

Synthesis and Antimicrobial Efficacy of Novel 1,3,4-Thiadiazole Derivatives Against Key Bacterial and Fungal Strains

Mohamed M. Eleribi,^{1,*} Fakhri A. Elabbar,² and Basma Saad Baaiu²

¹ Department of Chemistry, Faculty of Art and Science, Alabyar Branch, University of Benghazi, P. O. Box 1308, Benghazi, Libya.

² Department of Chemistry, Faculty of Science, Benghazi, University of Benghazi, P. O. Box 1308, Benghazi, Libya.

* Corresponding author: E-mail: mohamed.eribi@uob.edu.ly

Received: 05-14-2025

Abstract

Two series of new 1,3,4-thiadiazole derivatives were synthesized through heterocyclization of methyl 2-(3,5-dibromo-2-hydroxybenzylidene)hydrazine-1-carbodithioate (**4**) and methyl (*E*)-2-(1-(5,7-dibromobenzofuran-2-yl)ethylidene)hydrazine-1-carbodithioate (**5**) with various hydrazonoyl chlorides, respectively. The structures of the newly synthesized products were elucidated through elemental analysis and spectral data. Eight new compounds from the first series (i.e. containing dibromohydroxybenzene moiety) were evaluated for their antimicrobial activity against *Staphylococcus aureus* ATCC 6538-P as the Gram-positive bacteria, *Escherichia coli* ATCC 25933 as the Gram-negative bacteria, *Candida albicans* ATCC 10231 as a yeast, and the filamentous fungus *Aspergillus niger* NRRL-A326 in comparison with neomycin as a reference drug in the case of *S. aureus*, *E. coli* and *C. albicans* whereas cyclohexamide was used as a reference for filamentous fungi. The results showed that some of the novel compounds have promising antimicrobial activity.

Keywords: 1,3,4-thiadiazole, carbodithioate, hydrazonoyl chloride, antimicrobial activity.

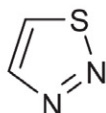
1. Introduction

Heterocyclic compounds have garnered significant interest among organic chemists, medical researchers, and those involved in drug discovery. Thiadiazole is a prominent class of heterocyclic compounds characterized by a five-membered ring containing two nitrogen atoms, one sulfur atom, and two carbon atoms. Thiadiazoles are categorized into four types: 1,3,4-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,2,3-thiadiazole (Figure 1), with 1,2,4-thiadiazole and 1,3,4-thiadiazole being the most extensively studied.¹

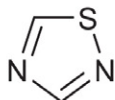
Compounds containing the 1,3,4-thiadiazole moiety have been shown to exhibit a broad spectrum of biological

activities, including antimicrobial,^{2,3} antituberculosis,⁴ anti-inflammatory,^{5–7} anticonvulsant,^{4,8,9} antihypertensive,¹⁰ local anesthetic,¹¹ and anticancer activities,^{12,13} 1,3,4-thiadiazole scaffold has been utilized in several FDA-approved¹⁴ drugs such as desaglybuzole, acetazolamide, sulfamethizole, litronesib, filanesib, and methazolamide¹⁵ (Figure 2).

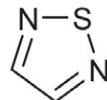
Various synthetic routes including cyclization reactions involving thioketones, hydrazines and various carbonyl compounds are utilized to synthesis thiadiazole. In this work, we aim to synthesize a new series of 1,3,4-thiadiazole derivatives which are expected to exhibit antimicrobial activity.



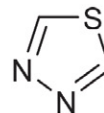
1,2,3-thiadiazole



1,2,4-thiadiazole



1,2,5-thiadiazole



1,3,4-thiadiazole

Figure 1. Structures of thiadiazoles

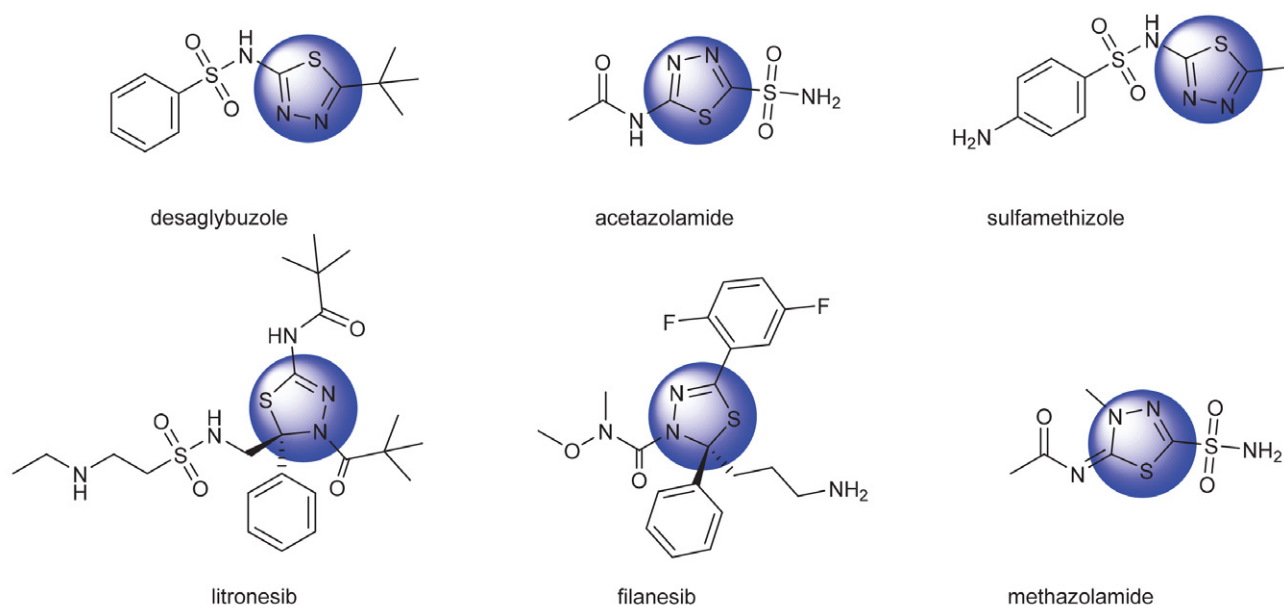


Figure 2. FDA-approved drugs contain thiadiazole

2. Experimental

Melting points were measured on an electrothermal digital apparatus. IR spectra (KBr disks) were recorded on a Shimadzu FT-IR 8201 PC Infrared spectrophotometer. ^1H NMR spectra were recorded in $\text{DMSO}-d_6$ solutions on a Bruker spectrometer operating at 400 MHz, ^{13}C NMR were recorded on a Bruker spectrometer at 100 MHz, and chemical shifts were referenced to that of the solvent. Mass spectra were recorded on a GCMS QP1000 EX Shimadzu. Elemental analyses were carried out by the Microanalytical Research Centre, Faculty of Science, Cairo University. Analytical C, H, N, and S results were within $\pm 0.4\%$ of the calculated values, hydrazonoyl halides **6a–h**^{16–19} were prepared as reported in the literature.

2.1. Chemistry

Synthesis of 3,5-Dibromo-2-hydroxybenzaldehyde (2)

Bromine 16 g (5 mL), 0.1 mol was added step-wise to salicylaldehyde (**1**) (22.12 g, 0.18 mol) in acetic acid (150 mL), while stirring for 1 hour in an ice bath. The reaction mixture was then poured on ice-cold water (1000 mL).^{20,21} The resulting solid residue compound **2** was collected and recrystallized from ethanol to give white crystals, yield 43.353 g (85%). M.p. 81–83 °C (ethanol); IR (KBr) ν 3347 (OH), 3176, 3067 (CH, aromatic), 1680 (C=O) cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.25 (s, 1H, CHO), 10.01 (s, 1H, OH), 7.95 (d, $J = 2.4$ Hz, 1H, Ar-H), 7.83 (d, $J = 2.4$ Hz, 1H, Ar-H); MS m/z (%): 281.87 ($[\text{M}+4]^+$, 22.64), 279.61 ($[\text{M}+2]^+$, 33.78), 278.08 (M^+ , 100). Anal. Calcd. for $\text{C}_7\text{H}_4\text{Br}_2\text{O}_2$ (279.96): C, 30.04; H, 1.44. Found: C, 29.83; H, 1.42 %.

Synthesis of 1-(5,7-Dibromobenzofuran-2-yl)ethan-1-one (3)

A total of 28 g (0.1 mol) of compound **2** was refluxed for 2 hours in a solution of potassium hydroxide (5.6 g, 0.1 mol) in ethanol. After cooling the reaction mixture to room temperature, 10 g (0.1 mol) of chloroacetone was added. The mixture was then refluxed for an additional 2 hours. Following this, the reaction mixture was filtered, and the resulting solution was allowed to cool at room temperature. Light green crystals of compound **3** were obtained with a yield 19.76 g (60%). M.p. 147–151 °C (ethanol); IR (KBr) ν 3117, 3094, 3091 (=C–H, aromatic), 1692 (C=O) cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.07 (d, $J = 1.7$ Hz, 1H, Ar-H), 7.97 (d, $J = 1.7$ Hz, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 2.58 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 188.15 (C=O), 153.83, 151.55, 133.11, 130.21, 126.08, 116.86, 114.54, 105.73, 27.06; MS m/z (%): 319.65 ($[\text{M}+4]^+$, 77.01), 317.50 ($[\text{M}+2]^+$, 19.42), 315.05 (M^+ , 25.53). Anal. Calcd for $\text{C}_{10}\text{H}_6\text{Br}_2\text{O}_2$ (317.96): C, 37.78; H, 1.89. Found C, 37.58; H, 1.88 %.

Synthesis of Methyl (E)-2-(3,5-Dibromo-2-hydroxybenzylidene)hydrazine-1-carbodithioate (4)

To a solution of 3,5-dibromo-2-hydroxybenzaldehyde (2.79 g, 10 mmol) in 20 mL of 2-propanol, 1.22 g (10 mmol) of methylhydrazinecarbodithioate was added. The mixture was warmed gently and stirred for 1 hour. The solid product was filtered off and recrystallized from dioxane to afford compound **4** as a pale yellow solid in yield 3.341 g (87%). M.p. 187–189 °C (dioxane); IR (KBr) ν 3575 (OH), 3428 (NH), 3219, 3127, 3091 (C–H, aromatic), 1628 (C=N), 1605 (C=C) cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.46 (s, 1H, NH), 11.83 (s, 1H, OH), 8.56 (d, $J = 1.7$ Hz,

1H, Ar-H), 8.55 (s, 1H, CH=N), 8.18 (d, $J = 1.7$ Hz, 1H, Ar-H), 2.56 (s, 3H, S-CH₃); ¹³C NMR (101 MHz, DM-SO-*d*₆) δ 199.01 (C=S), 165 (C-OH), 141.41 (C=N), 140.51, 127.66, 122.20, 120.80, 117.48, 17.30 (CH₃).

Synthesis of Methyl (*E*)-2-(1-(5,7-Dibromobenzofuran-2-yl)ethylidene)hydrazine-1-carbodithioate (5)

To a solution of 1-(5,7-dibromobenzofuran-2-yl)ethan-1-one (3) (3.17 g, 10 mmol) in 2-propanol (20 mL), methyl hydrazinecarbodithioate (1.22 g, 10 mmol) was added. The mixture was heated under reflux for 1 hour. The precipitated product was filtered off, recrystallized from dioxane to afford compound 5 as a white solid, yield 3.503 g (83%). M.p. 210 °C (acetic acid); FT-IR (KBr) ν 3199 (NH), 3065 (C-H, aromatic), 2955, 2856 (CH), 1645 (C=C), 1598 (C=N), 1238 (C=S), 704 (C-S) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.63 (s, 1H, NH), 7.97 (d, $J = 1.7$ Hz, 1H, Ar-H), 7.85 (d, $J = 1.7$ Hz, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 2.54 (s, 3H, S-CH₃), 2.41 (s, 3H, CH₃); MS m/z (%): 423.17 ([M+4]⁺, 7.45), 421.18 ([M+2]⁺, 22.46), 419.19 (M⁺, 23.59), 402.7 (100), 390.08 (22.44). Anal. Calcd for C₁₂H₁₀Br₂N₂OS₂ (422.15): C, 34.14; H, 2.37; N, 6.64; S, 15.19. Found: C, 34.06; H, 2.36; N, 6.62; S, 15.16%.

General Procedure for the Synthesis of 1,3,4-Thiadiazole Derivatives 10a–g

To a mixture of appropriate hydrazonoyl halides 6a–g (1 mmol) and hydrazine-1-carbodithioate derivative (4) (0.384 g, 1 mmol) in ethanol (20 mL), triethylamine (0.5 mL) was added, the mixture was warmed gently and stirred at room temperature for 1 hour.²² The resulting solid product was collected and recrystallized from the appropriate solvent to give the corresponding 1,3,4-thiadiazole derivatives 10a–g. The physical constants of products 10a–g are listed below.

4-(4-Chlorophenyl)-5-(((*E*)-3,5-dibromo-2-hydroxybenzylidene)hydrazineylidene)-*N*-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (10a)

Yellow solid, yield 0.534 g (88%). M.p. 230–232 °C (dioxane); FT-IR (KBr) ν 3382 (OH), 3310 (NH), 3070 (CH, aromatic), 2925 (CH), 1667 (C=O), 1601 (C=N), 1544 (C=N, thiadiazole) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.83 (s, 1H, OH), 8.70 (s, 1H, NH), 8.65 (s, 1H, CH=N), 8.24 (d, $J = 8.9$ Hz, 2H, Ar-H), 8.17 (d, $J = 8.9$ Hz, 2H, Ar-H), 7.86 (d, $J = 2.3$ Hz, 1H, Ar-H), 7.82 (d, $J = 2.3$ Hz, 1H, Ar-H), 7.76 (d, $J = 7.9$ Hz, 2H, Ar-H), 7.40 (t, $J = 7.9$ Hz, 2H, Ar-H), 7.18 (t, $J = 7.4$ Hz, 1H, Ar-H); MS m/z (%): 609.32 ([M+4]⁺, 23.14), 607.21 ([M+2]⁺, 20.78), 604.90 (M⁺, 60.81), 446.51 (100), 405.70 (52). Anal. Calcd. for C₂₂H₁₄Br₂ClN₅O₂S (607.71): C, 43.48; H, 2.32; N, 11.52; S, 5.28. Found: C, 43.36; H, 2.29; N, 11.48; S, 5.26%.

2,4-Dibromo-6-(((*E*)-((5-(furan-2-yl)-3-(4-nitrophenyl)-1,3,4-thiadiazol-2(3*H*)-ylidene)hydrazineylidene)methyl)phenol (10b)

Brown solid, yield 0.468 g (83%). M.p. 295–298 °C (dioxane); FT-IR (KBr) ν 3384 (OH), 3112, 3071 (CH, aromatic), 2923 (CH), 1743 (C=C, furan ring), 1605 (C=N), 1590 (C=N, thiadiazole), 693 (C-S) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.38 (s, 1H, OH), 8.81 (s, 1H, CH=N), 8.43 (s, 2H, Ar-H), 8.06 (d, $J = 1.6$ Hz, 1H, furan-H), 7.91 (d, $J = 2.3$ Hz, 1H, Ar-H), 7.89 (d, $J = 2.3$ Hz, 1H, Ar-H), 7.90 (d, $J = 8.12$ Hz, 2H, Ar-H), 7.46 (d, $J = 3.6$ Hz, 1H, furan-H), 6.82 (dd, $J = 3.6, 1.6$ Hz, 1H, furan-H); MS m/z (%): 566.53 ([M+4]⁺, 5.00), 564.17 ([M+2]⁺, 28.24), 562.97 (M⁺, 15.01), 440.47 (100), 429.35 (45.58). Anal. Calcd for C₁₉H₁₁Br₂N₅O₄S (565.20): C, 40.38; H, 1.96; N, 12.39; S, 5.67. Found: C, 40.33; H, 1.94; N, 12.37; S, 5.66%.

5-(((*E*)-3,5-Dibromo-2-hydroxybenzylidene)hydrazineylidene)-*N*,4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (10c)

Pale yellow solid, yield 0.441 g (77%). M.p. 187 °C (dioxane); FT-IR (KBr) ν 3382 (OH), 3310 (NH), 3070 (CH, aromatic), 2925 (CH), 1667 (C=O), 1601 (C=N), 1544 (C=N, thiadiazole) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.75 (s, 1H, OH), 8.66 (s, 1H, NH), 8.62 (s, 1H, CH=N), 8.07 (d, $J = 7.9$ Hz, 2H, Ar-H), 8.01 (d, $J = 7.9$ Hz, 2H, Ar-H), 7.83 (d, $J = 2.3$ Hz, 1H, Ar-H), 7.82 (d, $J = 2.3$ Hz, 1H, Ar-H), 7.56 (d, $J = 6.8$ Hz, 2H, Ar-H), 7.47–7.33 (m, 3H, Ar-H), 6.92 (d, $J = 7.8$ Hz, 1H, Ar-H); MS m/z (%): 574.16 ([M+4]⁺, 5.04), 572.46 ([M+2]⁺, 22.09), 570.61 (M⁺, 13.02), 273.67 (100), 260.89 (58.38). Anal. Calcd for C₂₂H₁₅Br₂N₅O₂S (573.93): C, 46.09; H, 2.64; N, 12.22; S, 5.59. Found: C, 46.10; H, 2.62; N, 12.22; S, 5.59%.

2,4-Dibromo-6-(((*E*)-((3-(4-nitrophenyl)-5-(thiophen-2-yl)-1,3,4-thiadiazol-2(3*H*)-ylidene)hydrazineylidene)methyl)phenol (10d)

Orange solid, yield 0.447 g (77%). M.p. >300 °C (acetic acid); FT-IR (KBr) ν 3444 (OH), 3108, 3065 (C-H aromatic), 2913 (CH), 1608 (C=N), 1589 (C=N thiadiazole), 1491 (C=C), 695 (C-S-C) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.37 (s, 1H, OH), 8.80 (s, 1H, CH=N), 8.41 (d, $J = 9.2$ Hz, 2H, Ar-H), 7.94 (d, $J = 5.1$ Hz, 1H, thiophene-H), 7.93 (d, $J = 1.8$ Hz, 1H, thiophene-H), 7.92 (d, $J = 9.2$ Hz, 2H, Ar-H), 7.90 (d, $J = 3.0$ Hz, 1H, Ar-H), 7.89 (d, $J = 3.0$ Hz, 1H, Ar-H), 7.28 (t, $J = 5.1$ Hz 1H, thiophene-H); MS m/z (%): 582.57 ([M+4]⁺, 28.40), 580.90 ([M+2]⁺, 23.47), 578.48 (M⁺, 32.64), 327.52 (61.54), 307.76 (24.94). Anal. Calcd for C₁₉H₁₁Br₂N₅O₃S₂ (581.26): C, 39.26; H, 1.91; N, 12.05; S, 11.03. Found: C, 39.05; H, 1.88; N, 11.98; S, 10.98%.

Ethyl 5-(((*E*)-3,5-Dibromo-2-hydroxybenzylidene)hydrazineylidene)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (10e)

Yellow solid, yield 0.447 g (85%). M.p. 205–207 °C (acetic acid); FT-IR (KBr) ν 3423 (OH), 3110, 3071 (C-H aromatic), 2991, 2922 (CH), 1746 (C=O), 1604 (C=N), 1555 (C=N thiadiazole), 687 (C-S-C) cm⁻¹; ¹H NMR (400 MHz,

DMSO- d_6) δ 10.89 (s, 1H, OH), 8.65 (s, 1H, CH=N), 7.86 (d, J = 8.6 Hz, 2H, Ar-H), 7.80 (d, J = 2.2 Hz, 1H, Ar-H), 7.78 (d, J = 2.2 Hz, 1H, Ar-H), 7.57 (t, J = 7.8 Hz, 2H, Ar-H), 7.46 (t, J = 7.4 Hz, 1H, Ar-H), 4.41 (q, J = 7.1 Hz, 2H, CH₂), 1.34 (t, J = 7.1 Hz, 3H, CH₃); MS m/z (%): 528.22 ([M+4]⁺, 13.73), 526.46 ([M+2]⁺, 10.12), 523.90 (M⁺, 8.77), 362.13 (53.28), 317.37 (100), 298.08 (43.31). Anal. Calcd for C₁₈H₁₄Br₂N₄O₃S (526.20): C, 41.09; H, 2.68; N, 10.65; S, 6.09. Found: C, 41.07; H, 2.66; N, 10.64; S, 6.09%.

1-(5-(((E)-3,5-Dibromo-2-hydroxybenzylidene)hydrazineylidene)-4-(para-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethan-1-one (10f)

Pale yellow solid, yield 0.405 g (75%). M.p. 220 °C (dioxane); FT-IR (KBr) ν 3423 (OH), 3110, 3071 (C–H aromatic), 2991, 2922 (CH), 1746 (C=O), 1604 (C=N), 1555 (C=N thiadiazole), 687 (C–S–C) cm⁻¹; ¹H NMR (400 MHz, DMSO- d_6) δ 10.68 (s, 1H, OH), 8.65 (s, 1H, CH=N), 7.87 (d, J = 2.3 Hz, 1H, Ar-H), 7.80 (d, J = 2.3 Hz, 1H, Ar-H), 7.72 (d, J = 8.3 Hz, 2H, Ar-H), 7.38 (d, J = 8.3 Hz, 2H, Ar-H), 4.41 (q, J = 7.0 Hz, 2H, CH₂), 2.39 (s, 3H, CH₃), 1.34 (t, J = 7.1 Hz, 3H, CH₃); MS m/z (%): 541.88 ([M+4]⁺, 18.7), 539.78 ([M+2]⁺, 14.33), 537.68 (M⁺, 28.74), 213.9 (100), 207.93 (43.55). Anal. Calcd for C₁₉H₁₆Br₂N₄O₃S (540.23): C, 42.24; H, 2.99; N, 10.37; S, 5.93. Found C, 42.13; H, 2.95; N, 10.34; S, 5.92%.

1-(5-(((E)-3,5-Dibromo-2-hydroxybenzylidene)hydrazineylidene)-4-(para-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethan-1-one (10g)

Orange solid, yield 0.459 g (90%). M.p. 285 °C (dioxane); FT-IR (KBr) ν 3422 (OH), 3083 (C–H aromatic), 2920 (CH), 1681 (C=O), 1601 (C=N), 1555 (C=N thiadiazole), 687 (C–S–C) cm⁻¹; ¹H NMR (400 MHz, DMSO- d_6) δ 10.71 (s, 1H, OH), 8.67 (s, 1H, CH=N), 7.87 (d, J = 2.3 Hz, 1H, Ar-H), 7.80 (d, J = 2.3 Hz, 1H, Ar-H), 7.79 (d, J = 8.4 Hz, 2H, Ar-H), 7.40 (d, J = 8.4 Hz, 2H, Ar-H), 2.59 (s, 3H, CH₃), 2.40 (s, 3H, CH₃); MS m/z (%): 511.29 ([M+4]⁺, 5.97), 509.52 ([M+2]⁺, 10.03), 507.33 (M⁺, 14.58), 467.31 (86.40), 419.28 (100). Anal. Calcd for C₁₈H₁₄Br₂N₄O₂S (510.20): C, 42.37; H, 2.77; N, 10.98; S, 6.28. Found: C, 42.28; H, 2.74; N, 10.96; S, 6.27%.

Synthesis of 6,6'-((1E,1'E)-((1,4-Phenylenebis(3-phenyl-1,3,4-thiadiazole-5(3H)-yl-2(3H)-ylidene))bis(hydrazine-2,1-diylidene))bis(methaneylylidene))bis(2,4-dibromophenol) (10h)

To a mixture of appropriate hydrazonoyl halide **6h** (1 mmol), and hydrazine-1-carbodithioate derivative compound **4** (0.768 g, 2 mmol) in ethanol (20 mL), triethylamine (0.5 mL) was added, the mixture was warmed gently and stirred at room temperature for 1 hour.²² The resulting solid product was collected and recrystallized from dioxane to give the corresponding 1,3,4-thiadiazole derivative **10h**. The physical constants of product **10h** are listed below.

Yellow solid, yield 1.37 g (70%). M.p. >300 °C (dioxane); FT-IR (KBr) ν 3420 (OH), 3064 (C–H aromatic), 2921 (CH), 1603 (C=N), 1554 (C=N thiadiazole), 692 (C–S–C) cm⁻¹; ¹H NMR (400 MHz, DMSO- d_6) δ 10.12 (s, 1H, OH), 8.69 (s, 1H, CH=N), 7.95 (s, 2H, Ar-H), 7.86 (d, J = 1.5 Hz, 1H, Ar-H), 7.81 (d, J = 1.4 Hz, 1H, Ar-H), 7.58 (t, J = 7.7 Hz, 2H, Ar-H), 7.39 (d, J = 8.0 Hz, 2H, Ar-H), 7.31 (t, J = 6.0 Hz, 1H, Ar-H); MS m/z (%): 985.85 ([M+8]⁺, 37.87), 982.66 ([M+4]⁺, 53.24), 386.73 (100), 339.25 (73.62). Anal. Calcd for C₃₆H₂₂Br₄N₈O₂S₂ (982.36): C, 44.02; H, 2.26; N, 11.41; S, 6.53. Found: C, 43.86; H, 2.23; N, 11.37; S, 6.51%.

General Procedure for the Synthesis of 1,3,4-Thiadiazole Derivatives 11a–e

To a mixture of appropriate hydrazonoyl halides **6a–e** (1 mmol) and hydrazine-1-carbodithioate derivative compound **5** (0.422 g, 1 mmol) in ethanol (20 mL), triethylamine (0.5 mL) was added, the mixture was warmed gently and stirred at room temperature for 1 hour.²² The resulting solid product was collected and recrystallized from the appropriate solvent to give the corresponding 1,3,4-thiadiazoles **11a–e**. The physical constants of products **11a–e** are listed below.

((E)-5-(((E)-1-(5,7-Dibromobenzofuran-2-yl)ethylidene)hydrazineylidene)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)(phenyl)methanone (11a)

Brown solid, yield 0.524 g (88%). M.p. 145–146 °C (acetic acid); FT-IR (KBr) ν 3066, 3024 (C–H Ar), 2918, 2852 (C–H), 1728 (C=O), 1599 (C=N), 1582 (C=N thiadiazole), 686 (C–S) cm⁻¹; ¹H NMR (400 MHz, DMSO- d_6) δ 8.10 (d, J = 1.7 Hz, 1H, Ar-H), 8.01 (d, J = 1.7 Hz, 1H, Ar-H), 7.95 (s, 2H, Ar-H), 7.78 (d, J = 6.0 Hz, 2H, Ar-H), 7.63–7.58 (m, 3H, Ar-H), 7.54 (s, 1H, Ar-H), 7.43–7.37 (m, 3H, Ar-H), 2.43 (s, 3H, CH₃); MS m/z (%): 597.94 ([M+4]⁺, 18.05), 596.39 ([M+2]⁺, 24.62), 594.17 (M⁺, 24.75), 300.17 (100), 277.25 (57.98). Anal. Calcd for C₂₅H₁₆Br₂N₄O₂S (596.30): C, 50.36; H, 2.70; N, 9.40; S, 5.38. Found C, 50.22; H, 2.68; N, 9.37; S, 5.36%.

(Z)-4-(4-Chlorophenyl)-5-(((E)-1-(5,7-dibromobenzofuran-2-yl)ethylidene)hydrazineylidene)-N-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (11b)

Green solid, yield 0.497 g (77%). M.p. 200–203 °C (acetic acid); FT-IR (KBr) ν 3390 (NH), 3106, 3073 (C–H aromatic), 2954, 2922 (C–H), 1691 (C=O), 1598 (C=N), 1578 (C=N thiadiazole), 686 (C–S) cm⁻¹; ¹H NMR (400 MHz, DMSO- d_6) δ 10.75 (s, 1H, NH), 8.29 (d, J = 9.0 Hz, 2H, Ar-H), 7.92 (d, J = 1.7 Hz, 1H, Ar-H), 7.80 (d, J = 1.7 Hz, 1H, Ar-H), 7.76 (d, J = 7.4 Hz, 2H, Ar-H), 7.65 (d, J = 9.0 Hz, 2H, Ar-H), 7.53 (s, 1H, Ar-H), 7.40 (t, J = 7.8 Hz, 2H, Ar-H), 7.18 (t, J = 7.4 Hz, 1H, Ar-H), 2.43 (s, 3H, CH₃); MS m/z (%): 646.95 ([M+4]⁺, 19.56), 643.51 ([M+2]⁺, 8.54), 642.61 (M⁺, 34.29), 334.94 (100), 263.22

(44.32). Anal. Calcd for $C_{25}H_{16}Br_2ClN_5O_2S$ (645.75): C, 46.50; H, 2.50; N, 10.85; S, 4.96. Found: C, 46.41; H, 2.47; N, 10.83; S, 4.96%.

2-(((E)-1-(5,7-Dibromobenzofuran-2-yl)ethylidene)hydrazineylidene)-3-phenyl-5-(para-tolyl)-2,3-dihydro-1,3,4-thiadiazole (11c)

Yellow solid, yield 0.454 g (78%). M.p. >300 °C (di-oxane); FT-IR (KBr) ν 3066, 3024 (C–H aromatic), 2918, 2852 (C–H), 1599 (C=N), 1582 (C=N thiadiazole), 683 (C–S) cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.15 (d, J = 8.4 Hz, 2H, Ar-H), 8.04 (d, J = 8.4 Hz, 2H, Ar-H), 7.87 (d, J = 1.8 Hz, 1H, Ar-H), 7.83 (d, J = 1.8 Hz, 1H, Ar-H), 7.79 (d, J = 7.9 Hz, 2H, Ar-H), 7.70 (t, J = 7.9 Hz, 2H, Ar-H), 7.58 (t, J = 7.9 Hz, 1H, Ar-H), 7.51 (s, 1H, Ar-H), 2.44 (s, 3H, CH₃), 2.39 (s, 3H, CH₃); MS m/z (%): 584.98 ([M+4]⁺, 24.67), 582.97 ([M+2]⁺, 18.12), 580.05 (M⁺, 25.19), 264.08 (100), 190.92 (64.69). Anal. Calcd for $C_{25}H_{18}Br_2N_4O_2S$ (582.31): C, 51.57; H, 3.12; N, 9.62; S, 5.51. Found: C, 51.33; H, 3.08; N, 9.58; S, 5.48 %.

(E)-2-(((E)-1-(5,7-Dibromobenzofuran-2-yl)ethylidene)hydrazineylidene)-5-(furan-2-yl)-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole (11d)

Brown solid, yield 0.464 g (77%). M.p. >300 °C (di-oxane); FT-IR (KBr) ν 3114, 3070 (C–H aromatic), 2920 (C–H), 1604 (C=N), 1593 (C=N thiadiazole), 683 (C–S) cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 8.53 (d, J = 9.2 Hz, 2H, Ar-H), 8.44 (d, J = 9.3 Hz, 2H, Ar-H), 8.10 (d, J = 1.7 Hz, 1H, Ar-H), 8.01 (d, J = 1.7 Hz, 1H, Ar-H), 7.95 (dd, J = 3.5, 1.7 Hz, 1H, furan-H), 7.83 (d, J = 1.7 Hz, 1H, furan-H), 7.57 (s, 1H, Ar-H), 7.35 (d, J = 3.5 Hz, 1H, furan-H), 2.58 (s, 3H, CH₃); MS m/z (%): 604.78 ([M+4]⁺, 22.44), 602.98 ([M+2]⁺, 18.11), 600.15 (M⁺, 26.02), 436.93 (98.87), 391.31 (52.40). Anal. Calcd for $C_{22}H_{13}Br_2N_5O_4S$ (603.25): C, 43.80; H, 2.17; N, 11.61; S, 5.31. Found: C, 43.75; H, 2.15; N, 11.60; S, 5.31%.

4-((E)-5-(((E)-1-(5,7-Dibromobenzofuran-2-yl)ethylidene)hydrazineylidene)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)-N-phenylbenzohydrazonoyl Chloride (11e)

Orange solid, yield 0.540 g (75%). M.p. 220 °C (chloroform); FT-IR (KBr) ν 3317 (NH), 3078, 3052 (C–H aromatic), 2918 (C–H), 1600 (C=N), 1573 (C=N thiadiazole), 692 (C–S) cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 10.02 (s, 1H, NH), 8.10 (d, J = 8.7 Hz, 2H, Ar-H), 8.05 (d, J = 8.7 Hz, 2H, Ar-H), 7.86 (d, J = 1.7 Hz, 1H, Ar-H), 7.83 (d, J = 1.7 Hz, 1H, Ar-H), 7.53 (s, 1H, Ar-H), 7.38 (d, J = 7.8 Hz, 4H, Ar-H), 7.29 (t, J = 7.9 Hz, 4H, Ar-H), 6.89 (t, J = 7.2 Hz, 2H, Ar-H), 2.40 (s, 3H, CH₃); MS m/z (%): 721.27 ([M+4]⁺, 17.82), 718.83 ([M+2]⁺, 15.17), 717.99 (M⁺, 39.38), 618.66 (65.29), 84.21 (100). Anal. Calcd for $C_{31}H_{21}Br_2ClN_6OS$ (720.87): C, 51.65; H, 2.94; N, 11.66; S, 4.45. Found: C, 51.62; H, 2.91; N, 11.65; S, 4.45%.

2. 2. Antimicrobial Activity Assay

The newly synthesized compounds were tested *in vitro* for antimicrobial activity against strains of pathogenic microorganisms, namely *Staphylococcus aureus* ATCC 6538-P (Gram-positive bacterium), *Escherichia coli* ATCC 25933 (Gram-negative bacterium), *Candida albicans* ATCC 10231 and *Aspergillus niger* NRRL-A326 (unicellular and multicellular fungi) using an agar well diffusion method.²³ Neomycin and cycloheximide were used as the standard antimicrobial drugs. Nutrient agar (NA) plates were inoculated deeply with 0.1 mL of 10^5 – 10^6 cells/mL for bacteria and yeast. Potato dextrose agar (PDA) plates were densely seeded with 0.1 mL (10^6 cells/mL) of fungal inoculum to assess antifungal activities. Compounds were prepared by dissolving 10 mg of the compound in 2 mL of dimethyl sulfoxide (DMSO).²⁴ The plates were desiccated, and a sterilized cork borer (7 mm in diameter) was used for punching the wells (2 wells) in agar medium. Wells were filled with 100 μ L of each compound and allowed to diffuse at room temperature for 1 hour, then the plates were placed in an incubator at 37 °C for 24 hours in the case of bacteria and at 27 °C for 48–72 hours in the case of fungi. After the incubation, the plates were observed for the formation of a clear inhibition zone around the well indicating the presence of antimicrobial activity. The absence of a clear zone around the well was taken as inactivity. The DMSO solvent was used as a negative control. The resulting diameters of zones of inhibition, including the diameter of the well, were measured using a ruler and reported in millimeters. To maintain the consistency of measurements, each zone of inhibition was measured twice (one vertical and one horizontal measurement), and the average value was taken. The experiment was performed in triplicate.²⁵

2. 3. Determination of Minimal Inhibitory Concentration (MIC) and Minimum Bactericidal/Fungicidal Concentration (MBC/MFC)

Test Microbes

Three pathogenic microbial strains: *Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 25933 and *Candida albicans* ATCC 10231. The tested microbes are grown on Mueller Hinton Agar (MHA) and Sabouraud Dextrose Agar (SDA).

Preparation of Microbial Culture

Clean microbial cells were prepared by cultivated test microbes in 100 mL bottles capped and incubated at 37 °C for 24 hours in the case of bacteria and 48 hours in the case of yeast. Cells were obtained under sterile conditions, in a cooling centrifuge at 4000 rpm for 15 min. The cells were washed using 20 mL of sterile normal saline un-

til the supernatant was clear. The optical density of the microbial suspension was measured at 500 nm, and serial dilutions were carried out with appropriate aseptic techniques until the optical density was in the range of 0.5–1.0. The actual number of colony-forming units was carried out to obtain a concentration of $5 \cdot 10^6$ cfu/mL.

Preparation of Resazurin Solution

The resazurin solution was prepared by dissolving a 270 mg tablet in 40 mL of sterile distilled water and shaken well with vortex mixer and sterilized by filtration through a membrane filter (pore size of 0.22–0.45 μ m).

Preparation of the Plates

Microplates with 96 wells were prepared and labeled under aseptic conditions. A volume of 500 μ L of test material in DMSO (a stock concentration of 5 mg/mL for purified compounds) was pipetted into the first row of the plate. To all other wells 50 μ L of broth medium was added. Serial dilutions were performed. To each well 10 μ L of resazurin indicator solution was added, and 10 μ L of microbial suspension ($5 \cdot 10^6$ cfu/mL) was added to each well. Each plate was wrapped loosely with parafilm to ensure that microbes did not become dehydrated. The plates were placed in an incubator at 37 °C for 24 hours in the case of bacteria and for 48 hours in the case of yeast. The color change was then assessed visually. Any color changes from purple to pink or colorless were recorded as positive. The lowest concentration at which color change occurred was taken as the MIC.²⁶

Determination of Minimum Bactericidal Concentrations (MBC) of Each Compound

Streaks were taken from the two concentrations higher than MIC and the plates exhibiting no growth were considered as MB.^{27,28}

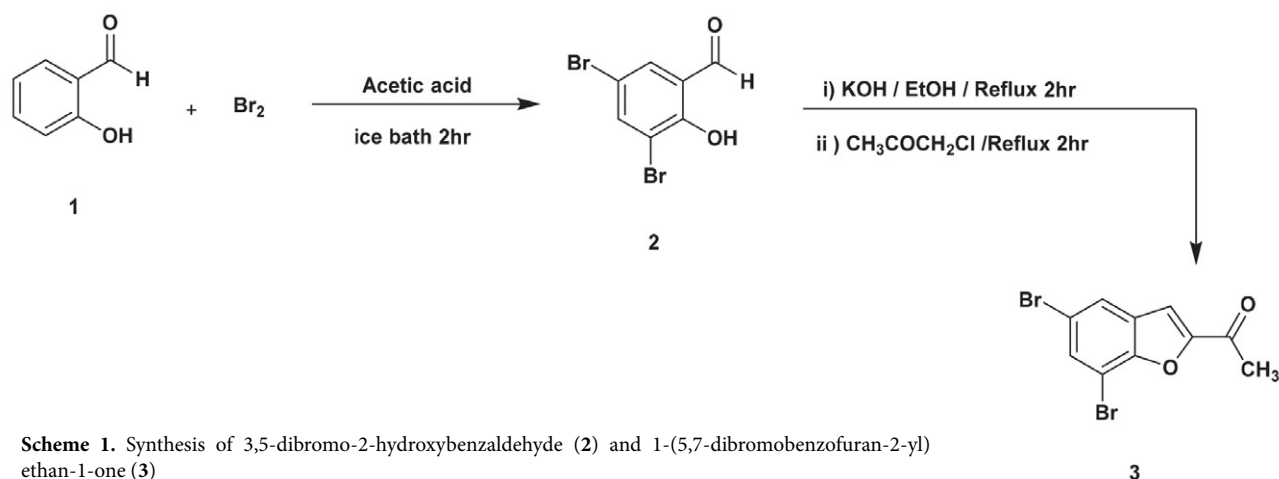
Determination of Minimum Fungicidal Concentrations (MFC)

Minimal fungicidal concentrations were determined according to the reported literature.²⁹ Briefly, MFC was evaluated by transporting 100 μ L from all clear MIC wells (no growth seen in microdilution trays) onto Sabouraud agar (SDA) plates. The MFC was the lowest sample concentration that killed $\geq 99.9\%$ of *Candida* cells.

3. Results and Discussion

3.1. Chemistry

The objective of this research was to synthesize novel heterocyclic compounds derived from 3,5-dibromosalicylaldehyde compound **2**. This compound was prepared by reacting salicylaldehyde with an equivalent amount of liquid bromine in the presence of acetic acid, as illustrated in Scheme 1. The structure of compound **2** was confirmed through spectral data analysis; thus, the IR spectrum displayed a broad absorption band at 3347 cm^{-1} which corresponds to the OH group, a strong band at 1680 cm^{-1} which is attributable to the carbonyl group. ^1H NMR spectrum data showed two doublets at δ 7.95 and 7.83 ppm with $J_{\text{meta}} = 2.4$ Hz, each one integrating for one proton; mass spectrum data confirmed molecular weight with a molecular ion peak at 278.08 (M^+), 281.87 ($\text{M}+4$) and 279.61 ($\text{M}+2$) peaks which are attributed to bromine isotopes 81 and 79, respectively. Chloroacetone was added to a mixture of compound **2** and ethanolic potassium hydroxide solution to afford compound **3**. The IR spectrum displayed no absorption bands in the region corresponding to the OH group, a strong band at 1692 cm^{-1} which is attributable to the carbonyl group. ^1H NMR spectrum data showed a singlet at δ 7.92 ppm which corresponds to one aromatic proton of the furan ring; also one singlet appeared at δ 2.58 ppm integrated for three protons of the ketonic methyl group; ^{13}C NMR showed a ketonic carbonyl signal at 188 ppm and methyl group at 27 ppm; mass spectrum data



Scheme 1. Synthesis of 3,5-dibromo-2-hydroxybenzaldehyde (**2**) and 1-(5,7-dibromobenzofuran-2-yl)ethan-1-one (**3**)

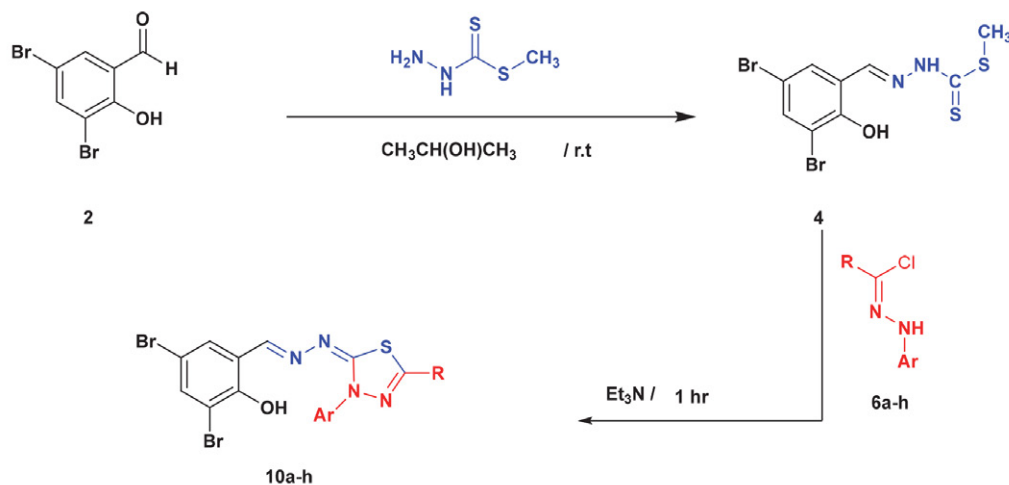
confirmed molecular weight with a molecular ion peak at 315 (M^+), 319 ($M+4$) and 317 ($M+2$) peaks which are attributed to bromine isotopes 81 and 79, respectively

Compound **2** was reacted with alkyl carbodithioate in 2-propanol to yield the corresponding methyl (*E*)-2-(3,5-dibromo-2-hydroxybenzylidene)hydrazine-1-carbodithioate **4**. Treatment of this compound with the appropriate hydrazonoyl chlorides **6a–h** in ethanolic triethylamine produced 1,3,4-thiadiazole derivatives **10a–h** (Scheme 2). The reaction mechanism outlined in Scheme 3 involves three steps: first, 1,3-addition of the C=S thiol tautomer to the nitrilimine **7** produces the thiohydrazonate ester **8** which subsequently undergoes nucleophilic cyclization to afford compound **9**. The latter compound is readily converted to final products **10,11**³⁰ through the elimination of alkylthiol. Structures **10a–h** were elucidated on the basis of spectral data: IR spectrum displayed absorption bands in the range of 3382–3444 cm^{-1} , corresponding to OH groups, strong bands at 1601–16081 cm^{-1} suggesting the presence of a C=N bond. Additionally, bands at 1544–1590 cm^{-1} were attributed to C=N in the thiadiazole ring. ^1H NMR spectral data showed singlet for the OH proton in the range δ 10.68–11.38 ppm for compounds **10a–h**. OH proton of compounds **10b** and **10d**

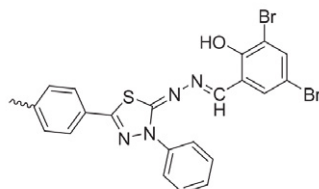
exhibited a downfield signal at δ 11.38 and 11.37 ppm, respectively. Another singlet appeared in the range of δ 8.65–8.80 ppm, attributable to the sp^2 proton ($\text{H}-\text{C}=\text{N}$). Compounds **10a** and **10c** showed singlets at δ 8.70 ppm and δ 8.66 ppm, respectively, corresponding to the H–N proton. Mass spectra confirmed the molecular weight with molecular ionic peak (M^+), ($M+4$) and ($M+2$) peaks attributed to bromine isotopes 81 and 79, respectively.

Analogously, treatment of compound **3** with the appropriate hydrazonoyl chlorides **6a–e** in ethanolic triethylamine at room temperature afforded 1,3,4-thiadiazole derivatives **11a–e**, respectively (Scheme 4).

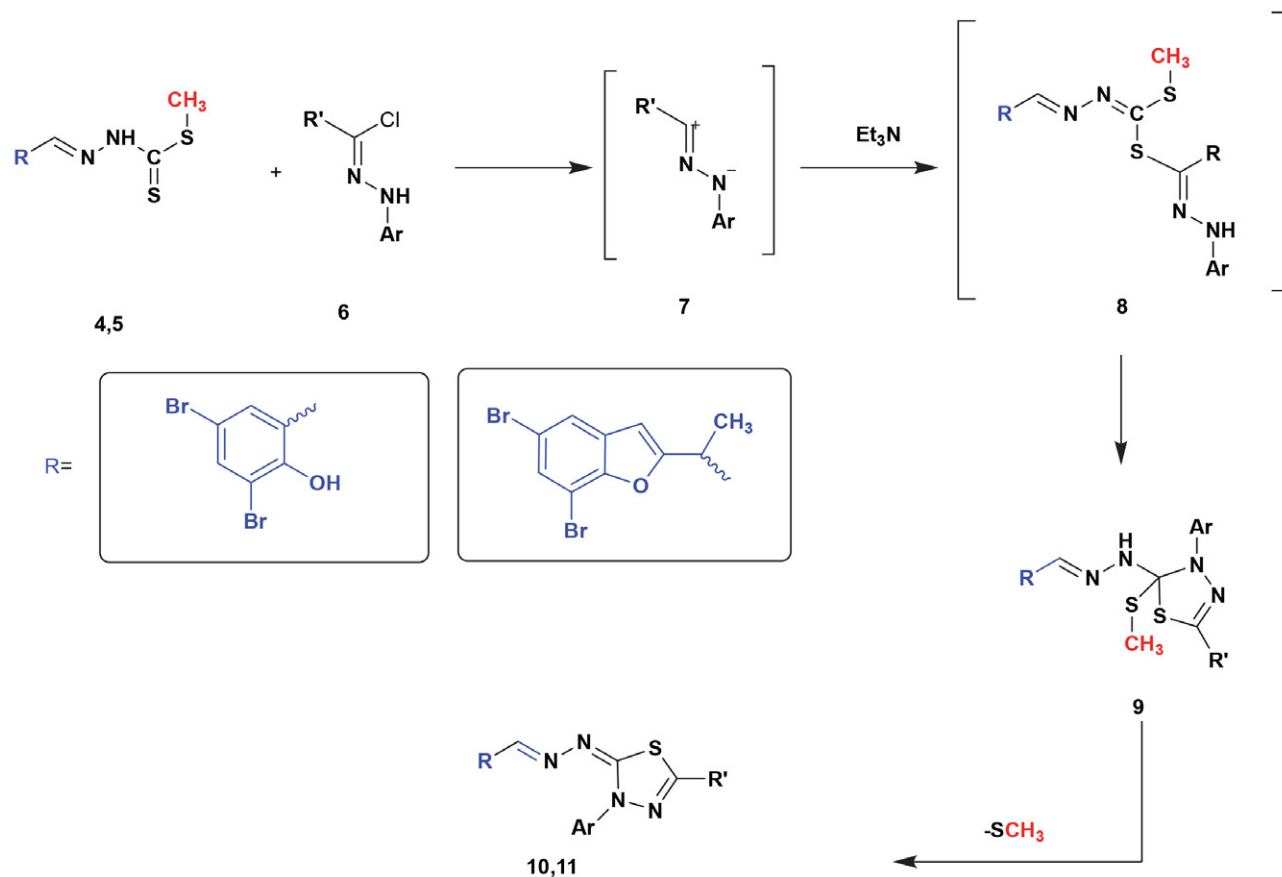
Structures **11a–e** were elucidated on the basis of their spectral data. The IR spectra showed no absorption bands in the region corresponding to carbonyl groups, while strong absorption bands in the range 1604–1599 cm^{-1} confirmed the presence of a C=N group, and bands at 1582–1598 cm^{-1} were attributed to C=N in thiadiazole ring. The ^1H NMR spectra displayed clear singlets in the range of δ 2.40–2.58 ppm for CH_3 protons, along with another singlet in the range of δ 7.50–7.57 ppm corresponding to the benzofuran ring. Additionally, compounds **11b** and **11e** exhibited singlets at δ 10.75 and 10.02 ppm for NH proton. Mass spectra showed ion peaks ($M+4$) and



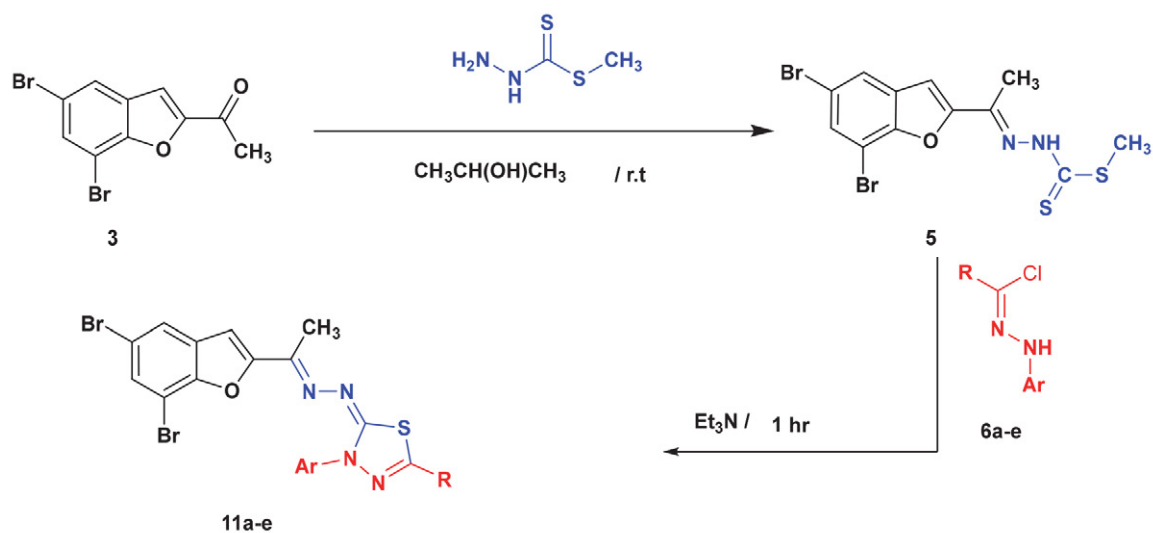
Compound 6,10	R	Ar
a	CONHC ₆ H ₅	4-ClC ₆ H ₄
b	C ₄ H ₃ O	4-NO ₂ C ₆ H ₄
c	CONHC ₆ H ₅	C ₆ H ₅
d	C ₄ H ₃ S	4-NO ₂ C ₆ H ₄
e	COOC ₂ H ₅	C ₆ H ₅
f	COOC ₂ H ₅	4-CH ₃ C ₆ H ₄
g	COCH ₃	4-CH ₃ C ₆ H ₄
h		C ₆ H ₅



Scheme 2. Synthesis of 1,3,4-thiadiazoles **10a–h**



Scheme 3. Proposed mechanistic pathway for the formation of 1,3,4-thiadiazoles 10,11



Compounds 6,11	R	Ar
a	COC ₆ H ₅	C ₆ H ₅
b	CONHC ₆ H ₅	4-ClC ₆ H ₄
c	4-CH ₃ C ₆ H ₄	C ₆ H ₅
d	C ₄ H ₃ O	4-NO ₂ C ₆ H ₄
e	4-C ₆ H ₄ NHNCClC ₆ H ₅	C ₆ H ₅

Scheme 4. Synthesis of 1,3,4-thiadiazoles 11a–e

(M+2) which are attributed to bromine isotopes 81 and 79, respectively.

3. 2. Biological Evaluation

In vitro Antimicrobial Activity

Using an agar well diffusion method, the newly synthesized 1,3,4-thiadiazole derivatives were investigated to evaluate their antimicrobial activity against *S. aureus* ATCC 6538-P, *E. coli* ATCC 25933, *C. albicans* ATCC 10231, and *A. niger* NRRL-A326. The inhibition zone diameter was observed for the synthesized compounds and the positive control, but not for the negative control. Evaluation of the antimicrobial activity of these newly synthesized compounds is presented in Table 1 and shown in Figure 3. It has been found that compound **10e** exhibited the highest activity against all tested microbial strains: *S. aureus* ATCC 6538-P, *E. coli* ATCC 25933, *C. albicans* ATCC 10231, and *A. niger* NRRL-A326, with inhibition zone diameters (IZDs) of 29, 28, 27, and 25 mm, respectively (Supplementary Information, Figure 52). Compounds **10a**, **10f**, and **10h** showed moderate activity against all tested microbial strains; the IZDs were 18, 17, and 18 mm on *S. aureus* ATCC 6538-P, and 17, 19, and 21 mm on *E. coli* ATCC 25933, while the IZDs were 21, 16, and 20 mm on *C. albicans* ATCC 10231, and 11, 16, and 12 mm on *A. niger* NRRL-A326. Additionally, it was found that compound **10c** showed activity only against the tested bacterial strains but

showed no inhibitory effect against the tested fungal strains. Compound **10d** showed low activity against *S. aureus* ATCC 6538-P and *C. albicans* ATCC 10231 with IZDs of 8 and 9 mm, but showed no inhibitory effect against *E. coli* ATCC 25933 and *A. niger* NRRL-A326. On the other hand, compounds **10b** and **10g** showed no activity against any of the tested microbial strains. Compound **10e** was more potent than the selected standard antibiotics, while other compounds were less effective.

The results listed in Table 1 show that compounds **10a**, **10e**, **10f**, and **10h** were the most effective against three tested microbial strains (*S. aureus* ATCC 6538-P, *E. coli* ATCC 25933, and *C. albicans* ATCC 10231); therefore, to determine the minimum inhibitory concentration (MIC) and minimum bactericidal/fungicidal concentration (MBC/MFC) against these microbial strains, experiments on these four compounds (**10a**, **10e**, **10f**, and **10h**) were conducted.

The MIC and MBC/MFC results are reported in Table 2 and in the Figure 4. The MIC values for compounds **10a**, **10e**, **10f**, and **10h** were 78.28, 2.58, 77.43, and 313.47 µg/mL, respectively, against *S. aureus* ATCC 6538-P, and 156.30, 4.88, 155.87, and 313.16 µg/mL against *E. coli* ATCC 25933, while they reached 39.14, 2.56, 78.30, and 156.25 µg/mL, respectively, against *C. albicans* ATCC 10231.

The MBC values for compounds **10a**, **10e**, **10f**, and **10h** were 313.68, 4.03, 158.33, and 627.11 µg/mL, respec-

Table 1. Zones of inhibition of the synthesized 1,3,4-thiadiazole derivatives, neomycin and cyclohexamide against tested microbial strains.

Compound no.	Inhibition zone measured in millimeters			
	<i>S. aureus</i> ATCC 6538-P	<i>E. coli</i> ATCC 25933	<i>C. albicans</i> ATCC 10231	<i>A. niger</i> NRRL-A326
10a	18.50 ± 0.50	17.33 ± 0.58	21.33 ± 0.58	11.00 ± 1.00
10b	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00
10c	15.75 ± 0.66	12.67 ± 0.58	00.00 ± 0.00	00.00 ± 0.00
10d	08.33 ± 0.58	00.00 ± 0.00	09.33 ± 0.58	00.00 ± 0.00
10e	29.00 ± 1.00	28.17 ± 0.29	27.33 ± 0.58	25.67 ± 0.00
10f	17.67 ± 0.58	19.00 ± 1.00	16.67 ± 0.58	16.33 ± 0.58
10g	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00
10h	18.67 ± 0.58	21.67 ± 0.58	20.00 ± 0.00	12.67 ± 0.58
C ⁺ Neomycin ¹⁷ *Cycloheximid ¹⁸	27	25	28	*22
C ⁻ DMSO	0	0	0	0

C⁺: Positive control, C⁻: Negative control.

Table 2. MIC and MBC/MFC of the synthesized 1,3,4-thiadiazole derivatives against highly susceptible microbial strains.

Compounds	<i>S. aureus</i> ATCC 6538-P		<i>E. coli</i> ATCC 25933		<i>C. albicans</i> ATCC 10231	
	MIC (µg/mL)	MBC (µg/mL)	MIC (µg/mL)	MBC (µg/mL)	MIC (µg/mL)	MFC (µg/mL)
10a	78.28 ± 1.07	313.68 ± 0.89	156.30 ± 0.96	314.08 ± 0.84	39.14 ± 0.93	156.46 ± 0.77
10e	2.58 ± 0.51	4.03 ± 0.55	4.88 ± 1.10	8.86 ± 0.98	2.567 ± 0.53	19.49 ± 1.07
10f	77.43 ± 1.08	158.33 ± 1.05	155.87 ± 1.47	311.68 ± 1.68	78.30 ± 1.08	156.36 ± 0.96
10h	313.47 ± 0.86	627.11 ± 1.61	313.16 ± 2.55	314.68 ± 1.07	156.25 ± 1.00	312.66 ± 1.09

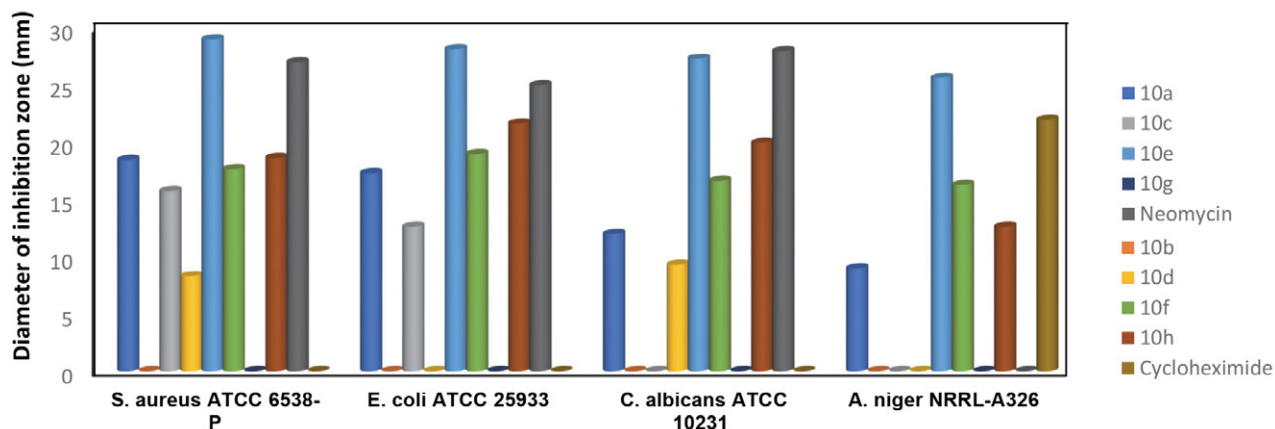


Figure 3. Effect of the synthesized 1,3,4-thiadiazole derivatives, neomycin and cycloheximide against tested microbial strains.

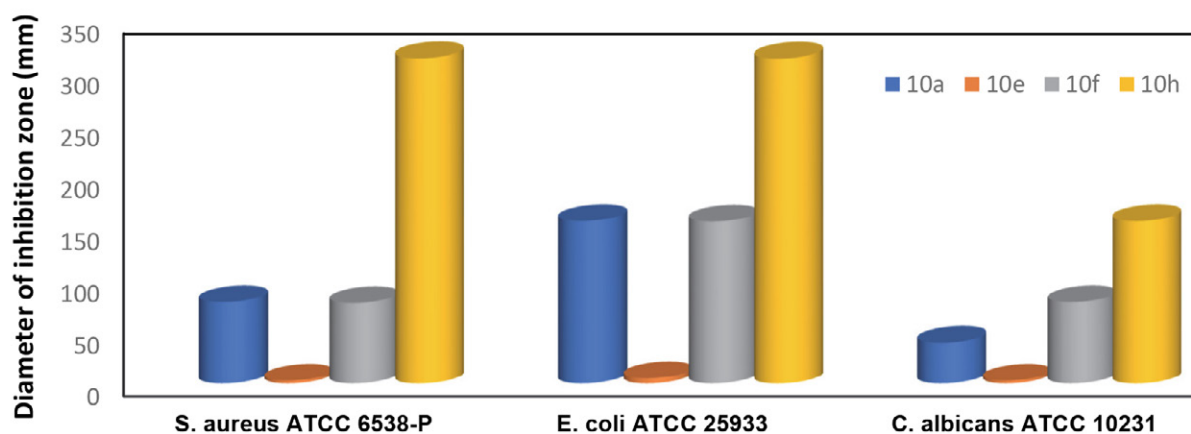


Figure 4. MIC of the synthesized 1,3,4-thiadiazole derivatives against highly susceptible microbial strains.

tively, against *S. aureus* ATCC 6538-P, and 314.08, 8.86, 311.68, and 314.68 $\mu\text{g/mL}$, respectively, against *E. coli* ATCC 25933. The MFC values for compounds **10a**, **10e**, **10f**, and **10h** were 156.46, 19.49, 156.36, and 312.66 $\mu\text{g/mL}$, respectively, against *C. albicans* ATCC 10231.

4. References

- Y. Li, J. Geng, Y. Liu, S. Yu, G. Zhao, *Chem. Med. Chem.* **2013**, *8*, 27–41. DOI:10.1002/cmdc.201200355
- M. N. Noolvi, H. M. Patel, S. Kamboj, S. S. Cameotra, *Arabian J. Chem.* **2016**, *9*, S1283–S1289. DOI:10.1016/j.arabjc.2012.02.003
- G. de Andrade Danin Barbosa, A. P. de Aguiar, *Rev. Virtual Quim.* **2019**, *11*, 806–848. DOI:10.21577/1984-6835.20190058
- C. B. Chapleo, P. L. Myers, A. C. B. Smith, I. F. Tulloch, D. S. Walter, *J. Med. Chem.* **1987**, *30*, 951–954. DOI:10.1021/jm00388a038
- Y. Song, D. T. Connor, A. D. Sercel, R. J. Sorenson, R. Doubleday, P. C. Unangst, B. D. Roth, V. G. Beylin, R. B. Gilbertsen, K. Chan, D. J. Schrier, A. Guglietta, D. A. Bornemeier, R. D. Dyer, *J. Med. Chem.* **1999**, *42*, 1161–1169. DOI:10.1134/S1070428008060158
- M. D. Mullican, M. W. Wilson, D. T. Connor, C. R. Kostlan, D. J. Schrier, R. D. Dyer, *J. Med. Chem.* **1993**, *36*, 1090–1099. DOI:10.1021/jm00060a017
- L. Labanauskas, V. Kalcas, E. Udrenaitė, P. Gaidelis, A. Brukstus, V. Dauksas, *Pharmazie* **2001**, *56*, 617–619. DOI:10.3390/12010103
- C. B. Chapleo, P. L. Myers, J. F. Saville, A. C. B. Smith, M. R. Stillings, I. F. Tulloch, D. S. Walter, A. P. Welbourn, M. Myers, *J. Med. Chem.* **1986**, *29*, 2273–2280. DOI:10.1021/jm00161a024
- Y. Murti, T. Agrawal, D. Pathak, *Indian Drugs* **2010**, *47*, 19–27. DOI:10.1007/s13312-010-0036-z
- S. Turner, M. Myers, B. Gadie, A. J. Nelson, R. Pape, J. F. Seville, J. C. Doxey, T. L. Berridge, *J. Med. Chem.* **1988**, *31*, 902–906. DOI:10.1021/jm00212a014
- G. Mazzone, R. Pignatello, S. Mazzone, A. Panico, G. Pennisi, R. Castana, P. Mazzone, *Farmaco* **1993**, *48*, 1207–1224. DOI:10.1016/0014-827X(93)90007-4
- J. Zhao, L. Xuan, H. Zhao, J. Cheng, X. Fu, S. Li, F. Jing, Y. Liu,

- B. Chen, *Chem. Res. Chin. Univ.* **2014**, *30*, 764–769.
DOI:10.1007/s40242-014-4080-4
13. D. Kumar, N. Maruthi Kumar, K. H. Chang, K. Shah, *Eur. J. Med. Chem.* **2010**, *45*, 4664–4668.
DOI:10.1016/j.bmcl.2011.07.089
14. G. Serban, *Molecules*. **2020**, *25*, 942.
DOI:10.3390/molecules25040942
15. M. Haroon, M. Khalid, T. Akhtar, M. N. Tahir, M. U. Khan, S. Muhammad, A. G. Al-Sehemi, S. Hameed, *J. Mol. Struct.* **2020**, *1202*, 127354. DOI:10.1016/j.molstruc.2019.127354
16. P. Wolko, *Can. J. Chem.* **1975**, *53*, 1–23.
DOI:10.1139/v75-183
17. A. R. Sayed, S. S. Al-Shihry, M. A.-M. Gomaa, *Eur. J. Chem.* **2014**, *5*, 267–271. DOI:10.5155/eurjchem.5.2.267-271.913
18. A. S. A. S. Shawali, A. Osman, *Tetrahedron*. **1971**, *27*, 2517–2528. DOI:10.1016/S0040-4020(01)90753-7
19. A. S. Shawali, A. O. Abdelhamid, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 321–324. DOI:10.3390/molecules21070929
20. C. M. Brewster, *J. Am. Chem. Soc.* **1964**, *277*, 2463–2468.
21. Ng. Ph. Buu-Hoï, Ng. Hoán, M. R. Khenissi, *J. Chem. Soc.* **1951**, 2307–2309. DOI:10.1039/JR9510002307
22. A. O. Abdelhamid, S. M. Gomha, N. A. Abdelrehem, A. M. Shalaby, S. M. Kandeel, *Synth. Commun.* **2018**, *48*, 677–684.
DOI:10.3390/molecules27206977
23. B. Athanassiadis, P. V. Abbott, N. George, L. J. Walsh, *Aust. Dent. J.* **2009**, *54*, 141–146.
DOI:10.1111/j.1834-7819.2009.01107.x
24. E. Tamam, A. A. Fadda, E. R. El-Sawy, M. S. Abdel-Aziz, E. H. Tawfik, *ChemistrySelect*. **2023**, *8*, e202302468.
DOI:10.1002/slct.202302468
25. M. M. Miloud, N. A. Senussi, *Acad. J. Microbiol. Res.* **2020**, *9*, 13–20. DOI:10.15413/ajmr.2020.1101
26. N. Ryad, A. A. Elmaaty, S. Selim, M. S. Almuhayawi, S. K. Al Jaouni, M. S. Abdel-Aziz, A. S. Alqahtani, I. Zaki, L. M. A. Abdel Ghany, *RSC Adv.* **2024**, *14*, 34005–34026.
DOI:10.1039/D4RA06712F
27. H. M. Abo-Salem, H. A. Abd El Salam, A. M. Abdel-Aziem, M. S. Abdel-Aziz, E. R. El-Sawy, *Molecules*. **2021**, *26*, 4112.
DOI:10.3390/molecules26144112
28. S. D. Sarker, L. Nahar, Y. Kumarasamy, *Methods*. **2007**, *42*, 321–324. DOI:10.1016/j.ymeth.2007.01.006
29. E. Cantón, J. Pemán, M. Gobernado, A. Viudes, A. Espinel-Ingroff, *Antimicrob. Agents. Chemother.* **2004**, *48*, 2477–2482. DOI:10.1128/AAC.48.7.2477-2482.2004
30. A. O. Abdelhamid, S. M. Gomha, N. A. Abdelrehem, A. M. Shalaby, S. M. Kandeel, *Synth. Commun.* **2018**, *48*, 677–684.
DOI:10.3390/molecules27206977

Povzetek

S pomočjo heterociklizacije metil 2-(3,5-dibromo-2-hidroksibenziliden)hidrazin-1-karboditioata (**4**) oz. metil (*E*)-2-(1-(5,7-dibromobenzofuran-2-il)etiliden)hidrazin-1-karboditioata (**5**) z različnimi hidrazonoil kloridi smo pripravili dve seriji novih 1,3,4-tiadiazolskih derivatov. Strukture novih produktov smo določili s pomočjo elementne analize in spektroskopskih podatkov. Osmim novim spojinam iz prve serije (ki vsebuje dibromohidroksibenzenski fragment) smo določili protimikrobno delovanje proti: *Staphylococcus aureus* ATCC 6538-P (kot primer Gram-pozitivne bakterije), *Escherichia coli* ATCC 25933 (Gram-negativna bakterija), *Candida albicans* ATCC 10231 (kvasovka) in glivi *Aspergillus niger* NRRL-A326 ter dobljene rezultate primerjali z vrednostmi za standardno referenčno učinkovino neomicin (v primeru *S. aureus*, *E. coli* and *C. albicans*) oz. cikloheksamid (v primeru glive *A. niger*). Rezultati kažejo, da imajo nekatere izmed novih spojin obetavne protimikrobne lastnosti.



Except when otherwise noted, articles in this journal are published under the terms and conditions of the Creative Commons Attribution 4.0 International License