Prodrugs for Improving Oral Delivery

- Oral delivery, the most desirable route of administration, is the most difficult to attain as bioavailability by this route is usually least efficient compared to other routes.

- It is very important to be aware of the physicochemical and biological factors that are restraining the oral bioavailability of a drug before starting a prodrug strategy.

- Aqueous solubility, low permeability, tendency to be an efflux substrate, rapid hepatic metabolism, and biliary excretion are important physicochemical and biological factors that may limit oral delivery.

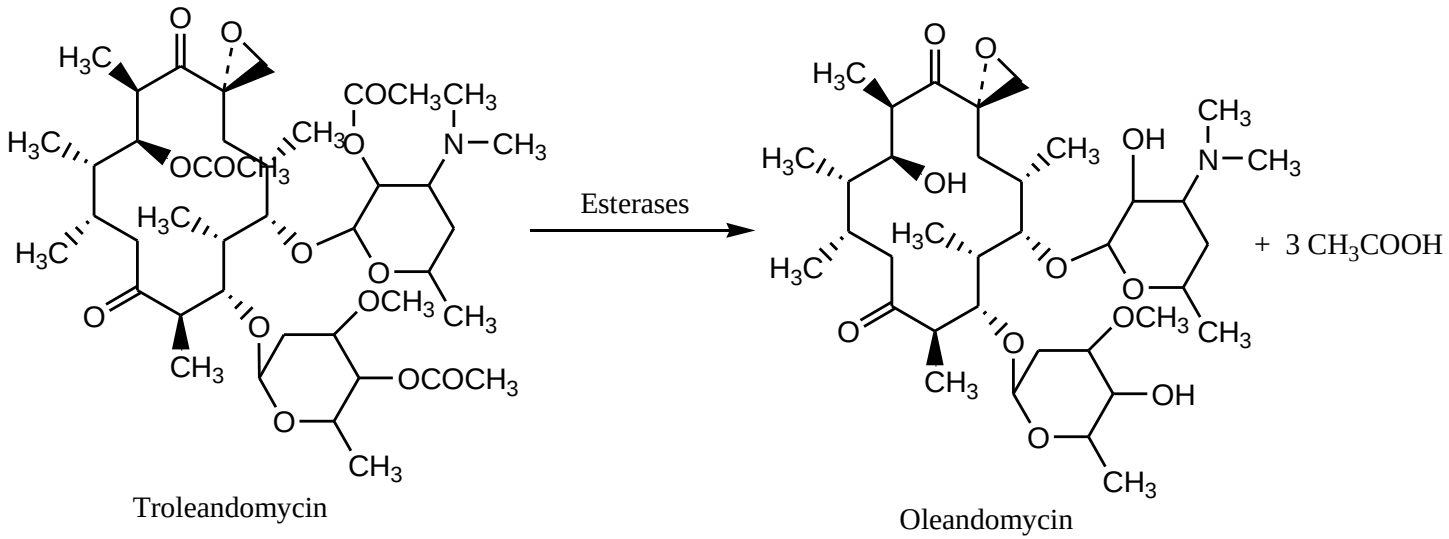
- The rationale behind the prodrug strategy for hydrophilic and/or charged compounds is to introduce lipophilicity and mask hydrogen bonding groups by the addition of another moiety.

- These prodrugs are often carboxylic acid esters, or phosphonic acid esters of poorly permeable but aqueous soluble parent drugs.

An ideal ester prodrug should have the following properties:

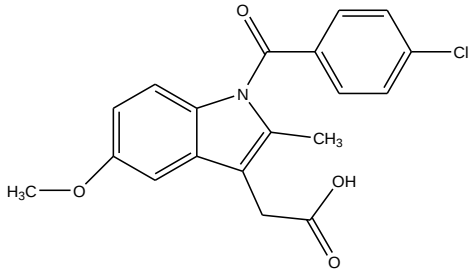
- No activity against any pharmacological target
- Good aqueous solubility
- Chemical stability across a pH range
- High transcellular absorption
- Resistance to breakdown during the absorption
- Rapid and quantitative hydrolysis to yield the active component post absorption.

- Oleandomycin is a polar macrolide antibiotic.
- Oleandomycin`s oral availability was significantly improved when administered as it triacetate.

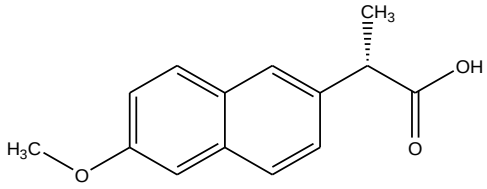


Troleandomycin

Oleandomycin



Indomethacin



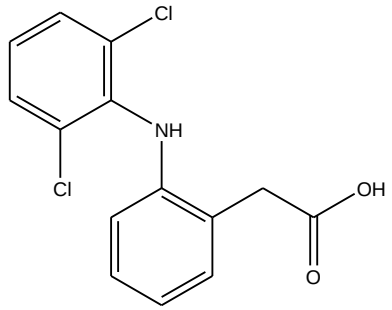
Naproxen

- In order to develop potential prodrugs of indomethacin and naproxen which cause less irritation to the gastrointestinal mucosa, the ester and amide prodrugs were synthesized.

- The chemical structures of the prodrugs were varied in terms of lipophilicity and reactivity during hydrolysis.

- Five indomethacin oligoethylene ester derivatives were synthesized. All the prodrugs showed good stability, and they were readily hydrolyzed in human plasma.

- They showed anti-inflammatory activity similar to that of indomethacin, and exhibited better or similar analgesic activity. These esters were significantly less irritating to the gastric mucosa than indomethacin, after oral administration.

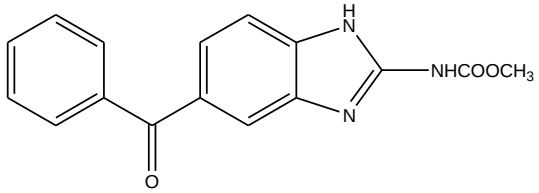


- Diclofenac is another widely used nonsteroidal anti-inflammatory drug.

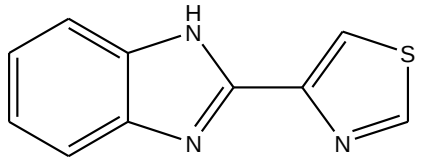
- Morpholinoalkyl esters of diclofenac were synthesized and evaluated *in vitro* and *in vivo* for their potential use as prodrugs for oral delivery.

- The morpholino esters were chosen because of their balance of improved solubility and lipophilicity relative to the parent carboxylic acid.

- All the prodrugs were water-soluble but partition coefficients increased.



Mebendazole



Thiabendazole.

- Mebendazole and thiabendazole are the broad-spectrum anthelmentic drugs, and their poor peroral absorption limits their usefulness for the treatment of systemic infections.

- The low bioavailability has mainly been attributed to the low aqueous solubility of the benzimidazoles. T

- To improve water solubility, bioreversible derivatization of thiabendazole and mebendazole were performed by N-acylation of the benzimidazole moiety with various chloroformates.

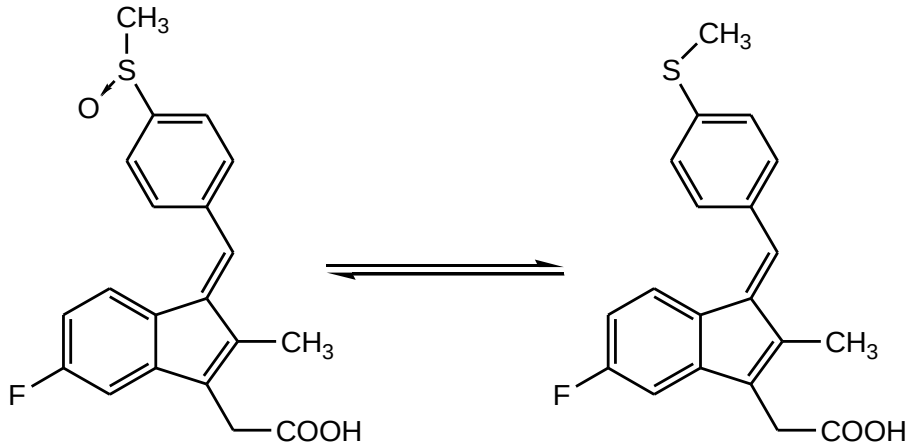
- N-alkoxycarbonyl derivatives were readily hydrolyzed to parent compounds in physiologic media.

- The water-solubility of the N-alkoxycarbonyl derivatives of thiabendazole and mebendazole were up to 12 and 16 times higher than that of the parent drug, respectively.

- Sulindac is a prodrug which, following absorption, rapidly attains a metabolic equilibrium with its active pharmacophore, the sulfide metabolite.

- The sulfoxide group is more polar, and therefore has better interaction with the solvent than the reduced sulfide.

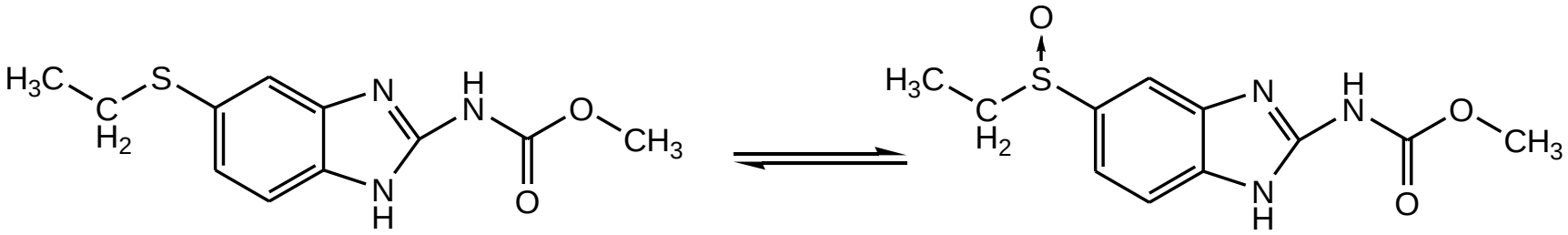
- This conversion provides a theoretical basis for the long plasma half-life of active drug and, in animal species, for the favorable gastrointestinal tolerance observed.



Sulindac Sulfide

- Albendazole is a broad spectrum anthelmintic benzimidazole with very low bioavailability.

- Unlike sulindac, albendazole is metabolized to its sulfoxide and its activity is due to this main metabolite, Albendazole sulfoxide, which is not only the more active component but is also more water-soluble



Albendazole

Albendazole sulfoxide