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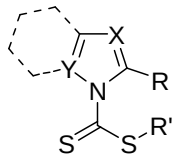

X, Y : N, CH
R : alkyl
R': alkyl, alkenyl

Azole-carbodithioate hybrids as vaginal anti-*Candida* contraceptive agents: design, synthesis and docking studies[#]

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Abstract

Azole and carbodithioate hybrids were synthesized as alkyl 1*H*-azole-1-carbodithioates (**7**–**27**) and evaluated for spermicidal/microbicidal activities against human sperm, *Trichomonas vaginalis* and *Candida* species. Seventeen compounds (**7**-**14**, **16**-**18** and **20**-**25**) showed spermicidal activity at MEC 1.0% (w/v) and permanently immobilized 100% normal human spermatozoa within ~30 second. Seventeen compounds (**7**–**11**, **13**–**18** and **20**–**25**) exhibited anti-*Candida* activity (IC_{50} 1.26–47.69 µg/mL). All compounds were devoid of bactericidal activity against four bacterial strains (50.00 µg/mL) and antiprotozoal activity against *Trichomonas vaginalis* (200.00 µg/mL). Four promising compounds (**10**, **17**, **20** and **22**) have better safety profile as compared to Nonoxynol-9 (N-9). Docking study was done to visualize the possible interaction of designed scaffold with prospective receptor (Cyp51) of *Candida albicans*.

Keywords

Anti-*Candida, spermicides, imidazole, docking, carbon disulfide, dithiocarbamate*

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1. Introduction

Approximately one-third of vulvovaginitis cases are attributable to *Candida* infection. *Candida* species form a part of the lower genital tract flora in many healthy asymptomatic women and reportedly ~50% female university students experience at least one physician-diagnosed episode of vulvovaginal candidiasis (VVC) by age of 25. The estimated cost of VVC is about 1 billion dollars in the US [1]. Fungal adhesion to the epithelium is a prerequisite for colonization, and infections are characterized by the invasion of vaginal epithelial cells. Additionally, hyphal formation damages epithelial tissue and contributes to symptomatic vaginal infections [2], which may lead to subsequent attack by sexually transmitted infections (STIs) and HIV.

Please insert Figure 1.

Imidazoles, especially clotrimazole (**1**; Figure 1) and bifonazole (**2**; Figure 1) are highly effective antifungal agents against mucosal infections caused by *Candida albicans* through inhibiting ergosterol biosynthesis [3]. However, the emerging resistance against these drugs [4, 5] has necessitated the search for new molecules.

In our enduring efforts to discover dually active vaginal microbicides [6-11], we have reported that the hybridization of nitroimidazole structure with dithiocarbamate/phenylpropyl groups leads to compounds with potent anti-*Trichomonas*, mild anti-*Candida* and spermicidal activities [12, 13]. Moreover, metronidazole and other nitroimidazole antiprotozoals are devoid of anti-*Candida* activity [14, 15] while similar compounds without a nitro group possess antifungal efficacy [16-19]. A careful study of the antifungal structures (**3**-**5**; Figure 1) revealed that none of these had a nitro group. Hence, it was anticipated that hybridization of various azoles lacking a nitro group with dithiocarbamate group (**6**; Figure 1) could lead to the discovery of a chemical entity with potent anti-*Candida*, anti-*Trichomonas* and spermicidal activities, since the dithiocarbamate group itself has been attributed with potent activities against human sperm and *Trichomonas* [20]. The compounds thus synthesized were evaluated *in vitro* against human sperm and various strains of *Candida albicans* and *Trichomonas vaginalis*. The promising compounds were subsequently assessed for their adverse effect on vaginal flora (*Lactobacillus*) and cervical epithelium (HeLa cells) for their possible utility as vaginal microbicides. A docking study was also carried out to find a suitable correlation between antifungal activity and inhibition of the prospective receptor. The synthesis, structure activity relationship (SAR) and docking study are being reported in this communication.

2. Results and discussion

2.1. Chemistry

The synthetic route for the synthesis of alkyl 1*H*-azole-1-carbodithioate (**7**–**27**) has been shown in Scheme 1. These compounds were synthesized by the reaction of azoles, carbon disulfide and alkyl or alkenyl halide in the presence of a strong base (sodium hydride) at 0–5 °C. Reaction with imidazole, 2-methylimidazole and benzimidazole was completed smoothly. When benzotriazole was used as reactant, an N-methylated product (**27,** Scheme 1)

was obtained, instead of methyl 1*H*-benzotriazole-1-carbodithioate, probably due to the presence of an additional nitrogen atom in the ring which decreased the basic strength at reactive site [21].

Please insert Scheme 1.

2.2. Evaluation of biological activities

2.2.1. Antifungal activity

Fifteen compounds (**9**, **11**–**22**, **25** and **27**) exhibited antifungal activity (Table 1) against one or more strains of fungi viz., *Sporothrix schenckii*, *Trichophyton mentagrophytes*, *Aspergillus fumigatus*, *Cryptococcus neoformans* with IC_{50} ranging from 0.69–24.93 µg/mL. Compounds **17** and **22** inhibited four strains while compounds **9**, **13** and **14** inhibited three strains of fungi. Additionally, the growth of *Sporothrix schenckii* was inhibited by three compounds (**16**, **22** and **27)** and that of *Trichophyton mentagrophytes* was inhibited by two compounds (**11** and **25)** at IC_{50} < 2.0 µg/mL. Compound **22** inhibited *Cryptococcus neoformans* with IC_{50} of 0.69 μg/mL while compound **11** also inhibited the growth of *Aspergillus fumigatus* with IC_{50} 6.21 μg/mL.

Please insert Table 1

2.2.2. Anti-Candida activity

Seventeen compounds (**7**–**11**, **13**–**18** and **20–25**) showed anti-*Candida* activity (Table 2) against one or more *Candida* strains. Three compounds (**10**, **16** and **22**) inhibited growth of all the six *Candida* strains. Furthermore, the growth inhibition was observed in five and four *Candida* strains by compounds **9**, **11**, **13**, **17** and compound **14**, respectively. Thirteen compounds (**7**, **10**, **11**, **13**-**18**, **20**-**22**, **25**) inhibited *Candida albicans* at IC_{50} ranging 1.26–36.03 µg/mL and four out of thirteen compounds (**10**, **17**, **20** and **22**) had remarkable IC_{50} ranging from 1.26 to 1.43 µg/mL. Five compounds (**8**-**10**, **16** and **22**) exhibited anti-*Candida* activity against *Candida parapsilosis* with IC_{50} ranging 1.46–10.15 µg/mL. Compound **22** was found to be very active against *Candida parapsilosis* with low IC_{50} of 1.46 µg/mL. Furthermore, anti-*Candida* data showed that compound **22** was the most active against PK3, PK9, PK13 and PK 30 (four additional strains of *Candida*) with IC_{50} of 1.79, 3.33, 1.79 and 1.75 µg/mL, respectively.

The structure activity relationship indicated that among azoles, decreasing the alkyl chain length and by combining phenyl ring with imidazole (imidazole was replaced by benzimidazole) gave rise to the most active compound (**22**). Furthermore, imidazol-1-yl and 2-methylimidazol-1-yl with allyl (**9**, **16**) or butyl (**10**, **17**) form a good combination for anti-*Candida* activity as these compounds generally inhibited all *Candida* strains at low IC_{50}. On the other hand, it was observed that on increasing the alkyl chain length, the anti-*Candida* activity reduced (**12**, **18** and **26**) in case of imidazol-1-yl, 2-methylimidazol-1-yl and benzimidazol-1-yl moieties. The introduction of additional nitrogen in the imidazole ring with allyl group (**21**) decreased the activity.

Please insert Table 2

2.2.3. Spermicidal activity

All the compounds (except **27**) showed spermicidal activity (Table 3) at 1.0% (w/v) concentration and irreversibly immobilized 95-100% normal human spermatozoa. Out of the total twenty one compounds, seventeen compounds (**7**–**14**, **16**–**18**, **20**–**25**) caused 100% immobilization at 1.0% while three compounds **15**, **19** and **26** caused 95% immobilization. Five compounds (**8**, **10**, **11**, **18** and **22**) demonstrated extremely potent sperm immobilizing potential and immobilized 80-100% human sperm at 0.1% (w/v) concentration. Compound **18** was found to be most potent spermicide in this series.

Please insert Table 3

2.2.4. Anti-Trichomonas activity

All the compounds (**7**–**27)** could not display trichomonacidal effect at 200.00 µg/mL (Table 3), the absence of nitro group attached with in azole ring may be the probable reason.

2.2.5. Antibacterial activity

Compounds (**7**–**27**) were also found to be inactive towards four bacterial strains such as *E. coli* (ATCC 9637), *Pseudomonas aeruginosa* (ATCC BAA-427), *Staphylococcus aureus* (ATCC 25923), *Klebsiella pneumoniae* (ATCC 27736) at 50.00 µg/mL (Table 1), which indicated high fungicidal selectivity.

2.2.6. Cytotoxic assay using human cervical (HeLa) cell line and compatibility with Lactobacillus

The four most active compounds (**10**, **17**, **20** and **22**) of this series displayed better safety towards HeLa cells (IC_{50} 48.70-85.45 µg/mL) and much better compatibility with *Lactobacillus* (IC_{50} 39.54-220.00 µg/mL) than Nonoxynol-9 (N-9) which showed IC_{50} 37.00 and 21.00 µg/mL respectively (Table 4), and therefore appeared apparently much safer for vaginal use. These compounds did not affect the viability of HeLa cells or growth of *Lactobacilli* during 24 hours of incubation.

Please insert Table 4

A closer look to SAR revealed that sixteen compounds were dually active and possessed spermicidal activity as well as antifungal activity against all the ten fungal strains (including six *Candida* strains). However, these compounds failed to possess anti-*Trichomonas* activity, plausibly due to the absence of nitro group in azole ring. Further structural optimization may yield active compounds possessing multiple activities i.e., spermicidal, antifungal and anti-*Trichomonas* activities.

2.3. Docking study

It is well documented that various azoles and non-azoles exhibit antifungal activity through inhibition of the prospective receptor Cyp51, a member of the cytochrome P450 superfamily [22-25]. In yeasts and fungi, $P450_{14DM}$ participates in ergosterol biosynthesis [25], which is an essential requirement for fungal viability. Selective inhibition of Cyp51 causes depletion of ergosterol and accumulation of lanosterol and some other 14-methyl sterols resulting in growth inhibition of fungal cells. To visualize the interaction of designed scaffold with Cyp51 of *Candida albicans*, docking studies were carried out. Docked conformations were calculated using homology model of *Candida albicans* Cyp51, which were used in previous studies as given in the supporting information [26, 27]. The four most active compounds (**10**, **17**, **20** and **22**) of this series were selected for the docking study and docked energy data is provided in Table 5.

Please insert Figure 2

Docking with compounds showed that there is common mode of interaction with Cyp51 through formation of co-ordinate bond between N atom of azole ring of inhibitors and Fe of heme prosthetic group of receptor (Figure 2). Long alkyl chain of compounds **10** and **17** was found to be close to hydrophobic residues Val509 and Val510. It has been reported that Val509 and Val510 come under structurally selective residues of active site of *Candida albicans* Cyp51 and interaction with these residues may have selectivity advantage to newly designed antifungals [24]. Compound **20** showed lowest docking energy in agreement with *in vitro* activity, which may be due to lack of alkyl chain. In case of compound **22**, presence of benzene ring stabilized the interaction by making hydrophobic contact with L376, which may account for higher docked energy than compound **20**. Other residues like Met306, Gly307, and Thr311 and Pro375 were found to be in close contact with docked conformation of all compounds.

Please insert Table 5

3. Conclusion

In this communication, hybrids of azole and carbodithioate scaffolds as alkyl 1*H*-azole-1-carbodithioates (**7**–**27**) have been reported, which were evaluated for their spermicidal as well as microbicidal activities against *Trichomonas vaginalis* and *Candida* species *in vitro*. Most of the compounds exhibited significant anti-*Candida* activity and sixteen compounds (**7**-**11**, **13**, **14**, **16**-**18**, **20**-**25**) co-possessed spermicidal activity as well. While lack of nitro group in azole scaffold imparted potent antifungal activity, carbodithioate group tendered appreciable spermicidal effects though it failed to incorporate antiprotozoal (anti-*Trichomonas*) efficacy. Our previous hybrid designs of nitro-azole and carbodithioate exhibited potent anti-*Trichomonas* and spermicidal effects [12], lacking noticeable antifungal property. Hence, it is apparent that in azole-carbodithioates hybrids, the presence of nitro group is the deciding factor for presence of antifungal or antiprotozoal activities. The two activities fail to co-exist due to the unique pharmacophoric properties of the nitro-group in azoles. Four promising

compounds (**10**, **17**, **20** and **22**) of this series had a better safety profile as compared to N-9 and could be used as lead molecules for designing antimicrobial contraceptives. The proposed docking analysis is noteworthy and can be utilized as a guideline for designing of promising anti-*Candida* agents.

4. Experimental section

4.1. Chemistry

In general, all reagents and solvents were of commercial quality and used without further purification. Melting points were determined in open capillary tubes on an electrically heated block and were uncorrected. IR spectra (ν_{max} in cm^{-1}) of the compounds were recorded on Perkin Elmer's FT-IR RX1 PC spectrophotometer. ^{1}H NMR & ^{13}C NMR spectra were recorded on Bruker Supercon Magnet Avance/DRX-300 spectrometers (300 MHz for ^{1}H; 75.4 MHz for ^{13}C) in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, *J* in Hz). Electrospray Ionisation Mass spectra (ESI-MS) were recorded on Thermo Lcq Advantage Max-IT. Elemental analyses were performed on Carlo Erba EA-1108 micro analyzer / Vario EL-III C H N S analyzer. All compounds were analyzed of C, H, N and the results obtained were within ± 0.4% of calculated values. 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 (60-120 Mesh). All compounds were characterized by TLC, ^{1}H and ^{13}C NMR and MS. Elemental analyses data meet the criteria of ≥95% purity. All chemicals and solvents were procured from Sigma-Aldrich/Merck India Ltd.

*4.1.1. Synthesis of methyl 1H-imidazole-1-carbodithioate (**7**)*

Into an ice-cooled suspension of sodium hydride (14.7 mmol, 60% in mineral oil) in THF (5.0 mL) was added a solution of imidazole (0.5 gm) in THF (10.0 mL) dropwise in 5 min, the mixture became dense by complete addition of imidazole. A solution of carbon disulfide (11.0 mmol, 0.7 mL) in THF (5.0 mL) was added dropwise in 5 and then the reaction mixture stirred at 0-5 °C for 15 min. The reaction mixture became clear and dark yellow into which a solution of iodomethane (9.5 mmol, 0.6 mL) in THF (5.0 mL) was added dropwise in 2 min then reaction mixture stirred for 10 min at 0-5 °C. Distilled water (2.0 mL) was added carefully to quench excess of sodium hydride. Solvents were evaporated under reduced pressure in rotavapor to provide dense reaction mixture. That was diluted with ethyl acetate (10.0 mL), washed with distilled water (3 x 5.0 mL), and dried over anhydrous sodium sulphate. Sodium sulphate was filtered off and washed with ethyl acetate (3 x 5.0 mL). Combined filtrate was concentrated in rotavapor to provide crude oil that was purified by column chromatography on silica-gel using chloroform as eluent to provide yellow oil.

Yield 95%; Yellow oil; IR (neat): 2940, 1635, 1580 cm^{-1}; ESI-MS (*m/z*): 159 (MH^{+}); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.51 (s, 1H), 7.80 (s, 1H), 7.12 (s, 1H), 2.81 (s, 3H); Anal. Calcd. for $C_5H_6N_2S_2$: C, 37.95; H, 3.82; N, 17.70; Found: C, 37.92; H, 3.80; N, 17.71.

The following compounds **8**–**27** were prepared using a procedure described for compound **7** from the corresponding azoles, carbon disulfide and alkyl halide/alkenyl halide. All the compounds were purified by column chromatography on silica-gel.

*4.1.2. 3-Cyanopropyl 1H-imidazole-1-carbodithioate (**8**)*

Eluent: 70% ethyl acetate-hexane; Yield 91%; Yellow oil; IR (neat): 2963, 2248, 1638, 1423 cm^{-1}; ESI-MS (*m/z*): 212 (MH^+); ^1H NMR ($CDCl_3$+CCl_4, 300 MHz): δ 8.45 (s, 1H), 7.76 (s, 1H), 7.10 (s, 1H), 3.55 (t, 2H, J = 7.3 Hz), 2.53 (t, 2H, J = 6.9 Hz), 2.22–2.12 (m, 2H); ^{13}C NMR ($CDCl_3$+CCl_4, 75.5 MHz): δ 196.7 (C=S), 135.7, 132.0, 118.0, 117.8, 34.7, 24.0, 16.6; Anal. Calcd. for $C_8H_9N_3S_2$: C, 45.47; H, 4.29; N, 19.89; Found: C, 45.42; H, 4.20; N, 19.88.

*4.1.3. Allyl 1H-imidazole-1-carbodithioate (**9**)*

Eluent: 40% ethyl acetate-hexane; Yield 86%; Semisolid; IR (neat): 3113, 2960, 1637, 1531, 1468, 1368, 1275, 765 cm^{-1}; ESI-MS (*m/z*): 185 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.47 (s, 1H), 7.78 (s, 1H), 7.10 (s, 1H), 5.99–5.85 (m, 1H), 5.42 (d, 1H, J = 16.9 Hz), 5.29 (d, 1H, J = 10.0 Hz), 4.06 (d, 2H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 197.2 (C=S), 135.7, 131.6, 129.7, 120.8, 117.8, 39.7; Anal. Calcd. for $C_7H_8N_2S_2$: C, 45.62; H, 4.38; N, 15.20; Found: C, 45.52; H, 4.24; N, 15.11.

*4.1.4. Butyl 1H-imidazole-1-carbodithioate (**10**)*

Eluent: 5% ethyl acetate-hexane; Yield 71%; Yellow oil; IR (neat): 2963, 1634, 1446, 1369, 1218, 766 cm^{-1}; ESI-MS (*m/z*): 201 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.49 (s, 1H), 7.80 (s, 1H), 7.10 (s, 1H), 3.40 (t, 2H, J = 7.4 Hz), 1.82–1.72 (m, 2H), 1.56–1.43 (m, 2H), 0.98 (t, 2H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 198.5 (C=S), 135.7, 131.4, 117.8, 36.8, 29.5, 22.2, 13.7; Anal. Calcd. for $C_8H_{12}N_2S_2$: C, 47.97; H, 6.04; N, 13.98; Found: C, 47.99; H, 6.14; N, 14.01.

*4.1.5. Octyl 1H-imidazole-1-carbodithioate (**11**)*

Eluent: 20% ethyl acetate-hexane; Yield 74%; Yellow oil; IR (neat): 2927, 2855, 1653, 1465, 1368, 754 cm^{-1}; ESI-MS (*m/z*): 257 (MH^+); ^1H NMR ($CDCl_3$+CCl_4, 300 MHz): δ 8.45 (s, 1H), 7.76 (s, 1H), 7.08 (s, 1H), 3.37 (t, 2H, J = 7.4 Hz), 1.83–1.73 (m, 2H), 1.46–1.44 (m, 2H), 1.29 (bs, 8H), 0.89–0.87 (m, 3H); ^{13}C NMR ($CDCl_3$+CCl_4, 75.5 MHz): δ 197.1 (C=S), 134.7, 130.6, 116.9, 36.1, 31.0, 28.3, 28.2, 26.7, 21.8, 13.3; Anal. Calcd. for $C_{12}H_{20}N_2S_2$: C, 56.21; H, 7.86; N, 10.92; Found: C, 56.12; H, 7.84; N, 10.81.

*4.1.6. Hexadecyl 1H-imidazole-1-carbodithioate (**12**)*

Eluent: 70% ethyl acetate-hexane; Yield 55%; Yellow solid; mp 40-41 °C; IR (KBr): 2926, 2854, 1628, 1465, 1368, 761 cm^{-1}; ESI-MS (*m/z*): 369 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.48 (s, 1H), 7.79 (s, 1H), 7.10 (s, 1H), 3.38 (t, 2H, J = 7.4 Hz), 1.83–1.73 (m, 2H), 1.56–1.41 (m, 2H), 1.26 (bs, 24H), 0.88 (t, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 198.5 (C=S), 135.7, 131.5, 117.8, 37.1, 32.0, 29.8, 29.7, 29.6, 29.5, 29.2, 29.0, 27.5, 22.8, 14.2; Anal. Calcd. for $C_{20}H_{36}N_2S_2$: C, 65.16; H, 9.84; N, 7.60; Found: C, 65.24; H, 9.73; N, 7.61.

*4.1.7. 2-(1,3-Dioxoisoindolin-2-yl)ethyl 1H-imidazole-1-carbodithioate (**13**)*

Eluent: 80% ethyl acetate-hexane; Yield 57%; Yellow solid; mp 152-153 °C; IR (KBr): 2946, 2850, 1715, 1613, 1467, 714 cm^{-1}; ESI-MS (*m/z*): 318 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.44 (s, 1H), 7.88–7.86 (m, 2H), 7.76–7.74 (m, 3H), 7.09 (s, 1H), 4.13 (t, 2H, *J* = 6.4 Hz), 3.77 (t, 2H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.8 (C=S), 168.0, 135.9, 134.4, 131.9, 131.7, 123.6, 118.0, 35.5, 34.9; Anal. Calcd. for $C_{14}H_{11}N_3O_2S_2$: C, 52.98; H, 3.49; N, 13.24; Found: C, 52.92; H, 3.47; N, 13.21.

*4.1.8. Methyl-2-methyl 1H-imidazole-1-carbodithioate (**14**)*

Eluent: chloroform; Yield 88%; Semisolid; IR (neat): 2926, 2853, 1636, 1420, 761 cm^{-1}; ESI-MS (*m/z*): 173 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.57 (d, 1H, *J* = 1.5 Hz), 6.92 (d, 1H, *J* = 1.4 Hz), 2.75 (s, 3H), 2.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 201.7 (C=S), 146.7, 127.5, 119.4, 21.1, 17.8; Anal. Calcd. for $C_6H_8N_2S_2$: C, 41.83; H, 4.68; N, 16.26; Found: C, 41.78; H, 4.84; N, 16.22.

*4.1.9. 3-Cyanopropyl-2-methyl 1H-imidazole-1-carbodithioate (**15**)*

Eluent: 80% ethyl acetae-hexane; Yield 71%; Yellow oil; IR (neat): 2926, 2853, 2248, 1635, 1549, 763 cm^{-1}; ESI-MS (*m/z*): 226 (MH^+); ^1H NMR ($CDCl_3$+CCl_4, 300 MHz). δ 7.57 (d, 1H, *J* = 1.6 Hz), 6.90 (d, 1H, *J* = 1.6 Hz), 3.47 (t, 2H, *J* = 7.3 Hz), 2.72 (s, 3H), 2.53 (t, 2H, *J* = 6.9 Hz) 2.21–2.11 (m, 2H); ^{13}C NMR ($CDCl_3$+CCl_4, 75.5 MHz): δ 199.2 (C=S), 147.3, 128.3, 119.1, 118.0, 35.8, 23.9, 18.6, 16.8; Anal. Calcd. for $C_9H_{11}N_3S_2$: C, 47.97; H, 4.92; N, 18.65; Found: C, 47.92; H, 4.91; N, 18.54.

*4.1.10. Allyl 2-methyl 1H-imidazole-1-carbodithioate (**16**)*

Eluent: chloroform; Yield 90%, Semisolid; IR (neat): 2928, 2856, 1637, 1437, 760 cm^{-1}. ESI-MS (*m/z*): 199 (MH^+); ^1H NMR ($CDCl_3$+CCl_4, 300 MHz): δ 7.56 (d, 1H, *J* = 1.6 Hz), 6.88 (d, 1H, *J* = 1.6 Hz), 5.97–5.84 (m, 1H), 5.41 (dd, 1H, *J* = 1.2, 16.9 Hz), 5.28 (dd, 1H, *J* = 10.0, 1.2 Hz), 3.97 (d, 2H, *J* = 7.0 Hz), 2.71 (s, 3H); ^{13}C NMR ($CDCl_3$+CCl_4, 75.5 MHz): δ 199.7 (C=S), 146.9, 129.9, 127.9, 120.8, 119.2, 41.0, 18.3; Anal. Calcd. for $C_8H_{10}N_2S_2$: C, 48.45; H, 5.08; N, 14.13; Found: C, 48.12; H, 5.24; N, 14.34.

*4.1.11. Butyl 2-methyl 1H-imidazole-1-carbodithioate (**17**)*

Eluent: 2% methanol-chloroform; Yield 64%; Semisolid; IR (neat): 2963, 1634, 1446, 1369, 1218, 766 cm^{-1}; ESI-MS (*m/z*): 215 (MH^+); ^1H NMR ($CDCl_3$+CCl_4, 300 MHz): δ 7.55 (d, 1H, *J* = 1.6 Hz), 6.87 (d, 1H, *J* = 1.6 Hz), 3.30 (t, 2H, *J* = 7.4 Hz), 2.70 (s, 3H), 1.81–1.71 (m, 2H), 1.56–1.43 (m, 2H), 0.99 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$+CCl_4, 75.5 MHz): δ 199.8 (C=S), 145.7, 126.7, 118.3, 36.9, 28.4, 21.4, 17.2, 12.8; Anal. Calcd. for $C_9H_{14}N_2S_2$: C, 50.43; H, 6.58; N, 13.07; Found: C, 50.42; H, 6.44; N, 13.10.

*4.1.12. Octyl 2-methyl 1H-imidazole-1-carbodithioate (**18**)*

Eluent: chloroform; Yield 82%; Yellow oil; IR (neat): 2927, 2856, 1637, 1460, 763 cm^{-1}; ESI-MS (*m/z*): 271 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.57 (d, 1H, *J* = 1.7 Hz), 6.90 (d, 1H, *J* = 1.7 Hz), 3.30 (t, 2H, *J* = 7.4 Hz), 2.70 (s, 3H), 1.82–1.72 (m, 2H), 1.50–1.41 (m, 2H), 1.29 (bs, 8H), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 201.3 (C=S), 146.7,

127.6, 119.5, 38.3, 31.9, 29.8, 29.2, 27.3, 22.7, 18.0, 14.2; Anal. Calcd. for $C_{13}H_{22}N_2S_2$: C, 57.73; H, 8.20; N, 10.36; Found: C, 57.70; H, 8.21; N, 10.25.

*4.1.13. Hexadecyl 2-methyl 1H-imidazole-1-carbodithioate (**19**)*

Eluent: chloroform; Yield 51%; Yellow oil; IR (neat): 2926, 2854, 1635, 1460, 765 cm^{-1}; ESI-MS (*m/z*): 383 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.57 (d, 1H, J = 1.6 Hz), 6.90 (d, 1H, J = 1.6 Hz), 3.30 (t, 2H, J = 7.4 Hz), 2.71 (s, 3H), 1.82–1.72 (m, 2H), 1.46–1.41 (m, 2H), 1.26 (m, 24H), 0.87 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 201.3 (C=S), 146.7, 127.6, 119.5, 38.3, 32.0, 29.8, 29.8, 29.8, 29.7, 9.5, 29.5, 29.2, 29.2, 27.3, 22.8, 18.1, 14.2; Anal. Calcd. for $C_{21}H_{38}N_2S_2$: C, 65.91; H, 10.01; N, 7.32; Found: C, 66.12; H, 10.12; N, 7.40.

*4.1.14. Methyl 1H-1,2,4-triazole-1-carbodithioate (**20**)*

Eluent: 80% chloroform-hexane; Yield 58%; Yellow crystalline solid; mp 45-46 °C; IR (KBr): 2923, 2853, 1619, 1369, 766 cm^{-1}; ESI-MS (*m/z*): 160 (MH^+); ^1H NMR ($CDCl_3$+CCl_4, 300 MHz): δ 9.14 (s, 1H), 8.04 (s, 1H), 2.75 (s, 3H); ^{13}C NMR ($CDCl_3$+CCl_4, 75.5 MHz): δ 199.5 (C=S), 153.5, 143.1, 19.7; Anal. Calcd. for $C_4H_5N_3S_2$: C, 30.17; H, 3.16; N, 26.39; Found: C, 30.32; H, 3.34; N, 26.28.

*4.1.15. Allyl 1H-1,2,4-triazole-1-carbodithioate (**21**)*

Eluent: 70% chloroform-hexane; Yield 35%; Oil; IR (neat) 2925, 2854, 1637, 1437, 760 cm^{-1}; ESI-MS (*m/z*): 186 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 9.13 (s, 1H), 8.04 (s, 1H), 5.99–5.86 (m, 1H), 5.43 (dd, 1H, J = 1.0, 16.9 Hz), 5.29 (dd, 1H, J = 10.0, 0.7 Hz), 3.98 (d, 2H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 197.8 (C=S), 153.4, 143.2, 129.9, 120.9, 39.3; Anal. Calcd. for $C_6H_7N_3S_2$: C, 38.90; H, 3.81; N, 22.68; Found: C, 38.95; H, 3.82; N, 22.97.

*4.1.16. Methyl 1H-benzo[d]imidazole-1-carbodithioate (**22**)*

Eluent: 50% chloroform-hexane; Yield 84%; Yellow solid; mp 62-64 °C; IR (KBr): 2925, 2856, 1675, 1599 cm^{-1}; ESI-MS (*m/z*) 209 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.86 (s, 1H), 8.53 (dd, 1H, J = 2.3, 5.6 Hz), 7.81–7.77 (m, 1H), 7.43–7.26 (m, 2H), 2.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 199.0 (C=S), 145.4, 141.7, 132.9, 125.8, 125.2, 121.1, 115.7, 20.0; Anal. Calcd. for $C_9H_8N_2S_2$: C, 51.89; H, 3.87; N, 13.45; Found: C, 51.62; H, 3.64; N, 13.34.

*4.1.17. 3-Cyanopropyl 1H-benzo[d]imidazole-1-carbodithioate (**23**)*

Eluent: 90% chloroform-hexane. Yield 62%; Yellow oil; IR (neat): 2963, 2364, 1626, 1499, 768 cm^{-1}; ESI-MS (*m/z*): 262 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.85 (s, 1H), 8.53 (dd, 1H, J = 2.3, 5.6 Hz), 7.82–7.76 (m, 1H), 7.43–7.39 (m, 2H), 3.57 (t, 2H, J=7.2 Hz), 2.55 (t, 2H, J = 6.9 Hz), 2.23–2.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.6 (C=S), 145.2, 141.7, 132.9, 126.1, 125.6, 121.1, 118.5, 115.8, 34.8, 23.9, 16.6; Anal. Calcd. for $C_{12}H_{11}N_3S_2$: C, 55.14; H, 4.24; N, 16.08; Found: C, 55.35; H, 4.47; N, 16.24.

*4.1.18. Allyl 1H-benzo[d]imidazole-1-carbodithioate (**24**)*

Eluent: 40% chloroform-hexane. Yield 87%; Yellow oil; IR (neat): 2924, 2852, 1635, 1458, 765 cm^{-1}; ESI-MS (*m/z*): 235 (M^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.85 (s, 1H), 8.55–5.52 (m, 1H), 7.80–7.77 (m, 1H), 7.43–7.35 (m, 2H), 6.03–5.89 (m, 1H), 5.45 (d, 1H, *J* = 17.0 Hz), 5.31 (d, 1H, *J* = 10.0 Hz), 4.10 (d, 2H, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 197.2 (C=S), 145.4, 141.7, 132.9, 130.0, 125.8, 125.3, 121.1, 120.9, 115.8, 39.9; Anal. Calcd. for $C_{11}H_{10}N_2S_2$: C, 56.38; H, 4.30; N, 11.95; Found: C, 56.61; H, 4.54; N, 11.84.

*4.1.19. Butyl 1H-benzo[d]imidazole-1-carbodithioate (**25**)*

Eluent: 60% chloroform-hexane. Yield 75%; Yellow semisolid; IR (neat): 2960, 2928, 2858, 1653, 1447, 763 cm^{-1}; ESI-MS (*m/z*): 251 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.87 (s, 1H), 8.56–8.53 (m, 1H), 7.81–7.77 (m, 1H), 7.43–7.35 (m, 2H), 3.45 (t, 2H, *J* = 7.5 Hz), 1.84–1.76 (m, 2H), 1.59–1.49 (m, 2H), 1.0 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 198.5 (C=S), 145.4, 141.7, 133.0, 125.7, 125.2, 121.1, 115.9, 37.0, 29.5, 22.3, 13.7; Anal. Calcd. for $C_{12}H_{14}N_2S_2$: C, 57.56; H, 5.64; N, 11.19; Found: C, 57.38; H, 5.43; N, 11.26.

*4.1.20. Octyl 1H-benzo[d]imidazole-1-carbodithioate (**26**)*

Eluent: 40% chloroform-hexane. Yield 55%, Yellow semisolid. IR (KBr): 2926, 2856, 1656, 1447, 763 cm^{-1}. ESI-MS (m/z): 307 (MH^+). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.87 (s, 1H), 8.55 (dd, 1H, *J* = 2.2, 6.0 Hz), 7.80 (dd, 1H, *J*=3.4, 6.6 Hz), 7.43–7.35 (m, 2H), 3.44 (t, 2H, *J*=7.4 Hz), 1.88–1.85 (m, 2H), 1.55–1.49 (m, 2H), 1.47 (bs, 8H), 0.89 (t, 3H, *J* = 4.3, 2.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 198.6 (C=S), 145.4, 141.7, 133.0, 125.7, 125.2, 121.1, 115.9, 37.3, 31.9, 29.8, 29.2, 27.5, 22.8, 14.2. Anal. Calcd. for $C_{16}H_{22}N_2S_2$: C, 62.70; H, 7.24; N, 9.14; Found: C, 62.56; H, 7.34; N, 9.27.

*4.1.21. 1-Methyl-1H-benzo[d][1,2,3]triazole (**27**)*

Eluent: 50% chloroform-hexane. Yield 67%; Light green solid; mp 70-71 °C. IR (KBr): 2962, 2856, 762 cm^{-1}; ESI-MS (*m/z*): 134 (MH^+); ^1H NMR ($CDCl_3$+CCl_4, 300 MHz): δ 8.02 (d, 1H, *J* = 8.3 Hz), 7.46–7.42 (m, 2H), 7.38–7.30 (m, 1H), 4.28 (s, 3H); ^{13}C NMR ($CDCl_3$+CCl_4, 75.5 MHz,): δ 146.1, 133.6, 127.3, 109.1, 123.8, 120.2, 34.1; Anal. Calcd. for $C_7H_7N_3$ C, 63.14; H, 5.30; N, 31.56; Found: C, 63.21; H, 5.25; N, 31.61.

4.2. Biology

4.2.1. Antifungal/ Anti-*Candida activity [11]*

The MIC of compounds were determined by broth micro-dilution technique as per the guidelines of National Committee for Clinical Laboratory Standards using RPMI 1640 media buffered with MOPS [3-(N-Morpholino)propanesulfonic acid]. Starting inoculum of test culture was 1–5 x 10^3 CFU/mL. Micro titre plates were incubated at 35 °C. MICs, IC_{50} were recorded spectrophotometrically at 492 nm after 48 h of incubation (Table 1 and 2).

4.2.2. Spermicidal activity [7]

Spermicidal assay was adapted from the standard procedure. 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% test solution. 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 then placed on a microscope slide, covered with a cover glass and examined under a phase contrast microscope in five fields of vision. The percentage of motile spermatozoa was determined by visual scoring in the next 60 seconds and recorded (Table 3).

4.2.3. Anti-Trichomonas activity [11]

Trichomonas vaginalis parasites to be used in drug susceptibility assays were grown in TYM (Trypticase Yeast-Extract Maltose) medium supplemented with 10% FCS (fetal calf serum), vitamin mixture and 100.0 U/mL penicillin/streptomycin, at 37 ℃ in 15.0 mL tubes for one day, followed by regular subculturing, and were in the log phase of growth. The cultures routinely attained a concentration 2 x 10^7 cells/mL in 48 h. Inoculum of 1 x 10^4 cells per tube was used for maintenance of the culture. *In vitro* drug susceptibility assays were carried out using the standard procedure. Stock solutions (100.0 µg/mL) of test compounds were prepared in DMSO. These stock solutions were serially diluted with TYM medium to obtain concentration upto 0.1 µg/mL in 48-well plates. DMSO/TYM was used as vehicle in control wells. Parasites (5 x 10^4 trophozoites/L) were added to these wells and incubated anaerobically at 37 ℃. Cells were checked for viability at different time intervals from 3 to 48 h under the microscope at 200X magnification. Viability of the cells was determined by trypan blue exclusion assay. Minimum concentration of the test agent at which all cells were found dead in 48 h was considered as its MIC. The experiment was repeated three times to confirm the MIC (Table 3)

4.2.4. Antibacterial activity [11]

The MIC of each test compound was determined against five bacterial isolates by broth microdilution technique as per guidelines of National Committee for Clinical Laboratory Standards. MIC was measured in 96 well tissue culture plate (Cellstar Greiner Bio One, Germany) using Mueller Hinton broth media (Sigma Chemical Co.). The inoculum of the test cultures was maintained at 1-5 ×10^3 cfu/mL. Micro-titer plates were incubated at 35 ℃ in a moist, dark chamber, and MIC and IC_{50} were recorded spectrophotometrically (Softmax pro® 4.3, Versamax microplate reader at 492 nm, Molecular Devices) after 48 h (Table 1).

4.2.5. Cytotoxicity towards human cervical (HeLa) cell line by lactate dehydrogenase – release assay [11]

A colorimetric assay for lactate dehydrogenase (LDH) release was used for the evaluation of the cytotoxicity of spermicidal compounds against the HeLa cell line (Table 4). Exponentially growing HeLa cells were seeded into 96-well tissue culture plates at a density of 2 ×10^4 cells per well (in triplicate). After 24 h incubation in a CO_2 incubator at 37 ℃ in 5% CO_2 , 95% air atmosphere, the culture medium [Dulbecco's modified Eagle's medium (DMEM)] was replaced with 100.0 µL of fresh medium containing serially diluted spermicidal compounds. Control wells contained the medium only. Culture plates were incubated for another 5 h, and then 50.0 µL of the supernatant from each well of the assay plate was pipetted into the corresponding well of a flat-bottom 96-well plate. Colour reaction for LDH assay and IC_{50} measurement for cytotoxicity were performed using CytoTox-96 kit

(Promega, Madison, WI, USA) by following the instructions of the manufacturer. Optical densities at 490 nm were measured in a micro-plate reader (μQuant, Bio-Tek, USA).

4.2.6. Effect on Lactobacillus acidophillus in vitro [11]

The effect of compounds exhibiting potent spermicidal activity on *Lactobacillus acidophillus* was determined by following the method published earlier [11]. Briefly, Rogosa SL agar plates (7.5%; containing 0.132% acetic acid), prepared with (experimental) or without (control) the addition of spermicidal compounds, were inoculated with *L. acidophillus* (~70 spores/10 cm^2) and incubated at 37 °C in 5% CO_2 and 95% air for 72 h. The number and size of colonies were recorded at the end of the experiment. The average colony size (% of control) was multiplied by the colony number and divided by 100 to arrive at the data presented. The aver-age colony size for the control was taken as 100% (Table 4).

4.3. Molecular modelling and docking studies

Minimized 3D structure of inhibitors except Fluconazole was generated by Sybyl7.1 [28] and used for docking study. Docking was carried out with inhibitors (Fluconozole, compounds **10**, **17**, **20**, **22**) using Autodock 3 [29]. Bound Fluconozole coordinate information was obtained from 3LD6 [30] and docking was performed to investigate that whether its binding to *C. albicans* CYP51 is similar or not. After getting the conformation close to co-crystallized Fluconazole, docking with other inhibitors was carried out. Heme group was processed separately by manually assigning the +3 charge on Fe and co-ordinate information was finally merged with receptor. Grid box was centred on Heme group and Lamarckian genetic algorithm [31] was used for calculation of 50 docking pose for each compound (Table 5).

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Supplementary data

Supplementary data like scan copies of ^{1}H NMR and ^{13}C NMR spectra can be found at http://dx.doi.org/

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Captions

Figure 1. Chemical structures of known antifungal agents **1-5** and azole-carbodithioate hybrids **6**

Scheme 1. Synthetic strategy for azole-carbodithioate hybrids **7**–**27**

Table 1. *In vitro* Antifungal and Antibacterial[a] activity of compounds **7-27**

Table 2. *In vitro* anti-*Candida* activity of compounds **7**–**27**

Table 3. Sperm immobilization and anti-*Trichomonas* activity of compounds **7**–**27**

Table 4. Toxicity of compounds **10**, **17**, **20**, **22**

Table 5. Docked energy and IC_{50} of compounds **10**, **17**, **20**, **22**

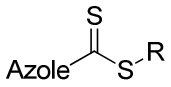
Figure 2. Docked conformation of compounds **10** (a), **17** (b), **20** (c) and **22** (d) into active site of *Candida albicans* Cyp51. Protein residues are shown in hot pink color with both stick and surface representaions. All docked compounds are shown in green color. Only polar hydrogens are shown for clarity.

Table 1.

Compound	Azole	R	Antifungal activity (IC_{50} in µg/mL) against[b]			
			Ss	Tm	Af	Cn
7		methyl	>50	>50	>50	>50
8		cyanopropyl	>50	ND	>50	>50
9		allyl	4.96	4.43	>50	5.75
10		butyl	>50	>50	ND	3.79
11		octyl	ND	1.48	6.21	>50
12		decahexyl	>50	18.43	>50	>50
13		ethylphthalimide	4.17	6.15	>50	28.59
14		methyl	4.41	11.68	>50	9.10
15		cyanopropyl	>50	24.93	>50	>50
16		allyl	1.50	>50	18.10	3.35
17		butyl	5.71	2.02	23.79	5.57
18		octyl	4.47	>50	>50	>50
19		decahexyl	>50	7.07	>50	>50
20		methyl	4.34	>50	>50	>50
21		allyl	5.78	>50	>50	>50
22		methyl	1.54	2.42	24.39	0.69
23		cyanopropyl	ND	ND	>50	>50
24		allyl	ND	>50	>50	>50
25		butyl	>50	1.40	>50	>50
26		octyl	>50	>50	>50	>50
27			1.58	>50	>50	>50
Fluconazole.			0.08	0.06	0.38	0.46

[a]Compounds (**7**–**27**) showed MIC at >50 µg/mL against four bacterial strains: *E. coli* (ATCC 9637), *Pseudomonas aeruginosa* (ATCC BAA-427), *Staphylococcus aureus* (ATCC 25923), *Klebsiella pneumonia*. [b]Ss: *Sporothrix schenckii*; Tm: *Trichophyton mentagrophytes*; Af: *Aspergillus fumigatus*; Cn: *Cryptococcus neoformans.*

Table 2.

Compound			Anti-*Candida* activity (IC_{50} in µg/mL) against[a]					
	Azole	R	Ca	Cp	PK3	PK9	PK13	PK30
7		methyl	5.75	>50	>50	>50	>50	>50
8		cyanopropyl	>50	5.27	>50	43.49	>50	10.77
9		allyl	>50	2.09	6.79	3.94	7.26	1.80
10		butyl	1.29	1.94	5.41	6.17	3.50	1.53
11		octyl	5.72	>50	4.61	31.39	7.68	1.06
12		decahexyl	>50	>50	>50	>50	>50	>50
13		ethylphthalimide	5.45	>50	11.09	30.95	19.53	16.02
14		methyl	7.24	>50	37.29	>50	36.82	25.95
15		cyanopropyl	36.03	>50	41.03	47.69	>50	>50
16		allyl	2.21	10.15	3.61	7.26	4.53	2.10
17		butyl	1.34	>50	4.69	7.64	5.09	2.12
18		octyl	7.21	>50	>50	19.03	>50	>50
19		decahexyl	>50	>50	>50	>50	>50	>50
20		methyl	1.43	>50	31.17	>50	38.03	>50
21		allyl	2.53	>50	>50	45.49	>50	>50
22		methyl	1.26	1.46	1.79	3.33	1.79	1.75
23		cyanopropyl	>50	>50	>50	3.86	>50	>50
24		allyl	>50	>50	40.09	39.32	>50	>50
25		butyl	6.39	>50	21.80	37.37	>50	>50
26		octyl	>50	>50	>50	>50	>50	>50
27			>50	>50	>50	>50	>50	>50
Fluconazole			0.13	0.46	0.21	-	-	-

[a]Ca: *Candida albicans*, Cp: *Candida parapsilosis* (cp ATCC- 22019), PK3: *Candida albicans* (MTCC-183), PK9: *Candida albicans* (patient isolate CDRI), PK13: *Candida albicans* (ATCC-10231), PK30: *Candida albicans* (patient isolate)

Table 3.

Compound	Percent sperm immobilizationtion		Anti-*Trichomonas* activity (MEC in µg/mL)
	1.0% (w/v)	0.1% (w/v)	
7	100%	0%	>200
8	100%	92-95%	>200
9	100%	0%	>200
10	100%	80%	>200
11	100%	80%	>200
12	100%	0%	>200
13	100%	0%	>200
14	100%	0%	>200
15	95%	0%	>200
16	100%	0%	>200
17	100%	0%	>200
18	100%	100%	>200
19	95%	0%	>200
20	100%	0%	>200
21	100%	0%	>200
22	100%	80%	>200
23	100%	0%	>200
24	100%	0%	>200
25	100%	0%	>200
26	95%	0%	>200
27	0%	0%	>200
Nonoxynol-9	100%	100%	37.4
Metronidazole	0%	0%	2.0

Table 4.

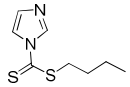
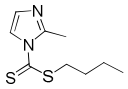
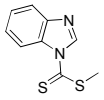
Compound	Structure	HeLa cell (IC_{50} in µg/mL)	*Lactobacillus acidophillus* (IC_{50} in µg/mL)
10		48.70	45.64
17		85.45	220.0
20		53.69	39.54
22		73.60	45.63
Nonoxynol-9		37.00	21.00

Table 5.

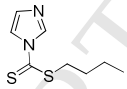
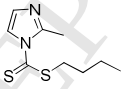
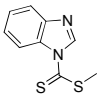
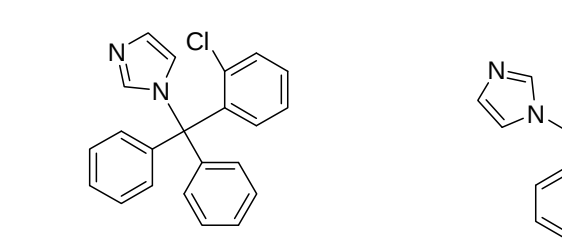
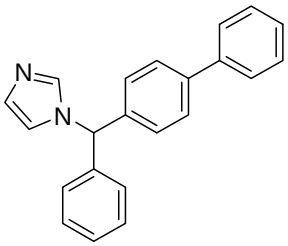
Compound	Structure	Anti-*Candida* activity (IC_{50} in µg/mL)	Docked energy (in Kcal/mole)
10		1.29	-7.78
17		1.34	-8.17
20		1.43	-5.74
22		1.26	-7.62
Fluconazole		0.13	-7.30

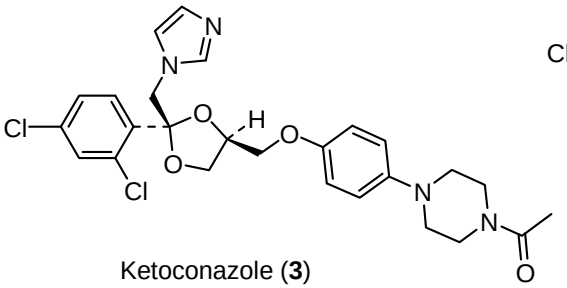
Figure 1.



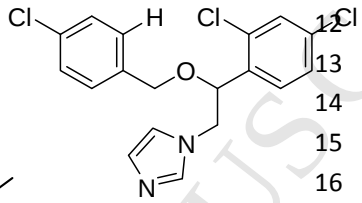
Clotrimazole (**1**)



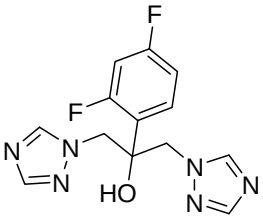
Bifonazole (**2**)



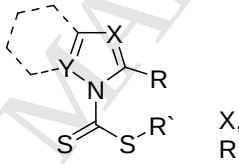
Ketoconazole (**3**)



Econazole (**4**)



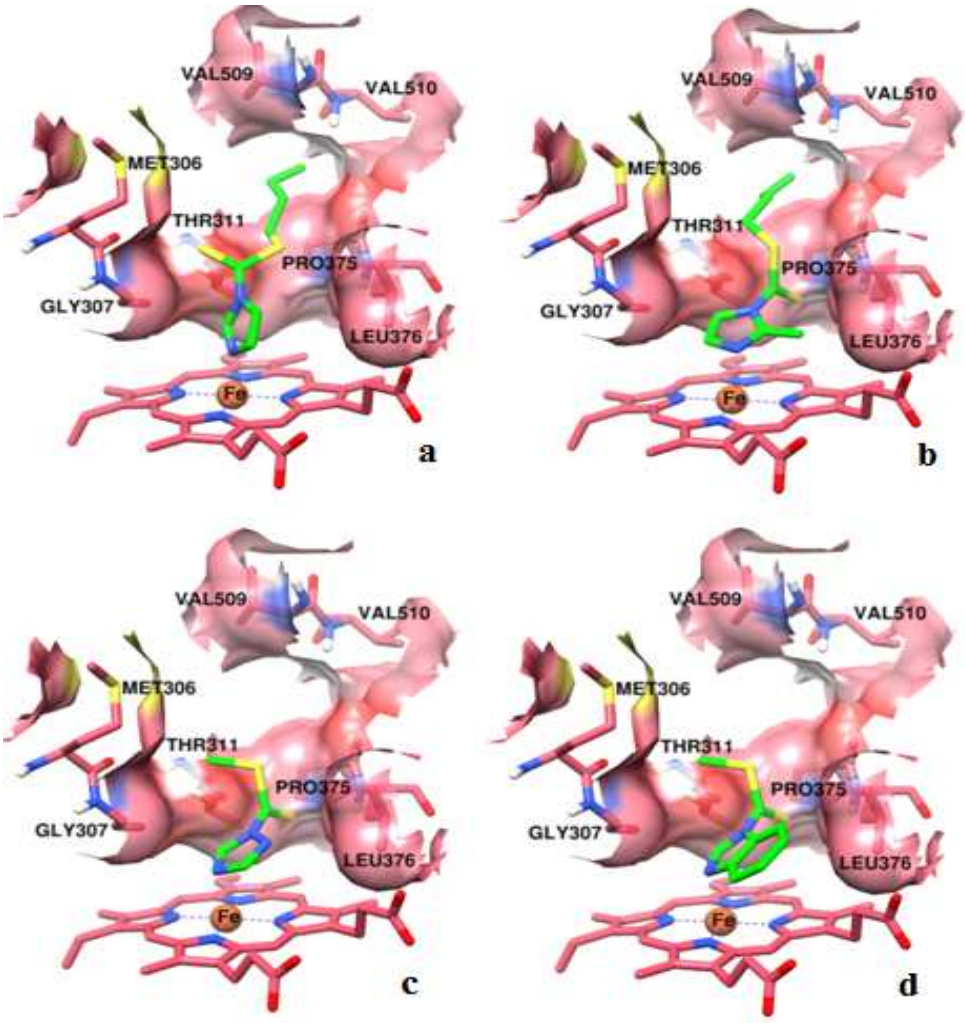
Fluconazole (**5**)



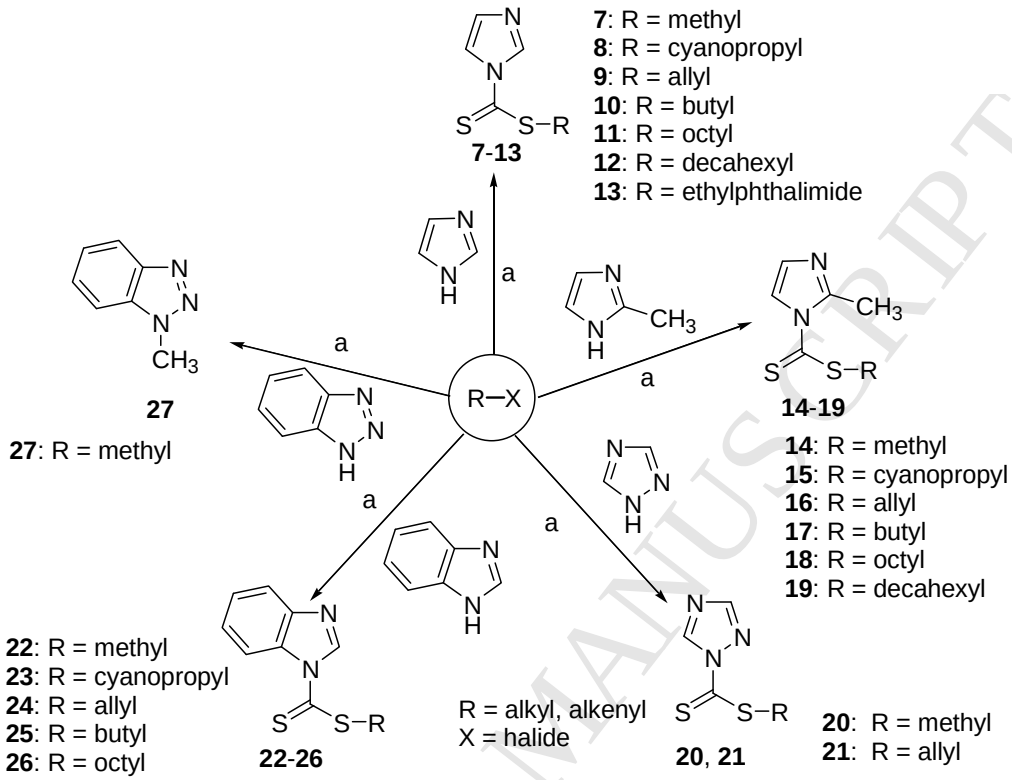
Azole-Carbodithioate Hybrids (**6**)

X, Y : N, CH
R, R`: alkyl

Figure 2.



Scheme 1.



Reagent and conditions; a: CS_2, NaH, THF, 0-5 °C - rt, 3-5 h.

Research Highlights

- Azole and carbodithioate hybrids were synthesized.
- Compounds were evaluated for spermicidal/microbicidal activity.
- Sixteen compounds were dually active against sperm and *Candida*.
- Promising compounds were safer than Nonoxynol-9.
- Docking study provided guidelines for designing anti-*Candida* agents.