利用Reaxys快速获取海量文献和专利中的关键化学信息

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Agenda

- Reaxys介绍与内容
  - Reaxys介绍
  - Reaxys对于科技文献的提炼
- Reaxys中的化学科学数据获取
  - Reaxys中的文献快速检索方法
  - Reaxys中物质理化性质的查询与结构反查
  - 利用Reaxys进行专利突破与全新分子的专利评估
  - Reaxys中结构面板详解，合成信息的检索与合成计划制作
- Q&A

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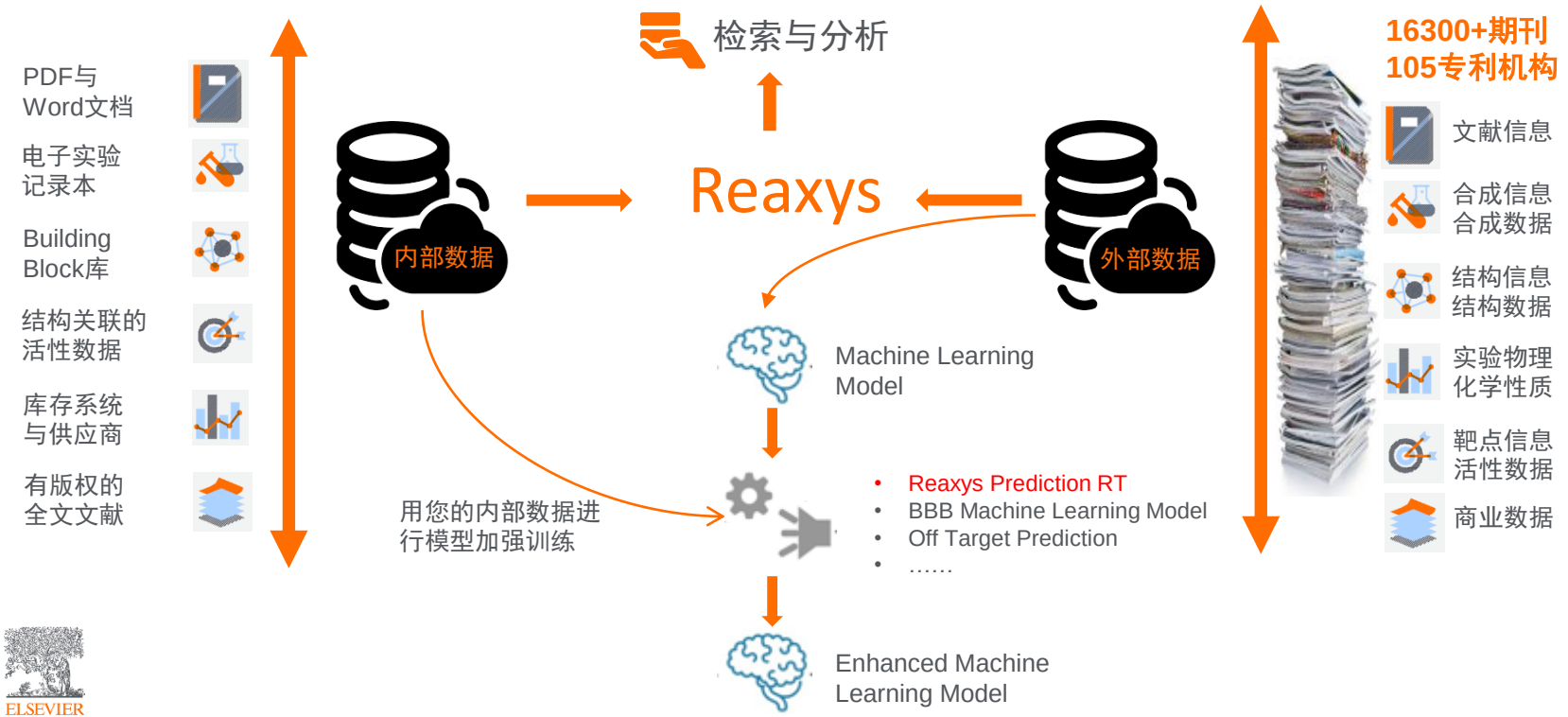
Elsevier Life Science一直致力于为全球用户提供科研数据支持

- 过去二十年， Elsevier Life Science长期以数据服务的形式为国内外的药物研究机构提供药物研发所需要的科研数据。

Reaxys—从科学数据到数据科学的跨越

Reaxys是Elsevier旗下Life Science产品线中基于数据深度提炼与挖掘，且可以整合内部与外部化学相关学科科学数据的信息检索，分析，数据科学应用平台。



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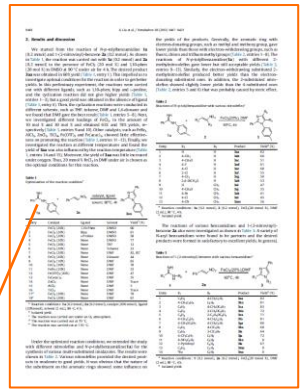
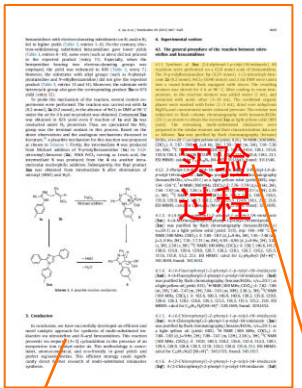
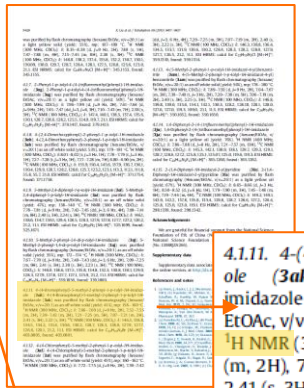
一篇常见的化学相关文献的构成





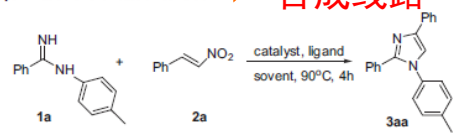


实验过程

一篇全文以及Support Information中有大量的数据，科研人员如果要获取，需要花费多的时间去阅读全文。

Table 1
Optimization of the reaction condition[a]

合成线路



结论

- 新的催化剂
- 3+2环化加成
- 区域选择性
- 环保

3. Conclusion

In conclusion, we have successfully developed an efficient and novel catalytic approach for synthesis of multi-substituted imidazoles via nitroolefins and *N*-aryl benzamidines. This reaction proceeds via stepwise [3+2] cycloaddition in the presence of an inexpensive iron catalyst under air. This methodology is convenient, atom-economical, and eco-friendly in good yields and prefect regioselectivities. This efficient strategy could significantly direct further research of multi-substituted imidazoles synthesis.

*4.1.11. 4-(4-Bromophenyl)-5-methyl-2-phenyl-1-p-tolyl-1H-imidazole (**3ak**).* 4-(4-Bromophenyl)-5-methyl-2-phenyl-1-*p*-tolyl-1*H*-imidazole (**3ak**) was purified by flash chromatography (hexane/EtOAc, v/v=20:1) as an off white solid (yield: 41%), mp: 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.66–7.69 (d, J=9 Hz, 2H), 7.52–7.55 (m, 2H), 7.39–7.42 (m, 2H), 7.21–7.25 (m, 5H), 7.07–7.21 (m, 2H), 2.41 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ: 146.3, 138.8, 134.5, 134.2, 131.4, 130.6, 130.2, 128.7, 128.3, 128.0, 127.9, 127.7, 126.6, 120.1, 21.2, 11.1. ESI HRMS: calcd for $C_{22}H_{19}N_2Br$ [M+H]$^+$: 403.0805, found: 403.0801.

化合物性质数据

4.1. The general procedure of the reaction between nitroolefins and benzamidines

*4.1.1. Synthesis of **3aa** (2,4-diphenyl-1-p-tolyl-1H-imidazole).* All reactions were performed on a 0.20 mmol scale of benzamidine. The *N*-*p*-tolylbenzamidine **1a** (0.20 mmol), 1-(2-nitrovinyl)-benzene **2a** (0.2 mmol), $FeCl_3$ (0.040 mmol) and 2 mL DMF were taken into a round bottom flask equipped with stirrer. The resulting mixture was stirred for 4 h at 90 °C. After cooling to room temperature, to the reaction mixture was added water (2 mL), and extracted with acetic ether (3×10 mL). The combined organic phases were washed with brine (2×5 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash column chromatography with hexanes/EtOAc (20:1) as eluent to obtain the desired **3aa** as light yellow solid (90% yield). The remaining multi-substituted imidazoles were

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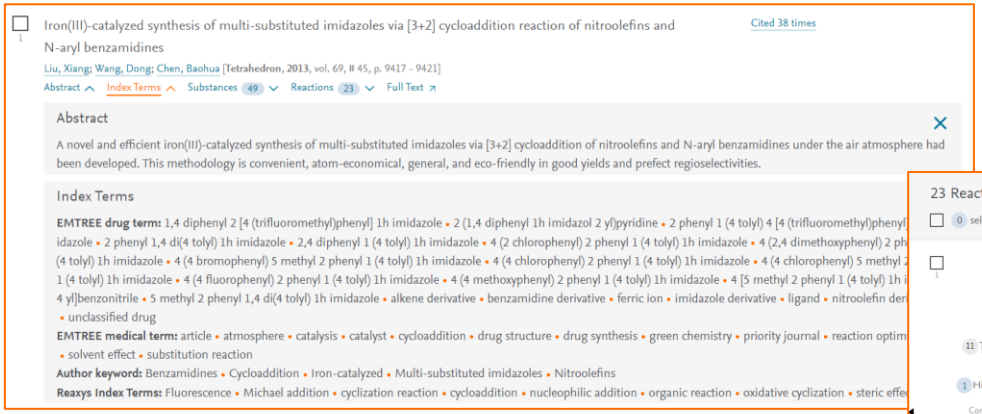
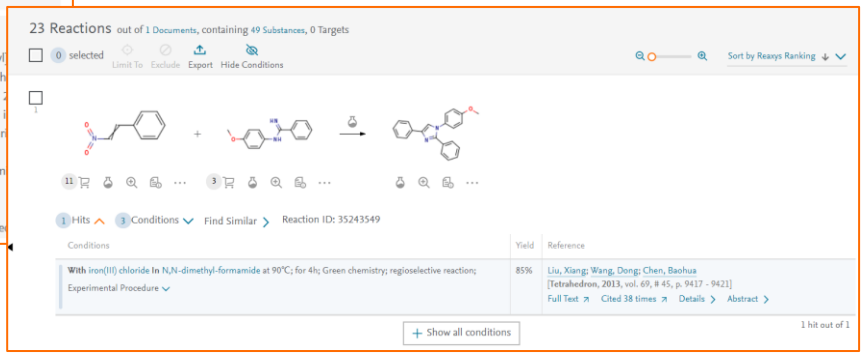
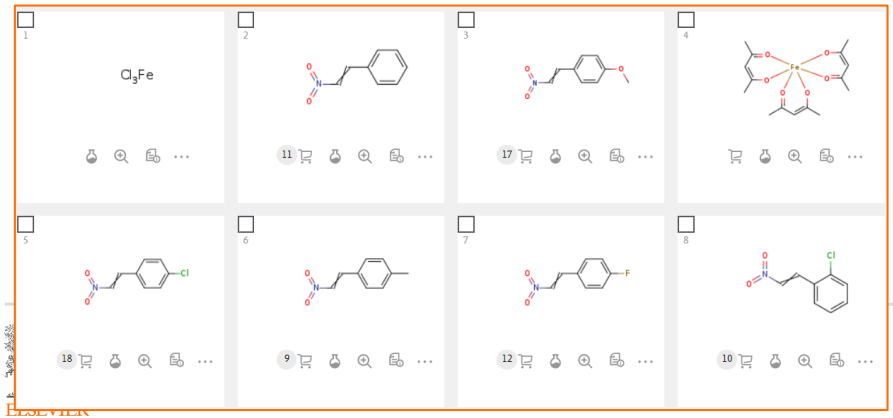
Reaxys对这篇全文的提炼—概览







Reaxys提炼全文中的：

- 题录，摘要，关键词
- 物质结构，
- 反应Scheme

Reaxys对全文中的化合物（产物）的相关数据提炼

*4.1.11. 4-(4-Bromophenyl)-5-methyl-2-phenyl-1-p-tolyl-1H-imidazole (**3ak**).* 4-(4-Bromophenyl)-5-methyl-2-phenyl-1-*p*-tolyl-1*H*-imidazole (**3ak**) was purified by flash chromatography (hexane/EtOAc, v/v=20:1) as an off white solid (yield: 41%), mp: 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.66–7.69 (d, *J*=9 Hz, 2H), 7.52–7.55 (m, 2H), 7.39–7.42 (m, 2H), 7.21–7.25 (m, 5H), 7.07–7.21 (m, 2H), 2.41 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ: 146.3, 138.8, 134.5, 134.2, 131.4, 130.6, 130.2, 128.7, 128.3, 128.0, 127.9, 127.7, 126.6, 120.1, 21.2, 11.1. ESI HRMS: calcd for $C_{22}H_{19}N_2Br$ $[M+H]^+$: 403.0805, found: 403.0801.

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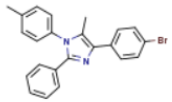

4-(4-bromophenyl)-5-methyl-2-phenyl-1-(p-tolyl)-1H-imidazole

$C_{23}H_{19}BrN_2$ 403.321 24040362 1462876-22-7

Hit Data - 6 | Druglikeness | Spectra - 3

Identification | Physical Data - 2

NMR Spectroscopy - 2 hits out of 2

Description (NMR Spectroscopy)	Nucleus (NMR Spectroscopy)	Solvents (NMR Spectroscopy)	Frequency (NMR Spectroscopy), MHz	Original Text (NMR Spectroscopy)
Chemical shifts, Spectrum	1H	chloroform-d1	300	^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.66-7.69 (d, J=9 Hz, 2H), 7.52-7.55 (m, 2H), 7.39-7.42 (m, 2H), 7.21-7.25 (m, 5H), 7.07-7.21 (m, 2H), 2.41 (s, 3H), 2.22 (s, 3H)
Chemical shifts, Spectrum	13C	chloroform-d1	100	^{13}C NMR (100 MHz, $CDCl_3$): δ: 146.3, 138.8, 134.5, 134.2, 131.4, 130.6, 130.2, 128.7, 128.3, 128.0, 127.9, 127.7, 126.6, 120.1, 21.2, 11.1

Description (Mass Spectrometry)

high resolution mass spectrometry (HRMS), electrospray ionisation (ESI), spectrum

Hit Data - 6

- Substance Label - 1 hits out of 1
- Melting Point - 1 hits out of 1
- Crystal Property Description - 1 hits out of 1
- NMR Spectroscopy - 2 hits out of 2
- Mass Spectrometry - 1 hits out of 1

Label

3ak

Melting Point, °C

158 - 160

Colour & Other Properties

white

Peak

403.0801 m/z

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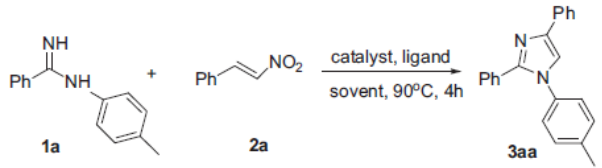
Reaxys对全文中的化合物（催化剂）的相关数据提炼

Table 1
Optimization of the reaction condition[a]



Entry	Catalyst	Ligand	Solvent	Yield[b] (%)
1	$FeCl_3$ (20%)	1,10-Phen	DMSO	60
2	$FeCl_3$ (20%)	Bipy	DMSO	61
3	$FeCl_3$ (20%)	L-Proline	DMSO	58
4	$FeCl_3$ (20%)	None	DMSO	77
5	$FeCl_3$ (20%)	None	THF	12
6	$FeCl_3$ (20%)	None	Toluene	23
7	$FeCl_3$ (20%)	None	DMF	82, 82[c]
8	$FeCl_3$ (20%)	None	Dioxane	44
9	$FeCl_3$ (10%)	None	DMF	65
10	$FeCl_3$ (30%)	None	DMF	78
11	$FeBr_3$ (20%)	None	DMF	53
12	$Fe(OTf)_3$ (20%)	None	DMF	47
13	$Fe(acac)_3$	None	DMF	55
14	$ZnCl_2$	None	DMF	Trace
15	$AlCl_3$	None	DMF	5
16	$TiCl_4$	None	DMF	Trace
17[d]	$FeCl_3$ (20%)	None	DMF	79
18[e]	$FeCl_3$ (20%)	None	DMF	67

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (20% mmol), ligand (20%mmol), solvent (2 mL), 90 °C, 4 h.
[b] Isolated yield.
[c] The reaction was carried out under an O_2 atmosphere.
[d] The reaction was carried out at 70 °C.
[e] The reaction was carried out at 110 °C.

Cl_3Fe

iron(III) chloride

Cl_3Fe 162.206 11323458 Retrieve CAS RN

Hit Data - 4 | Physical Data - 26
Identification | Spectra - 58
Druglikeness | Other Data - 128
Bioactivity (All)

Hit Data - 4

Catalyst Investigation - 4 hits out of 303

Show/Hide columns

Investigated characteristic(s)	Specification of catalysis	Type of reaction (Catalyst Investigation)	Co-catalyst/co-substrate name	Reference
Catalytic activity	Regioselective catalysis	Cycloaddition		Liu, Xiang; Wang, Dong; Chen, Baohua[Tetrahedron, 2013, vol. 69, # 45, p. 9417 - 9421] Full Text Cited 38 times Details Abstract
Catalytic activity	Regioselective catalysis	Cycloaddition	[2,2]bipyridinyl	Liu, Xiang; Wang, Dong; Chen, Baohua[Tetrahedron, 2013, vol. 69, # 45, p. 9417 - 9421] Full Text Cited 38 times Details Abstract
Catalytic activity	Regioselective catalysis	Cycloaddition	1,10-Phenanthroline	Liu, Xiang; Wang, Dong; Chen, Baohua[Tetrahedron, 2013, vol. 69, # 45, p. 9417 - 9421] Full Text Cited 38 times Details Abstract
Catalytic activity	Regioselective catalysis	Cycloaddition	L-proline	Liu, Xiang; Wang, Dong; Chen, Baohua[Tetrahedron, 2013, vol. 69, # 45, p. 9417 - 9421] Full Text Cited 38 times Details Abstract

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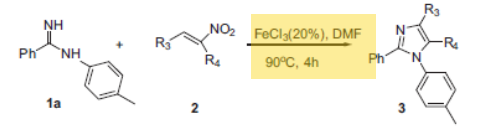
Reaxys对全文中的合成线路的相关数据提炼

Table 2
Reactions of *N*-*p*-tolylbenzamidine with various nitroolefins[a]



Entry	R_3	R_4	Product	Yield[b] (%)
1	H	H	**3aa**	82
2	4-CH_3	H	**3ab**	60
3	4-CH_3O	H	**3ac**	51
4	4-F	H	**3ad**	61
5	4-Cl	H	**3ae**	68
6	2-Cl	H	**3af**	55
7	4-CF_3	H	**3ag**	50
8	2,4-$DiCH_3O$	H	**3ah**	53
9	H	CH_3	**3ai**	47
10	4-CH_3O	CH_3	**3aj**	35
11	4-Br	CH_3	**3ak**	41
12	4-Cl	CH_3	**3al**	45
13	4-CN	CH_3	**3am**	56

3. Conclusion

In conclusion, we have successfully developed an efficient and novel catalytic approach for synthesis of multi-substituted imidazoles via nitroolefins and *N*-aryl benzamidines. This reaction proceeds via stepwise [3+2] cycloaddition in the presence of an inexpensive iron catalyst under air. This methodology is convenient, atom-economical, and eco-friendly in good yields and prefect regioselectivities. This efficient strategy could significantly direct further research of multi-substituted imidazoles synthesis.

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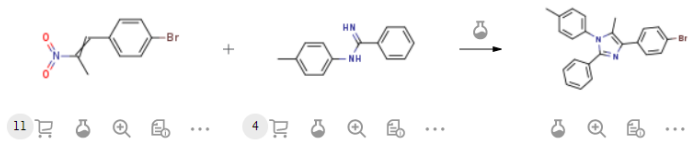

1 Hits/Conditions | Find Similar | Reaction ID: 36429699

Conditions	Yield	Reference
With iron(III) chloride In N,N-dimethyl-formamide at 90°C; for 4h; Green chemistry; regioselective reaction; Experimental Procedure	41%	Liu, Xiang; Wang, Dong; Chen, Baohua [Tetrahedron, 2013, vol. 69, # 45, p. 9417 - 9421] Full Text ↗ Cited 38 times ↗ Details ❯ Abstract ❯

11 The general procedure of the reaction between nitroolefins and benzamidines

General procedure: 4.1.1 Synthesis of 3aa (2,4-diphenyl-1-p-tolyl-1H-imidazole) All reactions were performed on a 0.20mmol scale of benzamidine. The N-p-tolylbenzamidine 1a (0.20mmol), 1-(2-nitrovinyl)-benzene 2a (0.2mmol), $FeCl_3$ (0.040mmol) and 2mL DMF were taken into a round bottom flask equipped with stirrer. The resulting mixture was stirred for 4h at 90°C. After cooling to room temperature, to the reaction mixture was added water (2mL), and extracted with acetic ether (3×10mL). The combined organic phases were washed with brine (2×5mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash column chromatography with hexanes/EtOAc (20:1) as eluent to obtain the desired 3aa as light yellow solid (90% yield). The remaining multi-substituted imidazoles were preparedin the similar manner and their characterization data are as follows: 3aa was purified by flash chromatography (hexane/EtOAc, v/v=20:1) as light yellow oil (yield: 82%). 4.1.11 4-(4-Bromophenyl)-5-methyl-2-phenyl-1-p-tolyl-1H-imidazole (3ak)
4-(4-Bromophenyl)-5-methyl-2-phenyl-1-p-tolyl-1H-imidazole (3ak) was purified by flash chromatography (hexane/EtOAc, v/v=20:1) as an off white solid (yield: 41%), mp: 158-160 °C. ^1H NMR (300 MHz, $CDCl_3$): δ: 7.66-7.69 (d, J=9 Hz, 2H), 7.52-7.55 (m, 2H), 7.39-7.42 (m, 2H), 7.21-7.25 (m, 5H), 7.07-7.21 (m, 2H), 2.41 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ: 146.3, 138.8, 134.5, 134.2, 131.4, 130.6, 130.2, 128.7, 128.3, 128.0, 127.9, 127.7, 126.6, 120.1, 21.2, 11.1. ESI HRMS: calcd for $C_{22}H_{19}N_2Br$ $[M+H]^+$: 403.0805, found: 403.0801.

实验过程与条件

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Reaxys从文献中提炼出来的内容

文献记录：
>94.7 million
16300+期刊
105专利机构的专利
38万书的章节

化合物记录：
>170 million
期刊，专利，商品
2022年中前完成105家专利机构中专利物质的回溯

化学反应记录：
>57.8 million
单步多步反应，同时提炼文献与专利中的实验过程

实验性质记录：
> 500 million
化合物实验数据，并提炼实验数据检测条件

生物活性记录：
> 41.9 million数据
> 35,000靶点
> 7.9 million化合物
化合物在不同生物体内活性数据

数据更新时间：2022/2/7

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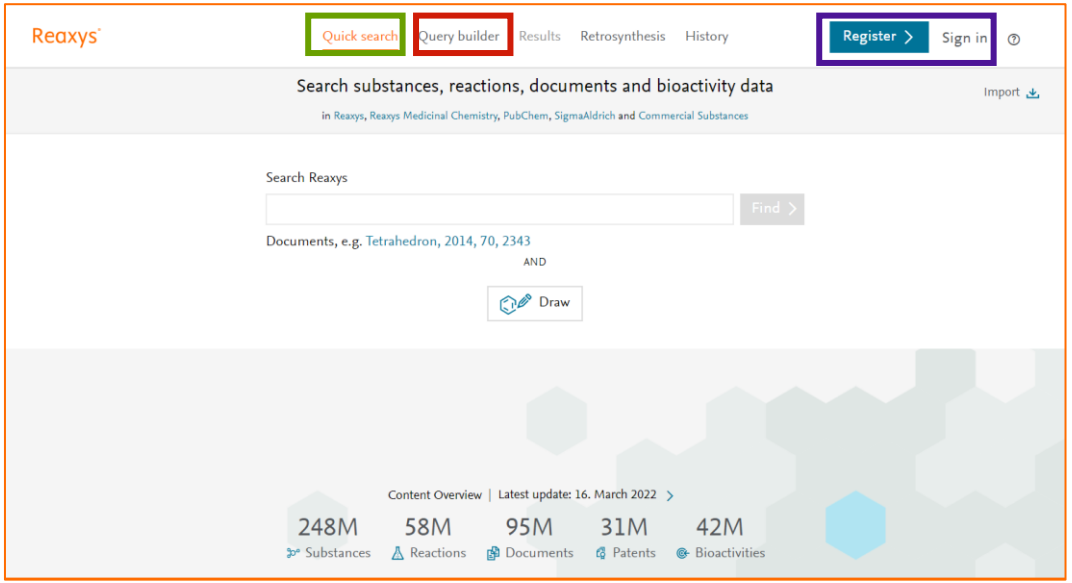
Reaxys的登录界面

- IP范围内，浏览器输入www.Reaxys.com或asia.Reaxys.com,可以直接进行检索，推荐Chrome，Firefox浏览器。



Tips:

1. 账号注册（可选），注册帐号后，可以使用提醒，结果集保存，结果导出功能
2. Quick Search，快速检索，结构反应检索，或者输入自然语言，Reaxys智能分析语义进行检索。
3. Query Builder，组合检索，利用Reaxys中的各种字段进行组合，实现不同检索需求。

视频介绍：

1. Reaxys主界面：https://www.bilibili.com/video/BV1T5411L7Ec
2. Quick Search：https://www.bilibili.com/video/BV1az4y1C7ZL
3. Query Builder：https://www.bilibili.com/video/BV1UK4y1774Q
4. Reaxys账号注册与应用https://www.bilibili.com/video/BV1NA41147if

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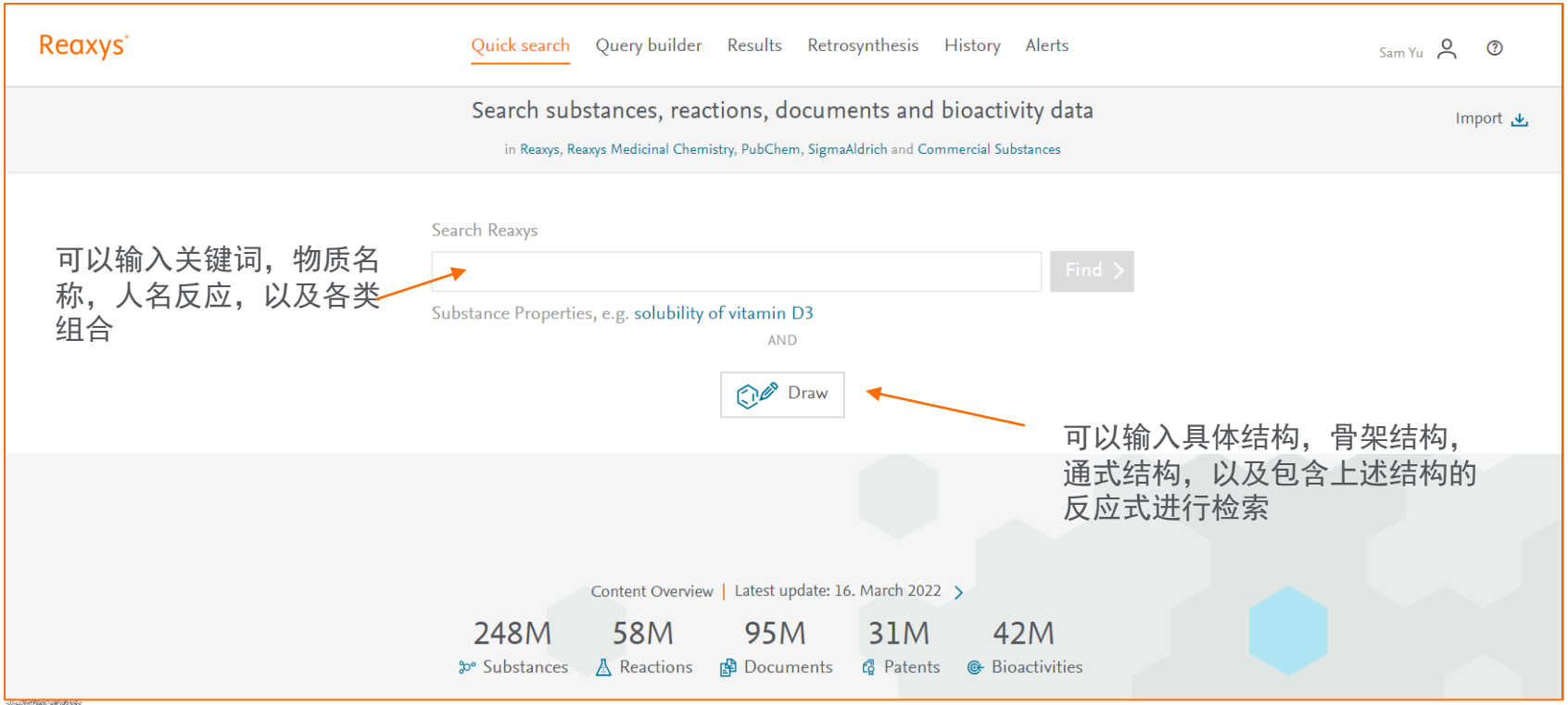
Quick Search界面



可以输入关键词，物质名称，人名反应，以及各类组合

可以输入具体结构，骨架结构，通式结构，以及包含上述结构的反应式进行检索

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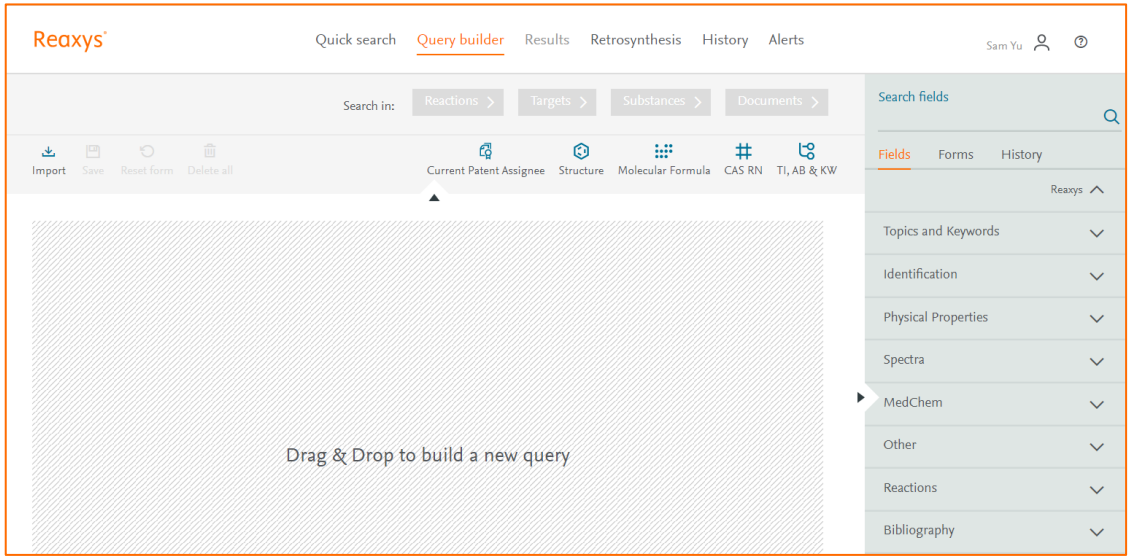
Reaxys中的Query Builder是一种高级的组合检索模式



Reaxys中的Query Builder可以按照一定的规则构建检索式，Reaxys一共提供180+字段和字段组，科研人员可以自由的对这些字段和字段组进行组合，同时Reaxys也根据一些常见的需求，内置了多种检索策略模板，如“天然产物”，“hERG”等

Query Builder的使用步骤，第一步是选择字段，第二步是输入条件，第三步是确定不同字段之间的逻辑关系

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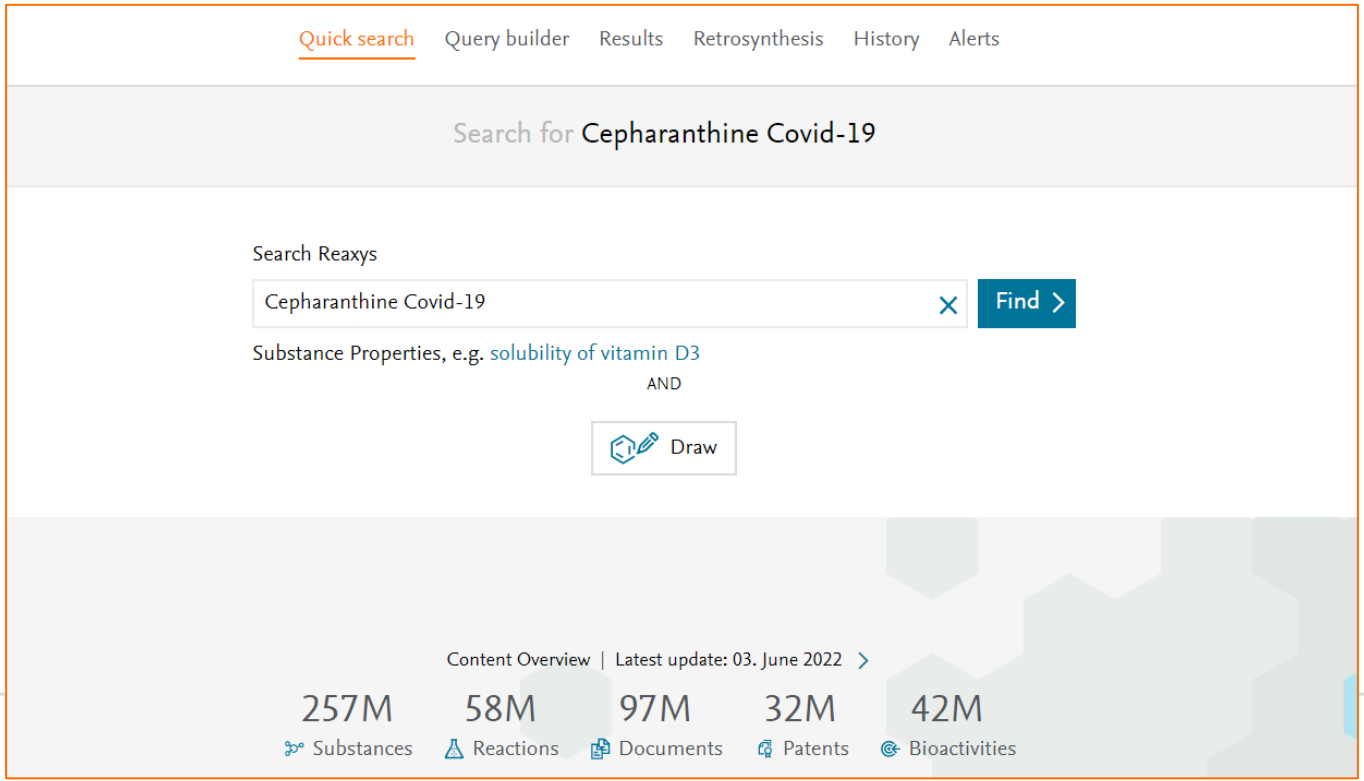
  - Reaxys中的文献快速检索方法
  - Reaxys中物质理化性质的查询与结构反查
  - 利用Reaxys进行专利突破与全新分子的专利评估
  - Reaxys中结构面板详解，合成信息的检索与合成计划制作
- Q&A

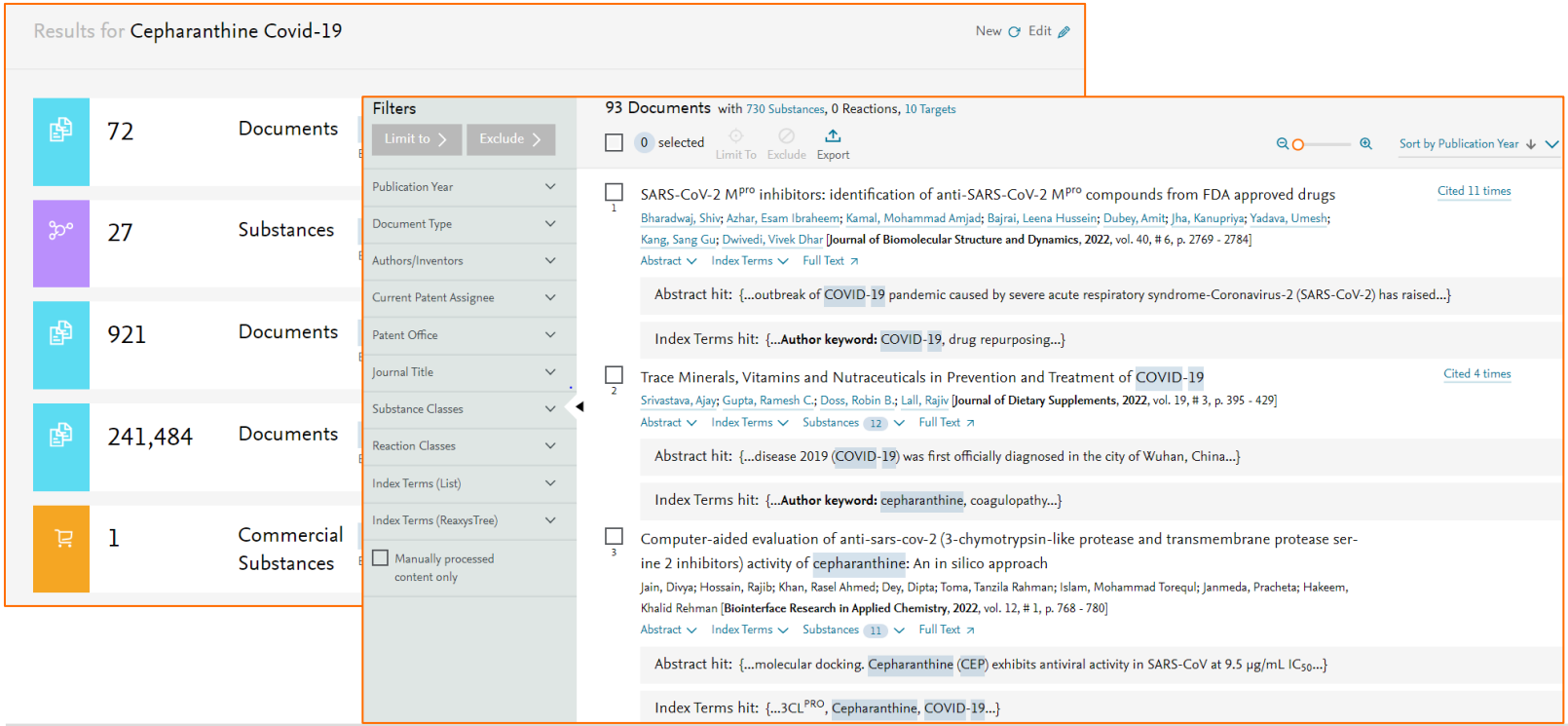
Case 1：关键词检索—千金藤素 Covid-19

- Cepharanthine Covid-19



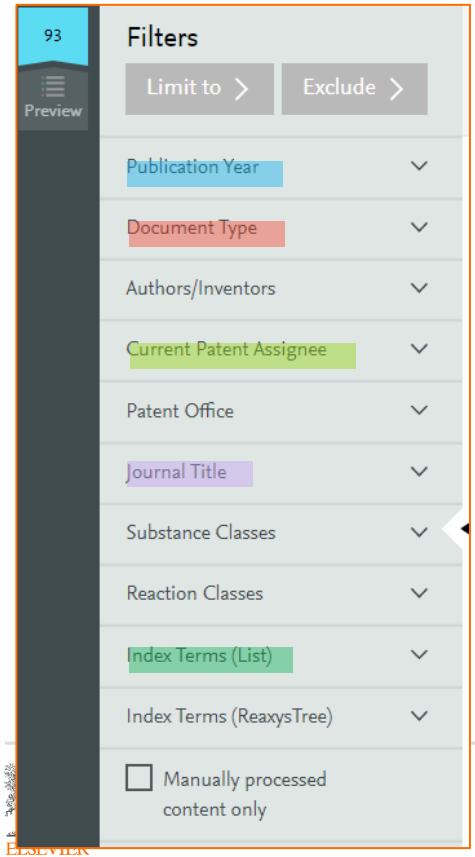
ELSEVIER

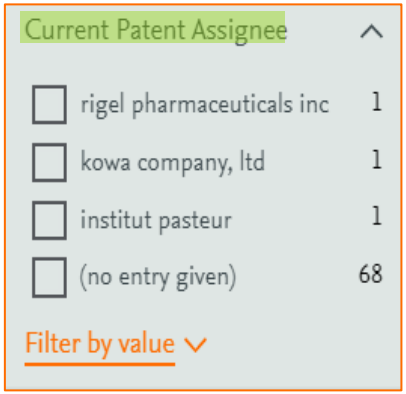
Reaxys中的检索结果

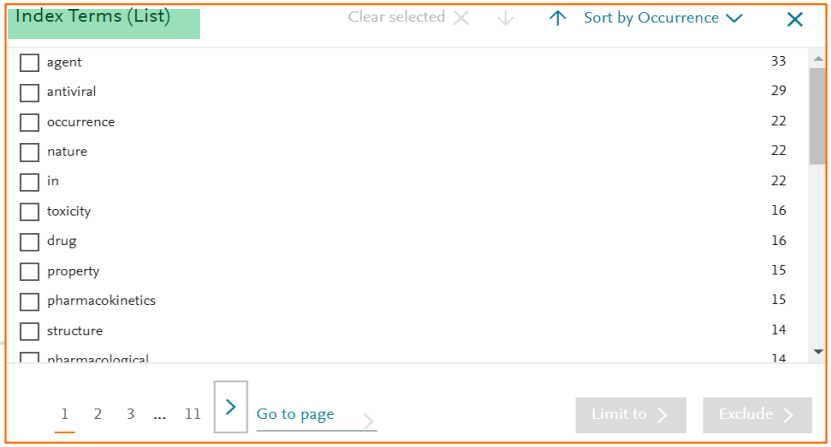


ELSEVIER

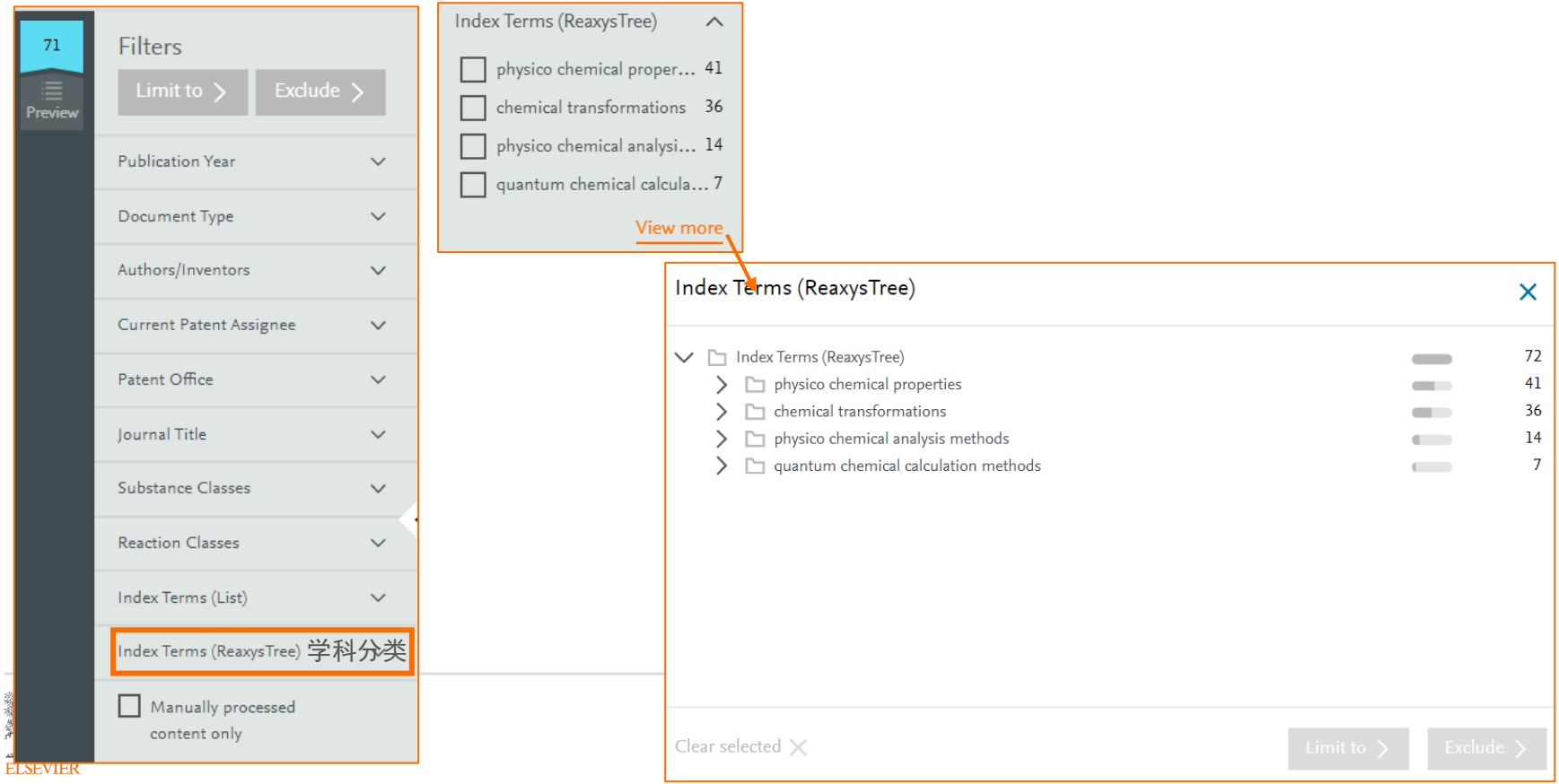
Reaxys中对于文献检索结果的分析



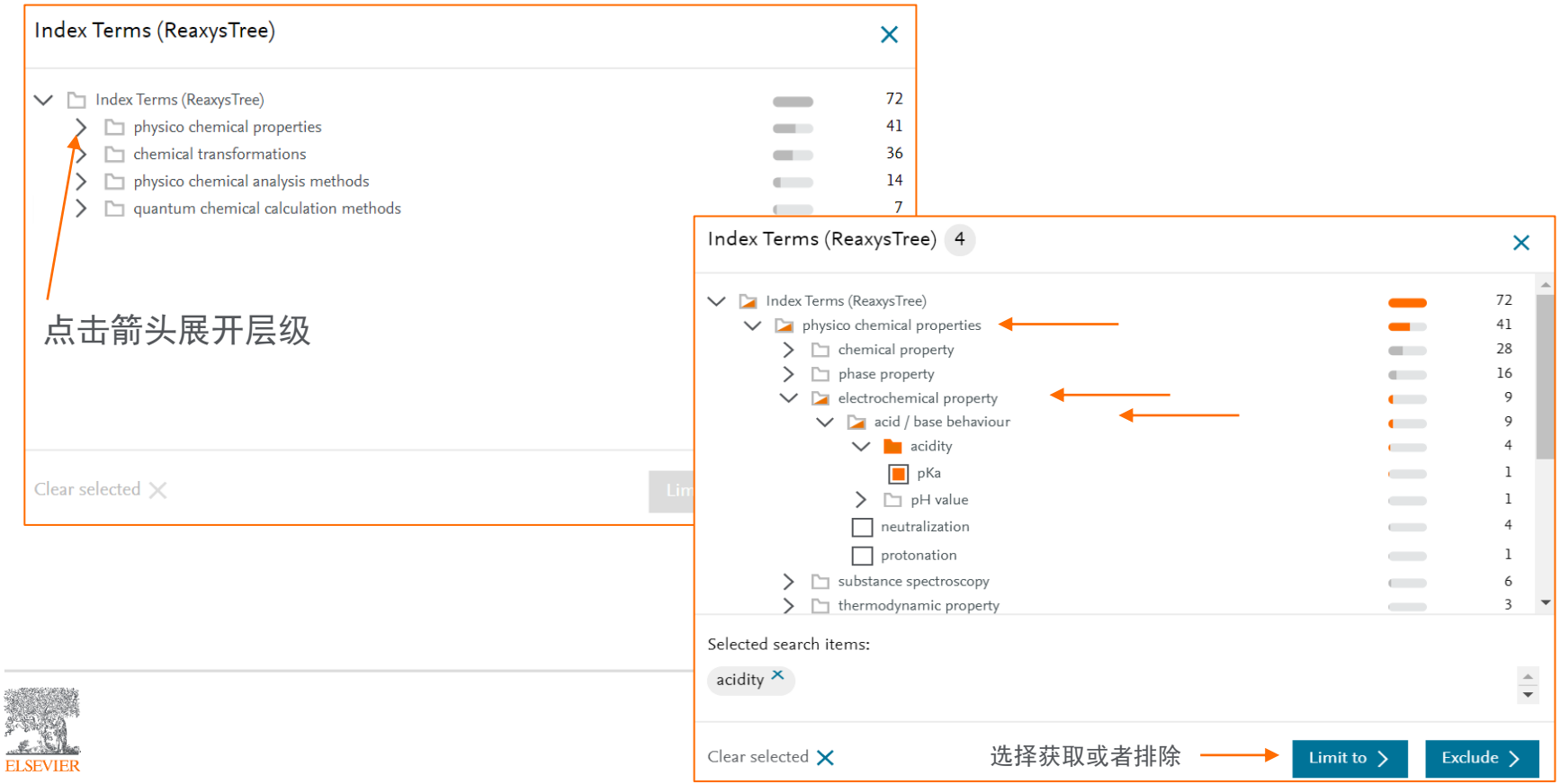




Reaxys中的Index Terms（Reaxys Tree）学科分类



利用树状图进行学科分类



ELSEVIER

最后的检索结果

2 Computer-aided evaluation of anti-sars-cov-2 (3-chymotrypsin-like protease and transmembrane protease serine 2 inhibitors) activity of cepharanthine: An in silico approach

Jain, Divya; Hossain, Rajib; Khan, Rasel Ahmed; Dey, Dipta; Toma, Tanzila Rahman; Islam, Mohammad Torequl; Janmeda, Pracheta; Hakeem, Khalid Rehman [**Biointerface Research in Applied Chemistry**, **2022**, vol. 12, # 1, p. 768 - 780]

Abstract ^ Index Terms ^ Substances 11 v Full Text ↗

全文链接，如果是OA或者学校已经订购可以直接打开

Abstract

3-chymotrypsin-like protease ($3CL^{PRO}$) is found in severe acute respiratory syndrome coronavirus (SARS CoV)-2, and transmembrane protease serine 2 (TMPRSS-2) in humans, both of them have a role in viral attachment and proliferation. $3CL^{PRO}$ and TMPRSS-2 are the most vital target for the discovery of an anti-corona virus. One efficient approach used to screen potential active compounds against specific target proteins, such as $3CL^{PRO}$ and TMPRSS-2, is molecular docking. Cepharanthine (CEP) exhibits antiviral activity in SARS-CoV at 9.5 μg/mL IC_{50} level. This study aims to perform an in silico study on CEP against non-structural SARS-CoV-2 $3CL^{PRO}$ and host transmembrane protease serine 2 protein. Molecular docking studies were carried out using compounds against $3CL^{PRO}$ and TMPRSS-2 proteins through Swiss model, Uniport, PROCHECK, Swiss PDB viewer, PyMol, and PyRx computerized software. CEP displayed strong binding interactions-8.5 and-7.4 Kcal/mol with the $3CL^{PRO}$, and TMPRSS-2 proteins. In all cases, CEP showed better binding affinities than FDA-approved anti-corona virus drug (Camostat mesylate, CAM) is currently underused in COVID-19. CEP may be one of the potentials leads to fighting against SARS-CoV-2. Further in vivo studies should be required to support the findings of this study.

Index Terms

Author keyword: $3CL^{PRO}$ • Cepharanthine • COVID-19 • Molecular docking • PkCSM, Swiss–ADME • TMPRSS2

Reaxys Index Terms: Hydrogen bond • IC50 • LD50 • Permeability • Pi-pi interaction • antiviral agent • bioavailability • hydrophobic surface • hydrophobicity • lipophilicity • occurrence in nature • pharmacokinetics • reactivity • toxicity

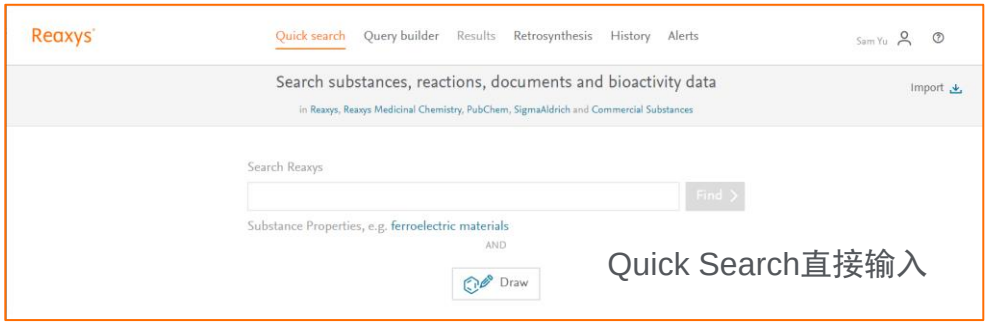
ELSEVIER

Agenda

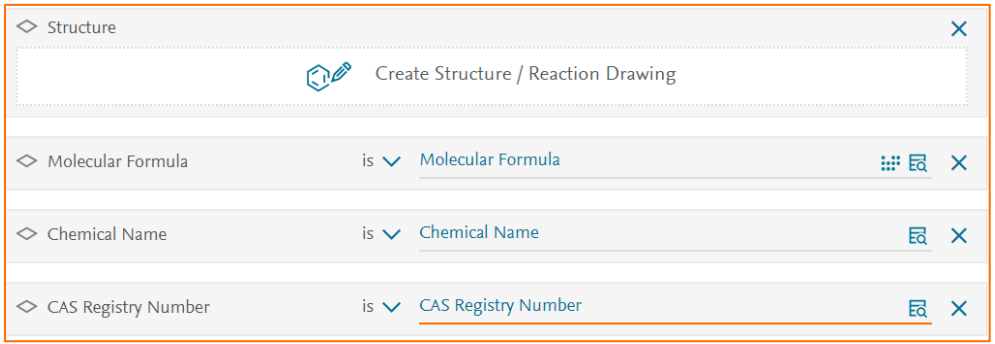
- Reaxys介绍与内容
  - Reaxys介绍
  - Reaxys对于科技文献的提炼
- Reaxys中的化学科学数据获取
  - Reaxys中的文献快速检索方法
  - Reaxys中物质理化性质的查询与结构反查
  - 利用Reaxys进行专利突破与全新分子的专利评估
  - Reaxys中结构面板详解，合成信息的检索与合成计划制作
- Q&A

Reaxys中的结构获取物质的常用方法小结

- Reaxys中获取物质的方法
  - 物质名称
  - 物质分子式
  - 物质结构式
  - CAS No



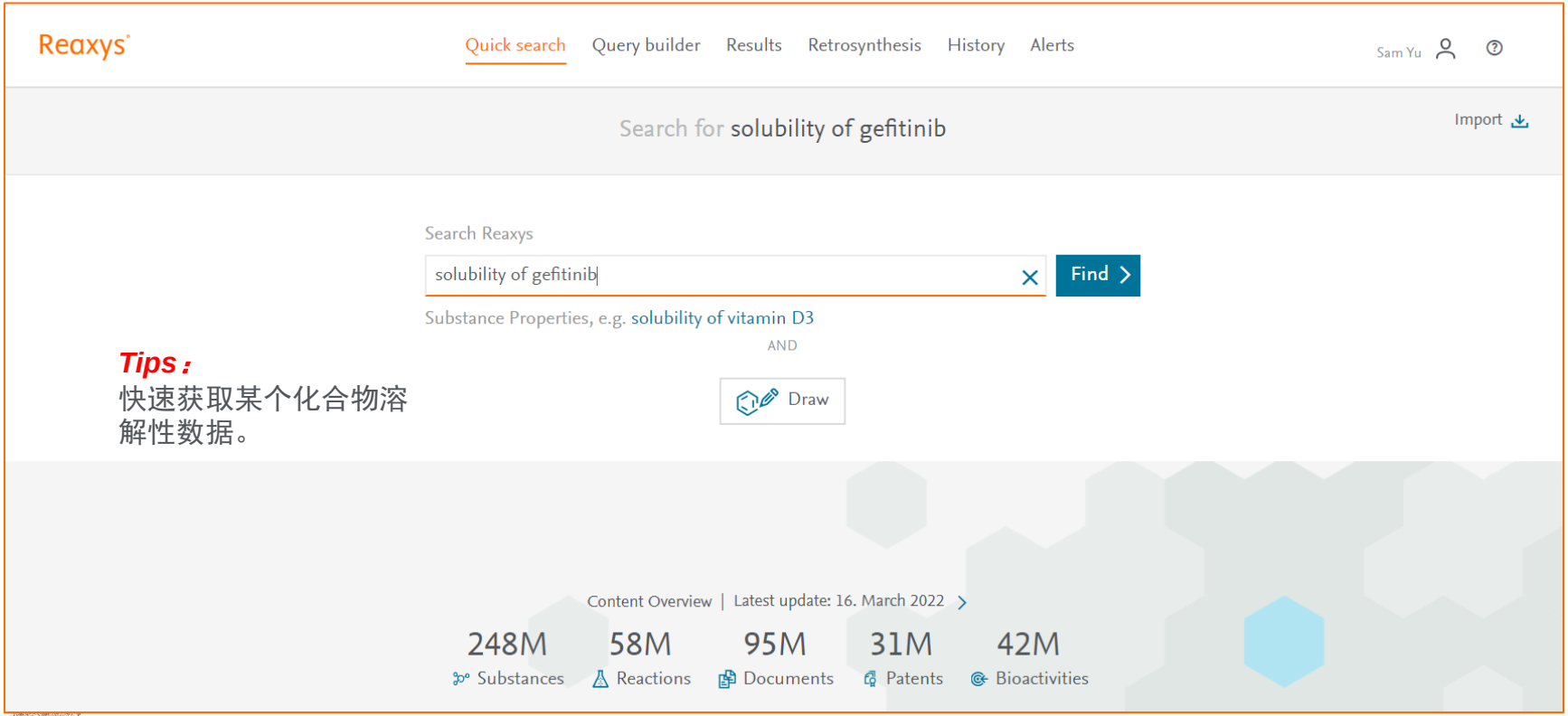
Quick Search直接输入



Query Builder选择不同字段

ELSEVIER

Case 2：Reaxys中化合物理化性质的快速获取

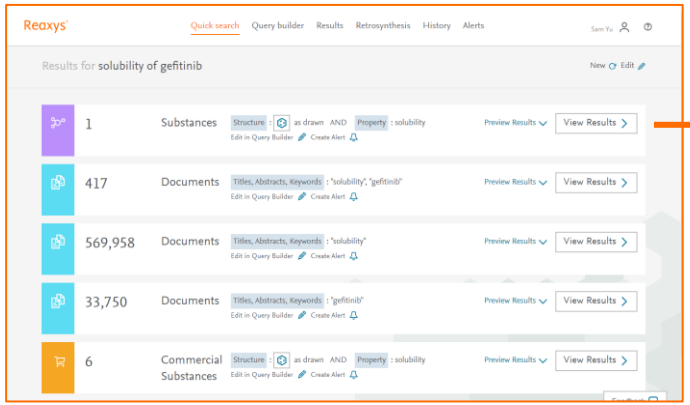


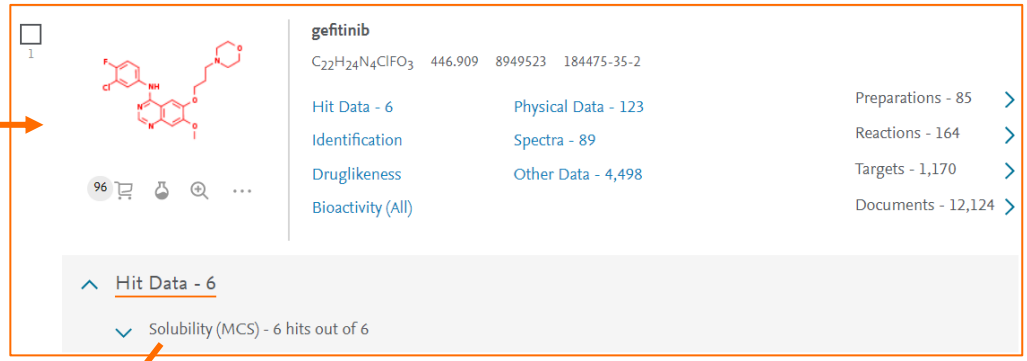
Tips：

快速获取某个化合物溶解性数据。

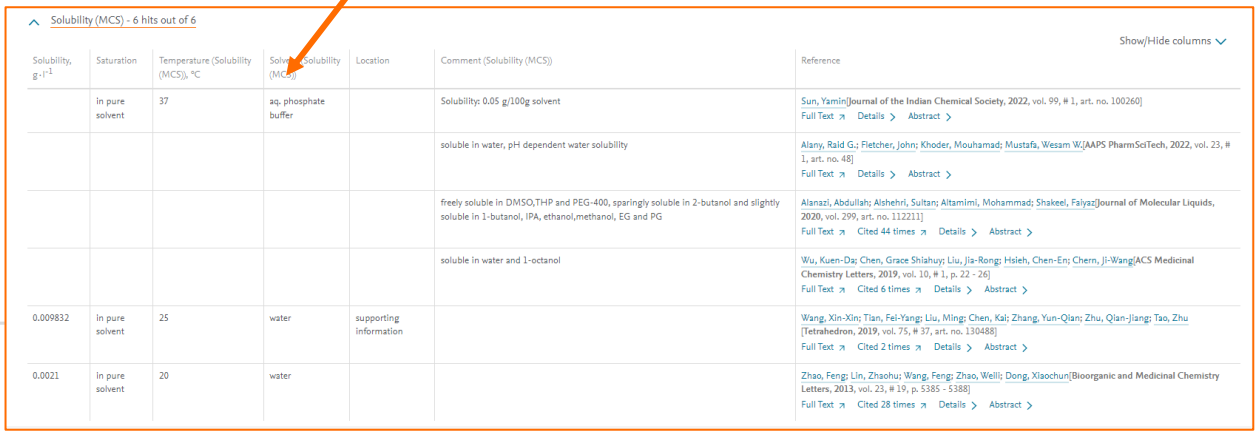
ELSEVIER

Reaxys中的结果



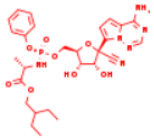


抽提的数据包括具体的数值，
或者相关的文字性描述



ELSEVIER

Reaxys中理化性质



(2S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate

$C_{27}H_{35}N_6O_8P$ 602.584 29506468 1809249-37-3

Identification | Bioactivity (All) | Spectra - 21

Druglikeness | Physical Data - 20 | Other Data - 89

Preparations - 79 >

Reactions - 85 >

Targets - 14 >

Documents - 108 >

Physical Data - 20

- Melting Point - 3
- Chromatographic Data - 6
- Crystal Phase - 3
- Crystal Property Description - 3
- Optical Rotatory Power - 2
- Space Group - 3

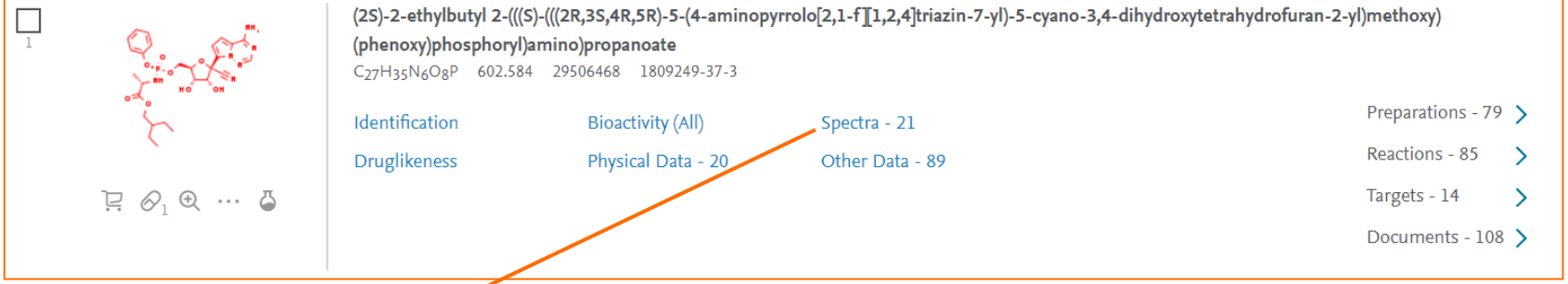
Optical Rotatory Power - 2

Show/Hide columns

Type (Optical Rotatory Power)	Concentration (Optical Rotatory Power)	Length of Path, cm	Solvent (Optical Rotatory Power)	Optical Rotatory Power, deg	Wavelength (Optical Rotatory Power), nm	Temperature (Optical Rotatory Power), °C	Location	Reference
[alpha]	0.2 g/100ml	5	dichloromethane	-24	589	25	supporting information	Chen, Jianzhong; Huo, Xiaohong; Li, Panpan; Wang, Mo; Wu, Zhengxing; Yuan, Qianjia; Zhang, Lu; Zhang, Wanbin; Zhang, Zhenfeng; Zou, Yashi[**Angewandte Chemie - International Edition, 2020**, vol. 59, # 47, p. 20814 - 20819][**Angew. Chem., 2020**, vol. 132, # 47, p. 21000 - 21005,6] Full Text ↗ Cited 18 times ↗ Details > Abstract >
[alpha]	1 g/100ml		methanol	-21	589	21		Siegel, Dustin; Hui, Hon C.; Doerffler, Edward; Clarke, Michael O.; Chun, Kwon; Zhang, Lijun; Neville, Sean; (...) Warren, Travis K.; Mackman, Richard L.[**Journal of Medicinal Chemistry, 2017**, vol. 60, # 5, p. 1648 - 1661] Full Text ↗ Cited 302 times ↗ Details > Abstract >

ELSEVIER

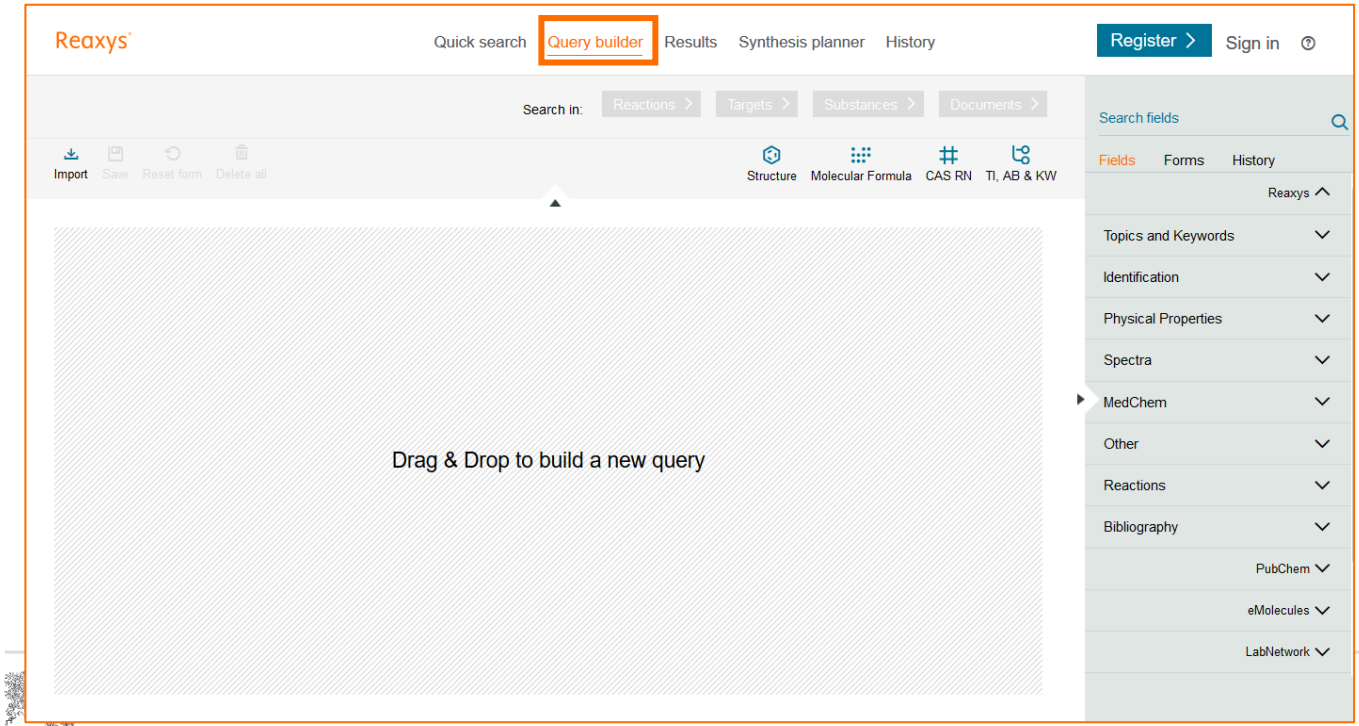
Reaxys中的谱图



ELSEVIER

Case 3：特定条件下理化性质的获取

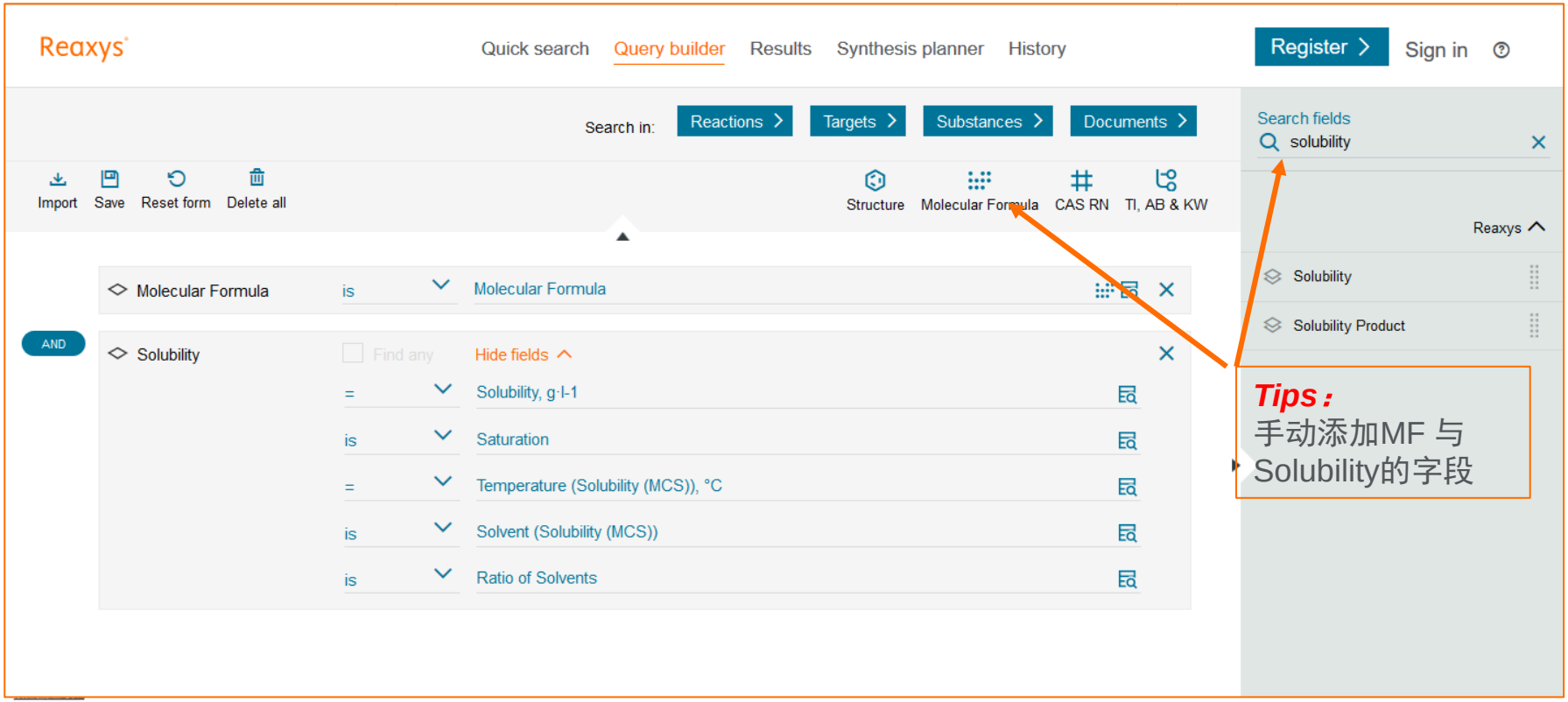
- 获取KCl在乙醇中的溶解度



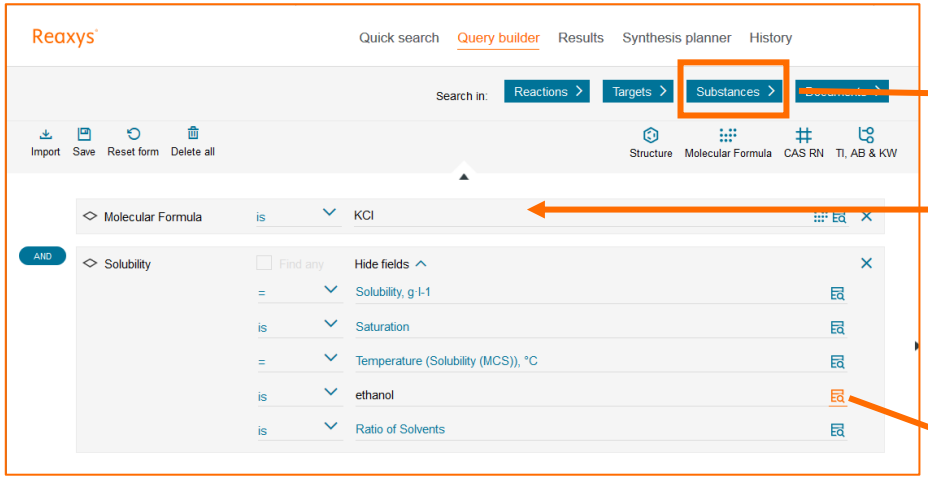
Reaxys中的Query Builder可以按照一定的规则构建检索式，Reaxys一共提供180+字段和字段组，科研人员可以自由的对这些字段和字段组进行组合，同时Reaxys也根据一些常见的需求，内置了多种检索策略模板，如“天然产物”，“hERG”等

ELSEVIER

检索策略的构建

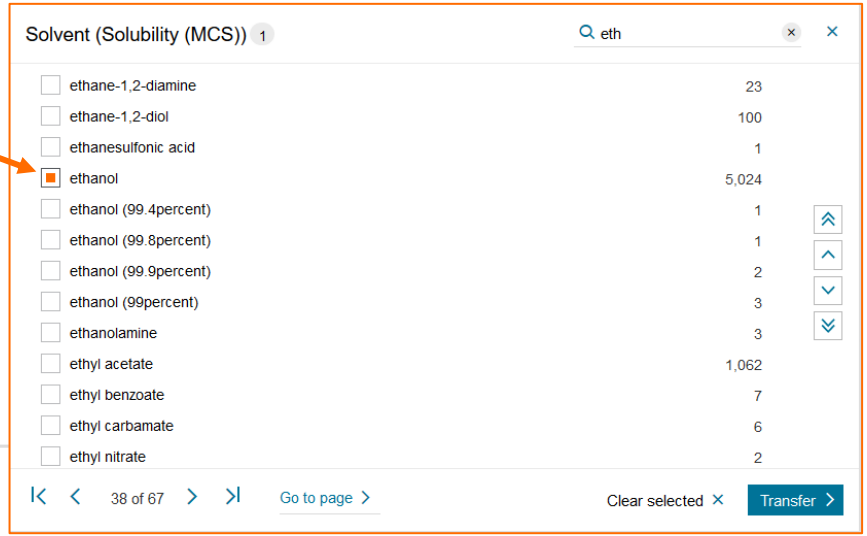

Reaxys
Quick search
Query builder
Results
Synthesis planner
History
Register
Sign in
Search in:
Reactions
Targets
Substances
Documents
Import
Save
Reset form
Delete all
Structure
Molecular Formula
CAS RN
TI, AB & KW
Molecular Formula
is
Molecular Formula
AND
Solubility
Find any
Hide fields
=
Solubility, g·l-1
is
Saturation
=
Temperature (Solubility (MCS)), °C
is
Solvent (Solubility (MCS))
is
Ratio of Solvents
Search fields
solubility
Reaxys
Solubility
Solubility Product
Tips：
手动添加MF 与
Solubility的字段

条件的输入



Step3：进行物质检索

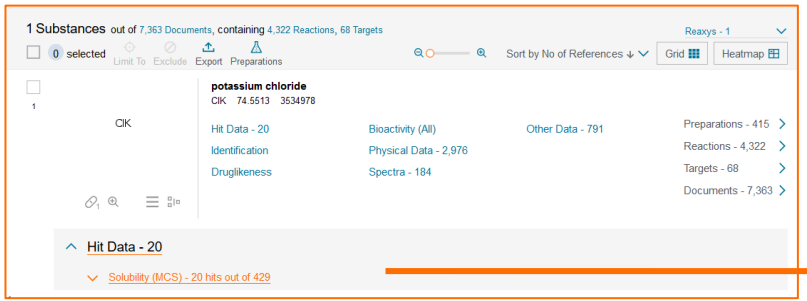
Step1：输入分子式KCl



Step2：在溶剂一块选择乙醇

ELSEVIER

最后的结果



Reaxys直接给出具体的数据和数据的文献出处，其实也可以设定更多的条件，如温度.....

Solubility (MCS) - 20 hits out of 429

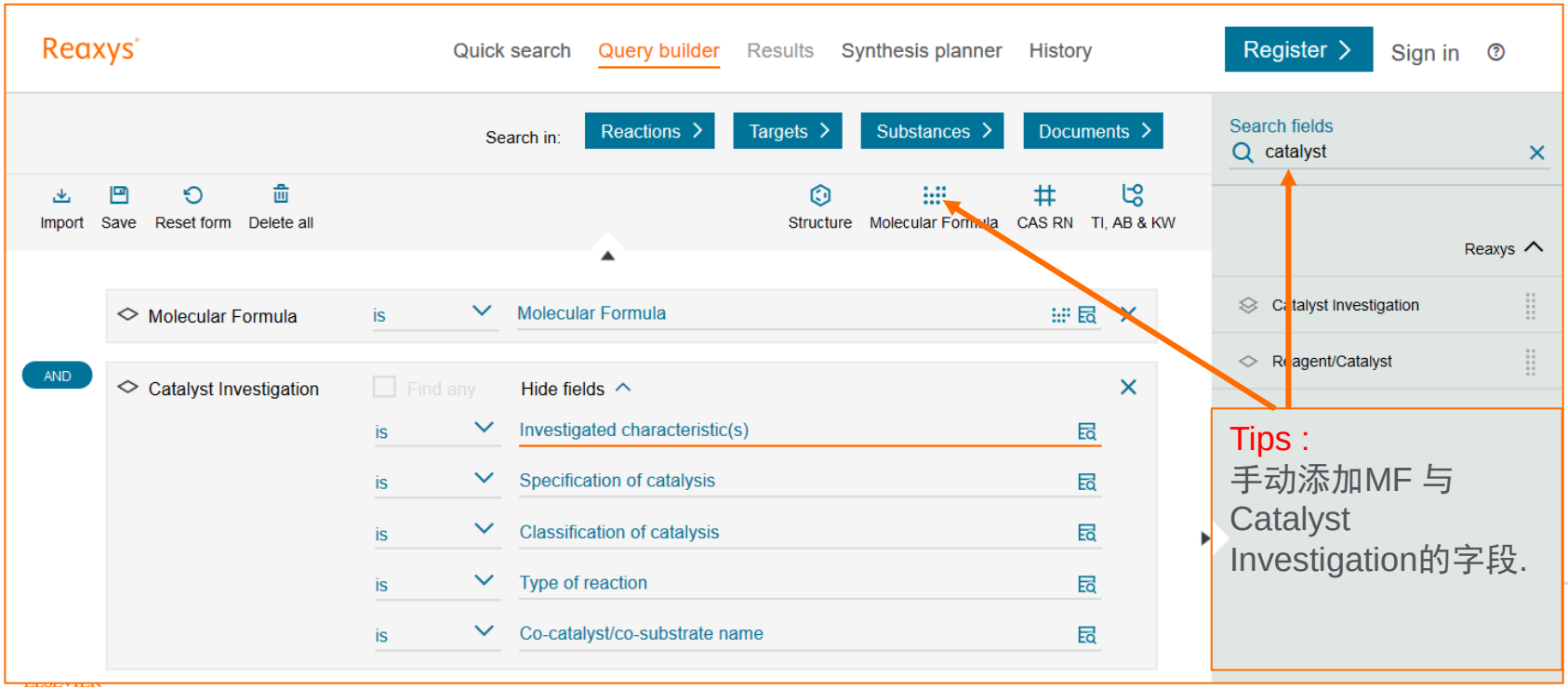
Show/Hide columns

Solubility, g·l-1	Temperature (Solubility (MCS)), °C	Solvent (Solubility (MCS))	Comment (Solubility (MCS))	Reference
	20	ethanol	Solubility: 0.012 mol/kg solvent	El-Dossoki[**Indian Journal of Chemistry, Section A: Inorganic, Physical, Theoretical and Analytical**, **2005**, vol. 44, # 8, p. 1594 - 1596] Full Text Cited 6 times Details Abstract
	25	ethanol	Solubility: 0.025 mol/kg solvent	El-Dossoki[**Indian Journal of Chemistry, Section A: Inorganic, Physical, Theoretical and Analytical**, **2005**, vol. 44, # 8, p. 1594 - 1596] Full Text Cited 6 times Details Abstract
	30	ethanol	Solubility: 0.037 mol/kg solvent	El-Dossoki[**Indian Journal of Chemistry, Section A: Inorganic, Physical, Theoretical and Analytical**, **2005**, vol. 44, # 8, p. 1594 - 1596] Full Text Cited 6 times Details Abstract
	35	ethanol	Solubility: 0.043 mol/kg solvent	El-Dossoki[**Indian Journal of Chemistry, Section A: Inorganic, Physical, Theoretical and Analytical**, **2005**, vol. 44, # 8, p. 1594 - 1596] Full Text Cited 6 times Details Abstract
0.320571		ethanol		Abakshin, V. A.; Eliseeva, O. V.; Krasnoperova, A. P.; Lebedeva, L. T.; Krestov, G. A.[**Doklady Physical Chemistry**, **1991**, vol. 317, p. 303 - 306][**Dokl. Phys. Chem. (Transl. of Dokl. Akad. Nauk.)**, **1991**, vol. 317, p. 1140 - 1143] Full Text Details
	20	ethanol	Solubility: 1.270E0 mol/1000mol solvent	Kirn; Dunlap[**Journal of the American Chemical Society**, **1931**, vol. 53, p. 393] Full Text Details
	45	ethanol	Solubility: 1.277E0 mol/1000mol solvent	Kirn; Dunlap[**Journal of the American Chemical Society**, **1931**, vol. 53, p. 393] Full Text Details

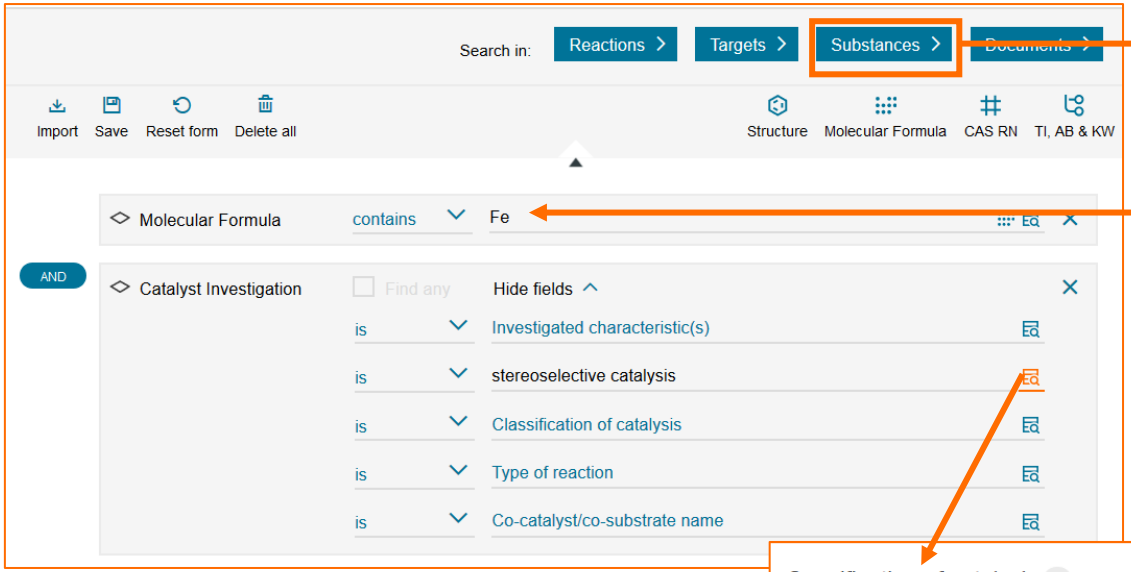
ELSEVIER

Case 4：“特定研究领域”的催化剂选择

- 检索可用于立体选择性催化的含Fe的催化剂

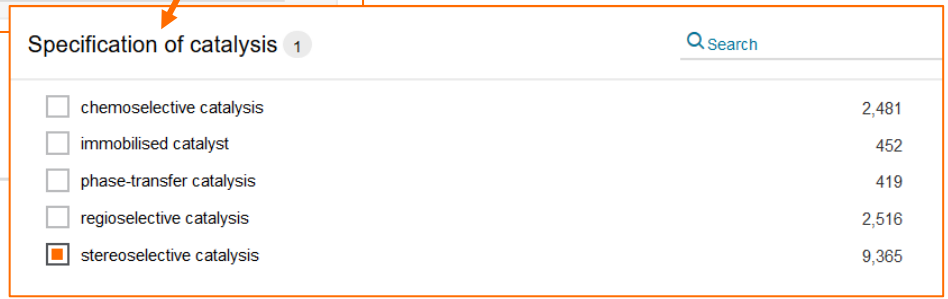


条件的输入



Step3：进行物质检索

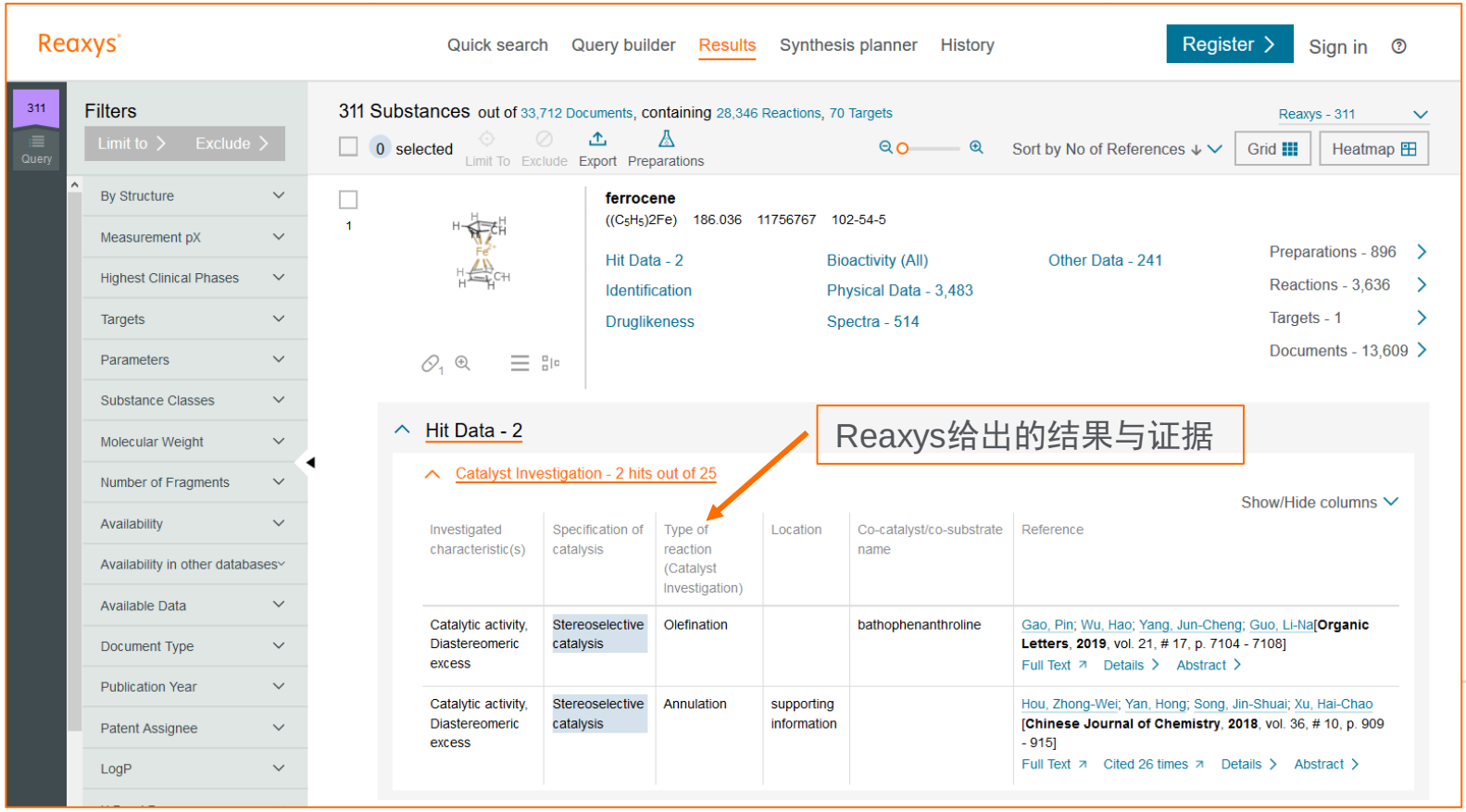
Step1：输入分子式Fe，并将逻辑关系改成“Contains”，即只要分子式中包含Fe，就检索出来



Step2：Specification of Catalysis部分选择
立体选择性催化

ELSEVIER

最后的结果


Reaxys
Quick search
Query builder
Results
Synthesis planner
History
Register
Sign in
311
Query
Filters
Limit to
Exclude
By Structure
Measurement pX
Highest Clinical Phases
Targets
Parameters
Substance Classes
Molecular Weight
Number of Fragments
Availability
Availability in other databases
Available Data
Document Type
Publication Year
Patent Assignee
LogP
311 Substances out of 33,712 Documents, containing 28,346 Reactions, 70 Targets
Reaxys - 311
0 selected
Limit To
Exclude
Export
Preparations
Sort by No of References
Grid
Heatmap
1
ferrocene
((C5H5)2Fe) 186.036 11756767 102-54-5
Hit Data - 2
Identification
Druglikeness
Bioactivity (All)
Physical Data - 3,483
Spectra - 514
Other Data - 241
Preparations - 896
Reactions - 3,636
Targets - 1
Documents - 13,609
Hit Data - 2
Reaxys给出的结果与证据
Catalyst Investigation - 2 hits out of 25
Show/Hide columns
Investigated characteristic(s)
Specification of catalysis
Type of reaction (Catalyst Investigation)
Location
Co-catalyst/co-substrate name
Reference
Catalytic activity, Diastereomeric excess
Stereoselective catalysis
Olefination
bathophenanthroline
Gao, Pin; Wu, Hao; Yang, Jun-Cheng; Guo, Li-Na[Organic Letters, 2019, vol. 21, # 17, p. 7104 - 7108]
Full Text
Details
Abstract
Catalytic activity, Diastereomeric excess
Stereoselective catalysis
Annulation
supporting information
Hou, Zhong-Wei; Yan, Hong; Song, Jin-Shuai; Xu, Hai-Chao [Chinese Journal of Chemistry, 2018, vol. 36, # 10, p. 909 - 915]
Full Text
Cited 26 times
Details
Abstract

Case 5：可见光下特定溶剂中呈现特定颜色的化合物

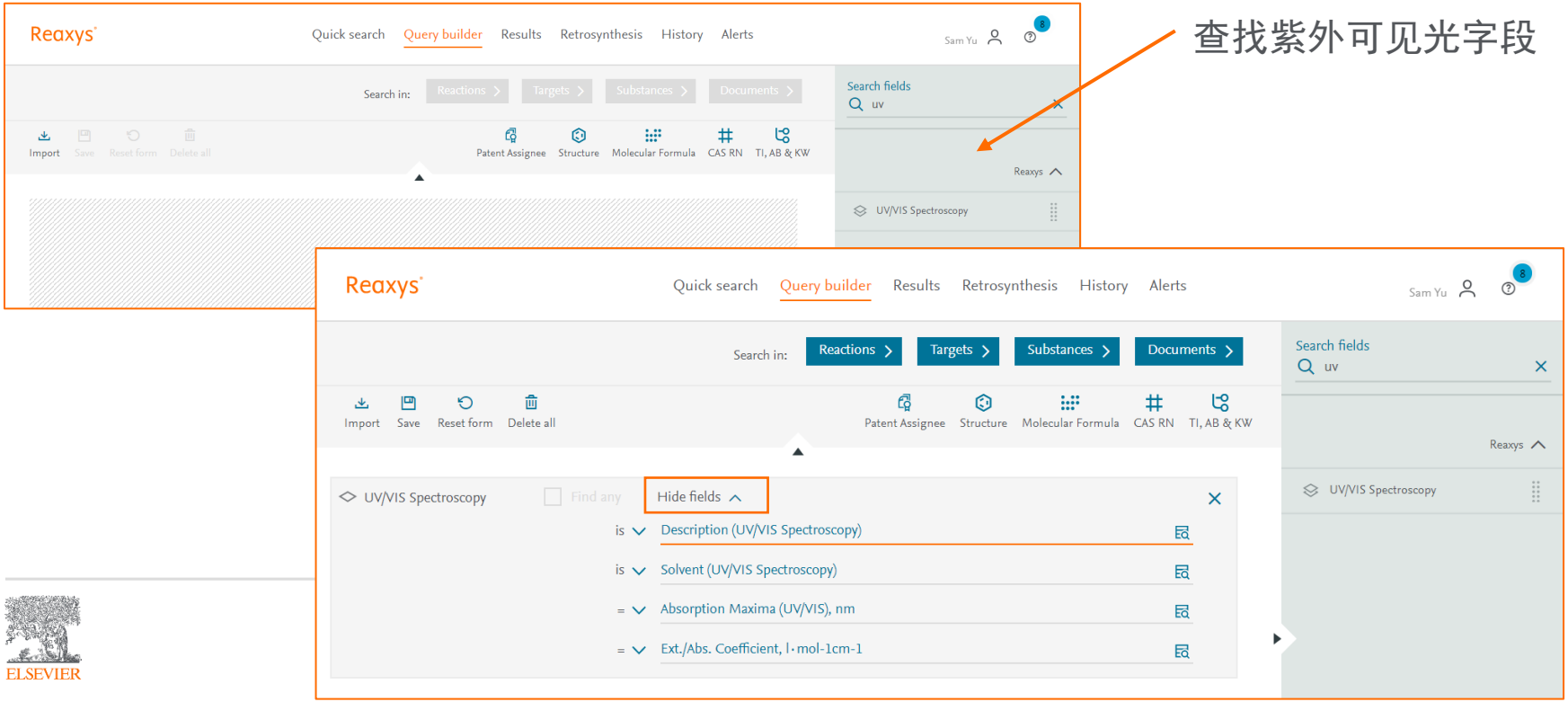
- 获取在可见光下，水溶液中呈现出紫罗兰色的化合物

检索前提：
一个化合物在可见光下显示什么颜色，需要知道他能吸收什么样的波长

波长（nm)	吸收颜色	可见颜色
400 ～ 450	紫	黄绿
450 ～ 480	蓝	黄
480 ～ 490	绿蓝	橙
490 ～ 500	蓝绿	红
500 ～ 560	绿	红紫
560 ～ 580	黄绿	紫
580 ～ 610	黄	蓝
610 ～ 650	橙	绿蓝
650 ～ 760	红	蓝绿

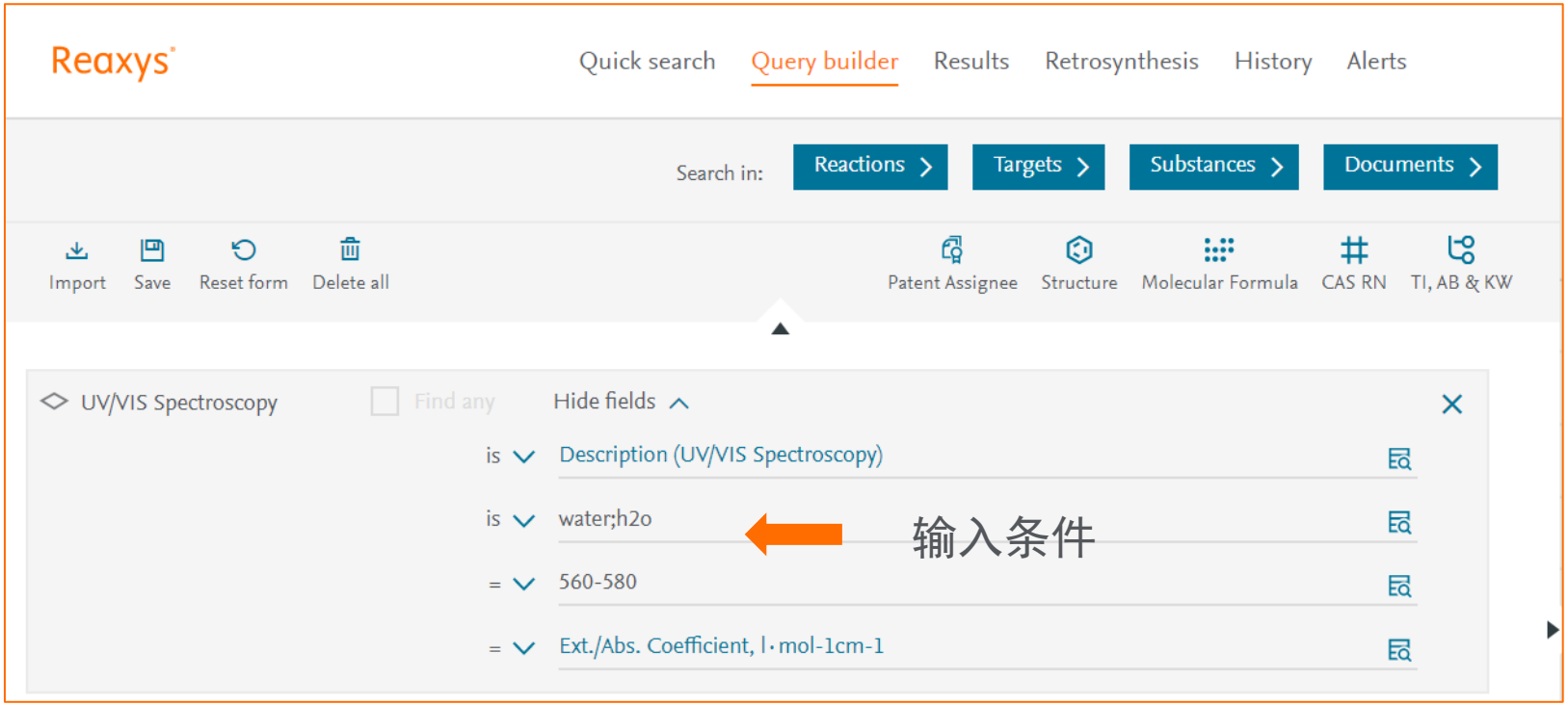
Reaxys中的检索策略

- Query Builder下用UV/VIS字段进行检索



ELSEVIER

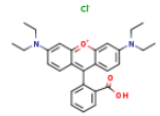
添加吸收光波长和溶剂



ELSEVIER

最后的结果

1



rhodamine B

$C_{13}H_6O(N(C_2H_5)2)2C_6H_4COOH^{(1+)}$*... 479.019 4091619 81-88-9

Hit Data - 6 | Bioactivity (All) | Other Data - 92

Identification | Physical Data - 699

Druglikeness | Spectra - 706

Preparations - 14

Reactions - 1,244

Targets - 7

Documents - 34,671

Hit Data - 6

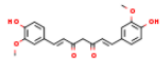
UV/VIS Spectroscopy - 6 hits out of 453

UV/VIS Spectroscopy - 6 hits out of 453

Show/Hide columns

Description (UV/VIS Spectroscopy)	Solvent (UV/VIS Spectroscopy)	Location	Absorption Maxima (UV/VIS), nm	Ext./Abs. Coefficient, l·mol^{-1}cm^{-1}	Reference
Spectrum	water		560		Bai, Yan; Chen, Lin-Lin; Dang, Dong-Bin; Li, Dan; Li, Ya-Min; Liu, Xin-Yu; Tan, Xiao-Li[Journal of Solid State Chemistry, 2022, vol. 305, art. no. 122694] Full Text Details Abstract
Spectrum	water	supporting information	560		Feng, Yongqiang; Sakaki, Masoud; Kim, Jae-hyun; Huang, Jianfeng; Kajiyoshi, Koji[New Journal of Chemistry, 2018, vol. 42, # 24, p. 20212 - 20218] Full Text Cited 6 times Details Abstract

2



curcumin

$(HOC_6H_3(OCH_3)CHCHCO)2CH_2$ 368.386 2306965 458-37-7

Hit Data - 1 | Bioactivity (All) | Other Data - 2,560

Identification | Physical Data - 273

Druglikeness | Spectra - 507

Preparations - 28

Reactions - 1,278

Targets - 628

Documents - 29,483

Hit Data - 1

UV/VIS Spectroscopy - 1 hits out of 223

UV/VIS Spectroscopy - 1 hits out of 223

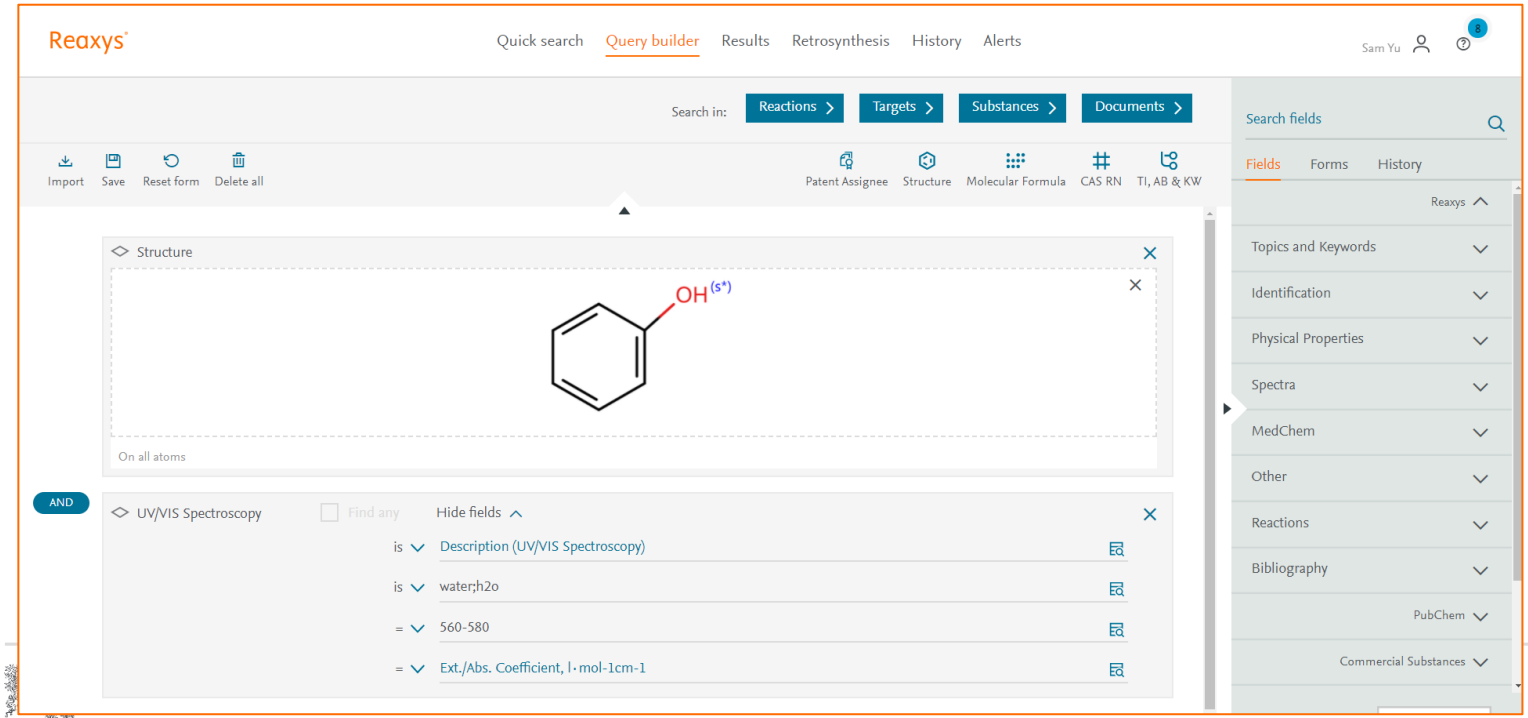
Show/Hide columns

Description (UV/VIS Spectroscopy)	Solvent (UV/VIS Spectroscopy)	Absorption Maxima (UV/VIS), nm	Reference
Spectrum	dimethyl sulfoxide, water, sodium hydroxide	571	Kim, Sung-Hoon; Gwon, Seon-Yeong; Burkinshaw; Son, Young-A.[Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2010, vol. 76, # 3-4, p. 384 - 387] Full Text Cited 18 times Details Abstract

ELSEVIER

如果还有更多的需求

- 获取在可见光下，水溶液中呈现出紫罗兰色的化合物，且该化合物必须包含以下片段



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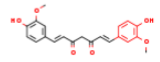
最后的结果

127 Substances out of 43,776 Documents, containing 17,443 Reactions, 716 Targets

Reaxys - 127

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

1



curcumin

$(HOC_6H_3(OCH_3)CHCHCO)2CH_2$ 368.386 2306965 458-37-7

Hit Data - 1 | Bioactivity (All) | Other Data - 2,560
Identification | Physical Data - 273
Druglikeness | Spectra - 507

Preparations - 28
Reactions - 1,278
Targets - 628
Documents - 29,483

Hit Data - 1

UV/VIS Spectroscopy - 1 hits out of 223

2

2-amino-phenol

$HO(C_6H_4)NH_2$ 109.128 606075 95-55-6

Hit Data - 1 | Bioactivity (All) | Other Data - 34
Identification | Physical Data - 371
Druglikeness | Spectra - 199

Preparations - 231
Reactions - 15,180
Targets - 30
Documents - 8,759

Hit Data - 1

UV/VIS Spectroscopy - 1 hits out of 68

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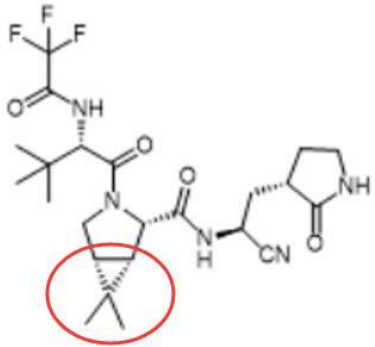
Agenda

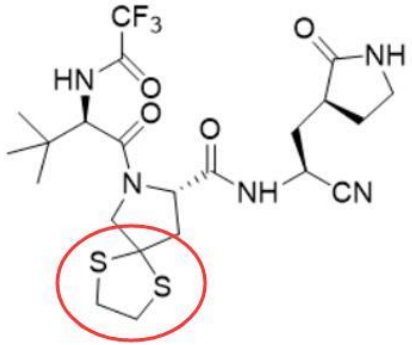
- Reaxys介绍与内容
  - Reaxys介绍
  - Reaxys对于科技文献的提炼
- Reaxys中的化学科学数据获取
  - Reaxys中的文献快速检索方法
  - Reaxys中物质理化性质的查询与结构反查
  - 利用Reaxys进行专利突破与全新分子的专利评估
  - Reaxys中结构面板详解，合成信息的检索与合成计划制作
- Q&A

Case 6：利用Reaxys中的专利数据进行专利突破

- 2023年1月底，国家药监局发布公告，批准先声药业的新冠口服药物“先诺欣”在国内上市。从作用机制看，先声药业的“先诺欣”和辉瑞的Paxlovid是相同的，且也是和Ritonavir组合包装的抗病毒药物。“先诺欣”的活性成分先诺特韦和辉瑞的Nirmatrelvir非常相像。



辉瑞：Nirmatrelvir



先声：先诺特韦

寻找专利突破点需要先调研原研专利

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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WIPO | PCT

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C07D 403/12 (2006.01) *C07D 497/04* (2006.01)
C07D 403/14 (2006.01) *A61K 31/4015* (2006.01)
A61P 31/14 (2006.01) *A61K 31/4025* (2006.01)

(21) International Application Number:
PCT/IB2021/057281

(22) International Filing Date:
06 August 2021 (06.08.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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63/194,241 28 May 2021 (28.05.2021) US

(71) Applicant: **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, New York 10017 (US).

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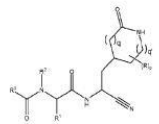
(74) Agent: **ZIELINSKI, Bryan C.**; PFIZER INC., 235 East 42nd Street, MS 235/9/86, New York, New York 10017 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

(54) Title: NITRILE-CONTAINING ANTIVIRAL COMPOUNDS

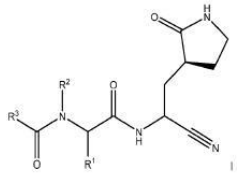


(I")

(57) Abstract: The invention relates to compounds of Formula (I") wherein R, R^1, R^2, R^3, p, q and q' are as defined herein, pharmaceutical compositions comprising the compounds, methods of treating coronavirus infection such as COVID-19 in a patient by administering therapeutically effective amounts of the compounds, and methods of inhibiting or preventing replication of coronaviruses such as SARS- CoV-2 with the compounds.

WO 2021/250648 A1

E1 is a compound of E45 or E59, hereinbelow, of Formula I



;

or a pharmaceutically acceptable salt thereof; wherein R^1 is selected from the group consisting of C_1-C_6 alkyl which is optionally substituted with a cyano or with one to five fluoro; C_2-C_6 alkynyl; and (C_3-C_6 cycloalkyl)-C_1-C_3 alkyl which is optionally substituted with one to two substituents selected from trifluoromethyl and C_1-C_3 alkyl or with one to five fluoro; R^2 is hydrogen or R^2 and R^1 taken together with the nitrogen and carbon atoms to which they are attached are a pyrrolidine or piperidine ring which is optionally substituted with one to four R^{2a}; R^{2a} at each occurrence is independently selected from the group consisting of fluoro, C_1-C_6 alkyl optionally substituted with one to three fluoro and C_1-C_6 alkoxy optionally substituted with one to three fluoro; or two R^{2a} groups when

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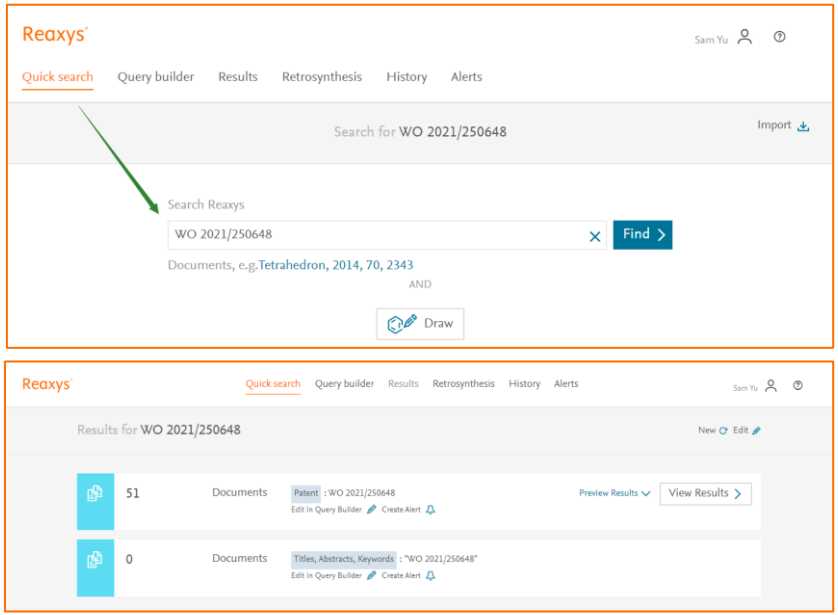
专利当中对于骨架结构的描述极其复杂，理解起来费时费力。

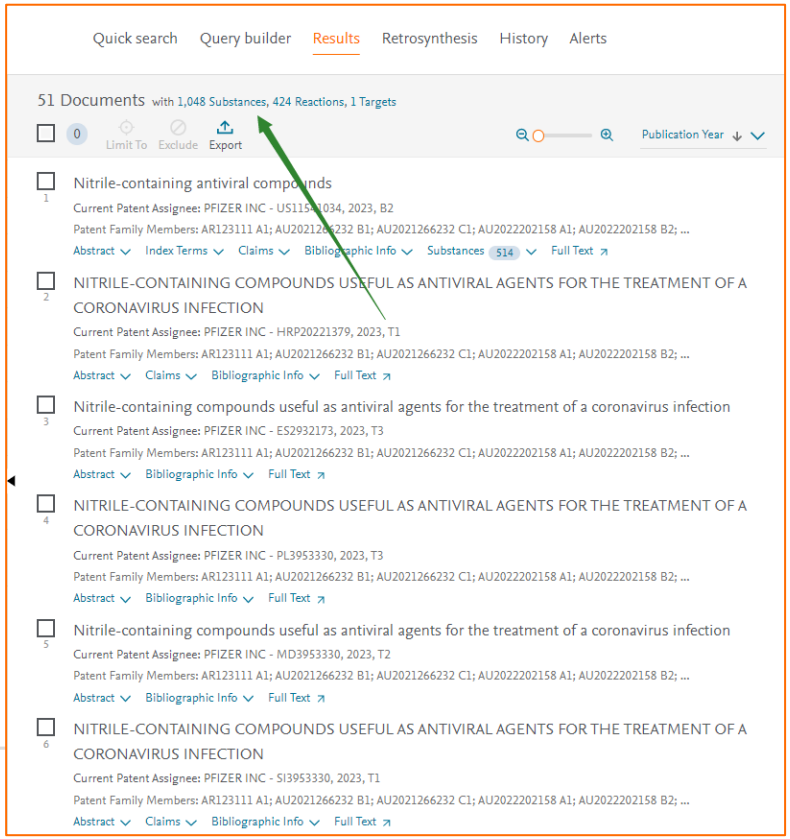
attached to adjacent carbons and taken together with the carbons to which they are attached are a fused C_3-C_6 cycloalkyl which is optionally substituted with one to four R^{2b}; or two R^{2a} groups when attached to the same carbon and taken together with the carbon to which they are attached are a spiro C_3-C_6 cycloalkyl which is optionally substituted with one to four R^{2b}; R^{2b} at each occurrence is independently selected from fluoro, C_1-C_3 alkyl optionally substituted with one to three fluoro, and C_1-C_3 alkoxy optionally substituted with one to three fluoro; R^3 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)-C_1-C_6 alkyl, C_2-C_6 alkynyl, C_2-C_6 alkynyloxy, C_3-C_{12} cycloalkyl optionally fused with a 5- to 6-membered heteroaryl or phenyl, (C_3-C_{12} cycloalkyl)-C_1-C_6 alkyl, C_3-C_{12} cycloalkoxy, (C_3-C_{12} cycloalkoxy)-C_1-C_6 alkyl, 4- to 12-membered heterocycloalkyl which is optionally fused with a 5- to 6-membered heteroaryl or phenyl and wherein said heterocycloalkyl comprises one to four heteroatoms independently selected from N, O and S(O)$_n$, (4- to 12-membered heterocycloalkyl)-C_1-C_6 alkyl wherein said heterocycloalkyl moiety comprises one to four heteroatoms independently selected from N, O and S(O)$_n$, C_6-C_{10} aryl optionally fused with a C_4-C_6 cycloalkyl or a 4- to 7-membered heterocycloalkyl, (C_6-C_{10} aryl)-C_1-C_6 alkyl, 5- to 10-membered heteroaryl comprising one to five heteroatoms independently selected from N, O and S, which is optionally fused with a C_5-C_6 cycloalkyl; (5- to 10-membered heteroaryl)-C_1-C_6 alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S; (C_6-C_{10} aryl)-(5- to 10-membered heteroaryl)- wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S, (5- to 10-membered heteroaryloxy)-C_1-C_6 alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S; (5- to 6-membered heteroaryl)-(5- to 6-membered heteroaryl)- wherein each heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S; (4- to 7-membered heterocycloalkyl)-(5- to 6- membered heteroaryl)- wherein the heterocycloalkyl moiety comprises one to three heteroatoms independently selected from N, O and S(O)$_n$ and the heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S; (5- to 6-membered heteroaryl)-(4- to 7-membered heterocycloalkyl)- wherein the heterocycloalkyl moiety comprises one to three heteroatoms independently selected from N, O and S(O)$_n$ and the heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S; wherein each R^3 group is optionally substituted with one to five R^4; R^4 at each occurrence is independently selected from the group consisting of oxo, halo, hydroxy, cyano, phenyl, benzyl, amino,

5

通过Reaxys对专利的提炼快速了解突破点



Reaxys中通过简单的链接，获取原研专利中的所有物质



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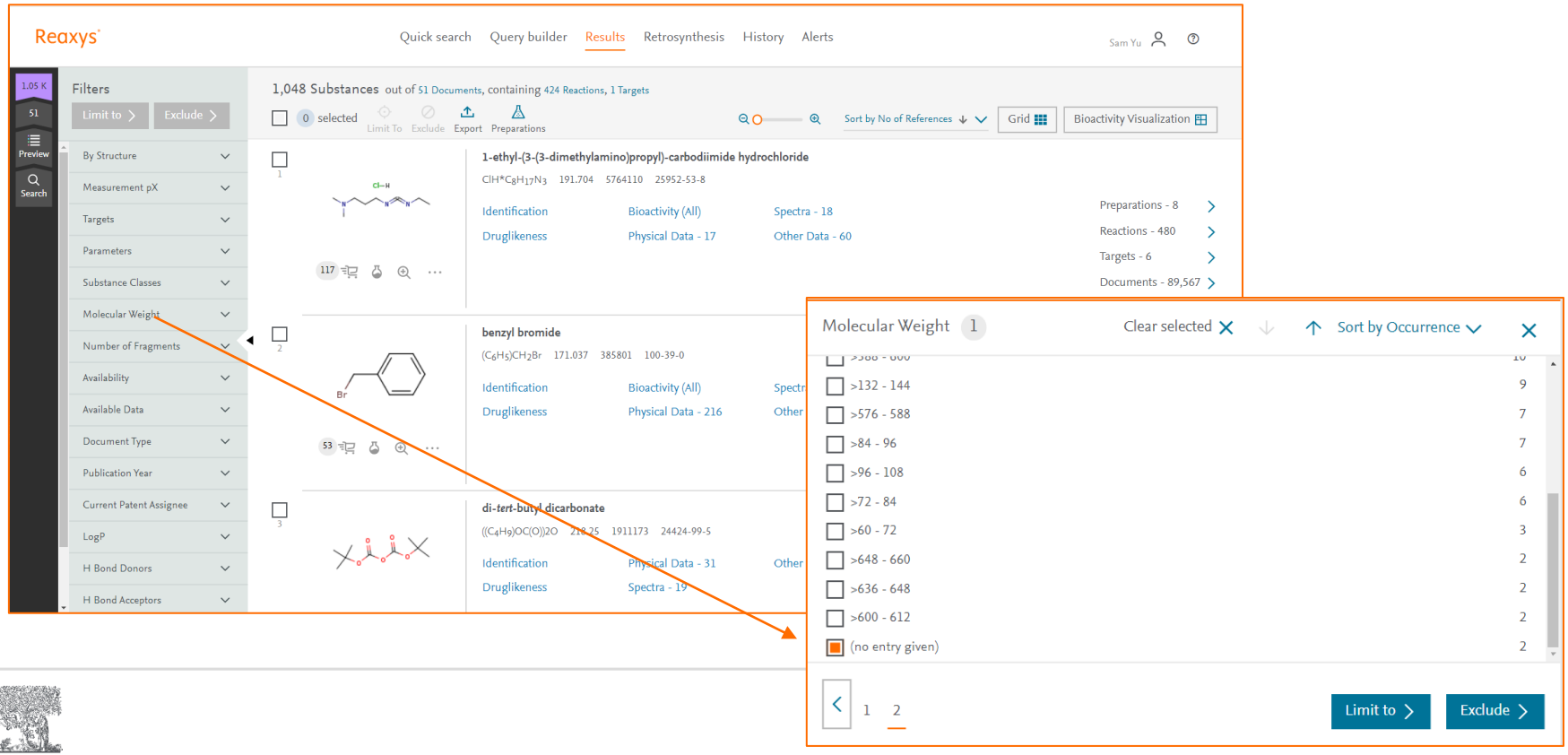
专利中的物质，并利用MW筛选出没有分子量报道的物质



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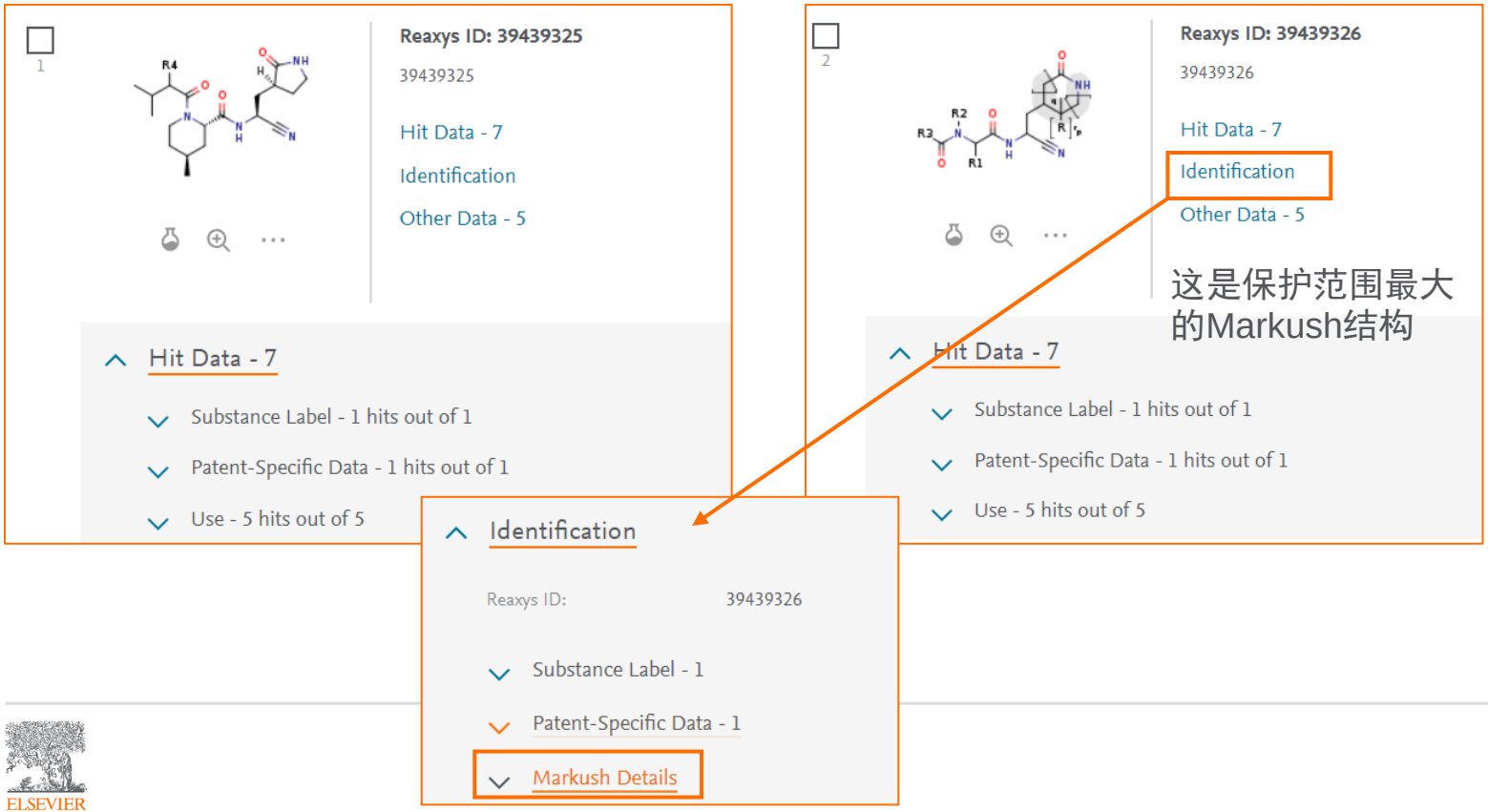
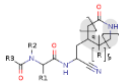
最后的结果


1
Reaxys ID: 39439325
39439325
Hit Data - 7
Identification
Other Data - 5
Hit Data - 7
Substance Label - 1 hits out of 1
Patent-Specific Data - 1 hits out of 1
Use - 5 hits out of 5
2
Reaxys ID: 39439326
39439326
Hit Data - 7
Identification
Other Data - 5
这是保护范围最大的Markush结构
Hit Data - 7
Substance Label - 1 hits out of 1
Patent-Specific Data - 1 hits out of 1
Use - 5 hits out of 5
Identification
Reaxys ID: 39439326
Substance Label - 1
Patent-Specific Data - 1
Markush Details

从Markush Detail中寻找突破点

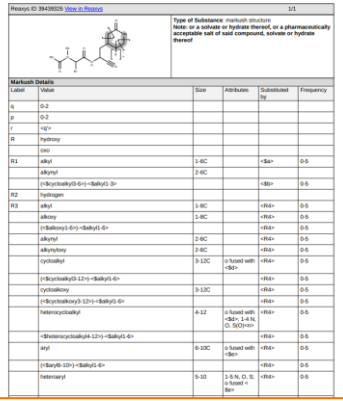
Markush Details



Label	Value	Size	Attributes	Substituted by	Frequency
q	0-2				
p	0-2				
r	q'				
R	hydroxy				
	oxo				
R1	alkyl	1-6C		$a	0-5
	alkynyl	2-6C			
	($cycloalkyl3-6)-$alkyl1-3			$b	0-5
R2	hydrogen				
R3	alkyl	1-8C		R4	0-5
	alkoxy	1-8C		R4	0-5
	($alkoxy1-6)-$alkyl1-6			R4	0-5
	alkynyl	2-6C		R4	0-5
	alkynyloxy	2-6C		R4	0-5
	cycloalkyl	3-12C	o fused with <$d>	R4	0-5
	($cycloalkyl3-12)-$alkyl1-6			R4	0-5
	cycloalkoxy	3-12C		R4	0-5
	($cycloalkoxy3-12)-$alkyl1-6			R4	0-5
	heterocycloalkyl	4-12	o fused with <$d>; 1-4 N, O, S(O)<n>	R4	0-5
	$heterocycloalkyl4-12)-$alkyl1-6			R4	0-5
	aryl	6-10C	o fused with <$e>	R4	0-5
	($aryl6-10)-$alkyl1-6			R4	0-5
	heteroaryl	5-10	1-5 N, O, S; o fused <$e>	R4	0-5
	($heteroaryl5-10)-$alkyl1-6			R4	0-5
	($aryl6-10)-($heteroaryl5-10)			R4	0-5
	($heteroaryloxy5-10)-$alkyl1-6			R4	0-5

也可以将Reaxys中的Markush Detail下载下来用表格的形式进行研究：

Reaxys®



Reaxys Reaxys ID 39439326 View in Reaxys 1/1

Type of Substance: markush structure
Note: or a solvate or hydrate thereof, or a pharmaceutically acceptable salt of said compound, solvate or hydrate thereof

Markush Details

Label	Value	Size	Attributes	Substituted by	Frequency
q	0-2				
p	0-2				
r	<q'>				
R	hydroxy				
	oxo				
R1	alkyl	1-6C		<$a>	0-5
	alkynyl	2-6C			
	(<$cycloalkyl3-6>)-<$alkyl1-3>			<$b>	0-5
R2	hydrogen				
R3	alkyl	1-8C		<R4>	0-5
	alkoxy	1-8C		<R4>	0-5
	(<$alkoxy1-6>)-<$alkyl1-6>			<R4>	0-5
	alkynyl	2-6C		<R4>	0-5
	alkynyloxy	2-6C		<R4>	0-5
	cycloalkyl	3-12C	o fused with <$d>	<R4>	0-5
	(<$cycloalkyl3-12>)-<$alkyl1-6>			<R4>	0-5
	cycloalkoxy	3-12C		<R4>	0-5
	(<$cycloalkoxy3-12>)-<$alkyl1-6>			<R4>	0-5
	heterocycloalkyl	4-12	o fused with <$d>; 1-4 N, O, S(O)<n>	<R4>	0-5
	<$heterocycloalkyl4-12>)-<$alkyl1-6>			<R4>	0-5
	aryl	6-10C	o fused with <$e>	<R4>	0-5
	(<$aryl6-10>)-<$alkyl1-6>			<R4>	0-5
	heteroaryl	5-10	1-5 N, O, S; o fused <$e>	<R4>	0-5

Reaxys®

$cycloalk-yl3-6	cycloalkyl	3-6C			
$alkyl1-3	alkyl	1-3C			
$b	trifluoromethyl				
	alkyl	1-3C			
	fluoro				
R1=R2	pyrrolidine			<R2a>	0-4
	piperidine			<R2a>	0-4
R2a	fluoro				
	hydroxy				
	alkyl	1-6C		fluoro	0-3
	alkoxy	1-6C		fluoro	0-3
R2a=R2b	cycloalkyl	3-6C		<R2b>	0-4
	spiro-cycloalkyl	3-6C		<R2b>	0-4
R2b	fluoro				
	hydroxy				
	alkyl	1-3C		<$c>	0-3
	alkoxy	1-3C		<$c>	0-3
$c	fluoro				
	hydroxy				
$al-koxy1-6	alkoxy	1-6C			
$alkyl1-6	alkyl	1-6C			
$d	heteroaryl	5-6			
	phenyl				
$cycloalk-yl3-12	cycloalkyl	3-12C			
$cycloal-koxy3-12	cycloalkoxy	3-12C			
n	0-2				
$hetero-cycloalk-yl4-12	heterocycloalkyl	4-12	1-4 N, O, S(O)n=n		
$e	cycloalkyl	4-6C			
	heterocycloalkyl	4-7			
$aryl6-10	cycloalkyl	5-6C			
$hetero-aryl5-10	heteroaryl	5-10	1-5 N, O, S		

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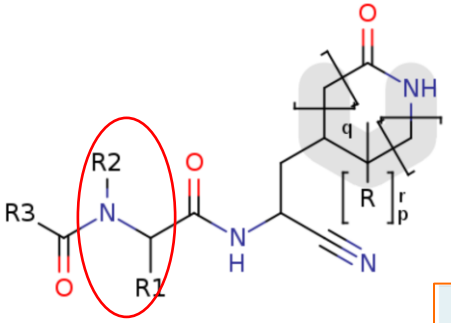
寻找简单的描述来进行突破



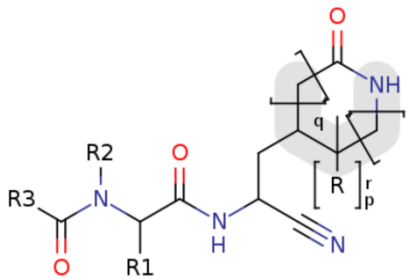
专利保护点：

1. R1+R2=吡咯烷，或哌啶，且可以被R2a取代，那突破点是否可以定在不一样的环？
2. R2a+R2a=3-6个C的环烷基，或者3-6个C的螺环烷基，那突破点是否可以是不一样的螺环？先声用螺杂环进行了突破。

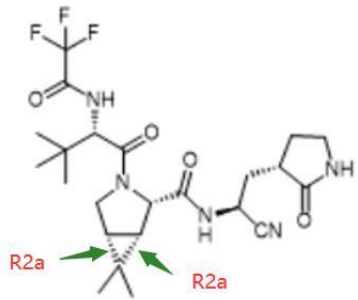
R1+R2	pyrrolidine			R2a	0-4
	piperidine			R2a	0-4
R2a	fluoro				
	hydroxy				
	alkyl	1-6C		fluoro	0-3
	alkoxy	1-6C		fluoro	0-3
R2a+R2a	cycloalkyl	3-6C		R2b	0-4
	spiro cycloalkyl	3-6C		R2b	0-4

ELSEVIER

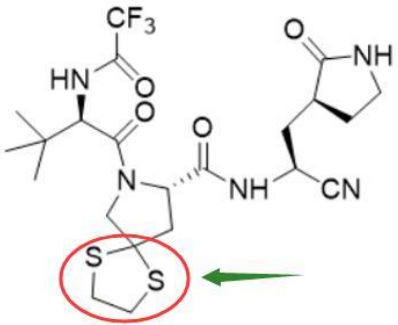
先声药业的突破点



attached to adjacent carbons and taken together with the carbons to which they are attached are a fused C_3-C_6 cycloalkyl which is optionally substituted with one to four R^{2b}; or two R^{2a} groups when attached to the same carbon and taken together with the carbon to which they are attached are a spiro C_3-C_6 cycloalkyl which is optionally substituted with one to four R^{2b}; R^{2b} at each occurrence is independently selected from fluoro, C_1-C_3 alkyl optionally substituted with one to three fluoro, and C_1-C_3 alkoxy optionally substituted with one to three fluoro; R^3 is selected from the group consisting of C_1-C_8 alkyl, C_1-C_8 alkoxy, (C_1-C_6 alkoxy)-C_1-C_6 alkyl, C_2-C_6 alkynyl, C_2-C_6 alkynyloxy, C_3-C_{12} cycloalkyl optionally fused with a 5- to 6-membered heteroaryl or phenyl, (C_3-C_{12}



辉瑞：
1：R1+R2=吡咯烷
2：R2a+R2a=环烷烃



先声：
1：R1+R2=吡咯烷
2：R2a+R2a=5元螺杂环

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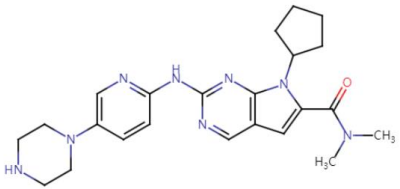
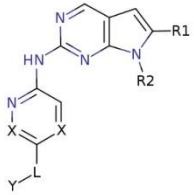
类似的策略可以继续用到CDK4/6的专利突破上

诺华CDK4/6药物Ribociclib

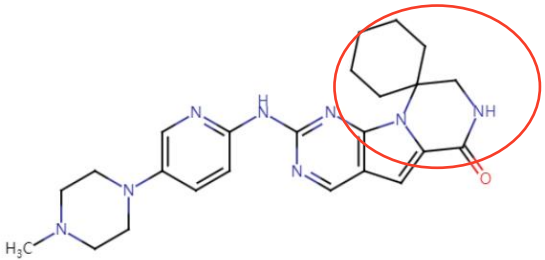


诺华保护的Markush



发现诺华保护的R1和R2都是单独的取代基团

R^1 is $C_{1\text{-}8}$alkyl, CN, C(O)OR^4 or $CONR^5R^6$, a 5-14 membered heteroaryl group, or a 3-14 membered cycloheteroalkyl group;
R^2 is $C_{1\text{-}8}$alkyl, $C_{3\text{-}14}$cycloalkyl, or a 5-14 membered heteroaryl group, and wherein R^2 may be substituted with one or more $C_{1\text{-}8}$alkyl, or OH;

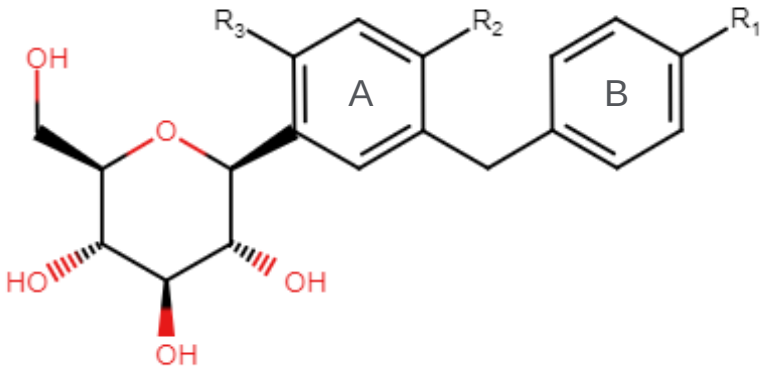


G1治疗与先声药业在R1+R2上做了突破，做了成环的突破

Markush Details

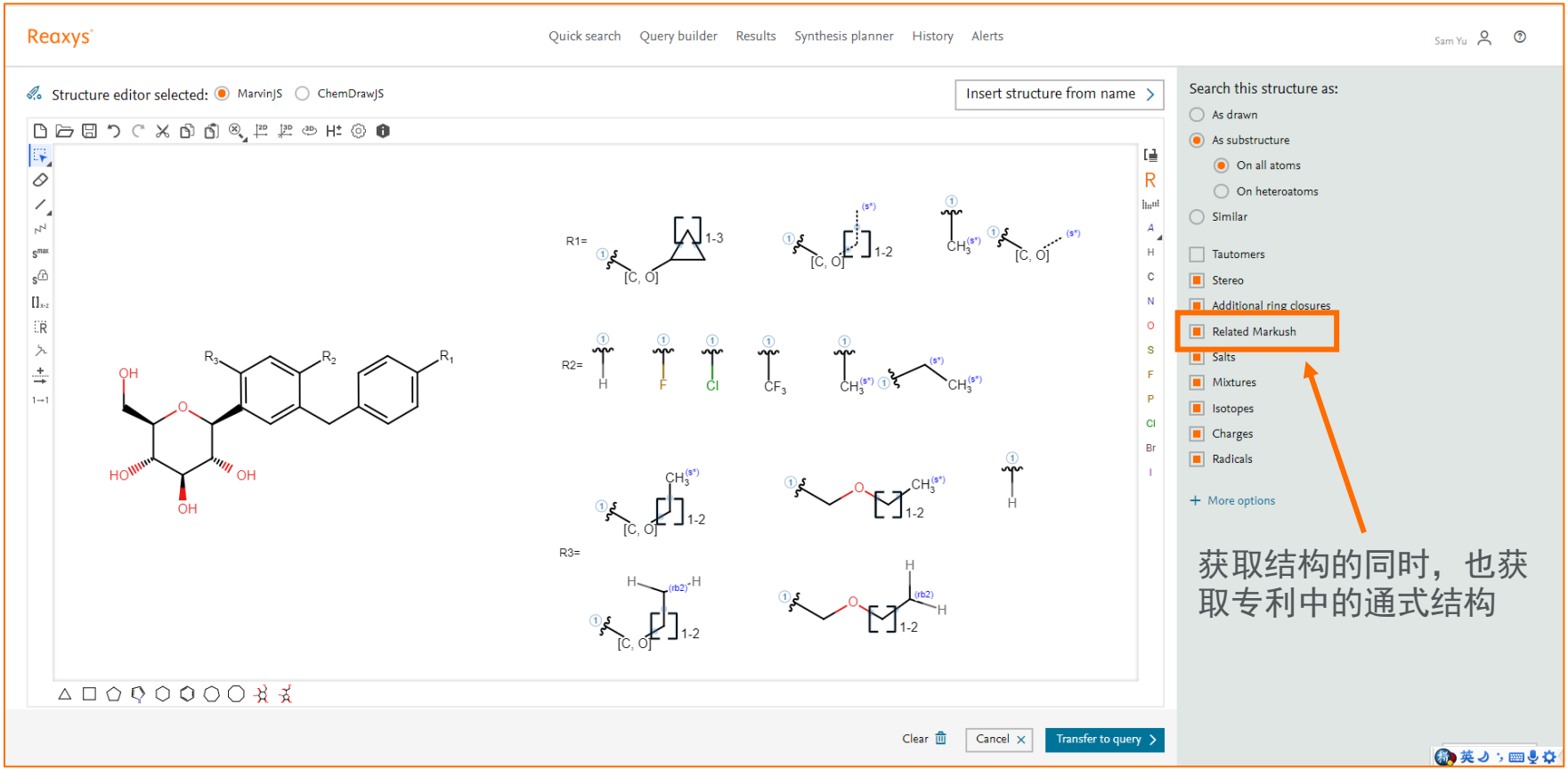
Label	Value	Size	Attributes	Substituted by	Frequency
R2	alkyl	1-8C		<$a>	0-?
	cycloalkyl	3-14C		<$a>	0-?
	heteroaryl	5-14		<$a>	0-?
R1	alkyl	1-8C			
	CN				
	C(O)O<R4>				
	CON<R5><R6>				
	heteroaryl	5-14			
	cycloheteroalkyl	3-14			

CASE 7: Reaxys中的全新化合物专利评估



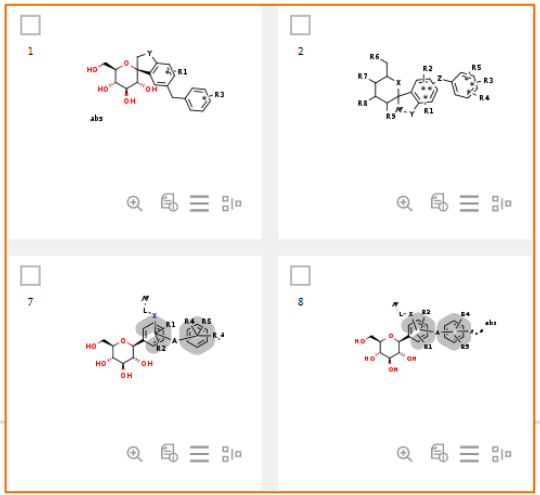
- 保持AB环和glucose的主要活性部分，考虑R1,R2,R3的变构
- R1为小位阻烷基，烷氧基，环烷基
- R2为H，F，Cl，CF3，Me，Et
- R3为H，或者短的烷基，烷氧基，醚，H，且允许和自身成环

Reaxys中通式结构的专利评估



Reaxys中的结果

Reaxys除了给出具体的结构，还能给出涉及这些结构的Markush通式



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利用分子量筛选获取所有的Markush结构

由于Markush结构是没有分子量的，所以可以通过分子量筛选获取所有的通式结构

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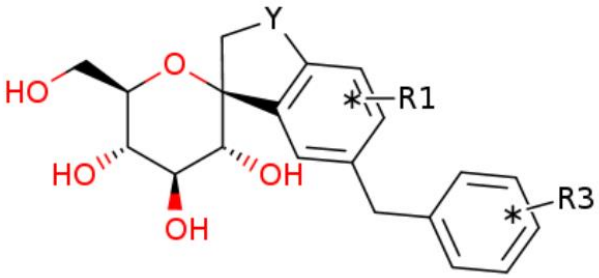
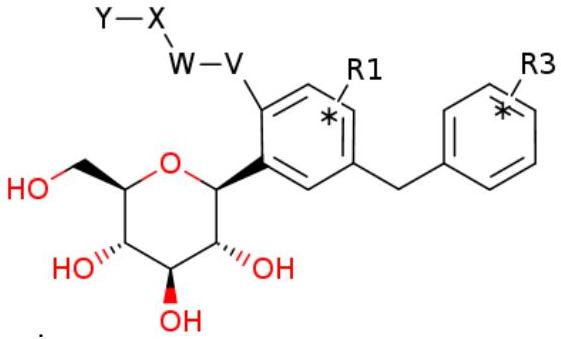
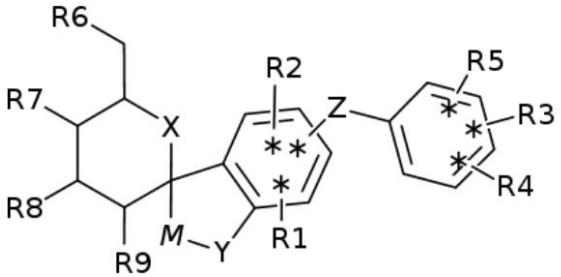
一些比较有意思的Markush结构







Tips：

- 这些Markush结构，和我们设计的结构非常的相似，如何突破专利，需要详细阅读专利Claim部分
- Reaxys可以帮助大家大大缩短阅读全文的时间

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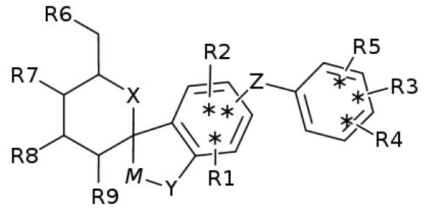
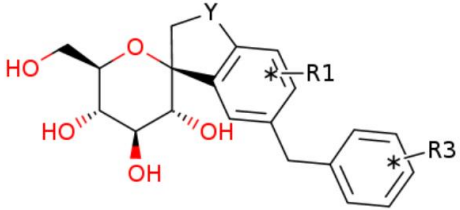
Markush结构在专利中的表达方式

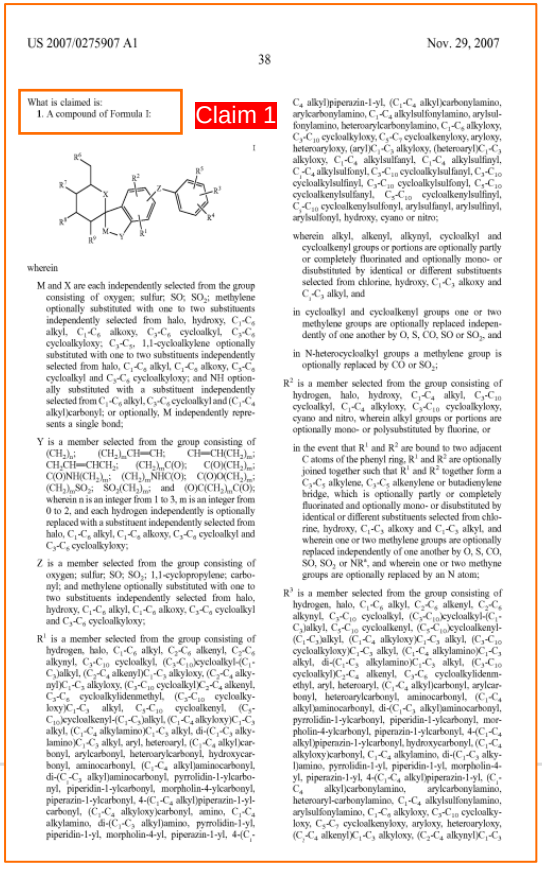


Claim 1



Claim 10

在US 2007/0275907这篇专利
出现了上面的2个Markush结构。



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What is claimed is:
1. A compound of Formula I:

Claim 1

wherein

M and X are each independently selected from the group consisting of oxygen; sulfur; SO; SO_2; methylene optionally substituted with one to two substituents independently selected from halo, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyloxy; C_3-C_{10} 1,1-cycloalkylene optionally substituted with one to two substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl and C_3-C_6 cycloalkyloxy; and NH optionally substituted with a substituent independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and (C_1-C_4 alkyl)carbonyl; or optionally, M independently represents a single bond;

Y is a member selected from the group consisting of $(CH_2)_n$; $(CH_2)_nCH{=}CH$; $CH{=}CH(CH_2)_m$; $CH_2CH{=}CHCH_2$; $(CH_2)_nC(O)$; $C(O)(CH_2)_m$; $C(O)NH(CH_2)_n$; $(CH_2)_nNHC(O)$; $C(O)O(CH_2)_m$; $(CH_2)_nSO_2$; $SO_2(CH_2)_m$; and $(O)C(CH_2)_nC(O)$; wherein n is an integer from 1 to 3, m is an integer from 0 to 2, and each hydrogen independently is optionally replaced with a substituent independently selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl and C_3-C_6 cycloalkyloxy;

Z is a member selected from the group consisting of oxygen; sulfur; SO; SO_2; 1,1-cyclopropylene; carbonyl; and methylene optionally substituted with one to two substituents independently selected from halo, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl and C_3-C_6 cycloalkyloxy;

R^1 is a member selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, $(C_3$-$C_{10})$cycloalkyl-$(C_1$-$C_3)$alkyl, $(C_2$-C_4 alkenyl)C_1-C_3 alkyloxy, $(C_2$-C_4 alkynyl)C_1-C_3 alkyloxy, $(C_3$-C_{10} cycloalkyl)C_2-C_4 alkenyl, C_3-C_6 cycloalkylidenmethyl, $(C_4$-C_{10} cycloalkyloxy)C_1-C_4 alkyl, C_1-C_{10} cycloalkenyl, $(C_3$-$C_{10})$cycloalkenyl-$(C_1$-$C_3)$alkyl, $(C_1$-C_4 alkyloxy)C_1-C_3 alkyl, (C_1-C_4 alkylamino)C_1-C_3 alkyl, di-(C_1-C_3 alkylamino)C_1-C_3 alkyl, aryl, heteroaryl, (C_1-C_4 alkyl)carbonyl, arylcarbonyl, heteroarylcarbonyl, hydroxycarbonyl, aminocarbonyl, (C_1-C_4 alkyl)aminocarbonyl, di-(C_1-C_3 alkyl)aminocarbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-(C_1-C_4 alkyl)piperazin-1-ylcarbonyl, (C_1-C_4 alkyloxy)carbonyl, amino, (C_1-C_4 alkyl)amino, di-(C_1-C_3 alkyl)amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-(C_1-C_4 alkyl)piperazin-1-yl, (C_1-C_4 alkyl)carbonylamino, arylcarbonylamino, (C_1-C_4 alkylsulfonyl)carbonylamino, arylsulfonylcarbonylamino, C_1-C_4 alkylsulfonylamino, arylsulfonylamino, heteroarylcarbonylamino, C_1-C_6 alkyloxy, C_3-C_{10} cycloalkyloxy, C_3-C_{10} cycloalkenyloxy, aryloxy, heteroaryloxy, (aryl)C_1-C_3 alkyloxy, (heteroaryl)C_1-C_3 alkyloxy, C_1-C_4 alkylsulfanyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, C_3-C_{10} cycloalkylsulfanyl, C_3-C_{10} cycloalkylsulfinyl, C_3-C_{10} cycloalkylsulfonyl, C_3-C_{10} cycloalkenylsulfanyl, C_3-C_{10} cycloalkenylsulfinyl, C_3-C_{10} cycloalkenylsulfonyl, arylsulfanyl, arylsulfinyl, arylsulfonyl, hydroxy, cyano or nitro;

wherein alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl groups or portions are optionally partly or completely fluorinated and optionally mono- or disubstituted by identical or different substituents selected from chlorine, hydroxy, C_1-C_3 alkoxy and C_3-C_5 alkyl, and

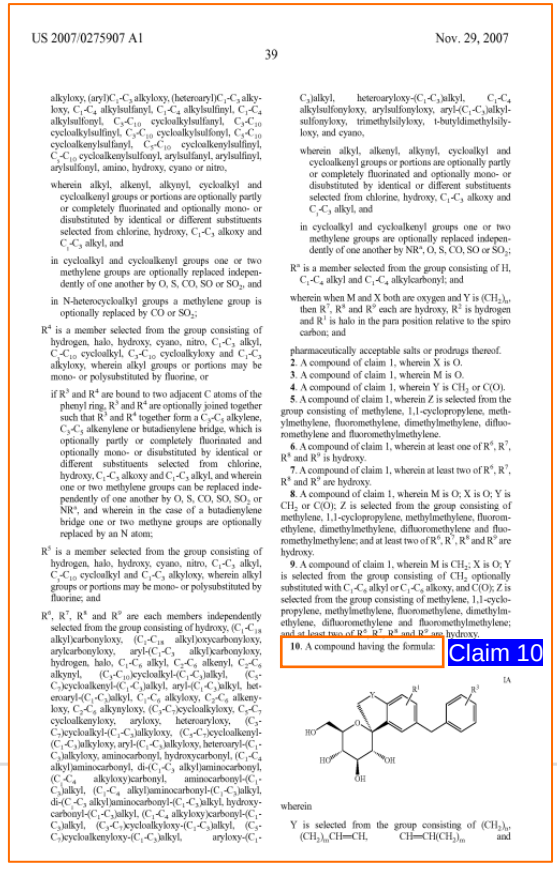
in cycloalkyl and cycloalkenyl groups one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO or SO_2, and

in N-heterocycloalkyl groups a methylene group is optionally replaced by CO or SO_2;

R^2 is a member selected from the group consisting of hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_3-C_{10} cycloalkyl, C_1-C_4 alkyloxy, C_3-C_{10} cycloalkyloxy, cyano and nitro, wherein alkyl groups or portions are optionally mono- or polysubstituted by fluorine, or

in the event that R^1 and R^2 are bound to two adjacent C atoms of the phenyl ring, R^1 and R^2 are optionally joined together such that R^1 and R^2 together form a C_3-C_5 alkylene, C_3-C_5 alkenylene or butadienylene bridge, which is optionally partly or completely fluorinated and optionally mono- or disubstituted by identical or different substituents selected from chlorine, hydroxy, C_1-C_3 alkoxy and C_1-C_3 alkyl, and wherein one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO, SO_2 or NR*, and wherein one or two methylene groups are optionally replaced by an N atom;

R^3 is a member selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, $(C_3$-$C_{10})$cycloalkyl-$(C_1$-$C_3)$alkyl, C_4-C_{10} cycloalkenyl, $(C_3$-$C_{10})$cycloalkenyl-$(C_1$-$C_3)$alkyl, $(C_2$-C_4 alkyloxy)C_1-C_3 alkyl, $(C_1$-C_4 alkylamino)C_1-C_3 alkyl, di-(C_1-C_3 alkylamino)C_1-C_3 alkyl, $(C_3$-C_{10} cycloalkyl)C_1-C_3 alkyl, C_3-C_6 cycloalkylidenmethyl, aryl, heteroaryl, (C_1-C_4 alkyl)carbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, (C_1-C_4 alkyl)aminocarbonyl, di-(C_1-C_3 alkyl)aminocarbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-(C_1-C_4 alkyl)piperazin-1-ylcarbonyl, hydroxycarbonyl, (C_1-C_4 alkyloxy)carbonyl, C_1-C_4 alkylamino, di-(C_1-C_3 alkyl)amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-(C_1-C_4 alkyl)piperazin-1-yl, (C_1-C_4 alkyl)carbonylamino, arylcarbonylamino, heteroarylcarbonylamino, C_1-C_4 alkylsulfonylamino, arylsulfonylamino, C_1-C_6 alkyloxy, C_3-C_{10} cycloalkyloxy, C_3-C_{10} cycloalkenyloxy, aryloxy, heteroaryloxy, (C_1-C_4 alkenyl)C_1-C_3 alkyloxy, (C_2-C_4 alkynyl)C_1-C_3



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alkyloxy, (aryl)C_1-C_3 alkyloxy, (heteroaryl)C_1-C_3 alkyloxy, C_1-C_4 alkylsulfanyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, C_3-C_{10} cycloalkylsulfanyl, C_3-C_{10} cycloalkylsulfinyl, C_3-C_{10} cycloalkylsulfonyl, C_3-C_{10} cycloalkenylsulfanyl, C_3-C_{10} cycloalkenylsulfinyl, C_3-C_{10} cycloalkenylsulfonyl, arylsulfanyl, arylsulfinyl, arylsulfonyl, amino, hydroxy, cyano or nitro,

wherein alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl groups or portions are optionally partly or completely fluorinated and optionally mono- or disubstituted by identical or different substituents selected from chlorine, hydroxy, C_1-C_3 alkoxy and C_3-C_5 alkyl, and

in cycloalkyl and cycloalkenyl groups one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO or SO_2, and

in N-heterocycloalkyl groups a methylene group is optionally replaced by CO or SO_2;

R^4 is a member selected from the group consisting of hydrogen, halo, hydroxy, cyano, nitro, C_1-C_3 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkyloxy and C_1-C_3 alkyloxy, wherein alkyl groups or portions may be mono- or polysubstituted by fluorine, or

if R^3 and R^4 are bound to two adjacent C atoms of the phenyl ring, R^3 and R^4 are optionally joined together such that R^3 and R^4 together form a C_3-C_5 alkylene, C_3-C_5 alkenylene or butadienylene bridge, which is optionally partly or completely fluorinated and optionally mono- or disubstituted by identical or different substituents selected from chlorine, hydroxy, C_1-C_3 alkoxy and C_1-C_3 alkyl, and wherein one or two methylene groups are optionally replaced independently of one another by O, S, CO, SO, SO_2 or NR*, and wherein in the case of a butadienylene bridge one or two methyne groups are optionally replaced by an N atom;

R^5 is a member selected from the group consisting of hydrogen, halo, hydroxy, cyano, nitro, C_1-C_3 alkyl, C_3-C_{10} cycloalkyl and C_1-C_3 alkyloxy, wherein alkyl groups or portions may be mono- or polysubstituted by fluorine; and

R^6, R^7, R^8 and R^9 are each members independently selected from the group consisting of hydroxy, $(C_1$-C_{18} alkyl)carbonyloxy, $(C_1$-C_{18} alkyl)oxycarbonyloxy, arylcarbonyloxy, aryl-$(C_1$-C_3 alkyl)carbonyloxy, hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(C_3$-$C_{10})$cycloalkyl-$(C_1$-$C_3)$alkyl, $(C_3$-$C_5)$cycloalkenyl-$(C_1$-$C_3)$alkyl, aryl-$(C_1$-$C_3)$alkyl, heteroaryl-$(C_1$-$C_3)$alkyl, C_1-C_6 alkyloxy, C_2-C_6 alkenyloxy, C_2-C_6 alkynyloxy, $(C_3$-$C_7)$cycloalkyloxy, C_4-C_7 cycloalkenyloxy, aryloxy, heteroaryloxy, $(C_3$-$C_7)$cycloalkyl-$(C_1$-$C_3)$alkyloxy, $(C_3$-$C_7)$cycloalkenyl-$(C_1$-$C_3)$alkyloxy, aryl-$(C_1$-$C_3)$alkyloxy, heteroaryl-$(C_1$-$C_3)$alkyloxy, aminocarbonyl, hydroxycarbonyl, (C_1-C_4 alkyl)aminocarbonyl, di-(C_1-C_3 alkyl)aminocarbonyl, (C_1-C_4 alkyloxy)carbonyl, aminocarbonyl-(C_1-C_3)alkyl, (C_1-C_4 alkyl)aminocarbonyl-(C_1-C_3)alkyl, di-(C_1-C_3 alkyl)aminocarbonyl-(C_1-C_3)alkyl, hydroxycarbonyl-(C_1-C_3)alkyl, (C_1-C_4 alkyloxy)carbonyl-(C_1-C_3)alkyl, (C_3-$C_7)$cycloalkyloxy-(C_1-C_3)alkyl, (C_3-$C_7)$cycloalkenyloxy-(C_1-C_3)alkyl, aryloxy-(C_1-C_3)alkyl, heteroaryloxy-(C_1-C_3)alkyl, C_1-C_4 alkylsulfonyloxy, arylsulfonyloxy, aryl-(C_1-C_3)alkylsulfonyloxy, trimethylsilyloxy, t-butyldimethylsilyloxy, and cyano,

wherein alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl groups or portions are optionally partly or completely fluorinated and optionally mono- or disubstituted by identical or different substituents selected from chlorine, hydroxy, C_1-C_3 alkoxy and C_1-C_3 alkyl, and

in cycloalkyl and cycloalkenyl groups one or two methylene groups are optionally replaced independently of one another by NR*, O, S, CO, SO or SO_2;

R* is a member selected from the group consisting of H, C_1-C_4 alkyl and C_1-C_4 alkylcarbonyl; and

wherein when M and X both are oxygen and Y is $(CH_2)_n$, then R^7, R^8 and R^9 each are hydroxy, R^2 is hydrogen and R^1 is halo in the para position relative to the spiro carbon; and

pharmaceutically acceptable salts or prodrugs thereof.

2. A compound of claim 1, wherein X is O.

3. A compound of claim 1, wherein M is O.

4. A compound of claim 1, wherein Y is CH_2 or C(O).

5. A compound of claim 1, wherein Z is selected from the group consisting of methylene, 1,1-cyclopropylene, methylmethylene, fluoromethylene, dimethylmethylene, difluoromethylene and fluoromethylene and fluoromethylmethylene.

6. A compound of claim 1, wherein at least one of R^6, R^7, R^8 and R^9 is hydroxy.

7. A compound of claim 1, wherein at least two of R^6, R^7, R^8 and R^9 are hydroxy.

8. A compound of claim 1, wherein M is O; X is O; Y is CH_2 or C(O); Z is selected from the group consisting of methylene, 1,1-cyclopropylene, methylmethylene, fluoromethylene, dimethylmethylene, difluoromethylene and fluoromethylmethylene; and at least two of R^6, R^7, R^8 and R^9 are hydroxy.

9. A compound of claim 1, wherein M is CH_2; X is O; Y is selected from the group consisting of CH_2 optionally substituted with C_1-C_4 alkyl or C_1-C_4 alkoxy, and C(O); Z is selected from the group consisting of methylene, 1,1-cyclopropylene, methylmethylene, fluoromethylene, dimethylmethylene, difluoromethylene and fluoromethylmethylene; and at least two of R^6, R^7, R^8 and R^9 are hydroxy.

10. A compound having the formula:

Claim 10

wherein

Y is selected from the group consisting of $(CH_2)_n$, $(CH_2)_nCH{=}CH$, $CH{=}CH(CH_2)_m$ and

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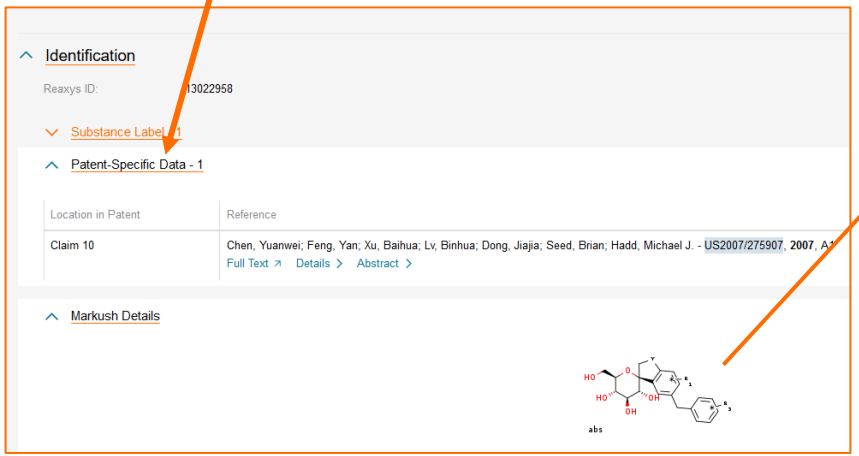
Reaxys对于专利中Markush的提炼



Label	Value	Size	Attributes	Substituted by
Y	(C$H2)n			
	(C$H2)mC$H=C$H			
	C$H=C$H(C$H2)m			
	C$H2C$H=CHCH2			
	(C$H2)mC(O)			
	C(O)(C$H2)m			
	C(O)N$H(C$H2)m			
	(C$H2)mN$HC(O)			
	C(O)O(C$H2)m			
	(C$H2)mSO2			
	SO2(C$H2)m			
	(O)C(C$H2)mC(O)			
R1	hydrogen			
	halo			
	alkyl	1-6C		de;fg
	alkenyl	2-6C		de;fg
	alkynyl	2-6C		de;fg
	cycloalkyl	3-10C	1-2 methylene groups o replaced by <$h>	de;fg
	$cycloalkyl310-$alkyl13			
	($alkenyl24)$alkyloxy13			

提炼了出现的位置和Markush的结构细节。

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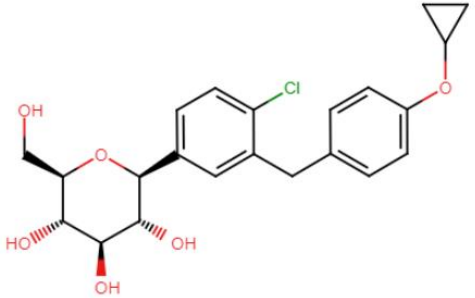
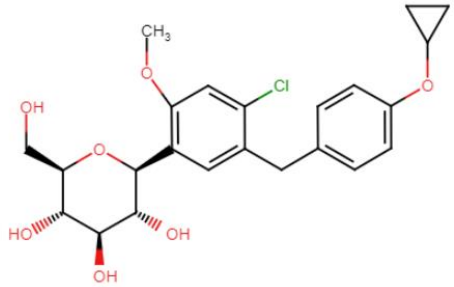
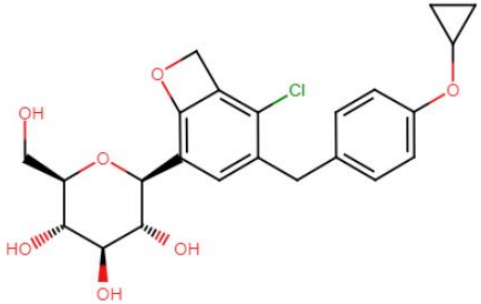
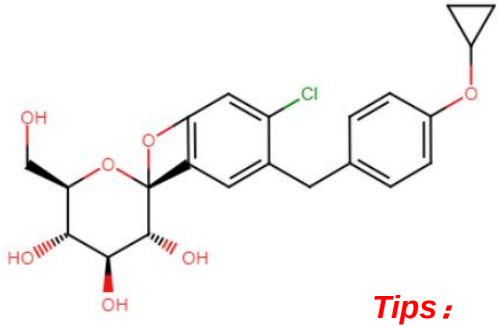
评估完专利后，设计一些全新化合物（假设下列结构无专利问题）









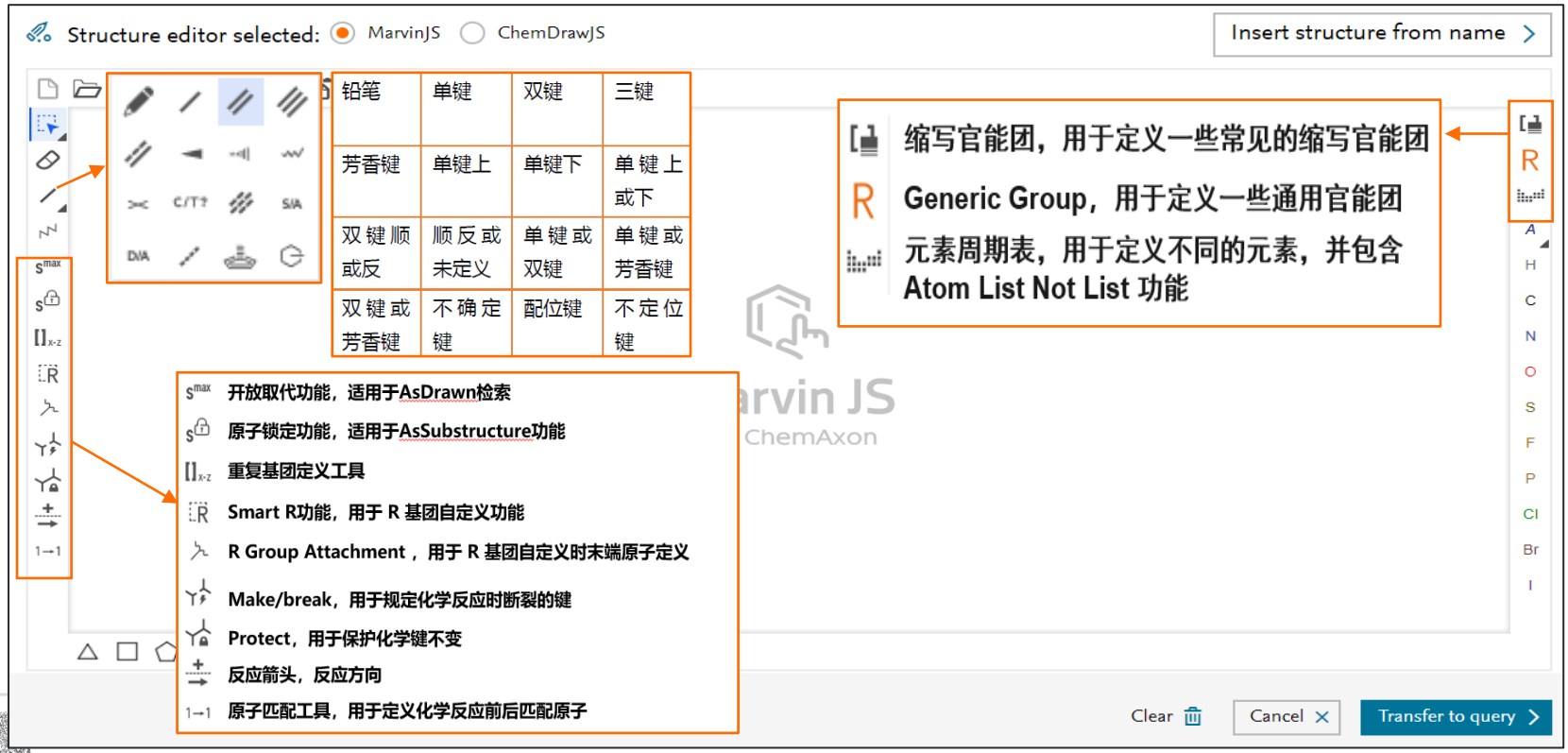
Tips：

案例制作当天，Reaxys中没有相同结构。

Agenda

- Reaxys介绍与内容
  - Reaxys介绍
  - Reaxys对于科技文献的提炼
- Reaxys中的化学科学数据获取
  - Reaxys中的文献快速检索方法
  - Reaxys中物质理化性质的查询与结构反查
  - 利用Reaxys进行专利突破与全新分子的专利评估
  - Reaxys中结构面板详解，合成信息的检索与合成计划制作
- Q&A

Reaxys中的结构面板



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结构面版功能合集

2022新版结构面板	视频链接		
1-最基本功能	https://www.bilibili.com/video/BV1Jm4y1F7hG		
2-不定位键	https://www.bilibili.com/video/BV1xP4y127G9		
3-缩写写官能团	https://www.bilibili.com/video/BV16K411o72c		
4-通用官能团与G	https://www.bilibili.com/video/BV16P4y1y7QA		
5-原子列表与列表非	https://www.bilibili.com/video/BV1w84y117yD		
	R基团与Linker：	关于R基团的讨论	
6,7-R基团的使用与讨论	https://www.bilibili.com/video/BV1Ze4y1p7hx	https://www.bilibili.com/video/BV1w14y1n7dD	
	讨论1：基本使用方法和逻辑	讨论2：取代基的控制	讨论3：As Draw的控制
8,9,10-检索模式的讨论	https://www.bilibili.com/video/BV1rG4y1V7Hw	https://www.bilibili.com/video/BV1aG4y1G7cb	https://www.bilibili.com/video/BV1k14y1n76d
11-反应的基本定义	https://www.bilibili.com/video/BV17W4y1p7p1		
12-配位化合物同位素盐	https://www.bilibili.com/video/BV15v4y1R7xb		
	属性列表讨论（上）	属性列表讨论（下）	
13,14-原子属性列表	https://www.bilibili.com/video/BV1UM411B7rQ	https://www.bilibili.com/video/BV1KW4y1T7Pv	
15-键的控制	https://www.bilibili.com/video/BV1LD4y1h79d		
16-More Option	https://www.bilibili.com/video/BV1U84y147ao		

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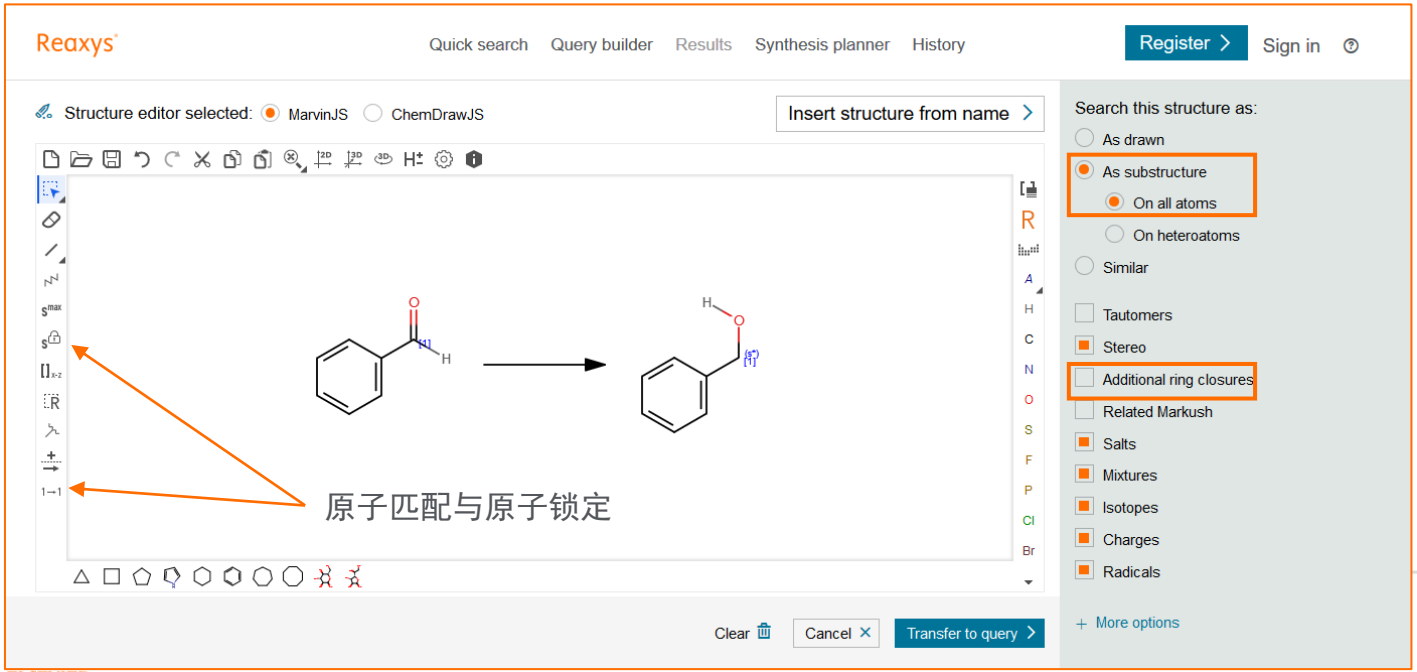
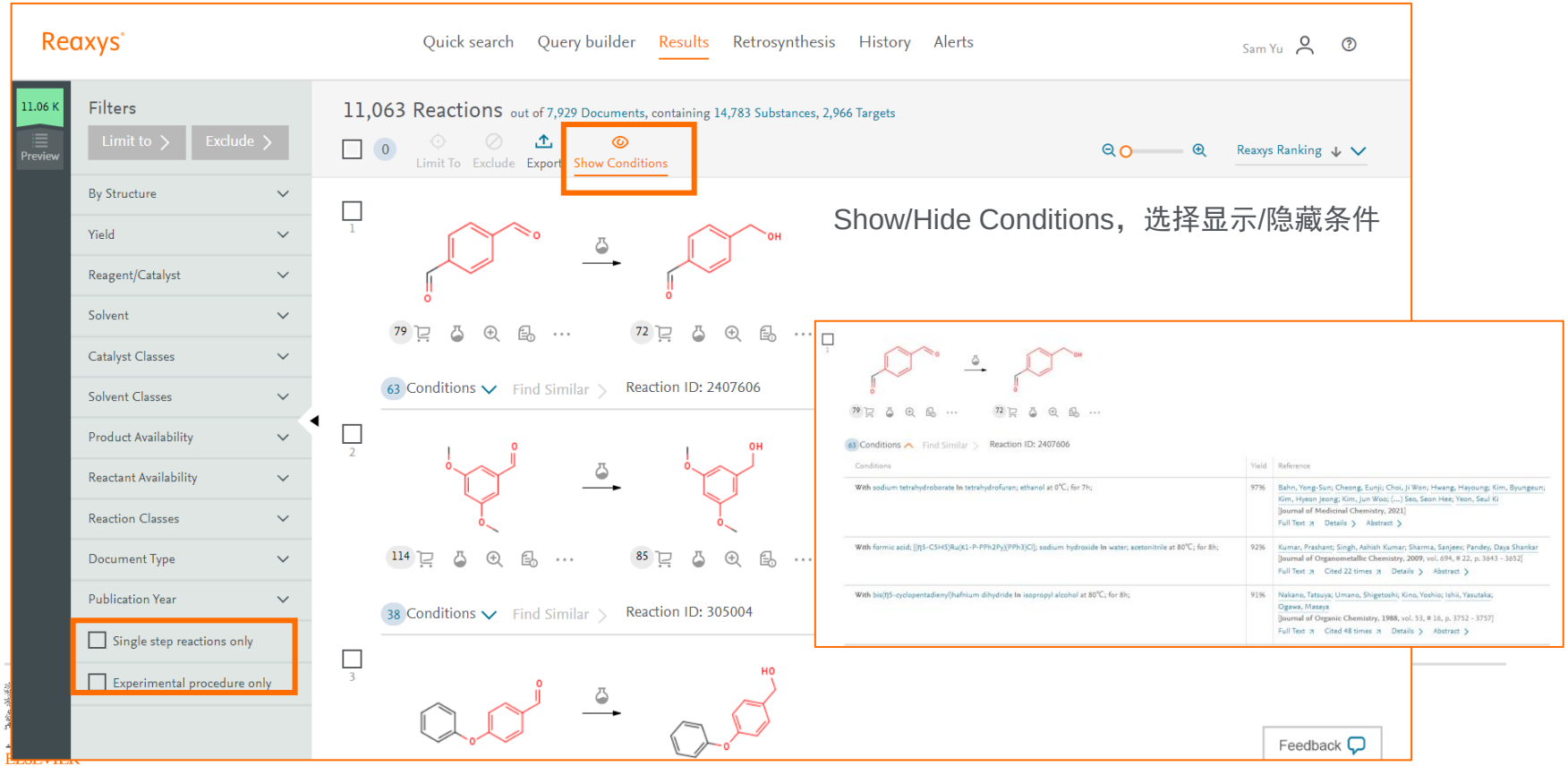
Case 8：Reaxys中最简单的反应定义与筛选

- 检索以下核心结构反应并进行反应筛选操作
- 视频操作过程
  - https://www.bilibili.com/video/BV1BT4y1F7vT



Reaxys中的结果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Quick search
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Document Type
Publication Year
Single step reactions only
Experimental procedure only
11,063 Reactions out of 7,929 Documents, containing 14,783 Substances, 2,966 Targets
Limit To
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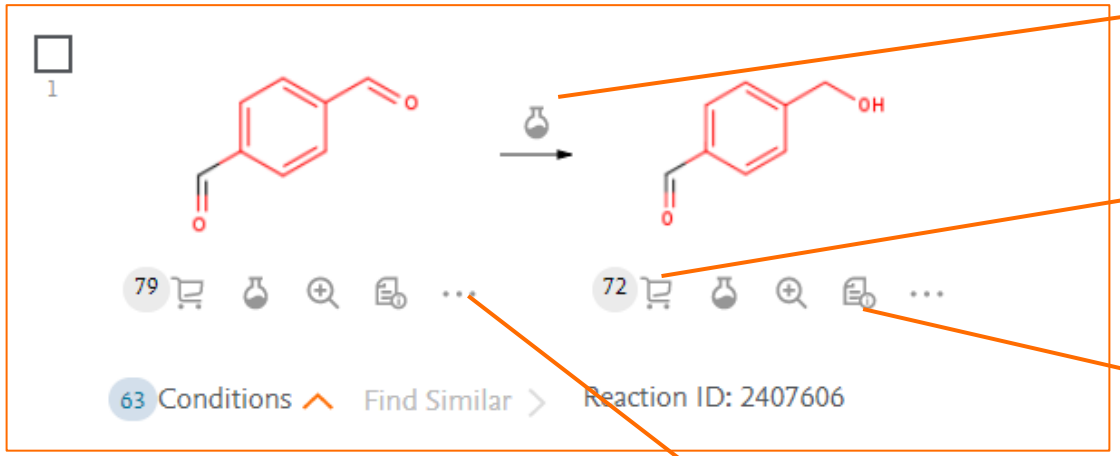
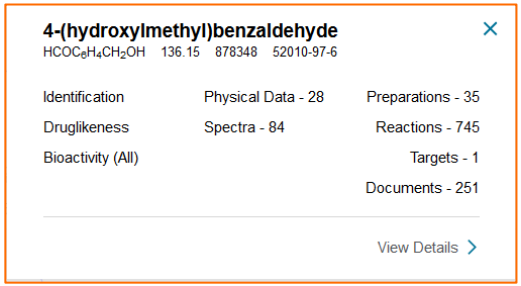
Export
Show Conditions
Reaxys Ranking
63 Conditions
Find Similar
Reaction ID: 2407606
114
85
38 Conditions
Find Similar
Reaction ID: 305004
Feedback
Show/Hide Conditions，选择显示/隐藏条件

Reaxys的一条反应的界面



进行合成计划

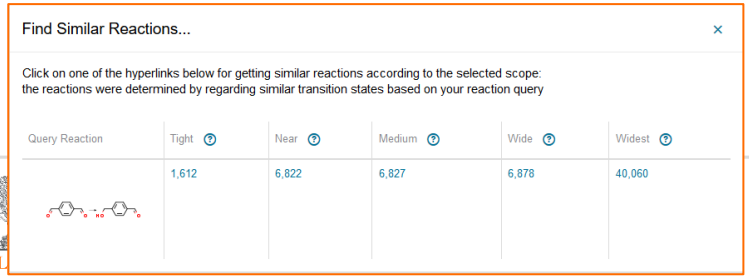
查看商业来源

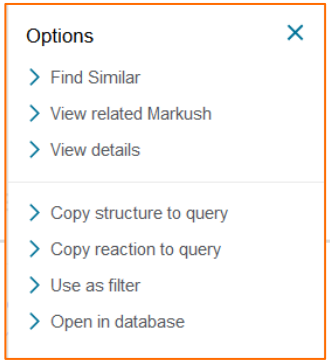


查看物质详情

查看条件

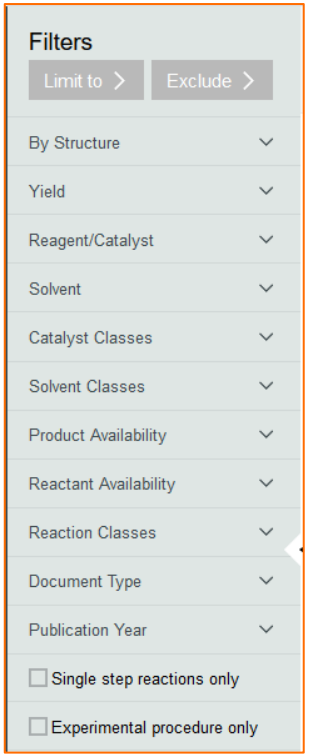
寻找相似反应

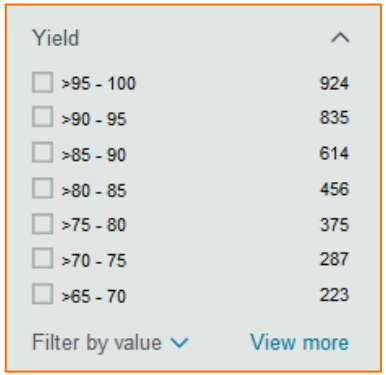


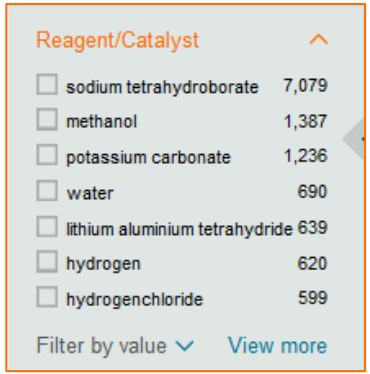


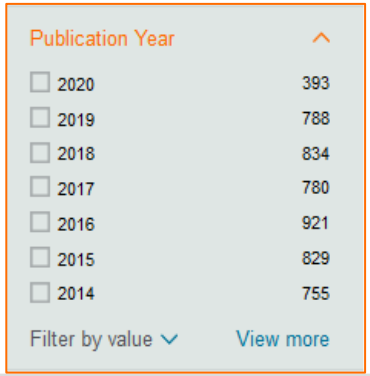
更多与物质相关操作

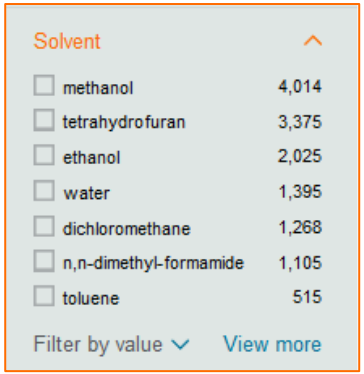
Reaxys的筛选操作











Tips:

常见的一些反应筛选工具，如:收率，催化剂/试剂，溶剂，文献类型，出版年限等

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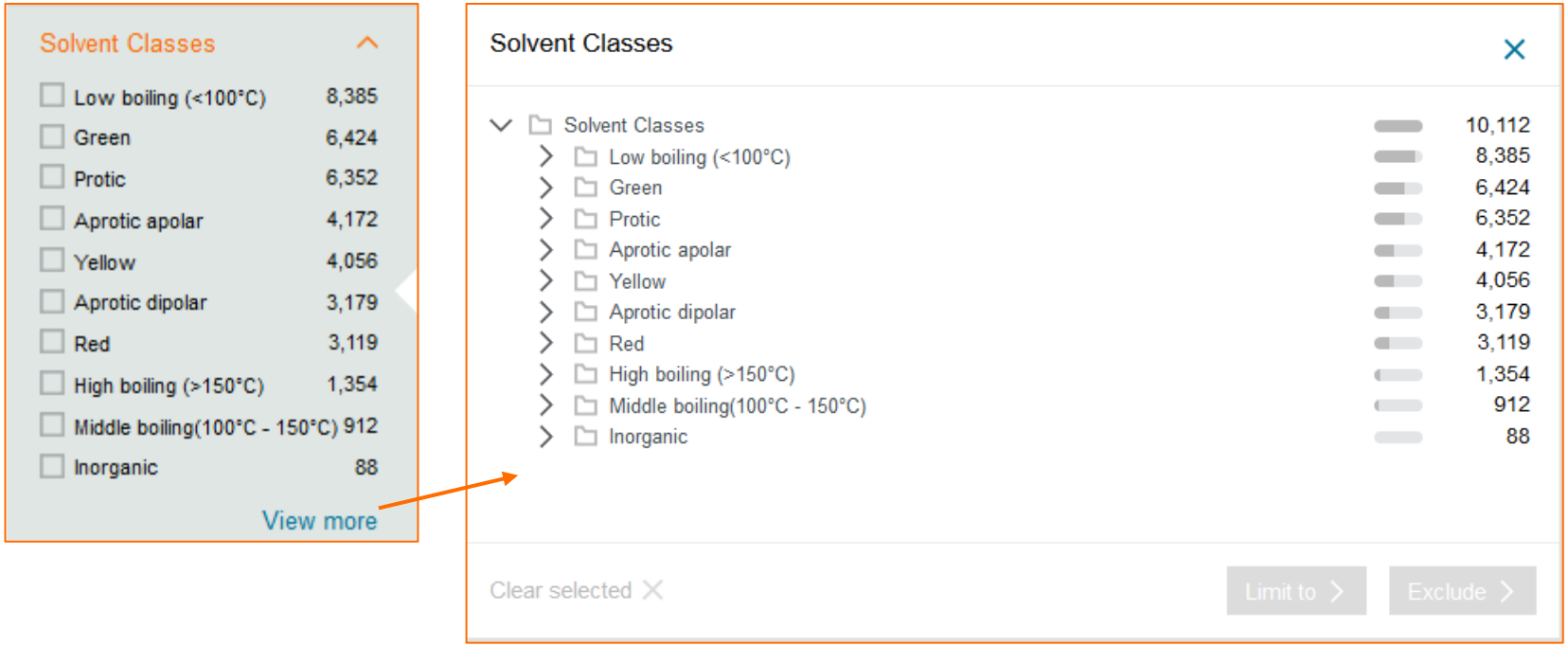
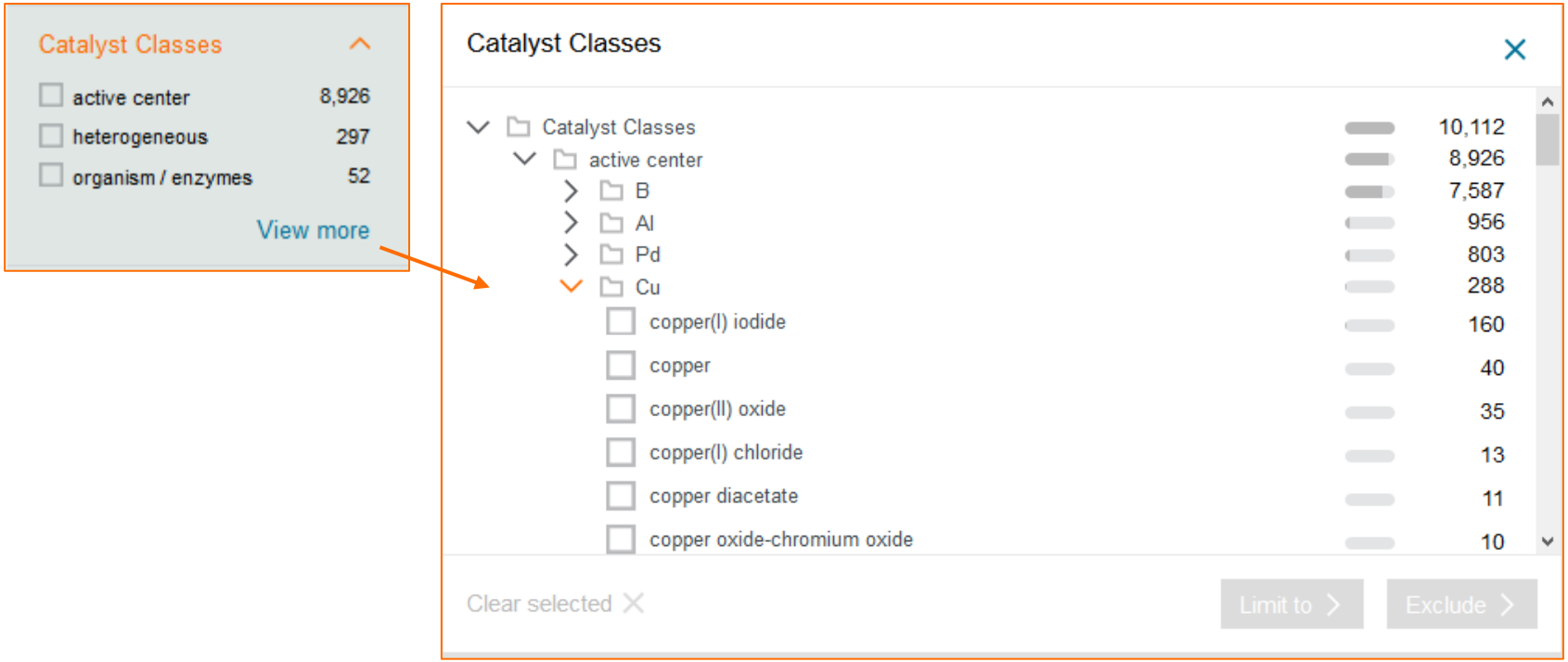
Reaxys中的一些特殊筛选工具—溶剂分类

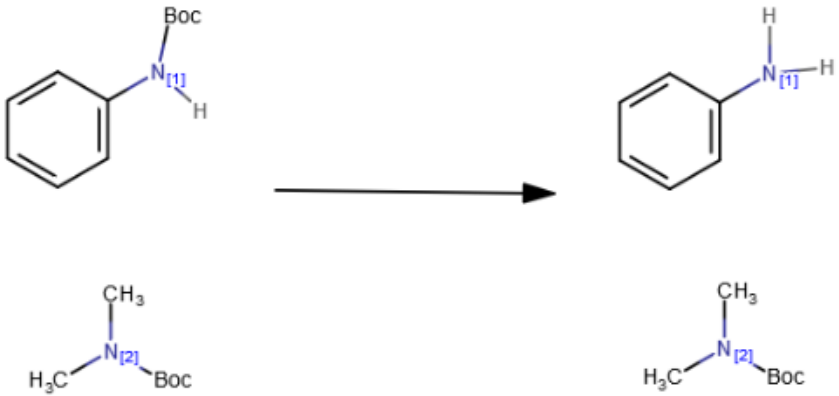


Reaxys中的一些特殊筛选工具—催化剂分类



Case 9：选择性氧化还原脱保护反应的定义

- 结构中两个带Boc的片段，两个片段以任意的形式相接在一个分子中
- 反应过后把其中一个片段的Boc脱掉，但是另外一个Boc不变



视频操作过程：
https://www.bilibili.com/video/BV1Vv411r7Bc

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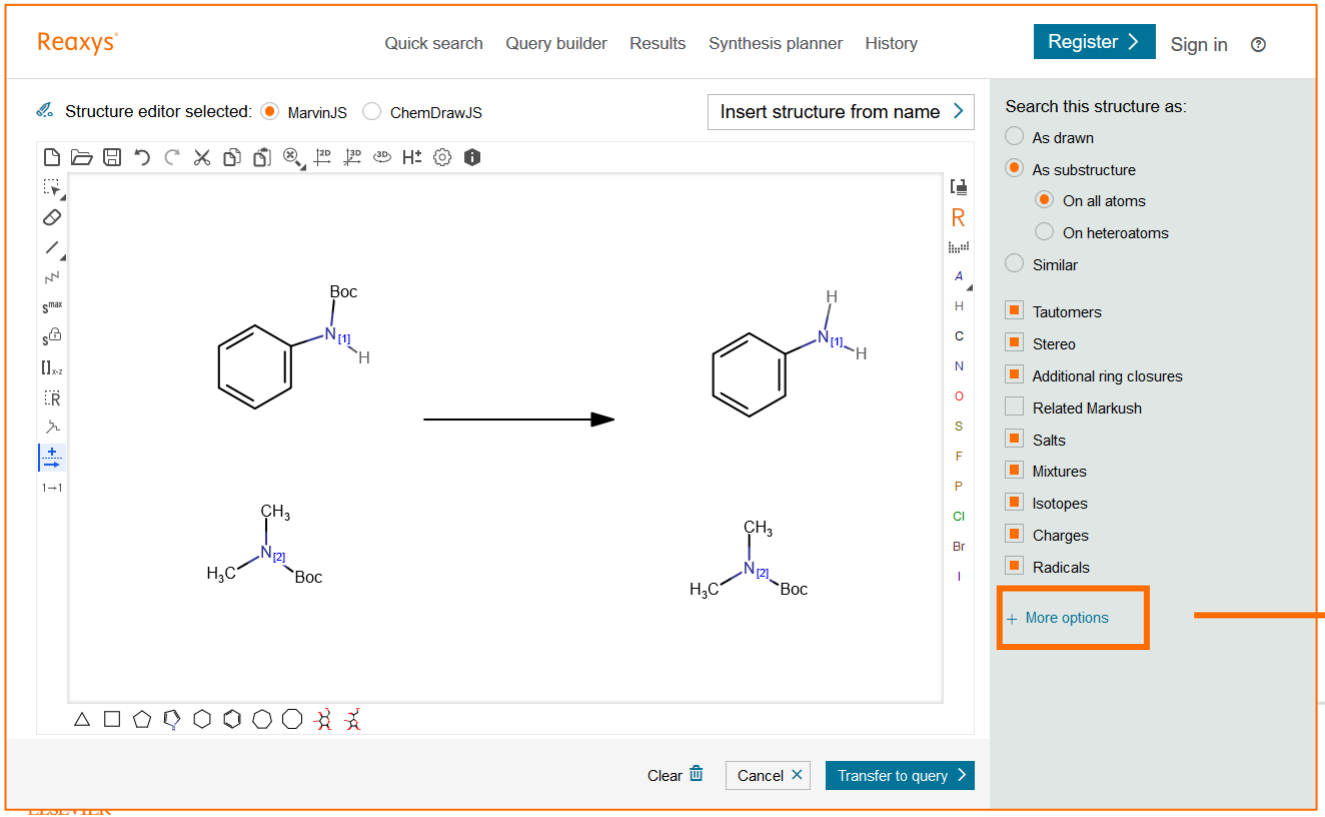
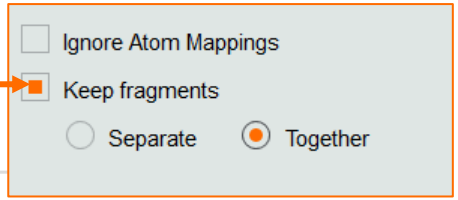
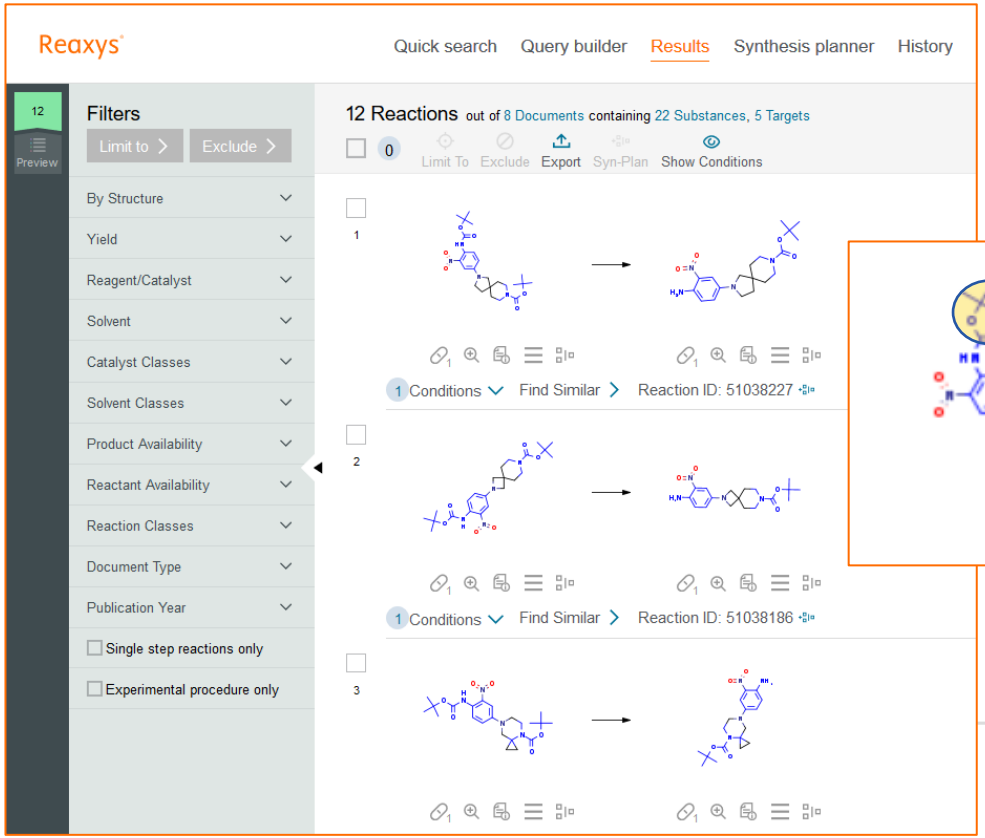
Reaxys中的结构定义





Reaxys可以直接设定这些片段在一个结构中

Reaxys中结果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Solvent
Catalyst Classes
Solvent Classes
Product Availability
Reactant Availability
Reaction Classes
Document Type
Publication Year
Single step reactions only
Experimental procedure only
12 Reactions out of 8 Documents containing 22 Substances, 5 Targets
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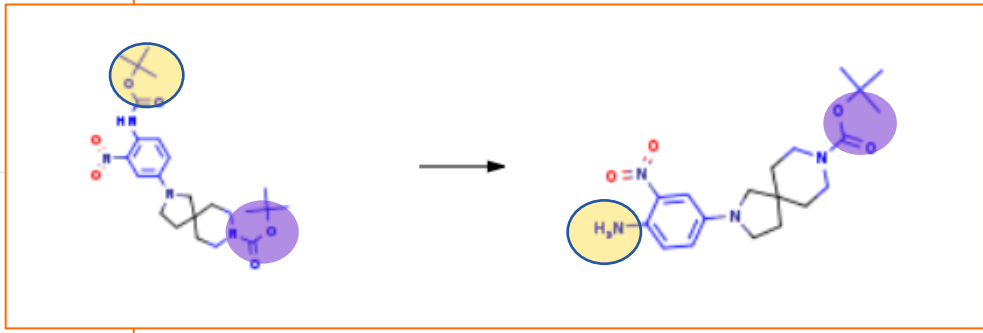
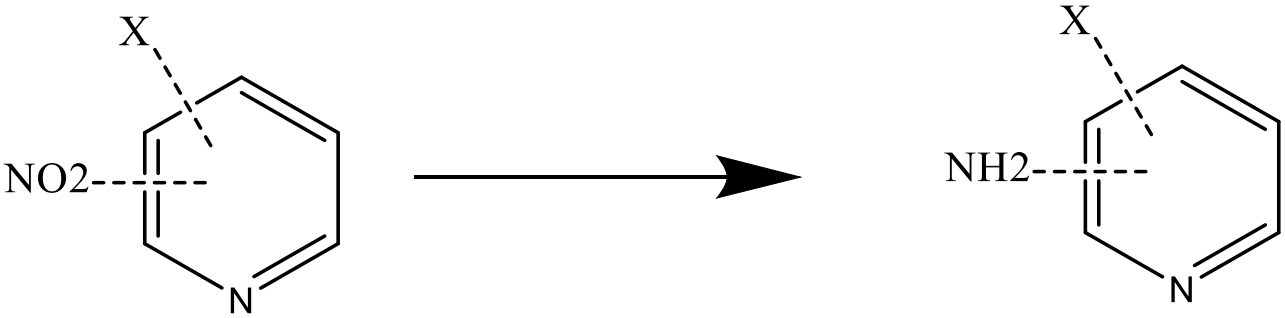


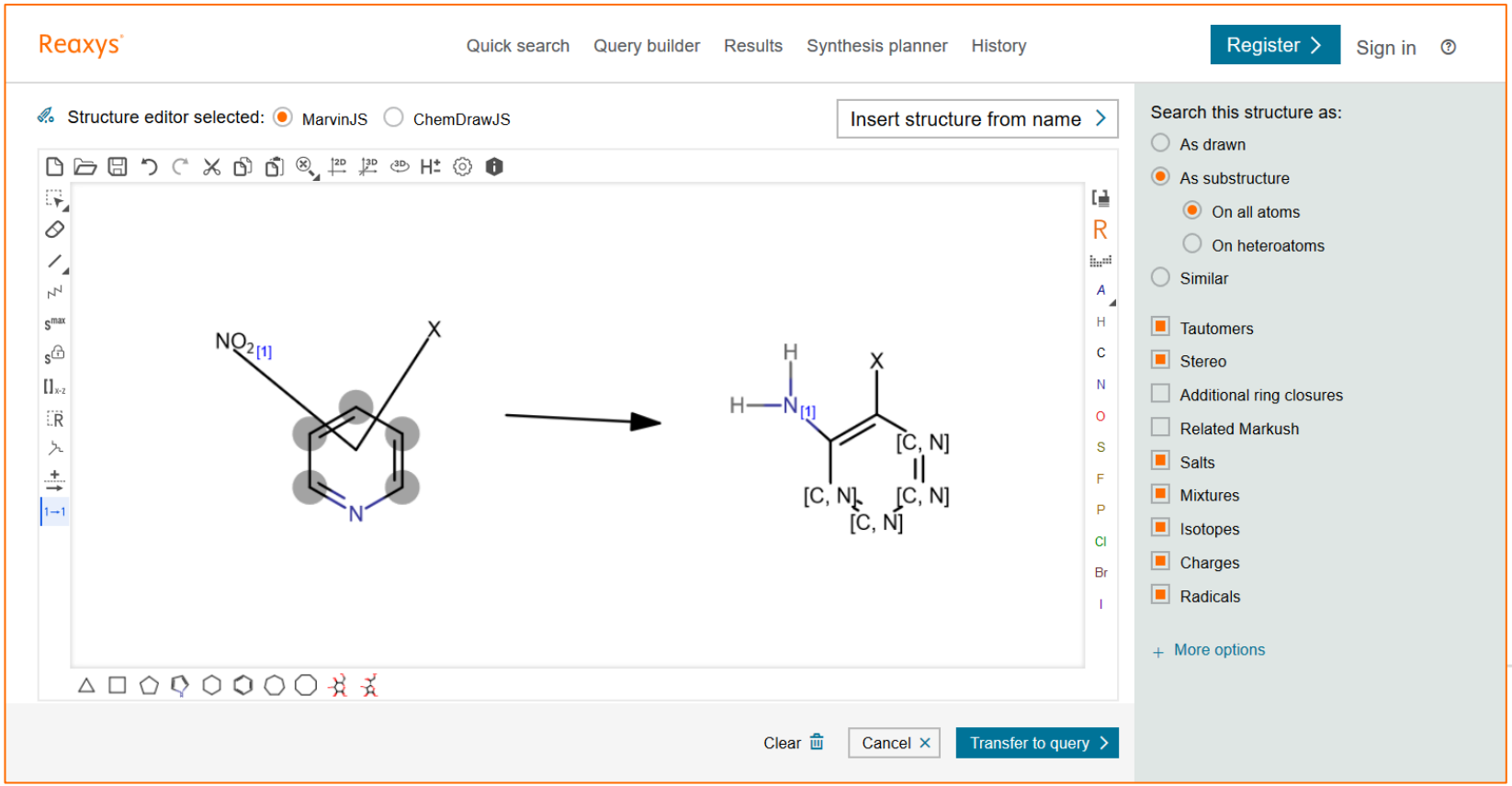
Case 10：结构中有特殊需求的反应定义

- 检索以下反应
  - 吡啶环上存在一个硝基，一个卤素，且这两个官能团处于邻位
  - 反应过后硝基还原成氨基
  - 定义难点：如果确保NO2和卤素处于邻位

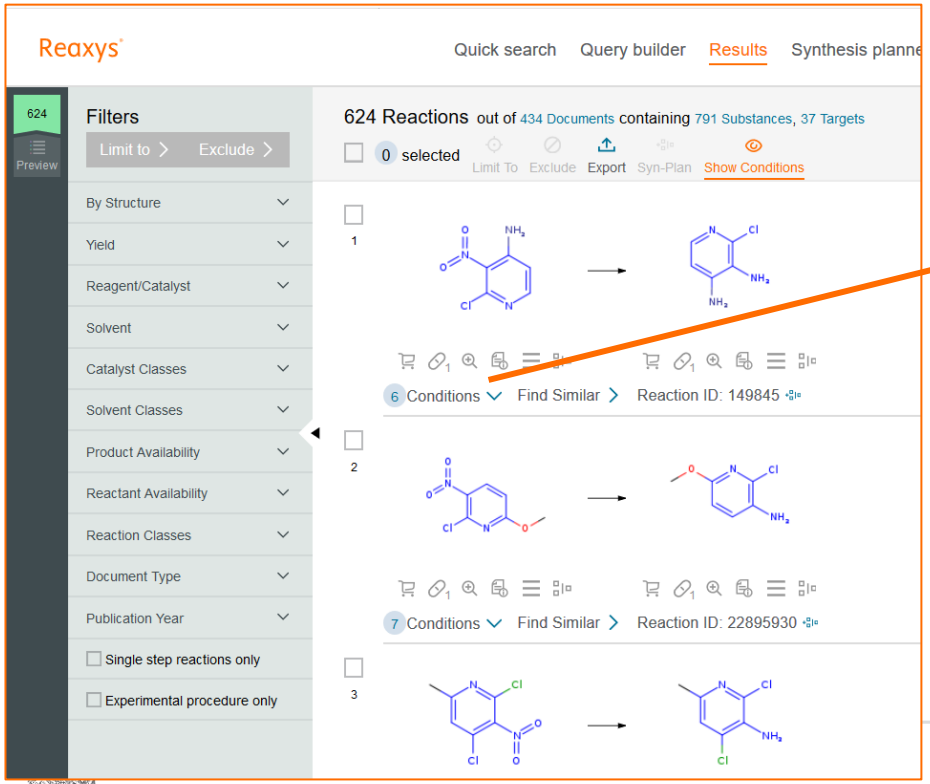


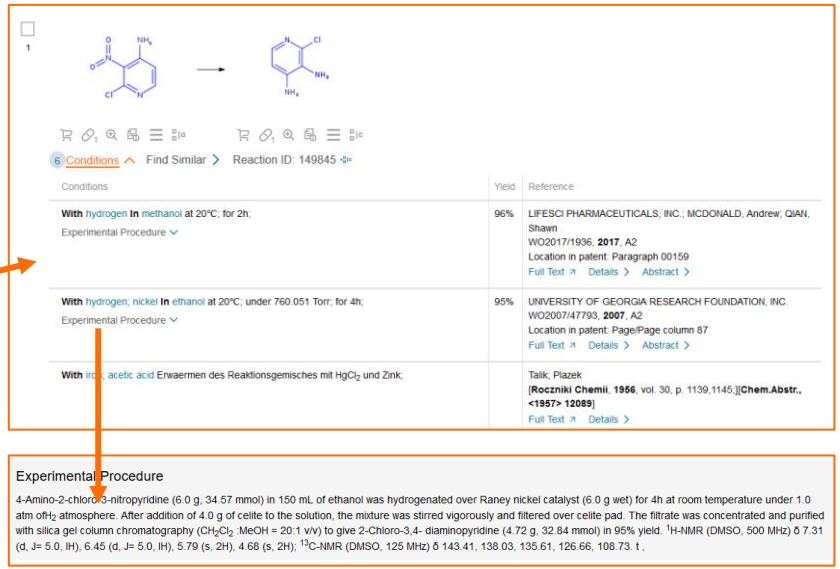
视频操作过程：
https://www.bilibili.com/video/BV1si4y177as

Reaxys中的结构定义



最后的结果





Experimental Procedure

4-Amino-2-chloro-3-nitropyridine (6.0 g, 34.57 mmol) in 150 mL of ethanol was hydrogenated over Raney nickel catalyst (6.0 g wet) for 4h at room temperature under 1.0 atm ofH_2 atmosphere. After addition of 4.0 g of celite to the solution, the mixture was stirred vigorously and filtered over celite pad. The filtrate was concentrated and purified with silica gel column chromatography (CH_2Cl_2 :MeOH = 20:1 v/v) to give 2-Chloro-3,4- diaminopyridine (4.72 g, 32.84 mmol) in 95% yield. ^{1}H-NMR (DMSO, 500 MHz) δ 7.31 (d, J= 5.0, lH), 6.45 (d, J= 5.0, lH), 5.79 (s, 2H), 4.68 (s, 2H); ^{13}C-NMR (DMSO, 125 MHz) δ 143.41, 138.03, 135.61, 126.66, 108.73. t ,

Reaxys将相同scheme的反应全部整合成1条反应，在同样的反应下列举不同的反应条件。

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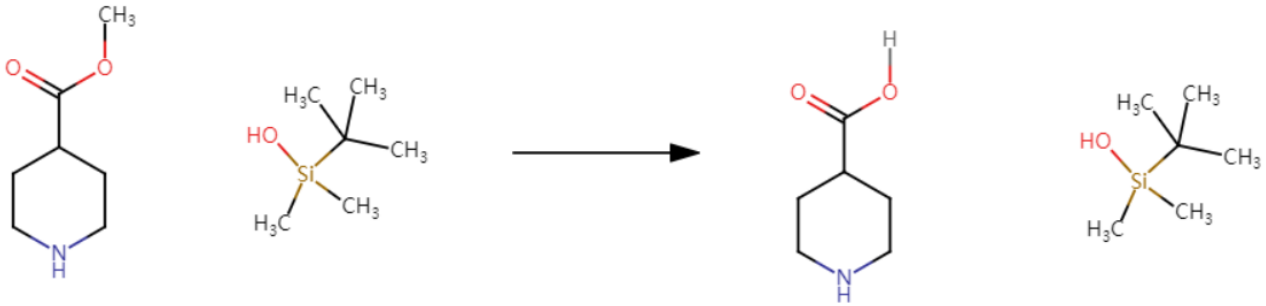
Case 11：检索结果不理性时的拓展策略

- 在硅基存在的情况下，水解脂基
- 利用Reaxys中的碎片反应检索，只能获取2条反应，如何扩展结果



视频操作: https://www.bilibili.com/video/BV14A41147gL

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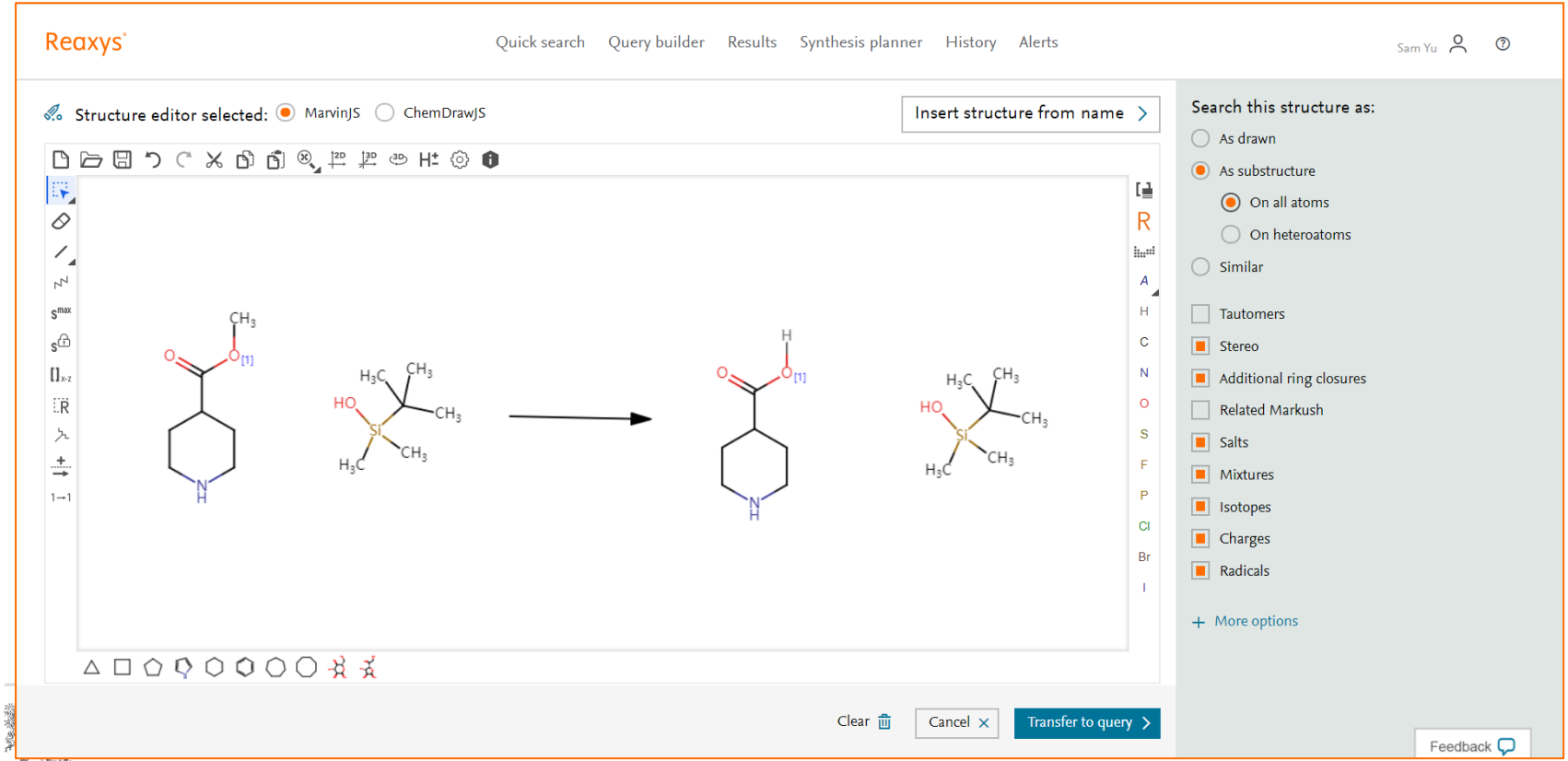
利用Reaxys的碎片反应检索策略



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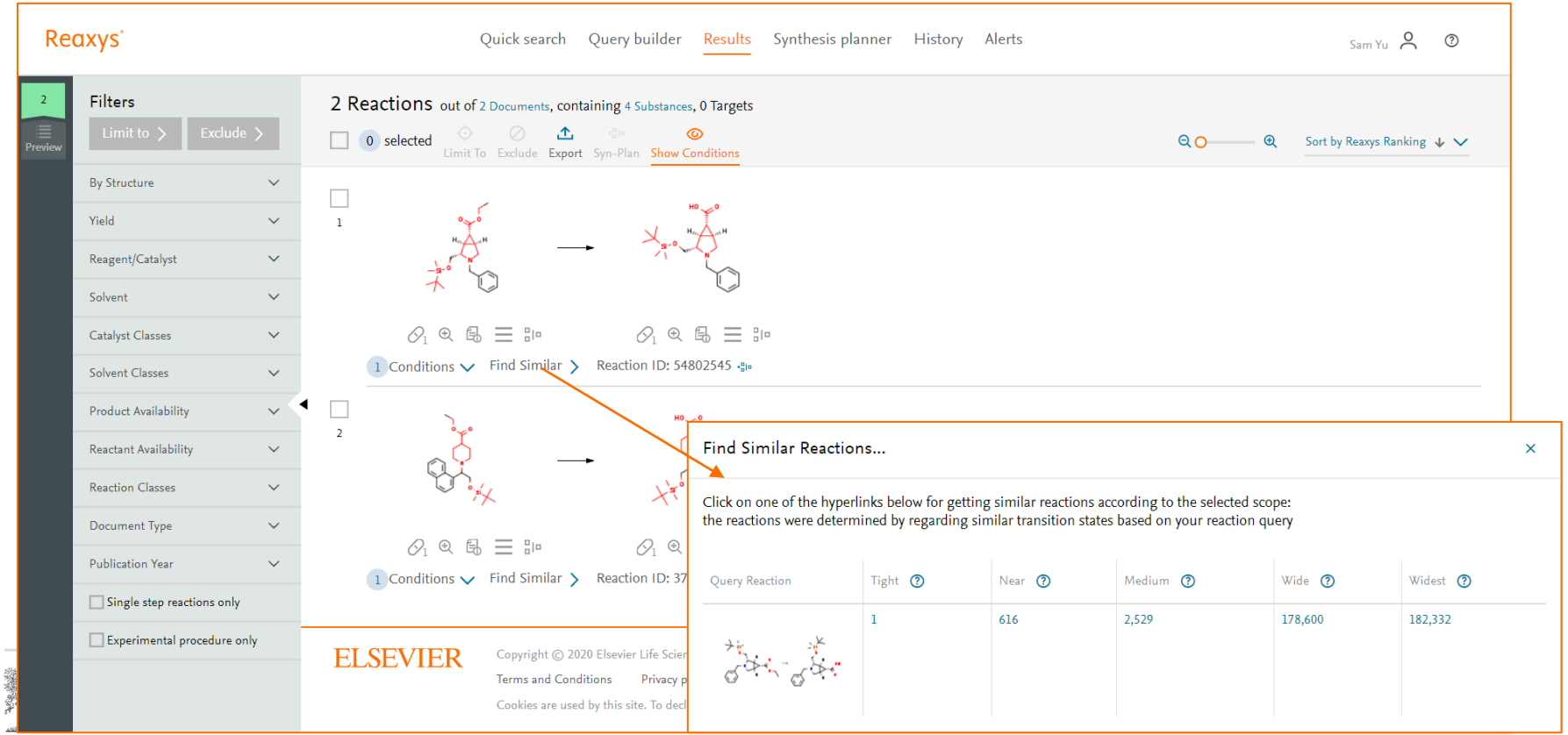
最后的结果


Reaxys
Quick search
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Alerts
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Solvent
Catalyst Classes
Solvent Classes
Product Availability
Reactant Availability
Reaction Classes
Document Type
Publication Year
Single step reactions only
Experimental procedure only
2 Reactions out of 2 Documents, containing 4 Substances, 0 Targets
0 selected
Limit To
Exclude
Export
Syn-Plan
Show Conditions
Sort by Reaxys Ranking
1
1 Conditions
Find Similar
Reaction ID: 54802545
2
1 Conditions
Find Similar
Reaction ID: 37
Find Similar Reactions...
Click on one of the hyperlinks below for getting similar reactions according to the selected scope:
the reactions were determined by regarding similar transition states based on your reaction query
Query Reaction
Tight
Near
Medium
Wide
Widest
1
616
2,529
178,600
182,332
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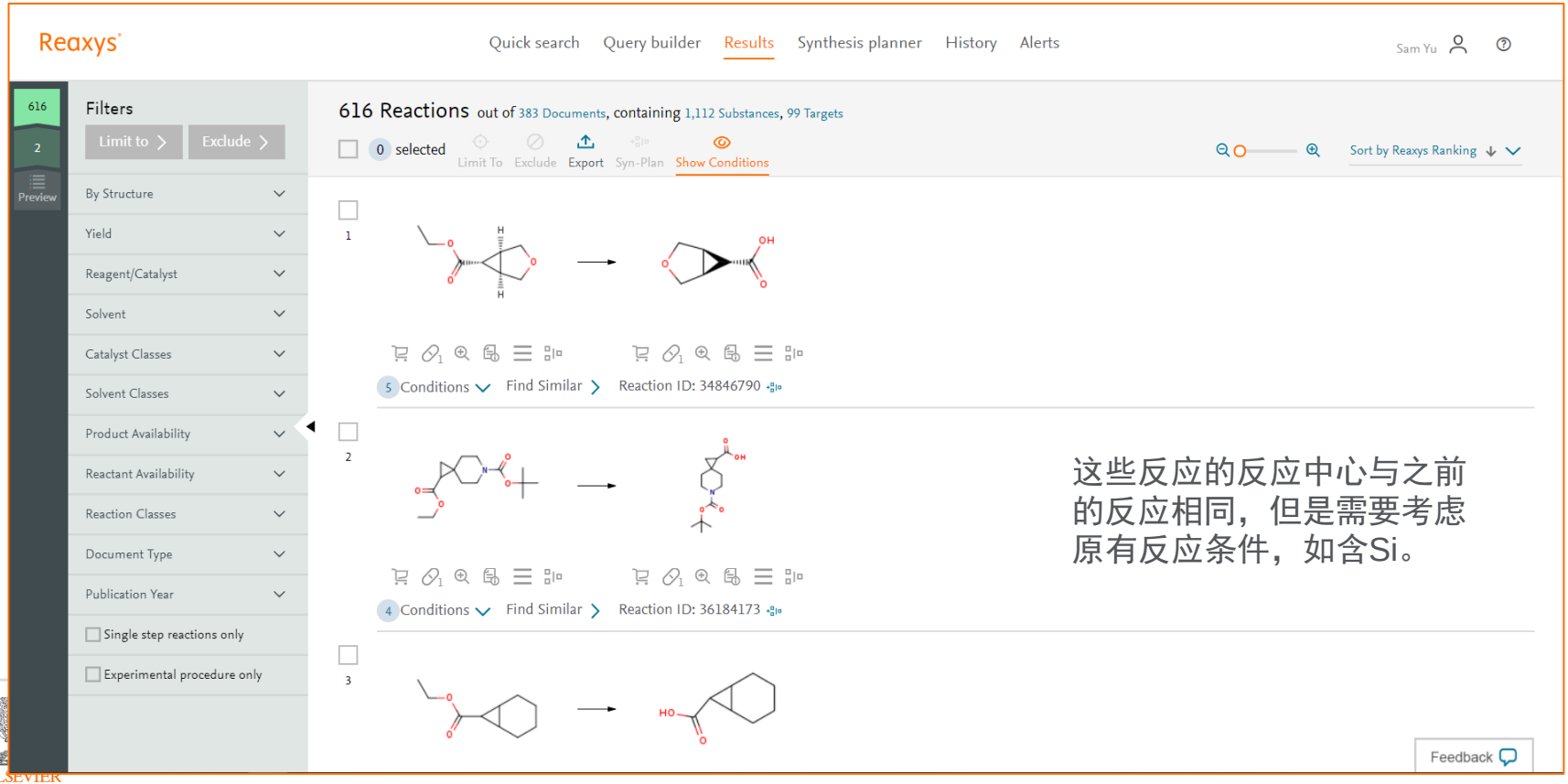
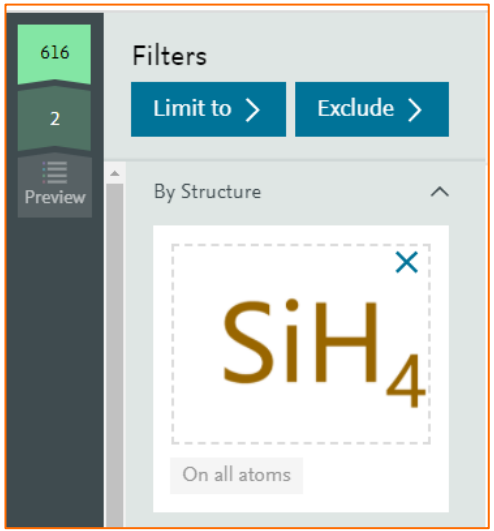
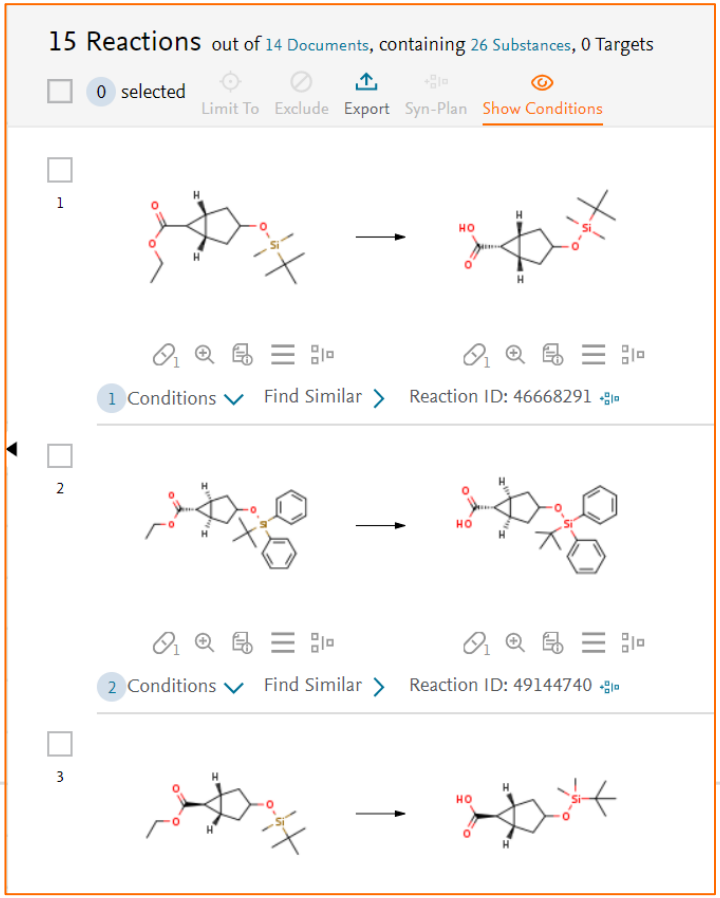
发现检索到的结果中并没有Si



这些反应的反应中心与之前的反应相同，但是需要考虑原有反应条件，如含Si。

限定Si





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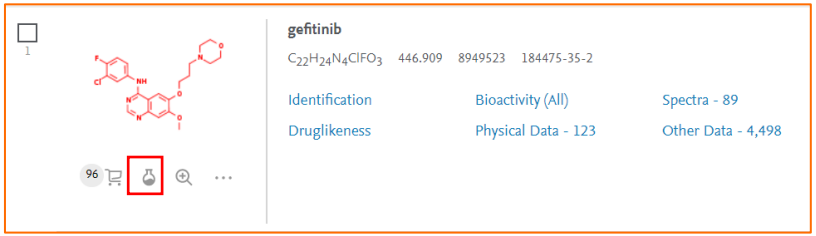
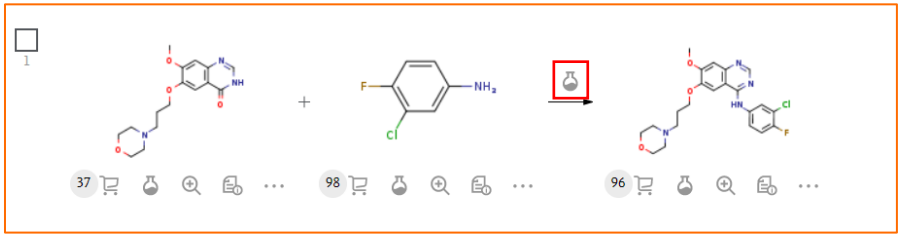
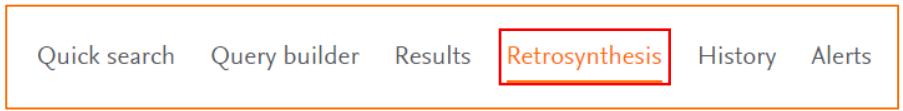
Case 12：Reaxys中合成计划的制作

- 针对具体的化合物进行合成计划制作
  - 需要自行注册账号才可以用这个功能
  - 可以直接从物质界面，或者反应界面直接进入，也可以通过Retrosynthesis功能进入

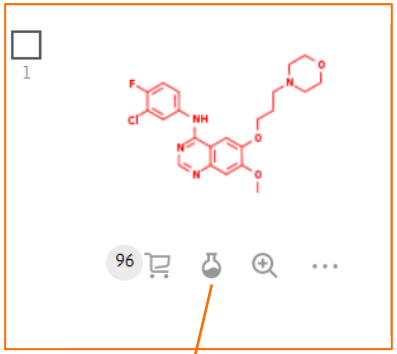


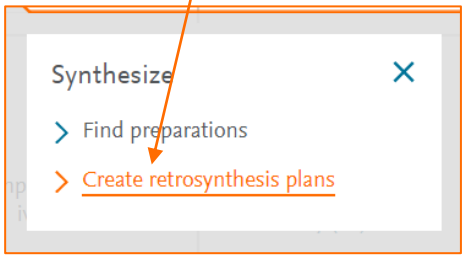


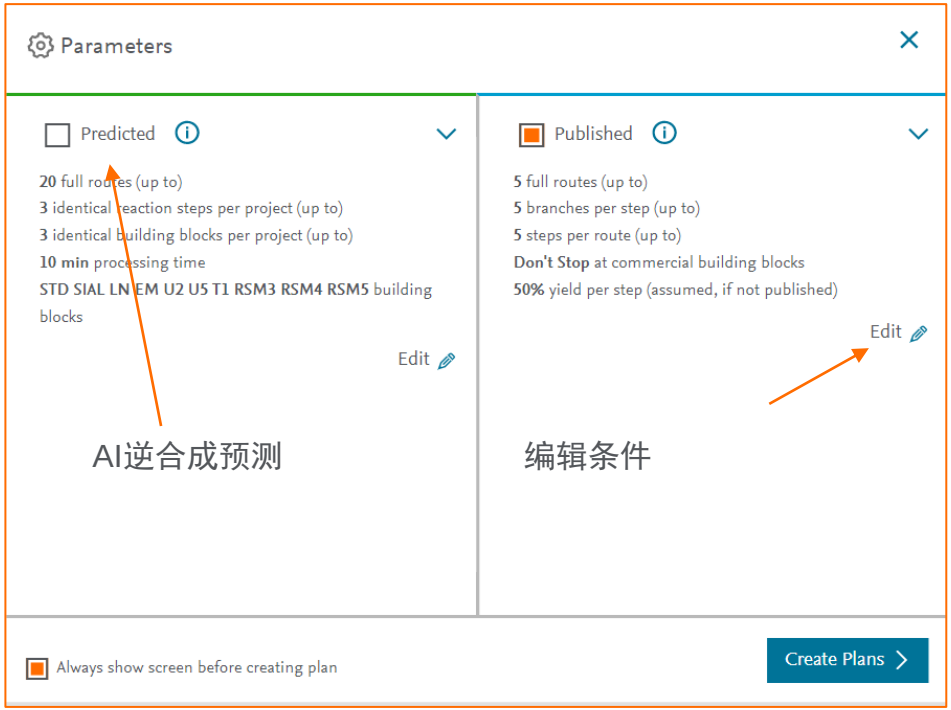


视频操作过程：
https://www.bilibili.com/video/BV1oL411u7yP

从具体物质出发的合成计划制作







条件的编辑及结果

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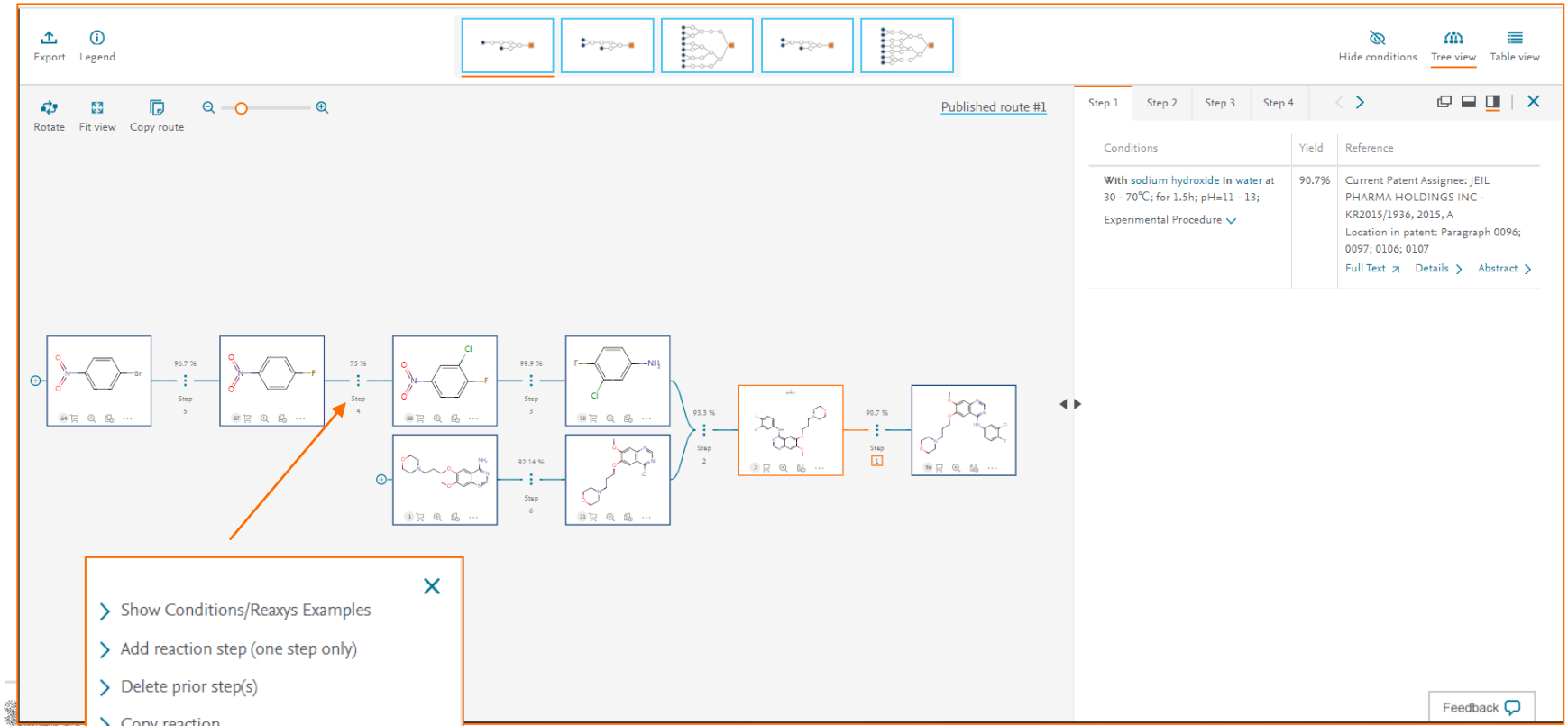
结果的呈现



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关于Reaxys 小分子逆合成预测工具简单介绍

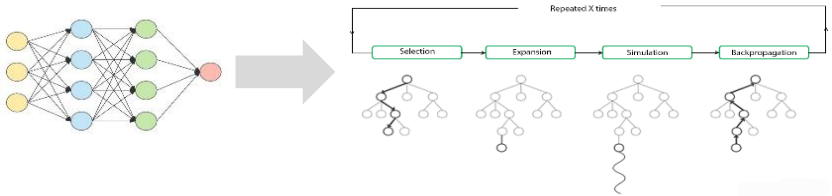
- Waller et al. wrote one of **the most cited works in the field of predictive retrosynthesis**, designing a predictive model based on neural networks and Monte-Carlo Tree search, that:

✓ Learns transformation rules from data

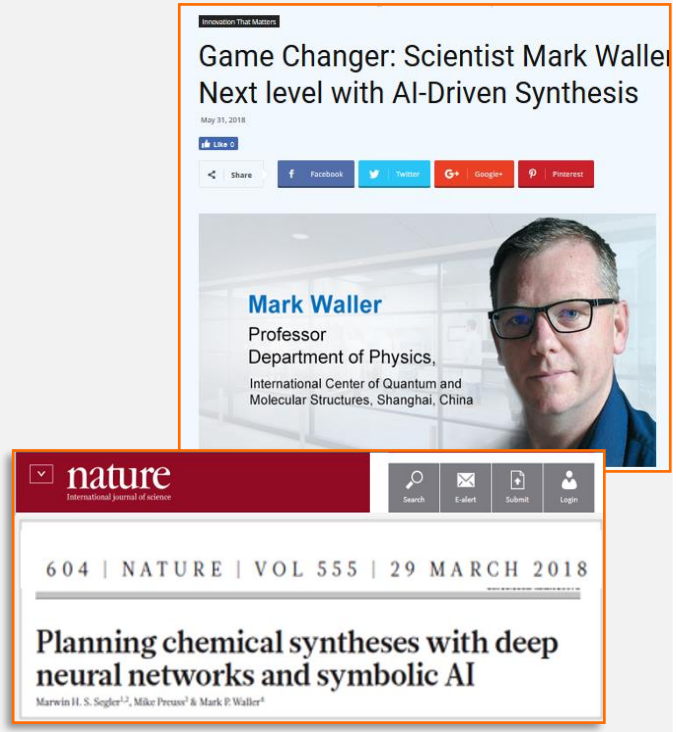
✓ Learns to prioritize rules

✓ Learns to predict reactions

✓ Uses modern efficient search methods



3 neural networks and Monte-Carlo-Tree-Search



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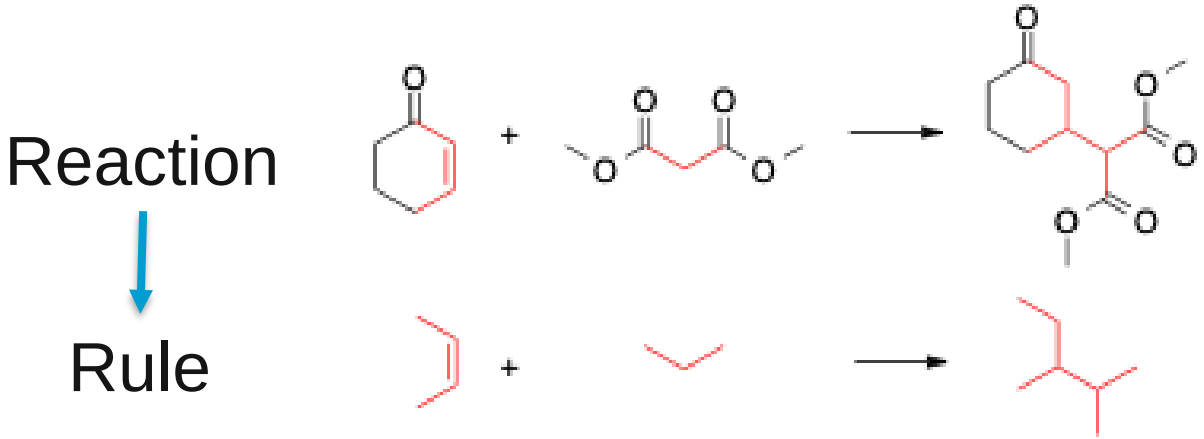
Reaxys-AI实现了自动化提取规则

Planning chemical syntheses with deep neural networks and symbolic AI

Marwin H. S. Segler[1,2], Mike Preuss[3] & Mark P. Waller[4]

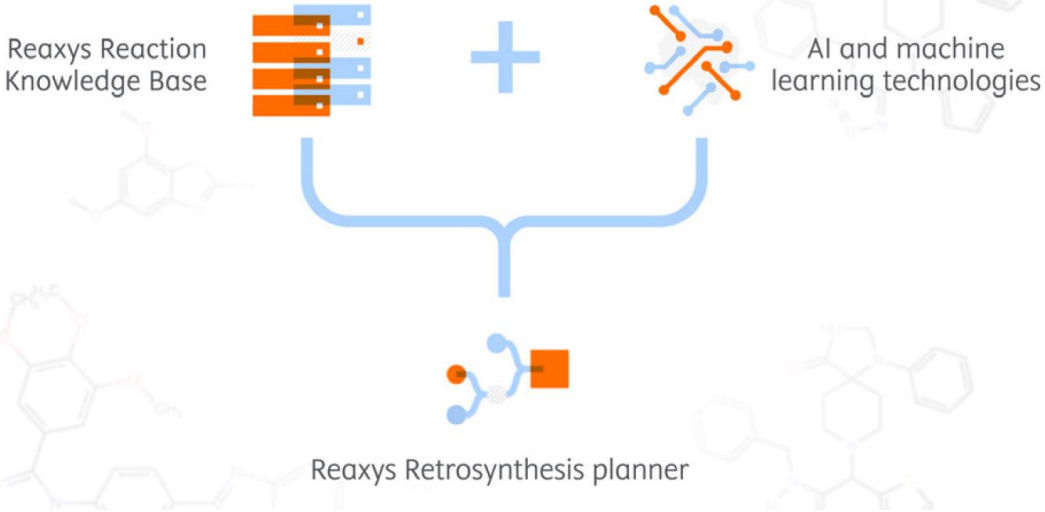
- 核心反应规则从Reaxys数据中获得
  作者从**来自Reaxys数据库的12.4M**的单步反应中，提取反应转换规则。



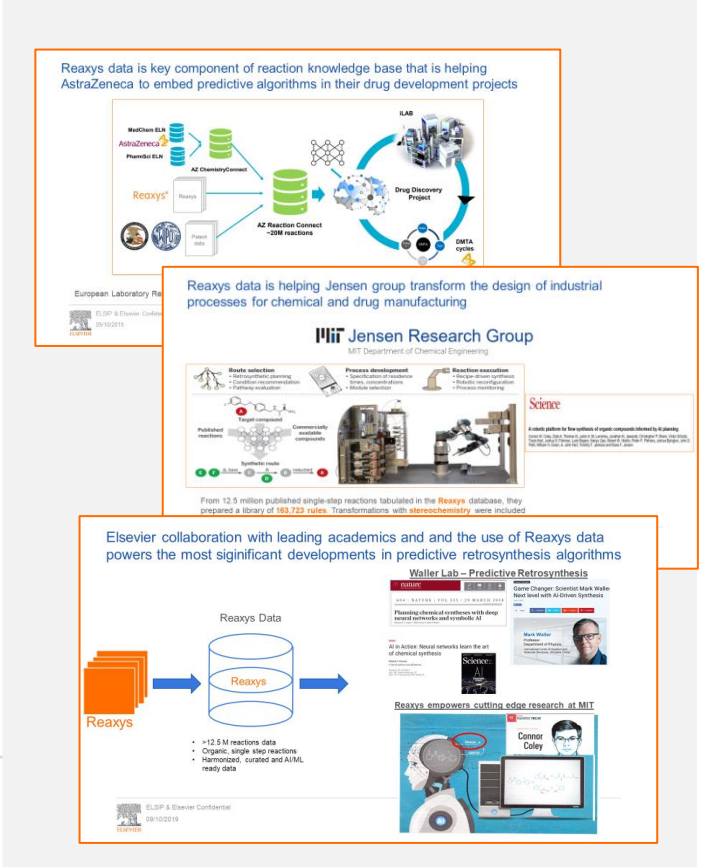
301,671条及17,134条规则分别被应用于拓展策略与快速落子策略神经网络中

Reaxys 能提供最高质量的化学数据用于模型训练

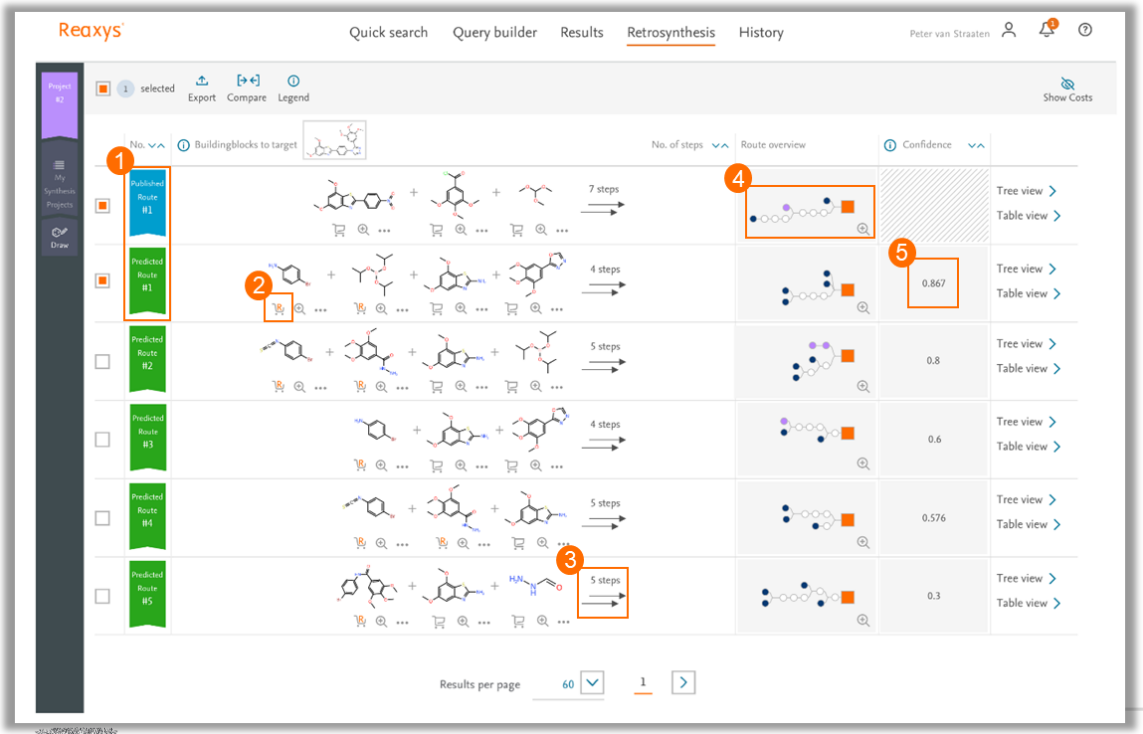
- 预测逆合成模型的成功取决于算法和实验数据的质量



可以结合客户数据训练
模型为客户定制RT工具



Reaxys RT –界面简洁使用方便



1. 同时查看，经典路线，文献路线，AI预测路线，便于对比
2. 从商业化化合物的角度构建，修正预测路线
3. 设计路线的反应步数
4. 对和路线的概况预览
5. 对合成路线的评分排序

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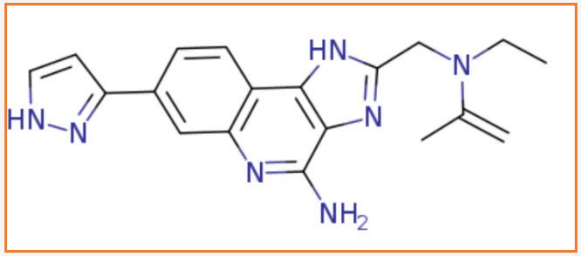


卤素与烯烃的加成

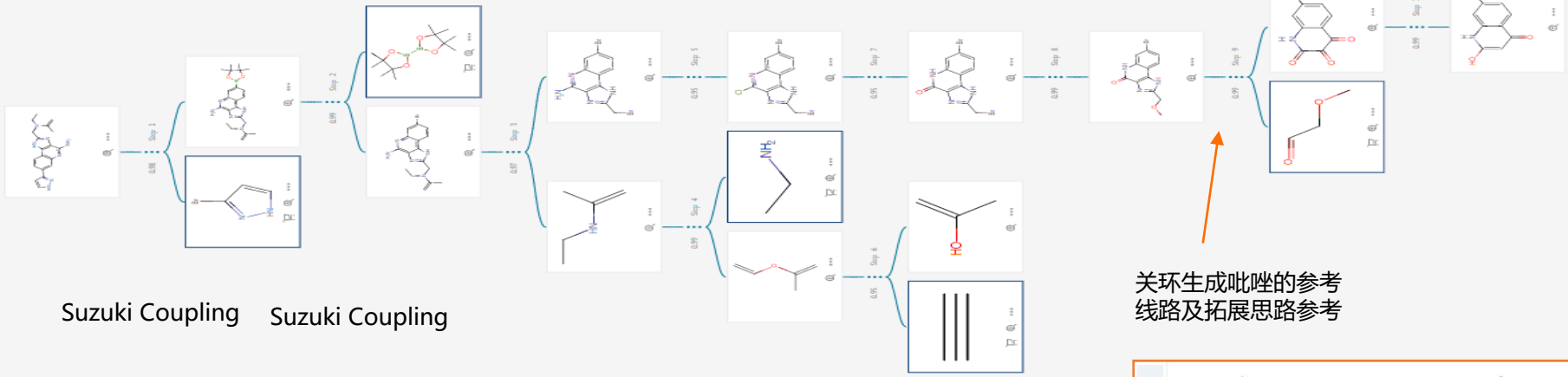
Cl转化成NH2

共轭环上OH的氯化

甲氧基转变成Br

关环生成吡唑

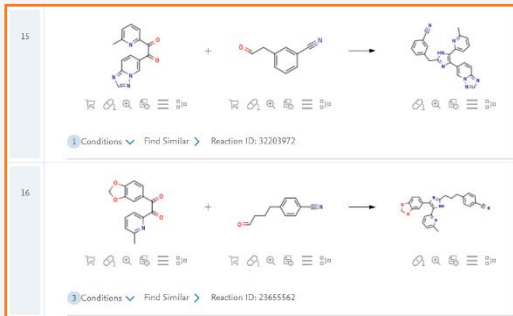
氧化



Suzuki Coupling

Suzuki Coupling

关环生成吡唑的参考线路及拓展思路参考



Rotate

总结

- Reaxys拥有便捷的使用方式，IP范围内授权，不限制同时登录人数，可以自由注册ID。
- Reaxys从大量文献中摘取和物质性质相关的所有数据，帮助科研人员获得标准化，规范化，格式化的物性数据列表及参考文献
- Reaxys中的结构面板，能实现科研人员绝大部分的结构绘制要求，帮助科研人员用最直接的方式获得相应的物质和反应
- Elsevier Life Science线上服务：
  - 微信群：添加Life Science微信小助手，ELS-LSS，邀请进群获取最新资料
  - 关注B站Up主（非官方）：ELS生命科学，获取所有Elsevier Life Science数据库的使用视频
  - 微信公众号（非官方）：闲谈化学药学数据获取，检索原理与检索心得分享

Reaxys培训问卷调查

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Q&A

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Thank you