Protozoa is a phylum of primitive animals. They are relatively large (length varying from 2-3 μm to several inches) microscopic species compared to yeasts and bacteria. They are generally motile, throughout the life cycle, a feature which they share with many bacteria. 'True' protozoa are devoid of chlorophyll and they lack tissues and organs. All protozoa live in a fluid medium containing varying amounts of moisture. The free living forms are found all over the world inhabiting fresh waters, seas, moist earth and sand, the surface of plants and organic infusions.

Protozoan diseases are especially prevalent in warm climates, but modern rapid means of transportation may permit isolated or localized outbreaks in areas far away from the tropics (1). Although there are a large number of protozoal diseases known to affect human being and domestic animals, the present work has been planned to investigate agents effective against amebiasis and trichomoniasis.

(A) Amebiasis is the most severe disease amongst the protozoal infections. According to the result of a survey conducted comparatively recently, amebic dysentery occupies 14th place as a cause of illness and 15th place as a cause of death among the 169 countries surveyed (2). It is caused by the protozoa, Entambea histolytica. It causes impairment to the productive capacity of the individual, physical and mental.

(B) Trichomoniasis is caused by flagellate parasites trichomonads which occur on mucosal surfaces of the intestinal or genitourinary tract. T. vaginalis, a parasite of the human genitourinary tract, T. foetus, a parasite of the genito-urinary tract of cattle and T. gallinae, a parasite of the genitourinary tract of
domestic fowl. It may cause an acute or chronic urethritis in either sex. Transmission is caused by sexual intercourse. It is responsible for sterility and abortion in cows (3,4).

Various drugs effective against these two types of diseases have been discussed here:

(A) Chemotherapy of Amebiasis:

Various antiamebic agents have been tested, beginning with the natural products, the search subsequently being fortified by the synthetic ingenuity of the modern chemist; but an ideal antiamebic agent is yet to be found out which can really eradicate the disease from the earth.

In order to find out a suitable drug against amebiasis, a large number of workers synthesised different types of compounds which are classified hereinbelow:

(a) Emetine and its structural analogues
(b) Conessine and its analogues
(c) Other plant products
(d) Antibiotics
(e) Organometallic compounds
(f) Halosacetamides
(g) 8-Quinolinols
(h) Quinolines and Isoquinolines
(i) Benzacridines
(j) Nitroheterocyclic compounds
(k) Miscellaneous compounds

Out of the above classified type of compounds, a short review of the last five groups of compounds have been given below:

(g) 8-Quinolinols:

For the intestinal amebiasis in man three iodinated 8-quinolinol derivatives, 7-iodo-8-quinolinol-5-sulfonate(chiniofon, I) (5), 5-chloro-7-iodo-8-quinolinol
(iodochlorohydroxyquin, II) (6,7) and 5,7-diiodo-8-quinolinol (diiodohydroxyquinoline, III) (8) have been used for many years. These drugs are administered orally and the last two compounds are among the most widely used antiamebic agents at the present day. These compounds have no effectiveness against extraintestinal amebiasis and their use is contraindicated in persons having iodine hypersensitivity.

Many early workers believed that the activity of the iodinated 8-quinolinols was due to the release of iodine in the host. The concept was based on the fact that (a) chlorine and bromine analogues of chiniofon are inactive, (b) the compounds release iodine in water, (c) the observation that in vitro action of serum from patients treated orally with the above drugs, is proportional to the amount of serum iodine. These concepts were counteracted from the fact that many noniodinated 8-quinolinols are highly effective against *E. histolytica* in vitro in man, in rats and dogs; for example - 5,7-dichloro-2-methyl-8-quinolinol (chloroquininaldeol, IV) (9-11), 5-chloro-8-quinolinol (12), 5,7-dibromo-8-quinolinol (broxiquinolina, V) (13).

According to the theory proposed by Albert and coworkers (14), 8-quinolinols act as amebicidal agents by virtue of chelation with polyvalent metals like iron, or cobalt present in the cytoplasmic contents of the cells, producing feebly dissociated complexes in which metals form that part of a heterocyclic ring system. The formation of metal complex is the cause of toxicity to the cells. Of the two complexes, the evidence favours VI rather than VII.
Albert and coworkers showed that the amebicidal substances have an optimal liposolubility enabling them to penetrate the cell walls and thus exert their effectiveness (15,16). Schukina and Savitskaya (17) observed appreciable amebicidal activity in a series of 8-phenoxyquinoline, its p-amino, p-acetamino, p-hydroxy derivatives, as well as in a series of 8-alkoxyquinolines.

This observation indicates the inadequacy of the proposed mechanism by Albert and coworkers. Various 5-chloro-7-[dialkylaminomethyl]-8-quinolinols (VIIa), salts of clamoxyquin (VIIb) have comparable amebicidal activity to that of emetine hydrochloride (18). Gopalchari and coworkers (19) as well as Iyer (20) prepared a number of compounds of the types IX and X. All these compounds possess 8-hydroxy or 8-methoxy and a substituted amino group at 4-position of the heterocyclic moiety. It was found that the quinaldines in general were more reactive than quinolines.
In vitro activity of 6,8-dimethoxyquinaldines (XI; R = n-heptyl or p-methoxy phenyl) is equal to that of emetine.

(h) Quinolines and Isoquinolines:

Chloroquin (XIIa), a potent antimalarial agent was found by Conan (21) to have effect on hepatic amebiasis in hamsters. Chloroquin, amodiaquin (XIIb), hydroxy chloroquin (XIIc) and sontoquin (XIID) are effective against hepatic amebiasis in men and hamsters; but unfortunately these cannot be used against intestinal amebiasis.

It was also observed (22) that compounds of the types (XIII) and (XIV) exhibited high amebicidal activity, the compounds (XIV; R = n-octyl, n-nonyl and 3-methyl 5-dimethylhexyl), being the most potent.
Popli and coworkers (23) prepared a few compounds by partial modification of cinchonine (XV; \( R = H \)) and quinine (XV; \( R = \text{methoxyl} \)) molecules. None of these compounds (XVI, XVII; \( R = H \) or methoxyl) however exhibited appreciable activity.

Fancher and coworkers (24) prepared several isoquinolines (XVIII) which were oversimplified emetine analogues, having high amebicidal activity. Ghosh and coworkers (25) prepared a few quinolinoisoquinolines of the type (XIX). One of those compounds (XIX; \( R = H \)) showed in vitro activity double that of emetine.
(1) Benzacridines:

A number of 7-(dialkyleminalkyl)aminobenzacridines prepared by Elslager and coworkers (26), intended for antimalarial screening, were found to be more effective antismemic agents than the known quinolines and acridines.

Short and coworkers (27) prepared a series of benzacridines of the type (XX; A = H or Cl; n = 3; R = alkyl or aralkyl). The compound (XX; A = H; n = 3; R = n-octyl) was found to be most active (28). Its *in vitro* antismemic activity was found to be almost equal to that of emetine, and 8-times more active than that of chloroquin against hepatic amebiasis in hamsters.
Nitroheterocyclic Compounds:

Cuckler and Kuferberg in 1955 observed that 2-acetamido-5-nitrothiazole (aminitrazole, XXI) cured intestinal amebiasis in rats and dogs (29). Lambert and coworkers (30) subsequently produced 2-amino-5-nitrothiazole derivative (niridazole, XXII) having strong antiamebic and schistosomiac activity. In vitro experiments showed that niridazole had a MIC against E. histolytica similar to that of emetine or 4,7-phenanthroline-5,6-quinone.

A new broad spectral antiprotozoal drug, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole, XXIII) having very striking effect against amebiasis and trichomoniasis (both intestinal and hepatic) and in contrast to niridazole, having no neuropsychiatric complications, was introduced (31,32). On the basis of these observations it may be considered a unique single direct acting amebicide, with low toxicity and its in vitro amebicidal activity is three times than that of emetine (33).

In addition to nitrothiazoles and nitroimidazoles, various nitropyroles (34), nitrofurans (35), nitropyridines (36-38) and nitropyrazoles (39) were found to possess antiamebic activity. Among them 1-(2-hydroxyethyl)-5-nitropyrrrole-2-carboxenamide (XXIV) was found to possess noteworthy activity against intestinal amebiasis in rats and hepatic amebiasis in hamsters (34).
L(+) threo-2-(5-nitro-2-furyl)-5-(p-nitrophenyl)-2-oxazoline-4-methanol (XXV) showed good activity against intestinal amebiasis in rats and dogs (40) while p-hydroxybenzoic acid-(5-nitrofurfurylidene)hydrazide (Erce' furyl) (XXVI) showed activity against amebic dysentry in men (35). 2-(4-Methoxybenzyl)pyrrolidines of the types (XXVII) and (XXVIII) showed potent amebicidal activity (41).

R = H, p-O2NC6H4CO- etc. R1= MeCO-, R2= H, X = 0 etc.

(XXVII) (XXVIII)

Metronidazole proved superior to nitrimidazine1-(N-β-ethylmorpholine)-5-nitroimidazole] and tinadazole (XXIXa) and about equal to α-chloromethyl-2-methyl-5-nitroimidazole ethanol (XXIXb) in amebic liver abscess (42).

(a) R = (CH2)2SO2C2H5; R' = CH3
(b) R = CH2CH(OH)CH2Cl; R' = CH3

(XXIX)

(k) Miscellaneous Compounds

Bliznick and Brckett (43) observed amebicidal activity in 5-bromomethylpyrimidine. Quinoxaline 1,4-dioxide (XXX) and its substituted compounds (44,45) were synthesised.
The compound (XXX) was found to have some efficacy in acute amebic dysentry in man, but could not be used clinically due to its toxic side effects.

4,7-Phenanthroline-5,6-quinone (XXXI) was found to possess amebicidal and antibacterial activity (46). 4,7-Phenanthroline-5,6-quinone was to be clinically effective in the treatment of both acute and chronic amebic infections in man, but it produced some gastrointestinal side effects at doses more than 10 mg/kg. It was subsequently introduced into the market in the name of 'Entobex'.

Sen and coworkers (47,48) prepared several Mannich bases of thiochromanones of the type (XXXII). The thiochromanones were found to possess better amebicidal activity than the corresponding chromanones in vitro, but their in vivo amebicidal activity was not of high order.
Amebicidal activity of camoform, \((4,4'-\text{dihydroxy}-3,3'-\text{diallyl}-5,5'-\text{diethylamino-}
\text{methyldiphenyldihydrochloride})\) (XXXIII) prepared by Burckhalter and coworkers (49)
as an antimalarial agent. Its amebicidal activity was discovered by Thomson and coworkers (50).
Sen and Arora (51) prepared a number of compounds of the type (XXXIV) which might be considered as simplified camoform. Kaushive observed high \textit{in vitro}
amebicidal activity in one compound of this series (XXXIV; \(X = \text{Cl}; R = \text{piperidino}\)).

Neal and Vincent (52) observed that amebicidal activity of 2-diethanolamino-5-
nitropyridine (XXXV) was equal to that of chiniofon in rats. A number of \(6-(\text{mono}
\text{and dialkylamino alkylamino})-3\text{-methyl}-7\text{H}-\text{dibenzo}[f,1,3] \text{-isoquinolines-2,7}[3\text{H}]\text{-diones}\)
(XXXVI) prepared by Elslager and Werbel (53) were found to have \textit{in vitro} amebicidal
property at concentrations of 2 to 67 \(\mu\text{g/ml}\), and all compounds were active against
intestinal amebiasis in rats.

\[
\begin{align*}
\text{XXXV} & \quad \text{XXXVI} \\
\begin{array}{c}
\text{O}_2\text{N} \\
\text{N} \quad \text{Y} = (\text{CH}_2)_2(\text{CH}_2)_3, \\
\text{CH}_2\text{CH}_2\text{OH} \\
\text{CH}_2\text{CH}_2\text{OH} \quad \text{(CH}_2)_5 \quad \text{NR}_1^1\text{R}_2^2 = \text{NET}_2, \text{NHCHMe}_2
\end{array}
\end{align*}
\]

Surrey and Richard (54) prepared a number of \(N,N'-\text{substituted } N,N'-\text{bis(halo-}
\text{acetyl)-1,4-xylylenediamines} \) which were found to be very potent antiasmebic agents, 
both \textit{in vitro} and \textit{in vivo}. Phenylcyclobutenedione tested by Smutny and Roberts (55)
for antiasmebic property, was found to have potent antiasmebic activity both \textit{in vitro}
and \textit{in vivo}.

Chlorophenoxamide ethyl ether was clinically tested by Guidicini and coworkers (56) in man and was found to have very potent amebicidal property.
Aralalkyl substituted resorcinols of the type (XXXVII, where $R^1 = R^2 = \text{5-morpholino-ethyl}; X = H \text{ or } Cl; \text{ Ar} = p-C_6H_4CH_3^-$) prepared by Lord and Wragg (57) were found to have \textit{in vitro} and \textit{in vivo} amebicidal activity against \textit{E. histolytica}. The compounds were active \textit{in vitro} at 1-100 µg/ml.

Aralalkyl alcohols of the type (XXXVIII; where, $X = Y = H; R^1 = R^2 = \text{Et, or } H_2NC_2H_5; n = 3$) were reported (58) to possess \textit{in vitro} antiamebic activity at concentrations of 4 to 100 µg/ml.

\begin{align*}
\text{(XXXVII)} & \quad \text{(XXXVIII)} \\
\end{align*}

A number of diimides of \textit{naphthalene-1,4,5,8-tetracarboxylic acids with basic substituents}, having the general formula (XXXIX; where $X = 3-(\text{diethylaminoethyl})$-phenyl; 4-(diethylaminoethyl)-phenyl; 2-(N-diethylidimino)-phenyl; 4-N-ethyl-N-(5-diethylaminoethyl)-aminophenyl; etc.) were found to have potent antiamebic activity (59).

\begin{align*}
\text{(XXXIX)}
\end{align*}

(B) \textit{Chemotherapy of Trichomomiosis}:

Various compounds were synthesised for finding out a suitable drug against \textit{trichomoniasis}. These compounds may be classified according to their chemical nature into the following groups:
(a) Antibiotics
(b) Quinoline and its derivatives
(c) Thiazoles
(d) Imidazoles
(e) Miscellaneous compounds

Of the above groups, compounds other than antibiotics have been discussed here.

(b) Quinoline and Its derivatives:

The triphosphate of 6-methoxy-2-(4-nitrostyryl)-4-(1-methyl-4-diethylamino-
butylemino)quinoline (XL) inhibited the growth of 7-strains of *T. vaginalis* at
concentrations of 1.5-5 μg/mL (60). 5-Nitro-8-hydroxyquinoline (XLI) and its
derivatives were also found to have activity against *T. vaginalis* (61) at 20-50 μg/mL.

\[
\text{XLI} \\
\text{XL}
\]

3-N-Acyl-4-phenyl-6-haloquinolines (XLII) were found to possess activity against
trichomonas (62). 4-Aryl-3-(thiacylamino)quinolines (XLIII) also showed activity
against trichomonas (63).

\[
\text{XLII}
\]

(e) R = Ac; R' = Br
(b) R = Ac; R' = Cl
(c) R = ClC₆H₄CH₂CO; R' = Cl
Members of this group of compounds possess the unusual property of systemic activity in experimental and natural infections with trichomonads, first observed by Stabler and Mellentin (64).

It is evident that the presence of both the nitro and the amino group was essential for high activity against T. vaginalis. Introduction of halogens, carboxyl group and additional substitutions in position 4, were unfavourable. Acylation of the amino group as in the homologous series of compounds generally resulted in compounds superior (65) to the parent substance entramline, 2-amino-5-nitrothiazole (XLIV). Its acetyl derivative [aminotrozole, acinitrozole, trichorad, tritheone (XLV)] was found to be the most active in animal experiments.

The in vitro activity of tritheone (XLV) was very similar to that of compound, 2-formamido-5-nitrothiazole (XLVI) as described by Bushby and coworkers (66), as well as by Bushby and Copp (67).

A related compound, 2-(2-thionylamino)-5-nitrothiazole (XLVII) prepared by Bret and Legros (68) inhibited growth of T. vaginalis at 100 μg/ml.
Some thiazole carbamates (XLVIII) and thiazolyl oxazolidinones (XLIX) showed trichomonacidal activity (69). 2-(5-Nitro-2-thiazolyl)guanidines (L) also showed activity against T. foetus (70).

Nitrothienyl thiazoles of the type (LI) (where R = 4-pyridyl, 3-methyl-2-pyridyl, or 3-pyridyl; R¹ = H or Me; R² = H, iso-Pr., Br or Cl) also showed activity against T. vaginalis both in vitro and in vivo (71).

Some benzothiazole derivatives like 2-phenoxyacetamido, 2-phenylacetamido and 2-(m-toluoylamino)-5-nitrothiazole showed very high trichomonacidal activity at dilutions 5x10⁻⁵-10⁻⁶ (72).
(d) Imidazoles:

Observation of some definite activity of 1-methyl-4-nitromidazole-5-carboxamide against *T. foetus* in mice led to the extensive investigation of antitrichomonal activity among related nitromidazoles. Antitrichomonal activity was observed in 1-methyl-5-nitromidazole (LII) (73) and its 2-substituted compounds (74, 75). Further investigation in this field led to the discovery of 1-(2-hydroxyethyl)-2-methyl-5-nitromidazole (XXIII) (metronidazole) as the most potent drug against trichomoniasis (76). Numerous (77, 78) clinical studies confirmed the therapeutic utility of metronidazole.

It was later observed that 2-alkyl derivatives of 1-(2-cyanoethyl)-5-nitromidazole (LIII) were about 5 times as active as metronidazole against *T. foetus* infections in mice (79). Furthermore 4-chloro-1-methyl-5-nitromidazole was reported to have a high antitrichomonal activity against *T. vaginalis* infections (80).

The metabolism of metronidazole in human system was studied by several workers. Ings and coworkers (81) isolated the major metabolite, 2-methyl-5-nitromidazolyl acetic acid, while others (82) isolated 1-(2-hydroxymethyl)-5-nitromidazole (oxidation of the 2-methyl group) as the major metabolite.

\[
\begin{align*}
\text{NO}_2 & \quad \text{Me} \\
| & \quad | \\
N & \quad R \\
\text{Me} & \quad \text{CH}_2\text{CH}_2\text{CN}
\end{align*}
\]

(R = F, Carbamoyloxymethyl, Morpholinomethyl)

The *in vivo* trichomonacidal properties of some nitromidazoles of the type (LIV) \((R = \text{H, Me, Et, Pr and Bu}; \ R^1 = \text{H and Me})\) were also determined (78). It was also observed that biological activity was associated with the 1-alkyl-5-nitromidazole nucleus and was strongly influenced by the partition coefficient. Steric
effects and possible metabolic effects were considered. However a few compounds of the structure \( L_{1}V \) also exhibited activity at least five times than that of metronidazole.

Among 5(4)-nitro-4(5)-arylimidazoles synthesised (83), several compounds exhibited high \textit{in vitro} antitrichomonal activity against \textit{T. vaginalis} and \textit{T. foetus} and moderate activity against \textit{E. histolytica}.

Several 1-substituted-2-methyl-5-nitroimidazoles and 1-substituted-2-methyl-4-nitroimidazoles in which the substituents were \( -CH_{2}CH_{2}R \) \( (R = Cl, Br, I, OPh, OEt, CH_{2}CH_{2}Cl, CH_{2}CH_{2}I \text{ or } CH_{2}CH_{2}OH) \), \( CH_{2}CO_{2}Et \), \( CH_{2}COOH \) or \( CH_{2}CN \) with potential antitrichomonal activity, were prepared (84).

\( N-(\beta\text{-Morpholinoethyl})-5\text{-nitroimidazole} \), \( N-(\beta\text{-pyrrolidinoethyl})-5\text{-nitroimidazole} \) and \( N-(\beta\text{-diethylaminoethyl})-5\text{-nitroimidazole} \) exhibited antitrichomonal activity (85).

5-Nitroimidazoles of the type \( LV \) were found to be effective particularly in the treatment against infections due to \textit{T. vaginalis} and \textit{T. foetus} in human and cattle respectively (86). In this series of imidazoles, compounds \( LV \) \( (R^{1} = Me; R^{2} = isopropyl) \) and \( LV \) \( (R^{1} = EtSO_{2}CH_{2}-CH_{2}; R^{2} = Me) \) were found to be about 8-times as effective as metronidazole.

The increased activity of these compounds was attributed due to their increased lipid solubility and non-metabolism \textit{in vivo}. 

\[ \text{Diagram of } LV \]
The use of nitroimidazoles for the treatment of protozoan and, to some extent, metazoan infections is becoming increasingly more important. Furthermore a given member of this class of compounds is frequently effective against a variety of parasites. The 5-nitroimidazoles have generally proved to be superior to the 4- and 2-nitroimidazoles (87) as antiparasitic agents.

Dimetridazole (XXIXc) continues to be used in veterinary medicine against trichomonas in cows (88). Metronidazole, the standard drug against T. vaginalis and T. foetus infections, has gained some prominence as an intestinal and hepatic amebicide (89). Ronidazole (XXIXd) (90) and ipronidazole (XXIXe) (91,92) have antitrichomonal properties (78). Compound (XXIXb) (E07-0207) was found to be highly active against E. histolytica, intestinal in rats and hepatic in hamsters (93). Tinidazole (XXIXa) (94), was found to be 4-16 times as active as metronidazole against T. vaginalis and T. foetus. Nitrimidazole (XXIXf) on clinical trial as a trichomonastat (95,96) was reported to be inferior to that of metronidazole (97). Panidazole (XXIXg) when tested clinically as an amebicide was found to be effective at doses of 100 mg, 2-times daily for 4 days (98). NIF-nitroimidazole (XXIXh) was reported to be particularly effective against amebiasis and flumidazole (MK-915) (XXIXi) against T. vaginalis and T. foetus (99). Compound (XXIXj) was reported to be 7-8 times as potent as metronidazole against trichomonas (100) and it was found to be an effective intestinal and hepatic amebicide (101). Compound (XXIXk) was reported to be an effective trichomonacide.
Some 2-styryl 5-nitroimidazoles were found to be comparable to that of metronidazole against trichomonas but in general inferior to the later in other protozoal infections (102).

Nitroimidazoles were studied from constitutional and physicochemical standpoints with respect to antitrichomonal activity (103). 1,1'-Di-methyl 2,2'-biimidazoles (LVIA, LVIB) (104) on nitration gave a variety of compounds which were evaluated against T. vaginalis, E. histolytica. It was observed that compounds with two nitro groups were generally more active than compounds with one nitro group. 2-Methyl-1-substituted-5-hydroxyalkyl-4-nitroimidazoles also showed antitrichomonal activity.
Some 2-(4-cetoxyctyryl)-5-nitro-1-vinyl-imidazole (LVII) and related compounds are active against *T. vaginalis*.

![Chemical structures of LVII and LVIII](image)

(e) *Miscellaneous Compounds*:

4,7-Phenanthroline-5,6-quinone (XXXI) and its mono semicarbazone derivative inhibited the growth of *T. foetus* in serum broth at a concentration of $1.6 \mu g/ml$ (46).

1-(2-Hydroxyethyl)-5-nitropyrrrole-2-carboxamide (XXIV) is equally effective to that of metronidazole against *T. vaginalis* (34, 105).

2-[2-(5-Nitro-2-furyl)vinyl]-5-amino-1,3,4-oxadiazole (LVIII), inhibited growth of *E. coli* and *T. vaginalis* (106).

$N$-(5-Nitro-2-furfurylidene)-3-amino-5-methyl-thiomethyl-2-oxazolidinone (LIX) was useful in the treatment of *T. vaginalis* (107).

![Chemical structures of LVIII and LIX](image)

Investigation on antitrichomonal activity of a large number of 2-substituted-5-nitrofuran derivatives against *T. vaginalis* revealed that a number of compounds...
possessing the general structure (LX) showed strong activity, at a minimum inhibitory concentration (MIC) of 1.00 μg/ml or less, where R was 2-benzimidazolyl, 6-(3-methylpyridyl) or similar substituent (108). 2-(5-Nitro-2-furyl)benzimidazole (LXI) was also found to be an effective antibacterial and antitrichomonal agent and its MIC against T. foetus was 0.39 μg/ml (109).

2-(5-Nitro-2-furyl)benzimidazoles (LXII) were used as bactericides, fungicides, protozoicides. MIC of (LXII: R = MeO; R' = H) was 1 μg/ml against T. vaginalis (112). Ethyl 2-acetyl-3-(5-nitro-2-furyl)acrylate (LXIII) showed trichomonacidal properties against T. vaginalis and it was only slightly active in vitro against E. histolytica (110). (5-Nitro-2-furyl)-thiadiazolyl hydantoins were found to be active against T. vaginalis at a concentration of 25 μg/ml. 3-Methyl-1-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl] hydantoin (LXIV) and its 3-ethyl and 5-ethyl-3-methyl analogues were found to be 4 times as active as metronidazole against T. vaginalis (111).
1-Phenyl-4-(alkyl)-2-piperazinones (LXV) possess trichomonacidal and antifungal activity (112).

2H-[1]Benzothiopyreno-[4,5,2-cd]indazole derivatives (LXVI) have bactericidal, schistosomicidal and trichomonacidal properties (113).

Pyrithione (LXVII) was found to inhibit the growth of T. vaginalis cultures in vitro at a concentration of 0.125 μg/ml (114).

Nitrimizazine (LXVIII) showed a faster trichomonacidal activity at in vitro testing against T. vaginalis than metronidazole (115) at the same concentration.

β-Substituted aryl or β-eryloxy β-phenethyl or γ-phenoxy propyl piperazines of the types (LXIXα and LXIXβ) showed trichomonacidal activity (116).

A wide variety of other nitroheterocyclic compounds like nitrothiophenes (117) and nitropyrazoles (39) possess activity in experimental trichomoniasis infections.

\[
\text{RXOCHR'}\text{CH}_2\text{N}^\text{Me} \quad \text{RXOCH(\text{CH}_2\text{OR'})CH}_2\text{N}^\text{Me}
\]

\[
\text{RXOCHR'}\text{CH}_2\text{N}^\text{Me} \quad \text{RXOCH(\text{CH}_2\text{OR'})CH}_2\text{N}^\text{Me}
\]

\[
\text{R} = \text{mono, di-, trichlorophenyl}
\]

\[
\text{R'} = 3,4-\text{Cl}_2\text{C}_6\text{H}_3\text{ etc.}
\]

\[
\text{X} = \text{CH}_2, \text{ CO etc.}
\]