

LoFT: Design of Combinatorial Libraries for the Exploration of Virtual Hits from Fragment Space Searches

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Introduction

At Boehringer Ingelheim fragment spaces based on reactions from combinatorial chemistry are successfully screened with Feature Trees [1] for the detection of new lead classes [2]. Once interesting scaffolds have been detected, corresponding combinatorial libraries have to be designed. For this purpose the software LoFT (Library Optimizer using Feature Trees) was developed [3]. LoFT enables the design of focused libraries optimized according to Feature Trees similarity to one or more queries and/or Feature Trees dissimilarity to one or more anti-queries. In addition, a desired range of physico-chemical properties for library compounds can be taken into account.

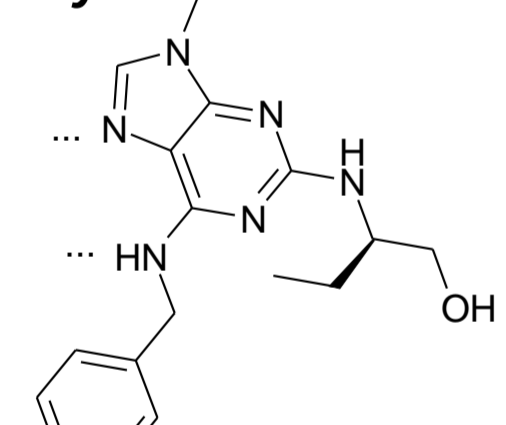
A special feature called FTMatch allows to restrict the parts of the queries where the reagents are permitted to match.

Here a case study is presented illustrating how a 3D scoring function can be simulated for the design of a focused CDK2 library.

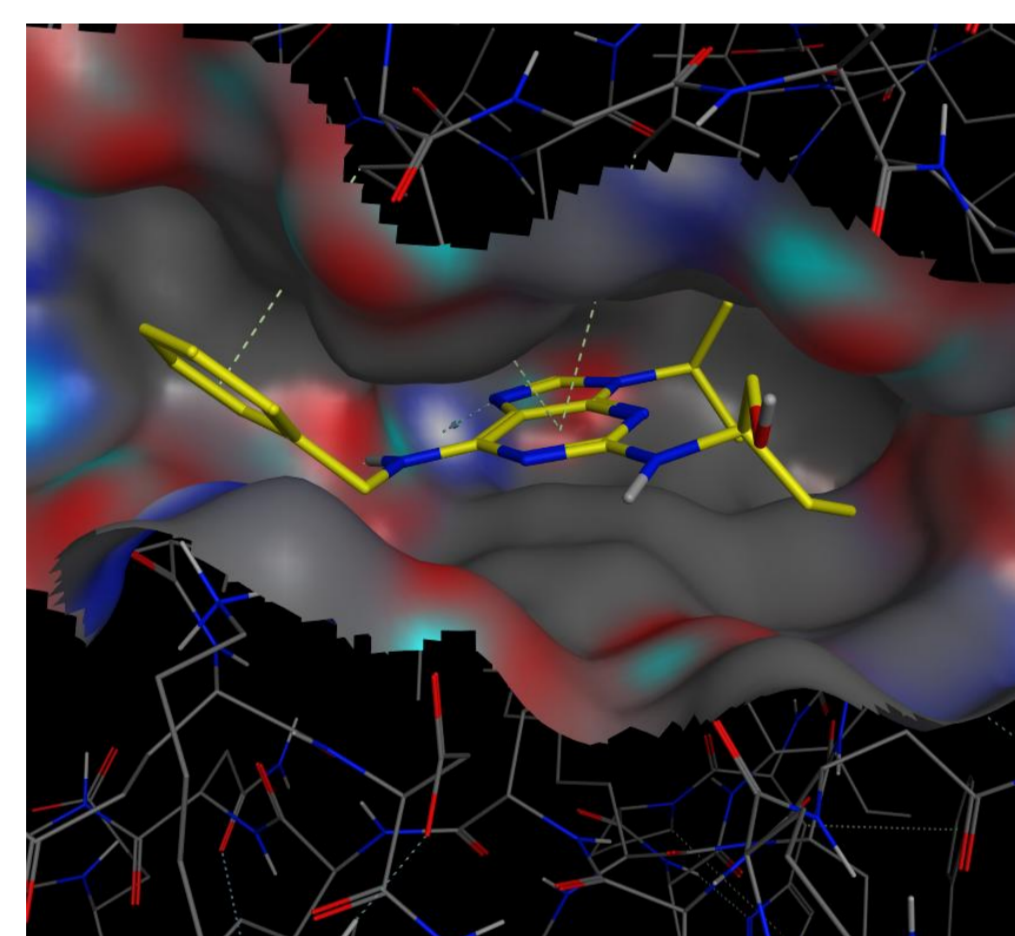
Basis:

CDK2 2a4l.pdb

Query:

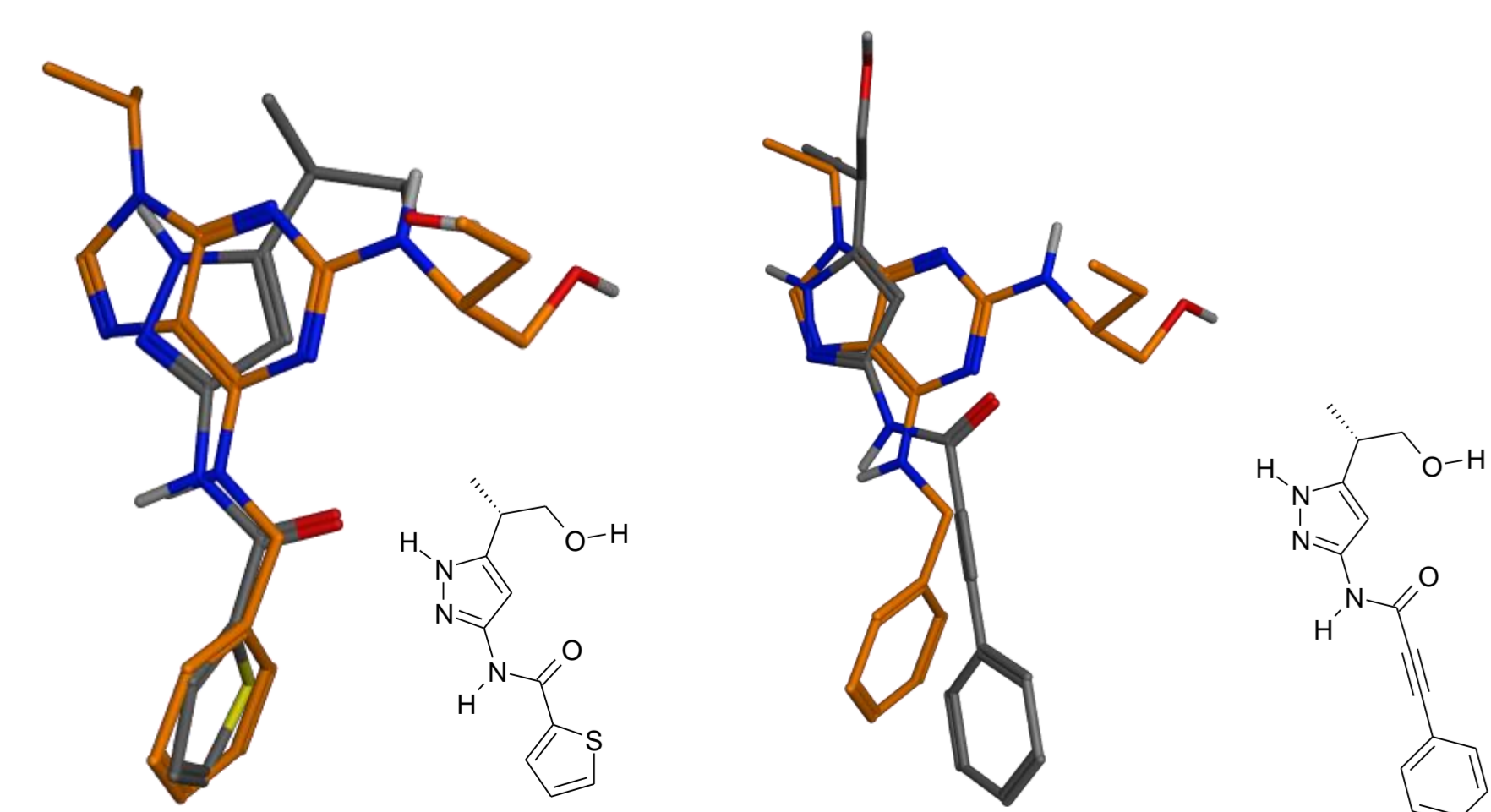


Roscovitine
100 nM



Feature Trees Fragment Space search

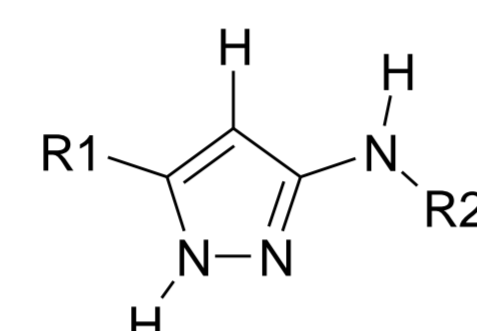
Selection of interesting scaffolds by post-processing e.g. by 3D-alignments with ROCS [4]:



⇒ design of a focused aminopyrazole library (10x10)

Design

Generation of an aminopyrazole fragment space:



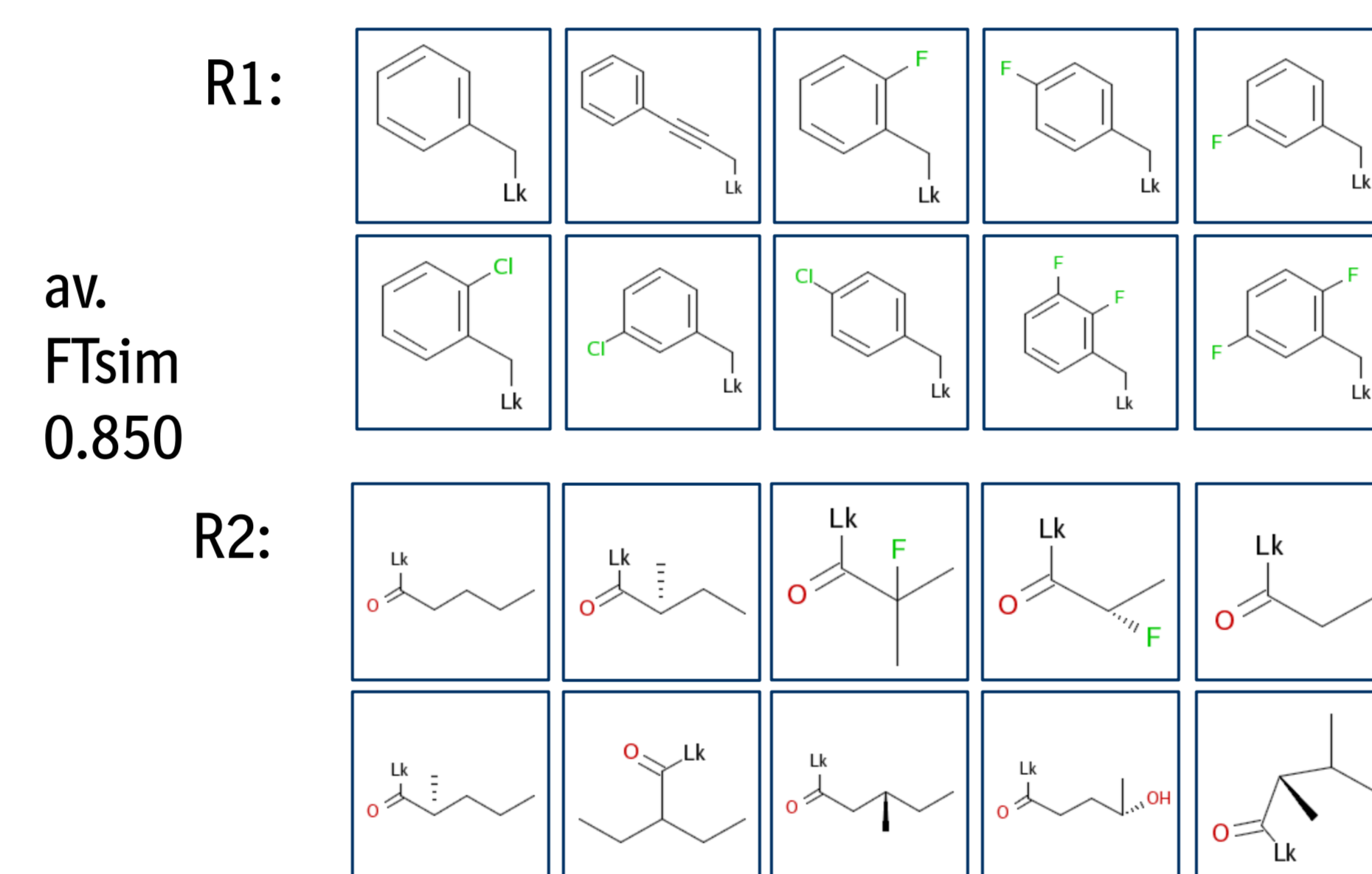
R1: Alkylhalogenides (2687)

R2: Carboxylic acids (6368)

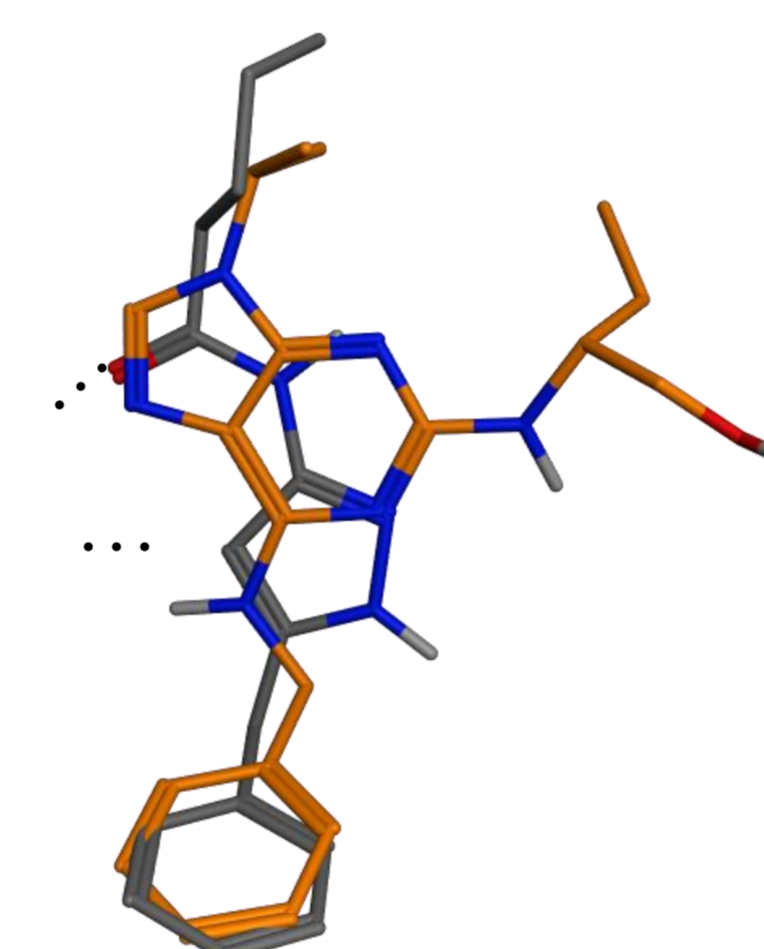
For plausibility check:

P. Pevarello et al., J. Med. Chem., 47, 3367-3380, 2004:
42 aminopyrazoles: 35 active, 7 inactive
derived from 12 different R1 and 29 different R2
those reagents were included in the virtual library

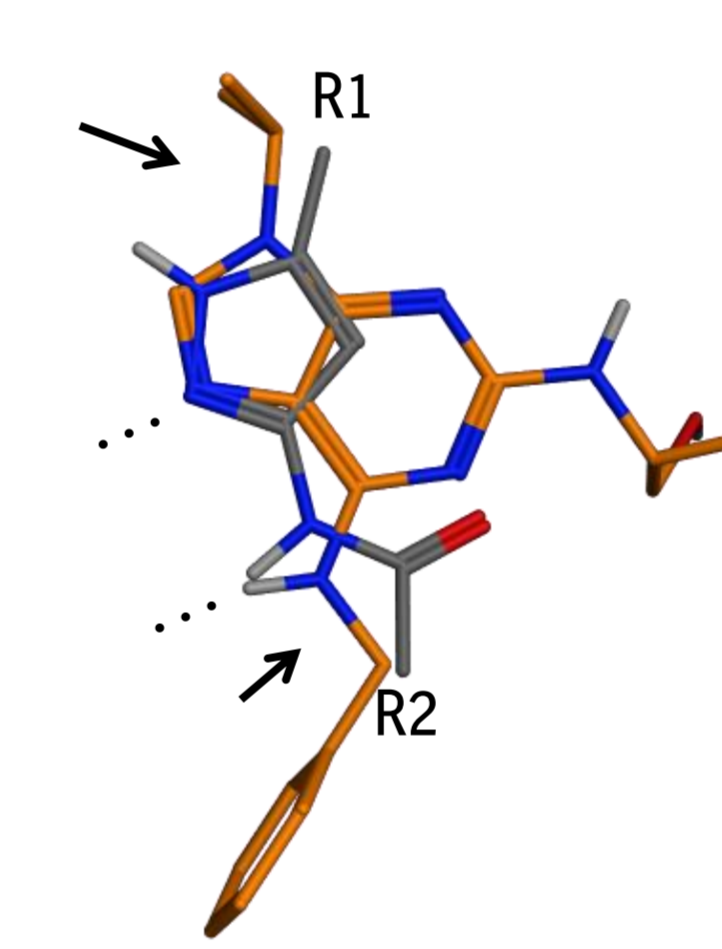
Free Design with LoFT, FTSim 1.0 :



Alignment of the first hit shows a “wrong orientation”:

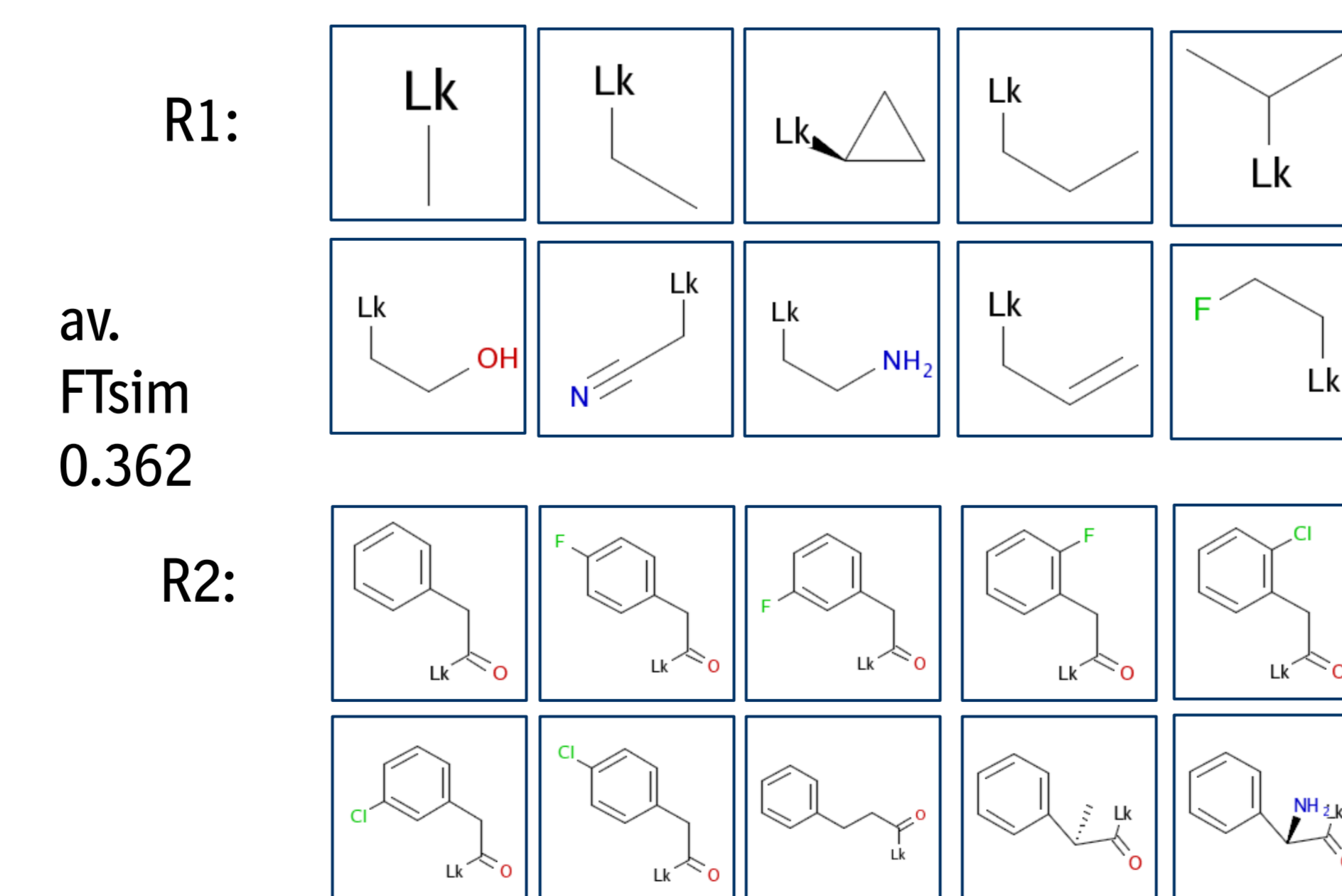


Desired matching:

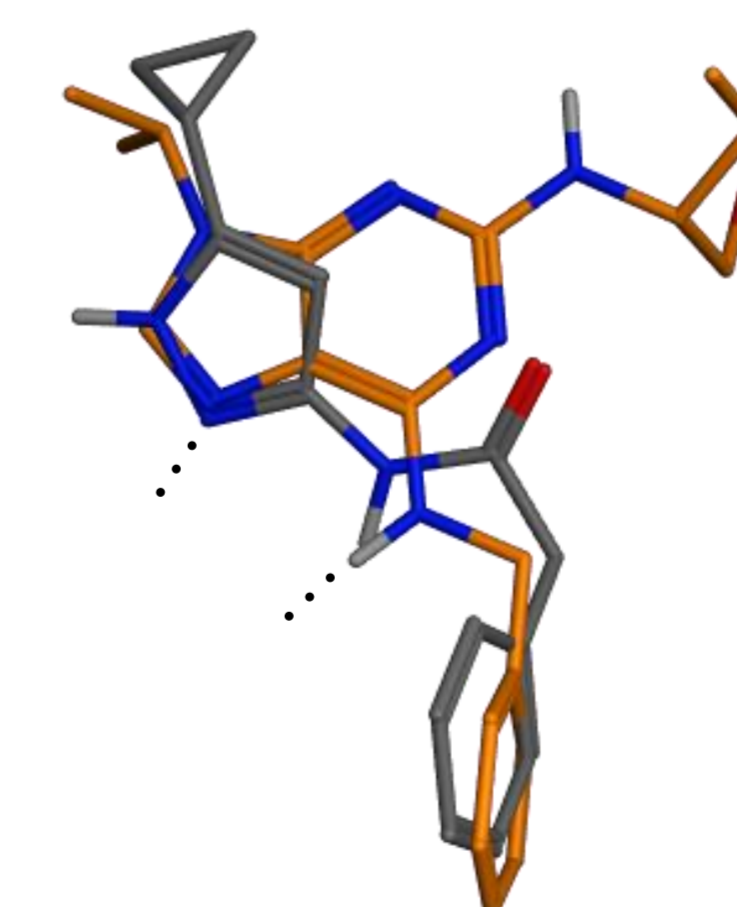


FTMatch for R1 and R2 to be applied

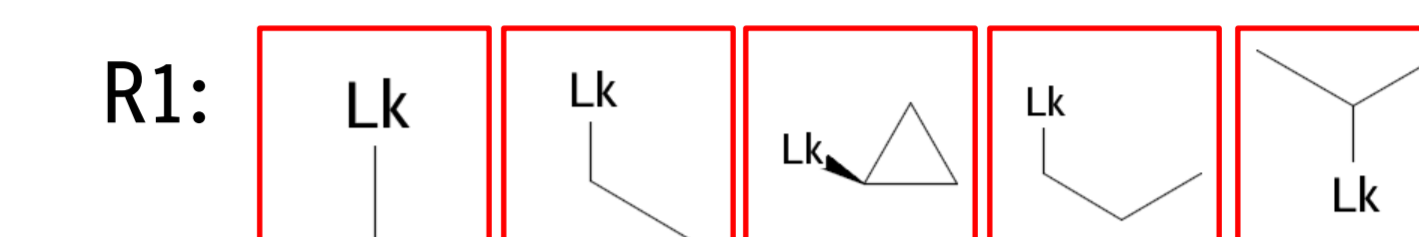
Design with FTMatch restriction of R1 and R2:



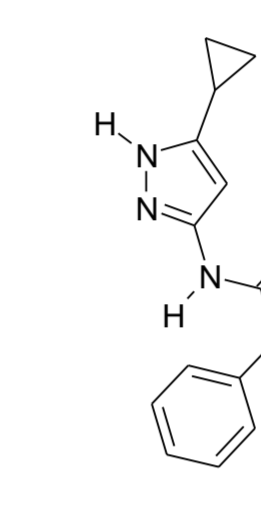
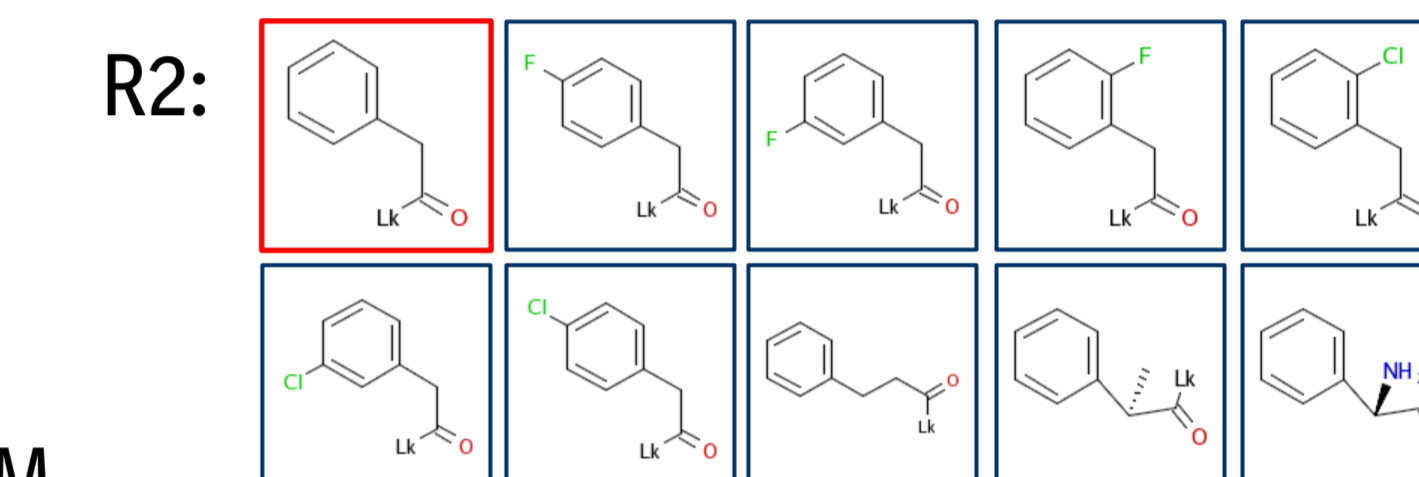
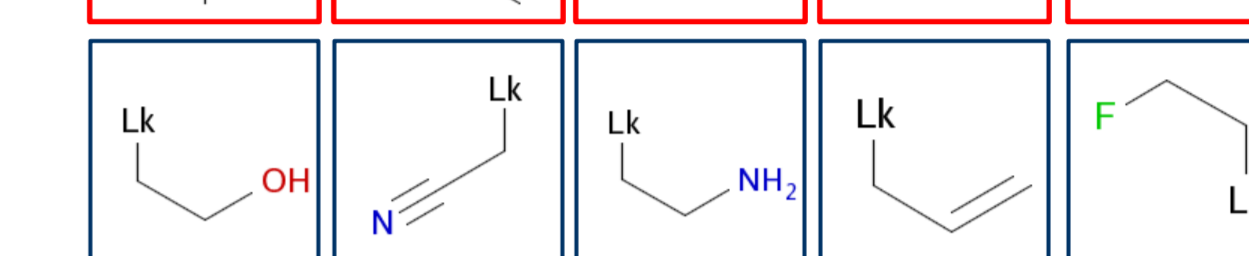
Alignment of one of the products with the query structure:



“Plausibility Check”



R2 = phenylacetyl only reported in combination with R1 = cyclopropyl



“Statistics“:

Fragment space contains
2648 fragments compatible with R1
6101 fragments compatible with R2
16,155,448 products

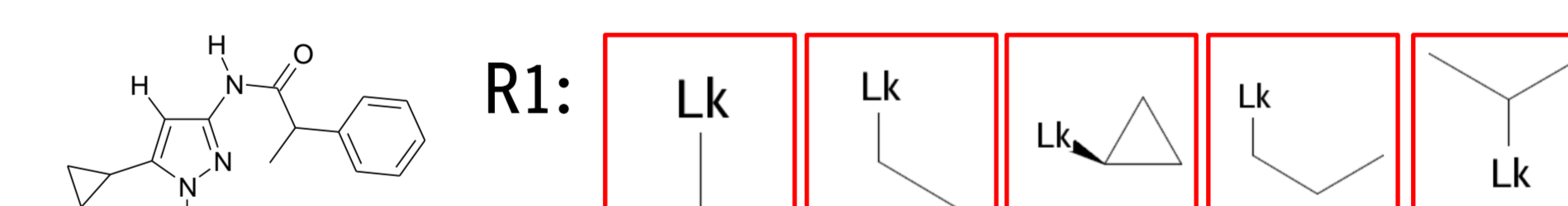
42 products described: 35 active, 7 inactive

2.5 ppm with known activity, 2.1 ppm known actives

1 hit in ~460,000 cpds. ⇔ 1 hit detected in 100 products

More actives:

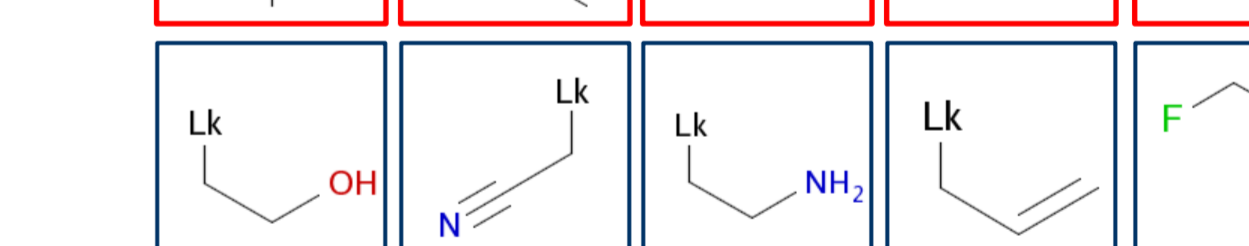
P. Pevarello, et al., J. Med. Chem., 48, 2944-2956, 2005:
39 aminopyrazoles with R1 = cyclopropyl: 37 active, 2 inactive



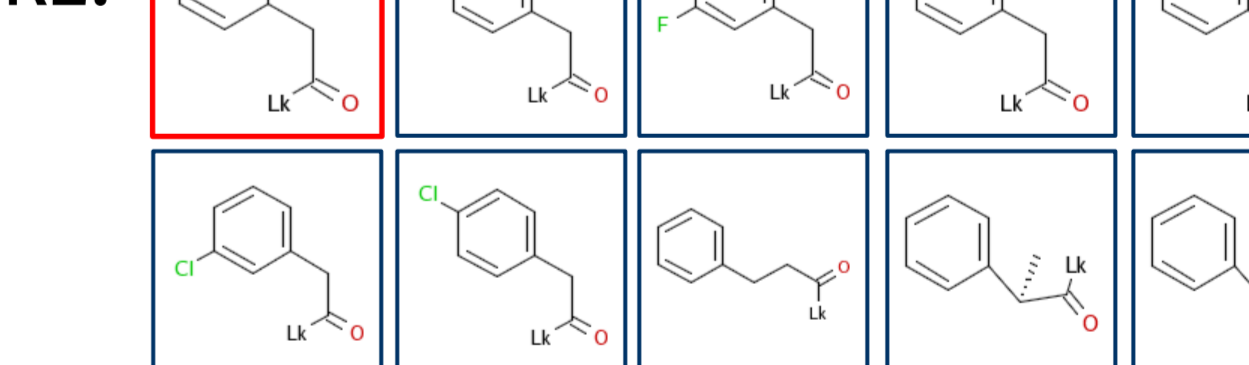
R,S: 169 nM

R: 6000 nM

S: 84 nM



R2:



S: 960 nM

↑ ↑
additionally detected building blocks of actives

Conclusions

In this study the retrospective design of a focused CDK2 library with LoFT is presented. It is shown how 3D criteria can be included in the design process by using the FTMatch feature in LoFT. The finally designed library contains known actives and some more compounds worth to be tested.

References

- [1]: M. Rarey, J. Dixon, J. Comput.-Aided Mol. Des., 12, 471-490, 1998
- [2]: U. Lessel et al., J. Chem. Inf. Model, 49, 270-279, 2009
- [3]: J. R. Fischer et al., J. Chem. Inf. Model., 50, 1-21, 2010
- [4]: ROCS, version 3.1.0, Open Eye Scientific Software: Santat Fe, NM., 2010

Acknowledgements

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