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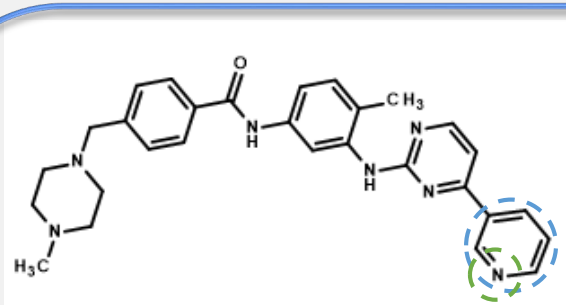
Привилегированные аннотированные библиотеки

Privileged Fragments Annotated library

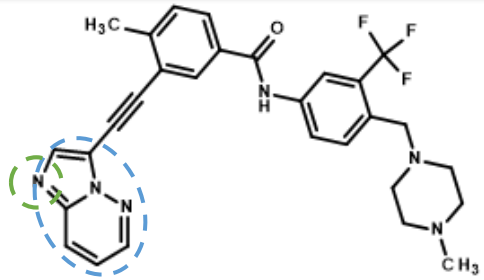
We improve the quality of life by creating new medicines

Main Concept

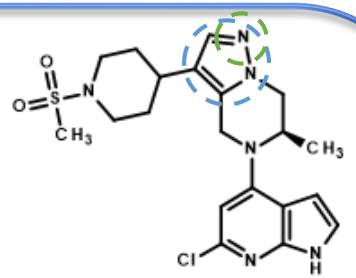
Molecules acting on a particular target or class of targets usually have characteristic moieties (PF) containing key binding points responsible for activity, e.g. hinge-binding fragments. We used this principle for the statistical analysis of the reported active molecules and corresponding targets for the annotation of pre-filtered *in house* collection



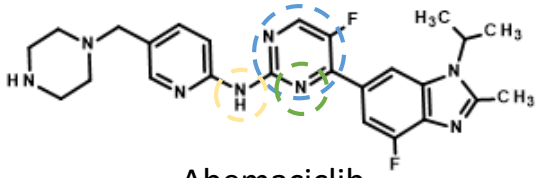
Imatinib



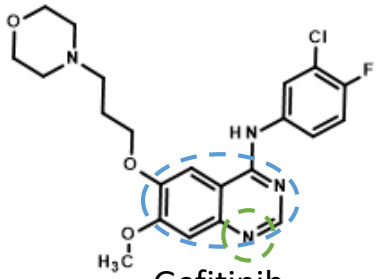
Ponatinib



ATR kinase inhibitor



Abemaciclib



Gefitinib

The main fragments of kinase inhibitors which provide activity due to binding in the hinge region of the ATP site.

Approach

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Input: the database of molecules annotated by target (or target class) and activity (ChEMBL hierarchy, activity ≤10 μM); more than 800K molecules and 6M activity records

ChEMBL

Automated privileged fragments (PFs) identification

(extract sets of structural fragments which are privileged for a target class)

PFs matching for a molecule:

- *for each PF - calculate contribution ratio: $\%(MW_{mol}/MW_{PF})$*
- *PFs sorting by the ratio*
- *calculate score: rank × PF score*
- *Final score normalization*

Annotation of molecules by score

Selection of target classes with a statistically significant number of active molecules (23 classes)

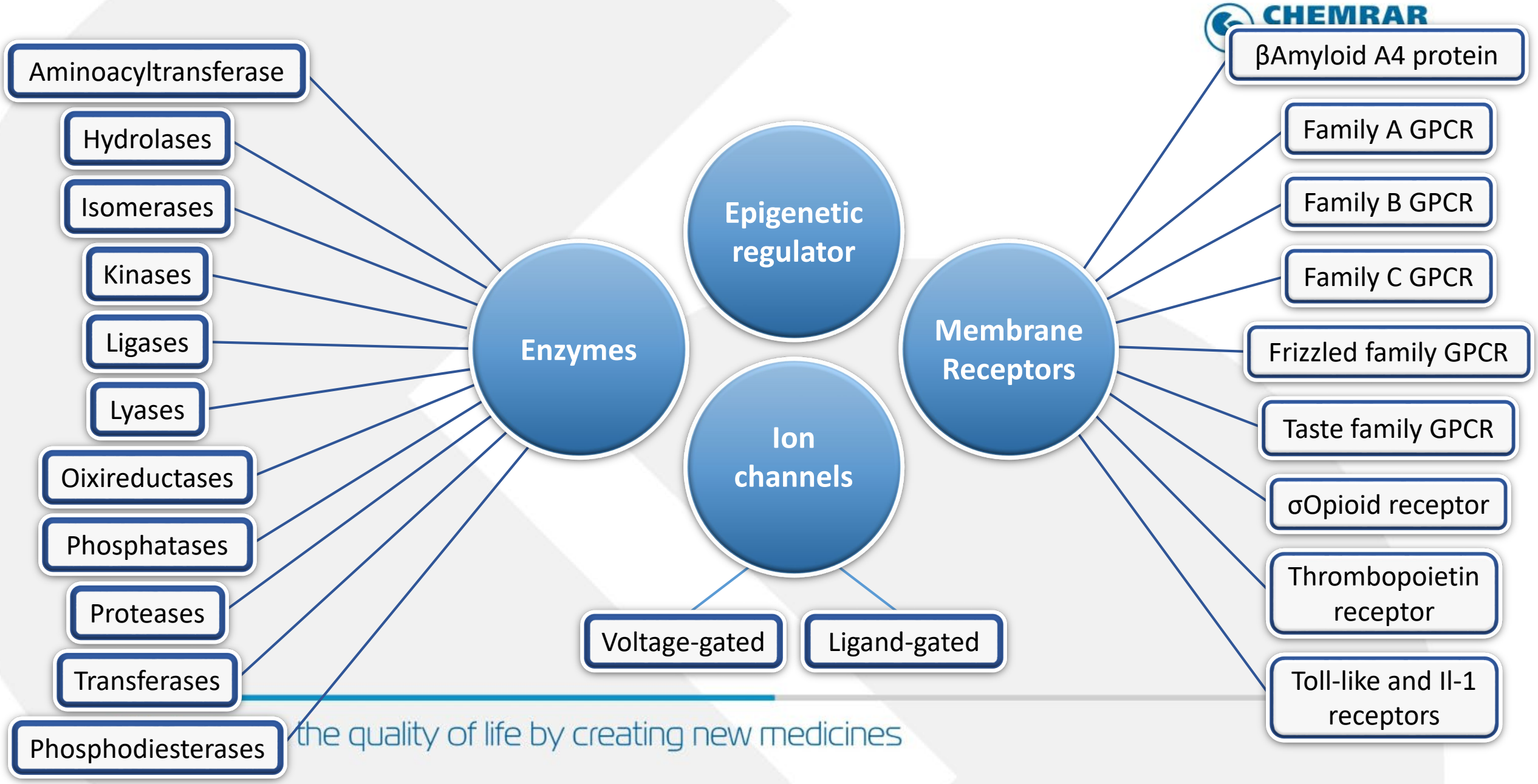
Statistical analysis:

Comparing fragments in classes:

- *Epigenetic regulator vs Membrane receptors, Enzymes, Ion Channels*
- *Ion Channels > Voltage-gated vs Ligand-gated*
- *Membrane receptors > each against each*
- *Enzymes > each against each*

Prioritization of the identified PFs by scoring function to select a set of the most significant fragments for obtaining an appropriate target-specific profile

Classification of PFs



Automated privileged fragments (PFs) identification

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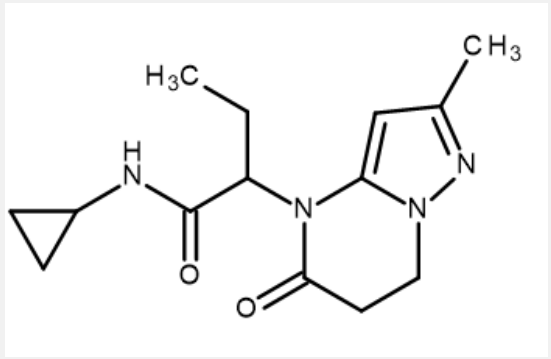
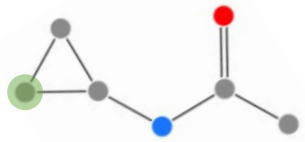
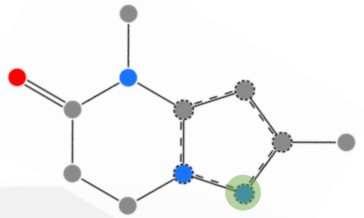
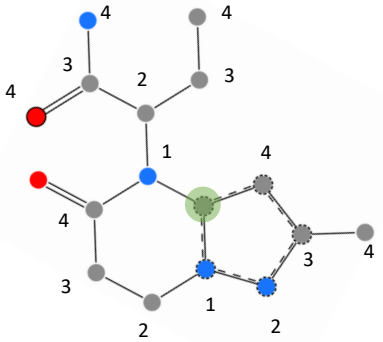


Morgan fingerprints examples

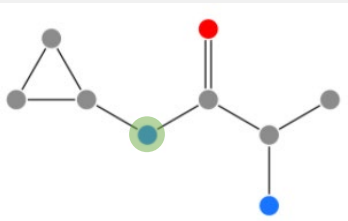
Radius 4

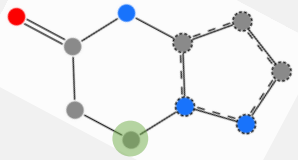


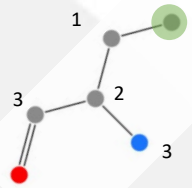




Radius 3







The molecule structure was separated by Morgan fingerprints:

- radius 3 and 4
- do not separate aromatic ring
- terminal atom includes an atom in a non-aromatic ring and the addition of a double bond
- remove duplicate fingerprints

PFs examples

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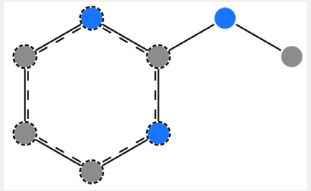
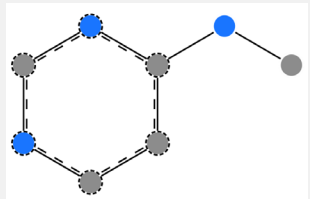
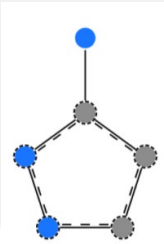
Kinases



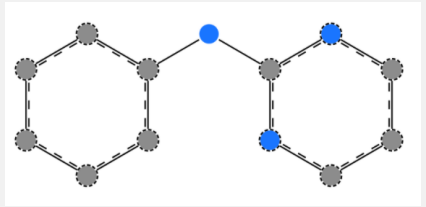
Score: 138.6



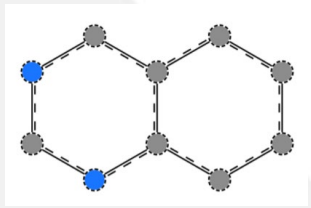
Score: 120.1



Score: 101.7

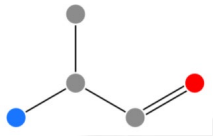


Score: 100.8

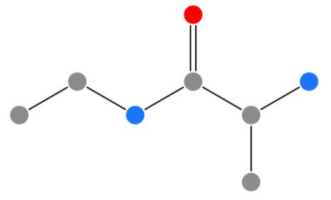


Score: 68.45

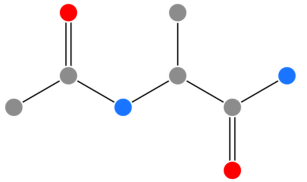
Proteases



Score: 220.7

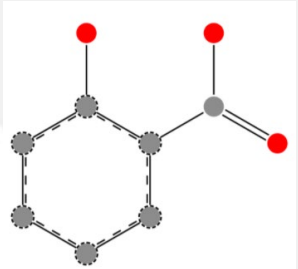


Score: 191.3

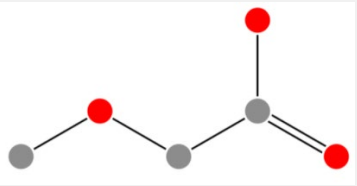


Score: 146.5

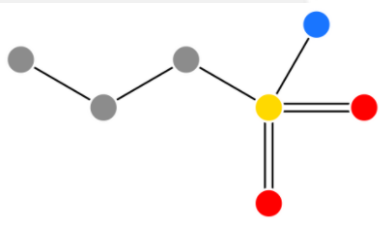
Phosphotases



Score: 55.42



Score: 53.66



Score: 34.36

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Examples

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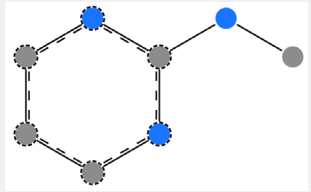
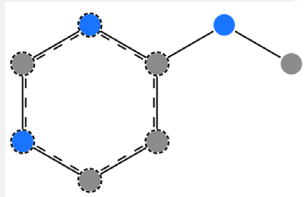
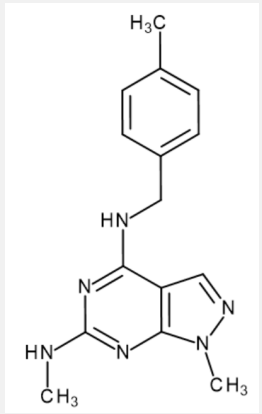
Kinase inhibitors

PF examples

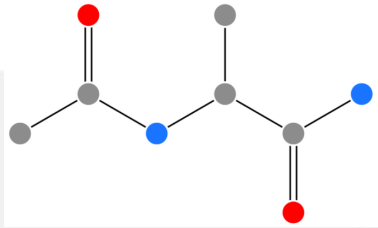


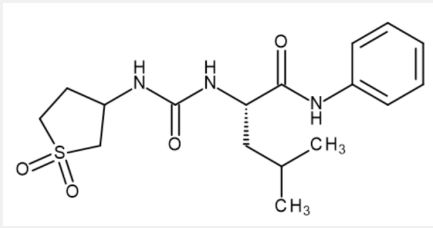


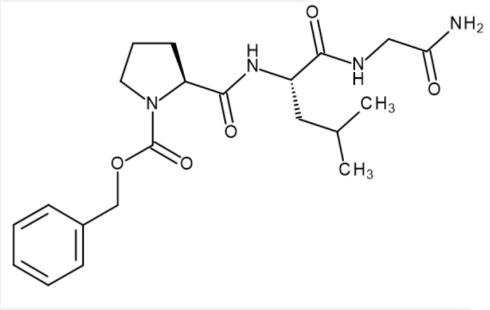


Protease inhibitors

PF example

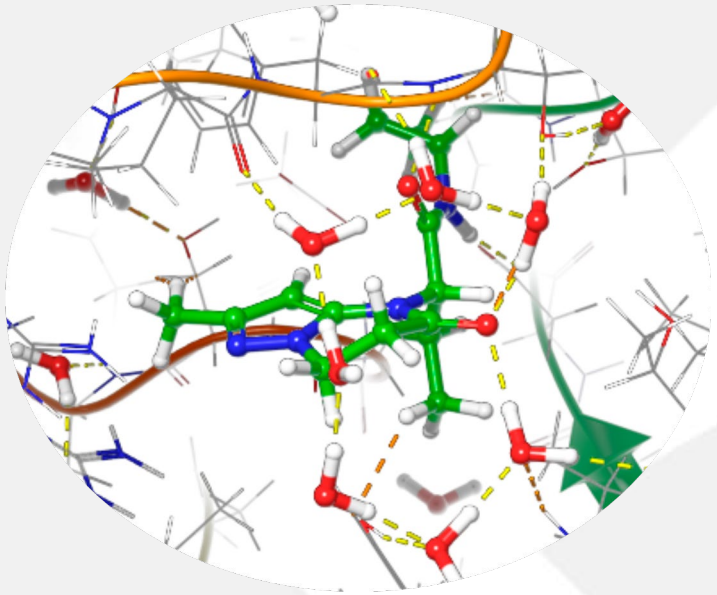




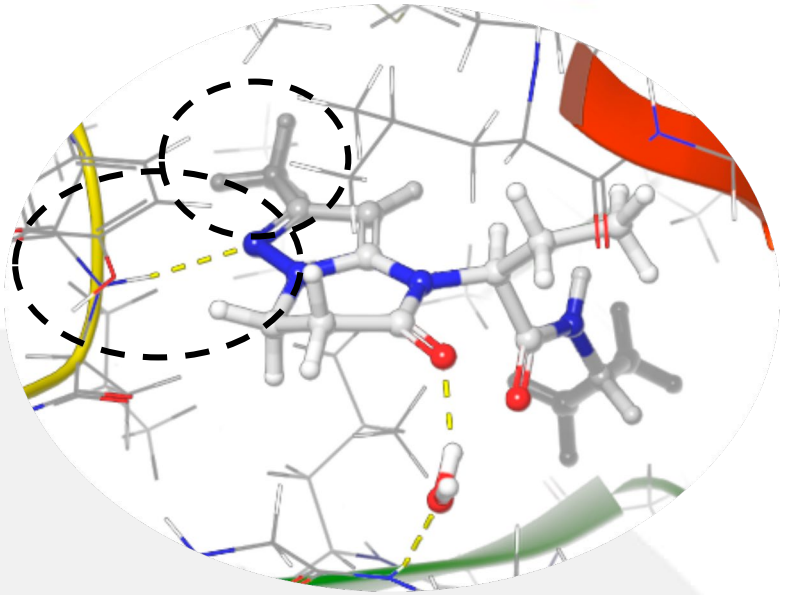


Molecular Docking

gatekeeper



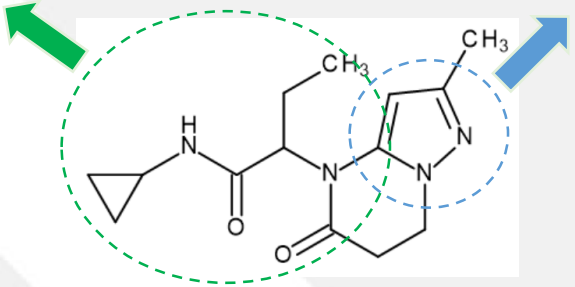
Hinge region



BACE1 binding site

JAK3 binding site

EXAMPLE:



This molecule was scored as potential protease and kinase inhibitor

LogP: 0.94
LogSw: -3.38
PSA: 67.23
HBD: 1
HBA: 3
FRB: 4

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Благодарим за внимание

Инструкция по заказу соединений из библиотеки «ХимРар»:

Наш сайт: https://chemrar.ru/library-full-list/

Направьте список интересующих соединений на email: vvk@chemrar.ru

В соответствии с вашим запросом менеджер выполнит подборку соединений и направит информацию о наличии. Имеется возможность сделать поиск по структуре/буквенному идентификатору (ID, CAS, MFCD), а также импортировать файл в различных форматах: SMILE, sdf, txt.