Quadrant II – Notes

Programme: Bachelor of Science (Third Year)

Subject: Chemistry

Paper Code: CHD104

Paper Title: Essentials in Pharmaceutical Chemistry

Unit 4: Introduction to Drug Design

Module Name: Prodrugs and Softdrugs

Module No: 10

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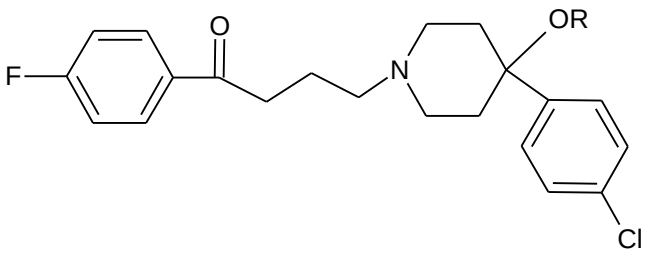
Prodrug

Prodrugs are biologically inert derivatives of drug molecules that undergo an enzymatic or chemical conversion in the body to release the pharmacologically active parent drug. The term prodrug was introduced in 1958 by Adrien Albert. It is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent compound.

Examples

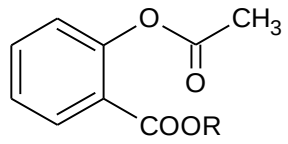
Prodrugs for slow and prolonged release :

It can best be achieved by making a long chain aliphatic ester because these esters hydrolyze slowly. Example haloperidol decanoate [R = $CO(CH_2)_8CH_3$] which when injected intramuscularly as a solution in sesame oil, its activity lasts for about one month in comparison to haloperidol [R = H] which lasts for about 2-6 hrs.



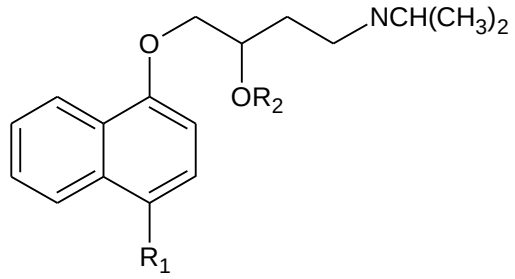
Prodrugs to lower toxicity profile :

The side-effects associated with the use of aspirin are gastric irritation and bleeding. Esterification of aspirin (R = alkyl) greatly suppresses gastric ulcerogenic activity.



Prodrugs for stability :

For example the oral administration of propranolol hemisuccinate (R_1 = H, R_2 = $COCH_2$ CH_2 COOH) which is resistant to first pass metabolism in the liver rather than propranolol (R_1 = R_2 = H) elevates plasma levels of propranolol.



Prodrugs for Improved absorption and distribution :

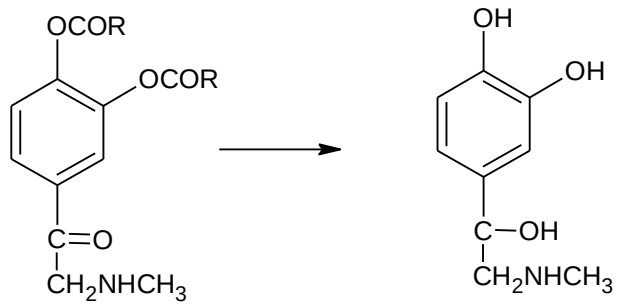
Drugs applied to the skin are poorly absorbed. Corticosteroids for the topical treatment of inflammatory, allergic and pruritic skin conditions can be made more suitable for topical absorption by esterification or acetonidation. Once absorbed through the skin, an esterase can release the drug. Examples Dipivaloylepinephrine (dipivefrin), a prodrug for epinephrine, has better cornea penetration rate than epinephrine and is used in the treatment of glaucoma.

Softdrug

Soft drugs are defined as therapeutically beneficial agents which are designed and synthesized in the active form but are converted by in vivo metabolism to non-toxic moieties, after they achieve their therapeutic role.

<u>Example</u>

It was found that diester derivatives of adrenolone have a high level of ocular sympathomimetic activity due to the conversion of former to adrenaline via a combined reduction-hydrolysis process in the eyes.



Diester of Adrenalone **Adrenaline**