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BIOVIA

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10 mins read

AI for All? How Pharma Partnerships Improve Software Solutions

Dassault Systèmes, BIOVIA solutions create an unmatched scientific management environment that can help science-based organizations create and connect biological, chemical and material innovations to improve the way we live. The industry-leading BIOVIA portfolio is committed to enhancing and speeding innovation, increasing productivity, improving quality and compliance, reducing costs and accelerating product development for customers in multiple industries.

Artificial Intelligence (AI) is revolutionizing data processing, with applications to drug discovery ranging from improving **cellular imaging** to **modeling protein folding**. Although numerous startups are developing methods to apply AI-driven drug discovery to develop proprietary assets, a remaining challenge is making these powerful tools usable by drug discovery companies without deep in-house AI/ML expertise. Many pharma companies have begun to **outsource the use of AI solutions through partnerships with AI-based companies.** While this has led to a number of **clinical programs**, this strategy can be costly for pharma, as it is not uncommon for licensing fees for AI partner-generated molecules to cost tens of millions of dollars upfront.

An emerging alternative approach is to put the AI/ML in the hands of experienced pharma scientists in-house through a software partnership model, such as that recently **published** and presented by Gilead Sciences and BIOVIA at ACS Chicago in 2022. In this model, the AI/

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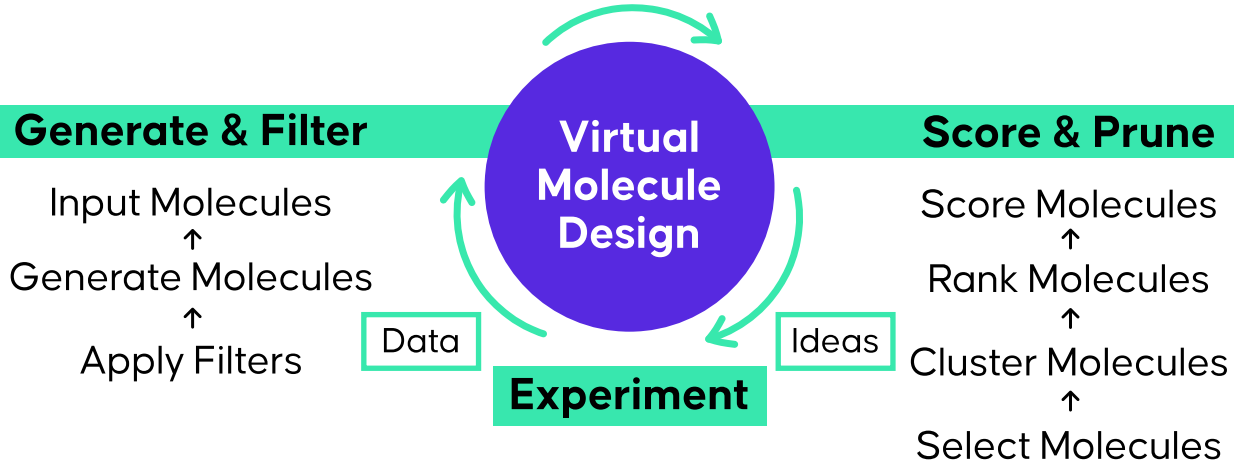
ML software provider (BIOVIA) provides software engineering and computational expertise to its pharma partners, while pharma partners can leverage their own internal data and experienced scientists but critically, retain all IP. This collaboration model may allow pharma partners to tailor software solutions to their needs more quickly. By working with a diverse range of partners on a variety of problems, BIOVIA has been able to better support new therapeutic areas out of the box. This case study featuring a recent partnership between BIOVIA and Gilead Sciences highlights how partnerships between software providers and pharma experts can rapidly enable new tools for the pharma partner while improving AI-driven drug discovery software for everyone.

Experienced Pharma Partners Augment AI/ML Software Solutions: A Case Study

What is Generative Therapeutics Design (GTD)?



Experienced Pharma Partners Augment AI/ML Software Solutions

Pharma Brings:

- High Quality Internal Data
- Experienced Scientists
- Experimental Feedback

BIOVIA Brings:

- Software Engineering
- Computing Power at Scale
- Scientific Support

GTD is, at its heart, an ideation tool that can help chemists generate pre-qualified ideas to choose from, rather than exploring familiar areas of chemical space and sinking time into repetitive tasks like calculating properties or manually reviewing past data. In GTD, multiple AI/ML tools come together to generate new chemical structures iteratively, virtually test those structures in models developed with in-house data and identify structures that optimally fulfill a collection of pre-selected characteristics. A vast array of molecular transformations is used to generate diverse analogs of input molecules, from classical medicinal chemistry reactions to broader framework and ring replacements. The most promising molecules are selected through a mix of filtering methods and multi-parameter ML model-based property prediction, trained on experimental data. This involves a multi-parameter optimization step to ensure many, often competing design characteristics are met. Additionally, using GTD, medicinal chemists can add their own preferences by controlling parameters by:

- Removing implausible/bad substructures (e.g. toxicophores)
- Filtering unknown fragments (ChEMBL, MDDR)
- Filtering based on user-guided preferences for molecule features
- Prioritizing based on calculatable physicochemical properties (e.g. AlogP, PSA, etc.)
- Prioritizing based on molecular property counts (rings, rotatable bonds, HBA, etc.)
- Assessing drug likeness based on filters and models
- Assessing binding potential (e.g. pharmacophore model, docking model)

Publicly available data, such as those for solubility, can also be used to build models. However, the data used to build these models will most often come from the company's experimental data for a given discovery program. Augmenting 2D ML models with robust 3D pharmacophore models of protein-ligand interactions appeared critical to enhance the quality of the molecules.

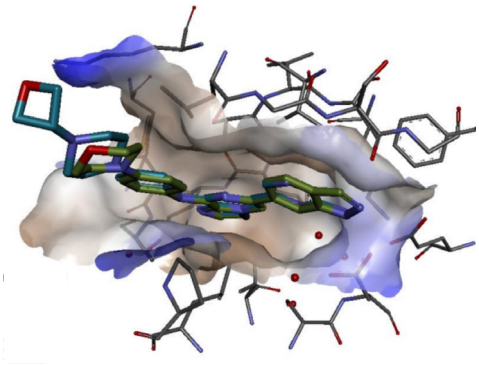
3D Modeling Embedded in AI/ML Workflow via Pharma Partnership

BIOVIA partnered with Gilead Sciences to test and improve GTD as a tool using Gilead's **spleen tyrosine kinase (SYK) inhibitor program** as a pilot. Early analyses showed that the 2D ML models built with the SYK data alone were of limited utility for generating viable structures. To improve the usefulness of the GTD platform, the Gilead team opted to develop and incorporate 3D pharmacophore models in their testing. 3D models are challenging to build without the expertise of a computational chemist or previous knowledge of the protein-ligand interface determined by X-ray crystallography or cryo-EM. BIOVIA came up with a way for computational chemists to build these in their expert environments and published these for the use of all chemists to use in their generative design work. The results of this collaboration were recently shared at the 2022 Fall Meeting of the American Chemical Society.

3D Modeling Embedded in AI/ML Workflow via Pharma Partnership

from U. Schmidt et al., Gilead Sciences + BIOVIA Presentation, ACS Chicago 2022

2D / 3D Lead Optimization

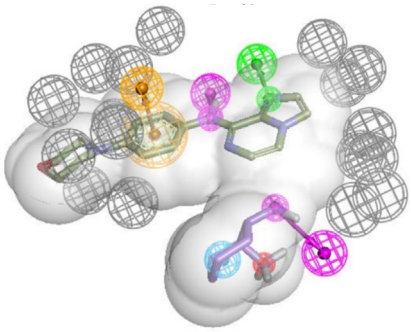


Pharmacophore model of binding site identifying high-value analogs of entospletinib

Scaffold Hopping

Representative **GTD results aligned to pharmacophore** derived from PRT-062607 and mivavotinib

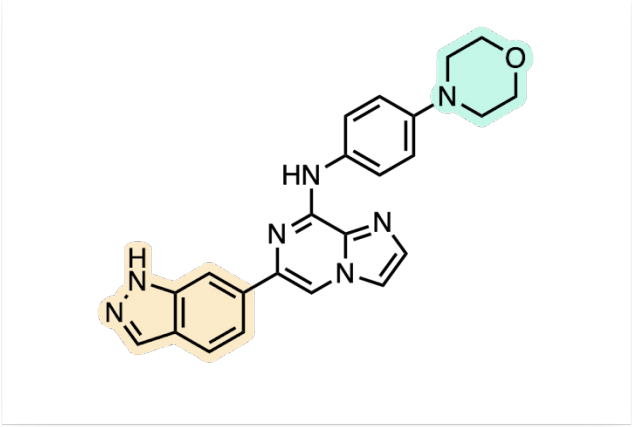
Scaffold Merging



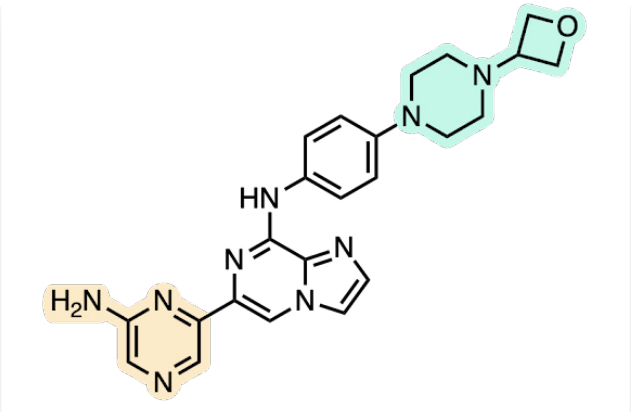
Hybrid pharmacophore with features from entospletinib and cyclohexandiamine

2D/3D Lead Optimization: Leveraging a 3D Pharmacophore Model to Reproduce a Known Clinical Candidate

Using a pharmacophore model of the binding site for the imidazopyrazine SYK inhibitor, entospletenib, GTD was challenged to produce lanraplenib. After five iterations under optimized input conditions, GTD generated lanraplenib, which as a past candidate naturally scored highly on GTD's "desirability score" index.



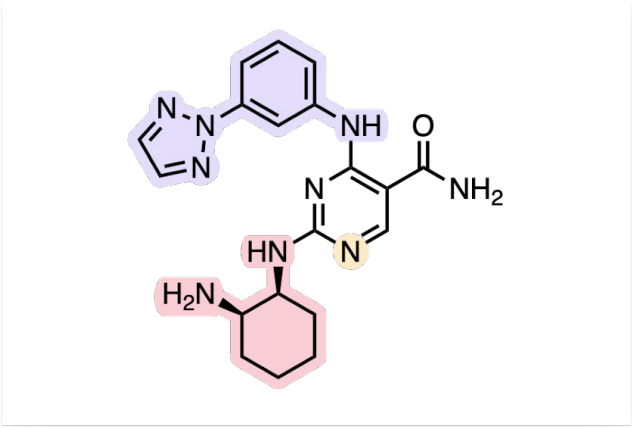
entospletenib



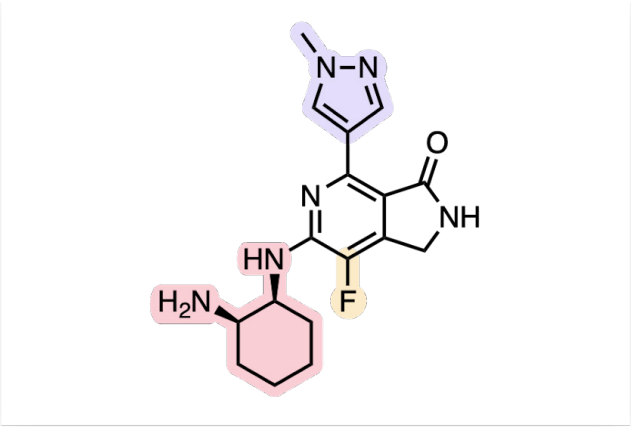
lanraplenib

Scaffold Hopping: Testing Diverse Molecules Against the 3D Pharmacophore Model to Morphing One Candidate into Another

Using the 2D SYK models derived from the Gilead data, their 3D pharmacophore model, various structural filters, and an input structure of PRT-062607 with a fixed cyclohexanediamine, GTD generated structures suggestive of mivavotinib (TAK-659)



PRT-062607



mivavotinib (TAK-659)

Scaffold Merging: Using a Hybrid 3D Pharmacophore Model to Generate Novel Chemical Matter from Known Scaffolds

Using a hybrid pharmacophore model built with features of two compounds, the team explored the ability of GTD to sample novel chemical space and to suggest new targets of interest. They selected entospletenib and PRT-062607 as the starting input structures and challenged GTD to generate molecules with similar shapes and space filing as the input structures. GTD was able to generate novel chemical matter with plausible activity, which the presenter stated were planned for further evaluation.

These results demonstrate that while GTD can be implemented without the intervention of computational experts, the process can be optimized with their input. Gilead benefited from a robust dataset and modeling experts who could build and optimally implement relevant 3D models. Overall, the team demonstrated proof-of-concept that the GTD process can indeed generate viable clinical candidate structures, given the right inputs.

How Will Pharma / Software Partnerships Evolve AI for All?

The design of good compounds to make can be a time-consuming and tedious process, but AI/ML-based workflows could start making things easier. The BIOVIA GTD platform was designed with the actual drug discovery process in mind and allows medicinal chemists to unite their intuition and knowledge with the problem-solving power of AI.

While AI/ML methods previously required significant overhead to implement or required companies to outsource computational work, commercial platforms like BIOVIA GTD are making these tools increasingly accessible without needing an in-house team of data scientists or computational chemists. In addition, if your organization requires assistance with model building, GTD method development, and optimization strategies, the BIOVIA team of scientists is available to support your work. BIOVIA has been serving pharma and biotech companies worldwide for decades, and as it improves its processes through partnerships with experienced pharma and biotech partners, its tools become better for everyone.

BEGIN YOUR PHARMA PARTNERSHIP →

Further Reading

- Accelerating Drug Discovery with AI
- Adding a Dimension to Generative Design
- AI/ML Webinar - Generative Therapeutics Design: Accelerating Drug Discovery with AI and Machine Learning
- Machine learning for molecular and materials science
- From machine learning to deep learning: progress in machine intelligence for rational drug discovery
- Applications of machine learning in drug discovery and development
- Artificial intelligence in drug discovery: what is realistic, what are illusions? Part 1: Ways to make an impact, and why we are not there yet

Helping drug discovery innovators discover more.

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