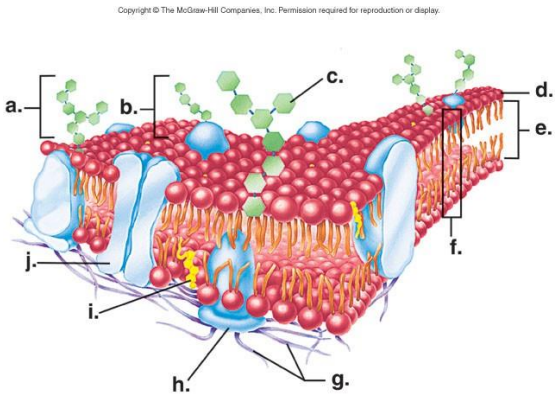
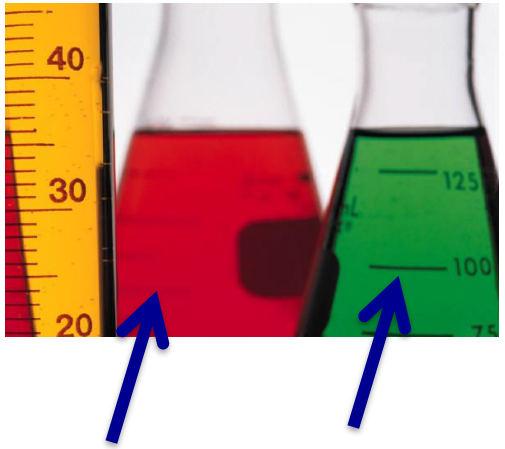
Liberation: prodrugs and drug delivery by nanocarriers

Human organism

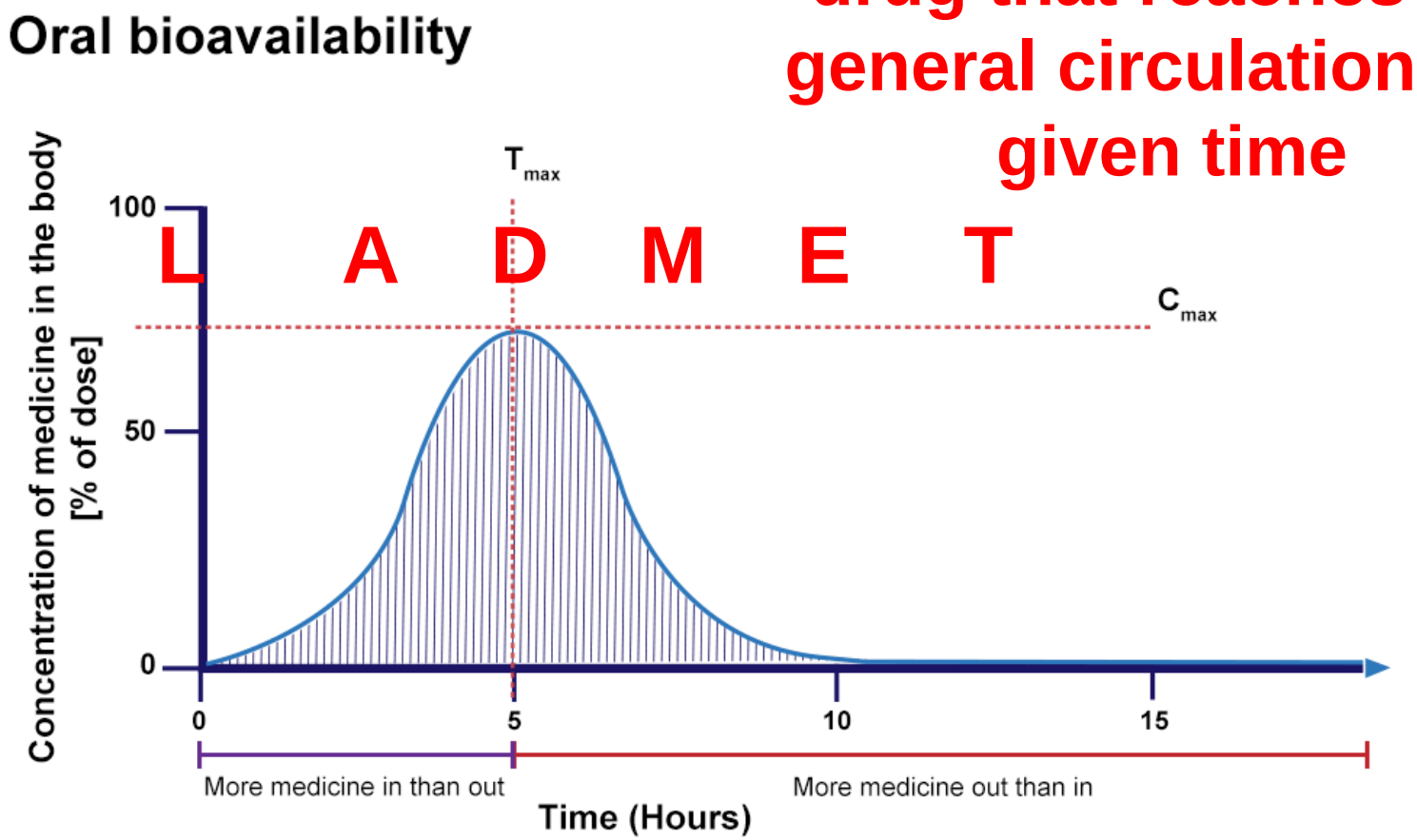
- Hydrophylic media: blood, other body fluids
- Hydrophobic environment: cell membranes, tissues barriers, blood-brain barrier (BBB), CNS





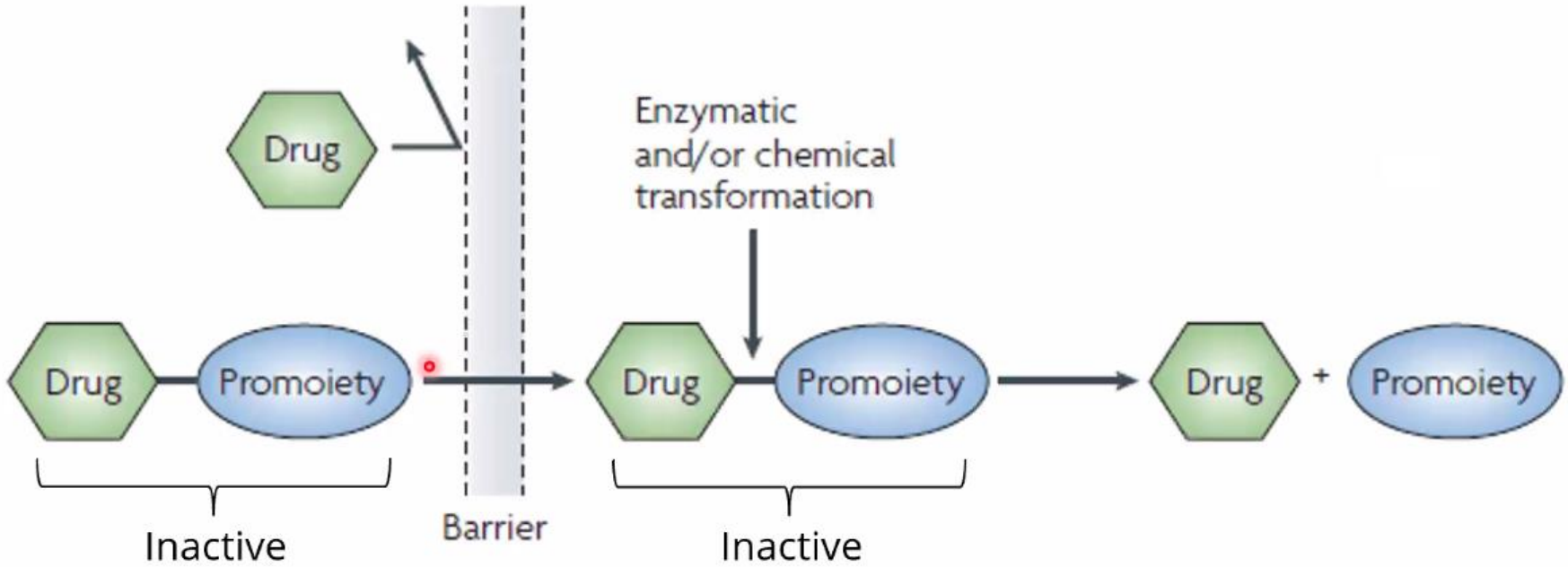
Octanol/water

Bioavailability: fraction of drug that reaches the general circulation in a given time



EUPATI
European Patients' Academy on Therapeutic Innovation
www.eupati.eu

Simplified prodrug concept



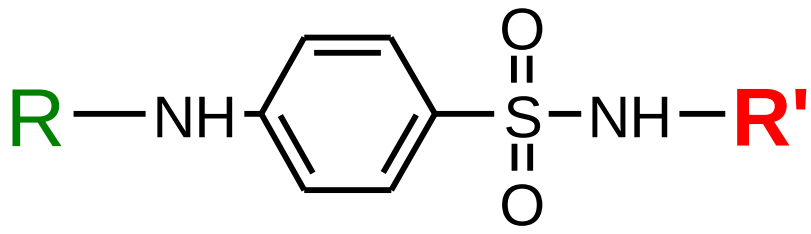
Rautio *et al.* Prodrugs - design and clinical applications. Nature Reviews Drug Discovery 7: 255-270, 2008

Prodrugs by serendipity

para-amminobenzensolfonilammide

(principio attivo)

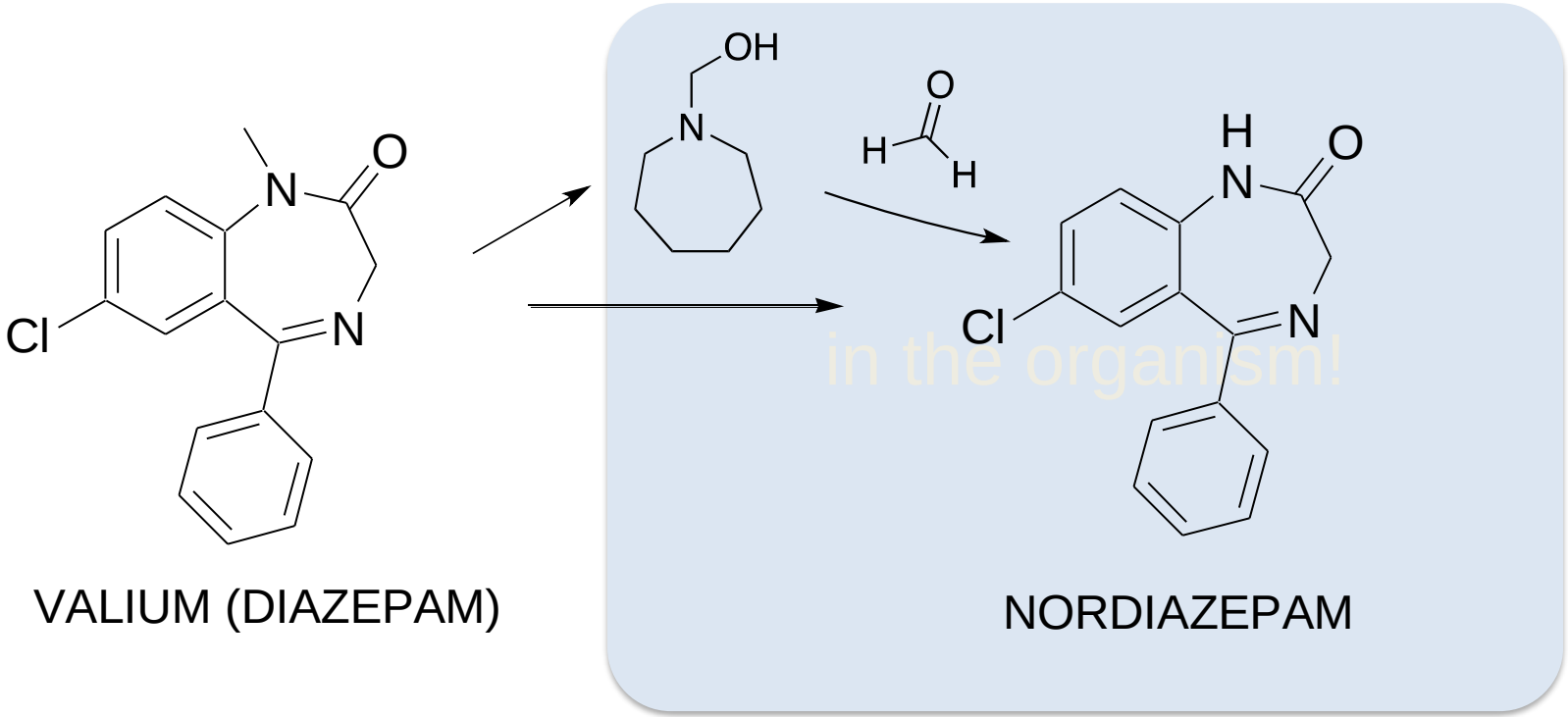
prontosyl red (dye) was transformed into animals (and humans) into the biologically active PABA sulfonamide



Old antibiotics: present use for infections of urinary and intestinal tracts, ocular infections.

Pro drugs by serendipity

- The Diazepam **(Valium ®)**, is a well known sedative and hypnotic drug, it is converted into the active principle, the nordiazepam by CyP450 catalyzed metabolic oxydation (demethylation)



The expanding role of prodrugs in contemporary drug design and development

Jarkko Rautio[1], Nicholas A. Meanwell[2], Li Di[3] and Michael J. Hageman[4]*

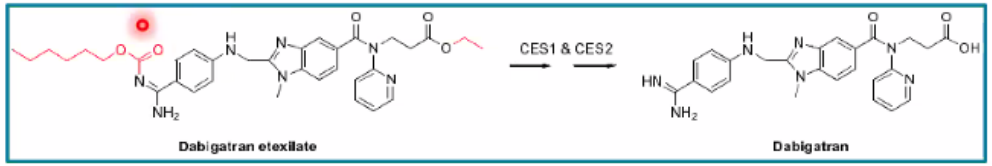
doi:10.1038/nrd.2018.46 Published online 27 Apr 2018

“it has become more and more common to invoke prodrug strategies during the design phase, rather than as a salvage effort once formulation and delivery strategies have been exhausted”

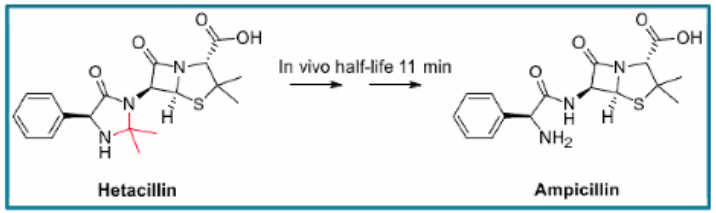
Rationale for prodrug design

- **Better drug formulation and administration options**
  - ✓ Increased aqueous solubility for liquid dosage forms
  - ✓ Improved shelf-life for solid or liquid dosage forms
- **Improved properties related to ADMET**
  - **Absorption ("A")**
    - ✓ Increased solubility
    - ✓ Improved permeability
  - **Distribution ("D")**
    - ✓ Enabling e.g. brain delivery
  - **Metabolism and excretion ("M" and "E")**
    - ✓ Decreased pre-systemic metabolism
  - **Toxicity (“T”)**
    - ✓ Better targeting
    - ✓ Decrease in abuse potential
  - **Life-cycle management**
    - ✓ Additional intellectual property (IP)

Broader space for prodrug design

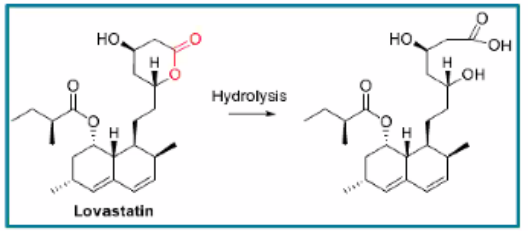


Addition of multiple promoieties (increase in MW)

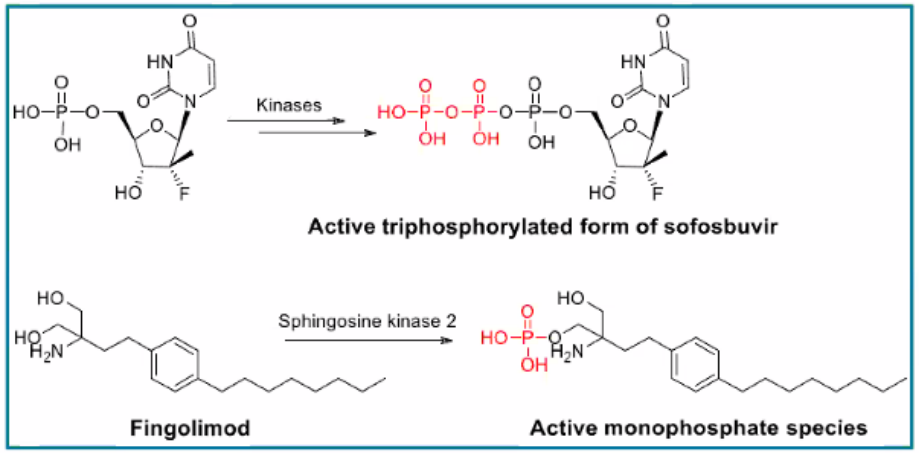


Addition of promoiety through multiple attachments (increase in MW)

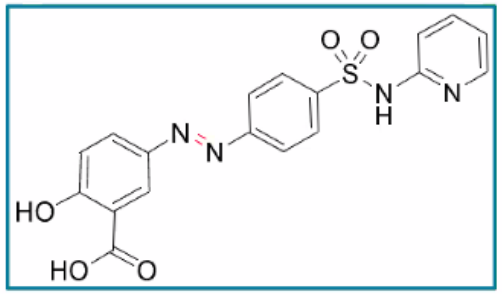
BIOPRECURSOR prodrugs



Rearrangement with no promoiety attachment (decrease in MW)



Subtraction of atoms – depends on later addition of groups (decrease in MW)

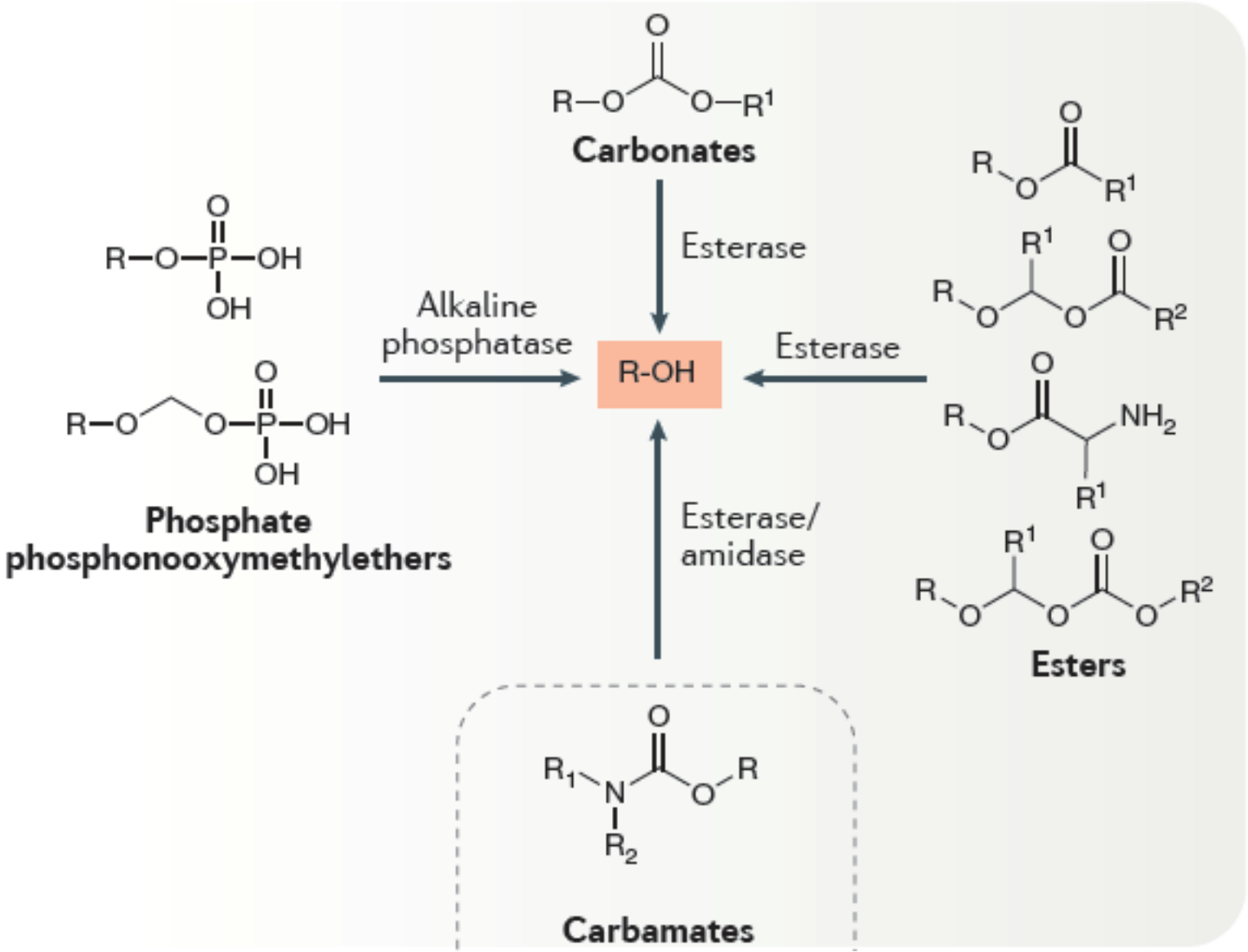


Coupling two active drugs together to form a *CODRUG* (increase in MW)

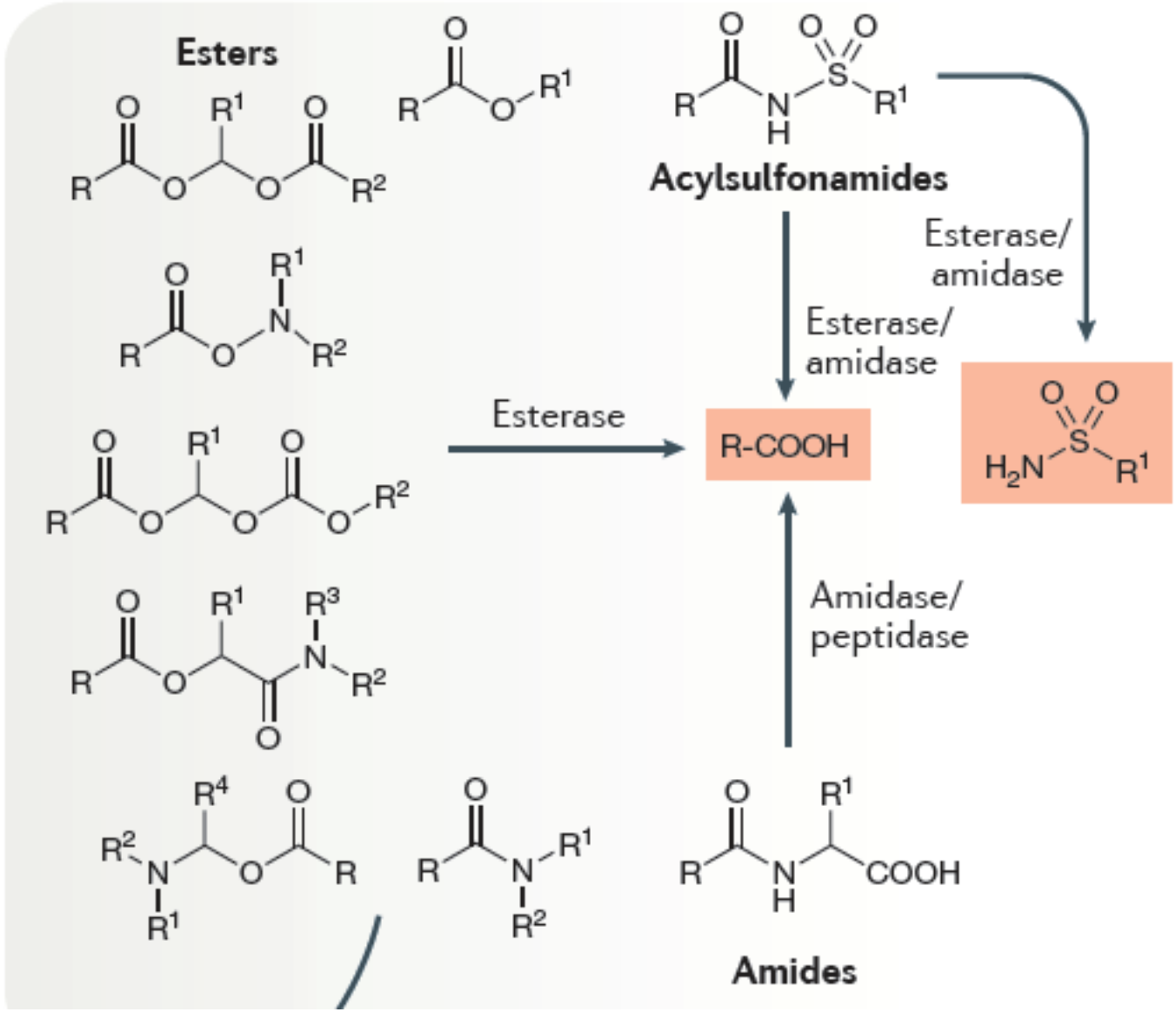
Similar to protecting groups…

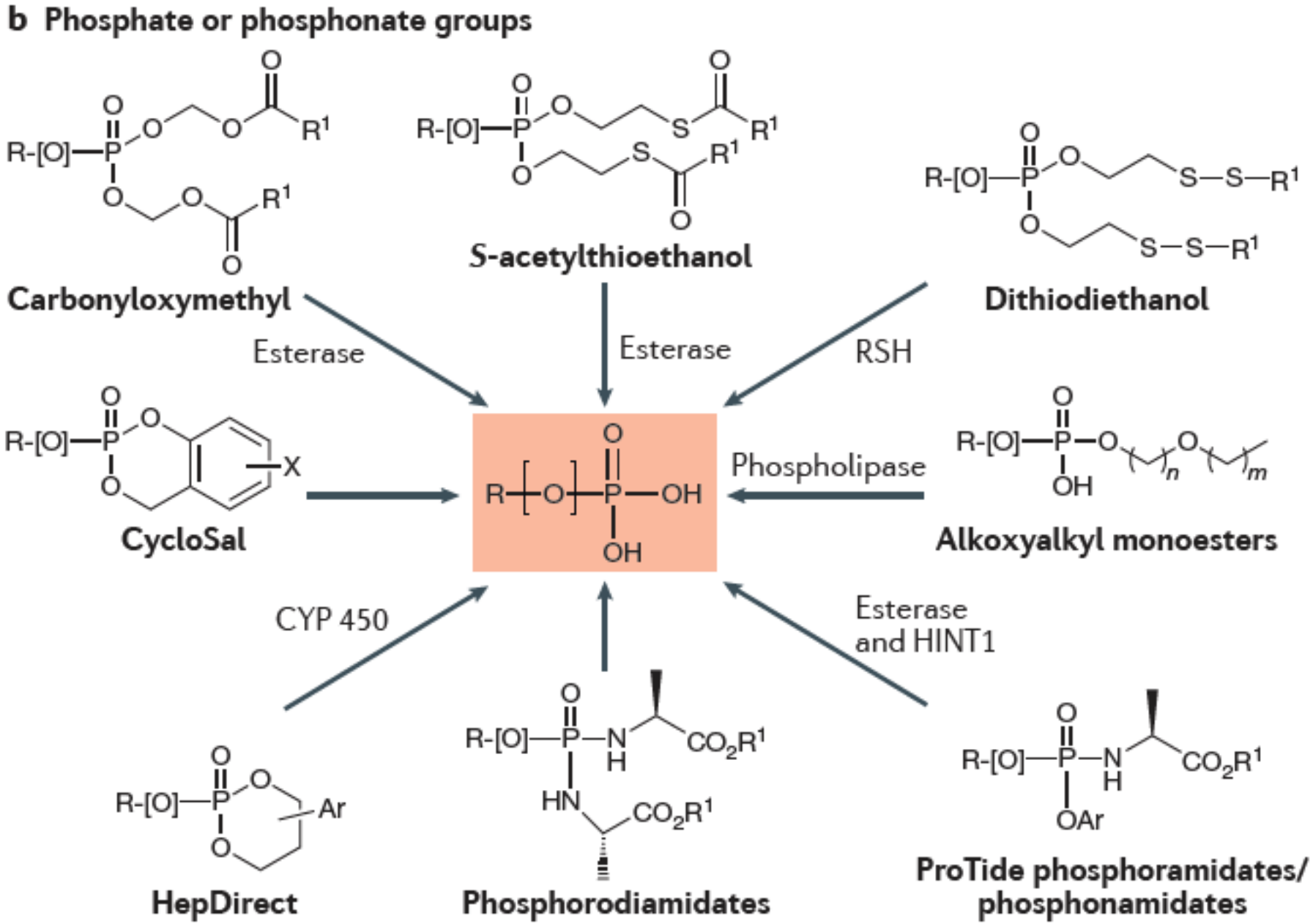
- Conversion liberates the active drug from the masking promoiety or drug carrier or triggers a structural modification or rearrangement (such as an intramolecular reaction or oxidation) such that the resulting molecule is an active metabolite.
- Prodrugs that undergo structural rearrangements are usually referred to as bioprecursor prodrugs.
- Prodrug strategies for the most common functional groups on parent drugs are described in the figure

Prodrugs strategies for the most common functional groups on parent drugs

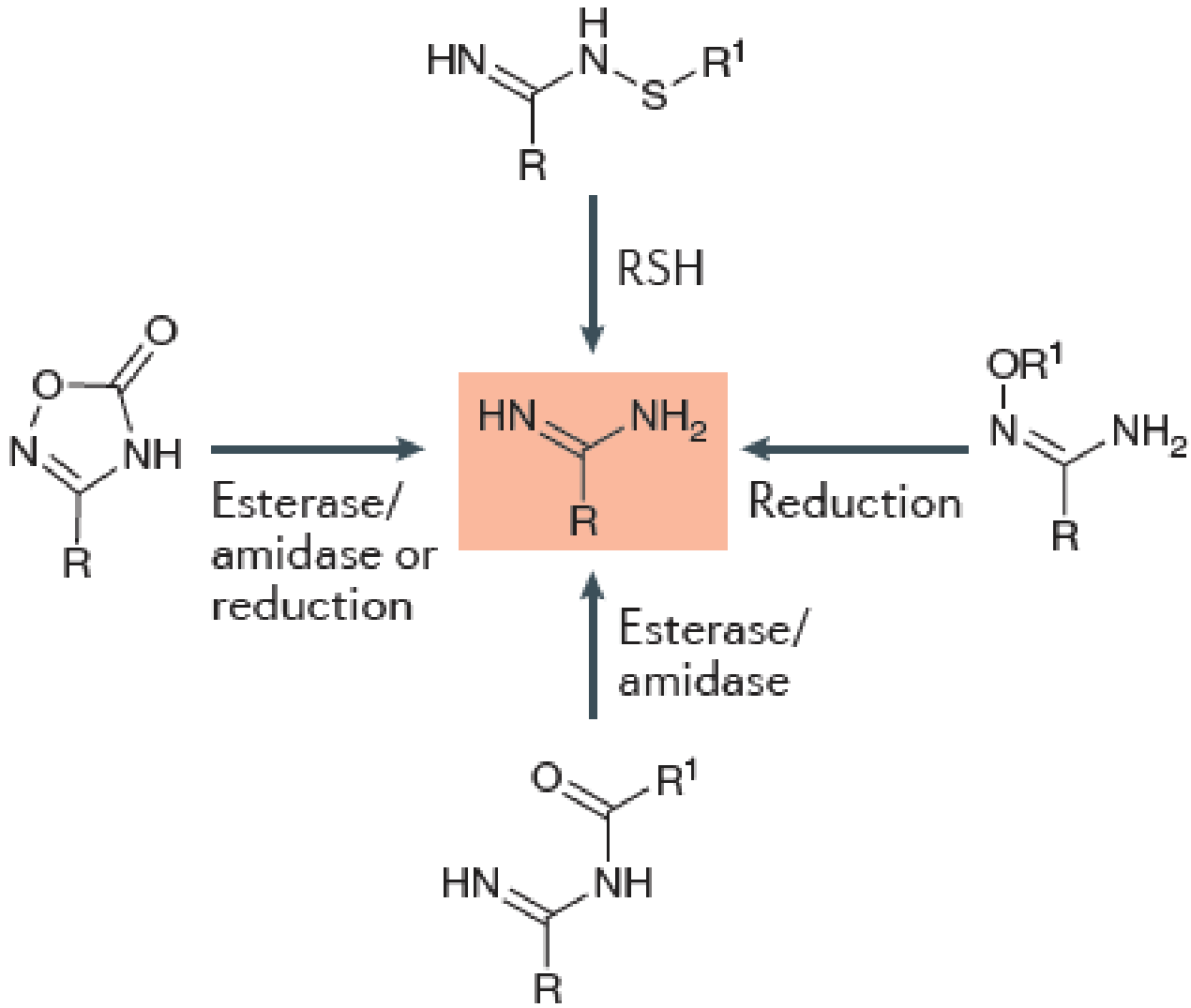


Carboxylic acids




b Phosphate or phosphonate groups
Carbonyloxymethyl
S-acetylthioethanol
Dithiodiethanol
Esterase
Esterase
RSH
CycloSal
Phospholipase
Alkoxyalkyl monoesters
CYP 450
Esterase
and HINT1
HepDirect
Phosphorodiamidates
ProTide phosphoramidates/
phosphonamidates

c Amidine or guanine groups



Progrug with increased solubility in water for oral delivery

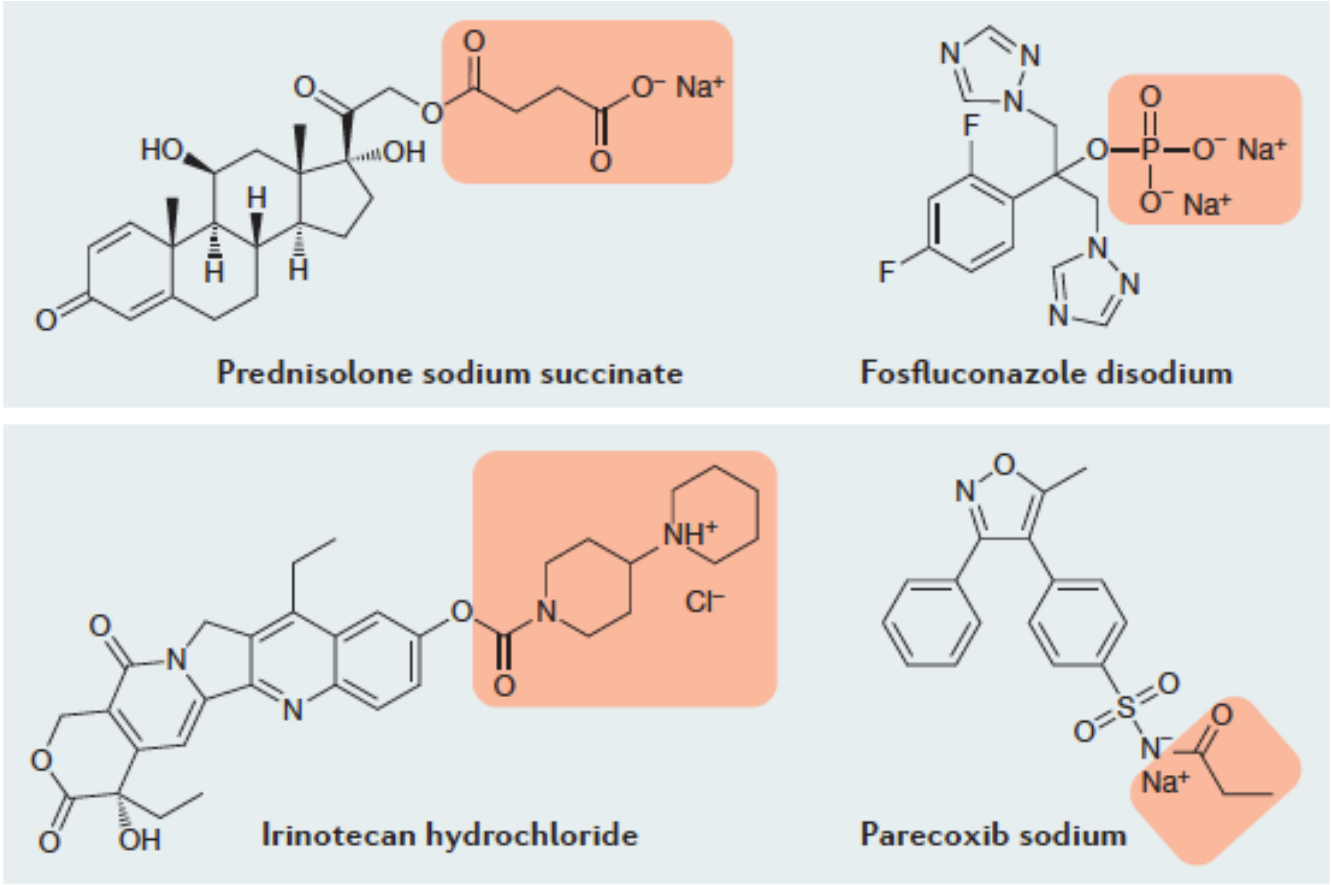
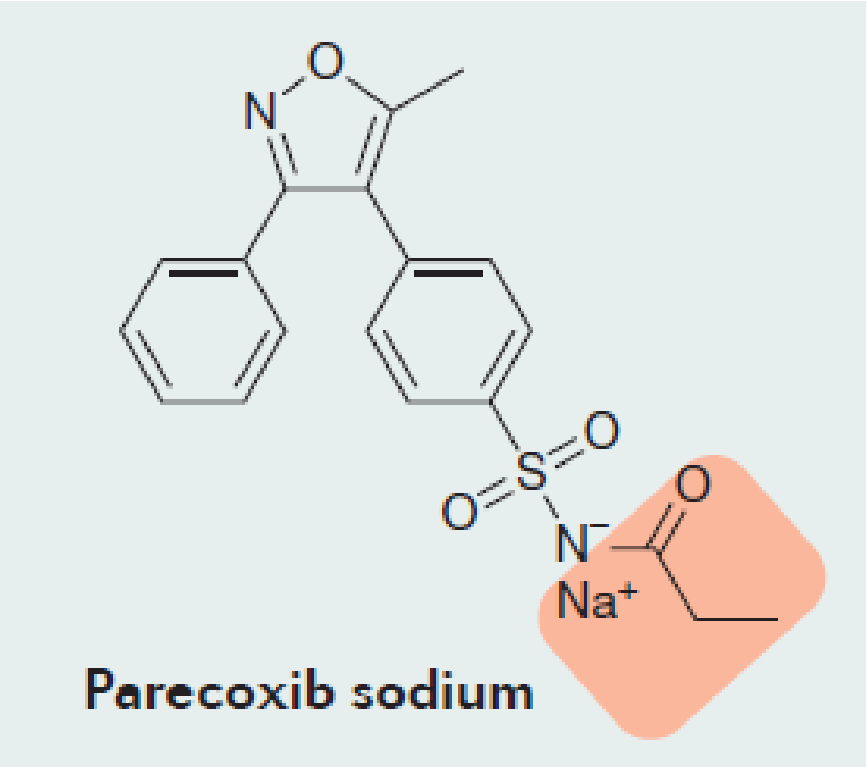
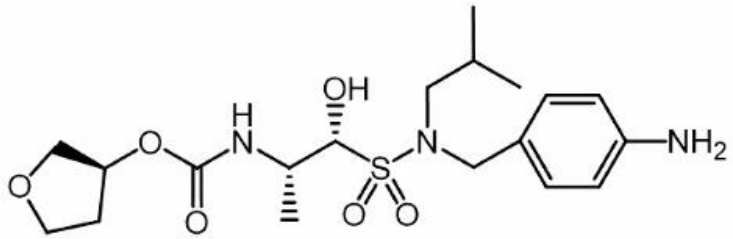


Figure 2 | **Water-soluble prodrugs with various prodrug strategies to increase aqueous solubility.** Utilization of a succinate ester (as in prednisolone sodium succinate), a phosphate group (as in fosfluconazole disodium), an alternative ionizable promoiety (irinotecan hydrochloride) and attachment of a neutral promoiety to create an ionizable element (parecoxib sodium) are applicable prodrug strategies that have been successfully used to increase aqueous solubility. Promoieties are shown in orange boxes.

In parecoxib (NSAID) the propionyl moiety mades more acidic the sulfonamide proton thus allowing its deprotonation at neutral pH and a charged prodrug is obtained



Increased solubility for oral delivery



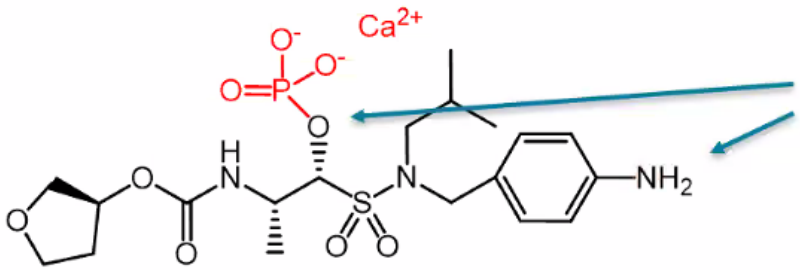
Amprenavir 150 mg soft-gel capsules

Amprenavir

- For the treatment of HIV infection
- Aqueous solubility in water is 0.041 mg/ml
- Good bioavailability (≈ 80%)
- High percentage of excipients (TPGS, PEG-400, PG etc.) due to low solubility requiring 8 capsules two times daily

Only dissolved drug can be absorbed!

Increased solubility for oral delivery



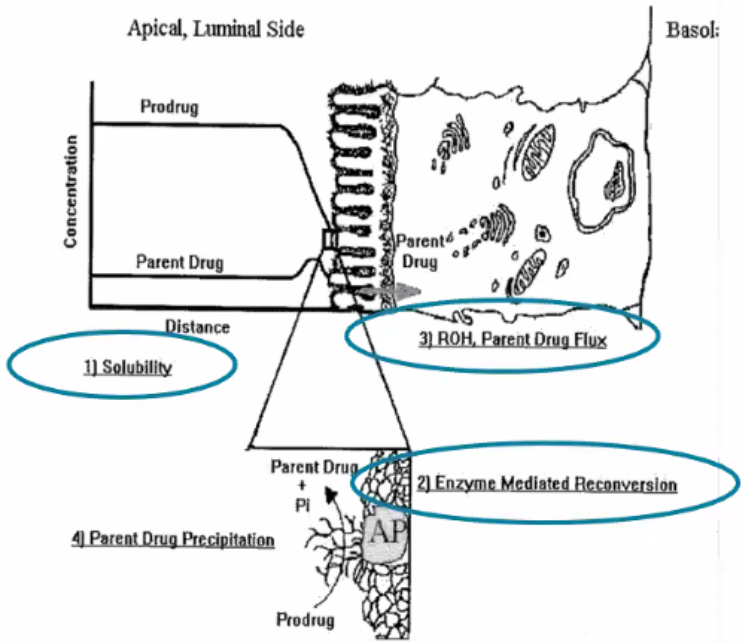
87 prodrugs screened in rats

- 81 prodrugs delivered no or very low APV exposure
- 3 prodrugs delivered 10 to 75% plasma APV exposure
- 3 prodrugs delivered equivalent or higher plasma APV exposure

Fosamprenavir 700 mg tablets

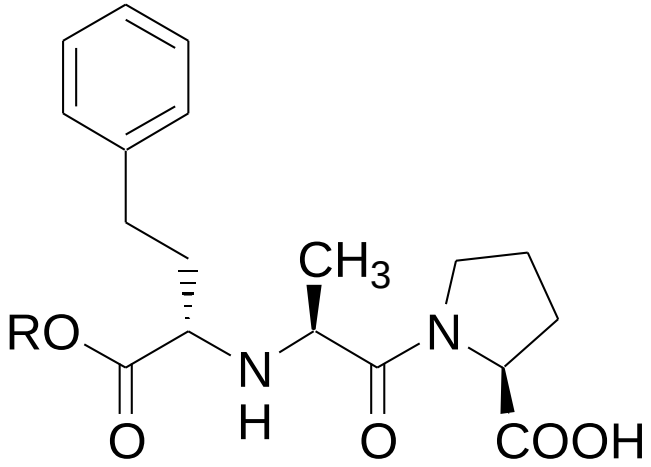
Fosamprenavir (Lexiva®)

- Aqueous solubility in water 0.31 mg/ml (max solubility of calcium salt >100 mg/ml at pH 3-4)
- Biological transformation by brush border gut phosphatase
- Equal bioavailability with amprenavir
- Due to better solubility requires only 2 tablets two times daily
- Patent protection continues longer



Esters to decrease polarity

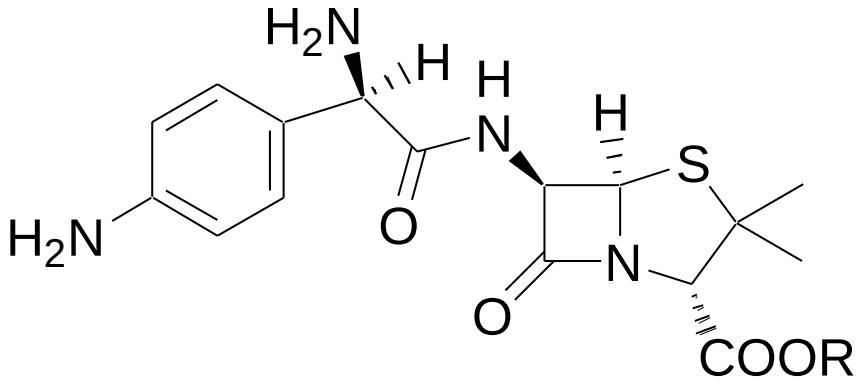
- Enalapril is the prodrug of antihypertensive agent enalaprilat



R = Et ENALAPRIL
R = H ENALAPRILAT

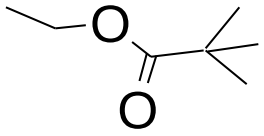
ESTERS of beta-lactamic antibiotics

- The low intestinal absorpion is due to the presence of carboxyl and amino groups. Prodrug with increased intestinal uptake:
- Pivampicillin
- Talampicillin
- Bacampicillin

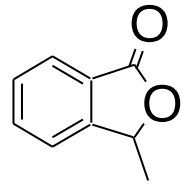


ampicillin
R = H

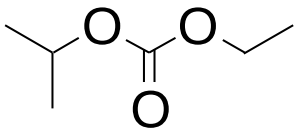
Pivampicillina: R =

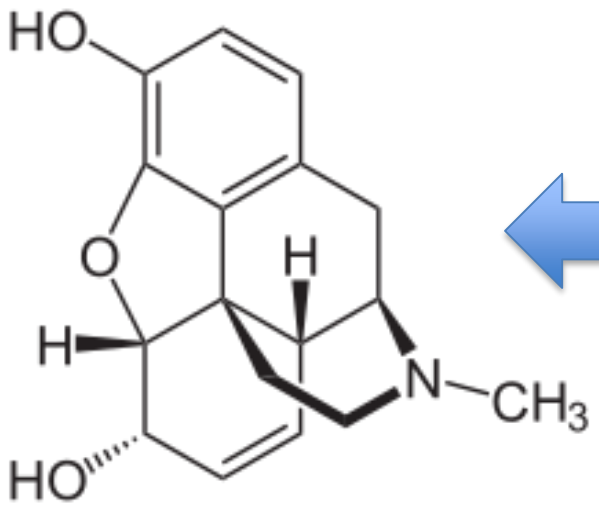


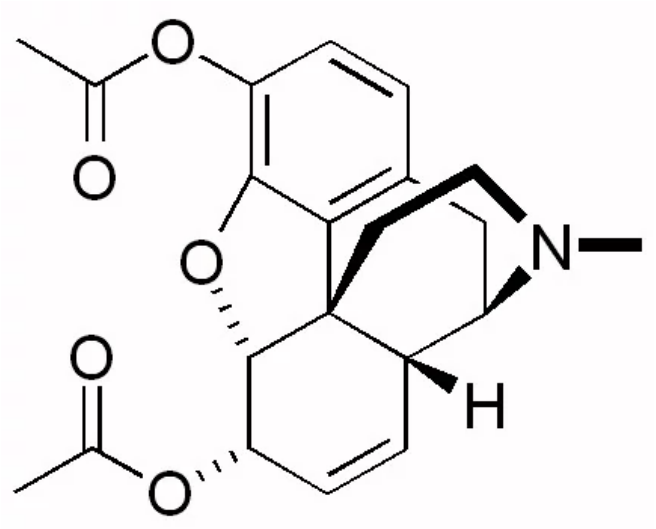
Talampicillina: R =



Bacampicillina: R =







MORPHINE

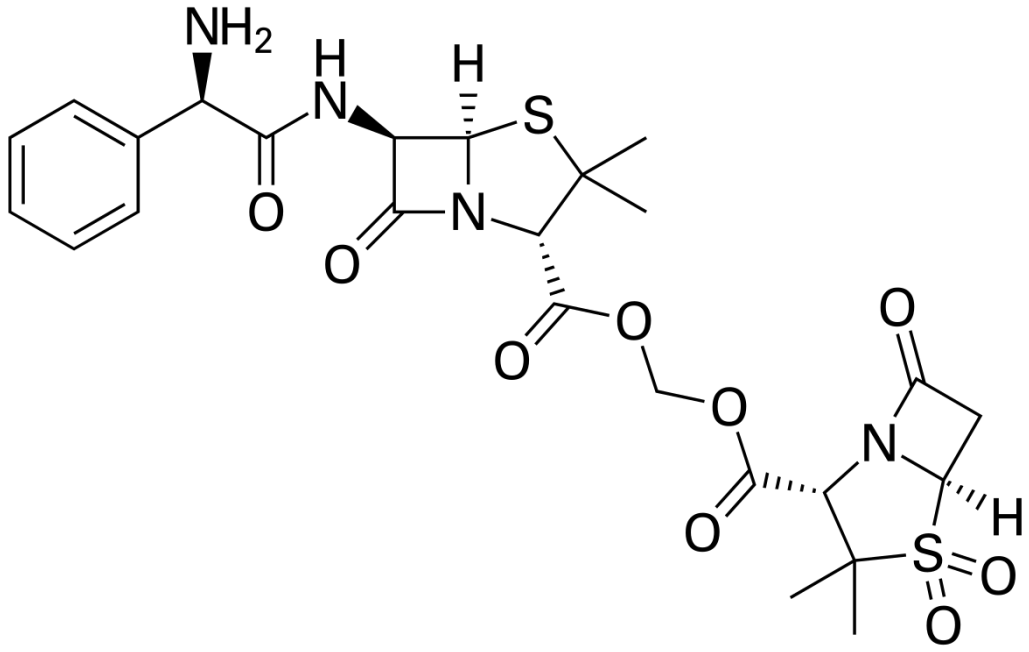
DIACETYLMORPHINE

Diacetylmorphine: higher penetration into the CNS, higher effect

CODRUGS

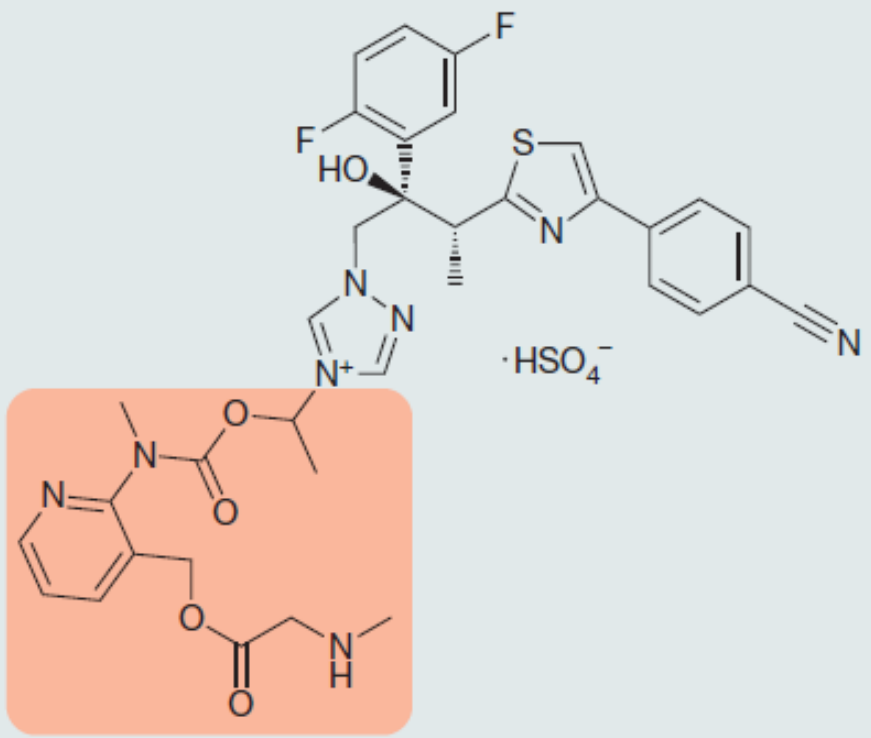
- Codrugs are similar to prodrugs in that they consist of pharmacologically active drugs, but for codrugs, two compounds are coupled together and each is the promoiety for the other.
- Upon bioconversion, codrugs liberate both active molecules in the same target tissue.
- A good example of a marketed codrug is the antibacterial agent sultamicillin, which releases both the β-lactam antibiotic ampicillin and the β-lactamase inhibitor penicillanic acid sulfone upon hydrolysis.

SULTAMICILLIN



- 2 antibiotic with synergic action

Isavuconazonium sulfate



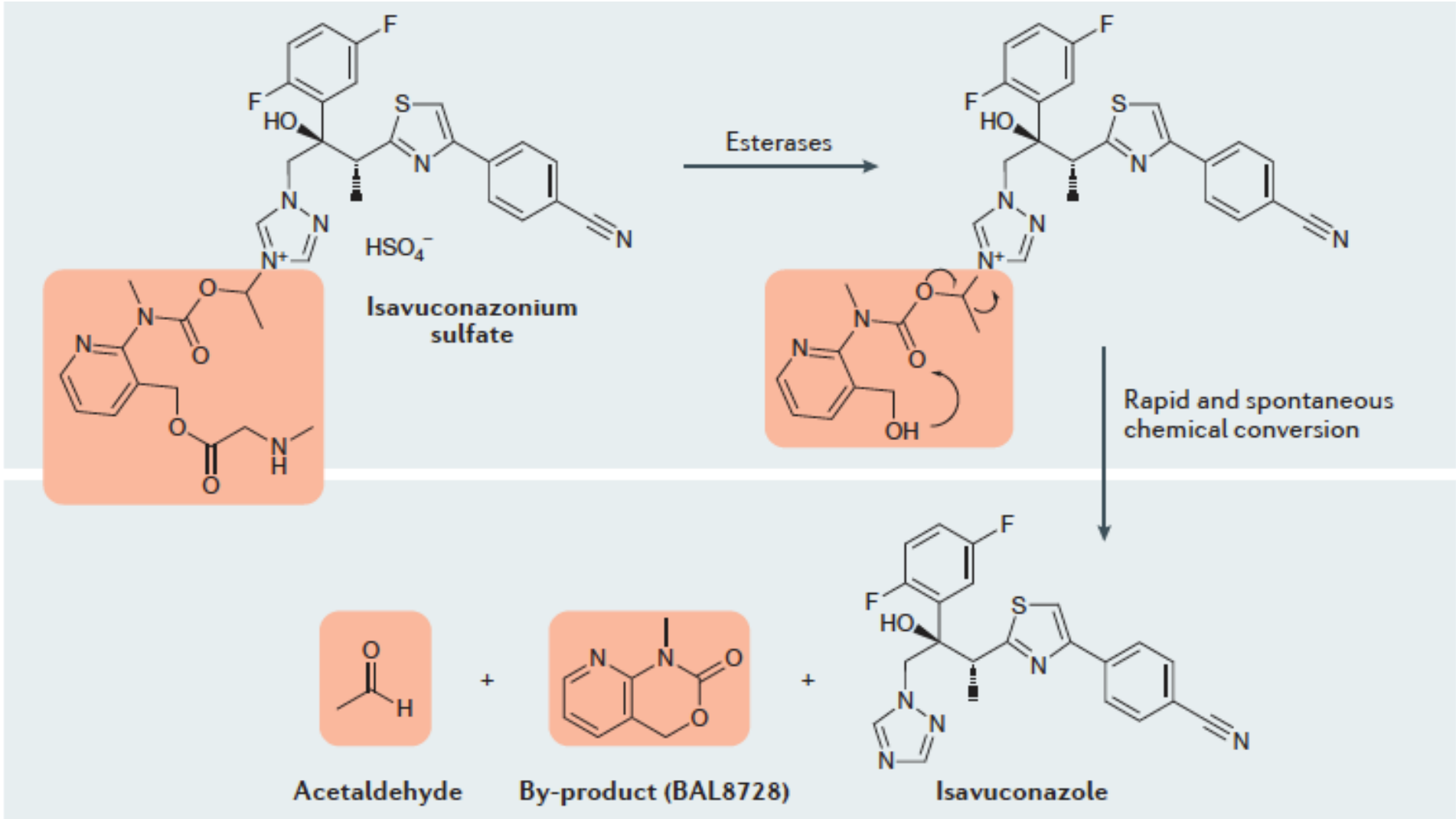
Isavuconazonium (Cresemba, isavuconazonium sulfate)

Invasive aspergillosis or invasive mucormycosis (azole antifungal; inhibits synthesis of ergosterol, a cell wall component)	• Sarcosine ester is cleaved to release an alcohol that self-immolates to release isavuconazole • Improved solubility[47]	6 Mar 2015

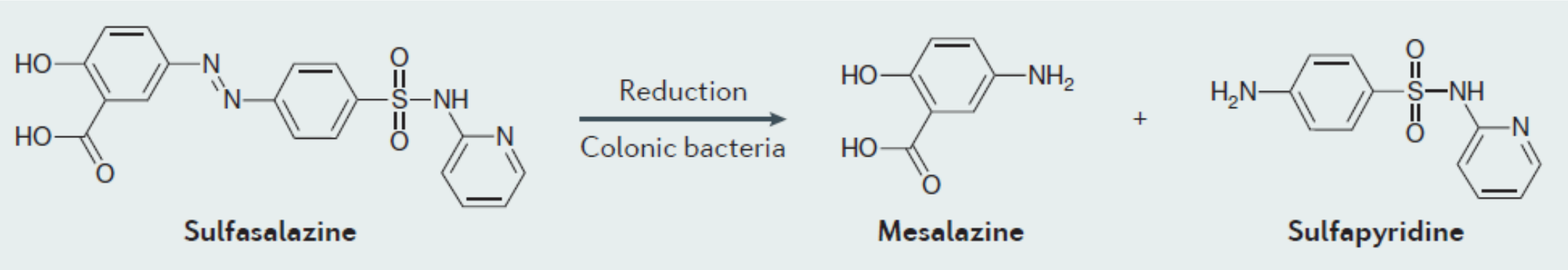
Bio-activation

Bioconversion of isavuconazonium to isavuconazole. Isavuconazonium sulfate is a salt-based prodrug of the broad-spectrum antifungal agent isavuconazole. In isavuconazonium, the positively charged triazolium ring and the sarcosine element of the promoiety improve aqueous solubility such that it can be administered orally or intravenously.

In vivo, isavuconazonium is hydrolysed by plasma esterases to a pyridin-3-ylmethanol intermediate, which subsequently undergoes an intramolecular cyclization that triggers N-dealkylation to release isavuconazole, an inactive and innocuous cyclic by-product (BAL8728) and acetaldehyde.

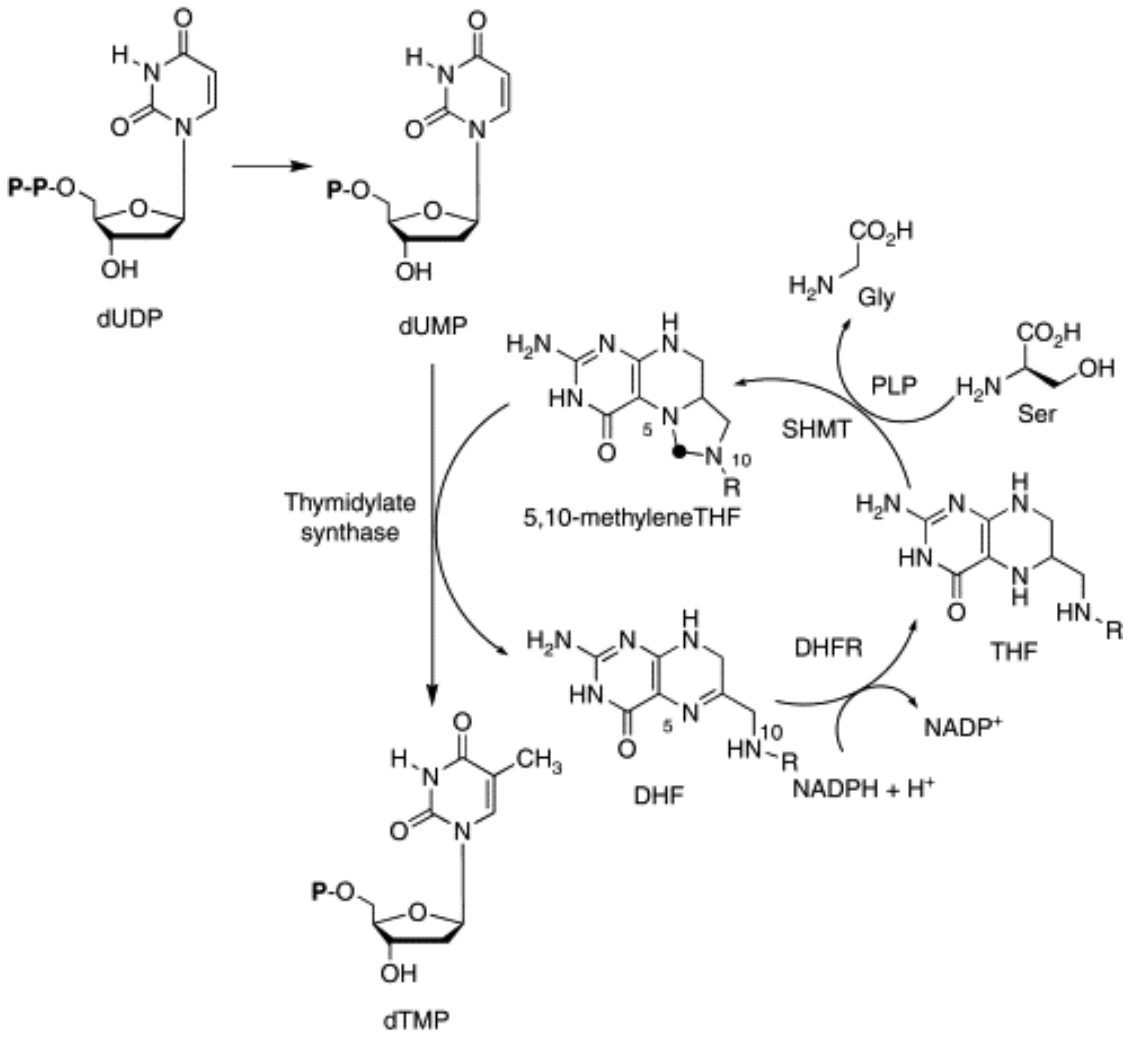

Esterases
Isavuconazonium sulfate
Rapid and spontaneous chemical conversion
Acetaldehyde
By-product (BAL8728)
Isavuconazole

Bioconversion by bacteria in the intestine (microbiota)

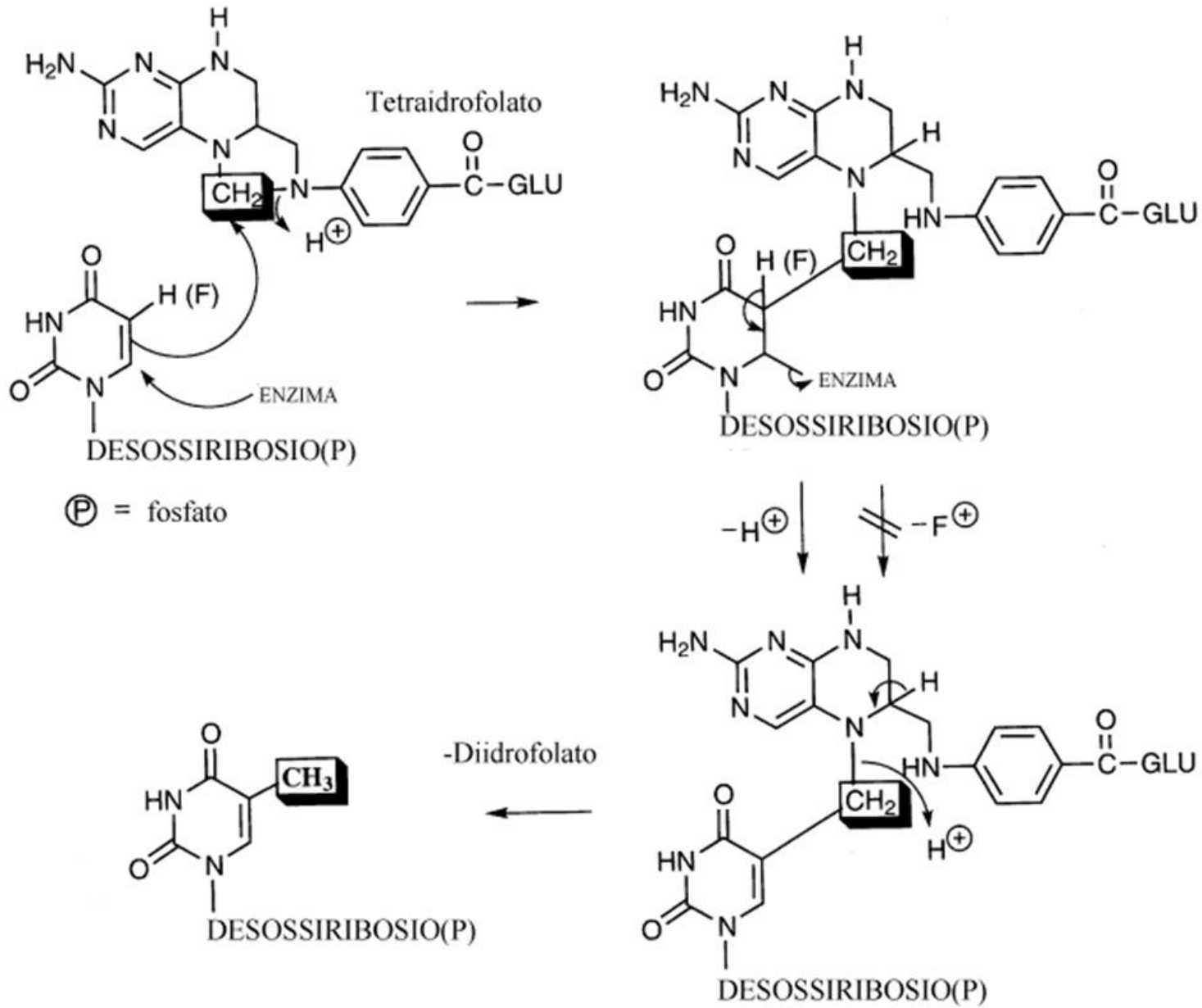


- The reduction of sulfasalazine (drug against Inflammatory Bowel Diseases) by microbiota liberates mesalazine (amtiinflammatory) and sulfapyridine (antibacterial)

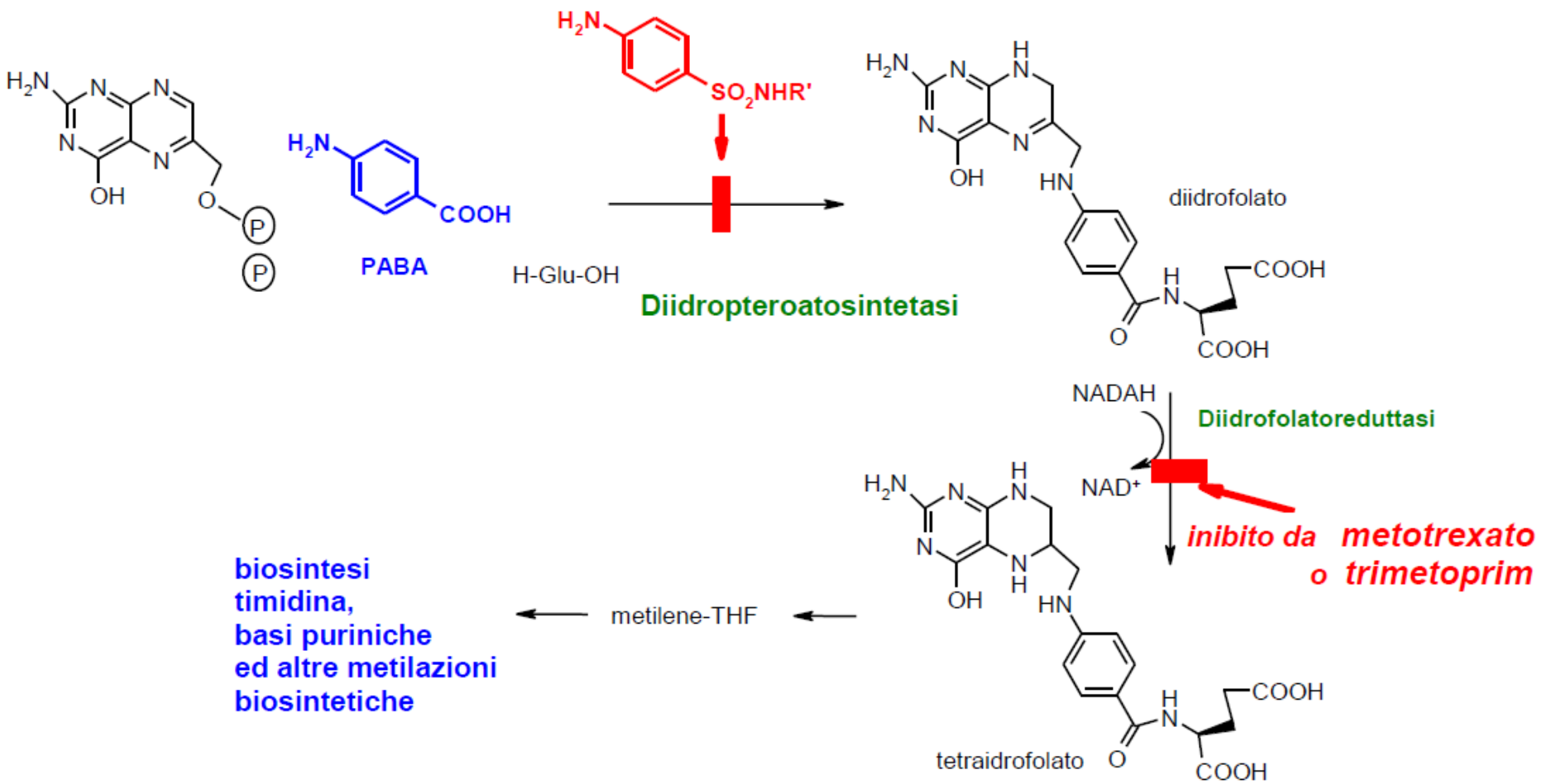
The timidalate synthase is an enzyme that catalyses the methylation of uridine to give timidine using the methylene tetrahydrofolate as cofactor



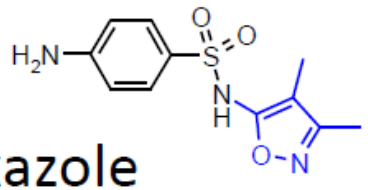
The biosynthesis of timidine is very important for DNA replication: tumor cells replicate faster than other cells and are affected by inhbition of this process


Tetraidrofolato
H (F)
ENZIMA
DESOSSIRIBOSIO(P)
Ⓟ = fosfato
HN
GLU
-H⊕
-F⊕
-Diidrofolato
CH3
CH2

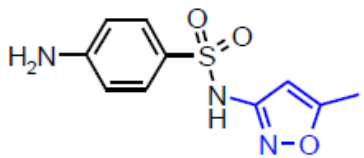
mechanism of action: inhibition of the folic acid biosynthesis



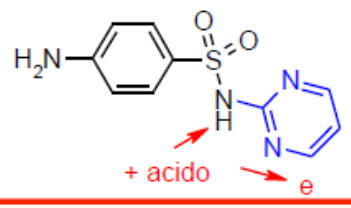
Sulfisoxazole



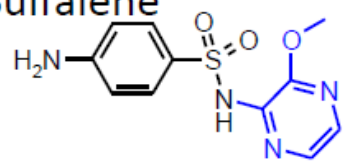
Sulfamethoxazole



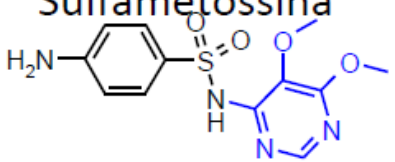
Sulfadiazina

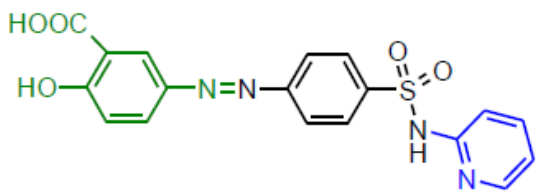


Sulfalene



Sulfametossina





Sulfasalazine

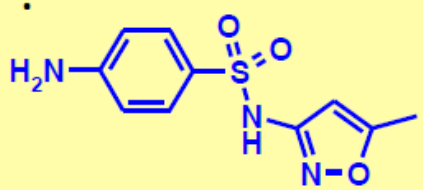
intestinal tract

mesalamine

sulfapyridine

BACTRIM :

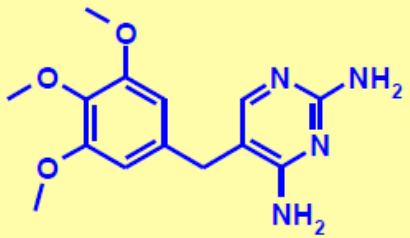
Sulfametossazolo



5

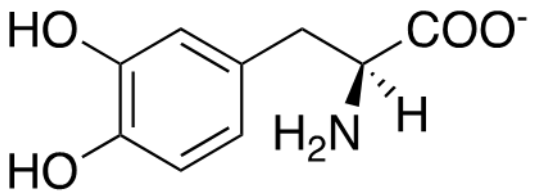
1

Trimethoprim



Prodrugs that exploit carrier-mediated transport

- On the BBB and in the intestinal epithelium there are amino acid transporters:
- 1) levodopa exploits the tyrosine transporter



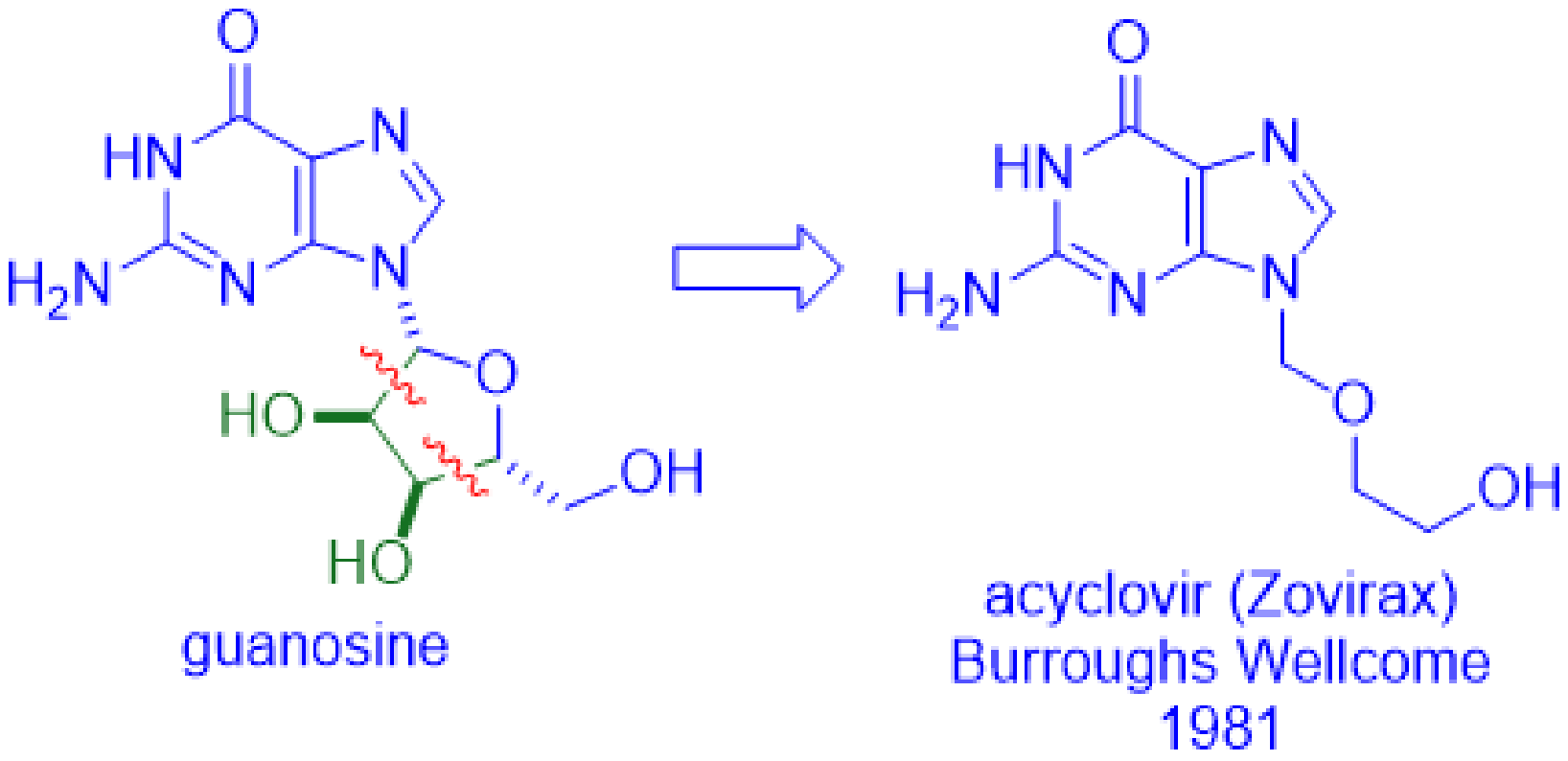
- 2) Intestinal peptide transporter PEPT1

Improved oral absorption of several amino acid prodrugs has been attributed to their carrier-mediated transport via intestinal peptide transporter 1 (PEPT1; also known as SLC15A1).

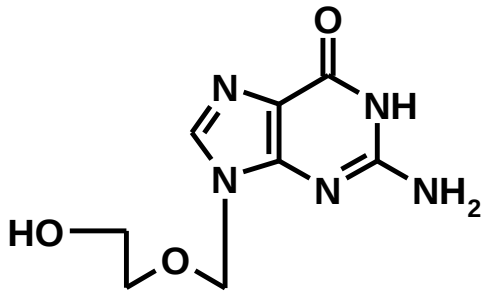
PEPT1 recognizes both dipeptides and tripeptides, and its expression increases from the duodenum to the ileum.

Valacyclovir and valganciclovir are the l-valine amino acid esters of the herpesvirus inhibitor acyclovir and the human cytomegalovirus inhibitor ganciclovir, respectively, and are the pioneering examples of marketed prodrugs that utilize PEPT1 to overcome the limited and variable oral bioavailability of the polar parent nucleoside-based drugs.

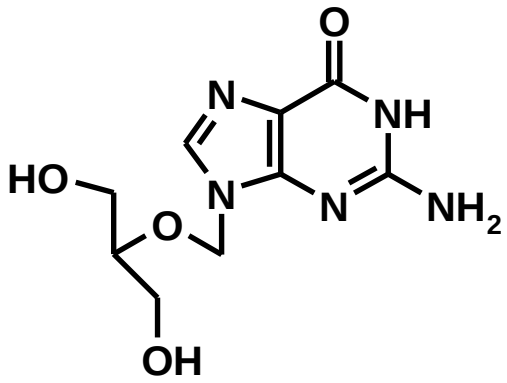
Acyclovir: inhibitor of DNA polymerase in herpes simplex virus (HSV)



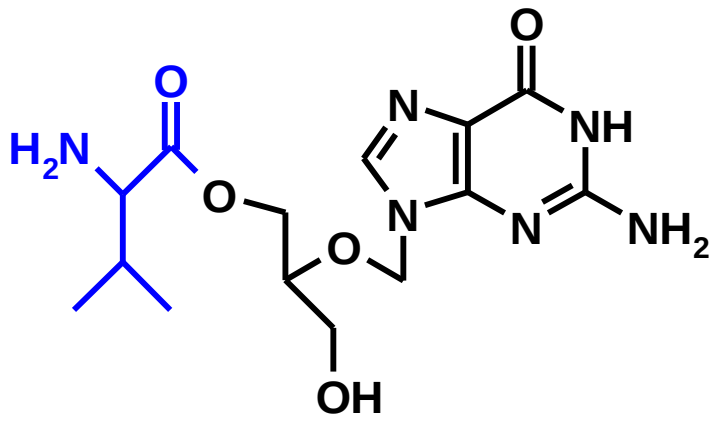
Nucleoside analogues prodrugs



acyclovir



gancyclovir



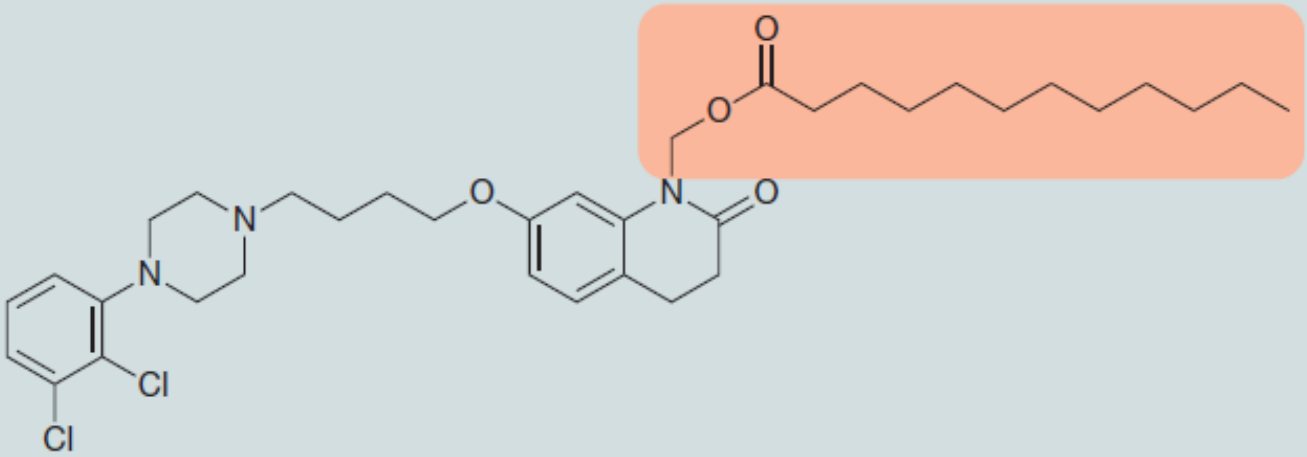
Valganciclovir (oral prodrug)

Prodrug to prologe the duration of action

- Sustained plasma levels and, consequently, a prolonged duration of drug action, are typically enabled by controlled-release formulations, such as suspensions and polymeric matrices. Advantages of such formulations are multifold, including reduced dosing frequency, improved patient compliance, elimination of variability in exposure and the blunting of high peaks of drug concentration in plasma. Prodrugs can be used to achieve controlled release of an active drug by modifying its aqueous solubility and dissolution properties in a way that affects the release rate of the active drug, the rate of absorption or its tissue distribution

- Aripiprazole lauroxil (Aristada) is the most recently approved intramuscularly administered prodrug that provides a prolonged duration of action and is used in the treatment of adults with schizophrenia.
- It is an *N*-acyloxymethyl prodrug of aripiprazole in which the *N*-hydroxymethyl group has been acylated with the very lipophilic dodecanoic acid. The solubilizing ingredients in the aripiprazole lauroxil suspension for intramuscular injection include sorbitan monolaurate and polysorbate .
- Once injected into the body, aripiprazole lauroxil likely undergoes enzyme-mediated hydrolysis to form the *N*-hydroxymethyl intermediate, which is susceptible to non-enzymatic chemical degradation to release aripiprazole and formaldehyde. Systemic appearance of aripiprazole following a single intramuscular injection of the prodrug occurs within 5–6 days, with elevated plasma levels persisting for an additional 36 days

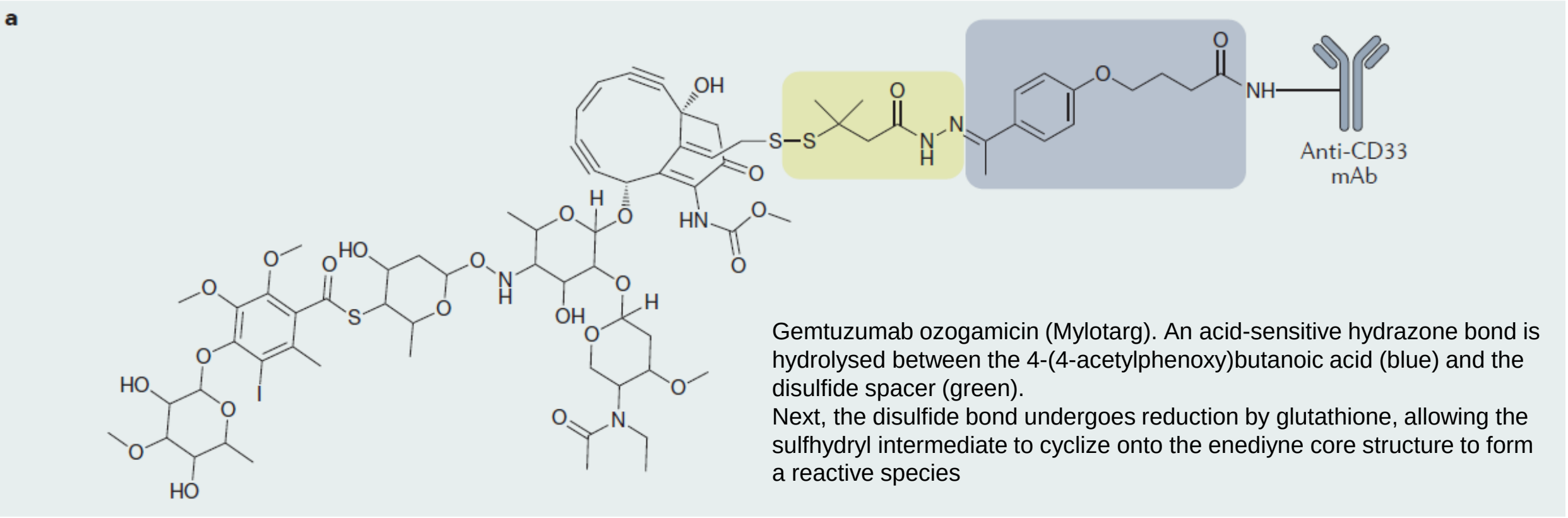
Aripiprazole lauroxyl (lauric ester)

21	 Aripiprazole lauroxil (Aristada)	Schizophrenia (antipsychotic; partially owing to inhibition of the D_2 receptor)	• *N*-Acyloxymethyl prodrug • Sustained release and prolonged duration of action following intramuscular administration[108]	6 Oct 2015

Antibody-drug conjugates (ADCs)

- Antibody–drug conjugates (ADCs) link an active drug to a monoclonal antibody, which specifically recognizes a cellular surface antigen and delivers the drug directly to the target cell (tumor cell).
- The chemical conjugation of the antibody to the cytotoxic drug has a major influence on the pharmacokinetics, selectivity and therapeutic index of the therapy. Because the conjugation is formed through a cleavable bond in most of the clinically used ADCs, these conjugates can be regarded as macromolecular prodrugs.

- This targeting strategy has been especially successful in the treatment of various cancers. For example, the enediyne anticancer agent calicheamicin is too toxic to be used as a chemotherapeutic. However, a slightly modified calicheamicin, linked to a humanized antibody through a spacer, was developed as gemtuzumab ozogamicin



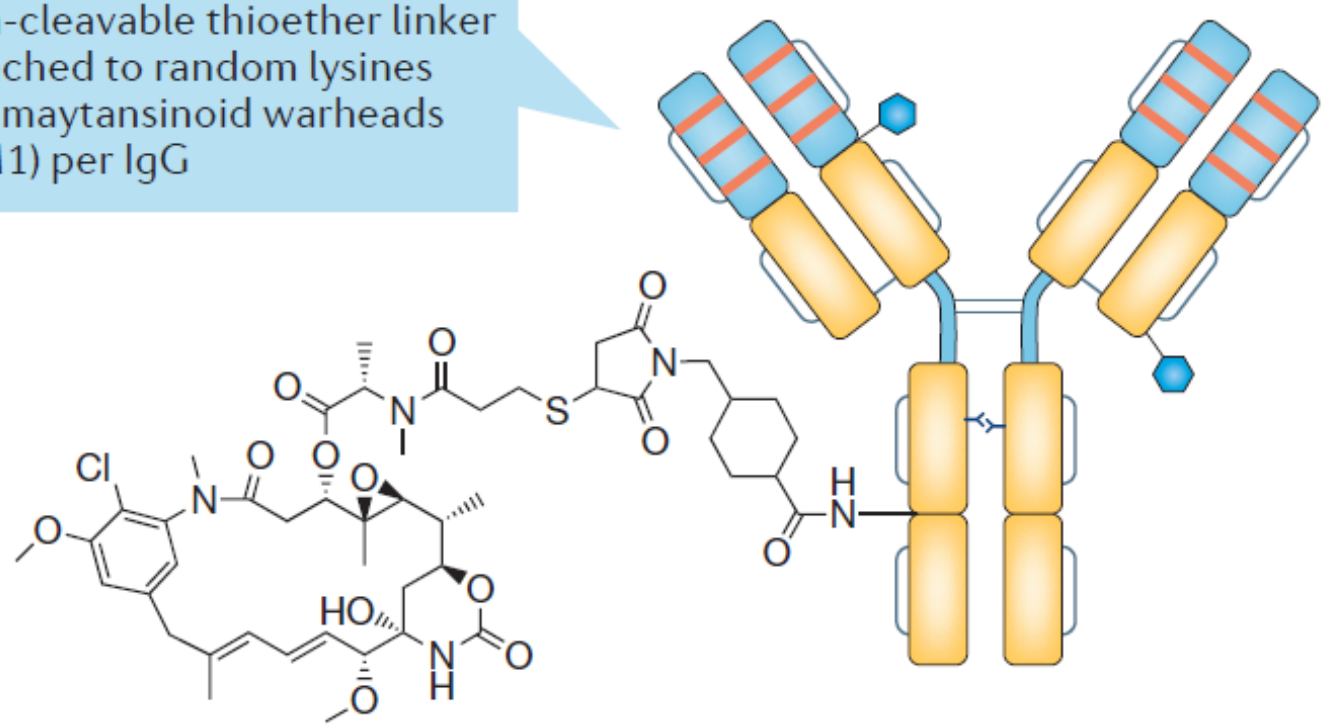
Gemtuzumab ozogamicin (Mylotarg). An acid-sensitive hydrazone bond is hydrolysed between the 4-(4-acetylphenoxy)butanoic acid (blue) and the disulfide spacer (green).
Next, the disulfide bond undergoes reduction by glutathione, allowing the sulfhydryl intermediate to cyclize onto the enediyne core structure to form a reactive species

Antibody-drug conjugates (antitumoral drugs)

- Antibody–drug conjugates (ADCs) consist of recombinant monoclonal antibodies (mAbs) that are covalently bound to cytotoxic chemicals (known as warheads) via synthetic linkers.
- Such immunoconjugates combine the antitumour potency of highly cytotoxic small-molecule drugs (300–1,000 Da, with subnanomolar half-maximal inhibitory concentration (IC50) values) with the high selectivity, stability and favourable pharmacokinetic profile of mAbs.

b Trastuzumab emtansine

Second generation
- IgG1 mAb
- Non-cleavable thioether linker attached to random lysines
- 3–4 maytansinoid warheads (DM1) per IgG



DRUG LIBERATION FROM CARRIERS
DRUG DELIVERY SYSTEMS

- Drug entrapment in:
- liposomes
- hydrogels
- micro-nanoparticles
- micro-nanocapsules
- Drug conjugation to:
- polymers
- nanoparticles

- In the past two decades, several therapeutics based on nanoparticles — particles in the size range 1–1,000 nm — have been successfully introduced for the treatment of cancer, pain and infectious diseases.
- These therapeutics harness the opportunities provided by nanomaterials to target the delivery of drugs more precisely, in order to improve their solubility, to extend their half-life, to improve their therapeutic index and to reduce their immunogenicity

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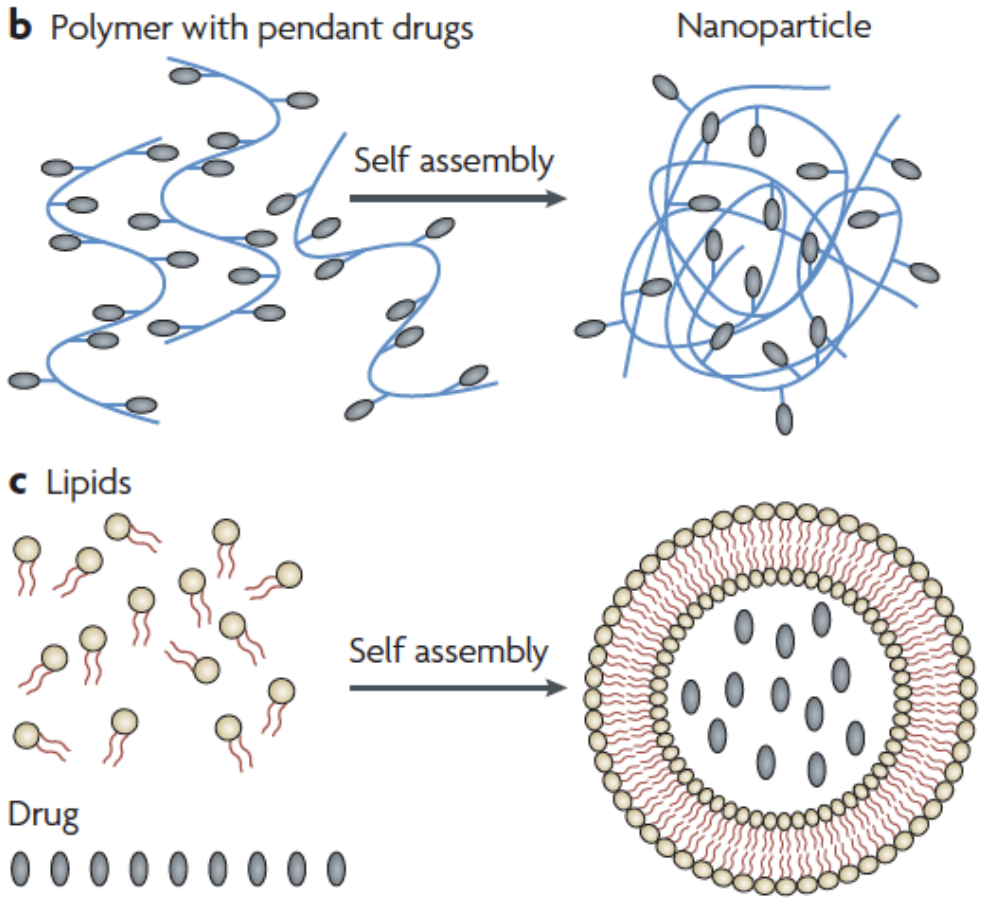
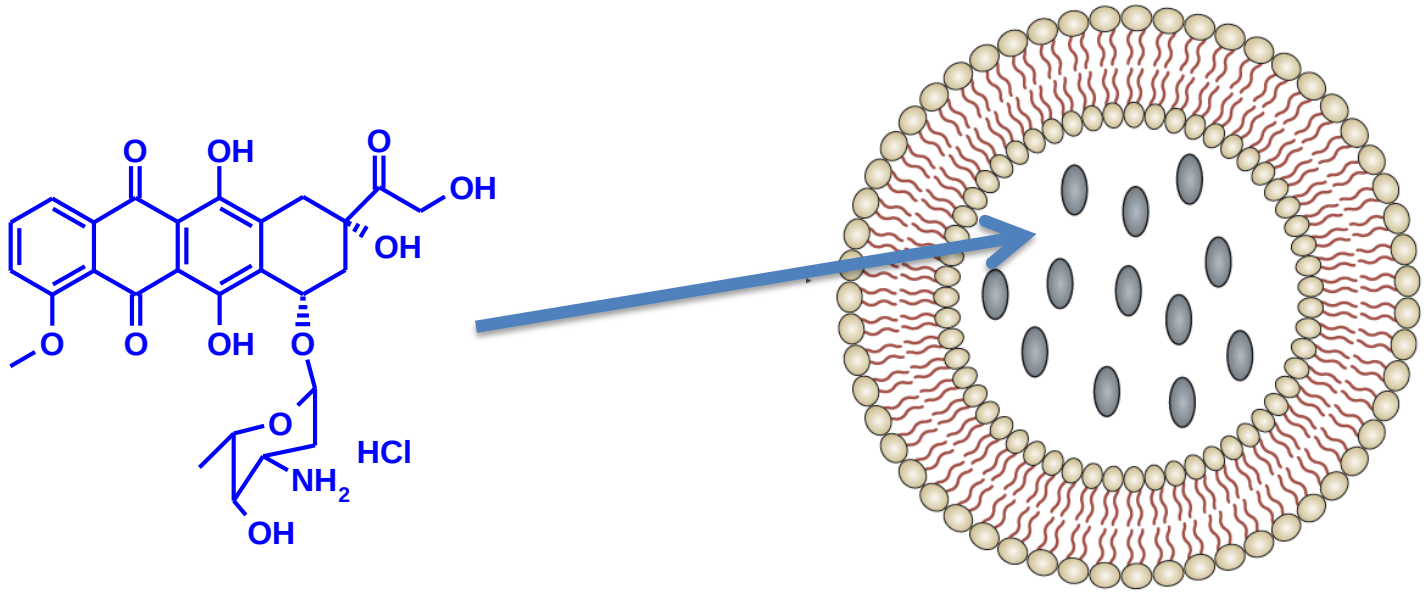
- These therapeutics harness the opportunities provided by nanomaterials to target the delivery of drugs more precisely, in order to improve their solubility, to extend their half-life, to improve their therapeutic index and to reduce their immunogenicity

- The first generation of nanoparticles used for drug deliveryare primarily based on liposomes and polymer–drug conjugates

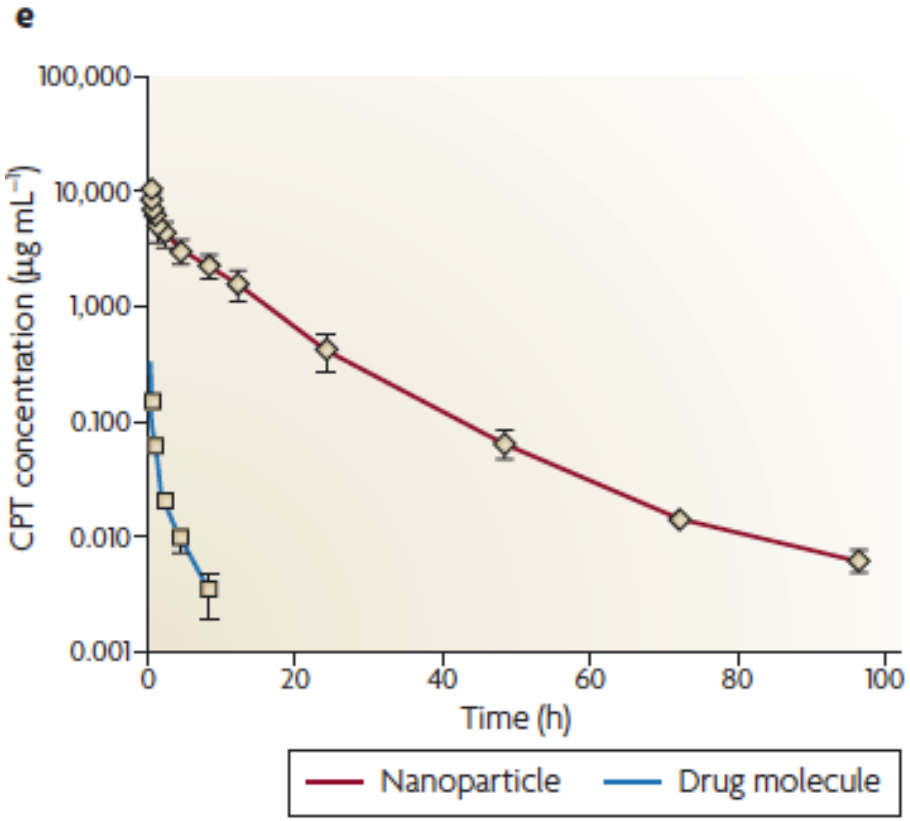


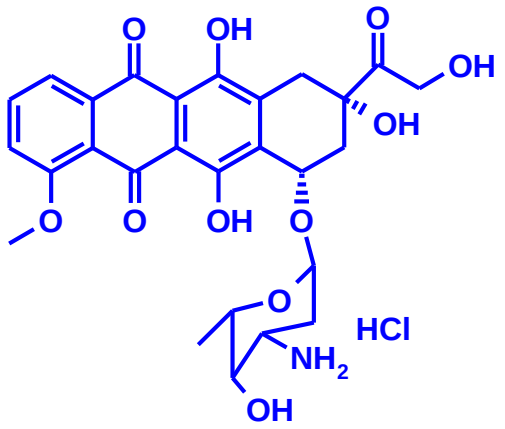
liposome-based drugs

- The first liposome-based therapeutic, liposome-encapsulated doxorubicin (Doxil; OrthoBiotech), was approved by the US Food and Drug Administration (FDA) in 1995 for the treatment of HIV-related Kaposi's sarcoma, and was subsequently approved for the treatment of ovarian cancer and multiple myeloma.



- Encapsulating the cytotoxic anticancer drug doxorubicin into a liposome carrier increases its half-life and enhances its deposition in tumours. Furthermore, Doxil has shown significantly reduced cardiotoxicity compared with free doxorubicin

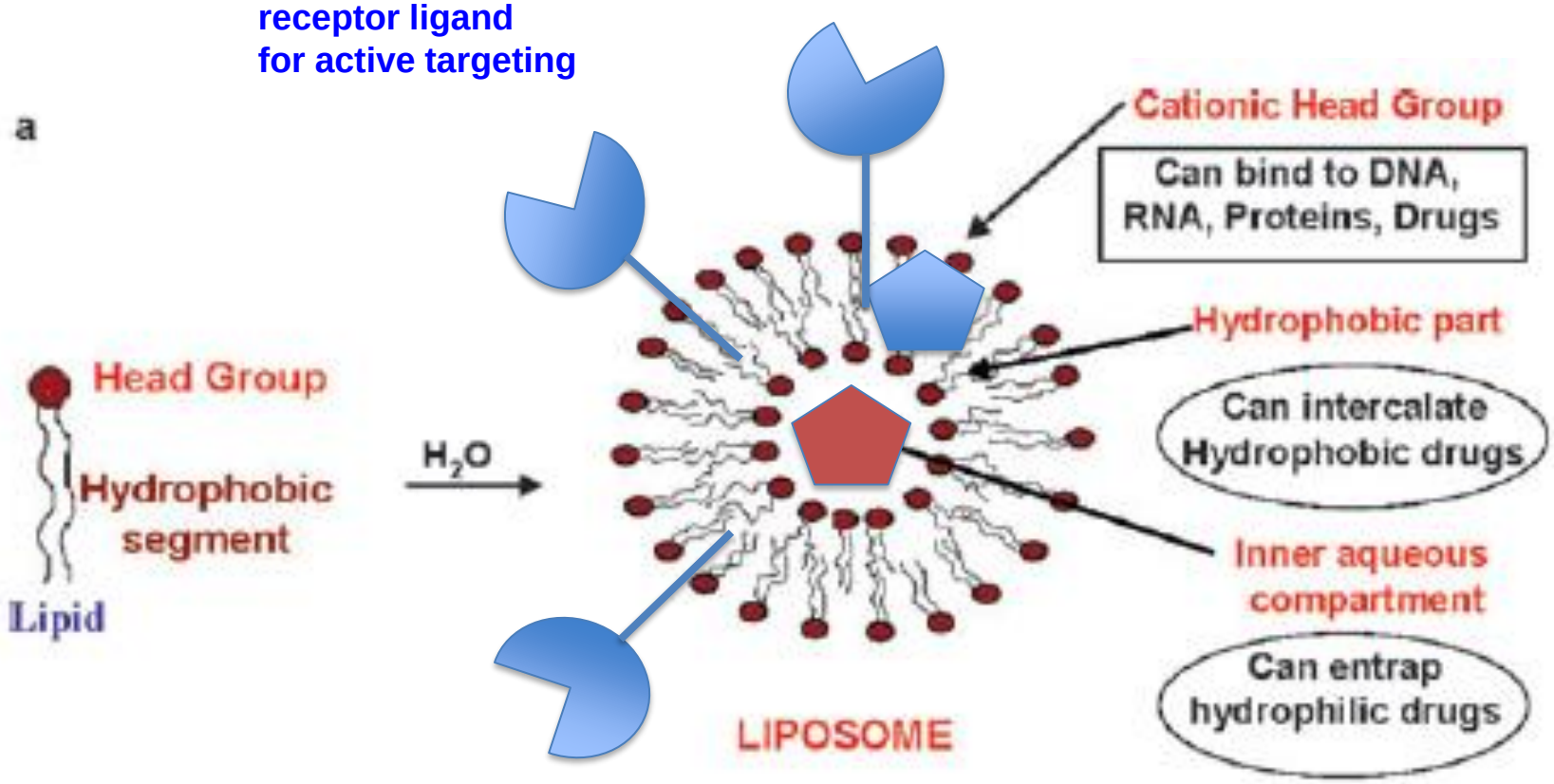




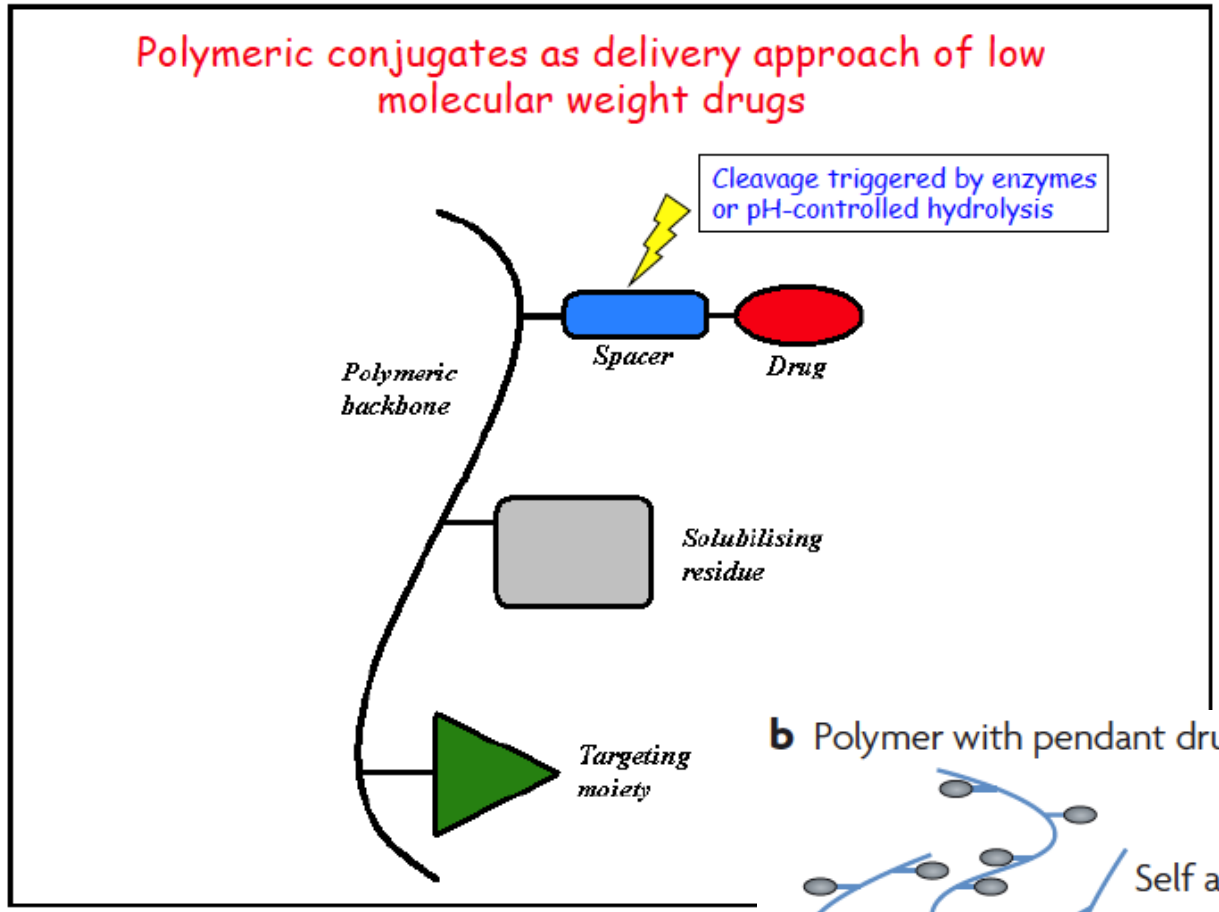
liposomes

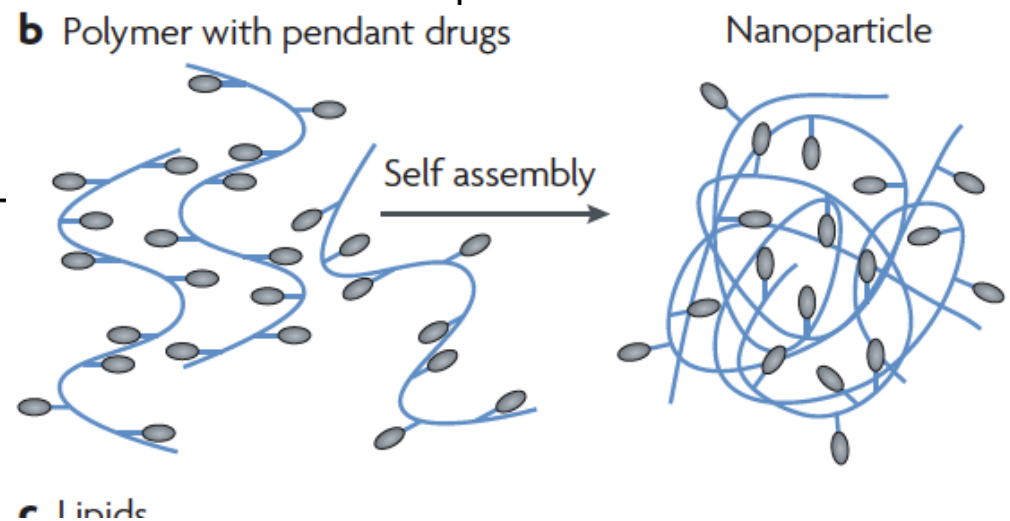
hydrophilic drug

hydrophobic drug



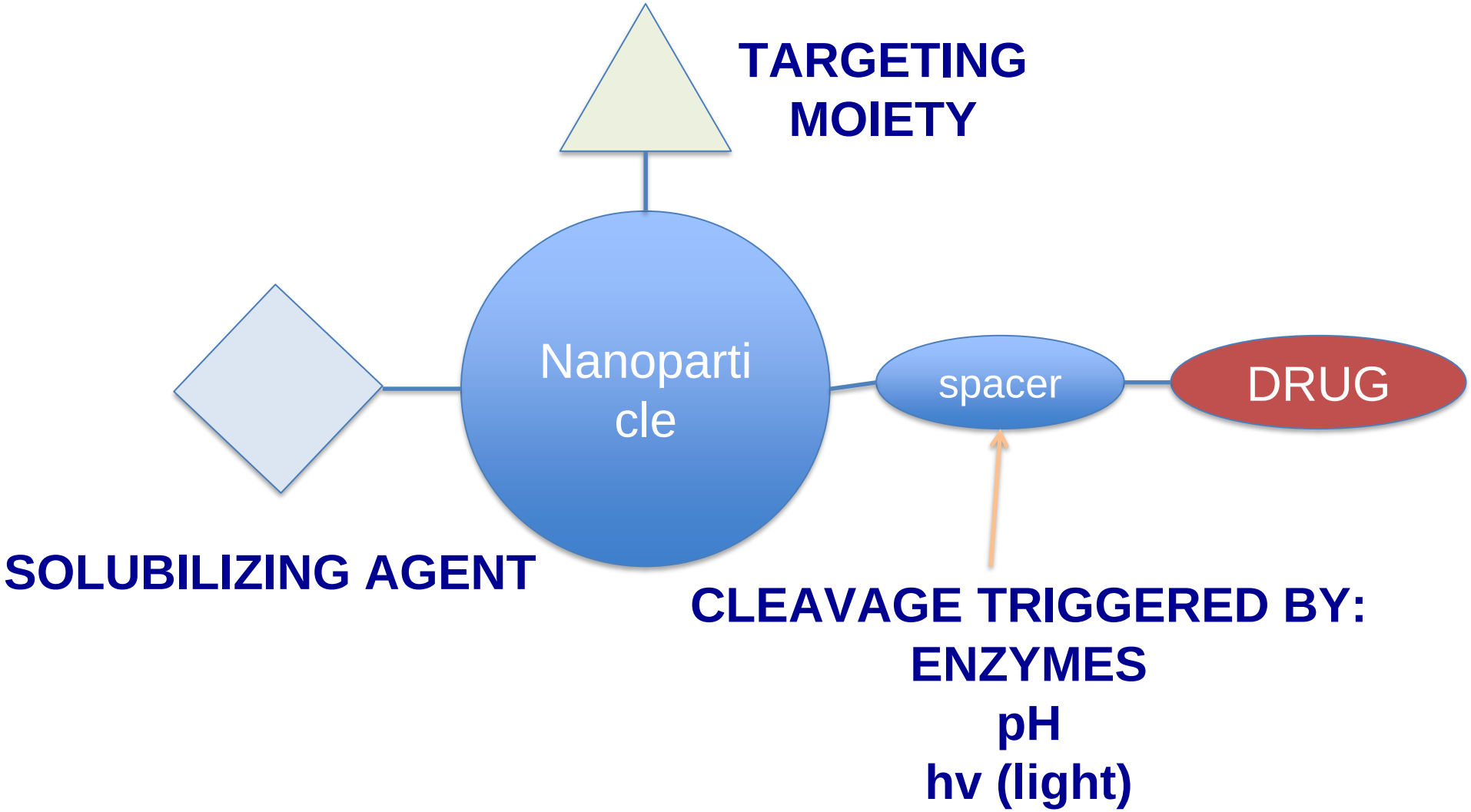
Polymeric conjugates as delivery approach of low molecular weight drugs



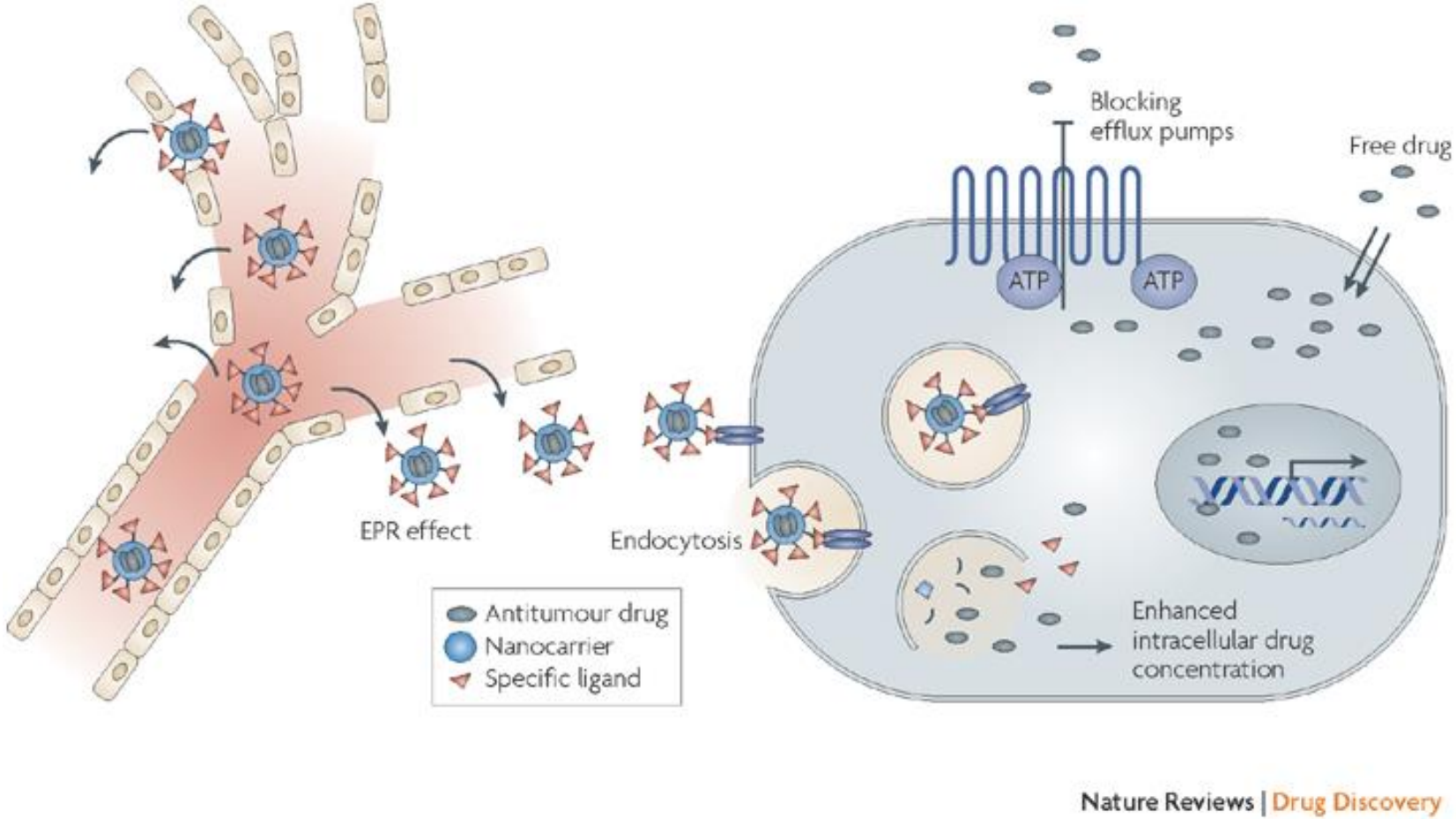


c Lipids

Nanoparticles conjugates



The "EPR effect" and nanoparticle localization into tumors sites: PASSIVE TUMOR TARGETING

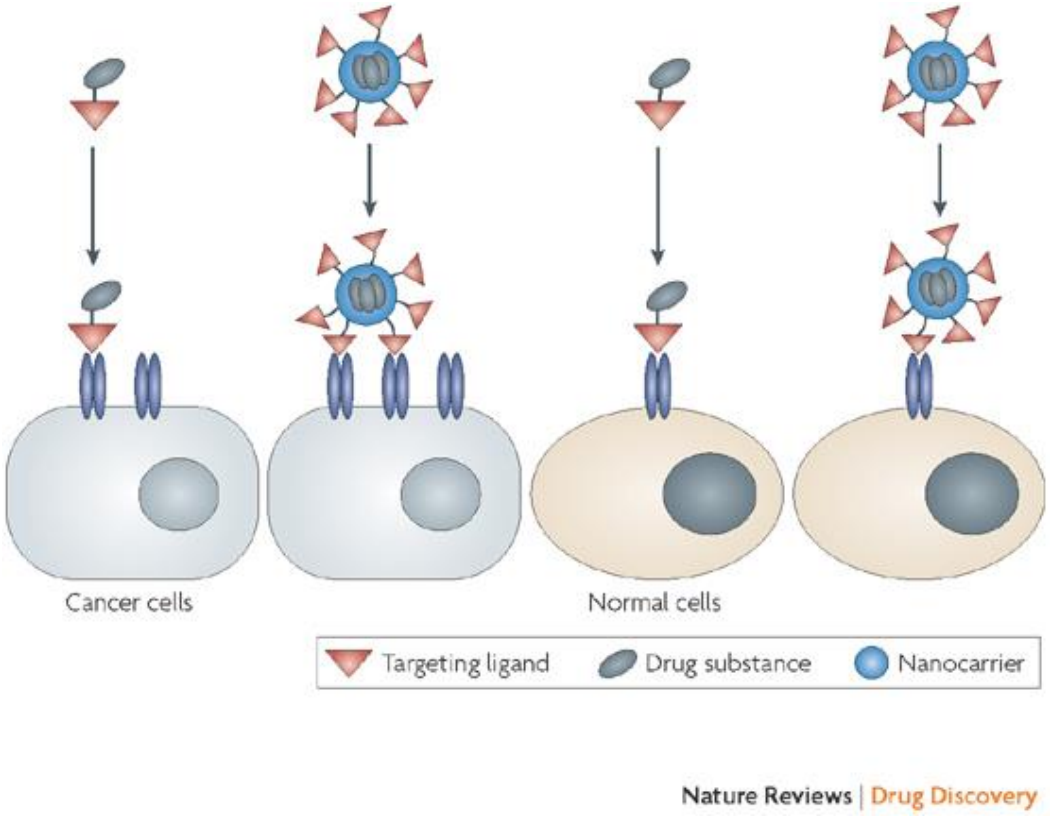


passive vs active targeting

- passive targeting: EPR effect. Utilization of the EPR effect is one of the pivotal strategies applied for delivery of nanocarriers to the tumors and, based solely on the pathophysiological characteristics of the target tissues is referred to as ‘passive targeting'
- active targeting: Active targeting involves attaching ligands to nanocarriers, which recognize a target within the tumor-affected organ, tissue, cell or intracellular organelle.

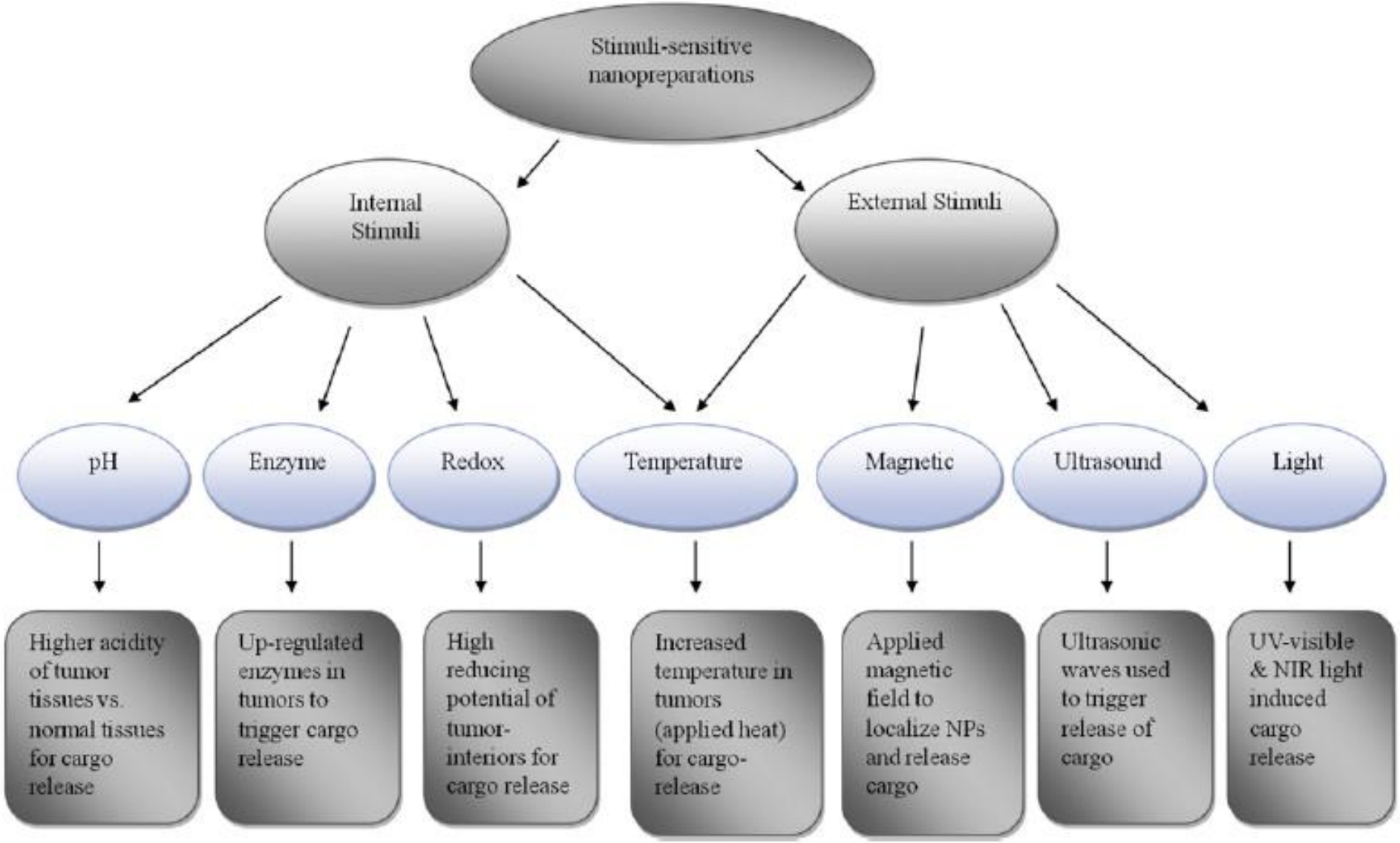
Active tumor targeting with ligands

- The addition of targeting ligands that provide specific nanoparticle–cell surface interactions can play a vital role in the ultimate location of the nanoparticle.
- For example, nanoparticles can be targeted to cancer cells if their surfaces contain moieties such as small molecules, peptides, proteins or antibodies.
- These moieties can bind with cancer cell-surface receptor proteins, such as transferrin receptors, that are known to be increased in number on a wide range of cancer cells. These targeting ligands enable nanoparticles to bind to cell-surface receptors and enter cells by receptor-mediated endocytosis



The concept of multivalent interaction

- When the surface density of the receptor is low on normal cells, then a molecular conjugate with a single targeting agent and a targeted nanoparticle can compete equally for the receptor as only one ligand–receptor interaction may occur. However, when there is a high surface density of the receptor on cancer cells (for example, the transferrin receptor), then the targeted nanoparticle can engage numerous receptors simultaneously (multivalency) to provide enhanced interactions over the one ligand–one receptor interaction that would occur with a molecular conjugate.


Stimuli-sensitive nanopreparations
Internal Stimuli
External Stimuli
pH
Enzyme
Redox
Temperature
Magnetic
Ultrasound
Light
Higher acidity of tumor tissues vs. normal tissues for cargo release
Up-regulated enzymes in tumors to trigger cargo release
High reducing potential of tumor-interiors for cargo release
Increased temperature in tumors (applied heat) for cargo-release
Applied magnetic field to localize NPs and release cargo
Ultrasonic waves used to trigger release of cargo
UV-visible & NIR light induced cargo release

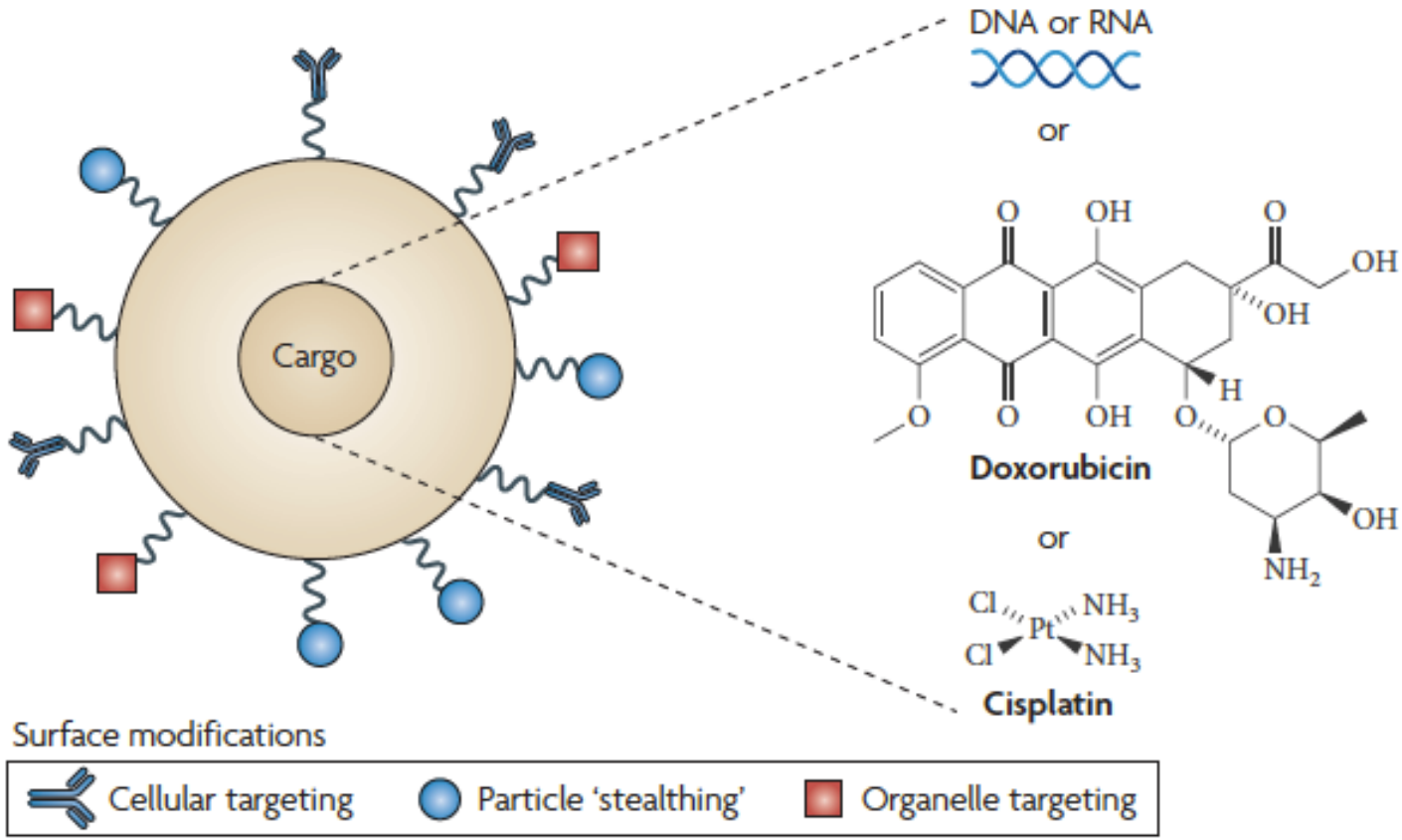


Figure 1 | **Schematic representation of an engineered nanoparticle.** The various surface modifications that are commonly pre-engineered, such as cellular targeting, particle 'stealthing' and organelle targeting, are highlighted. Ligands to extend circulation half-life and to reduce immunogenicity (usually polyethylene glycol (PEG) chains) are linked to the surface of the nanoparticle together with ligands to promote targeting. These ligands can be antibodies, aptamers or small molecules known to bind to surface proteins expressed on target cells or that are capable of guiding particle localization once inside the cell. Chemotherapeutics or other biologically relevant cargo are encapsulated inside the nanoparticle. Release of the cargo at the intended site of action is typically achieved through the incorporation of a stimuli-responsive material that changes state on exposure to the targeted environment (FIG. 4).

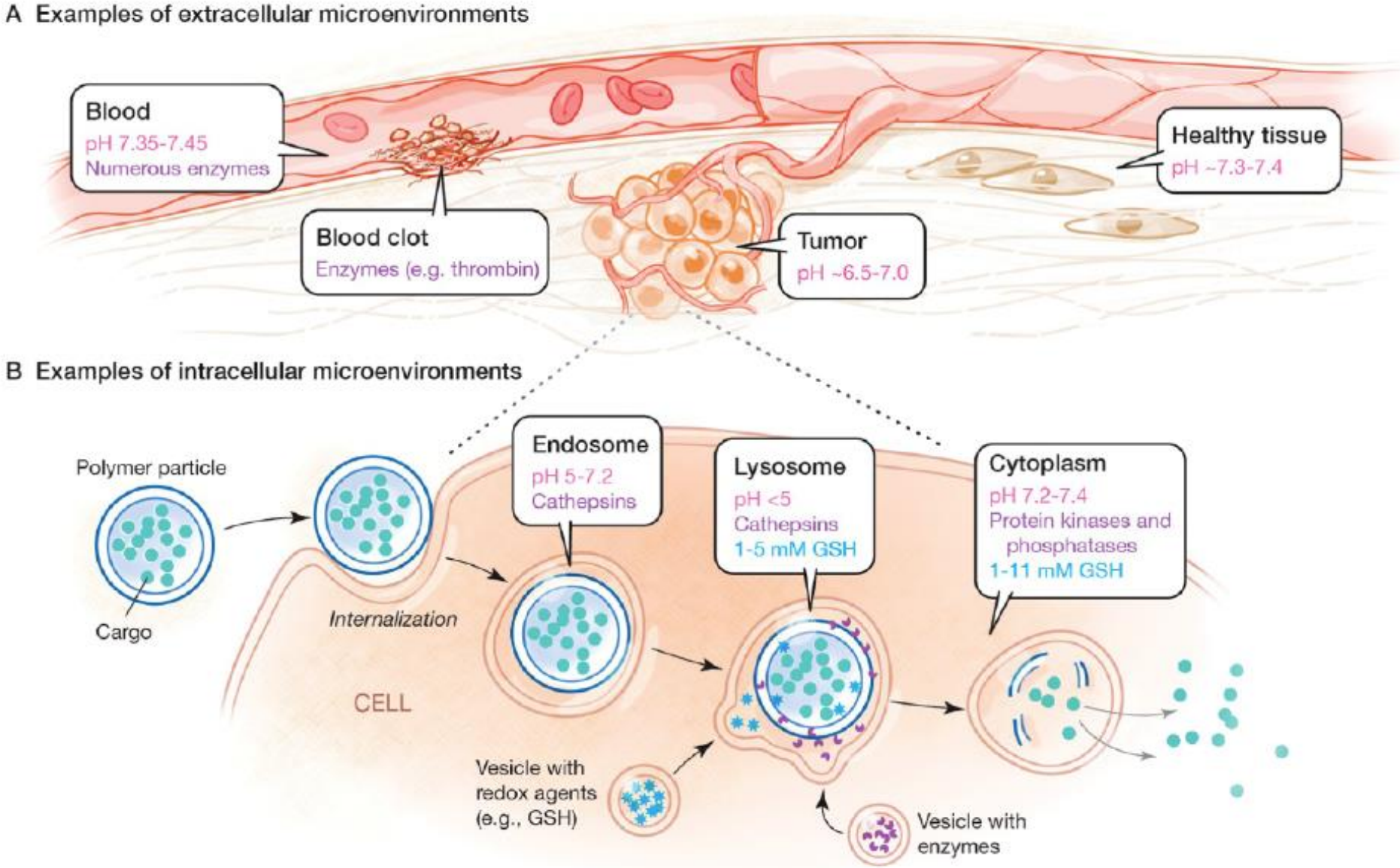
Stimuli-responsive delivery or smart delivery (liberation of drugs)

- One crucial material requirement of therapeutic polymer particles is their ability to degrade or disassemble to release the encapsulated cargo via biological stimuli in targeted micro- environments.
- During cellular internalization, particles will often be exposed to a decrease in pH, an increase in the amount of reducing agents, and an increase in enzyme concentration as they proceed from the extracellular fluid into the endosomes or lysosomes.
-

- The acidification of the endosome or lysosome can occur minutes after internalization, leading to a pH of ∼4–6. Similarly, various enzymes are pumped into the endosome, lysosome, or cytoplasm to further degrade and destroy both foreign and natural biological materials. Finally, cells also contain reducing agents, such as glutathione (GSH), that can cleave disulfide bonds.
- These three biological degrada tion mechanisms (pH, enzymes, reducing agents) allow for a broad spectrum of engineered responses in polymer particles, though other less common triggers, such as sugar gradients or shear, also exist.

Instrinsic and extrinsic stimuli

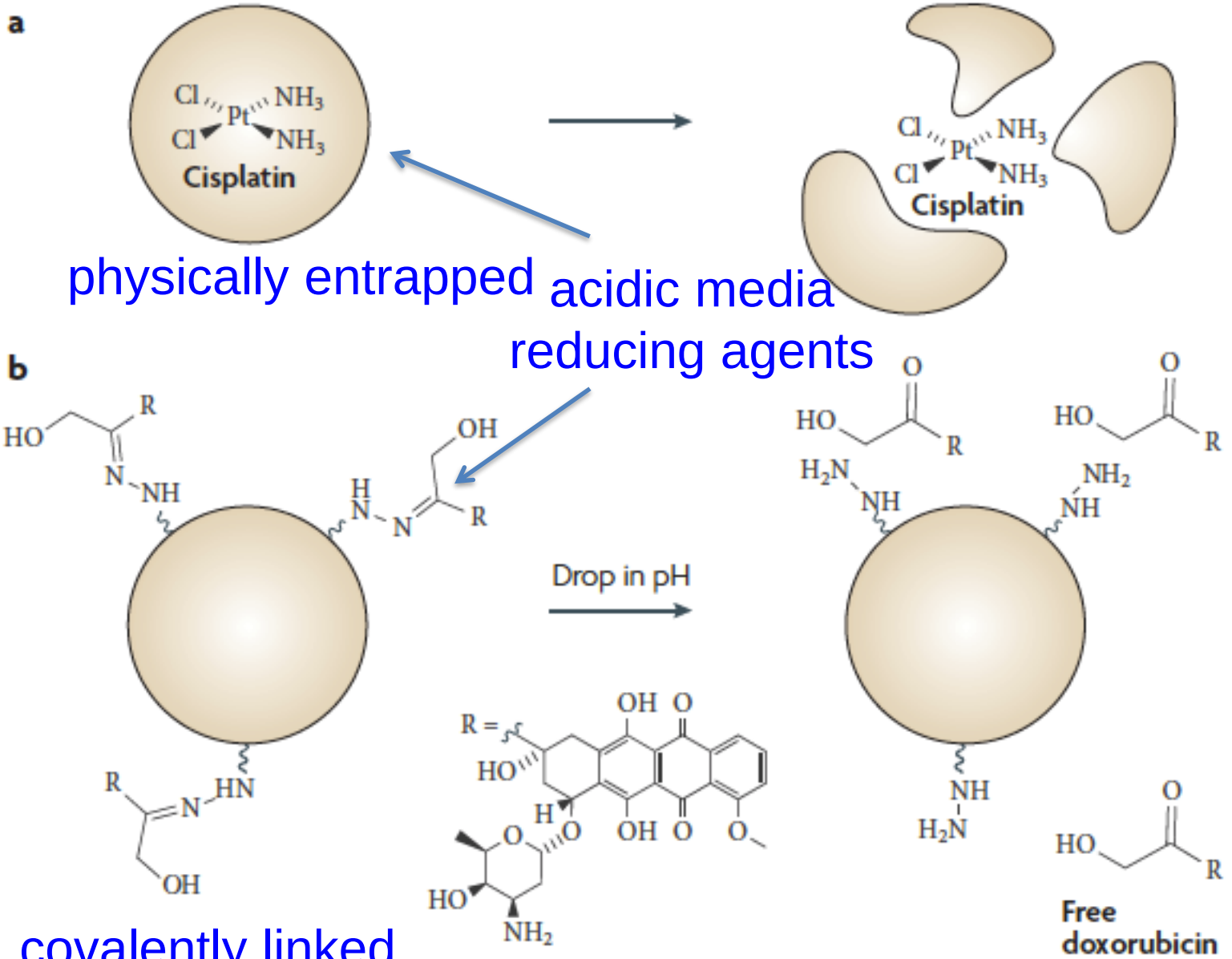
- pH, temperature, reducing potential are called “intrinsic stimuli” since they are local stimuli within the tumor tissues.
- Similarly, some stimuli can be induced in the region of interest such as by applying local heat to induce hyperthermia or ultrasound or near infrared light to bring about local delivery of cargo and are termed as “extrinsic stimuli”


A Examples of extracellular microenvironments
Blood
pH 7.35-7.45
Numerous enzymes
Blood clot
Enzymes (e.g. thrombin)
Tumor
pH ~6.5-7.0
Healthy tissue
pH ~7.3-7.4
B Examples of intracellular microenvironments
Polymer particle
Cargo
Internalization
CELL
Endosome
pH 5-7.2
Cathepsins
Lysosome
pH <5
Cathepsins
1-5 mM GSH
Cytoplasm
pH 7.2-7.4
Protein kinases and phosphatases
1-11 mM GSH
Vesicle with redox agents (e.g., GSH)
Vesicle with enzymes

acid-labile linkers

- Some of the materials used for acid–labile linkages, that degrade at the lower pH values characteristic of endosomes and the acidotic tumor mass are diortho esters, vinyl esters, acetals, hydrazones, oxymes which are stable at pH of around 7.5 but are broken down rapidly at a pH of 6 and below.
- A wide range of nanocarriers including liposomes, micelles, dendrimers and nanogels have been built using the above mentioned pH–labile components to achieve site-specific active delivery of chemotherapeutic agents and genes in cancer tissues

stimuli-responsive nanocarriers

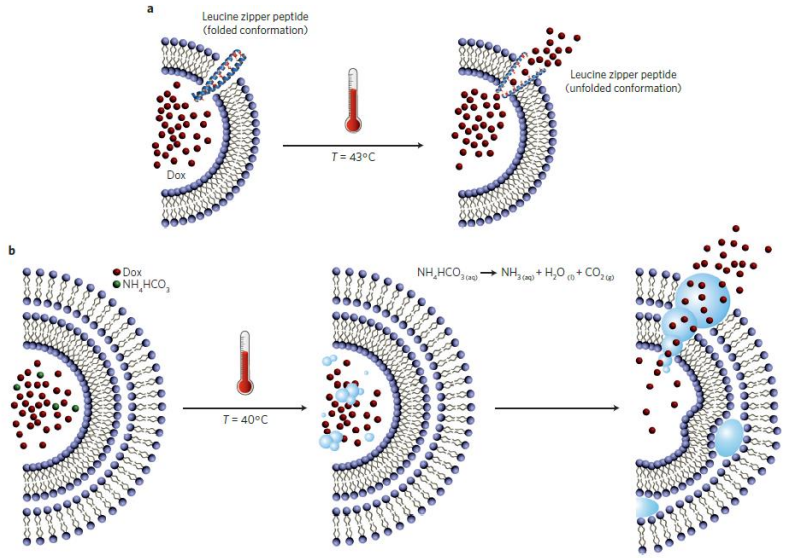


External stimuli

Thermoresponsive drug delivery is among the most investigated stimuli-responsive strategies, and has been widely explored in oncology.
Thermosensitive nanocarriers should retain their load at body temperature (~37 °C), and rapidly deliver the drug within a locally heated tumour (~40–42 °C) to counteract rapid blood-passage time and washout from the tumour

Thermosensive liposomes (TSL)

Thermosensitive liposomes (TSLs) are perhaps the most advanced thermoresponsive nanosystems, as shown by their use in several clinical trials.



leucine zipper peptide–liposome hybrids, which combine the advantages of traditional TSLs with the dissociative, unfolding properties of a temperature-sensitive peptide (Fig. 1a)3. Also promising are thermoresponsive bubble-generating liposomal systems. These rely on the creation of permeable defects in the lipid bilayer by means of the generation of carbon dioxide bubbles through decomposition of ammonium bicarbonate at mild hyperthermia (~42 °C).

Magnetically responsive systems.

The advantage of using a magnetic field relies on the different nature that the magnetic response can take, which can be a magnetic guidance under a permanent magnetic field, a temperature increase when an alternating magnetic field is applied, or both when alternately used. Therefore, magnetically responsive systems allow for diversity in the drug delivery pathway.
Furthermore, there is the possibility of performing magnetic resonance imaging, and hence to associate diagnostics and therapy within a single system (the so-called theranostic approach)10.

Candidate nanosystems for such a therapeutic approach are core– shell nanoparticles (a magnetic core made of magnetite (Fe_3O_4) coated with silica or polymer), magnetoliposomes (Fe_3O_4 or maghemite (Fe_2O_3) nanocrystals encapsulated in liposomes) and porous metallic nanocapsules. Most core–shell nanoparticles have shown promising results in vitro,

Pulsatile drug release

The heat generated by an AMF can also be used to achieve ondemand pulsatile drug release. Examples include: pseudorotaxane based nanovalves at the surface of mesoporous silica nanoparticles (MSNPs) that act as thermally sensitive gatekeepers (Fig. 2a); composite membranes containing thermoresponsive PNIPAM-based nanogels and magnetic nanoparticles that enable on–off drug delivery on de-swelling or swelling of the polymer35; a capping system for drug-loaded MSNPs based on complementary DNA sequences (Fig. 2b).

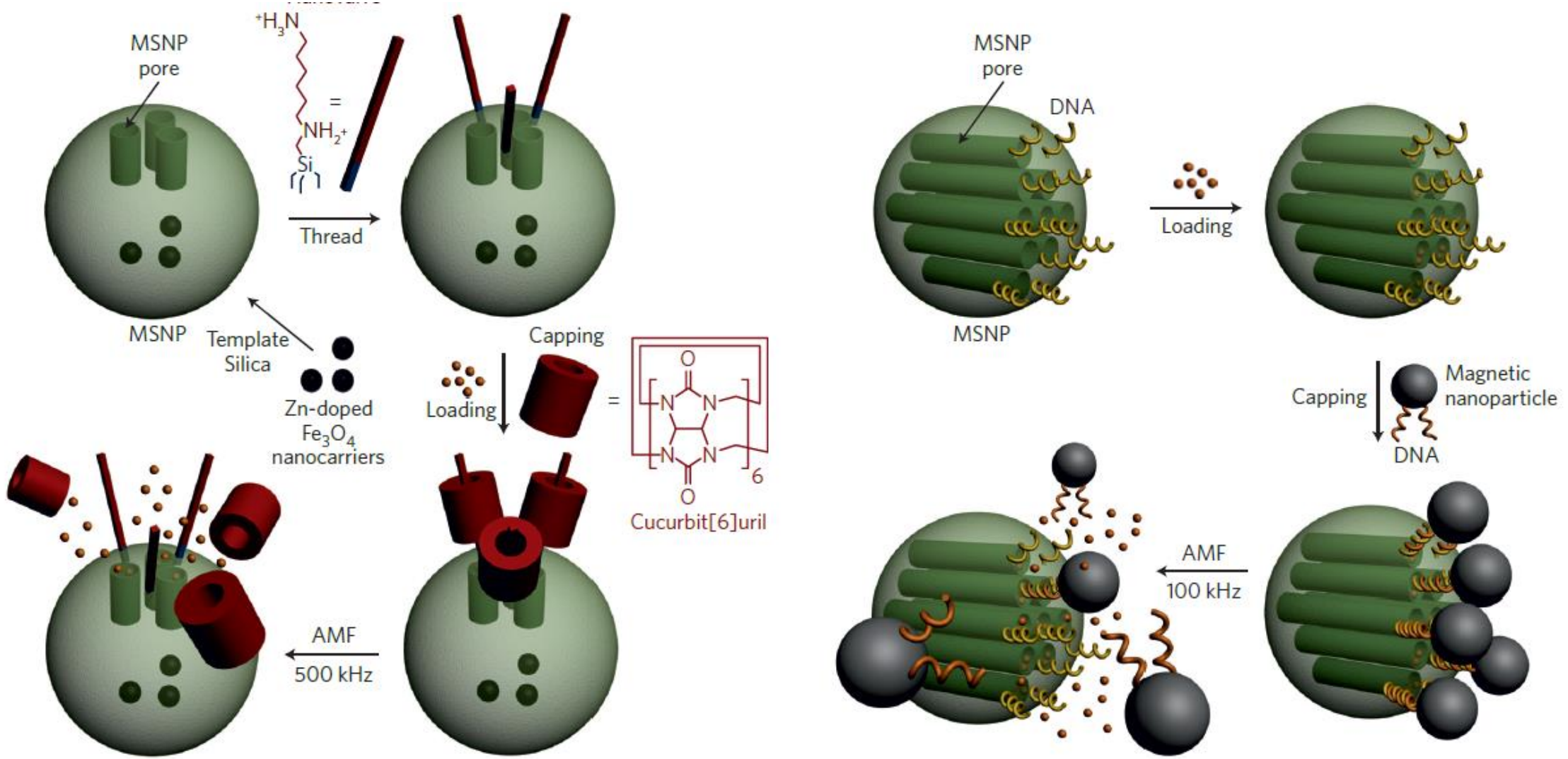


Figure 2 | Actuation mechanisms based on the heat generated by an alternating magnetic field (AMF) leading to on-demand pulsatile drug release from mesoporous silica nanoparticles (MSNPs). a, Pseudorotaxane-based nanovalves made of cucurbit[6]uril. **b**, Capping system based on complementary DNA sequences. Figure adapted with permission from: **a**, ref. 34, © 2010 ACS; **b**, ref. 36, © 2011 ACS.

Ultrasound-triggered drug delivery

Ultrasound waves can trigger the release of the drug from a variety of nanocarriers through the thermal and/or mechanical effects generated by cavitation phenomena or radiation forces. Indeed, it has been shown that physical forces associated with cavitation can induce nanocarrier destabilization, drug release and transient increase in vessel permeability, leading to the cellular uptake of therapeutic molecules.

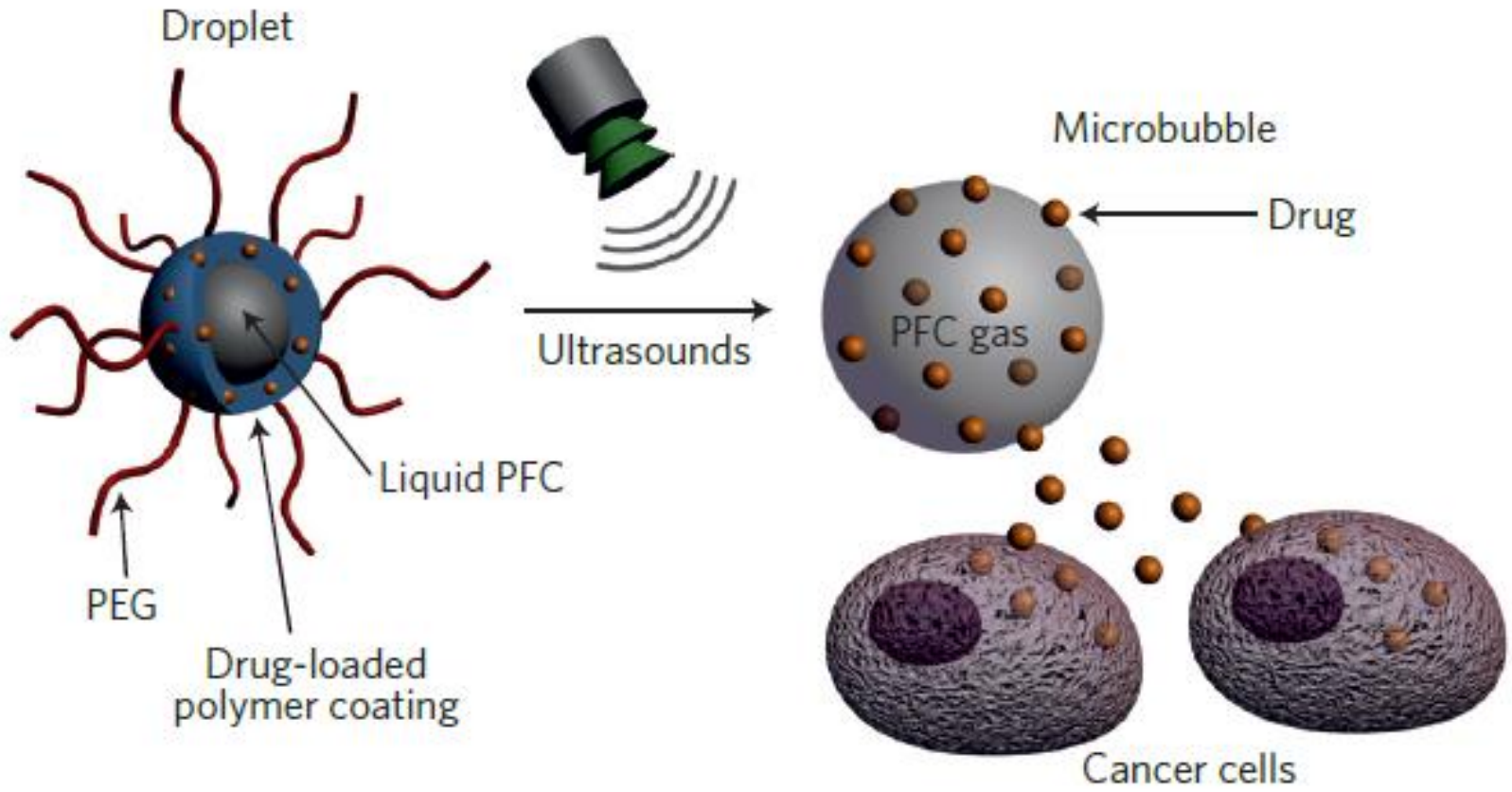


Figure 3 | Drug delivery from echogenic perfluorocarbon (PFC)-containing nanoemulsions. It is believed that the mechanism of delivery involves a droplet-to-bubble transition under the action of ultrasound, leading to drug transfer from the bubbles to neighbouring cells. Figure adapted with permission from ref. 41, © 2009 Elsevier.

Light-triggered drug delivery

For instance, the ultraviolet–visible reversible photoisomerization of the azobenzene group (and its derivatives) — from trans to cis on irradiation at 300–380 nm, and from cis to trans by shining light in the visible region — enables photoregulated control of drug release. This has been achieved through azobenzene functionalization of the pore interior of MSNPs50, by means of azo-modified DNA valves at the pore mouth.