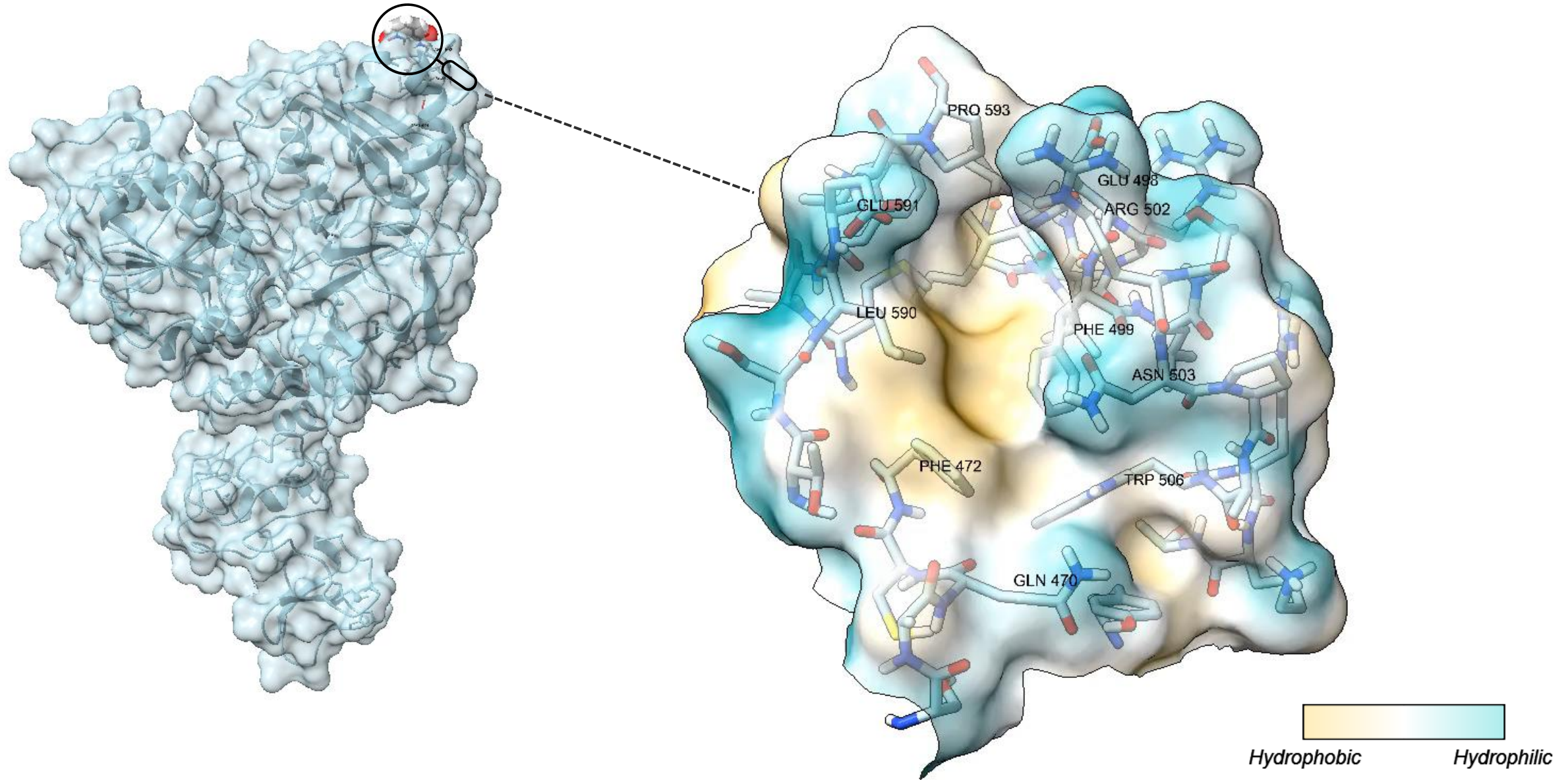
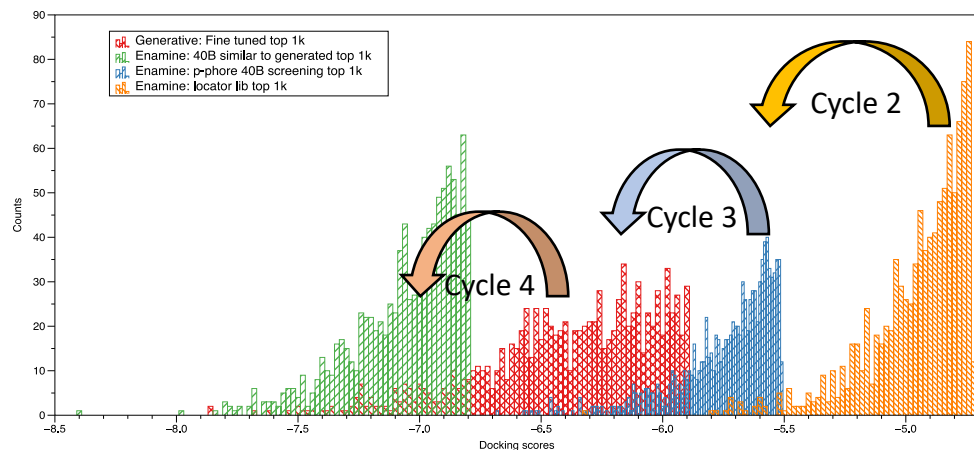
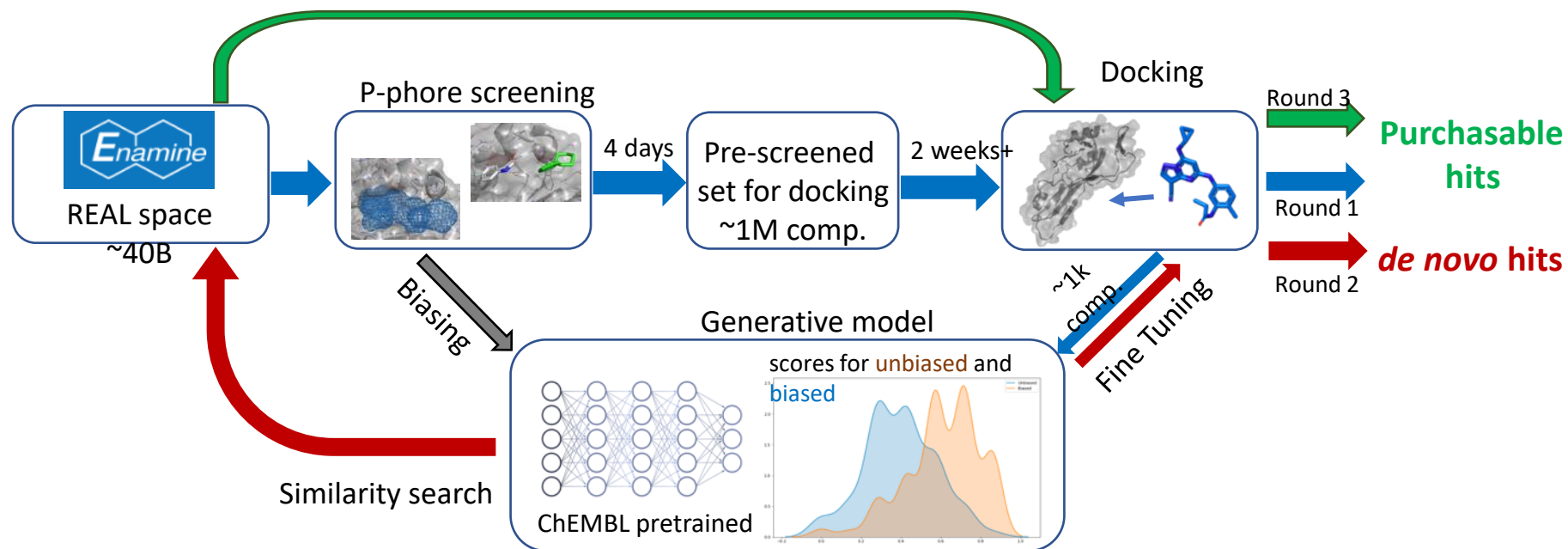


# Nsp13 Helicase C-terminus-B Pocket (Site 3)



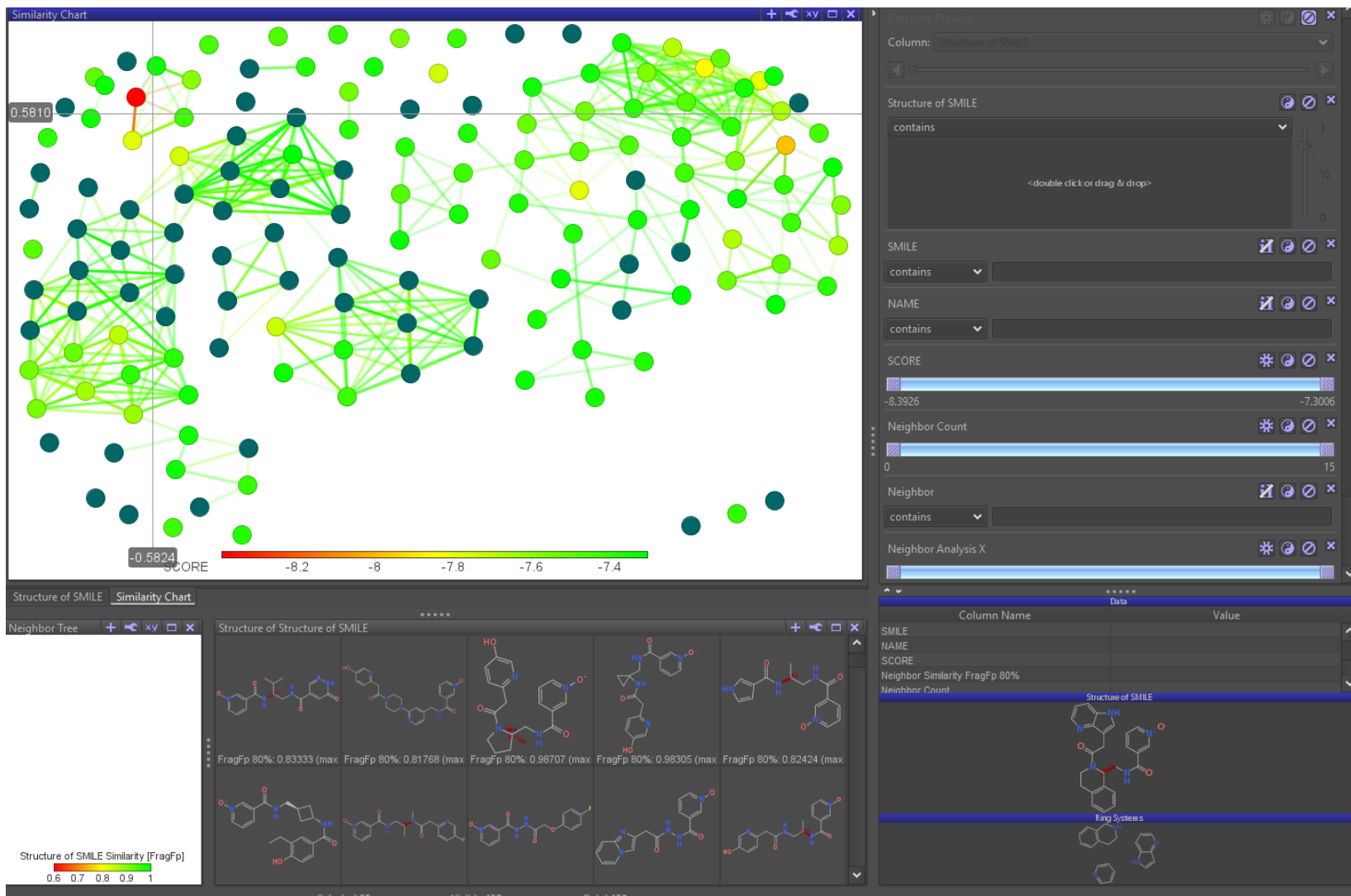
# Virtual Screening Workflow





- Pharmacophore screening of 40 Billion analogs
- Each cycle seeds the next generative model
- Iterative improvement in docking scores

# Enamine REAL Space (43 Billion Library) Top 150 List

DataWarrior zip files can be found on GitHub: <https://github.com/StructuralGenomicsConsortium/CNP4-Nsp13-C-terminus-B/issues/23#issuecomment-1181839847>



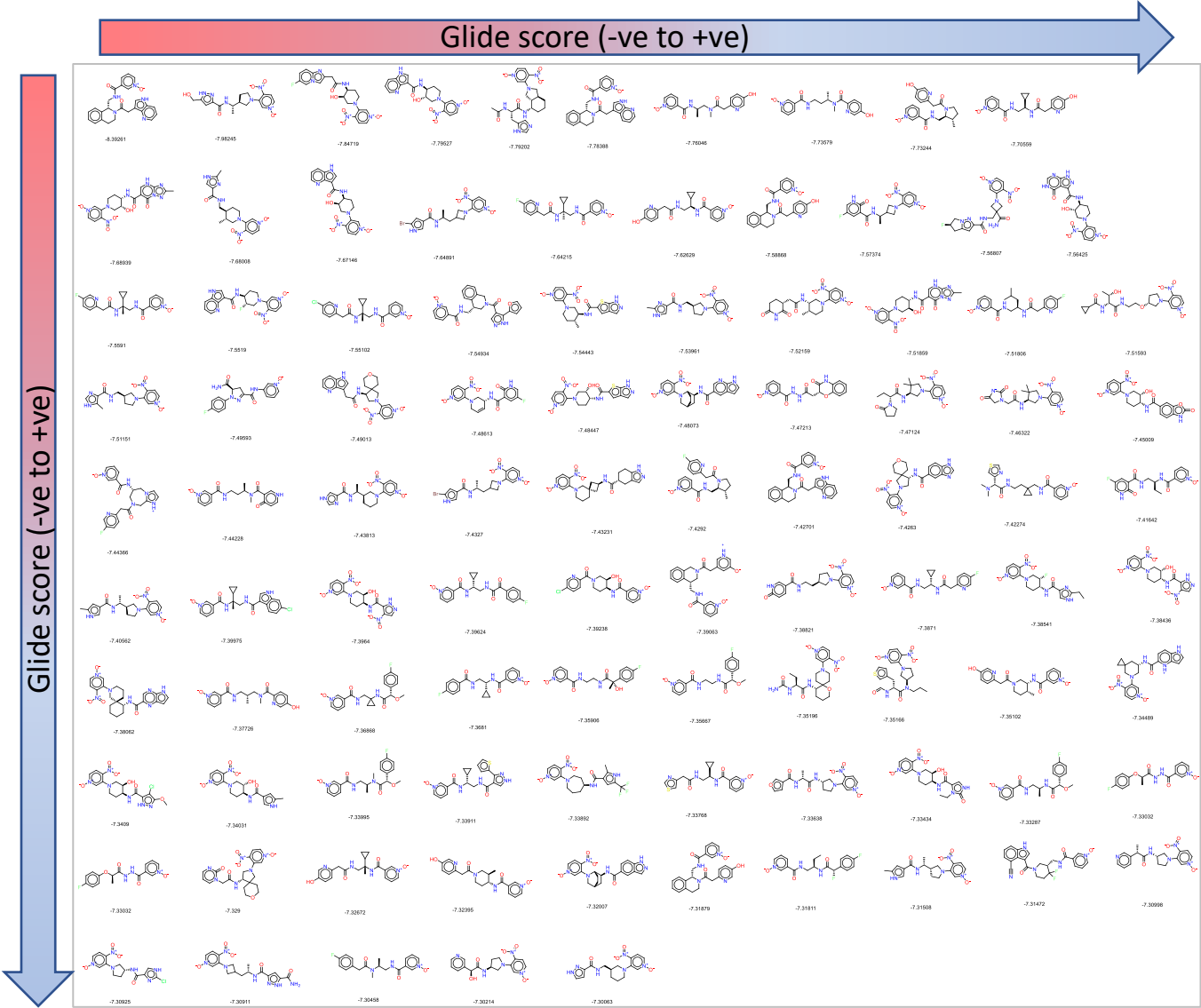
 Enamine MOD quote provided.  
 Glide score (lowest to highest).



# Enamine REAL space-trained 43 billion library: Top 150 compound list



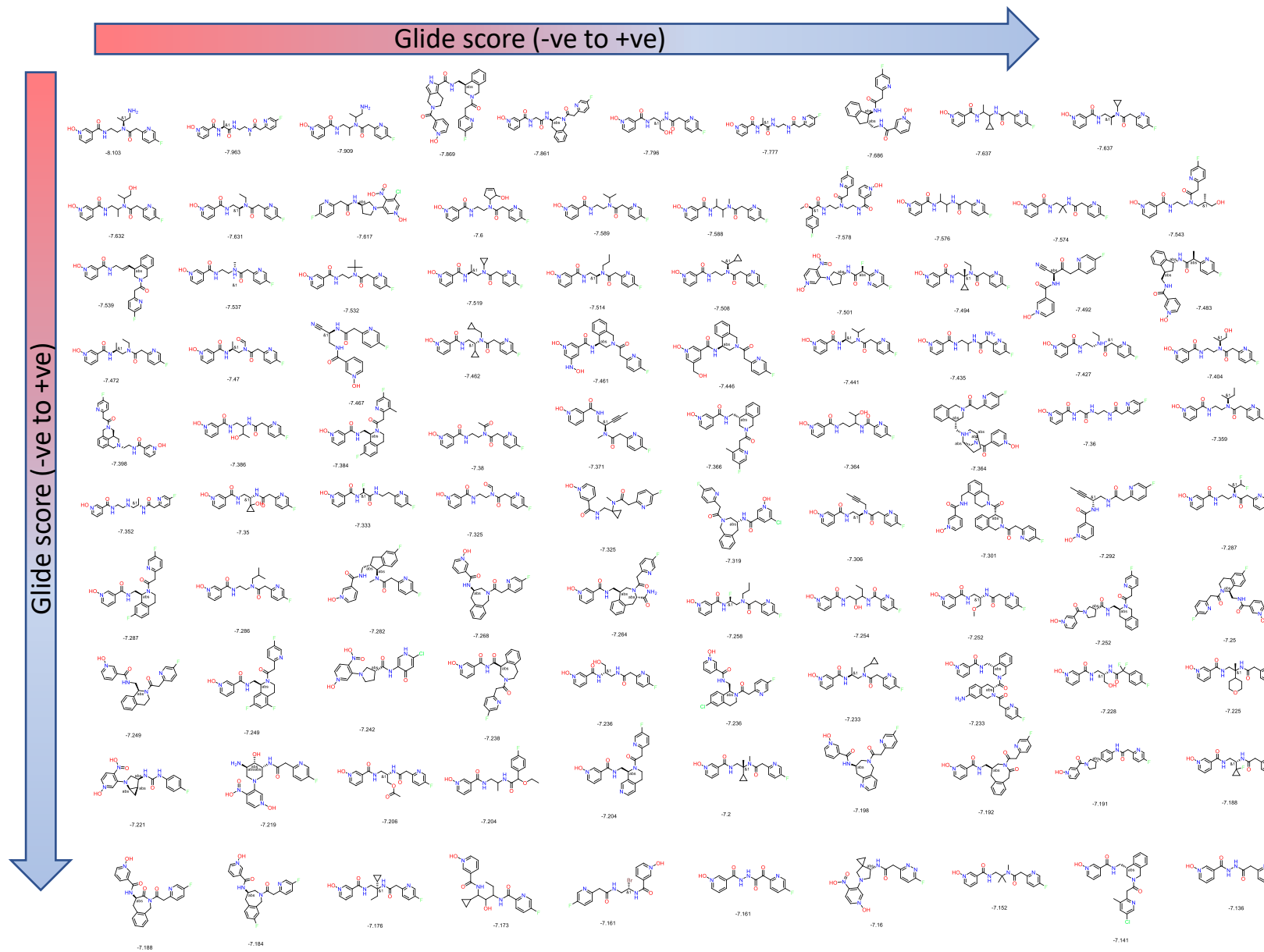
- 95 / 150 (1/3) compounds remaining to be made...





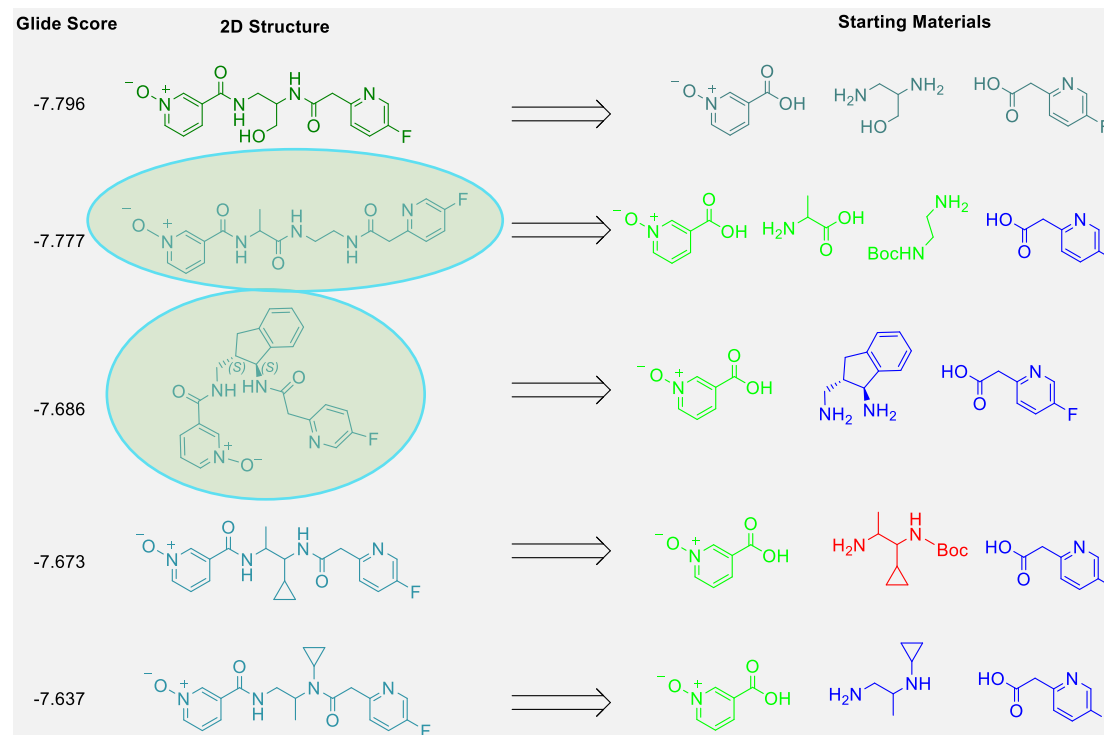
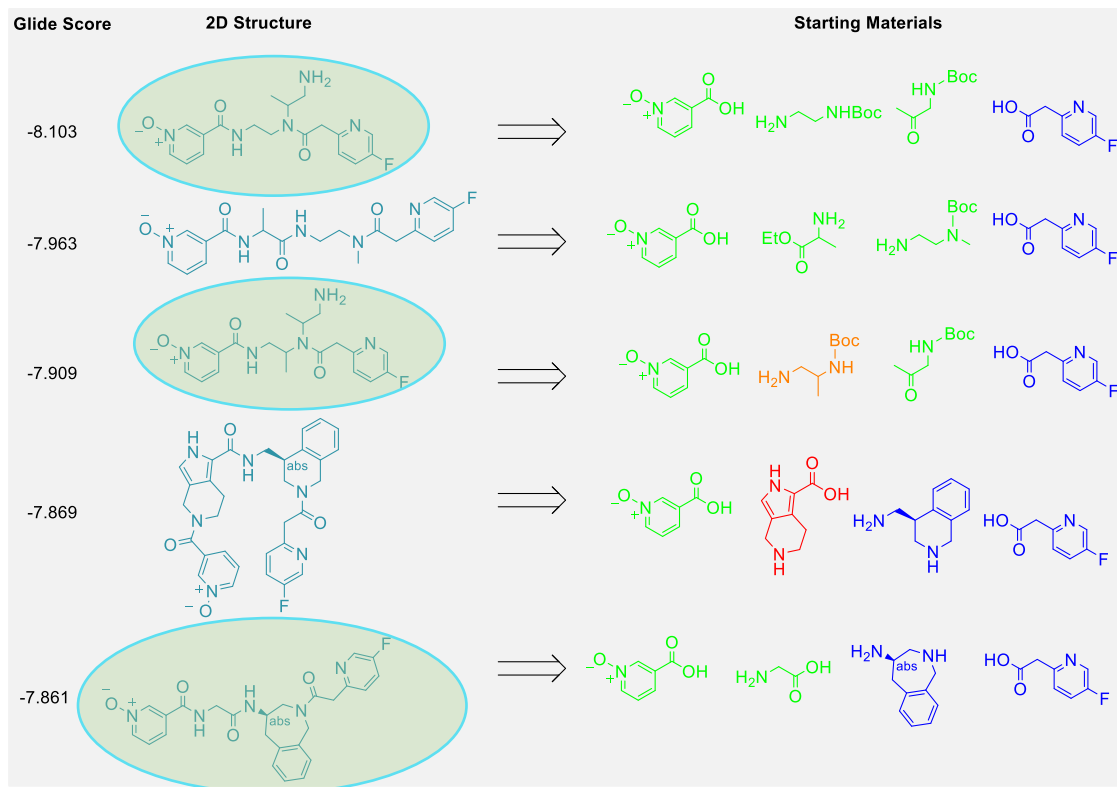
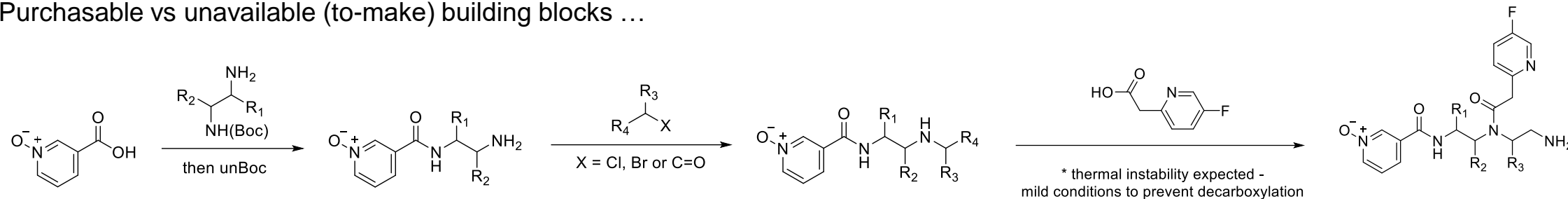


# De-novo generated compounds list: Glide top 100-scoring compounds



# De-Novo Generative Compounds: Top 10-scoring (Glide)

Purchasable vs unavailable (to-make) building blocks ...

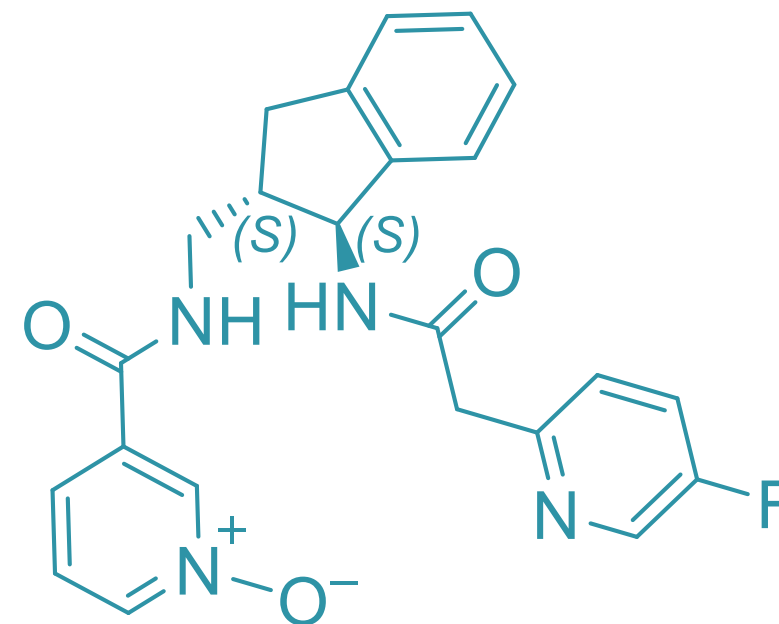
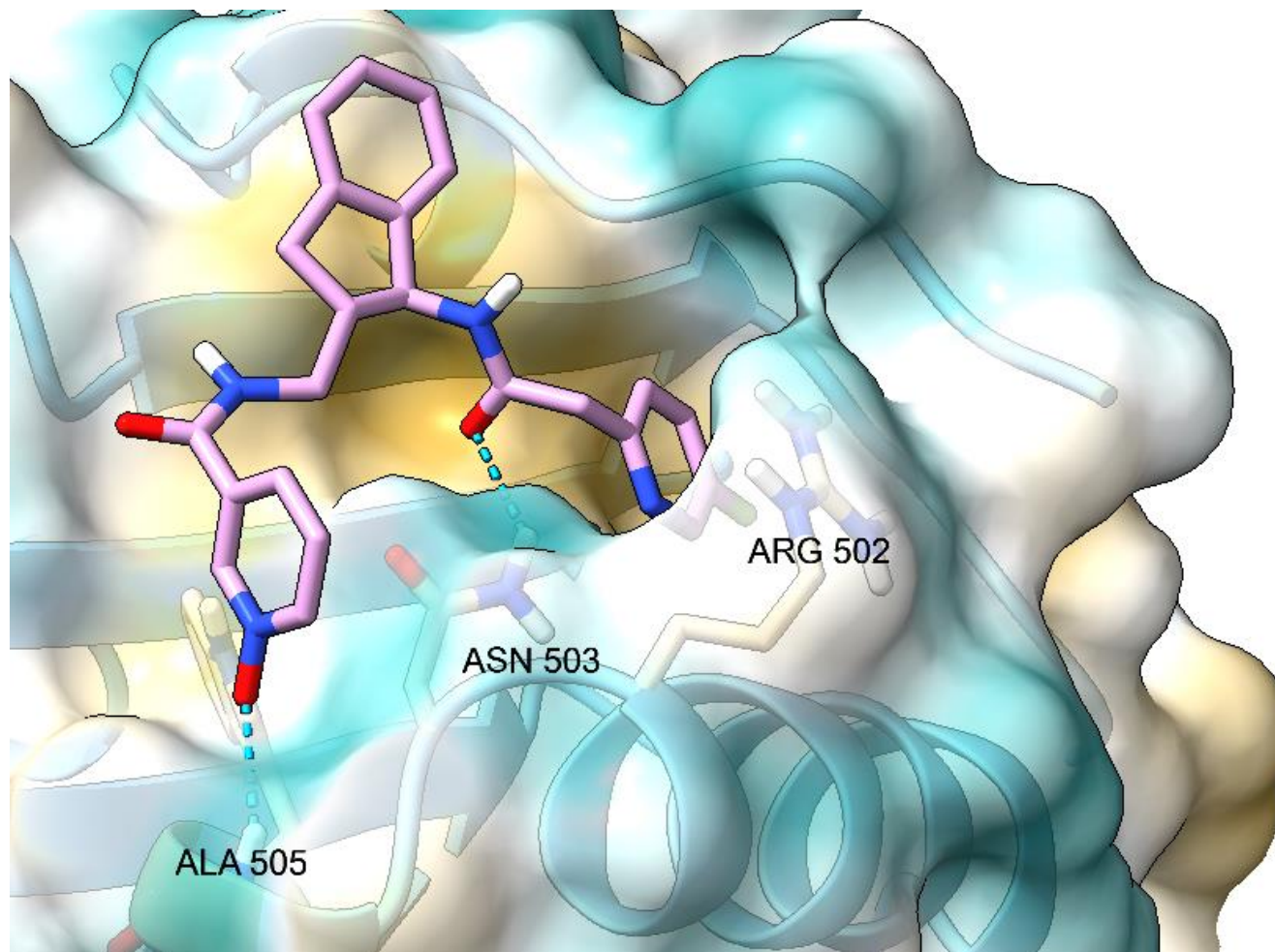


- Purchased
- Purchasable
- To make
- Unavailable
- Enamine MOD
- Current targets



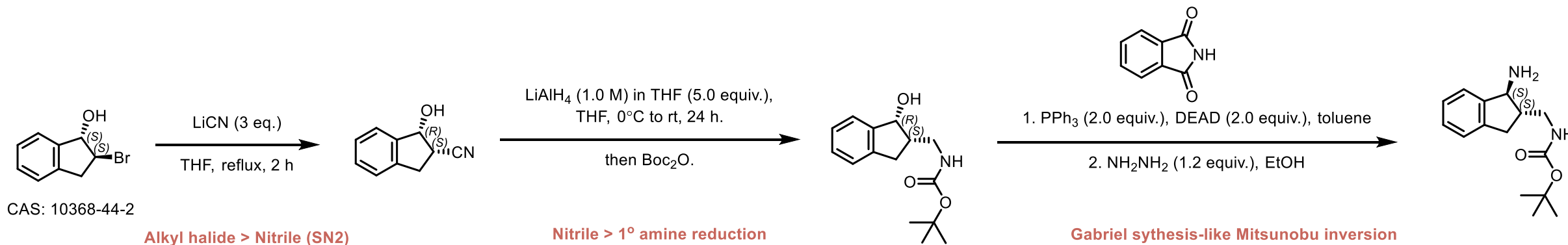
# De-Novo Generative Compounds:

GLIDE = -7.686



GLIDE: -7.686

# De-Novo Generative Compounds: GLIDE = -7.686 ; Route A.

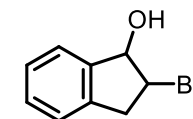
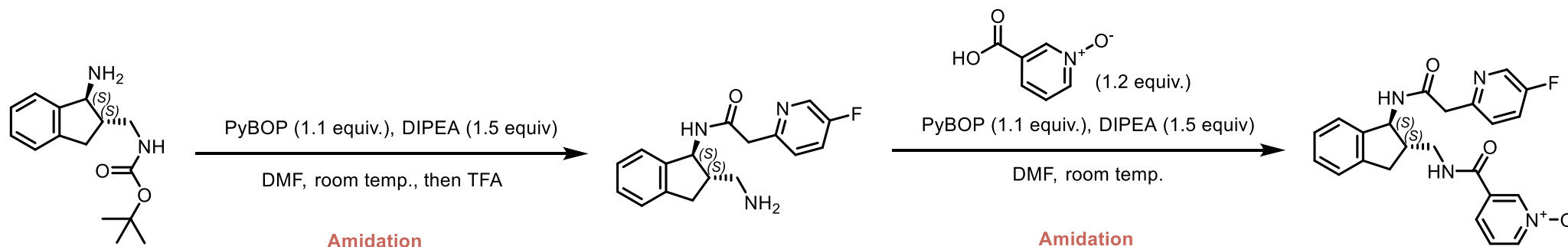


[https://doi.org/10.1016/S0040-4039\(00\)95575-8](https://doi.org/10.1016/S0040-4039(00)95575-8).  
NON-AQUEOUS CYANATION OF HALIDES USING LITHIUM CYANIDE.  
Tetrahedron Letters, Vol.28, No.36, pp 4189-4190, 1987.

Patent number: WO2011017600  
CAS Reaction Number: 31-520-CAS-7274455

C. Simon, S. Hosztafi and S. Makleit, Tetrahedron, 1994, 50, 9757.  
DOI: 10.1039/C5QO00016E (Review Article) Org. Chem. Front., 2015, 2, 739-752

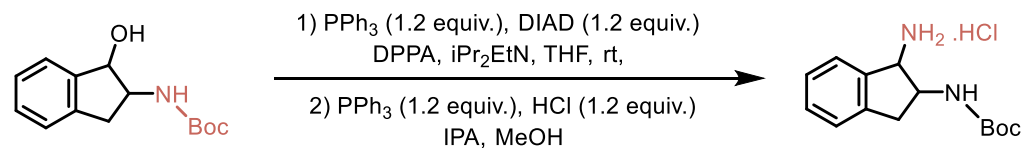
**SN2 favoured over E2 if:**  
**Polar, aprotic solvents are used (acetonitrile, acetone, DMSO, DMF, THF)**



CAS No: 5400-80-6  
GBP 5.00 / 10 g  
**Ordered**

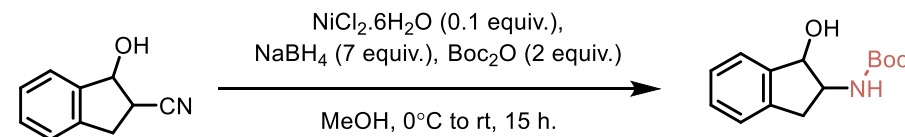
# De-Novo Generative Compounds: GLIDE = -7.686 ; Back-up routes.

## #1: One-Pot Mitsunobu inversion, then Staudinger reduction.



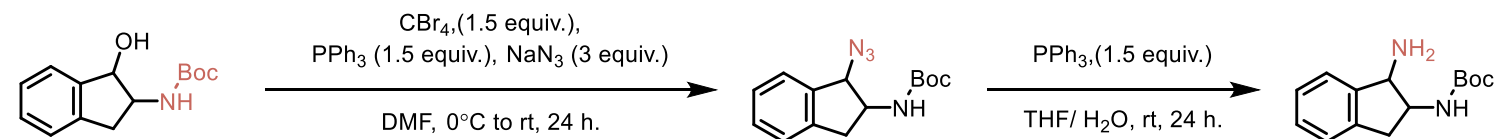
Mitsunobu Inversion of a Secondary Alcohol with Diphenylphosphoryl azide.  
Application to the Enantioselective Multikilogram Synthesis of a HCV Polymerase Inhibitor  
[dx.doi.org/10.1021/op200002u](https://doi.org/10.1021/op200002u) , Org. Process Res. Dev. 2011, 15, 1116–1123

## #2: Nickel-catalysed reduction (CN > NH<sub>2</sub>).



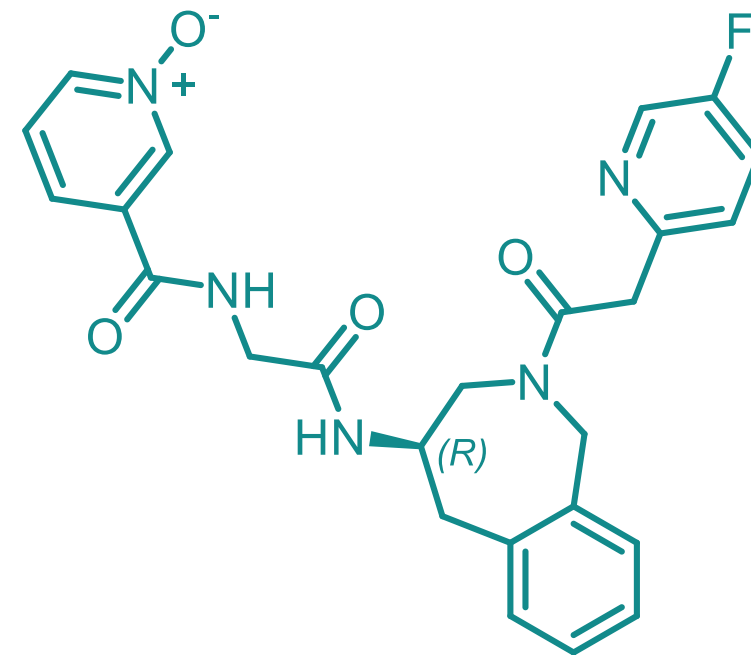
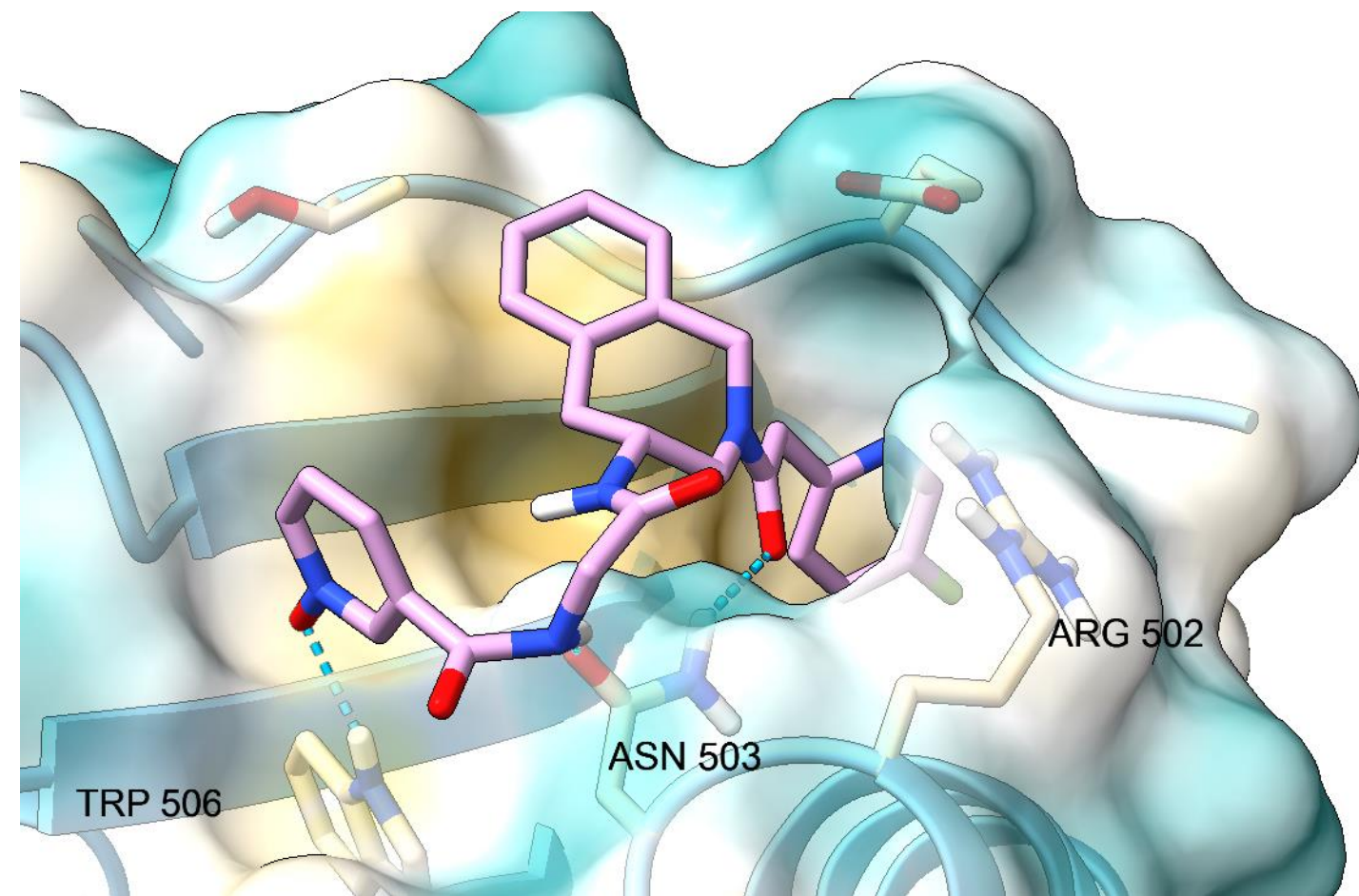
A generic approach for the catalytic reduction of nitriles  
S. Caddick et al. / Tetrahedron 59 (2003) 5417–5423.

## #3: Appel Reaction (OH > Br), then S<sub>N</sub>2 (Br > N<sub>3</sub>), then Staudinger reduction (N<sub>3</sub> > NH<sub>2</sub>).



N-(3-Acyloxy-2-benzylpropyl)-N'-[4-(methylsulfonylamino)benzyl]thiourea Analogues: Novel Potent and High Affinity Antagonists and Partial Antagonists of the Vanilloid Receptor  
J. Med. Chem. 2003, 46, 3116-3126

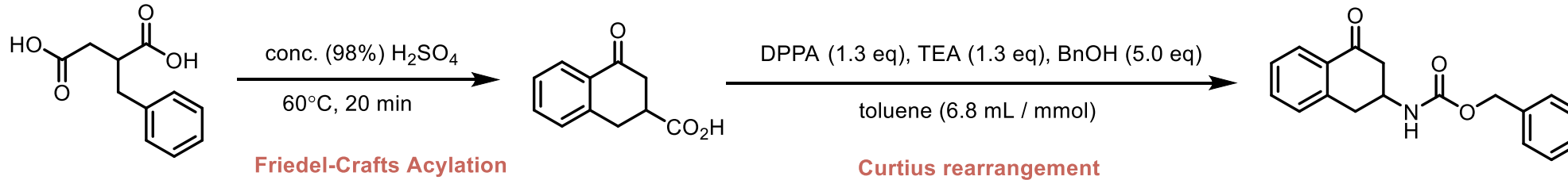
# De-Novo Generative Compounds: Top 10 Scoring (Glide)



GLIDE = -7.861

# De-Novo Generative Compounds: Top 10 Scoring (Glide)

- Suggestion from James...



CAS No: 884-33-3  
1 g = 81 GBP  
Ordered

Preparation of heteroarylaminotetralins and related compounds as glycogen phosphorylase inhibitors

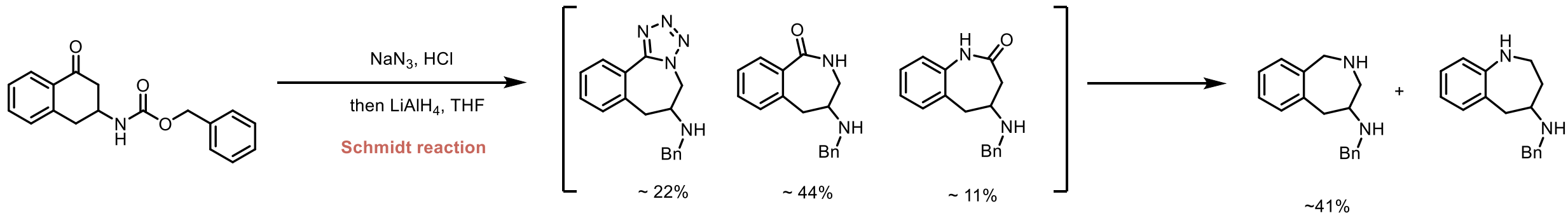
Patent Number: US20060111338 A1

Sher, Philip M.; Nirschl, Alexandra A.; Meng, Wei; Washburn, William N

Patent Number US2006/0111413 A1

Reaction No. [0207]

Tetrahedron: Asymmetry, Volume 14, Issue 3, 7 February 2003, Pages 381-387



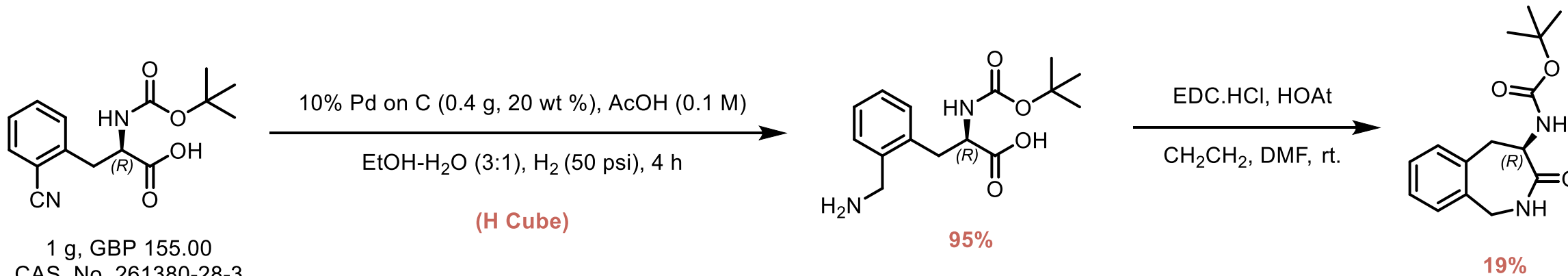
J. Med. Chem. 1996, 39, 3539-3546.

Hjelte, N. S.; Agback, T. Benzocycloalkanones in the Schmidt Reaction. Acta Chem. Scand. 1964, 18, 191-194.



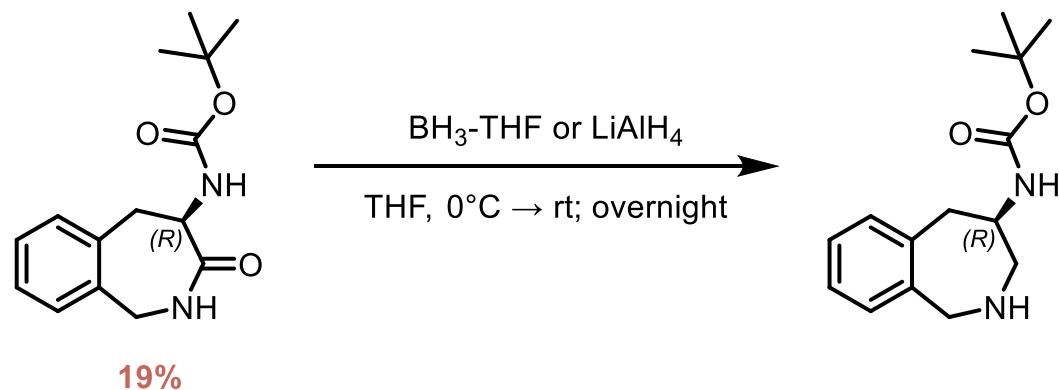
# De-Novo Generative Compounds: Top 10 Scoring (Glide)

- Alternative route... **WO 2020/197991**



Van den Eynde, Isabelle; et al. *Journal of Medicinal Chemistry* (2005), 48(10), 3644-3648.  
Simonin, Frederic; et al. World Intellectual Property Organization, WO2019170919 A1 2019-09-12.

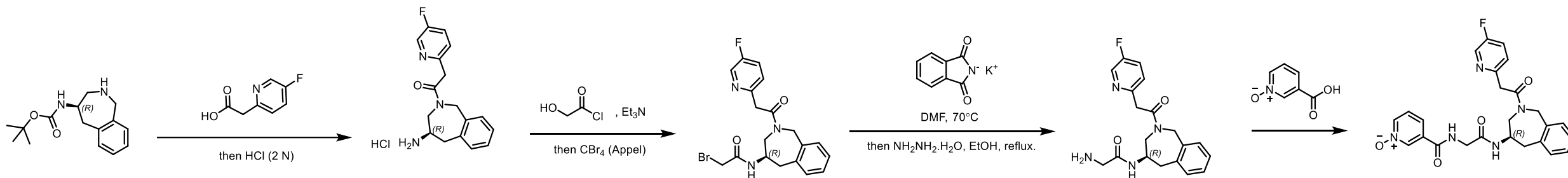
Isabelle Van den Eynde et al. *J. Comb. Chem.* 2004, 6, 4, 468-473.



Zawodny, Wojciech; et al. *Journal of the American Chemical Society* (2018), 140(51), 17872-17877.  
Shonberg, Jeremy; et al. *Journal of Medicinal Chemistry* (2015), 58(13), 5287-5307.  
WO 2020/197991, pg 271, Compound 80a.

# De-Novo Generative Compounds: Top 10 Scoring (Glide)

- Alternative route...



Koehler, Victor; et al  
Chemical Communications (Cambridge, United Kingdom) (2022), 58(62), 8618-8621