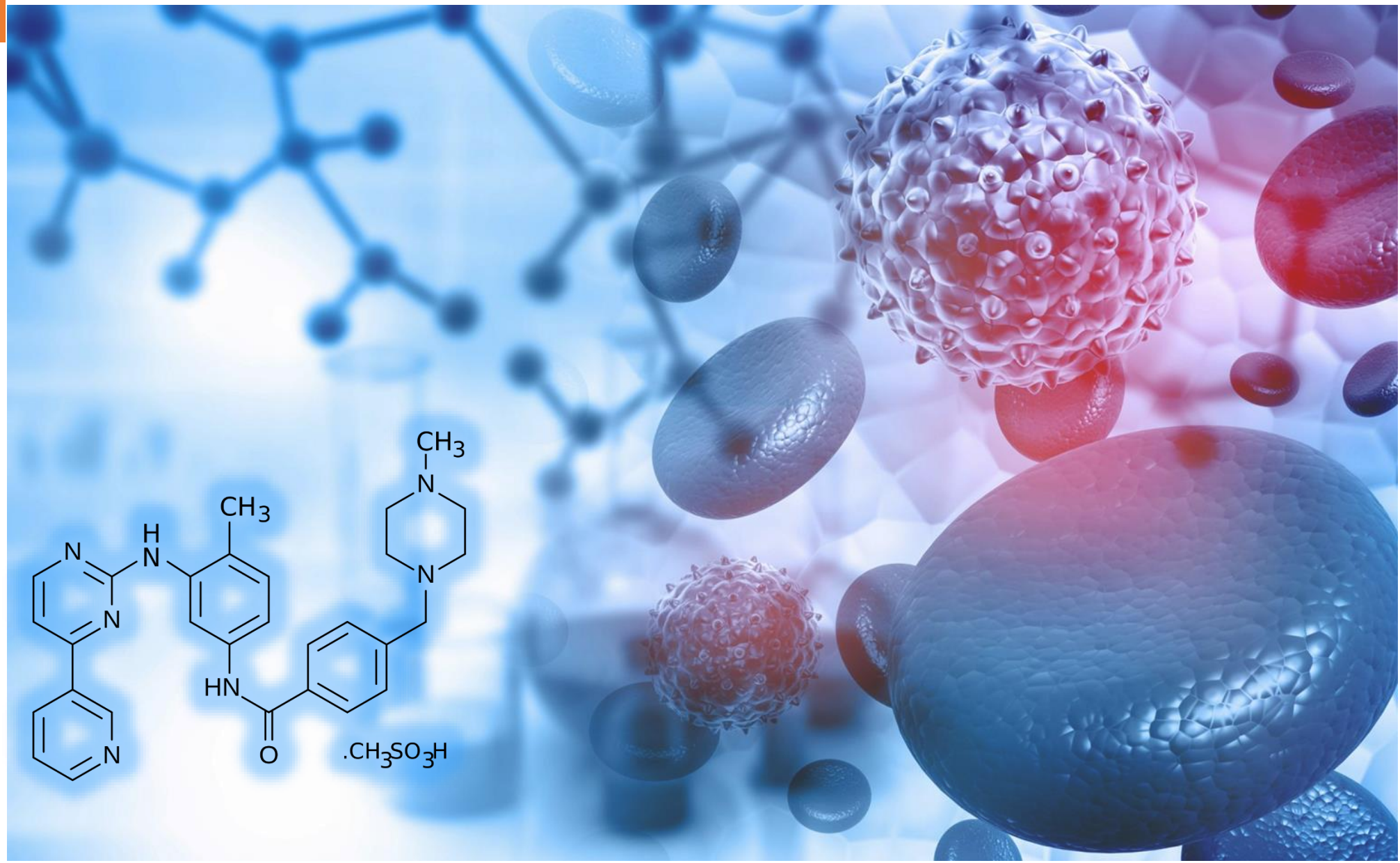
université PARIS-SACLAY
GRADUATE SCHOOL
Health and Drug Sciences

Main strategies of drug discovery - Synthetic Drugs

Pr. Abdallah HAMZE



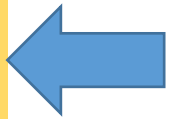
2024-2025

General program

The medicinal chemist's toolbox 1
TU 07
Code: M1S2U203
ECTS: 4
Second term

Program (Lectures and tutorials 28h, project 4h)

A- Introduction (4h)
- Main strategies of drug discovery



B- **Fundamental approaches for the synthesis of natural and synthetic drugs (16h)**
- C-C bond formation in total synthesis of natural products and drugs
- C-N and C-O bond formation in total synthesis of natural products and drugs

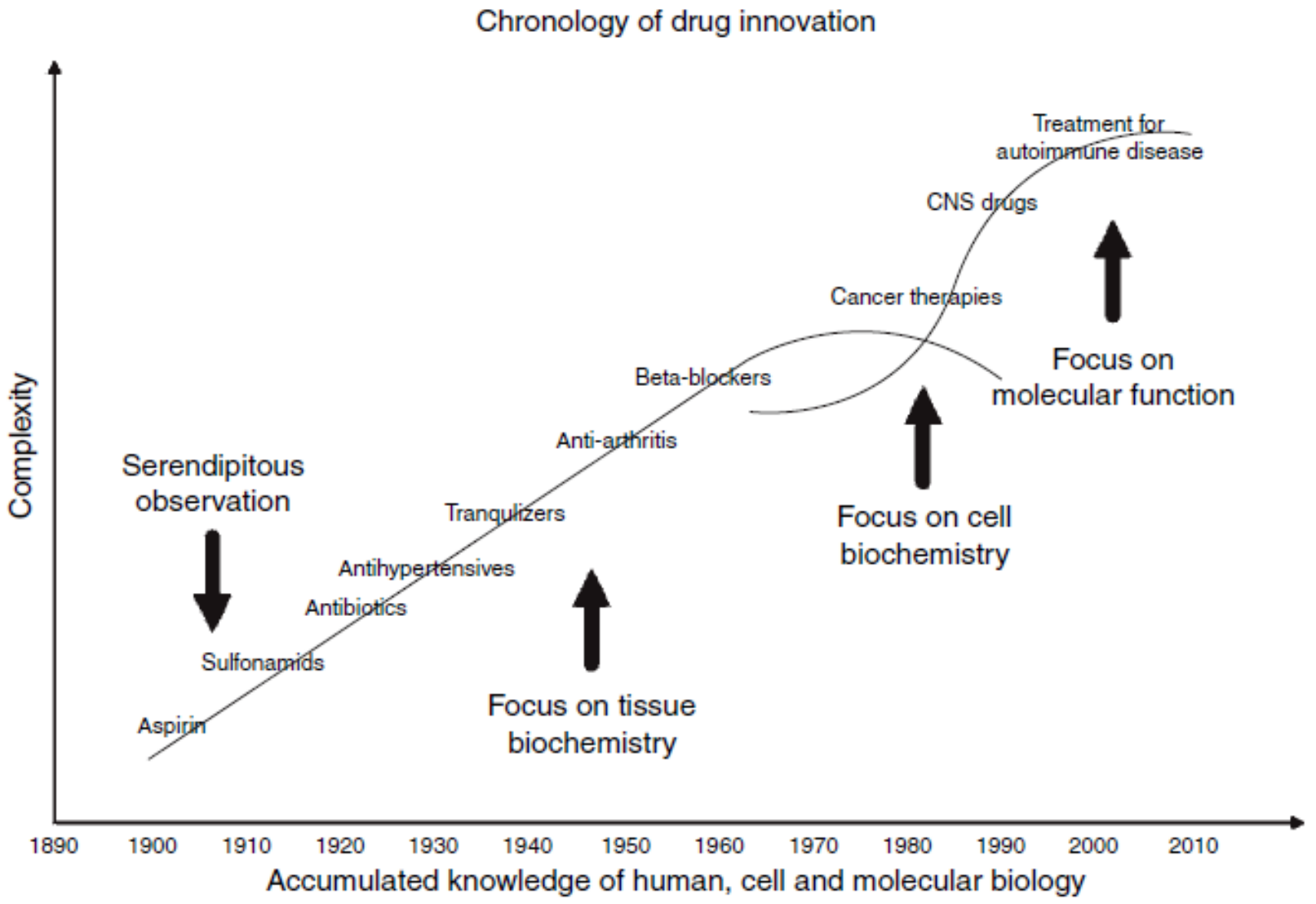
C- **Heterocycles in medicinal and natural product chemistry (8h)**
- Recent advances in multi-component modular synthesis of heterocycles
- Selective functionalization of heterocycles

D- Tutorial (4h)
- Project

COURSE OUTLINE

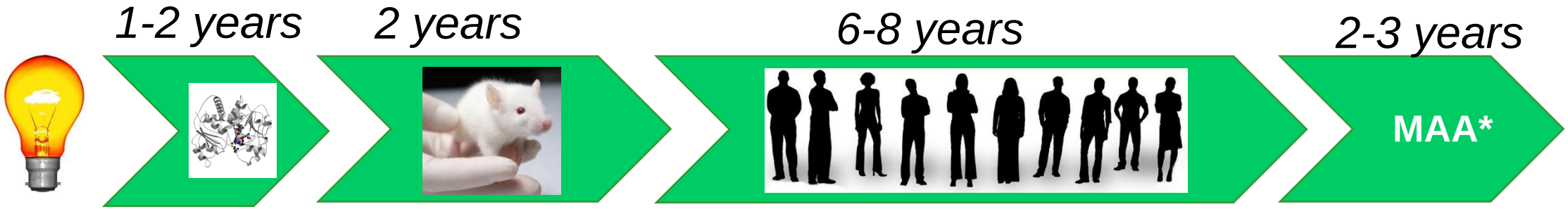
1. General points
2. ADMET, RO5, and systematic *in silico* ADMET evaluation
3. The discovery process in the pharmaceutical industry (R&D)
4. The choice of a drug target
5. Drug design strategies
6. Conclusion

Timeline of drug innovation



from “Biopharmaceutical Industry Contributions to State and US Economics

Development of a drug… long, perilous and expensive!

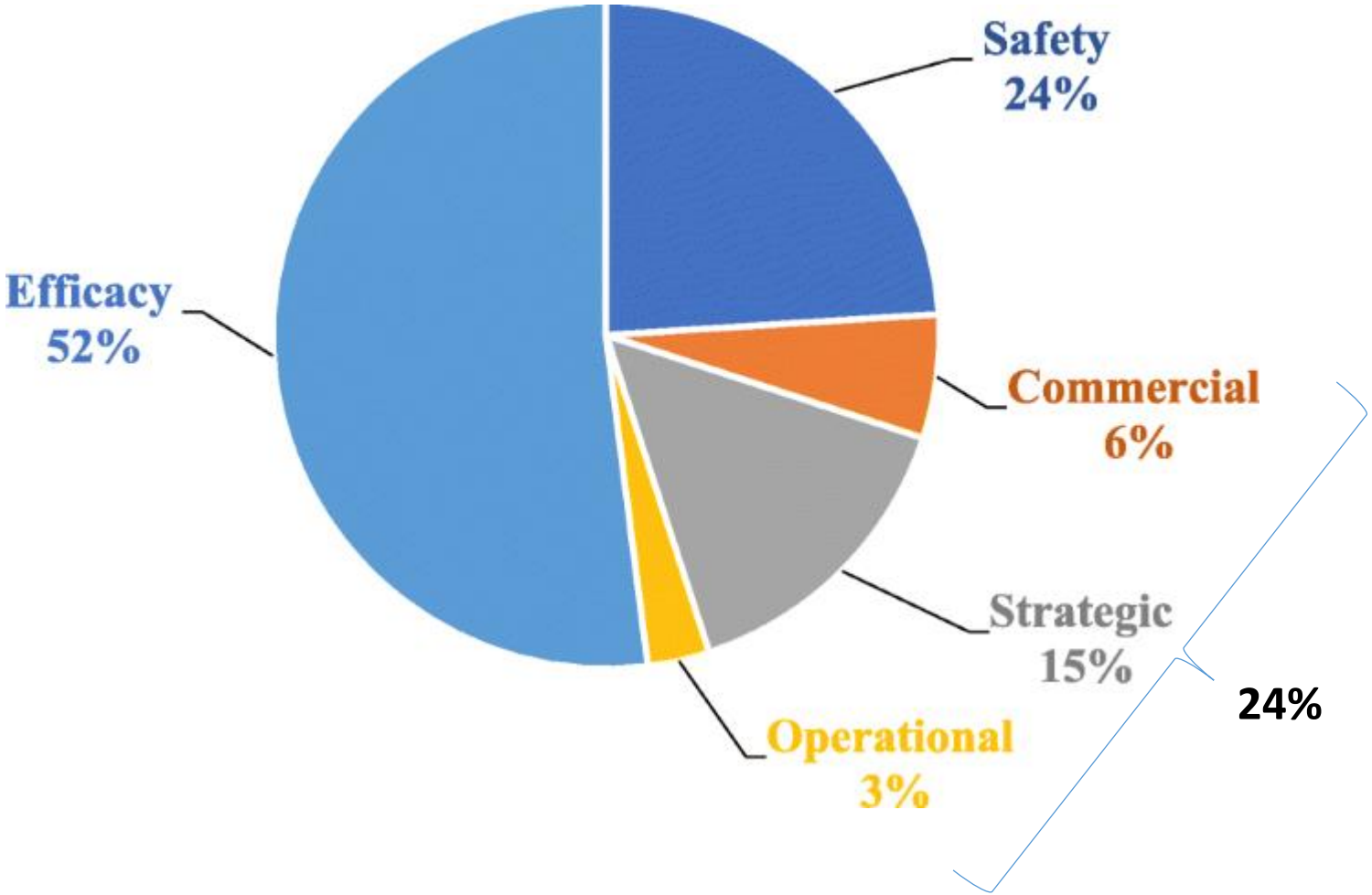


1,5-2 Bn€

MAA: Marketing Authorization Application*

Development of a drug… long, perilous and expensive!

Causes of **lack of success** in drug discovery and development



Future Journal of Pharmaceutical Sciences (2020) 6:27, https://doi.org/10.1186/s43094-020-00047-9

Some recent failures at an advanced stage[1]

Drug	Type	Indication	Company	Status when terminated	Reason for termination
AVE-5530	NCE	Hypercholesterolemia	SANOFI	Phase III	**Lac of efficacy**
Axitinib	NCE	Pancreatic cancer	Pfizer	Phase III	**Lac of efficacy**
Candesartan	NCE	Diabetic retinopathy	Takeda	Phase III	**Lac of efficacy**
Dexavanlafaxine	NCE	Fibromyalgia	Wyeth	Phase III	**Lac of efficacy**
Dirucotide	NCE	Multiple sclerosis	Lilly	Phase III	**Lac of efficacy**
DTP-hepB-HIb	NBE	Diphteria, tetanus, Pertussis, Hep B, Hib	SANOFI	Phase III	**Reallocation of resources**
Tanezumab	NBE	Pain, arthritis	Pfizer	Phase III	**Safety- Exacerbation of symptoms**
Mepolizumab	NBE	Hypereosinphilic syndrome	gsk	MAA Filled	**Insufficient Benefit-Risk**

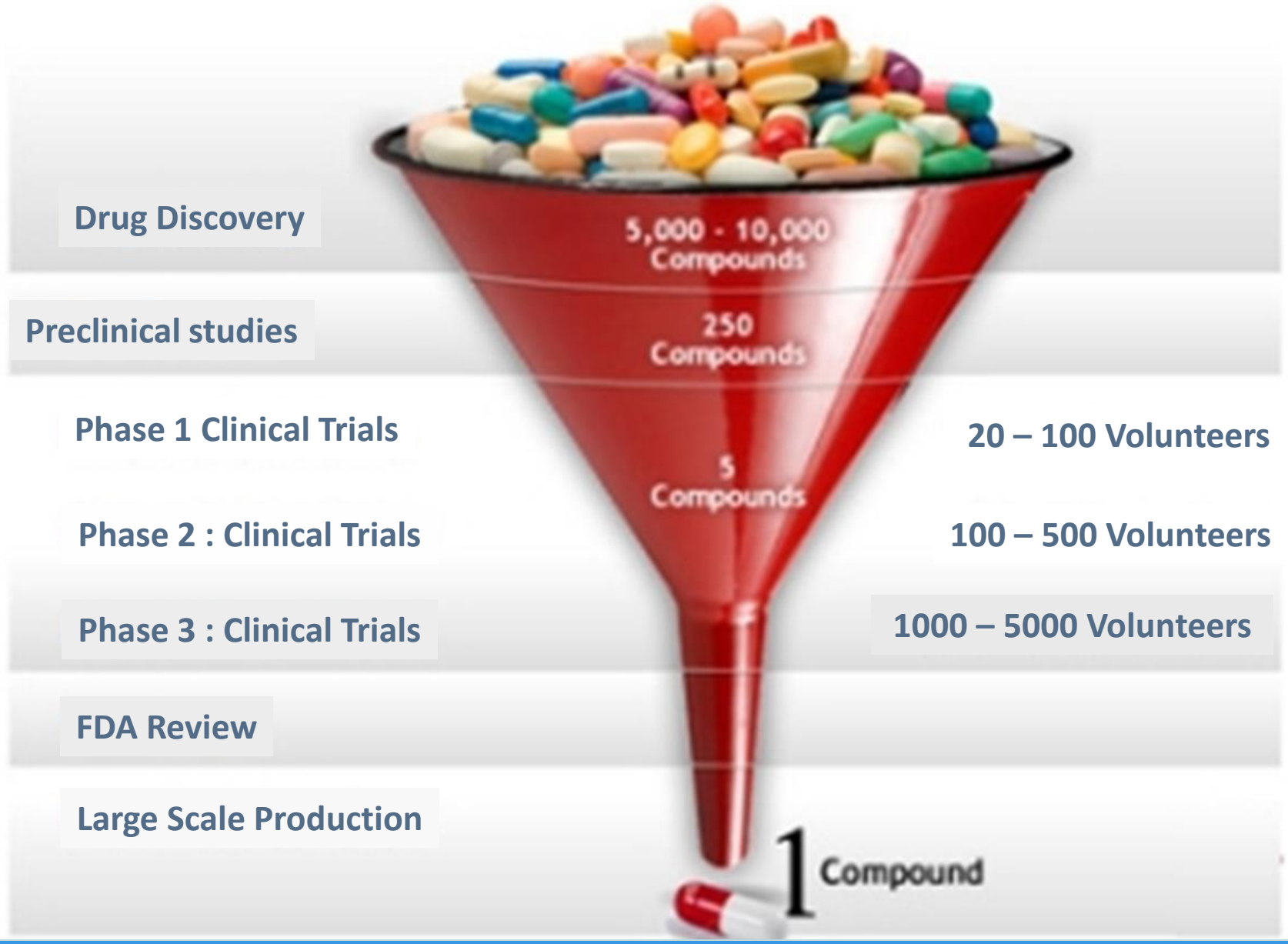
NCE = New chemical entities ; NBE = New biological entities ; (MAA) Marketing Authorization Application

1 CMR International, a Thomson Reuters Business. 2010 Global R&D Performance Metrics Program

The trilogy: the "hit", the "lead", the drug candidate

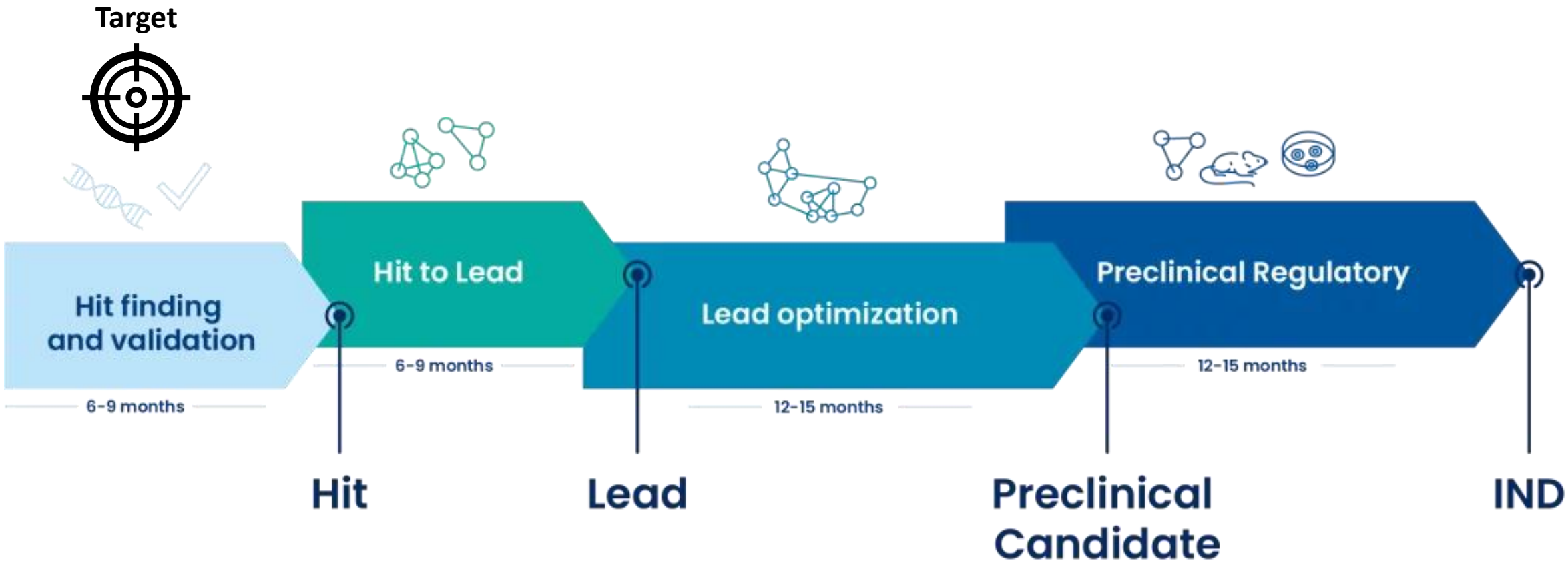
HIT	**An active molecule showing activity in a relevant *in vitro* functional test, endowed with a certain selectivity, which can lead to patentable structures.**
LEAD Compound	**Molecule from the hit series whose "SAR" are well established, presenting a potential for chemical optimization, physicochemical characteristics as well as an "ADME" profile, satisfactory to initiate an optimization program.**
Drug Candidate	**Molecule well characterized on the physicochemical level, which has acceptable ADME / Tox characteristics ("drug-like"), which, respecting the specifications ("product profile"), can enter development.**
New Chemical Entity (NCE)	**A New Chemical Entity (NCE)) is a drug or chemical that is without precedent among regulated and approved drug products.**

Development of a drug… long, perilous and expensive!



Development of a drug… long, perilous and expensive!

From target to clinical candidate

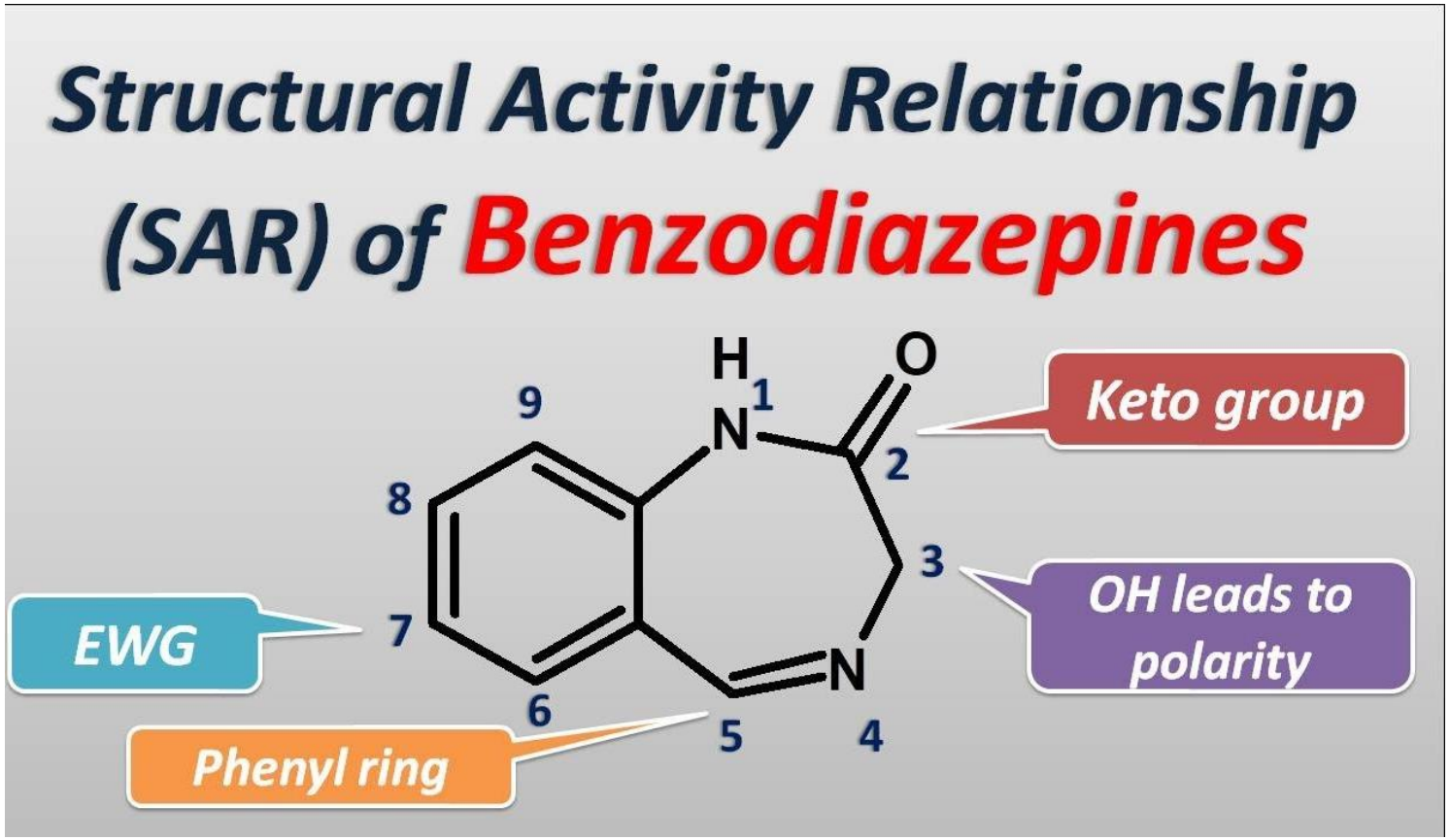


Investigational New Drug (IND) is a drug or biological drug that has not been approved for general use by the FDA. It is used in a clinical trial to investigate its safety and efficacy.

Structure-Activity Relationship (SAR)

Investigational New Drug (IND) is a drug or biological drug that has not been approved for general use by the FDA. It is used in a clinical trial to investigate its safety and efficacy.

Structure-Activity Relationship (SAR)



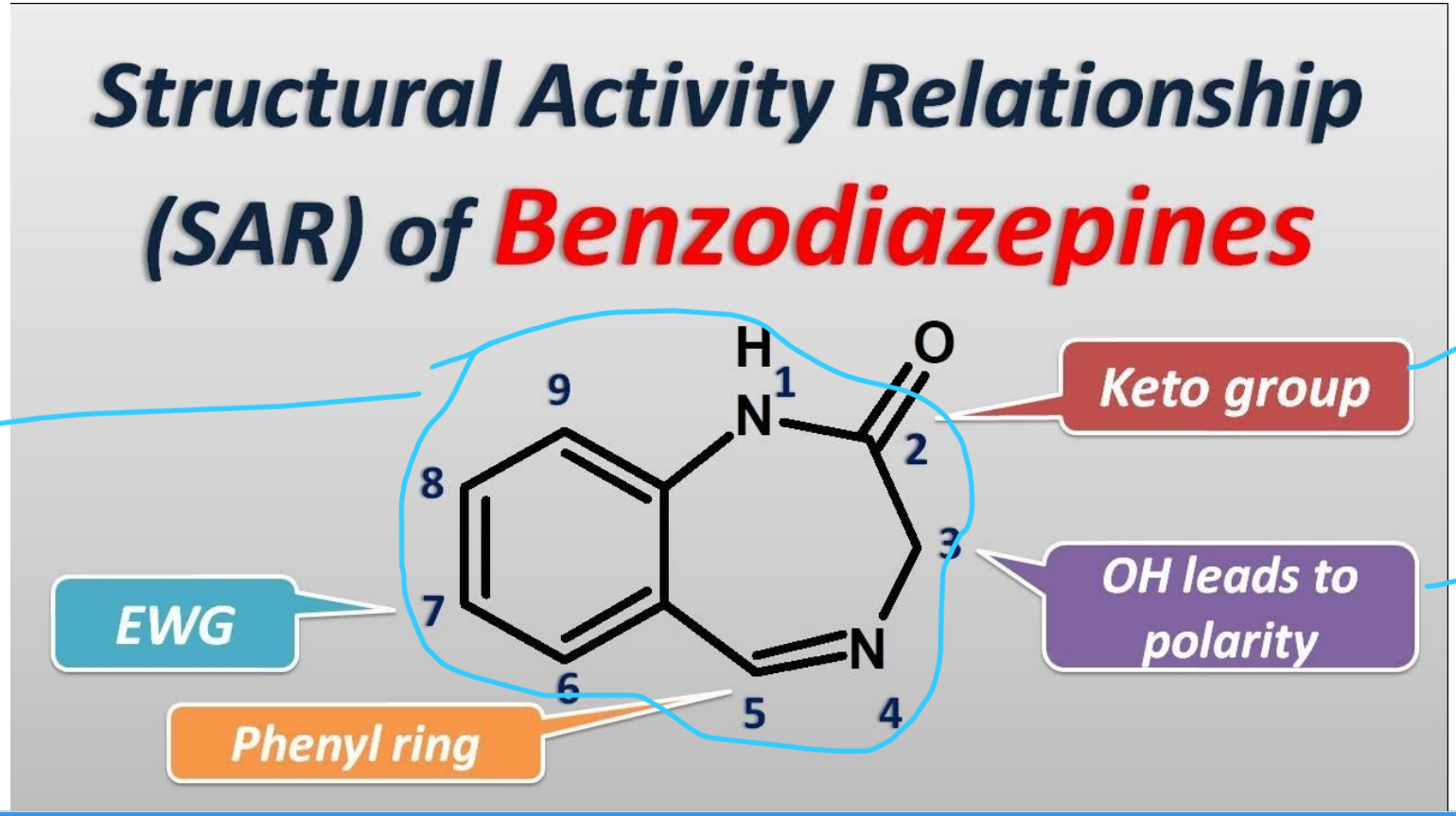
- The structure-activity relationship (**SAR**) of drugs used in therapy refers to the **relationship** between the **chemical structure** of a **drug** and **its biological activity** or **therapeutic effect**.

- **SAR** analysis is an important tool in the design and development of new drugs.

In general, the **SAR** of a drug can be divided into **two parts**: **pharmacophore** and **pharmacophoric elements**.

- The **pharmacophore** refers to the specific **three-dimensional shape** or structural features of a molecule **that are necessary and sufficient to bind to a target receptor and produce a biological effect**.

- The **pharmacophoric elements** refer **to specific functional groups within the molecule that contribute to the pharmacophore**.



Structure-Activity Relationship (SAR)

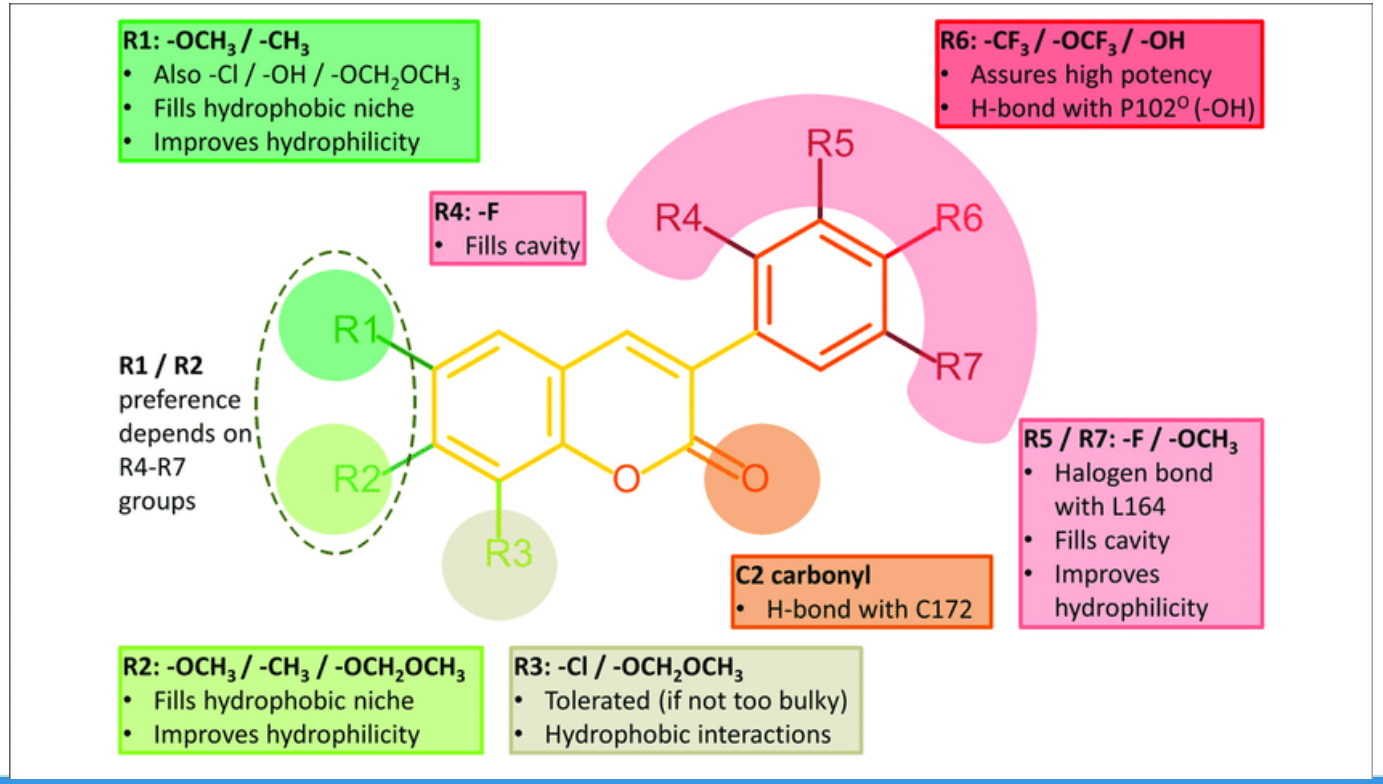
Some of the **key factors** that are considered **in SAR analysis** include:

Hydrogen bonding: Hydrogen bonding between the drug and the target receptor can greatly influence the activity of a drug.

Lipophilicity: The lipid solubility of a drug can impact its ability to penetrate cell membranes and reach its target receptor.

Charge: The charge of a drug can impact its ability to bind to its target receptor and produce a biological effect.

Stereochemistry: The arrangement of atoms within a molecule can impact its activity and specificity.



COURSE OUTLINE

1. General points
2. ADMET, RO5, and systematic *in silico* ADMET evaluation
3. The discovery process in the pharmaceutical industry (R&D)
4. The choice of a drug target
5. Drug design strategy
6. Case study

Typical drug properties: ADMET

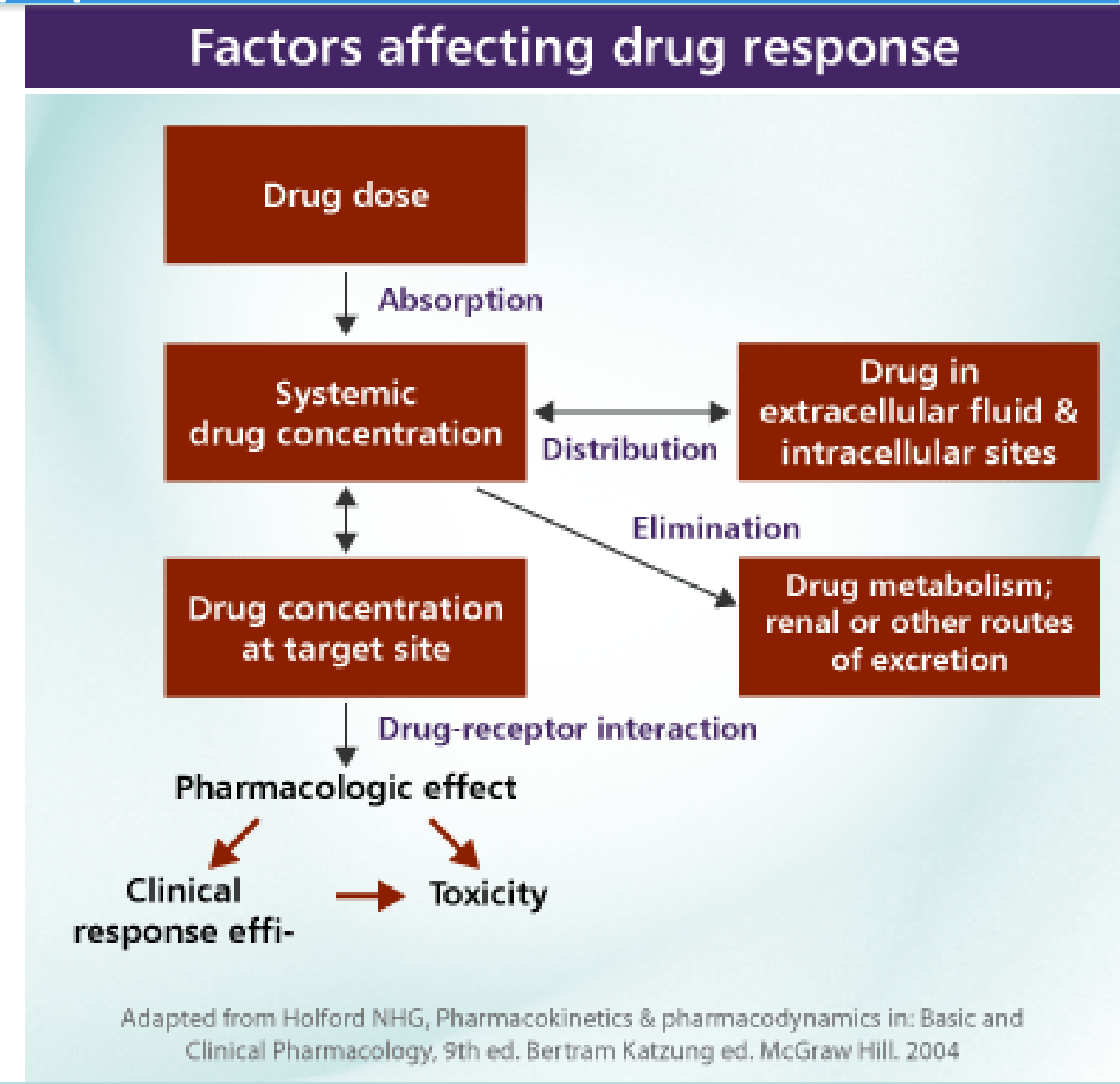
Absorption – moving of the drug from the GI tract to the bloodstream,

Distribution - moving of the drug to target tissues (e.g., blood brain barrier(BBB)),

Metabolism - Not readily metabolized,

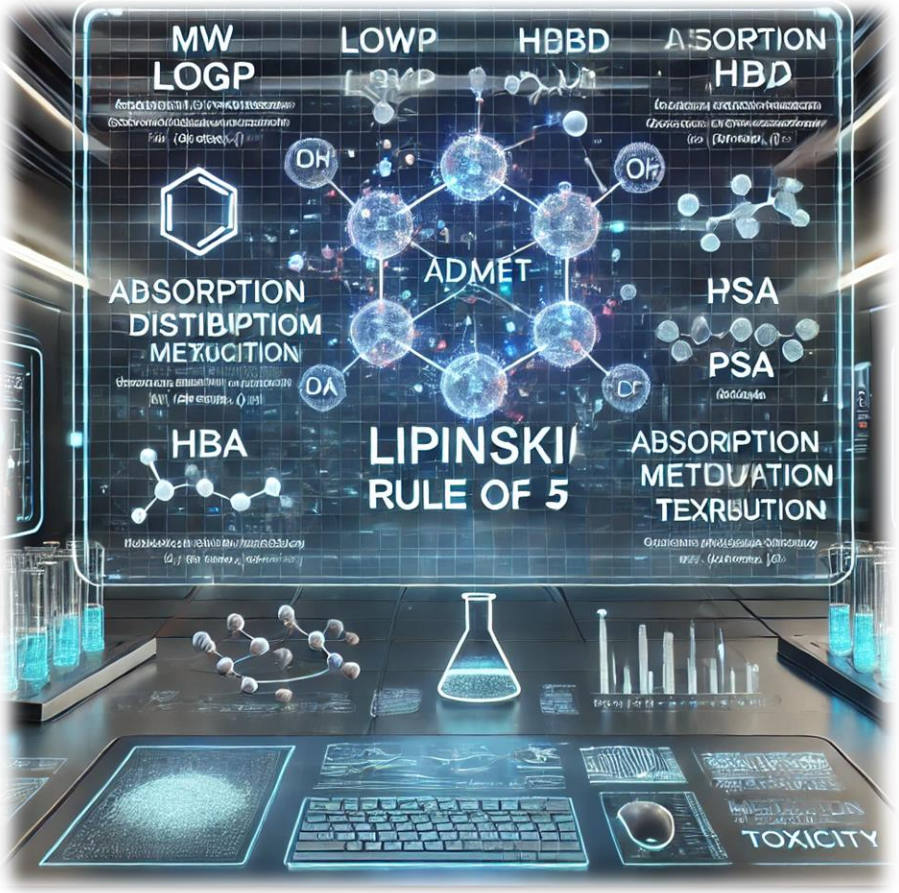
Excretion - Not easily secreted,

Toxicity - Non-toxic to other cells or tissues.

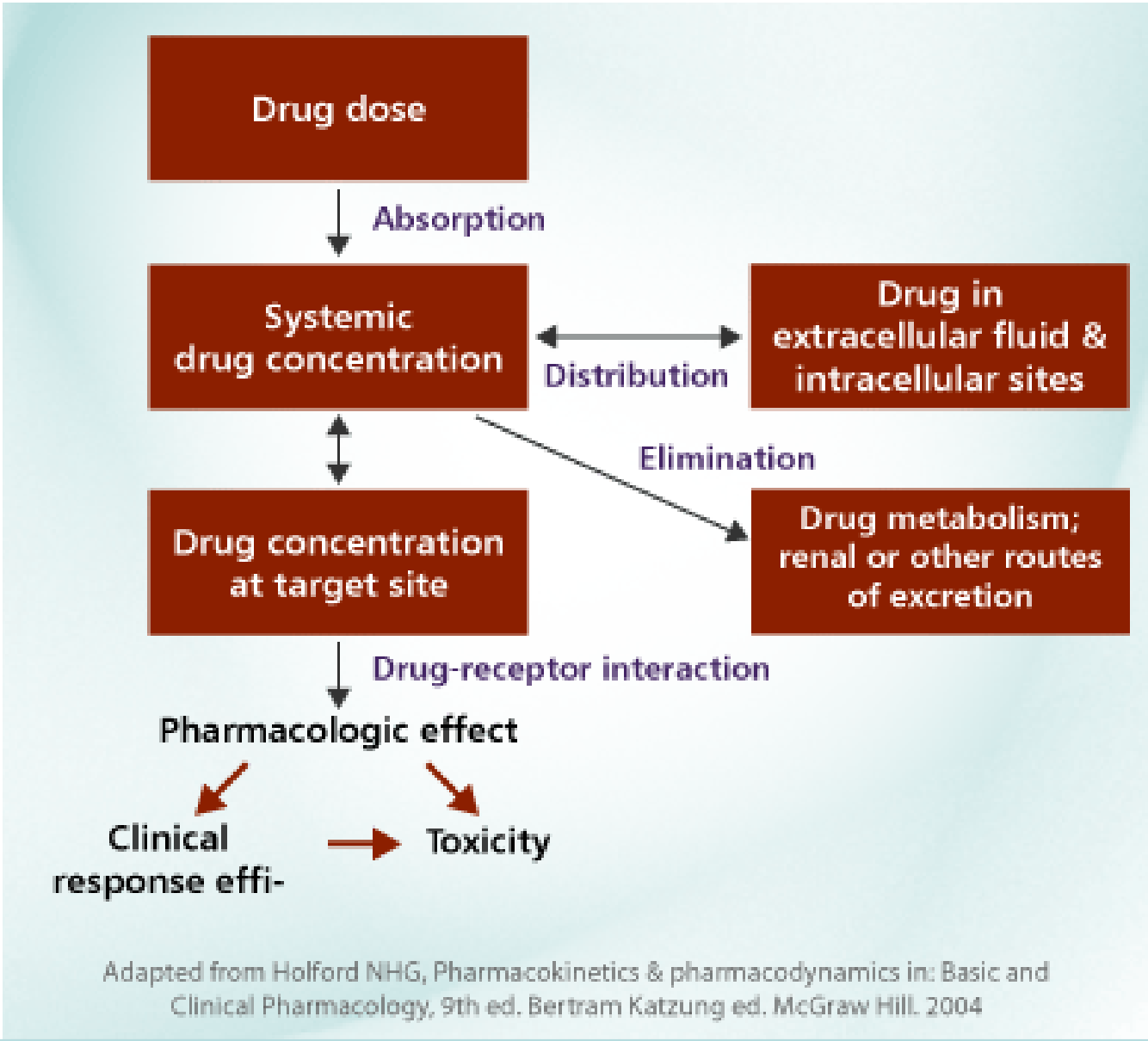


Typical drug properties: ADMET

Absorption – moving of the drug from the GI tract to the bloodstream,

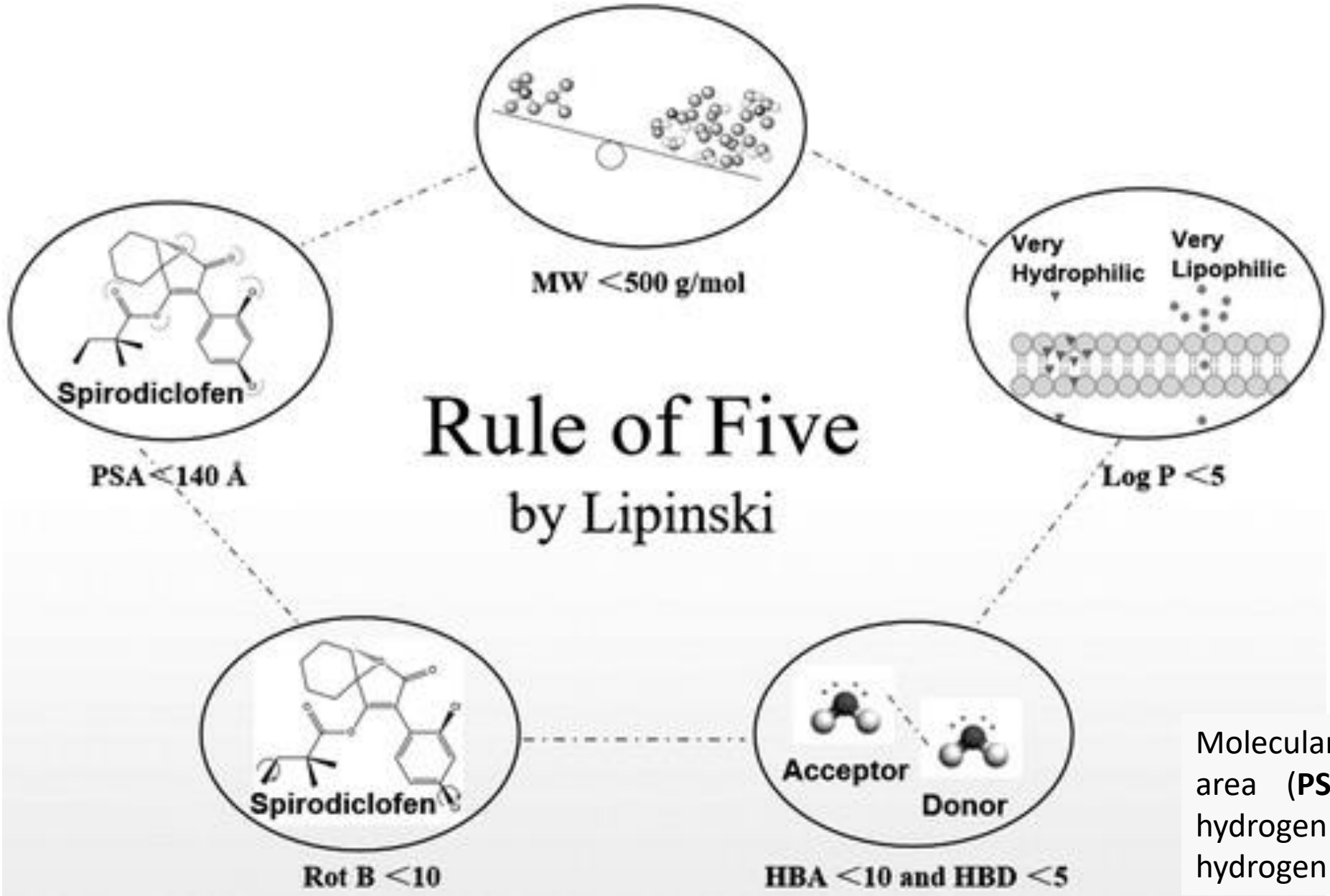


Factors affecting drug response



Adapted from Holford NHG, Pharmacokinetics & pharmacodynamics in: Basic and Clinical Pharmacology, 9th ed. Bertram Katzung ed. McGraw Hill. 2004

Typical drug properties: Rule of five and bioavailability

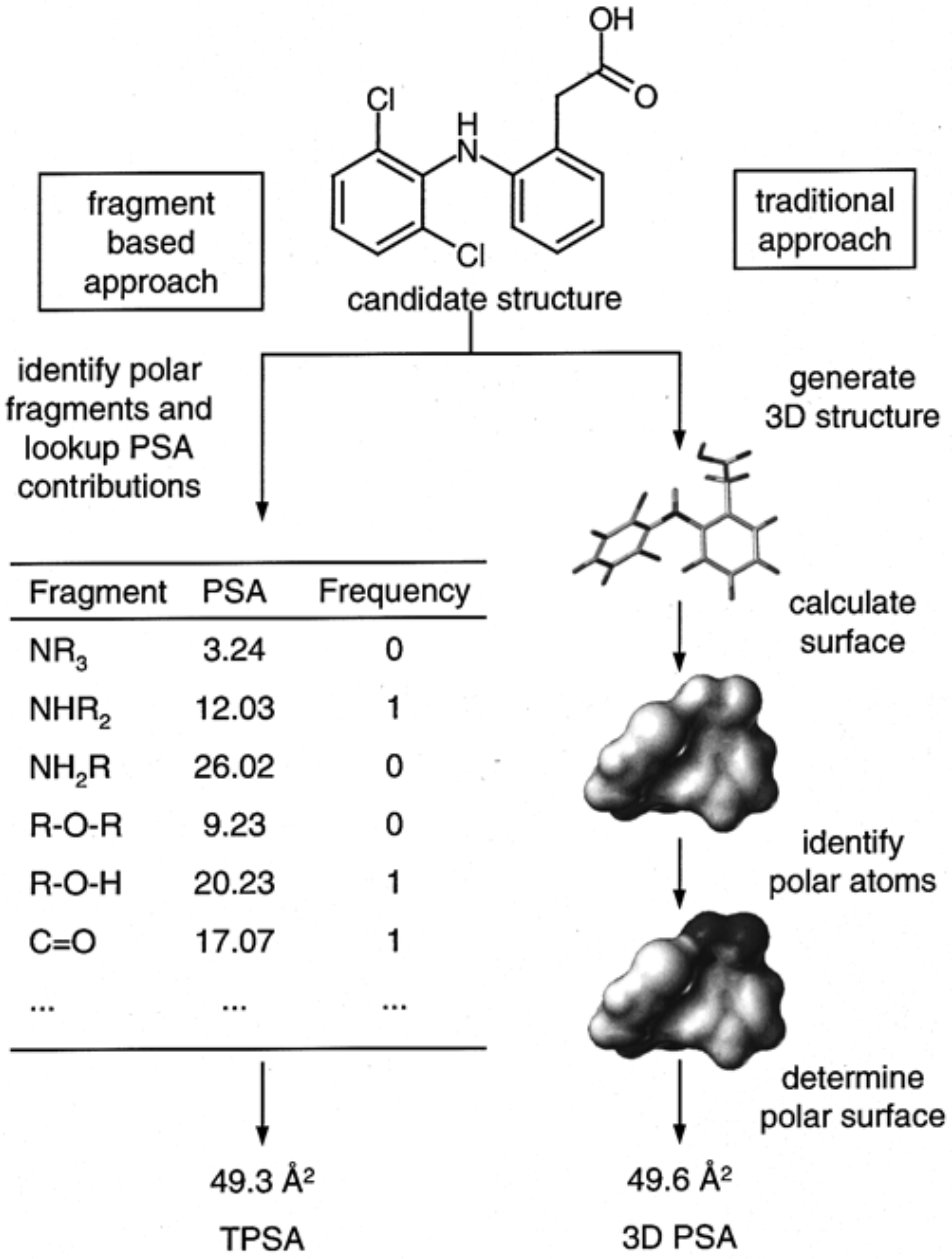


Christopher Lipinski
Originator of 'The Rule of Five'
Lipinski's rule of five

Molecular weight (**MW**), polar surface area (**PSA**), rotatable bonds (**RB**), hydrogen bond acceptors (**HBA**), hydrogen bond donors (**HBD**), **log P**.

C. Lipinski. *Drug Discovery Today*: Technologies. **2004**, 1, 337–341 ; Int. J. Pharmaceutics, **2018**, 549, 133-149

Typical drug properties: Rule of five and bioavailability



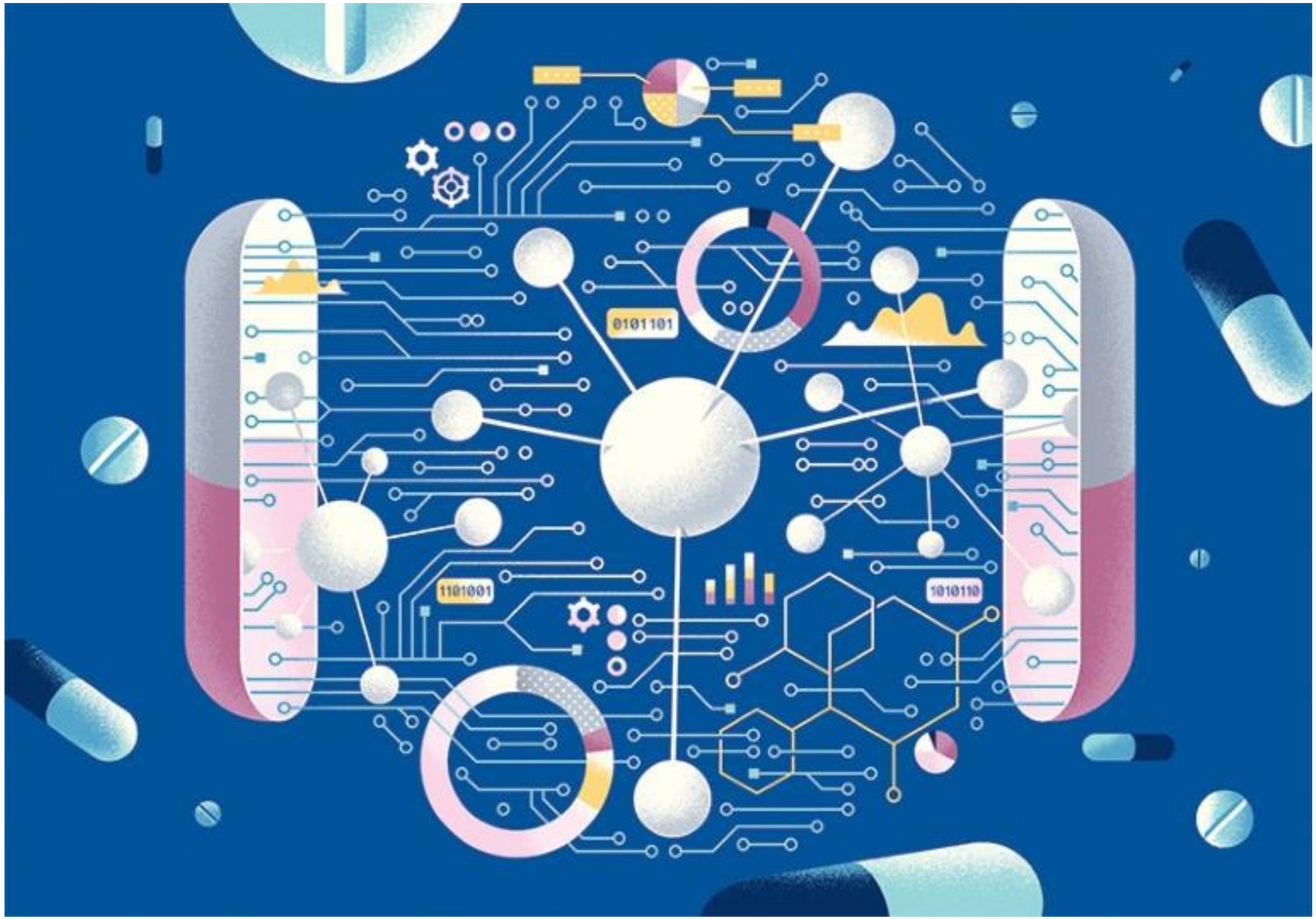
Fragment	PSA	Frequency
NR_3	3.24	0
NHR_2	12.03	1
NH_2R	26.02	0
R-O-R	9.23	0
R-O-H	20.23	1
C=O	17.07	1
...	...	...

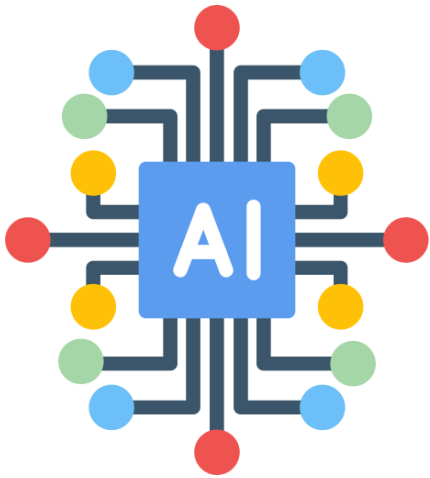
The **polar surface area** (PSA) or topological polar surface area (TPSA) of a molecule is defined as **the surface sum over all polar atoms or molecules, primarily oxygen and nitrogen**, also including their attached hydrogen atoms.

PSA is a commonly used medicinal chemistry metric for the optimization of a drug's ability to permeate cells. Molecules with a polar surface area of greater than 140 angstroms squared (Å2) tend to be poor at permeating cell membranes. For molecules to penetrate the blood–brain barrier (and thus act on receptors in the central nervous system), a PSA less than 90 Å2 is usually needed.

TPSA is a valuable tool in drug discovery and development. By analyzing a drug candidate's TPSA, scientists can predict its potential for oral bioavailability and ability to reach target sites within the body. This prediction hinges on a drug's ability to permeate biological barriers

Drug Discovery and artificial intelligence (AI)



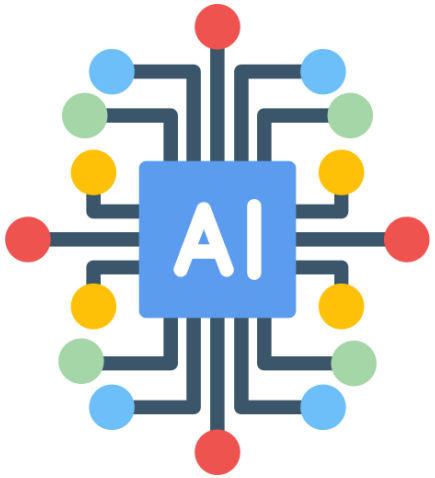


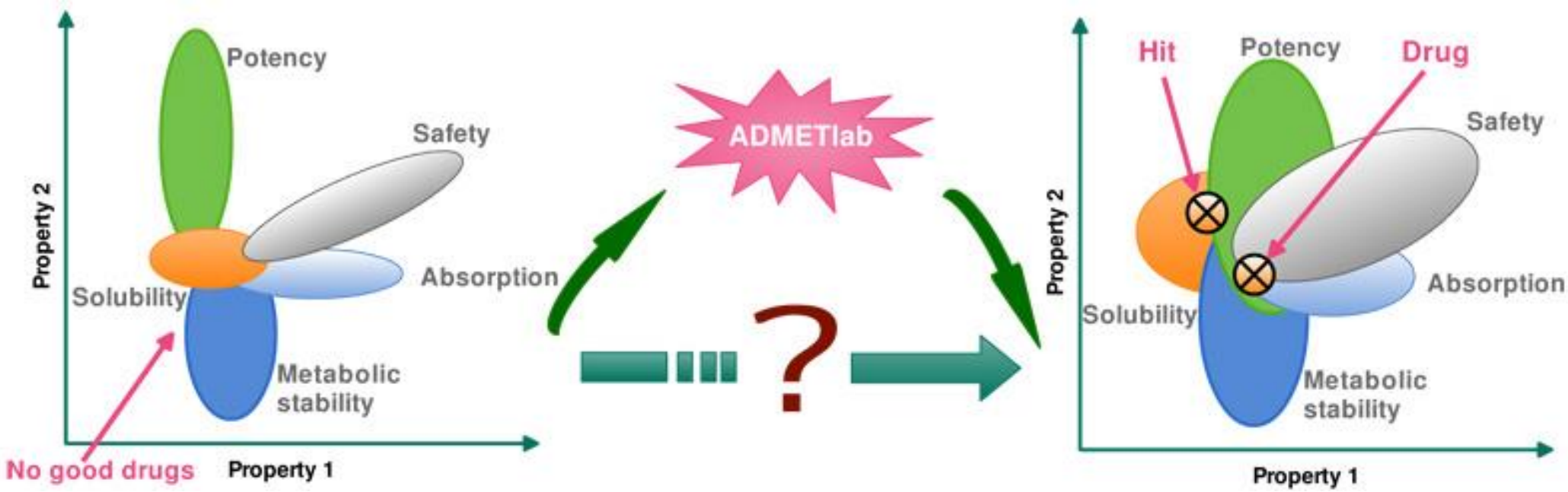
How artificial intelligence is changing drug discovery. Nature, 2018, 557, S55

Typical drug properties: ADMET

Before starting the synthesis of some analogs in medicinal chemistry →

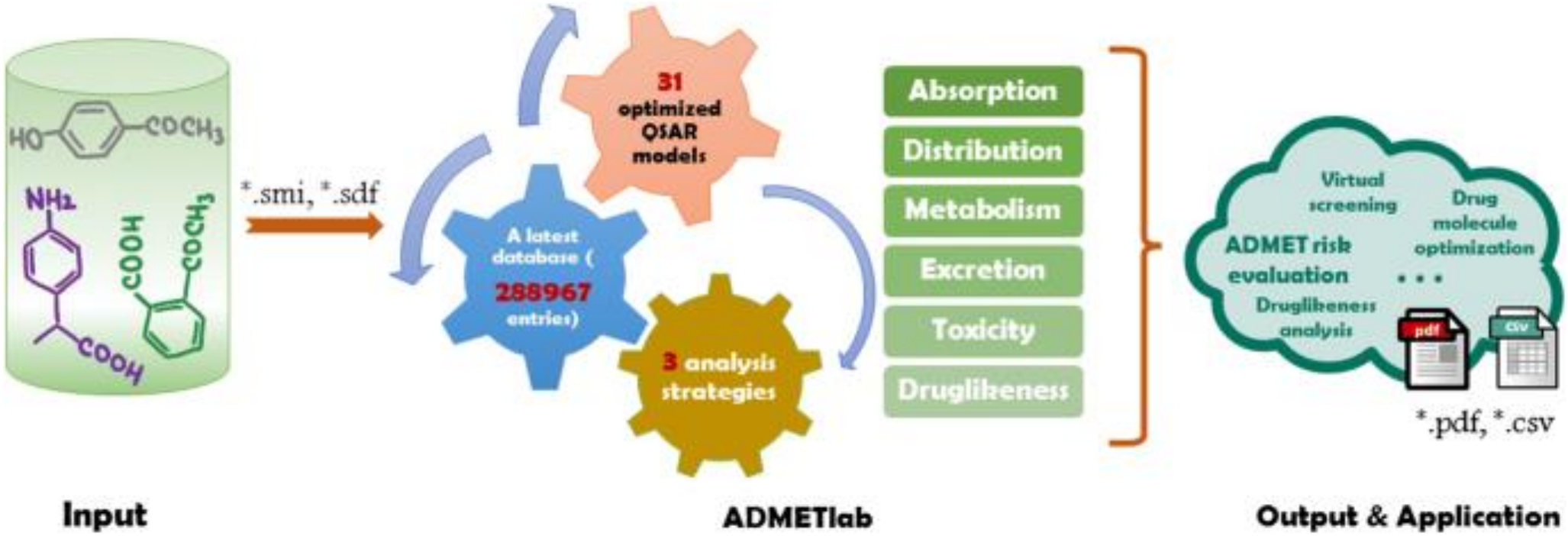
Using artificial intelligence, we can predict easily their physicochemical and ADMET **parameters.**





ADMETlab:

ADMETlab: a platform for systematic ADMET evaluation based on a comprehensively collected ADMET database.

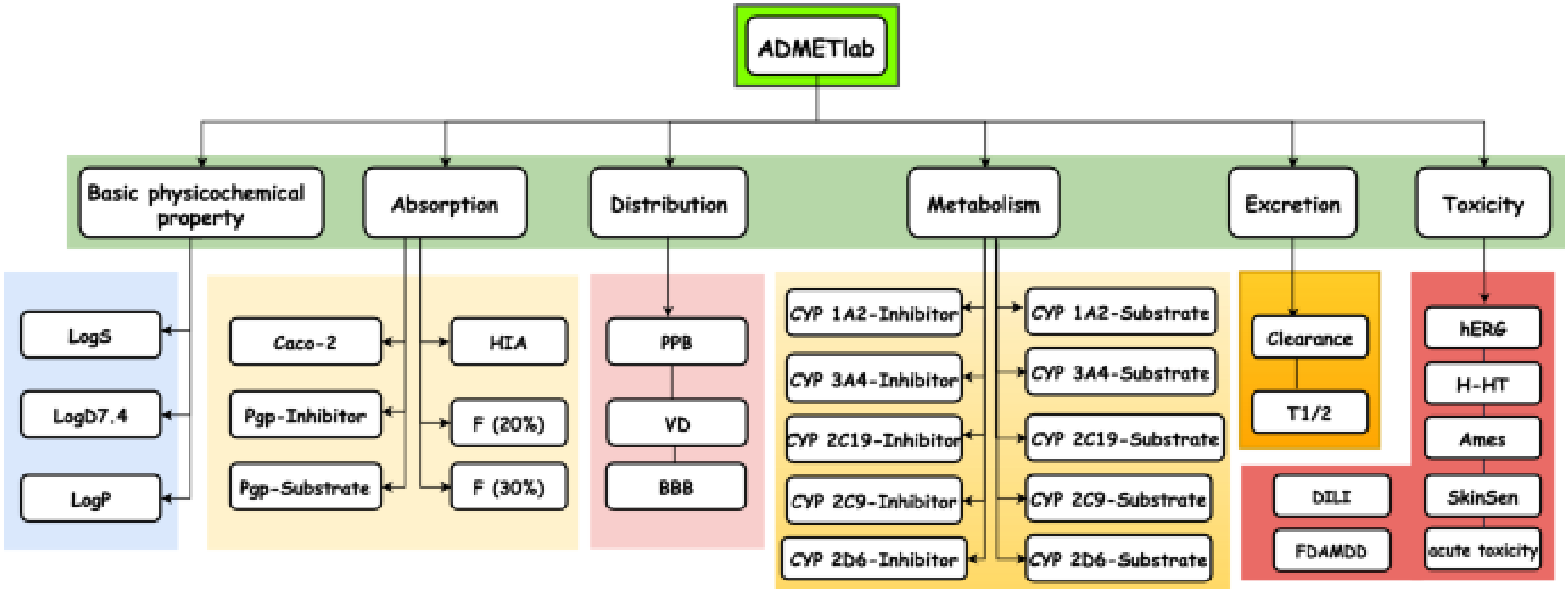


Quantitative Structure-Activity Relationship (QSAR) studies involve pattern discovery, **predictive analysis**, association analysis, regression, and **classification models that integrate information** from various **biological**, **physical**, and **chemical predictors**.

It relies on the **assumption that chemical molecules sharing similar properties** possess **similar safety profile**. **QSAR model** establishes a **relationship** between a **set of predictors and biological activity** (e.g., **binding affinity** or **toxicity**). Biological properties correlate with the size and shape of a molecule, the presence of specific bonds or chemical groups, lipophilicity, and electronic properties.

J Cheminform (2018) 10:29 https://doi.org/10.1186/s13321-018-0283-x3

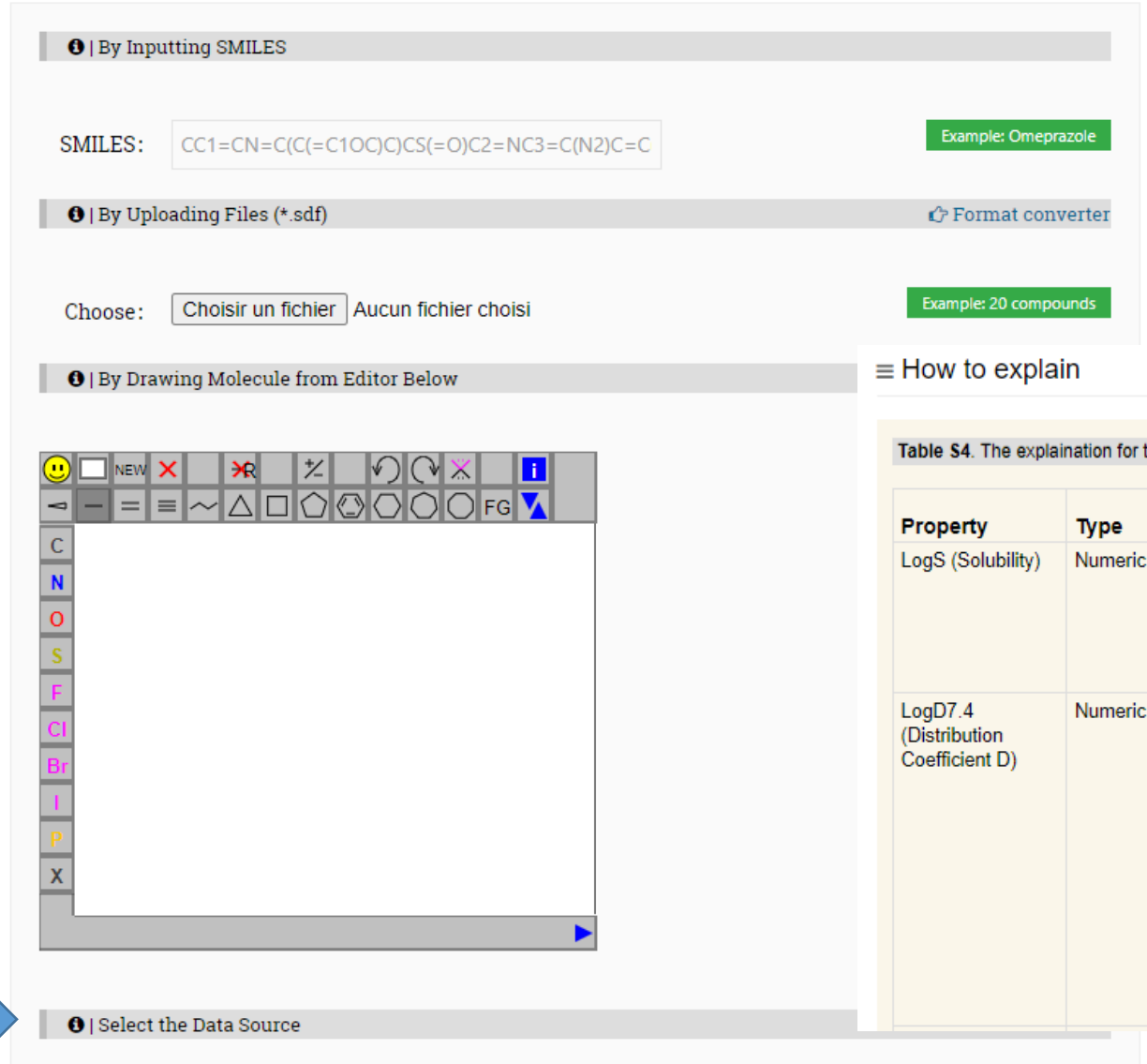
ADMETlab:



https://admet.scbdd.com/#

ADMETlab:

Exp/ Systematic Evaluation https://admet.scbdd.com/calcpre/index_sys/

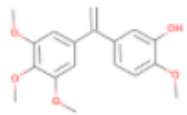


≡ How to explain

Table S4. The explaination for the coressponding ADME/T related properties

Property	Type	Units	Suggestions	Meaning & Preference	Reference
LogS (Solubility)	Numeric	log mol/L	> 10 μg/ml	• Optimal: higher than -4 log mol/L • <10 μg/mL: Low solubility; 10–60 μg/mL: Moderate solubility; >60 μg/mL: High solubility	• Book: ISBN: 9787562832287. pp. 14. • J PHARMACOL TOX MET. 2000, 44 (1), 235–249.
LogD7.4 (Distribution Coefficient D)	Numeric		1~5	• < 1: Solubility high; Permeability low by passive transcellular diffusion; Permeability possible via paracellular if MW < 200; Metabolism low. • 1 to 3: Solubility moderate; Permeability moderate; Metabolism low. • 3 to 5: Solubility low; Permeability high; Metabolism moderate to high. • > 5: Solubility low; Permeability high; Metabolism high.	• Methods and principles in medicinal chemistry 18 (pp. 21–45). Weinheim: Wiley-VCH.

Exp/ Systematic Evaluation https://admet.scbdd.com/calcpre/index_sys/



SMILES	C=C(c1ccc(OC)c(O)c1)c1cc(OC)c(OC)c(OC)c1
Molecular Weight	316.353
Log P (Crippen method)	3.488
HB Acceptor	5
HB Donor	1
TPSA	57.15

| Results

Physicochemical Property

Property	Predicted values	Suggestions	Meaning & Preference	Reference
LogS (Solubility)	-4.294 log mol/L (16.076 μg/mL)	> 10 μg/ml	• Optimal: higher than -4 log mol/L • <10 μg/mL: Low solubility; 10–60 μg/mL: Moderate solubility; >60 μg/mL: High solubility	• Book: ISBN: 9787562832287. pp. 14 • J PHARMACOL TOX MET. 2000, 44 (1), 235–249;
$LogD_{7.4}$ (Distribution Coefficient D)	1.26	1~5	• < 1: Solubility high; Permeability low by passive transcellular diffusion; Permeability possible via paracellular if MW < 200; Metabolism low. • 1 to 3: Solubility moderate; Permeability moderate; Metabolism low. • 3 to 5: Solubility low; Permeability high; Metabolism moderate to high. • > 5: Solubility low; Permeability high; Metabolism high.	• Methods and principles in medicinal chemistry 18 (pp. 21–45). Weinheim: Wiley-VCH.
LogP (Distribution Coefficient P)	3.488	0~3	• Optimal: 0< LogP <3 • LogP <0: poor lipid bilayer permeability. • LogP >3: poor aqueous solubility.	• Book: ISBN: 3-906390-22-5. pp. 127–182.

Exp/ Systematic Evaluation

Absorption

Property	Predicted values	Probability	Suggestions	Meaning & Preference	Reference
Papp (Caco-2 Permeability)	-4.847 cm/s		> -5.15 cm/s	Optimal: higher than -5.15 Log unit or -4.70 or -4.80	• J CHEM INF MODEL. 2016, 56 (4), pp 763−773.
Pgp-inhibitor	- - -	0.107		• The Pgp-inhibitor & non-inhibitor classification criteria refers the reference.	• J CHEM INF MODEL. 2010. 50(6): p. 1034-1041. • J MED CHEM. 2011. 54(6): p. 1740-1751.
Pgp-substrate	- - -	0.018		• More likely to be a Pgp substrate: N+O ≥ 8; MW > 400; Acid with pKa > 4 • More likely to be a Pgp non-substrate: N+O ≤ 4; MW < 400; Acid with pKa < 8	• J DRUG TARGET. 11, 391−406.
HIA (Human Intestinal Absorption)	+	0.699		• ≥30%: HIA+; <30%: HIA-	• RSC ADV. 2017, 7, 19007-19018
F (20% Bioavailability)	+	0.631		• ≥20%: F20+; <20%: F20-	• MOL PHARMACEUT, 2011. 8(3): p. 841-851 • J PHARMACEUT BIOMED, 2008. 47(4): p. 677-682.
F (30% Bioavailability)	+	0.662		• ≥30%: F30+; <30%: F30-	• MOL PHARMACEUT, 2011. 8(3): p. 841-851 • J PHARMACEUT BIOMED, 2008. 47(4): p. 677-682.

Exp/ Systematic Evaluation

Distribution

Property	Predicted values	Probability	Suggestions	Meaning & Preference	Reference
PPB (Plasma Protein Binding)	83.556 %		90%	• Significant with drugs that are highly protein-bound and have a low therapeutic index.	• ISBN: 978-0-1236-9520-8. pp. 194
BBB (Blood–Brain Barrier)	+	0.634		• BB ratio >=0.1: BBB+; BB ratio <0.1: BBB- • These features tend to improve BBB permeation: H-bonds (total) < 8–10; MW < 400–500; No acids.	• J NEUROCHEM. 70, 1781–1792

Metabolism

Property	Predicted values	Probability	Meaning & Preference	Reference
P450 CYP1A2 inhibitor	-	0.437	• Molecules that labeled inhibitor in PubChem BioAssay were regarded as inhibitor.	• NAT BIOTECHNOL. 2009, 27(11): 1050-1055. • BIOINFORMATICS. 2013, 29(16): 2051-2052.
P450 CYP1A2 Substrate	-	0.468	• Molecules that labeled substrate in PubChem BioAssay were regarded as substrate. • Characteristics of CYP1A2 substrate: 0.08< LogP <3.61; Planar amines and amides	• NAT BIOTECHNOL. 2009, 27(11): 1050-1055. • BIOINFORMATICS. 2013, 29(16):
P450 CYP2C9 substrate	+	0.538	• Molecules that labeled substrate in PubChem BioAssay were regarded as substrate. • Characteristics of CYP2C9 substrate: 0.89< LogP <5.18; Acidic (Nonionized)	• MOL INFORM. 2011. 30(10): p. 885-895. • J CHEM INF MODEL. 2013. 53(12): p. 3373-3383. • ISBN: 978-0-1236-9520-8. pp.

Exp/ Systematic Evaluation

Elimination

Property	Predicted values	Suggestions	Meaning & Preference	Reference
$T_{1/2}$ (Half Life Time)	1.748 h	> 0.5 h	• Range: >8h: high; 3h< Cl < 8h: moderate; <3h: low	• ISBN: 978-0-1236-9520-8. pp. 236

Toxicity

Property	Predicted values	Probability	Suggestions	Meaning & Preference	Reference

hERG (hERG Blockers)	+	0.588		• Where molecules with IC50 < 40 μM were regarded as blockers.
				• Features may lead to hERG blocker:
				  ◦ A basic amine (positively ionizable, pKa >7.3).
				  ◦ Hydrophobic/lipophilic substructure(s) (ClogP >3.7).
				  ◦ Absence of negatively ionizable groups or oxygen H-bond acceptors.
					• TRENDS PHARMACOL SCI. 2005, 26(3): 119-124
					• ISBN: 978-0-1236-9520-8. pp. 213
					• MOL PHARM. 2016, 13(8):2855−2866

H-HT (Human Hepatotoxicity)	+	0.64		• The H-HT positive(+) & negative(-) classification criteria refers the reference.	• CHEM RES TOXICOL, 2016, 29(5): 757-767.
AMES (Ames Mutagenicity)	---	0.18		• Ames positive(+) & negative(-): significantly induces revertant colony growth at least in one out of usually five strains, otherwise, negative.	• J CHEM INF MODEL. 2012, 52(11): 2840-2847.
SkinSen (Skin sensitization)	-	0.465		• Sensitizer & Non-sensitizer: The (r)LLNA experimental value. (r)LLNA: (Reduced) local lymph node assay.	• TOXICOL APPL PHARM, 2015 , 284 (2) :262-272
LD50 (LD50 of acute toxicity)	2.529 -log mol/kg (935.776 mg/kg)		> 500 mg/kg	• Median lethal dose (LD50) usually represents the acute toxicity of chemicals.It is the dose amount of a tested molecule to kill 50 % of the treated animals within a given period. • High-toxicity: 1~50 mg/kg; Toxicity: 51~500 mg/kg; low-toxicity: 501~5000 mg/kg.	• CHEM RES TOXICOL, 2009, 22 (12), pp 1913−1921 • J CHEMINFORMATICS, 2016 , 8 (1) :6

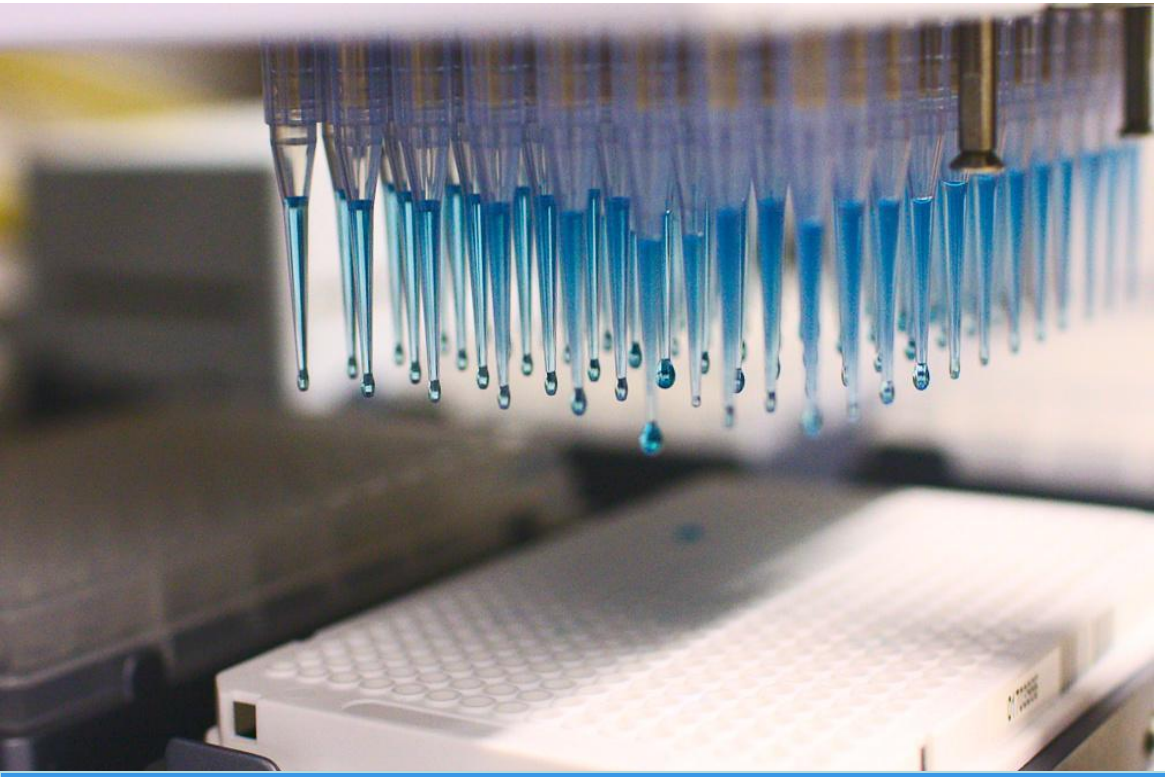
COURSE OUTLINE

1. General points
2. ADMET, RO5, and systematic in silico ADMET evaluation
3. The discovery process in the pharmaceutical industry (R&D)
4. The choice of a drug target
5. Drug design strategies
6. Conclusion

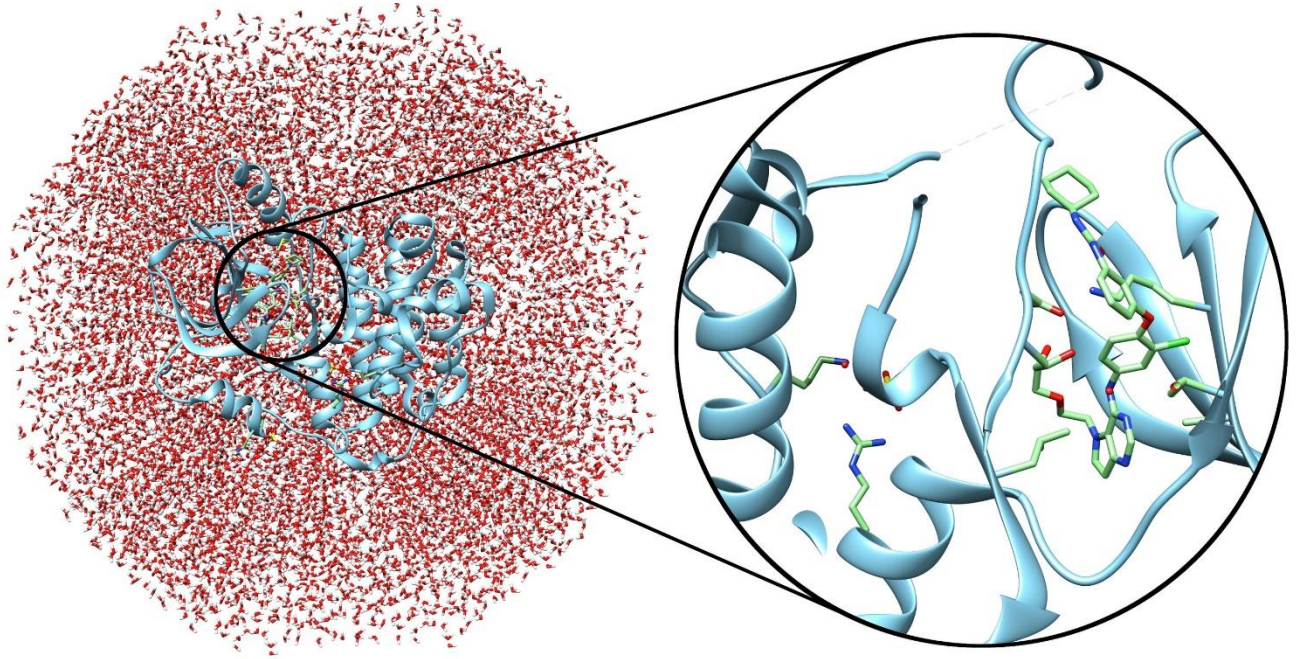
The discovery process in the pharmaceutical industry (R&D)

Generation of the LEAD

1st approach, HTS



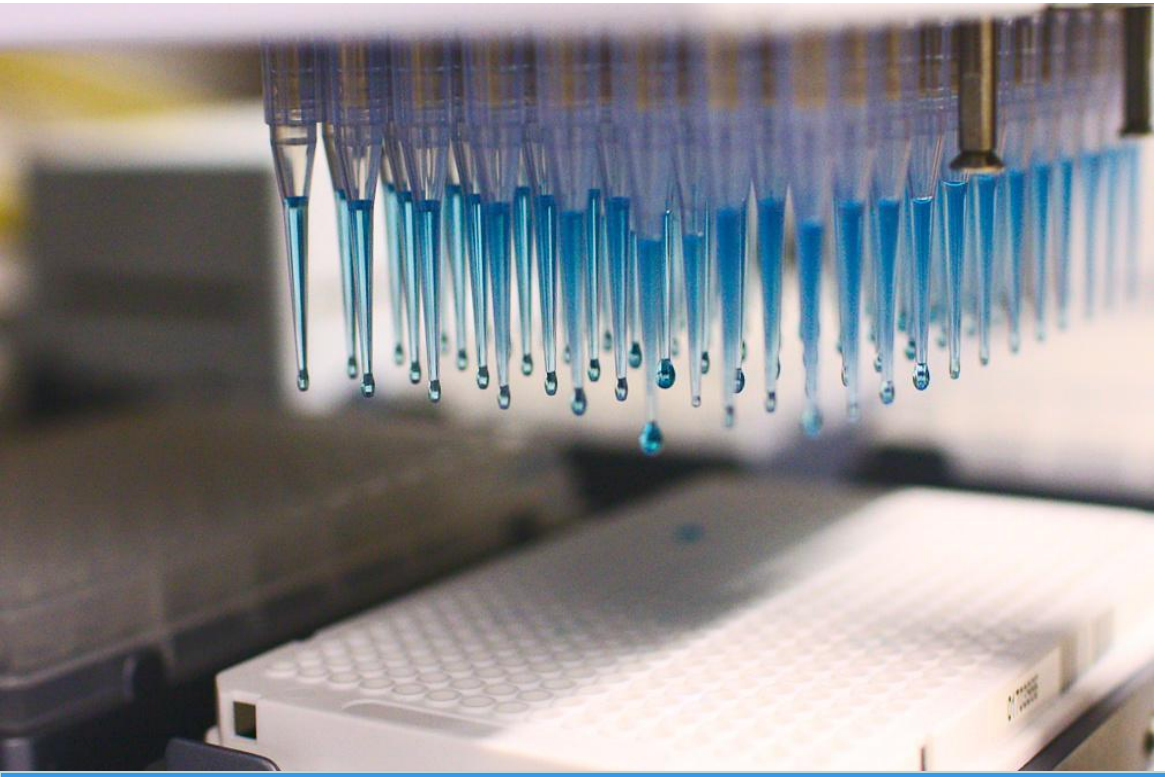
2nd approach, Rational drug design



The discovery process in the pharmaceutical industry (R&D)

Generation of the LEAD

1st approach, HTS



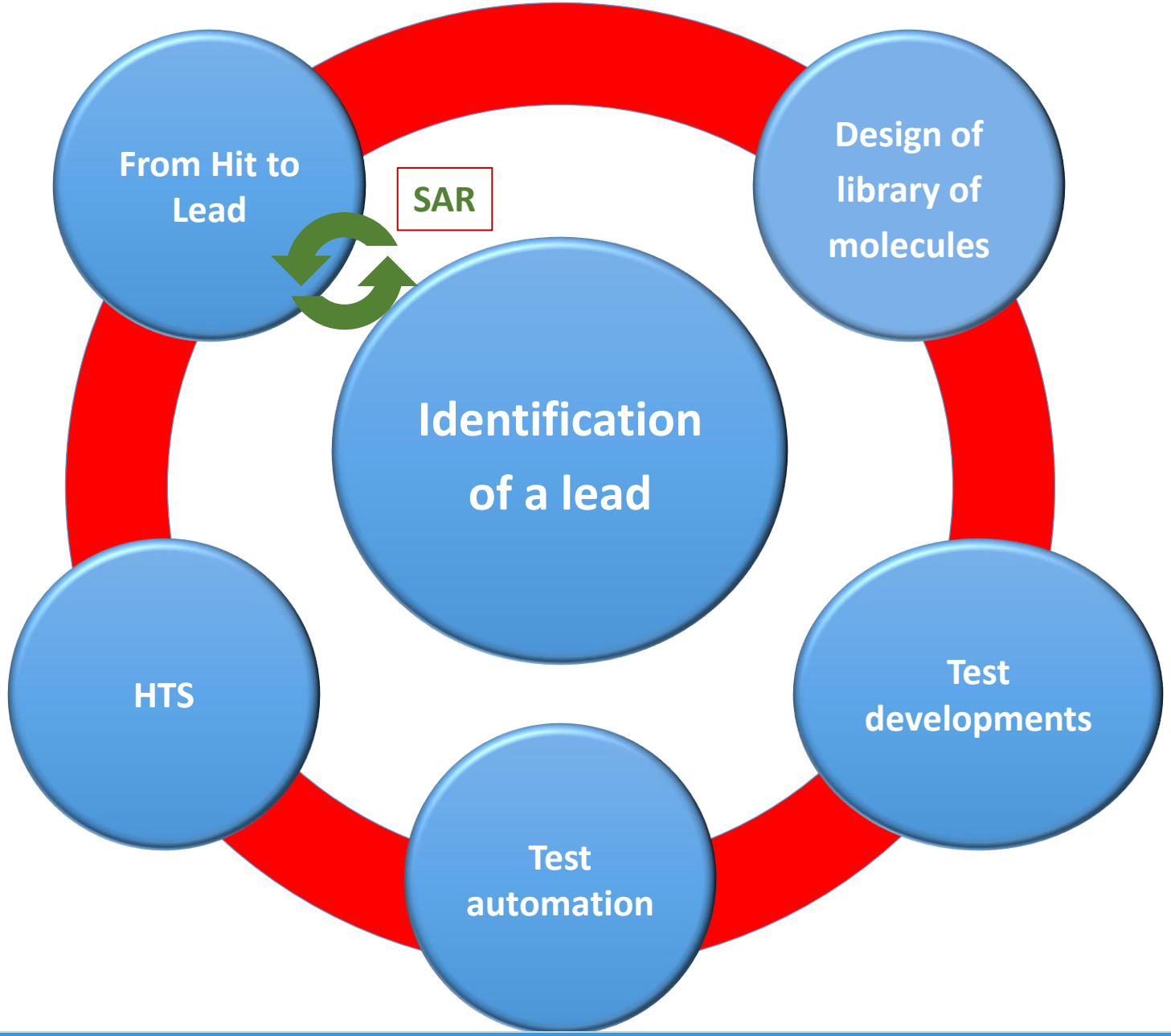
High **T**hroughput **S**creening (**HTS**):

H2L phase

Hit to Lead

The discovery process in the pharmaceutical industry (R&D)

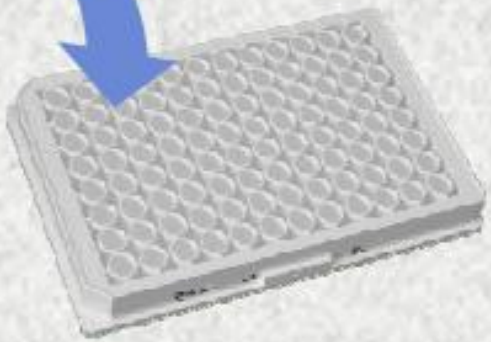
1st approach, HTS



The discovery process in the pharmaceutical industry (R&D)

Plate-forme HTS

Molécules



Tests

Détection

Chimiothèque

- Tests enzymatiques, Interaction hormone/récepteur,
- Interaction protéine/protéine, tests cellulaires, etc.

Fluorescence, Chemiluminescence, Absorbance, etc.

The discovery process in the pharmaceutical industry (R&D)

HTS (1st approach)
10000 compounds

Determination of IC_{50}, **selection of the hit**

Hit to lead
100 compounds

SAR, selectivity study, *in vitro* efficacy, physicochemical tests

Lead optimization
10 compounds

Efficacy *in vivo*, ADME

Generation of the LEAD, HTS (1st approach)

The discovery process in the pharmaceutical industry (R&D)

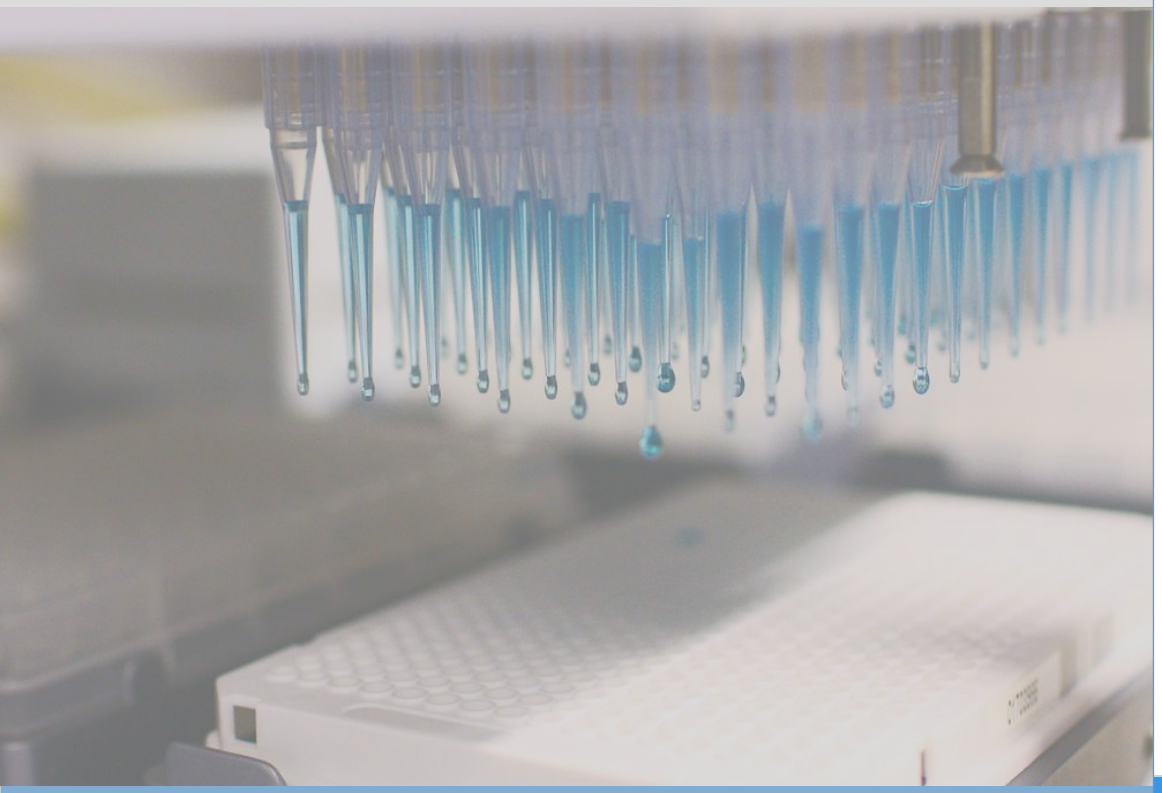
Table 1. List of Drugs Developed or Discovered by High-Throughput Screening[a]

drug (U.S. trade name, company)	indication	target class	year HTS was run	year of FDA approval
gefitinib (Iressa, AstraZeneca)	cancer	tyrosine kinase	ca. 1993	2003
erlotinib (Tarceva, Roche)	cancer	tyrosine kinase	ca. 1993	2004
sorafenib (Nexavar, Bayer/Onyx Pharmaceuticals)	cancer	tyrosine kinase	1994	2005
tipranavir (Aptivus, Boehringer Ingelheim)	HIV	protease	ca. 1993	2005
sitagliptin (Januvia, Merck & Company)	diabetes	protease	ca. 2000	2006
dasatinib (Sprycel, Bristol-Myers Squibb)	cancer	tyrosine kinase	1997	2006
maraviroc (Selzentry, Pfizer)	HIV	GPCR	1997	2007
lapatinib (Tykerb, GlaxoSmithKline)	cancer	tyrosine kinase	ca. 1993	2007
ambrisentan (Letairis, Gilead)	pulmonary hypertension	GPCR	ca. 1995	2007
etravirine (Intelence, Tibotec Pharmaceuticals)	HIV	reverse transcriptase	ca. 1992	2008
tolvaptan (Samsca, Otsuka Pharmaceutical)	hyponatremia	GPCR	ca. 1990	2009
eltrombopag (Promacta, GlaxoSmithKline)	thrombocytopenia	cytokine receptor	1997	2008

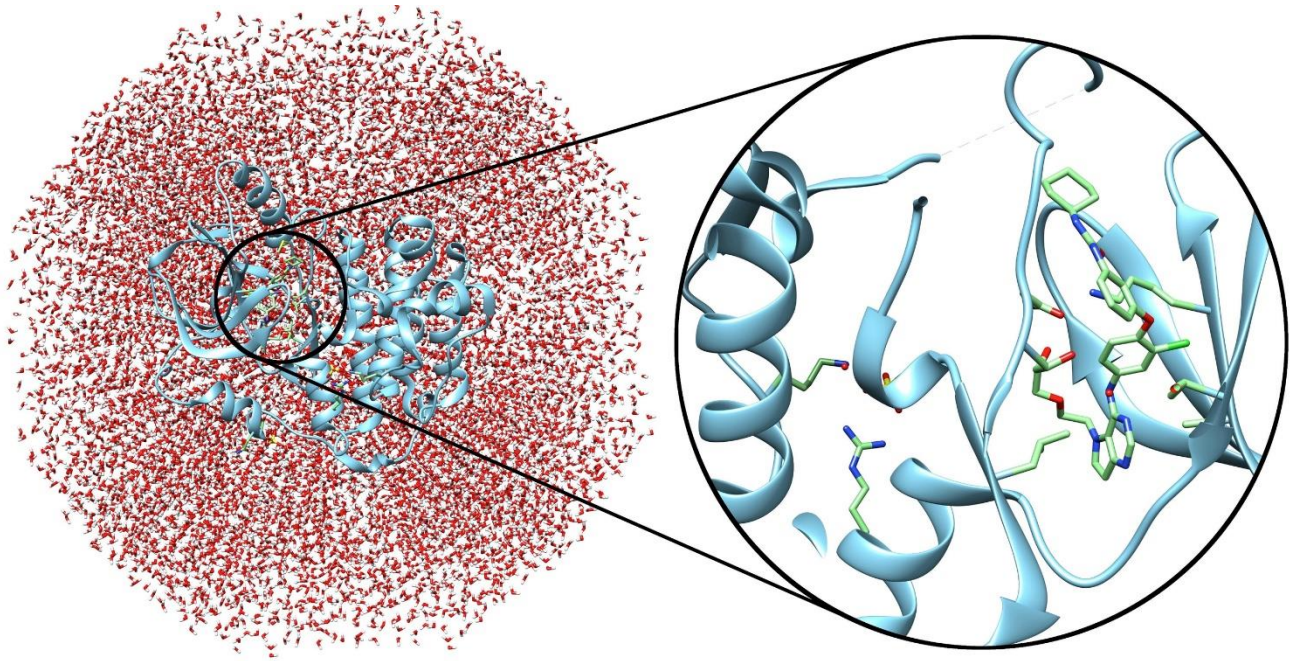
The discovery process in the pharmaceutical industry (R&D)

Generation of the LEAD

1st approach, HTS



2nd approach, Rational drug design



2nd approach, Rational Drug Design

Generation of a lead (2nd approach)

Structure of known target (X-ray)

Docking : Glide + ZINC (35 million purchasable compounds)

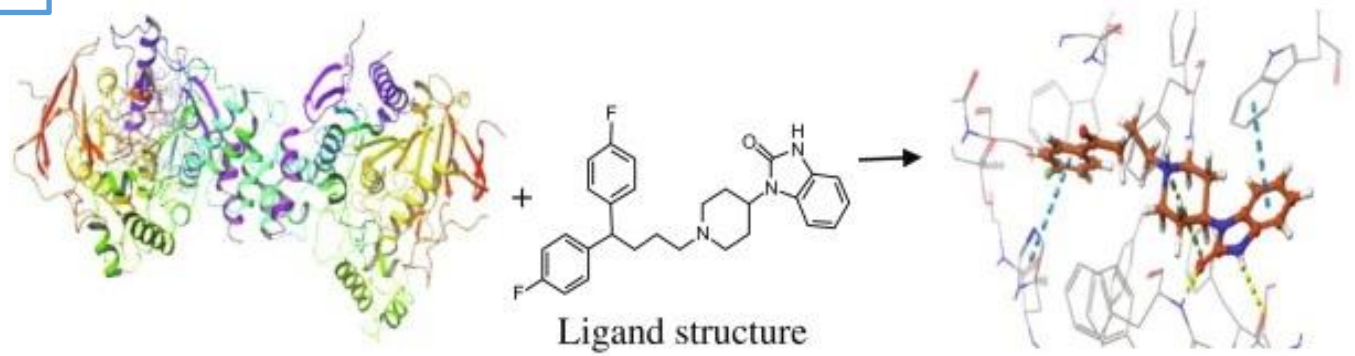
ADME Filtre

Purchase of products

Products synthesis

Biological tests

Hits µM



(B) Protein structure

Ligand-protein interaction

Generation of a lead

RCSB PDB Deposit Search Visualize Analyze Download Learn More MyPDB Login

RCSB PDB PROTEIN DATA BANK

An Information Portal to 126060 Biological Macromolecular Structures

Search by PDB ID, author, macromolecule, sequence, or ligands

Go

Advanced Search | Browse by Annotations

PDB-101 · Worldwide PDB · EMDataBank · Nucleic Acid Database · StructuralBiology Knowledgebase · Worldwide Protein Data Bank Foundation

Welcome

Deposit

Search

Visualize

Analyze

Download

Learn

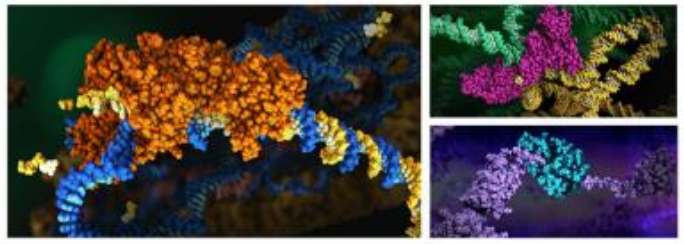
A Structural View of Biology

This resource is powered by the Protein Data Bank archive-information about the 3D shapes of proteins, nucleic acids, and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture, from protein synthesis to health and disease.

As a member of the wwPDB, the RCSB PDB curates and annotates PDB data.

The RCSB PDB builds upon the data by creating tools and resources for research and education in molecular biology, structural biology, computational biology, and beyond.

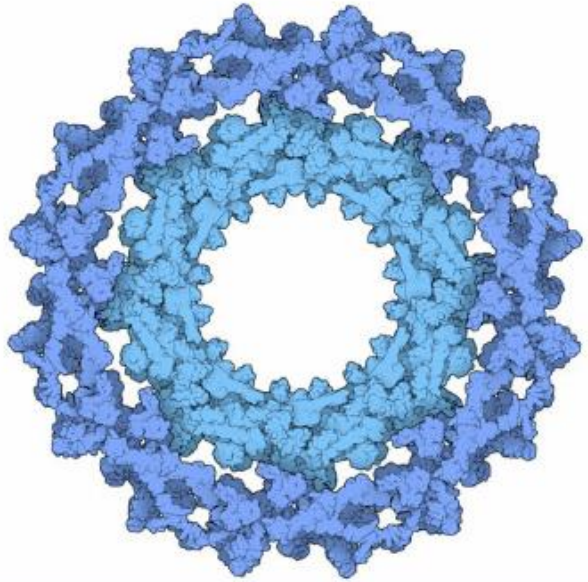
A Molecular View of HIV Therapy



2016 FASEB BioArt Winner

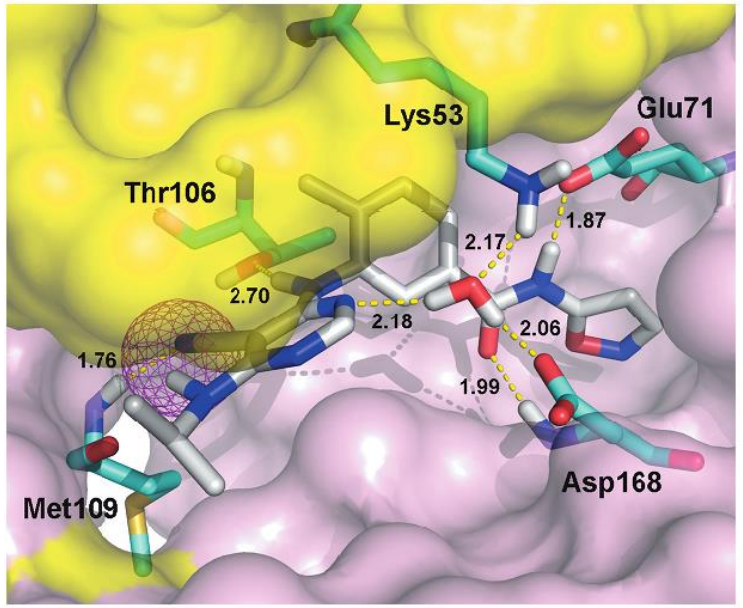
View animation on PDB-101

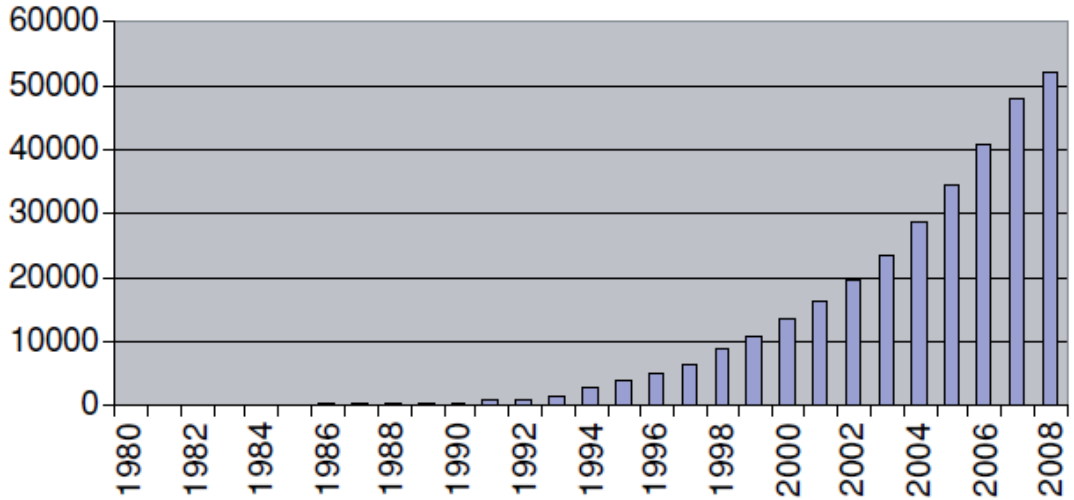
January **Molecule of the Month**



Nuclear Pore Complex

Generation of a lead





Growth of total crystal structures in the RCSB PDB database (www.rcsb.org).

Table 12.1. Resolution of protein crystal structures

Resolution (Å)	Structural features observable for a good data set[a]
5.5	Overall shape of the protein. Helices as rods.
3.5	Protein main chain (often some ambiguity).
3.0	Protein side chains partly resolved.
2.5	Side chains well resolved.
1.5	Heavy atoms well resolved.

Data taken from Enzyme Structure and Mechanism, 2nd edition

The discovery process in the pharmaceutical industry (R&D)

HTS (1st approach)
10000 compounds

Determination des IC_{50}, **selection of the hit**

Hit to lead
100 compounds

SAR, selectivity study, in vitro efficacy, physicochemical tests

Lead optimization
10 compounds

Efficacy in vivo, ADME

Preclinical proof of principle

Best candidate (1-3)

PK, PD, salt formation, evaluation of crystal forms

Preclinical studies

Genetic toxicity, in vivo toxicity in 2 different species

GLP batch preparation (Good Laboratory Practice)

Clinical studies

Phase I : tolerance in healthy volunteers
Phase II : efficacy of the molecule, and determination of the therapeutic dose
Phase III : comparative efficacy study

Optimisation Hit to Lead **H2L**

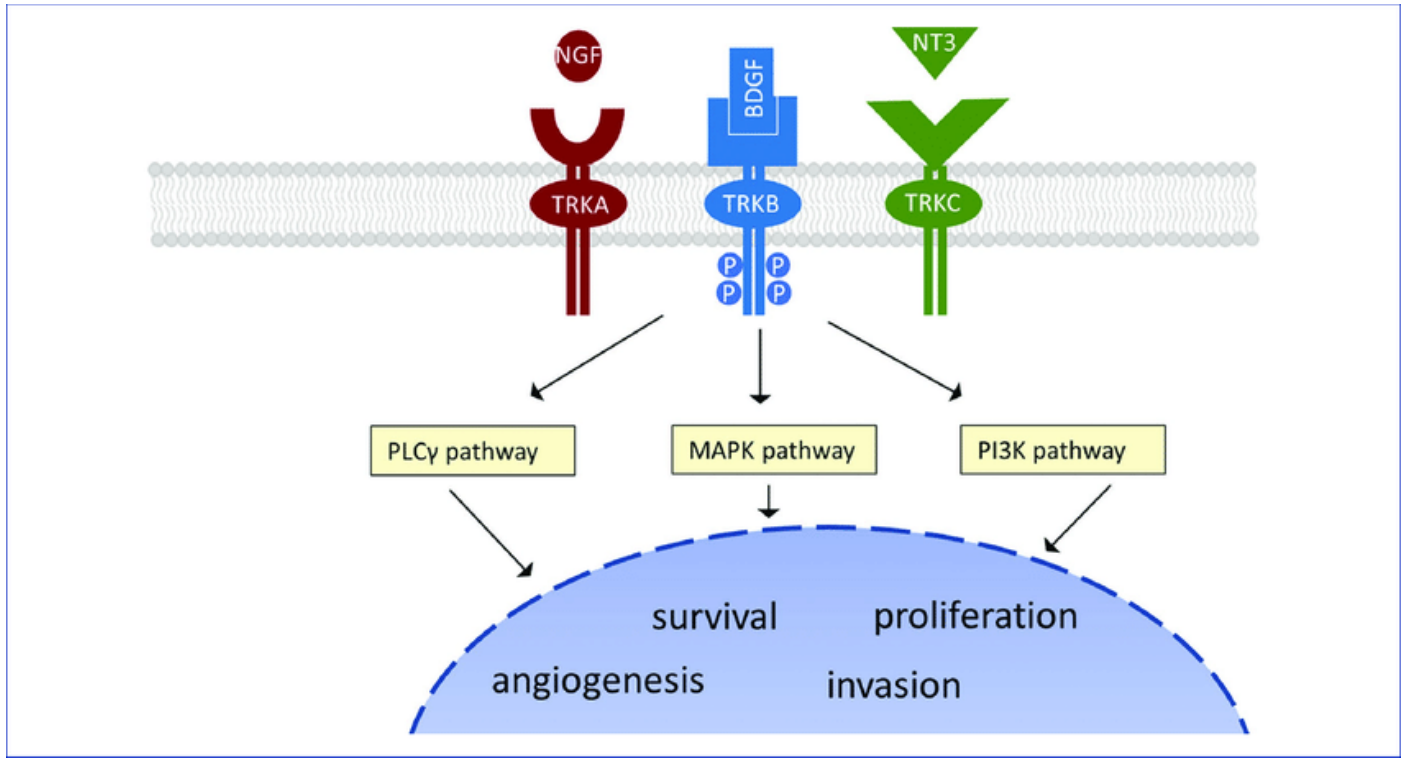
Optimisation Hit to Lead

Journal of Medicinal Chemistry
pubs.acs.org/jmc Article

Discovery of CH7057288 as an Orally Bioavailable, Selective, and Potent pan-TRK Inhibitor

Target = **t**ropomyosin **r**eceptor **k**inases (**TRK**)

Kinase fusions involving tropomyosin receptor kinases (**TRKs**) have been proven to act as **strong oncogenic drivers** and are therefore recognized as attractive therapeutic targets.

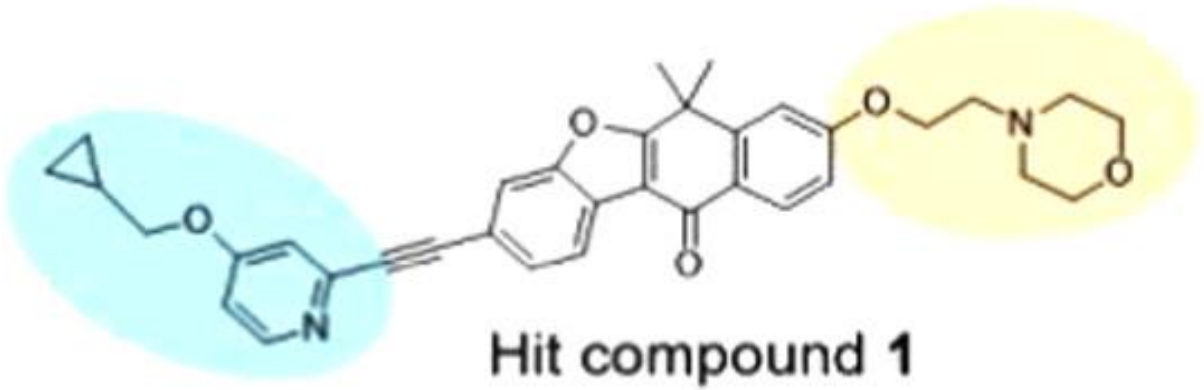


Optimisation Hit to Lead

Journal of Medicinal Chemistry
pubs.acs.org/jmc Article

Discovery of CH7057288 as an Orally Bioavailable, Selective, and Potent pan-TRK Inhibitor

Target = **t**ropomyosin **r**eceptor **k**inases (**TRK**)



Hit compound **1**

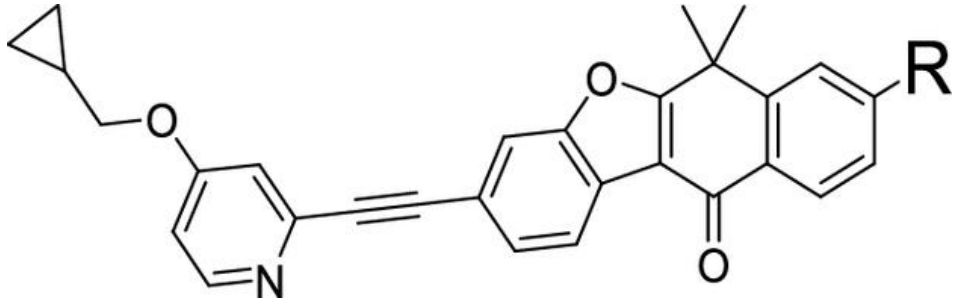
- TRKA IC_{50} 4.7 nM
- NIH 3T3 *MPRIP-NTRK1* IC_{50} 59 nM
- CYP3A4 induction risk High

TRKA = enzyme

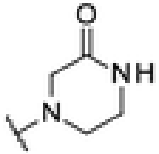
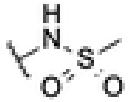
NIH3T3 = Cells expressing TRKA

J. Med. Chem. 2022,DOI: (10.1021/acs.jmedchem.2c01099)

Optimisation Hit to Lead

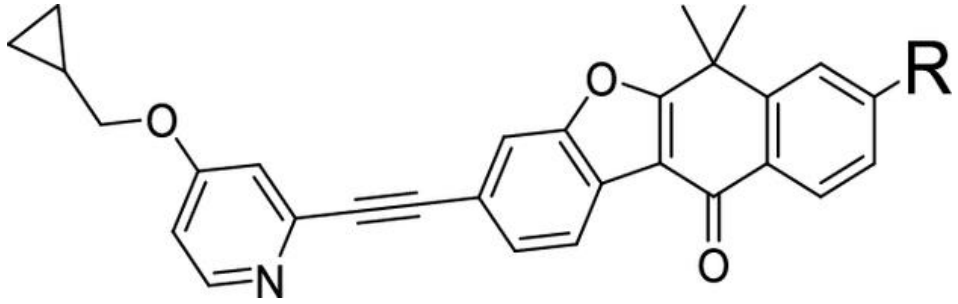


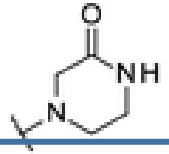
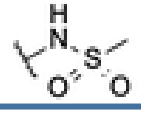
Inhibitions of kinase insert domain receptor (**KDR**) and lymphocyte-specific protein tyrosine kinase (**LCK**) are suspected to cause hypertension and pulmonary arterial hypertension, respectively.

Compound	R	IC_{50} (nM) TRKA	KDR*	LCK	** NIH3T3 *MPRIP-NTRK1*	CYP 3A4 fold induction (vs DMSO)	CYP 3A4 relative induction (% of Rif.)	calculated basic pKa
1		4.5	757	104	59	6.5	33%	6.15
5a		3.4	690	190	53	5.4	26%	3.77
5b		3.0	430	86	69	2.6	6.3%	3.00
5c		1.4	290	50	16	4.2	11%	3.38
5d		3.9	>1,000	223	75	1.2	0.9%	-

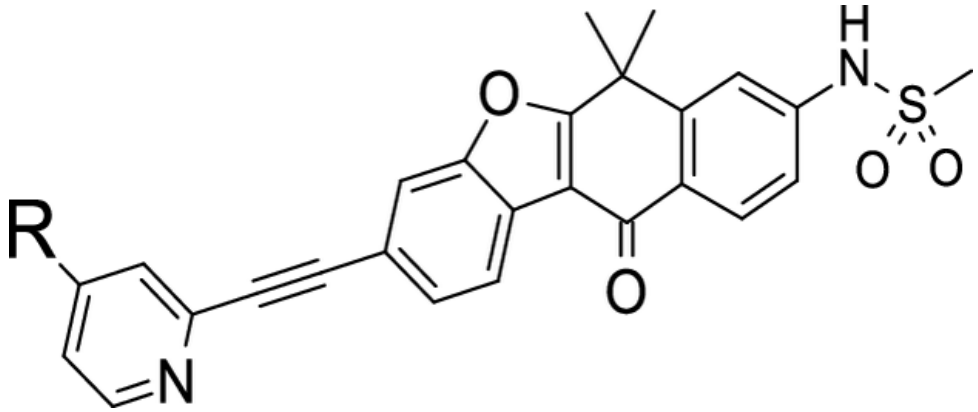
*kinase insert domain receptor (KDR) and ** lymphocyte-specific protein tyrosine kinase (LCK)

Optimisation Hit to Lead



Compound	R	IC_{50} (nM) TRKA	KDR	LCK	NIH3T3 *MPRIP-NTRK1*	CYP 3A4 fold induction (vs DMSO)	CYP 3A4 relative induction (% of Rif.)	calculated basic pKa
1		4.5	757	104	59	6.5	33%	6.15
5a		3.4	690	190	53	5.4	26%	3.77
5b		3.0	430	86	69	2.6	6.3%	3.00
5c		1.4	290	50	16	4.2	11%	3.38
5d		3.9	>1,000	223	75	1.2	0.9%	-

Optimisation Hit to Lead



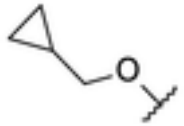
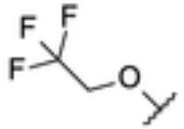
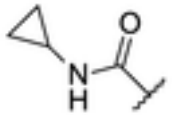
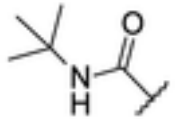
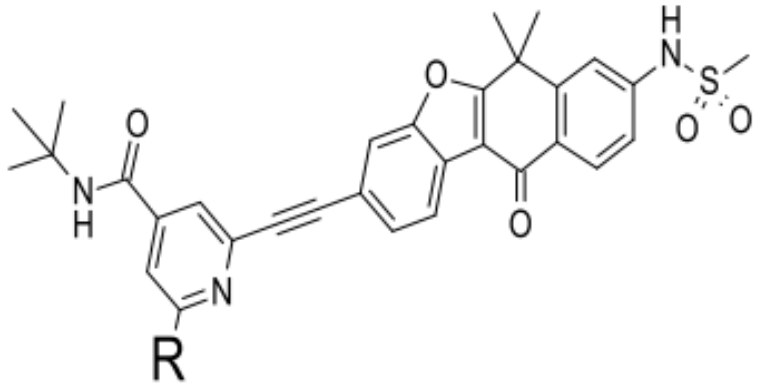
Compound	R	IC_{50} (nM)				CYP 3A4 fold induction (vs DMSO)	CYP 3A4 relative induction (% of Rif.)
		TRKA	KDR	LCK	NIH3T3 *MPRIP-NTRK1*		
5d		3.9	>1,000	223	75	1.2	0.9%
6a		2.2	997	159	67	3.4	11%
6b		2.4	>1,000	145	83	2.8	11%
6c		0.7	600	130	14	4.7	12%

Table 9. Exploration of Substituents at α-Position on the Pyridine Ring



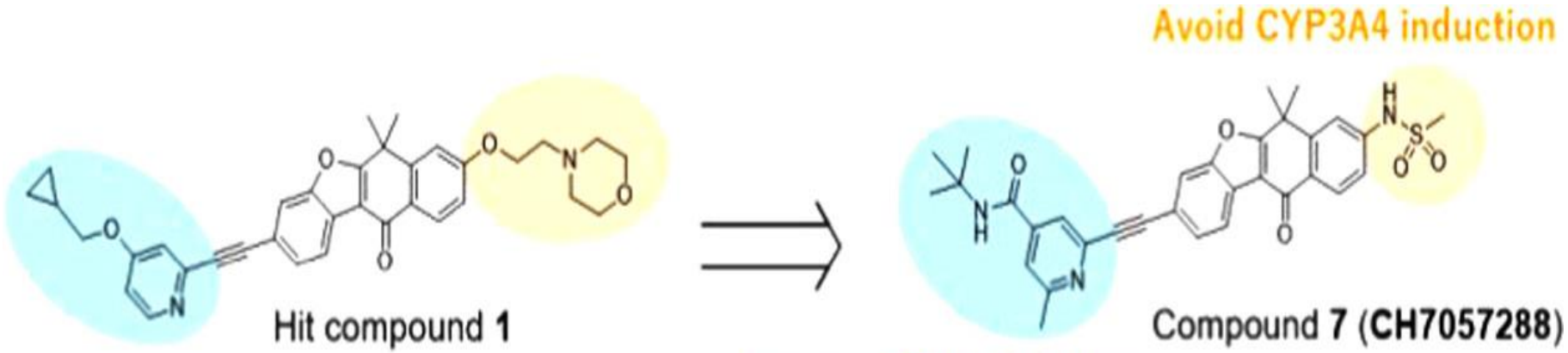
		IC_{50} (nM)					
compound	R	TRKA	KDR	LCK	NIH3T3 *MPRIP-NTRK1*	CYP3A4 fold induction (vs DMSO)	CYP3A4 relative induction (% of Rif.)
7 (CH7057288)	Me	1.2	>1000	300	8.4	3.0	7%
10a	Et	0.7	>1000	320	12	2.8	17%
10b	*n*-Pr	1.2	>1000	96	12	0.9	NC[a]
10c	CF_3	2.6	>1000	130	55	2.5	7%
10d	CI	2.2	>1000	180	48	3.0	11%
10e	CN	2.8	>1000	58	67	11	30%

[a]NC means "not calculated". CYP3A4 relative induction could not be calculated because the CYP3A4 fold induction was <1.

Optimisation **Hit** to **Lead**

Journal of Medicinal Chemistry
pubs.acs.org/jmc Article

Discovery of CH7057288 as an Orally Bioavailable, Selective, and Potent pan-TRK Inhibitor



• TRKA IC_{50}	4.7 nM
• NIH 3T3 *MPRIP-NTRK1* IC_{50}	59 nM
• CYP3A4 induction risk	High

• TRKA IC_{50}	1.2 nM
• NIH 3T3 *MPRIP-NTRK1* IC_{50}	8.4 nM
• CYP3A4 induction risk	Low

J. Med. Chem. 2022,DOI: (10.1021/acs.jmedchem.2c01099)

COURSE OUTLINE

1. General points
2. ADMET, RO5, and systematic in silico ADMET evaluation
3. The discovery process in the pharmaceutical industry (R&D)
4. The choice of a drug target
5. Drug design strategies
6. Conclusion

2. The choice of a drug target

2.1. the different types of targets

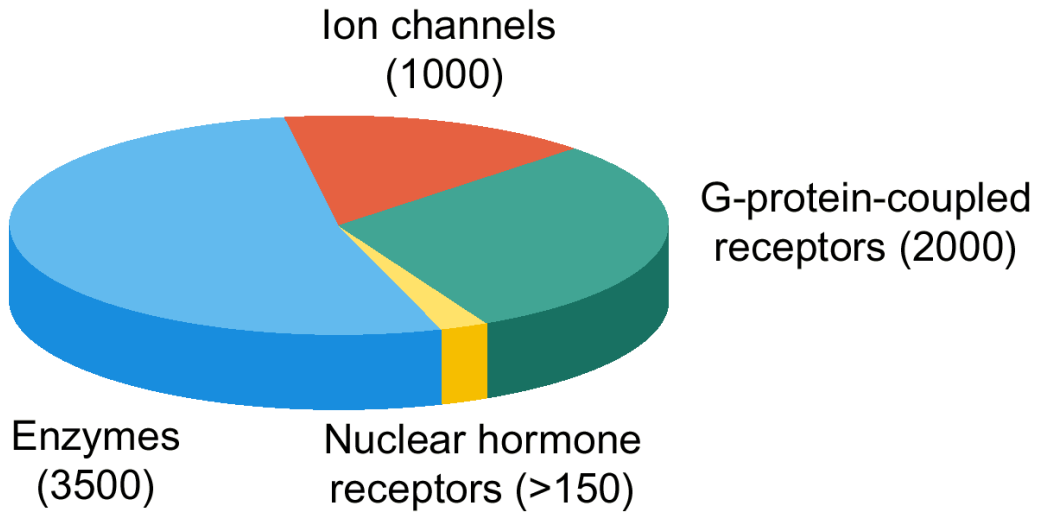
- **Nucleic acids**

- **Proteins :**

  ionic channels, transporters, enzymes (proteases, kinases, etc.), receptors (nuclear or transmembrane).

- **Sugars**

- **Lipids**



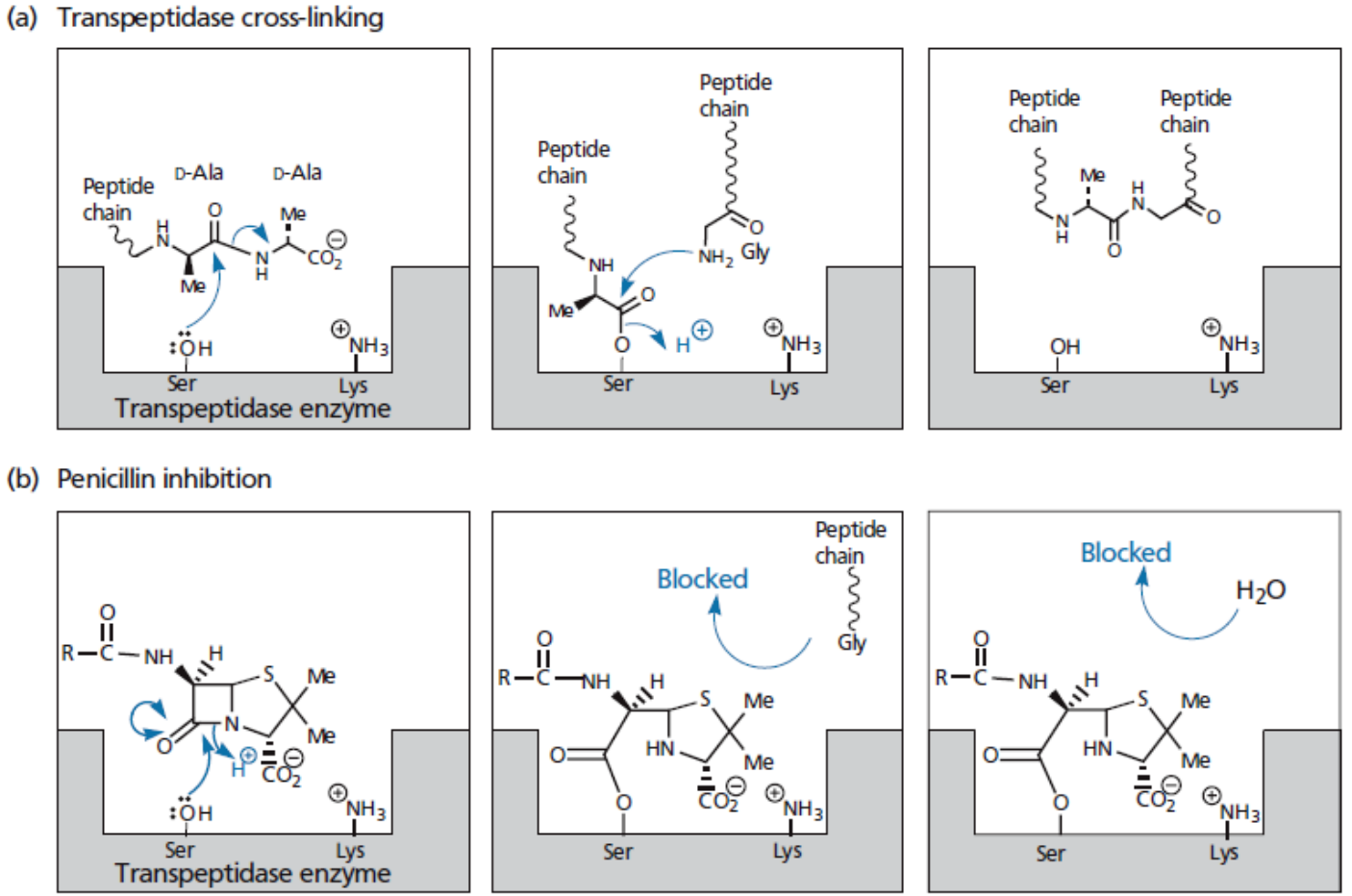
TRENDS in Pharmacological Sciences

2.2. Specificity of the target

- The more selective a drug is for its target, the less likely it is to interact with other targets → fewer side effects.

Species specificity

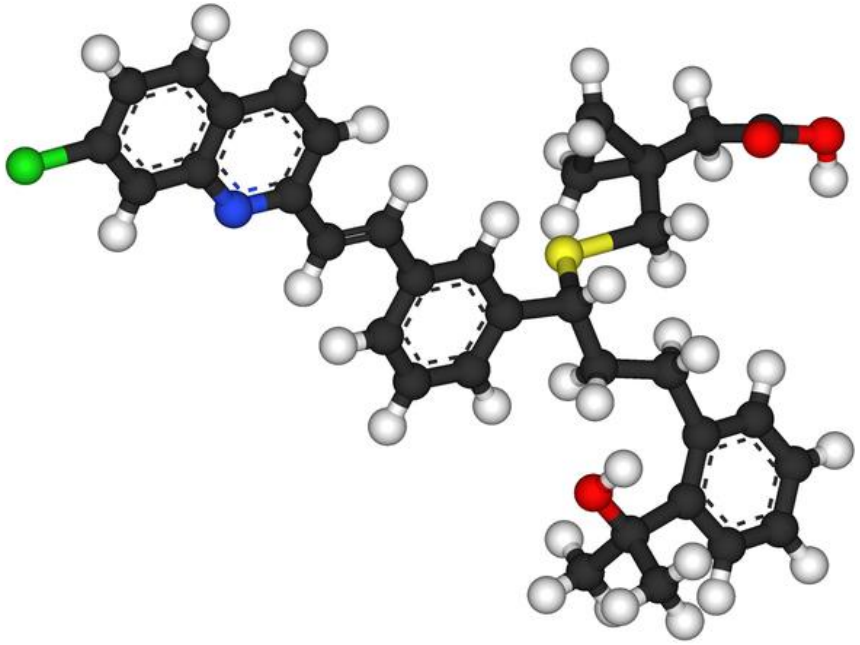
For example, penicillin targets an enzyme involved in the biosynthesis of the bacterial cell wall. Mammalian cells do not have a cell wall. ***Penicillin has few adverse effects in humans****.*

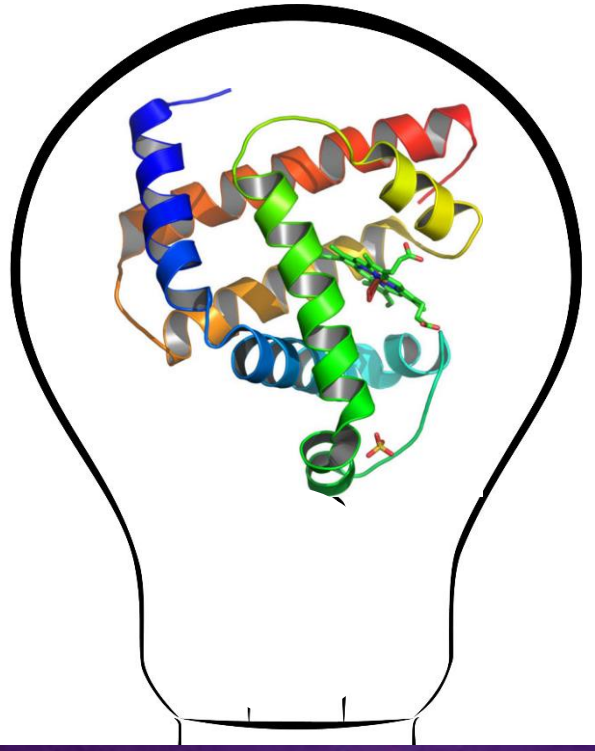


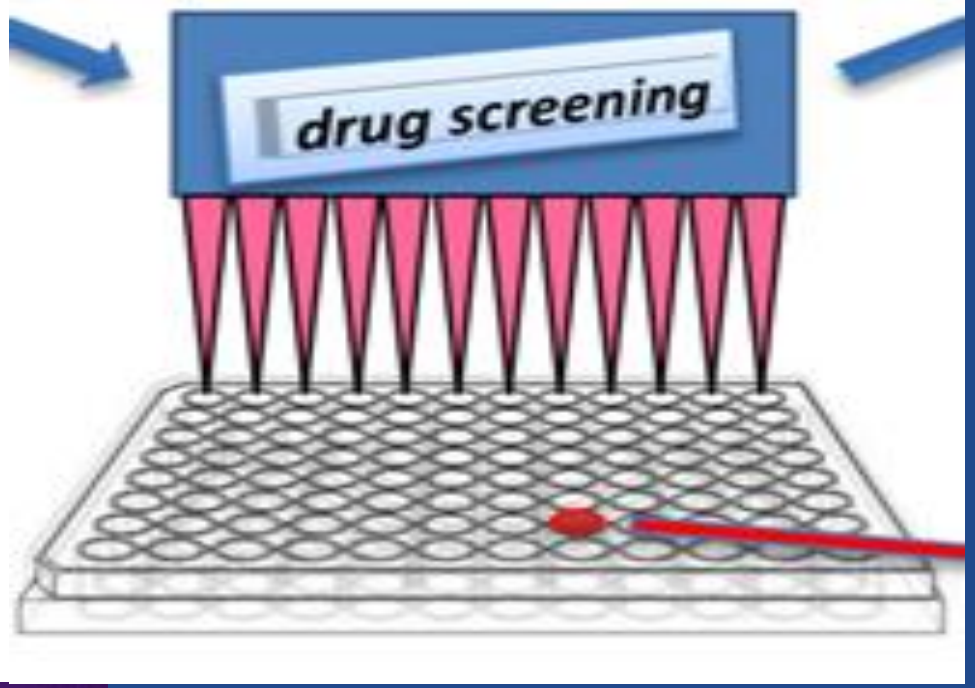
COURSE OUTLINE

1. General points
2. ADMET, RO5, and systematic in silico ADMET evaluation
3. The discovery process in the pharmaceutical industry (R&D)
4. The choice of a drug target
5. Drug design strategies
6. Conclusion

3. Drug design strategy

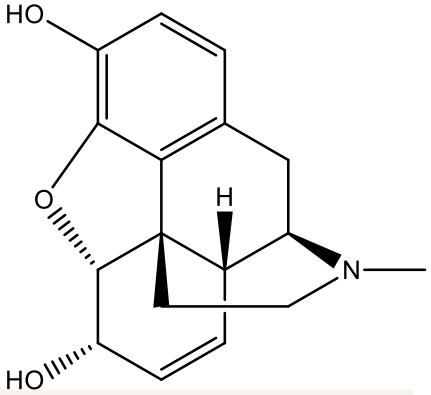




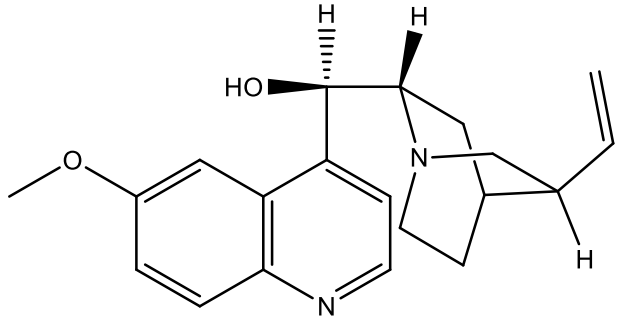


3.1. Screening of natural products

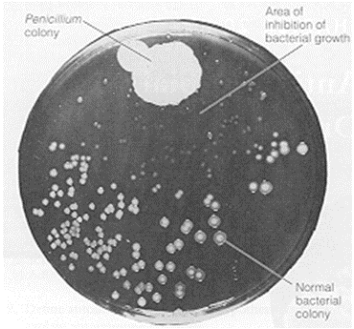
(the plant kingdom, the microbial world, the marine world, animal sources, venoms and toxins)

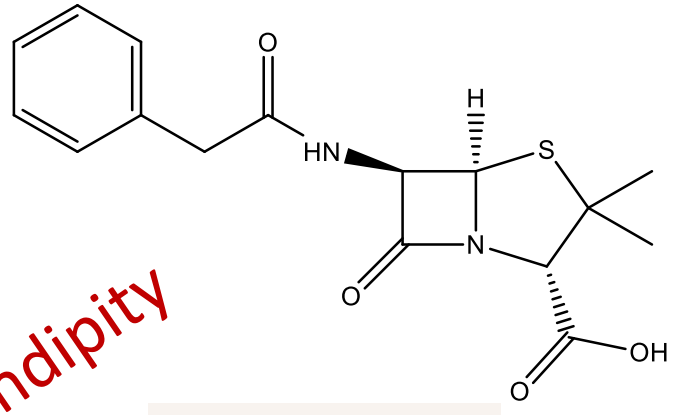


Morphine



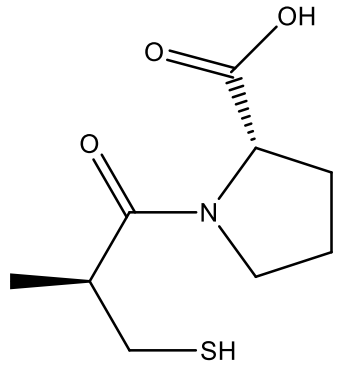
Quinine





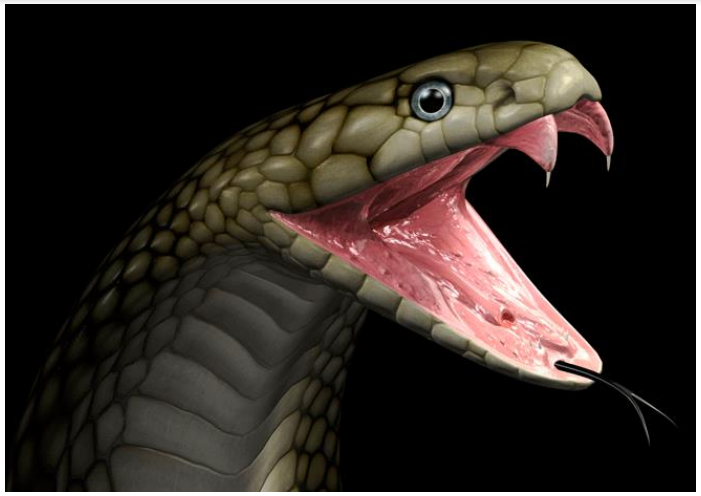
Serendipity

Penicillin G.



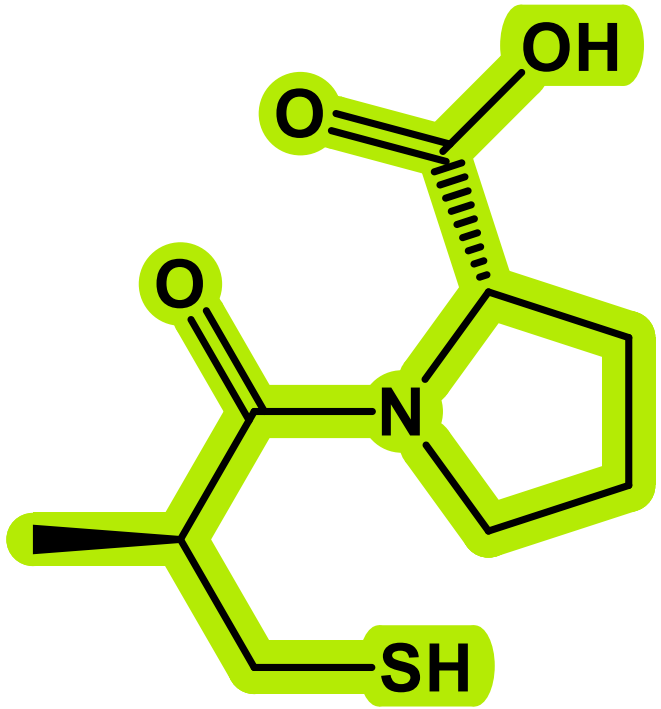
Captopril

3.1. Screening of natural products



Teprotide

SAR



Captopril

3.1 SAR: discovery of captopril

- **1948:** discovery of the vasodilator effect of snake venom..
- **1970** : Isolation of Bradykinin Potentiating Peptides (BPP) from the venom of the Brazilian viper *(Bothrops jararaca) ;*

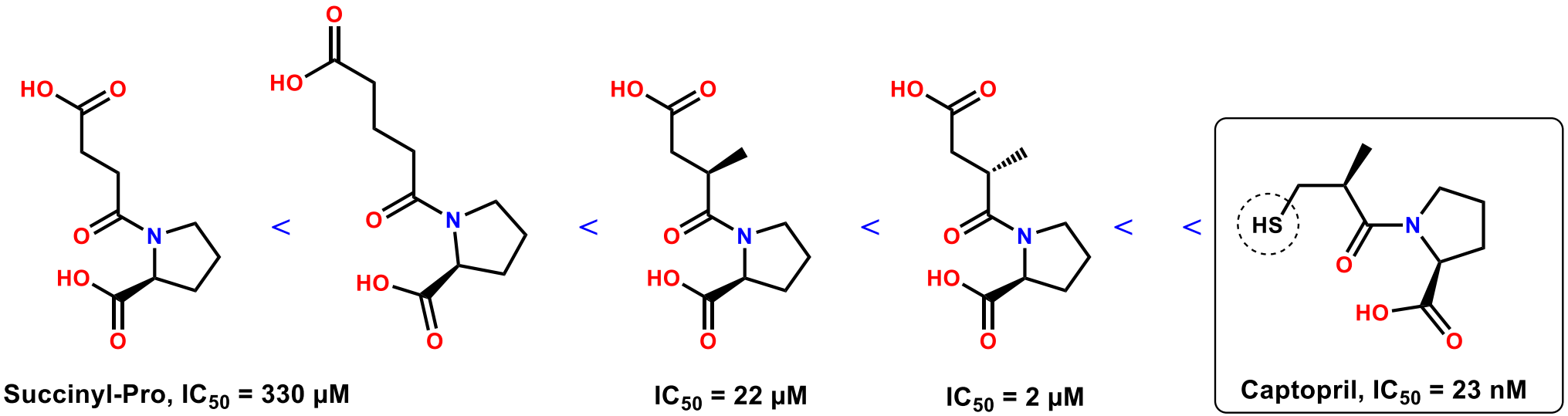
  BPP_{5a} : *Pyr-Lys-Trp-Ala-**Pro*** **(Ferreira and Vane).**
- Discovery of the **antihypertensive teprotide**, ACE inhibitor **(Ondetti et Cushman)**.

  Teprotide (nonapeptide) **:** 5-oxo-Prolyl-Trp-Pro-Arg-Pro-Glu-Ile-Pro-**Pro**-OH, CI_{50} = 250 nM.

  Teprotide lowers Blood Pressure (BP), but:

  - *inactive **by mouth** ;*
  - ***administered iv** (**serious problems for daily use**).*

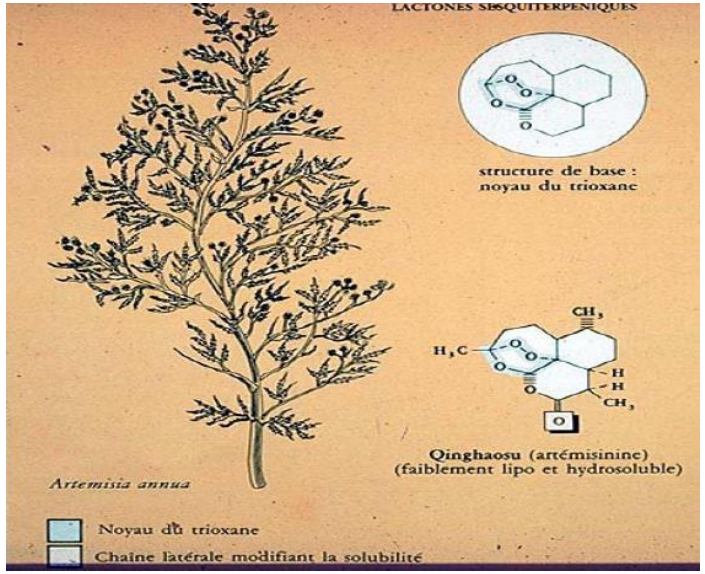
***SAR** study:*

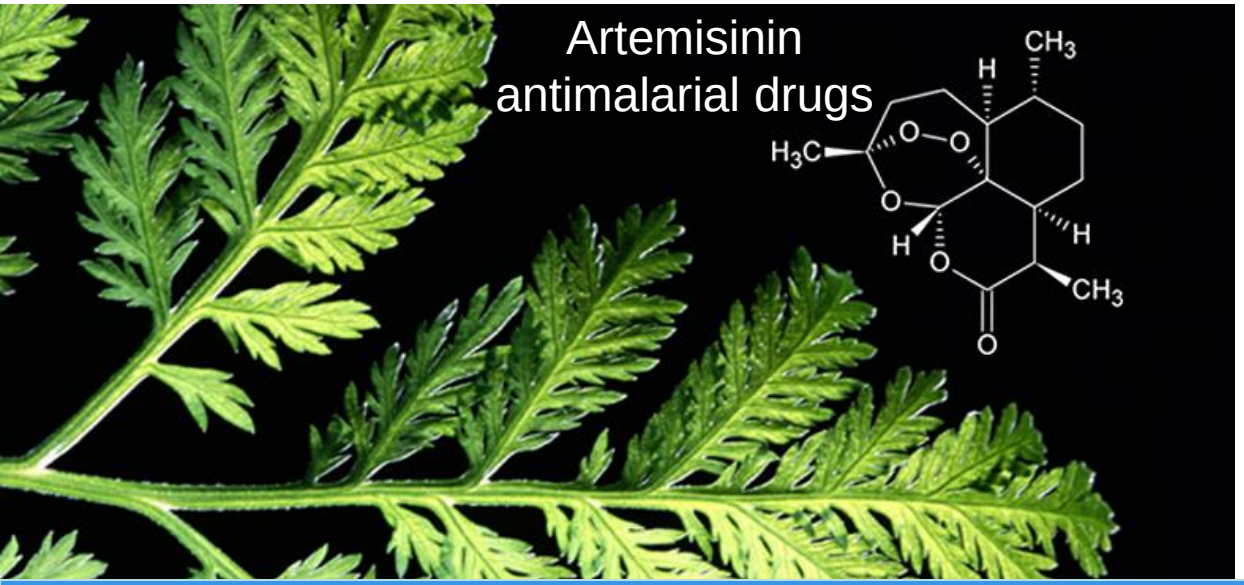


3.2. Popular Medicine

Example: Artemisia annua was used in traditional Chinese medicine.

"There are about 105 formulas dating back 2000 years, drugs that can be used to treat a wide range of conditions, from depression and insomnia to osteoporosis".





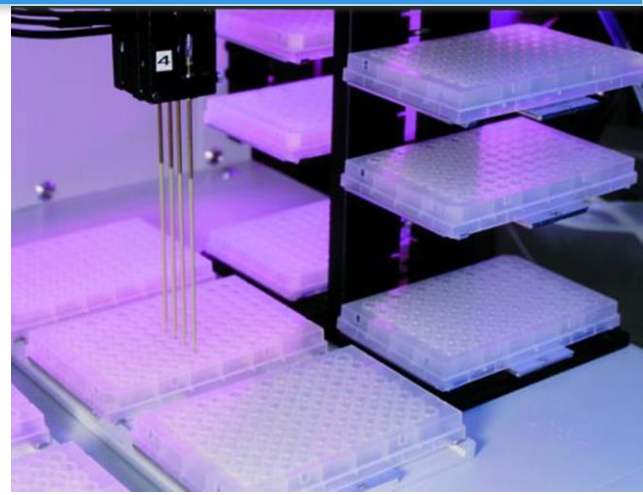
Tu Youyou,

Chinese pharmaceutical chemist

2015 Nobel Prize in Physiology or Medicine

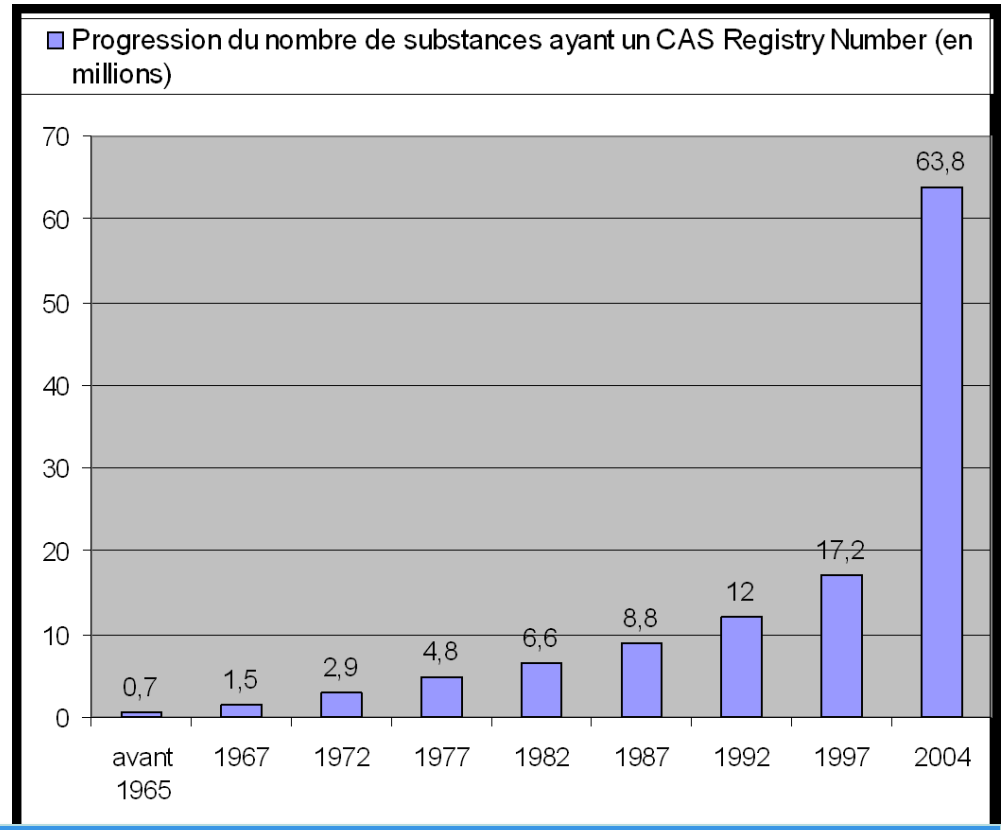
3.3. Screening of synthetic compounds "libraries".

Pharmaceutical companies examine their "library" to study a new target and find a lead compound.

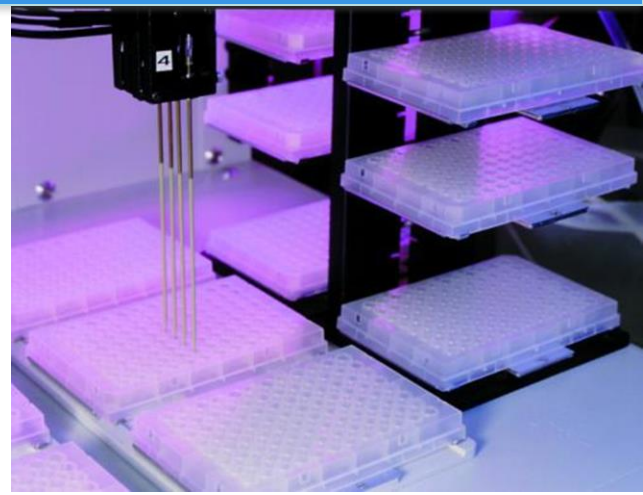


In academia (France) :

The National Chemical Library : regroups the collections of synthetic products and natural compounds existing in French public laboratories to promote scientific and industrial valorization.



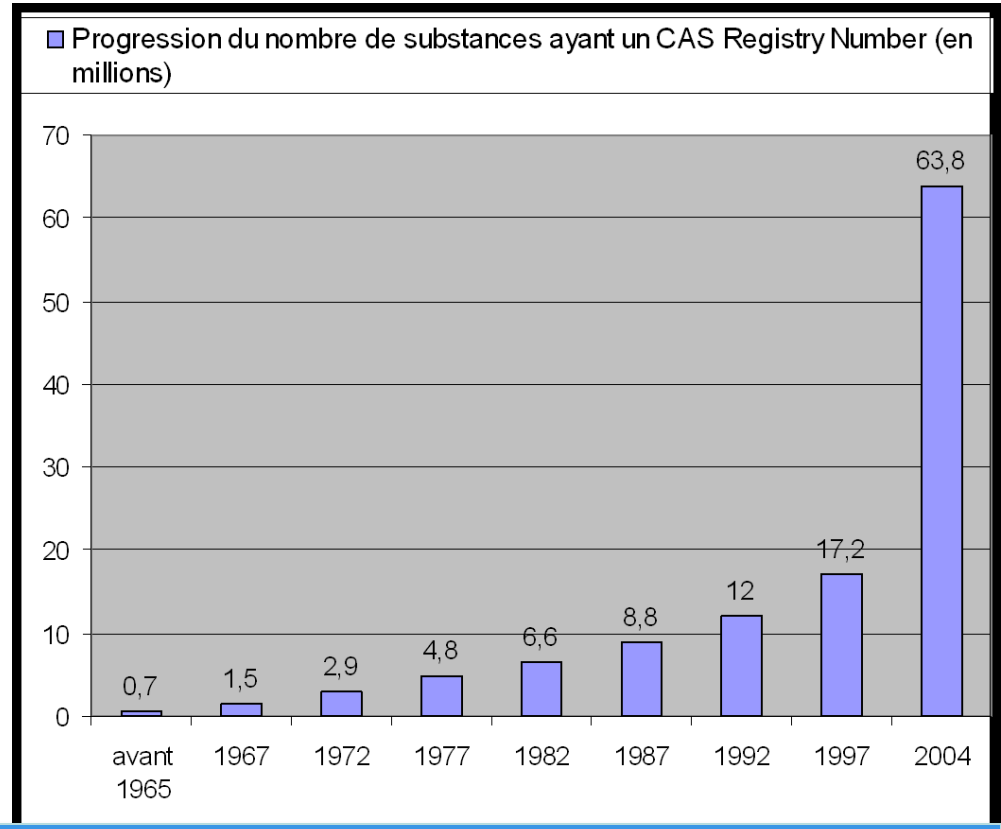
3.3. Screening of synthetic compounds "libraries"



- BioCIS: Local chemical library (1700 molecules)

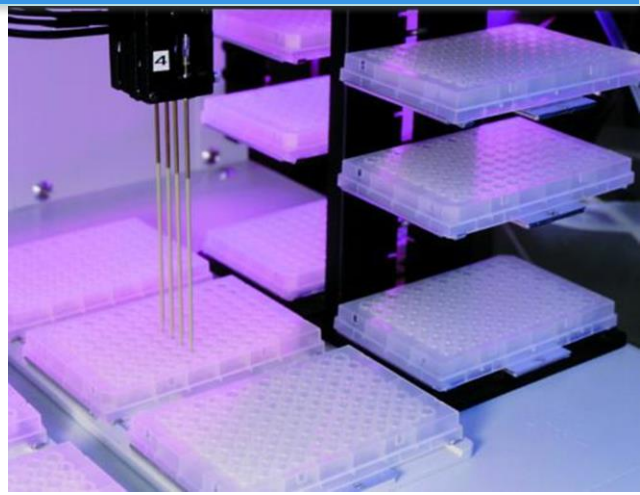
- Prestwick: Chemical library including FDA-approved drugs (1500 molecules)

- Greenpharma: druggable molecules (7200 molecules)

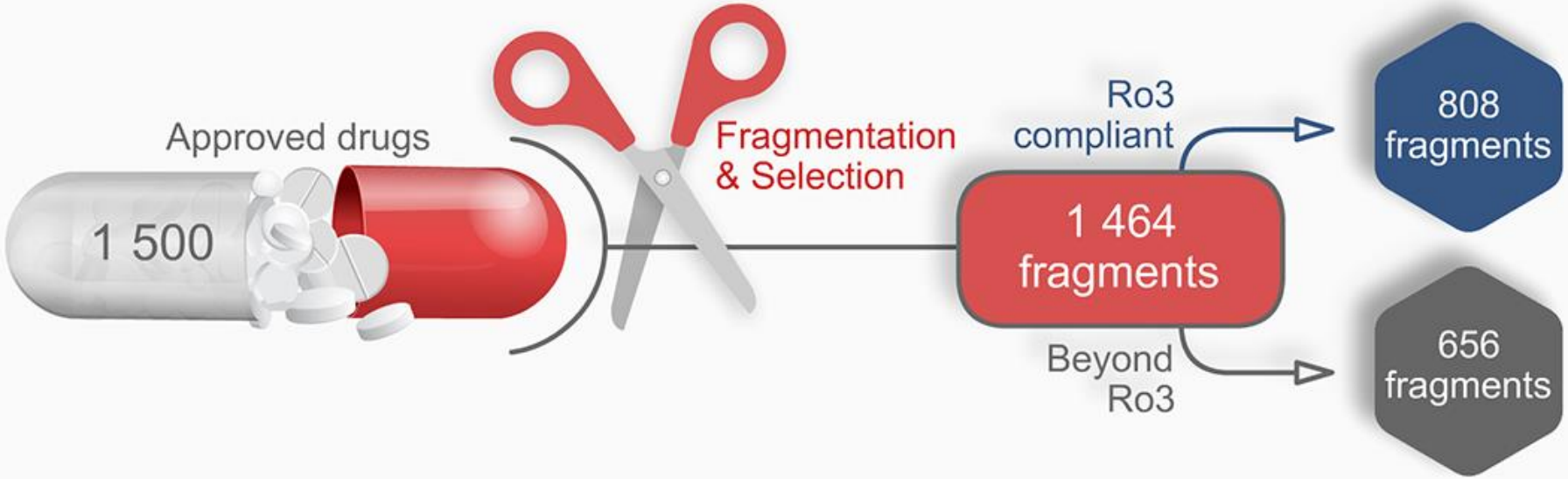


3.3. Screening of synthetic compounds ''libraries''

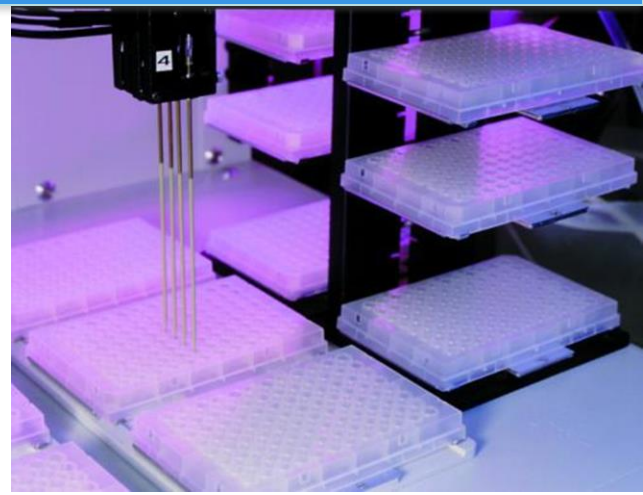
DRUG-FRAGMENT LIBRARY



PRESTWICK CHEMICAL



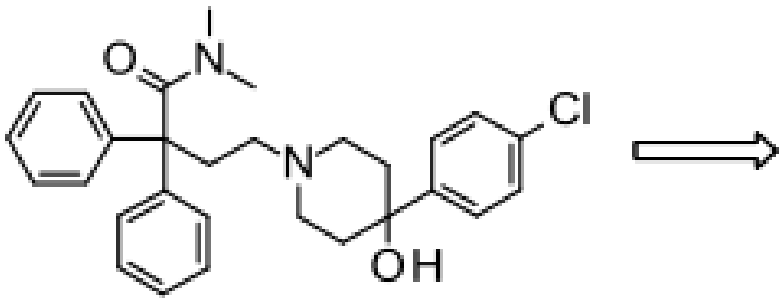
3.3. Screening of synthetic compounds ''libraries''



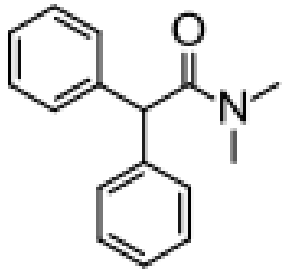
DRUG-FRAGMENT LIBRARY

PRESTWICK CHEMICAL

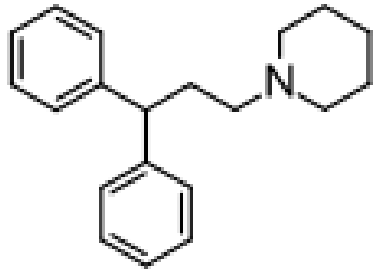
Example



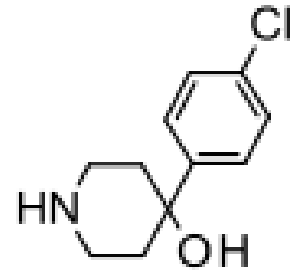
Loperamide



Prestw-Frag-1453



Prestw-Frag-1193



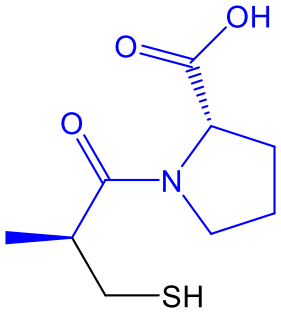
Prestw-Frag-1365

3.4.1. "me too drugs"

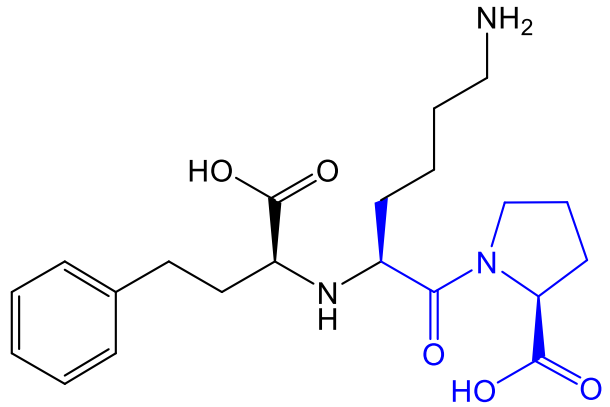
Many companies rely on drugs established by their competitors in order to design new molecules.

Mainly, **a modification of the structure is carried out in order to avoid patent restrictions**, while **maintaining the activity and improving the therapeutic properties**.

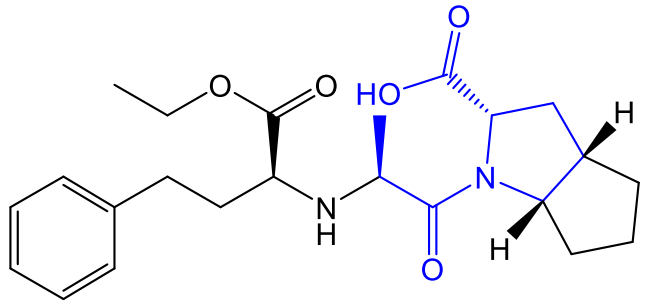
For example, Captopril* has been used as a lead compound by various companies to produce their own antihypertensive drugs (**15 me too drugs**).



Captopril (Bristol-Myers Squibb)

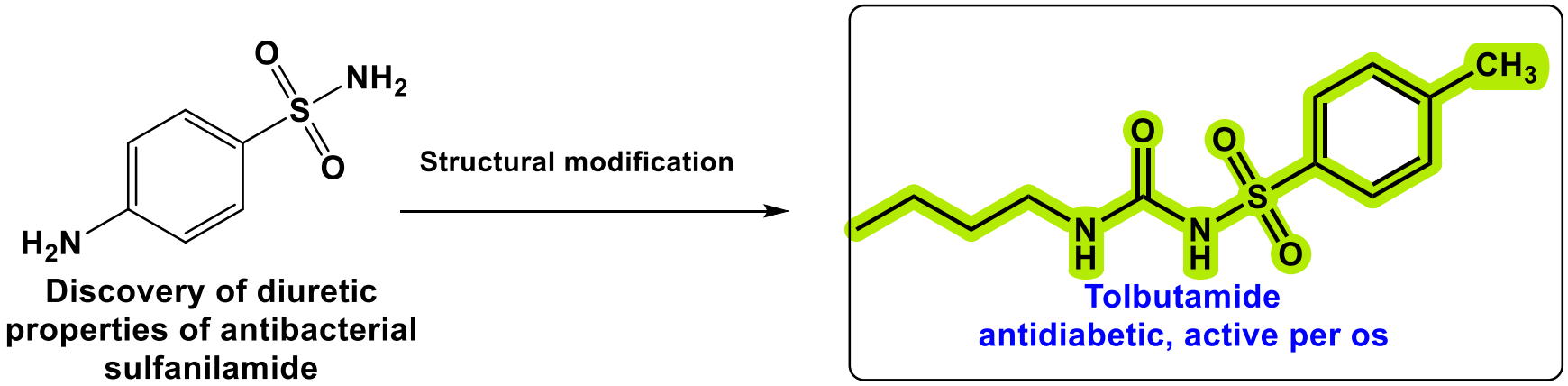


Lisinopril (Merck)



Ramipril (Aventis)

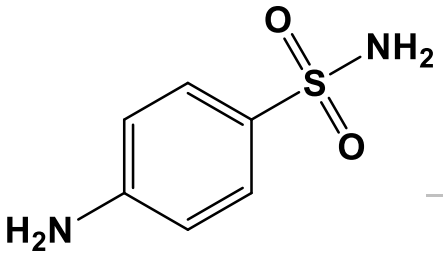
3.4.2. Improvement of a side effect : an existing drug may have a minor or undesirable side effect that could be used in another area of medicine.



Discovery of diuretic properties of antibacterial sulfanilamide

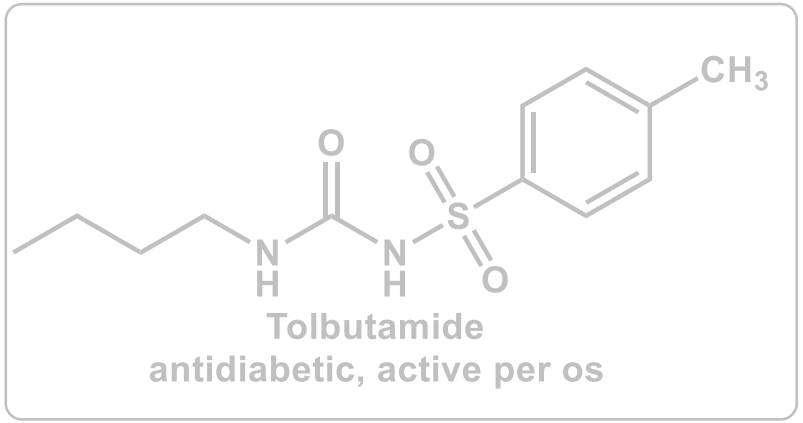
Tolbutamide
antidiabetic, active per os

3.4.2. Improvement of a side effect : an existing drug may have a minor or undesirable side effect that could be used in another area of medicine.

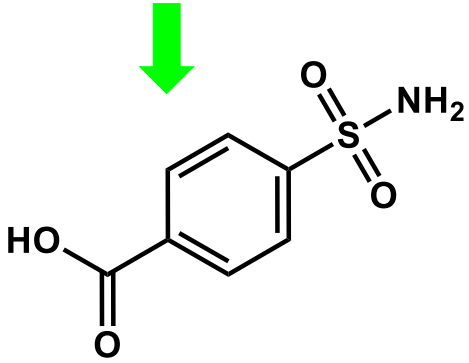


Discovery of diuretic properties of antibacterial sulfanilamide

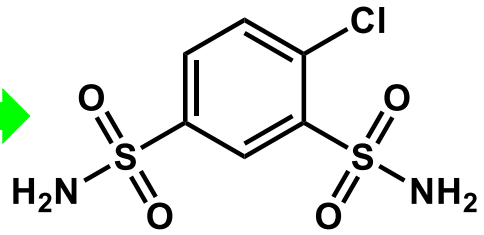
Structural modification



Tolbutamide
antidiabetic, active per os

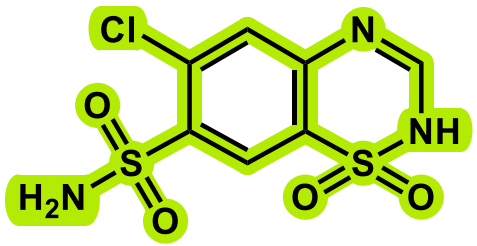


carzenide
↗ excretion of Cl^- ions
weak inhibition of carbonic anhydrase



2 sulfonamide groups
↗↗ Excretion of Cl- ions and inhibition of carbonic anhydrase

Regidification by formation of a cycle



Chlorothiazide
well tolerated diuretic,
active per os
with marked salidiuretic activity.

3.4.3. Drugs Repositioning:

drug repurposing (drug repositioning), drug reprofiling

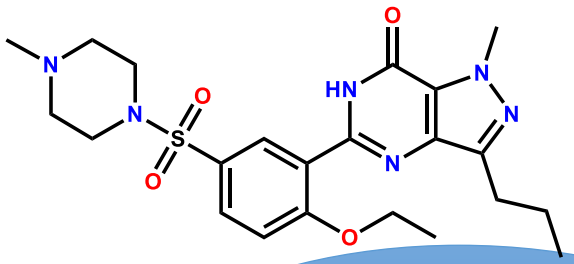
Strategy that seeks to discover new applications for an existing drug that were not previously referenced and not currently prescribed or investigated.

Note: Various additional synonymous terms have been used to describe the process of drug repurposing. All appear to be used interchangeably.

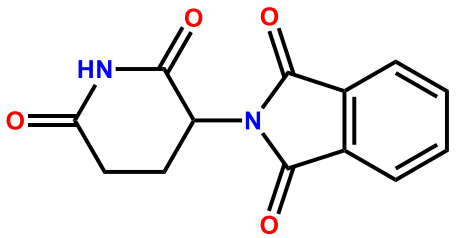
3.4.3. Drugs Repositioning:

30% It is estimated that the repositioning process accounts for more than **30% of new drugs and vaccines approved by the FDA** in recent years.

3.4.3. Drugs Repositioning:



Financial benefits per year



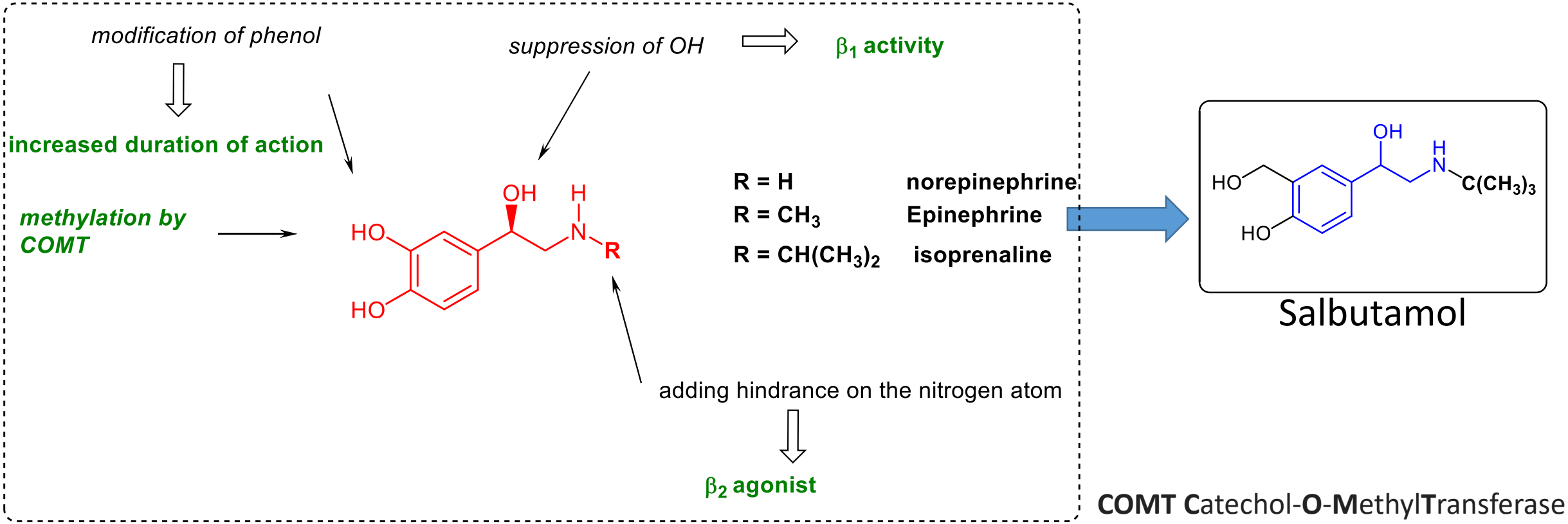
2 Milliards €/an
sildenafil (Viagra®)

500 M €/an
thalidomide

Symbol of the strategic success of the product repositioning from both a medical and financial perspective

3.5 From natural ligands or from the modulator

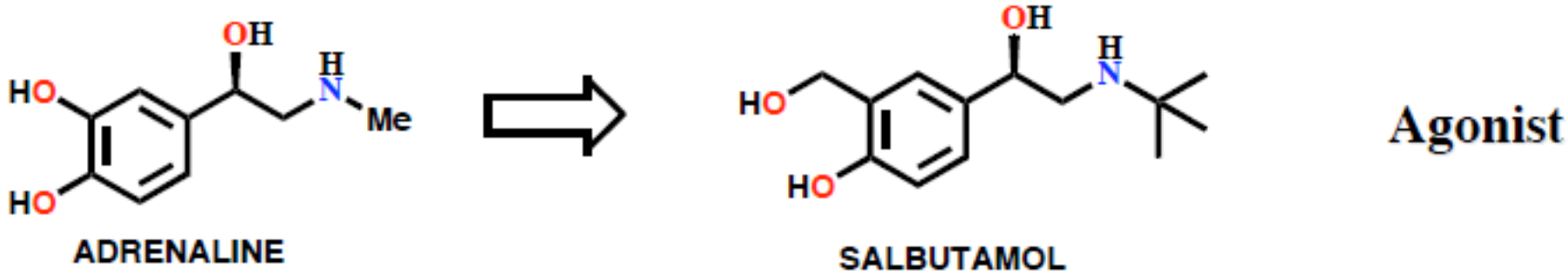
For example. Epinephrine and norepinephrine (natural neurotransmitters) have been used for the development of β-adrenergic agonists such as salbutamol.



COMT Catechol-**O**-Methyl**T**ransferase

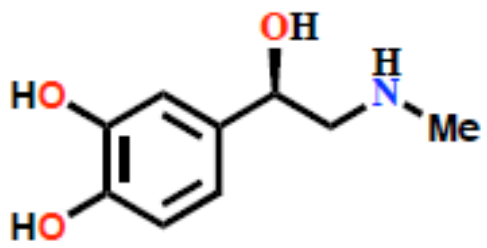
3.5 From natural ligands or from the modulator

Lead Compounds from ligands or from the modulator

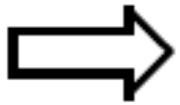


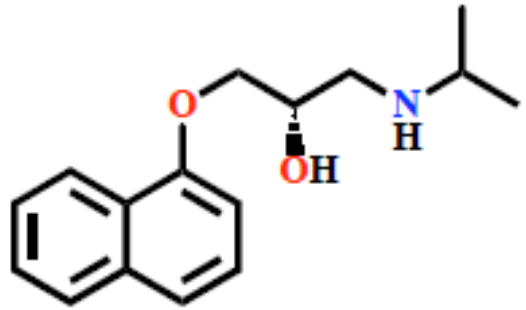
3.5 From natural ligands or from the modulator

Lead Compounds from ligands or from the modulator



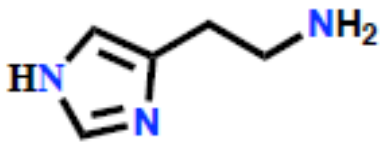
ADRENALINE



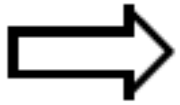


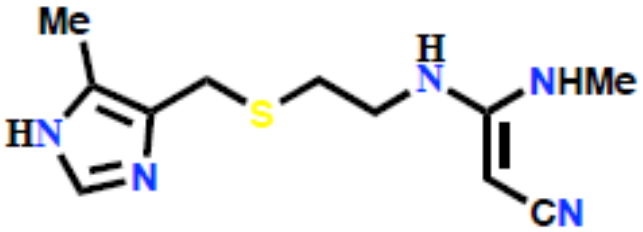
PROPRANOLOL

Antagonist



HISTAMINE



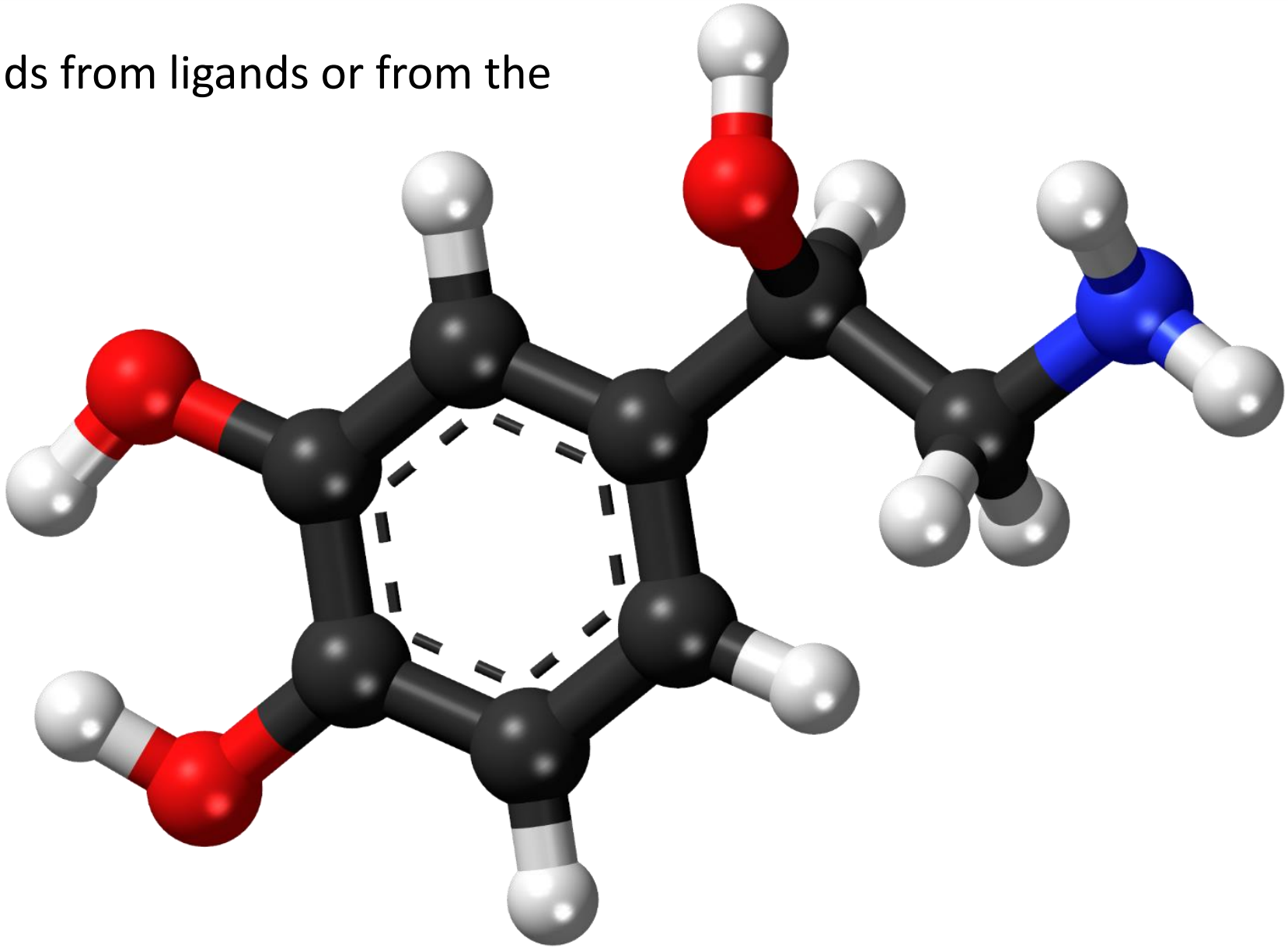


CIMETIDINE

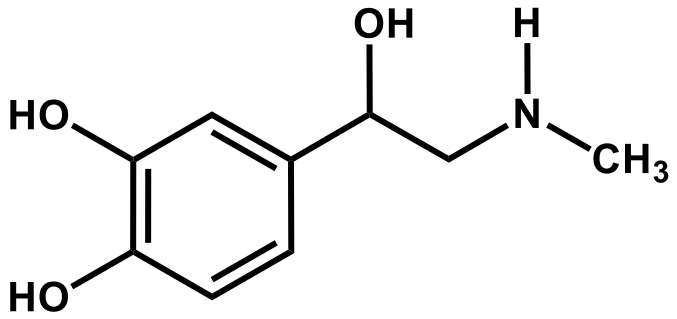
Antagonist

Case study 01: from epinephrine to selective β-2 agonists

Lead Compounds from ligands or from the modulator



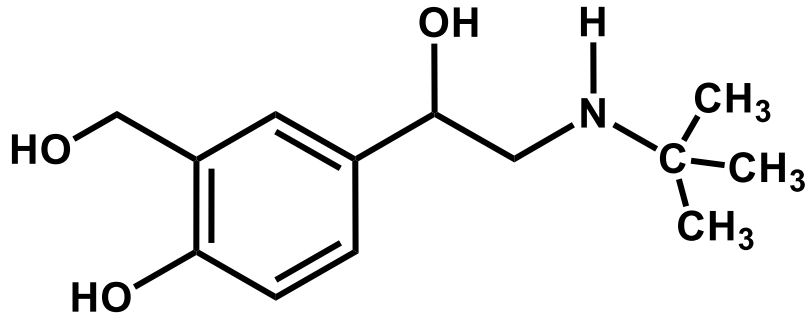
Case study 01: from adrenaline to selective β-2 agonists



Adrenaline (epinephrine)

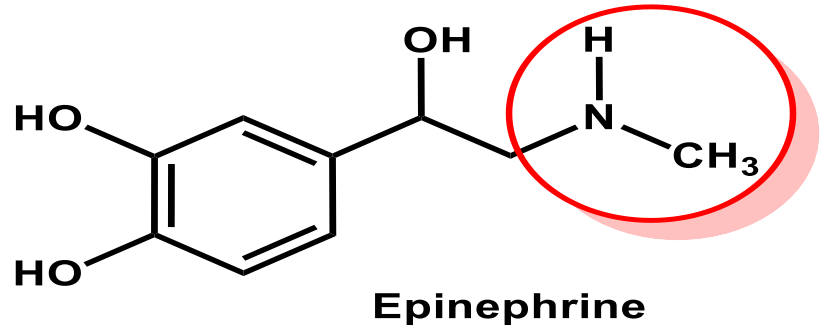
α +
β1+
β2 +

Selectivity

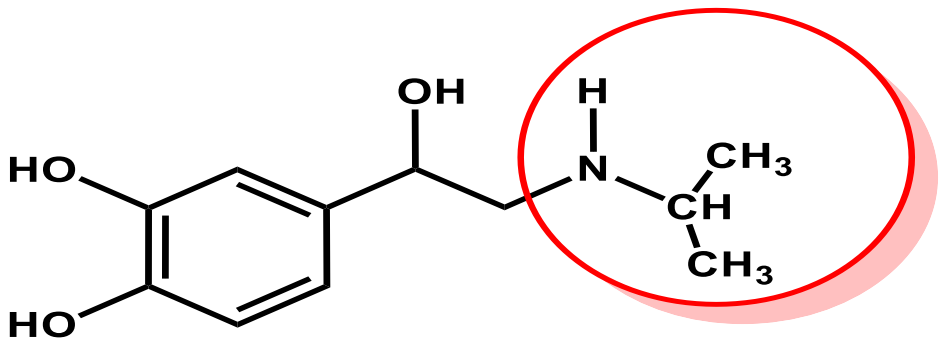


Salbutamol β2 +

Case study 01: from adrenaline to selective β-2 agonists



Epinephrine



Isoprenaline

Boehringer Ingelheim

Epinephrine

Effects on α and β adrenergic receptors

- Bronchodilators, **but hypertensive effect.** alpha1 effect (**vasoconstriction**).

Isoprenaline (Boehringer, 1941)

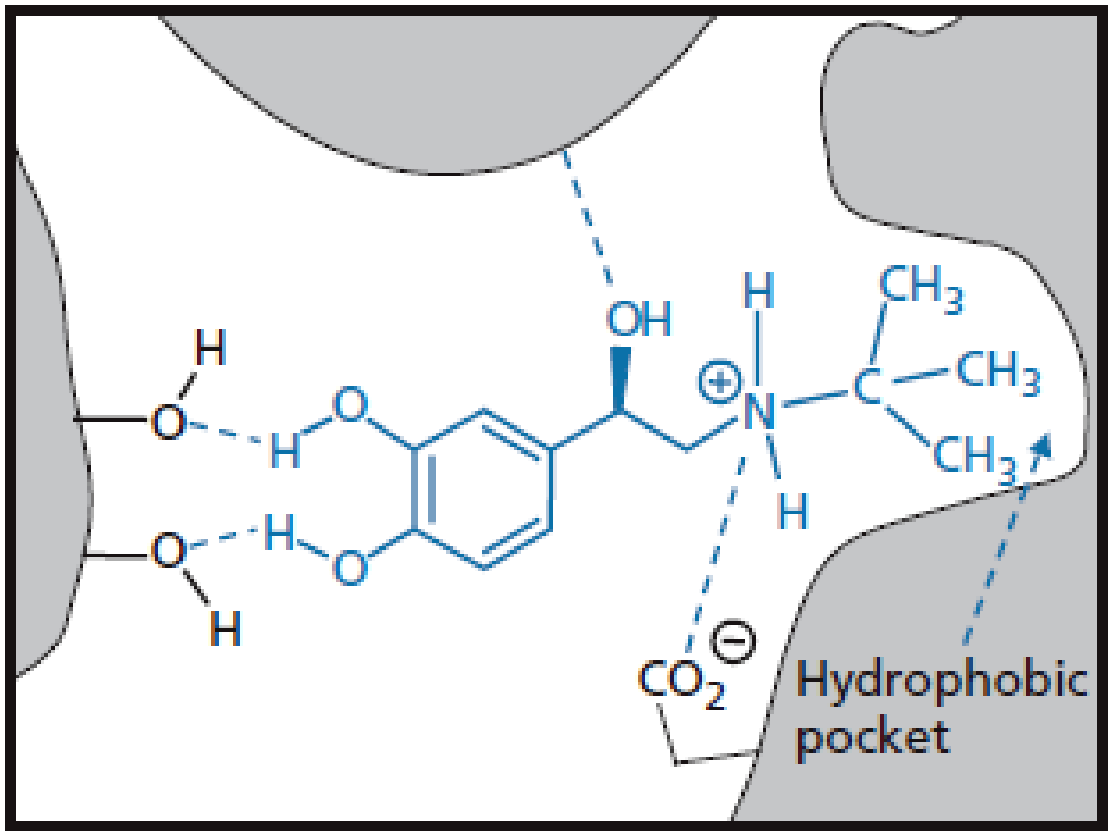
- Acts on both β_1 and β_2 **R** ,
- Bronchodilator effect **10 times >** epinephrine
- Without hypertensive effect;

- **Non-specific action, isoprenaline is no longer used in the treatment of asthma.**

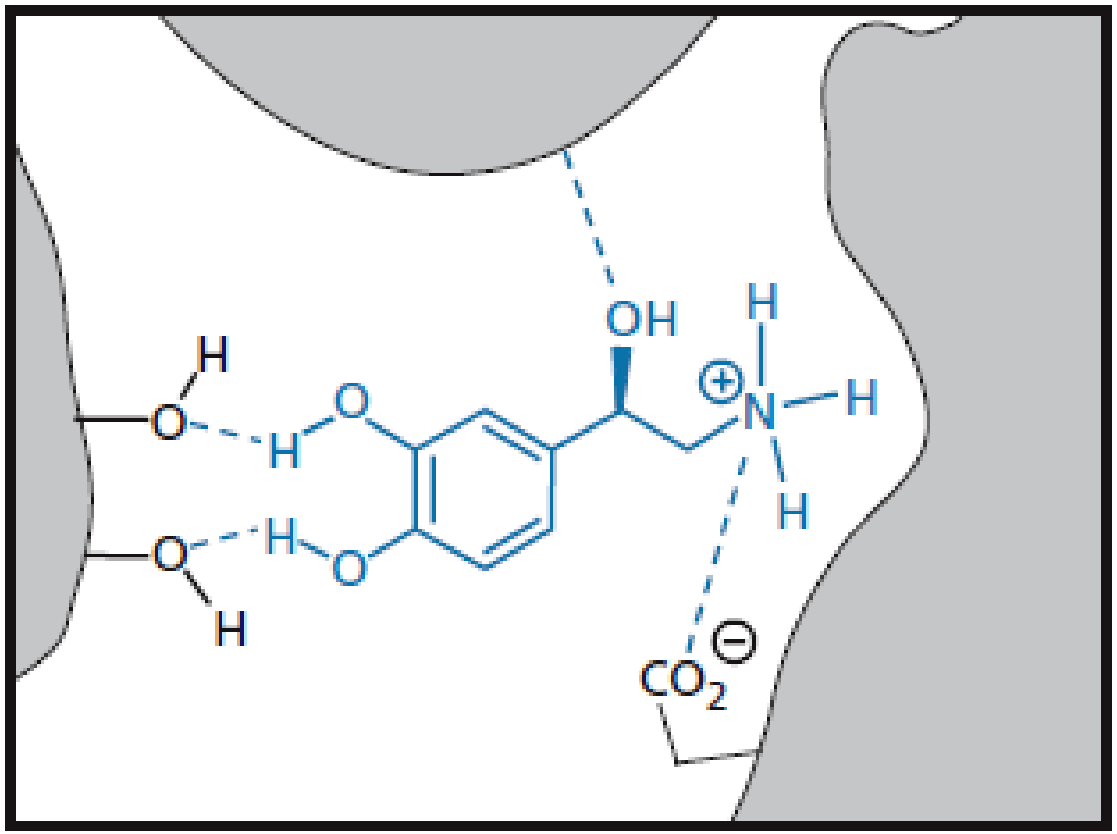
- Between 1963 and 1968, **3000 deaths in England (overdose, effect on the heart)**

Case study 01: from adrenaline to selective β-2 agonists

Effect of bulky group (nitrogen atom) to increase selectivity (β *vs* α **R**)

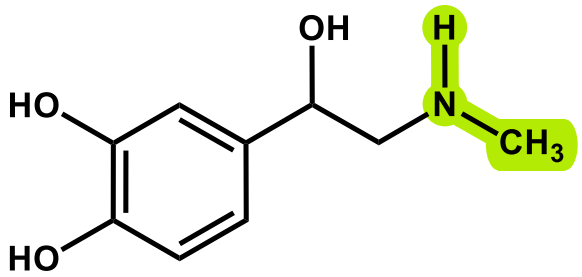


β Adrenergic receptor



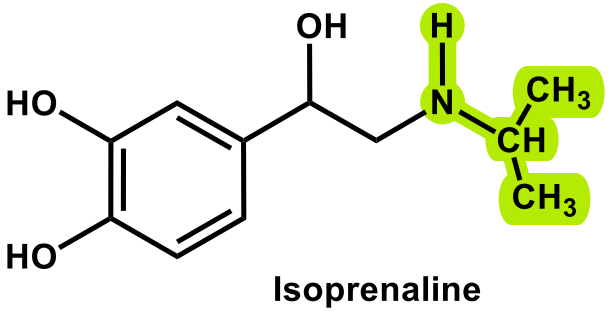
α Adrenergic receptor

Case study 01: from adrenaline to selective β-2 agonists



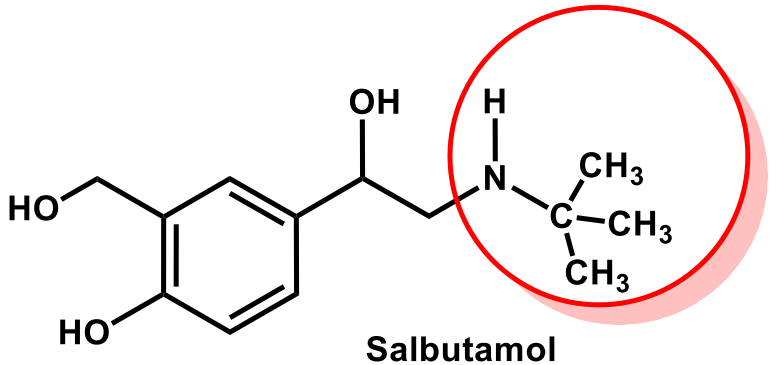
Epinpherine

Effect on α, **β1** and **β2 R**

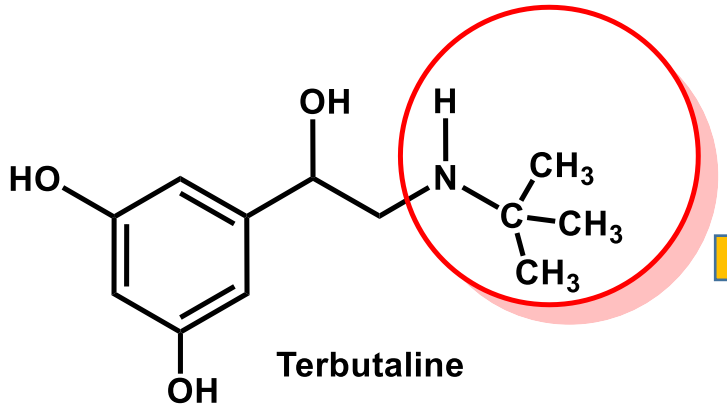


Isoprenaline

Effect on **β1** and **β2 R**



Salbutamol

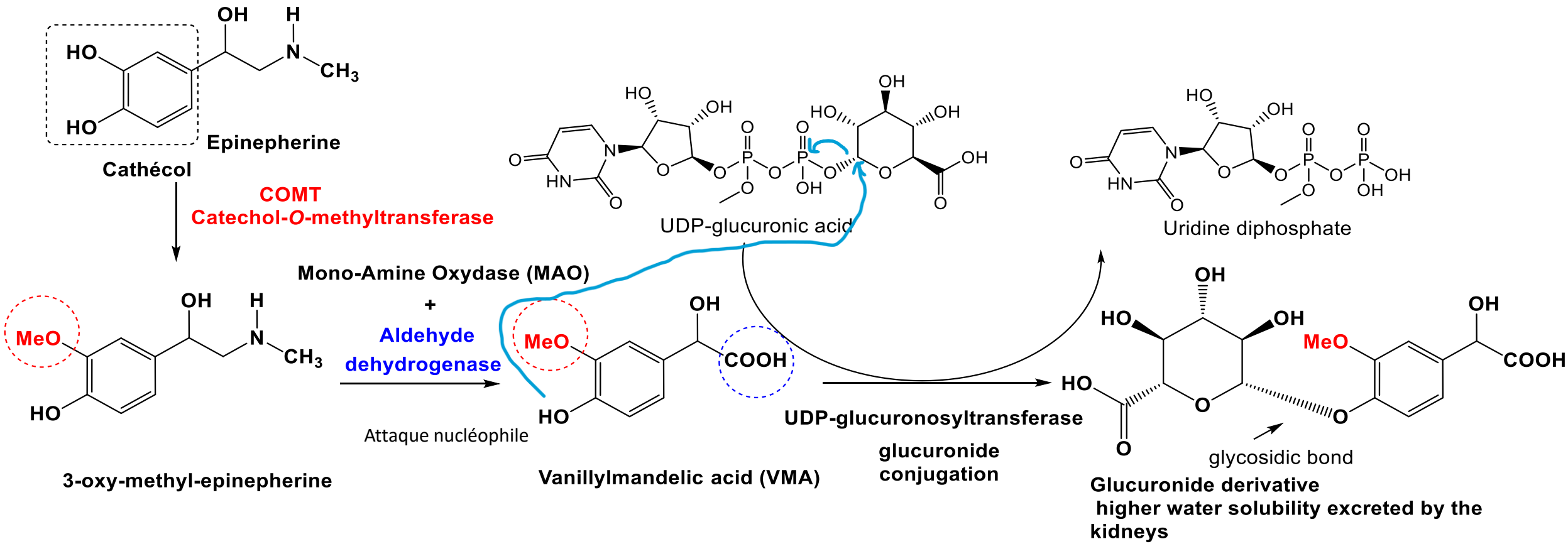


Terbutaline

Bulky group (*t*Bu) → better **Selectivity**
→ **bêta2 agoniste**

Case study 01: from adrenaline to selective β-2 agonists

Degradation of epinepherine by catechol *O*-methyltransferase (**COMT**) and by monoamine oxidases (**MAO**)

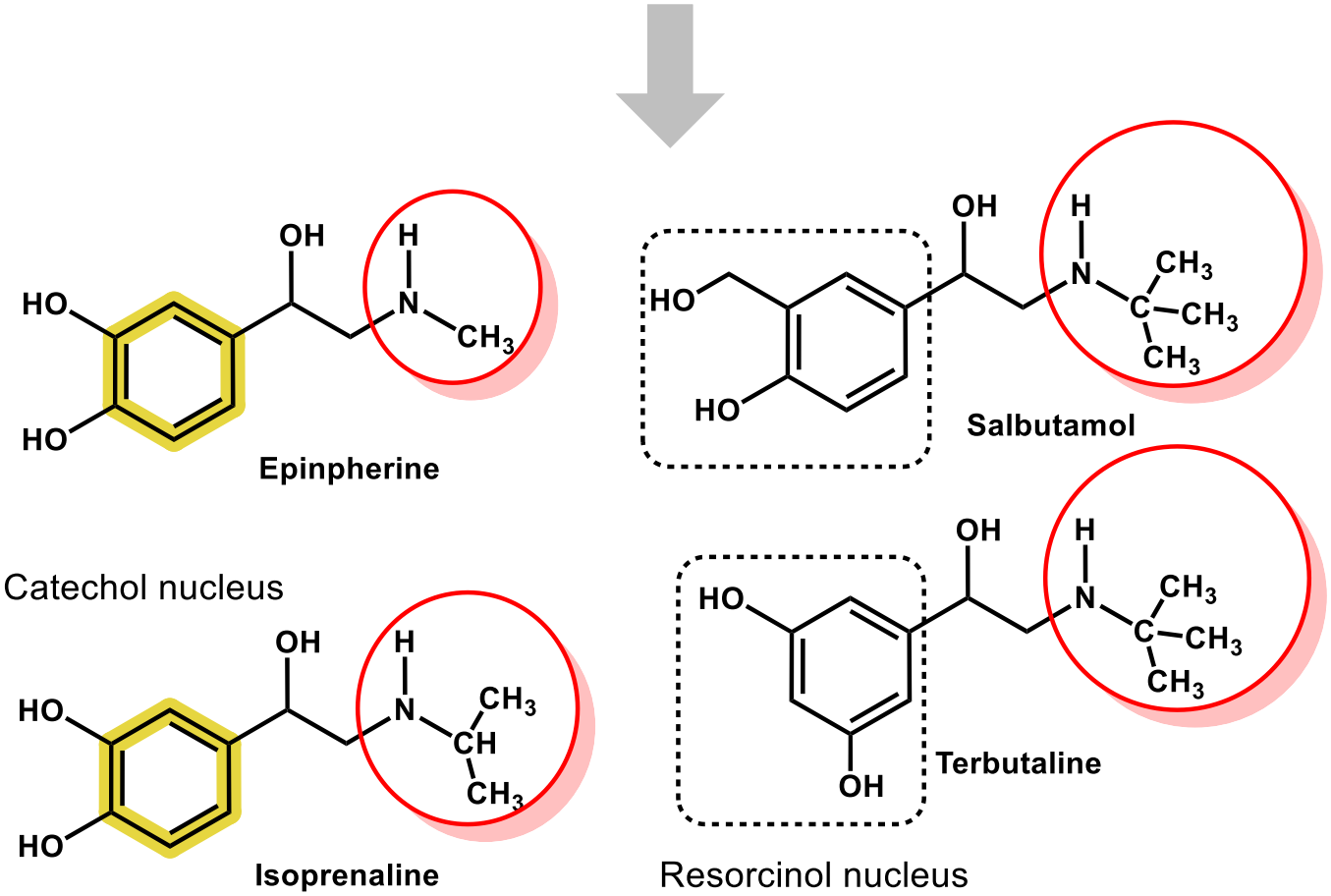


UGT = uridine 5'-diphosphate glucuronosyltransferase

Case study 01: from adrenaline to selective β-2 agonists

OH-Methyl group (Salbutamol), Resorcinol group (Terbutaline)

→ resistance to catechol *O*-methyltransferase **(COMT)**



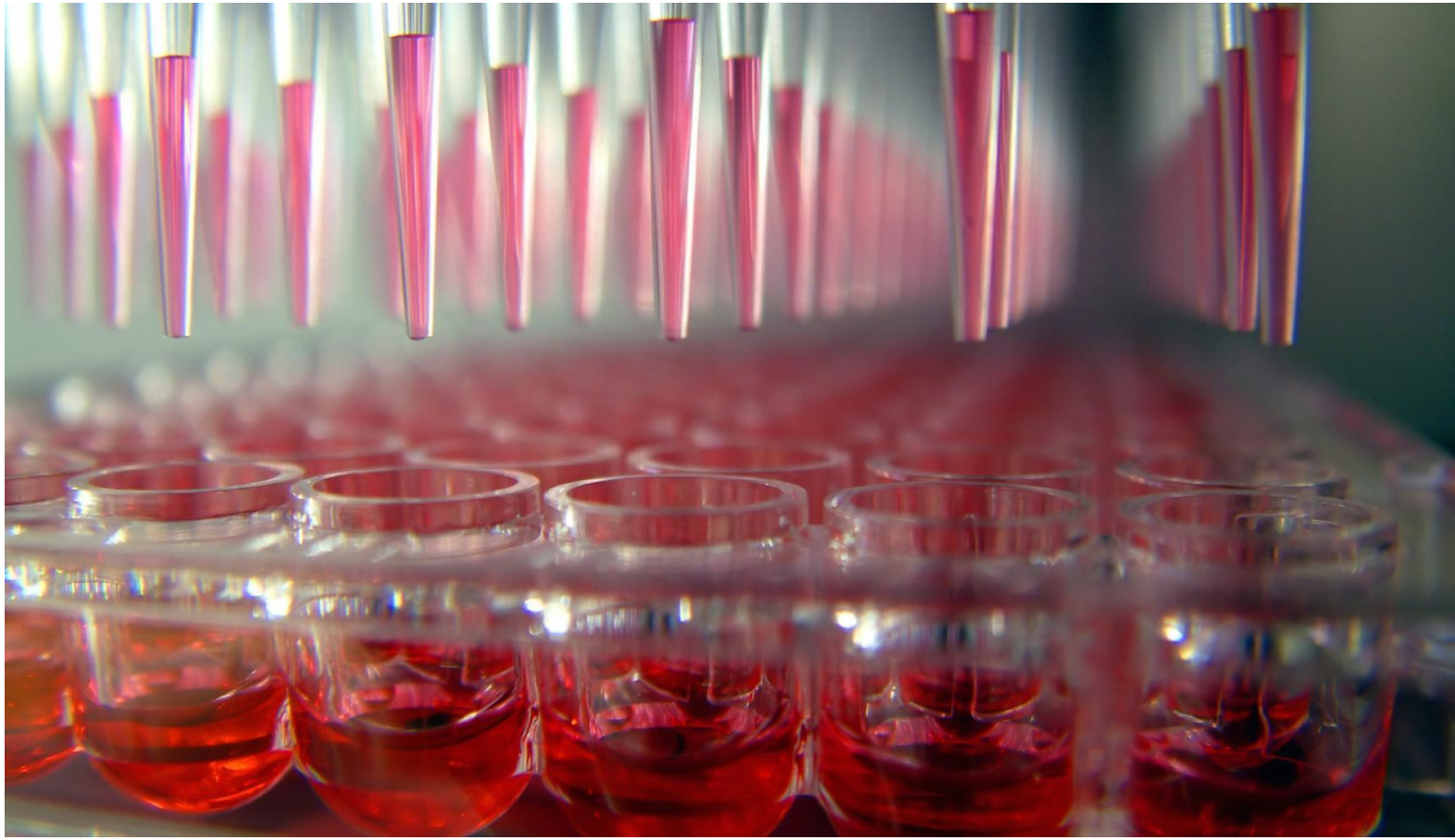
Salbutamol and terbutaline
Bulky side chain (*t*Bu)

→ Slower metabolism than epinepherine

→ Resistance to the action of monoamine oxidases **(MAO)**

3.6 Combinatorial synthesis

Combinatorial synthesis is an automated solid phase procedure aimed at producing as many different structures as possible in the shortest possible time.

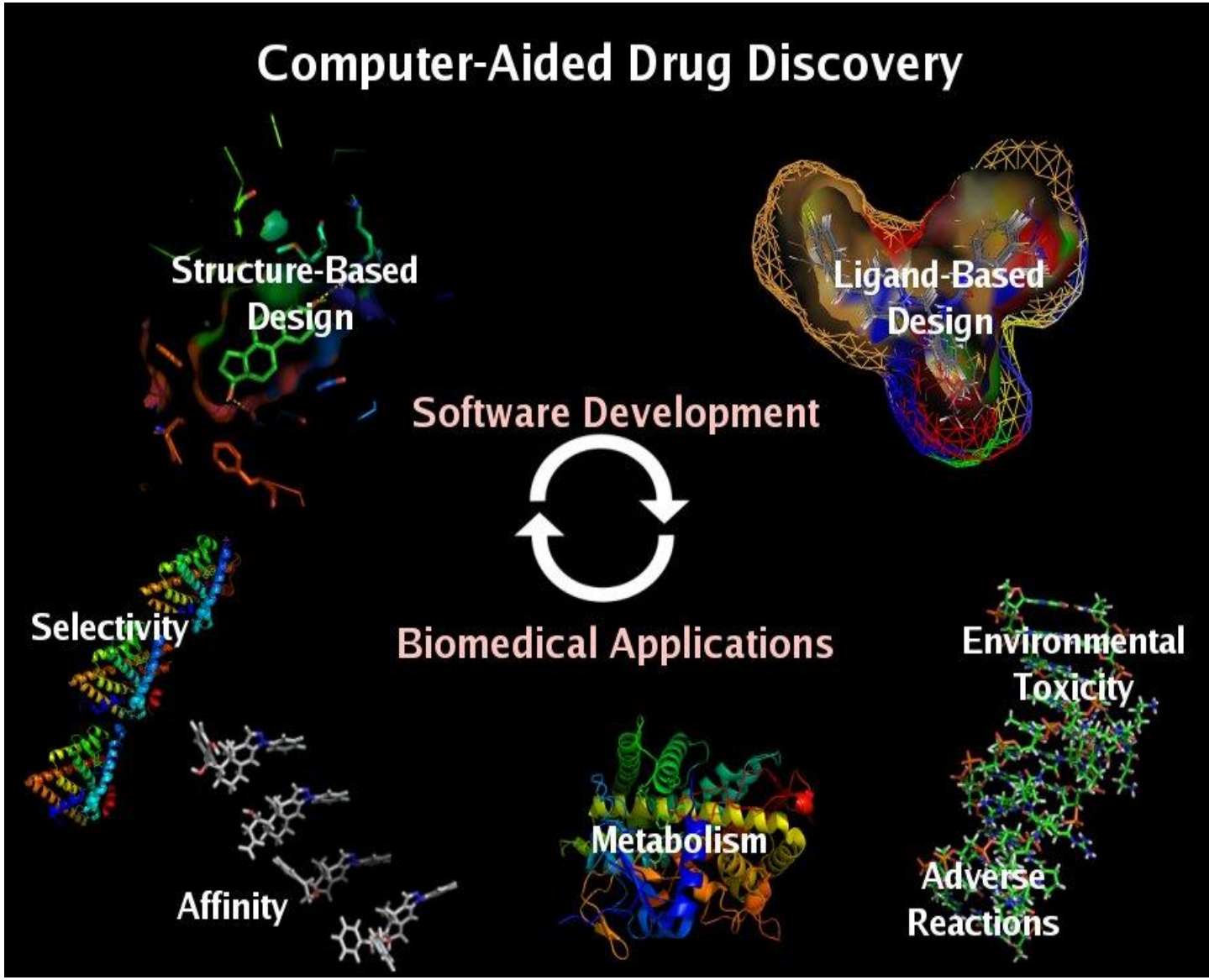


The reactions are carried out on a very small scale.

Any of these compounds may prove to be a useful lead compound.

3.7 Computer Aided Design

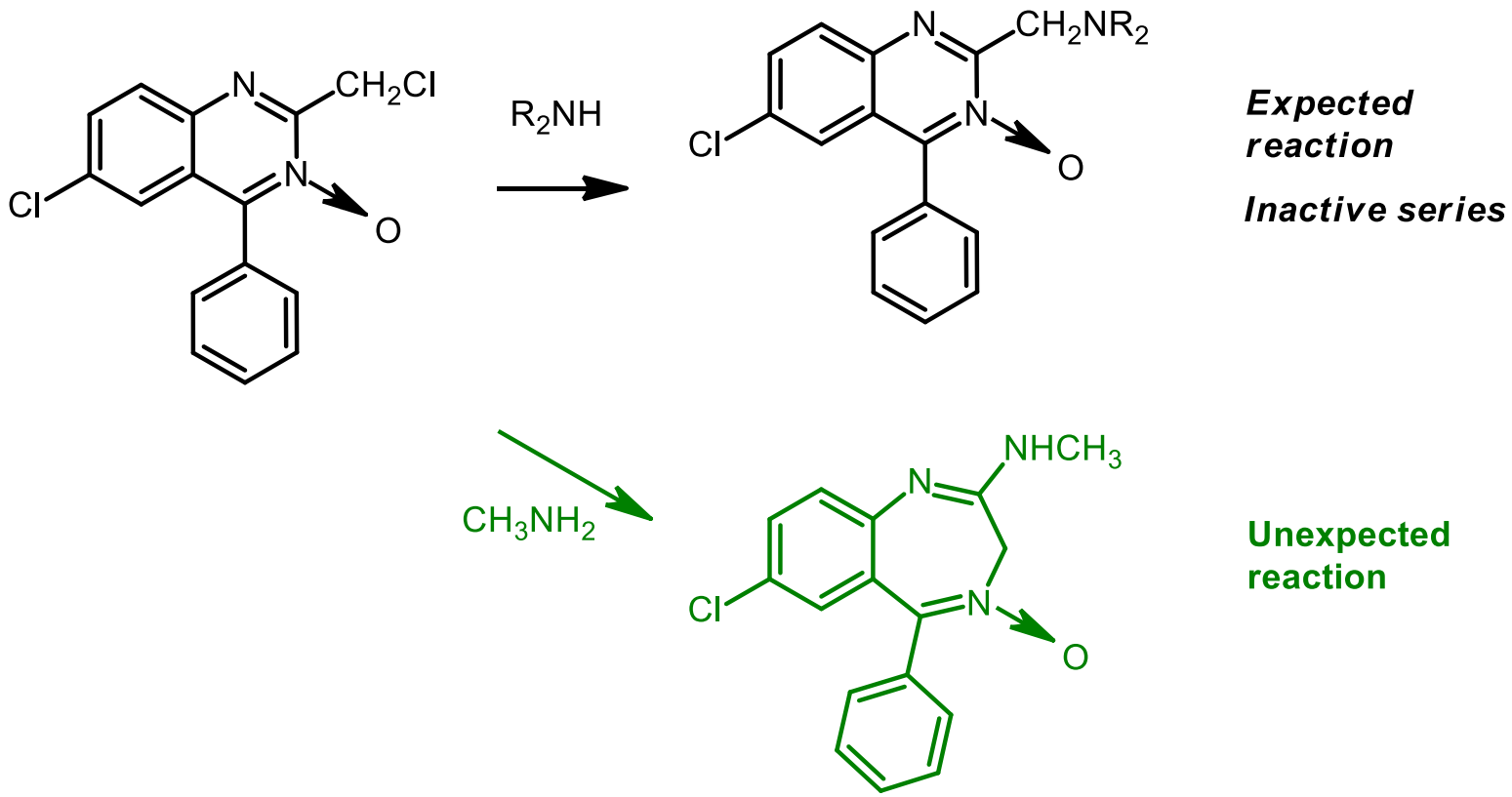
- Knowledge of the target binding site facilitates the design of new compounds intended to bind to that target.
- Enzymes and receptors can be crystallized, and their structure (protein structure and binding site) can be determined by X-ray crystallography.
- Molecular modeling software can be used to study the binding site and to design drugs.



Examples: cisplatin (Antitumor), penicillins, nitrates...

- **Chance ... and intuition (Sternbach, 1956):**
- **The saga of benzodiazepines.**

Leo H. Sternbach (1908–2005), the man responsible for the synthesis and introduction of the first benzodiazepines



Expected reaction

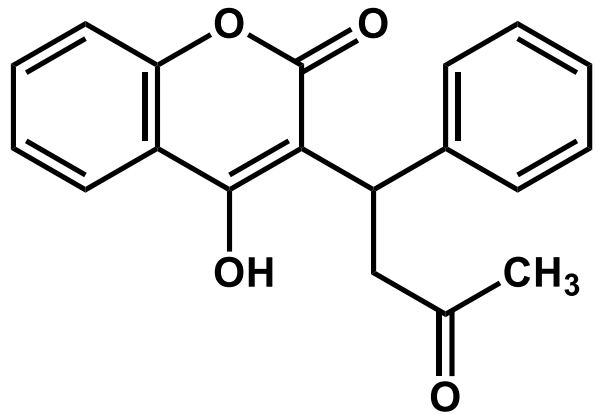
Inactive series

Unexpected reaction

Chlordiazepoxide

Anxiolytic

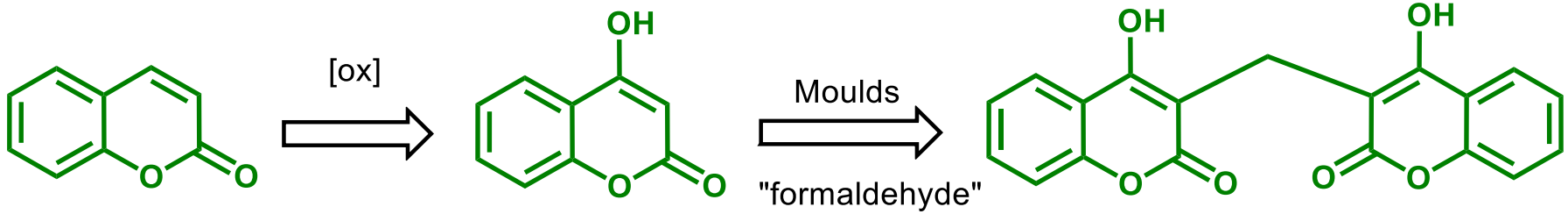
The antivitamins K ("oral" anticoagulants)



How to go from a chance observation to a drug?

3.9 Discovery of the First VKA

☞ Incidental observations: sweet clover disease (poisoning)



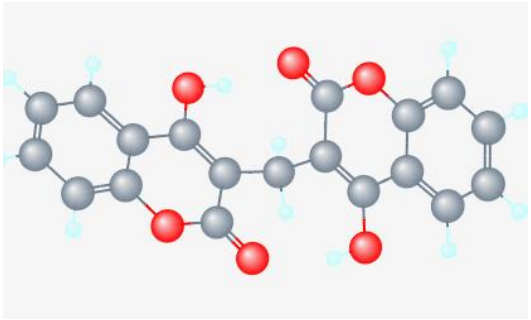
Coumarine | **4-Hydroxycoumarine** | **Dicoumarol (1er anticoagulant used 1941)**

bis-coumarines

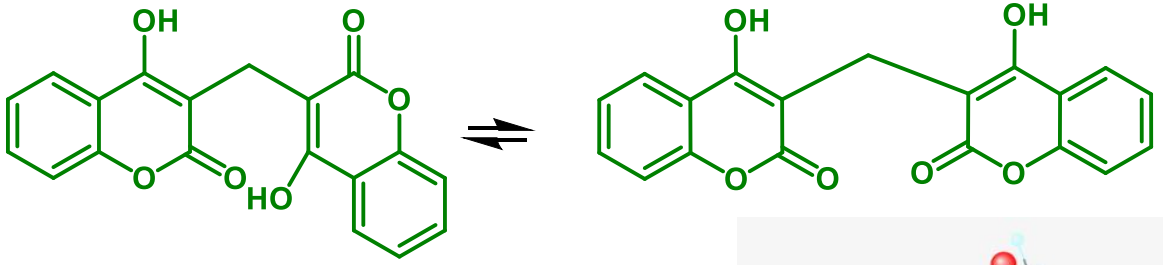
Dr. Karl Link

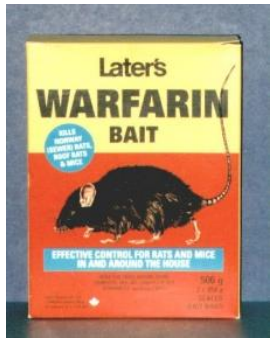
Melilotus officinalis,
Mélilot jaune

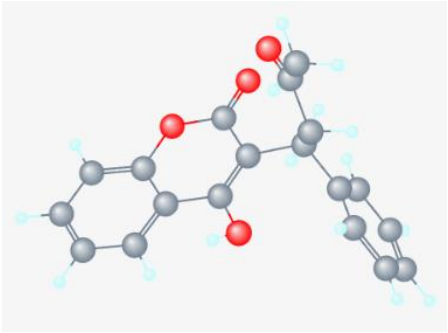
3.9 Discovery of the First VKA

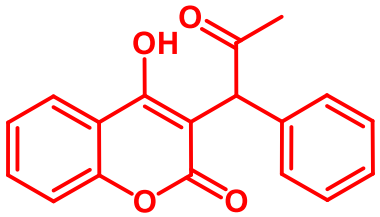


Dicoumarol









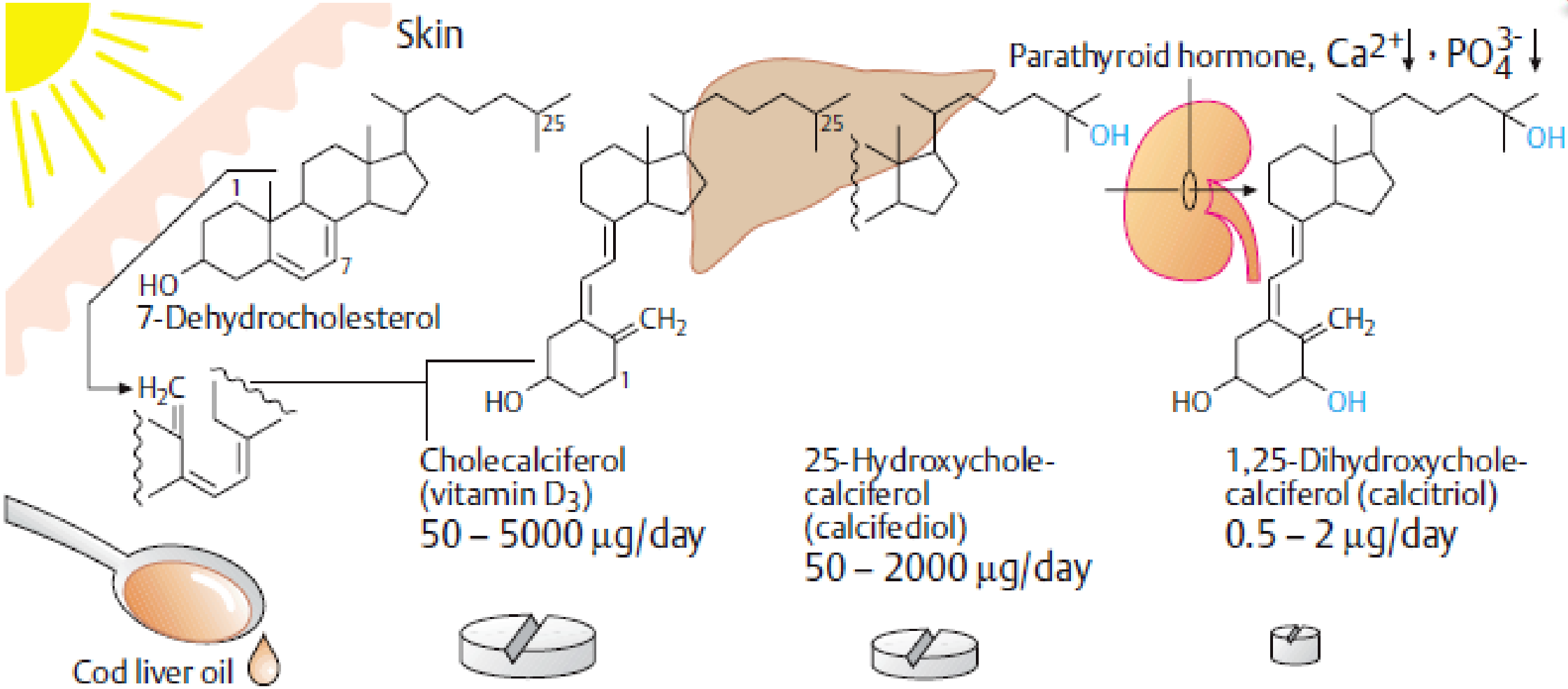
Monocoumarines
Warfarine

Prevention of thrombosis and thromboembolism

Karl Link promeut la warfarine comme rodenticide (avec la permission de l'Université du Wisconsin).

3.10 Discovery of drugs based on metabolic studies

A. Vitamins

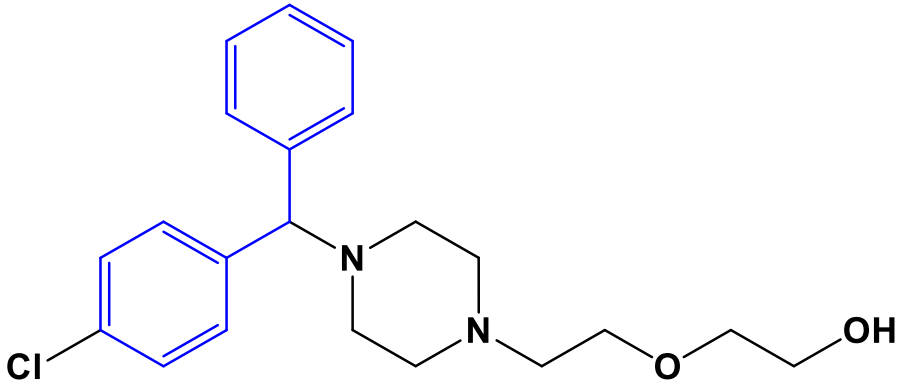


Efficacy : vitamine D < 25-OH-vitamine D < 1,25-di-OH vitamine D.

3.10 Discovery of drugs based on metabolic studies

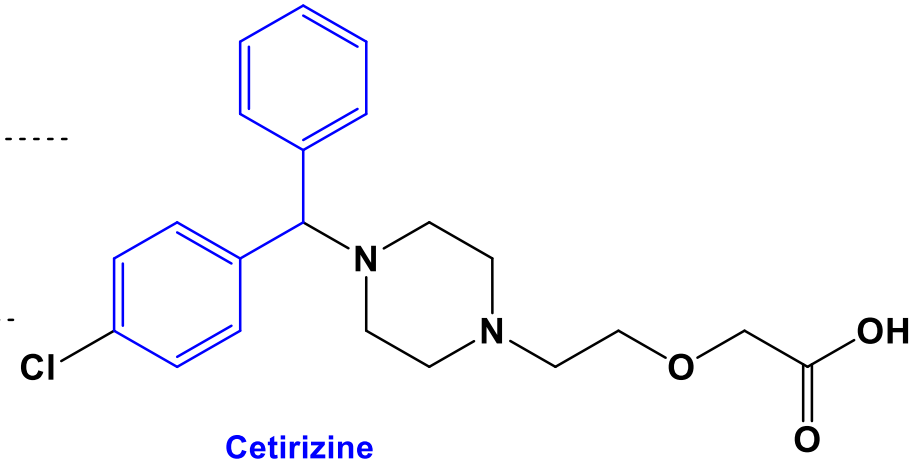
B. Anti-allergic drugs

2nd generation selective anti-H1
less sedative



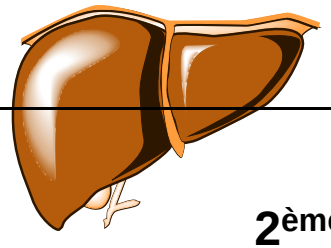
CNS
Sedation

mACh
receptor
antagonist



Hydroxyzine, Crosses the BBB:
Sedative, anxiolytic
logP = 3.4

Metabolization

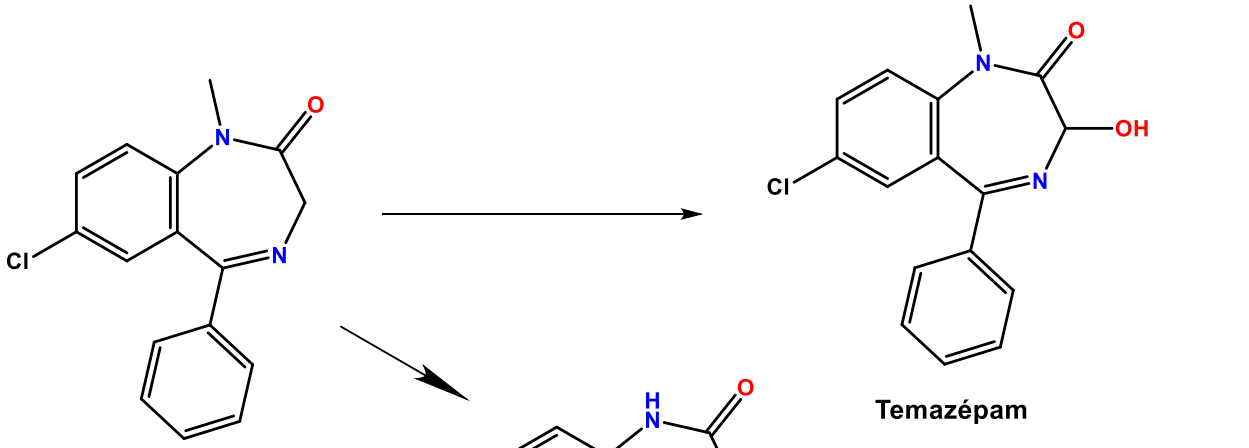


Cetirizine
logP = 2.8

2ème G → Faible passage au niveau de BHE

3.10 Discovery of drugs based on metabolic studies

C. Benzodiazepines

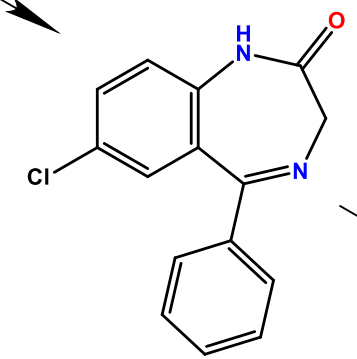


diazepam

$t_{1/2}$ = 20-80 h

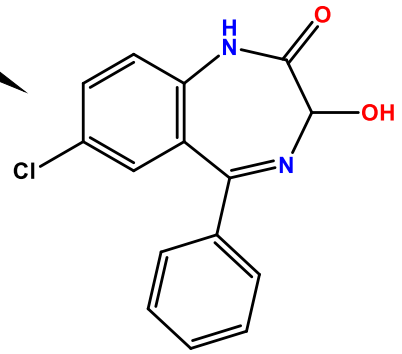
Temazépam

$t_{1/2}$ = 3 - 13 h



nordiazepam
active metabolite

$t_{1/2}$ = 30-97 h



oxazepam
active metabolite

$t_{1/2}$ = 5 - 10 h

COURSE OUTLINE

1. General points
2. ADMET, RO5, and systematic in silico ADMET evaluation
3. The discovery process in the pharmaceutical industry (R&D)
4. The choice of a drug target
5. Drug design strategies
6. Conclusion

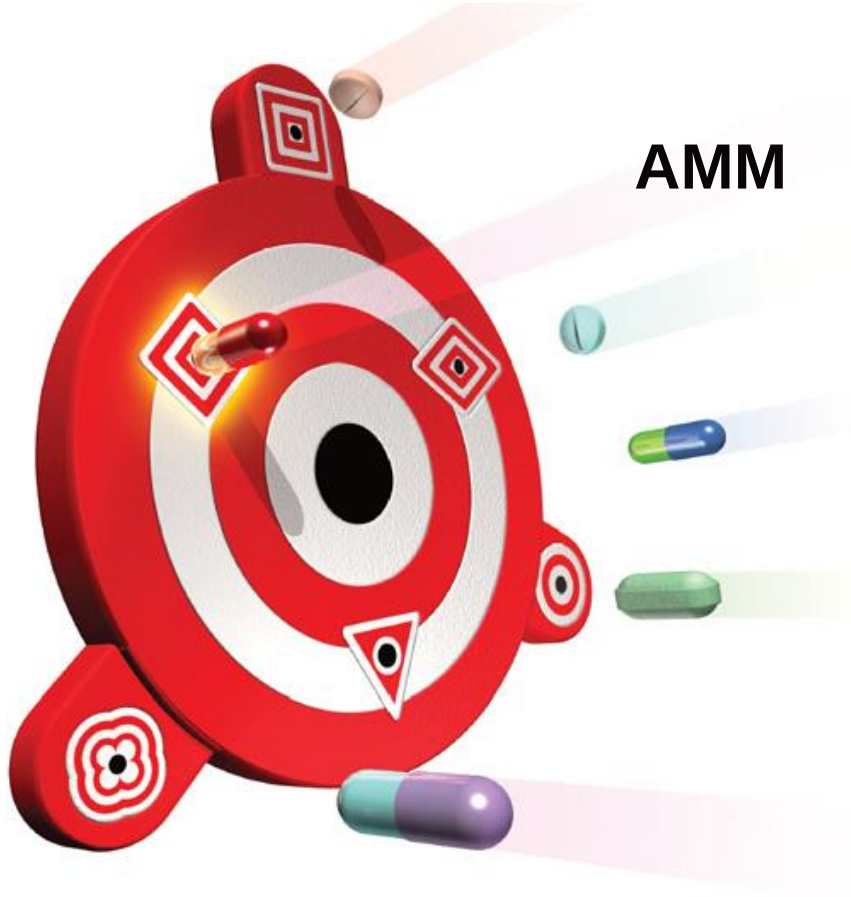
CONCLUSION

… the target: a very thoughtful choice!

- ✓ Have rapid and robust biological test (s), compatible with high throughput screening.
- ✓ Know its 3D structure for molecular modeling.
- ✓ Identify a biomarker,

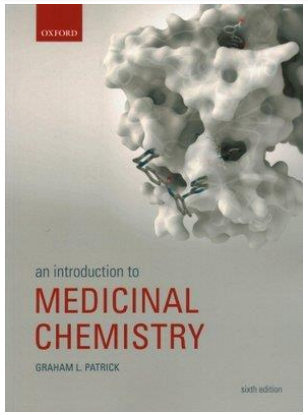
witness to the effectiveness of the modulation of the target by the new compound.

- ✓ Anticipate its ability to mutate and anticipate the consequences of resistance associated with the mutation.
- ✓ Analyze the state of the **I**ntellectual **P**ropriety ‘’IP“ around the target.

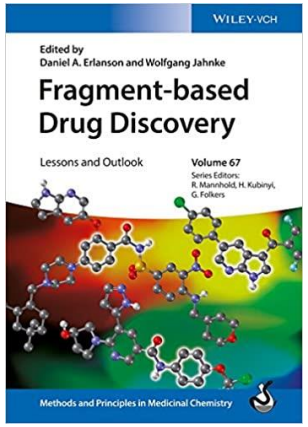



tusind tak
谢谢
dakujem vám
ありがとう
ngiyabonga
dziękuję
merci
suksema
danke
thank
you
baie dankie
धन्यवाद
molte grazie
gracias
obrigada
takk
dank u
tạ ơn
mahalo
obrigado
gràcies
teşekkür ederim
شكرا
tänan
tack så mycket

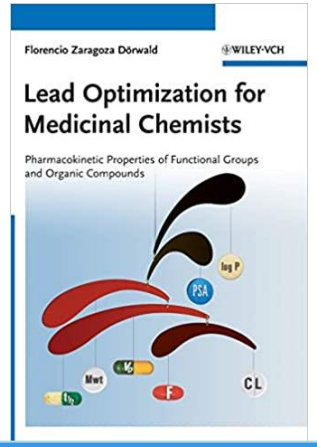
To go further ....



An Introduction to Medicinal Chemistry sixth edition

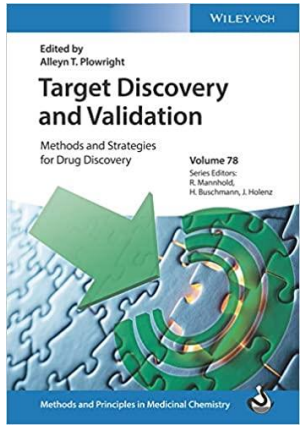


Fragment-based Drug Discovery: Lessons and Outlook

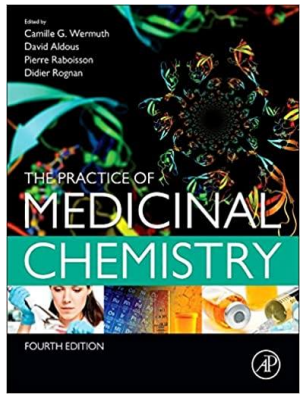


Lead Optimization for Medicinal Chemists: Pharmacokinetic Properties of Functional Groups and Organic Compounds

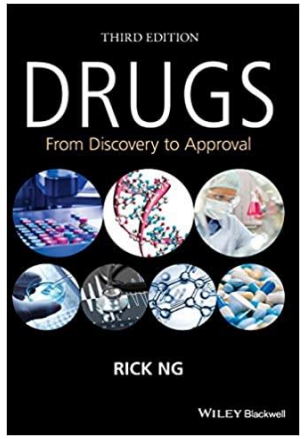
To go further ....



Target Discovery and Validation: Methods and Strategies for Drug Discovery



The Practice of Medicinal Chemistry 4th Edition



Drugs: From Discovery to Approval 3rd Edition