Structure of Estrogeic Steroids 18 carbon skeletons; A ring aromatic, absence of CH₃ at 19 position; presence of oxygen substituents at the 3 and 17-positions; estradiol is the most important estrogenic steroid.

Pharmacologic Activities of Estrogenic Steroids Together with progesterone, estrogens are female sex hormones responsible for reproduction and development of secondary sexual characters; Both play a major role in the female reproductive process (ovulation, pregnancy); Follicle stimulating hormone and luteinizing hormone (peptides) control the ovary and production of sex hormones. Both together bring about ovulation and secretion of estrogens and progestins. A negative feedback from sex hormones works to inhibit secretion of FSH and LH. Following ovulation, luteinization of ruptured follicle occurs to form corpus luteum. The process then moves towards menses. Levels of estrogens and progestins decline. In absence of pregnancy, levels of sex hormones remain low and therefore there is no feedback inhibition, so a new cycle is started. If pregnancy occurs, human chorionic gonadotrophin (hCG) is released which prolongs the life of corpus luteum. This maintains high sex hormone levels and thus retain feedback inhibition of FSH and LH. This inhibits ovulation and contractions.

Biosynthesis and Metabolism of Estrogens

Important Features in the Structure of Estradiol that give Activity

Synthetic Estrogens

Ethinyl estradiol  R = H
Mestranol     R = CH₃
Diethyl stilbestrol
Dienestrol
Chlorotrianisene
**Schüler’s Hypothesis** states that structures that mimic the oxygen at C-3 and hydrogen bonded water molecule at C-17β are estrogenic. DES are estrogenic because the phenolic oxygens are positioned exactly where the two important estrogenic oxygens should be.

**Estrogen Antagonists**

*Estrogen Derivatives*

ICI 164,384

ICI 182,780

*Triphenylethylene Derivatives*

Enclomiphene

Zuclomiphene

Tamoxiphen

4-Hydroxy tamoxiphen

*Selective Estrogen Receptor Modulators*

Raloxifene

Nafoxidine

**Points to Ponder**

- What are estrogenic steroids? What are their activities? What class of steroids do estrogens belong to?
  What is the need to make synthetic estrogens? What structural change introduces oral activity in this class of compounds? How can anabolic activity be separated from androgenic activity? What are androgenic antagonists? Against what disease state or disorder do they function? Develop a skill for identifying function activity of steroids from structure.
- Predict whether the following steroids will be estrogenic if taken orally.