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Dithiocarbamates: A Versatile Class of Compounds in Medicinal Chemistry

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Abstract: Dithiocarbamate (DTC) group is found in a number of biologically active molecules as a pharmacophore. Compounds containing DTC as pharmacophore exhibit diverse chemical and medicinal versatility. Dithiocarbamates have been used as pesticide and fungicide since 20th century but thereafter they have attracted the interest of medicinal chemists due to the strongly nucleophilic character and the unique redox properties of the sulfur atom which make it a key residue for enzyme catalysis, protein folding, and redox signaling and regulation. Owing to their strong metal-binding capacity, they can also act as enzyme inhibitors. One of the main objective of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. Present review collectively describes the most significant chemical and pharmacological properties of DTCs.

Keywords: Dithiocarbamate, Organosulfur, Anti-cancer, Anti-HIV, Spermicidal, Microbicidal

1.1. Introduction

Organosulfur compounds are important intermediates for the synthesis of various biologically active molecules.[1] Dithiocarbamates (DTCs) are a group of organosulfur compounds that have extensively been used as pesticides in agriculture for more than 50 years with some products being already introduced in the 1930s.[2] The first derivative of a DTC to achieve prominence as a fungicide was tetramethylthiuram disulfide (TMTDS, **1**, Figure 1), more commonly known as thiram.[2] The yearly consumption of DTCs is between 25,000 and 35,000 metric tonnes.[3] Most of the DTCs are applied as fungicides and some of them are classified by the World Health Organization (WHO) as being hazardous.[4] In industry, DTCs are used as accelerators for rubber vulcanization, rubber antioxidants, slimicides in pulp and paper as well as in sugar production, in waste water treatment, and as antifoulant for water cooling systems.[3,5,6]

The first DTCs were prepared from a monoamine and carbon disulfide in 1934.[7] In

1940, W. F. Hester of Rohm and Haas, Inc., prepared a dithiocarbamate from a diamine. Hester's compound, disodium ethylene bisdithiocarbamate (nabam), can be considered the first true ethylene bisdithiocarbamate (EBDC, **2**, Figure 1). A patent was awarded on the compound in 1943, and the published scientific report appeared in print in the same year.[8] Tetraethylthiuram disulfide (TETDS, **3**, Figure 1), better known as disulfiram, has been used in the treatment of alcoholism for more than 50 years.[9]

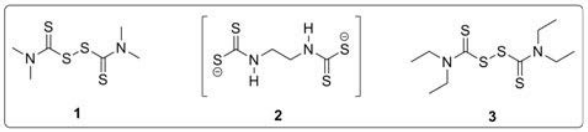

Figure 1: Structure of TMTDS (**1**), EBDC (**2**) and TETDS (**3**)

Now a days, DTCs have drawn a lot of attention due to their presence in various biologically active compounds.[10] Compounds having sulphur containing functional groups along with another functional groups are of massive interest due to more than one pharmacophore within one molecule.[11] DTC is a desirable functional group in various medicinally significant compounds and utilized as microbicidal spermicides,[12] anesthetic,[13] fungicidal,[14] anti-HIV,[15] mono glyceride lipase inhibitors,[16] anti-tumour,[17] anti-alcoholism [18] *etc*. Due to a wide range of uses and applications of DTC derivatives having different substitution patterns, a lot of chemistry is being done all over the world and we have explored a novel oxygen-sulphur rearrangement reaction recently using a cyclic dithiocarbonate as a substrate.[19] Additionally, we have discovered a green and facile regioselective synthesis of dithiocarbamate derivatives containing disulfide linkage by the ring opening reaction of trithiocarbonate with amines under solvent and catalyst free conditions.[19]

The strongly nucleophilic character and the unique redox properties of the sulfur atom in DTC group make it a key residue for enzyme catalysis, protein folding, and redox signaling and regulation,[20] which are important for cellular energy metabolism, motility and subsistence of cellular systems. Owing to their strong metal-binding capacity, they can also act as enzyme inhibitors, such as indoleamine 2,3-dioxygenase, which plays an important role in tumour growth.[21] DTCs have also been used in the synthesis of trifluoromethylamines,[22] thioureas,[23] aminobenzimidazoles,[24] isothiocyanates,[25] alkoxyamines,[26] 2-imino-1,3-dithiolane,[27] and total synthesis of (-)-aphanorphine.[28] These compounds can be used to synthesize the compounds of various biological interests. Furthermore, natural conjugated peptides with DTC have been the potent source of lead compounds in drug discovery albeit with limited utility due to their poor pharmacokinetic properties, rapid metabolism and low bio-availability.[29] The DTC functionality chelates heavy metals that make them versatile ligands,[30] and are applicable as NO scavengers. Furthermore, the functionalized DTCs such as benzamide-based thiocarbamates have been developed as HIV-I NCp7 inhibitors.[31] In correlation with other non-amide tethers such as ureas and carbamates, incorporation of DTC into peptide backbone may result in out of the ordinary class of molecules. Hence, a variety of dithiocarbamate-linked peptidomimetics have been developed to introduce drug-like character along with increased potency, target specificity and longer duration of action.[32] Additionally, DTCs have been used for the protection of amino groups in peptide chemistry,[33] as a linker in solid phase organic synthesis,[34] and recently in the synthesis of ionic liquids.[35]

The above properties of DTC group make it a versatile pharmacophore and hence, it is used in the compounds of biological interest. During the past decade, number of DTCs were synthesized and evaluated for various biological activities.[36]

Following are some important class of diseases where DTCs have shown crucial role as a pharmachophore.

1.2. DTCs in Cancer Chemotherapy

In present time, cancer is the biggest health hazard for the human being[37]. Despite the dramatic development of antitumour drugs, the cancer death rate is remain constant (200 deaths per 100,000 people) over the last 30 years. Cancer is the second most common cause of death in the US, exceeded only by heart disease and cancer accounts for 1 of every 4 deaths.[38,39] Cisplatin, carboplatin, oxaliplatin, nedaplatin and lobaplatin (**4**-**8** respectively; Figure 2), are currently used platinum based anticancer drugs.[40,41]

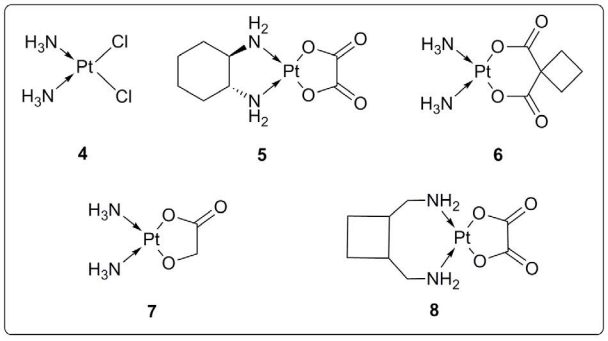

Figure 2: Structure of some platinum based anticancer drugs

Platinum based drugs are assumed to induce apoptosis (programmed cell death) in targeted organism by distorting its DNA and by triggering cellular processes.[42,43] These drugs have high affinity for sulphur atom and thus interact with sulphur containing biomolecules like amino acids (cysteines and methionines), peptides (glutathione), proteins (metallothionein) and many others.[44]

Since, DTC group contains two sulphur atom which would interact with metal atom to reduce the cytotoxicity of platinum based drugs by selective removal of platinum from enzymee thiol complex by nucleophilic attack of sulphur atoms on platinum moiety. In addition to this, they have the potency to protect the normal tissues without undermining the cytostatic activity of parent drugs.[45] On the basis of structure and thermodynamic resemblance between palladium(II) and platinum(II) complexes,[46,47] there is also much interest in the synthesis and designing of palladium substitutes that can have maximum pharmacological action. Mixed ligand DTC-amine complexes of palladium(II) have antitumour activity comparable to the cisplatin and circumvented the cross resistance to cisplatin. Additionally, DTCs have the ability to stabilize transition metals in a variety of oxidation states. [48]

Keeping view in these points, plenty of DTC complexes with Pd(II) (**9**, Figure 3) have been synthesyzed and evaluated for their antitumour activity. The antitumour screening of these comlexes verified them to be highly active against cisplatin resistant DU145 human prostate cancer cells and need further investigations to be marketed as a new anticancer drug.[48]

Similar to Pd(II) and Pt(II), it was put forward that the biological action of gold(III) complexes and their antitumor activity is possibly mediated by direct interaction with DNA.[49] Gold(III) compounds are emerging as a new class of metal complexes with outstanding cytotoxic properties and are presently being evaluated as potential antitumor agents. However, DTC complexes of Gold(III) (**10**-**13**, Figure 3) have been recently proved to be much more cytotoxic *in vitro* than cisplatin even toward human tumour cell lines intrinsically resistant to cisplatin itself via different mode of action.[50,51] Hence, a series of complexes with diethyldithiocarbamate ligand and three different metals (Ni, Cu, Zn) have also been prepared (**14**, Figure 3) and tested in human breast cancer MDA-MB-231 cells. These metal complexes with EtDTC have different capabilities to inhibit purified 20S

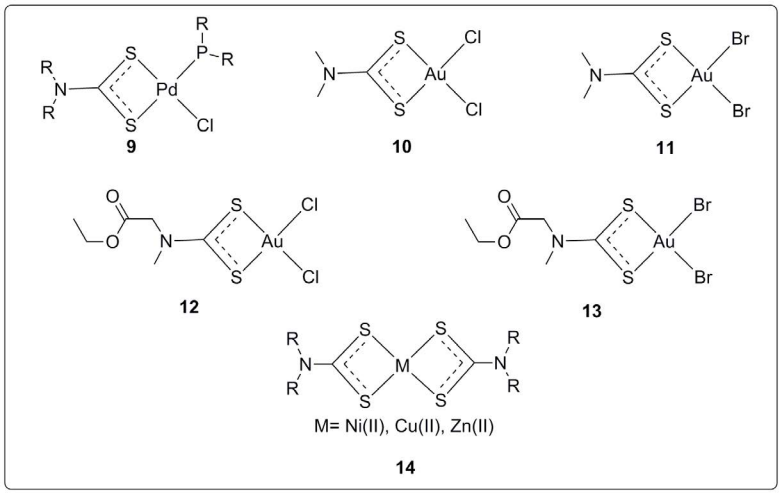

Figure 3: General structure of DTC complex of Pd(II) (**9**), Au(III) (**10**, **11**, **12**, **13**) and M(II) (**14**)

proteasome and cellular 26S proteasome.[52]

Along with above DTC metal complexes, number of simple DTC derivatives have been reported for their anti-proliferative action in the literature.[17] Some privileged structures receiving special attention have been found to possess excellent anti-tumour activity.[53,54] For example, butenolides-containing DTCs (**15**, Figure 4) have been synthesized and evaluated for their antitumor activity *in vitro*. The results are valuable for the construction of compound libraries and the screening of lead compound.[54b] Along with this, brassinin (**16**, Figure 4), a crucial plant defense, first isolated from cabbage, had cancer preventive activity.[55]

Recently, dithiocarbamic acid esters, a common class of organic molecules, have also attracted immense attention due to their cancer chemopreventive and anticancer action.[56,57] It is reported that when a suitable molecular scaffold was incorporated into dithiocarbamic acid esters as a key pharmacophore, the molecule exhibits significant anticancer activity, such as thalidomide dithiocarbamates,[58] quinazolinone dithio-carbamates.[59,60]

Taking into account the SAR of quinazoline with epidermal growth factor receptors (EGFR) inhibitors and the research progress on dithiocarbamic acid esters, a new class of EGFR inhibitors has been designed and synthesized by combining different dithiocarbamic acid esters and selected quinazoline scaffolds with two

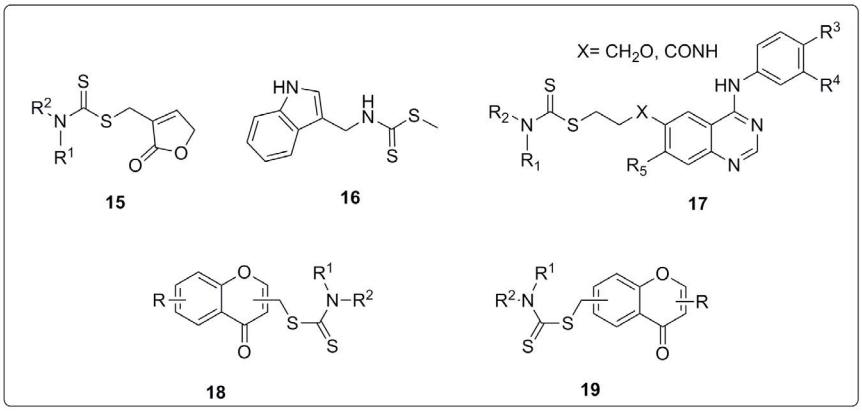

Figure 4: General structure of butenolides-containing DTC (**15**), brassinin (**16**), quinazoline DTC (**17**) and DTC substituted chromones (**18**, **19**)

kinds of linkers (**17**, Figure 4).[61]

It has been found that some flavonoids, the most representative families of plant secondary metabolites, displayed anticancer activity with novel mechanisms of actions, such as carcinogen inactivation, antiproliferation, cell cycle arrest, induction of apoptosis and differentiation, inhibition of angiogenesis, anti-oxidant action and reversal of multidrug resistance.[62] Pyrrolidine dithiocarbamate (PDTC) shows inhibitory ability against murine colon adenocarcinoma bearing mice through the inhibition of nuclear factor kB in the tumor tissue.[63,64] Considering the anti-cancer property of flavonoids and DTCs, both the scaffolds have been hybridized (**18**, **19**, Figure 4) by W. Huang *et. al*. to discover lead structure with promising broad-spectrum anticancer activity.[65a] A novel class of benzimidazoledithiocarbamate and chalcone dithiocarbamate derivatives have also been reported very recently. Although, these molecules showed less potency compared to cisplatin, toxicity wise these molecules can be considered as potent antimitotic agents.[65b]

This study provides a promising new strategy for the preparation of potent antitumour drug. On the basis of above discussion, it may be concluded that introduction of DTC group into a proven scaffold is decisive for anti-tumor activity and further investigations are required to develop a new anticancer drug candidate.

1.3. DTCs as Anti-tubercular Agents

More than 9.4 million people are infected by tuberculosis (TB) annually, and 1.7 million die each year.[66] New cases of TB are still increasing all over the world, especially in developing and low-income countries, and TB infection including both multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) is a leading cause of death worldwide. It is estimated that about one-third of the world population is currently infected with the bacillus in its latent form and that nearly nine million new cases develop each year.[67] According to WHO, MDR-TB is responsible for approximately 4.60 lacs new cases per year and for about 7.40 lacs new patients affected by both mycobacterium tuberculosis (MTB) and HIV/AIDS. Recent estimates show that 10% of all new TB infections are resistant to at least one anti-TB drug.[66] For the treatment of TB, a combination of drugs including, for example, isoniazid, rifampin, ethambutol and pyrazinamide are given for two months followed by a continuation phase in which isoniazid and rifampin are taken. Long-term therapies lasting for between six and nine months have frequently led to patients' non-compliance and, in turn, contributed to the emergence of MDR-TB.[68] No anti-TB drug has been developed for last many years and the ever-increasing drug resistance, toxicity, side effects of currently used anti-TB drugs, and the disappearance of their bactericidal activity necessitate new, safer, and more effective antimycobacterial compounds.[69] In last decade, the research on *M. tuberculosis* and possible drug candidates have made much progress with the genome unrevealed and the discovery of different biological targets.[70,71]

The antimycobacterial activity of PDTC, (**20**, Figure 5) and dialkyldithiocarbamate derivatives have been demonstrated.[72–75] On the other hand, sugar derivatives were also investigated for their antibacterial activity by T. Chiba *et. al*.[76] On the basis of hybridization concept in drug discovery, 2-acetamido-2-deoxy-β-D-glucopyranosyl N,N-dimethyldithiocarbamate (OCT313, **21**, Figure 5), was investigated for structure–activity relationships (SAR) and antibacterial activities against *M. tuberculosis*, including multidrug resistant *M. tuberculosis*. OCT313 consist both, sugar (N-acetyl-D-glucosamine) and dimethyldithiocarbamate.[76] It exhibits bactericidal and lytic activities against *M. tuberculosis* and *M. bovis* Bacillus Calmette Guerin (BCG). Furthermore, twenty five clinical

isolates of drug-resistant M. tuberculosis and nineteen drug-sensitive *M. tuberculosis* were sensitive to OCT313.[76] To determine the SAR, 2-acetamido-2-deoxy-β-D-glucopyranosyl pyrrolidine-1-carbodithioate (OCT313HK, **22**, Figure 5) which is substitute of OCT313, has also been synthesized and evaluated for anti-MTB and anti-*M. bovis* BCG activities. However, PDTC exhibited better anti-TB activity than OCT313 and OCT313HK.[77]

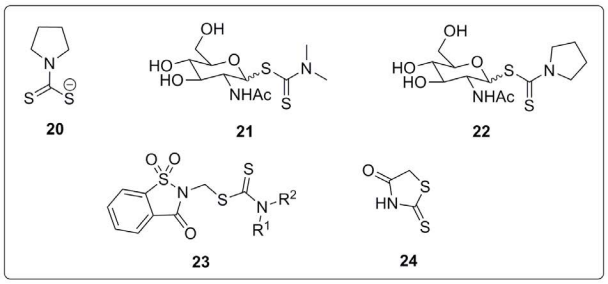

Figure 5: Structure of PDTC (**20**), OCT313 (**21**), OCT313HK (**22**), modified brassinin scaffold (**23**) and rhodanine (**24**)

Interestingly, OCT313HK exhibited unstained bacteriolytic activity compared to OCT313. The lytic activity of dithiocarbamate sugar derivatives is probably due to dithiocarbamate structure. Unexpectedly, DTC sugar-resistant colonies were unable to grow on 7H11 agar plate whereas, both anti-TB drug and DTC-resistant colonies were observed spontaneously.[77a] Furthermore, structural modification in brassinin scaffold (**23**, Figure 5) make the drug as an antitubercular framework.[77b] Like-wise, Rhodanine (**24**, Figure 5) acts as a purine base in the synthesis of nucleic acid and has been popular for having targets such as HCV NS3 protease and as anti-diabetic agents.[77c]

In conclusion, further work is required to clarify the specific targets of DTC and DTC sugar hybrid. The study has unknotted the potential of OCT313HK and OCT313 as valuable compounds for future pharmacological developments against MDR-TB and XDR-TB.

1.4. DTCs as Anti-HIV Agents

In 1981, the emergence of AIDS was first reported followed by the identification of HIV as the cause of the disease in 1983.[78-81] HIV/AIDS is now a global pandemic that has become the leading infectious killer of adults worldwide.[82] By 2006, more than 65 million people had been infected with the HIV virus worldwide and 25 million had died of AIDS.[83,84] This has caused tremendous social and economic damage worldwide, with developing countries. The HIV/AIDS epidemic in Asia and the Pacific has grown significantly since the beginning of the 21st century. Almost one million new people were infected in Asia and the Pacific in 2002, bringing the number of people living with the virus in the region to an estimated 7.2 million, a 10% increase since 2001.[85]

A cure for HIV/AIDS has been elusive in almost 30 years of research. Early treatments focused on antiretroviral drugs that were effective only to a certain degree. The first drug, zidovudine (**25**, Figure 6), was approved by the US FDA in 1987, leading to the approval of a total of 25 drugs to date, many of which are also available in fixed dose combinations and generic formulations for use in resource-limited settings (to date, only zidovudine and didanosine are available as true generics in the USA).[86,87] However, it was the advent of a class of drugs known as protease inhibitors and the introduction of triple-drug therapy in the mid-1990s that revolutionized HIV/AIDS treatment.[88,89] This launched the era of highly active antiretroviral therapy (HAART), where a combination of three or more different classes of drugs are administered simultaneously.[89] The current treatment modality for HIV/AIDS is HAART, where three or more antiretroviral drugs are given to patients simultaneously. Despite the remarkable successes with the current HAART treatment for HIV/AIDS, there are still various challenges remaining.

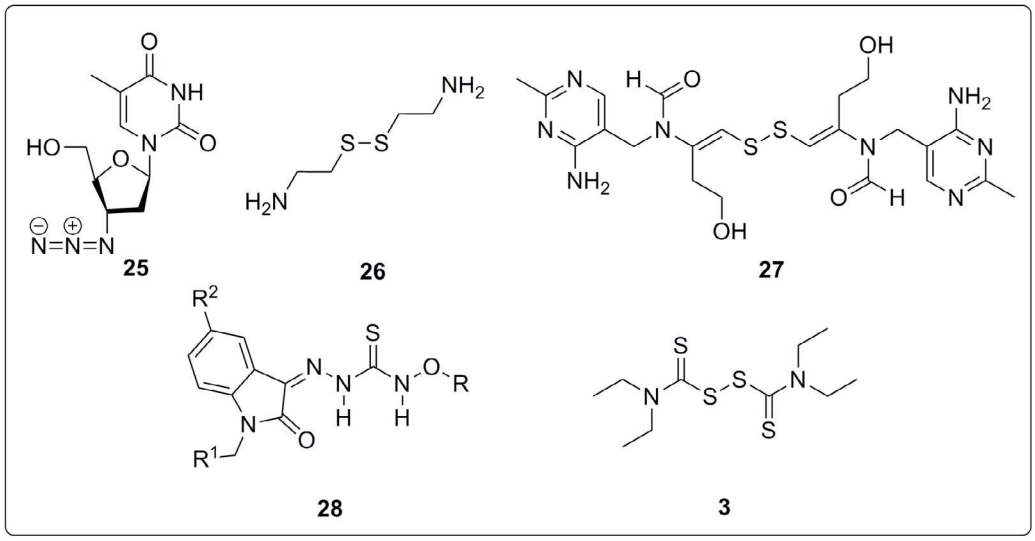

Figure 6: Genral structure of zidovudine (**25**), cystamine disulfide (**26**), thiamine disulfide (**27**) and 5-substituted isatins (**28**)

The major difficulty has been the failure of the treatment, typically due to poor patient compliance.[90] Due to the need to take the medication daily for a lifetime, patients fail to adhere to the treatment schedule, leading to ineffective drug levels in the body and rebound of viral replication.[91,92] Now a days, Nanotechnology has a great impact in the treatment and prevention of HIV/AIDS with various innovative approaches.[93] There has been remarkable progress in the understanding and design of molecules for microbicide development. However, recent clinical trials failed to show efficacy, indicating the need for more research and development to design better molecular systems.[94,95]

A literature search recognized cystamine disulfide (**26**, Figure 6), thiamine disulfide (**27**, Figure 6), and disulfiram (**3**, Figure 6) as compounds that have been shown to inhibit HIV-1 replication by poorly defined mechanisms and that have electrophilic functional groups that might react with the metal-coordinating sulfur atoms of the retroviral zinc fingers and cause zinc ejection.[96] The highly conserved and mutationally intolerant retroviral zinc finger motif of the HIV-1 nucleocapsid protein is an attractive target for drug therapy due to its participation in multiple stages of the viral replication cycle. Disulfide benzamide (DIBA),[97] is currently in clinical study in the United States,[98] and another is an azoic-based compound[99] that is in clinical form in Europe for advanced AIDS.[100] Disulfiram and its primary *in vivo* metabolite, diethyl dithiocarbamate, have been clinically evaluated against HIV-1 infection because of their immunoregulatory properties.[101-104] Moreover, dithiocarbamates and metal chelators can potently block the activation of nuclear factor κB (NF-κB), a transcription factor involved in human immunodeficiency virus type 1 (HIV-1) expression, signaling, and immediate early gene activation during inflammatory processes. Using cell cultures, the PDTC (**20**, Figure 5) is investigated in detail.[105]

The 2008 WHO report on TB, states that 0.7 million cases of HIV-TB co-infection were reported in 2006 and an estimate of 0.2 million of the global populace died due to HIV-TB co-infection.[106] TB and HIV have a harmonized effect on the progression of each other and hence become a lethal threat to the patient. DTCs are utilized as potent antitubercular agents as explained in the previous section. On the other

hand, isatin derivatives have been long reported for their anti-viral activities.[107,108] Hence, 3-(N-hydroxy/methoxy thio-semicarbazones) of 5-substituted isatins (**28**, Figure 6) have been synthesized by condensation of thiosemicarbazide hydrochloride (synthesized from DTCs) with substituted isatins. These isatin derivatives are reported as potential non-nucleoside reverse transcriptase inhibitor (NNRTI) which also inhibited the isocitrate lyase enzyme of MTB thereby tackling the issues of dormant tuberculosis, which often presents itself as an opportunistic infection in patients afflicted with AIDS.[109] Thus, it is assumed that these molecules would bypass the pharmacokinetic interferences of combination HIV-TB therapy, tackle the consequences arising due to immune reconstitution and also minimize the pill burden thereby increasing the prospects of patient compliance.

In short, because of establishment of DTCs in preclinical applications, clinical studies also seem to be possible. The suppressing effect of PDTC on the activation of the HIV-1 might stimulate further studies exploring effects of PDTC and other derivatives on the progression of HIV-AIDS.

1.5. DTCs as Anti-fungal Agents

The incidence of life-threatening fungal infections has multiplied dramatically as the population of immune-compromised individuals has increased.[110] Fungal infections have increased in the previous years affecting mainly those patients immuno-compromised.[111] These infections are ordinary in patients, those have been subjected to immuno-suppressive therapy, as in the cases of organ transplantation, critical diseases and patients with AIDS.[112,113] Many fungal infections such as insidious candidiasis, cryptococcosis and aspergillosis are caused by opportunistic pathogens that may be endogenous (Candida infections) or acquired from the environment (Cryptococcus, Aspergillus infections) have increased dramatically worldwide during the last two decades.[114-117] The most prominent fungal pathogens affecting human being are *Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis, Candida krusei, Aspergillus fumigatus,* and *Cryptococcus neoformans*.[118] *Candida albicans* remains the predominant cause of invasive candidiasis. Since 1997, mortality associated with invasive candidiasis remain stable, at approximately 1.0 deaths per 250,000 populations.[119] In 1956, Amphotericin B was considered as the drug of choice for the treatment of the most severe systemic mycoses. However, more recently there has been an expansion in a number of antifungal drugs available. The major classes of antifungal compounds that are currently used in clinical studies include azoles as fluconazole, ketoconazole, thiocarbamates tolciclate (**29, 30**, **31**, Figure 7), polyenes (Amphotericin B), and fluoropyrimidines.[120] Currently marketed antifungal drugs are mainly inhibitors of ergosterol biosynthesis except Amphotericin B.[121] The azole class is commonly used to treat *Candida* infections and inhibit the synthesis of ergosterol by binding to the heme cofactor located in the active site of the P450-dependent enzyme lanosterol 14α-demethylase (CYP-51).[122] Moreover, the extensive use of azole antifungal agents has led the problem due to development of resistance,[123] and use of amphotericin B is restricted due to its well known renal toxicity and bone marrow depression.[124,125] Despite the growing list of antifungal agents, treatment of fungal diseases remains unsatisfactory. Hence, there is an emergent demand for the discovery of new and safe antifungal agents, which can be administered both orally and parenterally.[126,127] Brassinin (**16**, Figure 4), a crucial plant defense agent, represent an important class of biologically active compounds having fungicidal, antibacterial and anticancer activities.[77b] The thiocarbamate class of drugs

are active against dermatophytes and are used clinically as a topical treatment for the fungal infection. Thiocarbamate derivatives disturbed the cell wall biosynthesis of the pathogen by inhibiting the ergosterol biosynthesis.[128]

Recently, it has been investigated that some complex, less commonly used inorganic anions as carbonic anhydrase inhibitors (CAIs),[129,130] detecting trithiocarbonate as an interesting inhibitor of several α-CA isoforms. It has also been proposed that compounds possessing zinc-binding function found in trithiocarbonate, such as for example the DTCs, might possess better inhibitory properties compared to the simple inorganic anion.[131] N-mono- and N,N-disubstituted DTCs are found to be inhibitors of three fungal β-CAs from the pathogens *C. neoformans*, *C. albicans*, and *C. glabrata*.[166] Rhodanine-3-acetic acid derivatives (**32**, Figure 7) has been reported as inhibitors of fungal protein mannosyl transferase1.[132a]

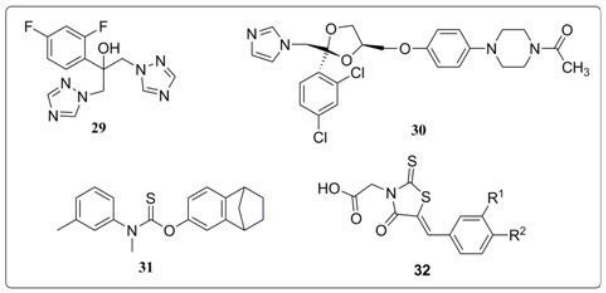

Figure 7: Structure of Fluconazole (**29**), ketoconazole (**30**), tolciclate (**31**) and Rhodanine-3-acetic acid derivative (**32**)

A group of benzyliden-rhodanines (**33**, Figure 8) is also found to be very potent fungicidal agents by M. Sortino *et al*.[132b] Tin complexes[133] as well as dithiocarbamates ligands are known for their biological interest as antifungal, anti-bacterial and biocide agents. Therefore, the coordination of tin with dithiocarbamates would enhance such biological aspects. Thus, in order to investigate the *in vitro* antifungal activity towards *C. albicans.* Hence, tin(IV) complexes of PDTC (**34**, Figure 8) have been synthesised and characterised as antifungal agents by D.C. Menezes *et al*.[134]

Metal-based drugs represent a therapeutic alternative against invasive microrganisms.[135] Studies of ruthenium compounds show its activity against filamentous fungi.[136] Transition-metal complexes with dithiocarbamate ligands were screened for their fungal toxicity in *in vitro* conditions; among them are molybdenum, platinum, vanadium and tungsten, or tin complexes, which showed biological activity.[134,137] Observing the antifungal activity of transition-metal complexes with DTCs, ruthenium dithiocarbamate compounds (**35**, Figure 8) have also been synthesyzed and evaluated for their antifungal activity against eight isolates of *Aspergillus*, comprising seven different species including *Aspergillus clavatus*, *A. flavus*, *A. fumigatus*, *A. niger*, *A. nomius*, *A. tamarii* and *A. terreus*.[138] This study is the first approach to the investigation of the potential usefulness of ruthenium complexes of DTC as antifungal agents.

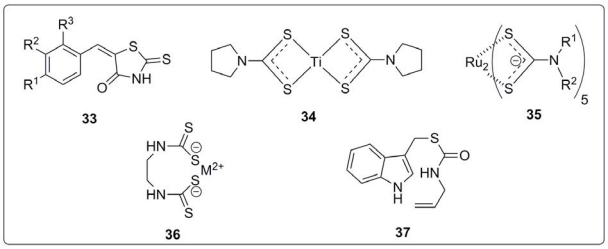

Figure 8: General structure of benzyliden-rhodanines (**33**), tin(IV) complex of PDTC (**34**), ruthenium complex of DTC (**35**), Mancozeb (**36**) and Brussalexin-A (**37**)

Phytoalexins, secondary metabolites of plants under stress, containing DTC or thiolcarbamate functionalities such as brassinin (**16**, Figure 4), brassitin, 1-methoxybrassinin, 1-methoxybrassitin, and 4-methoxybrassinin are produced by many species of crucifer plants.[139,140] Coincidentally but worthy of note,

DTC and thiocarbamate-containing compounds have been used for decades in a broad range of pesticides. For example, Mancozeb (**36**, Figure 8) is a broad spectrum fungicide,[141] Thiobencarb[142] is a widely used herbicide, and Cartap[143] is an insecticide. Brussalexin-A (**37**, Figure 8) is the first naturally occurring thiocarbamate in which the sulfur atom is attached to the 3-methylindolyl moiety. This phytoalexin has been isolated from Brussels sprouts, then synthesized and published as a crucial antifungal agent.[144]

Since there exist many known biochemical and molecular targets for antifungal compounds and many e□orts are being directed toward the identification and development of new ones, it is not possible to suggest a justified mode of action for DTCs. However, It can be concluded that simple organic DTCs as well as organometallic DTC complexes are really promising antifungal agents. The outstanding properties of this class of fungicidal substances deserve further investigation in order to clarify the mode of action at molecular level.

1.6. DTCs as Antibacterial Agents

A recent survey of novel small-molecule therapeutics revealed that the majority of them result from an analogue-based approach and that their market value represents two-thirds of all drug sales.[145] However, The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of MDR microbial pathogens with particular relevance for Gram positive bacteria.[146] There is no doubt that the existing arsenal of antimicrobial agents we have in hand for the treatment of infectious diseases is insufficient to protect us over the long term.[147] Resistance to antibiotics is an unavoidable side effect of their use. The time scale of the life cycle of microbes and the 'adapt or die' paradigm that is imposed with the current arsenal of agents that either stop growth or cause cell death conspire against the indefinite longevity of antibiotics.[148] We can neither avoid resistance nor can we predict with any accuracy the emergence of new infectious agents, but we can work to mitigate these issues with research that will yield new agents of novel mechanism and chemical class. Such research will include studies to validate and characterize novel targets for efforts in discovering and developing new leads for new antimicrobials. Filling the antimicrobial drug discovery pipeline has never been as challenging as it is now. The ever-mounting problem of resistance fuels the need for new agents; however, the retreat of many large pharmaceutical and biotechnology companies from the anti-infective arena guarantees that there will be fewer therapeutic options in the future.[149] Hence, in view of the above there is an emergent need to develop new antimicrobial agents having a new mode of action.

Tetrahydro-(2*H*)-1,3,5-thiadiazine-2-thione derivatives (THTT) has been known for several decades as antibacterial,[150,151] antifungal,[152,153] anthelmintic,[154] and tuberculostatic[155] agents. Besides its prominent antimicrobial activity, this versatile heterocycle has found increased application in the drug research arena as a biolabile prodrug[156] in the design of drug delivery system due to its high lipid solubility and enzymatic rate of hydrolysis. Another important advantage of THTT derivatives is their stability in simulated gastric fluid, which facilitates their stomach absorption in a less ionized form in the case of oral administration.[157] Hence, alkyl linked bis(2-thioxo-[1,3,5] thiadiazinan-3-yl) carboxylic acids (**38**, Figure 9) have been put out with the aim they could act as prodrugs able to inhibitthe cysteine proteinase of some protozoan. Preliminary biological evaluation demonstrated that some of the new compounds possess notable activity against *Trichomonas*

cruzi and *T. vaginalis*, suggesting potential for the development of useful antiparasitic agents.[158] Furthermore, to ascertain whether combining the THTT structural features with the deacylated chloramphenicol (**39**, Figure 9) might provide new antimicrobials with physicochemical properties differing from those of chloramphenicol. Accordingly, the hybrid scaffold is found to be new antimicrobials of different physicochemical properties.[159,160]

2-Thioxo-4-thiazolidinone (rhodanine) and its derivatives have broad spectrum of biological activities as antibacterial,[161] antifungal,[132] antidiabetic,[162] antitubercular,[163] and anti-HIV.[164] As we discussed earlier, sugar derivatives were also investigated for their antibacterial activity by T. Chiba *et. al*.[75] Thus, sugar and rhodanine nucleus have been merged together to obtain new N–glucopyranosyl rhodanine (**40**, Figure 9) derivatives and reported as more effective microbicidal agents.[165] Additionally, rhodanine derivatives have also been reported as inhibitors of Mur ligases[166] which catalyze the formation of a peptide bond with concomitant cleavage of ATP into ADP and inorganic phosphate. The synthesis and biochemical evaluation of a series of new 5-benzylidenerhodanine analogues (**41**, Figure 9) have been found out as inhibitors of MurD with IC_{50} in the range 45-206 μM for MurD from *E. coli*.[167]

As we have discussed earlier that organometallic class of compounds play a very crucial role in medical science. The interest in such complexes stems not only from their biological significance but also from their structural characteristics.[168] It was therefore considered useful to synthesize, characterize and assess the antibacterial activity of complexes formed from phenylmercury(II) and organotin(IV) cations with a variety of 1,1- and 1,2-dithio ligands. A comparison of the antibacterial activity of organomercury and organo-tin complexes has been carried out. In general organomercury dithio complexes (**42**, Figure 9) have been found to be more potential antibacterials than organotin dithio complexes.[169]

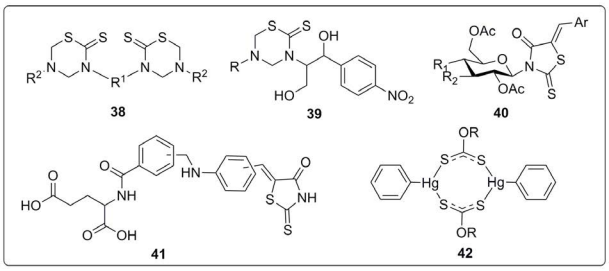

Figure 9: General structure of alkyl linked bis(2-thioxo-[1,3,5] thiadiazinan-3-yl) carboxylic acid (**38**), THTT derivative of deacylated chloramphenicol (**39**), N–glucopyranosyl rhodanine (**40**), 5-benzylidenerhodanine analogue (**41**) and organomercury dithio complexe (**42**)

Finally, above discussion revealed to know that hybridization of DTC with another pharmacophore may be a successful method to discover a new promising antimicrobial candidate of different physicochemical properties. Accordingly, they can be considered as lead to be used as antimicrobial agents. The combination of potent activity against microbial cell lines, together with the absence of cytotoxicity against normal cells, makes these agents of great interest in the exploration for novel potential antimicrobials able to reduce the danger of bacterial infections in the frequently immunocompromised patients. Research in this area must be continue if we want to address the real needs which will face over the next several years because of dramatically rising prevalence of MDR microbial infections.

Except the above well classified usefulness of DTCs as a pharmacophore, these compounds are also well known for their use as anti-arthritic,[170] Anti-methicillin-resistant *Staphylococcus aureus i.e.* MRSA (pathogens causing nosocomial infections) in form of dithiocarbamate carbapenem (**43**, Figure 10),[171]

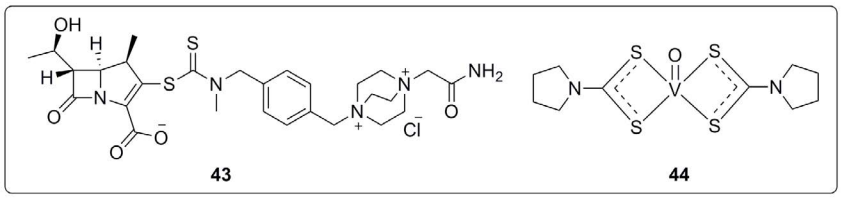

Figure 10: Structure of dithiocarbamate carbapenem (**43**) and oxo-vanadium comlex of PDTC (**44)**

and anti-diabetic in form of oxo-vanadium comlex of PDTC (**44**, Figure 10).[172] Furthermore, DTS derivatives are also used as herbicidal,[173] anthelmintic,[174] antifouling,[175] growth depressant,[176] algicidal,[177] antiparkinson,[178] antioxidant,[179] and antiradiation agents.[180]

1.7. DTCs as Double Edged Spermicidal Agents

Vaginal contraception is perhaps the oldest method of fertility regulation that has been practiced over the centuries. With minimal systemic involvement, it is also one of the safest methods of contraception. However, lack of interest and innovation in this important area of contraception made the available methods obsolete, resulting in poor efficiency and acceptability.[181] It also received a further setback with the introduction of oral contraceptive pills (OCPs) and intrauterine devices (IUDs) in the 1960s, and remained virtually forgotten for a few decades. Recently, there has been renewed interest in this area in search of prophylactic contraceptives that offer dual protection against both pregnancy as well as sexually transmitted diseases (STDs), including AIDS.[181]

According to United States Census Bureau, the current estimation of global population is 7 billion[182] and data from the World Resources Institute suggests that global population will project by 34% by 2050. Studies revealed that, India is the second most populous country in the world, and represents almost 17.31% of the world's population, which means one out of six people on this planet live in India. With the population growth rate at 2.1%, India is predicted to take the numero uno position by 2050.[183] Following are the three countries with the highest population (Past, Present and future)

The alarming rate of increase in the number of STD patients, estimated to be about 125 million new cases every year[184], calls for urgent measures to effectively curb this menace. Amongst these, 6.4 million human beings become infected with HIV[185], the causative agent of the dreaded AIDS. New cases of HIV in the United States have not diminished over the years, and explosive epidemics of AIDS in India and China seem inevitable.[186] It has been established beyond doubt that existing methods of fertility control do not provide any protection against STDs and AIDS. In fact, some studies have indicated increased incidence of chlamydial infection in OCP users and bacterial vaginosis in IUD users.[187] A role of these STDs, especially gonorrhoea and bacterial vaginosis, in acquisition of HIV is also suspected.[188] It is being felt very strongly that topical microbicidal spermicides can effectively control the STD menace[189] if used consistently with each coital act.

Country	Population		
	2000	2011	2050
China	1,268,853,362	1,336,718,015	1,303,723,332
India	1,004,124,224	1,189,172,906	1,656,553,632
USA	282,338,631	313,232,044	439,010,253

The scientific consensus is that the current population expansion accompanying increase in usage of resources is linked to threats to the ecosystem.[190] This may lead to many environmental problems, such as rising levels of atmospheric carbon dioxide, global warming, and pollution.[191] Some of the reasons for India's rapidly growing population are poverty, illiteracy, high fertility rate, quick decline in mortality rates. In 1952, Government of India included family planning as one of the major programs in order to get control on this rapid growth of population. Currently, the family planning efforts outlines primarily in areas of reducing infant and maternal mortality, meeting the unmet need for contraception, and enabling families to achieve their reproductive goals. There are various methods for family planning such as natural method, oral contraceptives, sterilization, intra uterine devices,[192] injections and barrier methods which include condoms and diaphragm. There is a natural affinity between the goals of family planning and disease prevention. However, the efforts done failed to achieve the ultimate aim.[193] Furthermore, the poor family planning provisions are enhancing the spread of STDs mainly HIV/AIDS, trichomoniasis, chlamydiasis, sphyilis etc. and risk of unwanted pregnancy. Unintended pregnancy is also a serious threat to the health and survival of women and newborns.

Generally, microbicidal spermicides are pharmacological agents and chemical substances designed to destroy microbes (bacteria, viruses, protozoa and fungi) as well as sperm during the coital act to reduce their infection as well as pregnancy.[12b] These can be formulated in different delivery systems such as gels, creams, films, or suppositories. At present this approach is investigational, although several broad-spectrum microbicidal spermicides have been clinically evaluated and many others are in developmental pipeline.[194] The great majority of vaginal microbicidal spermicides that are available throughout the world rely on surfactants as the spermicidal agent. The most commonly used compound is the neutral surfactant nonoxynol-9 (N-9, **45**, Figure 11). Though N-9 was the widely used surfactant is a detergent that disrupts cell wall by solubilizing membranes, have several disadvantages. N-9 increases the risk of HIV,[195] vulvovaginal candidiasis[196] and genital ulcers.[181] Currently all commercially available spermicidal microbicides[197] have detergent ingredients that disrupt cell membranes. The most widely used vaginal spermicide, N-9 has been shown to damage the cervicovaginal epithelium because of its membrane-disruptive properties, causing an acute inflammatory tissue response, altered vaginal microflora, and enhanced risk of opportunistic infections in the genitourinary tract. Such opportunistic infections are known to enhance the susceptibility of the ectocervical epithelium and the endocervical mucosa to HIV infection. Hence, despite its ability to inactivate HIV *in vitro*, the reported failure[198] of N-9 to prevent heterosexual vaginal transmission of HIV in clinical settings has prompted the search for new female-controlled, non-detergent, topical vaginal spermicidal microbicides that are more effective as well as safer than N-9.[199] Thus, a challenge is thrown open to chemists to design molecules with spermicidal and anti-HIV/STI activities.

Carbodithioic acid (**46**, Figure 11) and carbothioic acid group (**47**, Figure 11) are valuable pharmacophore that induces diverse biological activities when incorporated in a particular structure. Very significantly, dialkylaminocarbothioic acid esters have been shown to have non-detergent type of action as spermicide[12] and a number of alkyl/aryl esters of diethylaminocarbodithioic acid have been synthesized and evaluated for spermicidal activity.[199] 1-Dialkylaminocarbodithioic acid sodium/potassium salts and their esters exhibited antibacterial and antifungal activities.[198,199]

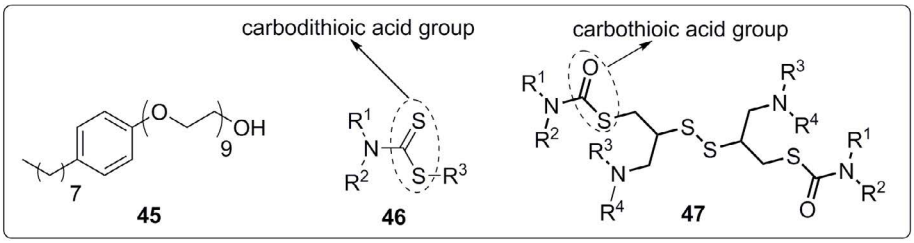

Figure 11: Structure of nonoxynol-9 (**45**), carbodithioic acid group (**46)** and disulfide ester (**47**)

Prior to fertilization the spermatozoa must undergo capacitation which is governed by oxidoreduction reactions. Sperm capacitation is linked with a low production of reactive oxygen species (ROS)[200-202] and a strong time-dependent increase in sperm membrane sulfhydryl groups.[203] Sulfhydryl groups of sperm membrane proteins maintain a dynamic equilibrium with their disulfides counterparts.[204] Further the fertilizing ability of spermatozoa is increased by the oxidation of sulfhydryl groups.[205] It is evident that the human sperm capacitation is induced by oxidants such as $O_2^{\bullet -2}$, H_2O_2, or both,[206,207] but $O_2^{\bullet -2}$ is not considered as a potent lipid peroxidation inducer may be due to its short half life and low reactivity. Conversely, $O_2^{\bullet -2}$ can react with sulfhydryl groups (-SH), forming thiyl radicals (2S$^{\bullet}$), which subsequently create a disulfide bridge (S–S) or a thiolation product with other sulfhydryl containing substances such as glutathione.[208] The sulfhydryl-disulfide pair formed is associated in the regulation of human sperm capacitation and $O_2^{\bullet -2}$ generation. Hence it can be concluded that the sperm capacitation can be prevented until appropriate conditions (location in the female genital tract, timing, etc.) occur and then be induced by the proper management of the sulfhydryl-disulfide pair. Free thiol groups play an important role in the survival of predominantly anaerobic cells such as spermatozoa[209] and *T. vaginalis*.[210] Consequently, the sperm membrane sulfhydryl groups are the important entities of the membrane and can be targeted for double edged contraceptive research and hence exploration of sulfhydryl-binding agents is necessary.

Introduction of DTC moiety into fluoxetine

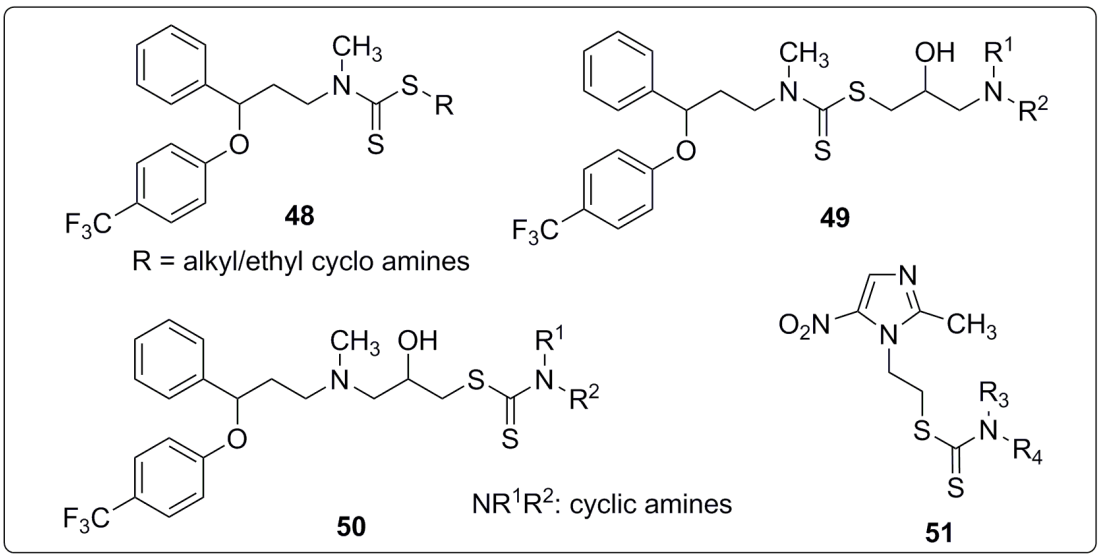

Figure 12: General structures of fluoxetine derived DTCs (**48**, **49**, **50**) and MTZ derived DTC (**51**)

scaffold (**48**, **49**, **50**, Figure 12) leads to compounds with better antifungal and antitrichomonas activities. 2-(Pyrrolidin-1-yl) ethyl methyl(3-phenyl-3-(4-(trifluoromethyl) phenoxy)propyl) carbamodithioate (**48**, Figure 12) has shown better activity profile than both fluoxetine and N-9.[211] Furthermore, dithiocarbamate group with non-spermicidal molecule MTZ (**51**, Figure 12) provided compounds possessing potent antitrichomonas and mild spermicidal activities.[212] The spermicidal activity in these molecules was due to interaction of dithiocarbamate with sulfhydryl group present over sperm membrane.

Literature survey exposed that various DTCs were screened as microbicidal spermicide with different mode of action. Some of them showed potent spermicidal activity along with other microbicidal activities. On the basis of whole discussion it may be concluded that exploration of molecules as sulfhydryl group binding agents would successfully give rise a double edged spermicide i.e., microbicidal spermicide.

1.8. Conclusion

On the basis of whole discourse exposition, it may be concluded that DTC group is a versatile pharmacohore in medicinal chemistry but their mode of action(s) in biological systems is not yet fully elucidated which may be the consequence of the versatile reactivity of the dithio-group comprising interactions with a variety of organic and inorganic compounds. Especially rapid covalent binding to various protein moieties is regarded challenging in the development of reliable robust bioanalytical assays used for monitoring a DTC drug in blood/plasma of human subjects and animals. Functionalization of the DTC moiety offers an attractive method for the generation of derivatives, which may constitute interesting medicinal and biological properties. In recent years, it has been realised by various researchers that the introduction of a carbamate functionality into various biologically active synthetic/natural/semisynthetic molecules significantly increases their biological activities. This important functional group class has considerable potential and no doubt will offer new and exciting medicinal chemistries in the near future.

1.9. Acknowledgment

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