CHAPTER 1

1.1 : NON-STEROIDAL CONTRACEPTIVE HETEROCYCLES

1.1.1 : Monocyclic heterocycles

1.1.2 : Bicyclic heterocycles

1.1.3 : Polycyclic heterocycles

1.2 : BASIS OF WORK
1.1 NON-Steroidal Contragestational Heterocycles

Chemical agents which provoke pregnancy failure by creating a situation in which the proper endocrine requirements have been disturbed to cause directly or indirectly antizygotic, blastolytic, blastotoxic or abortifacient activities, are termed as contragestational agents. Control of population, a prime need of the present age, may be achieved by these agents but the small and definite incidence of serious side-effects resulting from these agents should be carefully studied since inhibition of pregnancy must lead to minimum physiological insult. The most common type of contragestational agent effective by oral route of administration (oral contraceptives) represent a combination of an estrogen and a progestin since a progestin or an estrogen alone is clinically less acceptable. However, the need for a second generation of oral contraceptives has been realised because agents which do not exhibit any hormonal or antihormonal effect but are capable of evoking selective physiological imbalance in the uterus to cause pregnancy failure would be more acceptable. A desirable choice for designing a such contragestational agents are heterocycles and this has prompted to review the earlier reports of the contragestational efficacy of heterocycles and a brief report of the same is presented here.

1.1.1 Monocyclic heterocycles

The most conspicuous non-hormonal contraceptive agents, developed by Omodei-sale et al, are represented by 3,5-disubstituted-1H-1,2,4-triazoles (1). These inhibit pregnancy in hamsters at a dose of 5 mg/kg P.O. A more effective compound of this series,

\[ R = C_{1-4}^{\text{-alkyl}}; R^1 = H, F, Cl, MeO, EtO, C_{1-4}^{\text{-alkyl}}; \\
R^2 = H, F, Cl, C_{1-4}^{\text{-alkyl or alkoxy}}; R^2 R^3 = OCH_2O \]
namely \(3-(2\text{-ethylphenyl}-5\text{-}(3\text{-methoxyphenyl})-1H-1,2,4\text{-triazole}\) (2),
developed by Galliani et al\(^3\), exhibits antifertility effect by acting on the uteroplacental unit (UPU), resulting in resorption or expulsion of the conceptuses. This compound is active whether given orally, subcutaneously, intramuscularly or intravaginally but the requirement of a very high oral dose limits its usefulness. Another derivative of (R = CH\(_3\); R\(^1\), R\(^2\), R\(^3\) = H) also exhibits significant pregnancy terminating activity\(^3\). The ED\(_{50}\) values are 0.3 mg/kg/day s.c. in hamsters and 2 mg/kg/day s.c. in rats. Instead of three nitrogen atoms in the heterocyclic ring, pyrazole derivative (3) with two nitrogen atoms also exhibits pregnancy terminating activity\(^4\) and the reported ED\(_{50}\) values are 3 mg/kg/day in hamsters and 25 mg/kg/day in rats.

Oral administration of a representative of six-membered heterocycles namely 2', 3', 5'-tri-O-acetyl-6-azurine (4), at a dose of 300 mg/kg on days 8, 9, 10, 11 and 12 of pregnancy in rabbits, have been reported to inhibit pregnancy\(^5\) in all cases while derivatives of 2-[\(\alpha\text{-}(\text{orthosubstituted benzimidoyl})\text{benzyl}]\text{pyridine (5)} have been found to inhibit ovulation\(^6\).
1.1.2 Bicyclic Heterocycles

Compared to monocyclic heterocycles, more number of bicyclic heterocycles have been evaluated for their antifertility activity. Of these 3-(2-benzofuranyl)-3-alkyl-2,2-dimethyl propionic acids (6), substituted 2-anilino benzoxazoles (7) and 2-benzoyl-3-phenyl benzothiophene (or benzothiophene oxide) derivatives (8) have shown pregnancy inhibiting activity in rats.

\[
\begin{align*}
\text{6} & \quad \text{R} = \text{H, Me; } \text{R}^1 = \text{H, OMe; } \\
& \quad \text{R}^2 = \text{Me, Et; } \text{R}^3 = \text{R}^4 = \text{H} \\
\text{7} & \quad \text{R} = \text{H, alkyl, alkoxy, alkylxoy, CO}_2\text{H} \\
\text{8} & \quad \text{R, } \text{R}^1 = \text{OH, H, alkoxy; } \\
& \quad \text{R}^2 = \text{H, Cl, Br, OH, alkoxy; } \\
& \quad \text{R}^3 = \text{H, Pyrrolidinoethoxy; } \\
& \quad n = 0, 1
\end{align*}
\]

Derivatives of 2-aroyl-3-phenyl benzothiophenes (9) at 1 mg/day S.C. and 1,2-diphenyl-1,2,3,4-tetrahydroquinoline (10) at 50-100 mg in rats have been reported to prevent pregnancy.
R = H, 4-OMe, 4-OH, 4-Cyclo-
  phentyloxy, 3-OMe, 3-OH,
  2-OMe, 2-OH, 3-Cl, 4-Cl;
R^1 = H, OMe, OH

Bicyclic compounds such as indazole derivatives\(^\text{12}\) (\(\text{11}\)) and 1,2-diphenylindoles\(^\text{13}\) (\(\text{12}\)) also exhibit contraceptive activity.

\[\text{11} \]

\[\text{12} \]

\[ R = \text{Me, Ph, CH}_2\text{CHCH}_2\text{, Et;} \]
\[ R^1 = \text{Me, H, HC; CCH}_2, \text{H}_2\text{C:CHCH}_2\text{Ph} \]
\[ R^2 = \text{Cyclohexyl, Me}_2\text{CHCH}_2\text{Ph} \]
\[ R^3 = \text{H, CN} \]

\[ R = \text{MeO;} R^1 = \text{Et}_2\text{NCH}_2\text{CH}_2 \]

A chroman derivative namely 3,4-trans-2,2-dimethyl-3-phenyl-4-\(p\)-
(\(\beta\)-pyrrolidinoethoxy)phenyl]-7-methoxychroman\(^\text{14}\) (\(\text{13}\)) prevents conception at a single oral dose of 1.25 mg/kg in rats and mice and 2.5 mg/kg in dogs and rhesus monkeys immediately postcoitum. It also possesses estrogen, antiestrogen and antiprogestational properties.
The isoquinoline derivative, 1-N-methylpiperazine-2-chloro-4-nitroisoquinoline (14), exhibits anti-implantation activity in rats at $\geq 50$ mg/kg with maximum activity on days 4, 5 and 6 of pregnancy. Another class of bicyclic nitrogen heterocycles such as 3-[p-(ω-substituted aminoalkoxy)benzoyl]indoles (15) and α-methylarylamido-β-naphthyl(1-methylamino-2-methylbenzimidazolyl) ethers (16) possess anti-implantation activity in albino female rats.

A bicyclic sulphur containing heterocycle, 2-Phenyl-3-aroyl benzothiophenes (17), at 1 mg/kg/day S.C. in rats for 15 days completely inhibits fetus development.
1.1.3 Polycyclic Heterocycles:

A wider variety of tricyclic and/or polycyclic heterocycles exhibit antifertility activity. Tricyclic nitrogen containing compounds such as 18-24 are reported\(^1\) to be useful contraceptives.

Of the polycyclic oxygen containing heterocycles, benzofurobenzopyranones (25) cause ≤ 83.3% inhibition of fetal implantation at 10 mg/kg i.p. in rats\(^2\) and several derivatives of the nitrogen containing heterocycle 26 are luteolytic in rabbits at a dose of 1 mg/day for 14 days\(^2\).
Several substituted indeno, naphtho and cyclohepta pyrazoles (27) exhibit antifertility activity in rats at a dose of 1-100 mg/day\(^2\) and triazolisoindole derivatives (28) are postcoital contraceptives in rats. The ED\(_{50}\) values range between 1-10 mg/kg s.c.\(^2\).

R = 4-pyridyl
R\(^1\) = R\(^2\) = H;
n = 2

Nitrogen and sulfur containing heterocycles such as thieno [2,3-g] indazoles (29) at 50 mg/day\(^2\), 2H[1]-benzothiepino [4,5-C] pyrazoles (30) at 2 mg/day\(^2\) and methanobenco [b] thiophenes (31) at 5 mg/kg\(^2\) exhibit antifertility activity.
Eight membered tricyclic nitrogen containing heterocycle such as dibenzodiazocine\(^{27}\) (32) and the angular benzo [4,5] pyrano [2,3-\(\text{C}\)] pyrroles\(^{28}\) (33) with two different heteroatoms are reported to be useful contraceptives.

\[
\begin{align*}
X &= 2,8-\text{Cl}_2; \quad R = 2\text{-thienyl} \\
R, R^1 &= \text{H, alkyl, alkoxy, OH, halo, acyloxy;} \\
R^2 &= \text{H, alkyl, aralkyl, aminoalkyl}
\end{align*}
\]

Another class of compounds namely pyrazolo [5,1-\(\text{a}\)] isoquinoline (34; 2 mg/kg/day in hamsters)\(^{29}\) and aminindolobenzodiazepines\(^{30}\) (35) have been found to possess contraceptive efficacy.
The contraceptive efficacy of the members of the nitrogen containing tricyclic heterocycles (36-38) are as follows

\[
\begin{align*}
\text{ED}_{50} \text{ (mg/kg/day)} & \\
\text{Hamster} & \quad \text{Rat} \\
\end{align*}
\]

| R¹ | R² | A | ED₅₀ | |  \\
|----|----|---|------| |  \\
| H  | C₆H₅ | CH₂-CH₂ | 3.5 | 20 |  \\
| H  | C₆H₅ | CH = CH | 1 | 5 |  \\
| H  | m-(OCH₃)C₆H₄ | CH = CH | >5 | 25 |  \\
| CH₂OH | C₆H₅ | CH₂-CH₂ | ~10 | ~20 |  \\
| CH₃ | C₆H₅ | CH₂-CH₂ | >3 | 20 |  \\
| H  | C₆H₅ | CH₂ | 10 | >5 |  \\

1.2 BASIS OF WORK

The text of the preceeding section suggests that heterocycles are capable of terminating pregnancy but the available reports do not project a clear picture about their contraceptive efficacy by oral route of administration and the results of the follow up action in large number of cases have possibly remained unreported. However, the desired details concerning the profile of antifertility activity are available for triazole derivatives and this prompted an earlier effort in this laboratory to ascertain whether the isomeric triazoles (A&B) and the replacement of one of the nitrogen atom in these compounds by other heteroatoms could influence the contraceptive efficacy.
It has been found that isomeric triazoles (A&B) and oxadiazole derivatives (C) exhibit contraceptive activity but their efficacy by oral route of administration is extremely poor.

The present study represents an extension of the work initiated earlier in this laboratory and is directed to explore the contraceptive efficacy of other simpler heterocycles possessing only one phenyl ring. The stress on having a single phenyl ring in the molecular framework of simpler heterocycles is based on the assumption that two phenyl rings in simpler heterocycles at higher doses may lead to oestrogenicity. In view of these considerations, the syntheses and the evaluation of contraceptive efficacy of prototypes I-VI were undertaken.
Another approach in the present study for obtaining second generation contraceptive agents relates to the design of compounds which simulate two distinct type of pharmacophores in their molecular structures; the first one is concerned with its ability to alter membrane permeability while the second one is concerned with its capability to interfere oxido-reduction processes. The choice of these pharmacophores is based on the assumption that compounds capable of eliciting these activities in uterus would lead to inhibition of pregnancy. A situation such as this would generate fresh leads and this approach appears to have not been employed by earlier workers. In the present study two representative class of compounds namely 1,2,3,4-tetrahydroquinoline derivatives (VII) and 1,4-dihydro pyridine derivatives (VIII) have been identified for synthesis and biological evaluation as antifertility agents.