

## REVIEW ARTICLE

**CONTRACEPTIVE PROPERTY OF NITROGEN / OXYGEN  
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**ABSTRACT**

*Fertility regulation is certainly an essential pathway but not sufficient in itself to the optimization of population rise. A large variety of substances both natural and synthetic have been shown to intercept pregnancy either during the pre-implantation or post-implantation stages of pregnancy. The development of hormonal contraceptives is one of the greatest scientific achievements of the 20<sup>th</sup> Century. About three decades back, some important discoveries were made which opened a new era in the control of conception and fertility, viz: the discovery of the steroidal drugs, including steroidal contraceptives like estradiol and progesterone. This review concern the development on contraceptive property of the Non-Steroidal compounds. The Non-Steroidal compounds with a variety of nitrogen/oxygen & sulfur donor containing heterocycles developed mainly during last decade is reviewed.*

**Keywords:** *Hormonal Contraceptives, Chemical Contraception, Non-steroidal and Heterocyclic compounds,*

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**INTRODUCTION**

With the ever growing world population, contraception is an important health issue for the 21<sup>st</sup> century. Fertility is an issue of global and national public issues concerning the rapid growth of the country. The total world population of this century, the rate of increase of the population was about 10 million per year. Now it is increasing at a much faster rate of 100 million per year. If the rate of increase remains continuous at the same pace, it is expected to reach 7 billion by the end of the present century. The rapid increase of population has got an adverse effect on the international economy and as the increase is only limited to the developing countries, the problem becomes an acute one on the fruits of improvement in the different sectors, which are being eroded by the growing population. Moreover, increasing number of births has got a deleterious effect on the health of mother and child and hinders social and economic progress. The regulation of human fertility has global consequences in terms of resources depletion, population and poverty. Now, it has become one of the priorities of the National Family Programs and therefore, there is an urgent need to improve the access and the quality of contraceptive service in the country.

Contraceptive methods are, by definition, preventive methods to help women to avoid unwanted pregnancies. This includes all temporary and permanent measures to prevent pregnancy resulting from coitus. The last few years have witnessed a contraceptive revolution, i.e., man trying to interface with the ovulation cycle. It is now, generally recognized that contraceptive is safe,

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effective acceptable, inexpensive and reversible and simple to administration, is long lasting enough to avoid frequent administration and requiring little or no medical impression. The international efforts to develop improved means of fertility control are based on the promise that the nature of available fertility control technology is highly important determinant for the success of planning programs.

### **Background Informations:**

The primary requisite of an antifertility agent for human is that it should be non-toxic, non-teratogenic and should not interfere with the normal metabolic and behavioral process. Further, the method should be reversible. Therefore, exhaustive and prolonged studies on the safety and efficacy of contraceptive agents including their effect on progeny in laboratory animals should proceed studies on human volunteers. Each contraceptive method has its unique advantage and disadvantage. The success of any contraceptive method depends not only on its effectiveness in preventing pregnancy but on the rate of continuation of proper use.

For the last few decades scientific research spearheaded by WHO (World Health Organisation) is being conducted to achieve the population control. Many synthetic contraceptive procedures have been developed in this context but they involve serious health hazards. The task of developing alternative methods of contraceptive to those currently available is of paramount importance and urgency.

The selection and use of contraceptive methods are influenced by their intrinsic characteristics and social acceptability. The intrinsic characteristics include : medical safety, effectiveness, continuity of use and reversibility. The main aspects of social acceptability are : personal, cultural, religious, sexual, medical, organizational, logical, economical, political and philosophical.

In the quest for appropriate family size, it is surely axiomatic that the male partner should be able to share the benefits and risks of whatever contraceptive strategy the couple may follow. For men to have as wide a choice as women, however, there is clearly a need for a greater variety of safe antifertility methods capable of reversibly suppressing sperm production or sperm function in men without interfering with their libido.

At present only three methods are available that can be used by men : coitus interruptus, use of condoms and sterilization by vas occlusion. Even with these major limitations, it is estimated that almost one third of all couples around the world rely on methods requiring male cooperation. Although a major proportion of the Task Force activities in the period of 1982-1986 has gone towards establishing the safety and efficacy of immediate methods (for instance, vasectomy), it has also sustained strategies to provide safe and reversible methods based on hormonal, chemical or physical.<sup>1</sup>

The most popular contraceptive devices of male contraception now-a-days which are being used are – mechanical (use of condoms and intra-vas devices), physiological (oral pills or chemicals) and surgical (vasectomy).

The mechanical devices for male fertility control can be through copper devices and some ionophores transplanted into the vas. Silicon-Rubbers and plugs are some more recent advancements.<sup>2</sup> A variety of electrolytes, biochemical hormones and metabolite enzymes have been histochemically localised and biochemically estimated in the epididymal segments of several species of animals.

Male pills containing a combination of testosterone, estrogens and progesterone have also been tried to prevent spermatogenesis.

Biomedical research supported by WHO has investigated the potential of developing new male contraceptive methods that would function at any step in male reproductive process, from sperm production in the testes through to sperm-egg interactions in female genital tract.<sup>3</sup> Five main types of intervention have been investigated in this regard :

- Inhibition of sperm production.
- Interference with sperm function.
- Interruption of sperm transport.
- Prevention of sperm deposition.
- Prevention of sperm-egg interactions.

#### **Inhibition of Sperm Production:**

The production of sperms can be inhibited by preventing spermatogenesis. An effective block can be at two levels – where there is an interference with the endocrine control of spermatogenesis and where the specific anti-spermatogenic agents cause testicular pathology, causing maturation arrest to germinal cells and aplasia to tubular hyalinisation.

#### **Interference With Sperm Function:**

Function of sperms can be inhibited after their formation. Spermatozoal motility is necessary for fertilization of ovum specific agents have not yet been found which can alter the motility pattern of spermatozoa rendering them immotile. Sperm energy inhibitors and acrosomal inhibitors are very common to destabilize the fertility.

#### **Interruption of Sperm Transport:**

Epididymal milieu can be altered physiologically using spermicidal agents in the lumen in the development of antifertility agents for males.

#### **Prevention of Sperm-Egg Interactions:**

Various proteolytic and mucolytic enzymes are packed in the acrosome. They are responsible for the penetration of ovum. Interference with the synthesis or function of these enzymes might render the spermatozoan incapable of fertilizing the ovum.

The development of agents which cause reversible sterility in the male is receiving increasing attention. The major target area in which new research developments are taking place towards the regulation of male fertility include.<sup>3</sup>

- (i) Improvement in vasectomy and vaso-occlusive methods.
- (ii) Use of hormonal agents for suppression of spermatogenesis and
- (iii) Research oriented towards identification of drugs that interrupt sperm maturation in epididymis.

## CHEMICAL CONTRACEPTION

Chemical control of fertility in the male has received attention since quite some time and a large number of steroidal and non steroidal substances have been tested for their antispermatogenic and antiandrogenic effects but in general attempts made in this direction have failed to pass the initial laboratory and clinical trials. Practically, all major research on new oral contraceptives is based on synthetic compounds particularly; steroidal derivatives have considerable efforts so far being put forward to suppress spermatogenesis by variety of steroidal and non-steroidal agents. A large number of antispermatogenesis compounds have been reviewed amongst others by. To name a few dichloroacetyl diamines, derivatives of Sulphonic Acids, Dinitropyrrrol, Nutrofurin, methylhydrazine and Calcium Chloride effectively inhibit spermatogenesis in number of laboratories species. However, in none these were clinically promising since most of these had mutagenic, carcinogenic or most toxic side effects at the effective dose level. Also, the produced testicular changes in many instances were irreversible.

DL-204[2-(3-ethoxyphenyl), 5,6-diahydro(5,1-a)-iso-quinoline], is non-steroidal compound showed antiandrogenic activities by reducing accessory sex organ weight and also exhibited antispermatogenic activities<sup>4</sup> It is reported that DL-204 might be acting on testes and accessory reproductive organs by blocking androgen biosynthesis and/or antagonizing action of androgen<sup>4</sup>.

### 1. Metapiron

Administration of Metapiron resulted indegenerative changes in seminiferous tubules in testes of mice, gerbils and hedgehog<sup>5</sup>. Metapiron administration at 200-mg/kg-body weight dose resulted in loss of spermatogenetic elements in male dogs<sup>6</sup>.

a-cholorohydrin (3-chloro, 1-2propanediol)

Chronic administration of a-chlorohydrin (8 mg/kg b. wt.) for 30 days caused lesion in tested of dog. Epididymal cells height was greatly reduced and decreased RNA and Sialic acid contents in epididymis of dog<sup>7</sup> and male langur (*Presbytisentellus entellus Dufereus*)<sup>8</sup> was reported a-chlorohydrine at 4, 8 and 25 mg/kg body weight level caused decline in the activity of glyceraldehydes 3-phosphate dehydrogenase enzymes of spermatozoa in epididymis of rate, hamsters Guinea Pigs and Mice<sup>9</sup>.

### 2. Cisplatin

(Cis - diaminedichloroplatinum(ii)-CDDp). It is platinum co-ordinated compounds and is one of the most effective and widely used antitumor drugs. Single dose of cisplatin (8 mg/kg b. wt. ip.) reduced the number of primary spermatocytes, sperm motility and DNA contents of testes. Cisplatin caused a significant reduction in weight of sex accessory organs, testosterone level and an increase in FSH and LH levels<sup>10</sup>.

### 3. Sulfasalszine

(2-Hydroxy-s[4-(2-pyridinylamine)sulfonel]azo) benzoic acid. It caused a dose dependent and reversible reduction in the fertility of male rats<sup>11</sup>. Further reduction in sperm count, motility and increased number of abnormal spermatozoa were observed in the patient receiving sulfasalazine treatment<sup>12</sup>.

#### 4. Flutamide

(4'-Nitro-3'-trifluoromethylisobutyrylanilide). It is a potent non-steroidal antiandrogen produced a state of functional castration and increased level of plasma LH and testosterone in rats<sup>13</sup>. Administration of flutamide (5mg/100 gm body weight) caused a reduction in weight or reproductive organs and reduced activity of acid phosphatase and hyaluronidase enzymes in male rats<sup>14</sup>.

#### 5. Pathidine

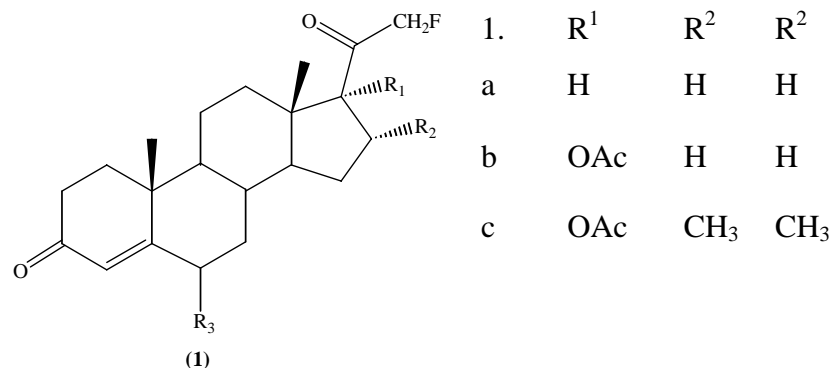
It is a synthetic opiod and analgesic and influences CNS and is known to alter the secretion and release of pituitary gonodotropins. It caused a significant reduction in the reproductive organ weight and a fall in cauda epididymal sperm counts testicular protein and sialic acid contents in male rats<sup>15</sup>.

#### 6. Ornidazole

It is nitroimidazole derivative of [ $\alpha$ -(chloromethyl)-2-methyl, 5-nitroimidazole-1-ethanol] and its administration in fertility in male rats resulted in reduced fertilizing ability of spermatozoa by affecting glycolytic enzyme activities<sup>16,17</sup>.

The development of hormonal contraceptives is one of the greatest scientific achievements of the 20th Century. About three decades back, some important discoveries were made which opened a new era in the control of conception and fertility, viz : the discovery of the steroidal drugs, including steroidal contraceptives like estradiol and progesterone. The oral administration of progesterone inhibits ovulation in the women but its side effects led to incidence of heavy bleeding which is controlled by estrogen.<sup>18</sup> This knowledge also lead to the development of a combination of pillas. Inhoffen et al.<sup>19,20</sup> in Germany synthesized ethisterone and ethiny lestradiol which were provided to be a very active oral estrogen.

Djerassi<sup>21,22</sup> synthesized 19-*nor*progesterone and *norethindrone*, which were more potent than the naturally occurring progesterone. After these discoveries, a large number of steroidal contraceptives were developed amongst which fluori-nated deri vatives, viz : 21-fluoroprogestosterone (**1a**) 21-fluoro-17 $\alpha$ -acetoxy progesterone, (**1b**) are 2 to 4 times as active as progesterone<sup>23,24</sup> and 21-fluoro-6 $\alpha$ , 16 $\alpha$ -dimethyl-17 $\alpha$ acetoxy progsterone (**1c**) was 20 times as active as ethisterone.<sup>25</sup>



The medicinal and pharmaceutical chemists are trying to overcome the serious incidence of heavy bleeding and this led to the synthesis of a number of non-steroidal heterocycles as antifertility agents which are broadly classified as follows :

- A. Nitrogen containing heterocycles.
- B. Oxygen containing heterocycles.
- C. Sulphur containing heterocycles.
- D. Nitrogen and sulphur containing heterocycles.
- E. Nitrogen and oxygen containing heterocycles.

## A. NITROGEN CONTAINING HETEROCYCLES.

### 1. Azirdine derivatives

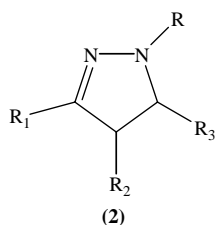
1,6 Hexamethylene bis(1-aziridine)carboxamide at 2% concentration induced 100% sterility in both male and female. *D. Singulatus*.<sup>26</sup>

### 2. Pyrrolidine derivatives

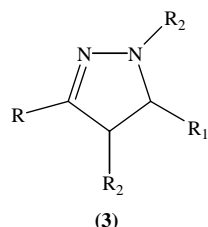
Pyrrolidine 2,4-diones affect fertility through affecting the prostaglandin activities<sup>27</sup>. 1-{2-[p- $\alpha$ (p-Methoxyphenyl)nitrostrylphen-oxy]}ethylpyrrolidine citrate prevented pregnancy 100% in rats (500 $\mu$ kg<sup>-1</sup>p.o.)<sup>28</sup>.

### 3. Pyrazole derivatives

A number of 4,5-dihydropyrazoles, **(2)** (R=COCH<sub>3</sub>, R<sub>1</sub>=R<sub>3</sub>=H, 3-4-MeOC<sub>6</sub>H<sub>4</sub>;R<sub>2</sub>=H, Me) are devoid of contraceptive properties<sup>29,30</sup>, however, the p.o. application of 1mg/ kg<sup>-1</sup>. d<sup>-1</sup> **(3)** (R=CONH<sub>2</sub>;R<sub>1</sub>=H; R<sub>2</sub>=2,5Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>NHN<3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>NHN<;R<sub>3</sub>=H)inhibited the pregnancy by 80 to 100% in rats.<sup>31</sup> 1-Acetyl/Pentafluorophenyl-(3-fluoroaryl-5-phenyl)furyl-4H-4,5-Pyrazolines, **(3)** synthesized by Joshi et al.<sup>32</sup> as antifertility agents exhibited promising antiimplantation activity in female rats (10mg.kg<sup>-1</sup>).



R = COCH<sub>3</sub>, CONH<sub>2</sub>  
 R<sup>1</sup>=R<sub>3</sub>=H,3-/4-MeOC<sub>6</sub>H<sub>4</sub>  
 R<sub>2</sub>=H, Me, = NHNMe<sub>2</sub>,C<sub>6</sub>H<sub>3</sub>



R = C<sub>6</sub>F<sub>5</sub>, 4-F-C<sub>6</sub>H<sub>4</sub>,3,4-F<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>  
 R<sub>1</sub> = Ph, 2-furyl  
 R<sub>2</sub> = Ac, C<sub>6</sub>F<sub>5</sub>

Amongst a series of 1-aryl-3-pyrazolidinones, 5-oxo-2-(m-methoxyphenyl)1-pyrazolidinehexanoic acid and showed prostaglandin like antifertility activity.<sup>33</sup>

In women taking oral contraceptives, the degradation rate of dimethylaminoantipyrene was prolonged by at least 2-exponential functions.<sup>34</sup>

N<sup>1</sup>, N<sup>2</sup>-Diphenyl-4/2-butyl-4-(methylenemonosuccinate)pyrazol-3,5-dione also exhibited slight antifertility activity in rats (200 mgkg<sup>-1</sup>)<sup>35</sup>.

#### 4. Imidazole derivatives

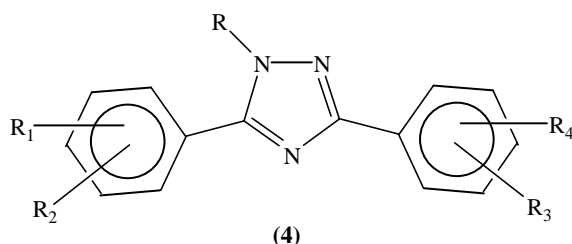
Imidazole have been used as both male and female contraceptives<sup>36-41</sup>. 1-Bis (aryl/alkyl) alkylimidazoles affect the motility of dog spermatozoa<sup>42</sup> while mercaptomethylimidazole makes female rats infertile<sup>43</sup>.

The contraceptive nitrothiazolidineisobutylaminomethyl-imidazolidinone (30, 40, 200 or 400mgkg<sup>-1</sup>xd<sup>-1</sup>) administered intraga-strically to male rats for 4h to 18d inhibited fertility<sup>44</sup>. Isoconazole nitrate (60 mgkg<sup>-1</sup>xd<sup>-1</sup>) was slightly toxic to rats during early pregnancy, parturition and lactation, but had no significant toxic effects on fetuses and new borns<sup>45</sup>. Econazole nitrate (20 and 50 mg.kg<sup>-1</sup>s.c.) given prior to early pregnancy inhibited the fertilization and fetal growth.<sup>46</sup>

Mizoribine<sup>47,48</sup> nifedipine fumarate<sup>49,50</sup>, propentofylline<sup>51</sup>, ronidazole<sup>52</sup> ketoconazole<sup>53,54</sup> and sulconazole nitrate<sup>55</sup> were also screened for their antifertility activity but no encouraging results are noticed.

#### 5. Triazole derivatives

3,5-Disubstituted-1H-1,2,4-triazole derivatives (4) are reported to be contraceptive agents<sup>56-63</sup>. 5-(2-Aminoacetomido)methyl-1-4-chloro-2-(o-chlorobenzoyl)phenyl-1N,N-dimethyl-1,1H-5-triazole-3-carboxamide hydrochloride dihydrate was administered (25,100 or 400 mg.kg<sup>-1</sup>,d<sup>-1</sup>) to Sprague Dawely rats and the effects were compared to that of tirazolam (400 mg.kg<sup>-1</sup>.d<sup>-1</sup>)<sup>64-65</sup>.

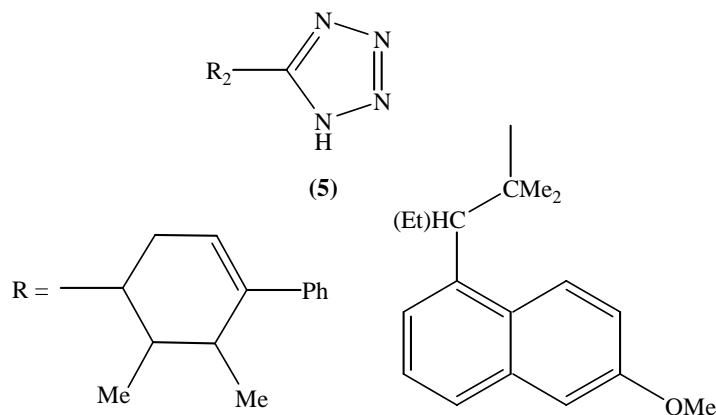


R=H, Acyl, Substituted Sulfonyl

R<sub>1</sub>=R<sub>4</sub>=Halogen, CF<sub>3</sub>, NMe<sub>2</sub>

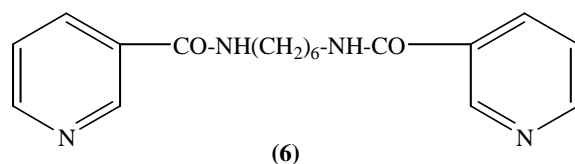
R<sub>3</sub>=R<sub>4</sub>=O-CH<sub>2</sub>O

#### 6. Tetrazole derivatives



Tetrazole derivatives (5) are not found to act as oral contraceptives but did exhibit a very weak estrogenic activity in mice<sup>66</sup>.

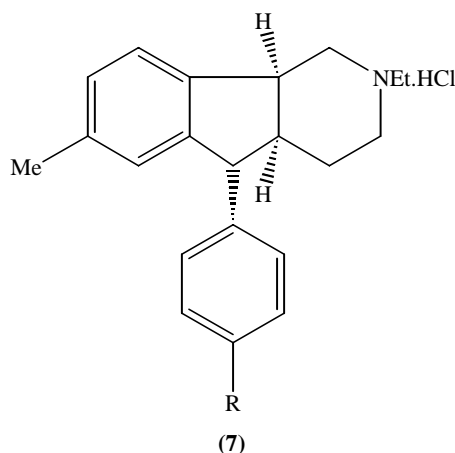
### 7. Pyridine derivatives



In mice,  $\beta$ -pyridine carboxamide allied derivatives (6) ( $3\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ ) are effective contraceptives<sup>67-70</sup>. The triarylpyridylethanols caused infertility and triaryl pyridylethylenes ( $30\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$  s.c.) reduced the pregnancy (6% to 14%) in hamsters<sup>71</sup>. The monoamine oxidase inhibitor iproniazid inhibited luteolysin in rats<sup>72</sup>.

2,2'Dithiodipyridine 1,1'-dioxide, when given to mice decreased the water intake and the number of corpusluteum, but it had no effect on male and female fertility instead the weight of fetus body increased if mothers were treated with  $6\text{mg}\cdot\text{kg}^{-1}$  s.c. daily for 3 weeks<sup>73</sup>. Sulfasalazine<sup>74</sup> and sulfapyridine<sup>75</sup> decrease the fertility of animals without affecting libido or testicular morphology.

Application of nicotine ( $5\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$  i.p. for 2d) to male mice for 1 week before mating decreases the fertility due to an increased incidence of prenatal mortality, which indicates damage to epidymal sperms<sup>76</sup>.



2,3,4,4a,5, 9b-Hexahydroindeno [1,2-c] pyridines (7) is an effective male contraceptive and tested in mice for their ability to reduce testes and disrupt spermatogenesis<sup>77</sup>. Sulfasalazine is used as an antifertility agent in male rats. Five-day administration of  $1250$  and  $250\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$  of sulfapyridine (SP) a metabolite of sulfasalazine (SASP) reduced the fertility<sup>78</sup>.

Imidazopyridinylethyleminopyrrolyl pyrrolopyridines and related compounds are used as effective contraceptives<sup>79,80</sup>.

Pyrrolopyridines are used as antifertility agents and act as antagonists of gonadotropin-releasing hormones<sup>81-84</sup>. Thienopyridines are used as effective contraceptives<sup>85,86</sup>.

### 8. Pyridiazinone derivatives

The oral administration (pre- and post-mating) of 4-ethoxy-2-methyl-5-morpholino-3-(2H)pyridazinones did not produce a significant effect on reproductive activity in male and female rats<sup>87,88</sup>.

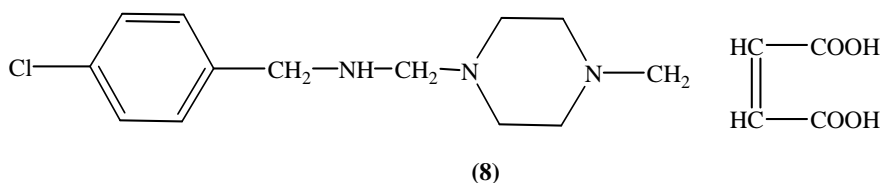


### 9. Pyridimethamine derivatives

Pyrimethamine ( $150 \text{ mg.ml}^{-1}$ ) inhibited *in vitro* growth of rabbit blastocysts but did not affect their implantation<sup>89</sup>. However, its i.p. injection (1 or 0.5 mg in 100 g.) into rats on the first and fourth day of pregnancy decreases the implantation sites and the fertility<sup>90</sup>. The clinical doses of sulfamethoxazole (in co-medication with pyrimethamine) exhibited contraceptive properties in female rabbits<sup>91</sup>.

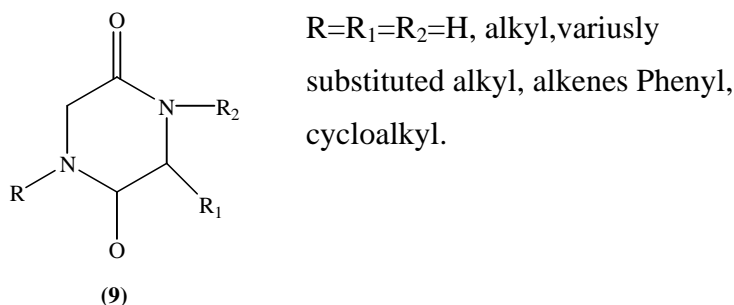
The i.p. administration 5-bromodeoxypuridine reduced the fertility to 72%, while complete sterility was noticed in male mice ( $100 \text{ mg. kg}^{-1}$ )<sup>92</sup>.

### 10. Piperazine derivatives



$\text{N}^1, \text{N}^4$ -Disubstituted piperazine and allied derivatives, (8) were found to immobilize human sperms and are useful contraceptives<sup>93,94</sup>.

Various substituted piperazinediones (9) show abortification activity and are useful as contraceptive<sup>95</sup>.



### 11. Triethylene melamine

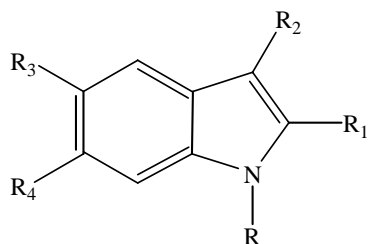
Triethylene melamine in 0.9% saline water solution when injected (i.p.) resulted in immediate sterility<sup>96,97</sup>.

### 12. Guanethidine

Local application of guanethidin hydrochloride caused permanent sterility at higher doses and temporary sterility at lower doses<sup>98</sup>.

### 13. Indole derivatives

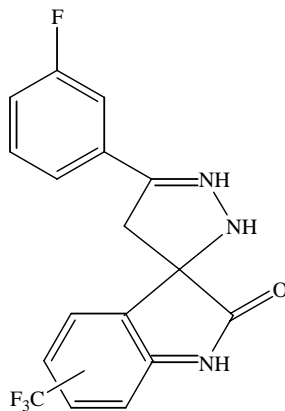
Various indole derivatives (10) act as effective antifertility agents<sup>99-111</sup>. Tryptamine derivatives (10) (R=R<sub>1</sub>=H; R<sub>2</sub>=CH<sub>2</sub>CH<sub>2</sub>NHCOMe; R<sub>3</sub>=MeO; R<sub>4</sub>=Cl) acts as ovulation inhibitors ( $1 \text{ mg.kg}^{-1} \text{d}^{-1}$  p.o.) in rats<sup>112</sup>. N-Acetyltryptophan [(10) R=R<sub>1</sub>=R<sub>3</sub>=R<sub>4</sub>=H, R<sub>2</sub>=CH<sub>2</sub>CH<sub>2</sub>(NHAc)COOH] after application of  $150\text{-}160 \text{ mg. x kg}^{-1} \text{d}^{-1}$  i.p. has no significant effect on animals fertility and caused no abnormalities<sup>113-114</sup>.



(10)

R=H, COCH, CPh, 4-COC<sub>6</sub>H<sub>4</sub>Cl  
 4-COC<sub>6</sub>H<sub>4</sub>OH, 4-CH<sub>2</sub>CH<sub>2</sub>N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>  
 R<sub>1</sub>=H, Ph, 4-FC<sub>6</sub>H<sub>4</sub>, Me  
 R<sub>2</sub>=H, CH<sub>2</sub>COOH, -CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>,  
 -CH<sub>2</sub>CH<sub>2</sub>NHCOMe, CH<sub>2</sub>(NHAc)COOH  
 R<sub>3</sub>=H, MeO, F  
 R<sub>4</sub>=H, Cl, F

Joshi *et al.* have synthesized spiro [3,3'-pyrozol]-2-ones (11) which showed antiimplanation activity (10 mg.kg<sup>-1</sup>) in pregnant rats.



(11)

Joshi<sup>115-116</sup> *et al.* use synthesize containing oxothiazoline derivatives of 2-arylindoles, amongst which 2-(4-fluorophenyl)[5-piperylidene-4-oxo-2-thiazolidinylidene]hydrazone-0-1H-indole-3-carboxaldehyde has shown testicular loss, vaculization and recosis of seminiferous tubules in rats (30 mg.kg<sup>-1</sup>.d<sup>-1</sup> 30d).

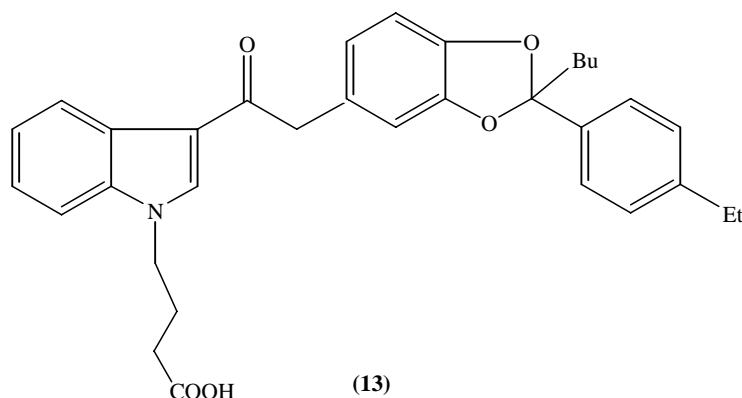
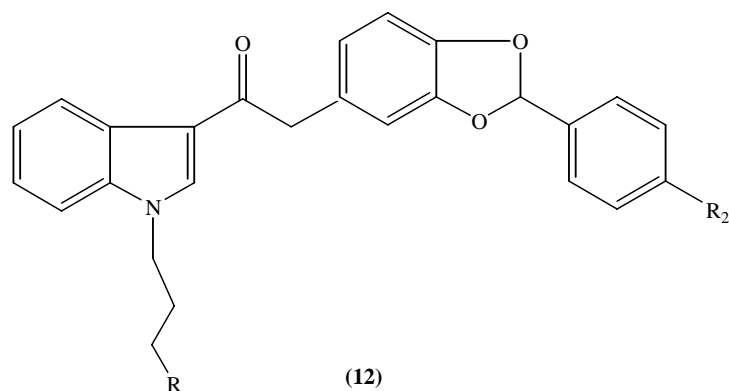
Finally, Joshi<sup>118</sup> *et al.* had synthesized a number of spiro [3H-indole-3,2-thiazolidine]-2,4(1H)-diones, which were screen for their antifertility activity; amongst which, 6-fluoro-3-(4-fluorophenyl)spiro[3H-indole-3,2-thiazolin-dine]-2,4(1H)-dione displayed antiimplantion activity (30 mg.kg<sup>-1</sup>) in rats.

The pyridoindole derivative DP 1031 resulted in an increased incidence of minor fetal abnormalities and a suppression of weight gain in offspring in rats (25 and 50 mg<sup>-1</sup>)<sup>119,120</sup>.

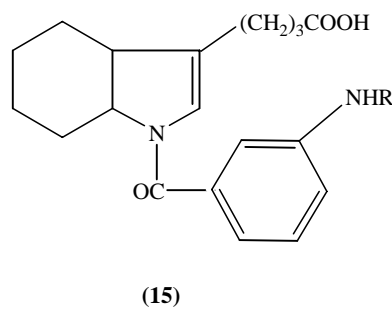
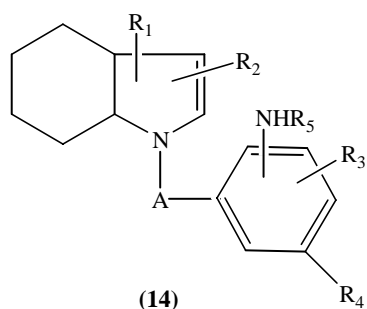
Yuchchukene, a bis-indole alkaloid isolated from *Murraya exotica* and *M. Paniculata* (L) Jack, when given to mated female rats (2.5 mg.kg<sup>-1</sup>p.o.) has shown antifertility activity<sup>121</sup>. Various synthetic Yuchchukene analoges exhibit potent antiimplantation activity in rats and are found to be potential fertility regulatory agents<sup>122,123</sup>.

Anand *et al*<sup>124,125</sup> have shown that 4-substitued-2-oxopyrimido [2,1:6,1]pyrido [3,4-b] indoles interrupted pregnancy by occlusion of the fallopian tubes of females and the vas deferens of males.

(2-Phenyl-1,3-benzodioxal-5-yl) alkyindole alkanooates used (12) and (13) as a testosterone 5- $\alpha$ -reductase intibitors. The title compound, (12) (R=carboxy, tetrazolyl, R<sub>1</sub>, R<sub>2</sub>=alkyl) were disclosed as steroid 5 $\alpha$  reductase inhibitor which are useful for treating disease such as being prostates hypertrophy<sup>126</sup>.



(N-Benzoylindolyl)alkanoates, **(14)** and **(15)** and their analog are used as a testosterone reductase inhibitors<sup>127</sup>.



A = CO, SO<sub>2</sub>, alkylene  
 R<sub>1</sub>=(un) Protected carboxyalkyl  
 R<sub>2</sub>=H, haloalkyl  
 R<sub>2</sub>,R<sub>4</sub>=H,alkyl  
 R<sup>5</sup> = (un)substituted aryalkyl

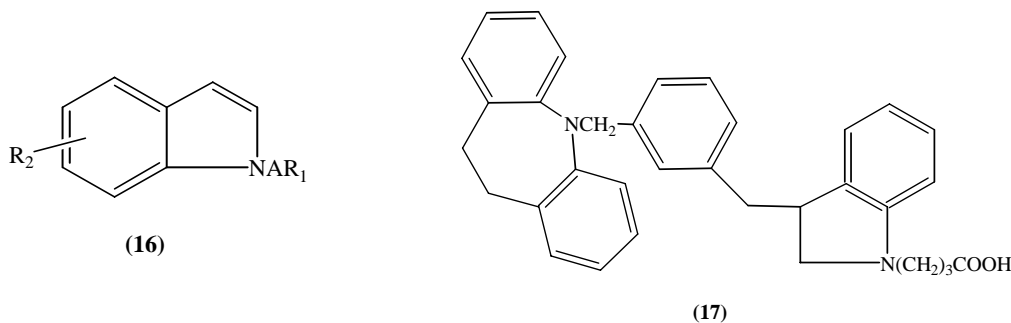
2-[4-Hydroxyphenylmethyl-1-{4(2-azepam-1-ly)ethoxy}]benzyl-1H-indol-5-ol used as a oral contraceptive and administered according to a 28 day monophasic regimen the doses with 1 at 2 mg. and levonorgestrol at 90 µg is prepared<sup>128</sup>.

Benzoylindole derivatives **(16)** act as a effective antifertility agents, [16, R<sub>1</sub>=(protected)carboxyalkyl; R<sub>2</sub>=H, alkyl, halogen, R<sub>3</sub>=H (substituted)alkyl, Z=CH<sub>2</sub>, O,NH;

$R_4$ =cycloalkyl,  $\text{NO}_2$ , alkoxy,  $R_5$ =H alkyl;  $R_4R_5=(\text{CH}_2)_4$  were prepared as testosterone-5  $\alpha$  reductase inhibitor<sup>129</sup>.

Indole-3-carbinol-diindolyethane and substituted analogs are asked as antiestrogen<sup>130</sup>. 4-(3-Benzoylindol-1yl)butyrates and their analogs, **(17)**, are used as testosterone 5- $\alpha$  reductase inhibitors which had  $\text{IC}_{50}$  of 0.93 nm against testosterone 5 $\alpha$ -reductase *in vitro*.<sup>131</sup>

(I-Benzylindole-3yl)-alkanoic acids **(16)** are novel nonsteroidal inhibitors of steroid 5 $\alpha$ -reductase.<sup>132</sup>



A = alkenylene(oxo)alkylene

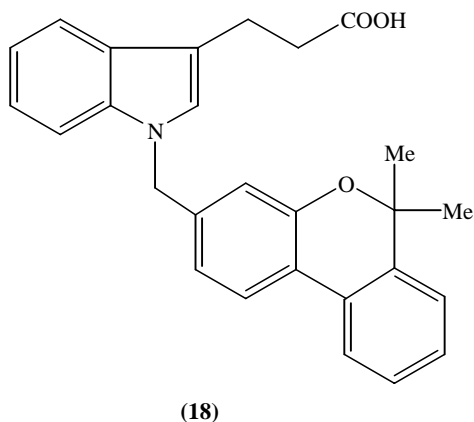
R = QXYZRS

$R_1$  = (un) Procted  $\text{CO}_2\text{H}$

$R_2$  = H, halo, alkyl

$R_3$  = aryl

Compounds **(18)** with a diaryl substituted at the 1-position of the indole ring displayed strong inhibitory activity *in vitro*. Amongst these, dimethyldibenzo[b,d]pyranylmethylindolbuycric acid **(18)** [FR 119680] displayed very high inhibitory activity *in vitro* against rat prostatic reductase [ $\text{IC}_{50}$  = 5.0 nm] and good *in vitro* activity in the castrated rat model.



(Imidazopyridylalkylaminoalkyl)indoles and related compounds are used as a antifertility agents and cut as a antagonists of gonadotropin releasing hormones.<sup>133,134</sup> Indolinones are antagonists of the progesterone receptor and are useful in inducing contraceptions and treating or preventing bening or malignant neoplastic disease.<sup>135</sup>

Tetrahydrobenzindolone derivatives are used as a effective antifertility agents.<sup>136</sup> Many substituted indoels are used as a possible antifertility agents.<sup>137</sup>

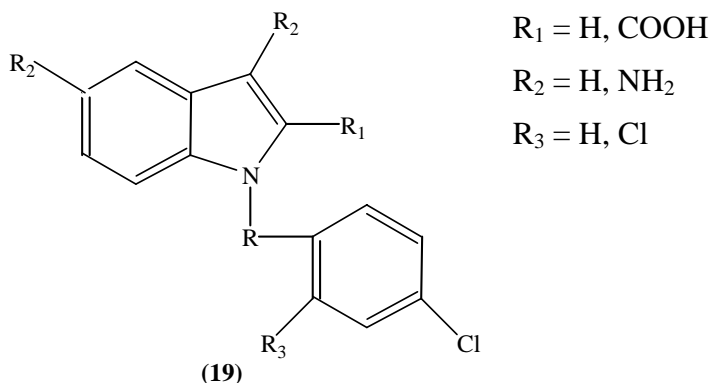
Indometacin ( $10\text{mg.kg}^{-1}$  i.p.) immediately following mating upto 4h decreased the number of implantation and increased the premature resorption and mortality in rats while trated after 8h of mating it decreased the pregnancies by 40%.<sup>138-141</sup>

### 15. Phthalimide derivatives

(Phthalimidomethylamino)benzanilides do not possess contraceptive properties,<sup>142</sup> whereas N-(substituted-benzylidene) aminophthalimides, dihydroisoindoses and 1,2,3,4-tetrahydroisoquinoliens prevent pregnancy in mice ( $20\text{mg.kg}^{-1}\text{ x d}^{-1}$ ). It has also been shown that the later compounds exhibited 100% abortifacient activity.<sup>143</sup>

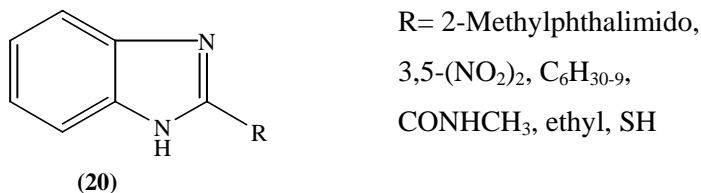
### 16. Indazole derivatives

Various indazole and tetrahydroindazoles, **(19)** are reported as antifertility agents.<sup>144-148</sup> Compound **(19)** ( $R_1=R_3=H$ ,  $R_2=NH_2$ ) disrupts spermatogenesis causing a long lasting antifertility effect and with  $R_1=COOH$ ;  $R_2=H$ ,  $R_3=Cl$  directly acts as a reversible antifertility agents.<sup>149-153</sup>



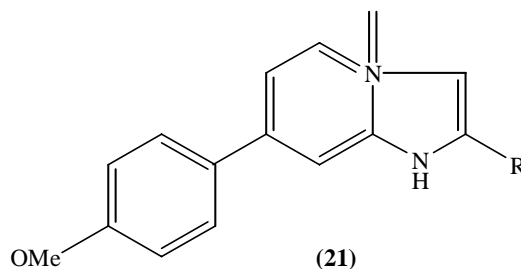
### 17. Benzimidazoles and benzotriazoles

Benzimidazoels **(20)** were tested for antiestro-genic activity but were found to be ineffective spermicides<sup>154</sup> as compared to germicide.<sup>155</sup>



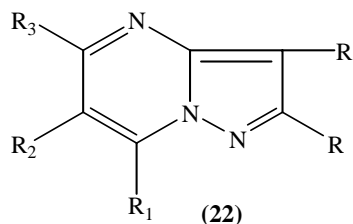
### 18. Pyridinopyrrole derivatives

1-Aza-4-(p-methoxyphenyl)bicyclo [4.3.0]non-3-en-9-ones, **(21)** are reported to be potential antifertility agents by Trehan *et al.*<sup>156</sup>



### 19. Pyrazolopyrimidines and Imidazopyrimidines

It was reported by Robin et al<sup>157</sup> that various pyrazolopyrimidines, (22) exhibited antifertility activity.



R=Halogen, CN, CONH<sub>2</sub>, NO<sub>2</sub>, NH<sub>2</sub>, substituted amino-

R<sub>1</sub>=alkyl, amino, OH, Cl

R<sub>2</sub>=H, OEt, COOEt

R<sub>3</sub>=alkyl, H

Imidazopyrimidines are used as a effective contraceptives.<sup>158</sup>

### 20. Microprofen

Microprofen (1,5 and 25 mg./Kg<sup>-1</sup> p.o.) exhibited no encouraging antifertility results.<sup>159</sup>

### 21. Benzopyrazoles

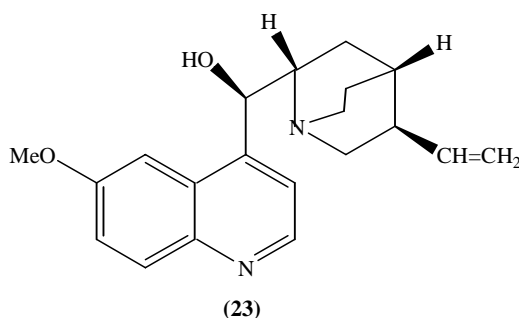
2,4-Diphenyl-2,3-disubstituted bnzo[c]pyrazoles were screened but no encouraging antifertility result were obtained.<sup>160</sup>

### 22. Theophylline and Caffeine

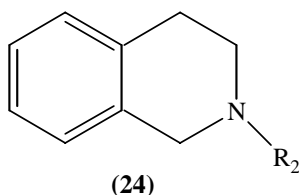
Theophylline<sup>161</sup> theobromine<sup>162</sup> and caffeine<sup>163,164</sup> were also studied as oral contraceptives.

### 23. Quinine Derivatives

A 5% suspension of quinine bisulfate in polyethylene glycol ointment base exhibited very weak spermicidal activity.<sup>165</sup>



### 24. Quinoline and isoquinoline derivatives



R<sub>1</sub> = H, 4-OH<sub>2</sub>CH<sub>2</sub>- Ph

R<sub>2</sub>=CH<sub>2</sub>CH(Me)Ph, N = CHPh

In addition, there are various quinoline<sup>166-172</sup> and isoquinoling<sup>173-175</sup> derivatives, (24) which were found to act as contraceptives. Compound (24) (R<sub>1</sub>=Pyrrolidinoethoxyphenyl; R<sub>2</sub>=CH<sub>2</sub>CHMePh) was 5 times more potent than estrone in rats.<sup>176-177</sup> Administration of 8-[2-chlorobenzylidene]]

aminoisoquinoline 20 mg.kg<sup>-1</sup>) to rats after 7d. of pregnancy was found to be 77% effective.<sup>178</sup> In addition 1H-quinolin-2-one derivatives are also used as a antifertility agents.<sup>179-180</sup>

### 25. Budralazine

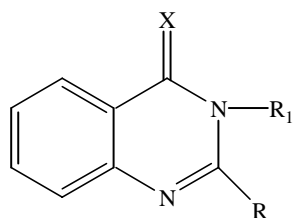
A fertility study was performed on rats with budralazine in the diet at low (5mg.kg<sup>-1</sup>.d<sup>-1</sup>) middle (40mg.kg<sup>-1</sup>.d<sup>-1</sup>) and high (80mg.kg<sup>-1</sup>.d<sup>-1</sup>) dose levels, but no significant differences have been observed between the treated and control groups. There were no adverse effects on fertility and fetal development of rats reported.

### 26. Procatrol

Procatrol, a  $\beta$ -adrenergic stimulant, did not exhibit antifertility activity (.01 - 5.250 mg.kg<sup>-1</sup>.p.o.).<sup>182</sup>

### 27. Quinazoline derivatives

Various quinazoline derivatives, (25) interrupted pregnancy by 40-50%.<sup>183-188</sup> 2-(N-N-Substitutedaminomethyl)-3-(2-pyridyl)-4-(3H)-oxo-3, 1 quinazolines<sup>189</sup> and 10, 12-substituted [1,4]-benzoxamino [3,4].quinazolin-8-one showed 12.5 to 37.5% antiimplantation activity (25 mg.kg<sup>-1</sup>).<sup>190</sup> Quinazolinones and benzoxazines are also used in various contraceptive compositions.<sup>191</sup>

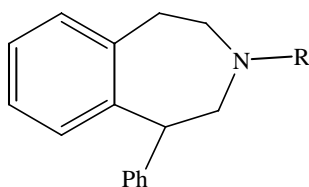


(25)

R = 2-Cl, 2-MeO, 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-  
 R<sub>1</sub> = CH<sub>3</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>-,  
 X = O, 4-MeOC<sub>6</sub>H<sub>4</sub>NH.

### 28. Benzazepine derivatives

Benzazepine derivatives, (26) were synthesized as antifertility agents, but did not show any significant antiimplantation activity.<sup>192</sup>



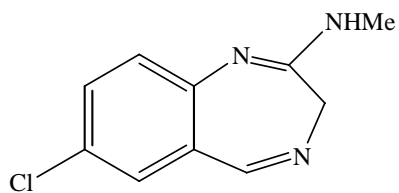
(26)

R = PhCH<sub>2</sub>CH<sub>2</sub>, PhCH(OH)CH<sub>2</sub>, MeOC-CH<sub>2</sub>-CH<sub>2</sub>-  
 Me<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>-, PhOCH<sub>2</sub>CH(OH)CH<sub>2</sub>-, 2-(4-Pyridyl)  
 ethyl.

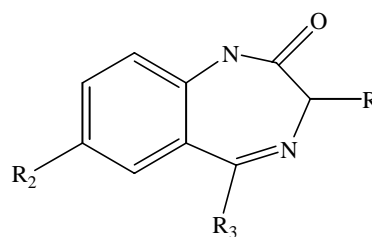
### 29. Diazepoxides

The disposition of chlordiazepoxide (27) was reported by Roberts *et al.*<sup>193</sup> in healthy young men and women receiving oral contraceptive for more than six months.

Lorazepam (28); R=H; R<sub>1</sub>=OH, R<sub>2</sub>=Cl, R<sub>3</sub>=2 ClPh), oxazepam (28); R=H, R<sub>1</sub>=OH, R<sub>2</sub>=Cl; R<sub>3</sub>=Ph<sup>194</sup>, prazepam (28); R=CH<sub>2</sub>-Cyclopropyl; R<sub>1</sub>=H; R<sub>2</sub>=CC;R<sub>3</sub>=Ph<sup>195</sup>, diazepam (28); R Me; R<sub>1</sub>=H; R<sub>2</sub>=Cl; R<sub>3</sub>=Ph<sup>196,197</sup> and nitrazepam<sup>198</sup> at different dose levels are oral contraceptives.



(27)

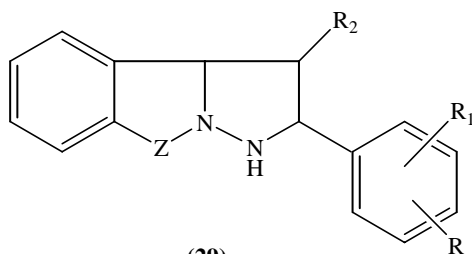


(28)

R = H, Me  
 R<sub>1</sub> = H, OH  
 R<sub>2</sub> = Cl, NO<sub>2</sub>  
 R<sub>3</sub> = Ph, 2-ClC<sub>6</sub>H<sub>4</sub>

### 30. Pyrazoloisoquinoline derivatives

Pyrazoloisoquinoline derivatives, (29) have been determined to be effective contraceptives (0.5 - 25 mg.kg<sup>-1</sup>.d<sup>-1</sup>).<sup>199-201</sup>

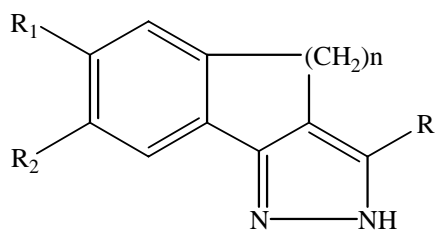


(29)

R = 2-Cl, 2-MeO, 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-,  
 R<sub>1</sub> = CH<sub>3</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>-.  
 X = O, 4-MeOC<sub>6</sub>H<sub>4</sub>NH-.

### 31. Indeno-, Naphtho-, and cycloheptapyrazole derivatives

A large number of indeno, naphtho, and cycloheptapyrazoles, (30) derivatives were tested for antifertility activity and were found to be active in rats (1-100 mg.kg<sup>-1</sup>).<sup>202-210</sup>

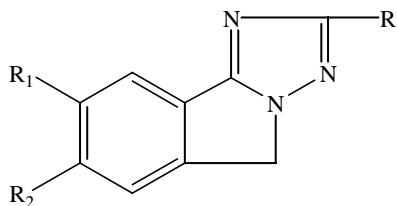


(30)

R = 3,4-Pyridyl, 2-Furyl, 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>-,  
 R<sub>1</sub> = H, Me, OMe, Cl, CF<sub>3</sub>;  
 R<sub>2</sub> = H, OMe;  
 R<sub>1</sub>, R<sub>2</sub> = OCH<sub>2</sub>O and  
 n = 1, 2, 3

### 32. Triazoloisoindole derivatives

Triazoloisoindoles, (31) possess post-coital antifertility activity in rats (1-10mg.kg<sup>-1</sup>.d<sup>-1</sup>s.c.).<sup>211</sup>

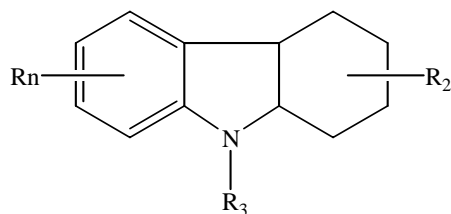


(31)

R = H, Me, Ph, NH<sub>2</sub>, SH  
 3 or 4 - Pyridyl  
 R<sub>1</sub> = R<sub>2</sub> = H, Cl, OMe



### 33. Carbazole derivatives



(32)

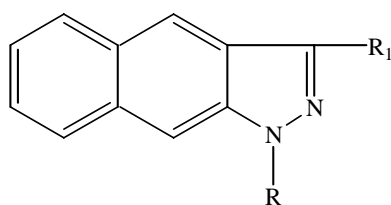
Rn = 6 or 7-F, 6-CF<sub>3</sub>, 6-Br; 6-NO<sub>2</sub>

5-Cl, 6, 7-OCH<sub>2</sub>O, 6-COOH

R<sub>1</sub>=COOEt, CH<sub>2</sub>CN, CH<sub>2</sub>OH, CH<sub>2</sub>OSO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-.

R<sub>1</sub> = R<sub>3</sub> = H or Me

Various carbazole derivatives, (32) useful as fertility inhibiting agents, have been reported by Biere *et al.*<sup>212</sup> 7-(2-Dimethylaminoethyl)-8-chloro-5, 6-dihydro-7-H-benzo [c] carbazole and 7-(2-piperidinoethyl)-10-methoxy-5,6-dihydro-7H-benzo [c] carbazole are the most active compounds (1000 mg x kg.<sup>-1</sup>d-l p.o./i.p.) in mice.<sup>213</sup>



(33)

R = H, Me, Et, CHMe<sub>2</sub>

R<sub>1</sub> = Ph, 4-C<sub>6</sub>H<sub>4</sub>R<sup>3</sup>

R<sub>2</sub> = H, Br

R<sub>3</sub> = Cl, F, Br, Me, MeO.

### 34. Indenopyridine derivatives

A number of indenopyridine derivatives were tested for antiimplantation activity, amongst which 2 ethyl-1,3,4, 4a, 5, 9b-hexahydro-7-methyl-5-p-tolyl-2H-indeno[1,2-c]pyridine hydrochloride produced long lasting inhibition in mice (10mg.xkg<sup>-1</sup>.d<sup>-1</sup>).<sup>214</sup>

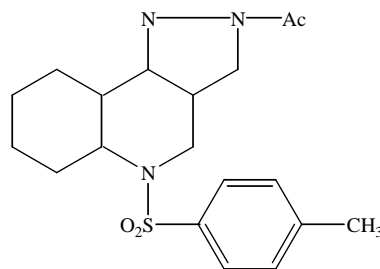
### 35. Benzindazole derivatives

Benzindazole derivatives, (33) were luteolytic in rabbits (1mg.d<sup>-1</sup> for 14d).<sup>215</sup>

### 36. Pyroquinoline derivatives

Pyroquinoline derivatives showed antiimplantation activity (10mg.kg<sup>-1</sup> s.c.), killing at least 60% of the fetuses when administered to rats for 6-10 during pregnancy.<sup>216</sup>

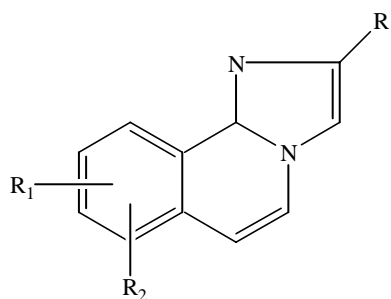
### 37. Pyrazoloquinoline derivatives



(34)

Various tetrahydropyrazolo [4,3-c] quinolines, (34) showed antiimplantation activity in female albino rats.<sup>217,218</sup> 3-Aryl-4,5-dihydro-2-substituted-5-tosyl-2H-Pyrazolo [4,3-c] quinolines and 2,4-dihydro-3-phenyl-benzoprano [4,3-c] pyrazoles were synthesized by Andand *et al.*<sup>219</sup> as antifertility agents but these compounds did not show any significant antifertility activity.

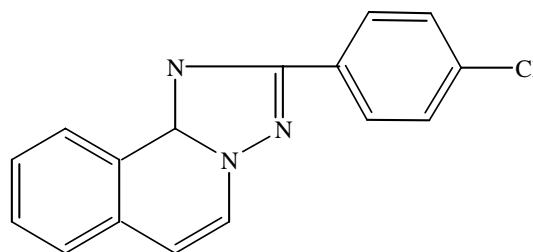
**38. Triazoloisoquinoline derivatives** A number of triazoloisoquinolines, (35) and their dihydro derivatives display fertility inhibiting activity when tested s.c. in dogs, hamster and rats.<sup>220-226</sup> Compound (35) (R=4-FC<sub>6</sub>H<sub>4</sub>; R<sub>1</sub>=R<sub>2</sub>=H) had ED<sub>50</sub> 0.025 mg.kg<sup>-1</sup> s.c. in hamsters.<sup>226</sup>



(35)

R = H, Me, NHAC, -  
NHCONH<sub>2</sub>SH, Ph, FC<sub>6</sub>H<sub>4</sub>  
R=R<sub>2</sub>=H, F, Cl, Br, C<sub>1-4</sub>  
alkoxy.

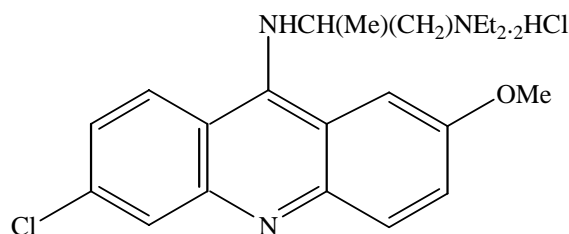
2,(4-Chlorophenyl)-3-triazole 5,1-a] isoquinoline, (36) showed highest antifertility activity when administered 10 mg.kg<sup>-1</sup> with the oil carriers in domestic animals.<sup>227,228</sup>



(36)

### 39. Quinacrine derivatives

Quinacrine dihydrochloride, (37) inhibited fertility in rats, mice, hamsters and gerbics.<sup>229-234</sup>



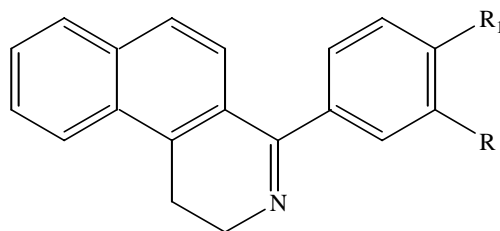
(37)

### 40. Phenazine derivatives

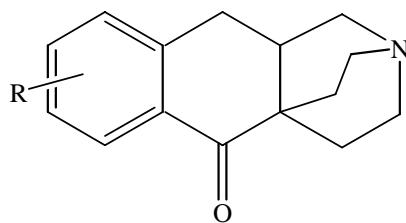
The phenazine-5-N-oxide affected the pregnancy rate, the survival rate and the neonatal development in male and female mice upto three generations.<sup>235</sup>

### 41. Benzoisoquinoline derivatives

Benzoisoquinoline derivatives, (38) have been found to be used for conception.<sup>236-237</sup> Ethanobez [g] isoquinolin-5-(1H)-ones, (39) showed antifertility activity in hamsters (30.0mg.kg<sup>-1</sup>d<sup>-1</sup>s.c.).<sup>238</sup>



(38)



(39)

#### 42. Benzomorphan

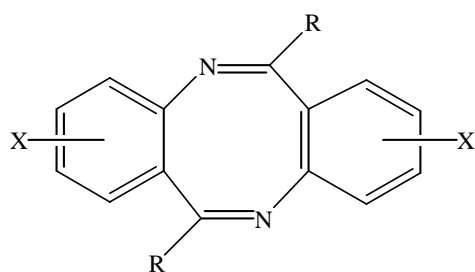
6,7 Bentomorphan exhibited luteinizing hormone secretion inhibiting activities ( $80.001-10 \text{ mg.kg}^{-1}$ ) or  $0.001-100 \text{ mg x kg}^{-1}$ ) in mice.<sup>239</sup>

#### 43. Benzazonine derivatives and riboflavin

1,4-Dimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine hydrobromide<sup>240</sup> and riboflavin affect the fertility by affecting the erycytcylce and biological functions.<sup>241</sup>

#### 44. Dibenzodiazocine derivatives

Yammoto et al.<sup>242,243</sup> reported that various dilbenzodiazocines, (40) exhibited antifertility proeptries.



(40)

X = H, halo, NO<sub>2</sub>, CF<sub>3</sub> alkyl, alkoxy

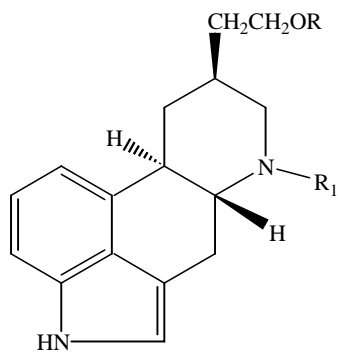
R = 0, 5 or 6 membered ring.

#### 45. Butorphenol

Butorphenol tartrate was administered s.c. to male rats for 63d and to female rats 14d of the pregestion (period) ( $25 \text{ mg. kg}^{-1}$ ). No significant result were observed on reproductive performances.<sup>244</sup>

#### 46. Ergot alkaloids

Some 6-alkyl derivatives, like D-8-ergolin-1-yl-acetamides, (41) showed prolaction inhbiting activity after p.o. application to rats but had higher antinidation and antilactation effects with low toxicity.<sup>245-258</sup>



(41)

R = NH<sub>2</sub>, Ac, Bz, 4-MeOC<sub>6</sub>H<sub>4</sub>CO,  
3,4,5-(MeO)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>CO, Caproyl, nicotinoyl  
R<sub>1</sub>=Me, Et, Pr

#### 47. Coronaridine hydrochloride

Coronaridine hydrochloride (30 mg.kg<sup>-1</sup>.p.o.) prevented pregnancy (100%) in rats on d 2,3,4 or 5 p.c., while the effect on 5,6,7 or 8 was only partial. Its p.o. administration (1-10 mg.kg<sup>-1</sup>) produced a uterotrophic effect and induced vaginal opening and cornification.<sup>259</sup>

#### 48. Reserpine

The contraceptive properties of DL-reserpine were measured *in-vitro* and *in-vivo* in rats (2 x 10<sup>-2</sup>M) and humans (2 x 10<sup>-3</sup>) and were found to acts as spermicide.<sup>260-263</sup>

#### 49. Indomethacin derivatives

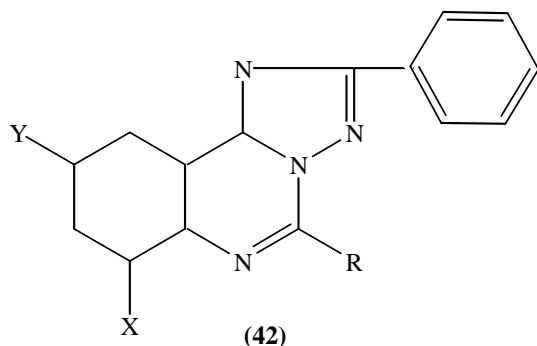
Indomethacin is used as a antifertility agents. Treatment with indomethacin significantly reduced the plasma progesterone concentration. Decreased progesterone concentration, in uterine flushing significantly decreased the total plasma proteins and particularly decreased albumin in the plasma and in the uterine flushings.<sup>264</sup>

#### 50. Ornidazole

Ornidazole is a useful male contraceptive and are used as a effective antifertility agent in male.<sup>265,266</sup>

#### 51. Benzimidazoquinazolines derivatives

Benzimidazoquinazolines, (42) are useful antifertility agents and which effectively reduce the fertility. Various 2-styrylbenzimidazo-1, 5-Cl<sub>2</sub> equinazolenes (x=H or Br, R=H, 4-Cl, 2NO<sub>2</sub>, 5-OMe, 2F, 4-one, 4-OH, 4-NMe<sub>2</sub> 3-one and vinyl) are used as a antifertility agents. Anti implantation effects caused by (42a) varied with the structure of the compound. (42a) (x = H, R =4-One; X = Br and R = 3,4-OMe, (DM) 4-NMe<sub>2</sub>-or-CH:CH<sub>2</sub>) showed marked activity.<sup>267</sup>



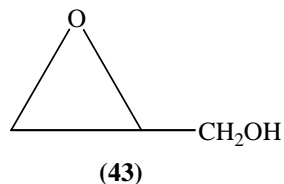
(42)

a; Y = CH=CH<sub>2</sub>, C<sub>6</sub>H<sub>4</sub>R  
b; X = Me.

## B. OXYGEN CONTAINING HETEROCYCLES

### 1. Glycidol derivatives

Glycidol, (**43**) has no antifertility activity ( $50 \text{ mg.kg}^{-1} \text{ i.p.14d}$ ) although it reduces spermatozoan motility<sup>268,269</sup> in male mice rats.

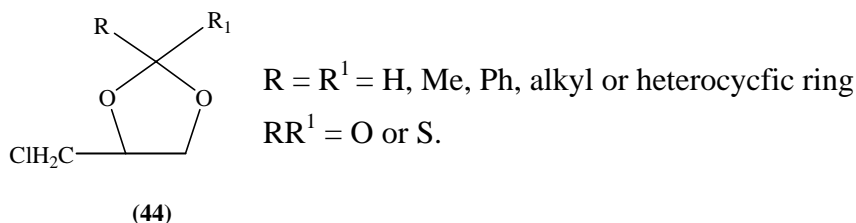


### 2. Furan derivatives

Anand et al.<sup>270, 271</sup> synthesized a large number of furan derivatives; amongst which 2-(*p*-hydroxyphenyl) furan derivatives and the corresponding 3-*t*-aminoethyl ether significantly inhibited pregnancy in rats.

The effects of natudioruryl on pregnant rabbits were examined ( $0.25, 0.7$  and  $2 \text{ mg.kg}^{-1} \text{ i.v.}$ ) but no effect on embryonic death and fetal development after 28 d of gestation was observed.<sup>272</sup> 9-Oxoprostaglandin compositions ( $2.5$  to  $10 \text{ mg.kg}^{-1}$ ) had shown antifertility activity.<sup>273</sup>

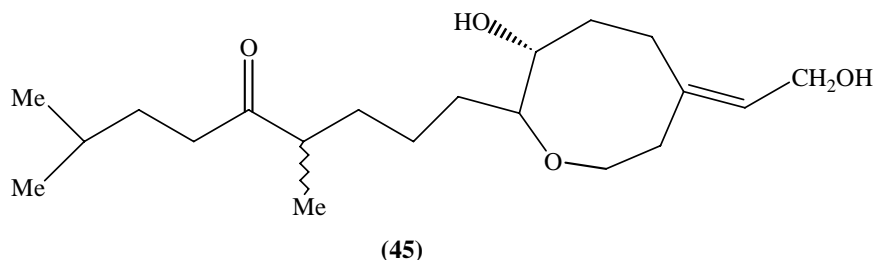
### 3. 1,3-Dioxalones



Substituted 1,3-dioxolanes, (**44**) were effective antifertility agents in male rats and hamsters.<sup>274-278</sup>

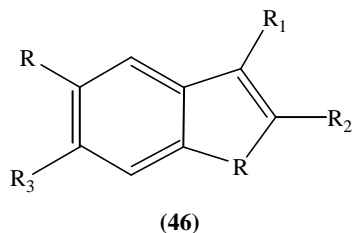
### 4. Deoxyzoapotanol derivatives

Deoxyzoapotanol derivatives are postimplant antigestational agents.<sup>279</sup> Kanojia et al.<sup>280</sup> have described the structural antifertility activity relationships of zoapotanol analogs, (**45**) and have noticed that conversion of the 5-oxo group into a hydroxy function on the noneny side chain increases the antifertility activity.

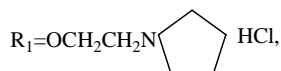
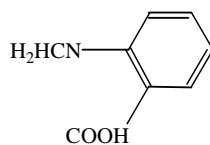


### 5. Benzofuran derivatives

A number of benzofuran derivatives, (**46**) were found to be effective antifertility agents at therapeutic doses.<sup>281-293</sup> The effect of daily p.o. administration of (**46**) ( $R=Ph$ ;  $R^1=1\text{-Pyrrolyl-2-ethoxy}$ ;  $R^2=OMe$ ,  $R^3=H$ ) was studied on the reproductive organs of monkeys ( $2\text{mg}\cdot\text{kg}^{-1}$ ).

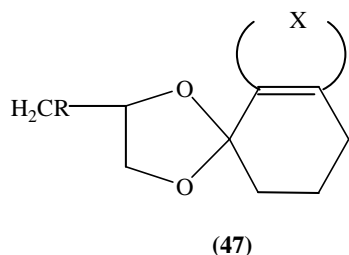


$R = \text{CH}(\text{Et})\text{CMe}_2\text{COOH}$ ,  
 $\text{C}(\text{OH})\text{MeCMe}_2\text{COOEt}$ , Ph,



-HNCOC<sub>6</sub>H<sub>4</sub>OMe<sub>2</sub>  
 $R_2=R_3=H$ , MeO, halogen, Me

### 6. Dioxospirodecane derivatives



$R = H$ , Halo, OH, alkoxy, NH<sub>2</sub>

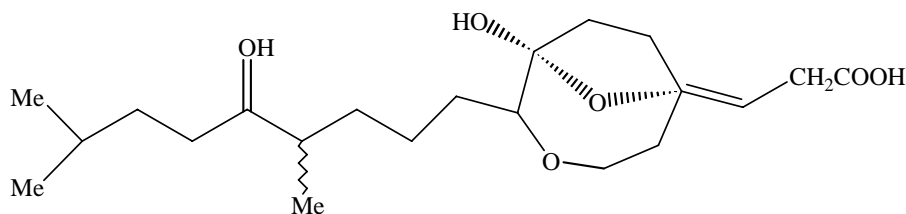
$X = 5$  or 6 membered ring

1,4-Dioxospiro [4,5] decane derivatives, (**47**) showed good antifertility activity.<sup>294,295</sup>

### 7. Dioxospiroundecane derivatives

Leshner *et al.*<sup>296</sup> reported that various 3,8-disubstituted-1,5-dioxospiroundecanes showed antifertility activity in rats.<sup>297</sup> Hajos *et al.*<sup>298</sup> recently reported dioxobicyclo [3,2.1] octanes and oxepans to be useful contraceptives.

The contragestational and general reproductive pharmacological properties of ORF 13811, (**48**) a synthetic analog of aozapotanol, (**48**) effectively prevented implantation in mice, rats, guinea pigs and dogs.<sup>299</sup>



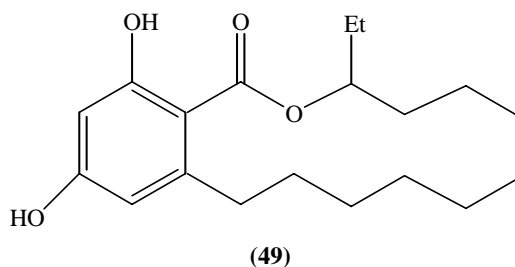
(48)

### 8. Chromane, coumarin, isoflavone and chalcone derivatives

A number of chromane derivatives have been synthesized and screened for their antifertility activity.<sup>300-307</sup> The most active chromanes are 3,4-*trans*-3-phenyl-4-[p-(β-

pyrrolidinoethoxy)phenyl] chromane<sup>308</sup> and 3,4-*trans*-2,2-dimethyl-3-phenyl-4-[*p*( $\beta$ -pyrrolidinoethoxy)phenyl]-7-methoxychromane which completely prevented conception (1.25 mg.kg<sup>-1</sup> p.o.).<sup>309</sup> Similarly, *cis*- and *trans*-3-oximino-4-phenylchloromane and allied derivatives prevented implantation (10 mg.kg<sup>-1</sup>) in rats.<sup>310</sup> (3R)-Clausequinone, a reduced chromane derivatives, given to rats in a single dose (200 ug x 100 g<sup>-1</sup> i.p. on the 4<sup>th</sup> d of gestation inhibited implantation and caused abortion in 32.3% of the implanted embryos.<sup>311</sup>

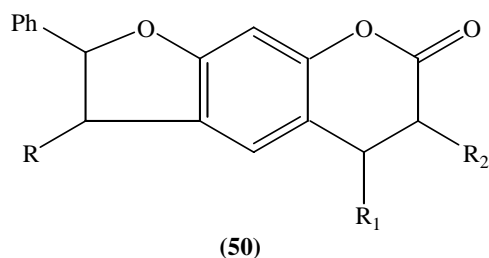
Various coumarin and furocoumarin derivatives have been shown to be effective contraceptives.<sup>312-316</sup> Arora et al.<sup>317</sup> reported the synthesis of 4-aminoalkylisocoumarins as potential antifertility agents; amongst which, 4-(diethylaminoethyl)-3,4,5 trimethoxybenzoate exhibited antifertility activity in rats (5mg.kg<sup>-1</sup>). Cyanidanol prevented fertility in 80% of tested mice.<sup>318</sup> A number of naturally occurring synthetic chalcones and isoflavones are estrogenic like stilbestro.<sup>319-324</sup> The general reproductive behaviour of ipriflavone<sup>325,326</sup>, ibedenone<sup>327</sup> and nipradiol<sup>328</sup> have been studied in rats, dogs and rabbits.



### 9. Benzoxacyclotetradecin derivatives

Daily administration of benzoxacyclotetradecin, (49) (0.01 to 10.0 mg.kg<sup>-1</sup> s.c.) inhibited 100% pregnancy in female rats.<sup>329,330</sup> Zearalenone had conception rates of 62% and 87%, respectively, in the treated and control virgin dairy heifers.<sup>331,332</sup>

### 10. Furobenzopyran derivatives



R = Ph, C<sub>6</sub>H<sub>3</sub>OR<sup>1</sup>R<sup>2</sup>

R<sub>1</sub>=H, Me

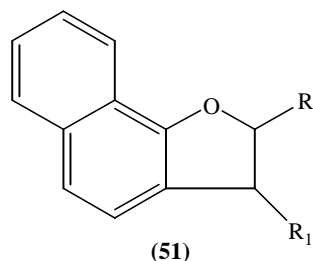
R<sub>2</sub>=Ph, C<sub>6</sub>H<sub>4</sub>NR<sub>2</sub>

R<sub>1</sub>R<sub>2</sub>=C<sub>6</sub>H<sub>4</sub>

NR<sub>2</sub>=NMe<sub>2</sub>,NEt<sub>2</sub>

Various substituted furobenzopyran derivatives, (50) showed significant antiimplantation properties in female albino rats.<sup>333-335</sup>

### 11. Naphthofuran derivatives



R = Halogen, C<sub>6</sub>H<sub>5</sub>, COC<sub>6</sub>H<sub>4</sub>-Me, C<sub>6</sub>H<sub>4</sub>-OMe

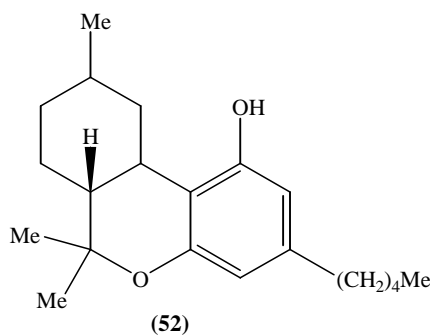
R<sub>1</sub> = H, Br, NO<sub>2</sub>, C<sub>6</sub>H<sub>5</sub>, 4MEC<sub>6</sub>H<sub>9</sub>

A number of naphthofuran derivatives, (51) showed significant contraceptive properties<sup>336-338</sup>; amongst which 2-phenyl-3-*p* (β-pyrrolidinoethoxyphenyl [2,3-*b*] naphthofuran prevented contraception (100%) in rats, mice and monkeys (single dose of 10 mg.kg<sup>-1</sup> p.c.<sup>339</sup> Tetrahydronaphthofuranones derivatives are used as a progesterone inhibitors and act as a antifertility agents.<sup>340</sup>

Female rhesus monkeys showed various degree of modification in the serum level of estradiol and progesterone on a diet containing 500 ppm of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin for 6-d.<sup>341,342</sup>

### 13. Cannabinol derivatives

Δ<sup>9</sup>-tetrahydrocannabinol, (52) caused a permanent reduction in fertility and altered ventral prostate gland morphology in male rats.<sup>343</sup>



### 14. Four membered rings

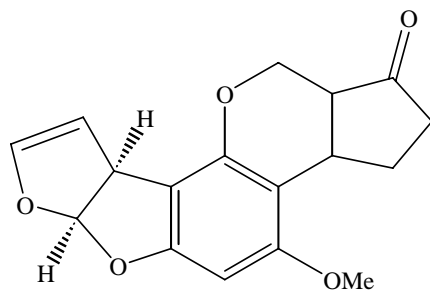
5-Oxo-5H-benzofuro [5,6-*c*] benzopyran caused ≤ 83% inhibition of fetal implantation in rats (10 mg.kg<sup>-1</sup> i.p.).<sup>344</sup>

4-Methyltetrahydrobenzofuran [7,6-*b*] coumarin showed antispermatogenic activity in gerbils (20 mg.kg<sup>-1</sup>).<sup>345</sup> The 2,3-diaryl phenanthrofurans showed no noteworthy antifertility activity.<sup>346</sup>

### 15. Five membered rings

Rats chronically treated with sub-lethal doses of flatoxin-8, (53), suffered from several testicular degenerations, impaired spermatocytogenesis with concomitant drop in the rate and efficiency of spermatozoal production.<sup>347</sup>

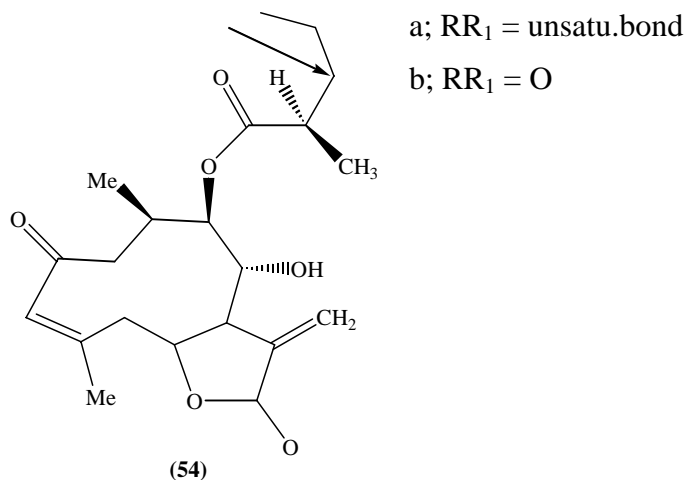




(53)

### 16. Vicolides

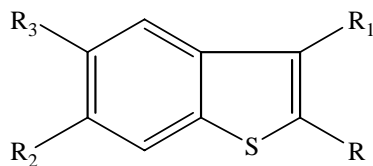
Vicolides (**54a**) and (**54b**) isolated from *Vicoa indies*, DC showed antifertility activity in rats. The mixture of (**54a**) and (**54b**) in ratio of 1:1 at a dose level of 100 gm. kg<sup>-1</sup> showed 28.08% inhibition of implantation and 70% antifertility activity.<sup>348</sup>



(54)

## C. SULPHUR CONTAINING HETEROCYCLES

### 1. Benzothiophene derivatives



(55)

R = CH<sub>2</sub>CH<sub>2</sub>NHAc

R = R<sub>1</sub> = Substituted benzoyl, phenyl, NH<sub>2</sub>, PhCH=CH

Ph 10 Me

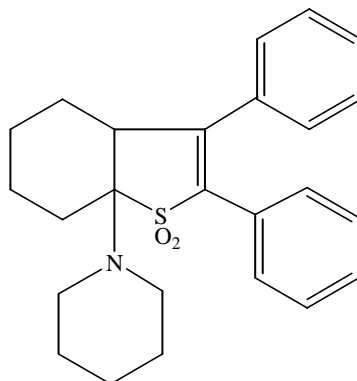
R<sub>2</sub>=R<sub>3</sub>=H, OH, OMe,  CH<sub>2</sub>

$R_4$  = Heterocyclic ring.

A number of benzothiophenes were found to be efficient antifertility agents. Compounds, (**55**) completely inhibited pregnancy at  $1\text{mg.kg}^{-1}$  s.c. in rats.

Methanobenzo [b] thiophene, (**56**) was reported to act as an antifertility agent<sup>349-356</sup> at dose level of  $5\text{mg.kg}^{-1}$  in rats<sup>357</sup>.

## 2. Thiophene derivatives

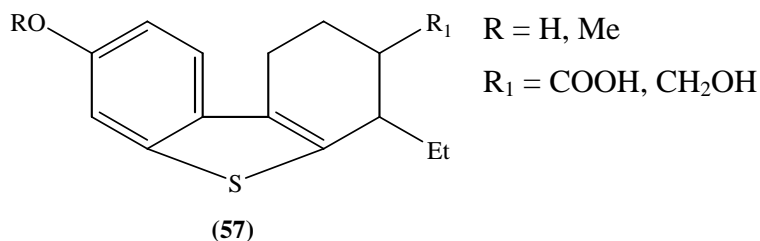


(56)

The effect of (+)-2-[p-(2-theonyl)phenyl]propionic acid (suprofen), (6,12 and  $24\text{mg.kg}^{-1}$  p.o., 63d) before and during the mating was studied and a slight suppression of body weight gain was found in both female and male mice. However, no significant difference in the copulation rate, pregnancy rate and implantation was observed<sup>358</sup>.

Methanobenzo[b]thiophene was reported to act as an antifertility agent in rats [ $5\text{mg.kg}^{-1}$ ].<sup>359</sup>

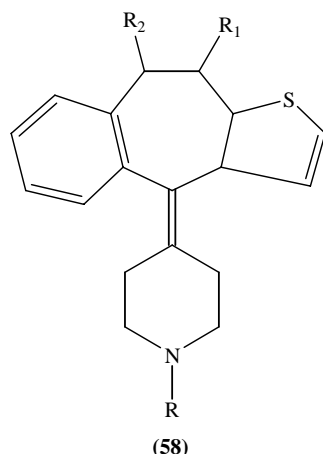
## 3. Dibenzothiophene derivatives



(57)

Tetrahydrodibenzo thiophene derivatives, (**57**) exhibit greater contraceptive properties in rats than expected from their level of estrogenicity. They prevent pregnancy in rats when given for 1-5d. ( $1\text{mg.kg}^{-1}.\text{d}^{-1}$  p.c.); when noted rats are dosed on 8-12h p.c., they are effective at the same dose.<sup>360</sup>

#### 4. Benzocycloheptathiophenes



R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, 3,4-alkyl, OH

R<sub>1</sub>-R<sub>2</sub> = H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, [CH<sub>3</sub>]<sub>2</sub>CH-

Benzocycloheptathiophene derivatives, (58) possess ovulation and luteinizing hormone inhibiting properties.<sup>361-363</sup>

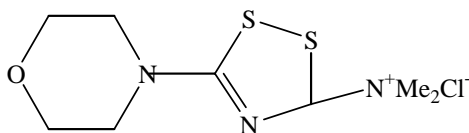
### D. NITROGEN AND SULPHUR CONTAINING HETEROCYCLES

#### 1. Thiazole and thiazolidine derivatives

Aztreonam administered to male and female rats ( $\approx 750 \text{ mg} \cdot \text{kg}^{-1}$  i.v.) had no effect on the estrous cycle, copulation, insemination and fertility indexes.<sup>364</sup> Thiadizolothiapyrano benzothiazoles and isoxazolo and pyrazolothiapyrano benzothiazoles are potential spermicides.<sup>365</sup> 5-Carboxy methylthiazolidine-2,4-dione derivatives showed powerful antispermatogenic activity.<sup>366</sup>

#### 2. Dithiazolium derivatives

3,5-Bis(substitutedamino-or imino)-1,2,4-dithiazolium, (59) salt and dithioburate intermediates inhibited fertility in male animals.<sup>367-370</sup>



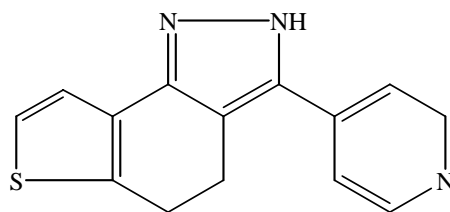
(59)

#### 3. Mezlocillin and their analogs

Mezlocillin<sup>371</sup>, ceftizoxime<sup>372</sup> and T-1982<sup>373</sup> were screened for their antifertility activity but no significant effects were observed.

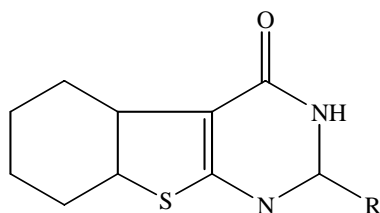
#### 4. Thienoindazole derivatives

4,5-Dihydro-3-(4-pyridyl)2H-thieno[2,3-g]indazole, (60) is an effective fertility control agent when administered to animals (50mg 4 times daily s.c.).<sup>374</sup>



(60)

### 5. Tetramethylenethienopyrimidine



(61)

R = PhCH=CPhCO,  
4-MeOC<sub>6</sub>H<sub>4</sub>-CH=CPhCO.

Tetramethylenethienopyrimidines (**61**) were tested as post-coital antifertility agents by Manhas *et al.*<sup>375</sup>

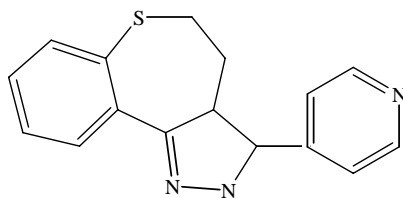
### 6. Furothiazepines or uroazepine derivatives

Administration of brotizolam (2.5 mg.kg<sup>-1</sup> p.o.) to male and female rats before and during mating in the early period of gestation indicated no effects on prenatal fertility.<sup>376</sup>

### 7. Promazine derivatives

Chlorpromazine (2.0 – 8.0 mg.kg<sup>-1</sup> p.o.) was not an effective antifertility agents.<sup>377</sup>

### 8. Benzothienopyrazoles



(62)

2H-[1]Benzothieno [5,4-c]pyrazoles, (**62**) act as antifertility agents in rats (2mg.kg<sup>-1</sup>-d<sup>-1</sup>).<sup>378</sup>

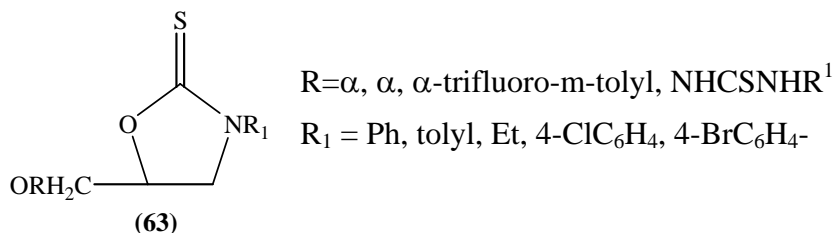
## E. NITROGEN AND OXYGEN CONTAINING HETEROCYCLES

### 1. Isoxazole derivatives

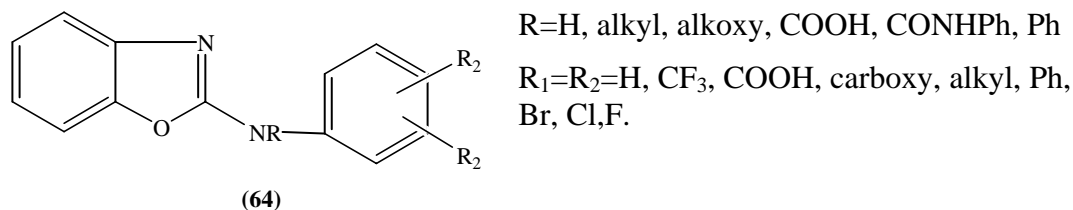
Isoxazole and 5-(*p*-substituted-arylstyryl)-3-methylisoxazoles (20, 100 mg kg<sup>-1</sup>) showed significant antiimplantation activity.<sup>379-380</sup>

### 2. Oxazolidinethione derivatives

2-Oxazolidinethiones, (**63**) antagonised the uterotropic effect of diethylstilbestrol and possessed an LD<sub>50</sub> of 400-800 mg. kg<sup>-1</sup> in female rats.<sup>381-385</sup>



### 3. Benzoxazole derivatives



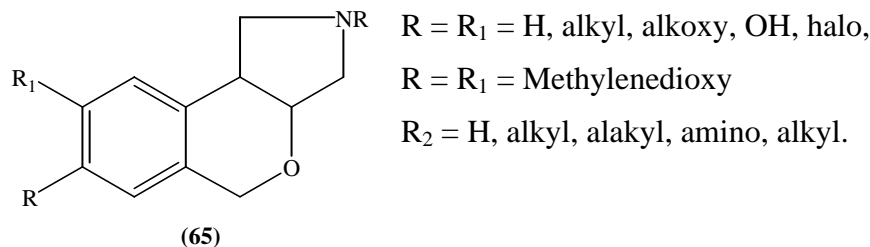
Various substituted benzoxazoles, (64) were shown to possess antifertility activity.<sup>386-388</sup>

### 4. Benzoxaline derivatives

Kulkarni *et al.*<sup>389,390</sup> reported the synthesis of some-2-substituted phenyl-3-aryl-4-oxo-4H-1,3-benzoxazine which exhibited  $\leq 50\%$  anti fertility activity at allowed dose level.<sup>175</sup>

### 5. Benzopyranopyrroles

Benzo[4,5]pyrano[2,3-c]pyrroles, (65) have been tested for antifertility activity and were found useful as contraceptives.<sup>391</sup>



## ACKNOWLEDGEMENT

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