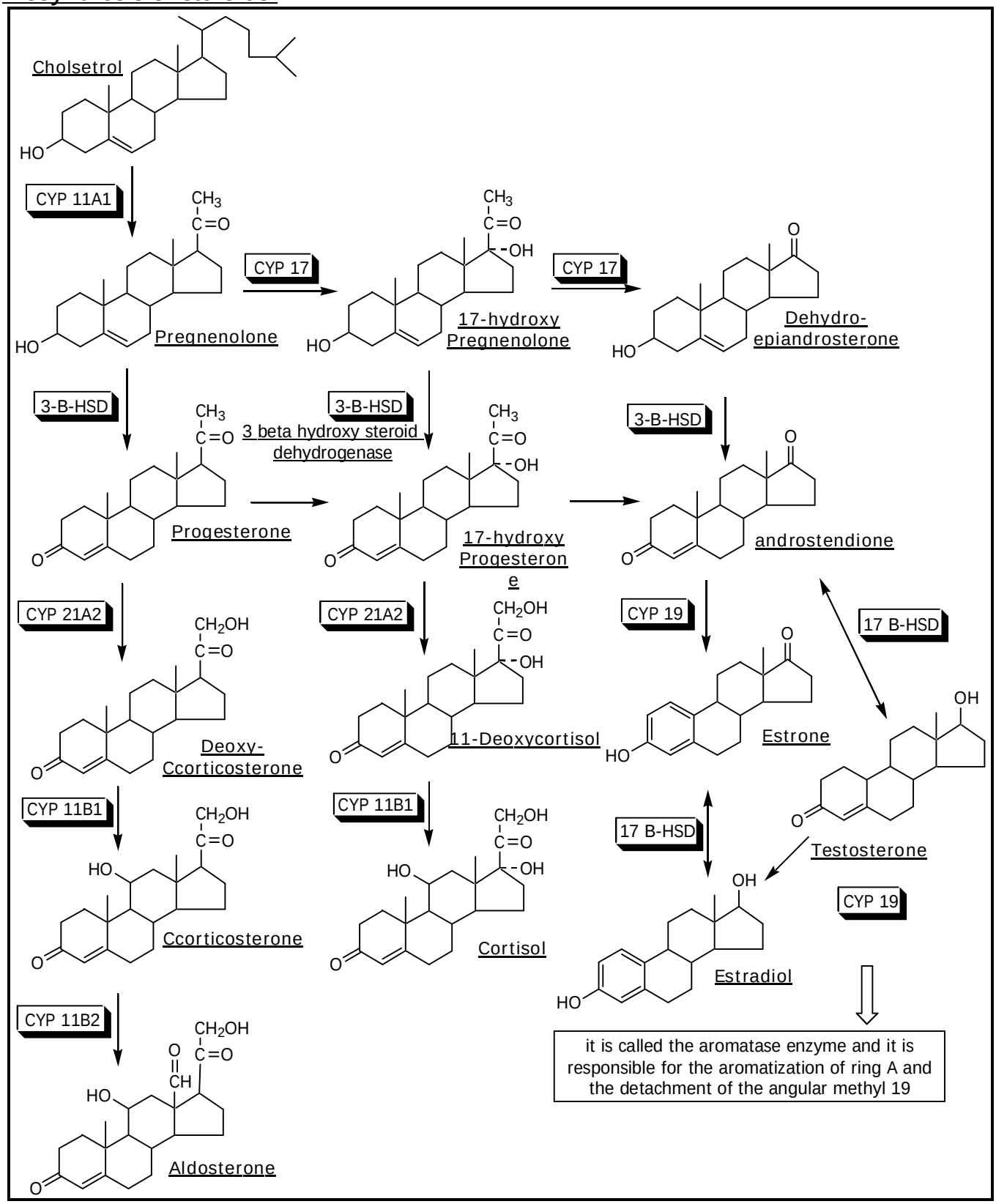
hormones

Lecture 8

Steroidal Hormones

Biosynthesis of steroids:

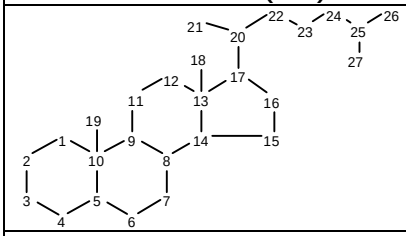
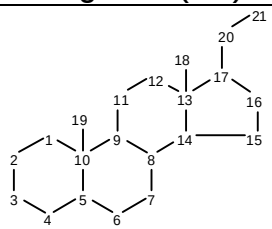
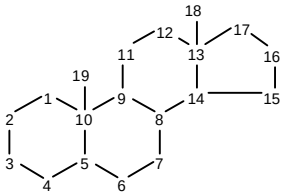
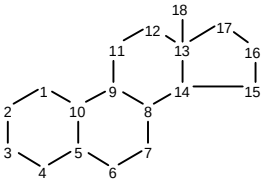


N.B.

- CYP 17 is described as 17-a-hydroxylase - C20-21 lyase. It's like 2 enzymes in one g First it introduces a hydroxyl to carbon 17 (hydroxylase), then it removes carbon 20 & 21 (lyase) leading finally to formation of a ketone.
- The major Progestagen g Progesterone.
- The major gonadal Estrogen → Estrone - Estradiol.
- The major gonadal Androgen → Testosterone.
- The major Mineralocorticoid [control electrolytes] → Aldosterone.
- The major Glucocorticoid [control metabolism] → Corticosterone - Cortisol → varied between Species.

General Chemistry of Steroidal Hormones

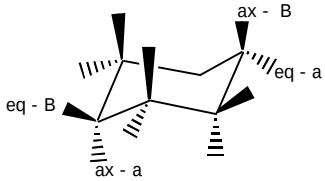
Main steroids skeletons:

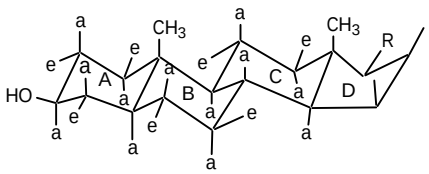
Cholestane (C_{27})	Pregnane (C_{21})	Androstane (C_{19})	Estrane (C_{18})
			
C_{18} & C_{19} g Angular Methyls			

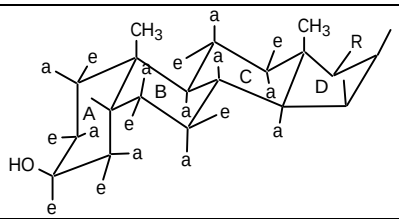
Conformational aspects of steroids:18

Substituents are:

- Axial (a) or equatorial (e).
- Above (α) or below (β) the plane of the ring.

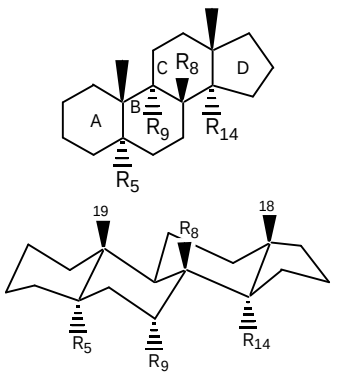
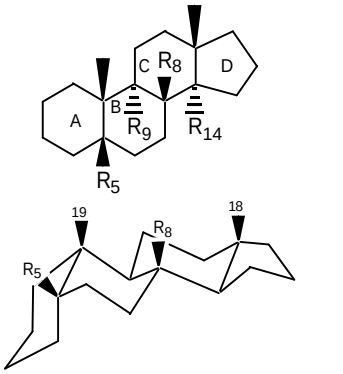






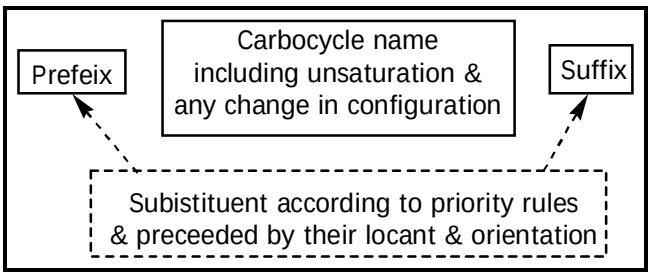
The ring fusion in natural hormones is:

- Trans/trans/trans.
- Cis/trans/trans in few examples.
- Trans A/B rings trans fusion may be referred to as 5-α.
- Trans or cis is determined by the substituents on the bridging carbons. eg: In pregnane. For trans bridging between A & B, susbstituents on carbon 10 (i.e methyl) and carbon 5 (i.e H) should be trans to each other. The methyl at carbon 10 is Beta thus the hydrogen on carbon 5 should be alpha in order to be trans (that's why they call it 5 alpha)

	
A/B trans - B/C trans - C/D trans	A/B Cis - B/C trans - C/D trans

Default g The substituents on carbons 10,13,17 are b and the rings are in trans

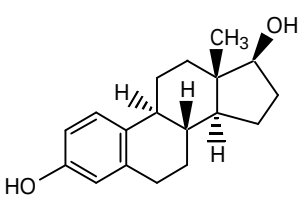
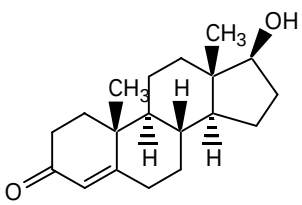
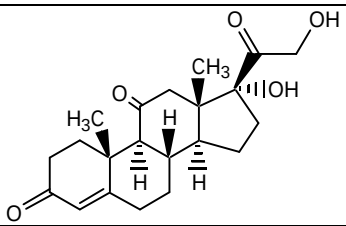
Nomenclature:



Nomenclature rules:

1. Trans A/B rings fusion is understood from writing the name of the carbocycle. A change in A/B rings fusion is indicated before the name of the carbocycle
2. Angular methyls (18 & 19) & the side chain at 17 are usually → beta oriented.
3. The carbocycle has to be drawn with ring A bottom left, and ring D top right.
4. The location and orientation of substituents should be indicated.
5. Single substitutent is written as suffix.
6. 2 substituents: one prefix, one suffix according to priority role.
7. More than one substituent → alkyl-halo-nitro as prefixes → others suffixes in alphabet order.

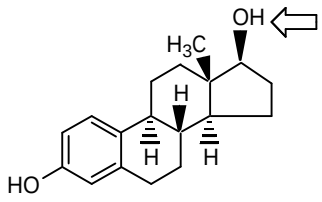
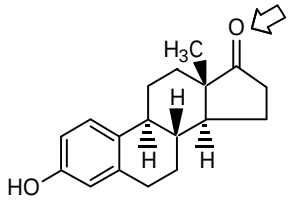
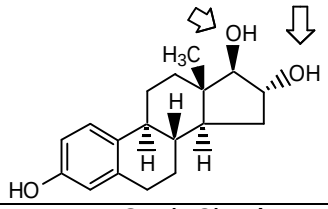
Examples:

Estradiol	Testosterone	Cortisone
		
Estra-1,3,5(10)-triene-3,17-β-diol	17β-Hydroxyandrost-4-ene-3-one	17,21-Dihydroxypregn-4-ene-3,11,20-trione

Sex (Gonads) Hormone

Female Sex hormones(Estrogens & Progestins)

Estrogens

Estradiol	Estrone	Estriol
		
Estra-1,3,5(10)-triene-3,17-β-diol	3-Hydroxyestra-1,3,5(10)-triene-17-one	Estra-1,3,5(10)-triene -3,16-α,17-β-triol
Most potent endogenous estrogen	Most abundant in serum	Most abundant in urine [Most hydrophilic cause of the 3 OH g It can be excreted as a free from or conjugate]
Synthesized mostly by ovaries and adrenal gland		synthesized mostly by placenta
All are excreted as their sulfate (3-OH) or glucouronides (3,17-OH) conjugates		

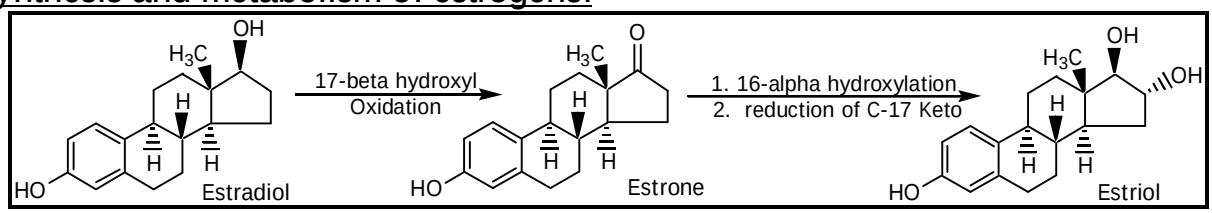
Estradiol

- Responsible for the 1ry and 2ry sex characters in female.
- Formed & excreted under FSH influence, so, ↑↑ estradiol level → -ve feed back effect on FSH level.
- Orally inactive → of short duration of action → due to degradation of ring D through the 17-β-OH by the intestinal bacterial flora and first pass effect.
- The 17-a-OH epimer → less active (limit test in estradiol) by HPLC.

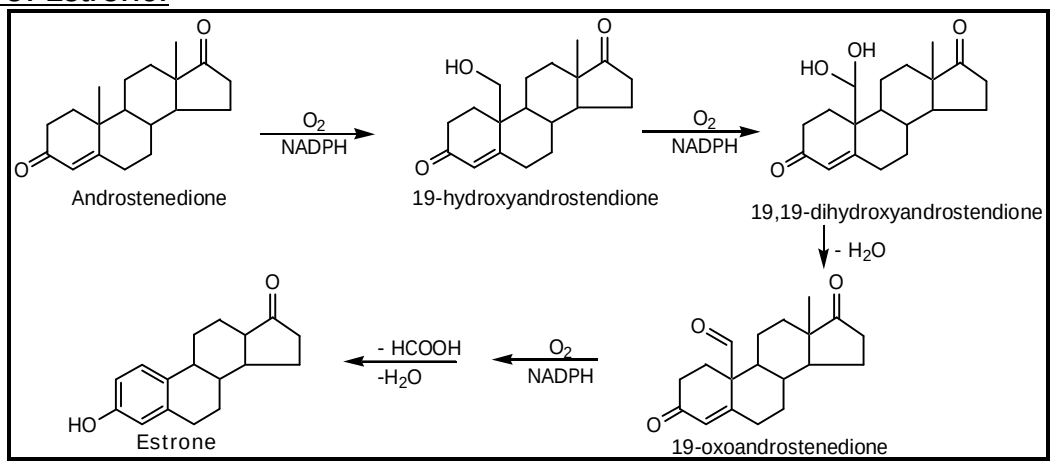
Estriol:

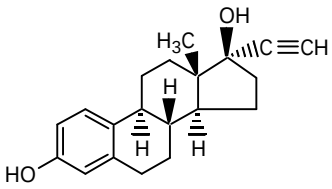
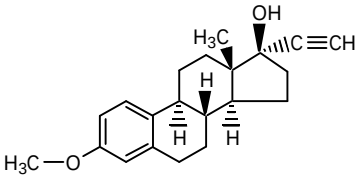
During pregnancy, estriol is synthesized from the placenta. Estradiol & estrone cause contraction of the uterus, while estriol doesn't (cause it is of low potency). Therefore it is luckily that this is the one synthesized form the placenta (not the other 2).

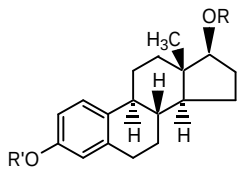
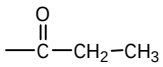
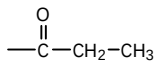
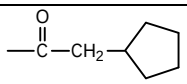
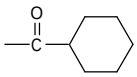
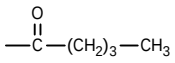
Biosynthesis and metabolism of estrogens:



Synthesis of Estrone:

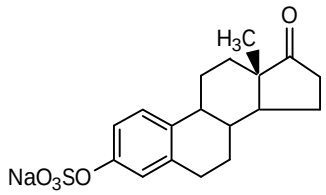
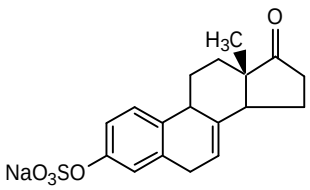
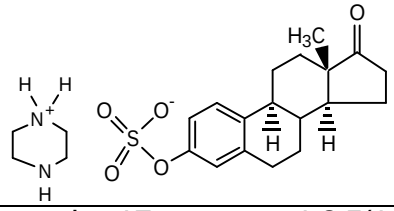


Orally active estrogens (α- phase protection) g Enzyme attacks from the alpha position to oxidize the β-hydroxyl, thus by making steric hinderance at the α-position, we block degradation.	
Ethinyl estradiol	Mestranol
	 NOT A PRODRUG
17α-Ethynylestra-1,3,5(10) triene-3,17β-diol	17α-Ethynyl-3-methoxyestra-1,3,5(10) triene-17β-ol
Used in: Oral contraceptive pills with a progestin [-ve feed back effect on FSH & LH].	
Assay of ethinyl estradiol: Add silver nitrate → give equivalent amount of HNO_3 → titrated with NaOH using bromocresol green (indicator)	

Long acting estradiol esters Most are oil soluble given I.M. [prodrugs] g They are long acting because they are prodrug that slowly release the active form and they are used during the menopause			
		R	R'
	1. Estradiol benzoate (Menovis) g 1 week duration.	H	
	2. Estradiol dipropionate		
	3. Estradiol cypionate g cyclopentyl propanoate ester		H
	4. Estradiol hexahydrobenzoate (Estra-1,3,5(10) triene-3,17β-diol-17-pentanoate)		H
	5. Estradiol Valerate (Progynova) orally bioavailable, Used as estradiol replacement therapy.		H

Conjugated (attenuated) estrogens

Weakened g Better than using potent ones to avoid the breast cancer and i the side effects.

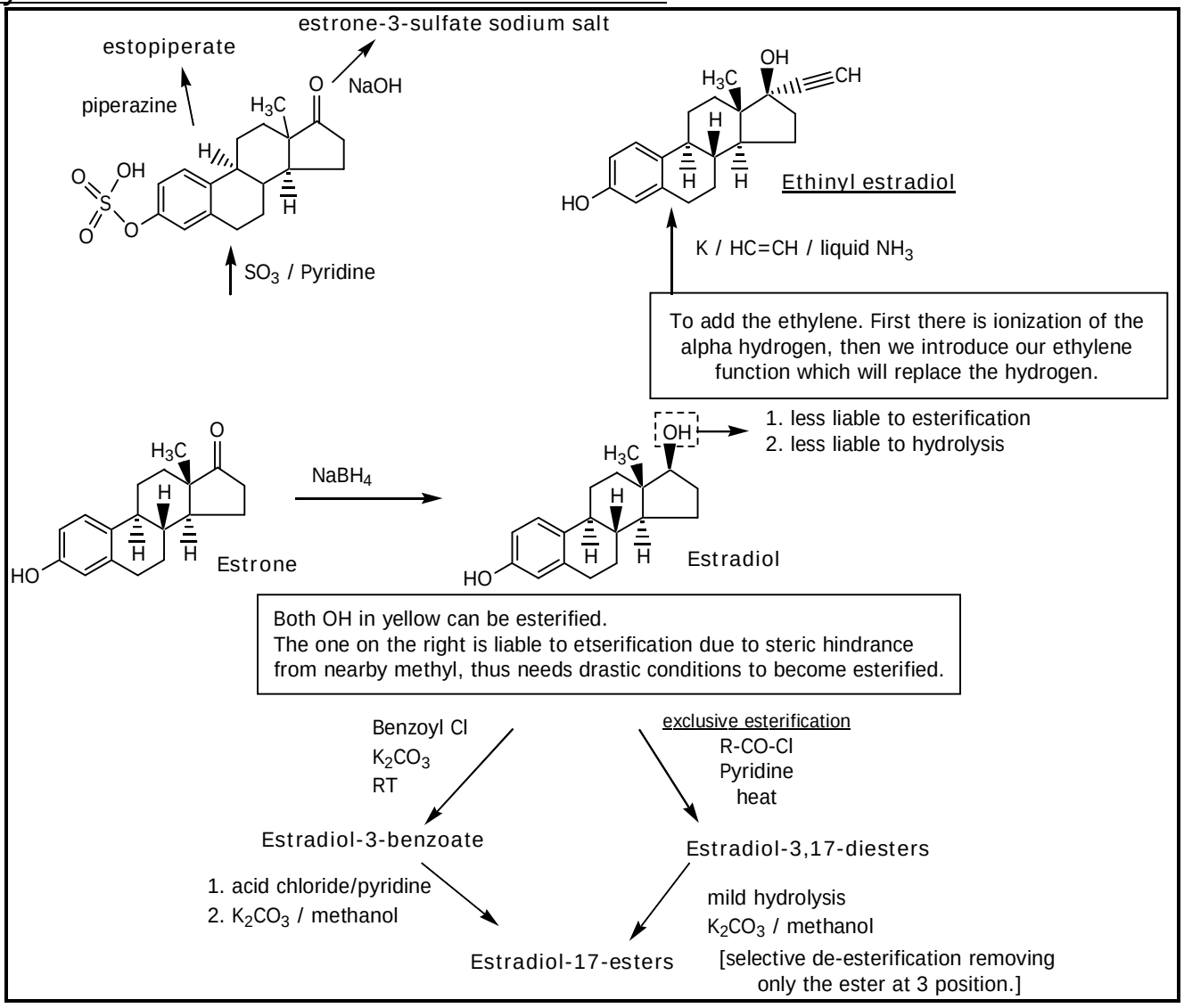
Estrone Na sulfate	Equilin Na sulfate (Premarin)	Estropipate
		
	Na 17-Oxo-estra1,3,5(10), 7-tetraene-3- sulfate	Piperazine 17-oxo-estra-1,3,5(10)-triene-3-yl-sulfate
Water soluble → orally bioavailable		More stable with acids

Used as → Hormonal replacement to treat postmenopausal climacteric symptoms & genitourinary tract atrophy.

Premarin® g consist of both (estrone & equilin Na_2SO_4) taken together. They ppt by the HCL in the stomach but still they are taken because not all will be ppt, some will not.

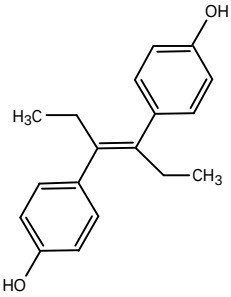
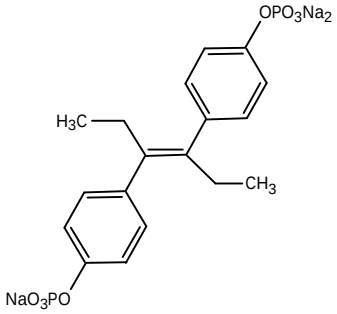
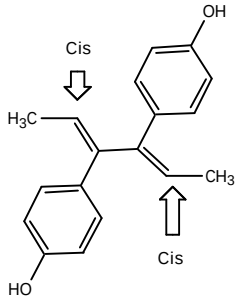
Estropipate: It is a piperazine sulfate. It contains 2 basic nitrogens and needs more acid to neutralize thus more stable.

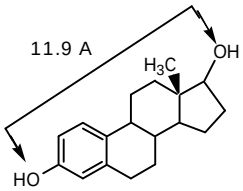
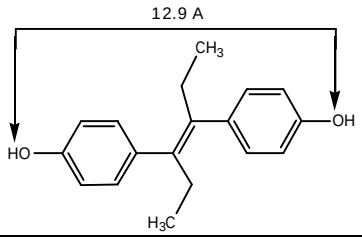
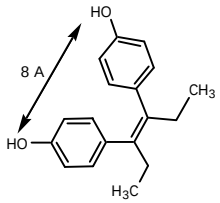
Synthesis of estradiol and estrone derivatives***:



Non-steroidal estrogens

[estrone nucleus is NOT necessary for activity]

Diethylstilbsterol (DES)	Fosfosterol	Dienesterol
 diphenyl ethene derivative		
trans isomer is 10X as estrogenic as its cis isomer [see below***]	more selective used for menopausal symptoms & prostate cancer	used as vaginal cream for postmenopausal vaginal atrophy

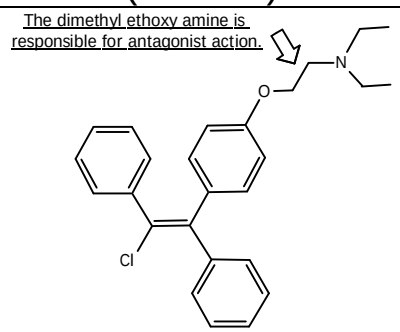
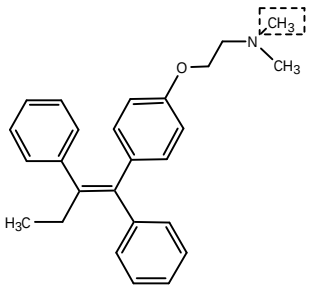
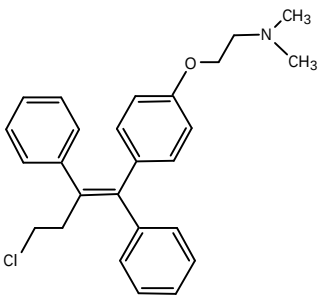
Estradiol	Trans-Diethylstilbsterol	Cis-Diethylstilbsterol
		

Estrogen antagonists

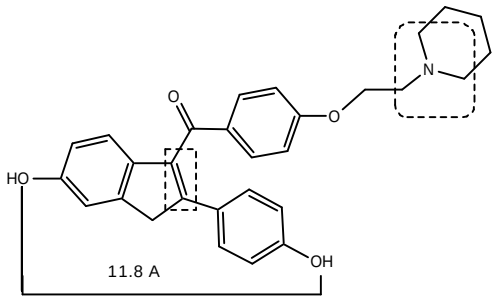
[Selective Estrogen Receptor Modulators] (SERM)

A. Triphenylethylene derivatives

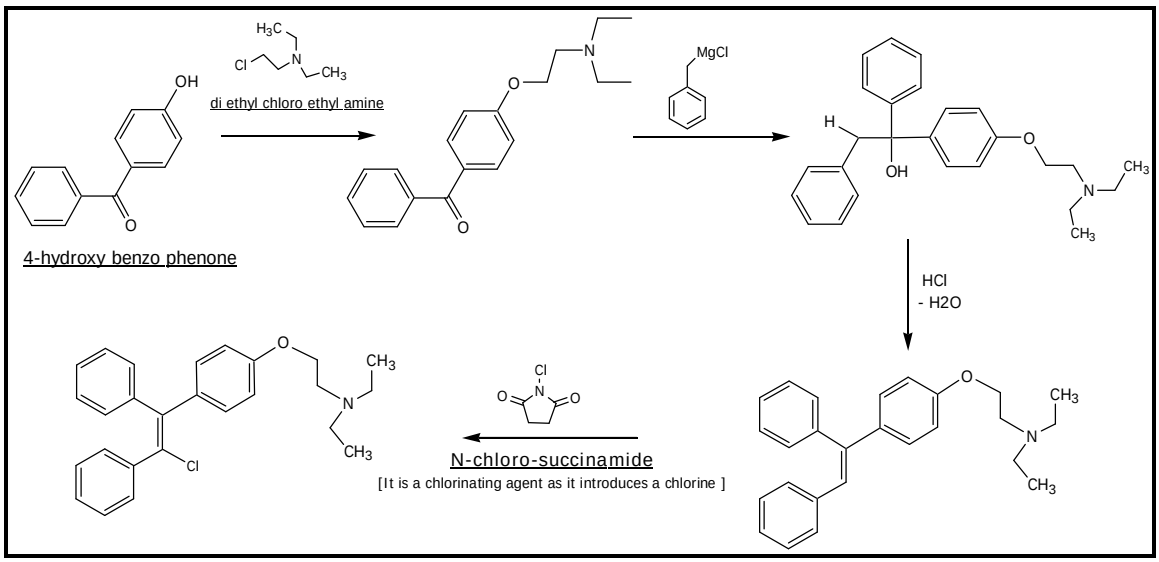
We can't describe it as anti estrogenic in a general term because of the geometrical isomers Z, E differ in the activity as Z is the agonist and E is the antagonist in a particular tissues so term SERM is used instead

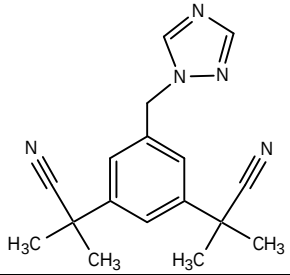
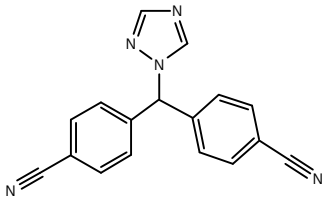
Clomiphene (Clomid®)	Tamoxiphene (Nolvadex®)	Toremiphene (Fareston®)
 2-(P-(2-Chloro-1,2-diphenylvinyl) phenoxy) triethylamine	 N-desmethyl metabolite contribute to the antiestrogenic activity	
• Mix of Z (cis) → estrogenic & E (trans) → anti-estrogenic. • Used in uterus - hypothalamus - Anovulatory infertility	• Z (trans) isomer → Estrogenic in uterus → anti-estrogenic in breast. • Used in treatment of bresat cancer. • ↑ Risk of uterine carcinoma.	

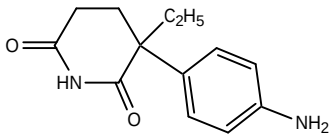
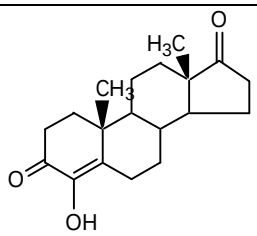
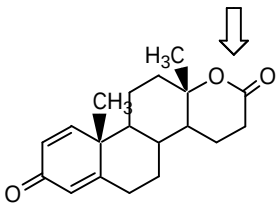
Clomiphen g [Anovulatory means decrease in ovulation]. E isomer is used to enhance the ovulation but the side effect is poly pregnancy. It is used to enhance the ovulation by sending false signals to the hypothalamus g h GnRH g h in the LH and the FSH g h estrogen

Raloxifene (Evista®)	
	• It's a Rigid analogue of triphenylethylenes [cyclic form] g we don't have different geometrical isomers (no problem arising from different isomers). • The distance between the 2 OH is similar to estradiol g h affinity to estrogen receptors. • Incorporation of the terminal N in a cyclic form g prolong the action and this is due to the resistance to the metabolism so it will be taken once daily. • –CO- function will lead to differing actions on ER e.g. it is anti-estrogenic on → breast - uterus BUT estrogenic on → bones, CVS. • Indications: 1. Postmenopausal osteoporosis. 2. Currently, studied for treatment of breast cancer. • Of i risk to induce uterine carcinoma.

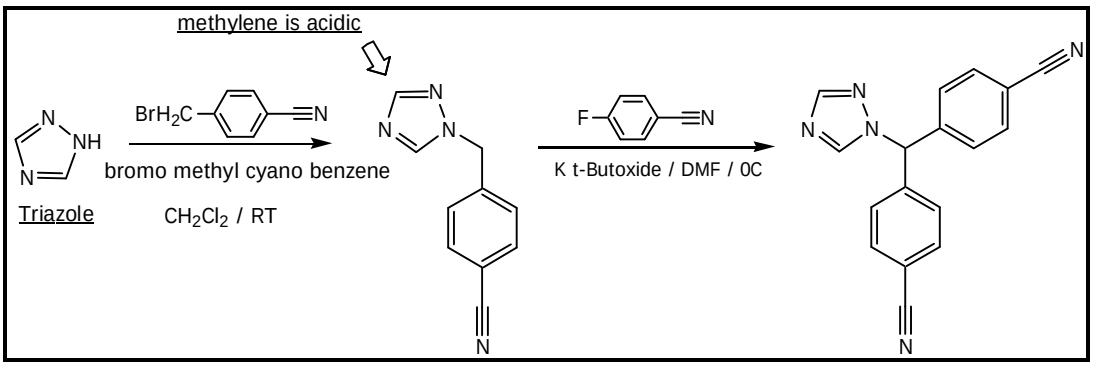
Synthesis of Clomiphene:



B. Aromatase (CYP 19) inhibitors	
Anstrozole (Arimidex®)	Letrozole (Femara®)
	
By the Coordination of the CYP 19 heme iron g by the chelation (due to triazole) of the heme of the enzyme and this will prevent the aromatization.	
Used for the treatment of breast carcinoma.	

Aminoglutethimide (Cytadren®)	Formestane (Lentaron®)	Testolactone (Teslac®)
	 4-hydroxy androstanedione	
• Non-specific aromatase inhibitor. • Used in ttt of Cushing`s syndrome.	• With androstane skeleton. • I.M. injection every 2 weeks. • Used in the treatment of the breast cancer.	• Androstane skeleton. • Non-specific inhibitor of CYP19. • Orally 4 times daily in large doses. • It's anabolic steroid.

Synthesis of Letrozole:



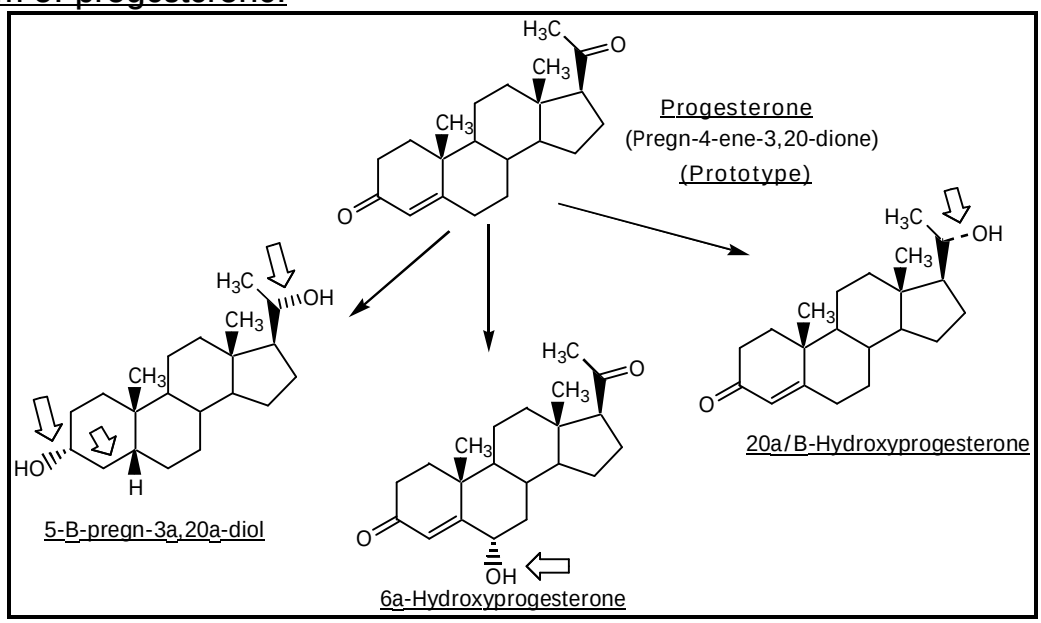
hormones

Lecture 9

Steroidal Hormones

Progestins, Progestogens or Progestional agents

Metabolism of progesterone:

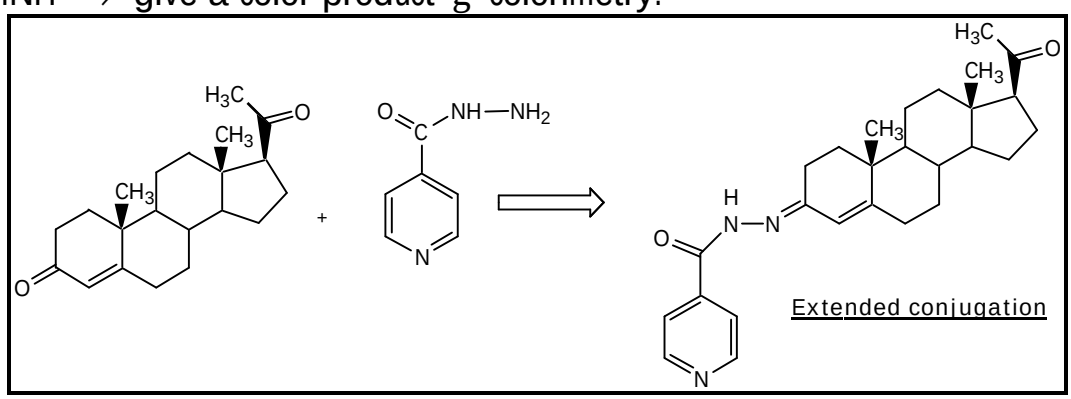


Progesterone is:

- Biosynthesized in ovaries - testis - adrenals → mainly under the control of LH [Progesterone has a negative feed back on LH].
- Orally inactive due to 1st pass & bacterial decomposition of ring D & reduction of the –CO- of ring A and ring D.
- A key intermediate in the biosynthesis of corticosteroids-androgens then estranes.
- Acts (complementarily with estrogens) to control menstrual bleeding-release of ovum - preparing the uterus to receive fertilized ovum suppression of ovulation during pregnancy-maintenance of pregnancy through depressing uterine contraction.

Assay of progesterone:

- By INH → give a color product g colorimetry.

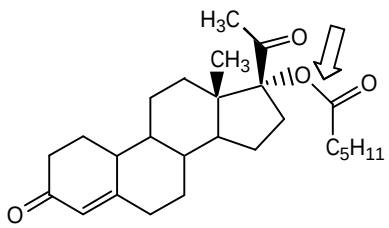
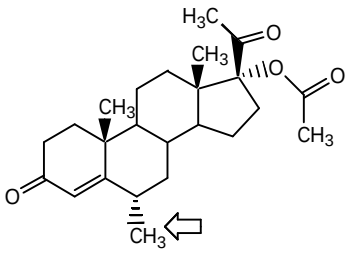
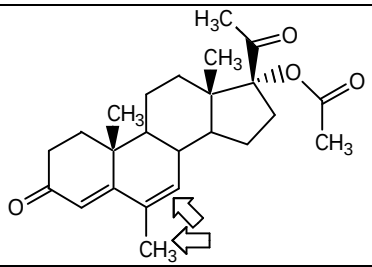


Uses of progestins:

1. Functional uterine bleeding - habitual and threatened abortion.
2. Endometriosis.
3. Anti-androgen for $\rightarrow$ treatment of prostate cancer.
4. Adjuvant therapy in endomtrial carcinoma.
5. Contraceptive $\rightarrow$ as single treatment or in combination with estrogens.

17-a-Hydroxyprogesterone derivatives

- 17α-hydroxy function to protect the –CO- from 17 keto reductase $\rightarrow$ enhance metabolic stability & oral bioavilability [Protection of a-phase]
- Make use of the –OH to form oil soluble esters (produgs, long acting).
- Blocking position 6 of ring B and/or introduction of unsaturation in ring B will enhance metabolic stability, too.

Hydroxyprogesterone caproate (Primolut-depot®)	Medroxyprogesterone acetate (Depo-Provera®)	Megesterol actate (Megace®)
		
3,20-Dioxopregn-4-ene-17α-yl caproate	17-Hydroxy-6α-methylpregn-4-ene-3,20-dione acetate	17-Hydroxy-6-methylpregn-4,6-diene-3,20-dione acetate
• Once weekly injection. • Used in habitual or threatened abortion.	• Injection every 3 months. • Used in: 1. Progestin only contraceptive. 2. Management of endometrial carcinoma. 3. Recently introduced monthly co-injection with estradiol cypionate (Lunelle).	Used as tablets in treatment of breast & endometrial carcinoma.

Medroxyprogesterone acetate: acetate ester will lead to:

- The slow release of the17 hydroxy progesterone.
- Resistant to the metabolism because of protecting function on the 17-α position.

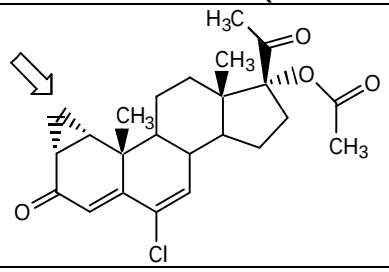
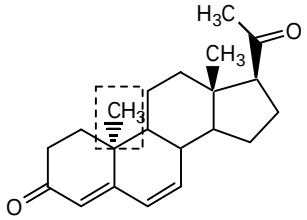
So these TWO factors will lead to prolonging the action up to three month

Megesterol actate:

It has been found that the progestins can compete with estradiol for the estrogenic receptors (antagonist action) so this compound which has the following properties:

- Hydroxy ester at C_{17}.
- Double bond at C_6.
- Methyl at C_6 to block metabolism

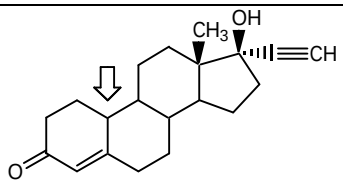
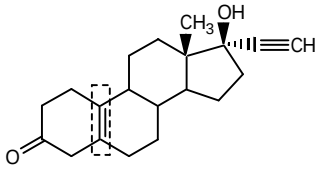
g can be used for the oral treatment of the breast cancer & endometrial carcinoma. [breast cancer & endometrial carcinoma is due to increased estrogen].

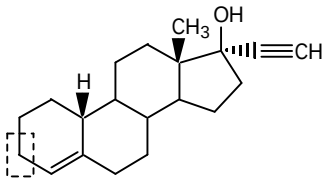
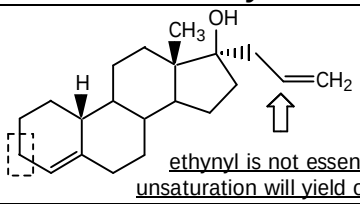
Cyproterone acteate (Androcur®)	Dydrogestone (Duphaston®)
	
6-Chloro-17-hydroxy-1-α,2-α-methylenepregn-4,6-diene-3,20- dione acetate	9-β,10α-Pregn-4,6-diene-3,20-dione
Uses: Anti-androgenic g treatment of prostate cancer.	Used as tablets in ttt of irregular duration & occurrence of period.
	Changing conformation of progesterone → orally active-no contraception-No virilizing action on fetus

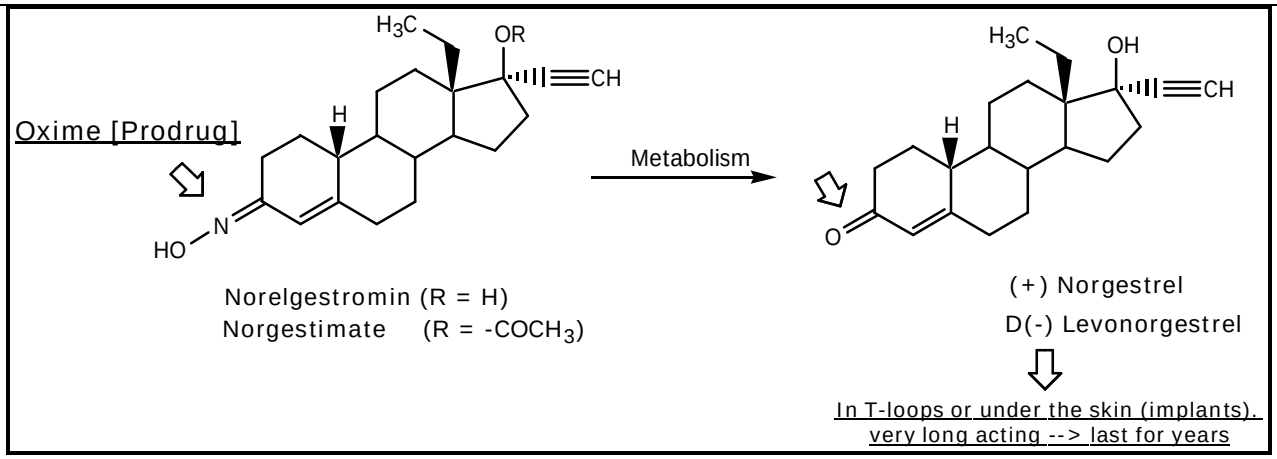
Cyproterone acteate:
Methylene bridge will yield affinity to the androgenic receptors (compete with testosterone & hydroxycortisone) g so it is used in the treatment of the prostate cance

17a-Ethinyl-19-Nortestosterone derivatives

- They are orally active.
- They are progestogenic agents by activity but not chemically
- Angular C_{19} is not essential for progestional activity.
- Introduction of 17a- ethynyl function OR 17a- unsaturation give ↑ oral activity- ↑ metabolic stability - ↓ androgenic activity.
- 17α-OH allows the formation of long acting esters.

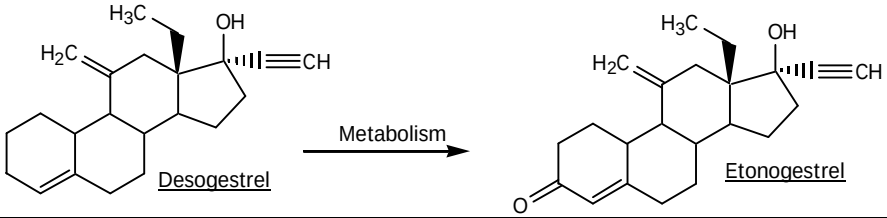
Norethisterone	Norethynodrel
 17α-Ethynyl-17-hydroxyestra-4-ene-3-one	 it is converted by the stomach acidity to give norethisterone ....interconvertable
Norethindrone = Norethisterone esters: Norethisterone acetate - Norethisteronenanthate	
• Norethindrone is 10X as active as norethynodrel. • Not longer used due to slow conversion by gastric acidity to norethisterone.	
Norethisterone: • Main skeleton is esterane and it can be synthesized from testerone by the removal of the angular methyl on C_{19} and the introduction of the ethynyl at C_{17} and this will yield a compound with estrogenic activity.	

Lynesternol	Allylsternol
	 ethynyl is not essential, any alkyl with unsaturation will yield orally active derivative.
Both have NO–CO at C_3 but oxidized in vivo to 4-ene-3-one system.	



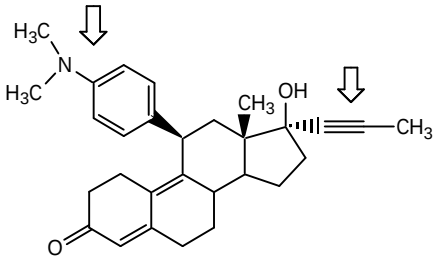
instead of the methyl there is the angular ethyl which will provide a compound of oral activity and long acting

- Levonorgestrel is the active enantiomer of Norgesterl → It is 100X as active as Norethisterone as the Et ↑ protection to ring D & make non-favorable steric interaction with the androgenic receptors.
- Levonorgetsrel is porgestin-only contraceptive used as tablets - subdermal capsules & intra-uterine devices (up to 5 years).
- Norelgestromin used as contraceptive cutaneous patches with estradiol.

Desogestrel

Etonogestrel used as subdermal implants & IU rings with ethinyl estradiol (monthly)

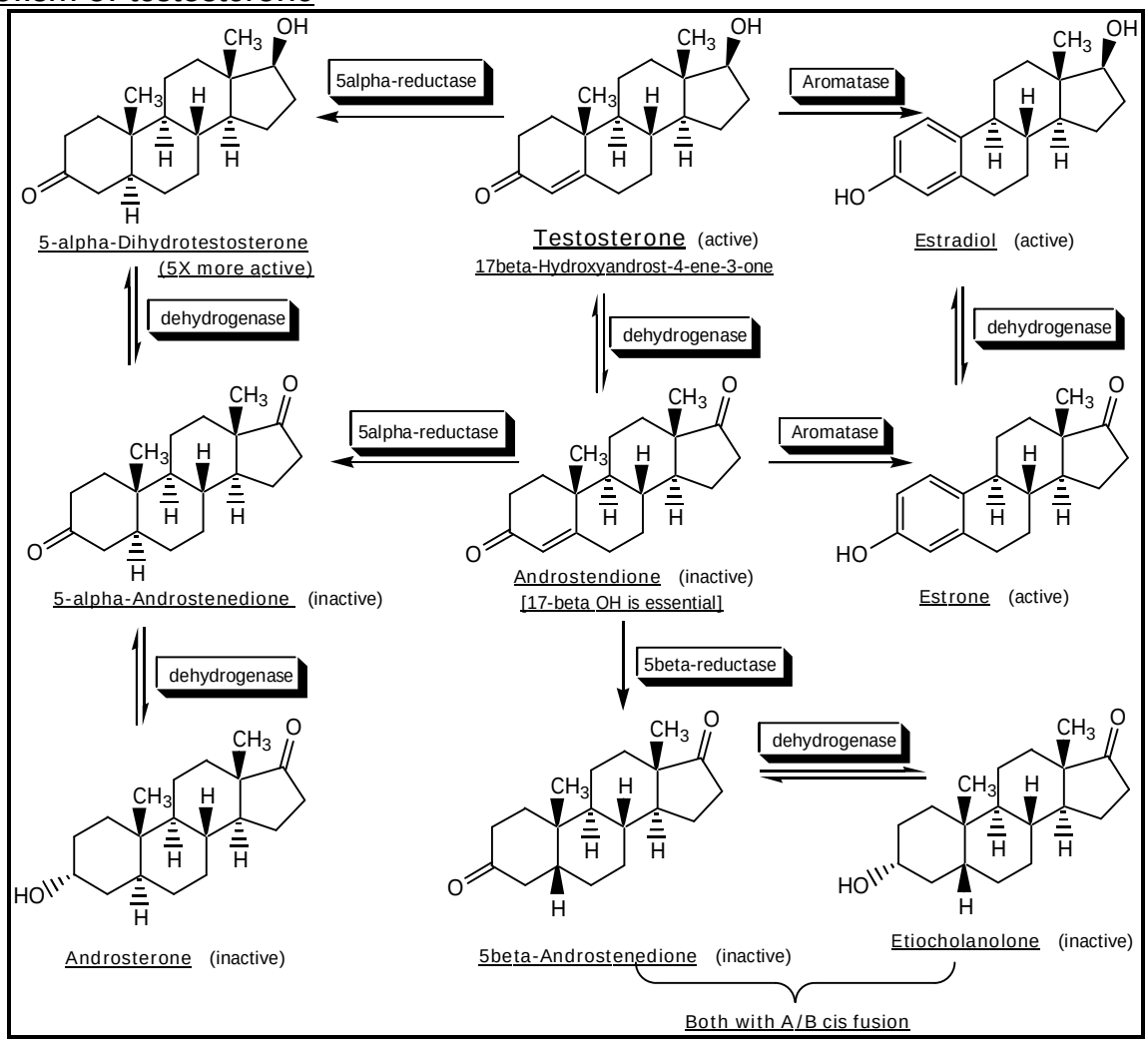
- All are used as oral contraceptive in combination with estrogens.
- BUT levonorgestrel is progesterone only type contraceptive & may be used as implants or to impregnate IUD.

Anti-Progesterone

Mifepristone (Mifegyne)
   11β-[4-(Dimethylamino)phenyl]- 17β-hydroxy propynyl)estra-4,9-dien-3-one
• Anti-progestogenic (competitive antagonist) → induce abortion (84%) up to the end of the 1st trimester g can be useful in case of rape or unsafe sex (use it within 72 hours) • The propynyl g ↑ affinity to progestogenic receptors. • Bulky Dimethyl amino phenyl → induces or stabilizes an inactive receptor conformation [responsible for antagonist effect]

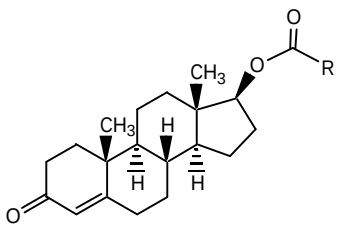
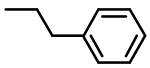
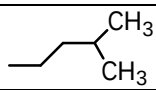
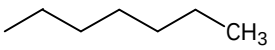
Androgens and Anabolics

Metabolism of testosterone



Testosterone:

- Short duration of action.
- Orally Inactive (not bioavailable) → due to attack & decomposition of ring D by the liver & intestinal bacterial.
- Have anabolic/androgenic activity.

Testosterone esters		
		R
	j Testosterone propionate [short onset & duration]	$-C_2H_5$
	k Testosterone phenyl propionate [intermediate onset & duration]	
	l Testosterone isocaproate [Long onset & duration]	
	m Testosterone heptanoate (enanthate) [long acting]	

- - onset & duration according to the size of the ester R.
- Used as a single agent OR mixture.
- It's Prodrugs → Given by I.M. injections.

- Sostanone ampoule® is composed of 1st three esters g given in a single injection g short onset of the propionate + long duration of action of isocaproate.

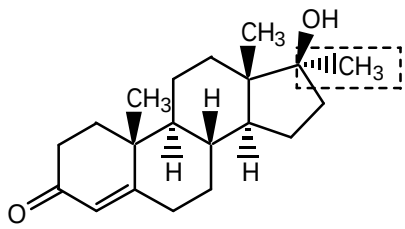
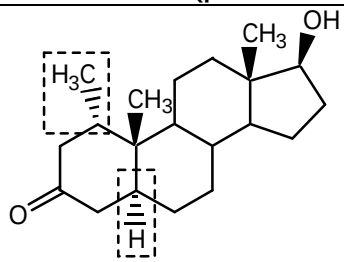
Uses of Androgens & anabolics:

1. Delayed puberty & growth in males.
2. Impotence & male climacteric.
3. Osteoporosis in males & females.
4. Debilitating illness and anemia.

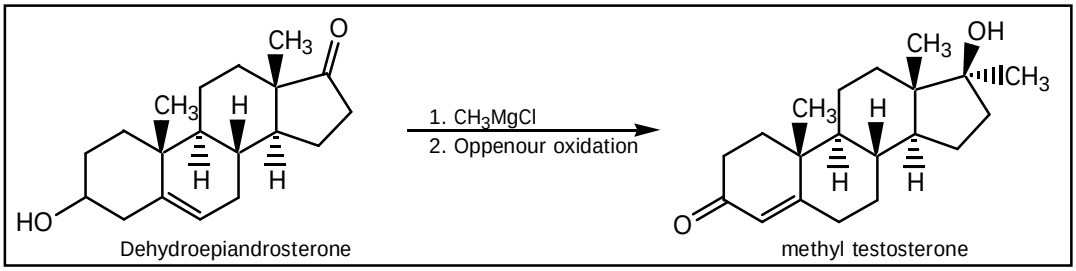
Orally bioavailable testosterone derivatives (anabolic/androgenic agents)

By:

1. Introduction of 17a-methyl → ↑ metabolic stability and oral activity.
2. - length of the alkyl [>Me] → ↓ both anabolic & androgenic activity.
3. Introduction of 17a–ethynyl → imparts progestogenic activity (ethisterone).
4. Alkylation at positions 1,2, 7 or 18 → ↑ anabolic/androgenic ratio.
5. Introduction of 4b &/or 11b–hydroxyl in methyltestosterone - introduction of F at C_9 or unsaturation to ring A → - the anabolic & ¯ androgenic activity.

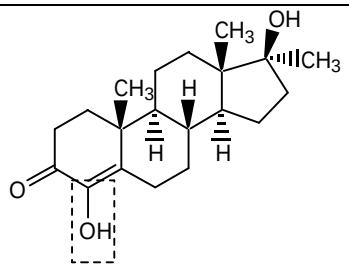
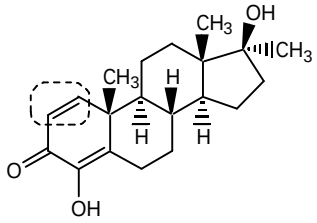
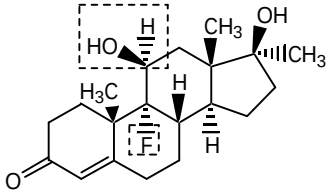
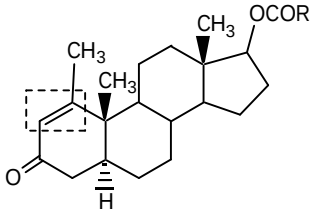
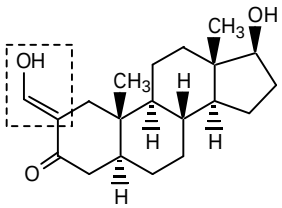
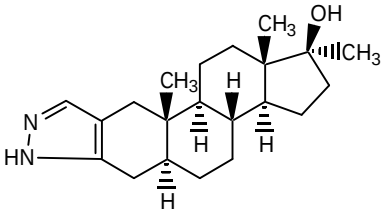
Mainly androgenic	
Methyl testosterone (Hormo-Gerobion®)	Mesterolone (proviron®)
	
17β-Hydroxy-17-methylandrost-4-en-3-one	17β-Hydroxy-1α-methyl androstan-3-one Although NOT protected at C_{17} g taken orally due to its h potency

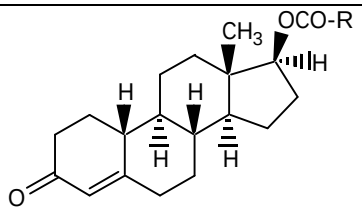
Synthesis of methyltestosterone:

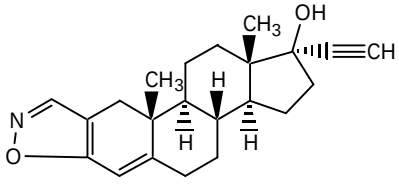


N.B.

- Oppenour oxidation → oxidation of a 2ry alcohol with a ketone (cyclohexanone) + Al isopropoxide → formation of -4-en-3-one conjugated system.
- There is no pure androgenic nor pure anabolic action.

Mainly androgenic		
Oxymestrone (oranabol®)	Methandrostenolone (Dianabol®)	Fluoxymestrone (Ultandren®)
	 Orally active	
4, 17β-Dihydroxy-17-methylandrost-4-en-3-one	17β-Hydroxy-17-methylandrost-l,4-dien-3-one	9-Fluoro-11β,17β-dihydroxyl-7-methylandrost-4-en-3-one 20X as anabolic – 10X as androgenic as methyl testosterone
Methenolone (primoblan®)	Oxymetholone (Anabolon®)	Stanozolol (Stromba)
		 Azasteroid
1-Methyl-3-oxo-androst-1-en-17β-yl acetate Methonolone acetate (Primoblan depot®)	17β-Hydroxy-2-hydroxymethylene-17-methyl androstan-3-one	17α-Methyl-2`H-androst-2-eno[3,2-c]-pyrazol-17-ol

Estrane anabolics
 17β-Hydroxyestra-4-en-3-one
R = H → Nandrolone (Durabolin®) g orally R = C_9H_{19} → Nandrolone decanoate (Decadurabolin®) g injection, long acting

Androstanes for treatment of endometriosis
Danazol (Danatrol®)
 May considered Pregnane or Androstane derivative
17α- Pregn-2,4-diene-20-yno(2,3-d)isoxazol-17β-ol

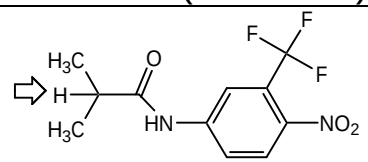
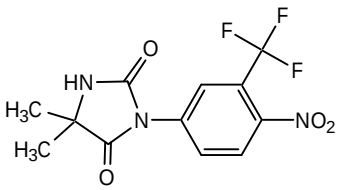
Anti-androgens and 5a–reductase inhibitors

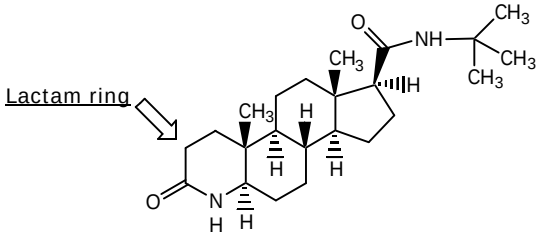
Uses:

1. Males → hypersexuality - benign prostatic hyperplasia - prostaic carcinoma.
2. Females → treatment of acne - hirsutism - alopecia - androgenetica.

Chemical nature:

- Steroids → e.g. cyproterone acetate - spironolactone.
- Non-steroidal → e.g. cimetidien - flutamide and its derivatives.

Flutamide (Flutamex®)	Nilutamide (Nilandron®)
 Metabolized to hydroxyl flutamide [active]	
3'-trifluoromethyl-4`-nitro-isobutyranilide	1-(3'-Trifluoromethyl-4'-nitrophenyl) -4,4-dimethylhydantoin
$t_{1/2}$ = 8 hrs	$t_{1/2}$ = 50 hrs

5 –Reductase inhibitors
Finasteride (Prostide®)

Inhibit conversion of testosterone to more active 5-dihydro

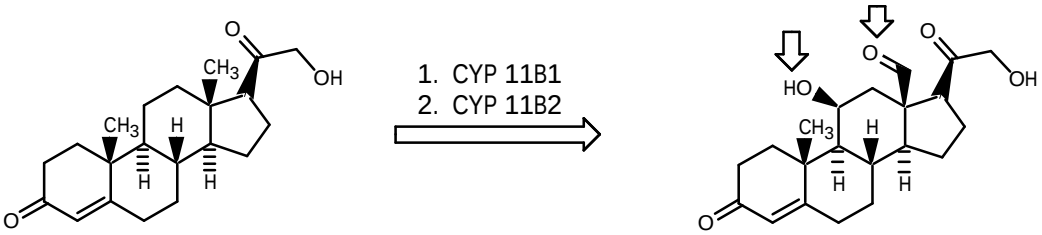
Lecture 10

hormones

Steroidal Hormones

Mineralocorticoids and Glucocorticoids

[i] Mineralocorticoids



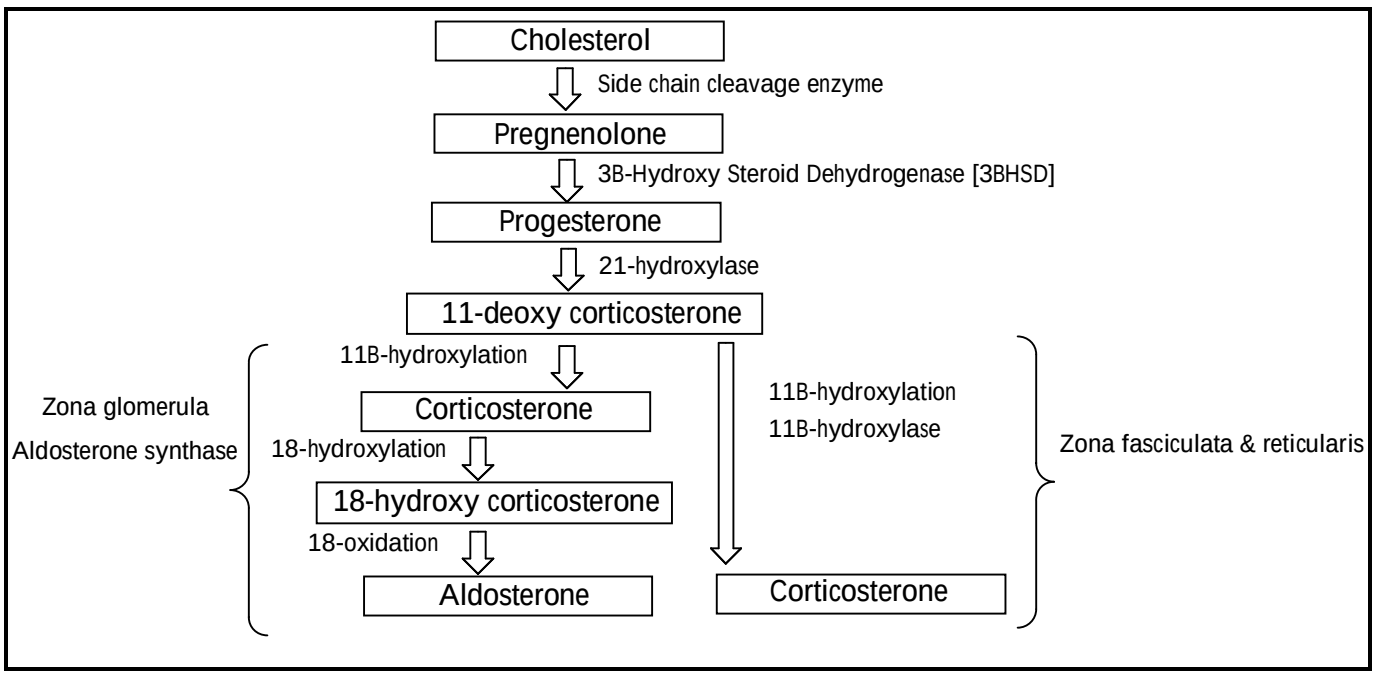
Deoxycorticosterone

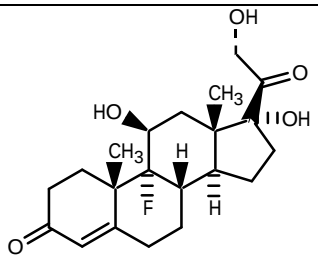
21-Hydroxypregn-4-ene-3,20-dione

Aldosterone

18-Formyl-11_,21-dihydroxy -pregn-4-ene-3,20-dione

- Biosynthesis is stimulated by ACTH, Angiotensin II and serum K^+.
- Enhances Na^+, H_2O re-absorption, K^+ excretion.



Fludrocortisone acetate
   9-Fluoro-11β,17,21-trihydroxypregn-4-ene-3,20-dione
• 9 a- Fluoro substituent h mineralocorticoid activity 500X and glucocorticoid activity 8 X as hydrocortisone.

- Mineralocorticoid used to treat adrenal insufficiency e.g. Addison's disease and to treat orthostatic hypotension.

[ii] Glucocorticoids

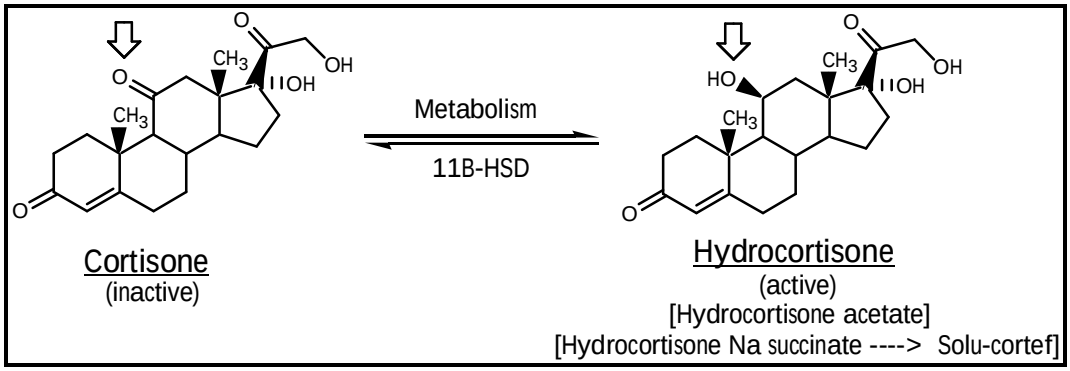
Uses of Glucocorticoids:

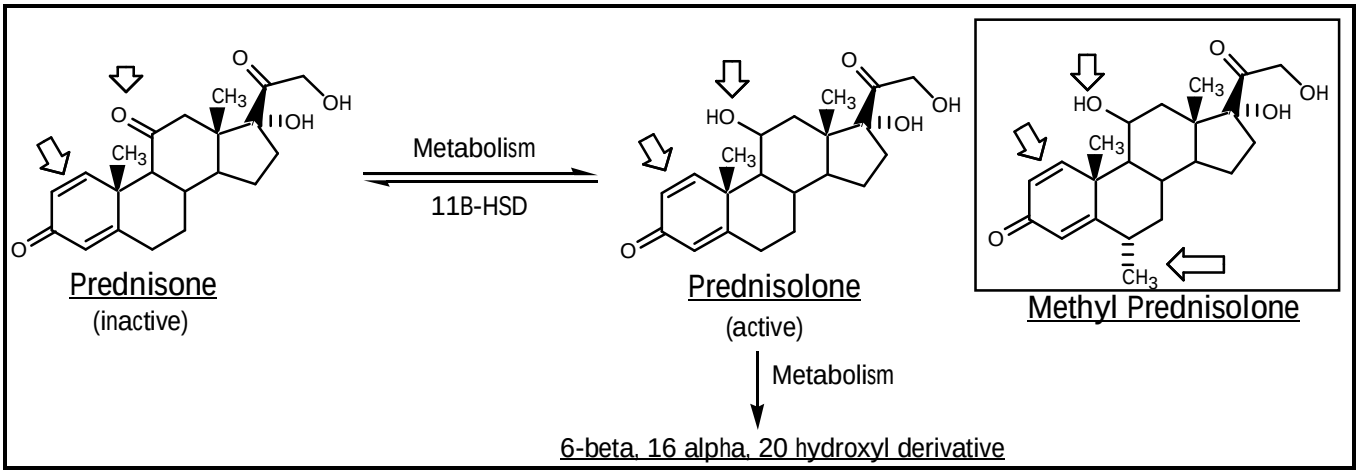
- Immunosuppressant in case of inflammatory diseases e.g. psoriasis, anaphylactic shocks, severe asthma, poison ivy dermatitis, ulcerative colitis, and rheumatoid Arthritis.
- Anti-allergic.
- Leukemia, lymphoma.
- Nausea associated with chemotherapy.

Cautious:
Diabetes, hypertension, water retention, infectious diseases and sudden withdrawal particularly after long term therapy, glaucoma, osteoporosis.

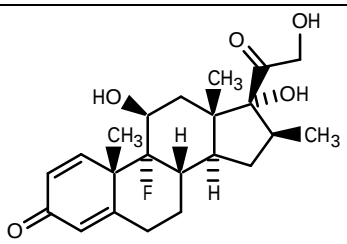
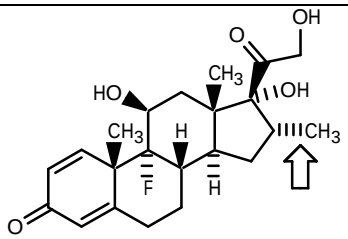
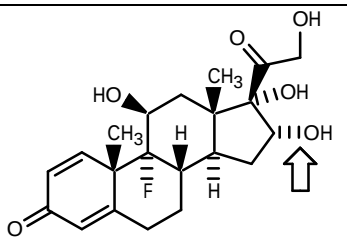
SAR of glucorticoids:

- They are all pregnane derivatives with the all trans ring fusion.
- Introduction of unsaturation at C_1 g h glucocorticoid activity.
- For all glucocorticoids and mineralocorticoids an 11b- hydroxyl function is essential for activity.
- The 9a- fluoro substituent will h ionization of 11β- hydroxyl function by inductive action, this enhances interaction with the receptor through H bonding. However, the 9-fluoro substituent will h glucocorticoid activity.
- 16a-hydroxyl or methyl will negate the sodium retention of the 9α- fluorine.
- 21 halo substituent greatly enhances lipophilicity and glucocorticoid activity, due to enhancement of the receptor binding, delays rate of dissolution and prolongs the duration of action.





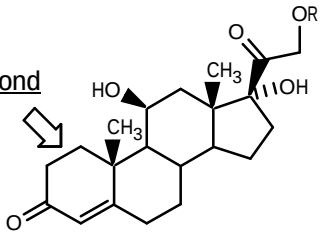
- All are Δ1 corticosteroids; 4-5 X as glucocorticoid and nearly equal mineralocorticoid to hydrocortisone.
- Ring A conformation :
  [Saturated g Chair] [4-en-3-one g half chair] [1,4-dien-3-one g flattened boat]

Betamethazone	Dexamethazone	Triamcinolone
		
9α-Fluoro-16 β-methyl-11β,17,21-trihydroxy pregn-1,4-diene-3,20-dione	9 α-Fluoro,16α-Methyl-11β-17,21-trihydroxy pregn-1,4-diene-3,20-dione	9α-Fluoro-11β,16-α,17,21-Tetrahydroxy pregn-1,4-diene-3,20-dione
We stabilize 17 ketol towards metabolism by 16 a or b substituent		
All with 40x glucorticoid and nearly zero mineralocorticoid relative to hydrocortisone		

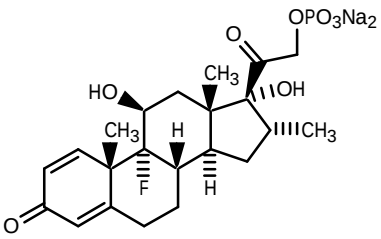
Triamcinolone:
With the highest hydrophilicity, lowest oral bioavailability and glucocorticoid activity but all are of better glucocorticoid and lower mineralocorticoid activity relative to hydrocortisone.

Steroidal Prodrugs to improve water solubility and shorten onset of action

Single or Double bond



Hydrocortisone Na phsophate	R = $-PO_3Na_2$
Hydrocortisone Na succinate	R = $-CO-(CH_2)_2-COONa$
Prednisone Na phosphate	
Prednisone Na succinate	

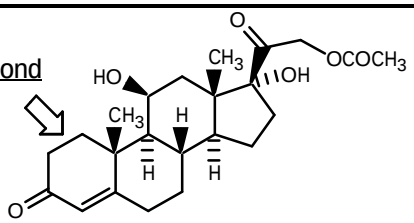


Dexamethazone Na phosphate

- Injection in acute pain, asthma and life saving conditions.
- Onset = 2 minutes in vivo, but 2 years on shelf!!!

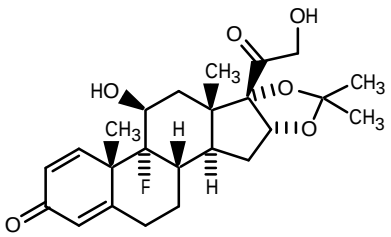
Steroidal Prodrugs to improve lipid solubility, prolong the duration of action and/or topical applications

Single or Double bond



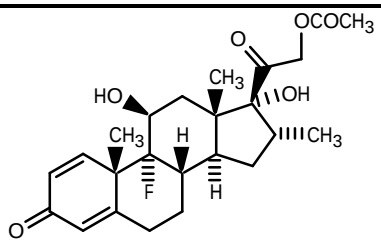
Hydrocortisone Acetate
Prednisone Acetate

2 Injections / Week



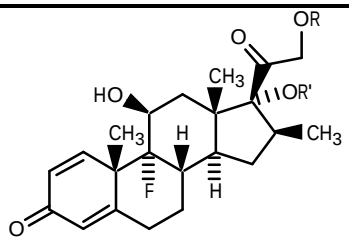
Triamcinolone acetonide [Kenacort]

Ointment / Cream / Long acting injection



Dexamethazone acetate [Fortecortin]

* Long acting injection twice weekly.
* For chronic treatment of pain & other conditions

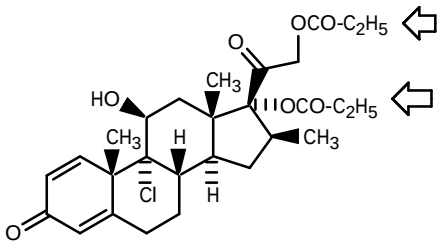
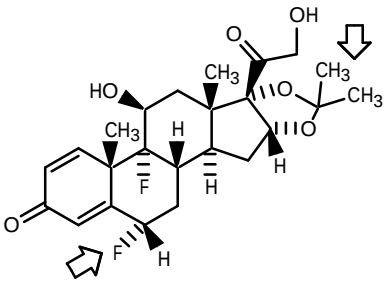
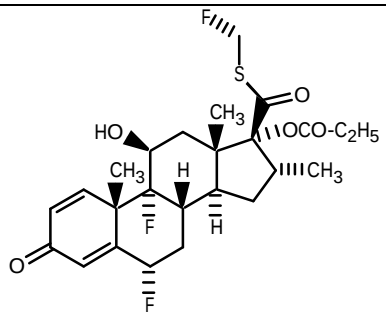


Betamethazone dipropionate R = R' = CO-Et
Betamethazone valerate R = H, R' = $CO-C_4H_9$

Ointment / Cream / Gel

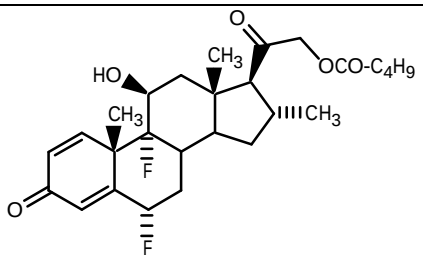
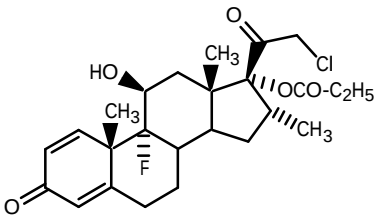
Topically only applied steroids

- Dihalo, halo-ester, diester corticosteroids Lipophilic (log p >4.5).
- With low H_2O solubility, Minimal absorption.

Beclomethazone dipropionate	Fluocinolone acetonide	Fluticasone propionate
		
Inhaler	Ointment / Cream	Ointment / Cream / Inhaler

Beclomethazone dipropionate:

- 5000 X as glucocoticoid as hydrocortisone.
- 500 x as betamethasone.
- Beclomethasone monopropionate g (17) is more active.

Diflucortolone valerate	**Clobetasol propionate**
	
Ointment / Cream	Ointment / Cream

Lecture 2-5

Anti-neoplastic agents

Neoplasm [Tumor] [Cancer]:

Relatively autonomous growth of tissues.

Types of Neoplasm:

There are various types of neoplasm BUT there is no system for their nommenclature :

- Some neoplasms are named according to their tissue or origin. For example:

Tissue	Name of Tumor
Epithelial	Carcinoma
Connective tissue	Sarcoma
Blood [abnormal # in leukocytes]	Leukemia
Fibrous tissue	Fibroma

- Others named after the individual who first describe the condition.

E.g. Hodgkin's disease.

Etiology of Cancer :

Many factors have been supposed to be the cause of cancer BUT none of them is the exact etiologic factor. E.g :

- Genetic factors : mutation & changed gene expression.
- Viral factor :

e.g. human T-lymphotropic virus type I [HTLV-I] " the cause of a form of leukemia.

- Physical factors : as long term exposure to chemical and/or irradiation.
- Hormonal factor.

Mechanism of Cancer formation :

By Mutation [Altered Gene Expression]

- Proto-Oncogenes : its function is to control cell growth.
- Oncogenes : normal proto-oncogene by mutation " incorrect proto-oncogene expression " Oncogene " synthesis of oncoprotein which is devoid of important regulatory elements " # DNA replication.
- Anti-Oncogene or Supressor gene : guard the cell ≠ oncogene action.

There are 2 fundamentally different genetic mechanisms exist :

- Enhance or aberrant oncogene expression.
- $ activity of anti-oncogenes " tumor suppressor genes".

Lines of treatment:

- Surgical methods : for large tumors "if it has not metastasized".
- , Radiotherapy :
  - Superior to surgery that it effectively destroys a tumor with minimal damage to surrounding normal tissues.
  - May be done after surgery to remove traces remain.
- *f* Chemotherapy : [Antineoplastic, Anticancer, Antitumor or Cytotoxic Drugs]

Chemotherapeutic Agents

[Antineoplastic, Anticancer, Antitumor or Cytotoxic Drugs]

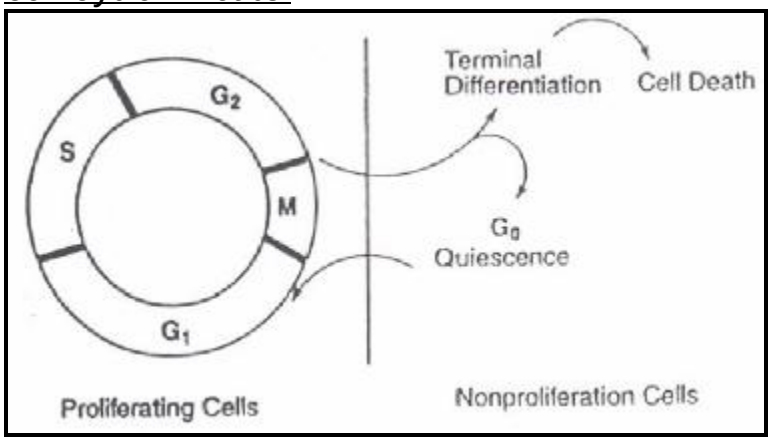
- Chemotherapy is not so much limited by metastasis.
- Ideal anti-cancer should theoretically eradicate cancer cells without harming normal cells.
- Anticancer act on cells in the process of division, so as tumor cells divide more rapidly than normal cells , they are most affected.
- That's why normal cells with high rate of division are also affected causing many side effects :for e.g.
- Hair follicles → hair loss.

k Lymphatic system [which is responsible for the defense mechanism of the body ≠ foreign matter] " decrease in immunity & # susceptibility to infection.

f Bone marrow → aplastic anaemia, leukemia.

m Mucous membrane of the stomach " nausea & vomiting.

Cell Cycle Kinetics:



G_1	Pre-synthetic phase
S	Synthetic phase
G_2	Synthesis of cellular components
M	Mitotic phase
G_o	Resting phase

Classification of cytotoxic drugs according to chemical nature , pharmacological action & M.O.A :

- Alkylating agents.
- , Anti-metabolites [Specific S].
- *f* DNA intercalating agents.
- „ Antibiotics.
- … Antimitotic agents [Specific M].
- † Hormones.
- **p** Miscellaneous cpds.

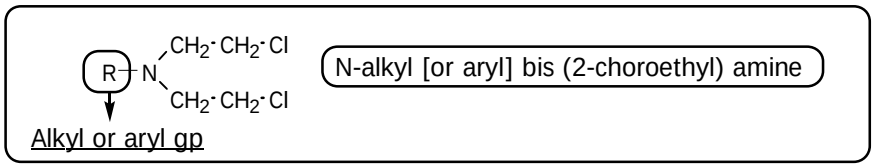
• Alkylating agents

- Act by alkylating DNA bases & nucleophilic attack on proteins.
- They includes:

[a] Nitrogen mustards. [b] Aziridines. [c] Alkyl sulphonates derivatives.
[d] Nitrosoureas. [e] Triazines.

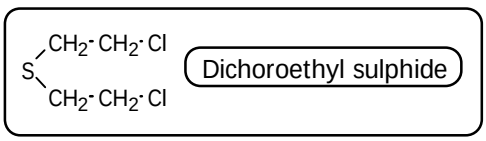
[a] Nitrogen mustard
[Bis (chloroethylamines)]

General formula:



History:

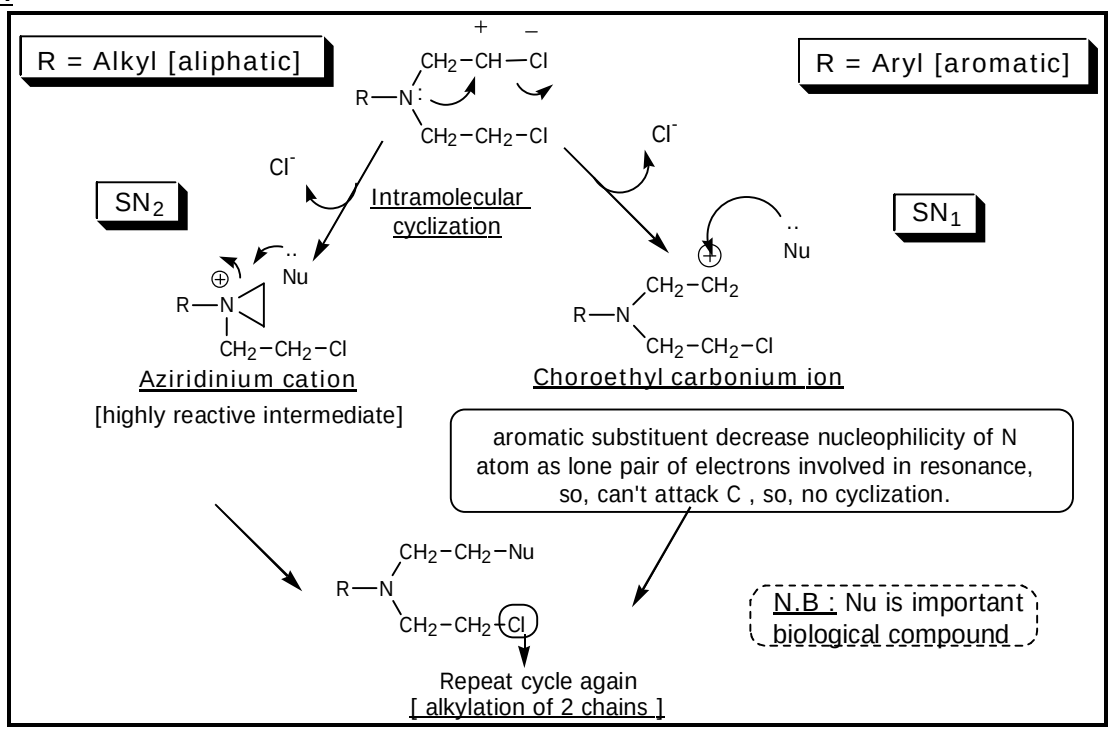
World War I : Usage of Sulphur mustard as *vesicant gas* [chemical warfare agent] →it was found to have sever *lymphoid aplasia* as well as pulmonary irritation.



So, we started clinical trials to find related but less toxic & more soluble derivative
This lead to development of nitrogen mustard from sulphur mustard **à** where, in addition to its vesicant effect on skin, they produce atrophy of lymphoid tissue & bone marrow.

Uses : limited to treatment of lymphomas especially Hodgkin's disease.

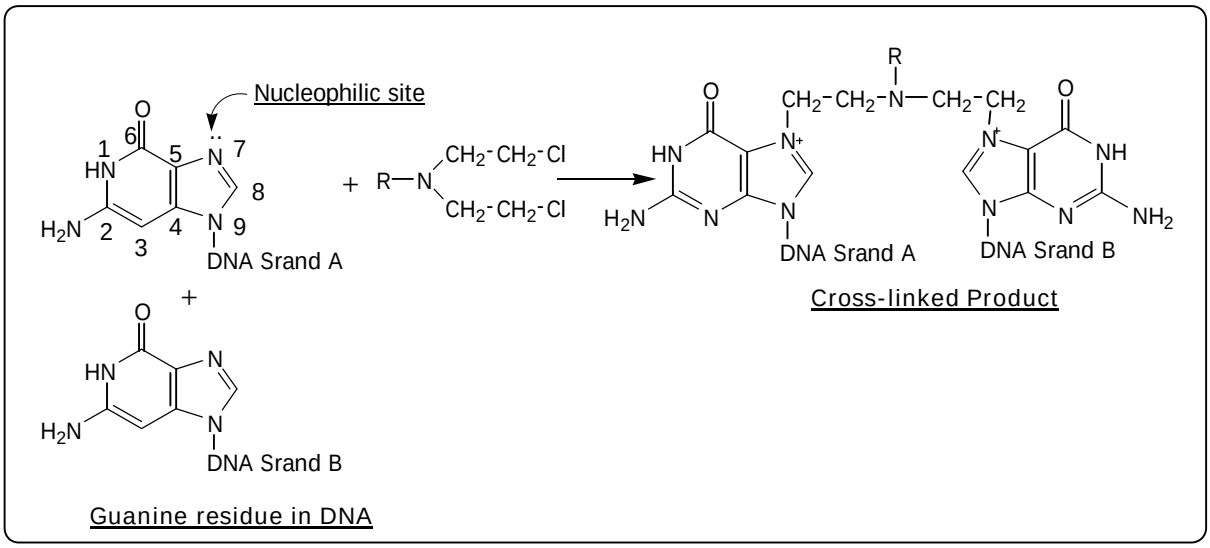
M.O.A.:



Examples on M.O.A. of nitrogen mustard agents:

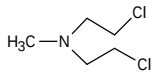
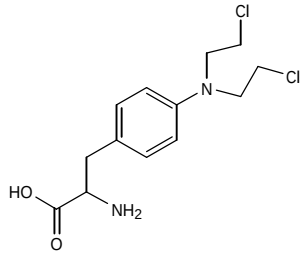
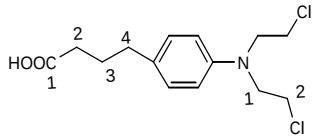
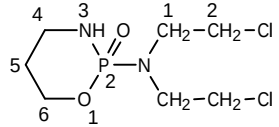
Alkylation of Guanine base of DNA:

Both aliphatic & aromatic nitrogen mustards react with 7-position of Guanine in each of double strands of DNA causing cross-linking [bifunctional alkylating agents], " interfere with separation of the strands " prevent mitosis.

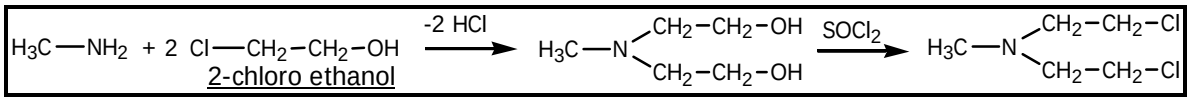


SAR of nitrogen mustards :

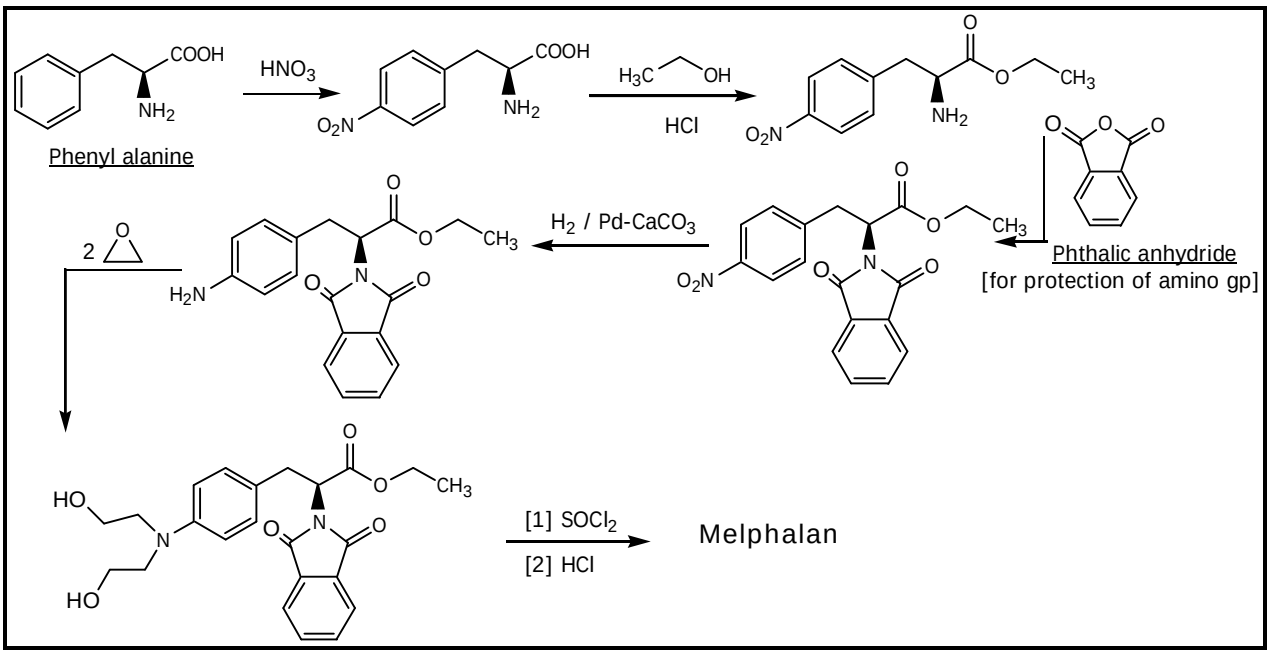
1. Bis (2-chloroethyl) is essential for activity.
2. Halogen other than chloride **à â** activity.
3. Ethylene moiety between the nitrogen & chloride is Essential for activity **à** due to formation of aziridinium ion.
   Methylene or trimethylene moiety **à** abolish this activity.

• Mechlorethamine [Mustine hydrochloride][HN2]	**k** Melphalan [Alkeran®]	**l** Chlorambucil [Leukeran®]	**m** Cyclophosphamide [Endoxan®]
 *N-methyl-bis-[2-chloroethyl] amine*	 *4-[bis (2-chloroethyl) amino] –L-phenylalanine* • Me too drug with phenylalanine substituting the methyl gp [e-donating] to N. • Mechanism : It's selective for *melanoma* cells due to presence of *phenyl alanine* which is the precursor of melanine " so, uptaked by these cells " DNA alkylation.	 *4-[4-[bis(2-chloroethyl) amino] phenyl] butyric acid.*	 *N,N-bis(2-chloroethyl) tetrahydro (2H)- 1,3,2-oxazo-phosphorin-2-amine-2-oxide.* [PRODRUG]
Route : I.V. infusion " strong vesicant that can't be taken orally.	Orally as HCl	Orally	Orally & parentrally → adv. over other alkylating agent.
Uses : • In Hodgkin's disease & non-Hodgkin's lymphomas.	**j** Skin cancer [melanoma cells]. Its designed ≠ melanoma tumor cells as phenylalanine derivative of nitrogen mustard. **k** Breast & ovarian cancer.	• In chronic lymphocytic leukemia. • Toxic effects: it's the *least toxic nitrogen mustard derivative, as it is the least active "act more slowly than others".*	• Lymphomas, leukemias, sarcomas & carcinomas of breast or ovaries. • Chlildhood malignancies.

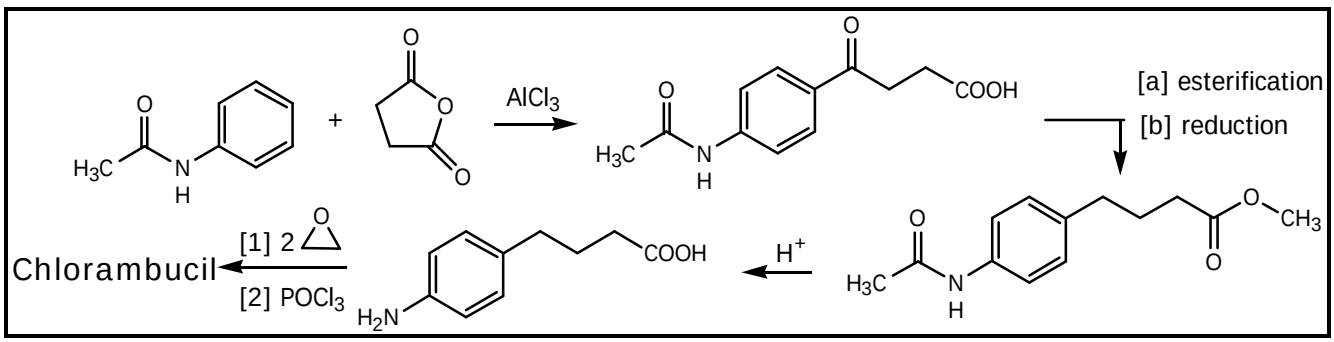
Synthesis of Mechlorethamine :



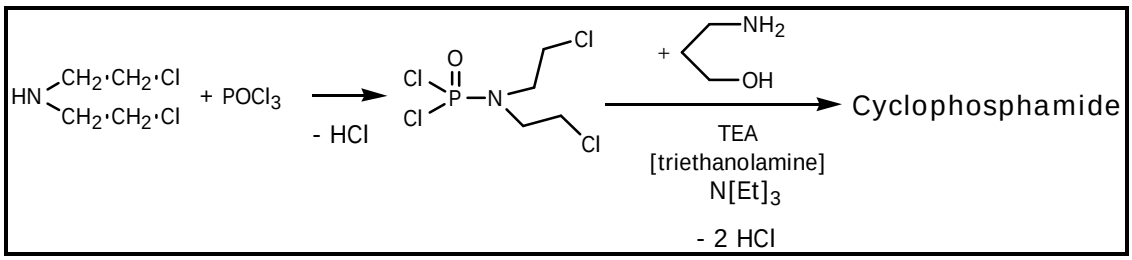
Synthesis of Melphalan :



Synthesis of Chlormabucil :

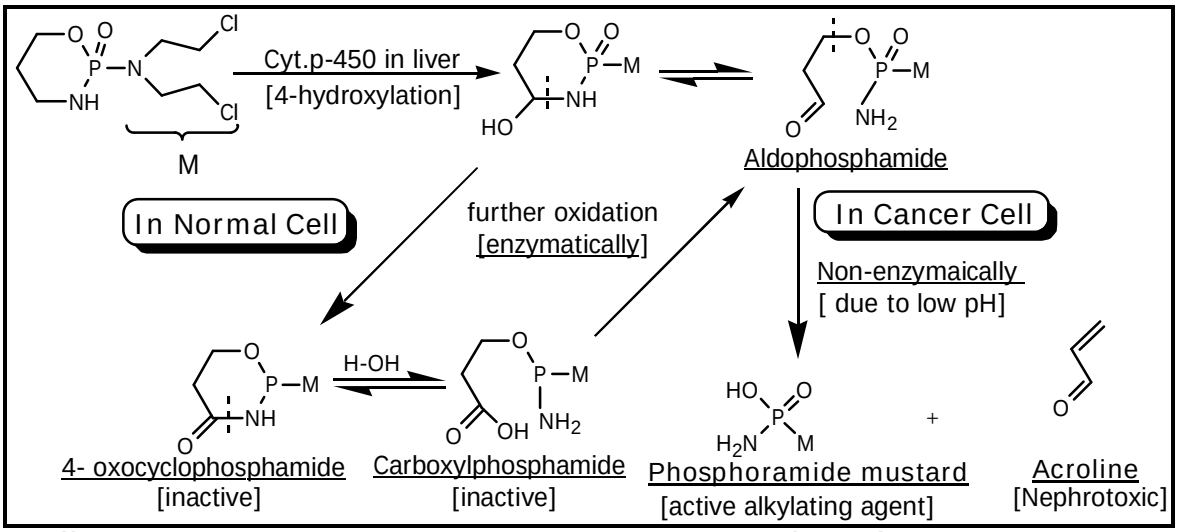


Synthesis of Cyclophosphamide :

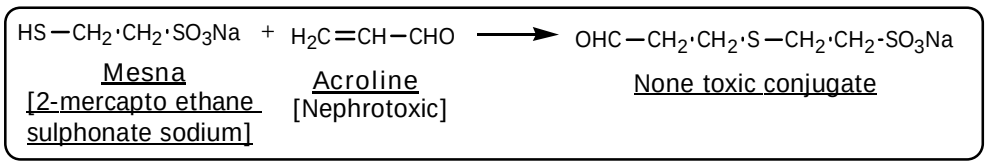


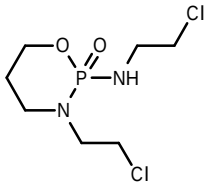
Biotransformation [Activation] of Cyclophosphamide:

Cyclophosphamide is inactive in vitro & must be converted to active form by metabolic process.



N.B. Acroline is nephrotoxic [cause cystitis], so, give N-acetylcystein or Mesna which are thiols to remove it as follow:

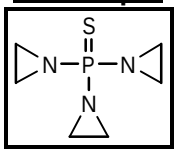


Ifosfamide	With the same M.O.A of Cylcophosfamide
	

[b] Aziridines

- They are strained ring system [aziridine ring].
- Activity of aziridine gp # by protonation.

Thiotepa



N,N',N''- triethylene thiophosphoramide.
OR Tris- [1-aziridinyl] phosphine sulphide.

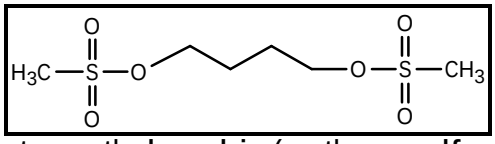
Uses :

- Breast & ovarian carcinomas.
- Malignant lymphoma.

N.B : thiotepa is most active at low pH.

[c] Alkyl Sulphonate derivatives

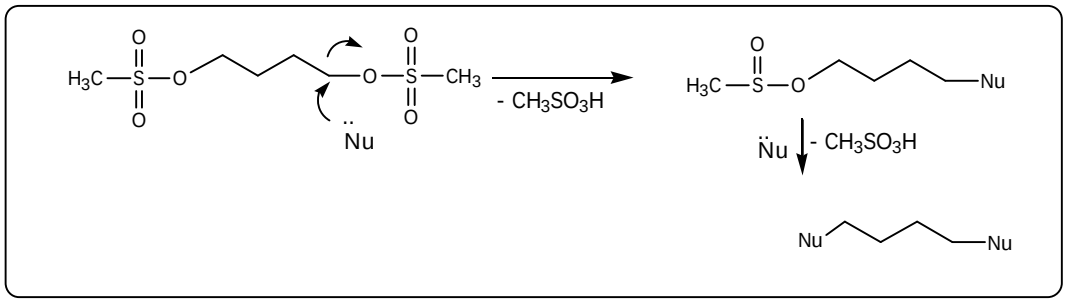
Busulphan [Myleran®]:



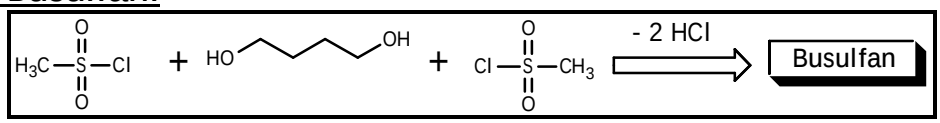
Tetramethylene-bis-(methane sulfonate)

M.O.A. :

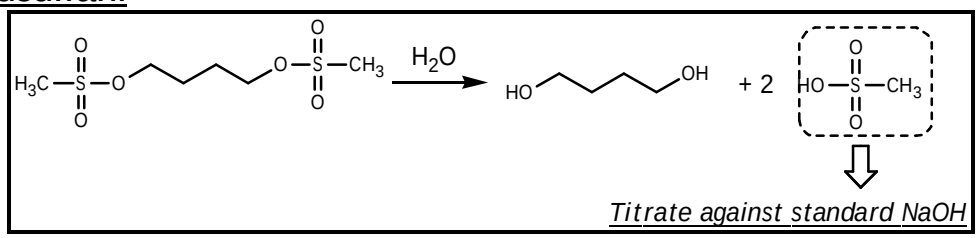
It undergo ionization to carbonium ion, then methyl sulphonate gp is displaced by Nu → Busulphan is a mono & bifunctional alkylating agent.



Synthesis of Busulfan:



Assay of Busulfan:

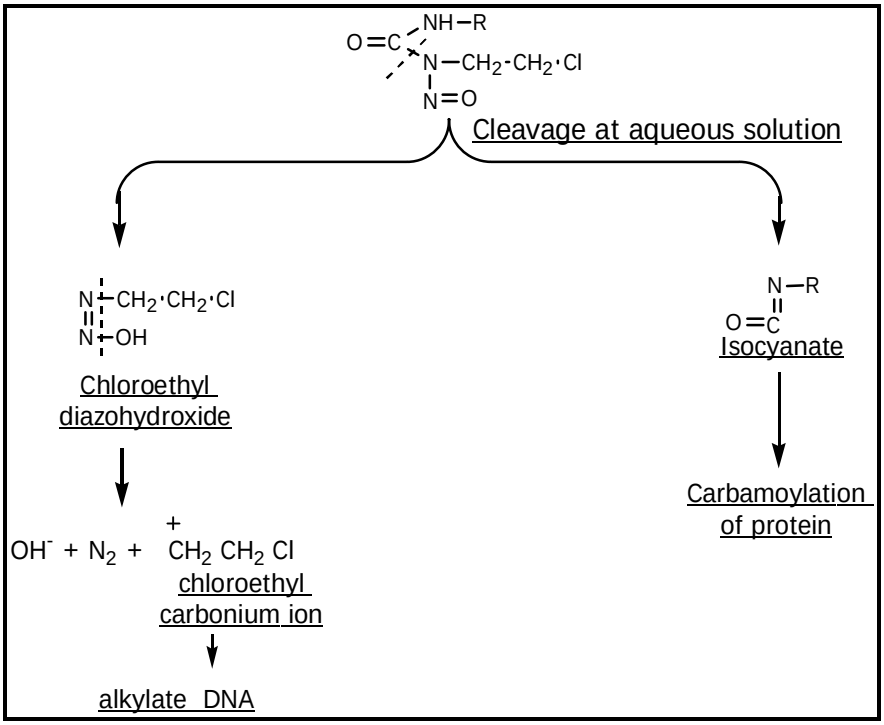


Uses:

Orally for chronic granulocytic leukemia.

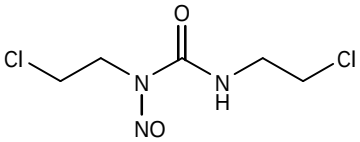
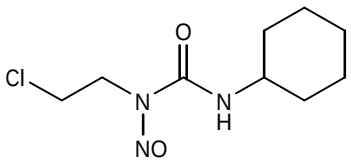
[d] Nitrosoureas

General M.O.A :



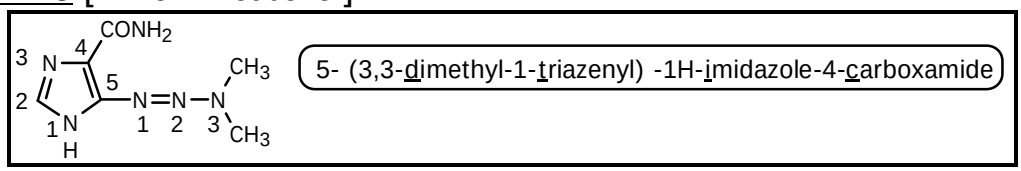
Uses :

1. Due to its high lipophilicity → it passes B.B.B. → used in brain carcinoma .
2. 2ry therapy of Hodgkin's disease & other leukemias.

Carmustine	Lamustine
	
1,3-bis(2-chloroethyl)-1-nitrosourea	1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea

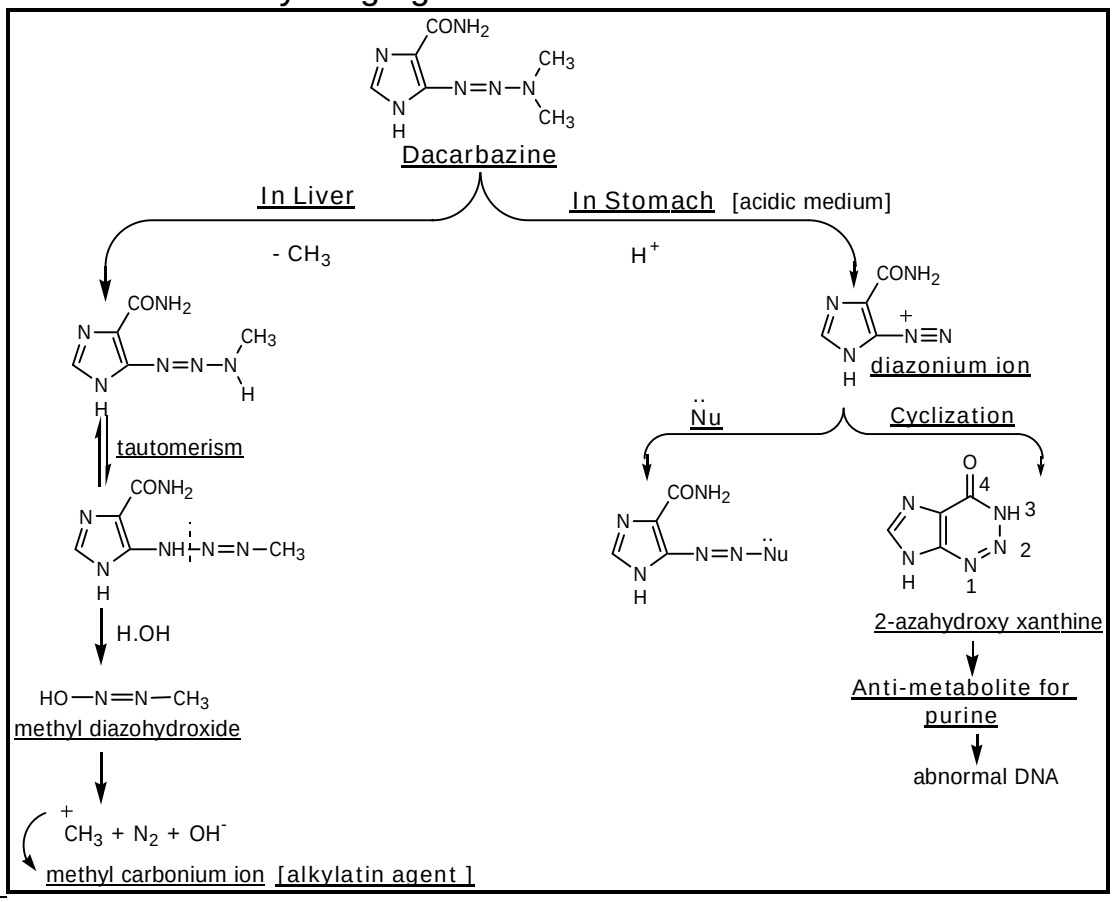
[e] Triazines

Dacarbazine [DTIC – Deticene]:

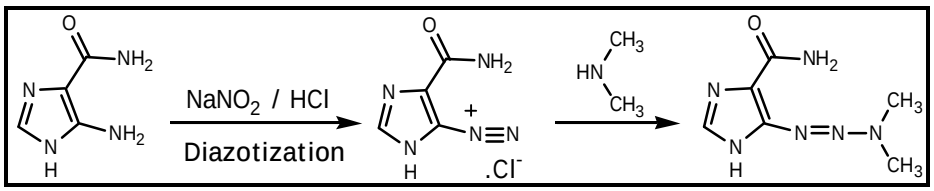


M.O.A.:

It's known to be both alkylating agent & anti-metabolite as follow:



Synthesis:



Uses : Parentrally [I.V]

1. For metastatic malignant melanoma.
2. In combination therapy for Hodgkin's disease.

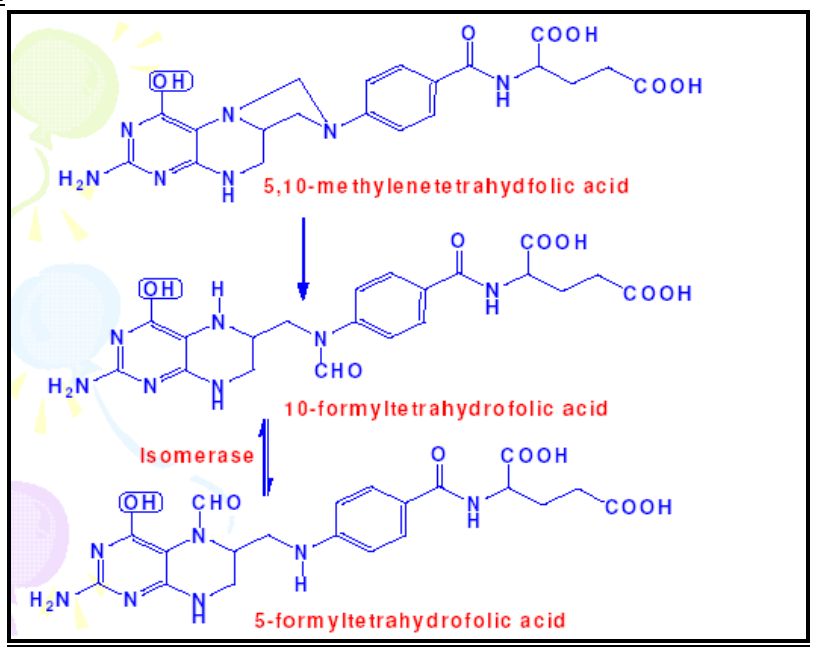
, Anti-metabolites

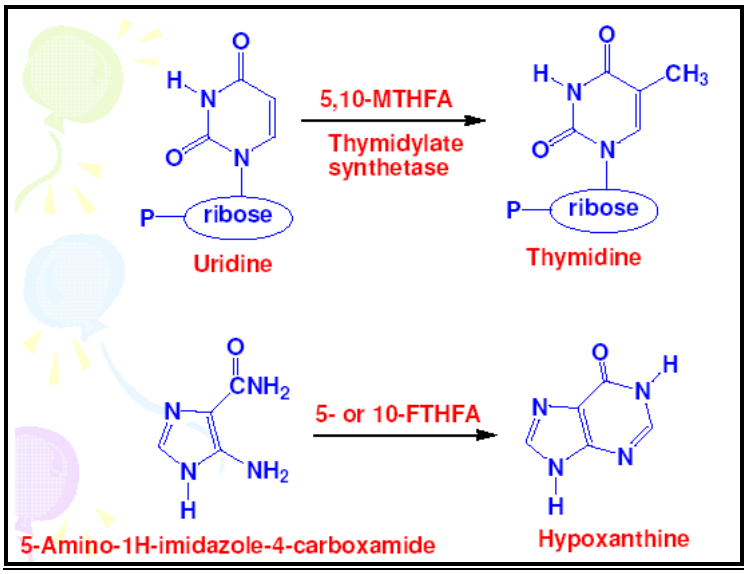
Definition:

- They are substances of structural similarity to normal metabolites → interfere with the utilization & biosynthesis of normal metabolites [as folate, purine & pyrimidine pathways that are required for DNA synthesis].
- Its selectivity ≠ cancer cells is due to differences in cell growth fractions.

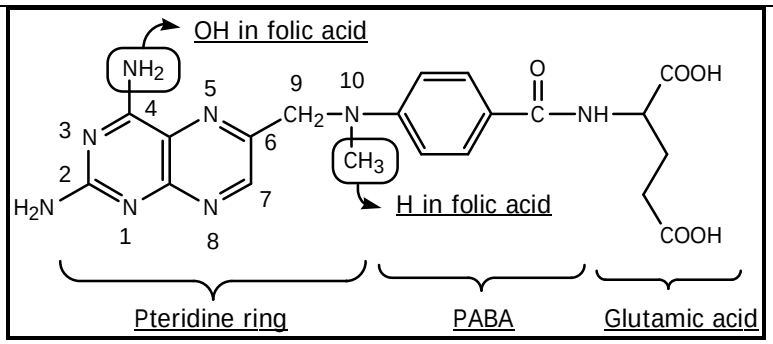
[a] Dihydrofolate reductase inhibitors

Role of folic acid:





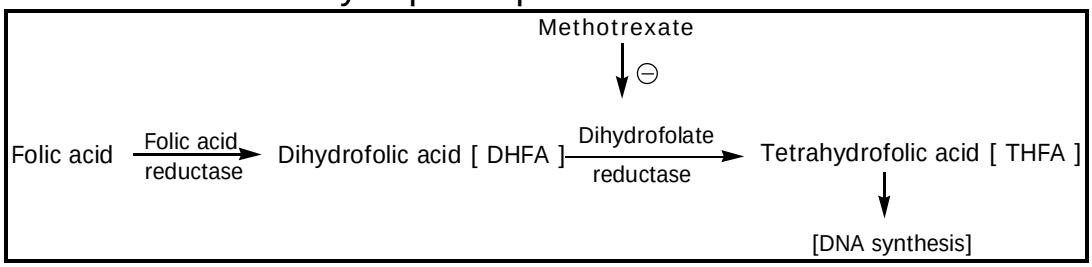
Methotrexate



L-(+)-N-{P-[[(2,4-diamino-6-pteridinyl)methyl] methyl amino] benzoyl }glutamic acid

M.O.A. of methotrexate :

• Methotrexate binds to dihydrofolate reductase 10^3 fold more firmly than DHFA, it bind in a stoichometric fashion to a hydrophobic pocket in DHFR.



Metabolism :

Mostly excreted in urine unchanged BUT following # dose therapy " 7-hydroxy methotrexate.

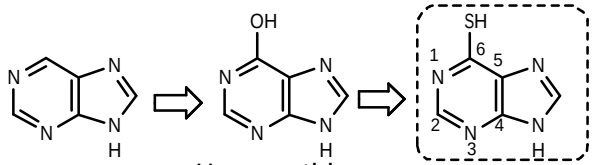
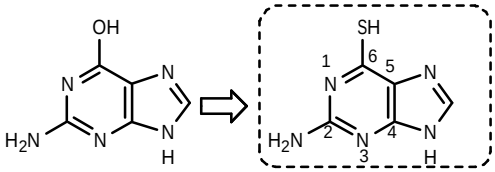
Resistance to Methotrexate by :

1. # DHFR which result from gene amplification.
2. $ its transport into tumor cells.

Route of administration : Orally or I.V.

Uses : For Acute Lymphocytic Leukemia.

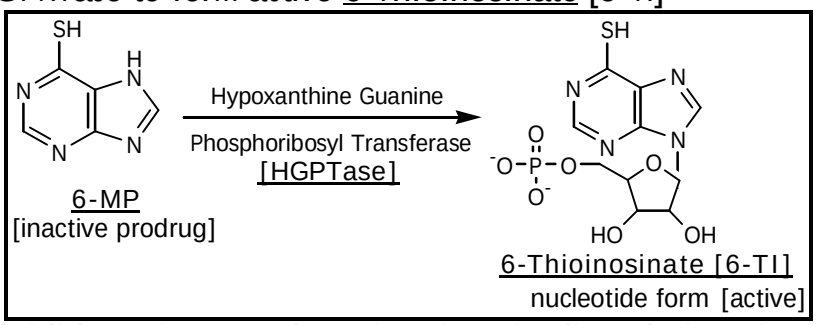
[b] Purine Antagonists

• 6-Mercaptopurine [6-MP]	, 6-Thioguanin [6-TG]
 Purine Hypoxanthine 6-MP	 Guanine 6-TG

- Interfere with purine biosynthesis & purine interconversion.
- Used orally for acute leukemia.
- Both are inactive until metabolized to respective monophosphate ribonucleotides by action of Hypoxanthine-Guanine Phosphoribosyl transferase [HGPRTase]

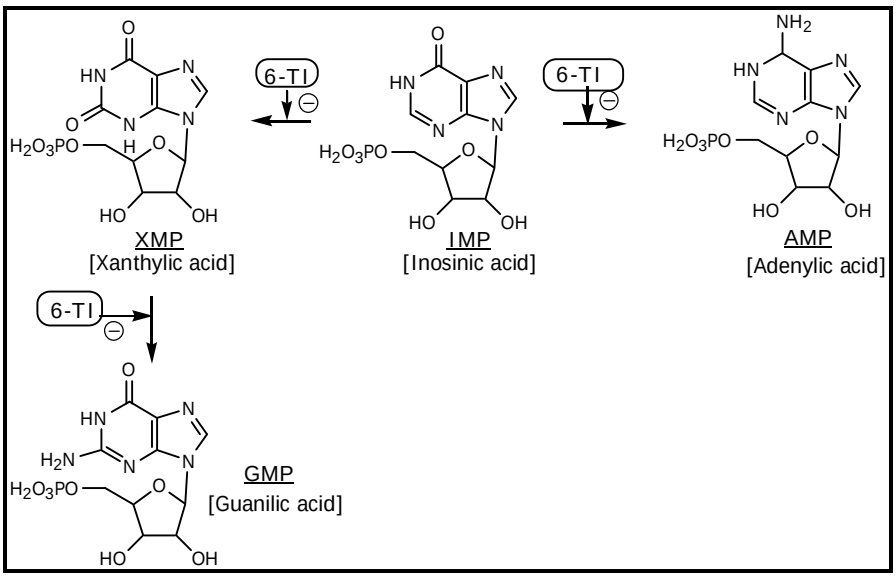
M.O.A. of 6-MP:

1) Activation by HGPRTase to form active 6-Thioinosinate [6-TI]



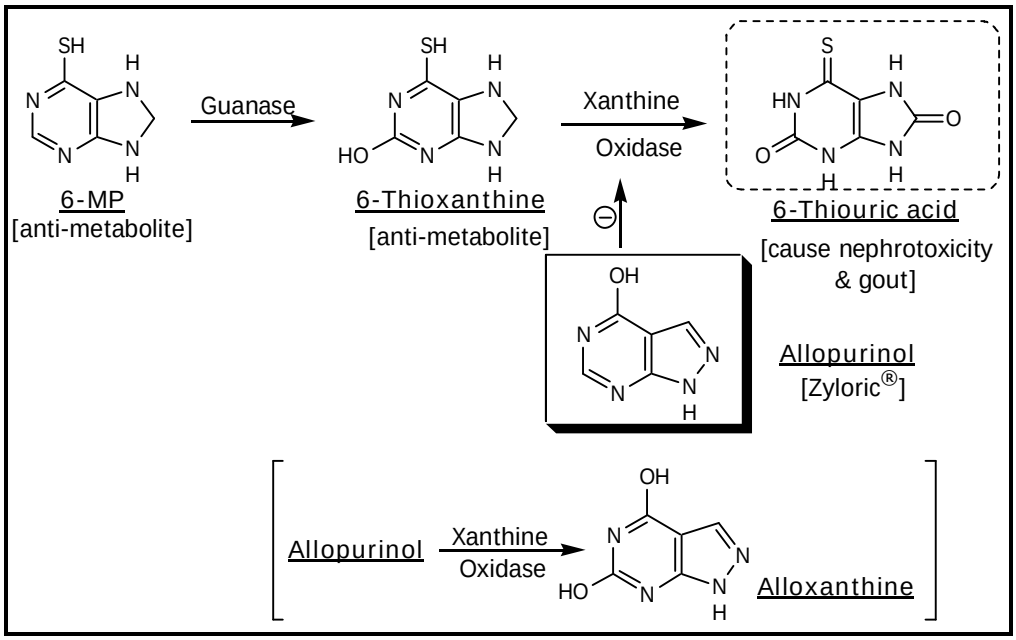
2) 6-TI is a potent inhibitor of conversion of 5-phosphoribosyl phosphate to 5-phosphoribosylamine [Rate controlling step in purine synthesis]

3) 6-TI **à** also inhibit conversion of of Inosine Monophosphate [IMP] to Adenine Monophosphate [AMP] & Xanthine Monophosphate [XMP] & limits availability of XMP to form Guanine Monophosphate [GMP] **à à** interfere with supply of purine precursors for nucleic acid synthesis.



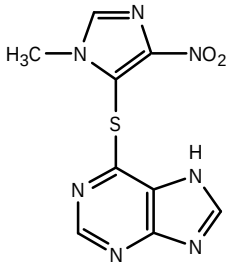
Catabolism of 6-MP:

1) By oxidation of 6-TI **à** 6-Thiouric acid [Gout & Nephrotoxicity].
2) So, Allopurinol is co-given **à** it's Xanthine Oxidase Inhibitor.
3) If give Allopurinol **à** inhibit metabolism of 6-MP **à á** toxicity, so, reduce dose of 6-MP by 25-30 % .



6-Thioguanine:

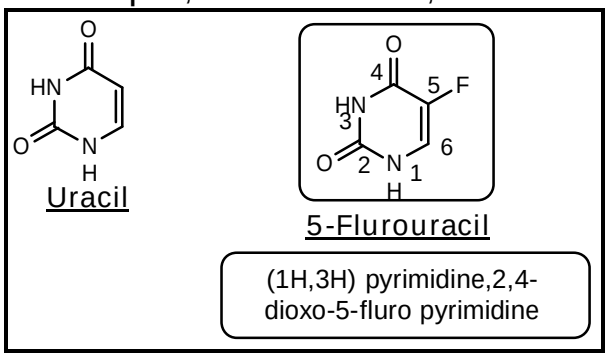
- When allopurinol is co-given with it [in case if cancerous patient is also with gout] **à** No need for dose reduction.
- With the same M.O.A. of 6-MP, differ only in: It's converted further into di- & tri-phosphate **à** incorporated in RNA structure & its deoxy form incorporated in DNA structure instead of normal Guanine **à** altered polynucleotide.

Azathioprine	
	Ø It's designed to protect 6-MP from catabolic reaction. Ø Not have better anti-cancer activity but used as immuno-suppressive in organ transplantation.

[c] Pyrimidine Antagonists

5-Flurouracil

[Flurouracil amp.® , Ezadex cream®, Effudex cream®]

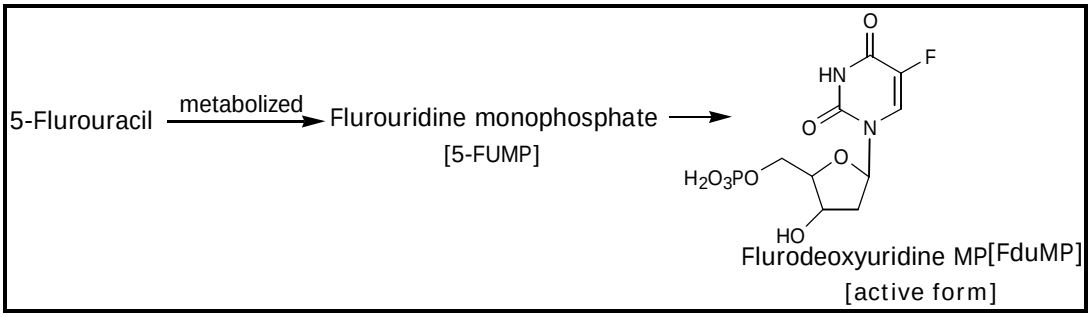


M.O.A.:

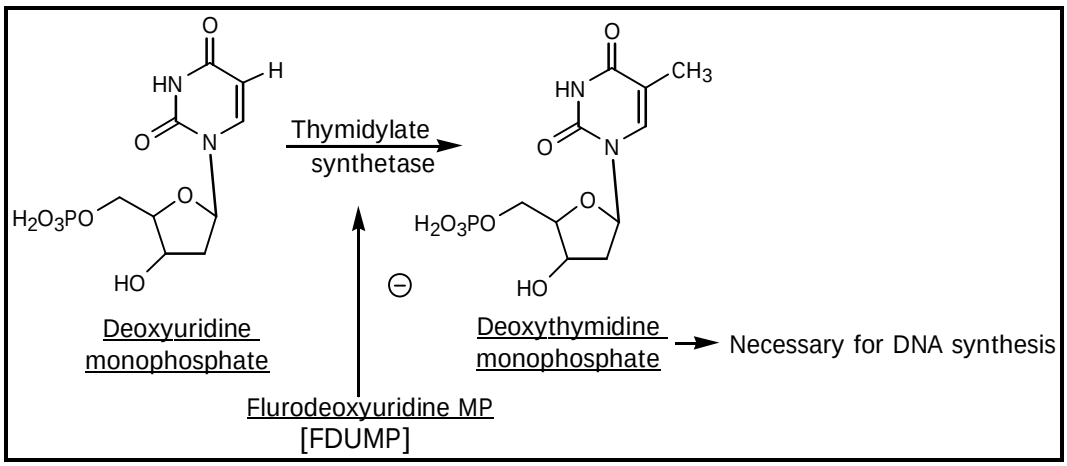
- It's anti-metabolite for thymine & uracil [Pyrimidine bases of DNA]:

C-F bond is extremely stable & prevent addition of methyl gp in 5-position " no formation of thymidine.

[a]



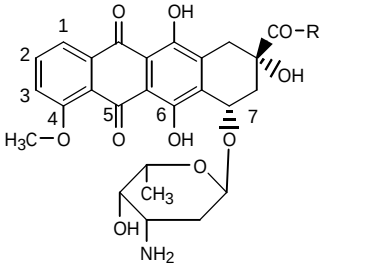
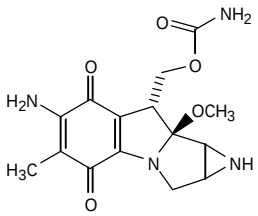
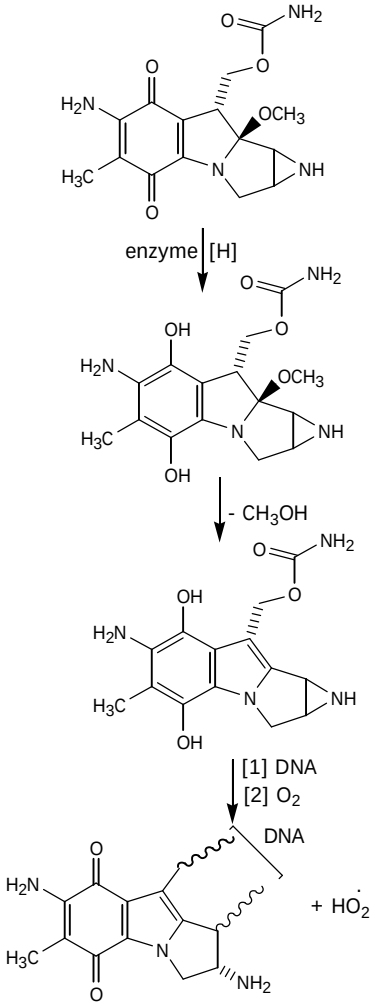
[b]



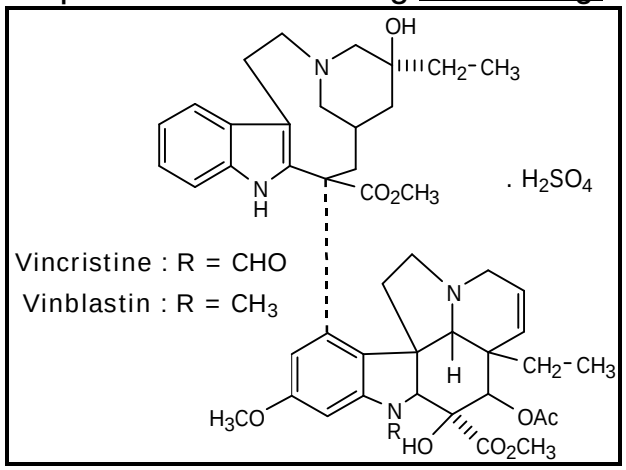
, Flurouridine monophosphate [FUMP] converted to triphosphate [FUTP] form which is incorporated in RNA causing error in base pairing during RNA transcription.

Uses : Parentrally [I.V] (although some 5-FU are absorbed orally)
for carcinoma of : breast, stomach, pancreas, colon & rectum in patients who can't be cured by surgery or other means.

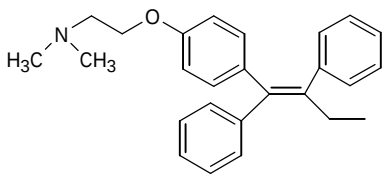
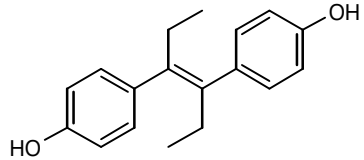
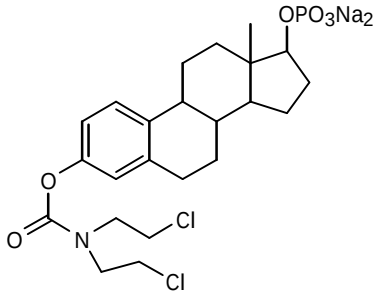
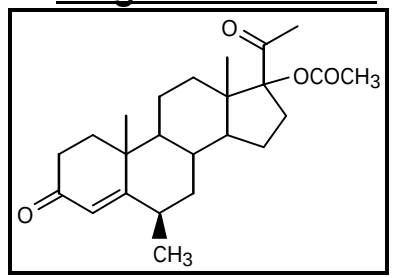
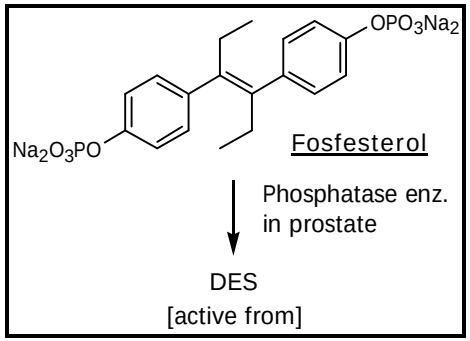
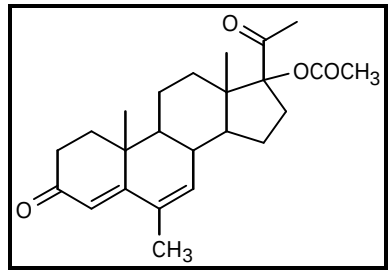
f Antibiotics

	[a] Anthracyclines [Doxorubicin & Daunorubicin]	[b] Mitomycin [Mitomycin C]
Structure	 R= CH_2OH ⟶ Doxorubicin R= CH_3 ⟶ Daunorubicin Planner anthraquinone nucleus attached to an amino sugar	
	Isolated from *Streptomyces peucetius.*	Isolated from *Streptomyces caespitosus.*
M.O.A.	1. DNA-RNA binding : they intercalate between base pairs on the double helix of DNA " partial unwinding of the helix " disrupt DNA polymerases & transcription. 2. Free Racidal Generation : F.R. formation which is highly reactive compounds with unpaired electrons " this occurs during the metabolism of anthracyclines. 3. Membrane interaction : anthracyclines bind to cell membrane " change in membrane glycoproteins, transmembrane flux of ions & membrane morphology. 4. Metal ion chelation : chelate divalent cations as Ca^{+2} & Fe^{+2} ions by quinine & phenolic functions.	 enzyme [H] - CH_3OH [1] DNA [2] O_2 DNA + $HO_2^{\cdot}$
	Uses : • Doxorubicin[Adriamycin®] " PARENTRALLY used in : 1. Solid tumors as carcinoma of breast, ovary, lung & thyroid. 2. Soft tissues sarcoma. • Daunorubicin[Daunomycin®] " PARENTRALLY in Acute lymphocytic & granulocytic leukemia.	

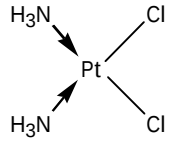
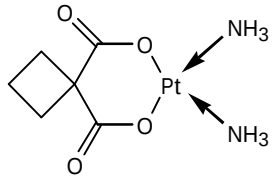
„ Aniti-Mitotic Agents

	• Vinca alkaloids	k Etoposide	l Taxanes Paclitaxel [Taxol®]
	• They are Vincristine & Vinblastin. • Family of important anti-tumor agents from plants. • With complex structure containing Indole Ring.  	Etoposide is semi-synthetic derivatives of podophyllotoxin which is a cytotoxic drug isolated from the root of May apple plant.	• One of the most important new classes of anti-tumor drugs. • Paclitaxel has been marketed in 1994 as Taxol®. • Isolated from the bark of yew tree & was produced semi-synthetically.
M.O.A	Bind to critical microtubular proteins within the cell which are essential contractile proteins of the mitotic spindle of dividing cells " mitotic arrest.	Cause metaphase arrest of the cell cylcle.	Act ≠ spindle assembly of dividing cells but in different fashion from that of Vinca alkaloids.
Uses	Vinblastin SO_4 [Velban®] [I.V.]: Used in testicular carcinoma. Vincristine SO_4 [Oncovin®] [I.V.]: • Acute lymphocytic leukemia. , Lymphomas, breast cancer, sarcomas & various childhood neoplasms.	Used in: [Orally & I.V] j Combination therapy ofTesticular carcinoma & aggressive forms of non-Hodgkin's lymphomas. k The most active single agent used in small-cell lung cancer.	Used I.V. in : • Ovarian & breast cancer. , Lung cancer & other cancers.

n Hormones

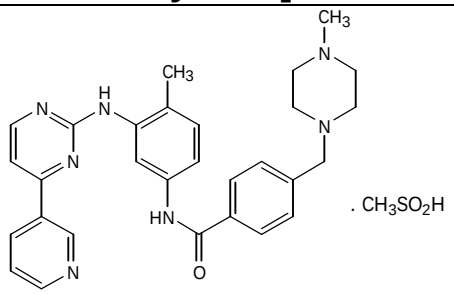
j Anti-estrogens	**k** Estrogens		**l** Progestins
Tamoxifen	Diethylstilbsterol [DES]	Estramustin Na_2PO_4	Megsterol acetate
			
Used in ttt of advanced breast cancer in postmenopausal women. N.B. # estrogen " breast cancer.	• Synthetic estrogen for prostate cancer. • S.E. feminization males. So, Fosfosterol is used w' target it to prostate tissue, as it's rich in phosphatase enz.  	• It's composeda of Nitrogen mustard + estradiol + phosphate ester. So, it's designed to targe nitrogen mustard to cells with estrogen receptors BUT it was found to act by Anit-Androgenic effect NOT by Alkylation. • Used for Prostatic Carcinoma	Medroxyprogesterone acetate  Used for endometrial carcinoma [they are used for cancer stimulated by estrogen] " act as anti-estrogenic by uncertain mechanism.

o Miscellaneous compounds

	• Heavy Metal Complexes		, Hydroxyurea [Hydrea®]
	Cisplatinum [Cisplatin®]	Carboplatin [Paraplatin®]	
Structure	 *Cis dichloro diamine platinum* The first heavy metal to be introduced as anti-cancer.	 *Cis-diamine(1,1-cyclobutane-dicarboxalato) platinum* Second generation cisplatin analogue with less nephorotoxic, neurotoxic & emesis action than parent compound.	
M.O.A	Potent inhibitor of DNA polymerase. Its activity & toxicity resemble alkylating agents " the 2 chlorine atoms are active & displaced by nitrogen or oxygen atoms of purines [Cross-linking].		Inhibit ribonucleotide reductase [which converts ribonucleotide to deoxyribonucleotide] " $ deoxyribonucleotide " inhibit DNA synthesis. * It may interfere with function of the enzyme by chelating with its Fe^{++} cofactor.
Uses	Parentrally in combination for : • Testicular & ovarian carcinoma. • Head & neck cancer. [highly active & curative].	• Ovarian cancer.	Orally for : • Melanoma. • Chronic myelocytic leukemia. • Metastatic ovarian carcinoma.

p New anti-neoblastic agents
Signal Transduction Inhibitors

Imatinib mesylate [Gleevec®]



4-[(4-methyl-1-piperazinyl) methyl] –N- [4-methyl -3- [[4-(3-pyridinyl) -2- pyrimidinyl] amino]- phenyl benzamide methansulfonate.

History:

- Identified in late 1990s by Dr. Brian J. Druker [Novartis].
- Started by identification of *bcr-abl* target.
- 1st they identify 2-phenyl amino pyrimidine **à** modification by addition of methyl & benzamide groups.

M.O.A. :

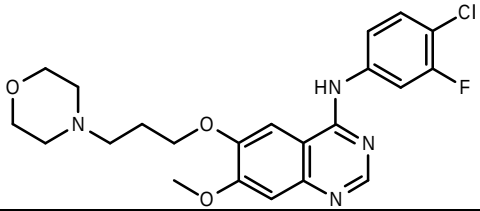
- Imatinib inhibit abnormal protein tyrosine kinase [termed *bcr-abl*] produced by Philadelphia chromosome abnormally in CML [Chronic Myeloid Leukemia] " inhibit proliferation & induce apoptosis in leukemic cells.

N.B. : Protein tyrosine kinase is important in transduction of signals initiating cell replication & transformation.

Uses :

Orally for CML [Chronic Myeloid Leukemia].

Gefitinib [Iressa®]



- The only indicated for treatment of locally advanced or metastatic non-small cell Lung Cancer [NSCLC] in patients who have previously received chemotherapy.
- It's the 1st selective inibitor of Epidermal Growth Factor Receptor [EGFR] tyrosine kinase [the target protein tyrosine kinase is referred to Her1 or ErbB-1].
- Used in treatment of other cancers where EGFR over expression is involved.