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ORIGINAL ARTICLE

Synthesis, Characterization, and Antimicrobial Activity of Some New 2,4-Dihydro-3*H*-1,2,4-Triazole-3-thione Derivatives

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ABSTRACT

Objectives: Antimicrobial resistance is a major problem in the treatment of infectious diseases. Therefore, it is important to develop new and effective antimicrobial agents. For this purpose, a new series of compounds with a 2,4-dihydro-3*H*-1,2,4-triazole-3-thione structure was synthesized.

Materials and Methods: 2,4-dihydro-3*H*-1,2,4-triazole-3-thione compounds (T1-T8) were synthesized by heating thiosemicarbazide derivatives under alkaline conditions. Infrared (IR), ^{1}H-NMR, and ^{13}C-NMR spectroscopic methods were used to elucidate the chemical structures of the compounds. The antimicrobial activity of the compounds against eight bacterial strains (five Gram-negative and three Gram-positive) and two fungal strains was evaluated using the microdilution method.

Results: Compounds T4, carrying a benzoyl group, and T6, carrying a phenethyl group, showed the best antibacterial activity against *Enterococcus faecalis* ATCC 29212, with minimum inhibitory concentrations (MICs) of 41.79 mg/L and 81.25 mg/L, respectively. Compound T6 also demonstrated the strongest antibacterial activity against *Staphylococcus epidermidis* ATCC 12228, with an MIC of 40.62 mg/L. Antifungal activity assays revealed that compounds T4, T6, and T8 were the most potent against *Candida albicans* ATCC 90028, with MIC values of 40.62–83.59 mg/L, and that T6, T7, and T8 were the most potent against *Candida glabrata* ATCC 90030, with MIC values of 40.62–162.5 mg/L.

Conclusion: Among the compounds, T6 appears to exhibit significant antimicrobial activity against both Gram-positive bacteria (e.g., *E. faecalis* ATCC 29212 and *S. epidermidis* ATCC 12228) and fungi (e.g., *Candida strains*).

Keywords: Triazole, antibacterial, antifungal

INTRODUCTION

Antimicrobial resistance has become a significant threat to both animal and human health because of the misuse and overuse of antibiotics. Many countries have strengthened controls on antibiotic use, including eliminating or reducing such use. However, the emergence of antimicrobial-resistant microorganisms has intensified the search for novel antimicrobial agents.[1] Given the promising potential of chemical compounds in this context, it is essential to investigate their antimicrobial properties.

Five-membered heterocyclic rings, such as nitrogen-containing triazoles, thiadiazoles, and oxadiazoles, are common structural motifs in many drugs.[2,3] Among these five-membered rings, 1,2,4-triazole rings, which are bioisosteres of other five-membered rings, are frequently synthesized in studies of drug-candidate molecules.[4] They have different biological activities such as antibacterial, antifungal, antiviral, anticancer, antidepressant, and anti-inflammatory.[5,6] As a result of the reaction of thiosemicarbazides in a basic medium, ring cyclization occurs, and 2,4-dihydro-3*H*-1,2,4-triazole-3-thione

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compounds, which are important pharmacophore structures, are readily obtained.[7]

There are many drugs with antimicrobial activity on the market, such as tazobactam, fluconazole, voriconazole, and itraconazole, which contain a triazole ring (Figure 1). Numerous studies have demonstrated the potent antimicrobial activity of 2,4-dihydro-3*H*-1,2,4-triazole-3-thione compounds.[8,9] Onkol et al.[10] synthesized a group of 1,2,4-triazole compounds based on thiosemicarbazides. 3-[(1(2*H*)-phthalazinone-2-yl)methyl]-4-methoxyphenyl-1,2,4-triazole-5-thione showed the best MIC values of 64 and 32 mg/mL against *Candida albicans* and *Candida parapsilosis*, respectively. Similarly, another study synthesized a group of compounds with a 2,4-dihydro-3*H*-1,2,4-triazole-3-thione structure from thiosemicarbazides. Among these compounds, 5-(3-hydroxynaphthalen-2-yl)-4-(2-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione exhibited strong bacteriostatic activity against Micrococcus luteus, with an MIC of 31.25 µg/mL.[11]

In this study, several new compounds containing 2,4-dihydro-3H-1,2,4-triazole-3-thione structures were synthesized. *In vitro* antimicrobial activity of the synthesized compounds against bacterial strains such as *Pseudomonas aeruginosa ATCC 27853, Escherichia coli ATCC 25922, Klebsiella pneumoniae ATCC 4352, Proteus vulgaris ATCC 13315, Enterococcus faecalis ATCC 29212, Staphylococcus epidermidis ATCC 12228, Staphylococcus aureus ATCC 29213, Acinetobacter baumannii ATCC 19606,* and fungal strains such as *C. albicans ATCC 90028, Candida glabrata ATCC 90030* was screened. In line with the need for new active pharmaceutical ingredients to combat antimicrobial resistance, this study aims to provide new data supporting the antimicrobial efficacy of 1,2,4-triazole structures reported in the literature.

MATERIALS AND METHODS

All solvents and other chemicals used in this study were purchased from Sigma-Aldrich. The melting points of the compounds were measured using a Schmelzpunktbestimmer SMP II apparatus. Infrared (IR) spectra of the compounds were recorded using a Shimadzu Fourier Transform Infrared Spectroscopy (FTIR)-8400S spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra of the compounds were recorded on a Bruker Avance III 600 MHz spectrometer. C, H, N, and S percentages in the compounds were measured using a Thermo Scientific Flash 2000 CHNS analyzer.

6-chloronicotinohydrazide and 2-(6-chloronicotinoyl)-*N*-substitutedhydrazine-1-carbothioamide derivatives (S1-S8) were obtained using the synthetic methods described in our previously reported study.[12]

N-Allyl-2-(6-chloronicotinoyl)hydrazine-1-carbothioamide (S1)

Yield: 80%; color: white powder; melting point: 164.3–165.3 °C. FTIR (cm^{-1}): 3223 and 3140 (N-H str.), 3088 (=C-H str.), 2974 and 2937 (C-H str.), 1678 (C=O str.), 1585, 1552, 1504, 1446 (C=N, C=C str., N-H b.), 1226 (C=S str.), 845 (=C-H b.). ^{1}H-NMR [dimethyl sulfoxide (DMSO)-d_6, 400 MHz, δ ppm]: 10.63 (s, 1H, NH), 9.47 (s, 1H, NH), 8.87 (dd, *J* = 2.5, 0.8 Hz, 1H, Ar-H), 8.38 (s, 1H, NH), 8.30 – 8.23 (m, 1H, Ar-H), 7.69 (d, *J* = 8.4 Hz, 1H, Ar-H), 5.80 (ddd, *J* = 22.2, 10.2, 5.0 Hz, 1H, allyl proton), 5.16 – 5.07 (m, 1H, allyl proton), 5.06 – 4.99 (m, 1H, allyl proton), 4.09 (s, 2*H*, allyl protons). ^{13}C-NMR (DMSO-d_6, 100 MHz, δ ppm): 185.90, 164.34, 153.71, 150.15, 139.83, 135.59, 128.40, 124.80, 115.96, 46.60.

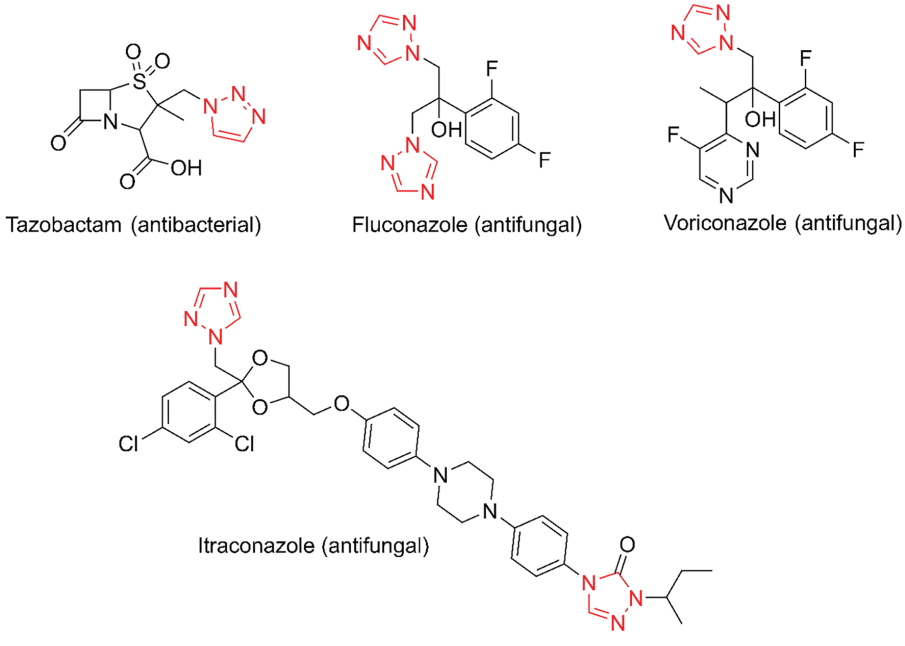


Figure 1. Some marketed antimicrobial drugs carrying a triazole ring

N-Butyl-2-(6-chloronicotinoyl)hydrazine-1-carbothioamide (S2)

Yield: 80%; color: white powder; melting point: 149.3–149.8 °C. FTIR (cm^{-1}): 3330 and 3132 (N-H str.), 3037 (=C-H str.), 2960 and 2874 (C-H str.), 1662 (C=O str.), 1585, 1556, 1519, 1452 (C=N, C=C str., N-H b.), 1242 (C=S str.), 846 (=C-H b.). ^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm):10.57 (s, 1H, NH), 9.33 (s, 1H, NH), 8.87 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.29 – 8.22 (m, 1H, Ar-H), 8.16 (s, 1H, NH), 7.72 – 7.65 (m, 1H, Ar-H), 3.41 (q, *J* = 8.0 Hz, 2*H*, $CH_2CH_2CH_2CH_3$), 1.49 – 1.42 (m, 2*H*, $CH_2CH_2CH_2CH_3$), 1.29 – 1.19 (m, 2*H*, $CH_2CH_2CH_2CH_3$), 0.85 (t, *J* = 8.0 Hz, 3*H*, $CH_2CH_2CH_2CH_3$). ^{13}C-NMR (DMSO-d_6, 100 MHz, δ ppm): 185.90, 164.30, 153.70, 150.12, 139.81, 128.43, 124.83, 44.10, 31.58, 20.13, 14.51.

N-(Pyridin-3-yl)-2-(6-chloronicotinoyl)hydrazine-1-carbothioamide (S3)

Yield: 75%; color: yellow powder; melting point: 164.9–165.5 °C. FTIR (cm^{-1}): 3284 and 3211 (N-H str.), 3051 (=C-H str.), 1654 (C=O str.), 1629 (C=N str. pyridine), 1585, 1541, 1506, 1456 (C=N, C=C str., N-H b.), 1253 (C=S str.), 840 (=C-H b.). ^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm): 11.21 and 10.93 (2s, 1H, NH), 10.07 (s, 1H, NH), 9.94 (s, 1H, NH), 8.92 (d, *J* = 2.4 Hz, 1H, Ar-H), 8.53 (s, 1H, Ar-H), 8.39 – 8.26 (m, 2*H*, Ar-H, Ar-H), 7.84 (s, 1H, Ar-H), 7.71 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.37 (dd, *J* = 8.2, 4.7 Hz, 1H, Ar-H).13C-NMR (DMSO-d_6, 100 MHz, δ ppm): 182.17, 163.85, 153.86, 153.13, 150.20, 149.31, 139.87, 138.97, 136.55, 134.40, 128.95, 128.27, 124.89, 123.67.

N-[2-(6-Chloronicotinoyl)hydrazine-1-carbonothioyl] benzamide (S4)

Yield: 75%; color: green powder; melting point: 210.0–210.9 °C. FTIR (cm^{-1}): 3132 and 3113 (N-H str.), 3061 (=C-H str.), 2950 and 2890 (C-H str.), 1666 (C=O str.), 1583, 1558, 1521, 1435 (C=N, C=C str., N-H b.), 1247 (C=S str.), 829 (=C-H b.). ^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm): 13.29 (s, 1H, NH), 12.34 and 11.82 (2s, 1H, NH), 11.45 (s, 1H, NH), 8.99 (d, *J* = 2.6 Hz, 1H, Ar-H), 8.41 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H, Ar-H), 8.12 (dt, *J* = 8.3, 1.2 Hz, 2*H*, Ar-H), 7.74 – 7.61 (m, 2*H*, Ar-H), 7.61 – 7.48 (m, 2*H*, Ar-H). ^{13}C-NMR (DMSO-d_6, 100 MHz, δ ppm): 181.58, 168.44, 165.91, 160.83, 153.99, 152.32, 149.90, 148.45, 139.69, 133.88, 131.91, 129.29, 128.10, 126.66, 125.65.

N-Benzyl-2-(6-chloronicotinoyl)hydrazine-1-carbothioamide (CAS Registry number 1388757-91-2) (S5)

Yield: 80%; color: white powder; melting point: 167.8–168.0 °C. FTIR (cm^{-1}): 3421 and 3149 (N-H str.), 3032 (=C-H str.), 2976 and 2937 (C-H str.), 1681 (C=O str.), 1585, 1552, 1504, 1446 (C=N, C=C str., N-H b.), 1226 (C=S str.), 845 (=C-H b.). ^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm): 10.69 (s, 1H, NH), 9.56 (s, 1H, NH), 8.88 (d, *J* = 2.4 Hz, 1H, Ar-H), 8.74 (s, 1H, NH), 8.27 (dt, *J* = 8.5, 2.1 Hz, 1H, Ar-H), 7.71 – 7.65 (m, 1H, Ar-H), 7.33 – 7.24 (m, 4H, Ar-H), 7.21 (s, 1H, Ar-H), 4.73 (d, *J* = 6.0 Hz, 2*H*, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz, δ ppm): 182.73, 164.41, 153.73, 150.15, 139.95, 139.83, 128.75, 128.37, 127.68, 127.32, 124.81, 47.39.

N-Phenethyl-2-(6-chloronicotinoyl)hydrazine-1-carbothioamide (S6)

Yield: 82%; color: yellow powder; melting point: 153.9–154.5 °C. FTIR (cm^{-1}): 3350 and 3157 (N-H str.), 3039 (=C-H str.), 2943 and 2926 (C-H str.), 1681 (C=O str.), 1583, 1545, 1494, 1454 (C=N, C=C str., N-H b.), 1247 (C=S str.), 842 (=C-H b.). ^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm): 10.68 (s, 1H, NH), 9.21 (s, 1H, NH), 8.76 (s, 1H, Ar-H), 8.38 (s, 1H, NH), 8.17 (dd, *J* = 8.4, 2.5 Hz, 1H, Ar-H), 7.69 – 7.63 (m, 1H, Ar-H), 7.33 – 7.15 (m, 5H, Ar-H), 4.18 (s, 2*H*, CH_2), 2.88 (t, *J* = 7.3 Hz, 2*H*, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz, δ ppm): 181.68, 164.12, 155.41, 152.19, 146.89, 139.61, 136.75, 129.47, 129.05, 126.92, 125.69, 120.72, 44.79, 35.43.

N-(m-Tolyl)-2-(6-chloronicotinoyl)hydrazine-1-carbothioamide (S7)

Yield: 75%; color: white powder; melting point: 149.2–150.0 °C. FTIR (cm^{-1}): 3319 and 3184 (N-H str.), 3055 (=C-H str.), 2916 (C-H str.), 1670 (C=O str.), 1589, 1545, 1489, 1460 (C=N, C=C str., N-H b.), 1224 (C=S str.), 854 (=C-H b.). ^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm): 10.82 (s, 1H, NH), 9.78 (s, 2*H*, NH), 8.91 (d, *J* = 2.5 Hz, 1H, Ar-H), 8.30 (dd, *J* = 8.4, 2.6 Hz, 1H, Ar-H), 7.69 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.21 – 7.18 (m, 3*H*, Ar-H), 6.97 (d, *J* = 7.1 Hz, 1H, Ar-H), 2.26 (s, 3*H*, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz, δ ppm): 181.62, 164.37, 153.74, 150.19, 139.85, 139.64, 137.97, 128.55, 128.41, 127.28, 126.61, 124.81, 123.99, 21.62.

N-(3-Methoxyphenyl)-2-(6-chloronicotinoyl)hydrazine-1-carbothioamide (S8)

Yield: 80%; color: white powder; melting point: 150.5–151.5 °C. FTIR (cm^{-1}): 3279 and 3144 (N-H str.), 3037 (=C-H str.), 2972 and 2831 (C-H str.), 1670 (C=O str.), 1585, 1556, 1521, 1456 (C=N, C=C str., N-H b.), 1251 (C=S str.), 848 (=C-H b.).^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm): 10.83 (s, 1H, NH), 9.83 (s, 2*H*, NH), 8.91 (t, *J* = 2.4 Hz, 1H, Ar-H), 8.30 (dt, *J* = 8.4, 2.4 Hz, 1H, Ar-H), 7.69 (dd, *J* = 8.4, 1.9 Hz, 1H, Ar-H), 7.22 (td, *J* = 8.1, 2.0 Hz, 1H, Ar-H), 7.07 (s, 1H, Ar-H), 7.00 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.77 – 6.65 (m, 1H, Ar-H), 3.72 (s, 3*H*, OCH_3).^{13}C-NMR (DMSO-d_6, 100 MHz, δ ppm): 181.50, 164.39, 159.63, 153.78, 150.19, 140.86, 139.85, 129.47, 128.39, 124.84, 118.88, 111.37, 55.79.

General synthesis method of 2,4-dihydro-3H-1,2,4-triazole-3-thione structures (T1-T8)

Add 5–6 mL of 2N NaOH solution to the 2-(6-chloronicotinoyl)-*N*-substituted hydrazine-1-carbothioamide derivatives. The mixture is heated in a water bath for 6 h. After reaction is confirmed by TLC, the mixture is neutralized with 1N HCl, and the solid is filtered and then crystallized from the appropriate solvent.[13]

4-Allyl-5-(6-chloropyridin-3-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (T1)

Yield: 75%; color: yellow powder; melting point: 249.5–250.0 °C. FTIR (cm^{-1}): 3088 (=C-H str.), 2928 and 2839 (C-H str.), 2766 (S-H str.), 1647 (C=N str.), 1597, 1558, 1531, 1498 (C=N and C=C str.), 839 (=C-H b.). ^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm): 14.22 and 13.96 (3s, 1H, NH), 7.78 – 7.71 (m, 1H, Ar-H),

7.65 (dd, *J* = 9.6, 2.7 Hz, 1H, Ar-H), 6.52 – 6.36 (d, *J* = 9.0 Hz, 1H, Ar-H), 5.85 (ddq, *J* = 17.2, 10.5, 4.4 Hz, 1H, allyl proton), 5.15 (ddq, *J* = 11.9, 10.2, 1.5 Hz, 1H, allyl proton), 4.89 (ddq, *J* = 17.2, 7.2, 1.6 Hz, 1H, allyl proton), 4.72 (ddt, *J* = 18.1, 5.0, 1.9 Hz, 2*H*, allyl protons). ^{13}C-NMR (DMSO-d_6, 150 MHz, δ ppm):167.86, 162.19, 152.71, 149.70, 149.09, 140.32, 137.55, 132.39, 124.95, 122.47, 120.72, 117.71, 104.76, 46.28. Anal. calcd for $C_{10}H_9ClN_4S$: C 47.53, H 3.59, N 22.17, S 12.69 %. Found: C 49.05, H 3.40, N 22.68, S 12.98 %.

4-Butyl-5-(6-chloropyridin-3-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (T2)

Yield: 80%; color: white powder; melting point: 262.8–263.5 °C. FTIR (cm^{-1}): 3107 (N-H str.), 3028 (=C-H str.), 2955 and 2872 (C-H str.), 1647 (C=N str.), 1602, 1568, 1533, 1496 (C=N and C=C str.), 1290 (C=S str.), 840 (=C-H b.). ^{1}H-NMR (DMSO-d6, 400 MHz, δ (ppm)): 7.82 (dd, J = 2.7, 0.8 Hz, 1H, Ar-H), 7.68 (dd, J = 9.5, 2.7 Hz, 1H, Ar-H), 6.47 (dd, J = 9.5, 0.7 Hz, 1H, Ar-H), 4.09 – 3.92 (m, 2*H*, CH2CH2CH2CH3), 1.63 – 1.43 (m, 2*H*, CH2CH2CH2CH3), 1.28 – 1.05 (m, 2*H*, CH2CH2CH2CH3), 0.79 (dt, J = 13.0, 7.3 Hz, 3*H*, CH2CH2CH2CH3). ^{13}C-NMR (DMSO-d_6, 150 MHz, δ ppm): 167.89, 162.21, 152.72, 149.91, 148.93, 148.41, 140.51, 140.22, 137.94, 125.22, 122.69, 120.76, 104.84, 43.77, 30.00, 19.55, 13.82. Anal. calcd for $C_{11}H_{13}ClN_4S$: C 49.16, H 4.88, N 20.85, S 11.93 %. Found: C 50.65, H 4.70, N 20.98, S 11.77 %.

4-(Pyridin-3-yl)-5-(6-chloropyridin-3-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (T3)

Yield: 80%; color: yellow powder; melting point: 295.1–296.0 °C. FTIR (cm^{-1}): 3182 (N-H str.), 3080 (=C-H str.), 1645 (C=N str.), 1606, 1583, 1550, 1471 (C=N and C=C str.), 1286 (C=S str.), 831 (=C-H b.). ^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm): 14.20 and 12.24 (s, 1H, NH), 8.89 (dd, *J* = 2.4, 0.8 Hz, 1H, Ar-H), 8.29 (dd, *J* = 8.3, 2.4 Hz, 1H, Ar-H), 7.98 (ddd, *J* = 10.4, 2.7, 0.7 Hz, 2*H*, Ar-H), 7.82 – 7.64 (m, 2*H*, Ar-H), 6.35 (dd, *J* = 9.6, 0.6 Hz, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, 150 MHz, δ ppm): 165.85, 162.86, 162.27, 159.11, 154.50, 151.30, 140.96, 140.85, 140.19, 137.19, 126.68, 124.99, 119.81, 109.47. Anal. calcd for $C_12H_8ClN_5S$: C 49.75, H 2.78, N 24.17, S 11.07 %. Found: C 51.50%, H 2.99%, N 23.86%, S 11.35%.

4-Benzoyl-5-(6-chloropyridin-3-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (T4)

Yield: 77%; color: green powder; melting point: 294.4–294.8 °C. FTIR (cm^{-1}): 3196 and 3117 (N-H str.), 3045 (=C-H str.), 1668 (C=N str.), 1583, 1558, 1521, 1433 (C=N and C=C str.), 1247 (C=S str.), 829 (=C-H b.). ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 13.34 (s, 1H, NH), 8.99 (dd, J = 2.6, 0.7 Hz, 1H, Ar-H), 8.41 (dd, J = 8.4, 2.5 Hz, 1H, Ar-H), 8.20–8.10 (m, 2*H*, Ar-H), 7.74–7.60 (m, 2*H*, Ar-H), 7.60–7.50 (m, 2*H*, Ar-H). ^{13}C-NMR (DMSO-d_6, 150 MHz, δ ppm): 166.46, 162.09, 157.95, 151.80, 148.07, 137.99, 133.19, 132.80, 129.03, 128.91, 126.83, 125.39. Anal. calcd for C14H9ClN4OS: C, 53.09; H, 2.86; N, 17.69; S, 10.12%. Found: C, 51.47; H, 3.01; N, 17.97; S, 9.75%.

4-Benzyl-5-(6-chloropyridin-3-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (T5)

Yield: 70%; color: white powder; melting point: 222.2–223.2 °C. FTIR (cm^{-1}): 3066 (=C-H str.), 2933 (C-H str.), 2750 (S-H str.), 1660 (C=N str.), 1597, 1541, 1494, 1448 (C=N and C=C str.), 833 (=C-H b.). ^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm): 14.14 and 11.99 (s, 1H, NH), 7.68 – 7.55 (m, 1H, Ar-H), 7.49 (dd, *J* = 9.6, 2.7 Hz, 1H, Ar-H), 7.37 – 7.17 (m, 3*H*, Ar-H), 7.13 – 6.98 (m, 2*H*, Ar-H), 6.35 (d, *J* = 9.6 Hz, 1H, Ar-H), 5.40 and 5.33 (2s, 1H, CH_2). ^{13}C-NMR (DMSO-d_6, 150 MHz, δ ppm): 168.42, 162.06, 152.67, 149.54, 149.13, 140.19, 137.54, 136.07, 129.16, 128.08, 127.03, 125.01, 122.41, 120.66, 47.02. Anal. calcd for C14H11ClN4S: C 55.54, H 3.66, N 18.50, S 10.59%. Found: C 54.66%, H 3.76%, N 18.33%, S 10.83%.

4-Phenethyl-5-(6-chloropyridin-3-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (T6)

Yield: 77%; color: yellow powder; melting point: 289.3–289.9 °C. FTIR (cm^{-1}): 3028 (=C-H str.), 2926 (C-H str.), 2760 (S-H str.), 1624 (C=N str.), 1600, 1558, 1494, 1454 (C=N and C=C str.), 837 (=C-H b.). ^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm):8.35 – 8.02 (m, 1H, Ar-H), 7.87 – 7.54 (m, 2*H*, Ar-H), 7.37 – 7.06 (m, 3*H*, Ar-H), 7.06 – 6.83 (m, 1H, Ar-H), 4.27 (dt, *J* = 17.2, 7.5 Hz, 2*H*, CH_2), 3.07 – 2.73 (m, 2*H*, CH_2). ^{13}C-NMR (DMSO-d_6, 150 MHz, δ ppm):164.32, 155.26, 149.17, 146.62, 139.40, 138.07, 136.48, 129.23, 129.21, 129.16, 128.91, 128.87, 128.82, 127.03, 126.68, 125.45, 124.72, 44.55, 35.28. Anal. calcd for $C_{15}H_{13}ClN_4S$: C 56.87, H 4.14, N 17.69, S 10.12 %. Found: C 58.22, H 4.37, N 18.01, S 9.85 %.

4-(m-Tolyl)-5-(6-chloropyridin-3-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (T7)

Yield: 82%; color: yellow powder; melting point: 239.1–240.0 °C. FTIR (cm^{-1}): 3292 (N-H str.), 3049 (=C-H str.), 2910 (C-H str.), 1635 (C=N str.), 1595, 1554, 1587, 1456 (C=N and C=C str.), 1247 (C=S str.), 846 (=C-H b.). ^{1}H NMR (DMSO-d6, 400 MHz): δ (ppm) 8.29 (dd, J = 2.5, 0.8 Hz, 1H, Ar-H), 7.68 (dd, J = 8.4, 2.5 Hz, 1H, Ar-H), 7.53 (dd, J = 8.4, 0.8 Hz, 1H, Ar-H), 7.48–7.08 (m, 4H, Ar-H), 2.32 (s, 3*H*, CH3). ^{13}C-NMR (DMSO-d_6, 150 MHz, δ ppm): 161.80, 151.70, 149.07, 139.49, 139.19, 134.89, 130.58, 129.66, 129.46, 129.01, 126.15, 124.72, 122.74, 118.89, 115.56, 21.24. Anal. calcd for C14H11ClN4S: C 55.54, H 3.66, N 18.50, S 10.59%. Found: C 54.20, H 3.74, N 18.88, S 10.02%.

4-(3-Methoxyphenyl)-5-(6-chloropyridin-3-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (T8)

Yield: 80%; color: yellow powder; melting point: 203.2–203.9 °C. FTIR (cm^{-1}): 3063 (=C-H str.), 2895 (C-H str.), 2735 (S-H str.), 1653 (C=N str.), 1604, 1564, 1539, 1489 (C=N and C=C str.), 835 (=C-H b.). ^{1}H-NMR (DMSO-d_6, 400 MHz, δ ppm): 14.25 (s, 1H, NH), 8.36 (dd, *J* = 2.4, 0.8 Hz, 1H, Ar-H), 7.74 (dd, *J* = 8.4, 2.5 Hz, 1H, Ar-H), 7.58 (dd, *J* = 8.4, 0.8 Hz, 1H, Ar-H), 7.53 – 7.34 (m, 1H, Ar-H), 7.34 – 7.09 (m, 1H, Ar-H), 7.09 – 7.00 (m, 1H, Ar-H), 6.94 (ddd, *J* = 7.8, 1.9, 1.0 Hz, 1H, Ar-H), 3.76 (s, 3*H*, OCH_3). ^{13}C-NMR (DMSO-d_6, 150 MHz, δ ppm): 169.29, 160.24, 160.19, 152.18, 149.49, 148.39, 148.00, 139.62, 135.42, 130.76, 124.75,

122.29, 121.16, 115.67, 55.96. Anal. calcd for C14H11ClN4OS: C 52.75, H 3.48, N 17.58, S 10.06%. Found: C 51.34, H 3.57, N 17.35, S 10.42%.

All IR, ^{1}H-NMR and ^{13}C-NMR spectra of the compounds were given in the supplementary file (Figure S1-S48).

Antimicrobial Activity

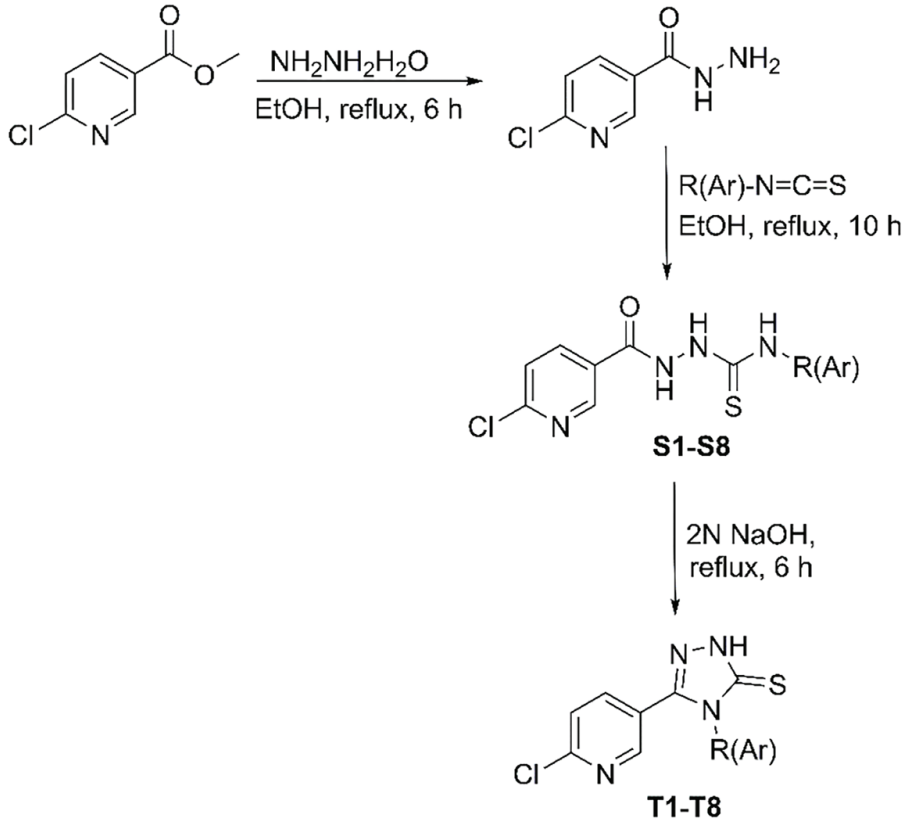
The minimum inhibitory concentration (MIC) values of the compounds were confirmed using reference strains following the guidelines established by the Clinical Laboratory Standards Institute.[14,15] Five Gram-negative bacteria (*P. aeruginosa ATCC 27853, K. pneumoniae ATCC 4352, E. coli ATCC 25922, P. vulgaris ATCC 13315, A. baumannii ATCC 19606)*, three Gram-positive bacteria *(E. faecalis ATCC 29212, S. aureus ATCC 29213, S. epidermidis ATCC 12228)*, and two yeasts *(C. albicans ATCC 10231, C. glabrata ATCC 90030)* were tested to determine the antimicrobial activity of the compounds.

All microorganisms tested in this study were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). The synthesized compounds were formulated in DMSO at a concentration of 10.000 mg L–1. Two-fold serial dilutions were prepared in the medium, ranging from 5000 mg/L to 2.4 mg/L. The inoculum of each strain was prepared from a broth culture incubated for 4–6 hours, while the broth cultures of yeast strains were incubated for 24 hours. The bacterial inocula were adjusted to a turbidity of 0.5 McFarland standard and diluted in Mueller-Hinton broth to a final concentration of 5×10^{5} colony-forming units per milliliter (colony-forming unit/mL). To prepare the yeast inocula, they were diluted in RPMI-1640 medium buffered with 0.165 M MOPS to pH 7.0. This dilution resulted in a final concentration of $0.5–2.5\times10^{3}$ in the test tray. The trays were securely covered and sealed in plastic bags to prevent evaporation. Incubation was performed at 35 ˚C: trays containing Mueller-Hinton broth for 18–24 hours and those with RPMI-1640 medium for 46–50 hours. The MIC was defined as the minimum concentration of fractions that completely inhibited detectable growth. Reference antimicrobial agents, such as meropenem and amphotericin B, were used. All experiments were performed in triplicate.

RESULTS

Chemistry

The target compounds, 4-substituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (T1-T8), were synthesized in three steps as shown in Figure 2. In the first step, the starting material, methyl 6-chloropyridine-3-carboxylate, was treated with hydrazine monohydrate to afford 6-chloronicotinohydrazide, a hydrazide. In the second step, thiosemicarbazide derivatives (S1–S8) were obtained by reacting this hydrazide compound with various isothiocyanates. In the last step, 2,4-dihydro-3*H*-1,2,4-triazole-3-thione compounds (T1–T8) were synthesized via ring cyclization of thiosemicarbazides by heating with 2N NaOH. The structures of the compounds were elucidated by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic methods.



Comp.	R(Ar)
T1	allyl
T2	butyl
T3	pyridin-3-yl
T4	benzoyl
T5	benzyl
T6	phenetyl
T7	*m*-tolyl
T8	*m*-(methoxy)phenyl

Figure 2. The synthesis pathway of 4-substituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones

IR spectra revealed that the synthesized compounds exist as thione and thiol tautomers. The IR spectra of the synthesized compounds T1, T5, T6 and T8 show the presence of thiol (S-H) absorption bands in the range 2735–2766 cm^{-1} and the absence of N–H stretching bands, indicating that these compounds are predominantly in the thiol form. Compounds T2, T3, T4, and T7 have N-H and C=S absorption bands in the ranges 3107-3292 cm^{-1} and 1247-1290 cm^{-1}, respectively, indicating that these compounds may also be primarily in the thione form.

The NH protons were detected in the range of 11.99–14.25 ppm in the 1H-NMR spectra of compounds T1, T3, T4, T5, and T8 from the series. The NH protons could not be detected because they were replaced by deuterium in the ^{1}H-NMR spectra of compounds T2, T6 and T7. Moreover, the carbons of the triazole ring were detected in the 13C NMR spectra of the compounds at 160.24–169.29 ppm.

The ^{13}C-NMR APT spectrum of Compound T1 was recorded. With this technique, carbon atoms bearing different numbers of attached protons (CH3, CH2, CH, C) can be readily distinguished, and their chemical shifts determined. Accordingly, carbon atoms with an even number of protons produced peaks above the baseline, whereas those with an odd number of protons produced peaks below the baseline. The methylene protons of the allyl substituent in compound T1 resonated above the baseline at 46.28 ppm and 104.76 ppm, whereas the methine carbon resonated below the baseline at 140.32 ppm. The carbon atoms that form the triazole ring and do not bear protons were detected above the baseline at 162.19 ppm and 167.86 ppm. Additionally, the aromatic carbon atoms bearing a single proton gave peaks below the baseline, whereas the ipso and imine carbons (C=N) gave peaks above the baseline.

Antimicrobial activity

The *in vitro* antimicrobial activity of synthesized compounds against five Gram-negative bacteria, three Gram-positive bacteria, and two fungi was evaluated by the broth microdilution technique, following Clinical and Laboratory Standards Institute recommendations.[14,15] The MIC values were compared with those of commonly used commercial antibiotics employed as standard drugs, as shown in Tables 1 and 2. Based on the antibacterial activity results for the compounds used in this study, the test cultures *E. coli ATCC 25922, K. pneumoniae ATCC 4352,* and *P. vulgaris ATCC 13315* appeared to be resistant to all tested compounds.

While T3 and T4 did not show any antibacterial activity against *P. aeruginosa ATCC 27853*, the other compounds showed moderate activity against this bacterium. Only compound T8 showed antibacterial activity against *A. baumannii ATCC 19606*.

While T4 and T6 have the best antibacterial activity against *E. faecalis ATCC 29212* with an MIC value of 41.79 mg/L and 81.25 subsequently. T1, T3, T5, T7, and T8 showed moderate antibacterial activity against this bacterium. All compounds showed moderate activity against *S. aureus ATCC 29213*. T6 has the highest antibacterial activity against *S. epidermidis ATCC 12228*, with an MIC of 40.62 mg/L.

Based on the antifungal results, T4, T6, and T8 exhibited the greatest antifungal activity against *C. albicans* ATCC 90028, with MIC values of 83.59, 40.62, and 82.81 mg/L, respectively. T6, T7, and T8 exhibited antifungal activity against *C. glabrata* ATCC 90030, with MIC values of 162.5, 159.37, and 82.81 mg/L, respectively, whereas the other compounds showed no activity against this fungus.

DISCUSSION

Increasing antibiotic resistance among microorganisms necessitates developing novel compounds that effectively function as antibiotics. Recently, there has been increased research into compounds with antimicrobial properties.[16] Many compounds with a 2,4-dihydro-3*H*-1,2,4-triazole-3-thione structure have been reported to exhibit antimicrobial activity.[17,18] Beyzaei et al.[19] investigated the potent antifungal activity of their synthesized 1,2,4-triazole-3-thione compounds and reported that the N1 nitrogen in the triazole ring plays a critical role in hydrogen bonding with target enzymes. Ezelarab et al.[20] reported that hybrid compounds synthesized based

Table 1. MICs values of the tested compounds for antibacterial activity

Compunds	*P. aeruginosa ATCC 27853*	*E. coli ATCC 25922*	*K. pneumoniae ATCC 4352*	*P. vulgaris ATCC 13315*	*E. faecalis ATCC 29212*	*E. faecalis ATCC 29212*	*S. aureus ATCC 29213*	*A. baumannii ATCC 19606*
T1	631.25	-	-	-	631.25	-	1262.5	-
T2	662.5	-	-	-	-	662.5	662.5	-
T3	-	-	-	-	656.25	656.25	656.25	-
T4	-	-	-	-	41.79	668.75	668.75	-
T5	637.5	-	-	-	637.5	-	637.5	-
T6	650	-	-	-	81.25	40.62	325	-
T7	637.5	-	-	-	318.75	159.37	318.75	-
T8	662.5	-	-	-	331.25	165.62	165.625	331.25
Reference	0.5[a]	0.06[a]	0.5[a]	0.125[a]	2[a]	0.25[a]	0.06[a]	0.5[a]

[a]Meropenem, MICs: Minimum inhibitory concentrations

Table 2. MICs values of the tested compounds for antifungal activity

Compounds	*C. albicans ATCC 90028*	*C. glabrata ATCC 90030*
T1	-	-
T2	-	-
T3	164.06	-
T4	83.59	-
T5	-	-
T6	40.62	162.5
T7	-	159.37
T8	82.81	82.81
Reference	0.5[b]	1[b]

[b]Amphotericin B, MICs: Minimum inhibitory concentrations

on the structures of ciprofloxacin and 1,2,4-triazole-3-thione showed stronger antifungal activity against *Candida strains* than itraconazole.

In this study, the antimicrobial activities of synthesized 2,4-dihydro-3*H*-1,2,4-triazole-3-thione compounds were evaluated. Some compounds demonstrated notable antimicrobial activity (Tables 1 and 2). T4 and T6 demonstrated potent antimicrobial effects against *E. faecalis ATCC 29212* and *S. epidermidis ATCC 12228*, and all compounds demonstrated antimicrobial effects against *S. aureus* is a significant human pathogen that can cause both hospital-associated and community-acquired infections.[21,22] It can rapidly acquire resistance to antimicrobial agents.[23,24] Additionally, methicillin-resistant *S. aureus* became a global pandemic, causing over 100,000 deaths in 2019.[25] Therefore, it is crucial to develop novel, effective antimicrobials against *S. aureus* and other staphylococci for both animal and human health.

The newly synthesized compounds were assessed for their antifungal activity against *C. albicans* and *C. glabrata*. T6 exhibited the strongest antifungal activity against *C. albicans*. Besides, T8 exhibited potent fungistatic activity against both *C. strains*. *Candida* species are significant fungal pathogens that can cause infections. Systematic surveillance conducted by the Centers for Disease Control and Prevention in the United States indicates that these infections are the fourth-leading cause of bloodstream infections and the third-leading cause of bloodstream infections in intensive care units.[26] *C. albicans* is a highly pathogenic fungal species and is responsible for more than 250,000 deaths and millions of recurrent infections annually.[27] *C. glabrata* is a significant pathogen due to its rising incidence and emerging resistance to various antifungal agents.[28] Therefore, it is significant to develop effective prevention and treatment strategies against *Candida* species.

Among Gram-negative bacteria, only compound T8 had antibacterial activity against *A. baumannii*, while other compounds, except T3 and T4, also had antibacterial activity against *P. aeruginosa* and *A. baumannii* are common causes of hospital-acquired infections. They survive extended periods in healthcare settings and are associated with multidrug resistance due to prolonged exposure to antibiotics. Therefore, identifying effective new compounds with antibacterial activity and demonstrating their efficacy are important parts of solving the problem of antibiotic resistance.[29]

CONCLUSION

The rapid development of resistance to existing antimicrobial agents in the fight against infections has encouraged medicinal chemists to develop new antimicrobials. In this context, we synthesized novel compounds bearing a 2,4-dihydro-3*H*-1,2,4-triazole-3-thione structure and assessed their antimicrobial activities. The compounds T4 and T6 in this series exhibited significant antibacterial activity against Gram-positive bacteria, except for *S. aureus*. Additionally, T4, T6, and T7 have potent antifungal activity. The MIC values of T6 against Gram-positive bacteria (*E. faecalis* and *S. epidermidis*) and fungal strains (*C. albicans* and *C. glabrata*) indicate that compound T6 may represent an important chemical scaffold for the development of novel antimicrobial agents.

Ethics

Ethics Committee Approval: Not required.

Informed Consent: Not required.

Footnotes

Authorship Contributions

Concept: F.T., Design: F.T., D.D.Ç., Data Collection or Processing: F.T., D.D.Ç., Analysis or Interpretation: F.T., D.D.Ç., Literature Search: F.T., D.D.Ç., Writing: F.T., D.D.Ç.

Conflict of Interest: The authors declare no conflicts of interest.

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