SimulationsPlus

MIDD+22

Model Informed Drug Development

AIDD with External Models

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Please note: this presentation, including questions from the audience, is being recorded and may be made available.

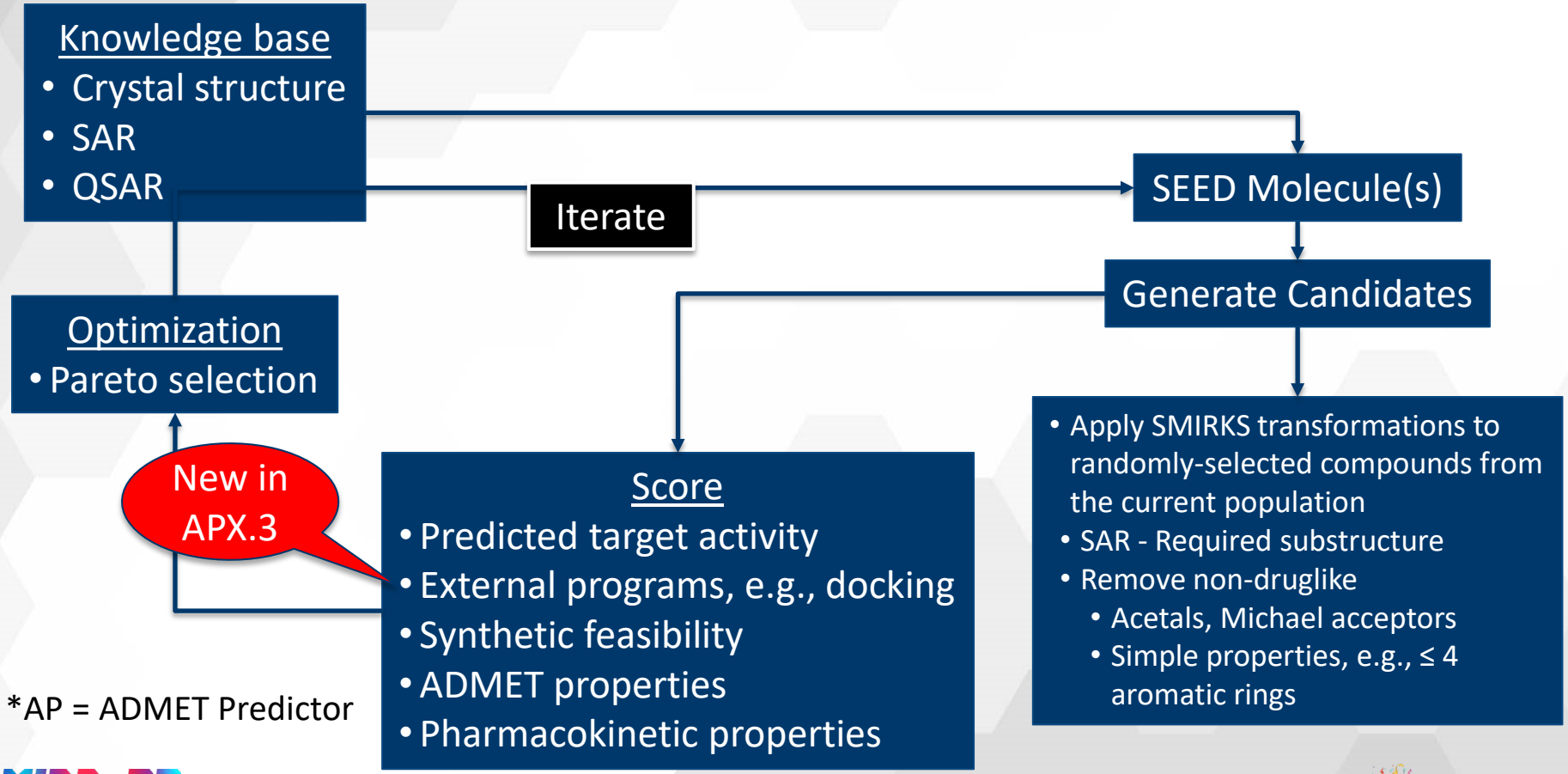
AIDD Module

Goal – design compounds that have:

- High potency at the primary target
- High synthetic feasibility
- Good ADMET and pharmacokinetic (PK) properties

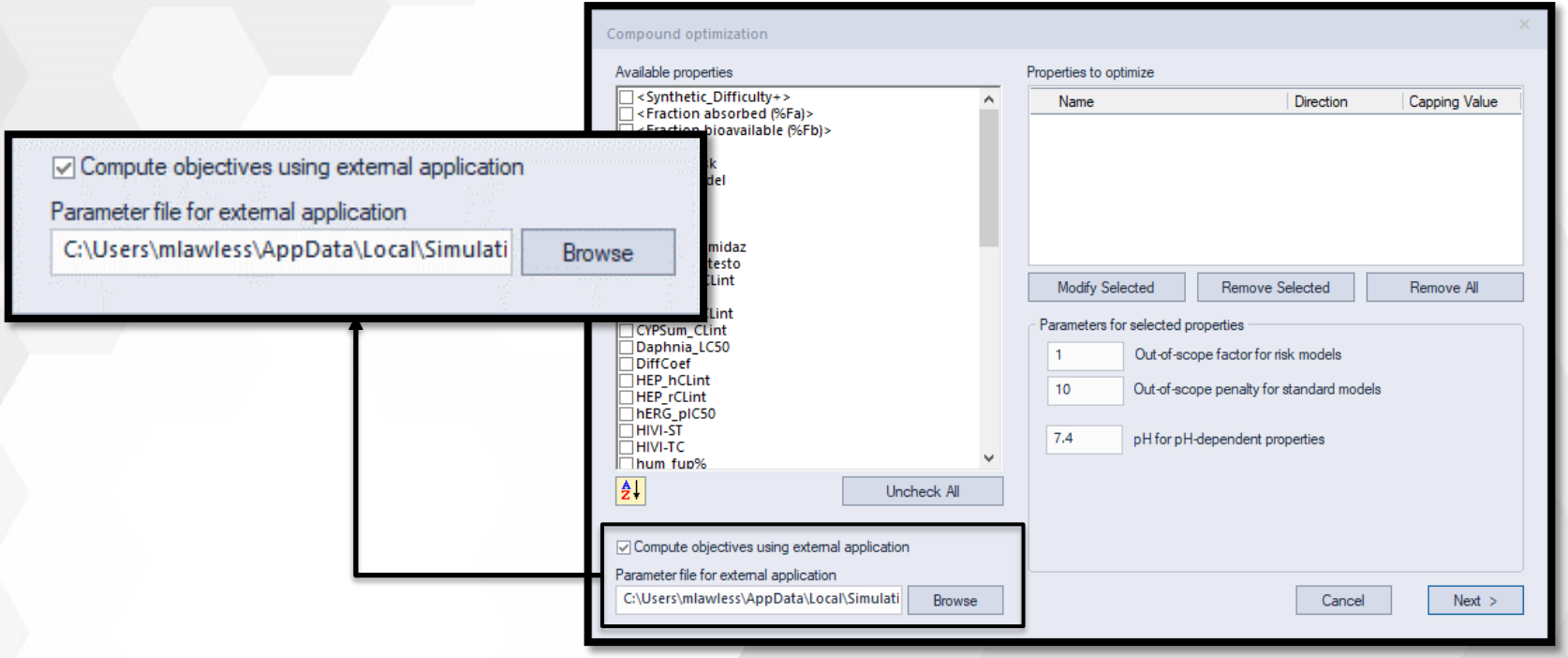
Can be used for hit finding, lead optimization, and scaffold hopping e.g., patent busting

AIDD Workflow



*AP = ADMET Predictor

AIDD External Application File



External File Parameters

filePathAlias – working directory

- Defines [PATH] variable
- Can be set to AIDD output directory

commandLine – script or executable program

- BAT or bash shell script

structureFile – name of file containing AIDD generated structures

- SDF or SMILES file

InputAttributes – comma separated list of AP attributes, e.g., S+logP, to be written to structure file

outputFile – name of temporary file containing 1 or more objective functions

- Created by external program

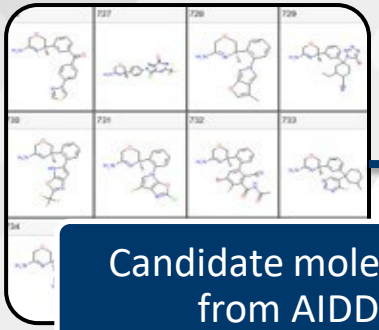
objectivesList – names of objective functions from external program

objectiveMaximize – 0 if minimum is preferred and 1 if maximum is preferred

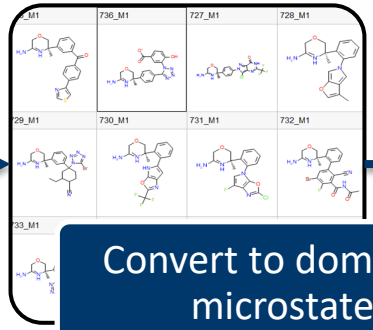
Acknowledgements

- AutoDock – Ravindranath PA, Forli S, Goodsell DS, Olson AJ, and Sanner MF. AutoDockFR: Advances in Protein-Ligand Docking with Explicitly Specified Binding Site Flexibility, *PLoS Computational Biology* **2015**, 11(12): e1004586.
- YASARA – Krieger E and Vriend G. YASARA View-molecular graphics for all devices-from smartphones to workstations, *Bioinformatics*, **2014**, 30(20), 2981-2982.
- Babel - O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: An open chemical toolbox. *J. Cheminf.* **2011**, *3*, 33.

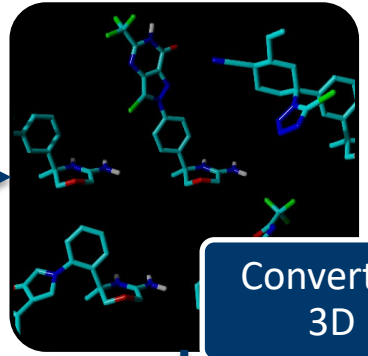
Workflow for AutoDock AIDD Example



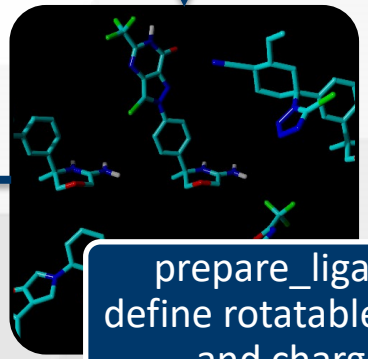
Candidate molecules from AIDD



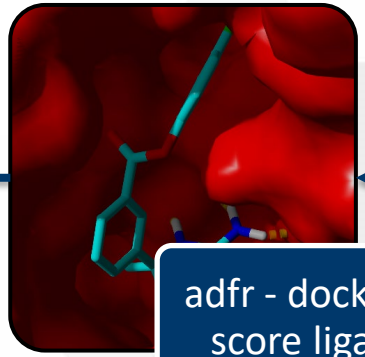
Convert to dominant microstate



Convert to 3D



prepare_ligand – define rotatable bonds and charges



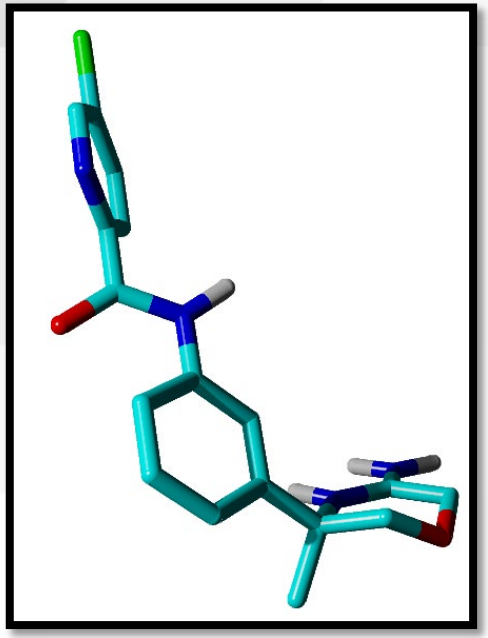
adfr - dock and score ligand

Return results to AIDD

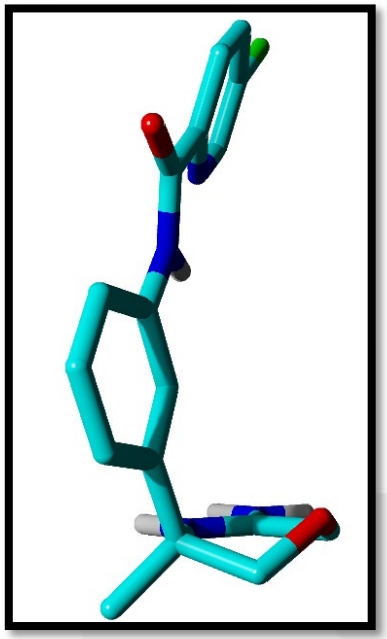
More on 3D Structure Generator

- Parameter file is first argument and parameters can be specified on the command line:
  - ADMET_Predictor.exe ms_generate_3d.txt –structureFile m.sdf –outputFile c_3D.sdf
- Multithreaded
- Multiple conformer generator
- MMFF94s force-field can be used to minimize structures
- 3D coordinates of ring systems can be specified in order to generate a specific ring conformation

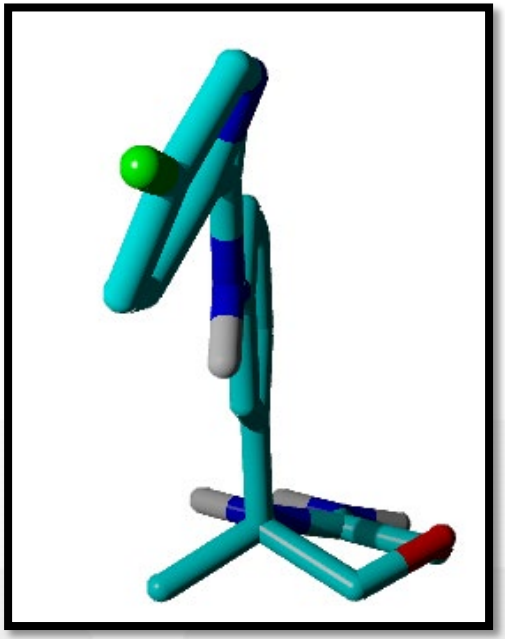
Dihydro-oxazine Conformation



Dihydro-oxazine oxygen is typically pointing “down” from 3D structure generators



Dihydro-oxazine oxygen points “up” in 6FGY and other oxazine crystal structures

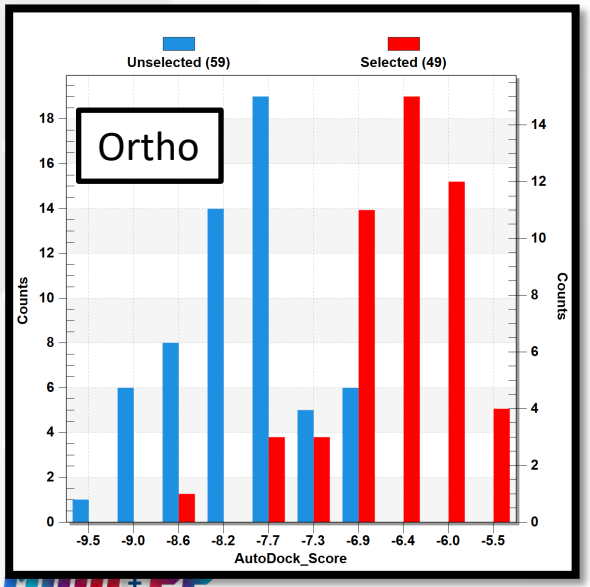


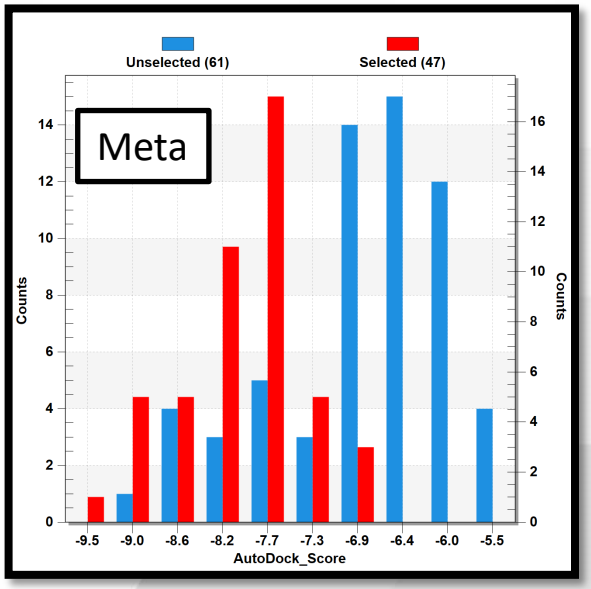
AP generated structure using dihydro-oxazine ring template

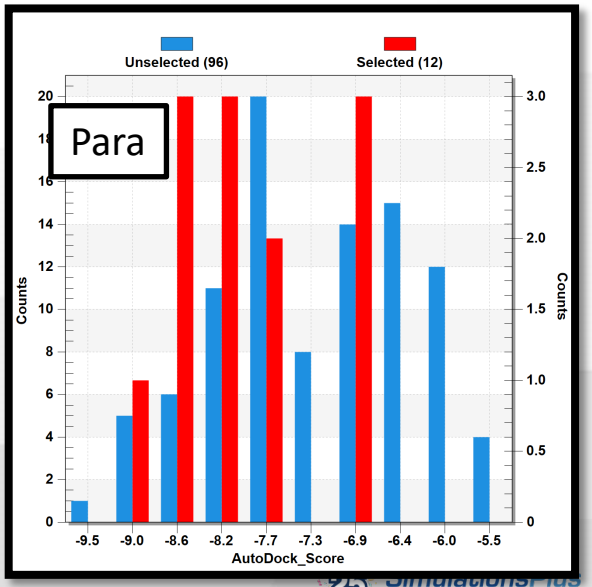
Docking Score Statistics

Phenyl substituent	Number	Best	Worst	Ave
Ortho	49	-8.5	-5.5	-6.5
Meta	47	-9.5	-7.0	-8.0
Para	12	-9.0	-6.8	-7.9

Meta substituents have best docking scores followed by molecules with substituents in the para position







AIDD with External Models

- The capabilities of the AIDD module have been expanded to include objective functions from external programs
- SDF or SMILES file of candidates from AIDD is written each generation
  - AP attributes can also be included
- AIDD External BAT or shell is called to execute other programs
- File containing results from external program is read into AIDD and included in Pareto optimization
- AIDD candidates were docked into a BACE1 crystal structure, and the scores were used as an objective function

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Q&A

Questions & Answers

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