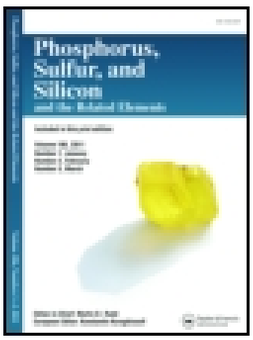

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Synthesis of novel 1,2,3-thiadizoles and 1,2,3-selenadiazoles as new antimicrobial agents

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ABSTRACT

A series of novel 1,2,3-thiadiazoles and 1,2,3-selenadiazoles having a long alkyl chain were synthesized by reacting semicarbazones with $SOCl_2$ and SeO_2, respectively. The structures of the target compounds **5–12** were confirmed by spectroscopy (IR, ^{1}H NMR, ^{13}C NMR, and MS) and elemental analysis. Their antibacterial and antifungal activities were evaluated against six bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Staphylococcus aureus*) and three fungi (*Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*). The results of bioassays indicated that the compounds 5-Dodecyl-4-(4-methoxy-phenyl)-[1-3]selenadiazole **(7),** 4-Methyl-5-tetradecyl-[1-3]selenadiazole **(8)** and 5-Dodecyl-4-(4-methoxy-phenyl)-[1-3]thiadiazole **(11)** displayed moderate antibacterial activity against *S. Epidermidis*. On the other hand, according to antifungal screening results, compounds 5-Dodecyl-4-phenyl-[1-3]selenadiazole **(5)**, 4-p-Tolyl-5-undecyl-[1-3]selenadiazole **(6)**, and 5-Dodecyl-4-(4-methoxy-phenyl)-[1-3]selenadiazole **(7)** exhibited significant antifungal activities studied yeast strains.

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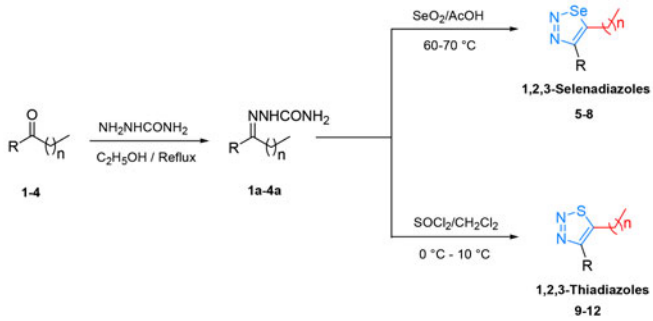
1,2,3-Thiadiazole; 1,2,3-selenadiazole; antibacterial activity; antifungal activity

GRAPHICAL ABSTRACT



Introduction

Synthetic methods for the preparation of organosulfur and organoselenium compounds annelated their importance for medicinal[1] and synthetic chemistry.[2,3] 1,2,3-Thiadiazoles and 1,2,3-selenadiazoles are well-known compounds, and researchers are interested in the synthesis of their intermediates.[4–11] Many substituted 1,2,3-thia- and 1,2,3-selenadiazole derivatives were synthesized and most of them have shown important antibacterial and antifungal activities.[12–16] When the 1,2,3-thiadiazole group is added to a known biologically active compound, the activity of the molecule changes and in some cases, the biological activity increases.[17,18]

Considering the above mentioned studies, in the present work, we have synthesized substituted new 1,2,3-thiadiazole and 1,2,3-selenadiazole compounds (Scheme 1). The synthesized compounds were subjected to antibacterial and antifungal activity testing, and the obtained results were evaluated.

According to the literature data, 1,2,3-thiadiazoles and 1,2,3-selenadiazoles have been prepared using aromatic, aliphatic and cyclic ketones with short alkyl chain lengths.[10,11] However, these products with long alkyl chain lengths are missing in the literature. Motivated by the aforementioned findings, we have designed and synthesized new 1,2,3-thiadiazole and 1,2,3-selenadiazoles using aryl, monosubstituted aryl, and aliphatic ketones with long alkyl chains.

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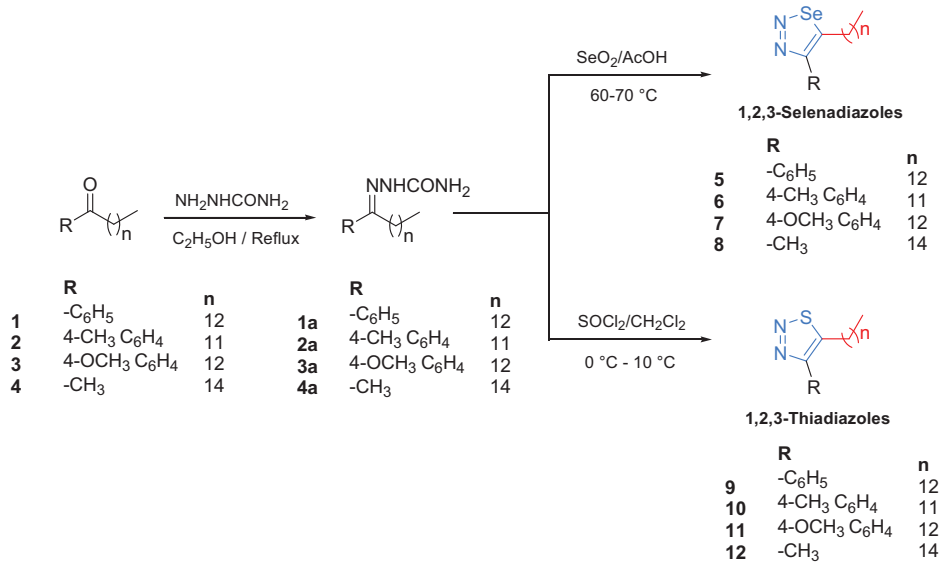

Scheme 1. Synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles.

We then investigated biological properties of these new compounds. Thus, we have examined the effect of the long alkyl chain added to 1,2,3-thiadiazole and 1,2,3-selenadiazole rings on their biological activities.

Results and discussion

Chemistry

The synthetic route to the target compounds **5–12** are depicted in Scheme 1. Ketones with aryl, monosubstituted aryl, and long alkyl chains **1–4** were synthesized and characterized in our previous works.[19–22] Ketones were converted into their semicarbazones by reacting **1–4** with semicarbazide hydrochloride.[23] The physical properties of semicarbazones **1a–4a** are given in Table S1 (Supplementary materials). On treatment with SeO_2/AcOH (Lalezari Method)[24,25] the semicarbazones gave the corresponding 1,2,3-selenadiazoles **5–8**. On the other hand, when the semicarbazones were subjected to the Hurd-Mori reaction process[26] with excess thionylchloride at −10 °C for 3 h, 1,2,3-thiadiazoles **9–12** were obtained in a one pot reaction (Scheme 1).

All reactions were monitored by TLC (petroleum ether: ethyl acetate: acetic acid, 2:0.6:0.1). The synthesized compounds were purified by column chromatography and characterized by FTIR, ^{1}H NMR, ^{13}C NMR, elemental analyses and mass spectrometry. The detailed spectral description of compounds **5–12** are given below. The FTIR spectra of the products **5-12** exhibited bands between 1463–1468 cm^{-1}, indicating the presence of N = N. The 1259-1282 cm^{-1} was assigned to be C–N stretching absorption bands. The absorption bands observed in the region of 801–889 cm^{-1} were assigned to C–S for **9–12.** ^{1}H NMR spectra of the synthesized compounds showed some characteristic peaks. All protons due to aromatic groups were found to be in their expected region. Aromatic protons in the spectra of the compounds **5,6,7,9,10,** and **11** were observed at 7.25–7.78 ppm. The ^{1}H NMR spectra of the compounds **5–12** exhibited a triplet signal for the methylene protons (belonging to the C6) being adjacent to 1,2,3-thiadiazole or 1,2,3-selenadiazole rings around at 2.79–3.08 ppm. In the ^{1}H NMR spectra, the methylene protons (belonging to the C7) showed a pentet signal at 1.52–1.55 ppm due to their position adjacent to two methylene groups (C6 and C8). The ^{13}C NMR spectra showed characteristic resonances for 1,2,3-thiadiazole and 1,2,3-selenadiazole rings. The typical ^{13}C NMR shifts for C4 being adjacent to N were observed around δ 156–163 ppm. Also C5 (adjacent to Se or S) showed a signal about δ 151–160 ppm. Aromatic carbons for the compounds **5,6,7,9,10,** and **11** were observed at δ 128-131 ppm. In ^{13}C NMR spectra, peaks due to aliphatic carbons were recorded between 12 ppm and 37 ppm. Mass spectra (EI) of 1,2,3- selenadizole compounds showed a molecular ion peak ($[M–N_2–Se]^+$) in line with their molecular formula. 1,2,3-Thiadizole compounds gave a molecular ion peak ($[M–N_2]^+$). Mass spectra (EI) and mass fragmentations of the products **6** and **10** were given as examples in supplemental materials. Also, the elemental analyses of the compounds was in agreement with the proposed structures of the compounds.

Antimicrobial activity

In vitro antibacterial activities of compounds against *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 4352, *Proteus mirabilis* ATCC 14153, *Enterococcus faecalis* ATCC 29212, *Staphylococcus epidermidis* ATCC 12228, *Staphylococcus aureus* ATCC 29213, and antifungal activities against *Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 22019, *Candida tropicalis* ATCC 750 were investigated. Minimum inhibitory concentrations (MICs) of compounds were determined by microbroth dilution technique as described by the Clinical and Laboratory Standards Institute[27,28] Serial two fold dilutions ranging from 5000 to 1.22 mg/L were prepared in Mueller-Hinton broth (MHB) for bacteria and

Table 1. In vitro antimicrobial activities of the synthesized 1,2,3-thiadiazole and 1,2,3-selenadiazole compounds **5–12** (mg/L).

Compounds	*P. aeruginosa* ATCC 27853	*E. coli* ATCC 25922	*K. pneumoniae* ATCC 4352	*P. mirabilis* ATCC 14153	*E. faecalis* ATCC 29212	*S. epidermidis* ATCC 12228	*S. aureus* ATCC 29213	*C. albicans* ATCC 10231	*C. parapsilosis* ATCC 22019	*C. tropicalis* ATCC 750
5	–	–	–	–	–	–	–	78.12	9.76	4.88
6	–	–	–	–	–	–	–	19.53	9.76	2.44
7	–	–	–	–	–	156.2	–	78.12	39.06	9.76
8	–	–	–	–	–	156.2	–	156.2	78.12	312.5
9	–	–	–	–	–	–	–	–	–	–
10	–	–	–	–	–	–	–	78.12	312.5	–
11	625	–	–	–	–	156.2	–	39.06	156.2	312.5
12	–	–	–	–	–	–	–	–	–	–

RPMI-1640 medium for yeast. Each well was inoculated with 50 μL of a 4–6 h broth culture that gave a final concentration of 5×10^5 cfu/mL for bacteria and 5×10^3 cfu/mL for yeast in the test tray. The trays were covered and placed in plastic bags to prevent evaporation. The trays containing MHB were incubated at 35 °C for 18–20 h, those containing RPMI-1640 medium at 35 °C for 46–50 h. The MIC was defined as the lowest concentration of compound producing complete inhibition of visible growth. Amikacin and fluconazole were used as reference antibiotics for bacteria and yeast, respectively. The MIC values of the amikacin and fluconazole were within the accuracy range in CLSI throughout the study.[29] The MIC values of the compounds are given in Table 1.

All the compounds were investigated for their *in vitro* antibacterial activities against three Gram-positive (*Staphylococcus aureus* ATCC 29213, *Staphylococcus epidermidis* ATCC 12228, *Enterococcus faecalis* ATCC 29212) and four Gram-negative bacteria (*Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 4352, *Proteus mirabilis* ATCC 14153). The antifungal activities were also tested against three yeasts, namely *Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 22019, *Candida tropicalis* ATCC 750. All the biological results of the tested compounds are given in Table 1. As seen in Table 1, all the studied compounds, have no antimicrobial activity against four Gram negative bacteria (*E. coli, K. Pneumoniae*, *P. Mirabilis,* and *E. faecalis*). However, in our study it is shown that compound **11** has a weak activity against *P. aeruginosa* (MIC = 625 mg/L). The present study showed that compounds **7, 8** and **11** showed moderate antibacterial activity against *S. epidermidis* (MIC = 156.2 mg/L). Moreover, compounds **5, 6** and **7** exhibited significant antifungal activity against studied yeast strains. However, compounds **9** and **12** were not shown to have any antimicrobial activity against the studied microorganisms.

Experimental

Materials and physical measurements

All reagents were obtained from commercial suppliers unless otherwise stated. Organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under argon. Solvents for chromatography were of technical grade and distilled prior to use. Thin layer chromatography (TLC) was carried out on Merck aluminum support plates Silica gel 60 F_{254}. Visualization was achieved under a UV mineral light. Column chromatography was performed using silica gel Merck 60 (particle size 0.2–0.063 mm). NMR spectra were recorded at 500 MHz for ^{1}H and at 125 MHz for ^{13}C using Me_4Si as the internal standard in $CDCl_3$ with a Varian UNITY INOVA 500 MHz NMR spectrometer. GC-MS were recorded on Shimadzu/QP2010 Plus. IR spectra were recorded on a Mattson 1000 FT-IR spectrometer. Melting points were determined with Büchi melting point B-540. Chemical yields refer to pure isolated substances. The Supplementary materials contains sample ^{1}H and ^{13}C NMR spectra for the products 5–12 (Figures S1–S18).

General procedure for the synthesis of semicarbazones [23] 1a–4a

Semicarbazide hydrochloride (67 g, 0.6 mol), along with sodium acetate (67 g, 0.8 mol) in ethanol (500 mL) were heated at reflux. The precipated sodium chloride was filtered from the hot solution, and the ketone (0.5 mol) was added. The mixture was heated at reflux for a further 2 h. Then water was added to the hot solution until precipitation started. After cooling, the crystals of the semicarbazone were collected, washed with water and air-dried. The product is sufficiently pure for further reactions.

General procedure for the synthesis of compounds [30] 5–8

The semicarbazone (0.05 mol) was dissolved in glacial acetic acid (15 mL) and warmed to 60 °C with stirring. To this, selenium dioxide (0.55 g, 0.05 mol) was added portionwise over a period of 30 min and the stirring was continued at 60 °C for 2–3 h until the evolution of gas ceased. After completion of the reaction, it was filtered to remove the deposited elemental selenium. The filtrate was poured over crushed ice and the solid obtained was filtered, and washed thoroughly with cold water and sodium carbonate and again with water. The crude product was purified by column chromatography (petroleum ether: ethyl acetate: acetic acid, 2:0.6:0.1) to yield substituted 1,2,3-selenadiazoles 5-8.

5-Dodecyl-4-phenyl-[1–3]selenadiazole (5)

Yield, 79%, orange slurry, m.p., 33–34 °C; IR (neat; υ, cm^{-1}): 3082 (aromatic CH), 2915 (aliphatic CH), 2846, 1468 (N = N), 1282 (C–N), 889, 769, 686. ^{1}H NMR ($CDCl_3$; δ, ppm): 7.61–7,58(m, 2H); 7.45-7.42(m, 2H); 7.38–7.36(m, 1H); 3.00(t, J = 7.5 Hz, 2H); 1.69–1.63(pentet, J = 5.0 Hz, 2H); 1.18–1.17(m, 18H); 0.80(t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$; δ, ppm): 163.9 (C4), 160.4 (C5); 133.3, 130.5, 129.6, 128.9, 35.2, 32.3, 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 23.0, 14.4. Anal. Calcd. for $C_{20}H_{30}N_2Se$ (M = 377.43), %: C, 63.65; H, 8.01; N, 7.42; Found, %: C, 63.78; H, 8.11; N, 7.36. **MS** (m/z)= 213, 227, 241, 255, 270 ([M–N_2–Se]$^+$).

4 -p-Tolyl-5-undecyl-[1–3]selenadiazole (6)

Yield, 75%, dark orange oil; FTIR (neat; υ, cm^{-1}): 3073 (aromatic CH), 2920 (aliphatic CH), 2850, 1463 (N = N), 1259 (C–N), 820, 723, 686. ^{1}H NMR ($CDCl_3$; δ, ppm): 7.50(d, J = 10.0 Hz, 2H); 7.25(d, J = 10.0 Hz, 2H); 3.00(t, J = 7.5 Hz, 2H); 2.37(s, 3H); 1.69–1.62(pentet, J = 6.0 Hz, 2H); 1.31–1.27(m, 2H); 1.21–1.17(m, 14H); 0.81(t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$; δ, ppm): 161.3 (C4), 158.3 (C5), 137.3, 128.4, 128.3, 127.2, 33.7, 30.9, 28.6, 28.5, 28.4, 28.3, 28.2, 28.1, 21.7, 20.3, 13.1. Anal. Calcd. for $C_{20}H_{30}N_2Se$ (M = 377.43), %: C, 63.65; H, 8.01; N, 7.42; Found, %: C, 63.71; H, 8.06; N, 7.39. **MS** (m/z)= 213, 227, 241, 255, 270 ([M–N_2–Se]$^+$).

5 -Dodecyl-4-(4-methoxy-phenyl)-[1–3]selenadiazole (7)

Yield, 69%, yellow slurry, m.p., 45-46 °C; FTIR (neat; υ, cm^{-1}): 3031 (aromatic CH), 2915 (aliphatic CH), 2850, 1468 (N = N), 1371, 1278 (C–N), 1181, 968, 806, 718. ^{1}H NMR ($CDCl_3$; δ, ppm): 7.78(d, J = 10.0 Hz, 2H); 7.17(d, J = 10.0 Hz, 2H); 2.85(t, J = 7.5 Hz, 2H); 2.33(s, 3H); 1.68–1.62 (multiplet, 2H); 1.29–1.18 (m, 18H); 0.81(t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$; δ, ppm): 161.3 (C4), 158.3 (C5), 142.5, 133.7, 128.4, 128.2, 127.2, 127.1, 37.6, 28.7, 28.5, 28.4, 28.3, 28.2, 23.6, 21.7, 13.1. Anal. Calcd. for $C_{21}H_{32}N_2OSe$ (M = 407.45), %: C, 61.90; H, 7.92; N, 6.88; Found, %: C, 62.01; H, 7.89; N, 6.93. **MS** (m/z) = 239, 253, 270, 281, 299 ([M–N_2–Se]$^+$).

4 -Methyl-5-tetradecyl-[1–3]selenadiazole (8)

Yield, 81%, yellow oil; FTIR (neat; υ, cm^{-1}): 2915 (aliphatic CH), 2850, 1465 (N = N), 1266 (C–N), 1167, 718. ^{1}H NMR ($CDCl_3$; δ, ppm): 2.33(t, J = 7.5 Hz, 2H); 2.05(s, 3H); 1.52–1.45(m, 2H); 1.24–1.19(m, 22H); 0.81(t, J = 5.0 Hz, 3H). ^{13}C NMR ($CDCl_3$; δ, ppm): 160.9 (C4), 155.3 (C5), 33.6, 32.1, 30.0, 29.9, 29.8, 29.7, 29.6, 29.4, 22.9, 14.3, 13.2. Anal. Calcd. for $C_{17}H_{32}N_2Se$ (M = 343.41), %: C, 59.46; H, 9.39; N, 8.16; Found, %: C, 59.37; H, 9.47; N, 8.11. **MS** (m/z)= 152, 180, 194, 211, 236 ([M–N_2–Se]$^+$).

General procedure for the synthesis of compounds [30] 9–12

The dried semicarbazone (10 mmol) was added portionwise to an excess of freshly distilled thionyl chloride (3 mL) at 0 °C with an ice/salt bath. The reaction mixture was allowed to stand at room temperature until the disappearance of semicarbazone (monitored by TLC). At the end of the reaction, methylene chloride (15 mL) was added and the resulting mixture was decomposed with saturated sodium carbonate. The organic layer was washed with water and dried on sodium sulfate. Products ***9–12*** were purified by column chromatography (petroleum ether: ethyl acetate: acetic acid, 2:0.6:0.1).

5 -Dodecyl-4-phenyl-[1–3]thiadiazole (9)

Yield, 75%, brown oil; FTIR (neat; υ, cm^{-1}): 3073 (aromatic CH), 2920 (aliphatic CH), 2850, 1463 (N = N), 1259 (C–N), 820 (C-S), 723, 686. ^{1}H NMR ($CDCl_3$; δ, ppm): 7.73–7.71(m, 2H); 7.55–7.46(m, 3H); 3.08(t, J = 7.5 Hz, 2H); 1.75(pentet, J = 7.5 Hz, 2H); 1.42–1.36(m, 2H); 1.31–1.26(m, 16H); 0.90(t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$; δ, ppm): 159.1 (C4), 153.3 (C5), 131.5, 128.9, 128.8, 128.7, 32.1, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 25.9, 22.7, 14.1. Anal. Calcd. for $C_{20}H_{30}N_2S$ (M = 330.53), %: C, 72.68; H, 9.15; N, 8.48; Found, %: C, 72.80; H, 9.01; N, 8.67. **MS** (m/z)= 203, 217, 270, 287, 302 ([M-N_2]$^+$).

4 -p-Tolyl-5-undecyl-[1–3]thiadiazole (10)

Yield, 84%, brown oil; FTIR (neat; υ, cm^{-1}): 3077 (aromatic CH), 2915 (aliphatic CH), 2850, 1463 (N = N), 1268 (C–N),

968, 801 (C–S), 723. ^{1}H NMR ($CDCl_3$; δ, ppm): 7.53(d, J = 10.0 Hz, 2H); 7.25(d, J = 10.0 Hz, 2H); 2.97(t, J = 7.5 Hz, 2H); 2.36(s, 3H); 1.68–1.62(pentet, J = 6.0 Hz, 2H); 1.32–1.27(m, 2H); 1.22–1.17(m, 14H); 0.80(t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$; δ, ppm): 159.0 (C4), 152.6 (C5), 138.4, 129.1, 128.4, 128.3, 31.2, 31.0, 28.7, 28.6, 28.5, 28.4, 28.2, 25.0, 21.8, 13.1. Anal. Calcd. for $C_{20}H_{30}N_2S$ (M = 330.53), %: C, 72.68; H, 9.15; N, 8.48; Found, %: C, 72.82; H, 9.03; N, 8.65. **MS** (m/z)= 203, 217, 270, 287, 302 ($[M–N_2]^+$).

5 -Dodecyl-4-(4-methoxy-phenyl)-[1–3]thiadiazole (11)

Yield, 72%, dark brown oil; FTIR (neat; υ, cm^{-1}): 3031 (aromatic CH), 2915 (aliphatic CH), 2850, 1468 (N = N), 1371, 1278 (C–N), 1181, 968, 868 (C–S), 714. ^{1}H NMR ($CDCl_3$; δ, ppm): 7.78 (d, J = 5.0 Hz, 2H); 7.16(d, J = 10.0 Hz, 2H); 2.84(t, J = 7.5 Hz, 2H); 2.32(s, 3H); 1.67–1.61 (pentet, J = 5.0 Hz, 2H); 1.31–1.26(m, 2H); 1.22–1.18 (m, 16H); 0.80 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$; δ, ppm): 158.1 (C4), 151.7 (C5), 142.5, 137.7, 133.7, 127.2, 37.5, 30.9, 28.6, 28.5, 28.4, 28.3, 28.2, 24.9, 21.7, 13.1. Anal. Calcd. for $C_{21}H_{32}N_2OS$ (M = 360.56), %: C, 69.95; H, 8.95; N, 7.77; Found, %: C, 69.99; H, 9.07; N, 7.61. **MS** (m/z)= 259, 273, 287, 302, 331 ($[M\text{-}N_2]^+$).

4 -Methyl-5-tetradecyl-[1–3]thiadiazole (12)

Yield, 83%, orange oil; FTIR (neat; υ, cm^{1}): 2915 (aliphatic CH), 2846, 1465 (N = N), 1265 (C–N), 992, 855 (C–S), 723. ^{1}H NMR ($CDCl_3$; δ, ppm): 2.79(t, J = 7.5 Hz, 2H); 2.55(s, 3H); 1.63–1.57(m, 2H); 1.22–1.18(m, 22H); 0.80(t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$; δ, ppm): 156.1 (C4), 152.1 (C5); 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 25.3, 22.9, 14.3, 12.5. Anal. Calcd. for $C_{17}H_{32}N_2S$ (M = 296.51), %: C, 68.86; H, 10.88; N, 9.45; Found, %: C, 69.04; H, 11.09; N, 9.51. **MS** (m/z)= 183, 207, 235, 253,268 ($[M–N_2]^+$).

Conclusions

A series of new 1,2,3-thiadiazoles and 1,2,3-selenadiazoles having a long alkyl chain were synthesized. The structures of newly synthesized products were verified by FTIR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis. The antibacterial and antifungal studies indicated that the compounds **5**, **6**, and **7** displayed significant activities against fungal strains. Moreover, the compounds **7, 8** and **11** showed moderate antibacterial activity against *S. Epidermidis*. The tested compounds exhibited promising antimicrobial activity could be utilized for the development of the lead compounds for new and more potent antimicrobial drugs.

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