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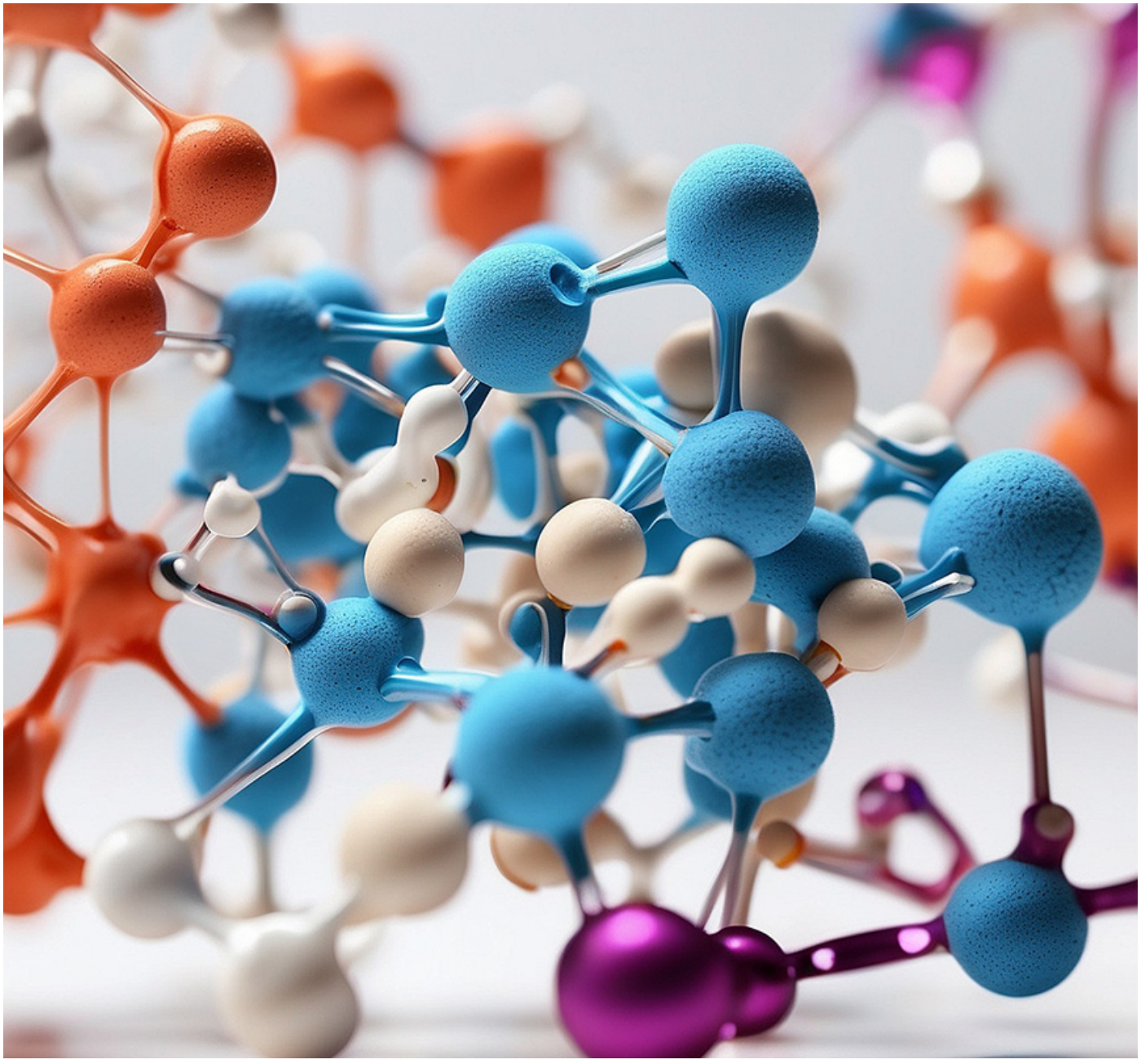
Value from Innovation

Wako

drug2drugs

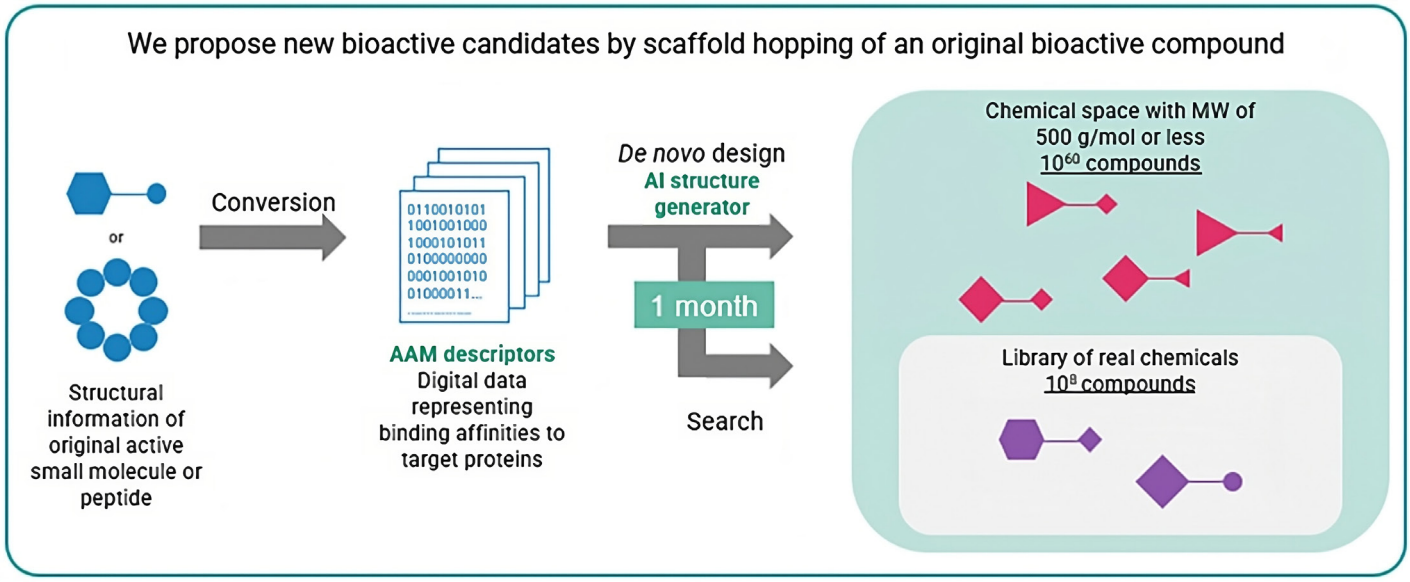
AI and chemical simulation-based drug discovery support service



OVERVIEW

Drug2drugs is an AI and chemical simulation-based drug discovery support service which generates many candidate compounds with different scaffolds from the structural information of one active compound.

Drug2drugs applies our proprietary AI-AAM (amino acid mapping) method, which is an innovative in silico method that combines amino acid interaction mapping with scaffold-hopping to identify structurally diverse compounds with improved drug properties and pharmacological activity. There is the potential for improved bioactivity, efficacy, thermal stability, synthesizability, and so on, which could even unlock the possibilities for avoiding drug toxicity and overhauling the drug delivery characteristics of the drug (i.e., potentially, a drug that must be injected intravenously can now be ingested orally after lead optimization through drug2drugs, with similar or improved pharmacological effects).



KEY FEATURES

Streamlined Lead Optimization

Our innovative AI-AAM technology simplifies the lead optimization process, requiring only the structural information of the bioactive region of the compound.

Efficient Drug Discovery & Development

Accelerate your drug development pipeline with our ability to quickly generate backup compounds and refine

Confidential and Secure

We require little to no experimental data from the client to acquire results, and we prioritize the confidentiality and security of your data throughout the process.

VALUE DRIVERS

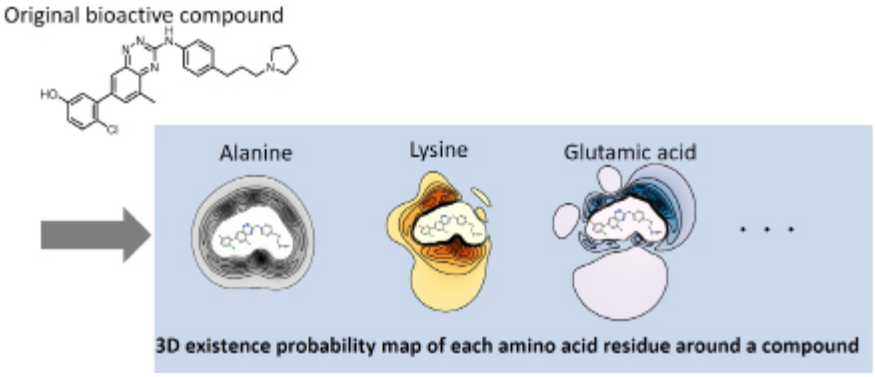
- Significant time & cost savings in R&D
- Increased chances of discovering a successful drug candidate or improving aspects of a drug
- Does not require target protein information, reducing the need to share experimental data

How does the AI-AAM method work?

The AI-AAM method consists of the computation of AAM descriptors and our de novo design AI structure generator.

1. AAM (Amino-Acid Mapping) Descriptors[1]

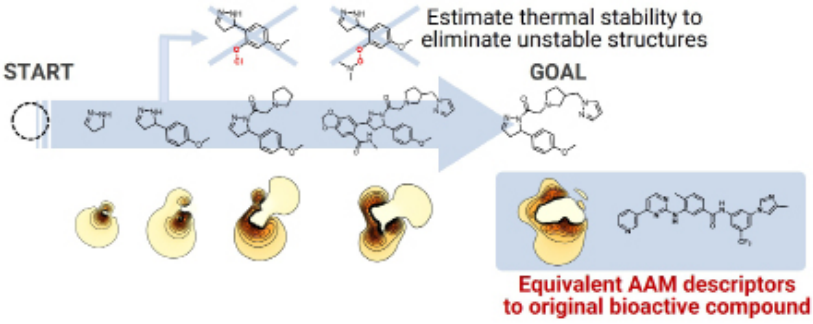
AAM descriptors are the set of the 3D existence probability map of 20 amino acid residues around each compound computed by chemical simulations. Two compounds with the same AAM descriptors but different scaffolds interact with the same amino acid residues and bind to proteins with the same binding pattern.



Performing chemical simulations with AAM descriptors allows us to quickly and efficiently predict bioactivity without calculating the interaction with the target protein. Furthermore, the three-dimensional structures of protein–ligand complexes is not required, and the calculation time is at least 10,000 times faster than QM/MM and takes only a few seconds per compound.

2. *De Novo* Design AI[2]

Our structure design AI enables the generation of a wide variety of structures, starting from nothing and gradually growing compounds with similar AAM descriptors to the AAM descriptor of the targeted bioactive compound, atom by atom. With this atom-based design, the number of chemical spaces that can be targeted is 10^60, which is the theoretical limit.

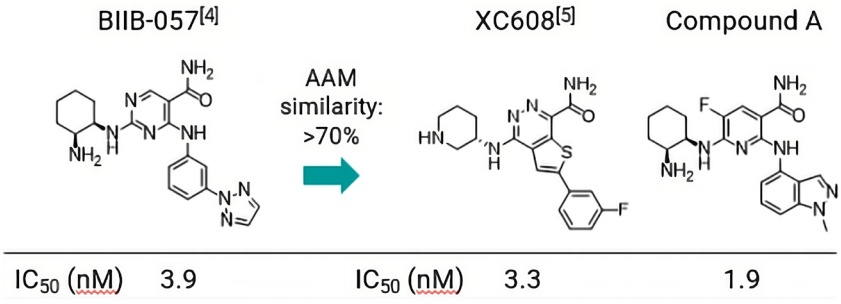


While this method of design often produces compounds that do not meet thermal stability requirements, we have incorporated innovations to select for thermal stability for practical use.

Experimental Validation of the AI-AAM Method

1. Scaffold Hopping (Kinase: Syk[6])

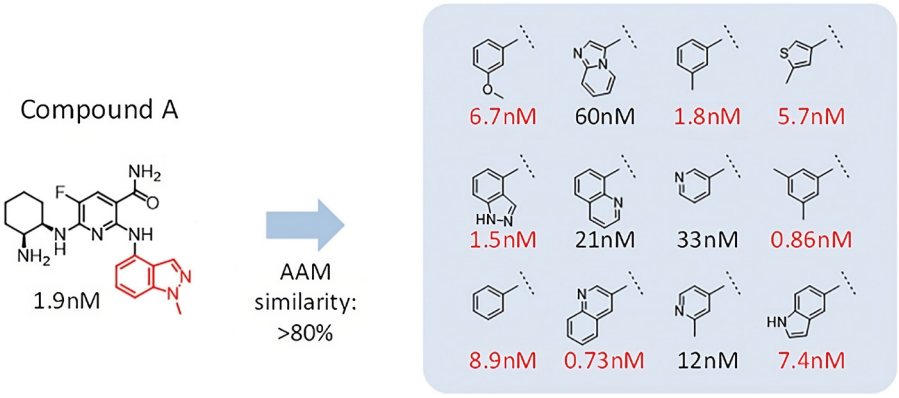
This first example shows a major conversion of the core structure of a lead compound while still maintaining its biological activity. Using the kinase Syk inhibitor BIIB-057 as the source compound, we searched from approximately 12 million compounds in the commercial compound library and extracted XC608 as the compound with the highest AAM similarity to BIIB-057.



In addition, Compound A was also discovered by conducting a re-search using our in-house compound library. The enzyme inhibitory activity of XC608 and Compound A was equivalent to that of the original compound, with lower IC50 values. These computations were completed in just one month.

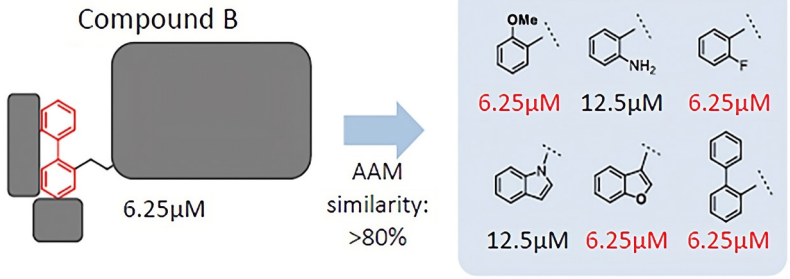
2. Partial Modification (Kinase: Syk[3,9])

150 compounds with greater than 80% AAM similarity to the original bioactive ligand were designed with strategic modifications. Out of these, 12 compounds were chosen and synthesized, with enzyme activity measurements ranging from 0.73 to 60 nM. Based on these results, it is possible to efficiently improve bioactivity through the AI-AAM method by repeating new design, synthesis and evaluation, or binding energy prediction using compounds with stronger binding affinity than Compound A as a new starting point.



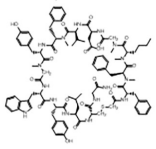
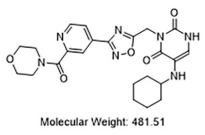
3. Partial Modification (Bacterial Membrane Protein[4,9])

In this example, 332 compounds with more than 80% AAM similarity to the initial bioactive ligand were designed with partial modification of ligand. Out of this selection, 5 compounds were synthesized successfully, with the cell bioactivity measured between 6.25 to 12.5 μM, showcasing comparable or slightly reduced bioactivity relative to the original compound.



4. Peptide to Small Molecule (Protein-Protein Interaction: PD-L1[10])

The small molecule, FF-ATC-001, was designed using our AI-AAM method from the partial AAM of the binding parts of Peptide-71. The pKi per molecular weight of FF-ATC-001 was 9.2, compared to 4.7 for Peptide-71, a 2-fold increase, resulting in a 2-fold increase in bioactivity efficiency per molecular weight. We believe that this is a very positive result for the strategy of extracting and converting the important parts of the interaction.

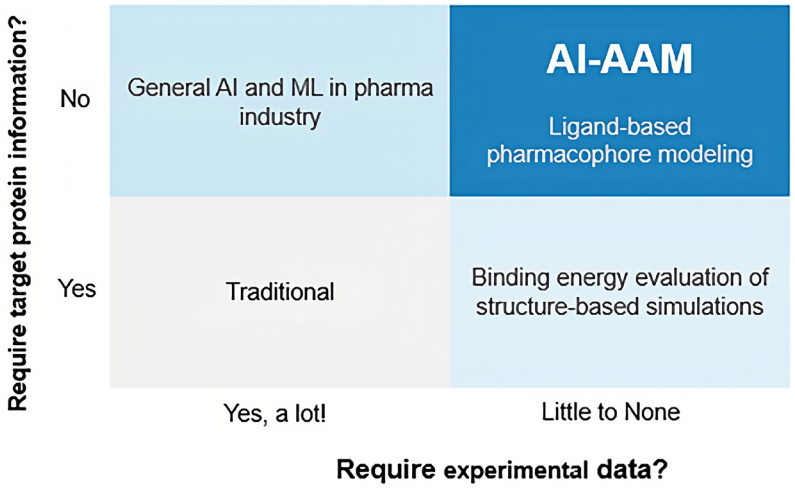
	Peptide-71	FF-ATC-001
		 Molecular Weight: 481.51
Ki ([μM])	0.004	39
BEI ([pK_i/Mw×1000])	4.7	9.2
MDCK-II Permeability ([10^{-6} cm/s])	0.08±0.02	11.1±0.8

The effect on PD-L1 is limited because it is an extracellular target, but cyclic peptides generally have low membrane permeability and cannot target intracellular proteins, making them difficult to make into oral drugs. Here we use MDCK2 cells to show how their membrane permeability has changed: PD-L1 hardly permeated the membrane, whereas FF-ATC-001 showed favorable membrane permeability, demonstrating the potential for conversion from injection to oral drug delivery.

Comparison with Other Drug Discovery Methods

One of the unique points about our service is that the AI-AAM method does not require protein structures or primary sequence of the target protein, nor does it require large amounts of experimental data.

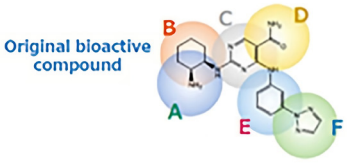
It only requires the structural information of the bioactive compound to produce results, accelerating your efforts in drug discovery in a secure, yet efficient manner.



Service Flow and Deliverables

The customer will need to provide the structural information of the bioactive compound. Based on this information, we will provide the following deliverables:

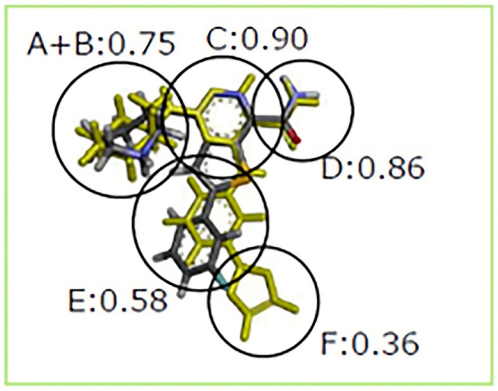
1. List of candidate compounds, including the chemical structure and AAM similarity
2. 3D images of the relationship between chemical group and AAM similarity.



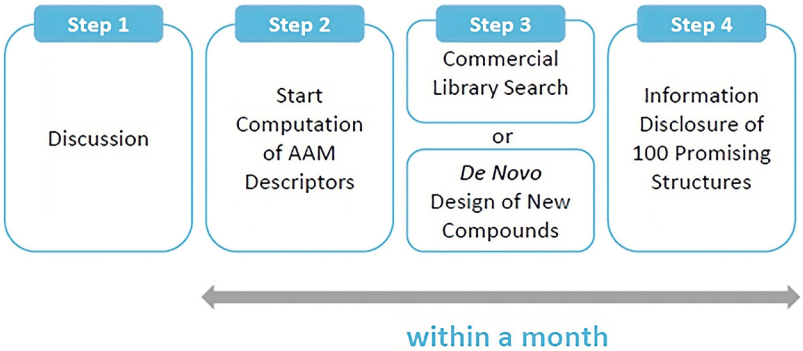
(1) List of AAM similarity

Chemical structure	A	B	C	D	E	F	Avg.
Compound 1	0.75	0.75	0.90	0.86	0.58	0.36	0.70
Compound 2	...	...	...	...	...	...	...
Compound 3	...	...	...	...	...	...	...

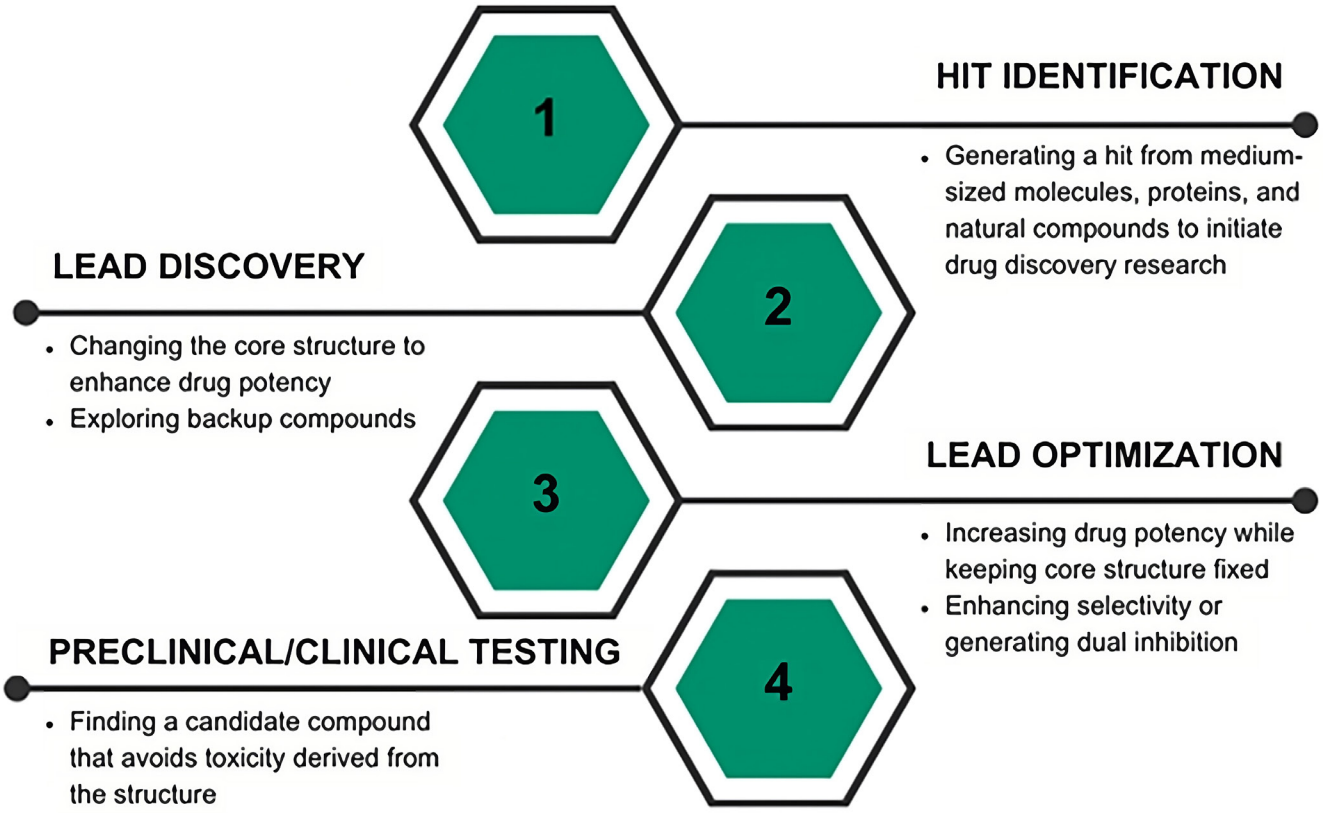
(2) Chemical structure with AAM similarity



The computation time takes 1 month, and upon completion, we provide the final report and other details in a confidential manner. We will provide the customer with further support to understand the report. Furthermore, as per a standard contract agreement, data will be used to train the AI model in a secure manner.



Example Use Cases



CITATIONS

[1] JP6826672B2. [2] JP7191969B2, JP7190498B2, and JP7116186B2. [3] Enzyme activity was measured by Syk kinase enzyme system and ADP-Glo™ Kinase Assay (Promega, USA). [4] Cell bioactivity was measured by bacterial growth assay. [5] P. Etrl and A. Schuffenhauer, J. Cheminfo. 2009, 1:8. [6]CBI Annual Meeting 2022, P08-14; bioRxiv (2023), doi:https://doi.org/10.1101/2023.07.03.547598. [7] WO 2009/136995. [8] WO 2011/035077. [9] CBI Annual Meeting 2023, P03-07. [10] CBI Annual Meeting 2022, P08-07, Excellent Poster Awards. [11] US20140294898 A1.

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