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(54) Title: CARBODITHIOATES WITH SPERMICIDAL ACTIVITY AND PROCESS FOR PREPARATION THEREOF

(57) Abstract: The present invention relates to the synthesis and biological evaluation of compound of formula I as spermicidal agents, and its pharmaceutically acceptable acid salt thereof. The invention provides bis(4- substituted-1-piperazinylthiocarbonyl) disulfide (when n = 0) and alkane-1,n-diylbis(4-substituted piperazine-1-carbodithioate) (when n = 0, 1, 2 or 3) as shown in figure 1 of the accompanying drawing. These compounds are found to be useful for spermicidal activity.

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CARBODITHIOATES WITH SPERMICIDAL ACTIVITY AND PROCESS FOR PREPARATION THEREOF

FIELD OF INVENTION

The present invention relates to Carbodithioates and process for preparation thereof. The present invention particularly relates to carbodithioates of formula (I) having spermicidal activity which kill/completely immobilize spermatozoa at very low concentration and are highly safe towards *lactobacilli* and HeLa cells at minimum effective concentration (MEC).

The present invention relates to novel carbodithioates that target human sperm very precisely without affecting the viability of HeLa (human cervical cell-line) and *Lactobacilli* (normal vaginal flora) at spermicidal concentration, and thus have contraceptive application. The present invention further relates to novel cabodithioates of formula (I) which irreversibly immobilize normal human spermatozoa very rapidly in ~30 seconds at very low concentrations that were found to be non-toxic to HeLa and Lactobacilli for up to 24 hours *in vitro*.

BACKGROUND OF THE INVENTION

Good reproductive health ensures that every child is wanted and every birth is safe. Though unwanted pregnancies often end in abortions (*Chemical and Engineering News*, **2012**, 90, 35-38) and they still account for ~3 out of 7 billion-crowd on the earth today. This indicates that the available methods of contraception fails to cater the unmet needs of many. Therefore, there is an urgent global need to develop safe, self-administrable and easy-to-use contraceptives. The vaginal contraceptives containing spermicides are 'women-controlled' and do not necessitate partner's consent for use, and hence could effectively control the epidemic of unwanted births/abortions.

Inactivating the spermatozoa soon after ejaculation in the female vagina is one of the time tested methods of contraception and spermicides have been used since long. Different vaginal creams, pastes, suppositories, and other vaginal inserts used were of uncertain quality, suspicious origin, and questionable effectiveness. Margaret Sanger and her followers took the lead until the FDA became involved and started to establish requirements for their safety and effectiveness. However by the 1950s modern spermicides were developed (*Eur. J. Contracept. Reprod. Health Care* **2002**, 7, 173–177), which are available as OTC products till-date. Most of these spermicides contain a strong detergent, mostly nonoxynol-9 (N-9), as the active ingredient, in standalone contraceptive preparation like vaginal gels, creams, films, foams *etc.*, or in impregnated sponges or medicated condoms. N-9 acts by disrupting the sperm membrane by its potent surfactant

action (*Drug Discov. Ther.* **2008**, 2, 200), thereby leaking the cellular contents and killing the cell. A few other surfactant spermicides like benzalkonium chloride and sodium cholate are used in some contraceptive sponges, and the former might also be available in Canada as a suppository. Surfactant plant saponins extracted from *Sapindus mukorosii* have also been used in spermicidal creams and marketed under brand name Consap in India (www.cdriindia.org).

The most widely used spermicide N-9 has a good spermicidal efficacy but its detergent action causes lesions in vagina on repeated applications and increases the risk of transmission of sexually transmitted infections, including the HIV (*JAMA* **2000**, 284, 949; *JAMA* **2002**, 287, 1117). The WHO and US-FDA have issued a caution that mandatorily needs to be printed on all N-9 products, indicating the non-suitability of N-9 as a vaginal contraceptive for susceptible users (*Fed. Regist.* **2007**, 72, 71769-71785). Therefore, urgent efforts are required to develop potent non-detergent and non-surfactant spermicides to replace N-9 in vaginal preparations.

The sulfhydryl and disulfide groups present over sperm membrane (Maan & Maan. *Male Reproductive Function and Semen; Springer*: Berlin, **1981**. Chapter X, p 288) can be targeted for spermicidal action as interactions with these groups does not disrupt the cell membrane but may affect structural/functional changes in the sperm cell. According to an estimate, human sperm contain approximately five times more thiols than erythrocytes, and while all sperm thiols are available for reaction, only 15% erythrocyte thiols are open for reaction (*Biol. Reprod.* **1976**, 14, 632-640). Furthermore, infertile asthenozoospermic men with immotile sperm have lesser number of thiols on their sperm than normozoospermic men with motile sperm (*J. Reprod. Fertil.* **1994**, 101, 435-443). Consequently, thiol agents can target germ (sperm) cells in the vagina quite specifically without affecting somatic (body) cells. The interconversion of sulfhydryl and disulfide groups plays an important role in sperm maturation, motility and energy metabolism (*Mol. Hum. Reprod.* **1997**, 3, 203; *Biochem. Biophys. Res. Commun.* **1998**, 247, 716). Cleavage of disulfide bonds in mouse spermatogenic cell-specific type 1 hexokinase isozyme is associated with increased hexokinase activity and initiation of sperm motility (*Biol. Reprod.* **2008**, 79, 537-545). Consequently, sulfhydryl binding agents can inactivate/immobilize the sperm cell for contraception as exemplified by N-ethyl maleimide (*J. Biol. Chem.* **1968**, 243, 3357), acrylophenone (*Eur. J. Med. Chem.* **2002**, 37, 855), quinolines (*Contraception* **2003**, 67, 403) and a variety of other thiol agents. (*Mol. Pharmacol.* **2009**, 76, 113-124).

Our ongoing efforts to design and synthesize non-detergent spermicides (*Bioorg. Med. Chem. Lett.* **2006**, 16, 2509-2512; *Bioorg. Med. Chem.* **2006**, 14, 6593-6600; *Bioorg. Med. Chem.* **2007**, 15, 6642-6648; *Eur. J. Med. Chem.* **2008**, 43, 2247-2256; *Eur. J. Med.*

Chem. **2010**, 45, 817-24; *Bioorg. Med. Chem. Lett.* **2011**, 21, 176–181; *Antimicrob. Agents Chemother.* **2011**, 55, 4343-4351; *ACS-Med. Chem. Lett.* **2012**, 3, 83-87; *Org. Lett.* **2011**, 13, 2330-2333), led to the discovery of disulfide esters (*Human Reprod.* **2007**, 22, 708), which were the first-generation thiol-interacting spermicides that were several times more potent than N-9 in immobilizing human sperm (*Indian Pat.* **2011**, IN 255815). These non-detergent molecules had a mechanism based detrimental action on human sperm, which was in sharp contrast to non-specific surfactant action of N-9. Accordingly these spermicides spared vaginal flora (*Lactobacilli*) and epithelium at spermicidal concentrations (*Human Reprod.* **2007**, 22, 708; *Human Reprod.* **2009**, 24, 590; *Human Reprod.* **2010**, 25, 1156). Thus, it was concluded that dithiocarbamate group and disulfide linkage enhanced spermicidal activity by providing free sulfhydryl groups at the site of action, i.e. the sperm cell. The present invention relates to our next generation spermicides where we attempted to design a molecule that would provide two sulfhydryl binding species, *i.e.* dithiocarbamic acid (*Antimicrob. Agents Chemother.* **2011**, 55, 4343-4351), to enhance the spermicidal activity multi-fold. Accordingly, bis(substituted aminothiocarbonyl)disulfides were evolved that had two dithiocarbamate moieties in one molecular framework, and these molecules surpassed the first generation molecules in activity and safety.

The invention relates to novel bis(substituted aminothiocarbonyl)disulfides as spermicides. Some structurally related bis(substituted aminothiocarbonyl)disulfides have been reported to have prominent use in rubber industry. For example, bis(dialkyl aminothiocarbonyl)disulfides have been used for making elastomeric rubber (WO2009025675A1), as vulcanizing agent in rubber industry (US2004164456A1) and as an active agent which manifests a desirable property in rubber. (WO2010006442A1) Bis(4-methylpiperazinothiocarbonyl)disulfide has demonstrated improved latex stability over polyisoprene. (US2003161975A1) However, some biological activities have also been documented like, bis(4-methylpiperazinothiocarbonyl)disulfide is found to have monoglyceride lipase inhibitory activity (*J. Med. Chem.* **2009**, 52, 7310-7314) and bis(4-ethylpiperazinothiocarbonyl)disulfide have been utilized as antifungal agent (US2004157837A1). Bis(diethylaminothiocarbonyl)disulfide (Disulfiram) finds its use in treatment of alcoholism (*Am. J. Med.* **1990**, 88, 647–55) and as polyisoprene elastomer (US2009272384A1). However, bis(substituted aminothiocarbonyl)disulfides have so for not been reported as spermicidal/sperm immobilizing agents.

OBJECTS OF THE INVENTION

The main objective of the present invention is to provide carbodithioates that can target (and irreversibly immobilize) the human sperm much more potently and specifically than the clinically used surfactant N-9, for vaginal contraception.

Another object of the invention is to provide a process for preparation of carbodithioate compounds.

Yet another object of the present invention is to provide a compound useful as spermicidal agent.

Further object of the invention is to provide compounds useful as spermicidal agents with high safety against vaginal/cervical flora (*Lactobacillus*) and epithelium (*HeLa* cells).

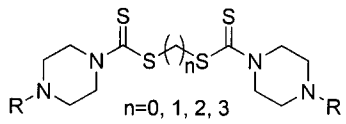
One more object of the invention is to provide pharmaceutically acceptable salts of the compounds of formula I.

Even further object of the present invention is to provide pharmaceutical compositions comprising therapeutically effective amount of the compounds of formula I.

Furthermore object is to provide the pharmaceutical compositions that are made in physical forms selected from the group consisting of pessary, foam tablet, vaginal foam or incorporated in lubricated condoms.

SUMMARY OF THE INVENTION

Accordingly the present invention provides a compound having formula **I** and pharmaceutically acceptable salts thereof,



Formula **I**

wherein n = 0 and R is selected from group consisting of C_4-C_{16} alkyl, halo-substituted C_4-C_{16} alkyl, amino-substituted C_4-C_{16} alkyl, hydroxy-substituted C_4-C_{16} alkyl, nitro-substituted C_4-C_{16} alkyl, trifluoromethyl-substituted C_4-C_{16} alkyl, cyclic amine-substituted C_2-C_{16} alkyl, thiohydroxy-substituted C_4-C_{16} alkyl, alkoxy-substituted C_4-C_{16} alkyl, thioalkoxy-substituted C_4-C_{16} alkyl, cyano-substituted C_4-C_{16} alkyl, cyanoalkyl-substituted C_4-C_{16} alkyl, substituted cycloalkyl-substituted C_4-C_{16} alkyl, aryl-substituted C_4-C_{16} alkyl, heteroaryl-

substituted C_4-C_{16} alkyl, alkylene-substituted C_4-C_{16} alkyl, alkoxyalkylene-substituted C_4-C_{16} alkyl, haloalkylene-substituted C_4-C_{16} alkyl and haloalkoxy-substituted C_4-C_{16} alkyl;

wherein n = 1, 2 or 3 and R is selected from group consisting of C_1-C_{16} alkyl, halo-substituted C_1-C_{16} alkyl, amino-substituted C_1-C_{16} alkyl, hydroxy-substituted C_1-C_{16} alkyl, nitro-substituted C_1-C_{16} alkyl, trifluoromethyl-substituted C_1-C_{16} alkyl, cyclic amine-substituted C_1-C_{16} alkyl, thiohydroxy-substituted C_1-C_{16} alkyl, alkoxy-substituted C_1-C_{16} alkyl, thioalkoxy-substituted C_1-C_{16} alkyl, cyano-substituted C_1-C_{16} alkyl, cyanoalkyl-substituted C_1-C_{16} alkyl, substituted cycloalkyl-substituted C_1-C_{16} alkyl, aryl-substituted C_1-C_{16} alkyl, heteroaryl-substituted C_1-C_{16} alkyl, alkylene-substituted C_1-C_{16} alkyl, alkoxyalkylene-substituted C_1-C_{16} alkyl, haloalkylene-substituted C_1-C_{16} alkyl and haloalkoxy-substituted C_1-C_{16} alkyl;

wherein n = 0,1,2 or 3 and R is selected from group consisting of cycloalkyl, acetyl, acyl, alkoxycarbonyl, aryl, heteroaryl, carbonyl, or thiocarbonyl and tosyl or mesyl;

wherein cycloalkyl is selected from group consisting of C_3-C_7 cycloalkyl, alkyl-substituted cycloalkyl, aryl-substituted cycloalkyl, halo-substituted cycloalkyl, cycloalkyl-substituted cycloalkyl, halocycloalkyl-substituted cycloalkyl, amino-substituted cycloalkyl, hydroxy-substituted cycloalkyl, nitro-substituted cycloalkyl, trifluoromethyl-substituted cycloalkyl, cyclic amine-substituted cycloalkyl, thiohydroxy-substituted cycloalkyl, alkoxy-substituted cycloalkyl, cyano-substituted cycloalkyl, cyanoalkyl-substituted cycloalkyl, thioalkoxy-substituted cycloalkyl, haloalkoxy-substituted cycloalkyl, heteroaryl-substituted cycloalkyl, alkylene-substituted cycloalkyl, alkoxyalkylene-substituted cycloalkyl, haloalkylene-substituted cycloalkyl and heteroatom (N, O, S).containing cycloalkyl with the same substitution pattern as in cycloalkyl;

wherein acetyl is selected from group consisting of aryl-substituted acetyl, haloaryl-substituted acetyl, aminoaryl-substituted acetyl, hydroxyaryl-substituted acetyl, nitroaryl-substituted acetyl, thiohydroxyaryl-substituted acetyl, trifuoromethylaryl-substituted acetyl, alkoxyaryl-substituted acetyl, haloalkoxyaryl-substituted acetyl, haloaryl-substituted acetyl, heteroaryl-substituted acetyl, haloaryl-substituted acetyl, arakylaryl-substituted acetyl, cyanoaryl-substituted acetyl, haloaryl-substituted acetyl, cyanoalkylaryl-substituted acetyl, thioalkoxyaryl-substituted acetyl, haloaryl-substituted acetyl, halo-substituted acetyl, trihalo-substituted acetyl, dihalo-substituted acetyl, amino-substituted acetyl, hydroxy-substituted acetyl, thiohydroxy-substituted acetyl, nitro-substituted acetyl, alkoxy-substituted acetyl, cyano-substituted acetyl, haloalkoxy-substituted acetyl, thioalkoxy-substituted acetyl and halothioalkoxy-substituted acetyl;

wherein acyl is selected from group consisting of aryl-substituted acyl, aryl-substituted acyl, haloaryl-substituted acyl, aminoaryl-substituted acyl, hydroxyaryl-substituted acyl, thiohydroxyaryl-substituted acyl, nitroaryl-substituted acyl, trifuoromethylaryl-substituted acyl, alkoxyaryl-substituted acyl, thioalkoxyaryl-substituted acyl, heteroaryl-substituted acyl, arakyl-substituted acyl, aralkylaryl-substituted acyl, cyanoaryl-substituted acyl, halo-substituted acyl, amino-substituted acyl, hydroxy-substituted acyl, thiohydroxy-substituted acyl, nitro-substituted acyl, alkoxy-substituted acyl, haloalkoxy-substituted acyl, thioalkoxy-substituted acyl, halothioalkoxy-substituted acyl and cyano-substituted acyl;

wherein alkoxycarbonyl is selected from group consisting of aryl substituted-alkoxycarbonyl, haloaryl-substituted alkoxycarbonyl, aminoaryl-substituted alkoxycarbonyl, hydroxyaryl-substituted alkoxycarbonyl, thiohydroxyaryl-substituted alkoxycarbonyl, nitroaryl-substituted alkoxycarbonyl, trifuoromethylaryl-substituted alkoxycarbonyl, alkoxyaryl-substituted alkoxycarbonyl, thioalkoxyaryl-substituted alkoxycarbonyl, heteroaryl-substituted alkoxycarbonyl, alkylaryl-substituted alkoxycarbonyl, aralkylaryl-substituted alkoxycarbonyl, cyanoaryl-substituted alkoxycarbonyl, halo-substituted alkoxycarbonyl, amino-substituted alkoxycarbonyl, hydroxy-substituted alkoxycarbonyl, thiohydroxy-substituted alkoxycarbonyl, nitro-substituted alkoxycarbonyl, alkoxy-substituted alkoxycarbonyl, haloalkoxy-substituted alkoxycarbonyl, thioalkoxy-substituted alkoxycarbonyl, halothioalkoxy-substituted alkoxycarbonyl and cyano-substituted alkoxycarbonyl;

wherein aryl is selected from group consisting of halo-substituted aryl, alkyl-substituted aryl, aryl-substituted aryl, cycloalkyl-substituted aryl, halocycloalkyl-substituted aryl, amino-substituted aryl, hydroxy-substituted aryl, nitro-substituted aryl, trifluoromethyl-substituted aryl, cyclic amine-substituted aryl, thiohydroxy-substituted aryl, alkoxy-substituted aryl, cyano-substituted aryl, cyanoalkyl-substituted aryl, thioalkoxy-substituted aryl, haloalkoxy-substituted aryl, heteroaryl-substituted aryl, alkylene-substituted aryl, alkoxyalkylene-substituted aryl and haloalkylene-substituted aryl;

wherein heteroaryl is selected from group consisting of halo-substituted heteroaryl, alkyl-substituted heteroaryl, aryl-substituted heteroaryl, cycloalkyl-substituted heteroaryl, halocycloalkyl-substituted heteroaryl, amino-substituted heteroaryl, hydroxy-substituted heteroaryl, nitro-substituted heteroaryl, trifluoromethyl-substituted heteroaryl, cyclic amine-substituted heteroaryl, thiohydroxy-substituted heteroaryl, alkoxy-substituted heteroaryl, cyano-substituted heteroaryl, cyanoalkyl-substituted heteroaryl, thioalkoxy-substituted heteroaryl, haloalkoxy-substituted heteroaryl, heteroaryl-substituted heteroaryl, alkylene-substituted heteroaryl, alkoxyalkylene-substituted heteroaryl and haloalkylene-substituted heteroaryl;

wherein carbonyl or thiocarbonyl is selected from group consisting of aryl substituted-carbonyl, haloaryl-substituted carbonyl, aminoaryl-substituted carbonyl, hydroxyaryl-substituted carbonyl, thiohydroxyaryl-substituted carbonyl, nitroaryl-substituted carbonyl, trifuoromethylaryl-substituted carbonyl, alkoxyaryl-substituted carbonyl, thioalkoxyaryl-substituted carbonyl, heteroaryl-substituted carbonyl, alkylaryl-substituted carbonyl, aralkylaryl-substituted carbonyl, cyanoaryl-substituted carbonyl, halo-substituted carbonyl, amino-substituted carbonyl, hydroxy-substituted carbonyl, thiohydroxy-substituted carbonyl, nitro-substituted carbonyl, alkoxy-substituted carbonyl, haloalkoxy-substituted carbonyl, thioalkoxy-substituted carbonyl, halothioalkoxy-substituted carbonyl and cyano-substituted carbonyl, alkylthiocarbonothioyl, arylthiocarbonothioyl;

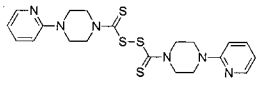
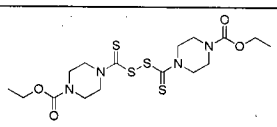
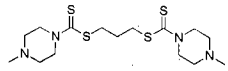
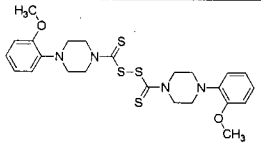
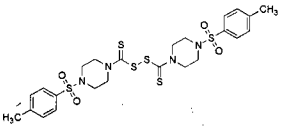
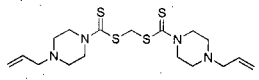
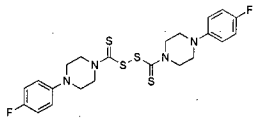
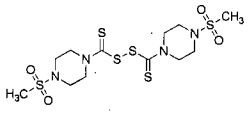
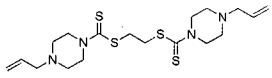
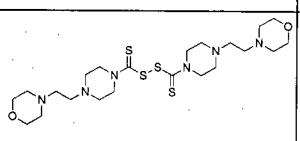
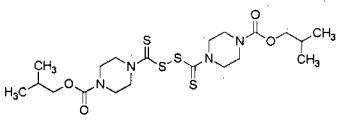
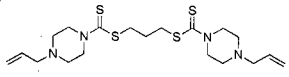
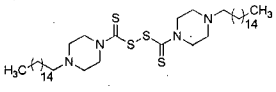
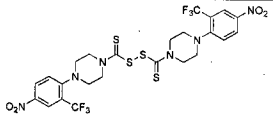
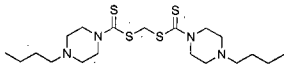
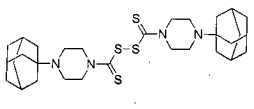
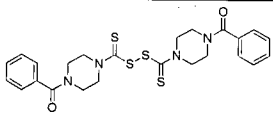
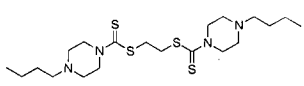
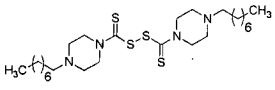
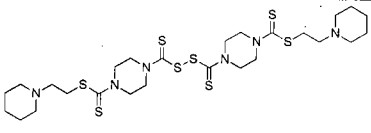
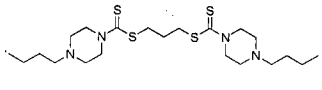
wherein tosyl or mesyl is selected from group consisting of aryl substituted-tosyl, haloaryl-substituted tosyl, aminoaryl-substituted tosyl, hydroxyaryl-substituted tosyl, thiohydroxyaryl-substituted tosyl, nitroaryl-substituted tosyl, trifuoromethylaryl-substituted tosyl, alkoxyaryl-substituted tosyl, thioalkoxyaryl-substituted tosyl, heteroaryl-substituted tosyl, aralkyl-substituted tosyl, aralkylaryl-substituted tosyl, cyanoaryl-substituted tosyl, halo-substituted tosyl, amino-substituted tosyl, hydroxy-substituted tosyl, thiohydroxy-substituted tosyl, nitro-substituted tosyl, alkoxy-substituted tosyl, haloalkoxy-substituted tosyl, thioalkoxy-substituted tosyl, halothioalkoxy-substituted tosyl and cyano-substituted tosyl, aryl substituted mesyl, haloaryl-substituted mesyl, aminoaryl-substituted mesyl, hydroxyaryl-substituted mesyl, thiohydroxyaryl-substituted mesyl, nitroaryl-substituted mesyl, trifuoromethylaryl-substituted mesyl, alkoxyaryl-substituted mesyl, thioalkoxyaryl-substituted mesyl, heteroaryl-substituted mesyl, aralkyl-substituted mesyl, aralkylaryl-substituted mesyl, cyanoaryl-substituted mesyl, halo-substituted mesyl, amino-substituted mesyl, hydroxy-substituted mesyl, thiohydroxy-substituted mesyl, nitro-substituted mesyl, alkoxy-substituted mesyl, haloalkoxy-substituted mesyl, thioalkoxy-substituted mesyl, halothioalkoxy-substituted mesyl and cyano-substituted mesyl.

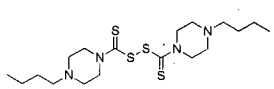
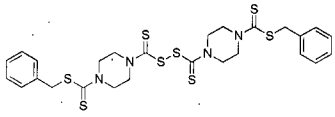
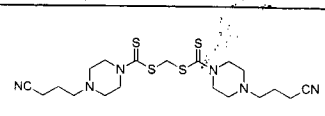
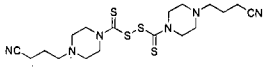
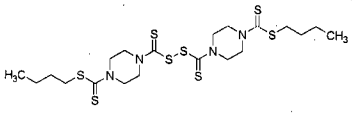
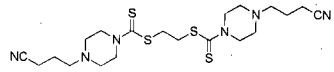
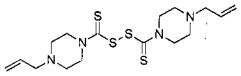
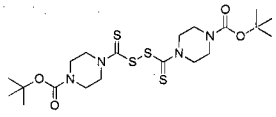
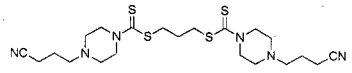
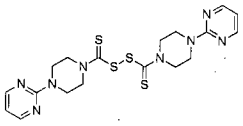
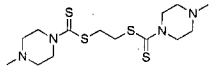
In an embodiment of the invention wherein the pharmaceutically acceptable salts of compound of formula I is obtained by reacting of (dl)-tartaric acid, (d)-tartaric acid, (l)-tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid, malonic acid, malic acid, mandelic acid or hydrochloric acid with compound of formula I.

In another embodiment of the invention, wherein the compound of formula I for use as spermicidal agents.

In yet another embodiment of the invention, wherein the compound exhibits *in vitro* and *in vivo* spermicidal activities with high safety against vaginal flora (*Lactobacillus*) and epithelium (*HeLa* cells).

In still another embodiment of the invention, wherein the representative compounds are

S. No.	Structure	S. No.	Structure	S. No.	Structure
1		12		23	
2		13		24	
3		14		25	
4		15		26	
5		16		27	
6		17		28	
7		18		29	

8		19		30	
9		20		31	
10		21		32	
11		22			

In still another embodiment of the invention, wherein the compound exhibits *in vitro* spermicidal activity at minimum effective concentration (MEC) in range of (0.001-1%).

In an embodiment of the invention, wherein the compound exhibits *in vivo* contraceptive activity in rabbit model.

In an embodiment of the invention, wherein the compound-8 lowers the pregnancy rates by ~ 40-80% at 10-50 mg vaginal dose in saline and by ~ 35 – 65 % at 10 – 20 mg vaginal dose in Jelly.

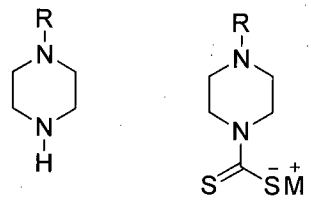
In an embodiment of the invention, wherein the compound exhibits cytotoxic effect against HeLa cell line at 112->1000 μg/ml (IC_{50}).

Accordingly the present invention provides a process for preparation of compound of formula **I** wherein the process comprising of following steps;

I. slowly adding an alkylating agent to a piperazine solution in presence of a solvent and triethyl amine to obtain monosubstituted piperazines of formula **III**,

II. adding carbon disulfide dropwise to a mixture of monosubstituted piperazines of formula III obtained from step (I) in presence of a metal hydroxide and solvent, followed by stirring to obtain reaction mixture concentrating and recrystallizing the reaction mixture

with methanolic ether to obtain the alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (**IV**),



III **IV**

Where M^+= Na^+, K^+, Li^+

Where R= C1-C16, alkyl, substituted alkyl, cycloalkyl, acetyl, acyl, alkoxycarbonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, benzyl, substituted benzyl, alkanoyl, benzoyl, tosyl, substituted tosyl, mesyl, substituted mesyl, sulfonyl, substituted sulfonyl, alkylthiocarbonothioyl, arylthiocarbonothioyl

Formula of intermediates

III. reacting the alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) obtained from step II with sodium nitrite in the presence of HCl and solvent to synthesize the compounds **1-21** of formula I or

IV. alternatively the alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) obtained from step II is treated with dihaloalkane in presence of a solvent to synthesize the compounds **22-32** of formula I.

V. converting the compound of formula **I** to its pharmaceutically acceptable salt form by treating it with (dl)-tartaric acid, (d)-tartaric acid, (l)-tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid , lactic acid, malonic acid, malic acid, mandelic acid or hydrochloric acid

In another embodiment of the invention the alkylating reagent used in step (I) is alkyl halide.

In an embodiment of the invention the solvent used in step (I) is selected from chloroform or dichloromethane and in step (II) the solvent used is ethyl acetate.

In an embodiment of the invention the reaction between the alkylating reagent and piperazine solution in step (I) is carried out for a period ranging between 3-8 hours.

In an embodiment of the invention the metal hydroxide used in step (II) is sodium hydroxide.

In an embodiment of the invention the reaction between the carbon disufide and mono substituted piperazine in step (II) is carried out at a temperature ranging between 0-5 °C.

In an embodiment of the invention wherein the reaction in step (III) is carried out by reacting the alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) with sodium nitrite in presence of HCl at a temperature ranging between 25 - 35 °C for a period ranging between 0.25 - 0.5 hour to obtain the compound **1-21**

In an embodiment of the invention wherein the reaction in step (IV) is carried out by reacting the alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) with dihaloalkane at a temperature ranging between 25 - 35 °C for a period ranging between 12 - 15 hours to obtain the compound **22-32**.

In an embodiment of the invention wherein the solvent used in step (III) is water and in step (IV) is acetonitrile.

In an embodiment of the invention wherein the pharmaceutically acceptable salt is prepared by reacting the compounds of formula (**I**) with corresponding acid which is selected from a group consisting of (dl)-tartaric acid, (d)-tartaric acid, (l)-tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid, malonic acid, malic acid, mandelic acid or hydrochloric acid

In an embodiment of the invention wherein the alkali metal salt of N-substituted piperazine dithiocarbamic acid of formula (IV) is selected from a group consisting of lithium salt, sodium salt and potassium salt.

The present invention also provides a pharmaceutical composition comprising therapeutically effective amount of the compounds of formula **I** in combination with the pharmaceutically acceptable vehicles and additives at a concentration ranging between 1-2% for vaginal delivery.

In an embodiment of the invention wherein the additive used is selected form a group consisting of Jelly, Gel, Cream, Foam, Foaming Tablet, Suppository, Vaginal Film etc.

ABBREVIATIONS

%	:	Percentage
δ	:	Chemical shift (parts per million)
Anal	:	Analysis
Aq.	:	Aqueous

	Bs	:	Broad singlet
	°C	:	Degree Celsius
	Cacld	:	Calculated
	$CDCl_3$	:	Deuterated chloroform
5	$CHCl_3$	:	Chloroform
	CH_3CN	:	Acetonitrile
	Conc.	:	Concentration
	d	:	Doublet
	dd	:	Double doublets
10	DMSO	:	Dimethyl sulfoxide
	DSE	:	Disulfide ester
	ESIMS	:	Electron Spray Ionization Mass Spectrometry
	EtOAc	:	Ethyl acetate
	EtOH	:	Ethanol
15	FDA	:	Food and Drug Administration
	FTIR	:	Fourier Transformed-Infra Red
	g	:	Gram
	h	:	Hour
	HPLC	:	High-Performance Liquid Chromatography
20	Hz	:	Hertz
	IC_{50}	:	Inhibitory concentration at 50%
	IR	:	Infrared
	J	:	Coupling constant
	KBr	:	Potassium Bromide
25	KI	:	Potassium Iodide
	K_2CO_3	:	Potassium Carbonate
	m	:	Multiplet
	Me	:	Methyl
	MeOH	:	Methanol
30	MHz	:	Mega hertz
	Mg	:	Milligram
	min	:	Minute
	mL	:	Millilitre
	mmol	:	Millimole
35	mp	:	Melting point
	MS	:	Mass Spectrometry
	m/z	:	mass-to-charge ratio

Na_2SO_4	:	Sodium sulphate
µg	:	Microgram
µL	:	Microlitres
NMR	:	Nuclear Magnetic Resonance
N-9	:	Nonoxynol-9
pH	:	logarithm of the activity of dissolved hydrogen ions (H+)
ppm	:	Parts per million
q	:	Quartet
Rf	:	Retention Factor
rt	:	Room temperature
SAR	:	Structure activity relationship
SSRI	:	Selective serotonin reuptake inhibitor
STD	:	Sexually transmitted disease
STI	:	Sexually transmitted infection
WHO	:	World Health Organisation
TLC	:	Thin Layer Chromatography
TMS	:	Tetramethyl silane
v/v	:	Volume by volume
wt	:	Weight

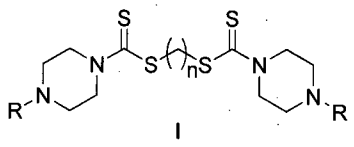
BRIEF DESCRIPTION OF DRAWINGS

Fig. 1: General scheme for preparation of the claimed compounds.

Fig. 2: Selective Spermicidal Activity of Examples **8**,**9**,**10** vs Nonoxynol-9.

DETAILED DESCRIPTION OF INVENTION

The present invention relates to the synthesis and biological activity of novel carbodithioates of formula I as spermicidal agents and pharmaceutically acceptable acid salt thereof. The invention further provides bis(4- substituted-1-piperazinylthiocarbonyl) disulfide (when n = 0) and alkane-1,n-diyl bis(4-substituted piperazine-1-carbodithioate) (when n = 1, 2 or 3) as shown in figure 1 of the accompanying drawing. These compounds are tested for their spermicidal activity and found to be very useful for the purpose.



I

Figure 1: Structure of bis(4- substituted-1-piperazinylthiocarbonyl) disulfide and alkane-1,n-diyl bis(4-substituted piperazine-1-carbodithioate)

Wherein n = 0, and R is selected from group consisting of C_4-C_{16} alkyl, halo-substituted C_4-C_{16} alkyl, amino-substituted C_4-C_{16} alkyl, hydroxy-substituted C_4-C_{16} alkyl, nitro-substituted C_4-C_{16} alkyl, trifluoromethyl-substituted C_4-C_{16} alkyl, cyclic amine-substituted C_2-C_{16} alkyl, thiohydroxy-substituted C_4-C_{16} alkyl, alkoxy-substituted C_4-C_{16} alkyl, thioalkoxy-substituted C_4-C_{16} alkyl, cyano-substituted C_4-C_{16} alkyl, cyanoalkyl-substituted C_4-C_{16} alkyl, substituted cycloalkyl-substituted C_4-C_{16} alkyl, aryl-substituted C_4-C_{16} alkyl, heteroaryl-substituted C_4-C_{16} alkyl, alkylene-substituted C_4-C_{16} alkyl, alkoxyalkylene-substituted C_4-C_{16} alkyl, haloalkylene-substituted C_4-C_{16} alkyl and haloalkoxy-substituted C_4-C_{16} alkyl.

Wherein n = 1, 2 or 3 and R is selected from group consisting of C_1-C_{16} alkyl, halo-substituted C_1-C_{16} alkyl, amino-substituted C_1-C_{16} alkyl, hydroxy-substituted C_1-C_{16} alkyl, nitro-substituted C_1-C_{16} alkyl, trifluoromethyl-substituted C_1-C_{16} alkyl, cyclic amine-substituted C_1-C_{16} alkyl, thiohydroxy-substituted C_1-C_{16} alkyl, alkoxy-substituted C_1-C_{16} alkyl, thioalkoxy-substituted C_1-C_{16} alkyl, cyano-substituted C_1-C_{16} alkyl, cyanoalkyl-substituted C_1-C_{16} alkyl, substituted cycloalkyl-substituted C_1-C_{16} alkyl, aryl-substituted C_1-C_{16} alkyl, heteroaryl-substituted C_1-C_{16} alkyl, alkylene-substituted C_1-C_{16} alkyl, alkoxyalkylene-substituted C_1-C_{16} alkyl, haloalkylene-substituted C_1-C_{16} alkyl and haloalkoxy-substituted C_1-C_{16} alkyl.

wherein n = 0,1,2 or 3 and R is selected from group consisting of cycloalkyl, acetyl, acyl, alkoxycarbonyl, aryl, heteroaryl, benzyl, carbonyl or thiocarbonyl and tosyl or mesyl.

Wherein cycloalkyl is selected from group consisting of C_3-C_7 cycloalkyl, alkyl-substituted cycloalkyl, aryl-substituted cycloalkyl, halo-substituted cycloalkyl, cycloalkyl-substituted cycloalkyl, halocycloalkyl-substituted cycloalkyl, amino-substituted cycloalkyl, hydroxy-substituted cycloalkyl, nitro-substituted cycloalkyl, trifluoromethyl-substituted cycloalkyl, cyclic amine-substituted cycloalkyl, thiohydroxy-substituted cycloalkyl, alkoxy-substituted cycloalkyl, cyano-substituted cycloalkyl, cyanoalkyl-substituted cycloalkyl, thioalkoxy-substituted cycloalkyl, haloalkoxy-substituted cycloalkyl, heteroaryl-substituted cycloalkyl,

alkylene-substituted cycloalkyl, alkoxyalkylene-substituted cycloalkyl, haloalkylene-substituted cycloalkyl and heteroatom (N, O, S).containing cycloalkyl with the same substitution pattern as in cycloalkyl.

Wherein acetyl is selected from group consisting of aryl-substituted acetyl, haloaryl-substituted acetyl, aminoaryl-substituted acetyl, hydroxyaryl-substituted acetyl, nitroaryl-substituted acetyl, thiohydroxyaryl-substituted acetyl, trifuoromethylaryl-substituted acetyl, alkoxyaryl-substituted acetyl, haloalkoxyaryl-substituted acetyl, haloaryl-substituted acetyl, heteroaryl-substituted acetyl, haloaryl-substituted acetyl, arakylaryl-substituted acetyl, cyanoaryl-substituted acetyl, haloaryl-substituted acetyl, cyanoalkylaryl-substituted acetyl, thioalkoxyaryl-substituted acetyl, haloaryl-substituted acetyl, halo-substituted acetyl, trihalo-substituted acetyl, dihalo-substituted acetyl, amino-substituted acetyl, hydroxy-substituted acetyl, thiohydroxy-substituted acetyl, nitro-substituted acetyl, alkoxy-substituted acetyl, cyano-substituted acetyl, haloalkoxy-substituted acetyl, thioalkoxy-substituted acetyl and halothioalkoxy-substituted acetyl.

Wherein acyl is selected from group consisting of aryl-substituted acyl, aryl-substituted acyl, haloaryl-substituted acyl, aminoaryl-substituted acyl, hydroxyaryl-substituted acyl, thiohydroxyaryl-substituted acyl, nitroaryl-substituted acyl, trifuoromethylaryl-substituted acyl, alkoxyaryl-substituted acyl, thioalkoxyaryl-substituted acyl, heteroaryl-substituted acyl, arakyl-substituted acyl, aralkylaryl-substituted acyl, cyanoaryl-substituted acyl, halo-substituted acyl, amino-substituted acyl, hydroxy-substituted acyl, thiohydroxy-substituted acyl, nitro-substituted acyl, alkoxy-substituted acyl, haloalkoxy-substituted acyl, thioalkoxy-substituted acyl, halothioalkoxy-substituted acyl and cyano-substituted acyl.

Wherein alkoxycarbonyl is selected from group consisting of alkoxycarbonyl, aryl substituted-alkoxycarbonyl, haloaryl-substituted alkoxycarbonyl, aminoaryl-substituted alkoxycarbonyl, hydroxyaryl-substituted alkoxycarbonyl, thiohydroxyaryl-substituted alkoxycarbonyl, nitroaryl-substituted alkoxycarbonyl, trifuoromethylaryl-substituted alkoxycarbonyl, alkoxyaryl-substituted alkoxycarbonyl, thioalkoxyaryl-substituted alkoxycarbonyl, heteroaryl-substituted alkoxycarbonyl, alkylaryl-substituted alkoxycarbonyl, aralkylaryl-substituted alkoxycarbonyl, cyanoaryl-substituted alkoxycarbonyl, halo-substituted alkoxycarbonyl, amino-substituted alkoxycarbonyl, hydroxy-substituted alkoxycarbonyl, thiohydroxy-substituted alkoxycarbonyl, nitro-substituted alkoxycarbonyl, alkoxy-substituted alkoxycarbonyl, haloalkoxy-substituted alkoxycarbonyl, thioalkoxy-substituted alkoxycarbonyl, halothioalkoxy-substituted alkoxycarbonyl and cyano-substituted alkoxycarbonyl.

Wherein aryl is selected from group consisting of halo-substituted aryl, alkyl-substituted aryl, aryl-substituted aryl, cycloalkyl-substituted aryl, halocycloalkyl-substituted aryl, amino-substituted aryl, hydroxy-substituted aryl, nitro-substituted aryl, trifluoromethyl-substituted aryl, cyclic amine-substituted aryl, thiohydroxy-substituted aryl, alkoxy-substituted aryl, cyano-substituted aryl, cyanoalkyl-substituted aryl, thioalkoxy-substituted aryl, haloalkoxy-substituted aryl, heteroaryl-substituted aryl, alkylene-substituted aryl, alkoxyalkylene-substituted aryl and haloalkylene-substituted aryl.

Wherein heteroaryl is selected from group consisting of halo-substituted heteroaryl, alkyl-substituted heteroaryl, aryl-substituted heteroaryl, cycloalkyl-substituted heteroaryl, halocycloalkyl-substituted heteroaryl, amino-substituted heteroaryl, hydroxy-substituted heteroaryl, nitro-substituted heteroaryl, trifluoromethyl-substituted heteroaryl, cyclic amine-substituted heteroaryl, thiohydroxy-substituted heteroaryl, alkoxy-substituted heteroaryl, cyano-substituted heteroaryl, cyanoalkyl-substituted heteroaryl, thioalkoxy-substituted heteroaryl, haloalkoxy-substituted heteroaryl, heteroaryl-substituted heteroaryl, alkylene-substituted heteroaryl, alkoxyalkylene-substituted heteroaryl and haloalkylene-substituted heteroaryl.

Wherein benzyl is selected from group consisting of halo-substituted benzyl, alkyl-substituted benzyl, aryl-substituted benzryl, cycloalkyl-substituted benzyl, halocycloalkyl-substituted benzyl, amino-substituted benzyl, hydroxy-substituted benzyl, nitro-substituted benzyl, trifluoromethyl-substituted benzyl, cyclic amine-substituted benzyl, thiohydroxy-substituted benzyl, alkoxy-substituted benzyl, cyano-substituted benzyl, cyanoalkyl-substituted benzryl, thioalkoxy-substituted benzyl, haloalkoxy-substituted benzyl, heteroaryl-substituted benzryl, alkylene-substituted benzryl, alkoxyalkylene-substituted benzryl and haloalkylene-substituted benzyl.

Wherein carbonyl or thiocarbonyl is selected from group consisting of aryl substituted-carbonyl, haloaryl-substituted carbonyl, aminoaryl-substituted carbonyl, hydroxyaryl-substituted carbonyl, thiohydroxyaryl-substituted carbonyl, nitroaryl-substituted carbonyl, trifuoromethylaryl-substituted carbonyl, alkoxyaryl-substituted carbonyl, thioalkoxyaryl-substituted carbonyl, heteroaryl-substituted carbonyl, alkylaryl-substituted carbonyl, aralkylaryl-substituted carbonyl, cyanoaryl-substituted carbonyl, halo-substituted carbonyl, amino-substituted carbonyl, hydroxy-substituted carbonyl, thiohydroxy-substituted carbonyl, nitro-substituted carbonyl, alkoxy-substituted carbonyl, haloalkoxy-substituted carbonyl, thioalkoxy-substituted carbonyl, halothioalkoxy-substituted carbonyl and cyano-substituted carbonyl.

Wherein tosyl or mesyl is selected from group consisting of aryl substituted-tosyl, haloaryl-substituted tosyl, aminoaryl-substituted tosyl, hydroxyaryl-substituted tosyl, thiohydroxyaryl-substituted tosyl, nitroaryl-substituted tosyl, trifuoromethylaryl-substituted tosyl, alkoxyaryl-substituted carbonyl, thioalkoxyaryl-substituted carbonyl, heteroaryl-substituted carbonyl, aralkyl-substituted carbonyl, aralkylaryl-substituted carbonyl, cyanoaryl-substituted carbonyl, halo-substituted carbonyl, amino-substituted tosyl, hydroxy-substituted tosyl, thiohydroxy-substituted tosyl, nitro-substituted tosyl, alkoxy-substituted tosyl, haloalkoxy-substituted tosyl, thioalkoxy-substituted tosyl, halothioalkoxy-substituted tosyl and cyano-substituted tosyl. aryl substituted mesyl, haloaryl-substituted mesyl, aminoaryl-substituted mesyl, hydroxyaryl-substituted mesyl, thiohydroxyaryl-substituted mesyl, nitroaryl-substituted mesyl, trifuoromethylaryl-substituted mesyl, alkoxyaryl-substituted mesyl, thioalkoxyaryl-substituted mesyl, heteroaryl-substituted mesyl, aralkyl-substituted mesyl, aralkylaryl-substituted mesyl, cyanoaryl-substituted mesyl, halo-substituted mesyl, amino-substituted mesyl, hydroxy-substituted mesyl, thiohydroxy-substituted mesyl, nitro-substituted mesyl, alkoxy-substituted mesyl, haloalkoxy-substituted mesyl, thioalkoxy-substituted mesyl, halothioalkoxy-substituted mesyl and cyano-substituted mesyl.

DEFINITION OF TERMS:

Definitions of various terms used in the specification and claims to describe the present invention are given below.

To avoid confusion, it is to be considered that the specification "C_4-C_{16}" means a carbon radical having 4, 5, 6, 7, or 16 carbon atoms. In this specification "C" means carbon atom, "N" means nitrogen atom, "S" means sulphur atom and "O" means oxygen atom.

In the case where n = 0 means the two radicals are directly bonded without any linker carbon chain and n = 1, 2 or 3 means the length of linker carbon chain contains 1, 2 or 3 carbon atoms.

In this specification "C_3-C_7 cycloalkyl" mean the cyclic carbon chain containing 3, 4, 5, 6 or 7 carbons without any heteroatom and including mono-, bi-, or tricyclic saturatedcabocycle as well as fused ring systems. Heteroatom containing cycloalkyl means the cyclic chain has one, two or more heteroatom.

In this specification, the term "alkyl" include both straight and/or branched chain alkyl radical.

In this specification, the term "alkylene" include both straight and/or branched difunctional saturated hydrocarbon alkyl radicals.

In this specification, the term "aryl" means an optionally substituted monocyclic, bi-cyclic or tri-cyclic hydrocarbon ring system with at least one unsaturated aromatic ring.

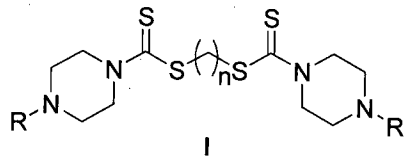
The term "heteroaryl" refers an optionally substituted monocyclic, bi-cyclic or tri-cyclic aromatic ring system with at least one heteroatom selected independently from nitrogen, oxygen or sulphur.

The term "halo" refers the radical fluoro, chloro, bromo or iodo.

In this specification, the term "aralkyl" means the particular aryl radical itself contain an optionally alkyl substituent.

In this specification, the terms "alkylenearyl", "alkyleneheteroaryl" and "alkylenecycloalkyl" means a substituent that is bonded via an alkyl radical to an aryl, heteroaryl and cycloalkyl respectively.

Accordingly, the present invention relates to the synthesis and biological evaluation of compound of formula (**I**) as potent spermicidal agents.



I

Formula I

Wherein R is C_4-C_{16} (when n = 0) alkyl, C_1-C_{16} (when n = 1, 2 or 3) alkyl, substituted alkyl, cycloalkyl, acetyl, acyl, alkoxycarbonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, benzyl, substituted benzyl, alkanoyl, benzoyl, tosyl, substituted tosyl, mesyl, substituted mesyl, sulfonyl, substituted sulfonyl, alkylthiocarbonothioyl, arylthiocarbonothioyl and n is 0, 1, 2 or 3 carbon atoms' chain for structure activity relationship.

In an embodiment, the alkali metal salts of N-substituted piperazine dithiocarbamic acid were prepared by the process reported by Tripathi *et.al.* (*Acta Pharm.* **1996**, 46, 169-176). To the mixture of N-substituted piperazine (1.0 mol) in ethyl acetate and sodium hydroxide (1.0 mol, dissolved in minimum water) was added carbon disulfide dropwise at 0-5 °C. The reaction mixture was further stirred for one hour, concentrated and recrystallized with methanolic ether.

In another embodiment, the alkali metal salts of N-substituted piperazine dithiocarbamic acid are selected from sodium salt, potassium salt and lithium salt.

In yet another embodiment, the N-substituted piperazine is selected from 4-pyridin-2-yl, 4-(2-methoxyphenyl), 4-(4-fluorophenyl), 4-(2-morpholinoethyl), 4-hexadecyl, 4-adamentyl, 4-octyl, 4-butyl, 4-cyanopropyl, 4-allyl, 4-pyrimidin-2-yl, 4-acetyl, 4-ethoxycarbonyl, 4-tosyl, 4-methyl sulfonyl, 4-isobutoxycarbonyl, 4-(4-nitro-2-(trifluoromethyl)pheny), 4-benzoyl, 4-phenyl, 4-(substituted phenyl) or their substituted product.

In yet another embodiment, the final product bis(4- substituted-1-piperazinylthiocarbonyl) disulfide (**I**, where n = 0) is synthesized using the reported procedure by Coco N. Kapanda, *et.al.* (*J. Med. Chem.* **2009**, 52, 7310-7314) wherein A mixture of the alkali metal salts of N-substituted piperazine dithiocarbamic acid (15.8 mmol) and water (15 mL) was stirred for 10 minutes. To this solution sodium nitrite (15.8 mmol) in 1 mL of methanol was added, and under cooling (0-5 °C) and stirring, concentrated HCl (3 mL) was added dropwise. The precipitated product was collected and crystallized from ethanol to yield the desired compound.

In yet another embodiment, the water soluble salts of free base bis(4- substituted-1-piperazinylthiocarbonyl) disulfide (**I**) are obtained by reacting with corresponding acids selected from group consisting of, (dl)-tartaric acid, (d)-tartaric acid, (l)-tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid or hydrochloric acid

The process of present invention is depicted in Scheme 1 of accompanying drawing (wherein n = 0) consist of following steps:

1. N-substituted piperazines were prepared by the reaction of a halo substituted reagent with piperazine in the presence of triethyl amine and appropriate solvent. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 7-10%. The purification of monosubstituted piperazines by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided [Example **8-10**]. The remaining N-substituted piperazines [Example **4-7**, **12-21**] were purified through column chromatography using methanol in chloroform as eluent.

2. Then alkali metal salts of N-substituted piperazine dithiocarbamic acid were obtained using conventional methods. Either the product obtained in step 1 [Example **4-10**, **12-21**] or commercially available N-substituted piperazine [Example **1-3**, **11**] was used as such in this step as the reaction occurs only with free NH group i.e., with monosubstituted piperazines. The disubstituted piperazine present if any, gets washed with organic solvent during work up.

3. The final product bis(4-substituted-1-piperazinylthiocarbonyl) disulfide (**I**) as shown in figure 1, is synthesized using conventional method.

4. The water soluble salts of free base bis(4- substituted-1-piperazinylthiocarbonyl) disulfide (**I**, where n = 0) are obtained by reacting it with corresponding acids.

The synthesis of compounds according to formula **I** (Table 1, where n = 1, 2 or 3,) can be done by the general procedure as shown in Scheme 1.

N-substituted piperazines were prepared by the reaction of a halo substituted reagent with piperazine in the presence of triethyl amine and appropriate solvent. Then alkali metal salts of N-substituted piperazine dithiocarbamic acid were obtained using conventional methods. The alkali metal salts of N-substituted piperazine dithiocarbamic acid were further condensed with different carbon chain using corresponding dihaloalkane in the presence of triethyl amine and CH_3CN at room temperature. The mixture of sodium salts of N-substituted piperazine dithiocarbamic acid (11.16 mmol) and diiodomethane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried on Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (100-200 mesh) using MeOH/$CHCl_3$ as eluent to afford the desired compounds alkane-1,n-diyl bis(4-substitutedpiperazine-1-carbodithioate) (**22-32**) of general structure **I** of accompanying drawing where n = 1, 2, 3

Finally **I** (where n = 1, 2, 3) was converted in to their salts by conventional method. The salts may be a (dl) tartrate, (d) tartrate, (l) tartrate, citrate, oxalate, escorbate, acetate, lactate or hydrochloride.

In an embodiment, the alkali metal salts of N-substituted piperazine dithiocarbamic acid were prepared by the process reported by Tripathi *et.al.* (*Acta Pharm.* **1996**, 46, 169-176). In the mixture of N-substituted piperazine (1.0 mol) in ethyl acetate and sodium hydroxide (1.0 mol, dissolved in minimum water) was added carbon disulfide dropwise at 0-5 °C. The reaction mixture was further stirred for one hour, concentrated and recrystallized with methanolic ether.

In another embodiment, the alkali metal salts of N-substituted piperazine dithiocarbamic acid are selected from sodium salt, potassium salt and lithium salt.

In yet another embodiment, the alkali metal salts of N-substituted piperazine dithiocarbamic acid were further condensed with different carbon chain using

corresponding dihaloalkane in the presence of triethyl amine and CH_3CN at room temperature.

In yet another embodiment, the water soluble salts of free base alkane-1,n-diyl bis(4-substitutedpiperazine-1-carbodithioate) (**I**, where n = 1, 2, or 3) are obtained by reacting with corresponding acids such as (dl) tartaric acid, (d) tartaric acid, (l) tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid or hydrochloric acid

The process of present invention is depicted as steps shown in scheme 1 (where n = 1, 2, 3) of accompanying drawing consist of following steps:

1. N-substituted piperazines were prepared by the reaction of a halo substituted reagent with piperazine in the presence of triethyl amine and appropriate solvent. The possible formation of disubstituted product [Example **24-32**] was minimized by slow addition of alkyl halide to 7-10%. The purification of monosubstituted piperazines by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided.

2. Then alkali metal salts of N-substituted piperazine dithiocarbamic acid were obtained using conventional methods. Either the product obtained in step 1 [Example **24-32**] or commercially available N-substituted piperazine [Example **22**, **23**] was used as such in this step as the reaction occurs only with free NH group i.e., with monosubstituted piperazines. The disubstituted piperazine present if any gets washed with organic solvent during work up.

3. The alkali metal salts of N-substituted piperazine were further condensed with different carbon chain using corresponding dihaloalkane in the presence of triethyl amine and CH_3CN at room temperature to give the final product alkane-1,n-diyl bis(4-substitutedpiperazine-1-carbodithioate) (**I**, where n = 1, 2 or 3).

4. The water soluble salts of free base alkane-1,n-diyl bis(4-substitutedpiperazine-1-carbodithioate) (**I**, where n = 1, 2 or 3) are obtained by reacting it with corresponding acids.

Methods of synthesis:

The synthesis of compounds according to the invention, specially the compounds according to formula **I** (Table 1, where n = 0) by the general procedure as shown in Scheme 1

N-substituted piperazines were prepared by the reaction of a halo substituted reagent with piperazine in the presence of triethyl amine and appropriate solvent. Then alkali metal

salts of N-substituted piperazine dithiocarbamic acid were obtained using conventional methods. The mixture of sodium salts of N-substituted piperazine dithiocarbamic acid (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 0-5 °C for 5 minutes. Then concentrated HCl (1 mL) was added drop wise and the reaction mixture was stirred at 0-5 °C for 10 minutes. The white solid which separated was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2) and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis(4- substituted-1-piperazinylthiocarbonyl) disulfide (**I, 1-21**) (where n = 0) was yielded as colourless crystals after re-crystallization with ethanol-chloroform mixture.

Finally **I** (where n = 0) was converted in to its salts by conventional method. The salts may be a (dl) tartrate (Example **1-21**), (d) tartrate (Example **8**), (l) tartrate (Example **8**), citrate (Example **8**), oxalate (Example **8**), ascorbate (Example **8**), acetate (Example **8**), lactate (Example **8**) (Example **8**), maliate (Example **8**), mandelate (Example **8**) or hydrochloride (Example **8**).

In an embodiment, the alkali metal salts of N-substituted piperazine dithiocarbamic acid were prepared by the process reported by Tripathi *et.al* (*Acta Pharm.* **1996**, 46, 169-176). To the mixture of N-substituted piperazine (1.0 mol) in ethyl acetate and sodium hydroxide (1.0 mol, dissolved in minimum water) was added carbon disulfide dropwise at 0-5 °C. The reaction mixture was further stirred for one hour, concentrated and recrystallized with methanolic ether.

In another embodiment, the alkali metal salts of N-substituted piperazine dithiocarbamic acid are selected from sodium salt, potassium salt and lithium salt.

In yet another embodiment, the N-substituted piperazine is selected from 4- pyridin-2-yl, 4-(2-methoxyphenyl), 4-(4-fluorophenyl), 4-(2-morpholinoethyl), 4-hexadecyl, 4-adamentyl, 4-octyl, 4-butyl, 4-cyanopropyl, 4-allyl, 4-pyrimidin-2-yl, 4-acetyl, 4-ethoxycarbonyl, 4-tosyl, 4-methyl sulfonyl, 4-isobutoxycarbonyl, 4-(4-nitro-2-(trifluoromethyl)pheny), 4-benzoyl, 4-phenyl, 4-(substituted phenyl) or their substituted product.

In yet another embodiment, the final product bis(4- substituted-1-piperazinylthiocarbonyl) disulfide (**I**, where n = 0) is synthesized using the reported procedure by Coco N. Kapanda, *et.al.* (*J. Med. Chem.* **2009**, 52, 7310-7314) wherein a mixture of the alkali metal salts of N-substituted piperazine dithiocarbamic acid (15.8 mmol) and water (15 mL) was stirred for 10 minutes. To this solution sodium nitrite (15.8 mmol) in 1 mL of methanol was

added, and under cooling (0-5 °C) and stirring, concentrated HCl (3 mL) was added dropwise. The precipitated product was collected and crystallized from ethanol to yield the desired compound.

In yet another embodiment, the water soluble salts of free base bis(4- substituted-1-piperazinylthiocarbonyl) disulfide (**I**, n=0) are obtained by reacting with corresponding acids such as (dl)-tartaric acid (Example **1-21**), (d)-tartaric acid (Example **8**), (l)-tartaric acid (Example **8**), citric acid (Example **8**), oxalic acid (Example **8**), ascorbic acid (Example **8**), acetic acid (Example **8**), lactic acid (Example **8**), malonic acid (Example **8**), malic acid (Example **8**), mandelic acid (Example **8**) or hydrochloric acid (Example **8**) using aliphatic alcohol containing C_1-C_4 carbon atoms as a solvent.

The process of present invention is depicted according to scheme shown in Scheme 1 of accompanying drawing which consists of following steps:

1. N-substituted piperazines were prepared by the reaction of a halo substituted reagent with piperazine in the presence of triethyl amine and appropriate solvent. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 7-10%. The purification of monosubstituted piperazines by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided [Example **8-10**]. The remaining N-substituted piperazines [Example **4-7**, **12-21**] were purified through column chromatography using methanol in chloroform as eluent.

2. Then alkali metal salts of N-substituted piperazine dithiocarbamic acid were obtained using conventional methods. Either the product obtained in step 1 [Example **4-10**, **12-21**] or commercially available N-substituted piperazine [Example **1-3**, **11**] was used as such in this step as the reaction occurs only with free NH group i.e., with monosubstituted piperazines. The disubstituted piperazine present if any, gets washed with organic solvent during work up.

3. The final product bis(4- substituted-1-piperazinylthiocarbonyl) disulfide (**I**) as shown in figure 1, is synthesized using conventional method.

4. The water soluble salts of free base bis(4- substituted-1-piperazinylthiocarbonyl) disulfide (**I**, where n = 0) are obtained by reacting it with corresponding acids such as (dl)-tartaric acid (Example **1-21**), (d)-tartaric acid (Example **8**), (l)-tartaric acid (Example **8**), citric acid (Example **8**), oxalic acid (Example **8**), ascorbic acid (Example **8**), acetic acid (Example **8**), lactic acid (Example **8**), malonic acid (Example **8**), malic acid (Example **8**), mandelic acid (Example **8**) or hydrochloric acid (Example **8**)

The synthesis of compounds according to the invention, specially the compounds according to formula **I** (Table 1, where n = 1, 2 or 3) by the general procedure as shown below in Scheme 1.

N-substituted piperazines were prepared by the reaction of a halo substituted reagent with piperazine in the presence of triethyl amine and appropriate solvent. Then alkali metal salts of N-substituted piperazine dithiocarbamic acid were obtained using conventional methods. The alkali metal salts of N-substituted piperazine dithiocarbamic acid were further condensed with different carbon chain using corresponding dihaloalkane in the presence of triethyl amine and CH_3CN at room temperature. The mixture of sodium salts of N-substituted piperazine dithiocarbamic acid (11.16 mmol) and diiodomethane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure and crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and the combined organic layers were dried on Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (100-200 mesh) using MeOH/$CHCl_3$ as eluent to afford the desired compounds alkane-1,n-diyl bis(4-substitutedpiperazine-1-carbodithioate) (**22-32**) of general structure **I** of accompanying drawing where n = 1, 2 or 3

Finally **I** (where n = 1, 2 or 3) was converted in to their salts by conventional method. The salts may be a (dl) tartrate (Example **22-32**), (d) tartrate, (l) tartrate, citrate, oxalate, escorbate, acetate, lactate, maliate, mandelate or hydrochloride.

In an embodiment, the alkali metal salts of N-substituted piperazine dithiocarbamic acid were prepared by the process reported by Tripathi *et.al* (*Acta Pharm.* **1996**, 46, 169-176). To the mixture of N-substituted piperazine (1.0 mol) in ethyl acetate and sodium hydroxide (1.0 mol, dissolved in minimum water) was added carbon disulfide dropwise at 0-5 °C. The reaction mixture was further stirred for one hour, concentrated and recrystallized with methanolic ether.

In another embodiment, the alkali metal salts of N-substituted piperazine dithiocarbamic acid are selected from sodium salt, potassium salt and lithium salt

In yet another embodiment, the alkali metal salts of N-substituted piperazine dithiocarbamic acid further condensed with different carbon chain using corresponding dihaloalkane in the presence of triethyl amine and CH_3CN at room temperature.

In yet another embodiment, the water soluble salts of free base alkane-1,n-diyl bis(4-substitutedpiperazine-1-carbodithioate) (**I**, where n = 1, 2 or 3) are obtained by reacting

with corresponding acids such as (dl) tartaric acid (Example **22-32**), (d) tartaric acid, (l) tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid or hydrochloric acid

The process of present invention is depicted in scheme 1 (where n = 1, 2 or 3 of accompanying drawing and consist of following steps:

1. N-substituted piperazines were prepared by the reaction of a halo substituted reagent with piperazine in the presence of triethyl amine and appropriate solvent. The possible formation of disubstituted product [Example **24-32**] was minimized by slow addition of alkyl halide to 7-10%. The purification of monosubstituted piperazines by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided.

2. Then alkali metal salts of N-substituted piperazine dithiocarbamic acid were obtained using conventional methods. Either the product obtained in step 1 [Example **24-32**] or commercially available N-substituted piperazine [Example **22**, **23**] was used as such in this step as the reaction occurs only with free NH group *i.e.*, with monosubstituted piperazines. The disubstituted piperazine, if any present, gets washed with organic solvent during work up.

3. The alkali metal salts of N-substituted piperazine dithiocarbamic acid further condensed with different carbon chain using corresponding dihaloalkane in the presence of triethyl amine in CH_3CN at room temperature to give the final product alkane-1,n-diyl bis(4-substitutedpiperazine-1-carbodithioate) (**I**, where n = 1, 2 or 3).

4. The water soluble salts of free base alkane-1,n-diyl bis(4-substitutedpiperazine-1-carbodithioate) (**I**, where n = 1, 2 or 3). are obtained by reacting it with corresponding acids selected from group consisting of, (dl)-tartaric acid (Example **22-32**), (d)-tartaric acid, (l)-tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid, malonic acid, malic acid, mandelic acid or hydrochloric acid

In general, all reagents and solvents were commercial quality and were used without further purification. All chemicals and solvents were procured from Sigma-Aldrich / Merck India Ltd. The reaction progress was routinely monitored by thin layer chromatography (TLC) on pre-coated silica gel plates (Aldrich). Column chromatography was performed over Merck silica gel (100-200 Mesh).

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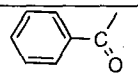
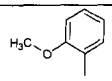
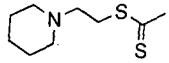
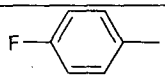
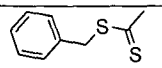
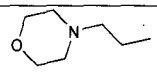
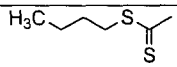
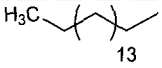
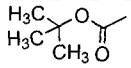
1		0	**17**		0
2		0	**18**		0
3		0	**19**		0
4		0	**20**		0
5		0	**21**		0
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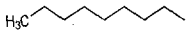
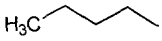
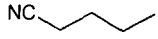
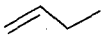
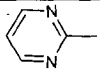
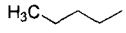
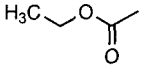
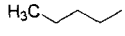
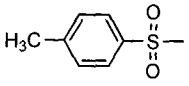
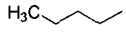
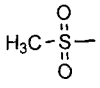
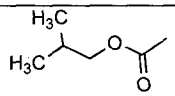
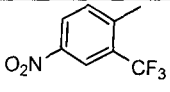
7		0	**23**	H_3C-	3
8		0	**24**		1
9		0	**25**		2
10		0	**26**		3
11		0	**27**		1
12		0	**28**		2
13		0	**29**		3
14		0	**30**		1
15		0	**31**		2
16		0	**32**		3

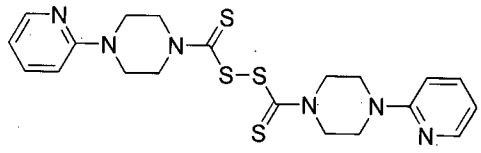
Table 1: Different synthesized examples of general formula **I**

EXAMPLES:

The invention is described by way of illustrative examples and should not be construed to limit the scope of the invention to the accompanying formula drawings.

Example 1:

Bis(4- pyridin-2-yl-1-piperazinylthiocarbonyl) disulfide (Final compound 1):



Sodium 4-(pyridin-2-yl)piperazine-1-carbodithioate:

According to scheme 1, step 2: Commercially available 1-(pyridin-2-yl)piperazine (3.0 mmol) was taken in ethyl acetate (20 mL) to this aqueous sodium hydroxide (3.8 mmol, 30%) was added keeping the temperature 5 °C, carbon disulfide (3.8 mmol) dissolved in ethyl acetate (5 mL) was further added drop-wise with stirring at 5 °C. The reaction mixture was stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was re-crystallised by methanolic ether to get sodium 4-(pyridin-2-yl)piperazine-1-carbodithioate as a white powder.

Bis(4- pyridin-2-yl-1-piperazinylthiocarbonyl) disulfide (1):

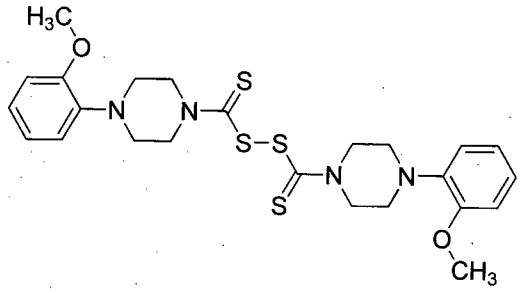
According to scheme 1, step 3: The mixture of sodium 4-(pyridin-2-yl)piperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 2 °C for 5 minutes. Then concentrated HCl (1 mL) was added dopwise and the reaction mixture was stirred at 2 °C for 10 minutes. The white solid which separated was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2) and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis(4- pyridin-2-yl-1-piperazinylthiocarbonyl) disulfide (**1**) was yielded as colourless crystals (melting point 168–170 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2944, 1657, 1561, 1474; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20–8.14 (2H, m); 7.57–7.48 (2H, m); 6.72–6.68 (4H, m); 4.42 (8H, bs), 3.79 (8H bs); ^{13}C (75 MHz, $CDCl_3$): δ 188.3 (C=S), 56.0, 50.0, 25.7, 23.3; ESI-MS: (*m/z*) 477 (MH^+); Anal. calcd. for $C_{20}H_{24}N_6S_4$: C, 50.39; H, 5.07; N, 17.63; found, C, 50.55; H, 5.32; N, 17.41.

Bis(4- pyridin-2-yl-1-piperazinylthiocarbonyl) disulfide (1).ditartrate:

Bis(4-pyridin-2-yl-1-piperazinylthiocarbonyl) disulfide (**1**, 0.5 mmol) was dissolved in absolute alcohol (20 mL). dl-Tartaric acid (1 mmol) dissolved in absolute alcohol (10 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccators to obtain ditartrate salt of bis(4- pyridin-2-yl-1-piperazinylthiocarbonyl) disulfide (**1**).

Example 2:

Bis[4-(2-methoxyphenyl)-1-piperazinylthiocarbonyl] disulfide (Final compound 2):



Sodium 4-(2-methoxyphenyl)piperazine-1-carbodithioate:

According to scheme 1, step 2: Commercially available 1-(2-methoxyphenyl)piperazine (3.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (3.8 mmol, 30%) was added keeping the temperature 4 °C, carbon disulfide (3.8 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 4 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was re-crystallised by methanolic ether to get sodium 4-(2-methoxyphenyl)piperazine-1-carbodithioate as a white powder.

Bis[4-(2-methoxyphenyl)-1-piperazinylthiocarbonyl] disulfide (2):

According to scheme 1, step 3: The mixture of sodium 4-(2-methoxyphenyl)piperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 0 °C for 5 minutes. Then concentrated HCl (1 mL) was added dopwise and the reaction mixture was stirred at 0 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis[4-(2-methoxyphenyl)-1-piperazinylthiocarbonyl] disulfide (**2**) was yielded as colourless crystals (melting point 125–127 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2998, 1592, 1474, 1429; ^1H NMR (300 MHz, $CDCl_3$): δ 7.08–6.89 (8H, m), 4.48 (8H m), 3.89 (8H, s), 3.24 (8H, m);

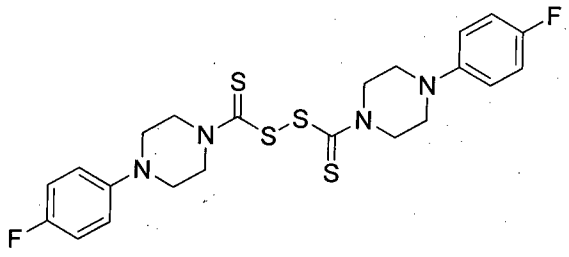
^{13}C (75 MHz, $CDCl_3$): δ 193.6 (C=S), 152.3, 139.9, 123.9, 121.1, 118.6, 111.5, 55.5, 50.4; ESI-MS: (m/z) 535 (MH^+); Anal. calcd. for $C_{24}H_{30}N_4O_2S_4$: C, 53.90; H, 5.65; N, 10.48; found, C, 53.08; H, 5.52; N, 10.39.

Bis[4-(2-methoxyphenyl)-1-piperazinylthiocarbonyl] disulfide (2).ditartrate:

[Bis[4-(2-methoxyphenyl)-1-piperazinylthiocarbonyl] disulfide (**2**, 0.5 mmol) was dissolved in absolute alcohol (20 mL). dl-Tartaric acid (1 mmol) dissolved in absolute alcohol (10 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccators to get ditartrate salt of bis[4-(2-methoxyphenyl)-1-piperazinylthiocarbonyl] disulfide (**2**).

Example 3:

Bis[4-(4-fluorophenyl)-1-piperazinylthiocarbonyl] disulfide (Final compound 3):



Sodium 4-(4-fluorophenyl)piperazine-1-carbodithioate:

According to scheme 1, step 2: Commercially available 1-(4-fluorophenyl)piperazine (3.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (3.8 mmol, 30%) was added keeping the temperature 1 °C, carbon disulfide (3.8 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 1 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(4-fluorophenyl)piperazine-1-carbodithioate as a white powder.

Bis[4-(4-fluorophenyl)-1-piperazinylthiocarbonyl] disulfide (3):

According to scheme 1, step 3: The mixture of sodium 4-(4-fluorophenyl)piperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 3 °C for 5 minutes. Then concentrated HCl (1 mL) was added dopwise and the reaction mixture was stirred at 3 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2) and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid

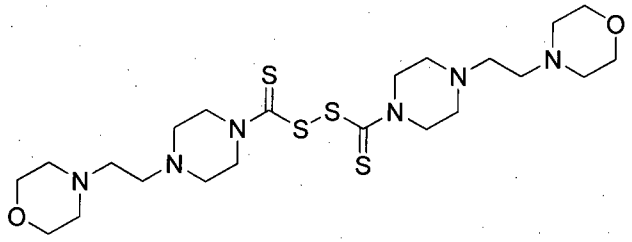
was obtained. The pure product bis[4-(4-fluorophenyl)-1-piperazinylthiocarbonyl] disulfide (**3**) was yielded as colourless crystals (melting point 140–142 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2924, 1586, 1474, 1429; ^1H NMR (300 MHz, $CDCl_3$): δ 7.04–6.90 (8H, m), 4.47 (8H, m), 3.32 (8H, m); ^{13}C (75 MHz, $CDCl_3$): δ 193.9 (C=S), 159.5, 147.0, 118.8, 118.6, 116.1, 115.8, 50.3; ESI-MS: (m/z) 511 (MH^+); Anal. calcd. for $C_{22}H_{24}F_2N_4S_4$: C, 51.74; H, 4.74; 10.97; found, C, 51.59; H, 4.85; N, 10.87.

Bis[4-(4-fluorophenyl)-1-piperazinylthiocarbonyl] disulfide (3).ditartrate:

Bis[4-(4-fluorophenyl)-1-piperazinylthiocarbonyl] disulfide (**3**, 0.5 mmol) was dissolved in absolute alcohol (20 mL). dl-Tartaric acid (1 mmol) dissolved in absolute alcohol (10 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccators to get the ditartrate salt of bis[4-(4-fluorophenyl)-1-piperazinylthiocarbonyl] disulfide (**3**).

Example 4:

Bis[4-(2-morpholinoethyl)-1-piperazinylthiocarbonyl] disulfide (Final compound 4):



1-(2-morpholinoethyl)piperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4mmol) was added and then 4-(2-chloroethyl)morpholine (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within one hour with stirring under reflux. The reaction mixture was further refluxed for two hours. The reaction was over and solvent was evaporated under reduced pressure to get crude. The desired product 1-(2-morpholinoethyl)piperazine was obtained by column chromatography using chloroform-methanol as eluent. The compound 1-(2-morpholinoethyl)piperazine was obtained as colourless oil.

Sodium 4-(2-morpholinoethyl)piperazine-1-carbodithioate:

According to scheme 1, step 2: 1-(2-morpholinoethyl)piperazine (3.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (3.8 mmol, 30%) was added keeping the temperature 5 °C, carbon disulfide (3.8 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 5 °C. The reaction mixture was further stirred at

room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(2-morpholinoethyl)piperazine-1-carbodithioate as a white powder.

Bis[4-(2-morpholinoethyl)-1-piperazinylthiocarbonyl] disulfide (4):

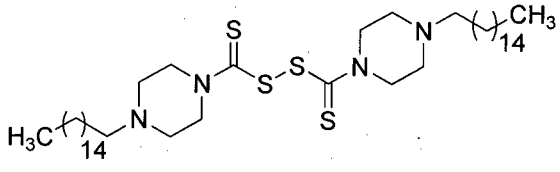
According to scheme 1, step 3: The mixture of sodium 4-(2-morpholinoethyl)piperazine-1-carbodithioate (1.7 mmol), sodium nitrite (1.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 2 °C for 5 minutes. Then concentrated HCl (0.5 mL) was added drop-wise and the reaction mixture was stirred at 2 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and the filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis[4-(2-morpholinoethyl)-1-piperazinylthiocarbonyl] disulfide (**4**) was yielded as colourless crystals (melting point 110–112 °C) after re-crystallization with ethanol-chloroform mixture. IR ν (KBr) (cm^{-1}): 2955, 1589, 1471, 1430; ^1H NMR (300 MHz, $CDCl_3$): δ 4.28 (8H, bs), 3.73–3.70(8H m), 2.67–2.48 (24H, m); ^{13}C (75 MHz, $CDCl_3$): δ 193.6 (C=S), 67.0, 56.4, 56.3, 55.4, 55.0, 54.2, 53.3, 53.0, 51.5; ESI-MS: (m/z) 549 (MH^+); Anal. calcd. for $C_{22}H_{40}N_6O_2S_4$: C, 48.14; H, 7.35; N, 15.31; found, C, 48.42; H, 7.21; N, 15.42.

Bis[4-(2-morpholinoethyl)-1-piperazinylthiocarbonyl] disulfide (4).ditartrate:

Bis[4-(2-morpholinoethyl)-1-piperazinylthiocarbonyl] disulfide (**4**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccators to get the ditartrate salt of bis[4-(2-morpholinoethyl)-1-piperazinylthiocarbonyl] disulfide (**4**).

Example 5:

Bis(4-hexadecyl-1-piperazinylthiocarbonyl) disulfide (Final compound 5):



1-hexadecylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 1-bromohexadecane (6.7 mmol) dissolved in chloroform (10 mL) was added slowly

within three hour with stirring under reflux. The reaction mixture was further refluxed for three hours. The reaction was over and solvent was evaporated under reduced pressure to get crude. The desired product 1-hexadecylpiperazine was obtained by column chromatography using chloroform-methanol as eluent. The compound 1-hexadecylpiperazine was obtained as colourless oil.

4-hexadecylpiperazine-1-carbodithioate Sodium:

According to scheme 1, step 2: 1-hexadecylpiperazine (3.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (3.8 mmol, 30%) was added keeping the temperature 5 °C, carbon disulfide (3.8 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 5 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-hexadecylpiperazine-1-carbodithioate as a white powder.

Bis(4-hexadecyl-1-piperazinylthiocarbonyl) disulfide (5):

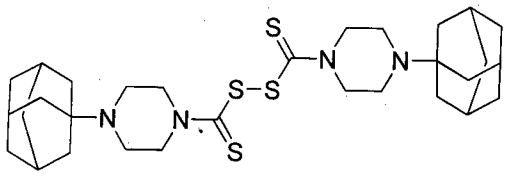
According to scheme 1, step 3: The mixture of sodium 4-hexadecylpiperazine-1-carbodithioate (1.7 mmol), sodium nitrite (1.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 2 °C for 5 minutes. Then concentrated HCl (0.5 mL) was added drop-wise and the reaction mixture was stirred at 2 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis(4-hexadecyl-1-piperazinylthiocarbonyl) disulfide (**5**) was yielded as colourless crystals (melting point 95–98 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2926, 1586, 1471, 1430; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.44–4.30 (8H, m), 2.60–2.50 (8H m), 2.40–2.36 (4H, m), 1.49 (4H, m), 1.26 (52H, m), 0.89 (6H, t, J = 7.2 Hz); ^{13}C (75 MHz, $CDCl_3$): δ 193.4 (C=S), 58.1, 52.7, 31.9, 29.7, 29.6, 29.5, 294, 27.4, 26.8, 22.7, 14.1; ESI-MS: (m/z) 772 (MH^+); Anal. calcd. for $C_{42}H_{82}N_4S_4$: C, 65.40; H, 10.71; N, 7.26; found, C, 65.55; H, 10.61; N, 7.19.

Bis(4-hexadecyl-1-piperazinylthiocarbonyl) disulfide (5).ditartrate:

Bis(4-hexadecyl-1-piperazinylthiocarbonyl) disulfide (**5**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccators to get the ditartrate salt of bis(4-hexadecyl-1-piperazinylthiocarbonyl) disulfide (**5**).

Example 6:

Bis(4-admentyl-1-piperazinylthiocarbonyl) disulfide (Final compound 6):



1-Admantylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 1-bromoadmatane (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within five hour with stirring under reflux. The reaction mixture was further refluxed for five hours. The reaction was over and solvent was evaporated under reduced pressure to get crude. The desired product 1-admantylpiperazine was obtained by column chromatography using chloroform-methanol as eluent. The compound 1-admantylpiperazine was obtained as colourless oil.

Sodium 4-admantylpiperazine-1-carbodithioate:

According to scheme 1, step 2: 1-admantylpiperazine (3.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (3.8 mmol, 30%) was added keeping the temperature 4 °C, carbon disulfide (3.8 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 4 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-admantylpiperazine-1-carbodithioate as a white powder.

Bis(4-admentyl-1-piperazinylthiocarbonyl) disulfide (6):

According to scheme 1, step 3: The mixture of sodium 4-admantylpiperazine-1-carbodithioate (1.7 mmol), sodium nitrite (1.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 3 °C for 5 minutes. Then concentrated HCl (0.5 mL) was added drop-wise and the reaction mixture was stirred at 3 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis(4-admentyl-1-piperazinylthiocarbonyl) disulfide (**6**) was yielded as colourless crystals (melting point 125–127 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2927, 1590, 1433, 1374; ^1H NMR (300 MHz, $CDCl_3$): δ 4.27 (4H, bs), 2.57 (4H bs), 2.38–2.33 (2H, m), 1.66–1.46

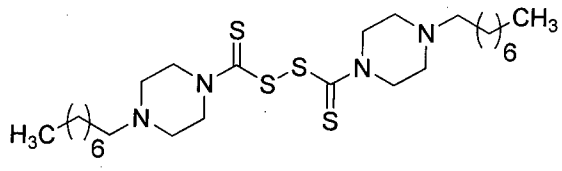
(4H, m), 1.24 (28H, bs), 0.86–0.84 (4H, m); ESI-MS: (m/z) 591 (MH^+); Anal. calcd. for $C_{30}H_{46}N_4S_4$: C, 60.97; H, 7.85; N, 9.48; found, C, 61.15; H, 8.10; N, 9.25.

Bis(4-admentyl-1-piperazinylthiocarbonyl) disulfide (6).ditartrate:

Bis(4-admentyl-1-piperazinylthiocarbonyl) disulfide (**6**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt of bis(4-admentyl-1-piperazinylthiocarbonyl) disulfide (**6**).

Example 7:

Bis(4-octyl-1-piperazinylthiocarbonyl) disulfide (Final compound 7):



1-Octylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 1-bromooctane (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within five hour with stirring under reflux. The reaction mixture was further refluxed for five hours. The reaction was over and solvent was evaporated under reduced pressure to get crude. The desired product 1-octylpiperazine was obtained by column chromatography using chloroform-methanol as eluent. The compound 1-octylpiperazine was obtained as colourless oil.

Sodium 4-octylpiperazine-1-carbodithioate:

According to scheme 1, step 2: 1-octylpiperazine (5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 4 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 4 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-octylpiperazine-1-carbodithioate as a white powder.

Bis(4-octyl-1-piperazinylthiocarbonyl) disulfide (7):

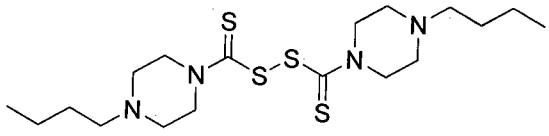
According to scheme 1, step 3: The mixture of sodium 4-octylpiperazine-1-carbodithioate (2.4 mmol), sodium nitrite (2.4 mmol, dissolved in 1 mL methanol) and distilled water (10 mL) was stirred at 2 °C °C for 5 minutes. Then concentrated HCl (1 mL) was added drop-wise and the reaction mixture was stirred at 2 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis(4-octyl-1-piperazinylthiocarbonyl) disulfide (**7**) was yielded as colourless crystals (melting point 93–95 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2930, 1585, 1471, 1430; ^1H NMR (300 MHz, $CDCl_3$): δ 4.29 (8H, bs), 2.60 (8H bs), 2.38 (4H, t, J = 7.3 Hz), 1.50 (4H, bs), 1.29 (20H, bs), 0.89 (6H, t, J = 6.9 Hz); ^{13}C (75 MHz, $CDCl_3$): 193.4 (C=S), 58.2, 52.8, 31.9, 29.6,29.3, 27.5, 26.9, 22.7, 14.2; ESI-MS: (m/z) 548 (MH^+); Anal. calcd. for $C_{26}H_{50}N_4S_4$: C, 57.09; H, 9.21; N, 10.24; found, C, 57.39; H, 9.12; N, 10.10.

Bis(4-octyl-1-piperazinylthiocarbonyl) disulfide (7).ditartrate:

Bis(4-octyl-1-piperazinylthiocarbonyl) disulfide (**7**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt of bis(4-octyl-1-piperazinylthiocarbonyl) disulfide (**7**).

Example 8:

Bis(4-butyl-1-piperazinylthiocarbonyl) disulfide (Final compound 8):



1-Butylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (500 mmol) was dissolved in chloroform. To this solution, Triethylamine (500 mmol) was added and then 1-bromobutane (250 mmol) dissolved in chloroform (75 mL) was added slowly within 7-8 hours with stirring under reflux. The reaction mixture was further refluxed for three hours. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 7%. The purification of monosubstituted piperazine by column

chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided.

Sodium 4-butylpiperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-butylpiperazine piperazines. The disubstituted piperazine present if any, gets washed with organic solvent during work up.1-butylpiperazine (~108 mmol) was taken in ethyl acetate (150 mL), to this, aqueous sodium hydroxide (135 mmol, 30%) was added keeping the temperature 1 °C, carbon disulfide (190 mmol) dissolved in ethyl acetate (50 mL) was added drop-wise with stirring at 1 °C. The reaction mixture was further stirred at room temperature for 10 hours to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-butylpiperazine-1-carbodithioate as a white powder.

Bis(4-butyl-1-piperazinylthiocarbonyl) disulfide (8):

According to scheme 1, step 3: The mixture of sodium 4-butylpiperazine-1-carbodithioate (21 mmol), sodium nitrite (21 mmol, dissolved in 5 mL methanol) and distilled water (100 mL) was stirred at 0 °C °C for 5 minutes. Then 5% HCl (42 mmol) was added drop-wise and the reaction mixture was stirred at 0 °C for two hours. White solid separated which was extracted with chloroform (50 mL × 2). Combined organic layer was washed with distilled water (20 mL × 2) and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A light yellow solid was obtained. The pure product bis(4-butyl-1-piperazinylthiocarbonyl) disulfide (**8**) was yielded as light yellow crystals (melting point 105–108 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2957, 1586, 1473, 1430; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 (8H, bs), 2.63 (8H bs), 2.39 (4H, t, J = 7.2 Hz), 1.54–1.26 (8H, m), 0.95 (6H, t, J = 7.2 Hz); ^{13}C (75 MHz, $CDCl_3$): δ 193.4 (C=S), 57.8, 53.3, 52.8, 51.8, 29.0, 20.6, 14.0; ESI-MS: (*m/z*) 435 (MH^+); Anal. calcd. for $C_{18}H_{34}N_4S_4$: C, 49.73; H, 7.88; N, 12.89; found, C, 49.53; H, 7.98; N, 12.80. HPLC purity 99.6% (Retention time 14.57 minute) by using methanol-water system on C-18 column.

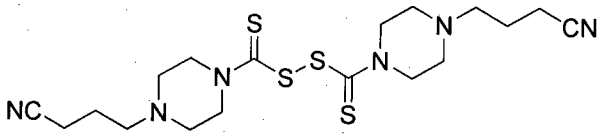
Bis(4-butyl-1-piperazinylthiocarbonyl) disulfide (8).ditartrate:

Bis(4-butyl-1-piperazinylthiocarbonyl) disulfide (**8**, 0.5 mmol) was dissolved in absolute alcohol (20 mL). dl-Tartaric acid (1.0 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of bis(4-butyl-1-piperazinylthiocarbonyl) disulfide (**8**). Similarly, (d)-tartaric acid (hygroscopic), (l)-tartaric acid (hygroscopic), citric acid (hygroscopic), oxalic acid (hygroscopic), ascorbic acid

(hygroscopic), acetic acid (hygroscopic), lactic acid (hygroscopic), malonic acid (hygroscopic), malic acid (hygroscopic), mandelic acid (hygroscopic) or hydrochloric acid salts (hygroscopic) have been prepared using aliphatic alcohol containing C_1-C_4 carbon atoms as a solvent.

Example 9:

Bis[4-(3-cyanoproyl)-1-piperazinylthiocarbonyl] disulfide (Final compound 9):



1-(3-cyanopropyl)piperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 3-bromopropanenitrile (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within two hours with stirring under reflux. The reaction mixture was further refluxed for one hour. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 8%. The purification of monosubstituted piperazine by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided. The compound 1-(3-cyanopropyl)piperazine was obtained as colourless oil.

Sodium 4-(3-cyanopropyl)piperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-(3-cyanopropyl)piperazine. The disubstituted piperazine present if any, gets washed with organic solvent during work up. 1-(3-cyanopropyl)piperazine (~5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 3 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 3 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(3-cyanopropyl)piperazine-1-carbodithioate as a white powder.

Bis[4-(3-cyanoproyl)-1-piperazinylthiocarbonyl] disulfide (9):

According to scheme 1, step 3: The mixture of sodium 4-(3-cyanopropyl)piperazine-1-carbodithioate (5.4 mmol), sodium nitrite (5.4 mmol, dissolved in 2 mL methanol) and

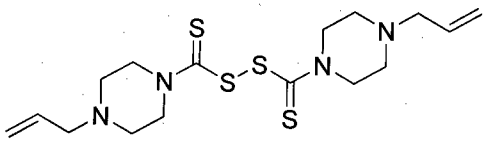
distilled water (20 mL) was stirred at 3 °C for 5 minutes. Then concentrated HCl (1.6 mL) was added drop-wise and the reaction mixture was stirred at 3 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A light yellow solid was obtained. The pure product bis[4-(3-cyanoproyl)-1-piperazinylthiocarbonyl] disulfide (**9**) was yielded as light yellow crystals (melting point 108–110 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2951, 1585, 1473, 1429; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.30(8H, bs), 2.63–2.44 (16H, m), 1.85 (4H, t, J = 6.8 Hz); ^{13}C (75 MHz, CDCl3): δ 193.6 (C=S), 119.6, 55.7, 52.6, 22.6, 15.0; ESI-MS: (m/z) 457 (MH^+); Anal. calcd. for $C_{18}H_{28}N_6S_4$: C, 47.34; H, 6.18; N, 18.40; found, C, 47.15; H, 6.37; N, 18.26.

Bis[4-(3-cyanoproyl)-1-piperazinylthiocarbonyl] disulfide (9).ditartrate:

Bis[4-(3-cyanoproyl)-1-piperazinylthiocarbonyl] disulfide (**9**, 0.5 mmol) was dissolved in absolute alcohol (20 mL). dl-Tartaric acid (1.0 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of bis[4-(3-cyanoproyl)-1-piperazinylthiocarbonyl] disulfide (**9**).

Example 10:

Bis(4-allyl-1-piperazinylthiocarbonyl) disulfide (Final compound 10):



1-Allylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 3-bromoprop-1-ene (6.7 mmol) dissolved in dichloromethane (10 mL) was added slowly within two hours with stirring at room temperature. The reaction mixture was stirred for one hour at room temperature. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 7%. The purification of monosubstituted piperazine by column chromatography was not required as the product can be used as

such in next step. Thus, uneconomical column chromatographic separation was avoided. The compound 1-allylpiperazine was obtained as colourless oil.

Sodium 4-allylpiperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-allylpiperazine. The disubstituted piperazine present if any, gets washed with organic solvent during work up. 1-allylpiperazine (5.0 mmol) was taken in ethyl acetate (20 mL), to this; aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 4 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 4 °C. The reaction mixture was further stirred at room temperature for 1.5 hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-allylpiperazine-1-carbodithioate as a white powder.

Bis(4-allyl-1-piperazinylthiocarbonyl) disulfide (10):

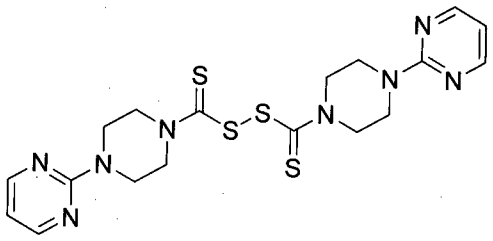
According to scheme 1, step 3: The mixture of sodium 4-allylpiperazine-1-carbodithioate (5.4 mmol), sodium nitrite (5.4 mmol, dissolved in 2 mL methanol) and distilled water (20 mL) was stirred at 2 °C for 5 minutes. Then concentrated HCl (1.6 mL) was added drop-wise and the reaction mixture was stirred at 2 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A light yellow solid was obtained. The pure product bis(4-allyl-1-piperazinylthiocarbonyl) disulfide (**10**) was yielded as light yellow crystals (melting point 105–107 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2919, 1588, 1471, 1425; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.92–5.78 (2H, m), 5.25–5.18 (4H, m), 4.30 (8H, bs), 3.06 (4H, d, J = 6.5 Hz), 2.63–2.60 (8H, m); ^{13}C (75 MHz, $CDCl_3$): δ 193.6 (C=S), 134.2, 118.9, 61.1, 54.0, 52.6, 51.3; ESI-MS: (m/z) 403 (MH^+); Anal. calcd. for $C_{16}H_{26}N_4S_4$: C, 47.72; H, 6.51; N, 13.91; found, C, 47.96; H, 6.21; N, 13.74.

Bis(4-allyl-1-piperazinylthiocarbonyl) disulfide (10).ditartrate:

Bis(4-allyl-1-piperazinylthiocarbonyl) disulfide (**10**, 0.5 mmol) was dissolved in absolute alcohol (20 mL). dl-Tartaric acid (1.0 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of bis(4-allyl-1-piperazinylthiocarbonyl) disulfide (**10**).

Example 11:

Bis(4- pyrimidin-2-yl -1-piperazinylthiocarbonyl) disulfide (Final compound 11):



Sodium 4-(pyrimidin-2-yl)piperazine-1-carbodithioate:

According to scheme 1, step 2: Commercially available 1-(pyrimidin-2-yl)piperazine (3.0 mmol) was taken in ethyl acetate (20 mL), to this aqueous sodium hydroxide (3.8 mmol, 30%) was added keeping the temperature 3 °C, carbon disulfide (3.8 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 3 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(pyrimidin-2-yl)piperazine-1-carbodithioate as a white powder.

Bis(4- pyrimidin-2-yl -1-piperazinylthiocarbonyl) disulfide (11):

According to scheme 1, step 3: The mixture of sodium 4-(pyrimidin-2-yl)piperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 0 °C for 5 minutes. Then concentrated HCl (1 mL) was added dopwise and the reaction mixture was stirred at 0 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis(4- pyrimidin-2-yl -1-piperazinylthiocarbonyl) disulfide (**11**) was yielded as colourless crystals (melting point 125–127 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2991, 2861, 1586, 1552, 1481, 1420, 1352, 1221; ^1H NMR (300 MHz, CDCl3): δ 8.35 (4H, d, J = 4.7 Hz), 6.60–6.57 (2H, m), 4.39 (8H, bs), 4.05 (8H, m); ESI-MS: (m/z) 479 (MH^+); Anal. calcd. for $C_{18}H_{22}N_8S_4$: C, 45.16; H, 4.63; N, 23.41; found, C, 45.29; H, 4.42; N, 23.24.

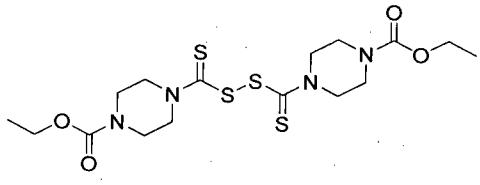
Bis(4- pyrimidin-2-yl -1-piperazinylthiocarbonyl) disulfide (11).ditartrate:

Bis(4- pyrimidin-2-yl -1-piperazinylthiocarbonyl) disulfide (**11**, 0.5 mmol) was dissolved in absolute alcohol (20 mL). dl-tartaric acid (1 mmol) dissolved in absolute alcohol (10 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high

vacuum desiccators to obtain ditartrate salt (hygroscopic) of bis(4- pyrimidin-2-yl -1-piperazinylthiocarbonyl) disulfide (**11**).

Example 12:

Bis(4-ethoxycarbonyl -1-piperazinylthiocarbonyl) disulfide (Final compound 12):



1-(ethoxycarbonyl)piperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, triethylamine (13.4 mmol) was added keeping the temperature 1 °C and then ethyl chloromethanoate (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within two hours with stirring at 1 °C keeping the reaction condition dry. The reaction mixture was further stirred for one hour at room temperature. The reaction was over and solvent was evaporated under reduced pressure to get crude. The desired product 1-acetylpiperazine was obtained by column chromatography using chloroform-methanol as eluent. The compound 1-(ethoxycarbonyl)piperazine was obtained as colourless oil.

Sodium 4-(ethoxycarbonyl)piperazine-1-carbodithioate:

According to scheme 1, step 2: 1-(ethoxycarbonyl)piperazine (2.5 mmol) was taken in ethyl acetate (10 mL), to this, aqueous sodium hydroxide (3.1 mmol, 30%) was added keeping the temperature 5 °C, carbon disulfide (3.1 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 5 °C. The reaction mixture was further stirred at room temperature for 2 hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(ethoxycarbonyl)piperazine-1-carbodithioate as a white powder.

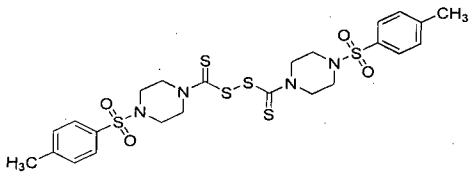
Bis(4-ethoxycarbonyl -1-piperazinylthiocarbonyl) disulfide (12):

According to scheme 1, step 3: The mixture of sodium 4-(ethoxycarbonyl)piperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (10 mL) was stirred at 4 °C for 5 minutes. Then concentrated HCl (1 mL) was added drop-wise and the reaction mixture was stirred at 4 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A white

solid was obtained. The pure product bis(4-ethoxycarbonyl -1-piperazinylthiocarbonyl) disulfide (**12**) was yielded as white crystals (melting point 126–128 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2978, 2901, 1686, 1479, 1418, 1282, 1162, 1126; ^1H NMR (300 MHz, $CDCl_3$): δ 5.92–4.29 (8H, bs), 4.22–4.15 (4H, q, J = 7.1 Hz), 3.70–3.67 (8H, m), 1.29 (6H, t, J = 7.1 Hz); ^{13}C (75 MHz, $CDCl_3$): δ 194.0 (C=S), 155.3 (C=O), 62.0, 52.0, 43.3, 14.7; ESI-MS: m/z 467 (MH^+); Anal. calcd. for $C_{16}H_{26}N_4O_4S_4$: C, 41.18; H, 5.62; N, 12.01; found, C, 41.34; H, 5.41; N, 12.32.

Example 13:

Bis(4-tosyl-1-piperazinylthiocarbonyl) disulfide (Final compound 13):



1-Tosylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added, keeping the temperature 1 °C. Tosyl chloride (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within two hours with stirring at 1 °C keeping the reaction condition dry. The reaction mixture was further stirred for one hour at room temperature. The reaction was over and solvent was evaporated under reduced pressure to get crude. The desired product 1-acetylpiperazine was obtained by column chromatography using chloroform-methanol as eluent. The compound 1-tosylpiperazine was obtained as colourless oil.

Sodium 4-tosylpiperazine-1-carbodithioate:

According to scheme 1, step 2: 1-tosylpiperazine (5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 2 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 2 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-tosylpiperazine-1-carbodithioate as a white powder.

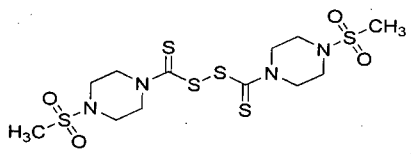
Bis(4-tosyl-1-piperazinylthiocarbonyl) disulfide (13):

According to scheme 1, step 3: The mixture of sodium 4-tosylpiperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (10 mL) was stirred at 2 °C for 5 minutes. Then concentrated HCl (1 mL) was added drop-

wise and the reaction mixture was stirred at 2 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A white solid was obtained. The pure product bis(4-tosyl-1-piperazinylthiocarbonyl) disulfide (**13**) was yielded as white crystals (melting point 140–142 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) (cm-1): 2969, 1742, 1530, 1364, 1263, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.61(4H, m), 7.36–7.27(m, 4H,), 4.38–4.33(5H, m), 3.93–3.89 (2H, m), 3.27–2.98 (10H, m), 2.44 (6H, s); ESI-MS: m/z 653 (M^+ + Na); Anal. calcd. for $C_{24}H_{30}N_4O_4S_6$: C, 45.69; H, 4.79; N, 8.88; found, C, 45.58; H, 4.95; N, 8.70.

Example 14:

Bis(4- methylsulfonyl -1-piperazinylthiocarbonyl) disulfide (Final compound 14):



1-(methylsulfonyl)piperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added, keeping the temperature 2 °C. Methanesulfonyl chloride (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within two hours with stirring at 2 °C keeping the reaction condition dry. The reaction mixture was further stirred for one hour at room temperature. The reaction was over and solvent was evaporated under reduced pressure to get crude. The desired product 1-acetylpiperazine was obtained by column chromatography using chloroform-methanol as eluent. The compound 1-(methylsulfonyl)piperazine was obtained as colourless oil.

Sodium 4-(methylsulfonyl)piperazine-1-carbodithioate:

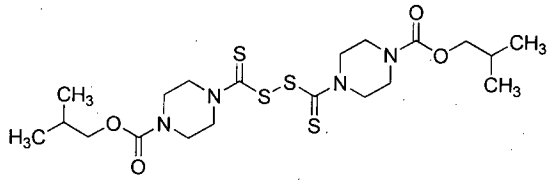
According to scheme 1, step 2: 1-(methylsulfonyl)piperazine (5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 5 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 5 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(methylsulfonyl)piperazine-1-carbodithioate as a white powder.

Bis(4- methylsulfonyl -1-piperazinylthiocarbonyl) disulfide (14):

According to scheme 1, step 3: The mixture of sodium 4-(methylsulfonyl)piperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (10 mL) was stirred at 3 °C for 5 minutes. Then concentrated HCl (1 mL) was added drop-wise and the reaction mixture was stirred at 3 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2) and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A white solid was obtained. The pure product bis(4- methylsulfonyl -1-piperazinylthiocarbonyl) disulfide (**14**) was yielded as white crystals (melting point 138–140 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) (cm-1): 2969, 1742, 1530, 1364, 1263, ^{1}H NMR (300 MHz, CDCl3): δ 4.41(4H, t, J = 5.20Hz), 3.96(4H, t, J = 5.4Hz), 3.50(4H, t, J = 5.16Hz), 3.24(4H, t, J = 5.3Hz), 2.84 (6H s); ESI-MS: m/z 479 (MH^+); Anal. calcd. for $C_{12}H_{22}N_4O_4S_6$: C, 30.11; H, 4.63; N, 11.70; found, C, 30.40; H, 4.90; N, 11.52.

Example 15:

Bis(4-isobutoxycarbonyl -1-piperazinylthiocarbonyl) disulfide (Final compound 15):



1-(isobutoxycarbonyl)piperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added, keeping the temperature 0 °C. isobutyl chloromethanoate (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within two hours with stirring at 0 °C keeping the reaction condition dry. The reaction mixture was further stirred for one hour at room temperature. The reaction was over and solvent was evaporated under reduced pressure to get crude. The desired product 1-acetylpiperazine was obtained by column chromatography using chloroform-methanol as eluent. The compound 1-(isobutoxycarbonyl)piperazine was obtained as colourless oil.

Sodium 4-(isobutoxycarbonyl)piperazine-1-carbodithioate:

According to scheme 1, step 2: 1-(isobutoxycarbonyl)piperazine (5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 2 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 2 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the

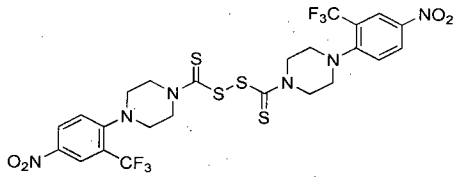
crude was recrystallised by methanolic ether to get sodium 4-(isobutoxycarbonyl)piperazine-1-carbodithioate as a white powder.

Bis(4-isobutoxycarbonyl -1-piperazinylthiocarbonyl) disulfide (15):

According to scheme 1, step 3: The mixture of sodium 4-(isobutoxycarbonyl)piperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (10 mL) was stirred at 3 °C for 5 minutes. Then concentrated HCl (1 mL) was added drop-wise and the reaction mixture was stirred at 3 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5×2 mL).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A white solid was obtained. The pure product bis(4-isobutoxycarbonyl -1-piperazinylthiocarbonyl) disulfide (**15**) was yielded as white crystals (melting point 130–132 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}): 2927, 2866, 1639, 1455, 1412; ^1H NMR (300 MHz, $CDCl_3$): δ 4.30 (8H, bs), 3.92 (4H, d, J = 6.63 Hz),3.70 (8H, bs), 2.03-1.89 (2H, m), 0.95 (12H, d, J = 6.72 Hz); ESI-MS: m/z 523(MH^+); Anal. calcd. for $C_{20}H_{34}N_4O_4S_4$: C, 45.95; H, 6.56; N, 10.72; found, C, 46.12; H, 6.65; N, 10.85.

Example 16:

Bis[4-(4-nitro-2-(trifluoromethyl)phenyl)-1-piperazinylthiocarbonyl] disulfide (Final compound 16):



1-(4-nitro-2-(trifluoromethyl)phenyl)piperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 1-chloro-4-nitro-2-(trifluoromethyl)benzene (6.7 mmol) dissolved in acetonitrile (10 mL) was added slowly within two hours with stirring under reflux. The reaction mixture was further refluxed for one hour. The reaction was over and solvent was evaporated under reduced pressure to get yellow coloured crude. The crude was dissolved in ethyl acetate (20 mL) and washed with water (10 mL x 2). The organic layer was concentrated under reduced pressure to obtain yellow oil. The desired product 1-(4-nitro-2-(trifluoromethyl)phenyl)piperazine was obtained by column chromatography using chloroform-methanol as eluent. The compound 1-(4-nitro-2-(trifluoromethyl)phenyl)piperazine was obtained as yellow dense oil.

Sodium 4-(4-nitro-2-(trifluoromethyl)phenyl)piperazine-1-carbodithioate:

According to scheme 1, step 2: 1-(4-nitro-2-(trifluoromethyl)phenyl)piperazine (5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 0 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 0 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a yellow solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(4-nitro-2-(trifluoromethyl)phenyl)piperazine-1-carbodithioate as a yellow powder.

Bis[4-(4-nitro-2-(trifluoromethyl)phenyl)-1-piperazinylthiocarbonyl] disulfide (16):

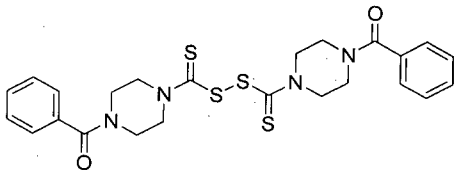
According to scheme 1, step 3: The mixture of sodium 4-(4-nitro-2-(trifluoromethyl)phenyl)piperazine-1-carbodithioate (5.4 mmol), sodium nitrite (5.4 mmol, dissolved in 2 mL methanol) and distilled water (20 mL) was stirred at 4 °C for 5 minutes. Then concentrated HCl (1.6 mL) was added drop-wise and the reaction mixture was stirred at 4 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A light yellow solid was obtained. The pure bis[4-(4-nitro-2-(trifluoromethyl)phenyl)-1-piperazinylthiocarbonyl] disulfide (**16**) was yielded as yellow crystals (melting point 146–148 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) (cm-1): 2925, 2854, 1535, 1468, 1425,1327,1221; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (2H, d, J = 1.41Hz), 7.75 (2H, dd, J = 8.64, 1.78 Hz), 7.22 (2H, d, J = 8.6 Hz), 4.49 (8H, bs), 3.38 (8H, t, J = 4.90 Hz) ; ESI-MS: m/z 701 (MH^+); Anal. calcd. for $C_{24}H_{22}F_6N_6O_4S_4$: C, 41.14; H, 3.16; N, 11.99; found, C, 41.37; H, 3.19; N, 12.15.

Bis[4-(4-nitro-2-(trifluoromethyl)phenyl)-1-piperazinylthiocarbonyl] disulfide (16).ditartrate:

Bis[4-(4-nitro-2-(trifluoromethyl)phenyl)-1-piperazinylthiocarbonyl] disulfide (**16**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of bis[4-(4-nitro-2-(trifluoromethyl)phenyl)-1-piperazinylthiocarbonyl] disulfide (**16**).

Example 17:

Bis(4-benzoyl-1-piperazinylthiocarbonyl) disulfide (Final compound 17):



1-Benzoylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added, keeping the temperature 1 °C. benzoyl chloride (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within two hours with stirring at 1 °C keeping the reaction condition dry. The reaction mixture was further stirred for one hour at room temperature. The reaction was over and solvent was evaporated under reduced pressure to get crude. The desired product 1-benzoylpiperazine was obtained by column chromatography using chloroform-methanol as eluent. The compound 1-benzoylpiperazine was obtained as colourless oil.

Sodium 4-benzoylpiperazine-1-carbodithioate:

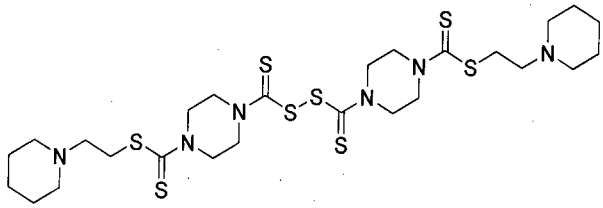
According to scheme 1, step 2: 1-benzoylpiperazine (5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 2 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 2 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-benzoylpiperazine-1-carbodithioate as a white powder.

Bis(4-benzoyl-1-piperazinylthiocarbonyl) disulfide (17):

According to scheme 1, step 3: The mixture of sodium 4-benzoylpiperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (10 mL) was stirred at 3 °C for 5 minutes. Then concentrated HCl (1 mL) was added drop-wise and the reaction mixture was stirred at 3 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A white solid was obtained. The pure product bis(4-benzoyl-1-piperazinylthiocarbonyl) disulfide (**17**) was yielded as white crystals (melting point 150–152 °C) after re-crystallization with ethanol-chloroform mixture. ; IR (KBr) (cm-1): 2969, 1742, 1530, 1364, 1263, ^{1}H NMR (300 MHz, CDCl3): ∂ 7.44–7.42 (10H, m), 3.85–3.70 (16H, m); ESI-MS: m/z 531 (MH^+); Anal. calcd. for $C_{24}H_{26}N_4O_2S_4$: C, 54.31; H, 4.94; N, 10.56; found, C, 54.12; H, 5.15; N, 10.69.

Example 18:

Bis[4-((2-(piperidin-1-yl)ethylthio)carbonothioyl)-1-piperazinylthiocarbonyl] disulfide (Final compound 18)



Sodium 4-((2-(piperidin-1-yl)ethylthio)carbonothioyl)piperazine-1-carbodithioate: According to scheme 1, step 2: 2-(piperidin-1-yl)ethyl piperazine-1-carbodithioate (3.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (3.8 mmol, 30%) was added keeping the temperature 2 °C, carbon disulfide (3.8 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 2 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-((2-(piperidin-1-yl)ethylthio)carbonothioyl)piperazine-1-carbodithioate.

Bis[4-((2-(piperidin-1-yl)ethylthio)carbonothioyl)-1-piperazinylthiocarbonyl] disulfide (18):

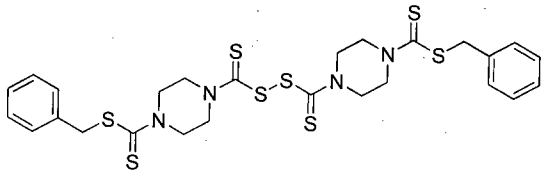
According to scheme 1, step 3: The mixture of sodium 4-((2-(piperidin-1-yl)ethylthio)carbonothioyl)piperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 4 °C for 5 minutes. Then concentrated HCl (1 mL) was added dopwise and the reaction mixture was stirred at 4 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis[4-((2-(piperidin-1-yl)ethylthio)carbonothioyl)-1-piperazinylthiocarbonyl] disulfide (**18**) was yielded as colourless crystals (melting point 182–184 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}); 2928, 2817, 1642, 1472, 1429, 1218; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41-4.40 (16H, m), 3.51 (4H, t, J = 7.3 Hz), 2.66 (4H, t, J = 7.3 Hz), 2.48 (8H, bs), 1.59-1.58 (8H, m), 1.45-1.38 (4H, m); ESI-MS *m/z*: 697 (MH^+); Anal calcd for $C_{26}H_{44}N_6S_8$; C, 44.79; H, 6.36; N, 12.05; found C, 44.54; H, 6.42; N, 12.17.

Bis[4-((2-(piperidin-1-yl)ethylthio)carbonothioyl)-1-piperazinylthiocarbonyl] disulfide (18).ditartrate:

Bis[4-((2-(piperidin-1-yl)ethylthio)carbonothioyl)-1-piperazinylthiocarbonyl] disulfide (**18**, 0.5 mmol) was dissolved in absolute alcohol (20 mL). dl-Tartaric acid (1 mmol) dissolved in absolute alcohol (10 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccators to get the ditartrate salt (hygroscopic) of bis[4-((2-(piperidin-1-yl)ethylthio)carbonothioyl)-1-piperazinylthiocarbonyl] disulfide (**18**).

Example 19:

Bis(4-benzylthiocarbonothioyl-1-piperazinylthiocarbonyl) disulfide (Final compound 19):



Sodium 4-(benzylthiocarbonothioyl)piperazine-1-carbodithioate:

According to scheme 1, step 2: benzyl piperazine-1-carbodithioate (3.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (3.8 mmol, 30%) was added keeping the temperature 5 °C, carbon disulfide (3.8 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 5 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get Sodium 4-(benzylthiocarbonothioyl)piperazine-1-carbodithioate as a white powder.

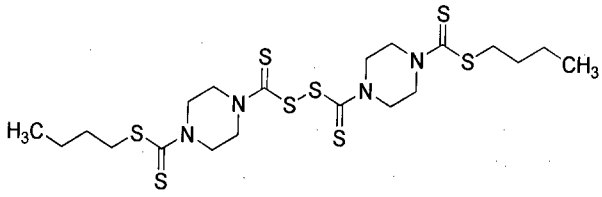
Bis(4-benzylthiocarbonothioyl-1-piperazinylthiocarbonyl) disulfide (19):

According to scheme 1, step 3: The mixture of sodium 4-(benzylthiocarbonothioyl)piperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 0 °C for 5 minutes. Then concentrated HCl (1 mL) was added dopwise and the reaction mixture was stirred at 0 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis(4-benzylthiocarbonothioyl-1-piperazinylthiocarbonyl) disulfide (**19**) was yielded as colourless crystals (melting point 135–137 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}); 2926, 2856, 1649, 1561, 1458, 1412, 1215; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.26 (10H, m), 4.59 (4H, s), 4.40-4.38 (16H, m); ESI-MS *m/z*:

655 (MH^+); Anal calcd for $C_{26}H_{30}N_4S_8$; C, 47.67; H, 4.62; N, 8.55; found C, 47.87; H, 4.76; N, 8.69.

Example 20:

Bis(4-butylthiocarbonothioyl-1-piperazinylthiocarbonyl) disulfide (Final compound 20):



Sodium 4-(butylthiocarbonothioyl)piperazine-1-carbodithioate:

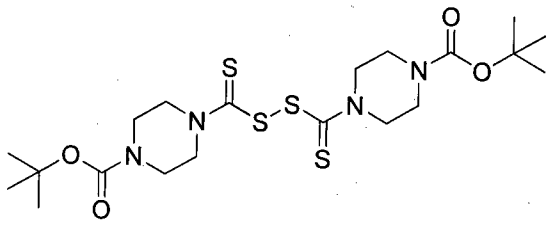
According to scheme 1, step 2: butyl piperazine-1-carbodithioate (3.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (3.8 mmol, 30%) was added keeping the temperature 3 °C, carbon disulfide (3.8 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 3 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(butylthiocarbonothioyl)piperazine-1-carbodithioate as a white powder.

Bis(4-butylthiocarbonothioyl-1-piperazinylthiocarbonyl) disulfide (20):

According to scheme 1, step 3: The mixture of sodium 4-(butylthiocarbonothioyl)piperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 0 °C for 5 minutes. Then concentrated HCl (1 mL) was added dopwise and the reaction mixture was stirred at 0°C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis(4-butylthiocarbonothioyl-1-piperazinylthiocarbonyl) disulfide (**20**) was yielded as colourless crystals (melting point 172–174 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}); 2927, 2865, 1639, 1455, 1412, 1216; ^1H NMR (300 MHz, $CDCl_3$) δ 4.41-4.39 (16H, m), 3.34 (4H, t, J = 7.4 Hz), 1.76-1.66 (4H, m), 1.52-1.40 (4H, m), 0.96 (6H, t, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 196.8, 194.0, 48.8,37.2, 30.6, 22.2, 13.8; ESI-MS *m/z*: 587 (MH^+); Anal calcd for $C_{20}H_{34}N_4S_8$; C, 40.92; H, 5.84; N, 9.54; found C, 41.12; H, 5.97; N, 9.65.

Example 21:

Bis(4-tert-butoxycarbonyl-1-piperazinylthiocarbonyl) disulfide (Final compound 21)



Sodium 4-(tert-butoxycarbonyl)piperazine-1-carbodithioate:

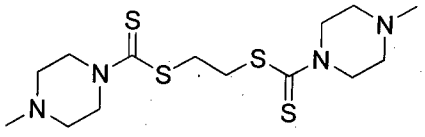
According to scheme 1, step 2: Tert-butyl piperazine-1-carboxylate (3.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (3.8 mmol, 30%) was added keeping the temperature 4 °C, carbon disulfide (3.8 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 4 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(tert-butoxycarbonyl)piperazine-1-carbodithioate as a white powder.

Bis(4-tert-butoxycarbonyl-1-piperazinylthiocarbonyl) disulfide (21):

According to scheme 1, step 3: The mixture of sodium 4-(tert-butoxycarbonyl)piperazine-1-carbodithioate (2.7 mmol), sodium nitrite (2.7 mmol, dissolved in 1 mL methanol) and distilled water (5 mL) was stirred at 2 °C for 5 minutes. Then concentrated HCl (1 mL) was added dopwise and the reaction mixture was stirred at 2 °C for 10 minutes. White solid separated which was extracted with chloroform (10 mL × 2). Combined organic layer was washed with distilled water (5 mL × 2).and dried over sodium sulphate. Sodium sulphate was filtered off and filtrate was concentrated under reduced pressure. A colourless solid was obtained. The pure product bis(4-tert-butoxycarbonyl-1-piperazinylthiocarbonyl) disulfide (**21**) was yielded as colourless crystals (melting point 163–165 °C) after re-crystallization with ethanol-chloroform mixture. IR (KBr) ν (cm^{-1}); 2976, 2925, 1690, 1467, 1419, 1228; ^1H NMR (300 MHz, $CDCl_3$) δ; 4.27 (8H, bs), 3.65-3.62 (8H, m), 1.49 (18H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 193.9, 154.4, 80.8, 52.3, 43.2, 28.4; ESI-MS *m/z*: 523 (MH^+); Anal calcd for $C_{20}H_{34}N_4O_4S_4$; C, 45.95; H, 6.56; N, 10.72; found C, 45.81; H, 6.65; N, 10.79.

Example 22:

4-Methyl-1-Piperazinecarbodithioic acid 1,1'-ethylene ester (Final compound 22):



Sodium 4-methylpiperazine-1-carbodithioate:

According to scheme 1, step 2: 1-methylpiperazine (10.0 mmol) was taken in ethyl acetate (30 mL), to this, aqueous sodium hydroxide (12.4 mmol, 30%) was added keeping the temperature 1 °C, carbon disulfide (12.4 mmol) dissolved in ethyl acetate (10 mL) was added drop-wise with stirring at 1 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was re-crystallised by methanolic ether to get sodium 4-methylpiperazine-1-carbodithioate as a white powder.

4-Methyl-1-piperazinecarbodithioic acid 1,1'-ethylene ester (22):

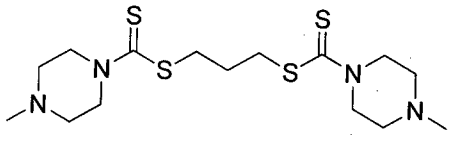
According to scheme 1, step 3: The mixture of sodium 4-methylpiperazine-1-carbodithioate (11.2 mmol) and 1,2-dibromoethane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried over sodium sulphate, filtered off, and concentrated under reduced pressure. The crude product was purified by column chromatography using $MeOH/CHCl_3$ as eluent to afford 4-methyl-1-piperazinecarbodithioic acid 1,1'-ethylene ester (**22**) as white solid (melting point 150–152 °C). IR (KBr) ν (cm^{-1}): 2931, 2854, 1630; ^1H NMR (300 MHz, $CDCl_3$): δ 4.35 (4H, bs), 3.96 (4H, bs), 3.68 (4H, s), 2.48–2.52 (8H, m), 2.33 (6H, s); ESI-MS: (*m/z*) 379 (MH^+); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.3 (C=S), 54.5, 51.2, 50.0, 45.7, 35.8; Anal. calcd. for $C_{14}H_{26}N_4S_4$: C, 44.41; H, 6.92; N, 14.80; found C, 44.26; H, 7.16; N, 14.72.

4-Methyl-1-piperazinecarbodithioic acid 1,1'-ethylene ester(22).ditartrate:

4-Methyl-1-piperazinecarbodithioic acid 1,1'-ethylene ester (**22**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of 4-methyl-1-piperazinecarbodithioic acid 1,1'-ethylene ester (**22**).

Example 23:

4-Methyl-1-piperazinecarbodithioic acid 1,1'-propylene ester (Final compound 23):



Sodium 4-methylpiperazine-1-carbodithioate:

According to scheme 1, step 2: 1-methylpiperazine (10.0 mmol) was taken in ethyl acetate (30 mL), to this, aqueous sodium hydroxide (12.4 mmol, 30%) was added keeping the temperature 5 °C, carbon disulfide (12.4 mmol) dissolved in ethyl acetate (10 mL) was added drop-wise with stirring at 5 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was re-crystallised by methanolic ether to get sodium 4-methylpiperazine-1-carbodithioate as a white powder.

4-Methyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (23):

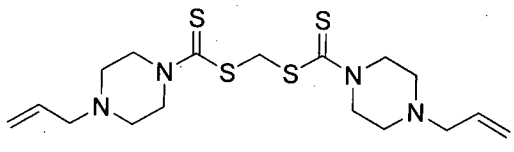
According to scheme 1, step 3: The mixture of sodium 4-methylpiperazine-1-carbodithioate (11.2 mmol) and 1,3-dibromopropane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried over sodium sulphate, filtered off, and concentrated under reduced pressure. The crude product was purified by column chromatography using $MeOH/CHCl_3$ as eluent to afford 4-methyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (**23**) as white solid (melting point 120–122 °C). IR (KBr) ν (cm^{-1}): 2927, 2853, 1654; ^1H NMR (300 MHz, $CDCl_3$): δ 3.98–4.32 (8H, m), 3.43 (4H, t, J = 7.2 Hz), 2.47–2.50 (8H, m), 2.32 (6H, s), 2.09–2.19 (2H, m); ESI-MS: (*m/z*) 393 (MH^+); Anal. calcd. for $C_{15}H_{28}N_4S_4$: C, 45.88; H, 7.19; N, 14.27; found C, 45.67; H, 7.21; N, 14.47.

4-Methyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (23).ditartrate:

4-Methyl-1-Piperazinecarbodithioic acid 1,1′-propylene ester (**23**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of 4-methyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (**23**).

Example 24:

4-Allyl-1-piperazinecarbodithioic acid 1,1′-methylene ester (Final compound 24



1-Allylpiperazine:

According to scheme1, step 1: Commercially available anhydrous piperazine (26.8 mmol) was dissolved in chloroform (30 mL). To this solution, Triethylamine (26.8 mmol) was added and then 3-bromoprop-1-ene (13.4 mmol) dissolved in dichloromethane (15 mL) was added slowly within two hours with stirring at room temperature. The reaction mixture was stirred for one hour at room temperature. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 9%. The purification of monosubstituted piperazine by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided. The compound 1-allylpiperazine was obtained as colourless oil.

Sodium 4-allylpiperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-allylpiperazine. The disubstituted piperazine present if any, gets washed with organic solvent during work up. 1-allylpiperazine (~10 mmol) was taken in ethyl acetate (25 mL), to this, aqueous sodium hydroxide (12.4 mmol, 30%) was added keeping the temperature 2 °C, carbon disulfide (12.4 mmol) dissolved in ethyl acetate (10 mL) was added drop-wise with stirring at 2 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was re-crystallised by methanolic ether to get sodium 4-allylpiperazine-1-carbodithioate as a white powder.

4-Allyl-1-piperazinecarbodithioic acid 1,1′-methylene ester (24):

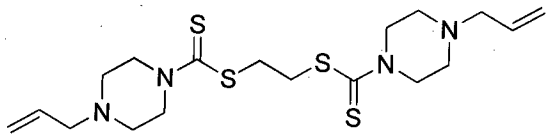
According to scheme 1, step 3: The mixture of sodium 4-allylpiperazine-1-carbodithioate (11.2 mmol) and diiodomethane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried over sodium sulphate, filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using $MeOH/CHCl_3$ as eluent to afford 4-allyl-1-piperazinecarbodithioic acid 1,1′-methylene ester (**24**) as white solid (melting point 125–127 °C). IR (KBr) ν (cm^{-1}): 2908, 2804, 1646; ^1H NMR (300 MHz, $CDCl_3$): δ 5.79–5.88 (2H, m), 5.43 (2H, s), 5.18–5.24 (4H, m), 4.34 (4H, bs), 3.89 (4H, m), 3.03 (4H, d, J = 6.5 Hz), 2.53 (8H, bs,); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.8 (C=S), 134.2, 118.8, 61.2, 52.4, 51.6, 50.1, 45.7; ESI-MS: (*m/z*) 417 (MH^+); Anal. calcd. for $C_{17}H_{28}N_4S_4$: C, 49.00; H, 6.77; N, 13.45; found C, 49.25; H, 6.67; N, 13.59.

4-Allyl-1-piperazinecarbodithioic acid 1,1′-methylene ester (24).ditartrate:

4-Allyl-1-piperazinecarbodithioic acid 1,1'-methylene ester (**24**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of 4-allyl-1-piperazinecarbodithioic acid 1,1'-methylene ester **(24)**.

Example 25:

4-Allyl-1-piperazinecarbodithioic acid 1,1'-ethylene ester (Final compound 25):



1-Allylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (26.8 mmol) was dissolved in chloroform (30 mL). To this solution, Triethylamine (26.8 mmol) was added and then 3-bromoprop-1-ene (13.4 mmol) dissolved in dichloromethane (15 mL) was added slowly within two hours with stirring at room temperature. The reaction mixture was stirred for one hour at room temperature. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 8%. The purification of monosubstituted piperazine by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided. The compound 1-allylpiperazine was obtained as colourless oil.

Sodium 4-allylpiperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-allylpiperazine. The disubstituted piperazine present if any, gets washed with organic solvent during work up. 1-allylpiperazine (~10 mmol) was taken in ethyl acetate (25 mL), to this, aqueous sodium hydroxide (12.4 mmol, 30%) was added keeping the temperature 3 °C, carbon disulfide (12.4 mmol) dissolved in ethyl acetate (10 mL) was added drop-wise with stirring at 3 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was re-crystallised by methanolic ether to get sodium 4-allylpiperazine-1-carbodithioate as a white powder.

4-Allyl-1-piperazinecarbodithioic acid 1,1'-ethylene ester (25):

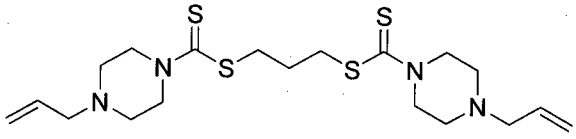
According to scheme 1, step 3: The mixture of sodium 4-allylpiperazine-1-carbodithioate (11.2 mmol) and 1,2-dibromoethane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried over sodium sulphate, filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using MeOH/$CHCl_3$ as eluent to afford 4-allyl-1-piperazinecarbodithioic acid 1,1′-ethylene ester (**27**) as white solid (melting point 140–142 °C. IR (KBr) ν (cm^{-1}): 2925, 2856, 1659; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 5.78–5.87 (2H, m), 5.16–5.22 (4H, m), 3.89–4.37 (8H, m), 3.64 (4H, s), 3.02 (4H, d, J = 6.4 Hz), 2.53 (8H, bs); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 196.2 (C=S), 134.7, 118.9, 61.5, 52.7, 51.0, 35.9; ESI-MS: (*m/z*) 431 (MH^+); Anal. calcd. for $C_{18}H_{30}N_4S_4$: C, 50.19; H, 7.02; N, 13.01; found C, 50.28; H, 7.32; N, 13.30.

4-Allyl-1-piperazinecarbodithioic acid 1,1′-ethylene ester (25).ditartrate:

4-Allyl-1-piperazinecarbodithioic acid 1,1′-ethylene ester (**25**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of 4-allyl-1-piperazinecarbodithioic acid 1,1′-ethylene ester (**25**).

Example 26:

4-Allyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (Final compound 26):



1-Allylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (26.8 mmol) was dissolved in chloroform (30 mL). To this solution, Triethylamine (26.8 mmol) was added and then 3-bromoprop-1-ene (13.4 mmol) dissolved in dichloromethane (15 mL) was added slowly within two hours with stirring at room temperature. The reaction mixture was stirred for one hour at room temperature. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 7%. The purification of monosubstituted piperazine by column chromatography was not required as the product

can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided. The compound 1-allylpiperazine was obtained as colourless oil.

Sodium 4-allylpiperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-allylpiperazine. The disubstituted piperazine present if any, gets washed with organic solvent during work up. 1-allylpiperazine (~10 mmol) was taken in ethyl acetate (25 mL), to this, aqueous sodium hydroxide (12.4 mmol, 30%) was added keeping the temperature 3 °C, carbon disulfide (12.4 mmol) dissolved in ethyl acetate (10 mL) was added drop-wise with stirring at 3 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was re-crystallised by methanolic ether to get sodium 4-allylpiperazine-1-carbodithioate as a white powder.

4-Allyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (26):

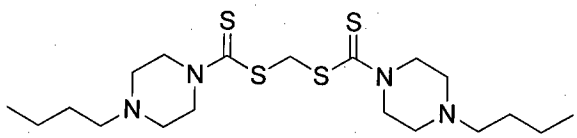
According to scheme 1, step 3: The mixture of sodium 4-allylpiperazine-1-carbodithioate (11.2 mmol) and 1,3-dibromopropane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried over sodium sulphate, filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using $MeOH/CHCl_3$ as eluent to afford 4-allyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (**26**) as white solid (melting point 108–110 °C). ; IR (KBr) ν (cm^{-1}): 2923, 2807, 1632; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 5.78–5.89 (2H, m), 5.18–5.24 (4H, m), 3.97–4.33 (8H, m), 3.42 (4H, t J = 7.2 Hz), 3.03 (4H, d, J = 6.5 Hz), 2.51–2.54 (8H, m), 2.09–2.18 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 196.4 (C=S), 134.6, 118.6, 61.3, 52.5, 51.0, 50.0, 35.9, 28.2; ESI-MS: (*m/z*) 445 (MH^+); Anal. calcd. for $C_{19}H_{32}N_4S_4$: C, 51.31; H, 7.25; N, 12.60; found C, 51.28; H, 7.37; N, 12.73.

4-Allyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (26).ditartrate:

4-Allyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (**26**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of 4-allyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (**26**).

Example 27:

4-Butyl-1-piperazinecarbodithioic acid 1,1'-methylene ester (Final compound 27):



1-Butylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 1-bromobutane (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within one hour with stirring under reflux. The reaction mixture was further refluxed for one hour. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 8%. The purification of monosubstituted piperazine by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided. The compound 1-butylpiperazine was obtained as colourless oil.

Sodium 4-butylpiperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-butylpiperazine. The disubstituted piperazine present if any, gets washed with organic solvent during work up. 1-butylpiperazine (~5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 4 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 4 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-butylpiperazine-1-carbodithioate as a white powder.

4-Butyl-1-piperazinecarbodithioic acid 1,1'-methylene ester (27):

According to scheme 1, step 3: The mixture of sodium 4-butylpiperazine-1-carbodithioate (11.2 mmol) and diiodomethane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried over sodium sulphate, filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using MeOH/$CHCl_3$ as eluent to afford 4-butyl-1-piperazinecarbodithioic acid 1,1'-methylene ester (**27**) as white solid (melting point 116–118 °C). IR (KBr) ν (cm^{-1}): 2933, 2847, 1642; ^1H NMR (300

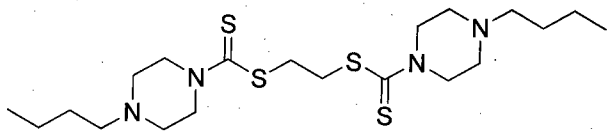
MHz, $CDCl_3$ + CCl_4): δ 5.39 (2H, s), 3.89–4.30 (8H, m), 2.50 (8H, bs), 2.32–2.37 (4H, m), 1.30–1.49 (8H, m), 0.93 (6H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 195.6 (C=S), 58.0, 52.8, 51.5, 50.2, 45.7, 29.1, 20.8, 14.2; ESI-MS: (*m/z*) 449 (MH^+); Anal. calcd. for $C_{19}H_{36}N_4S_4$: C, 50.85; H, 8.09; N, 12.48; found C, 50.74; H, 8.21; N, 12.29.

4-Butyl-1-piperazinecarbodithioic acid 1,1′-methylene ester (27).ditartrate:

4-Butyl-1-piperazinecarbodithioic acid 1,1′-methylene ester (**27**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of 4-butyl-1-piperazinecarbodithioic acid 1,1′-methylene ester (**27**).

Example 28:

4-Butyl -1-piperazinecarbodithioic acid 1,1′-ethylene ester (Final compound 28):



1-Butylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 1-bromobutane (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within one hour with stirring under reflux. The reaction mixture was further refluxed for one hour. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 8%. The purification of monosubstituted piperazine by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided. The compound 1-butylpiperazine was obtained as colourless oil.

Sodium 4-butylpiperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-butylpiperazine. The disubstituted piperazine present if any, gets washed with organic solvent during work up. 1-butylpiperazine (~5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 1 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 1 °C.

The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-butylpiperazine-1-carbodithioate as a white powder.

4-Butyl -1-piperazinecarbodithioic acid 1,1'-ethylene ester (28):

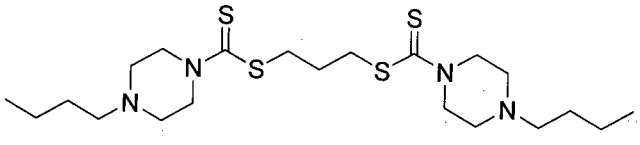
According to scheme 1, step 3: The mixture of sodium 4-butylpiperazine-1-carbodithioate (11.2 mmol) and 1,2-dibromoethane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried over sodium sulphate, filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using MeOH/$CHCl_3$ as eluent to afford 4-butyl -1-piperazinecarbodithioic acid 1,1'-ethylene ester (**28**) as white solid (melting point 120–122 °C). IR (KBr) ν (cm^{-1}): 2927, 2821, 1639; ^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 3.97–4.29 (8H, m), 3.64 (4H, s), 2.49–2.52 (8H, m), 2.33–2.38 (4H, m), 1.31–1.50 (8H, m), 0.93 (6H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 195.9 (C=S), 58.0, 52.8, 51.3, 50.3, 35.8, 29.2, 20.8, 14.3; ESI-MS: (*m/z*) 463 (MH^+); Anal. calcd. for $C_{20}H_{38}N_4S_4$: C, 51.90; H, 8.28; N, 12.11; found C, 52.11; H, 8.39; N, 12.23.

4-Butyl -1-piperazinecarbodithioic acid 1,1'-ethylene ester (28).ditartrate:

4-butyl -1-Piperazinecarbodithioic acid 1,1'-ethylene ester (**28**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of 4-butyl -1-piperazinecarbodithioic acid 1,1'-ethylene ester (**28**).

Example 29:

4-Butyl-1-piperazinecarbodithioic acid 1,1'-propylene ester (Final compound 29):



1-Butylpiperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 1-bromobutane (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within one hour with stirring under reflux. The reaction mixture was further refluxed for one

hours. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 10%. The purification of monosubstituted piperazine by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided. The compound 1-butylpiperazine was obtained as colourless oil.

Sodium 4-butylpiperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-butylpiperazine. The disubstituted piperazine present if any, gets washed with organic solvent during work up. 1-butylpiperazine (~5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 2 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 2 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-butylpiperazine-1-carbodithioate as a white powder.

4-Butyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (29):

According to scheme 1, step 3: The mixture of sodium 4-butylpiperazine-1-carbodithioate (11.2 mmol) and 1,3-dibromopropane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried over sodium sulphate, filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using MeOH/$CHCl_3$ as eluent to afford 4-butyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (**29**) as white solid (melting point 80–82 °C). IR (KBr) ν (cm^{-1}): 2926, 2816, 1643; ^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 3.98–4.29 (8H, m), 3.41 (4H, t, J = 7.1 Hz), 2.49–2.52 (8H, m), 2.33–2.38 (4H, m), 2.08–2.17 (2H, m), 1.31–1.50 (8H, m), 0.93 (6H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 196.4 (C=S), 58.0, 52.9, 50.6, 36.0, 29.2, 28.3, 20.8, 14.3; ESI-MS: (*m/z*) 477 (MH^+); Anal. calcd. for $C_{21}H_{40}N_4S_4$: C, 52.90; H, 8.46; N, 11.75; found C, 52.78; H, 8.31; N, 11.55.

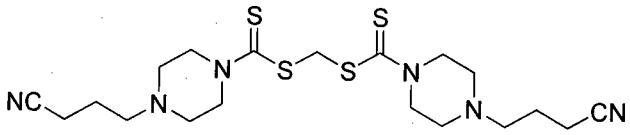
4-Butyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (29).ditartrate:

4-Butyl-1-piperazinecarbodithioic acid 1,1′-propylene ester (**29**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high

vacuum desiccator to get the ditartrate salt (hygroscopic) of 4-butyl-1-piperazinecarbodithioic acid 1,1'-propylene ester **(29)**.

Example 30:

4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1'-methylene ester (Final compound 30):



1-(3-cyanopropyl)piperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 3-bromopropanenitrile (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within two hours with stirring under reflux. The reaction mixture was further refluxed for one hour. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 8%. The purification of monosubstituted piperazine by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided. The compound 1-(3-cyanopropyl)piperazine was obtained as colourless oil.

Sodium 4-(3-cyanopropyl)piperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-(3-cyanopropyl)piperazine. The disubstituted piperazine present if any, gets washed with organic solvent during work up. 1-(3-cyanopropyl)piperazine (~5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 3 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 3 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(3-cyanopropyl)piperazine-1-carbodithioate as a white powder.

4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1'-methylene ester (30):

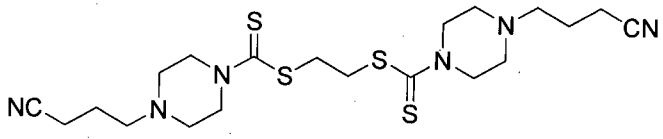
According to scheme 1, step 3: The mixture of sodium -(3-cyanopropyl)piperazine-1-carbodithioate (11.2 mmol) and diiodomethane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced

pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried over sodium sulphate, filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using MeOH/$CHCl_3$ as eluent to afford 4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-methylene ester (**30**) as white solid (melting point 130–132 °C). IR (KBr) ν (cm^{-1}): 2944, 2822, 2246, 1647; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 5.37 (2H, s), 3.91–4.29 (8H, m), 2.42–2.53 (16H, m), 1.79–1.88 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 195.8 (C=S), 119.1, 55.9, 52.6, 50.0, 45.7 , 22.8, 15.0; ESI-MS: (*m/z*) 471 (MH^+); Anal. calcd. for $C_{19}H_{30}N_6S_4$: C, 48.48; H, 6.42; N, 17.85; found C, 48.59; H, 6.32; N, 17.62.

4-(3-Cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-methylene ester (30).ditartrate: 4-(3-Cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-methylene ester (**30**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of 4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-methylene ester (**30**).

Example 31:

4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-ethylene ester (Final compound 31):



1-(3-cyanopropyl)piperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 3-bromopropanenitrile (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within two hours with stirring under reflux. The reaction mixture was further refluxed for one hour. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 8%. The purification of monosubstituted piperazine by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided. The compound 1-(3-cyanopropyl)piperazine was obtained as colourless oil.

Sodium 4-(3-cyanopropyl)piperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-(3-cyanopropyl)piperazine. The disubstituted piperazine present if any, gets washed with organic solvent during work up. 1-(3-cyanopropyl)piperazine (~5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 5 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 5 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(3-cyanopropyl)piperazine-1-carbodithioate as a white powder.

4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-ethylene ester (31):

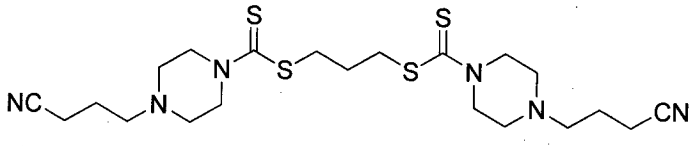
According to scheme 1, step 3: The mixture of sodium 4-(3-cyanopropyl)piperazine-1-carbodithioate (11.2 mmol) and 1,2-dibromoethane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried over sodium sulphate, filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using MeOH/$CHCl_3$ as eluent to afford 4-(3-cyanoproyl)-1-Piperazinecarbodithioic acid 1,1′-ethylene ester **(31)** as white solid (melting point 152–154 °C). IR (KBr) ν (cm^{-1}): 2929, 2814, 2248, 1632; ^1H NMR (300 MHz, $CDCl_3$): δ 3.97–4.33 (8H, m), 3.68 (4H, s), 2.44–2.55 (16H, m), 1.80--1.89 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.3 (C=S), 119.6, 55.8, 52.5, 50.2, 35.8, 22.7, 15.0; ESI-MS: (*m/z*) 485 (MH^+); Anal. calcd. for $C_{20}H_{32}N_6S_4$: C, 49.55; H, 6.65; N, 17.34; found C, 49.75; H, 6.39; N, 17.19.

4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-ethylene ester (31).ditartrate:

4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-ethylene ester **(31**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of 4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-ethylene ester **(31)**.

Example 32:

4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-propylene ester (Final compound 32):



1-(3-Cyanopropyl)piperazine:

According to scheme 1, step 1: Commercially available anhydrous piperazine (13.4 mmol) was dissolved in chloroform. To this solution, Triethylamine (13.4 mmol) was added and then 3-bromopropanenitrile (6.7 mmol) dissolved in chloroform (10 mL) was added slowly within two hours with stirring under reflux. The reaction mixture was further refluxed for one hour. The reaction was over and solvent was evaporated under reduced pressure to get crude. The possible formation of disubstituted product was minimized by slow addition of alkyl halide to 7%. The purification of monosubstituted piperazine by column chromatography was not required as the product can be used as such in next step. Thus, uneconomical column chromatographic separation was avoided. The compound 1-(3-cyanopropyl)piperazine was obtained as colourless oil.

Sodium 4-(3-cyanopropyl)piperazine-1-carbodithioate:

According to scheme 1, step 2: The product obtained in step 1 was used as such in this step as the reaction occurs only with free NH group i.e., with 1-(3-cyanopropyl)piperazine. The disubstituted piperazine present if any, gets washed with organic solvent during work up. 1-(3-cyanopropyl)piperazine (~5.0 mmol) was taken in ethyl acetate (20 mL), to this, aqueous sodium hydroxide (6.2 mmol, 30%) was added keeping the temperature 2 °C, carbon disulfide (6.2 mmol) dissolved in ethyl acetate (5 mL) was added drop-wise with stirring at 2 °C. The reaction mixture was further stirred at room temperature for one hour to furnish a white solid. Solvent was distilled off and the crude was recrystallised by methanolic ether to get sodium 4-(3-cyanopropyl)piperazine-1-carbodithioate as a white powder.

4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-propylene ester (32):

According to scheme 1, step 3: The mixture of sodium 4-(3-cyanopropyl)piperazine-1-carbodithioate (11.2 mmol) and 1,3-dibromopropane (3.72 mmol) in CH_3CN (20 mL) was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure, crude product was treated with water (10 mL) and extracted by EtOAc (10 mL × 3). EtOAc layer was washed with water (5 mL × 3) and combined organic layers were dried over sodium sulphate, filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using MeOH/$CHCl_3$ as eluent to afford 4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-propylene ester **(32)** as white solid (melting point 118–120 °C). IR (KBr) ν (cm^{-1}): 2942, 2823, 2248, 1646; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 4.06–4.35 (8H, m), 3.40 (4H, t, *J*

= 7.1 Hz), 2.42–2.55 (16H, m), 2.07–2.17 (2H, m), 1.80–1.89 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 196.5 (C=S), 119.1, 55.9, 52.6, 50.7, 35.9, 28.2, 22.8, 15.0; ESI-MS: (*m/z*) 499 (MH^+); Anal. calcd. for $C_{21}H_{34}N_6S_4$: C, 50.57; H, 6.87; N, 16.85; found C, 50.72; H, 6.99; N, 16.75.

4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-propylene ester (32).ditartrate: 4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-propylene ester (**32**, 0.25 mmol) was dissolved in absolute alcohol (10 mL). dl-Tartaric acid (0.5 mmol) dissolved in absolute alcohol (5 mL) was added and the resulting solution was stirred at room temperature for four hours. The resulting clear solution was concentrated under reduced pressure and dried in high vacuum desiccator to get the ditartrate salt (hygroscopic) of 4-(3-cyanoproyl)-1-piperazinecarbodithioic acid 1,1′-propylene ester (**32**).

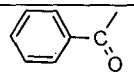
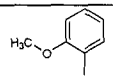
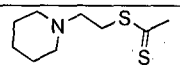
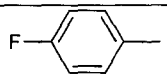
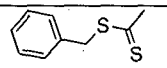
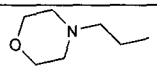
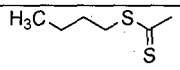
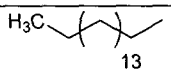
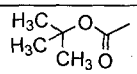
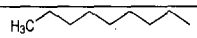
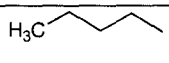
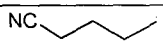
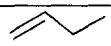
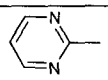
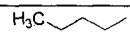
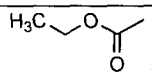
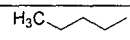
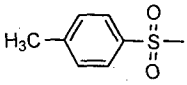
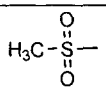
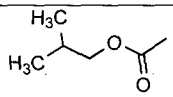
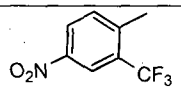
Biological Assay:

Spermicidal activity (*in vitro*): Human semen samples were obtained from young and healthy volunteers, collected directly in a sterile vial by masturbation. Minimum effective (spermicidal) concentration (MEC) was determined by the modified Sander-Cramer assay as detailed earlier (*Hum. Reprod.* **2009**, 24, 590-601). Briefly, the test compounds were dissolved in a minimum volume of DMSO and diluted with physiological saline (0.85% NaCl in distilled water) to make a 10.0 mg/ml (1.0%) solution, which was further serially diluted to 0.0005 % with saline. A spermicidal test was performed with each compound solution starting from 1.0 % until the minimum effective concentration (MEC) was arrived at. For this purpose 0.05 ml of liquefied human semen was added to 0.25 ml of test solution and vortexed for 10 seconds at low speed. A drop of the mixture was immediately placed on a microscope slide, covered with a cover glass and immediately examined under a phase contrast microscope in five fields of vision. The results were scored positive if 100% spermatozoa became completely immotile in 20-50 seconds and remained immotile after dilution with 1.0 ml of Kreb Ringer bicarbonate buffer for another 30 min at 37°C. The MEC was determined in three individual semen samples from different donors. The minimum concentration of compound capable of killing 100% sperm in 30-60 sec in all the three semen samples was denoted as minimum effective concentration (MEC) (Table 2).

Table 2: Spermicidal activity (*in vitro*) of synthesized compounds

* Tested as ditartrate salts

Spermicidal activity (*in vivo*):

Example	R	n	Spermicidal Activity (MEC %)	Example	R	n	Spermicidal Activity (MEC %)
1*		0	1.0	17		0	0.5
2*		0	1.0	18		0	0.5
3*		0	>1.0	19		0	>1.0
4*		0	0.005	20		0	>1.0
5*		0	1.0	21		0	>1.0
6*		0	1.0	22*		2	0.5
7*		0	0.1	23*		3	0.5
8*		0	0.001	24*		1	1.0
9*		0	0.001	25*		2	0.5
10*		0	0.001	26*		3	0.5
11*		0	1.0	27*		1	0.5
12		0	0.1	28*		2	0.5
13		0	>1.0	29*		3	0.5
14		0	1.0	30*		1	0.5
15		0	>1	31*		2	0.5
16		0	0.1	32*		3	0.5

One of the most promising compound (Table 2, example **8**; HPLC purity > 99%, column RP C-18, mobile phase methanol/water, UV detector 254 and 272 nm, retention time 14.57 minutes) was tested for contraceptive efficacy *in vivo*, in rabbit model. This compound was selected on the basis of its ease and economy of preparation and stability of the molecular structure. Young, adult female Belgian rabbits were given intravaginal instillation of compound (dissolved in saline) by inserting a 15 cm long catheter attached to a plastic syringe. A vaginal dose of 0, 10, 15, 20, or 50 mg of test compound was instilled in 2.0 – 5.0 ml saline or 1-2% Jelly (Johnson and Johnson Limited, India). 10 min after instillation, treated rabbits were mated once with a fertile buck. Mating was re-confirmed by presence of sperm in the vaginal smear. The mated rabbits were then kept in separate cages and allowed to complete gestation of 30-35 days. The pregnancies and litter size was recorded at completion of the gestation (Table 3).

Table 3: *In vivo* spermicidal activity of Example **8**

Dose (mg)	**Vehicle**	**No. pregnant**	**Average Litter Size**
0	Saline (2.0 ml)	6/6	7.8
10	Saline (2.0 ml)	1/6	0.66
15	Saline (2.0 ml)	4/7	2.57
20	Saline (5.0 ml)	2/5	1.8
50	Saline (5.0 ml)	2/7	0.85
10	Jelly (2.0 ml)	5/8	2.5
15	Jelly (2.0 ml)	3/8	2.0
20	Jelly (2.0 ml)	3/6	1.83

COMPATIBILITY OF COMPOUNDS WITH *LACTOBACILLUS* (normal vaginal flora):

Spores of *Lactobacillus jensenii* [ATCC 25258, strain 62G] were procured from ATCC, USA, and grown in 6% Rogosa SL broth medium (Hi Media, India) containing 0.132% acetic acid, at 37 °C. The effect of 3 most promising test compounds (examples **8**, **9**, **10**)

on *Lactobacillus jensenii* growth was determined by the method published earlier with slight modification (*Human Reprod.* **2009**, 24, 590-601). Briefly, Rogosa SL broth medium was prepared in Milli-Q water, boiled for 2-3 min and distributed in 48-well plates (200µL/well). Serial dilutions of test compounds were added to experimental wells and vehicle to control wells, in triplicate, and ~1000 cfu of *Lactobacillus jensenii* were inoculated in each well. The plates were incubated at 37°C in a humidified atmosphere containing 5% CO_2 for 24 h. At the end of the experiment, the cultures were mixed thoroughly and 100µL volume from each well was transferred to the corresponding well of a 96 well plate and number of *Lactobacilli* were estimated by measuring the turbidity (OD) at 610 nm in a microplate reader. The results have been given in Fig. 2.

CYTOTOXICITY OF COMPOUNDS TOWARDS HUMAN CERVICAL (*HELA*) CELLS:

We used HeLa cell monolayers as an *in vitro* model of cervicovaginal epithelium (*Parasitol. Res.* **2004**, 93, 332–337) for testing cytotoxicity of 3 most promising new compounds examples **8**,**9**,**10**). HeLa cells procured from National Centre for Cell Sciences (NCCS), Pune, India, were grown in Dulbecco's modified Eagle's medium (DMEM, Sigma-Aldrich) supplemented with fetal bovine serum (10%), and antibiotics (100 U/mL penicillin/streptomycin mixture). Cells at 80–90% confluence were split by trypsin (0.25% in phosphate-buffered saline (PBS), pH 7.4) and medium was changed at every 24 h interval. Cultures were maintained in a CO_2 incubator at 37 °C in 5% CO_2/95% air atmosphere. The MTT (3-[4,5-dimethyl thiazol-2-yl]-2,5-diphenyltetrazolium bromide) based cell-viability assay for evaluation of cyto-toxicity of new compounds against human cervical cell line (HeLa) was adopted (*Biol. Reprod.* **1999**, 60, 1419–1428). Cells seeded at a density of 5.0 X 10^4 per well in 96 well plates were incubated in culture medium (DMEM with 10% FCS) for 24 hours at 37°C in 5%CO2/95% air atmosphere. After 24 hours, culture medium was replaced with fresh medium containing dilutions of test compounds in experimental wells and vehicle in control wells. After incubation for another 24 hours, 5 µl of MTT solution (5 mg/ml in PBS, pH 7.4) was added to each well. The formazan crystals formed inside the viable cells were solubilized in DMSO and the OD was recorded at 540 nm in a microplate reader (Microquant, Bio-Tek, USA). The results have been given in Fig. 2.

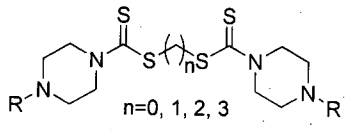
RESULTS:

Amongst the synthesized compounds (**1-32**) that were tested for their spermicidal action *in vitro* we identified twenty six compounds (**1**, **2**, **4-12**, **14**, **16**, **17**, **18-28**) with activity in the concentration range of 1-0.001% (w/v, MEC). Seven compounds (**1**, **2**, **5**, **6**, **11**, **14**, **20**) showed spermicidal effect at 1.0% (MEC), ten compounds (**18**, **19**, **21-28**) at 0.5%, three compounds (**7**, **12**, **16**) at 0.1%, one compound (**4**) at 0.005% and three compounds (**8**, **9**, **10**) at 0.001%. Nonoxynol-9 (N-9), the marketed spermicide, exhibited spermicidal

activity at MEC ~0.015%. One of the promising compounds (**8**) exhibited higher potency than N-9, and was tested for *in vivo* contraceptive activity in rabbit model. Pregnancy rates of rabbits treated with compound-8 were significantly inhibited by ~ 40-80% at 10-50 mg vaginal dose of (**8**) in saline, and by ~ 35 – 65 % at 10 – 20 mg vaginal dose of (8) in Jelly. The pregnancy rates were not inhibited by 100% upto 50 mg vaginal dose and a strict concentration dependent trend in inhibition of fertility was not evident. Given that the fertility of rabbits far exceeds that of humans by having ~100% conception rates (~30% in humans), extremely high inseminating doses of sperm and multiple ovulation after mating (*Contraception* 1998, **58,** 51-60); even strong detergent based vaginal products fail to show 100% contraceptive efficacy in rabbit assays. A modest 30% reduction in fertility rate of rabbits has been reported with 25 mg N-9 in OTC vaginal cream formulation (*Contraception* 1976, **13**, 479-488). However, the most active compounds (examples **8**, **9**, **10**) had good safety margin as their IC_{50} values against HeLa and Lactobacilli were much higher than their spermicidal MEC against human sperm *in vitro*. This was in sharp contrast to nonoxynol-9 that killed HeLa and Lactobacilli more efficiently than sperm (Fig 2).

WE CLAIM:

1. A compound having formula I and pharmaceutically acceptable salts thereof,



Formula I

wherein n = 0 and R is selected from group consisting of C_4-C_{16} alkyl, halo-substituted C_4-C_{16} alkyl, amino-substituted C_4-C_{16} alkyl, hydroxy-substituted C_4-C_{16} alkyl, nitro-substituted C_4-C_{16} alkyl, trifluoromethyl-substituted C_4-C_{16} alkyl, cyclic amine-substituted C_2-C_{16} alkyl, thiohydroxy-substituted C_4-C_{16} alkyl, alkoxy-substituted C_4-C_{16} alkyl, thioalkoxy-substituted C_4-C_{16} alkyl, cyano-substituted C_4-C_{16} alkyl, cyanoalkyl-substituted C_4-C_{16} alkyl, substituted cycloalkyl-substituted C_4-C_{16} alkyl, aryl-substituted C_4-C_{16} alkyl, heteroaryl-substituted C_4-C_{16} alkyl, alkylene-substituted C_4-C_{16} alkyl, alkoxyalkylene-substituted C_4-C_{16} alkyl, haloalkylene-substituted C_4-C_{16} alkyl and haloalkoxy-substituted C_4-C_{16} alkyl;

wherein n = 1, 2 or 3 and R is selected from group consisting of C_1-C_{16} alkyl, halo-substituted C_1-C_{16} alkyl, amino-substituted C_1-C_{16} alkyl, hydroxy-substituted C_1-C_{16} alkyl, nitro-substituted C_1-C_{16} alkyl, trifluoromethyl-substituted C_1-C_{16} alkyl, cyclic amine-substituted C_1-C_{16} alkyl, thiohydroxy-substituted C_1-C_{16} alkyl, alkoxy-substituted C_1-C_{16} alkyl, thioalkoxy-substituted C_1-C_{16} alkyl, cyano-substituted C_1-C_{16} alkyl, cyanoalkyl-substituted C_1-C_{16} alkyl, substituted cycloalkyl-substituted C_1-C_{16} alkyl, aryl-substituted C_1-C_{16} alkyl, heteroaryl-substituted C_1-C_{16} alkyl, alkylene-substituted C_1-C_{16} alkyl, alkoxyalkylene-substituted C_1-C_{16} alkyl, haloalkylene-substituted C_1-C_{16} alkyl and haloalkoxy-substituted C_1-C_{16} alkyl;

wherein n = 0,1, 2 or 3 and R is selected from group consisting of cycloalkyl, acetyl, acyl, alkoxycarbonyl, aryl, heteroaryl, carbonyl, or thiocarbonyl and tosyl or mesyl;

wherein cycloalkyl is selected from group consisting of C_3-C_7 cycloalkyl, alkyl-substituted cycloalkyl, aryl-substituted cycloalkyl, halo-substituted cycloalkyl, cycloalkyl-substituted cycloalkyl, halocycloalkyl-substituted cycloalkyl, amino-substituted cycloalkyl, hydroxy-substituted cycloalkyl, nitro-substituted cycloalkyl, trifluoromethyl-substituted cycloalkyl, cyclic amine-substituted cycloalkyl, thiohydroxy-substituted cycloalkyl, alkoxy-substituted cycloalkyl, cyano-substituted cycloalkyl, cyanoalkyl-substituted cycloalkyl, thioalkoxy-substituted cycloalkyl, haloalkoxy-substituted cycloalkyl, heteroaryl-substituted cycloalkyl, alkylene-substituted cycloalkyl, alkoxyalkylene-substituted cycloalkyl, haloalkylene-

substituted cycloalkyl and heteroatom (N, O, S).containing cycloalkyl with the same substitution pattern as in cycloalkyl;

wherein acetyl is selected from group consisting of aryl-substituted acetyl, haloaryl-substituted acetyl, aminoaryl-substituted acetyl, hydroxyaryl-substituted acetyl, nitroaryl-substituted acetyl, thiohydroxyaryl-substituted acetyl, trifuoromethylaryl-substituted acetyl, alkoxyaryl-substituted acetyl, haloalkoxyaryl-substituted acetyl, haloaryl-substituted acetyl, heteroaryl-substituted acetyl, haloaryl-substituted acetyl, arakylaryl-substituted acetyl, cyanoaryl-substituted acetyl, haloaryl-substituted acetyl, cyanoalkylaryl-substituted acetyl, thioalkoxyaryl-substituted acetyl, haloaryl-substituted acetyl, halo-substituted acetyl, trihalo-substituted acetyl, dihalo-substituted acetyl, amino-substituted acetyl, hydroxy-substituted acetyl, thiohydroxy-substituted acetyl, nitro-substituted acetyl, alkoxy-substituted acetyl, cyano-substituted acetyl, haloalkoxy-substituted acetyl, thioalkoxy-substituted acetyl and halothioalkoxy-substituted acetyl;

wherein acyl is selected from group consisting of aryl-substituted acyl, aryl-substituted acyl, haloaryl-substituted acyl, aminoaryl-substituted acyl, hydroxyaryl-substituted acyl, thiohydroxyaryl-substituted acyl, nitroaryl-substituted acyl, trifuoromethylaryl-substituted acyl, alkoxyaryl-substituted acyl, thioalkoxyaryl-substituted acyl, heteroaryl-substituted acyl, arakyl-substituted acyl, aralkylaryl-substituted acyl, cyanoaryl-substituted acyl, halo-substituted acyl, amino-substituted acyl, hydroxy-substituted acyl, thiohydroxy-substituted acyl, nitro-substituted acyl, alkoxy-substituted acyl, haloalkoxy-substituted acyl, thioalkoxy-substituted acyl, halothioalkoxy-substituted acyl and cyano-substituted acyl;

wherein alkoxycarbonyl is selected from group consisting of aryl substituted-alkoxycarbonyl, haloaryl-substituted alkoxycarbonyl, aminoaryl-substituted alkoxycarbonyl, hydroxyaryl-substituted alkoxycarbonyl, thiohydroxyaryl-substituted alkoxycarbonyl, nitroaryl-substituted alkoxycarbonyl, trifuoromethylaryl-substituted alkoxycarbonyl, alkoxyaryl-substituted alkoxycarbonyl, thioalkoxyaryl-substituted alkoxycarbonyl, heteroaryl-substituted alkoxycarbonyl, alkylaryl-substituted alkoxycarbonyl, aralkylaryl-substituted alkoxycarbonyl, cyanoaryl-substituted alkoxycarbonyl, halo-substituted alkoxycarbonyl, amino-substituted alkoxycarbonyl, hydroxy-substituted alkoxycarbonyl, thiohydroxy-substituted alkoxycarbonyl, nitro-substituted alkoxycarbonyl, alkoxy-substituted alkoxycarbonyl, haloalkoxy-substituted alkoxycarbonyl, thioalkoxy-substituted alkoxycarbonyl, halothioalkoxy-substituted alkoxycarbonyl and cyano-substituted alkoxycarbonyl;

wherein aryl is selected from group consisting of halo-substituted aryl, alkyl-substituted aryl, aryl-substituted aryl, cycloalkyl-substituted aryl, halocycloalkyl-substituted aryl,

amino-substituted aryl, hydroxy-substituted aryl, nitro-substituted aryl, trifluoromethyl-substituted aryl, cyclic amine-substituted aryl, thiohydroxy-substituted aryl, alkoxy-substituted aryl, cyano-substituted aryl, cyanoalkyl-substituted aryl, thioalkoxy-substituted aryl, haloalkoxy-substituted aryl, heteroaryl-substituted aryl, alkylene-substituted aryl, alkoxyalkylene-substituted aryl and haloalkylene-substituted aryl;

wherein heteroaryl is selected from group consisting of halo-substituted heteroaryl, alkyl-substituted heteroaryl, aryl-substituted heteroaryl, cycloalkyl-substituted heteroaryl, halocycloalkyl-substituted heteroaryl, amino-substituted heteroaryl, hydroxy-substituted heteroaryl, nitro-substituted heteroaryl, trifluoromethyl-substituted heteroaryl, cyclic amine-substituted heteroaryl, thiohydroxy-substituted heteroaryl, alkoxy-substituted heteroaryl, cyano-substituted heteroaryl, cyanoalkyl-substituted heteroaryl, thioalkoxy-substituted heteroaryl, haloalkoxy-substituted heteroaryl, heteroaryl-substituted heteroaryl, alkylene-substituted heteroaryl, alkoxyalkylene-substituted heteroaryl and haloalkylene-substituted heteroaryl;

wherein carbonyl or thiocarbonyl is selected from group consisting of aryl substituted-carbonyl, haloaryl-substituted carbonyl, aminoaryl-substituted carbonyl, hydroxyaryl-substituted carbonyl, thiohydroxyaryl-substituted carbonyl, nitroaryl-substituted carbonyl, trifuoromethylaryl-substituted carbonyl, alkoxyaryl-substituted carbonyl, thioalkoxyaryl-substituted carbonyl, heteroaryl-substituted carbonyl, alkylaryl-substituted carbonyl, aralkylaryl-substituted carbonyl, cyanoaryl-substituted carbonyl, halo-substituted carbonyl, amino-substituted carbonyl, hydroxy-substituted carbonyl, thiohydroxy-substituted carbonyl, nitro-substituted carbonyl, alkoxy-substituted carbonyl, haloalkoxy-substituted carbonyl, thioalkoxy-substituted carbonyl, halothioalkoxy-substituted carbonyl and cyano-substituted carbonyl, alkylthiocarbonothioyl, arylthiocarbonothioyl;

wherein tosyl or mesyl is selected from group consisting of aryl substituted-tosyl, haloaryl-substituted tosyl, aminoaryl-substituted tosyl, hydroxyaryl-substituted tosyl, thiohydroxyaryl-substituted tosyl, nitroaryl-substituted tosyl, trifuoromethylaryl-substituted tosyl, alkoxyaryl-substituted tosyl, thioalkoxyaryl-substituted tosyl, heteroaryl-substituted tosyl, aralkyl-substituted tosyl, aralkylaryl-substituted tosyl, cyanoaryl-substituted tosyl, halo-substituted tosyl, amino-substituted tosyl, hydroxy-substituted tosyl, thiohydroxy-substituted tosyl, nitro-substituted tosyl, alkoxy-substituted tosyl, haloalkoxy-substituted tosyl, thioalkoxy-substituted tosyl, halothioalkoxy-substituted tosyl and cyano-substituted tosyl, aryl substituted mesyl, haloaryl-substituted mesyl, aminoaryl-substituted mesyl, hydroxyaryl-substituted mesyl, thiohydroxyaryl-substituted mesyl, nitroaryl-substituted mesyl, trifuoromethylaryl-substituted mesyl, alkoxyaryl-substituted mesyl, thioalkoxyaryl-substituted mesyl, heteroaryl-substituted mesyl, aralkyl-substituted mesyl, aralkylaryl-

substituted mesyl, cyanoaryl-substituted mesyl, halo-substituted mesyl, amino-substituted mesyl, hydroxy-substituted mesyl, thiohydroxy-substituted mesyl, nitro-substituted mesyl, alkoxy-substituted mesyl, haloalkoxy-substituted mesyl, thioalkoxy-substitutedmesyl, halothioalkoxy-substituted mesyl and cyano-substituted mesyl.

2.The compound as claimed in claim 1, wherein the pharmaceutically acceptable salts is obtained by treating of (dl)-tartaric acid, (d)-tartaric acid, (l)-tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid, malonic acid, malic acid, mandelic acid or hydrochloric acid with compound of formula **I**.

3. The compound as claimed in claim 1, for use as spermicidal agents.

4. The compound as claimed in claim 1, wherein the compound exhibit *in vitro* and *in vivo* spermicidal activities with high safety against vaginal flora (*Lactobacillus*) and epithelium (*HeLa* cells).

5. The compound as claimed in claim 1, wherein the representative compounds are;

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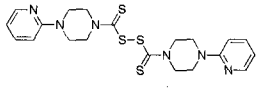
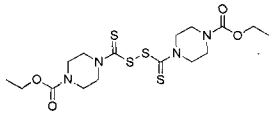
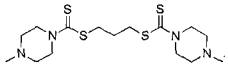
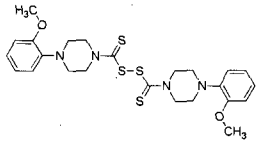
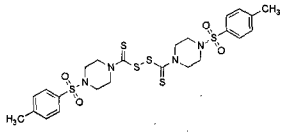
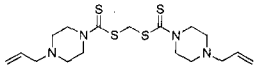
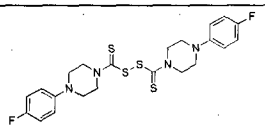
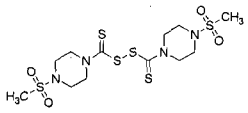
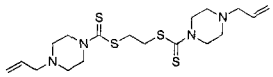
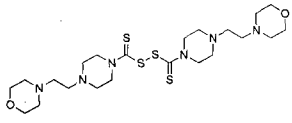
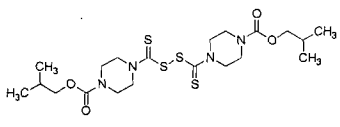
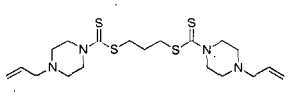
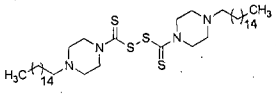
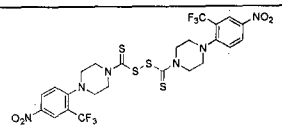
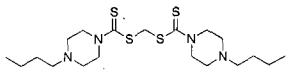
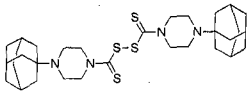
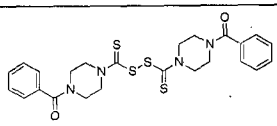
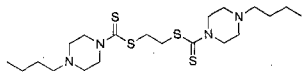
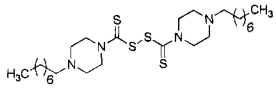
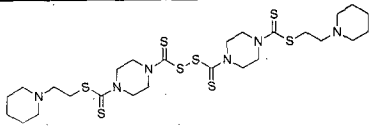
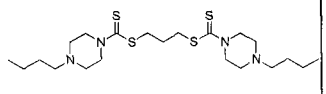
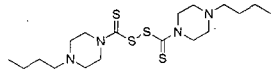
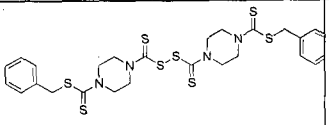
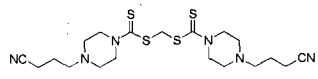
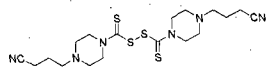
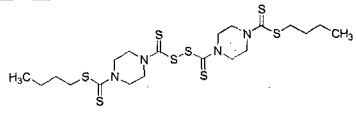
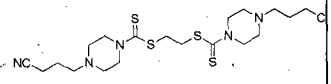
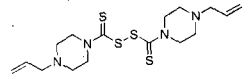
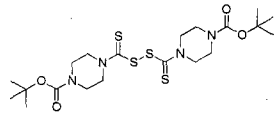
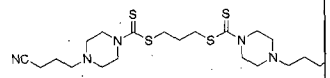
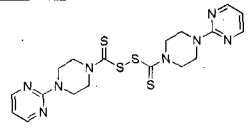
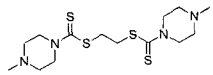
1		12		23	
2		13		24	
3		14		25	
4		15		26	

5		16		27	
6		17		28	
7		18		29	
8		19		30	
9		20		31	
10		21		32	
11		22			

6. The compound as claimed in claim 1, wherein the compound exhibits *in vitro* spermicidal activity at minimum effective concentration (MEC) in range of 0.001-1%.

7. The compound as claimed in claim 1, wherein the compound exhibits *in vivo* contraceptive activity in rabbit model.

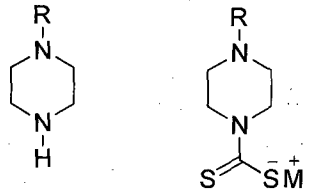
8. The compounds as claimed in claim 1, wherein the compound-8 lowers the pregnancy rate by ~ 40-80% at 10-50 mg vaginal dose in saline, and by ~ 35 – 65 % at 10 – 20 mg vaginal dose in Jelly.

9. The compound as claimed in claim 1, wherein the compound exhibits cytotoxic effect against HeLa cell line at 112->1000 μg/ml (IC_{50}).

10. A process for preparation of compounds of formula **(I)** as claimed in claim 1, wherein the process comprising of following steps;

I. slowly adding an alkylating agent to a piperazine solution in presence of a solvent and triethyl amine to obtain monosubstituted piperazines of formula **III**,

II. adding carbon disulfide dropwise to a mixture of monosubstituted piperazines of formula **III** obtained from step (I) in presence of a metal hydroxide and solvent, followed by stirring to obtain a reaction mixture, concentrating and recrystallizing the said reaction mixture with methanolic ether to obtain alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (**IV**),



III **IV**

Where M^+= Na^+, K^+, Li^+

Where R= C1-C16 , alkyl, substituted alkyl, cycloalkyl, acetyl, acyl, alkoxycarbonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, benzyl, substituted benzyl, alkanoyl, benzoyl, tosyl, substituted tosyl, mesyl, substituted mesyl, sulfonyl, substituted sulfonyl, alkylthiocarbonothioyl, arylthiocarbonothioyl

Formula of intermediates

III. reacting the alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) obtained from step (II) with sodium nitrite in the presence of HCl and solvent to synthesize the compounds **1-21** of formula I or

IV. alternatively the alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) obtained from step (II) is treated with dihaloalkane in the presence of solvent to synthesize the compounds **22-32** of formula I

V. converting the compound of formula **I** to its pharmaceutically acceptable salt by treating it with (dl)-tartaric acid, (d)-tartaric acid, (l)-tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid, malonic acid, malic acid, mandelic acid or hydrochloric acid

11. The process as claimed in claim 10, wherein the alkylating reagent used in step (I) is alkyl halide.

12. The process as claimed in claim 10, wherein the solvent used in step (I) is selected from chloroform or dichloromethane and in step (II) the solvent is ethyl acetate.

13. The process as claimed in claim 10, wherein the reaction between the alkylating reagent and piperazine solution in step (I) is carried out for a period ranging between 3-8 hours.

14. The process as claimed in claim 10, wherein the metal hydroxide used in step (II) is sodium hydroxide.

15. The process as claimed in claim 10, wherein the reaction between the carbon disufide and mono substituted piperazine in step (II) is carried out at a temperature ranging between 0-5 °C.

16. The process as claimed in claim 10, wherein the reaction between alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) with sodium nitrite in step (III) is carried out at a temperature ranging between 25 - 35 °C for a period ranging between 0.25 - 0.5 hour to obtain the compound 1-21.

17. The process as claimed in claim 10, wherein the reaction in step IV is carried out by reacting the alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) with dihaloalkane at a temperature ranging between 25- 35°C for a period ranging between 12 - 15 hours to obtain the compound 22-32.

18. The process as claimed in claim 10 wherein the solvent used in step (III) is water and in step (IV) is acetonitrile.

19. The process as claimed in claim 10 wherein the pharmaceutically acceptable salt is prepared by reacting the compounds of formula (I) with corresponding acid selected from a group consisting of (dl)-tartaric acid, (d)-tartaric acid, (l)-tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid, malonic acid, malic acid, mandelic acid and hydrochloric acid.

20. The process as claimed in claim 10, wherein the alkali metal salt of N-substituted piperazine dithiocarbamic acid of formula (IV) is selected from a group consisting of lithium salt, sodium salt and potassium salt.

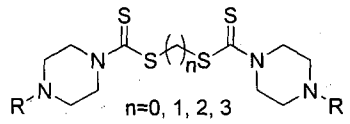
21. A pharmaceutical composition comprising therapeutically effective amount of the compounds as claimed in claim 1 in combination with pharmaceutically acceptable vehicles and additives at a concentration ranging between 1-2% for vaginal delivery.

22. The composition as claimed in claim 21, wherein the additive used is selected from a group consisting of Jelly, Gel, Cream, Foam, Foaming Tablet, Suppository and Vaginal Film.

AMENDED CLAIMS
received by the International Bureau on 10 June 2014 (10.06.2014)

WE CLAIM:

1. A compound having formula I and pharmaceutically acceptable salts thereof,



Formula I

wherein n = 0 and R is selected from group consisting of C_4-C_{16} alkyl, halo-substituted C_4-C_{16} alkyl, amino-substituted C_4-C_{16} alkyl, hydroxy-substituted C_4-C_{16} alkyl, nitro-substituted C_4-C_{16} alkyl, trifluoromethyl-substituted C_4-C_{16} alkyl, cyclic amine-substituted C_2-C_{16} alkyl, thiohydroxy-substituted C_4-C_{16} alkyl, , thioalkoxy-substituted C_4-C_{16} alkyl, cyano-substituted C_4-C_{16} alkyl, cyanoalkyl-substituted C_4-C_{16} alkyl, substituted cycloalkyl-substituted C_4-C_{16} alkyl, aryl-substituted C_4-C_{16} alkyl, heteroaryl-substituted C_4-C_{16} alkyl, alkylene-substituted C_4-C_{16} alkyl, alkoxyalkylene-substituted C_4-C_{16} alkyl, haloalkylene-substituted C_4-C_{16} alkyl and haloalkoxy-substituted C_4-C_{16} alkyl;

wherein n = 1, 2 or 3 and R is selected from group consisting of C_1-C_{16} alkyl, halo-substituted C_1-C_{16} alkyl, amino-substituted C_1-C_{16} alkyl, hydroxy-substituted C_1-C_{16} alkyl, nitro-substituted C_1-C_{16} alkyl, trifluoromethyl-substituted C_1-C_{16} alkyl, cyclic amine-substituted C_1-C_{16} alkyl, thiohydroxy-substituted C_1-C_{16} alkyl, alkoxy-substituted C_1-C_{16} alkyl, thioalkoxy-substituted C_1-C_{16} alkyl, cyano-substituted C_1-C_{16} alkyl, cyanoalkyl-substituted C_1-C_{16} alkyl, substituted cycloalkyl-substituted C_1-C_{16} alkyl, aryl-substituted C_1-C_{16} alkyl, heteroaryl-substituted C_1-C_{16} alkyl, alkylene-substituted C_1-C_{16} alkyl, alkoxyalkylene-substituted C_1-C_{16} alkyl, haloalkylene-substituted C_1-C_{16} alkyl and haloalkoxy-substituted C_1-C_{16} alkyl;

wherein n = 0,1, 2 or 3 and R is selected from group consisting of cycloalkyl, acetyl, acyl, alkoxycarbonyl, aryl, heteroaryl, carbonyl, or thiocarbonyl and tosyl or mesyl;

wherein cycloalkyl is selected from group consisting of C_3-C_7 cycloalkyl, alkyl-substituted cycloalkyl, aryl-substituted cycloalkyl, halo-substituted cycloalkyl, cycloalkyl-substituted cycloalkyl, halocycloalkyl-substituted cycloalkyl, amino-substituted cycloalkyl, hydroxy-substituted cycloalkyl, nitro-substituted cycloalkyl, trifluoromethyl-substituted cycloalkyl, cyclic amine-substituted cycloalkyl, thiohydroxy-substituted cycloalkyl, alkoxy-substituted cycloalkyl, cyano-substituted cycloalkyl, cyanoalkyl-substituted cycloalkyl, thioalkoxy-

substituted cycloalkyl, haloalkoxy-substituted cycloalkyl, heteroaryl-substituted cycloalkyl, alkylene-substituted cycloalkyl, alkoxyalkylene-substituted cycloalkyl, haloalkylene-substituted cycloalkyl and heteroatom (N, O, S).containing cycloalkyl with the same substitution pattern as in cycloalkyl;

wherein acetyl is selected from group consisting of aryl-substituted acetyl, haloaryl-substituted acetyl, aminoaryl-substituted acetyl, hydroxyaryl-substituted acetyl, nitroaryl-substituted acetyl, thiohydroxyaryl-substituted acetyl, trifuoromethylaryl-substituted acetyl, alkoxyaryl-substituted acetyl, haloalkoxyaryl-substituted acetyl, haloaryl-substituted acetyl, heteroaryl-substituted acetyl, haloaryl-substituted acetyl, arakylaryl-substituted acetyl, cyanoaryl-substituted acetyl, haloaryl-substituted acetyl, cyanoalkylaryl-substituted acetyl, thioalkoxyaryl-substituted acetyl, haloaryl-substituted acetyl, halo-substituted acetyl, trihalo-substituted acetyl, dihalo-substituted acetyl, amino-substituted acetyl, hydroxy-substituted acetyl, thiohydroxy-substituted acetyl, nitro-substituted acetyl, alkoxy-substituted acetyl, cyano-substituted acetyl, haloalkoxy-substituted acetyl, thioalkoxy-substituted acetyl and halothioalkoxy-substituted acetyl;

wherein acyl is selected from group consisting of aryl-substituted acyl, aryl-substituted acyl, haloaryl-substituted acyl, aminoaryl-substituted acyl, hydroxyaryl-substituted acyl, thiohydroxyaryl-substituted acyl, nitroaryl-substituted acyl, trifuoromethylaryl-substituted acyl, alkoxyaryl-substituted acyl, thioalkoxyaryl-substituted acyl, heteroaryl-substituted acyl, arakyl-substituted acyl, aralkylaryl-substituted acyl, cyanoaryl-substituted acyl, halo-substituted acyl, amino-substituted acyl, hydroxy-substituted acyl, thiohydroxy-substituted acyl, nitro-substituted acyl, alkoxy-substituted acyl, haloalkoxy-substituted acyl, thioalkoxy-substituted acyl, halothioalkoxy-substituted acyl and cyano-substituted acyl;

wherein alkoxycarbonyl is selected from group consisting of aryl substituted-alkoxycarbonyl, haloaryl-substituted alkoxycarbonyl, aminoaryl-substituted alkoxycarbonyl, hydroxyaryl-substituted alkoxycarbonyl, thiohydroxyaryl-substituted alkoxycarbonyl, nitroaryl-substituted alkoxycarbonyl, trifuoromethylaryl-substituted alkoxycarbonyl, alkoxyaryl-substituted alkoxycarbonyl, thioalkoxyaryl-substituted alkoxycarbonyl, heteroaryl-substituted alkoxycarbonyl, alkylaryl-substituted alkoxycarbonyl, aralkylaryl-substituted alkoxycarbonyl, cyanoaryl-substituted alkoxycarbonyl, halo-substituted alkoxycarbonyl, amino-substituted alkoxycarbonyl, hydroxy-substituted alkoxycarbonyl, thiohydroxy-substituted alkoxycarbonyl, nitro-substituted alkoxycarbonyl, alkoxy-substituted alkoxycarbonyl, haloalkoxy-substituted alkoxycarbonyl, thioalkoxy-substituted alkoxycarbonyl, halothioalkoxy-substituted alkoxycarbonyl and cyano-substituted alkoxycarbonyl;

wherein aryl is selected from group consisting of halo-substituted aryl, alkyl-substituted aryl, aryl-substituted aryl, cycloalkyl-substituted aryl, halocycloalkyl-substituted aryl, amino-substituted aryl, hydroxy-substituted aryl, nitro-substituted aryl, trifluoromethyl-substituted aryl, cyclic amine-substituted aryl, thiohydroxy-substituted aryl, alkoxy-substituted aryl, cyano-substituted aryl, cyanoalkyl-substituted aryl, thioalkoxy-substituted aryl, haloalkoxy-substituted aryl, heteroaryl-substituted aryl, alkoxyalkylene-substituted aryl and haloalkylene-substituted aryl;

wherein heteroaryl is selected from group consisting of halo-substituted heteroaryl, alkyl-substituted heteroaryl, aryl-substituted heteroaryl, cycloalkyl-substituted heteroaryl, halocycloalkyl-substituted heteroaryl, amino-substituted heteroaryl, hydroxy-substituted heteroaryl, nitro-substituted heteroaryl, trifluoromethyl-substituted heteroaryl, cyclic amine-substituted heteroaryl, thiohydroxy-substituted heteroaryl, alkoxy-substituted heteroaryl, cyano-substituted heteroaryl, cyanoalkyl-substituted heteroaryl, thioalkoxy-substituted heteroaryl, haloalkoxy-substituted heteroaryl, heteroaryl-substituted heteroaryl, alkylene-substituted heteroaryl, alkoxyalkylene-substituted heteroaryl and haloalkylene-substituted heteroaryl;

wherein carbonyl or thiocarbonyl is selected from group consisting of aryl substituted-carbonyl, haloaryl-substituted carbonyl, aminoaryl-substituted carbonyl, hydroxyaryl-substituted carbonyl, thiohydroxyaryl-substituted carbonyl, nitroaryl-substituted carbonyl, trifuoromethylaryl-substituted carbonyl, alkoxyaryl-substituted carbonyl, thioalkoxyaryl-substituted carbonyl, heteroaryl-substituted carbonyl, alkylaryl-substituted carbonyl, aralkylaryl-substituted carbonyl, cyanoaryl-substituted carbonyl, halo-substituted carbonyl, amino-substituted carbonyl, hydroxy-substituted carbonyl, thiohydroxy-substituted carbonyl, nitro-substituted carbonyl, alkoxy-substituted carbonyl, haloalkoxy-substituted carbonyl, thioalkoxy-substituted carbonyl, halothioalkoxy-substituted carbonyl and cyano-substituted carbonyl, alkylthiocarbonothioyl, arylthiocarbonothioyl;

wherein tosyl or mesyl is selected from group consisting of aryl substituted-tosyl, haloaryl-substituted tosyl, aminoaryl-substituted tosyl, hydroxyaryl-substituted tosyl, thiohydroxyaryl-substituted tosyl, nitroaryl-substituted tosyl, trifuoromethylaryl-substituted tosyl, alkoxyaryl-substituted tosyl, thioalkoxyaryl-substituted tosyl, heteroaryl-substituted tosyl, aralkyl-substituted tosyl, aralkylaryl-substituted tosyl, cyanoaryl-substituted tosyl, halo-substituted tosyl, amino-substituted tosyl, hydroxy-substituted tosyl, thiohydroxy-substituted tosyl, nitro-substituted tosyl, alkoxy-substituted tosyl, haloalkoxy-substituted tosyl, thioalkoxy-substituted tosyl, halothioalkoxy-substituted tosyl and cyano-substituted tosyl, aryl substituted mesyl, haloaryl-substituted mesyl, aminoaryl-substituted mesyl, hydroxyaryl-substituted mesyl, thiohydroxyaryl-substituted mesyl, nitroaryl-substituted

mesyl, trifuoromethylaryl-substituted mesyl, alkoxyaryl-substituted mesyl, thioalkoxyaryl-substituted mesyl, heteroaryl-substituted mesyl, aralkyl-substituted mesyl, aralkylaryl-substituted mesyl, cyanoaryl-substituted mesyl, halo-substituted mesyl, amino-substituted mesyl, hydroxy-substituted mesyl, thiohydroxy-substituted mesyl, nitro-substituted mesyl, alkoxy-substituted mesyl, haloalkoxy-substituted mesyl, thioalkoxy-substitutedmesyl, halothioalkoxy-substituted mesyl and cyano-substituted mesyl.

2.The compound as claimed in claim 1, wherein the pharmaceutically acceptable salts is obtained by treating of (dl)-tartaric acid, (d)-tartaric acid, (l)-tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid, malonic acid, malic acid, mandelic acid or hydrochloric acid with compound of formula **I**.

3. The compound as claimed in claim 1, for use as spermicidal agents.

4. The compound as claimed in claim 1, wherein the compound exhibit *in vitro* and *in vivo* spermicidal activities with high safety against vaginal flora (*Lactobacillus*) and epithelium (*HeLa* cells).

5. The compound as claimed in claim 1, wherein the representative compounds are;

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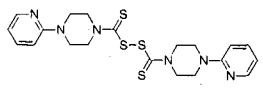
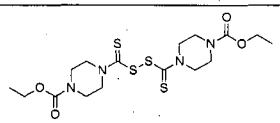
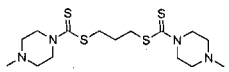
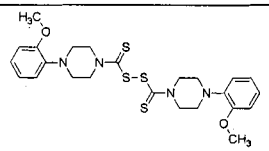
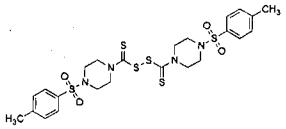
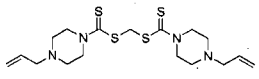
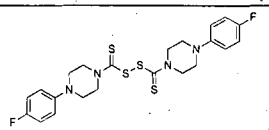
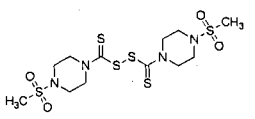
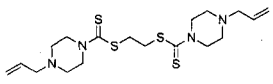
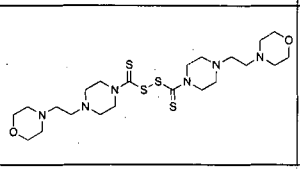
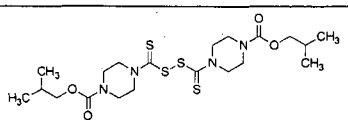
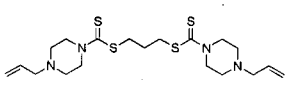
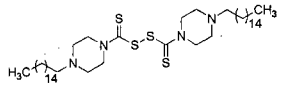
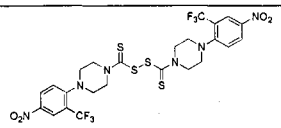
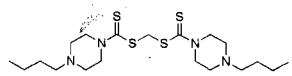
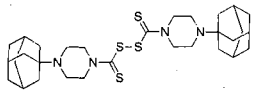
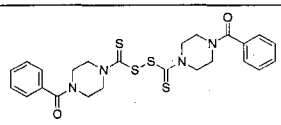
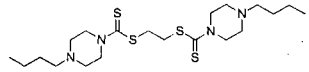
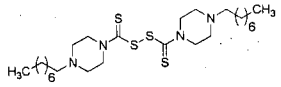
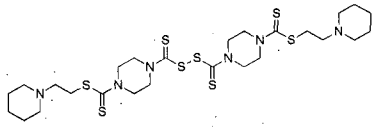
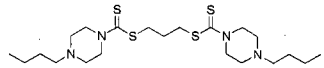
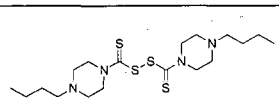
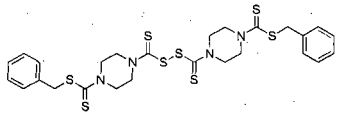
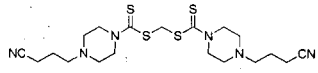
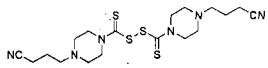
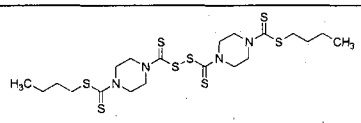
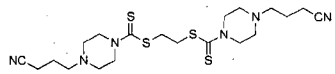
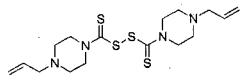
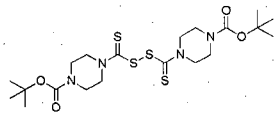
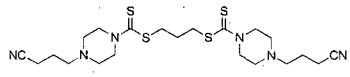
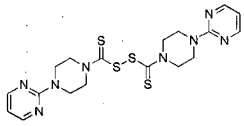
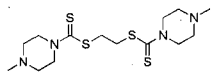
1		12		23	
2		13		24	
3		14		25	
4		15		26	

5		16		27	
6		17		28	
7		18		29	
8		19		30	
9		20		31	
10		21		32	
11		22			

6. The compound as claimed in claim 1, wherein the compound exhibits *in vitro* spermicidal activity at minimum effective concentration (MEC) in range of 0.001-1%.

7. The compound as claimed in claim 1, wherein the compound exhibits *in vivo* contraceptive activity in rabbit model.

8. The compounds as claimed in claim 1, wherein the compound-8 lowers the pregnancy rate by ~ 40-80% at 10-50 mg vaginal dose in saline, and by ~ 35 – 65 % at 10 – 20 mg vaginal dose in Jelly.

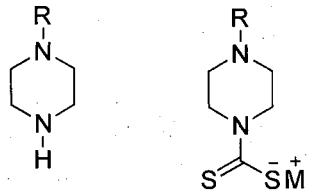
AMENDED SHEET (ARTICLE 19)

9. The compound as claimed in claim 1, wherein the compound exhibits cytotoxic effect against HeLa cell line at 112->1000 μg/ml (IC_{50}).

10. A process for preparation of compounds of formula **(I)** as claimed in claim 5, wherein the process comprising of following steps;

I. slowly adding an alkylating agent to a piperazine solution in presence of a solvent and triethyl amine to obtain monosubstituted piperazines of formula **III**,

II. adding carbon disulfide dropwise to a mixture of monosubstituted piperazines of formula **III** obtained from step (I) in presence of a metal hydroxide and solvent, followed by stirring to obtain a reaction mixture, concentrating and recrystallizing the said reaction mixture with methanolic ether to obtain alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (**IV**),



III **IV**

Where M^+= Na^+, K^+, Li^+

Where R= C1-C16 , alkyl, substituted alkyl, cycloalkyl, acetyl, acyl, alkoxycarbonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, benzyl, substituted benzyl, alkanoyl, benzoyl, tosyl, substituted tosyl, mesyl, substituted mesyl, sulfonyl, substituted sulfonyl, alkylthiocarbonothioyl, arylthiocarbonothioyl

Formula of intermediates

III. reacting the alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) obtained from step (II) with sodium nitrite in the presence of HCl and solvent to synthesize the compounds **1-21** of formula I or

IV. alternatively the alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) obtained from step (II) is treated with dihaloalkane in the presence of solvent to synthesize the compounds **22-32** of formula I

V. converting the compound of formula **I** to its pharmaceutically acceptable salt by treating it with (dl)-tartaric acid, (d)-tartaric acid, (l)-tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid, malonic acid, malic acid, mandelic acid or hydrochloric acid

11. The process as claimed in claim 10, wherein the alkylating reagent used in step (I) is alkyl halide.

12. The process as claimed in claim 10, wherein the solvent used in step (I) is selected from chloroform or dichloromethane and in step (II) the solvent is ethyl acetate.

13. The process as claimed in claim 10, wherein the reaction between the alkylating reagent and piperazine solution in step (I) is carried out for a period ranging between 3-8 hours.

14. The process as claimed in claim 10, wherein the metal hydroxide used in step (II) is sodium hydroxide.

15. The process as claimed in claim 10, wherein the reaction between the carbon disufide and mono substituted piperazine in step (II) is carried out at a temperature ranging between 0-5 °C.

16. The process as claimed in claim 10, wherein the reaction between alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) with sodium nitrite in step (III) is carried out at a temperature ranging between 25 - 35 °C for a period ranging between 0.25 - 0.5 hour to obtain the compound 1-21.

17. The process as claimed in claim 10, wherein the reaction in step IV is carried out by reacting the alkali metal salts of N-substituted piperazine dithiocarbamic acid of formula (IV) with dihaloalkane at a temperature ranging between 25- 35°C for a period ranging between 12 - 15 hours to obtain the compound 22-32.

18. The process as claimed in claim 10 wherein the solvent used in step (III) is water and in step (IV) is acetonitrile.

19. The process as claimed in claim 10 wherein the pharmaceutically acceptable salt is prepared by reacting the compounds of formula (I) with corresponding acid selected from a group consisting of (dl)-tartaric acid, (d)-tartaric acid, (l)-tartaric acid, citric acid, oxalic acid, ascorbic acid, acetic acid, lactic acid, malonic acid, malic acid, mandelic acid and hydrochloric acid.

20. The process as claimed in claim 10, wherein the alkali metal salt of N-substituted piperazine dithiocarbamic acid of formula (IV) is selected from a group consisting of lithium salt, sodium salt and potassium salt.

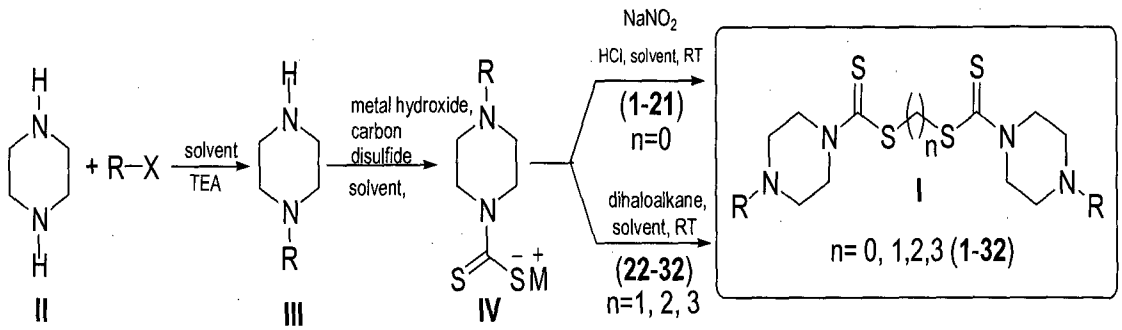
21. A pharmaceutical composition comprising therapeutically effective amount of the compounds as claimed in claim 1 in combination with pharmaceutically acceptable vehicles and additives at a concentration ranging between 1-2% for vaginal delivery.

22. The composition as claimed in claim 21, wherein the additive used is selected from a group consisting of Jelly, Gel, Cream, Foam, Foaming Tablet, Suppository and Vaginal Film.

STATEMENT UNDER ARTICLE 19(1)

With reference to the search report and written opinion of the International Searching Authority [ISA/EP], we are suitably amending the claims 1 & 10. Kindly note that any addition in the claims have been indicated by underlined and any deletion in the claims have been indicated by strike through.

The amended claims do not go beyond the disclosure of the International application as filed and have no impact on the description and drawings as filed.



Where M^+= Na^+, K^+, Li^+

Where R= C1-C16 (when n = 0, 1, 2 or 3) alkyl, substituted alkyl, cycloalkyl, acetyl, acyl, alkoxycarbonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, benzyl, substituted benzyl, alkanoyl, benzoyl, tosyl, substituted tosyl, mesyl, substituted mesyl, sulfonyl, substituted sulfonyl, alkylthiocarbonothioyl, arylthiocarbonothioyl

Figure 1

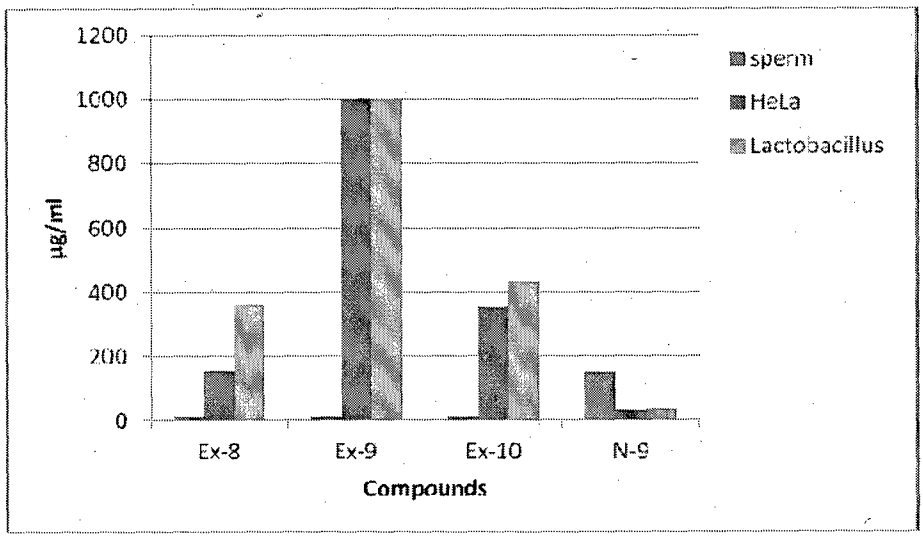


Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2014/000023

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D413/14 C07D295/14 C07D295/16 C07D295/185
A61P15/18 A61K31/496 A61K31/495
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	TARUNKUMAR NANJIBHAI AKHAJA ET AL: "New carbodithioate derivatives: synthesis, characterization, and in vitro antibacterial, antifungal, antitubercular, and antimalarial activity", MEDICINAL CHEMISTRY RESEARCH, vol. 22, no. 10, 19 October 2013 (2013-10-19), pages 4700-4707, XP055109094, ISSN: 1054-2523, DOI: 10.1007/s00044-013-0472-0 page 4702; compound 6 table 2 ----- -/--	1,2,4, 6-9,21

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2014	31/03/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Österle, Carmen

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2014/000023

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D. R. SUWIER ET AL: "Flexibilized styrene-N-substituted maleimide copolymers. II. Multiblock copolymers prepared from PTHF-based iniferters", JOURNAL OF POLYMER SCIENCE PART A: POLYMER CHEMISTRY, vol. 38, no. 19, 1 October 2000 (2000-10-01), pages 3558-3568, XP055109160, ISSN: 0887-624X, DOI: 10.1002/1099-0518(20001001)38:19<3558::AID-POLA110>3.0.CO;2-T scheme 2; page 3562; compound (a)	1,2,4, 6-20
X	JP H03 148269 A (NIPPON CHEMIPHAR CO) 25 June 1991 (1991-06-25)	1,2,4, 6-22
A	page 918; compound 5 page 917, right-hand column; figure 1	3,5
X	COCO N. KAPANDA ET AL: "Bis(dialkylaminethiocarbonyl)disulfides as Potent and Selective Monoglyceride Lipase Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, vol. 52, no. 22, 26 November 2009 (2009-11-26), pages 7310-7314, XP055109096, ISSN: 0022-2623, DOI: 10.1021/jm901323s	10-20
A	the whole document	1-9,21, 22
X	SE 345 271 B (ASTRA AB [SE]) 23 May 1972 (1972-05-23) page 4; examples	10-20
A	A. JAIN ET AL: "Novel Trichomonacidal Spermicides", ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 55, no. 9, 1 September 2011 (2011-09-01), pages 4343-4351, XP055109100, ISSN: 0066-4804, DOI: 10.1128/AAC.00199-11 the whole document	1-22

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2014/000023

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DWIVEDI ET AL: "Synthesis of disulfide esters of dialkylaminocarbothioic acid as potent, non-detergent spermicidal agents", BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB, vol. 15, no. 21, 14 September 2007 (2007-09-14), pages 6642-6648, XP022244793, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2007.08.024 the whole document -----	1-22
A	TRIPATHI R P ET AL: "SYNTHESES AND SPERMICIDAL ACTIVITIES OF DITRIOCARBAMATES", ACTA PHARMACEUTICA, CROATIAN PHARMACEUTICAL SOCIETY, HR, vol. 46, no. 3, 1 January 1996 (1996-01-01), pages 169-176, XP000900606, ISSN: 1330-0075 the whole document -----	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2014/000023

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP H03148269 A	25-06-1991	NONE	
SE 345271 B	23-05-1972	NONE	