Repurposing of Approved Drugs for Alzheimer's Disease

Devaraja Mudeppa
Data Scientist
04/16/2024

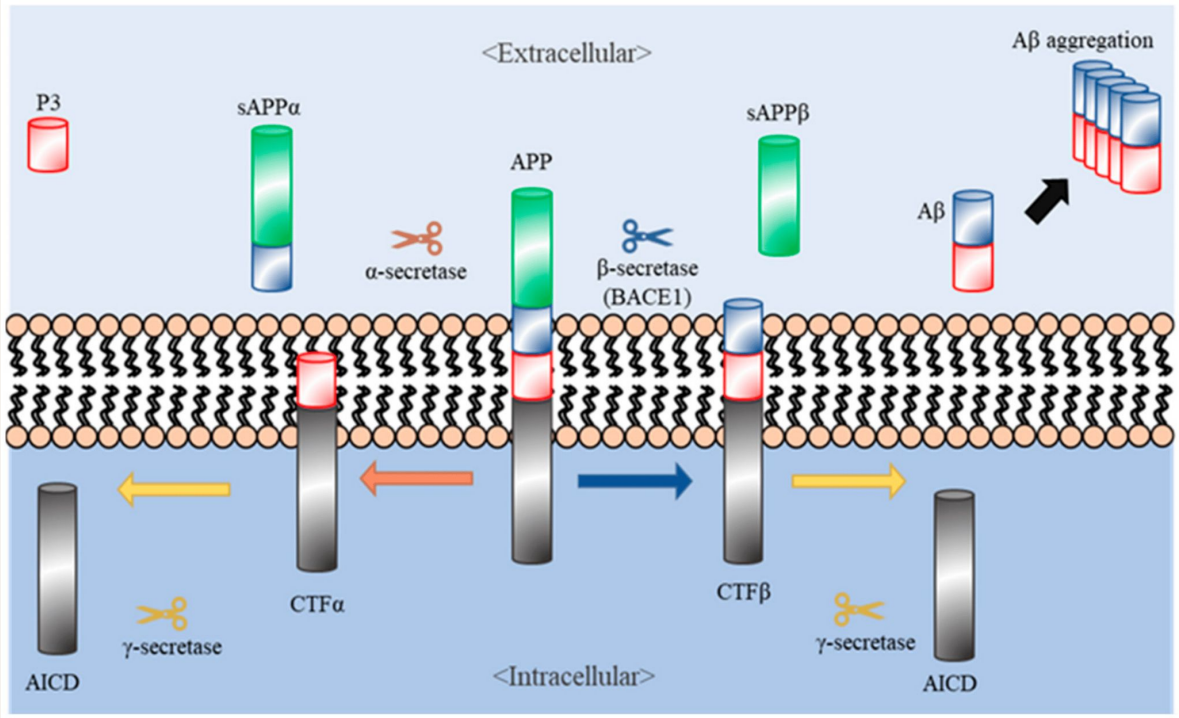
Table of contents

Alzheimer's Disease

- A brain disorder — affects older people
- Gradually declines memory and cognitive abilities
- 55 million cases worldwide, 7 million in the USA
- 10 million new cases each year
- 1.3 trillion USD global economic burden
- Memory and thinking task based diagnosis
- No cure

https://www.who.int/news-room/fact-sheets/detail/dementia

β-Secretase(BACE1) is a validated drug target



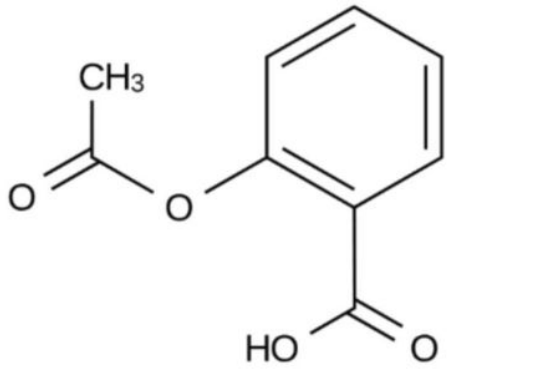
The β-secretase enzyme BACE1 as a therapeutic target for Alzheimer's disease | Alzheimer's Research & Therapy (springer.com)

IJMS | Free Full-Text | Natural Products Targeting Amyloid Beta in Alzheimer's Disease (mdpi.com)

Retrieve BACE1 inhibitors and approved drugs

chEMBL database

- Over 2.4 million molecules
- From early stage inhibitors to approved drugs
- Bioactivities, targets, assays
- User friendly download options



Acetylsalicylic Acid (Aspirin)

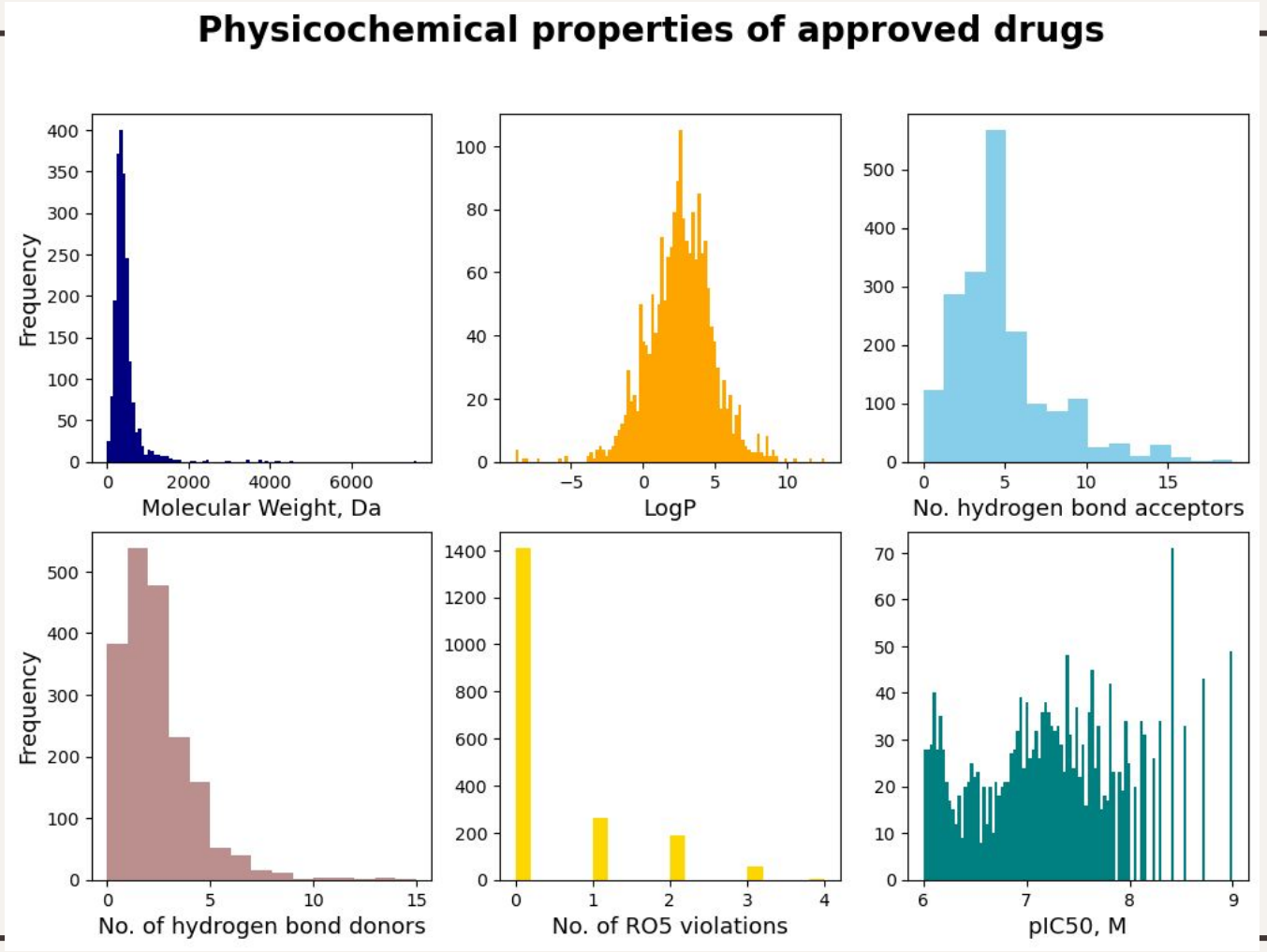
CC(=O)Oc1ccccc1C(=O)O

- 3336 approved drugs
- 10619 BACE1 inhibitors
- Simplified Molecular Input Line Entry System — SMILES

EDA: Approved Drugs

Lipinski rule of 5:

1. Mol. weight ≤ 500 Da
2. H-bond donors ≤ 5
3. H-bond acceptors ≤ 10
4. logP ≤ 5
5. Good absorption & permeation



EDA: BACE1 inhibitors

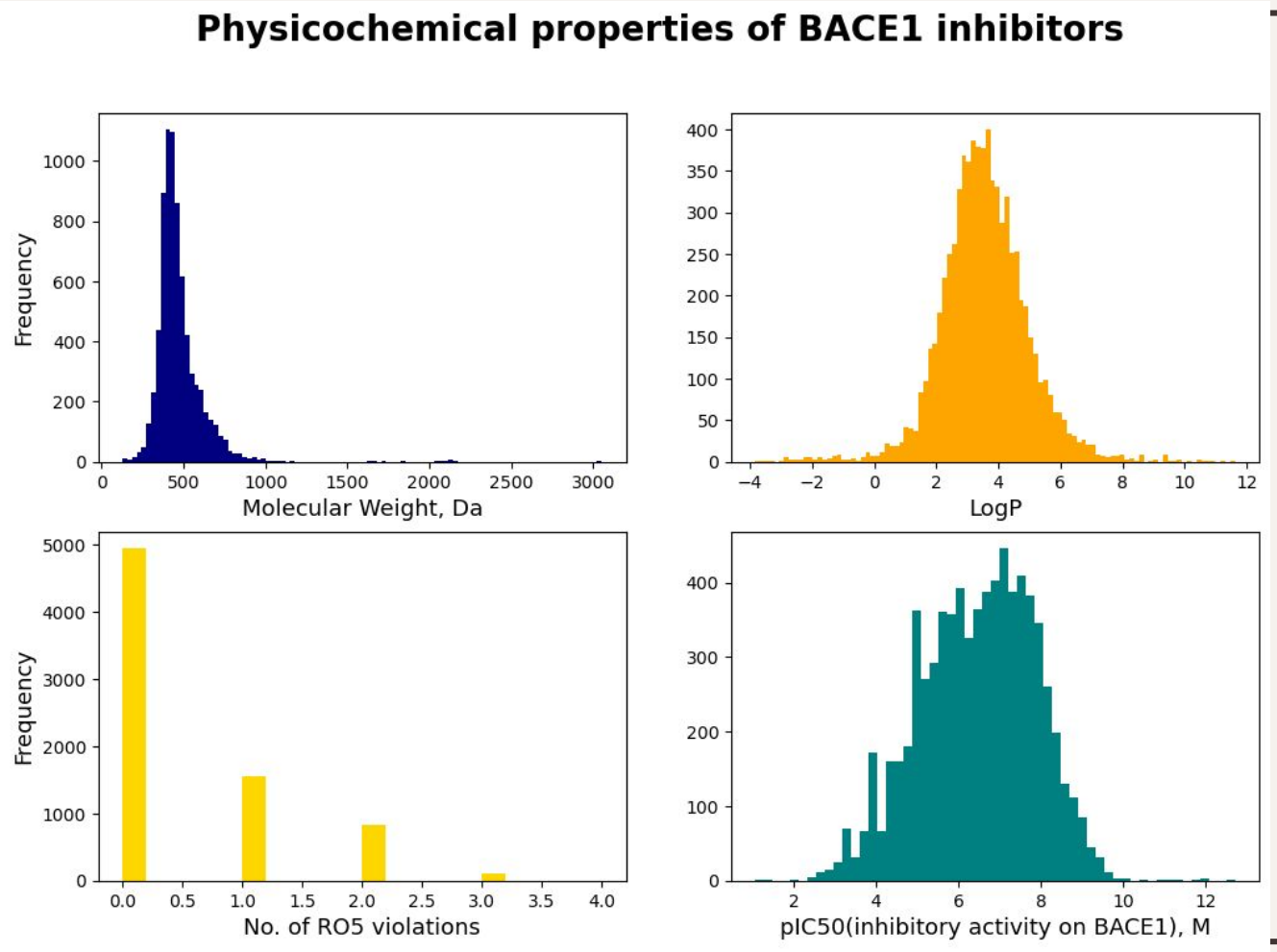
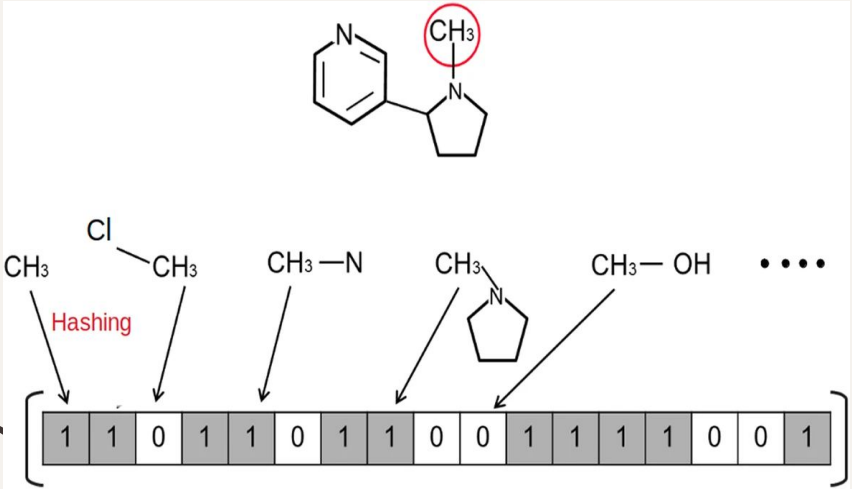


Table of contents

Vectorization of molecules for ML

CN1CCCC1c2ccccc2

SMILES - based on ASCII strings



- Molecular ACCess Systems keys (MACCSkeys) fingerprint
- 167-bit morgan fingerprints
- Each bit is either on(1) or off(0)
- Commonly used for molecular similarity Search

Convolutional architectures for virtual screening | BMC Bioinformatics (springer.com)

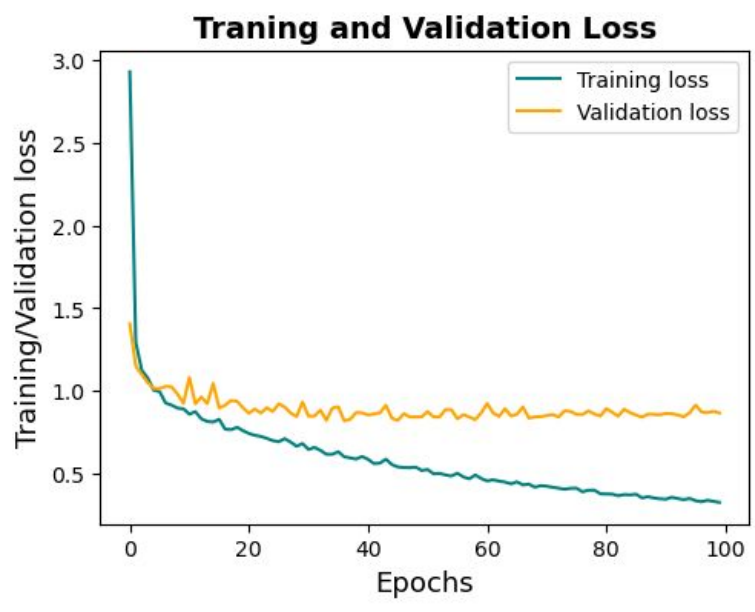
Convolutional neural net model

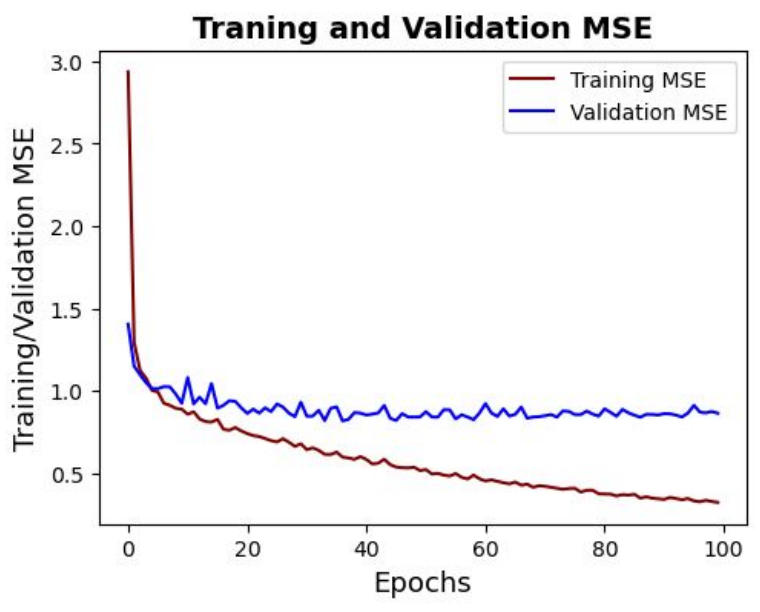
- X : Molecular Fingerprints
- y : Activity(pIC50)
- Split the data

```
model = Sequential([
    Conv1D(32, 3, activation = 'relu', input_shape = (167, 1)),
    MaxPooling1D(2),
    Conv1D(64, 3, activation = 'relu'),
    MaxPooling1D(2),
    Flatten(),
    Dense(64, activation = 'relu'),
    Dense(1, activation = 'linear')
])
```

```
model.compile(
    loss = 'mean_squared_error',
    optimizer = 'adam',
    metrics = ['mse', 'mae']
)
```

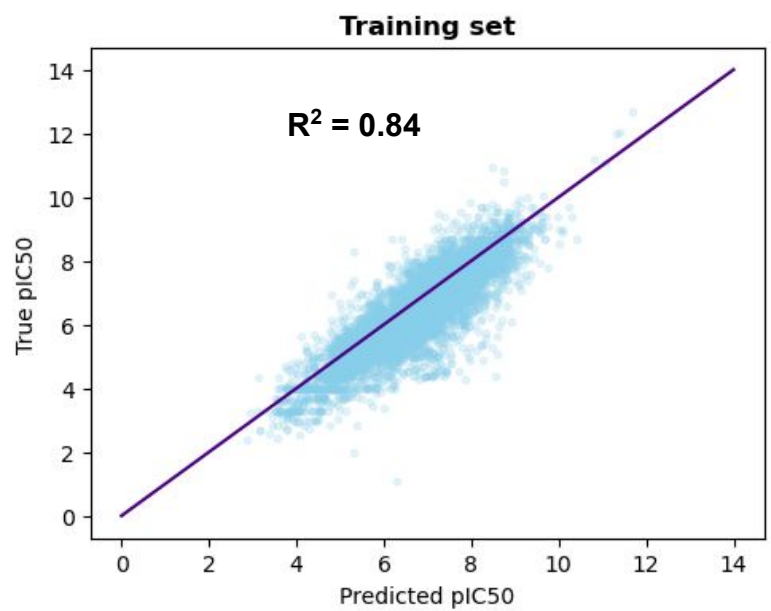
Performance of CNN model

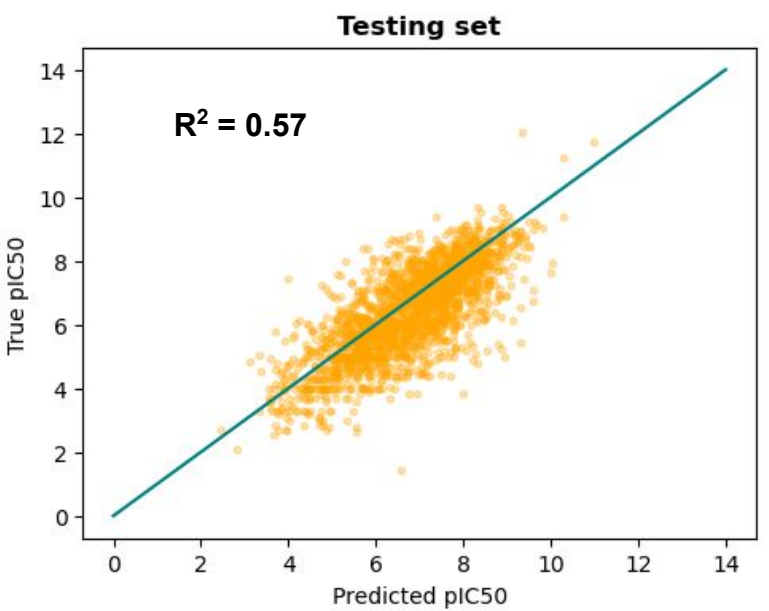




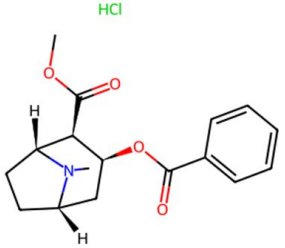
MSE: 0.71; MAE: 0.86

Correlation of true vs predicted values

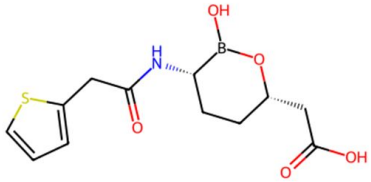




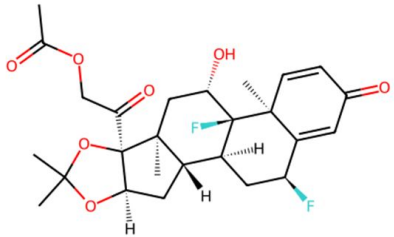
Top 5 hits as BACE1 inhibitors from approved drugs



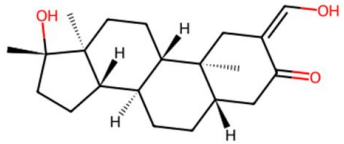
pIC50 value: 3.60



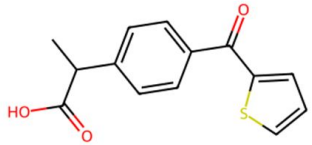
pIC50 value: 3.61



pIC50 value: 3.61

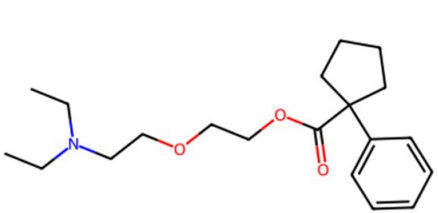


pIC50 value: 3.61

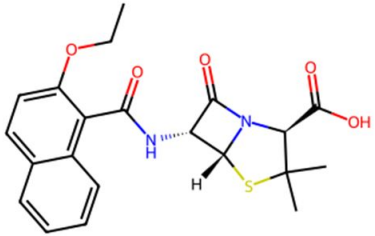


pIC50 value: 3.62

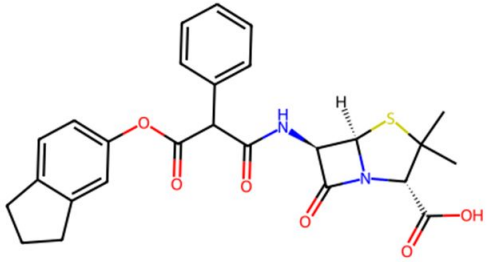
Bottom 5 hits as BACE1 inhibitors from approved drugs



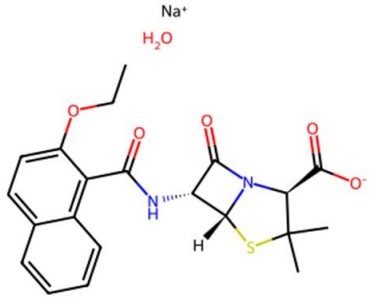
pIC50 value: 10.43



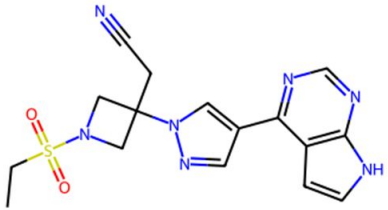
pIC50 value: 10.21



pIC50 value: 9.15



pIC50 value: 9.06



pIC50 value: 9.05

Table of contents

Acquisition of BACE1 structure from PDB

Parameters to fetch BACE1 structures:

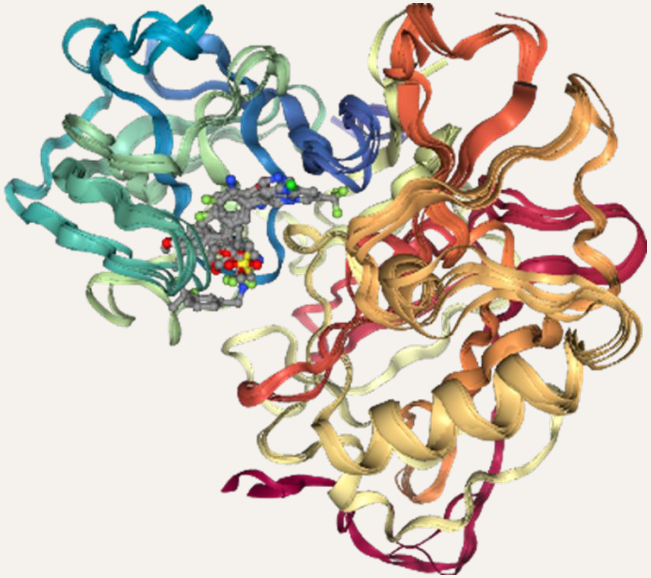
Uniport ID:	**P56817**
Deposition date:	**Upto date**
Experimental method:	**X-ray diffraction**
Maximum resolution:	**2.0 Angstrom**
Number of chains:	**1**
Minimum ligand MW:	**100.0**

Total structures: 431
Structures met parameters: 143

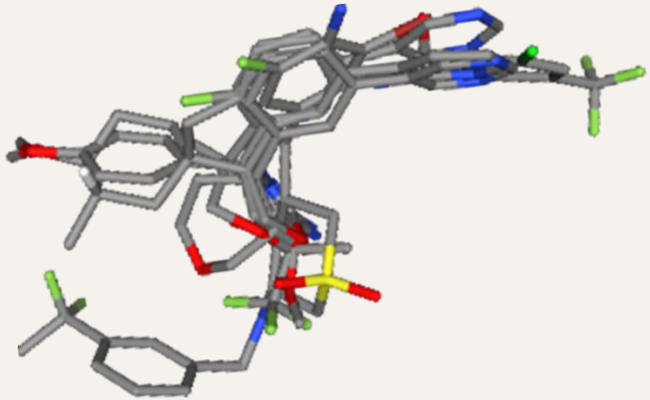
Picked for molecular modeling: 5

Align BACE1 structures to visualize inhibitor binding sites

Aligned BACE1 structures



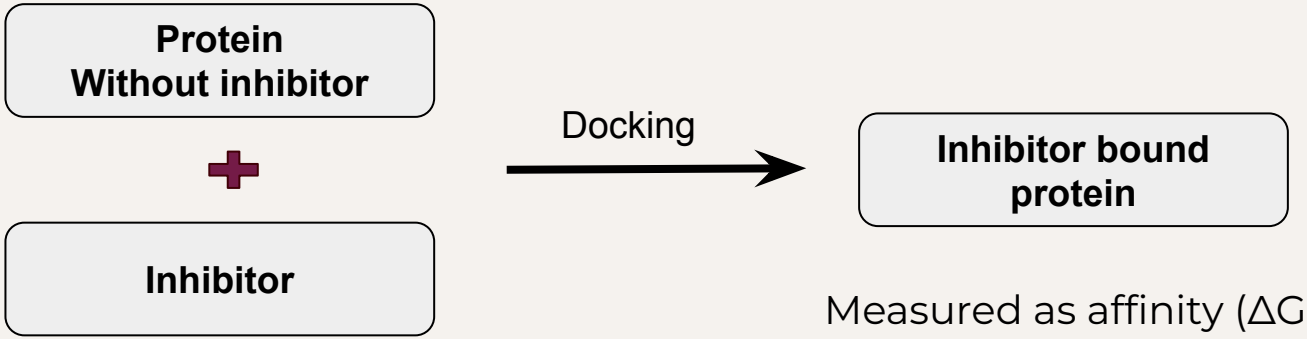
Aligned BACE1-inhibitor structures



OpenCADD from **Volkamer Lab**

Rdkit and other routine python modules

Protein-inhibitor docking



Measured as affinity (ΔG)
Lower the energy, better the binding

Inhibitors stripped from BACE1(PDBQT)
Inhibitors extracted(PDBQT) from BACE1 structures
AutoDock Vina

BACE1 docking with an inhibitor

[13]:
```
output_text = run_smina(
    DATA / "ligand.pdbqt",
    DATA / "protein.pdbqt",
    DATA / "docking_poses.sdf",
    pocket_center,
    pocket_size,
)
print(output_text)
```

```
 _______  _______ _________ _        _______
(  ____ \(       )\__   __/( (    /|(  ___  )
| (    \/| () () |   ) (   |  \  ( || (   ) |
| (_____ | || || |   | |   |   \ | || (___) |
(_____  )| |(_)| |   | |   | (\ \) ||  ___  |
      ) || |   | |   | |   | | \   || (   ) |
/\____) || )   ( |___) (___| )  \  || )   ( |
\_______)|/     \|\_______/|/    )_)|/     \|


smina is based off AutoDock Vina. Please cite appropriately.

Weights      Terms
-0.035579    gauss(o=0,_w=0.5,_c=8)
-0.005156    gauss(o=3,_w=2,_c=8)
0.840245     repulsion(o=0,_c=8)
-0.035069    hydrophobic(g=0.5,_b=1.5,_c=8)
-0.587439    non_dir_h_bond(g=-0.7,_b=0,_c=8)
1.923        num_tors_div

Using random seed: 828557488
```

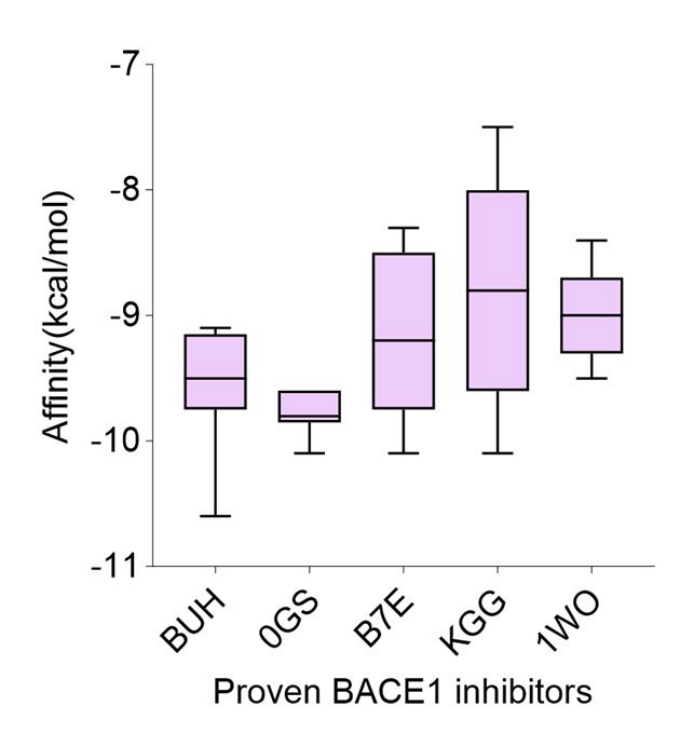
```
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
1       -9.7       0.000      0.000
2       -9.2       2.724      7.743
3       -8.7       2.742      7.685
4       -8.6       2.208      3.425
5       -8.5       2.713      4.033
6       -7.6       3.320      4.870
7       -6.7       1.305      1.911
Refine time 10.179
Loop time 10.842
```

BACE1 docking with proven inhibitors

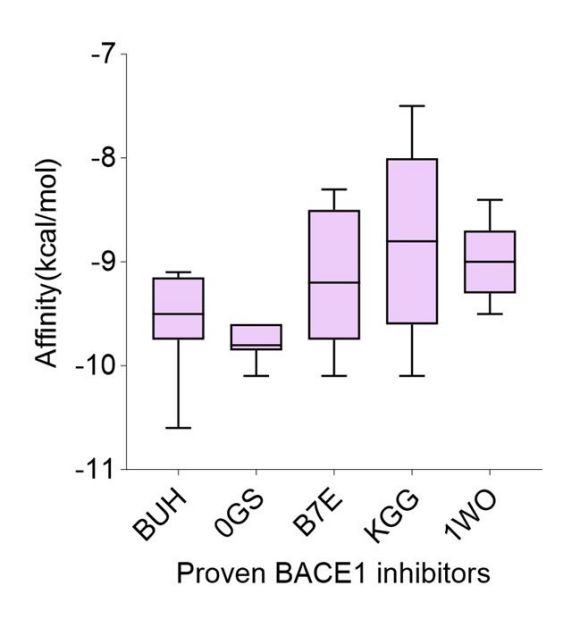
Inhibitors stripped from BACE1

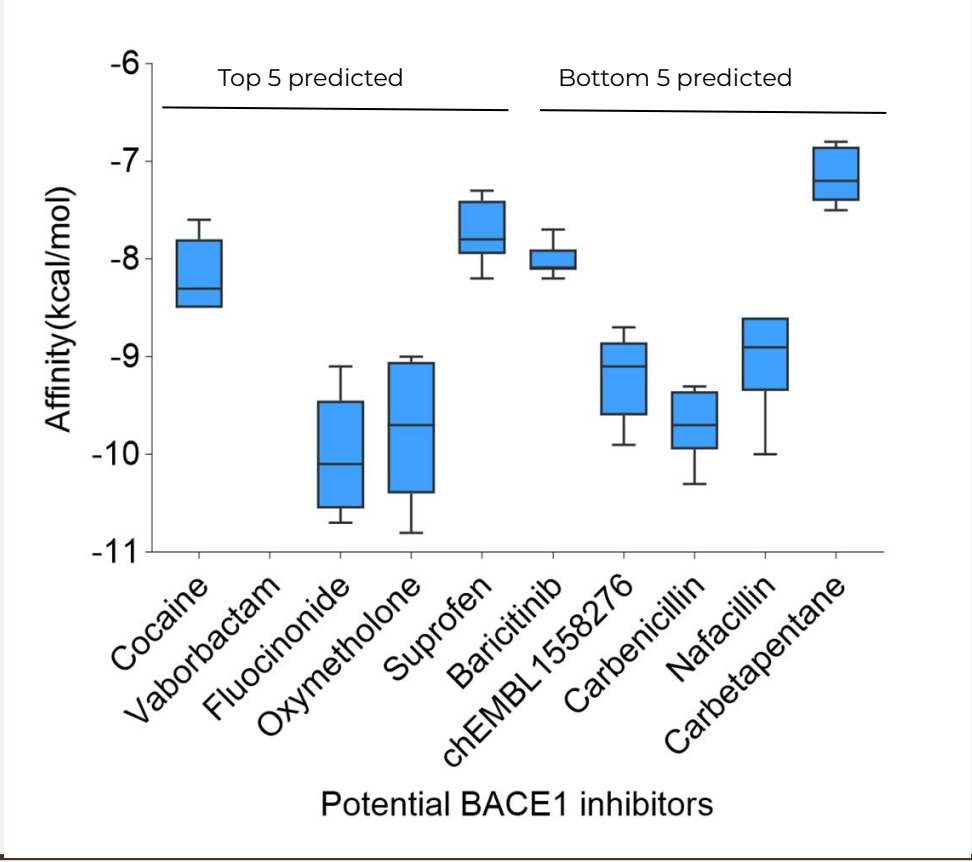
Inhibitors extracted from BACE1 structures

AutoDock Vina



BACE1 docking with predicted approved drugs

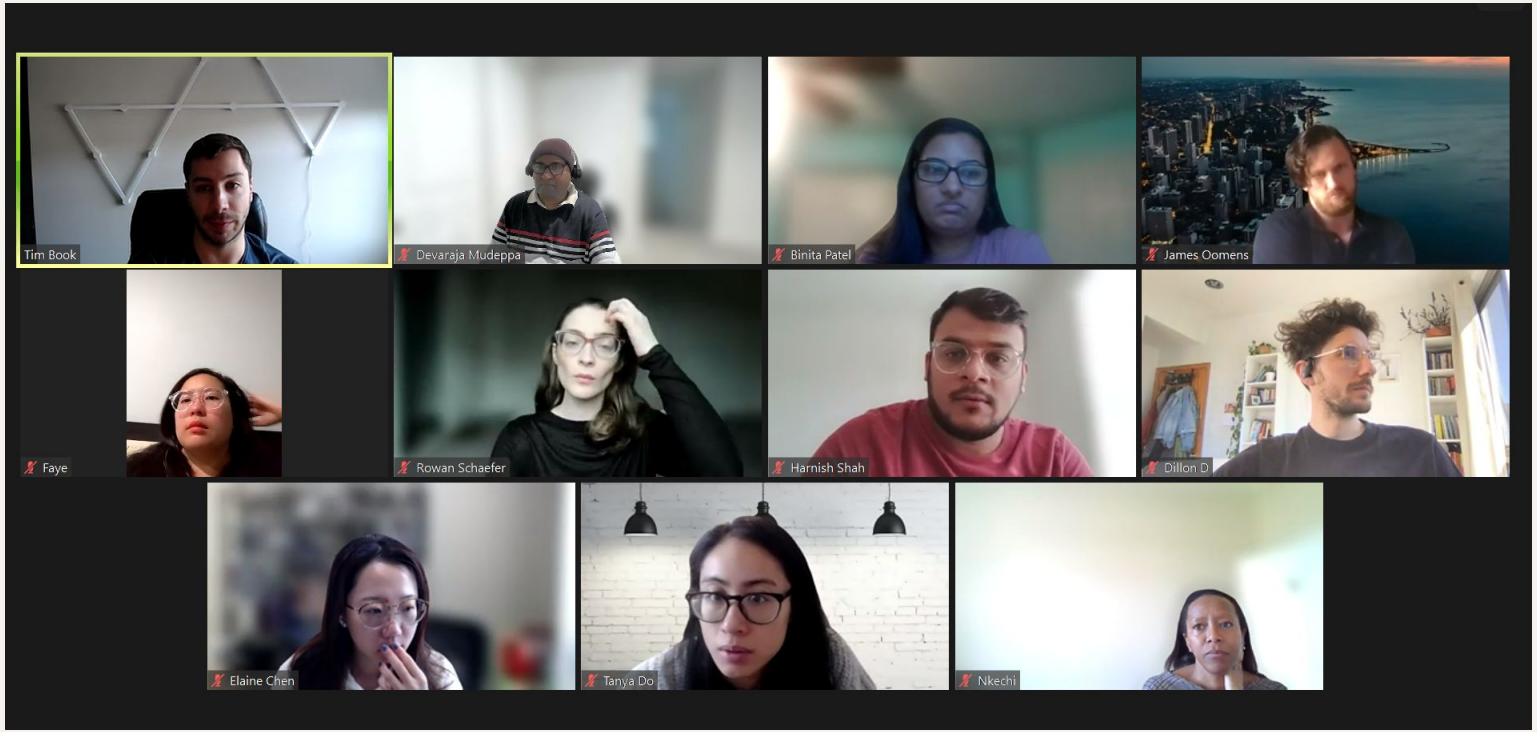




Summary

- There is urgent need to find a cure to Alzheimer's Disease
- Virtual screening offers cost-effective option to test molecules against target
- Docking molecules to target validates the selected molecules
- Significant efforts are underway to improve the predictions using neural nets
- Molecular graphs are considered to better represent chemical structures

THANKS!!!!



Questions?