
Invoking Prodrugs as Part of the Lead Optimization Strategy-Should We?

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Compilation of Prodrug Approaches

Prodrugs: Challenges and Rewards

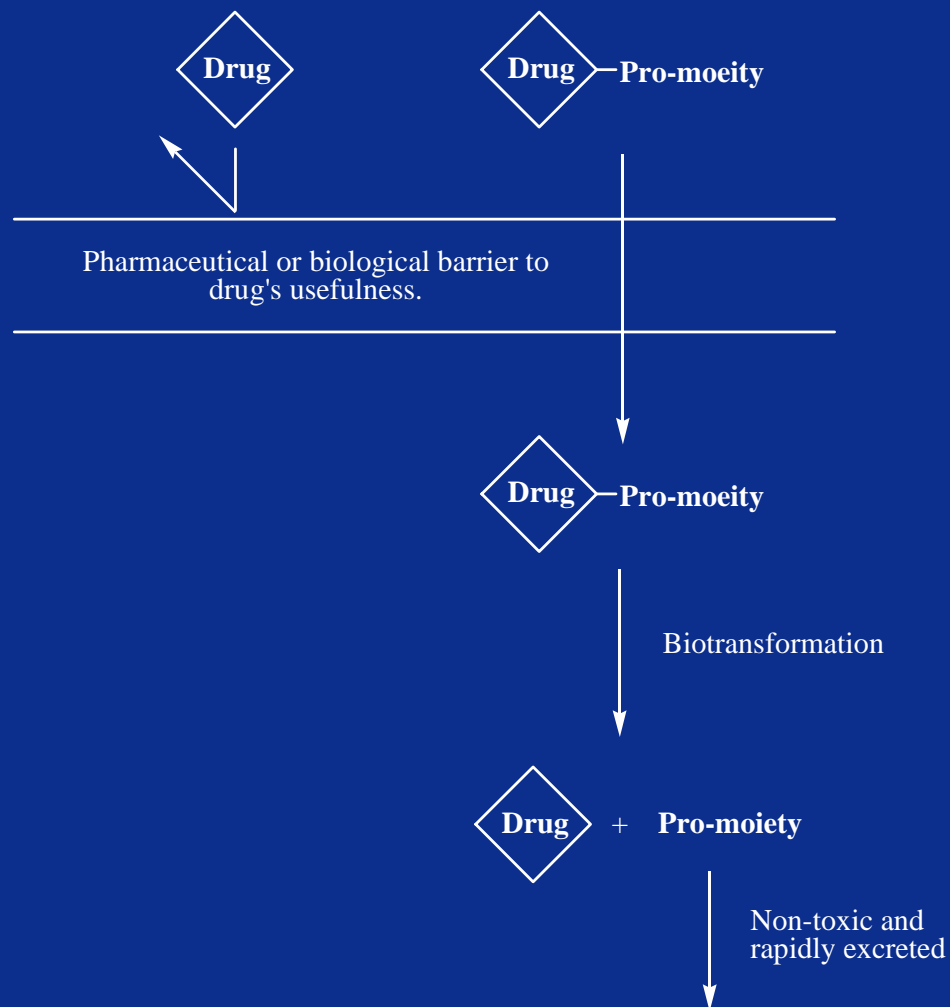
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**This work was published in the series
Biotechnology: Pharmaceutical Aspects (2007)**

The Utilization of Prodrug Approach

- Prodrug strategy consists of a transient modification of the physicochemical properties of a given compound through chemical modification(s) while the inherent pharmacological properties of the parent drug remain unchanged.
- Such chemical modification(s) are designed to:
 - Improve bioavailability
 - Enhance chemical/physical stability
 - Alter aqueous solubility
 - Drug targeting (intracellular prodrugs)

Prodrug Concept



Implementation of Prodrug Strategy

- Parent drug is a commercial product– Prodrug strategy is applied overcome ADME/PK and formulation liabilities (Lexiva®, Valcyte®, Valtrex®, and XP-13512)
- Parent drug is in clinical development – Prodrug strategy is applied to overcome ADME/PK and formulation liabilities (Viread® and Hepsera®)
- Parent drug is a new chemical entity– Prodrug strategy is applied at the pre-clinical stage (Tamiflu®)

Key Issues in Prodrug Development

- Applying prodrug strategy at early stages of pre-clinical development is important and perhaps most rewarding
- A comprehensive understanding of the ADME/PK of the prodrug and the parent drug is critical
- Depending on the rate of conversion and the site of metabolism, prodrugs may alter the tissue distribution, efficacy, and the toxicity of the parent drug
- The promoiety should ideally be safe and rapidly excreted from the body

Key Issues in Prodrug Development

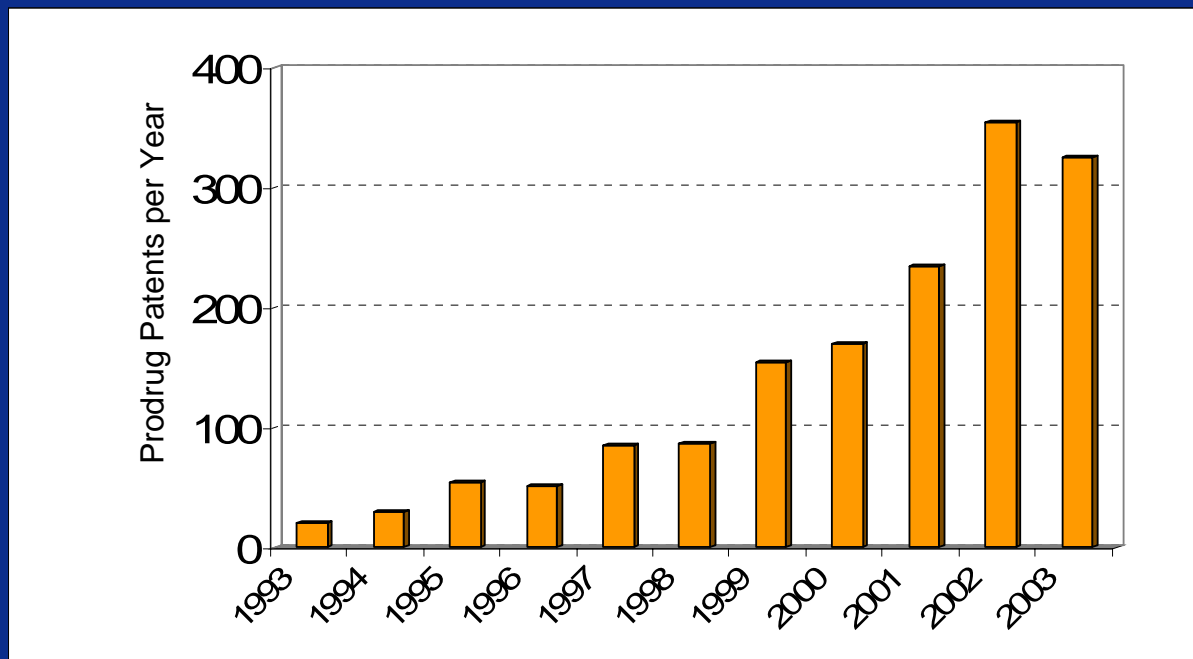
- The choice of promoiety should be considered with respect to the disease state, dose, and the duration of therapy
- The degradation by-products can affect chemical and physical stability and lead to the formation of new degradation products
- A novel prodrug concept can extent patent protection

In vitro and *In Vivo* Prodrug Screens

- Physico-chemical characterization (solubility, chemical stability, and lipophilicity)
- Hepatic/microsomal/Tissue homogenate/ plasma stability
- Caco-2 and PAMPA assays
- Understanding absorption mechanism(s)
- Are active or prodrug a substrate for efflux?
- Understanding disposition of active (parent) and prodrug compound

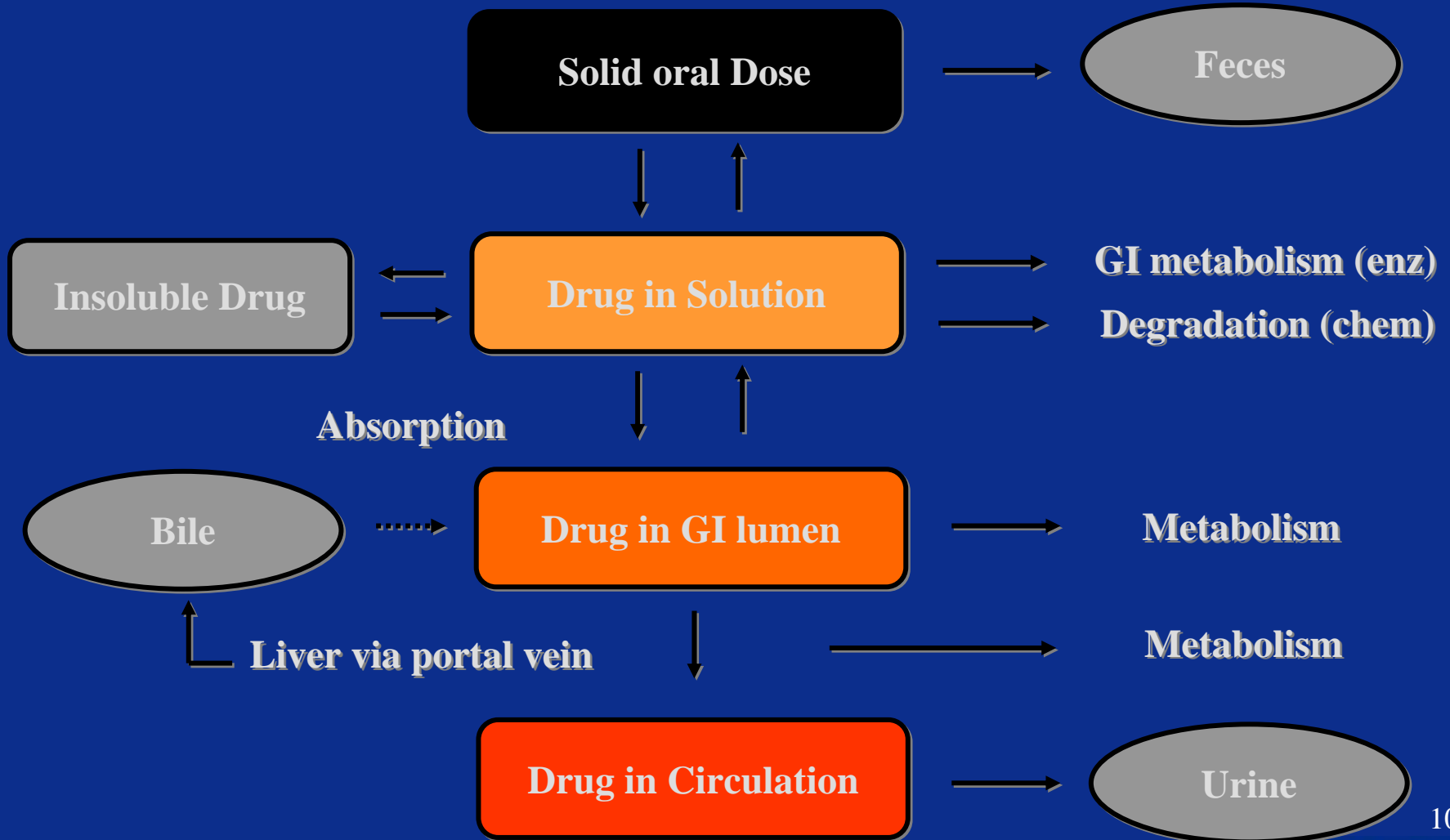
History: Current

5-7% of all approved drugs can be classified as prodrugs
15% of new drugs approved in 2001-2002 were prodrugs



Adopted from Prodrugs: Challenges and Rewards, eds: Stella et al., Springer/AAPS Press, 2007

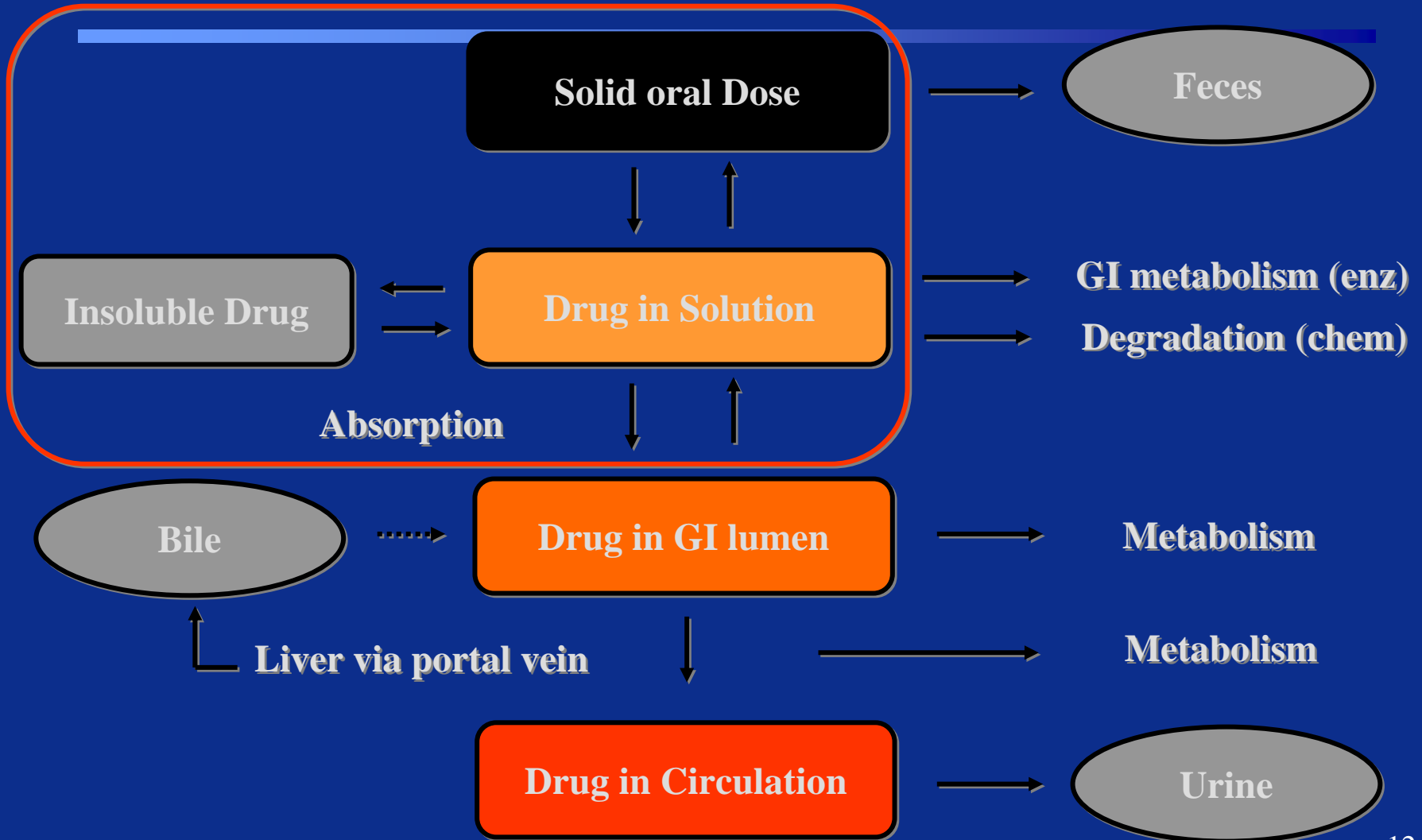
Fate of an Orally Administered Drug



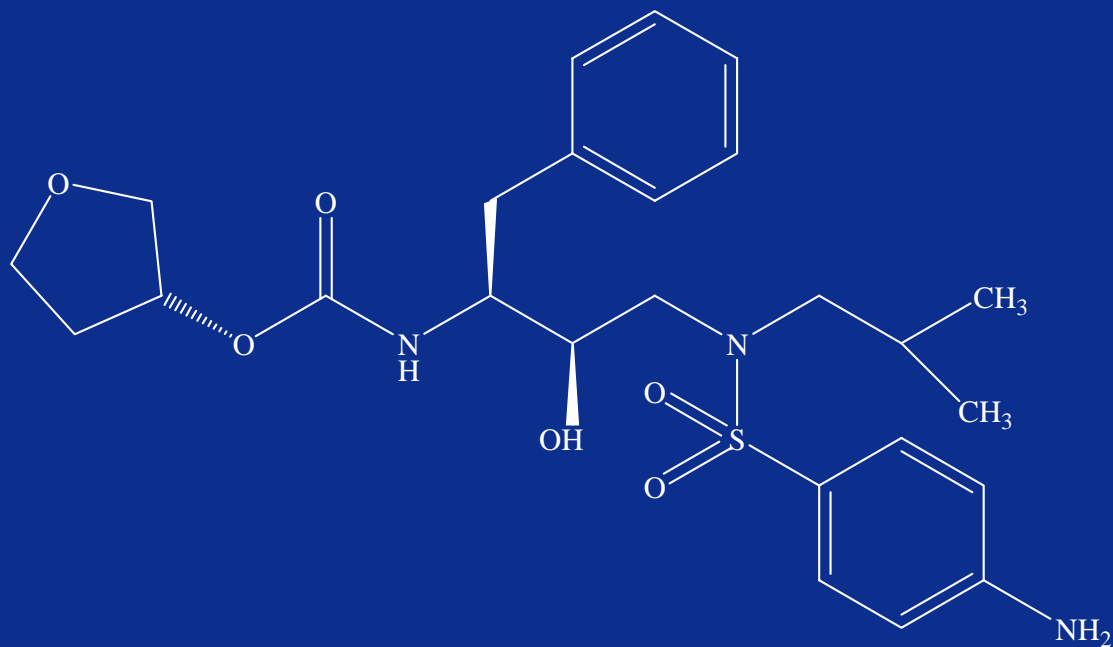
Absorption Mechanisms

- Passive
 - Permeation through cell membrane of enterocytes (transcellular)
- Paracellular
 - Diffusion through tight junctions between enterocytes (restricted to hydrophilic, low MW compounds)
- Active
 - Transporter mediated (influx or efflux) e.g. PEPT1, MCT, etc.

Fate of an Orally Administered Drug



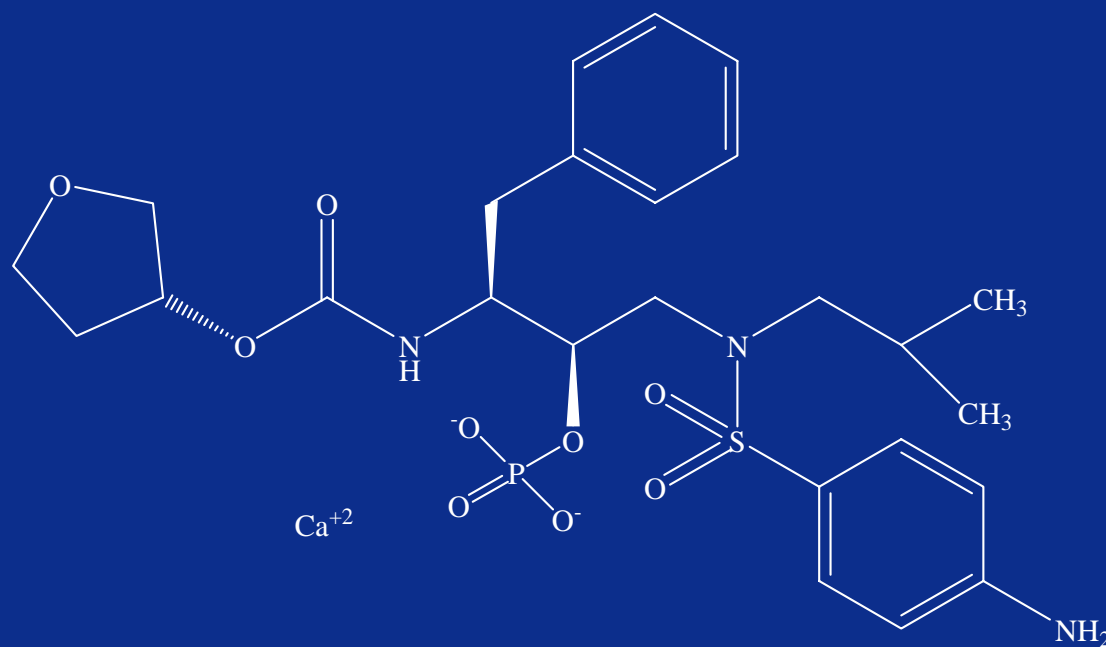
Amprenavir (Agenerase™)



Physicochemical Characterization of Amprenavir

- Low aqueous solubility and intrinsic dissolution rate
- Dosed in softgel formulation solubilized drug in GI tract and aided absorption
- Solubility in the softgel formulation limited capsule loading
- Final product label: 8 softgels bid, or 4 softgels bid + 100 mg ritonavir

Fosamprenavir (GW 433908)

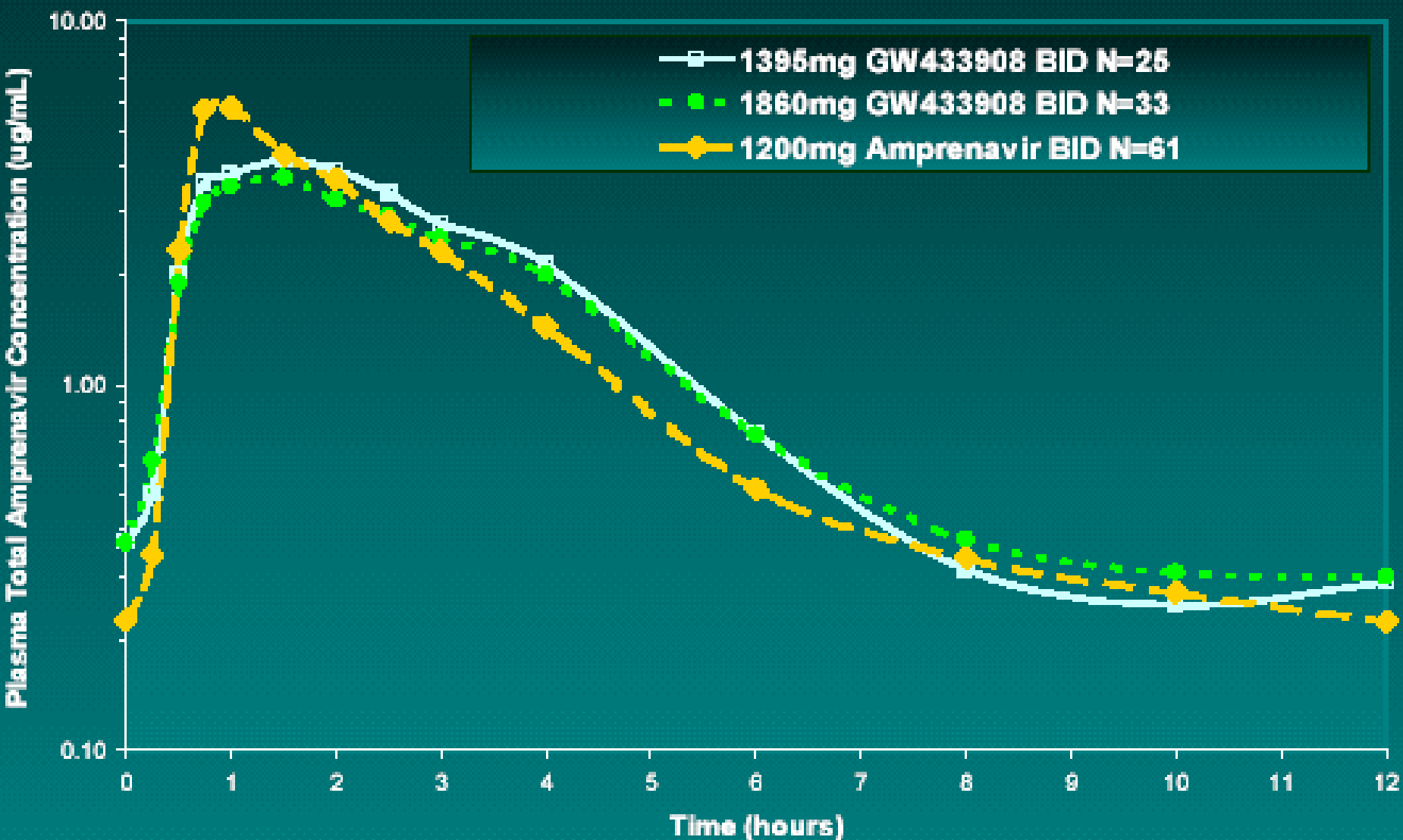


Fosamprenavir calcium

MW = 624

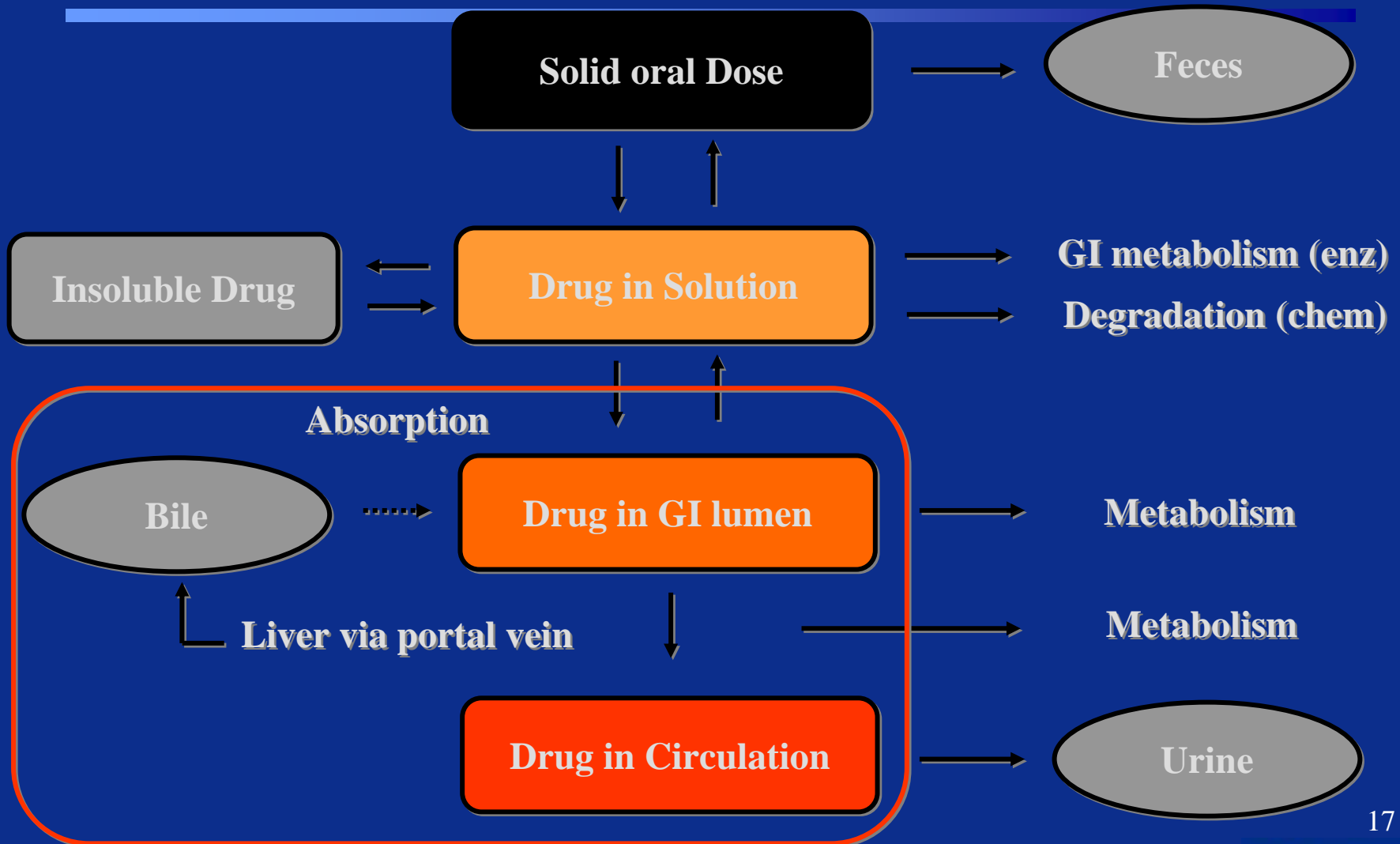
APV20001

Median Steady-State Plasma Total APV Concentration-Time Profiles

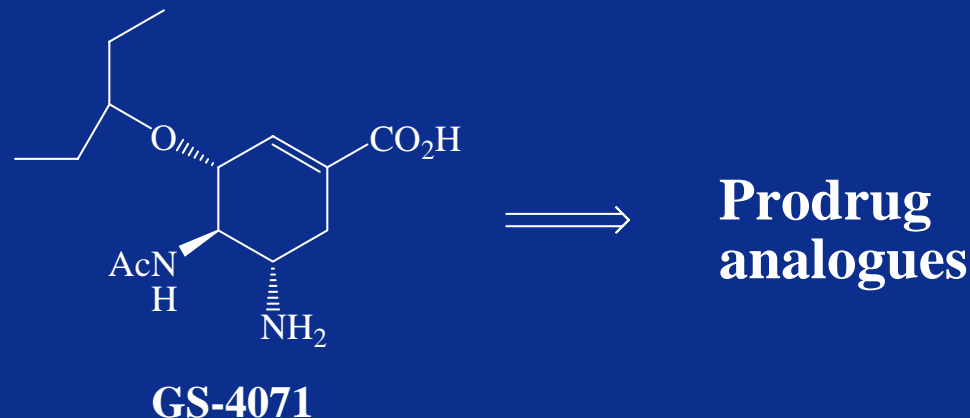


LEXIVA® / TELZIR®

Fate of an Orally Administered Drug

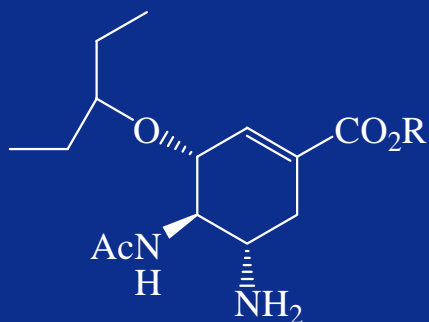


Oseltamivir Carboxylate (GS-4071)



- Oseltamivir carboxylate is an inhibitor of influenza virus neuraminidase
- Exists as a zwitter ionic ($\log P = -1.4$) amino acid with poor oral absorption
- Oral bioavailability = 4% (Rats)

Oseltamivir Carboxylate Prodrugs

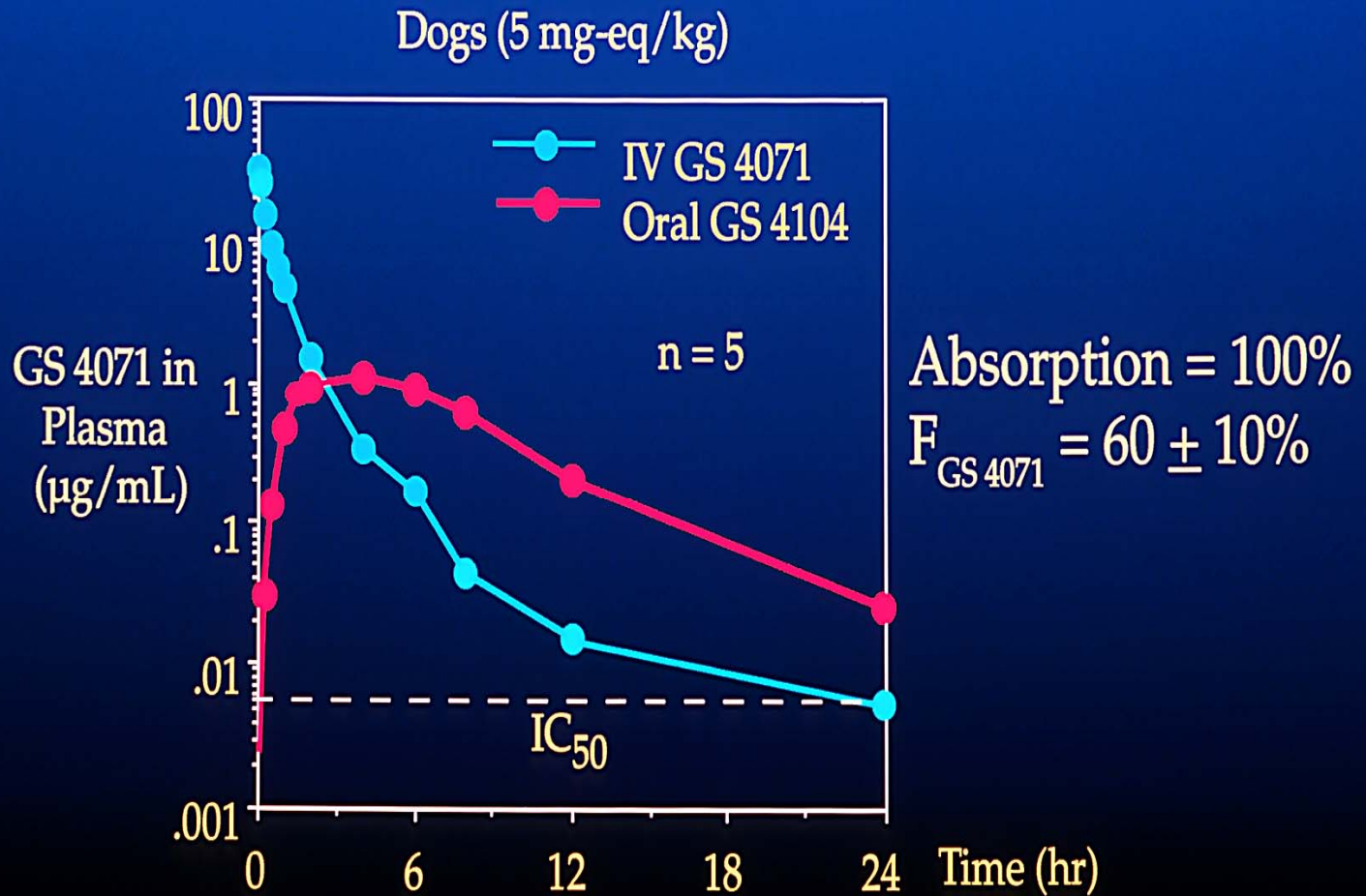


R	liver homogenate (t 1/2, min)		
	Rat	Dog	Human
CH ₃ CH ₂ (GS 4104)	>60	>60	3.2
CH ₃ CH ₂ CH ₂	>60	44	3.3
CH ₃ CH ₂ CH ₂ CH ₂	50	28	3.3
phCH ₂ CH ₂	51	34	4.6

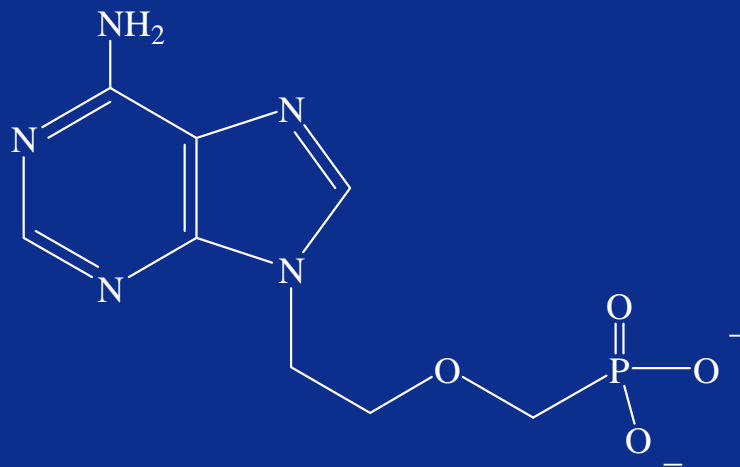
GS 4104 (oseltamivir)

- Log P = + 0.5
- F = 35 - 100% (mice, rats, dogs)
- Rapidly generate oseltamivir carboxylate in all species

Oseltamivir: Pharmacokinetics in Dogs

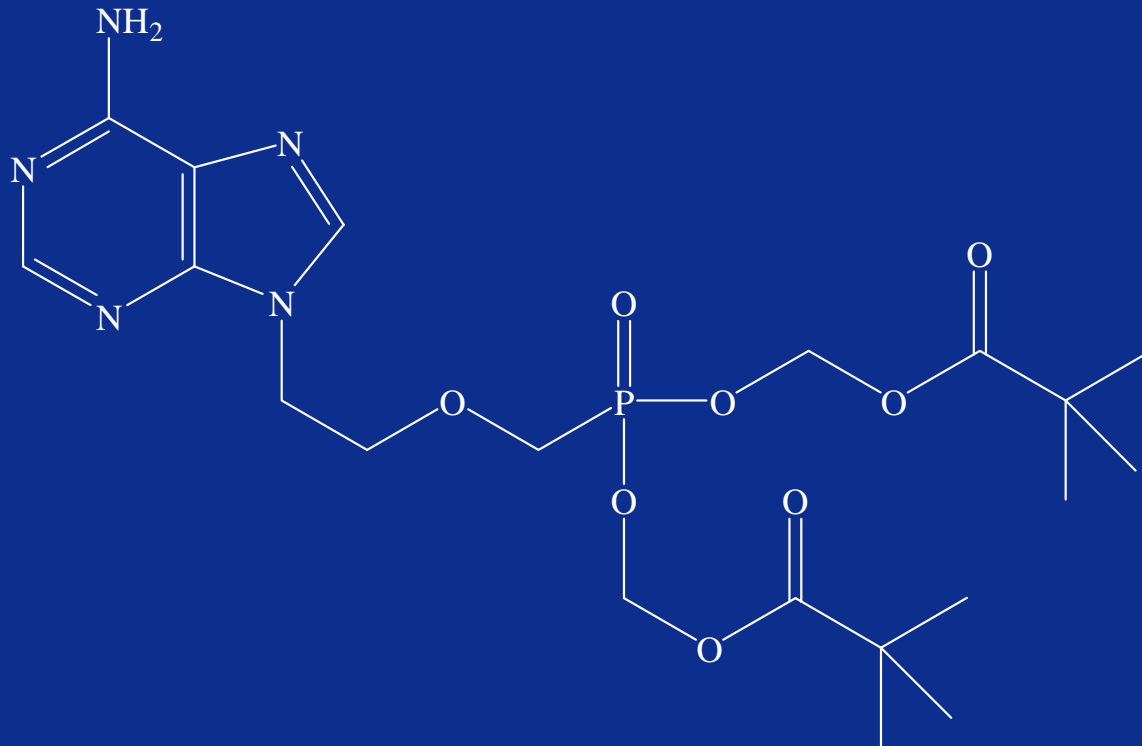


Adefovir



- Adefovir (9-[(R)-2-(phosphonmethoxy) ethyl]adenine, PME_A) is an acyclic nucleotide phosphonate
- Mimics a nucleoside monophosphate
- Adefovir is phosphorylated in situ by host kinases to the virologically active adefovir diphosphate

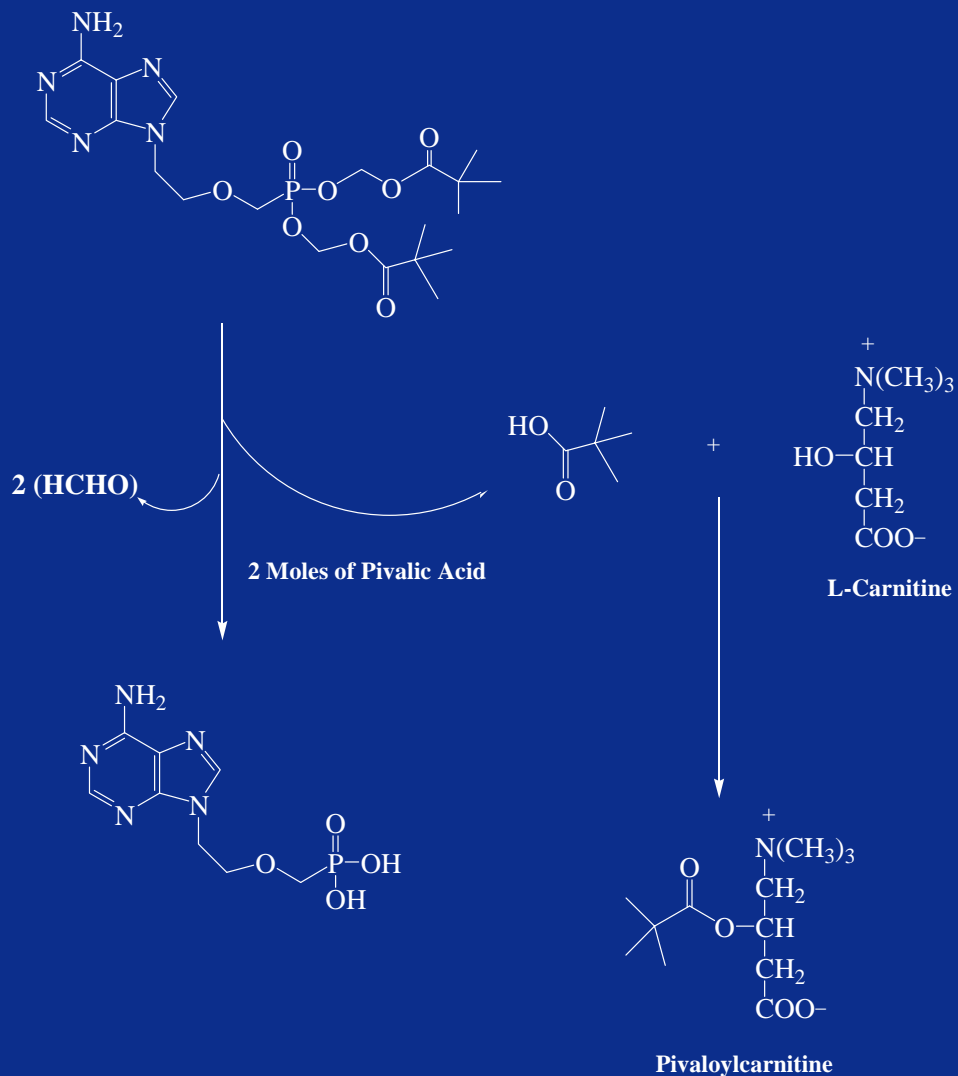
Adefovir Dipivoxil



Oral Bioavailability of Adefovir from Adefovir Dipivoxil in Various Species

Specie	Oral Bioavailability (%)
Rat	17
Dog	42
Human	59

Pivalic Acid Mediated Depletion of Carnitine



Issues Related to Pivalate Prodrugs

- Use of a pivalate prodrug will inevitably result in perturbed carnitine homeostasis
- Adefovir dipivoxil is unique amongst pivalate prodrugs used clinically in that it is approved for chronic treatment
- The daily pivalate load from Hepsera is only 0.04 mmol/day is small compared with the normal daily total carnitine production rate and the total body carnitine pool (120 mmoles)
- Regulatory authorities have mandated that pivalate prodrug antibiotics incorporate language addressing potential toxicity related to carnitine deficiency

Tenofovir



- Tenofovir (9-[(R)-2-(phosphonomethoxy)propyl]adenine, PMPA) is an acyclic nucleotide phosphonate
- Mimics a nucleoside monophosphate
- Tenofovir is phosphorylated in situ by host kinases to the virologically active tenofovir diphosphate

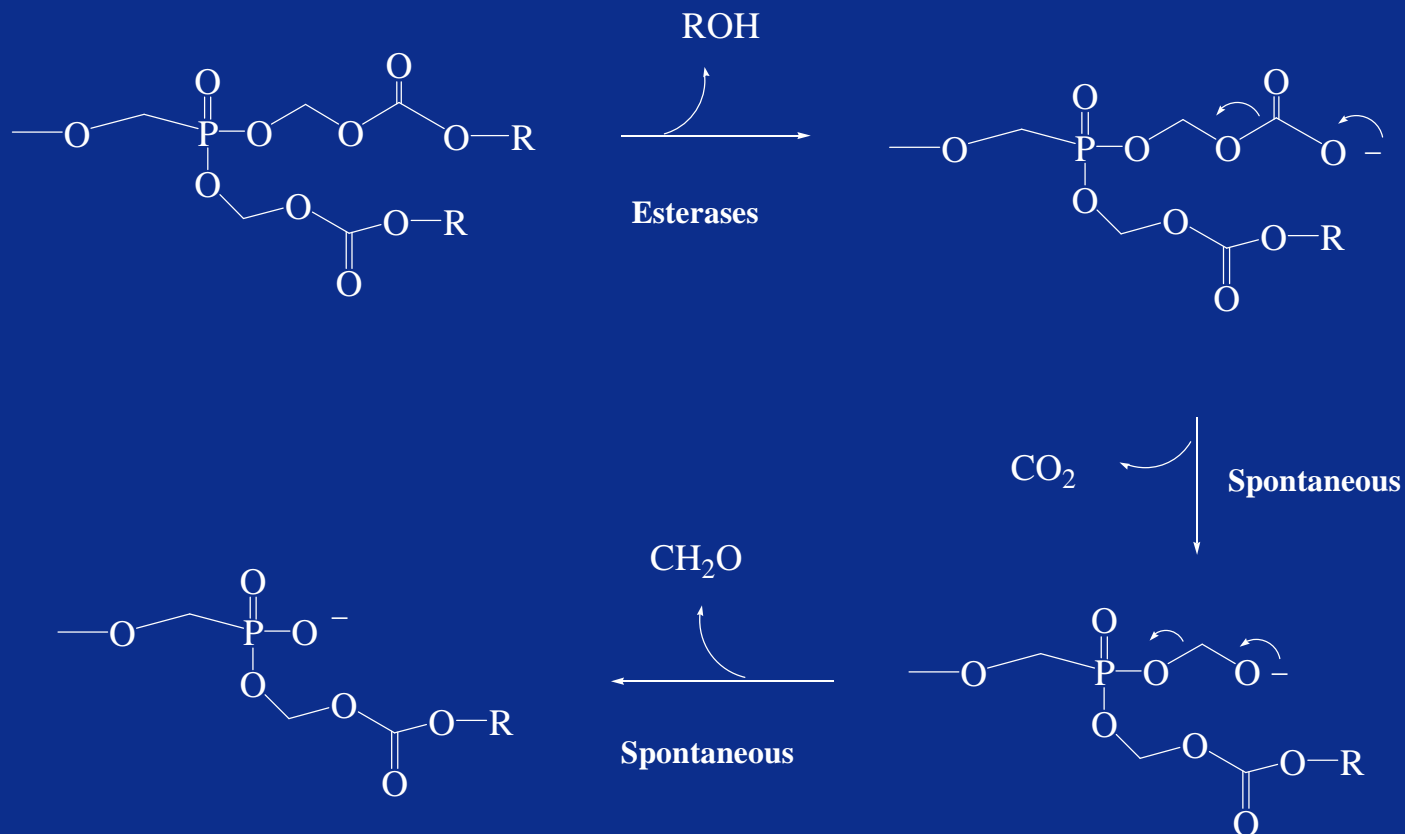
Change in Plasma HIV-1 RNA level after Intravenous Administration of Tenofovir in HIV-Infected Adults

Dosage of Tenofovir	Median log ₁₀ Change in Plasma HIV-1 RNA level from that of Baseline (copies/mL)
Placebo	0.1
1 mg/kg/day	- 0.6
3 mg/kg/day	- 1.1

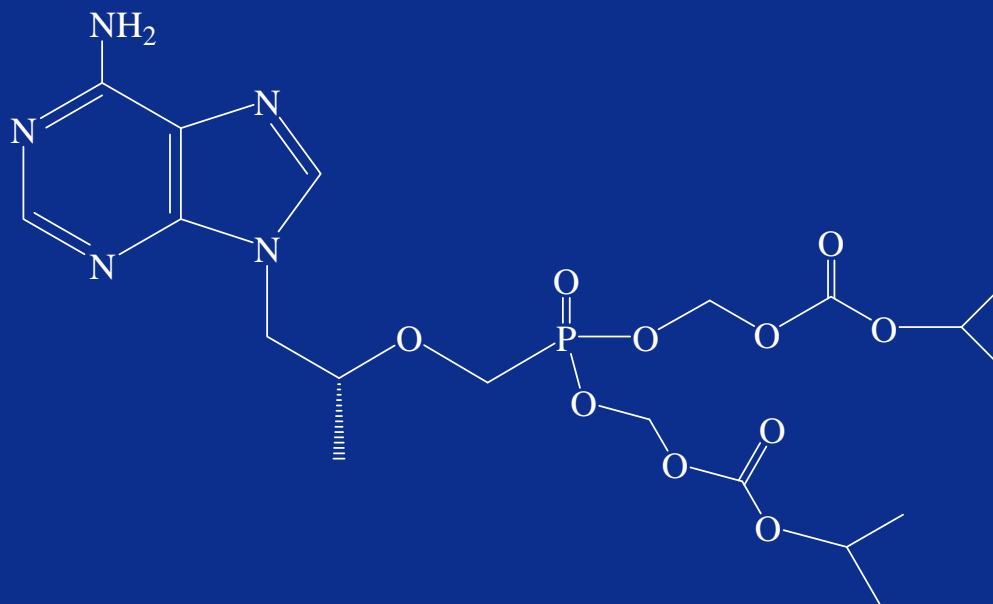
Clinical Goals for Tenofovir

- Significant HIV RNA reductions
- Durable activity against nucleoside resistant HIV
- Favorable safety profile
- Convenient oral dosing
- One tablet, once daily oral dosing

Conversion of Oxymethyloxycarbonyl Linker as Phosphonate Promoiety



Tenofovir Disoproxil

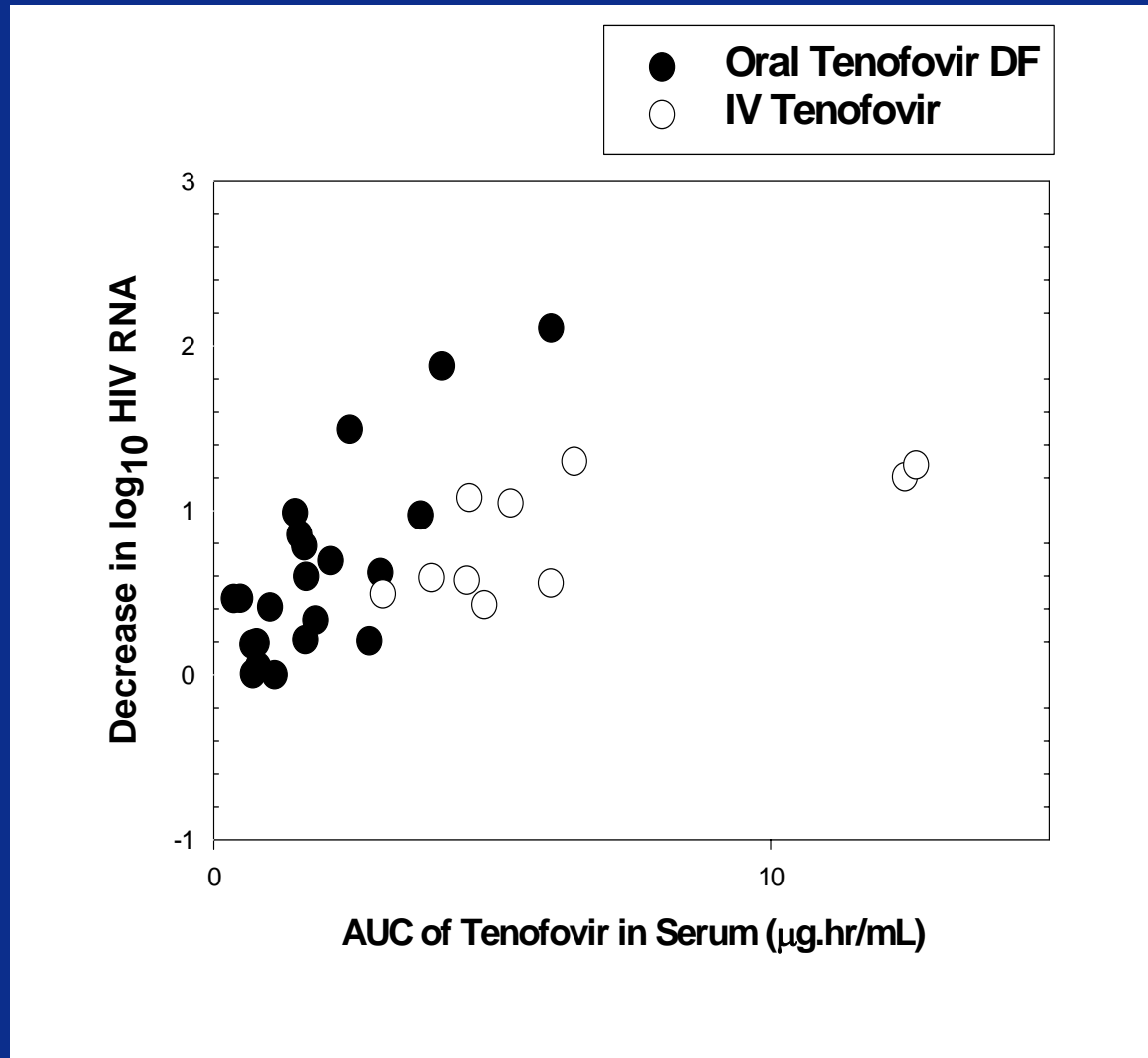


- Molecular weight of 519.4 (C₁₉H₃₀N₅O₁₀P)
- pKa = 3.75 (N⁶ of purine ring) and Log P of 1.3
- Intrinsic solubility of free base = 8.5 mg/mL
- 15 H-bond acceptors and 2 H-bond donors
- Molecular polar surface area of 184.4 Å²
- Metabolic by products: 2 moles of IPA, CH₂O and CO₂

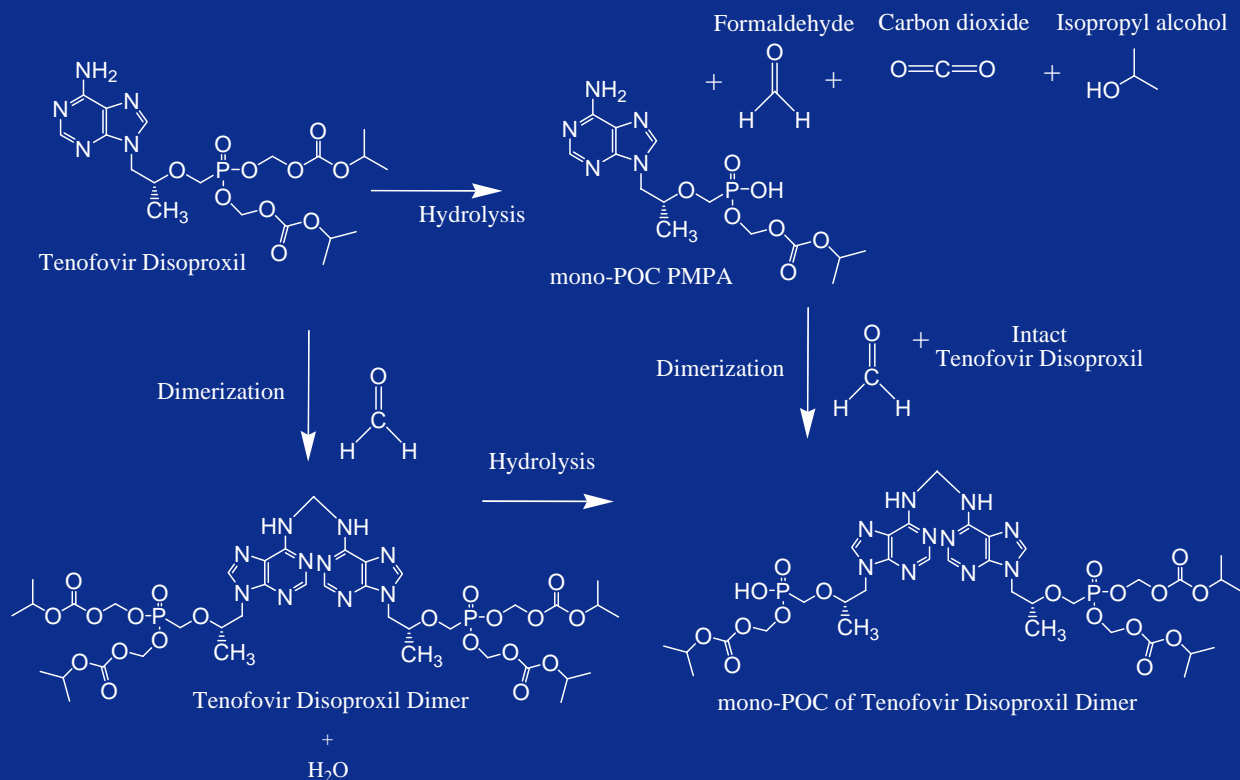
Oral Bioavailability of Tenofovir from Tenofovir Disoproxil in Various Species

Specie	Oral Bioavailability (%)
Human (Fed)	43
Human (Fasted)	29
Dog	30
Mice	20
Rat	13

Tenofovir AUC in Serum vs. Δ HIV RNA after 7 (q.d.) doses of Tenofovir (i.v.) or Tenofovir DF (p.o.)

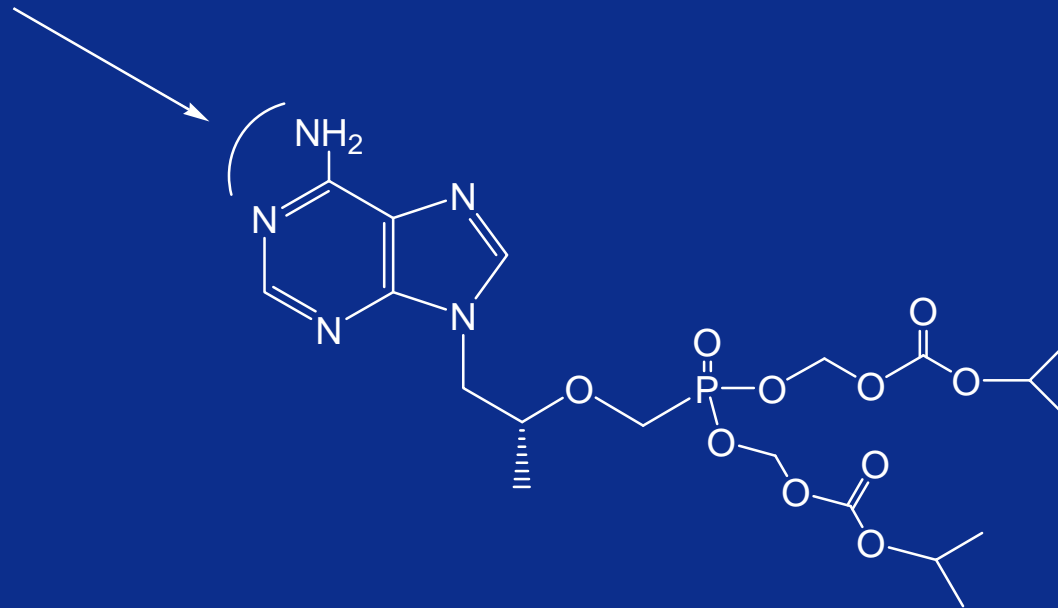


Degradation Schematic for Tenofovir Disoproxil in Solid State



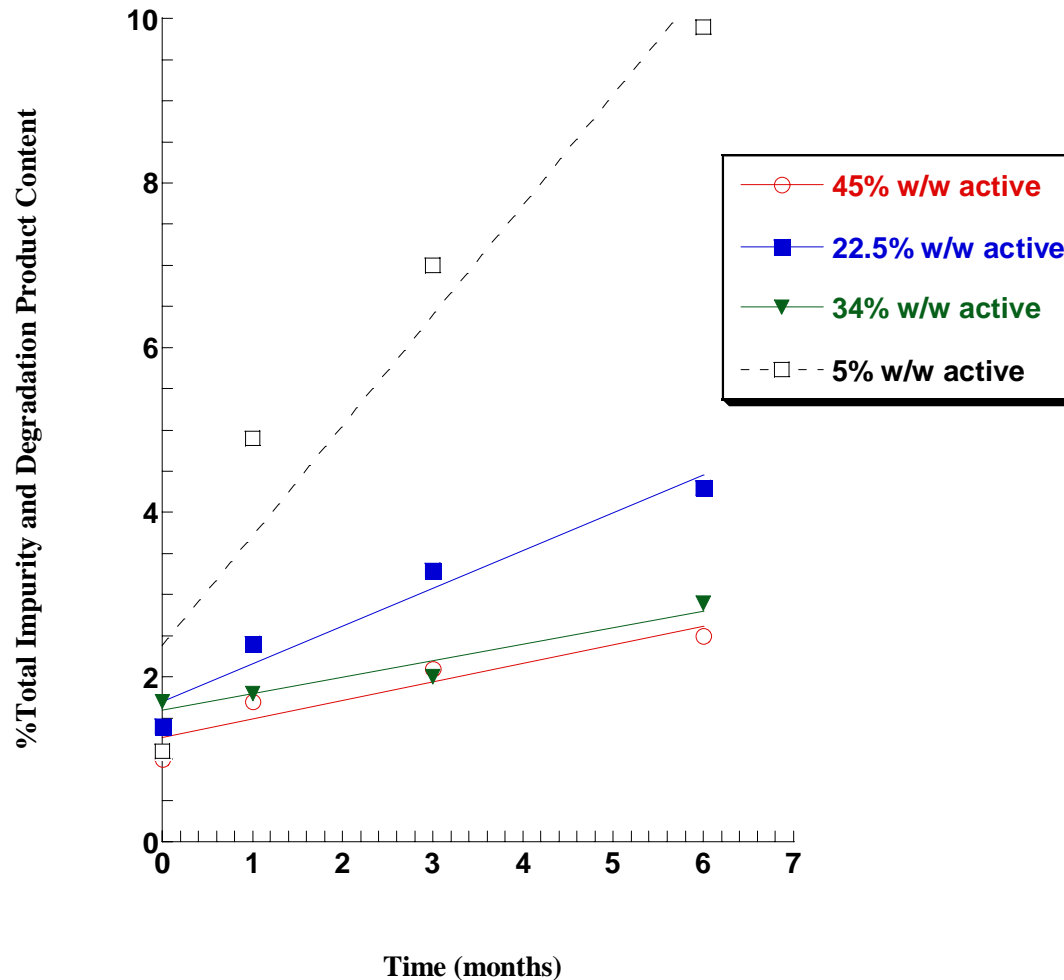
Rationale for Salt Selection

Ionizable Functional Group



- Minimizes the extent of dimerization in solid state

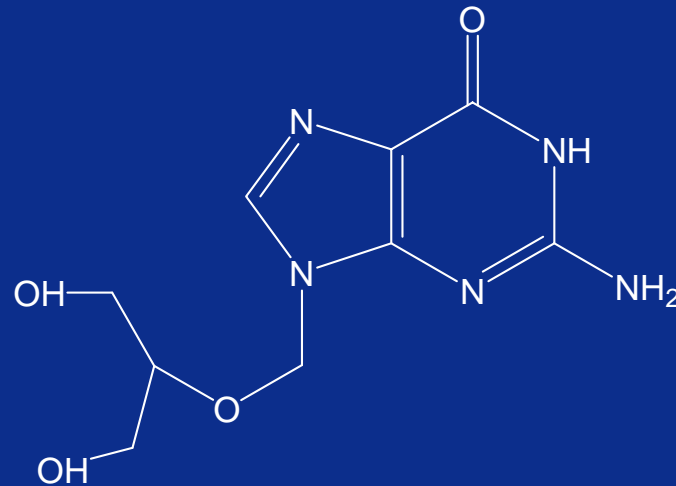
Degradation of Tenofovir Disoproxil Fumarate Tablets at 40°C and 75% Relative Humidity



Active Transporter

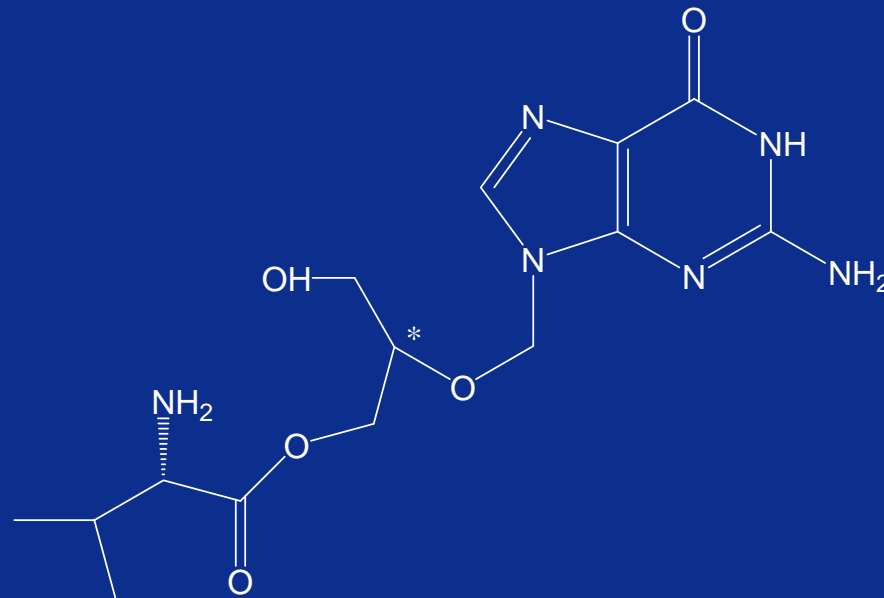
- Amino acids transporters
- Oligopeptides transporters (PepT-1, PepT-2, etc.)
- Monocarboxylic acids transporters (MTC1, MTC2, etc.)
- Bile salts transporters
- Sodium-dependent multivitamin transporters (SMVT)

Ganciclovir



- Ganciclovir is a potent antiviral agent for the treatment of cytomegalovirus infections
- Ganciclovir is a polar compound ($\log P = -1.65$) limiting its passive permeability
- Oral bioavailability of ganciclovir is about 7% in human subjects

Valganciclovir

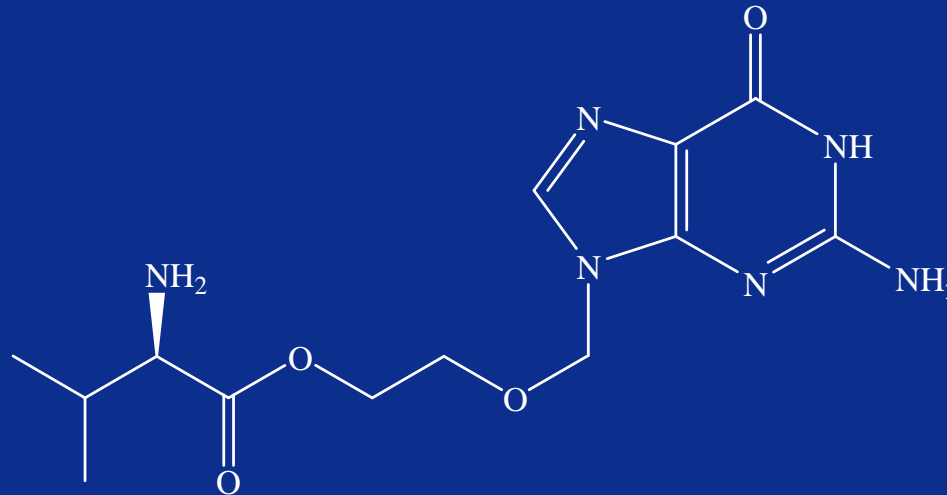


- Valganciclovir is a L-valine ester prodrug of ganciclovir
- Valganciclovir is a substrate of peptide transporter PEPT1 present in intestinal epithelial cells

Oral Bioavailability of Ganciclovir from Valganciclovir in Various Species

Specie	Oral Bioavailability (%)
Human	60
Cynomolgus Monkey	50
Dog	100
Mice	100
Rat	56

Valacyclovir

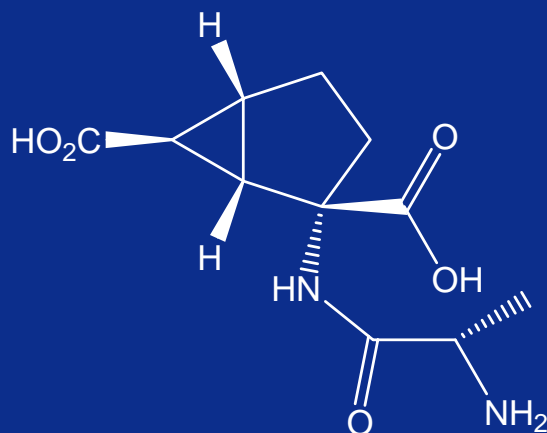


- Valacyclovir is a L-valine ester prodrug of acyclovir
- Valacyclovir is a substrate of peptide transporter PEPT1 present in intestinal epithelial cells

Oral Bioavailability of Acyclovir from Valacyclovir in Various Species

Specie	Oral Bioavailability (%)
Human	54
Cynomolgus Monkey	50
Rat	65

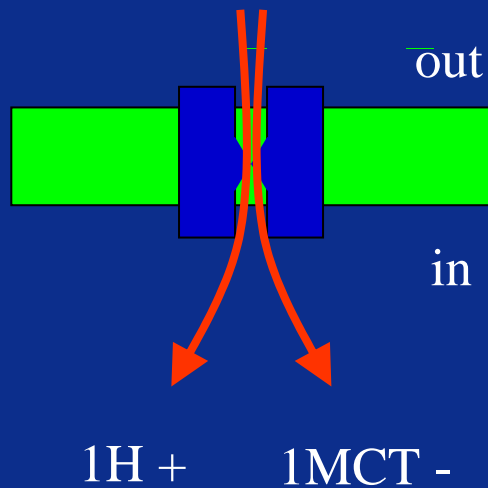
LY544344: L-Alanine prodrug of LY354740



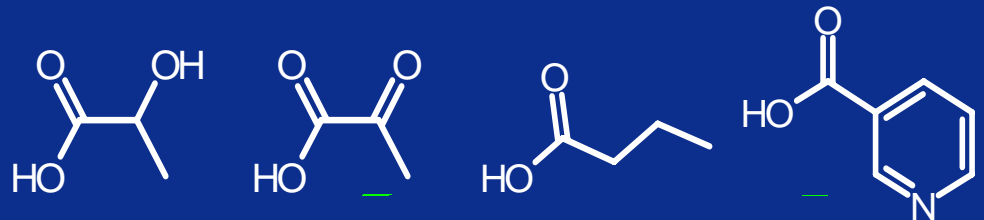
- A substrate for intestinal peptide transporter hPepT1
- Enzymatically hydrolyzed to release molar equivalents of alanine and LY354740 in vivo
- Prodrug increases systemic LY354740 exposure by approximately 13-fold compared with equivalent LY354740₄₂ doses

Monocarboxylate Transporters (MCTs)

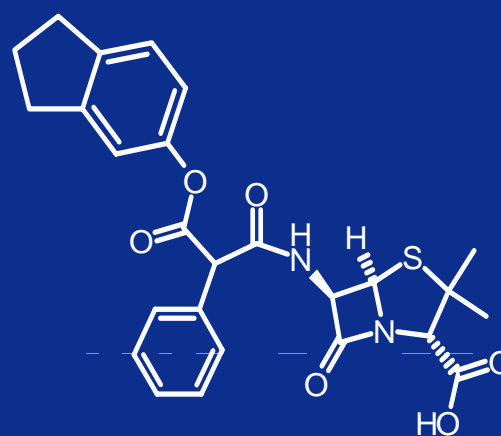
- Recognize structurally diverse monocarboxylates
- Absorbs short-chain fatty acids from carbohydrate fermentation by bacteria in colon



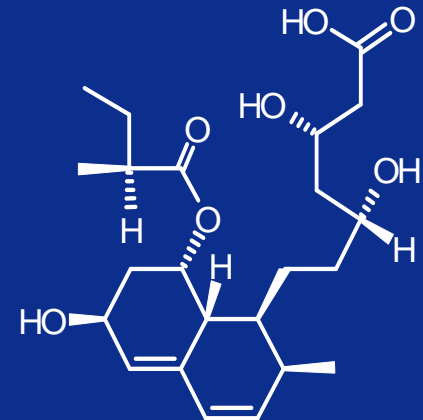
Natural Substrates



Known Drug Substrates (MCT-1)

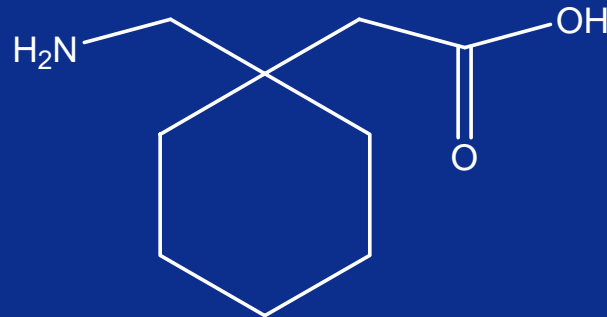


Carindacillin



Pravastatin

Gabapentin



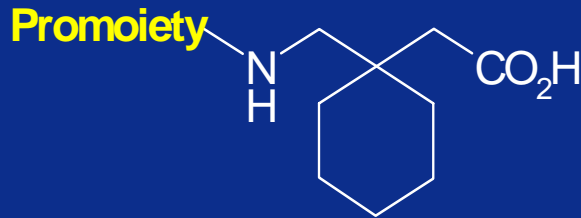
- Gabapentin is approved for treatment of epilepsy and post-herpetic neuralgia
- Gabapentin is believed to be a substrate for a low capacity amino acid transporter localized in the small intestine
- Saturable absorption: maximum limit to blood levels
- High inter-patient variability in oral absorption

Making an MCT Substrate from Gabapentin



Gabapentin:

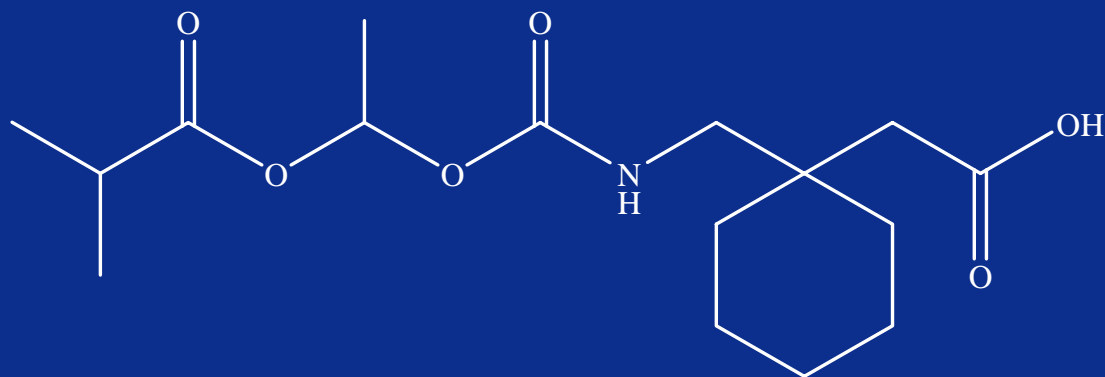
No interaction with monocarboxylate transporters



Prodrug:

Blocking amine functionality of gabapentin with an enzymatically labile promoiety generates prodrugs that are transported by MCTs

XP13512



- XP13512 undergoes enzymatic hydrolysis *in vivo* to liberate
- Gabapentin, isobutyrate, acetaldehyde, and CO₂

XP13512 Clinical Capsules – PK in Monkeys

