Prodrug Design

Literature Talk

Sept 10th, 2025

Esther Kang

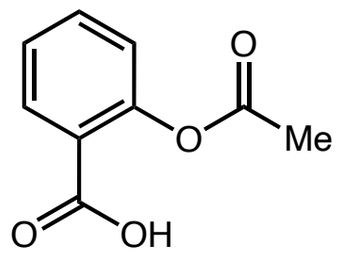
MacMillan Group

One of the earliest blockbuster synthetic drugs

Aspirin™

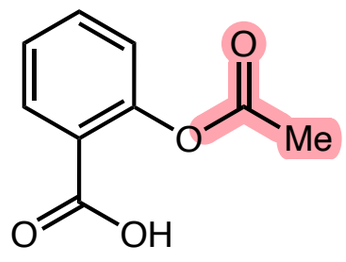
(Approval in 1899)

One of the earliest blockbuster synthetic drugs



Aspirin™

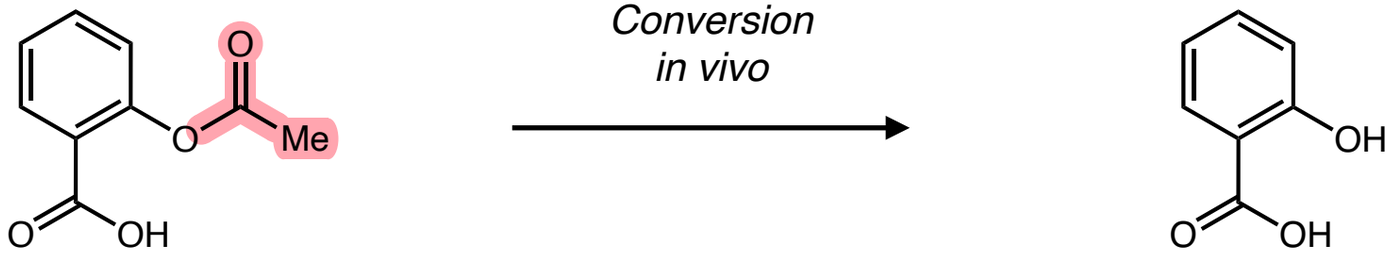
One of the earliest blockbuster synthetic drugs



Aspirin™

First prodrug by rational design

One of the earliest blockbuster synthetic drugs



Aspirin™ ***Salicylic acid***

(Active metabolite)

First prodrug by rational design

How are prodrugs designed?

Overview

- ***Introduction***

- ***Prodrug design to improve ADME properties***

- 'A' of ADME

- 'D' of ADME

- 'M' of ADME

- 'E' of ADME

- ***Prodrug beyond science***

- patent

- regulatory

- ***Conclusion and final thoughts***

What is prodrug?

Prodrug: Drug substance that is inactive in the intended pharmacological actions and must be converted into the pharmacologically active agent by metabolic or physicochemical transformation

- ***First coined the term ‘prodrug’ in 1958***
- ***Later apologised for having invented an inaccurate term, because ‘predrug’ would have been a more descriptive term***

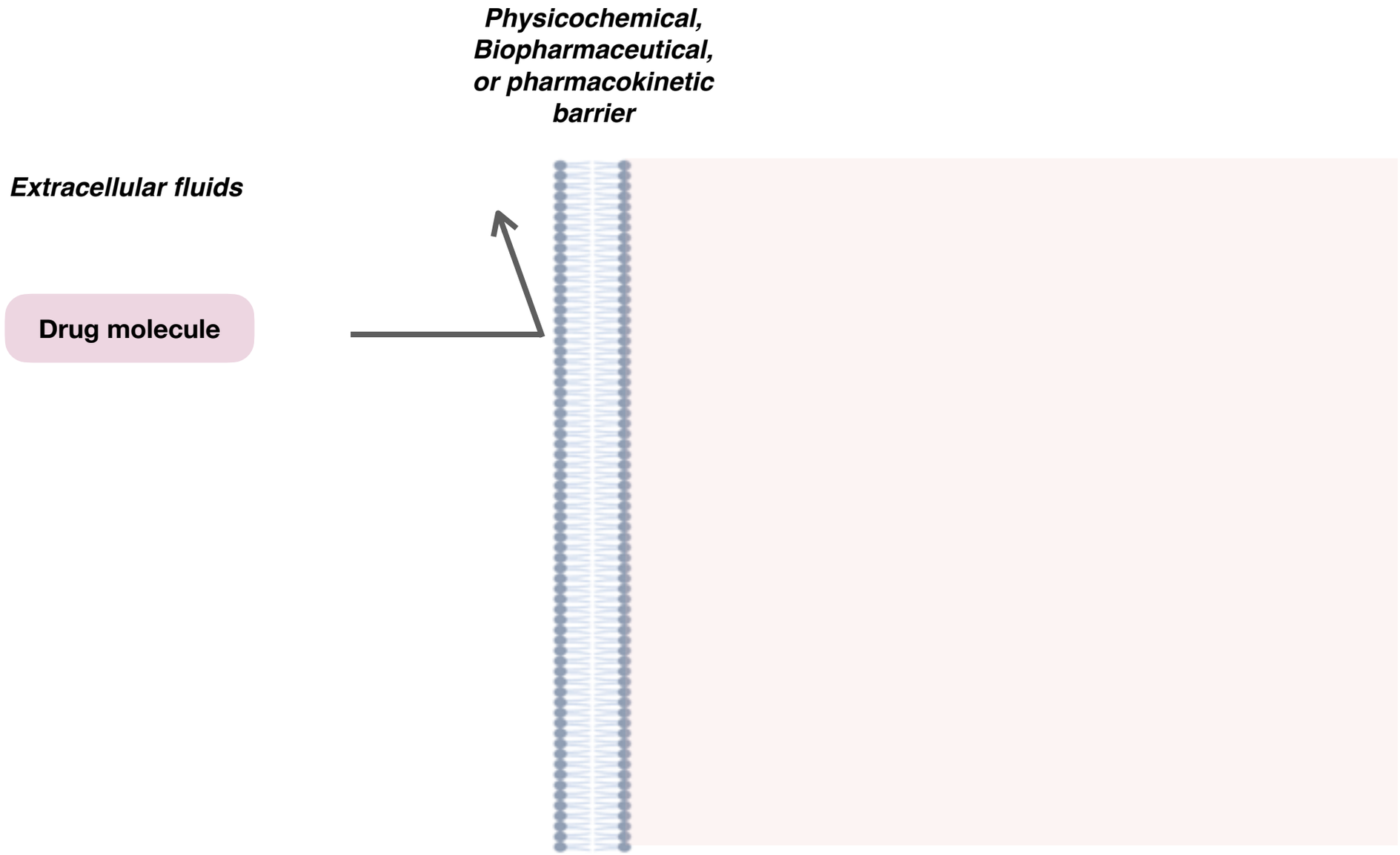
Adrien Albert

Australian medicinal chemist

(1907 - 1989)

Albert, A. *Nature* **1958**, *182* (4633), 421.

What is prodrug?



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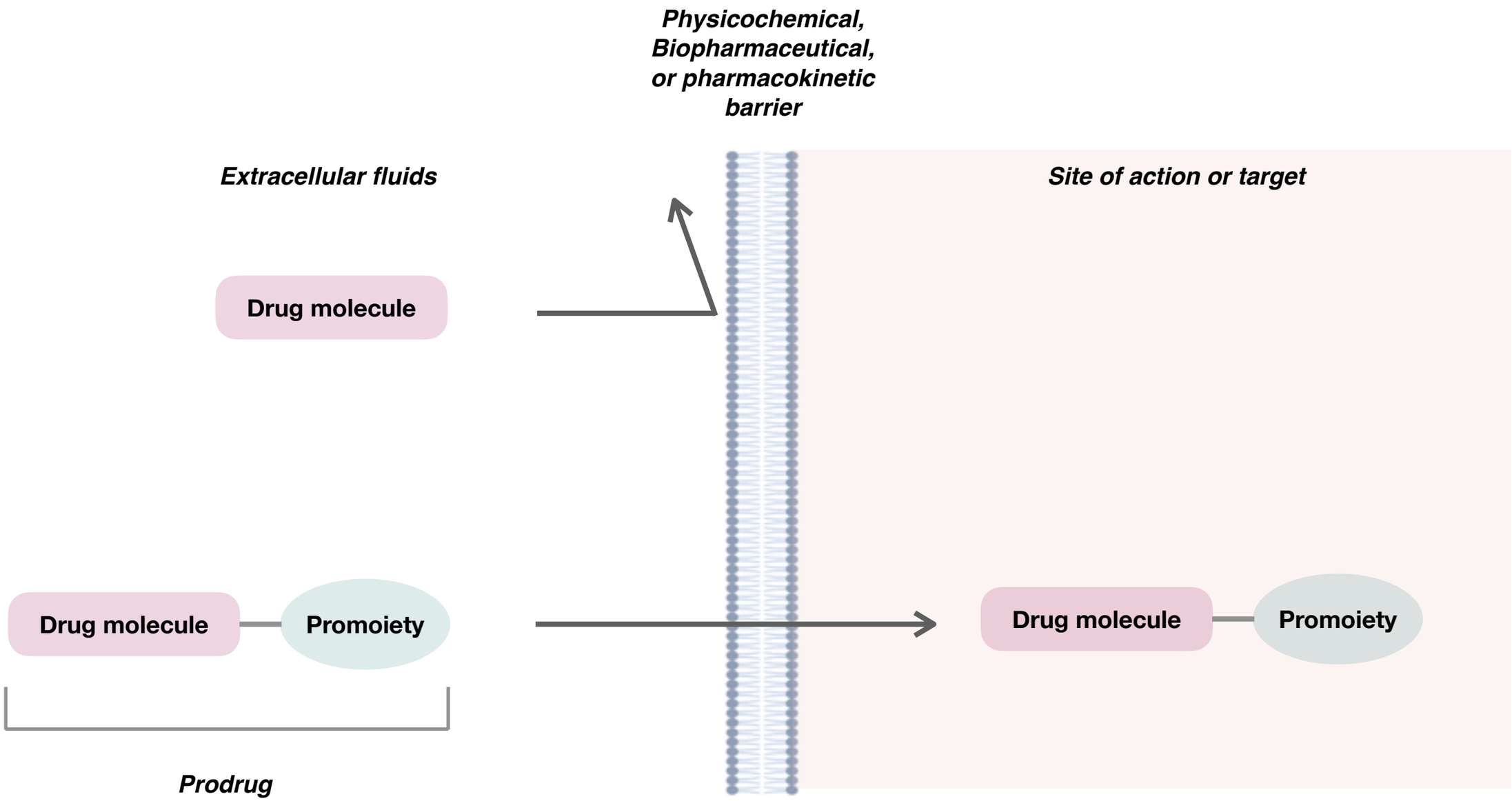

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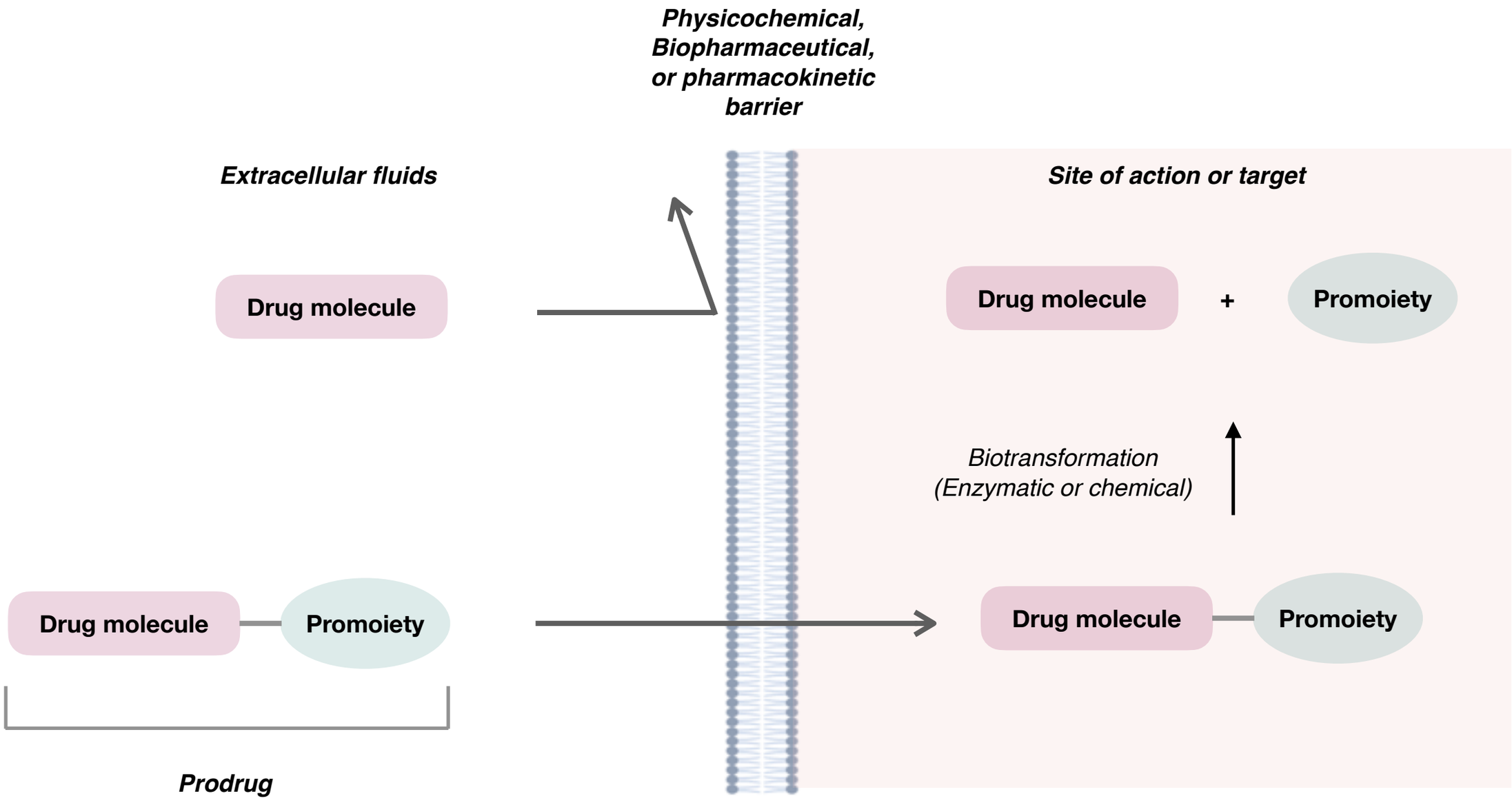
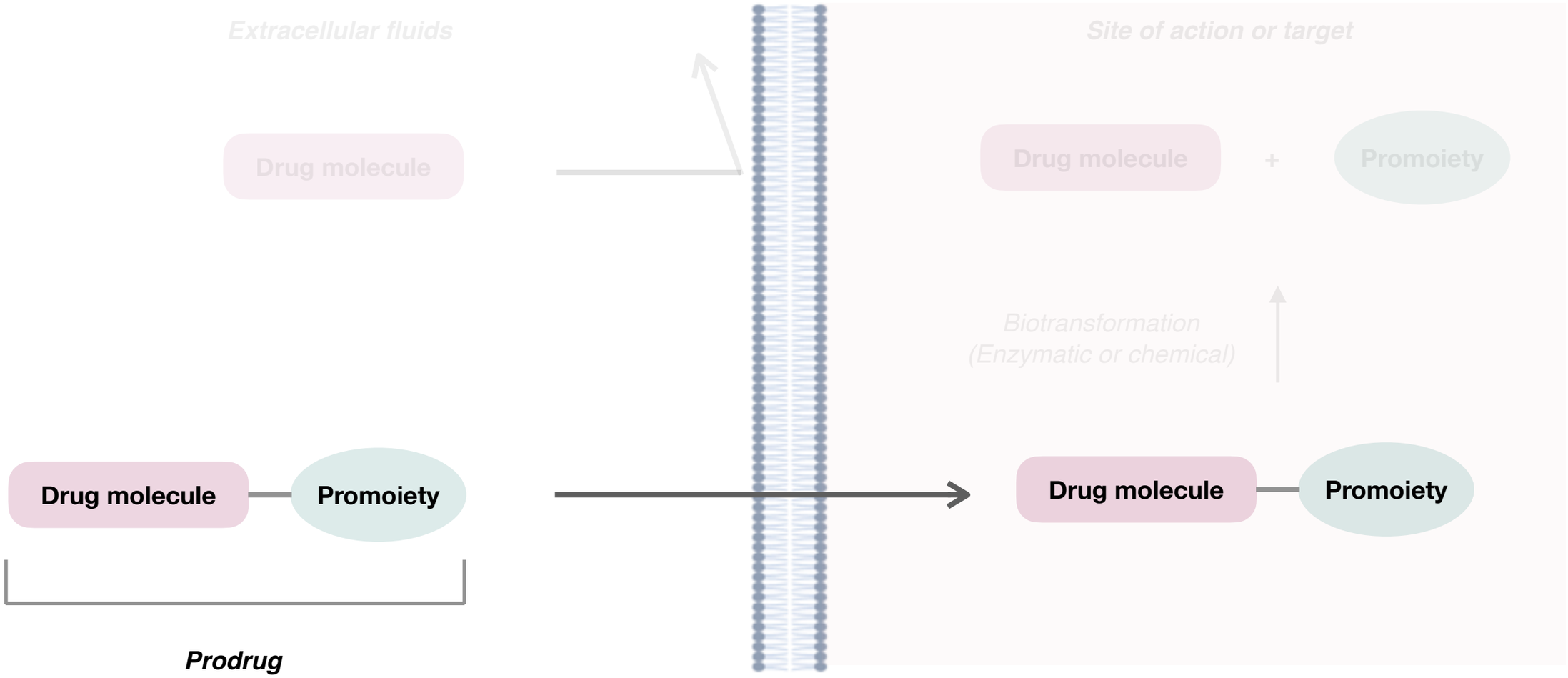


Why prodrug?

Physicochemical, Biopharmaceutical, or pharmacokinetic barrier



To optimize drug-like properties

Classifications of prodrug

Classifications of prodrug

Carrier-linked Prodrug

Bioprecursor Prodrug

Mutual Prodrug

Classifications of prodrug

Carrier-linked Prodrug

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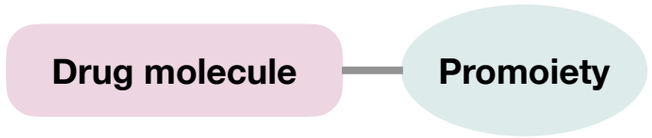
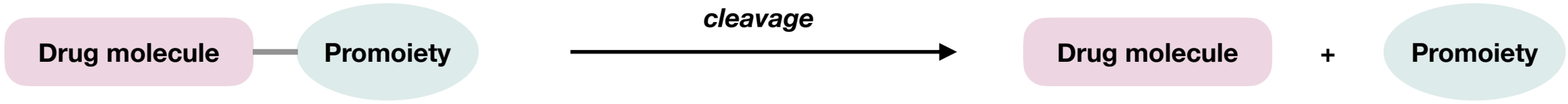
Mutual Prodrug

Carrier-linked prodrug



Carrier-linked prodrug

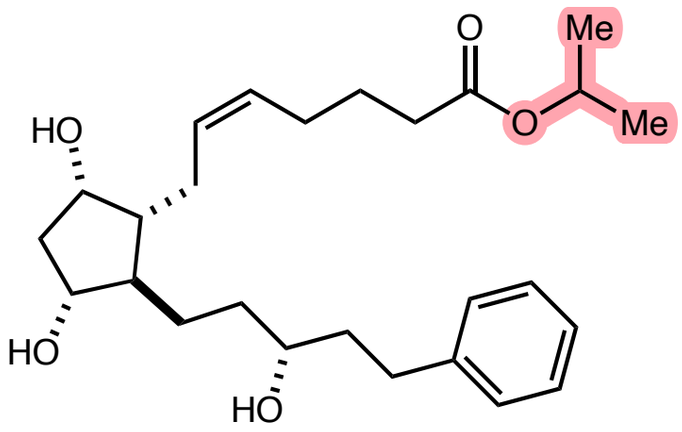


Carrier-linked prodrug

Latanoprost

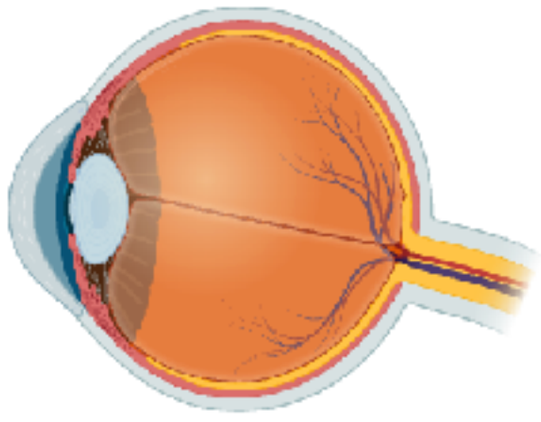
Drug molecule — **Promoiety** ⟶ ***Enzymatic or chemical cleavage*** ⟶ **Drug molecule** + **Promoiety**

Carrier moiety



Latanoprost isopropyl ester

Treatment for glaucoma



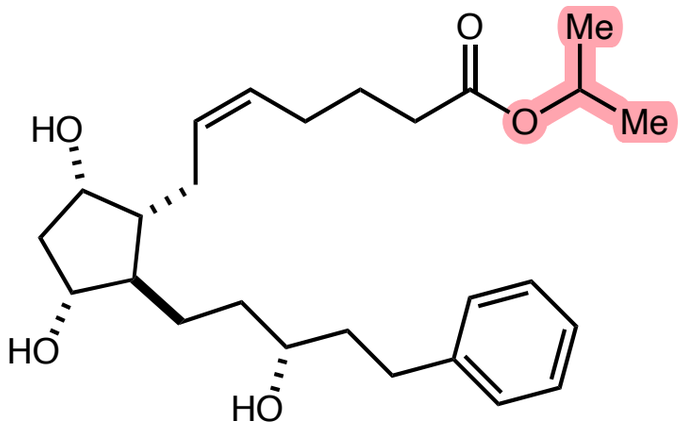
*With a **Lipophilic carrier**, latanoprost readily penetrates the cornea after ocular instillation*

Carrier-linked prodrug

Latanoprost

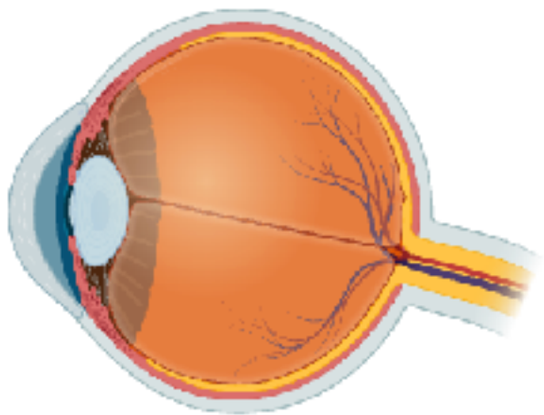
Drug molecule — **Promoiety** → ***Enzymatic or chemical cleavage*** → **Drug molecule** + **Promoiety**

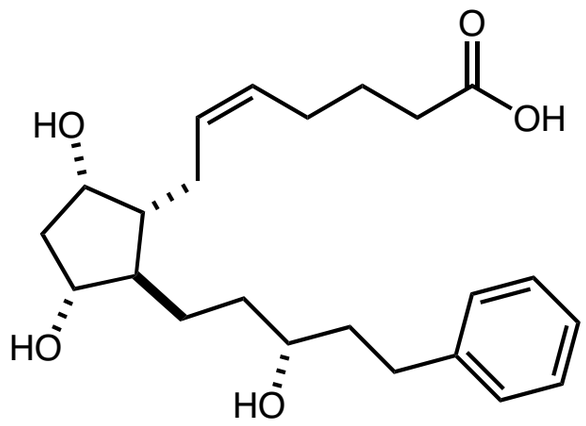
Carrier moiety



Latanoprost isopropyl ester

Hydrolysis
(by ocular esterase in cornea)

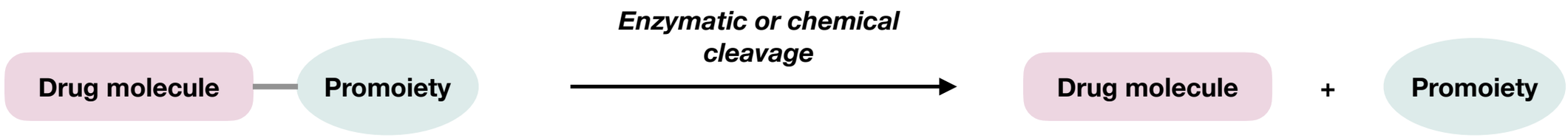


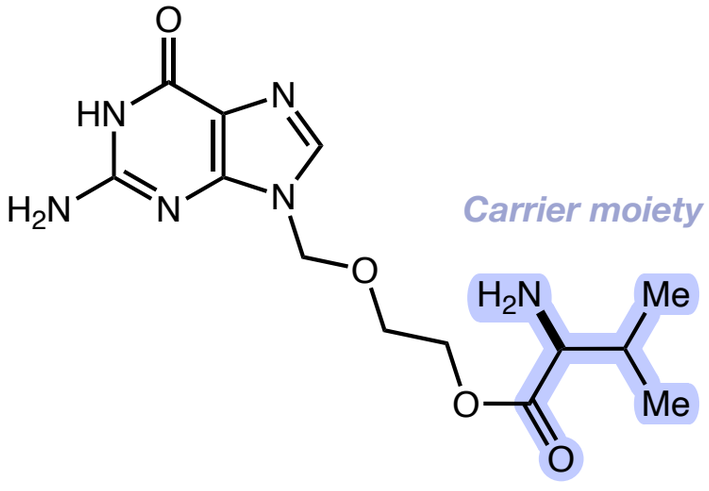


Latanoprost active form

Carrier-linked prodrug

Valtrex™

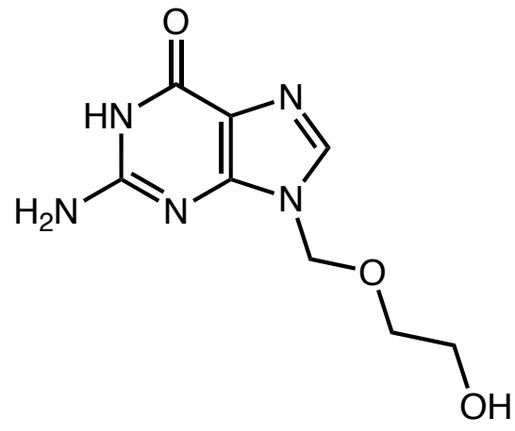




Valacyclovir (Valtrex™)

Treatment for herpes virus infection

Absorption by PEPT1 (peptide transporter 1)



Active metabolite

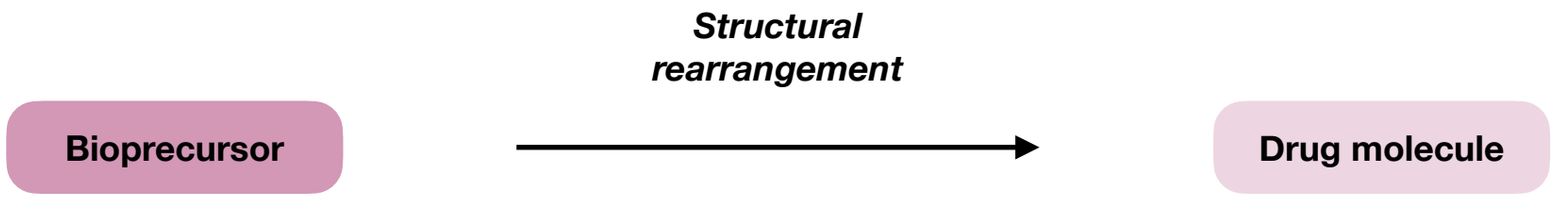
Classifications of prodrug

Carrier-linked Prodrug

Bioprecursor Prodrug

Mutual Prodrug

Bioprecursor prodrug

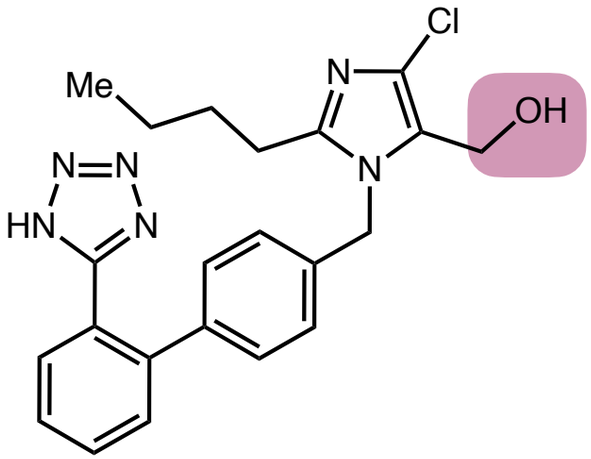


Bioprecursor prodrug

Cozaar™

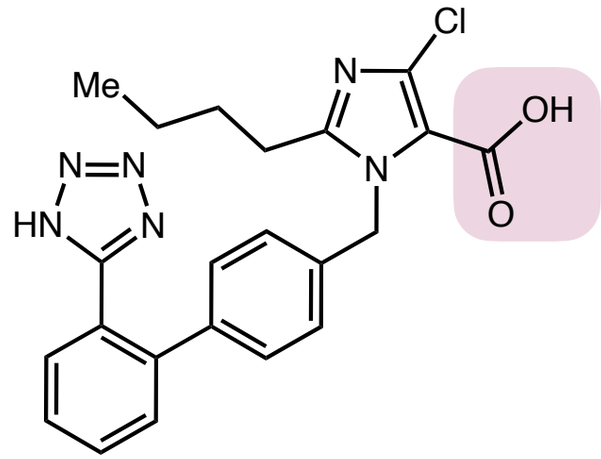
Structural rearrangement

Bioprecursor → **Drug molecule**



Oxidation

Cytochrome P450



Losartan (Cozaar™)

Antihypertensive medication

Angiotensin II type 1 receptor antagonist

Active metabolite

~10-40 fold more potent

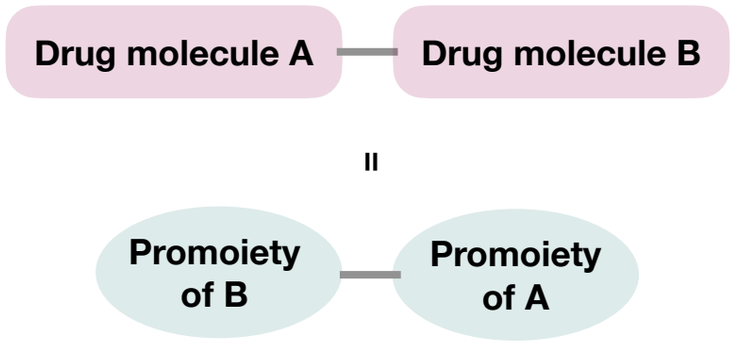
Classifications of prodrug

Carrier-linked Prodrug

Bioprecursor Prodrug

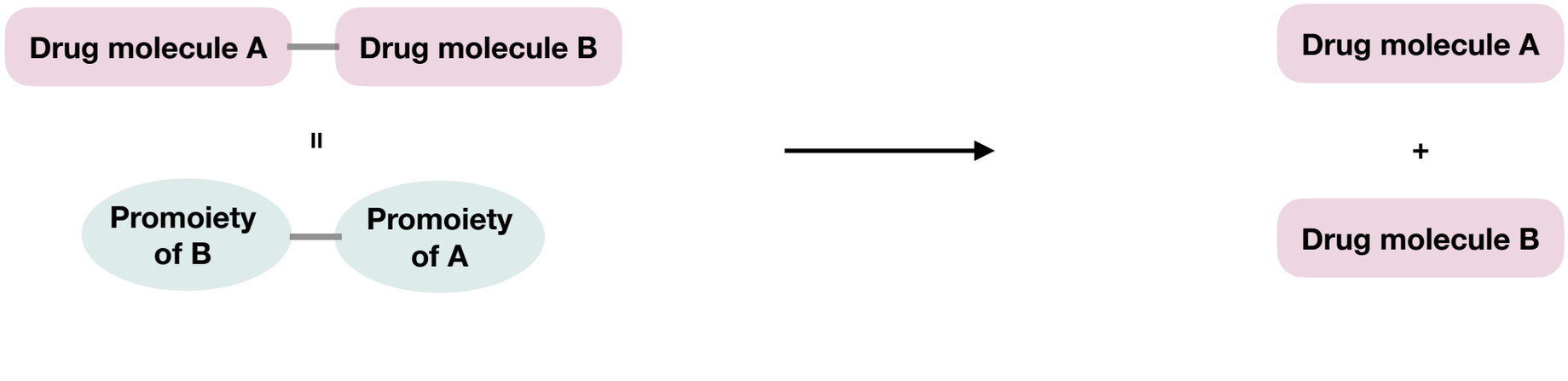
Mutual Prodrug

Mutual prodrug



"Co-drug"

Mutual prodrug



"Co-drug"

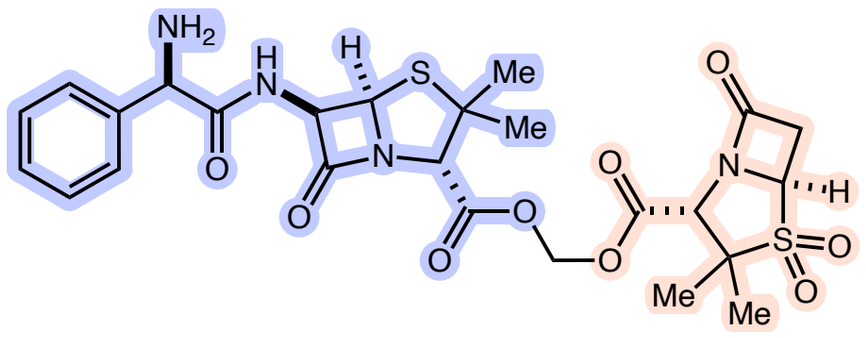
Mutual prodrug

Drug molecule A — **Drug molecule B**

II

Promoiety of B — **Promoiety of A**

"Co-drug"



Sultamicillin (Unasyn™)

Antibiotics

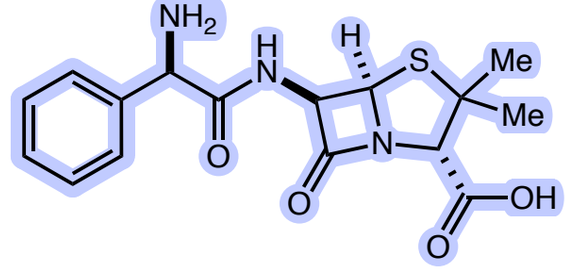
Treatment for gonorrhea

Hydrolysis by esterase

Drug molecule A

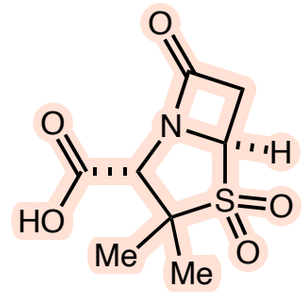
+

Drug molecule B



Ampicillin (β-lactam antibiotic)

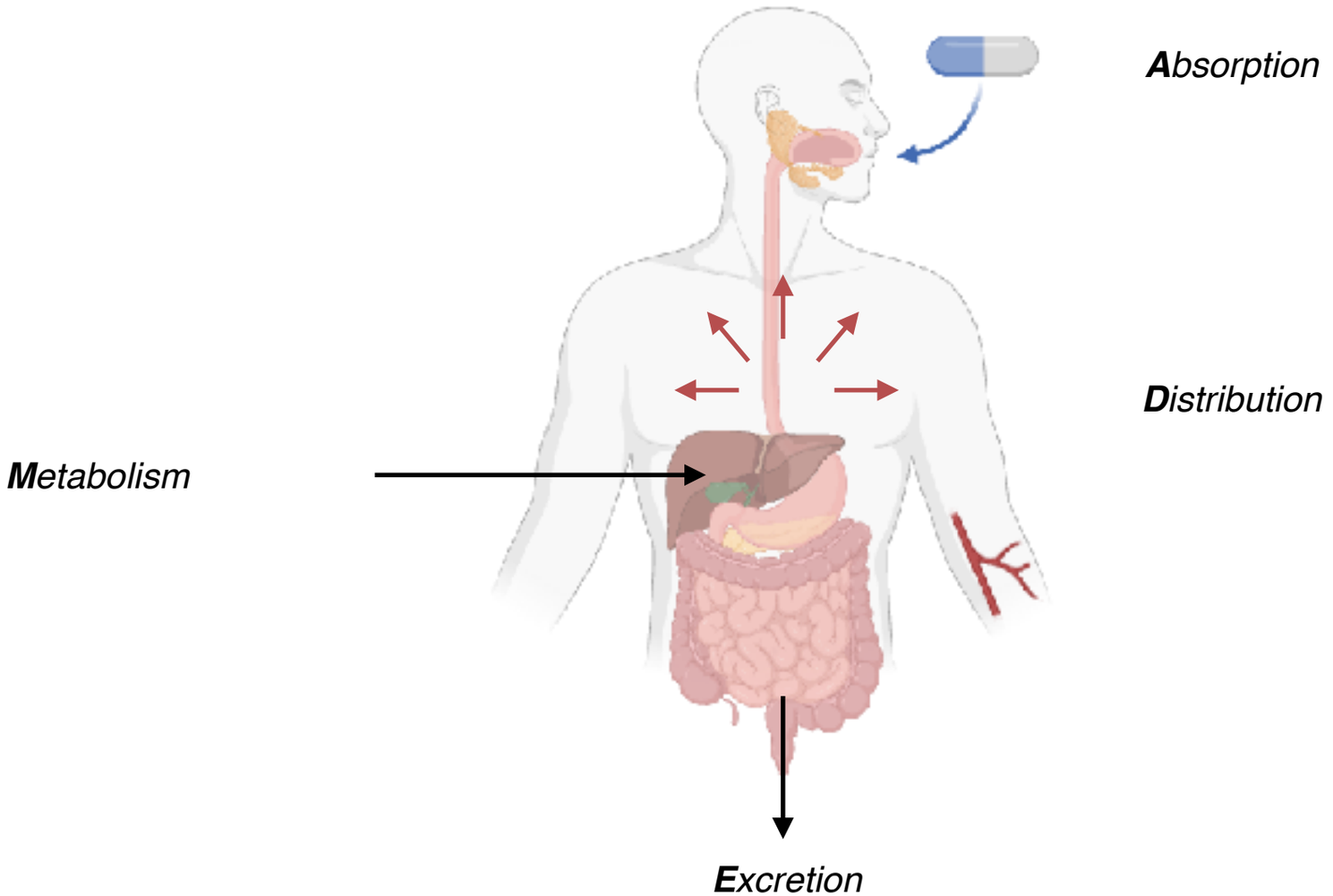
+



Sulbactam (β-lactamase inhibitor)

Active metabolites liberated at the same target

How do prodrugs improve drug-like properties?



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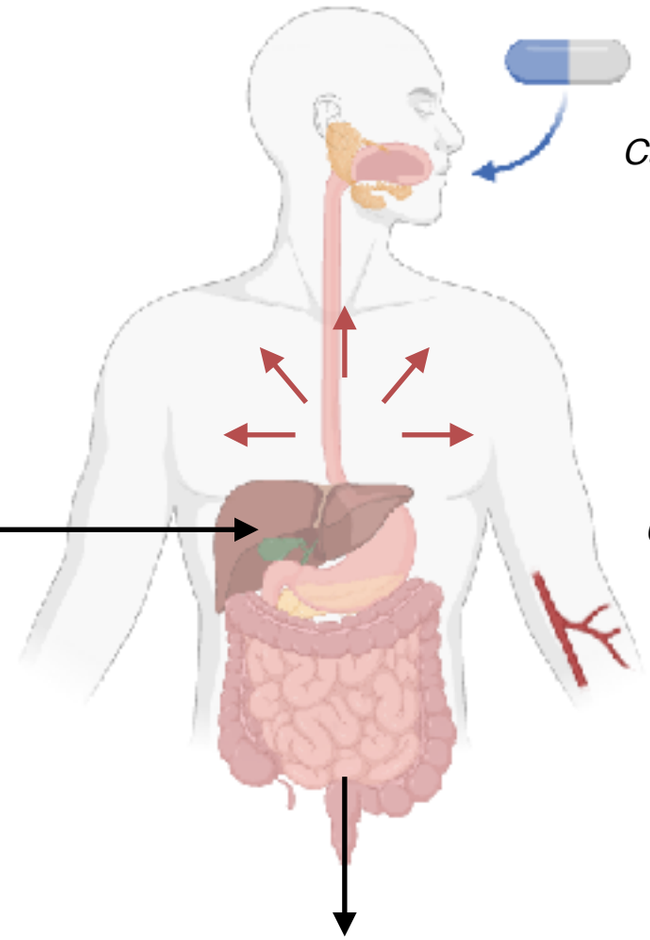


***A**bsorption*

Can the drug get into the body?

***D**istribution*

Can it reach the right tissue?

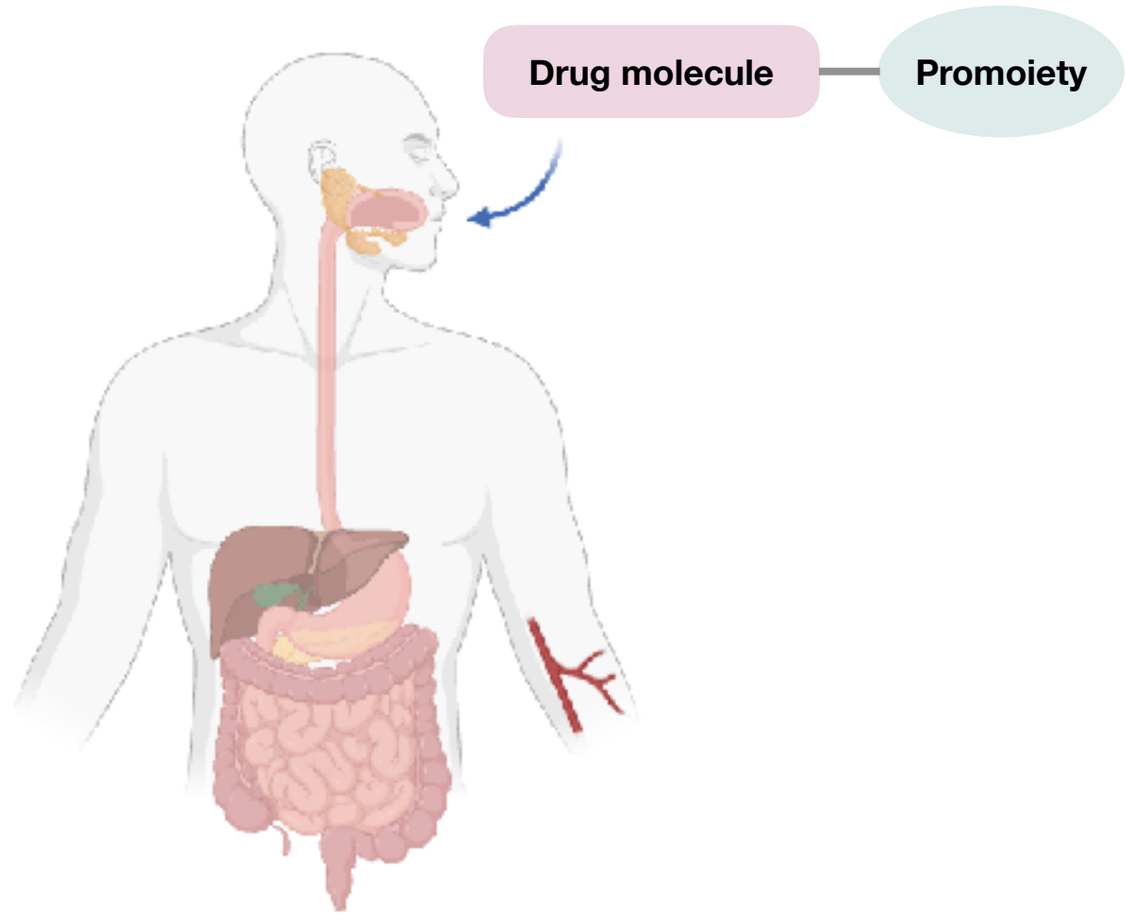
***M**etabolism*

How is it broken down?

***E**xcretion*

How fast is it cleared out?

How do prodrugs improve drug-like properties?



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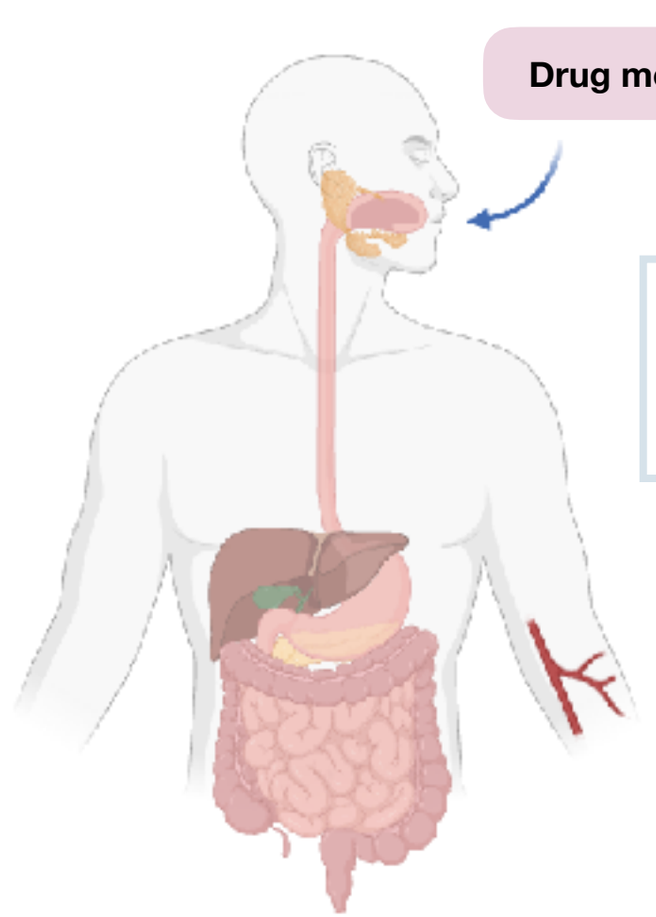
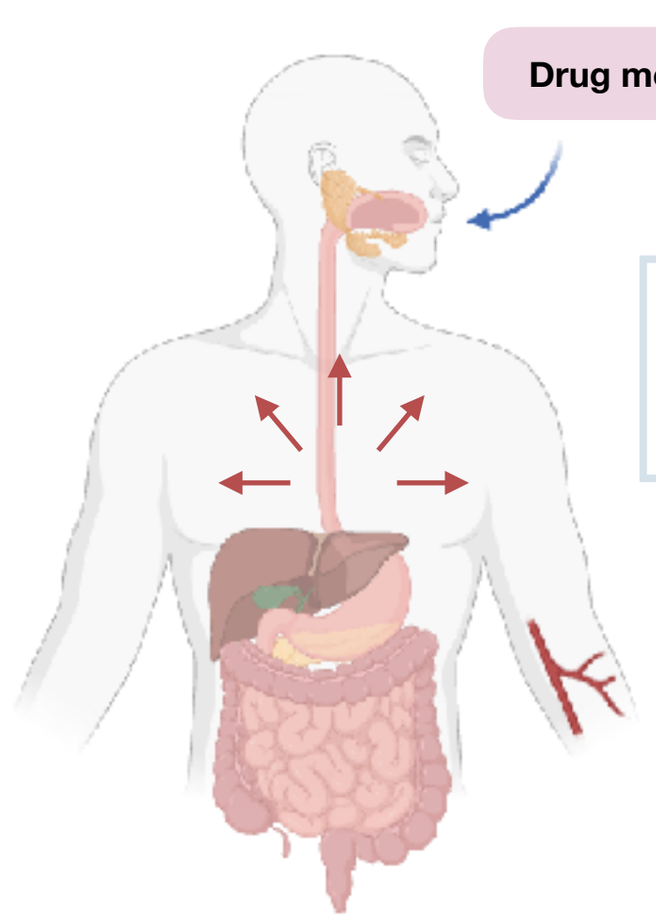


Drug molecule — **Promoiety**

***A**bsorption*

- *Higher aqueous solubility*
- *Better membrane premeation*

How do prodrugs improve drug-like properties?



Drug molecule — **Promoiety**

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- *Higher aqueous solubility*
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***D**istribution*

- *Effective concentrations at difficult-to-target tissues*

How do prodrugs improve drug-like properties?

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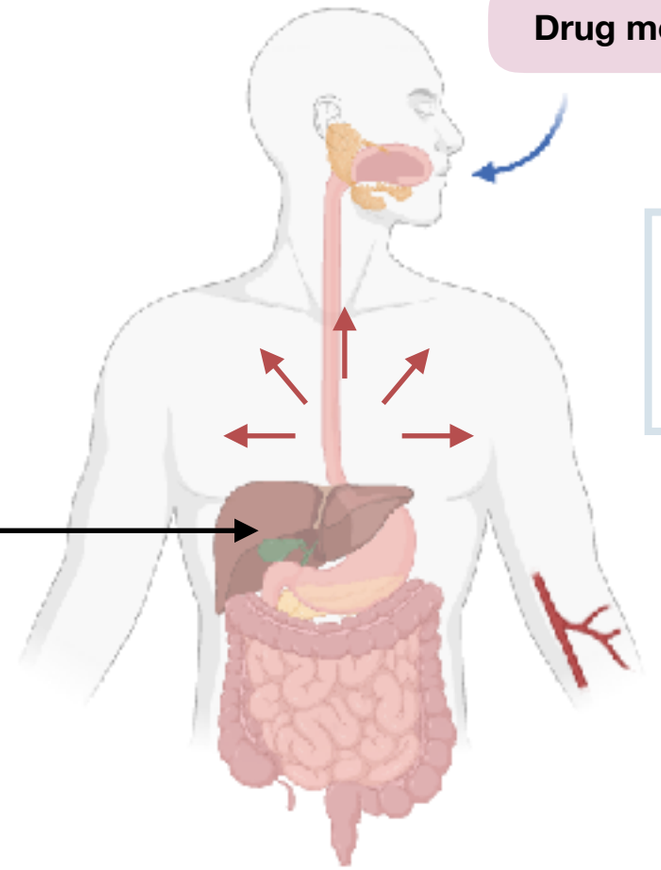

***A**bsorption*

- *Higher aqueous solubility*
- *Better membrane premeation*

***M**etabolism*

- *Protect active drugs from first-pass effect (pre-systemic metabolism)*

***D**istribution*

- *Effective concentrations at difficult-to-target tissues*

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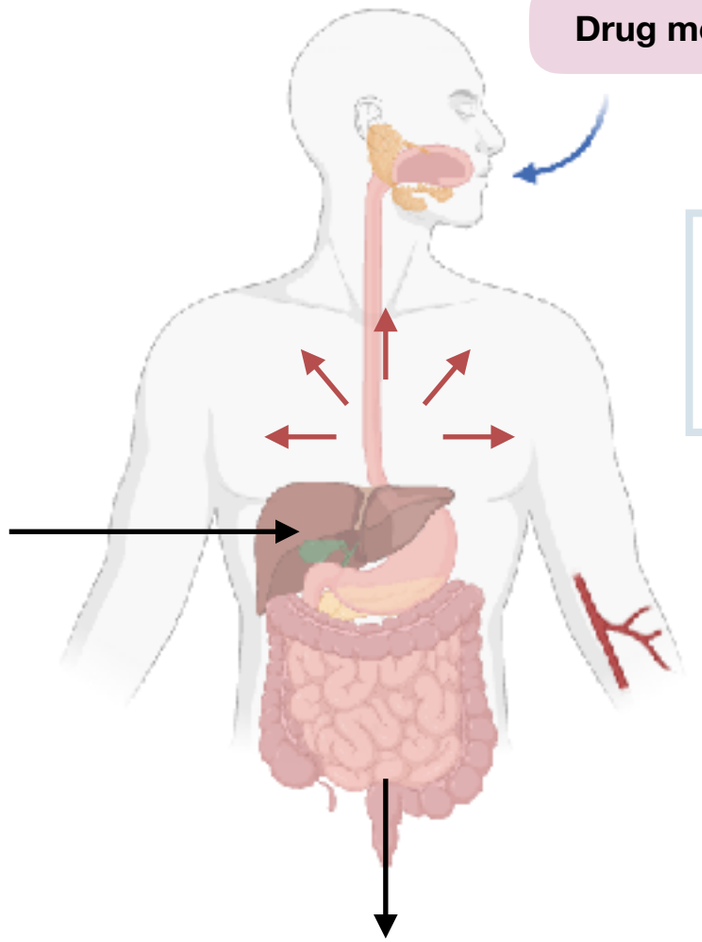


***A**bsorption*

- *Higher aqueous solubility*
- *Better membrane premeation*

***M**etabolism*

- *Protect active drugs from first-pass effect (pre-systemic metabolism)*

***D**istribution*

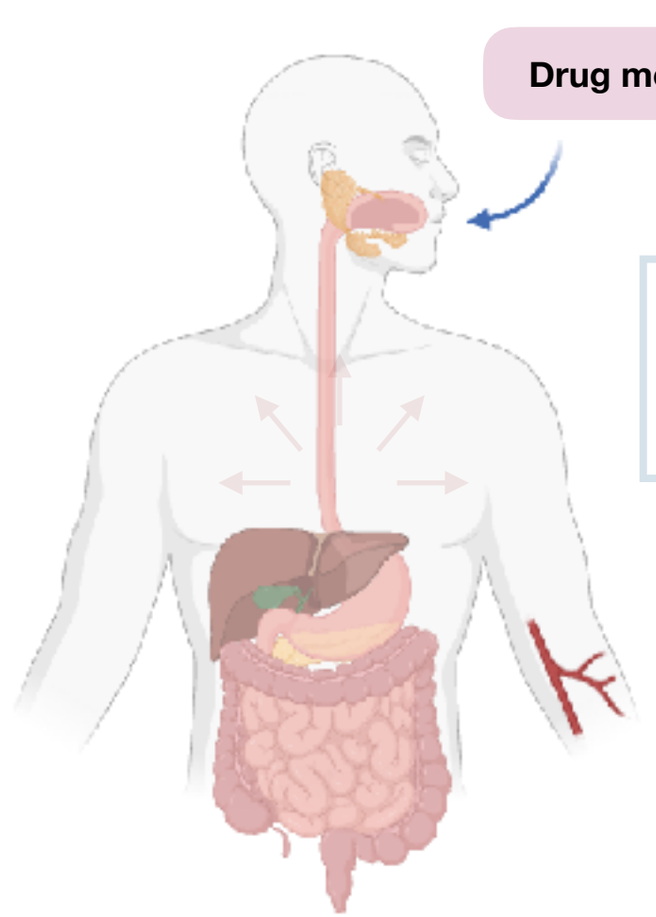
- *Effective concentrations at difficult-to-target tissues*

***E**xcretion*

- *Delayed excretion to reduce dosing frequency*

Prodrug design to improve 'A' in ADME

Absorption



Drug molecule — **Promoiety**

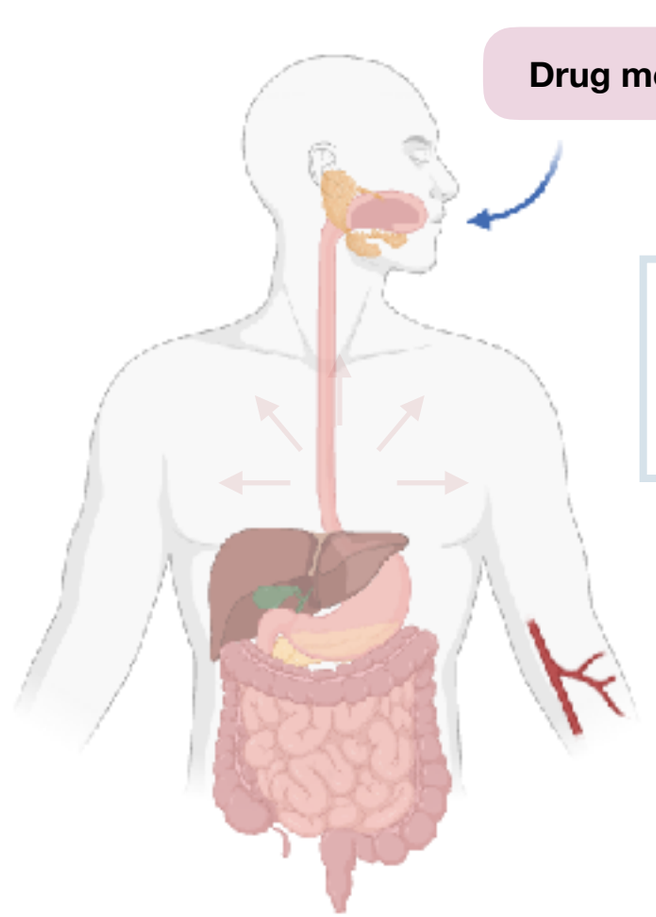
***A**bsorption*

- *Higher aqueous solubility*
- *Better membrane permeation*

- ***Increasing aqueous solubility***
  - *phosphate*
  - *non-phosphate*
- ***Increasing membrane permeation***
  - *ester*

Prodrug design to improve 'A' in ADME

Absorption



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- *Better membrane permeation*

- ***Increasing aqueous solubility***
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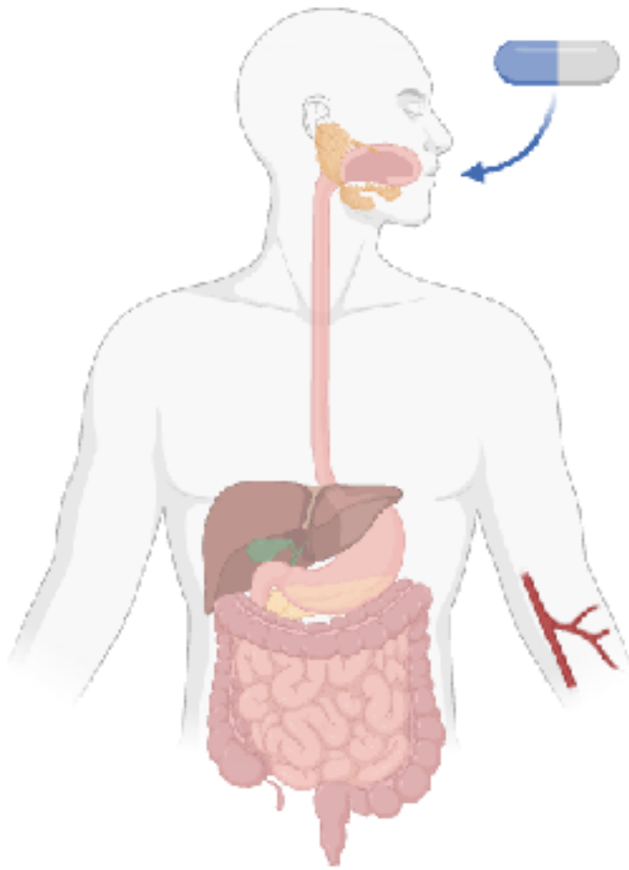
- *Increasing membrane permeation*
  - *ester*

Prodrug design to increase aqueous solubility

Why should drug be water-soluble

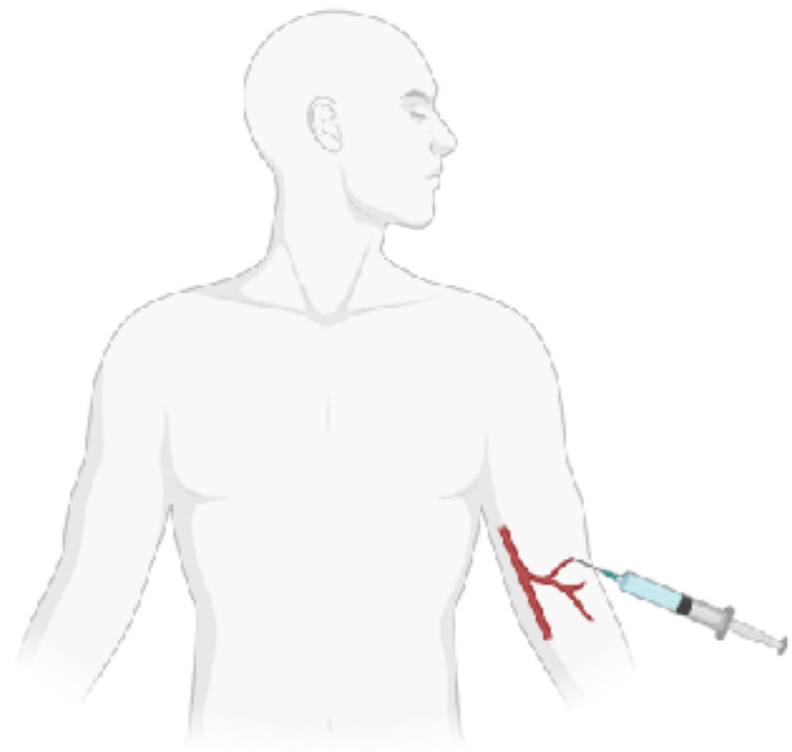


Oral intake

Aqueous solubility required to dissolve in GI fluids

Prodrug design to increase aqueous solubility

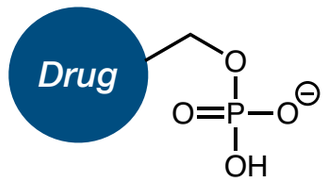
Why should drug be water-soluble



Parenteral administration (injection)

Aqueous solubility required to be formulated for injection

Phosphate prodrug design to increase aqueous solubility



Prodrug

(Phosphate linked via methylene bridge)

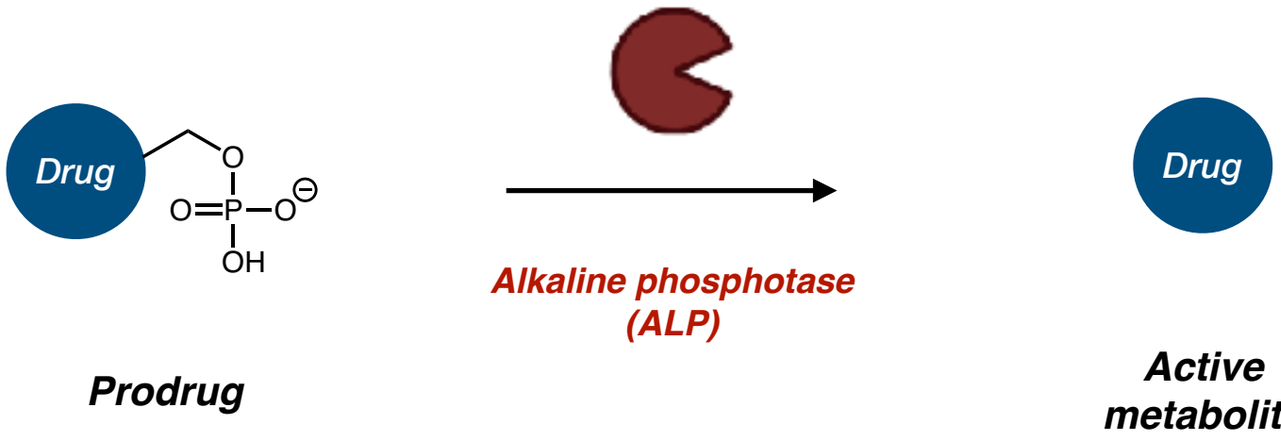
✓ *Stable in solution*

✓ *Dianionic form at most physiological pH values → aqueous solubility*

✓ *Work well for both oral and IV drugs*

Subbaiah, M. A. M.; Rautio, J.; Meanwell, N. A. *Chem. Soc. Rev.* **2024**, *53* (4), 2099.

Phosphate prodrug design to increase aqueous solubility



Prodrug ***Active metabolite***

✓ *Stable in solution*

✓ *Dianionic form at most physiological pH values → aqueous solubility*

✓ *Work well for both oral and IV drugs*

✓ *Quantitative conversion in vivo by alkaline phosphotase (ALP)*

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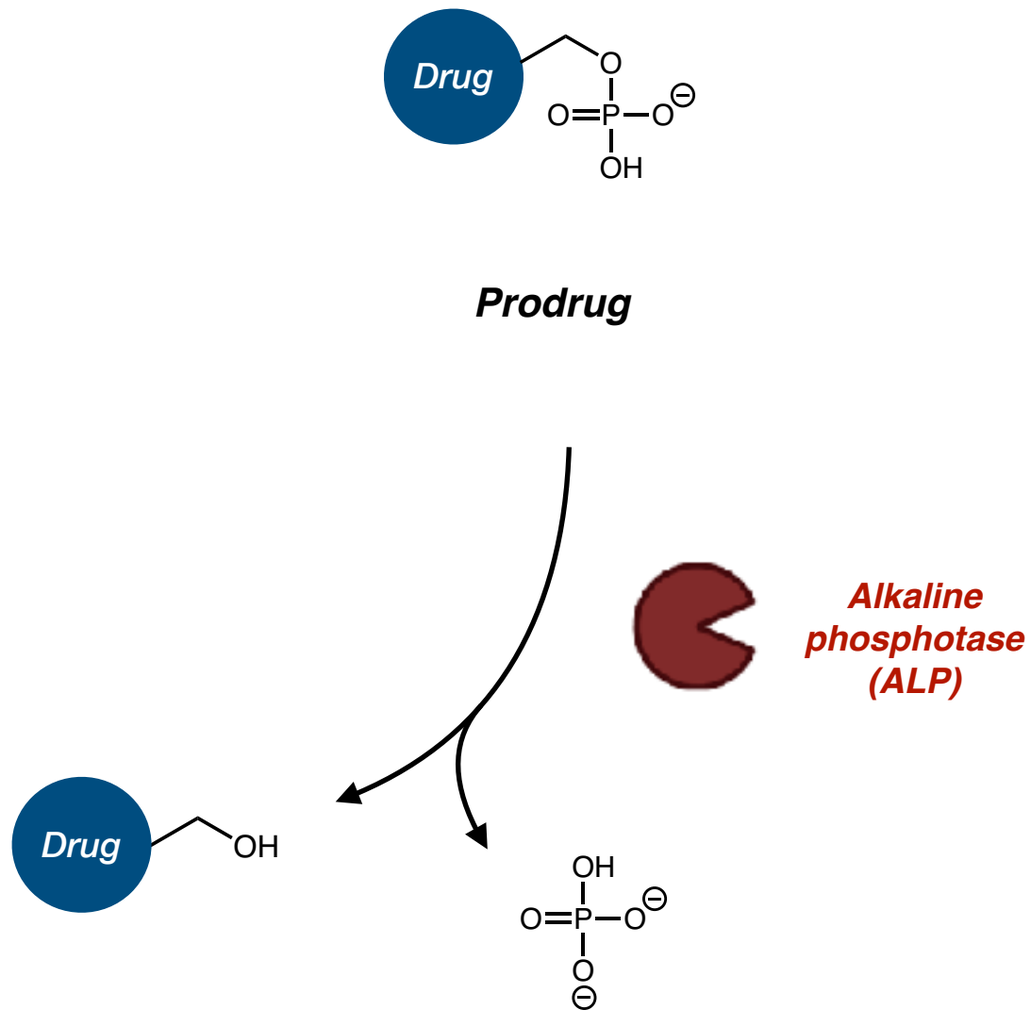
Phosphate prodrug design to increase aqueous solubility



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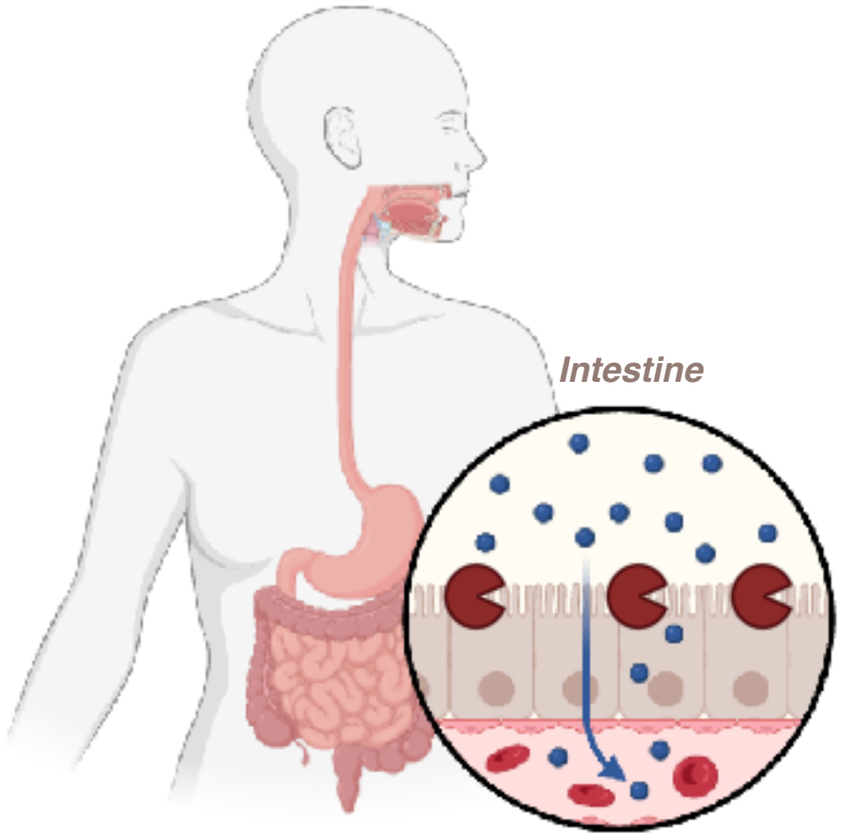
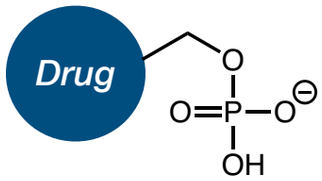
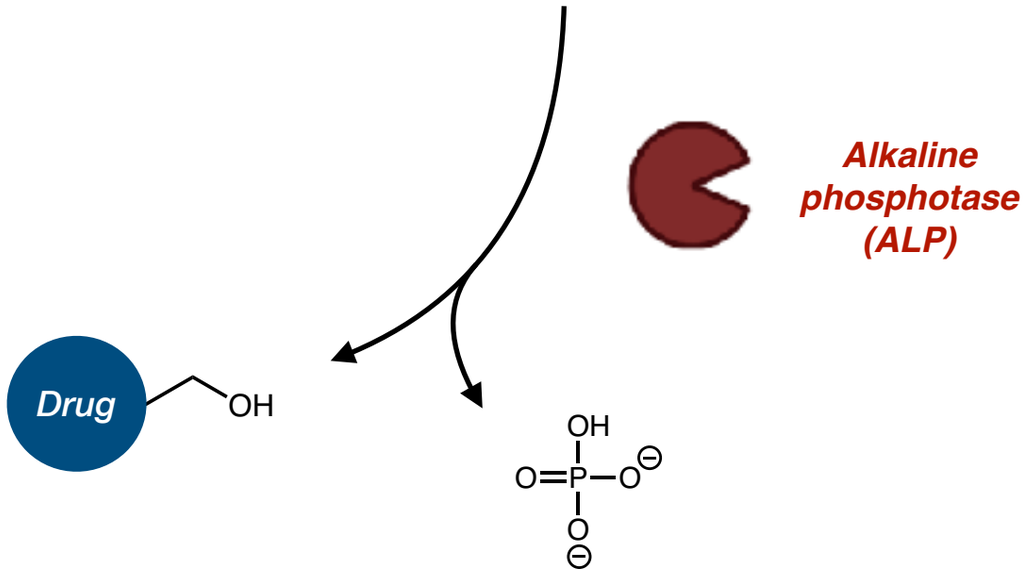


***ALP** is highly expressed on the brush border of intestine enterocytes*



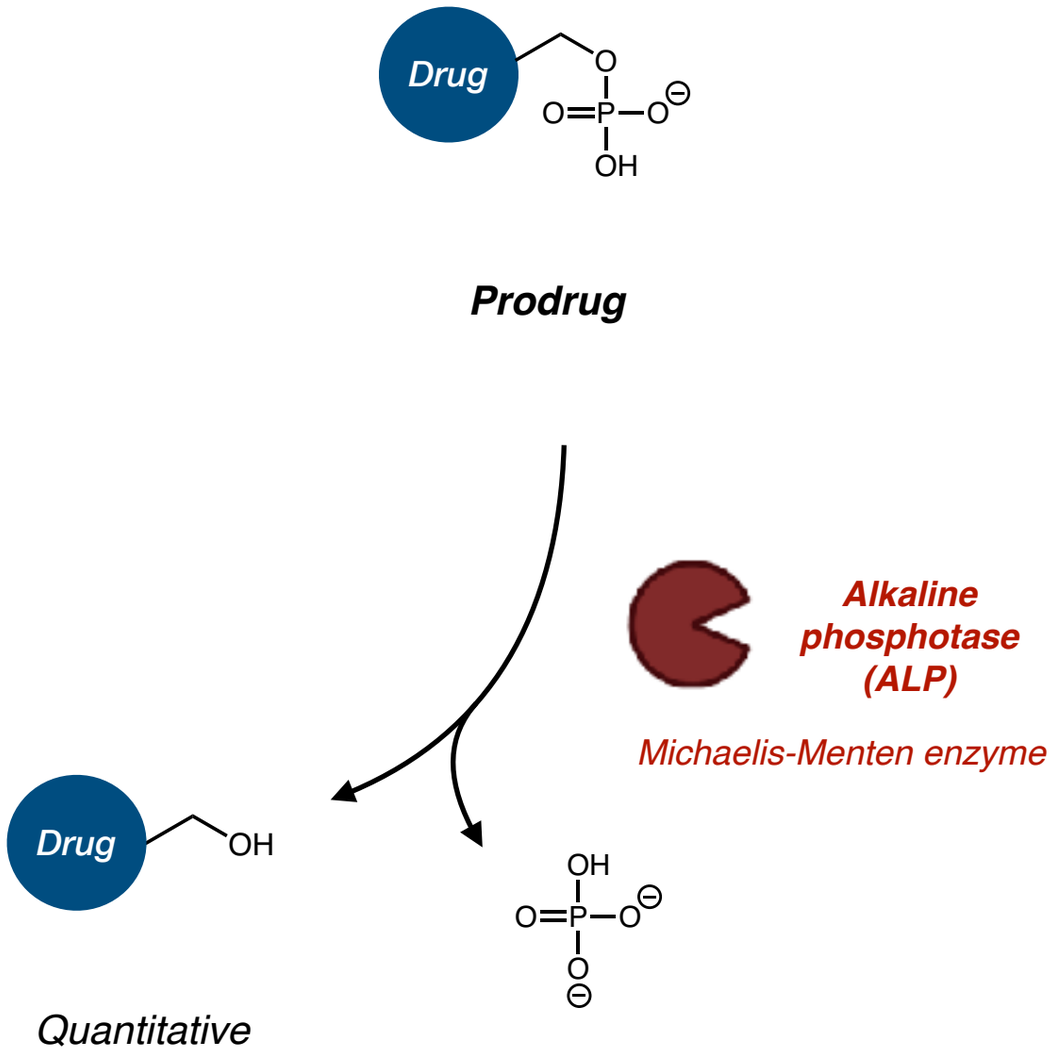
Prodrug



Alkaline phosphotase (ALP)

Subbaiah, M. A. M.; Rautio, J.; Meanwell, N. A. *Chem. Soc. Rev.* **2024**, *53* (4), 2099.

Phosphate prodrug design to increase aqueous solubility



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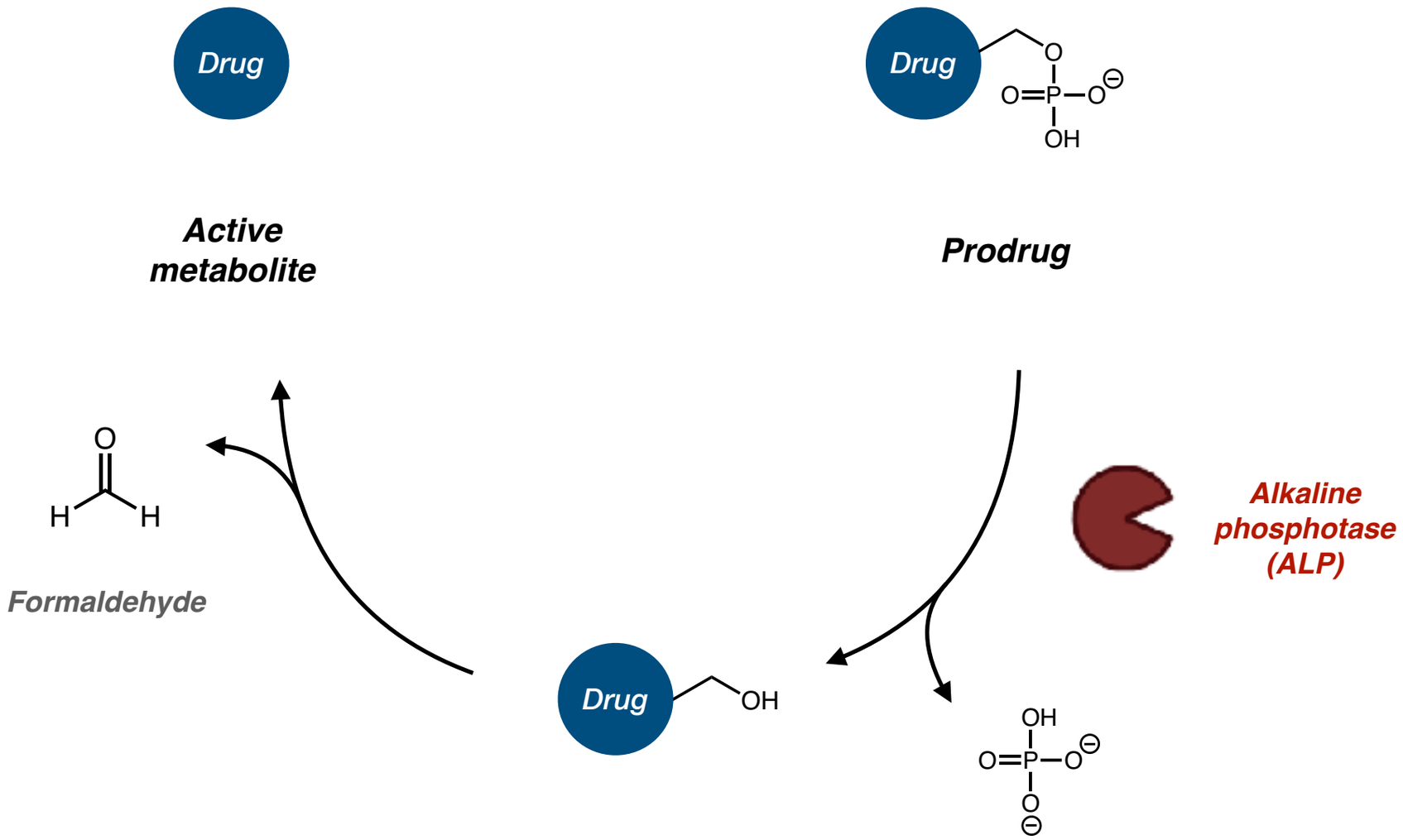

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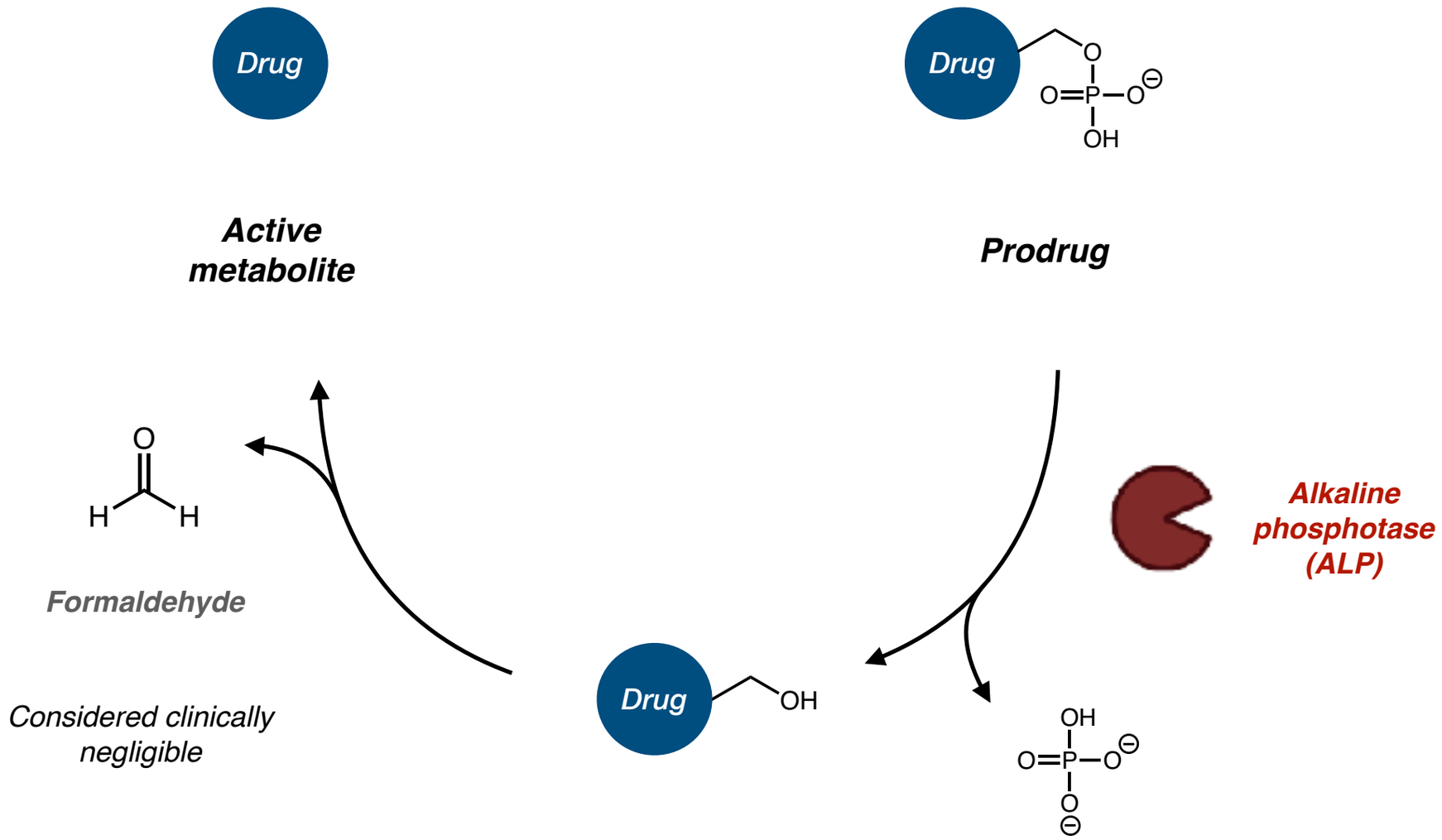
Phosphate prodrug design to increase aqueous solubility



Dhareshwar, S. S.; Stella, V. J. *J. Pharm. Sci.* **2008**, *97* (10), 4184.

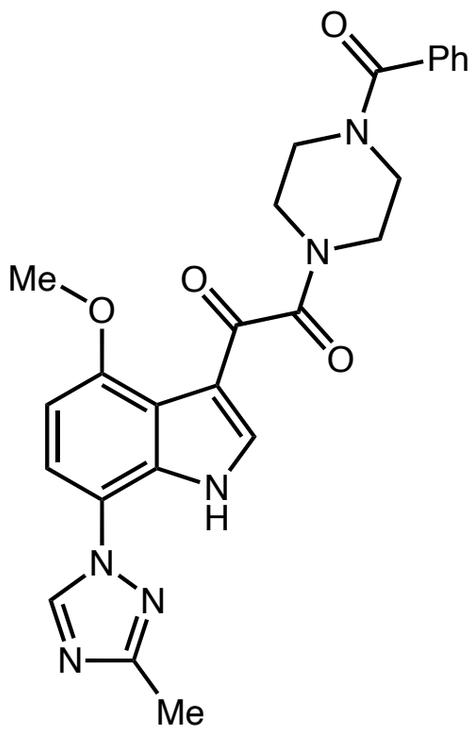
Phosphate prodrug design to increase aqueous solubility

Temsavir (Active metabolite) and Rukobia™ (phosphate prodrug)

Phosphate prodrug design to increase aqueous solubility

Temsavir (Active metabolite) and Rukobia™ (phosphate prodrug)

Temsavir



HIV-1 attachment inhibitor

Bristol Myers Squibb

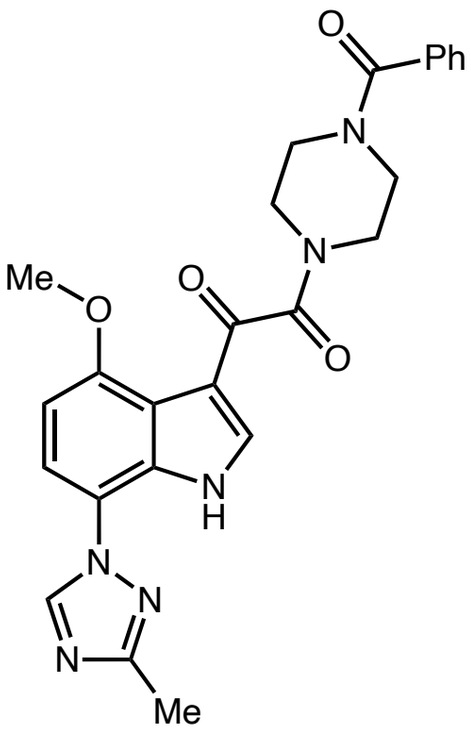
(2005)

Meanwell, N. A.; Krystal, M. R.; Nowicka-Sans, B.; Langley, D. R.; Conlon, D. A.; Eastgate, M. D.; Grasela, D. M.; Timmins, P.; Wang, T.; Kadow, J. F. *J. Med. Chem.* **2018**, *61* (1), 62.

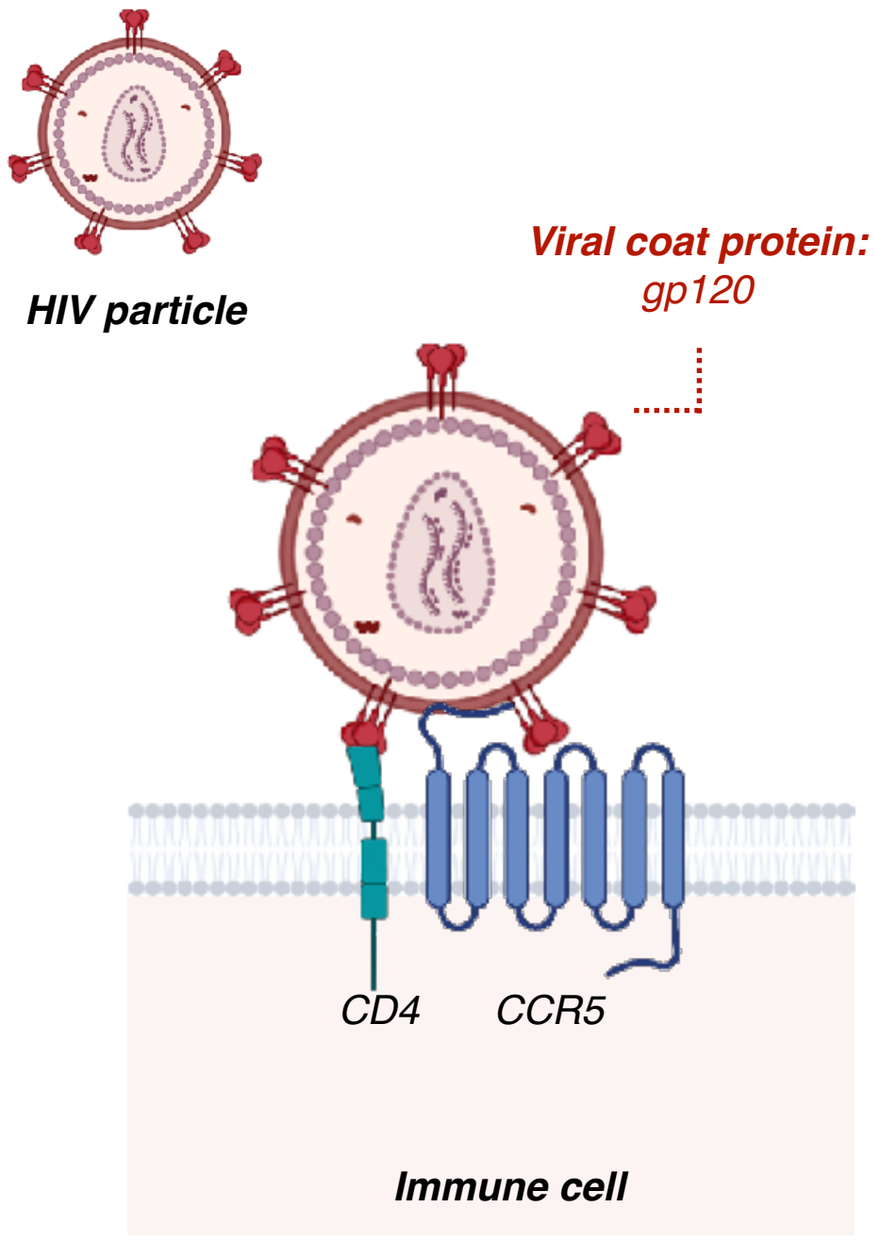
Phosphate prodrug design to increase aqueous solubility

Temsavir (Active metabolite) and Rukobia™ (phosphate prodrug)

Temsavir



HIV-1 attachment inhibitor

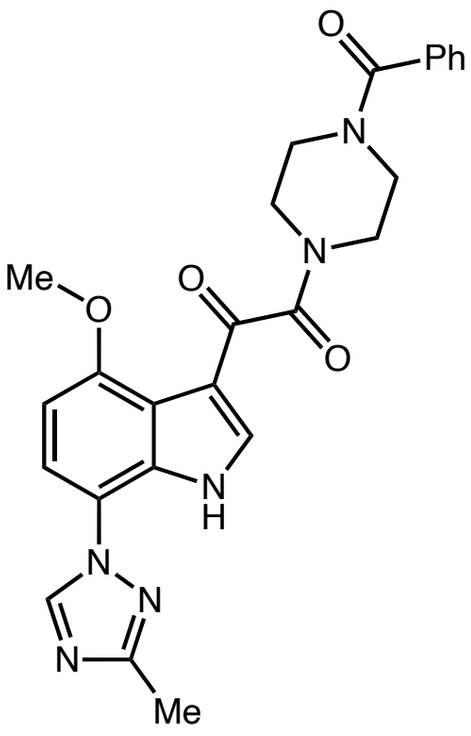


Meanwell, N. A.; Krystal, M. R.; Nowicka-Sans, B.; Langley, D. R.; Conlon, D. A.; Eastgate, M. D.; Grasela, D. M.; Timmins, P.; Wang, T.; Kadow, J. F. *J. Med. Chem.* **2018**, *61* (1), 62.

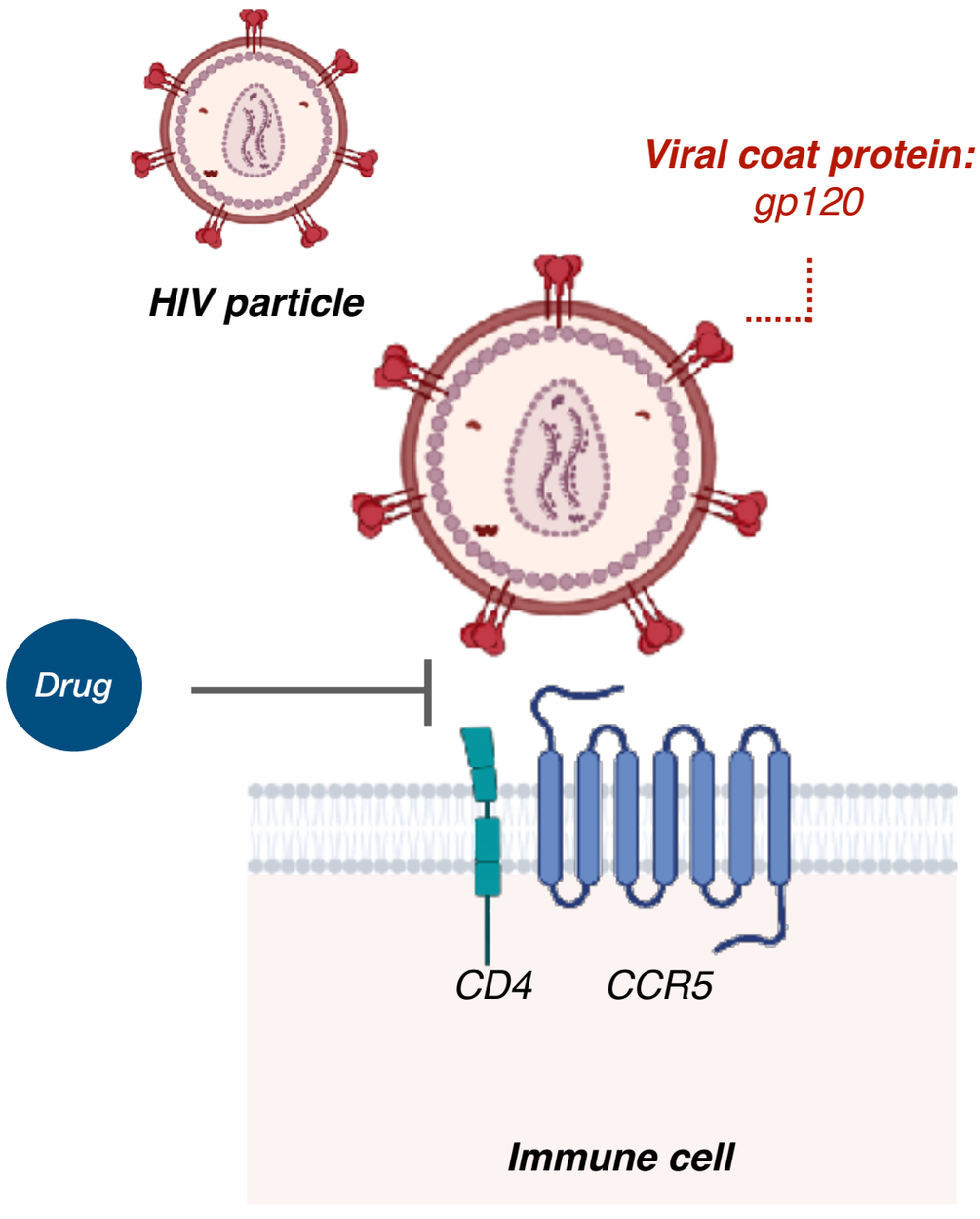
Phosphate prodrug design to increase aqueous solubility

Temsavir (Active metabolite) and Rukobia™ (phosphate prodrug)

Temsavir



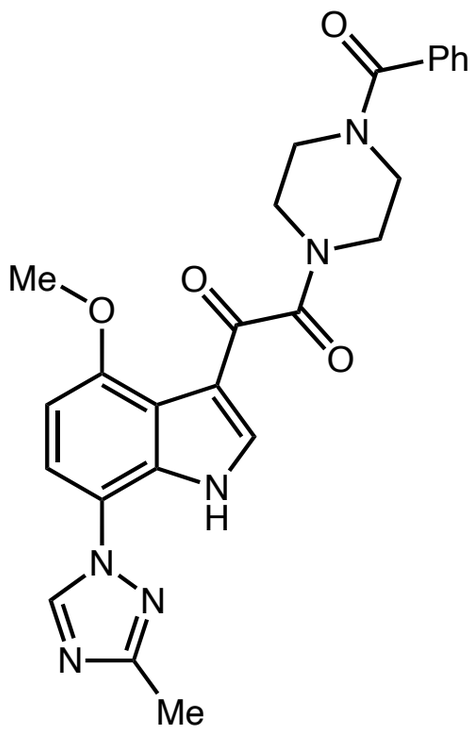
HIV-1 attachment inhibitor



Phosphate prodrug design to increase aqueous solubility

Temsavir (Active metabolite) and Rukobia™ (phosphate prodrug)

Temsavir



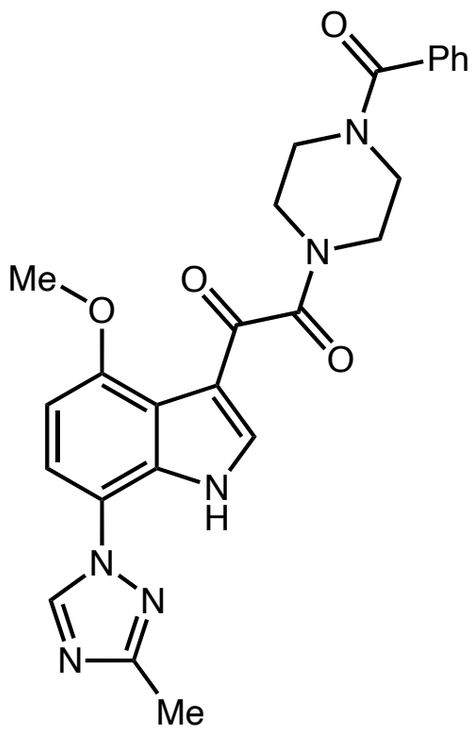
Aqueous solubility: 0.022mg/mL (pH 7.4)

Poor 'A' of ADME

Phosphate prodrug design to increase aqueous solubility

Temsavir (Active metabolite) and Rukobia™ (phosphate prodrug)

Temsavir



Aqueous solubility: 0.022mg/mL (pH 7.4)

Poor 'A' of ADME

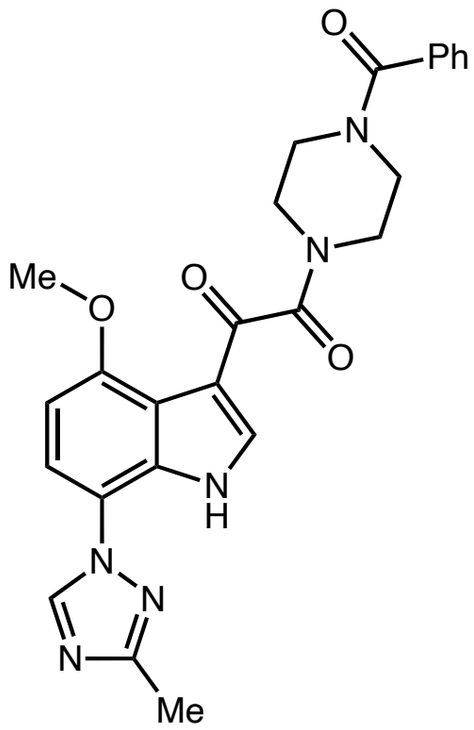
*Failed to show **dose-proportionality** in preclinical studies*

***Flip-flop** pharmacokinetic (PK) profile*

Phosphate prodrug design to increase aqueous solubility

Temsavir (Active metabolite) and Rukobia™ (phosphate prodrug)

Temsavir



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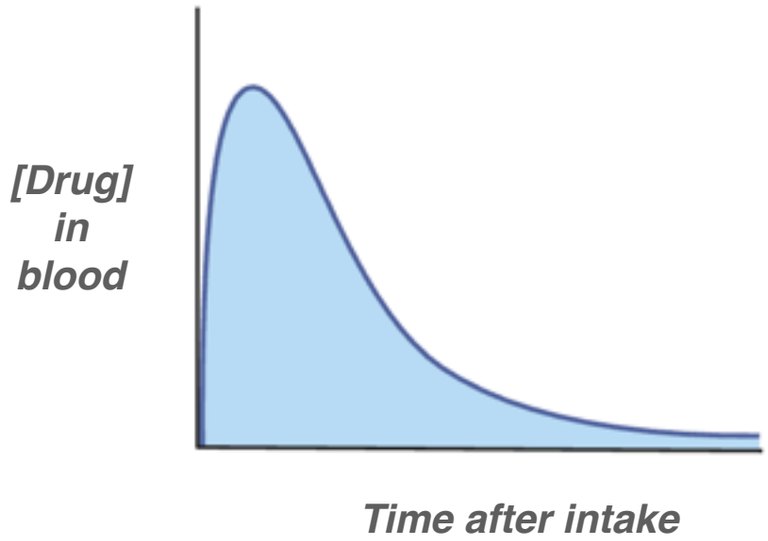
***Flip-flop** pharmacokinetic (PK) profile*

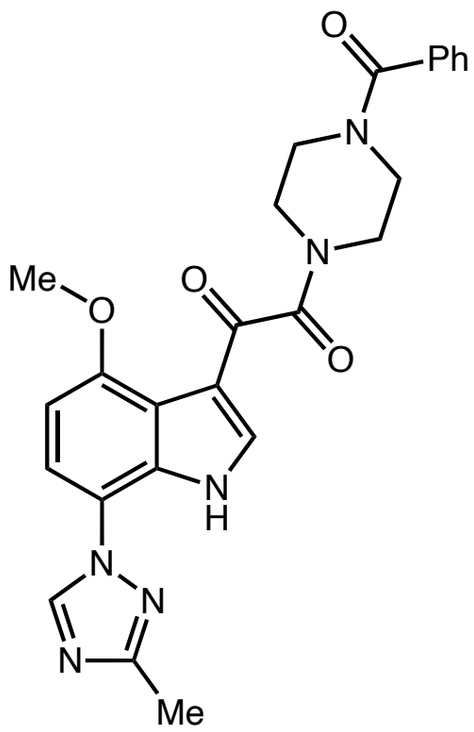
Normal PK profile (good absorption)



Phosphate prodrug design to increase aqueous solubility

Temsavir (Active metabolite) and Rukobia™ (phosphate prodrug)

Temsavir



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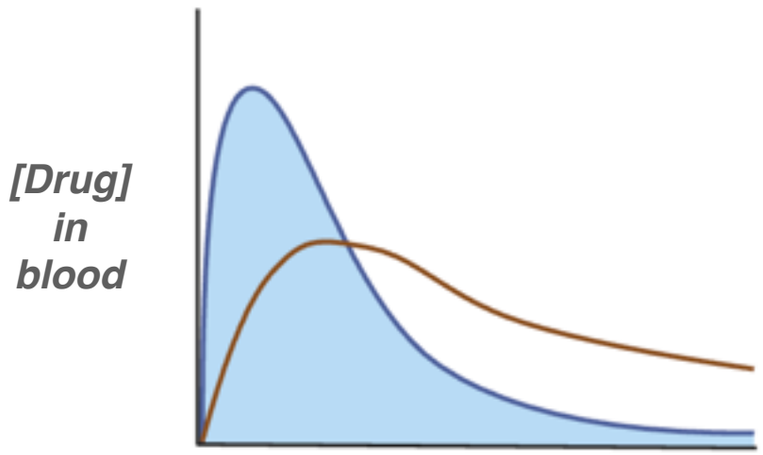
Poor 'A' of ADME

*Failed to show **dose-proportionality** in preclinical studies*

***Flip-flop** pharmacokinetic (PK) profile*

Normal PK profile (good absorption)

***Flip-flop PK profile** (bad absorption)*



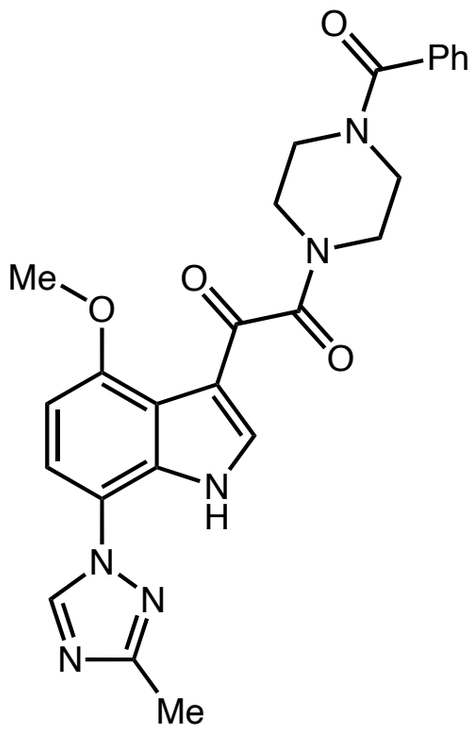
K_a (absorption constant) <<< K_e (elimination constant)

Half-life misinterpretation

Phosphate prodrug design to increase aqueous solubility

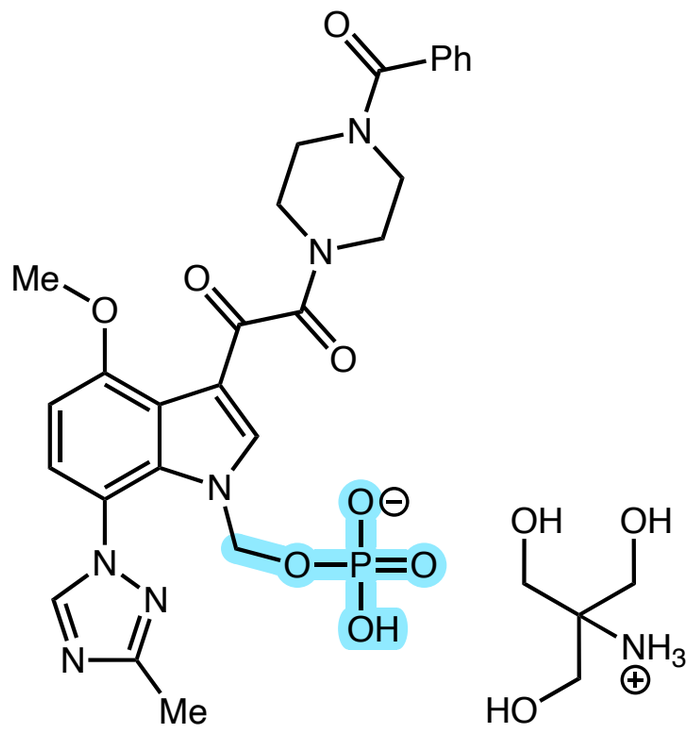
Temsavir (Active metabolite) and Rukobia™ (phosphate prodrug)

Temsavir



Aqueous solubility: 0.022 mg/mL (pH 7.4)

Rukobia™

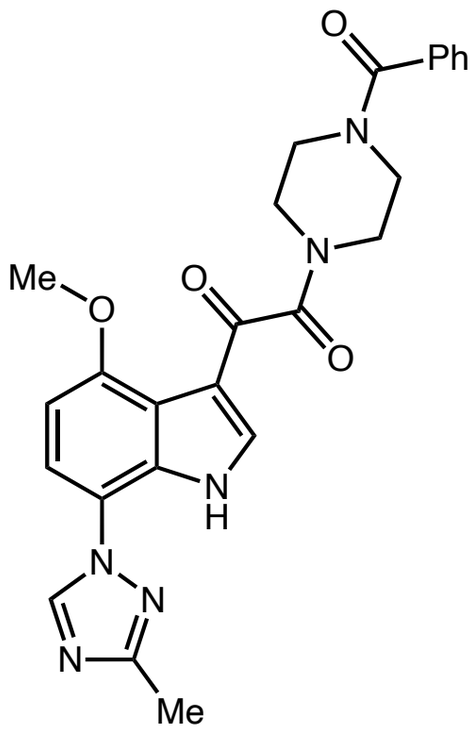


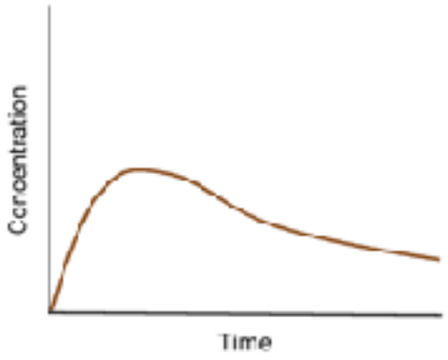
Aqueous solubility: 11 mg/mL (pH 1.5-8.2)

Phosphate prodrug design to increase aqueous solubility

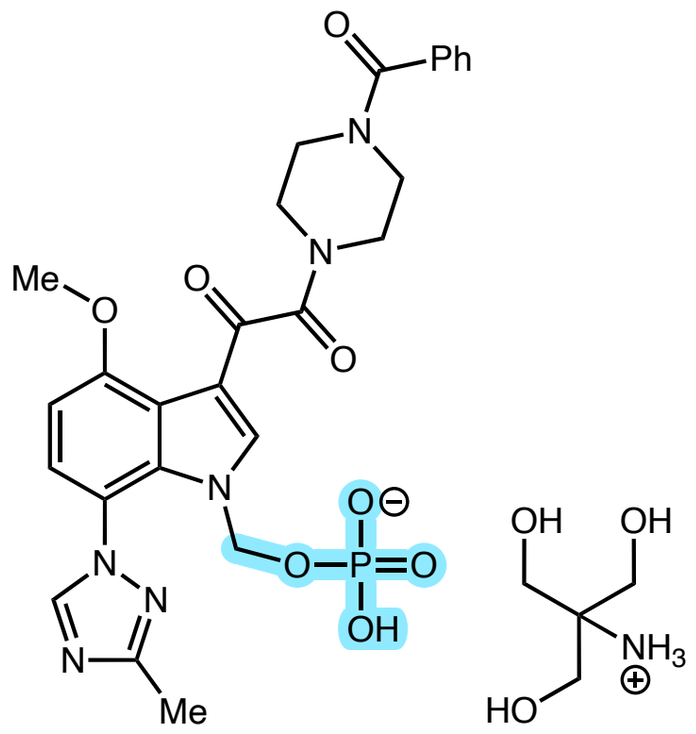
Temsavir (Active metabolite) and Rukobia™ (phosphate prodrug)

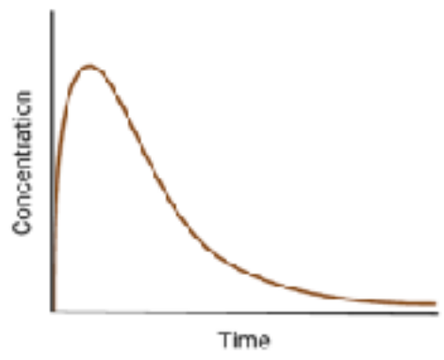
Temsavir





Rukobia™



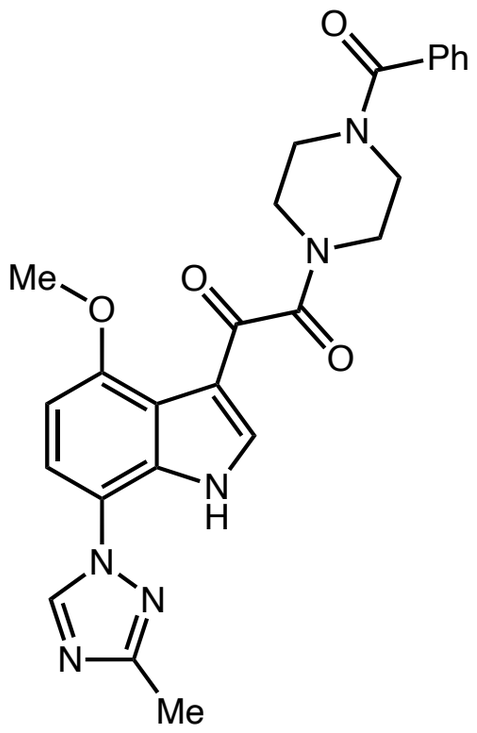


✓ *Enabled dose-proportionality and correct interpretation of half-life*

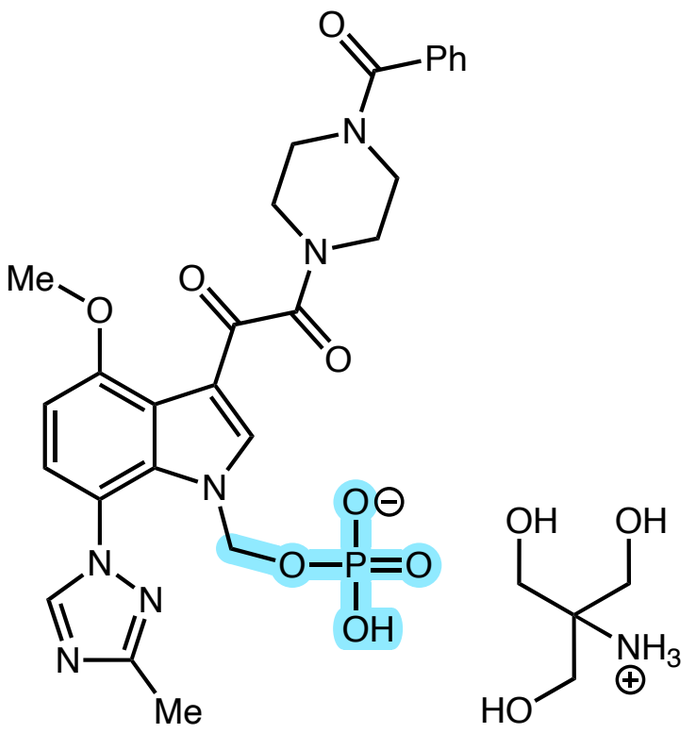
Phosphate prodrug design to increase aqueous solubility

Temsavir (Active metabolite) and Rukobia™ (phosphate prodrug)

Temsavir



Rukobia™



FDA approval in Jul 2020

Phosphate prodrug design to increase aqueous solubility

Propofol (active metabolite) and Fospropofol (phosphate prodrug)

Phosphate prodrug design to increase aqueous solubility

Propofol (active metabolite) and Fospropofol (phosphate prodrug)

THE TIMES

Friday June 26 2009 timesonline.co.uk

Newspaper of the Year 90p

Michael Jackson, the king of pop, dies at 50

● Star reported to have suffered heart attack ● British tour was due to start next month

Michael Jackson in the video for the single Billie Jean, taken from Thriller, the biggest-selling album in history

IN THE NEWS

There's a job to do, Brown tells The Times

Neda Soltan's legacy

Licence fee expenses

BP appoints chairman

Murray in a hurry

Farrah Fawcett
Charlie's Angels star and pin-up for a generation dies

First-time buyers
The return of the 100% mortgage

Bricks & Mortar

Michael Jackson Had 'Lethal Levels' of Propofol Before Death

Jackson Doc Conrad Murray admits giving the singer several drugs prior to death.

Phosphate prodrug design to increase aqueous solubility

Propofol (active metabolite) and Fospropofol (phosphate prodrug)

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"Milk of Amnesia"

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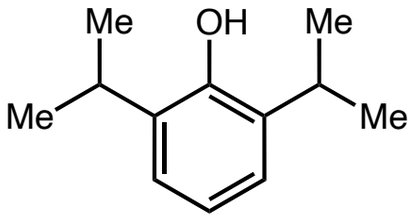
Phosphate prodrug design to increase aqueous solubility

Propofol (active metabolite) and Fospropofol (phosphate prodrug)

Diprivan™



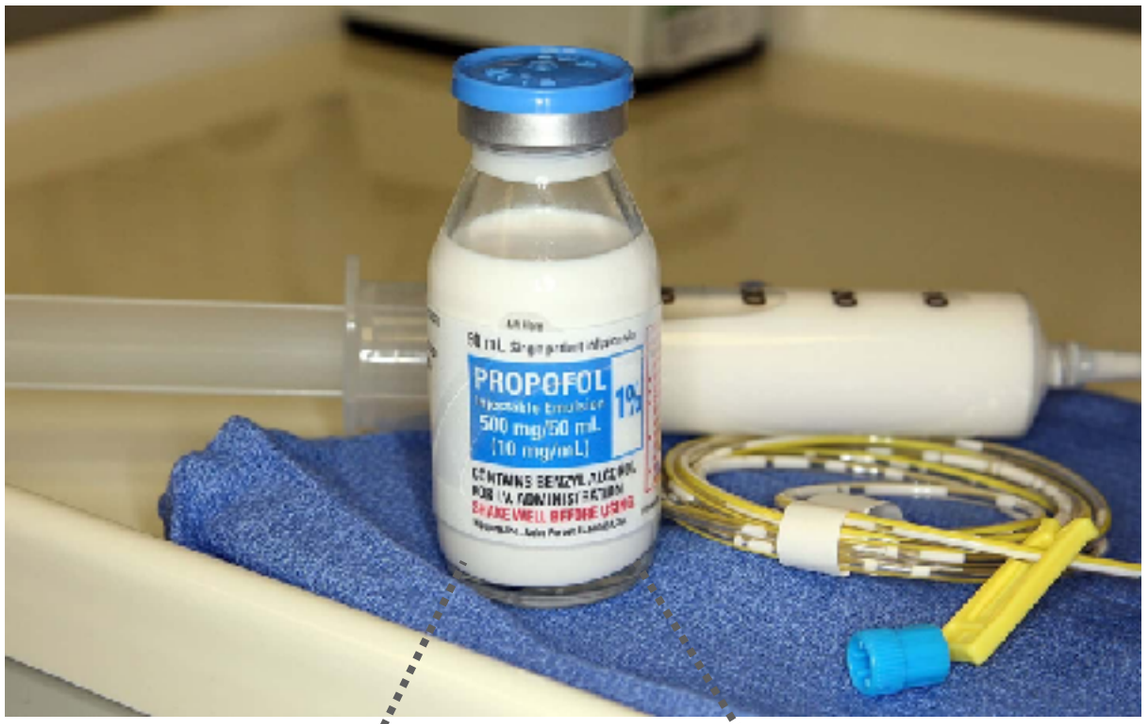
Propofol

Anesthetic

Approval in 1989

Aqueous solubility: 150 µg/mL

IV administration requires emulsion-based formulation



Propofol

Soybean oil (lipid base)

Egg lecithin (emulsifier)

Glycerol

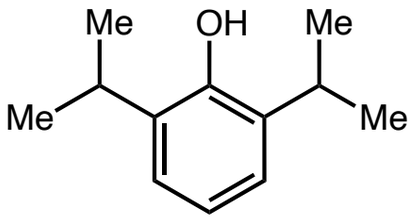
"Milk of Amnesia"

Baker, M. T.; Naguib, M.; Warltier, D. C. *Anesthesiology* **2005**, *103* (4).

Phosphate prodrug design to increase aqueous solubility

Diprivan™ (Active metabolite) and Lusedra™ (phosphate prodrug)

Diprivan™



Propofol

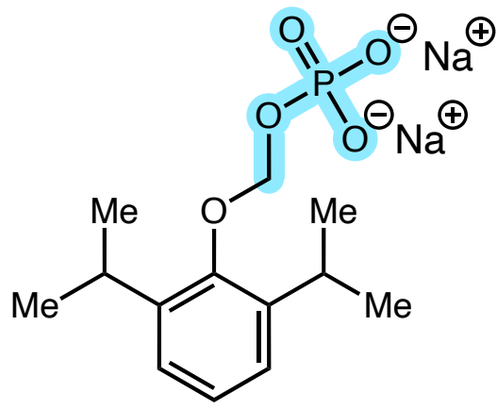
Anesthetic

Approval in 1989

Aqueous solubility: 150 µg/mL

IV administration requires emulsion-based formulation

Lusedra™



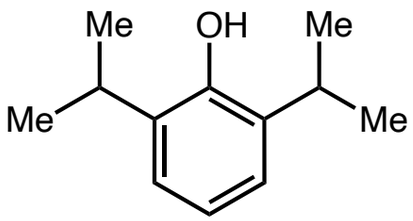
Fospropofol disodium

Eisai

Phosphate prodrug design to increase aqueous solubility

Diprivan™ (Active metabolite) and Lusedra™ (phosphate prodrug)

Diprivan™



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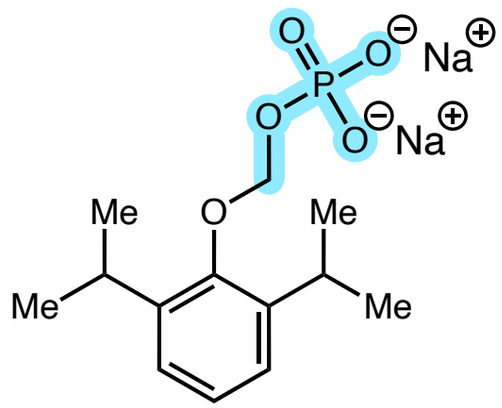
Lusedra™



Fospropofol disodium

Eisai

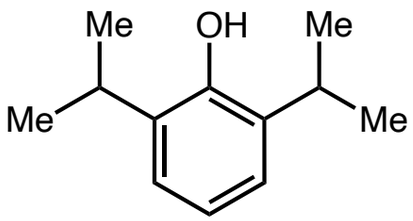
Aqueous solubility: 500 mg/mL

Schywalsky, M.; Ihmsen, H.; Tzabazis, A.; Fechner, J.; Burak, E.; Vornov, J.; Schwilden, H. *Eur. J. Anaesthesiol.* **2003**, *20* (3), 182.

Phosphate prodrug design to increase aqueous solubility

Diprivan™ (Active metabolite) and Lusedra™ (phosphate prodrug)

Diprivan™



Propofol

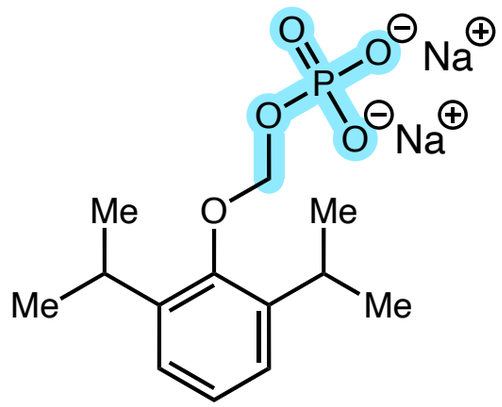
Anesthetic

Approval in 1989

Aqueous solubility: 150 µg/mL

IV administration requires emulsion-based formulation

Lusedra™



Fospropofol disodium

Aqueous solubility: 500 mg/mL

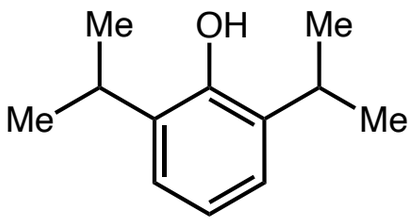
Clear solution

Schywalsky, M.; Ihmsen, H.; Tzabazis, A.; Fechner, J.; Burak, E.; Vornov, J.; Schwilden, H. *Eur. J. Anaesthesiol.* **2003**, *20* (3), 182.

Phosphate prodrug design to increase aqueous solubility

Diprivan™ (Active metabolite) and Lusedra™ (phosphate prodrug)

Diprivan™



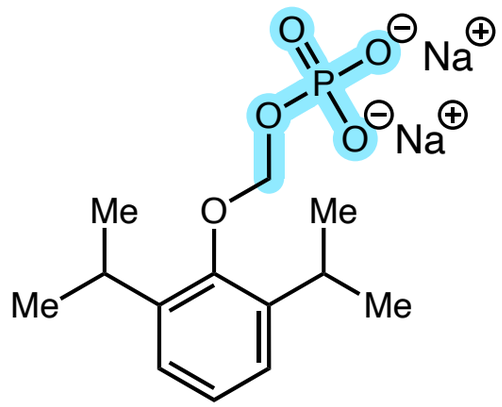
Propofol

Requires oil (lipid base) for emulsion formulation

✓ *Risk of contamination*

✓ *Risk of hyperlipidemia with prolonged use*

Lusedra™



Fospropofol disodium

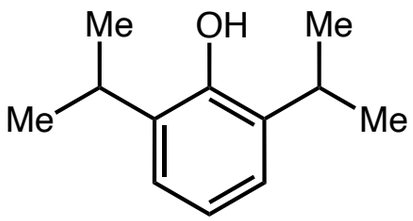
Risk eliminated

Schywalsky, M.; Ihmsen, H.; Tzabazis, A.; Fechner, J.; Burak, E.; Vornov, J.; Schwilden, H. *Eur. J. Anaesthesiol.* **2003**, *20* (3), 182.

Phosphate prodrug design to increase aqueous solubility

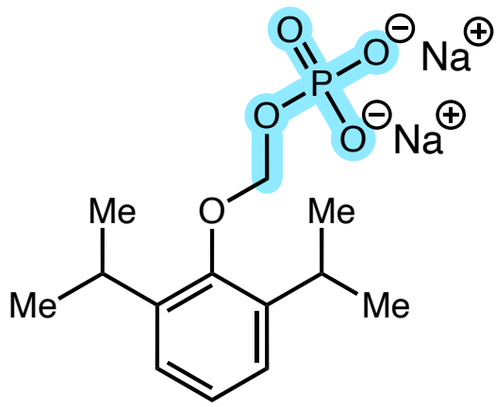
Diprivan™ (Active metabolite) and Lusedra™ (phosphate prodrug)

Diprivan™



Propofol

Lusedra™



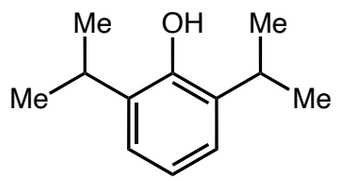
Fospropofol disodium

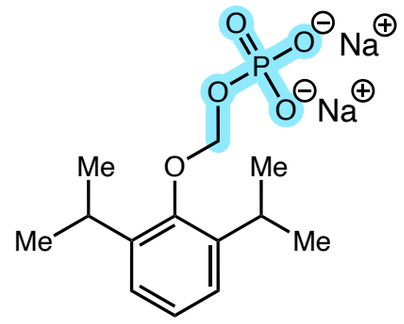
Discontinued in 2012 due to poor sales

Why?

Phosphate prodrug design to increase aqueous solubility

Diprivan™ (Active metabolite) and Lusedra™ (phosphate prodrug)



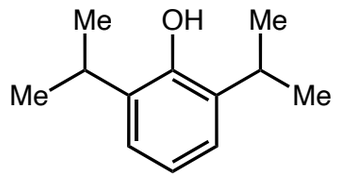


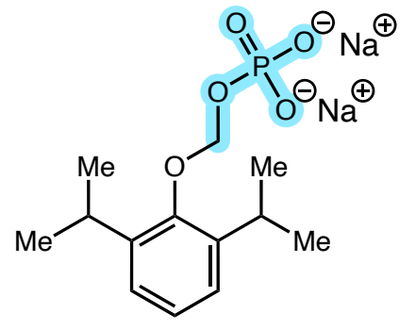
MAC sedation	Propofol	Fospropofol
Dosing[a,b]	1–2 mg/kg[b]	6.5 mg/kg[a]
Formulation	Lipid Emulsion	Aqueous
Pharmacokinetics	Propofol C_{max} following 2 mg/kg dose = 2.023 ± 0.516 mcg/mL at 2 mi Multiple elimination half-lives Distribution half-life = 1–4 min First elimination half-life = 30–60 min Terminal half-life = 1.5–11 hrs Vd = variable (3–60 L/kg)	Propofol C_{max} following 6 mg/kg FP dose = 1.08 ± 0.33 mcg/mL at 12 min FP hydrolysis half-life = 7.2 min FP terminal half-life = 0.81 hrs FP Vd = 0.33 ± 0.069 L/kg
Pharmacodynamics	Onset: seconds to 1 min[c] Duration: 3–10 min[c]	Onset: 4–8 min[c] Duration: 5–18 min[c]
Current Clinical Applications	MAC sedation, short-term procedural sedation,[d] sedation of mechanically ventilated patient, general anesthesia	MAC sedation, short-term procedural sedation[d]
Common adverse effects	Injection site pain	Pruritus, paresthesia
Serious adverse effects	Hypoxemia, apnea, hypotension, bradycardia	Hypoxemia, apnea, hypotension

Mueller, S. W.; Moore, G. D.; MacLaren, R. *Clin. Med. Insights Ther.* **2010**, *2*, 1179559X1000200003.

Phosphate prodrug design to increase aqueous solubility

Diprivan™ (Active metabolite) and Lusedra™ (phosphate prodrug)





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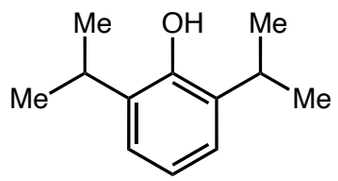
Common adverse effects	Injection site pain	Pruritus, paresthesia
Serious adverse effects	Hypoxemia, apnea, hypotension, bradycardia	Hypoxemia, apnea, hypotension

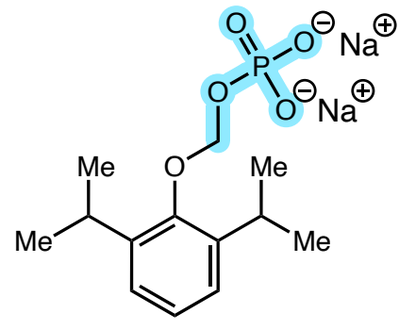
Slower onset of sedation limits appeal for rapid procedure (ex. endoscopy)

Mueller, S. W.; Moore, G. D.; MacLaren, R. *Clin. Med. Insights Ther.* **2010**, *2*, 1179559X1000200003.

Phosphate prodrug design to increase aqueous solubility

Diprivan™ (Active metabolite) and Lusedra™ (phosphate prodrug)





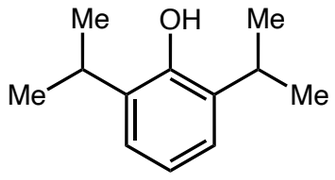
MAC sedation	Propofol	Fospropofol
Dosing[a,b]	1–2 mg/kg[b]	6.5 mg/kg[a]
Formulation	Lipid Emulsion	Aqueous
Pharmacokinetics	Propofol C_{max} following 2 mg/kg dose – 2.023 ± 0.516 mcg/mL at 2 mi Multiple elimination half-lives Distribution half-life = 1–4 min First elimination half-life = 30–60 min Terminal half-life = 1.5–11 hrs Vd – variable (3–60 L/kg)	Propofol C_{max} following 6 mg/kg FP dose – 1.08 ± 0.33 mcg/mL at 12 min FP hydrolysis half-life = 7.2 min FP terminal half-life = 0.81 hrs FP Vd – 0.33 ± 0.069 L/kg
Pharmacodynamics	Onset: seconds to 1 min[c] Duration: 3–10 min[c]	Onset: 4–8 min[c] Duration: 5–18 min[c]
Current Clinical Applications	MAC sedation, short-term procedural sedation,[d] sedation of mechanically ventilated patient, general anesthesia	MAC sedation, short-term procedural sedation[d]
Common adverse effects	Injection site pain	Pruritus, paresthesia
Serious adverse effects	Hypoxemia, apnea, hypotension, bradycardia	Hypoxemia, apnea, hypotension

Lusedra™ (fospropofol): Severe itching/burning (pruritus) in perineal region

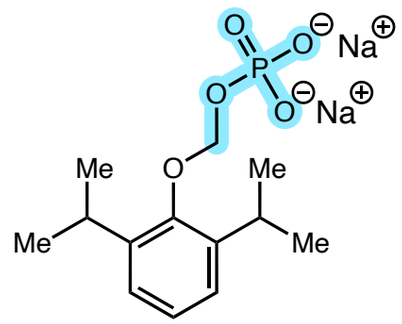
Mueller, S. W.; Moore, G. D.; MacLaren, R. *Clin. Med. Insights Ther.* **2010**, *2*, 1179559X1000200003.

Phosphate prodrug design to increase aqueous solubility

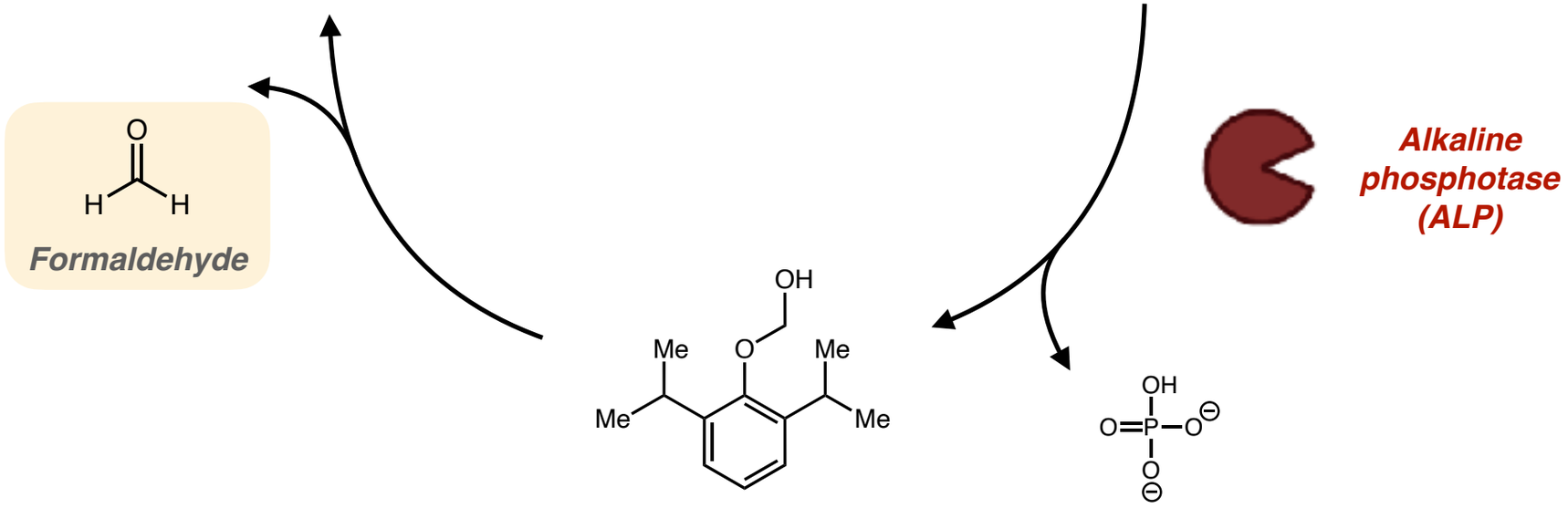
Diprivan™ (Active metabolite) and Lusedra™ (phosphate prodrug)



Active metabolite



Prodrug

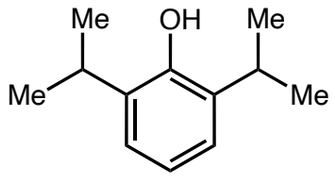


Formaldehyde suspected, though not clinically confirmed

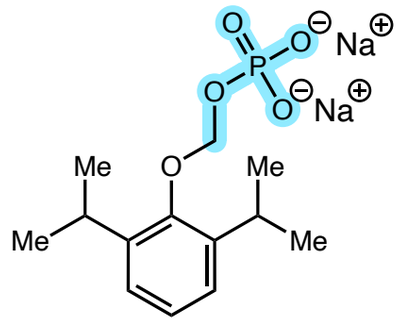
Atlas, G. *J. Anaesthesiol. Clin. Pharmacol.* **2011**, *27* (3), 303.

Phosphate prodrug design to increase aqueous solubility

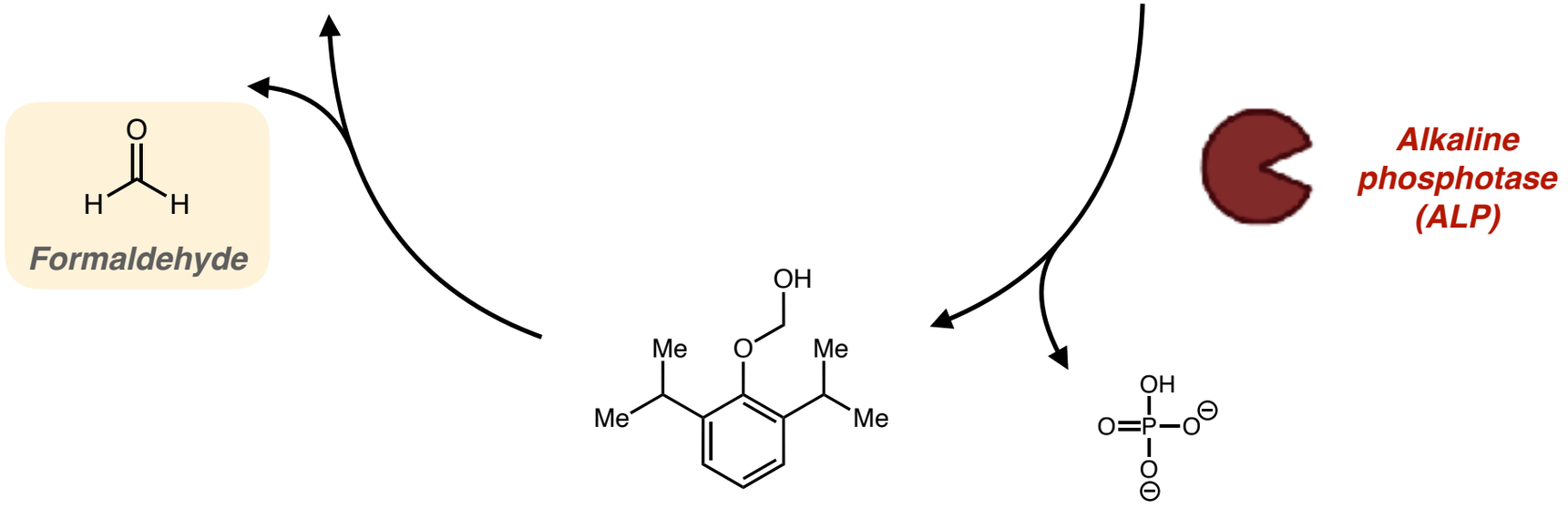
Diprivan™ (Active metabolite) and Lusedra™ (phosphate prodrug)



Active metabolite



Prodrug



Phosphate prodrug can improve 'A' in ADME, but success depends on clinical context

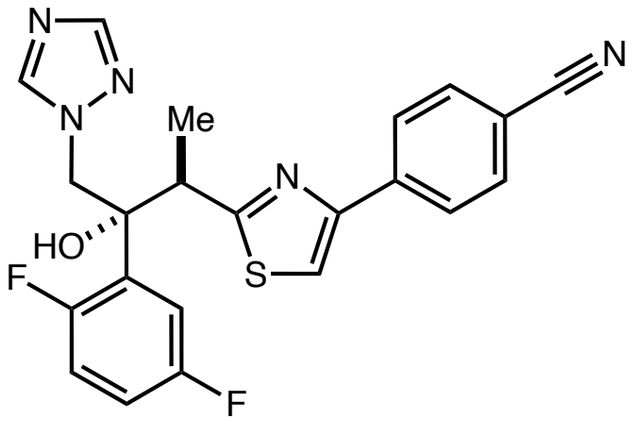
Non-phosphate prodrug design to increase aqueous solubility

Acyloxyalkyl triazolium salt

Non-phosphate prodrug design to increase aqueous solubility

Acyloxyalkyl triazolium salt

Isavuconazole



Anti-fungal agent

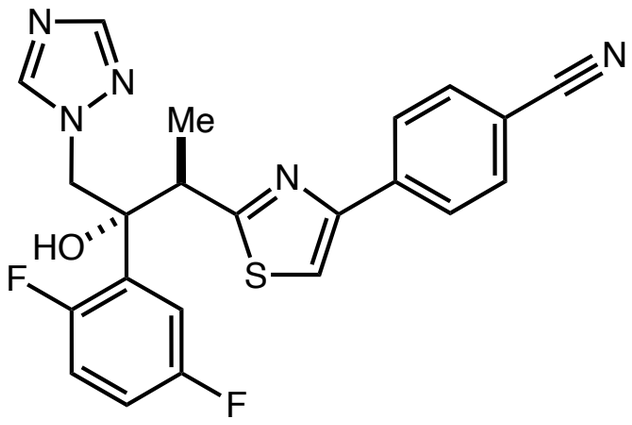
(Lung infection treatment)

basilea

Non-phosphate prodrug design to increase aqueous solubility

Acyloxyalkyl triazolium salt

Isavuconazole



Anti-fungal agent

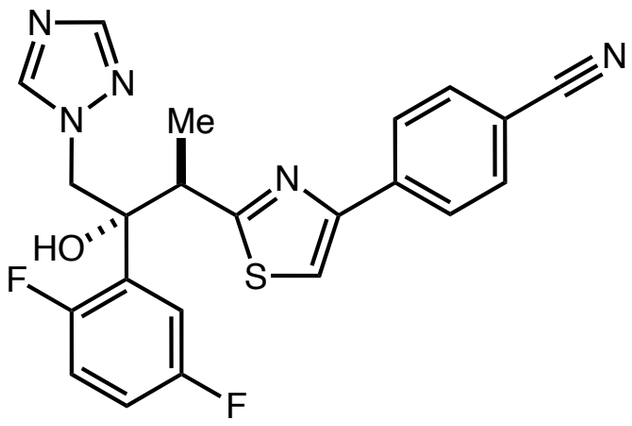
Aqueous solubility: 0.25 mg/mL

Plano, D.; Rudolph, N.; Saal, C.; Abrahamsson, B.; Cristofoletti, R.; Kambayashi, A.; Langguth, P.; Mehta, M.; Parr, A.; Polli, J. E.; Shah, V. P.; Charoo, N.; Dressman, J. *J. Pharm. Sci.* **2024**, *113* (2), 386.

Non-phosphate prodrug design to increase aqueous solubility

Acyloxyalkyl triazolium salt

Isavuconazole



Anti-fungal agent

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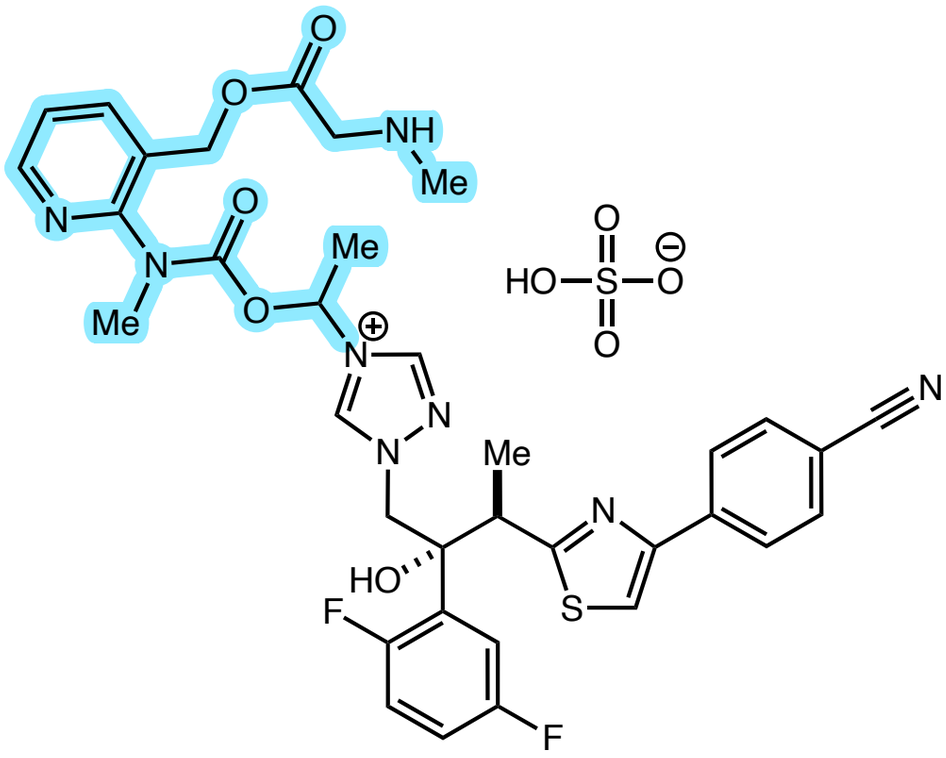
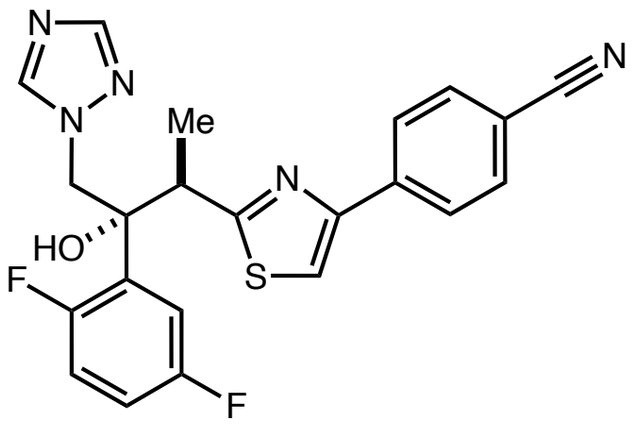
Cresemba™



Non-phosphate prodrug design to increase aqueous solubility

Acyloxyalkyl triazolium salt

Isavuconazole



Anti-fungal agent

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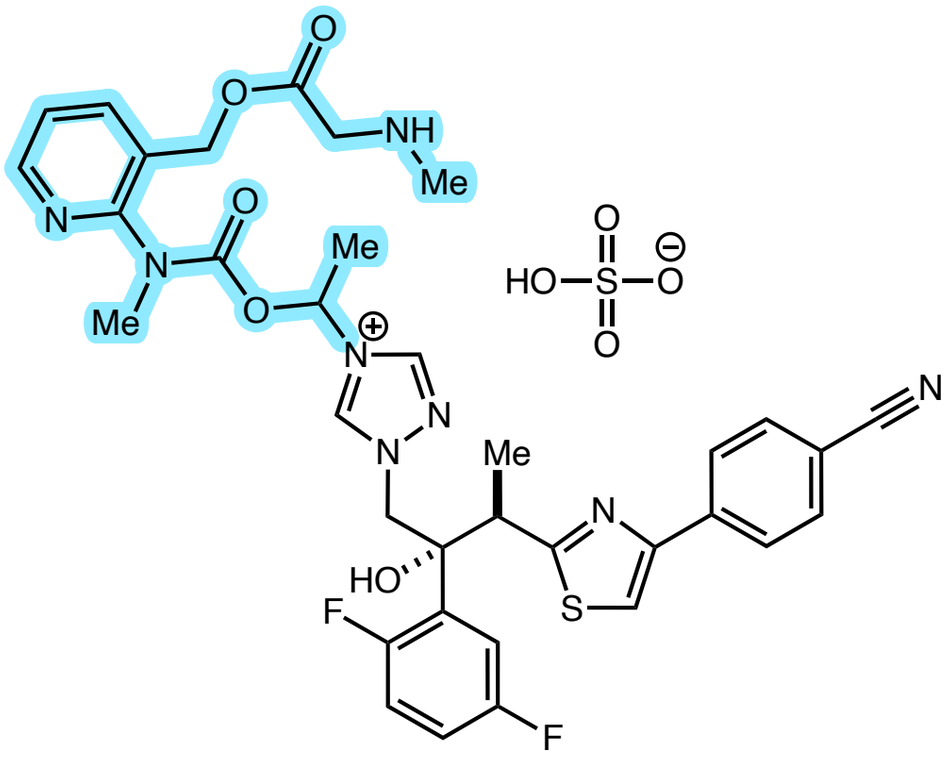
Cresemba™



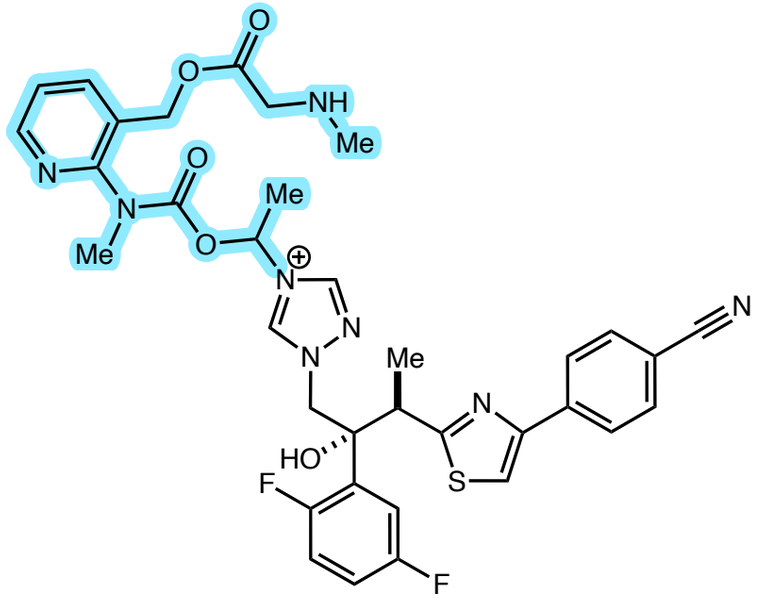
Aqueous solubility: >100 mg/mL

Salt-based prodrug

Miceli, M. H.; Kauffman, C. A. *Clin. Infect. Dis.* **2015**, *61* (10), 1558.

Non-phosphate prodrug design to increase aqueous solubility

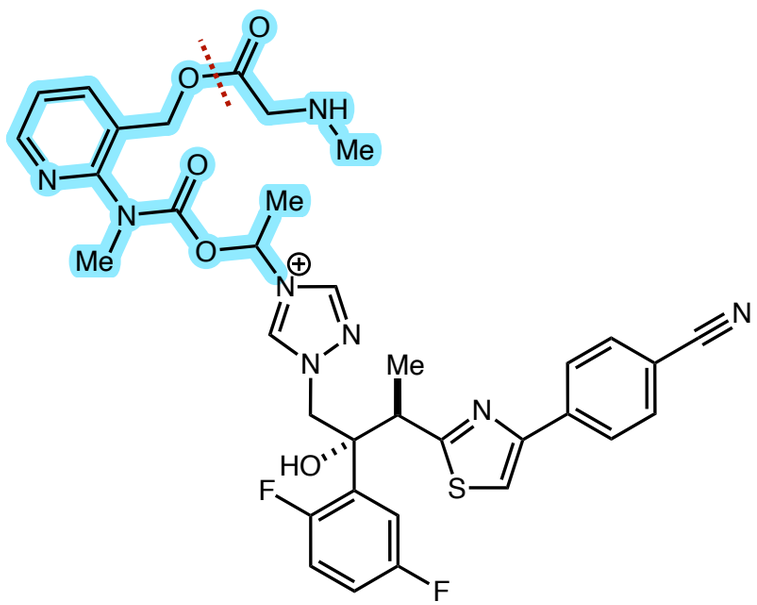
Isavuconazole (active metabolite) and Cresemba™ (salt-based prodrug)



isavuconazonium sulfate
(Cresemba™)

Non-phosphate prodrug design to increase aqueous solubility

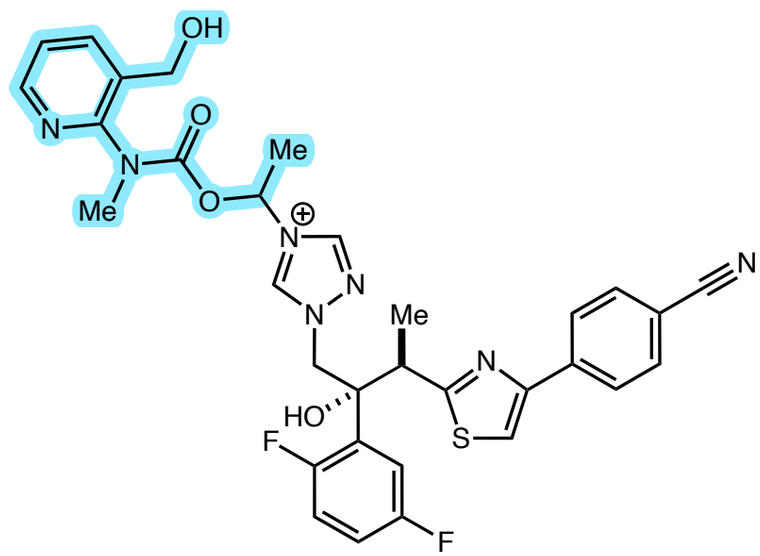
Isavuconazole (active metabolite) and Cresemba™ (salt-based prodrug)



isavuconazonium sulfate

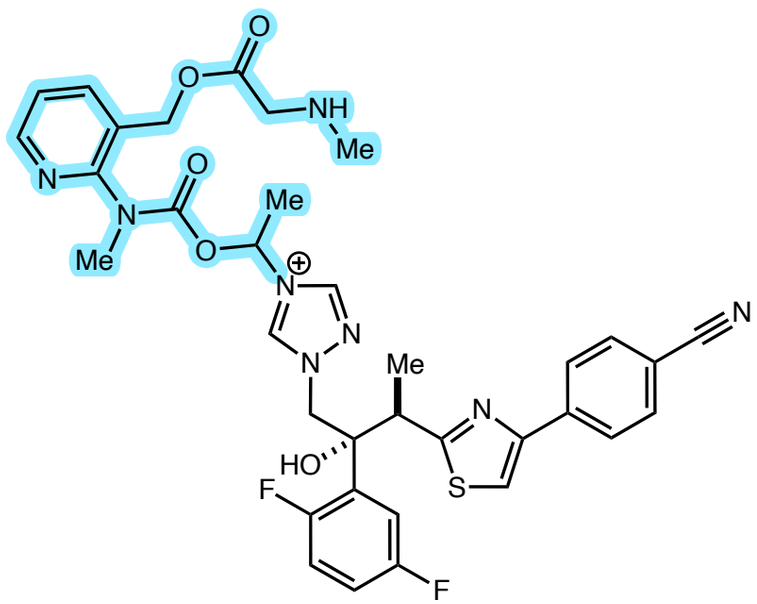
(Cresemba™)

Butyrylcholinesterase



Non-phosphate prodrug design to increase aqueous solubility

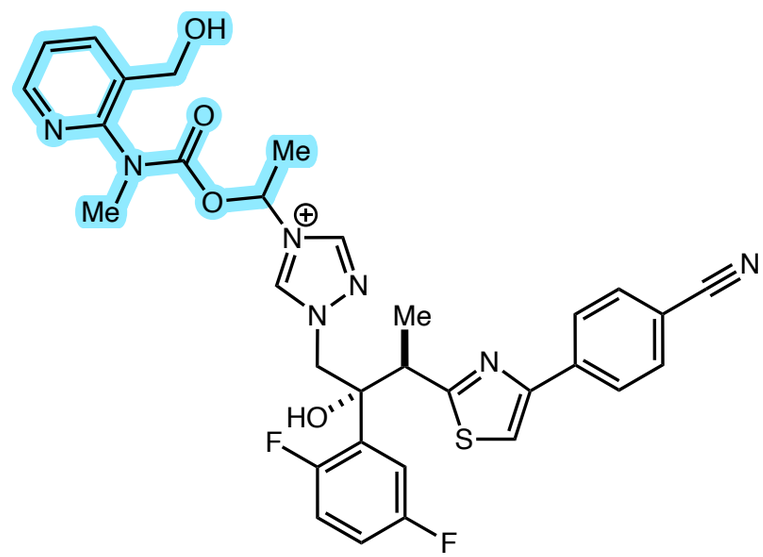
Isavuconazole (active metabolite) and Cresemba™ (salt-based prodrug)

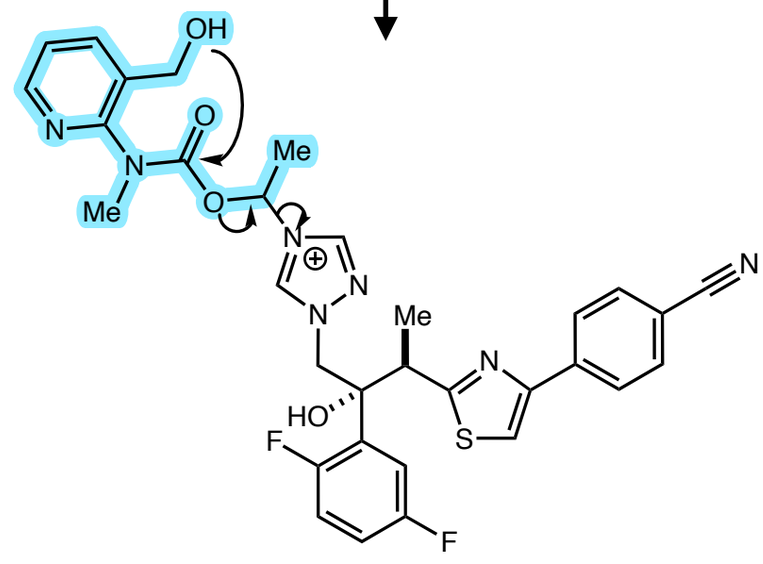


isavuconazonium sulfate

(Cresemba™)

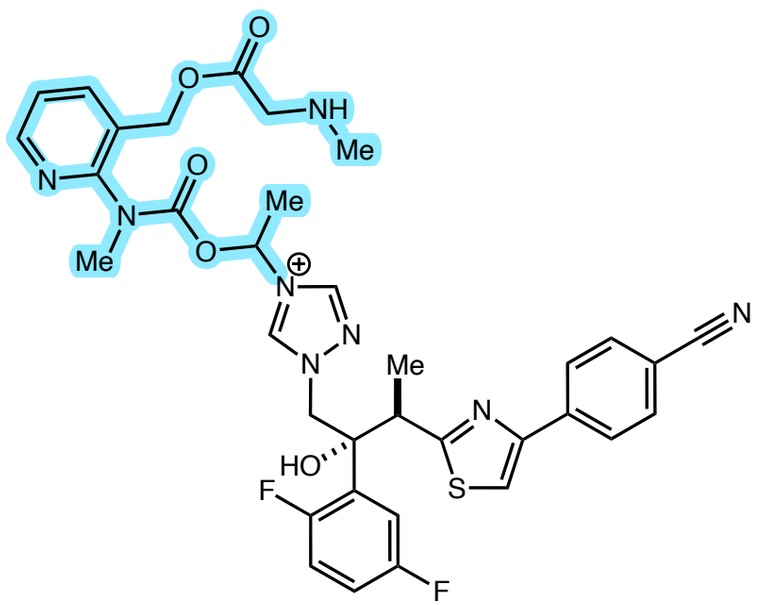
Butyrylcholinesterase





Non-phosphate prodrug design to increase aqueous solubility

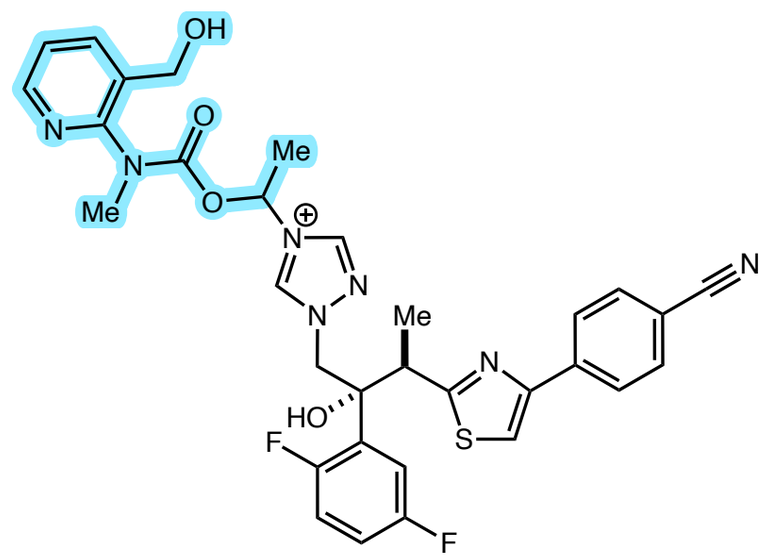
Isavuconazole (active metabolite) and Cresemba™ (salt-based prodrug)

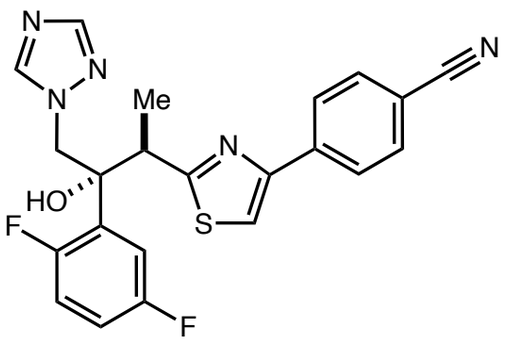


isavuconazonium sulfate

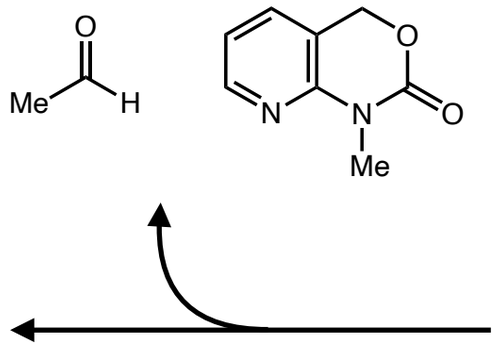
(Cresemba™)

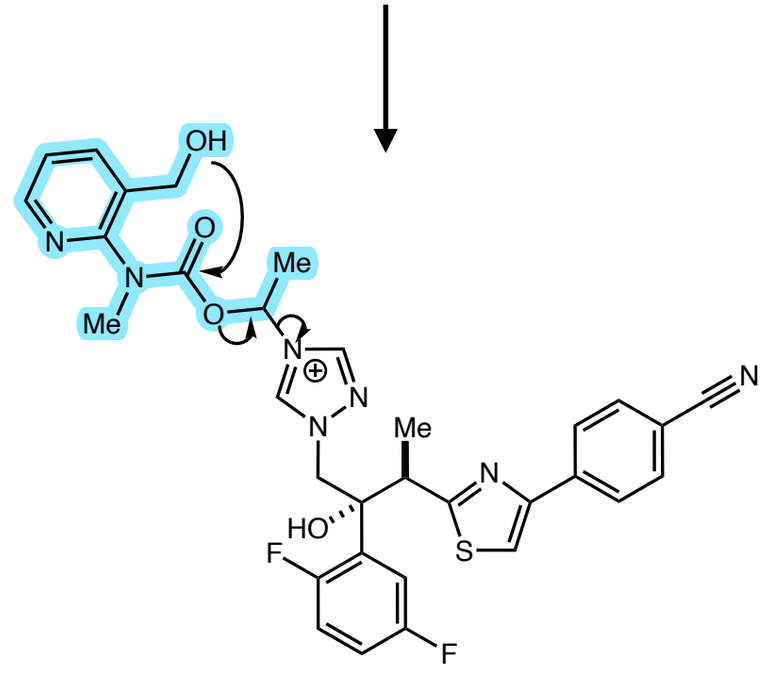
Butyrylcholinesterase





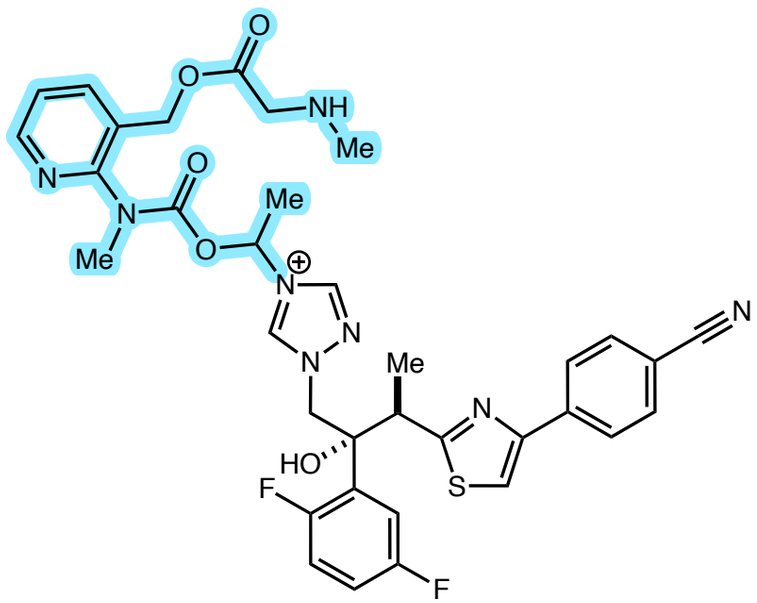
Isavuconazole





Non-phosphate prodrug design to increase aqueous solubility

Isavuconazole (active metabolite) and Cresemba™ (salt-based prodrug)

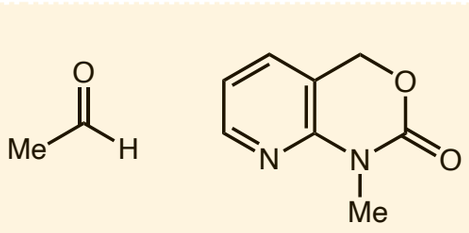


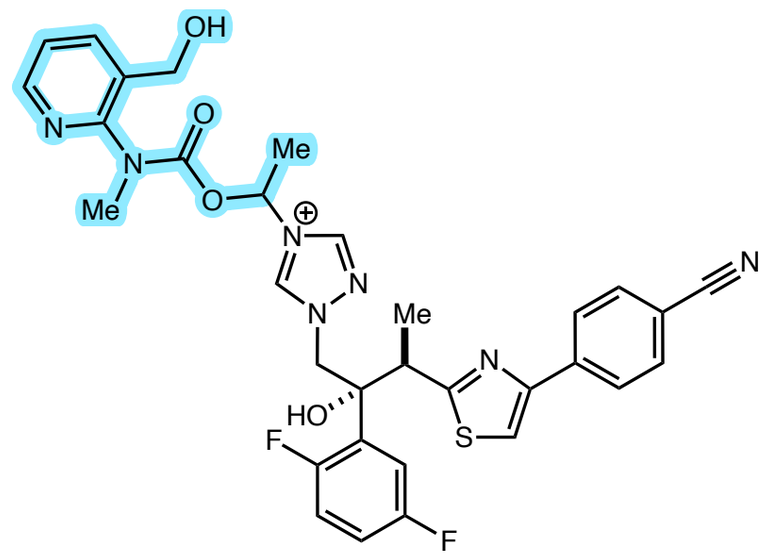
isavuconazonium sulfate

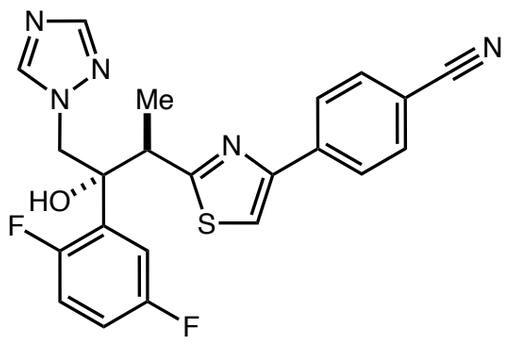
(Cresemba™)

Butyrylcholinesterase

Innocuous byproducts



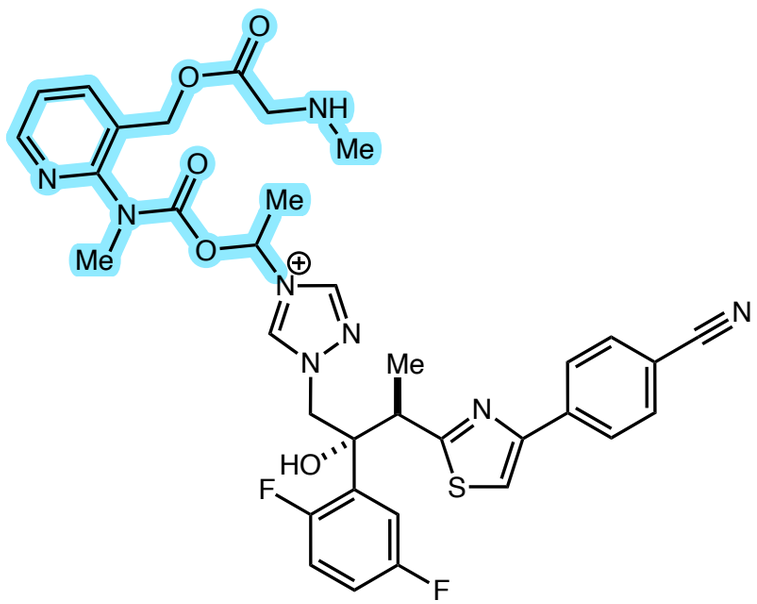




Isavuconazole

Non-phosphate prodrug design to increase aqueous solubility

Isavuconazole (active metabolite) and Cresemba™ (salt-based prodrug)

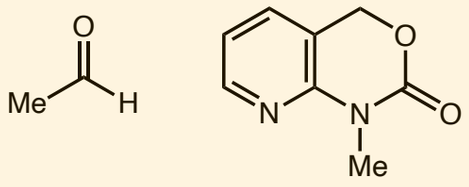


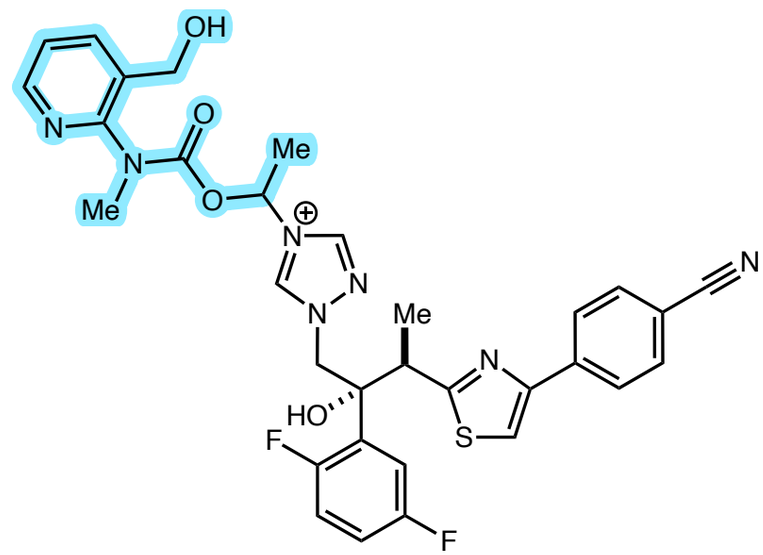
isavuconazonium sulfate

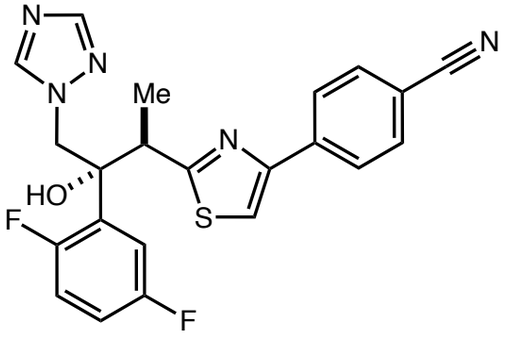
(Cresemba™)

Butyrylcholinesterase

Innocuous byproducts





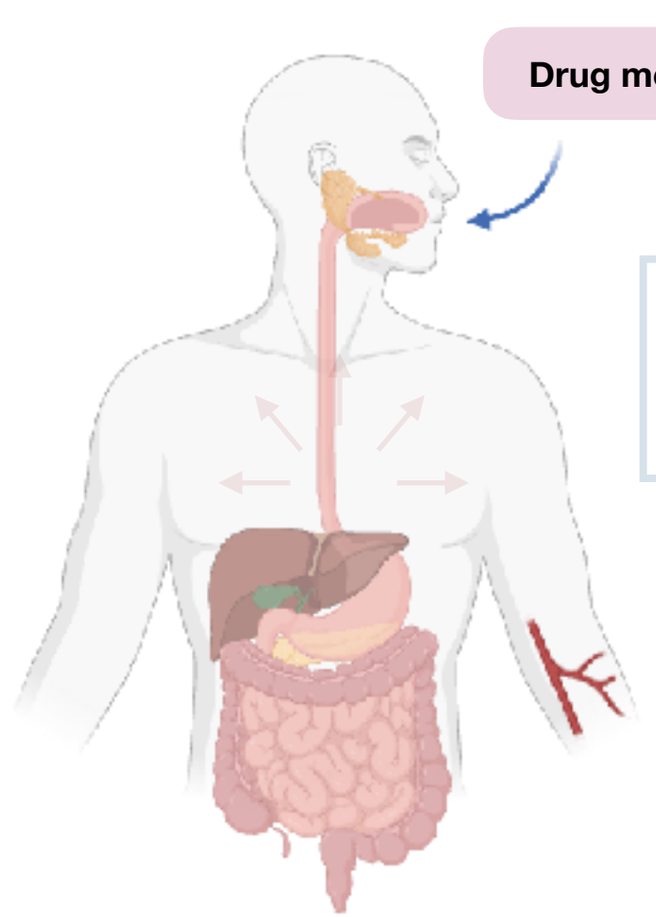


Isavuconazole

Unprecedented prodrug strategy for improved aqueous solubility: potential alternative to direct phosphorylation

Prodrug design to improve 'A' in ADME

Absorption



Drug molecule — **Promoiety**

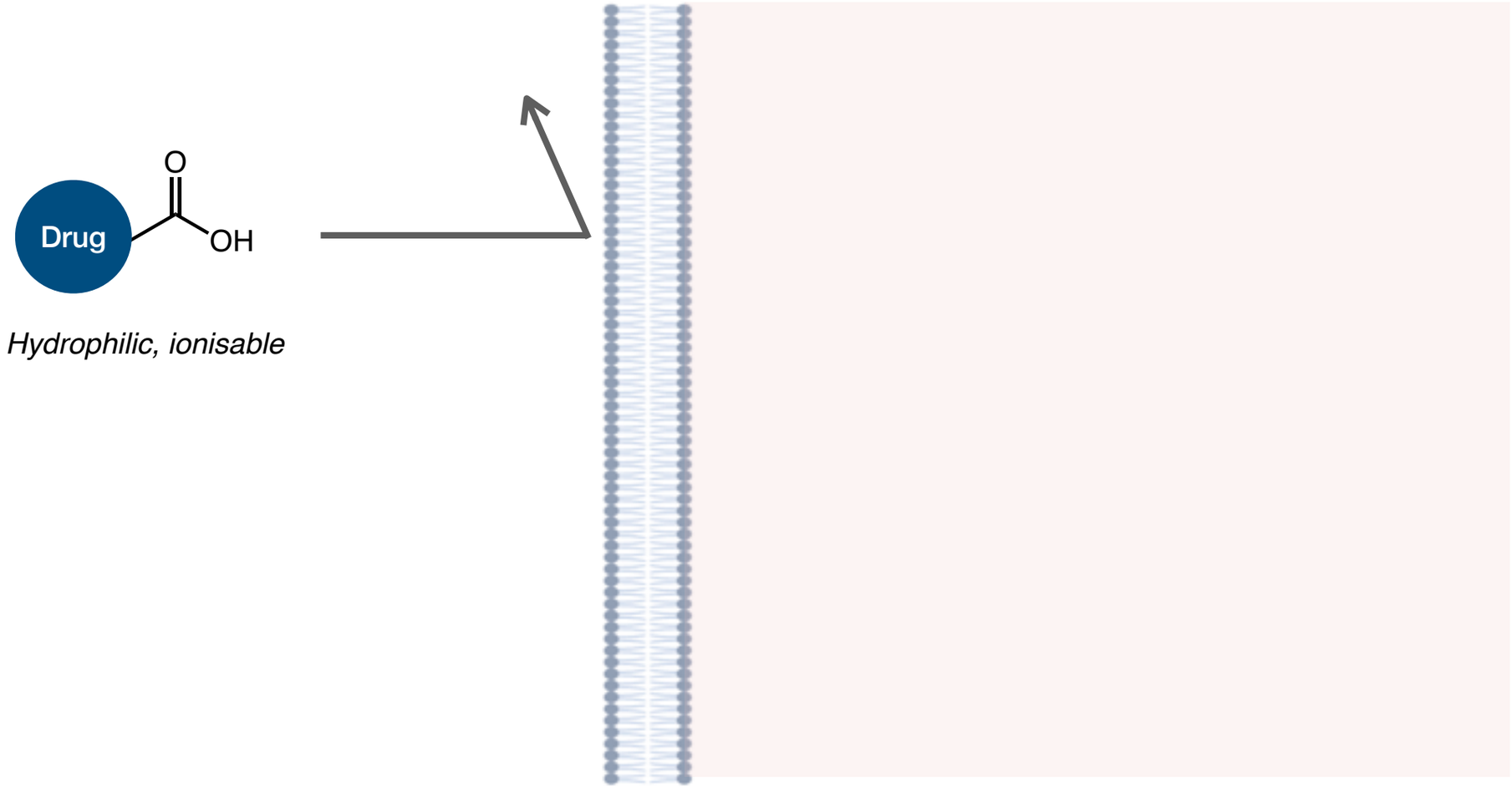
***A**bsorption*

- *Higher aqueous solubility*
- *Better membrane permeation*

- ***Increasing aqueous solubility***
  - *phosphate*
  - *non-phosphate*

- ***Increasing membrane permeation***
  - *ester*

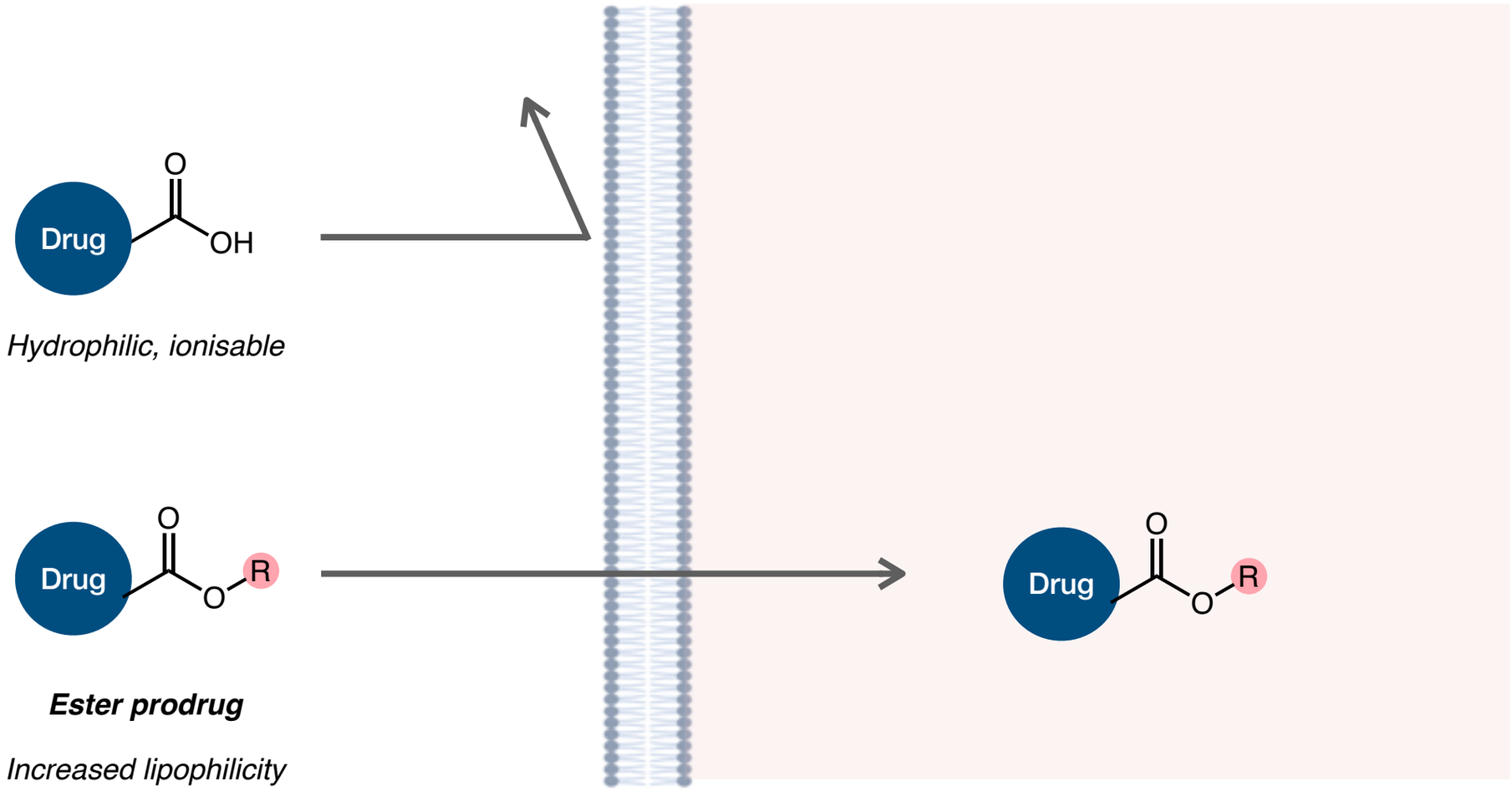
Ester prodrug design to increase membrane permeation



Hydrophilic, ionisable

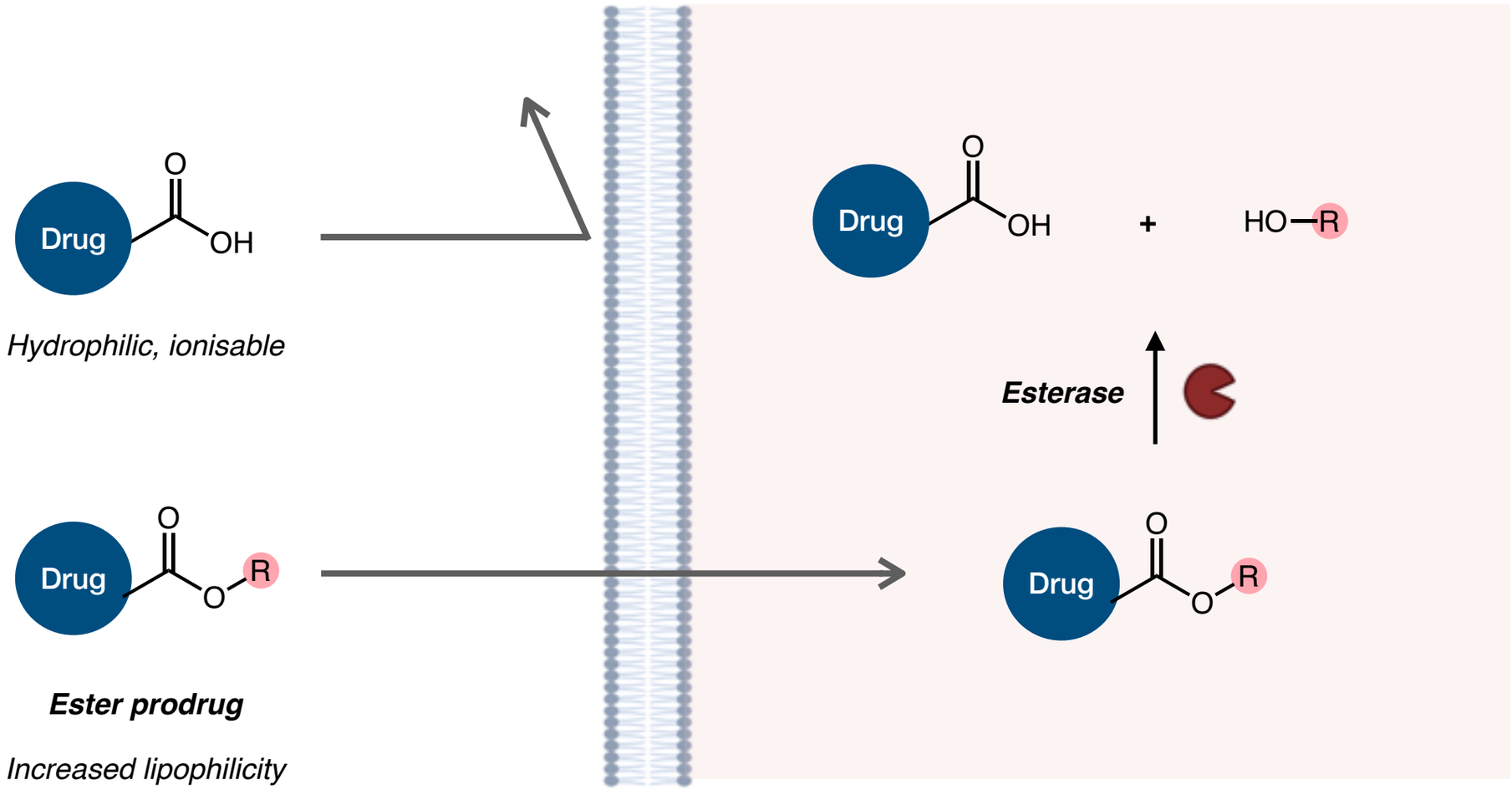
Ester prodrug design to increase membrane permeation

Membrane permeation enabled by increased lipophilicity



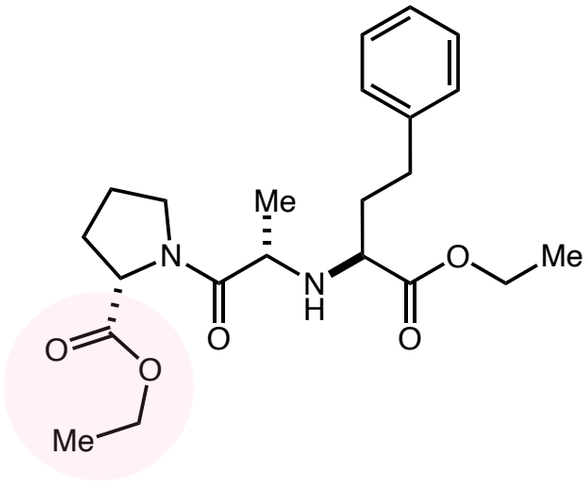
Ester prodrug design to increase membrane permeation

Membrane permeation enabled by increased lipophilicity



Ester prodrug design to increase membrane permeation

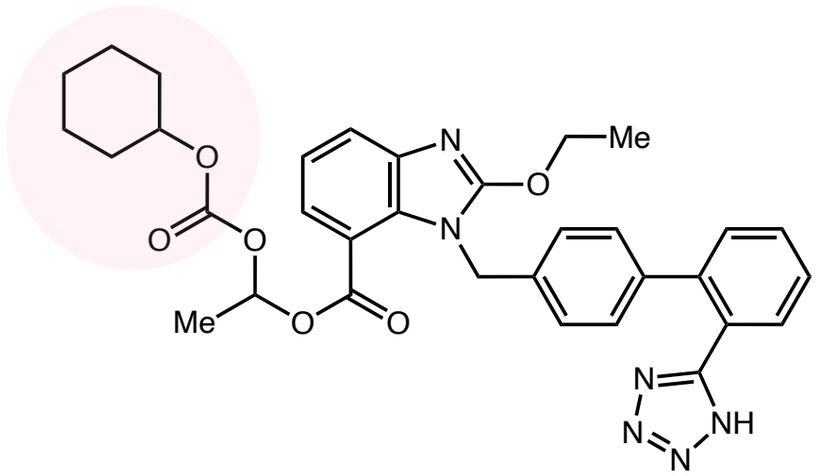
Ester prodrugs in market



Vasotec™

Hypertension

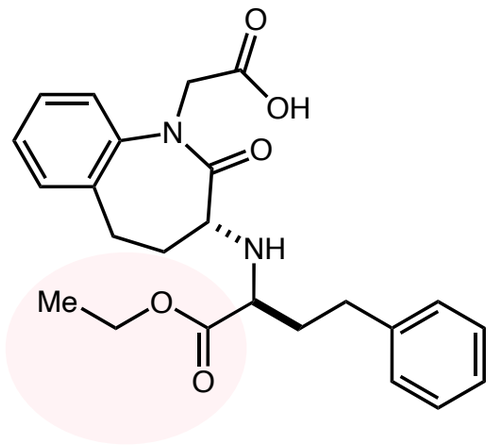
MERCK



Atacand™

Hypertension

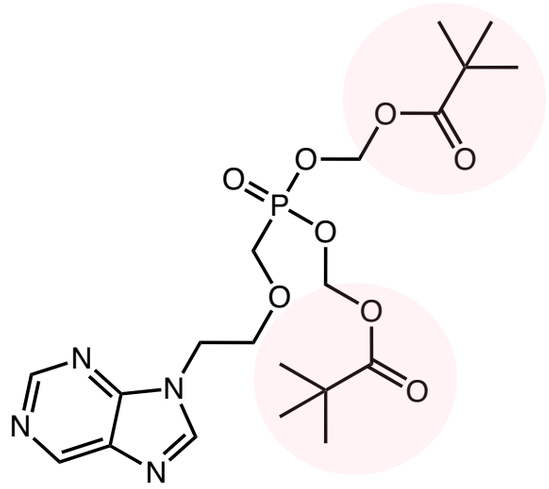
Takeda



Lotensin™

Hypertension

NOVARTIS



Hepsera™

Hepatitis B

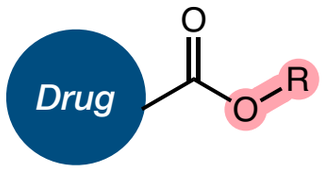
GILEAD

Ester prodrugs constitute a large percentage (almost 50%) of marketed prodrugs

Wang, D.; Zou, L.; Jin, Q.; Hou, J.; Ge, G.; Yang, L. *Acta Pharm. Sin. B* **2018**, *8* (5), 699.

Ester prodrug design to increase membrane permeation

Why ester prodrugs are popular



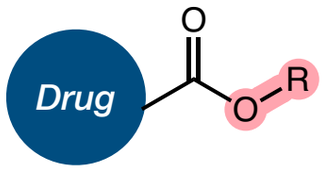
Ubiquitous nature of esterase

✓ Reliable activation

✓ Broad substrate scope

Ester prodrug design to increase membrane permeation

Why ester prodrugs are popular



Ubiquitous nature of esterase

✓ *Reliable activation*

✓ *Broad substrate scope*

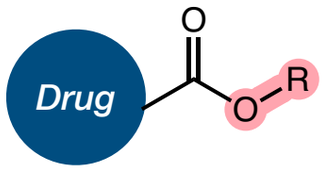
also translate to…

✓ *Lack of selectivity*

✓ *Inter-individual variability*

Ester prodrug design to increase membrane permeation

Why ester prodrugs are popular



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✓ *Reliable activation*

✓ *Broad substrate scope*

also translate to…

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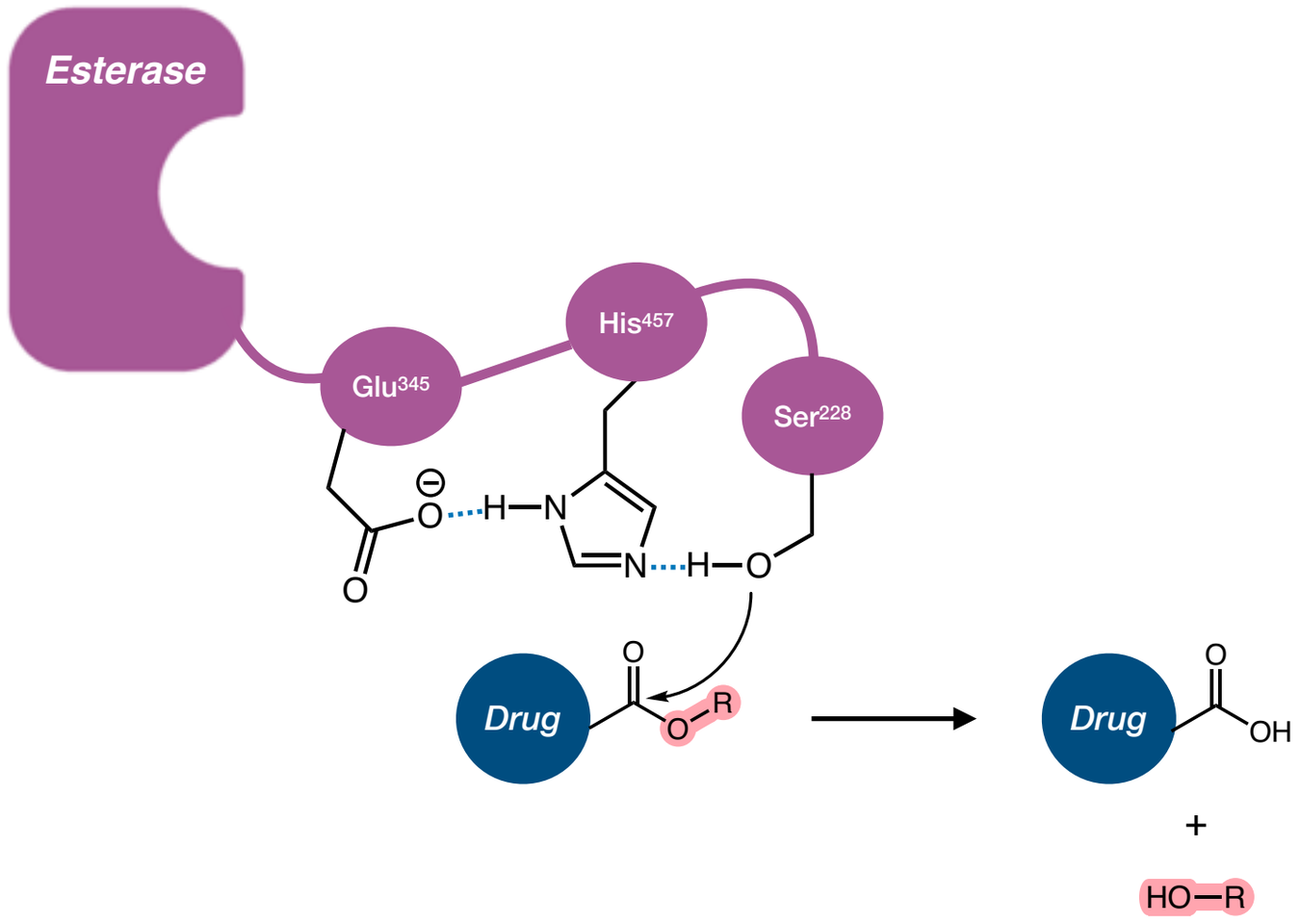
✓ *Inter-individual variability*

Ester prodrug design to increase membrane permeation

Esterase selectivity

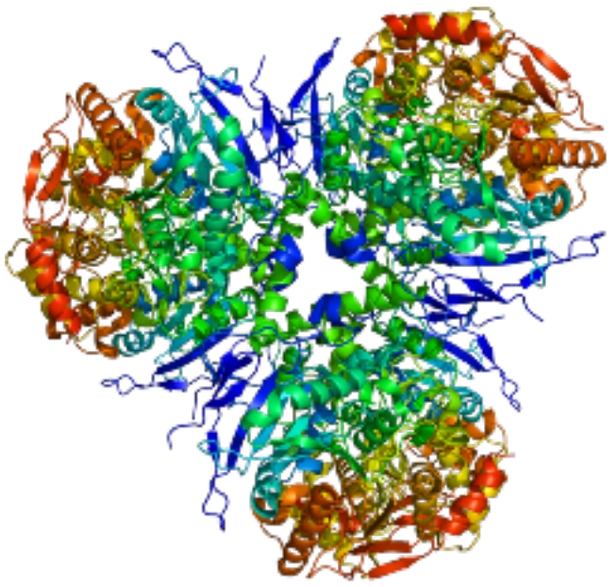


α/β hydrolase superfamily

Ester prodrug design to increase membrane permeation

Esterase selectivity

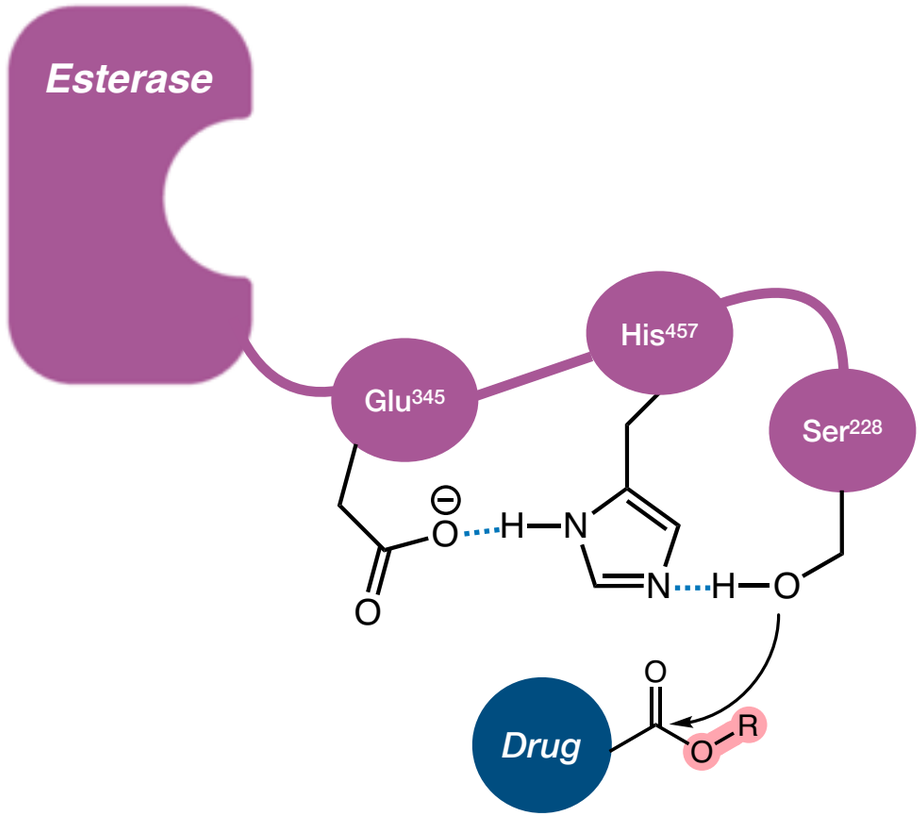
Carboxylesterase 1



PDB 1MX5

180 kD (Trimer)

Carboxylesterase 2



60 kDa (Monomer)

Ester prodrug design to increase membrane permeation

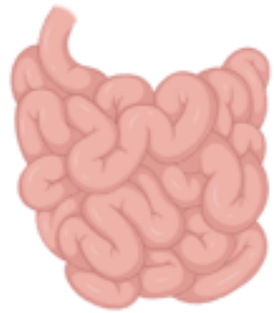
Esterase selectivity

Carboxylesterase 1

Highly expressed in liver

Carboxylesterase 2

Enriched in small intestine

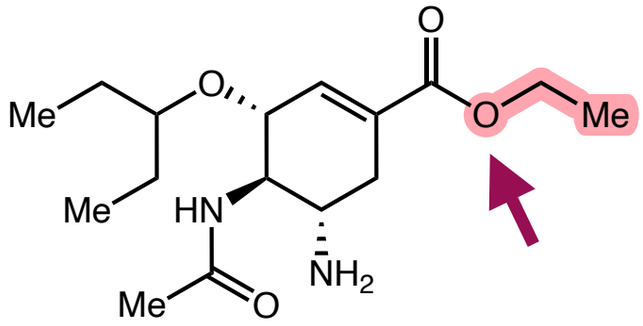


Ester prodrug design to increase membrane permeation

Esterase selectivity

Carboxylesterase 1

Highly expressed in liver

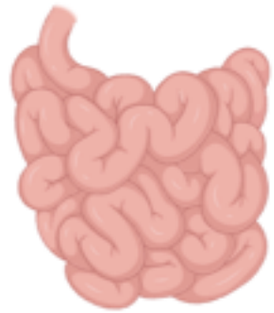


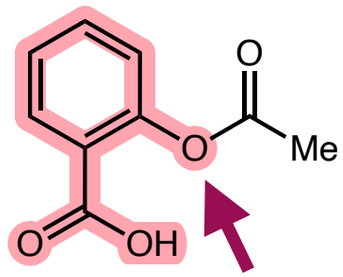
Oseltamivir

Prefers
Small alcohols
Large carboxylic acid

Carboxylesterase 2

Enriched in small intestine



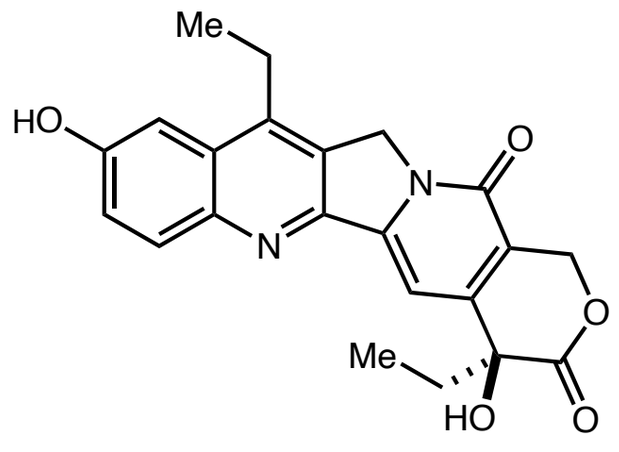


Aspirin

Prefers
Large alcohols
Small carboxylic acid

Ester prodrug design to increase membrane permeation

Esterase selectivity and prodrug design



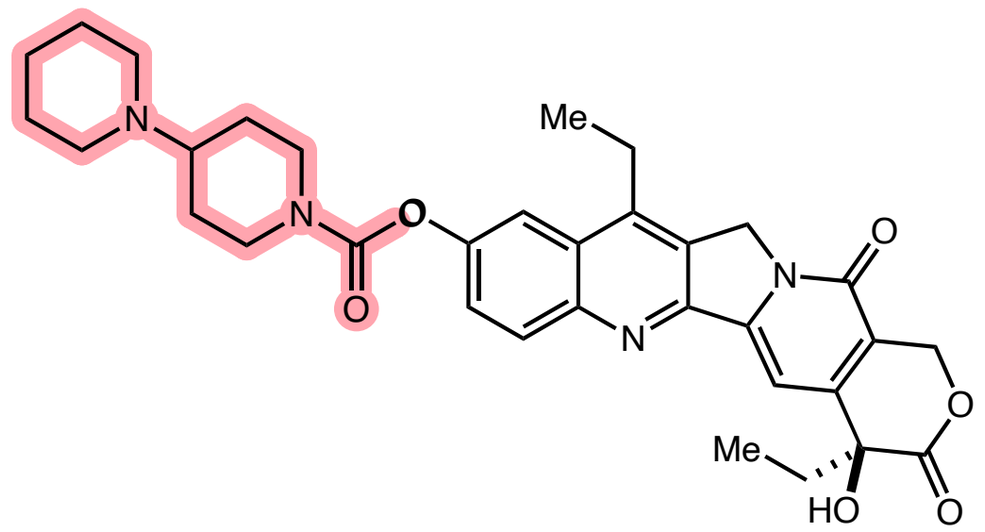
SN-38

Topoisomerase I inhibitor

Anticancer drug

Ester prodrug design to increase membrane permeation

Esterase selectivity and prodrug design

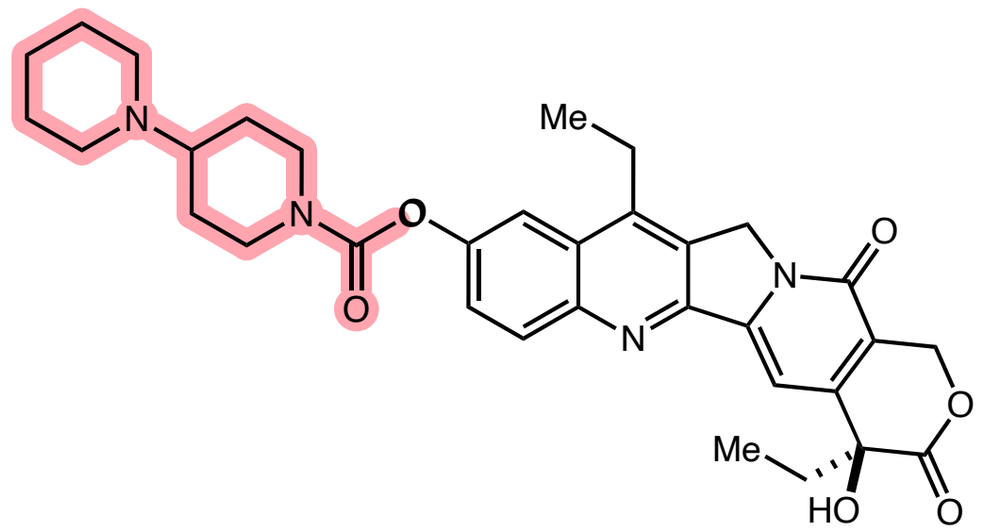


Irinotecan (Camptosar™)

Pfizer

Ester prodrug design to increase membrane permeation

Esterase selectivity and prodrug design



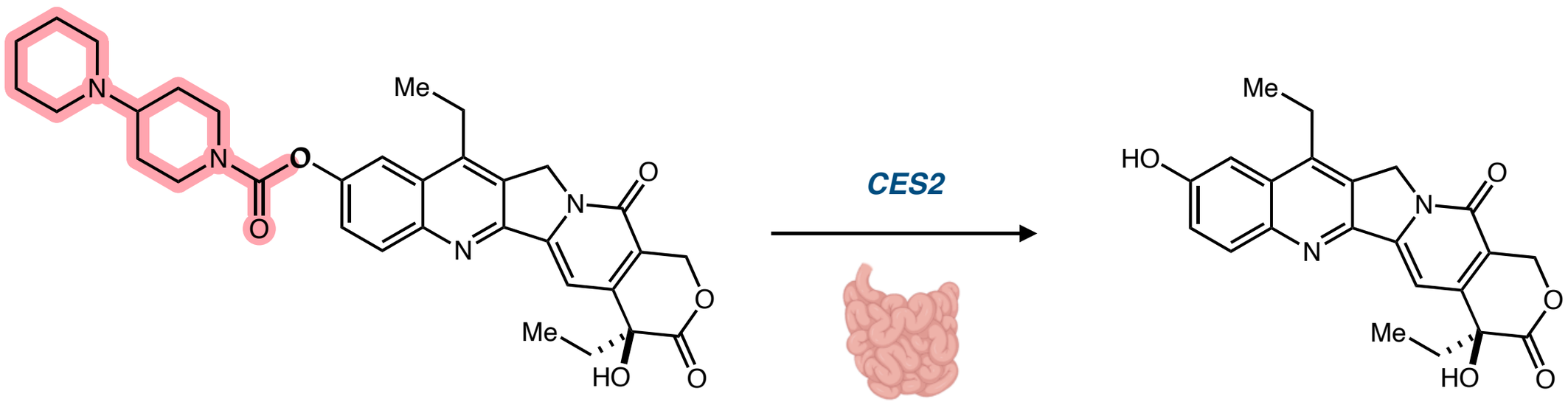
Irinotecan (Camptosar™)

Lack of esterase selectivity in design resulted in dose-limiting toxicity

*Relatively large alcohol and small carboxylic acid → good substrate for **CES2** (abundant in small intestine)*

Ester prodrug design to increase membrane permeation

Esterase selectivity and prodrug design



Irinotecan (Camptosar™) *SN-38 built up in small intestine*

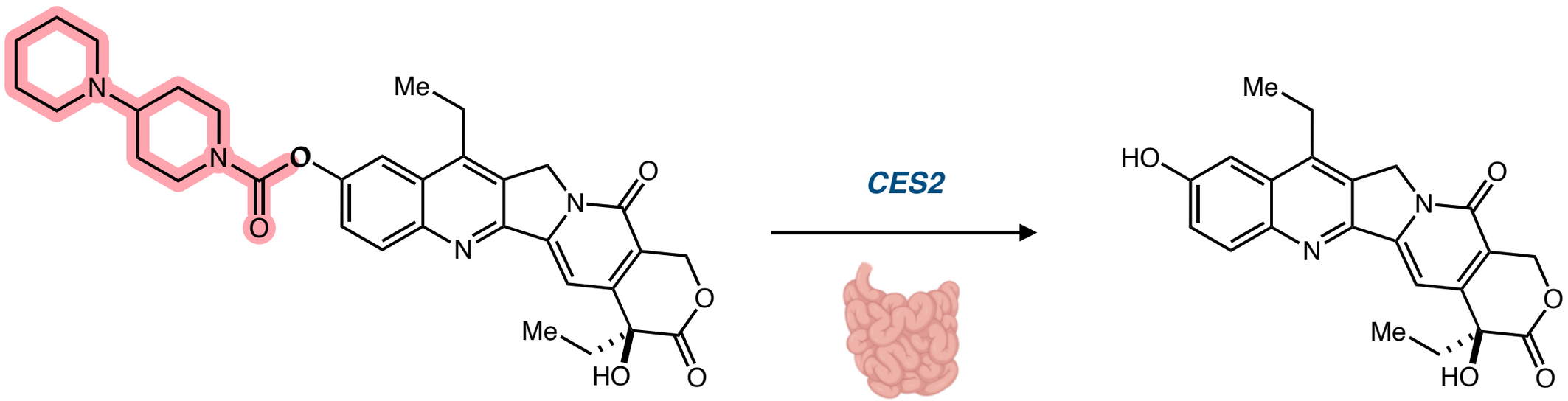
Common adverse event: severe diarrhea (kidney injury, dehydration)

(30-40% experience grade 3-4 episodes)

Stein, A.; Voigt, W.; Jordan, K. *Ther. Adv. Med. Oncol.* **2010**, *2* (1), 51.

Ester prodrug design to increase membrane permeation

Esterase selectivity and prodrug design



Irinotecan (Camptosar™) *SN-38 built up in small intestine*

Common adverse event: severe diarrhea (kidney injury, dehydration)

(30-40% experience grade 3-4 episodes)

Could the toxicity of irinotecan be designed out by choosing an ester that is a poor substrate of CES2?

Yanni, S.; Thakker, D. R. Springer New York: New York, NY, 2007; Vol. V, pp 1043

Ester prodrug design to increase membrane permeation

Inter-individual variability

Ubiquitous nature of esterase

✓ *Reliable activation*

✓ *Broad substrate scope*

also translate to…

⇨

✓Lack of selectivity

✓Inter-individual variability

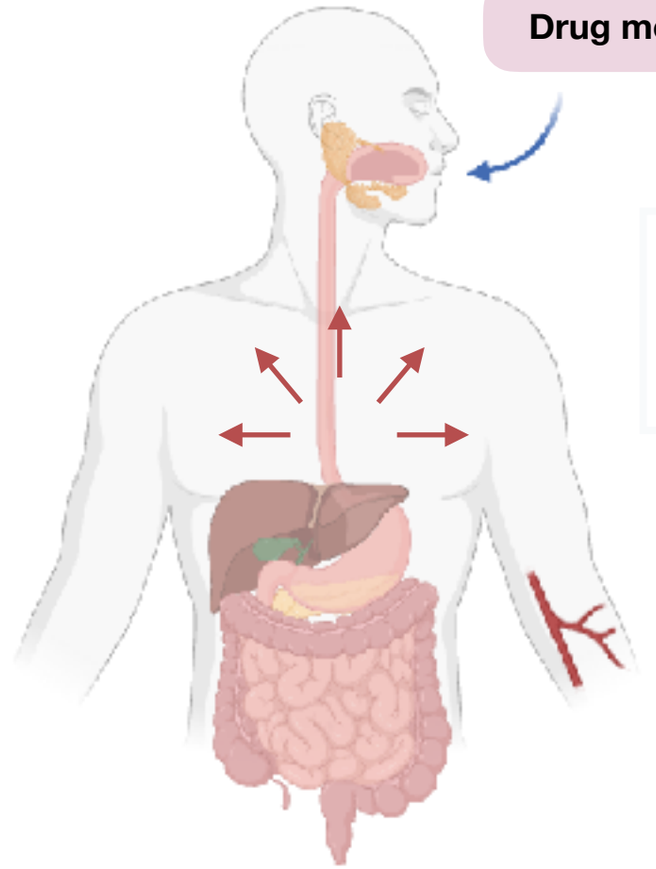
CES1/CES2 genetic variability can markedly influence efficacy and safety of ester prodrugs

No FDA-cleared clinical tests exist for CES1 or CES2 activity

No drug labels currently recommend CES genotyping for treatment decisions

Prodrug design to improve 'D' in ADME

Distribution



Drug molecule — **Promoiety**

***A**bsorption*

- *Higher aqueous solubility*
- *Better membrane permeation*

***D**istribution*

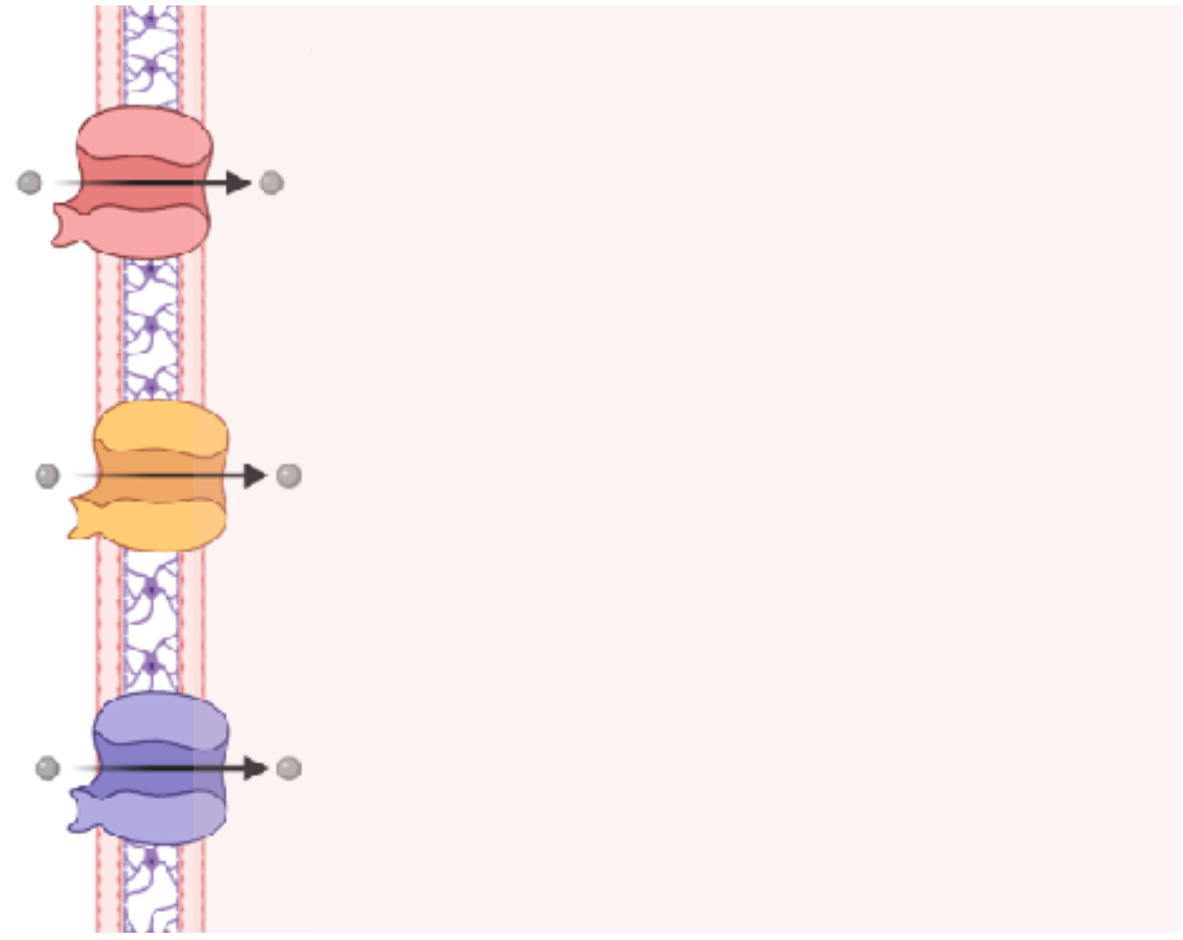
- *Effective concentrations at difficult-to-target tissues*

- ***Prodrug design to deliver drugs into the central nervous system (CNS)***

Prodrug design to deliver drugs into the central nervous system

Passing through the blood-brain barrier (BBB)

Blood brain barrier (BBB)



✓ *Tight junctions*

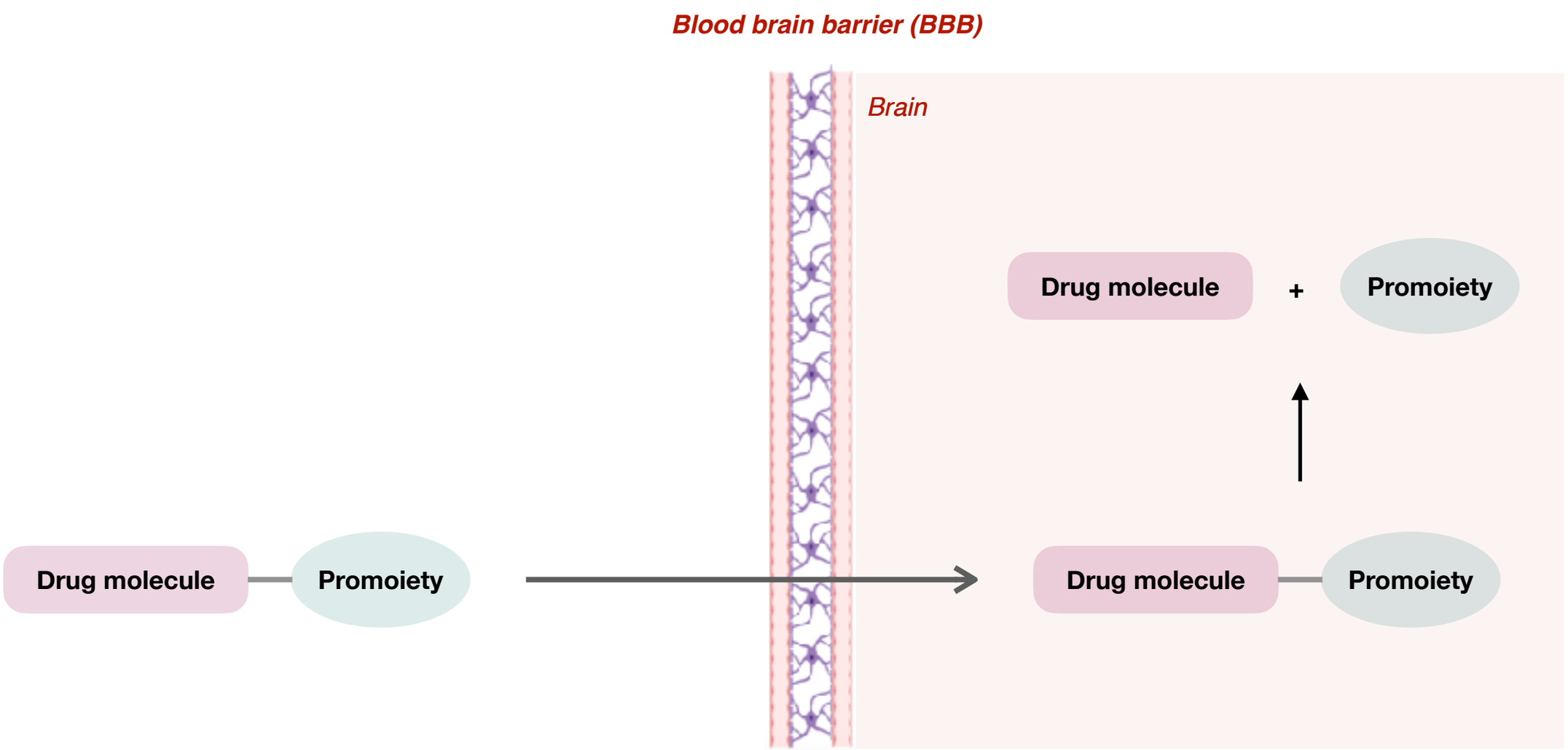
✓ *Apically directed efflux transporters*

✓ *Various drug-metabolising enzymes*

Demailly, A.; Moreau, C.; Devos, D. *J. Park. Dis.* **2024**, *14* (5), 925.

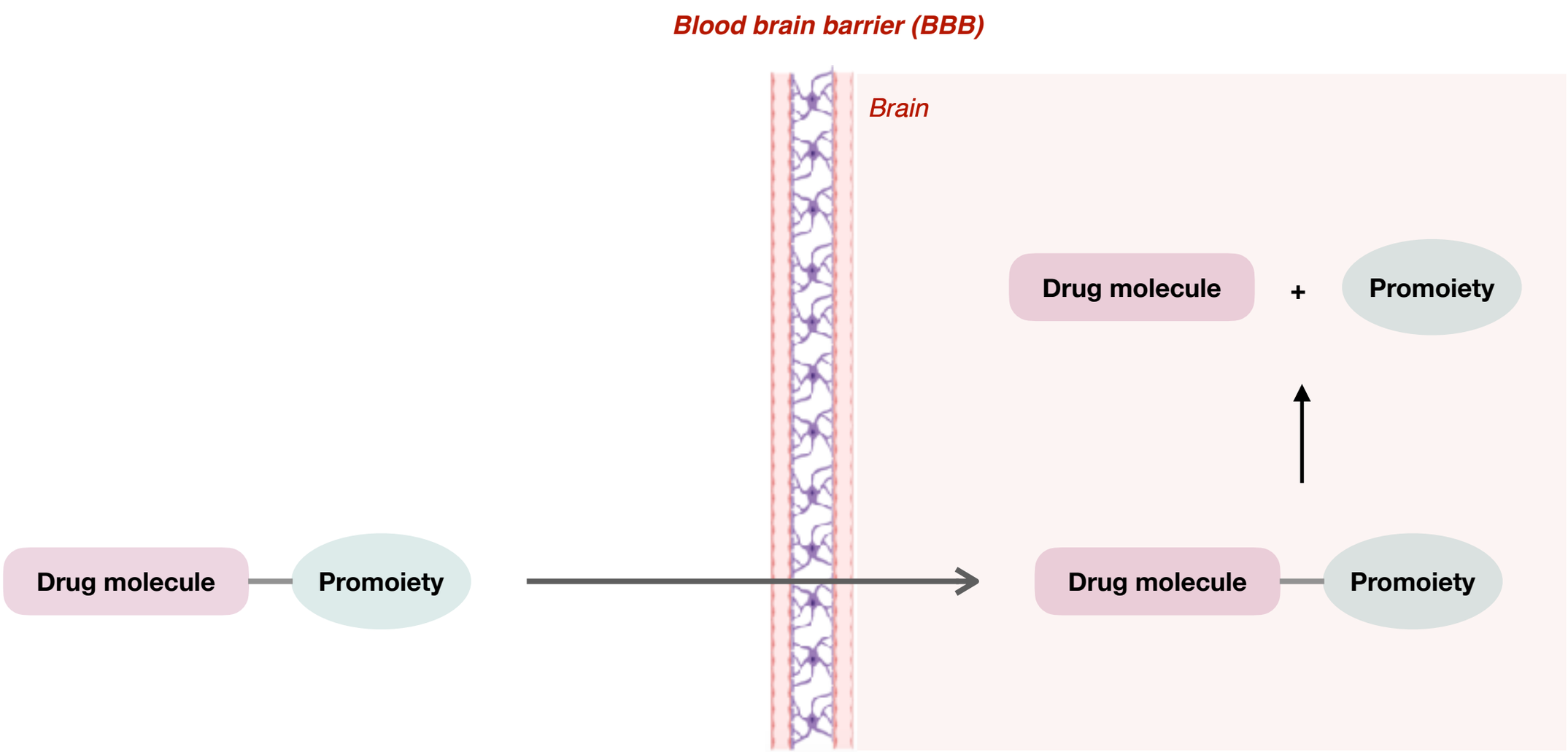
Prodrug design to deliver drugs into the central nervous system

Passing through the blood-brain barrier (BBB)



Prodrug design to deliver drugs into the central nervous system

Passing through the blood-brain barrier (BBB)

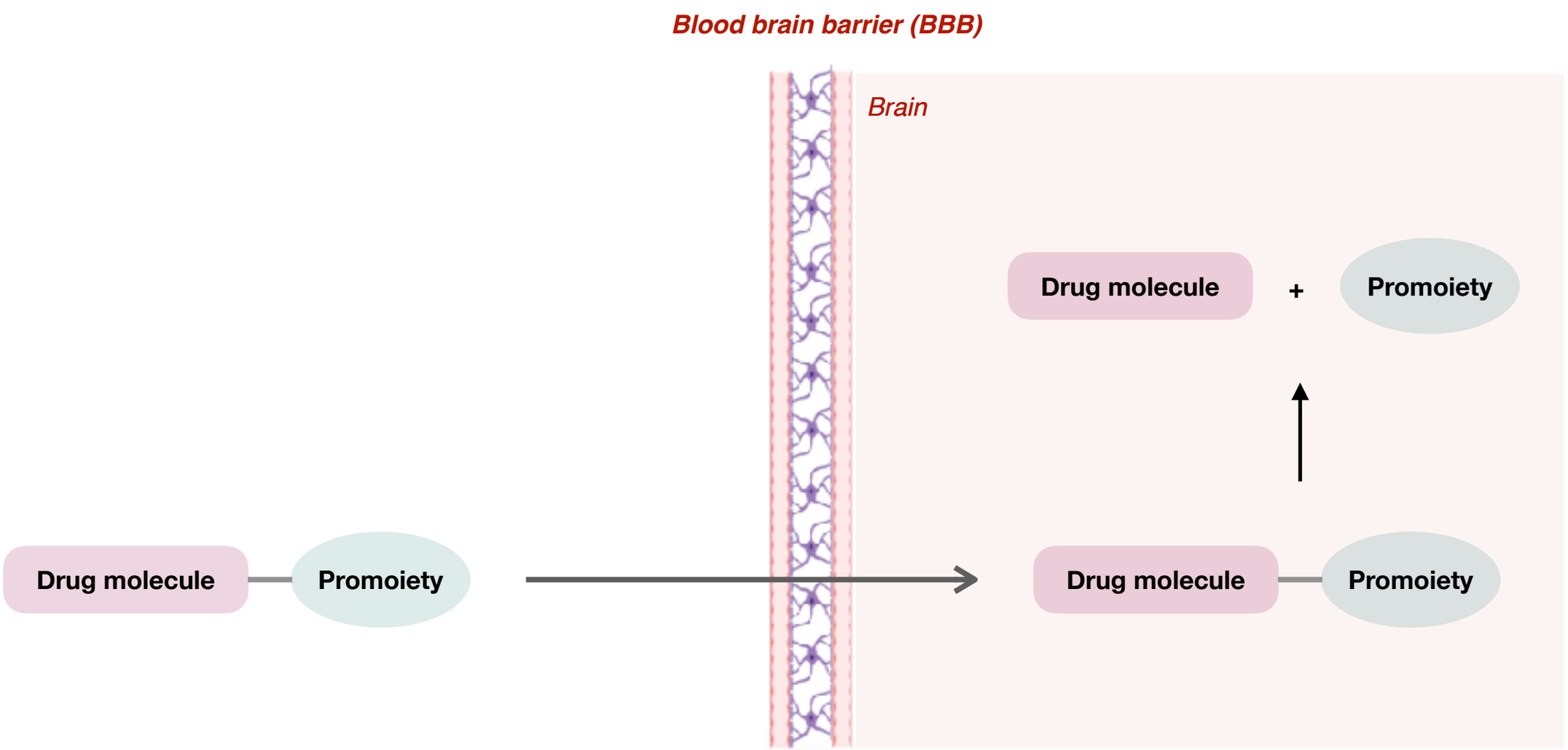


✓ *Improving lipophilicity is not enough*

Demailly, A.; Moreau, C.; Devos, D. *J. Park. Dis.* **2024**, *14* (5), 925.

Prodrug design to deliver drugs into the central nervous system

Passing through the blood-brain barrier (BBB)



✓ *Improving lipophilicity is not enough*

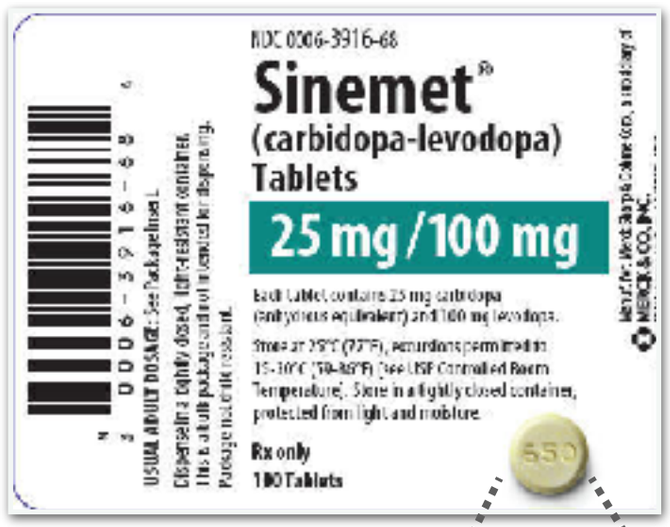
✓ *Bioconversion should be brain-specific*

✓ *Active metabolite should be trapped in the brain*

Demailly, A.; Moreau, C.; Devos, D. *J. Park. Dis.* **2024**, *14* (5), 925.

Prodrug design to deliver drugs into the central nervous system

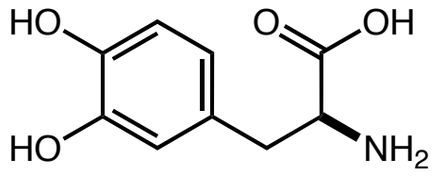
Passing through the blood-brain barrier (BBB)



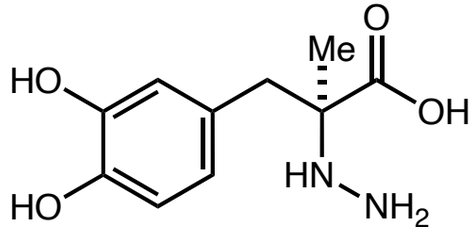
Treatment for Parkinson's disease

Successful prodrug design for CNS distribution

L-DOPA



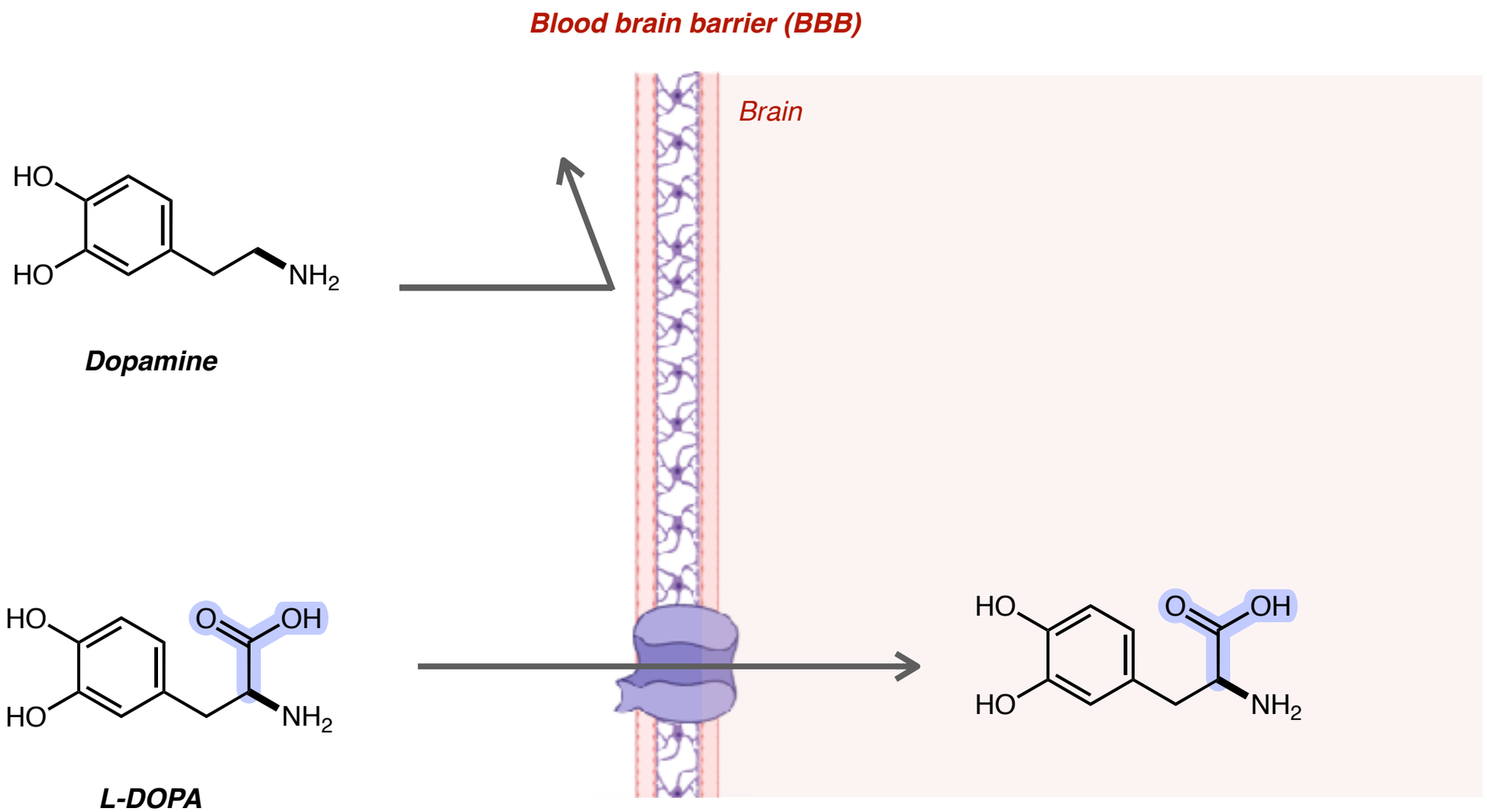
Carbidopa



MERCK

Prodrug design to deliver drugs into the central nervous system

Passing through the blood-brain barrier (BBB)

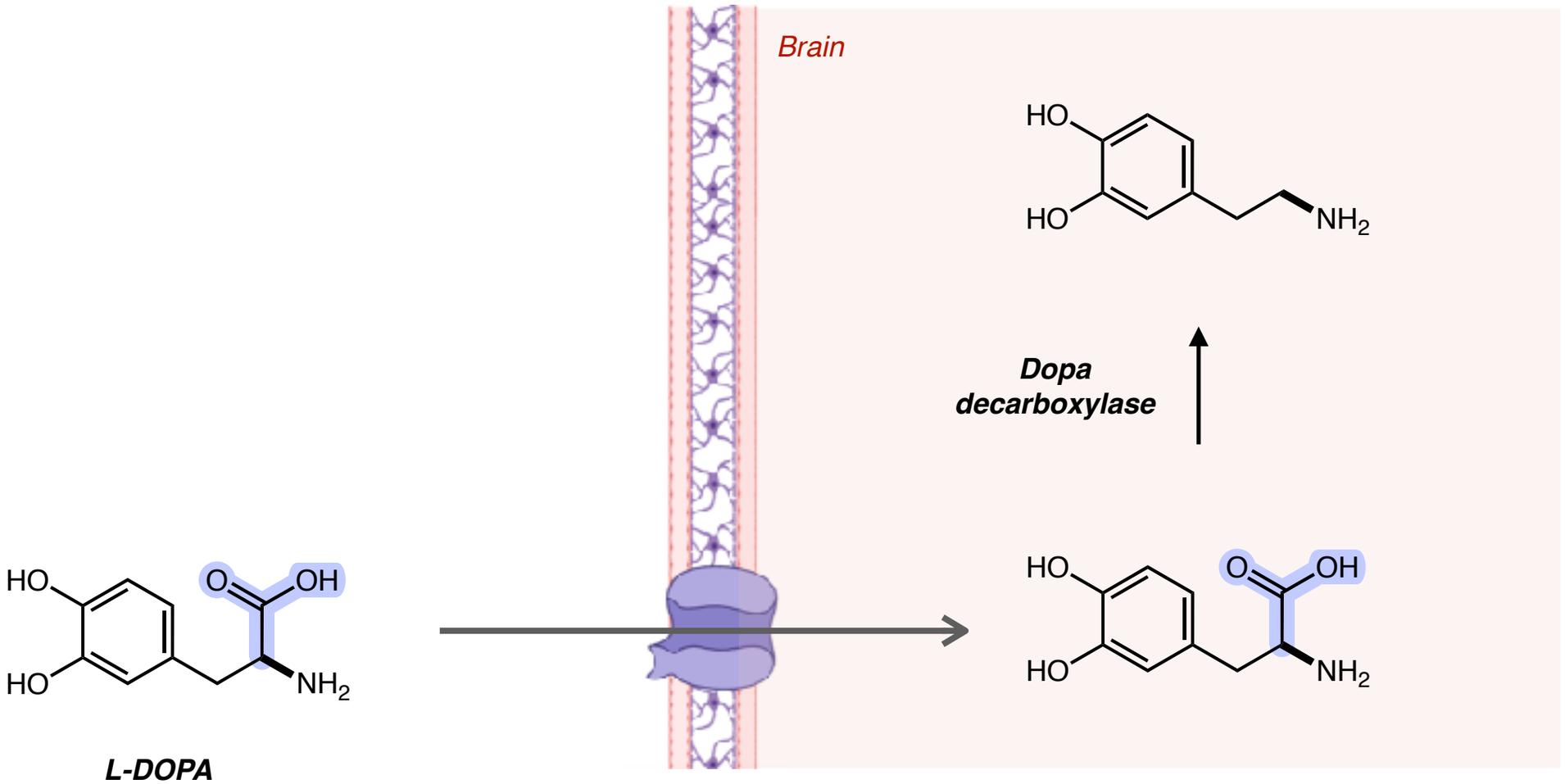


Large neutral amino acid transporters present in the BBB

Prodrug design to deliver drugs into the central nervous system

Passing through the blood-brain barrier (BBB)

Blood brain barrier (BBB)



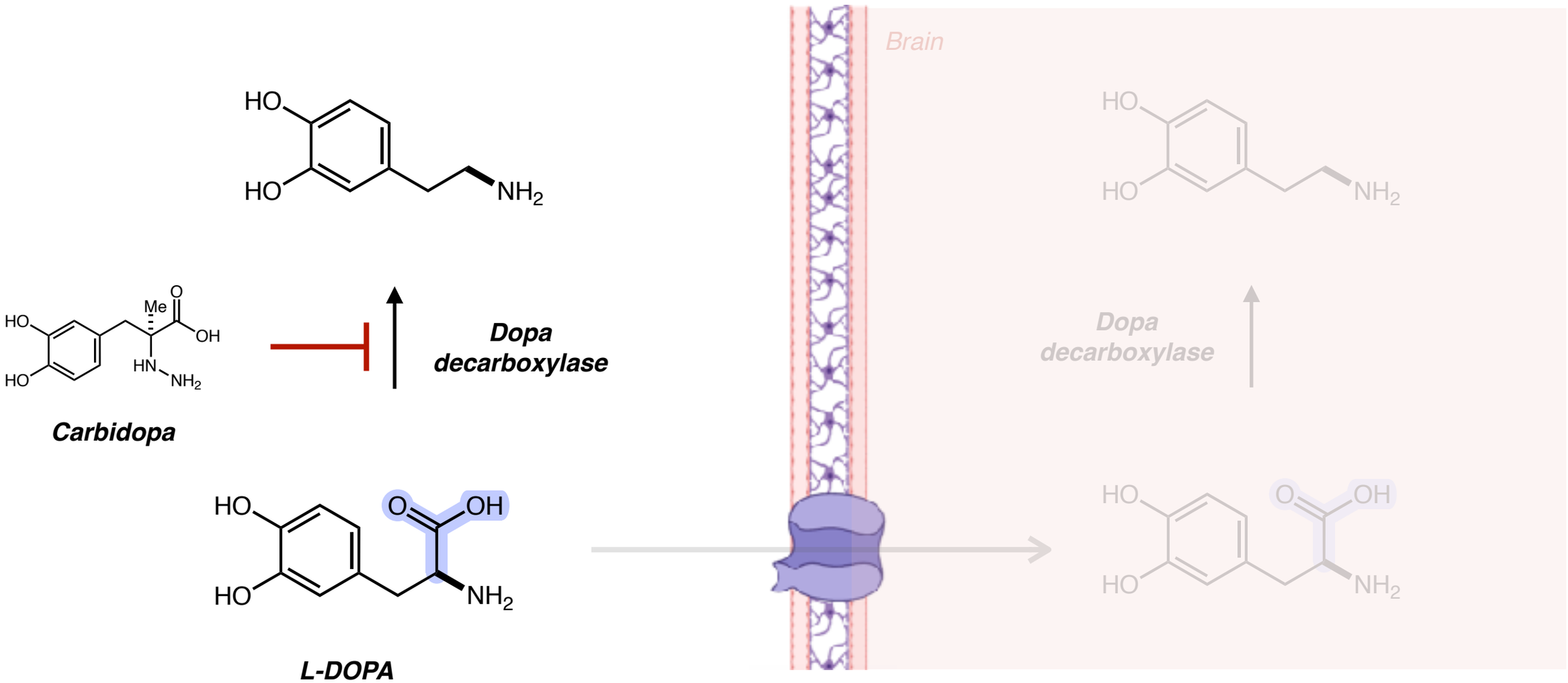
L-DOPA

L-type amino acid transporter 1 (LAT1)

Prodrug design to deliver drugs into the central nervous system

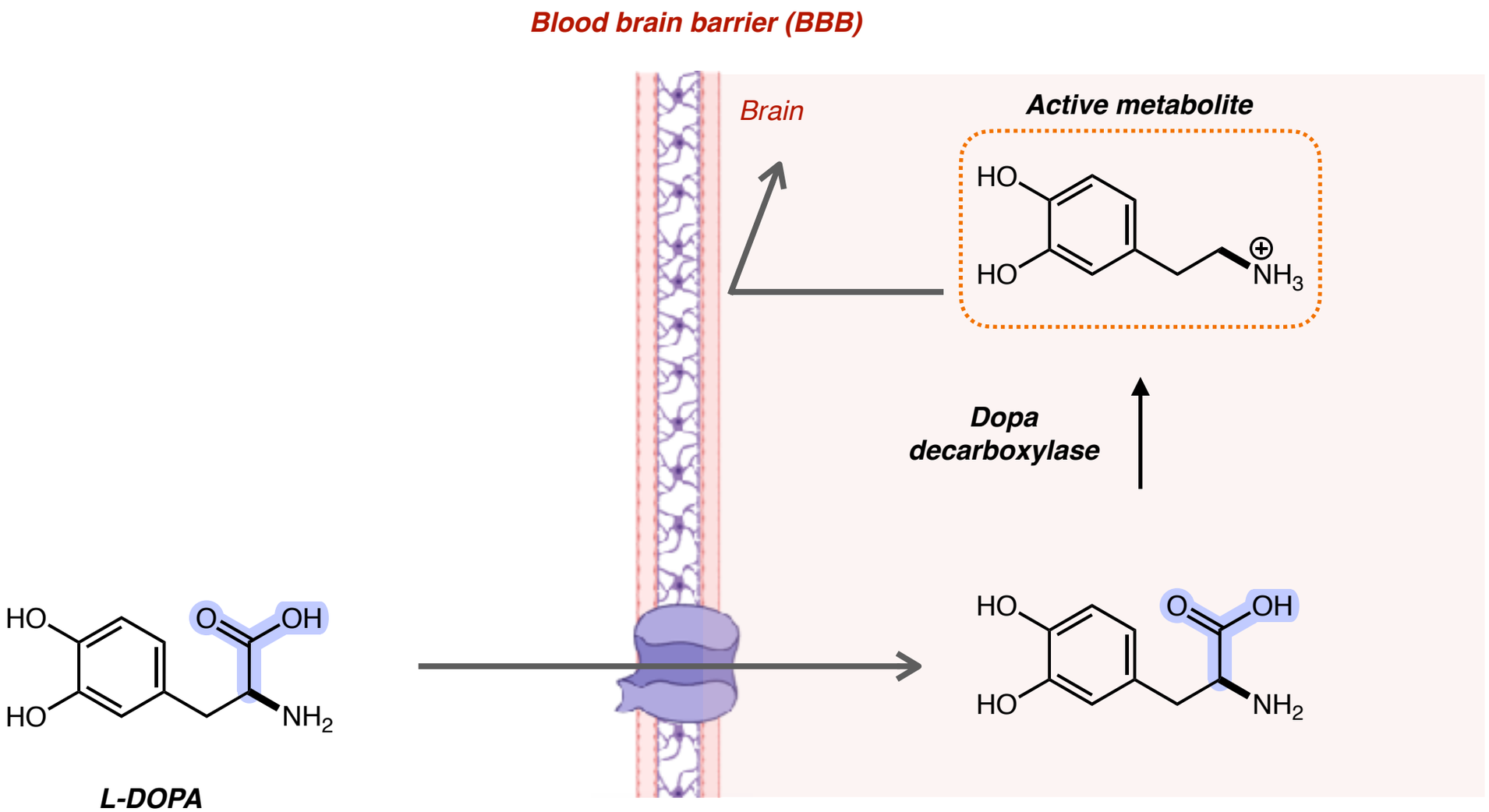
Passing through the blood-brain barrier (BBB)

Blood brain barrier (BBB)



Prodrug design to deliver drugs into the central nervous system

Passing through the blood-brain barrier (BBB)



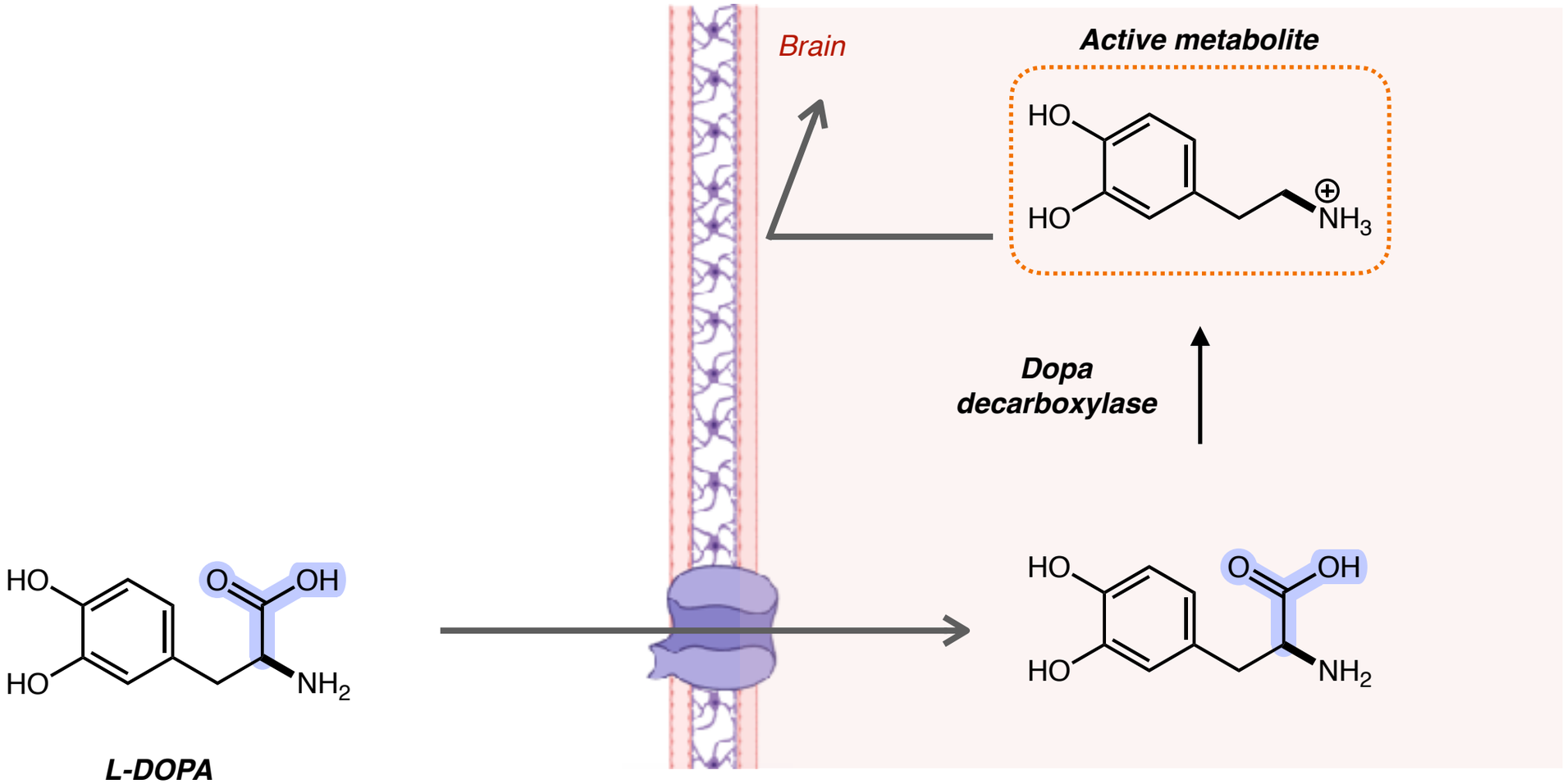
Large neutral amino acid transporters present in the BBB

Active metabolite (dopamine) is unable to diffuse out into the systemic circulation

Prodrug design to deliver drugs into the central nervous system

Passing through the blood-brain barrier (BBB)

Blood brain barrier (BBB)



L-DOPA

L-type amino acid transporter 1 (LAT1)

Large neutral amino acid transporters present in the BBB

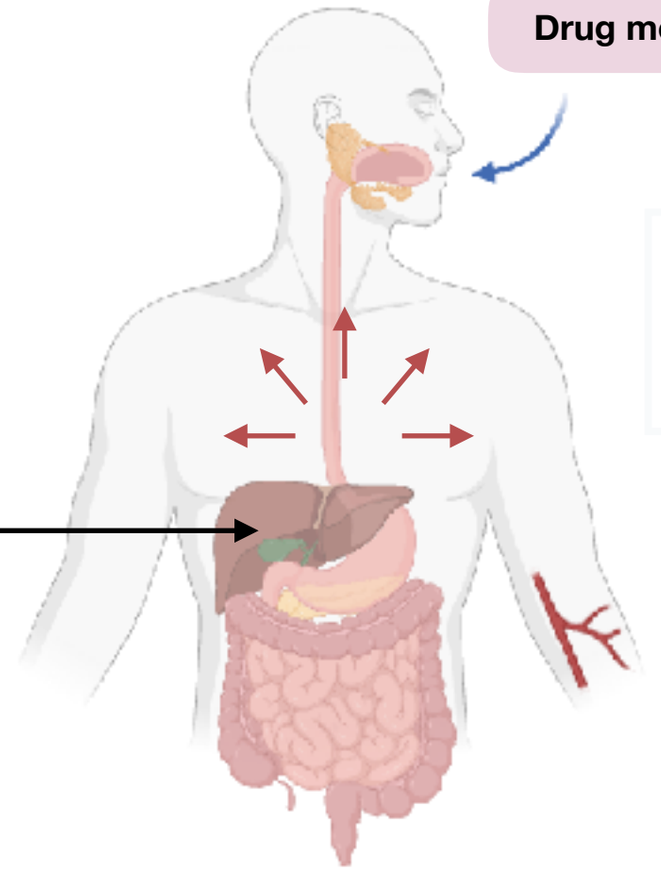
Active metabolite (dopamine) is unable to diffuse out into the systemic circulation

⇨ ***Effective concentrations at the target tissue (brain)***

Prodrug design to improve 'M' in ADME

Metabolism

Drug molecule — **Promoiety**



Absorption

- *Higher aqueous solubility*
- *Better membrane premeation*

Distribution

- *Effective concentrations at difficult-to-target tissues*

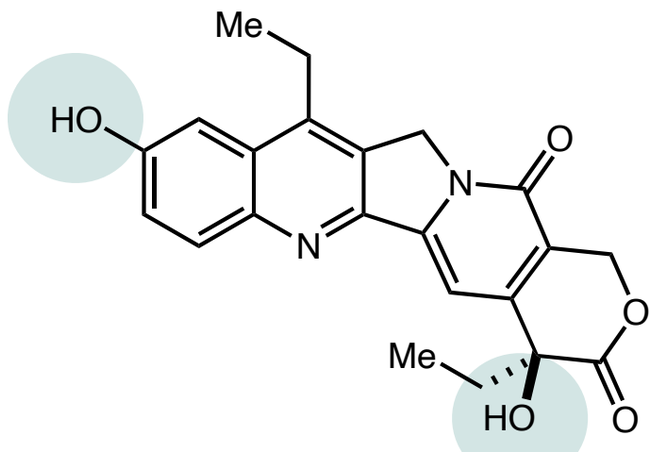
Metabolism

- *Protect active drugs from first-pass effect (pre systemic metabolism)*

- ***Prodrug design to protect metabolically labile group***

Prodrug design to protect metabolically labile group

Why SN-38 (active metabolite) cannot be used directly



SN-38

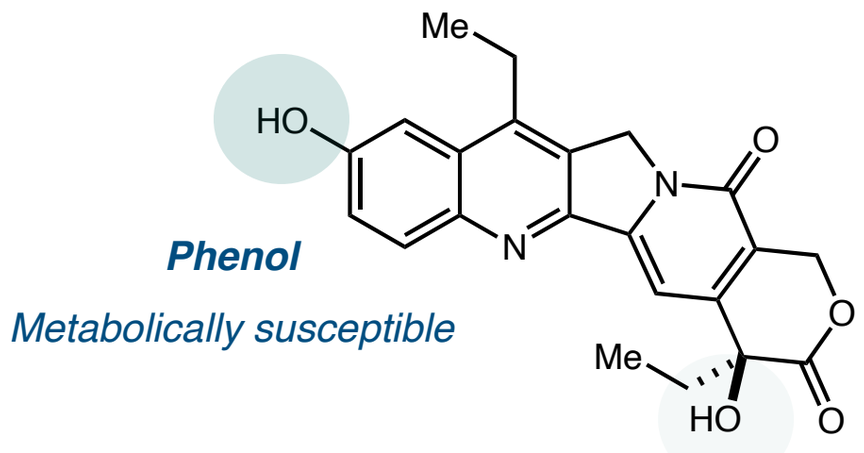
Topoisomerase I inhibitor

Anticancer drug

Which site to esterify?

Prodrug design to protect metabolically labile group

Why SN-38 (active metabolite) cannot be used directly

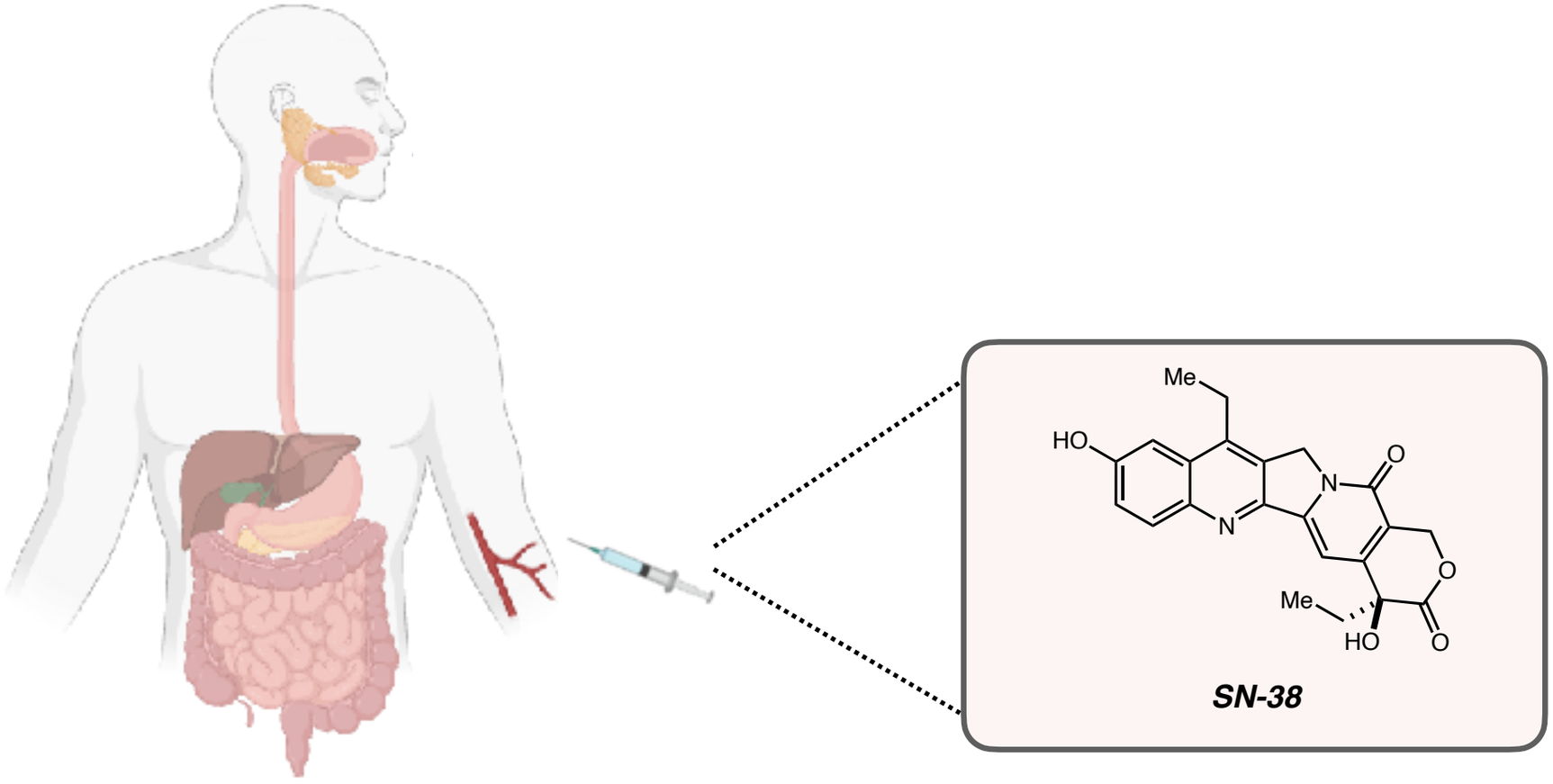


Phenol

Metabolically susceptible

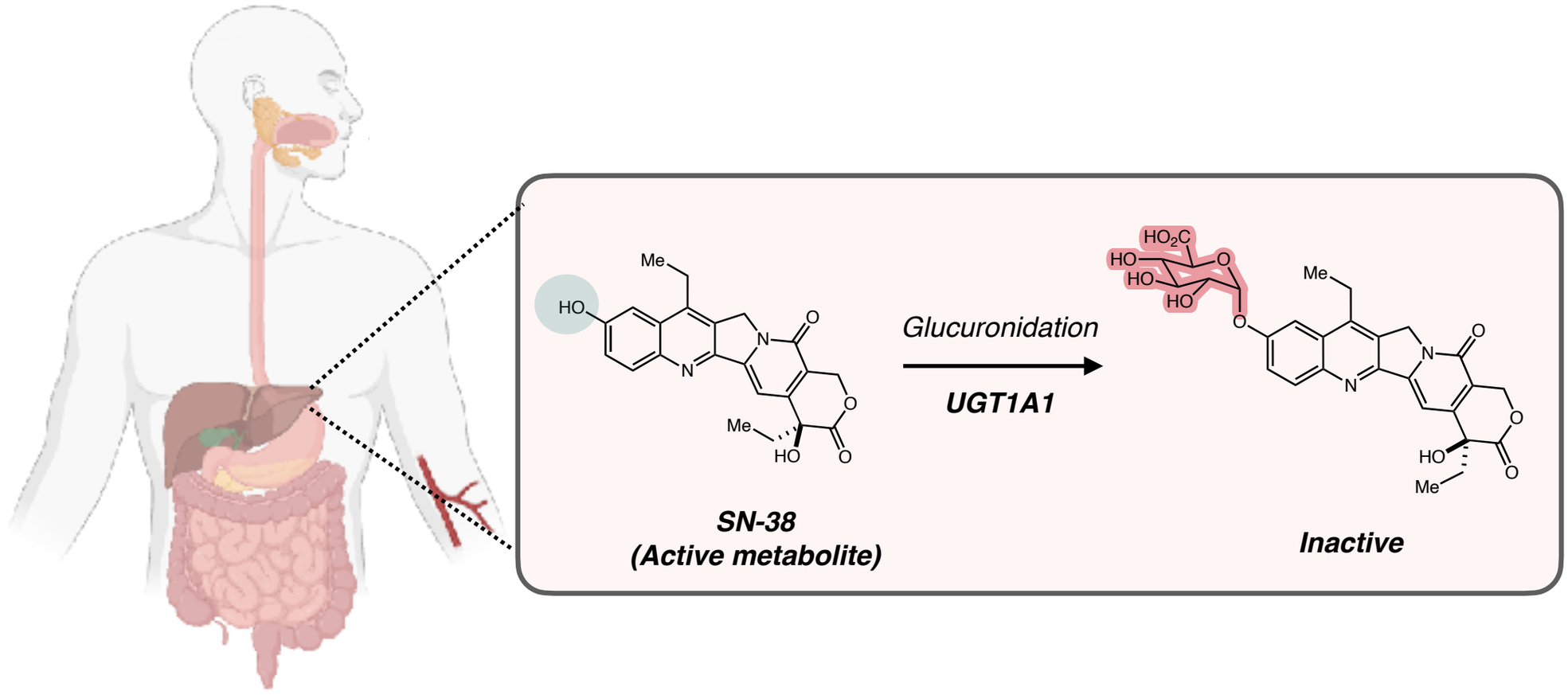
Prodrug design to protect metabolically labile group

Why SN-38 (active metabolite) cannot be used directly



Prodrug design to improve 'M' in ADME

Why SN-38 (active metabolite) cannot be used directly

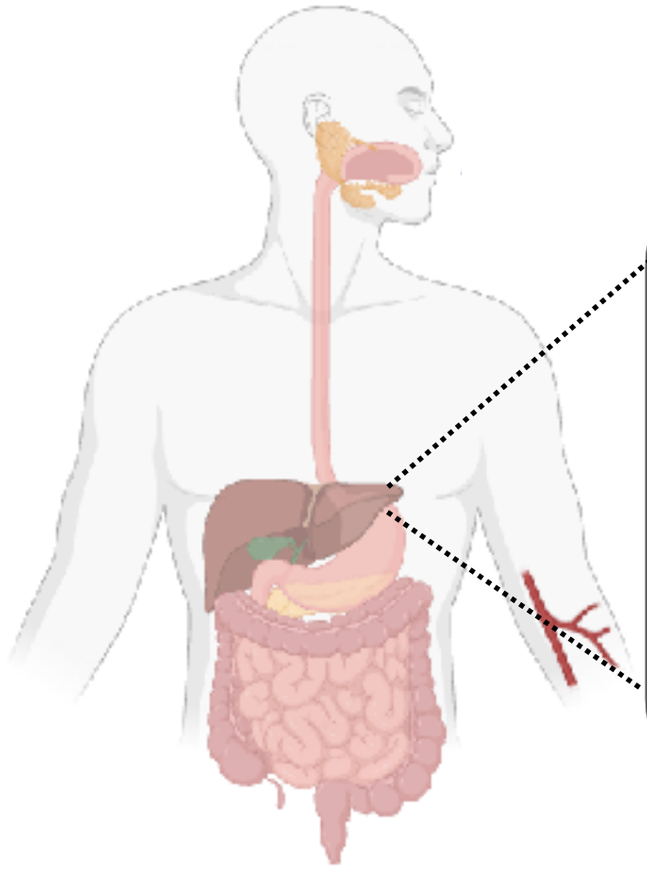


SN-38
(Active metabolite)

Inactive

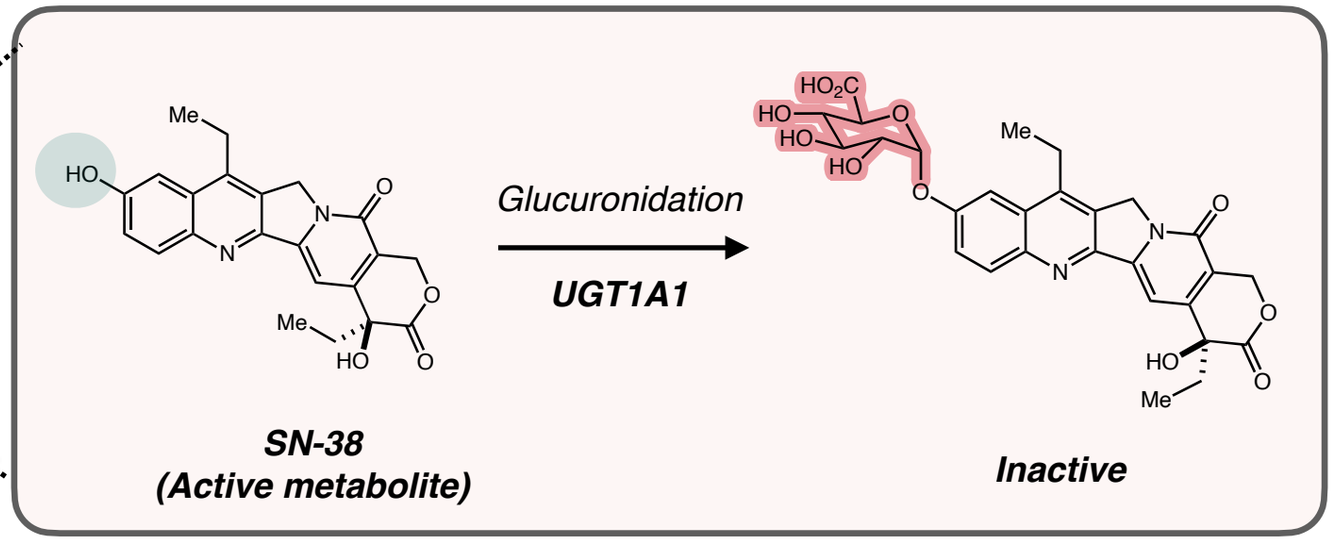
Prodrug design to improve 'M' in ADME

Why SN-38 (active metabolite) cannot be used directly



Phase II metabolism

Attachment of bulky, polar groups to drug metabolites to make them more water-soluble and easier to excrete

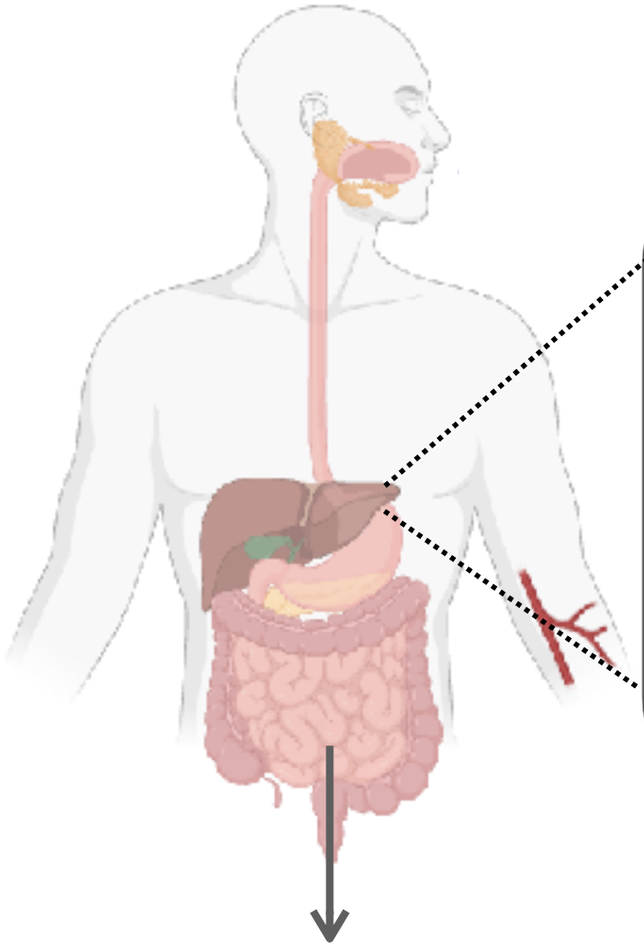


SN-38 (Active metabolite)

Inactive

Prodrug design to improve 'M' in ADME

Why SN-38 (active metabolite) cannot be used directly

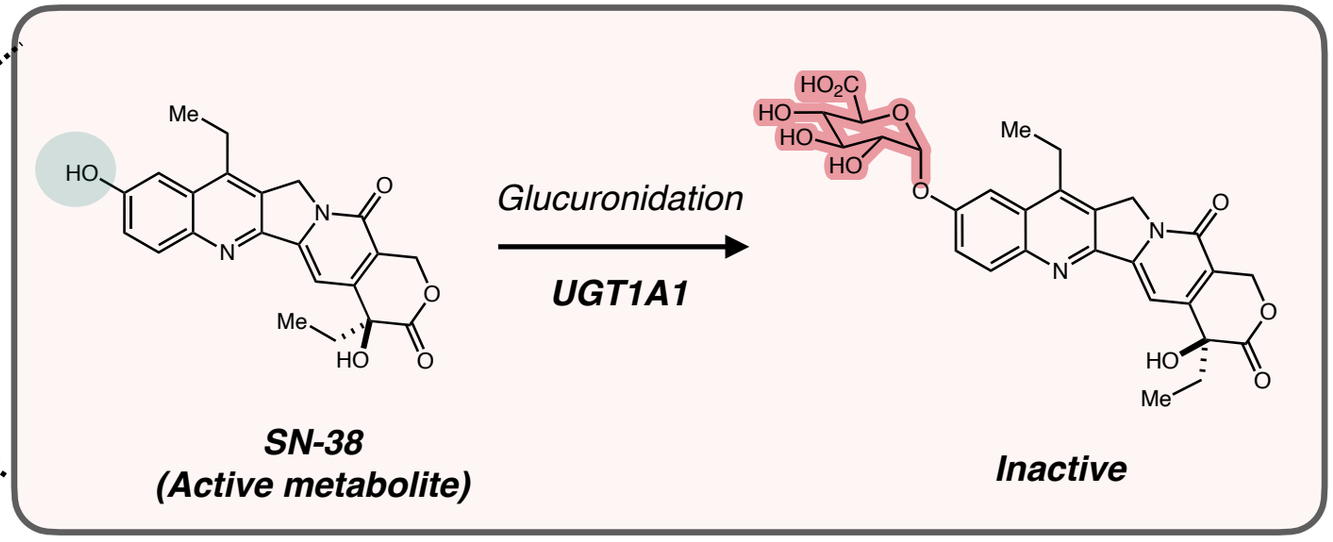


Urine

Glucuronidated SN-38

Phase II metabolism

Attachment of bulky, polar groups to drug metabolites to make them more water-soluble and easier to excrete



SN-38 (Active metabolite)

Inactive

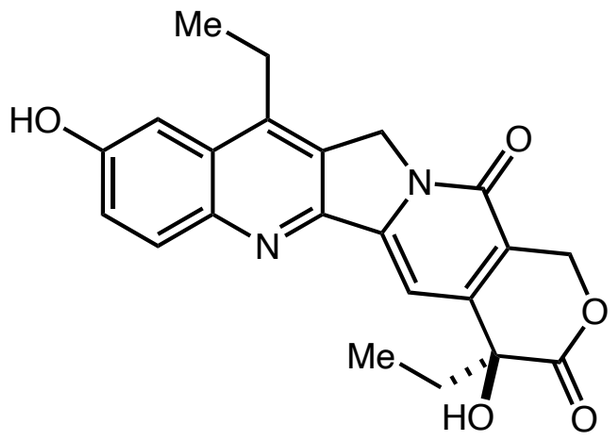
First-pass effect

Glucuronidated SN-38 is highly water-soluble and gets excreted before systemic circulation

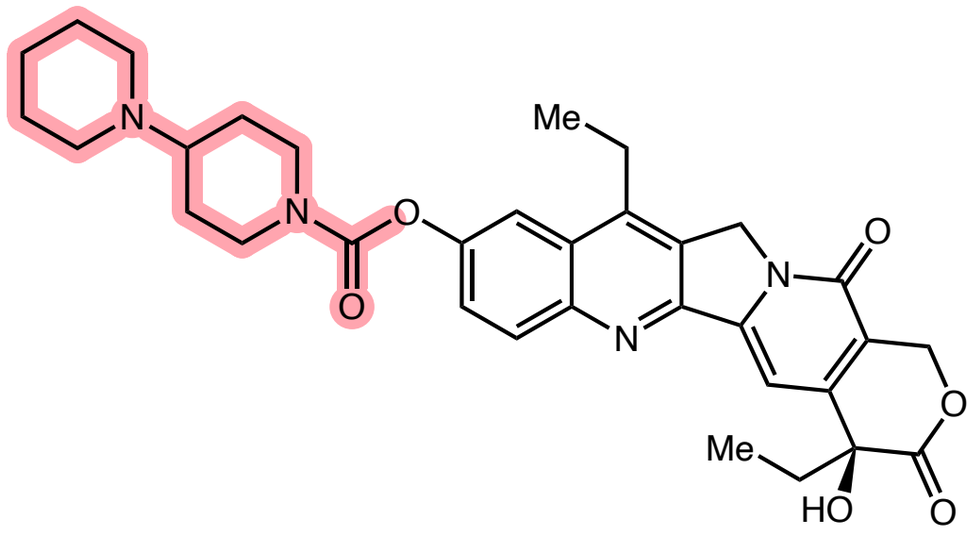
Prodrug design to improve 'M' in ADME

Why SN-38 (active metabolite) cannot be used directly

SN-38



Camptosar™



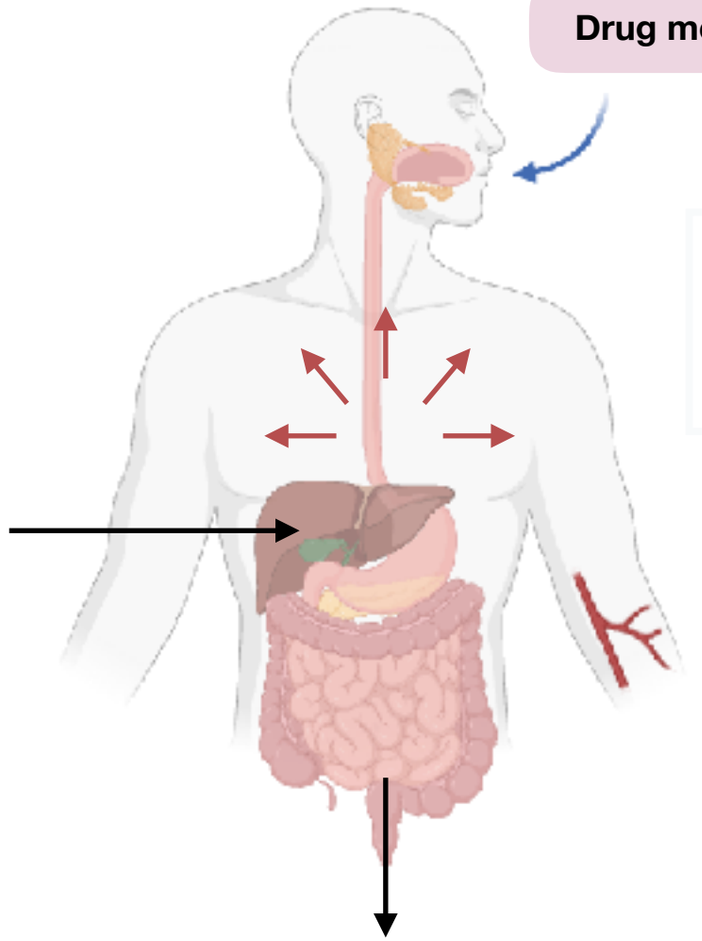
Irinotecan (Camptosar™)

Pfizer

Prodrug design to control 'E' in ADME

Excretion

Drug molecule — **Promoiety**



***A**bsorption*

- *Higher aqueous solubility*
- *Better membrane premeation*

***M**etabolism*

- *Protect active drugs from first-pass effect (pre-systemic metabolism)*

***D**istribution*

- *Effective concentrations at difficult-to-target tissues*

***E**xcretion*

- *Delayed excretion to reduce dosing frequency*

- ***Prodrug design to extend drug half-life***

Why would you want to delay excretion of a drug?

Why would you want to delay excretion of a drug?

Mental illness patients

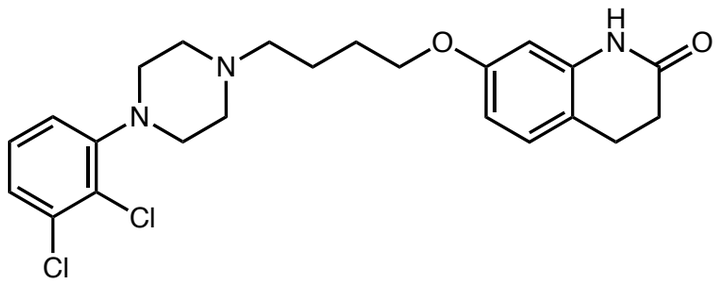
Difficulty managing daily pills

Poor adherence

Prodrug design to delay 'E' in ADME

Abilify™ and Aristada™

Abilify™

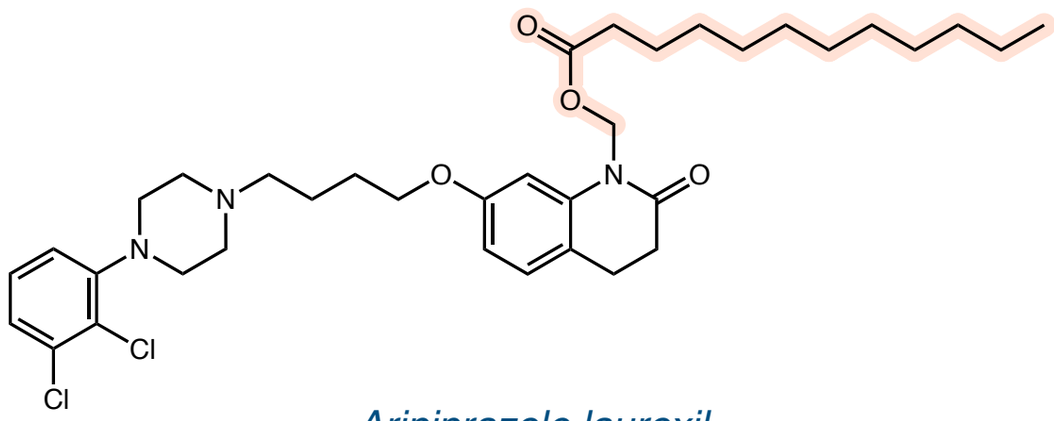


Aripiprazole

Dopamine-serotonin system stabiliser

Otsuka

Aristada™



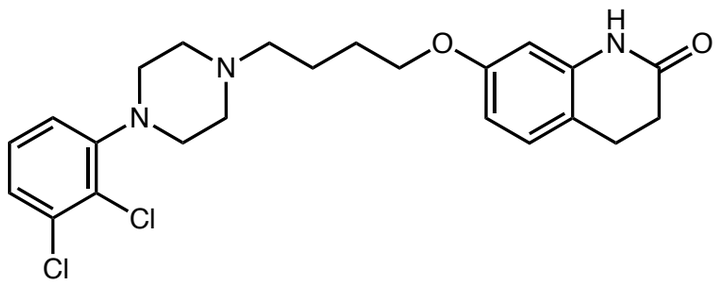
Aripiprazole lauroxil

Alkermes

Prodrug design to delay 'E' in ADME

Abilify™ and Aristada™

Abilify™

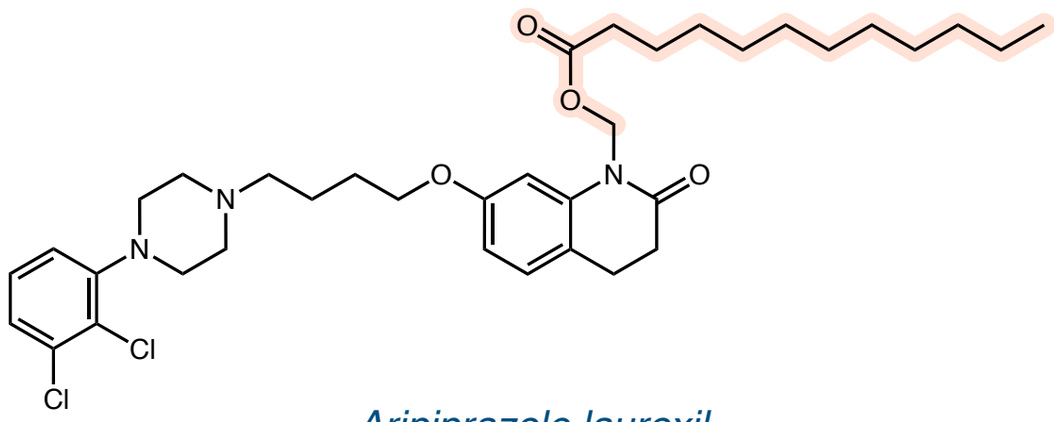


Aripiprazole

Oral intake

Once (10-15 mg)/ day

Aristada™



Aripiprazole lauroxil

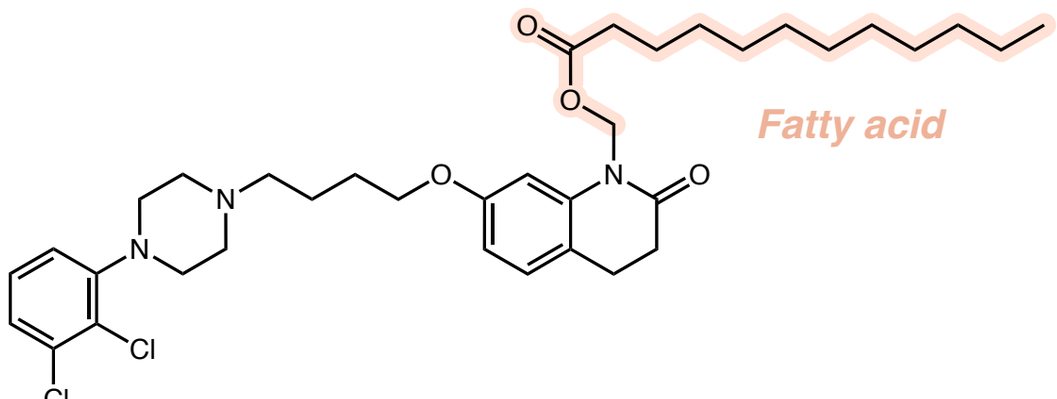
Long-acting injectable

Once/ 4-8 weeks

Prodrug design to delay 'E' in ADME

Abilify™ and Aristada™

Aristada™



Fatty acid

Aripiprazole lauroxil

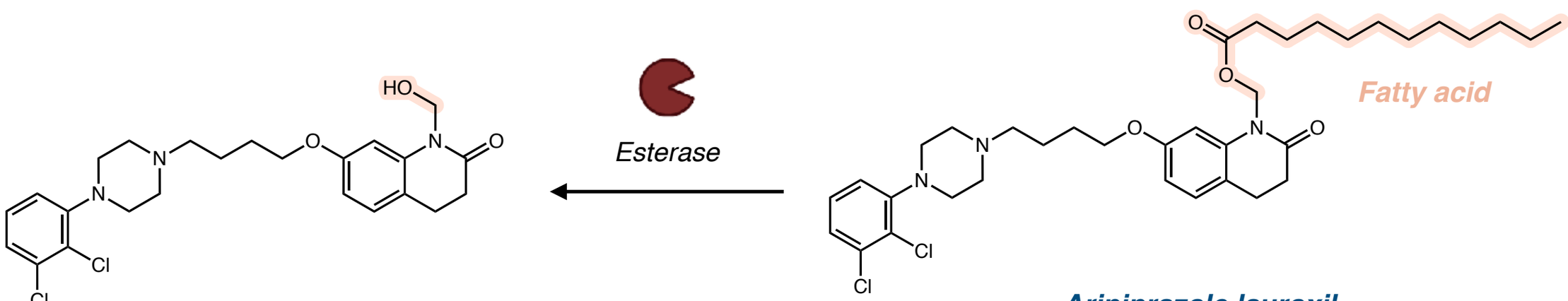
Long-acting injectable

Once/ 4-8 weeks

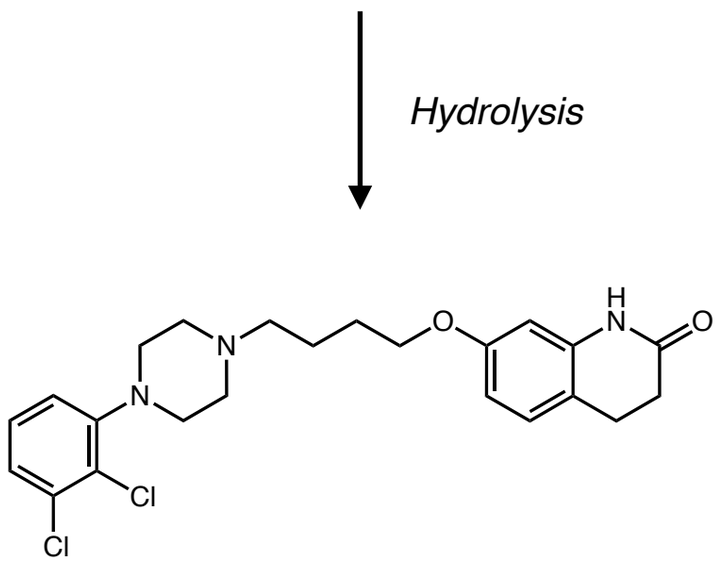
Prodrug design to delay 'E' in ADME

Abilify™ and Aristada™

Aristada™



Aripiprazole lauroxil



Aripiprazole
(Active metabolite)

Long-acting injectable

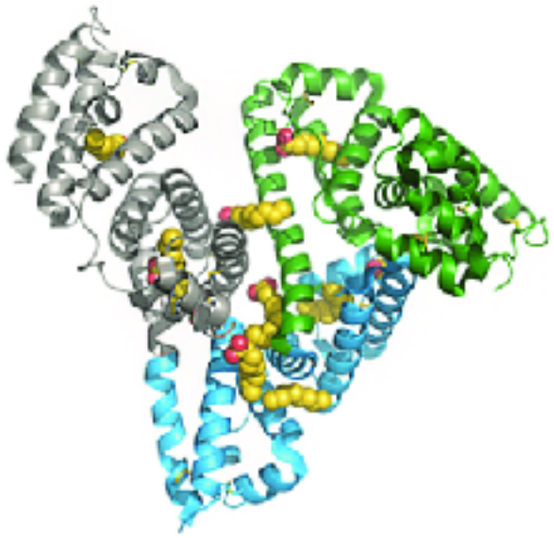
Once/ 4-8 weeks

Citrome, L.; Correll, C.; Cutler, A.; Dunbar, M.; Hoberg, A.; B.; Weiden, P.; McDonnell, D. *Neuropsychiatr. Dis. Treat.* **2025**, *21*, 575.

Prodrug design to delay 'E' in ADME

Abilify™ and Aristada™

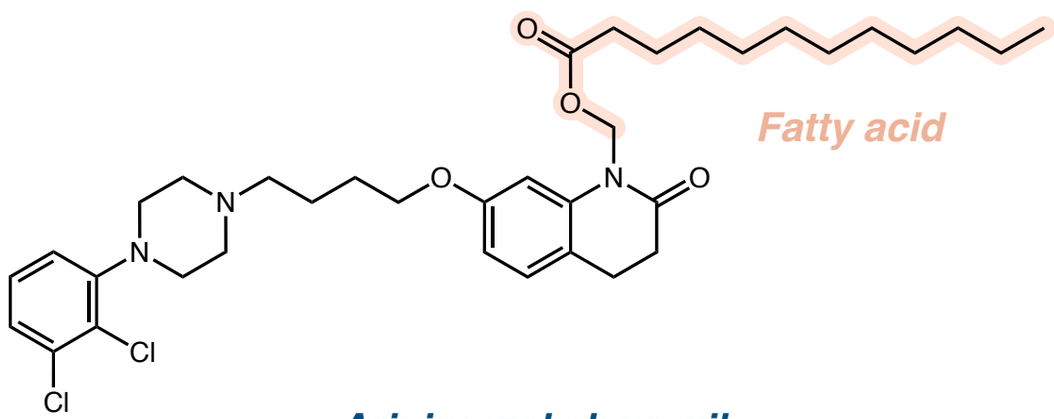
Albumin-fatty acid complex



PDB: 1E7E

7 binding sites for fatty acid

Aristada™



Aripiprazole lauroxil

Long-acting injectable

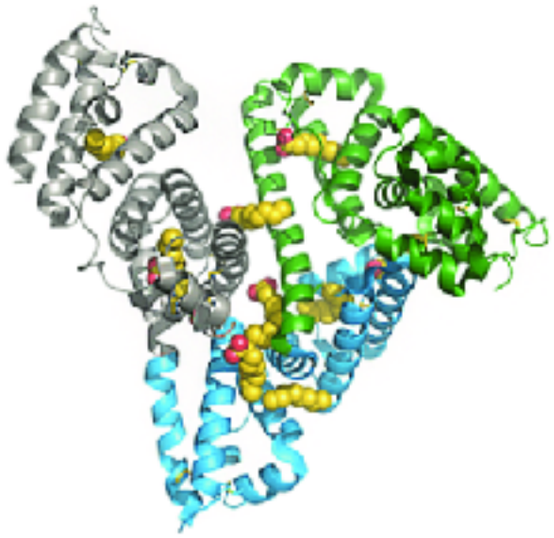
Once/ 4-8 weeks

Li, Y.; Wang, Y.; Wei, Q.; Zheng, X.; Tang, L.; Kong, D.; Gong, M. *Sci. Rep.* **2015**, *5* (1), 18039.

Prodrug design to delay 'E' in ADME

Abilify™ and Aristada™

Albumin-fatty acid complex



PDB: 1E7E

7 binding sites for fatty acid

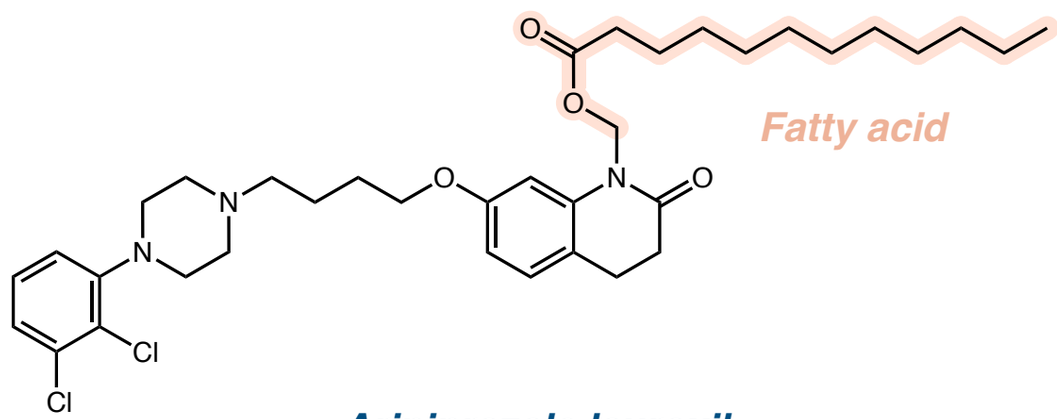
Albumin's naturally long half-life

~ 19 days

⇩

Reduced excretion rate of fatty acid-functionalized drugs

Aristada™



Fatty acid

Aripiprazole lauroxil

Long-acting injectable

Once/ 4-8 weeks

Prodrug design to delay 'E' in ADME

Patient and caregiver experiences with long-acting injectable antipsychotic drugs

"[After injection], at least you wouldn't become others' burden, you could gain more self-control.
(Like who?) Mother, my family, or my boss."

Participant F14 (female, 52 years old, schizophrenia)

"I hope to totally replace oral pills. I don't know how to explain if others ask me about what pills I take at my workplace. I am afraid to tell them I have mental illness."

Participant M06 (male, 39 years old, schizophrenia)

Avoiding daily oral medication increased patients' sense of independence and shielded them from social stigma

Chiu, L.-L.; Liu, C.-H.; Chu, C.-L.; Lin, H.-L.; Lii, S.-C. *Neuropsychiatr. Dis. Treat.* **2019**, *Volume 15*, 1797.

Prodrug design to delay 'E' in ADME

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Participant M06 (male, 39 years old, schizophrenia)

"Before my son's disease, I liked going to the gym, walking in the park, and riding a bike. I absolutely couldn't do it anymore because I must take care of my son… [with once-monthly LAI], life became more comfortable and balanced"

Caregiver of schizophrenic son

Reducing dosing frequency lessened caregiver burden

Pappa, S.; Yildirim, M.; Loomer, S.Nag, S.; Guillaume, X.; Oladini, B.; Madera-McDonough, J.; Such, P. *Patient Prefer. Adherence* **2025**, *Volume 19*, 1179.

Prodrug design to delay ‘E’ in ADME

Patient and caregiver experiences with long-acting injectable antipsychotic drugs

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[with once-monthly LAI], life became more comfortable and balanced”

Caregiver of schizophrenic son

Prodrug design can extend drug half-life by harnessing biological carriers

Prodrugs beyond science: business & regulatory strategy

- ***Prodrug: patent evergreening strategy***
- ***Prodrug: built-in shortcut to FDA approval***

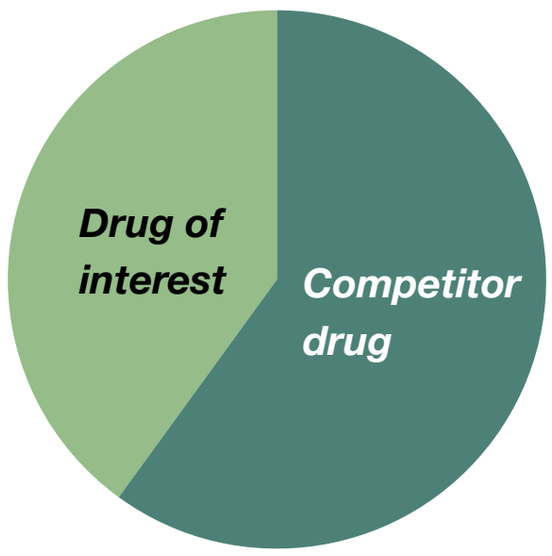
Prodrugs beyond science: business & regulatory strategy

- ***Prodrug: patent evergreening strategy***
- *Prodrug: built-in shortcut to FDA approval*

Prodrug: patent evergreening strategy

Patent lifecycle

Drug molecule



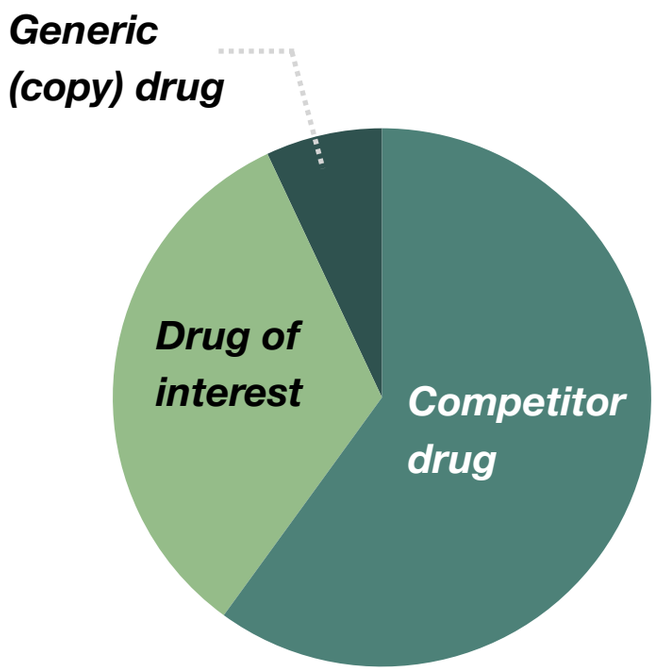
Gadiya, Y.; Gribbon, P.; Hofmann-Apitius, M.; Zaliani, A. *Artif. Intell. Life Sci.* **2023**, *3*, 100069.

Prodrug: patent evergreening strategy

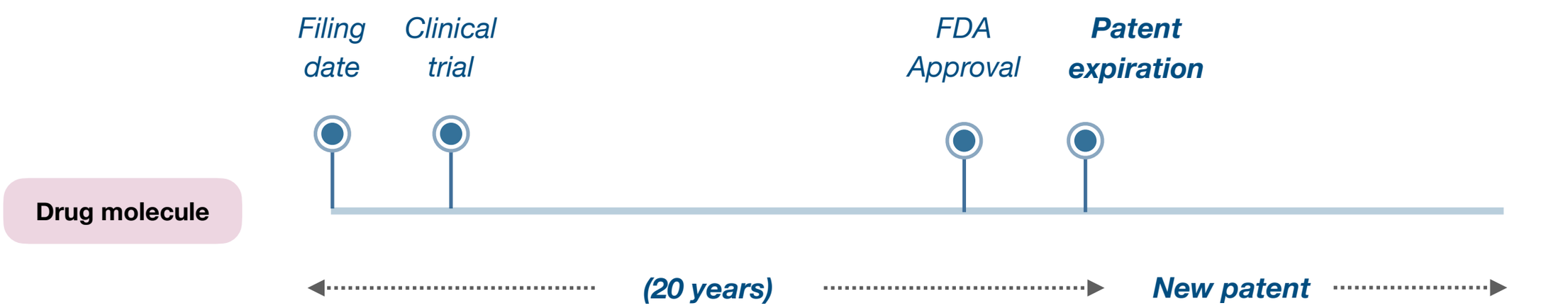
Patent lifecycle

Drug molecule

[After patent expiration]



Prodrug: patent evergreening strategy

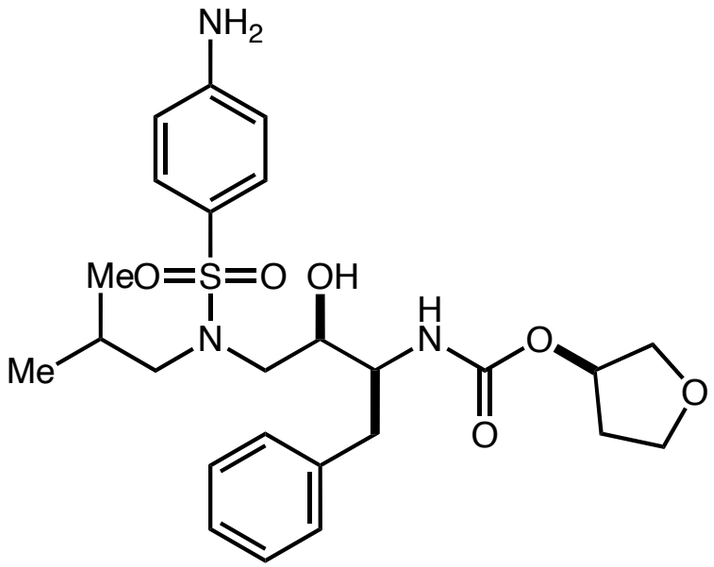


Developing a prodrug creates a new patentable molecule

Prodrug: patent evergreening strategy

Extending market exclusivity

Agenerase™



Amprenavir

HIV-1 protease inhibitor

Lexiva™

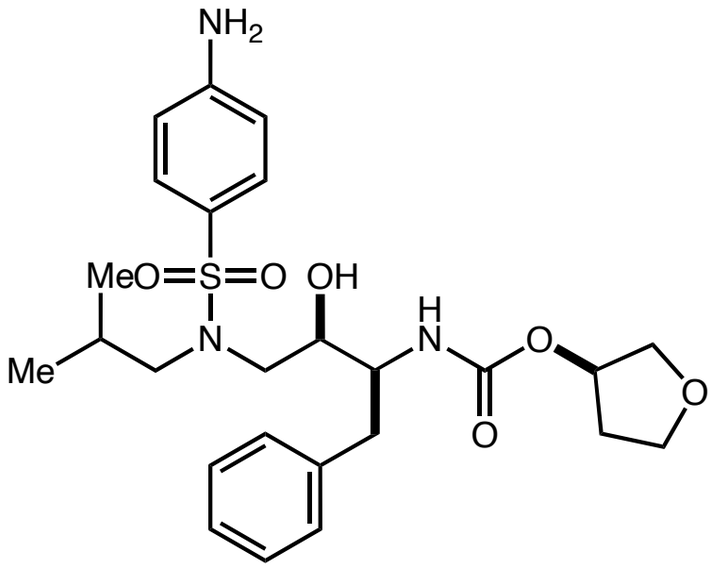
gsk GlaxoSmithKline

Wire, M. B.; Shelton, M. J.; Studenberg, S. *Clin. Pharmacokinet.* **2006**, *45* (2), 137.

Prodrug: patent evergreening strategy

Extending market exclusivity

Agenerase™



Amprenavir

HIV-1 protease inhibitor

Patent valid until 2013

Lexiva™

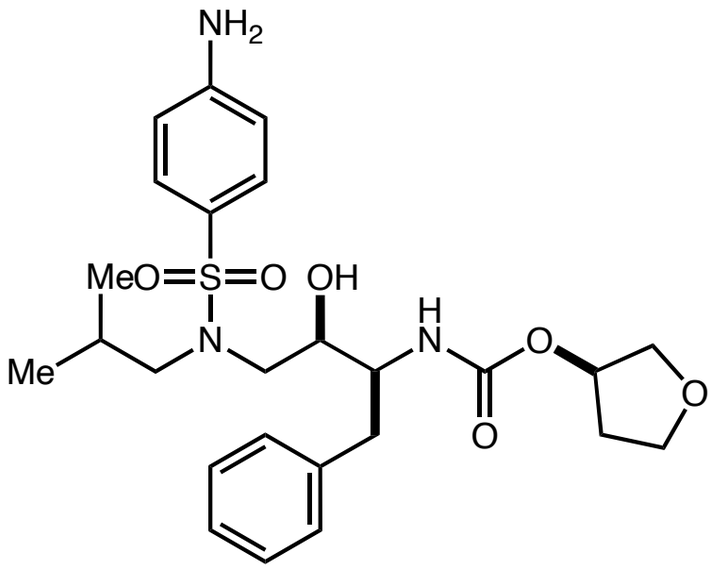
GlaxoSmithKline

Wire, M. B.; Shelton, M. J.; Studenberg, S. *Clin. Pharmacokinet.* **2006**, *45* (2), 137.

Prodrug: patent evergreening strategy

Extending market exclusivity

Agenerase™

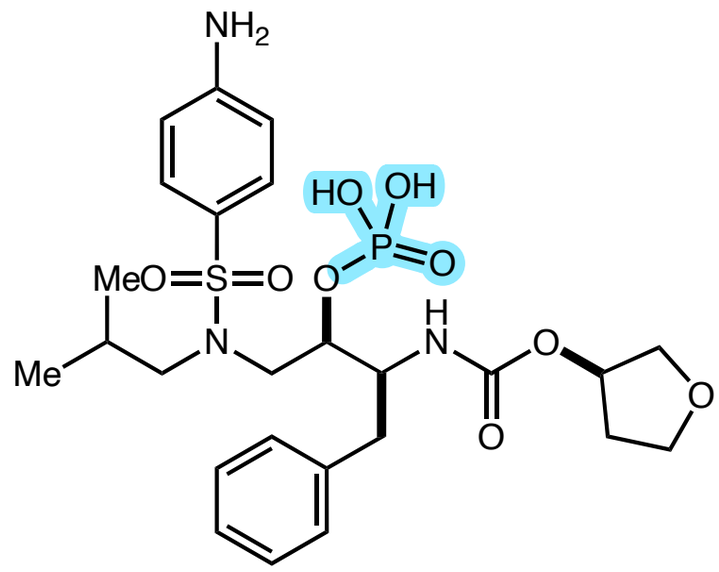


Amprenavir

HIV-1 protease inhibitor

Patent valid until 2013

Lexiva™



Fosamprenavir

Patent valid until 2017

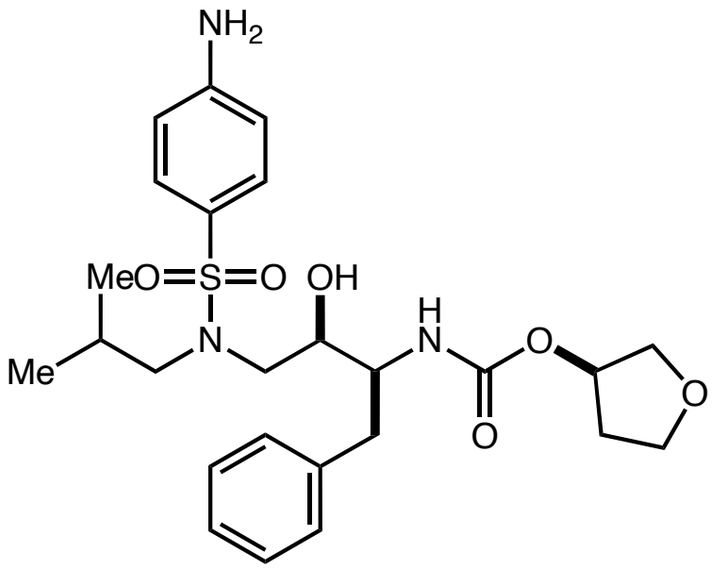
GlaxoSmithKline

Wire, M. B.; Shelton, M. J.; Studenberg, S. *Clin. Pharmacokinet.* **2006**, *45* (2), 137.

Prodrug: patent evergreening strategy

Extending market exclusivity

Agenerase™

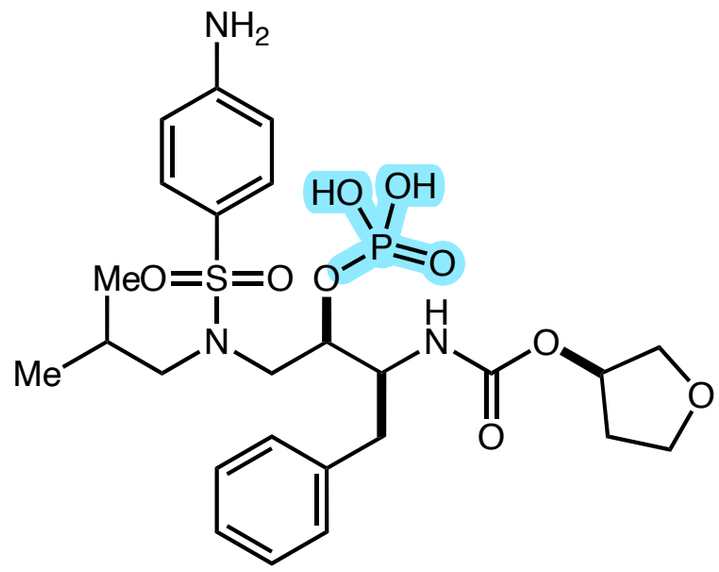


Amprenavir

HIV-1 protease inhibitor

Patent valid until 2013

Lexiva™



Fosamprenavir

Patent valid until 2017

GlaxoSmithKline

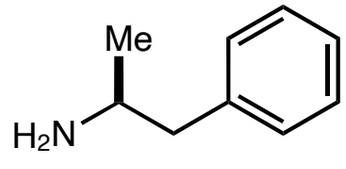
Prodrug design had extended the patent duration

Prodrug: patent evergreening strategy

Case of Vyvanse™

Prodrug: patent evergreening strategy

ADHD drug Dexedrine™



Dexedrin™

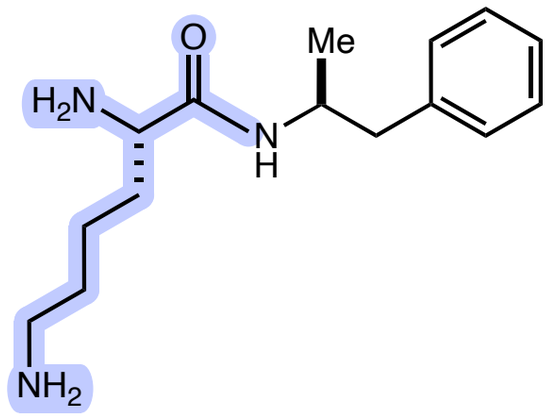
(d-amphetamine)

Treatment for ADHD

Initial approval in 1976

Prodrug: patent evergreening strategy

Vyvanse™: Prodrug of Dexedrine™



***Pro-moiety:** L-Lysine*

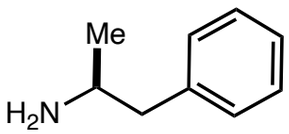
NEW RIVER PHARMACEUTICALS

Takeda

Prodrug: patent evergreening strategy

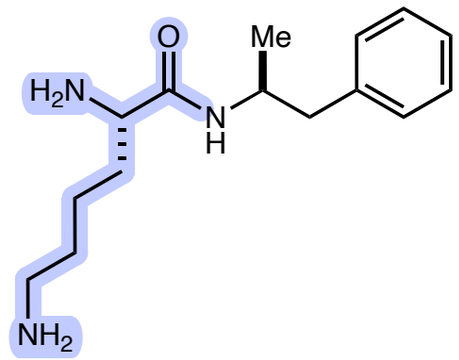
Advantages of Vyvanse™ (prodrug) over Dexedrine™ (active metabolite)

Dexedrine™



No patent protection

Vyvanse™



Patent filing date: ***Dec 2005***

Main patent expiry: ***Feb 2023***

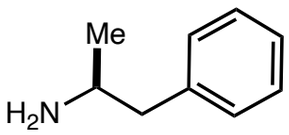
Pedriatic exclusivity granted until Aug 2023

Siddalingaiah, S.; Fugh-Berman, A. *J. Eval. Clin. Pract.* **2022**, *28* (6), 1119.

Prodrug: patent evergreening strategy

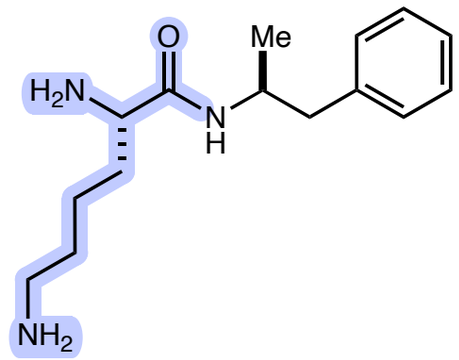
Advantages of Vyvanse™ (prodrug) over Dexedrine™ (active metabolite)

Dexedrine™



$ 15-30/month

Vyvanse™



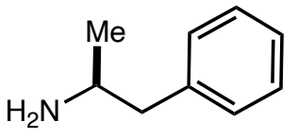
$ 300-375/month

GoodRx and drugs.com (Vyvanse and Dexedrine)

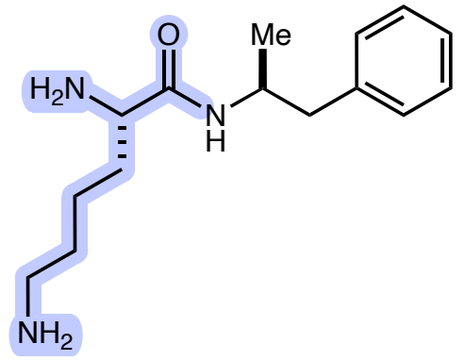
Prodrug: patent evergreening strategy

Advantages of Vyvanse™ (prodrug) over Dexedrine™ (active metabolite)

Dexedrine™



Vyvanse™



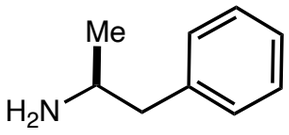
Cumulative global revenues
$ 30 billion

Peak annual sales (2022)
$ 4.3 billion

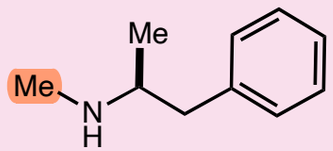
Prodrug: patent evergreening strategy

Advantages of Vyvanse™ (prodrug) over Dexedrine™ (active metabolite)

Dexedrine™



(c.f. Methamphetamine "Meth")



Vyvanse™

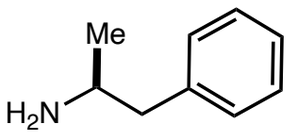
Dexedrine™ (active metabolite): significant abuse potential

Huttunen, K. M.; Raunio, H.; Rautio, J. *Pharmacol. Rev.* **2011**, *63* (3), 750.

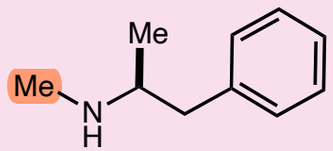
Prodrug: patent evergreening strategy

Advantages of Vyvanse™ (prodrug) over Dexedrine™ (active metabolite)

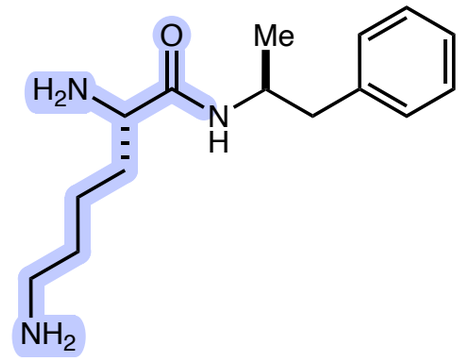
Dexedrine™



(c.f. Methamphetamine "Meth")



Vyvanse™



No intrinsic activity

Hydrolysis to release the active metabolite is rate-limited

- Cannot produce a rapid CNS spike

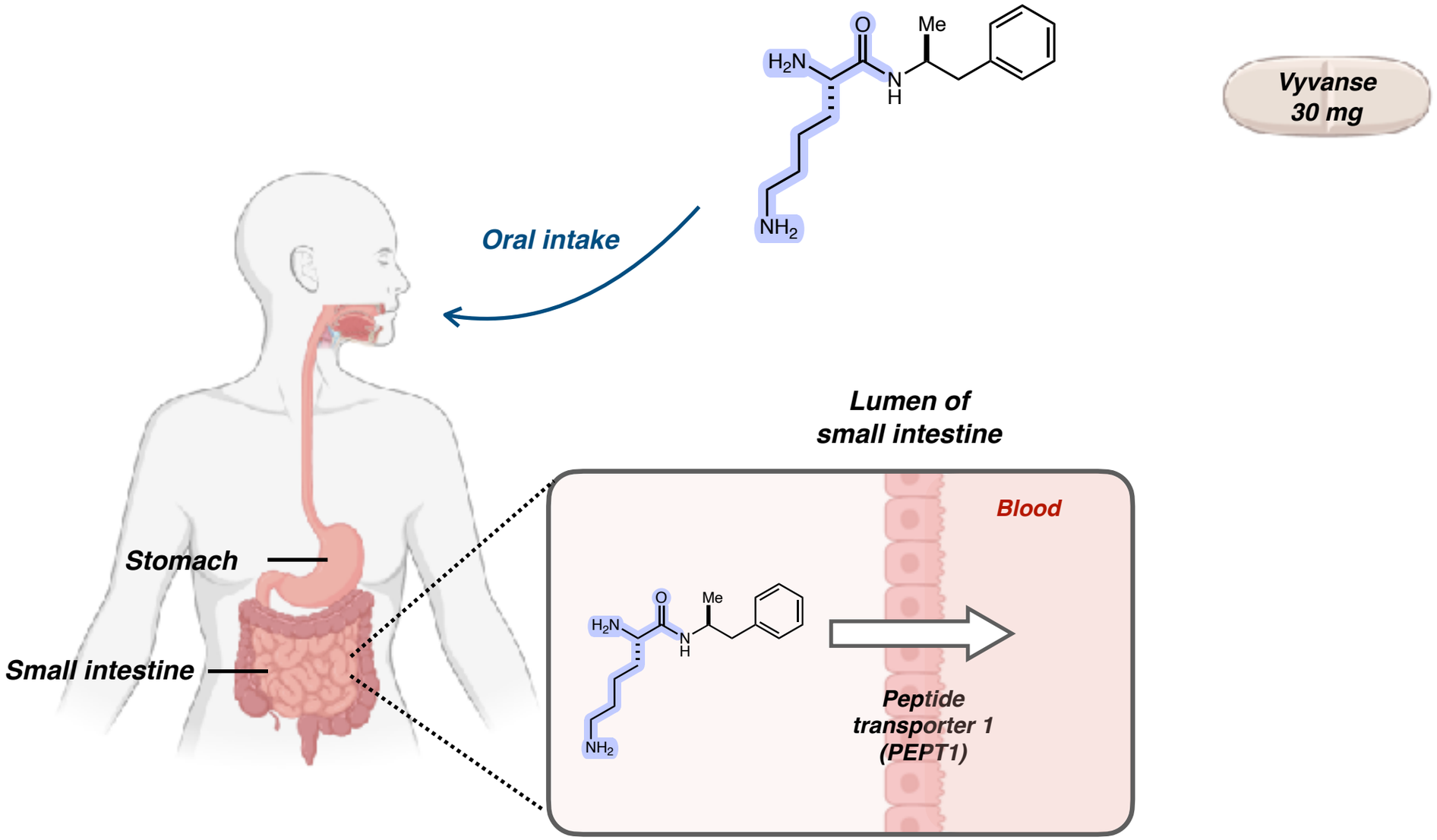
- Snorting/injecting ineffective

Vyvanse™ (prodrug): lower abuse potential

Huttunen, K. M.; Raunio, H.; Rautio, J. *Pharmacol. Rev.* **2011**, *63* (3), 750.

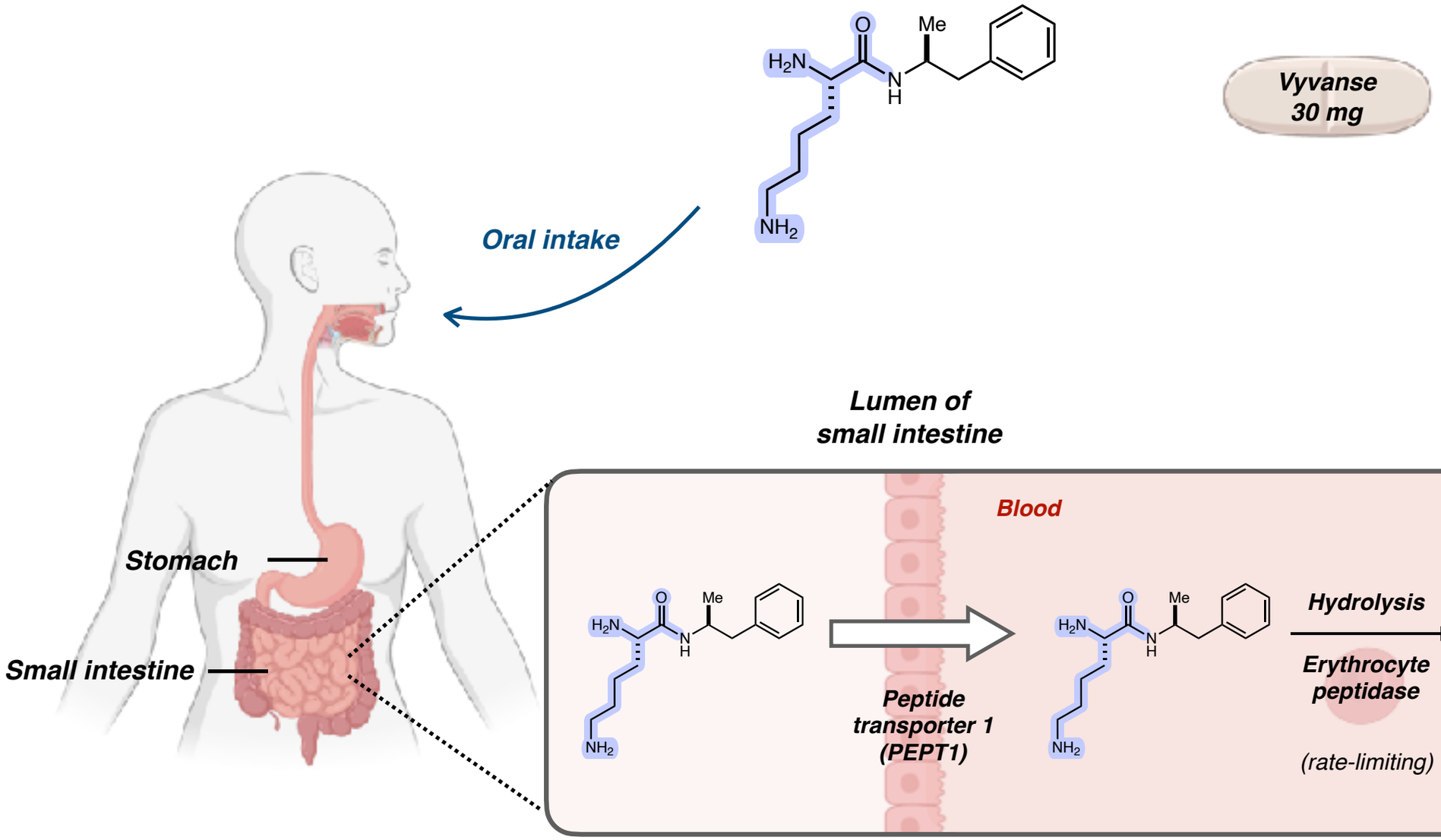
Prodrugs: Patent evergreening strategy

Case of Vyvanse™



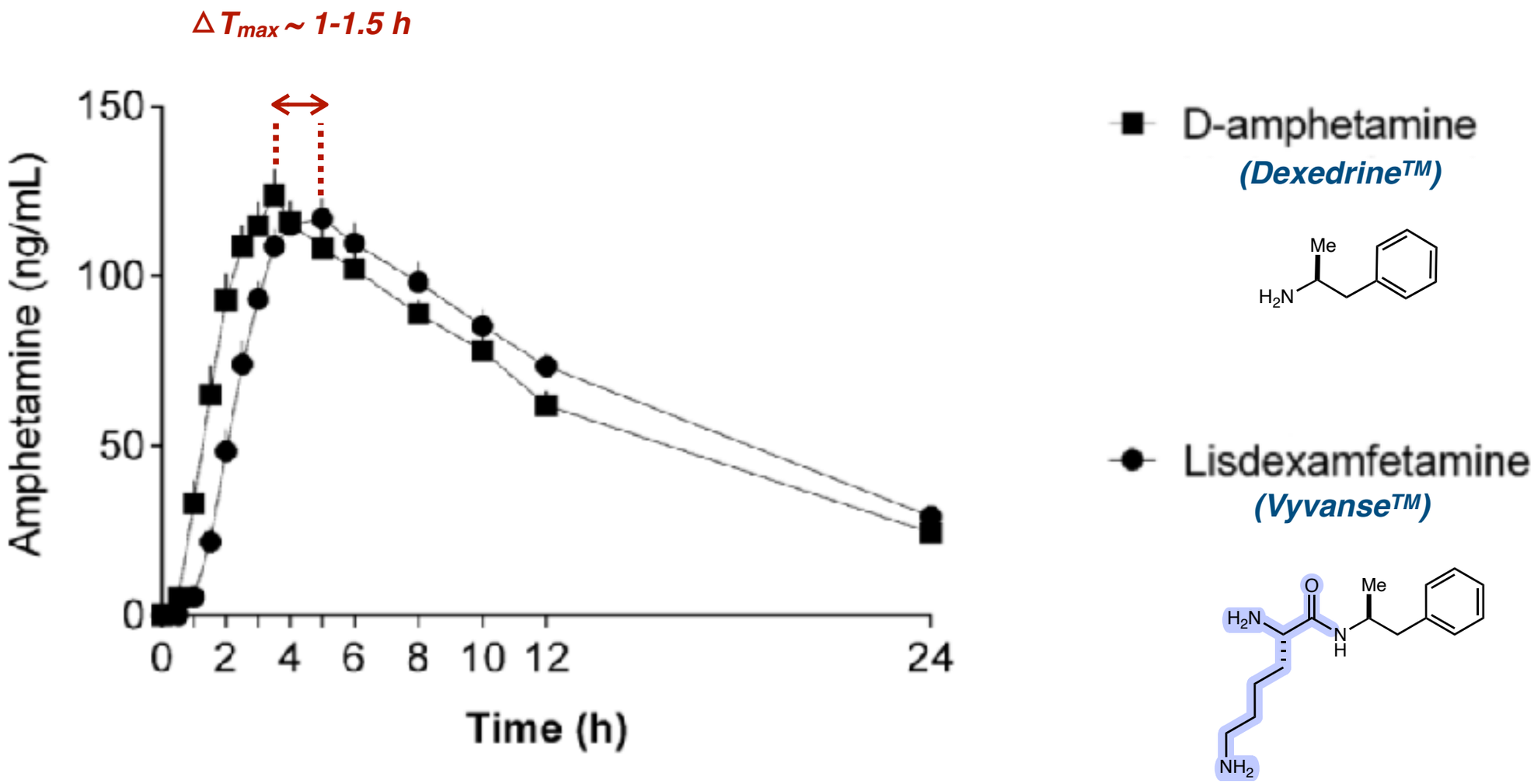
Prodrugs: Patent evergreening strategy

Case of Vyvanse™



Prodrugs: Patent evergreening strategy

Advantages of Vyvanse™ (prodrug) over Dexedrine™ (active metabolite)



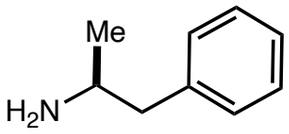
Vyvanse™ (prodrug): delayed T_{max} → longer-lasting effect

Dolder, P. C.; Strajhar, P.; Vizeli, P.; Hammann, F.; Odermatt, A.; Liechti, M. E. *Front. Pharmacol.* **2017**, *8*, 617.

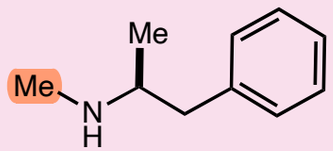
Prodrug: patent evergreening strategy

Advantages of Vyvanse™ (prodrug) over Dexedrine™ (active metabolite)

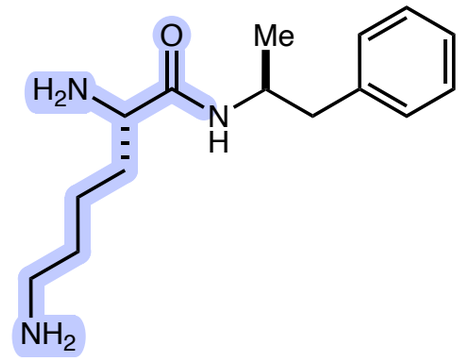
Dexedrine™



(c.f. Methamphetamine "Meth")



Vyvanse™



Takeda

Cumulative global revenues
$ 30 billion

Peak annual sales (2022)
$ 4.3 billion

Beyond novel patent space, prodrug design enables safer prescriptions

Prodrugs beyond science: business & regulatory strategy

- *Prodrug: patent evergreening strategy*
- ***Prodrug: built-in shortcut to FDA approval***

Prodrug: built-in shortcut to FDA approval

Section 505(b)(2) of FDA guideline

Section 505 of the Act describes three types of new drug applications: (1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1)); (2) an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)); and (3) an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (section 505(j)). Note that a supplement to an application is a new drug application.

FDA

U.S. Food and Drug Administration. Guidance for Industry, Center for Drug Evaluation and Research (CDER), October 1999.

Prodrug: built-in shortcut to FDA approval

Section 505(b)(2) of FDA guideline

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What this means:

If active metabolite is already FDA-approved,
prodrug can reference existing data without right of access

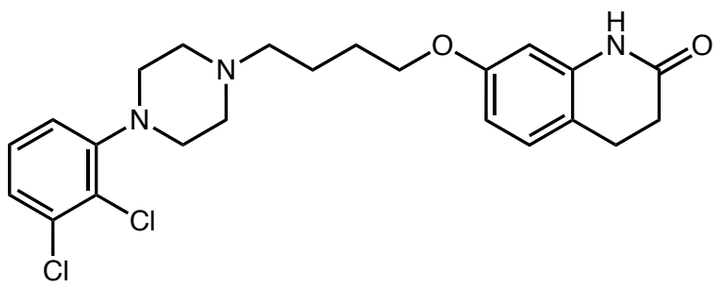
→ shortens approval path

Freije, I.; Lamouche, S.; Tanguay, M. *Ther. Innov. Regul. Sci.* **2020**, *54* (1), 128.

Prodrug: built-in shortcut to FDA approval

Aristada™: prodrug approved via 505(b)(2)

Abilify™

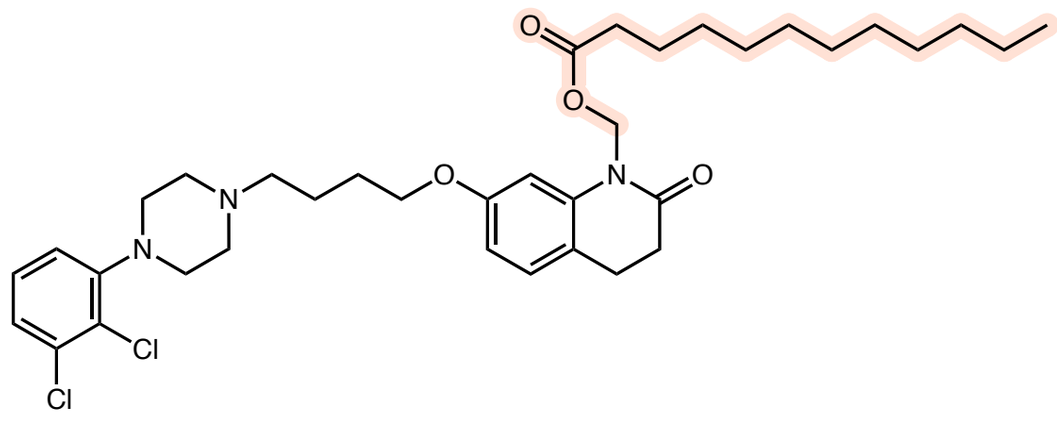


FDA approval in 2002

Patent expiry in 2015

Otsuka

Aristada™



FDA approval in 2015

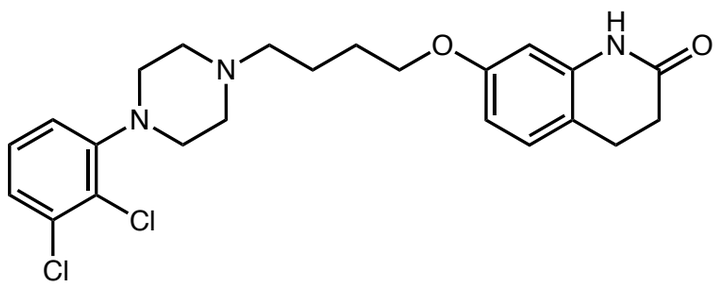
Alkermes

Holman, C. M. *Biotechnol. Law Rep.* **2023**, *42* (3), 118.

Prodrug: built-in shortcut to FDA approval

Aristada™: prodrug approved via 505(b)(2)

Abilify™

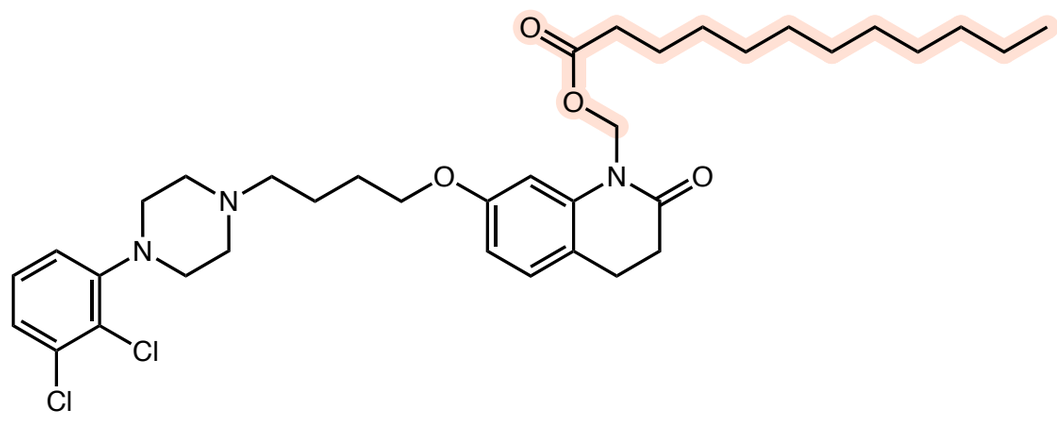


FDA approval in 2002

Pivotal Phase 2,3 efficacy studies in schizophrenia

Large-scale preclinical and toxicology studies

Aristada™



Leveraged the existing data

Pivotal Phase 2,3 efficacy studies in schizophrenia

Large-scale preclinical and toxicology studies

Newly carried out studies

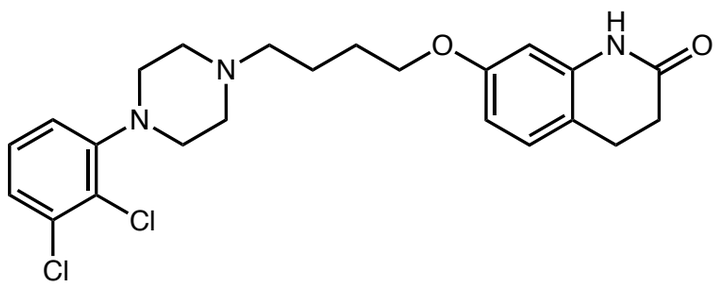
Bridging clinical work to show that Aristada™ does not introduce unexpected risks

Holman, C. M. *Biotechnol. Law Rep.* **2023**, *42* (3), 118.

Prodrug: built-in shortcut to FDA approval

Aristada™: prodrug approved via 505(b)(2)

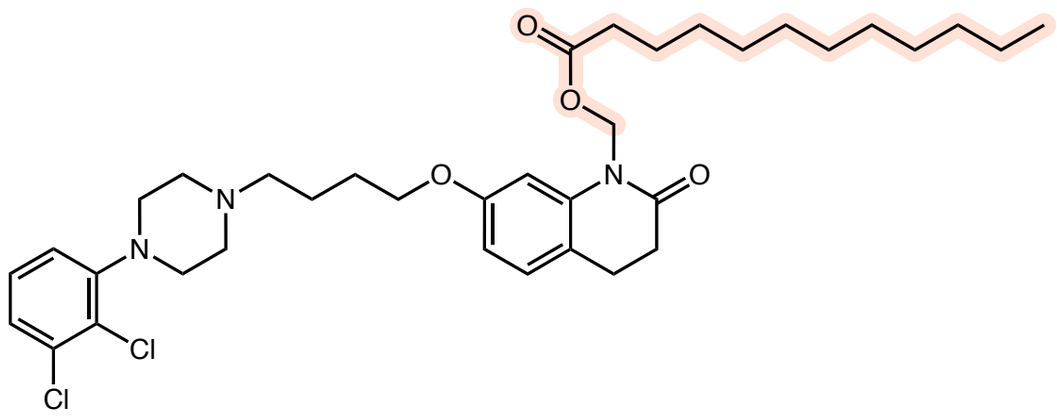
Abilify™



~10 years from clinical entry to market

Otsuka

Aristada™



Phase 1 start: 2012

FDA approval: 2015

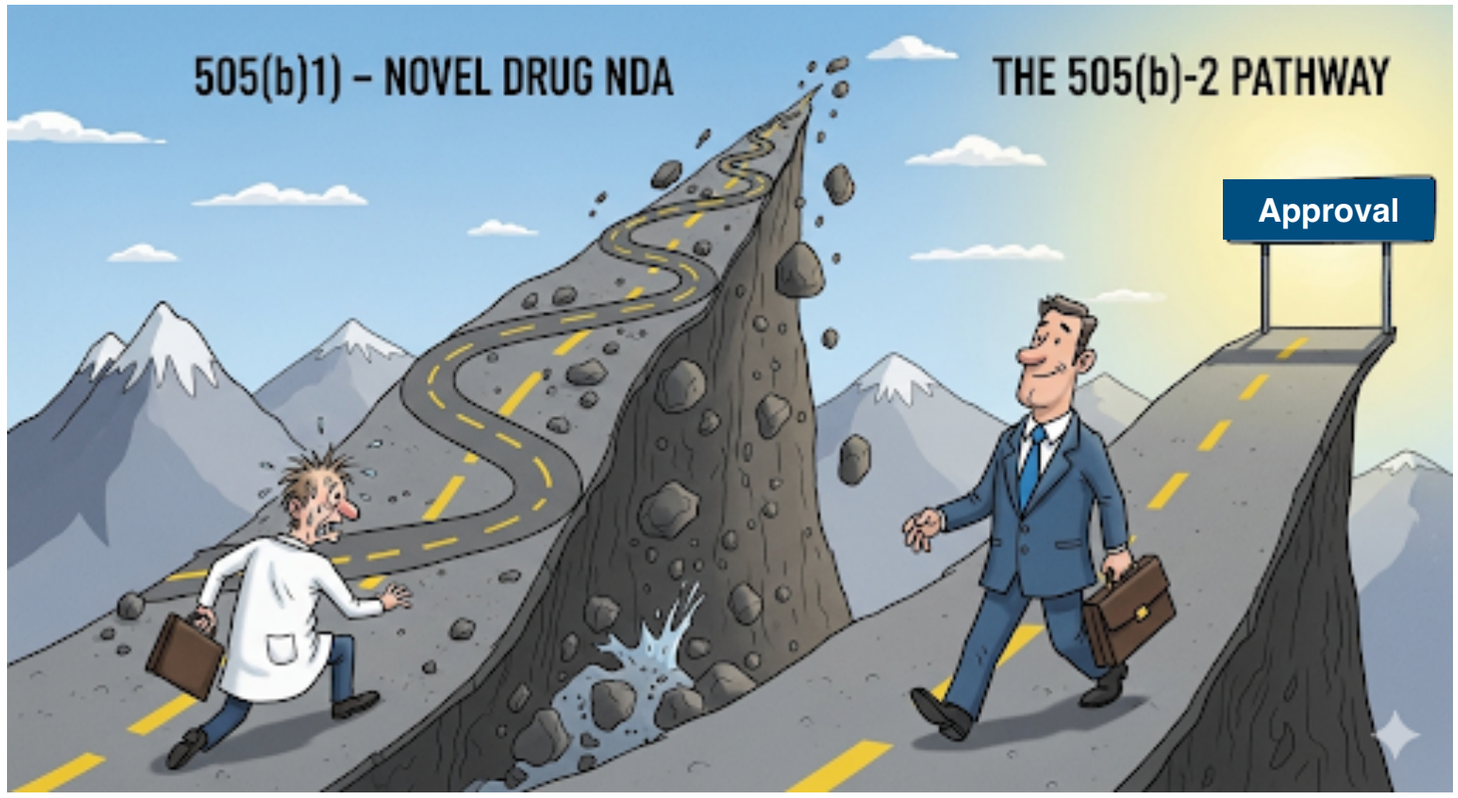
~3 years from clinical entry to market

Alkermes

Holman, C. M. *Biotechnol. Law Rep.* **2023**, *42* (3), 118.

Prodrug: built-in shortcut to FDA approval

Section 505(b)(2) of FDA guideline



Prodrug design leverages the 505(b)(2) pathway, enabling faster approval

Image credit: DrugPatentWatch

Conclusion and outlooks

Final thoughts

- ***Prodrug = pre-drug***
- ***Balancing lipophilicity and solubility is a core challenge in drug design, prodrugs can provide a solution where appropriate***
- ***Practical advantages in industry: patent evasion, faster approval, safer prescriptions, and the long-acting injectable formulation***
- ***Not the ‘last resort’ of drug development, but a strategic choice that must be considered in discovery***

Conclusion and outlooks

Final thoughts

- ***A wider toolbox of synthetic methods to covalently attach promoiety will enable translation of more drug candidates into the clinic***

Deoxyphosphonylation of alcohol (J. Am. Chem. Soc., 2024)

1 equiv. 2–2.5 equiv. ***P(V)*** *product*

Acknowledgements

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Questions?