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RESEARCH ARTICLE

Synthesis, characterization, and antimicrobial evaluation of some new hydrazinecarbothioamide, 1,2,4-triazole and 1,3,4-thiadiazole derivatives

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Abstract

In this work, we reported the synthesis and evaluation of antibacterial and antifungal activities of three new compound series obtained from 6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazole-3-acetic acid hydrazide: 2-{[6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetyl}-N-alkyl/arylhydrazinecarbothioamides (**2a–d**), 4-alkyl/aryl-2,4-dihydro-5-{[6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl]methyl}-3*H*-1,2,4-triazole-3-thiones (**3a–n**), and 2-alkyl/arylamino-5-{[6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl]methyl}-1,3,4-thiadiazoles (**4a–g**). The newly synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR (APT), mass and elemental analysis. Their antibacterial and antifungal activities were evaluated against *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, *Candida albicans* ATCC 10231, *C. parapsilosis* ATCC 22019, *C. krusei* ATCC 6258, *Trichophyton mentagrophytes var. erinacei* NCPF 375, *Microsporum gypseum* NCPF 580, and *T. tonsurans* NCPF 245. **3c, 3f**, **3m, 3n,** and **4e** showed the highest antibacterial activity. Particularly **3c, 3f, 3g, 3k, 3n, 4a, 4e,** and **4g** showed the highest antifungal activity against tested fungi.

Keywords: Imidazo[2,1-b]thiazole, hydrazinecarbothioamide, 1,2,4-triazole, 1,3,4-thiadiazole, antibacterial activity, antifungal activity

Introduction

The rapidly expanding population of immunocompromised patients results in a corresponding increase of diseases caused by bacteria, yeasts, and other fungi. Although not life-threatening, superficial mycosis and infections of keratinized tissues such as nails, skin, and hair cause prolonged periods of distress. Dermatophytoses which are most prevalent among superficial mycosis are currently treated by the imidazole derivatives clotrimazole, miconazole, econazole, (Figure 1) and other azole antifungals which interfere with fungal ergosterol synthesis by inhibiting lanosterol 14-demethylase[1]. Meanwhile, fusion of imidazole and thiazole moieties into a single drug gave a potent immunomodulating drug called levamisole, which is 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole (Figure 1) [2]. The imidazo[2,1-*b*]thiazole derivatives have been reported in the literature as antibacterial[3], antifungal[4], and antitumour[5] agents. On the other hand, there are a number of antimicrobial compounds containing a 1,2,4-triazole ring in their structures such as fluconazole and ravuconazole, that are important antifungal drugs (Figure 1)[6].

Heterocycles containing a 1,2,4-triazole or 1,3,4-thiadiazole moiety, and the compounds consisting of 1,2,4-triazole and 1,3,4-thiadiazole condensed nucleus systems constitute a class of compounds possessing a wide spectrum of biological activities such as antibacterial[7], antifungal[8], antitubercular[9], anticonvulsant[10], anticancer[11] activities.

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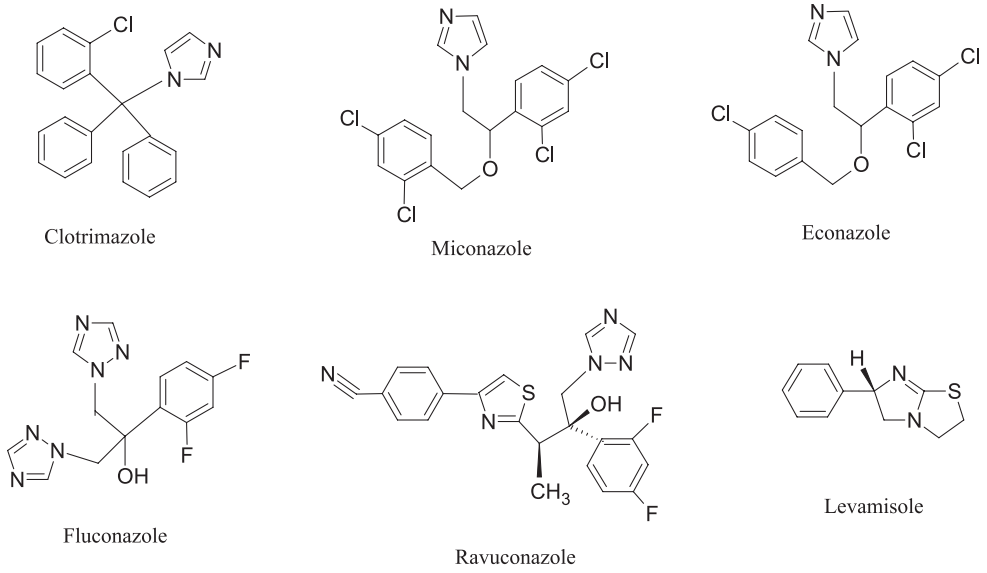


Figure 1. Chemical structures of some azole antifungals and Levamisole.

In view of these facts and as a continuation of our research on the biological properties of 1,2,4-triazole- and 1,3,4-thiadiazole containing derivatives[12–18], we have designed and synthesized a number of imidazo[2,1-*b*]thiazole substituted fused 1,2,4-triazole and 1,3,4-thiadiazole systems, as potential antibacterial and antifungal agents.

Materials and methods

Chemistry

All chemicals for synthesis were commercially available. Melting points were determined by using a Büchi 530 melting point apparatus (Flawil, Switzerland) in open capillary tubes and are uncorrected. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer (Milano, Italy). IR spectra were recorded on KBr discs, using a Perkin Elmer 1600 FT-IR spectrophotometer (Waltham, MA, USA). ^{1}H NMR (*DMSO*-d_6/*TMS*) and ^{13}C NMR (Attached Proton Test) (*DMSO*-d_6/*TMS*) spectra were measured on Bruker AC 200 (200 MHz), Varian^{UNITY} INOVA (500 MHz) spectrometer. Electron impact mass spectra were recorded on a VG Zab Spec (70 eV) instrument. The starting materials were either commercially available or synthesized according to the references cited.

General procedure of the synthesis of 2-{[6-(phenyl/4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl]acetyl}-N-alkyl/arylhydrazinecarbothioamides (2a–d)

To a solution of 6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazole-3-acetic acid hydrazide (0.005 mol) (**1**) in EtOH (30 mL), an appropriate isothiocyanate (0.005 mol) was added. The resulting mixture was heated under reflux for 3 h. After cooling, the precipitate was separated and purified by washing with hot EtOH.

2-{[6-Phenylimidazo[2,1-b]thiazol-3-yl]acetyl}-N-phenylhydrazinecarbothioamide (2a)

IR (KBr, ν, cm^{-1}): 3215 (N-H), 1670 (C=O); ^{1}H NMR (200 MHz, δ, ppm, DMSO-d_6): 3.88 (s, 2H, CH_2CO), 7.09 (s, 1H, C_2-H), 7.14–7.57 (m, 8H, ar), 7.79 (d, 2H, *J* = 7.3 Hz, ar), 8.22 (s, 1H, C_5-H), 9.64 (s, 1H, NH), 9.77 (s, 1H, NH), 10.36 (s, 1H, NH); EIMS (70 eV) *m/z* (%): 407 (M^+, 0.3), 272 (58), 241 (16), 214 (44), 135 (100), 93 (37), 77 (92).

General procedure of the synthesis of 4-alkyl/aryl-2,4-dihydro-5-{[6-(phenyl/4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl]methyl}-3H-1,2,4-triazole-3-thiones (3a–n)

A solution of an appropriate hydrazinecarbothioamide (0.005 mol) (**2**) in 2 N aqueous NaOH (20 mL) was heated under reflux for 2 h. After cooling the reaction mixture was acidified by the addition of 12.5% aqueous HCl. The precipitate thus obtained was collected by filtration, washed with water several times and purified by washing with hot C_2H_5OH.

4-Methyl-2,4-dihydro-5-{[6-phenylimidazo[2,1-b]thiazol-3-yl]methyl}-3H-1,2,4-triazole-3-thione (3a)

IR (KBr, ν, cm^{-1}): 3432 (N-H), 1602, 1579, 1513, 1491 (C=N, C=C); ^{1}H NMR (500 MHz, δ, ppm, DMSO-d_6): 3.49 (s, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.15 (s, 1H, C_2-H), 7.23–7.26 (m, 1H, ar), 7.36–7.39 (m, 2H, ar), 7.79 (d, 2H, *J* = 8.3 Hz, ar), 8.19 (s, 1H, C_5-H), 13.60 (s, 1H, NH). ^{13}C NMR (APT) (125 MHz, δ, ppm, DMSO-d_6): 24.98 (CH_2), 30.69 (CH_3), 109.27 (C_5), 111.42 (C_2), 125.78 (C_3), 125.31, 127.74, 129.36, 134.87 (ar C), 146.70 (C_6), 149.29 (C_{7a}), 148.75 (triazole C_5), 167.86 (C=S).

4-Phenyl-2,4-dihydro-5-{[6-(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl]methyl}-3H-1,2,4-triazole-3-thione (3n)

IR (KBr, ν, cm^{-1}): 3480, 3103 (O-H/N-H), 1592, 1579, 1535, 1496 (C=N, C=C); ^{1}H NMR (500 MHz, δ, ppm, DMSO-d_6): 4.13 (s, 2H, CH_2), 6.94 (s, 1H, C_2-H), 7.43–7.45 (m, 2H, ar), 7.48–7.53 (m, 3H, ar), 7.55–7.58 (m, 2H, ar), 7.81 (d, 2H, *J* = 8.4 Hz, ar), 8.17 (s, 1H, C_5-H), 13.82 (s, 1H, NH).

General procedure of the synthesis of 2-alkyl/arylamino-5-{[6-(phenyl/4-chlorophenyl) imidazo[2,1-b]thiazol-3-yl]methyl}-1,3,4-thiadiazoles (4a–g)

The appropriate hydrazinecarbothioamide (0.005 mol) (**2**) was dissolved in 5.3 ml of H_2SO_4 (96%) and allowed to stand for 30 min. The solid then was poured in crushed ice and neutralized with Na_2CO_3. The precipitate thus obtained was filtered and recrystallized from C_2H_5OH-H_2O.

2-Methylamino-5-{[6-phenylimidazo[2,1-b]thiazol-3-yl] methyl}-1,3,4-thiadiazoles (4a)

IR (KBr, ν, cm^{-1}): 3284 (N-H), 1543, 1470, 1440, 1400 (C=N, C=C); ^{1}H NMR (500 MHz, δ, ppm, DMSO-d_6): 2.83 (s, 3H, CH_3), 4.49 (s, 2H, CH_2), 7.10 (s, 1H, C_2-H), 7.23–7.27 (m, 1H, ar), 7.36–7.40 (m, 2H, ar), 7.62 (q, 1H, J = 4.8 Hz, NH), 7.80 (d, 2H, J = 8.3 Hz, ar), 8.14 (s, 1H, C_5-H). ^{13}C NMR (APT) (125 MHz, δ, ppm, DMSO-d_6): 28.74 (CH_2), 31.87 (CH_3), 108.77 (C_5), 110.61 (C_2), 128.83 (C_3), 125.39, 127.80, 129.37, 134.79 (ar C), 146.86 (C_6), 149.45 (C_{7a}), 152.63 (thiadiazole C_5), 170.73 (thiadiazole C_2).

Microbiology

All compounds to be tested were dissolved in DMSO at a stock concentration of 3200 μg.cm^{-3}. The final desired concentration were prepared with RPMI 1640 medium for *Candida* species and dermatophytes and with Mueller-Hinton broth of bacteria. The final DMSO concentration was reduced to 1%.

Antibacterial activity

Minimum inhibitory concentrations (MICs) were determined by the microbroth dilution method using the National Committee for Clinical Laboratory Standards (NCCLS) recommendations[19]. Mueller-Hinton broth (Oxoid, Hemakim, Turkey) was used as the test medium. An inoculum of ~5×10^5 CFU.cm^{-3} was delivered per well. Serial twofold dilutions of the test compounds (64–0.25 μg.cm^{-3}) and extra dilutions (0.12–0.015 μg cm^{-3}) for antibiotic standards were prepared. Plates were incubated for 16–20 h at 35°C in an ambient air incubator. The lowest concentration of the test compounds inhibiting visible growth was taken as the MIC value.

Antifungal activity

Antifungal activity for Candida *species*

MICs were determined by the microbroth dilution method using the NCCLS recommendations[20]. RPMI broth was prepared from RPMI 1640 medium (Sigma, St. Louis, MO) supplemented with 0.3 g of glutamine/dm^3, bufferred with 3-(N-morpholino)-propanesulfonic acid (MOPS), and adjusted to pH 7.0. A working suspension of the inoculum was prepared by a 1:100 dilution of the 0.5 McFarland standards yeast suspension in 0.85% saline followed by a 1:20 dilution in RPMI broth.

Twofold dilutions of test compounds from 64 to 0.25 μg cm^{-3} were prepared with the working suspension of the inoculum. Extra dilutions (0.12–0.015 mg.cm^{-3}) were added for itraconazole. The plates were incubated at 35°C for 48 h in ambient air. The MIC is the lowest concentration of a compound that inhibits growth of the organism as detected visually.

Antifungal activity for dermatophytes

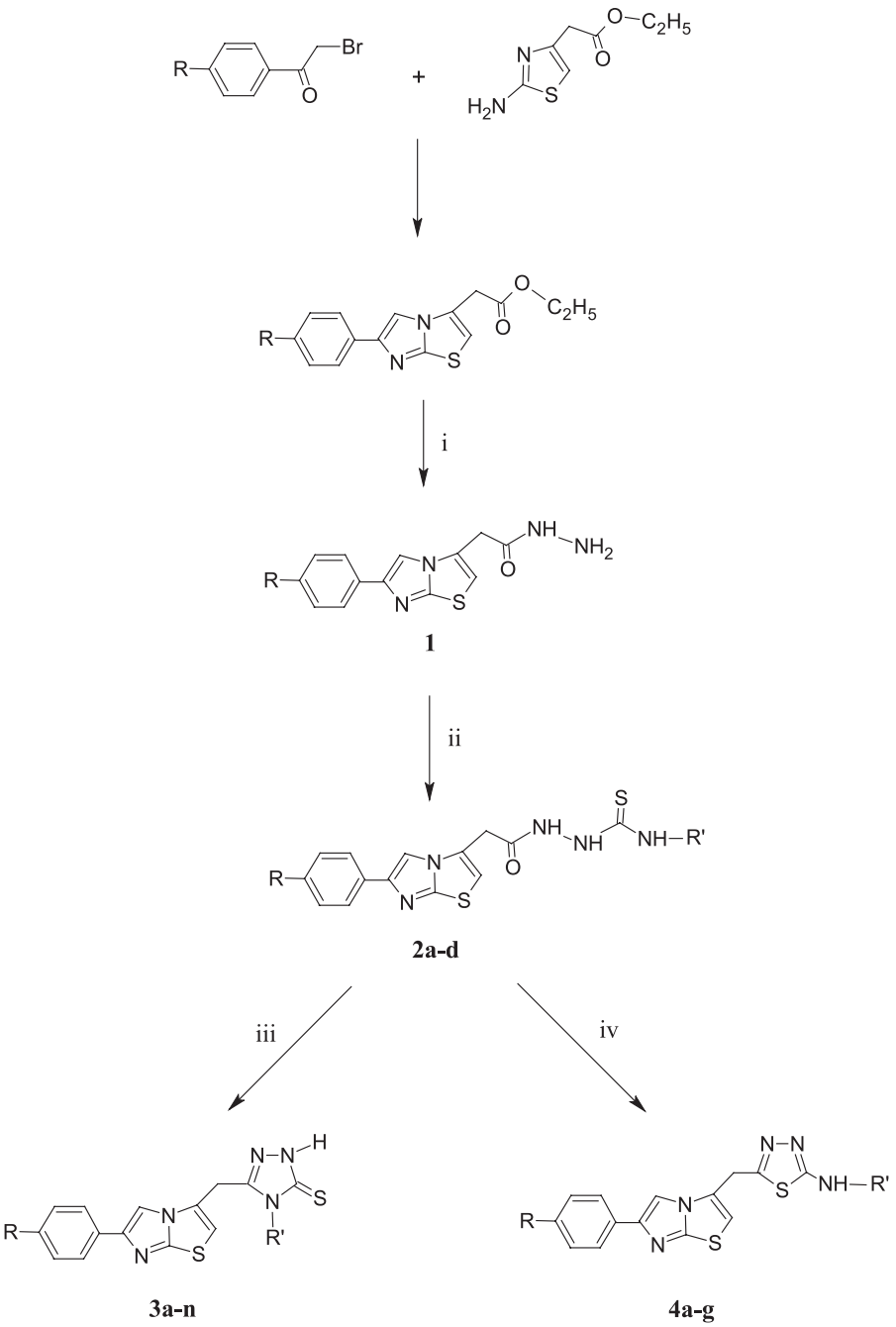
Microdilution method was used according to a standard protocol by NCCLS[19]. RPMI 1640 broth with L-glutamine without sodium bicarbonate was and 0.165 M MOPS buffer (34.54 g/lt) and used. The medium was adjusted to pH 7.0 at 25°C. Preparation of inoculum suspensions of dermatophytes were based according to the NCCLS guidelines[21] and previously described procedure[22].

The isolates were subcultured on to potato dextrose agar plates at 28°C, during 7–14 days. The fungal colonies were covered with 1 mL of sterile 0.85% saline, and suspensions were made by gently probing the surface with the tip of Pasteur pipette. The resulting mixture of conidia and hyphal fragments was withdrawn and transferred to a sterile tube. Heavy particles were allowed to settle for 15–20 min at room temperature; the upper suspension was mixed with a vortex for 15 s. The turbidity of supernatants was measured spectrophotometrically at a wavelength of 530 nm, and transmission was adjusted to 65–75 %. These stock suspensions were diluted to 1:50 in RPMI medium to obtain the final inoculum sizes, which range from 0.4×10^4 to 5×10^4 CFU/mL. Microdilution plates were prepared and frozen at –70°C until needed. Rows from 2 to 12 contained the series of drug dilutions in 100 μL volumes and first row contained 100 μL of drug-free medium, which served as the growth control. Each well was inoculated on the day of the test with 100 μL of the corresponding inoculum. This step brought the drug dilutions and inoculum size to the final test concentrations given above. The microplates of dermatophytes were incubated at 28°C during 7 days. The microplates were read visually with the aid of an inverted reading mirror after 7 days for dermatophytes. For all drugs, the MIC was defined as the lowest concentration showing 100% inhibition of growth.

Results and discussion

The target compounds were prepared from 6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazole-3-acetic acid hydrazide (**1**) [2], by a three step synthesis as shown in Scheme 1. 2-{[6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*] thiazol-3-yl]acetyl}-N-alkyl/arylhydrazinecarbothioamides (**2a–d**) were obtained from **1** and the corresponding alkyl/arylisothiocyanates.

Alkaline cyclisation of the compounds **2** using sodium hydroxide afforded the corresponding 4-alkyl/aryl-2,4-dihydro-5-{[6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*] thiazol-3-yl]methyl}-3*H*-1,2,4-triazole-3-thiones (**3a–n**). The reaction of hydrazinecarbothioamide (**2**) with



Scheme 1. Synthesis of the title compounds: (i) $NH_2NH_2.H_2O$, (ii) R′NCS, (iii) NaOH, (iv) H_2SO_4.

concentrated sulphuric acid at room temperature resulted in the formation of the corresponding 2-alkyl/arylamino-5-{[6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl]methyl}-1,3,4-thiadiazoles (**4a–g**).

The structures of the synthesized compounds were confirmed by analytical (**Supplementary Table 1**) and spectral data (IR, ^{1}H NMR, ^{13}C NMR, EIMS). The IR spectra of **2a–d**, **3a–n**, and **4a–g** exhibited N-H bands in the 3500-3195, 3500-3102, and 3284-3181 cm^{-1}, respectively. The absorption bands at 1613-1436 and 1624-1400 cm^{-1} are due to the presence of -C=N- stretch of the triazole and thiadiazole ring system, respectively. The C=O stretchings of **2a–d** were observed at 1676-1670 cm^{-1}. Absence of the C=O absorptions in **3a–n** and **4a–g** provided definitive proof for the formation of new products. The three ^{1}H NMR resonances located in the region of 10.40-8.08 ppm were assigned to the NH protons of the carbothioamides and supported the structures of **2a–d**[23]. The ^{1}H NMR of **3a–n** (except **3c, 3e,** and **3i**) showed single NH resonances in the region of 13.93-13.57 ppm. In the ^{1}H NMR spectra of **3c, 3e,** and **3i**, the NH protons were not observed due to rapid proton deuteron exchange reaction in deuterated dimethyl sulfoxide solvent. In the ^{1}H NMR spectra of **4b**, **4f**, **4g,** and **4e**, the NH proton at 2-position of 1,3,4-thiadiazole ring appeared at 7.63, 8.19, 10.32 ppm as a singlet and 7.48-7.44 ppm together

with Ar-H as a multiplet, respectively. In the ^{1}H NMR spectra of **4a**, **4c,** and **4d**, the NH proton appeared at 7.62 and 7.67 ppm as a quartet and triplet, respectively. The exocyclic -CH_2- protons of **3a–n** and **4a–g** resonated at 4.13–4.51 and 4.48–4.60 ppm, respectively. The protons of the imidazo[2,1-*b*]thiazole nucleus and the other protons resonated at the expected regions[24]. In the APT ^{13}C NMR spectra of **3a** and **4a** chosen as prototypes, all the carbons resonated in the expected regions[24]. The EIMS of compounds **2a**, **2d**, **3f**, **3k**, **4b,** and **4e** displayed molecular ions which confirmed their molecular weights. Fragmentation followed the route in accordance with literature[25].

Compounds **2a–d**, **3a–n,** and **4a–g** were evaluated for *in vitro* antibacterial activity against *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, and *Escherichia coli* ATCC 25922 as well as for antifungal activity against *Candida albicans* ATCC 10231, *C. parapsilosis* ATCC 22019, *C. krusei* ATCC 6258, *Trichophyton mentagrophytes var. erinacei* NCPF 375, *Microsporum gypseum* NCPF 580 and, *T. tonsurans* NCPF 245 using the microbroth dilution method[19]. As can be seen in **Supplementary Table 2**, 3f (R = H, R′ = C_6H_5), **3n** (R = Cl, R′ = C_6H_5), and **4e** (R = Cl, R′ = C_3H_7), showed the highest activity against *S. aureus* ATCC 29213 and *E. coli* ATCC 25922 (MIC = 32 μg.cm^{-3}). **3c** (R = H, R′ = C_3H_7), showed the highest activity against *E. coli* ATCC 25922 (MIC = 32 μg.cm^{-3}). **3m** (R = Cl, R′ = allyl), showed the highest activity against *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 25922 (MIC = 32 μg.cm^{-3}). Derivatives **3c** (R = H, R′ = C_3H_7), were most active against *M. gypseum* NCPF 580 (MIC = 8 μg.cm^{-3}, Table 1).

Compounds **3c** (R = H, R′ = C_3H_7) and **3n** (R = Cl, R′ = C_6H_5) showed the highest activity against *C. parapsilosis* ATCC 22019 (MIC = 16 μg.cm^{-3}). Compounds **3g** (R = H, R′ = 4-ClC_6H_4) and **3n** (R = Cl, R′ = C_6H_5) showed the highest activity against *C. krusei* ATCC 6258 (MIC = 16 μg.cm^{-3}). Compounds **3f** (R = H, R′ = C_6H_5), **3k** (R = Cl, R′ = C_3H_7), **3n** (R = Cl, R′ = C_6H_5), **4a** (R = H, R′ = CH_3), **4e** (R = Cl, R′ = C_3H_7), and **4g** (R = Cl, R′ = C_6H_5) showed the highest activity against *T. mentagrophytes var. erinacei* NCPF 375 (*MIC* = 16 μg.cm^{-3}). Compounds **3f** (R = H, R′ = C_6H_5), **3k** (R = Cl, R′ = C_3H_7), **3n** (R = Cl, R′ = C_6H_5) showed the highest activity against *M. gypseum* NCPF 580 (MIC = 16 μg.cm^{-3}). Compounds **3c** (R = H, R′ = C_3H_7), **3f** (R = H, R′ = C_6H_5), **3g** (R = H, R′ = 4-ClC_6H_4), **3k** (R = Cl, R′ = C_3H_7), **3n** (R = Cl, R′ = C_6H_5), **4a** (R = H, R′ = CH_3), **4e** (R = Cl, R′ = C_3H_7), and **4g** (R = Cl, R′ = C_6H_5) also showed the highest activity against *T. tonsurans* NCPF 245 (MIC = 16 μg.cm^{-3}). As can be seen from **Supplementary Table 2** and Table

Table 1. Antifungal activity of compounds **2a–d**, **3a–n**, and **4a–g** (MIC μg/mL).

Compound	*Candida albicans* ATCC 10231	*Candida parapsilosis* ATCC 22019	*Candida krusei* ATCC 6258	*Trichophyton mentagrophytes var. erinacei* NCPF 375	*Microsporum gypseum* NCPF 580	*Trichophyton tonsurans* NCPF 245
2a	>64	64	>64	64	>64	64
2b	>64	64	64	64	>64	64
2c	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
2d	>64	>64	>64	>64	>64	>64
3a	64	>64	>64	>64	>64	64
3b	>64	64	32	64	32	64
3c	32	16	32	32	8	16
3d	64	>64	64	64	64	64
3e	>64	>64	>64	>64	64	>64
3f	64	32	32	16	16	16
3g	64	32	16	32	32	16
3h	>64	32	64	>64	64	>64
3i	32	32	64	32	32	64
3j	64	64	64	64	64	>64
3k	64	32	32	16	16	16
3l	>64	64	>64	64	64	64
3m	32	64	32	32	32	32
3n	32	16	16	16	16	16
4a	64	32	64	16	32	16
4b	64	64	>64	64	32	64
4c	>64	>64	>64	32	>64	>64
4d	64	>64	64	32	>64	>64
4e	32	64	64	16	32	16
4f	64	>64	>64	64	>64	64
4g	32	32	32	16	32	16
Itraconazole	0.12	0.06	0.12	n.t.	n.t.	n.t.
Amphotericin B	n.t.	n.t.	n.t.	0.5	0.5	0.25

MIC, minimum inhibitory concentration; n.t., not tested.

1, triazole (**3a–n**) and thiadiazole derivatives (**4a–g**) were generally more active than the hydrazinecarbothioamide derivatives (**2a–d**). The antimicrobial activity results indicated that some of the tested compounds showed the most promising antibacterial and antifungal activities.

In summary, a new series of hydrazinecarbothioamides **2a–d**, 1,2,4-triazoles **3a–n**, and 1,3,4-thiadiazoles **4a–g** have been synthesized and evaluated for their antibacterial and antifungal activities. Derivatives **3c** (R = H, R′ = C_3H_7), were most active against *M. gypseum* NCPF 580 (MIC = 8 μg.cm^{-3}). Triazole (**3a–n**) and thiadiazole derivatives (**4a–g**) were generally more active than the hydrazinecarbothioamide derivatives **2a–d**. The antimicrobial activity results indicated that some of the tested compounds showed the most promising antibacterial and antifungal activities. Further studies are in progress in our laboratories and will be reported upon in the future.

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Declaration of interest

The authors report no conflicts of interest.

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