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Review Paper

5-Nitroimidazole derivatives: A scope of Modification for Medicinal chemists

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Abstract

The 5-nitroimidazole is an important class of imidazole based drugs. The 5-nitroimidazoles are a well-established group of protozoal and bactericidal agents but after discovery of imidazole drugs many protozoa and bacteria has developed resistance towards drugs in market. Due to this fact there is a need for medicinal chemists to work on this pharmacophore and develop new hybrid molecules which may give lead molecule for further studies. Many modifications have been done on 5-nitroimidazole nucleus and new hybrid molecules have been synthesized but still there is a huge scope of modification. The imidazole moiety exhibit wide range of biological activities. This article aims to review the work done in past few years, on 5-nitroimidazoles derivatives synthesis and activity of resulting hybrid molecules.

Keywords: *Trichomonas vaginalis*, *Gardnerella vaginalis,* anti-tubercular, dithiocarbamate, *Proteus mirabilis.*

Introduction

Parasitic and bacterial infections of the gastrointestinal tract are responsible for significant morbidity and mortality worldwide. 5-Nitroimidazoles class of drugs are a well-established group of antiprotozoal and antibacterial agents that have potential to inhibit the growth of anaerobic bacteria and certain anaerobic protozoa, for example *Trichomonas vaginalis*, *Entamoeba histolytica* and *Giardia lamblia*[1,2]. The importance of imidazole is prevalent from the fact that large number of drugs in use today contain this moiety and several 5-nitroimidazole derivatives such as metronidazole (1), tinidazole (2), ornidazole (3), secnidazole (4), ronidazole (5) and azomycin (6) have been used since long time, for the treatment of crtical cases of infections caused by protozoa and anaerobic bacteria[3-5]. They have many other biological activities of therapeutic importance such as radiosensitizers in treatment of cancer[6-8], control of fertility[9] and use as antitubercular agent[10,11]. 5-nitroimidazole derivatives have also been tested in cell-based assays and in enzyme assays against HIV-1 recombinant reverse transcriptase[12,13]. 2-Nitroimidazoles play a vital role as bioreductive markers for tumour hypoxia, as radiosensitizers[14-16] and some are also known to demonstrate antiprotozoan activity. Some dinitro and mononitro imidazole derivatives were found as potent radiosensitizers, antibacterial or antiepileptic and antiprotozoal agents[17].

5-Nitro imidazole drugs: Since long time large number of 5-nitroimidazole based drugs are in use. The important drugs are metronidazole (1), tinidazole (2), ornidazole (3), secnidazole (4), ronidazole (5), Azanidazole (7), Dimetridazole (8) and Nimorazole (9). Initially, azomycin (6) was discovered as an antiprotozoal and antibacterial agent and later metronidazole (MTZ, 1-[2-hydroxyethyl]-2-methyl-5-nitroimidazole) replaced it because of its less side effects and more effectiveness against protozoal and bacterial infections[18,19]. MTZ has been a drug of choice in the treatment of anaerobic infections and prophylactically in gynaecological and colonic surgery[20,21]. MTZ has been used effectively in the treatment of anti-infectious diseases against protozoa such as *Entamoeba histolytica, Trichomonas vaginalis*, *Giardia intestinalis* and various other infections caused by Gram-positive and Gram-negative anaerobic bacteria[22,23,24]. Due to its vital role in defence against *Helicobacter pylori* infections, metronidazole has been included in the ''essential medicines'' list by the WHO[25,26,27]. More often, MTZ has been used for the treatment of infections caused by *Clostridium difficile* and anaerobic infections after bowel surgery[28]. Some other uses of MTZ include radiosensitization of hypoxic tumors and treatment of Crohn's disease[29]. After discovery of MTZ in 1959, it has been among the top 100 most prescribed drugs in the US and is one of the 10 most prescribed drugs used during pregnancy all over the world[30]. After oral administration MTZ is quickly and completely absorbed and penetrates body tissues and secretions such as saliva, vaginal secretions and semen. The drug is metabolized in the liver and is excreted in the urine. However, resistance to MTZ have been developed in *Bacteroides fragilis* and *trichomonads*, in both natural and *in vitro* under drug pressure-induced populations[31,32]. Protozoa and anaerobic bacteria develop resistance to metronidazole by abolishing or reducing the activity of elements of series of electron transport reactions, this result in an insufficient rate of accumulation of reduced metabolites or by increasingly futile cycling, also oxygen is found to alter the effectiveness of metronidazole. Tinidazole is an anti-parasitic drug used against protozoan infections. After its discovery in 1972[33], it has been drug of choice throughout Europe and the developing world for treatment of a variety of parasitic and amoebic infections. Secnidazole is another important nitroimidazole anti-infective agent which is effective in the treatment of *Aopobium vaginae* and against *dientamoebiasis*[34,35].

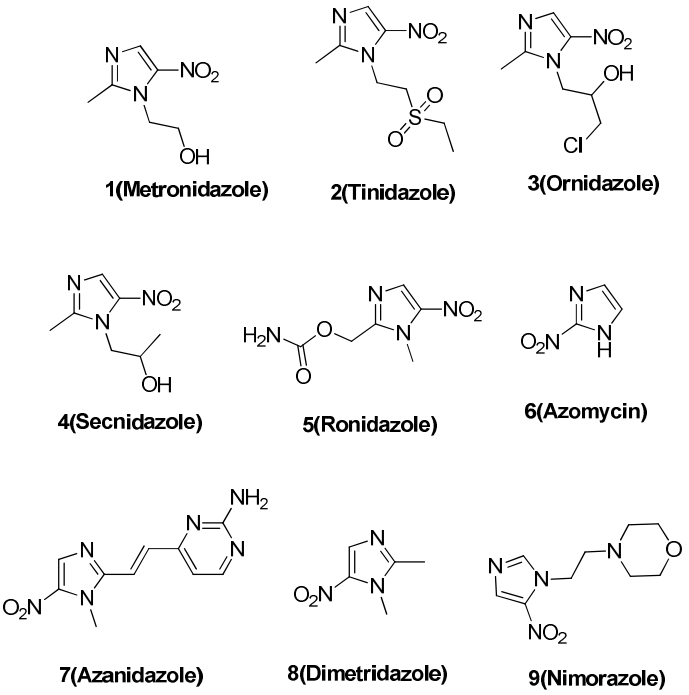


Figure-1
Nitroimidazole drugs

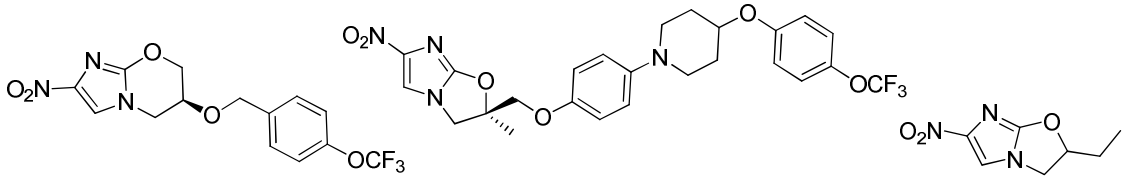


Figure-2
Nitroimidazole compounds under clinical trials.

Ornidazole is a widely used drug in protozoan infections and also been found effective in treatment of Crohn's disease after bowel resection[36].

Nitroimidazole based compounds were found effective in the treatment of tuberculosis and this lead to the discovery of many potent nitroimidazole based anti-TB agents. Two nitroimidazole analogues PA824 (10) and OPC67683 (11) are currently in the clinical trials[33,34]. It has been found that under low oxygen conditions *Mycobacterium tuberculosis* (M.tb.) cultures become sensitive on treatment with MTZ[35-37]. The 4-nitroimidazoles analogues of MTZ initially synthesized as radiosensitizing agents were later found to have potent activity against *M. tb*.[38-40]. Among large number of 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole derivatives, compound 2-ethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (9, CGI-17341) emerged as an interesting compound with significant activity *in vitro* and *in vivo* against *M. tb* strains. The nitroimidazole (S)-2-nitro-6-(4-(trifluoromethoxy)-benzyloxy)-6,7-dihydro-5H-imidazo [2,1-b][1,3] oxazine (10, PA824), is a new class of compound which is found to show anti-tubercular activity under hypoxic conditions, efficacy in the mouse model of TB infection with no cross resistance to current TB drugs[41]. At present, PA824 is being developed as a drug molecule by the Global Alliance for TB Drug Development[42].

Mechanism of Action: Nitroimidazoles are cytotoxic to anaerobic bacteria such as *Gardnerella vaginalis* and *Helicobacter pylori* [43]. Mechanism against anaerobic bacteria can be divided into four-step process:

Entry into the microorganism: Due to its low Metronidazole diffuses across the cell membranes of aerobic and anaerobic microorganisms. However, antimicrobial activity is shown only against anaerobes[43].

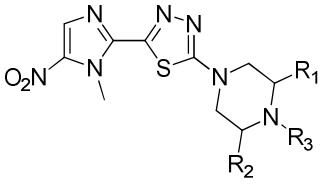
Reductive activation by intracellular transport proteins: Due to reduction of MTZ by pyruvate ferredoxin oxidoreductase system in the mitochondria of obligate anaerobes its chemical structure is altered. Normal function of Pyruvate ferredoxin oxidoreductase is to generate ATP via oxidative decarboxylation of pyruvate. Due to presence of nitroimidazole in the cellular environment, electrons that would usually be transferred to hydrogen ions in the cycle are captured by nitro group. Reduction of nitroimidazole creates a concentration gradient that drives more amount of drug into cell of obligate anaerobes, and this further promotes formation of intermediate compounds and free radicals that are toxic to the cell of obligate anaerobes[43-45].

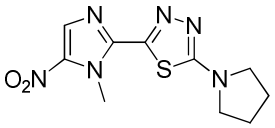
Interaction with DNA of bacteria: Reduced intermediate species formed are Cytotoxic to obligate anaerobes. These intermediate compounds and free radicals interact with host cell DNA, resulting in DNA strand breakage and fatal destabilization of the DNA helix[46,47].

Breakdown of cytotoxic intermediate products: Finally, the toxic intermediate compounds decay into inactive end products[48]. Nitroimidazole derivatives exerts rapid bactericidal effects against anaerobic bacteria and killing rate is found proportional to drug concentration[49,50]. Concentration-dependent killing has been observed in case of *Trichomonas vaginalis* and *Entamoeba histolytica*[51,52]. Clindamycin is found to kill *bacteroides fragilis* and *Clostridium perfringens* less rapidly as compared with Nitroimidazole derivatives[53].

Synthesis of derivatives of 5-nitroimidazoles and their biological activities

Mohammad Hassan et al. synthesized 5-nitroimidazole derivatives. A series of 5-nitroimidazole- 1,3,4-thiadiazoles hybrid molecules were synthesized and screened for antibacterial activity against *Helicobacter pylori* (figure-3).



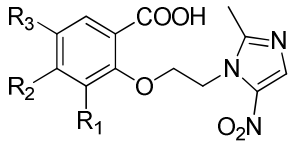


7

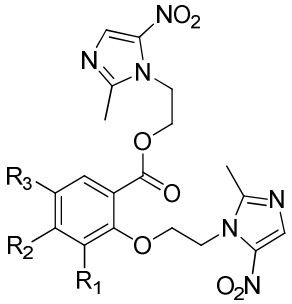
6a: R_1= R_2= R_3= H
6b: R_1= R_2= H, R_3= Me
6e: R_1= Me, R_2= R_3= H
6f: R_1= R_2= Me, R_3= H

Figure-3

The *anti-H. pylori* activity of newly synthesized hybrid molecules along with standard drug metronidazole was evaluated by the paper disc diffusion bioassay. The inhibition zone diameters were determined for new molecules and standard drug. It was found that compound 6a, 6b, 6e, 6f and 7 showed activity better than standard drug metronidazole [54]. Wen-Jun Mao et al. synthesized metronidazole derivatives and those derivatives exhibited potent *Helicobacter pylori* urease inhibitor activity. The acetohydroxamic acid was used as standard which is very potent *H. pylori* urease inhibitor. Some of the derivatives exhibited activity comparable with standard drug. The structure activity relationship was better understood from docking studies[55] (figure-4).



3a: R_1= H, R_2= Me, R_3= H
3b: R_1= H, R_2= NH_2, R_3= H
3c: R_1= NO_2, R_2= H, R_3= NO_2
3d: R_1= I, R_2= H, R_3= I
3e: R_1= Br, R_2= H, R_3= Br
3f: R_1= Cl, R_2= H, R_3= Cl



4a: R_1= H, R_2= Me, R_3= H
4b: R_1= H, R_2= H, R_3= Br
4c: R_1= H, R_2= H, R_3= I
4d: R_1= H, R_2= H, R_3= SO_3
4e: R_1= H, R_2= H, R_3= Me
4f: R_1= Me, R_2= H, R_3= H
4g: R_1= H, R_2= H, R_3= Cl
4h: R_1= H, R_2= Cl, R_3= H

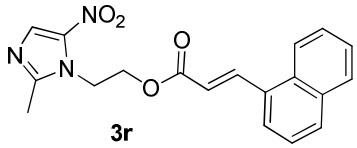
Figure-4

Yong et al. synthesized cinnamic acid metronidazole esters. These novel compounds acted as potential HER-2 kinase and EGFR inhibitors. These hybrid molecules on anti-proliferative essay showed good anti-proliferative against MCF-7. Hybrid molecule 3h which exhibit potent inhibitory activity in tumour growth may act as lead in development of potent anticancer agents[56] (figure-5).

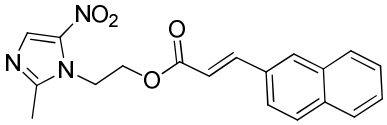
Beena et al. synthesized various metronidazole-triazole conjugates. These compounds were screened for antibacterial activity against gram negative and gram positive bacteria. These molecules showed weak to potent antibacterial activity. In comparison with standard drug some hybrid molecules exhibited equal or better activity against gram negative and gram positive bacteria[57] (figure-6).

Javier et al. synthesized nitroimidazole containing Tc complexes with intention to develop potential ^{99m}Tc-radiopharmaceuticals for imaging hypoxia based on the formation of Tc-nitrido complexes; two novel metronidazole containing Tc-dithiocarbamate derivatives were synthesized in excellent yield[58] (figure-7).

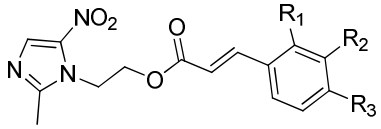
Bertinaria et al. synthesized NO-donor metronidazole hybrids. These compounds were tested for activity against various strains of *Helicobacter pylori*. All synthesized analogues exhibited good *Helicobacter pylori* activity[59] (figure-8).



3r



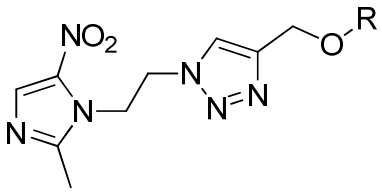
3s

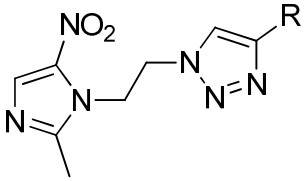


3a:R_1=H, R_2=H, R_3=F
3b:R_1=H, R_2=H, R_3=Cl
3c:R_1=H, R_2=H, R_3=Br
3d:R_1=H, R_2=H, R_3=H
3e:R_1=H, R_2=H, R_3=Me
3f:R_1=H, R_2=H, R_3=OMe
3g:R_1=H, R_2=H, R_3=*i*-Pr
3h:R_1=H, R_2=H, R_3=Ph
3i:R_1=H, R_2=H, R_3=$PhCH_2O$

3j:R_1=F, R_2=H, R_3=H
3k:R_1=Cl, R_2=H, R_3=H
3l:R_1=Br, R_2=H, R_3=H
3m:R_1=NO_2, R_2=H, R_3=H
3n:R_1=OMe, R_2=H, R_3=H
3o:R_1=H, R_2=NO_2, R_3=H
3p:R_1=H, R_2=F, R_3=H
3q:R_1=H, R_2=OMe, R_3=H

Figure-5



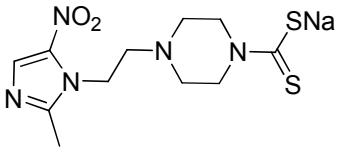


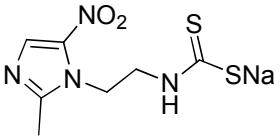
6a, R=H; 6b, R=Me;
6c, R=COEt; 6d, R=THP;
6e, R=Ph; 6f, R=*o*-Me-Ph;
6g, R=*p*-Me-Ph; 6h, R=*m*-Me-Ph;
6i, R=*o*-NO_2-Ph; 6j, R=*p*-NO_2-Ph;
6k, R=*o*-CHO-Ph; 6l, R=*p*-CHO-Ph;
6m, R=*p*-CH_3CO-Ph; 6n, R=*o*-Cl-Ph;
6o, R=*p*-Cl-Ph

7a, R=CH_2CH_2OH; 7b, R=CH_2Br
7c, R=Ph; 7d, R=2-Pyridine;
7e, R=3-Pyridine; 7f, R=1-Cyclohexanol

Figure-6

Dithiocarbamates





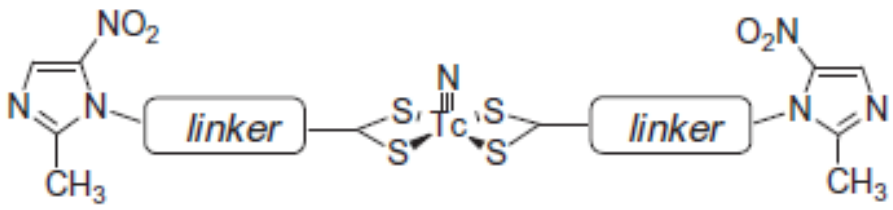


Figure-7

Seref et al. synthesized 5-nitroimidazole derivatives and screened these molecules for antibacterial activity. These compound exhibited good antibacterial activity. The hybrid molecules were also screened for anti-fungal activity but they were found ineffective against fungi[60] (figure-9).

Lalit et al. synthesized Imidazole derivatives which exhibited potent activity against microbicides. These compounds were also found active against *Trichomonas vaginalis* and were able to immobilize spermatozoa at very low concentration. Most of the compounds were found highly safe towards HeLa[61] cell line upto 200 µg/ml (figure-10).

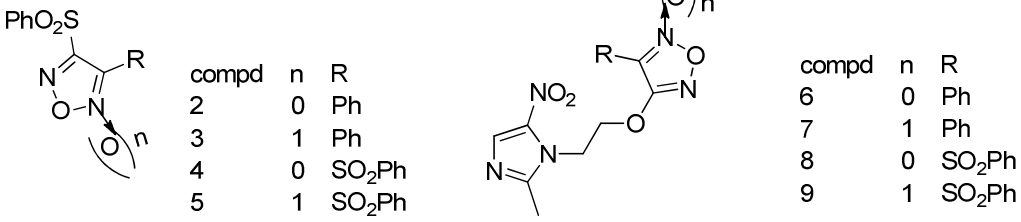
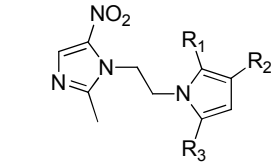


Figure-8



comp.	R1	R2	R3
5a	H	H	H
5b	CH_3	H	CH3
5c	CH_3	$COOC_2H_5$	Ph
5d	CH_3	$COOC_2H_5$	4-OMe-Ph
5e	CH_3	$COOC_2H_5$	4-Cl-Ph
5f	CH_3	$COOC_2H_5$	4-NO_2-Ph

Figure-9

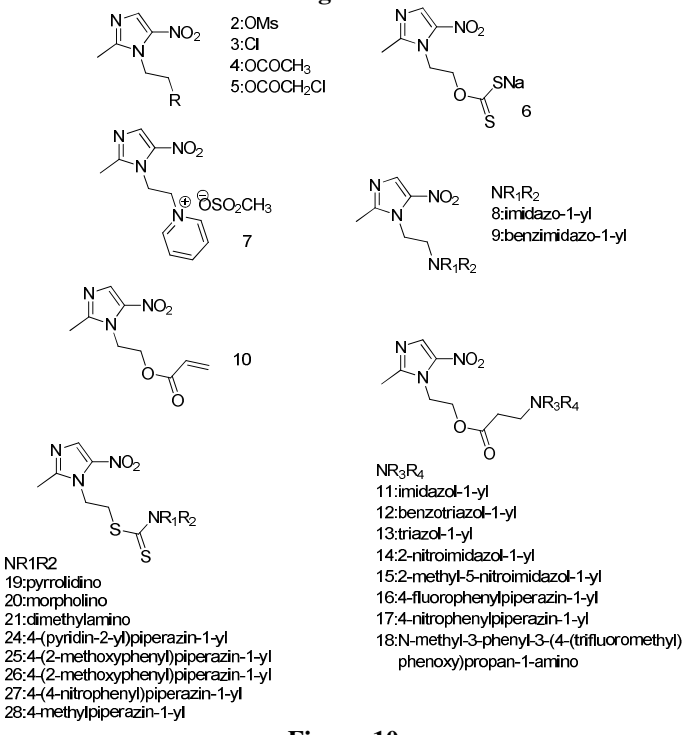


Figure-10

Haythem et al. synthesized nitroimidazole derivatives which showed good activity against *Giardia intestinalis* and *Entamoeba histolytica*[62] (figure-11).

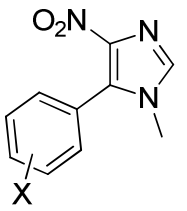


Figure-11

Abdul Jabar Khatia synthesized metronidazole hybrid molecules containing 1,3-oxazoline, thiadiazole, Schiff's bases, 1,2,4-triazole moieties and oxadiazole. The imidazole derivatives were tested for antibacterial activity by the agar disc-diffusion method against *Proteus mirabilis, Staphylococcus aureus* and *Escherichia coli* bacteria. Some of the hybrid molecules exhibited excellent activity against *Staphylococcus aureus, Proteus mirabilis* and *Escherichia coli* bacteria[63] (figure-12).

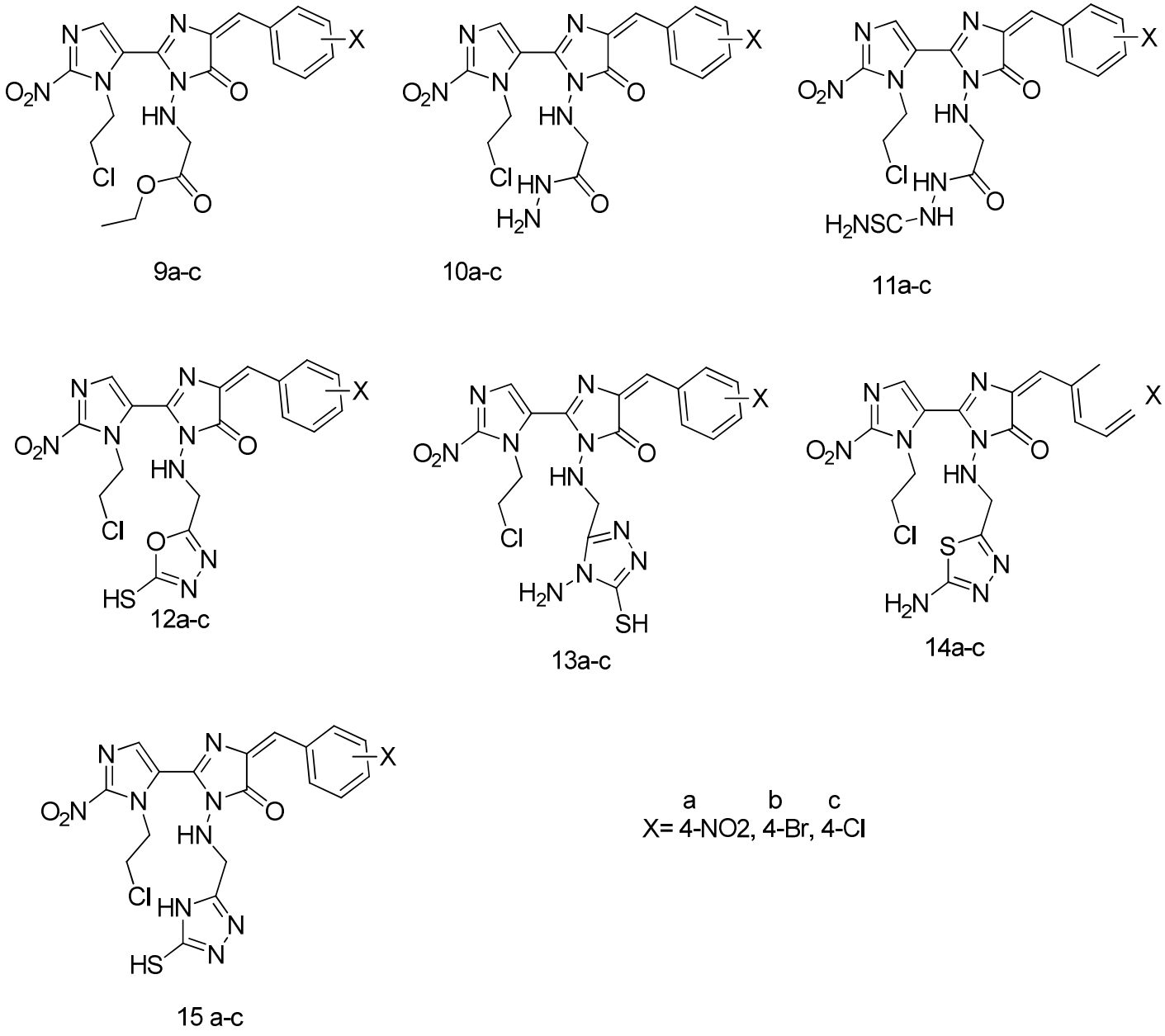
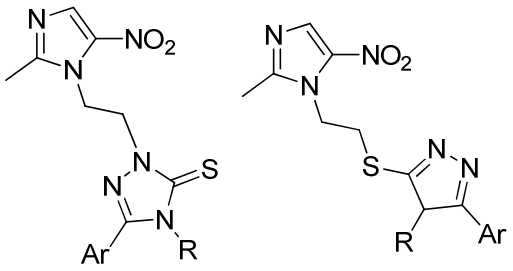


Figure-12

Haythem et al. synthesized 1,2,3-triazol-2-thiol derivatives of nitroimidazoles. These molecules exhibited antibacterial and antifungal activities[64] (figure-13).

Lalit *et al*. synthesized nitroimidazole Scaffold which exhibited activity against resistant *Trichomonas* and the experimental results were confirmed with docking studies to study structure activity relationship[65] in better way (figure-14).

Abid *et al.* synthesized nitroimidazole derivatives which exhibited potent anti-amoebic activity[66] (figure-15).



Ar= 4-pyridyl, 3- pyridyl
R=-Me, Ph, 4-OMe-Ph, 1-Napthyl

Figure-13

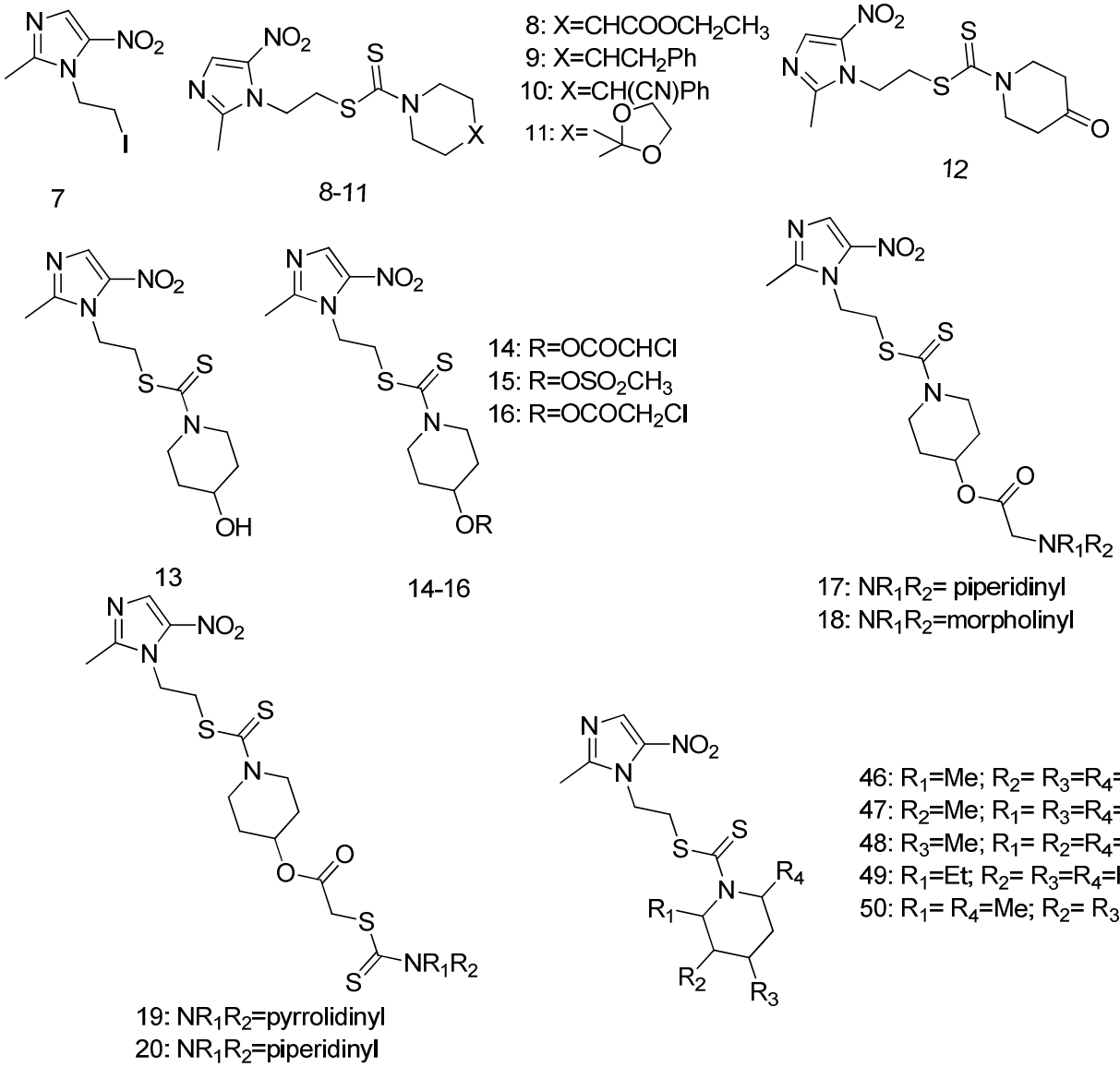
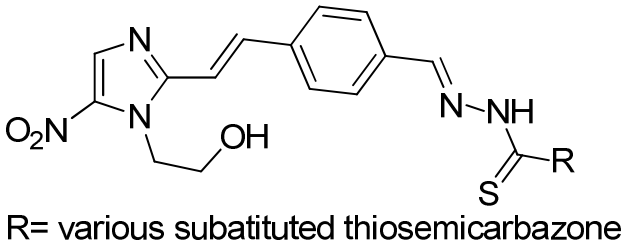


Figure-14



R= various subatituted thiosemicarbazone

Figure-15

Conclusion

On basis of above literature survey, it could be concluded that nitroimidazoles are very important class of pharmacophores with wide range of biological activities. Also it could be understood that nitroimidazoles are active against bacteria and protozoa which are responsible for diseases with high morbidity. The work done on these compounds is meager. The ease of reactions of nitroimidazoles allows medicinal chemist to easily modify the existing molecules and synthesize hybrid molecules for biological screening. There is huge scope of modification on existing nitroimidazole drug molecules by synthesizing hybrid molecules. The nitroimidazole drugs like metronidazole , tinidazole, ornidazole and secnidazole contains functional groups like –OH which can be easily converted into various other functional groups this increases ease of medicinal chemist to synthesize hybrid molecules. Some of resulting hybrid molecules may give lead molecule which can be considered for further modification. Nitroimidazole is a moiety which needs attention of medicinal chemists so that more hybrid molecules are synthesized which show better effect and low toxicity.

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