverse COX-2 Inhibitors Unleashing Versatile Drug Optimization

Bioisosterism: Crafting Success in Medicinal Chemistry Through Atom Swapping

Bioisosterism stands as a fundamental principle in medicinal chemistry, strategically replacing atoms or groups with chemically similar alternatives to tailor a drug molecule without compromising its desired properties—think of it as skillfully swapping molecular Lego blocks to enhance the overall structure and function.

Illustrative Example:

Consider the transformation from sulfonamides to trimethoprim: Prontosil, an early antibacterial drug, featured a sulfonamide group vulnerable to bacterial enzyme cleavage. By substituting it with the bioisostere trimethoprim—a counterpart with a similar shape and size but less prone to enzymatic breakdown—the result was a remarkably more potent and durable antibiotic.

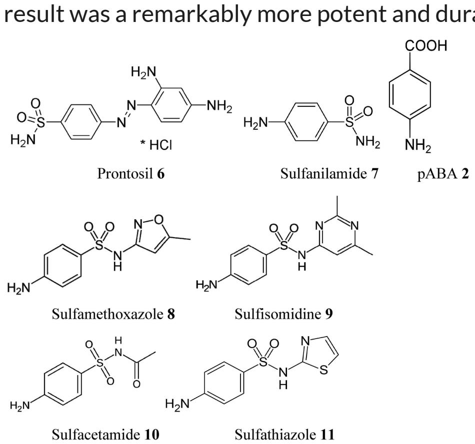


Figure 7. : Transforming Antibacterial Efficacy from Sulfonamides to Trimethoprim