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Short communication

Carbodithioic acid esters of fluoxetine, a novel class of dual-function spermicides☆

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Abstract

Carbodithioic acid esters of fluoxetine have been prepared by replacing the methylamino function in aminopropane chain with carbodithioic acid ester group and by adding various *S*-2-hydroxypropyl ester of dialkyl carbodithioic acid at 3-methylamino group. Some of these compounds showed spermicidal, antifungal and anti-*Trichomonas* activities. The study revealed that incorporation of carbodithioic acid residue directly into fluoxetine structure leads to compounds with better antifungal and anti-*Trichomonas* activities, and *N*-methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]carbodithioic acid *S*-(2-pyrrolidino-ethyl) ester (**14**) has shown better profile than both fluoxetine and nonoxynol-9. Further lead optimization may yield a potent dual-function spermicide.

Keywords: Carbodithioic acid esters; Fluoxetine derivatives; Spermicidals and anti-*Trichomonas*

1. Introduction

The acquired immune deficiency syndrome (AIDS) appears to thrive in the presence of overpopulation [1], poverty and other sexually transmitted diseases (STDs) [2,3]. In spite of the firm resistance of healthy human vagina to HIV infection [4], ~5 million new patients are added annually to ~40 million living with HIV, half of which are women [5]. This indicates, (a), high prevalence of HIV in heterosexual contacts and (b), increase in number of women with compromised vaginal integrity induced by vaginally applied chemical products and/or STD pathogens. While nonoxynol-9 (N-9), the most widely used vaginal spermicide, has been shown to increase the risk of HIV transmission [6] due to its surfactant-type of action [7], some very common STDs like trichomoniasis significantly increase vulnerability to HIV [8]. Therefore, developing user-controlled, non-detergent, topical vaginal spermicides that can provide protection against pregnancy as well as some very common sexually transmitted pathogens has become an urgent global priority [1]. Such agents can effectively alleviate the global crisis of unwanted pregnancies and AIDS [9]. Efforts are underway to develop such novel, dually active agents [10–13].

During our ongoing efforts to develop novel dual-function spermicides, we reported that fluoxetine showed spermicidal as well as anti-*Trichomonas* activities [14], and the anti-*Candida* activity of imidazole analogues of fluoxetine has already been demonstrated [15]. Thus modifications in fluoxetine structure (**I**; Fig. 1) may lead to compounds having spermicidal as well as anti-STI activities. Here in this communication the synthesis and biological activity of carbodithioic acid esters of fluoxetine are being reported. Carbodithioic acid group (**II**; Fig. 1) is a valuable pharmacophore that induces diverse

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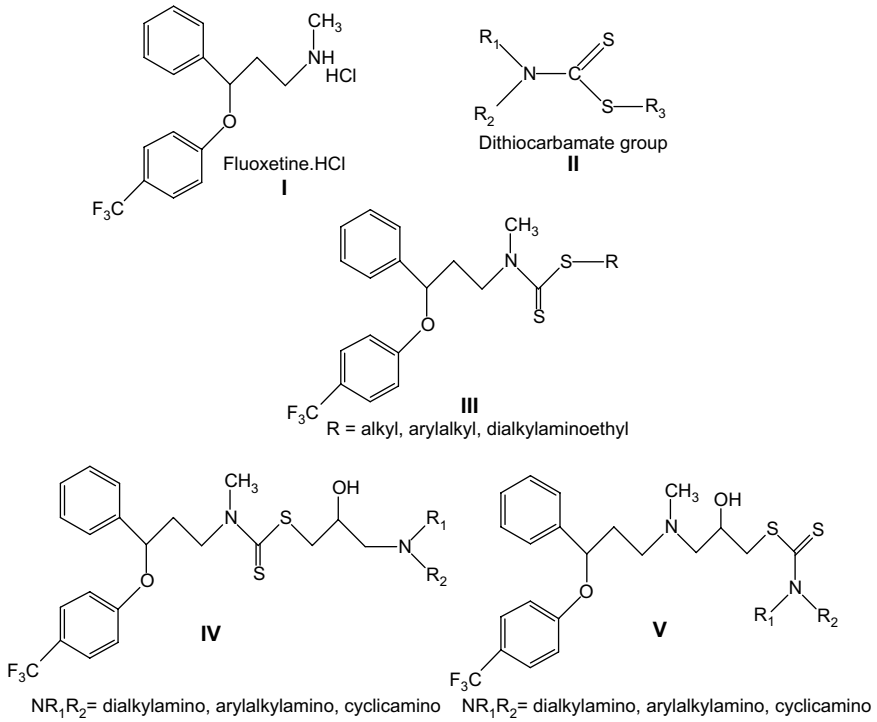


Fig. 1.

biological activities when incorporated in a particular structure. Very significantly, dialkylaminocarbothioic acid esters have been shown to have non-detergent type of action as spermicide [16] at a test concentration of 0.002%, and a number of alkyl/aryl esters of diethylamino carbodithioic acid have been synthesized and evaluated for spermicidal activity [17]. 1-Dialkylamino carbodithioic acid sodium/potassium salts and their esters exhibited antibacterial and antifungal activities [18–21]. Pyrrolidinecarbodithioic acid [22] has been shown to produce antioxidant-induced changes in AP-1 transcription complex thereby selectively suppressing the human papillomavirus transcription while its sodium salt enhanced the immunostimulatory effect [23] of interleukin-12 and exhibited antiviral activity [24] on human rhinovirus.

These observations prompted us to introduce carbodithioic acid group at 3-amino terminus of fluoxetine structure and thus *S*-substituted alkyl esters of fluoxetine carbodithioic acid (**III**; Fig. 1) were synthesized. Since propranolol [25] has been found to be a potent inhibitor of sperm motility and one of the pharmacophore present in propranolol is 1-[3-dialkylaminopropan-2-ol], therefore, it was considered worthwhile to prepare a series of *S*-[3-dialkylamino propan-2-ol] ester of fluoxetine carbodithioic acid (**IV**; Fig. 1). In another modification, fluoxetine was introduced as dialkylamine in propanolamino group, which was introduced as side chain in carbodithioic acid esters of different dialkylamines (**V**; Fig. 1). All the synthesized compounds were evaluated for spermicidal and antifungal activities. The compounds, which showed spermicidal activity, were also tested for anti-*Trichomonas* activity. Nonoxynol-9 was used as reference standard [14] for biological evaluations.

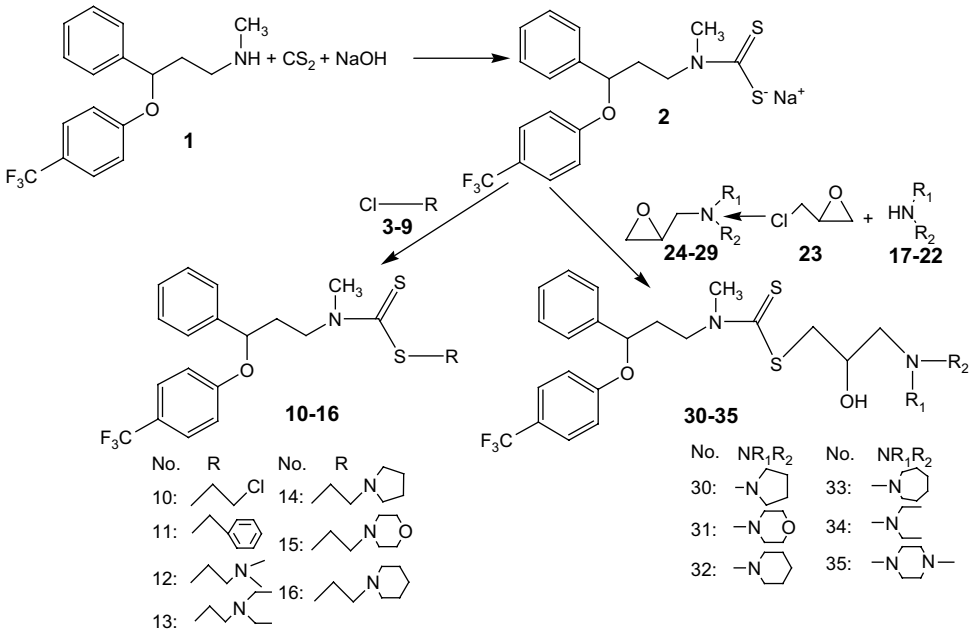
2. Chemistry

*2.1. N-Methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-carbodithioic acid S-(substituted-alkyl) esters (**10–16**; Scheme 1)*

The free base of the compound *N*-methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amine hydrochloride salt was obtained by reaction with sodium bicarbonate and the free base (**1**) was taken into ethyl acetate and reacted with carbon disulphide in the presence of aqueous NaOH to form sodium salt of *N*-methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino carbodithioic acid (**2**). The formed sodium salt was characterized by spectral data and used in further reaction with chloro derivatives (**3–9**) to get the final products *N*-methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-carbodithioic acid *S*-(substituted-alkyl) esters (**10–16**; Scheme 1).

*2.2. N-Methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-carbodithioic acid 3-dialkylamino-2-hydroxy-propyl esters (**30–35**; Scheme 1)*

N-Methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-carbodithioic acid 3-dialkylamino-2-hydroxy-propyl esters (**30–35**) were synthesized by reaction of *N*-methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-carbodithioic acid sodium salt (**2**) with epoxy compounds (**24–29**) obtained from reaction of dialkylamines (**17–22**) with epichlorohydrin (**23**) in the presence of triethylamine.



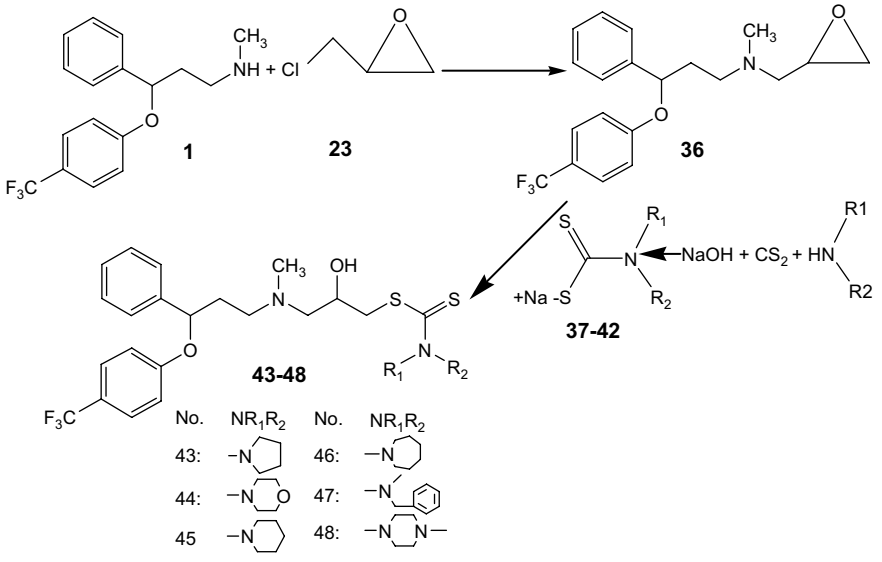
Scheme 1.

2.3. Dialkylamino carbodithioic acid 2-hydroxy-3-{methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino}-propyl esters (43–48; Scheme 2)

N-Methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amine (**1**) on reaction with epichlorohydrin (**23**) in the presence of triethylamine gave the corresponding epoxy compound *N*-methyl-oxiranylmethyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amine (**36**). This epoxy compound **36** was reacted with sodium salts of dialkylamino carbodithioic acid (**37–42**) synthesized by reaction of carbon disulfide and amine, to give the final products dialkylamino carbodithioic acid 2-hydroxy-3-{methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino}-propyl esters (**43–48**; Scheme 2).

3. Results and discussion

Twenty compounds (**2**, **10–16**, **30–35**, **43–48**) were evaluated *in vitro* for their spermicidal and antifungal activities. Twelve compounds (**2**, **10–14**, **16**, **30**, **33–35**, **48**) showed spermicidal activity at concentrations ranging from 0.05–1.0%. Eleven compounds (**10**, **12–14**, **16**, **30**, **33–35**, **44**, **48**) exhibited antifungal activity at concentrations ranging from 1.56–50 μg/ml. Ten compounds (**10**, **12–14**, **16**, **30**, **33–35**, **48**) showed both spermicidal and antifungal activities. These compounds were also evaluated for anti-*Trichomonas* activity. Seven compounds (**12–14**, **16**, **30**, **35**, **48**) showed anti-*Trichomonas* activity at 7–52 μg/ml concentrations. Fluoxetine and N-9 showed spermicidal MEC of 0.05%. The



Scheme 2.

Table 1
Biological activity of the compounds

Compound no.	Spermicidal MEC (%)	Antifungal MIC (μg/ml)						Anti-*Trichomonas* MIC (μg/ml) (mean ± SE)
		1	2	3	4	5	6	
2	1.0	–	25	–	–	–	–	96 ± 5.1
10	1.0	50	50	25	12.5	50	25	>200
11	1.0	–	–	–	–	–	–	>200
12	1.0	50	50	12.5	6.25	25	50	52 ± 2.55
13	1.0	50	50	6.25	12.5	6.25	50	24 ± 1.87
14	0.05	6.25	3.12	25	12.5	12.5	3.12	14 ± 0.61
15	–	–	–	–	–	–	–	NS
16	1.0	3.12	1.56	6.25	6.25	12.5	1.56	13.5 ± 0.61
30	0.5	–	–	50	25	50	50	6.95 ± 0.34
31	–	–	–	–	–	50	–	NS
32	–	–	–	–	50	–	50	NS
33	0.5	50	–	–	25	25	50	>200
34	0.5	–	–	–	25	50	50	>200
35	0.5	50	25	25	25	25	50	12 ± 0.94
43	–	–	–	–	–	–	–	NS
44	–	–	–	25	12.5	–	50	NS
45	–	–	25	–	–	–	–	NS
46	–	–	–	–	–	–	–	NS
47	–	–	–	–	–	–	–	NS
48	1.0	–	12.5	–	25	–	–	6.68 ± 0.33
Fluoxetine	0.05	50	25	50	50	–	50	28 ± 1.22
Nonoxynol-9	0.05	–	–	–	–	–	50	23 ± 1.24
Metronidazole	–	–	–	–	–	–	–	0.54 ± 0.03

1. *Candida albicans*, 2. *Cryptococcus neoformans*, 3. *Sporothrix schenckii*, 4. *Trichophyton mentagrophytes*, 5. *Aspergillus fumigatus*, 6. *Candida parapsilosis* (ATCC-22019); MEC = minimum effective concentration; MIC = minimum inhibitory concentration; NS = not screened; (–) = inactive.

antifungal and anti-*Trichomonas* MIC of fluoxetine were 25–50 and 28 μg/ml, while that of N-9 were 50 (only 1 strain) and 23 μg/ml, respectively. (Table 1). Metronidazole exhibited anti-*Trichomonas* activity at 0.54 μg/ml.

The objective of this study was to evaluate the effect of introduction of carbodithioic acid moiety into fluoxetine structure on spermicidal, antifungal and anti-*Trichomonas* activities (Table 1). While carbodithioic acid sodium salt (**2**) of fluoxetine showed spermicidal (MEC: 1%), antifungal (MIC: 25 μg/ml, one strain) and anti-*Trichomonas* activities (MIC: 96 μg/ml), it was less effective as compared to fluoxetine·HCl (MEC: spermicidal 0.05%, antifungal 25–50 μg/ml, anti-*Trichomonas* 28 μg/ml). Among the carbodithioic acid *S*-substituted alkyl esters of fluoxetine (**10**–**16**), five compounds (**10**, **12**–**14**, **16**) showed very good to moderate activities. The 2-substituted aminoethyl derivatives (**12**–**14**, **16**) were most active but 2-morpholino analogue (**15**) was inactive. The replacement of amino group by chloride (**10**) or a change in alkyl chain i.e., benzyl derivative (**11**) resulted in either decrease or complete loss of activities. The 2-pyrrolidinoethyl analogue (**14**) showed much better activity profile than nonoxynol-9 and fluoxetine while spermicidal activity was retained at the same level (0.05%), antifungal and anti-*Trichomonas* activities were markedly improved i.e., 8-fold to 16-fold increase against two strains of *Candida* with a 2-fold increase in anti-*Trichomonas* activity. The piperidino ethyl derivative (**16**) exhibited similar activities except that there was decrease in spermicidal activity (1%). In dimethylamino (**12**) and diethylamino (**13**) derivatives the three activities were retained.

In *S*-(3-substituted amino-2-hydroxy-propyl) esters of fluoxetine carbodithioic acid (**30**–**35**), four compounds (**30**, **33**–**35**) retained all the three activities, whereas two compounds (**31**, **32**) were inactive in spermicidal and moderately active in antifungal evaluation. The pyrrolidino (**30**) and *N*-methyl piperazino (**35**) compounds were most active as their anti-*Trichomonas* activity was enhanced approximately 4 and 2.5-folds over fluoxetine, but their spermicidal activity was decreased and antifungal activity was comparable. Morpholino (**31**) and piperidino (**32**) compounds showed moderate activity in antifungal tests and were inactive in spermicidal evaluations. Azepino (**33**) and diethylamino (**34**) compounds showed spermicidal and antifungal activities almost comparable to pyrrolidino compound (**30**) but failed to show any activity in anti-*Trichomonas* evaluation. The activity profile of compounds **30**, **32** and **33** suggests that increasing the methylene group in amino ring results in reduction or complete loss of activities. The presence of oxygen (**31**) in the cyclic amino ring resulted in reduction/loss of activities whereas acyclic amine residue (**34**) resulted in loss of anti-*Trichomonas* activity though mild spermicidal and antifungal activities were retained.

Among compounds utilizing fluoxetine as an amine (**43**–**48**) only one compound (**48**) with *N*-methylpiperazine residue has shown weak spermicidal activity while others are inactive. This suggests that the carbodithioic acid residue must be directly attached to the fluoxetine structure for spermicidal activity. On the other hand, compound (**48**) exhibited good anti-*Trichomonas* activity along with moderate antifungal activity.

The most active compound (**14**) was tested for anti-*Candida* activity against seven more *Candida* strains and

Table 2
Activity of compound **14** against *Candida* strains

Compound no.	Anti-*Candida* activity (μg/ml)								
	1	2	3	4	5	6	7	8	9
14	6.25	3.125	6.25	6.25	6.25	3.125	6.25	6.25	6.25
Fluconazole	0.5	0.5	2.0	1.0	4.0	1.0	1.0	0.25	0.25

1. *Candida albicans*, 2. *Candida albicans* MTCC 183, 3. *Candida albicans* MTCC 1346, 4. *Candida albicans* ATCC 10231, 5. *Candida kuisei* ATCC 6258, 6. *Candida parapsilosis* ATCC 22019, 7. *Candida albicans* ATCC 10453, 8. *Candida albicans* ATCC 6019, 9. *Candida albicans* ATCC 66027.

results are given in Table 2. The compound showed very good anti-*Candida* activity at 3.12–6.25 μg/ml concentrations.

4. Conclusion

The study demonstrated that incorporation of carbodithioic acid residue directly into fluoxetine structure leads to compounds with better antifungal and anti-*Trichomonas* activity and *N*-methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-carbodithioic acid *S*-(2-pyrrolidino-ethyl) ester (**14**) has shown better profile than both fluoxetine and nonoxynol-9. Further lead optimization may result into a potent dual-function spermicide. On the other hand, nonoxynol-9 has been proposed for an additive therapy in metronidazole-resistant cases of vaginal trichomoniasis [26]. However, nonoxynol-9 use is associated with surfactant-type of cytotoxicity that may increase susceptibility to HIV and STD infections, and therefore, the non-surfactant structures **14**, **16**, **30**, **35** and **48** (with more potent anti-*Trichomonas* activity) may serve as safer options in such cases.

5. Experimental section

5.1. Chemistry

Melting points were determined in open capillary tubes on an electrically heated block and are uncorrected. IR spectra (ν_{max} in cm^{-1}) of the compounds were recorded on Perkin–Elmer's FTIR 8201 PC spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-200 FT spectrometer in deuterated solvents with TMS as internal reference (chemical shifts in δ parts per million, J in hertz). Mass spectra were recorded on Jeol/SX-102/DA-6000 FABMS spectrometer. Elemental analyses were performed on Carlo Erba EA-1108 micro analyzer. All compounds were analyzed for C, H, N and the results obtained were within ±0.4% of calculated values. Thin layer chromatography was performed on precoated alumina plastic plates (Aldrich). Anhydrous sodium sulphate was used as drying agent. All chemicals and solvents are procured from Sigma–Aldrich/Merck India Ltd. 1-Oxiranylmethyl-dialkylamines (**24**–**29**) [27] and 1-dialkylamino carbodithioic acid sodium salts (**37**–**42**) [17] were prepared by known procedures.

5.1.1. Synthesis of *N*-methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine carbodithioic acid sodium salt (*2*)

To a pre-cooled mixture of *N*-methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine hydrochloride (**1**, 0.3 mol) in ethyl acetate, aqueous sodium bicarbonate (10%, 1.5 equiv) was added dropwise with stirring in an ice bath. The reaction mixture was brought to room temperature and stirred till it became clear. The ethyl acetate layer was separated, washed and dried over sodium sulphate. Sodium sulphate was filtered off and ethyl acetate was concentrated under reduced pressure in rotavapor to get the free base. The free base (**1**, 0.1 mol) was dissolved in ethyl acetate and cooled in an ice bath with stirring. NaOH (0.15 mol, 30%) was added dropwise followed by CS_2 (0.12 mol) and kept stirring for 3 h. Later the reaction mixture was brought to room temperature and stirring continued for another 3 h. The ethyl acetate was concentrated under reduced pressure in rotavapor and dried by evaporating few times with acetone. The residue obtained was taken into hexane and cooled. The separated white solid was filtered and dried in vacuum desiccator.

Yield: 90%, mp 94 °C. Anal. Calcd for $C_{18}H_{17}F_3NNaOS_2$. Found: C, 53.29; H, 4.53; N, 3.29. Required: C, 53.06; H, 4.21; N, 3.44. IR (KBr, cm^{-1}): 2940.7, 2834.1, 1598.9, 1481.3, 1249.2, 1111.0, 966.0. ^1H NMR (200 MHz, $CDCl_3$): δ 2.01–2.50 (m, 2H, CH_2CHOR), 3.20 (s, 3H, N–CH_3), 3.98–4.32 (m, 2H, N–CH_2), 5.23–5.25 (m, 1H, CHOR), 6.62 (d, 2H, $J = 8.0$ Hz, ArH *ortho* to O), 7.00–7.08 (m, 7H, ArH of Ph, *ortho* to CF_3).

5.1.2. Synthesis of *N*-methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine carbodithioic acid esters (***10–16***)

N-Methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine carbodithioic acid sodium salt (**2**, 0.1 mol) was taken into methanol and stirred at room temperature to which chloro derivatives (**3**–**9**, 0.12 mol) were added. The reaction mixture was further stirred at room temperature for 12 h (as monitored by TLC). The methanol was concentrated under reduced pressure in rotavapor and the residue was taken into ethyl acetate. The ethyl acetate layer was washed and dried over sodium sulphate. Sodium sulphate was filtered off and ethyl acetate was concentrated under reduced pressure in rotavapor. The compounds were further purified by column chromatography with ethyl acetate/hexane (1:3) mixture.

5.1.2.1. *N*-Methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine carbodithioic acid *S*-[2-chloro-ethyl] ester (***10***).

Yield: 60%, oil. Anal. Calcd for $C_{20}H_{21}ClF_3NOS_2$. Found: C, 53.49; H, 4.58; N, 3.07. Required: C, 53.62; H, 4.73; N, 3.13. IR (neat, cm^{-1}): 3021.5, 2928.4, 1609.2, 1440.3, 1323.7, 1251.5, 1111.6, 770.7. ^1H NMR (200 MHz, $CDCl_3$): δ 2.09–2.15 (m, 2H, CH_2CHOR), 2.92 (s, 3H, N–CH_3), 3.12 (t, 2H, $J = 3.5$ Hz,

S–CH_2), 3.33–3.38 (m, 2H, N–CH_2), 3.43 (t, 2H, $J = 7.1$ Hz, CH_2–Cl), 5.08–5.14 (m, 1H, CHOR), 6.81 (d, 2H, $J = 8.5$ Hz, ArH *ortho* to O), 7.25 (s, 5H, ArH of Ph), 7.36 (d, 2H, $J = 8.3$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 448 ($M^+ + 1$), 401, 352, 327, 232, 207, 117.

*5.1.2.2. N-Methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine carbodithioic acid S-[2-benzyl] ester (**11**).* Yield: 95%, oil. Anal. Calcd for $C_{25}H_{24}F_3NOS_2$. Found: C, 62.93; H, 5.07; N, 3.26. Required: C, 63.14; H, 5.09; N, 2.95. IR (neat, cm^{-1}): 3020.8, 2985.4, 1657.3, 1614.9, 1489.8, 1326.8, 1216.8, 1119.2, 1068.0, 764.6. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.12–2.32 (m, 2H, CH_2CHOR), 3.29–3.48 (m, 3H, N–CH_3), 4.10–4.32 (m, 2H, N–CH_2), 4.45 (s, 2H, S–CH_2Ph), 5.19–5.31 (m, 1H, CHOR), 6.73–6.91 (m, 2H, ArH *meta* to CF_3), 7.24–7.37 (m, 10H, ArH of Ph × 2), 7.39–7.43 (m, 2H, ArH *ortho* to CF_3). MS (FAB): *m/z* 476 ($M^+ + 1$), 352, 314, 277, 248, 117, 91.

*5.1.2.3. N-Methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine carbodithioic acid S-[2-dimethyl amino-ethyl] ester (**12**).* Yield: 77%, oil. Anal. Calcd for $C_{22}H_{27}F_3N_2OS_2$. Found: C, 57.69; H, 5.69; N, 6.31. Required: C, 57.87; H, 5.96; N, 6.14. IR (neat, cm^{-1}): 3021.7, 2931.2, 1620.2, 1488.7, 1326.4, 1217.4, 1118.6, 1065.7, 761.0. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.29–2.34 (m, 8H, 2 × N–CH_3, CH_2CHOR), 2.41–2.65 (m, 2H, N–CH_2), 3.32–3.47 (m, 6H, N–CH_3, S–CH_2, N–CH_2), 4.20–4.41 (m, 1H, N–CH_2), 5.18–5.29 (m, 1H, CHOR), 6.89 (d, 2H, $J = 8.5$ Hz, ArH *ortho* to O), 7.32 (s, 5H, ArH of Ph), 7.43 (d, 2H, $J = 8.3$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 457 ($M^+ + 1$), 412, 391, 352, 307, 248, 117.

*5.1.2.4. N-Methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine carbodithioic acid S-[2-diethyl amino-ethyl] ester (**13**).* Yield: 85%, oil. Anal. Calcd for $C_{24}H_{31}F_3N_2OS_2$. Found: C, 59.29; H, 6.28; N, 5.96. Required: C, 59.48; H, 6.45; N, 5.78. IR (neat, cm^{-1}): 3019.4, 2971.9, 2929.8, 1616.4, 1487.9, 1326.4, 1248.0, 1118.2, 1067.6, 759.4. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 (t, 6H, $J = 7.0$ Hz, 2 × CH_3 of ethyl), 2.21–2.31 (m, 2H, CH_2CHOR), 2.56–2.66 (m, 6H, 3 × N–CH_2 of ethyl), 3.30–3.48 (m, 6H, N–CH_3, S–CH_2, N–CH_2), 4.15–4.20 (m, 1H, N–CH_2), 5.20–5.28 (m, 1H, CHOR), 6.89 (d, 2H, $J = 8.4$ Hz, ArH *ortho* to O), 7.32 (s, 5H, ArH of Ph), 7.43 (d, 2H, $J = 8.3$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 485 ($M^+ + 1$), 469, 412, 307, 248, 205, 117.

*5.1.2.5. N-Methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine carbodithioic acid S-[2-pyrrolidino-ethyl] ester (**14**).* Yield: 85%, oil. Anal. Calcd for $C_{24}H_{29}F_3N_2OS_2$. Found: C, 59.58; H, 5.97; N, 5.67. Required: C, 59.73; H, 6.06; N, 5.80. IR (neat, cm^{-1}): 3021.5, 2934.0, 1605.3, 1398.7, 1216.3, 1116.7, 1065.4, 760.7. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79 (s, 4H, 2 × CH_2 of pyrrolidine), 2.30–2.33 (m, 2H, CH_2CHOR), 2.58 (s, 4H, 2 × N–CH_2 of pyrrolidine), 2.79–2.86 (m, 2H, N–CH_2), 3.32–3.48 (m, 5H, N–CH_3, S–CH_2), 4.00–4.17 (m, 2H, N–CH_2), 5.27–5.30 (m, 1H, CHOR), 6.89 (d, 2H, $J = 8.7$ Hz, ArH *ortho* to O), 7.32 (s, 5H, ArH of Ph), 7.43 (d, 2H, $J = 8.0$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 483 ($M^+ + 1$), 412, 352, 248, 147, 117.

*5.1.2.6. N-Methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine carbodithioic acid S-[2-morpholino-ethyl] ester (**15**).* Yield: 92%, oil. Anal. Calcd for $C_{24}H_{29}F_3N_2O_2S_2$. Found: C, 57.67; H, 5.94; N, 5.98. Required: C, 57.81; H, 5.86; N, 5.62. IR (neat, cm^{-1}): 3017.1, 2931.7, 1615.5, 1487.9, 1325.6, 1218.1, 1118.3, 1066.4, 760.4. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.19–2.33 (m, 2H, CH_2CHOR), 2.51–2.59 (m, 4H, 2 × N-CH_2 of morpholine), 2.72–2.75 (m, 2H, N–CH_2), 3.32–3.48 (m, 5H, N–CH_3, S–CH_2), 3.68–3.70 (m, 4H, 2 × O–CH_2 of morpholine), 3.96–4.25 (m, 2H, N–CH_2), 5.19–5.24 (m, 1H, CHOR), 6.86 (d, 2H, $J = 8.3$ Hz, ArH *ortho* to O), 7.32 (s, 5H, ArH of Ph), 7.43 (d, 2H, $J = 8.6$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 499 ($M^+ + 1$), 412, 352, 248, 205, 113.

*5.1.2.7. N-Methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine carbodithioic acid S-[2-piperidino-ethyl] ester (**16**).* Yield: 75%, oil. Anal. Calcd for $C_{25}H_{31}F_3N_2OS_2$. Found: C, 60.13; H, 6.17; N, 5.98. Required: C, 60.46; H, 6.29; N, 5.64. IR (neat, cm^{-1}): 2933.8, 2855.4, 1614.5, 1384.2, 1324.2, 1248.8, 1116.4, 1062.0, 756.4. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.56–1.64 (m, 6H, 3 × CH_2 of piperidine), 2.30–2.33 (m, 2H, CH_2CHOR), 2.44–2.46 (m, 6H, 2 × N–CH_2 of piperidine and N–CH_2), 3.31–3.48 (m, 5H, N–CH_3, S–CH_2), 4.16–4.22 (m, 2H, N–CH_2), 5.19–5.45 (m, 1H, CHOR), 6.89 (d, 2H, $J = 8.5$ Hz, ArH *ortho* to O), 7.32 (s, 5H, ArH of Ph), 7.43 (d, 2H, $J = 8.6$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 497 ($M^+ + 1$), 412, 352, 248, 112.

*5.1.3. Synthesis of N-methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino carbodithioic acid 3-(dialkylamino)-2-hydroxy-propyl esters (**30–35**)*

1-Oxiranylmethyl-dialkylamines (**24–29**, 0.01 mol) was dissolved in methanol and *N*-methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine carbodithioic acid sodium salt (**2**, 0.01 mol) was added at room temperature with stirring and the stirring was continued for 12 h until the reaction was over (as monitored by TLC). The methanol was evaporated under reduced pressure in rotavapor and the residue was taken into ethyl acetate. The ethyl acetate layer was washed and dried over sodium sulphate. Sodium sulphate was filtered off and ethyl acetate was evaporated under reduced pressure in rotavapor to get the oily compound. The oily compounds were further purified by column chromatography using ethyl acetate/hexane (1:3) mixture as eluent.

*5.1.3.1. N-Methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino carbodithioic acid 3-(pyrrolidino)-2-hydroxy-propyl ester (**30**).* Yield: 72%, oil. Anal. Calcd for $C_{25}H_{31}F_3N_2O_2S_2$.

Found: C, 58.39; H, 6.02; N, 5.58. Required: C, 58.57; H, 6.10; N, 5.46. IR (neat, cm^{-1}): 3399, 3012, 2931, 2369, 1615, 1326, 1248, 1116, 766. ^1H NMR (200 MHz, $CDCl_3$): δ 1.65–1.77 (m, 4H, $CH_2 \times 2$-pyrrolidine), 2.09–2.21 (m, 4H, N–CH_2, CH_2 CHOR), 2.55–2.65 (m, 4H, N–$CH_2 \times 2$-pyrrolidine), 3.19–3.27 (m, 3H, N–CH_3), 3.31–3.41 (m, 2H, N–CH_2), 3.91–4.02 (m, 1H, CHOH), 4.03–4.18 (m, 2H, S–CH_2), 5.16 (t, 1H $J = 7.6$ Hz, CHOR), 6.82 (d, 2H, $J = 8.3$ Hz, ArH *meta* to CF_3), 7.19–7.25 (m, 5H, ArH oh Ph), 7.36 (d, 2H, $J = 8.3$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 513 ($M^+ + 1$), 442, 310, 248, 232, 205, 160, 110.

*5.1.3.2. N-Methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino carbodithioic acid 3-(morpholino)-2-hydroxy-propyl ester (**31**).* Yield: 79%, oil. Anal. Calcd for $C_{25}H_{31}F_3N_2O_3S_2$. Found: C, 56.65; H, 5.79; N, 5.52. Required: C, 56.80; H, 5.91; N, 5.30. IR (neat, cm^{-1}): 3403, 3010, 2924, 2372, 1616, 1491, 1327, 1218, 1116, 769. ^1H NMR (200 MHz, $CDCl_3$): δ 2.31–2.55 (m, 6H, $2 \times$ N–CH_2 morpholine, CH_2 CHOR), 2.60–2.65 (m, 2H, N–CH_2), 3.31 (s, 3H, N–CH_3), 3.49–3.59 (m, 2H, N–CH_2), 3.68–3.70 (m, 4H, O–CH_2 morpholine), 3.95–3.98 (m, 2H, S–CH_2), 4.10–4.13 (m, 1H, CHOH), 5.19–5.32 (m, 1H, CHOR), 6.89 (d, 2H, $J = 8.5$ Hz, ArH *meta* to CF_3), 7.22–7.32 (m, 5H, ArH of Ph), 7.43 (d, 2H, $J = 8.6$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 529 ($M^+ + 1$), 453, 442, 248, 232, 147, 117, 100.

*5.1.3.3. N-Methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino carbodithioic acid 3-(piperidino)-2-hydroxy-propyl ester (**32**).* Yield: 73%, oil. Anal. Calcd for $C_{26}H_{33}F_3N_2O_2S_2$. Found: C, 59.05; H, 6.15; N, 5.55. Required: C, 59.29; H, 6.32; N, 5.32. IR (neat, cm^{-1}): 3428, 2922, 2833, 2381, 1652, 1616, 1325, 1249, 1114, 1066, 837. ^1H NMR (200 MHz, $CDCl_3$): δ 0.75–0.80 (m, 2H, CH_2 of piperidine), 1.18–1.91 (m, 6H, $CH_2 \times 2$-piperidine, CH_2CHOR), 2.06–2.51 (m, 6H, N–CH_2, N–$CH_2 \times 2$-piperidine), 2.82–2.91 (m, 3H, N–CH_3), 3.20–3.24 (m, 2H, S–CH_2), 3.41–3.45 (m, 2H, N–CH_2), 4.08–4.19 (m, 1H, CHOH), 5.07 (t, 1H, $J = 7.8$ Hz, CHOR), 6.89 (d, 2H, $J = 5.5$ Hz, ArH *ortho* to O), 7.32–7.39 (m, 5H, ArH oh Ph), 7.42 (d, 2H, $J = 8.3$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 527 ($M^+ + 1$), 451, 232, 175, 117, 98.

*5.1.3.4. N-Methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino carbodithioic acid 3-(azepino)-2-hydroxy-propyl ester (**33**).* Yield: 72%, oil. Anal. Calcd for $C_{27}H_{35}F_3N_2O_2S_2$. Found: C, 59.79; H, 6.38; N, 5.02. Required: C, 59.98; H, 6.52; N, 5.18. IR (neat, cm^{-1}): 3428, 2927, 2855, 2373, 1617, 1326, 1249, 1115, 758. ^1H NMR (200 MHz, $CDCl_3$): δ 1.18 (s, 4H, $CH_2 \times 2$-azepine), 1.51–1.62 (m, 4H, $CH_2 \times 2$-azepine), 2.10–2.26 (m, 2H, CH_2CHOR), 2.60–2.71 (m, 6H, N–CH_2, N–$CH_2 \times 2$-azepine), 3.16–3.27 (m, 3H, N–CH_3), 3.41–3.67 (m, 2H, N–CH_2), 3.84–3.92 (m, 2H, S–CH_2), 4.09–4.21 (m, 1H, CHOH), 5.16 (t, 1H, $J = 7.8$ Hz, CHOR), 6.82 (d, 2H, $J = 8.0$ Hz, ArH *ortho* to O), 7.19–7.25 (m, 5H, ArH oh Ph), 7.36 (d, 2H, $J = 8.0$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 541 ($M^+ + 1$), 507, 442, 255, 156, 138, 112.

*5.1.3.5. N-Methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino carbodithioic acid 3-(diethyl amino)-2-hydroxy-propyl ester (**34**).* Yield: 71%, oil. Anal. Calcd for $C_{25}H_{33}F_3N_2O_2S_2$. Found: C, 58.18; H, 6.29; N, 5.29. Required: C, 58.34; H, 6.29; N, 5.44. IR (neat, cm^{-1}): 3398, 3010, 2930, 2366, 1614, 1515, 1327, 1249, 1114, 836. ^1H NMR (200 MHz, $CDCl_3$): δ 2.12–2.32 (m, 6H, $CH_3 \times 2$), 2.44–2.50 (m, 2H, CH_2 CHOR), 2.53–2.68 (m, 2H, N–CH_2), 2.87–3.05 (m, 2H, N–CH_2), 3.24–3.54 (m, 7H, N–CH_3, N–$CH_2 \times 2$), 3.81–3.98 (m, 2H, S–CH_2), 4.03–4.45 (m, 1H, CHOH), 5.31–5.36 (m, 1H, CHOR), 6.94 (d, 2H, $J = 8.4$ Hz, ArH *meta* to CF_3), 7.26–7.45 (m, 7H, ArH of Ph, ArH *ortho* to CF_3). MS (FAB): *m/z* 515 ($M^+ + 1$), 442, 352, 248, 232, 205.

*5.1.3.6. N-Methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino carbodithioic acid 3-(4-methyl-piperazino)-2-hydroxy-propyl ester (**35**).* Yield: 68%, oil. Anal. Calcd for $C_{26}H_{34}F_3N_3O_2S_2$. Found: C, 57.42; H, 6.21; N, 7.89. Required: C, 57.65; H, 6.33; N, 7.76. IR (neat, cm^{-1}): 3399, 3029, 2929, 2374, 1615, 1326, 1249, 1113, 767. ^1H NMR (200 MHz, $CDCl_3$): δ 1.97–2.23 (m, 7H, N–CH_3 piperazine, N–CH_2, CH_2CHOR), 2.30–2.54 (m, 4H, N–CH_2 piperazine), 2.84–2.98 (m, 4H, N–CH_2 piperazine), 3.28 (s, 3H, N–CH_3), 3.41–3.50 (m, 4H, N–CH_2, S–CH_2), 3.74–4.10 (m, 1H, CHOH), 5.13–5.17 (m, 1H, CHOR), 6.82 (d, 2H, $J = 8.5$ Hz, ArH *meta* to CF_3), 7.19–7.25 (m, 5H, ArH of Ph), 7.35 (d, 2H, $J = 6.9$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 542 ($M^+ + 1$), 543 ($M^+ + 2$), 442, 322, 251, 232, 218, 175, 117.

*5.1.4. Synthesis of methyl-oxiranylmethyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amine (**36**)*

To a pre-cooled mixture of *N*-methyl-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propylamine hydrochloride (**1**, 0.3 mol) in ethyl acetate, aqueous sodium bicarbonate (10%, 1.5 equiv) was added dropwise with stirring in an ice bath. The reaction mixture was brought to room temperature and stirred until it became clear. The ethyl acetate layer was separated, washed and dried over sodium sulphate. Sodium sulphate was filtered off and ethyl acetate was concentrated under reduced pressure in rotavapor to get the free base. The free base (0.1 mol) was dissolved in methanol cooled in an ice bath and triethylamine (0.015 mol) was added. Epichlorohydrin (0.012 mol) was added dropwise to the reaction mixture and stirring was continued in and ice bath for 3 h until the reaction was completed (as monitored by TLC). The methanol was evaporated under reduced pressure in rotavapor and the residue was taken into ethyl acetate. The solid triethylamine hydrochloride was filtered and the ethyl acetate layer was washed and dried over sodium sulphate. Sodium sulphate was filtered and ethyl acetate was concentrated under reduced pressure in rotavapor. The formed compound was used as it is without further purification.

*5.1.5. Synthesis of dialkylamino carbodithioic acid 2-hydroxy-3-{methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino}-propyl esters (**43–48**)*

Methyl-oxiranylmethyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amine (**36**, 0.01 mol) was dissolved in methanol and 1-dialkylamino carbodithioic acid sodium salts (**37–42**, 0.01 mol) were added at room temperature with stirring. The stirring was continued for 6 h till the reaction was over (as monitored by TLC). The methanol was evaporated under reduced pressure in rotavapor and the residue was taken into ethyl acetate. The ethyl acetate layer was washed and dried over sodium sulphate. Sodium sulphate was filtered off and ethyl acetate was evaporated under reduced pressure in rotavapor to get the oily compound. The compounds were further purified by column chromatography using ethyl acetate/hexane (1:3) mixture as eluent.

*5.1.5.1. Pyrrolidine-1-carbodithioic acid 2-hydroxy-3-{methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino}-propyl ester (**43**).* Yield: 89%, oil. Anal. Calcd for $C_{25}H_{31}F_3N_2O_2S_2$. Found: C, 58.82; H, 6.36; N, 5.28. Required: C, 58.57; H, 6.10; N, 5.46. IR (neat, cm^{-1}): 3019.5, 2975.4, 1614.5, 1515.7, 1436.2, 1327.0, 1217.6, 1119.2, 1063.5, 762.4. ^1H NMR (200 MHz, $CDCl_3$): δ 1.93–2.10 (m, 6H, $2 \times CH_2$ of pyrrolidine, CH_2CHOR), 2.29 (s, 3H, N–CH_3), 2.47 (t, 2H, $J = 5.1$ Hz, N–CH_2), 2.61 (d, 2H, $J = 6.7$ Hz, N–CH_2CHOH), 3.02–3.41 (m, 1H, CHOH), 3.62–3.69 (m, 4H, $2 \times$ N–CH_2 of pyrrolidine), 3.89–3.95 (m, 2H, S–CH_2), 5.25–5.27 (m, 1H, CHOR), 6.89 (d, 2H, $J = 8.5$ Hz, ArH *ortho* to O), 7.32 (s, 5H, ArH of Ph), 7.41 (d, 2H, $J = 8.4$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 513 ($M^+ + 1$), 479, 348, 322, 251, 204, 114.

*5.1.5.2. Morpholine-1-carbodithioic acid 2-hydroxy-3-{methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino}-propyl ester (**44**).* Yield: 63%, oil. Anal. Calcd for $C_{25}H_{31}F_3N_2O_3S_2$. Found: C, 56.58; H, 5.79; N, 5.57. Required: C, 56.80; H, 5.91; N, 5.30. IR (neat, cm^{-1}): 3434, 3024, 2928, 1637, 1460, 1327, 1218, 1165, 1116, 763. ^1H NMR (200 MHz, $CDCl_3$): δ 2.16–2.23 (m, 2H, CH_2CHOR), 2.38 (s, 3H, N–CH_3), 2.56 (t, 2H, $J = 5.0$ Hz, N–CH_2), 2.67–2.76 (m, 2H, N–CH_2), 3.31 (t, 1H, $J = 5.0$ Hz, CHOH), 3.53–3.55 (m, 1H, S–CH_2), 3.65–3.75 (m, 4H, N–CH_2 morpholine), 3.93–4.32 (m, 5H, O–CH_2 morpholine, S–CH_2), 5.26 (t, 1H, $J = 3.0$ Hz, CHOR), 6.89 (d, 2H, $J = 5.6$ Hz, ArH *meta* to CF_3), 7.30–7.33 (m, 5H, Ph), 7.42 (d, 2H, $J = 5.6$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 528 (M^+), 402, 366, 322, 220, 130.

*5.1.5.3. Piperidine-1-carbodithioic acid 2-hydroxy-3-{methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino}-propyl ester (**45**).* Yield: 87%, oil. Anal. Calcd for $C_{26}H_{33}F_3N_2O_2S_2$. Found: C, 59.11; H, 6.16; N, 5.55. Required: C, 59.29; H, 6.32; N, 5.32. IR (neat, cm^{-1}): 3431.8, 2937.9, 2857.5, 2369.0, 1615.2, 1428.8, 1325.3, 1246.8, 1116.3, 1066.8, 760.7. ^1H NMR (200 MHz, $CDCl_3$): δ 1.58–1.71 (m, 6H, $CH_2 \times 3$ of piperidine), 2.03–2.20 (m, 2H, CH_2CHOR), 2.30 (s, 3H, N–CH_3), 2.47 (t, 2H, $J = 8.0$ Hz, N–CH_2), 2.61 (d, 2H, $J = 8.0$ Hz, N–CH_2CHOH), 3.31–3.37 (quintet, 1H, CHOH), 3.63–3.66 (m, 1H, S–CH_2), 3.67–3.81 (m, 3H, N–CH_2 piperidine, S–CH_2), 3.94–3.96 (m, 2H, N–CH_2 piperidine), 5.32–5.19 (m, 1H, CHOR), 6.88 (d, 2H, $J = 10.0$ Hz, ArH *meta* to CF_3), 7.29–7.36 (m, 5H, ArH of Ph), 7.41 (d, 2H, $J = 10.0$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 527 ($M^+ + 1$), 348, 322, 216, 128, 100.

*5.1.5.4. Azepine-1-carbodithioic acid 2-hydroxy-3-{methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino}-propyl ester (**46**).* Yield: 91%, oil. Anal. Calcd for $C_{27}H_{35}F_3N_2O_2S_2$. Found: C, 59.69; H, 6.31; N, 5.32. Required: C, 59.98; H, 6.52; N, 5.18. IR (neat, cm^{-1}): 3436.5, 3029.5, 2936.2, 2373.9, 1630.3, 1489.9, 1326.4, 1217.7, 1117.4, 760.8. ^1H NMR (200 MHz, $CDCl_3$): δ 1.57–1.6 (m, 4H, $2 \times CH_2$ of azepine), 1.78–1.92 (m, 4H, $2 \times CH_2$ of azepine), 2.08–2.21 (m, 2H, CH_2CHOR), 2.29 (s, 3H, N–CH_3), 2.45–2.48 (m, 2H, N–CH_2), 2.58–2.64 (m, 2H, N–CH_2CHOH), 3.31–3.38 (m, 1H, S–CH_2), 3.61–3.64 (m, 1H, S–CH_2), 3.89–3.96 (m, 3H, CHOH, N–CH_2 of azepine), 4.14–4.22 (m, 2H, N–CH_2 of azepine), 5.21–5.27 (m, 1H, CHOR), 6.89 (d, 2H, $J = 8.3$ Hz, ArH *ortho* to O), 7.32 (s, 5H, ArH of Ph), 7.41 (d, 2H, $J = 8.5$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 541 ($M^+ + 1$), 507, 348, 322, 232, 142, 100.

*5.1.5.5. Benzyl methyl-amino-1-carbodithioic acid 2-hydroxy-3-{methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino}-propyl ester (**47**).* Yield: 66%, oil. Anal. Calcd for $C_{29}H_{33}F_3N_2O_2S_2$. Found: C, 61.73; H, 5.79; N, 5.12. Required: C, 61.90; H, 5.91; N, 4.98. IR (neat, cm^{-1}): 3405.7, 3031.4, 2932.5, 2372.7, 1615.4, 1480.0, 1386.0, 1324.9, 1251.1, 1165.4, 1114.5, 761.5. ^1H NMR (200 MHz, $CDCl_3$): δ 2.01 (t, 2H, $J = 7.3$ Hz, CH_2CHOR), 2.12–2.20 (m, 3H, N–CH_3), 2.31 (s, 3H, N–CH_3), 2.49 (d, 2H, $J = 8.4$ Hz, N–CH_2CHOH), 2.60 (t, 2H, $J = 6.2$ Hz, N–CH_2), 3.18–3.29 (m, 2H, S–CH_2), 3.34–3.46 (m, 1H, CHOH), 3.73–3.74 (m, 1H, CH_2 of benzyl), 3.87–3.42 (m, 1H, CH_2 of benzyl), 5.23–5.29 (m, 1H, CHOR), 6.89 (d, 2H, $J = 8.6$ Hz, ArH *ortho* to O), 7.25–7.32 (m, 10H, ArH of Ph), 7.41 (d, 2H, $J = 8.2$ Hz, ArH *ortho* to CF_3). MS (FAB): *m/z* 563 ($M^+ + 1$), 529, 364, 348, 322, 251, 218, 117.

*5.1.5.6. 4-Methyl-piperazine-1-carbodithioic acid 2-hydroxy-3-{methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-amino}-propyl ester (**48**).* Yield: 71%, oil. Anal. Calcd for $C_{26}H_{34}F_3N_3O_2S_2$. Found: C, 57.58; H, 6.25; N, 7.95. Required: C, 57.65; H, 6.33; N, 7.76. IR (neat, cm^{-1}): 3422.9, 2941.3, 2851.2, 2375.0, 1615.0, 1425.5, 1324.9, 1247.0, 1116.4, 1066.5, 758.4. ^1H NMR (200 MHz, $CDCl_3$): δ 1.74–2.07 (m, 2H, CH_2CHOR), 2.28 (s, 3H, N–CH_3), 2.32 (s, 3H, N–CH_3), 2.45–2.48 (m, 4H, $2 \times$ N–CH_2 of piperazine), 2.58–2.61 (m, 2H, N–CH_2), 3.30–3.36 (m, 1H, CHOH), 3.40–3.60 (m, 2H, N–CH_2CHOH), 3.62–3.71 (m, 2H, N–CH_2 of piperazine), 3.92–3.96 (m, 2H, N–CH_2 of piperazine), 4.27–4.38 (m, 2H, S–CH_2), 5.23–5.26 (m, 1H, CHOR), 6.88 (d, 2H, $J = 10.0$ Hz, ArH *ortho* to O), 7.32 (s, 5H, ArH of Ph), 7.41 (d, 2H, $J = 10.0$ Hz, ArH *ortho* to CF_3). MS

(FAB): *m/z* 542 ($M^+ + 1$), 508, 366, 322, 251, 218, 175, 143, 117.

5.2. Biology

5.2.1. Spermicidal activity

Minimum effective (spermicidal) concentration (MEC) was determined by the standard procedure [7]. 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 1.0% (10 mg/ml) solution. The solutions were further diluted serially with saline. A spermicidal test was performed with each dilution starting from 1.0% until the minimum effective concentration (MEC) was arrived. For this purpose 0.05 ml of liquefied human semen was added to 0.25 ml of test solution and vortexed for 10 s. 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 immotile in 20 s. The MEC was determined in three individual semen samples from different donors. The minimum concentration of compound capable of killing 100% sperm in ~20 s in "all" the semen samples was denoted as MEC and is recorded in Table 1.

5.2.2. Anti-Trichomonas activity

Trichomonas vaginalis parasites to be used in drug susceptibility assays were grown in TYM medium [28] for one day following regular subculturing and were in the log phase of growth. *In vitro* drug susceptibility assays were carried out using the standard procedure [29]. Stock solutions (100 μg/μl) of test compounds were prepared in DMSO and were diluted with TYM medium to obtain a concentration of 200 μg/ml in a 48-well plate. This was further serially diluted with the same medium up to a concentration of 3.125 μg/ml. DMSO/TYM was used as vehicle in control wells. Parasites (5×10^3 trophozoites/well) were added to these wells and incubated anaerobically at 37 °C. Trophozoite growth and viability in drug containing wells were monitored by trypan blue staining and cell number score on a daily basis, in comparison to control. Assay results were clearly defined after 48 h in terms of minimum inhibitory concentration (MIC). Using this MIC value as a reference, finer dilutions of the active compounds were prepared and the drug susceptibility assay was repeated to obtain the final MIC precisely through a concentration versus viable–trophozoite–number curve.

5.2.3. Antifungal activity

The MIC of compounds were determined [30] by broth micro-dilution technique as per guide lines of National Committee for Clinical Laboratory Standards using RPMI 1640 media buffered with MOPS [3-(*N*-morpholino)propanesulfonic acid]. Starting inoculums of test culture was $1-5 \times 10^3$ CFU/ml. Micro titer plates were incubated at 35 °C. MICs were recorded after 48 h of incubation.

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