Hindawi
Journal of Chemistry
Volume 2022, Article ID 5228067, 10 pages
https://doi.org/10.1155/2022/5228067

Research Article

Synthesis, Characterization, and Antimicrobial Activity of New 1,2,3-Thiadiazole and 1,2,3-Selenadiazole Derivatives

Mousa L. Al-Smadi,[1] **Fatima Esmadi**,[2] **Mohammad Al-Smadi**,[1] **Karem H. Alzoubi**,[3,4] **Osama Alzoubi**,[5] **and Yousef S. Khader**[6]

[1]*Department of Chemistry, Faculty of Science and Arts, Jordan University of Science and Technology, Irbid 22110, Jordan*
[2]*Department of Chemistry, Faculty of Science, Yarmouk University, Irbid, Jordan*
[3]*Department of Pharmacy Practice and Pharmacotherapeutics, University of Sharjah, Sharjah, UAE*
[4]*Department of Clinical Pharmacy, Jordan University of Science and Technology, Irbid, Jordan*
[5]*School of Medicine, The University of Jordan. Amman, Jordan*
[6]*Department of Public Health and Community Medicine, Faculty of Medicine, Jordan University of Science and Technology, Irbid 22110, Jordan*

Correspondence should be addressed to Mousa L. Al-Smadi; mariam10@just.edu.jo

Received 29 May 2022; Revised 3 July 2022; Accepted 6 August 2022; Published 7 September 2022

Academic Editor: Liviu Mitu

1,2,3-Thiadiazole, 1,2,3-selenadiazole, and semicarbazones that are prepared from ketones are promising moieties for lead compound development. New 1,2,3-thiadiazole (2c-4c) and 1,2,3-selenadiazole derivatives (2d–4d) were prepared from the corresponding semicarbazones (2b-4b). The semicarbazones (2b-4b) were prepared from the corresponding ketones (2a-4a). Characterization of the synthesized compounds was performed using infrared spectra (IR), proton nuclear magnetic resonance (^{1}H-NMR) spectra, carbon nuclear magnetic resonance (^{13}C-NMR), ultraviolet spectra, mass spectrometry, and elemental analysis. The antimicrobial activity of the prepared compounds was explored in vitro against various pathogenic microbes. All heterocyclic compounds had positive antimicrobial activity, but these activities varied in the extent of antimicrobial coverage. Compounds (2c) and (2d) had positive activity against *Staphylococcus aureus* and *Escherichia coli* but without any anti-pseudomonal activity. Compound (3c) had the most activity against *Candida albicans* with potential as a novel antifungal agent along with activity against some Gram-positive and Gram-negative bacteria. Compounds (4c) and (4d) exhibited broad-spectrum coverage in which both compounds demonstrated antimicrobial activity against all microorganisms explored. Interestingly, they both had substantial antipseudomonal activity against local resistant *Pseudomonas aeruginosa* and reference *P. aeruginosa* (ATCC 27853). This may suggest the potential for compounds (4c) and (4d) as novel broad-spectrum antibacterial agents with promising antipseudomonal activity. In conclusion, new 1,2,3-thiadiazole (2c-4c) and 1,2,3-selenadiazole (2d-4d) derivatives were identified as potential lead compounds for novel antibacterial agents.

1. Introduction

1,2,3-thiadiazole or 1,2,3-selenadiazole, are five-membered aromatic ring compounds containing three contiguous heteroatoms: one sulfur or selenium and two nitrogen atoms. Further exploration of the therapeutic potential of new 1,2,3-thiadiazole or 1,2,3-selenadiazole is an active area of research. Previous studies have demonstrated that some of the new 1,-2,3-thiadiazole or 1,2,3-selenadiazole derivatives exhibit antifungal [1, 2] antiviral [3, 4], and anticancer activities [5]. The concept of isosteric exchange has long been used as a tool for modifying the activity of biologically important molecules. The incorporation of the isosteric pair (sulfur and selenium) as heteroatoms in the heterocyclic system is an important example [6].

Hurd and Mori have previously prepared 1,2,3-thiadiazoles through cyclization reaction of hydrazones upon reaction with thionyl chloride [7–9]. This method is widely

employed for the synthesis of 1,2,3-thiadiazoles with high yields [7, 9, 10]. The synthesis of 1,2,3-selenadiazoles by analogy with the 1,2,3-thiadiazole system by Hurd and Mori has been previously reported [7–9]. In the present study, we report the synthesis of new 1,2, 3-thiadiazole and 1 2 3-selenadiazole derivatives using the methods of Hurd and Mori and Lalezari et al. [7, 8] with subsequent characterization of the synthesized compounds by infrared spectra (IR), proton nuclear magnetic resonance (^{1}H-NMR) spectra, carbon nuclear magnetic resonance (^{13}C-NMR), ultraviolet spectra (UV), mass spectrometry, and elemental analysis. Furthermore, we explored the antimicrobial activity of these newly synthesized heterocyclic compounds against common human pathogenic organisms by the hole diffusion method. Spectrum of antimicrobial action against Gram-positive bacteria (*Staphylococcus aureus*), Gram-negative bacteria *Escherichia coli*, local resistant *Pseudomonas aeruginosa* and reference *Pseudomonas aeruginosa* (ATCC 27853), and fungus (*Candida albicans*) were examined and reported. The extent of antimicrobial activity was compared between different compounds by reporting the diameter of the inhibition zone at a constant compound concentration. This study gives insight into compounds with potential as novel antibacterial and antifungal agents. This comes in the current situation where antibacterial, as well as antifungal, resistance among *Candida* species is a major problem [11–14].

2. Method

Acetone was dried and distilled prior to use from phosphorus pentoxide (P_2O_5). Chloroform was dried and distilled over anhydrous calcium chloride, collected over magnesium sulfate then filtered, and stored over molecular sieves (3 A°). Absolute ethanol and glacial acetic acid were used without further drying. All solvents were obtained from Scharalab. 4-hydroxy acetophenone, selenium dioxide, and thionyl chloride were obtained from ACROS. These chemicals were used without further purification. Semicarbazide hydrochloride was obtained from Schuchardt (Merck). Sodium acetate anhydrous extra pure, potassium carbonate, Aliquat 336, and sodium bicarbonate were obtained from Scharalau. 4-chloro-3-methylphenol, 4-nitrobenzyl bromide, 2-bromo-4-chlorophenol, and 1,2-dibromoethane were obtained from Aldrich.

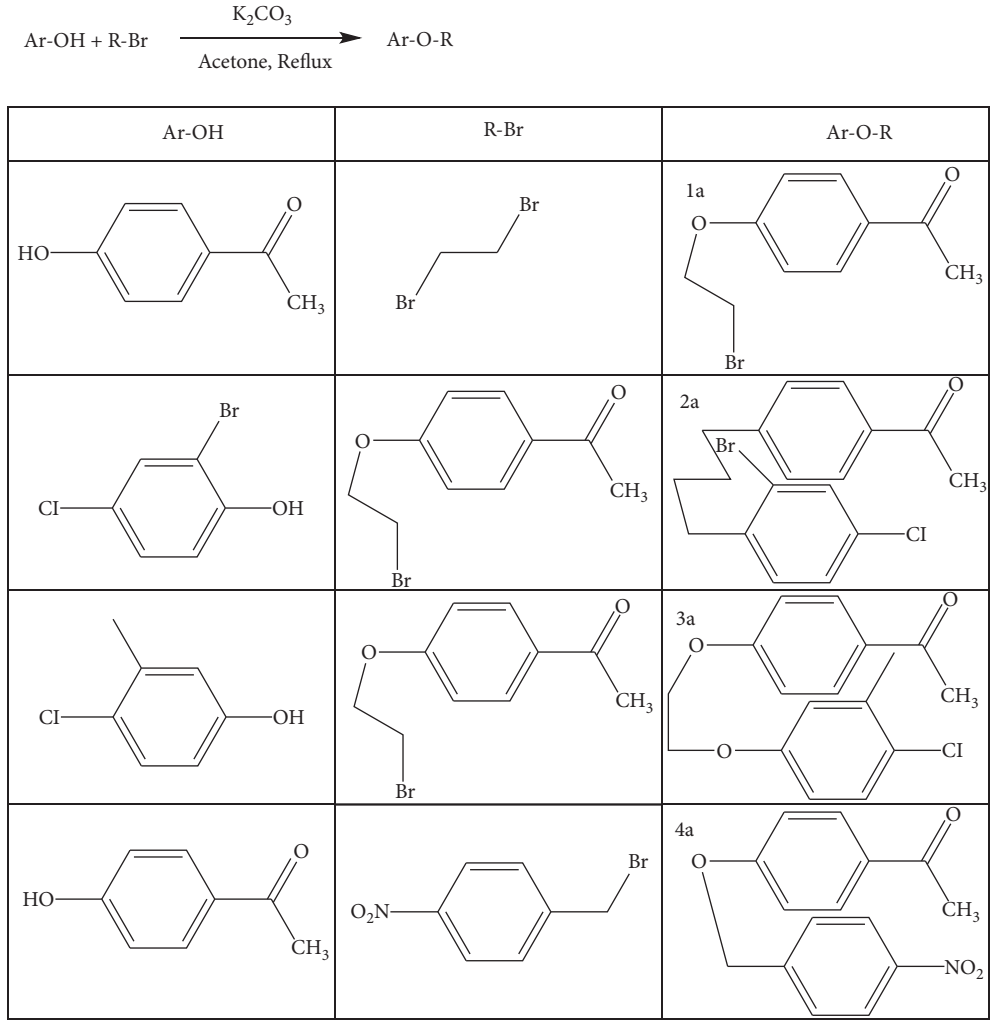
Melting points (mp) were determined on electrothermal digital melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded using IR Prestige-21 Fourier transform spectrophotometers version 1.50 as KBr pellets. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on 400 MHz (JEOL, JNM = ECP400, FT-NMR system), (200 MHz with AC200 Instrument from Bruker company), tetramethylsilane (TMS) was used as an internal reference. Carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on 100 MHz (JEOL, JNM-ECP400, FT-NMR System), (50 MHz with AC200 Instrument from Bruker company). Ultraviolet spectra were recorded using UV-1700 Pharma. Spec. Shimadzu corporation spectrometer. The mass spectra were carried out using instruments MAT CH7A of Varian Company (EI: 70Ev ionization energy, electron ionization) and using MAT95 of Finnigan Company (FD: 5 KV ionizing energy, field desorption). The signals were given as m/z with the relative intensity between brackets. The analytical thin layer chromatography (TLC) was carried out using TLC-silica plates (0.2 mm) from Merck Company. The elemental analysis was carried out by using an elemental analyzer from NCHS Euro 3000Italy.

2.1. General Preparative Procedures

2.1.1. Synthesis of 1-(4-(2-Bromoethoxy) Phenyl) Ethanone (1a). The synthesis was carried out according to the method described in the literature [7–9]. A mixture of 4-hydroxyacetophenone (3.4 g, 25 mmol), with an excess amount of 1,2-dibromoethane (46.96 g, 250 mmol), potassium carbonate (34.6 g, 250 mmol), and a few drops of Aliquat 336 in 150 mL dry acetone was refluxed for 40 hours. The reaction was followed with TLC in chloroform until completion. The reaction mixture was cooled, and the precipitated salt was removed by filtration. The solvent and excess of 1,2-dibromoethane were removed under vacuum and the product was purified using silica gel column chromatography (40 cm). Traces of 1,2-dibromoethane was eluted with petroleum ether (40–70°C), then the product at the top of the column was eluted by chloroform. The solvent was evaporated under a vacuum to obtain a white powder (2.5 g, 74%), which melts at 62–63°C. Spectroscopic and analytical results of compound **(1a)** are shown in supplementary Table 1. Synthesis of compounds (**1a**-**4a**) is illustrated in Scheme 1.

2.1.2. Synthesis of 1-(4-(2-(2-Bromo-4-Chlorophenoxy) Ethoxy) Phenyl) Ethanone (2a) and 1-(4-(2-(4-Chloro-3-Methylphenoxy) Ethoxy) Phenyl) Ethanone (3a). A mixture of 1-(4-(2-bromoethoxy) phenyl) ethanone **(1a)** (2.45 g, 10 mmol) and either 2-bromo-4-chlorophenol (2.07 g, 10 mmol) or 4-chloro-3-methylphenol (1.43 g, 10 mmol), potassium carbonate (1.38 g, 10 mmol), and few drops of Aliquat 336 in 100 mL dry acetone was refluxed for 40 hours. The reaction was followed with TLC in chloroform until completion. The reaction mixture was then cooled, the precipitated salt was removed by simple filtration, and the solution was evaporated to dryness under vacuum. The remaining white solid was washed using a small amount of cold ethanol and dried to give 3.6 g for both compounds (97% for **(2a)** and 92% for **(3a)**. Spectroscopic and analytical results of compounds **(2a)** and **(3a)** are shown in supplementary Tables 2 and 3. Synthesis of compounds **(2a)** and **(3a)** is illustrated in Scheme 1.

2.1.3. Synthesis of 1-(4-((4-Nitrobenzyl) Oxy) Phenyl) Ethanone (4a). A similar procedure to that used for the preparation of compounds **(2a)** and **(3a)** was followed for the preparation of compound **(4a)** except that 3.4 g, 10 mmol of 4-hyroxyacetophenone, and 5.4 g, 25 mmol 4-nitrobenzyl bromide were used. After the drying step, a pale-yellow oil



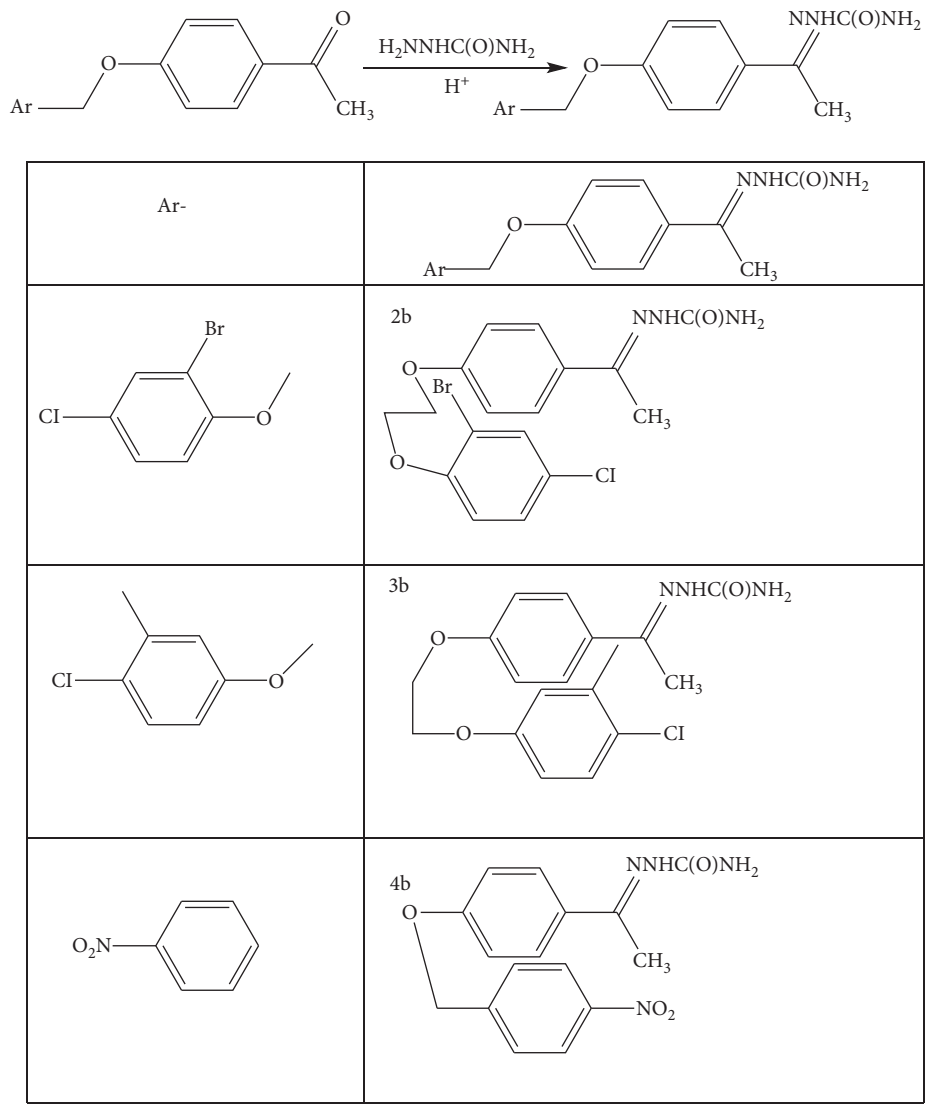
Scheme 1: Synthesis of ketones (1a–4a).

was obtained, which quickly transformed into solid at room temperature to give 7.47 g, 97% of the product. Spectroscopic and analytical results of compound **(4a)** are shown in supplementary Table 4. Synthesis of compound **(4a)** is illustrated in Scheme 1.

2.1.4. Synthesis of (E)-2-(1-(4-(2-(2-Bromo-4-Chlorophenoxy) ethoxy) Phenyl) Ethylidene) Hydrazinecarboxamide (2b) and (E)-2-(1-(4-(2-(4-Chloro-3-Methylphenoxy) Ethoxy) Phenyl) Ethylidene) Hydrazinecarboxamide (3b). A mixture of semicarbazide hydrochloride (1.67 g, 15 mmol) and sodium acetate (1.23 g, 15 mmol) was dissolved in 50 mL absolute ethanol and heated to reflux for 30 minutes. The mixture was filtered while hot, to remove precipitated sodium chloride salt. Then, an equivalent amount (15 mmol) of ketones **(2a,** 5.54 g**)** or **(2a),** 4.58 g was added to the hot filtrate. The mixture was refluxed for 1 hour and water generated was continuously removed using succulent with magnesium sulfate. After 30 minutes, the reaction started producing precipitate. After precipitation completes, the reaction mixture was cooled to room temperature. Then, the precipitated semicarbazone was filtered off, washed with cold ethanol, and dried to give a white solid (5.2 g, 81.3%) of **(2b)** and 4.62 g, 85% of **(3b)**. Spectroscopic and analytical results of compounds **(2b)** and **(3b)** are shown in supplementary Tables 5 and 6. Synthesis of compounds **(2b)** and **(3b)** is illustrated in Scheme 2.

2.1.5. Synthesis of (E)-2-(1-(4-((4-Nitrobenzyl) Oxy) Phenyl) Ethylidene) Hydrazinecarboxamide (4b). A similar procedure to that used for the preparation of semicarbazones **(2b)** and **(3b)** was used for the preparation of semicarbazone **(4b)** from ketone **(4a).** The product obtained was a yellow solid (3.94 g, 80% yield) of semicarbazone **(4b)**. Spectroscopic and analytical results of compound **(4b)** are shown in supplementary Table 7. Synthesis of compound **(4b)** is illustrated in Scheme 2.

2.1.6. Synthesis of 4-(4-(2-(2-Bromo-4-Chlorophenoxy)Ethoxy)Phenyl)-1,2,3-Thiadiazole (2c) and 4-(4-(2-(4-Chloro-3-Methylphenoxy)Ethoxy)Phenyl)-1,2,3-Thiadiazole (3c). 10 mmol of semicarbazones **(2b**, 4.27 g) or **(3b**, 3.62 g) were slowly added to thionyl chloride (20 g, 16 mmol) in several

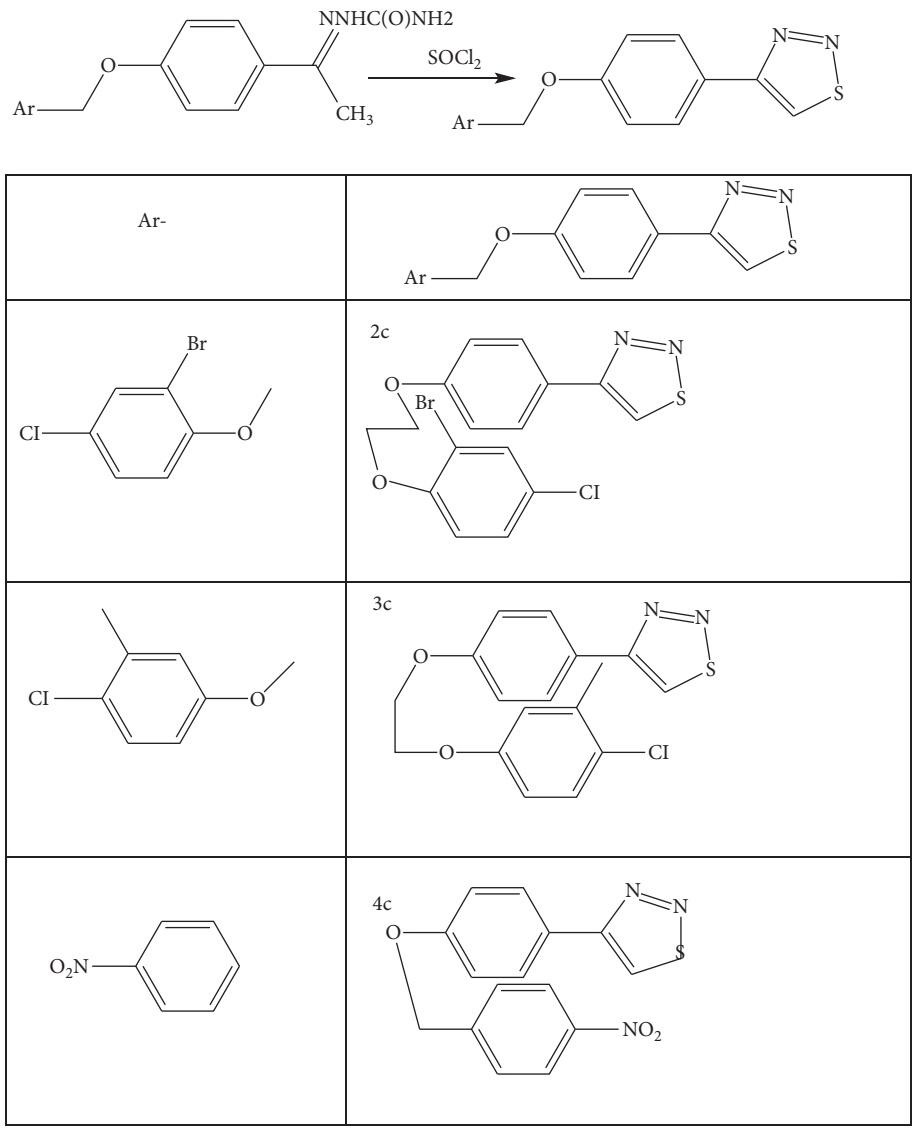


Scheme 2: Synthesis of semicarbazone derivatives (2b–4b).

portions with vigorous stirring. The mixture was stirred overnight at room temperature until no more hydrogen chloride is being produced. The excess thionyl chloride was removed under vacuum. The remaining residues were washed with several portions of petroleum ether (60–70°C). The products have pale-yellow color and included 2.9 g, 70% yield of **(2c)** and 2.1 g, 60% yield of **(3c)**. Spectroscopic and analytical results of compounds **(2c-3c)** are shown in supplementary Tables 8 and 10. Synthesis of compounds **(2c-3c)** is illustrated in Scheme 3.

2.1.7. Synthesis of 4-(4-(2-(2-Bromo-4-Chlorophenoxy) Ethoxy) Phenyl)-1,2,3-Selenadiazole (2d) and 4-(4-(2-(4-Chloro-3-Methylphenoxy) Ethoxy) Phenyl)-1,2,3-Selenadiazole (3d). Compound **(2b)** (1.7 g, 4 mmol) or **(3b)** (1.45 g, 4 mmol) was dissolved in 50 mL glacial acetic acid with vigorous stirring and gentle heating (35–40°C). The solution was treated with selenium dioxide powder (0.6 g, 5.41 mmol), and the mixture color became red after 2 minutes of treatment. The mixture was kept under gentle heating and vigorous stirring overnight followed by TLC until the reaction was complete. The precipitated solid was removed by simple filtration and the filtrate was poured over ice water and extracted with chloroform (3 × 50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution and dried using magnesium sulfate. The solvent was removed under vacuum and the remaining product was recrystallized from acetone to give the brown solid (1.1 g, 60% yield) of compound **(2d)** and 0.94 g, 60% yield of compound **(3d)**. Spectroscopic and analytical results of compounds **(2d-3 d)** are shown in supplementary Tables 9 and 11. Synthesis of compounds **(2d)** and **(3d)** is illustrated in Scheme 4.

2.1.8. Synthesis of 4-(4-((4-Nitrobenzyl) Oxy) Phenyl)-1,2,3-Thiadiazole (4c). Similar procedure to that used for the preparation of compounds **(2c-3c)** was used for the preparation of compound **(4c)** from semicarbazone (**4b**) (2.10 g,



Scheme 3: Synthesis of 1,2,3-thiadiazole derivatives (2c–4c).

6.00 mmol). The product obtained is a yellow solid with a 70% yield (0.66 g). Spectroscopic and analytical results of compound **(4c)** are shown in supplementary Table 12. Synthesis of compound **(4c)** is illustrated in Scheme 3.

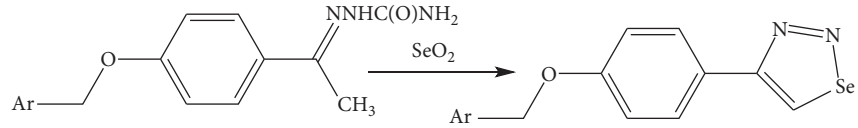
2.1.9. Synthesis of 4-(4-((4-Nitrobenzyl) Oxy) Phenyl)-1,2,3-Selenadiazole (4d). Similar procedure to that used for the preparation of compounds **(2d-3d)** was followed for the preparation of compound **(4d)** from semicarbazone **(4b)** (1.2 g, 3.49 mmol). The product obtained was a light brown solid (1.86 g, 84% yield). Spectroscopic and analytical results of compound **(4d)** are shown in supplementary Table 13. Synthesis of compound **(4d)** is illustrated in Scheme 4.

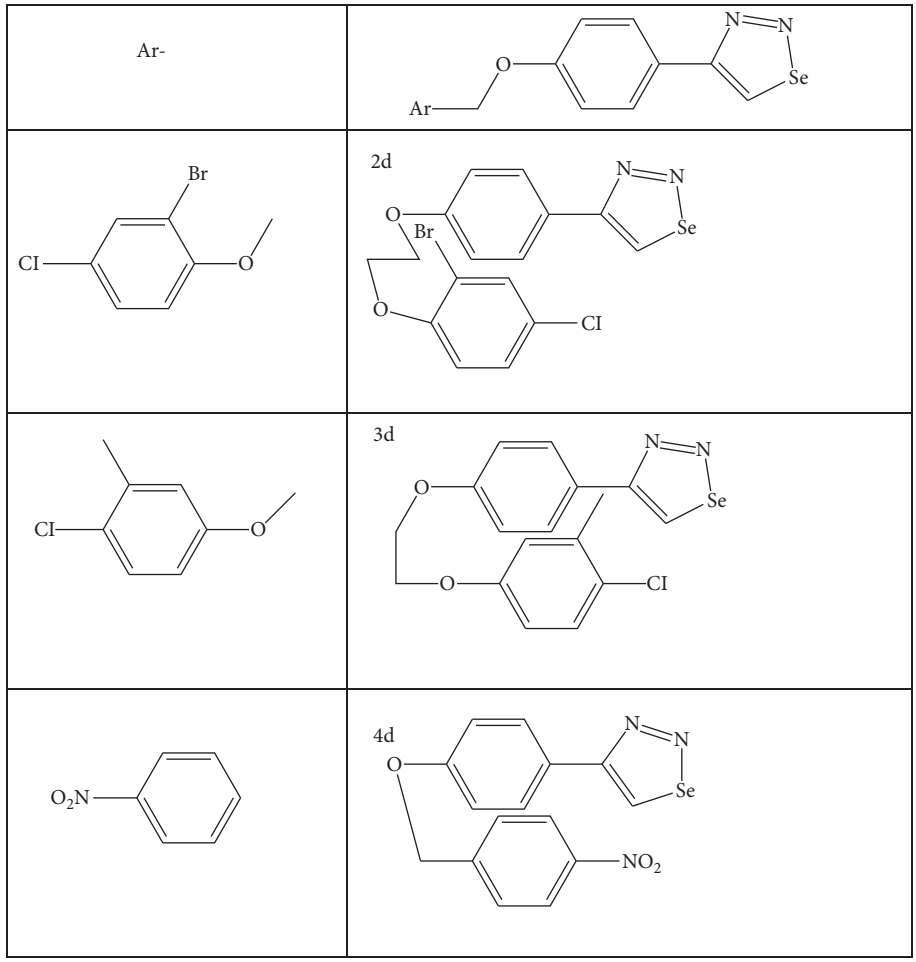
2.2. Antimicrobial Activity. The antimicrobial activity of the heterocyclic compounds **(2c), (2d), (3c),** and **(3d)** was tested against certain human pathogenic microbes including Gram-positive bacteria (*Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli*), local resistant *Pseudomonas aeruginosa* and a reference *Pseudomonas aeruginosa* ATCC 27853), and the fungus, *Candida albicans*, by the hole diffusion method, grown on nutrient agar as previously described [9,15]. The solutions of compounds **(2c), (2d), (3c), (3d), (4c),** and **(4d)** were prepared by dissolving them in 0.01 g/mL dimethylsulfoxide (DMSO). Standard antimicrobials were used for each of the above-tested microorganisms. The diameter of the inhibition zone was measured at the constant low concentration of 0.01 g/mL.

3. Results and Discussion

New 1,2,3-thiadiazole, and 1,2,3-selenadiazole derivatives were prepared via methods that were first reported by Hurd and Mori for 1,2,3-thiadiazole compounds and by Lalezari *et al* for 1,2,3-selenadizole compounds [7–9]. In both methods, the semicarbazones derived from the corresponding ketones were applied for the preparation of 1,2,3-

Scheme 4: Synthesis of 1,2,3-selenadiazole derivative (2d-4d)





Scheme 4: Synthesis of 1,2,3-selenadiazole derivatives (2d–4d).

thiadiazole and 1,2,3-selenadiazole derivatives. To obtain the 1,2,3-thiadiazoles and 1,2,3-selenadiazoles, the starting ketones and semicarbazones have been prepared and characterized as illustrated in Schemes 1–4. The IR, MS, elemental analysis, UV, ^{1}H-NMR, ^{13}C-NMR data, and physical properties of compounds **(1a–4a)**, **(2b–4b)**, **(2c–4c)**, and **(2d–4d)** are shown in supplementary Tables 1–13. The IR, ^{1}H-NMR, and ^{13}C-NMR spectra of compounds **(1a–4a)**, **(2b–4b)**, **(2c–4c),** and **(2d–4d)** are shown in supplementary Figures 1–39.

3.1. Ketones. Scheme 1 shows the preparation of **(1a)** by the reaction of the commercially available 4-hydroxyacetophenone with 1,2-dibromoethane in the presence of potassium carbonate and 2–3 drops of Aliquat 336 (catalyst) in refluxing acetone. The potassium carbonate was added to the phenol derivative (acid) to undergo an acid-base reaction to convert the weak nucleophile (the phenol derivative) into a stronger nucleophile (the potassium phenoxide derivative) that can accomplish the S_N2 substitution reaction with the primary alkyl halide faster. The reaction goes to completion in about 40 hours to give the expected ketone **(1a)**.

The reaction is a nucleophilic substitution one. Compound **(1a)** is the starting material for the preparation of ketones **(2a)** and **(3a)**.

The structure of ketone **(1a)** was confirmed by spectroscopic measurements. The IR-spectrum of ketone **(1a)** exhibited a band at 1668 cm^{-1} for the carbonyl group (supplementary Table 1). The ^{1}H-NMR spectrum showed a single peak at 2.51 ppm for CO(C$\underline{H}_3$) and two triplets at 4.5 and 3.84 ppm for –C$\underline{H}_2$C$\underline{H}_2$–O, whereas the aromatic protons appeared as two doublets in the aromatic region from 7.10 to 8.01 ppm. The ^{13}C-NMR spectrum showed one peak for CH_3-carbon at 26.5 ppm and the carbonyl carbon at 196.13 ppm. The mp, mass spectroscopy, elemental analysis,

and UV-spectra are shown in supplementary Table 1. Scheme 2 shows the preparation of compounds **(2a)** and **(3a)**. The reaction involves nucleophilic substitution reaction of ketone **(1a)** with 2-bromo-4-chlorophenol or 4-chloro-3-methylphenol in presence of potassium carbonate and 2–3 drops of Aliquat 336 (catalyst) in refluxing acetone. The reaction undergoes completion in about 40 hours to give expected ketones **(2a), (3a)**.

The structures of ketones **(2a), (3a)** were confirmed by spectroscopic measurements. The IR spectra of ketones **(2a)** and **(3a)** exhibited bands at 1677 or 1665 cm^{-1} for the carbonyl group, supplementary Tables 2–3, respectively. The ^{1}H-NMR spectra showed single peaks at 2.51 or 2.58 ppm for CO($C\underline{H}_3$) and two triplets at 4.4 and 4.38, 4.43 ppm for –$C\underline{H}_2$ $C\underline{H}_2$–O, the aromatic protons appeared as four doublets in the aromatic region from 6.8 to 7.97 ppm and for both ketones **(2a)** and **(3a)**, one singlet at 7.9 for ketone **(2a)** and at 6.99 ppm for ketone **(3a)** and one singlet at 2.36 ppm for the methyl group of ketone **(3a)**. The ^{13}C-NMR spectra of ketones **(2a), (3a)** showed peaks for carbon $\underline{C}H_3$ at 26.3, 26.37 ppm and for carbonyl carbon at 196.7, 196.78 ppm, respectively. The mp, mass spectroscopy, elemental analysis, and UV-spectra are shown in supplementary Tables 2–3.

Ketone **(4a)** was prepared by nucleophilic substitution reaction of the commercially available 4-hydroxyacetophenone with 4-nitrobenzyl bromide in presence of potassium carbonate and 3 drops of Aliquat 336 (catalyst) in refluxing acetone. Again, this reaction undergoes completion in about 40 hours to give the expected ketone **(4a)** as shown in Scheme 3. The structure of ketone **(4a)** was confirmed by spectroscopic measurements. The IR-spectrum of ketone **(4a)** exhibited a band at 1675 cm^{-1} for the carbonyl group. The ^{1}H-NMR spectrum showed two single peaks at 2.49 ppm for CO($C\underline{H}_3$) and 5.36 ppm for –$C\underline{H}_2$-O, whereas the aromatic protons appeared as four doublets in the aromatic region from 6.84 to 7.92 ppm. The ^{13}C-NMR spectrum showed a peak for carbon atom of $\underline{C}H_3$ at 25.58 ppm and carbonyl carbon at 195.57 ppm. The mp, mass spectroscopy, elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR, and UV-spectra results are shown in supplementary Table 4.

3.2. Semicarbazones. Semicarbazones **(2b–4b)** were prepared by condensation reaction between ketones **(2a–4a)** and the semicarbazide in refluxing ethanol as shown in Schemes 1 and 2. The semicarbazones **(2b–4b)** were obtained as white powders with 81.3, 82.8, 80% yields and mp 203–205, 196, 238–240 C, respectively.

The structure of compounds **(2b–4b)** was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopic measurements. The IR spectra of the semicarbazones **(2b–4b)** showed characteristic bands at 3480, 3334, 3427 cm^{-1} for–NH, (3233, 3194), (3100, 3066), (3203, 3175) cm^{-1} for–NH_2, and 1678, 1675, 1689 cm^{-1} for carbonyl group, respectively. ^{1}H-NMR spectra showed the disappearance of the characteristic peak of CH_3–C=*O* and the formation of new peak for $\underline{C}H_3$–C=N at 2.14, 1.31, 2.13 ppm (s, 3H). ^{13}C-NMR showed peaks at 20.24, 20.24, 13.26 ppm for $\underline{C}H_3$ and at 147.7, 137.03, 147.07 ppm for $\underline{C}$=*N*, respectively. In addition, the appearance of two singlet peaks, one of them for –NH at 9.18, 8.36, 6.99 ppm and the second for –NH_2 at 6.42, 5.59, 6.44 ppm, respectively, confirms the formation of the semicarbazones. The ^{1}H-NMR, ^{13}C-NMR, elemental analysis, UV-spectra, and mass spectroscopy are shown in supplementary Tables 5–7.

In previous studies, the preparation of semicarbazones $R_1R_2C = NNHC(O)NH_2$, showed that the configuration of the C=N bond exists mostly in the *E* form, which was found to be the major product according to the nuclear over house effect experiments of the ^{1}H-NMR spectra due to less steric factor [7]. Therefore, the structures of compounds **(2b-4b)** are drawn in the *E* form depending on ^{1}H-NMR spectra.

3.3. 1,2,3-Thiadiazoles. The 1,2,3-thiadiazoles were obtained by treating semicarbazones **(2b-4b)** with thionyl chloride at room temperature as shown in Scheme 3. 1,2,3-Thiadiazoles **(2c-4c)** were obtained in 70, 60, and 68.4% yields and found to decompose at 140, 135, and 180 C, respectively. IR spectra for compounds **(2c-4c)** from supplementary Tables 8, 10, and 12 showed the absence of the bands at 3480, 3334, and 3427 cm^{-1} for–NH and formation of new bands at (1469, 1442), (1477, 1450), (1514, 1449) cm^{-1} for the 1,2,3-thiadiazole rings, respectively.

^{1}H-NMR spectra showed a singlet peak at 8.53, 8.56, 8.51 ppm, respectively, which is attributed to the proton at carbon number five of the 1,2,3-thiadiazole ring. ^{13}C-NMR spectra showed that the peaks due to C_4 and C_5 appeared at 162.6, 161.07, 162.7 ppm and 129.93, 130.10, 158.77 ppm, respectively. From these data, the active α-methyl group of the semicarbazones **(2b-4b)** had disappeared. The ^{1}H-NMR, ^{13}C-NMR, IR, mp, mass spectroscopy, and elemental analysis data of compounds **(2c-4c)** are shown in supplementary Tables 8, 10, and 12.

3.4. 1,2,3-Selenadiazoles. The 1,2,3-selenadiazole compounds **(2d-4d)** were obtained by treating semicarbazones **(2b-4b)** with selenium dioxide in glacial acetic acid as shown in Scheme 1. Compounds **(2d)** and **(3d)** were obtained in 60% yield whereas **(4d)** was obtained in 68.4% yield. The reaction of semicarbazones **(2b-4b)** is very slow due to low solubility in acetic acid.

IR spectra of the 1,2,3-selenadiazoles **(2d–4d)** showed appearance of characteristic bands in 1421–1480 cm^{-1} region for 1,2,3-selenadiazole heterocyclic ring and the disappearance of the peaks at 3480, 3334, 3427 cm^{-1} that is characteristic of semicarbazones–NH group. The ^{1}H-NMR spectra showed a single peak that appears downfield at 9.26, 9.19, 9.31 ppm which is due to the proton at carbon number five of the heterocyclic ring. The ^{13}C-NMR spectra showed a chemical shift due to C_4 and C_5 at 162.60, 162.79, 162.70 ppm and 129.93, 131.94, 156.79 ppm for 1,2,3-selenadiazoles **(2d–4d)**, respectively. The ^{1}H-NMR, ^{13}C-NMR, IR, mp, mass spectroscopy, and elemental analysis data of compounds **(2c–4c)** are shown in supplementary Tables 9, 11, and 13.

Table 1: Sensitivity of human pathogenic microbes to the new synthetic heterocyclic compounds, and some complexes using the hole method.

Compound	Compound concentration (g/mL)	*Staphylococcus aureus*	*Escherichia coli*	*Candida albicans*	Local resistant *Pseudomonas aeruginosa*	Reference *Pseudomonas aeruginosa* ATCC 27853
2c	0.01	+++	+	+	−	−
2d	0.01	+	+	−	−	−
3c	0.01	+++	++	++	+	−
3d	0.01	−	++	+	++	−
4c	0.01	+++	+++	+	+++	+++
4d	0.01	+++	++	+	+++	+++

Results were expressed as ranges of diameters of zones of inhibition of antimicrobial activity. An inhibition zone diameter (ID) < 5 mm was denoted as "+", ID of 10 mm-5 mm was denoted as "++", and ID of >10 mm was denoted as "+++". The "−" indicates no inhibition zone. Standard antimicrobials were used for each of the above-tested microorganisms, where the zone of inhibition for each standard compound was >10 mm "+++" for its corresponding microorganism.

3.5. Antimicrobial Activity. The activity of the heterocyclic compounds **(2c), (2d), (3c), (3d), (4c),** and **(4d)** was tested against some human pathogenic microbes including Gram-positive *S. aureus*, Gram-negative *E. coli*, local resistant *P. aeruginosa* and reference *P. aeruginosa* (ATCC 27853), and *C. albicans* by the hole diffusion method [9,15]. As shown in Table 1, all six heterocyclic compounds had positive antimicrobial activity at a concentration of 0.01 g/mL, but they varied in their antimicrobial coverage. The extent of antimicrobial action also differed among compounds as noted by examining the diameter of the inhibition zone at a constant low concentration when using the hole diffusion technique. Heterocyclic compounds (2c) and (2d) had positive activity against *S. aureus* and *E. coli*, along with some activity of compound (2c) against *C. albicans*. However, they did not show any antipseudomonal activity. Compound (3c), like compound (2c), showed positive activity against *S. aureus* and even better activity against *E. coli* and *C. albicans*. Furthermore, compounds (3c) and (3d) showed positive antimicrobial activity against local resistant *P. aeruginosa*.

Another remarkable finding was the broad-spectrum coverage of heterocyclic compounds (4c) and (4d) in which both compounds exhibited antimicrobial activity against all microorganisms explored. After examining the diameter of inhibition zone, interestingly, they both had substantial antipseudomonal activity against local resistant *P. aeruginosa* and reference *P. aeruginosa* (ATCC 27853). The solvent showed no activity against any of the tested pathogens.

The results of the present study demonstrated that heterocyclic compounds (4c) and (4d) have high potential as novel broad-spectrum antibacterial agents with promising antipseudomonal activity. Additionally, by observing the diameter of the inhibition zone, heterocyclic compound (3c) had the most activity against *C. albicans* with activity against some Gram-positive and Gram-negative bacteria. Thus, compound (3c) has potential as a novel antifungal and antibacterial agent.

4. Conclusions

New compounds of ketones, semicarbazones, 1,2,3-thiadiazoles, and 1,2,3-selenadizoles were prepared. All prepared compounds were fully characterized by spectroscopic techniques. The antimicrobial activity of the prepared heterocyclic 1,2,3-thiadiazoles and 1,2,3-selenadizoles was explored. All heterocyclic compounds had positive antimicrobial activity but differed in their spectrum of antimicrobial coverage and extent of action. Results were promising of several compounds with broad-spectrum antimicrobial and antipseudomonal action, in addition to other compounds with antifungal activity. These results come at the time of urgent need to develop novel antimicrobial agents to overcome the emerging resistance worldwide. Future work based on the current study should focus on molecular docking and X-ray crystallographic analysis. In the present study, the compounds were obtained as fine amorphous powder. In a future study, we recommend obtaining fine crystals to carry out the X-ray crystallographic study for other compounds. We also recommend preparing their metal complexes and testing their antimicrobial activity against certain standard or reported drug.

Data Availability

Data will be available upon request via e-mailing the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This research was funded by the Deanship of Research at Jordan University of Science and Technology (grant number JUST-112-2010).

Supplementary Materials

Supplementary Table 1: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (1a). Supplementary Table 2: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (2a). Supplementary Table 3: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (3a). Supplementary Table 4: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of

compound (4a). Supplementary Table 5: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (2b). Supplementary Table 6: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (3b). Supplementary Table 7: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (4b). Supplementary Table 8: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (2c). Supplementary Table 9: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (2d). Supplementary Table 10: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (3c). Supplementary Table 11: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (3d). Supplementary Table 12: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (4c). Supplementary Table 13: IR, MS, Elemental analysis, UV, ^{1}H-NMR, and ^{13}C-NMR data of compound (4d). Supplementary Figure 1: IR-Spectrum of compound (1a) in KBr disk. Supplementary Figure 2: IR-Spectrum of compound (2a) in KBr disk. Supplementary Figure 3: IR-Spectrum of compound (3a) in KBr disk. Supplementary Figure 4: IR-Spectrum of compound (4a) in KBr disk. Supplementary Figure 5: IR-Spectrum of compound (2b) in KBr disk. Supplementary Figure 6: IR-Spectrum of compound (3b) in KBr disk. Supplementary Figure 7: IR-Spectrum of compound (4b) in KBr disk. Supplementary Figure 8: IR-Spectrum of compound (2c) in KBr disk. Supplementary Figure 9: IR-Spectrum of compound (2d) in KBr disk. Supplementary Figure 10: IR-Spectrum of compound (3c) in KBr disk. Supplementary Figure 11: IR-Spectrum of compound (3d) in KBr disk. Supplementary Figure 12: IR-Spectrum of compound (4c) in KBr disk. Supplementary Figure 13: IR-Spectrum of compound (4d) in KBr disk. Supplementary Figure 14: ^{1}H-NMR spectrum of compound (1a) in Acetone-d_6. Supplementary Figure 15: ^{1}H-NMR spectrum of compound (2a) in Chloroform–d_3. Supplementary Figure 16: ^{1}H-NMR spectrum of compound (3a) in Chloroform–d_3. Supplementary Figure 17: ^{1}H-NMR spectrum of compound (4a) in DMSO-d_6. Supplementary Figure 18: ^{1}H-NMR spectrum of compound (2b) in DMSO-d_6. Supplementary Figure 19: ^{1}H-NMR spectrum of compound (3b) in DMSO-d_6. Supplementary Figure 20: ^{1}H-NMR spectrum of compound (4b) in DMSO-d_6. Supplementary Figure 21: ^{1}H-NMR spectrum of compound (2c) in DMSO-d_6. Supplementary Figure 22: ^{1}H-NMR spectrum of compound (2d) in DMSO-d_6. Supplementary Figure 23: ^{1}H-NMR spectrum of compound (3c) in DMSO-d_6. Supplementary Figure 24: ^{1}H-NMR spectrum of compound (3d) in DMSO-d_6. Supplementary Figure 25: ^{1}H-NMR spectrum of compound (4c) in Chloroform–d_3. Supplementary Figure 26: ^{1}H-NMR spectrum of compound (4d) in Chloroform–d_3. Supplementary Figure 27: ^{13}C-NMR Spectrum of compound (1a) in acetone–d_6. Supplementary Figure 28: ^{13}C-NMR Spectrum of compound (2a) in Chloroform–d_3. Supplementary Figure 29: ^{13}C-NMR Spectrum of compound (3a) in Chloroform–d_3. Supplementary Figure 30: ^{13}C-NMR Spectrum of compound (4a) in DMSO-d_6. Supplementary Figure 31: ^{13}C-NMR Spectrum of compound (2b) in DMSO-d_6. Supplementary Figure 32: ^{13}C-NMR Spectrum of compound (3b) in DMSO-d_6. Supplementary Figure 33: ^{13}C-NMR Spectrum of compound (4b) in DMSO-d_6. Supplementary Figure 34: ^{13}C-NMR Spectrum of compound (2c) in DMSO-d_6. Supplementary Figure 35: ^{13}C-NMR Spectrum of compound (2d) in DMSO-d_6. Supplementary Figure 36: ^{13}C-NMR Spectrum of compound (3c) in DMSO-d_6. Supplementary Figure 37: ^{13}C-NMR Spectrum of compound (3d) in DMSO-d_6. Supplementary Figure 38: ^{13}C-NMR Spectrum of compound(4c) in Chloroform–d_3. Supplementary Figure 39: ^{13}C-NMR Spectrum of compound **(4d)** in Chloroform–d_3. (*Supplementary Materials*)

References

[1] B. Giray, A. E. Karadag, O. S. Ipek, H. Pekel, M. Guzel, and H. B. Kucuk, "Design and synthesis of novel cylopentapyrazoles bearing 1, 2, 3-thiadiazole moiety as potent antifungal agents," *Bioorganic Chemistry*, vol. 95, Article ID 103509, 2020.

[2] H. Xu, C. Cao, X. Wang et al., "Discovery of 1, 2, 3-selenadiazole analogues as antifungal agents using a scaffold hopping approach," *Bioorganic Chemistry*, vol. 115, Article ID 105182, 2021.

[3] P. Zhan, X. Liu, Z. Fang, C. Pannecouque, and E. D. Clercq, "1, 2, 3-Selenadiazole thioacetanilides: synthesis and anti-HIV activity evaluation," *Bioorganic and Medicinal Chemistry*, vol. 17, no. 17, pp. 6374–6379, 2009.

[4] P. Zhan, X. Y. Liu, Z. Y. Li, Z. J. Fang, C. Pannecouque, and E. Clercq, "1, 2, 3-thiadiazole thioacetanilides. Part 2: synthesis and biological evaluation of a new series of 2-{[4-(3, 4-dichlorophenyl)-1, 2, 3-thiadiazol-5-yl]sulfanyl}acetanilides as HIV-1 inhibitors," *Chemistry and Biodiversity*, vol. 7, no. 7, pp. 1717–1727, 2010.

[5] C. Wang, Z. Wang, M. Gao et al., "Design, synthesis and anticancer activity of 5-aryl-4-(4-arylpiperazine-1-carbonyl)-1, 2, 3-thiadiazoles as microtubule-destabilizing agents," *Bioorganic Chemistry*, vol. 106, Article ID 104199, 2021.

[6] D. B. Reddy, V. Padmavathi, A. Padmaja et al., "α-Ketomethylene functionality—a versatile source for the synthesis of some interesting selenadiazoles," *ChemInform*, vol. 37, no. 26, 2006.

[7] M. Al-Smadi and S. Ratrout, "New 1, 2, 3-selenadiazole and 1, 2, 3-thiadiazole derivatives," *Molecules*, vol. 9, no. 11, pp. 957–967, 2004.

[8] N. M. Mhaidat, M. Al-Smadi, F. Al-momani, K. H. Alzoubi, I. Mansi, and Q. Al-Balas, "Synthesis, antimicrobial and in vitro antitumor activities of a series of 1, 2, 3-thiadiazole and 1, 2, 3-selenadiazole derivatives," *Drug Design, Development and Therapy*, vol. 9, pp. 3645–3652, 2015.

[9] M. L. Al-Smadi, R. Mansour, A. Mahasneh, O. F. Khabour, M. M. Masadeh, and K. H. Alzoubi, "Synthesis, characterization, antimicrobial activity, and genotoxicity assessment of two heterocyclic compounds containing 1, 2, 3-selena- or 1, 2, 3-thiadiazole rings," *Molecules*, vol. 24, no. 22, p. 4082, 2019.

[10] H. Sugimura, R. Takeuchi, S. Ichikawa, E. Nagayama, and I. Sasaki, "Synthesis of 1, 2, 3-triazines using the base-mediated cyclization of (Z)-2, 4-Diazido-2-alkenoates," *Organic Letters*, vol. 20, no. 11, pp. 3434–3437, 2018.

[11] A. G. Stewart and D. L. Paterson, "How urgent is the need for new antifungals?" *Expert Opinion on Pharmacotherapy*, vol. 22, no. 14, pp. 1857–1870, 2021.

[12] M. A. Pfaller, G. J. Moet, S. A. Messer, R. N. Jones, and M. Castanheira, "Geographic variations in species distribution and echinocandin and azole antifungal resistance rates among Candida bloodstream infection isolates: report from the SENTRY Antimicrobial Surveillance Program (2008 to 2009)," *Journal of Clinical Microbiology*, vol. 49, no. 1, pp. 396–399, 2011.

[13] E. Christaki, M. Marcou, and A. Tofarides, "Antimicrobial resistance in bacteria: mechanisms, evolution, and persistence," *Journal of Molecular Evolution*, vol. 88, no. 1, pp. 26–40, 2020.

[14] S. Bhattacharya, S. Sae-Tia, and B. C. Fries, "Candidiasis and mechanisms of antifungal resistance," *Antibiotics*, vol. 9, no. 6, p. 312, 2020.

[15] M. M. Masadeh, N. M. Mhaidat, K. H. Alzoubi, S. I. Al-Azzam, and A. I. Shaweesh, "Ciprofloxacin-induced antibacterial activity is reversed by vitamin E and vitamin C," *Current Microbiology*, vol. 64, no. 5, pp. 457–462, 2012.