Workshop

Drug lifecycle control in Subsaharan Africa

From production to responsible safe disposal and elimination in wastewater treatment plants

(Med4Africa)

HOW TO TURN A NATURAL OR SYNTHETIC COMPOUND INTO A DRUG SUBSTANCE

A Medicinal Chemistry Approach

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Medicinal Chemist

Drug Lifecycle Control in Subsaharan Africa
29.08.2022

DRUG DEVELOPMENT ROAD

Medicinal Chemistry Research → **Drug Develop-ment** → **Marketing/ Evolution**

Target Selec-tion	Com-pound Discov-ery	Preclin-ical Study	Clinical Study (I,II,III)	Applica-tion/App roval	Market-ing	Reexami-nation

MEDICINAL CHEMISTS PLAYGROUND

- SAR
- Activity
- PK/ADME
- Toxicity
- Environ-mental Load

SOURCES OF DRUGS

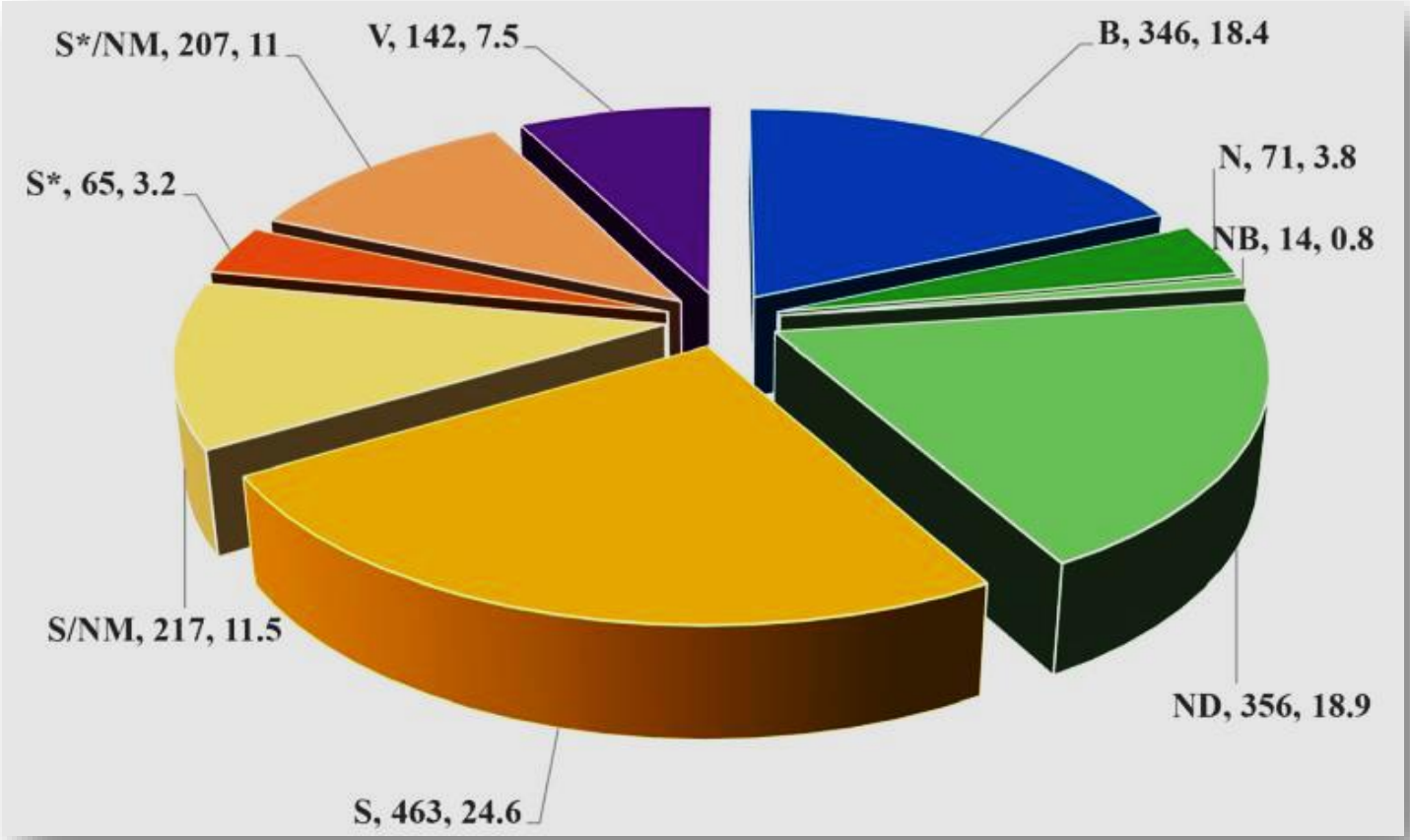

Figure. Newman DJ, Cragg GM *J. Nat. Prod.* 2020, 83, 770-803

N – unmodified natural product, **ND** – modified natural product,
S – synthetic compound with no natural compound conception,
S*, **S*/NM** – synthetic compound with natural product pharmacophore/
NM competitive inhibition, **S/NM** – synthetic compound showing competitive inhibition of the natural product substrate, **V** – vaccine, **B** – biologicals, **NB** – botanical drug

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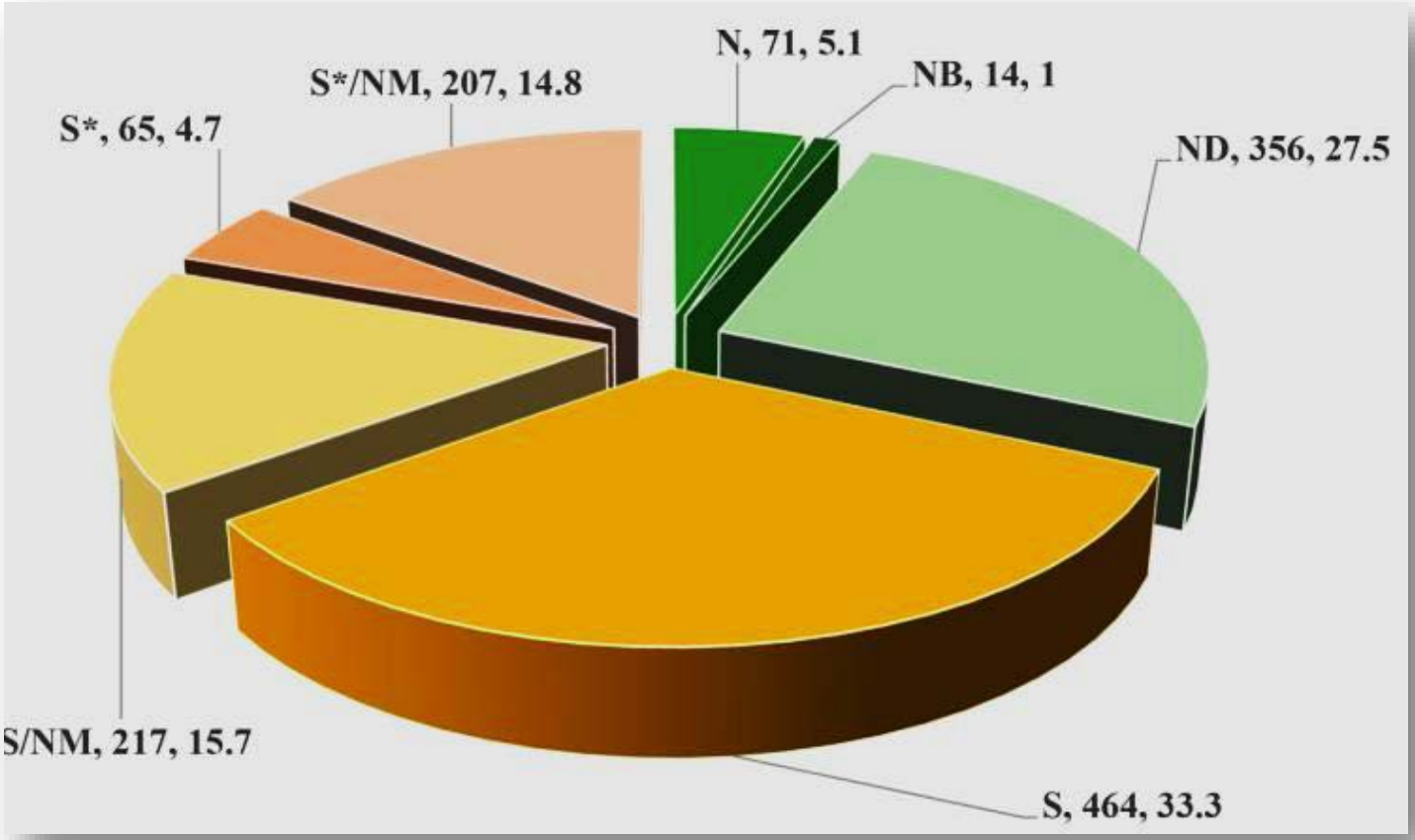

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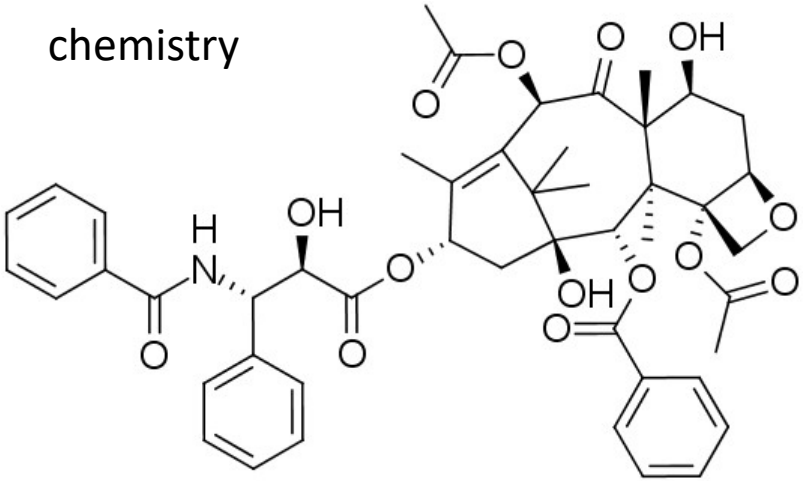
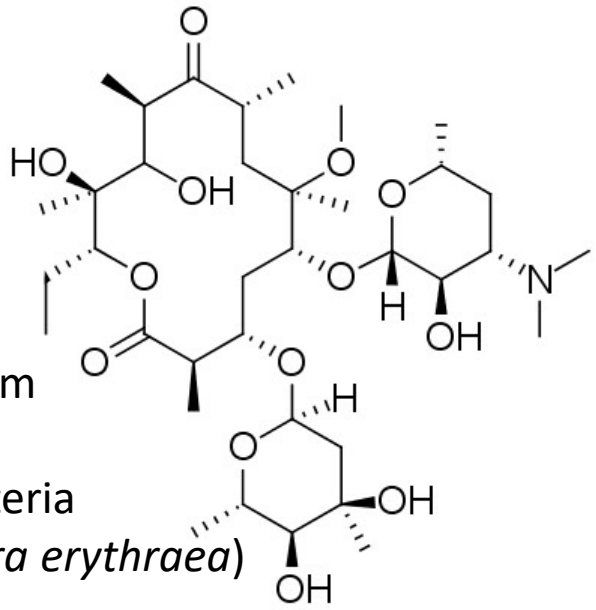
THE IMPORTANCE OF NATURAL PRODUCTS IN R&D

- **Complex structures**, few of them would have been discovered without natural products chemistry



Paclitaxel, cancer therapy, isolated from Pacific Yew (*Taxus brevifolia*)

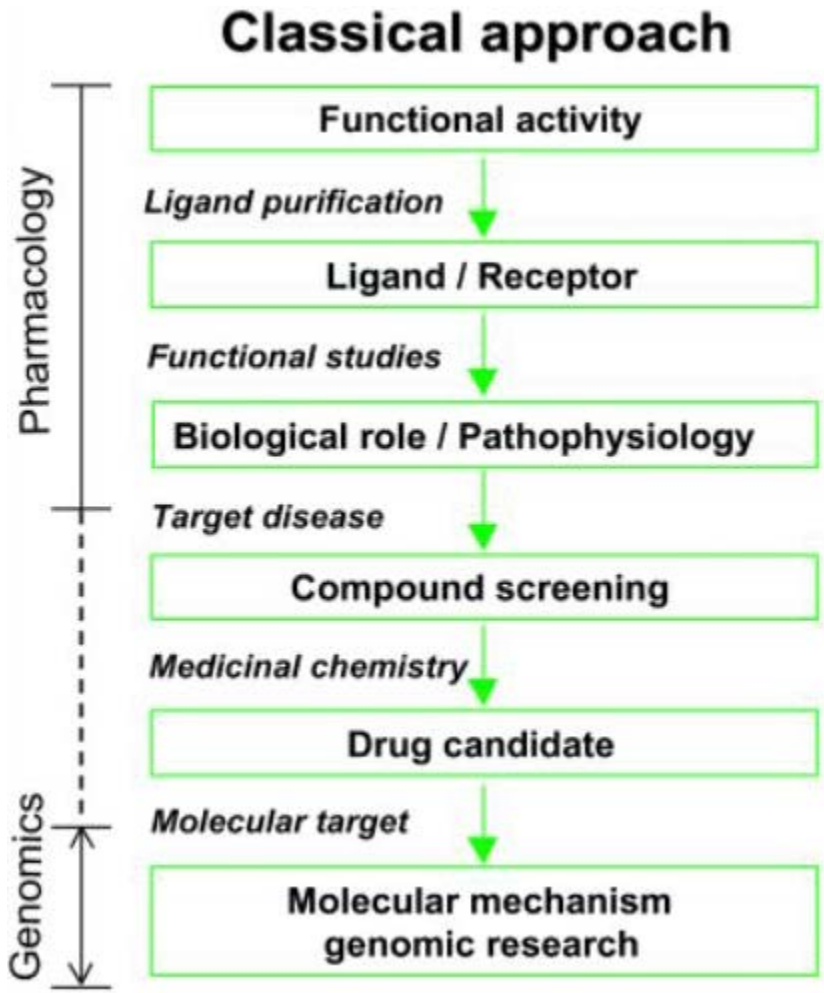


Clarithromycin, antibiotic drug, semi-synthetic from Erythromycin, isolated from bacteria (*Saccharopolyspora erythraea*)

- combination with **combinatorial chemistry** provides a powerful tool to access smart compound libraries
- identification of novel pharmacophores from TAM and further derivatisation bears a potential to develop preclinical drug candidates (Chibale, K Drug Discovery in Africa, 2012)

HOW TO FIND ACTIVITY

Classical vs Reverse Pharmacology



Takenaka T *BJU International* 2001, 88(Suppl. 2), 7-10

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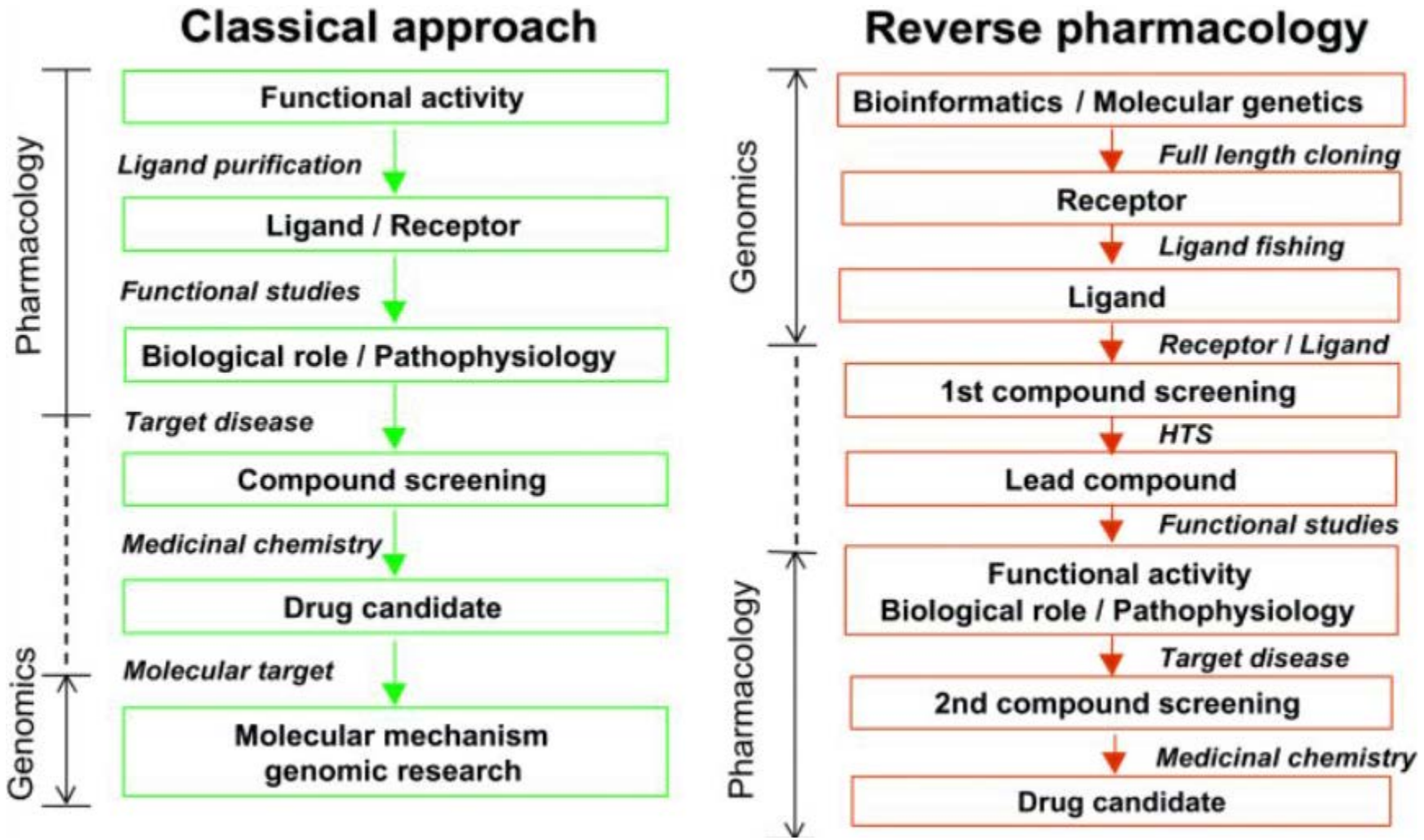

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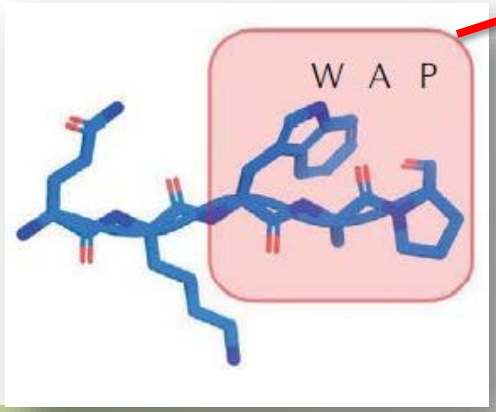
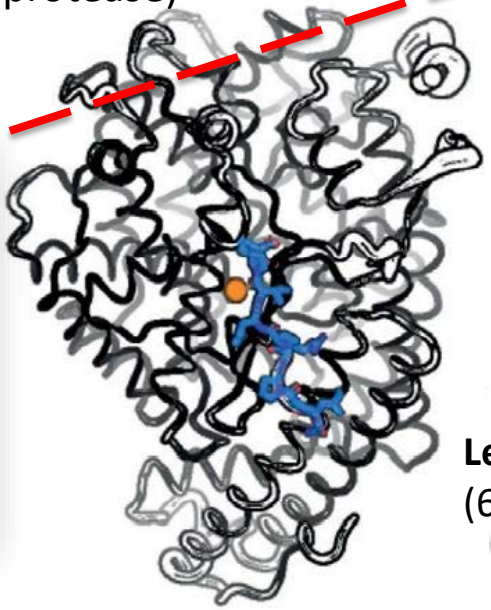
HOW TO FIND ACTIVITY

Development of Angiotensin- converting-enzyme (ACE) inhibitors for anthypertensive therapy

- venom of the pit viper, *Bothrops jararaca,* causes hypotension in prey
- C-terminal domaine of bradykinine potentiating peptides (BPPs)
- inhibit ACE (Zn^{2+} metalloprotease) competitively

Top Figure. https://reptile-database.reptarium.cz/species?genus=bothrops&species=jararaca





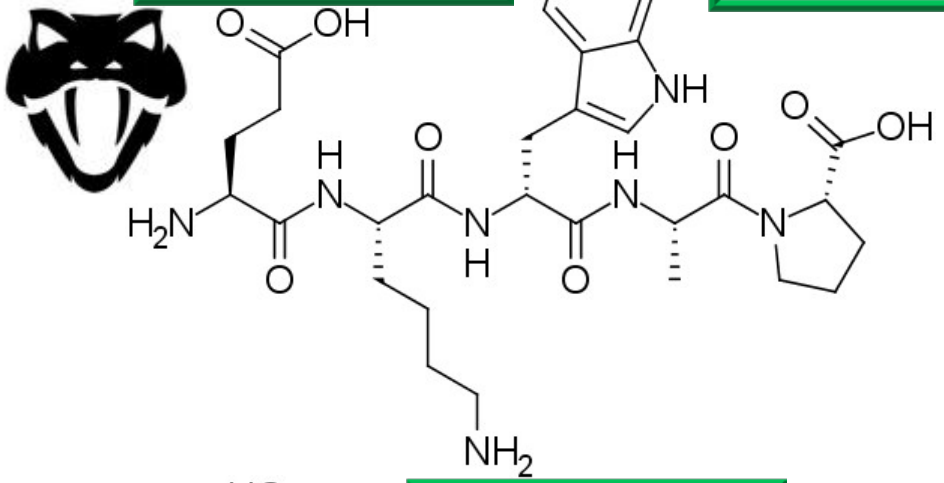
Left Figure. Oliveira AL *et al. Nature Reviews* 2022, (6), 451-469

HOW TO FIND ACTIVITY

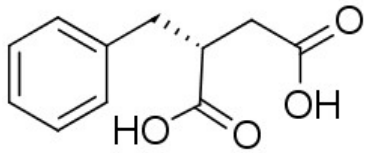
Extraction of snake venom

Isolation of BBP_{5a}

WAP (FAP, more stable)

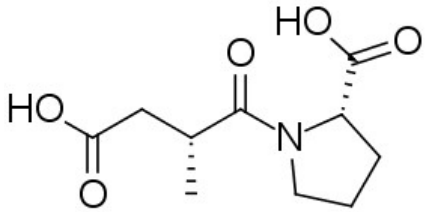


ACE inhibitor, **WAP** domaine binds to enzyme, short lived in hypertensive animal model (enzymatic degradation)



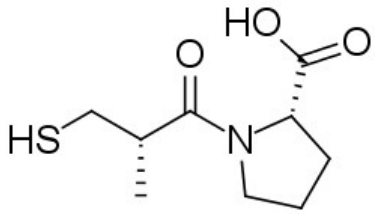
L-Benzyl-succinic acid

strong inhibitor of carboxypeptidase A analog of phenylalanine



Pro-*N*-2-methylsuccinate

Combination of Ala-Pro ACE binding motive and succinyl-based peptidase inhibition

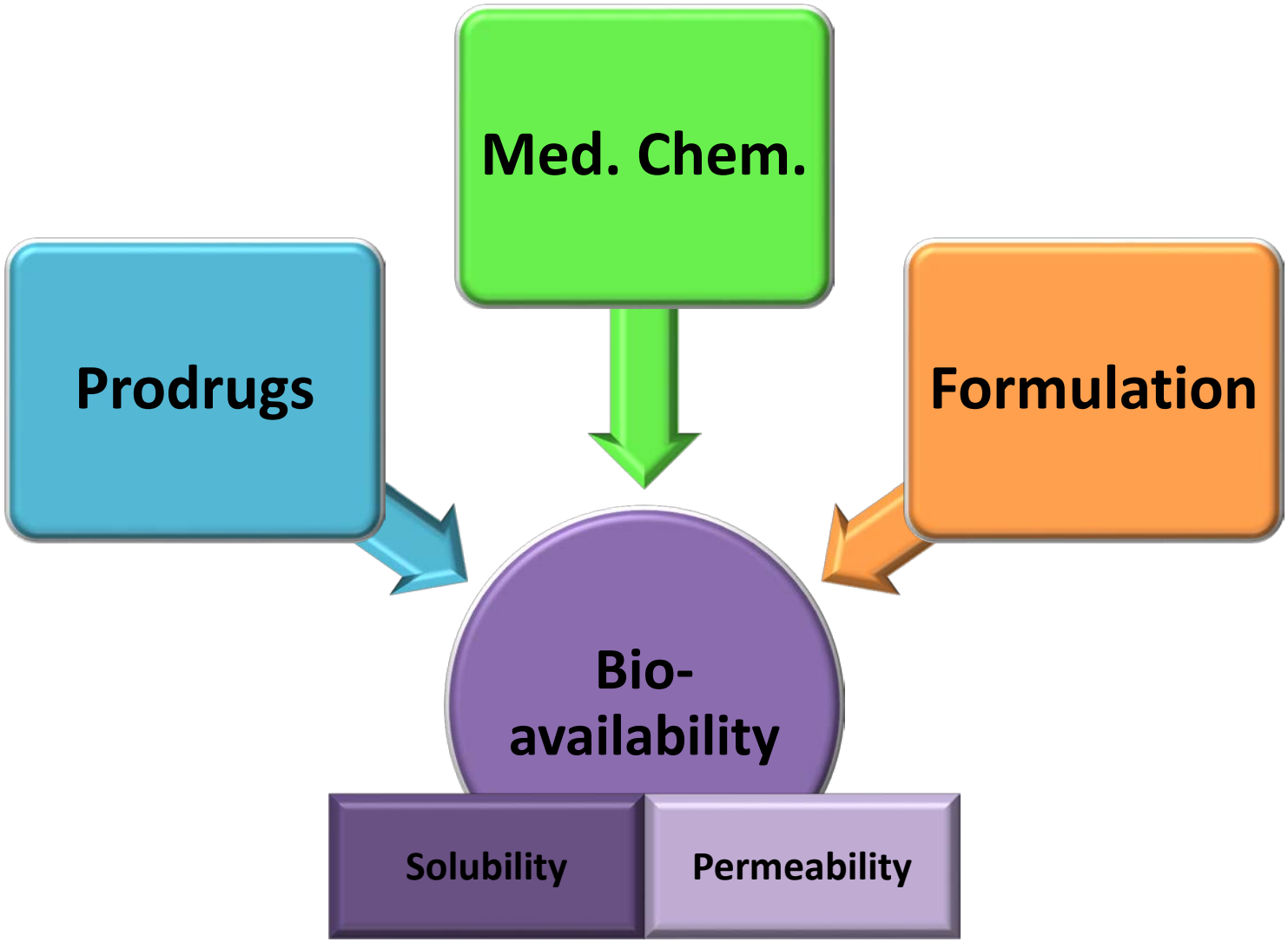


Captopril

Orally active, improved bioavailability, Sulfhydryl moiety led to 2,000 fold increased activity compared to Pro-*N*-2-methylsuccinate, approved in 1981 (FDA)

Cushman DW, Ondetti MA *Hypertension* 1991, 17(4), 589-592

HOW TO IMPROVE BIOAVAILABILITY



Gomez-Orellana I *Expert Opin. Deliv*. 2005, 2(3), 419-433

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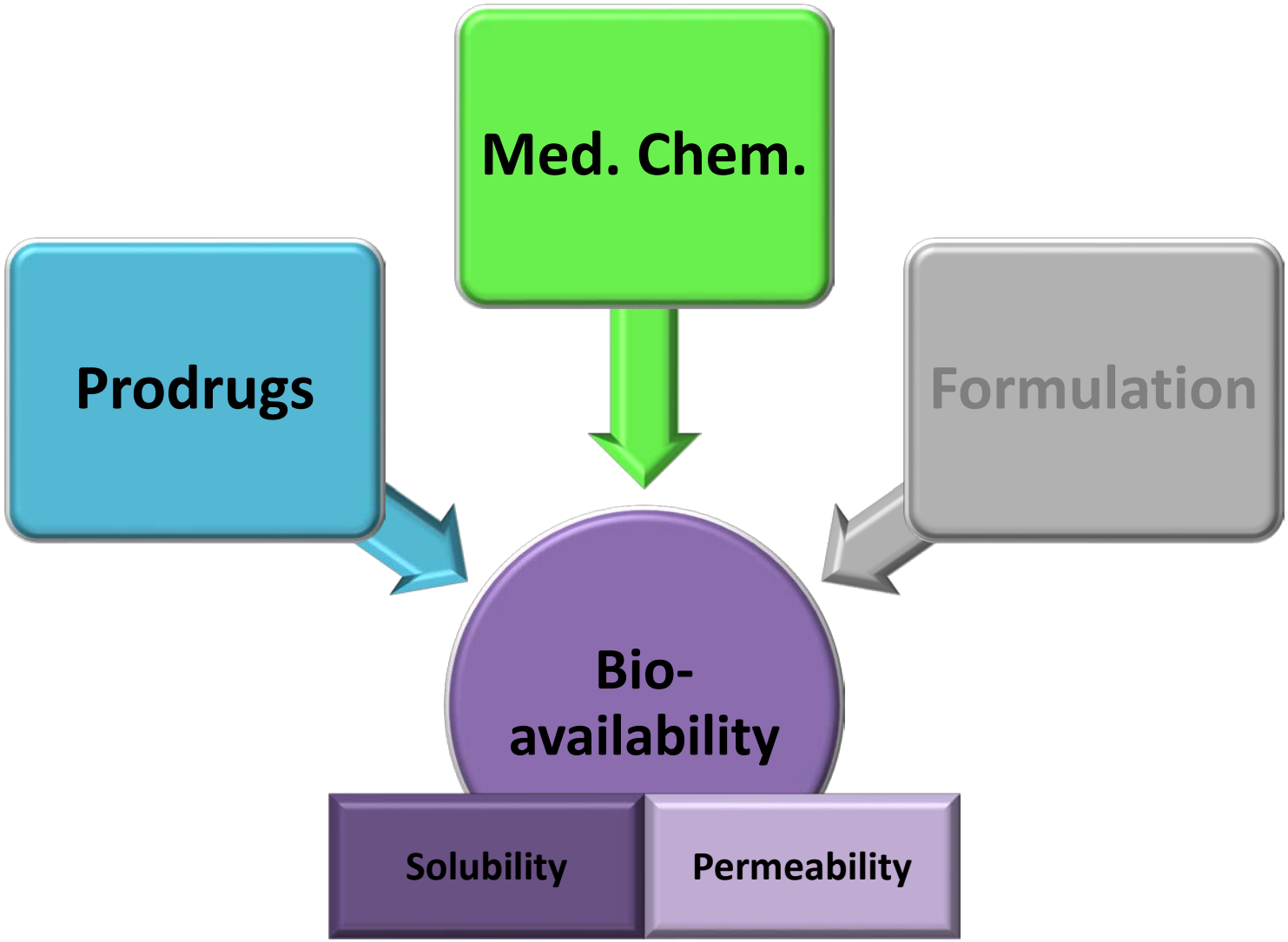

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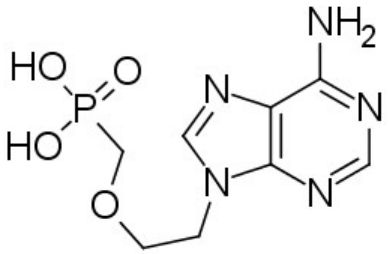
PRODRUGS – IMPACT ON BIOAVAILABILITY

- **Prodrugs**, targeted transformation inside the body (hydrolysis or enzmatic reaction)
- **Covalent** attachment that alters physicochemical properties of the drug and thereby improve bioavailability



Adefovir, antiviral therapy, nucleotide analog reverse-transcriptase inhibitor
BA > 1 %

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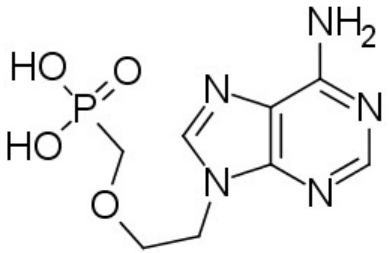

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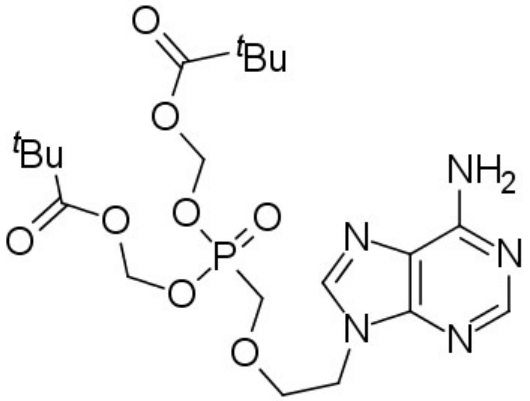

Adefovir dipivoxil
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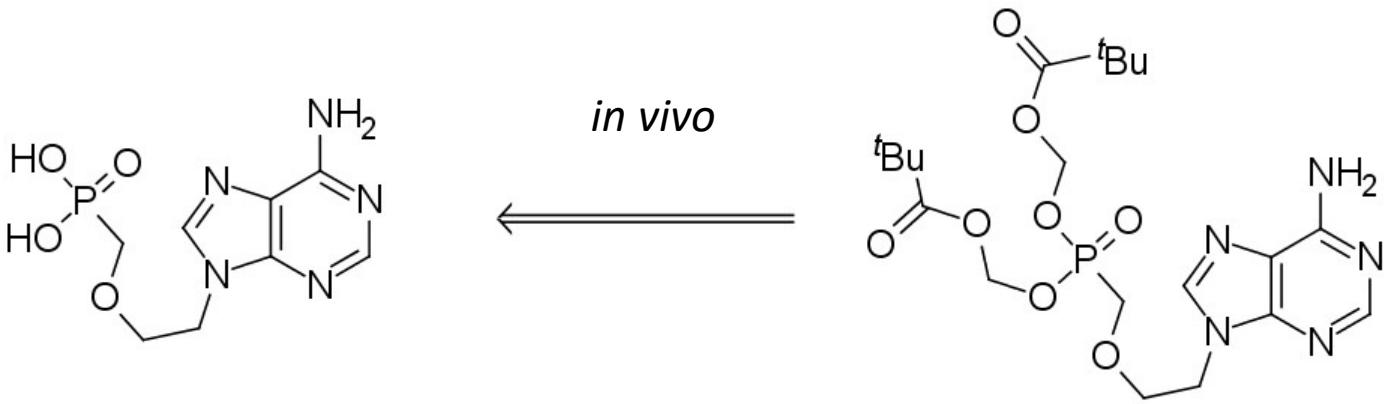

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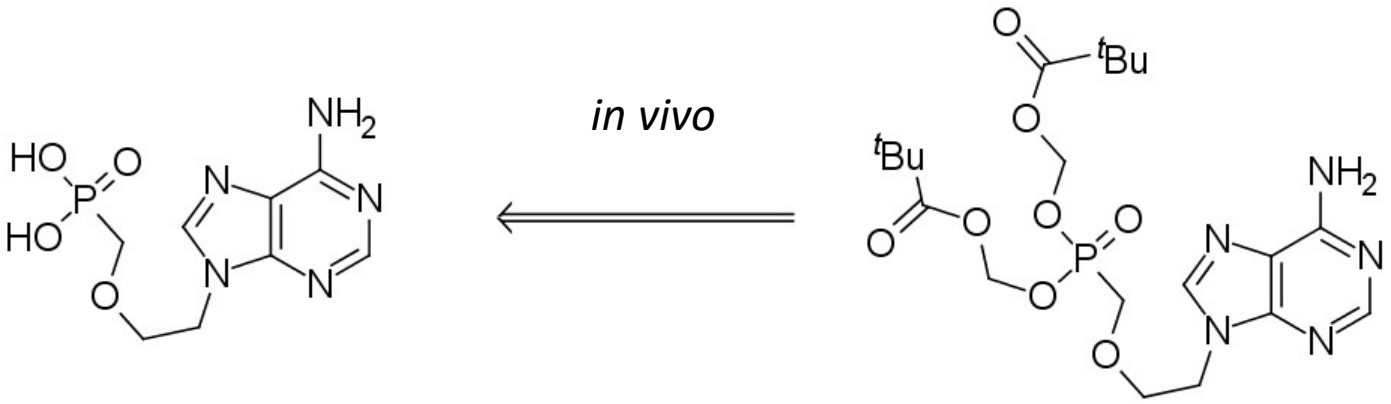
PRODRUGS – IMPACT ON BIOAVAILABILITY

- **Prodrugs**, targeted transformation inside the body (hydrolysis or enzmatic reaction)
- **covalent** attachment that alters physicochemical properties of the drug and thereby improve bioavailability
- downside, drug **accumulation** inside the cell



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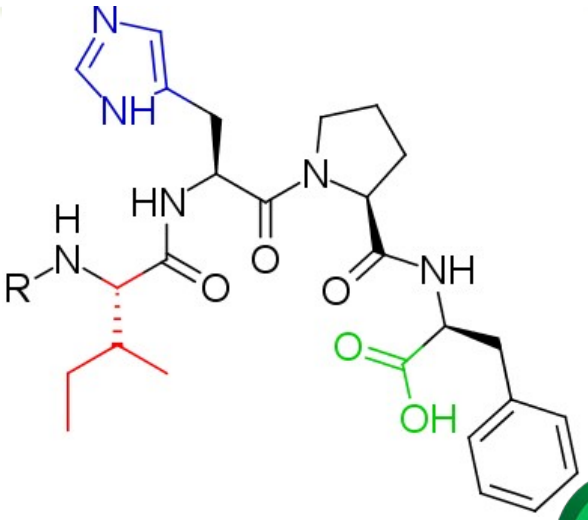
MED CHEM – IMPACT ON BIOAVAILABILITY



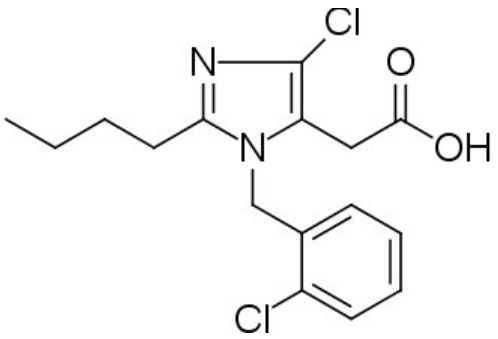
Angiotensin II

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe, endogenous AT_1 **agonist**

Saralasin

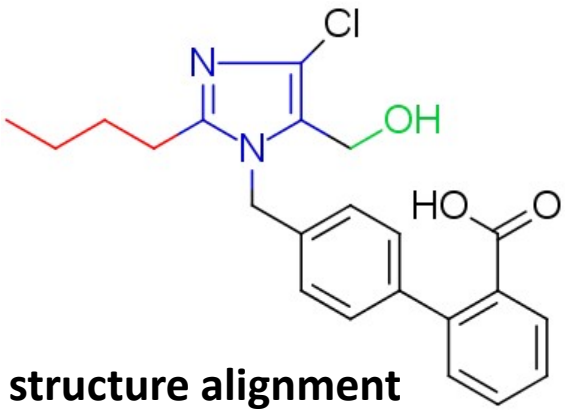
Sar-Arg-Val-Tyr-Val-His-Pro-Ala, AT_1 **antagonist**

S-8307



small molecule AT_1 inhibitor, poor activity

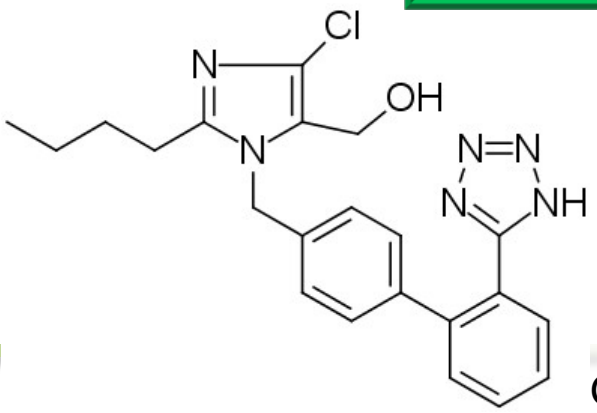
EXP7711



structure alignment
improved activity but poor bioavailability

Losartan

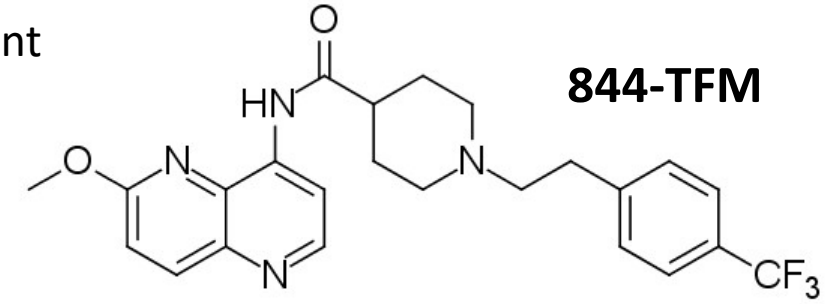
bioisosteric replacement of carboxyl with tetrazole, improved oral potency



Georgiou N *Molecules* 2021, 26, 2927

HOW TO IMPROVE MOUSE PLASMA STABILITY

- **844-TFM**, synthetic lead compound with potent *in vitro* activity against NTM; MoA Novel Bacterial Topoisomerase Inhibitor (**NBTI**)

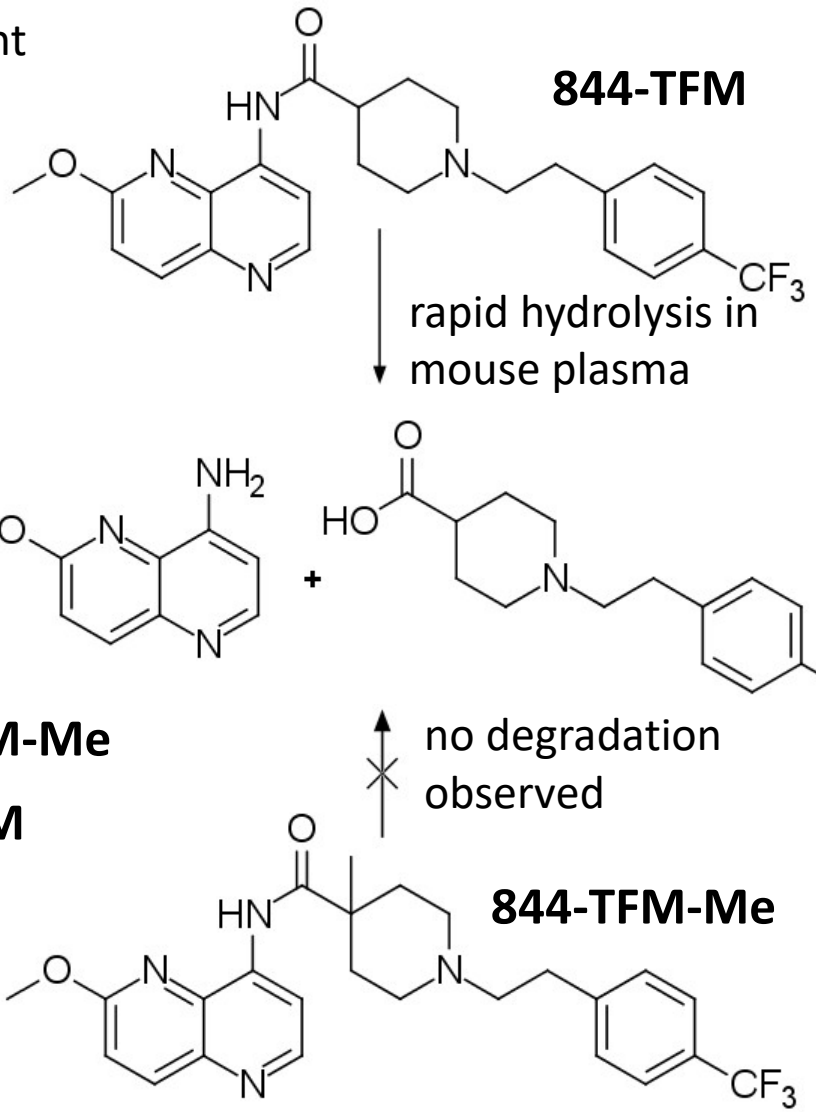


844-TFM

Negatu DA *et al. Antimicrob. Agents Chemother.* 2021, 65(8)

HOW TO IMPROVE MOUSE PLASMA STABILITY

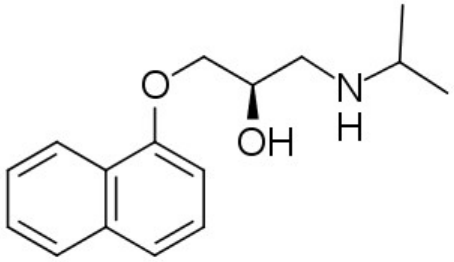
- **844-TFM**, synthetic lead compound with potent *in vitro* activity against NTM; MoA Novel Bacterial Topoisomerase Inhibitor (**NBTI**)
- PK investigation revealed general **mouse plasma instability** of the central amide
- Attachment of an α-methyl group led to **improved** *in vitro* **stability** and *in vivo* **bioavailability**



Beuchel A *et al. ACS Med. Chem. Lett.* 2022, 13(3), 417-427

HOW TO REDUCE ENVIRONMENTAL BURDEN

- Worldwide contamination of aquatic systems with pharmaceuticals (often toxic, non-degradable)
- Re-design of existing molecules, improve biodegradability



Propranolol (**PPL**)
anti hypertensive drug, non-biodegradable

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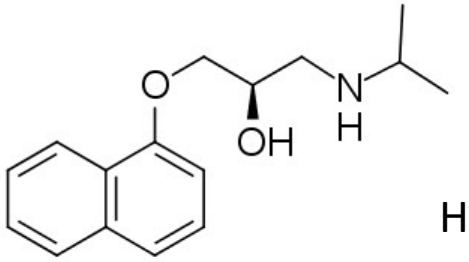
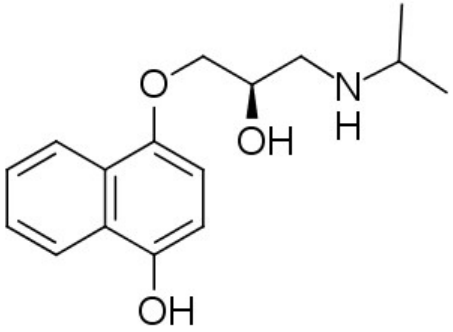


UV-photolysis

HPLC analysis of mixture



4-OH-PPL
pharmacol. activity confirmed (*in vitro*)

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Rastogi T *et al. Environ. Sci. Technol.* 2015, 49, 11756-11763

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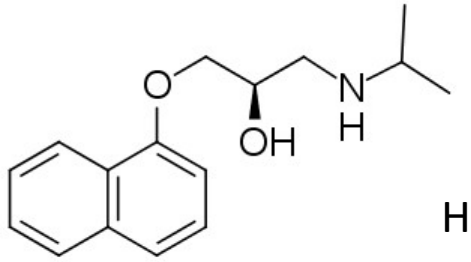

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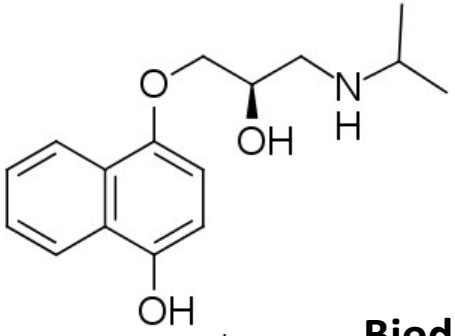

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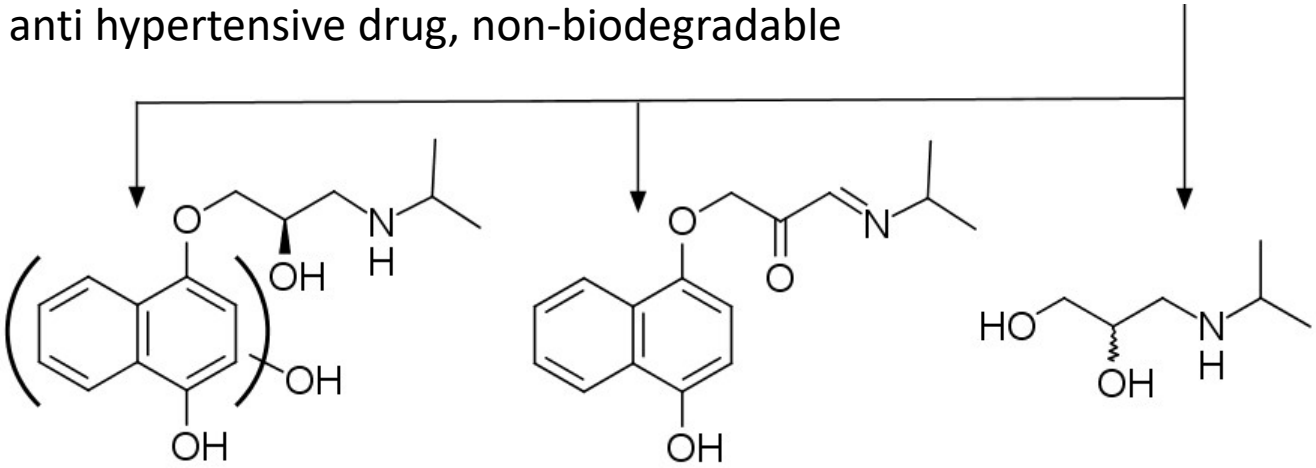
Biodegradable Screening, **4-OH-PPL** shows improved biodegradability and is unlikely to accumulate in aquatic systems



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HOW TO DEVELOP A DRUG

- The search for **activity** is only the first step in a **multidisciplinary** approach, which is necessary for drug development.
- **Reverse pharamacology** offers a beneficial method to shorten the drug development time.
- **Pharmacokinetics** is the bottleneck in drug development, 2nd only to finding activity.
- Future pharmaceuticals should be designed with **biodegradability** in mind.



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Drug Lifecycle Control in Subsaharan Africa
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