

Fragment Evolution using SPROUT-HitOpt

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SPROUT Family

SPROUT

- Sophisticated *de novo* design tool
- Design new hit compounds from scratch within the active site of your target
- Build structures using imported fragments – recore as standard feature
- Excellent synergy with fragment-based hit discovery
- Predicts binding affinity and synthetic feasibility (via complexity analysis)
- Proven record of success

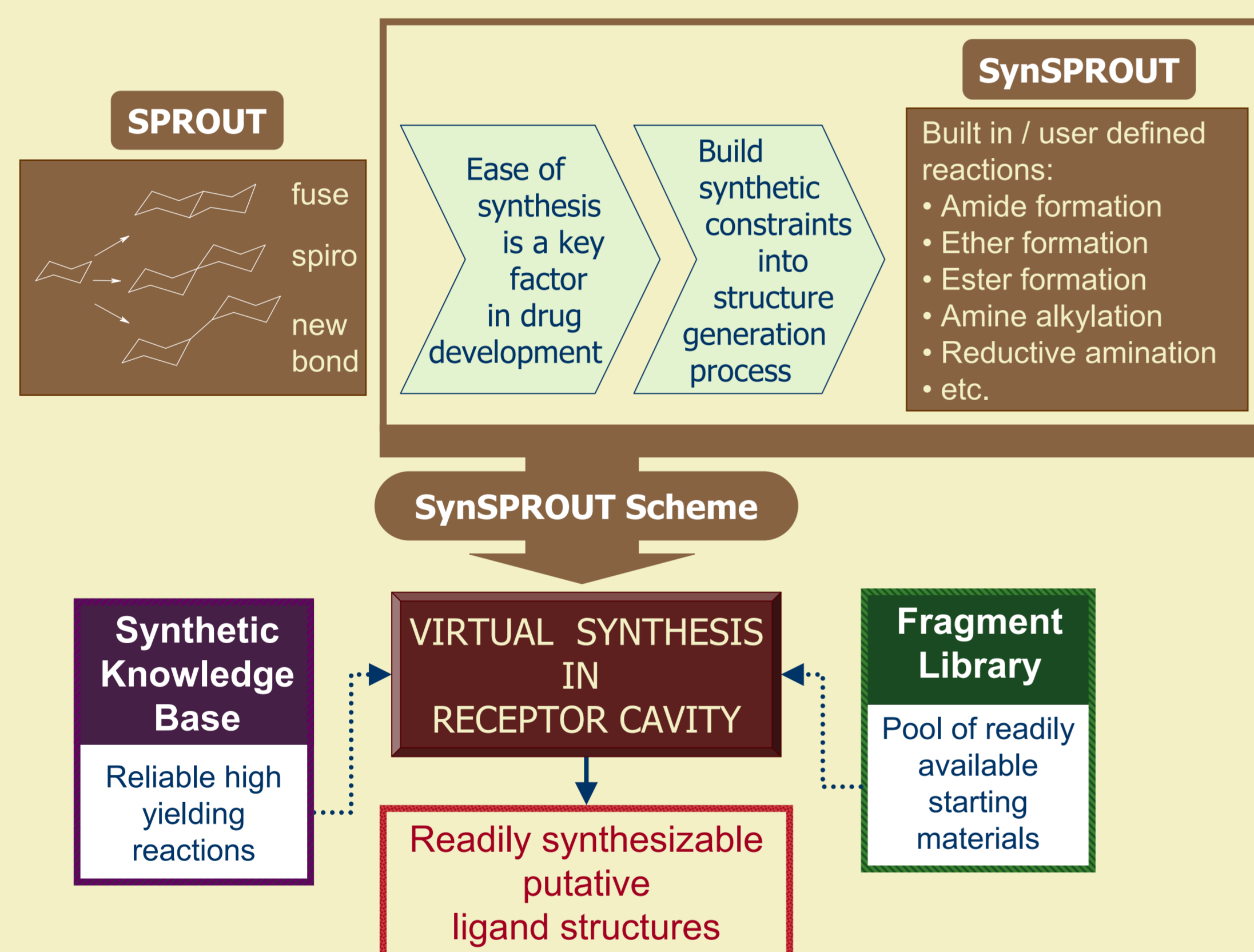
SynSPROUT

- Generate synthetically accessible ligands by virtual chemistry within protein cavity
- Use a library of readily available starting materials (monomers)
- Editable reaction knowledge base

SPROUT-HitOpt

- Optimize hit compounds with the target's active site
- Synthetic constraints ensure only synthetically accessible structures are generated
- Two modes of optimization – Core Extension and Monomer Replacement

SynSPROUT Approach



Synthetic Knowledge Base

CHEMICAL-LABEL <Carboxylic Acid>
C[SPCENTRE=2](=O)-O[HS=1]

CHEMICAL-LABEL <Primary Amine>
C-N[HS=2];[CONNECTION=1]

RULE Amide Formation
IF Carboxylic Acid INTER Primary Amine
THEN delete-atom 3
 change-hybridization 5 to SP2
 form-bond - between 1 and 5

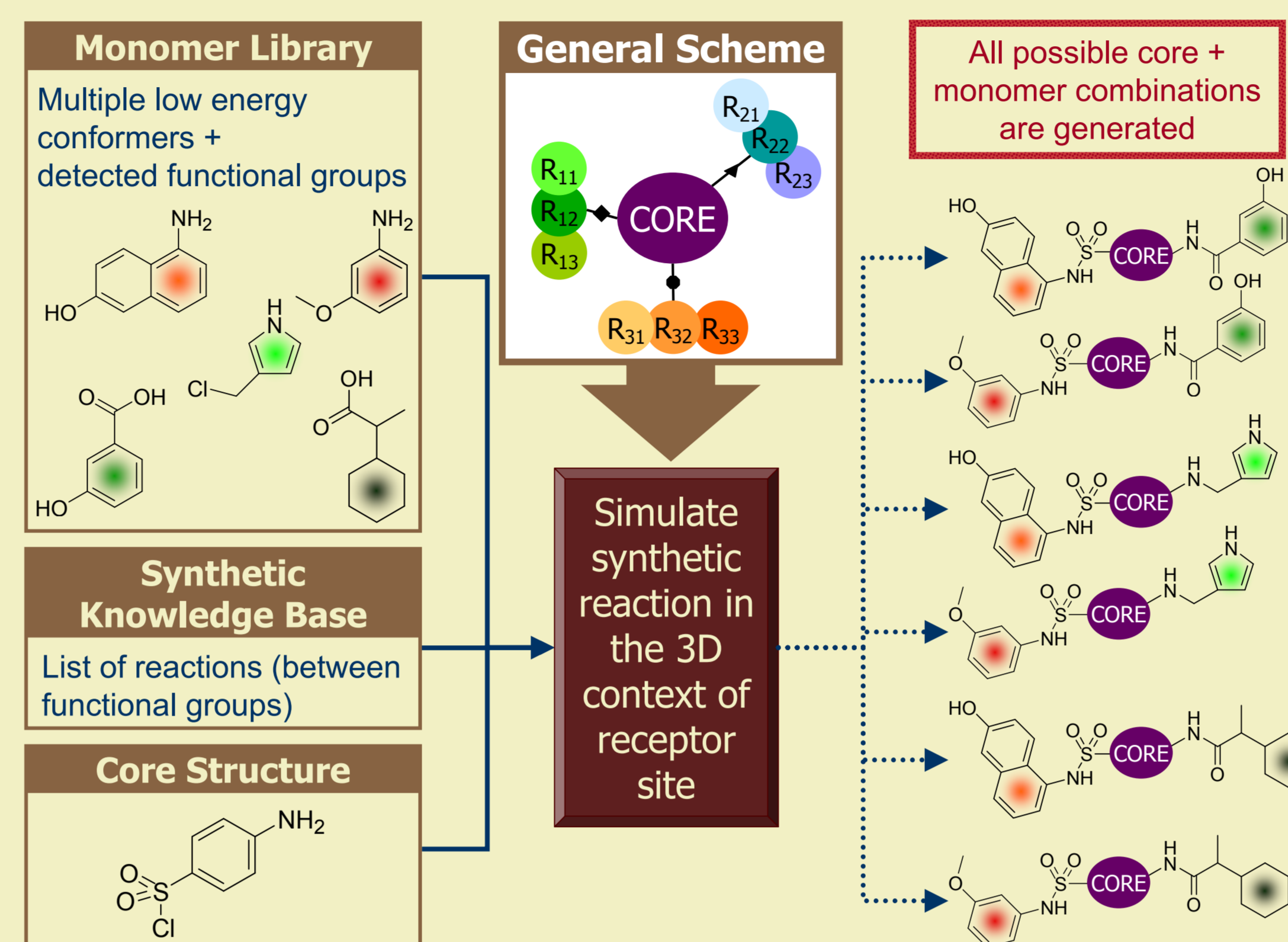
DIHEDRAL-ATOMS 2 1 5 4
DIHEDRAL 0 0
BOND-LENGTH 1.35
END-THEN

Steps of Joining Rules

- Steps of formation
- Hybridization changes
- Bond type
- Bond length
- Dihedral penalty/angle

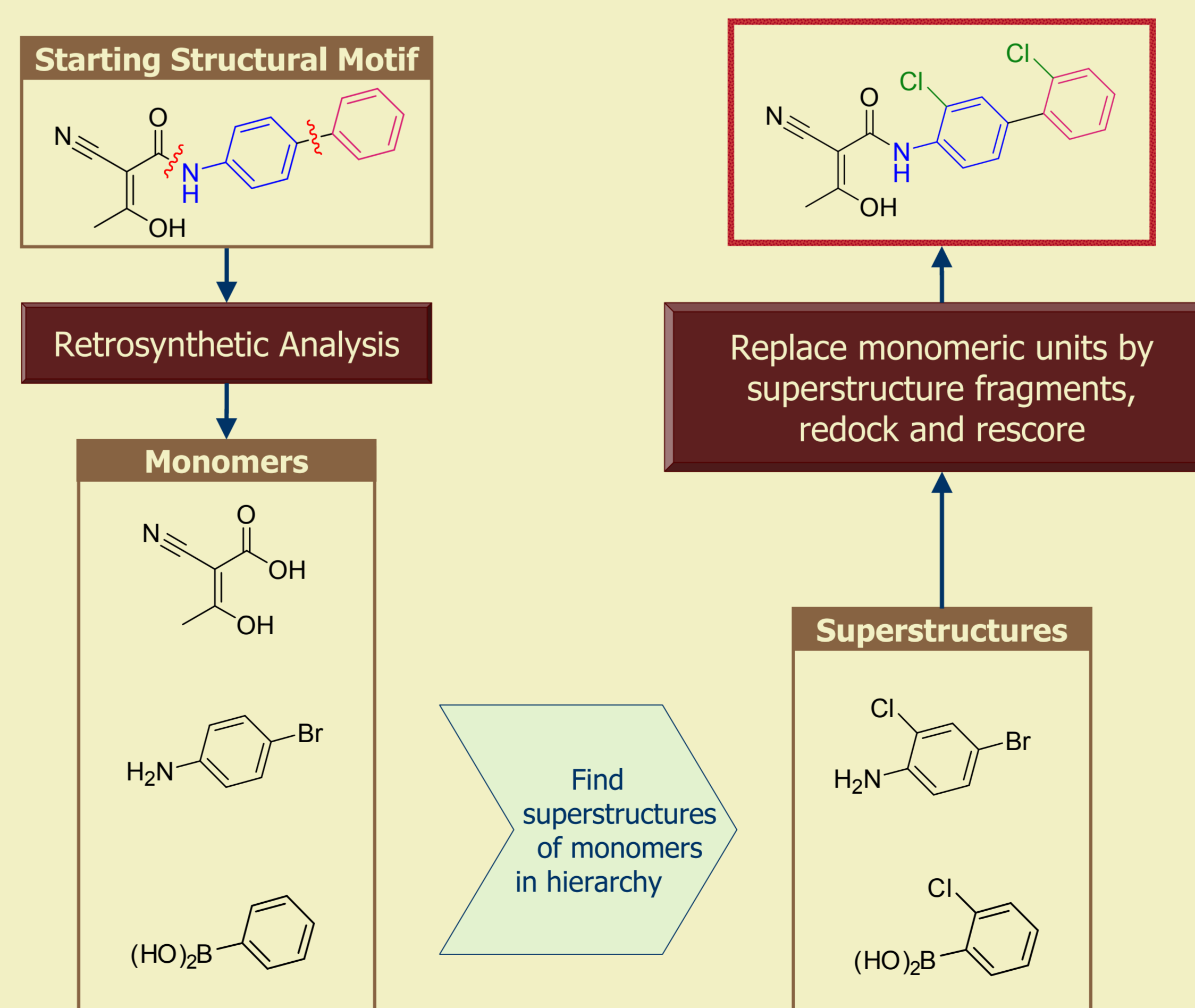
Core Extension in SPROUT-HitOpt

- **Identification** of reactive functional groups as possible extension points
- **Adding** monomers from a user-defined monomer library at the extension points via synthetic reactions
- **Scoring** the binding affinity of each core + monomer product to automatically select the best scored conformations

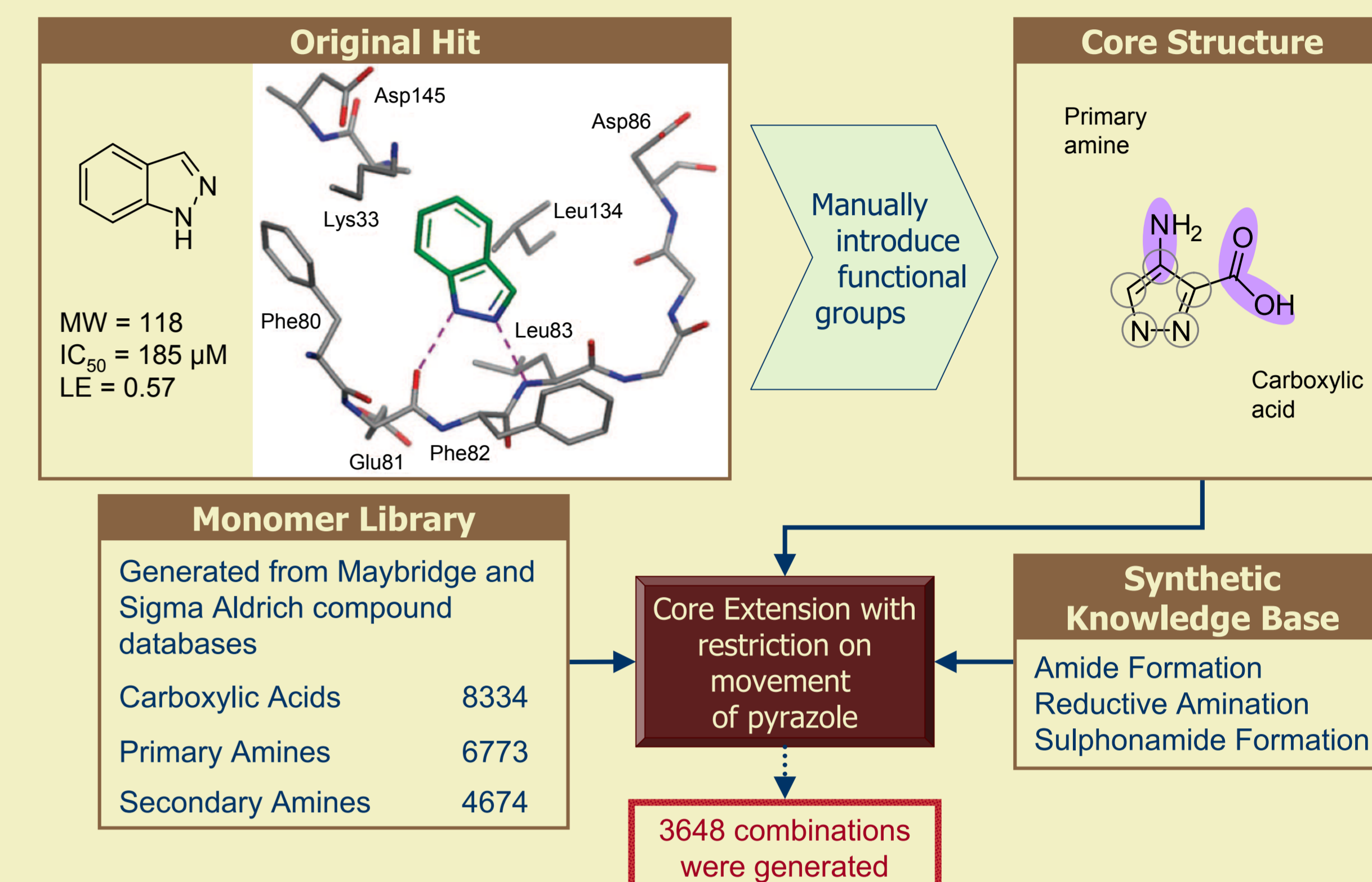


Monomer Replacement in SPROUT-HitOpt

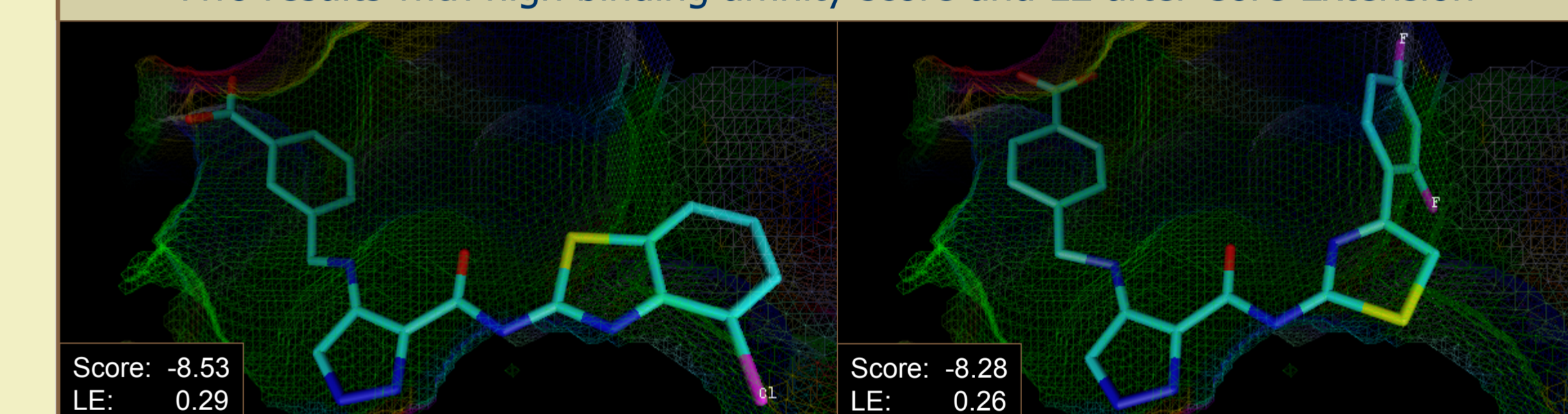
- **Identification** of monomers through retrosynthetic analysis
- **Replacing** the monomers by similar ones taken from a user-defined monomer library, making use of a pre-built structure-based hierarchy of the monomers to improve efficiency
- **Scoring** the binding affinity of the modified structures



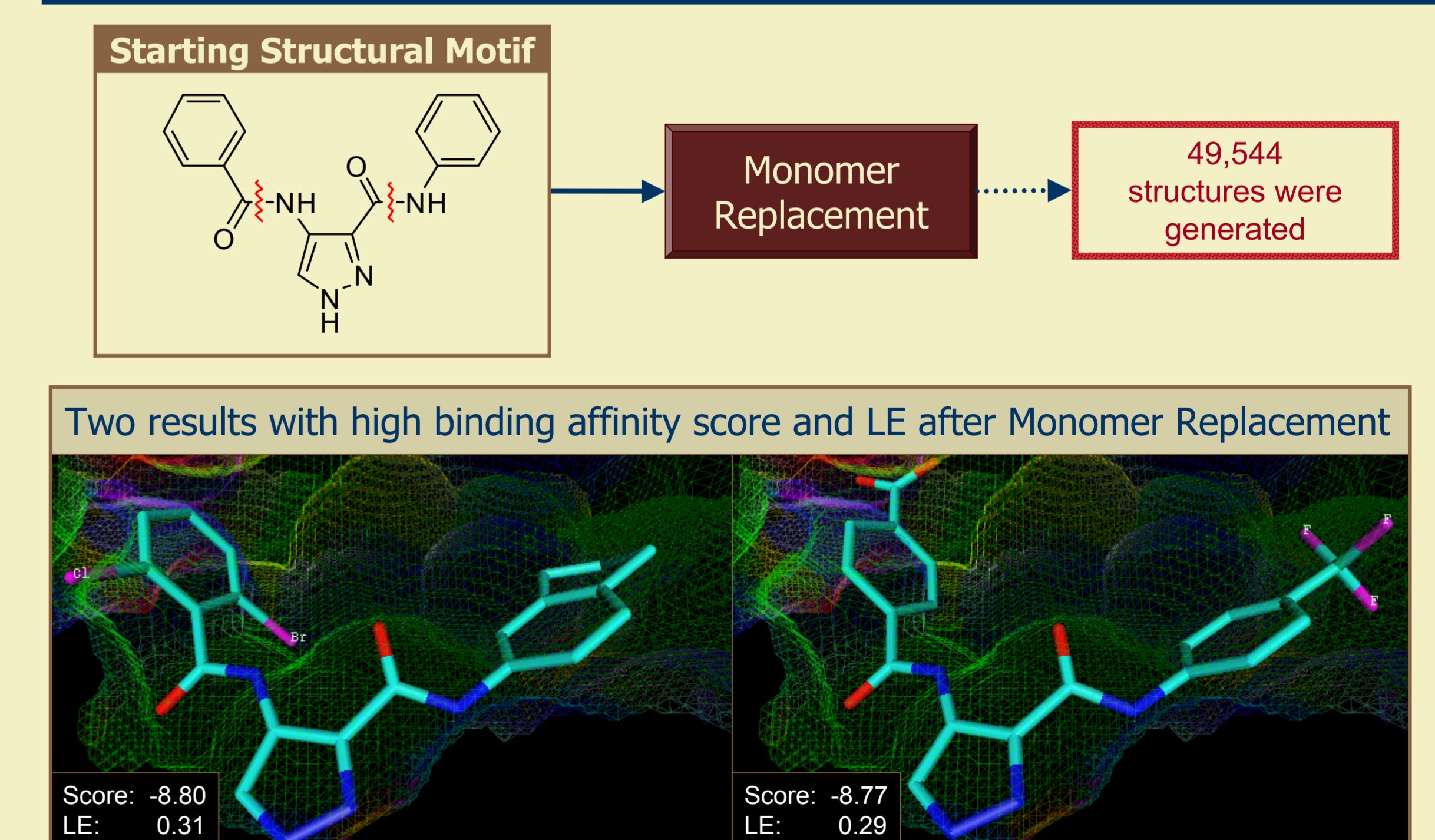
Optimization of a CDK2 fragment based on indazole [1]



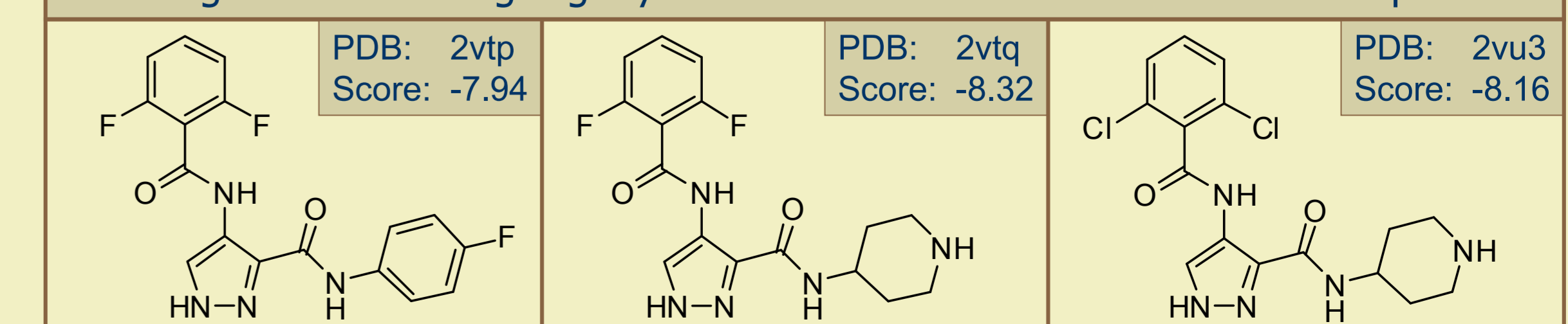
Two results with high binding affinity score and LE after Core Extension



Optimization of a CDK2 fragment based on pyrazole [1]



Structures very similar to med. chem. optimization end results were also generated having slightly lower estimated scores in SPROUT-HitOpt



[1]: P. G. Wyatt et al. J. Med. Chem. 2008, 51, 16.