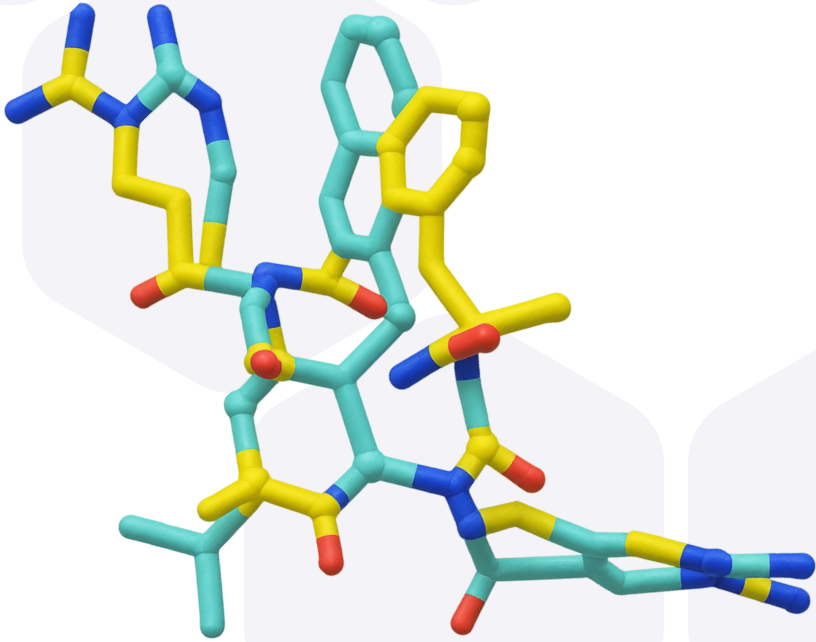
MEDVOLT

AI-Powered Small Molecule Hit Discovery for Challenging Therapeutic Targets



Leveraging Deep Generative Models, Knowledge Graphs, and Physics-Based Simulations

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Kinase-Like Protein

AI-Guided Scaffold Optimization for a Conserved Regulatory Enzyme

Target Overview & Challenges

Central modulator in programmed cell death (necroptosis) and inflammatory signaling, playing a regulatory role across multiple stress and immune response pathways

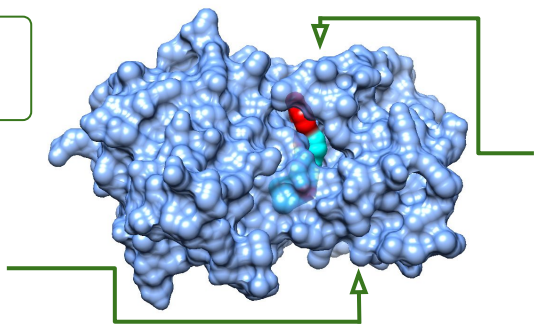
Therapeutics Areas

- **Oncology**: Colorectal, pancreatic, glioblastoma, liver, lung cancers
- **Neurodegeneration**: Alzheimer's, ALS, MS, stroke
- **Autoimmune/Inflammation**: RA, IBD, psoriasis, SLE
- **Other**: Sepsis, ischemic injury

Key Challenges

- Designing selective inhibitors in a **highly conserved kinase fold**
- Stabilizing ligands in **flexible, allosteric sites**
- Designing novel scaffolds distinct from known kinase inhibitors
- Ensuring **robust ADMET** profiles for downstream translation

Target Class: Serine/Threonine Kinase-like Protein



Discovery Strategy & AI Workflow

Engineer selective and novel allosteric inhibitors with optimal binding affinity, pharmacokinetics, and synthetic feasibility, using an AI-accelerated pipeline

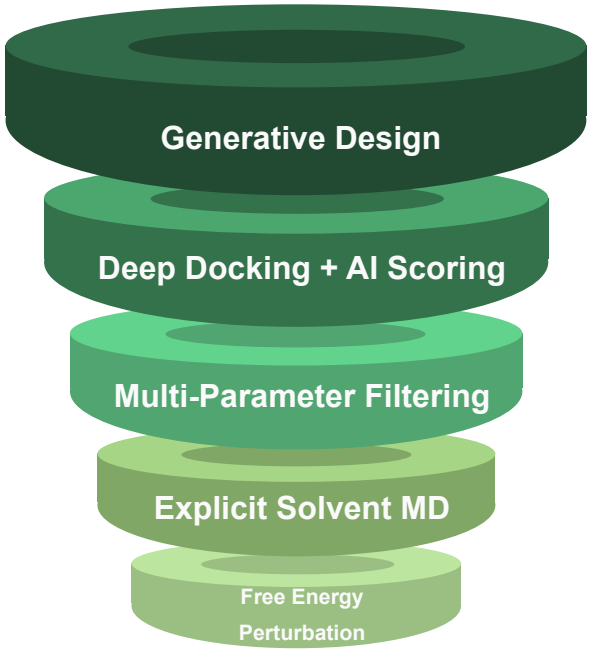
01 **Generative Design**
Scaffold-based exploration for allosteric grooves

02 **Deep Docking + AI based Rescoring**
AutoDock-GPU + Medvolt Rescoring Engine

03 **Multi-Parameter Filtering**
ADMET profiling (PK/PD, toxicity), synthetic accessibility

04 **Explicit Solvent MD**
50 ns simulation for dynamic stability & pocket retention

05 **Free Energy Perturbation**
Accurate ΔG estimation for final hit ranking



Results & Molecular Insights

Top Virtual Hits

- 19 novel scaffolds with Docking Score –9.8 to -13.11kcal/mol
- Tanimoto similarity ≤ 0.28 → high novelty (diverse chemical space)
- Synthetic Accessibility Score ≤ 3.0 → synthesis ready

Molecular Dynamics Insights

- RMSD ≤ 2.2 Å: stable binding throughout 50 ns
- Persistent hydrogen bonding to allosteric binding region
- Pocket volume conserved; minimal collapse under dynamic stress

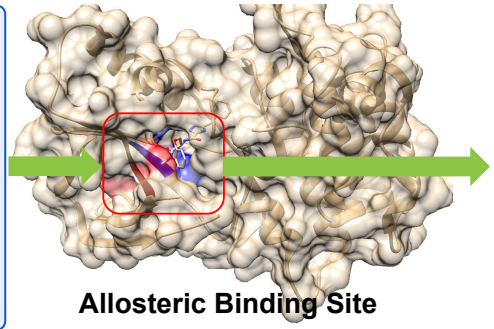
MMPBSA Insights

- ΔG range: –10.1 to –12.4 kcal/mol
- Favorable thermodynamics for all top ligands
- This narrow range indicating strong and specific binding across all ligands

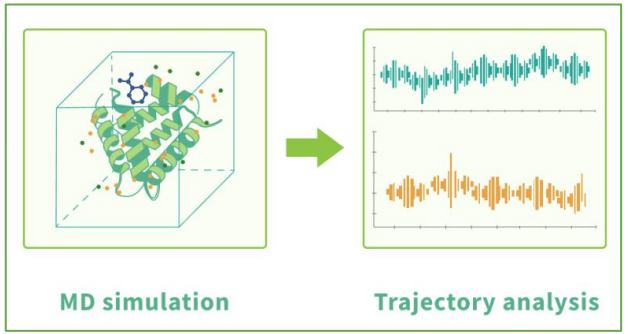
Medicinal Chemist-Guided Hit Expansion

- 23 new scaffolds with docking scores ranging from –7.06 to –12.57 kcal/mol
- Stable 50 ns MD trajectories (RMSD ≤ 2 Å)
- MMPBSA binding free energy: –9.6 to –15.6 kcal/mol

- De Novo molecule library generation
- Molecular Docking with In house proprietary tools
- AI based Rescoring



Allosteric Binding Site



MMPBSA Free energy calculation

↓

Hit Prioritization

↓

Medicinal Chemist-Guided Hit Expansion

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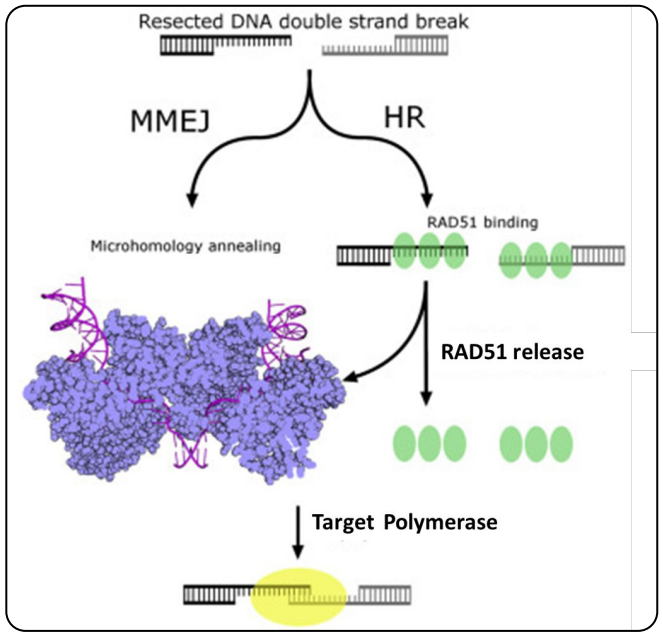
DNA Repair Polymerase

Fragment-Based Discovery for a DNA-Processing Enzyme with Clinical Relevance

Target Overview & Therapeutic Relevance

This target is a specialized DNA repair polymerase playing a critical role in the alternative end-joining (alt-EJ) pathway of the DNA Damage Response (DDR). Unlike classical repair mechanisms, alt-EJ introduces greater mutagenic potential and becomes particularly active in HR-deficient cancers.



Therapeutic Relevance

- **Overexpressed** in breast, ovarian, gastric, colorectal, and lung cancers
- Low expression in healthy tissues, enabling selective targeting
- Synthetic lethality observed in **BRCA1/2** or **53BP1** deficient tumors
- Applicable to **TNBC (Triple Negative Breast Cancer), HR-deficient ovarian cancer (~50%)**, and select **prostate and pancreatic cancers**

Key Challenges, Objectives & Scientific Rationale

Drug Discovery Challenges

- High structural homology with other human DNA polymerases complicates selectivity
- Solvent-exposed, flexible active site results in conformation-dependent ligand affinity
- Complex solvation patterns inside the binding tunnel
- Need for hits that balance potency, selectivity, ADMET profile, and synthesizability

Medvolt Objectives

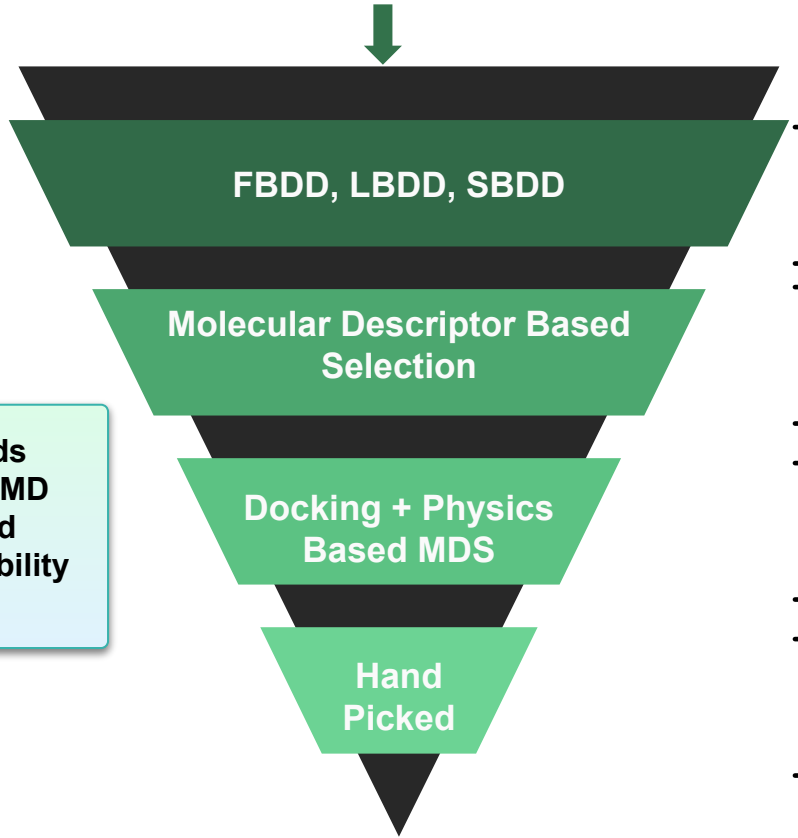
- Identify novel, drug-like, and structurally diverse inhibitors for the target
- Leverage proprietary generative-AI pipelines for diverse chemical space exploration
- Use physics-informed and ML-enhanced scoring to refine binding predictions
- Prioritize hits for further MD simulation and ADMET optimization

Scientific Rationale

- Exploitable vulnerability in BRCA-mutated or 53BP1-suppressed tumors
- Increasing evidence for resistance bypass via this polymerase in PARP inhibitor–treated patients
- Drugging this polymerase enables precision oncology with minimized off-target toxicity

Workflow & Methodology

Input ~ 2.5 lakh curated fragments



~ **10,000** *de novo* Hits

1034 *de novo* hits using medicinal chemistry (synthesizability score) & physicochemical filters (ADMET, permeability, carcinogenicity) filters

222 compounds showing good binding scores, AI-based binding affinities and drug-likeness scores

124 hits identified through visual inspection and interaction with key amino acid residues

Final compounds underwent short MD simulations and protein–ligand stability screening

Results & Preliminary Insights

Hit Novelty and Scaffold Diversity

- The **124** shortlisted hits showed high novelty vs. known inhibitors
- Tanimoto Coefficient (TC) with known compounds: Max **TC = 0.69**, average much lower
- Scaffold clustering indicates broad divergence from literature precedents

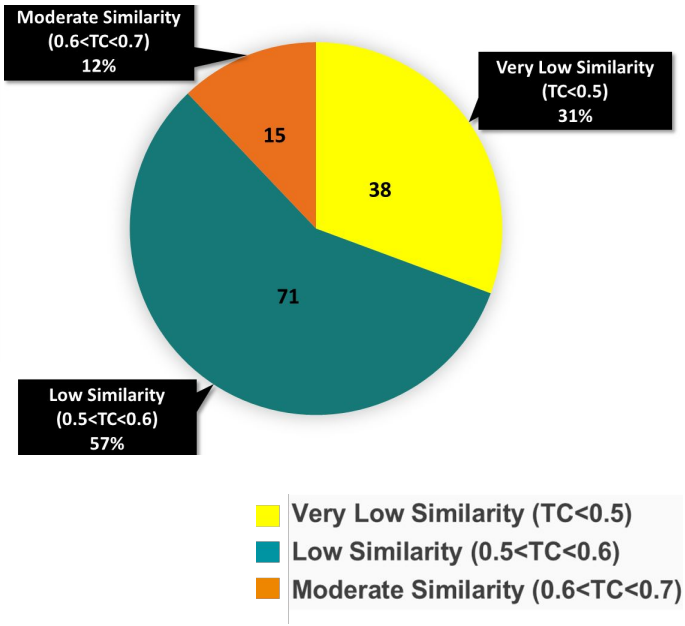
Binding Mode Analysis

- Key interaction residues conserved across high-affinity hits
- Multiple non-classical hydrogen bonding and pi-pi stacking patterns seen
- Hits show differential affinity toward solvation-pocket conformations

Next Step

- Prioritize top 20 hits for 50–100 ns MD simulations and binding energy decomposition
- Potential for wet-lab evaluation in BRCA-deficient in collaboration

Tanimoto Similarity Between MedGraph-generated Hits Vs Reported DNA Pol Theta Inhibitors



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BRCA1 BRCT Domain

Disrupting Protein–Protein Interfaces in DNA Damage Signaling

Target Objective & Overview

To identify non-covalent, drug-like PPI disruptors targeting the phosphopeptide binding site of this domain, with high specificity and favorable bioavailability.

Therapeutic Relevance

- DDR dysregulation is implicated in multiple cancers (e.g., breast, ovarian, glioblastoma, AML)
- Inhibition of BRCT-mediated PPIs can rewire DNA repair fidelity, sensitizing tumor cells to chemotherapy or PARP inhibitors

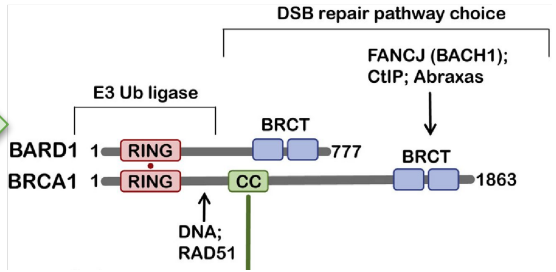
Structural Characteristics

- Compact α/β fold with a shallow, solvent-exposed binding groove
- Surface-accessible polar patch with conserved acidic residues enabling phosphopeptide anchoring
- High flexibility and conformational adaptability in loop regions

Target Class: BRCT-like phosphopeptide-binding domain

Biological Role: Key mediator of protein-protein interactions (PPI) in the DNA damage response (DDR) cascade via phosphoserine recognition.

Domain architecture



Ligand Library Strategy

Ligand Library Composition

- Initial pool: **~10,000** curated small molecules curated from:
  - FDA-approved drugs
  - Investigational compounds
  - Clinical-stage small molecules
  - Non-FDA approved bioactive scaffolds
- This curated chemical space was chosen to maximize downstream translational potential

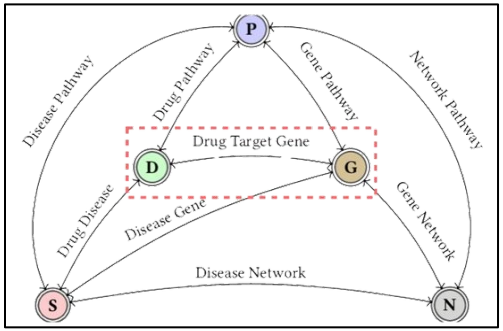
Multi-tier Docking & AI-Based Rescoring

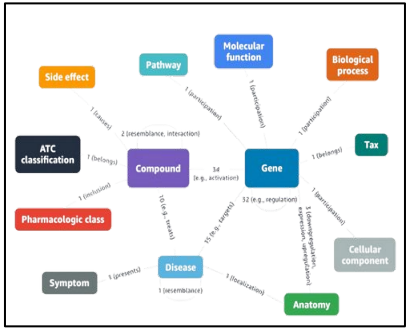
- High-resolution crystal structure of the target used as a reference
- Targeted docking against the phosphopeptide binding cleft
- Scoring optimized for shape complementarity, surface burial, and interaction density
- Prioritized molecules exhibited anchoring within the charged groove and strong occupancy of the conserved polar cavity
- AI-based rescoring using Pafnucy and SFCNN

Target Prioritization & Knowledge Discovery

Literature mining and ontology-based curation confirm role in resistance and genome stability

Physicochemical evaluation of the groove highlights key anchor points for phosphomimetic ligands

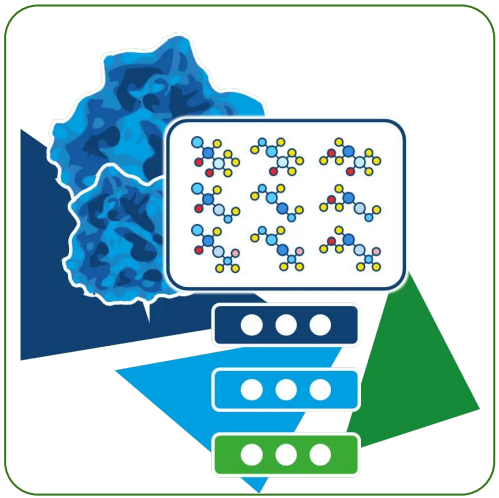




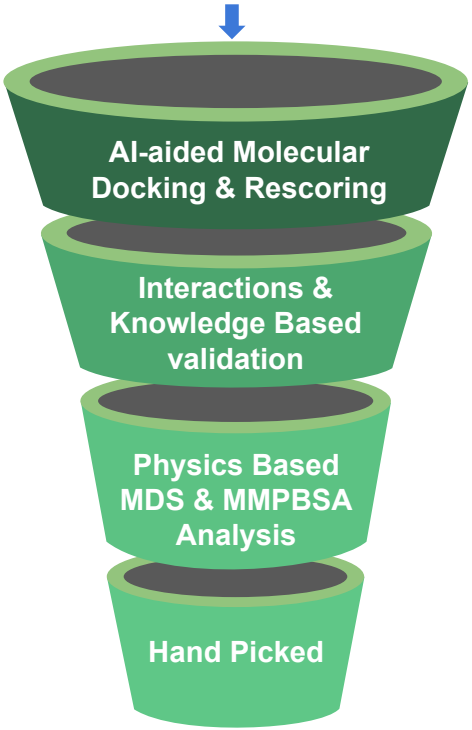
Virtual Screening Workflow & Key Outcomes

Top Hit Characteristics

- Anchored via multi-point polar contacts
- Hydrophobic stacking with adjacent surface grooves
- Electrostatic bridging with charged amino acid clusters
- Molecules exhibited minimal steric clash and favourable desolvation energies



Input ~ 10K approved & investigational drugs



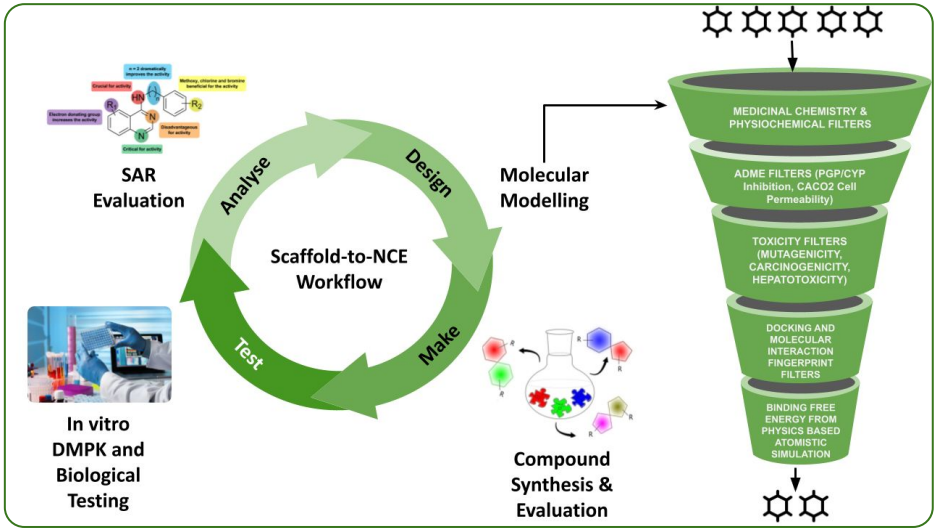
~ 55 hits showing good binding affinities
Docking Score ≤ **7 kcal/mol**

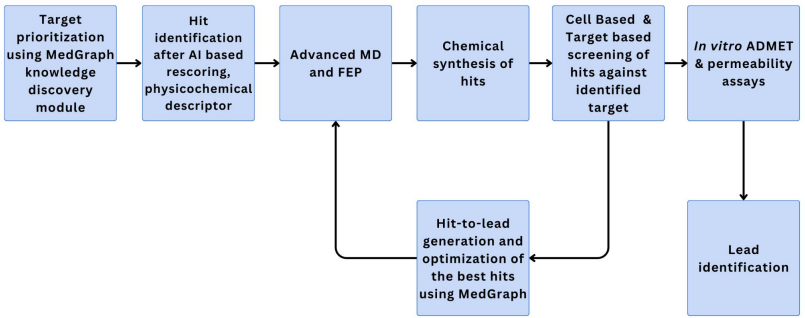
20 hits demonstrated interactions with key catalytic and active site residues
Docking score **-7.52** to **-10.71** kcal/mol

14 hits showing good binding free energy (**-8.37** to **-10.04** kcal/mol) comparable to standard drugs

14 hits selected for biological evaluation

Insights & Path Forward





Key Insights

- Shallow PPI interface is druggable with mimetics enriched for negative charge and planar scaffolds
- Identified ligands demonstrate both site-specific anchoring and structural stability
- Medvolt's closed-loop AI + simulation workflow allowed systematic refinement of weak binders into pharmacologically robust candidates

Next Steps

- Expand scaffold-to-lead optimization through fragment linking and analog enumeration
- Consider dynamic pharmacophore modeling to capture transient interaction hotspots
- Wet-lab binding validation of top-ranked candidates

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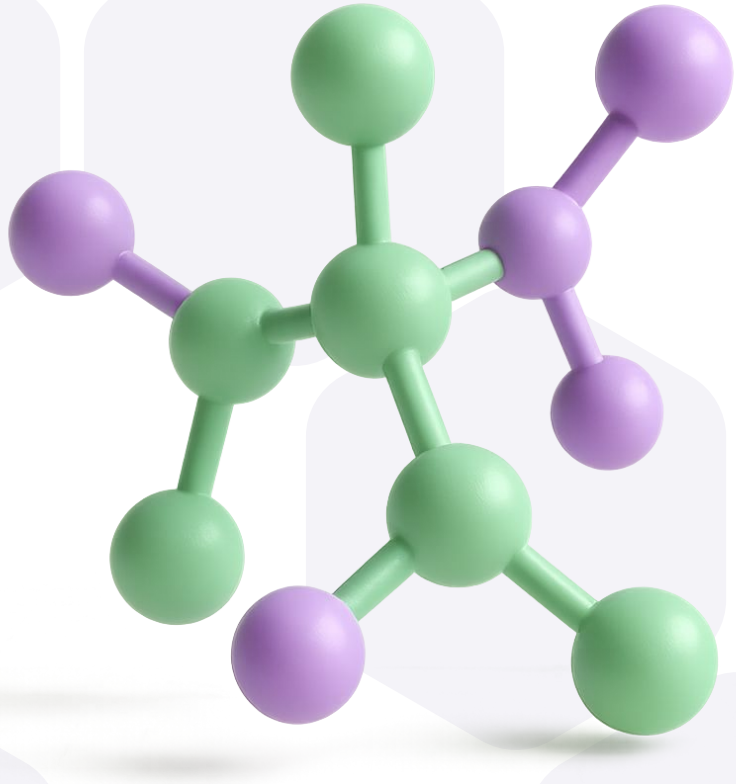
THANK YOU



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