

Supplementary Subject - Hilary 2010

Aromatic and Heterocyclic Pharmaceutical Chemistry

Supplementary Subject

Introduction to Pharmaceutical Chemistry

5 Lectures - Ben Davis

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Introduction to Medicinal Chemistry: Drugs and their action. Competitive, noncompetitive and allosteric enzyme inhibition. Drug action at receptors. Examples of Neurotransmitters.

Agonist and Antagonists: Design. The drug development process. Structure-Activity Relationships (SARs). Analogue Synthesis. Introduction to pharmacology Chemical and metabolic stability. Hydrophobicity; P, log P. Isosteres. Prodrugs. Lipinski Rules of 5

Anti-ulcer drugs: The world's best selling drugs. Histamine H₂ antagonists. Cimetidine: (Tagamet, GSK), Ranitidine (Zantac, GSK).

Painkillers and anti-Emetics: Different 5-hydroxy tryptamine (5-HT, serotonin) receptor antagonists. 5-HT_{1D} antagonists (anti-migraine), Sumatriptan (GSK), 5-HT₃ antagonists (anti-emetics), Ondansetron (Zofran, GSK). Granisetron (Kytril, GSK).

Other Big Loot Drugs: . Sex, Viagra (Pfizer). The world's biggest: Omeprazole (Losec, AZ) and its improvement Esomeprazole. Relenza (GSK) and Tamiflu. Amlodipine (Istin, Pfizer)

Good books:

G.L. Patrick *An Introduction to Medicinal Chemistry*, OUP, 1995

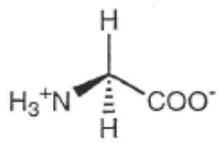
J. Saunders *Top Drugs, Top Synthetic Routes*, OCP 90, OUP, 2000

J. Mann *Murder, Magic. Medicine*, OUP, 1992

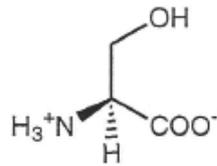
S.M. Roberts, B.J. Price *Medicinal Chemistry - the Role of Organic Chemistry in Drug Research*, Academic Press. 1985

The 20 Proteinogenic Amino Acids

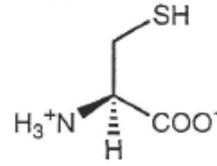
Polar



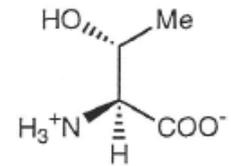
Glycine



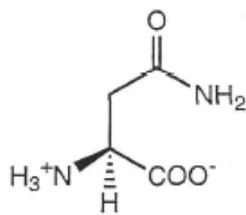
Serine



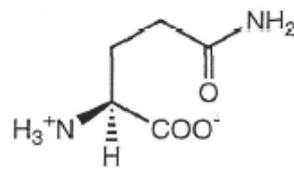
Cysteine



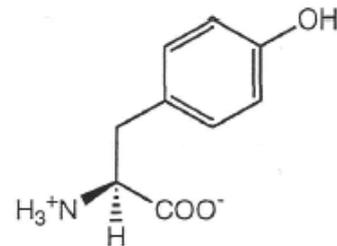
Threonine



Asparagine



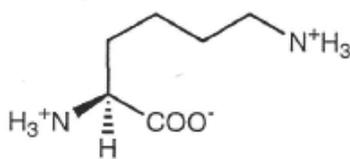
Glutamine



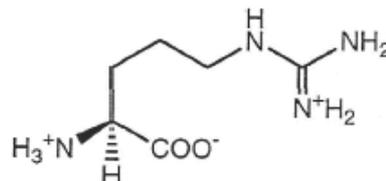
Tyrosine

Ionized

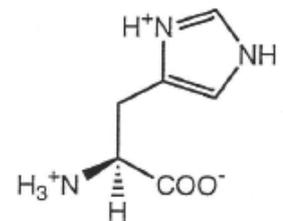
Bases



Lysine

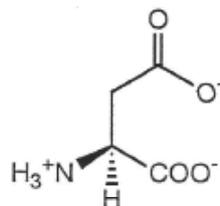


Arginine

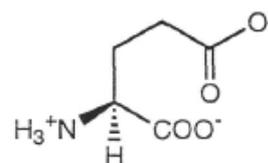


Histidine

Acids



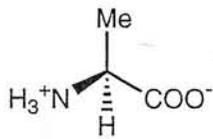
Aspartic Acid



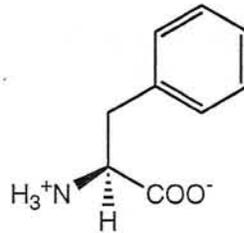
Glutamic Acid

The 20 Proteinogenic Amino Acids

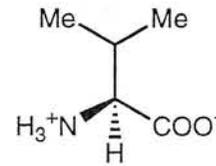
Non Polar : Hydrophobic



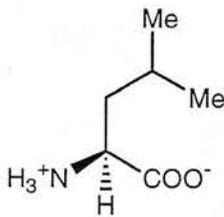
Alanine



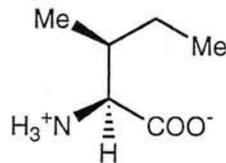
Phenylalanine



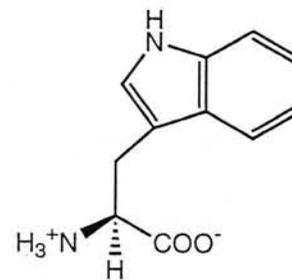
Valine



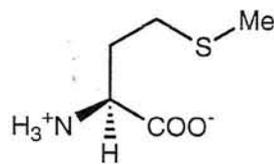
Leucine



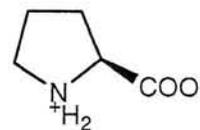
Isoleucine



Tryptophan

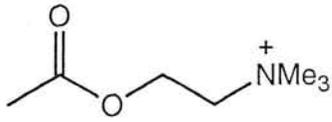


Methionine



Proline

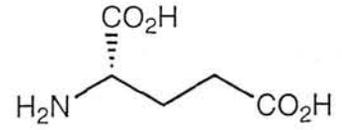
Some Neurotransmitters



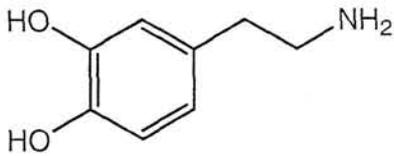
acetyl choline



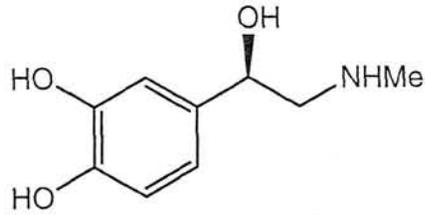
γ amino butyric acid
(GABA)



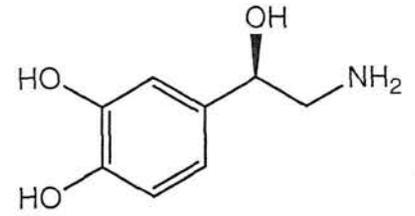
glutamic acid



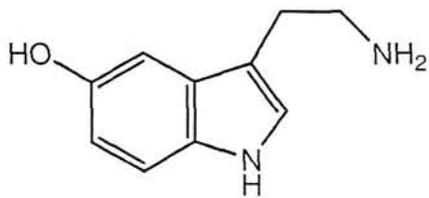
dopamine



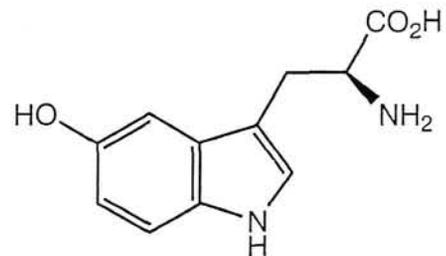
adrenaline



noradrenaline



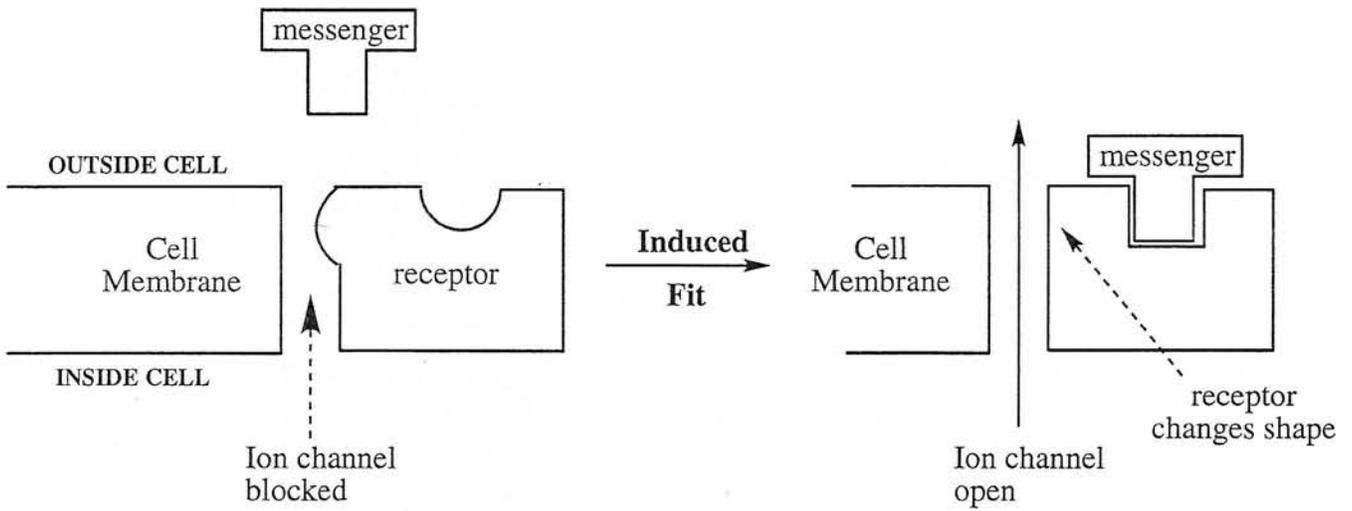
5-hydroxytryptamine
(5-HT)
or serotonin



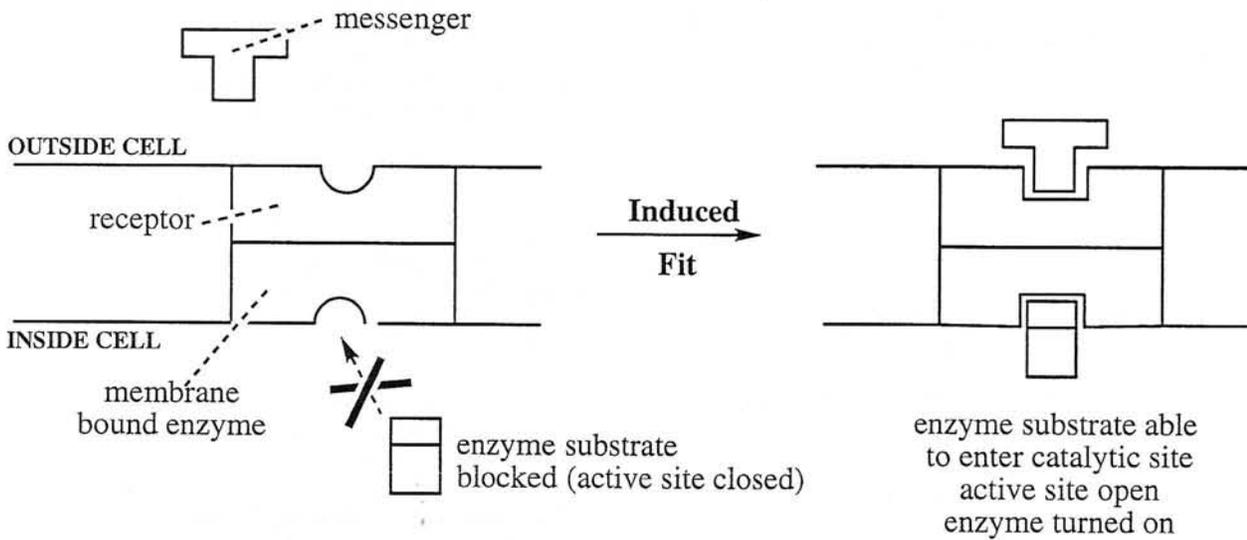
5-hydroxytryptophan

Receptor Action

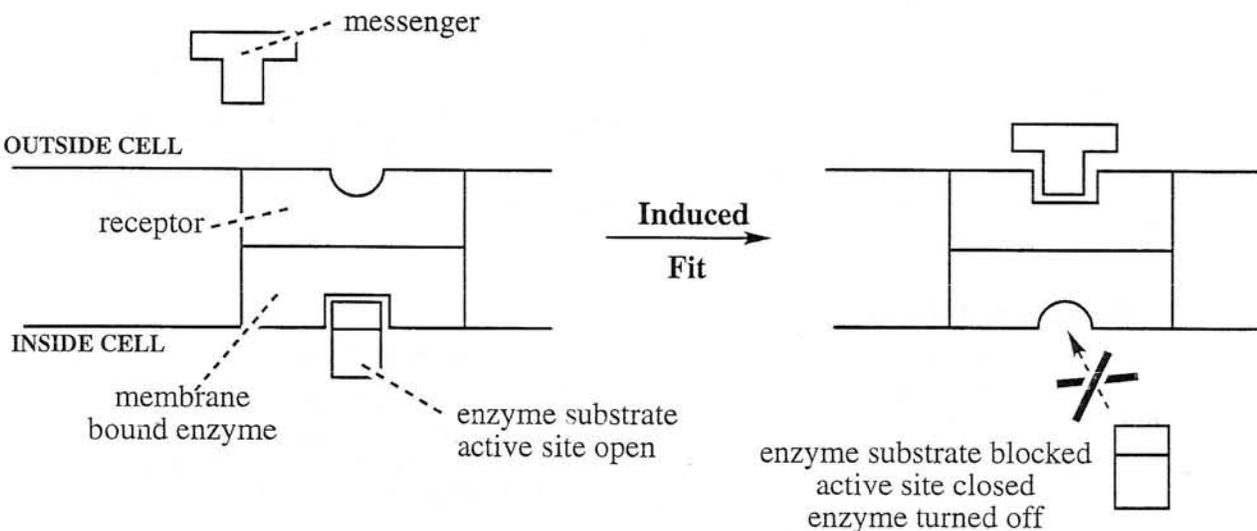
(i) Opening of an Ion Channel



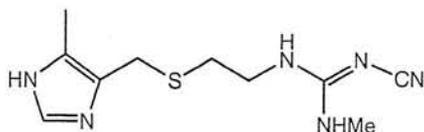
(ii) Activation of a Membrane Bound Enzyme



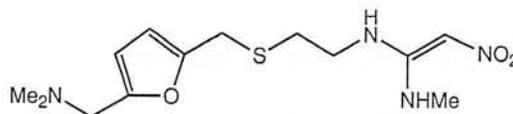
(iii) Deactivation of a Membrane Bound Enzyme



Some Billion Dollar selling drugs



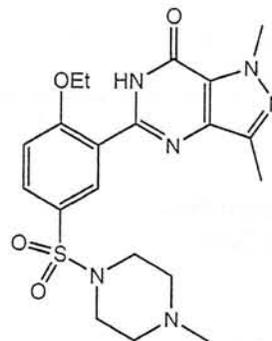
Cimetidine
Trade name - Tagamet
Smith Kline and French (now SKB)
Launched 1976
Achieved sales of \$1 billion per annum
Was the world's best selling drug



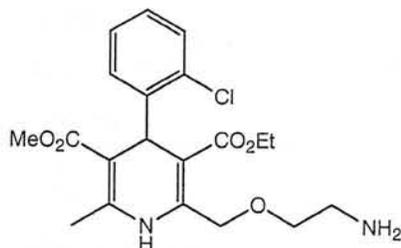
Ranitidine
Trade name - Zantac
Glaxo
Launched 1981
Achieved sales of \$2 billion per annum
By 1988 became the world's best selling drug



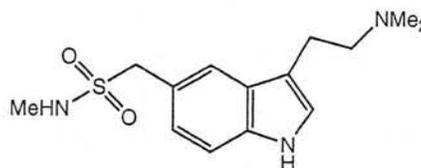
Fluconazole
Trade name Diflucan
Pfizer
Sales in 1999 \$1 billion
The world's best selling anti fungal drug



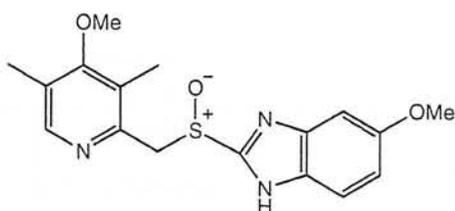
Sildenafil
Trade name Viagra
Pfizer
Treatment of male erectile dysfunction
Sales in 1998 \$788 million



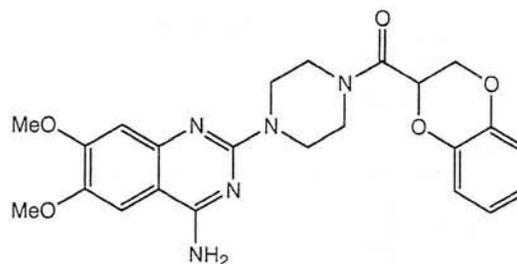
Amlodipine
Trade name Istin
Pfizer
Treatment of heart disease and hypertension
Sales in 1999 \$3 billion



Sumatriptan
Trade name - Imigran
Glaxo
Launched 1991
60% of market share of migraine treatment
Sales in 1999 of \$1 billion



The worlds best selling drug
Omeprazole
Trade name - Losec
AstraZeneca
Launched 1988
Sales of ~ \$6 billion per annum



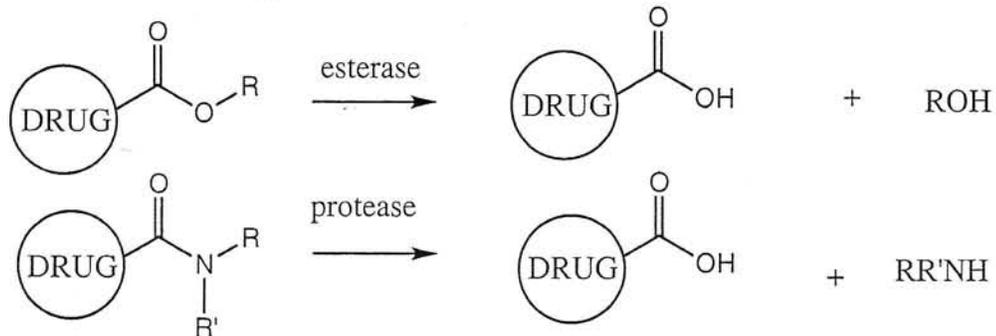
Doxazosin
Trade name - Cardura
Pfizer
Launched 1988
Sales of \$800 million per annum
 α -adrenoreceptor antagonist for the treatment of high blood pressure and hypertension

Drug Metabolism

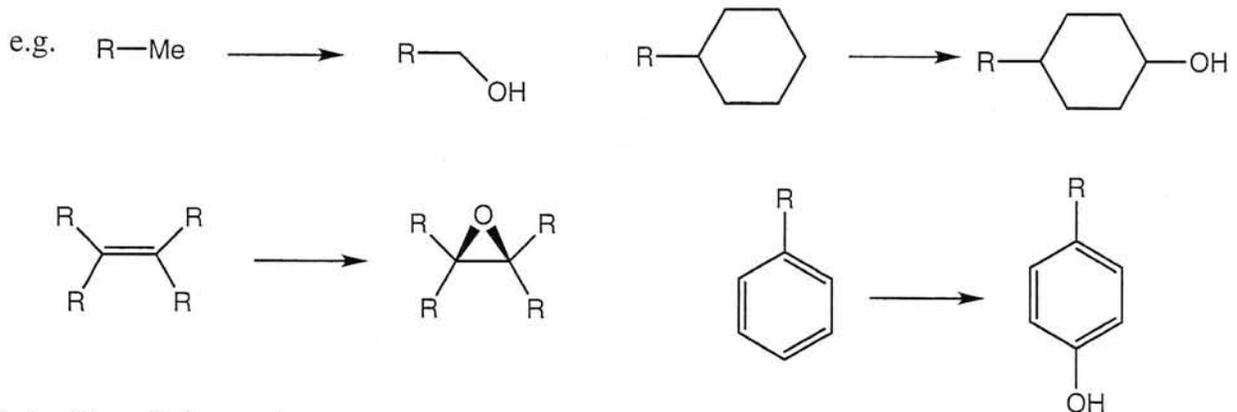
Phase I

Enzyme catalysed drug modification involving the addition of a polar handle to the foreign drug molecule. Some of the most common transformations are:

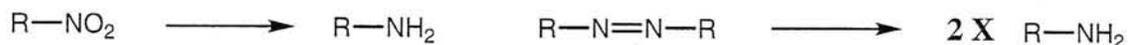
Hydrolysis of esters or amides



Oxidation of exposed alkyl groups, alkenes and aromatic rings (by cytochrome P-450 enzyme)



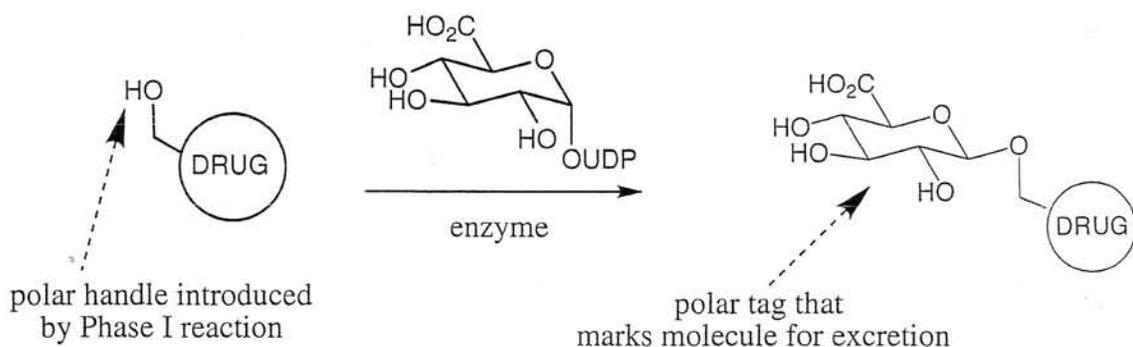
Reduction of nitro and azo groups

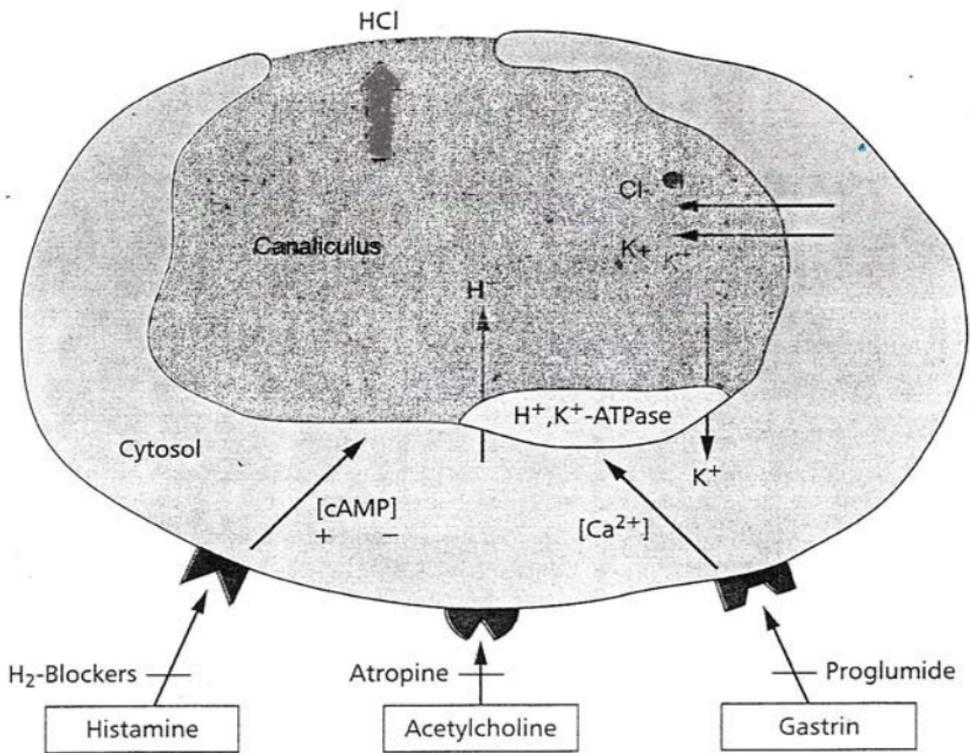


Phase II

Involves the addition of a further polar molecule to the polar 'handle' that has been placed on the 'foreign' drug by the Phase I reaction. This increases the polarity of the drug even further and targets it for excretion in bile or urine

e.g. glucuronidation - enzymatic addition of a polar glucuronic acid residue to a hydroxyl group





Secretory canaliculus

