ELSEVIER

Reaxys系列之

事实型实验数据的运用与物质检索

提纲

- 常见的与物质物质检索有关的困难案例
- Reaxys中的解决方案
  - Reaxys中的Query Builder检索模式
  - Reaxys中的困难案例解决方案
  - Reaxys中的更多与性质检索有关技巧
- Reaxys物质检索小结

Case Study 1：“特定溶剂”下物质溶解度的查询

- 检索要求：
  - 如何快速获得物质的溶解度
  - 氯化钾在乙醇中的，20 ℃， 25 ℃， 30 ℃ 下的溶解度

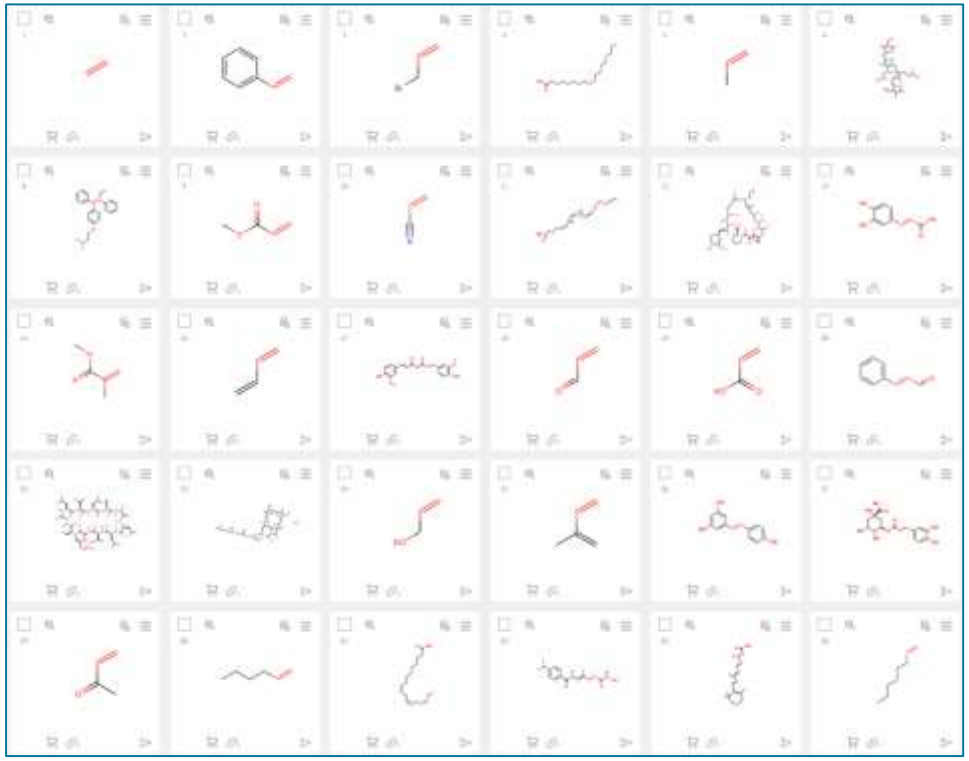
H2O

Ethanol

Case Study 2：具备“特殊性能”的物质检索

- 检索要求
  - 乙烯衍生物，不能成环
  - 具备机械性能报道，尤其是涉及“弹性性能”报道的化合物

C2H4



Case Study 3：“特定研究领域”的催化剂选择

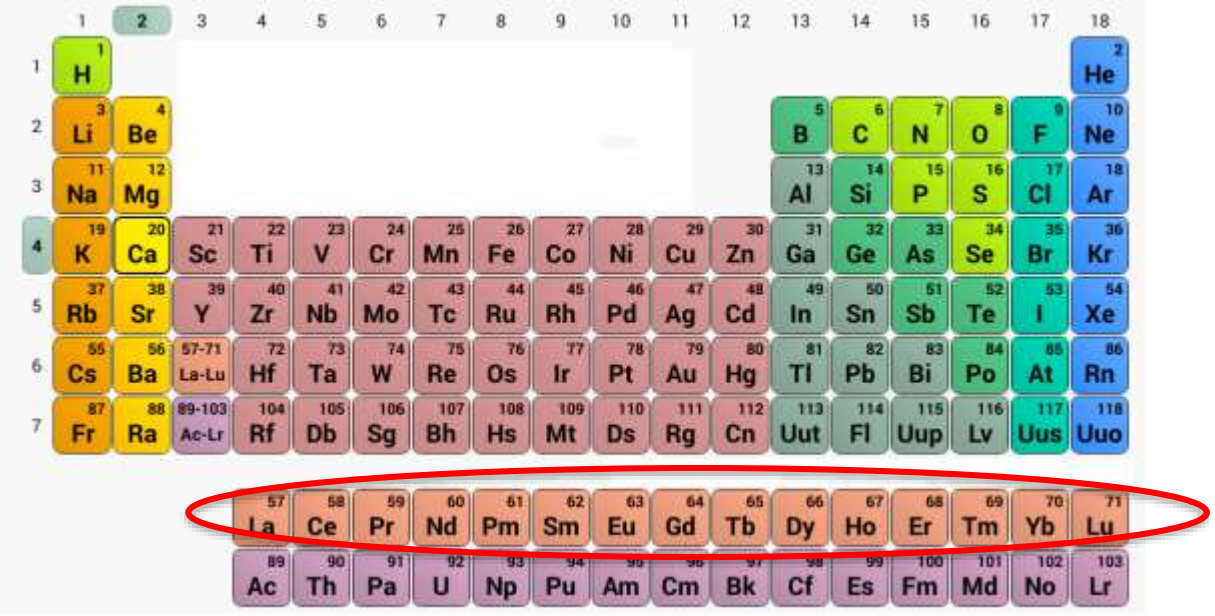
- 检索可用于立体选择性催化的含Fe的，或者含镧系金属的催化剂

Chemoselectivity

Stereoselective

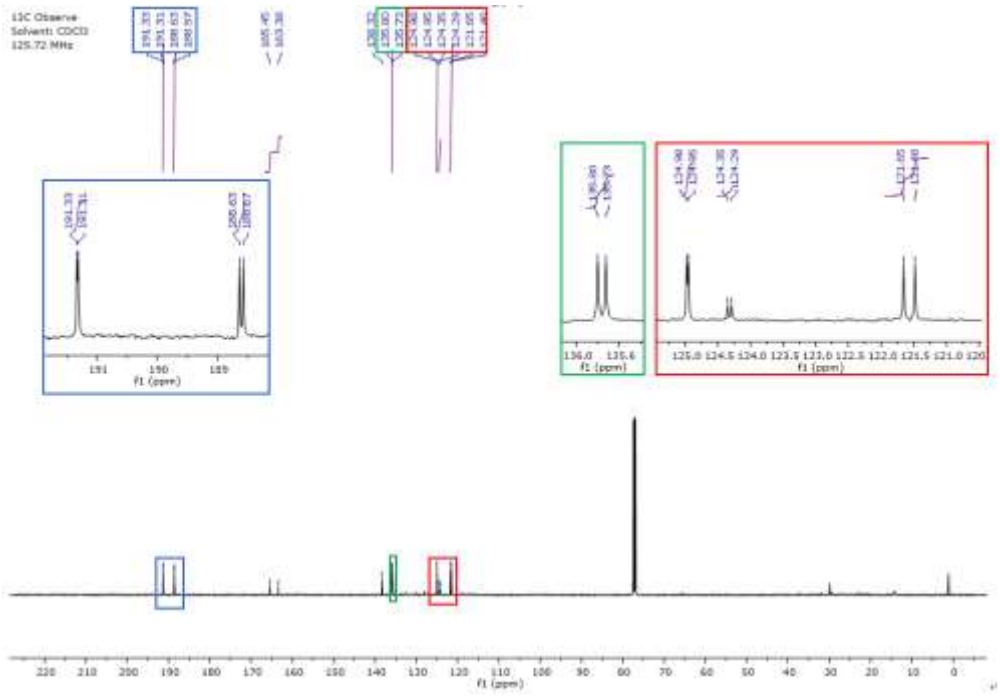
Regioselectivity

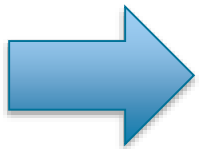
Fe



Case Study 4：如何利用数据进行化合物解谱

- 常见的情况
  - 知道是天然产物
  - 分子量348.456
  - 从谱图上可以看到一些明显的片段结构
  - 有多组谱图的数据





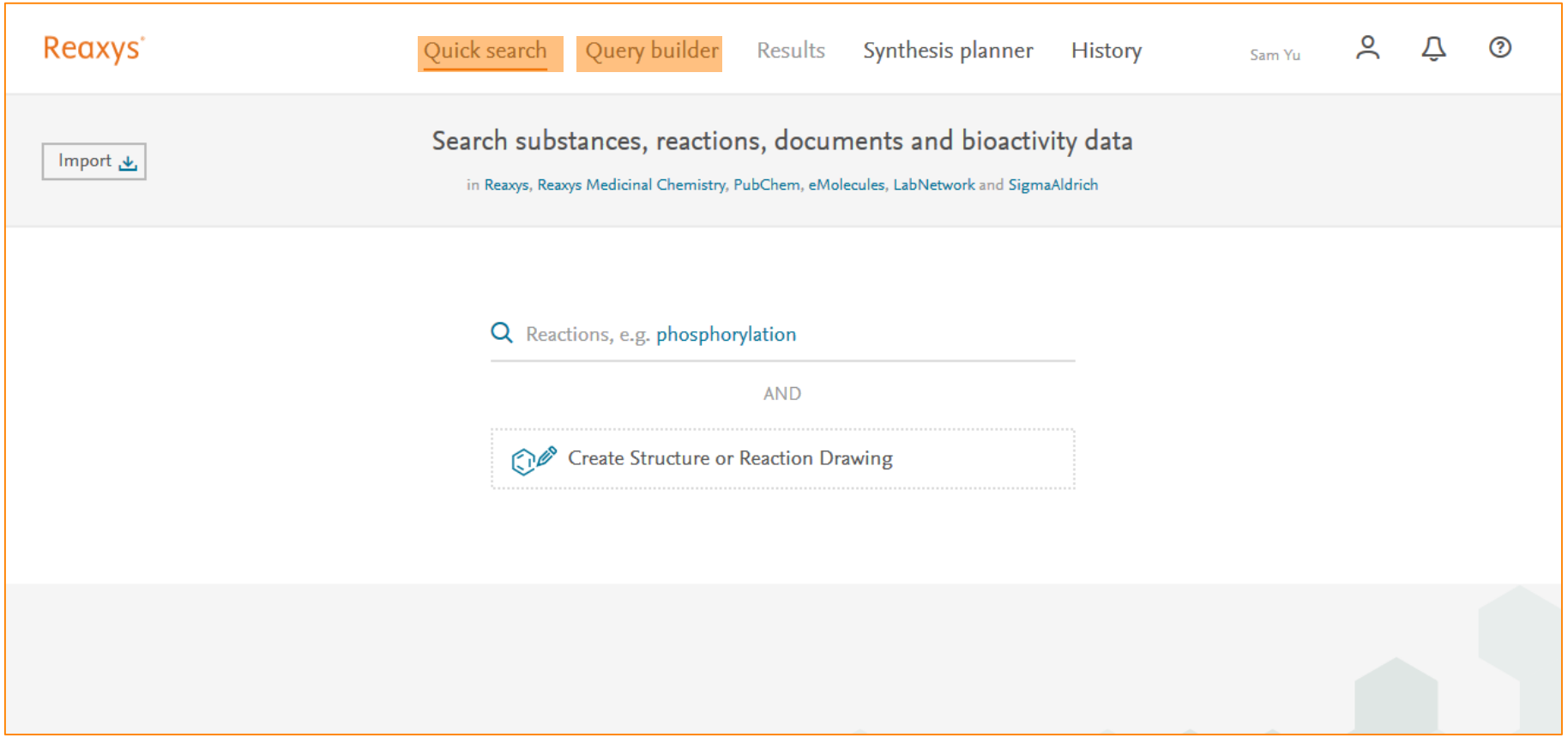
提纲

- 常见的与物质物质检索有关的困难案例
- Reaxys中的解决方案
  - Reaxys中的Query Builder检索模式
  - Reaxys中的困难案例解决方案
  - Reaxys中的更多与性质检索有关技巧
- Reaxys物质检索小结

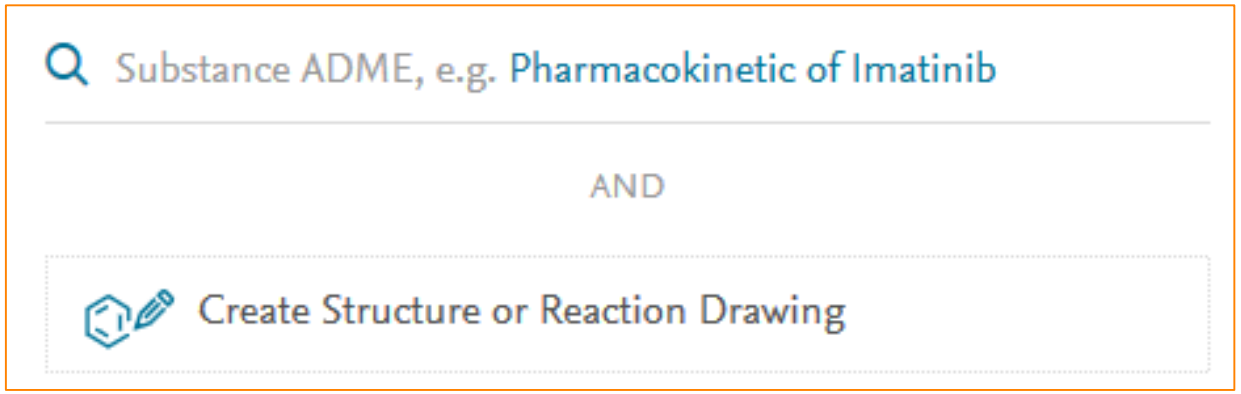
Reaxys的界面

- www.reaxys.com

Quick Search Query Builder



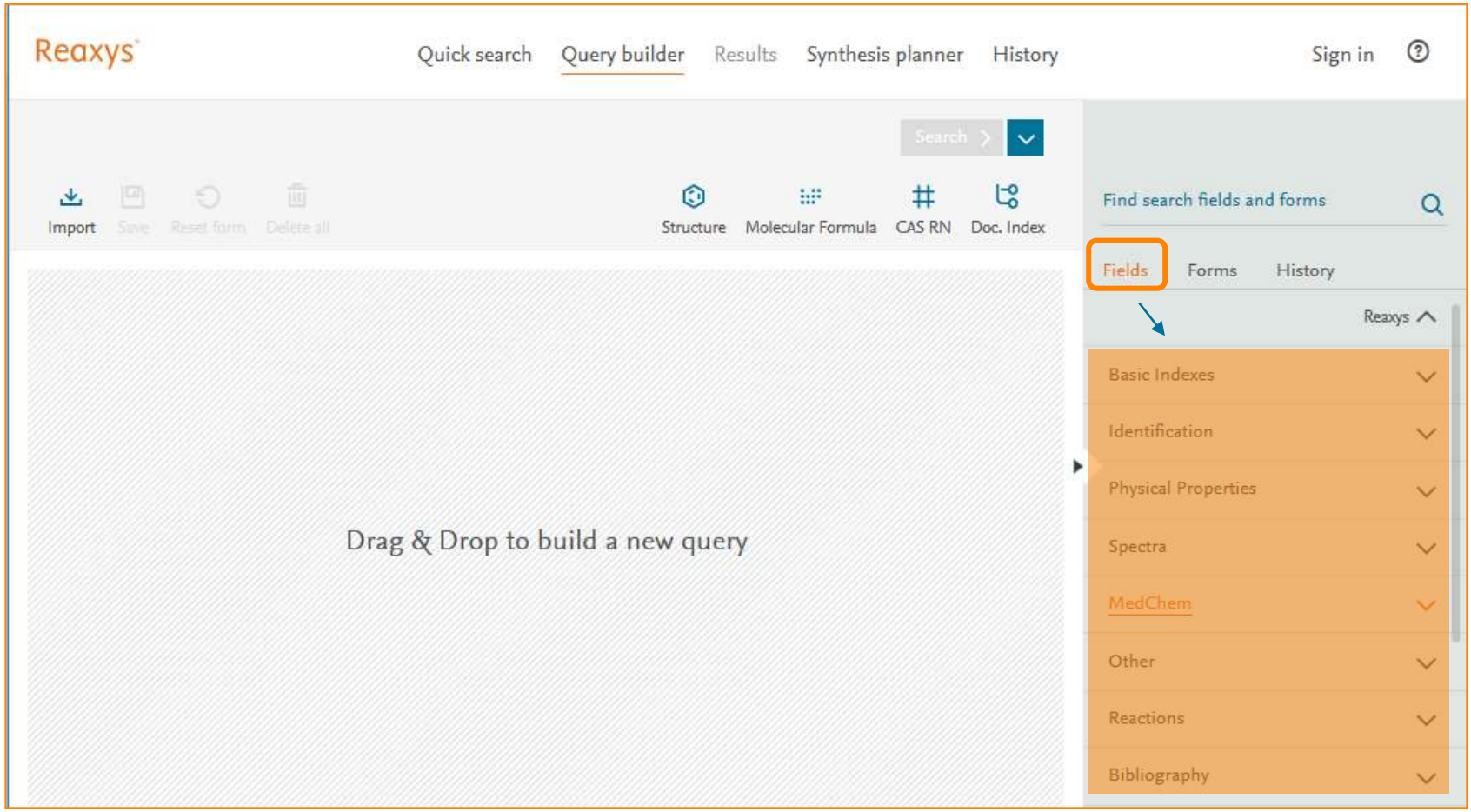
Reaxys的检索方式—Quick Search



Quick Search中可以使用的方式：

1. 物质名称，Gefitinib
2. 反应名称，Wittig Reaction
3. 物质理化性质，Solubility of Gefitinib
4. 物质的谱图，NMR of Gefitinib
5. 分子式，C22H24ClFN4O3
6. 反应类型，Substitution
7. 关键词，Immunology Oncology
8. 反应结构，物质结构

Reaxys的检索方式—Query Builder

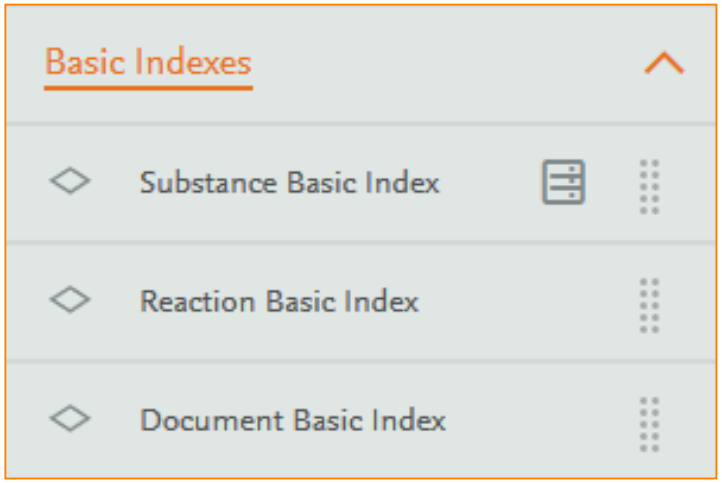


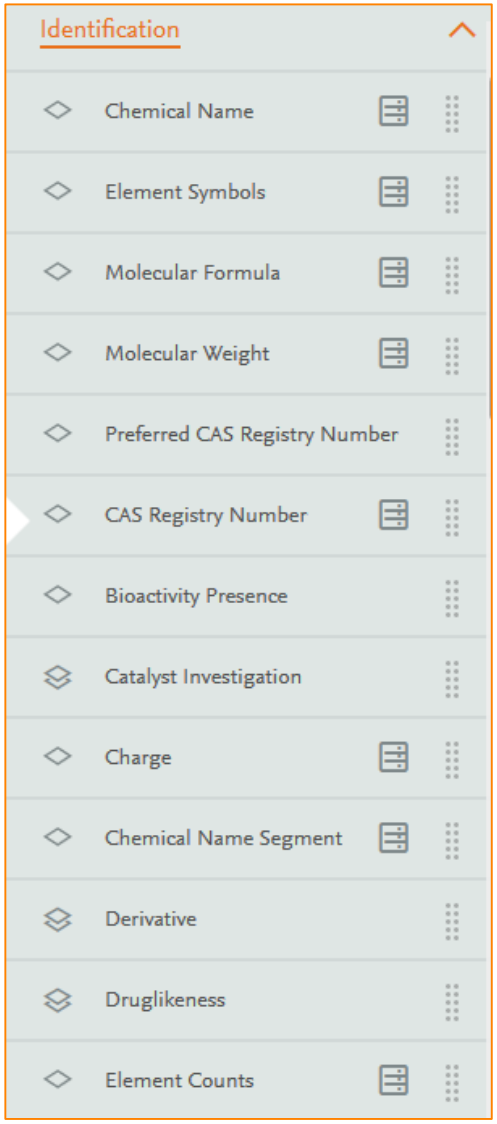
Query Builder模块下，Fields中可以选择不同类型的字段进行自由组合检索

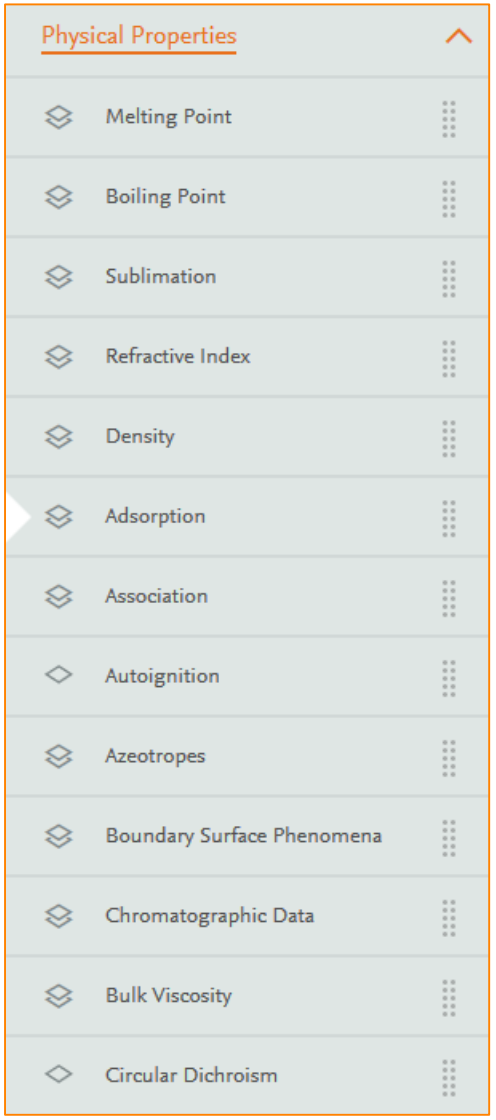
Reaxys中的字段检索

Tips:

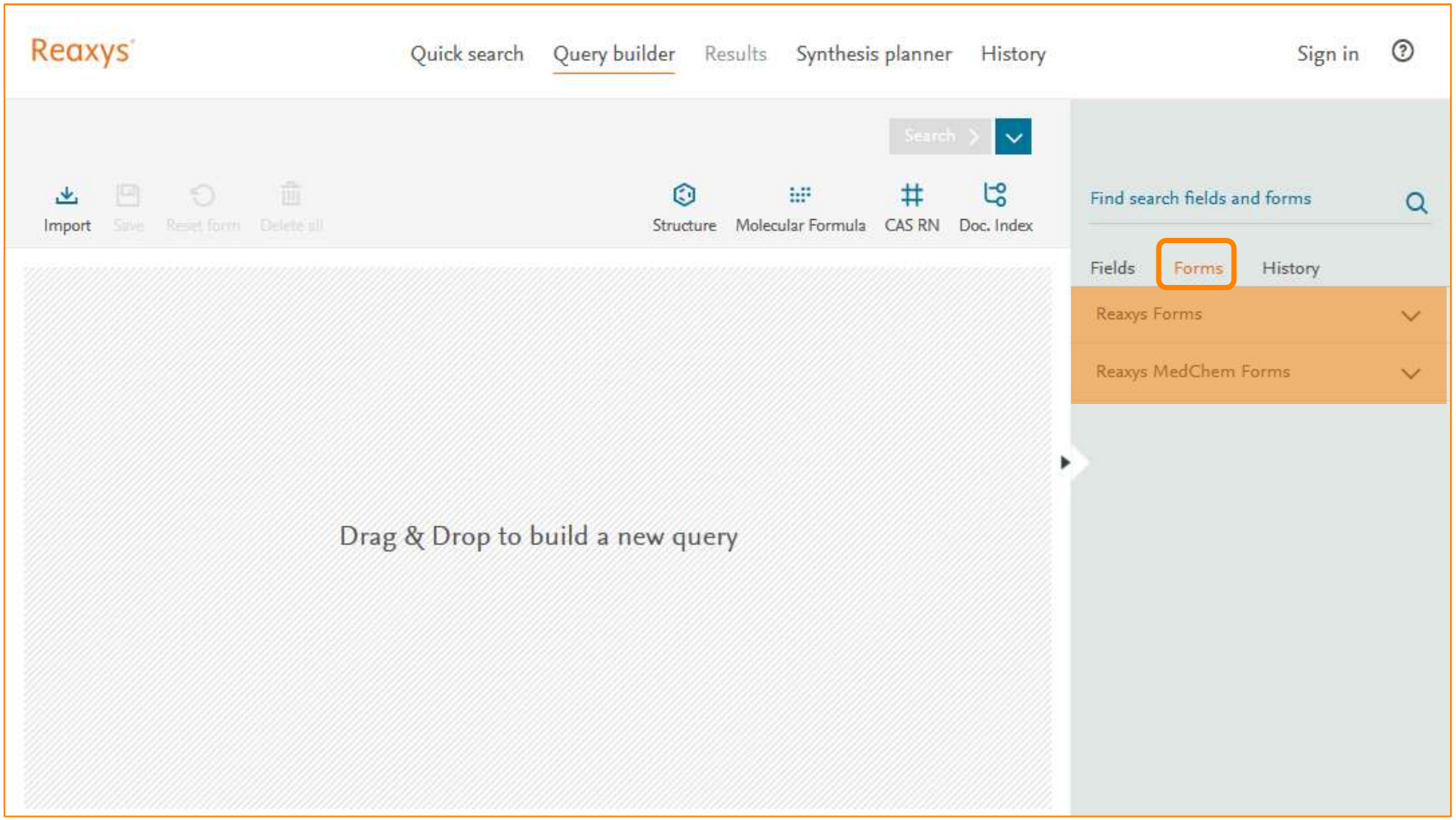
Reaxys提供8种不同的分类，每种分类中拥有和这种分类相关的多种字段，可以依据这些字段自由组合进行检索





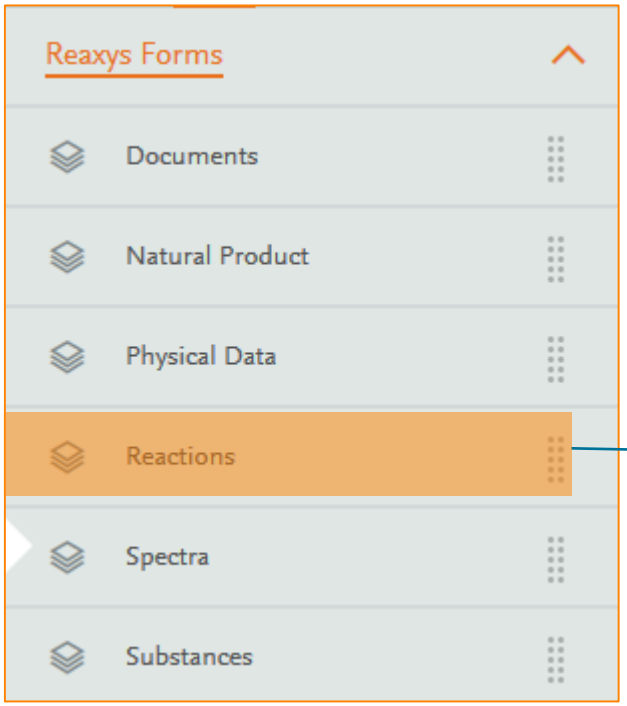


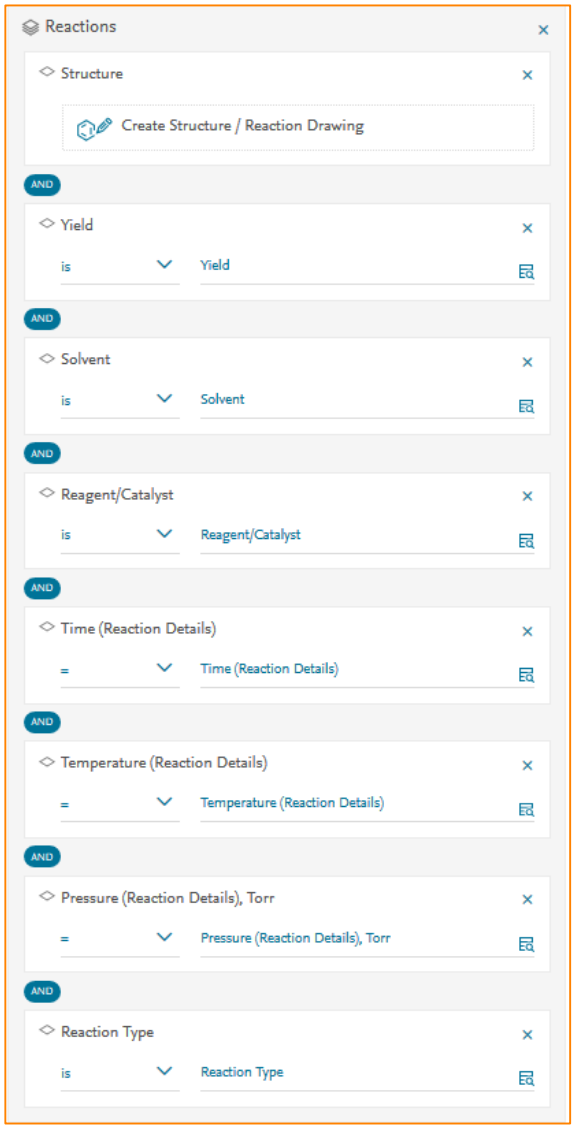
Reaxys检索方式—Query Builder Forms



Query Builder模块下，Forms中Reaxys和RMC的预设模块检索

Reaxys Form中的预设模块





反应结构

反应收率

反应溶剂

试剂催化剂

反应时间

反应温度

反应压力

反应类型

提纲

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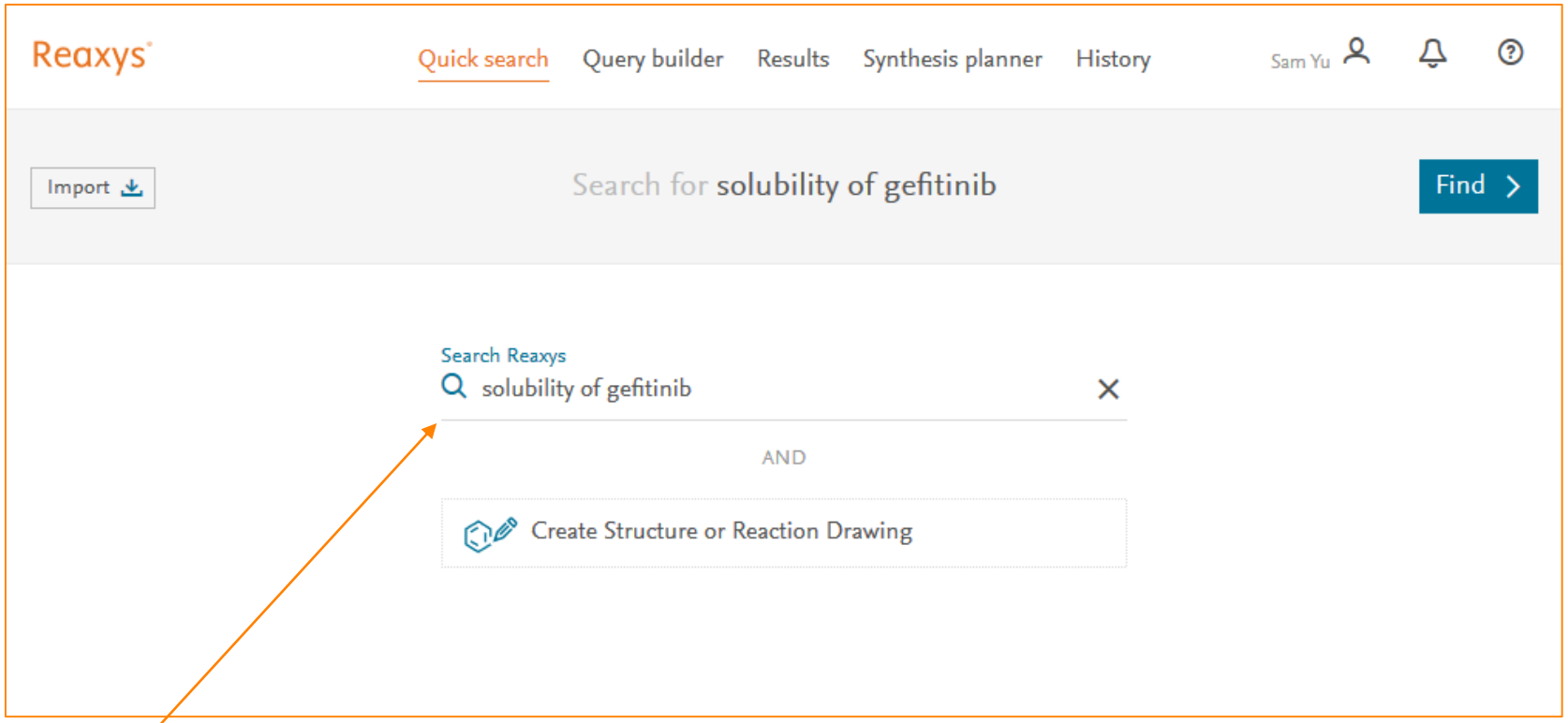
  - Reaxys中的Query Builder检索模式
  - Reaxys中的困难案例解决方案
  - Reaxys中的更多与性质检索有关技巧
- Reaxys物质检索小结

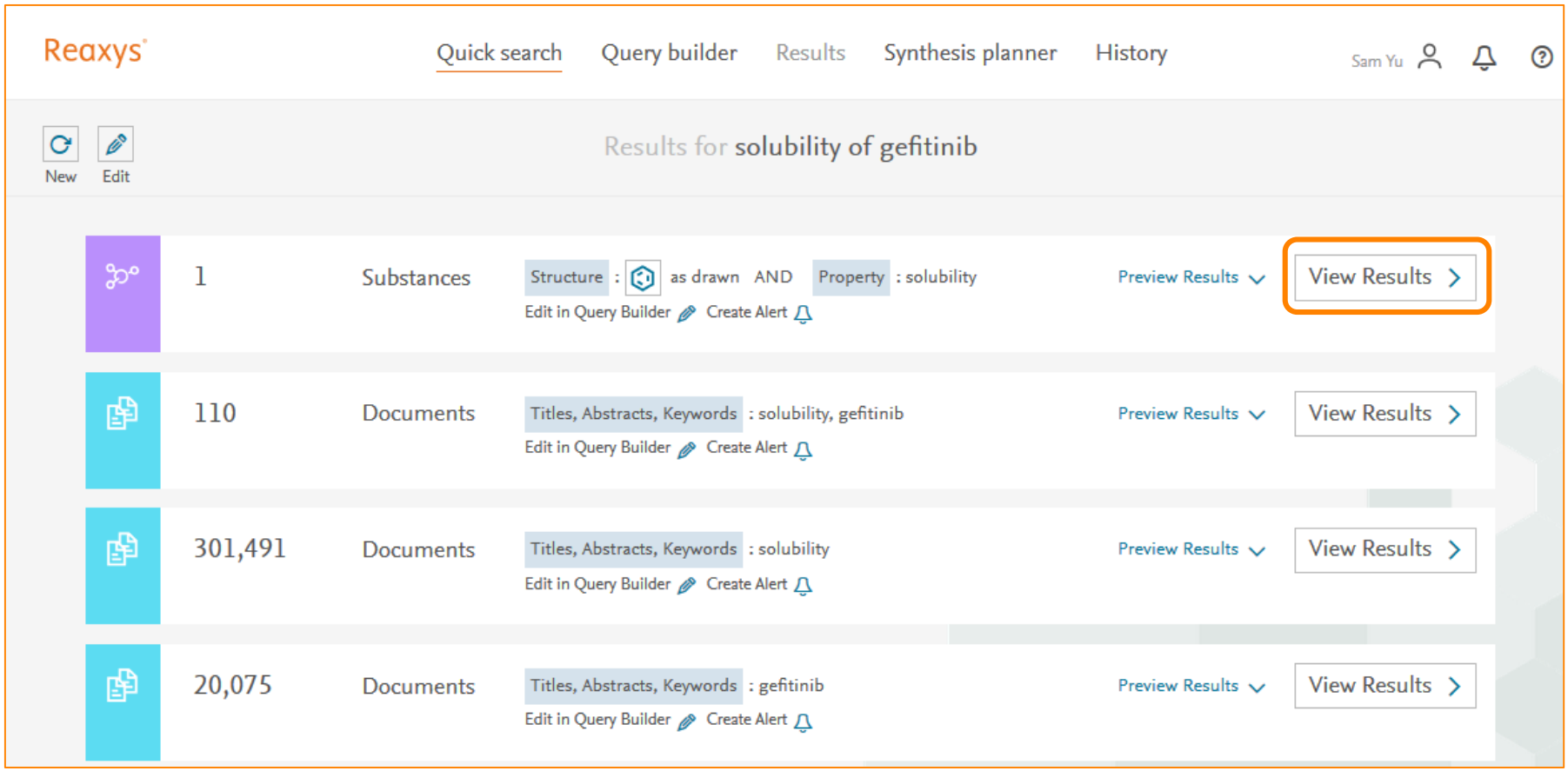
Case Study 1：快速获得物质的理化性质

- 快速的案例
- 检索具体化合物的溶解性数据（Gefitinib）

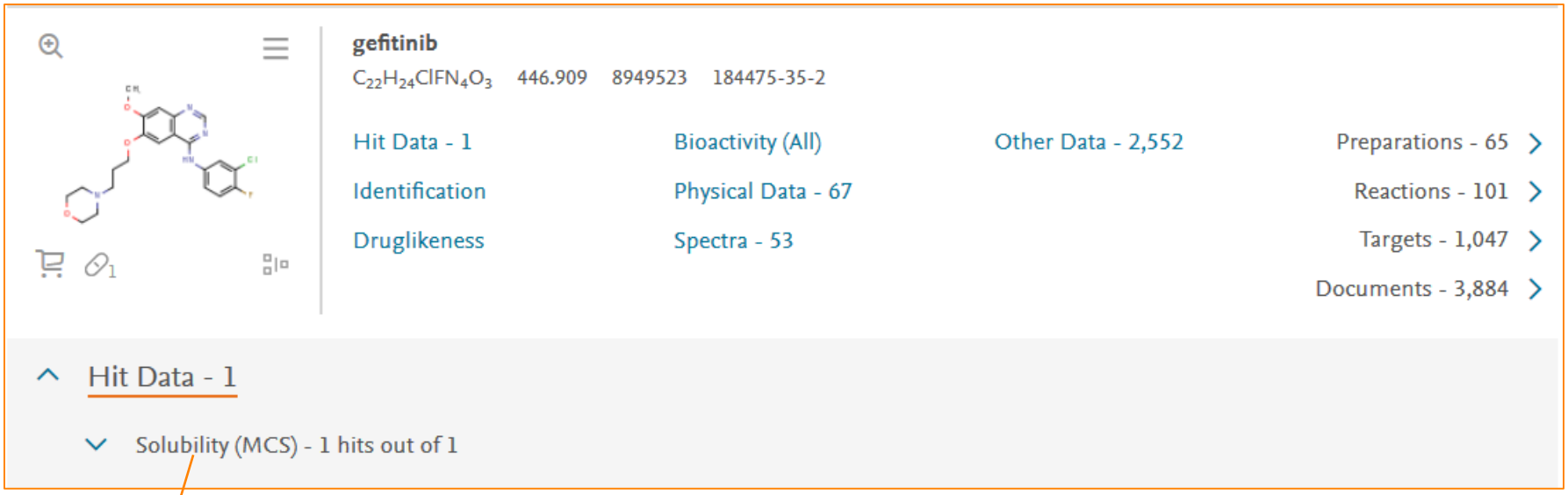


直接用自然语言在输入，solubility of gefitinib，检索

Reaxys直接给出结果

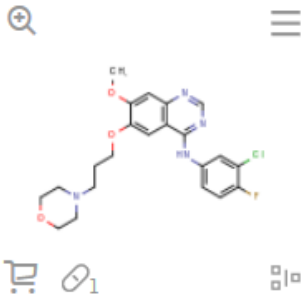


最后的结果



Hit Data直接给出具体的实验数据，以及检测条件和全文链接

Reaxys中的物质理化性质



gefitinib

$C_{22}H_{24}ClFN_4O_3$ 446.909 8949523 184475-35-2

Hit Data - 1 | Bioactivity (All) | Other Data - 2,552 | Preparations - 65 >

Identification | Physical Data - 67 | Reactions - 101 >

Druglikeness | Spectra - 53 | Targets - 1,047 >

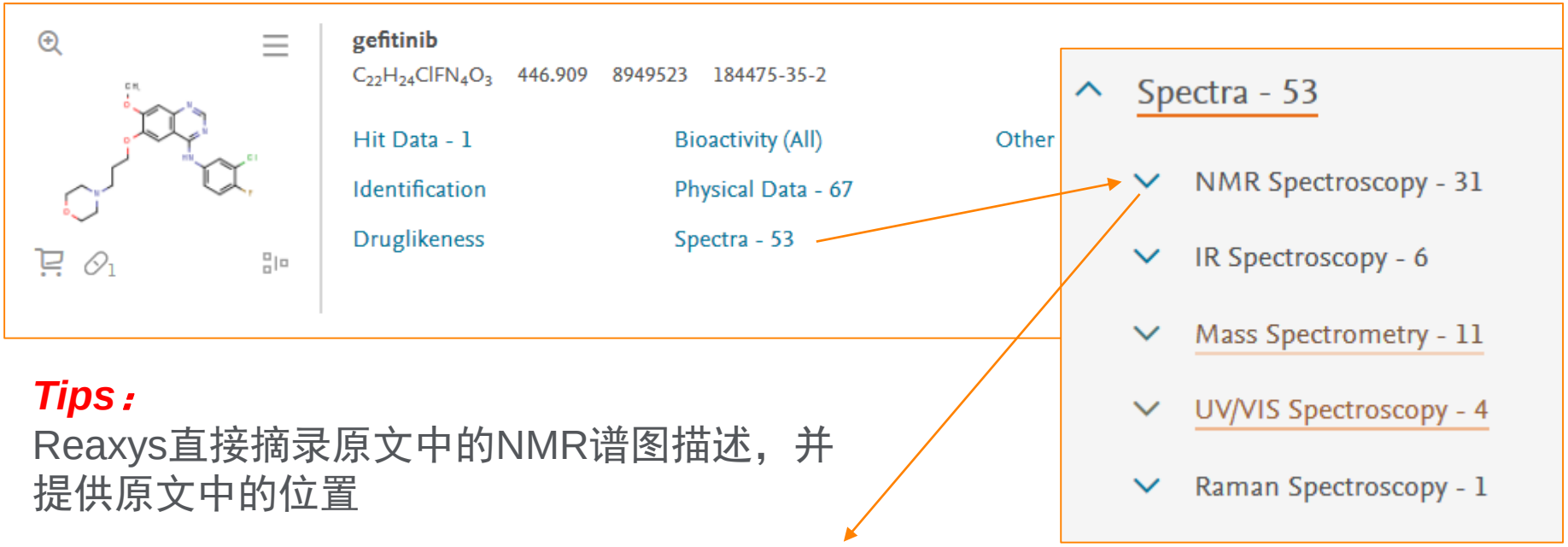
Documents - 3,884 >

- Physical Data - 67
  - Melting Point - 21
  - Association (MCS) - 1
  - Chromatographic Data - 4
  - Conformation - 1
  - Crystal Phase - 7
  - Crystal Property Description - 14
  - Crystal System - 1
  - Dissociation Exponent - 2
  - Further Information - 1
  - Interatomic Distances and Angles - 2

Colour & Other Properties	Location	Reference
white	Paragraph 0037	CSPC Zhongqi Pharmaceutical Technology(Shijiazhuang)Corporation Limited; CSPC Ouyi Pharmaceutical Co., Ltd; Zhang, Yanqiao; Li, Xiaofang; Sun, Wentao; Zhang, Sujuan; Geng, Jia - CN103319422, 2016, B Full Text Details Abstract No author - CN106854184, 2017, A Full Text Details Abstract
white	Paragraph 0037; 0047	No author - CN106854185, 2017, A Full Text Details Abstract
white	Paragraph 0065	Chongqing Laimei Longyu Pharmaceutical Co., Ltd.; Wen Huiying; Ren Sixiao; Xu Xiaofang; Tang Qunlian; Yang Shengxi - CN107098863, 2017, A Full Text Details Abstract
white	Paragraph 0015	Zhengzhou University The First Affiliated Hospital; Cheng Weiyan; Zhang Xiaojian; Tian Xin - CN106432202, 2017, A Full Text Details Abstract
yellow	supporting information	Kang, Sung Kwon; Lee, Seung Wook; Woo, Daekoo; Sim, Jaehoon; Suh, Young-Ger - Synthetic Communications, 2017, vol. 47, # 21, p. 1990 - 1998 Full Text Details Abstract
white	Paragraph 0126; 0133	shanghai tianci shengwu gu Biological Engineering Co., Ltd.; Li, Han Pu; Li, Jianzhi; Liu, hai; Hu, xu Hua; Zheng, Xiaoli; Sun, Li; Xie, Lin - CN105218476, 2016, A Full Text Details Abstract

Feedback

Reaxys中的谱图

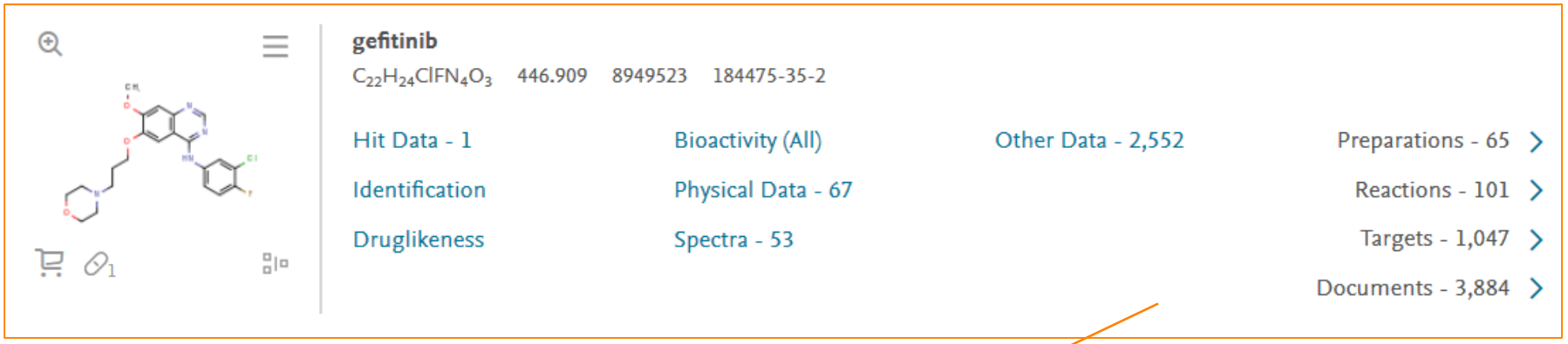


Tips：

Reaxys直接摘录原文中的NMR谱图描述，并提供原文中的位置

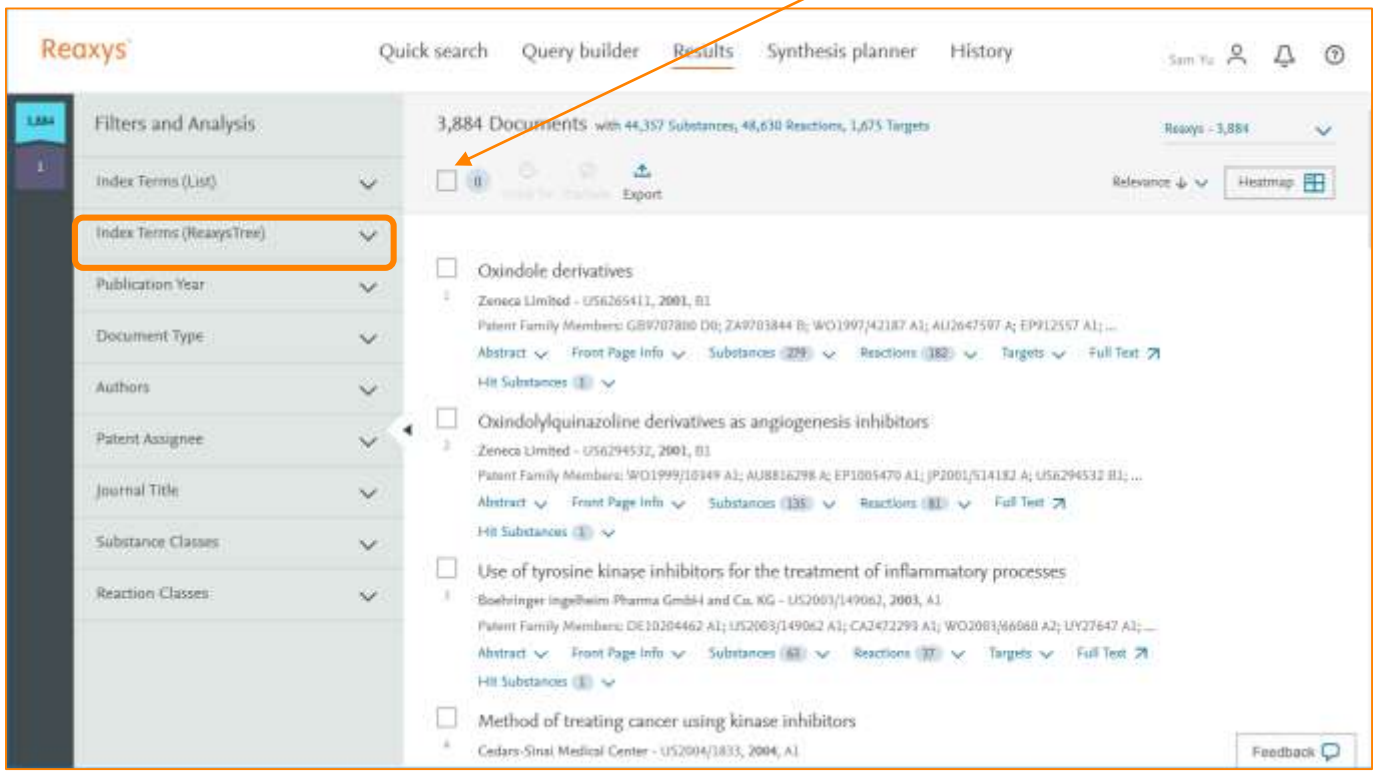
1H NMR (400 MHz, d6-DMSO) O 9.44 (5, 1H), 8.50 (5, 1H), 8.12 (dd, J= 6.9, 2.7 Hz,1H), 7.80 (m, 2H), 7.44 (t, 1H), 7.20 (5, 1H), 4.18 (t, J= 6.7 Hz, 2H), 3.94 (5, 3H), 3.59(t, J = 4.4 Hz, 4H), 2.49 (t, J = 6.9 Hz, 2H), 2.41 (bs, 4H), 2.00 (m, 2H).	Paragraph 0035	**SCINOPHARM (CHANGSHU) PHARMACEUTICALS, LTD.; ZHANG, Xiao-heng; LV, Xizhou** - WO2015/188318, 2015, A1 Full Text ↗ Show details ›
13C NMR (100 MHz, d6-DMSO) O 156.48, 154.94, 153.57 (J = 241 Hz), 153.05,148.74, 147.43, 137.33 (J = 3 Hz), 123.91, 122.77 (J = 7 Hz), 119.19 (J = 19 Hz),116.90 (J=21 Hz), 109.26,107.72,103.14,67.59,66.43,56.31,55.35,53.73,26.13.	Paragraph 0035	**SCINOPHARM (CHANGSHU) PHARMACEUTICALS, LTD.; ZHANG, Xiao-heng; LV, Xizhou** - WO2015/188318, 2015, A1 Full Text ↗ Show details ›

Reaxys中的分析文献的获取

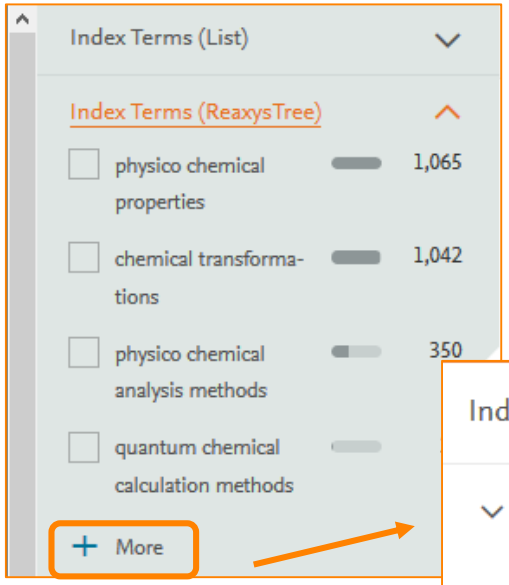


Tips:

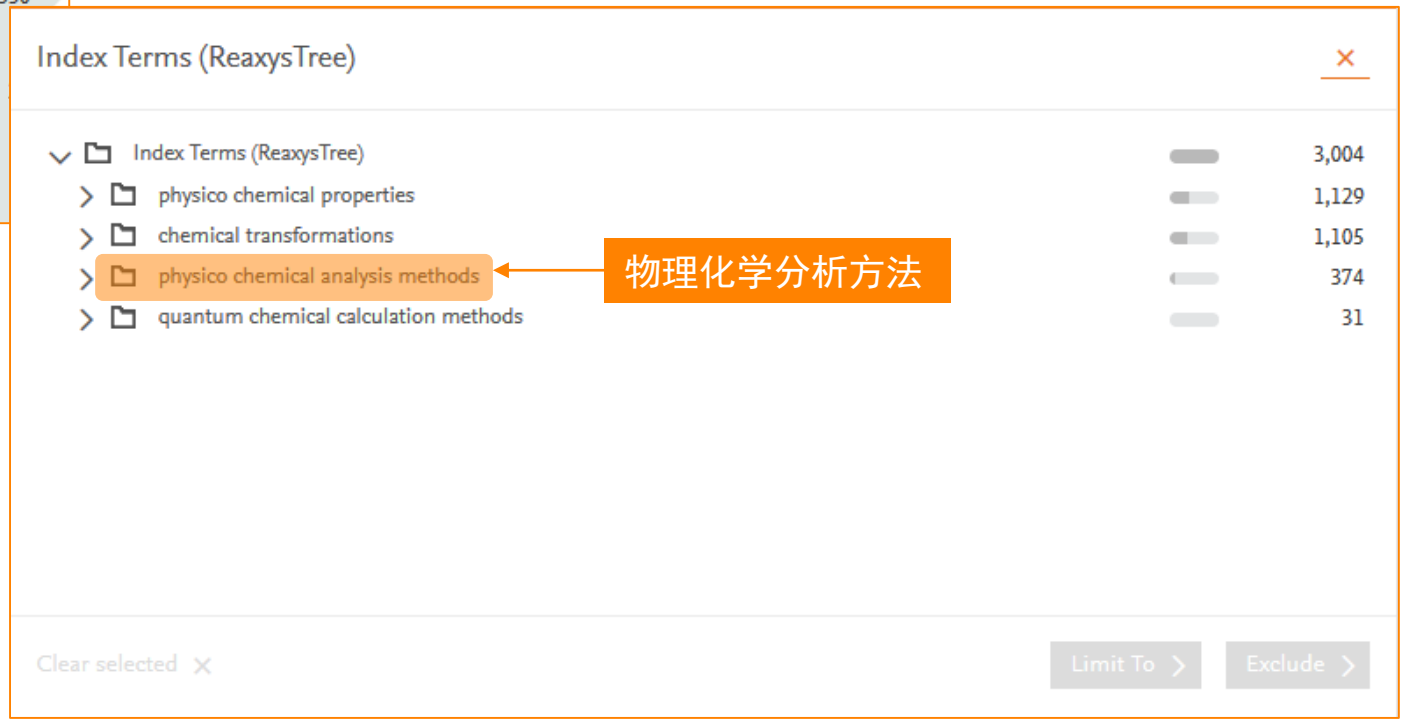
获得文献后，可以通过Reaxys的文献过滤工具对文献进行后处理



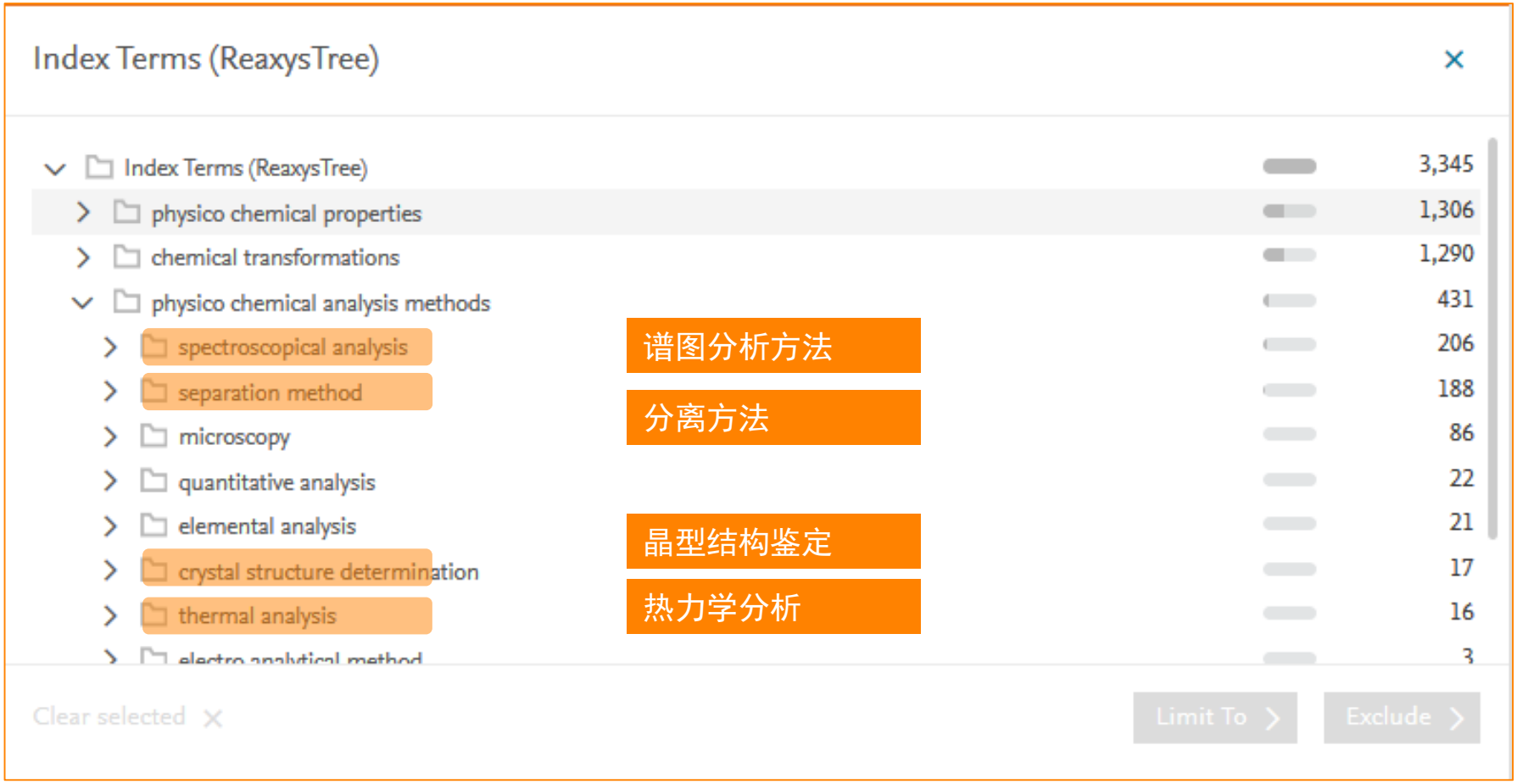
Index Term Reaxys Tree的应用



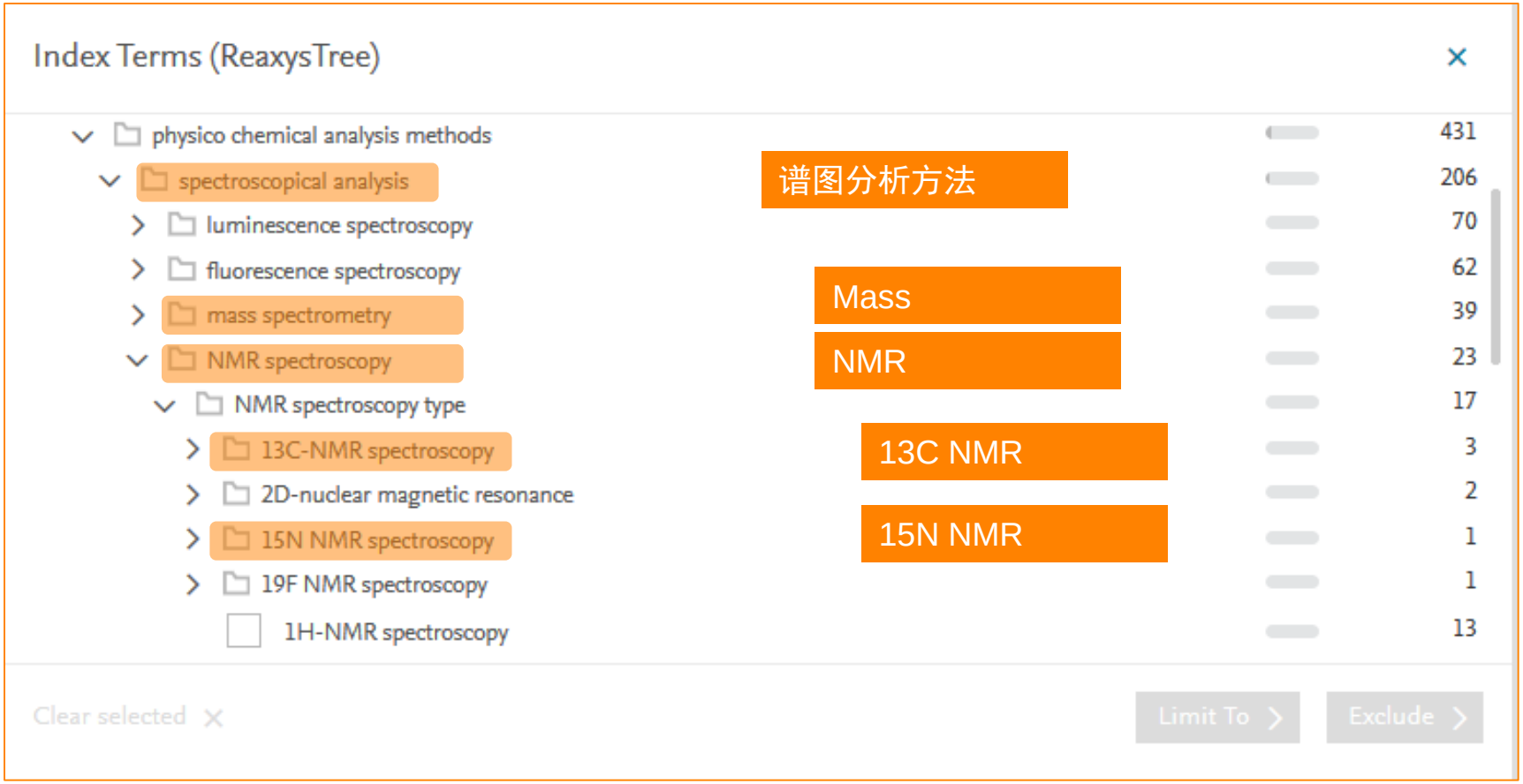
Reaxys通过Index Term Reaxys Tree的方式，将文献进行精确分类，帮助大家快速定位所需分析文献。



物理化学分析方法中的细节性分类

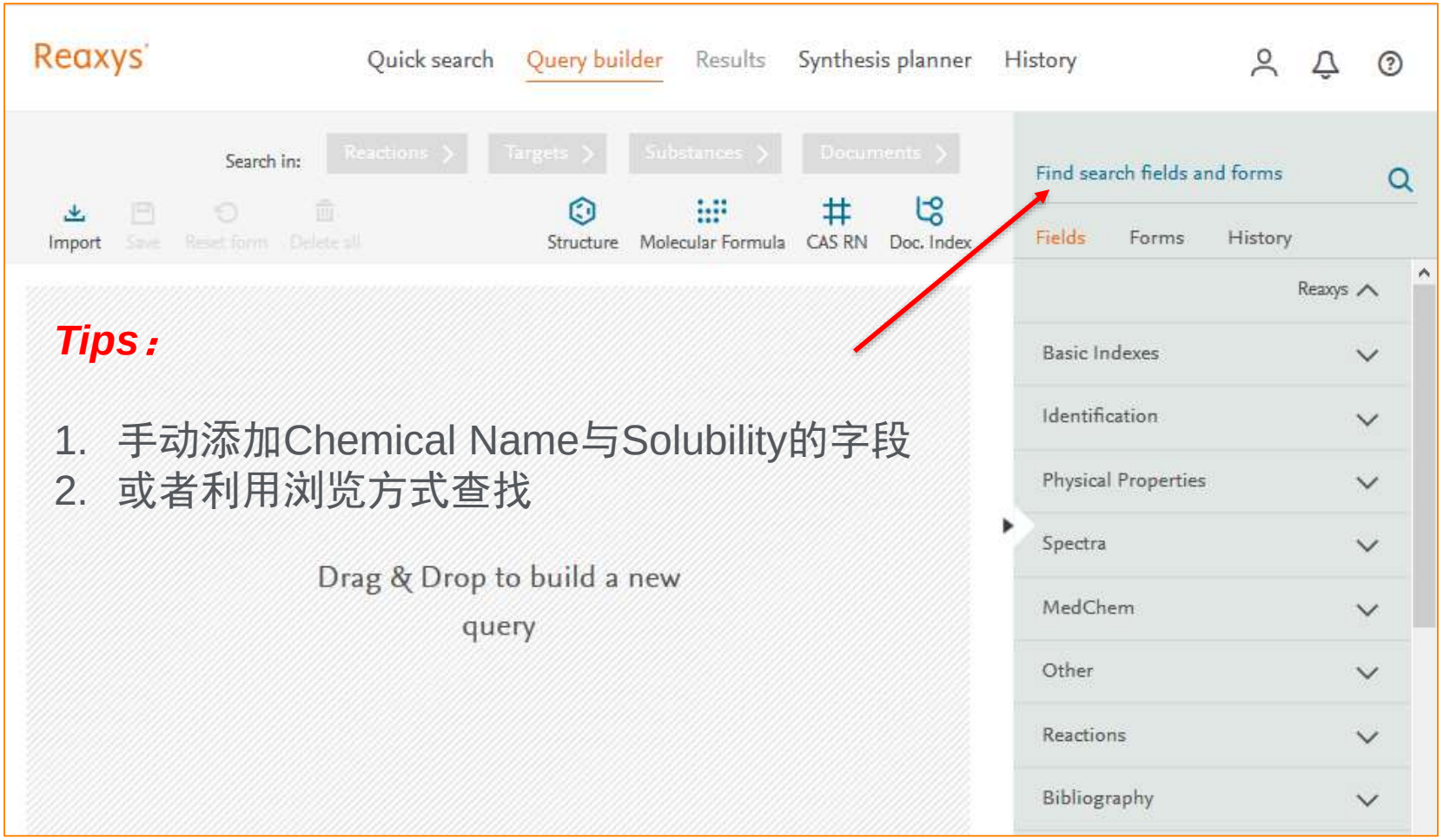


谱图分析方法下面的细节分类



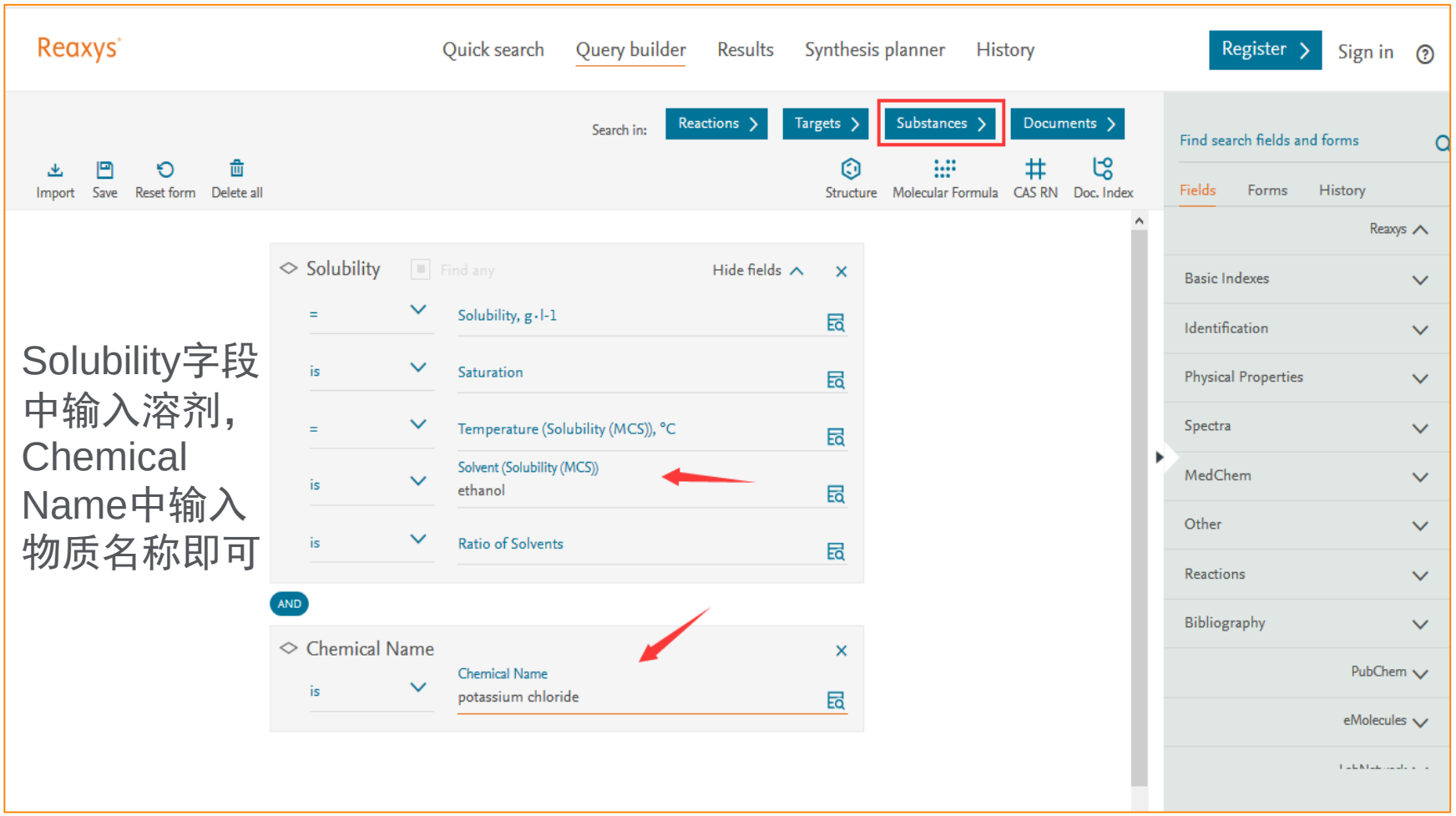
案例的衍生：理化性质的高级应用

- 检索检索氯化钾在乙醇中的溶解度



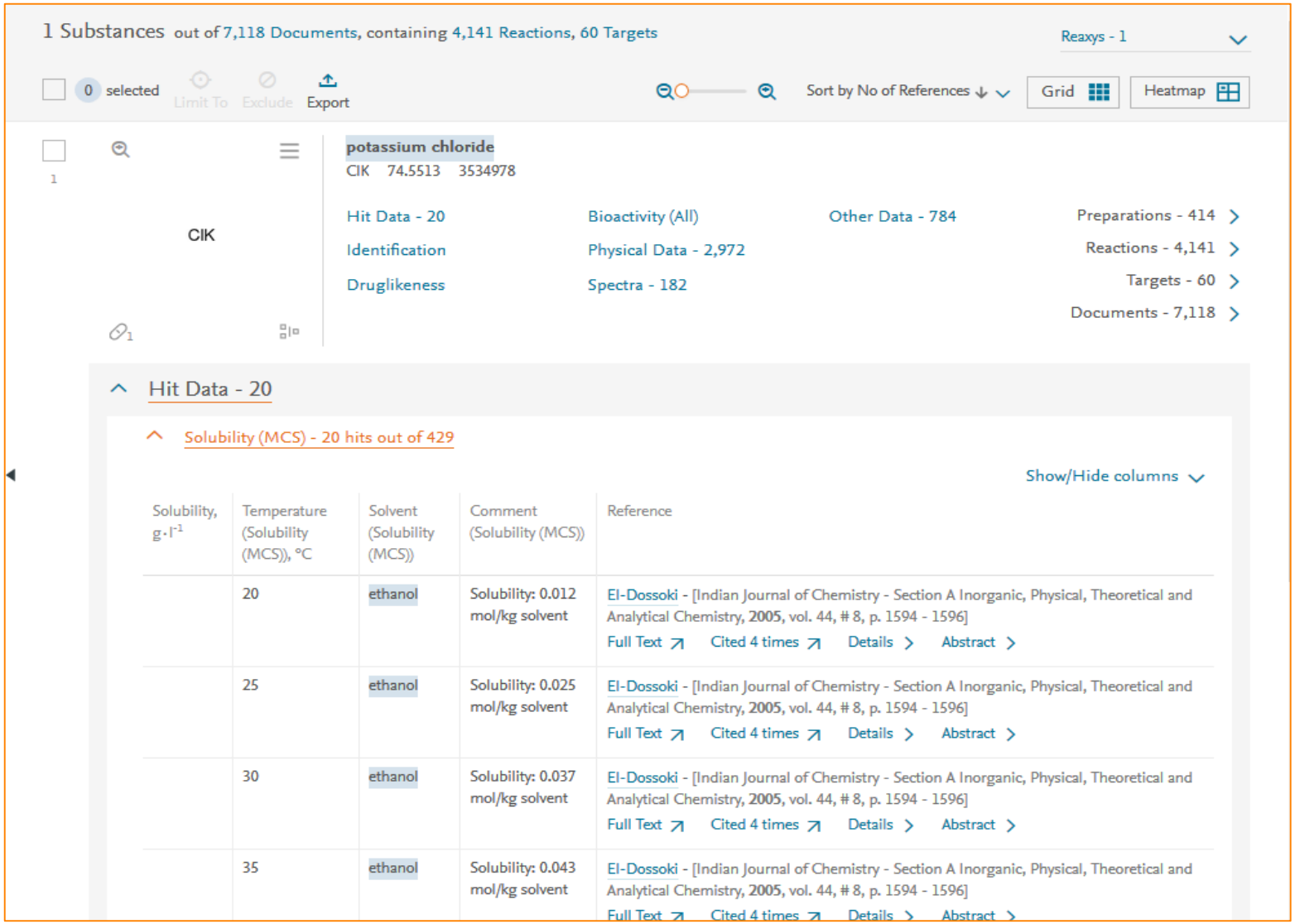
利用Query Builder创建检索式

- Reaxys中的检索策略



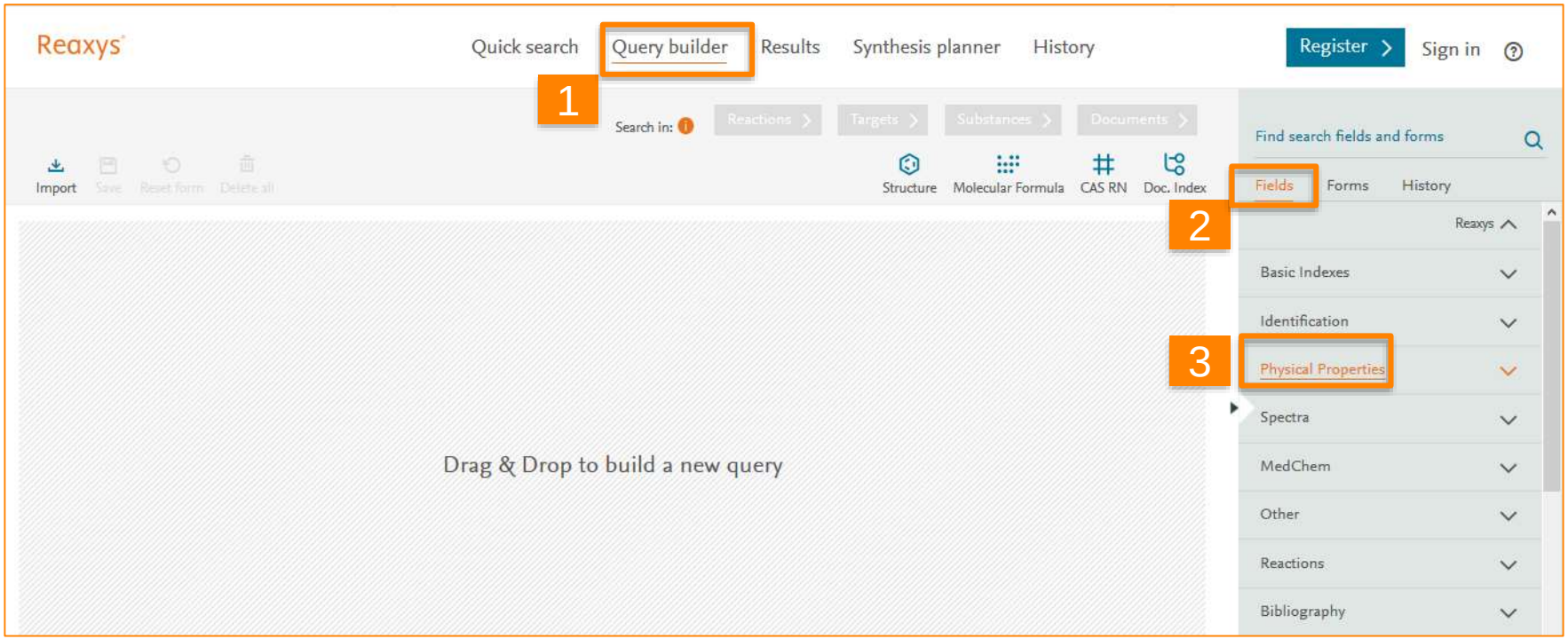
Solubility字段中输入溶剂，Chemical Name中输入物质名称即可

Reaxys直接给出结果

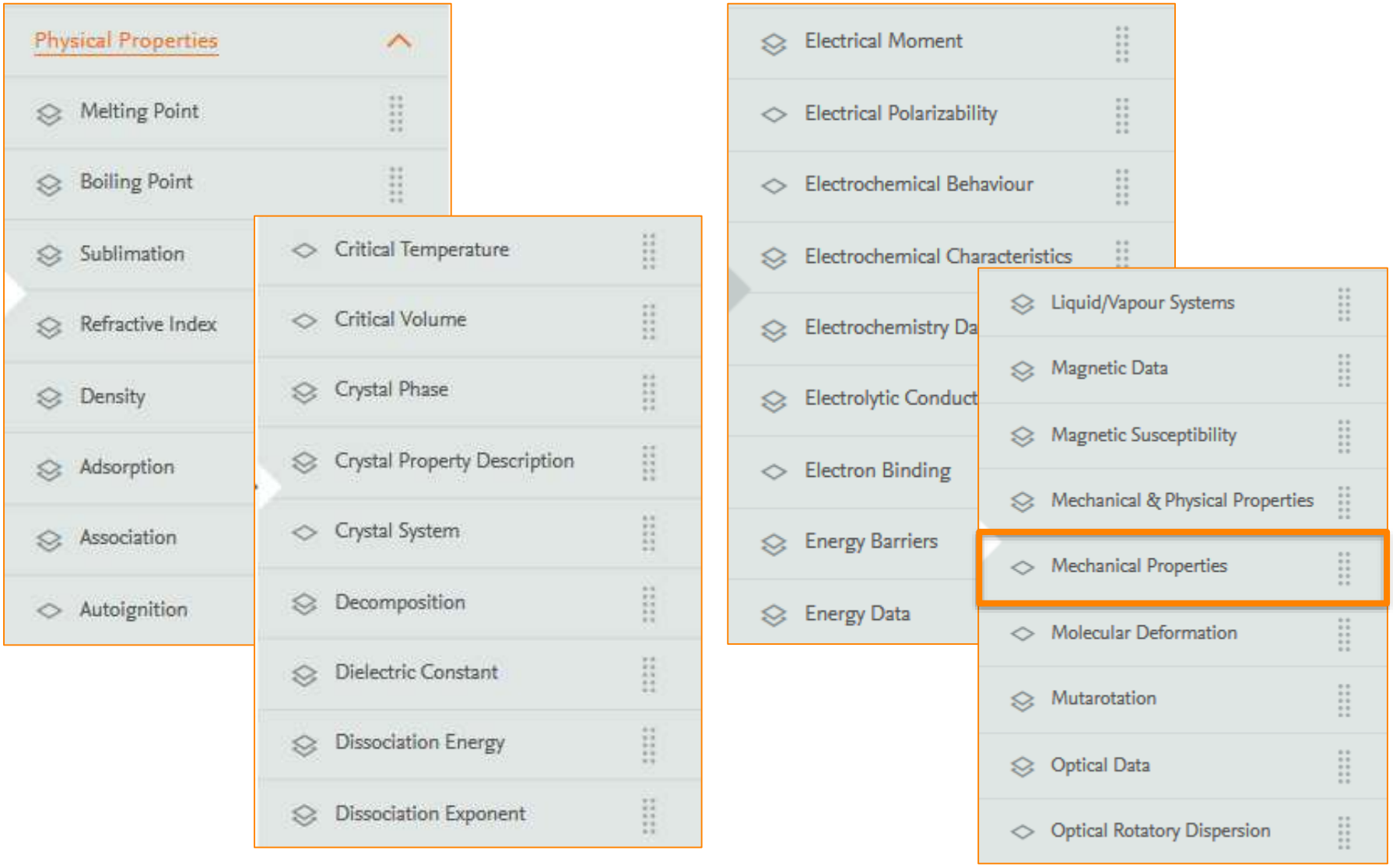


Case Study 2：具备“特殊性能”的物质检索

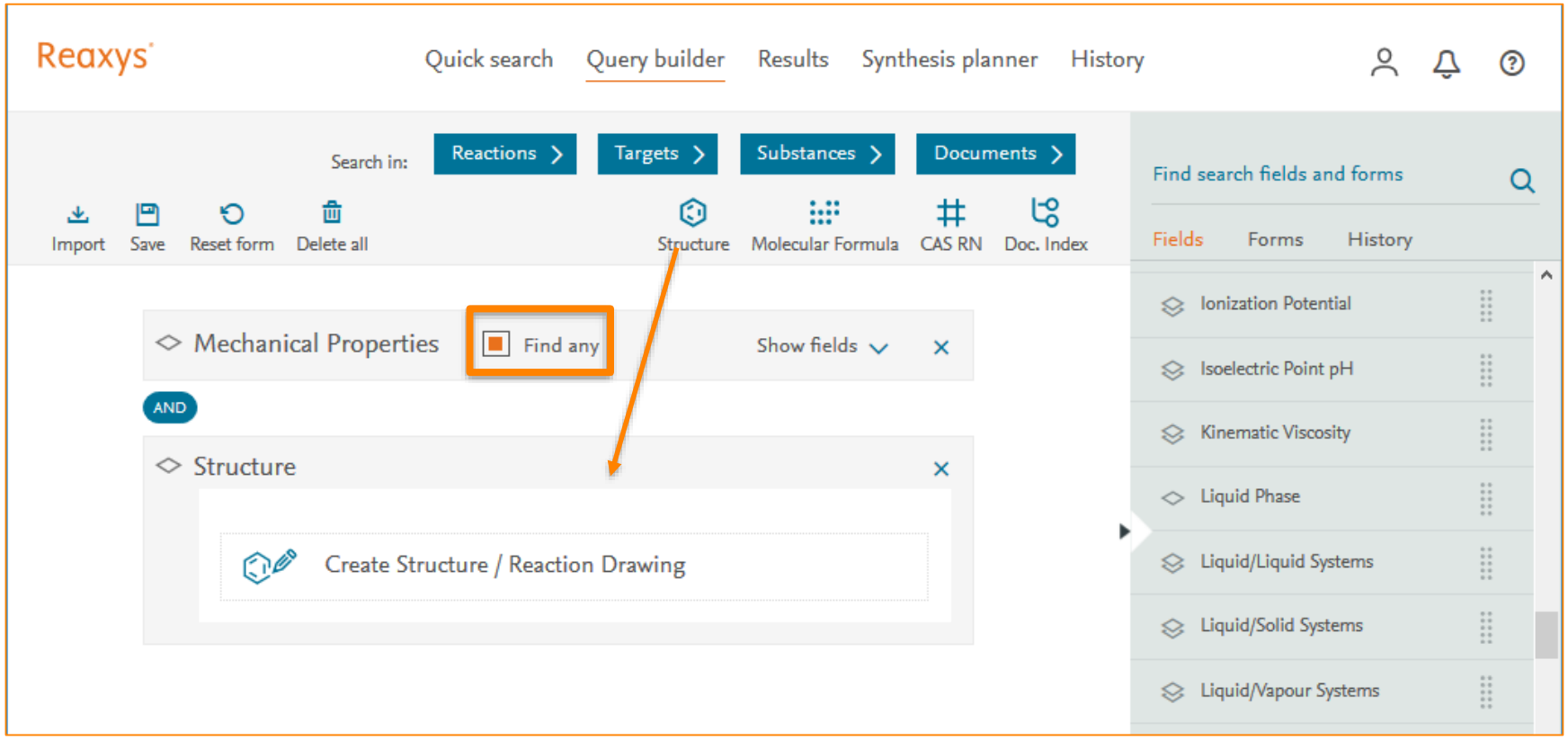
- 检索要求
  - 乙烯衍生物，不能成环
  - 具备“机械性能”报道的化合物
  - 按照以下的标签顺序进行“理化性质”反推的检索
  - “弹性性能”在案例衍生中解决



Reaxys的理化性质列表



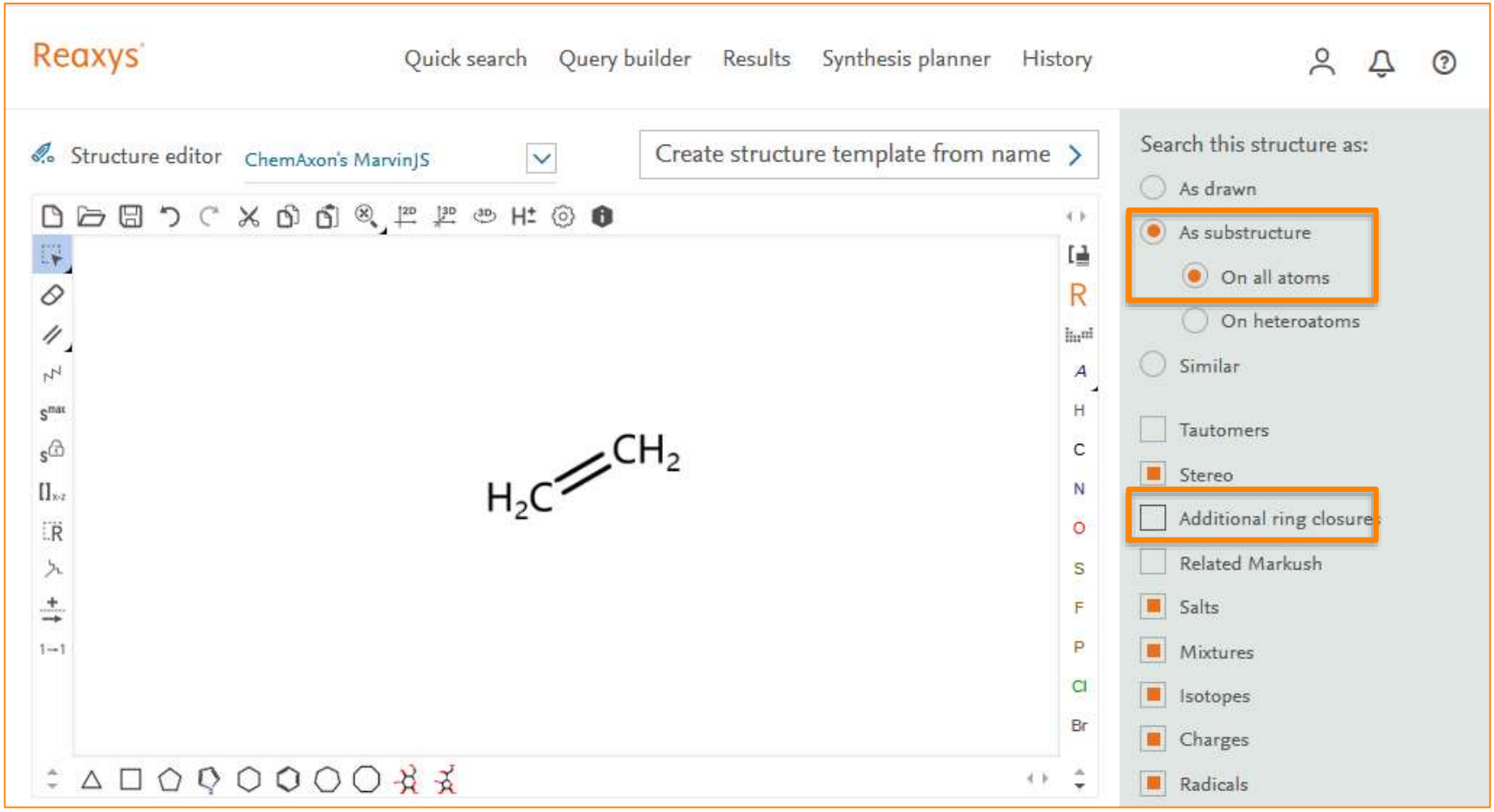
添加“机械属性”列表与结构属性



Tips：

通过Query Builder将结构和“机械属性”联合起来，点击结构添加“乙烯”

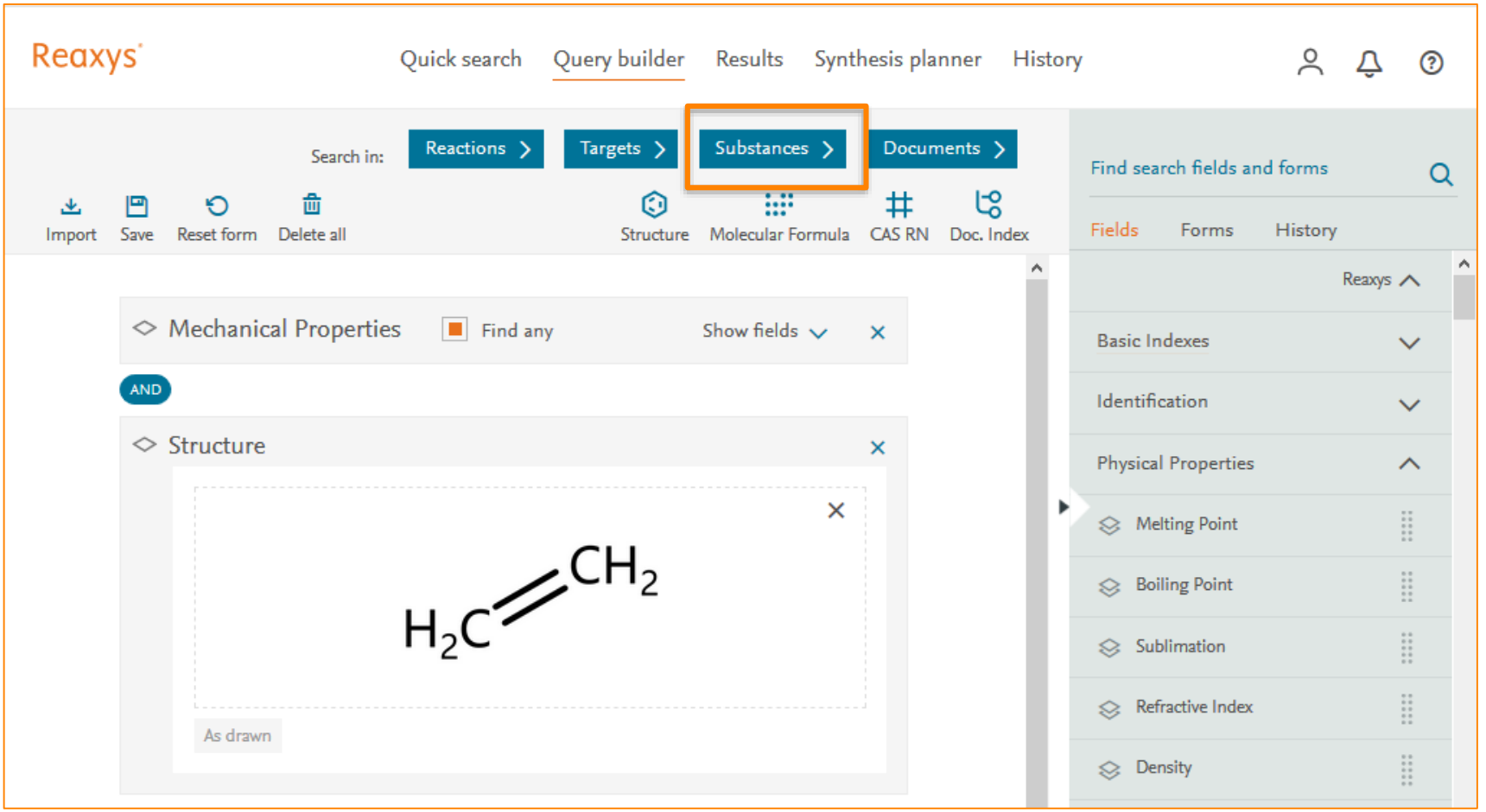
结构的绘制



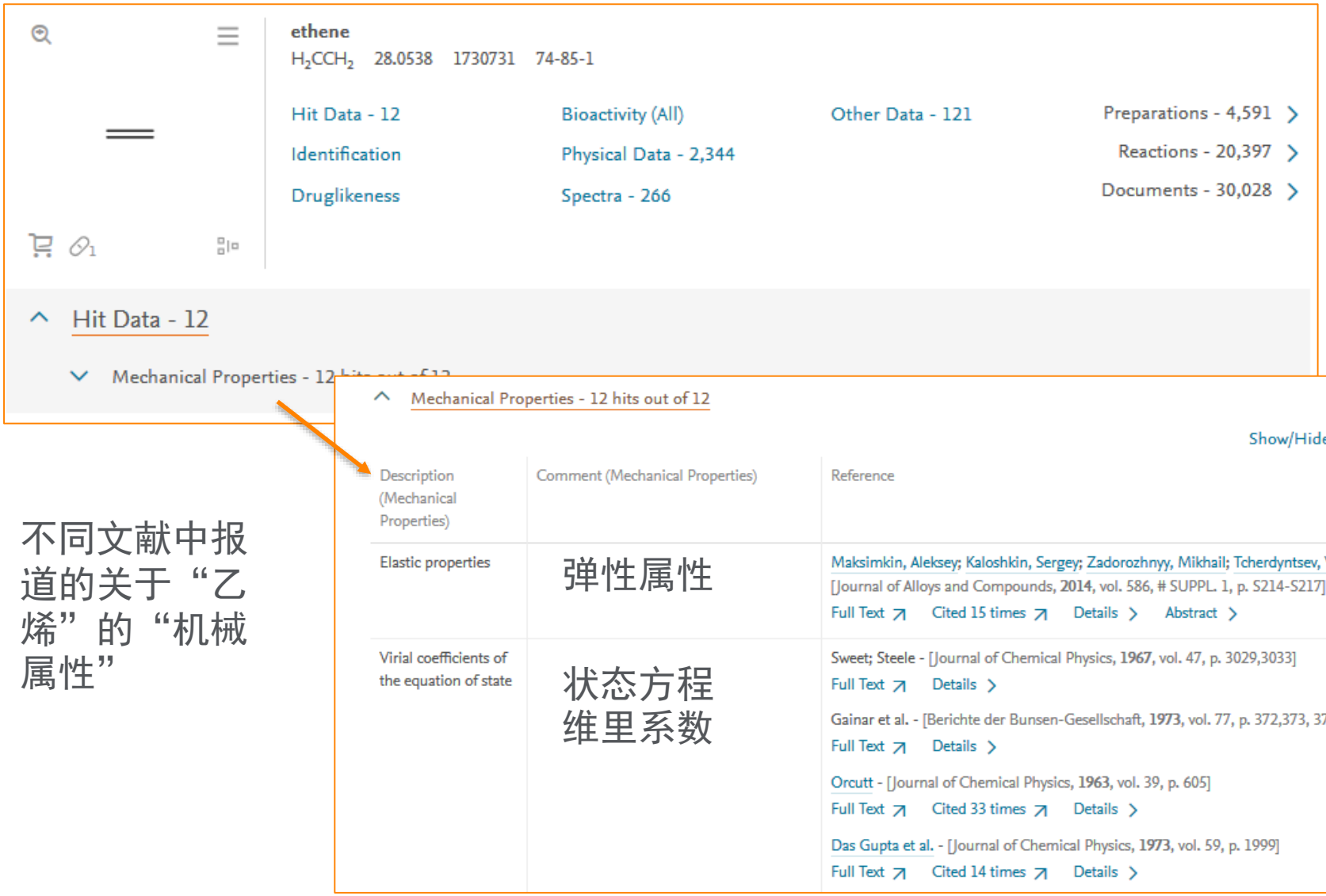
Tips：

亚结构检索确保是乙烯衍生物，Additional Ring Closure去掉确保不成环。

最后的检索式

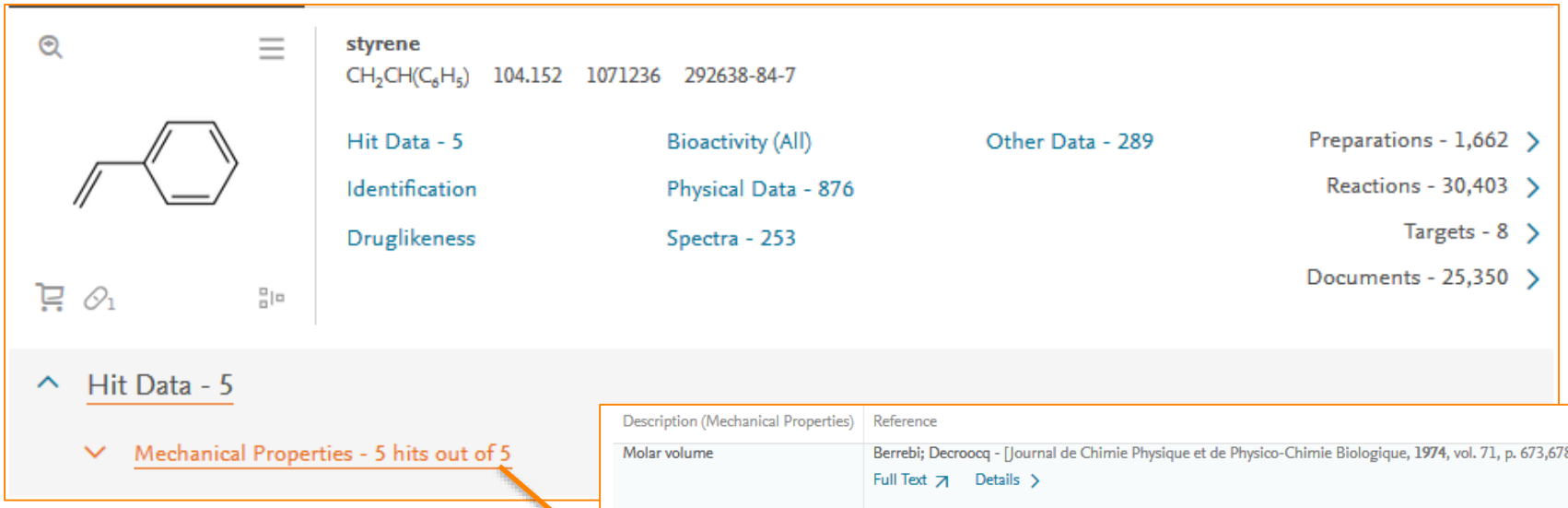

Reaxys
Quick search
Query builder
Results
Synthesis planner
History
Search in:
Reactions
Targets
Substances
Documents
Import
Save
Reset form
Delete all
Structure
Molecular Formula
CAS RN
Doc. Index
Find search fields and forms
Fields
Forms
History
Reaxys
Mechanical Properties
Find any
Show fields
AND
Structure
As drawn
Basic Indexes
Identification
Physical Properties
Melting Point
Boiling Point
Sublimation
Refractive Index
Density

最后的结果—乙烯的数据



不同文献中报道的关于“乙烯”的“机械属性”

最后的结果—衍生物的数据

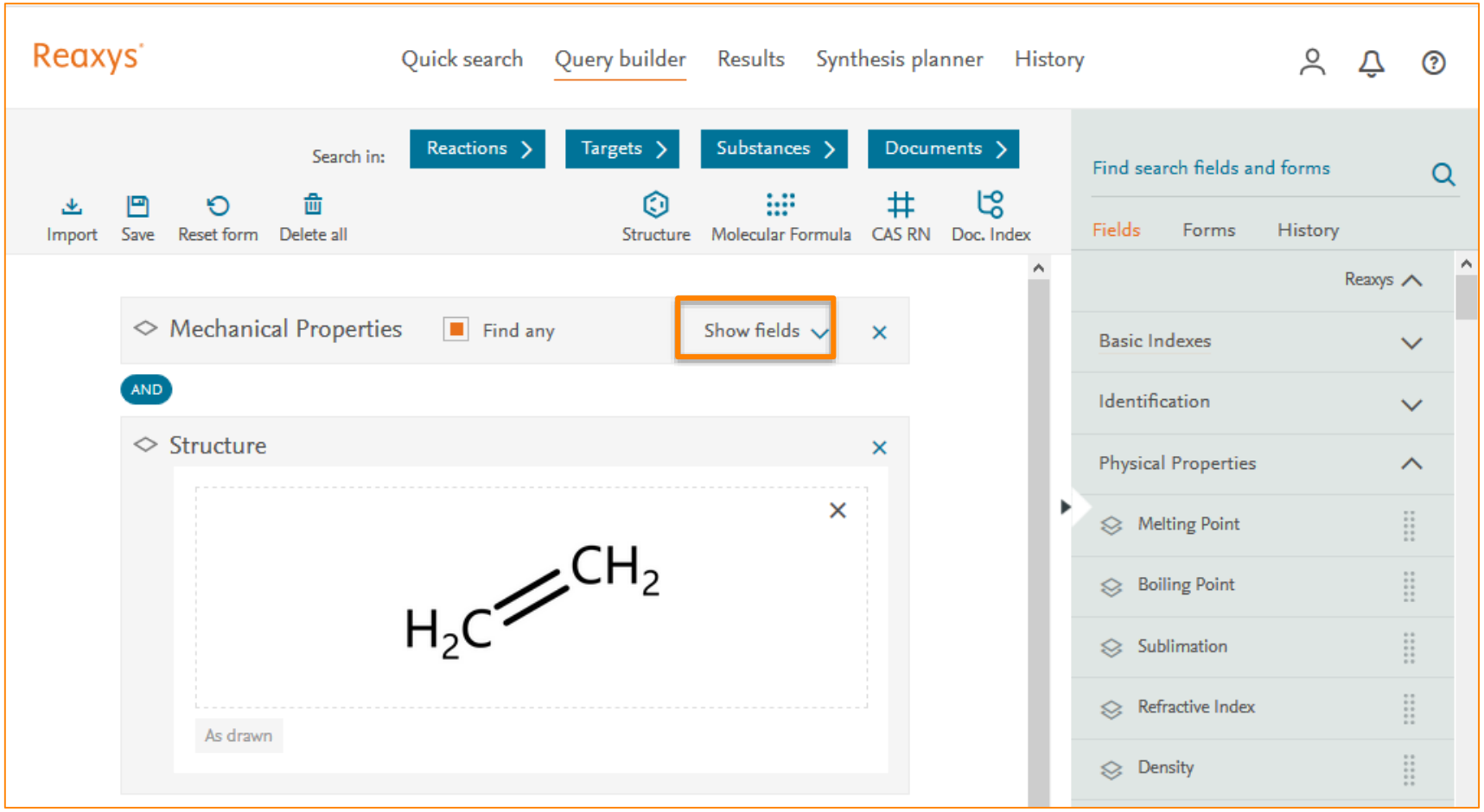


涉及到“苯乙烯”的摩尔体积，可压缩性，维里系数，粘性方面的报道

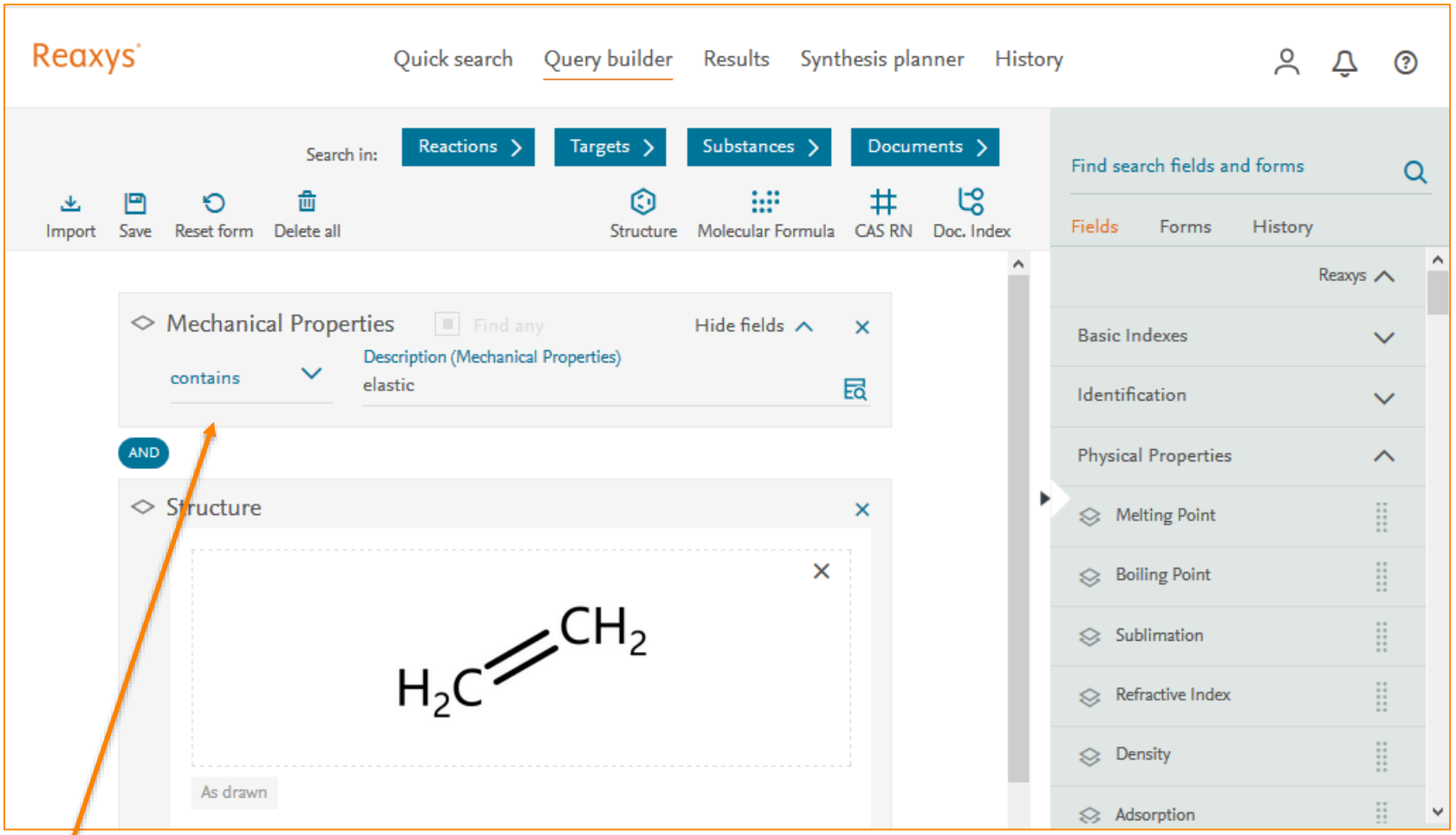
Description (Mechanical Properties)	Reference
Molar volume	Berrebi; Decroocq - [Journal de Chimie Physique et de Physico-Chimie Biologique, **1974**, vol. 71, p. 673,678] Full Text Details Miller et al. - [Journal of Chemical and Engineering Data, **1975**, vol. 20, p. 417,418, 419] Full Text Details Ghosal, Saswati; Samoc, Marek; Prasad, Paras N.; Tufariello, Joseph J. - [Journal of Physical Chemistry, **1990**, vol. 94, # 7, p. 2847 - 2851] Full Text Cited 101 times Details Abstract Hayduk, Walter; Minhas, Bhupender S. - [Journal of Chemical & Engineering Data, **1987**, vol. 32, # 3, p. 285 - 290] Full Text Details Abstract
Virial coefficients of the equation of state	Balashova, I. M.; Mokrushina, L. V.; Morachevskii, A. G. - [J. Appl. Chem. USSR (Engl. Transl.), **1989**, vol. 62, # 12, p. 2744 - 2750,2546 - 2551] Full Text Details Abstract
PVT Relationship	Sasuga et al. - [Journal of Physical Chemistry, **1979**, vol. 83, p. 3290] Full Text Cited 6 times Details
Compressibility	Yakusheva et al. - [Russian Journal of Physical Chemistry, **1977**, vol. 51, p. 973] [p. 1657] Full Text Details
Viscosity	Olaj - [Monatshefte fuer Chemie, **1971**, vol. 102, p. 648] Full Text Cited 3 times Details

案例衍生—如果特指与“弹性”有关的性能报道

- 对于以下的检索，该如何修改

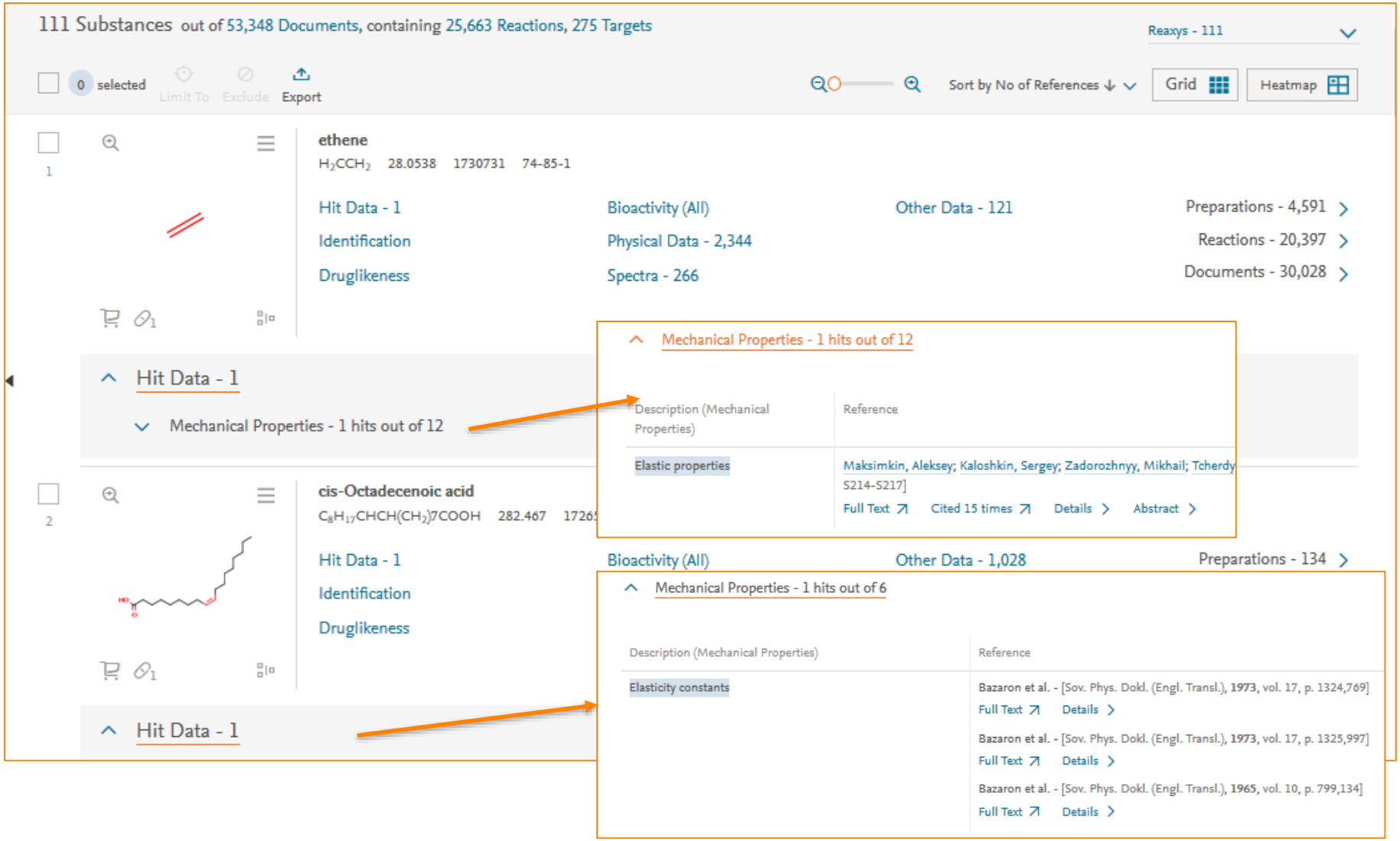


修改检索条件

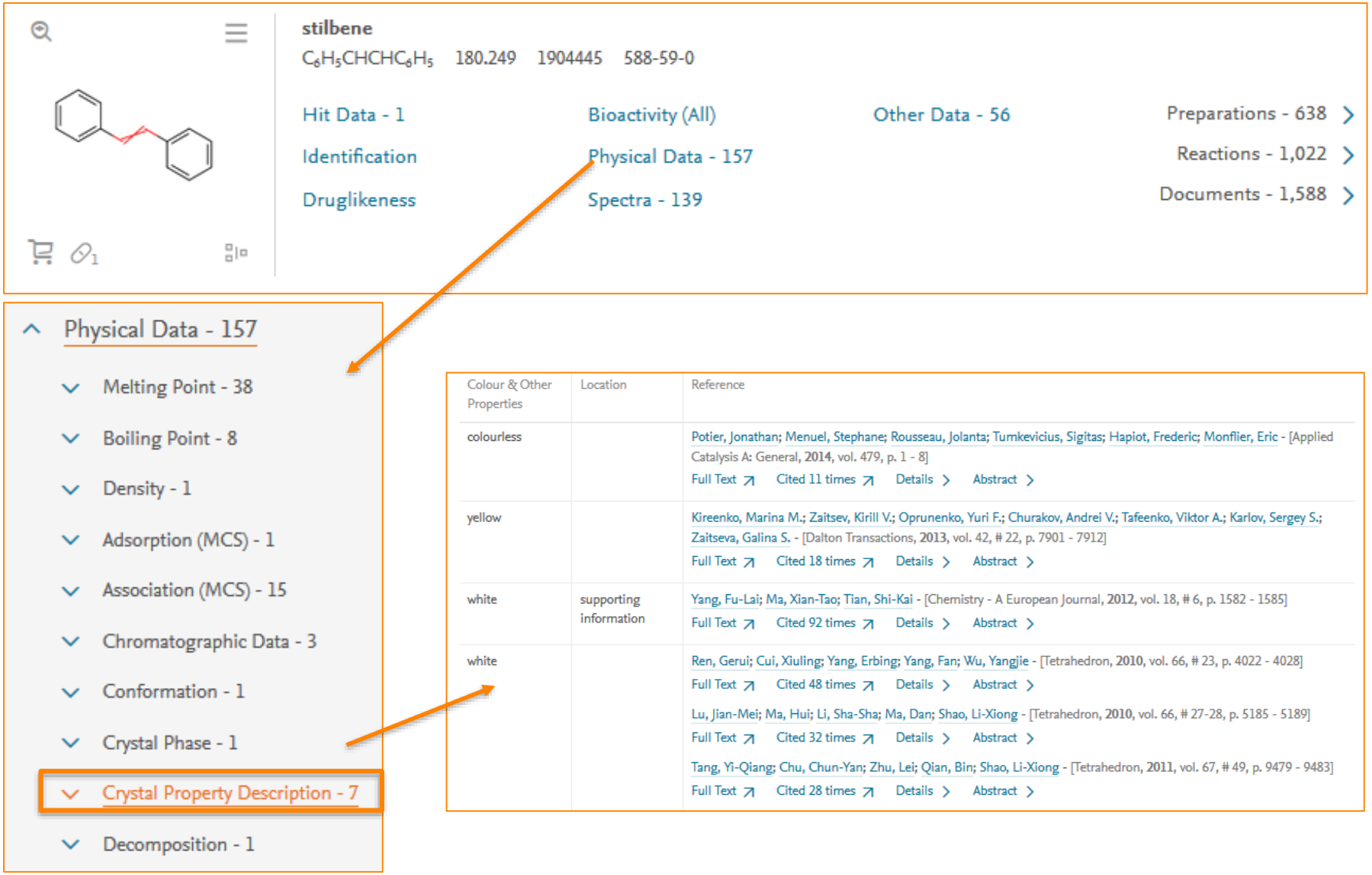


注意修改成Contains, 并添加为“弹性”词条。

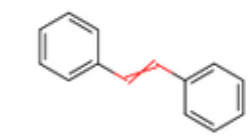
最后的结果


111 Substances out of 53,348 Documents, containing 25,663 Reactions, 275 Targets
Reaxys - 111
0 selected
Limit To
Exclude
Export
Sort by No of References
Grid
Heatmap
1
ethene
H2CCH2 28.0538 1730731 74-85-1
Hit Data - 1
Identification
Druglikeness
Bioactivity (All)
Physical Data - 2,344
Spectra - 266
Other Data - 121
Preparations - 4,591
Reactions - 20,397
Documents - 30,028
Hit Data - 1
Mechanical Properties - 1 hits out of 12
Mechanical Properties - 1 hits out of 12
Description (Mechanical Properties)
Reference
Elastic properties
Maksimkin, Aleksey; Kaloshkin, Sergey; Zadorozhnyy, Mikhail; Tcherdy
S214-S217]
Full Text
Cited 15 times
Details
Abstract
2
cis-Octadecenoic acid
C8H17CHCH(CH2)7COOH 282.467
Hit Data - 1
Identification
Druglikeness
Bioactivity (All)
Other Data - 1,028
Preparations - 134
Hit Data - 1
Mechanical Properties - 1 hits out of 6
Description (Mechanical Properties)
Reference
Elasticity constants
Bazaron et al. - [Sov. Phys. Dokl. (Engl. Transl.), 1973, vol. 17, p. 1324,769]
Full Text
Details
Bazaron et al. - [Sov. Phys. Dokl. (Engl. Transl.), 1973, vol. 17, p. 1325,997]
Full Text
Details
Bazaron et al. - [Sov. Phys. Dokl. (Engl. Transl.), 1965, vol. 10, p. 799,134]
Full Text
Details

其中一个化合物—理化性质



其中一个化合物—理化性质



stilbene

$C_6H_5CHCHC_6H_5$ 180.249 1904445 588-59-0

Hit Data - 1

Identification

Druglikeness

Bioactivity (All)

Physical Data - 157

Spectra - 139

Other Data -

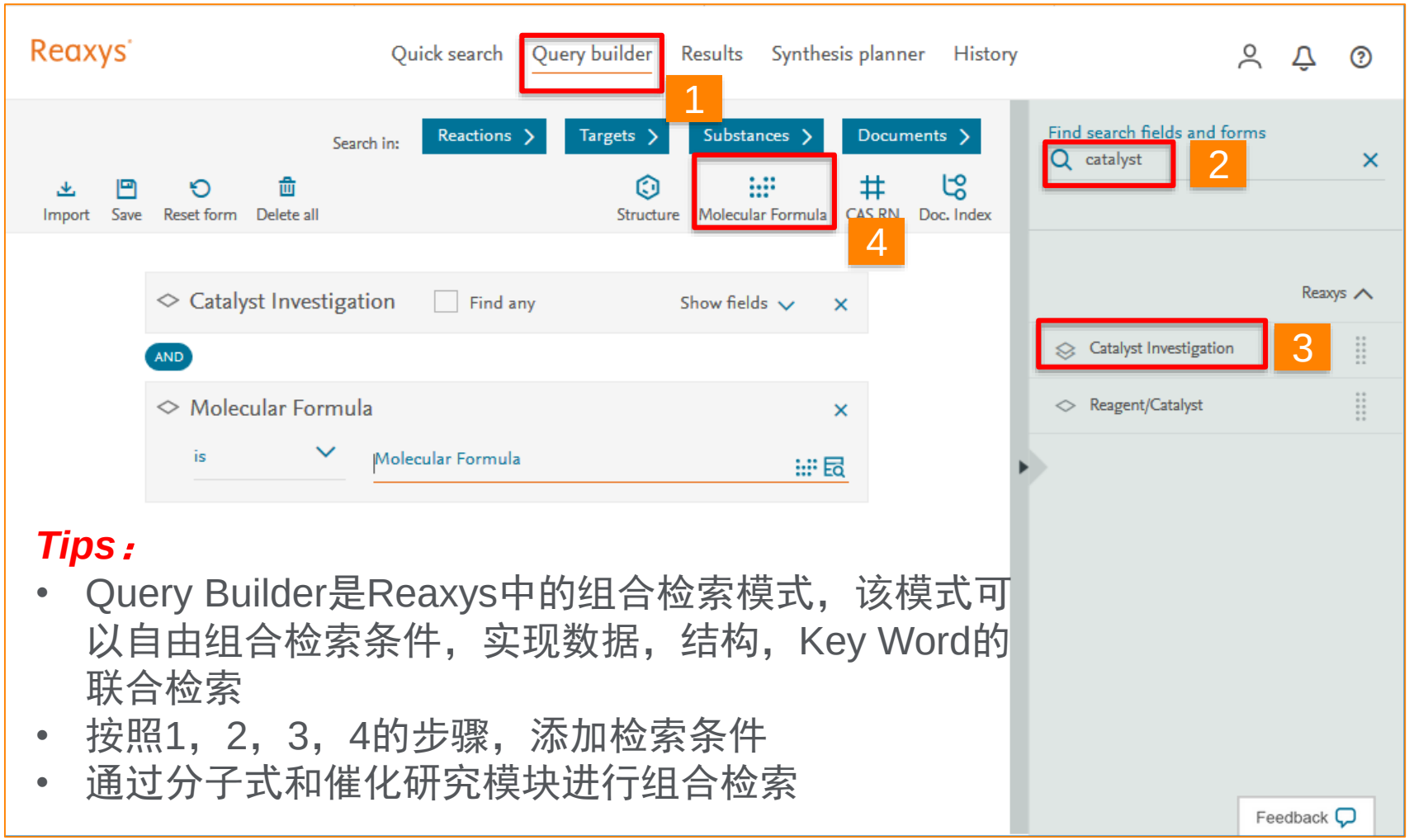
Spectra - 139

- NMR Spectroscopy - 67
- IR Spectroscopy - 8
- Mass Spectrometry - 17
- UV/VIS Spectroscopy - 17
- ESR Spectroscopy - 2

Description (NMR Spectroscopy)	Nucleus (NMR Spectroscopy)	Coupling Nuclei	Solvents (NMR Spectroscopy)	Temperature (NMR Spectroscopy), °C	Frequency (NMR Spectroscopy), MHz	Original Text (NMR Spectroscopy)	Location	Comment (NMR Spectroscopy)	Signals, ppm	Kind of signal	Reference
shifts, Spectrum						MHz, $CDCl_3$) δ: 7.12 (s, 2H), 7.27 (t, J = 7.4 Hz, 2H), 7.37 (t, J = 7.4 Hz, 4H), 7.53 (dd, J = 1.4 and 8.4 Hz, 3H)	information				- [Tetrahedron, **2017**, vol. 73, # 27-28, p. Full Text Details Abstract
Chemical shifts, Spectrum	13C		chloroform-d1		125	^{13}C NMR (125 MHz, $CDCl_3$) δ: 127.4, 128.5, 129.5, 138.22	supporting information		127.4, 128.5, 129.5, 138.22		Tanaka, Chihiro; Nakamura, Kimiaki; Ni - [Tetrahedron, **2017**, vol. 73, # 27-28, p. Full Text Details Abstract

Case Study 3：“特定研究领域”的催化剂选择

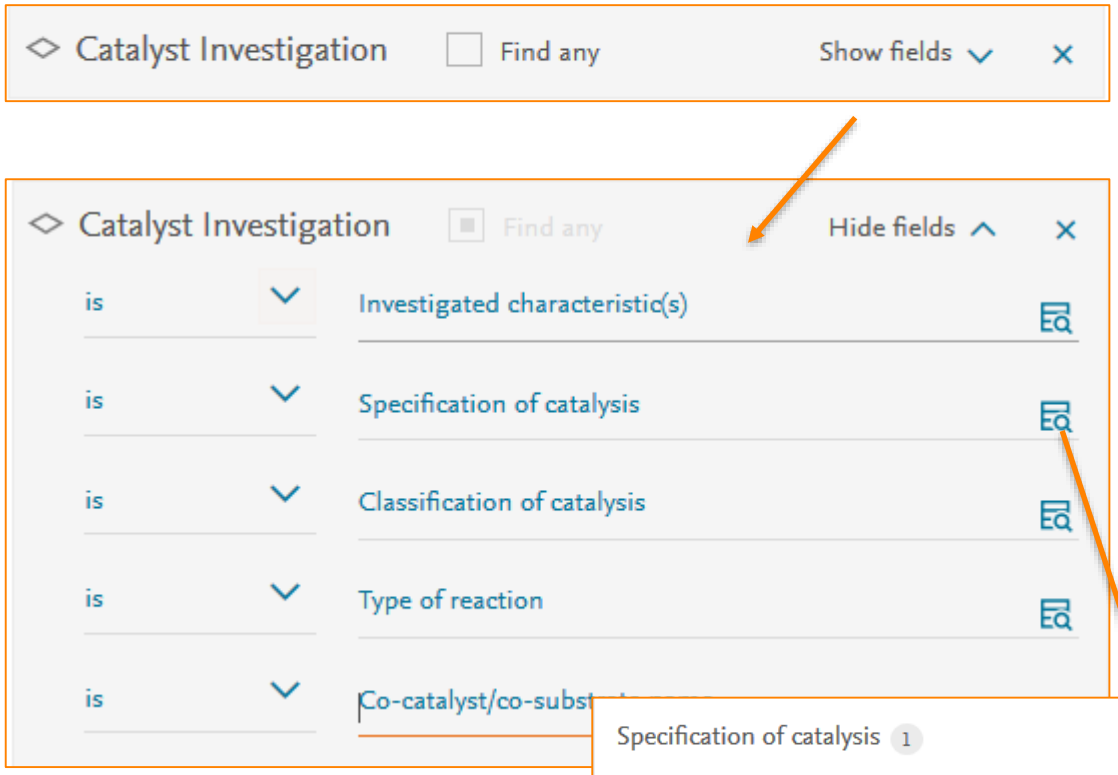
- 检索可用于立体选择性催化的含Fe的催化剂



Tips：

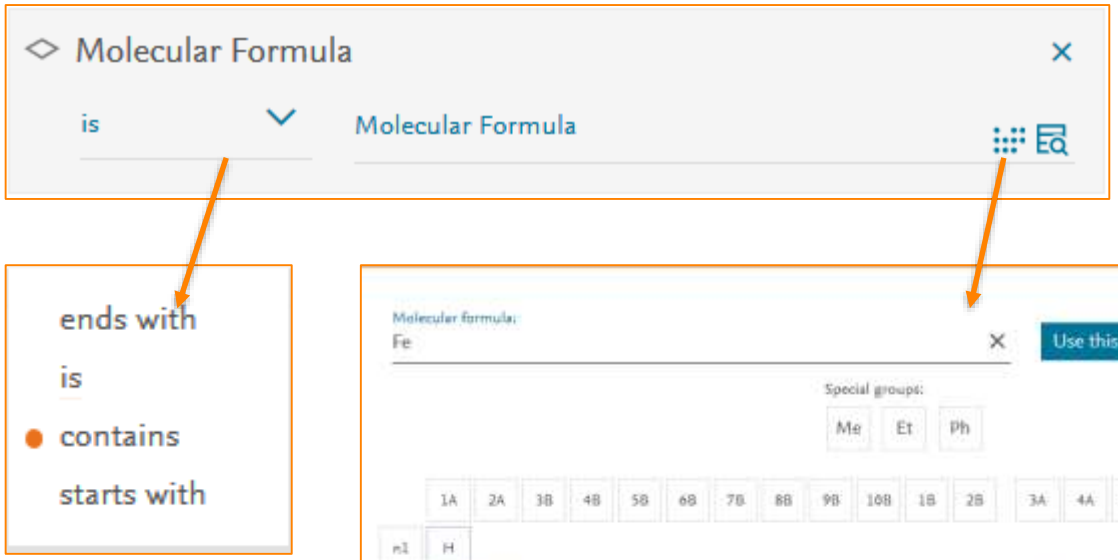
- Query Builder是Reaxys中的组合检索模式，该模式可以自由组合检索条件，实现数据，结构，Key Word的联合检索
- 按照1，2，3，4的步骤，添加检索条件
- 通过分子式和催化研究模块进行组合检索

条件的逐渐添加—Catalyst Investigation



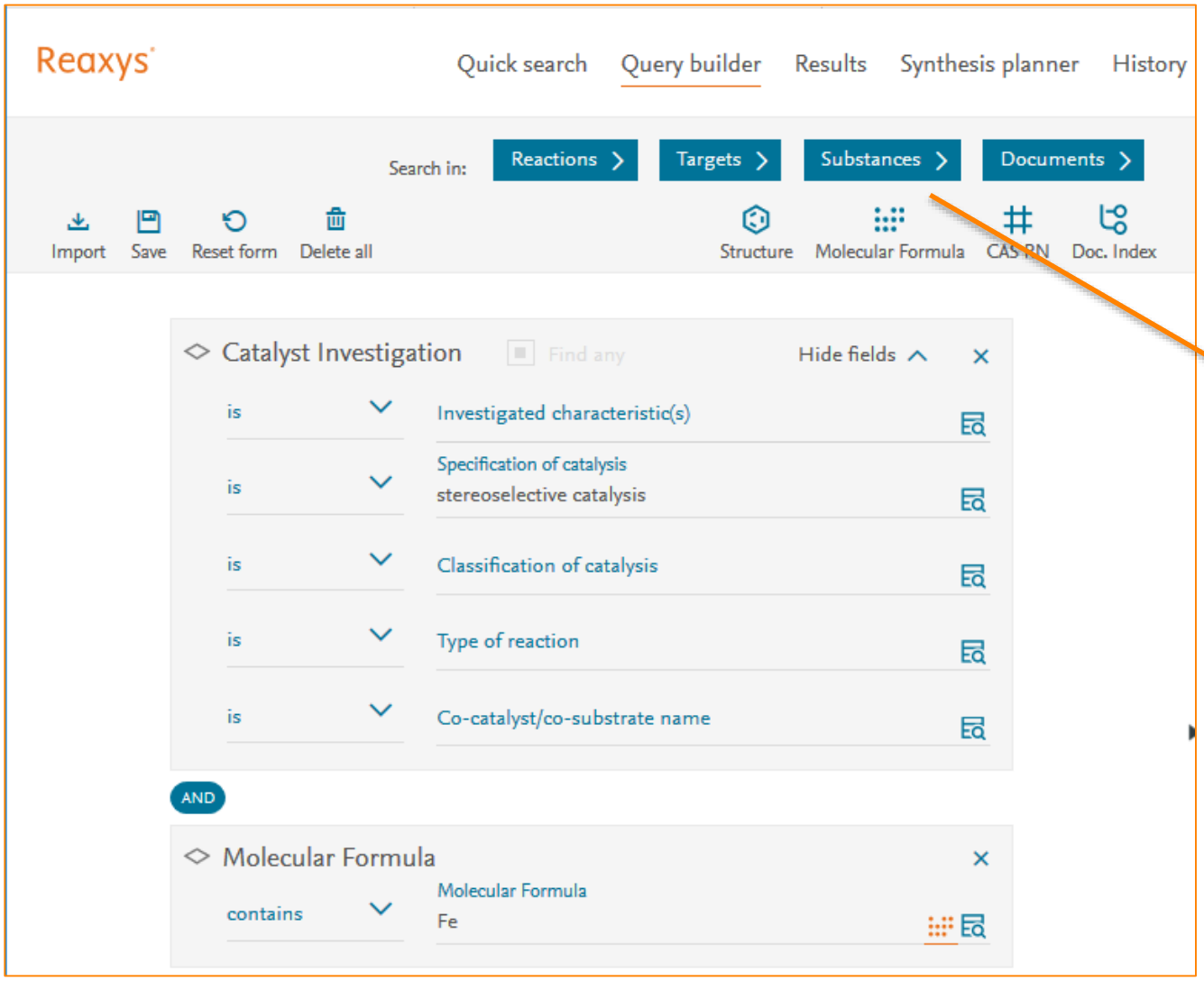
逐渐添加Catalyst Investigation中的参数

条件的逐渐添加—MF的添加



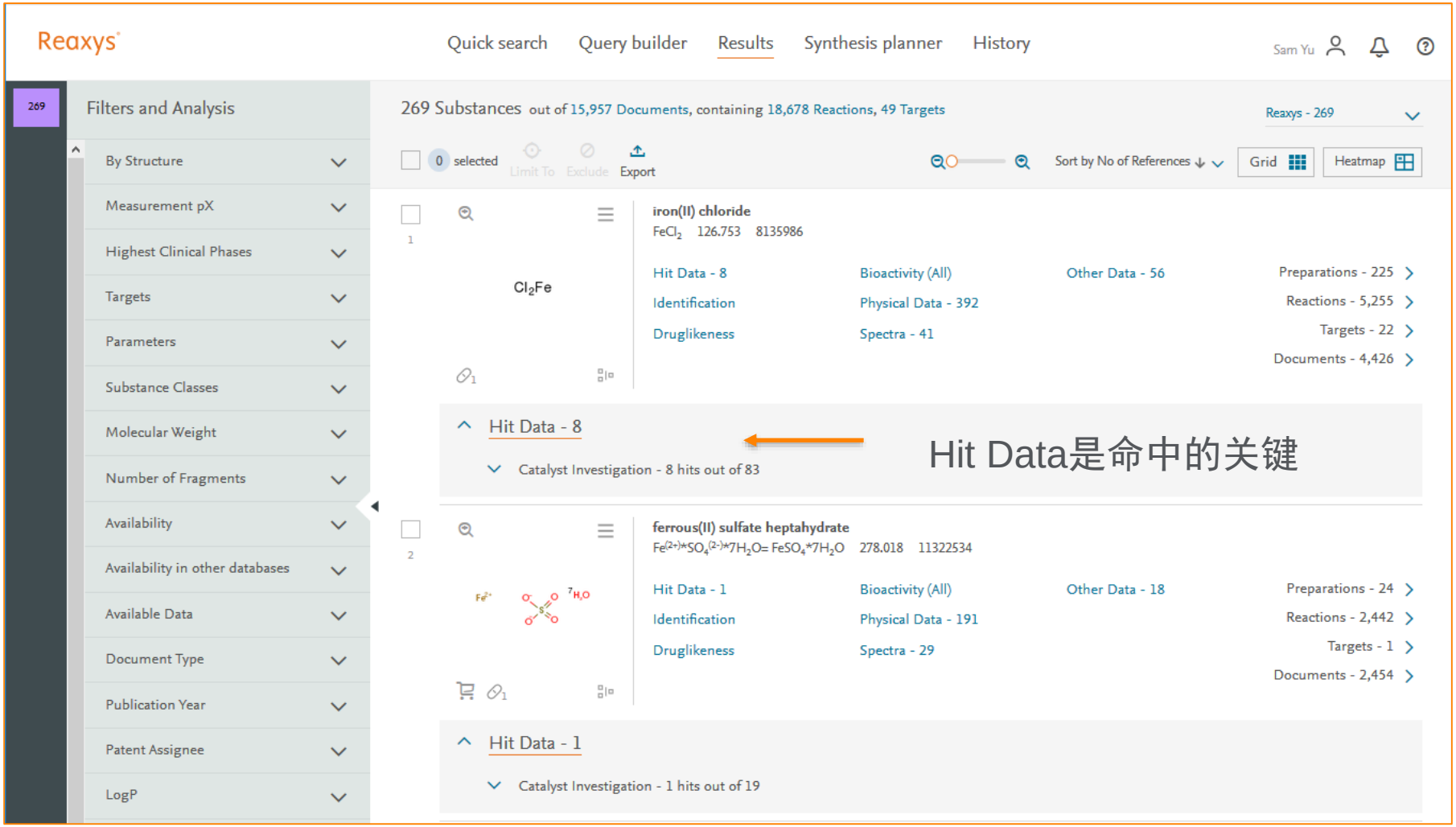
可以按照种类进行选择，过渡态金属，镧系金属等

完成的检索式

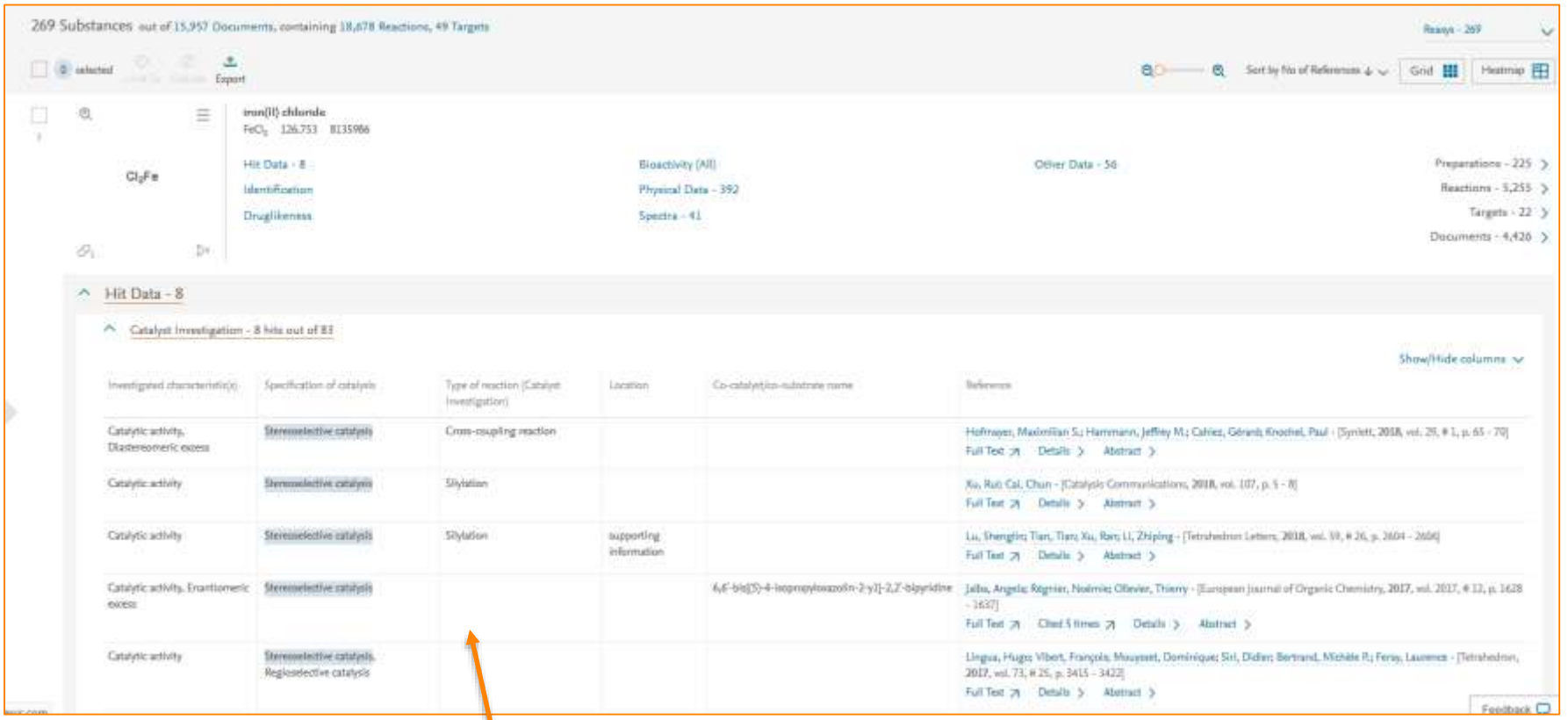

Reaxys
Quick search
Query builder
Results
Synthesis planner
History
Search in:
Reactions
Targets
Substances
Documents
Import
Save
Reset form
Delete all
Structure
Molecular Formula
CAS RN
Doc. Index
Catalyst Investigation
Find any
Hide fields
is
Investigated characteristic(s)
Specification of catalysis
stereoselective catalysis
Classification of catalysis
Type of reaction
Co-catalyst/co-substrate name
AND
Molecular Formula
contains
Molecular Formula
Fe

物质检索

最后的结果


Reaxys
Quick search
Query builder
Results
Synthesis planner
History
Sam Yu
269
Filters and Analysis
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
269 Substances out of 15,957 Documents, containing 18,678 Reactions, 49 Targets
Reaxys - 269
0 selected
Limit To
Exclude
Export
Sort by No of References
Grid
Heatmap
1
iron(II) chloride
FeCl2 126.753 8135986
Cl2Fe
Hit Data - 8
Bioactivity (All)
Other Data - 56
Preparations - 225
Identification
Physical Data - 392
Reactions - 5,255
Druglikeness
Spectra - 41
Targets - 22
Documents - 4,426
Hit Data - 8
Catalyst Investigation - 8 hits out of 83
Hit Data是命中的关键
2
ferrous(II) sulfate heptahydrate
Fe(2+)*SO4(2-)*7H2O= FeSO4*7H2O 278.018 11322534
Hit Data - 1
Bioactivity (All)
Other Data - 18
Preparations - 24
Identification
Physical Data - 191
Reactions - 2,442
Druglikeness
Spectra - 29
Targets - 1
Documents - 2,454
Hit Data - 1
Catalyst Investigation - 1 hits out of 19

其中一个化合物中的命中记录



Reaxys给出结果的逻辑是，先给答案，再给出支持答案的文献出处。

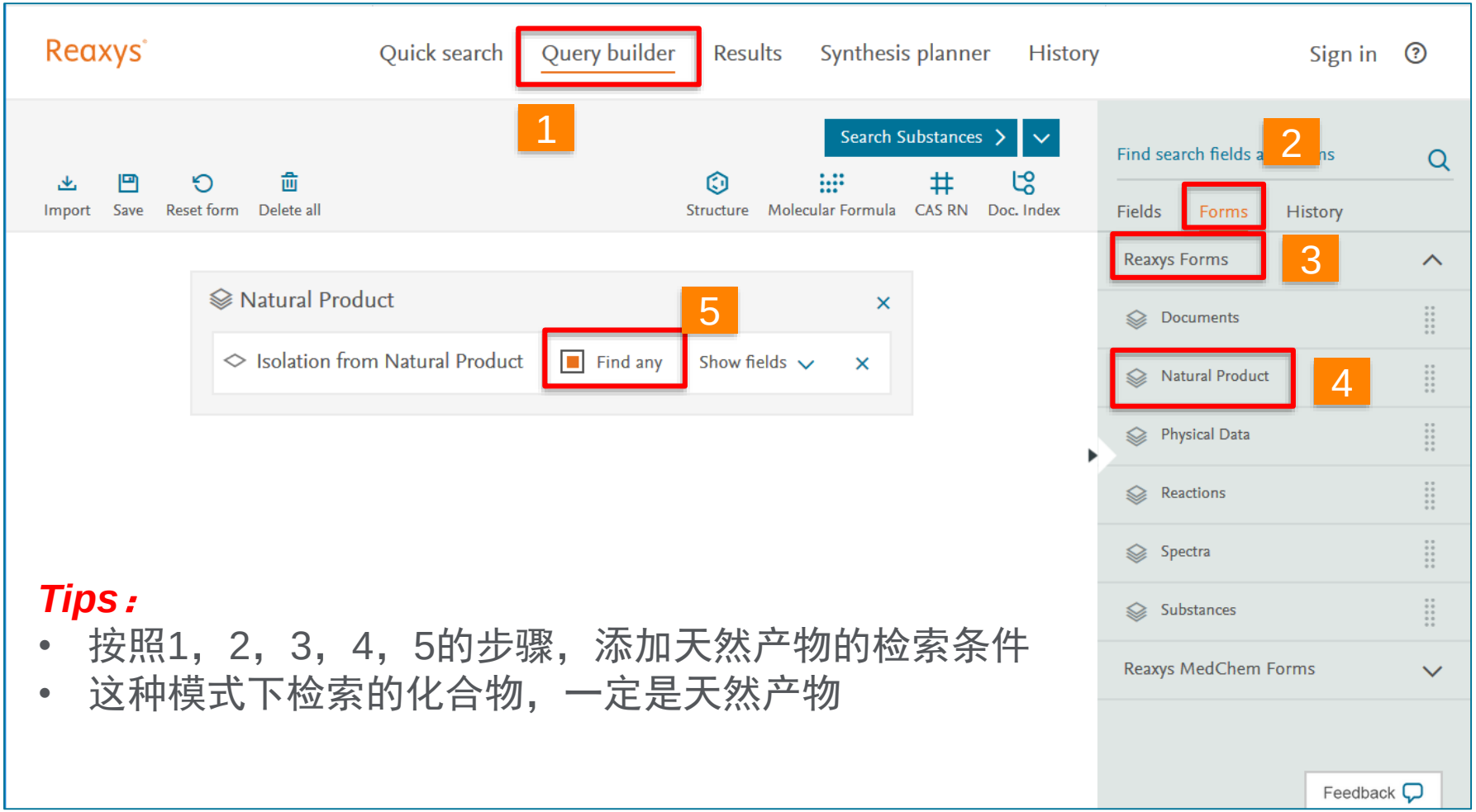
Case Study 4：如何利用数据进行化合物解谱

- 常见的情况
  - 知道是天然产物
  - 分子量348.456
  - 从谱图上可以看到一些明显的片段结构
  - 有一组NMR的数据

- 检索策略
  - Query Builder，添加天然产物选项
  - 分子量设定为>=348，且<=349，避免一些误差
  - 有明确结构的时候，可以同时添加结构片段，或在后期进行筛选
  - 有谱图数据的话，可以直接添加谱图数据（案例衍生中涉及）
  - Reaxys中Substance Class分析结构

Query Builder检索式的创建

- 首先添加天然产物模块

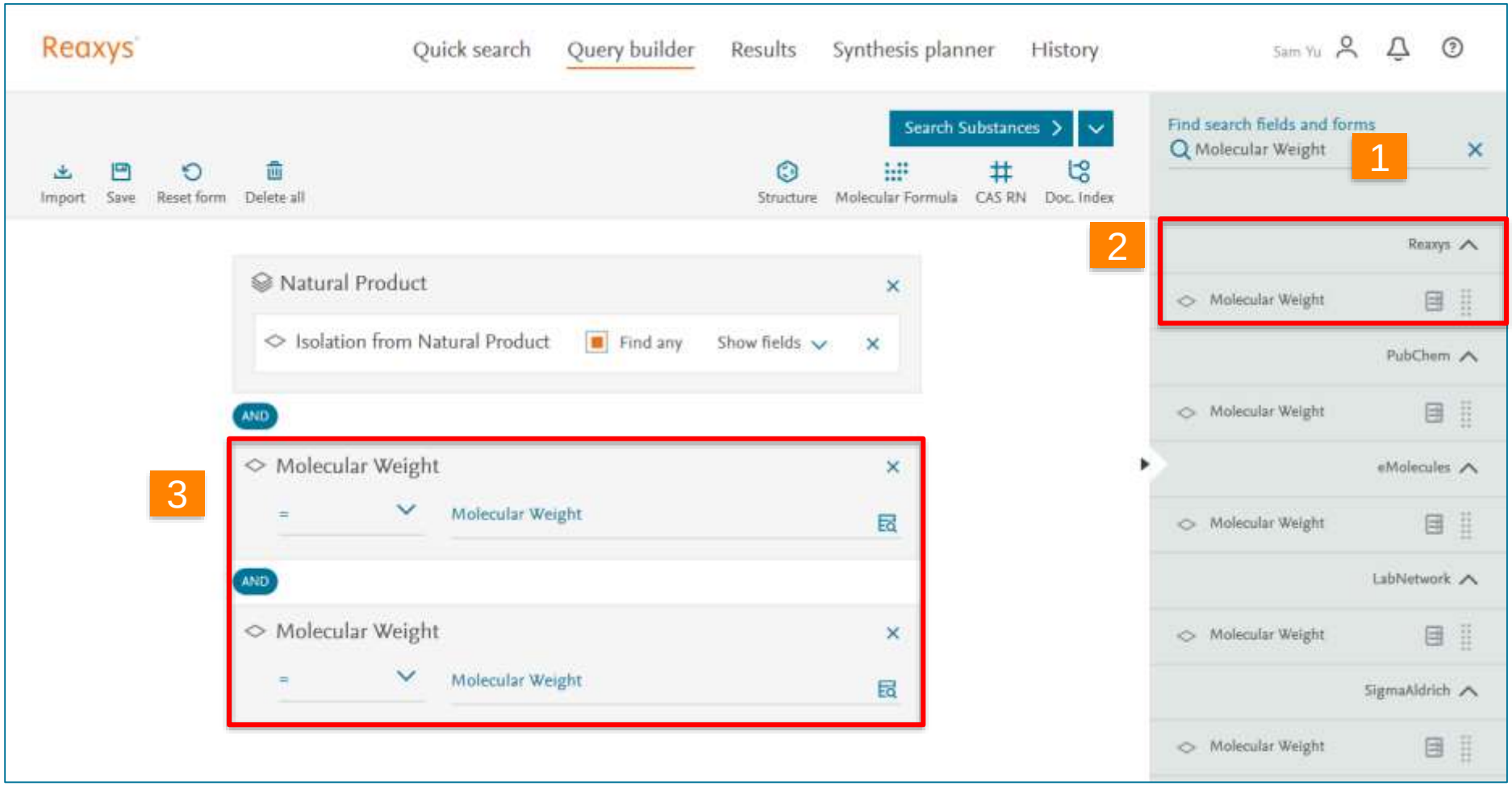


Tips：

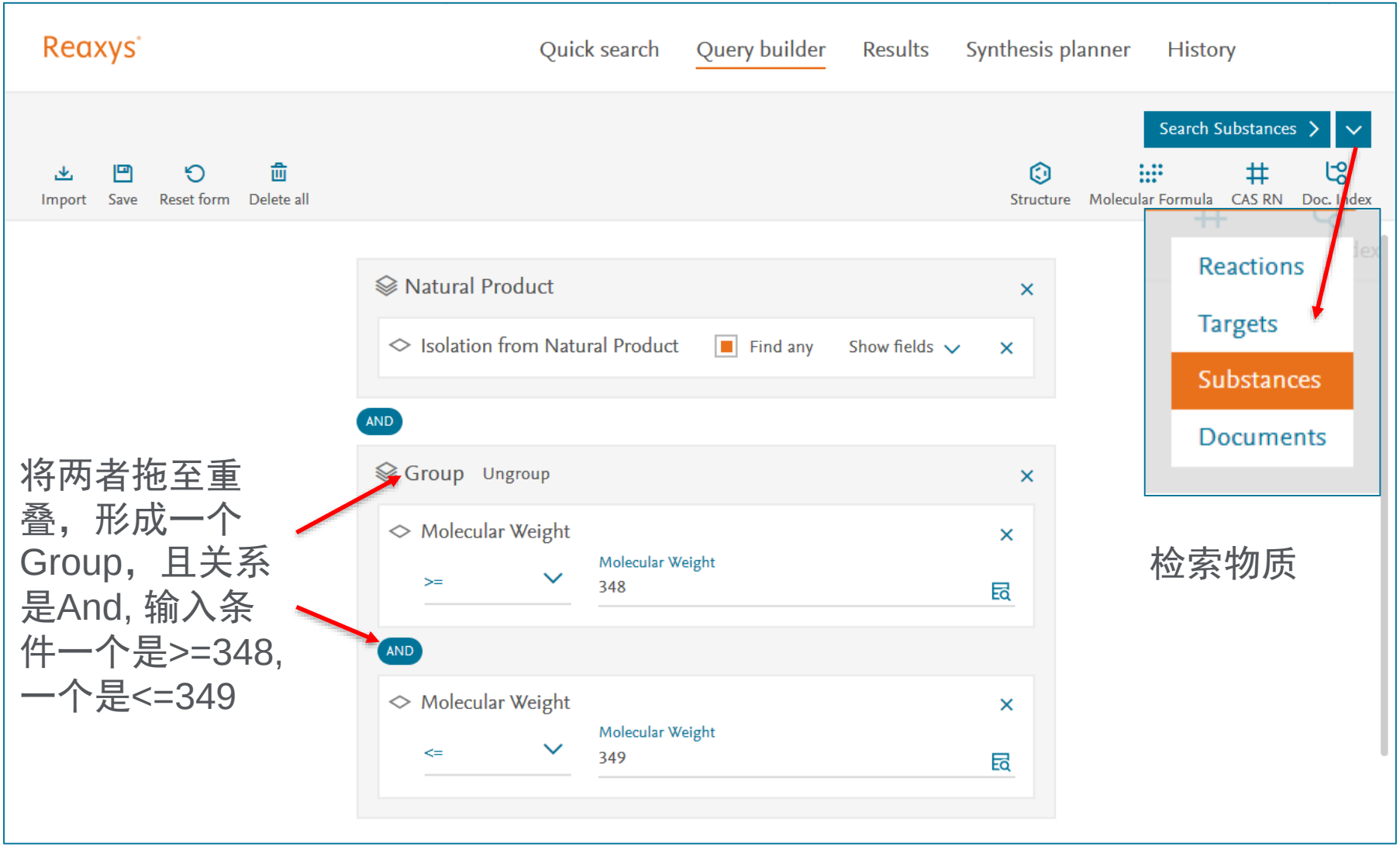
- 按照1，2，3，4，5的步骤，添加天然产物的检索条件
- 这种模式下检索的化合物，一定是天然产物

Query Builder检索式的创建

- 分子量条件的添加，在1的地方输入分子量，点击两下2，可以看到3



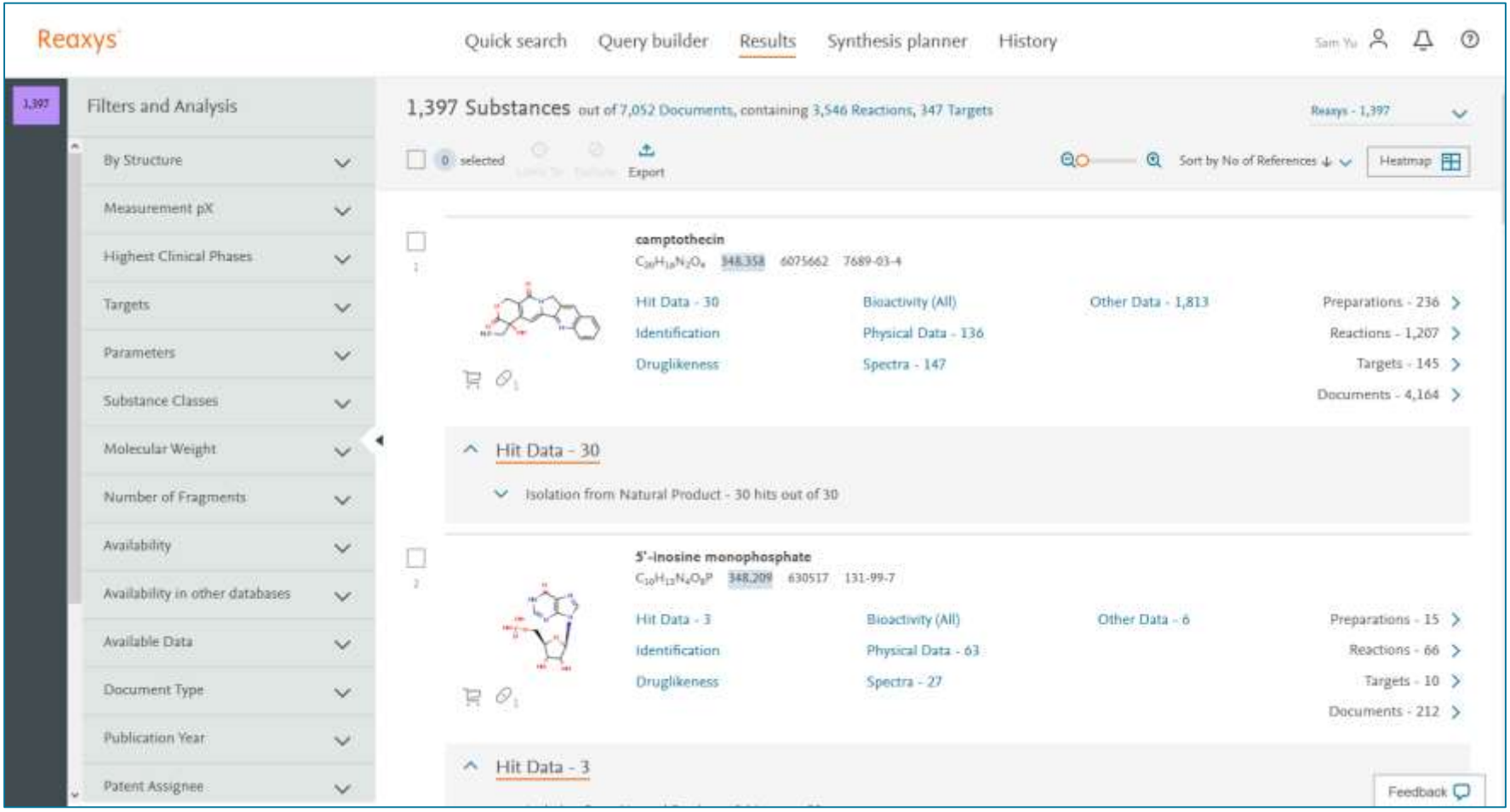
条件的组合



将两者拖至重叠，形成一个Group，且关系是And, 输入条件一个是>=348, 一个是<=349

检索物质

Reaxys的初步检索结果

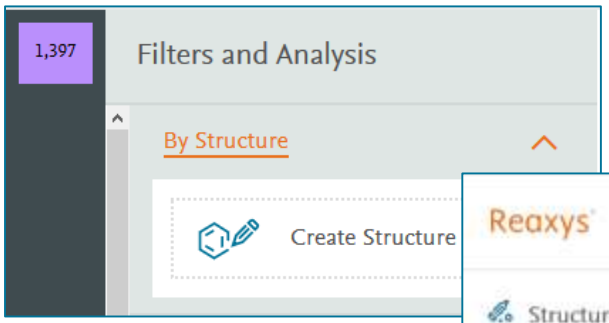


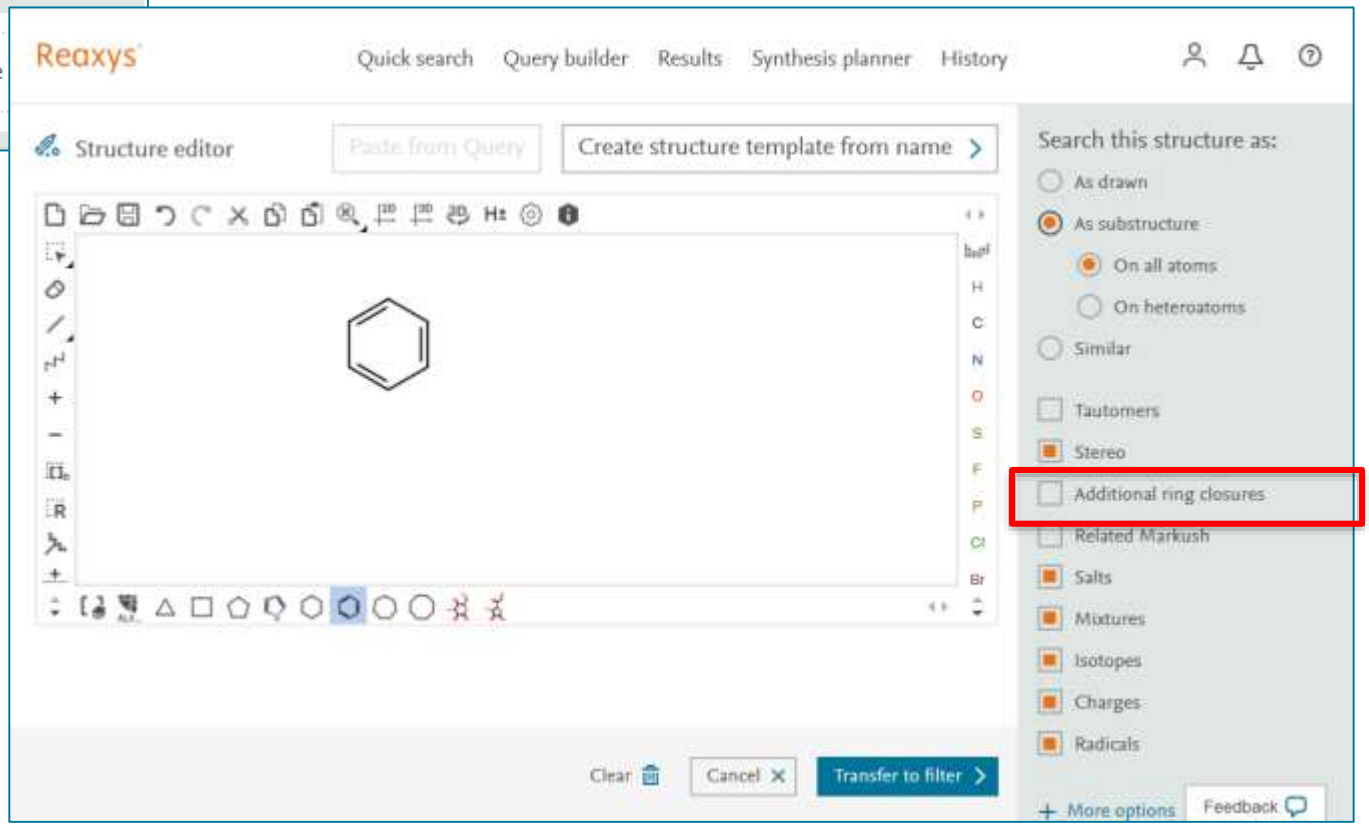
其中的一个物质

罂粟科植物人血草的地上部分和根部

如何筛选—利用碎片结构进行筛选

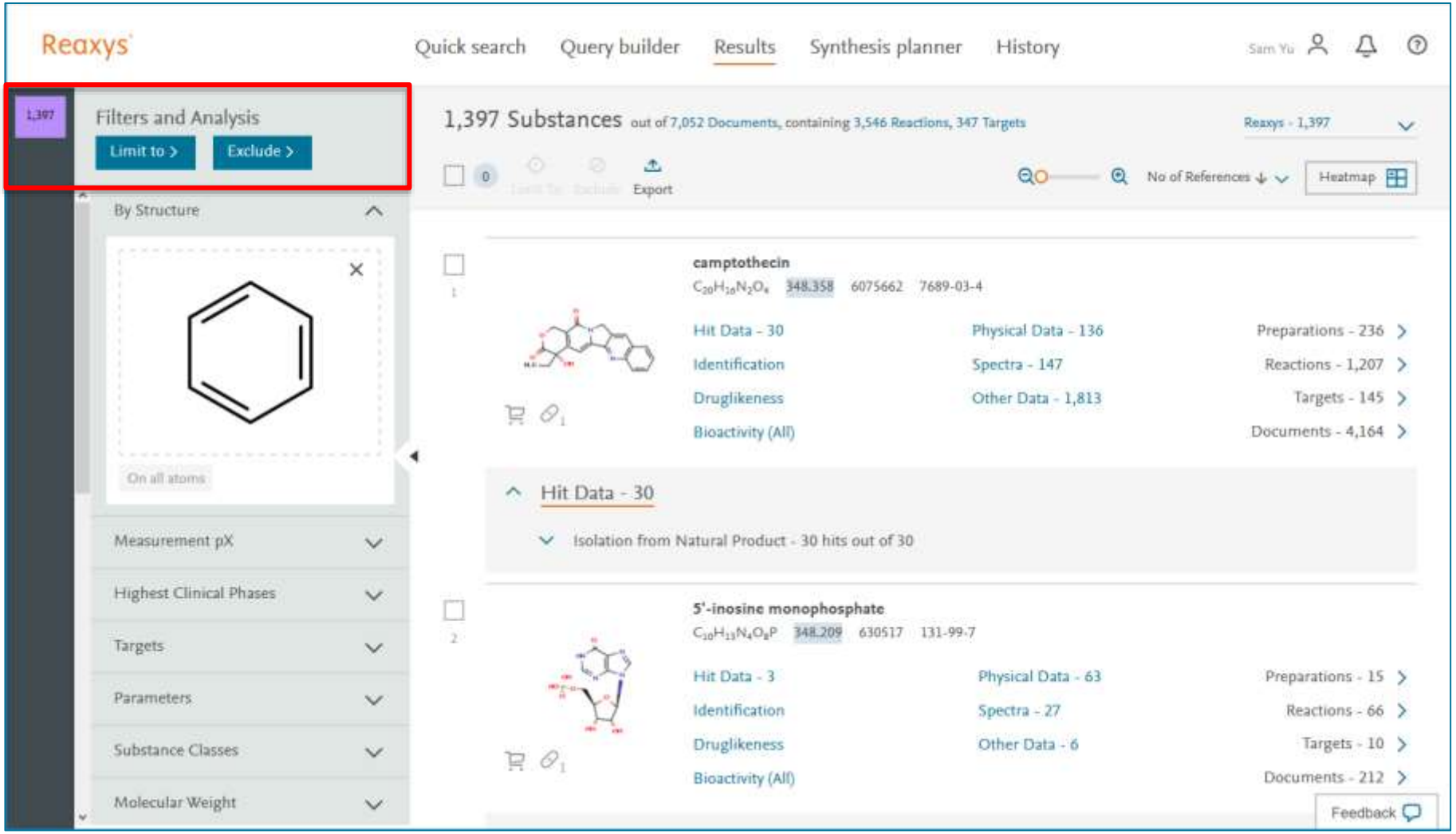
- 如果已经知道结构中存在，或者不存在的片段，可以添加结构定义





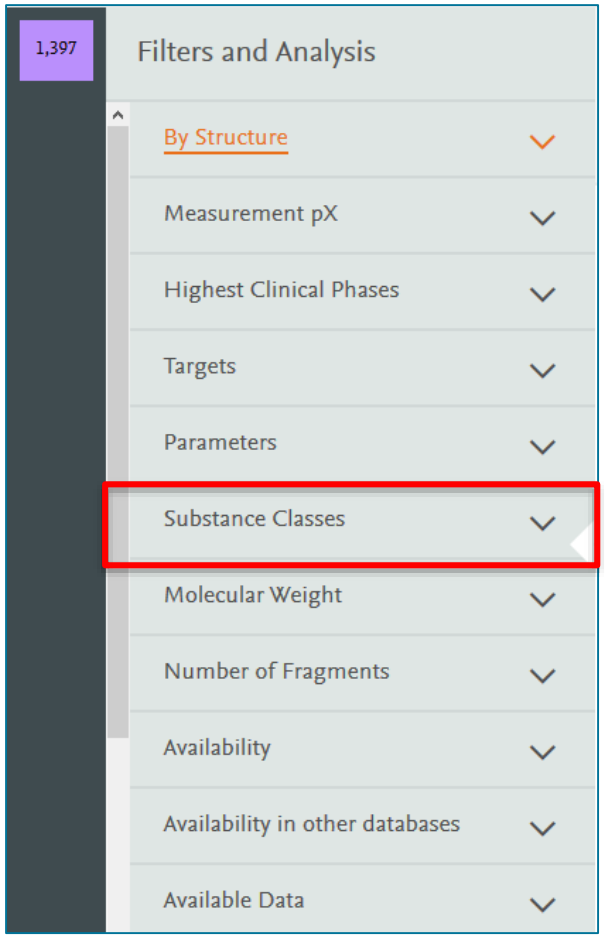
Tips：
定义时需要明确该苯环是否允许稠环

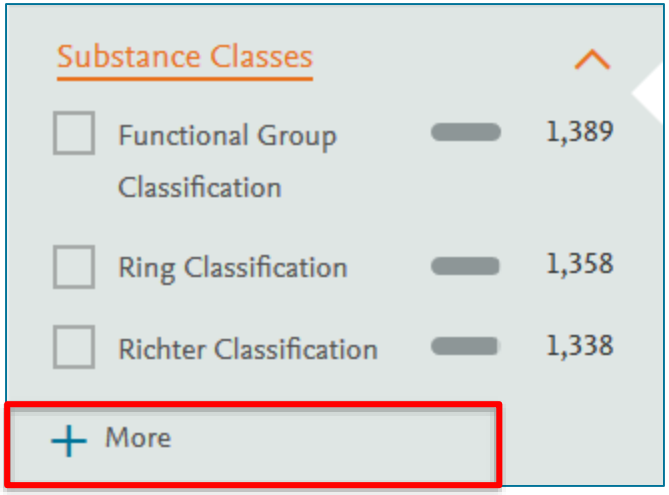
如何筛选—添加的时候可以进行Limit/Exclude操作



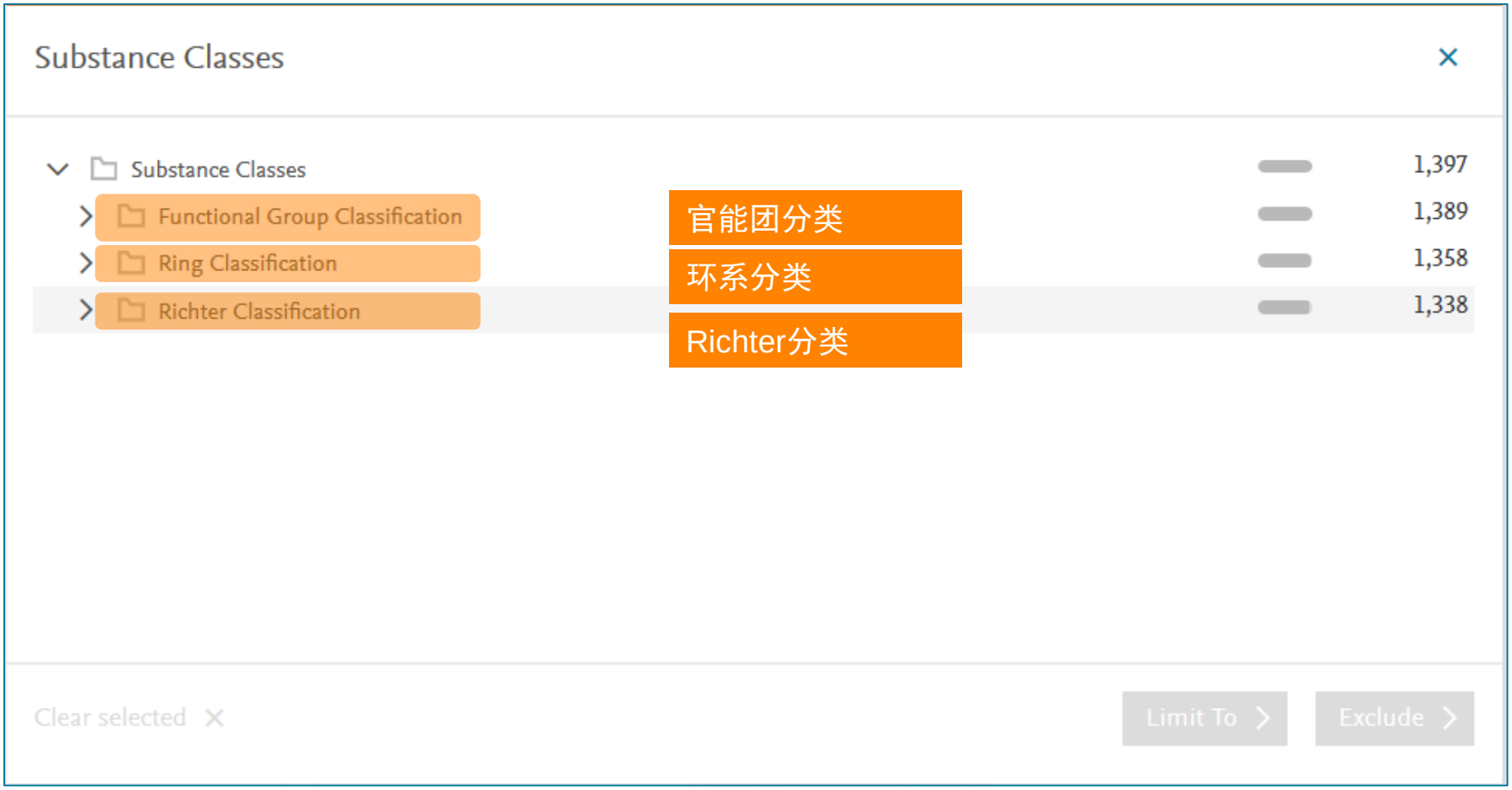
更多结构上的筛选工具

- 在不知道结构的情况下，Reaxys可以帮助分析这些结构中的共性

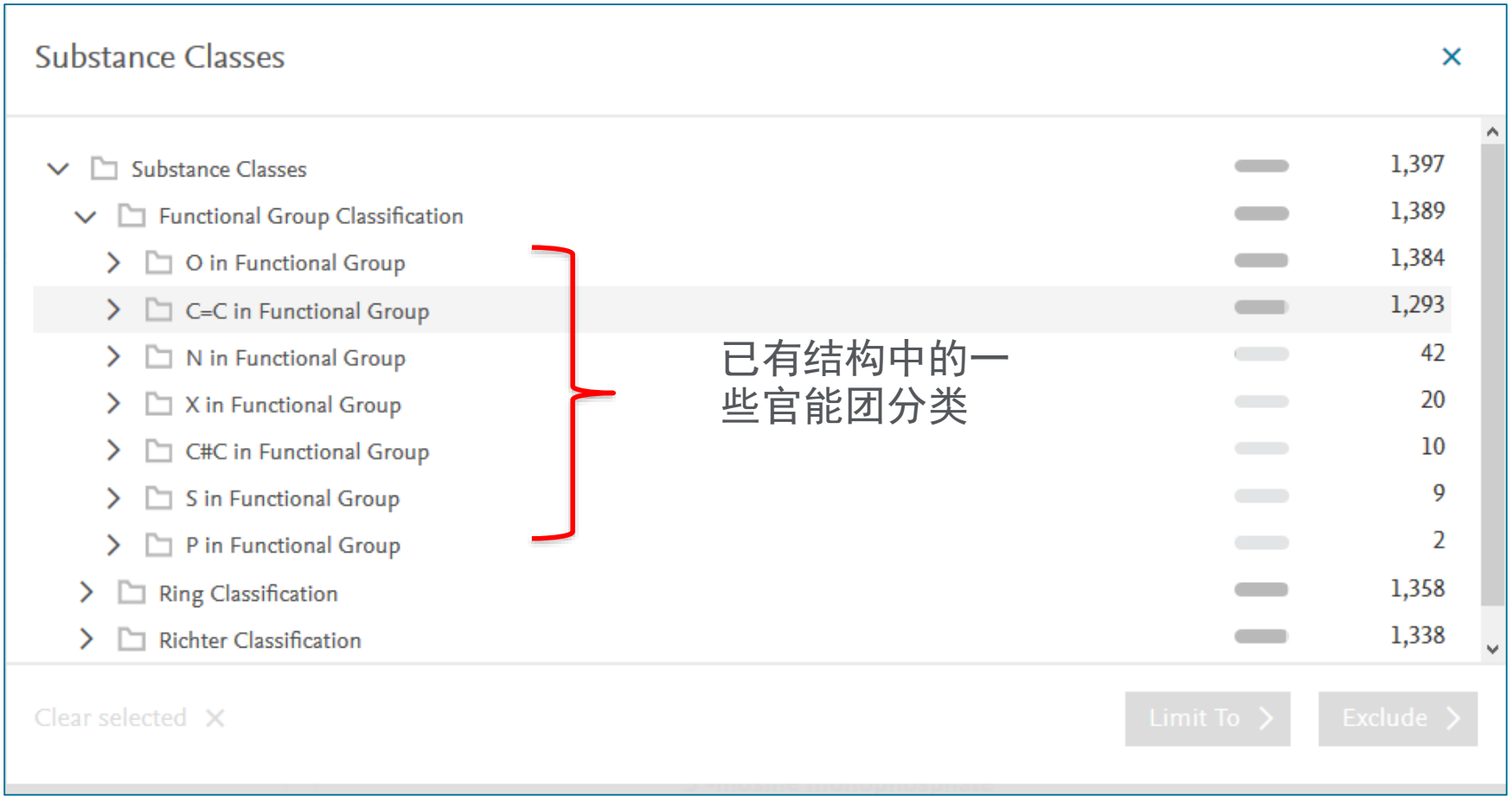




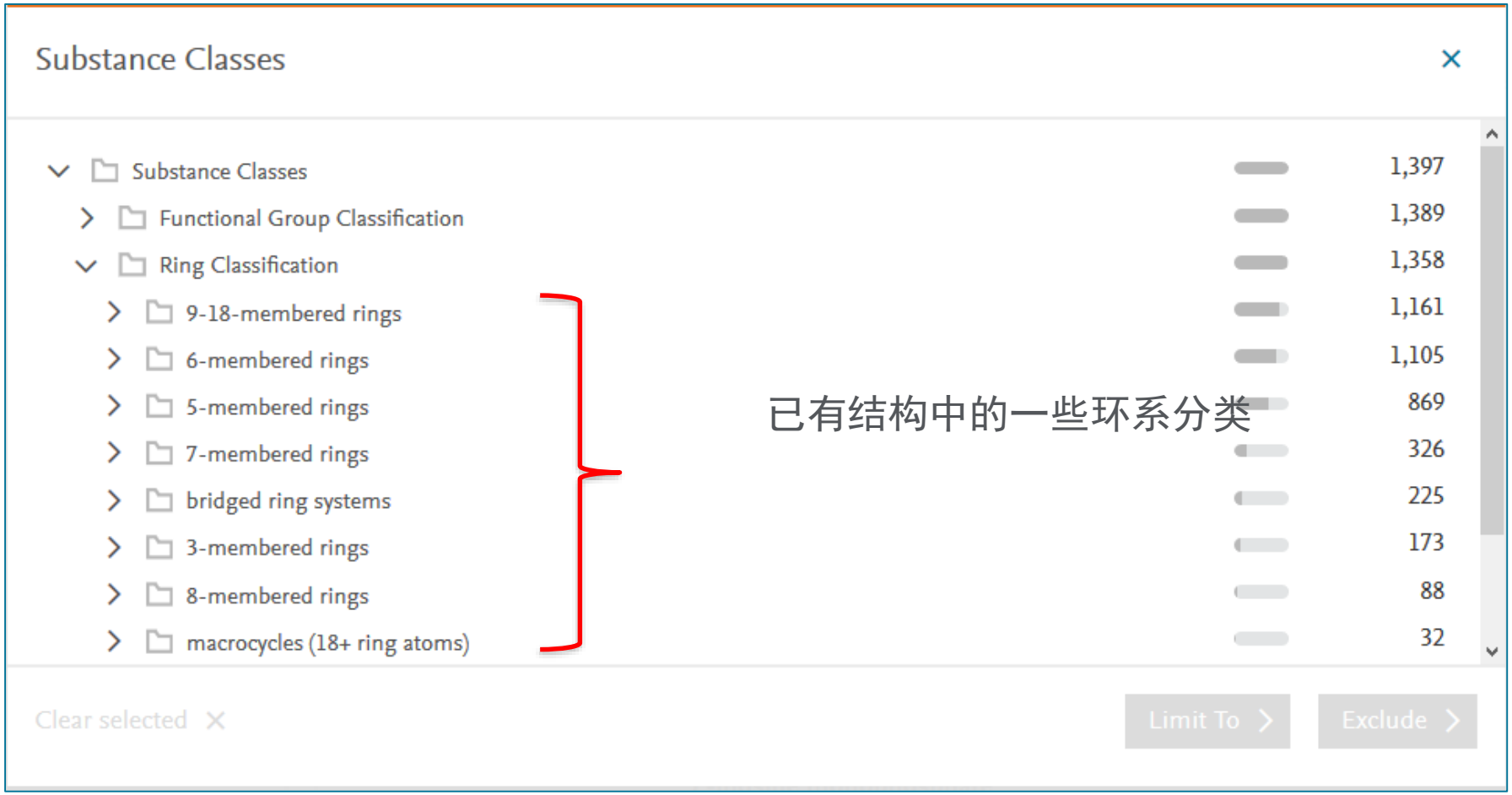
Substance Class树状图



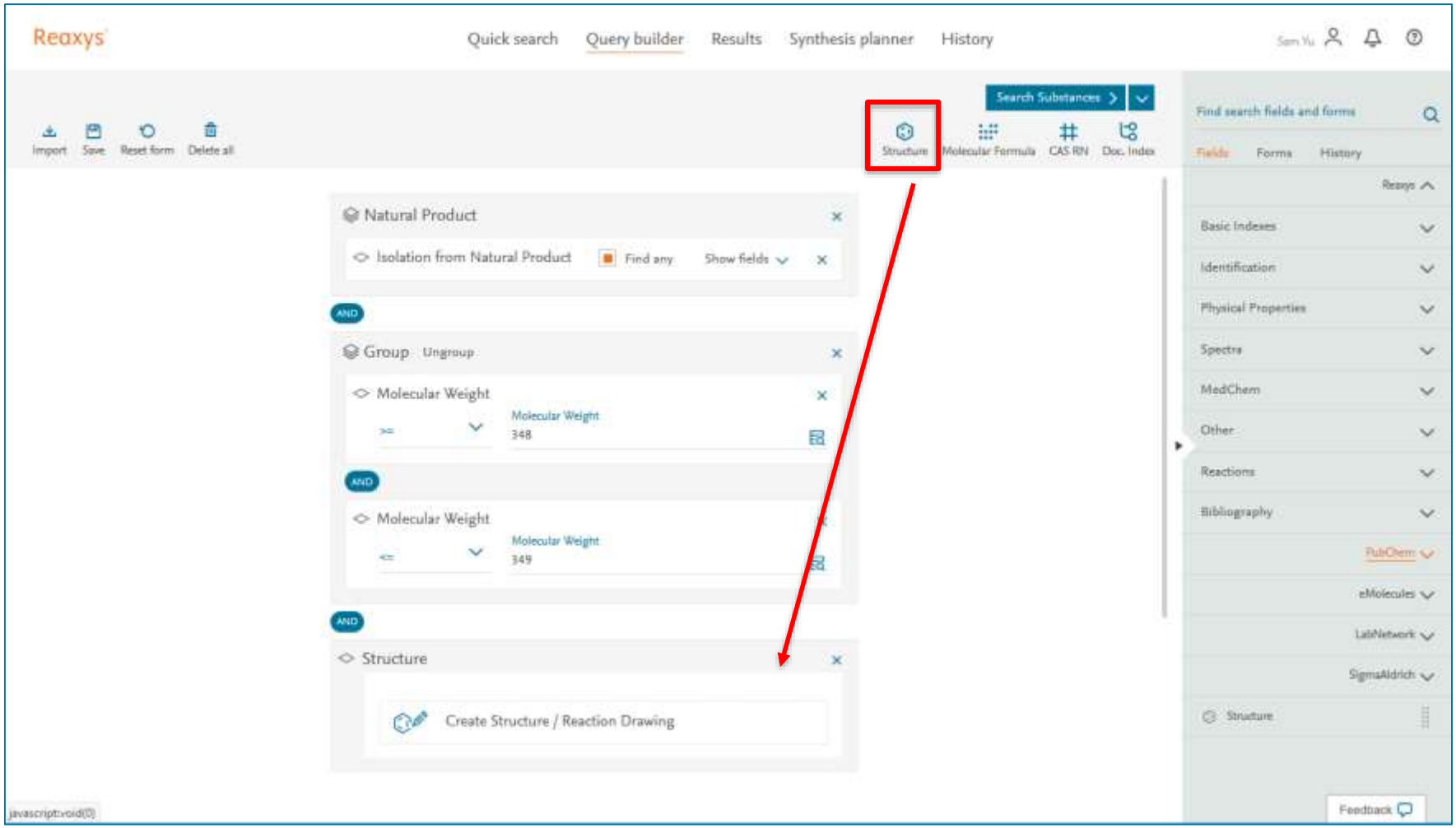
Functional Group分类



Ring Classification



案例的衍生1—如何一开始就加入结构片段



案例的衍生2—如果有NMR的数据

- 分子量348.456
- 天然产物
- NMR的数据：13C NMR (DMSO-d6, 150 MHz) δ 173.5, 157.8, 153.4, 150.1, 148.1, 145.9, 131.6 ,130.4, 130.2, 129.2, 128.7, 128.1, 127.8, 120.1 ,96.9, 73.6, 65.6, 50.8, 30.2, 7.8
- 想法：
  - 既然Reaxys中包含大量的谱图数据，那么能否利用谱图数据直接给出结构？
- 问题：
  - 如何解决数据的容差
- 解决方案
  - 节选部分数据的整数，且小数部分在0.5左右

案例的衍生2—如果有NMR的数据

- 数据的节选
- 13C NMR (DMSO-d6, 150 MHz) δ 173.5, 157.8, 153.4, 150.1, 148.1, 145.9, 131.6 ,130.4, 130.2, 129.2, 128.7, 128.1, 127.8, 120.1 ,96.9, 73.6, 65.6, 50.8, 30.2, 7.8

Tips：

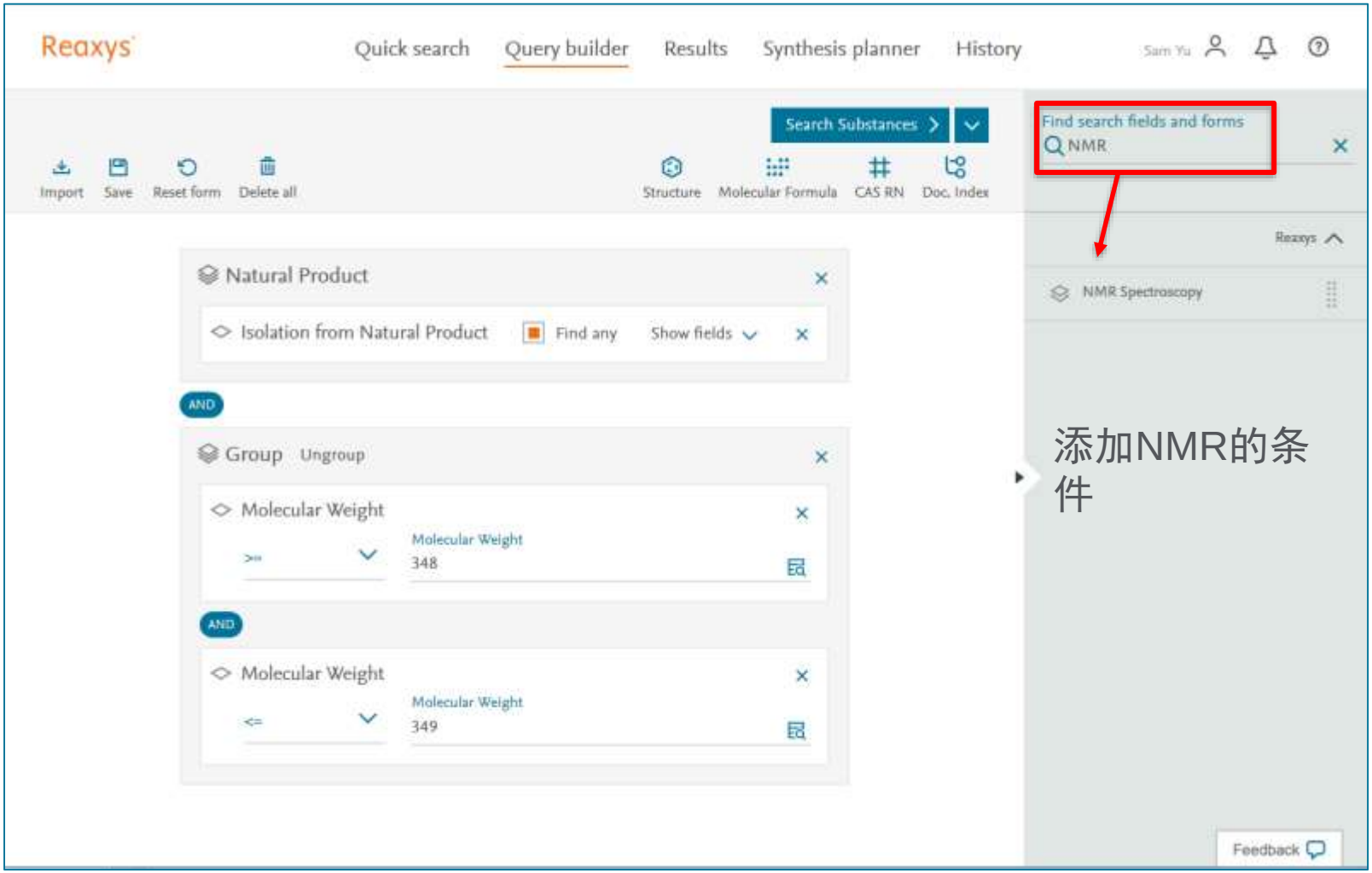
1. 设定谱图数据中，包含，173，153，130，可以将上述的谱图找到，这样就可以解决容差问题，其实是在寻找包含173.0-173.9的谱图

2. 由于容差问题，不太建议加太多的数据上去

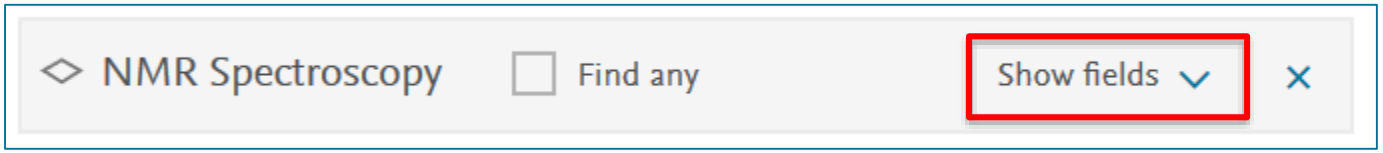
3. 常见做法，选择一个数据，然后检索该数据+-1的范围，如选择173.5.那么可以考虑检索，172，173，174，这样会有更大的容差范围

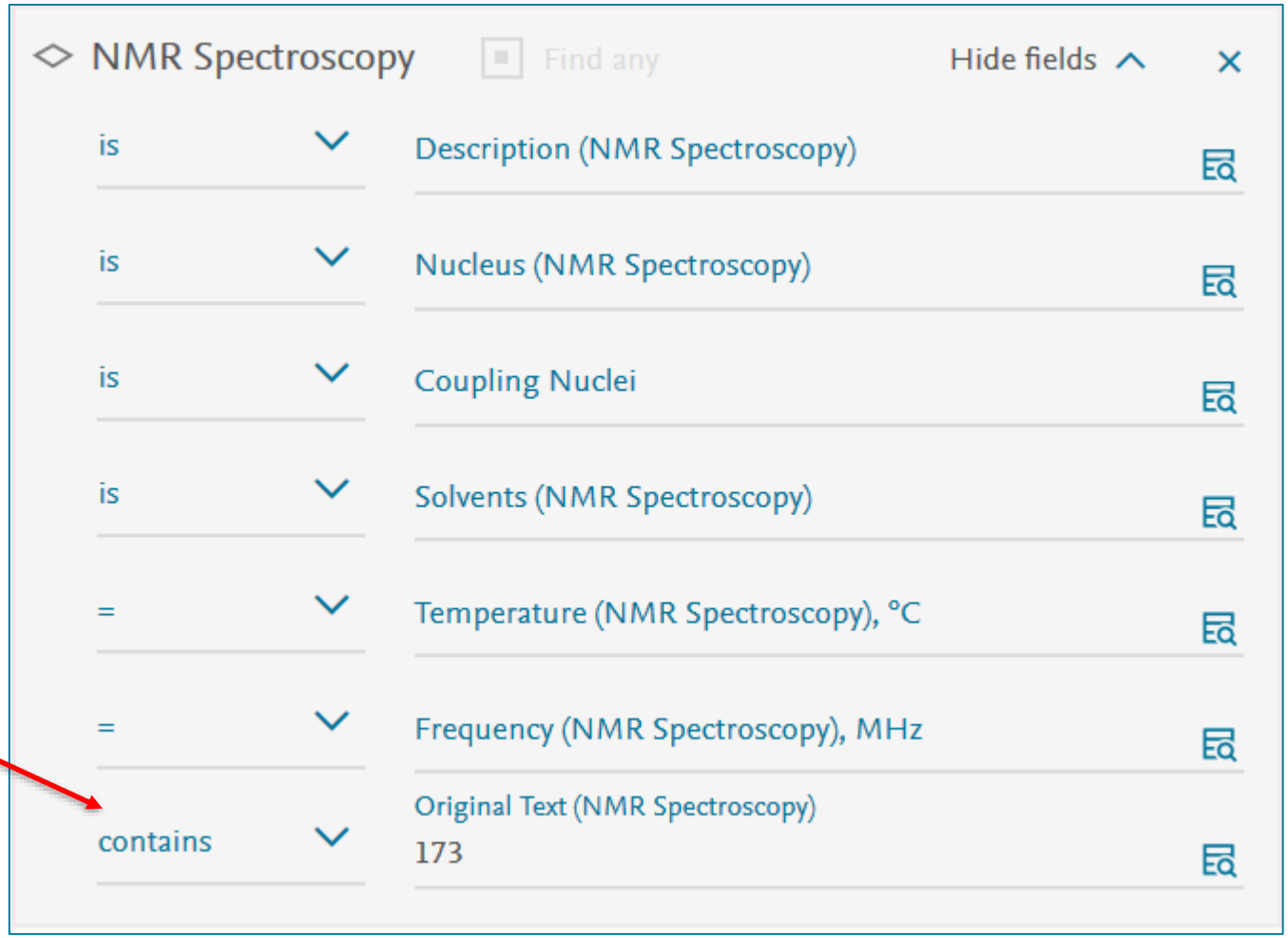
案例的衍生2—如果有NMR的数据，如何做

- Query Builder，添加如之前的检索条件如下



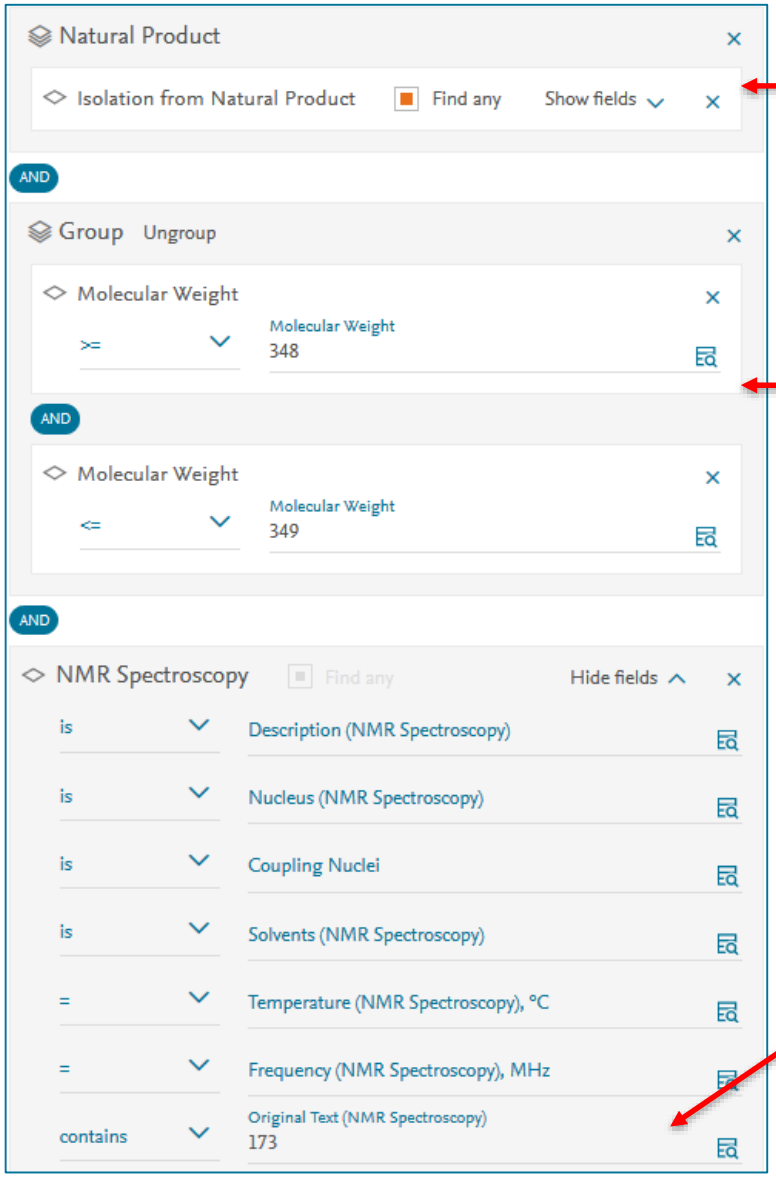
NMR条件的设定





Tips：
Original Text中选择Contains，可以解决容差问题，

最后完成的Query Builder

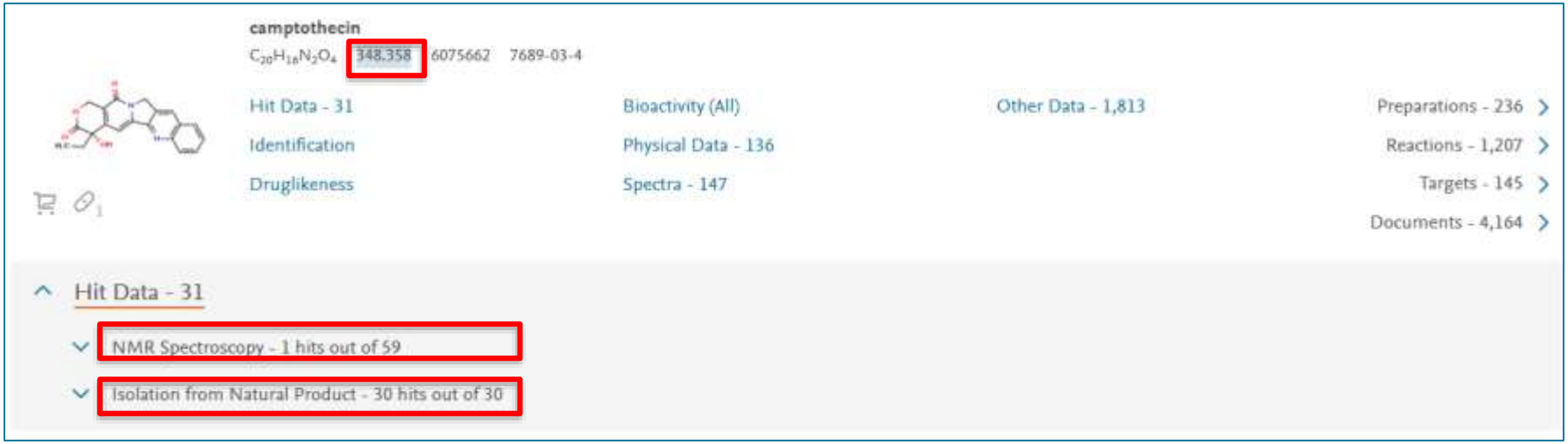


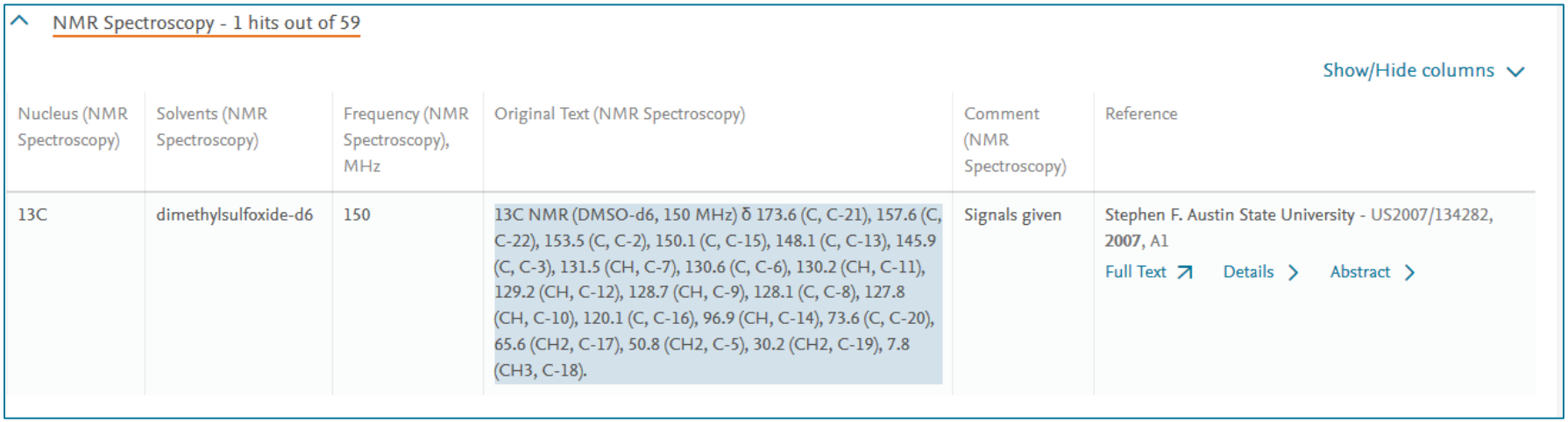
条件1：检索天然产物

条件2：分子量组合，348<=MW<=349

条件3：NMR数据中包含173，即检索173.0-173.9的数据

物质检索的结果





Nucleus (NMR Spectroscopy)	Solvents (NMR Spectroscopy)	Frequency (NMR Spectroscopy), MHz	Original Text (NMR Spectroscopy)	Comment (NMR Spectroscopy)	Reference
13C	dimethylsulfoxide-d6	150	13C NMR (DMSO-d6, 150 MHz) δ 173.6 (C, C-21), 157.6 (C, C-22), 153.5 (C, C-2), 150.1 (C, C-15), 148.1 (C, C-13), 145.9 (C, C-3), 131.5 (CH, C-7), 130.6 (C, C-6), 130.2 (CH, C-11), 129.2 (CH, C-12), 128.7 (CH, C-9), 128.1 (C, C-8), 127.8 (CH, C-10), 120.1 (C, C-16), 96.9 (CH, C-14), 73.6 (C, C-20), 65.6 (CH2, C-17), 50.8 (CH2, C-5), 30.2 (CH2, C-19), 7.8 (CH3, C-18).	Signals given	Stephen F. Austin State University - US2007/134282, 2007, A1 Full Text Details Abstract

提纲

- 常见的与物质物质检索有关的困难案例
- Reaxys中的解决方案
  - Reaxys中的Query Builder检索模式
  - Reaxys中的困难案例解决方案
  - Reaxys中的更多与性质检索有关技巧
- Reaxys物质检索小结

化合物的文献定位

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Assessment of the regioselectivity in the condensation reaction of unsymmetrical o-phthaldialdehydes with alanine

Agathe C.A. D'Hollander, Nicholas J. Westwood*

School of Chemistry and Biomedical Sciences Research Complex, University of St Andrews and EaStCHEM, North Haugh, St Andrews, Fife, KY16 9ST, UK

ARTICLE INFO

Article history:
Received 27 July 2017
Received in revised form
5 November 2017
Accepted 13 November 2017
Available online 16 November 2017

Keywords:
o-phthaldialdehyde
Condensation reaction
Regioselectivity
Mechanistic understanding

ABSTRACT

One approach for the synthesis of isoindolinones, a privileged bioactive heterocyclic core structure, involves a condensation reaction of o-phthaldialdehydes with a suitable nitrogen-containing nucleophile. This fascinating reaction is revisited here in the context of the use of o-phthaldialdehydes that contain additional substituents in the aromatic ring leading to a detailed analysis of the regioselectivity of the reaction. Eleven monosubstituted o-phthaldialdehydes were synthesised and reacted with alanine. The regioselectivity observed across the eleven substrates led to the design of a disubstituted substrate that reacted with very high control. A gram-scale reaction followed by esterification gave one major regioisomer in high yield. In addition, the regioselectivity observed on reaction of two novel mono-deuterated substrates led to an increased mechanistic understanding.

1. Introduction

The isoindolinones make up an important class of bioactive molecules that includes the known drugs Pazinaclone (1),[1a] Indoprofen (2)[2b] and Chlorthalidone (3)[2c] (Fig. 1a).

Common methods of obtaining isoindolinones that are unsubstituted in the aromatic ring, for example compound 4 (Fig. 1b), include selective reduction of 5,[2] reductive amination-cyclisation of 6[3] or 7[4] with a primary amine (RNH_2) and, of interest here, the condensation reaction of o-phthaldialdehyde (8) with a primary amine (RNH_2).[5,6a]

To date, the majority of studies performed on this condensation reaction have focused on evaluating the scope of the amine nucleophile that can be tolerated in the reaction[5a,5b,5d,6a,6b] and/or proposing potential reaction mechanisms.[5a,5b,6] In contrast, examples of the use of this condensation reaction with monosubstituted o-phthaldialdehydes are rare (SI1 part I). One report describes a regioselectivity of 1:1 for the products 11:12 resulting from the condensation of 9 with 10 (Scheme 1a).[5] However, the observed regioselectivity was measured only after filtration or purification by column chromatography. Isolated yields for the formation of a single isomer, 14 in most cases, resulting from the condensation of 13 with various amines have also been reported (Scheme 1b).[6]

Other studies have provided only isolated yield(s) after purification (for one or for each isomer), incomplete regioisomeric ratio (rr) data within a series or have claimed to form a single regioisomer (no yield provided) without discussing the other possible isomer (SI1 part I).[5–9]

The work reported here revisits this issue by presenting a detailed study of the regiochemical outcome of the condensation of alanine (15) with 3-monosubstituted o-phthaldialdehydes 17 (to give 18 and 19, Scheme 1c) and with 4-monosubstituted o-phthaldialdehydes 20 (to give 21 and 22, Scheme 1d). Based on the initial results, the design of a highly regioselective substrate was achieved consistent with an improved understanding of the reaction. Further mechanistic insights were provided by the use of novel mono-deuterated substrates.

2. Results and discussion

2.1. Synthesis of monosubstituted o-phthaldialdehydes

Five 3-substituted o-phthaldialdehydes 17a-e were synthesised using 2–5 step routes involving either a Swern oxidation of the corresponding diol 23 or an acetal deprotection of the corresponding monoacetal 24 or diacetal 25 (Scheme 2 and SI1 part II.1 for more details). It should be noted that the synthesis of pure samples of 17a-e was particularly challenging (in line with literature reports[7b]) with significant decomposition occurring during purification attempts and on storage. In several cases freshly

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https://doi.org/10.1016/j.tet.2017.11.015
0040-4020/

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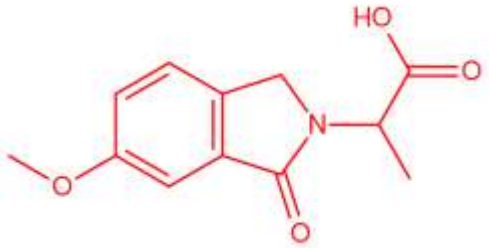

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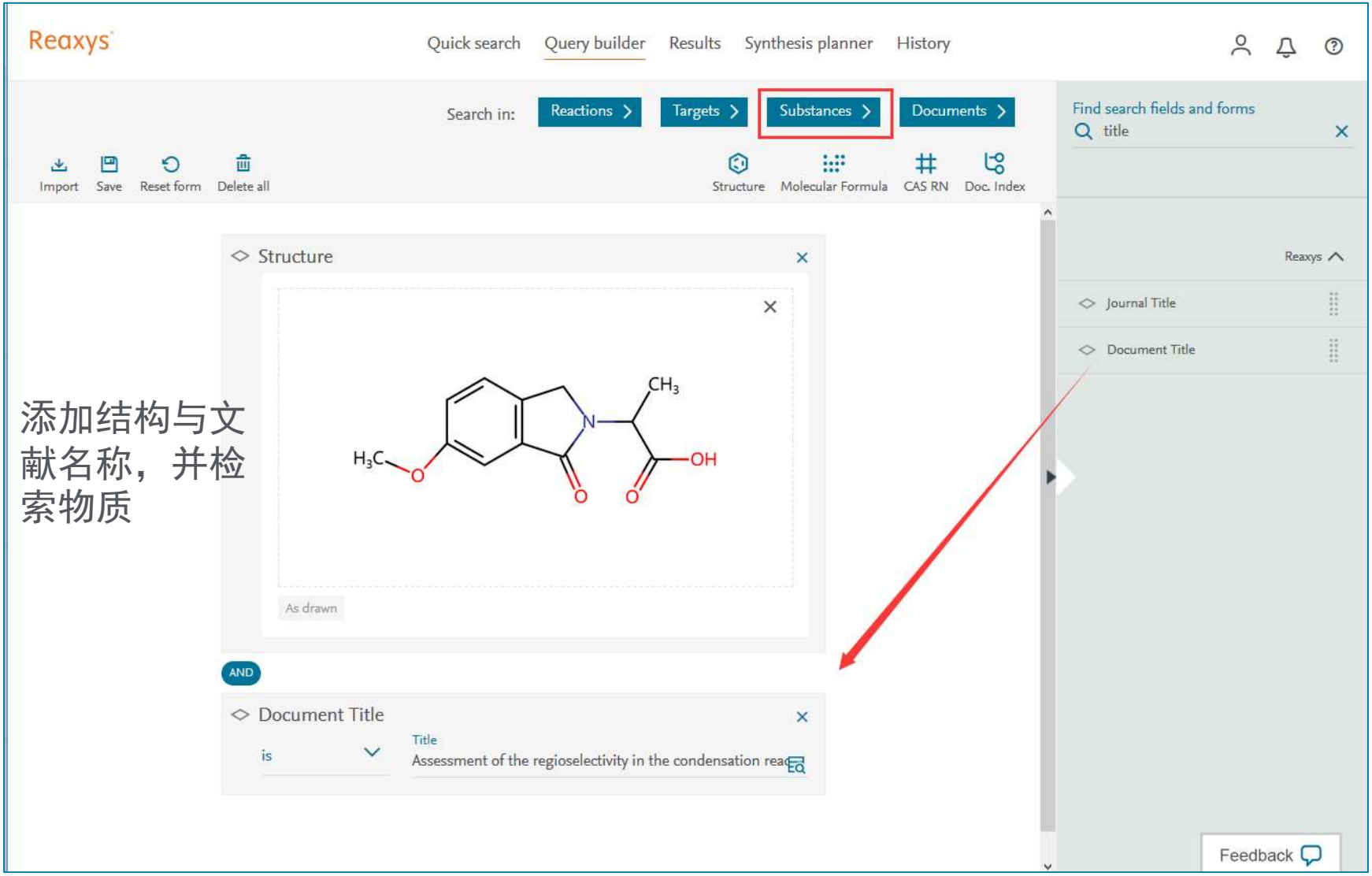

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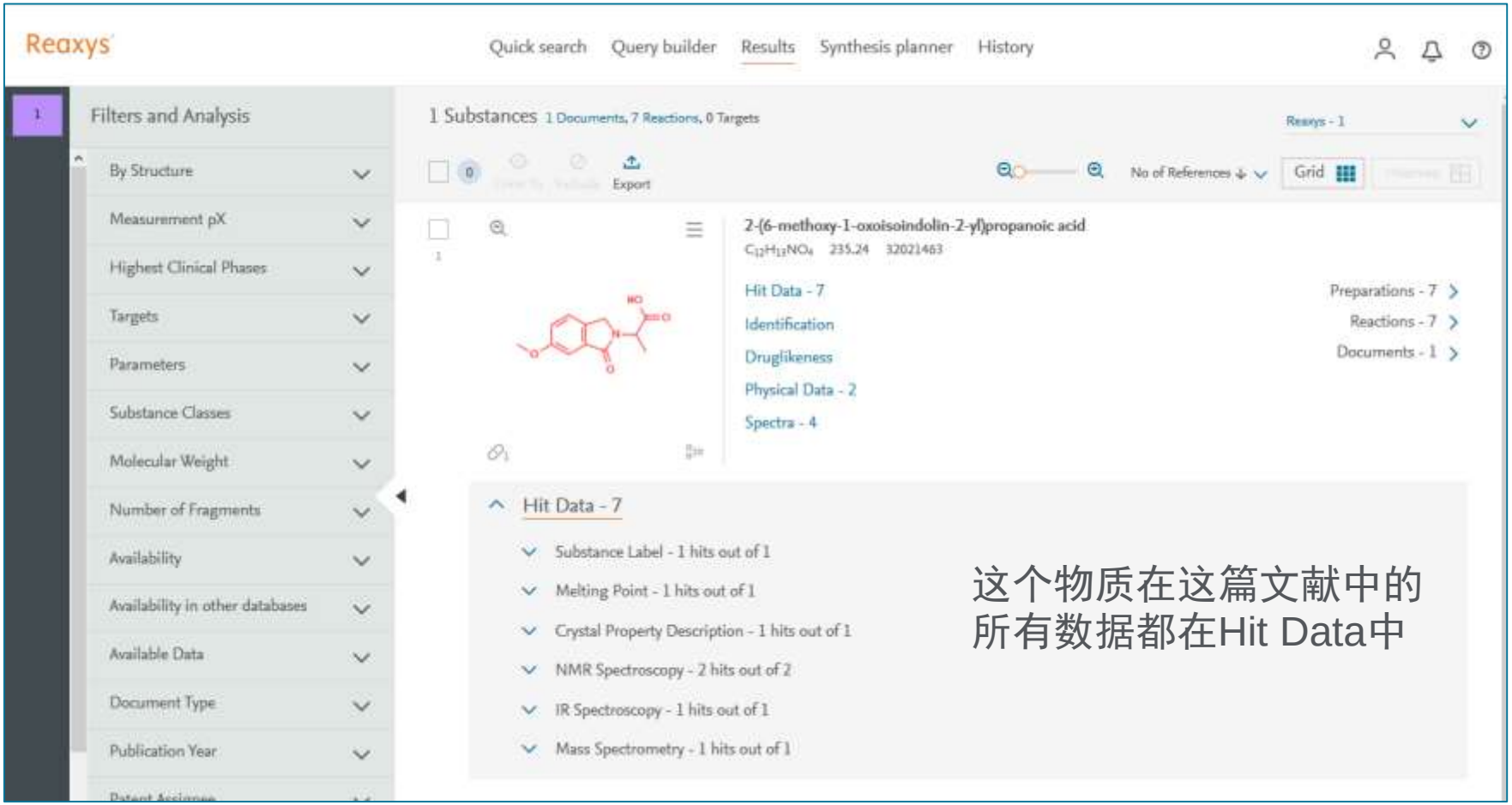
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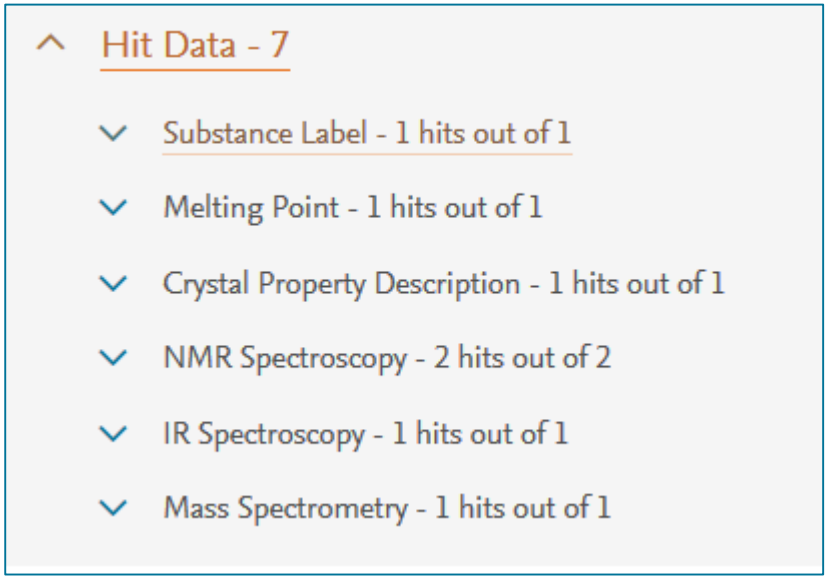

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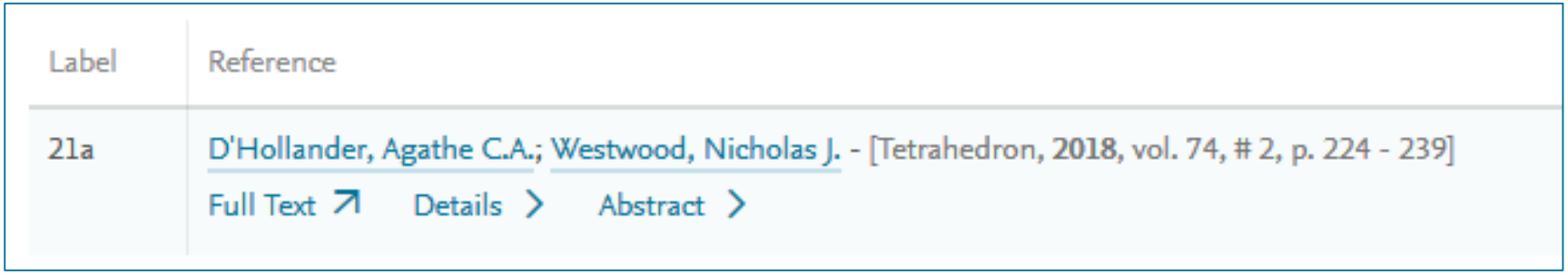

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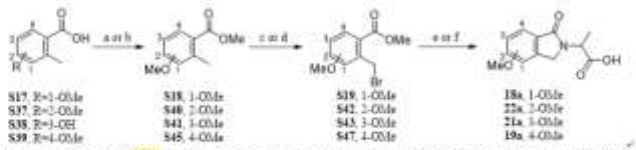
2.2. Regioselectivity of the condensation reaction of mono-substituted o-phthaldialdehydes

The mono-substituted *o*-phthaldialdehydes **17a-e** and **20a-f** were refluxed for 4 h with alanine (**16**, 1.2 equivalents) in anhydrous acetonitrile before the reaction was concentrated *in vacuo*. The crude reaction mixtures (except when specified, Table 1) were then analysed using a quantitative ^{1}H NMR experiment. A baseline correction was applied using MestReNova-9 software and integrations were calculated relative to one proton on deconvoluted peaks (see Fig. 2 for an example of the analysis applied to the formation of **18a**/**19a** and SI1 part III.1 for the rest of the NMR analysis; also see the experimental section below for a detailed explanation of the analytical protocol used).

In two of the condensation reactions the structure of the major regioisomer was identified by comparison with the ^{1}H NMR spectrum of a pure sample of one of the regioisomers (for **18a**/**19a**, **21a**/**22a**, for the synthesis of authentic isomers see SI1 part III.2). In the rest of the cases, advanced NMR techniques (HSQC, HMBC, COSY) applied to the crude reaction mixture were used to assign the structure of the major regioisomer. Considering the analysis of the regioisomeric mixture of **18b**/**19b** as an example (Fig. 3), the proximity of a carbonyl was observed to shift the signal corresponding to the aromatic H7 proton in **18b** and the methyl H1′ protons in **19b** downfield (Fig. 3a and b). Identification of H7 in **18b** was further validated by its correlation with C1 in the HMBC analysis of the regioisomeric mixture (Fig. 3a). In contrast, H4 in **19b** showed a correlation with C3 in this HMBC analysis (Fig. 3c). Using the correlations observed in the COSY spectrum (Fig. 3d), the signals corresponding to H5 and H6 for **18b** and **19b** were finally assigned. The value of the integrals in the 1D quantitative ^{1}H NMR

III.2. Synthesis of pure isoindolinones 18a, 19a, 21a and 22a.



Scheme S 10: Synthesis of **18a**, **19a**, **21a** and **22a**. Reagents and conditions: (a) MeOH, H_2SO_4, reflux, 7-24 h, quant. for **S18**, 84% for **S40**; (b) MeI, K_2CO_3, DMF, 70 °C 17-18 h, 92% for **S41**, 99% for **S45**; (c) NBS, AIBN, $CHCl_3$, reflux, 2.5-21.0 h, 97% for **S19**, crude **S42** and **S43** were directly used in the next step; (d) NBS, AIBN, CCl_4, reflux, 2 h, crude **S47** was directly used in the next step; (e) alanine (**16**), MeOH, K_2CO_3, reflux 19-21 h, 61% for **18a**, 55% (2 steps) for **19a**; (f) alanine (**16**), MeOH, NEt_3, reflux 2-23 h, 4% (2 steps) for **21a**, 4% (2 steps) for **22a**.

Esterification of **S17**, **S37**, **S38** and **S39** was achieved in excellent yield using iodomethane or methanol with sulfuric acid (Scheme S 10).[8] Radical monobromination[9] of **S18**, **S40**, **S41** formed **S19**, **S42**, **S43** which were directly reacted[9] with alanine (**16**) to obtain **18a**, **22a** and **21a** respectively. To investigate the poor yield over two steps (2% for **18a**, 4% for **21a** and 4% for **22a**), radical monobromination of **S18** was repeated and the succinimide side product from *N*-bromosuccinimide was removed by a basic wash using NaOH (1 M) leading to pure **S19** in 97% yield. Reaction of **S19** with **16** and NEt_3 afforded **18a** in only 8% yield. However, concentration of the aqueous phase showed **S44** as the major product (identified by NMR spectroscopy (Figure S 5) and supported by mass spectrometric analysis (**HRMS** (ES^+) *m/z* calculated for $C_{16}H_{26}NO_3$ $[M]^+$: 280.1907; found: 280.1910) along with the remaining NEt_3 and alanine (**16**). Formation of **S44** was prevented by reacting **S19** with K_2CO_3 instead of NEt_3 to provide **18a** in good yield. This optimisation could be applied for the synthesis of **21a** and **22a** but was not performed since sufficient material was available.

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