Prodrugs for Improving Topical Delivery

1. Ophthalmic Drug Delivery

The ocular absorption of topically applied drugs is limited by the corneal epithelium barrier, the rapid precorneal drug elimination and systemic absorption from the conjunctival.

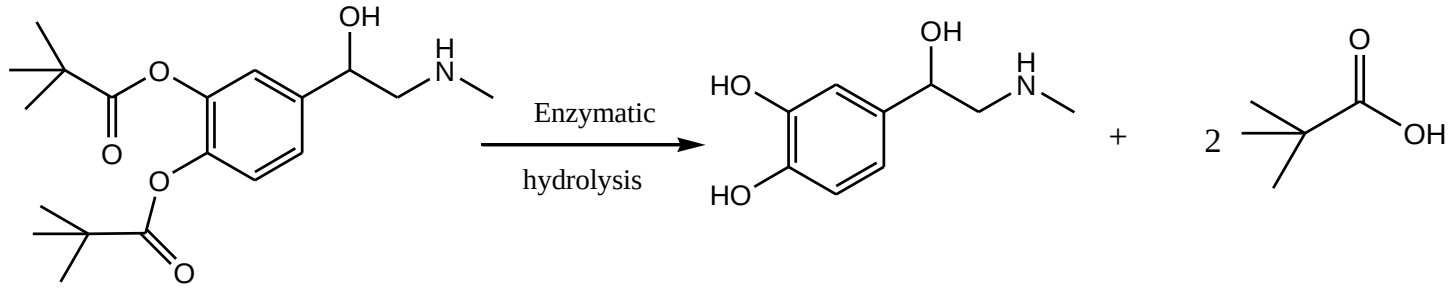
Prodrugs were introduced to ophthalmology about 35 years ago when ocular absorption of epinephrine was substantially improved by its prodrug.

- Dipivefrine is a dipivalic acid ester prodrug of epinephrine which is able to release the parent drug within the eye at a rate that meets therapeutic need.

- Dipivefrine penetrates cornea 17 times better than epinephrine due to its higher lipophilicity at pH 7.2.

- Dipivefrine at 0.1% concentration is slightly less effective than 2% epinephrine at lowering intraocular pressure, but it has less systemic side effects and no cardiovascular effects.

- Therefore, dipivefrine has currently replaced epinephrine in glaucoma treatment. Prodrug is metabolized to epinephrine and pivalic acid.



Dipivalyl Epinephrine

Epinephrine

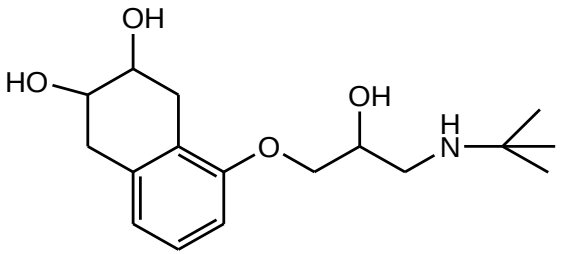
pivalic acid

- β-adrenergic receptor blockers are used for the treatment of glaucoma.

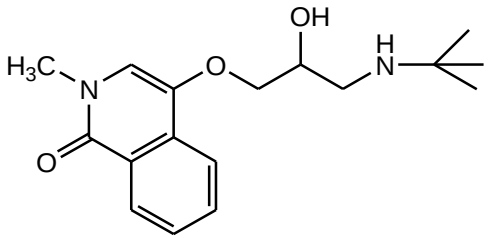
- Their therapeutic value is limited by poor ocular bioavailability. Many of these drugs are applied in high concentrations which give rise to both ocular and systemic side-effects.

- To increase corneal penetration properties, a series of alkyl, cycloalkyl, and aryl ester prodrugs of the nonselective β-adrenergic antagonist timolol were prepared by esterifying the hydroxyl group of timolol.

- Also, these prodrugs for hydrophilic nadolol and tilisolol have been prepared. These prodrugs were found to be more lipophilic than the active drugs and have enhanced ocular absorption.



Nadolol



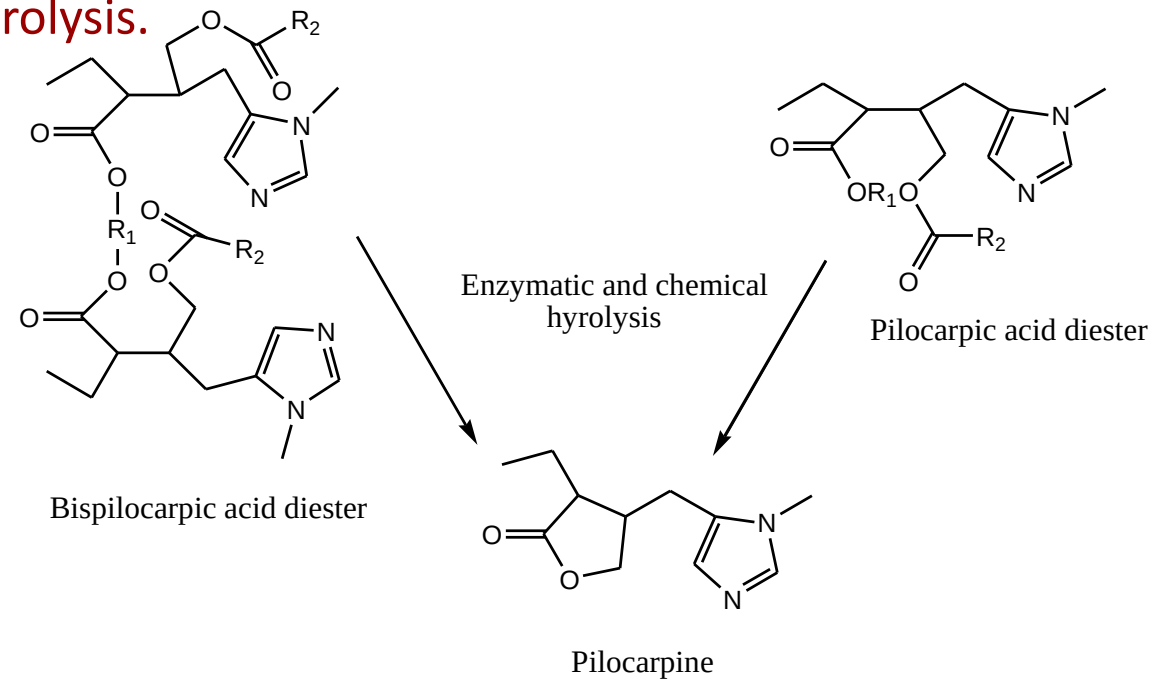
Tilisolol

- Pilocarpine is used for the control of elevated intraocular pressure associated with glaucoma.

- It has poor corneal permeability and low ocular bioavailability because of the low lipophilicity of the drug.

- Diesters of pilocarpic acid and bispilocarpic acid were prepared by esterification of the two hydroxyl groups.

- The studies showed that they penetrate the cornea more easily than the parent compound and are converted to pilocarpine by enzymatic and chemical hydrolysis.



2. Dermal Drug Delivery

- Dermal drug delivery has some advantages over more conventional treatments such as delivery of therapeutic level of drug to the application site in a more effective and safer way.

- Thus, it has been getting increasing popularity. But, most drugs present inappropriate physicochemical properties to efficiently penetrate the skin. Therefore, many attempts have been carried out to increase drug permeation through the skin.

- Drugs containing polar functional groups have problems of membrane permeability and biphasic solubility which limit their dermal delivery.

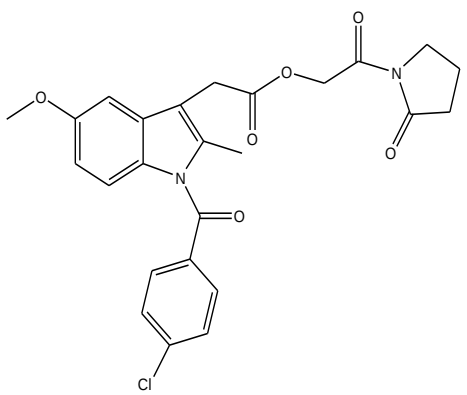
- The prodrug approach is masking these polar functional groups as esters which then hydrolize to the parent drug either enzymatically or chemically.

- Recent studies have shown that prodrug needs to have adequate lipid as well as water solubility to permeate the skin effectively because the skin represents a lipid-aqueous biphasic barrier to permeation due to nature of the stratum corneum. Thus, prodrugs should increase not only lipid but also aqueous solubility as needed.

- Indomethacin is a potent anti-inflammatory drug and its topical use is limited by its inability to penetrate the skin.

- Indomethacin N-acyllactam esters were synthesized to evaluate the physicochemical properties and skin permeation of the prodrugs.

- Indomethacin N-acyllactam esters showed increased water stability, but they were not stable enough to be formulated in aqueous vehicles. Only compounds **1-3** showed high solubility compared to the parent drugs, provided good skin permeation.



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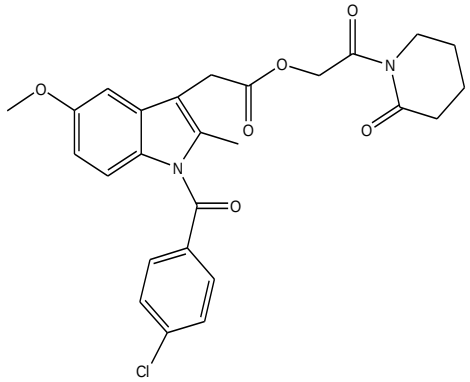

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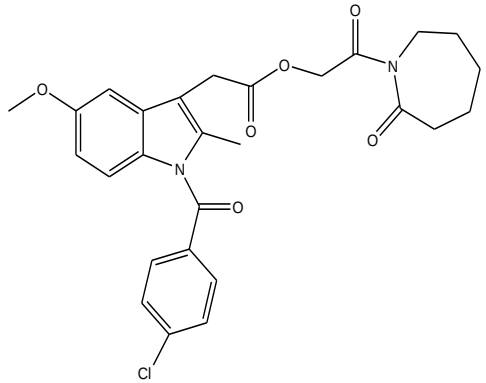

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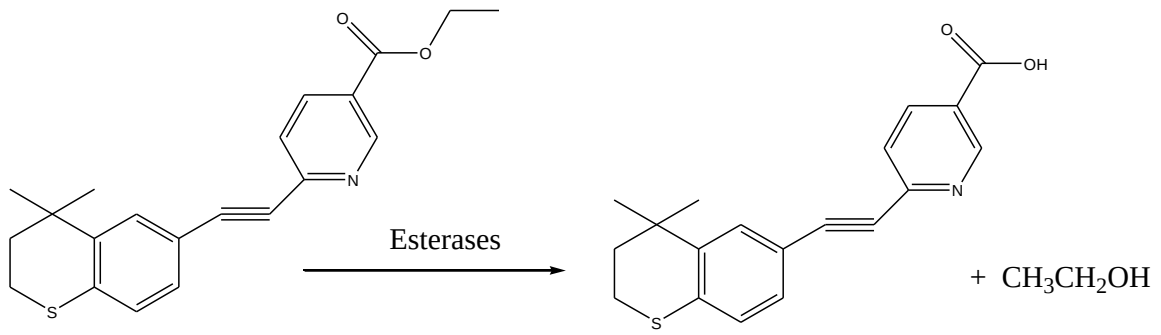
- Retinoids have been successfully used in treating mild to moderate plaque psoriasis over the last 50 years.
- The first topical receptor-selective retinoid to be approved is tazarotene.
- Tazarotene is the ethyl ester prodrug of tazarotenic acid, and it is rapidly cleaved in the skin to the biologically active tazarotenic acid.
- It improves lipophilicity and maintains adequate aqueous solubility, and it has better skin permeation.
- The pharmacological selectivity of tazarotene and limited systemic exposure result in minimal systemic effects and therefore reduced side effects.



Tazarotene Tazarotenic Acid Ethanol