XXXI Symposium on
Bioinformatics and Computer-Aided
Drug Discovery
20 - 22 October, 2025 | **Oral presentation**

Ligand Pro | Skoltech
Skolkovo Institute of Science and Technology

Do-No-Harm Molecular Generation: 12-Model Benchmark and KRAS G12D Case Study

Presented by: D. Ryabchenko[1,2], podariya12@gmail.com
Joint work with: P. Gurevich[1,2], S. Kadyrov[1], O. Tinkov[1], S. Nikolenko[1], D. Frolova[1,2], A. Shapeev[1,2], M. Pak[1,2]

[1]*Ligand Pro, Moscow, Russia;*
[2]*Skolkovo Institute of Science and Technology, Moscow, Russia*

Monday, 20th October, 2025

Moscow, 2025

INTRODUCTION

FIVE-STAGE FILTERING PIPELINE

RESULTS

CONCLUSION & DISCUSSION

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CONCLUSION & DISCUSSION

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Molecule Generation

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- Generate a small molecule, known as *ligand*, that is
  - chemically valid, synthesizable,
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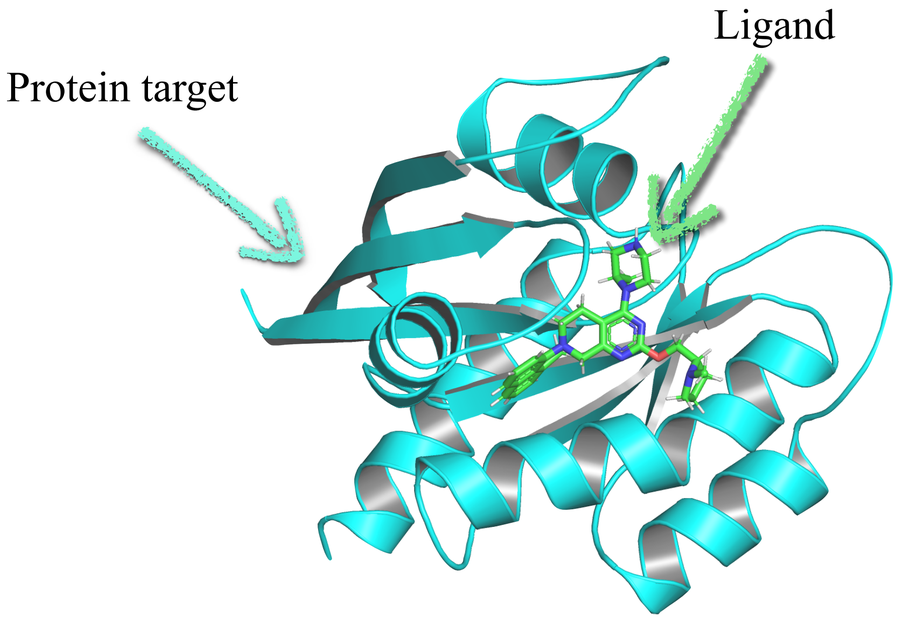

source: KRAS G12D molecule,
provided by the author, illustrated via PyMol

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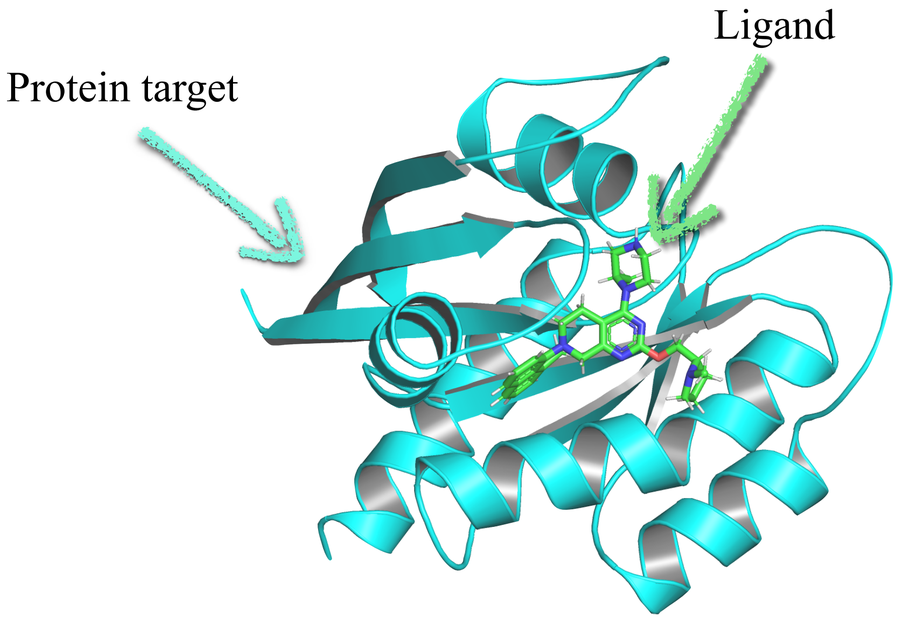

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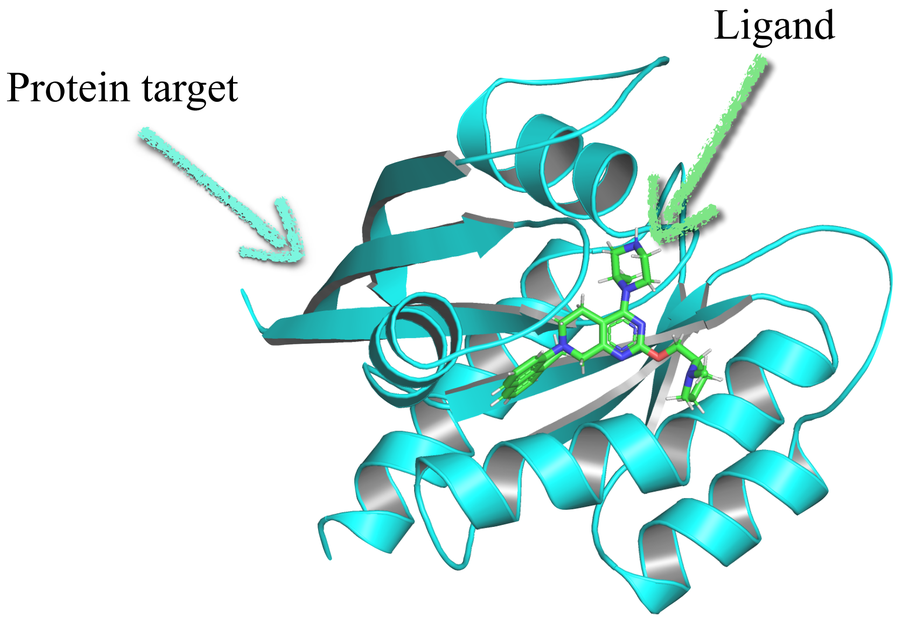
- **SOLUTION:** Comprehensive, practice-oriented benchmark for evaluation under realistic medicinal chemistry constraints



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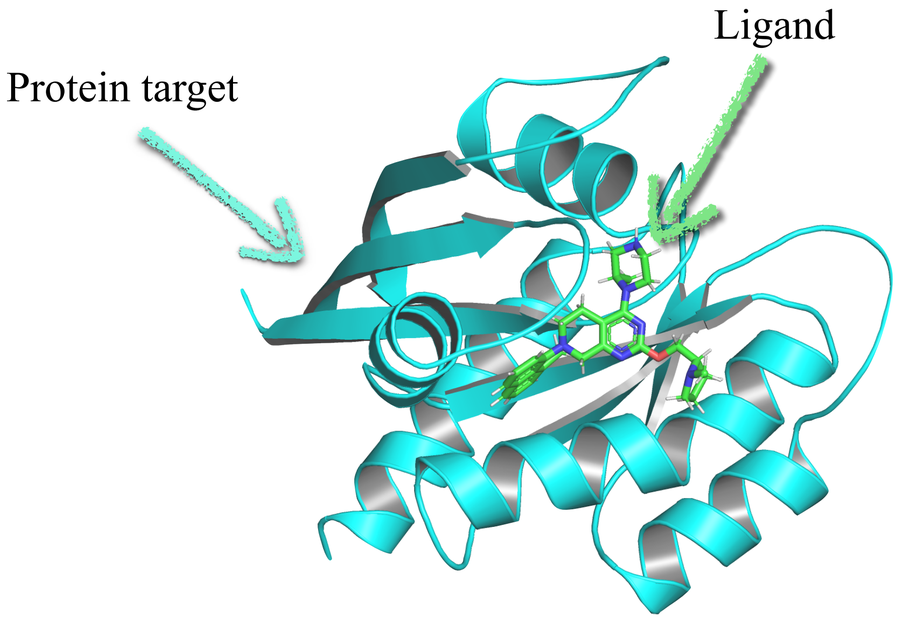

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- **PRESENTING:** Molecule generators and their performance evaluation via *Five-Stage Filtering Pipeline*. Reproducible pipelines will be released on our GitHub (https://github.com/LigandPro)

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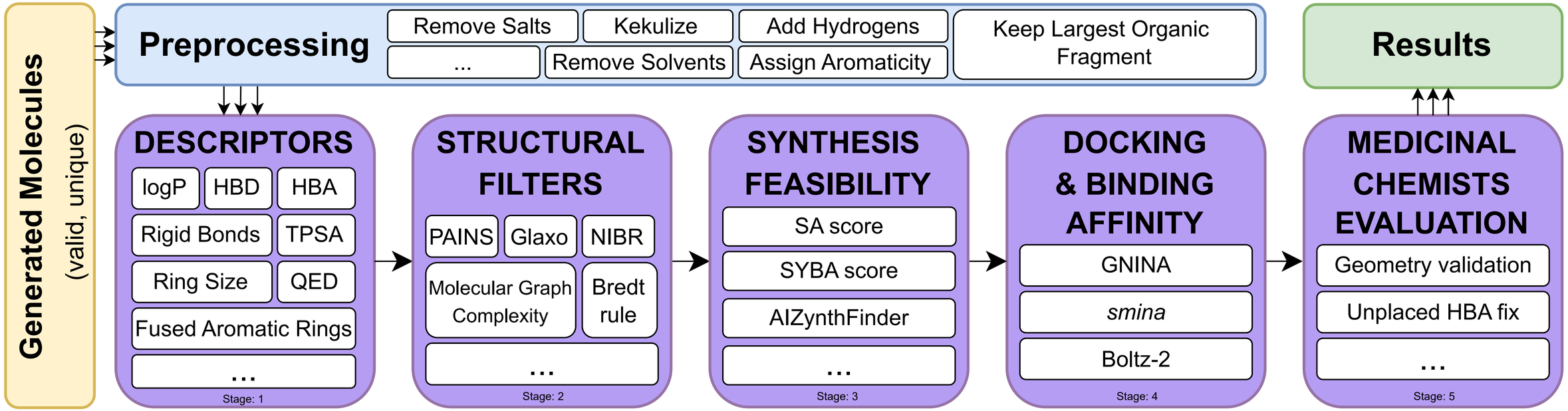

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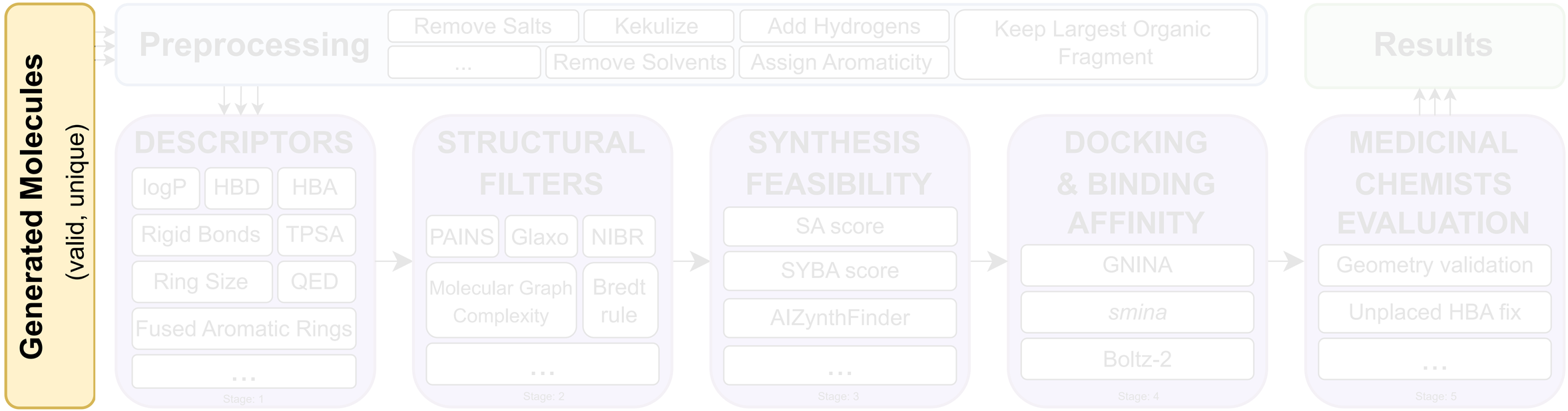
Five-Stage Filtering Pipeline

Generate Molecules



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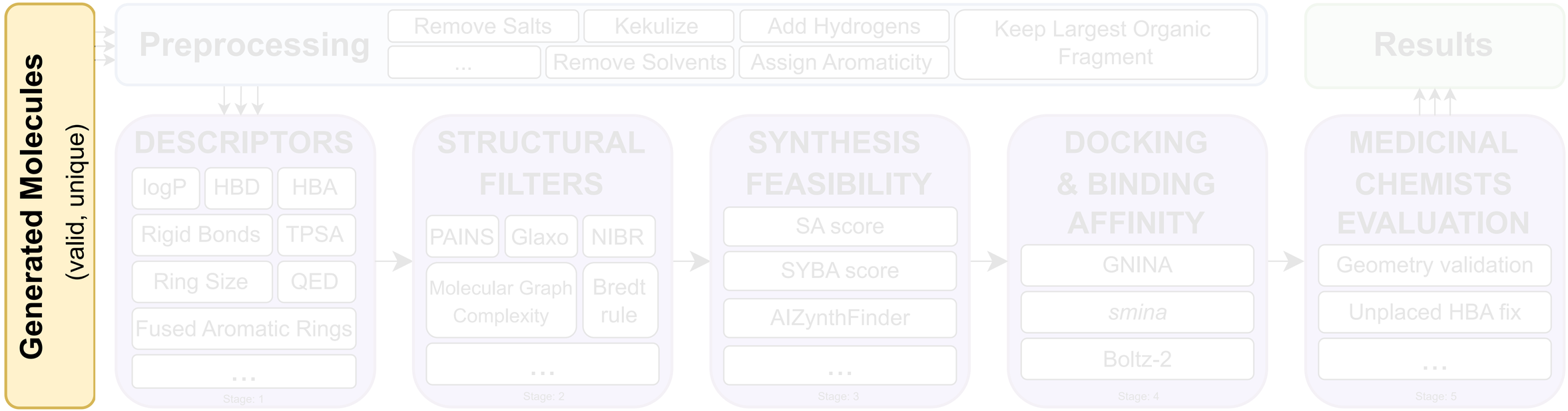
Five-Stage Filtering Pipeline

Generate Molecules

- Baseline models collection of *ligand-based,* and *protein-based* models (total 12 models).



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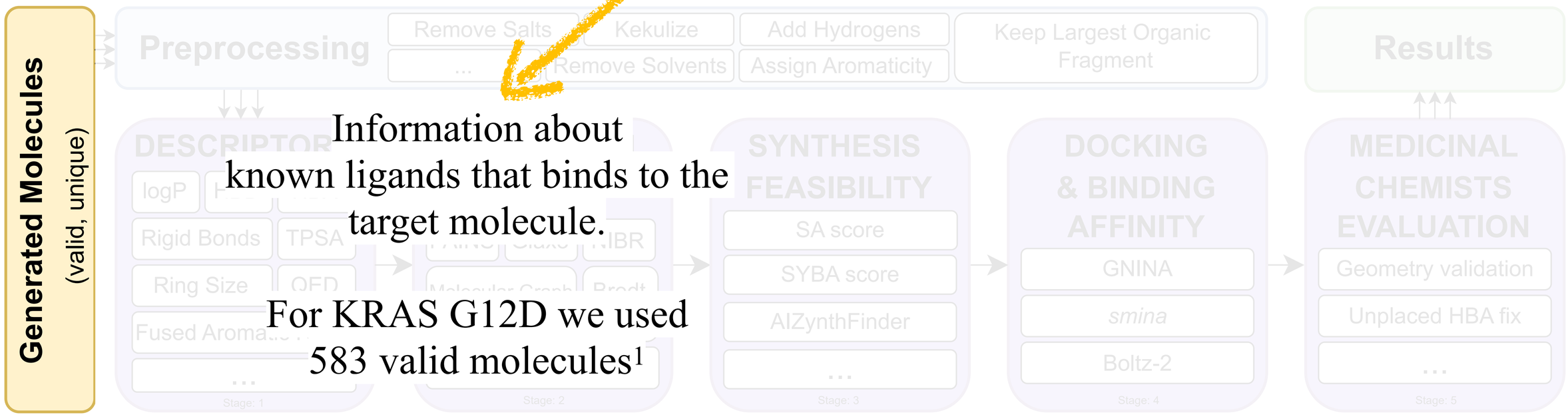

Information about known ligands that binds to the target molecule.

For KRAS G12D we used 583 valid molecules[1]

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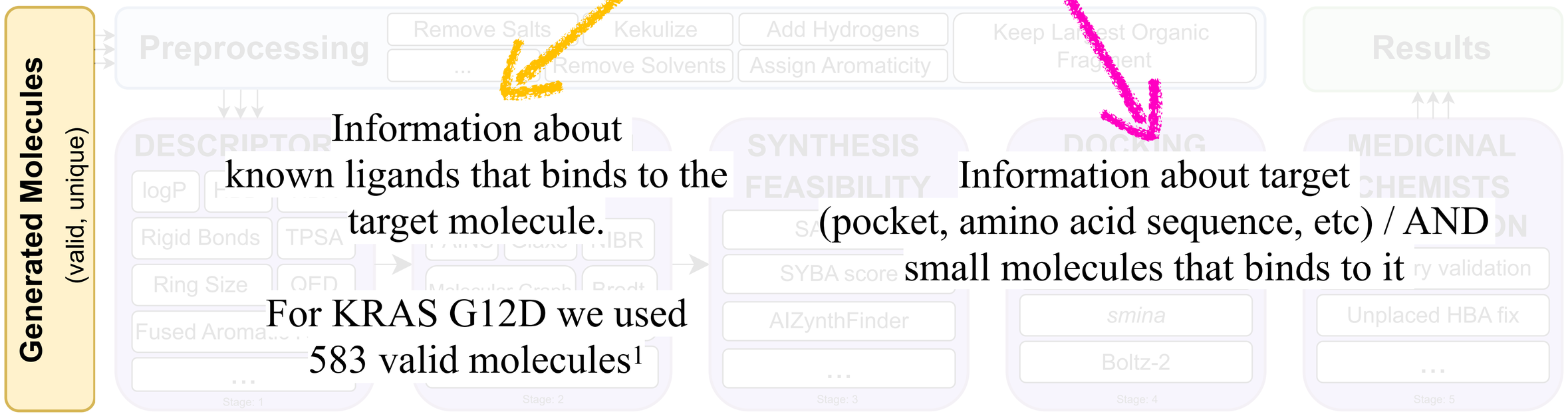

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Information about target (pocket, amino acid sequence, etc) / AND small molecules that binds to it

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Five-Stage Filtering Pipeline

Generate Molecules

Table 1: Taxonomy of molecular generators considered in our benchmark, by model class (rows) and primary input representation (columns)

Architecture /Model Type	LIGAND-BASED	PROTEIN-BASED
Genetic Algorithm	MolFinder (Kwon & Lee, 2021)	—
Variational Autoencoder	GENTRL (Zhavoronkov et al., 2019)	—
Autoregressive	GCPG (Zou et al., 2025) PGMG (Zhu et al., 2023) REINVENT4 (Loeffler et al., 2024)	Dragonfly (Atz et al., 2024) Pocket2Mol (Peng et al., 2022) ResGen (Zhang et al., 2023)
Diffusion	—	DiffSBDD (Schneuing et al., 2024) ProtoBind-Diff (Mistryukova et al., 2025) TargetDiff (Guan et al., 2023)
Flow matching	—	DrugFlow (Schneuing et al., 2025)

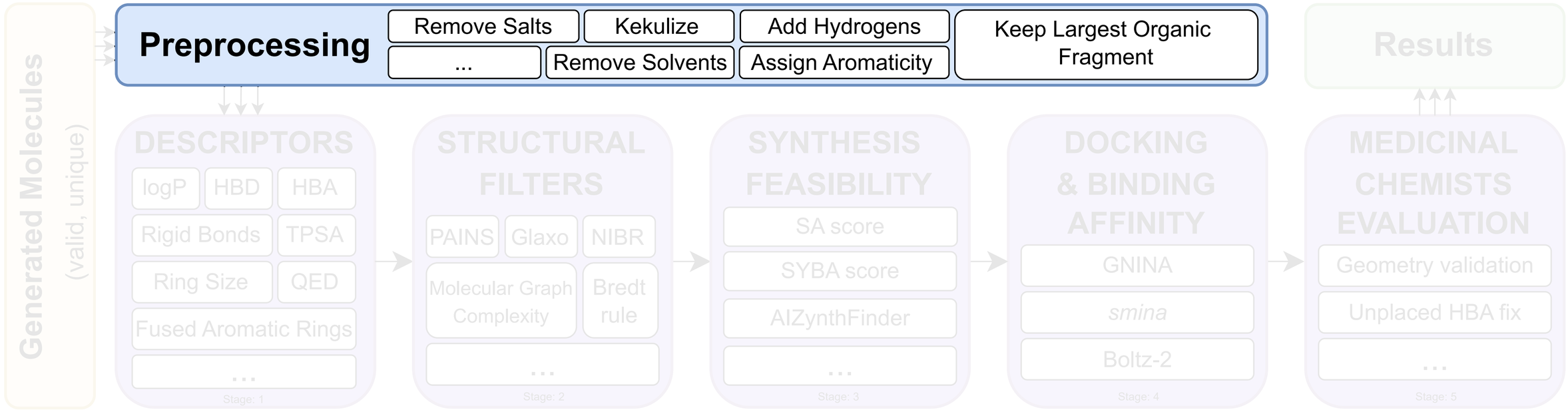
Generated Molecules (valid, unique)

Each model generates **10,000 unique and valid molecules** for further evaluation

source: provided by the author

Five-Stage Filtering Pipeline

Molecules Preprocessing



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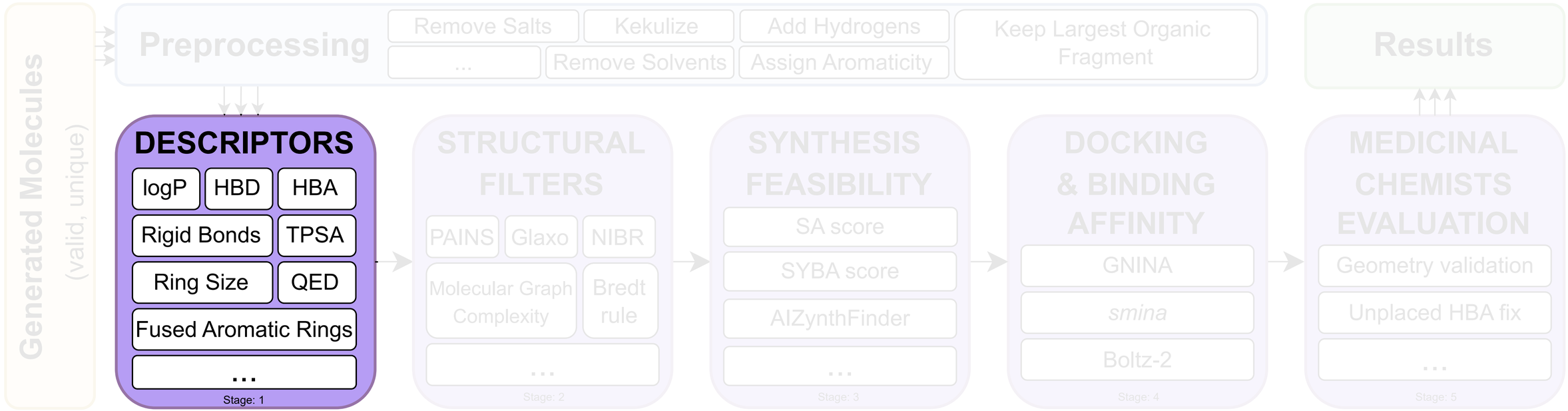
Five-Stage Filtering Pipeline

Stage 1: Descriptors



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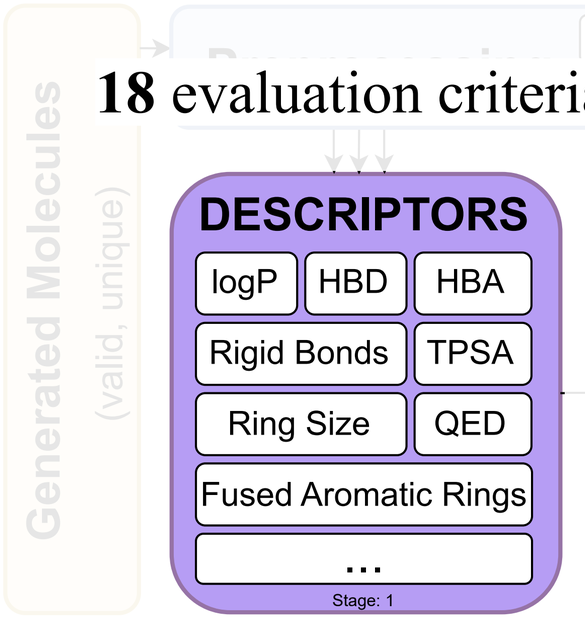
Five-Stage Filtering Pipeline

Stage 1: Descriptors

18 evaluation criteria



Metric	Threshold
Chars	$[C, N, S, O, F, Cl, Br, H]$
#atoms	$[10, 100]$
#heavy atoms	$[10, 50]$
#hetero atoms	$[2, 15]$
#Nitrogen atoms	$[0, 10]$
MW	$[100, 1000]$
logP	$[-2, 10]$
ring size	$[3, 12]$
#rings	$[0, 8]$
#aroma rings	$[0, 5]$
#fused aroma rings	$[0, 2]$
#rigid bonds	$[0, 30]$
#RotB	$[2, 8]$
HBD	≤ 5
HBA	$[3, 12]$
f_{sp^3}	$[0.15, 0.8]$
TPSA	$[40, 140]$
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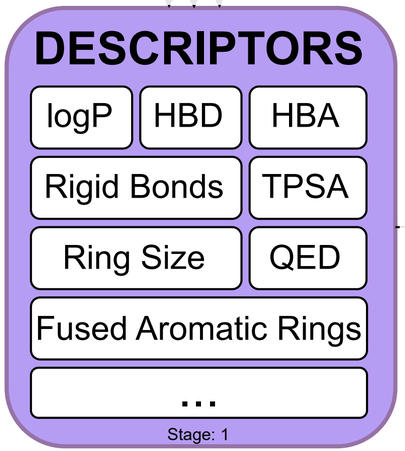

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source: provided by the author

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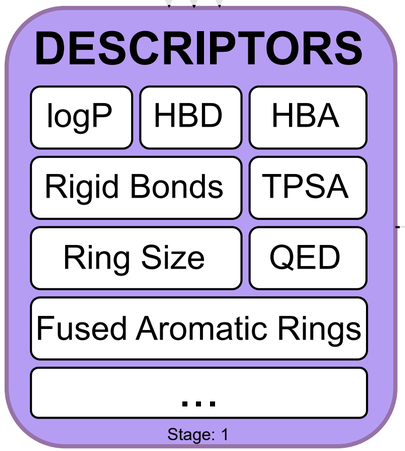

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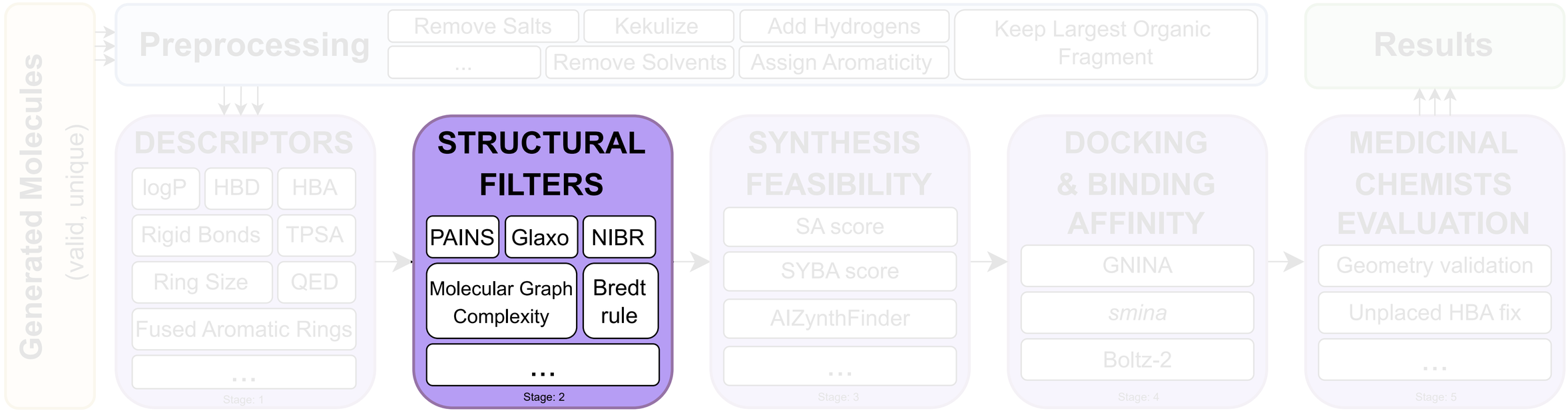
Molecules passed *Stage 1* go to the *Stage 2*

Five-Stage Filtering Pipeline

Stage 2: Structural Filters



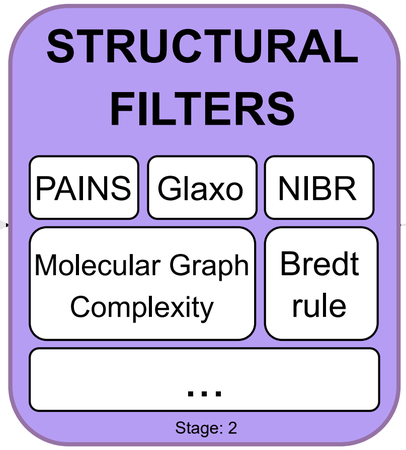
source: provided by the author

Five-Stage Filtering Pipeline

Stage 2: Structural Filters

5 rule sets and
~2500 SMARTS patterns

Rule set
Common Alerts
MolGraph statistics
MolComplexity
NIBR
Bredt



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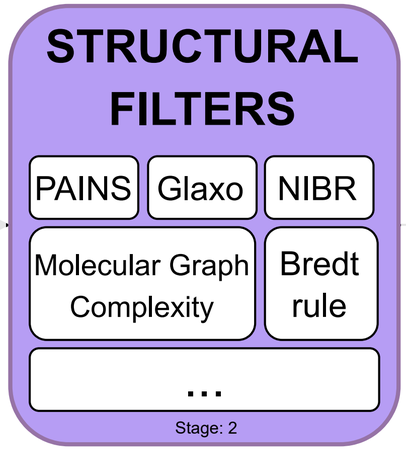
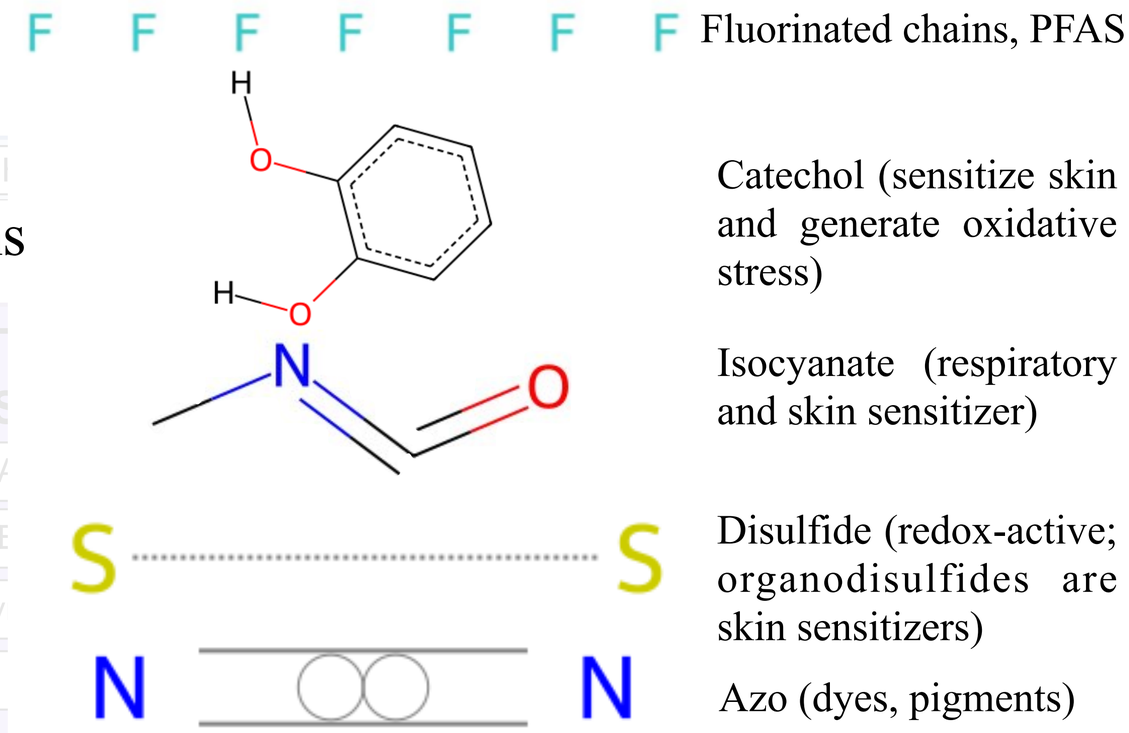


Toxic or reactive chemical substructures



Fluorinated chains, PFAS

Catechol (sensitize skin and generate oxidative stress)

Isocyanate (respiratory and skin sensitizer)

Disulfide (redox-active; organodisulfides are skin sensitizers)

Azo (dyes, pigments)

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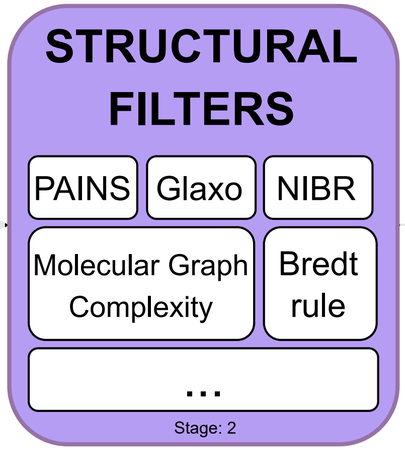


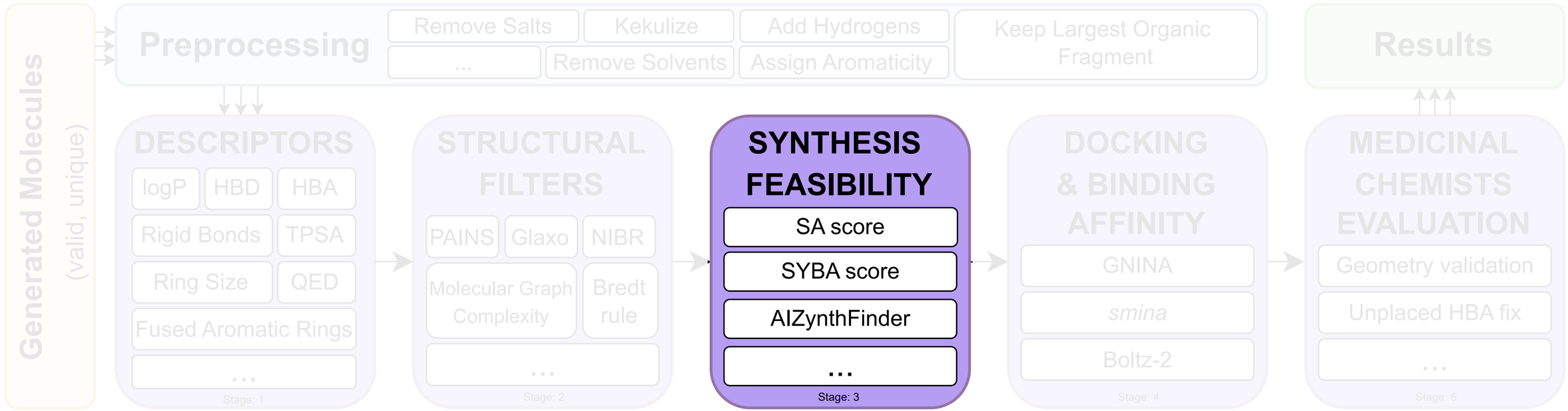
A molecule should not contain **ANY** of prohibited SMARTS patterns to pass the 2nd filtering stage

source: provided by the author

Molecules passed *Stage 2* go to the *Stage 3*

Five-Stage Filtering Pipeline

Stage 3: Synthesis Feasibility



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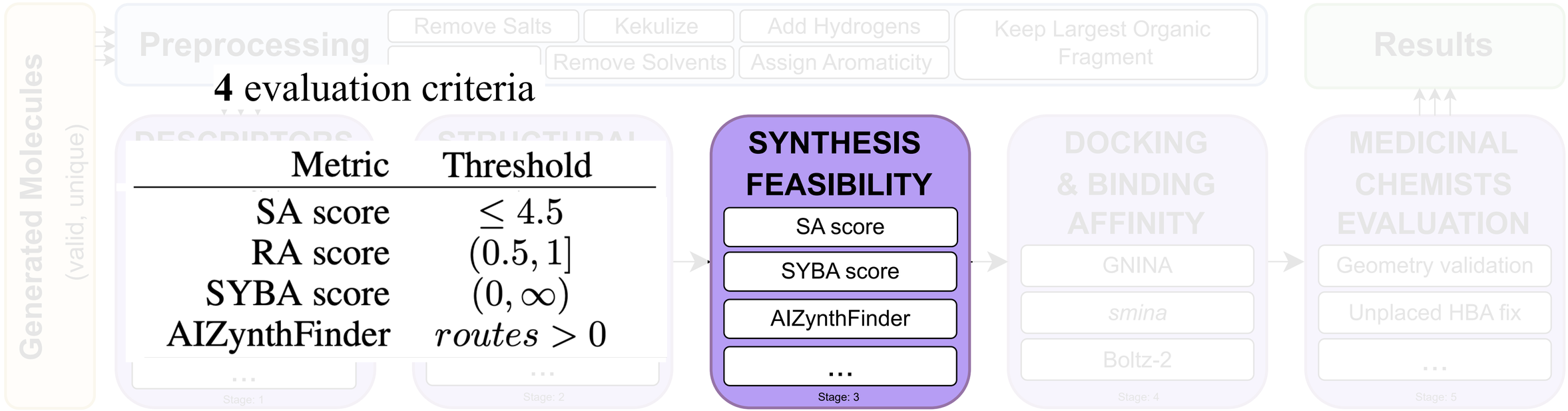

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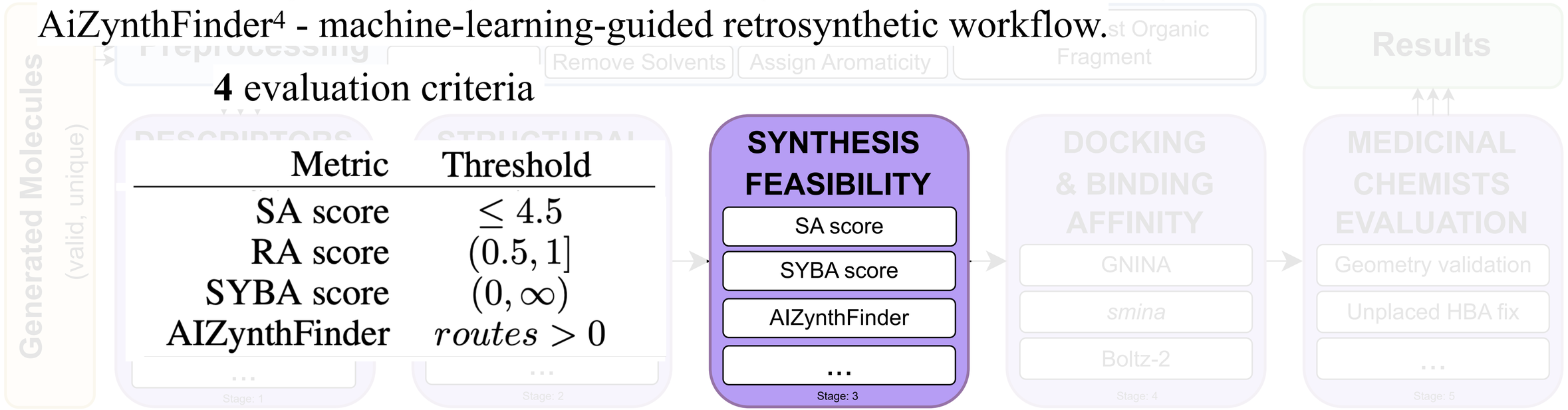
Five-Stage Filtering Pipeline

Stage 3: Synthesis Feasibility

SA score - Synthetic Accessibility score[1] - synthetic complexity score from 1 (easy) to 10 (hard).
RA score - Retrosynthetic Accessibility score[2] - probability of being a synthetic path for a compound.
SYBA score - Synthetic Bayesian Accessibility score[3] - classifier as easy or hard to synthesize.
AiZynthFinder[4] - machine-learning-guided retrosynthetic workflow.

4 evaluation criteria

Metric	Threshold
SA score	≤ 4.5
RA score	$(0.5, 1]$
SYBA score	$(0, \infty)$
AIZynthFinder	$routes > 0$



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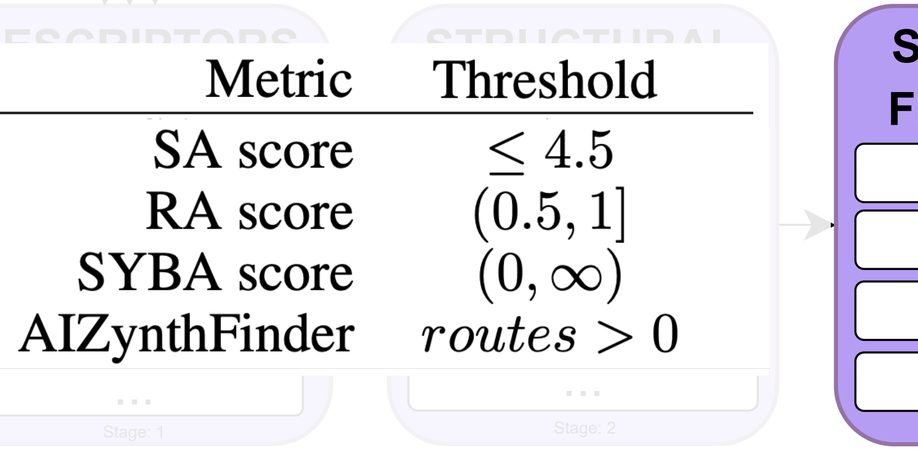

A molecule should pass all synthetic feasibility criteria **simultaneously** to pass the 3rd filtering stage

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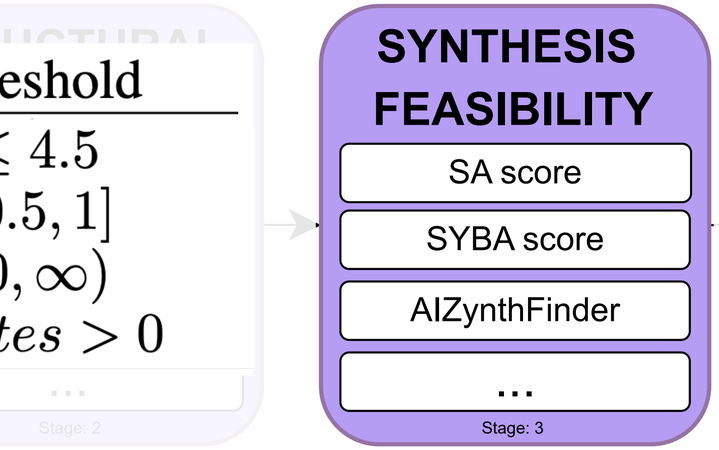

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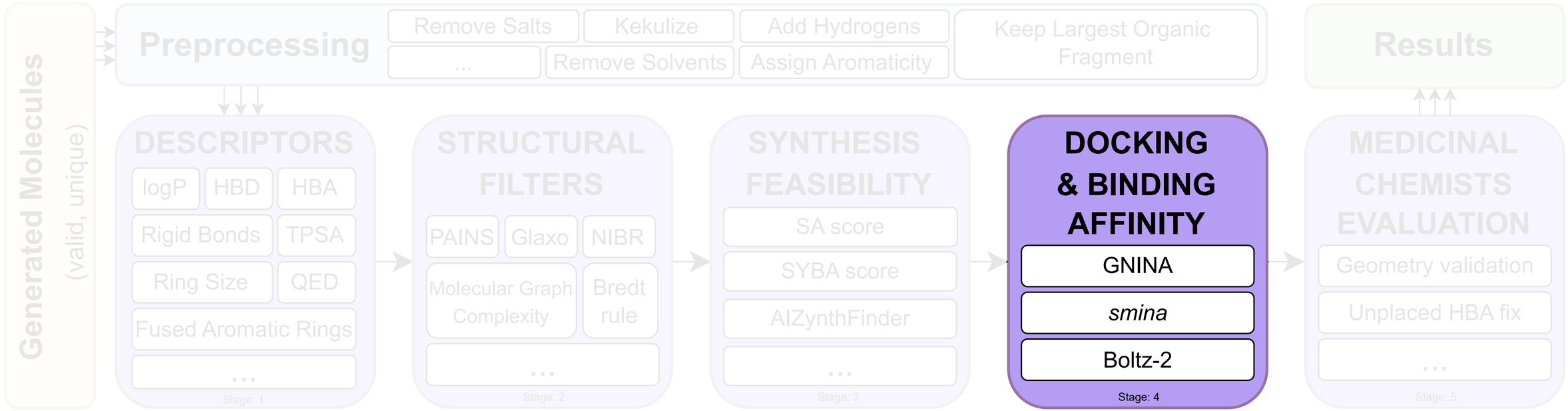
Five-Stage Filtering Pipeline

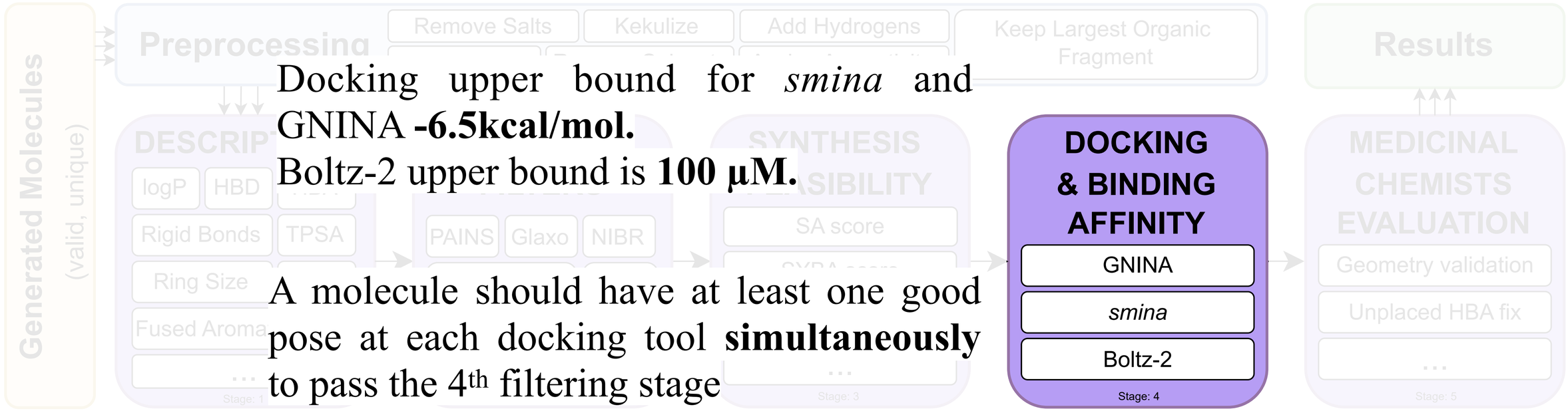
Stage 4: Docking and Binding Affinity Estimation



source: provided by the author

Five-Stage Filtering Pipeline

Stage 4: Docking and Binding Affinity Estimation



Docking upper bound for *smina* and GNINA **-6.5kcal/mol.**
Boltz-2 upper bound is **100 μM.**

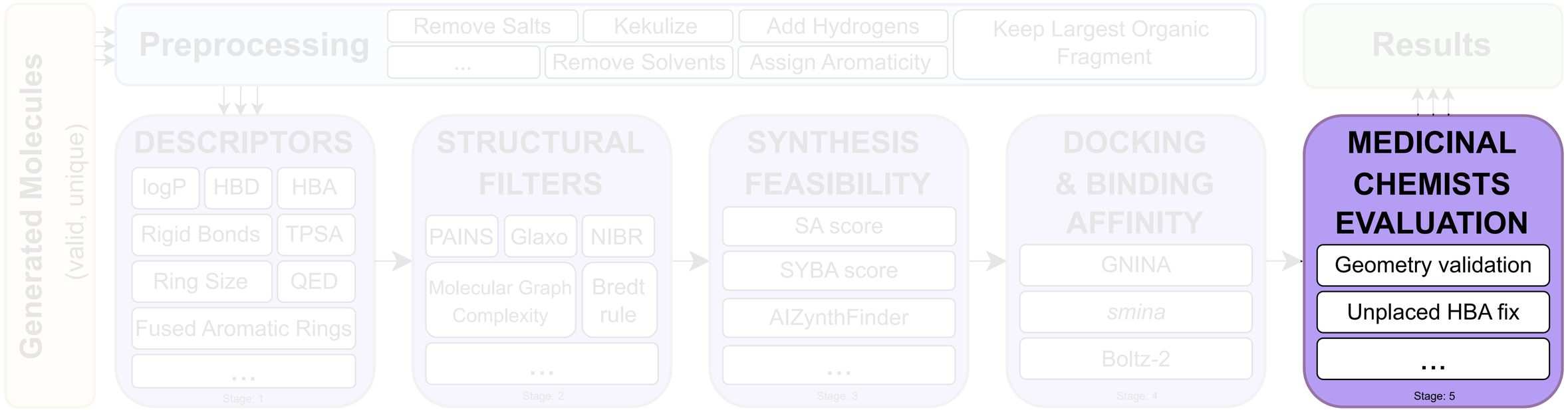
A molecule should have at least one good pose at each docking tool **simultaneously** to pass the 4th filtering stage

source: provided by the author

Molecules passed *Stage 4* go to the *Stage 5*

Five-Stage Filtering Pipeline

Stage 5: Medicinal Chemists Evaluation



source: provided by the author

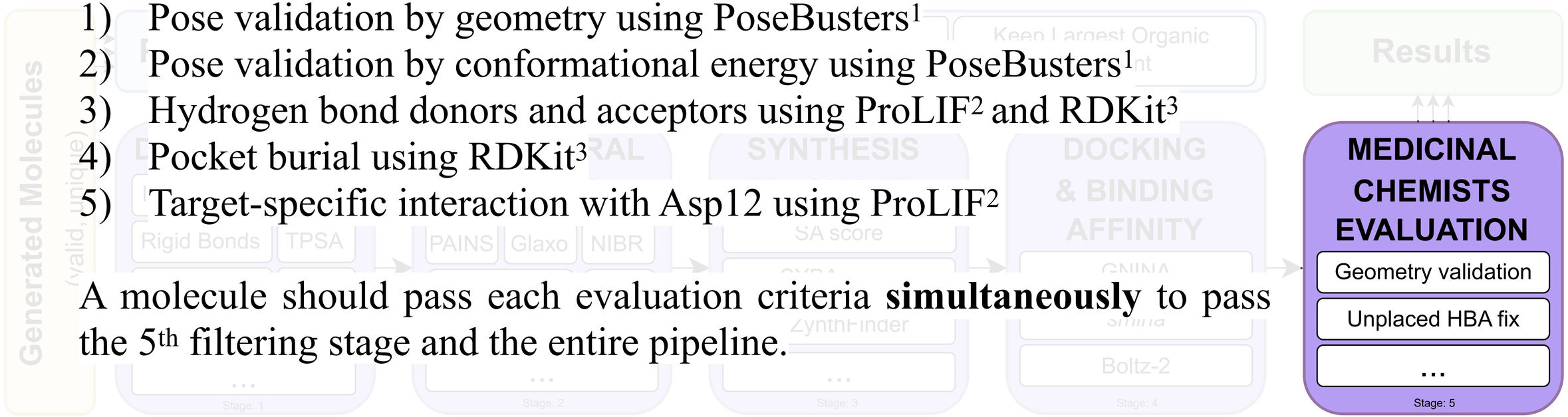
Five-Stage Filtering Pipeline

Stage 5: Medicinal Chemists Evaluation

Evaluation criteria:

1) Pose validation by geometry using PoseBusters[1]
2) Pose validation by conformational energy using PoseBusters[1]
3) Hydrogen bond donors and acceptors using ProLIF[2] and RDKit[3]
4) Pocket burial using RDKit[3]
5) Target-specific interaction with Asp12 using ProLIF[2]

A molecule should pass each evaluation criteria **simultaneously** to pass the 5th filtering stage and the entire pipeline.



[1]Martin Buttenschoen, Garrett M Morris, and Charlotte M Deane. Posebusters: Ai-based docking methods fail to generate physically valid poses or generalise to novel sequences. *Chemical Science*, 15(9):3130–3139, 2024.
[2]Ce´dric Bouysset and Se´bastien Fiorucci. Prolif: a library to encode molecular interactions as fingerprints. Journal of cheminformatics, 13(1):72, 2021.
[3]Greg Landrum. Rdkit documentation. *Release*, 1(1-79):4, 2013.

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12 models and 15 model setups

Table 2: Comparison of ligand-based models, each with initial number of N_{gen} = 10,000 molecules

Stage /Model	GCPG	GENTRL	MOLFINDER	PGMG	REINVENT4 (V)	REINVENT4 (P)	REINVENT4 (TL)
Descriptors	**6616**	5669	1592	195	4089	936	1204
Structural Filters	**4168**	1925	366	37	1325	593	413
Synthesis Feasibility	**1064**	303	265	22	918	222	276
Docking & Binding Aff.	**648**	238	200	19	518	72	164
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Table 3: Comparison of protein-based models, each with initial number of N_{gen} = 10,000 molecules

Stage /Model	DIFFSBDD	DRAGONFLY	DRAGONFLY (B)	DRUGFLOW	POCKET2MOL	PROTOBIND-DIFF	RESGEN	TARGETDIFF
Descriptors	3665	2779	1022	**5464**	2657	1466	1080	3444
Structural Filters	197	**1459**	218	1392	682	195	255	136
Synthesis Feasibility	24	**1207**	38	453	137	102	62	4
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REINVENT4[1] (V, vanilla): unmodified, out-of-the-box model
REINVENT4 (P, prior): provided prior with mol2mol medium Tanimoto similarity threshold of 0.7
REINVENT4 (TL, transfer-learning): fine-tuned REINVENT4 (V) on 583 known KRAS G12D inhibitors[2]

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Dragonfly[3]: unmodified, out-of-the-box model
Dragonfly (b, biased): condition sampling on target compound descriptors

[1]Hannes H Loeffler, Jiazhen He, Alessandro Tibo, Jon Paul Janet, Alexey Voronov, Lewis H Mervin, and Ola Engkvist. Reinvent 4: modern ai–driven generative molecule design. *Journal of Cheminformatics*, 16(1):20, 2024.
[2]Mohammad Ghazi Vakili, Christoph Gorgulla, Jamie Snider, AkshatKumar Nigam, Dmitry Bezrukov, Daniel Varoli, Alex Aliper, Daniil Polykovsky, Krishna M Padmanabha Das, Huel Cox Iii, et al. Quantum-computing-enhanced algorithm unveils potential kras inhibitors. *Nature Biotechnology*, pp. 1–6, 2025.
[3]Kenneth Atz, Leandro Cotos, Clemens Isert, Maria Ha˚kansson, Dorota Focht, Mattis Hilleke, David F Nippa, Michael Iff, Jann Ledergerber, Carl CG Schiebroek, et al. Prospective de novo drug design with deep interactome learning. *Nature Communications*, 15(1):3408, 2024.

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Descriptors	**6616**	5669	1592	195	4089	936	1204	20,301 / 70,000 = 29.0014
Structural Filters	**4168**	1925	366	37	1325	593	413	8,827 / 70,000 = 12.61
Synthesis Feasibility	**1064**	303	265	22	918	222	276	3,070 / 70,000 = 4.3857
Docking & Binding Aff.	**648**	238	200	19	518	72	164	1,859 / 70,000 = 2.6557
Med.Chem. Evaluation	**110**	24	7	4	93	17	32	287 / 70,000 = 0.41
Pass	**110**	**24**	**7**	**4**	**93**	**17**	**32**	

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Structural Filters	197	**1459**	218	1392	682	195	255	136	4,534 / 80,000 = 5.6675
Synthesis Feasibility	24	**1207**	38	453	137	102	62	4	2,027 / 80,000 = 2.5338
Docking & Binding Aff.	13	**575**	15	344	69	66	37	0	1,119 / 80,000 = 1.3988
Med.Chem. Evaluation	0	**227**	4	62	12	7	6	0	318 / 80,000 = 0.3975
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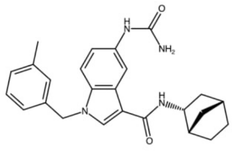
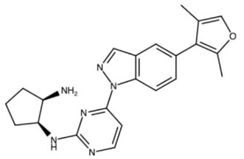
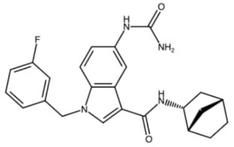


GCPG-07684
consensus score = 0.830



GCPG-00516
consensus score = 0.779



GCPG-06646
consensus score = 0.742

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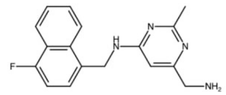
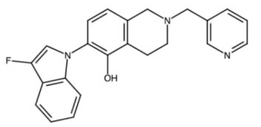
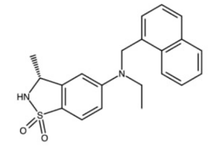


DrugFlow-03063
consensus score = 0.722



DrugFlow-08439
consensus score = 0.716



DrugFlow-04620
consensus score = 0.715

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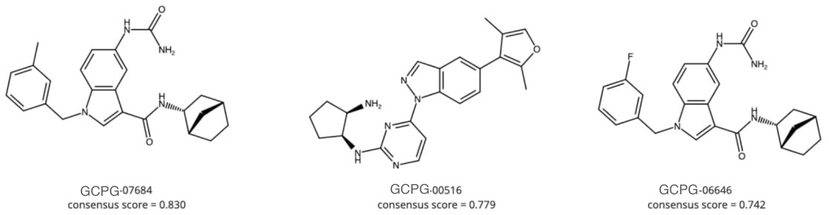

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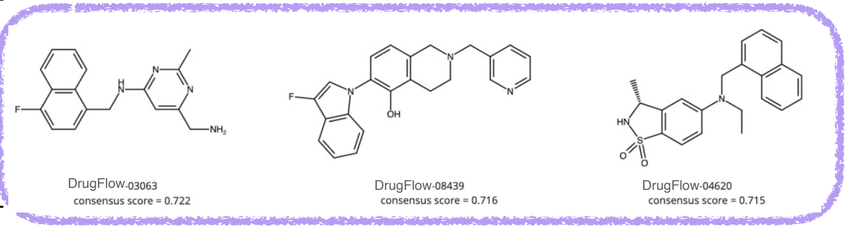

Small number of left molecules does not highlight overall poor performance. DrugFlow[1] molecules are 4th, 5th and 6th top molecules according to consensus score

[1]Arne Schneuing, Ilia Igashov, Adrian W Dobbelstein, Thomas Castiglione, Michael Bronstein, and Bruno Correia. Multi-domain distribution learning for de novo drug design. *arXiv preprint arXiv:2508.17815*, 2025.

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Conclusion and Discussion

- **Standard generative benchmarks are not good** proxies for real-world performance; optimizing for validity, synthesis or pocket fidelity independently is insufficient for actionable chemical space
- **Rigorous filtration** is essential for improving success rates and reducing costs by collecting and proceeding those molecules that meet chemical, medicinal, and task-dependent criteria
- Our *Five-Stage Filtering Pipeline* prioritizes **stress-testing** molecular generators against constraints that matter in early drug discovery
- Under our *Five-Stage Filtering Pipeline*, only a small fraction (less that 1%) of generated molecules pass all filters and remain applicable for future work

Research Team

https://ligandpro.ru/en

Ligand Pro | Skoltech

Skolkovo Institute of Science and Technology

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