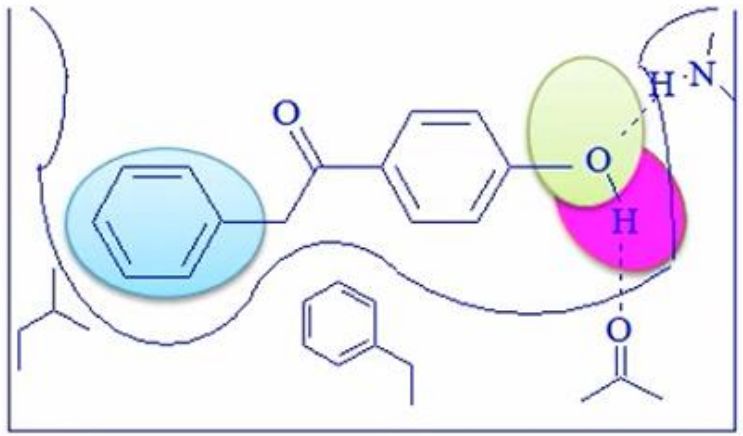
药效团 （Pharmacophore）

- 药效团（**Ehrilich P. 1909**）指活性化合物所共有的，对化合物的活性有重要影响的一组原子或基团的空间排列组合。
- 这些原子或基团称为“药效特征元素”，是配体与受体发生相互作用是的活性部位，可以是某些具体的原子或原子团，比如氧原子、羟基、苯环等，也可以指某些特定的化学功能结构，如疏水团、氢键给体、氢键受体等。
- 药效团反映的是活性位点氨基酸的需求，药效团特征与分子对接的作用方式是一致的。



Hydrophobic (HP)
Hydrogen bond donor (HBD)
Hydrogen bond acceptor (HBA)

药效特征元素

氢键受体： =O —O— =S =NH ≡N

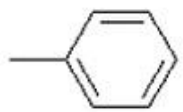
Hydrogen bond acceptor (HBA)

氢键供体： —OH —NH_2 —NH—

Hydrogen bond donor (HBD)

疏水中心：

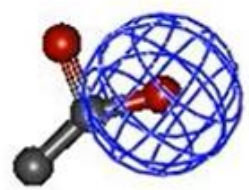
Hydrophobic sphere (HP) —CH_3 —C_2H_5



电荷中心：

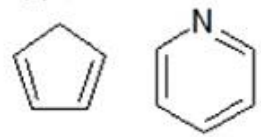
Positive charged N^+ (碱性氮原子）

Negative charged COO^-（羧基）

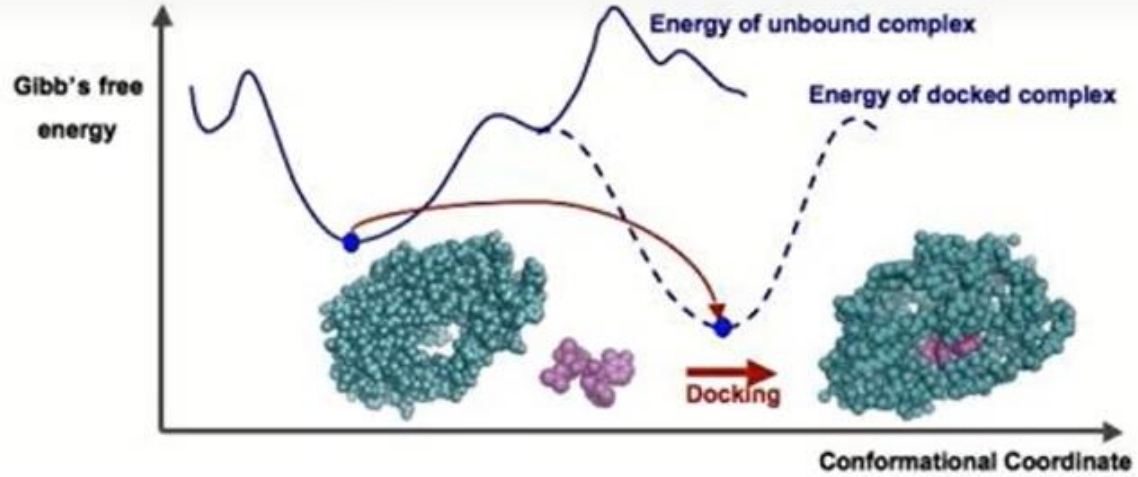


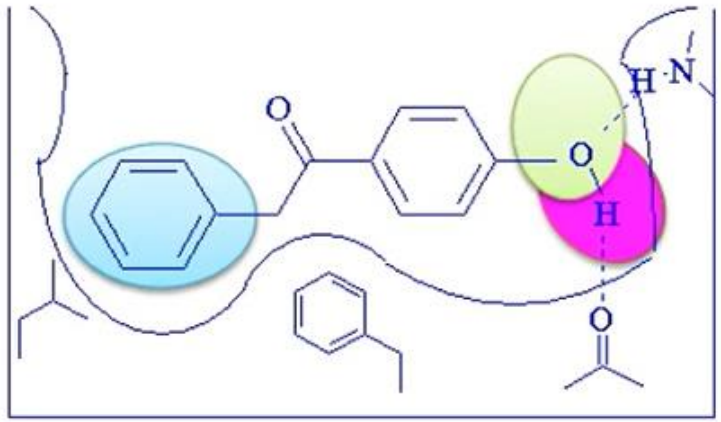
芳环中心：形成π-π相互作用

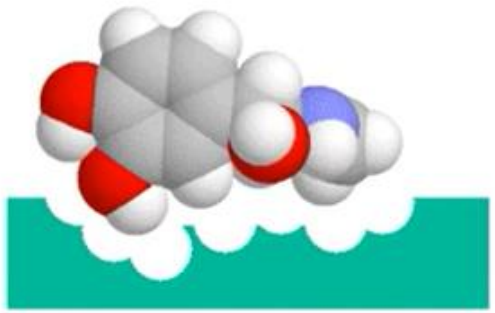
Aromatic group (AR)



药效团 （Pharmacophore）





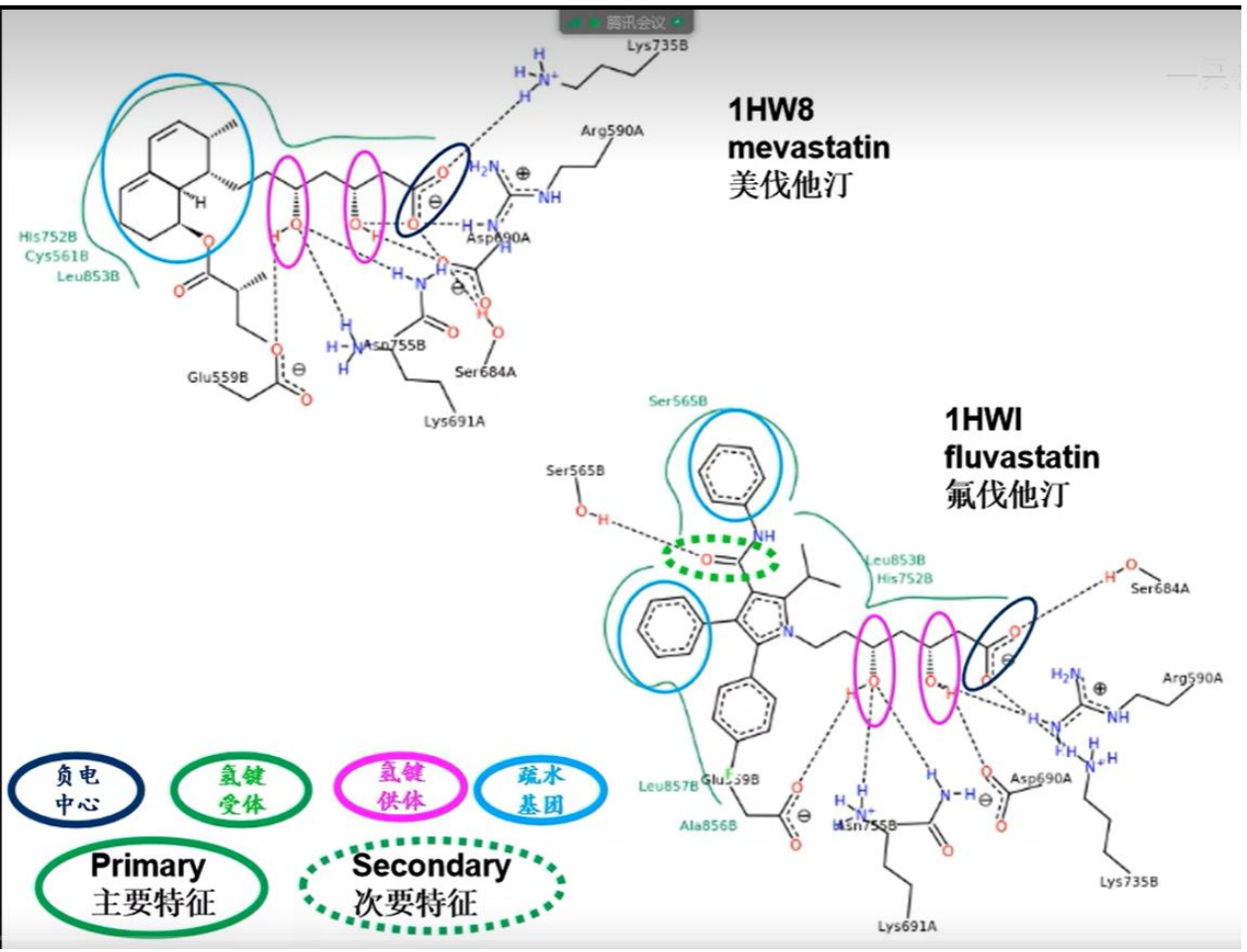


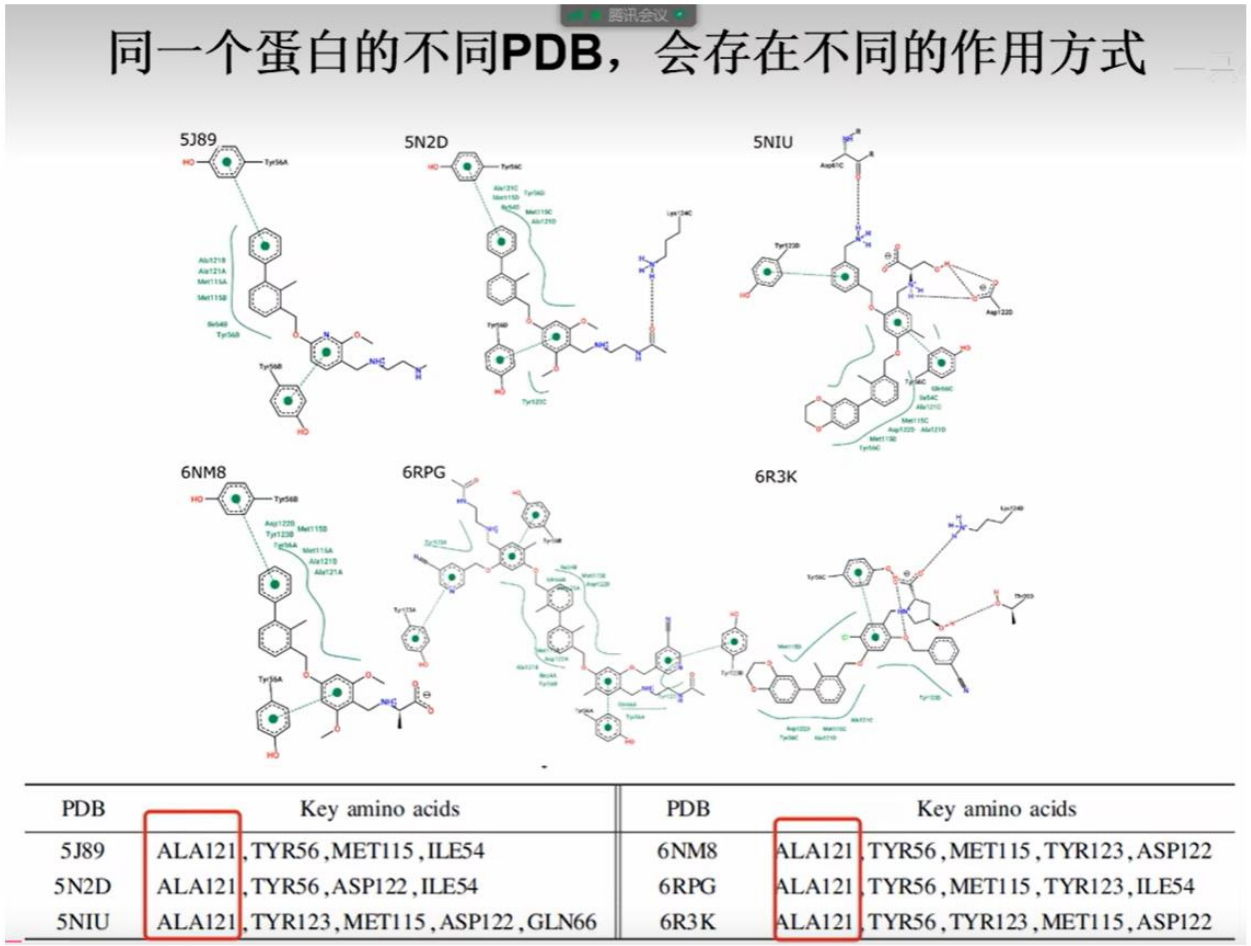
Hydrophobic (HP) 疏水基团

Hydrogen bond donor (HBD) 氢键供体

Hydrogen bond acceptor (HBA) 氢键受体

方法1. 分析一个蛋白的多个结晶结构寻找共性药效团特征





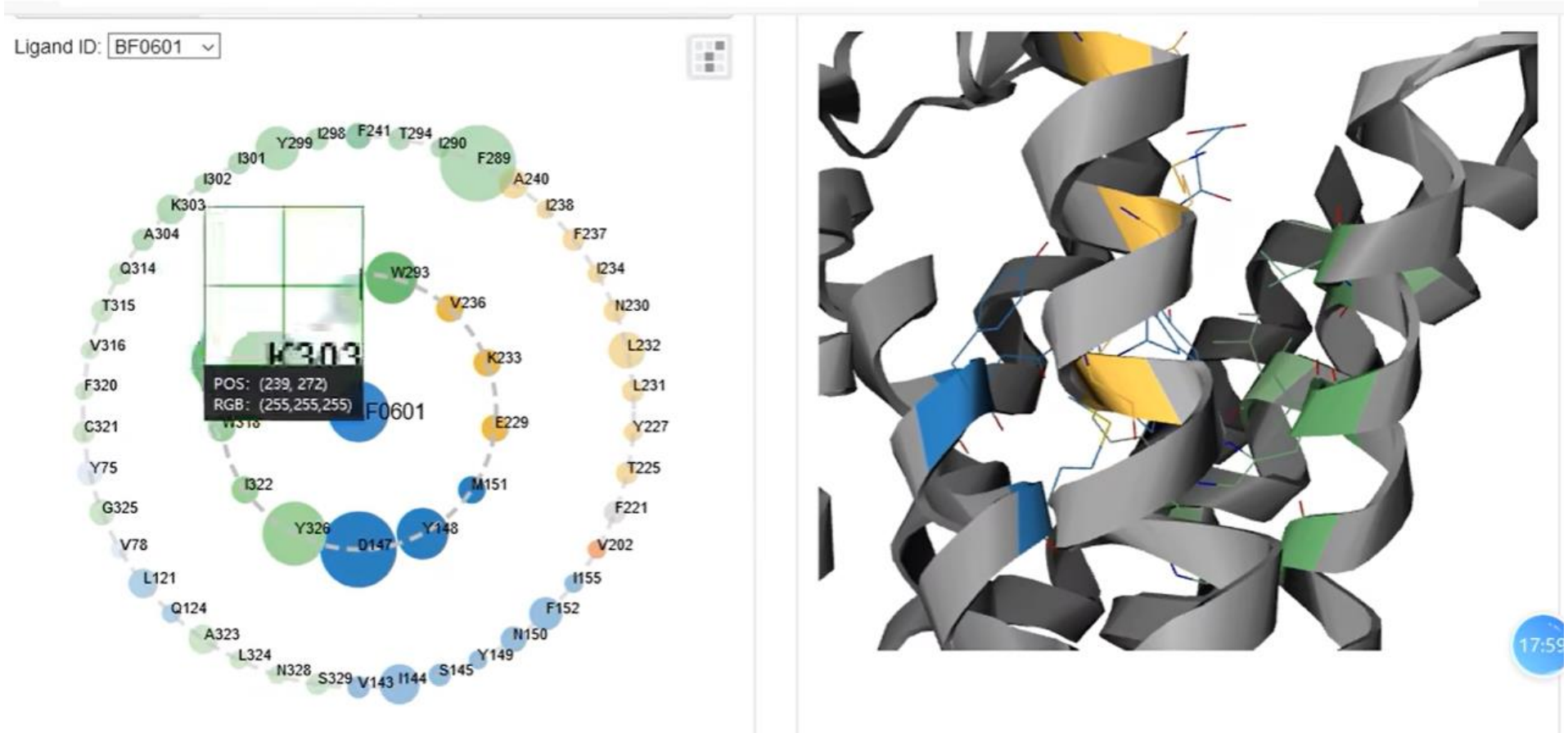
PDB	Key amino acids	PDB	Key amino acids
5J89	ALA121, TYR56, MET115, ILE54	6NM8	ALA121, TYR56, MET115, TYR123, ASP122
5N2D	ALA121, TYR56, ASP122, ILE54	6RPG	ALA121, TYR56, MET115, TYR123, ILE54
5NIU	ALA121, TYR123, MET115, ASP122, GLN66	6R3K	ALA121, TYR56, TYR123, MET115, ASP122

2. 通过Atlas 网站获取关键氨基酸

Protein Contacts Atlas:

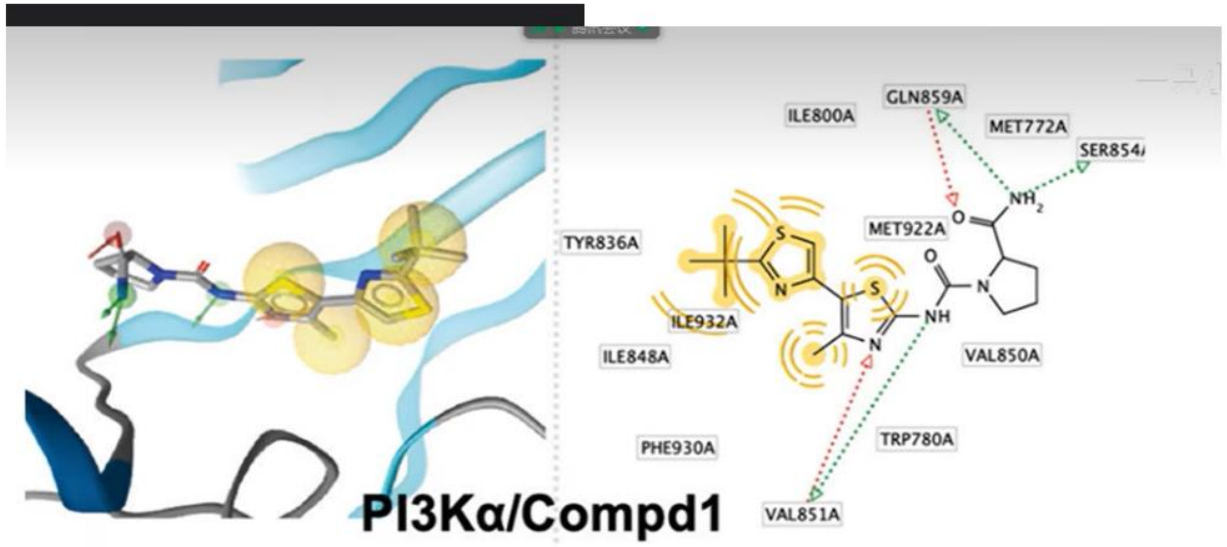
https://www.mrc-lmb.cam.acuk/rajini/index.html

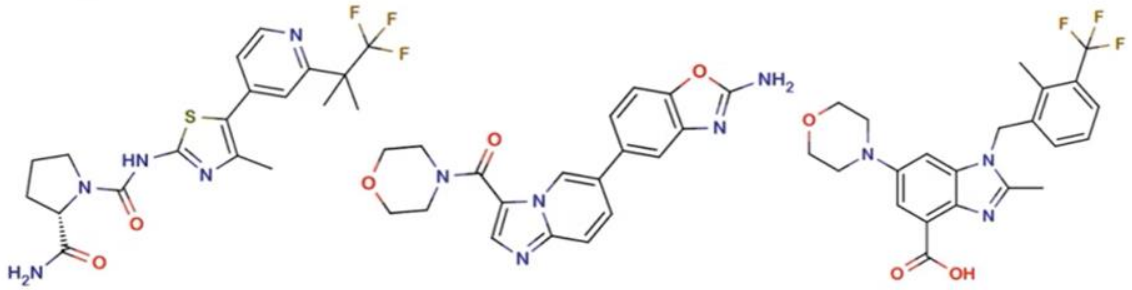
Protein Plus, Pharmit.



方法3. 从文献中获取活性/非活性化合物验证药效团模型

找阳性对照药物验证药效团



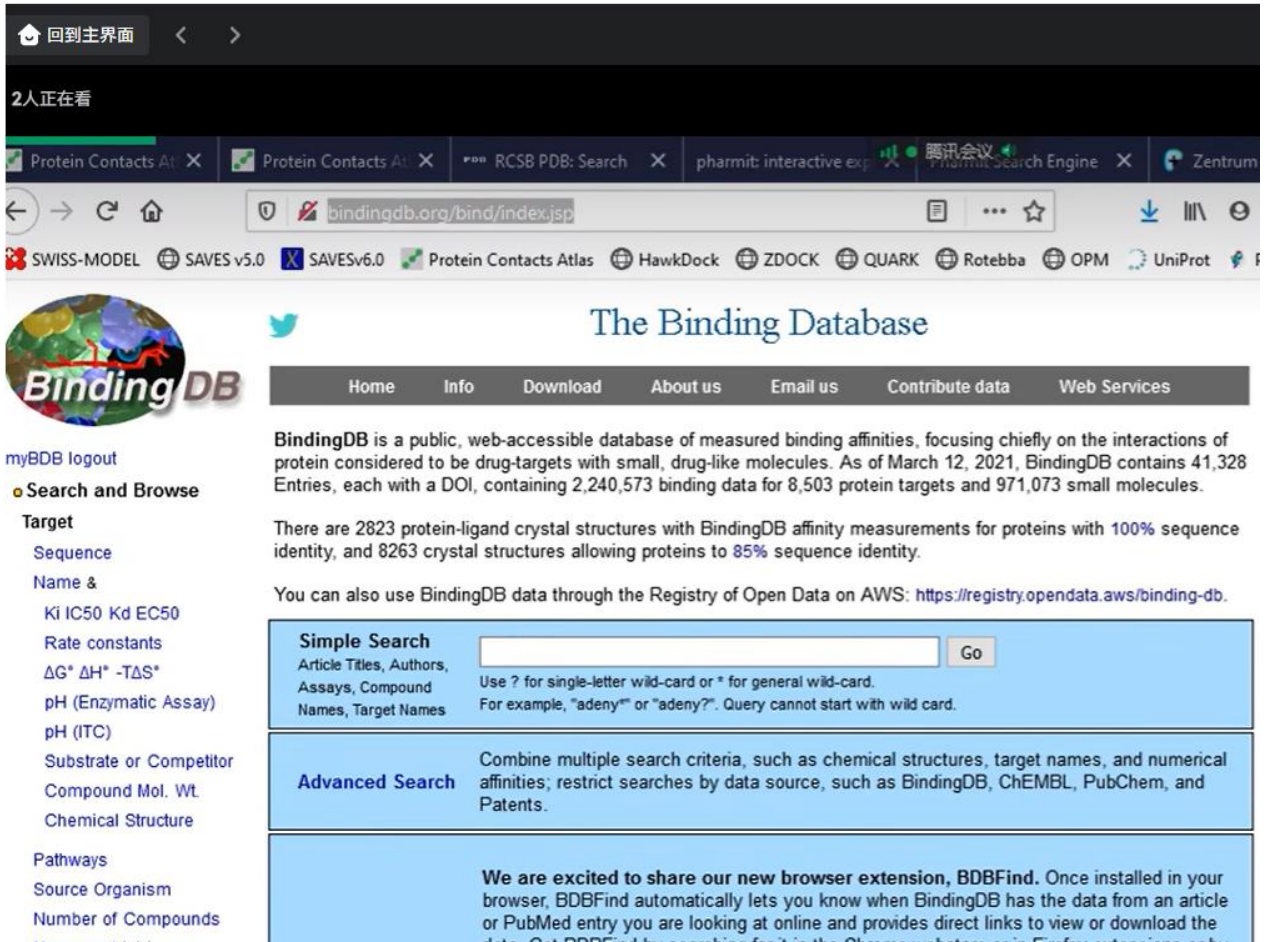


Alpelisib (**1**)
PI3Kα IC_{50} = 4.6 nM

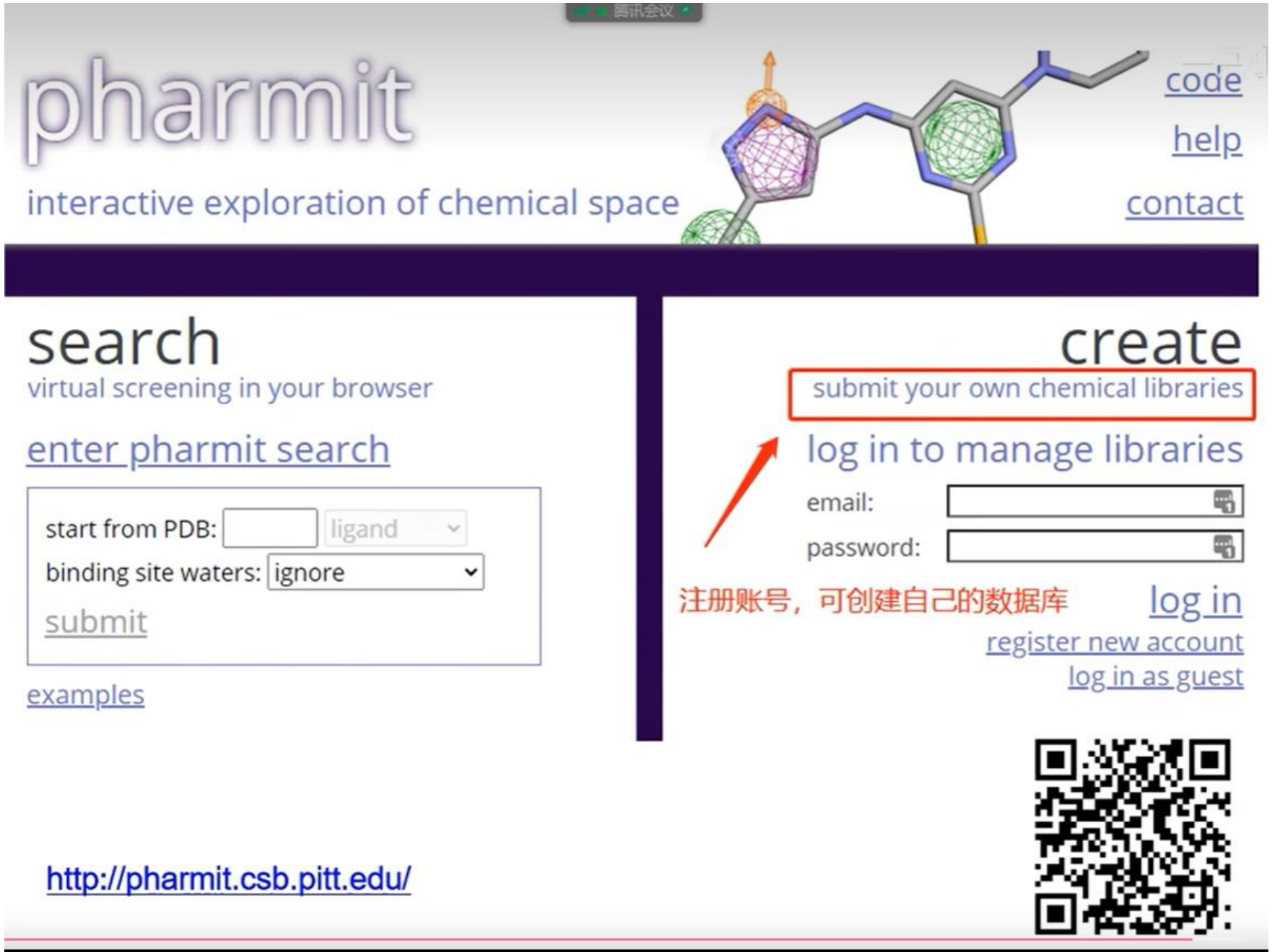
Serabelisib (**2**)
PI3Kα IC_{50} = 15 nM

GSK2636771 (**3**)
PI3Kα IC_{50} > 5800nM

输入受体蛋白,从网站下载获取(阳性)小分子来验证

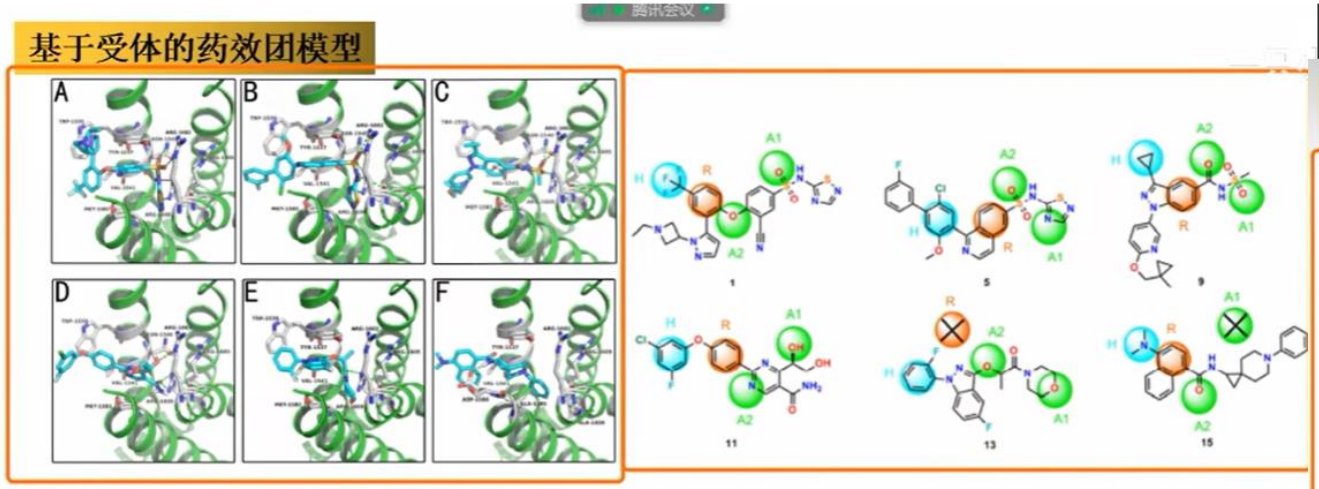


也可用下面网站建立小分子库

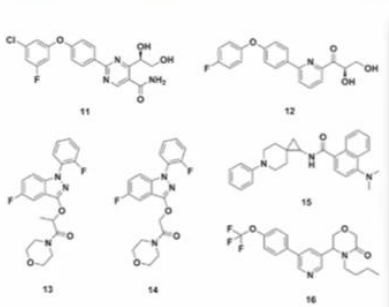


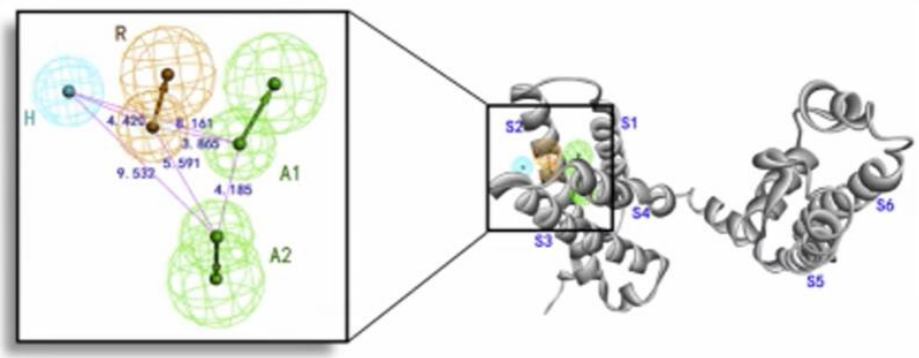
方法4. 基于受体和配体药效团模型相互验证

基于受体的药效团模型

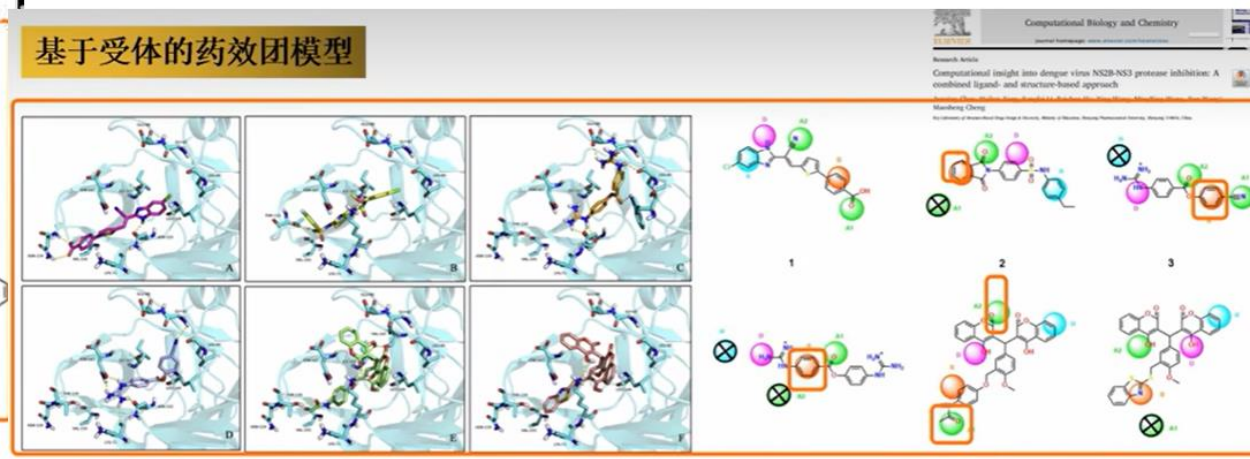


基于配体的药效团模型

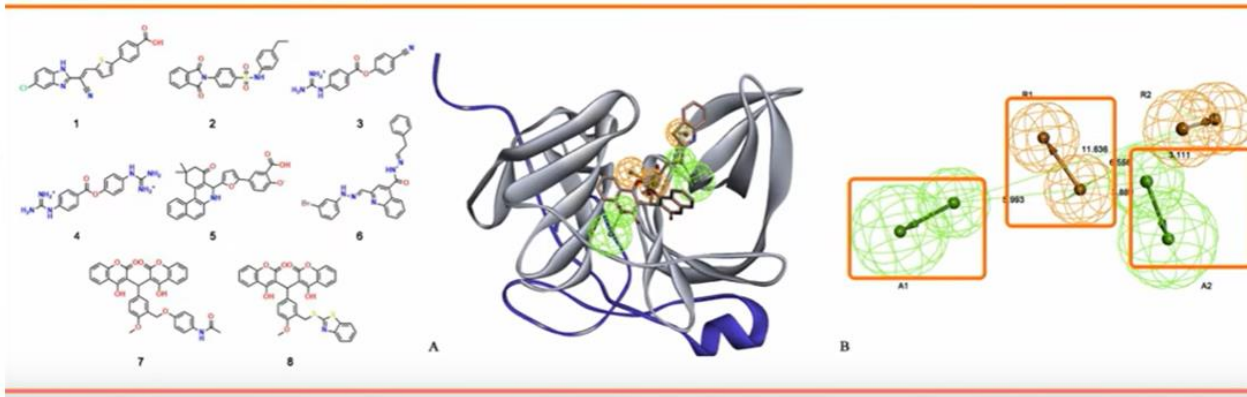




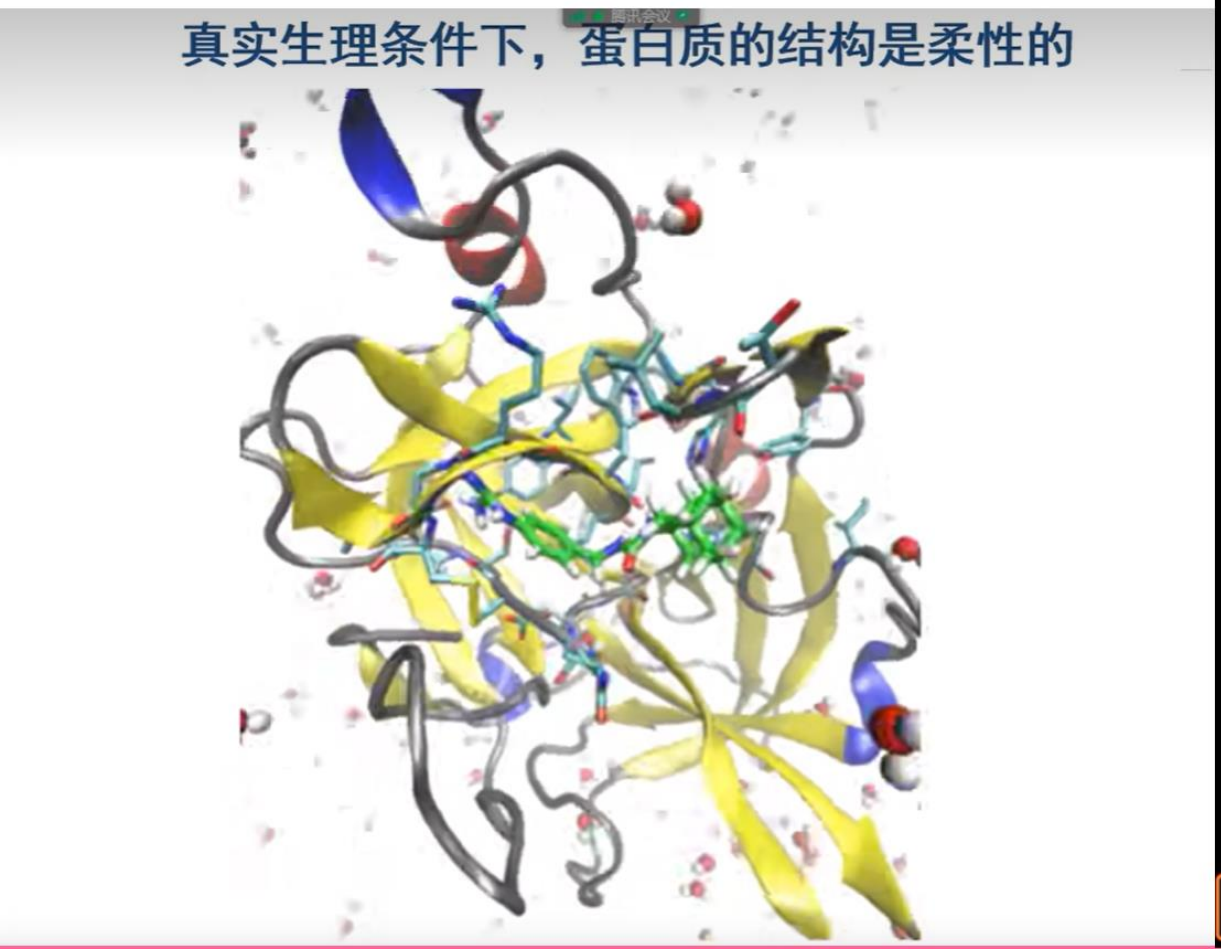
基于受体的药效团模型

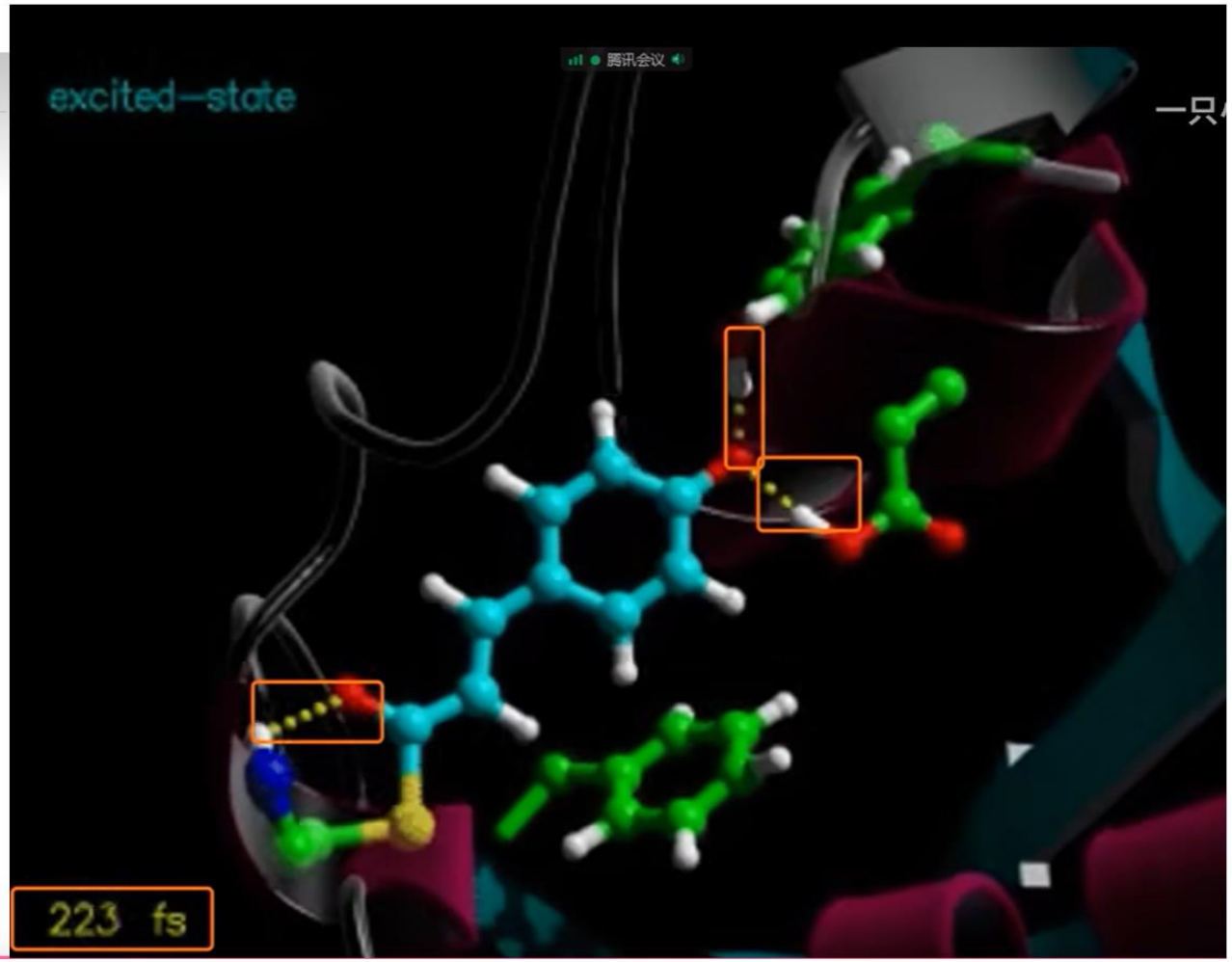


基于配体的药效团模型



方法5. 基于分子动力学模拟获知关键氨基酸





Molecular Graphics

- **Discovery Studio Visuliazer**
  http://accelrys.com/resource-center/downloads/freeware/index.html

- **PyMOL**
  https://pymol.org/2/

- **Maestro Academic**
  https://www.schrodinger.com/freemaestro

- **ICM Browser**
  http://www.molsoft.com/icm_browser.html

- **UCSF Chimera**
  http://www.cgl.ucsf.edu/chimera/download.html

准备化合物结构

- 在电脑安装程序，自己画结构式
  - Discovery Studio
  - Marvin Sketch

- 利用在线程序，自己画结构式
  - SwissADME http://www.swissadme.ch/
  - Marvin Sketch https://chemicalize.com/app/drawing
  - Corina Online https://www.mn-am.com/online_demos/corina_demo

- 从网上数据库下载
  - PubChem https://pubchem.ncbi.nlm.nih.gov/
  - ZINC http://zinc.docking.org/

BioXGEM.iGEMDOCK

BioXGEM GEMDOCK BioLink

- What's GEMDOCK
- iGEMDOCK
- Method
- Results
- References
- Download
- Visitor tracking
- Contact Us

Introduction

iGEMDOCK - A Graphical Environment for Recognizing Pharmacological Interactions and Virtual Screenin

Pharmacological interactions are useful for identifying lead compounds and understanding ligand binding m
active compounds that were acquired experimentally. Moreover, most docking programs loosely coupled th
analysis. An integrated VS environment, which provides the friendly interface to seamlessly combine differ
compounds, is valuable for drug discovery. Here, we developed an easy-to-use graphic environment, iGEM
iGEMDOCK can enrich the hit rate and provide biological insights by deriving the pharmacological interacti
residues that often form binding pockets with specific physico-chemical properties to play the essential fun
(root-mean-square derivations below 2.0 angstrom) on 305 protein-compound complexes. For virtual scree
enrich the hit rates on three public sets (i.e., estrogen receptor α for antagonists (ER) and agonists (ERA)
mechanisms and discovering lead compounds.

Download :

iGEMDOCK is available for free on non-commercial researches.

- **iGEMDOCK v2.1**
  - iGEMDOCK v2.1 for windows XP/windows 7
  - iGEMDOCK v2.1 for CentOS 5
  - iGEMDOCK v2.1 for Suse Linux 9
  - iGEMDOCK v2.1 for Ubuntu Linux
  - iGEMDOCK user guide (PDF or zip)

- iGEMDOCK v2.0
  - iGEMDOCK v2.0 for windows XP/Vista
  - iGEMDOCK v2.0 for CentOS 5
  - iGEMDOCK v2.0 for Suse Linux 9
  - iGEMDOCK v2.0 for Ubuntu Linux

http://gemdock.life.nctu.edu.tw/dock/igemdock.php

准备化合物结构

王健

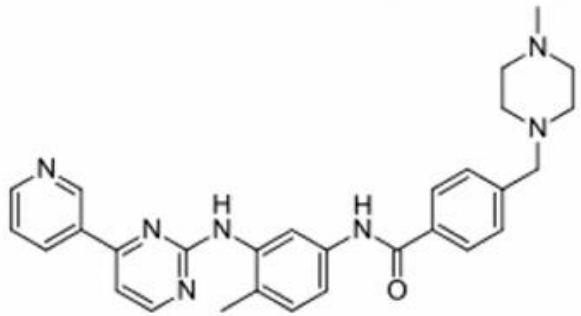
1D

- Smiles (.smi)

```
CC1=C(C=C(C=C1)NC(=O)C2=C
C=C(C=C2)CN3CCN(CC3)C)NC4
=NC=CC(=N4)C5=CN=CC=C5
```

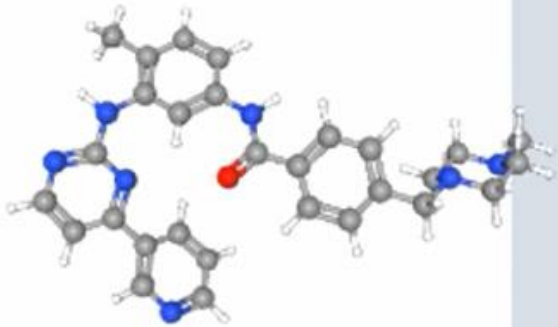
2D

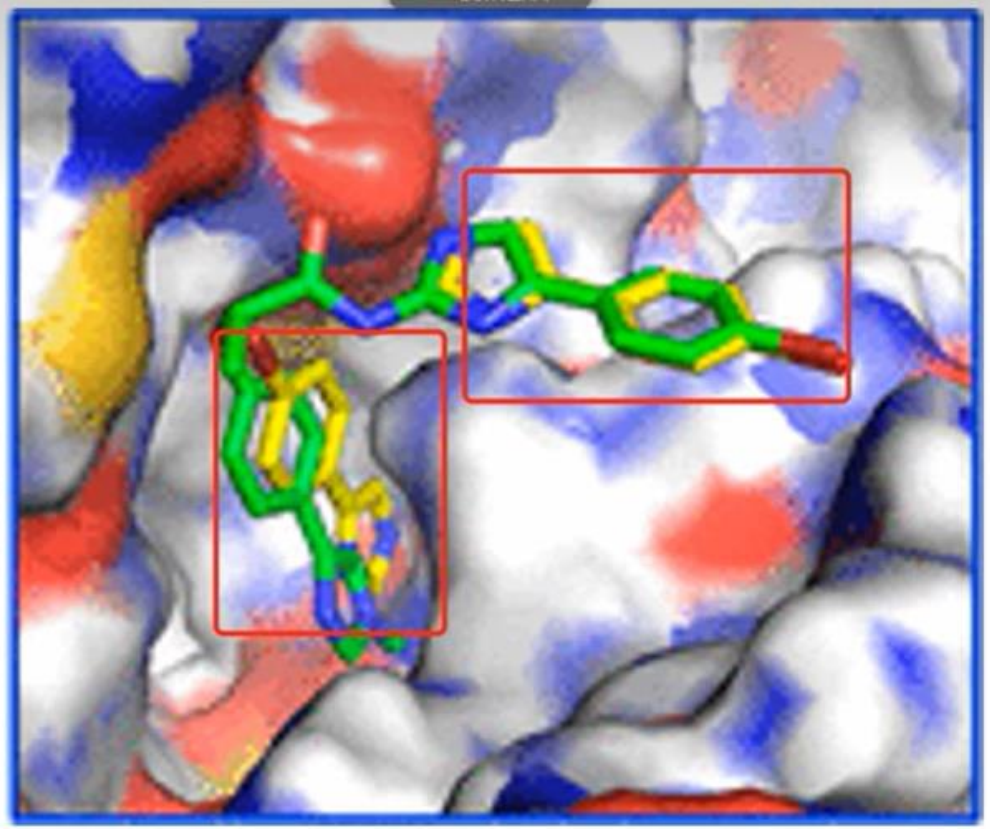
- MDL mol (.mol)

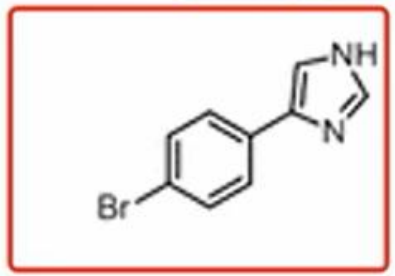


3D

- sdf
- mol2

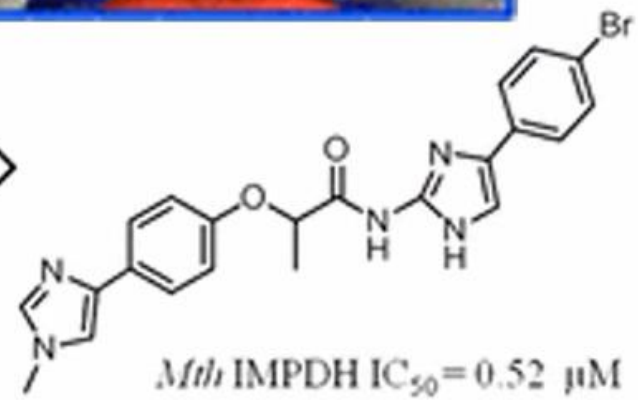






Mth IMPDH IC_{50} = 674 μM

Fragment Screening



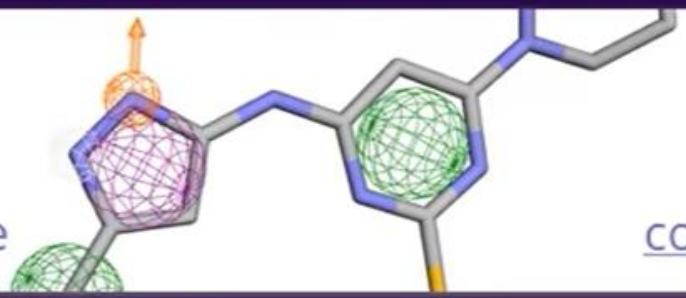
Mth IMPDH IC_{50} = 0.52 μM

≈ 1300-fold potency improvement

J. Med. Chem., **2018**, *61* (7), pp 2806–2822
DOI: 10.1021/acs.jmedchem.7b01622

pharmit

interactive exploration of chemical space



search

virtual screening in your browser

enter pharmit search

start from PDB: 4dkl BF0

binding site waters: ignore

submit

examples

create

submit your own chemical libraries

log in to manage libraries

email:

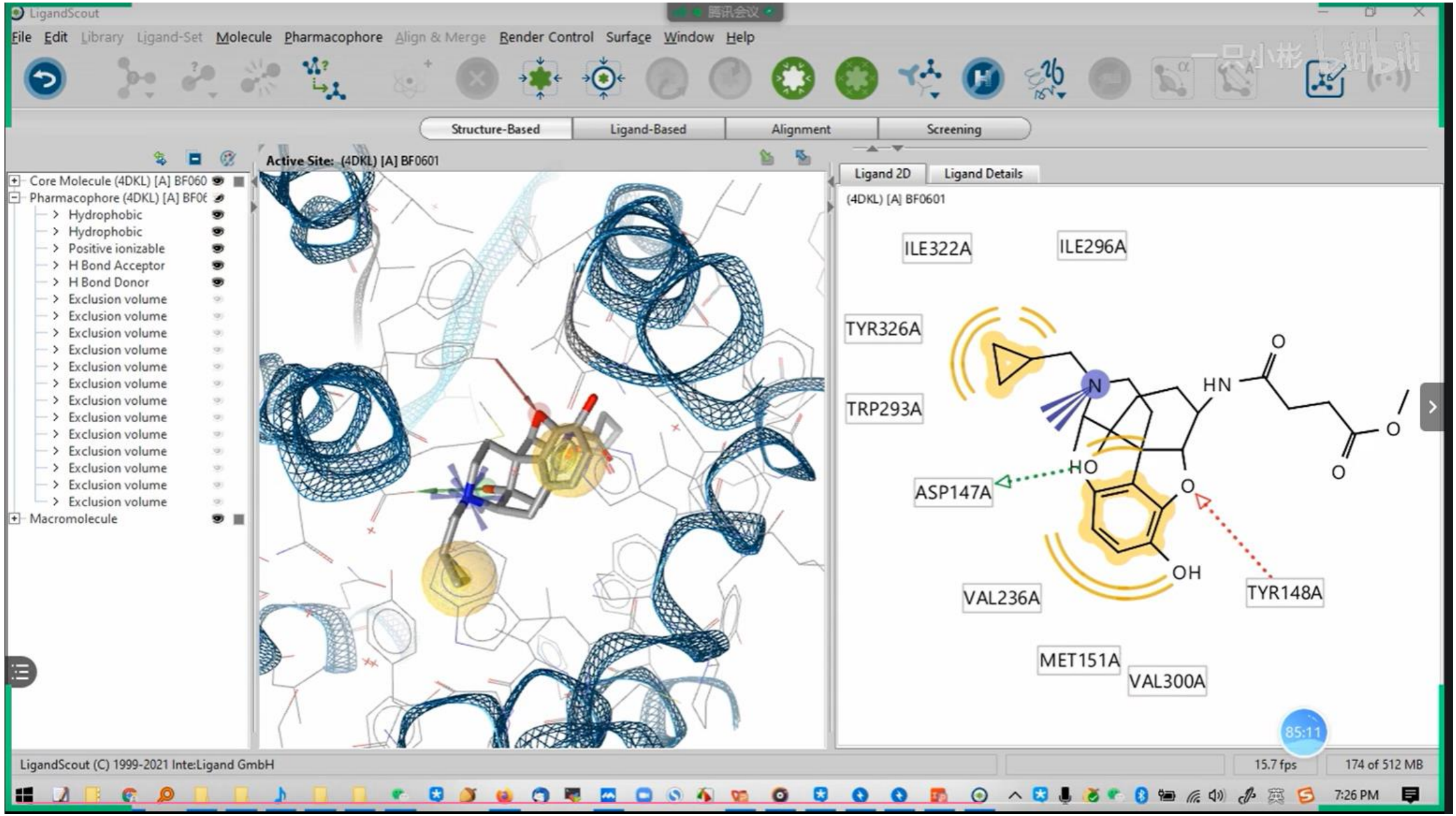
password:

log in

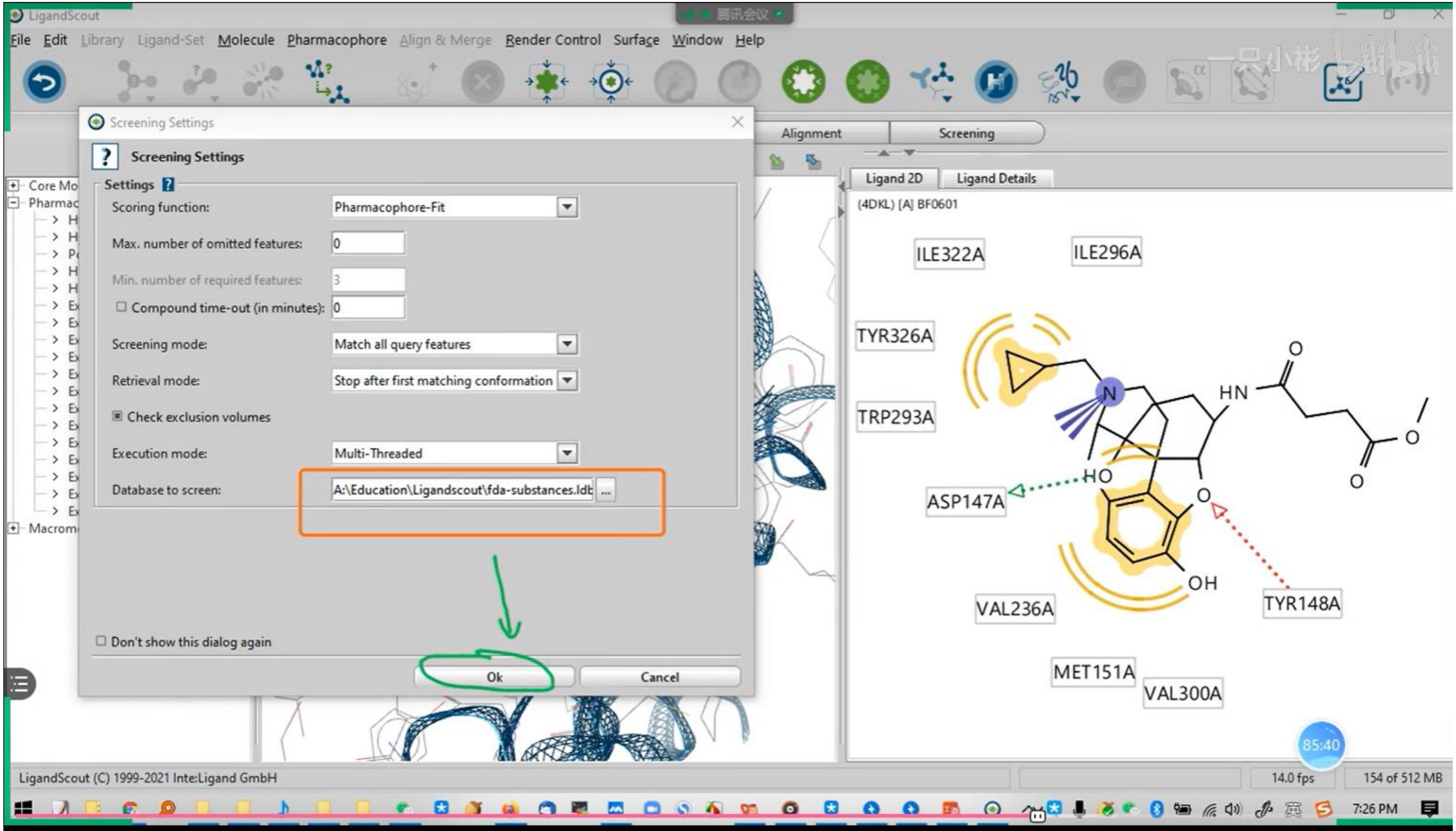
register new account

log in as guest

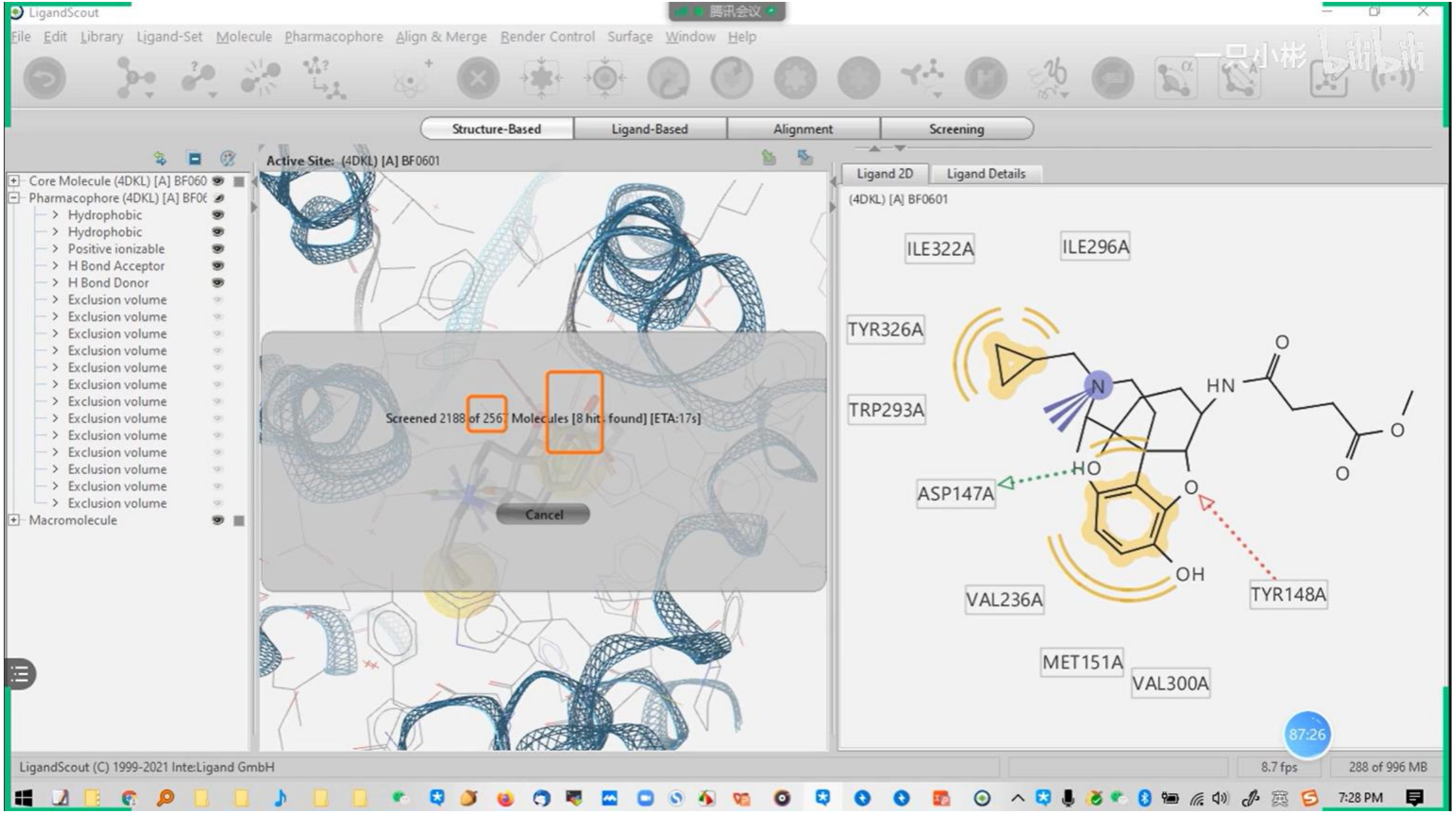
本地药库筛选-通过软件连接网站构建药效团

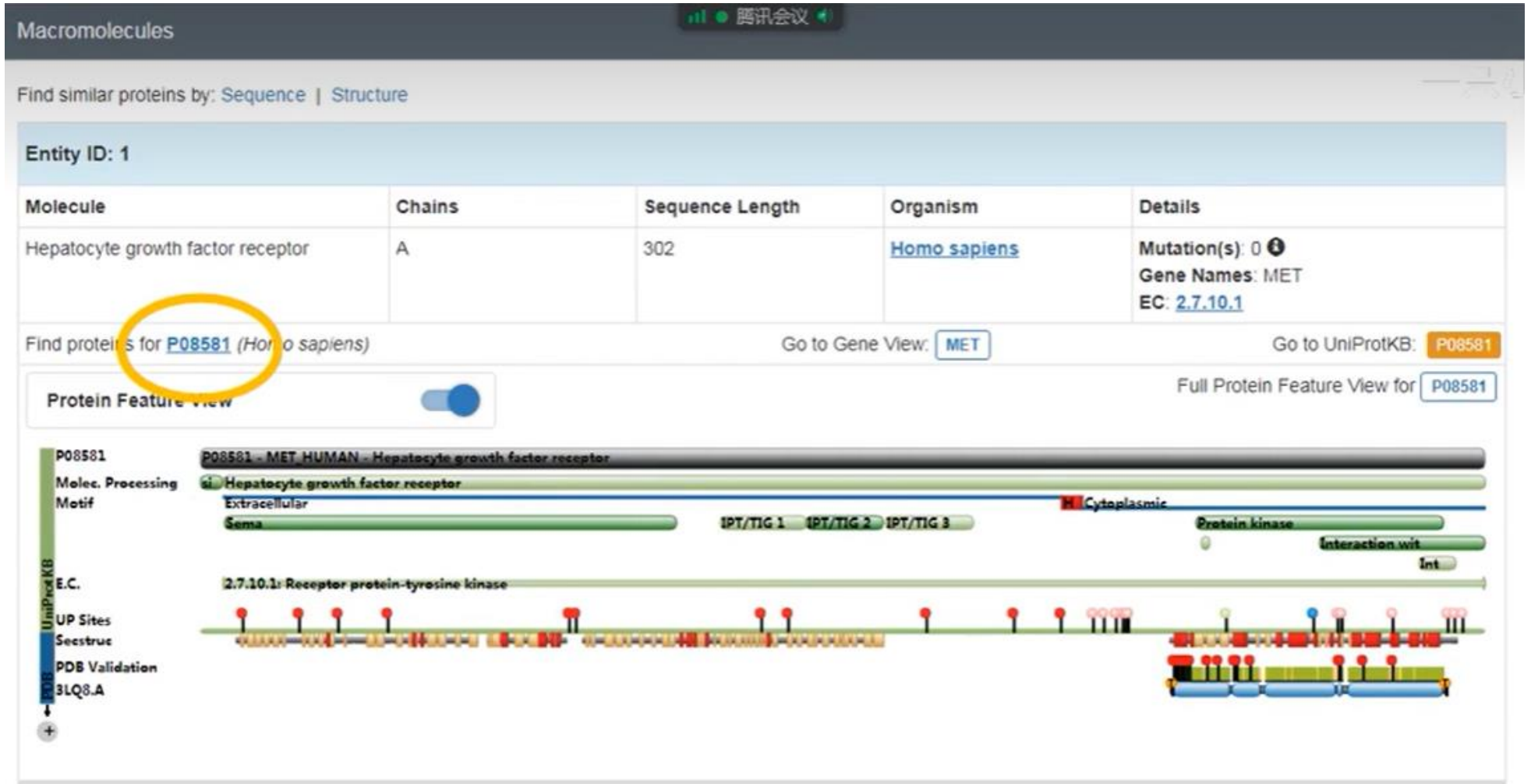


用药效团筛选本地药库


LigandScout
File Edit Library Ligand-Set Molecule Pharmacophore Align & Merge Render Control Surface Window Help
Screening Settings
Screening Settings
Settings
Scoring function: Pharmacophore-Fit
Max. number of omitted features: 0
Min. number of required features: 3
Compound time-out (in minutes): 0
Screening mode: Match all query features
Retrieval mode: Stop after first matching conformation
Check exclusion volumes
Execution mode: Multi-Threaded
Database to screen: A:\Education\Ligandscout\fda-substances.ldb
Don't show this dialog again
Ok
Cancel
Alignment
Screening
Ligand 2D
Ligand Details
(4DKL) [A] BF0601
ILE322A
ILE296A
TYR326A
TRP293A
ASP147A
VAL236A
TYR148A
MET151A
VAL300A
LigandScout (C) 1999-2021 Inte:Ligand GmbH
14.0 fps
154 of 512 MB
7:26 PM

从药库中筛选到的小分子




Macromolecules
腾讯会议
Find similar proteins by: Sequence | Structure
Entity ID: 1
Molecule
Chains
Sequence Length
Organism
Details
Hepatocyte growth factor receptor
A
302
Homo sapiens
Mutation(s): 0
Gene Names: MET
EC: 2.7.10.1
Find proteins for P08581 (Homo sapiens)
Go to Gene View: MET
Go to UniProtKB: P08581
Protein Feature View
Full Protein Feature View for P08581
P08581
Molec. Processing
Motif
E.C.
UP Sites
Secstruc
PDB Validation
3LQ8.A
UniProtKB
PDB
P08581 - MET_HUMAN - Hepatocyte growth factor receptor
Hepatocyte growth factor receptor
Extracellular
Cytoplasmic
Sema
IPT/TIG 1
IPT/TIG 2
IPT/TIG 3
Protein kinase
Interaction wit
Int
2.7.10.1: Receptor protein-tyrosine kinase

PDB找链接序列

Display

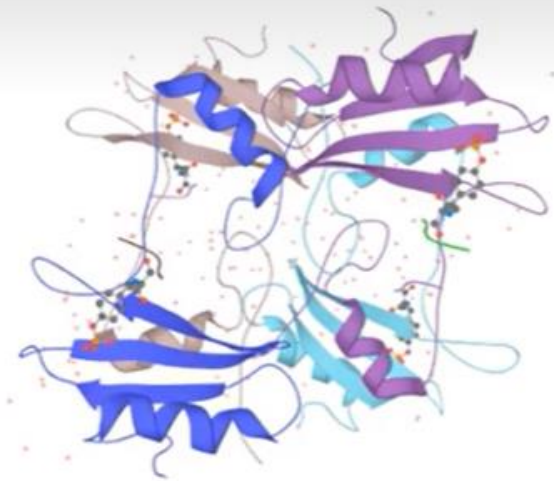
Structure

- Entry
- Publications
- Feature viewer
- Feature table

None

- Function
- Names & Taxonomy
- Subcellular location
- Pathology & Biotech
- PTM / Processing
- Expression
- Interaction
- Structure
- Family & Domains
- Sequences (3+)
- Similar proteins
- Cross-references
- Entry information
- Miscellaneous

Top



PDB Entry	Method	Resolution	Chain	Positions	Links
1FYR	X-ray	2.40 Å	I/J/K/L	1356-1359	PDBe RCSB PDB PDBj PDBsum
1R0P	X-ray	1.80 Å	A	1049-1360	PDBe RCSB PDB PDBj PDBsum
1R1W	X-ray	1.80 Å	A	1049-1360	PDBe RCSB PDB PDBj PDBsum
1SHY	X-ray	3.22 Å	B	25-567	PDBe RCSB PDB PDBj PDBsum
1SSL	NMR		A	519-562	PDBe RCSB PDB PDBj PDBsum
1UX3	Model		A	25-656	PDBe

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Secondary structure

1 390

Legend: Helix Turn Beta strand PDB Structure known for this area

Show more details

3D structure databases

ProteinModelPortal	P08581
SMR	P08581
ModBase	Search...

Uniprot 找不同长度的蛋白序列及结构

https://www.uniprot.org/uniprot/P08581#structure

与共结晶化合物作用的氨基酸，是活性位点的关键氨基酸

PDBSum找出作用方式