Drug metabolism and toxicity

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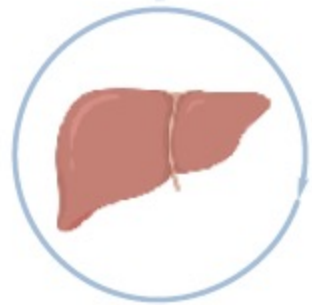
20211213

Introduction to drug metabolism

- Common biotransformations



Metabolism-induced toxicity

- Mechanisms of adverse reactions
  - Reactive intermediates and structural alerts

Applications to drug design

- Designing around metabolism

Applications to drug design

- Designing around drug-induced toxicity
- Challenges in predicting adverse effects

Introduction to drug metabolism

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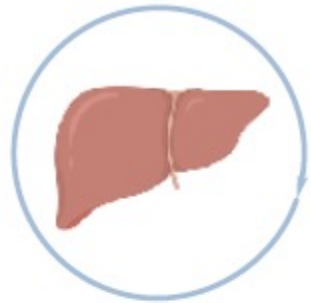

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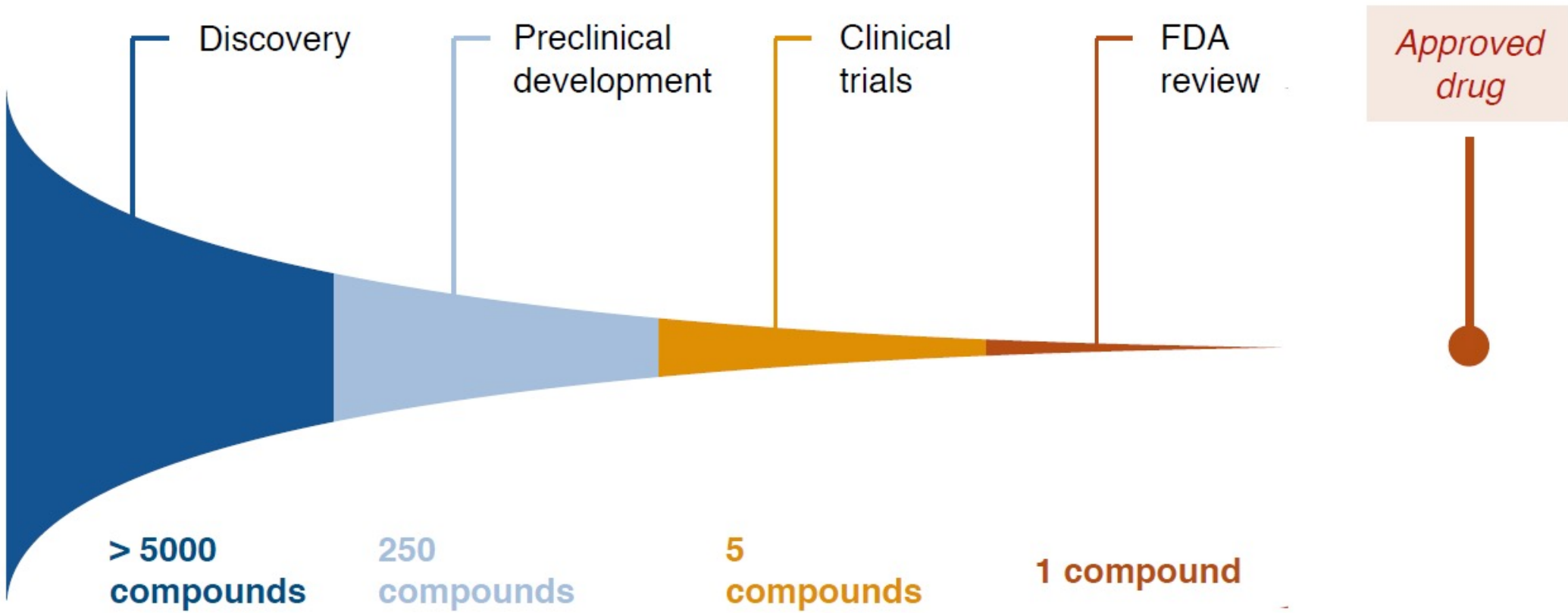
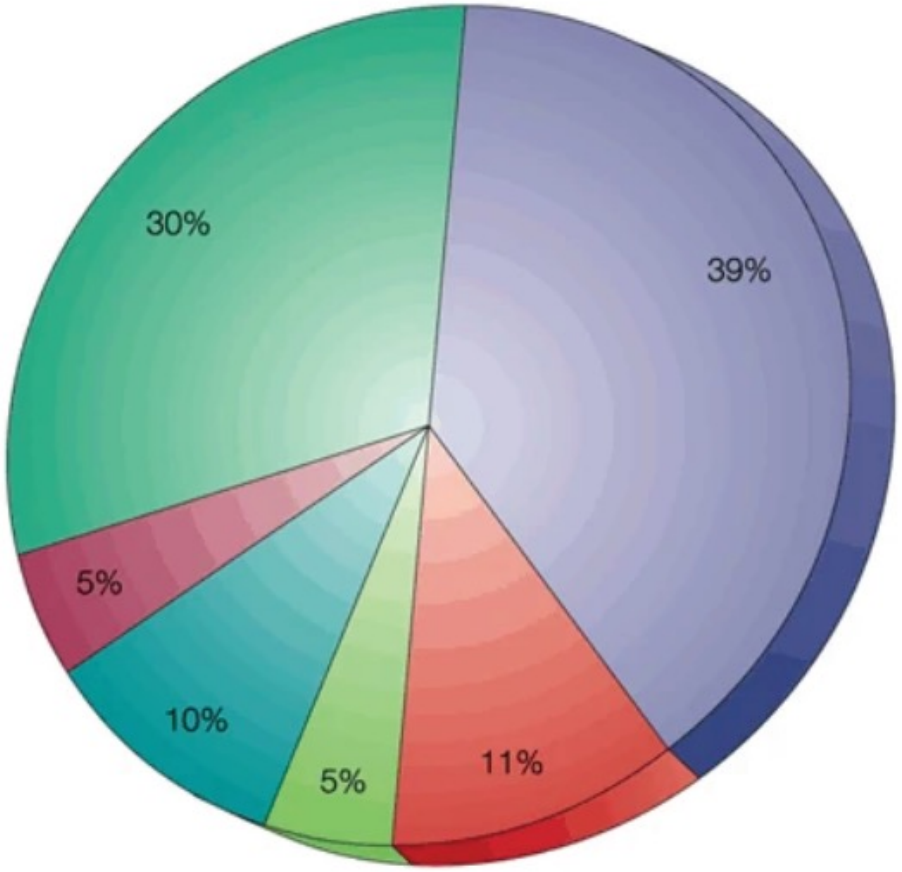
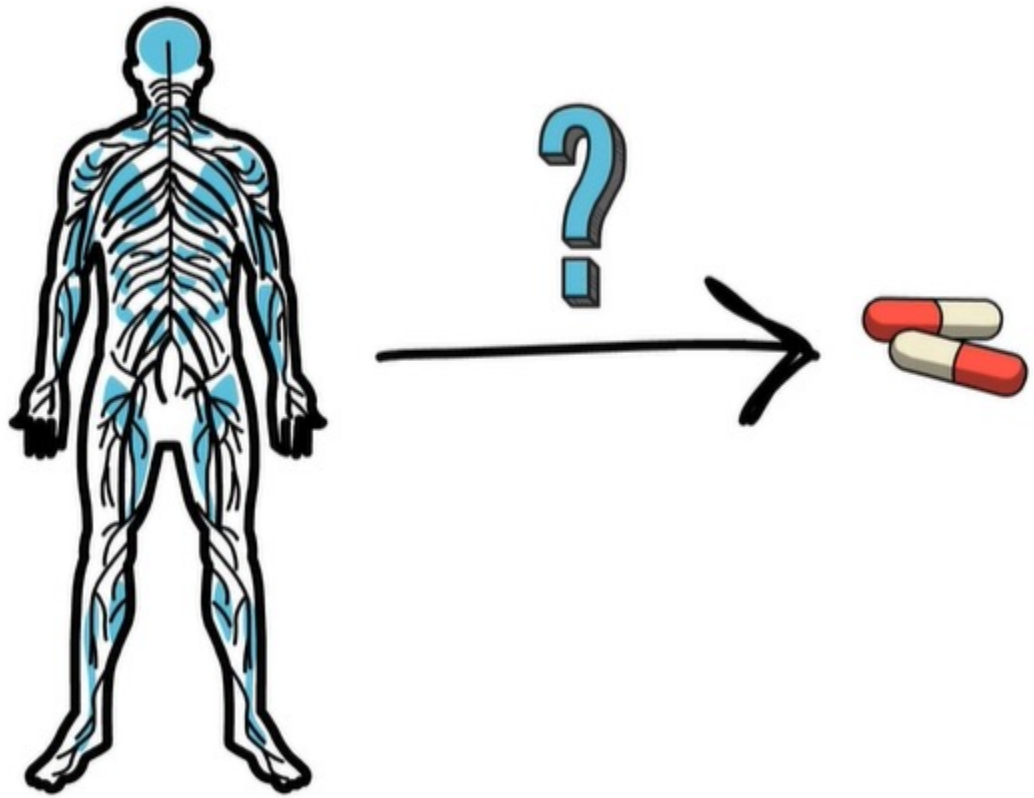

Discovery
Preclinical development
Clinical trials
FDA review
Approved drug
> 5000 compounds
250 compounds
5 compounds
1 compound



Causes of drug failure

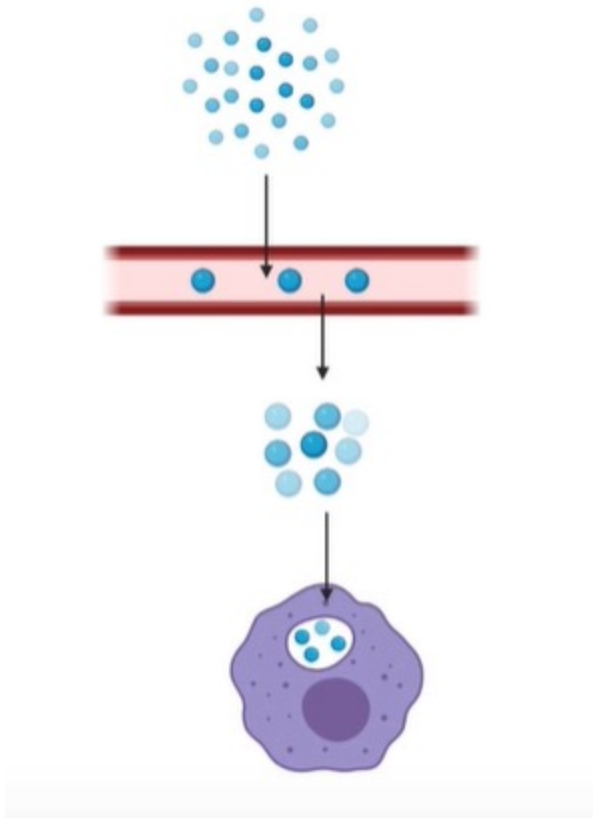
- Pharmacokinetics
- Adverse effects in man
- Animal toxicity
- Commercial reasons
- Miscellaneous
- Lack of efficacy



Pharmacokinetics

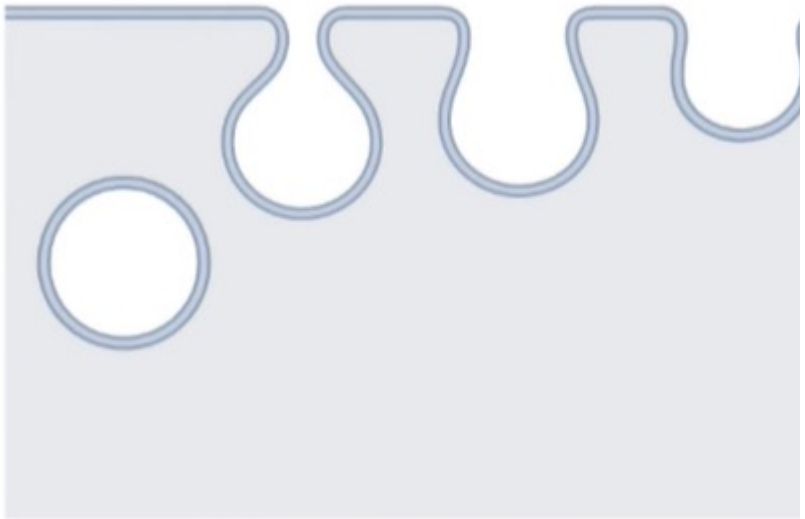
- Absorption
- Distribution
- Metabolism
- Elimination

Absorption

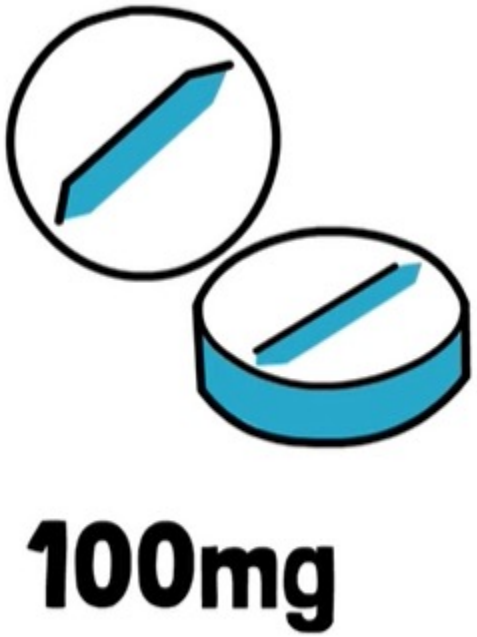


Absorption

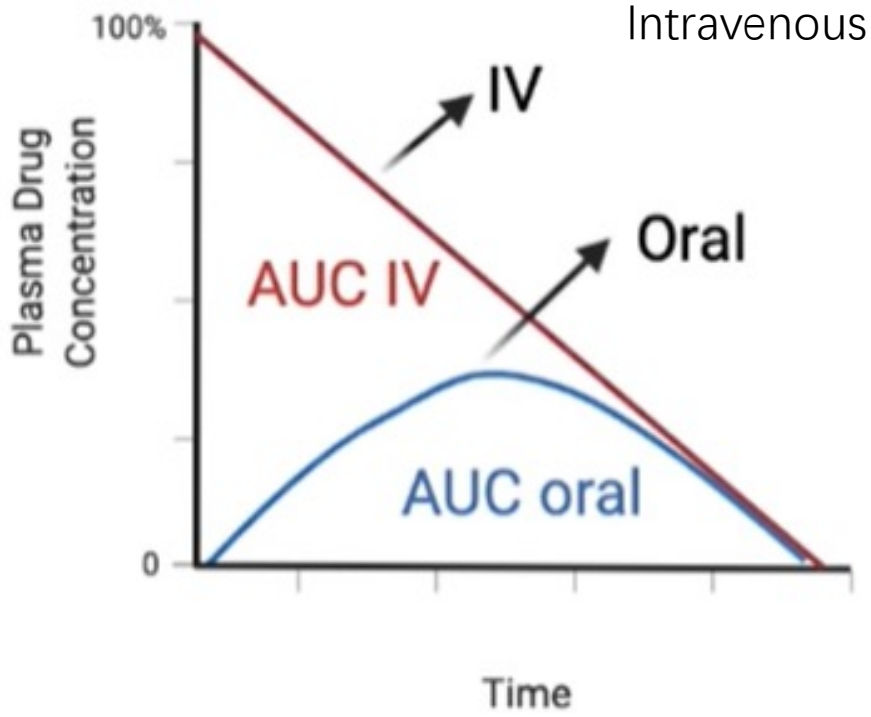
被动扩散 (Passive Diffusion)	高浓度到低浓度
易化扩散 (Facilitated Diffusion)	借助转运蛋白
主动转运 (Active Transport)	消耗ATP
胞吞 (Endocytosis)	细胞膜包裹



If you take a 100mg drug, how much enters the body ?



Bioavailability



Intravenous injection

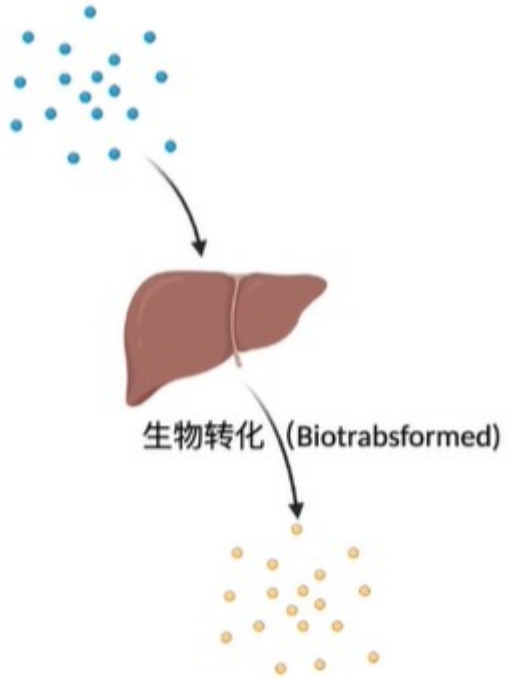
生物利用度 (Bioavailability) = (AUC oral / AUC IV)*100%

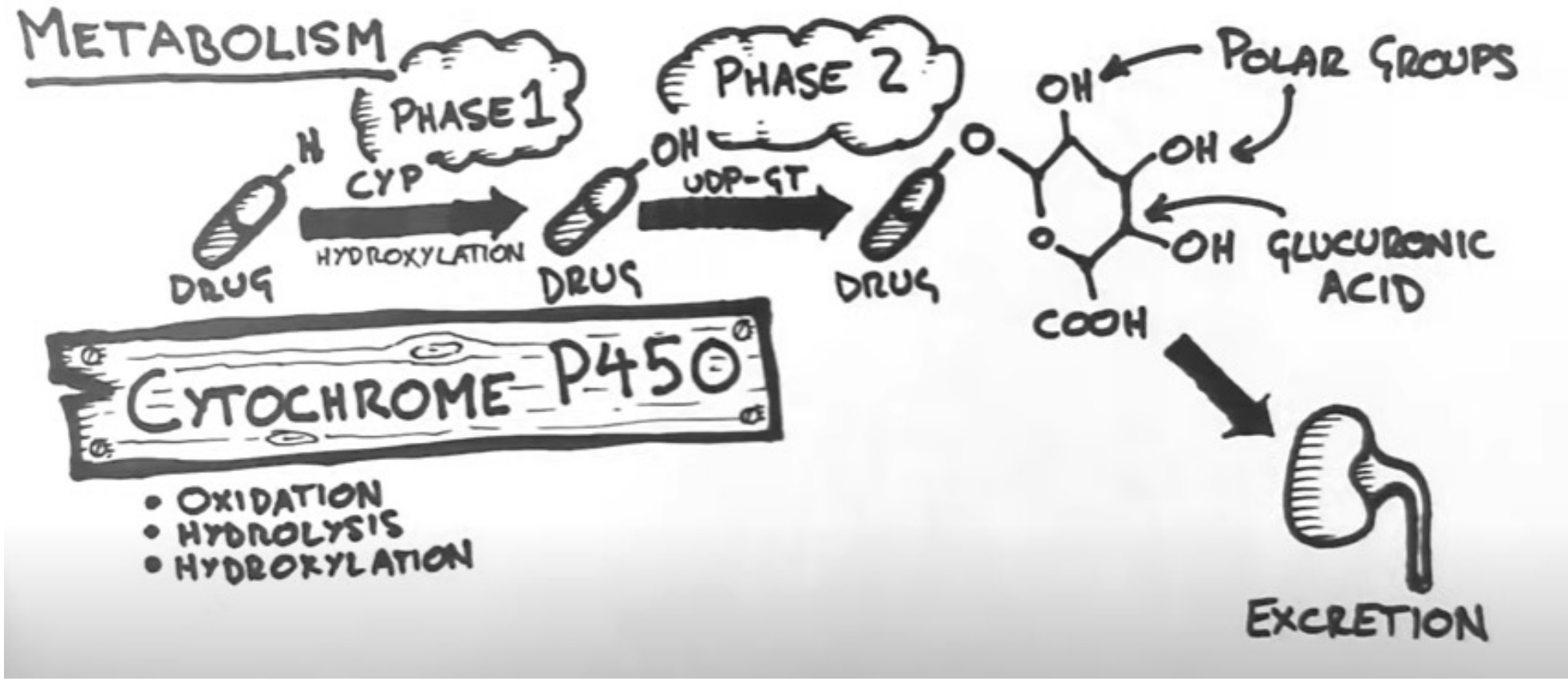
Distribution

表观分布容积（Vd）

↓ Vd = （在体内的药物量）/（血药浓度）↑

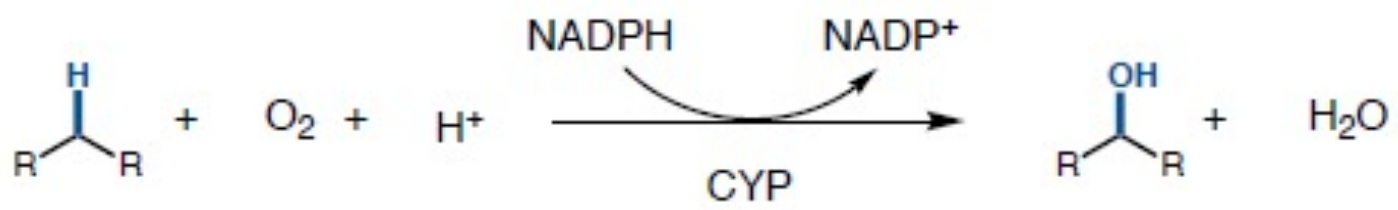
Metabolism



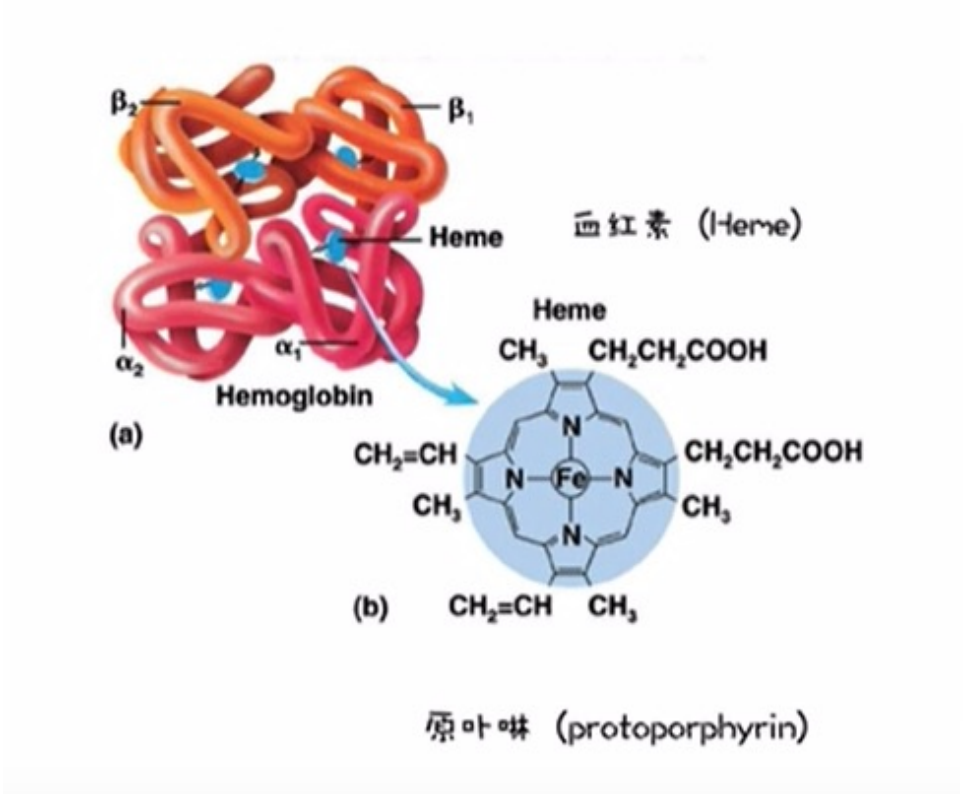

METABOLISM
PHASE 1
PHASE 2
CYP
UDP-GT
HYDROXYLATION
DRUG
DRUG
DRUG
POLAR GROUPS
OH
OH
OH
OH
COOH
GLUCURONIC ACID
CYTOCHROME P450
• OXIDATION
• HYDROLYSIS
• HYDROXYLATION
EXCRETION

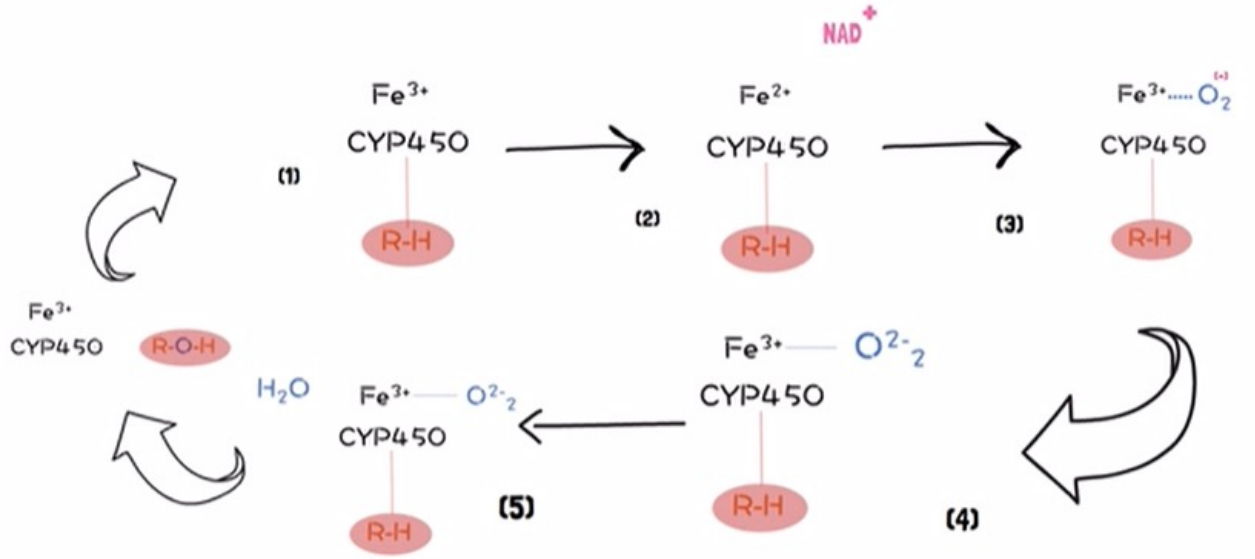
一阶段 修改 biotransformation

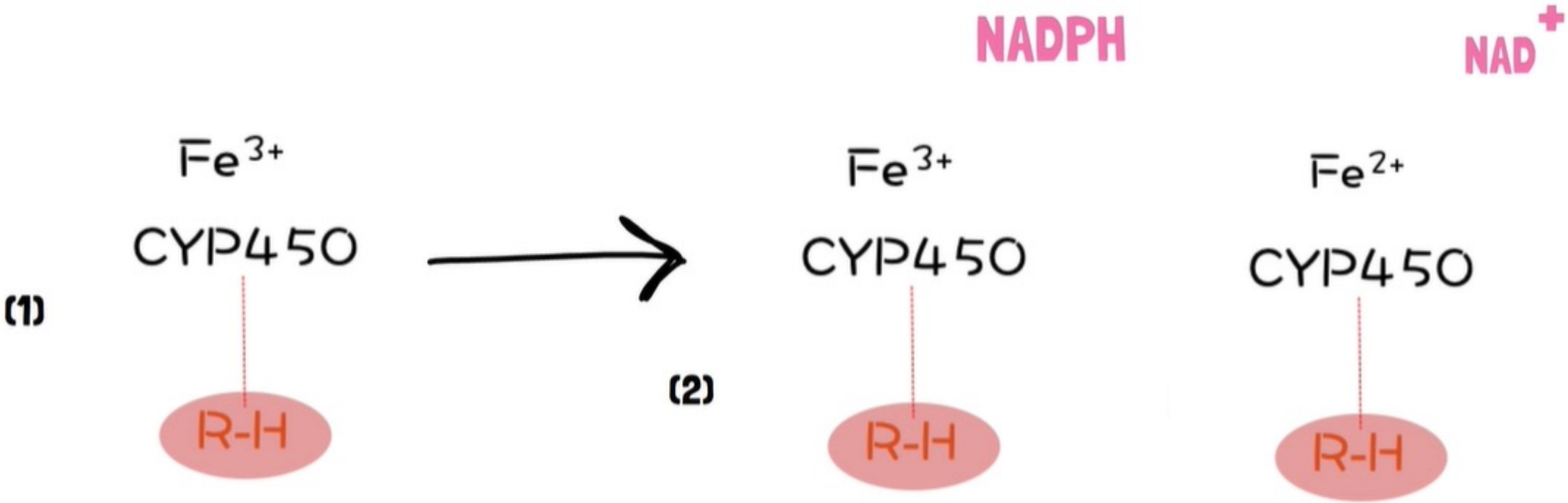
由CYP（其他也行）更改药物分子，添加极性基团



CYP450的反应

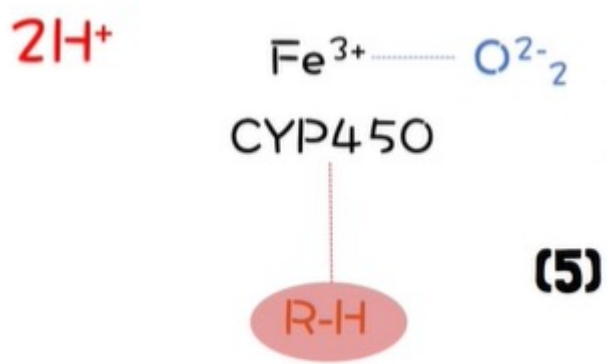

β2
β1
Heme
血红素 (Heme)
α2
α1
Hemoglobin
(a)
Heme
CH3
CH2CH2COOH
CH2=CH
CH2CH2COOH
CH3
CH3
(b)
CH2=CH
CH3
原卟啉 (protoporphyrin)

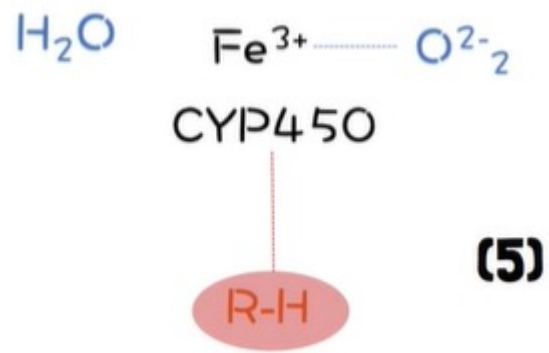

NAD+
Fe3+
CYP450
R-H
(1)
Fe2+
CYP450
R-H
(2)
Fe3+..... O2 (-1)
CYP450
R-H
(3)
(4)
Fe3+ O2 2-
CYP450
R-H
(5)
Fe3+ O2 2-
CYP450
R-H
H2O
Fe3+
CYP450
R-O-H

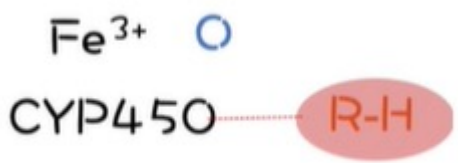

NADPH
NAD+
Fe3+
CYP450
(1)
R-H
(2)
Fe3+
CYP450
R-H
Fe2+
CYP450
R-H

(3)

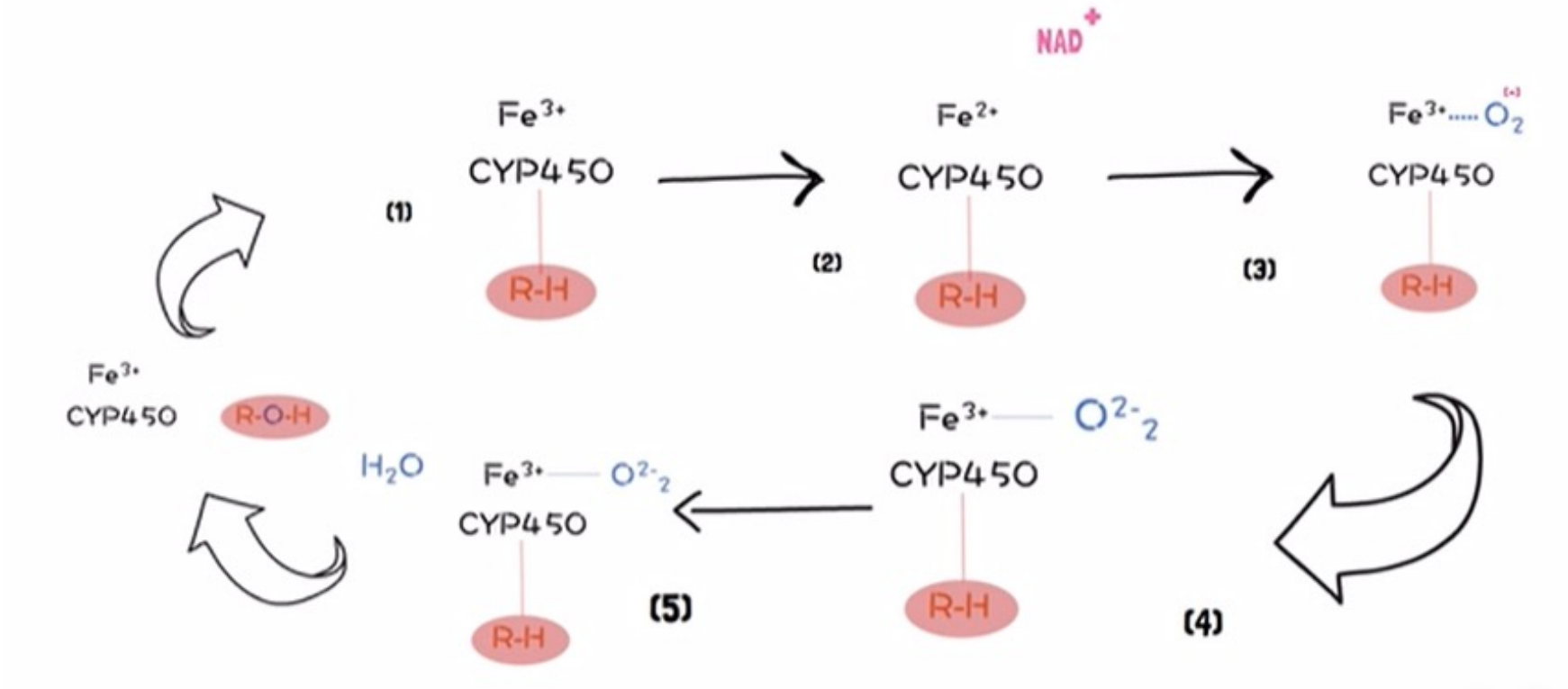

NADPH
Fe3+ O-2
CYP450
R-H
(4)
Fe3+ O2-2
CYP450
R-H


2H+
Fe3+
O2-2
CYP450
R-H
(5)


H2O
Fe3+
O2-2
CYP450
R-H
(5)

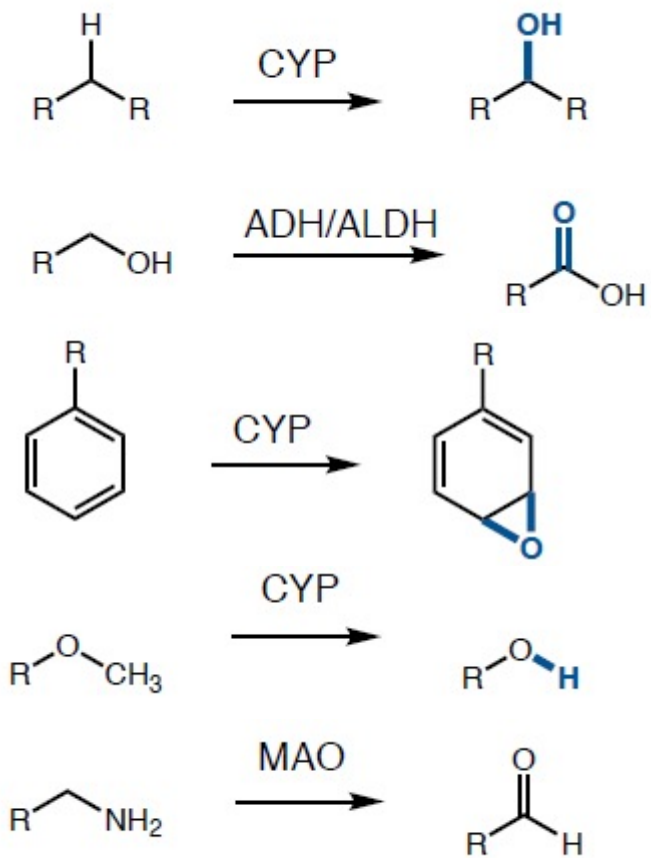

Fe3+
O
CYP450
R-H

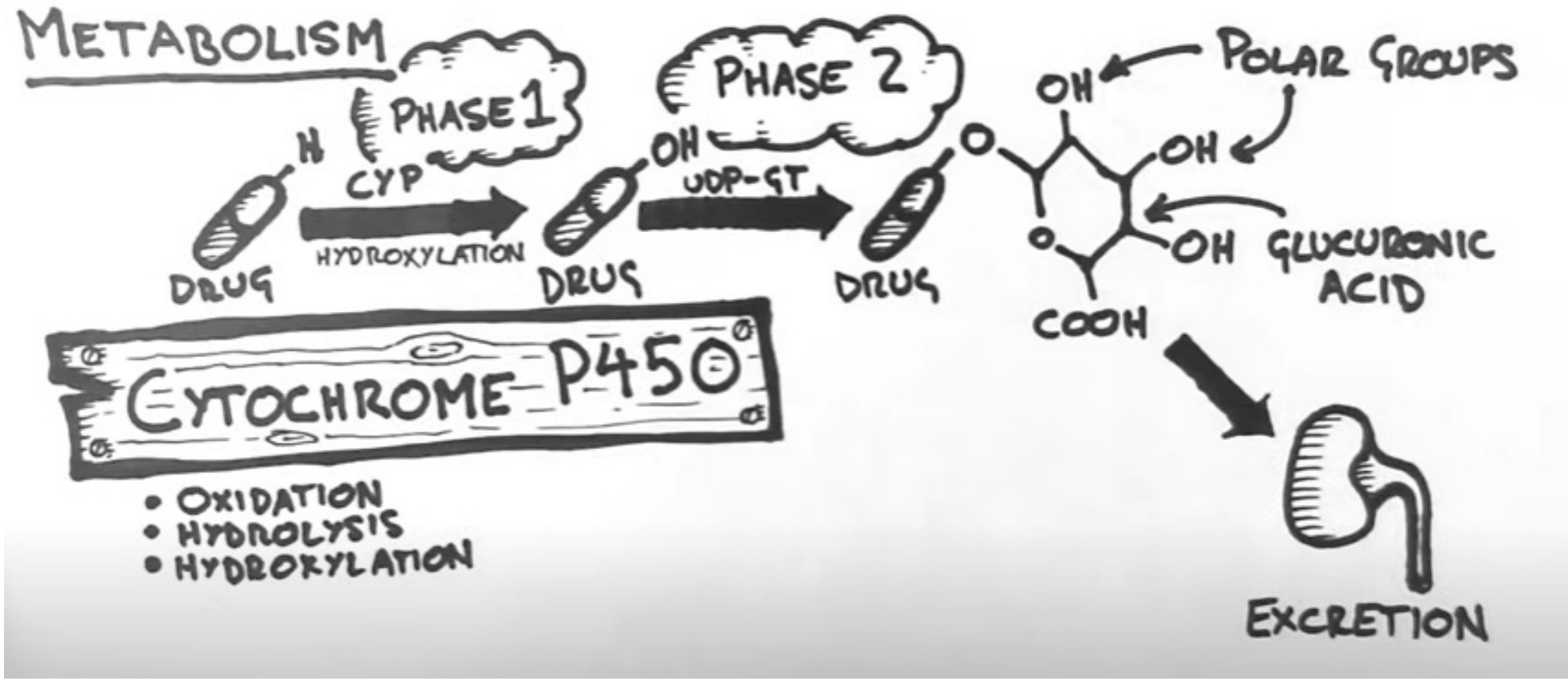

Fe3+
CYP450
R-O-H


NAD+
Fe3+
CYP450
R-H
(1)
Fe2+
CYP450
R-H
(2)
Fe3+..... O2 (-)
CYP450
R-H
(3)
Fe3+ —— O2 2-
CYP450
R-H
(4)
Fe3+ —— O2 2-
CYP450
R-H
(5)
H2O
Fe3+
CYP450
R-O-H

分类

- Hydroxylation羟基化
- Oxidation 氧化
- Epoxidation环氧化
- Dealkylation 脱烷基
- Deamination 脱氨基

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HYDROXYLATION
DRUG
DRUG
DRUG
POLAR GROUPS
OH
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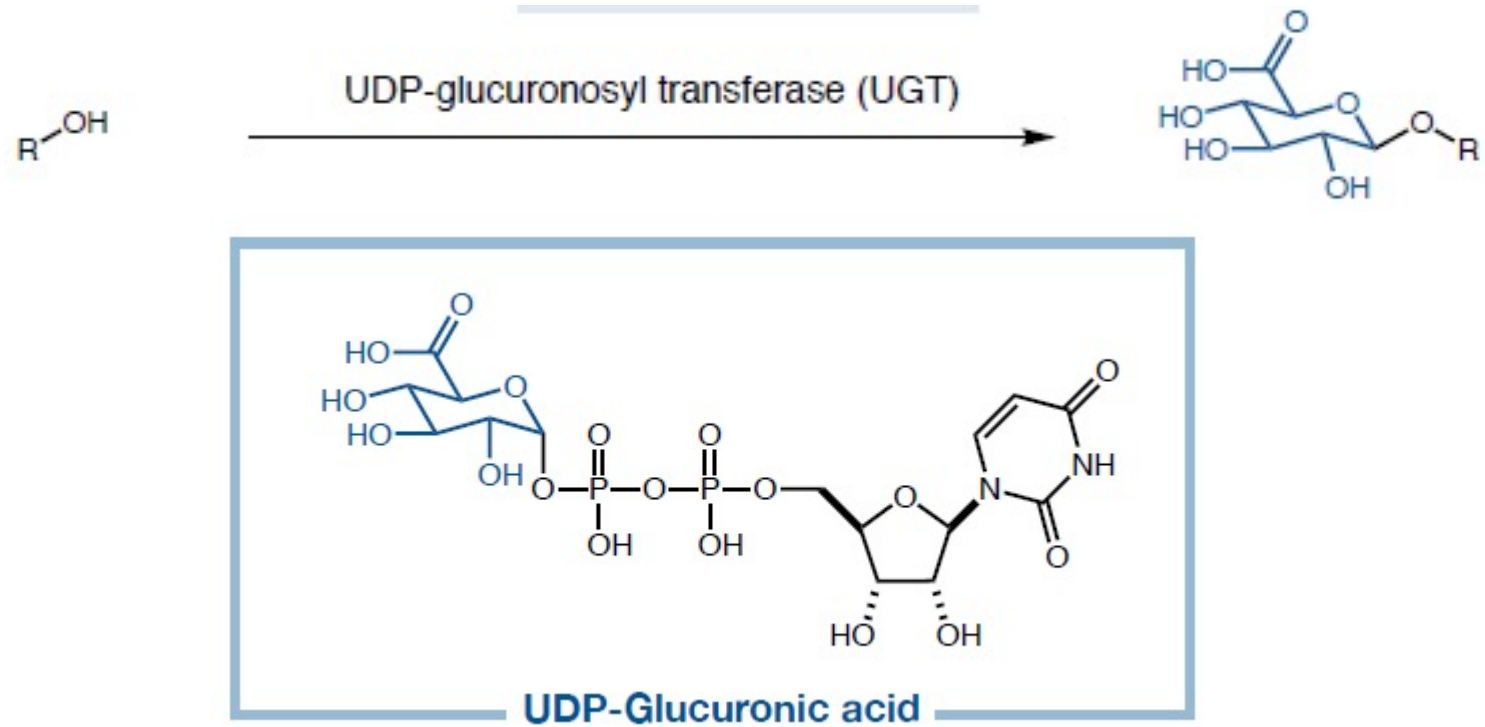
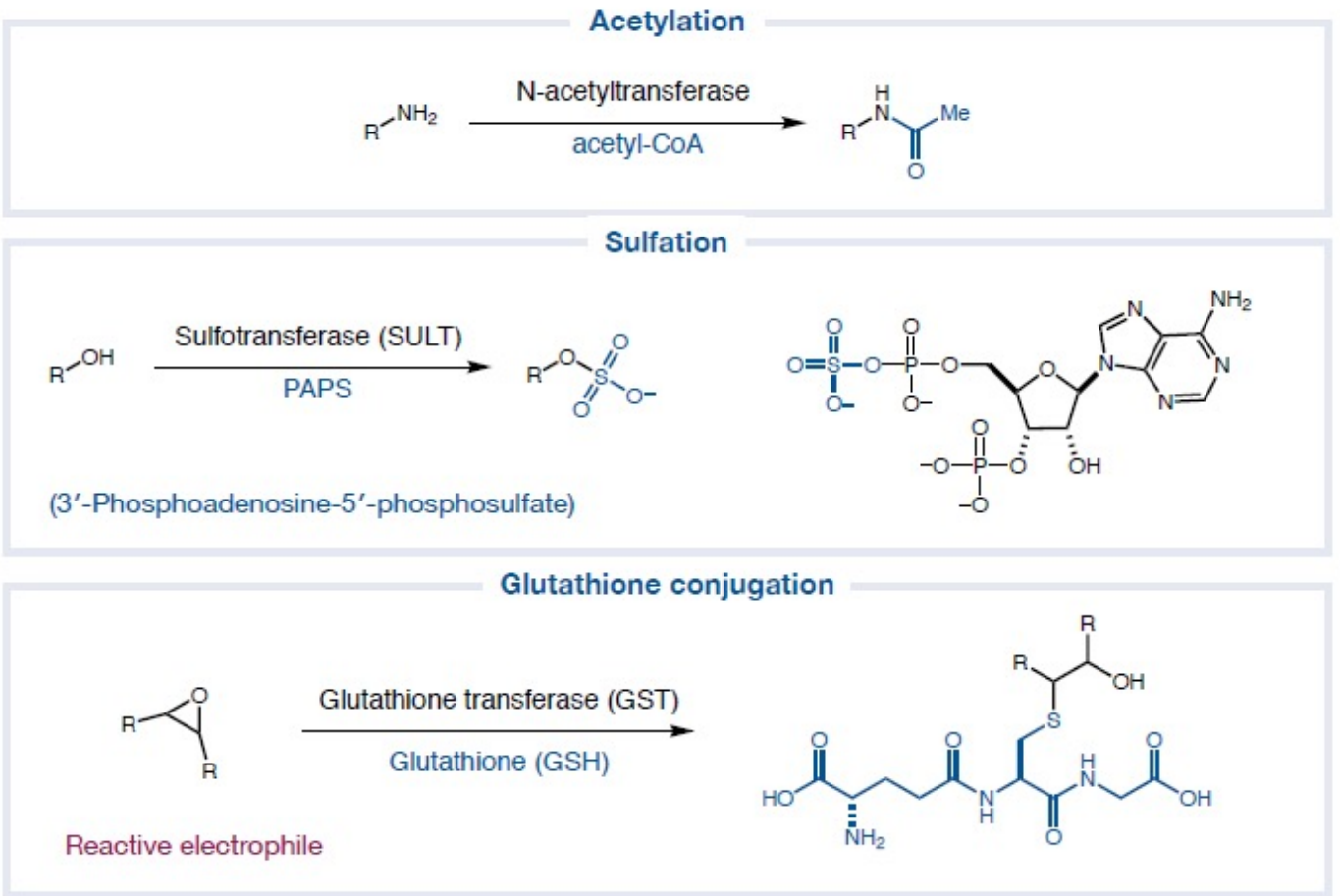
OH
OH
COOH
GLUCURONIC ACID
CYTOCHROME P450
• OXIDATION
• HYDROLYSIS
• HYDROXYLATION
EXCRETION

二阶段 结合 Glucuronidation（葡萄干酸化）

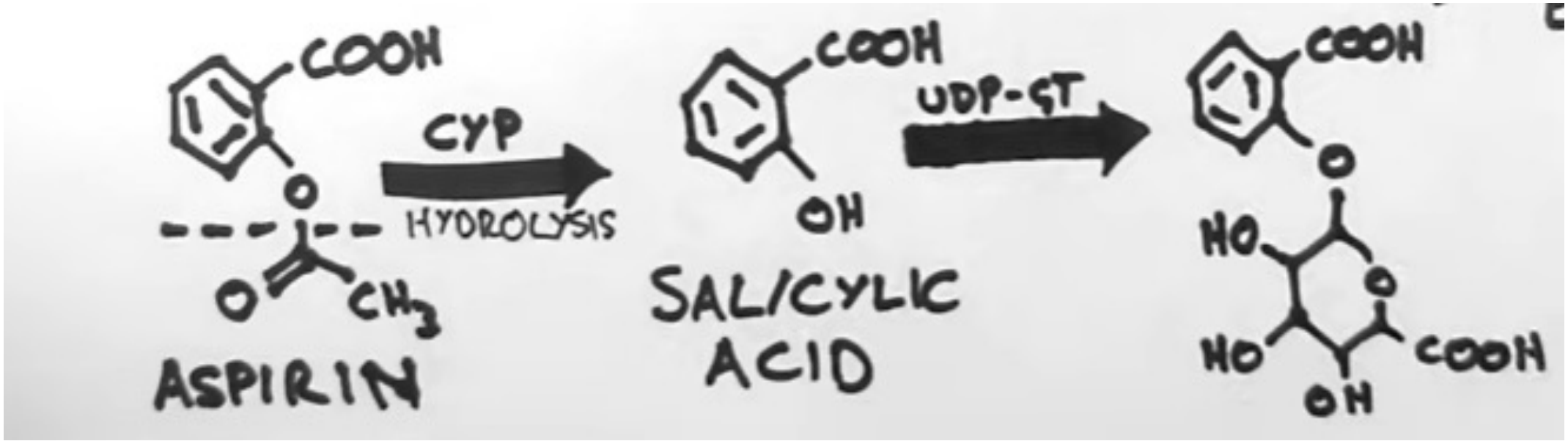
- 越来越极性，溶于水然后进肾脏

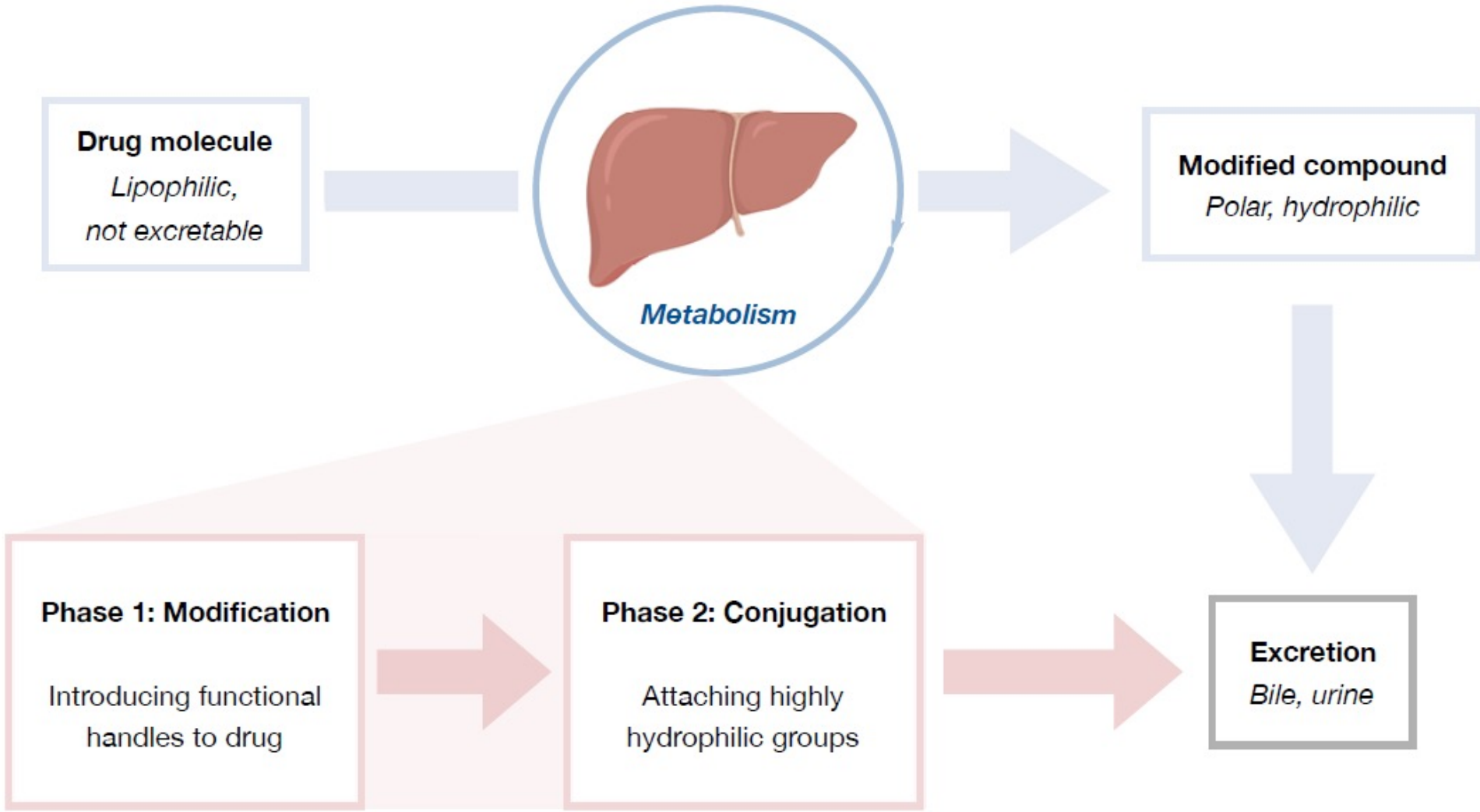


还有其他的酶


Acetylation
N-acetyltransferase
acetyl-CoA
Sulfation
Sulfotransferase (SULT)
PAPS
(3′-Phosphoadenosine-5′-phosphosulfate)
Glutathione conjugation
Glutathione transferase (GST)
Glutathione (GSH)
Reactive electrophile

阿司匹林的代谢


COOH
CYP
HYDROLYSIS
O
O
CH3
ASPIRIN
COOH
OH
SALICYLIC
ACID
UDP-GT
COOH
O
HO
HO
O
OH
COOH


Drug molecule
Lipophilic,
not excretable
Metabolism
Modified compound
Polar, hydrophilic
Phase 1: Modification
Introducing functional handles to drug
Phase 2: Conjugation
Attaching highly hydrophilic groups
Excretion
Bile, urine

Elimination

消除（Elimination）

$$Cl_{总} = Cl_{肝} + Cl_{肾} + Cl_{胆} + Cl_{其它}$$

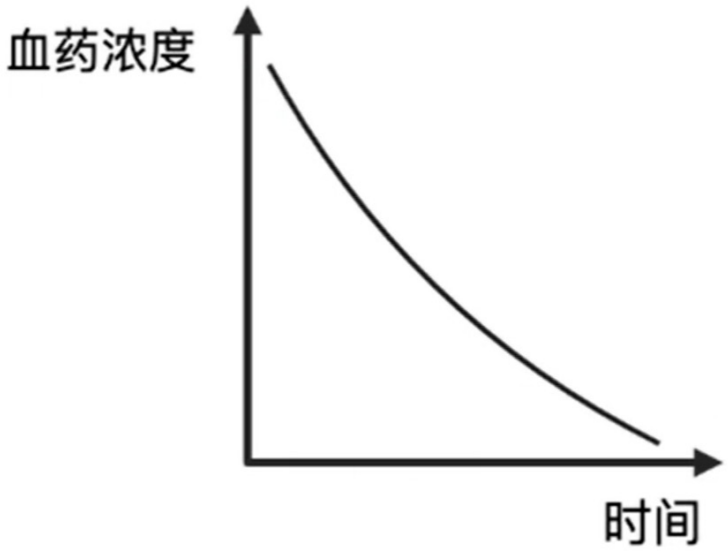
总清除率是各个器官清除率之和

一级动力学消除（First Order Kinetics）

消除速率与血药浓度成正比

-16%　　-16%　　-16%

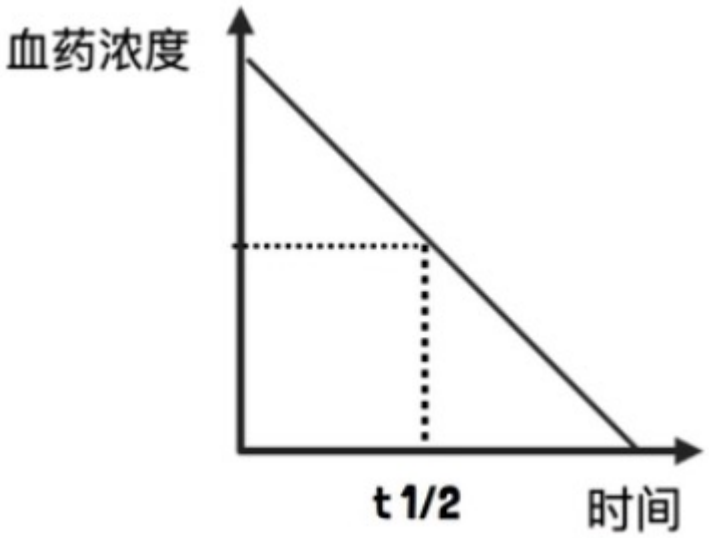
1000mg → 840mg → 706mg → 593mg



零级动力学消除（zero-kinetics）

1000mg → 800mg → 600mg → 400mg

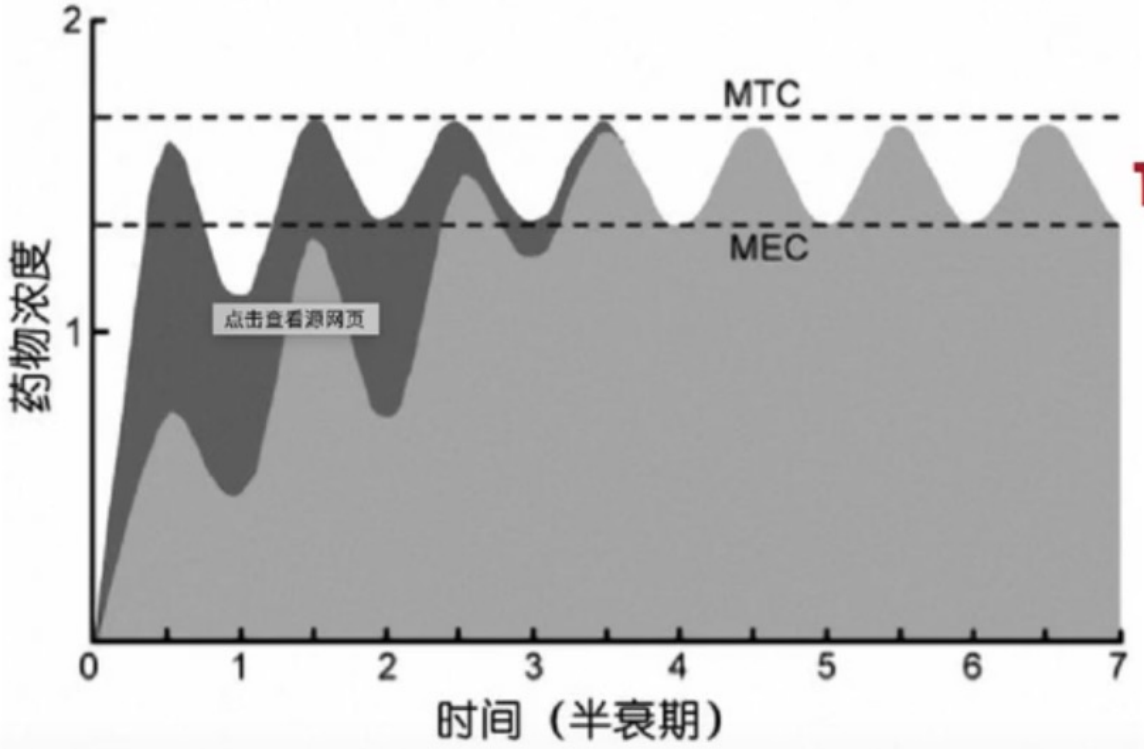
-200mg



半衰期：血压浓度降低一半所需要的时间

稳态（Steady State）

药物的吸收速率 = 药物的消除速率



Therapeutic Window

有效治疗窗

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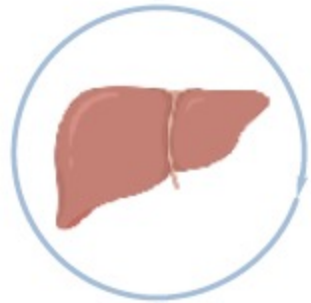

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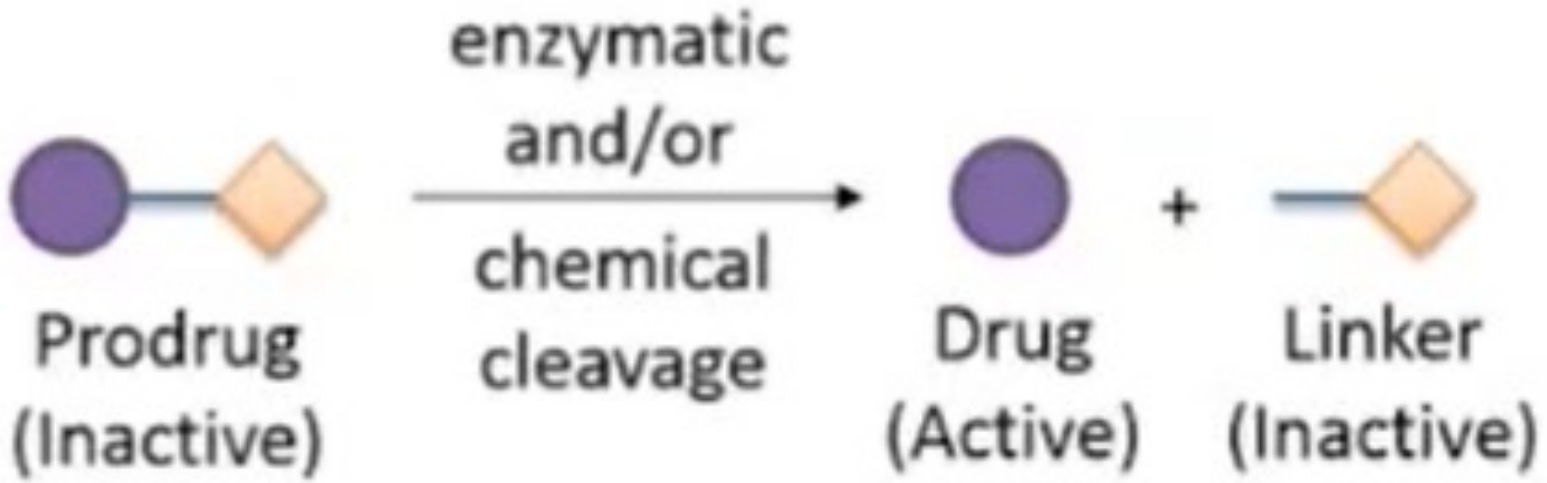
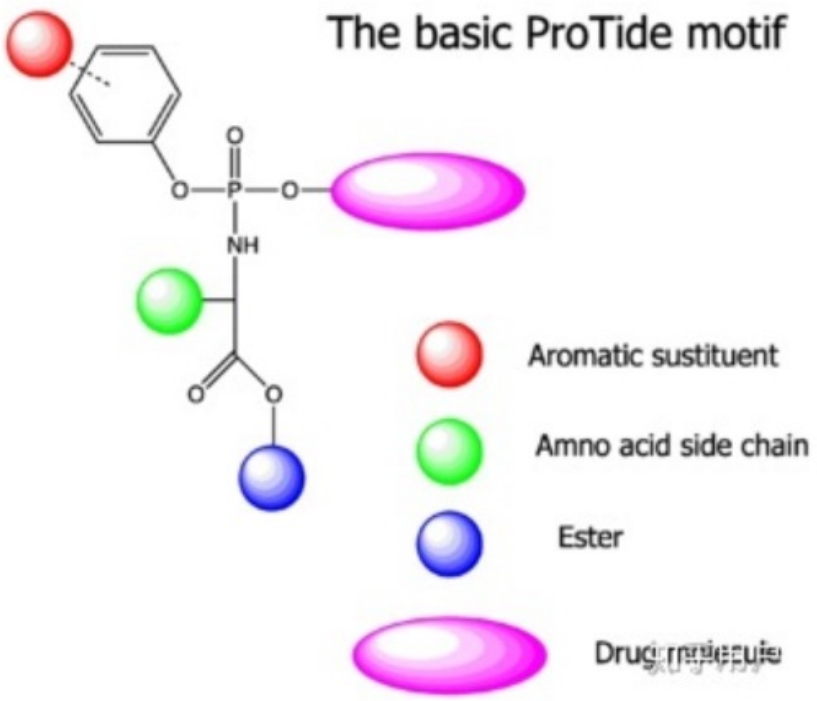
药物前体（Prodrugs）

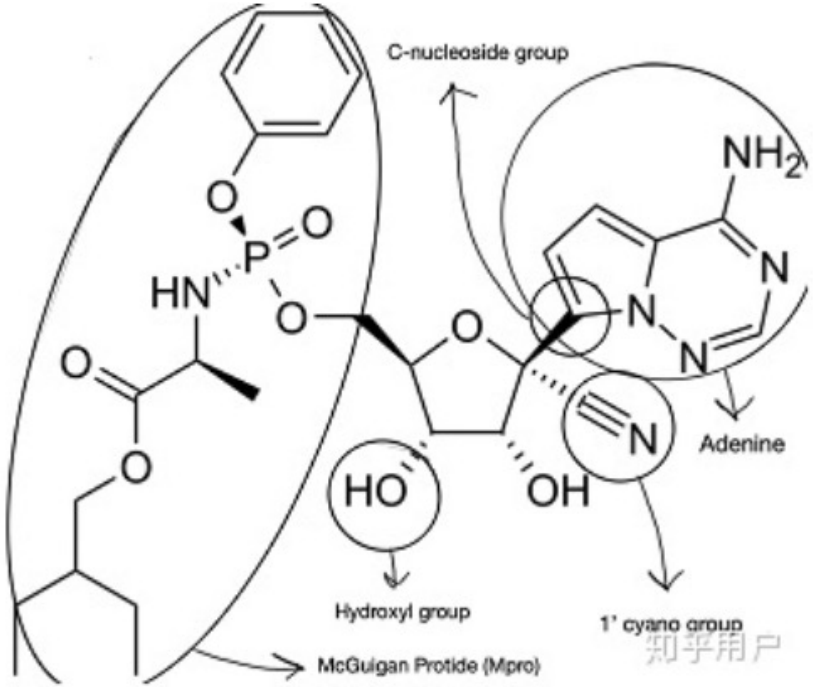
- - inactive form of drug
- - become active from after metabolism

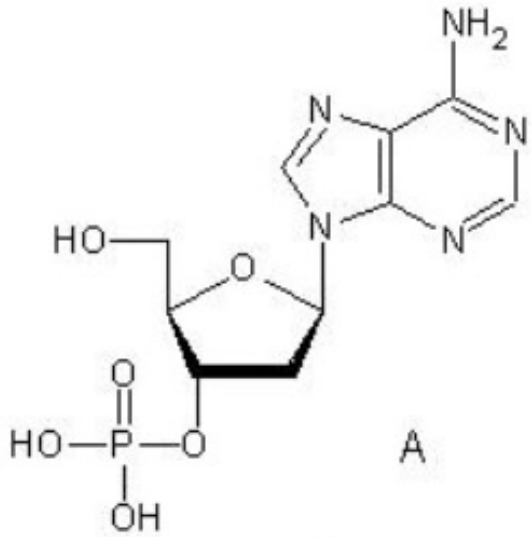


Pro Tide技术

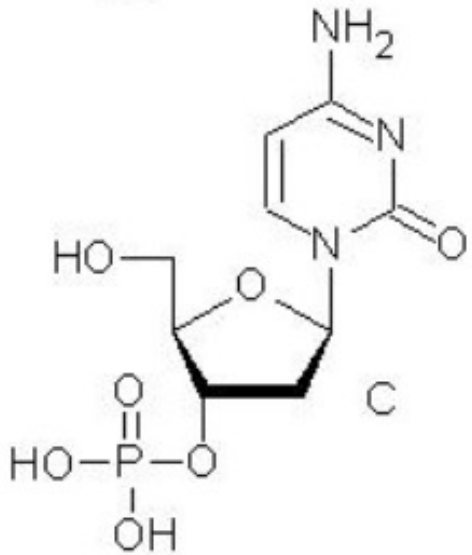
- 核苷酸类似物的作用：模仿含氮碱基



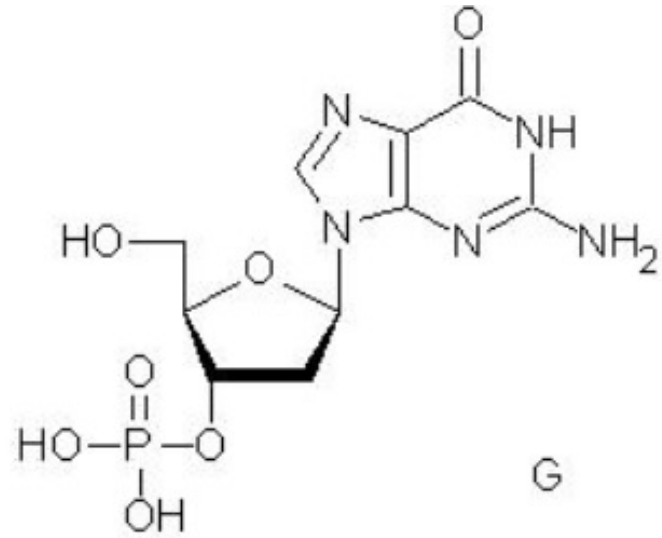



NH2
N
N
N
N
HO
O
HO
P
O
O
OH

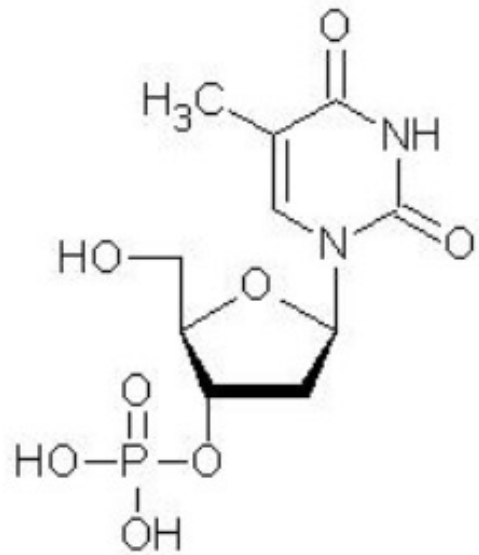
A


NH2
N
N
O
HO
O
HO
P
O
O
OH

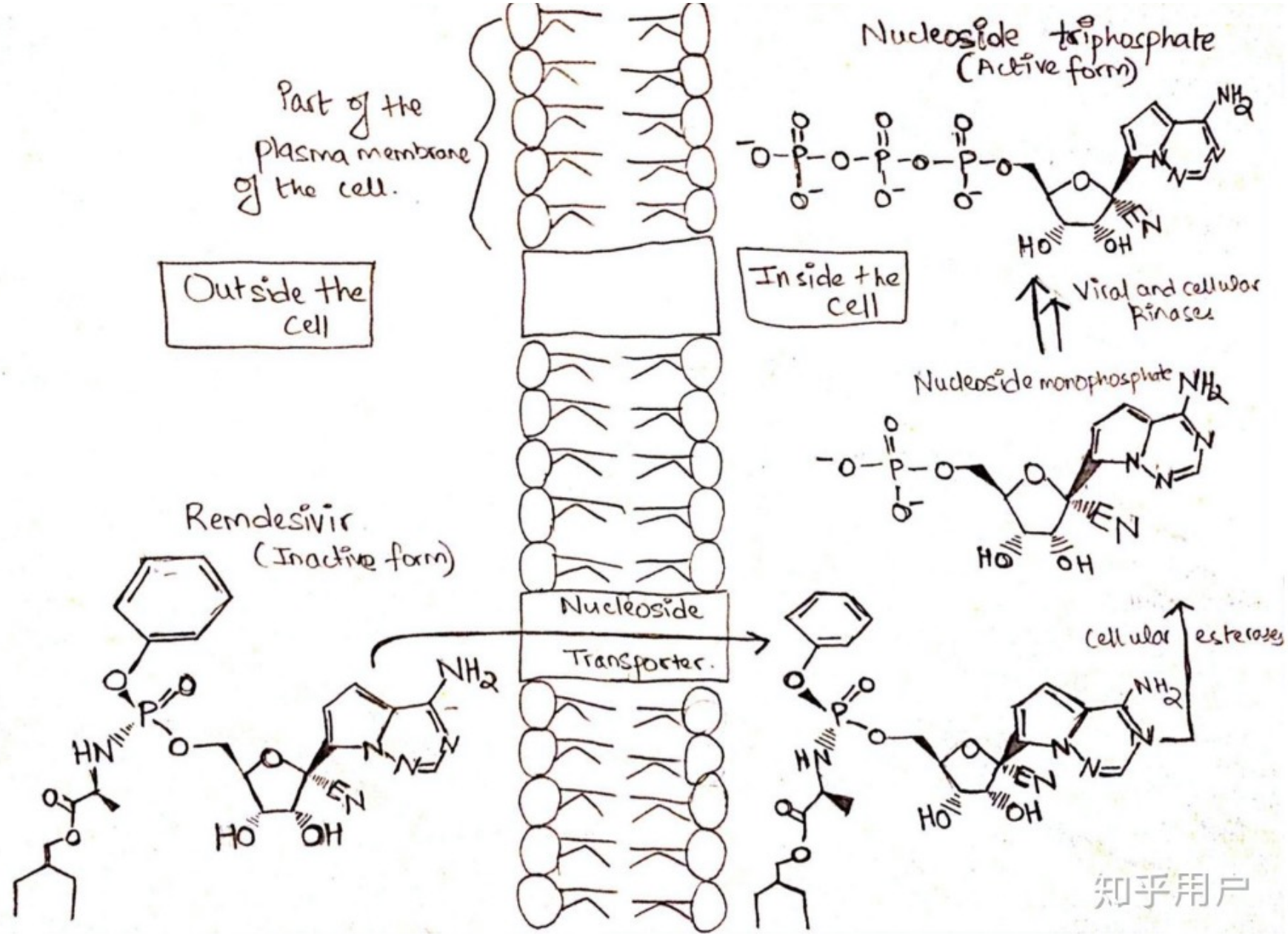
C


O
N
NH
N
N
NH2
HO
O
HO
P
O
O
OH

G


O
H3C
NH
N
O
HO
O
HO
P
O
O
OH

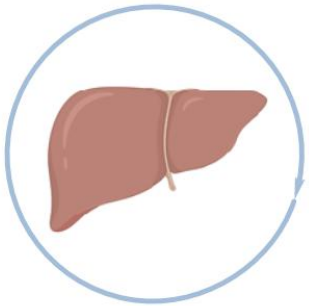
T


Part of the plasma membrane of the cell.
Outside the cell
Inside the cell
Nucleoside triphosphate (Active form)
Viral and cellular Kinases
Nucleoside monophosphate
Remdesivir (Inactive form)
Nucleoside Transporter.
Cellular esterases
知乎用户

Outline

Introduction to drug metabolism

- Common biotransformations



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- Designing around metabolism

Applications to drug design

- Designing around drug-induced toxicity
- Challenges in predicting adverse effects

不良药物反应

Adverse drug reactions (ADRs)

对一种对人有害，无意识发生，随计量影响的对药物产生的反应

Type 1

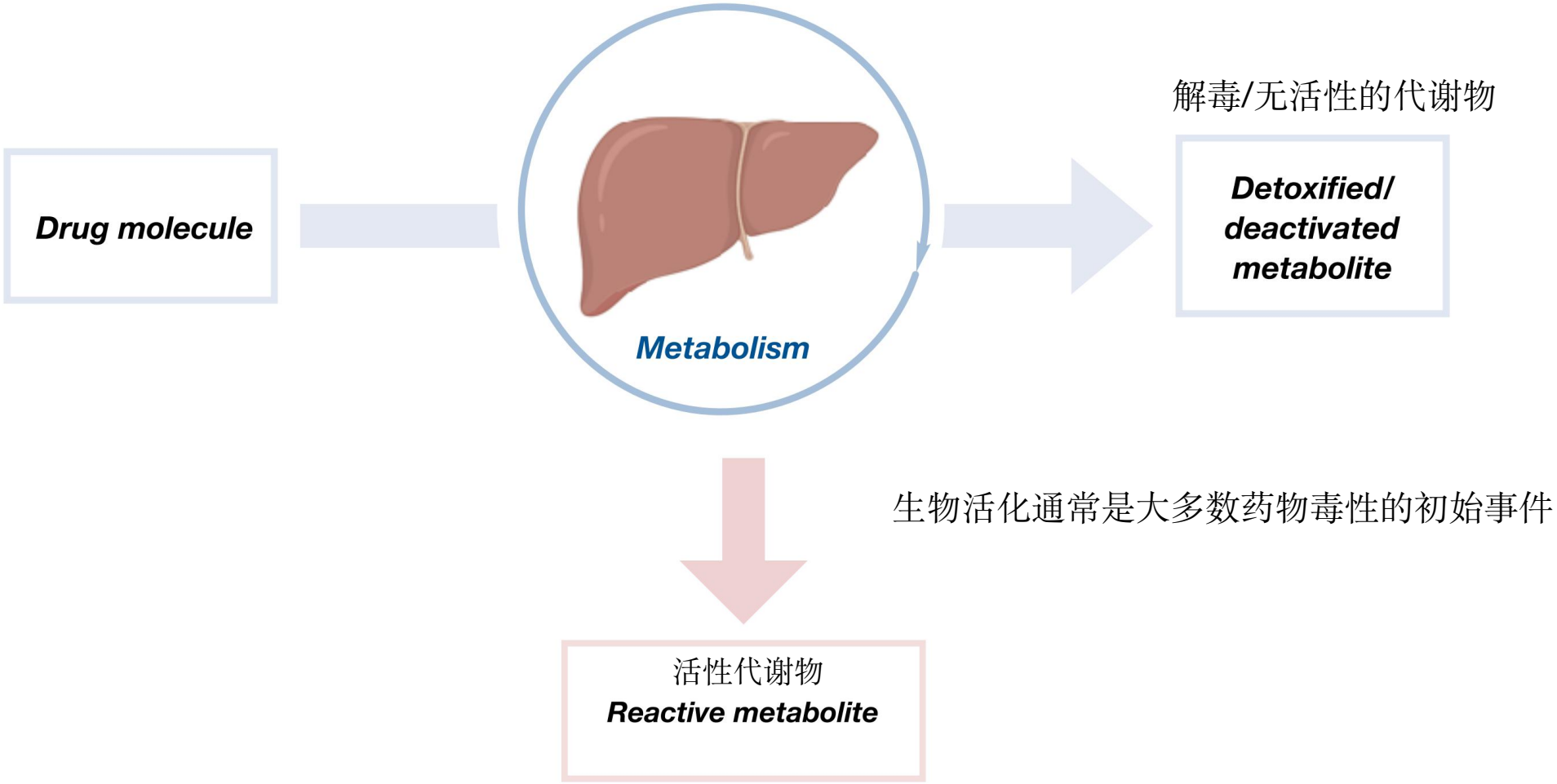
- 与初级药理学有关的药物
- 通常在动物模型中发现/临床试验
- 可以减轻通过剂量调整

Type 2 (idiosyncratic 特殊的 ADRs)

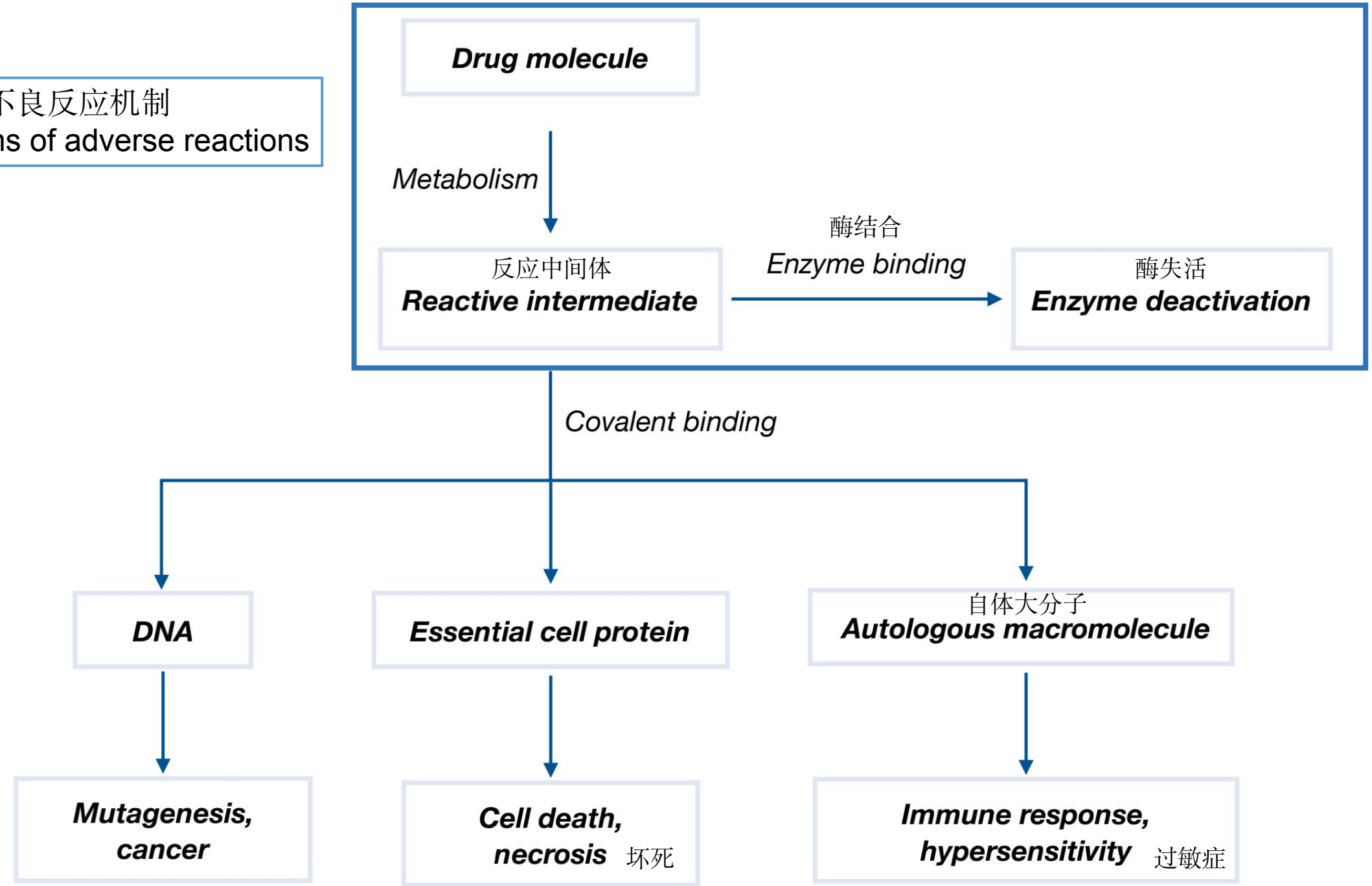
- 与初级药理学无关，机制通常不清楚
- 对大多数人来说，在任何剂量下都不会发生
  与动物模型相关性差
- 通常在药物接触到大量患者后才被发现

活性代谢物的生物活化
Bioactivation to reactive metabolites

生物活化（Bioactivation），是指毒物在有机体内积累，经过转化，形成更高浓度的有害物质的现象。

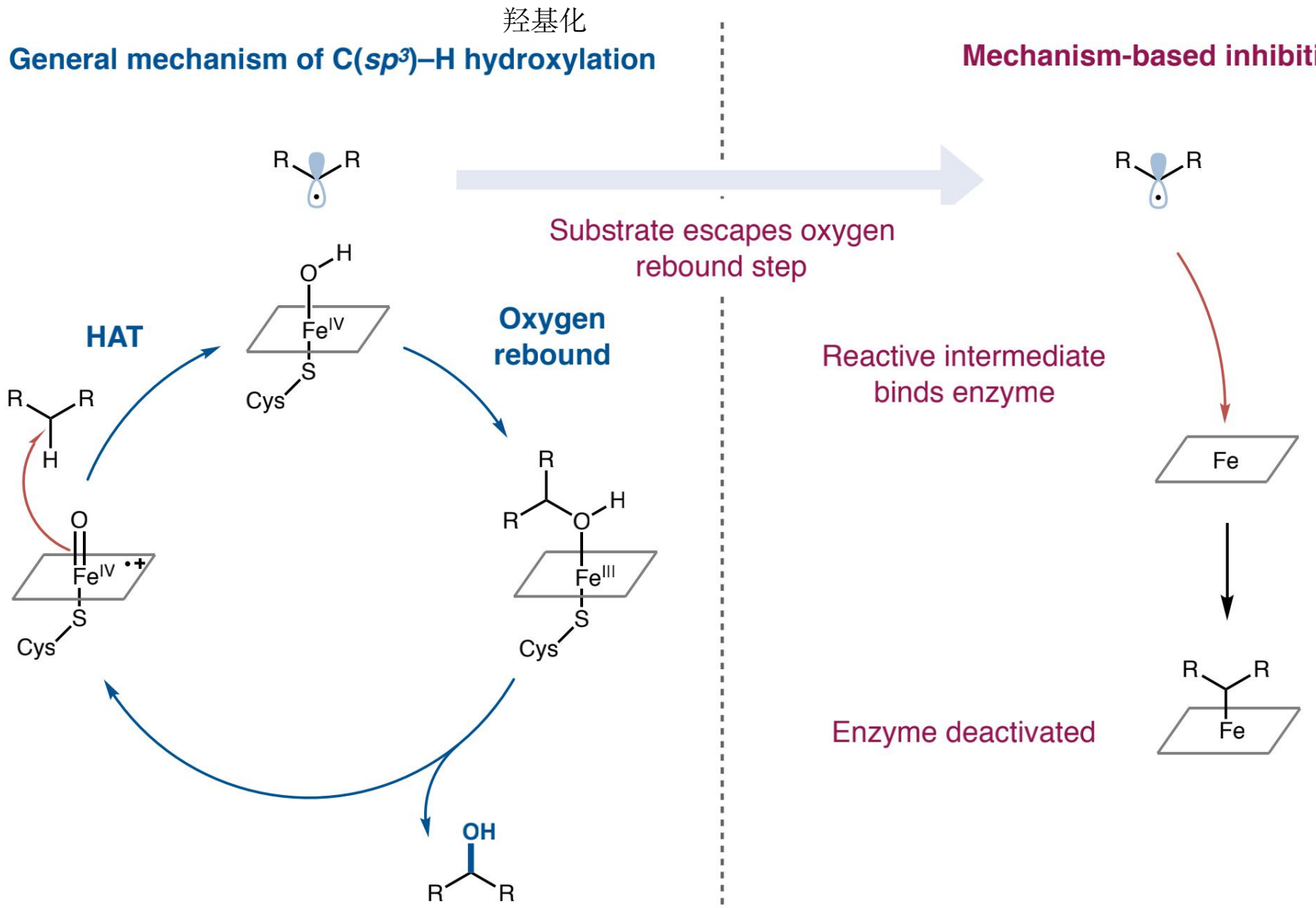


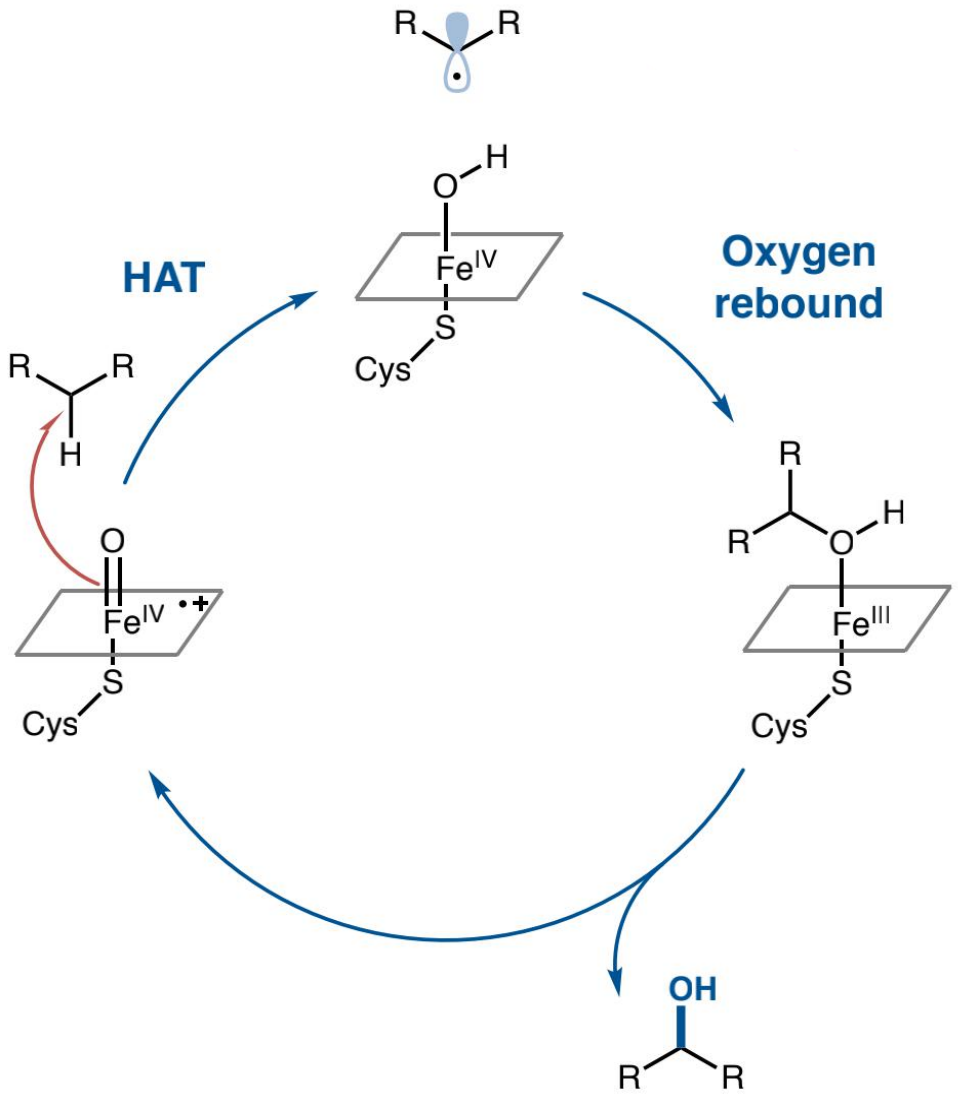
不良反应机制
Mechanisms of adverse reactions

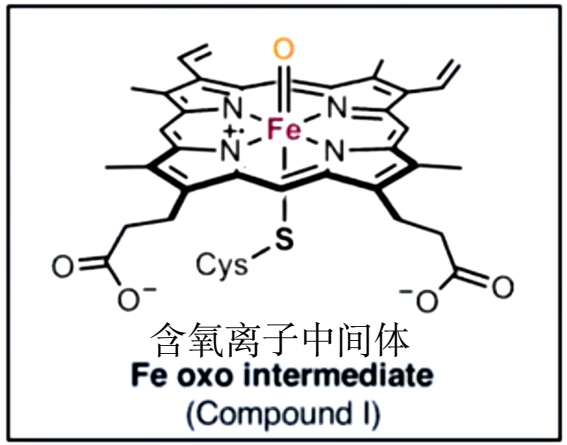


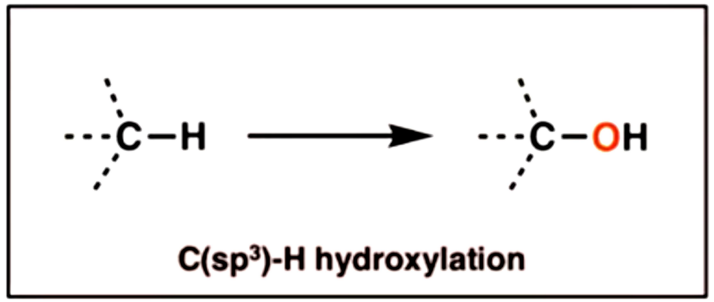
机理性抑制 Mechanism-based inhibition

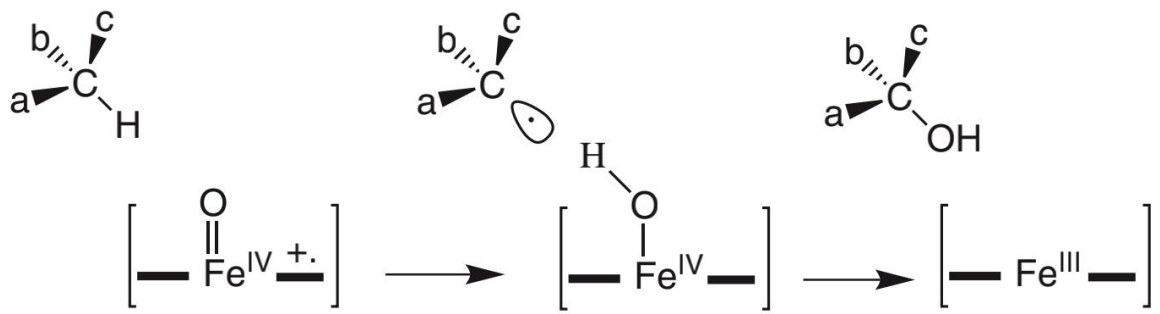
在某些情况下，底物可以逃脱氧反弹步骤，结合CYP并导致失活




HAT
Oxygen rebound
R
R
H
O
Fe^IV
S
Cys
Fe^III
Fe^IV •+
OH


O
Fe
N
Cys
S
含氧离子中间体
Fe oxo intermediate
(Compound I)


C–H
C–OH
C(sp³)-H hydroxylation

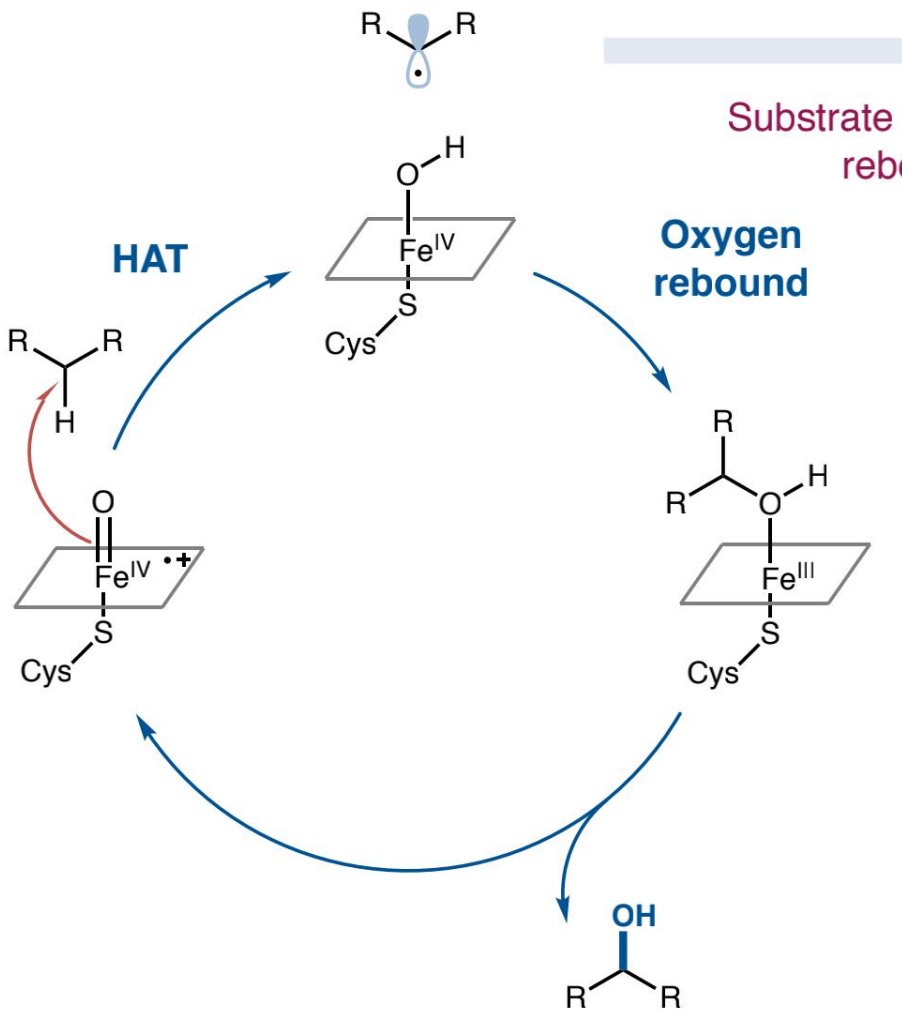

a
b
c
H
OH
O
Fe^IV +.
Fe^IV
Fe^III

机理性抑制 Mechanism-based inhibition

在某些情况下，底物可以逃脱氧反弹步骤，结合CYP并导致失活

羟基化

General mechanism of C(sp^3)–H hydroxylation

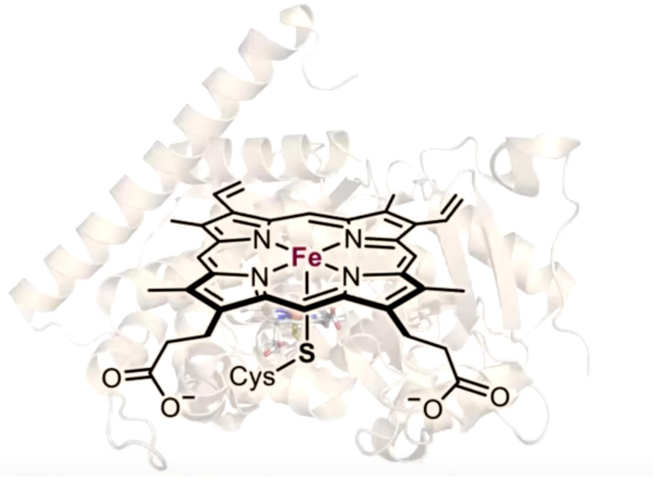


Mechanism-based inhibition

Substrate escapes oxygen rebound step

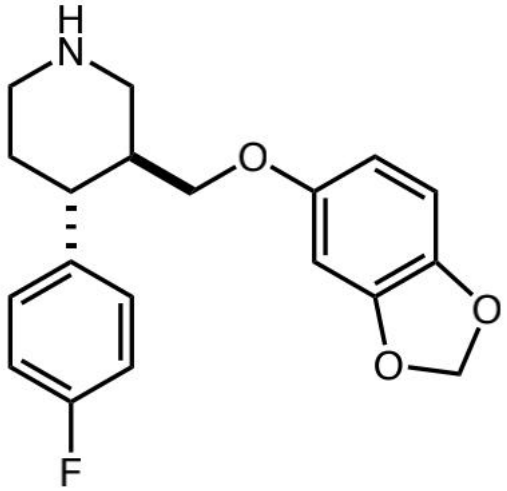
Reactive intermediate binds enzyme

Enzyme deactivated

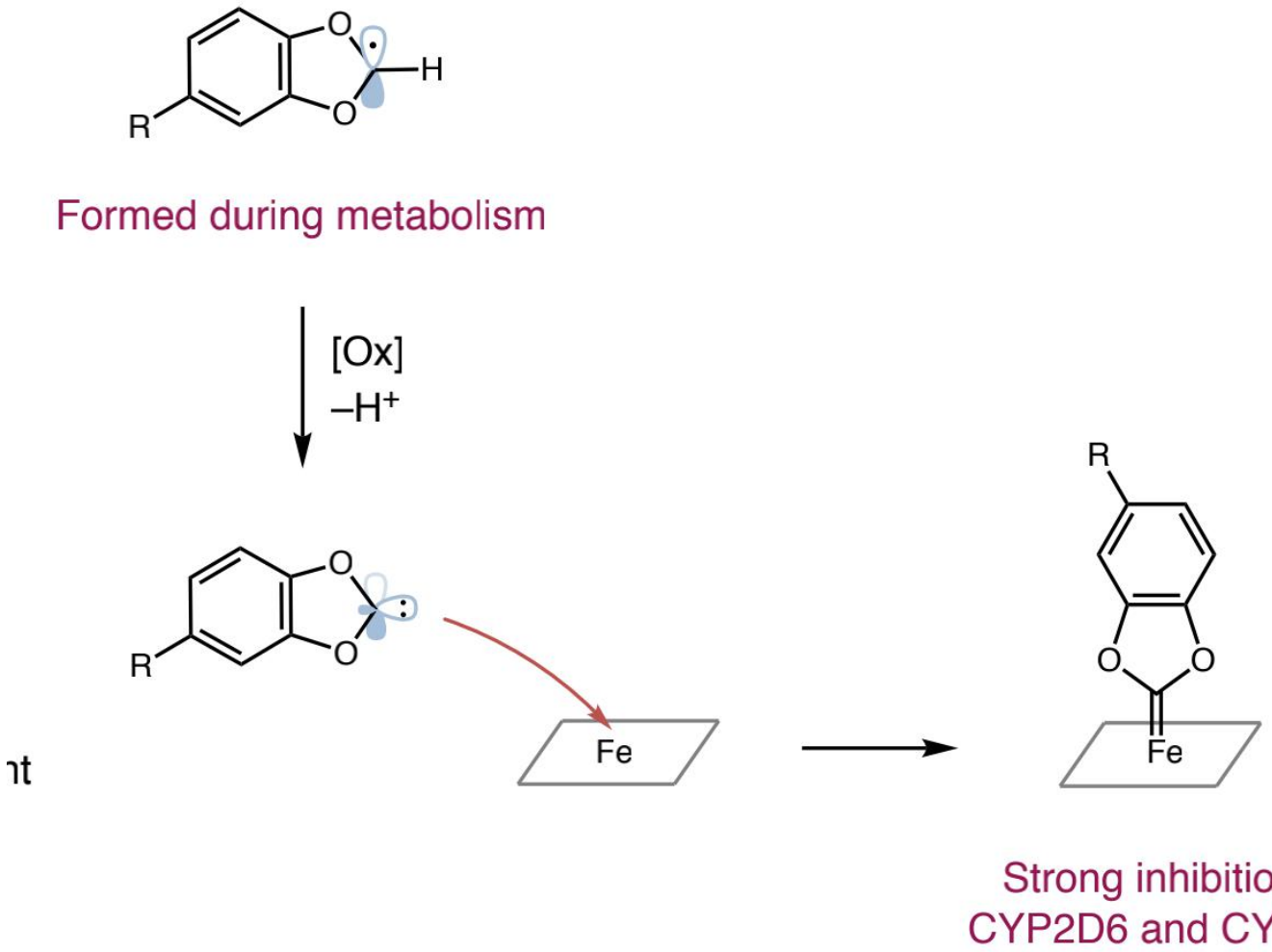


帕罗西汀 Paroxetine

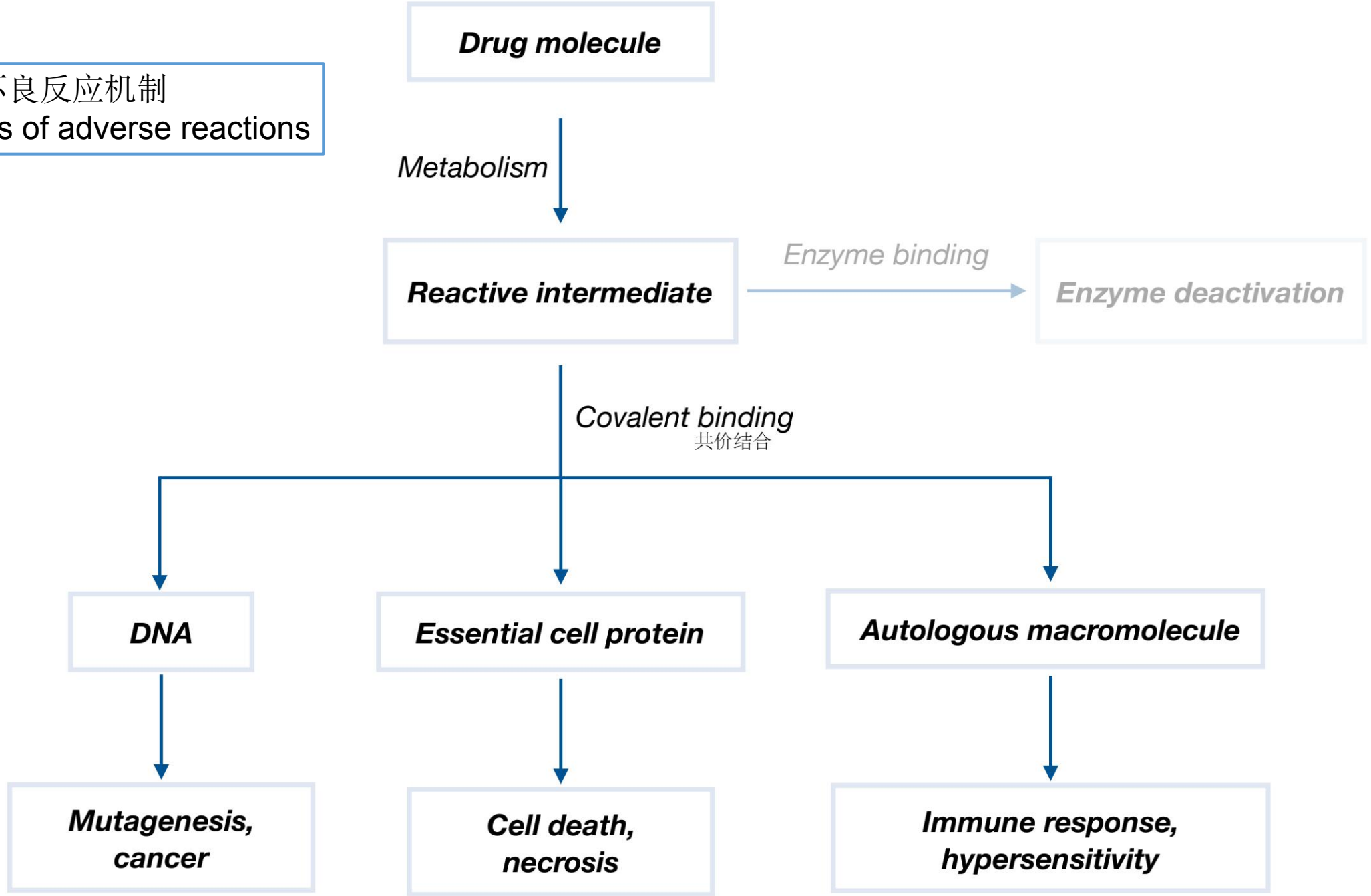
处方指南警告说帕罗西汀是不能与其他药物一起服用



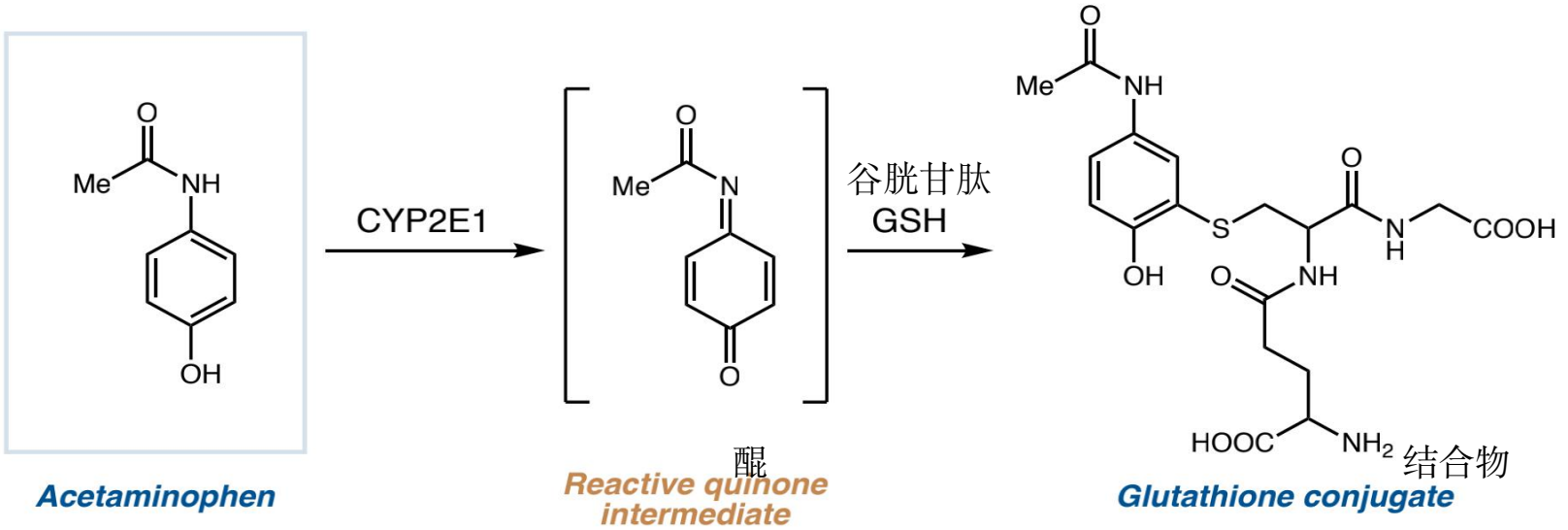
- 1992年批准用作抗抑郁药
- 2018年第74最多的处方药
- 导致药物之间的相互作用



不良反应机制
Mechanisms of adverse reactions



经典
对乙酰氨基酚 (acetaminophen) 引起肝损伤



- 在美国和欧洲最常用的治疗疼痛和发烧的药物
- 世卫组织基本药物清单
- 导致西方国家急性肝功能衰竭和药物过量的主要原因

Endogenous GSH levels depleted

内源谷胱甘肽水平下降

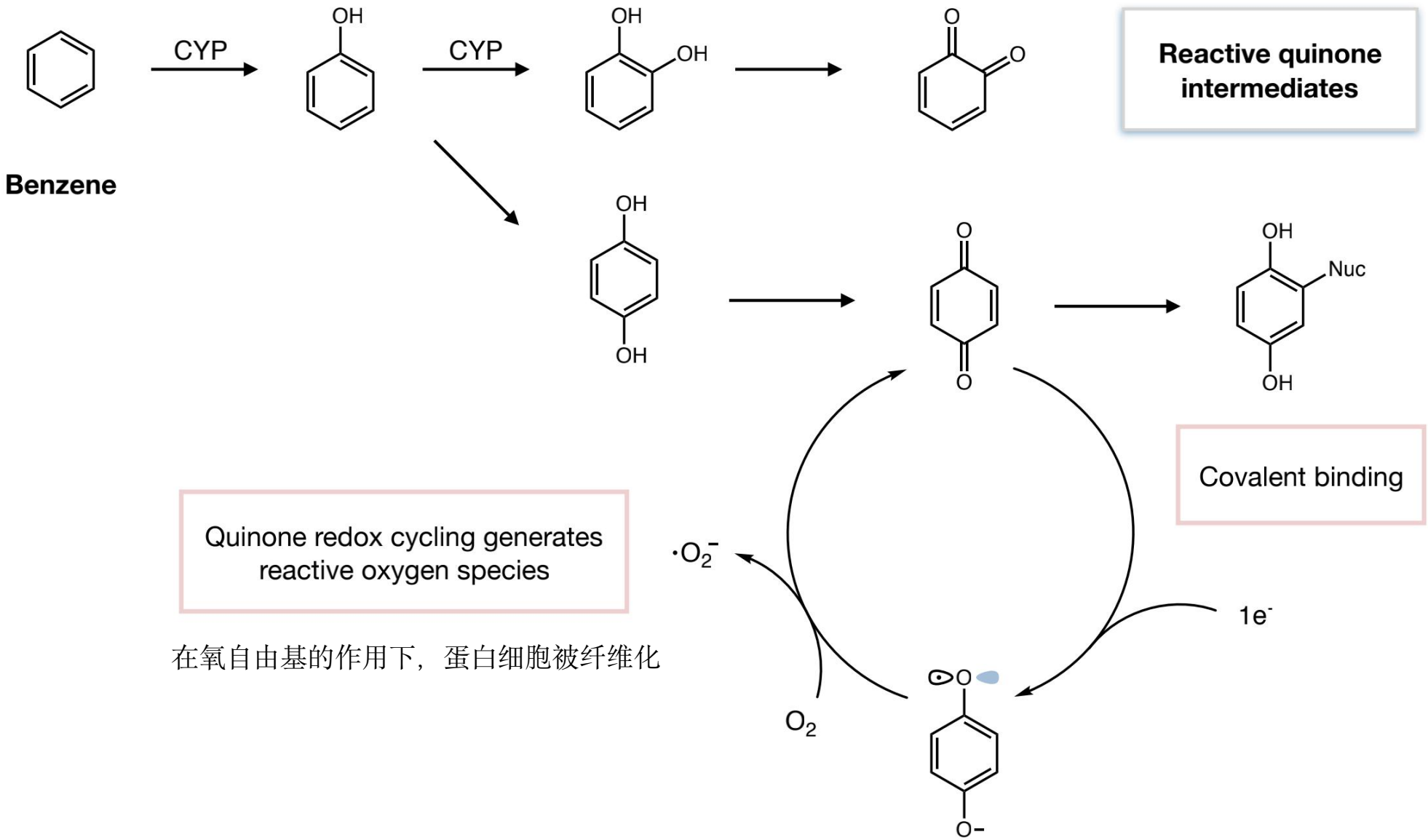
谷胱甘肽能防止如自由基、过氧化物等物质对细胞重要成分的损害

Covalent binding to hepatic proteins

肝的

Cell death, liver damage

经典
苯的毒性 Toxicity of benzene



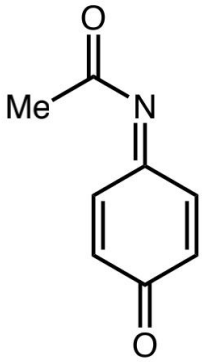
在氧自由基的作用下，蛋白细胞被纤维化

结构警报 The structural alert concept

在与不良反应相关的药物中经常发现的官能团

肝的一百种死法

和肝蛋白不可逆结合

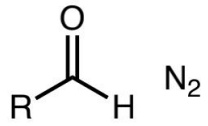


乙酰苯丙胺

Acetanilides

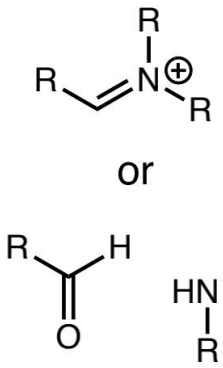
Michael acceptors

迈克尔反应受体



酰肼类

Hydrazides

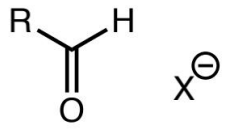


胺类

Amines

Alkylating/acylating agents

烷基化和酰化剂

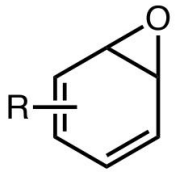


卤代化合物

Halogenated compounds

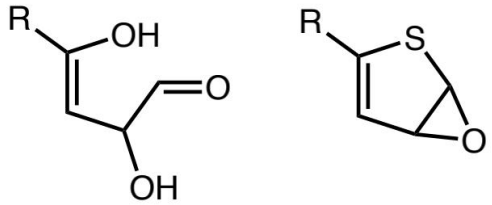
Acylating agents, possible fluoride toxicity

酰化剂，可能有氟化物毒性



苯基环

Phenyl rings

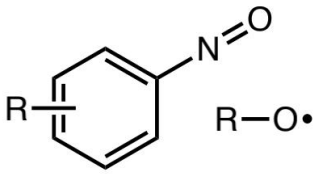


杂芳族化合物

Heteroaromatics

Epoxidation leading to reactive intermediates

环氧化产生活性中间体



硝基芳烃

Nitroaromatics

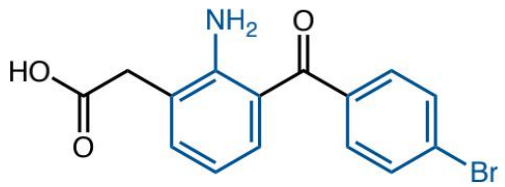
Reactive oxygen species

活性氧

- 撤出药物68个有55个都有结构警报
- 55中有形成反应代谢物的倾向

在有氧条件下，自由基可降低分子氧形成超氧阴离子formsuperoxide anion，可形成各种有毒氧 toxic oxygen speciesa，伤肺

因特征性药物性肝损伤而被召回的药物

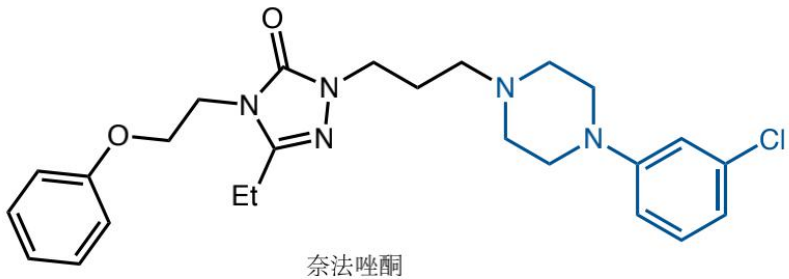


溴芬酸

Bromfenac 苯胺,溴苯

Structural alerts: Aniline, bromobenzene

Withdrawn in: 1998



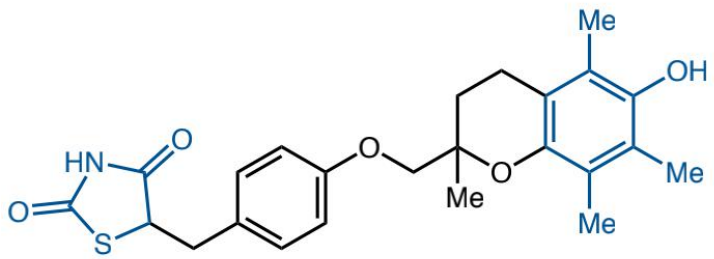
奈法唑酮

Nefazodone

Structural alerts: *N*-aryl piperazine

Withdrawn in: 2004

Hepatotoxicity is leading cause of idiosyncratic adverse drug reactions

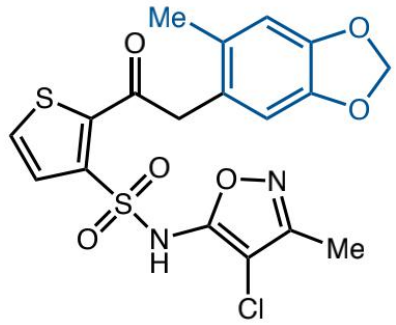


Troglitazone

Structural alerts: Thiazolidinedione, phenol

Withdrawn in: 2000

Linked to 63 cases of liver-failure deaths



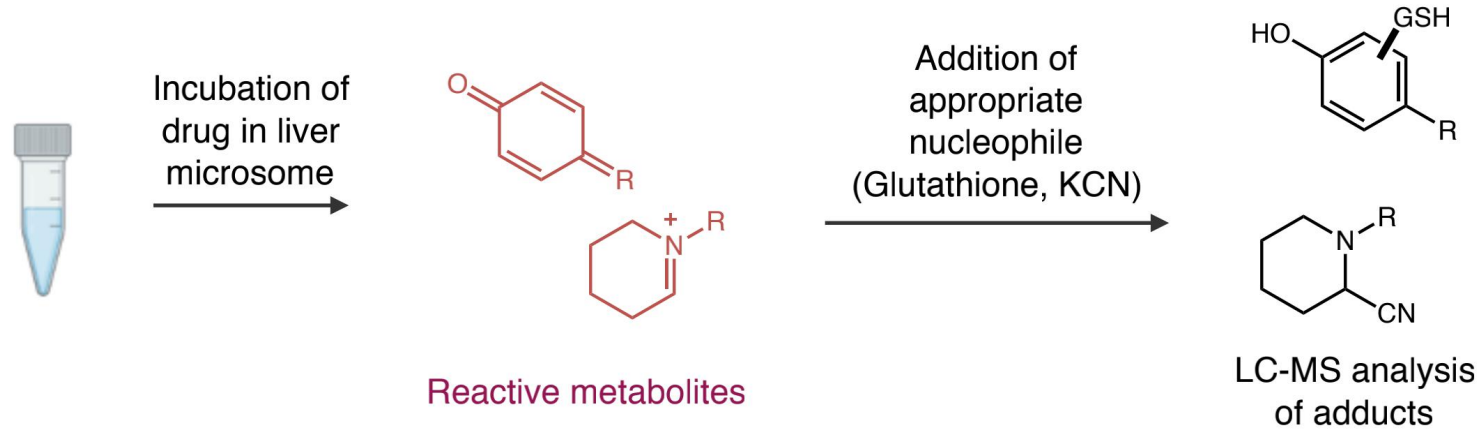
Sitaxentan

Structural alerts: 1,3-benzodioxole

Withdrawn in: 2010

分析活性代谢物的形成

- 活性代谢物捕获分析 Reactive metabolite trapping assays



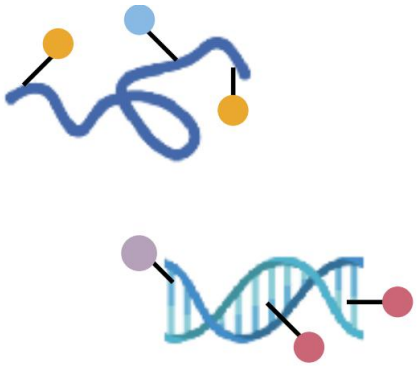
- 放射性标记分析 Radiolabeling assays

使用放射性的标记物

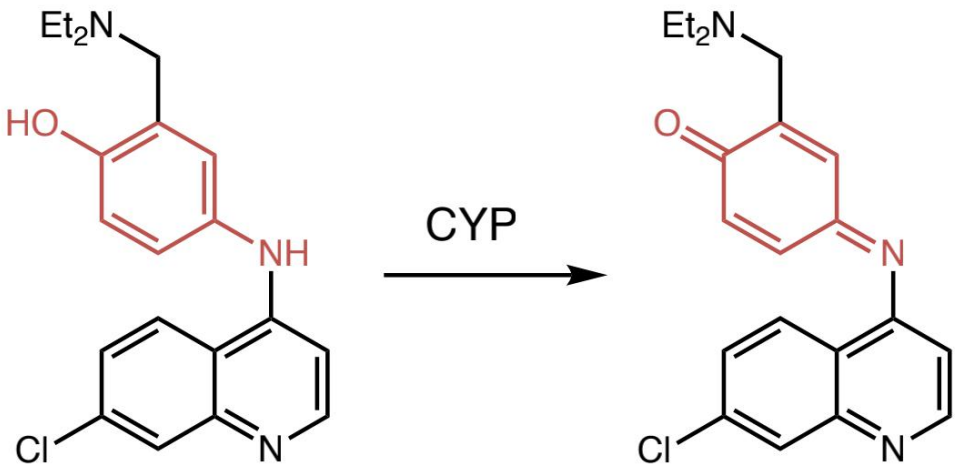
Administration of radio labeled (^{3}H /^{14}C) compounds

Isolate and quantify radioactive covalently bound proteins and DNA

分离并量化放射性共价结合蛋白和DNA



减轻结构性警报影响的策略



Amodiaquine

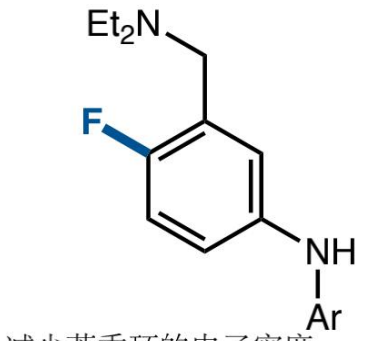
阿莫地喹

Reports of hepatotoxicity, agranulocytosis

肝毒性、粒细胞缺乏症报告

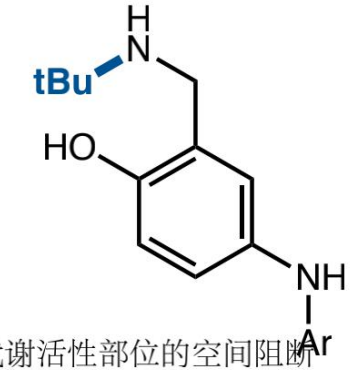
具有改进的安全特性的类似物

Analogues with improved safety profile



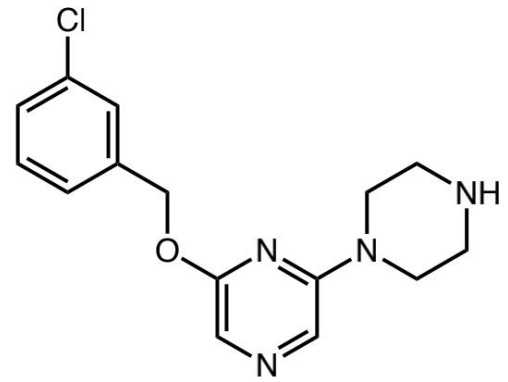
减少芳香环的电子密度

- Reduce electron density of aromatic rings



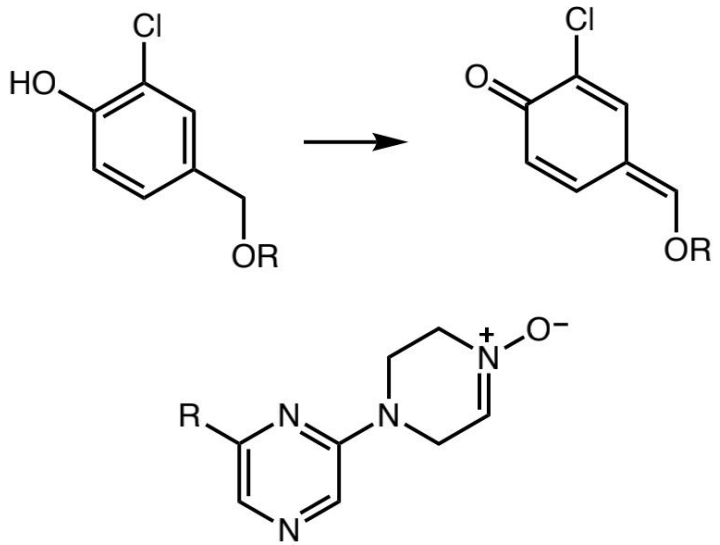
代谢活性部位的空间阻断

- Steric blocking of metabolically active sites



5-HT2C (serotonin) receptor agonist 收缩筋；兴奋剂
(Pfizer)

致突变的
Ames positive (mutagenic)
一个突变测试

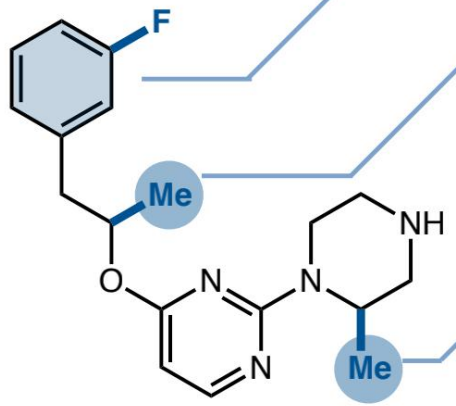


Reactive intermediates observed

■ Remove structural alert

■ Block metabolically labile sites

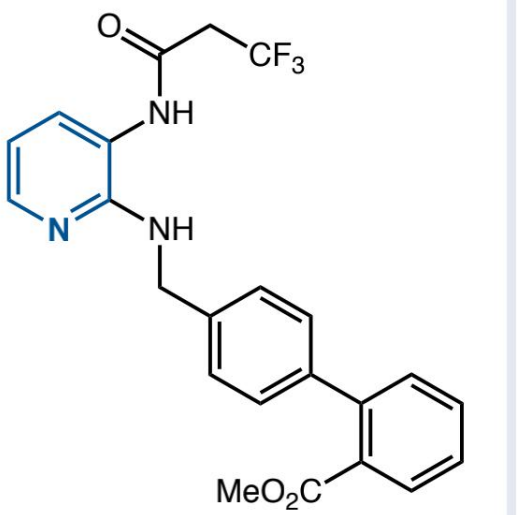
代谢不稳定位点



Redesigned compound

Ames negative

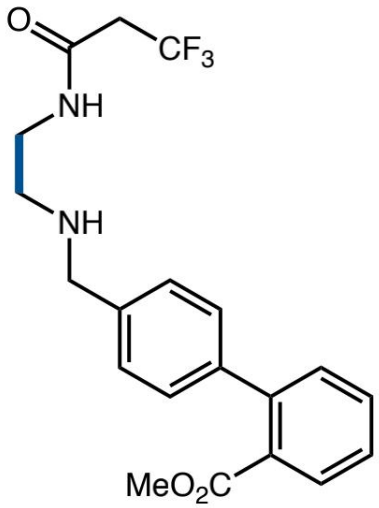
结构警报的生物等容替代（替代不必要的结构）



Lead compound

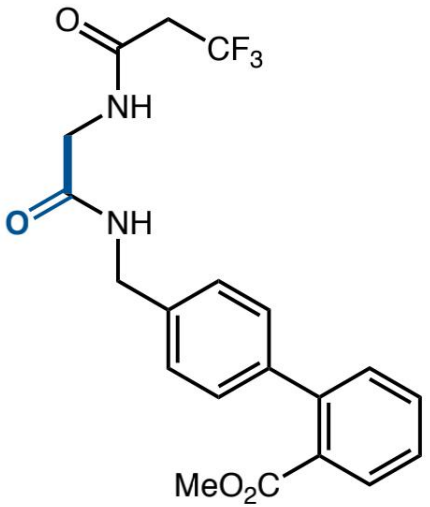
Design principle:
Replace 2,3-DAP with nonaromatic linker

设计原则:用非芳香连接剂代替2,3- dap



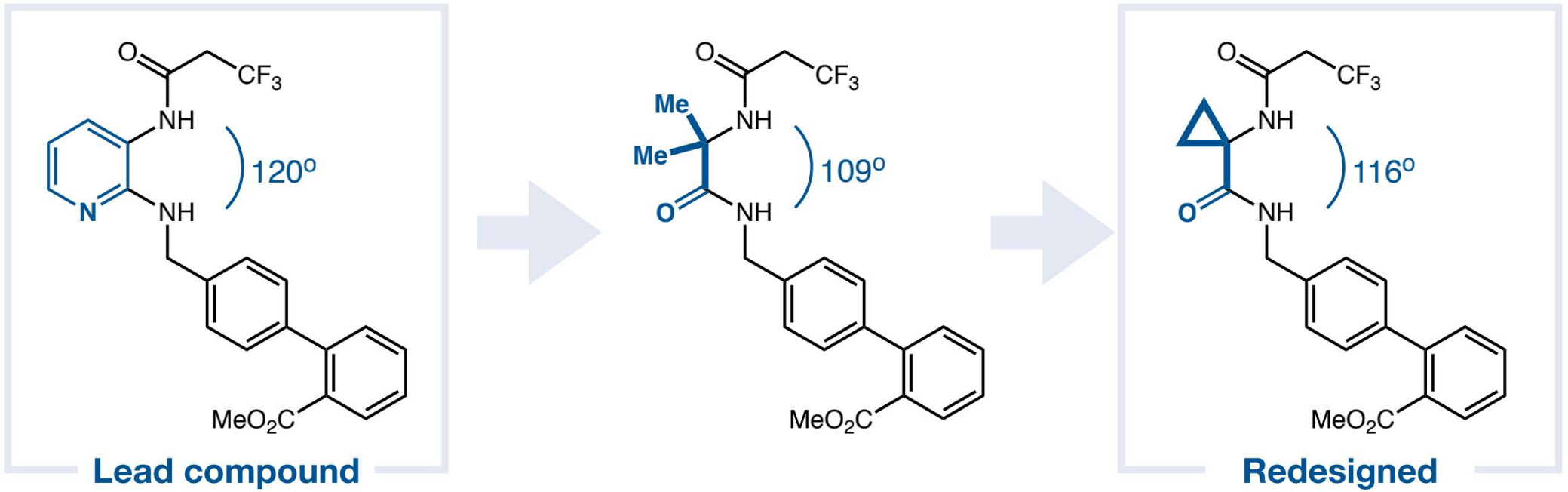
简化成乙二胺

Simplify to ethylene diamine



增加构象约束和氢键能力

Add conformational constraint and hydrogen bonding capability

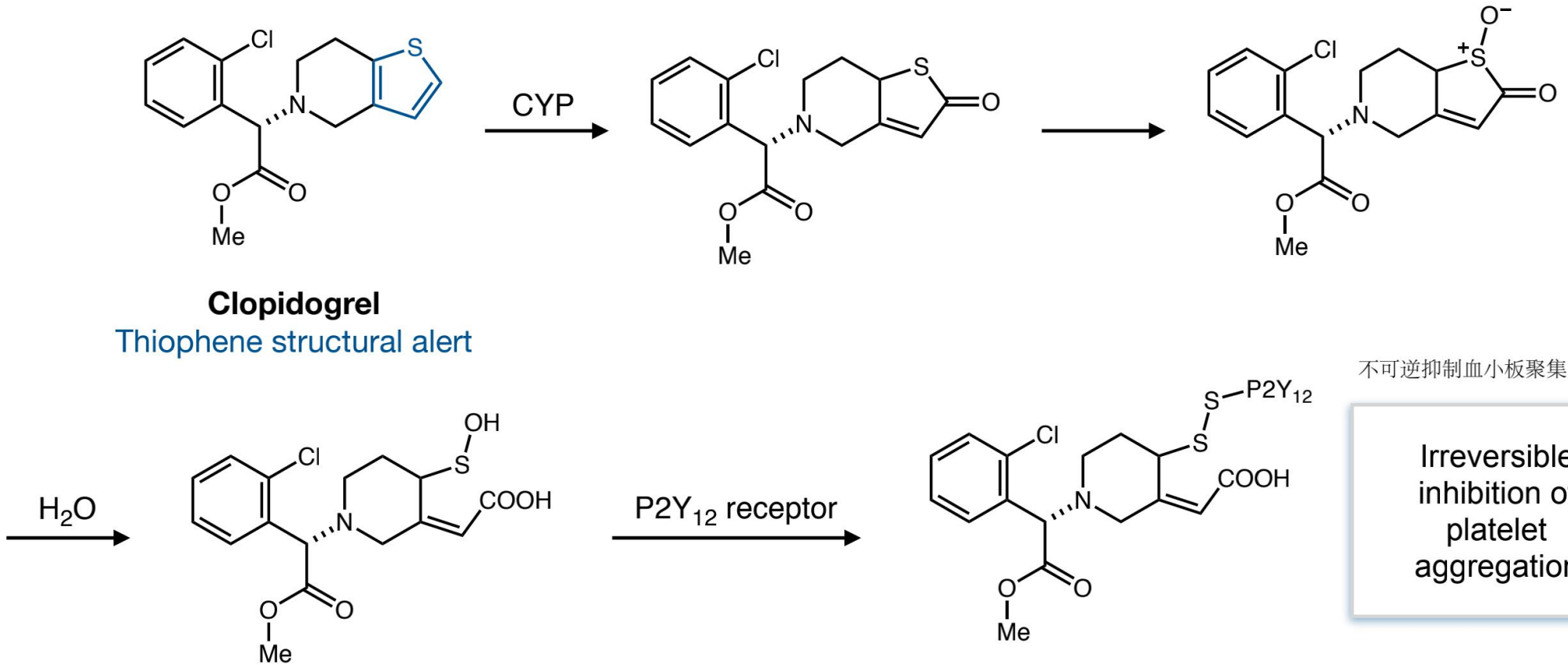


Thorpe-Ingolde效应允许2,3-二氨基吡啶键角的生物等位模拟
很大改善老鼠药代动力学资料是因为加剧代谢稳定性

预测药物负面影响的问题

并不是所有的结构性警报都会导致毒性

2009年，108种处方最多的药物中有53%具有结构性警报



结构警报缺点

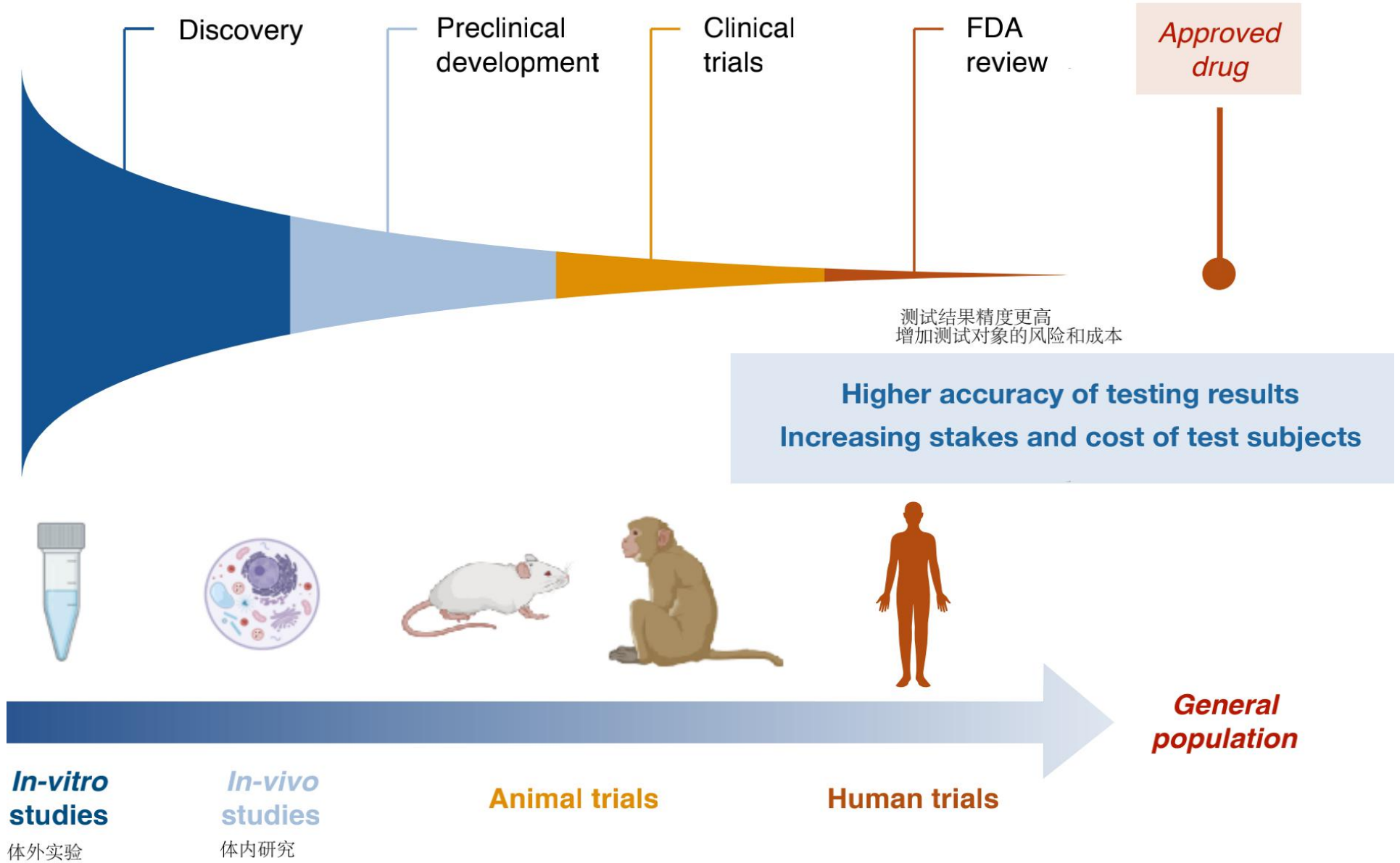
- 不是所有对人有害的药都有结构性警报
- 不是所有有结构性警报的药就不能用

如果药物化学家因为苯环被认为是一种结构警报而放弃合成含苯环的化合物，人类将失去无数救命药物

预测不良影响的问题

- 缺乏区分关键和非关键蛋白的彻底的特性
- 结构警报分析通常不准确
- 药物代谢的物种间和物种内差异
- 预测药物生物活化是否会导致器官或免疫毒性的能力非常有限

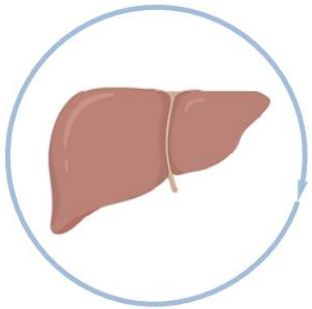
Drug discovery and development



Outline

Introduction to drug metabolism

- Common biotransformations



Metabolism-induced toxicity

- Mechanisms of adverse reactions
  - Reactive intermediates and structural alerts

Applications to drug design

- Designing around metabolism

Applications to drug design

- Designing around drug-induced toxicity
- Challenges in predicting adverse effects