

如何利用Reaxys和RMC进行全新药物分子设计和专利评估

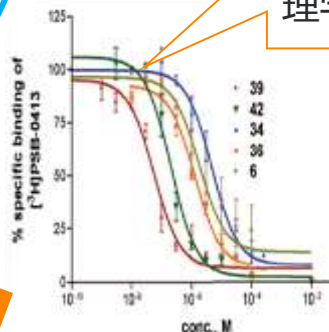
药物Discovery的过程

疾病，适应症，副作用跟踪

确认靶点

化合物结构计算，SAR构效分析等

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

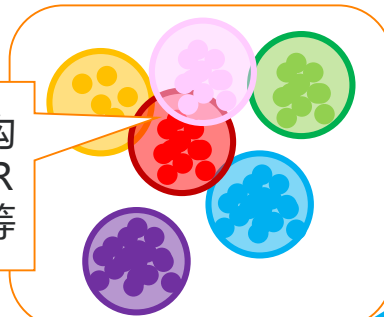
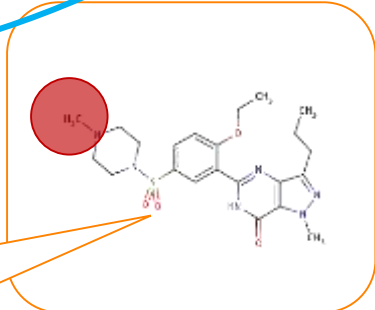


(pre)clinical



动物模型，动物毒理等，生物利用率，越早成功，成本越少

化合物初步筛选，生物初筛活性数据 (IC50, EC50等)



Discovery中常见的科学性问题

是否能利用这些片段进行全新化合物设计，SAR分析

影响活性的片段

DMPK的研究

DMPK, P450, caco-2, 药理, 毒理研究的方法

不同靶点之间的选择性问题

化合物对于不同靶点，是否可以，双抑制，选择性抑制，


化合物生物活性数据

公开报道的化合物在靶点上的生物活性数据


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

 Substance ADME, e.g. Pharmacokinetic of Imatinib

AND

 Create Structure or Reaction Drawing

Quick Search中可以使用的的方式:

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

The screenshot displays the Reaxys Query Builder interface. At the top, there are navigation tabs: 'Quick search', 'Query builder' (which is underlined), 'Results', 'Synthesis planner', and 'History'. A 'Sign in' button and a help icon are in the top right. Below the navigation, there are icons for 'Import', 'Save', 'Reset form', and 'Delete all'. In the center, there are icons for 'Structure', 'Molecular Formula', 'CAS RN', and 'Doc. Index'. A search bar with a 'Search' button and a dropdown arrow is located above the main workspace. The main workspace is a large grey area with the text 'Drag & Drop to build a new query'. On the right side, there is a sidebar titled 'Find search fields and forms' with a search icon. The sidebar has tabs for 'Fields', 'Forms', and 'History'. The 'Fields' tab is selected and highlighted with an orange box. Below the tabs, there is a list of search fields: 'Basic Indexes', 'Identification', 'Physical Properties', 'Spectra', 'MedChem', 'Other', 'Reactions', and 'Bibliography'. The 'MedChem' field is highlighted with an orange box, and an orange arrow points from the 'Fields' tab to it.

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

The screenshot displays the Reaxys Query Builder interface. At the top, the Reaxys logo is on the left, and navigation tabs for 'Quick search', 'Query builder', 'Results', 'Synthesis planner', and 'History' are in the center. A 'Sign in' button and a help icon are on the right. Below the navigation, a toolbar contains icons for 'Import', 'Save', 'Reset forms', and 'Delete all'. A secondary toolbar includes 'Structure', 'Molecular Formula', 'CAS RN', and 'Doc. Index'. A search bar with a dropdown arrow is positioned above the main workspace. The main workspace is a large grey area with the text 'Drag & Drop to build a new query'. On the right side, a sidebar contains a search bar labeled 'Find search fields and forms'. Below it, a 'Fields' section has a dropdown menu with 'Forms' selected and highlighted by an orange box. Underneath, there are two expandable sections: 'Reaxys Forms' and 'Reaxys MedChem Forms', with the latter also highlighted by an orange box.

Query Builder模块下，Forms中RMC预设模块的检索

RMC Forms 预设模块检索

- Affinity on target
- Cell proliferation: inhibition
- Selectivity Profile
- Animal models: Tumor xenografts
- Bioavailability
- Volume of distribution
- Absorption (C_{max}, C_{avg})
- Caco-2 permeability
- Caco-2 Active transport
- Blood-Brain Barrier Penetration (BBB)

- Cytotoxicity
- hERG inhibition
- Cytochrome inhibition (CYP3A4)
- Metabolism by cytochrome (CYP2D6)
- Microsomal stability
- Protein binding (blood, plasma)
- Cardiotoxicity

hERG inhibition

- Structure
 - Create Structure / Reaction Drawing
- AND
- Target Name
 - Target Name: 'Potassium voltage-gated channel subfamily H mem'
- AND
- Target Nature
 - Target Nature: 'Wild'
- AND
- Measurement Parameter
 - Measurement Parameter: 'IC50'; 'Ki'; 'Kd'
- AND
- Measurement pX
 - Measurement pX: 6

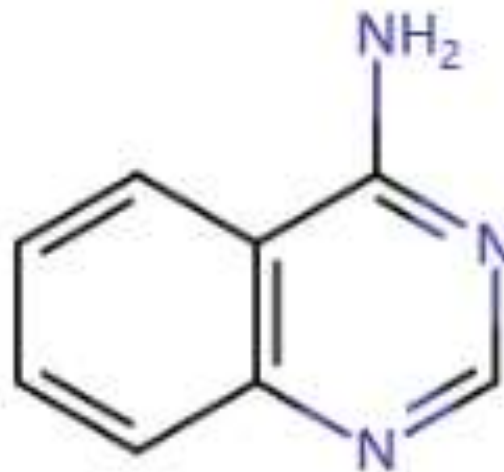
RMC Forms 预设了一些常见的检索策略，只需要选择对应模块，并添加相应条件，即可进行检索



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

The screenshot displays the Reaxys Query Builder interface. At the top, there are navigation tabs: 'Quick search', 'Query builder' (highlighted), 'Results', 'Synthesis planner', and 'History'. A 'Search' button is visible on the right. Below the navigation, there are utility icons for 'Import', 'Save', 'Reset form', and 'Delete all'. The main query builder area shows three conditions stacked vertically, separated by 'AND' operators:

- Structure**: A field with a 'Create Structure / Reaction Drawing' button.
- Target Name**: A field with the value 'is' and a dropdown menu set to 'Target Name'.
- Measurement Parameter**: A field with the value 'is' and a dropdown menu set to 'Measurement Parameter'.

On the right side, a sidebar titled 'Find search fields and forms' is open, showing a list of available fields under the 'MedChem' category. The 'Target Name' field is highlighted in orange. Other fields listed include 'Substance Action on Target', 'Substance Effect', 'Measurement pX', 'Target Nature', 'Target Mutant/Chimera Details', 'Target Transfection', and 'Substance RN'.

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

The screenshot displays the Reaxys Structure editor interface. At the top, there are navigation tabs: Quick search, Query builder, Results, Synthesis planner, and History. A 'Sign in' button and a help icon are also present. The main area is titled 'Structure editor' and contains a 'Create structure template from name' button. Below this is a toolbar with various editing tools. The central workspace shows the chemical structure of 2-aminobenzimidazole. To the right of the workspace is a search configuration panel titled 'Search this structure as:'. It includes several options: 'As drawn', 'As substructure' (selected), 'On all atoms' (selected), 'On heteroatoms', and 'Similar'. Below these are checkboxes for 'Tautomers', 'Stereo', 'Additional ring closures', 'Related Markush', 'Salts', 'Mixtures', 'Isotopes', 'Charges', and 'Radicals'. A '+ More options' link is at the bottom of the panel. At the bottom of the editor, there are 'Clear', 'Cancel', and 'Transfer to query' buttons.

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

◇ Target Name ×

is ▼ Target Name 🔍

输入EGFR并回车，一键转化所有EGFR靶点

Target Name × 3576280 ×

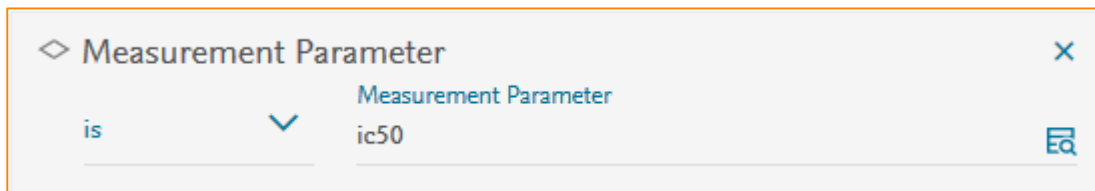
- > 📁 Targets 18,839,700
- > 📁 protein 15,203,250
- > 📁 binding protein 10,076,444
- > 📁 heterocyclic compound binding protein 3,260,624
- > 📁 nucleic acid binding protein 1,264,051
- > 📁 DNA binding protein 1,064,053
- > 📁 structure-specific DNA binding protein 147,781
- > 📁 double-stranded DNA binding protein 147,137
- > 📁 Epidermal growth factor receptor (EGFR (Epidermal growth factor receptor)) 62,930
- > 📁 Epidermal growth factor receptor [human] (EGFR) 59,040
- Epidermal growth factor receptor [dog] (EGFR) 2
- Epidermal growth factor receptor [Mus musculus] (Fofr) 3,723

Selected search items:

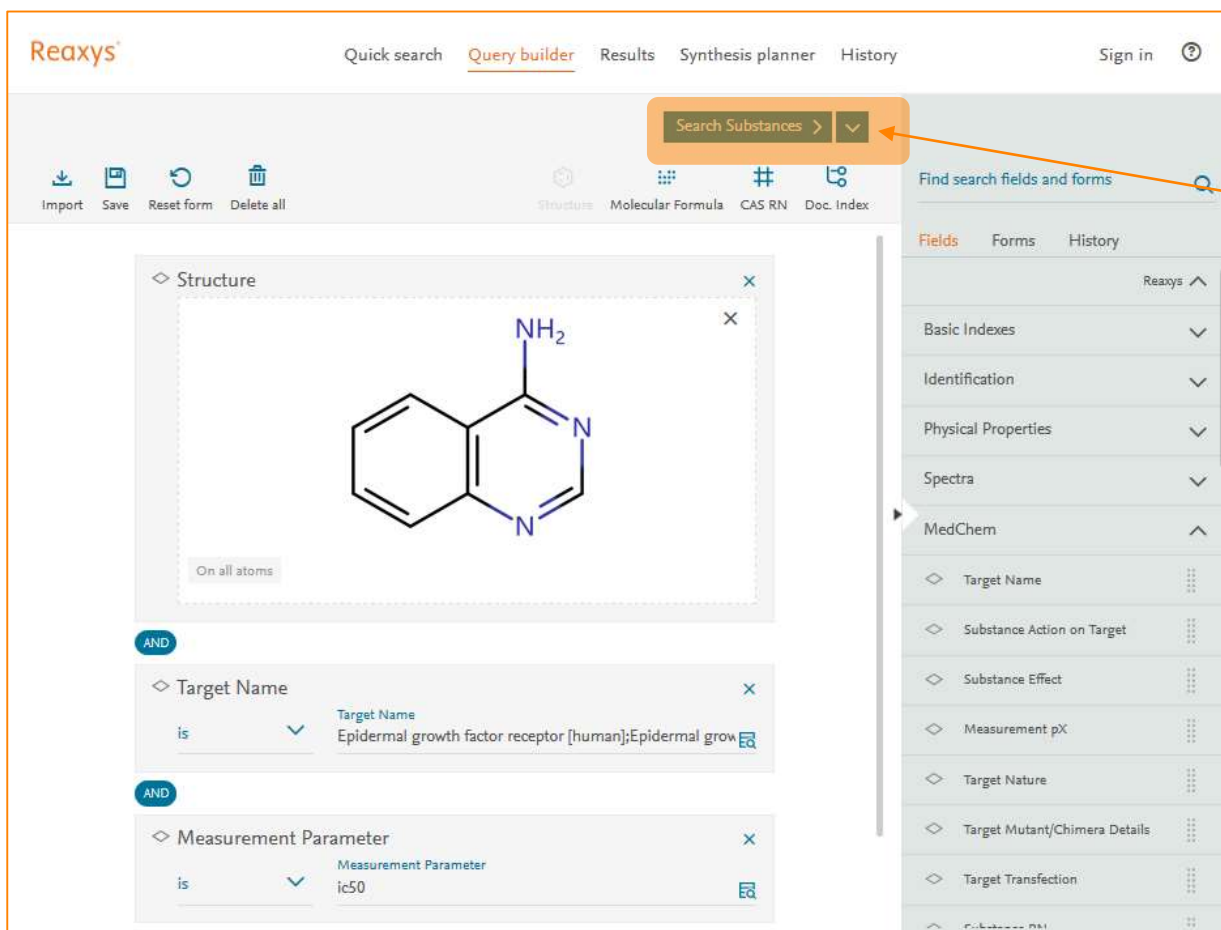
Epidermal g... [human] ×
Epidermal g... or [dog] ×
Epidermal g... usculus] ×
Epidermal g... vegicus] ×
More +

Clear selected Transfer >

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

Reaxys

Quick search Query builder Results Synthesis planner History Sign in

8,311 Filters and Analysis

8,311 Substances out of 886 Documents, containing 13,013 Reactions, 150 Targets

selected Export Sort by No of References Heatmap

Structure	Name	Chemical Formula	Pub ID	Pub ID	Pub ID	Other Data	Preparations	Reactions	Targets	Documents
	gefitinib	$C_{22}H_{14}ClFN_2O_3$	446,909	8949523	184473-31-2	2,446	55	85	1,028	2,934
	lapatanib	$C_{20}H_{16}ClFN_2O_3S$	581,067	10502247	231277-92-2	1,010	53	121	687	1,576
	erlotinib	$C_{21}H_{13}N_3O_4$	395,442	8798958	183321-74-6	2,403	35	88	997	790

Heat Map的设置

Heatmap settings ×

Value of X-axis: Targets ▼

Value of Y-axis: Substances ▼

Value of Cells: Maximum of pX ▼

Show substances: Names Structure drawing

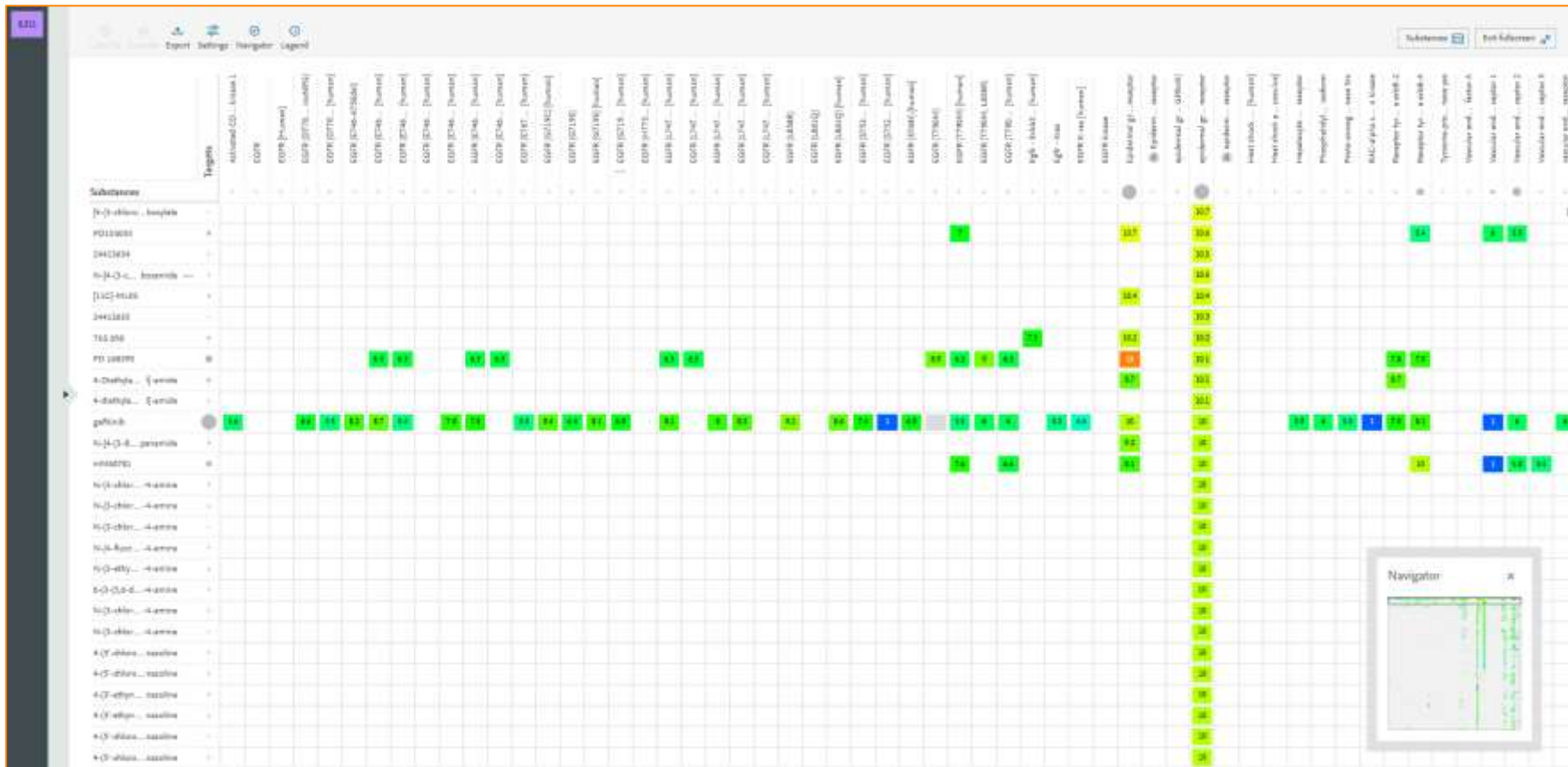
Display mode: Normal Full Screen

Always show settings Apply >

- Bioassays
- Targets
- Target Species
- Biological Species
- Effects
- Parameter
- Cell Lines
- Substances

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

<input checked="" type="checkbox"/>	human	12,736
<input type="checkbox"/>	mus musculus	47
<input type="checkbox"/>	baculoviridae	6
<input type="checkbox"/>	taurine cattle	1
<input type="checkbox"/>	(no entry given)	10,134

Measurement pX 6

<input checked="" type="checkbox"/>	>12 - 13	3
<input checked="" type="checkbox"/>	>11 - 12	59
<input checked="" type="checkbox"/>	>10 - 11	67
<input checked="" type="checkbox"/>	>9 - 10	599
<input checked="" type="checkbox"/>	>8 - 9	2,155
<input checked="" type="checkbox"/>	>7 - 8	4,176
<input type="checkbox"/>	>6 - 7	2,729

+ More

Targets 2

<input checked="" type="checkbox"/>	epidermal growth factor receptor	2,602
<input checked="" type="checkbox"/>	vascular endothelial growth factor receptor 2	767
<input type="checkbox"/>	egfr (e746-a750del)	53
<input type="checkbox"/>	receptor tyrosine-protein kinase erbb-2	48
<input type="checkbox"/>	epidermal growth factor receptor (l858r)	41
<input type="checkbox"/>	egfr (t790m)	40
<input type="checkbox"/>	vascular endothelial growth factor receptor 1	39

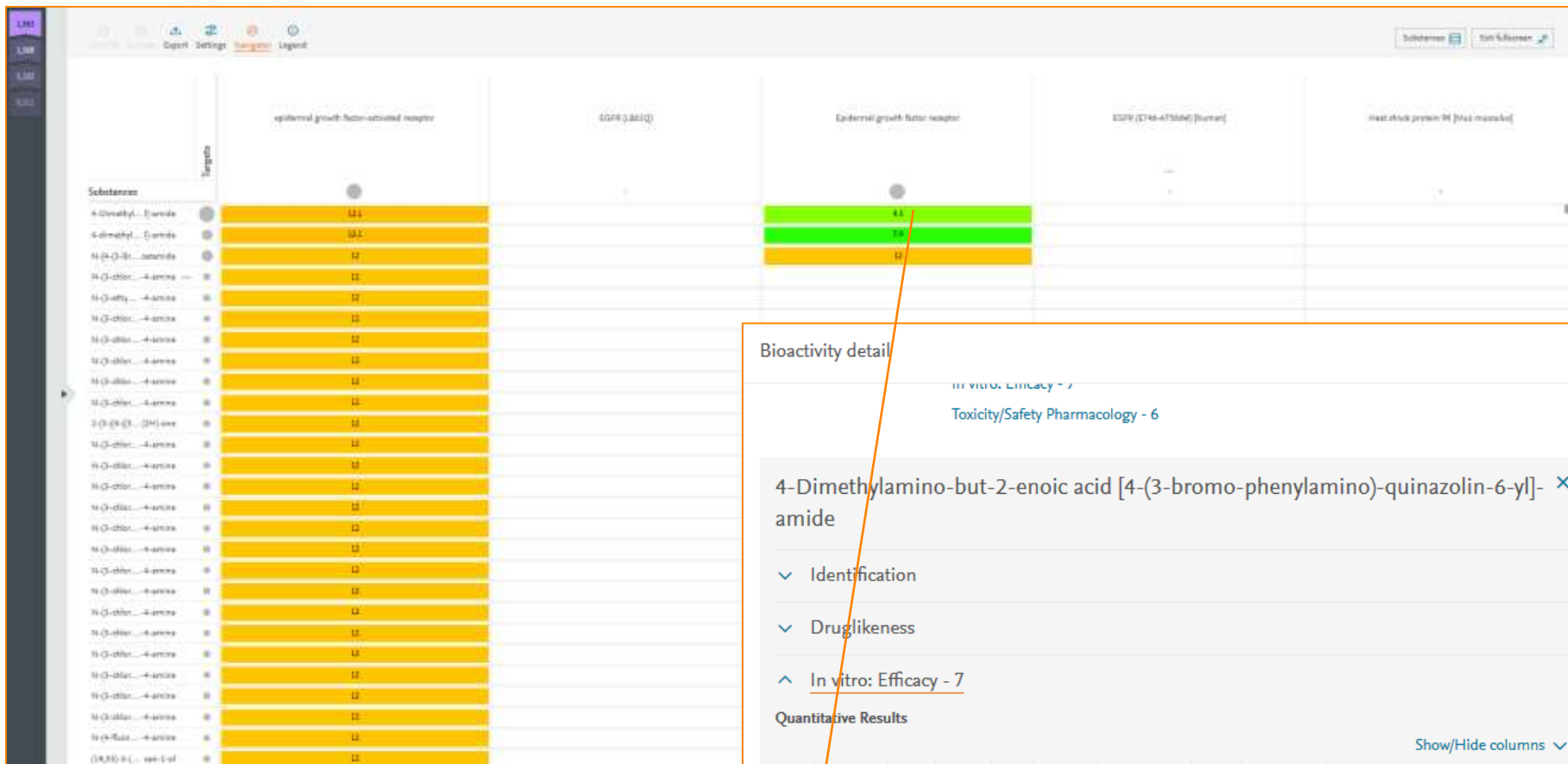
+ More

种属，PX值进行筛选后的结果

The screenshot displays a software interface with a table of substances and their activity values. The table has columns for substance names and various activity values. A 'Row options' menu is open, showing options like 'Sort by activity', 'Limit to selected row(s)', 'Exclude selected row(s)', 'Copy structure to', and 'All substance details'. The 'Sort by activity' option is highlighted in orange. The table shows various substances with activity values ranging from 0 to 100. The interface includes a top navigation bar with 'Report', 'Settings', 'Navigator', and 'Legend' buttons. A 'Substances' list is visible on the left side of the table.

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



Bioactivity detail

In vitro: Efficacy - 7

Toxicity/Safety Pharmacology - 6

4-Dimethylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-quinazolin-6-yl]-amide

Identification

Druglikeness

In vitro: Efficacy - 7

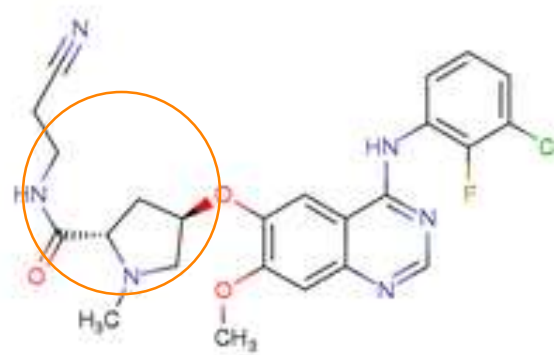
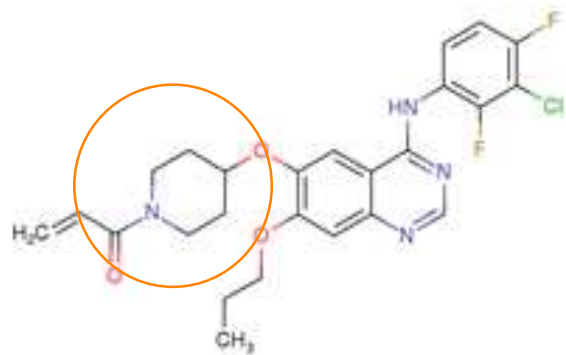
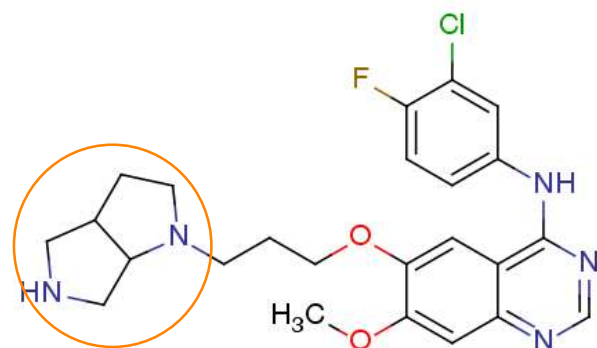
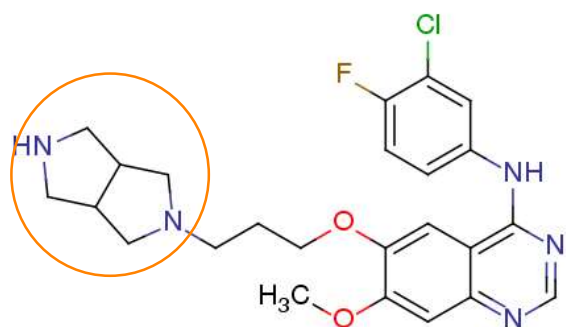
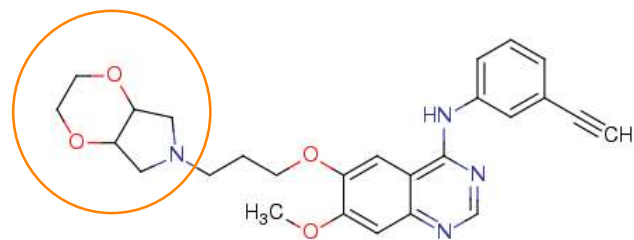
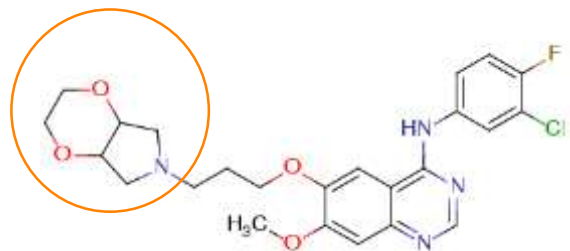
Quantitative Results

pX	Parameter	Value (qual)	Value (quant)	Unit	Action on target	Target	Cell	Bioassay	Reference
9.39	IC50		0.41	nM		Epidermal growth factor receptor [human]:Wild	A-431	Enzymology inhibition	Mishani, Eyal; Abourbeh, Galith; Jacobson, Dissoki, Samar; Ben Daniel, Revital; Rozen, Mazal; Levitzki, Alexander - Journal of Med Chemistry, 2005, vol. 48, # 16, p. 5337 - 53

Show/Hide columns

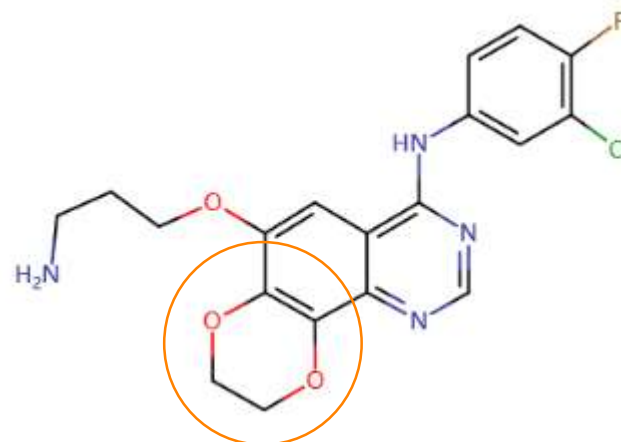
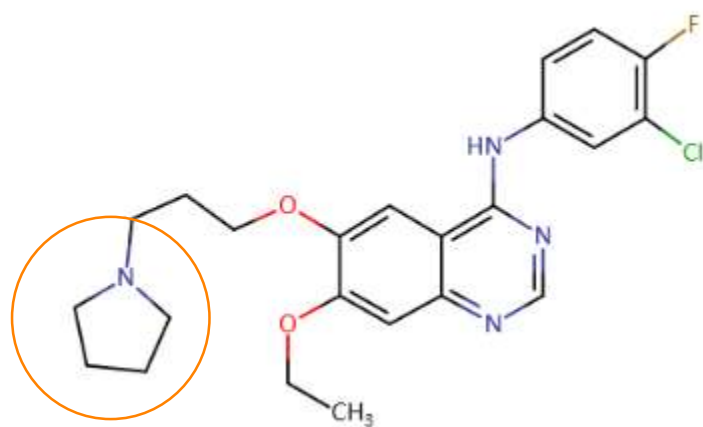
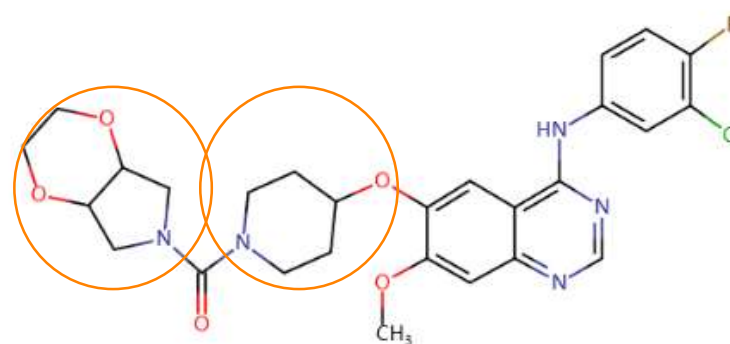
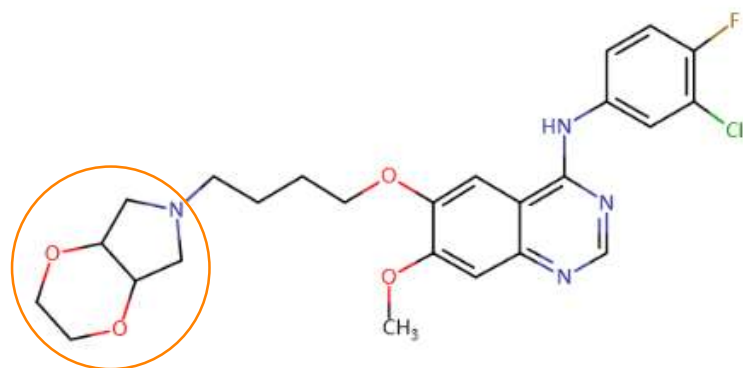
文献中的以Mol为单位的数值全部转换成PX

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

The screenshot displays the Reaxys software interface. At the top, there are navigation tabs: "Quick search", "Query builder", "Results", "Synthesis planner", and "History". The user's name "Sam Yu" and a help icon are visible in the top right corner.

The main area is the "Structure editor", which contains a large central workspace. On the left side of this workspace is a vertical toolbar with various icons for editing and drawing. The central workspace shows a complex chemical structure on the left, which is a benzimidazole derivative with substituents R_1 , R_2 , and R_3 . To the right of this main structure are several smaller chemical structures labeled R1, R2, and R3, representing different substituents. R1 is a piperidine ring with a wavy line and a circled '1' indicating a Markush group. R2 is a wavy line with a circled '1' and the letter 'X' below it. R3 consists of three options: a wavy line with a circled '1' and 'H' below it, a wavy line with a circled '1' and 'ALK' below it, and a wavy line with a circled '1' and 'ARY' below it.

On the right side of the interface is a search configuration panel titled "Search this structure as:". It includes several radio buttons and checkboxes for search criteria:

- As drawn
- As substructure
 - On all atoms
 - On heteroatoms
- Similar

Below these are "Include" options with checkboxes:

- Tautomers
- Stereo
- Additional ring closures
- Related Markush
- Salts
- Mixtures
- Isotopes
- Charges
- Radicals

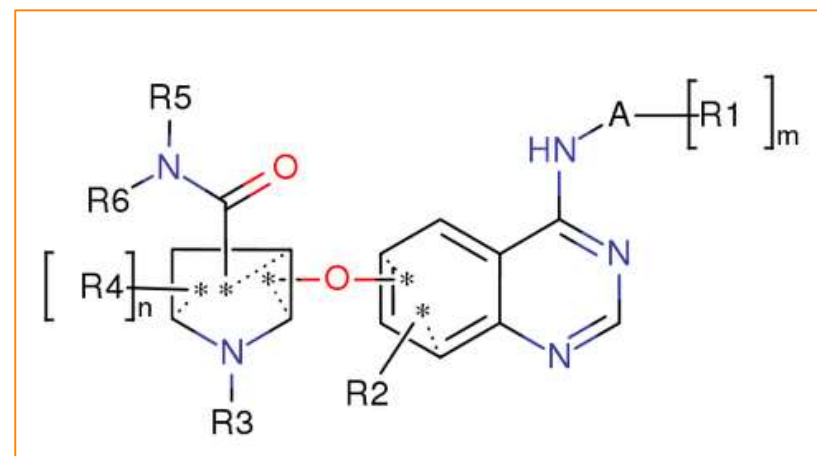
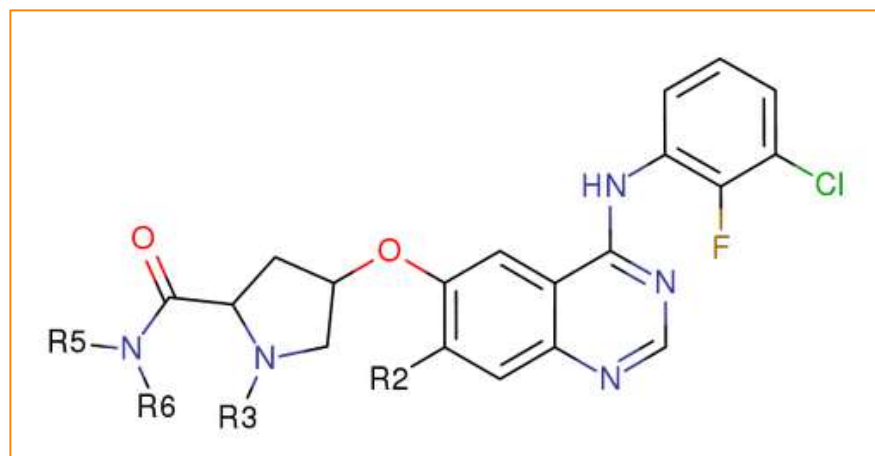
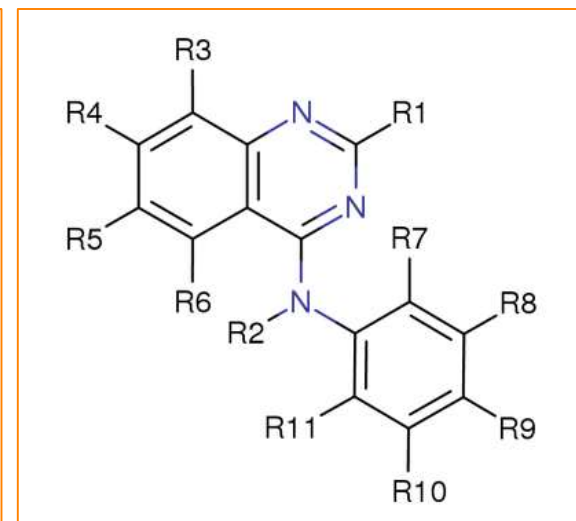
At the bottom of the search panel is a "+ More options" link. At the bottom of the main workspace, there are buttons for "Clear", "Cancel", and "Transfer to query". A "Feedback" button is located in the bottom right corner.

Tips:

盐，混合物去掉，Related Markush勾选，亚结构勾选

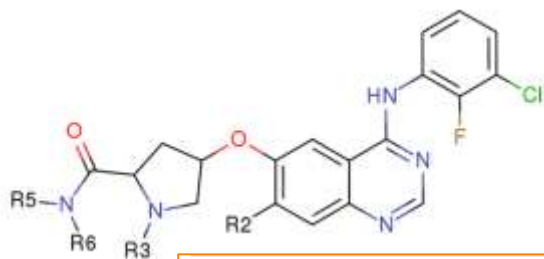
利用分子量筛选，筛出Markush结构

Reaxys interface showing search results for 37 substances. The interface includes a sidebar for filters and analysis, a search bar, and a list of results with chemical structures and identifiers.

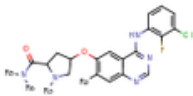


其中的一个Markush结构

Reaxys中的Markush标记出该结构在专利Claim中的位置



Reaxys ID: 12250782
12250782

 Identification Documents - 1 >

Identification

Reaxys ID: 12250782

Chemical Names:

CAS Registry Number(s):

Molecular Formula:

Molecular Weight:

InChIKey:

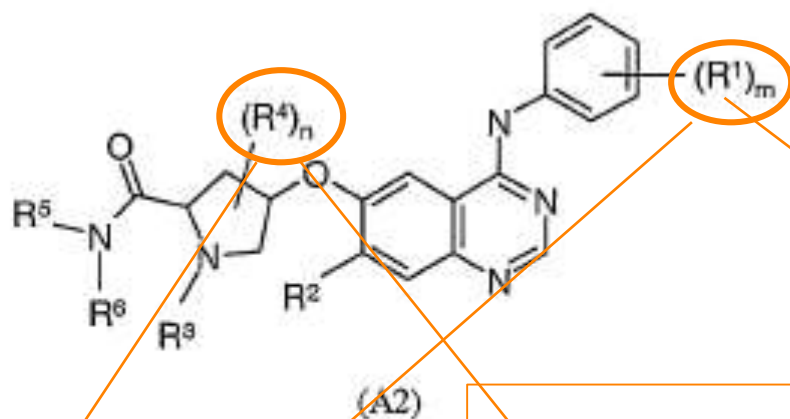
Location in Patent	Reference
Claim 24	ASTRAZENECA AB; ASTRAZENECA UK LIMITED - WO2005/30757, 2005, A1 Full Text ↗ Show details >

Substance Label - 1

Patent-Specific Data - 1

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



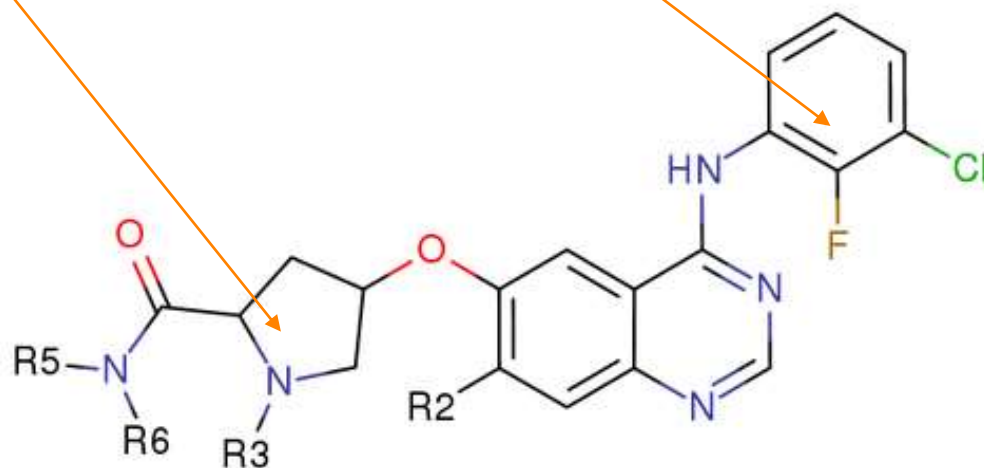
wherein:

m is 2 and R¹ is 2-fluoro and 3-chloro;

R² is methoxy;

R³ is methyl;

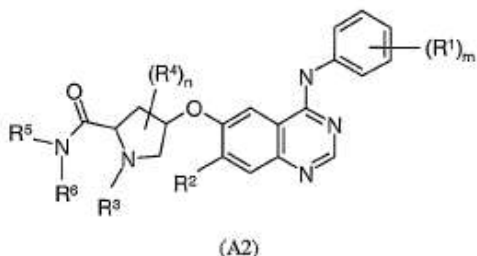
n is 0;



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



wherein:

m is 2 and R¹ is 2-fluoro and 3-chloro;

R² is methoxy;

R³ is methyl;

n is 0;

WO 2005/030757

- 184 -

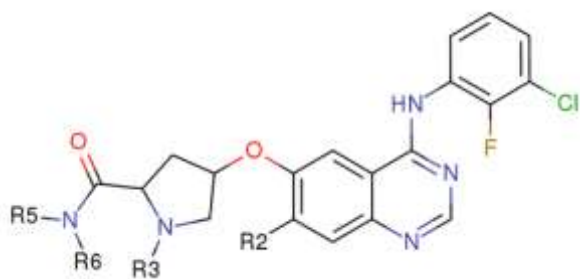
PCT/GB2004/004085

and R⁵ is hydrogen or (1-6C)alkyl and R⁶ 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 R⁶ 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 R⁶ is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by (1-4C)alkyl or (2-4C)alkanoyl, or R⁵ and R⁶ 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 R⁶ 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 R⁶ is optionally substituted (on

专利原文用文字进行结构的描述

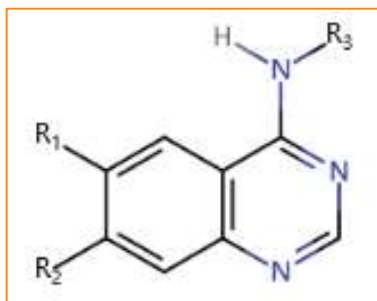
Reaxys将结构翻译成图表



图表形式的解读更容易帮助理解结构保护的围

Label	Value	Size	Attributes	Substituted by	Frequency	
R2	methoxy					
R3	methyl					
R5	hydrogen					
R6	alkyl	1-6C		ss8	0-3	
	hydrogen					
	alkyl	1-6C				
	alkenyl	2-8C				
	alkynyl	2-8C				
	alkoxy	1-6C				
	cycloalkyl	3-7C				
	alkylsulfonyl	1-6C				
	heterocyclyl				ss9	0-2
	heteroaryl					
	*\$cylalk37\$*alk13					
	*\$hetar\$*alk13					
	*\$hets\$*alk13					
ss1	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

The screenshot displays the Reaxys Structure editor. The main window shows a chemical structure of a benzimidazole derivative with a methoxy group (CH₃O) and a highlighted 'GH' group. The right sidebar contains search options: 'As drawn' (selected), 'As substructure', 'Similar', 'Tautomers', 'Stereo', 'Additional ring closures', 'Related Markush', 'Salts', 'Mixtures', 'Isotopes', 'Charges', 'Radicals', and '+ More options'. The bottom of the editor has 'Clear', 'Cancel', and 'Transfer to query' buttons.

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

The screenshot displays the Reaxys search results interface. The top navigation bar includes 'Quick search', 'Query builder', 'Results', 'Synthesis planner', and 'History'. The main header shows '1,116 Substances out of 3,123 Documents, containing 2,360 Reactions, 1,075 Targets'. A sidebar on the left lists various filters, with 'Parameters' highlighted. The main content area shows a list of substances, with the first two entries expanded to show their chemical structures and associated data.

Substance 1: gefitinib
Chemical formula: $C_{22}H_{24}ClFN_4O_3$ | CAS: 446.909 | PubChem: 8949523 | ECHA: 184475-35-2
Data: Identification, Bioactivity (All), Spectra - 45, Preparations - 55, Druglikeness, Physical Data - 53, Other Data - 2,446, Reactions - 85, Targets - 1,028, Documents - 2,934

Substance 2: 4-(3-chloro-4-fluorophenylamino)-6-hydroxy-7-methoxyquinazoline
Chemical formula: $C_{15}H_{11}ClFN_3O_2$ | CAS: 319.723 | PubChem: 8928756 | ECHA: 184475-71-6
Data: Identification, Bioactivity (All), Spectra - 28, Preparations - 34, Druglikeness, Physical Data - 10, Reactions - 200, Targets - 7, Documents - 57

Parameters Filter (1 selected):

Parameter	Count
qualitative	577
ic50	448
clint	75
% inhibition	62
gi50	54
id50	43
f(%)	41
+ More	

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

75 Substances out of 4 Documents, containing 465 Reactions, 0 Targets

0 selected Limit To Exclude Export Sort by No of References Heatmap

1 **gefitinib**
C22H24ClFN4O3 446.909 8949523 184475-35-2
 Identification Bioactivity (All) Other Data - 2,446 Preparations - 55 >
 Druglikeness Physical Data - 53 Reactions - 85 >
 Bioactivity (Hit Data) Spectra - 45 Targets - 1,028 >
 Documents - 2,934 >

2 **4-[(3-chloro-4-fluoro-phenyl)amino]-7-methoxy-6-[3-[[1R,6S]-2,5-dioxo-8-azabicyclo[4.3.0]nonane-8-yl]propoxy]-quinazoline**
C24H26ClFN4O4 488.946 27215159
 Identification Reactions - 13 >
 Druglikeness Targets - 1 >
 Bioactivity (Hit Data) Documents - 7 >
 Bioactivity (All)

3 **(Z)-N-(4-((3-chloro-4-fluorophenyl)amino)-7-methoxy-6-[3-[[1R,6S]-2,5-dioxo-8-azabicyclo[4.3.0]nonane-8-yl]propoxy]-quinazolin-2-yl)propan-1-amine**
C21H20ClF2N5O2 447.872 26428465 1420
 Identification Reactions - 1 >
 Druglikeness Reactions - 2 >
 Targets - 22 >
 Documents - 4 >

Heatmap settings

Value of X-axis: Parameter

Value of Y-axis: Substances

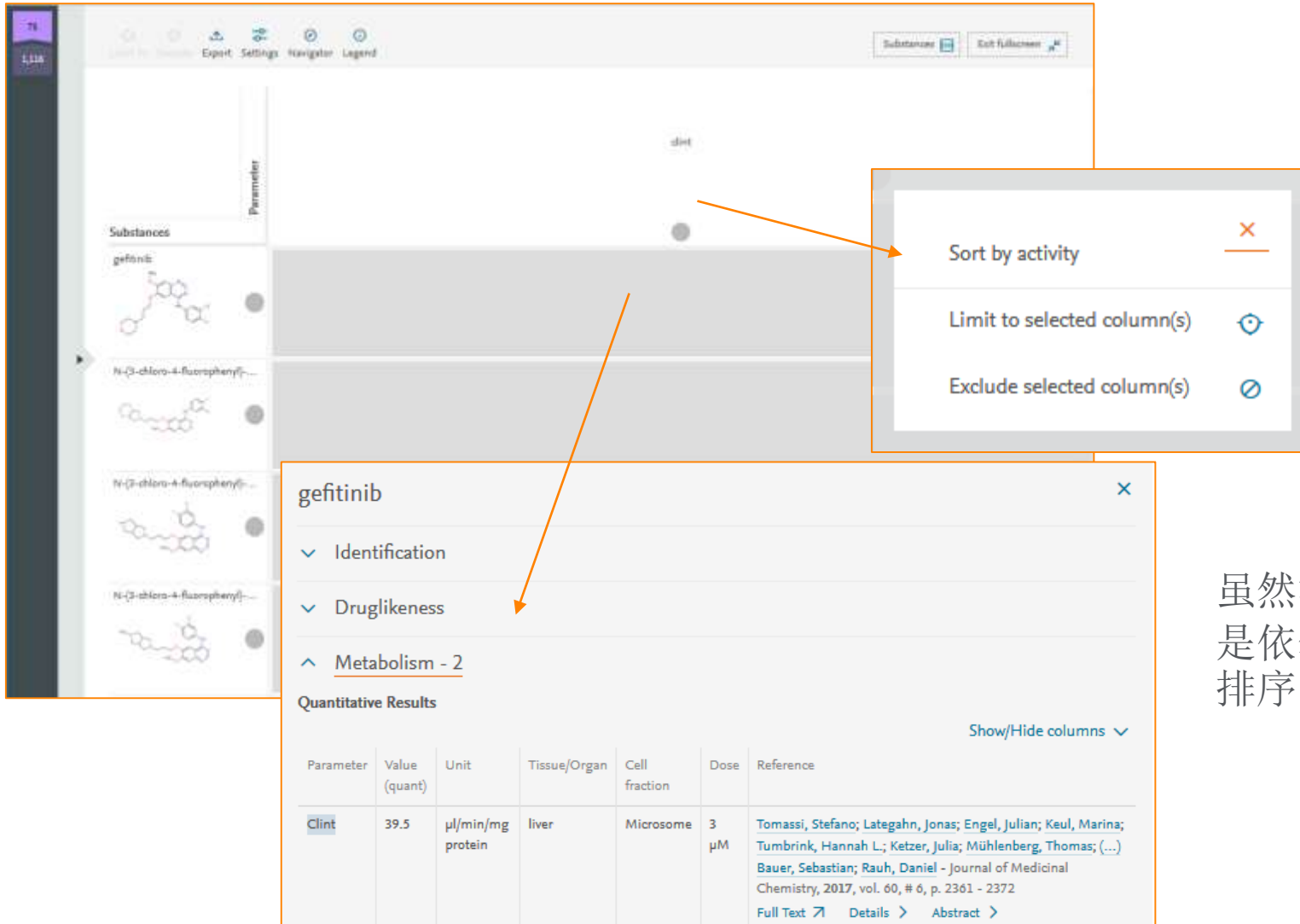
Value of Cells: Maximum of pX

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



The screenshot displays a software interface with a sidebar on the left containing a list of substances. The main area shows a search result for 'Clint'. A context menu is open over the search result, offering options: 'Sort by activity', 'Limit to selected column(s)', and 'Exclude selected column(s)'. A detailed view for 'gefatinib' is also shown, featuring a table of quantitative results.

gefatinib

- Identification
- Druglikeness
- Metabolism - 2

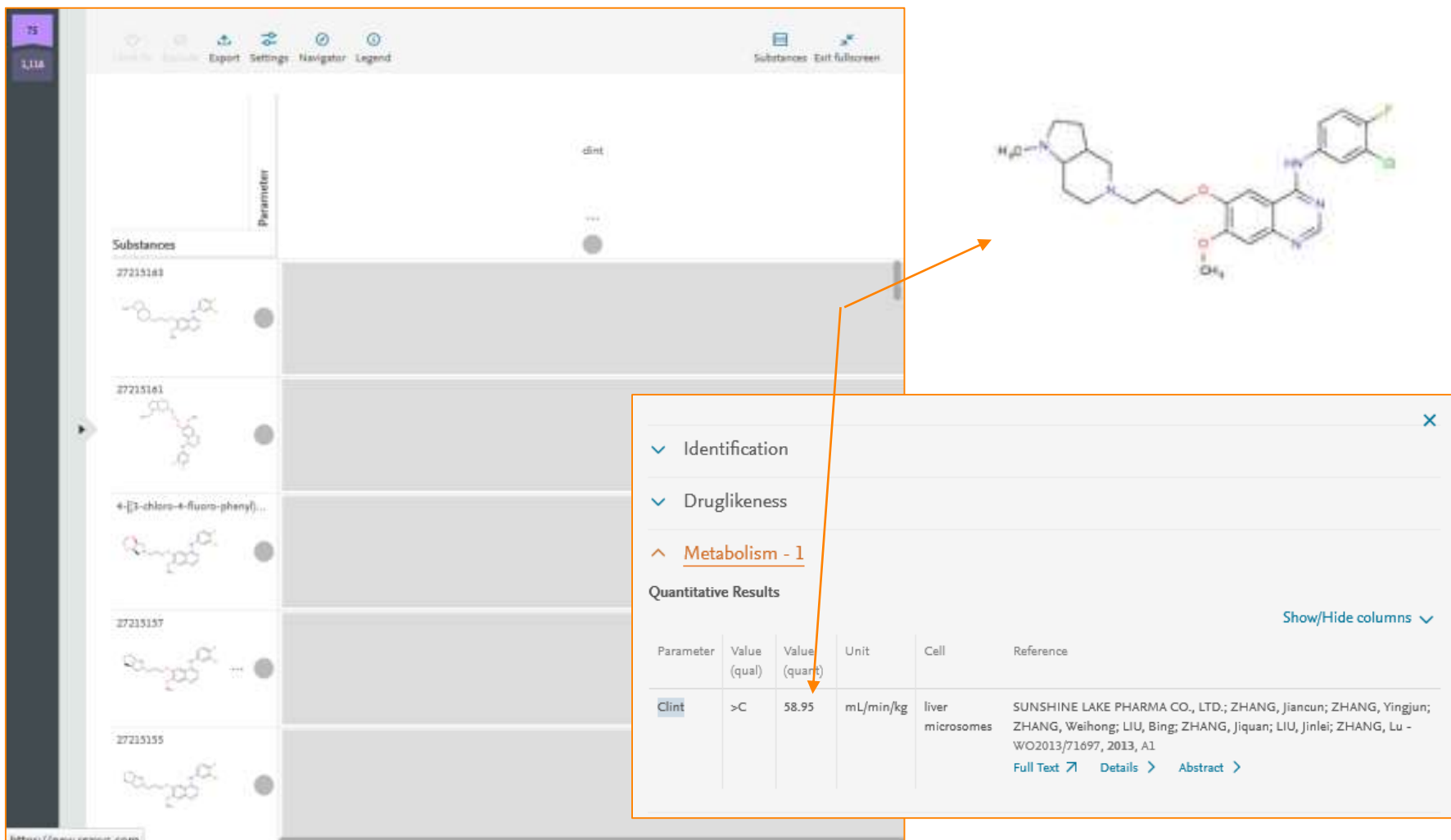
Quantitative Results

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

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



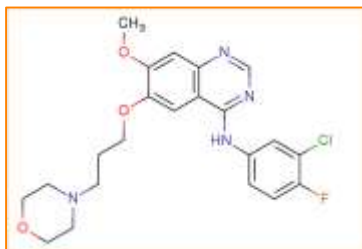
The screenshot displays a software interface for substance analysis. On the left, a list of substances is shown, including their IDs and chemical structures. The substance with ID 27215157 is highlighted. On the right, a detailed view of this substance is shown, including its chemical structure and a table of quantitative results.

The detailed view includes the following information:

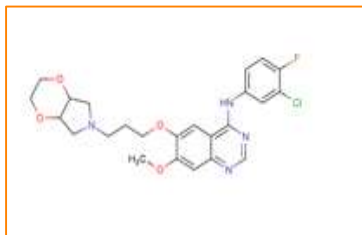
- Identification
- Druglikeness
- Metabolism - 1
- Quantitative Results

Parameter	Value (qual)	Value (quant)	Unit	Cell	Reference
Clint	>C	58.95	mL/min/kg	liver microsomes	SUNSHINE LAKE PHARMA CO., LTD.; ZHANG, Jiancun; ZHANG, Yingjun; ZHANG, Weihong; LIU, Bing; ZHANG, Jiquan; LIU, Jinlei; ZHANG, Lu - WO2013/71697, 2013, A1 Full Text Details Abstract

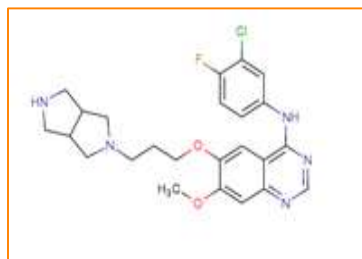
和阳性化合物比较的结果



Parameter	Value (quant)	Unit	Tissue/Organ	Cell fraction	Dose	Reference
Clint	39.5	$\mu\text{l}/\text{min}/\text{mg}$ protein	liver	Microsome	3 μM	Tomassi, Stefano; Lategahn, Jonas; Engel, Julian; Keul, Marina; Tumbriak, 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	$\text{ml}/\text{min}/\text{kg}$	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	$\text{ml}/\text{min}/\text{kg}$	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:

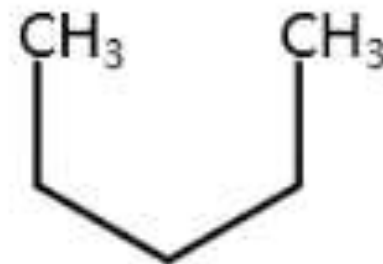
1. 从清除率上看，这一系列侧链的对母核分子在‘清除率’数据上贡献并不好，
2. 作为参考，如果是同母核的化合物，是否可以将这类侧链化合物的合成和检测退后，合理安排资源
3. 作为参考，如果是其他母核，是否在IC50结果好的情况下，优先测试‘clint’，以避免成本浪费



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

The screenshot displays the Reaxys Structure editor. The main workspace contains three chemical structures: guanidine (NC(=N)N), 2,2,4-trimethylpentane (CC(C)(C)CC(C)C), and acetamide (CC(=O)N). The acetamide structure has a Markush label $H_3C^{(*)}$ on the methyl carbon. The right sidebar shows search options for the structure, with 'As substructure' selected and 'On all atoms' chosen. The 'More options' button is highlighted. At the bottom, there are buttons for 'Clear', 'Cancel', and 'Transfer to query'.

Tips:

把Markush勾选上，一次性获得将对应的Markush结构也获得

- Ignore Atom Mappings
- Keep fragments
 - Separate
 - Together

Reaxys中的检索结果

Reaxys® Quick search Query builder Results Synthesis planner History Sam Yu

470 Filters and Analysis 470 Substances Reaxys - 470

By Structure Measurement pX Highest Clinical Phases Targets Parameters Substance Classes **Molecular Weight** Availability Availability in other databases Available Data Document Type Publication Year Patent Assignee

1 **Peramivir**
C15H28N4O4 328.412 8722482
 Identification Preparations - 4 >
 Druglikeness Reactions - 4 >
 Bioactivity (All) Targets - 6 >
 Other Data - 69 Documents - 168 >

2 **peramivir**
C15H28N4O4 328.412 9011170 229614-55-5

3

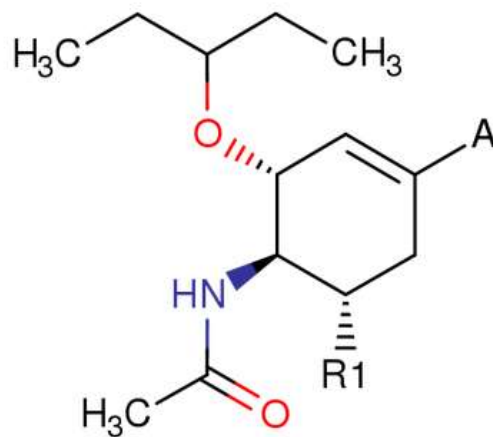
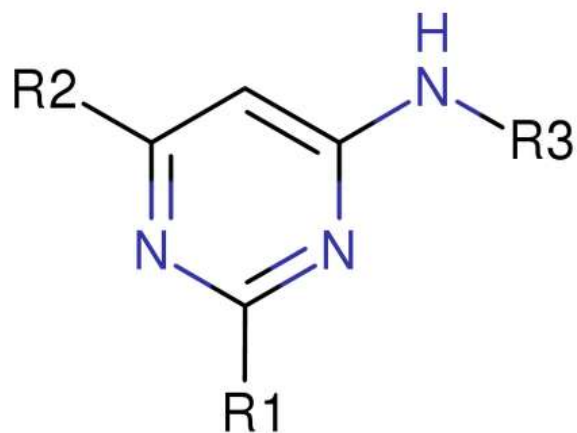
Limit to看Markush结构
 Exclude获得结构

Molecular Weight 1 Clear selected x Sort by Occurrence v x

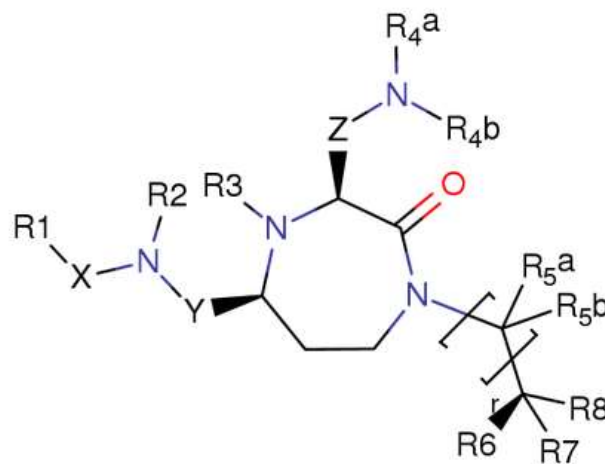
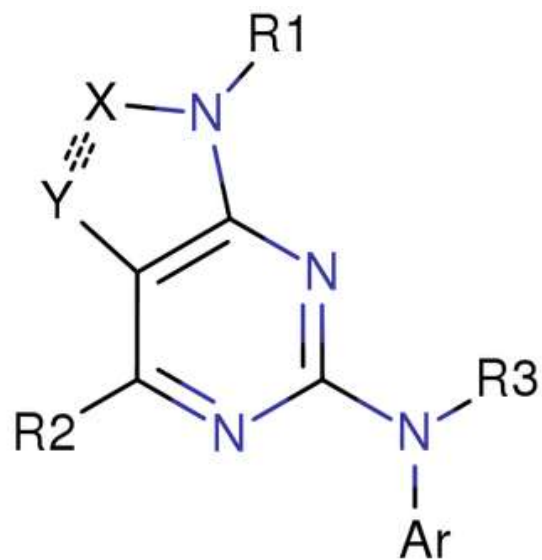
<input type="checkbox"/> >648 - 660 5	<input type="checkbox"/> >780 - 792 5	<input type="checkbox"/> >936 - 948 1
<input type="checkbox"/> >660 - 672 3	<input type="checkbox"/> >792 - 804 4	<input type="checkbox"/> >1464 - 1476 1
<input type="checkbox"/> >672 - 684 3	<input type="checkbox"/> >804 - 816 1	<input type="checkbox"/> >1500 - 1512 1
<input type="checkbox"/> >684 - 696 3	<input type="checkbox"/> >816 - 828 1	<input type="checkbox"/> >2400 - 2412 2
<input type="checkbox"/> >696 - 708 2	<input type="checkbox"/> >828 - 840 2	<input type="checkbox"/> >2424 - 2436 2
<input type="checkbox"/> >708 - 720 2	<input type="checkbox"/> >852 - 864 1	<input checked="" type="checkbox"/> (no entry given) 19
<input type="checkbox"/> >720 - 732 3	<input type="checkbox"/> >864 - 876 2	
<input type="checkbox"/> >732 - 744 2	<input type="checkbox"/> >876 - 888 2	
<input type="checkbox"/> >744 - 756 1	<input type="checkbox"/> >912 - 924 1	
<input type="checkbox"/> >768 - 780 2	<input type="checkbox"/> >924 - 936 1	

< 1 2 Limit to > Exclude >

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

The screenshot displays the Reaxys search results page. The top navigation bar includes 'Quick search', 'Query builder', 'Results', 'Synthesis planner', and 'History'. The user 'Sam Yu' is logged in. The main header shows '451 Substances out of 316 Documents, containing 1,980 Reactions, 159 Targets'. A sidebar on the left titled 'Filters and Analysis' shows various filters, with 'Molecular Weight' expanded to show a list of weight ranges and their corresponding counts. The main content area lists three substances: Peramivir, peramivir, and GOCarb, each with its chemical structure, molecular formula, and a list of associated data points like 'Preparations', 'Reactions', 'Targets', and 'Documents'.

Reaxys Quick search Query builder Results Synthesis planner History Sam Yu

451 Filters and Analysis 470

By Structure Measurement pX Highest Clinical Phases Targets Parameters Substance Classes Molecular Weight

Molecular Weight

- >276 - 288 1
- >300 - 312 1
- >312 - 324 10
- >324 - 336 22
- >336 - 348 12
- >348 - 360 14
- >360 - 372 10

+ More

451 Substances out of 316 Documents, containing 1,980 Reactions, 159 Targets Reaxys - 451

0 Limit To Exclude Export No of References Heatmap

1 **Peramivir**
C₁₅H₂₈N₄O₄ 328.412 8722482
Identification Preparations - 4 >
Druglikeness Reactions - 4 >
Bioactivity (All) Targets - 6 >
Other Data - 69 Documents - 168 >

2 **peramivir**
C₁₅H₂₈N₄O₄ 328.412 9011170 229614-55-5
Identification Physical Data - 5 Preparations - 12 >
Druglikeness Spectra - 8 Reactions - 14 >
Bioactivity (All) Other Data - 75 Targets - 35 >
Documents - 42 >

3 **GOCarb**
C₁₅H₂₆N₄O₄ 326.396 8042965
Identification Physical Data - 11 Preparations - 8 >
Druglikeness Spectra - 18 Reactions - 8 >

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

Targets ^

<input checked="" type="checkbox"/>	sialidase		69
<input checked="" type="checkbox"/>	neuraminidase		57
<input type="checkbox"/>	cyclin-dependent kinase 2		38
<input type="checkbox"/>	cyclin-dependent kinase 4		37
<input type="checkbox"/>	cdk2/cyclin (cyclin a)		37
<input type="checkbox"/>	cyclin-dependent kinase 1		36
<input type="checkbox"/>	tyrosine-protein kinase jak3		33

+ More

唾液酸酶，神经胺酶

Measurement pX 5 ^

<input checked="" type="checkbox"/>	>10 - 11		6
<input checked="" type="checkbox"/>	>9 - 10		20
<input checked="" type="checkbox"/>	>8 - 9		40
<input checked="" type="checkbox"/>	>7 - 8		50
<input checked="" type="checkbox"/>	>6 - 7		40
<input type="checkbox"/>	>5 - 6		44
<input type="checkbox"/>	>4 - 5		15

+ More

Reaxys中的结果

Reaxys[®] Quick search Query builder Results Synthesis planner History Sam Yu

77 Filters and Analysis

77 Substances out of 51 Documents, containing 416 Reactions, 75 Targets

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

0 Limit To Exclude Export No of References Heatmap

1 **peramivir**
C₁₅H₂₈N₄O₄ 328.412 9011170 229614-55-5

Identification Physical Data - 5 Preparations - 12 >
Druglikeness Spectra - 8 Reactions - 14 >
Bioactivity (Hit Data) Other Data - 75 Targets - 35 >
Bioactivity (All) Documents - 42 >

2 **GOCarb**
C₁₅H₂₆N₄O₄ 326.396 8042965

Identification Bioactivity (All) Preparations - 8 >
Druglikeness Physical Data - 11 Reactions - 8 >
Bioactivity (Hit Data) Spectra - 18 Targets - 28 >
Documents - 23 >

3 **peramivir**
C₁₅H₂₈N₄O₄ 328.412 9154944

Identification Bioactivity (All) Targets - 16 >
Druglikeness Physical Data - 1 Documents - 20 >

Reaxys中的结构分析

Substance Classes

- Functional Group Classification 77
- Ring Classification
- Richter Classification

+ More

不同的分类规则可以帮助对批量结构进行归纳处理

Substance Classes 2

- Substance Classes 77
 - Functional Group Classification 77
 - Ring Classification 77
 - Richter Classification 48**
 - Alicyclic Compounds 23
 - Arenes and Related Compounds 21
 - Heterocyclic Compounds 4**
 - 6-Membered Heterocycles Containing a Single N Atom 2**
 - 5-Membered Heterocycles Containing a Single Heteroatom in the Ring 1
 - 6-Membered Heterocycles Containing Two Heteroatoms 1
 - Heterocyclic Compounds - not further classified 4

Richter分类

杂环化合物

6元含有1个N原子的杂环

Selected search items:
6-Membered ... e N Atom X

Clear selected X

Limit To > Exclude >

Reaxys中的结构分析—Function Group Classification

The screenshot displays the 'Substance Classes' interface in Reaxys, showing a hierarchical tree of functional group classifications. The tree is expanded to show the 'Enol Ethers' class, which is highlighted in orange. Chinese annotations with arrows point to specific levels of the hierarchy:

- 官能团分类 (Functional Group Classification) points to the 'Functional Group Classification' folder.
- 官能团中有C=C (C=C in Functional Group) points to the 'C=C in Functional Group' folder.
- 脂肪族结构 (Aliphatic structure) points to the 'Aliphatic' folder.
- 烯醇醚结构 (Enol ether structure) points to the 'Enol Ethers' folder.

The interface also shows a 'Selected search items' section with 'Enol Ethers' selected, and buttons for 'Clear selected', 'Limit To', and 'Exclude'.

Substance Class	Count
Substance Classes	77
Functional Group Classification	77
N in Functional Group	77
O in Functional Group	77
C=C in Functional Group	45
Aliphatic	45
Alkenes	45
Enol Ethers	5
Enols	1
Aromatic	24
X in Functional Group	16
Bi-Functional Group	15

Reaxys中的结构分析—Ring Classification

The screenshot displays the 'Substance Classes' interface in Reaxys. The main list shows a hierarchical structure of substance classes with counts and toggle switches. Three items are highlighted with orange boxes and arrows pointing to Chinese labels:

- 'Ring Classification' is highlighted and labeled '环分类' (Ring Classification).
- 'cyclohexene and derivatives' is highlighted and labeled '环己烯及衍生物' (Cyclohexene and derivatives).
- 'benzene and derivatives' is highlighted and labeled '苯环及衍生物' (Benzene ring and derivatives).

Below the list, the 'Selected search items:' section shows 'cyclohexene a... ivatives' with a close button. At the bottom, there are buttons for 'Clear selected', 'Limit To', and 'Exclude'.

Substance Class	Count	Toggle
Substance Classes	77	On
Functional Group Classification	77	Off
Ring Classification	77	On
6-membered rings	51	On
cyclohexene and derivatives	50	On
6-membered rings, substituted	24	Off
benzene and derivatives	21	Off
pyridine and derivatives	2	Off
1,4,5,6-tetrahydropyridazine and derivatives	1	Off
6-membered rings, disubstituted	1	Off
6-membered rings, fused systems	1	Off
cyclohexa-1,3-diene and derivatives	1	Off

这些结构的SAR热图

