# Reaxys & Reaxys Medicinal Chemistry

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OUR SHARED PURPOSE

# TO ACCELERATE SCIENCE TO IMPROVE HEALTH

A Knowledge & Information Analytics Company

OUR PROMISE

Partners in propelling research and innovation forward to transform the way you bring new medicines to the world

## OUR KEY DIFFERENTIATORS

- Customer First Commitment
- Our Roots As A Knowledge Company
- Open Integrated Systems
- Accelerating Data-Driven Decisions
- Market-Leading Talent

**140+**

years of scientific knowledge curated as semantically rich content to enable tomorrow's medical breakthroughs

RELX

**$1.4bn**

on technology annually

**~30,000**

employees

Serving customers in

**180+ countries**

Partnering with

**90%**

of top Pharma companies

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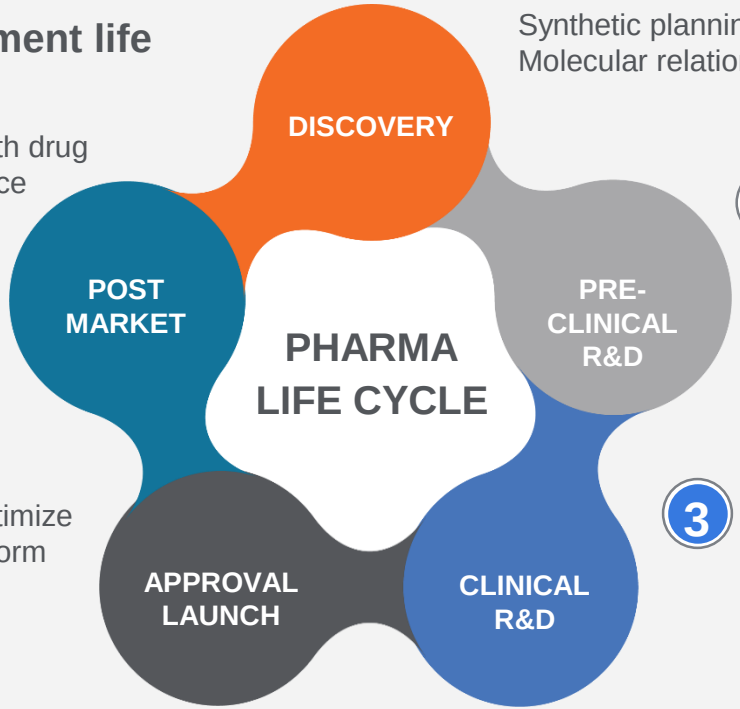
## Elsevier scientific content and tools fuel data-driven decisions throughout the development life cycle




1 **DISCOVERY** Target discovery; Understanding disease and biological pathways

Synthetic planning; Hit identification; Lead optimization; Molecular relationships; Drug design optimization

2 **PRE-CLINICAL R&D** Cull leads more quickly for safety & efficacy; Inform translational research

Efficient scale-up; Product formulation

3 **CLINICAL R&D** Optimize design, patient population and primary endpoint for clinical trials

Inform regulatory approval strategies

4 **APPROVAL LAUNCH** Optimize supply chain efficiency; Inform HEOR and Market Access strategies

5 **POST MARKET** Comply with drug safety and pharmacovigilance regulations; Adverse events monitoring and reporting

ScienceDirect Professional Services Embase Pathway Studio Chemtiva™
PharmaPendium QUOSA™ Entellect™ Reaxys Reaxys Medicinal Chemistry

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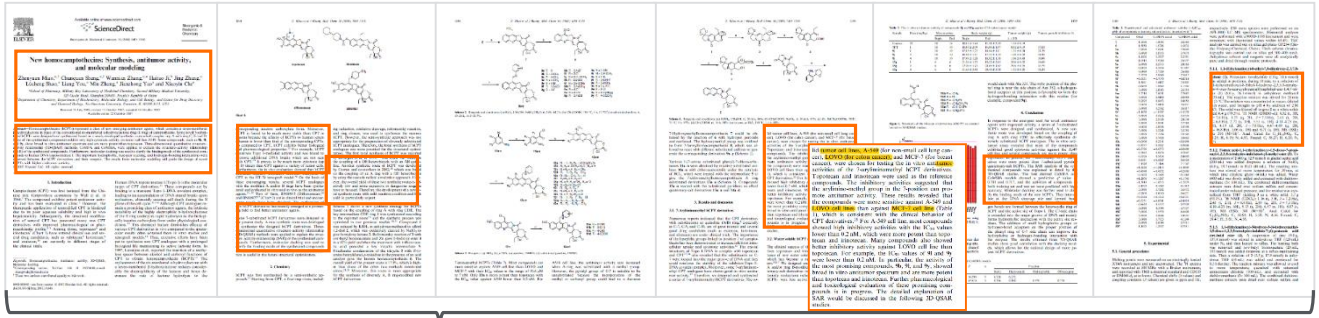
# Agenda

1. Why should you log in to Reaxys?
2. Quick Search (Search by text)
3. Structure Search
4. Query Builder (e.g. Natural compounds searches)
5. Synthesis Planer
6. Structural Activity Relationship (RMC module) New! (e.g. Real pharmaceutical case)

# Reaxys索引的內容—文獻內容



Reaxys提煉了文獻的書目資訊，摘要，題錄，並用不同角度的索引詞對文獻內容進行描述。

**bibliographic**

New homocamptothecins: Synthesis, antitumor activity, and molecular modeling

Cited 23 times

Miao, Zhenyuan; Sheng, Chunquan; Zhang, Wannian; Ji, Haitao; Zhang, Jing; Shao, Luecheng; You, Liang; Zhang, Min; Yao, Jianzhong; Che, Xiaoyin - Bioorganic and Medicinal Chemistry, **2008**, vol. 16, # 3, p. 1493 - 1510

Abstract | Index Terms | Substances 124 | Reactions 78 | Full Text

Abstract

Homocamptothecins (hCPTs) represent a class of new emerging antitumor agents, which contains a seven-membered β-hydroxylactone in place of the conventional six-membered α-hydroxylactone ring (E ring) of camptothecins. Some novel 7-substituted hCPTs were designed and synthesized based on a newly developed synthetic route which couples ring A with ring C, E and D. Most of the synthesized compounds exhibit very high cytotoxic activity on tumor cell line A549. Some compounds, such as 9b, 9l, and 9y, show broad in vitro antitumor spectrum and are more potent than topotecan. Three-dimensional quantitative structure-activity relationship (3D-QSAR) methods, CoMFA and CoMSIA, were applied to explain the structure-activity relationship (SAR) of the synthesized compounds. Furthermore, molecular docking was used to clarify the binding mode of the synthesized compounds to human DNA topoisomerase I. The important hydrophobic, base-pair stacking, and hydrogen-bonding interactions were observed between the hCPT derivatives and their receptor. The results from molecular modeling will guide the design of novel hCPTs with higher antitumor activity.

**Manual [digital] Indexing**

Index terms

**EMTREE drug term:** 10 methyl 11 chloro 7 (pyridiniummethyl)homocamptothecin chloride, 7 (2 bromophenyl)iminomethy methoxyphenyl)iminomethylhomocamptothecin, 7 (2 methylphenyl)iminomethylhomocamptothecin, 7 (2,4 dichlorophenyl dichlorophenyl)iminomethylhomocamptothecin, 7 (3 chloro 4 fluorophenyl)iminomethylhomocamptothecin, 7 (3 chloro 4 fluorophenyl)iminomethylhomocamptothecin, 7 (3 methylphenyl)iminomethylhomocamptothecin, 7 (3,4 dichlorophenyl)im dimethylphenyl)iminomethylhomocamptothecin, 7 (3,5 dichlorophenyl)iminomethylhomocamptothecin, 7 (3,5 dimethylph chlorophenyl)iminomethylhomocamptothecin, 7 (4 cyanophenyl)iminomethylhomocamptothecin, 7 (4 methylphenyl)imino phenyliminomethylhomocamptothecin, antineoplastic agent, camptothecin derivative, irinotecan, topotecan, unclassified d

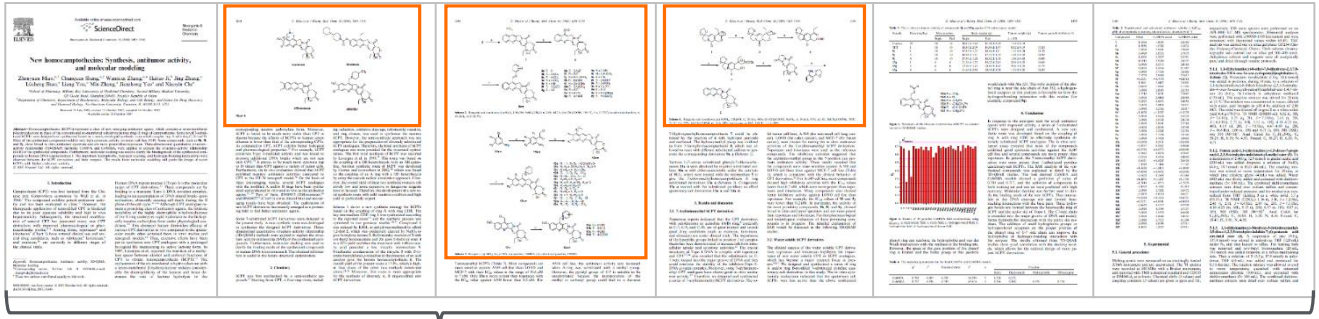
**EMTREE medical term:** animal experiment, animal model, antineoplastic activity, article, colon cancer, comparative molecu protein binding, drug structure, drug synthesis, human, human cell, hydrogen bond, hydrophobicity, male, molecular dock imaging, tumor cell

tumor cell line

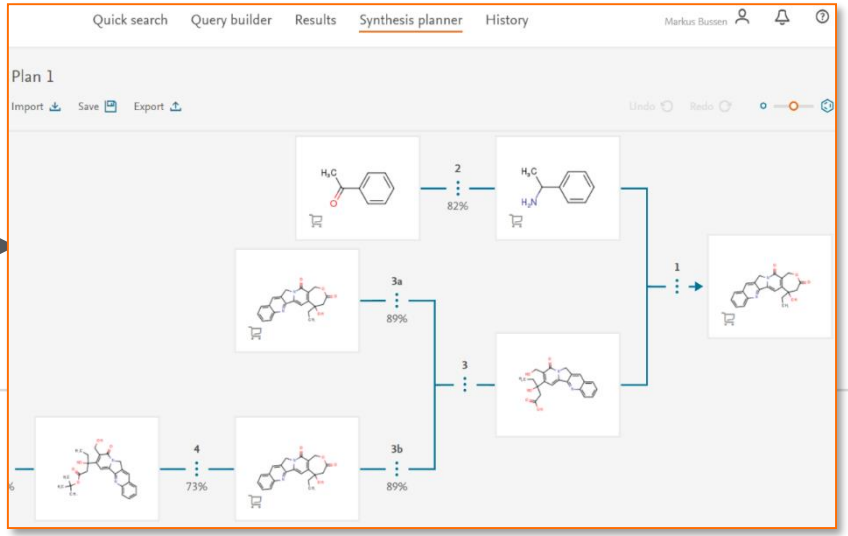
**Author keyword:** 3D amptothecins, Molecular docking

**Reaxys Index Terms** hydrophobic surface

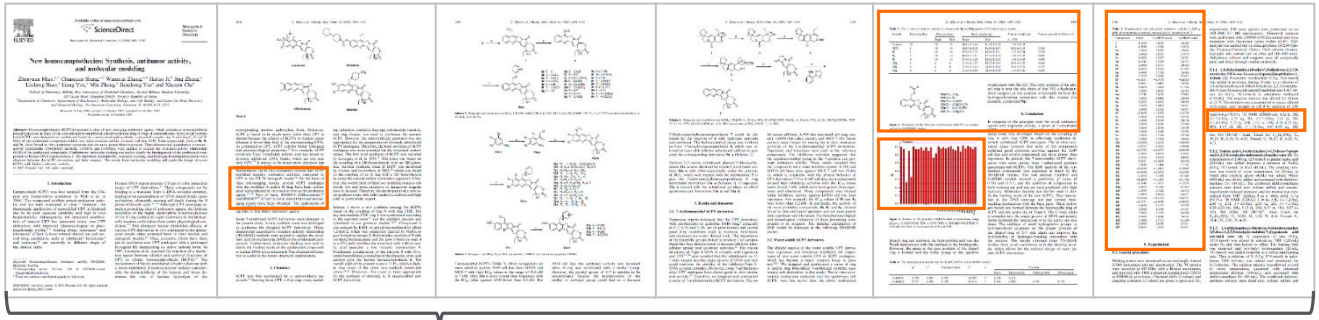
# Reaxys索引的內容—結構與反應



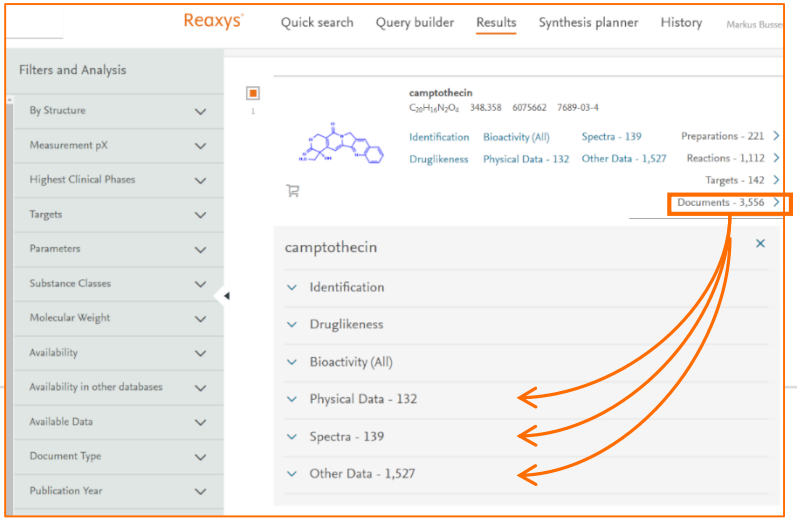
Reaxys的反應記錄，抽提了所有相關的資料，包括收率，催化劑，溶劑，反應類型等



# Reaxys索引的內容—文獻中的資料



Reaxys的物性記錄，抽提了超過500中不同的物性實驗資料，生物活性資料，環境資料，以及譜圖資料等等



# What is Reaxys？

- 化學研究不可缺少之「**數據**」資料庫
- 從化學相關論文及專利萃取有用取**必要**的「**數據**」

Reaxys®


**>118 Million**
有機、無機及有機金屬物質
**>500 Million**
公開實驗數據
(物性、光譜、生物活性等)

**>49 Million**
化學反應(反應條件、溶劑、催化劑及產率等)

**>54 M 文獻記錄**
**>16,000 期刊，專利**
涉及有機化學，材料化學，生物醫藥，地球科學，工程等多種領域

Reaxys® Medicinal Chemistry

**>20,000 藥物作用標的**
**>33 M 生物活性資料點**
結構活性關係資料
動物活體細胞研究
細胞外療效
藥物動力學
毒性資料
安全性資料

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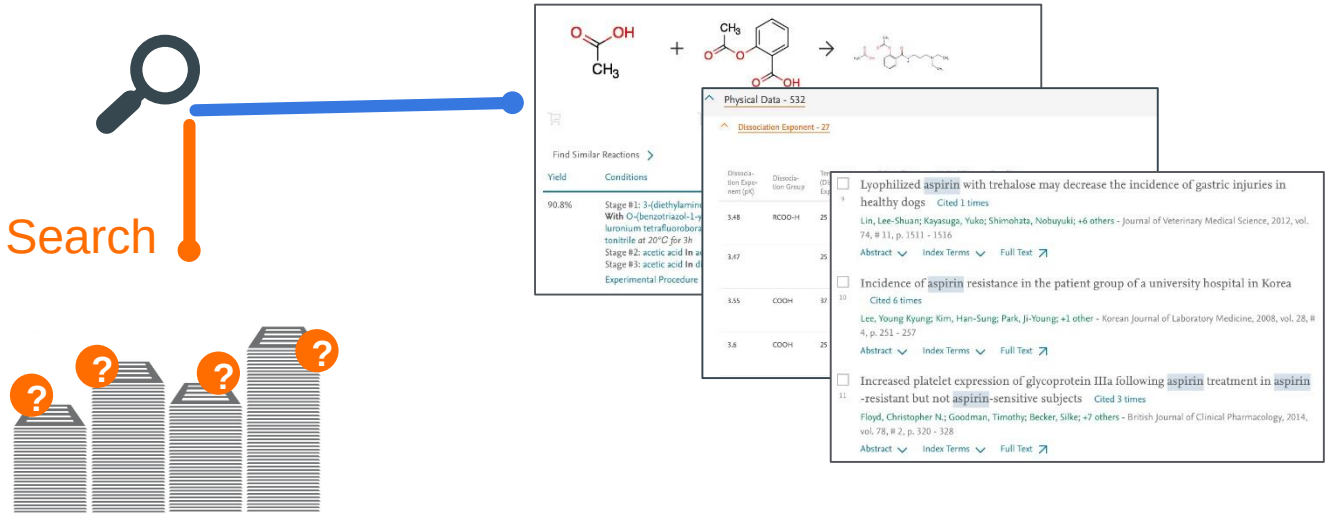
# *Reaxys core philosophy* "Using information" not "searching for information"



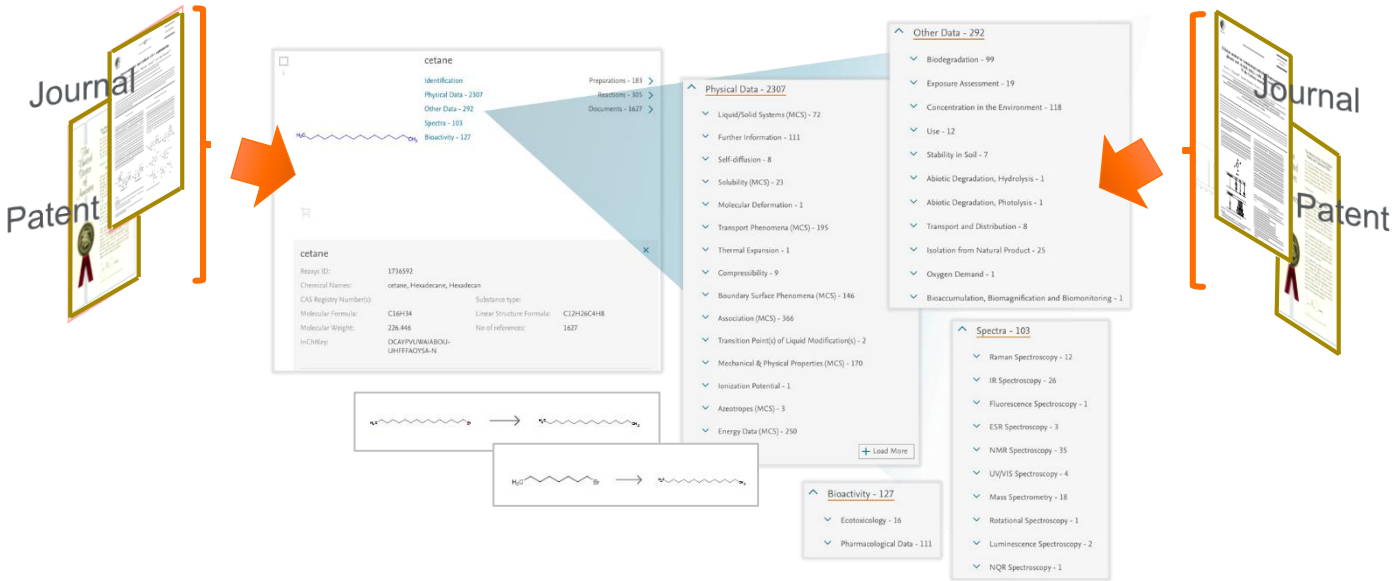

**Delivering lists of references** that may be relevant to a query…

**Deliver relevant answers on the spot:**

- References ranked by relevance
- Reactions with experimental details
- Substances with extensive properties

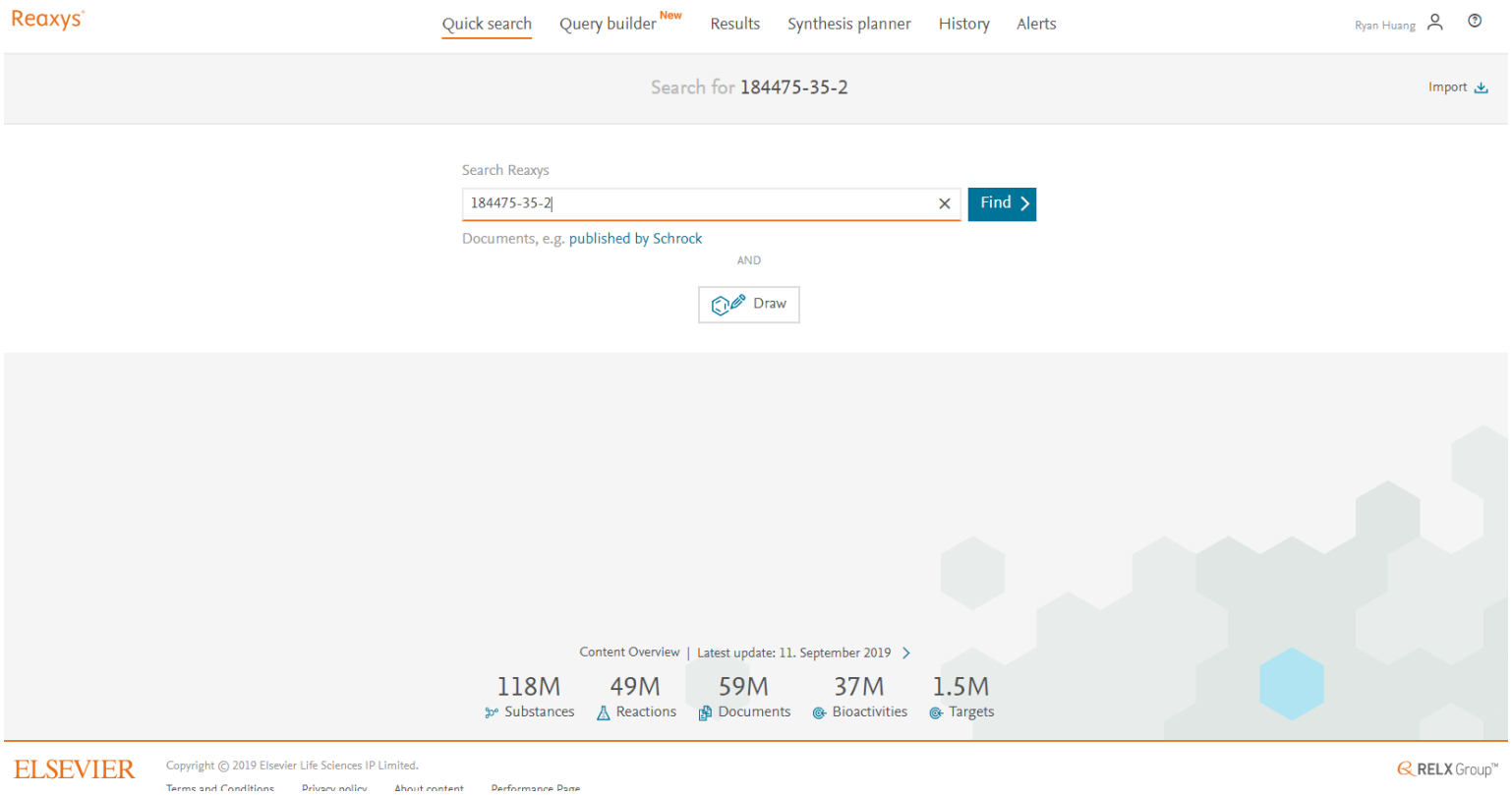
# Reaxys的資料結構

- 從多個資料來源將化合物及反應彙整到1筆紀錄
- 並且保留資料來源的連結

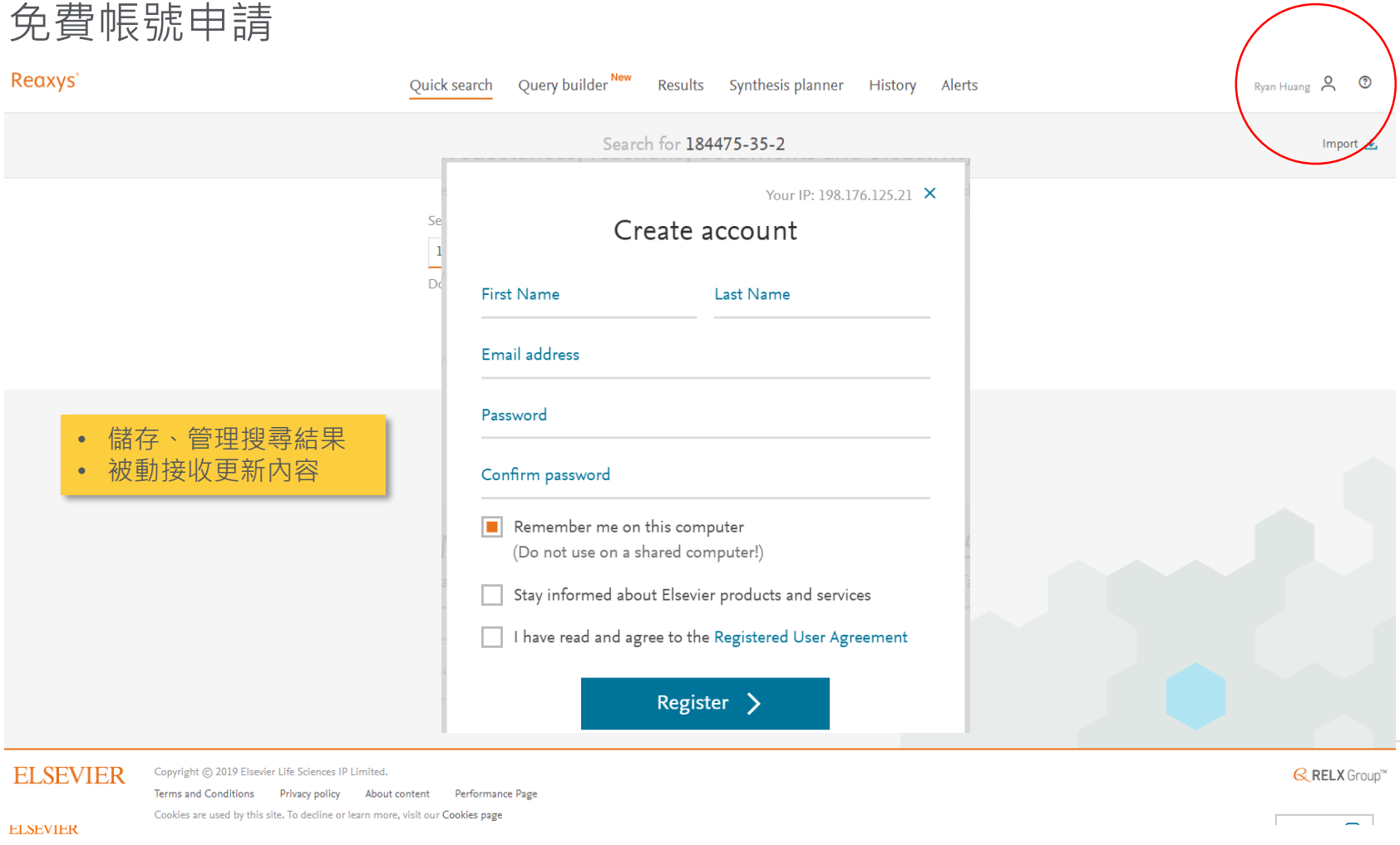


# How do you get access to Reaxys

## Go to http://reaxys.com



# 免費帳號申請


Reaxys
Quick search
Query builder New
Results
Synthesis planner
History
Alerts
Ryan Huang
Search for 184475-35-2
Import
Your IP: 198.176.125.21
Create account
First Name
Last Name
Email address
Password
Confirm password
Remember me on this computer
(Do not use on a shared computer!)
Stay informed about Elsevier products and services
I have read and agree to the Registered User Agreement
Register
• 儲存、管理搜尋結果
• 被動接收更新內容
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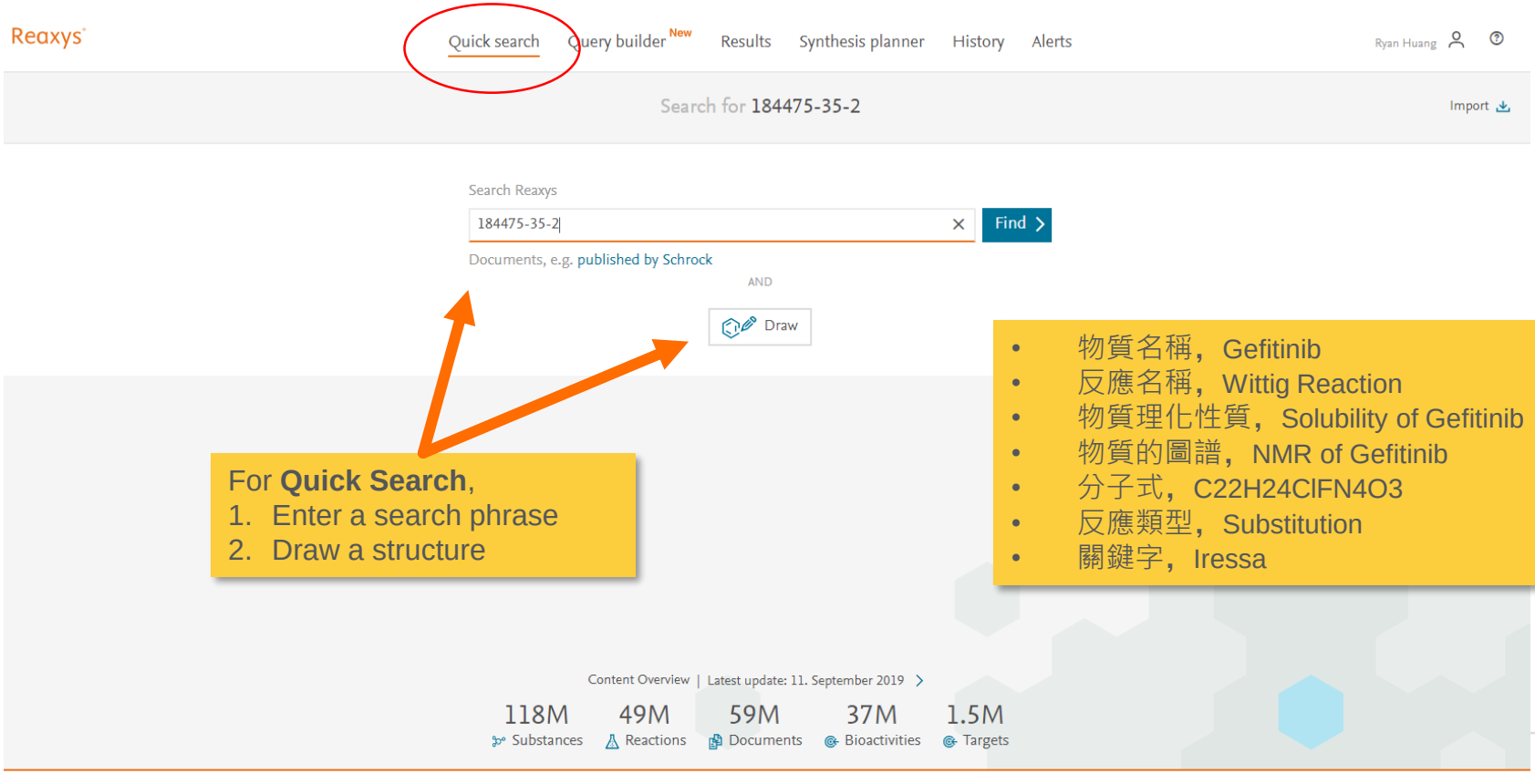
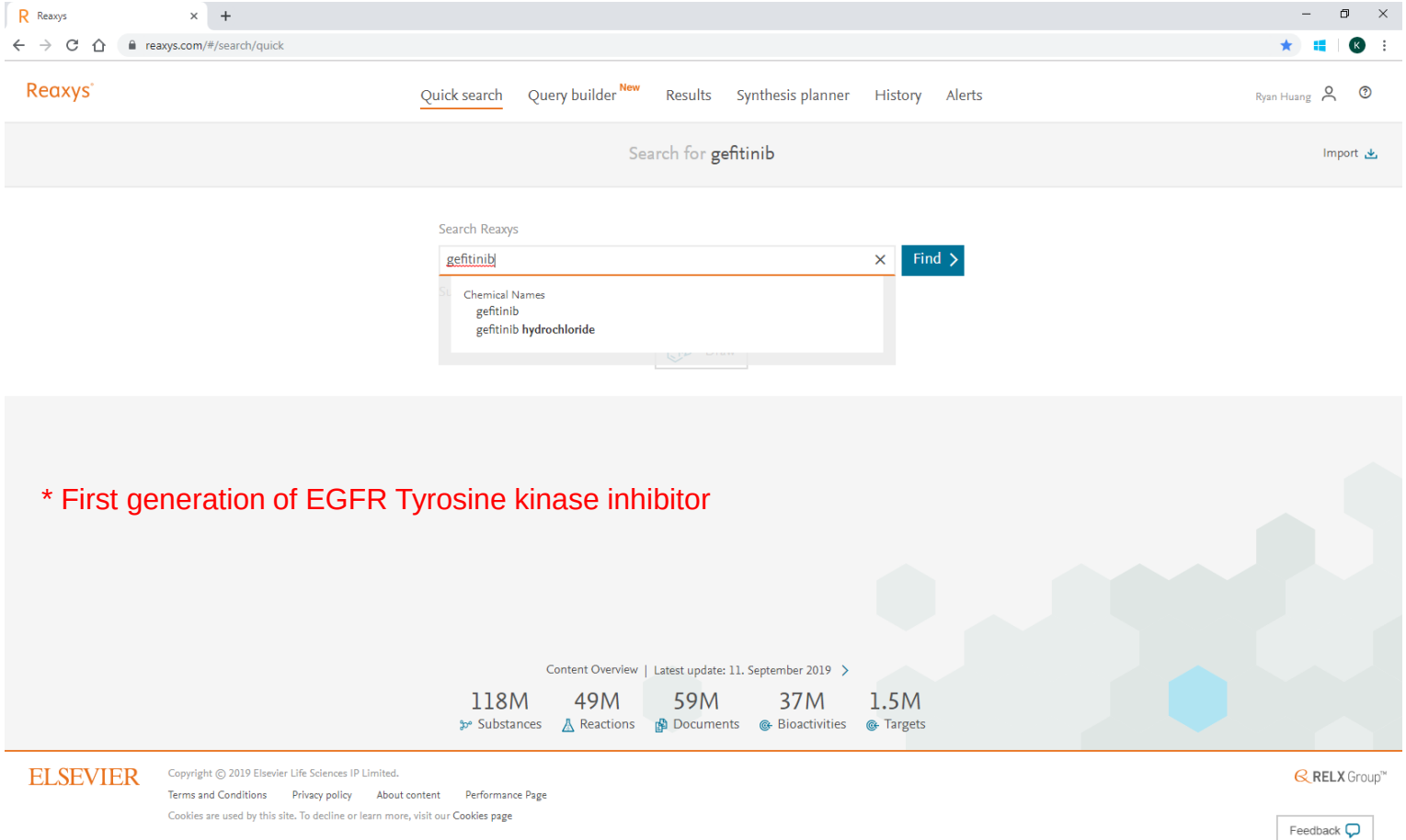
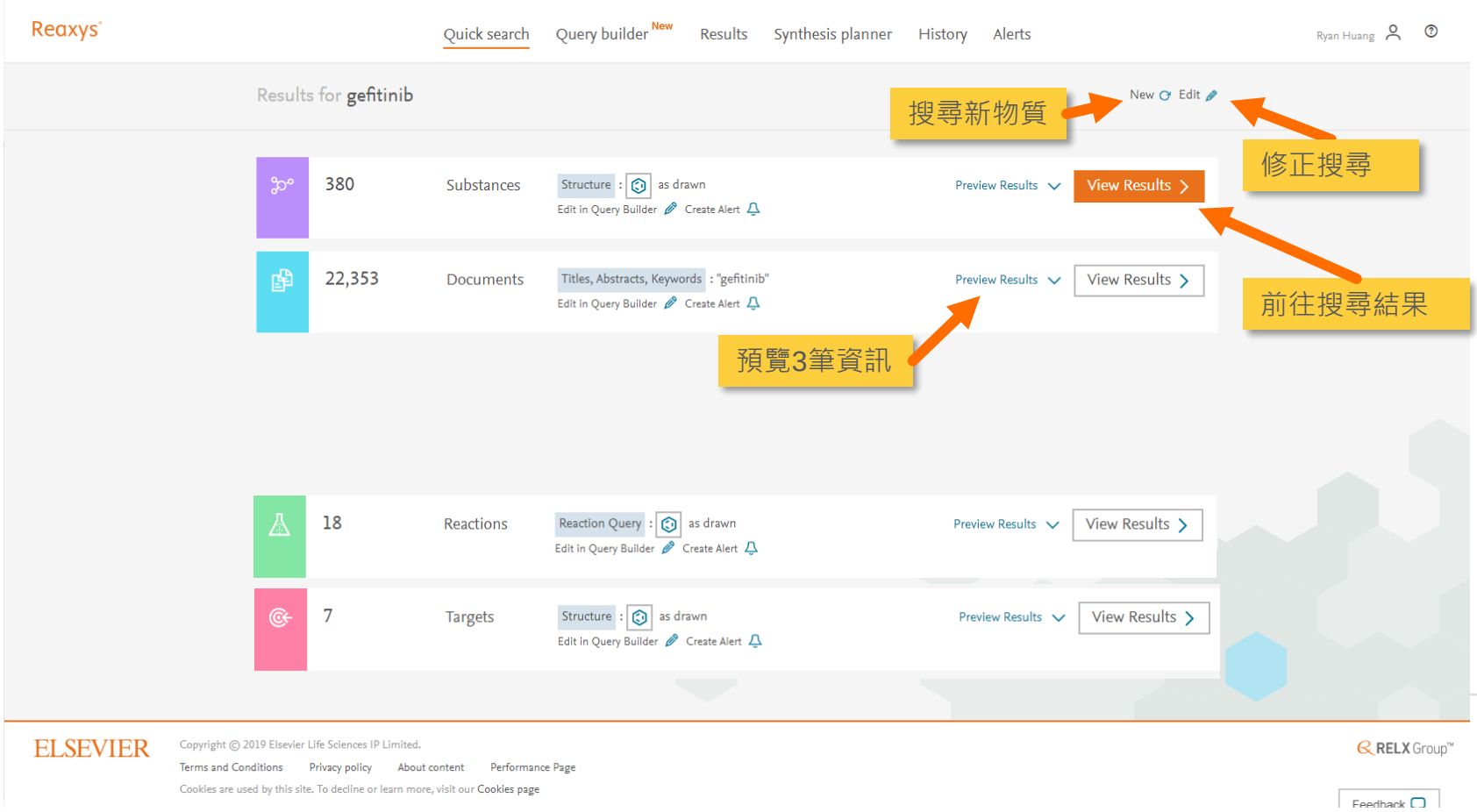
# Quick Search



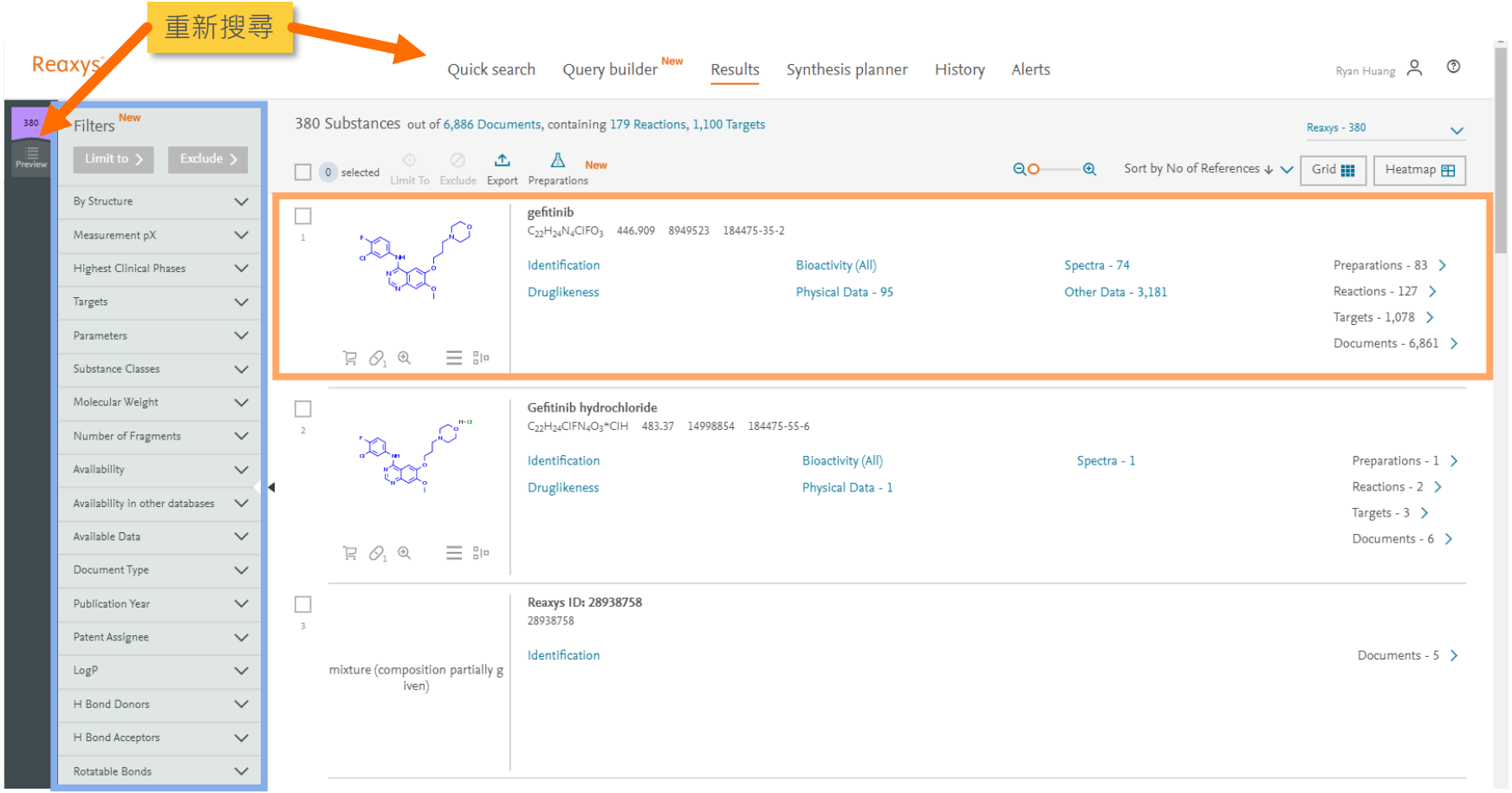
# Quick Search - 範例一



# Quick Search – Preview Page



# Results Page



# Hands on #1

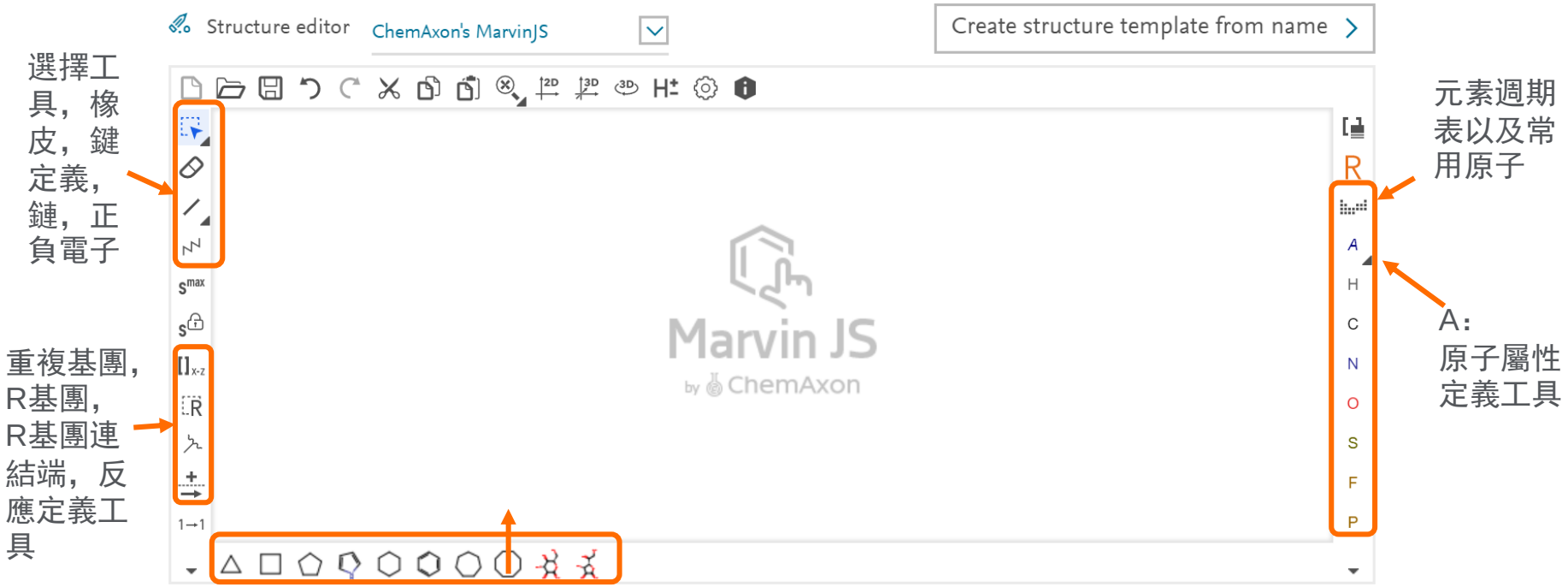
1. 請試著創造帳號並登入
2. 以Quick Search功能搜尋以下物質的溶解度

    - Morphin
    - $C_{17}H_{19}NO_3$
    - CAS # 57-27-2
    - Roxanol

**Pentoxifylline**

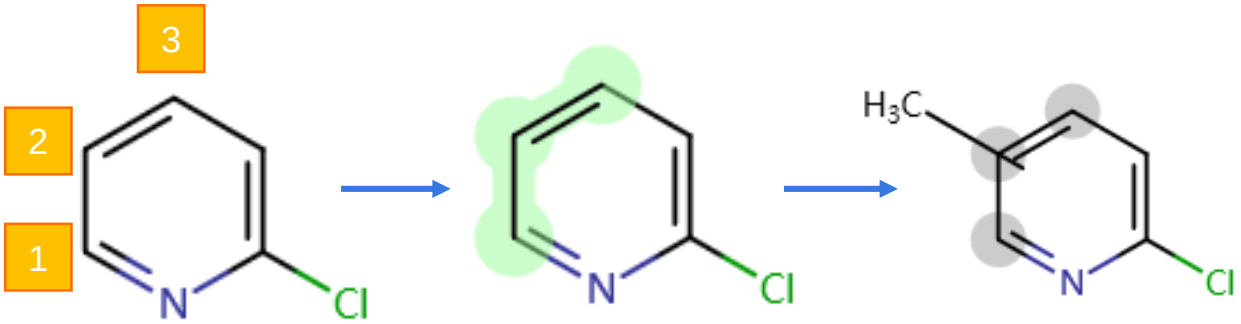
# Structure Search

# Reaxys中Marvin JS結構編輯器使用



# 不定位取代鍵的使用

- 不定位取代鍵：
  - 在選定的原子上進行基團的連結
  - 可以使用在鏈上，也可以使用在環上




***繪製要求：***

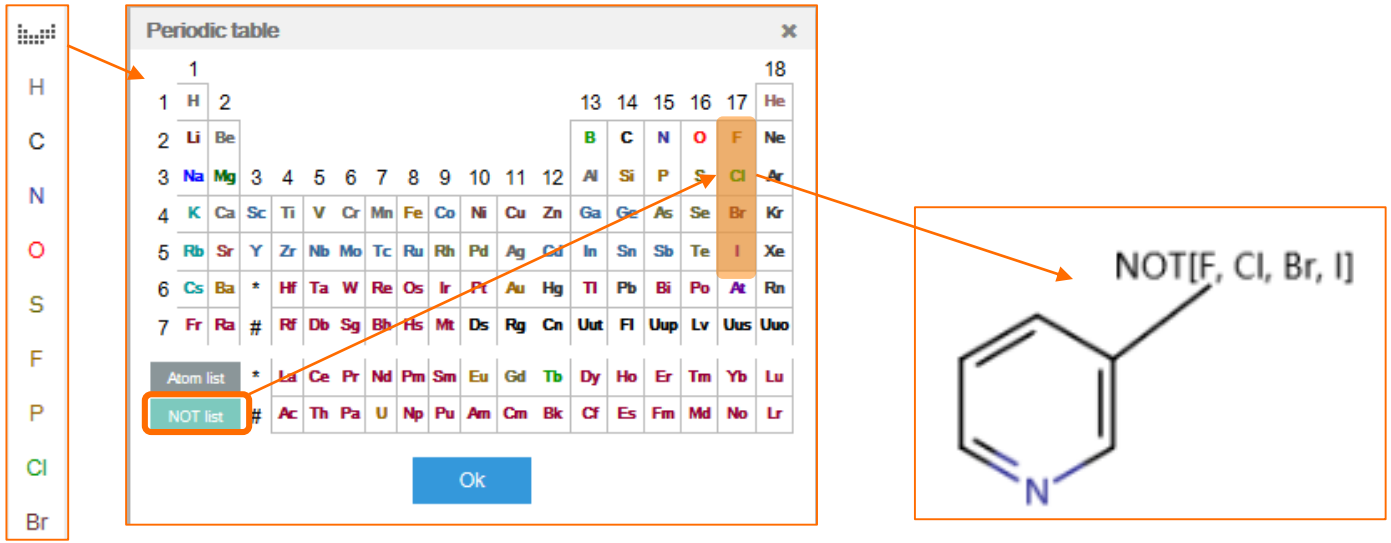
希望1，2，3C上存在一個NH2

***繪製步驟：***

1. 用選擇工具選擇1，2，3號C原子，
2. 添加不定位取代，系統預設添加CH3
3. 將CH3換成NH2

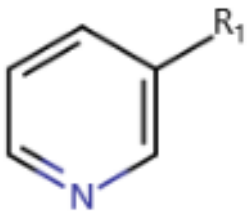
# Not List的應用

- 案例:
  - 定義某位點上不能發生F, Cl, Br, I取代

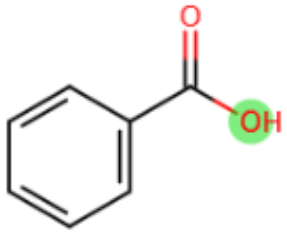


# 自訂R基團

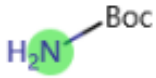
- 案例
  - 定義一個結構A
  - R1分別是下面的這些結構，結構中綠色原子與A結構相連接




A

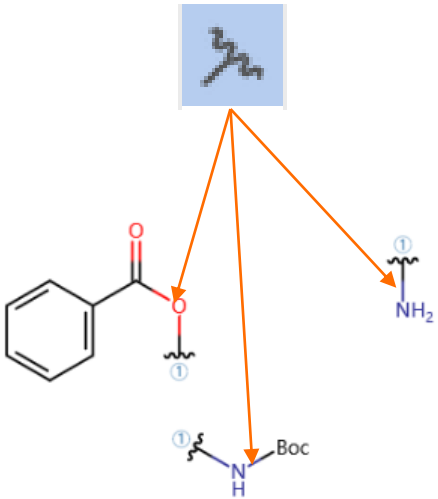


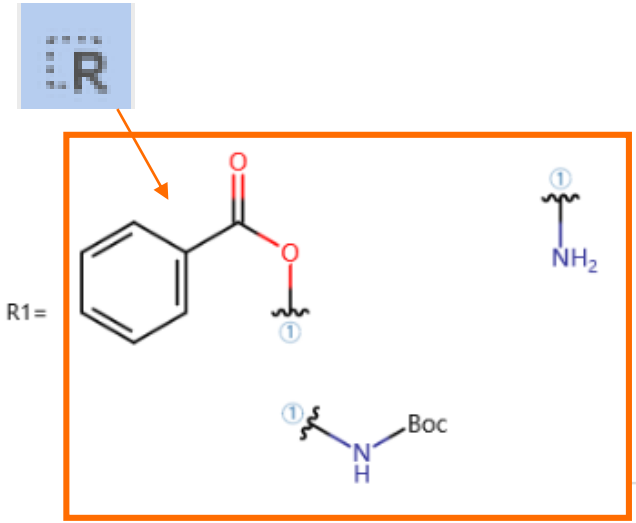




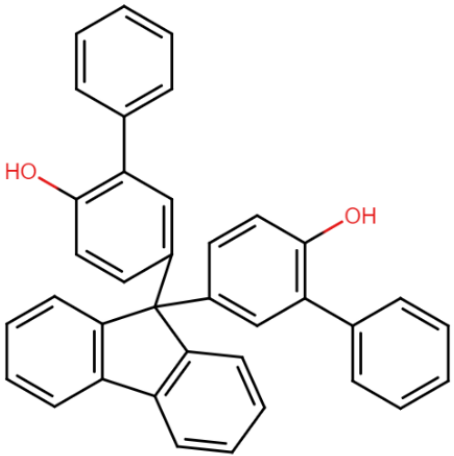
# 繪製方法

- 定義步驟：
  - 使用R基團末端定義工具定義綠色原子
  - 使用R基團定義工具，選擇全部片段，即可完成R1的定義



# Hands on #2



# Query Builder: 查詢範例

① 多條件查詢(**天然物、抗菌活性、分子式**)

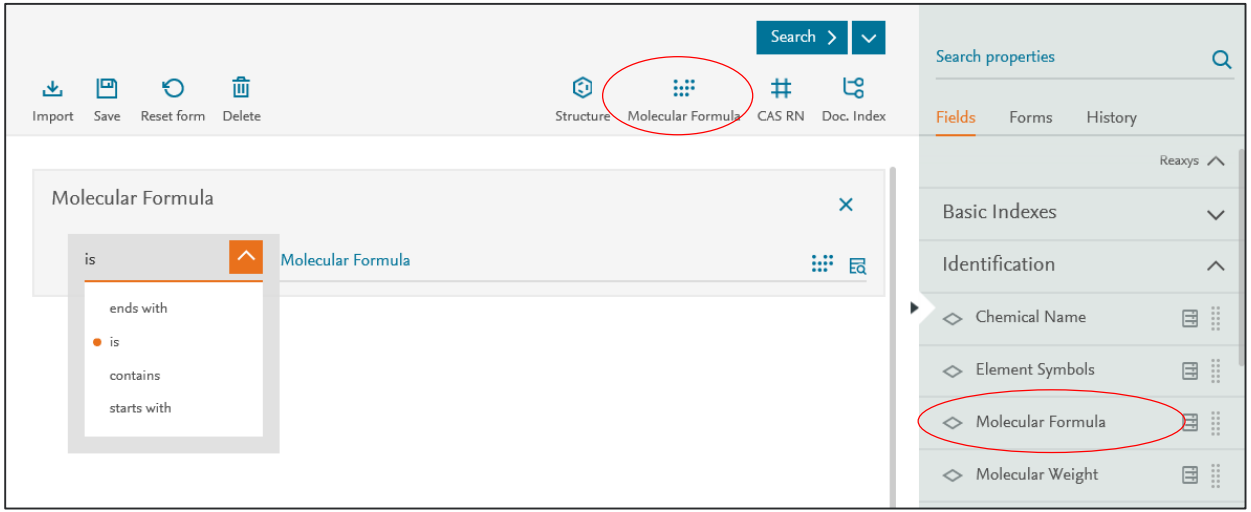
② 排除雜訊 (History Crosslink)

# Query Builder查詢範例1(1/4)

## 查詢範例:

是從天然物中萃取出來的化合物，分子式帶有30個碳並具有抗菌效果

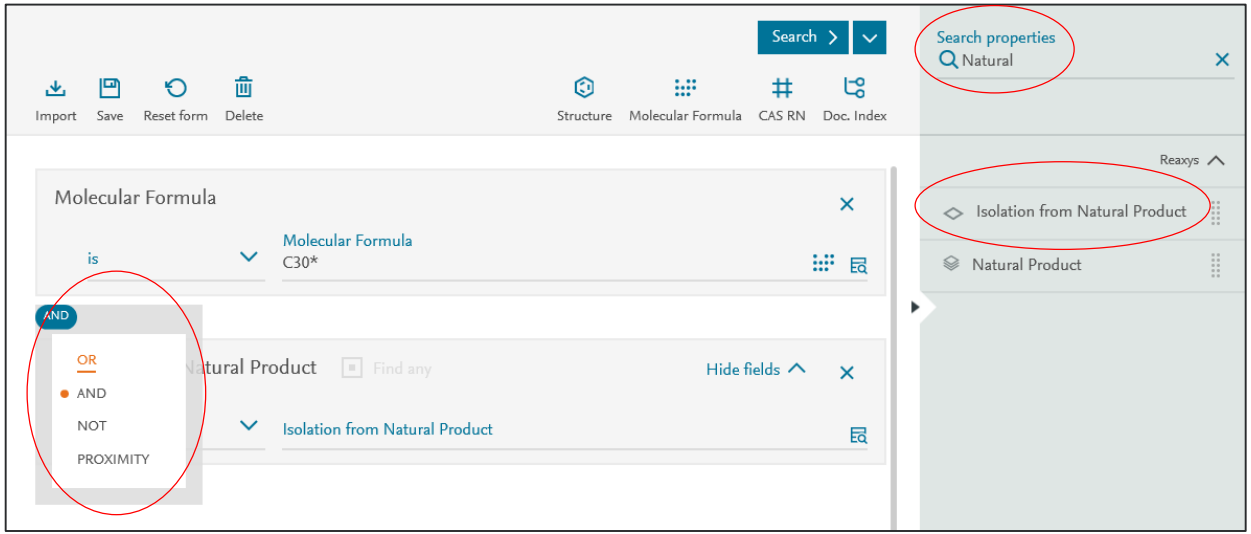
- Molecular formular/Natural product/Substance basic index




① 點擊右方的Identification>Molecular Formula

② 因為不知道其他成分，選擇"is"、，再輸入「C30*」

# Query Builder查詢範例1(2/4)

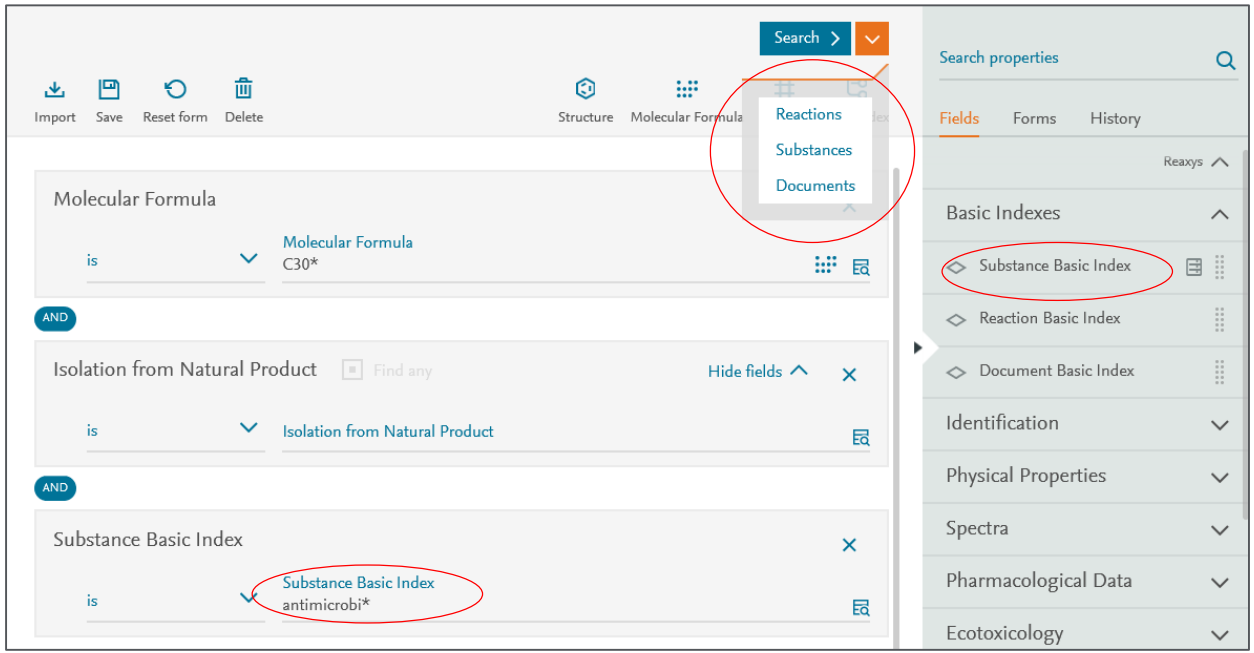



＊可使用關鍵字查詢篩選條件

③ 在右上方Find search and fields and form 輸入”Natural”，點擊「Isolation from Natural Product」

④ 在左方的運算子選擇AND，內容可不輸入

# Query Builder查詢範例1(3/4)

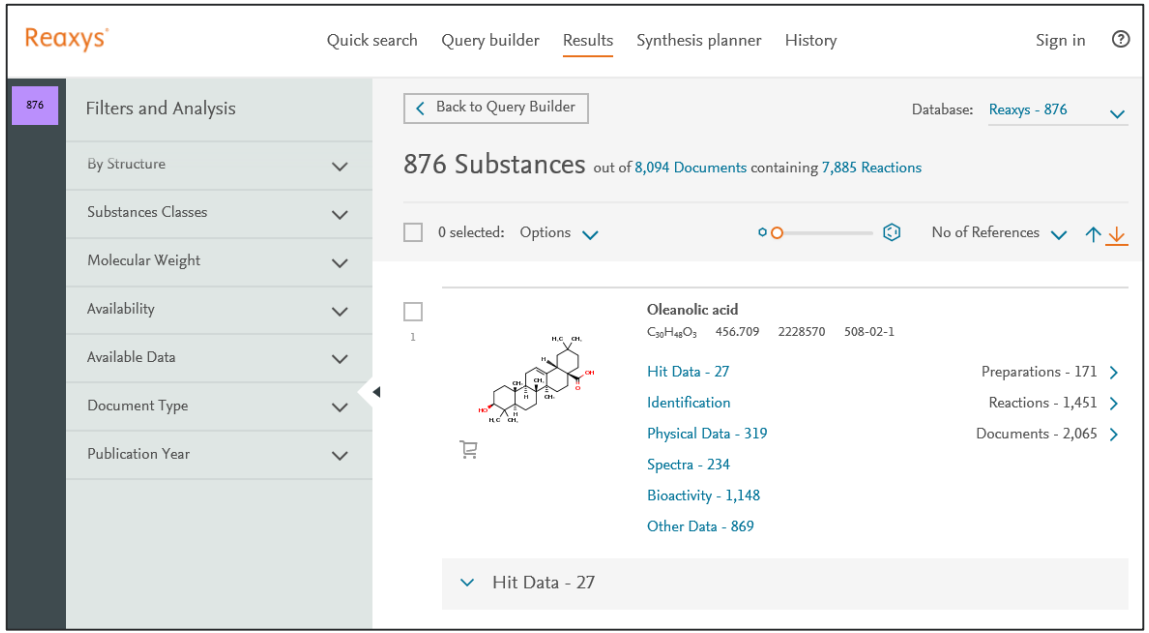



⑤ 點擊右方Basic Indexes>「Substance Basic Index」

⑥ 輸入“antimicrobi*”

⑦ 因為要找化合物，所以在右上的Search選擇Substance

# Query Builder查詢範例1(4/4)




查詢結果畫面:

分子式，化學名，測試項目，合成方法，衍生物的合成方法等都可以得到確認，

如果有其他條件，可透過左方的篩選功能縮小範圍。

# Hands on #3

- 試著搜尋以下物質：
  - 知道是天然產物
  - 分子量知道是348.453
  - 有一組NMR的數據
- 检索策略
  - Query Builder，添加天然產物選項
  - 分子量設定為>=348, 且<=349，避免一些誤差
  - 若有明確結構，可以同時添加結構片段，或在後期進行篩選
  - 有圖譜數據的話，可以直接添加圖譜數據

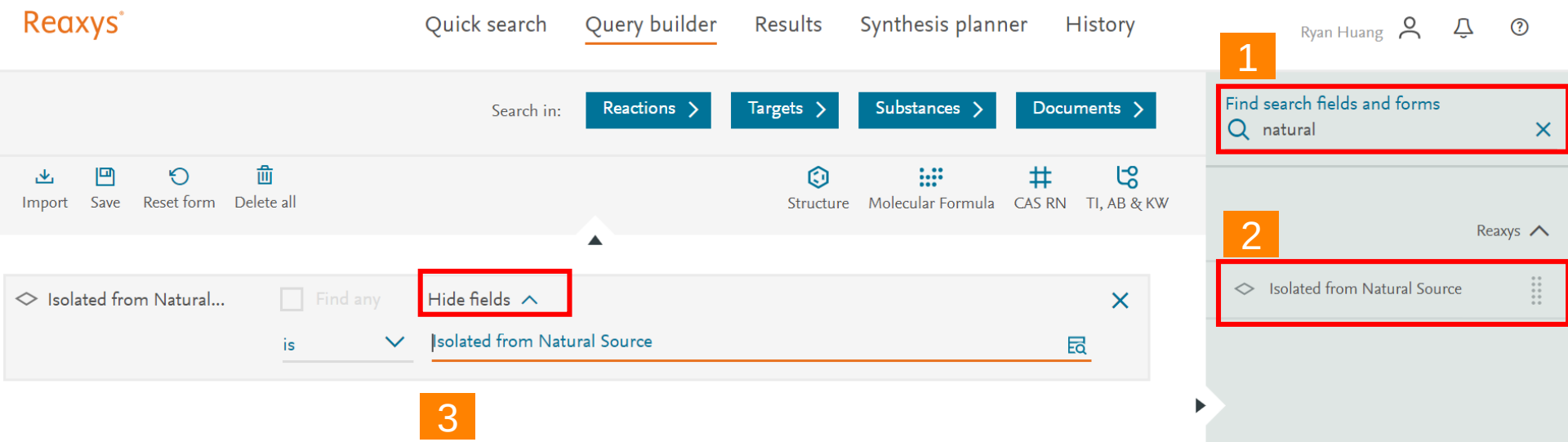
# Hands on #3 衍生範例

- 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：設定圖譜數據中，包含173, 153, 130, 可以將上述的圖譜找到，設定173其實是尋找173.0-173.9的圖譜

# Query Builder

- 添加天然物萃取模組




***Tips：***

- 按照1, 2, 3步驟，添加天然產物的搜索條件
- 這種模式下的搜尋結果，一定是天然產物

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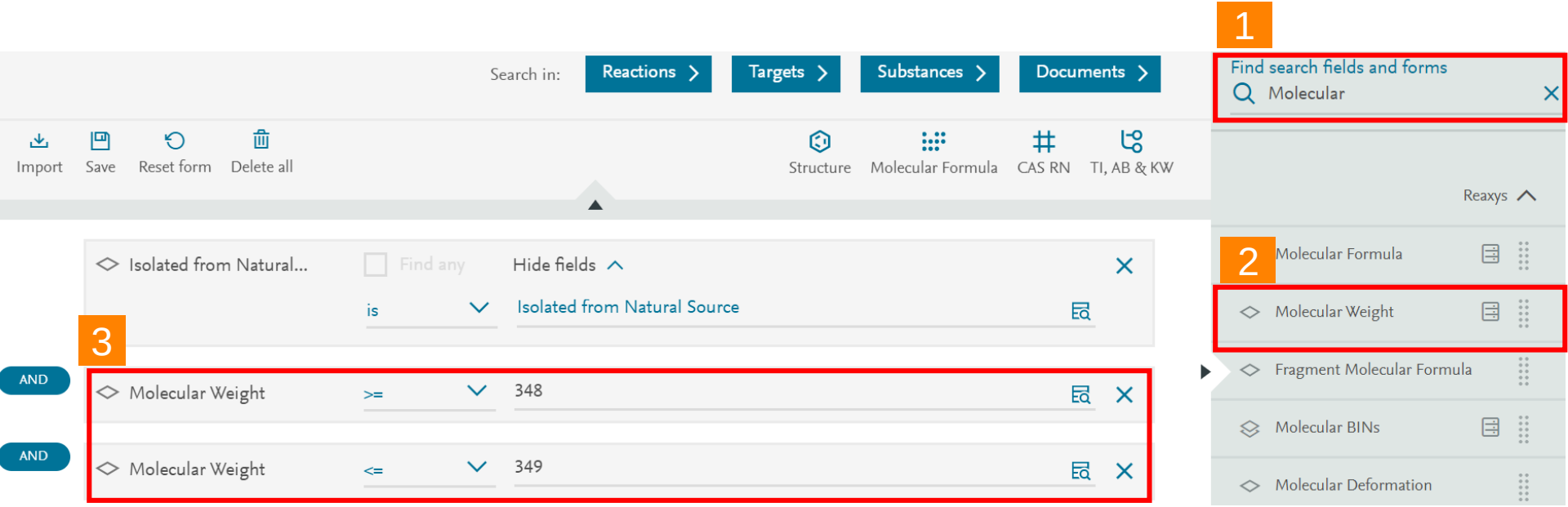
# Query Builder

- 添加分子量模組

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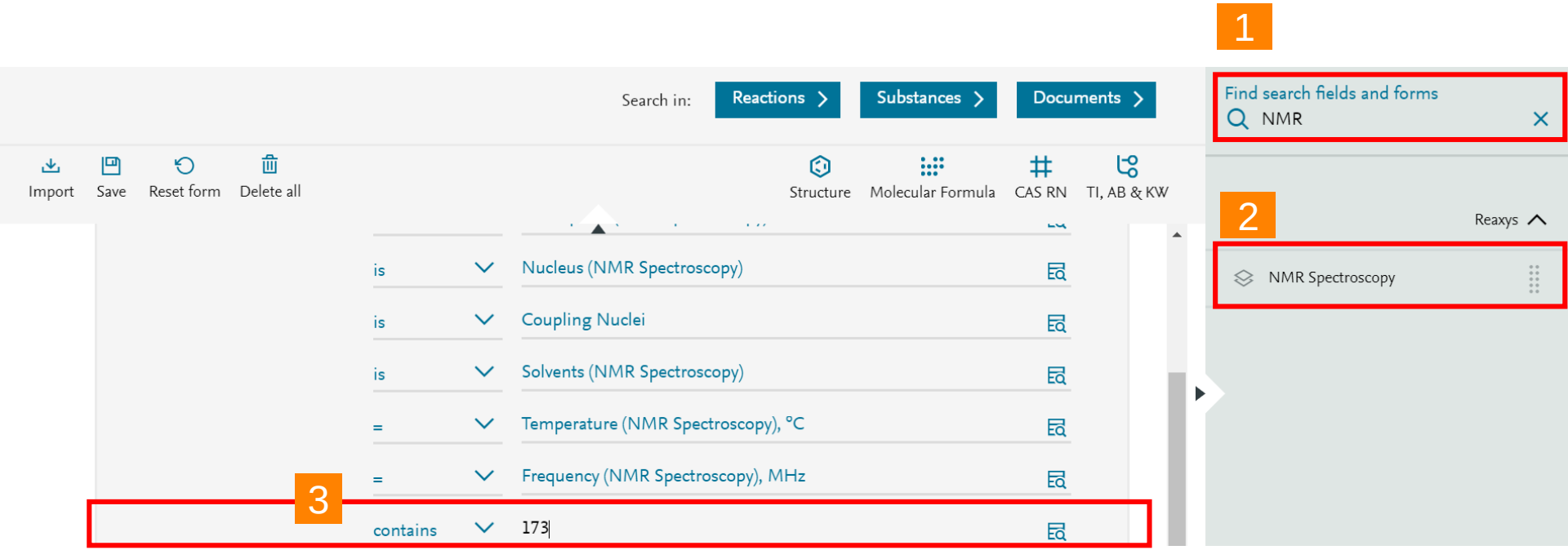
# Query Builder

- 添加NMR模組

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# Synthesis Planner

# 建構合成路徑(1/3)

Synthesis Planner：可透過逆合成分析建構合成路徑

- 畫面上可同時提供多種合成方式，便利比較評估
- 也可於化合物查詢結果頁面進入Synthesis Planner

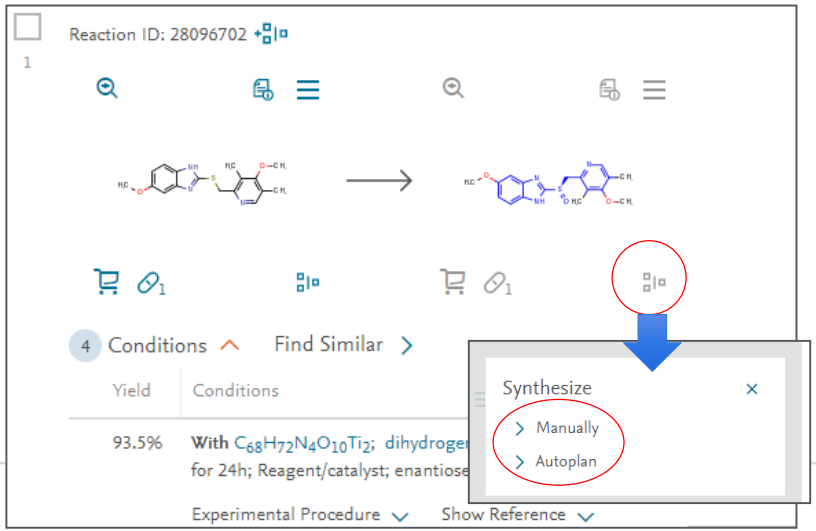
## 查詢範例：*Omeprazole*的合成

從反應查詢結果進入Synthesis Planner。

① 點擊 ，將該化合物作為起始點

② 可選擇使用Manually或Autoplan啟動Synthesis Planner

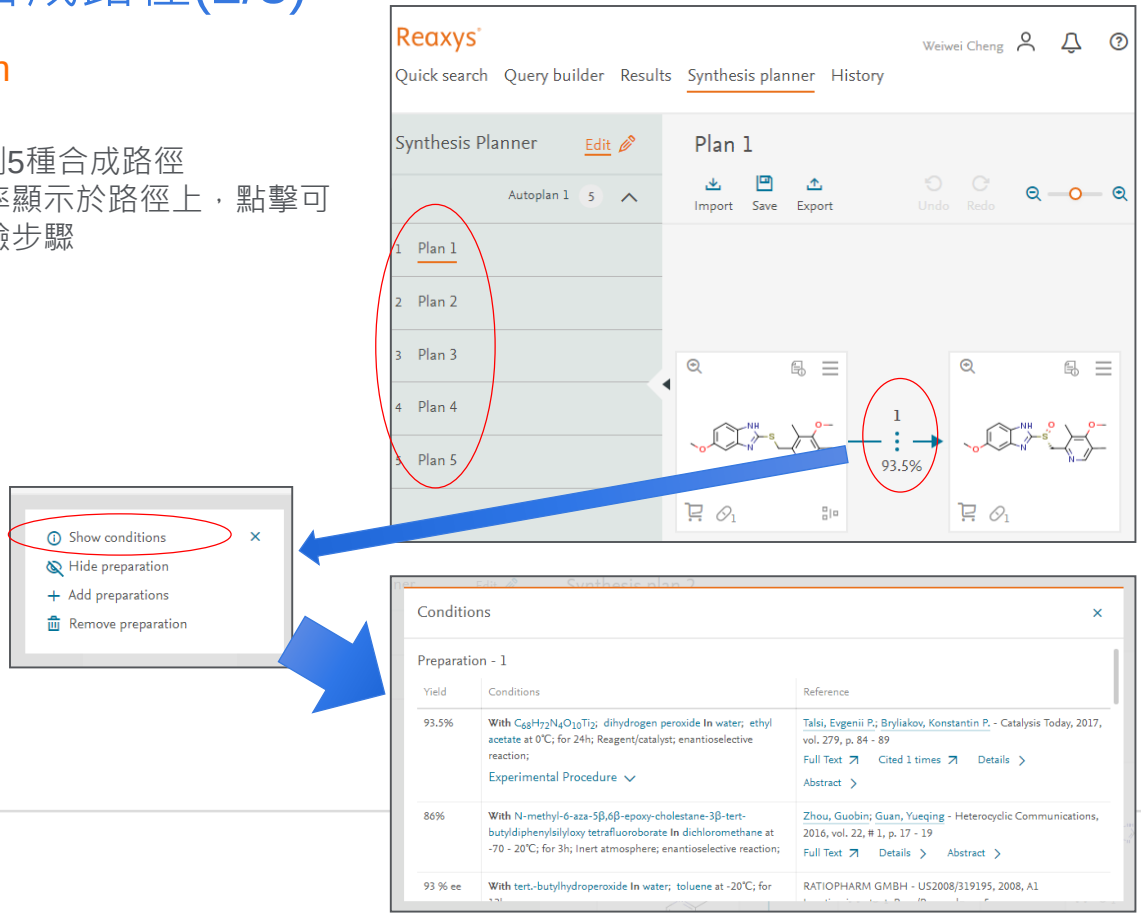
- Manually：手動逐步建立合成路徑
- Autoplan：顯示Reaxys建議合成路徑



# 建構合成路徑(2/3)

## Autoplan

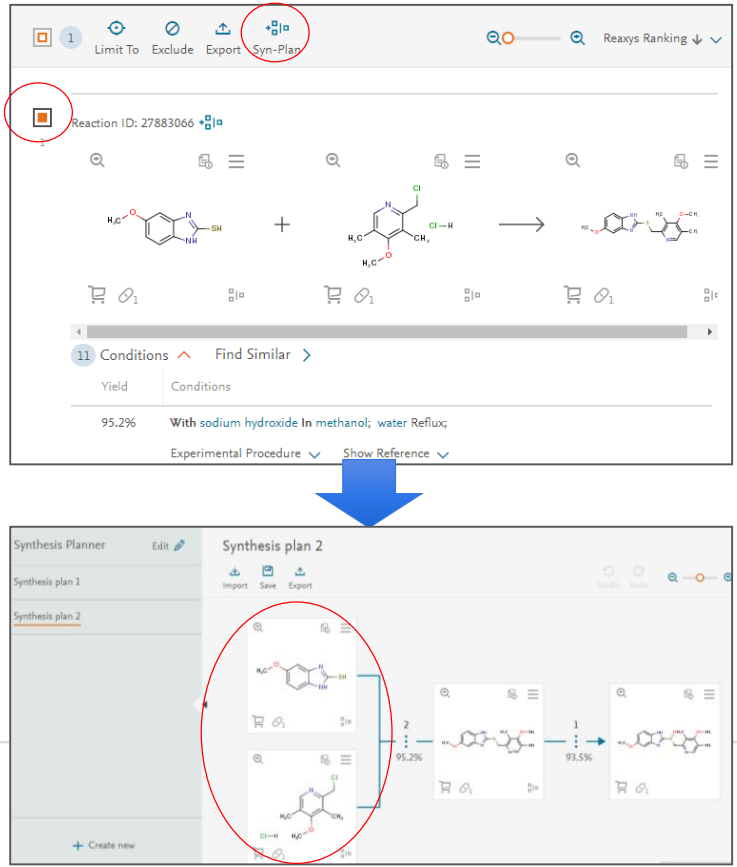
- 自動規劃5種合成路徑
- 反應產率顯示於路徑上，點擊可顯示實驗步驟



# 建構合成路徑(3/3)

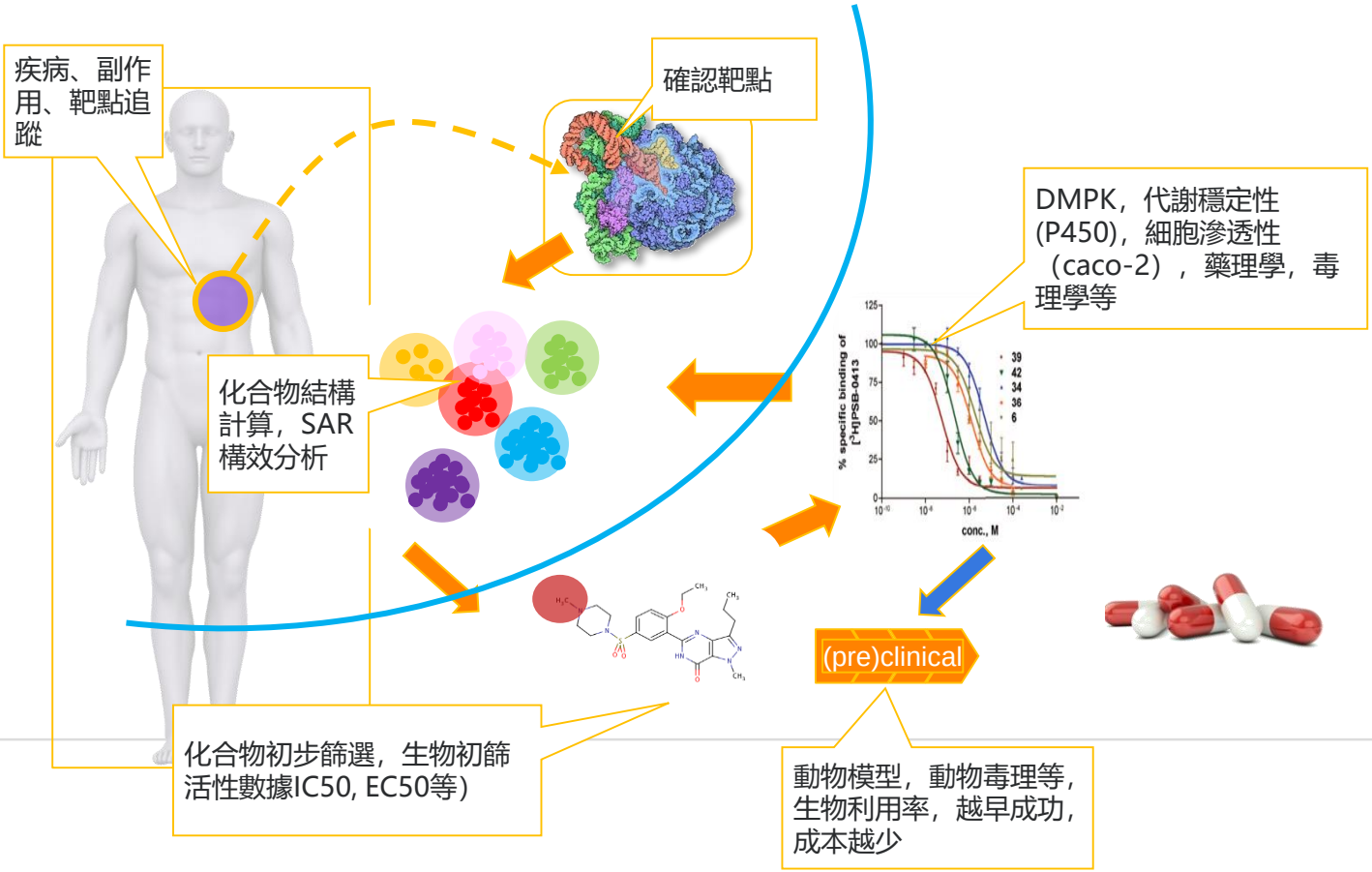
## Manually

•選擇要加入的反應，按下Syn-Plan
•反應直接加入於合成路徑



# Structure Activity Relationship

# Reaxys/RMC如何輔助小分子藥物設計流程

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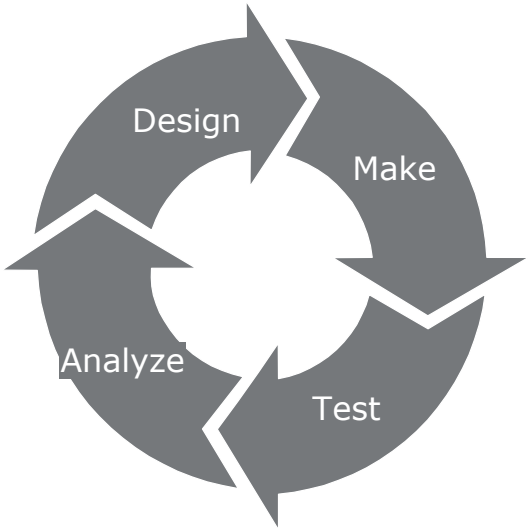
# The design, make, test and analyze cycle lies at the core of drug design

**Drug target**

Chemical starting point (Hit) found through HTS, DEL, fragment screening or prior knowledge
- Weakly active
- Target unselective
- Toxicity risk
- Low metabolic stability



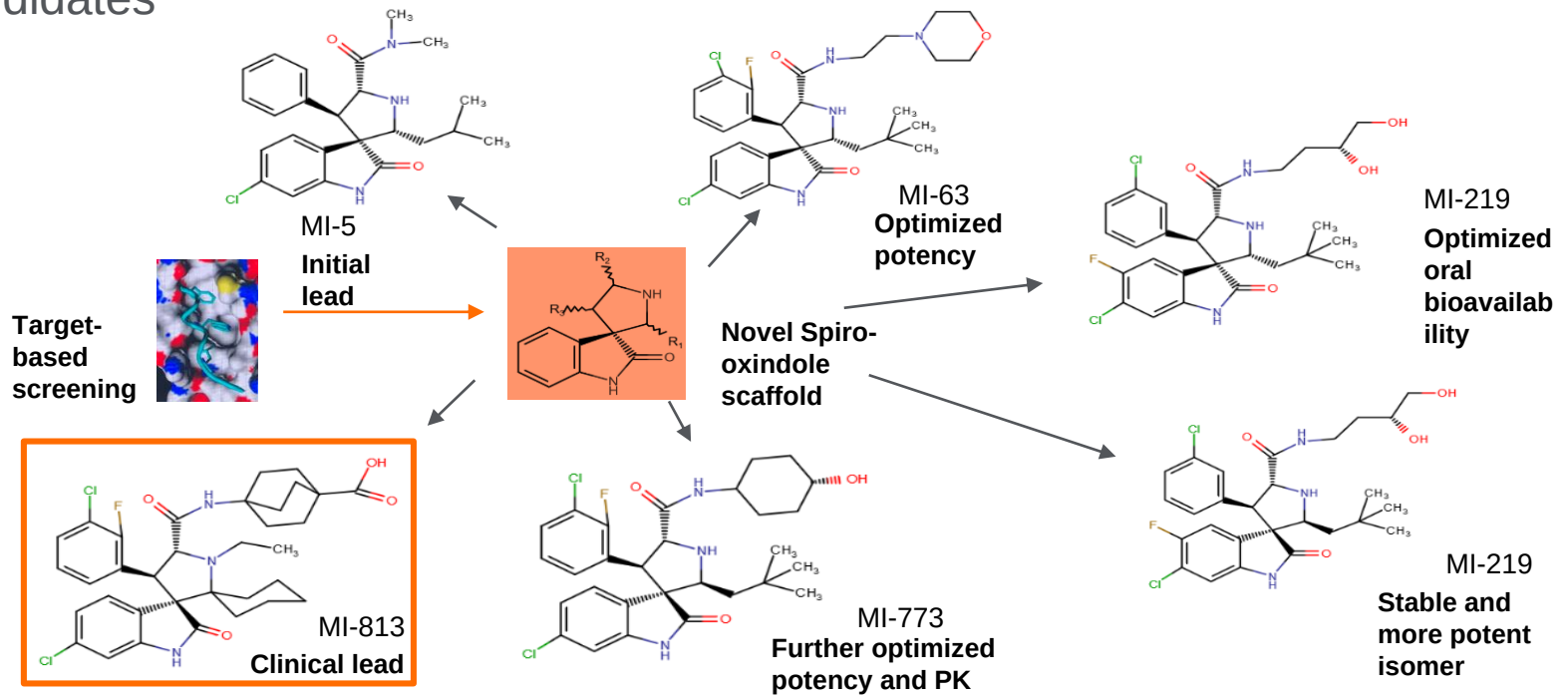

Candidate drug
- Highly potent
- Effective in *in vitro & in vivo* models
- Metabolically stable
- No toxicity issues

~3 years

- Multiple of DMTA cycles & hand-overs between multiple labs
- Each cycle between 4-8 weeks

*HTS: High througput screening; DEL: DNA-encoded chemical libraries

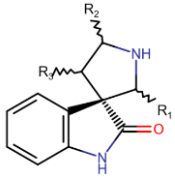
# Rational drug design begins with screening against a “druggable” target that is associated with disease state and developing libraries of potential drug candidates



# Researchers need to address a number of questions when developing a new drug candidate (competitive landscape, novelty search, synthesis planning, building blocks..)

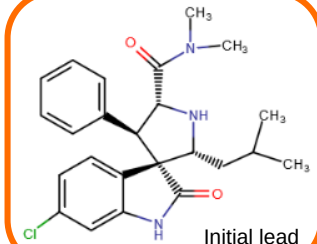
Target

Target-based screening



Spiro-oxindole scaffold

Design of initial lead

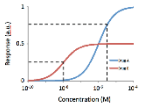


Initial lead

- What are its **ADME** and **TOX** profile?
- Is there **CYP**, **HERG inhibition**?
- Is it negative in **AMES test**?

Pharmacology

- Is it **active** and **efficacious**?
- Is it **selective**?
- Is there **off-target activity**?



MedChem properties

- What is known about the **target**?
- **Who** is working on it?
- What other **companies** work on?


Competitive intelligence

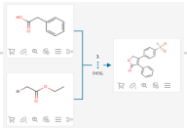
- Is it **novel/patentable**?
- Is there **freedom to operate**?


Novelty searching

- What are its **PhysChem properties**?
- Is it a **druglike** compound?

PhysChem properties

- How to **synthesize** it?
- Is **starting material** available?



Synthesis planning

- How to **purify** product?
- How to **analyse** product (NMR, HPLC, UV, IR)?

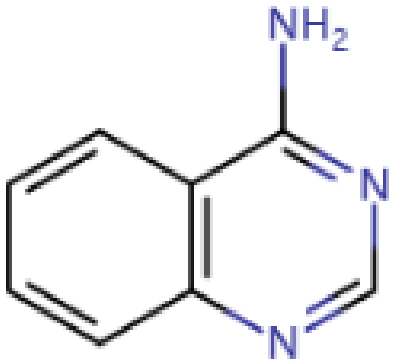
Product analysis

# Reaxys + RMC
# Use Case #2

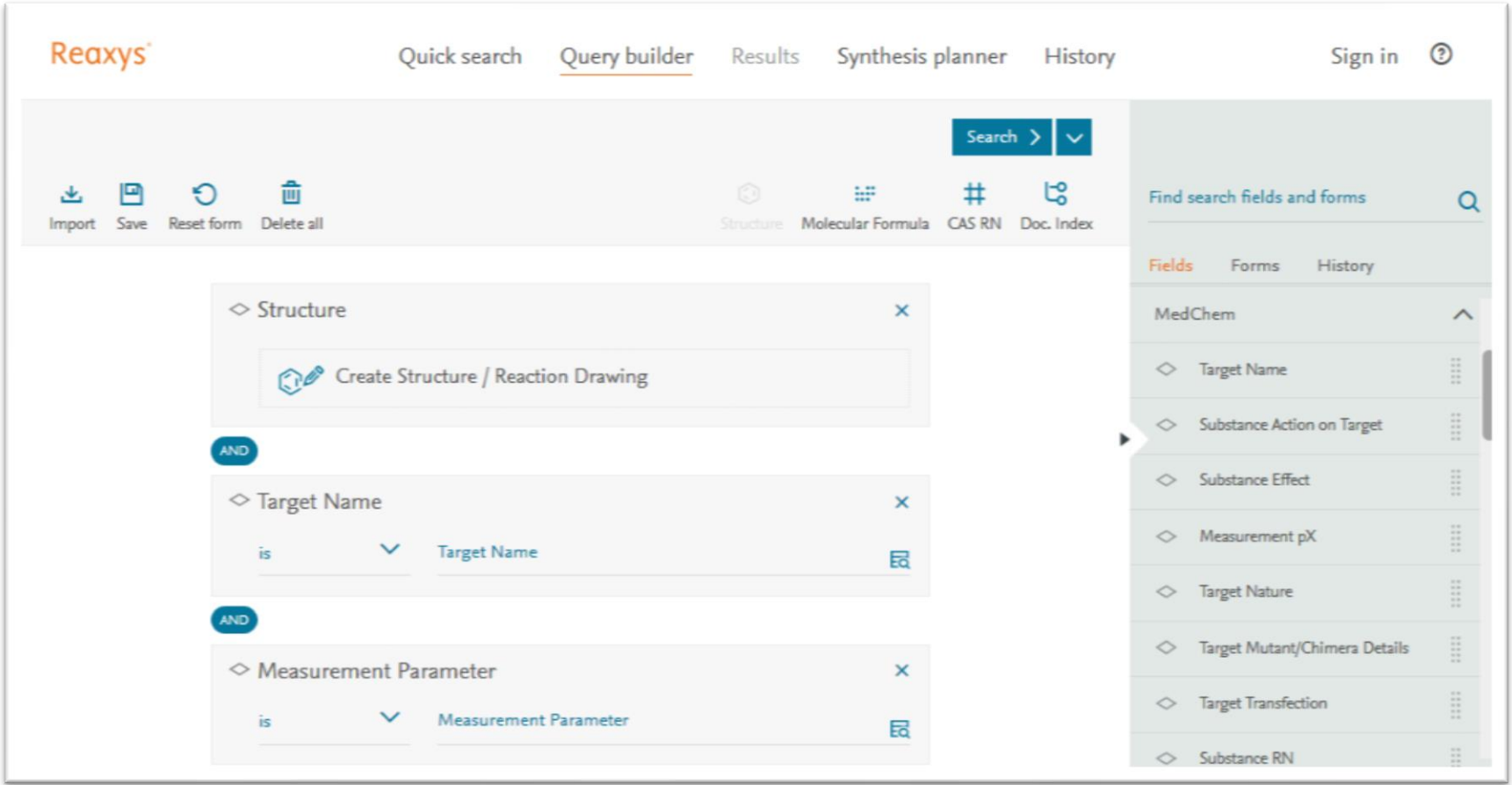
# 學名藥廠由已知(專利過期)母核結構進行 ”Me TOO” “Me BETTER“ Project

**Challenge:** a general scaffold has good activity at the EGFR receptor, we need to identify:

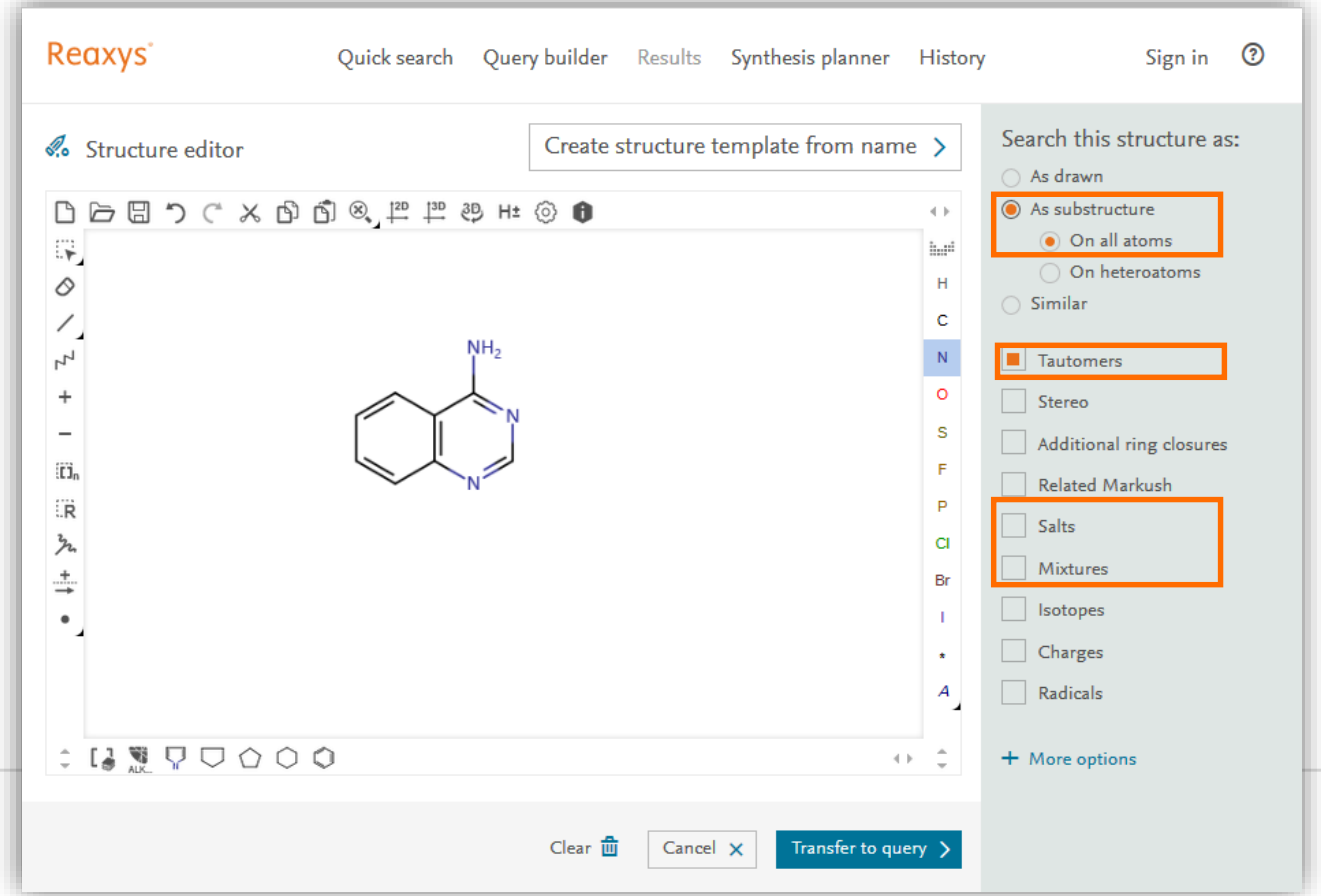
- 可以作用在EGFR上、所有含有母核結構的已知化合物，找出所有的IC50 data
- 找出影響活性的可能官能基
- 設計新的結構
- 進行專利評估



Query builder allows the user to setup comprehensive search strategy defining the structure, target and bioactivity



# Search for all derivatives of the general structure by selecting from the filter options

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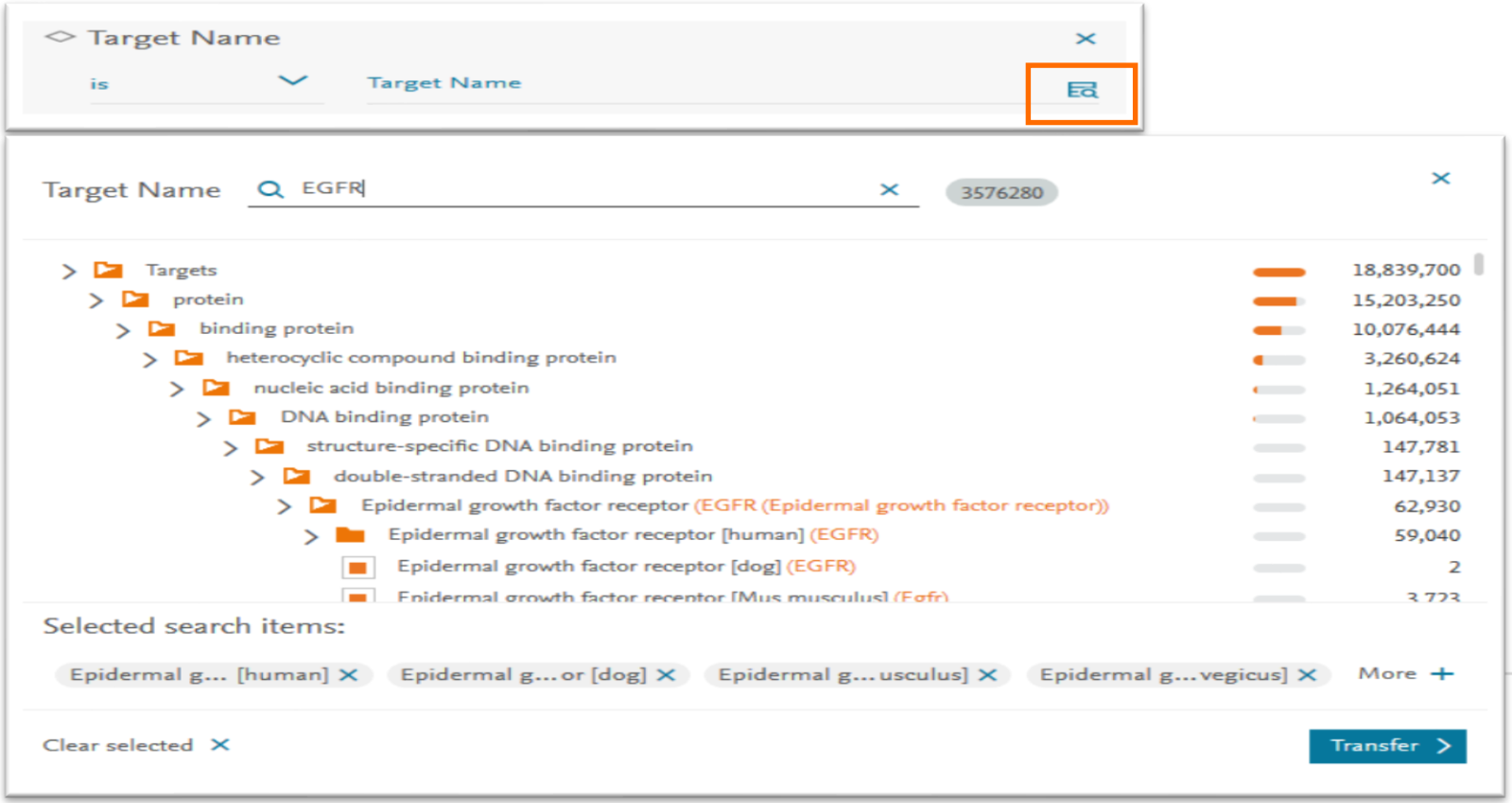
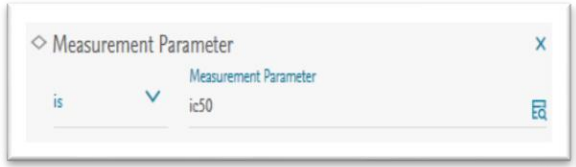
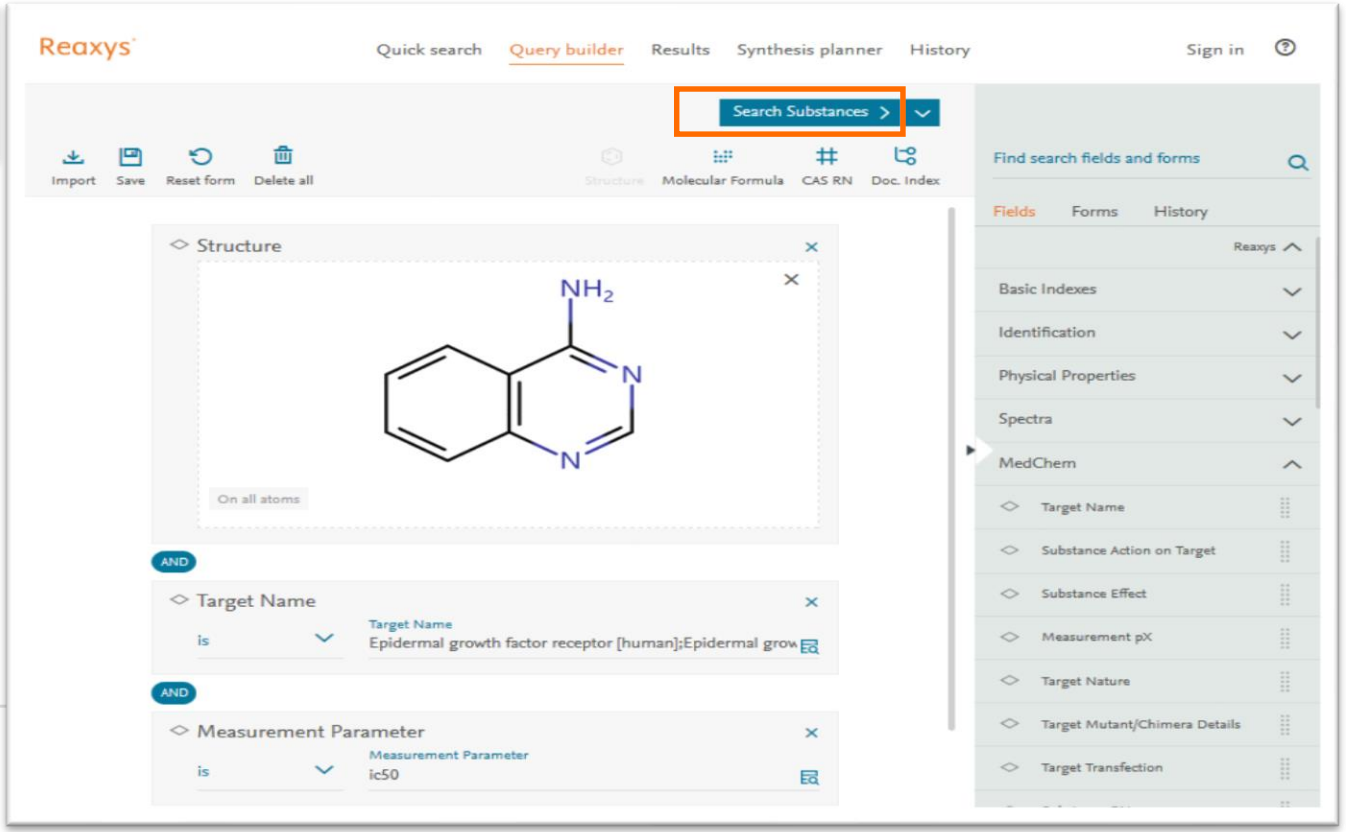
# Define the target as EGFR



# Add the measurement parameter as IC50 and run the search

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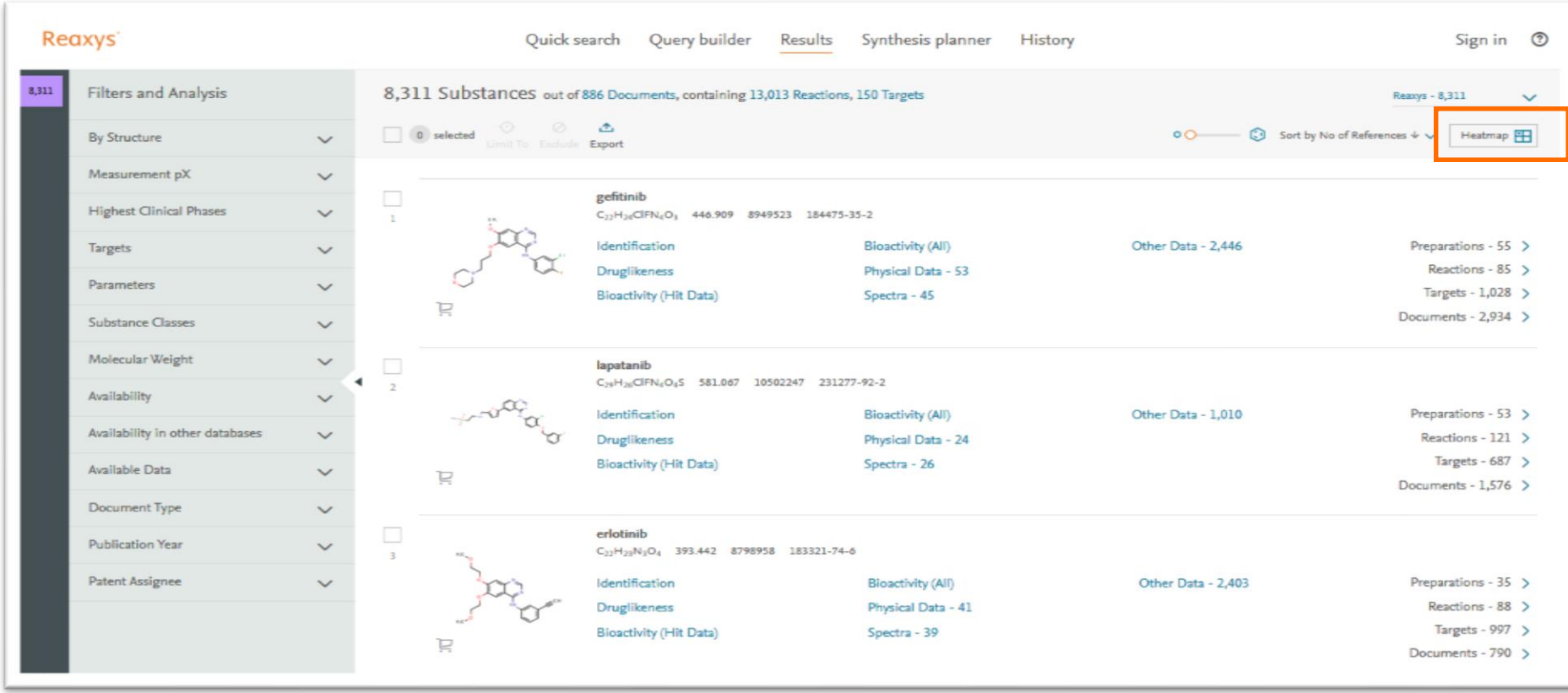
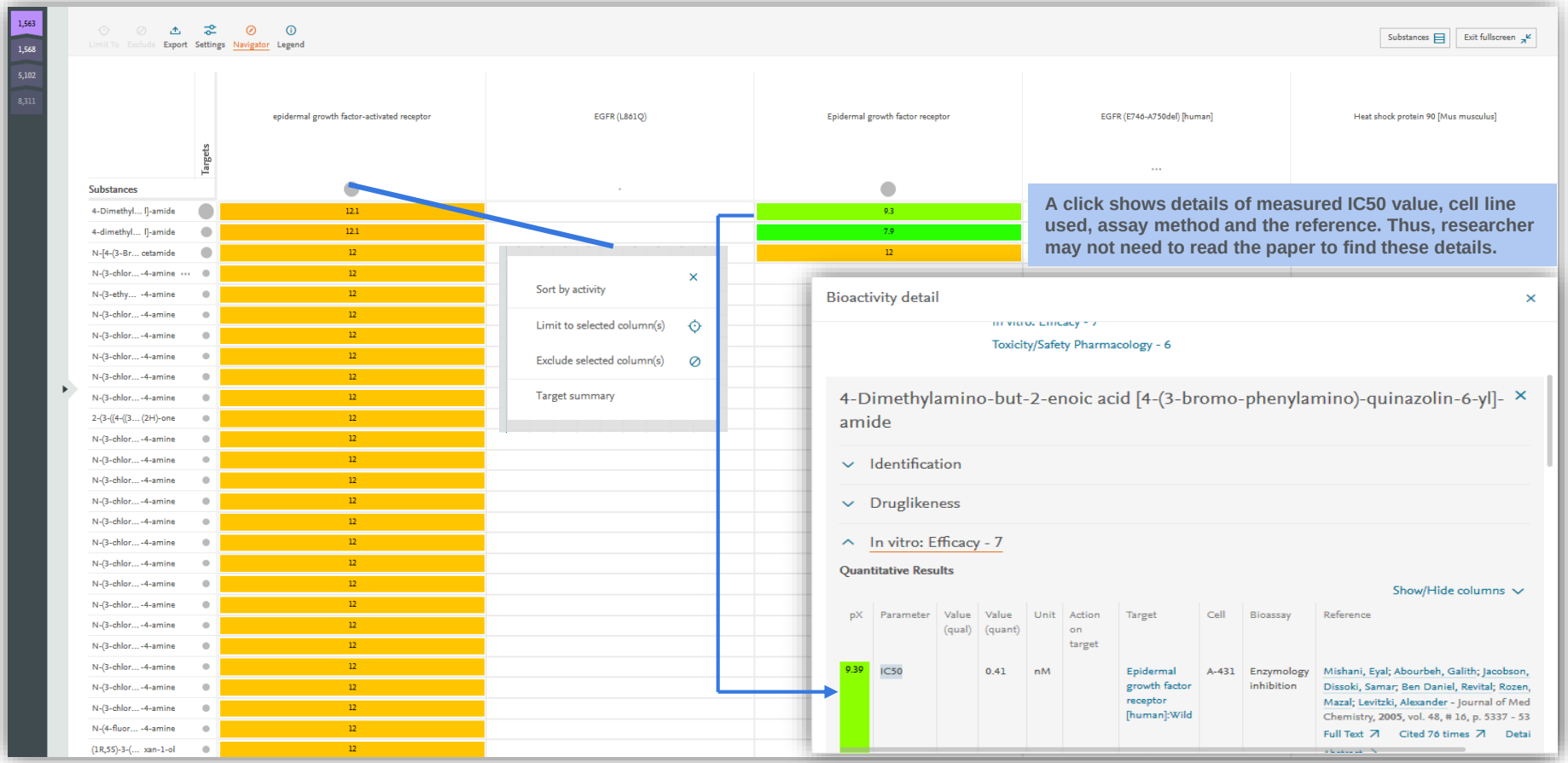
# Reaxys provides 8,311 substances matching the criteria defined by the user in their search strategy

Review substance results & switch to Heatmap view:

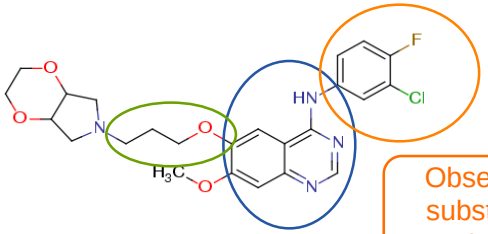


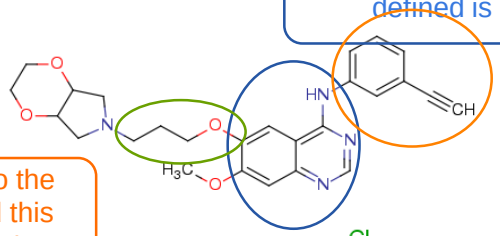
# Heatmap view allows for the rapid assessment of the substance and target interactions



# SAR analysis: What structures give high and low activity?

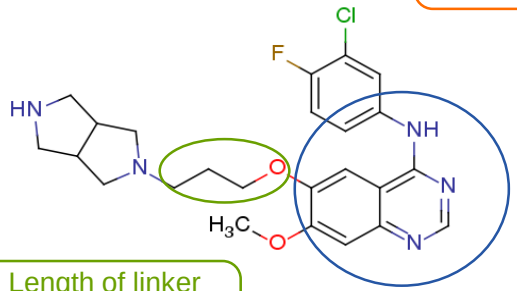
Observation 1: Core ring as defined is present in all





pX=12

Observation 3: Changes to the substituent pattern around this ring seems well tolerated



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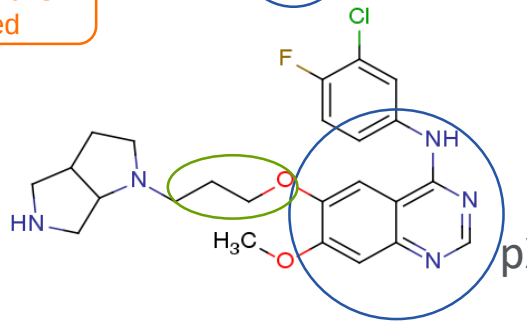
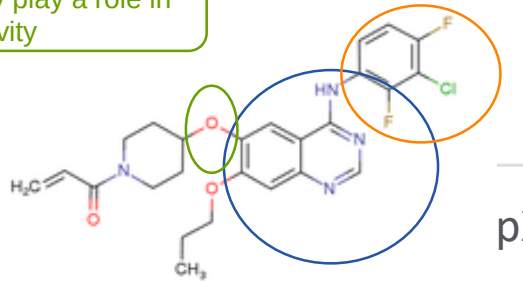


pX=12

Observation 2: Length of linker from the core may play a role in bioactivity



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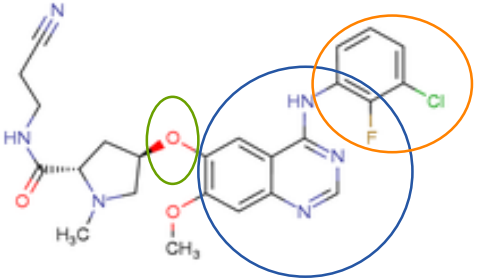
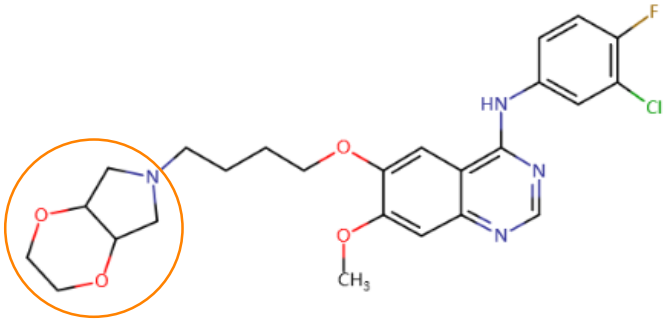
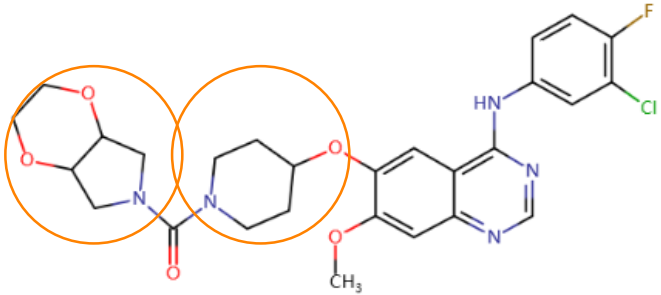
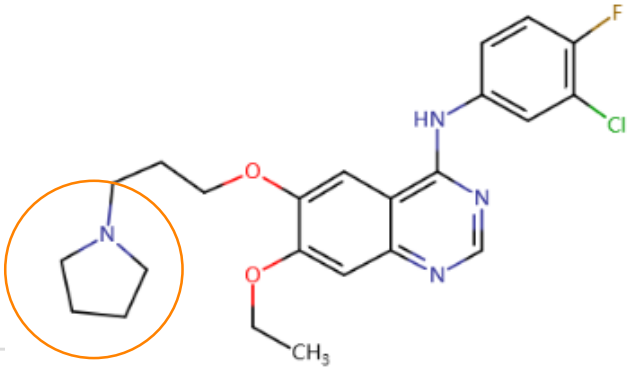


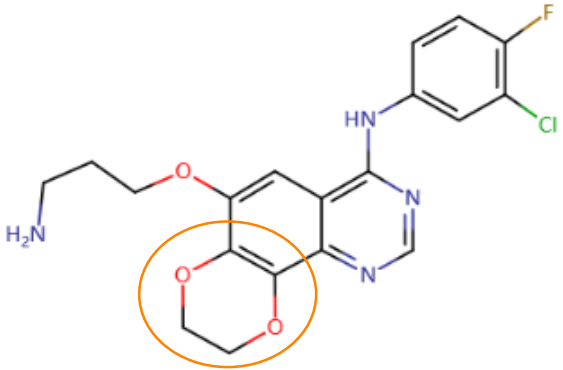
pX=9

# Based on SAR observations researchers could potentially design some new compounds



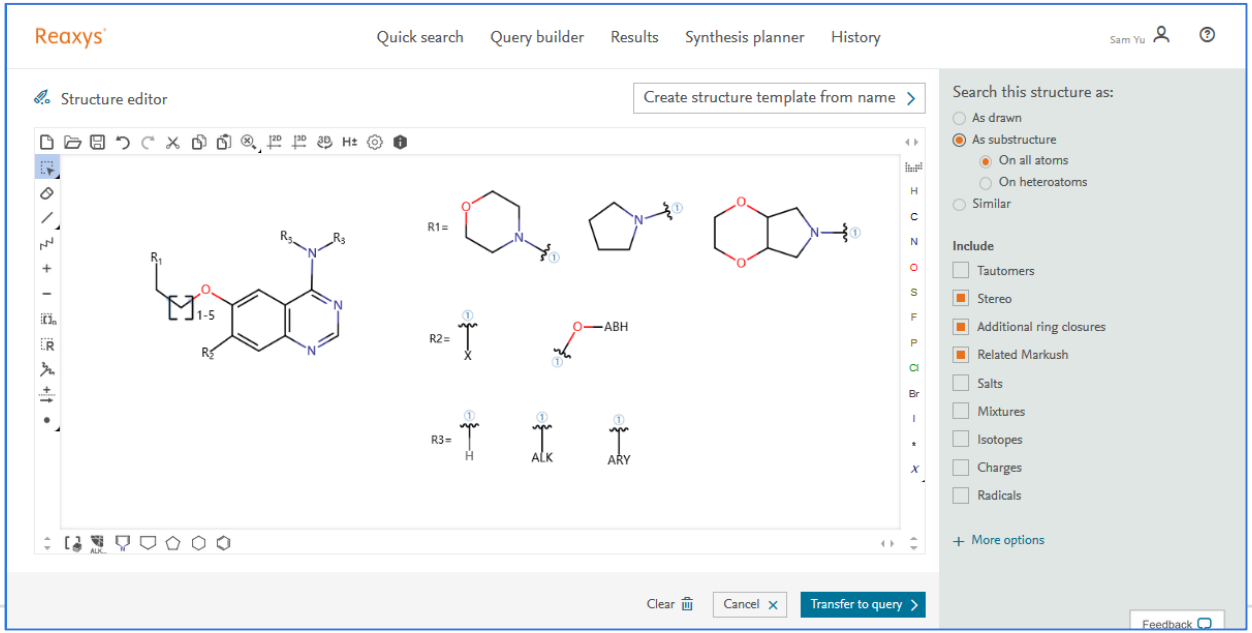




**NOTE:** These molecules cannot be found in Reaxys

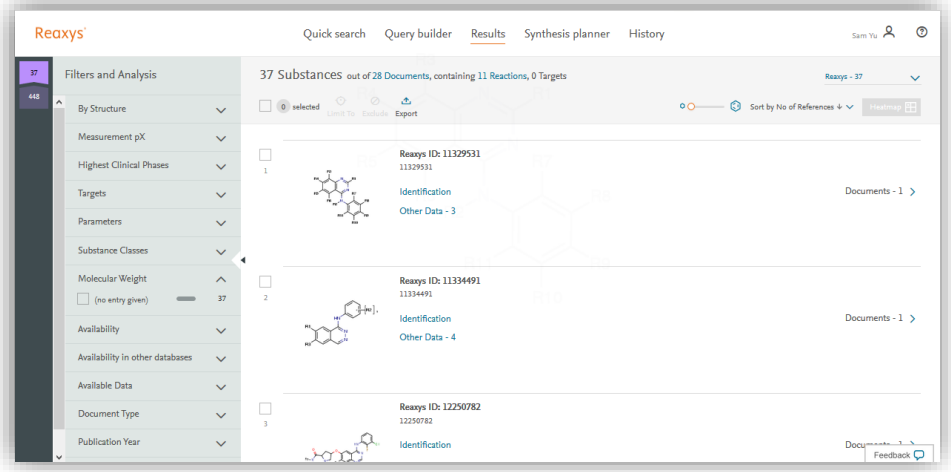
# However, before synthesising the new molecules the researcher might want to check if the molecules are patented or not. This will help prevent wastage of time, effort & money

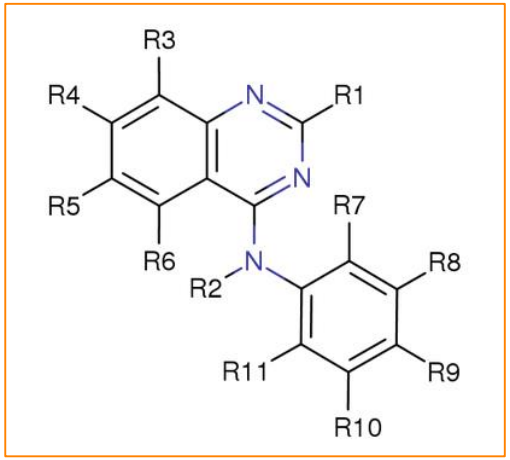
Markush search functionality coupled with powerful structure editor allows researcher to define the R-groups, control the length of side chains etc. thus enabling the researcher to define and search for patent related information

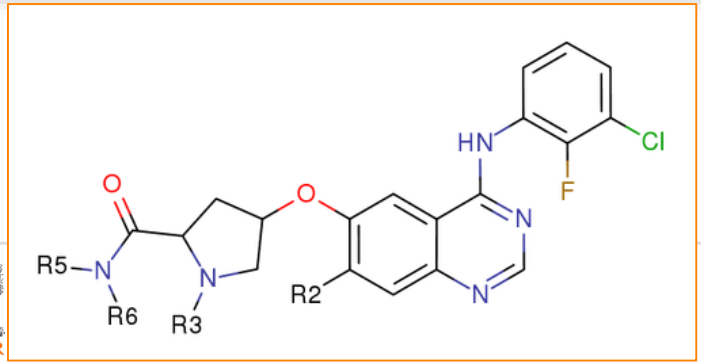


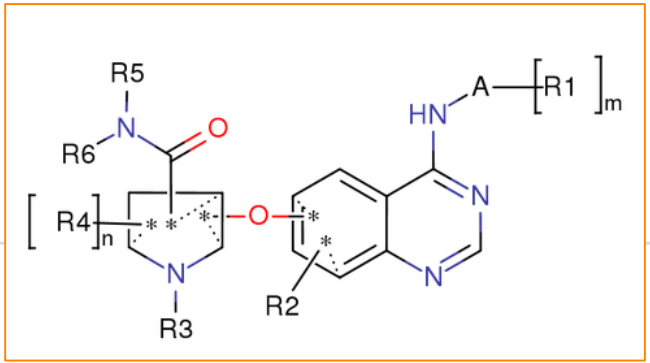

**Tips：** Salts and Mixtures are disabled, Related Markush and As substructure are included

37 Markush structures are obtained from the search and the 3 examples provided show the structure to be similar to the proposed new compounds, thus further analysis on their coverage and claim need to be conducted

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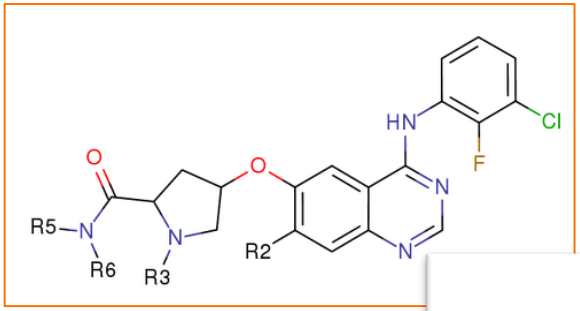
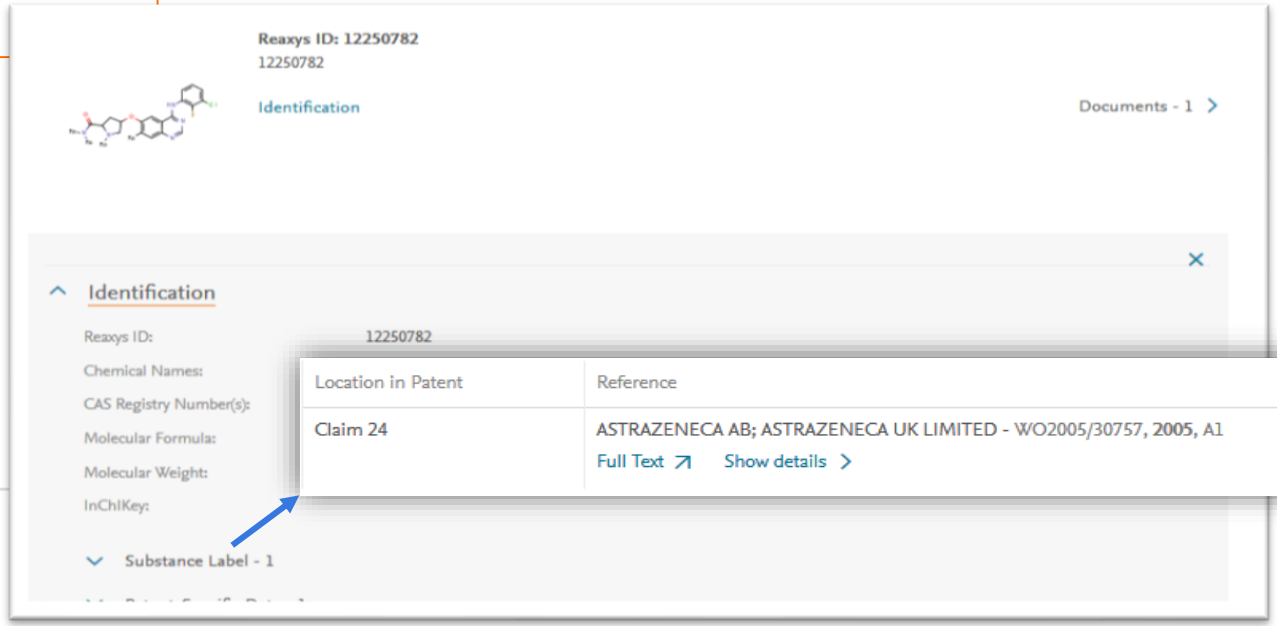
This particular compound is quite similar to the proposed structure and we can see that it has been claimed in an AstraZeneca patent



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