CAS BIOFINDER DISCOVERY PLATFORM™

快速使用指南 (QUICK GUIDE)

China@acs-i.org

美国化学文摘社(CAS)北京代表处

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提纲

- CAS BioFinder 简介与检索界面介绍 (Introduction and Interface)
- 配体检索与配体详情信息(Ligands and Details Overview)
- 骨架检索与构效关系分析(Scaffolds and SAR Analysis)
- 蛋白/通路/靶点、疾病与生物标志物(Proteins & Pathways; Diseases & Biomarkers)
- 生物活性预测 (Predictive Analytics)

科学信息管理对新药研发至关重要

低增长时代的特点对创新的要求极大提升，而在当今的创新环境下，数据管理任务艰巨

- 信息鸿沟会导致创新管线薄弱、研发效率低下，以及意外的知识产权风险
- 由于数据量和数据类型日益复杂，药物发现流程中，整合和分析关键的研发数据信息，对于迅速做出关键决策至关重要。
- 持续的数据管理有助于开发差异化的成果，支撑创新药物的发现，确保药物研发成功进入审批阶段，并可避免后续知识产权问题。

来源：CAS Insights洞察报告 Challenges and opportunities in data for drug discovery | CAS

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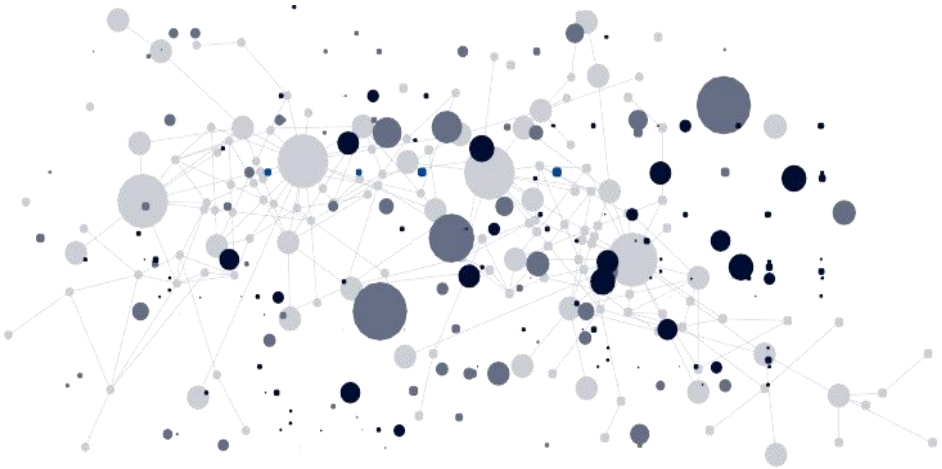
生命科学领域研究离不开重要的数据信息基础，但为什么却难以加以利用？

缺乏关联性

生命科学研究和数据分散在各个数据库、期刊和专利等众多互不关联的资源之中



未一致化

不同资源对相同信息的描述各不相同，因此很难对数据进行分析和比较

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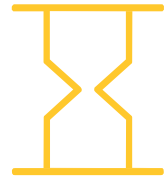
数据问题导致延缓创新进程，增加财务风险

遗漏见解

这些见解能够为研究人员制定研发战略提供指导

仅在美国，每年就有 **5,000 到 6,000 起专利侵权和专利无效**的诉讼，法院判定的赔偿金额**接近 50 亿美元**[1]。

耗费时间



生命科学数据量每 14 年翻一番[2]

数据科学家将 **50%-80% 的时间都花费**在收集和整理用于分析模型的数据信息的琐碎的工作中[3]

1. Vuleta, B. (2023). 25 Patent Litigation Statistics - High-Profile Feuds about Intellectual Property. LegalJobs. https://legaljobs.io/blog/patent-litigation-statistics/
2. Bornmann, L. et al. (2021). Growth rates of modern science: a latent piecewise growth curve approach to model publication numbers from established and new literature databases. (Humanities and Social Sciences Communications), 8, 224. https://doi.org/10.1057/s41599-021-00903-w
3. Lohr, S. (2014.) For Big-Data Scientists, 'Janitor Work' Is Key Hurdle to Insights. The New York Times. August 17, 2014. https://www.nytimes.com/2014/08/18/technology/for-big-data-scientists-hurdle-to-insights-is-janitor-work.html
4. Genetic Engineering & Biotechnology News Top 25 Biotech Companies of 2019. 5. Pharm Exec's Top 50 Companies 2020.6. Shanghai Ranking's Global Ranking of Academic Subjects 2020.

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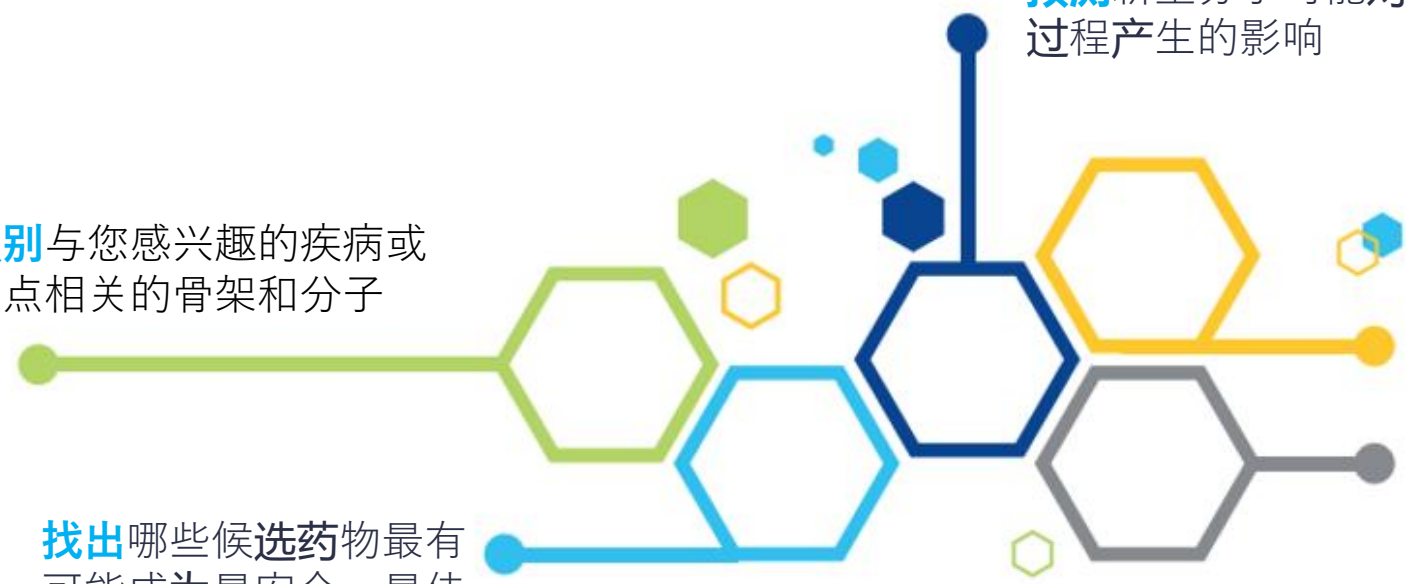
利用CAS BioFinder 加速早期药物研发

预测新型分子可能对生物过程产生的影响

识别与您感兴趣的疾病或靶点相关的骨架和分子



发现与您感兴趣的疾病相关的生物标志物

找出哪些候选药物最有可能成为最安全、最佳的先导化合物

持续开发中的更多内容与功能（序列、抗体、PDC、药物情报等）

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CAS BioFinder 检索界面

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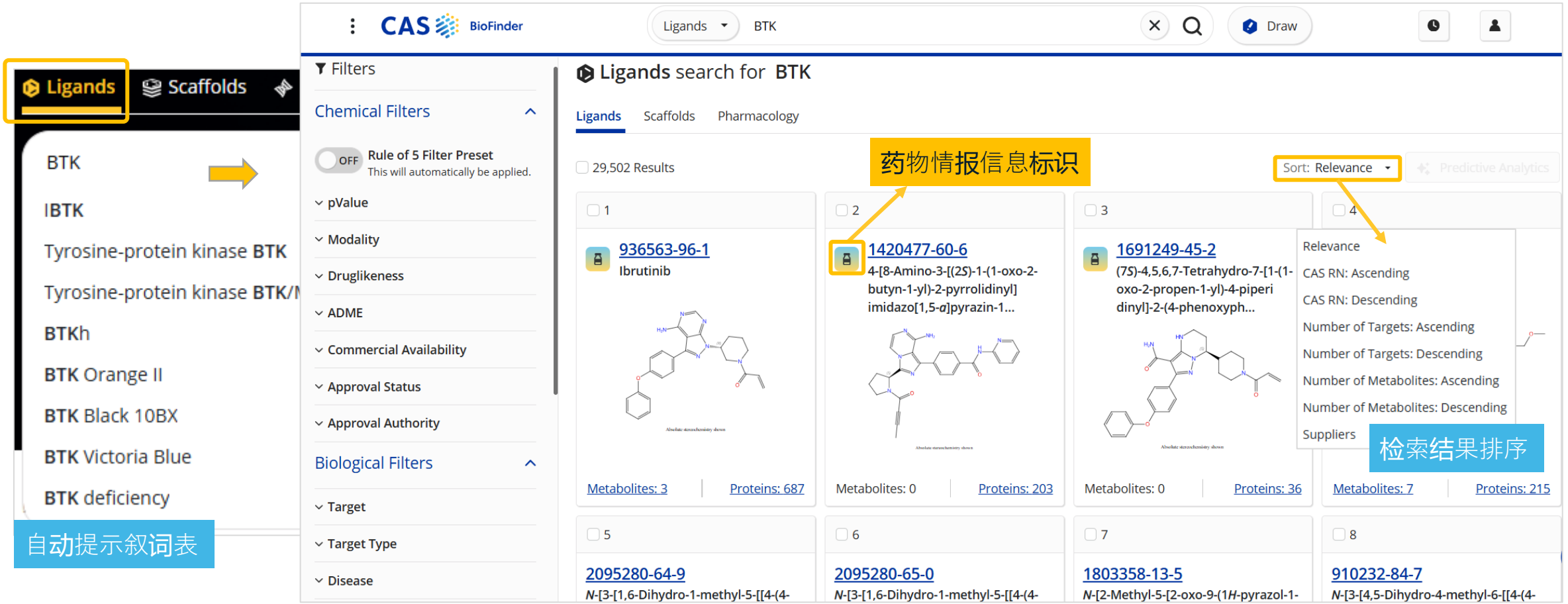
基于靶点、疾病、药物名称以及结构，检索配体信息



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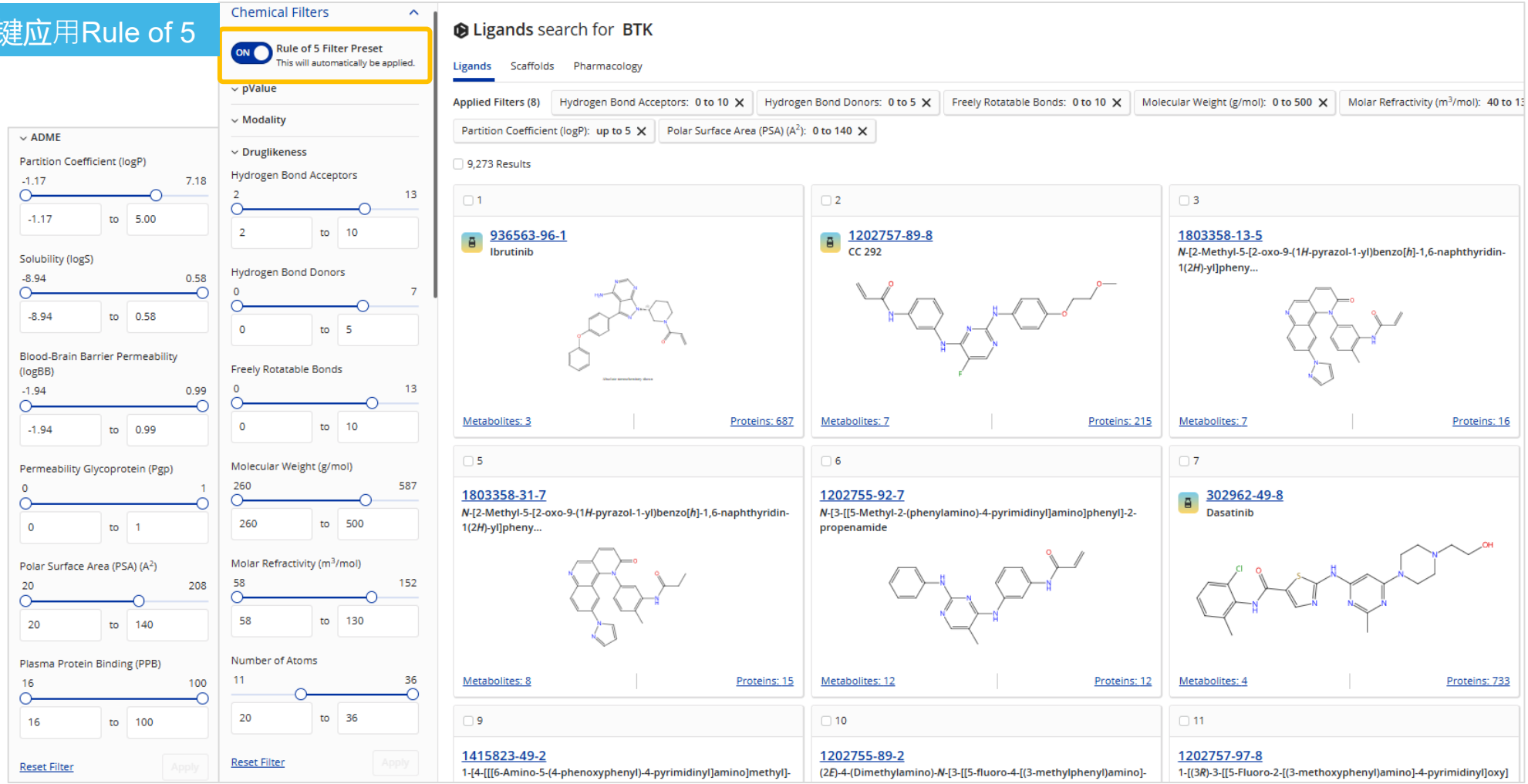
筛选具有类似先导化合物特性的小分子配体

一键应用Rule of 5



- 氢键受体 <10
- 氢键供体 <5
- 自由旋转键 <10
- 分子量 <500
- 摩尔折射率：
  40-130 m^3/mol
- 原子数: 20-70

- logP <5
- 极性表面积：
  0-140 Å²

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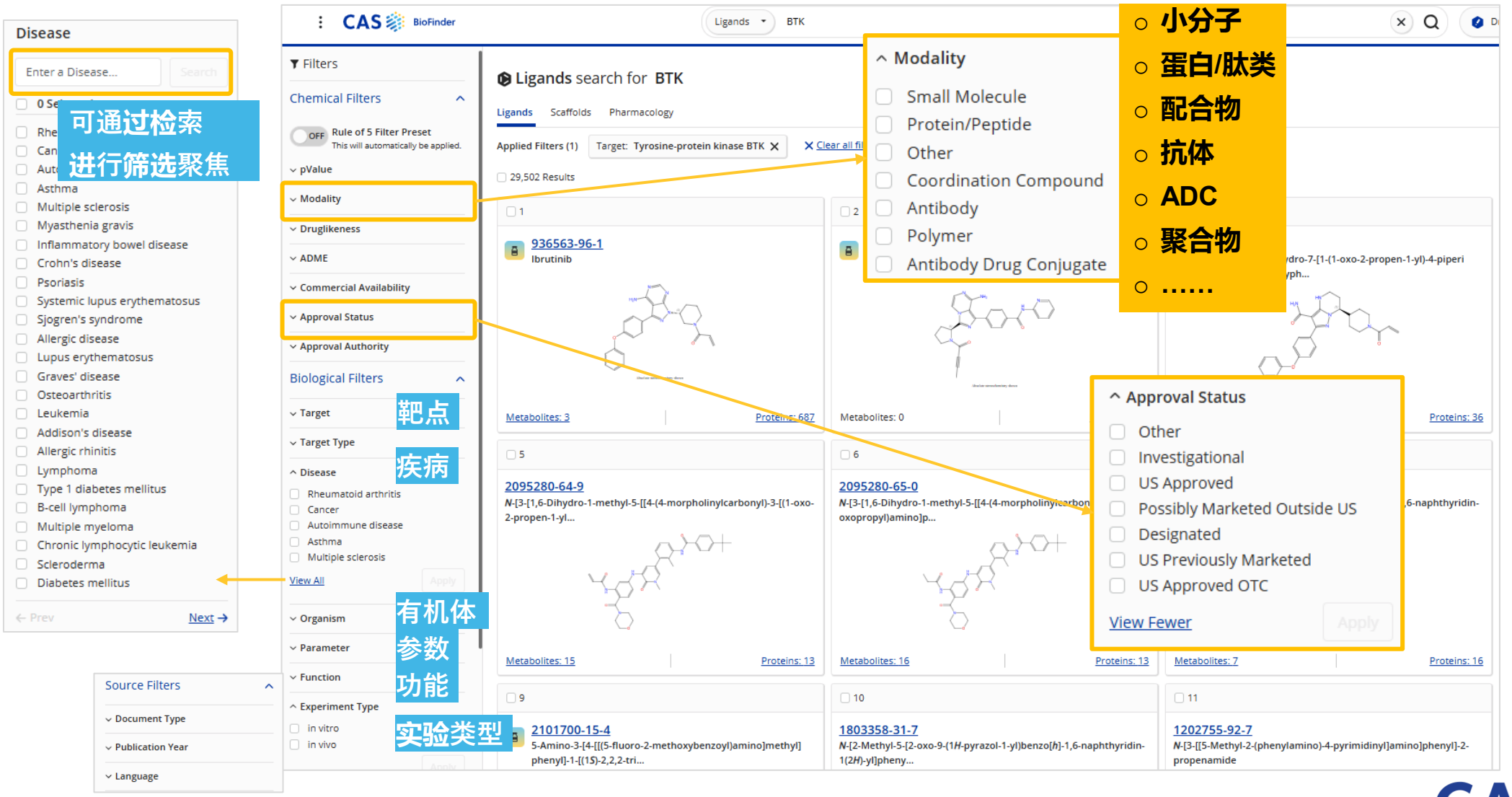
配体检索结果的纵览与聚焦



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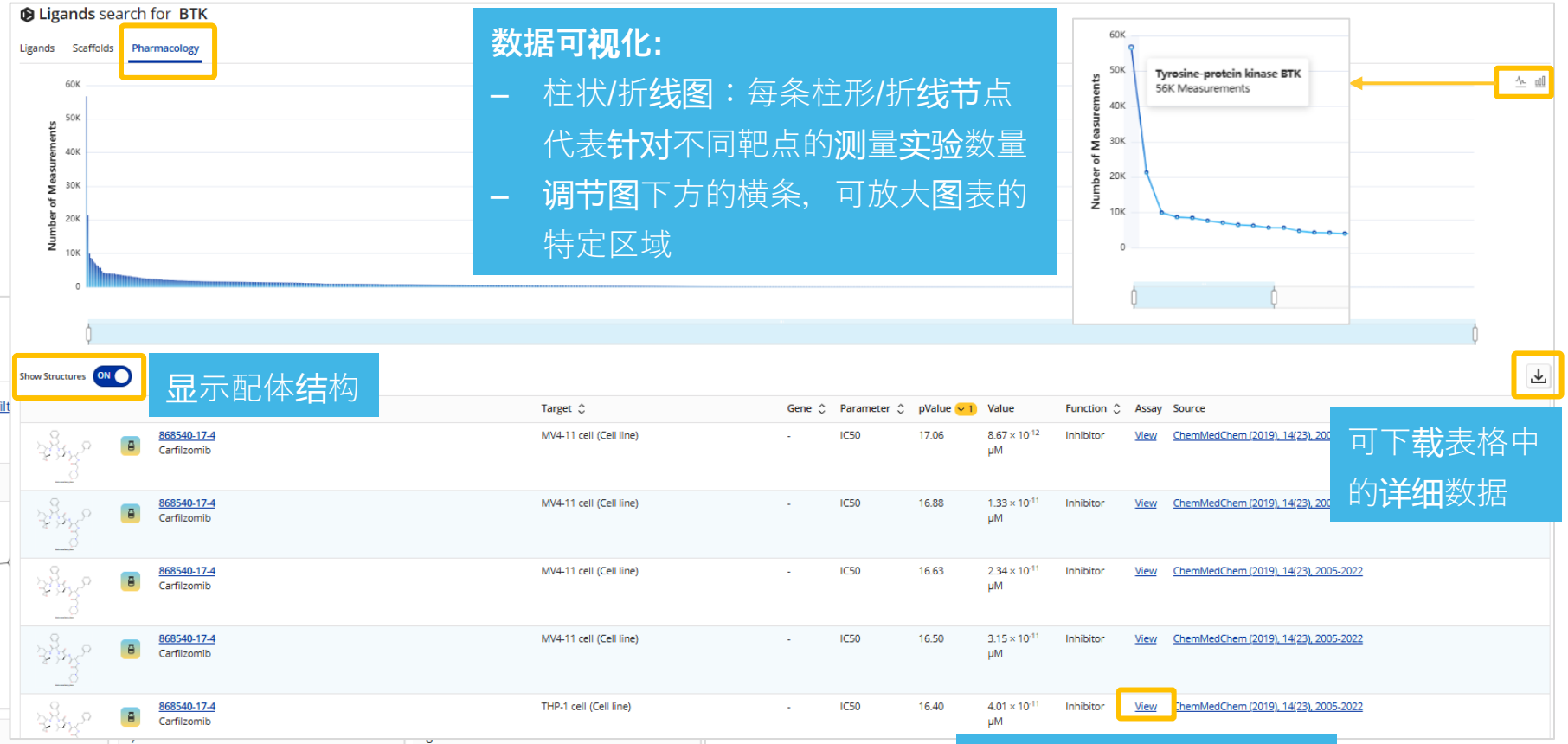
纵览配体检索结果集相关骨架结构与药理学数据

查看配体检索结果关联的骨架结构

数据可视化:

- 柱状/折线图：每条柱形/折线节点代表针对不同靶点的测量实验数量
- 调节图下方的横条， 可放大图表的特定区域



可下载表格中的详细数据

点击View， 可查看原文中的Assay的细节

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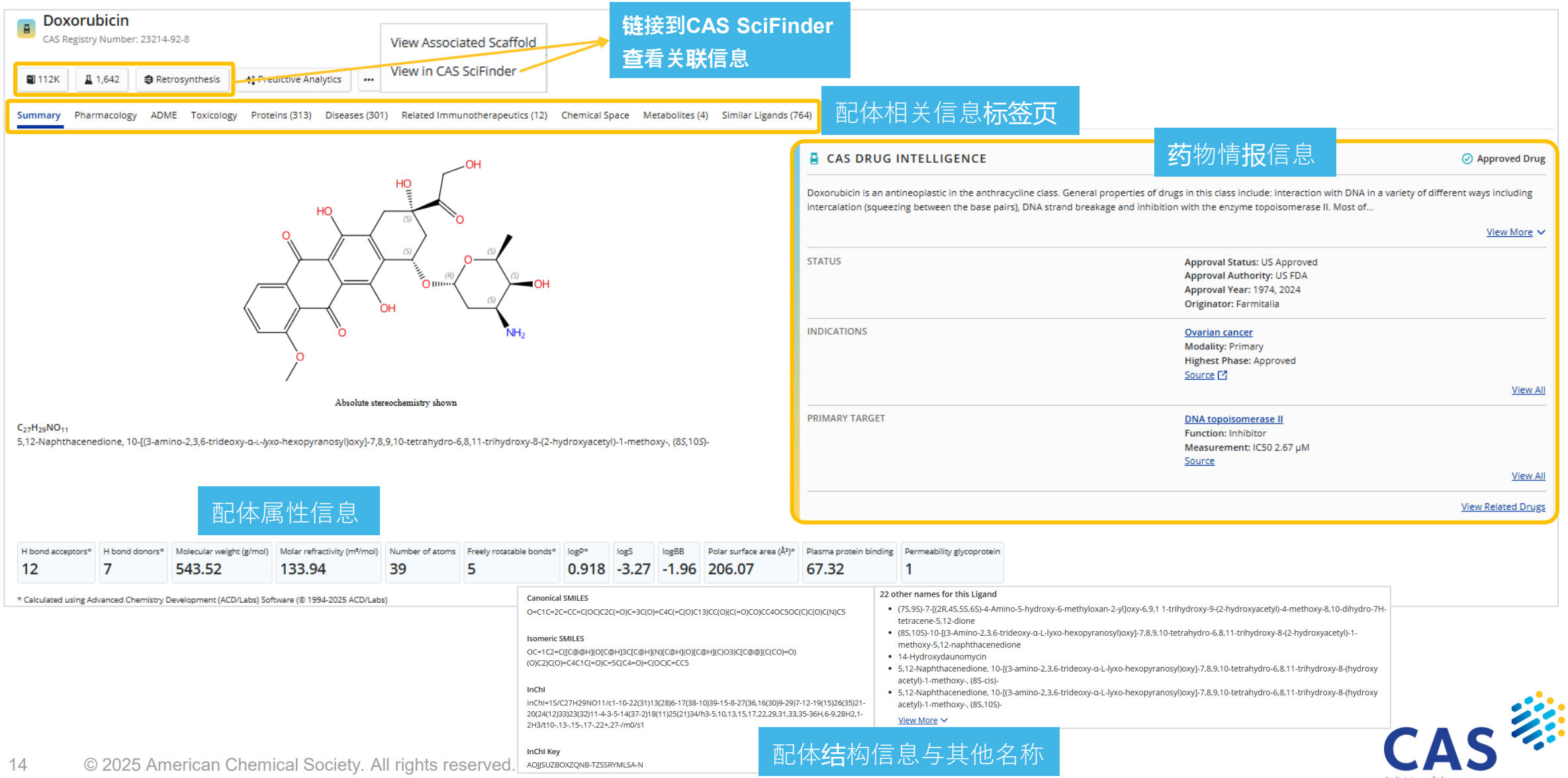
探索配体的详细信息



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药物情报信息 (Drug Intelligence)

CAS DRUG INTELLIGENCE — Approved Drug

Doxorubicin is an antineoplastic in the anthracycline class. General properties of drugs in this class include: interaction with DNA in a variety of different ways including intercalation (squeezing between the base pairs), DNA strand breakage and inhibition with the enzyme topoisomerase II. Most of...

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STATUS

Approval Status: US Approved
Approval Authority: US FDA
Approval Year: 1974, 2024
Originator: Farmitalia

INDICATIONS

Ovarian cancer
Modality: Primary
Highest Phase: Approved
Source

View All

PRIMARY TARGET

DNA topoisomerase II
Function: Inhibitor
Measurement: IC50 2.67 μM
Source

View All

View Related Drugs

Targets

相关靶标

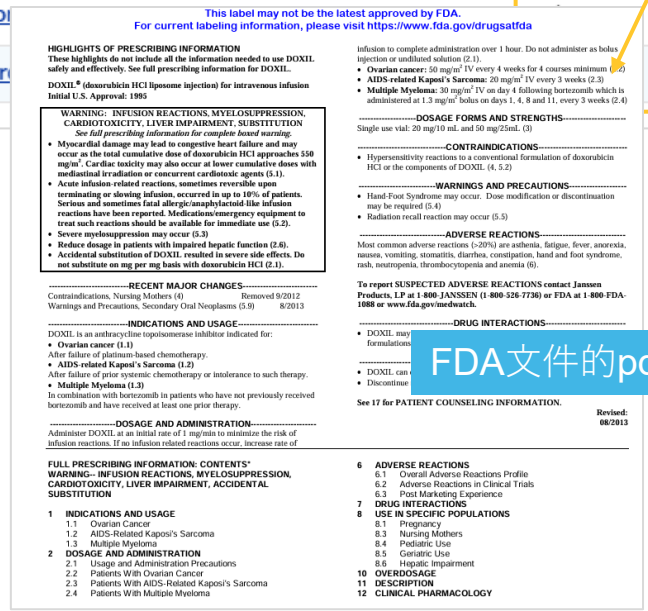
Primary Target	Function	Measurement
DNA topoisomerase II	Inhibitor	IC50 2.67 μM
Albumin	Binding Agent	-
DNA gyrase	Inhibitor	-
DNA topoisomerase II	Inhibitor	IC50 2.67 μM
A673	Inhibitor	IC50 200.0 nM
HepG2	Inhibitor	IC50 24.68 μM
Human ovarian cancer cell line	Inhibitor	IC50 0.074 μM

Indications

相关适应症

所处临床阶段和获批信息

Name	Modality	Highest Phase	Source
Ovarian cancer	Primary	Approved	View
AIDS-related Kaposi's sarcoma	Primary	Approved	View
Multiple myeloma	Primary	Approved	View
Locally advanced or unresectable soft tissue sarcoma	Primary	Phase III	View
Kaposi's sarcoma	Primary	Phase II	View
Glioblastoma	Primary	Phase II	View
Lung non-small cell carcinoma			View
Pancreatic ductal adenocarcinoma			View



This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DOXIL safely and effectively. See full prescribing information for DOXIL.

DOXIL® (doxorubicin HCl liposome injection) for intravenous infusion
Initial U.S. Approval: 1995

WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, SUBSTITUTION
See full prescribing information for complete boxed warning.

- Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m². Cardiac toxicity may also occur at lower cumulative doses with mediastinal irradiation or concurrent cardiotoxic agents (5.1).
- Acute infusion-related reactions, sometimes reversible upon terminating or slowing infusion, occurred in up to 10% of patients. Serious and sometimes fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications/emergency equipment to treat such reactions should be available for immediate use (5.2).
- Severe myelosuppression may occur (5.3)
- Reduce dosage in patients with impaired hepatic function (2.6).
- Accidental substitution of DOXIL resulted in severe side effects. Do not substitute on mg per mg basis with doxorubicin HCl (2.1).

FDA文件的pdf

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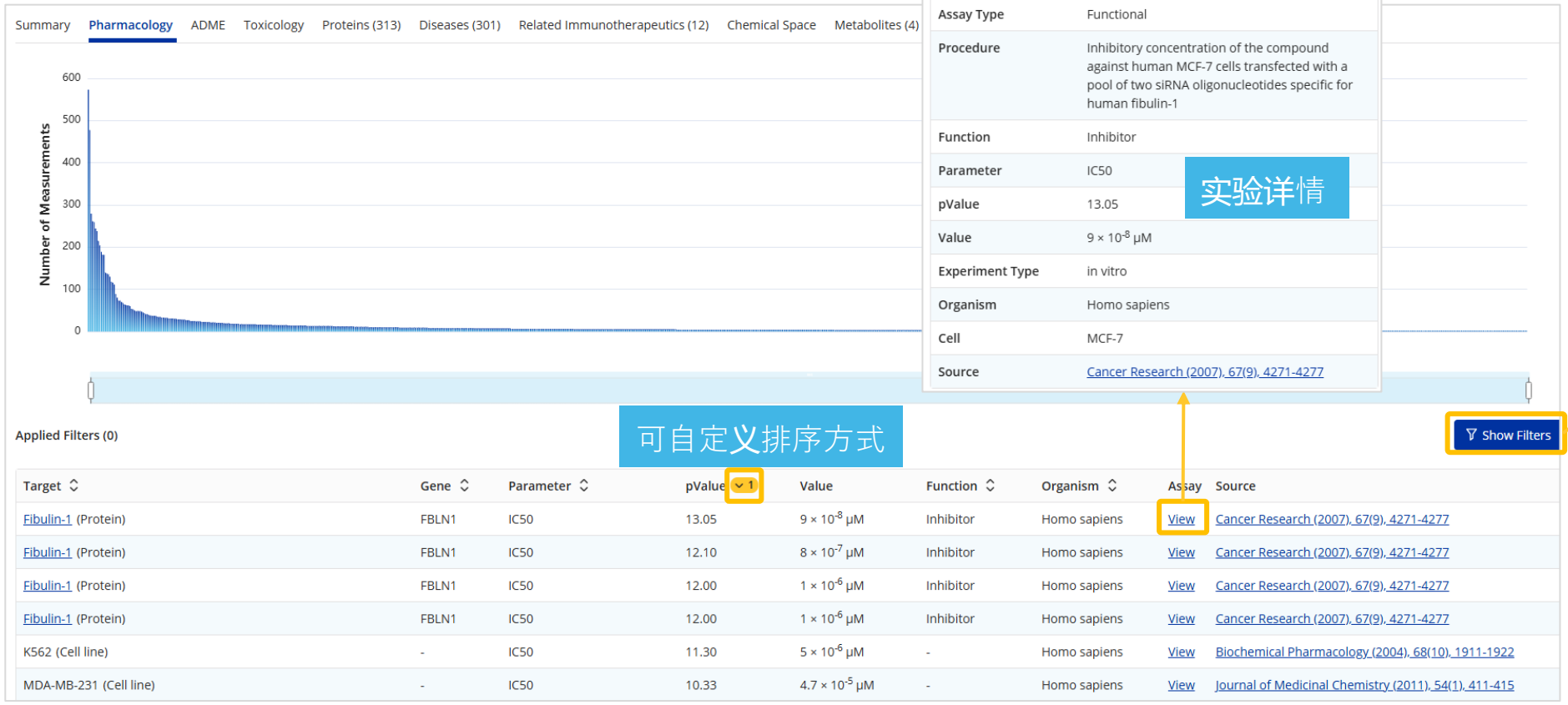
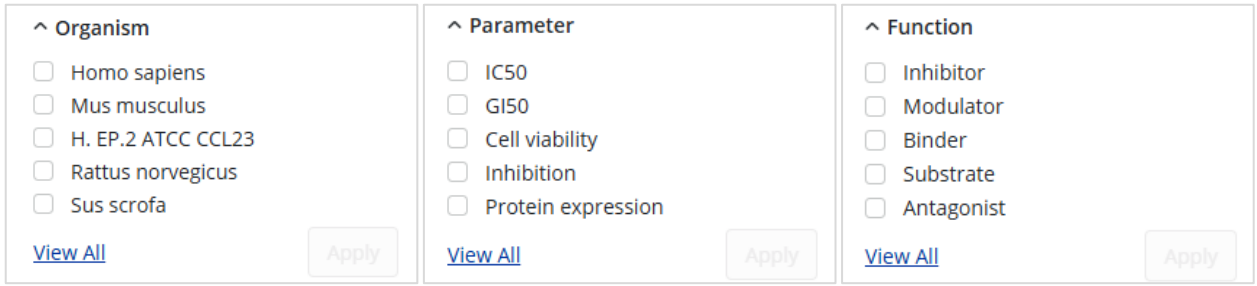
配体药理学信息





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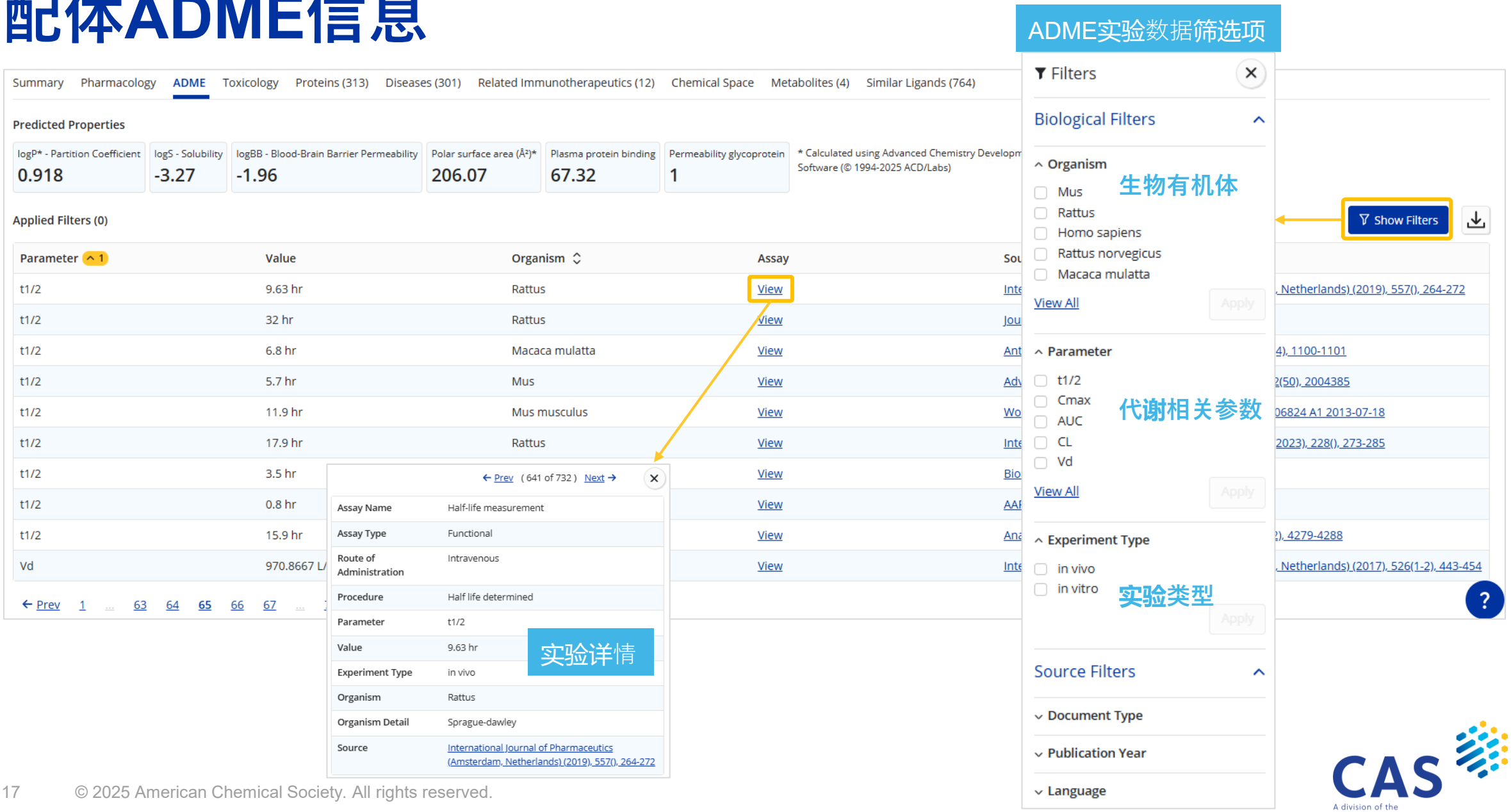
配体ADME信息



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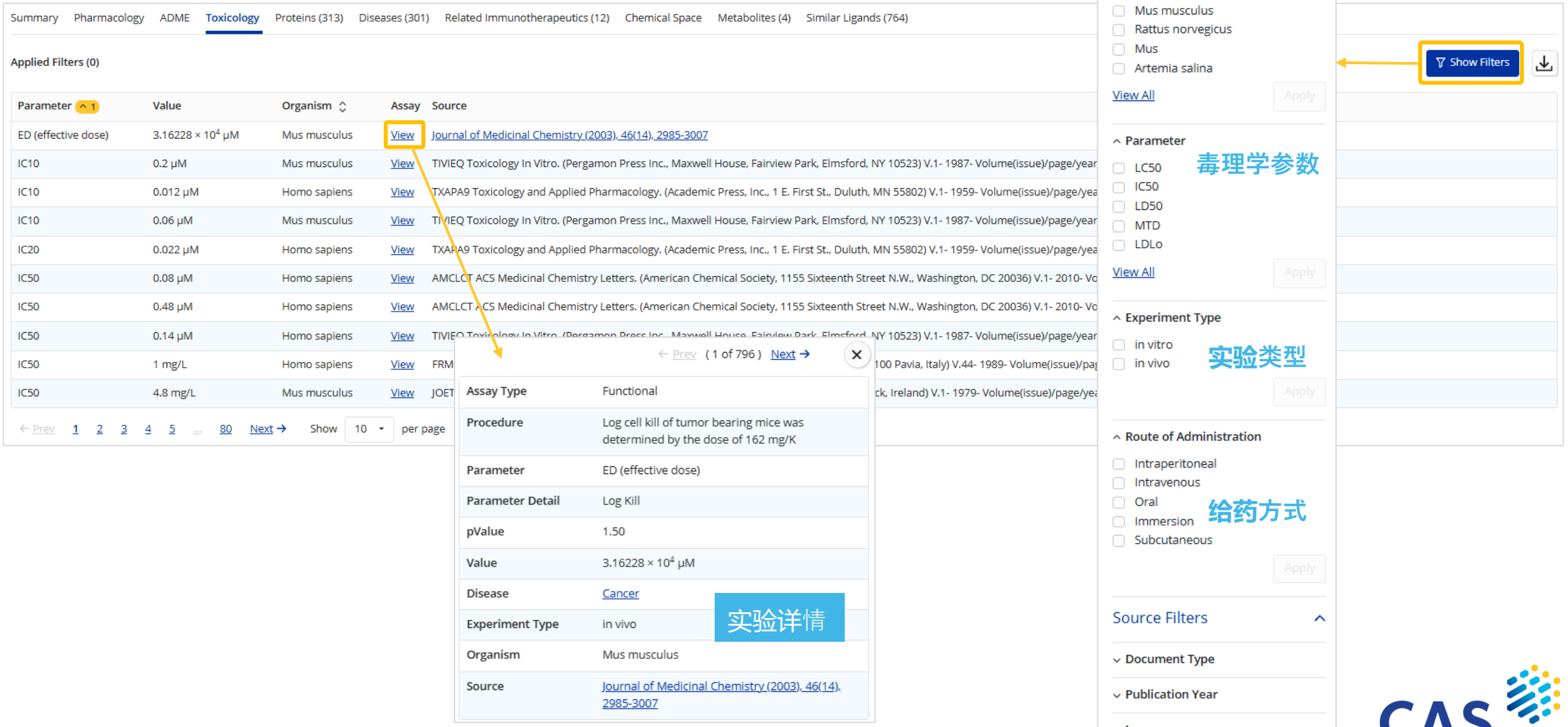
配体毒理学信息



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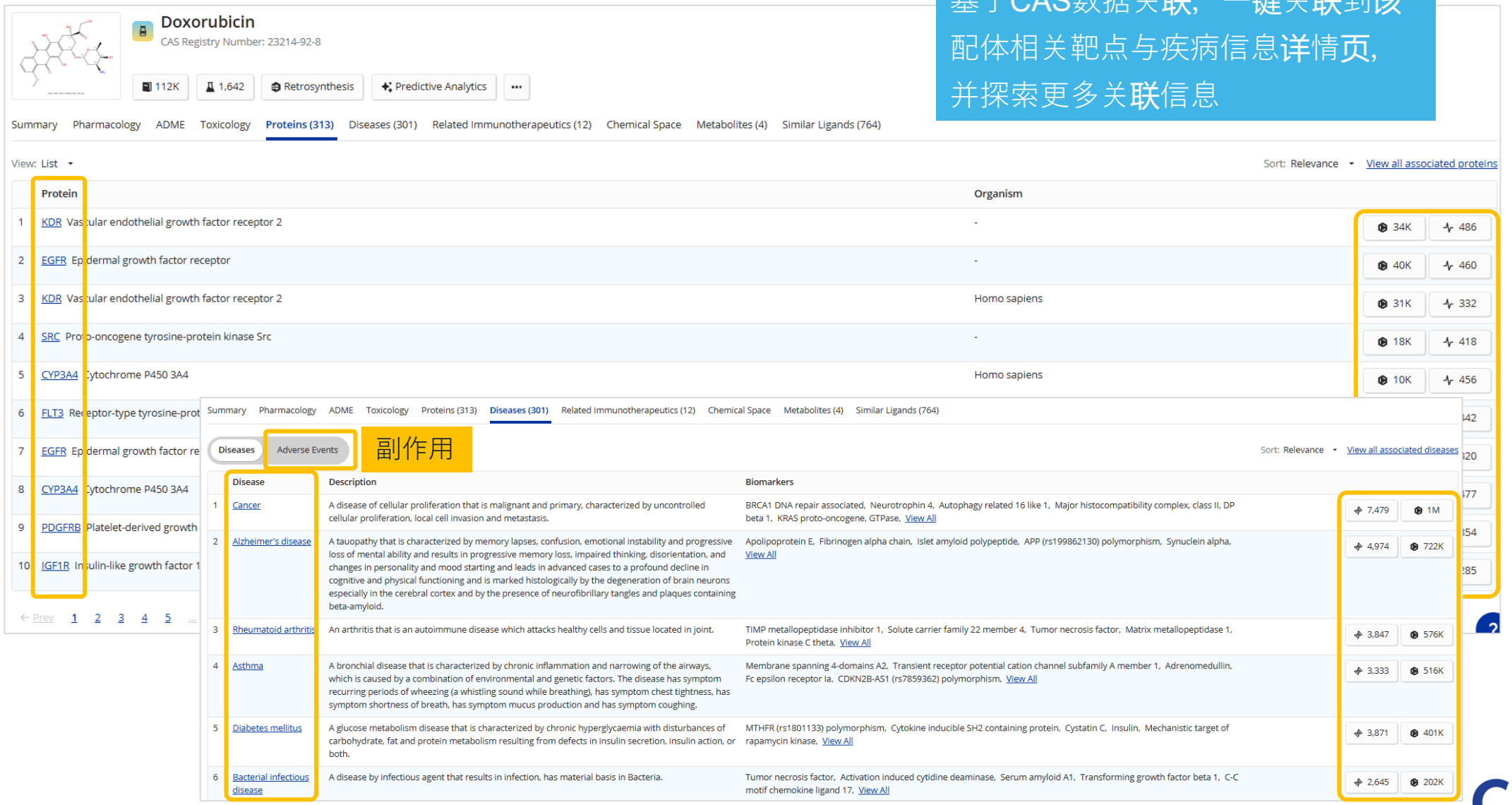
配体相关靶点与疾病信息

基于CAS数据关联，一键关联到该配体相关靶点与疾病信息详情页，并探索更多关联信息



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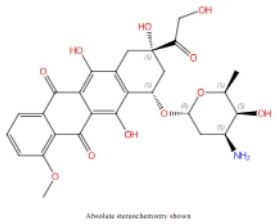
配体相关免疫疗法信息

Summary | Pharmacology | ADME | Toxicology | Proteins (313) | Diseases (301) | **Related Immunotherapeutics (12)** | Chemical Space | Metabolites (4) | Similar Ligands (764)

MAb-DMBA-SIL-Dox

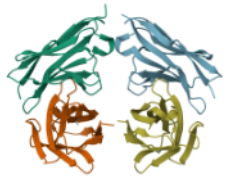


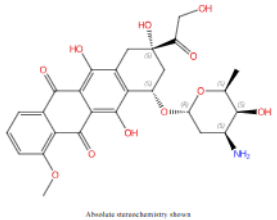
抗体与配体结构信息

Antibody	Cetuximab
Antigen	Epidermal growth factor receptor (EGFR)
Payload	Doxorubicin
Therapeutic Target	DNA topoisomerase 2-alpha
Drug-Antibody Ratio	5.57
Linker	DMBA-SIL
Method	Site-specific conjugation with the respective EGFR mAb via thiolmaleimide Michael addition.

免疫疗法详情

Trastuzumab-PC4AP-DOX





Antibody	Trastuzumab
Antigen	Receptor tyrosine-protein kinase erbB-2 (ERBB2)
Payload	Doxorubicin
Therapeutic Target	DNA topoisomerase 2-alpha
Drug-Antibody Ratio	2
Linker	Photocaged C4AP
Method	Random conjugation through reduced inter-chain cysteines.

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ADC药物详情页

Trastuzumab emtansine

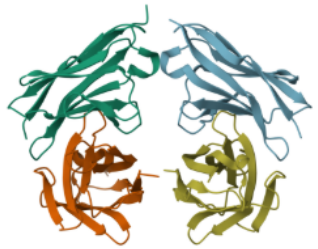
CAS Registry Number: 1018448-65-1

1,972 | 8 | Retrosynthesis | Predictive Analytics | ...

Summary | Pharmacology | ADME | Proteins (2) | Diseases (1)

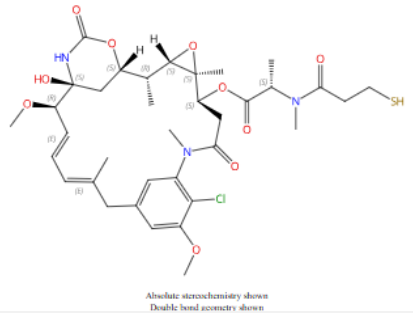
Antibody	Trastuzumab
Antigen	Receptor tyrosine-protein kinase erbB-2 (ERBB2)
Payload	Mertansine DM1
Therapeutic Target	Microtubule
Drug-Antibody Ratio	3.5
Linker	Succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC)
Method	Random conjugation through nucleophilic lysines.

ADC药物详情



抗体3D结构图

药物分子结构



CAS DRUG INTELLIGENCE

药物情报信息

Approved Drug

Trastuzumab emtansine (ado-trastuzumab emtansine, trade name Kadcyla) is a combination between a monoclonal antibody and a small-molecule drug. Each molecule of trastuzumab emtansine consists of a single trastuzumab molecule with several molecules of DM1, a cytotoxic maytansinoid, attached. SMCC, or...

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STATUS	**Approval Status:** US Approved **Approval Authority:** US FDA **Approval Year:** 2013 **Originator:** Genentech
INDICATIONS	Breast cancer **Modality:** Primary **Highest Phase:** Approved Source
PRIMARY TARGET	Receptor tyrosine-protein kinase erbB-2 **Function:** Blocker Source

Heavy Chain Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYSRWGGDG
FYAMDYDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL
TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Light Chain Sequence

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYQQHYTTPPTPTFGQG
TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV
TKSFNRGEC

CDR序列

HCDR1	HCDR2	HCDR3	LCDR2	LCDR1	LCDR3
GFNIKDTY	IYPTNGYT	SRWGGDGFYAMDY	SAS	QDVNTA	QQHYTTPPT

重链/轻链序列

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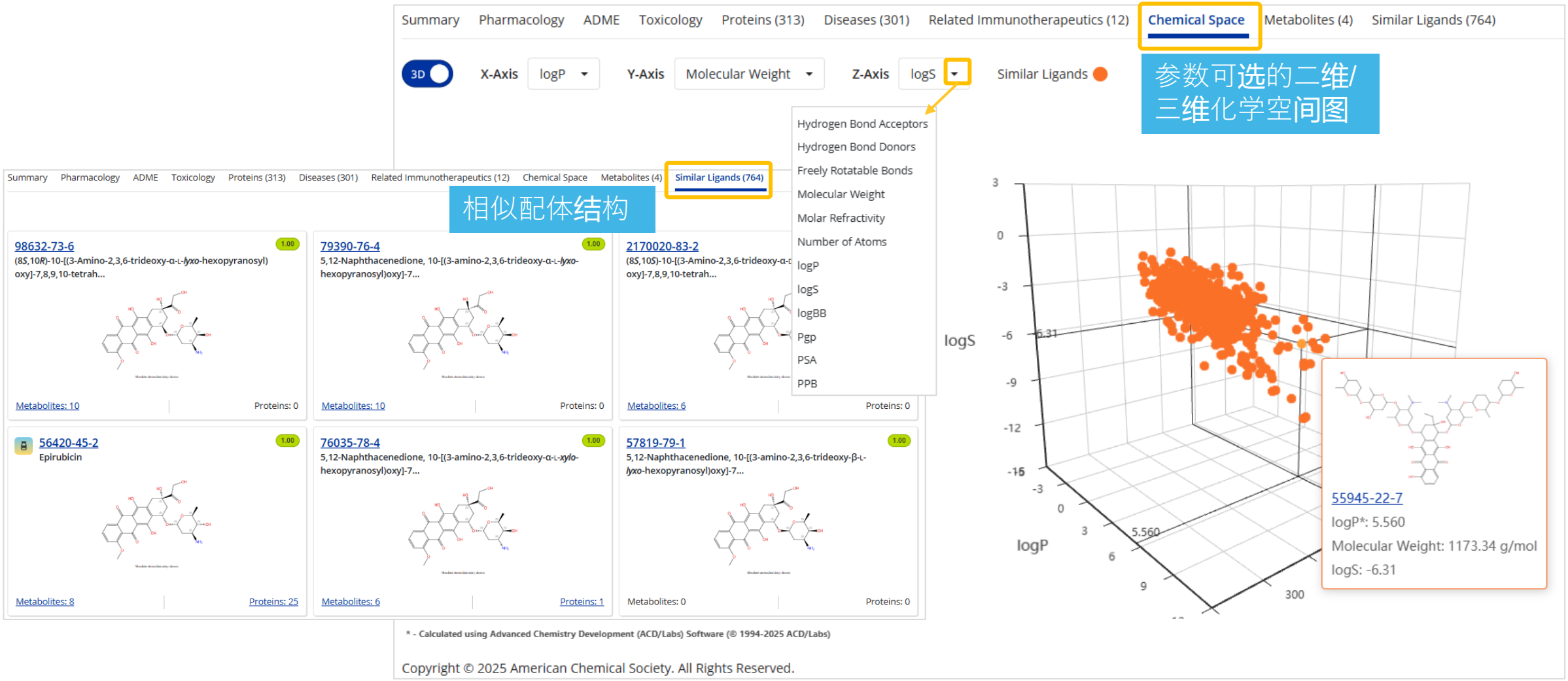
相似配体结构与可视化分析



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探索配体代谢产物

已知代谢产物：Known
预测代谢产物：Confidence Score置信度分值，表示发生该生物转化的概率

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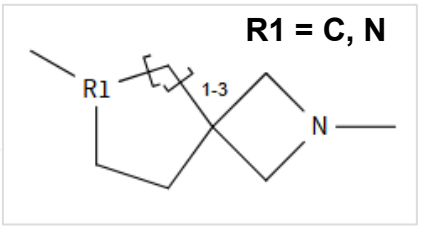
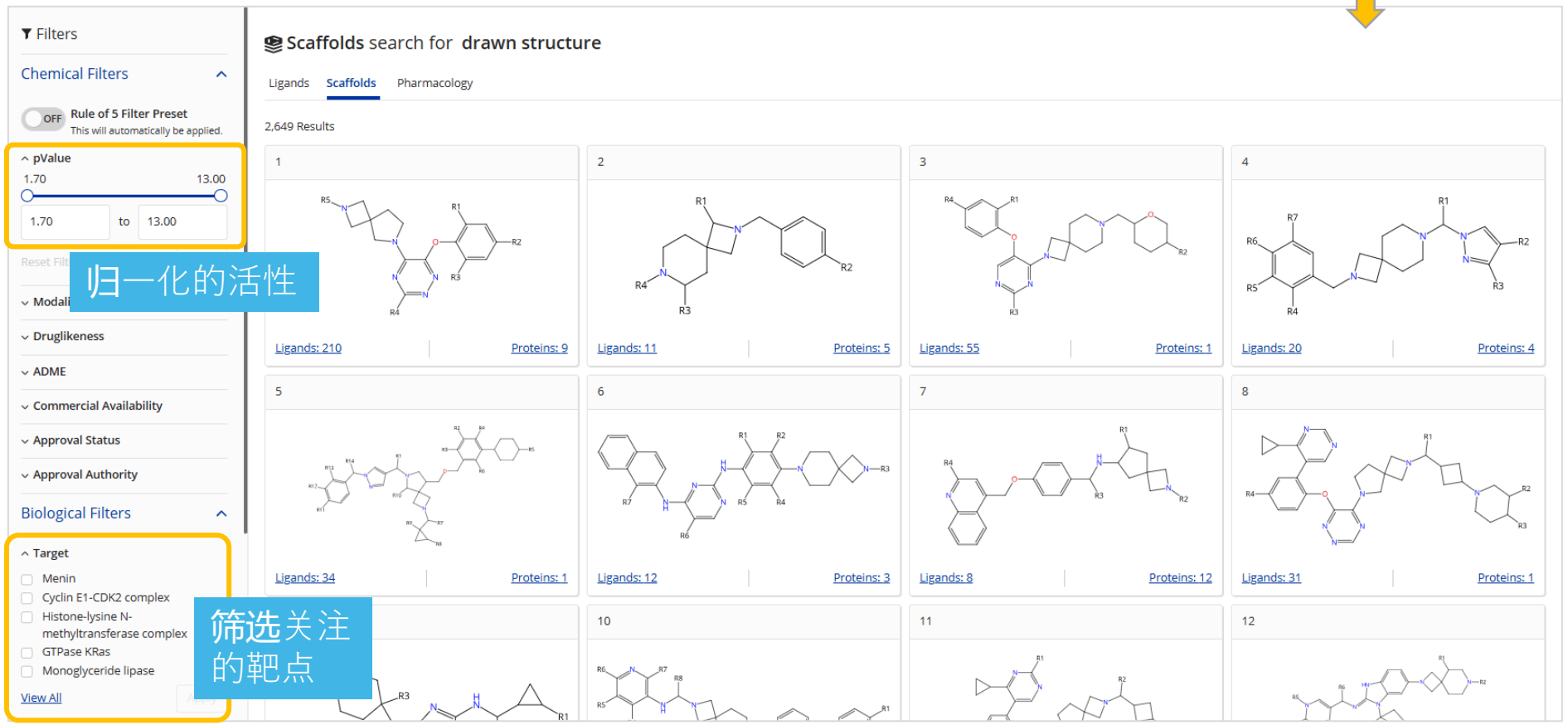
基于靶点或结构片段，探索活性结构骨架

绘制核心结构片段





归一化的活性

筛选关注的靶点

$$pKa = -\log_{10} Ka$$

$$pIC50 = -\log_{10} IC50$$

IC50越小，pValue越大，抑制活性越高。

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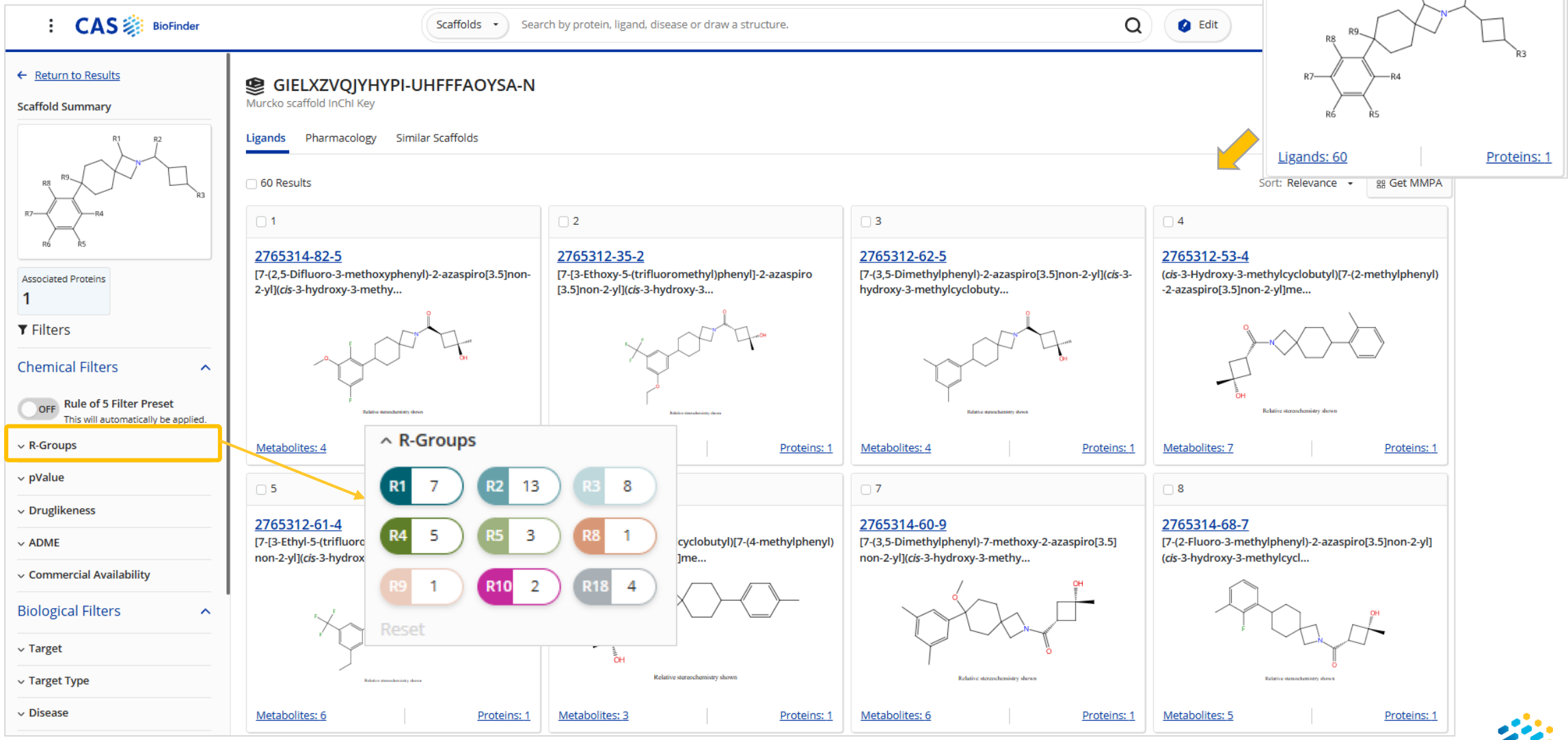
探索目标结构骨架的SAR数据



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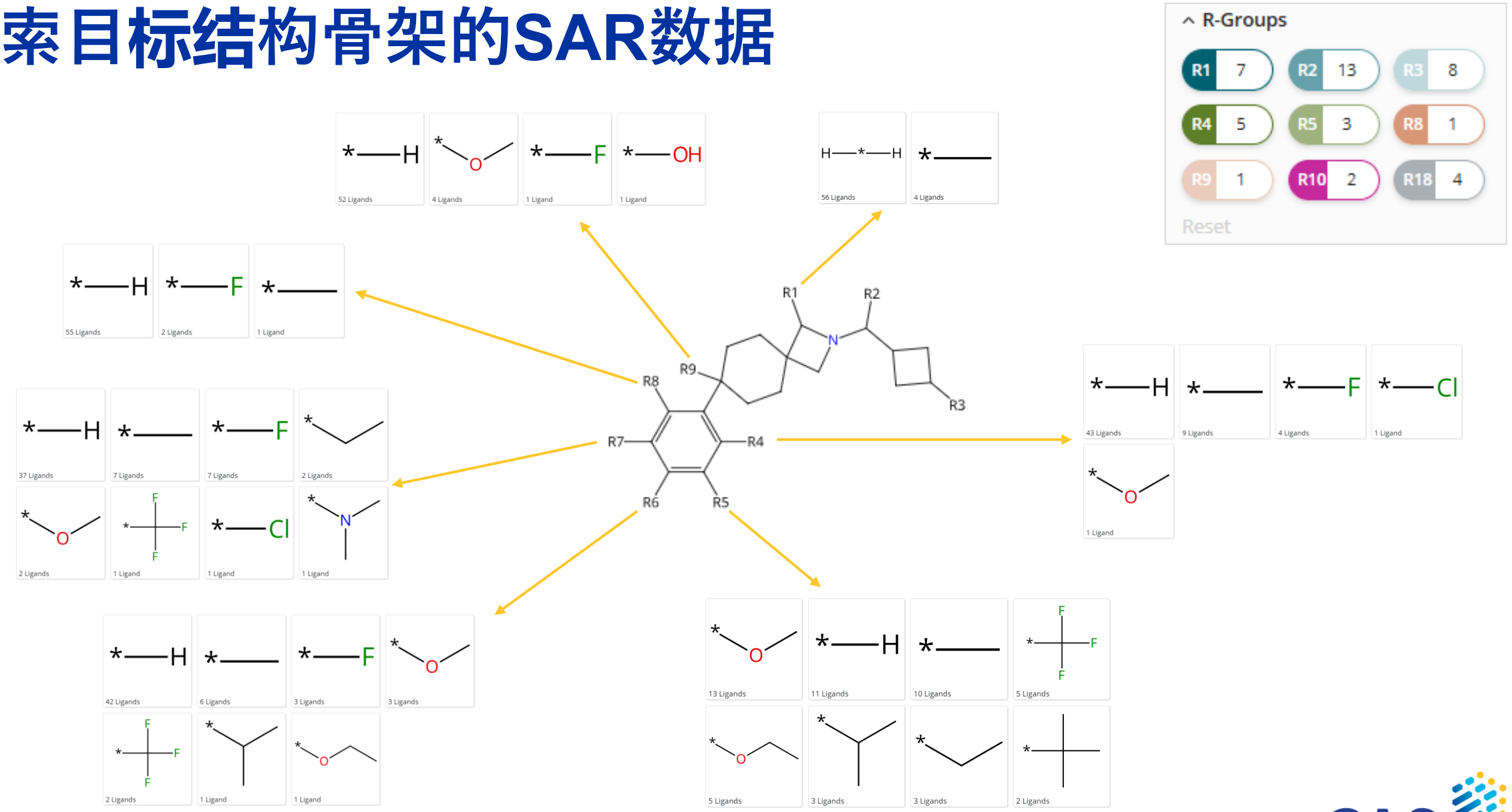
探索目标结构骨架的SAR数据



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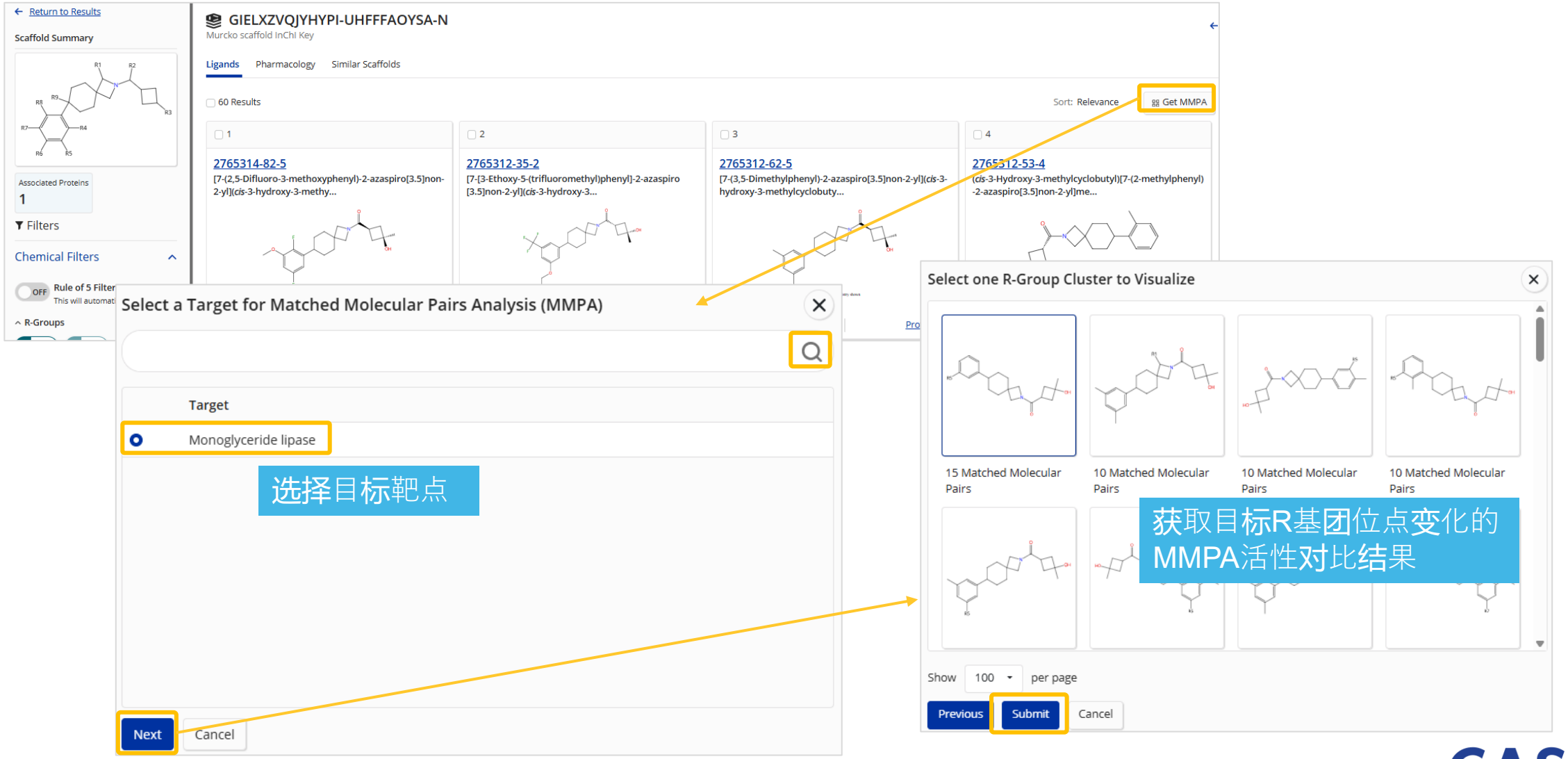
匹配分子对分析 (MMPA)



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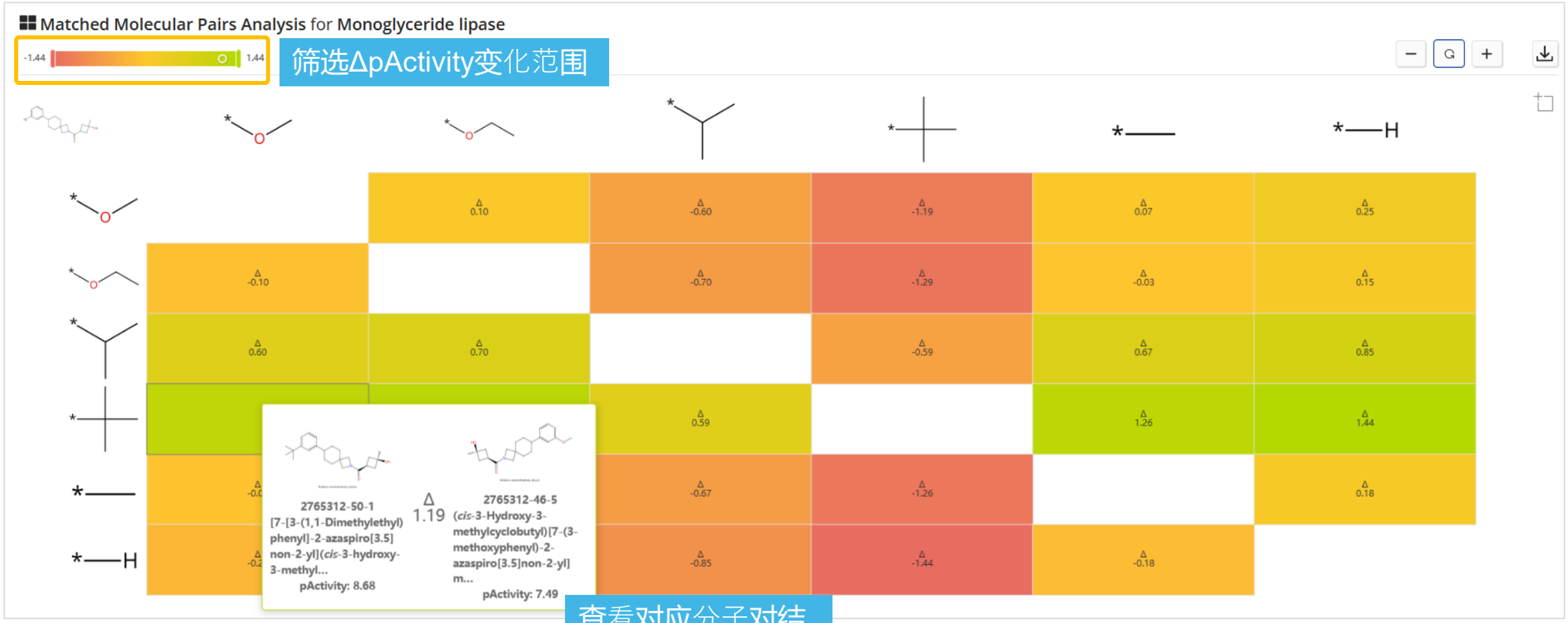
匹配分子对分析 (MMPA)

快速直观获取匹配分子对ΔpActivity热图



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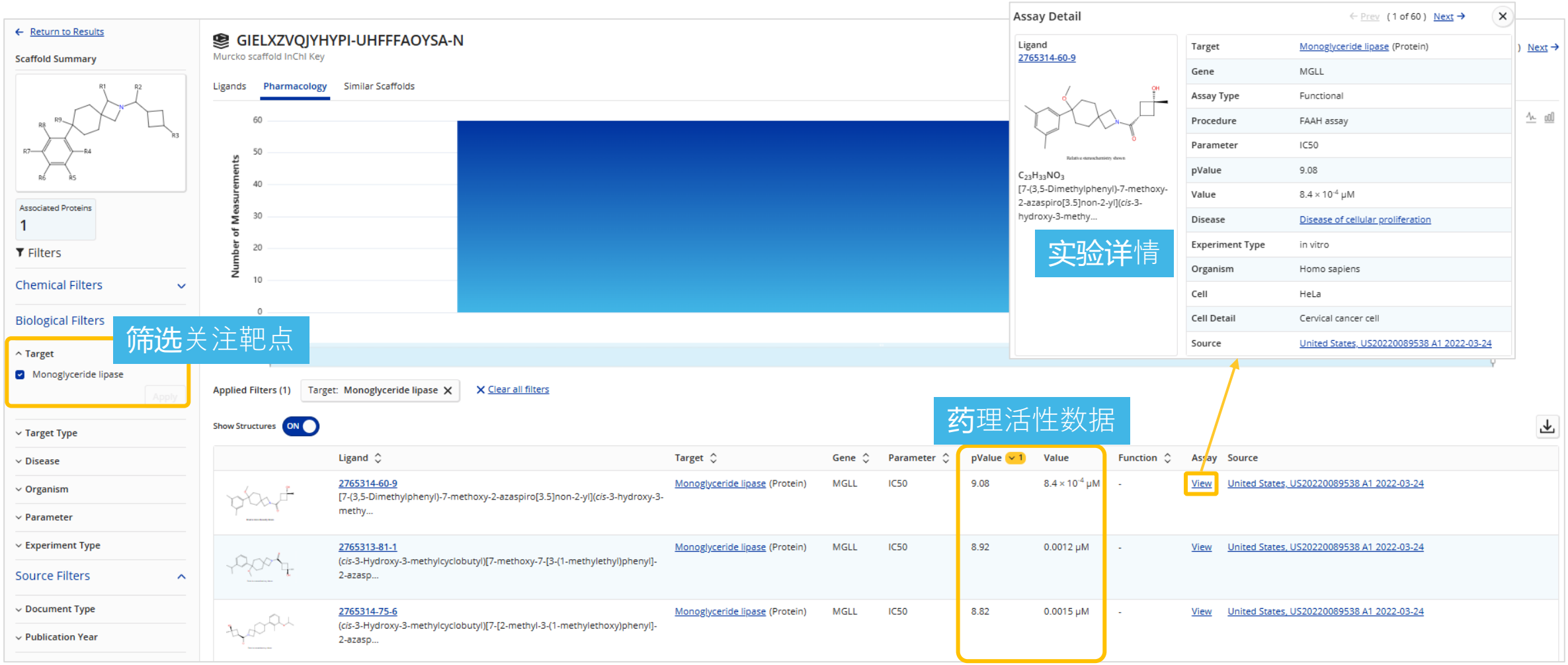
查看同一结构骨架中的配体药理活性



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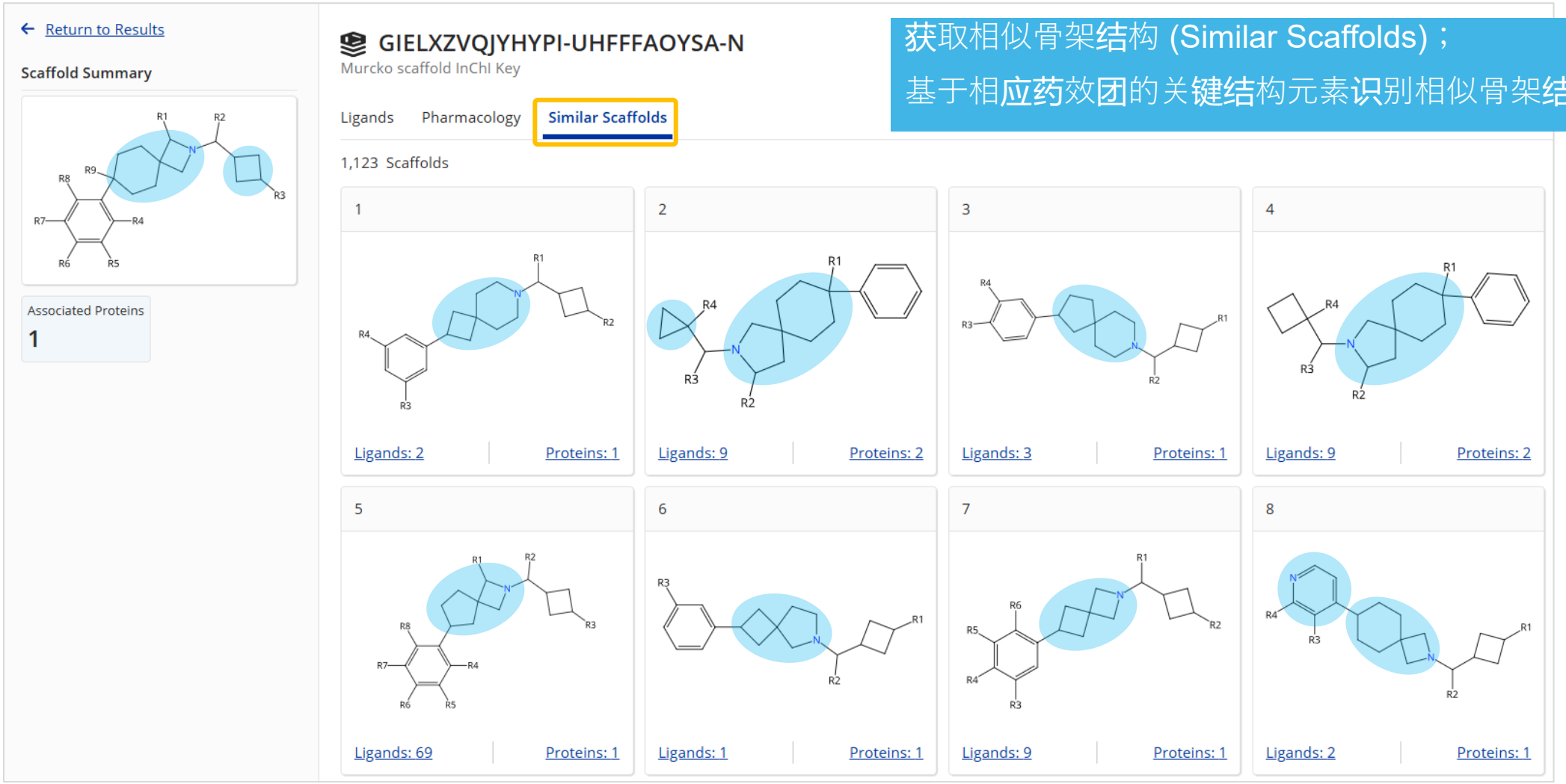
获取与目标骨架相似骨架结构，启发新的SAR假设



获取相似骨架结构 (Similar Scaffolds)；

基于相应药效团的关键结构元素识别相似骨架结构

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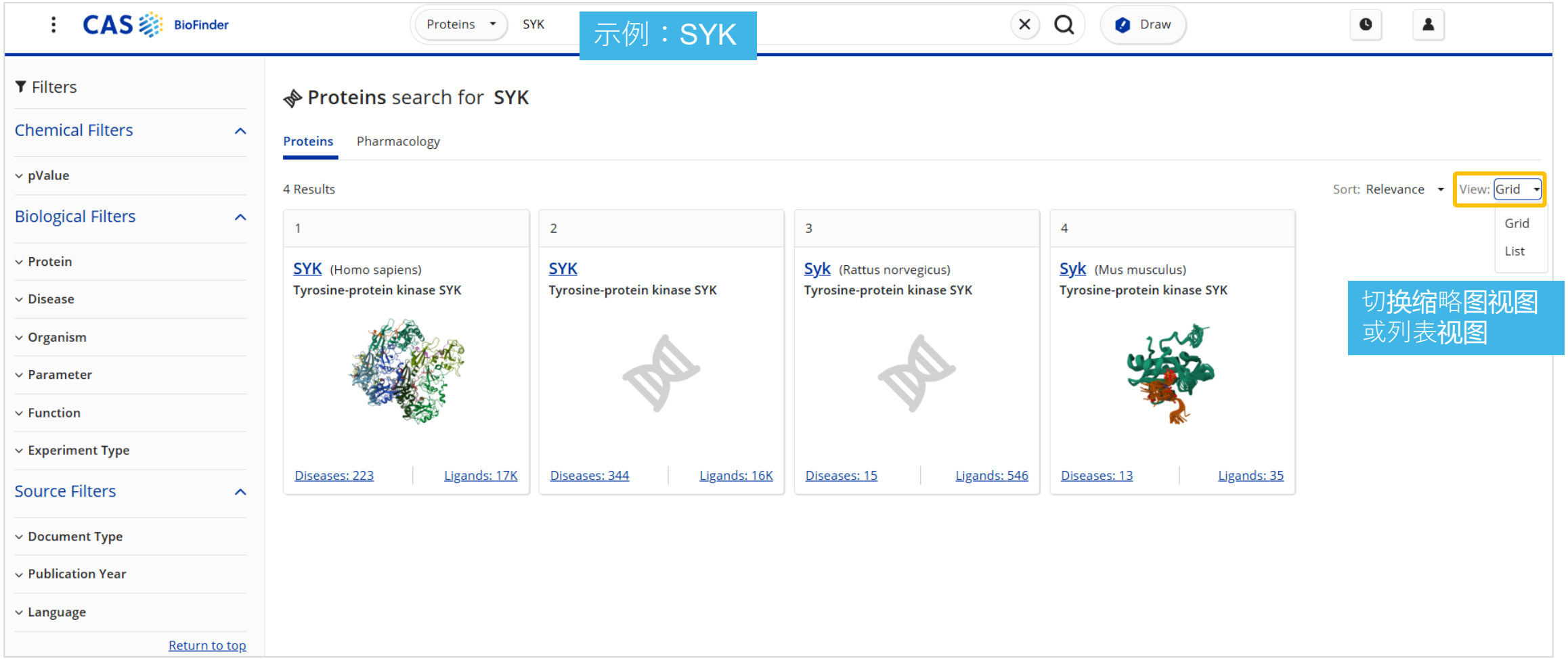
提纲

- CAS BioFinder 简介与检索界面介绍 (Introduction and Interface)
- 配体检索与配体详情信息(Ligands and Details Overview)
- 骨架检索与构效关系分析(Scaffolds and SAR Analysis)
- 蛋白/通路/靶点、疾病与生物标志物(Proteins & Pathways; Diseases & Biomarkers)
- 生物活性预测 (Predictive Analytics)

通过靶点、疾病或配体，获取归一化的蛋白检索结果



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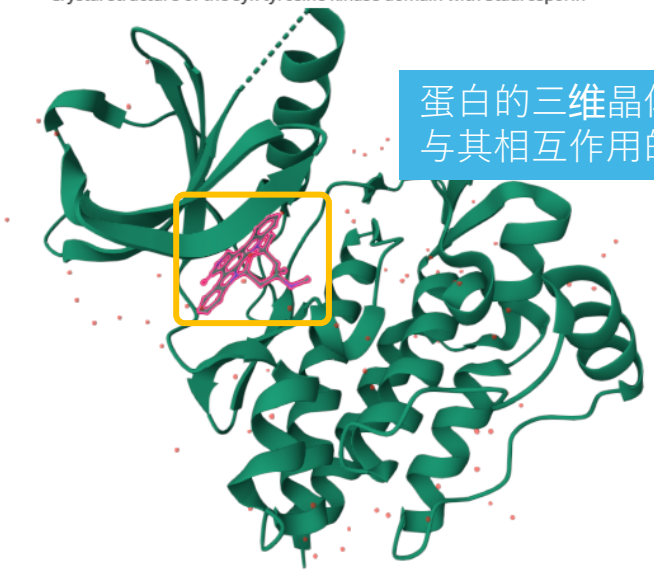
蛋白详情信息与立体结构展示

SYK
Tyrosine-protein kinase SYK

Summary | Pharmacology | Ligands (31K) | Diseases (388) | Chemical Space | Pathways

Crystal structure of the syk tyrosine kinase domain with Staurosporin



蛋白的三维晶体结构及与其相互作用的小分子

STAUROSPORINE
1XBC | Model 1 | Instance ASM_1 | B [auth A] | STU 1

1XBC | 下载cif格式结构文件

Homo sapiens
unspecified
Rattus norvegicus
Mus musculus

来源有机体

Organism: Homo sapiens | GET FASTA | Copy Sequence

```
>P43405-1|Tyrosine-protein kinase SYK|Homo sapiens
MASSGMADSANHLPFFFGNITREEAEDYLVQGGMSDGLYLLRQSRNYLGGFALSVAHGRKAHHYTIERELNGTYAIAGGRTHASPADLCHYHSQESDGLVCLLKKPFNRPQGVQPK
TGPFEDLKENLIREYVKQTWNLQGQALEQAIISQKPQLEKLIATTAHEKMPWFHGKISREESEQIVLIGSKTNGKFLIRARDNNGSYALCLLHEGKVLHYRIDKDKTGKLSIPEGK
KFDTLWQLVEHYSYKADGLLRVLTVPCQKIGTQGNVNFGGRPQLPGSHPATWSAGGIISRIKSYSFPKPGHRKSSPAQGNRQESTVSFNPYEPELAPWAADKGPQREALPMDTEVY
ESPYADPEEIRPKEVYLDRKLLTLEDKELGSGNFGTVKKGYYQMKKVVKTVAVKILKNEANDPALKDELLAEANVMQQLDNPYIVRMIGICEAESWMLVMEMAELGPLNKYLQQNR
HVKDKNIIELVHQVSMGMKYLEESNFVHRDLAARNVLLVTQHYAKISDFGLSKALRADENYYKAQTHGKWPVKWYAPECINYYKFSSKSDVWSFGVLMWEAFSYGQKPYRGMKGSE
VTAMLEKGERMGCPAGCPREMYDLMNLCWTYDVENRPGFAAVELRLRNYYYDVVN
```

序列详情

Identifier	Method	Resolution	Chain	Positions	Source
1A81	X-Ray	3.0 Å	A/C/E/G/I/K	9 - 262	PDB
1CSY	NMR	-	A	163 - 265	PDB
1CSZ	NMR	-	A	163 - 265	PDB
1XBA	X-Ray	2.00 Å	A	353 - 635	PDB
1XBB	X-Ray	1.57 Å	A	353 - 635	PDB
1XBC	X-Ray	2.00 Å	A	353 - 635	PDB
3BUW	X-Ray	1.450 Å	A/C	317 - 329	PDB
				349 - 635	PDB

External Links and Identifiers

Alliance of Genome Resources: HGNC:11491
CHEMBL: CHEMBL2599
Ensembl gene: ENSG00000165025.15, ENSG00000165025
HGNC: HGNC:11491
NCBI Gene: 6850
OMIM: 600085
Uniprot reviewed: P43405
View Less

归一化的靶点名称与其他详情信息

Synonyms

Spleen associated tyrosine kinase
Spleen tyrosine kinase

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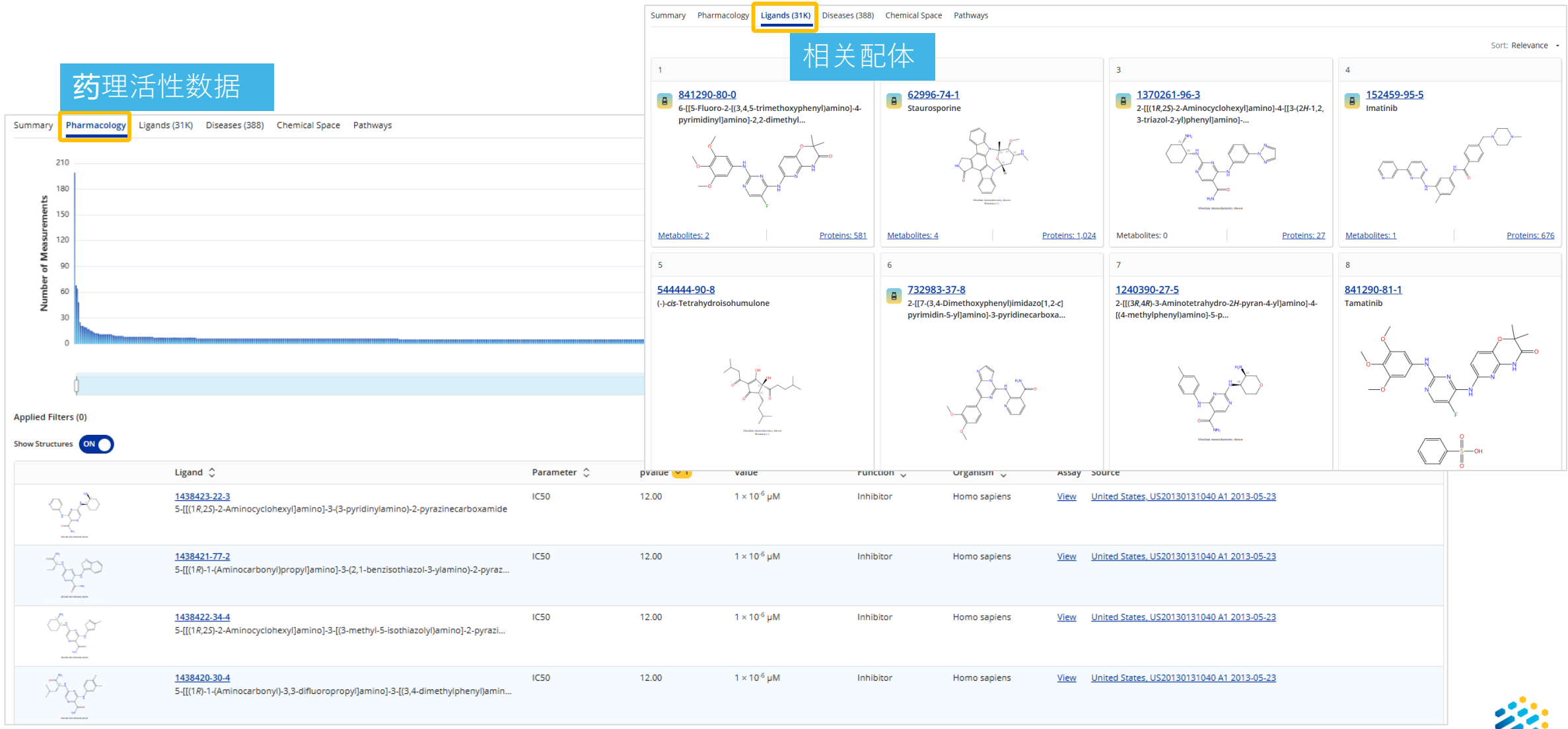
相关配体与药理活性数据

药理活性数据

相关配体



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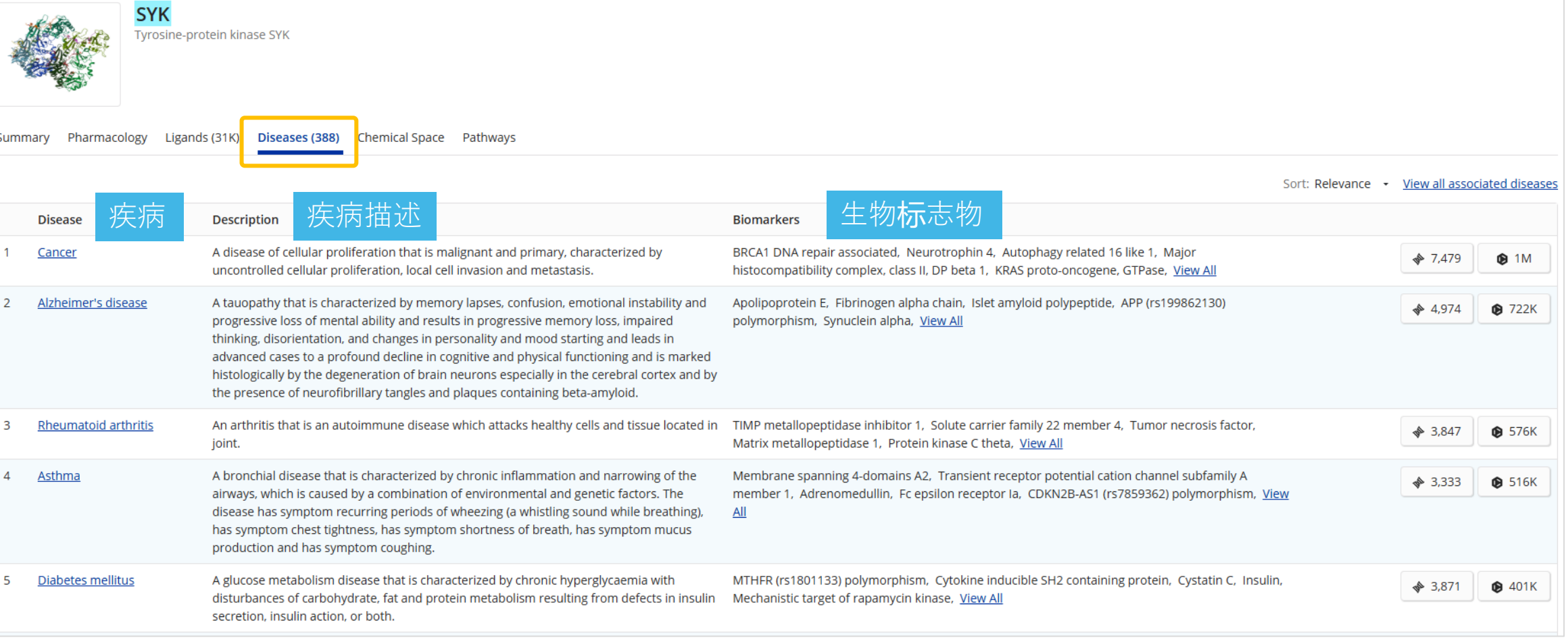
蛋白相关疾病信息



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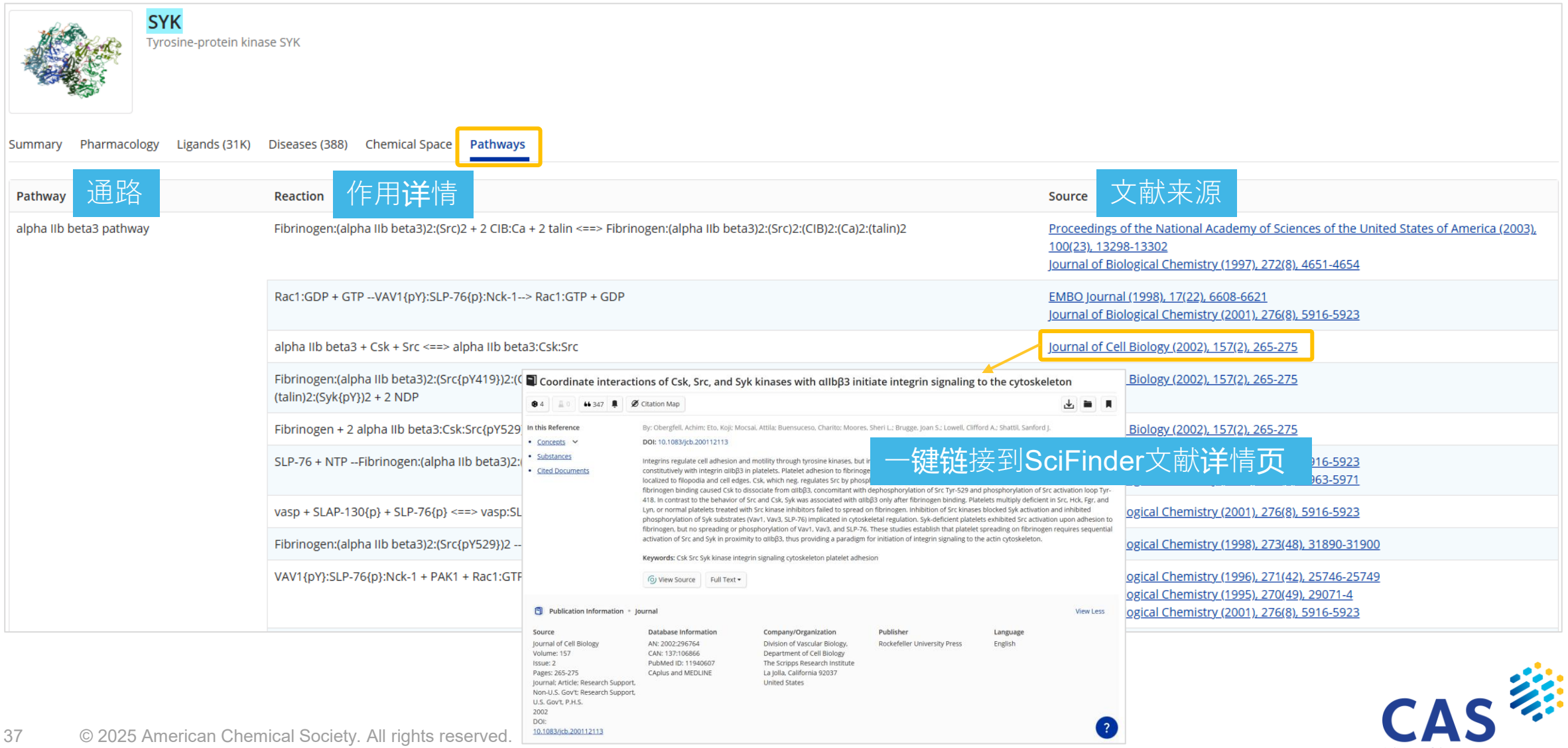
蛋白的生物通路信息



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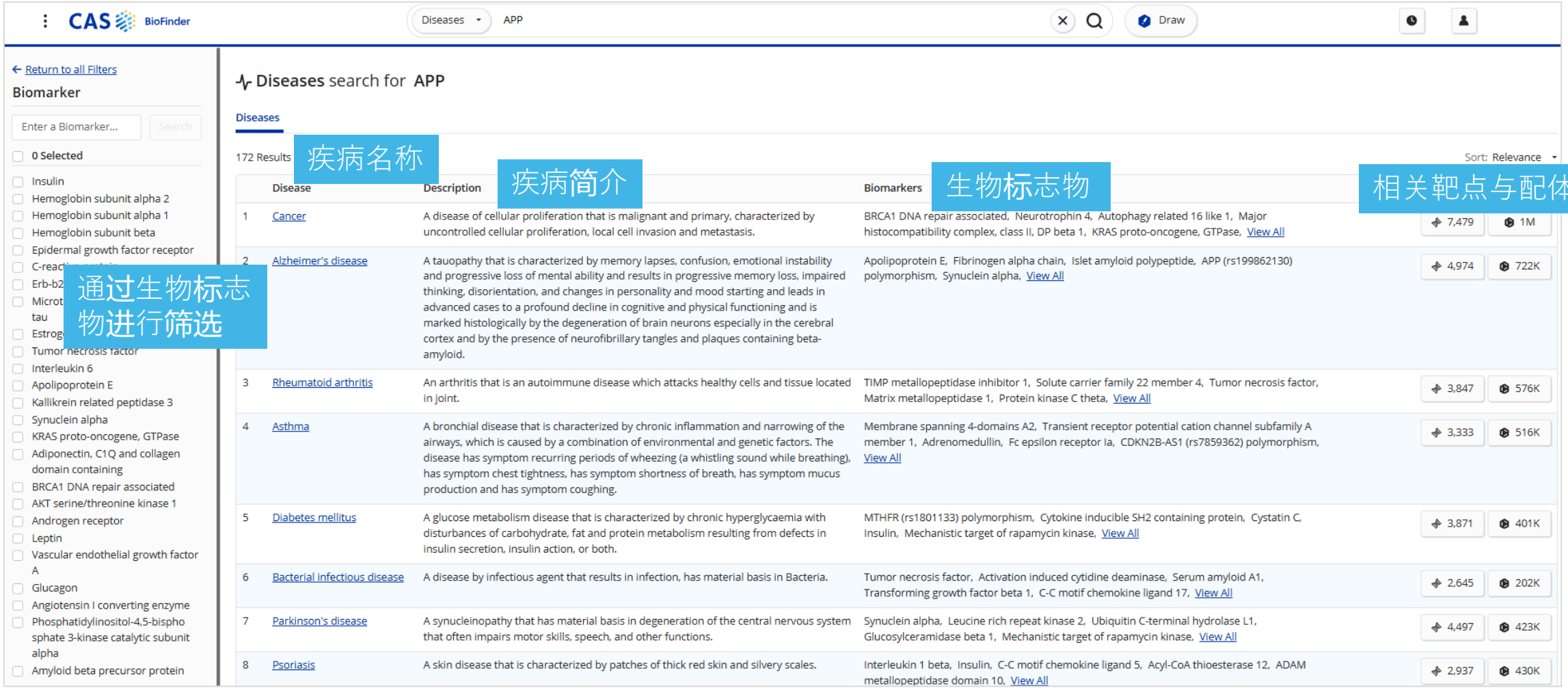
通过疾病名称、靶点或配体，检索相关疾病信息



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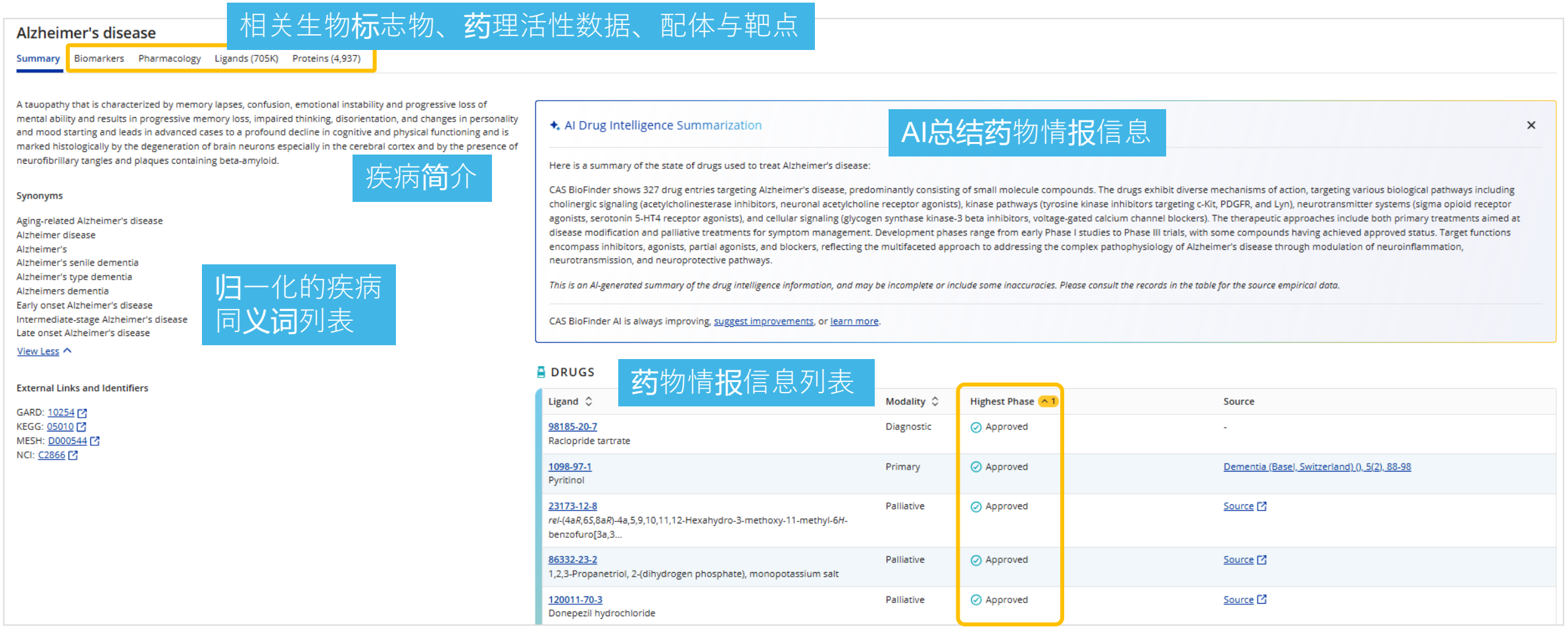
疾病详情页与相关药物信息



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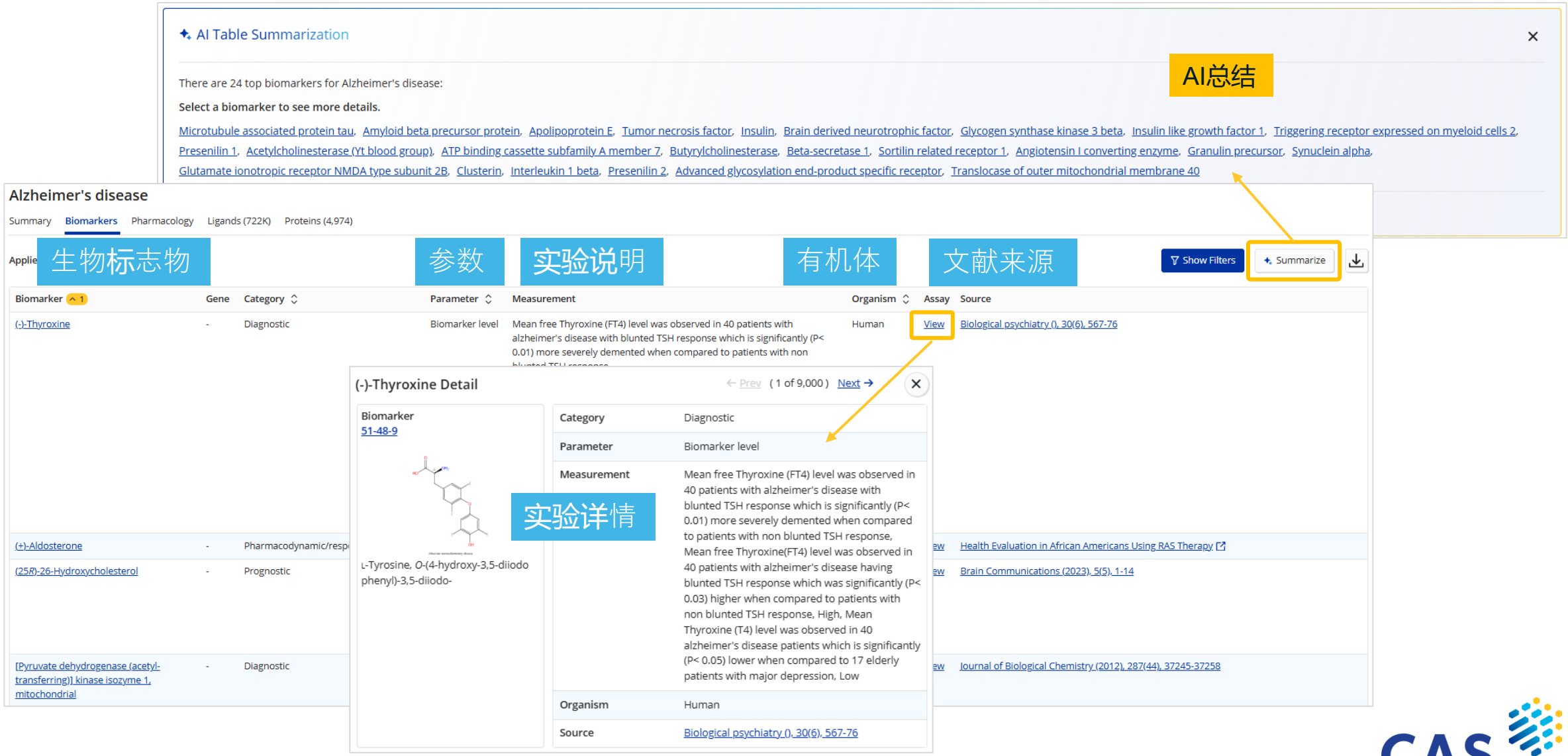
疾病与生物标志物



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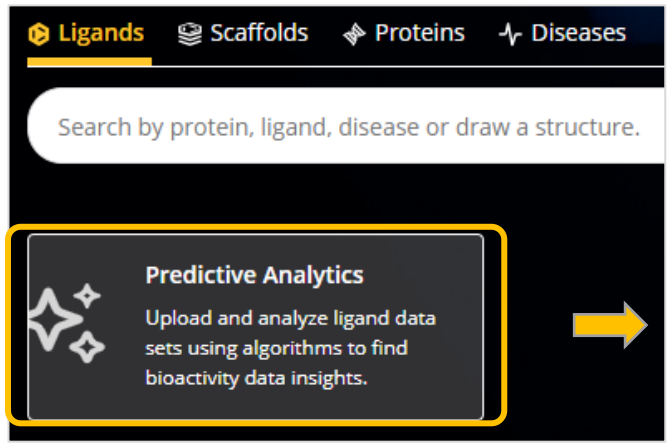
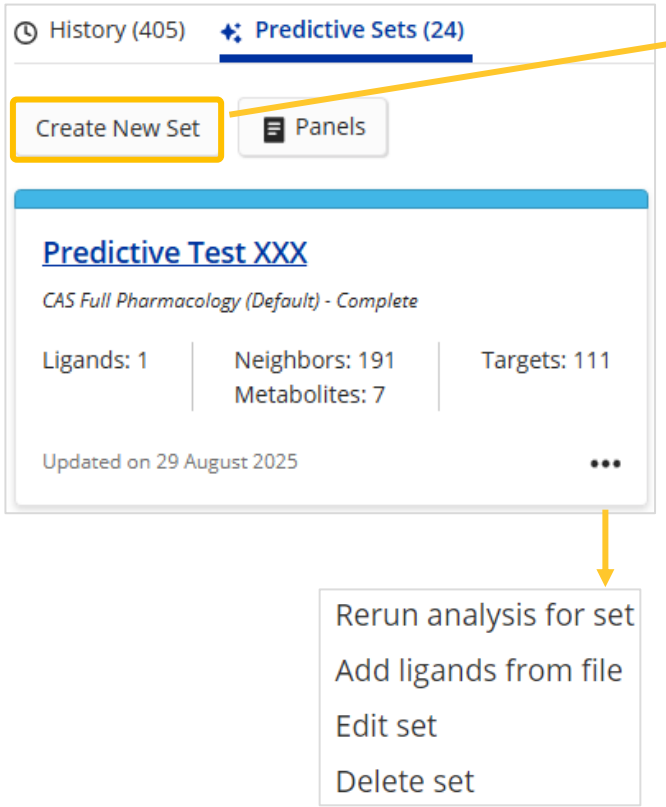
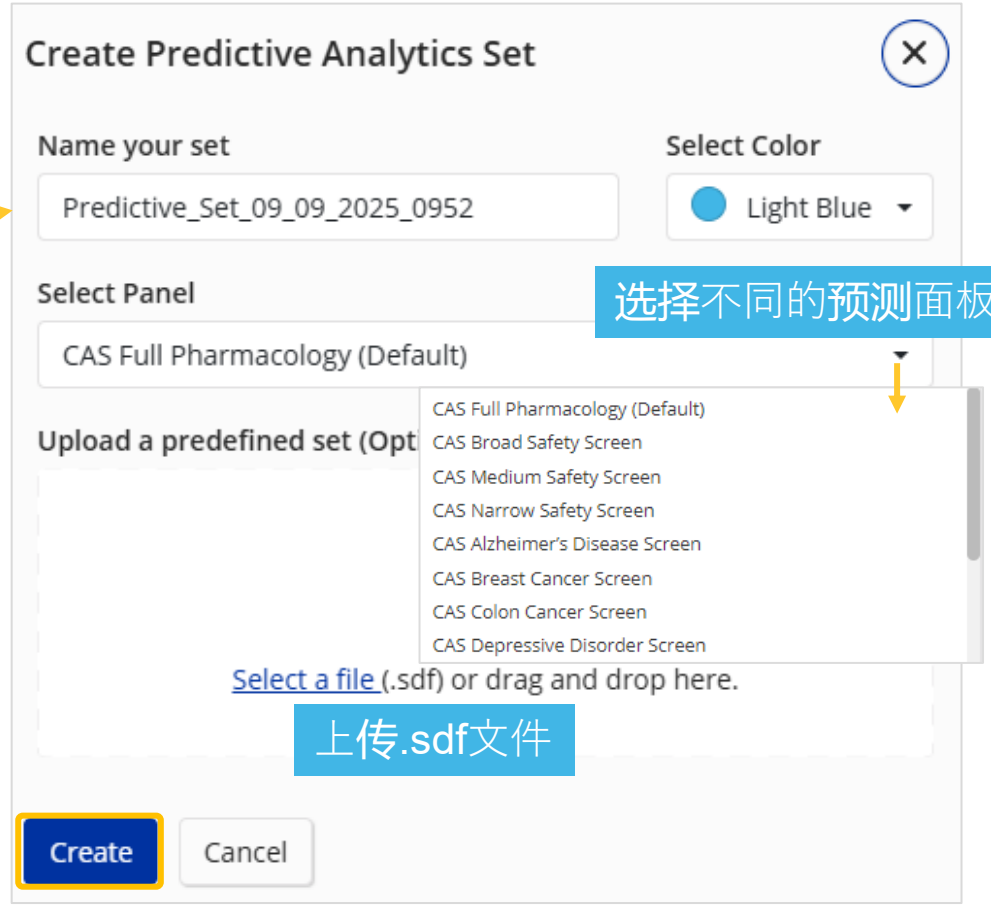
Predictive Analytics：通过算法预测配体对不同靶点的生物活性数据







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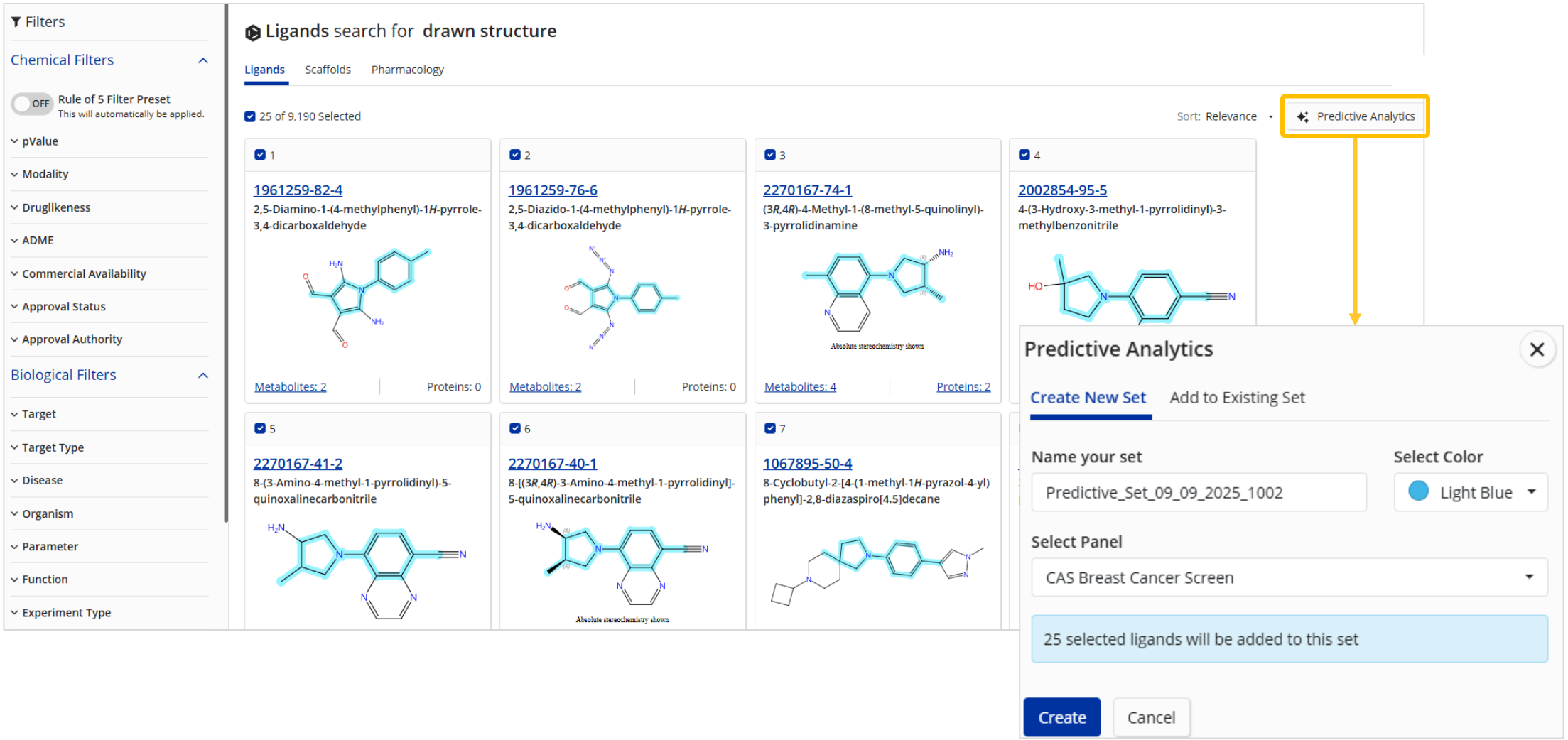
可从检索结果集中添加配体结构



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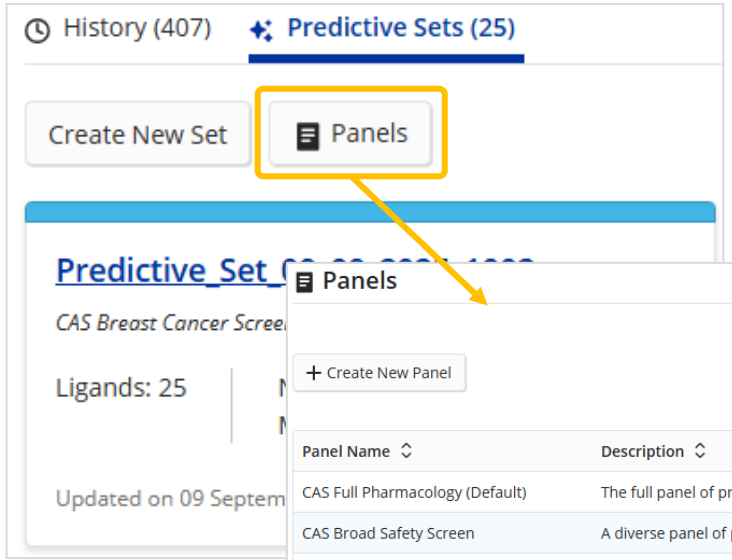
不同的蛋白靶点面板说明



Panels

+ Create New Panel

Search panels by name...

Panel Name	Description	Targets
CAS Full Pharmacology (Default)	The full panel of protein target models available through CAS to highlight potential safety concerns and treatment options	All
CAS Broad Safety Screen	A diverse panel of protein targets to widely test the safety of your drug candidate	192
CAS Medium Safety Screen	Panel of protein targets likely to be implicated to adverse drug reactions (ADRs) based off of known structure activity relationships (SARs)	115
CAS Narrow Safety Screen	Panel of protein targets established as being involved in adverse drug reactions (ADRs). These targets are essential for early safety screening of drugs	49
CAS Alzheimer's Disease Screen	Panel of protein targets potentially implicated in Alzheimer's Disease	81
CAS Breast Cancer Screen	Panel of protein targets potentially implicated in breast cancer and neoplasms	70
CAS Colon Cancer Screen	Panel of protein targets potentially implicated in colon cancer and neoplasms	92
CAS Depressive Disorder Screen	Panel of protein targets potentially implicated in depressive disorder and major depressive disorder	51
CAS Diabetes Screen	Panel of protein targets potentially implicated in diabetes	78
CAS Inflammation Screen	Panel of protein targets potentially implicated in inflammation	33
CAS Liver Cancer Screen	Panel of protein targets potentially implicated in liver cancer and neoplasms	73
CAS Lung Cancer Screen	Panel of protein targets potentially implicated in lung cancer and neoplasms	66
CAS Parkinson's Disease Screen	Panel of protein targets potentially implicated in Parkinson's disease	46
CAS Prostate Cancer Screen	Panel of protein targets potentially implicated in prostate cancer and neoplasms	70

点击查看详细靶点名称列表

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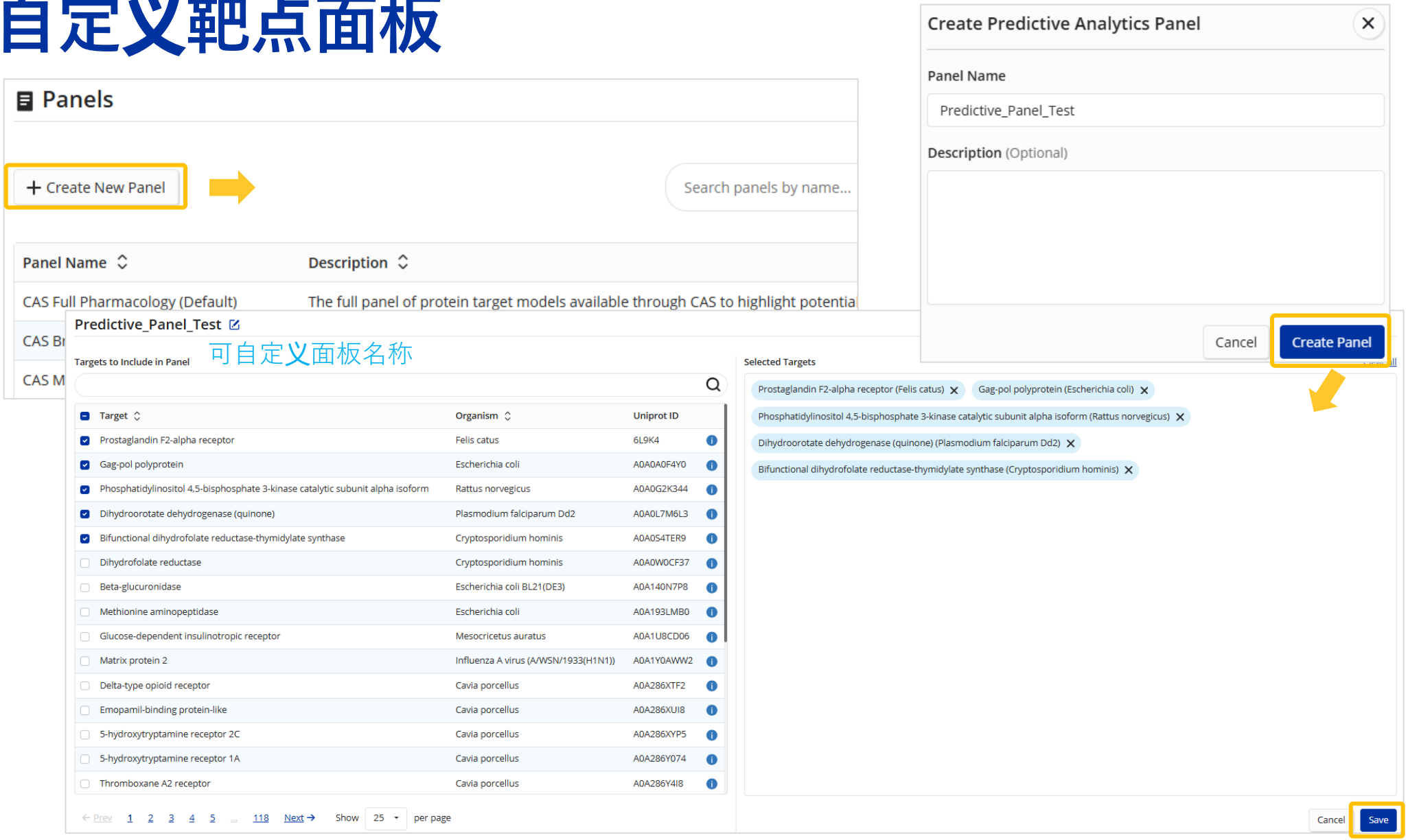
自定义靶点面板



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生物活性预测结果

使用左侧筛选功能可对这些数据进行细化分析：
- 活性值(pActivity)
- 置信度分数(Confidence score)
- 靶点(Target)
- 有机体(Organism)

助于探索特定范围内的pAct，或有较高可信度的预测信息。

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总结

配体检索 (Ligands)

- 基于药物名称、CAS RN、结构、靶点、疾病等，获取配体信息
- 通过类药性、ADME、实验参数、药物功能、生物有机体等，进行筛选聚焦
- 查看并评估化合物的药理学、ADME、毒理学和代谢物信息及可视化展示

骨架检索 (Scaffolds)

- 基于结构或靶点等信息，高效获取相关骨架结构，并通过官能团R-Groups，进行构效关系分析
- 通过 SAR 以及MMPA，优化目标骨架或先导化合物的效力和选择性
- 探索针对关注靶点同一结构骨架中活性最高的配体，获取相似骨架结构与拓展

蛋白/通路/靶点与疾病检索(Proteins & Diseases)

- 高效获取蛋白质通路/靶点与疾病生物标志物信息，探索药物作用机制和适应症

预测配体与不同靶点的生物活性(Predictive Analytics)

- 预测特定结构针对特定靶点的药理活性信息
- 关注配体的脱靶效应与药物再利用

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相关资源 Learn More

https://biofinder.cas.org/

获取CAS BioFinder登录访问网址

https://www.cas.org/solutions/biofinder-discovery-platform

了解更多关于CAS BioFinder的信息

https://cas-biofinder.zendesk.com/hc/en-us

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Between problems and progress are connections that matter

谢 谢 ！

China@acs-i.org

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