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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



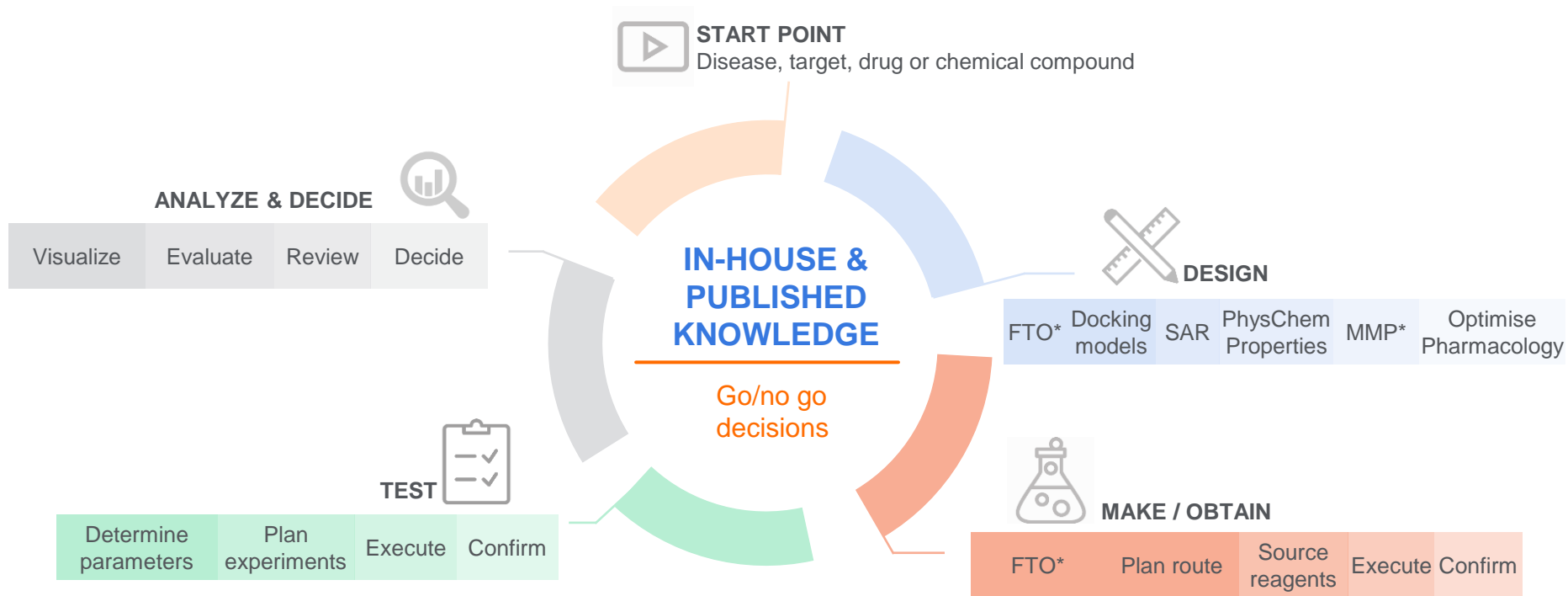
Elsevier 生命科学解决方案



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

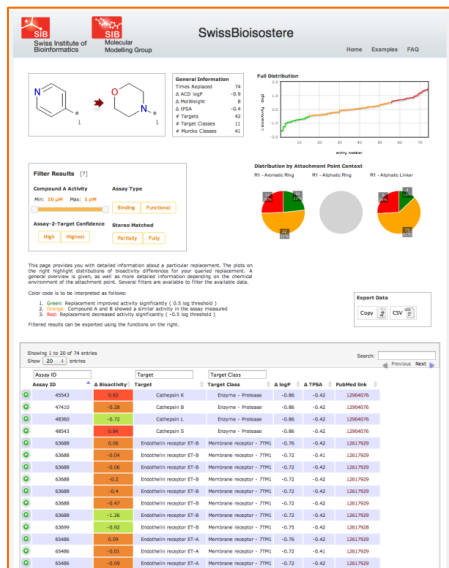


我们的整体战略是支持小分子的开发周期，并提供一个化学生态系统



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

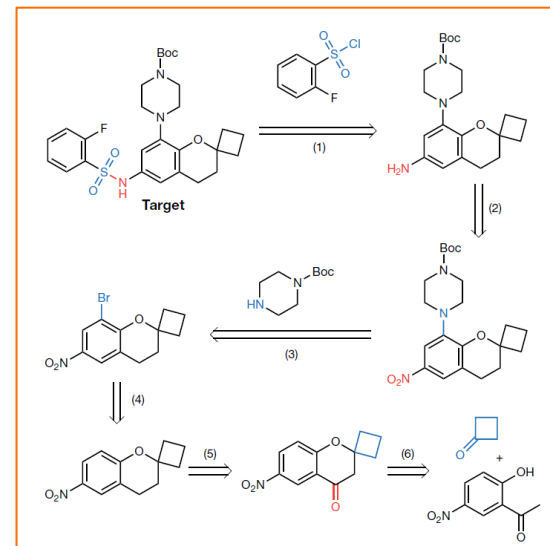


靶点预测

Target prediction

Target	Common name	Uniprot ID	Target Class	Probability*	Known actives (3D / 2D)
Adenosine receptor A2a	ADORA2A	P29274	Membrane receptor	100%	584 / 465
Adenosine receptor A2b	ADORA2B	P29275	Membrane receptor	100%	170 / 232
Adenosine receptor A1	ADORA1	P30542	Membrane receptor	100%	488 / 691
Adenosine receptor A3	N/A	P33765	Membrane receptor	100%	690 / 639
Neuropeptide Y receptor type 5	NPY5R	Q15781	Membrane receptor	100%	299 / 149
Cannabinoid receptor 1	CNR1	P21554	Membrane receptor	100%	1418 / 305
5-hydroxytryptamine receptor 2A	HTR2A	P28223	Membrane receptor	100%	108 / 42
5-hydroxytryptamine receptor 2C	HTR2C	P28335	Membrane receptor	100%	54 / 34
Cannabinoid receptor 2	CNR2	P34972	Membrane receptor	100%	1633 / 133
Corticotropin-releasing factor receptor 1	CRHR1	P34988	Membrane receptor	100%	218 / 123
Sodium-dependent serotonin transporter	SLC6A4	P31645	Transporter	100%	12 / 33
Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform	PIK3CD	O00329	Enzyme	100%	100 / 135
Cathepsin L1	CTSL	P07711	Cysteine Protease	100%	159 / 65
Epidermal growth factor receptor	EGFR	P00533	Tyr Kinase	100%	674 / 53
Cyclin-dependent kinase 2	CDK2	P24941	Ser_Thr Kinase	100%	160 / 518

合成预测

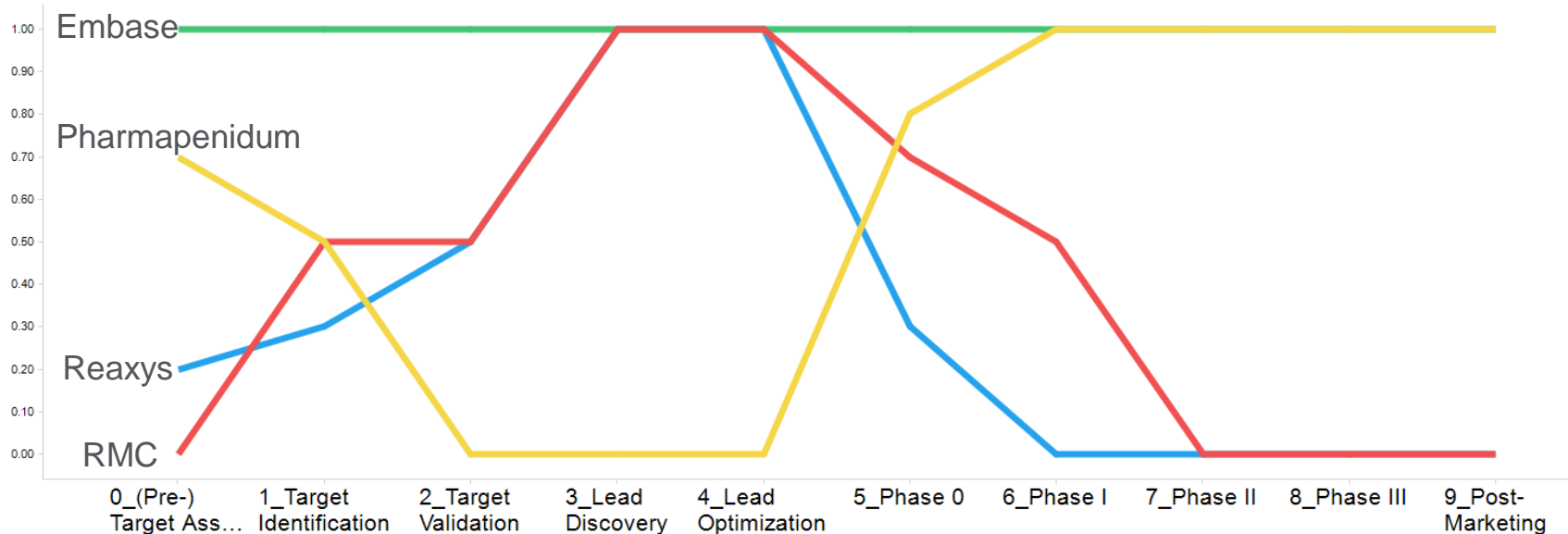


Elsevier Life Science Solution中已经开始融入不同领域的AI技术

Elsevier 生命科学解决方案对不同药物研发阶段的支持力度



- Pharmapendium
- Embase
- Pharmapendium
- Embase
- Reaxys
- RMC
- Embase
- Reaxys
- RMC
- Embase
- Reaxys
- RMC
- Embase
- Pharmapendium
- Embase
- Pharmapendium
- Embase
- Pharmapendium
- Embase
- Pharmapendium
- 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。



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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:

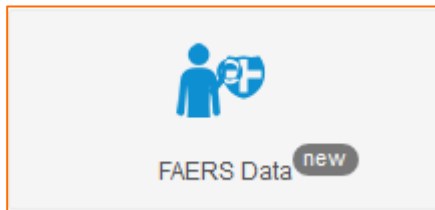
- PharmaPendium帮助找到这些“临床未满足需求”
- Reaxys帮助找到在结构上的原因
- Embase帮助寻找生物学上的原因



项目立项



- 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
 -

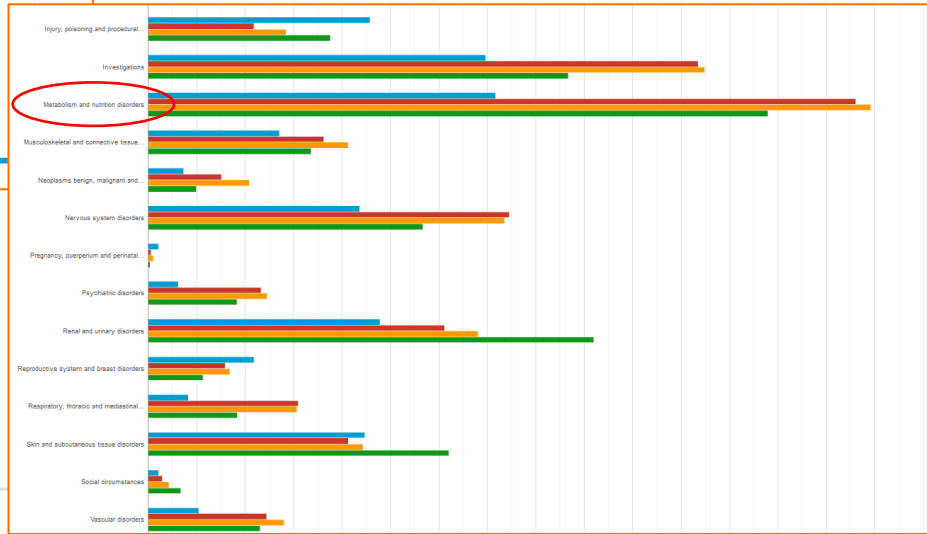
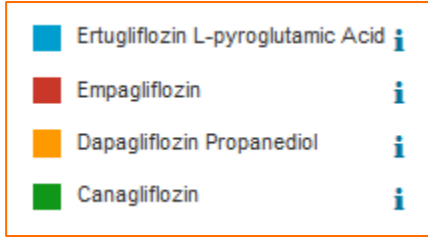
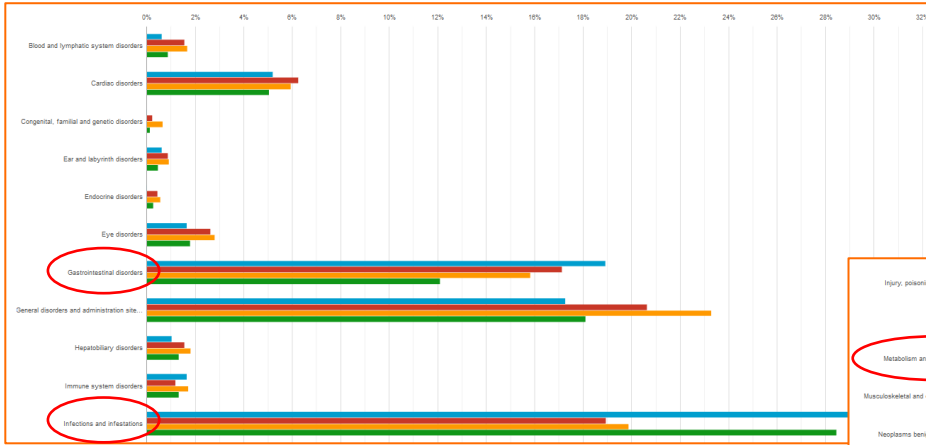


Add Drugs

by name or class **by primary target or target class** by indication

- By SuperFamily Add
 - Transporters Add
 - Sodium and Chloride Dependent Transporters Add
 - Sodium-dependent glucose cotransporters Add
 - SGLT2, sodium-glucose cotransporter 2 Add

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

代谢稳定性判断

PharmaPendium®

Browse Search My tools | IP-authorized

Pharmacokinetic data search Clinical & preclinical data

Drugs

- Canagliflozin
- Dapagliflozin Propanediol
- Empagliflozin
- Ertugliflozin L-pyroglutamic Acid

Parameter ranges

- Metabolic stability
- Above
- Below

Species

- Add species

Sources

- Add sources



Preclinical Data Clinical Data All Data

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 %	

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SGLT2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



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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

The screenshot displays the Reaxys Query Builder interface. The main area shows a 'Selectivity Profile' with two target-specific filters:

- SGLT2 Target:** Target Name is 'sglt2'. A filter is applied: Measurement pX ≥ 6 and Measurement Parameter is 'IC50'. A handwritten note in Chinese states: '该部分定义SGLT2靶点的IC50数据PX ≥ 6 '.
- SGLT1 Target:** Target Name is 'sglt1'. A filter is applied: Measurement pX ≤ 3 and Measurement Parameter is 'IC50'. A handwritten note in Chinese states: '该部分定义SGLT1靶点的IC50数据PX ≤ 3 '.

The interface includes a search bar, navigation tabs (Reactions, Targets, Substances, Documents), and a sidebar with search fields like Topics and Keywords, Identification, Physical Properties, Spectra, MedChem, and Bibliography.

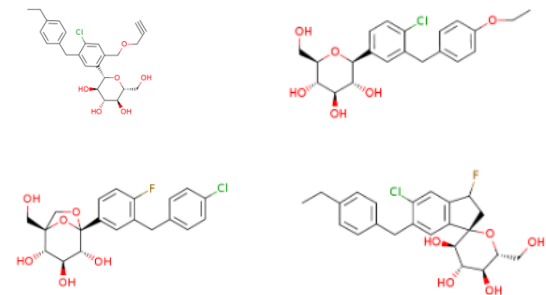
Reaxys/RMC提供“靶点选择性策略”的标准检索式，我们对其稍作修改，添加测量参数是IC50，对已知化合物进行筛选。

RMC给出的结果

Reaxys interface showing search results for 221 substances. The results are filtered to show 3 substances containing 724 reactions and 1 target.

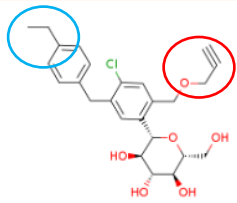
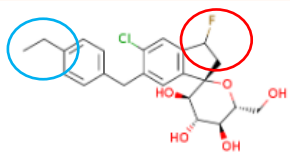
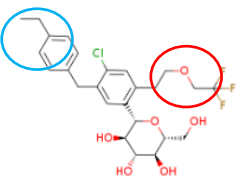
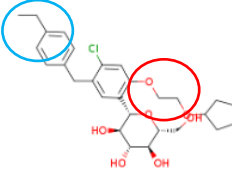
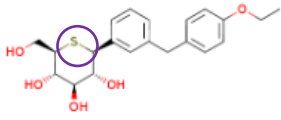
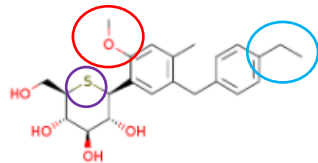
Substance Name	Chemical Formula	Biological Activity	Physical Data	Spectra
phloretin	C ₁₅ H ₁₂ O ₆	Biological Activity (42)	Physical Data - 55	Spectra - 136
Apigetrin	C ₁₅ H ₁₀ O ₆	Biological Activity (40)	Physical Data - 52	Spectra - 16
(1S)-1,5-anhydro-1-(4-chlorophenyl)-4-methoxy-4-methylphosphorin-3-ylidene-D-glucitol	C ₁₄ H ₁₄ O ₄	Biological Activity (42)	Physical Data - 9	Spectra - 7
apigenin	C ₁₅ H ₁₀ O ₆	Biological Activity (40)	Physical Data - 52	Spectra - 16

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

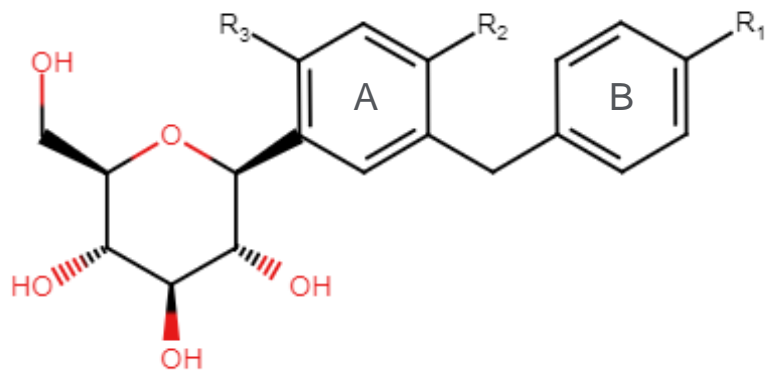
一些比较有意思的结构

化合物结构	活性差异	化合物结构	活性差异
	SGLT2=9.5 SGLT1=1		SGLT2=9 SGLT1=1
	SGLT2=6 SGLT1=1		SGLT2=6 SGLT1=1
	SGLT2=7.1 SGLT1=1.5		SGLT2=8.7 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
- **蓝色**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® Quick search Query builder Results Synthesis planner History Alerts Sam Yu

Structure editor selected: MarvinJS ChemDrawJS

Insert structure from name >

Search this structure as:

- As drawn
- As substructure
- On all atoms
- On heteroatoms
- Similar
- Tautomers
- Stereo
- Additional ring closures
- Related Markush
- Salts
- Mixtures
- Isotopes
- Charges
- Radicals

+ More options

获取结构的同时，也获取专利中的通式结构

Clear Cancel x Transfer to query >

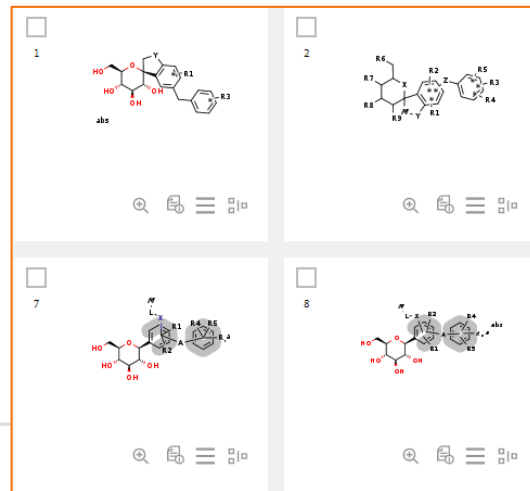
Reaxys中的结果

133 Substances out of 17 Documents, containing 302 Reactions, 2 Targets

0 selected Limit To Exclude Export Preparations

<input type="checkbox"/> 1 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 3 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<input type="checkbox"/> 7 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 8 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 9 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 10 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<input type="checkbox"/> 13 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 14 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 15 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 16 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

Reaxys除了给出具体的结构，还能给出涉及这些结构的Markush通式



利用分子量筛选获取所有的Markush结构

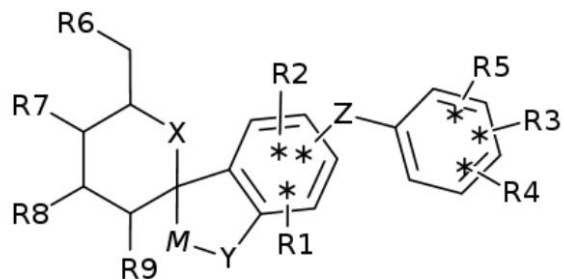
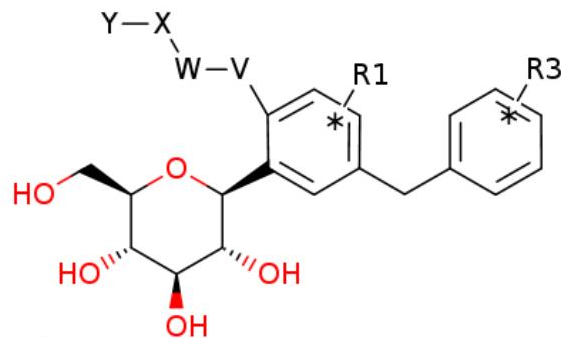
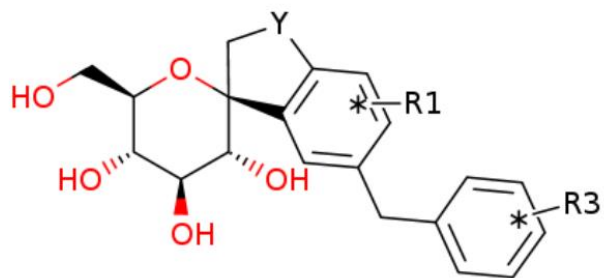
The screenshot displays a search interface with a 'Filters' sidebar on the left and a 'Molecular Weight' filter panel on the right. The 'Molecular Weight' panel shows a list of ranges with checkboxes and counts. The 'no entry given' option is selected, and the results are sorted by occurrence.

Molecular Weight Range	Count
>408 - 420	4
>420 - 432	5
>432 - 444	9
>444 - 456	22
>456 - 468	23
>468 - 480	11
>480 - 492	6

Molecular Weight Range	Count
>864 - 876	1
>768 - 780	1
>744 - 756	1
>720 - 732	1
>708 - 720	1
>636 - 648	1
>612 - 624	1
>588 - 600	1
>576 - 588	1
>540 - 552	1
(no entry given)	13

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

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

Reaxys对于专利中Markush的提炼

Reaxys ID: 13022958
13022958

Identification
Other Data - 24

Documents - 1 >



Identification

Reaxys ID: 13022958

Substance Label

Patent-Specific Data - 1

Location in Patent	Reference
Claim 10	Chen, Yuanwei; Feng, Yan; Xu, Baihua; Lv, Binhua; Dong, Jiajia; Seed, Brian; Hadd, Michael J. - US2007/275907, 2007, A1 Full Text > Details > Abstract >

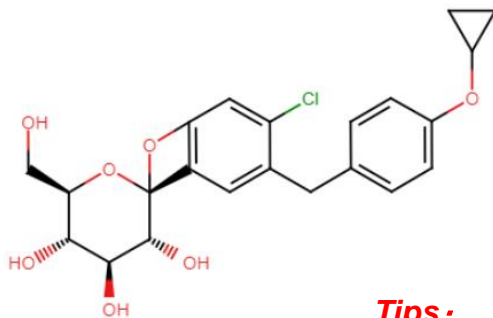
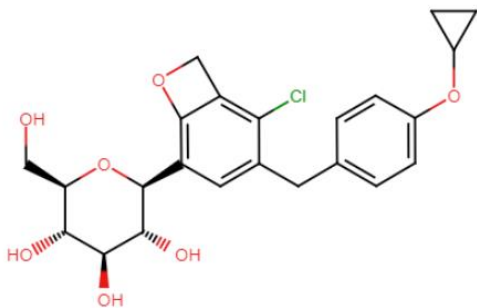
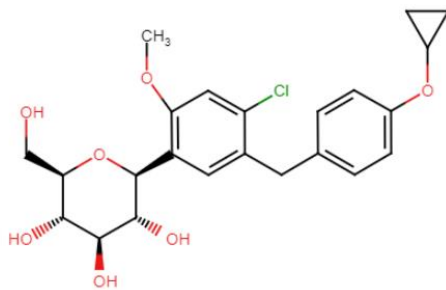
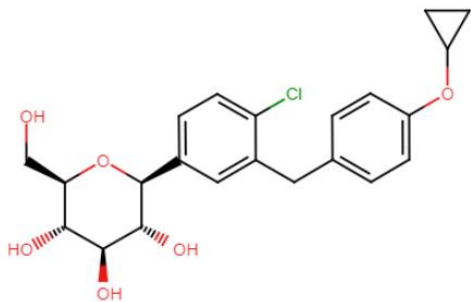
Markush Details



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			
R1	SO2(C#H2)m			
	(O)C(C#H2)mC(O)			
	hydrogen			
	halo			
	allyl	1-6C		\$dSe;\$f\$g
	alkenyl	2-6C		\$dSe;\$f\$g
	alkynyl	2-6C		\$dSe;\$f\$g
	cycloalkyl	3-10C	1-2 methylene groups o replaced by <\$h>	\$dSe;\$f\$g
	Scycloalkyl1310-\$alkyl13			
	(\$alkenyl24)\$alkyloxy13			

提炼了出现的位置和Markush的结构细节。

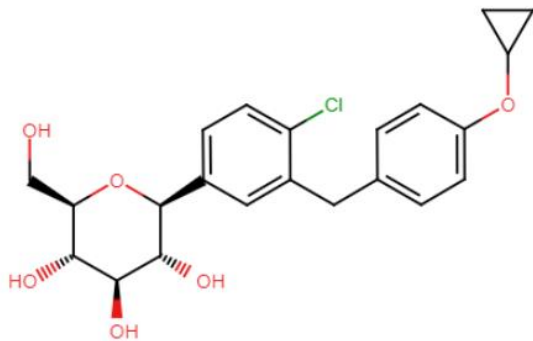
评估完专利后，设计一些全新化合物（假设下列结构无专利问题）



Tips:

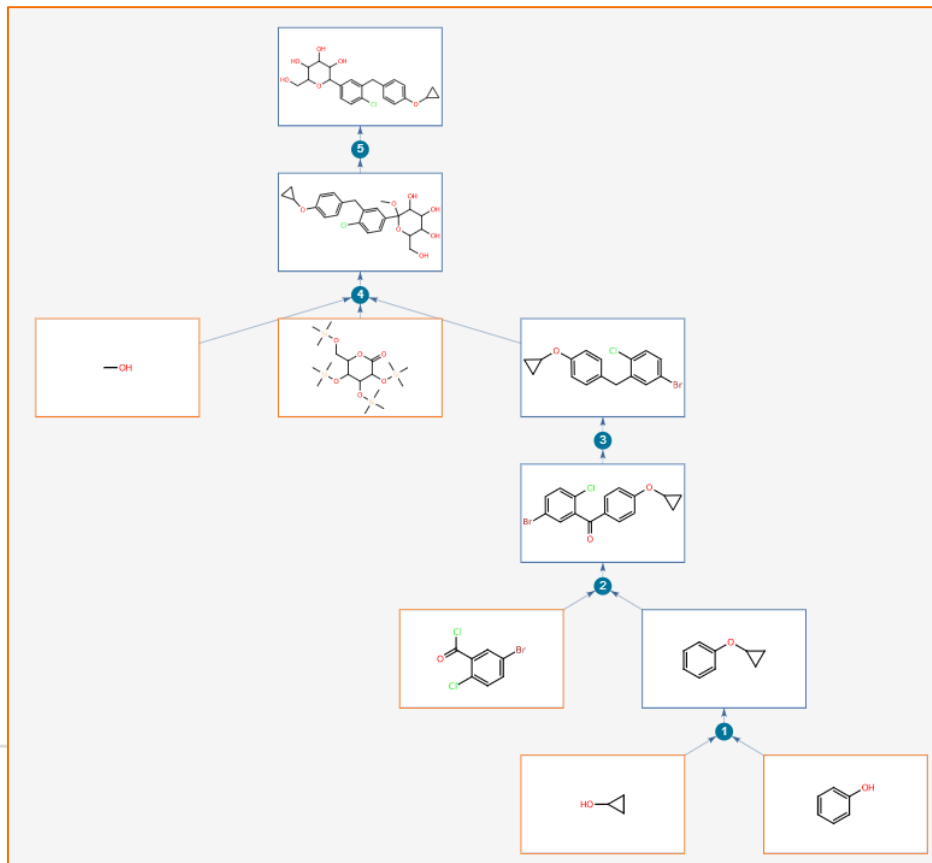
案例制作当天，Reaxys中没有相同结构。

Reaxys AI帮助提供全新化合物合成策略，开拓思路



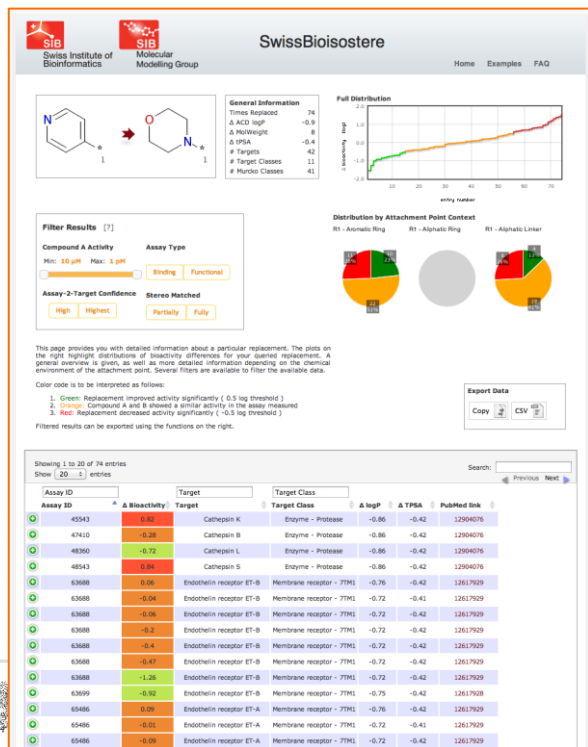
Tips:

- 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**



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	<div style="width: 100%; height: 10px; background-color: green;"></div>	584 / 485
Adenosine receptor A2b	ADORA2B	P29275	Membrane receptor	<div style="width: 100%; height: 10px; background-color: green;"></div>	170 / 232
Adenosine receptor A1	ADORA1	P30542	Membrane receptor	<div style="width: 100%; height: 10px; background-color: green;"></div>	488 / 591
Adenosine receptor A3	N/A	P33765	Membrane receptor	<div style="width: 100%; height: 10px; background-color: green;"></div>	690 / 639
Neuropeptide Y receptor type 5	NPY5R	Q15761	Membrane receptor	<div style="width: 100%; height: 10px; background-color: green;"></div>	299 / 149
Cannabinoid receptor 1	CNR1	P21554	Membrane receptor	<div style="width: 80%; height: 10px; background-color: green;"></div>	1418 / 305
5-hydroxytryptamine receptor 2A	HTR2A	P28223	Membrane receptor	<div style="width: 60%; height: 10px; background-color: green;"></div>	108 / 42
5-hydroxytryptamine receptor 2C	HTR2C	P28335	Membrane receptor	<div style="width: 40%; height: 10px; background-color: green;"></div>	54 / 34
Cannabinoid receptor 2	CNR2	P34972	Membrane receptor	<div style="width: 70%; height: 10px; background-color: green;"></div>	1633 / 123
Corticotropin-releasing factor receptor 1	CRHR1	P34998	Membrane receptor	<div style="width: 50%; height: 10px; background-color: green;"></div>	218 / 123
Sodium-dependent serotonin transporter	SLC6A4	P31645	Transporter	<div style="width: 30%; height: 10px; background-color: green;"></div>	12 / 33
Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform	PIK3CD	O00329	Enzyme	<div style="width: 20%; height: 10px; background-color: green;"></div>	100 / 135
Cathepsin L1	CTSL	P07711	Cysteine Protease	<div style="width: 10%; height: 10px; background-color: green;"></div>	159 / 65
Epidermal growth factor receptor	EGFR	P00533	Tyr Kinase	<div style="width: 15%; height: 10px; background-color: green;"></div>	674 / 53
Cyclin-dependent kinase 2	CDK2	P24941	Ser_Thr Kinase	<div style="width: 10%; height: 10px; background-color: green;"></div>	160 / 518

Tips:

- 属于RMC中的一个功能，开发中。



ELSEVIER

临床前，临床实验

这个阶段，我们需要解决:

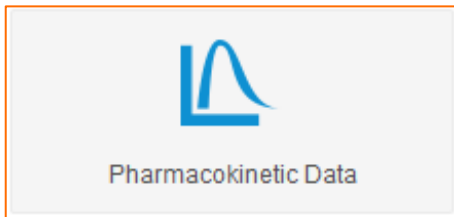
- 药物安全的市场标准是什么？
- 如何与监管机构沟通新分子的优势？
- 新分子可能存在哪些DDI

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



- 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® Browse ▾ Search ▾ My tools ▾

Pharmacokinetic data search Clinical & preclinical data

Drugs

Canagliflozin ✕ Dapagliflozin Propanediol ✕ Empagliflozin ✕

Ertugliflozin L-pyroglytamic Acid ✕

+ Add drugs by drug class or drug name

+ Add drugs by primary target or primary target class

+ Add drugs by indication

Parameter ranges

Half life ✕

+ Add parameter ranges

Species

+ Add species

Sources

+ Add sources

PharmaPendium中的结果

PharmaPendium®

Browse Search My tools | IP-authorized

Pharmacokinetic data search results

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

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

Filters Clear all Apply

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 disease, 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	

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®

IP-authorized

Browse Search My tools

Efficacy data search Clinical & preclinical data

Reset all Search

Drugs

- Canagliflozin
- Dapagliflozin Propanediol
- Empagliflozin
- Ertugliflozin L-pyroglyutamic Acid

+ Add drugs by drug class or drug name

+ Add drugs by primary target or primary target class

+ Add drugs by indication

Indication Type

- Diabetes mellitus type 2

+ Add indications

Species

+ Add species

Sources

+ Add sources

Endpoints

+ Add endpoints

PharmaPendium中的结果

Efficacy data search results

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

Filters [clear all](#) [Apply](#)

Preclinical Data **Clinical Data**

ID	Drug	Study Design	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, pioglitazone
4	Canagliflozin	ed, double-blind, e-controlled, ip	Human	Male	Adult-aged	Diabetes mellitus type 2	Type 2 diabetes mellitus		Oral	Canagliflozin 0 mg
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 mg sulfonylurea

Pharmapendium中的筛选

Primary/Secondary

- co-primary (165)
- exploratory (84)
- primary (2710)
- secondary (2344)

Endpoints

🔍 Type endpoint to search

- Diabetes (2710)
 - Blood pressure (38)
 - Clinical chemistry (1861)
 - Clinical chemistry response (225)
 - Clinical response (22)
 - Events/Outcomes (543)
 - Functional tests (4)
 - Physical measurements (15)
 - Treatment need (2)

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

- Glycated hemoglobin (HbA1c) (1827)
 - Additional HbA1c reduction (3)
 - Adj. Mean Change From Baseline HbA1c level (3)
 - Adj. Mean Change From Baseline HbA1c level by Age: 65+ (2)
 - Adj. Mean Change From Baseline HbA1c level by Age: < 65 (2)
 - Adj. Mean Change From Baseline HbA1c level by Race: Asian (2)
 - Adj. Mean Change From Baseline HbA1c level by Race: Black/ African-American (2)
 - Adj. Mean Change From Baseline HbA1c level by Race: Other (2)
 - Adj. Mean Change From Baseline HbA1c level by Race: White (2)
 - Adj. Mean Change From Baseline HbA1c level by Region: Rest of world (3)
 - Adj. Mean Change From Baseline HbA1c level by Region: U.S. (3)
 - Adjusted mean change from baseline HbA1c at week 24 (6)
 - Adjusted mean change from baseline HbA1c at week 24 by Age: <65 (2)
 - Adjusted mean change from baseline HbA1c at week 24 by Age: <66 (2)
 - Adjusted mean change from baseline HbA1c at week 24 by Age: ≥65 (4)
 - Adjusted Mean Change From Baseline HbA1c level (16)
 - Adjusted Mean Change From Baseline HbA1c level by Age: <65 years (2)
 - Adjusted Mean Change From Baseline HbA1c level by Age: ≥65 years (2)

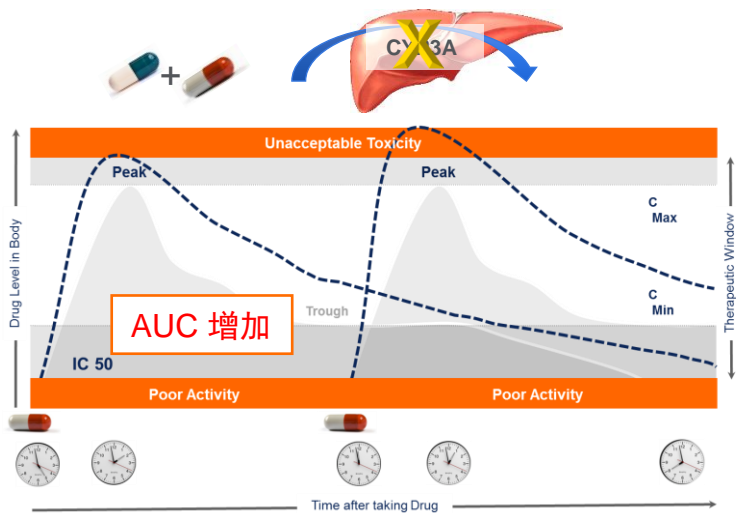
- Difference from metformin in glycosylated hemoglobin A1 level (2)
- Difference from placebo in change from baseline in glycosylated hemoglobin (HbA1c) level (2)
- Difference from placebo in change of HbA1c from baseline (36)
- Difference from placebo in glycosylated hemoglobin (HbA1c) level (17)
- Difference from placebo in glycosylated hemoglobin A1 level (27)
- Difference from placebo in HbA1c level (21)
- Difference from sitagliptin in HbA1c level (1)
- Difference in LS mean change from baseline in HbA1c (67)
- Difference in LS mean decrease from baseline in HbA1c (1)
- Glycosylated hemoglobin A1 level (8)
- Groups difference in HbA1c changes from baseline (1)
- HbA1c change from baseline (190)
- HbA1c reduction (9)
- Least square mean change from baseline of HbA1c level (12)
- LS Mean change from baseline in glycosylated hemoglobin (HbA1c) level (124)
- LS mean change from baseline in HbA1c (121)
- LS Mean Change From Baseline in HbA1c level (16)
- LS mean Change from Baseline to Week 24 in HbA1c level (3)

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。

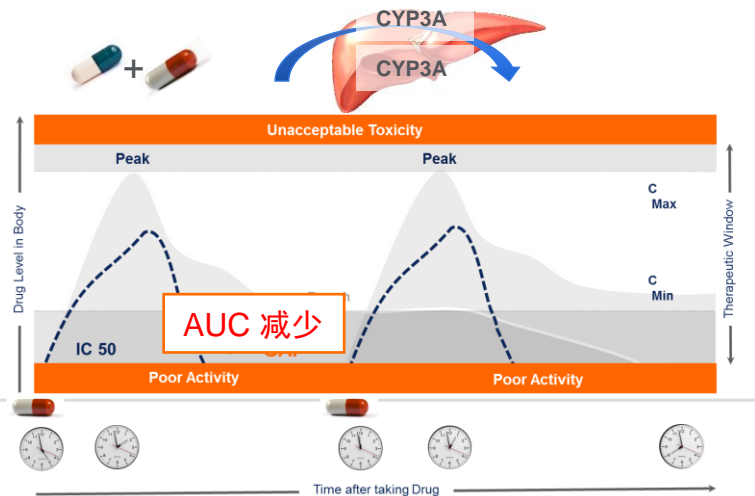
DDI情况之一:

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

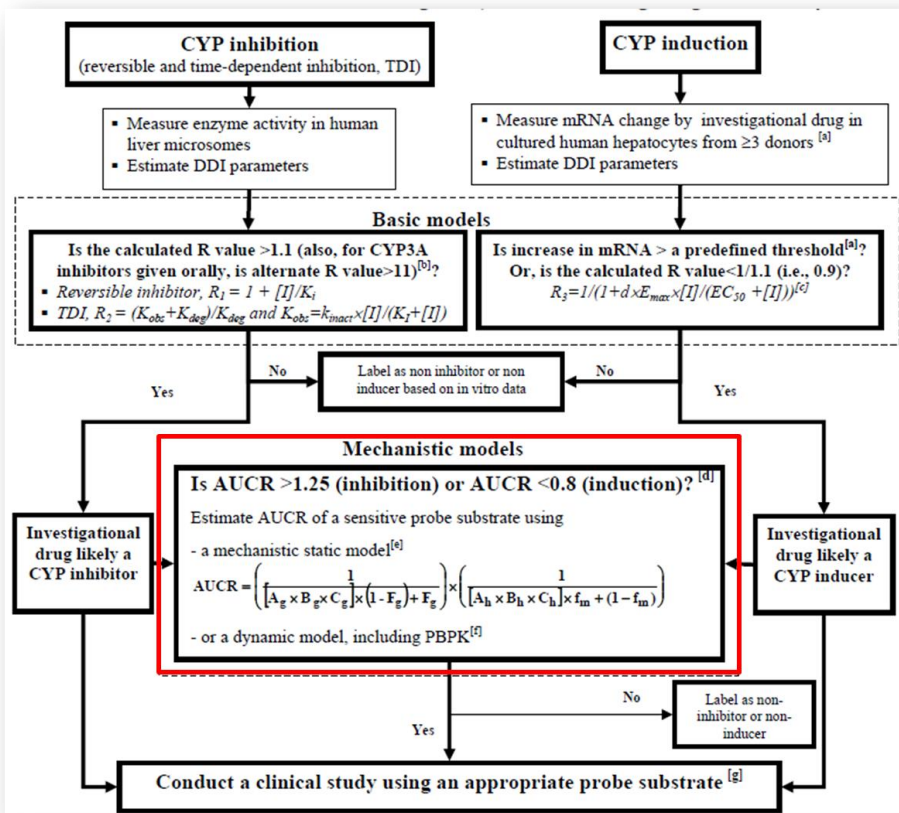


DDI情况之二:

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



DDI risk calculator

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。

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%

Proprietary Victim Drug

Victim Perpetrators

Please enter proprietary data for the victim drug:

Victim definition

*Compound name:

Hepatic Metabolism

User Defined

Predicted

Enzyme(s)

▼

▼

▼

kdeg (min⁻¹) **i**

i

i

fmE

Predict interactions

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 AUC/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	Blue
No risk	0.8 ≤ AUC ratio < 1.25	Green
Low risk	1.25 ≤ AUC ratio < 2	Yellow
Medium risk	2 ≤ AUC ratio < 5	Orange
High risk	5 ≤ AUC ratio	Red

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

PharmaPendium®

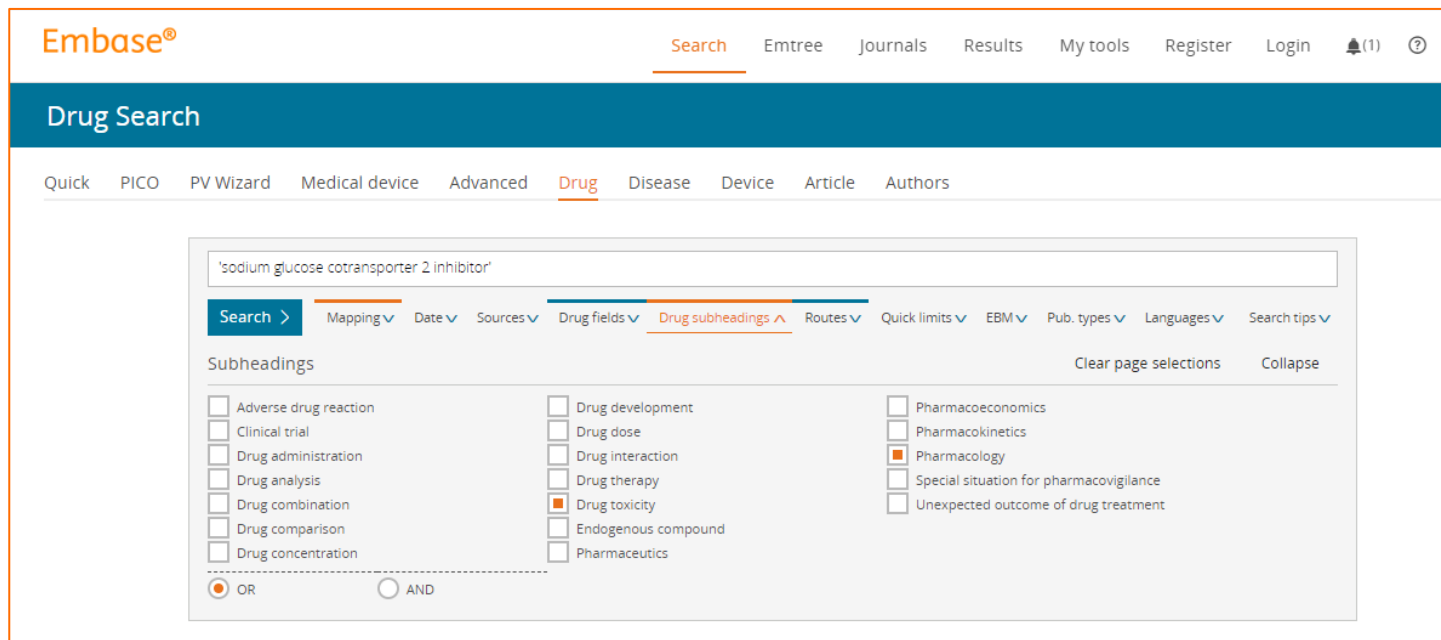
DDI Prediction

228 records from DDI Risk Calculator: victim: New-1

Results

ID	Perpetrator	Dose	MBI	AUC Ratio	Count	Min	Max	Mean	SD	Med	5-95th Perc.
1	(+)-Citalopram 147856 Antidepressant Dev. + Drug Type: Approved	Multiple			132	1.003	1.018	1.006	0.004	1.005	1.003-1.015
2	(+)-Propoxyphene 91412 Analgesic: narcotic/opiate Dev. + Drug Type: Approved	Multiple			4	1.414	2.194	1.805	0.389	1.806	1.415-2.194
3	(+)-Warfarin 162426 Antithrombotic Dev. + Drug Type: Experimental/Investigation	0.007 g			1	1.16	1.16	1.16	0.0	1.16	1.16-1.16
4	(-)-Omeprazole 162627 Antulcerative Proton pump inhibitor Dev. - Drug Type: Approved	Multiple			176	1.009	1.064	1.032	0.015	1.028	1.013-1.057
5	(-)-Warfarin 161583 Antithrombotic Dev. - Drug Type: Experimental/Investigation	0.007 g			5	1.07	1.381	1.239	0.1	1.239	1.102-1.359
6	AMG 487	Multiple			3	1.867	1.986	1.939	0.062	1.963	1.876-1.983

SGLT2药物的毒理药理文献有哪些？（临床药理，试验药理……）



The screenshot displays the Embase® Drug Search interface. At the top, the navigation bar includes 'Search', 'Entree', 'Journals', 'Results', 'My tools', 'Register', 'Login', and a notification bell with '(1)'. Below this is a dark blue header with 'Drug Search' in white text. A secondary navigation bar contains 'Quick', 'PICO', 'PV Wizard', 'Medical device', 'Advanced', 'Drug' (highlighted), 'Disease', 'Device', 'Article', and 'Authors'. The main search area features a search box with the text 'sodium glucose cotransporter 2 inhibitor'. Below the search box is a 'Search >' button and a series of filter tabs: 'Mapping', 'Date', 'Sources', 'Drug fields', 'Drug subheadings' (active), and 'Routes'. Under the 'Drug subheadings' tab, there are three columns of checkboxes for filtering results. The first column includes 'Adverse drug reaction', 'Clinical trial', 'Drug administration', 'Drug analysis', 'Drug combination', 'Drug comparison', and 'Drug concentration'. The second column includes 'Drug development', 'Drug dose', 'Drug interaction', 'Drug therapy', 'Drug toxicity', 'Endogenous compound', and 'Pharmaceutics'. The third column includes 'Pharmacoeconomics', 'Pharmacokinetics', 'Pharmacology' (checked), 'Special situation for pharmacovigilance', and 'Unexpected outcome of drug treatment'. At the bottom of the filter section, there are radio buttons for 'OR' (selected) and 'AND'. On the right side of the filter section, there are links for 'Clear page selections' and 'Collapse'.

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

Embase中的结果

Embase® Search Entree Journals **Results** My tools Register Login (1) ?

Results

'sodium glucose cotransporter 2 inhibitor/exp/mj/dd_to,dd_pd'

Search > Mapping ▾ Date ▾ Sources ▾ Fields ▾ Quick limits ▾ EBM ▾ Pub. types ▾ Languages ▾ Gender ▾ Age ▾ Animal ▾ Search tips ▾

Results Filters

+ Expand - Collapse all Apply >

Sources ▾

Drugs ▾

Diseases ▾

Devices ▾

Floating Subheadings ▾

Age ▾

Gender ▾

Study types ▾

Publication types ▾

Journal titles ▾

Publication years ▾

Authors ▾

Conference Abstracts ▾

Drug Trade Names ▾

History Save | Delete | Print view | Export | Email **Combine >** using And Or ^ Collapse

#2 'sodium glucose cotransporter 2 inhibitor/exp/mj/dd_to,dd_pd' 1,095

#1 'sodium glucose cotransporter 2 inhibitor/exp/dd_to,dd_pd' 1,444

1,095 results for search #2 [Set email alert](#) [Set RSS feed](#) [Search details](#) [Index miner](#)

Results View | Print | Export | Email | Order | Add to Clipboard 1 — 25 >

Select number of items ▾ Selected: 0 (clear) Show all abstracts | Sort by: Relevance Publication Year Entry Date

1 SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease
Kim S.R., Lee S.-G., Kim S.H., Kim J.H., Choi E., Cho W., Rim J.H., Hwang I., Lee C.J., Lee M., Oh C.-M., Jeon J.Y., Gee H.Y., Kim J.-H., Lee B.-W., Kang E.S., Cha B.-S., Lee M.-S., Yu J.-W., Cho J.W., Kim J.-S., Lee Y.-H.
Nature Communications 2020 11:1 Article Number 2127 Cited by: 2
Embase MEDLINE [Abstract](#) [Index Terms](#) [View Full Text](#) [Similar records >](#)

2 Effect of sodium-glucose co-transporter 2 inhibitors on lipid profile: A systematic review and meta-analysis of 48 randomized controlled trials
Sanchez-Garcia A., Simental-Mendia M., Millan-Alanis J.M., Simental-Mendia L.E.
Pharmacological Research 2020 160 Article Number 105068
Embase MEDLINE [Abstract](#) [Index Terms](#) [View Full Text](#) [Similar records >](#)

3 Evolving understanding of cardiovascular protection by SGLT2 inhibitors: focus on renal protection, myocardial effects, uric acid, and magnesium balance
Ray E.C.
Current Opinion in Pharmacology 2020 54 (11-17)
Embase MEDLINE [Abstract](#) [Index Terms](#) [View Full Text](#) [Similar records >](#)

如何确定是临床药理，实验药理？

Embase中的筛选

Study types

- human 849
- nonhuman 455
- controlled study 435
- animal experiment 235
- animal model 214
- animal tissue 156
- randomized controlled trial 129
- randomized controlled 126

+ More > Export

Study types

- phase 3 clinical trial topic 107
- major clinical study 100
- animal cell 98
- clinical article 88
- in vitro study 77
- double blind procedure 75
- human cell 63

+ More > Export

Embase®

Search Entree Journals **Results** My tools Register Login (1)

Search Mapping Date Sources Fields Quick limits EBM Pub. types Languages Gender Age Animal Search tips

Results Filters

+ Expand - Collapse all Apply

Sources

Drugs

Diseases

Devices

Floating Subheadings

Age

Gender

Study types

- human 107
- phase 3 clinical trial topic 107
- randomized controlled trial topic 69
- phase 2 clinical trial topic 53
- nonhuman 30
- phase 1 clinical trial topic 21
- meta analysis topic 14

+ More > Export

Publication types

Journal titles

History Save | Delete | Print view | Export | Email Combine using And Or Collapse

- #3 #2 AND 'phase 3 clinical trial topic'ide 107
- #2 'sodium glucose cotransporter 2 inhibitor'/exp/m/dd_to_dd_pd 1,095
- #1 'sodium glucose cotransporter 2 inhibitor'/exp/dd_to_dd_pd 1,444

107 results for search #3 Set email alert Set RSS feed Search details Index miner

Results View | Print | Export | Email | Order | Add to Clipboard 1 -- 25

Select number of items Selected: 0 (clear) Show all abstracts Sort by: Relevance Publication Year Entry Date

- 1 Dapagliflozin and cardiovascular outcomes in patients with Type 2 diabetes
Al-Bazz D.Y., Wilding J.P.H.
Future Cardiology 2020 16:2 (77-88) Cited by: 0
Embase MEDLINE Abstract Index Terms View Full Text Similar records
- 2 Renal effects of a sodium-glucose cotransporter 2 inhibitor, tofogliflozin, in relation to sodium intake and glycaemic status
Nunoi K., Sato Y., Kaku K., Yoshida A., Suganami H.
Diabetes, Obesity and Metabolism 2019 21:7 (1715-1724) Cited by: 0
Embase MEDLINE Abstract Index Terms View Full Text Similar records
- 3 Model-based characterization of the relationship between dapagliflozin systemic exposure and HbA1c response in patients with type 1 diabetes mellitus
Parkinson J., Tang W., Åstrand M., Melin J., Ekholm E., Hamren B., Bouillon D.W.
Diabetes, Obesity and Metabolism 2019 21:6 (1381-1387) Cited by: 0
Embase MEDLINE Abstract Index Terms View Full Text Similar records
- 4 Effect of ertugliflozin on blood pressure in patients with type 2 diabetes mellitus: A post hoc pooled analysis of randomized controlled trials
Liu J., Pong A., Gallo S., Darekar A., Terra S.G.
Cardiovascular Diabetology 2019 18:1 Article Number 59 Cited by: 5
Embase MEDLINE Abstract Index Terms View Full Text Similar records



ELSEVIER

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



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 政府信息报送

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。

Embase中的PV检索（以Dapagliflozin为例）

Embase® Search Entree Journals Results My tools Register Login (1) ?

PV Wizard - Drug Name

Quick PICO **PV Wizard** Medical device Advanced Drug Disease Device Article Authors

Find best term

EMA's MLM searches >

Drug name

Alternative drug names

Adverse drug reactions

Special situations

Human limit

Drug name

dapagliflozin Clear field

Subheadings

Adverse drug reaction Drug combination Special situation for pharmacovigilance

Drug toxicity Drug comparison Unexpected outcome of drug treatment

Drug interaction Drug therapy

Search details

Summary:

[drug]/[subheading] OR [drug]-induced:de,ab,ti

Full search strategy

Show 702 results >

Next step >

Embase中的PV检索策略的构建

Embase®
PV Wizard - Alternative Drug Names

Quick PICO **PV Wizard** Medical device Advanced Drug Disease Device Article Authors

13 variants for Dapagliflozin

ALL

1 [4 chloro 3 (4 ethoxybenzyl) phenyl] 1 deoxy beta d...

2 [3 (4 ethoxybenzyl) 4 chlorophenyl] 6 hydroxymeth...

2 [4 chloro 3 (4 ethoxybenzyl) phenyl] 6 (hydroxymet...

2 [4 chloro 3 [(4 ethoxyphenyl) methyl] phenyl] 6 (hy...

bms512148

bms512148

dapagliflozin

Drug name Alternative drug names

Dapagliflozin.de OR - 13 variants

13 variants for Dapagliflozin from Emtree have been added to your search (see the panel on the left)

+ Add more alternative drug names 🔁 Reset form

Embase®
PV Wizard - Adverse Drug Reactions

Search Entree Journals Results My tools Register Login (1) (1)

Quick PICO **PV Wizard** Medical device Advanced Drug Disease Device Article Authors

Find best term

Drug name Alternative drug names **Adverse drug reactions** Special situations Human limit

EMA's MLM searches >

'adverse drug reaction'/exp OR 'adverse drug reaction'/ink OR adverse:de,ab,t OR (side OR undesirable OR unwanted) NEXT/2 (effect* OR reaction* OR event* OR outcome*)de,ab,t OR 'side effect'/ink OR 'side effect'/exp OR 'complication'/ink OR 'complication'/exp OR 'complication*':de,ab,t OR 'worsening':de,ab,t OR 'case report*':de,ab,t OR 'pharmacovigilance':de,ab,t OR 'postmarketing surveillance'/exp OR 'drug interaction'/ink OR 'drug interaction'/exp OR 'toxicity'/exp OR 'drug toxicity'/ink OR 'toxic*':de,ab,t OR 'intox*':de,ab,t OR 'safety':de,ab,t OR 'poison*':de,ab,t OR 'pharmacotox*':de,ab,t OR 'neurotox*':de,ab,t OR 'cardiotox*':de,ab,t OR 'nephrotox*':de,ab,t OR 'hepatotox*':de,ab,t OR 'immunotox*':de,ab,t OR 'immunocytox*':de,ab,t OR 'cytox*':de,ab,t OR 'carcinogen*':de,ab,t OR 'cancerogen*':de,ab,t OR 'mutagen*':de,ab,t OR 'terato*':de,ab,t OR 'fatal outcome'/exp OR 'death'/exp OR 'death*':de,ab,t OR 'suicide'/exp OR 'suicid*':de,ab,t OR 'mortal*':de,ab,t OR 'fatal*':de,ab,t OR 'risk'/exp OR 'nocebo':de,ab,t OR 'lethal concentration'/exp OR 'iatrogenic disease'/exp OR 'fertility'/exp OR 'substance-related disorders'/exp OR 'chemically induced':de,ab,t OR 'morbidity':de,ab,t OR 'congenital disorder':de,ab,t OR 'infertility'/exp OR 'injury'/exp

Embase®
PV Wizard - Human Limit

Search Entree Journals Results My tools Register Login (1) (1)

Quick PICO **PV Wizard** Medical device Advanced Drug Disease Device Article Authors

Find best term

Drug name Alternative drug names Adverse drug reactions **Special situations** Human limit

EMA's MLM searches >

human/exp OR human OR hcn OR weath OR cbbd OR boy OR get

Clear query 🔁 Reset form

Limit to:

Publication years (including)

2018 ▼ to 2020 ▼

Records added to Emtree (including end date)

01-01-2019

Search details

Summary:

(((Glnq[unavailable] OR [mg]measur[de,ab,t] OR [mg]de OR [human]de) AND (AND) (Governe[de,ab,t] OR Special[de,ab,t])) AND (human limit)) AND (base limit)

Full search strategy

Embase®
PV Wizard - Special Situations

Search Entree Journals Results My tools Register Login (1) (1)

Quick PICO **PV Wizard** Medical device Advanced Drug Disease Device Article Authors

Find best term

Drug name Alternative drug names Adverse drug reactions **Special situations** Human limit

EMA's MLM searches >

'pregnancy'/exp OR pregnant*':de,ab,t OR pregnanc*':de,ab,t OR 'pregnancy complication'/exp OR 'pregnancy disorder'/exp OR 'abortion'/exp OR 'abortion*':de,ab,t OR 'lactation'/exp OR 'breast feeding':de,ab,t OR 'breast milk':de,ab,t OR 'reproduction'/de OR 'fetus'/de OR 'embryo'/de OR 'prenatal*':de,ab,t OR 'perinatal*':de,ab,t OR 'newborn*':de,ab,t OR 'parameters concerning the fetus, newborn and pregnancy'/exp OR 'aged-exp OR elderly':de,ab,t OR 'geriatric*':ab OR (environmental OR occupational) NEXT/1 exposure*':de,ab,t OR 'compassionate use*':de,ab,t OR named NEXT/1 (use OR patient*):ab,t OR 'inappropriate prescri*':de,ab,t OR 'drug metabolism'/exp OR 'organ dysfunction':de,ab,t OR 'organ failure':de,ab,t OR 'hypersensitivity*':de,ab,t OR 'allerg*':de,ab,t OR 'counterfeit':de,ab,t OR 'falsified drug*':de,ab,t OR ('unavailable' NEAR/2 drug):de,ab,t OR 'drug resistance'/exp OR 'drug resistance*':de,ab,t OR 'withdrawal syndrome'/de OR (drug* NEAR/3 (withdrawal OR toleran* OR interact* OR exposure* OR induc* OR resist* OR ineff* OR nonrespon* OR unrespon*))de,ab,t OR 'drug tolerance'/exp OR (drug* OR treatment) NEXT/1 (failure* OR contraindication*):de,ab,t OR 'medication error'/exp OR (near NEXT/1 miss*):ab,t OR 'ineff*':de,ab,t OR 'nonrespon*':de,ab,t OR 'unrespon*':de,ab,t OR (lack OR no OR non OR not) NEXT/2 (eff* OR respon*):ab,t OR 'device failure*':de,ab,t OR 'manufacturing near/3 (error OR fault OR mistake OR failure OR contamination OR impurity) OR 'patient compliance'/exp OR 'overdos*':de,ab,t OR 'drug abuse'/exp OR abus*':de,ab,t OR misus*':de,ab,t OR 'off label':de,ab,t OR 'unlicensed':de,ab,t

Clear query 🔁 Reset form

最后的结果与提醒

Embase® Search Entree Journals Results My tools Register Login (1) ⓘ

Search Mapping Date Sources Fields Quick limits EBM Pub. types Languages Gender Age Animal Search tips

Results Filters + Expand - Collapse all Apply

- Sources
- Drugs
- Diseases
- Devices
- Floating Subheadings
- Age
- Gender
- Study types
- Publication types
- Journal titles
- Publication years
- Authors
- Conference Abstracts
- Drug Trade Names
- Drug Manufacturers
- Device Trade Names

History Save | Delete | Print view | Export | Email Combine using And Or Collapse

#1 (dapagliflozin/... 1,040

2,104 results for search #1 Set email alert Set RSS feed Search details Index minder

Results View | Print | Export | Email | Order | Add to clipboard

Select number of items Selected: 0 (clear)

- 1 Therapeutic approaches to diabetic cardiomyopathy: Targeting the antioxidant pathway
Arad M., Waldman M., Abraham N.G., Hochhauser E.
Prostaglandins and Other Lipid Mediators 2020 150 Article Number 106454 Cited by: 0
Embase MEDLINE Abstract Index Terms View Full Text
- 2 Separation of achiral anti-diabetic drugs using sub/supercritical fluid chromatography with a docking study
Pandya P.A., Shah P.A., Shrivastav P.S.
Journal of Pharmaceutical and Biomedical Analysis 2020 189 Article Number 113452
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- 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年将扩展到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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