XXXII Symposium on
Bioinformatics and Computer-Aided
Drug Discovery
19 - 21 October, 2026 | **Oral presentation**

Ligand Pro | Skoltech
Skolkovo Institute of Science and Technology

SPELL: Interactive Tool for Structure-Guided Ligand Design and Fragment Replacement

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[2]*Skolkovo Institute of Science and Technology, Moscow, Russia*

Tuesday, 20th October, 2026

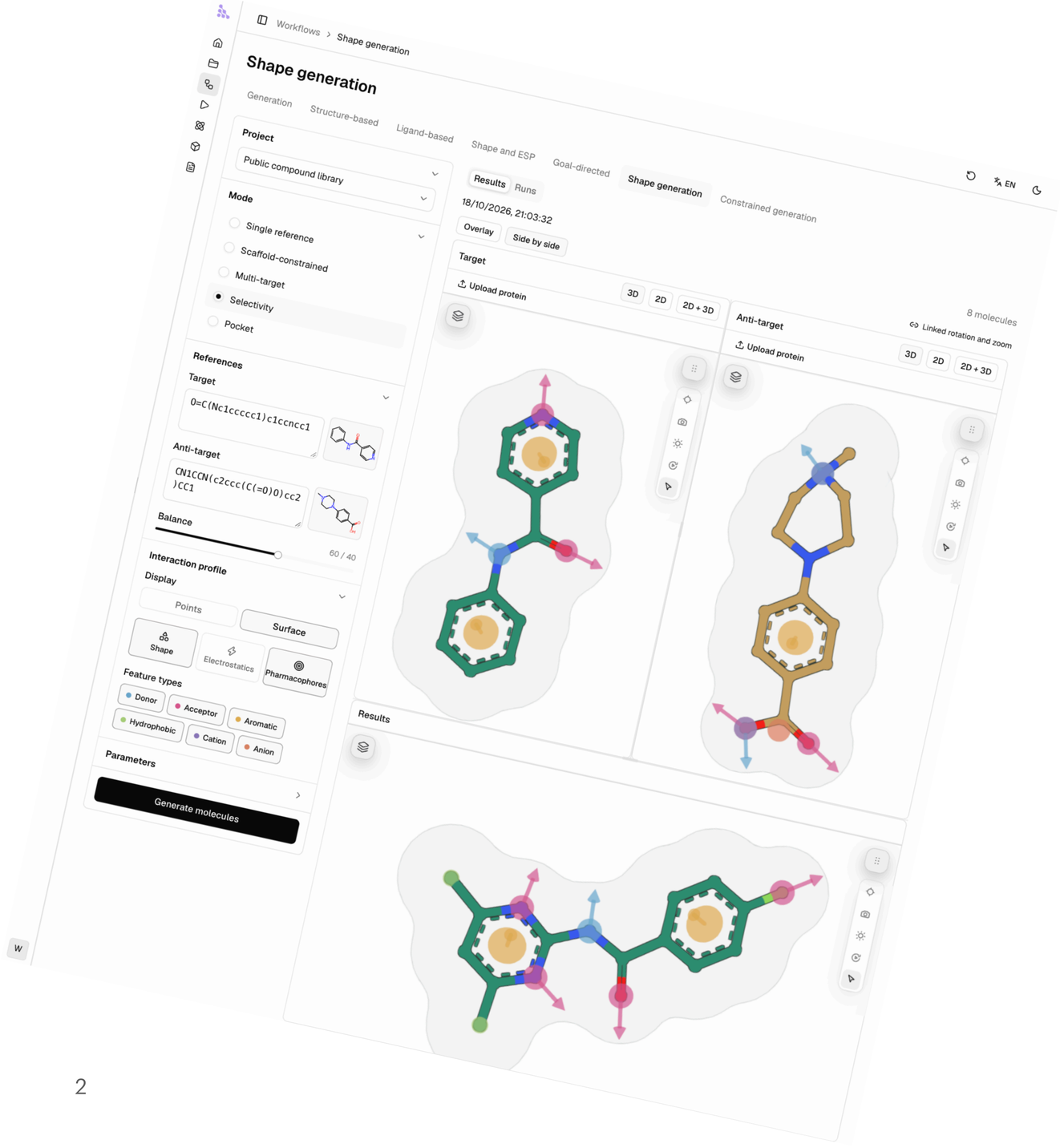
Moscow, 2026

Introduction

ShEPhERD

SPELL

Conclusions

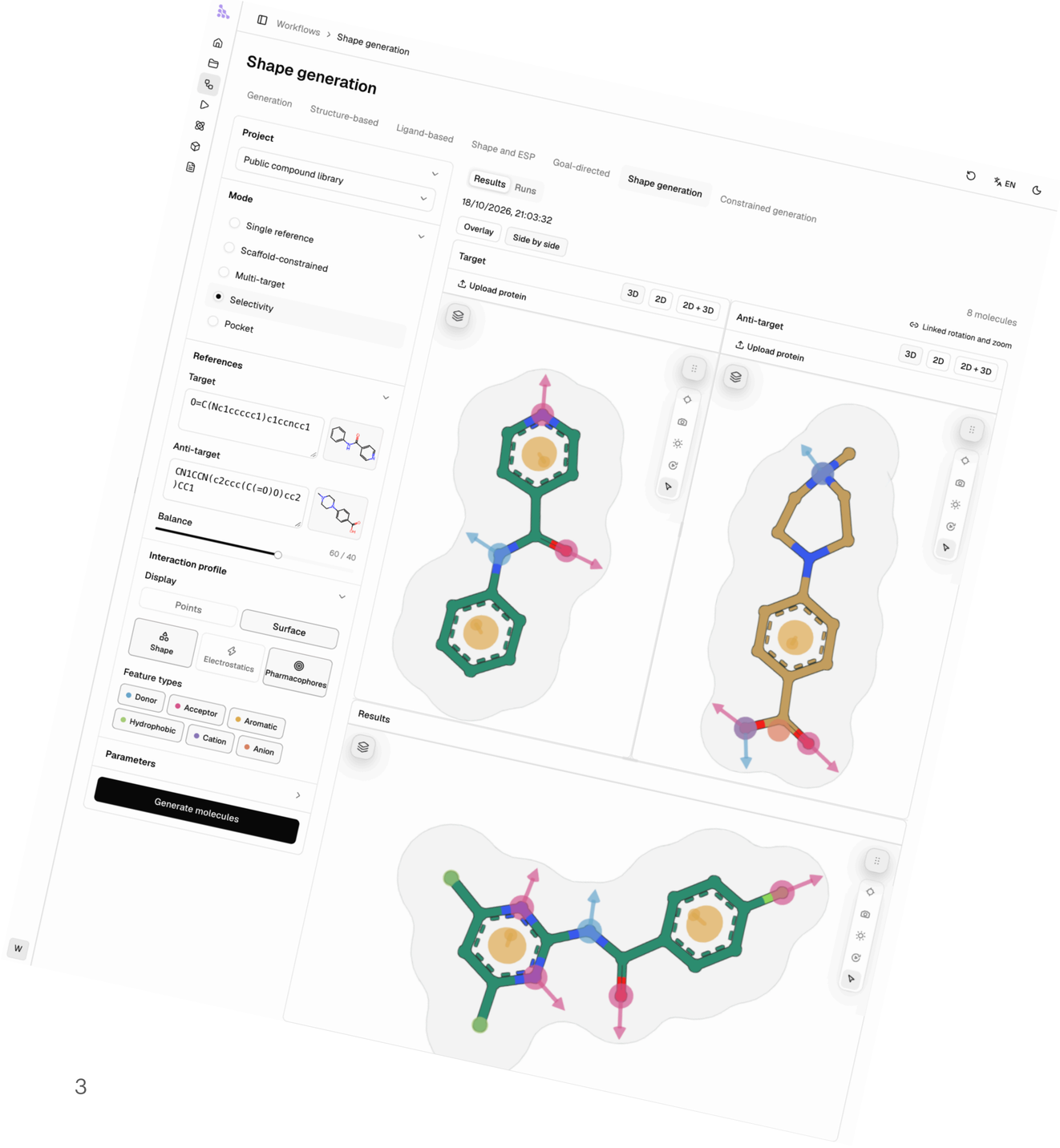


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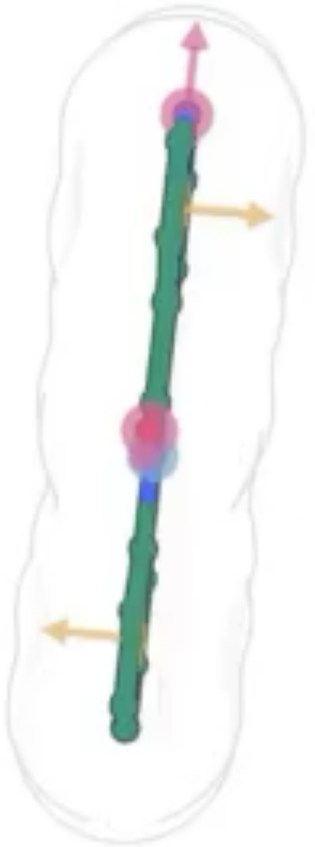
Conclusions



Introduction

Structure-based molecular generation allows to:

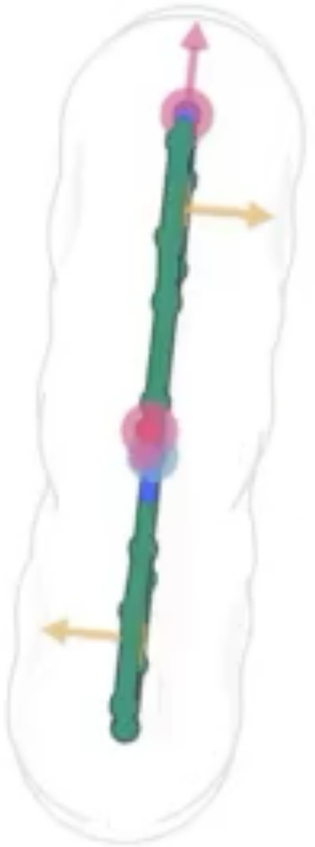
- preserve important molecular scaffolds and protein-ligand interactions;



Introduction

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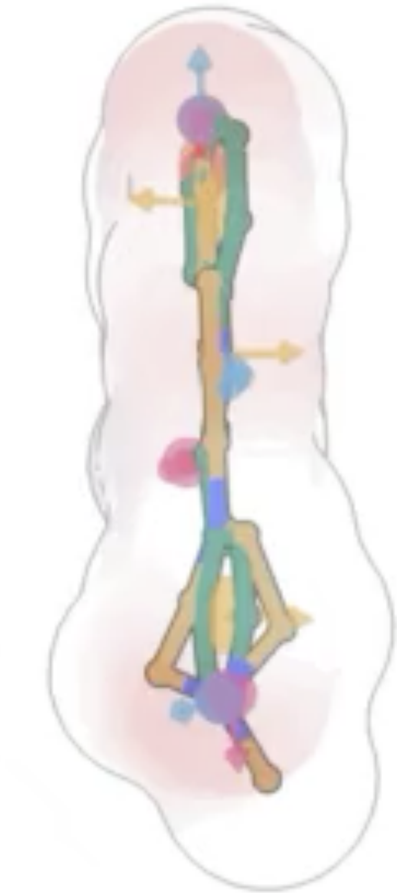
- preserve important molecular scaffolds and protein-ligand interactions;
- modify specific molecular scaffold;



Introduction

Structure-based molecular generation allows to:

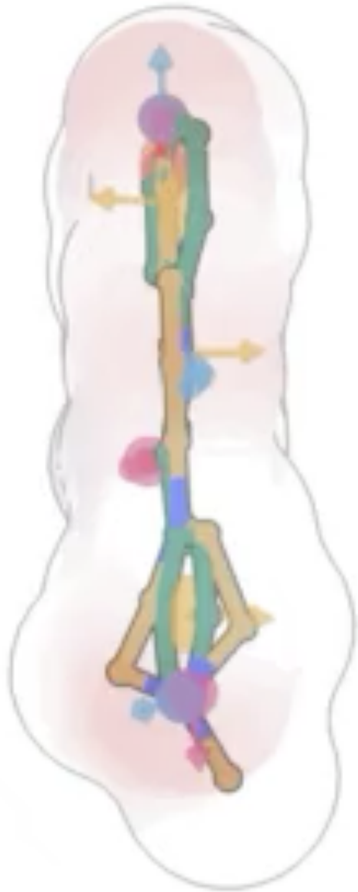
- preserve important molecular scaffolds and protein-ligand interactions;
- modify specific molecular scaffold;
- explore fragments with better complementarity to the binding pocket;



Introduction

Structure-based molecular generation allows to:

- preserve important molecular scaffolds and protein-ligand interactions;
- modify specific molecular scaffold;
- explore fragments with better complementarity to the binding pocket;
- control the generation process



Introduction

Current limitations:

- generative models are not always integrated into the practical workflow of structure-based ligand optimization;

Introduction

Current limitations:

- generative models are not always integrated into the practical workflow of structure-based ligand optimization;
- currently, generated molecules often require additional postprocessing and evaluation, including docking, filtering, and structural inspection;

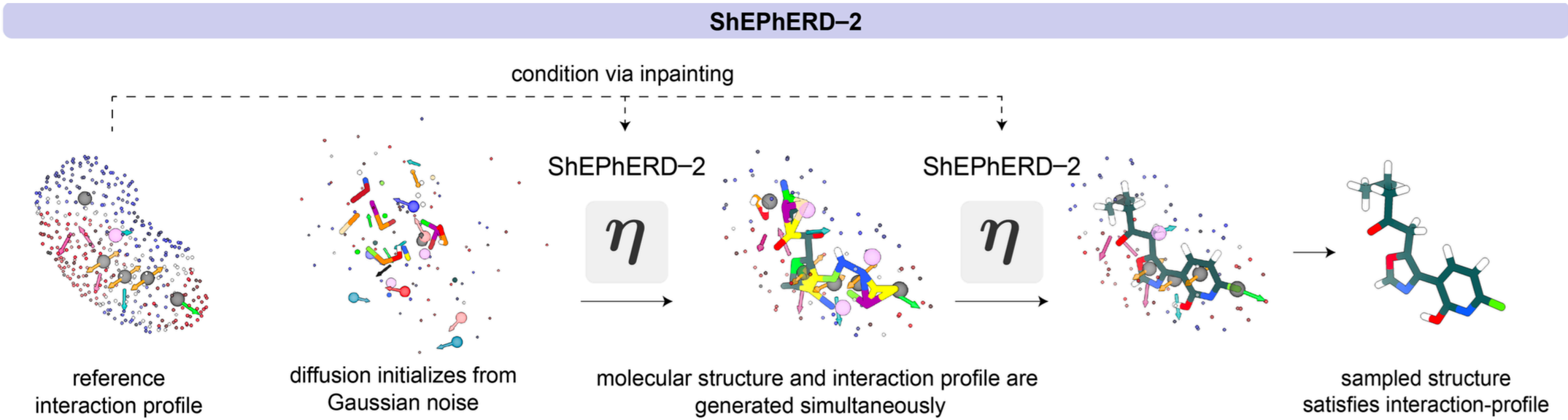
Introduction

ShEPhERD

SPELL

Conclusions

ShEPhERD


ShEPhERD–2
condition via inpainting
ShEPhERD–2
ShEPhERD–2
reference
interaction profile
diffusion initializes from
Gaussian noise
molecular structure and interaction profile are
generated simultaneously
sampled structure
satisfies interaction-profile

Introduction

ShEPhERD

SPELL

Conclusions

SPELL

Shape-**P**harmacophore-**E**lectrostatic **L**igand **L**earner

SPELL integrates:

- Molecular visualization: graphical interface of protein-ligand complex
- Controlled 3D generation: customize parameters for generation
- Structural conditioning: fragment generation preserving key interactions with a protein
- Results evaluation: medicinal chemistry aware metrics, docking, and more

Ligand Pro

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Projects
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Patents
API

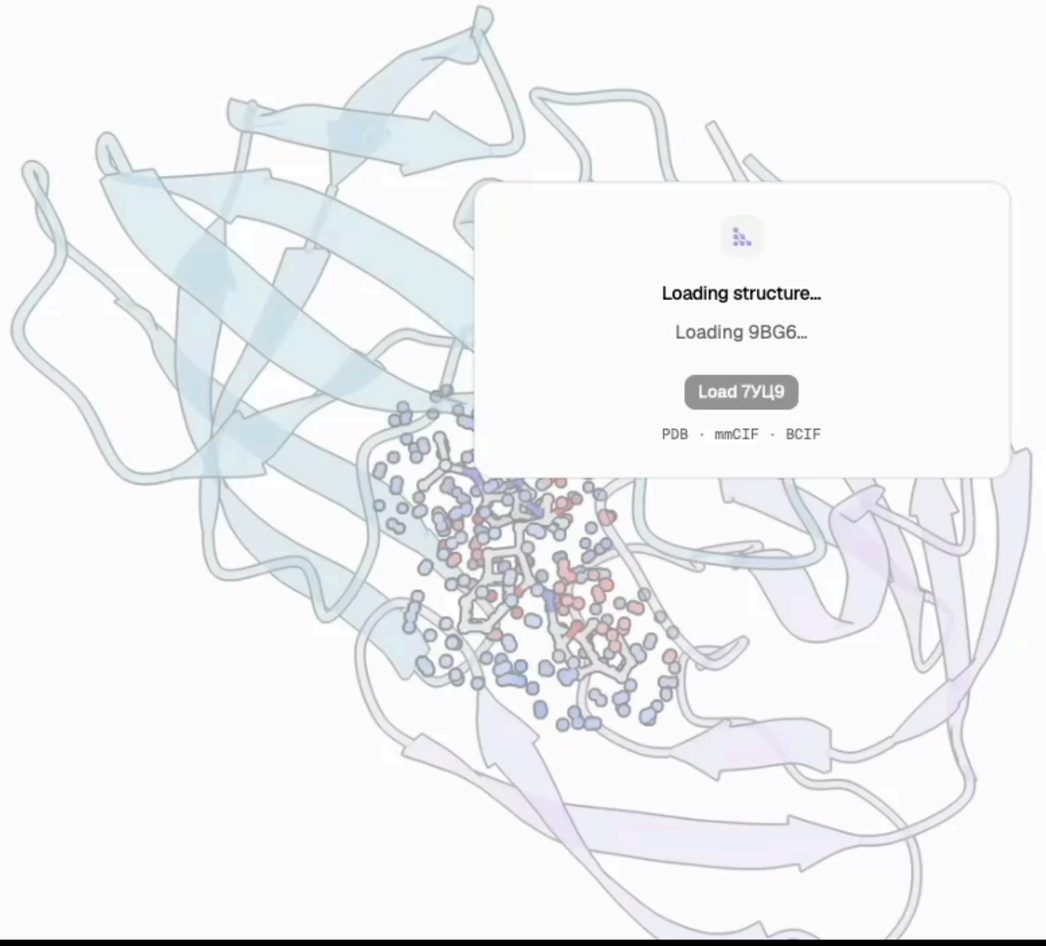
D d.ryabchenko
d.ryabchenko

https://app.ligandpro.ru/workflows/generation

Workflows > Generation

EN

SPELL 7УЦ9 Load Loading 9BG6...



Load structure
Activity Manuals

Ligand-based Protein-based

Generation Molecules

Upload a molecule or load a protein.

Ligand Pro

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Workflows > Generation

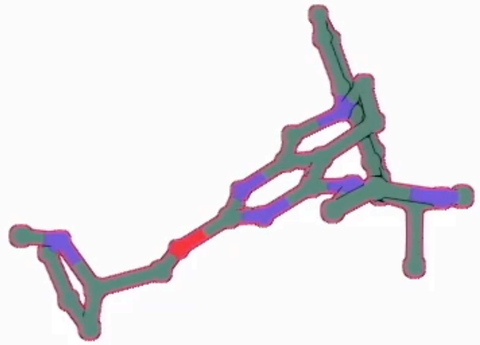
EN

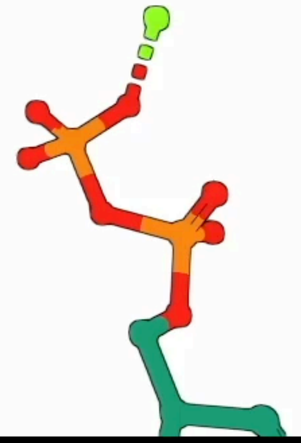
SPELL 7EW9 Load Loaded 7EW9. Select a ligand in the stage.

Automatic Symmetry Dark

SCENE

7EW9 1512 elements
Polymer 1345 elements
Cartoon
Ligand 65 elements
Ball & Stick
Water 102 elements
Ion 1 element
Ball & Stick
Null
Null
Unit Cell P 1 21 1
Measurements





05C (asym E) Activity Manuals

Ligand-based Protein-based

Generation Molecules

Generation
05C · whole ligand
Start generation



GDP

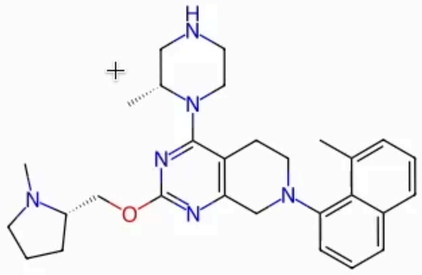
MgH_2 MG

Surface & selection

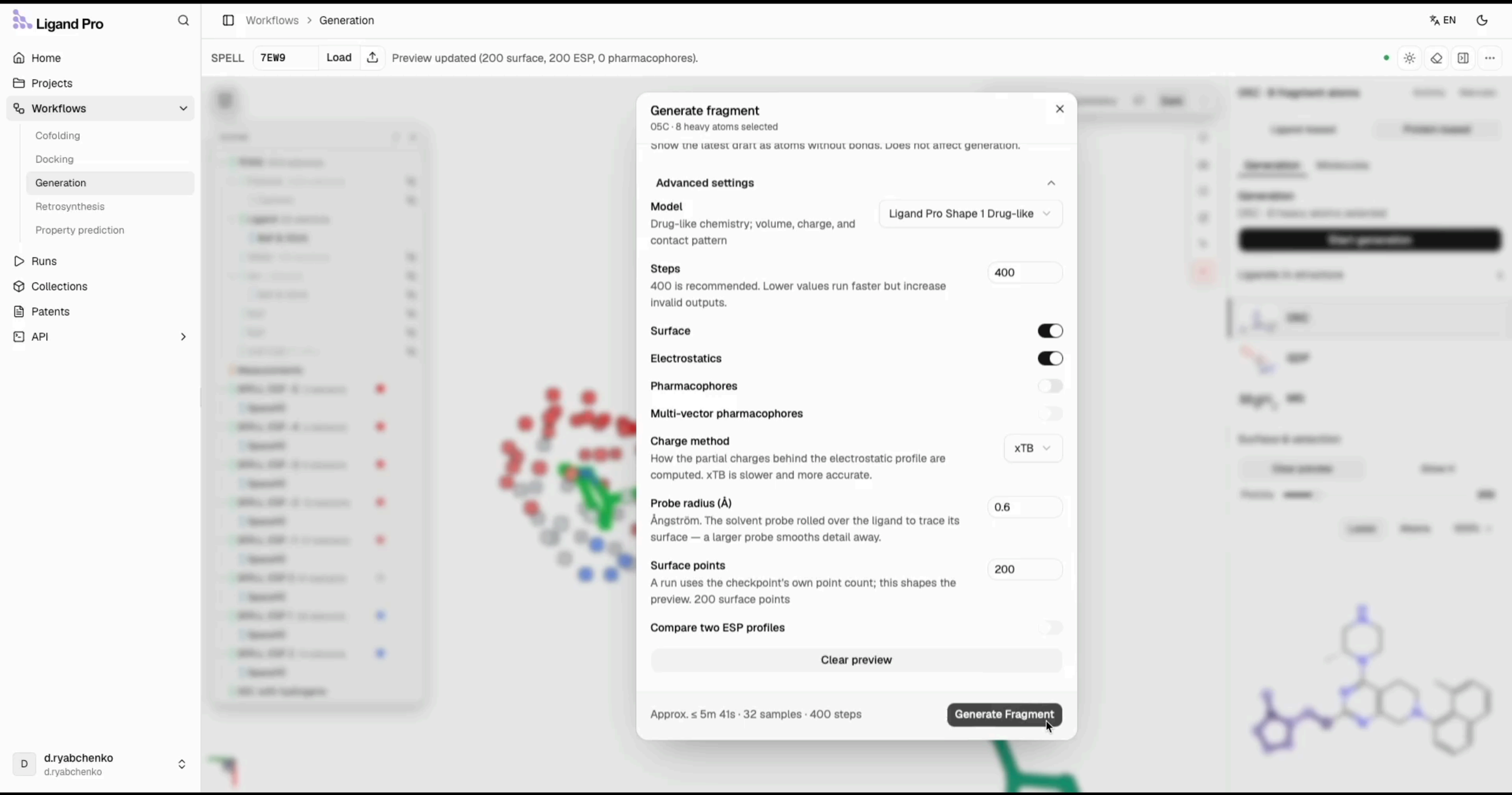
Preview surface Show H

Points 200

Lasso Atoms 100%

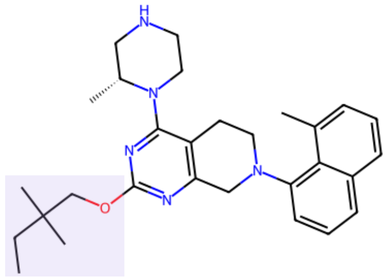
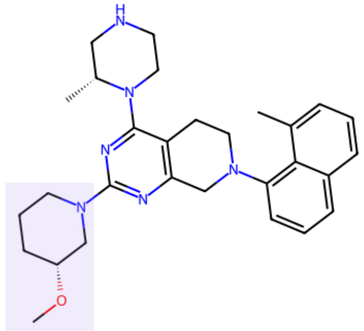
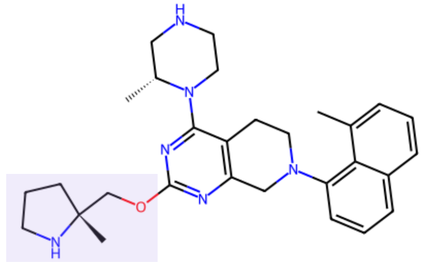
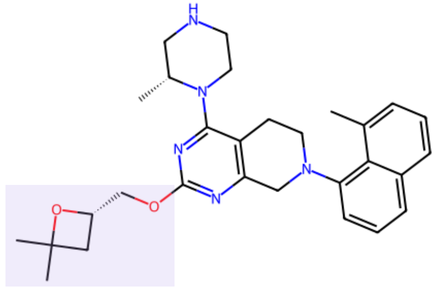
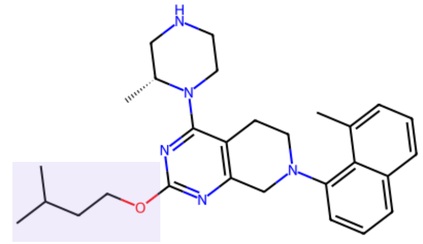
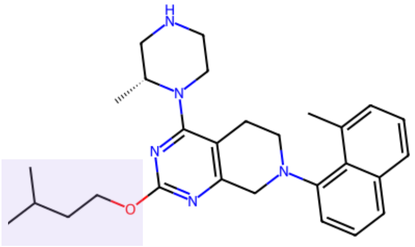
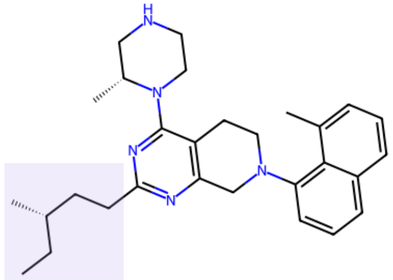
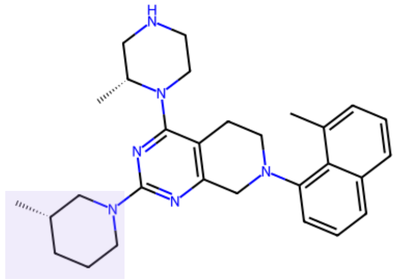
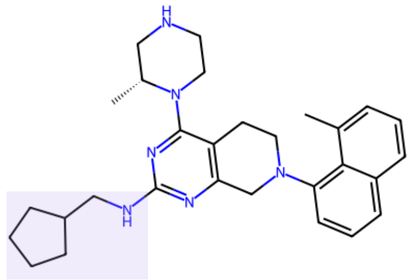
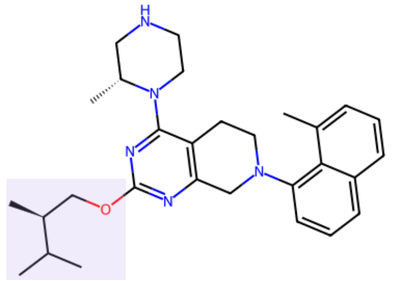
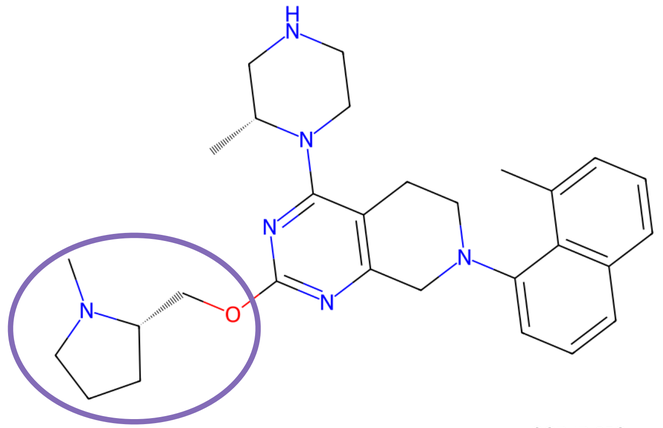


Cc1cccc2cccc(N3CCc4c(nc(OC[C@@H]5CCCN5


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Workflows > Generation
EN
SPELL
7EW9
Load
Preview updated (200 surface, 200 ESP, 0 pharmacophores).
Generate fragment
05C · 8 heavy atoms selected
Show the latest draft as atoms without bonds. Does not affect generation.
Advanced settings
Model
Drug-like chemistry; volume, charge, and contact pattern
Ligand Pro Shape 1 Drug-like
Steps
400 is recommended. Lower values run faster but increase invalid outputs.
400
Surface
Electrostatics
Pharmacophores
Multi-vector pharmacophores
Charge method
How the partial charges behind the electrostatic profile are computed. xTB is slower and more accurate.
xTB
Probe radius (Å)
Ångström. The solvent probe rolled over the ligand to trace its surface — a larger probe smooths detail away.
0.6
Surface points
A run uses the checkpoint's own point count; this shapes the preview. 200 surface points
200
Compare two ESP profiles
Clear preview
Approx. ≤ 5m 41s · 32 samples · 400 steps
Generate Fragment

SPELL

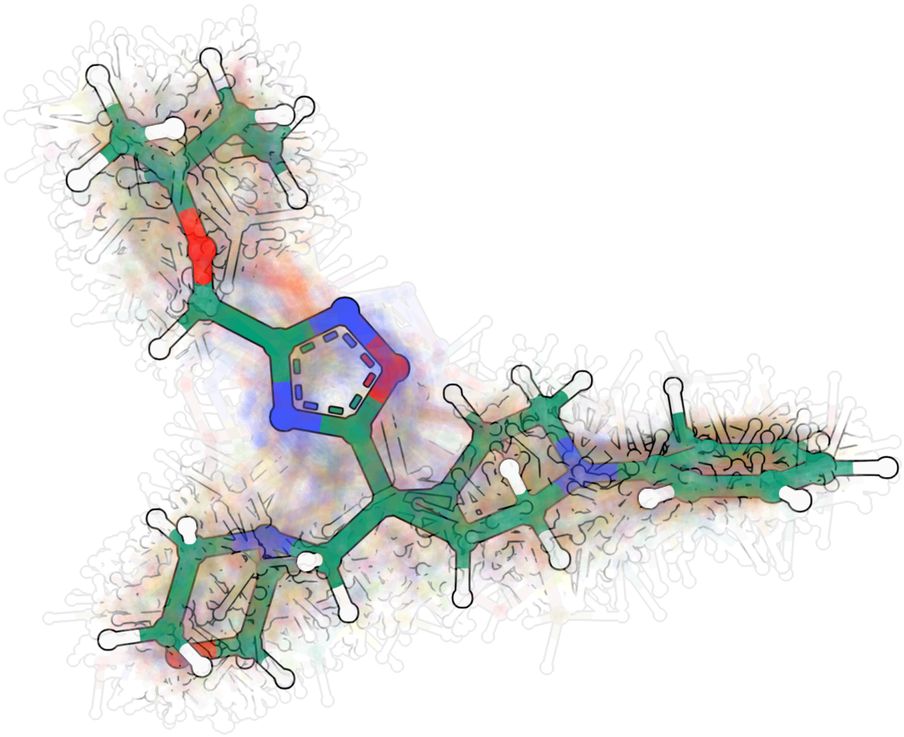
Examples of fragment replacement

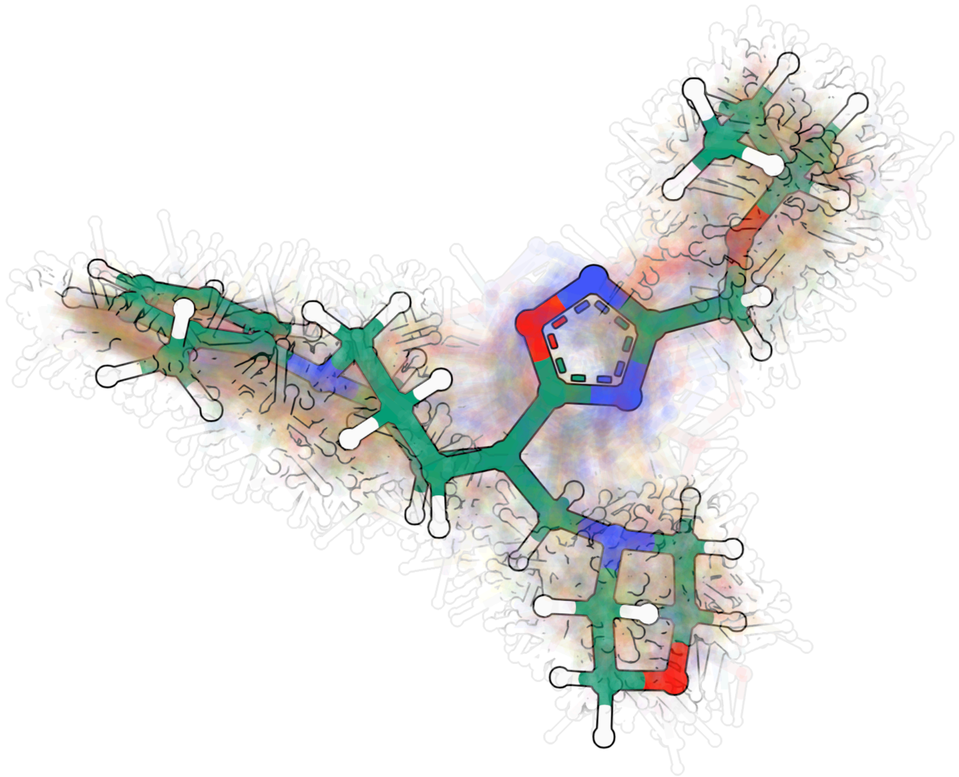












CCD ID 05C

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Perfect reference shape matching





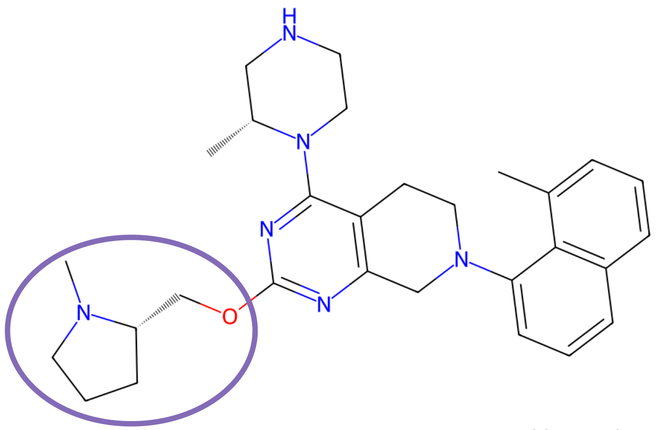
SPELL

Results

Fragment replacement (inpainting). Each setup asked for 100 molecules to be generated

	Validity	Uniqueness	Novelty, %	FCD	SNN* to KRAS	Similarity to ligand	Internal diversity
Generation from scratch, molecules	85	85	100	23.65	0.208	0.157	0.834
Inpainting, molecules	95	77	100	19.47	0.486	0.663	0.350

*SNN - similarity to the nearest neighbor, по Morgan fingerprints к GDB17. Less -> less similar



CCD ID 05C

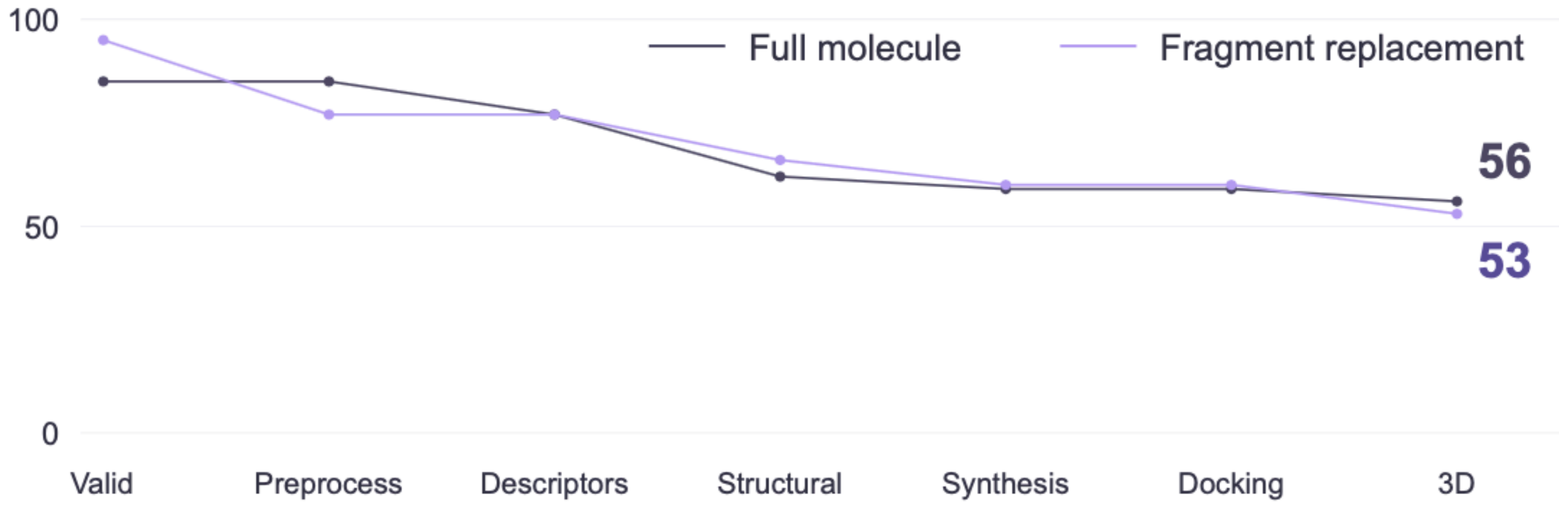
SPELL

Results

HEDGEHOG (accepted *Briefings in Bioinformatics*).

Each model generated 100 molecules .

	Initial	Preprocessing	Descriptors	Structural Filters	Synthesis Feasibility	Docking	3D Filters
Generation from scratch, molecules	85	85	77	62	59	59	56
Inpainting, molecules	95	77	77	66	60	60	53



SPELL

Results

ShEPhERD VS ShEPhERD2 VS SPELL

	validity,% ↑	uniqueness,%↑	novelty,% ↑	FCD	SNN*	QED↑	Time, s/mol↓
ShEPhERD	**85.3±1.2**	99.8±0.1	94.6±0.6	8.8±0.2	0.42±0.00	0.58±0.01	12.1±0.1
ShEPhERD2	82.8±0.7	**100.0±0.0**	**100.0±0.0**	18.7±0.6	0.29±0.00	**0.75±0.00**	2.1±0.1
Ours	70.6±0.6	**100.0±0.0**	97.8±0.7	4.1±0.1	0.38±0.00	0.59±0.00	**0.3±0.0**

*SNN - similarity to the nearest neighbor, по Morgan fingerprints к GDB17. Less -> less similar

Introduction

ShEPhERD

SPELL

Conclusions

Conclusions

1) SPELL addresses controlled ligand modification by connecting an interactive 3D viewer, local fragment replacement, structural conditioning, and candidate analysis in one workflow.

2) In our initial comparison, fixed-scaffold inpainting increased the number of valid outputs and kept generated structures closer to the reference, with a corresponding reduction in diversity.

3) We presented our own SPELL generative model, which demonstrates promising results in terms of generation speed, uniqueness, novelty, and FCD compared with the models included in our benchmark.

4) The next step is to expand model support and evaluate the approach on broader design problems.

Research Team

https://ligandpro.ru/en

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