# Elsevier
# Life Science Solution
# 获取药物研发信息系列主题培训

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# Agenda

- 7月8日
  - 15：00-15：10：Elsevier Life Science整体解决方案介绍
  - 15：10-16：30：物质结构/合成信息的获取与精炼
- 7月15日
  - 15：00-16：00：生物活性数据与文献的获取与提炼
- 7月22日
  - 15：00-16：00：药物毒理药理学文献的获取
- 7月29日
  - 15：00-16：00： Elsevier Life Science整体解决方案数据库使用答疑
- 8月5日
  - 15：00-16：00：如何将Elsevier Life Science整体解决方案贯穿药物研发的全流程

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# 如何将Elsevier Life Science整体解决方案贯穿药物研发的全流程

涉及：Reaxys，RMC， Embase，PharmaPendium

# Elsevier 生命科学解决方案

PATHWAY STUDIO

REAXYS Medicinal Chemistry

REAXYS

PHARMAPENDIUM

EMBASE


LIFE SCIENCE SOLUTIONS Text Mining & Data Integration

EMBASE

药物研发的全生命周期的每一个阶段都有专业化的解决方案

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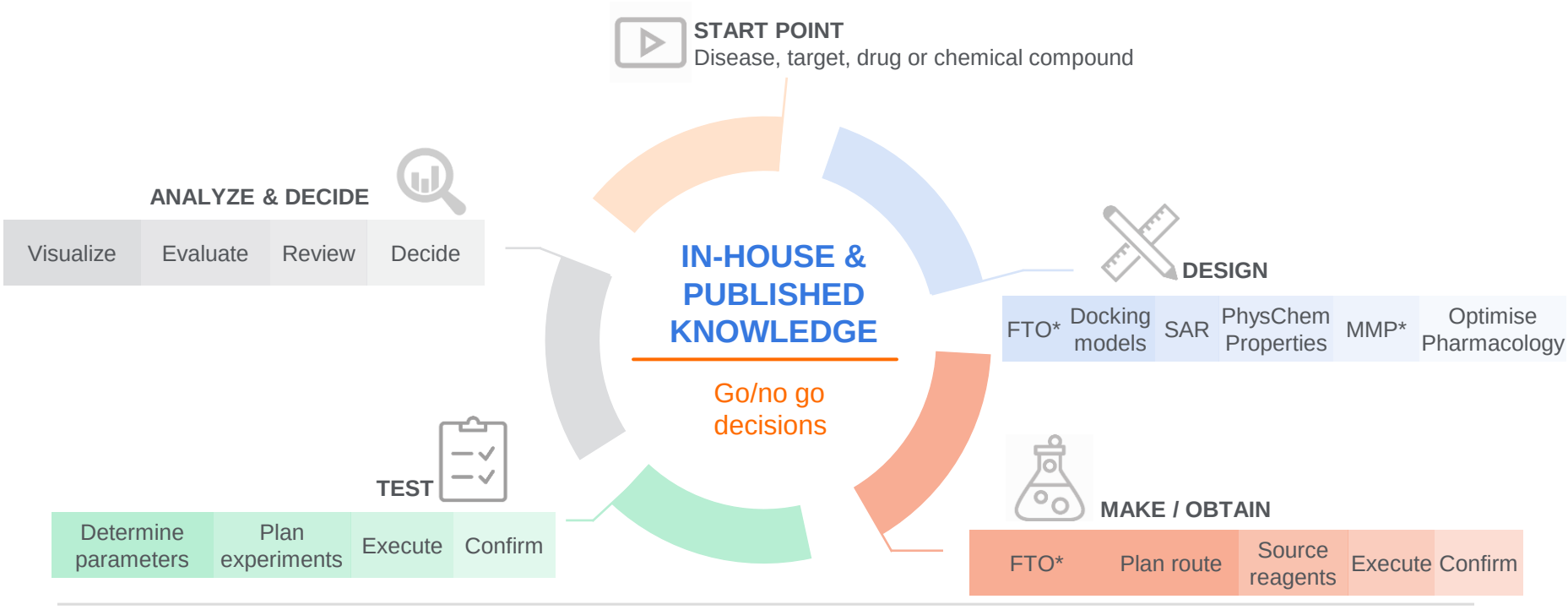
# 我们的整体战略是支持小分子的开发周期，并提供一个化学生态系统




*Freedom to operate
*Matched Molecular Pairs

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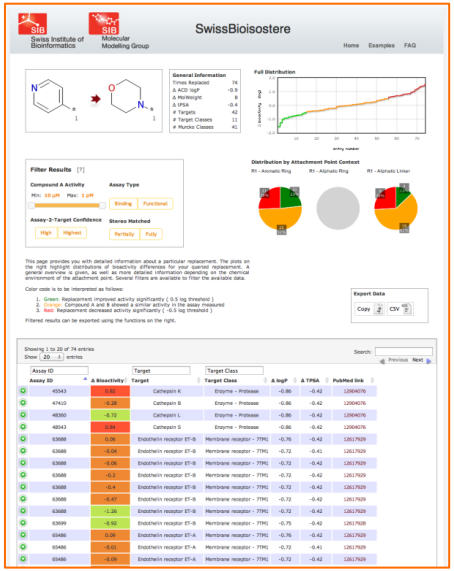
# 利用AI/ML技术， 从数据库发展成为支持分析与决策的解决方案

MMP分析

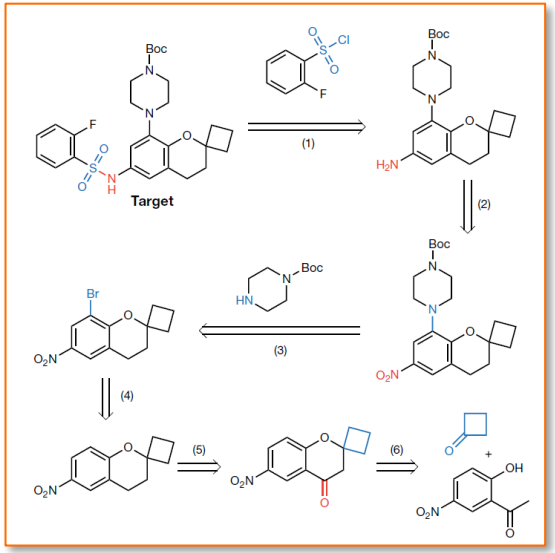



靶点预测

Target prediction

| Target | Common name | Uniprot ID | Target Class | Probability* | Known actives (3D / 2D) |
|---|---|---|---|---|---|
| Adenosine receptor A2a | ADORA2A | P29274 | Membrane receptor | | 584 / 465 |
| Adenosine receptor A2b | ADORA2B | P29275 | Membrane receptor | | 170 / 232 |
| Adenosine receptor A1 | ADORA1 | P30542 | Membrane receptor | | 488 / 591 |
| Adenosine receptor A3 | N/A | P33765 | Membrane receptor | | 690 / 639 |
| Neuropeptide Y receptor type 5 | NPY5R | Q15761 | Membrane receptor | | 299 / 149 |
| Cannabinoid receptor 1 | CNR1 | P21554 | Membrane receptor | | 1418 / 305 |
| 5-hydroxytryptamine receptor 2A | HTR2A | P28223 | Membrane receptor | | 108 / 42 |
| 5-hydroxytryptamine receptor 2C | HTR2C | P28335 | Membrane receptor | | 54 / 34 |
| Cannabinoid receptor 2 | CNR2 | P34972 | Membrane receptor | | 1633 / 133 |
| Corticotropin-releasing factor receptor 1 | CRHR1 | P34998 | Membrane receptor | | 216 / 123 |
| Sodium-dependent serotonin transporter | SLC6A4 | P31645 | Transporter | | 12 / 33 |
| Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform | PIK3CD | O00329 | Enzyme | | 100 / 135 |
| Cathepsin L1 | CTSL | P07711 | Cysteine Protease | | 159 / 65 |
| Epidermal growth factor receptor | EGFR | P00533 | Tyr Kinase | | 674 / 53 |
| Cyclin-dependent kinase 2 | CDK2 | P24941 | Ser_Thr Kinase | | 160 / 518 |

合成预测




**Elsevier Life Science Solution中已经开始融入不同领域的AI技术**

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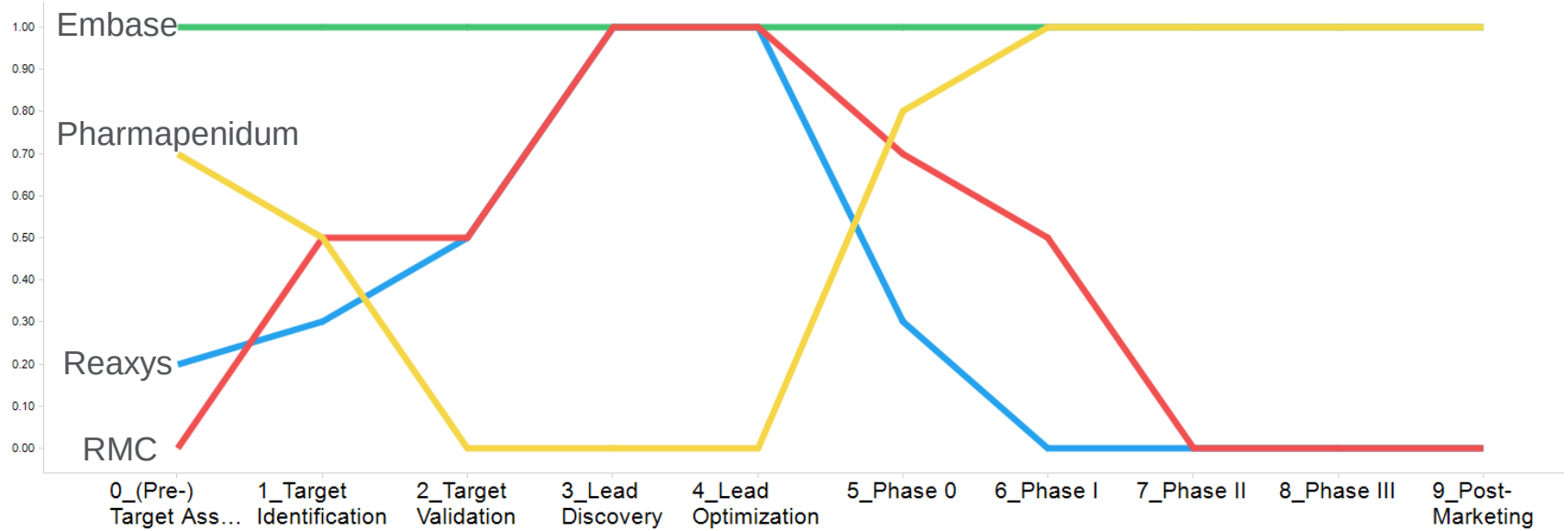
# Elsevier 生命科学解决方案对不同药物研发阶段的支持力度

| (Pre-)Target Assessment | Target Identification | Target Validation | Lead Discovery | Lead Optimization | Phase 0 | Phase I | Phase II | Phase III | Post-Marketing |
|---|---|---|---|---|---|---|---|---|---|
| • Pharmapenidum<br>• Embase | • Pharmapenidum<br>• Embase<br>• Reaxys<br>• RMC | • Embase<br>• Reaxys<br>• RMC | • Embase<br>• Reaxys<br>• RMC | • Reaxys<br>• RMC<br>• Embase | • Pharmapendium<br>• Reaxys<br>• RMC<br>• Embase | • Pharmapendium<br>• Embase<br>• RMC | • Pharmapendium<br>• Embase | • Pharmapendium<br>• Embase | • Pharmapendium<br>• Embase |



# 案例讨论


- Ertugliflozin，Empagliflozin，Dapagliflozin，Canagliflozin是目前已经上市的SGLT2靶点上的二型糖尿病的小分子药物，如果想继续开发在SGLT2靶点的药物，那么项目的立足点在哪里？
- 需要解决的问题
  - 项目立项：需要开发一个什么样的SGLT2的药物，才可以继续在市场上立足
  - 结构设计：在相同/类似的母核前提下，如何规避专利风险，设计新分子
  - 分子合成：新分子的合成策略是什么
  - 临床试验：药物安全的市场Benchmark是什么，临床终点是什么，DDI如何，如何体现新分子优势
  - 上市后管理：药物警戒如何进行

***TIPS：***

药物设计是一个极其复杂和严谨的过程，且有很多不可控因素，本案例中出现的所有结论，分子结构的设计，均出于案例本身的需求与假设。

# 项目立项

这个阶段，我们需要解决:

- 有哪些“临床未满足”需求存在?
- 他们的原因是什么?
- 我们可以选择哪一个进行开发?

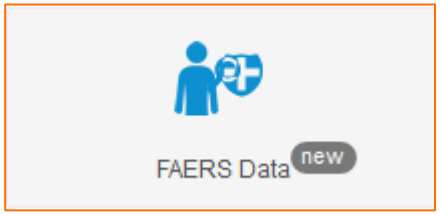
Elsevier Life Solution:

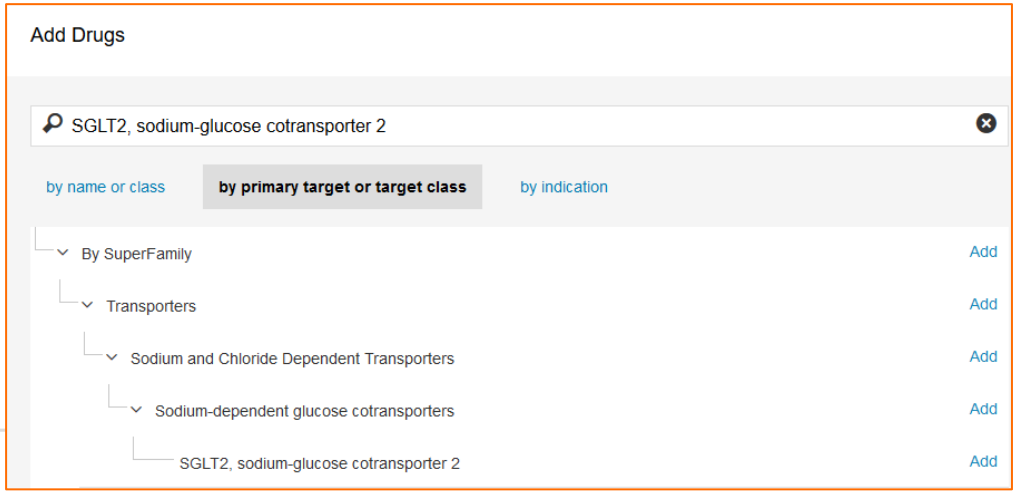
- PharmaPendium帮助找到这些“临床未满足需求”
- Reaxys帮助找到在结构上的原因
- Embase帮助寻找生物医学上的原因

# 项目立项

(Pre-)Target Assessment → Target Identification → Target Validation → Lead Discovery → Lead Optimization → Phase 0 → Phase I → Phase II → Phase III → Post-Marketing

- 开发一个什么样的SGLT2的药物，可以继续在市场上立足
  - 当前SGLT2药物会存在哪些问题，寻求新药设计突破点
    - 靶点选择性如何
    - 代谢稳定性如何
    - ……

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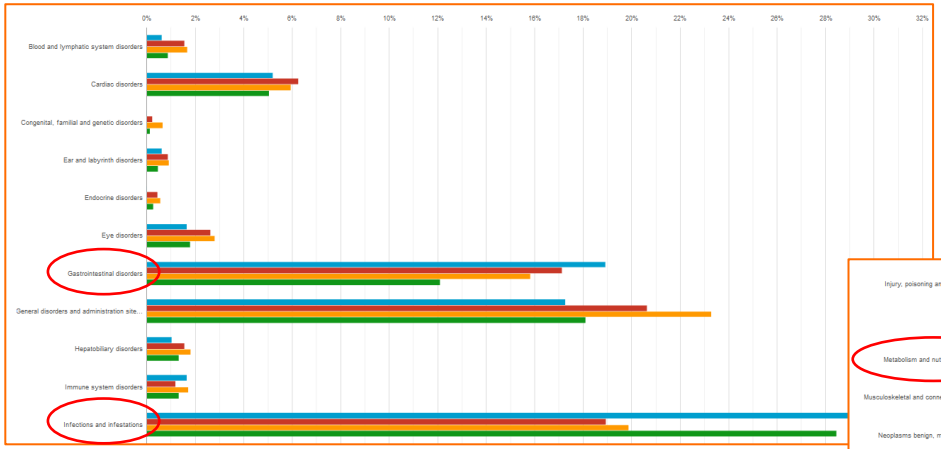
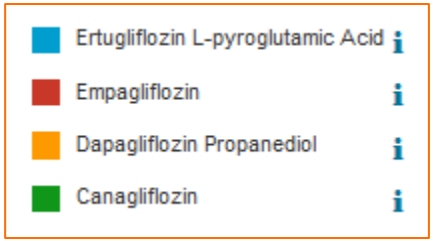
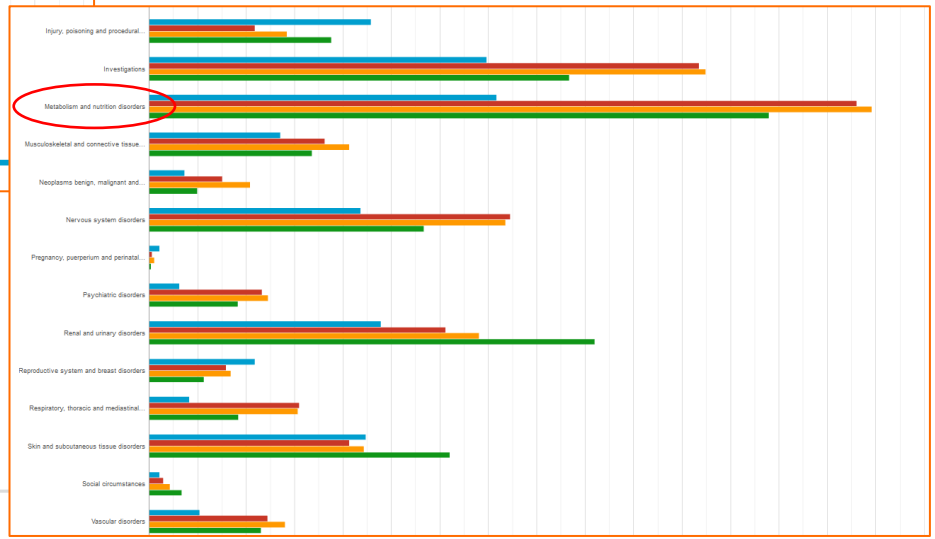
# 已经上市药物的临床表现




最主要的不良临床表现：

- 感染
- 代谢和营养失调
- 给药位点失调和胃肠混乱

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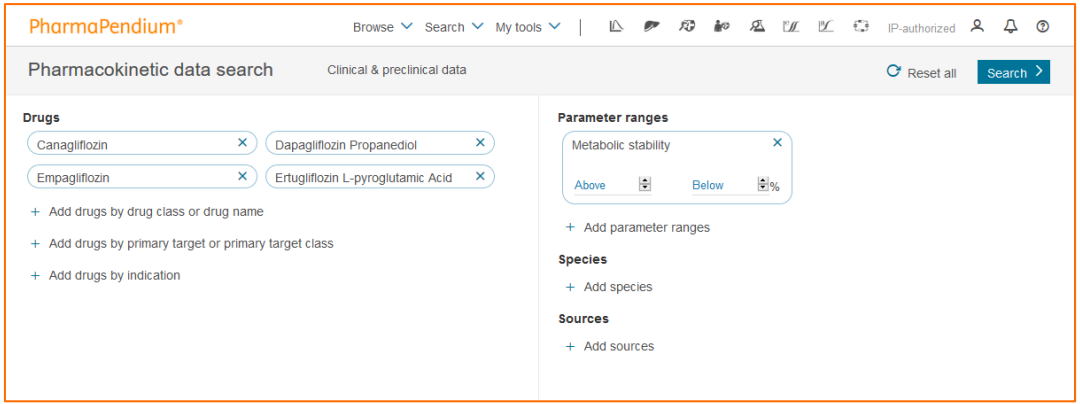
# 代谢稳定性判断





Preclinical Data | Clinical Data | All Data

Hide Filters

| ID | Drug | Species | Study Group | Dose | Route | Parameter | Parameter Value | SD |
|---|---|---|---|---|---|---|---|---|
| 1 | Dapagliflozin Propanediol (14C-labelled) | Human | healthy | 50 mg | Oral | Metabolic stability(AUC0-12 h-based) | 39.0 % | |
| 2 | Empagliflozin (14C-labelled) | Human | | Unreported | Oral | Metabolic stability | 75.5% - 77.4% | |
| 3 | Ertugliflozin L-pyroglutamic Acid (14C-labelled) | Human | healthy | 25 mg | Oral | Metabolic stability | 49.9 % | |

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# 经过分析发现

- SGLT2/SGLT1靶点，肾脏主要表达SGLT2，抑制SGLT2会抑制肾脏对葡萄糖的吸收，肠道主要表达SGLT1，抑制SGLT1会抑制胃肠道对葡萄糖的吸收。
  - 感染是由于药物抑制肾脏中的SGLT2靶点，使得尿液中葡萄糖浓度较高，容易滋生细菌，发生感染
  - 但是如果同时也抑制SGLT1，就会导致肠胃混乱
  - SGLT1也会在心脏有所表达，所以如果对于糖尿病患者而言，长期用药可能会增加心脏类的风险
- 几款SGTL2的抑制剂连接键都是氧苷键，体内容易被葡萄糖苷酶水解导致产生稳定性较差的代谢产物
- 所以我们想设计一款符合如下要求的SGLT2药物：
  - SGLT2/SGLT1选择性强
  - 提高代谢稳定性

# 结构设计与化合物合成

这个阶段，我们需要解决:

- 全新分子设计
- 全新分子合成
- 全新化合物专利评估

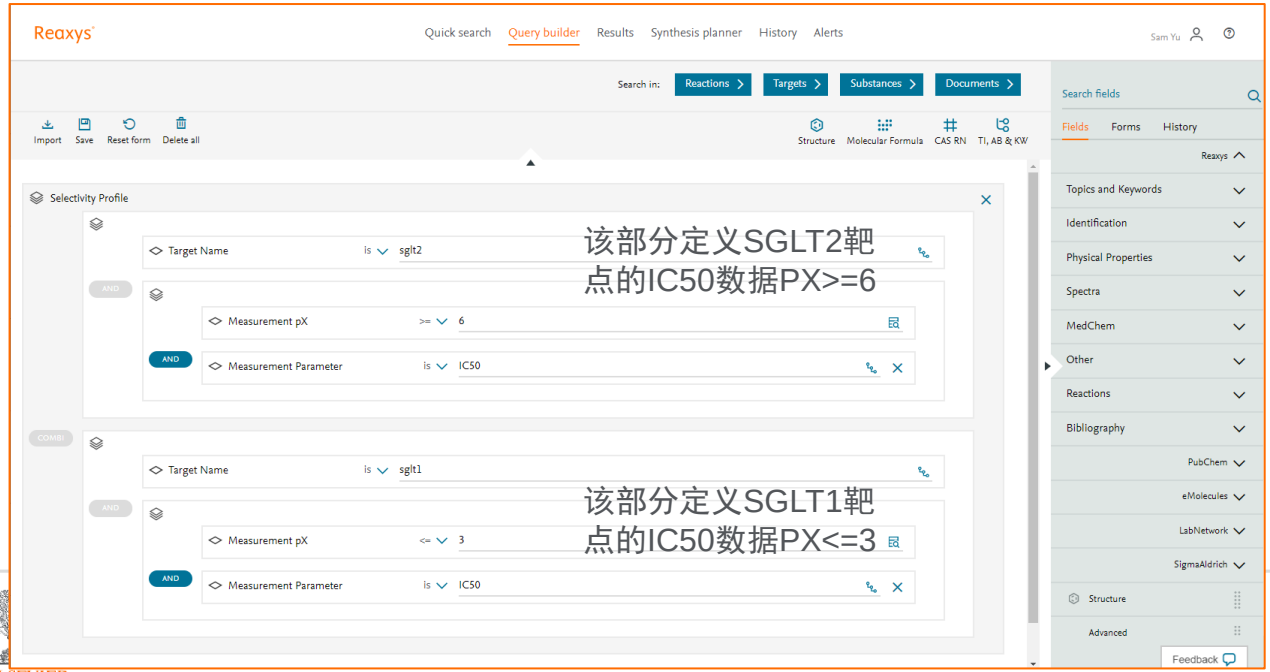
Elsevier Life Solution:

- RMC帮助构建SAR，帮助结构设计
- Reaxys / Reaxys AI ，帮助提供化合物合成线路
- Reaxys 帮助做专利评估
- RMC新功能帮助做靶点预测

# 结构设计

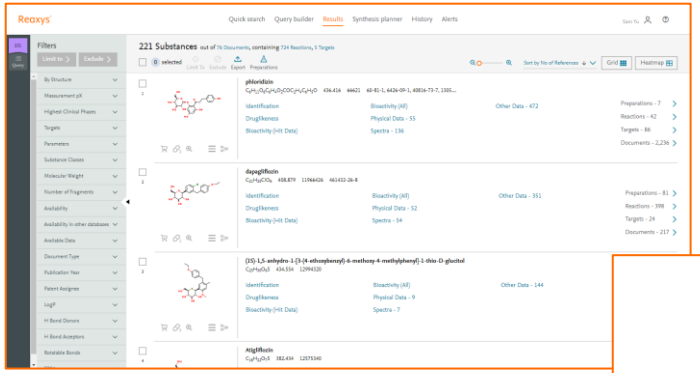
(Pre-)Target Assessment | Target Identification | Target Validation | Lead Discovery | Lead Optimization | Phase 0 | Phase I | Phase II | Phase III | Post-Marketing

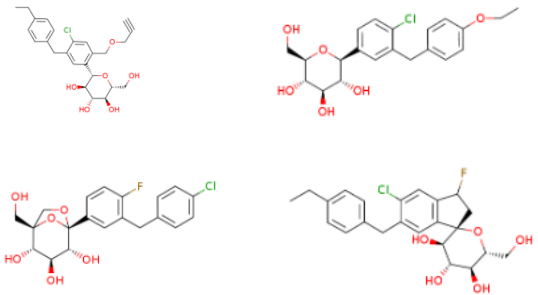
- 利用RMC获取在SGLT2和SGLT1上具有靶点选择性的化合物进行结构分析




Reaxys/RMC提供“靶点选择性策略”的标准检索式，我们对其稍作修改，添加测量参数是IC50，对已知化合物进行筛选。

# RMC给出的结果



文献中报道的左侧化合物在SGLT2/SGLT1靶点上的活性数据

| Substances | Targets | Sodium/glucose cotransporter 1 | Sodium/glucose cotransporter 2 |
|---|---|---|---|
| (2S,3R,4R,5S,6... ,5-triol | | 1 | 9.5 |
| dapagliflozin | | 1 | 9.3 |
| (1S,2S,3S,4R,5S...,4-triol | | 1 | 9.1 |
| (1S,3'R,4'S,5'S,6... 5'-triol | | 1 | 9 |
| (2S,3R,4R,5S,6... ,5-triol | | 1 | 8.8 |
| (1S)-1,5-anhyd... glucitol | | 2.4 | 8.8 |
| (1S,2S,3S,4R,5S...,4-triol | | 1 | 8.7 |
| (1S,3'R,4'S,5'S,6... 5'-triol | | 1 | 8.7 |
| (1S)-1,5-anhyd... glucitol | | 2.5 | 8.7 |
| (1S)-1,5-anhyd... glucitol | | 2.9 | 8.7 |

Feedback

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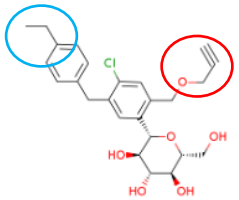
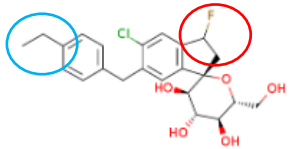
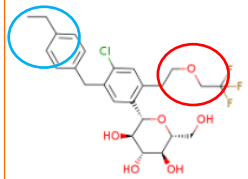
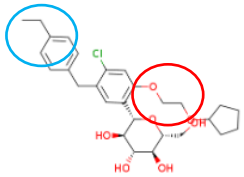
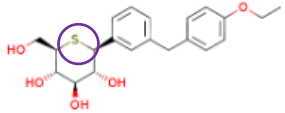
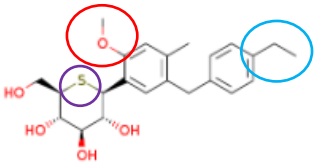
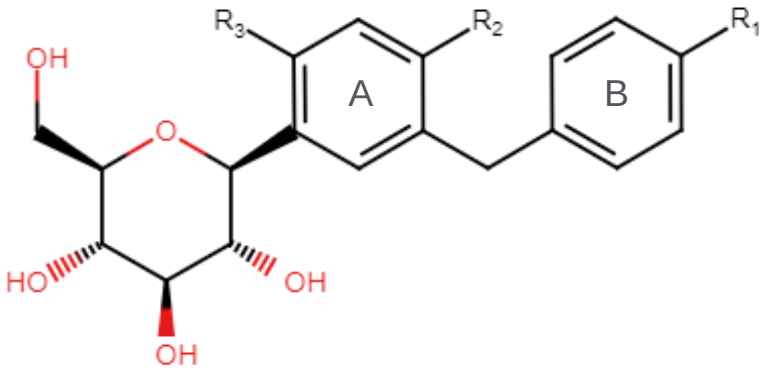
# 一些比较有意思的结构

| 化合物结构 | 活性差异 | 化合物结构 | 活性差异 |
| --- | --- | --- | --- |
|  | SGLT2=9.5<br>SGLT1=1 |  | SGLT2=9<br>SGLT1=1 |
|  | SGLT2=6<br>SGLT1=1 |  | SGLT2=6<br>SGLT1=1 |
|  | SGLT2=7.1<br>SGLT1=1.5 |  | SGLT2=8.7<br>SGLT1=2.5 |

构效关系：

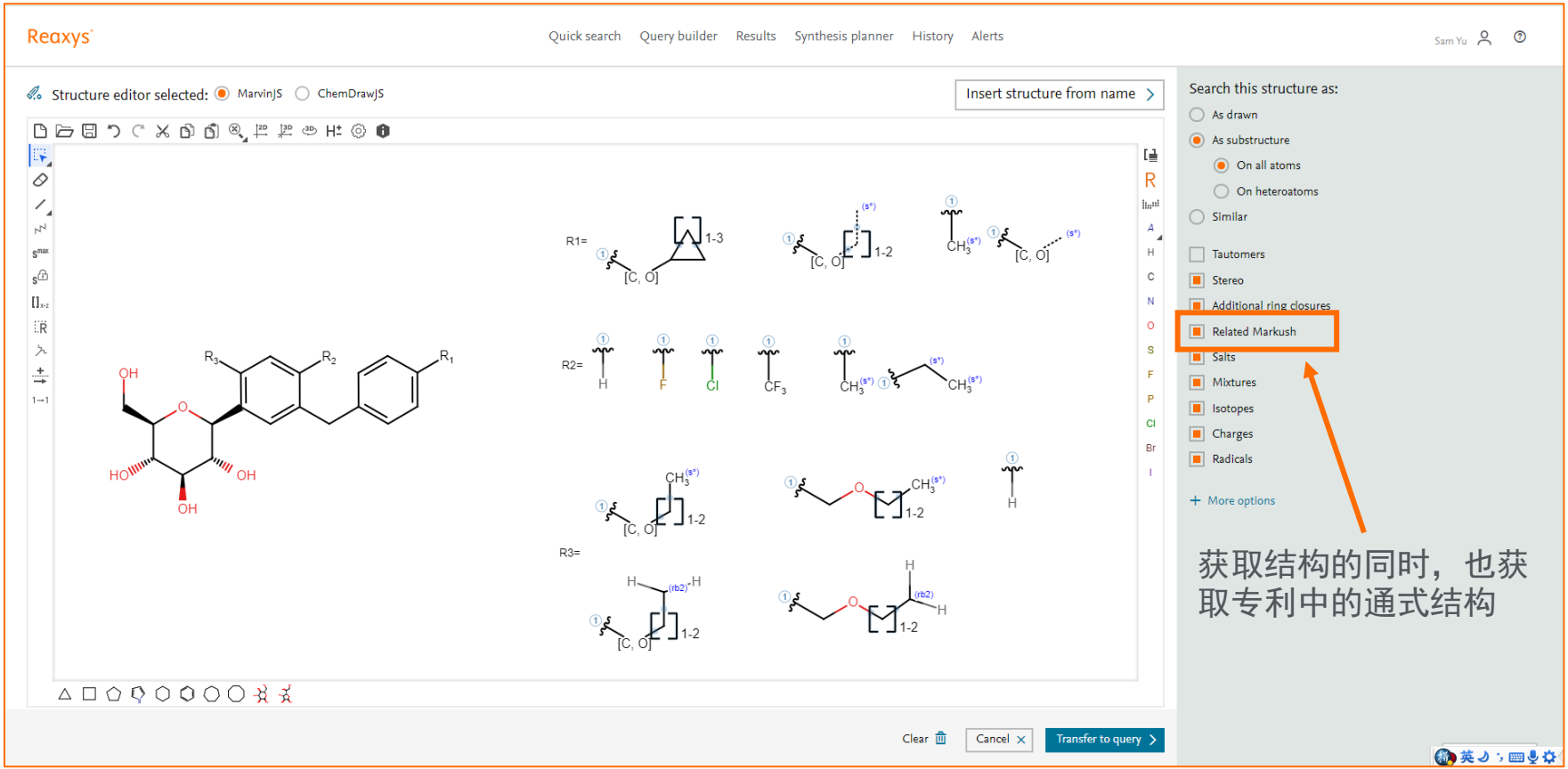
- 红色部分支链的长短对于SGLT2活性是有影响的，但是如果链长达到一定程度，则没太多效用，红色部分短链为好，含O的链会有增强活性的影响
- 紫色部分应该对SGLT1是有正向影响，但是可以通过调节红色部分的长短来消除这部分的影响
- 兰色部分过长对于SGLT2的活性没有正向影响，所以还是以短的链为主

# 依据分析结果设计出来的通式结构



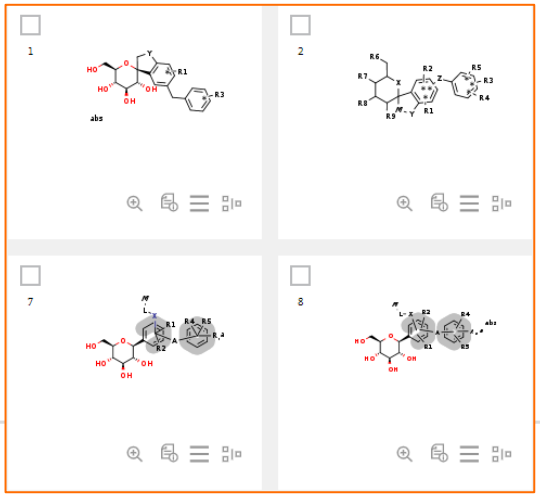

- 保持AB环和glucose的主要活性部分，考虑R1,R2,R3的变构
- R1为小位阻烷基，烷氧基，环烷基
- R2为H，F，Cl，CF3，Me，Et
- R3为H，或者短的烷基，烷氧基，醚，H，且允许和自身成环

# 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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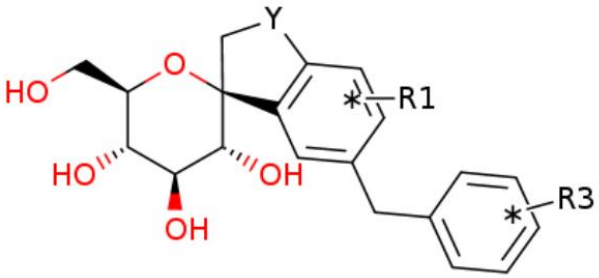
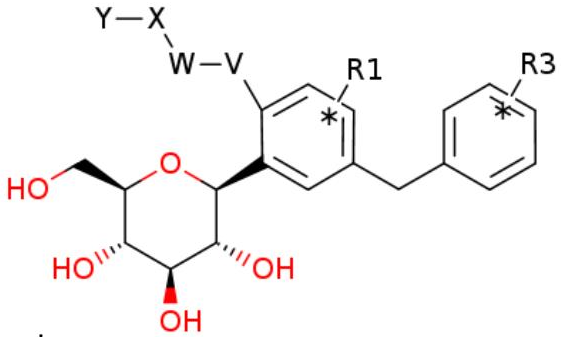
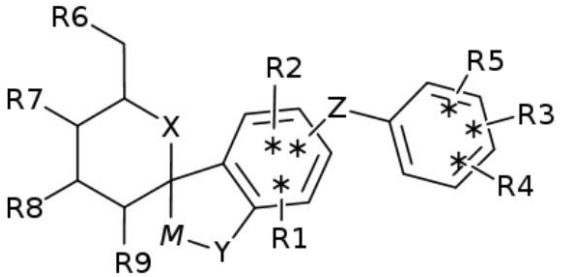
# 一些比较有意思的Markush结构



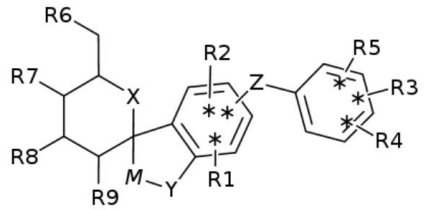



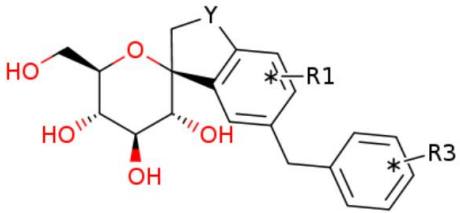

***Tips：***

- 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

# Markush结构在专利中的表达方式

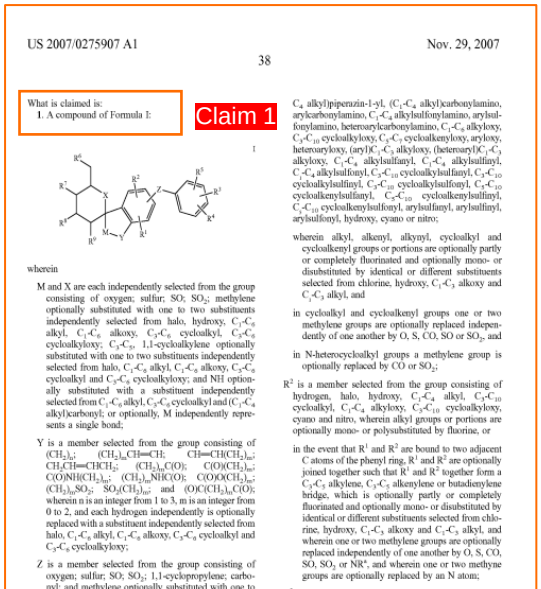



Claim 1




Claim 10

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



US 2007/0275907 A1 Nov. 29, 2007
38

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, $C_1$-$C_3$ alkyl, $C_1$-$C_4$ alkoxy, $C_3$-$C_4$ cycloalkyl, $C_3$-$C_4$ cycloalkyloxy; $C_3$-$C_5$ 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, $C_3$-$C_6$ cycloalkyldenmethyl, $(C_4$-$C_{10}$ 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, $C_1$-$C_4$ 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, $(C_1$-$C_4$ alkylamino)carbonyl, arylcarbonylamino, arylsulfonylamino, heteroarylcarbonylamino, $C_1$-$C_6$ alkyloxy, $C_3$-$C_{10}$ cycloalkyloxy, $C_3$-$C_5$ 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 methyne 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, $C_2$-$C_{10}$ 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, $(C_3$-$C_{10}$ cycloalkyloxy)$C_1$-$C_3$ alkyl, $C_2$-$C_4$ alkenyl, $C_3$-$C_6$ cycloalkyldienmethyl, 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-1)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, $C_3$-$C_5$ cycloalkenyloxy, aryloxy, heteroaryloxy, $(C_1$-$C_4$ alkenyl)$C_1$-$C_3$ alkyloxy, $(C_2$-$C_4$ alkynyl)$C_1$-$C_3$ 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, $(C_3$-$C_5)$cycloalkyloxy, $C_4$-$C_7$ cycloalkenyloxy, aryloxy, heteroaryloxy, $(C_3$-$C_5)$cycloalkyl-$(C_1$-$C_3)$alkyloxy, $(C_3$-$C_5)$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, $(C_3$-$C_5)$cycloalkyloxy-$(C_1$-$C_3)$alkyl, $(C_3$-$C_5)$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 $R^1$, $R^8$ 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.

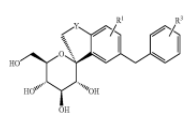
**7**. A compound of claim 1, wherein at least two of $R^6$, $R^7$, $R^8$ and $R^9$ are hydroxy.

**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:

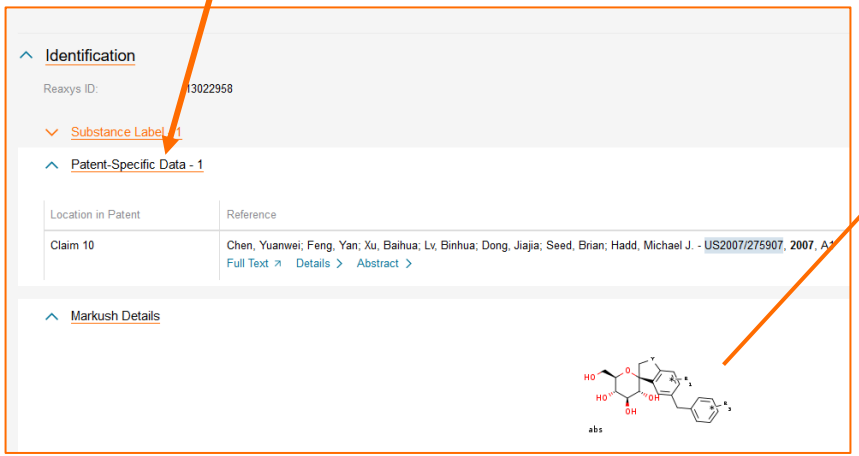
Claim 10



wherein

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

# 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$H=C$HC$H2 | | | |
| | (C$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 | | $d$e;$f$g |
| | alkenyl | 2-6C | | $d$e;$f$g |
| | alkynyl | 2-6C | | $d$e;$f$g |
| | cycloalkyl | 3-10C | 1-2 methylene groups o replaced by <$h> | $d$e;$f$g |
| | $cycloalkyl310-$alkyl13 | | | |
| | ($alkenyl24)$alkyloxy13 | | | |

提炼了出现的位置和Markush的结构细节。

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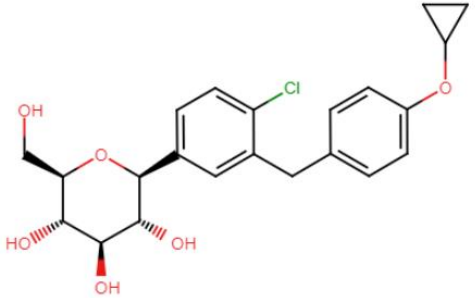
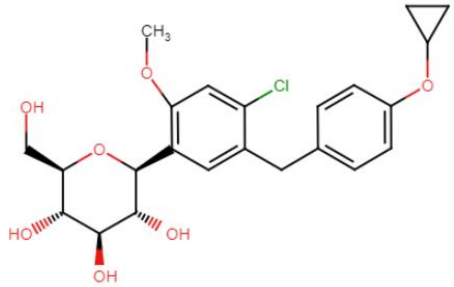
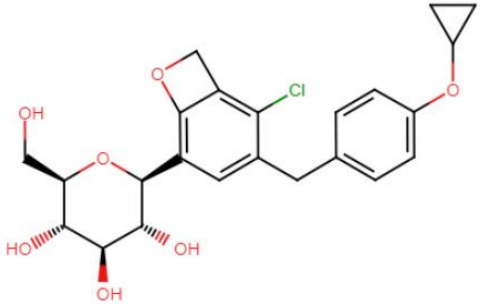
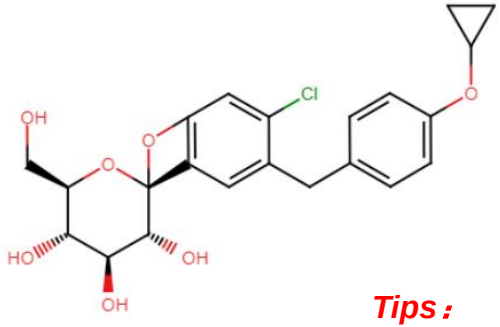
# 评估完专利后，设计一些全新化合物（假设下列结构无专利问题）



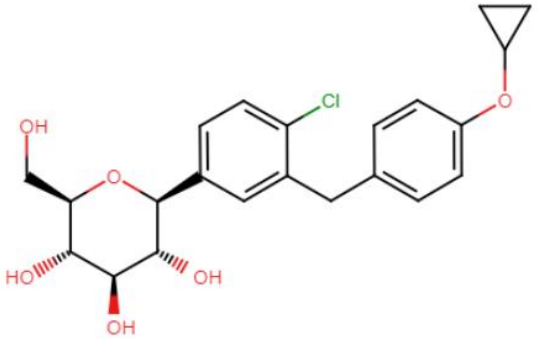




***Tips：***

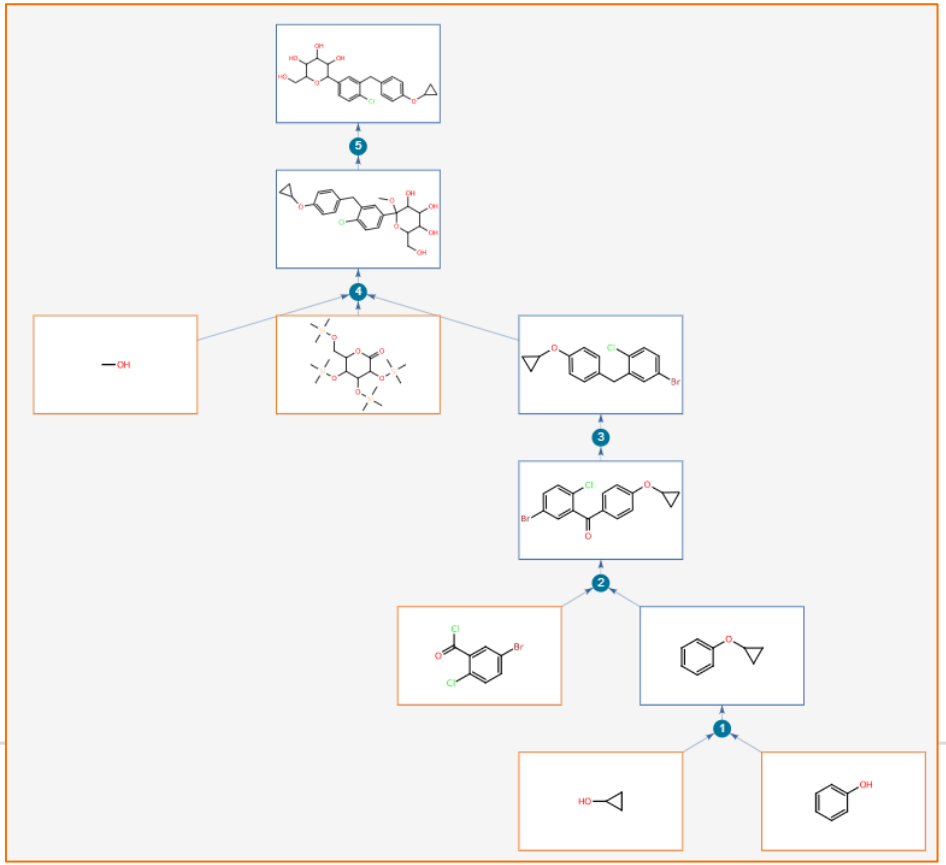
案例制作当天，Reaxys中没有相同结构。

# Reaxys AI帮助提供全新化合物合成策略，开拓思路




*Tips：*

- 对于全新分子，科研人员可以依据Reaxys中已有的反应，进行路线设计。
- 也可以利用Reaxys AI进行逆合成路线设计，Reaxys AI是一个基于自动提取规则和深度学习的逆合成工具

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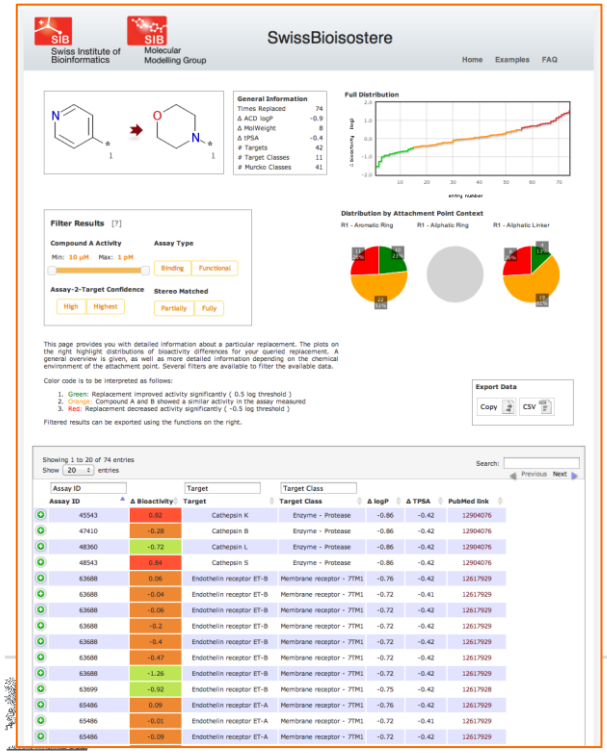
# RMC帮助全新化合物的靶点活性预测（该部分功能开发中）

## Matched Molecular Pair analysis




## Target Predictions

Target prediction

| Target | Common name | Uniprot ID | Target Class | Probability* | Known actives (3D / 2D) |
|---|---|---|---|---|---|
| Adenosine receptor A2a | ADORA2A | P29274 | Membrane receptor | | 584 / 465 |
| Adenosine receptor A2b | ADORA2B | P29275 | Membrane receptor | | 170 / 232 |
| Adenosine receptor A1 | ADORA1 | P30542 | Membrane receptor | | 488 / 591 |
| Adenosine receptor A3 | N/A | P33765 | Membrane receptor | | 690 / 639 |
| Neuropeptide Y receptor type 5 | NPY5R | Q15761 | Membrane receptor | | 299 / 149 |
| Cannabinoid receptor 1 | CNR1 | P21554 | Membrane receptor | | 1418 / 305 |
| 5-hydroxytryptamine receptor 2A | HTR2A | P28223 | Membrane receptor | | 108 / 42 |
| 5-hydroxytryptamine receptor 2C | HTR2C | P28335 | Membrane receptor | | 54 / 34 |
| Cannabinoid receptor 2 | CNR2 | P34972 | Membrane receptor | | 1633 / 133 |
| Corticotropin-releasing factor receptor 1 | CRHR1 | P34998 | Membrane receptor | | 216 / 123 |
| Sodium-dependent serotonin transporter | SLC6A4 | P31645 | Transporter | | 12 / 33 |
| Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform | PIK3CD | O00329 | Enzyme | | 100 / 135 |
| Cathepsin L1 | CTSL | P07711 | Cysteine Protease | | 159 / 65 |
| Epidermal growth factor receptor | EGFR | P00533 | Tyr Kinase | | 674 / 53 |
| Cyclin-dependent kinase 2 | CDK2 | P24941 | Ser_Thr Kinase | | 160 / 518 |

*Tips：*

- 属于RMC中的一个功能，开发中。

# 临床前，临床实验

这个阶段，我们需要解决:

- 药物安全的市场标准是什么?
- 如何与监管机构沟通新分子的优势?
- 新分子可能存在哪些DDI

Elsevier Life Solution:

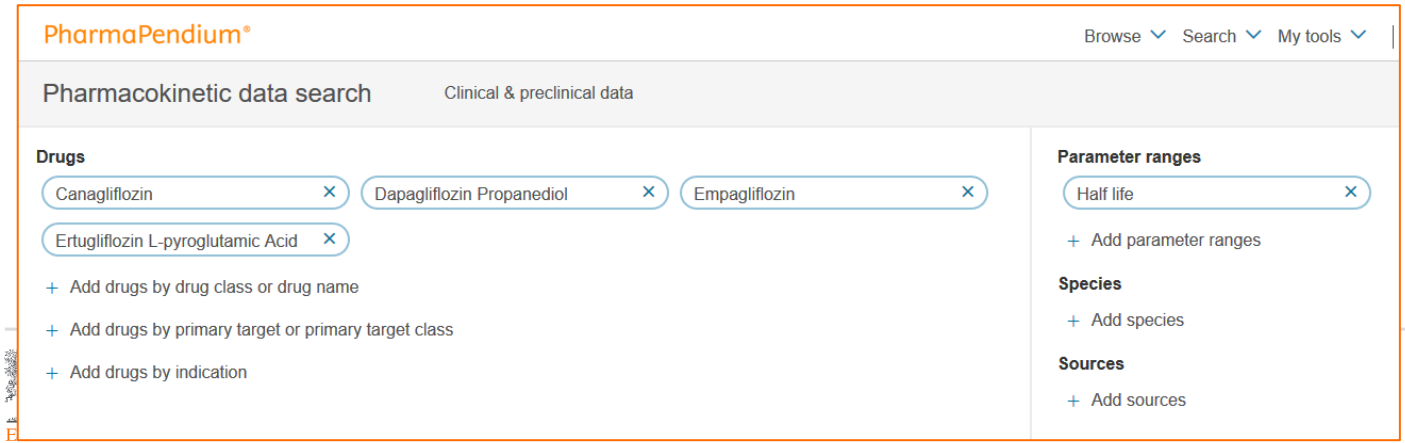
- PharmaPendium 帮助寻找市场标准
- PharmaPendium为与监管机构沟通提供证据.
- Embase 帮助找寻涉及临床试验的文献
- PharmaPendium DDIRC 帮助找寻潜在的DDI风险

# 临床前/临床试验

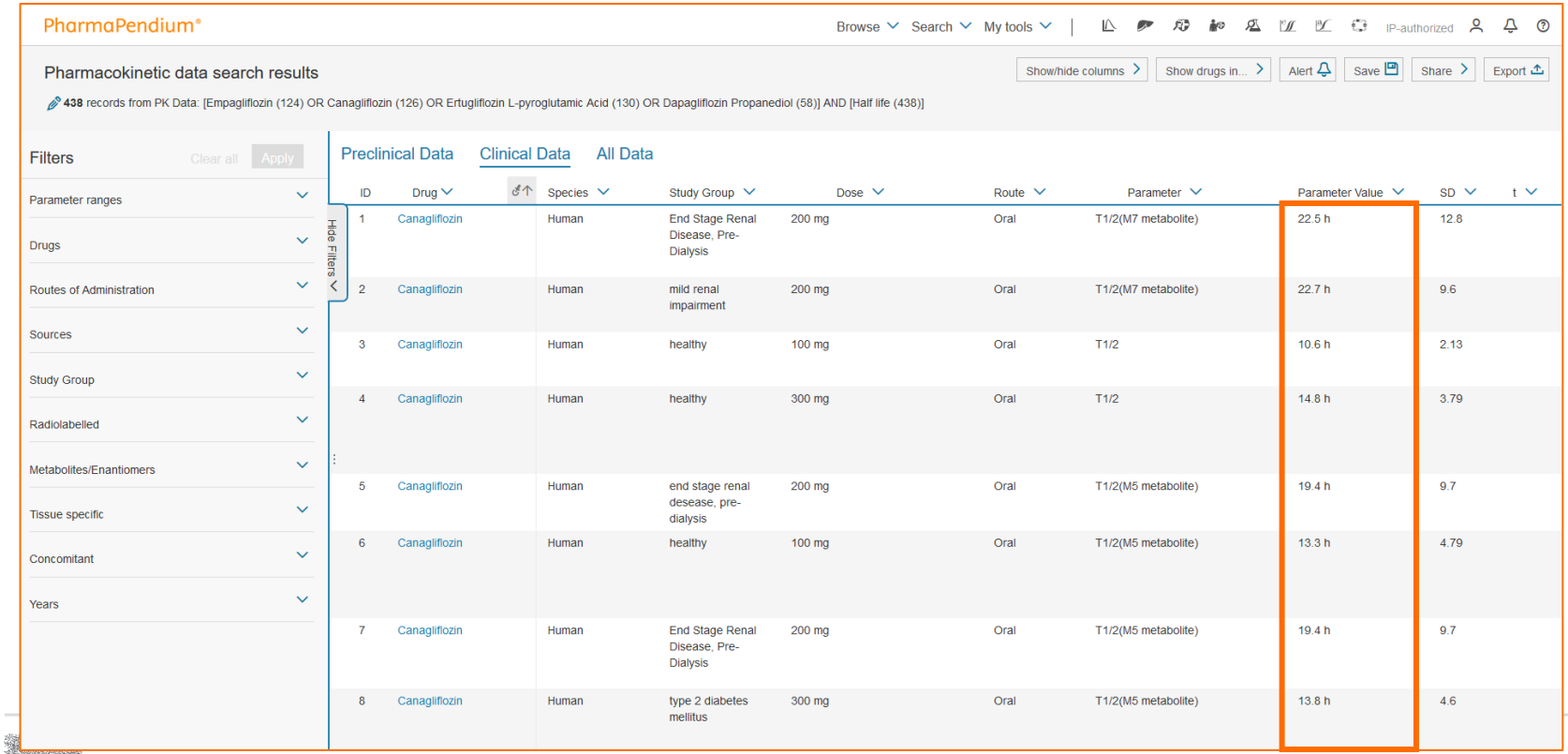
(Pre-)Target Assessment → Target Identification → Target Validation → Lead Discovery → Lead Optimization → Phase 0 → Phase I → Phase II → Phase III → Post-Marketing

Pharmacokinetic Data

- 当前市场SGLT2药物的半衰期是多少
- SGLT2药物的临床试验终点可以是什么
- 新分子可能会和哪些分子出现DDI?
- SGLT2药物的毒理药理文献有哪些？（临床药理，试验药理……）



# PharmaPendium中的结果



PharmaPendium®

Browse Search My tools IP-authorized

Pharmacokinetic data search results

Show/hide columns Show drugs in... Alert Save Share Export

438 records from PK Data: [Empagliflozin (124) OR Canagliflozin (126) OR Ertugliflozin L-pyroglutamic Acid (130) OR Dapagliflozin Propanediol (58)] AND [Half life (438)]

Filters Clear all Apply

- Parameter ranges
- Drugs
- Routes of Administration
- Sources
- Study Group
- Radiolabelled
- Metabolites/Enantiomers
- Tissue specific
- Concomitant
- Years

Hide Filters

Preclinical Data | Clinical Data | All Data

| ID | Drug | Species | Study Group | Dose | Route | Parameter | Parameter Value | SD | t |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Canagliflozin | Human | End Stage Renal Disease, Pre-Dialysis | 200 mg | Oral | T1/2(M7 metabolite) | 22.5 h | 12.8 | |
| 2 | Canagliflozin | Human | mild renal impairment | 200 mg | Oral | T1/2(M7 metabolite) | 22.7 h | 9.6 | |
| 3 | Canagliflozin | Human | healthy | 100 mg | Oral | T1/2 | 10.6 h | 2.13 | |
| 4 | Canagliflozin | Human | healthy | 300 mg | Oral | T1/2 | 14.8 h | 3.79 | |
| 5 | Canagliflozin | Human | end stage renal desease, pre-dialysis | 200 mg | Oral | T1/2(M5 metabolite) | 19.4 h | 9.7 | |
| 6 | Canagliflozin | Human | healthy | 100 mg | Oral | T1/2(M5 metabolite) | 13.3 h | 4.79 | |
| 7 | Canagliflozin | Human | End Stage Renal Disease, Pre-Dialysis | 200 mg | Oral | T1/2(M5 metabolite) | 19.4 h | 9.7 | |
| 8 | Canagliflozin | Human | type 2 diabetes mellitus | 300 mg | Oral | T1/2(M5 metabolite) | 13.8 h | 4.6 | |

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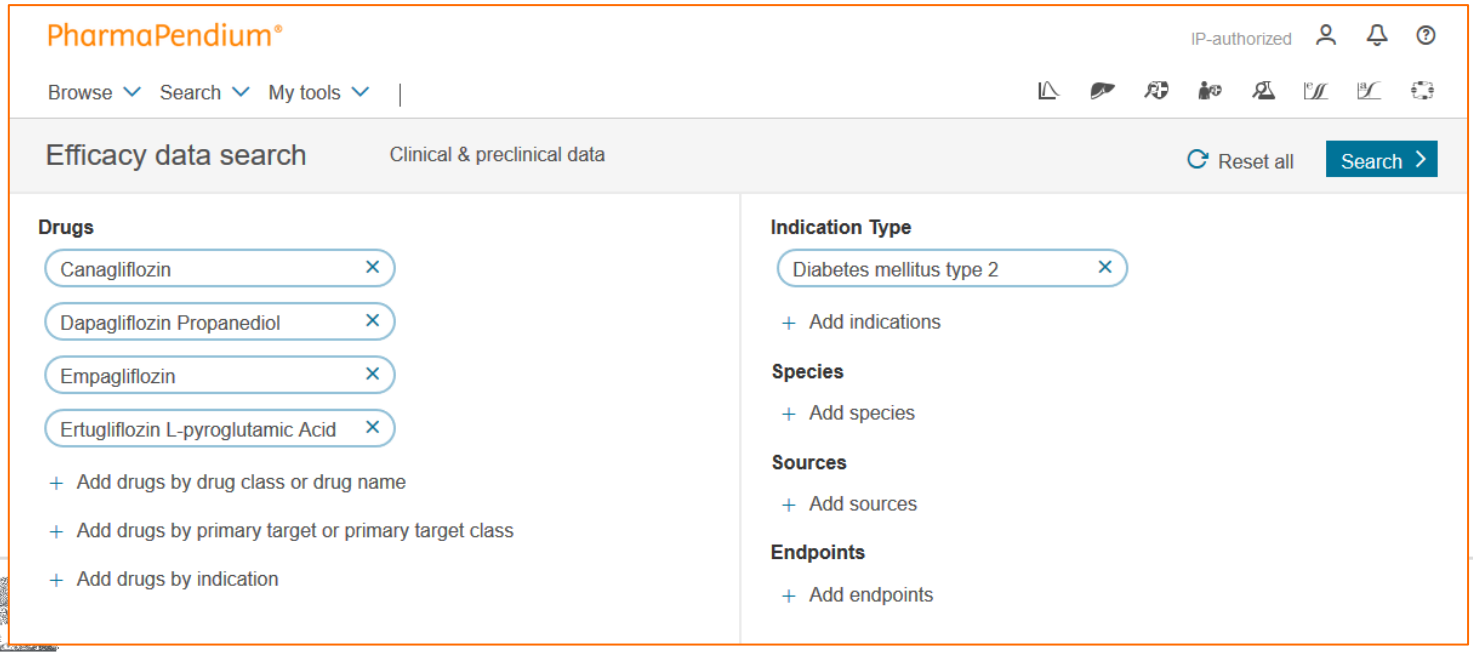
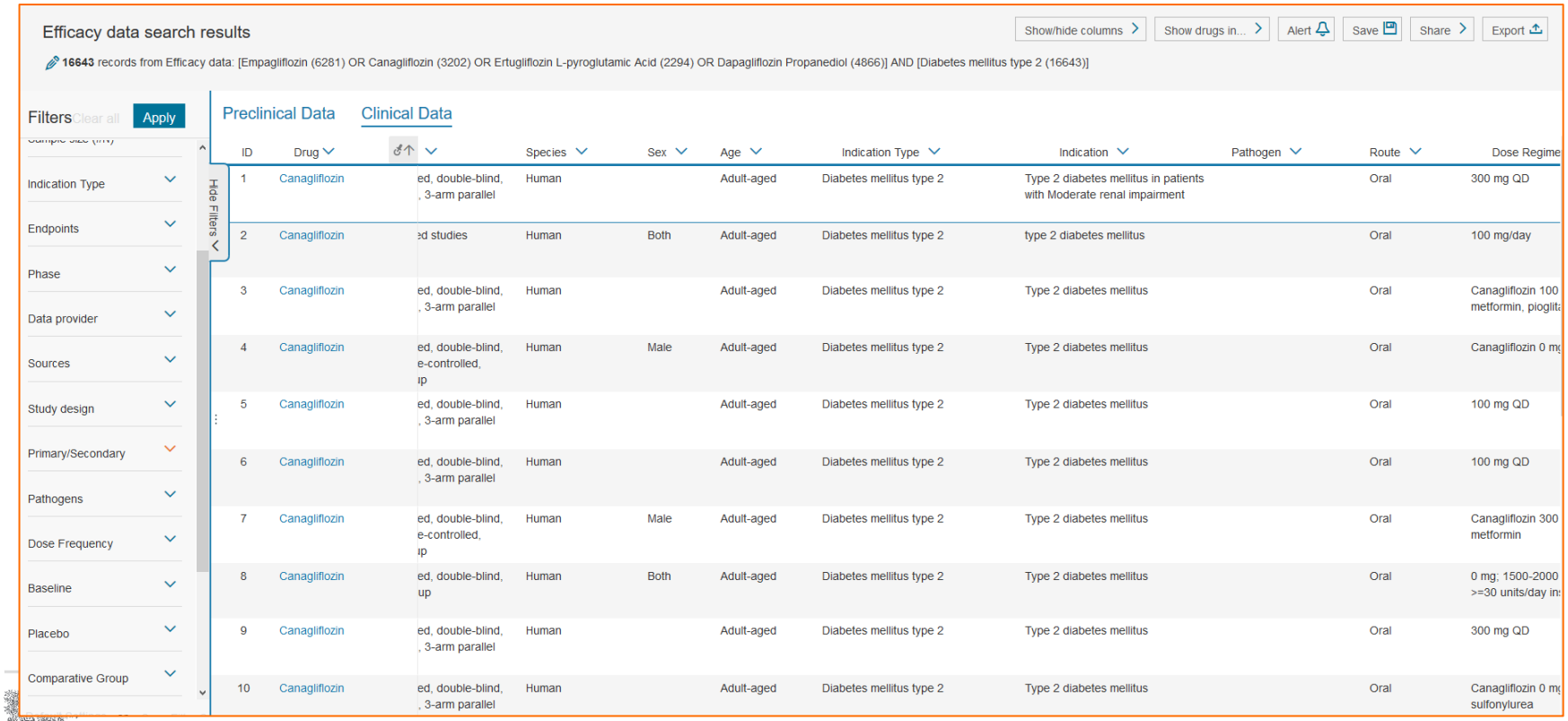
# SGLT2的主要临床终点有哪些

- 临床终点有哪些，主要次要终点有哪些？
- 有没有一些细节需要注意？

# PharmaPendium中的结果



Efficacy data search results

Show/hide columns | Show drugs in... | Alert | Save | Share | Export

**16643** records from Efficacy data: [Empagliflozin (6281) OR Canagliflozin (3202) OR Ertugliflozin L-pyroglutamic Acid (2294) OR Dapagliflozin Propanediol (4866)] AND [Diabetes mellitus type 2 (16643)]

Filters Clear all Apply

Indication Type
Endpoints
Phase
Data provider
Sources
Study design
Primary/Secondary
Pathogens
Dose Frequency
Baseline
Placebo
Comparative Group

Hide Filters

Preclinical Data | Clinical Data

| ID | Drug | | Species | Sex | Age | Indication Type | Indication | Pathogen | Route | Dose Regime |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Canagliflozin | ed, double-blind, , 3-arm parallel | Human | | Adult-aged | Diabetes mellitus type 2 | Type 2 diabetes mellitus in patients with Moderate renal impairment | | Oral | 300 mg QD |
| 2 | Canagliflozin | ed studies | Human | Both | Adult-aged | Diabetes mellitus type 2 | type 2 diabetes mellitus | | Oral | 100 mg/day |
| 3 | Canagliflozin | ed, double-blind, , 3-arm parallel | Human | | Adult-aged | Diabetes mellitus type 2 | Type 2 diabetes mellitus | | Oral | Canagliflozin 100 metformin, pioglit |
| 4 | Canagliflozin | ed, double-blind, e-controlled, ip | Human | Male | Adult-aged | Diabetes mellitus type 2 | Type 2 diabetes mellitus | | Oral | Canagliflozin 0 m |
| 5 | Canagliflozin | ed, double-blind, , 3-arm parallel | Human | | Adult-aged | Diabetes mellitus type 2 | Type 2 diabetes mellitus | | Oral | 100 mg QD |
| 6 | Canagliflozin | ed, double-blind, , 3-arm parallel | Human | | Adult-aged | Diabetes mellitus type 2 | Type 2 diabetes mellitus | | Oral | 100 mg QD |
| 7 | Canagliflozin | ed, double-blind, e-controlled, ip | Human | Male | Adult-aged | Diabetes mellitus type 2 | Type 2 diabetes mellitus | | Oral | Canagliflozin 300 metformin |
| 8 | Canagliflozin | ed, double-blind, up | Human | Both | Adult-aged | Diabetes mellitus type 2 | Type 2 diabetes mellitus | | Oral | 0 mg; 1500-2000 >=30 units/day in |
| 9 | Canagliflozin | ed, double-blind, , 3-arm parallel | Human | | Adult-aged | Diabetes mellitus type 2 | Type 2 diabetes mellitus | | Oral | 300 mg QD |
| 10 | Canagliflozin | ed, double-blind, , 3-arm parallel | Human | | Adult-aged | Diabetes mellitus type 2 | Type 2 diabetes mellitus | | Oral | Canagliflozin 0 m sulfonylurea |

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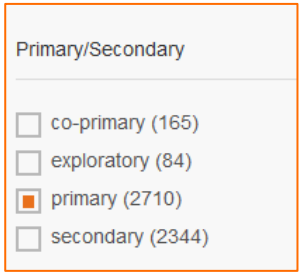
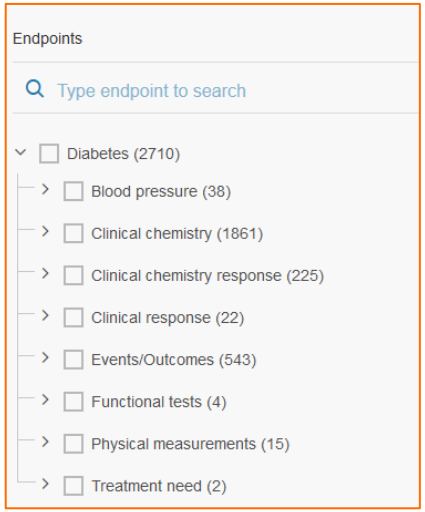
# Pharmapendium中的筛选

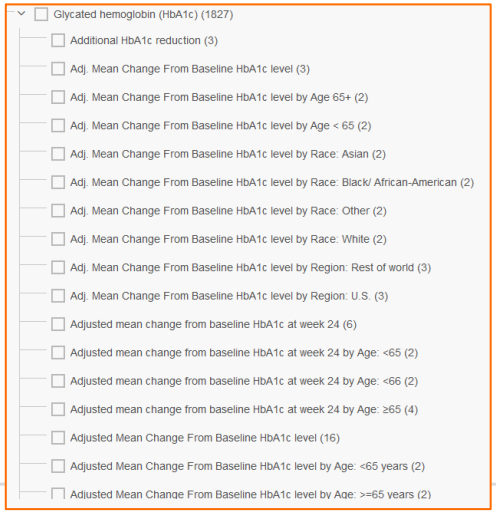


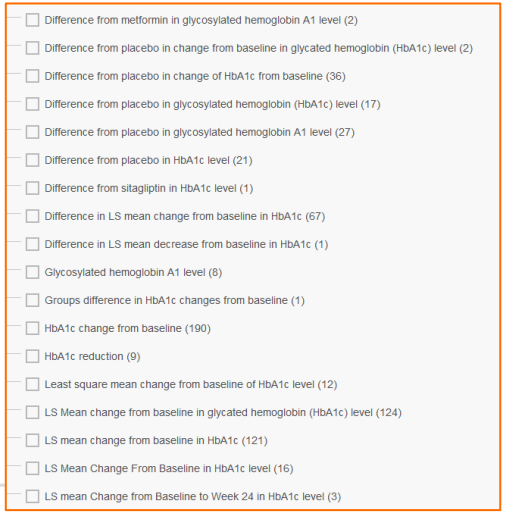

临床终点分类




***Tips：***

不同的临床设计中，对于同一类型终点定义不同，PharmaPendium标准化分类能够便捷检索，获取细节

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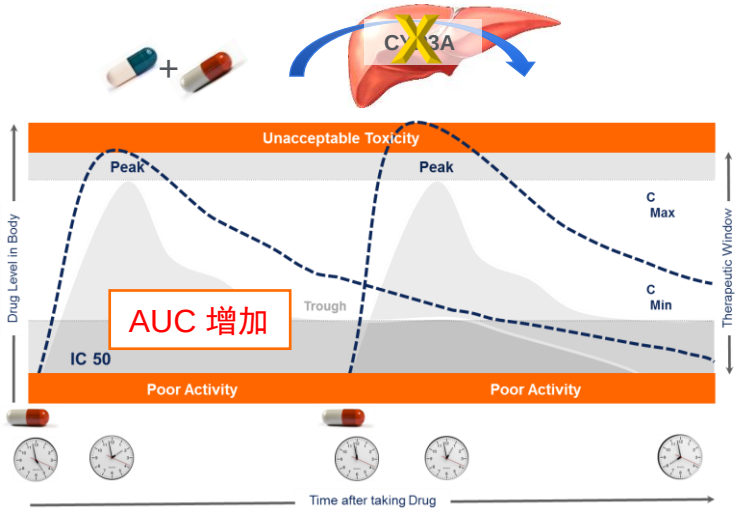
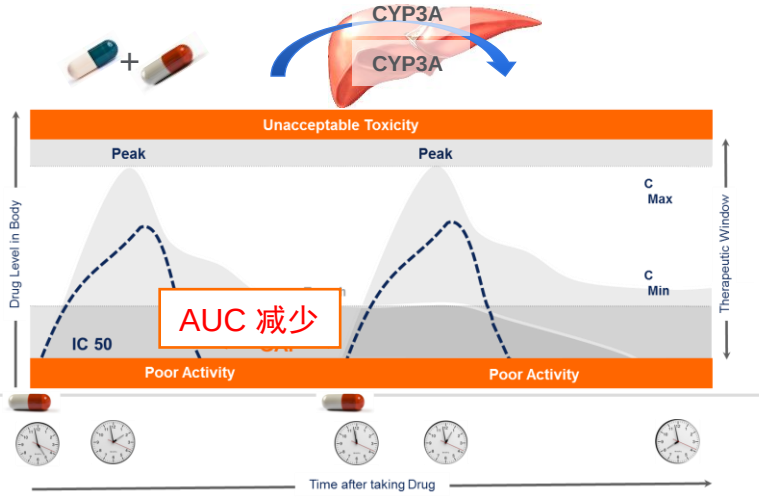
# Drug Drug Interaction（DDI）：早期和持续评估至关重要

- 据FDA称，与DDI相关的药物不良反应报道数量正在上升。
  - 越来越多的药物，以及更多的药物联用方案被用于临床治疗，比以往任何时候都多
  - 药物-药物相互作用可增加毒性或降低临床疗效。

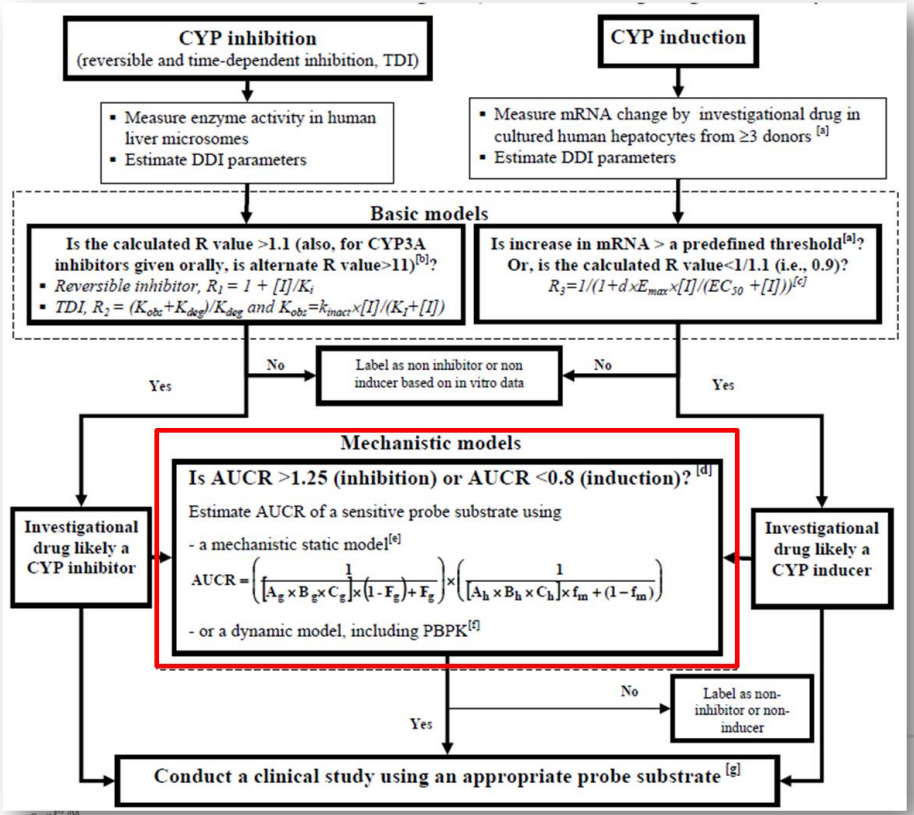
*DDI情况之一*：
药物A由CYP3A代谢，药物B抑制CYP3A的活性，药物A不再以相同的速率代谢，导致毒性浓度的累积




*DDI情况之二*：
药物A由CYP3A代谢，药物B诱导CYP3A的活性，药物A不再以相同的速率代谢，导致导致浓度降低，疗效下降。



# PharmaPendium中DDI Risk计算器，依据FDA指南设计




**Guidance for Industry Drug Interaction Studies**
**Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations**
**February 2012**

*“本指南反映了监管机构的观点，即在药物开发过程中，作为对药物安全性和有效性的充分评估的一部分，应确定研究性新药和其他药物之间的药代动力学相互作用。”*

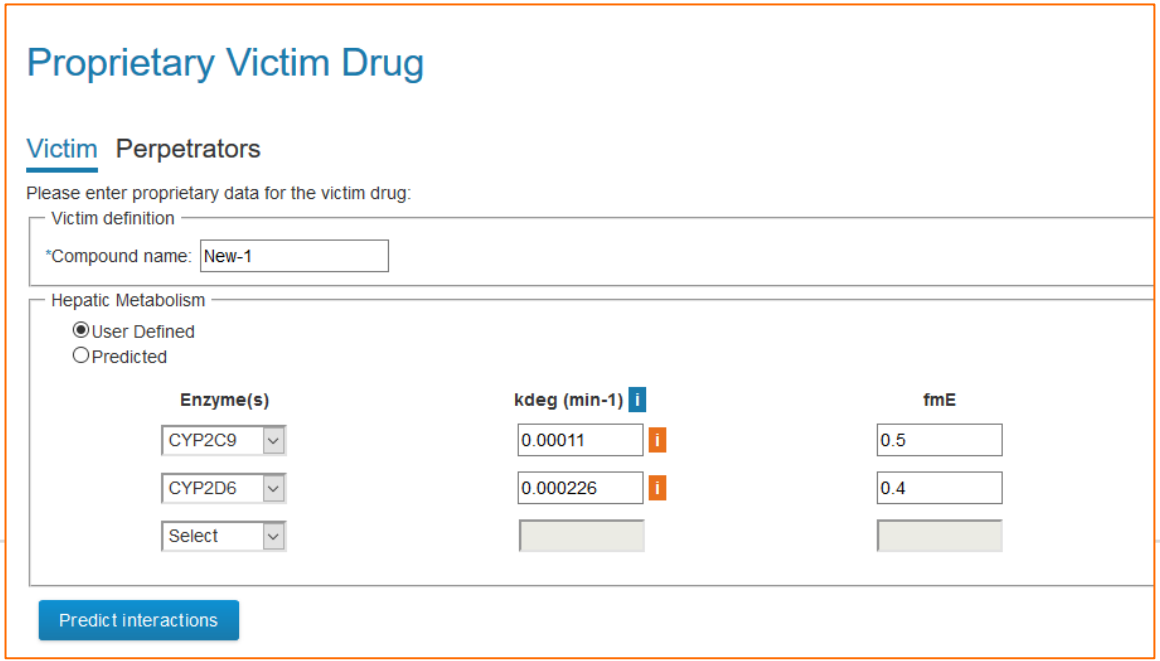
# PharmaPendium中DDI Risk计算器，帮助预测新分子的可能DDI风险


假设：

- 假设新分子可以被CYP2C9代谢，代谢率为50%
- 假设新分子可以被CYP2D6代谢，代谢率为40%

***Tips：***

- Victim：影响其他药物的药代动力学
- Perpetrators：由于与其他药物的作用，从而影响了自身的药代动力学。

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# PharmaPendium中的结果

**直接给出可能出现风险的药物，用于决策：**

- 新分子可能由于过多的药物相互作用问题，导致在与其他药联用时需要改变剂量使用，或者联用药物需要改变剂量
- 是否有任何相互作用需要额外的治疗监测
- 如果减低剂量仍然不能降低风险，是否应该有药物联用的限制使用措施。

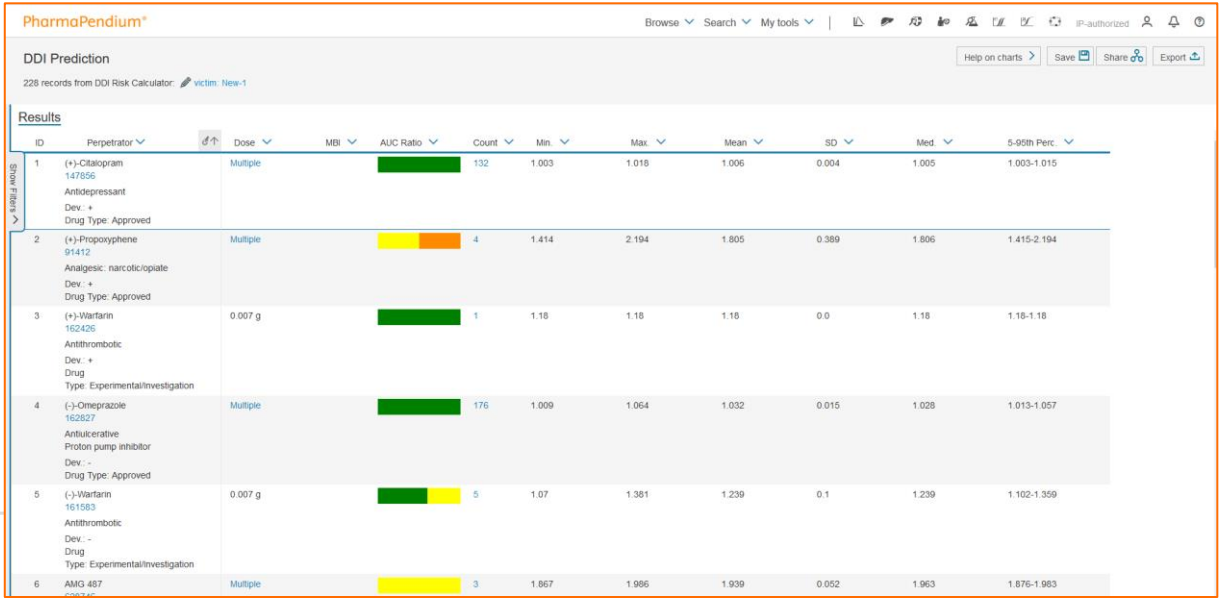
**Bar chart information**

The bar chart displayed in the DDI table is a color coded graphical overview of the risk assessment.

Color codes represent AUCi/AUC ratio ranges corresponding to the FDA classification [1] of CYP inhibitor and inducer potency. The size of each colored segment in the bar represents the percentage of the total number of calculated AUC ratios (for a given victim/perpetrator couple) that falls into one of the following categories:

| Category | AUC ratio range | | | Colour |
|---|---|---|---|---|
| Risk(Induction) | | AUC ratio < | 0.8 | |
| No risk | 0.8 | ≤ AUC ratio < | 1.25 | |
| Low risk | 1.25 | ≤ AUC ratio < | 2 | |
| Medium risk | 2 | ≤ AUC ratio < | 5 | |
| High risk | 5 | ≤ AUC ratio | | |

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory...

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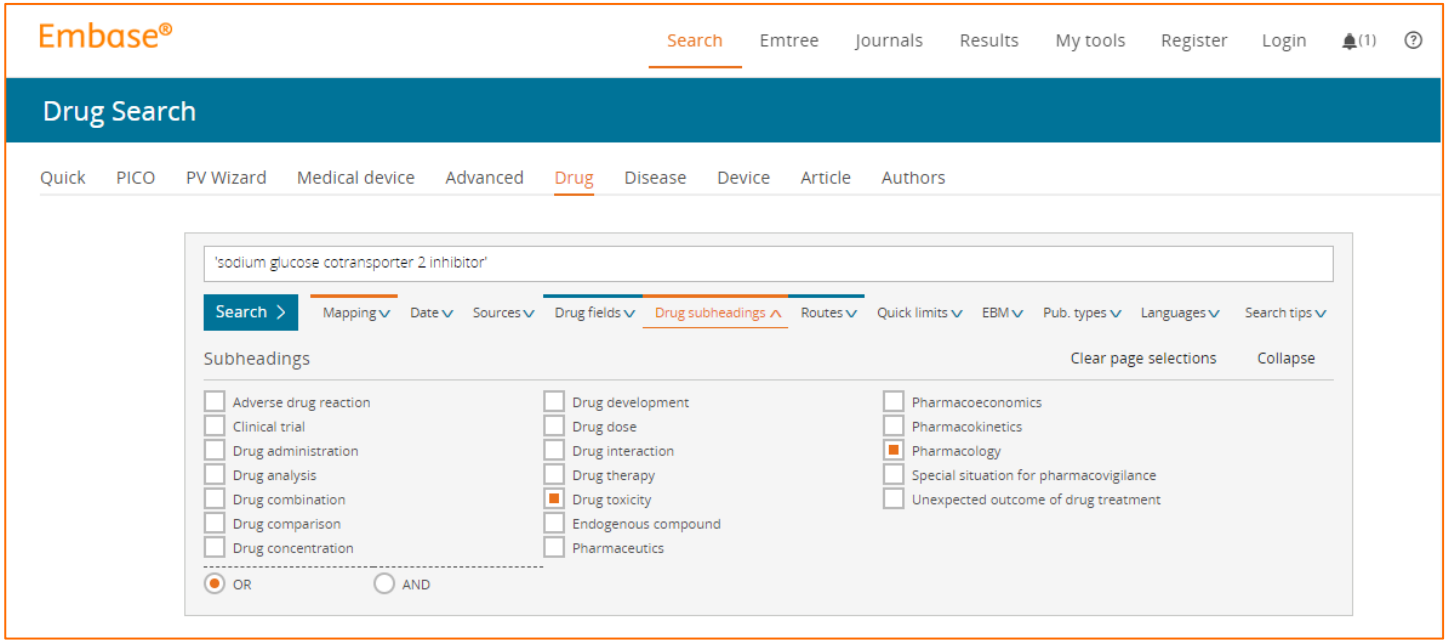
# SGLT2药物的毒理药理文献有哪些？（临床药理，试验药理……）




可以通过Embase中的药物模块，直接获取SGLT2药物的药理，毒理文献

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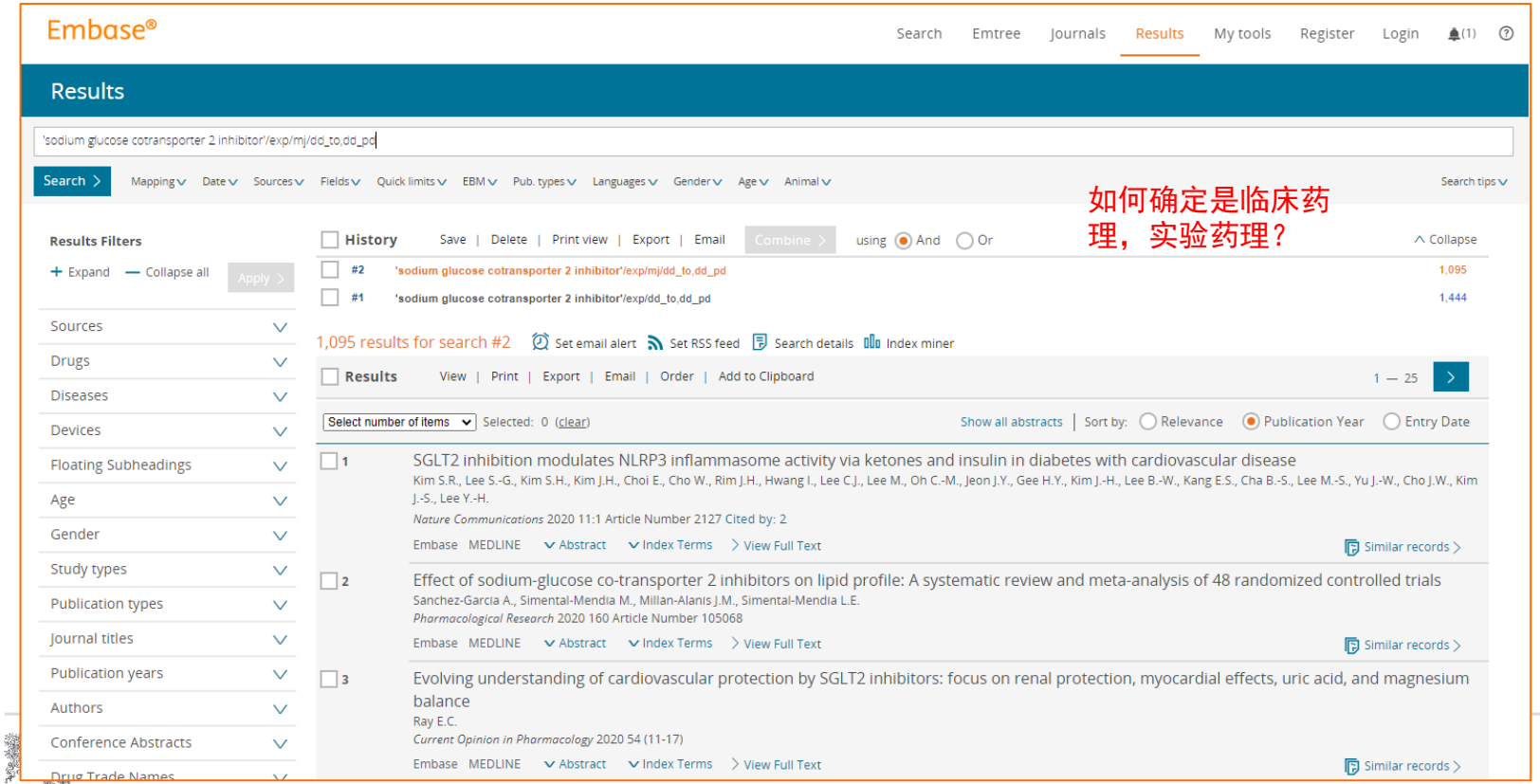
# Embase中的结果

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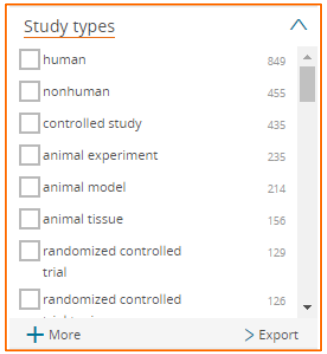
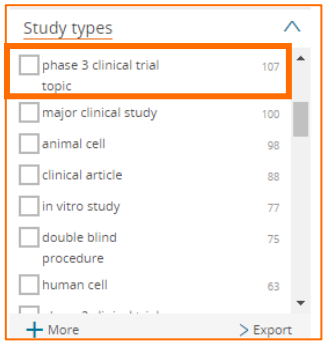
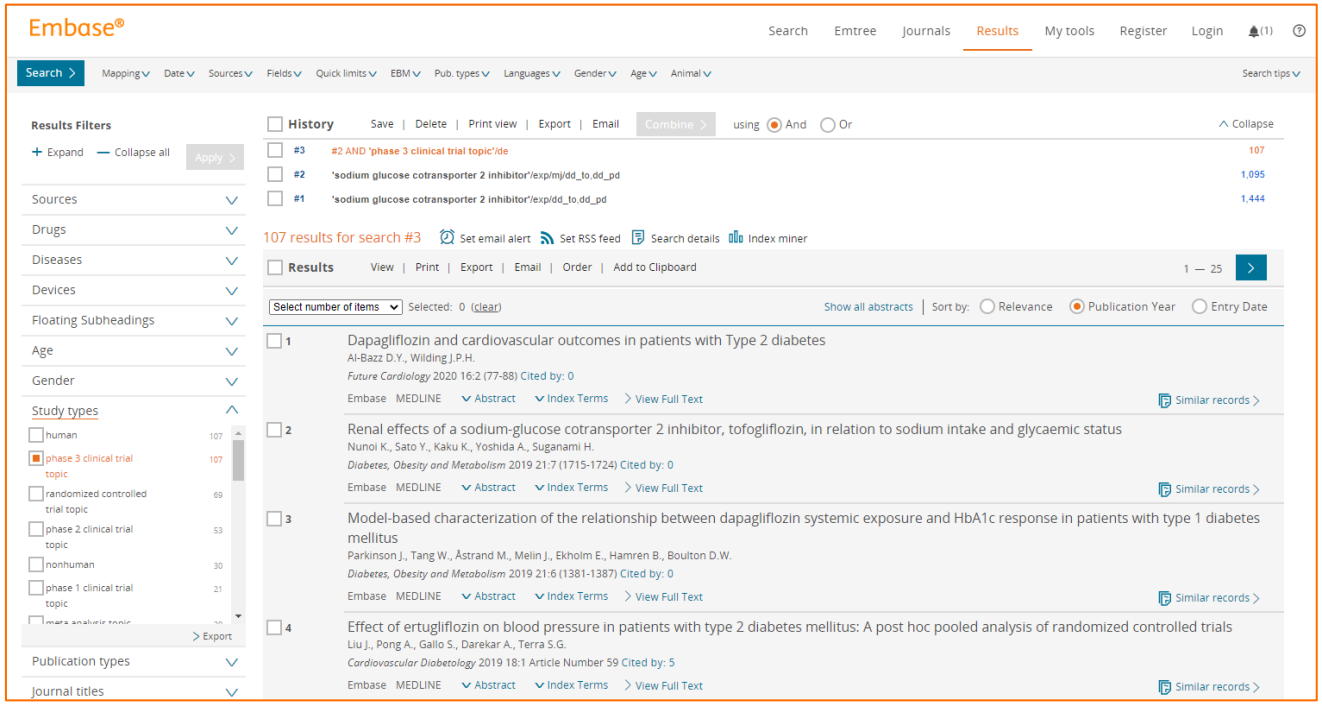
# Embase中的筛选

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# 上市后研究/监管

这个阶段，我们需要解决:

- 更多的临床试验(条件性上市，或者适应症扩展)
- 药物警戒

Elsevier Life Solution:

- PP 和 Embase 继续提供在临床研究阶段的支持
- Embase 提供药物警戒研究

# 上市后管理

(Pre-)Target Assessment → Target Identification → Target Validation → Lead Discovery → Lead Optimization → Phase 0 → Phase I → Phase II → Phase III → Post-Marketing

国家药品监督管理局
National Medical Products Administration

中国药品监管 中国药闻 中国药监APP 邮箱 政务信息报送
请输入关键字

关于发布个例药品不良反应收集和报告指导原则的通告（2018年第131号）

2018年12月21日 发布

为规范持有人药品上市后不良反应监测与报告工作，落实持有人直接报告药品不良反应主体责任，遵循国际人用药品注册技术协调会（ICH）指导原则相关规定，国家药品监督管理局组织制定了《个例药品不良反应收集和报告指导原则》，现予发布。

特此通告。

附件：个例药品不良反应收集和报告指导原则

国家药监局

2018年12月19日

国家药品监督管理局2018年第131号通告附件.doc

2018年12月21日，国家药品监督管理局发布药品不良反应收集和报告指导原则公告。

1.4 学术文献

学术文献是高质量的药品不良反应信息来源之一，持有人应定期对文献进行检索，并报告文献中涉及的个例不良反应。持有人应制定文献检索规程，对文献检索的频率、时间范围、文献来源、文献类型、检索策略等进行规定。

对于首次上市或首次进口五年内的新药，文献检索至少每两周进行一次，其他药品原则上每月进行一次，也可根据品种风险情况确定。检索的时间范围要有连续性，不能间断。

持有人应对广泛使用的文献数据库进行检索，如中国知网（CNKI）、维普网（VIP）、万方数据库等国内文献数据库和PubMed、Embase、Ovid等国外文献数据库。国内外文献均要求至少要同时检索两个数据库。

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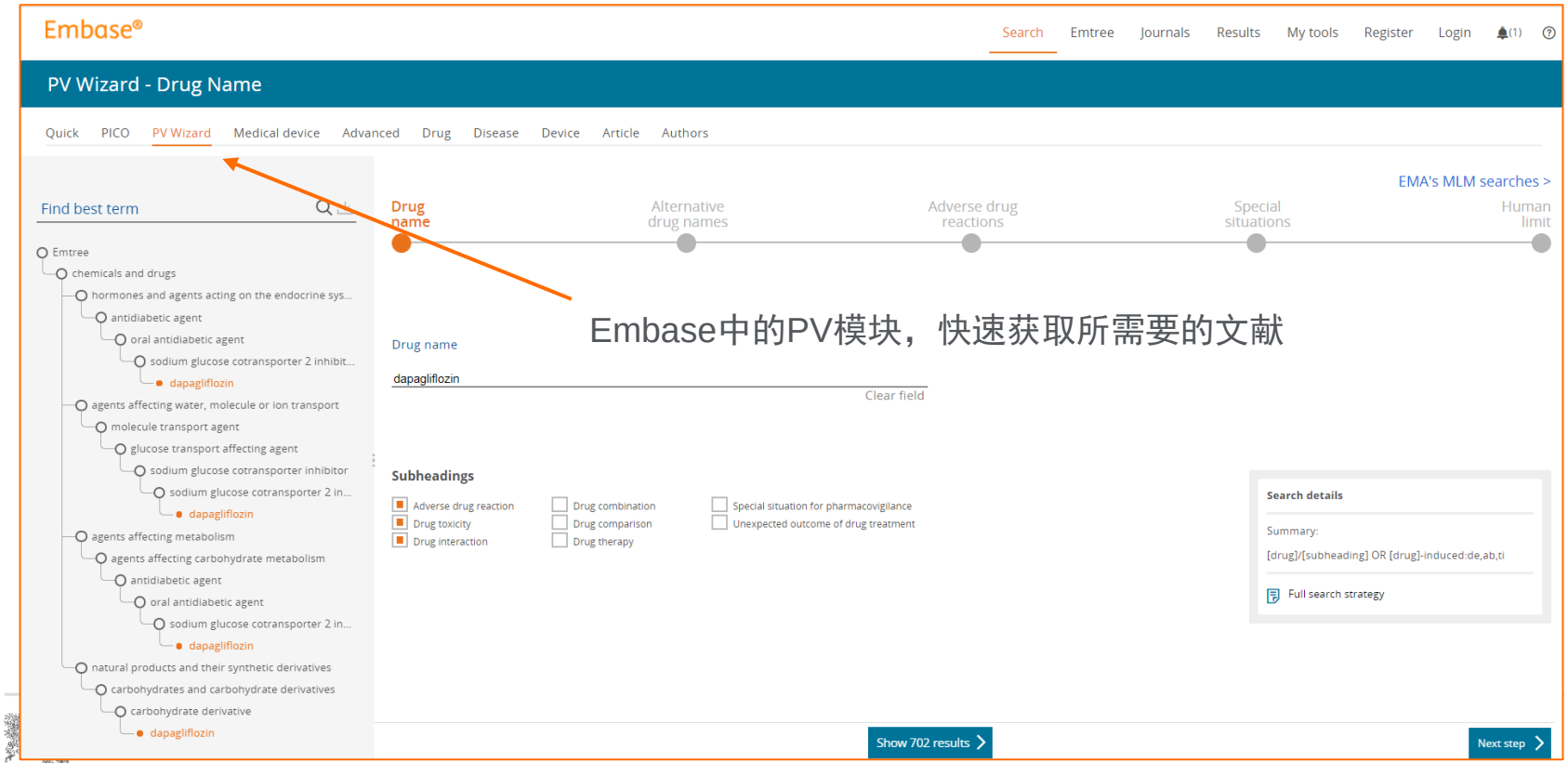
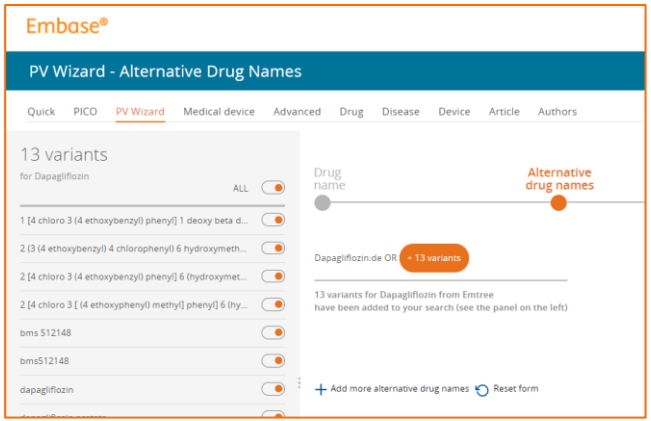
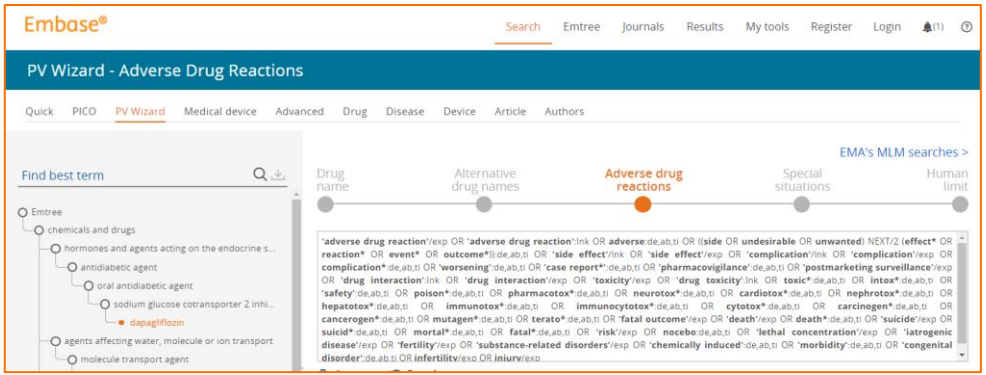
# Embase中的PV检索（以Dapagliflozin为例）

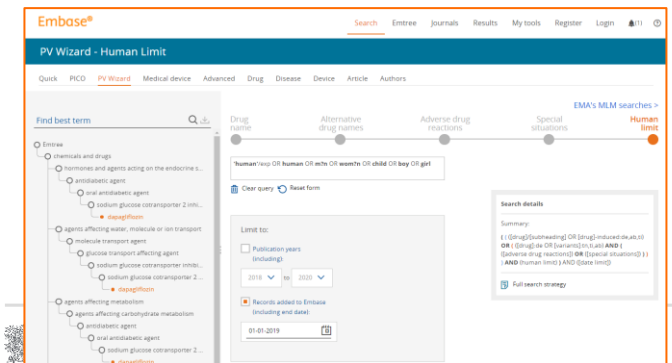


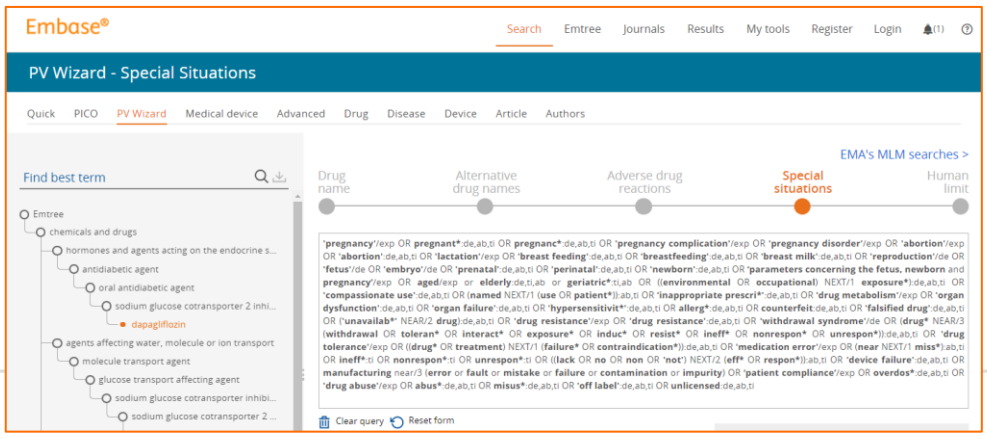

Embase中的PV模块，快速获取所需要的文献

# Embase中的PV检索策略的构建

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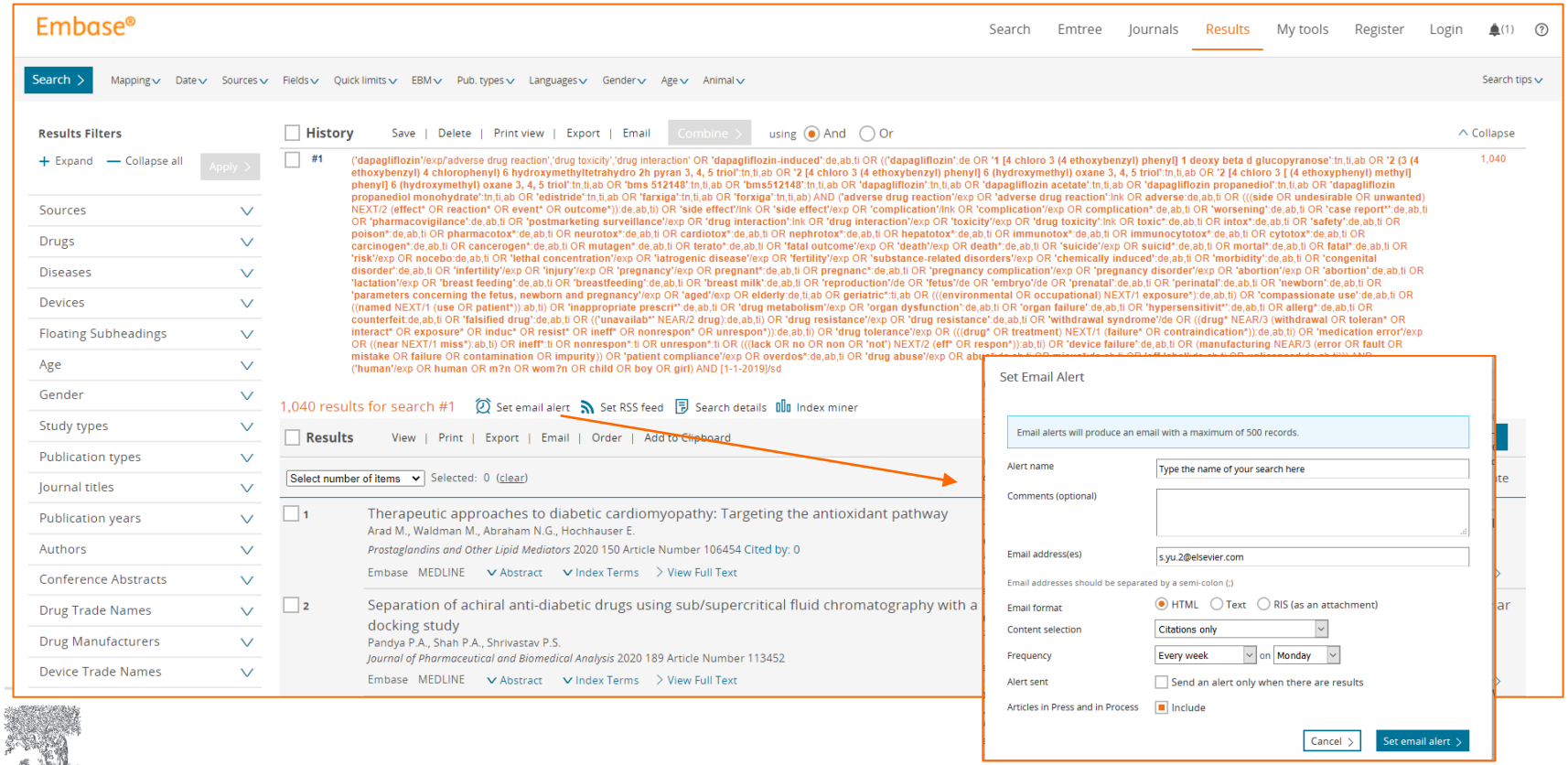
# 最后的结果与提醒

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# Elsevier Life Science Solution小结

- Elsevier Life Science Solution为药物研发全流程提供全面的科研信息
- Elsevier Life Science Solution融入越来越多的AI/ML技术，这将大大的提高科研人员的研究效率，拓展新的思路，尽早发现风险
- Elsevier Life Science Solution单独数据库也越来越朝更多的细分领域进行深入拓展
  - Reaxys/RMC，2020年将拓展到100家专利机构的专利，2021年完成专利中结构，反应，活性数据的提炼
  - Embase，2020年加入与中医药相关的词表（北京中医药大学合作项目）
  - PharmaPendium，与更多药企，FDA等监管机构合作开发的预测模型

# Elsevier Life Science Solution系列回放链接

- Elsevier Life Science Solution培训中心网址
  - https://www.elsevier.com/zh-cn/rd-solutions/pharma-and-life-sciences-solutions/life-sciences-online-training-center
- Elsevier Life Science Solution获取药物研发信息系列主题培训回放链接
  - Topic 1：物质结构/合成信息的获取与精炼，https://b23.tv/R55KYJ
  - Topic 2：生物活性数据与文献的获取与精炼，https://b23.tv/WnTbMX
  - Topic 3：毒理药理学文献的获取，https://b23.tv/cUi3GY


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扫码进群
或添加Elsevier Life Science小助手微信号：ELS-LSS邀请进群

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# Thank you