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MEDICINAL CHEMISTRY - II

UNIT 4

TOPIC :

- **Oral contraceptives : Mifepristone, Norgestril, Levonorgestrol**



Oral Contraceptives

- Oral contraceptives (OCPs) are drugs taken orally to prevent pregnancy.
- They work mainly by inhibiting ovulation and altering cervical mucus and endometrium to prevent fertilization and implantation.
- Types:
 1. Combined Oral Contraceptives (COCs): Contain estrogen + progestin
 2. Progestin-only Pills (POPs / Mini-pill): Contain progestin only

Mechanism of Action

A. Combined Oral Contraceptives (COCs)

1. Inhibit ovulation:
 - Estrogen and progestin suppress FSH and LH → prevent follicle maturation and LH surge → no ovulation.
2. Cervical mucus thickening:
 - Progestin makes mucus thicker, hindering sperm penetration.
3. Endometrial changes:
 - Progestin causes endometrial atrophy, reducing implantation potential.

B. Progestin-only Pills (POPs)

- No ovulation in some cycles, primarily thicken cervical mucus and alter endometrium.
- Useful in breastfeeding women because they do not affect milk production.

Classification

Type	Composition	Examples	Main Use
Combined Oral Contraceptives (COCs)	Estrogen + Progestin	Ethinylestradiol + Levonorgestrel / Norgestimate	Prevent pregnancy, regulate cycles
Progestin-only Pills (POP)	Progestin only	Norethisterone, Levonorgestrel	Pregnancy prevention, breastfeeding women
Emergency Contraceptive Pills (ECPs)	High-dose progestin ± estrogen	Levonorgestrel, Ulipristal acetate	Prevent pregnancy after unprotected intercourse

Clinical Uses

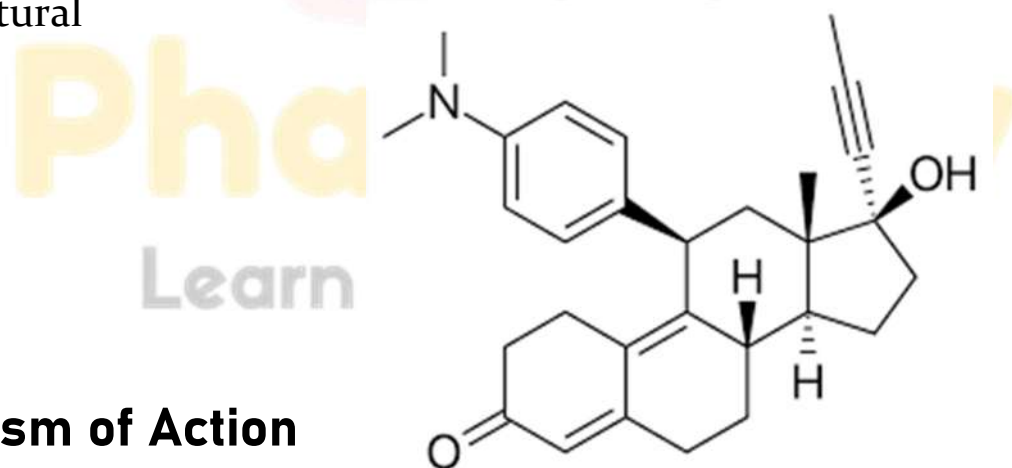
1. Contraception: Primary use
2. Regulation of menstrual cycles: Oligomenorrhea, dysmenorrhea
3. Treatment of hormonal disorders: Polycystic ovary syndrome (PCOS), endometriosis
4. Reduction of risk: Ovarian and endometrial cancers

Mifepristone

- Mifepristone is a synthetic steroidal antiprogesterone, also known as the “abortion pill”.
- Developed to block the action of progesterone, essential for maintaining pregnancy.
- It is used for medical termination of early pregnancy, induction of labor, and management of Cushing’s syndrome (as a glucocorticoid receptor antagonist).
- Administered orally and often combined with misoprostol for medical abortion.

Chemical Structure

- Chemical name: 11β -(4-(dimethylamino)phenyl)-17 α -hydroxy-17-(1-propynyl)estra-4,9-dien-3-one
- Molecular formula: $C_{29}H_{35}NO_2$
- Molecular weight: 429.6 g/mol
- Chemical class: Steroidal antiprogesterin; 19-norprogesterone derivative
- Structural



Mechanism of Action

- Target: Progesterone receptors (PR) in uterus, endometrium, and other target tissues

Stepwise Mechanism:

1. Mifepristone competitively binds to progesterone receptors, preventing endogenous progesterone from binding.

2. In the endometrium:
 - Decidual breakdown occurs → uterine lining cannot support pregnancy
 - Increased prostaglandin production → uterine contractions
3. In cervix:
 - Softening and dilation occur → facilitates expulsion of uterine contents
4. In placenta:
 - Trophoblastic detachment occurs → termination of pregnancy

Additional Action:

- At higher doses, Mifepristone acts as a glucocorticoid receptor antagonist, useful in Cushing's syndrome.

Synthesis

1. Starting material: 19-norprogesterone or related steroidal precursors
2. Step 1: Introduction of 11 β -(4-dimethylaminophenyl) group via arylation
3. Step 2: Introduction of 17 α -propynyl group
4. Step 3: Oxidation and double bond formation at C₄-C₅ and C₉-C₁₀
5. Purification: Crystallization to yield pharmaceutical-grade mifepristone

Uses

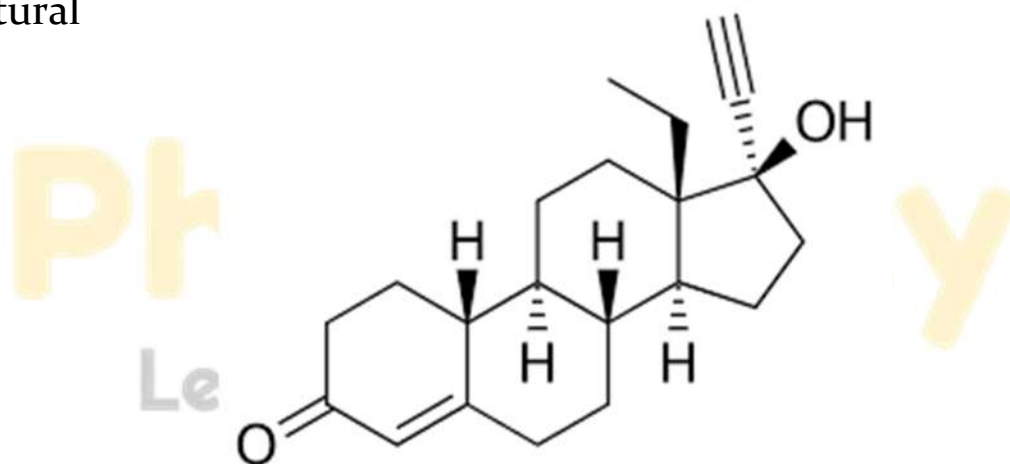
- Therapeutic Uses:
 1. Medical termination of intrauterine pregnancy (up to 10 weeks gestation)
 2. Labor induction (in combination with prostaglandins)
 3. Cushing's syndrome (glucocorticoid receptor antagonist)
 4. Emergency contraception (off-label in certain countries)

Norgestril

- Norgestril is a synthetic progestin, belonging to the 19-nortestosterone derivative class.
- It is used primarily as a component of oral contraceptives due to its progestational activity.
- Norgestril exhibits strong progestogenic effects with minimal androgenic or estrogenic activity.
- It is mainly available in combination formulations with ethinylestradiol.

Chemical Structure

- Chemical name: 13-Ethyl-17 α -ethynylgon-4-en-17 β -ol
- Molecular formula: C₂₁H₂₆O
- Molecular weight: 302.44 g/mol
- Chemical class: 19-nortestosterone derivative; synthetic progestin
- Structural



Mechanism of Action

- Target: Progesterone receptors (PR) in reproductive tissues

Stepwise Mechanism:

1. Norgestril binds to nuclear progesterone receptors, mimicking natural progesterone.

2. Hormone-receptor complex modulates gene transcription in endometrial and hypothalamic cells.
3. Physiological effects:
 - Endometrium: Converts proliferative endometrium into secretory type → prevents implantation
 - Hypothalamic-pituitary axis: Inhibits gonadotropin release → prevents ovulation
 - Cervix: Thickens cervical mucus → reduces sperm penetration
 - Uterus: Alters motility, preventing fertilization/implantation

Synthesis

1. Starting material: Testosterone or related 19-nortestosterone derivatives
2. Step 1: Removal of C₁₉ methyl → 19-nor derivative
3. Step 2: Introduction of 17 α -ethynyl group → improves oral bioavailability
4. Step 3: Purification and crystallization → Norgestril

Uses

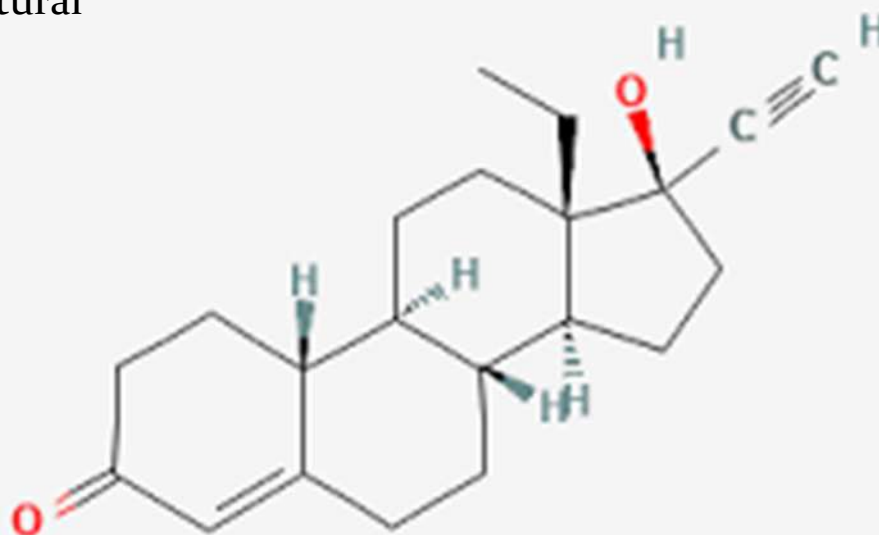
- Therapeutic Uses:
 1. Oral contraception (mainly in combination with ethinylestradiol)
 2. Hormonal therapy for menstrual disorders (rare)
 3. Endometriosis and dysmenorrhea (off-label, less common)

Levonorgestrel

- Levonorgestrel (LNG) is a synthetic progestin of the 19-nortestosterone group.
- It is highly potent and used in contraception, both emergency contraception and long-term hormonal contraceptives.
- Exhibits strong progestational activity with minimal androgenic effects.
- Available in oral, intrauterine, and implant formulations.

Chemical Structure

- Chemical name: (17 α)-17-ethynyl-18-methyl-19-nortestosterone
- Molecular formula: C₂₁H₂₈O₂
- Molecular weight: 312.45 g/mol
- Chemical class: 19-nortestosterone derivative; synthetic progestin
- Structural



Mechanism of Action

- Target: Progesterone receptors (PR) in reproductive tissues

Stepwise Mechanism:

1. Levonorgestrel binds to nuclear progesterone receptors, mimicking natural progesterone.

2. Hormone-receptor complex modulates gene transcription in endometrial and hypothalamic cells.
3. Physiological effects:
 - Endometrium: Converts proliferative endometrium into secretory type → prevents implantation
 - Hypothalamic-pituitary axis: Inhibits gonadotropin release → prevents ovulation
 - Cervix: Thickens cervical mucus → reduces sperm penetration
 - Uterus: Alters motility → prevents fertilization/implantation

Synthesis

1. Starting material: 19-nortestosterone derivatives
2. Step 1: Removal of C₁₉ methyl → 19-nor derivative
3. Step 2: Introduction of 17 α -ethynyl group → increases oral bioavailability
4. Step 3: Introduction of 18-methyl group → enhances progestational activity
5. Purification: Crystallization → Levonorgestrel

Uses

- Therapeutic Uses:
 1. Oral contraceptives (combined or progestin-only pills)
 2. Emergency contraception (single high-dose or multiple-dose regimen)
 3. Intrauterine device (IUD) → levonorgestrel-releasing system
 4. Subdermal implants for long-term contraception
 5. Menstrual disorders (off-label, e.g., heavy menstrual bleeding)