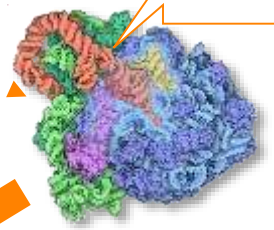
如何利用Reaxys和RMC进行全新药物分子设计和专利评估

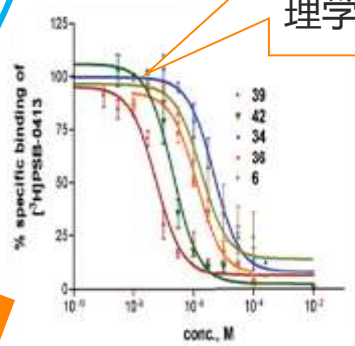
药物Discovery的过程

疾病，适应症，副作用跟踪

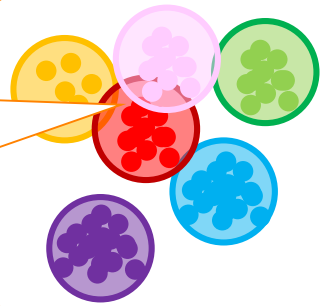
确认靶点

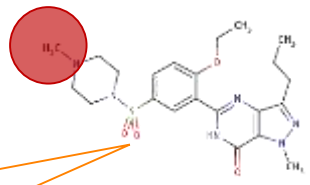


DMPK，代谢稳定性(P450)，细胞渗透性（caco-2），药理学，毒理学等



化合物结构计算，SAR构效分析等





化合物初步筛选，生物初筛活性数据（IC50, EC50等）

(pre)clinical

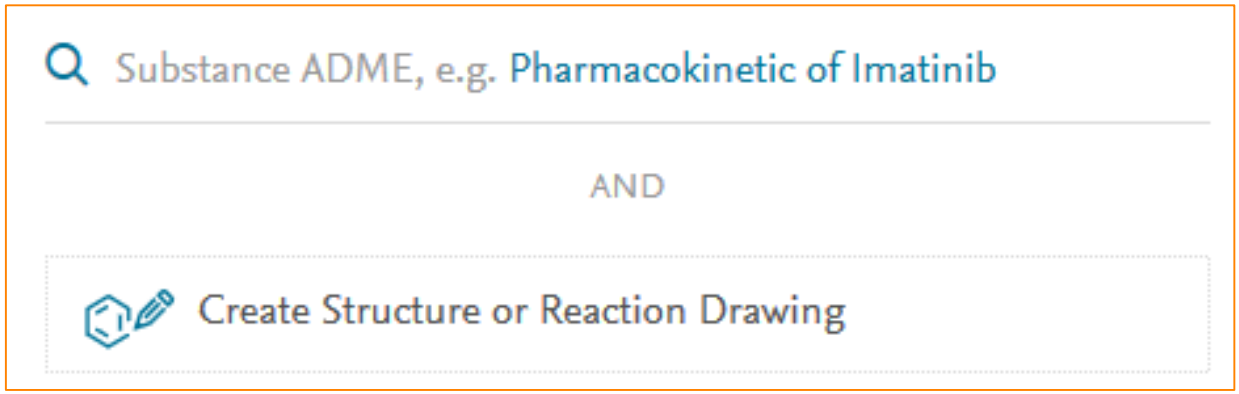
动物模型，动物毒理等，生物利用率，越早成功，成本越少

Discovery中常见的科学性问题

今天探讨的问题：

如何利用RMC解决这些科学性问题，并用Reaxys解决可专利性问题

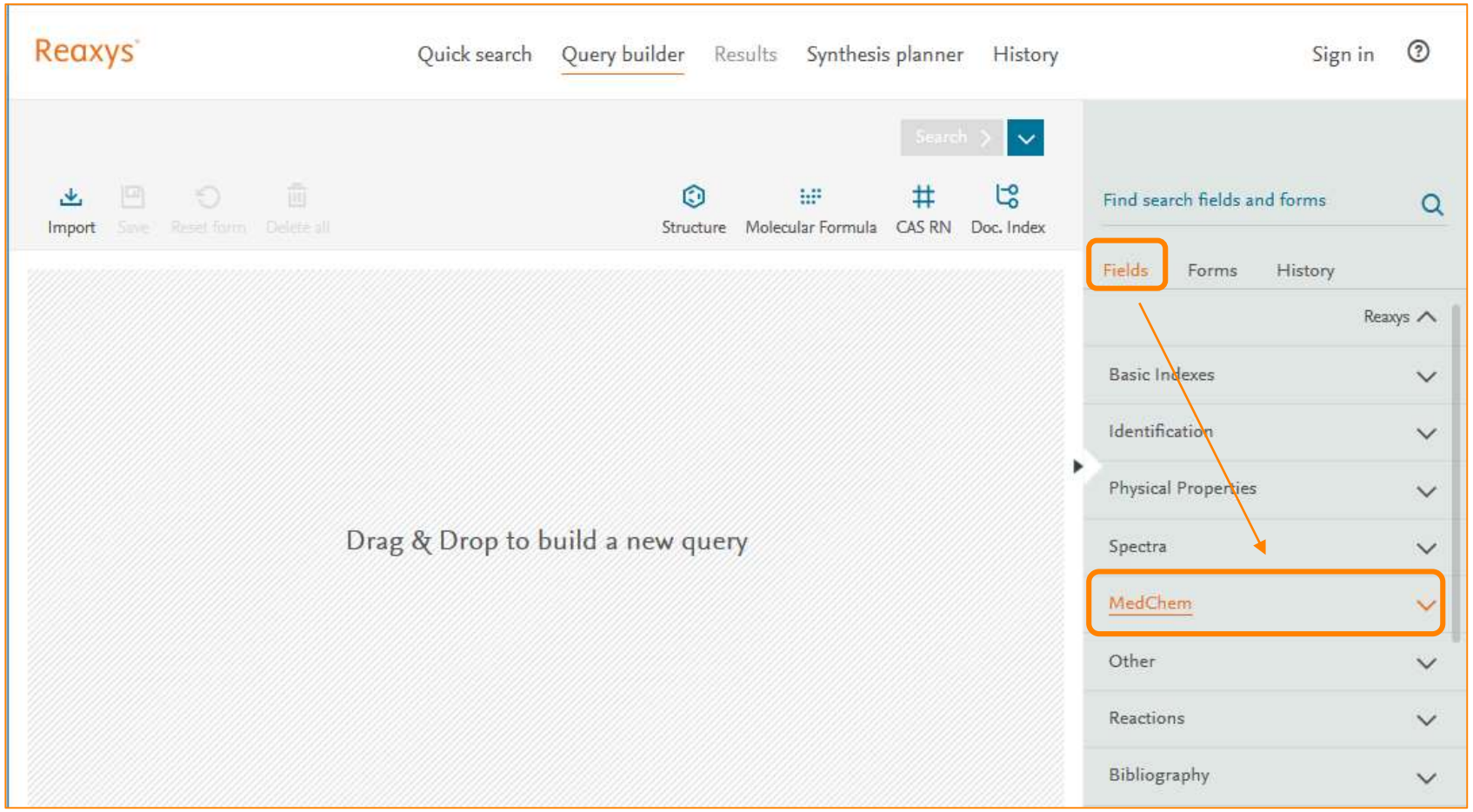
RMC的检索方式—Quick Search



Quick Search中可以使用的方式：

1. 靶点，或者基因名称，	5-ht1a
2. 靶点活性，	PIP4K2C Activity
3. 靶点抑制性，	Inhibitors of CXCR4
4. 物质在靶点上的抑制性，	PIP4K2C by imatinib
5. 靶点作用机制，	Agonist of GLP-1
6. 物质作用效果，	Atenolol Pharmacological effect
7. 物质药物代谢动力学研究，	Pharmacokinetic of Imatinib
8. 结构	

RMC检索方式—Query Builder Fields



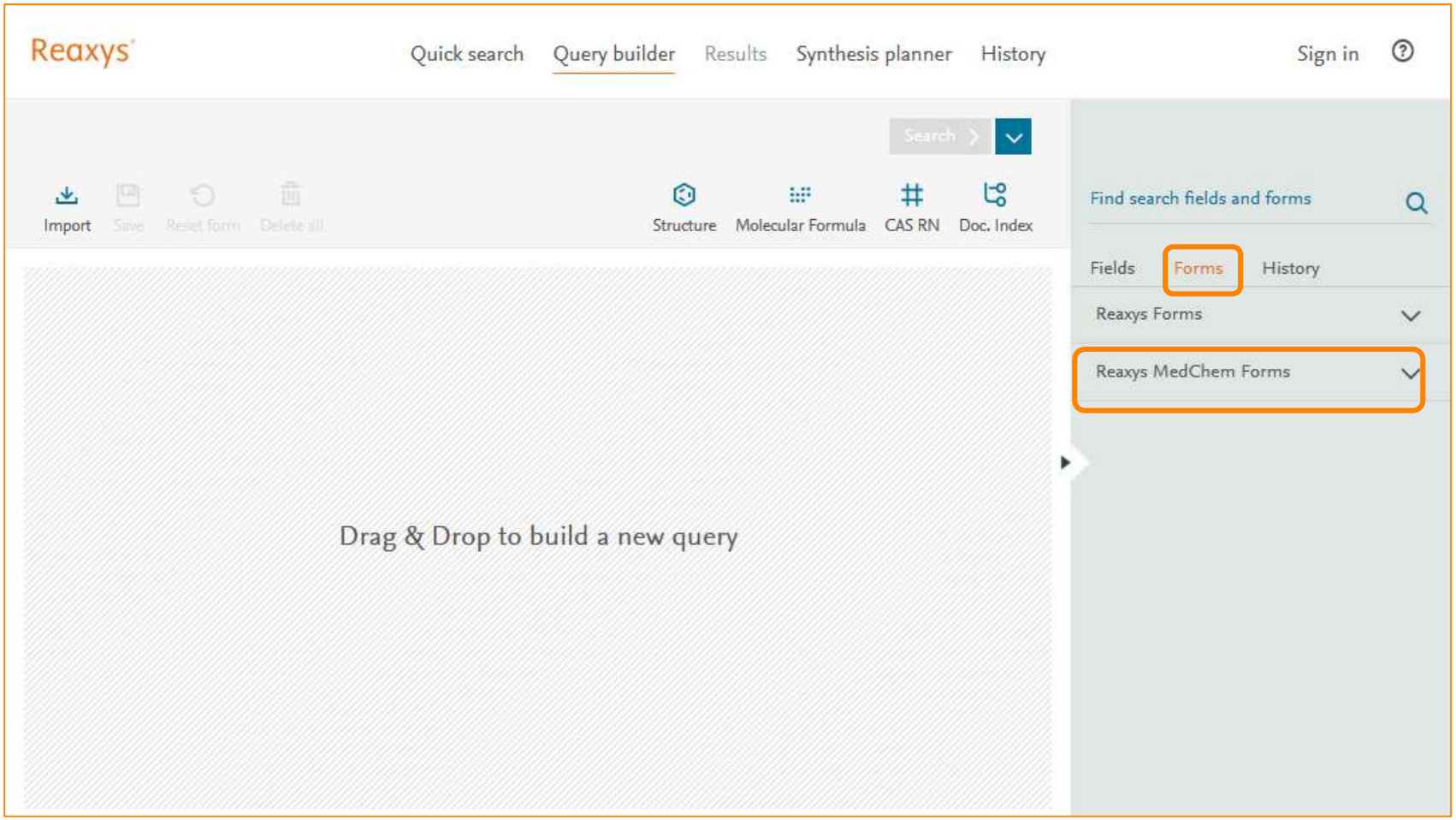
Query Builder模块下，Fields中MedChem进行字段组合检索

MedChem中的字段

- Target Name
- Substance Action on Target
- Substance Effect
- Measurement pX
- Target Nature
- Target Mutant/Chimera Details
- Target Transfection
- Substance RN
- Substance Route of Adm.
- Substance Dosing Regimen
- Substance Dose
- Substance Highest Clin. Phase
- Substrate RN
- Substrate Name
- Bioassay Category
- Bioassay Subcategory
- Bioassay Name
- Bioassay Animal Model
- Bioassay Details
- Biological Material Name
- Biological Species
- Bioassay Population
- Organs/Tissues
- Cells/Cell Lines
- Cell Fraction
- Measurement Parameter
- Measurement Qualitative
- Measurement Unit
- Measurement Value
- Measurement Details

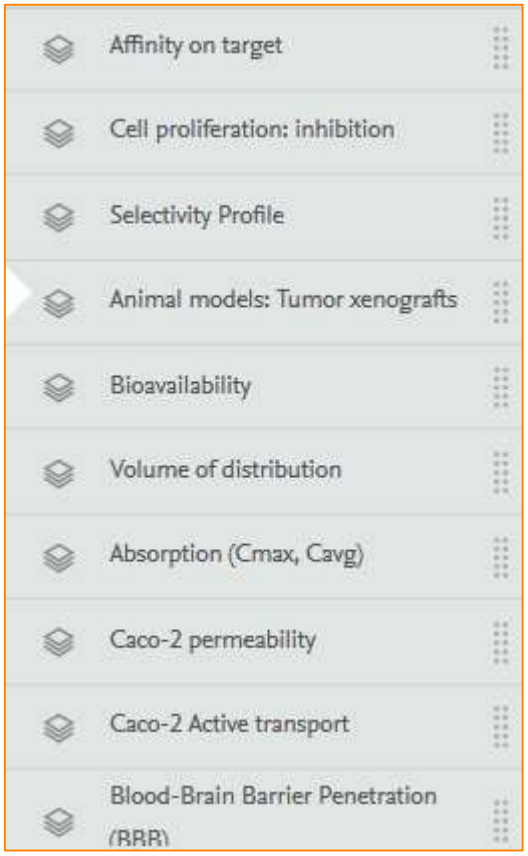
一共31种字段的检索，可以自由组合

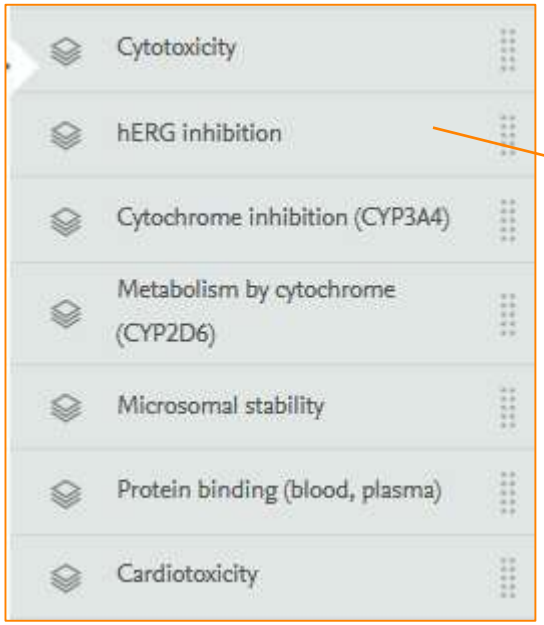
RMC检索方式—Query Builder Forms

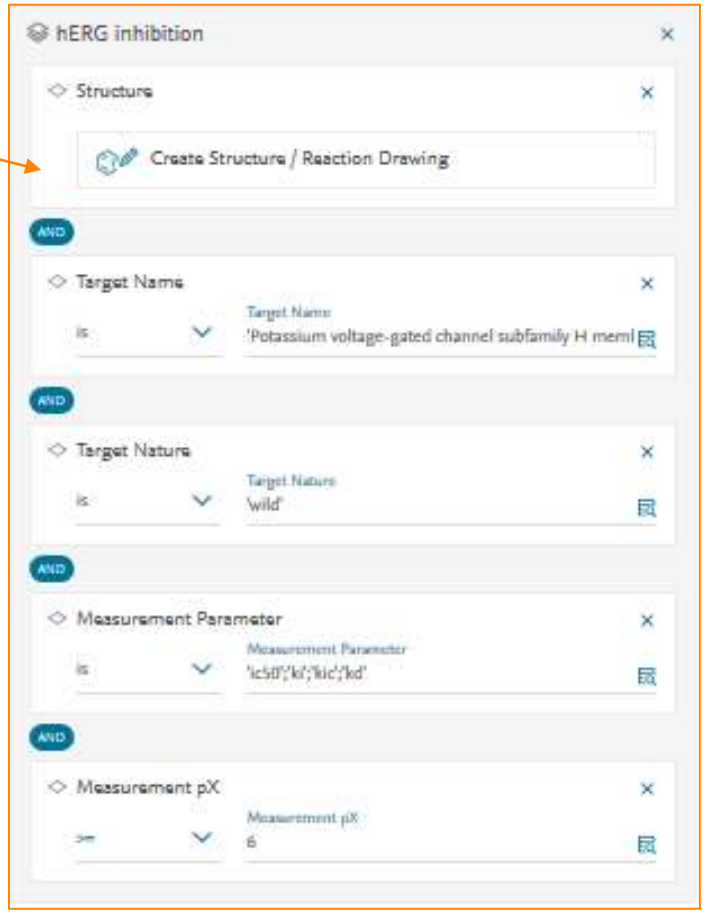


Query Builder模块下，Forms中RMC预设模块的检索

RMC Forms预设模块检索





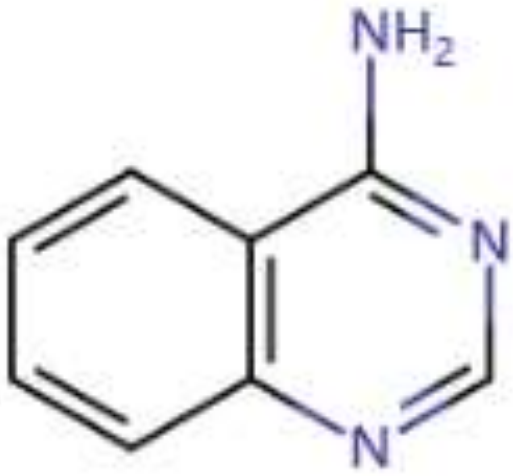


RMC Forms预设了一些常见的检索策略，只需要选择对应模块，并添加相应条件，即可进行检索

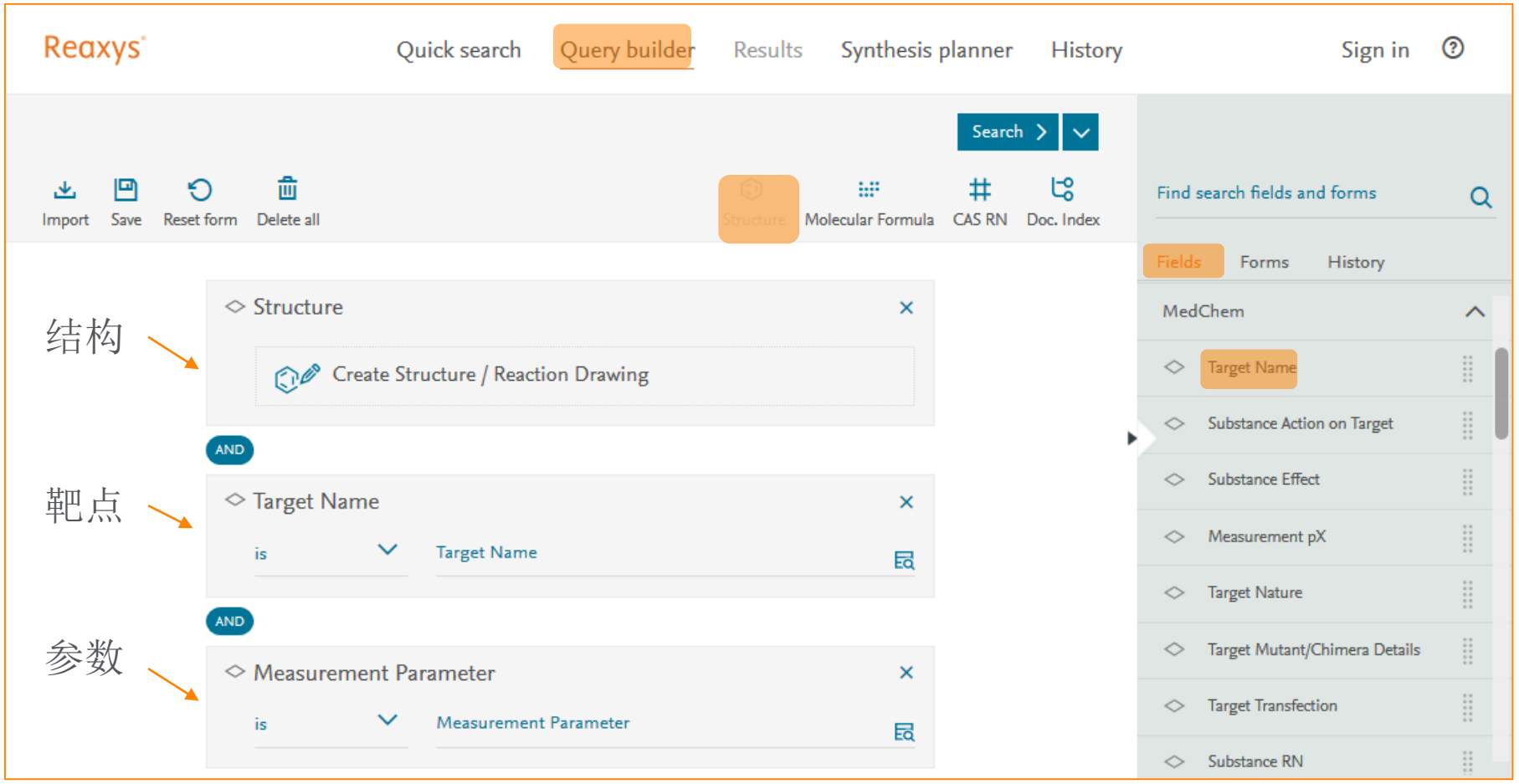
CASE 1 Me Better药物的开发

Me Better药物往往和原研药物有一个相同或相似的母核

- 获得同母核化合物在同靶点上全部的数据
- 寻找潜在的对活性有影响的片段，设计新化合物
- 初步的专利评估
- 如何利用SAR构效关系优化实验设计
  - 清除率Clint
  - Cmax, Tmax, Caco2, hERG, P450
  - 生物利用度%F
  - ……



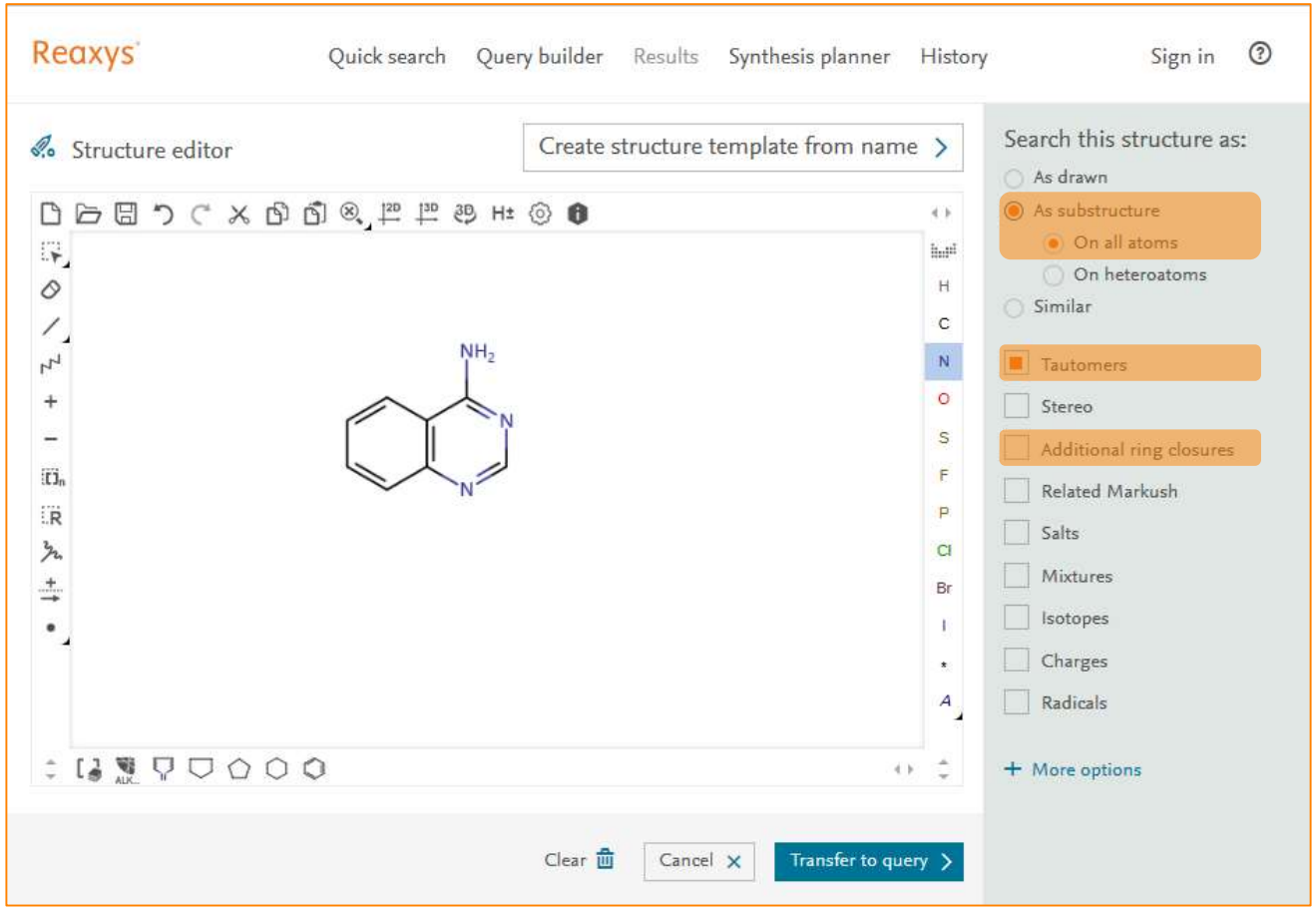
利用Query Builder构建检索



Tips：

在Query Builder下，添加结构，同时添加MedChem中的字段进行检索，Target，Parameter

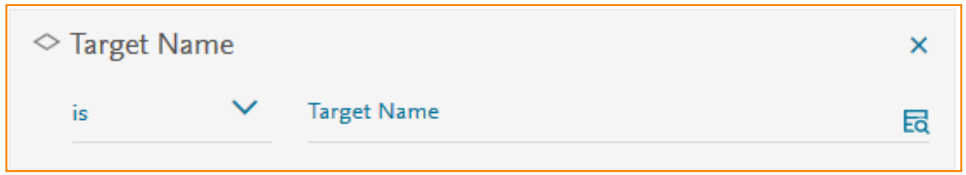
添加的过程—结构



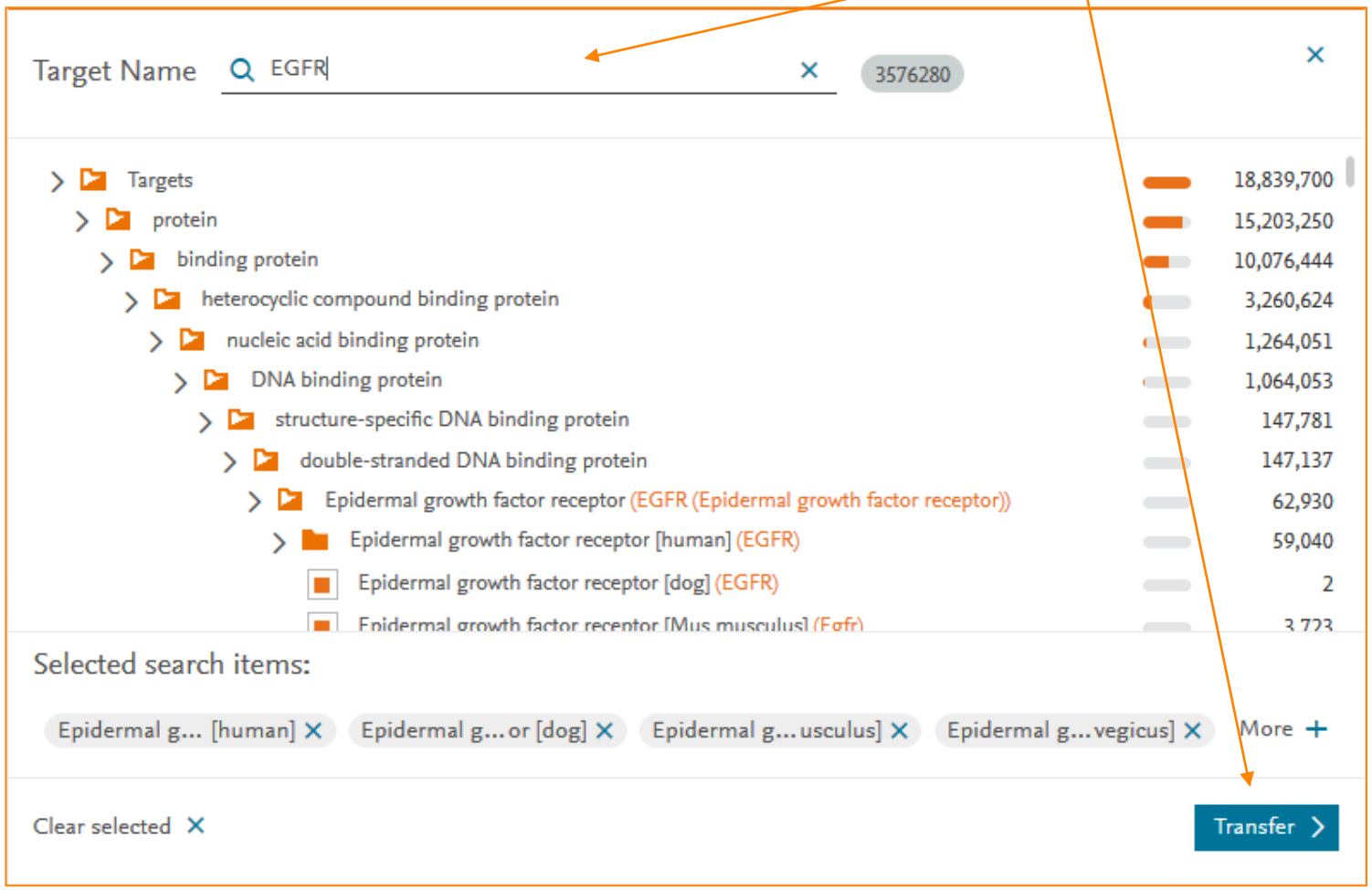
Tips：

1. 用亚结构检索获得所有母核相同的化合物。
2. Additional Ring Closures保护环系
3. 去除所有的盐
4. 允许有互变

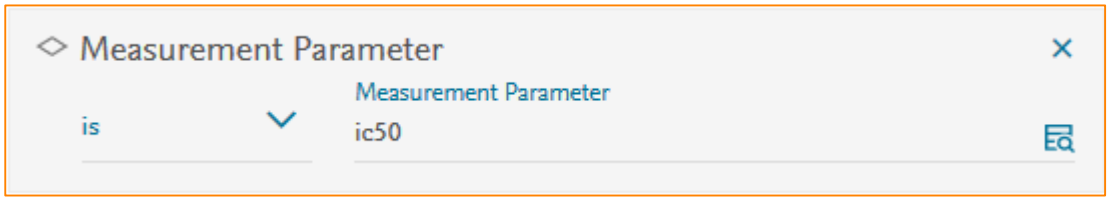
添加的过程—靶点



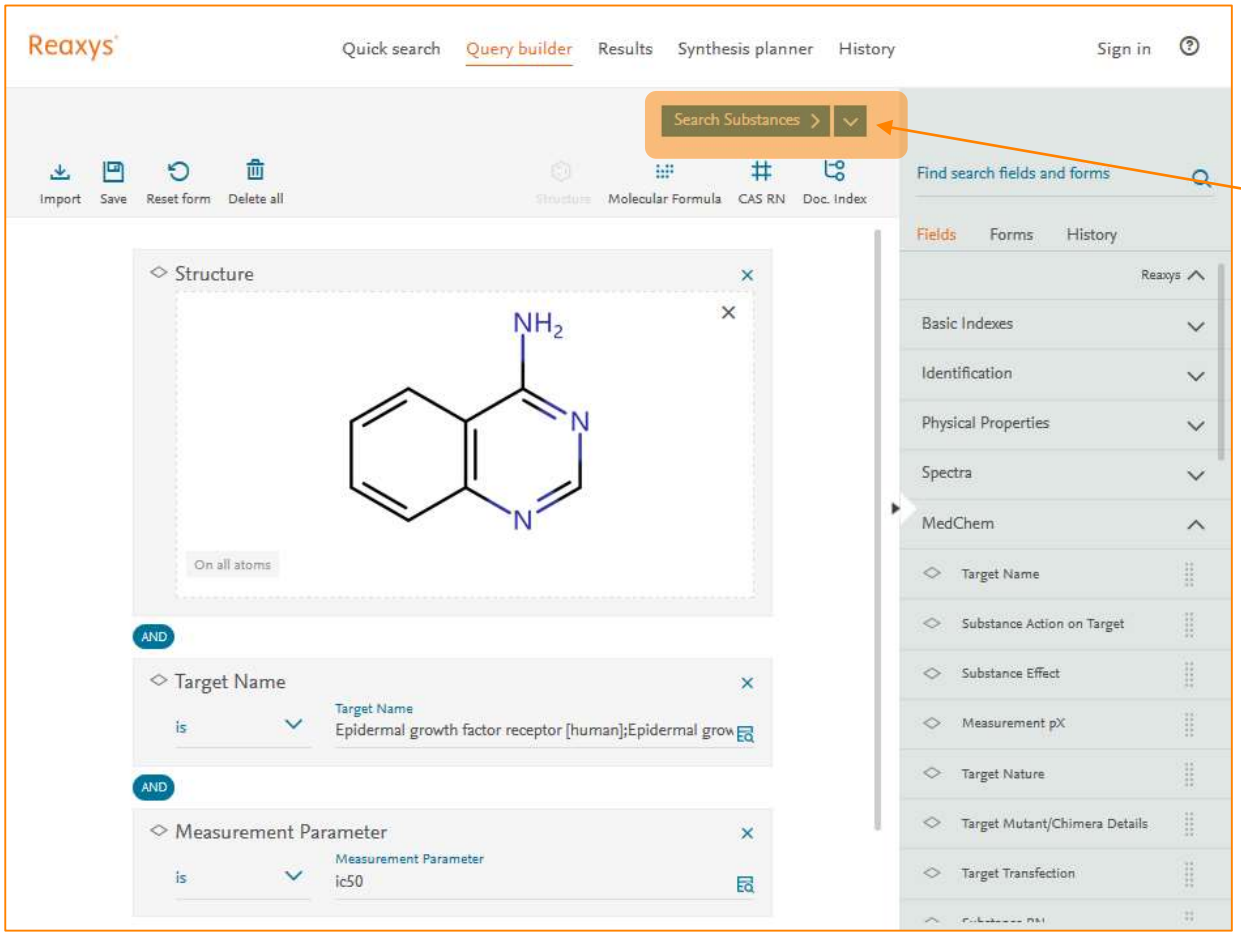
输入EGFR并回车，一键转化所有EGFR靶点



添加的过程—参数



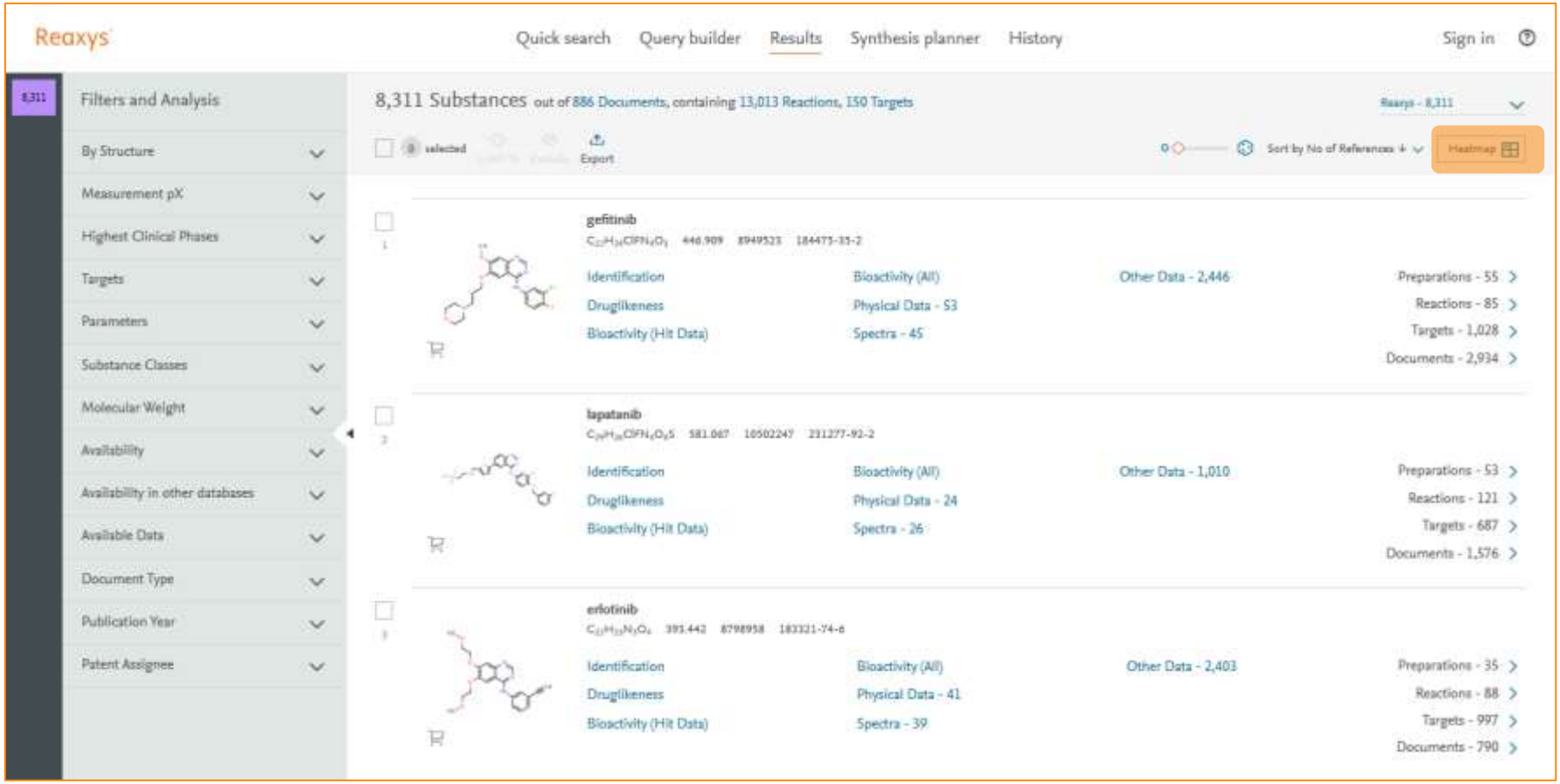
直接输入IC50即可



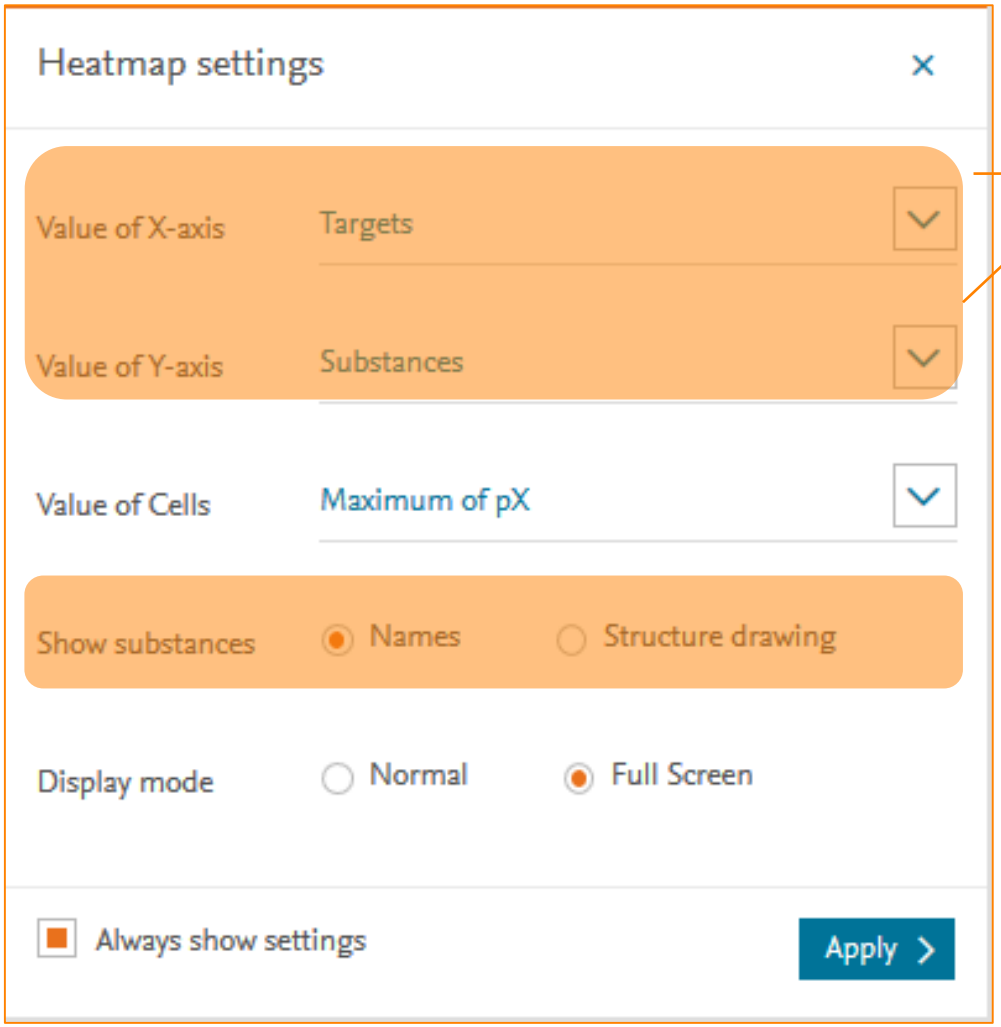
选择检索物质

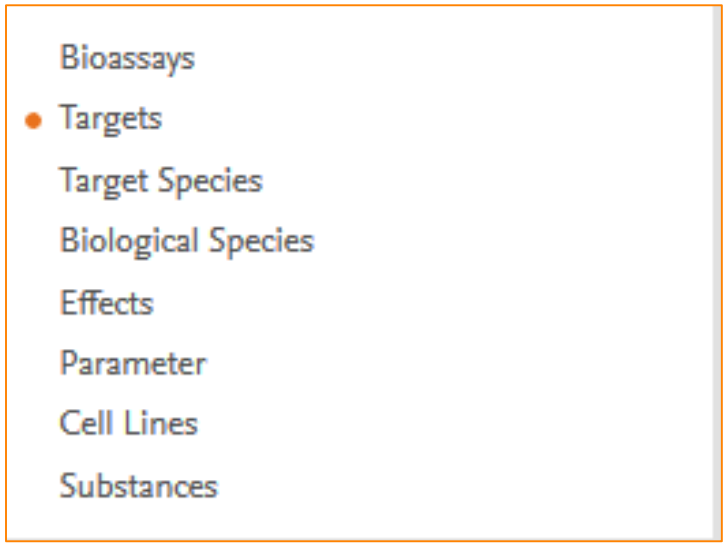
Reaxys中的结果

- 包含这个母核，且在EGFR上有IC50数据的化合物



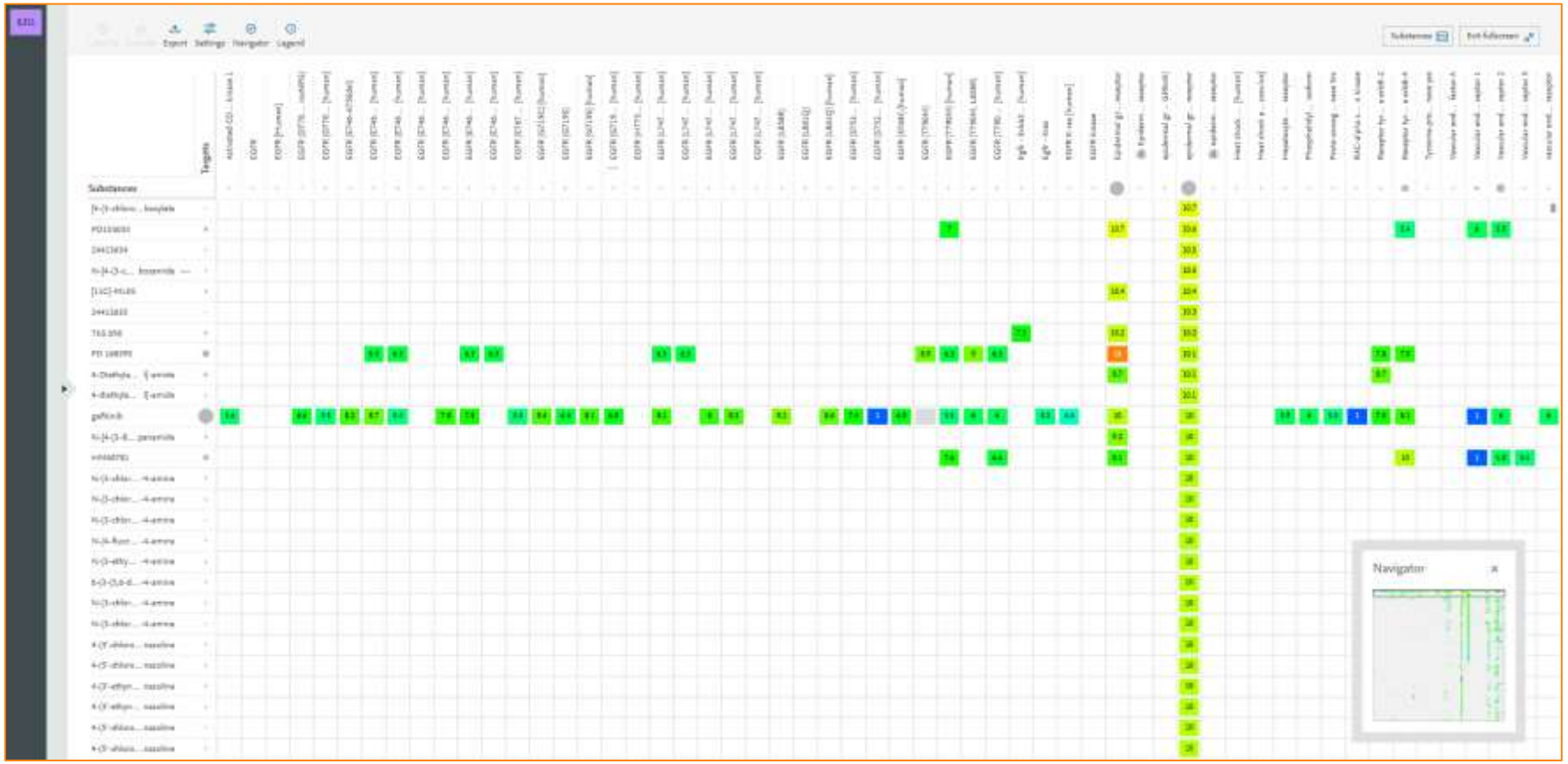
Heat Map的设置





利用任意两个选项生成可视化热图，寻找靶点，物质，效用，细胞系，参数之间的关系。

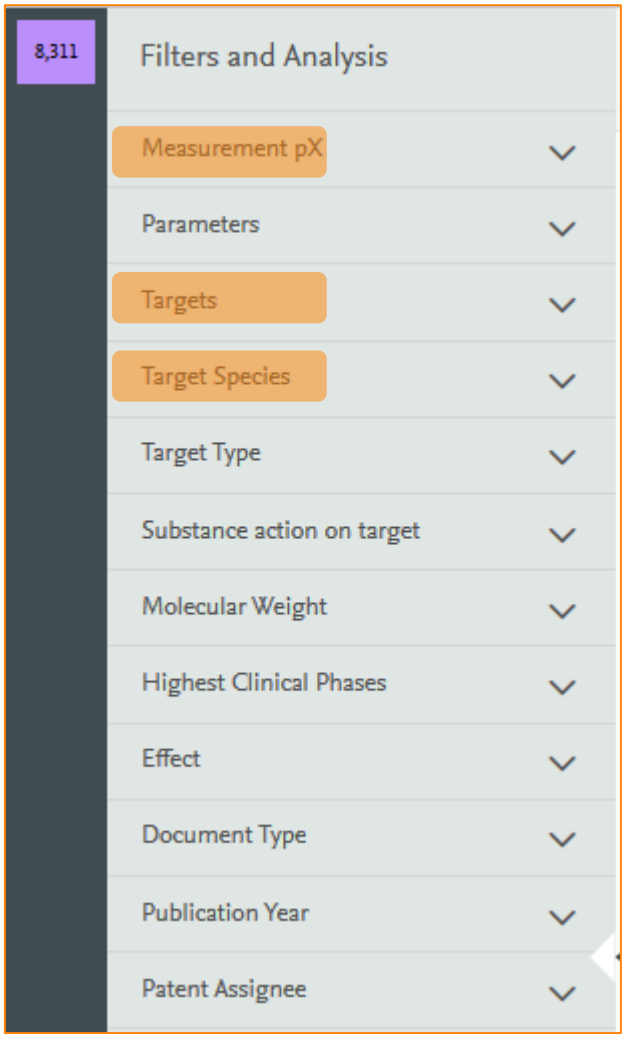
Heat Map—Substance and Target

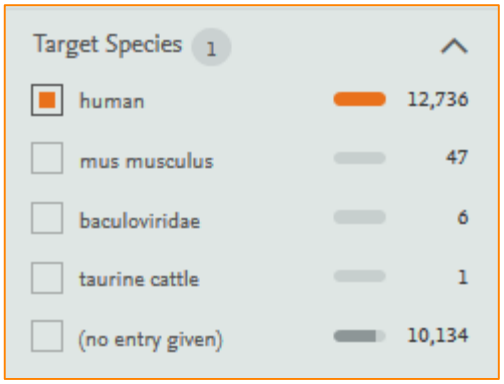


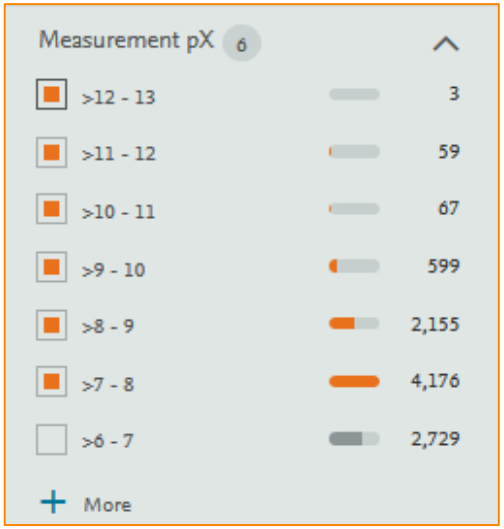
Tips：

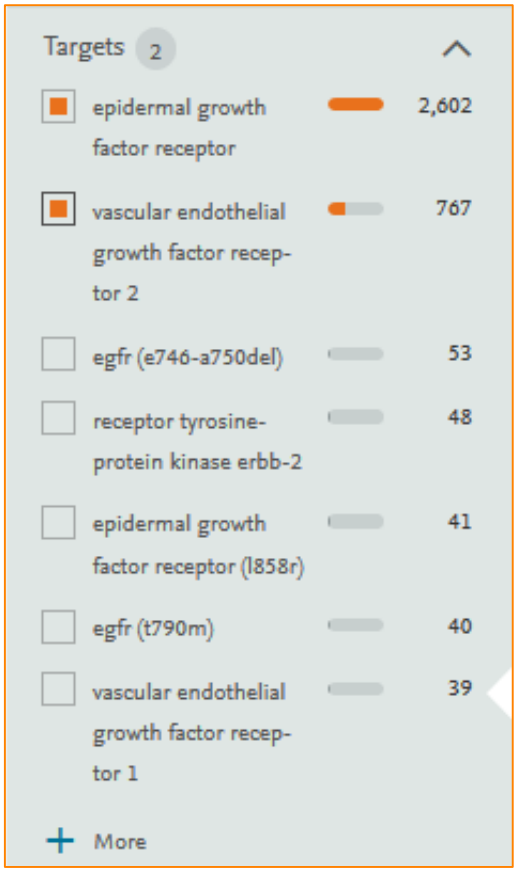
直接给出不同化合物在靶点上的生物活性数据，RMC将文献中报道的数据全部进行标准化处理，用PX数据并配以颜色呈现在面前。

参考数据筛选的过程


8,311
Filters and Analysis
Measurement pX
Parameters
Targets
Target Species
Target Type
Substance action on target
Molecular Weight
Highest Clinical Phases
Effect
Document Type
Publication Year
Patent Assignee


Target Species 1
human 12,736
mus musculus 47
baculoviridae 6
taurine cattle 1
(no entry given) 10,134

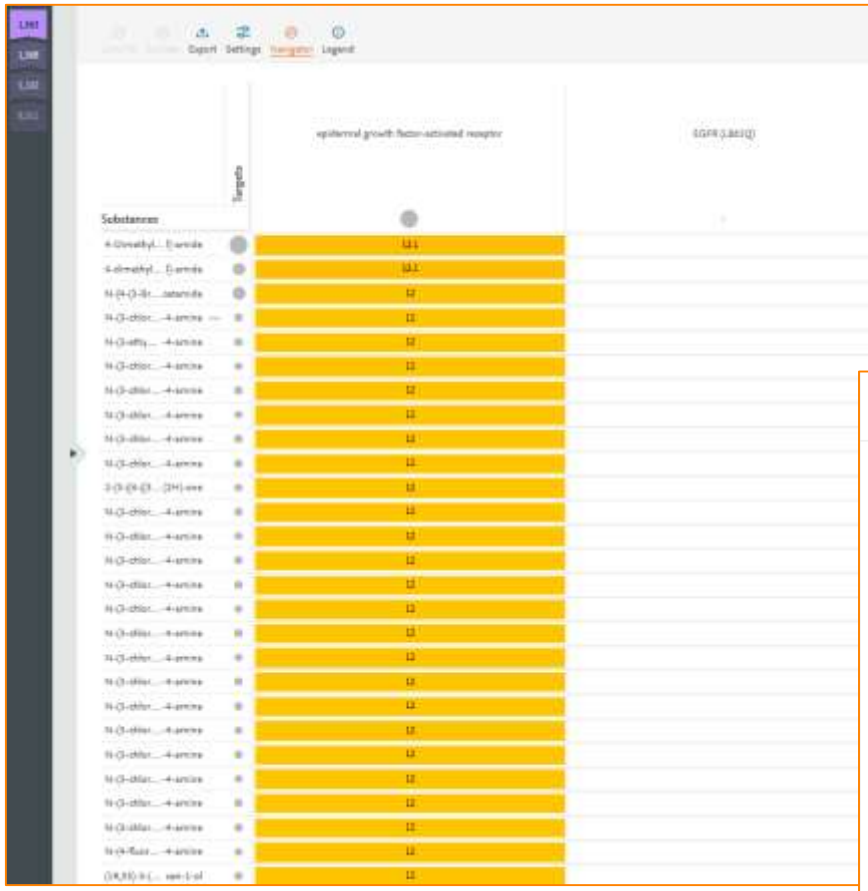

Measurement pX 6
>12 - 13 3
>11 - 12 59
>10 - 11 67
>9 - 10 599
>8 - 9 2,155
>7 - 8 4,176
>6 - 7 2,729
More

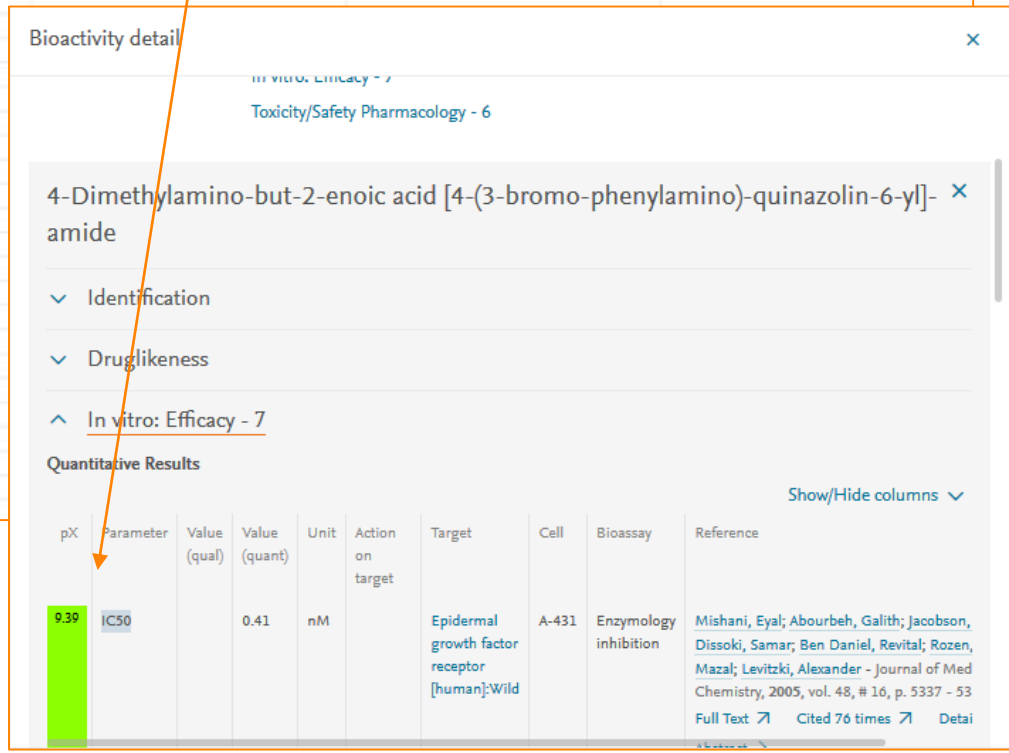

Targets 2
epidermal growth factor receptor 2,602
vascular endothelial growth factor recep-tor 2 767
egfr (e746-a750del) 53
receptor tyrosine-protein kinase erbb-2 48
epidermal growth factor receptor (l858r) 41
egfr (t790m) 40
vascular endothelial growth factor recep-tor 1 39
More

种属，PX值进行筛选后的结果

可以利用排序功能，对结果进行排序

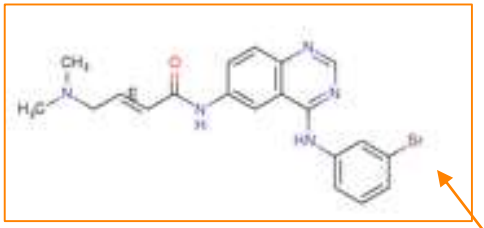
继续利用靶点筛选后的结果

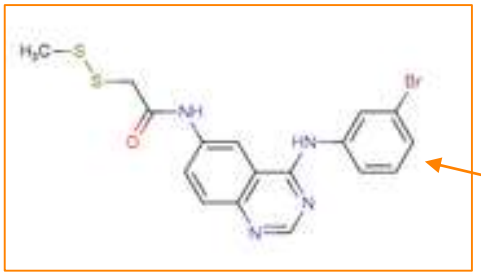


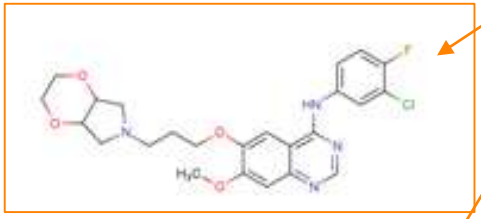


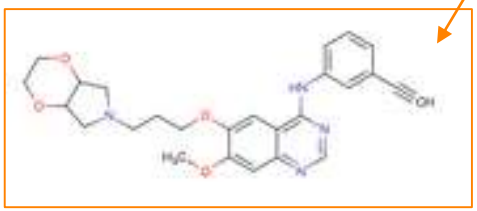
文献中的以Mol为单位的数值全部转换成PX

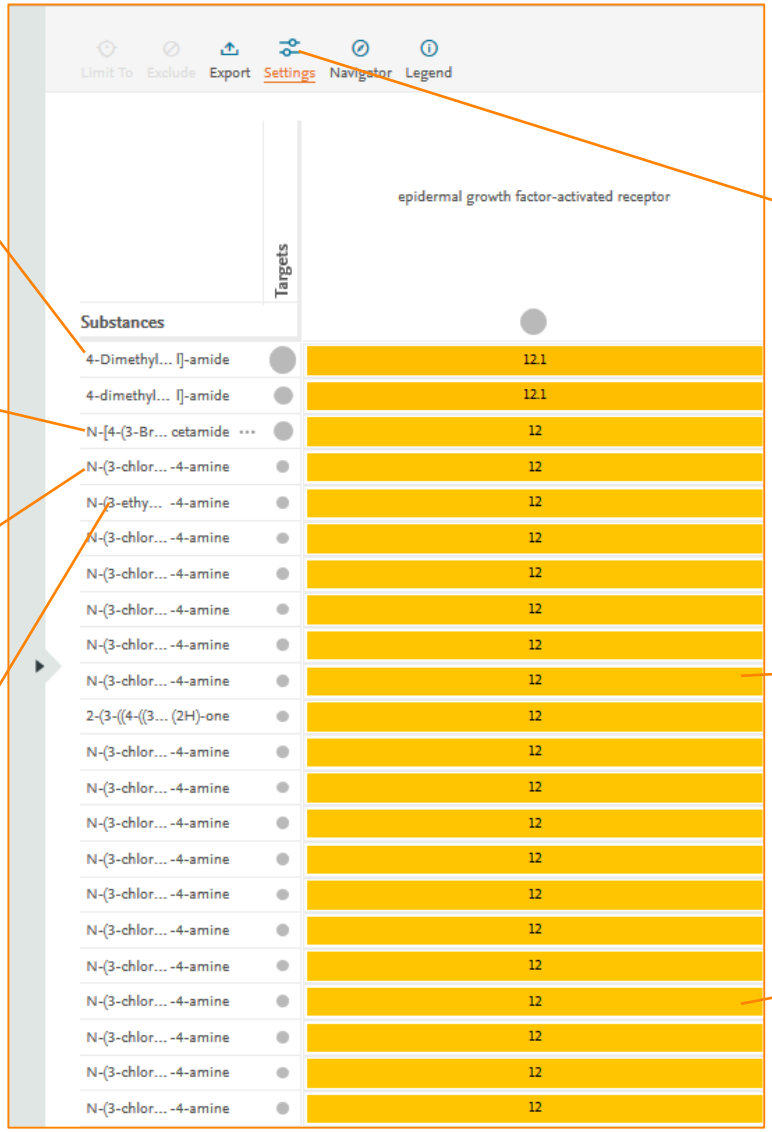
局部的截屏

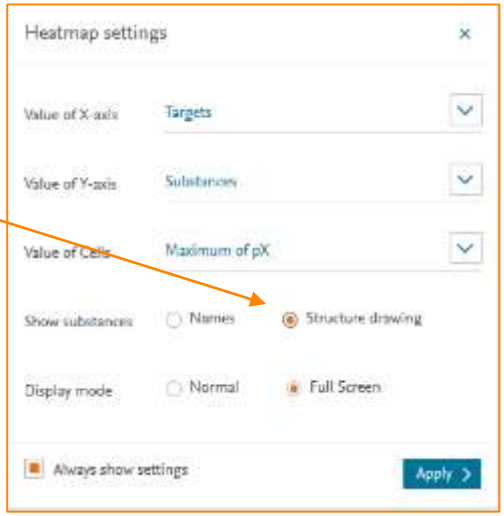


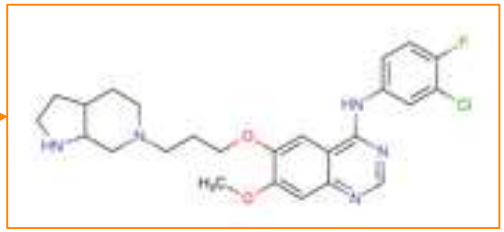


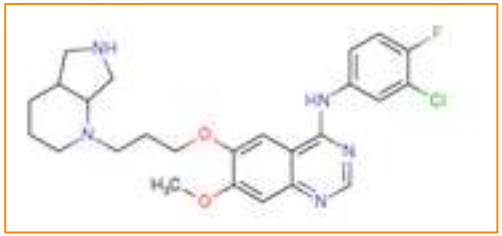




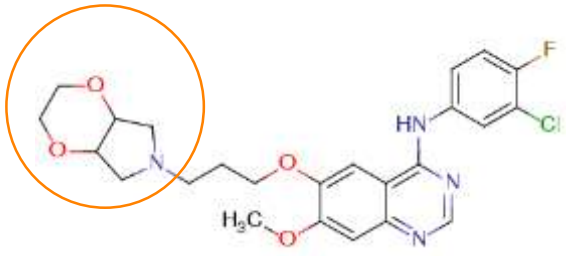

Limit To
Exclude
Export
Settings
Navigator
Legend
Targets
epidermal growth factor-activated receptor
Substances
4-Dimethyl... l]-amide 12.1
4-dimethyl... l]-amide 12.1
N-[4-(3-Br... cetamide 12
N-(3-chlor...-4-amine 12
N-(3-ethy... -4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
2-(3-((4-((3... (2H)-one 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12
N-(3-chlor...-4-amine 12

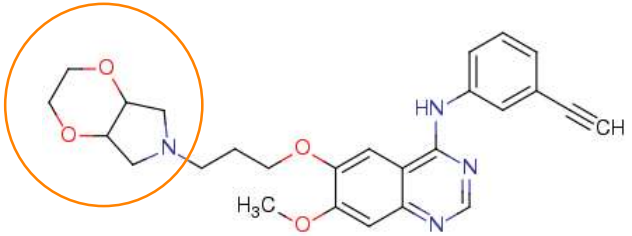

Heatmap settings
Value of X-axis
Targets
Value of Y-axis
Substances
Value of Cells
Maximum of pX
Show substances
Names
Structure drawing
Display mode
Normal
Full Screen
Always show settings
Apply

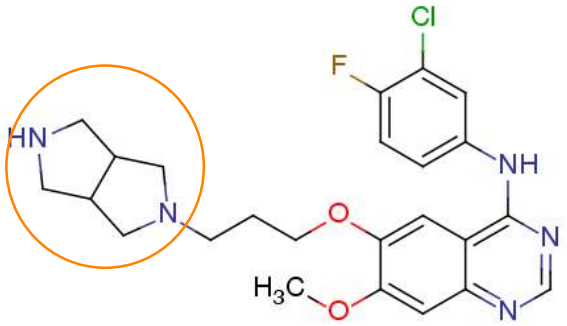


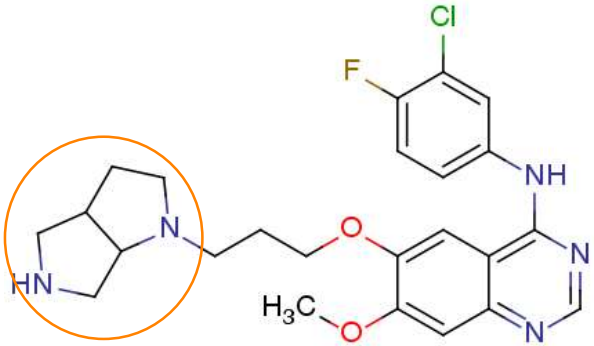


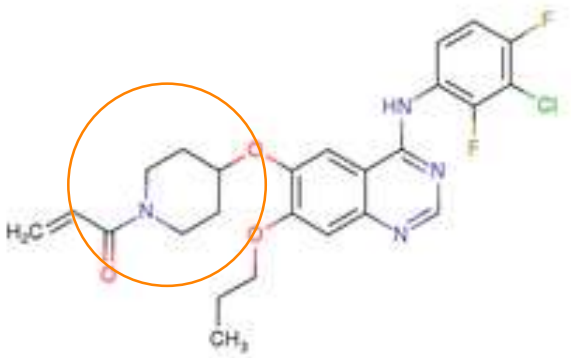
一些高活性的化合物

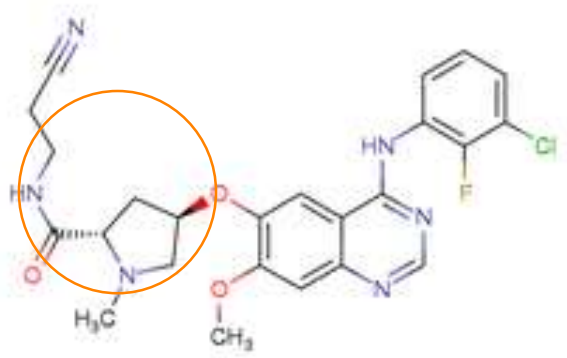






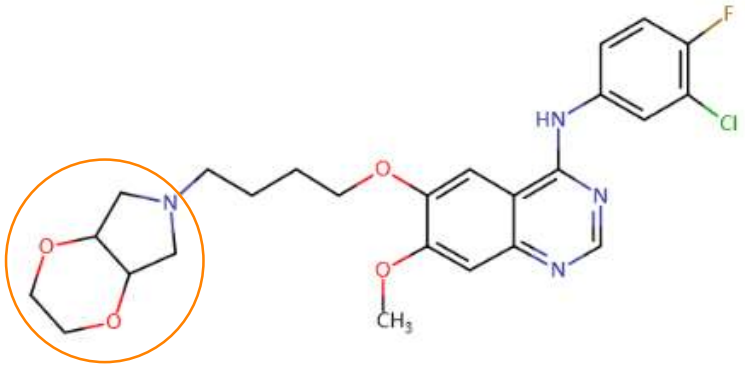


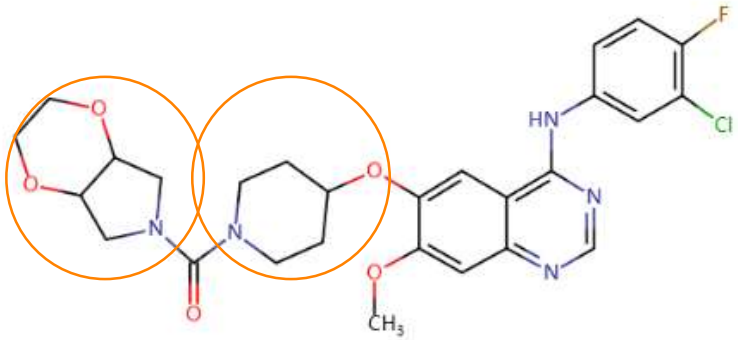


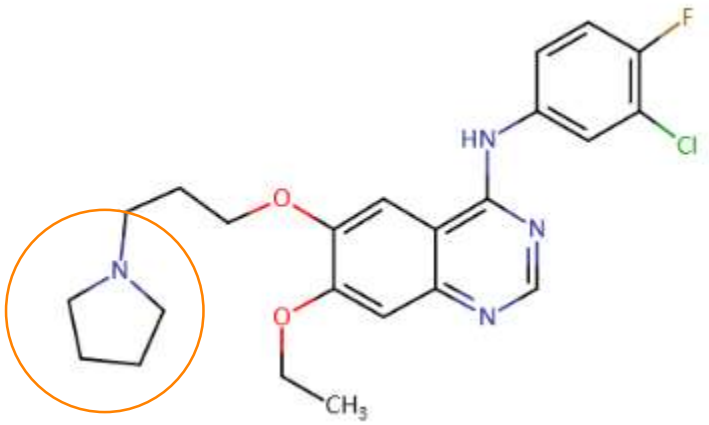


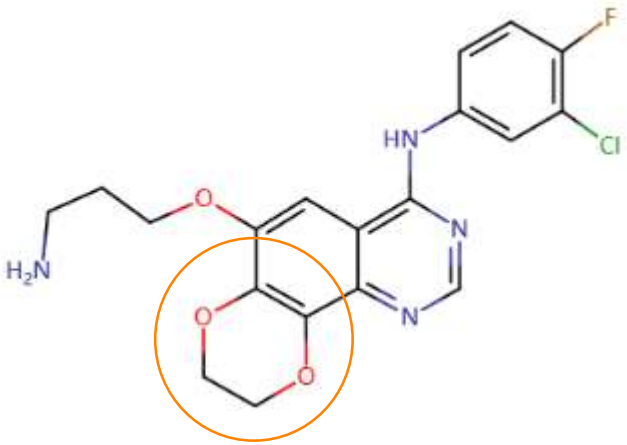
基于这些高活性的片段，设计的新化合物

一般都会有上百个化合物

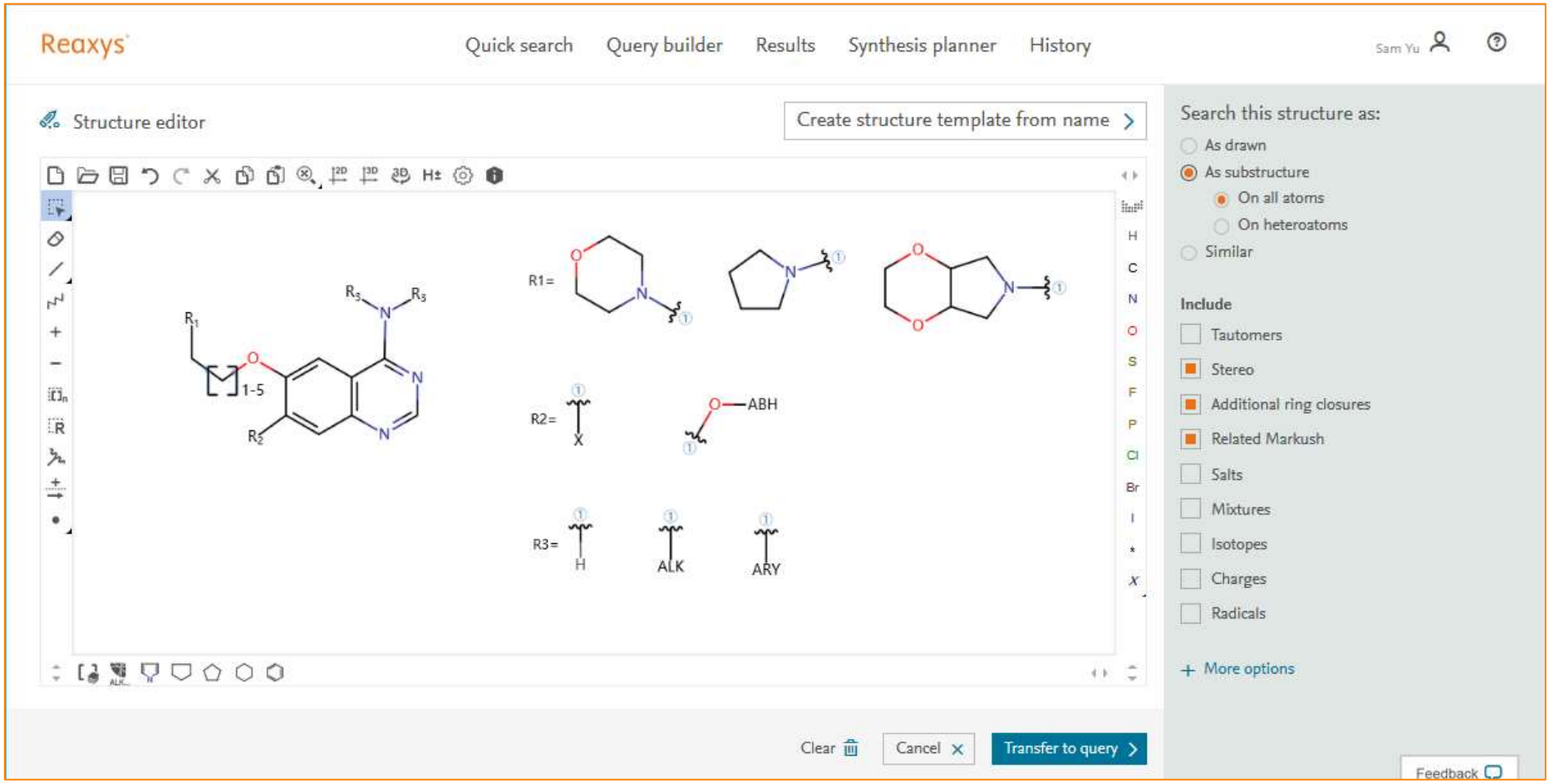








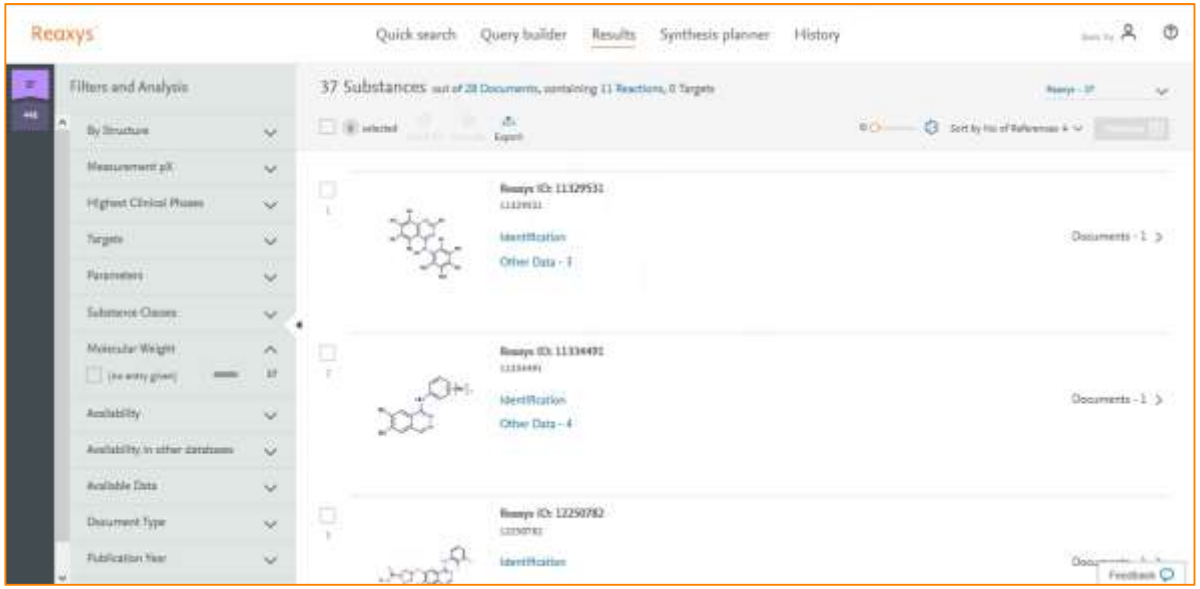
利用Reaxys中的Markush检索判断这些新化合物的可专利性

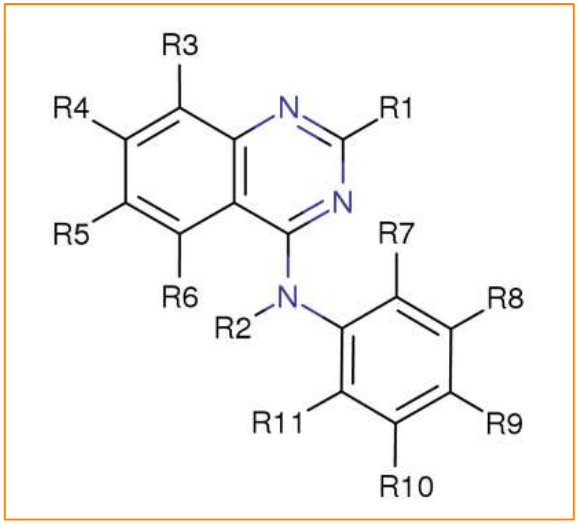


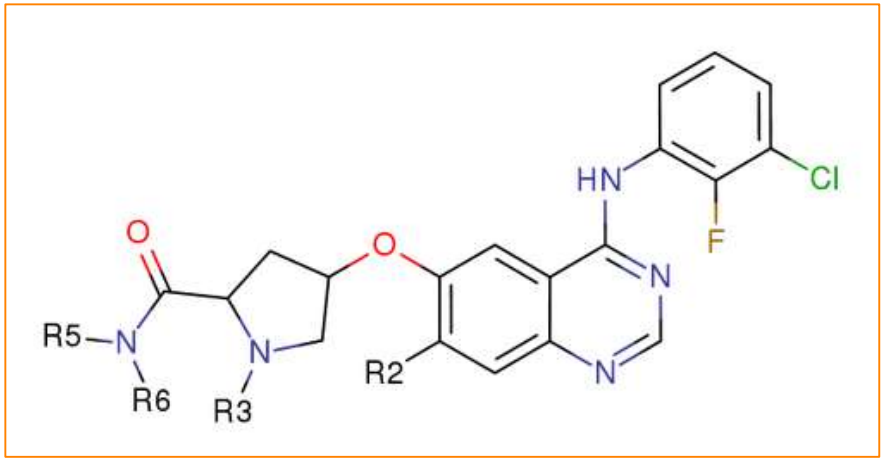
Tips：

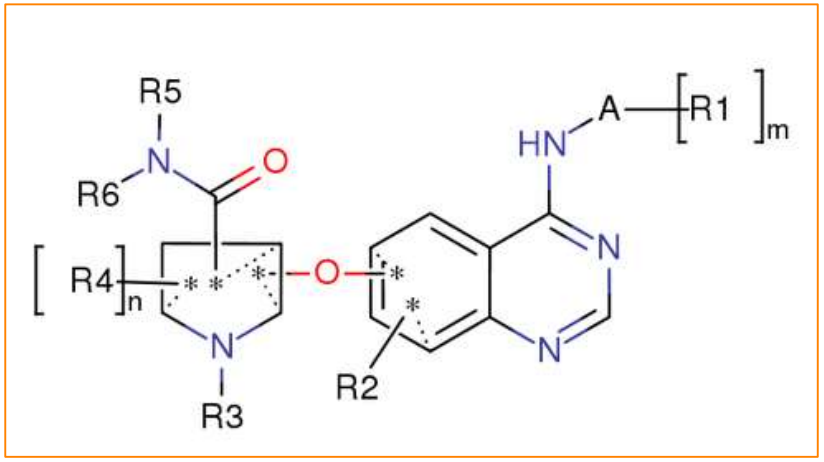
盐，混合物去掉，Related Markush勾选，亚结构勾选

利用分子量筛选，筛出Markush结构

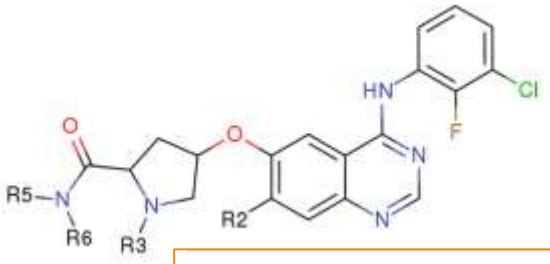




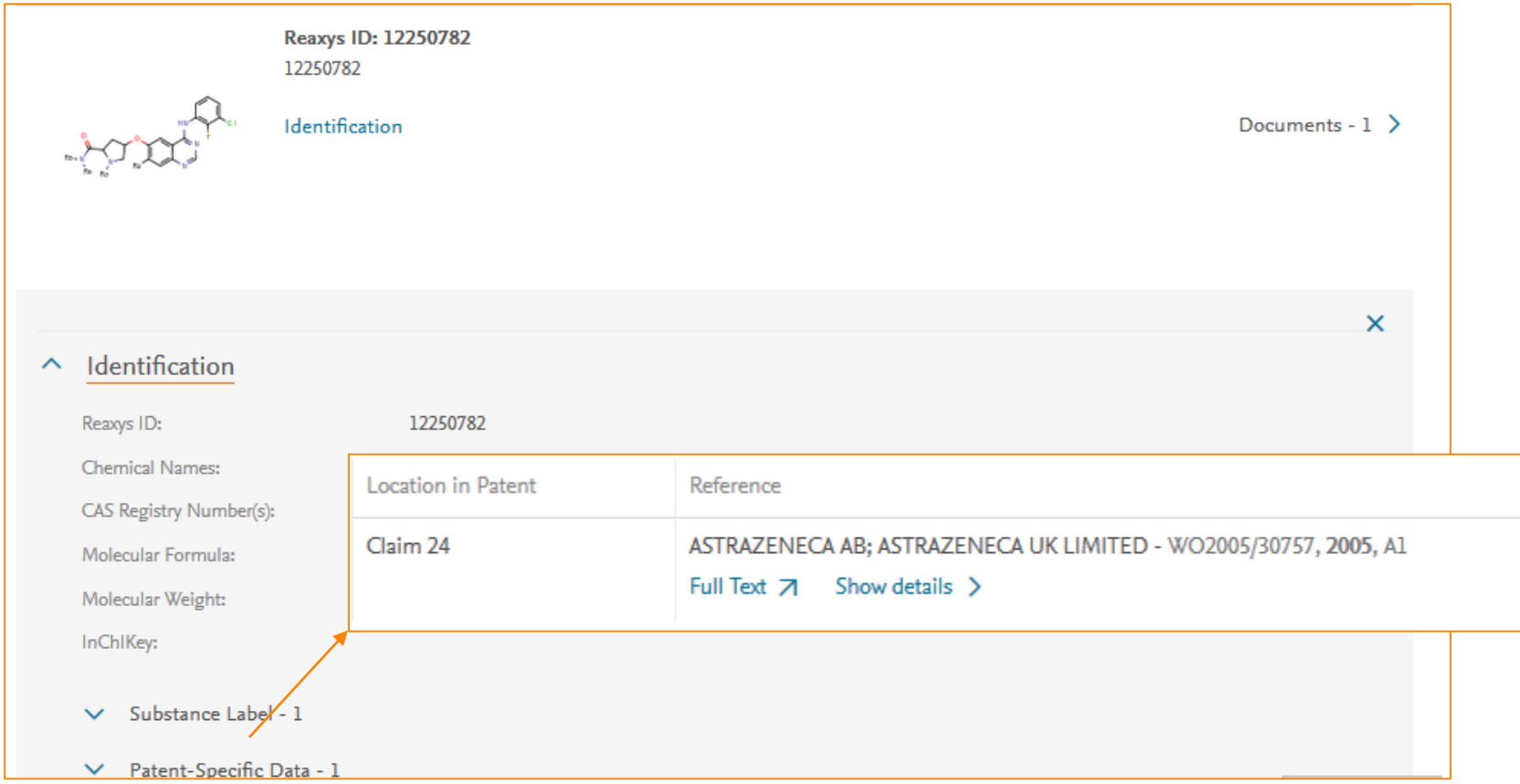




其中的一个Markush结构

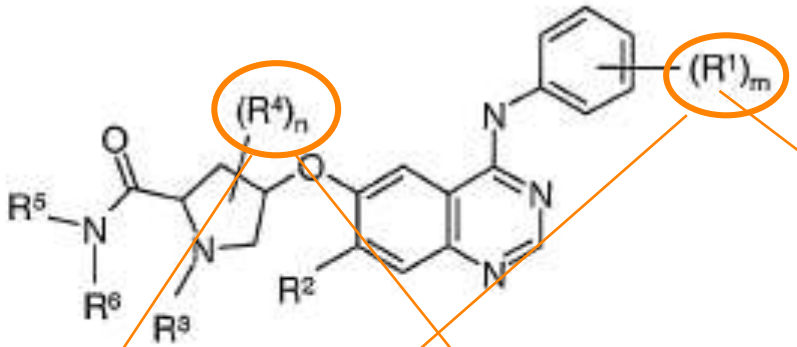


Reaxys中的Markush标记出该结构在专利Claim中的位置



专利中Claim的Markush结构

24. A quinazoline derivative according to any one of the preceding claims having a structural sub-formula A2



(A2)

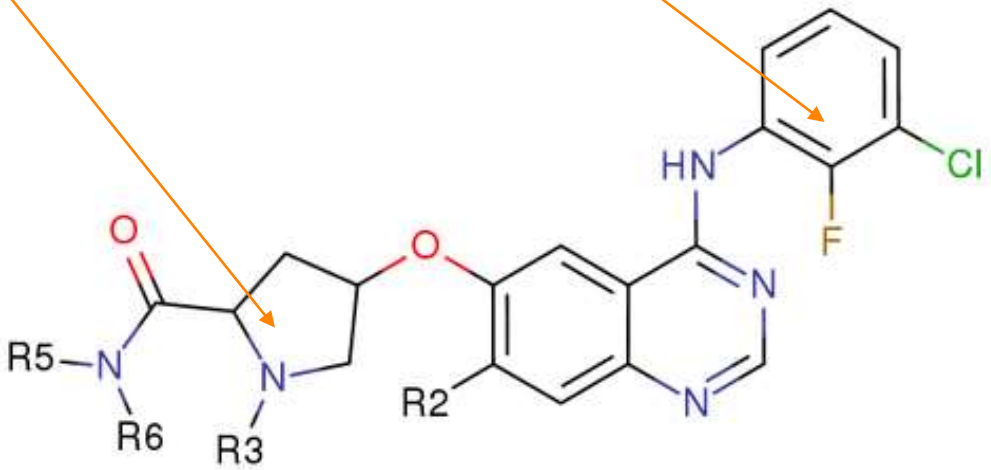
wherein:

m is 2 and R^1 is 2-fluoro and 3-chloro;

R^2 is methoxy;

R^3 is methyl;

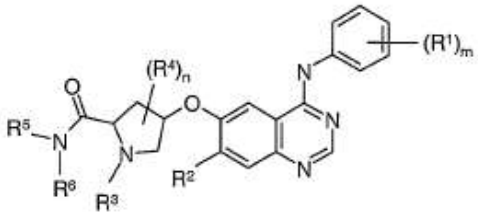
n is 0;



Reaxys不单单是摘结构，更多的对结构的解读。

专利原文中对该结构的描述

24. A quinazoline derivative according to any one of the preceding claims having a structural sub-formula A2



(A2)

wherein:

m is 2 and R^1 is 2-fluoro and 3-chloro;

R^2 is methoxy;

R^3 is methyl;

n is 0;

专利原文用文字进行结构的描述

and R^5 is hydrogen or (1-6C)alkyl and R^6 is selected from substituted-(1-6C)alkyl (wherein substituted-(1-6C)alkyl is (1-6C)alkyl substituted by 1, 2 or 3 substituents independently selected from (1-6C)alkoxycarbonyl, carbamoyl, (2-6C)alkanoylamino, and oxo or a (1-6C)alkoxycarbonyl together with a hydroxy group), (1-6C)alkoxy, (1-6C)alkylsulfonyl, (3-7)heterocyclyl (wherein the heterocyclyl is carbon linked), heteroaryl, (3-7)heterocyclyl(1-6C)alkyl (wherein the heterocyclyl is carbon linked to the (1-6C)alkyl moiety) and heteroaryl(1-6C)alkyl,

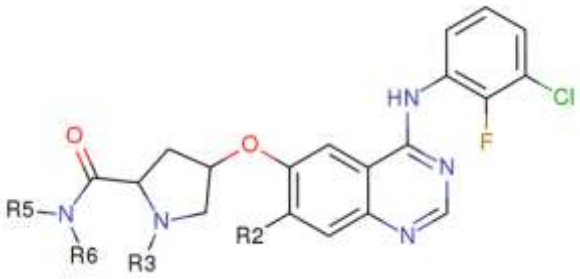
and wherein any heteroaryl or (3-7)heterocyclyl group within R^6 is optionally substituted (on any available carbon atoms) by 1, 2 or 3 substituents independently selected from halogeno, (1-6C)alkyl, hydroxy(1-6C)alkyl, (1-6C)alkoxycarbonyl, carbamoyl, (2-6C)alkanoylamino and hydroxy and/or optionally a substituent selected from oxo, cyano, nitro and (1-4C)alkoxy, and wherein any heteroaryl or heterocyclyl group within R^6 is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by (1-4C)alkyl or (2-4C)alkanoyl, or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4, 5 or 6 membered ring which contains one or two nitrogen atoms as the only heteroatoms present in the ring and which is optionally and which is substituted on an available ring carbon atom by 1 or 2 substituents independently selected from carbamoyl and (1-3C)alkylenedioxy.

25. A quinazoline derivative according to claim 24, wherein R^6 is selected from (3-7)heterocyclyl (wherein the heterocyclyl is carbon linked), heteroaryl, (3-7)heterocyclyl(1-6C)alkyl (wherein the heterocyclyl is carbon linked to the (1-6C)alkyl moiety) and heteroaryl(1-6C)alkyl,

and wherein any heteroaryl or (3-7)heterocyclyl group within R^6 is optionally substituted (on

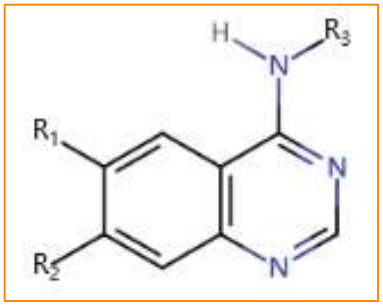
Reaxys将结构翻译成图表

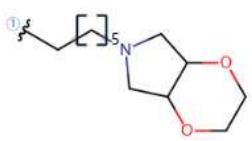
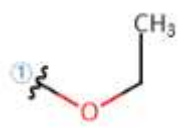
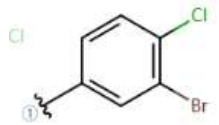
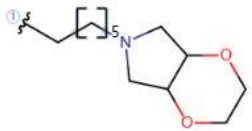
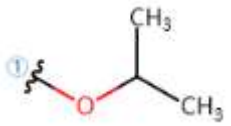
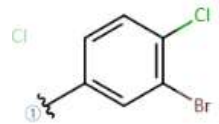
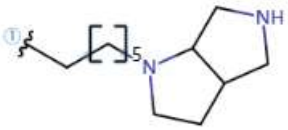
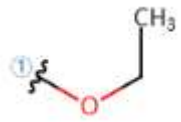
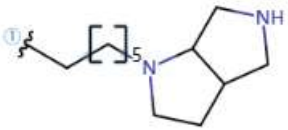
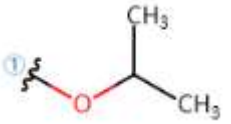
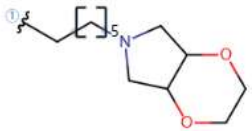
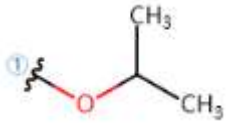
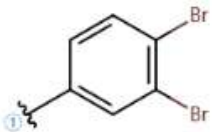


图表形式的解读更容易帮助理解结构保护的范围

Label	Value	Size	Attributes	Substituted by	Frequency
R2	methoxy				
R3	methyl				
R5	hydrogen				
R6	alkyl	1-6C		$s8	0-3
	hydrogen				
	alkyl	1-6C			
	alkenyl	2-8C			
	alkynyl	2-8C			
	alkoxy	1-6C			
	cycloalkyl	3-7C			
	alkylsulfonyl	1-6C			
	heterocyclyl			$s9	0-?
	heteroaryl				
	$*cyclalk37$*alk13				
	$*hetar$*alk13				
	$*het$*alk13				
$s1	alkyl	1-4C			

假设……这里的化合物没有专利方面的问题

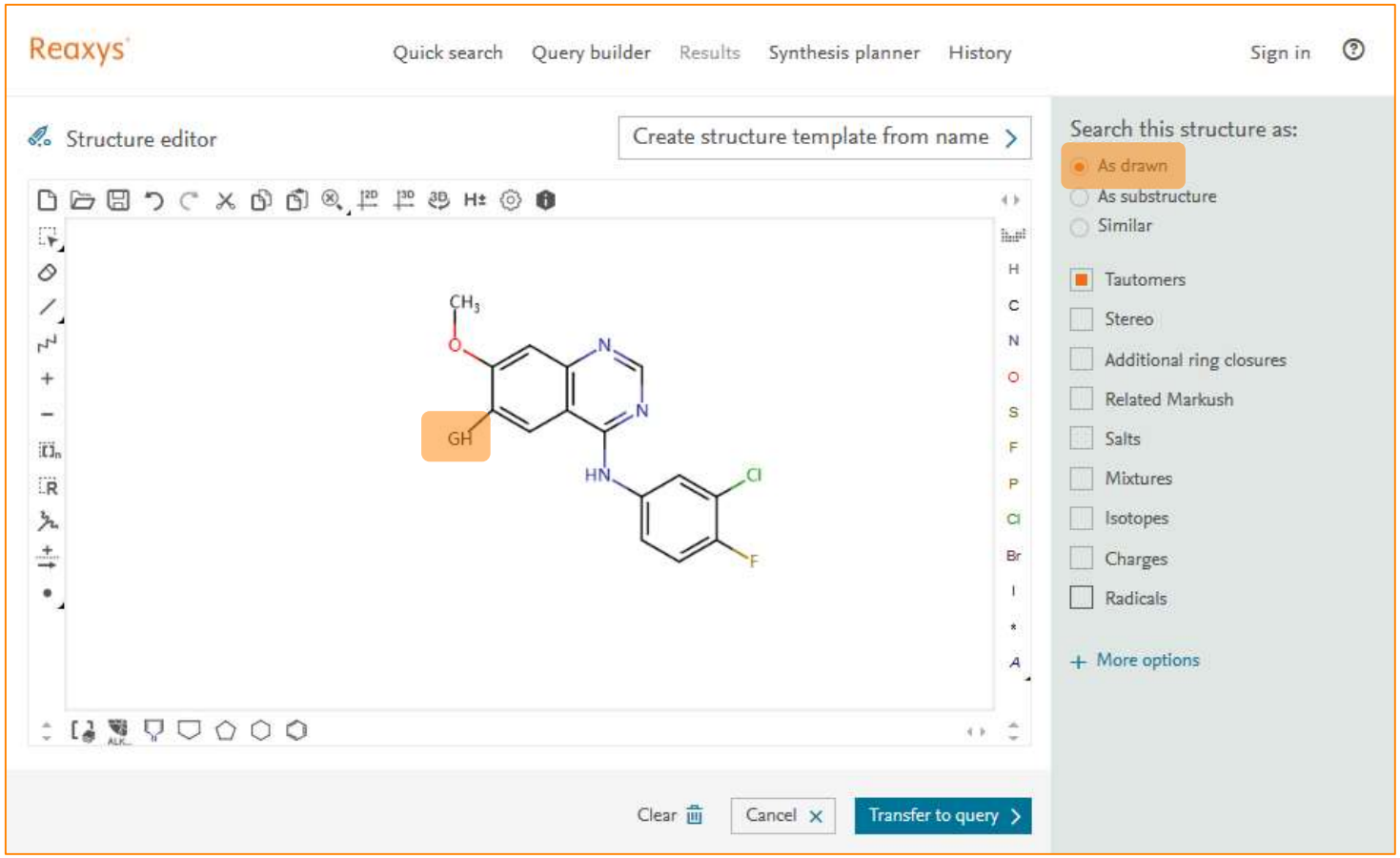


	R1	R2	R3
Compound 1			
Compound 2			
Compound 3			
Compound 4			
Compound 5			
……			

优化的问题：

1. 都合成？
2. 所有活性都测？
3. 能否用RMC评估侧链的影响情况，从而决定化合物合成的顺序，省钱，省人工，优化实验进程。

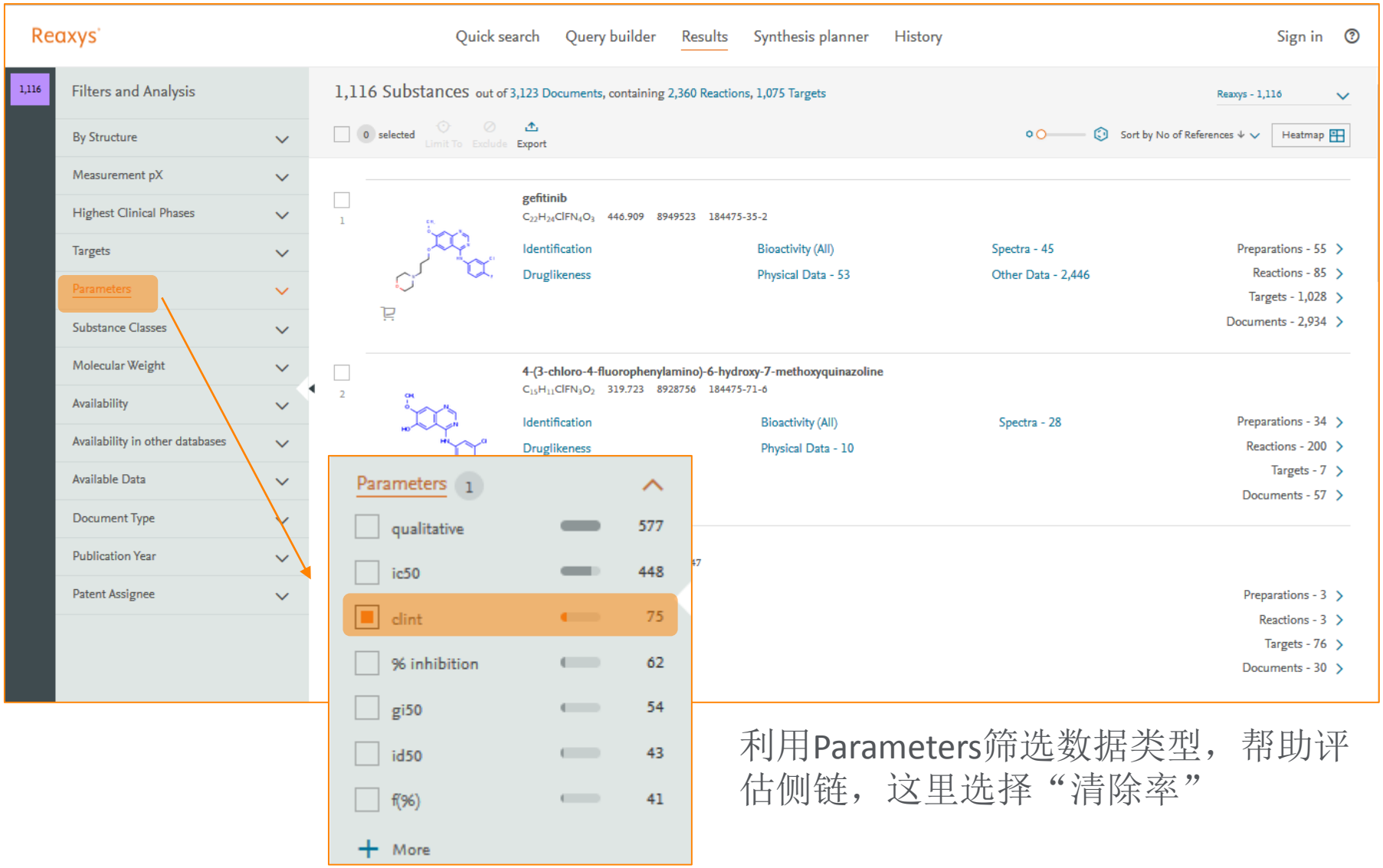
Me Better药物的评估侧链方式



Tips:

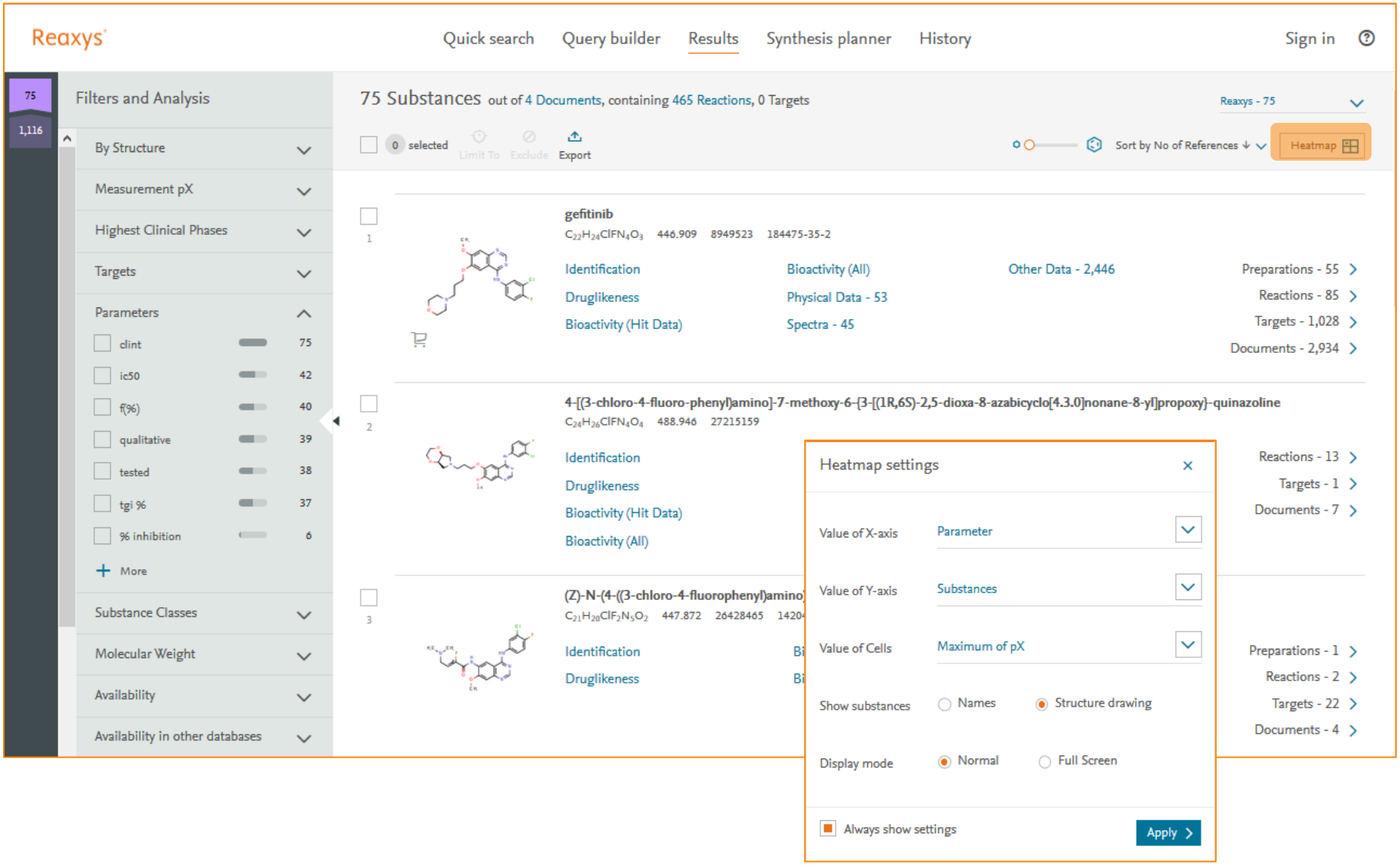
1. 通过阳性化合物开放1个位点，判断这个侧链上的修饰对成药的影响
2. As Draw检索，
3. 去除盐，混合物，保留互变异构体

直接检索物质后的结果

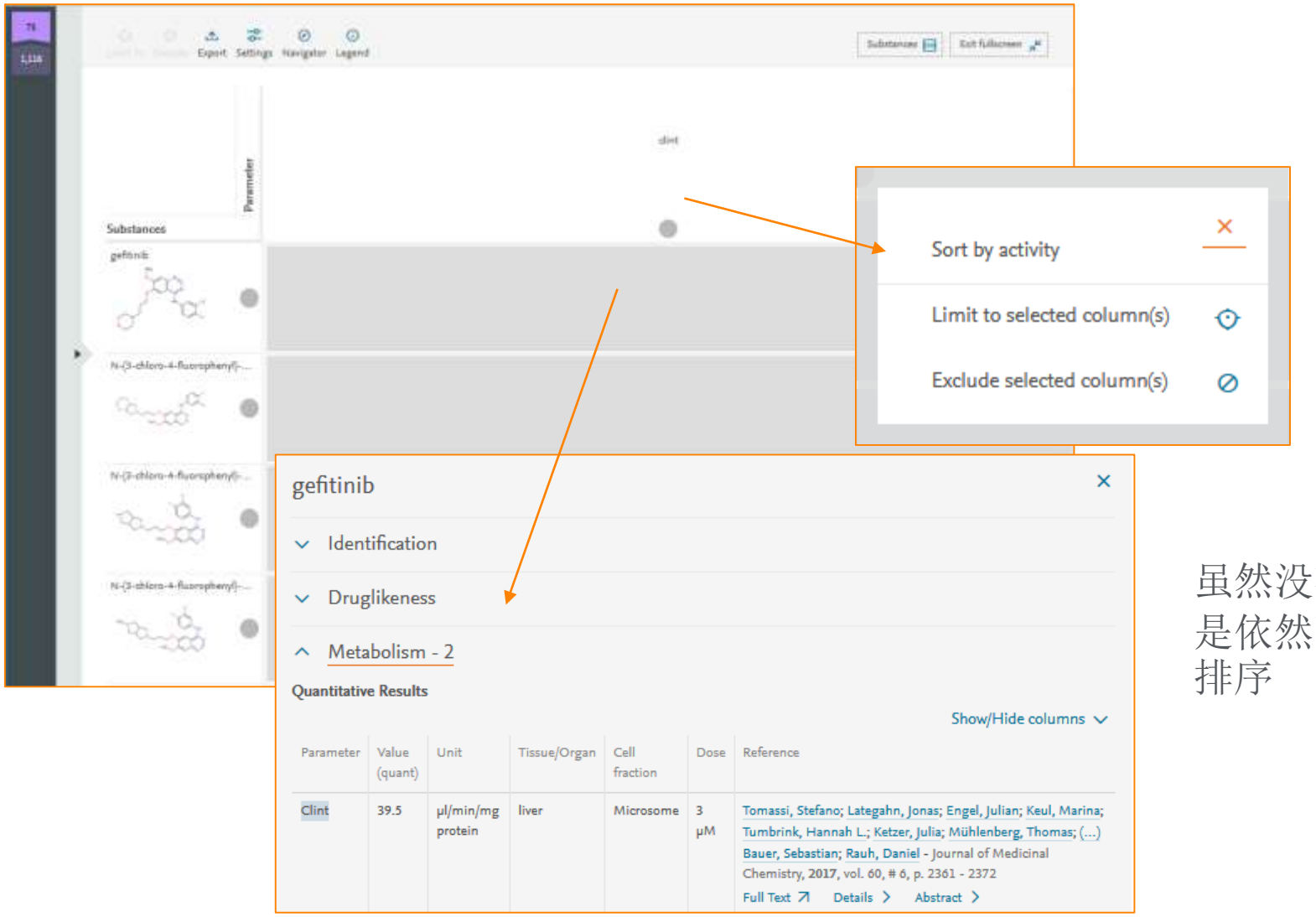


利用Parameters筛选数据类型，帮助评估侧链，这里选择“清除率”

含有清除率数据的结构


Reaxys
Quick search
Query builder
Results
Synthesis planner
History
Sign in
75
1,116
Filters and Analysis
By Structure
Measurement pX
Highest Clinical Phases
Targets
Parameters
clint 75
ic50 42
f(%) 40
qualitative 39
tested 38
tgi % 37
% inhibition 6
More
Substance Classes
Molecular Weight
Availability
Availability in other databases
75 Substances out of 4 Documents, containing 465 Reactions, 0 Targets
Reaxys - 75
0 selected
Limit To
Exclude
Export
Sort by No of References
Heatmap
1
gefitinib
C22H24ClFN4O3 446.909 8949523 184475-35-2
Identification
Druglikeness
Bioactivity (Hit Data)
Bioactivity (All)
Physical Data - 53
Spectra - 45
Other Data - 2,446
Preparations - 55
Reactions - 85
Targets - 1,028
Documents - 2,934
2
4-[(3-chloro-4-fluoro-phenyl)amino]-7-methoxy-6-{3-[(1R,6S)-2,5-dioxa-8-azabicyclo[4.3.0]nonane-8-yl]propoxy}-quinazoline
C24H26ClFN4O4 488.946 27215159
Identification
Druglikeness
Bioactivity (Hit Data)
Bioactivity (All)
Reactions - 13
Targets - 1
Documents - 7
3
(Z)-N-(4-((3-chloro-4-fluorophenyl)amino)
C21H20ClF2N5O2 447.872 26428465 1420
Identification
Druglikeness
Preparations - 1
Reactions - 2
Targets - 22
Documents - 4
Heatmap settings
Value of X-axis
Parameter
Value of Y-axis
Substances
Value of Cells
Maximum of pX
Show substances
Names
Structure drawing
Display mode
Normal
Full Screen
Always show settings
Apply

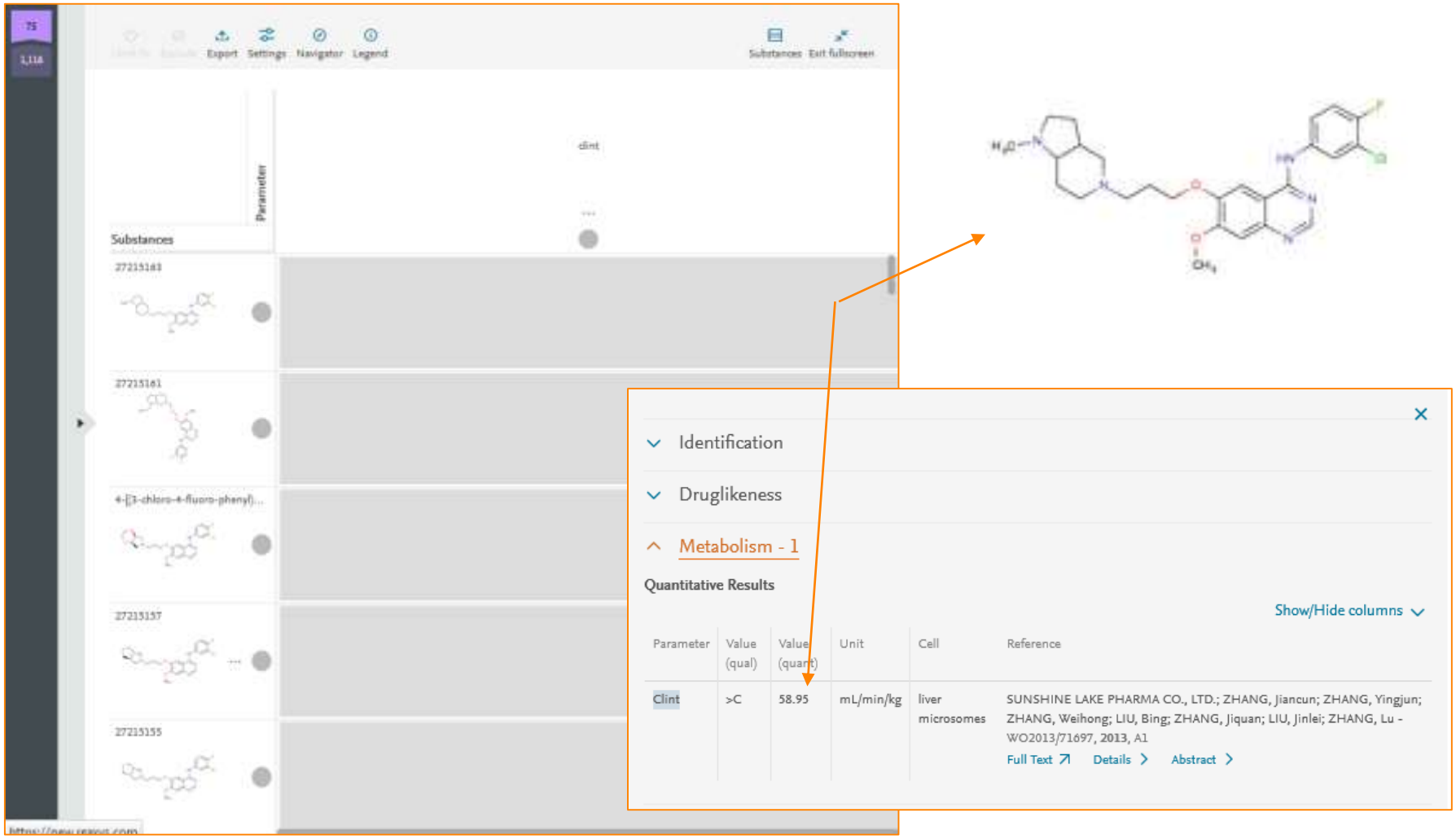
因为清除率不是以M为单位，所以没有PX



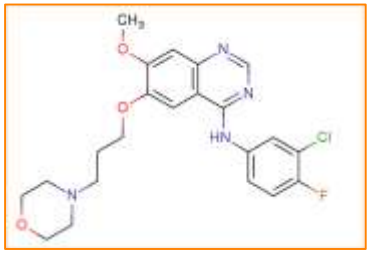
虽然没有PX，但是依然可以进行排序

按照清除率从大到小进行排序

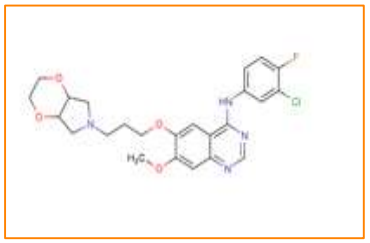
- 从而筛选出一些在清除率上可能存在负面影响的片段



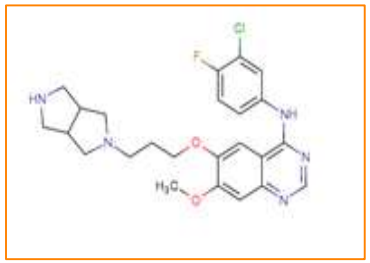
和阳性化合物比较的结果



Parameter	Value (quant)	Unit	Tissue/Organ	Cell fraction	Dose	Reference
Clint	39.5	µl/min/mg protein	liver	Microsome	3 µM	Tomassi, Stefano; Lategahn, Jonas; Engel, Julian; Keul, Marina; Tumbrink, Hannah L.; Ketzer, Julia; Mühlenberg, Thomas; (...) Bauer, Sebastian; Rauh, Daniel - Journal of Medicinal Chemistry, 2017, vol. 60, # 6, p. 2361 - 2372 Full Text Details Abstract



Parameter	Value (qual)	Value (quant)	Unit	Tissue/Organ	Cell fraction	Dose	Reference
Clint	>	58.95	ml/min/kg	Liver	Microsome	1.5 µM	SUNSHINE LAKE PHARMA CO., LTD.; Zhang, Jiancun; Zhang, Yingjun; Zhang, Weihong; Liu, Bing; Zhang, Jiquan; Liu, Jinlei; Zhang, Lu - US2014/228361, 2014, A1 Full Text Details Abstract



Parameter	Value (qual)	Value (quant)	Unit	Tissue/Organ	Cell fraction	Dose	Reference
Clint	>	58.95	ml/min/kg	Liver	Microsome	1.5 µM	SUNSHINE LAKE PHARMA CO., LTD.; Zhang, Jiancun; Zhang, Yingjun; Zhang, Weihong; Liu, Bing; Zhang, Jiquan; Liu, Jinlei; Zhang, Lu - US2014/228361, 2014, A1 Full Text Details Abstract

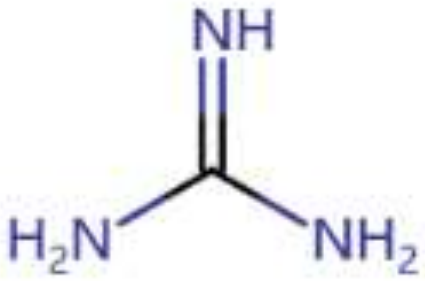
案例值得思考的地方:

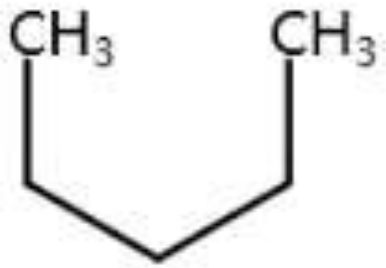
1. 从清除率上看，这一系列侧链的对母核分子在‘清除率’数据上贡献并不好，
2. 作为参考，如果是同母核的化合物，是否可以将这类侧链化合物的合成和检测退后，合理安排资源
3. 作为参考，如果是其他母核，是否在IC50结果好的情况下，优先测试‘clint’，以避免成本浪费

CASE 2 通过已知的一些活性片段进行结构设计

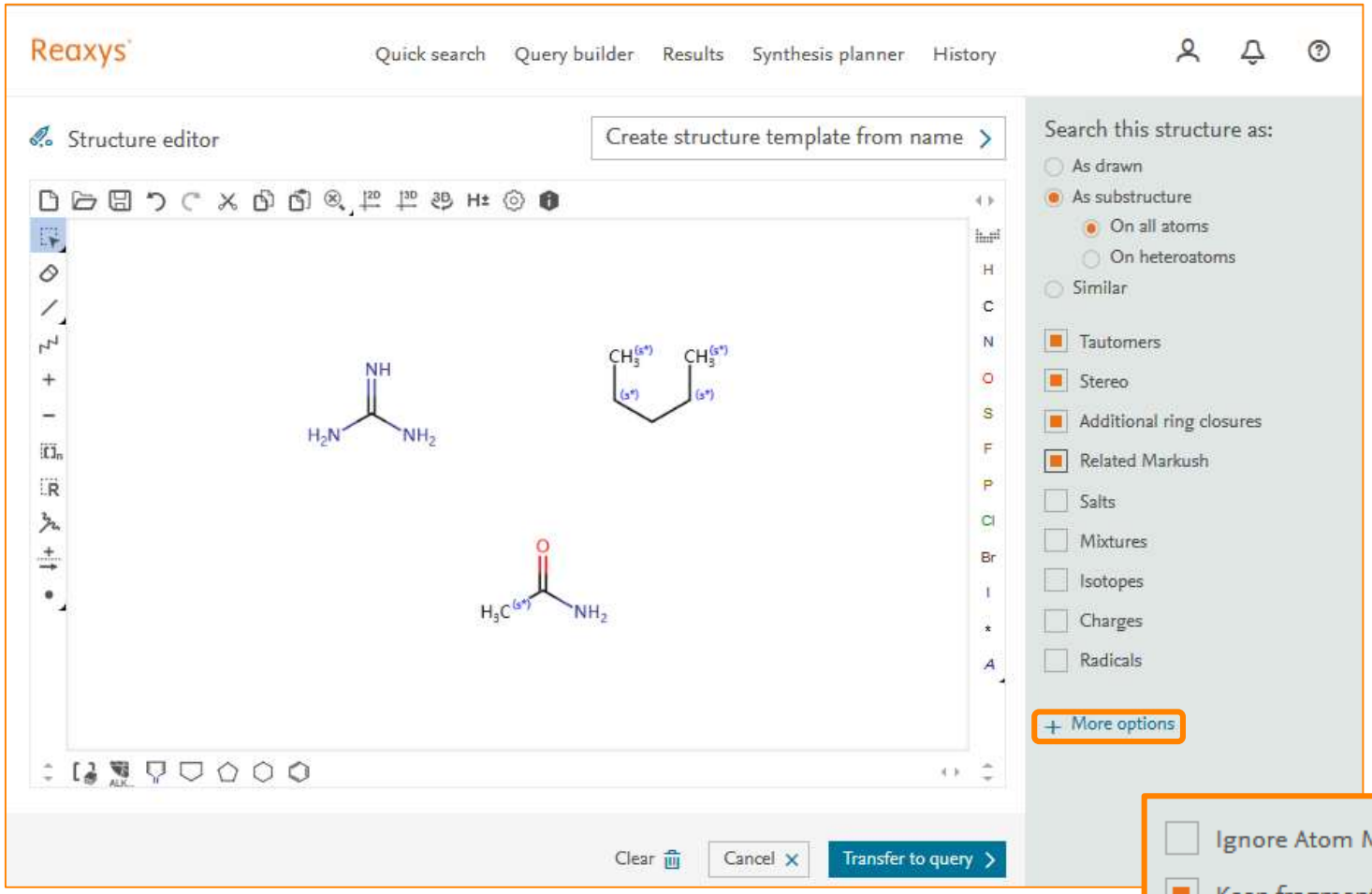
包含以下片段的化合物检索

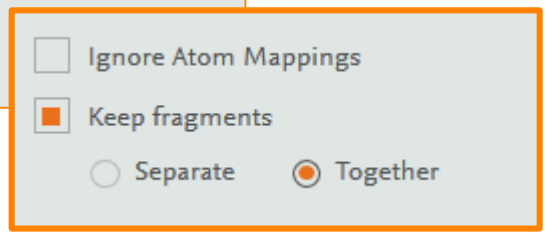
- 结构中需要有……
- 已经报道的化合物都在哪些靶点上有比较好的活性
- 这些结构都有什么样的核……





Reaxys中的检索

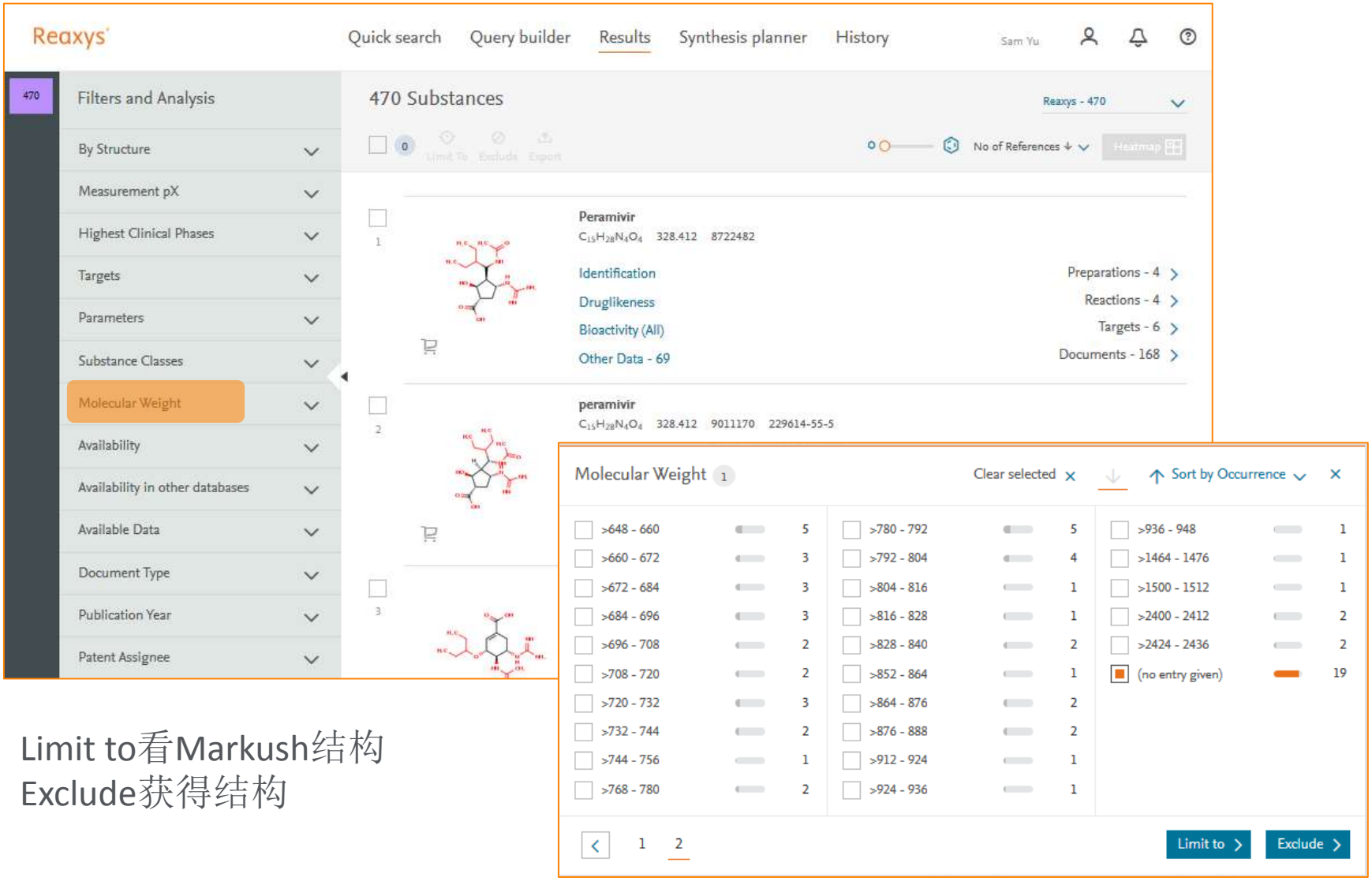




Tips:

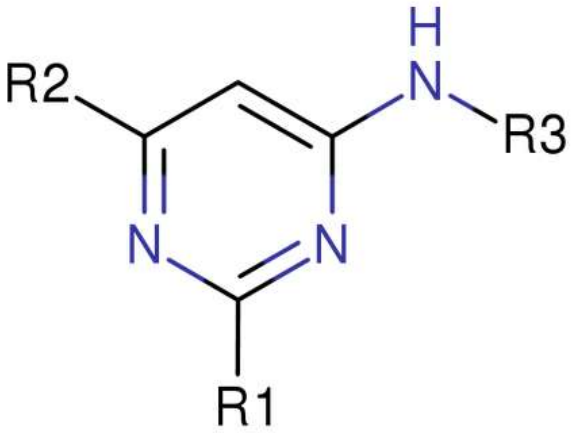
把Markush勾选上，一次性获得将对应的Markush结构也获得

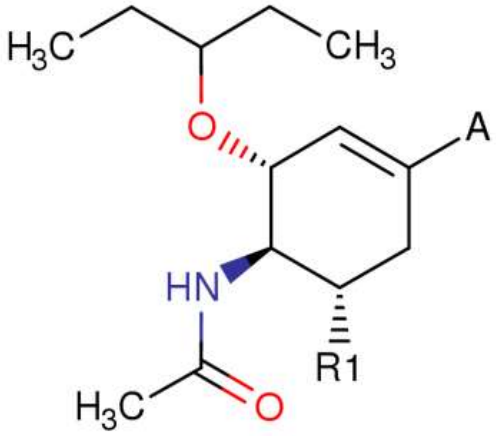
Reaxys中的检索结果



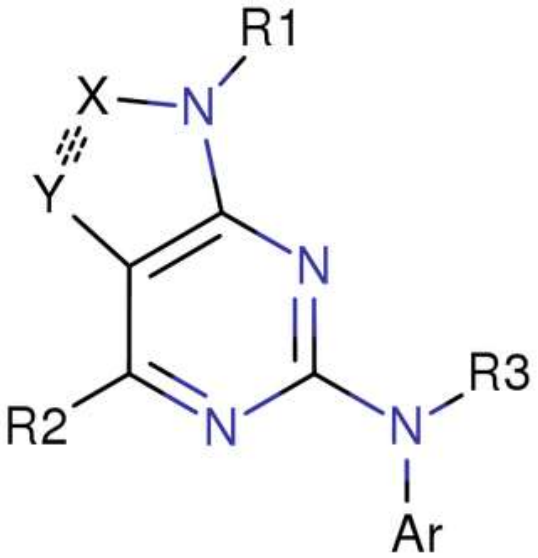
Limit to看Markush结构
Exclude获得结构

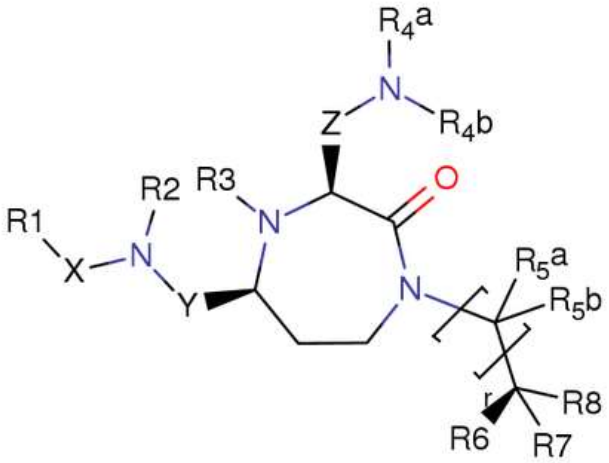
其中的Markush结构



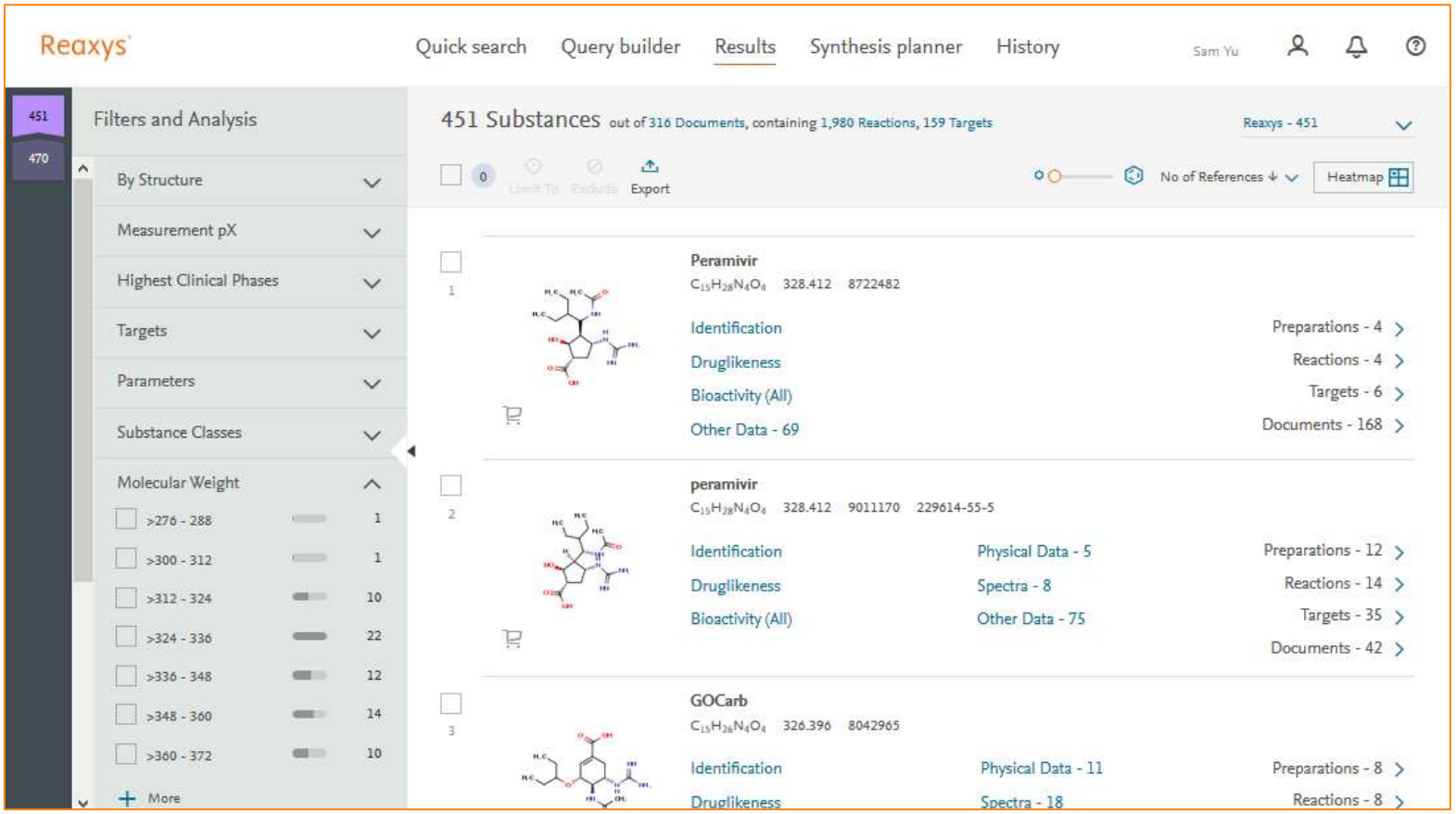


可以看到一些可能将这些片段链接在一起的骨架结构



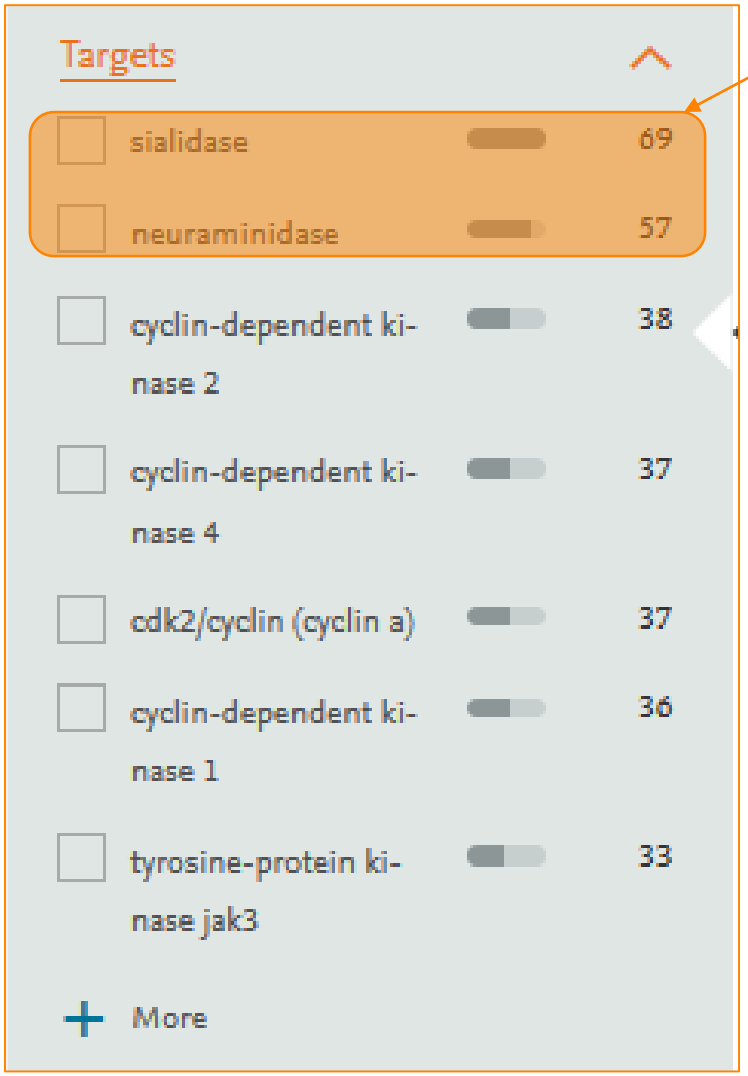


Exclude没有分子量的结果

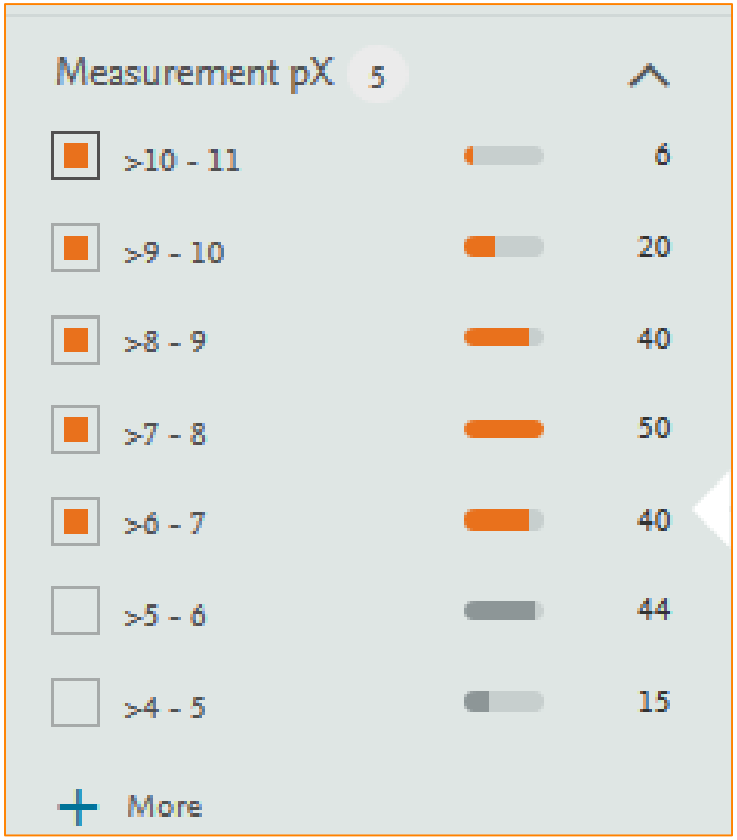


只知道片段，找连接方法，核结构，可以从靶点和PX找到主要的方向.....

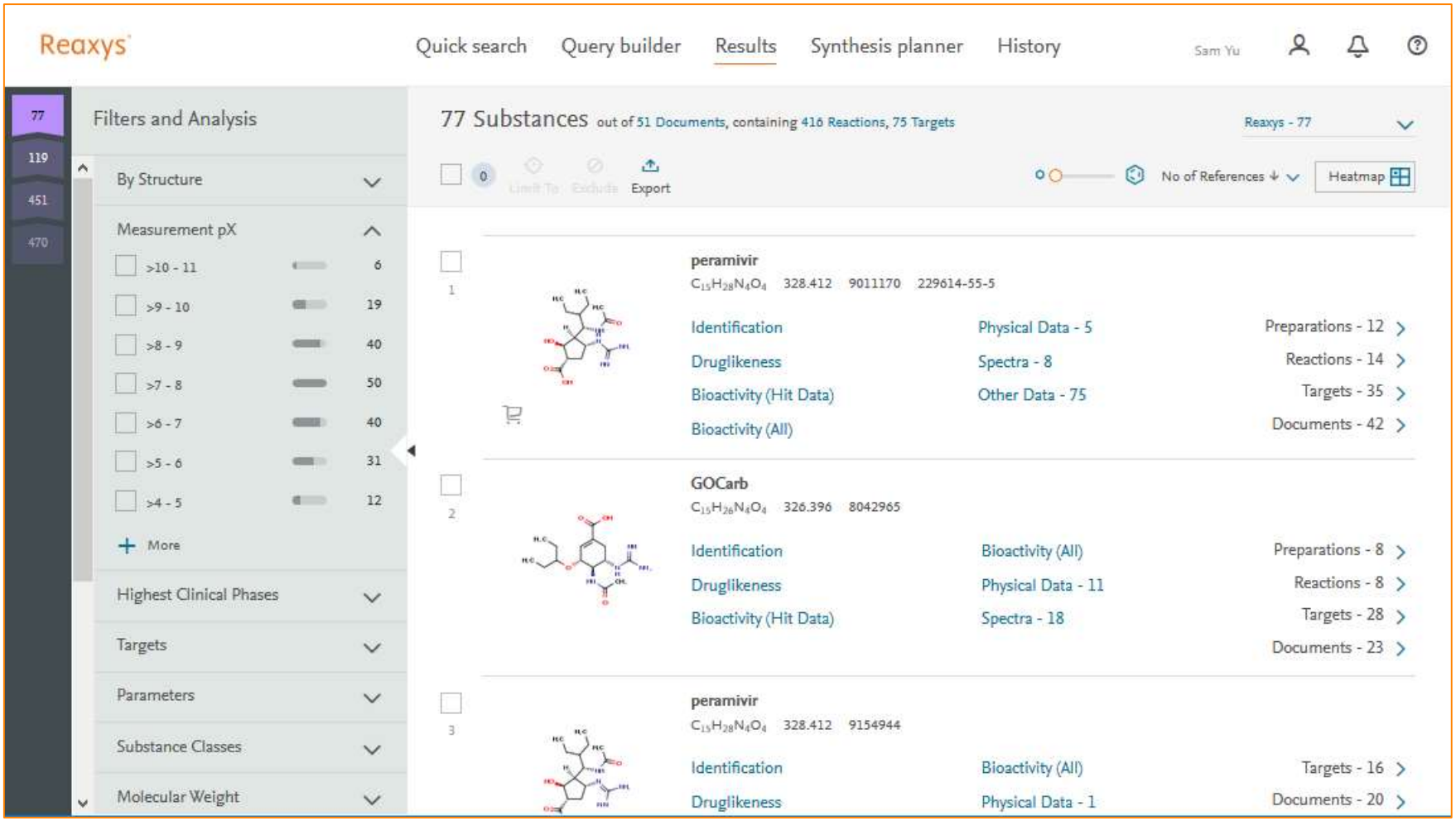
Reaxys中的筛选



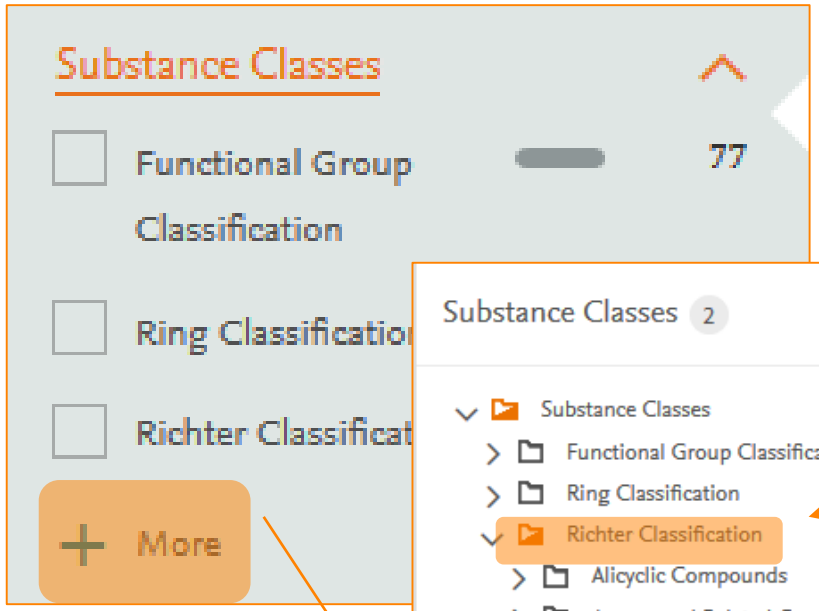
唾液酸酶，神经胺酶



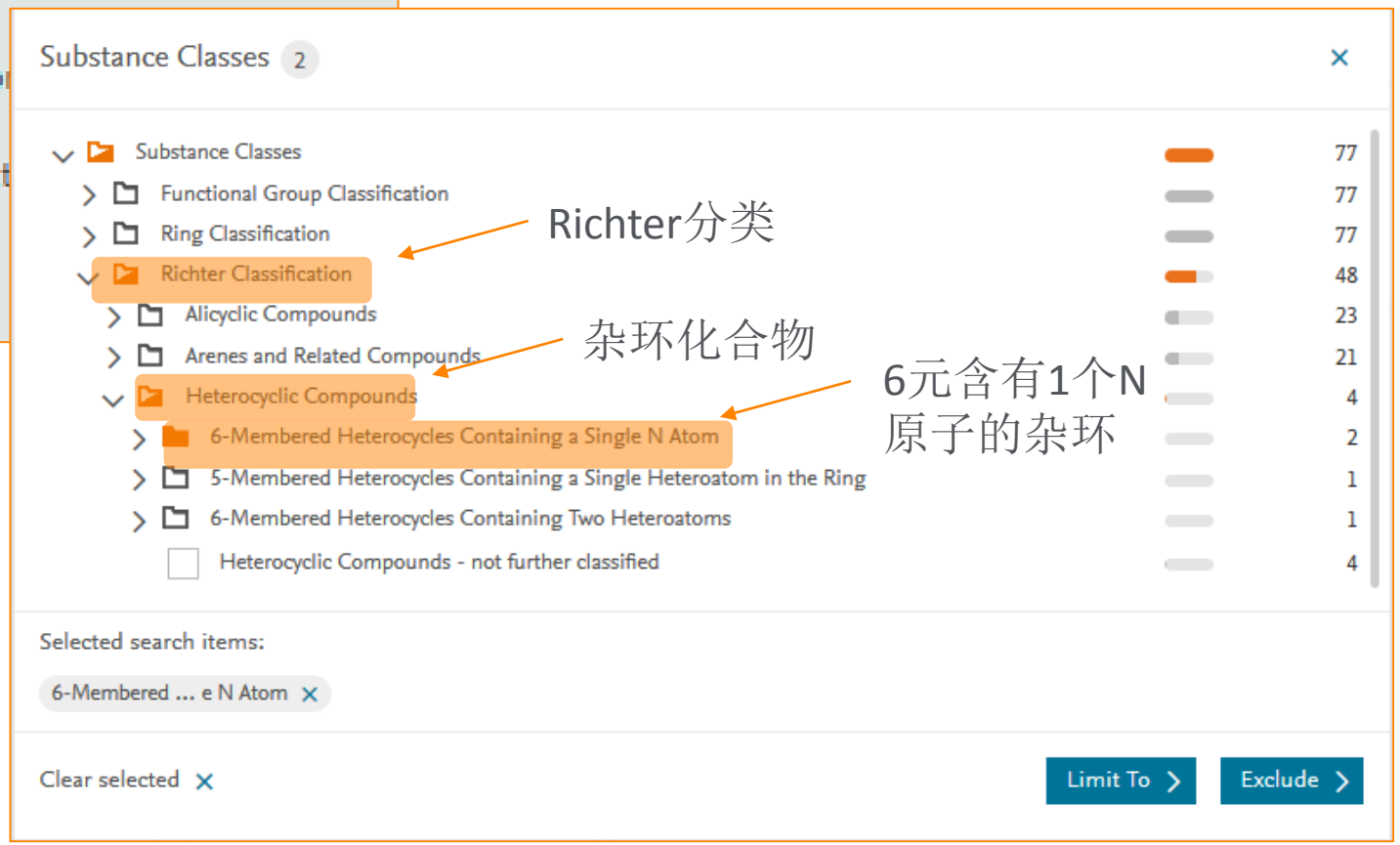
Reaxys中的结果


Reaxys
Quick search
Query builder
Results
Synthesis planner
History
Sam Yu
77
119
451
470
Filters and Analysis
77 Substances out of 51 Documents, containing 416 Reactions, 75 Targets
Reaxys - 77
0
Export
No of References
Heatmap
By Structure
Measurement pX
>10 - 11 6
>9 - 10 19
>8 - 9 40
>7 - 8 50
>6 - 7 40
>5 - 6 31
>4 - 5 12
More
Highest Clinical Phases
Targets
Parameters
Substance Classes
Molecular Weight
1
peramivir
C15H28N4O4 328.412 9011170 229614-55-5
Identification
Druglikeness
Bioactivity (Hit Data)
Bioactivity (All)
Physical Data - 5
Spectra - 8
Other Data - 75
Preparations - 12
Reactions - 14
Targets - 35
Documents - 42
2
GOCarb
C15H26N4O4 326.396 8042965
Identification
Druglikeness
Bioactivity (Hit Data)
Bioactivity (All)
Physical Data - 11
Spectra - 18
Preparations - 8
Reactions - 8
Targets - 28
Documents - 23
3
peramivir
C15H28N4O4 328.412 9154944
Identification
Druglikeness
Bioactivity (All)
Physical Data - 1
Targets - 16
Documents - 20

Reaxys中的结构分析

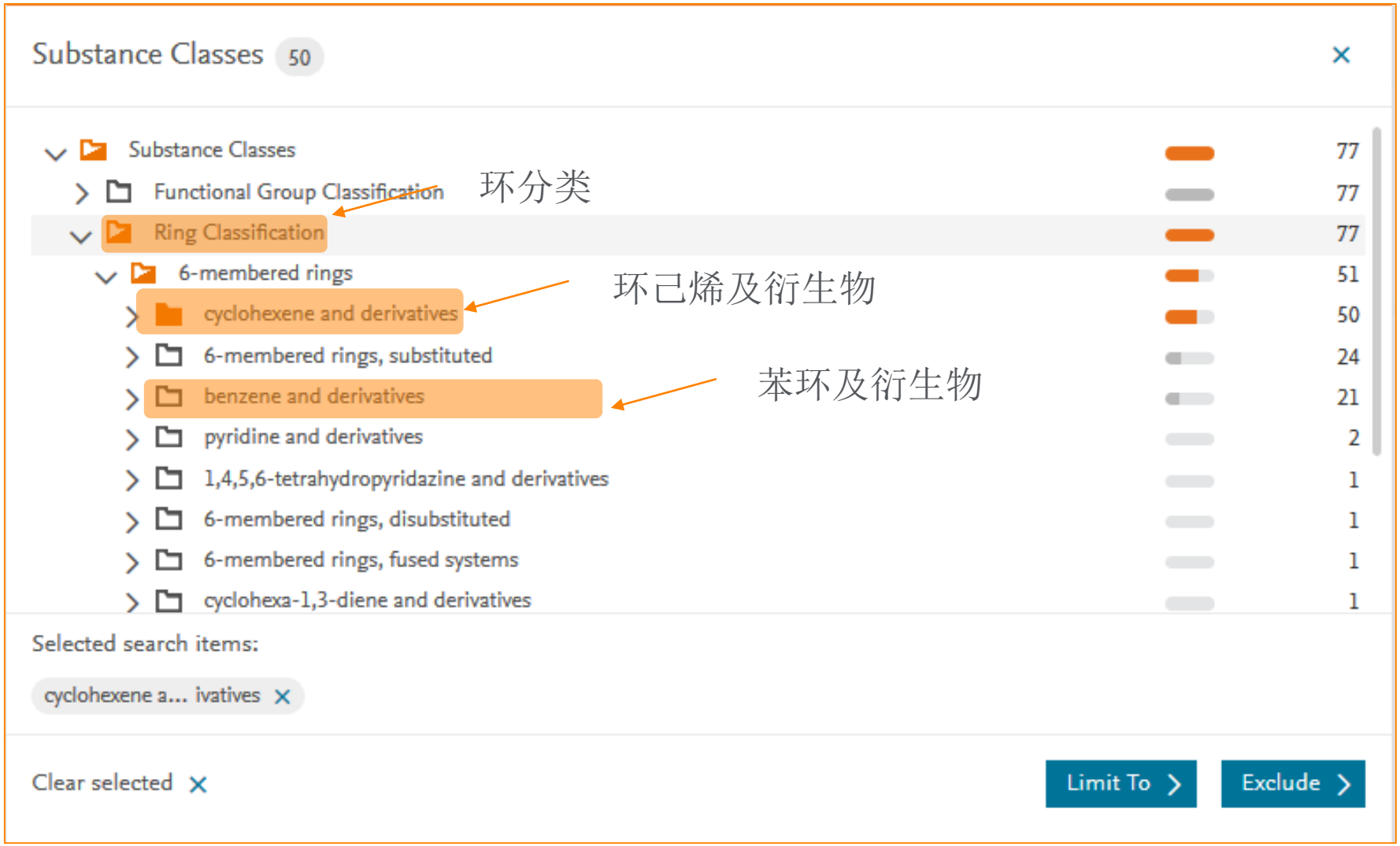


不同的分类规则可以帮助对批量结构进行归纳处理

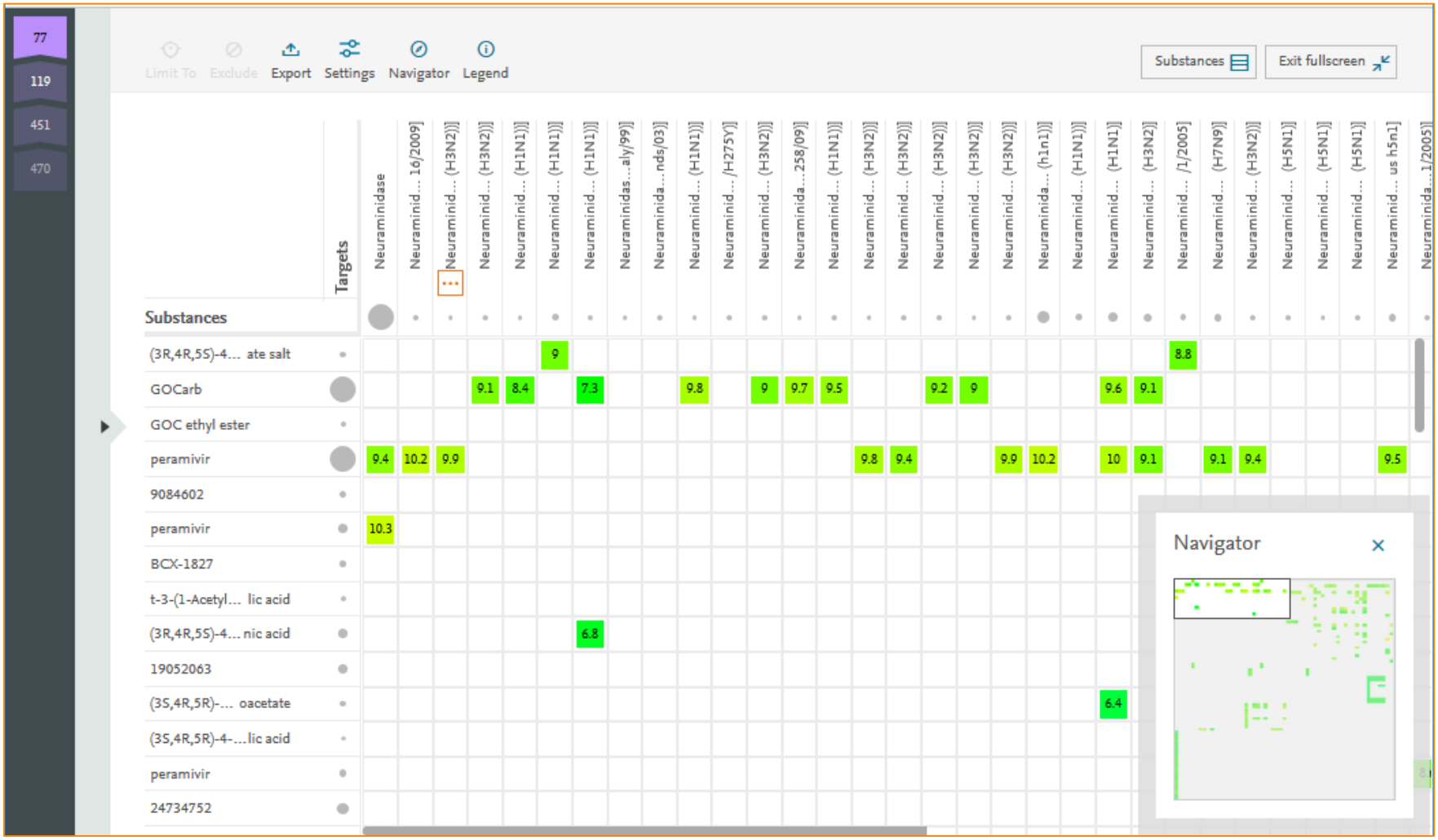


Reaxys中的结构分析—Function Group Classification

Reaxys中的结构分析—Ring Classification



这些结构的SAR热图


77
119
451
470
Limit To
Exclude
Export
Settings
Navigator
Legend
Substances
Exit fullscreen
Targets
Substances
(3R,4R,5S)-4... ate salt
GOCarb
GOC ethyl ester
peramivir
9084602
peramivir
BCX-1827
t-3-(1-Acetyl... lic acid
(3R,4R,5S)-4... nic acid
19052063
(3S,4R,5R)-... oacetate
(3S,4R,5R)-4-...lic acid
peramivir
24734752
Navigator