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Original Research

Synthesis and Characterization of Novel 4-(α-tocopheryl) methyl)-1,2,3-Thia/Selenadiazole Derivatives as Antibacterial Agents

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Abstract

A new series of vitamin e (α-Tocopherol) bearing 1,2,3-thiadiazole and selenadiazole derivatives (4, 5, 9a-d and 10a-d) were isolated by using thionyl chloride and selenium dioxide respectively with α-tocopherol/semicarbazone derivatives (3 and 8a-d) as precursor compounds. The equivalent reaction with tellurium dioxide did not yield the related α-tocopherol fused 1,2,3-telluradiazole derivatives. The newly synthesized compounds 4, 5, 9a-d and 10a-d were evaluated against four bacteria *Bacillus subtilis and Staphylococcus aureus* (Gram-positive bacteria) and *Pseudomonas aeruginosa* and *Salmonella typhimurium* (Gram-negative bacteria). The results of bioassays indicated that the compounds 4-(α-tocopheryl) methyl)-1,2,3-thiadiazole (4) and 5-(4-substitutedphenyl)-4 -(α-tocopheryl) methyl)-1,2,3-thiadiazole (9a-c) displayed broad spectrum against both Gram-positive and Gram-negative bacteria. Derivatives 4-(α-tocopheryl) methyl)-1,2,3-selenadiazole (5) and 5-(4-substitutedphenyl)-4-(α-tocopheryl) methyl)-1,2,3-selenadiazole (10a-d) have moderate activity against Gram-positive bacteria. Spectroscopic methods IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectra and elemental analysis have been used to elucidate and validate all newly synthesized compounds.

Keywords: vitamin E; 1,2,3-Thiadiazole, 1,2,3-Selenadiazole, 1,2,3-Telluradiazole, antibacterial activity

Introduction

The synthesis of vitamin E-containing sulfa drug derivatives was reported previously [1]. The functionalization of vitamin E linked to seleno/ heterocyclic derivatives as well as their cytotoxicity effects on the human breast cancer cell line [2] were also demonstrated, revealing that the α-Tocopherol bearing seleno/nicotine moiety when compared to the other anticancer drugs seleno/pyridine, seleno/pyridazine and seleno/coumarine moieties, has the highest cytotoxic activity. In addition, according to a literature survey, the synthesis of 1,2,3-selenadiazole and 1,2,3-thiadiazole molecules has stimulated the interest of numerous researchers due to their antibacterial and antifungal activities, in addition anticancer activity [3-9]. In consideration of the above-mentioned investigations of vitamin e connected to sulfa drugs as an antibacterial agent[1] as well as the effect of vitamin e bearing some seleno heterocyclic compounds [2], we created and

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evaluated 1,2,3-selenadaizole and 1,2,3-thiadaizole derivatives attached to α-Tocopherol in order to get access to new families of biological active compounds.

Material and Methods

General

Column chromatography was carried out on 0.04-0.063 mm (Merck) silica gel, thin layer chromatography was carried out on aluminum backed silica plates by Merck and plates were revealed using a UV 254 light. Infrared (KBr, cm^{-1}) spectroscopy was calculated on a Pye-Unicam SP3-100 instrument. ^1H NMR spectra were detected at King Abdel-Aziz University using a Varian (400 MHz) EM 390 USA instrument. The peaks of the spectroscopy were recorded as Single (s), Double (d), Triple (t) and Quartet (q). ^{13}C-NMR spectra were recorded at King Abdel- Aziz University, Saudi Arabia, on a JNM – LA spectrometer (100 MHz). Chloroform was used for both ^1H and ^{13}C-NMR using TMS. Mass spectra were recorded at the National Research Centre, Cairo , Egypt on a JEOL -JMS-AX 500. On an analyzer (Elementar Vario EL 1150ºC) the elemental analysis was reported.

Compounds 4, 5, 6a-d, 7a-d, 8a-d 9a-d and 10a-d, -(((R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yloxy) = (α-tocopheryl)

Synthesis of 1-((R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl) chroman-6-yloxy)propan-2-one (2).

A mixture of compound 1 (α-tocopherol) (2.15 g, 0.005 mol), chloroacetone (0.41 mL, 0.005 mol) and NaOH (0.20 g, 0.005 mol) in dimethylformamide (20 mL) were stirred for 24 h at room temperature, ethylacetate (25 mL) and brine (10 mL) were added, the aqueous was extracted with ethylacetate (10 mL × 2), the combined ethylacetate was washed with brine (10 mL × 2) and water (10 mL x 1), dried over $MgSO_4$. Then, the solvent was removed, to obtain derivative 2 as colorless oil, 1.57 g, yield, 65%. IR (KBr) ν_{max} 1700 (C=O) cm^{-1}. ^1H NMR (Chloroform) δ, ppm: 5.20 (2H, s, OCH_2), 2.35 (3H, s, CH_3, O=C-CH_3), 2.20 (3H, s, CH_3), 2.10 (3H, s, CH_3), 1.92 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.97 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.6, 12.5, 15.7, 19.5, 20.4, 21.5, 22.5, 22.7, 23.9, 24.5, 24.6, 24.8, 25.9, 27.9, 31.3, 31.5, 32.2, 36.3, 37.5, 38.6, 39.4, 40.1, 70.2, 74.7, 117.5, 123.1, 125.5, 128.3, 129.1, 147.9, 148.1, 206.0 (C, CO). MS m/z (%): 486 [M^+-1, 60], Anal. Calcd. for $C_{32}H_{54}O_3$: C, 78.96; H, 11.18. Found C, 78.77; H, 11.00.

2-(1-((R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yloxy) propan-2-ylidene)hydrazinecarboxamide (3).

In ethanol (50 mL) semicarbazide hydrochloride (1.12 g, 0.01 mmol), mixed with sodium acetate (1.23 g, 0.015 mol) was refluxed for 30 min. The precipitated sodium chloride was filtered from the hot solution and derivative (2) (4.86 g, 0.01 mol) was added to the hot solution. The reaction mixture was heated at reflux for a further 2hrs., then diluted with ethylacetate (50 mL) and brine (30 mL), the aqueous was extracted with ethylacetate (15 mL × 2), the combined ethylacetate was washed with brine (20 mL × 2), water (20 mL × 1), dried over $MgSO_4$. After removal of the solvent, the residue was purified by Colum chromatography (hexane/ ethylacetate V/V 10:1) to give pale yellow oil, 3.26 g, yield 60%. IR (KBr) ν_{max} 3400, 3350, 3149 (NH, NH_2); 1655 (C=O-amide) cm^{-1}. ^1H NMR (Chloroform) δ, ppm: 8.95 (1H, s, NH); 6.01 (2H, s, NH_2); 4.20 (2H, s, OCH_2), 1.91 (3H, s, CH_3), 2.20 (3H, s, CH_3), 2.10 (3H, s, CH_3), 1.92 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.46 (22H, m, $11CH_2$), 0.95 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.9, 12.5, 15.7, 19.4, 20.4, 21.3, 22.7, 22.8, 23.7, 24.4, 24.5, 24.6, 25.9, 27.9, 31.3, 31.5, 32.3, 36.3, 37.5, 38.5, 39.4, 40.2, 70.1, 74.5, 117.7, 123.1, 125.5, 128.4, 129.2, 147.7, 148.2, 155.5, 157.0 (C, CO). MS m/z (%): 544 [M^+, 20], Anal. Calcd. for $C_{33}H_{57}N_3O_3$: C, 72.88; H, 10.56; N,7.73. Found C, 72.65; H, 10.38; N,7.55 .

4-(α-tocopheryl) methyl)-1,2,3-thiadiazole (4).

Thionyl chloride (5 mL) was stirred at 0ºC and the semicarbazone 3 (5.44 g, 0.01 mol) was added in small portion. The mixture was stirred at room temperature overnight until no more hydrogen chloride was produced. The remaining thionyl chloride was evaporated under vacuum. 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 anhydrous sodium sulfate. The product 4 was purified by column chromatography (hexane/ethylacetate V/V 10:1) to give colorless oil, 2.90 g, yield 60%. IR (KBr) ν_{max} 3073, 2920, 2850, 1463 cm^{-1}. ^1H NMR (Chloroform) δ, ppm: 8.15 (1H, s, CH-Thiadiazole), 4.23 (2H, s, OCH_2), 2.22 (3H, s, CH_3), 2.11 (3H, s, CH_3), 1.90 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.96 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.8, 12.6, 15.7, 19.5, 20.5, 21.3, 22.8, 22.9, 23.7, 24.5, 24.6, 24.8, 25.9, 27.9 , 31.3, 31.5, 32.2, 36.3, 37.3, 38.5, 39.1, 40.3, 70.2 , 74.7, 117.5, 123.2, 125.5, 128.1, 132.1, 147.6, 148.1, 155.6. MS m/z (%): 529 [M^+-1, 15], Anal. Calcd. for $C_{32}H_{52}N_2O_2S$: C, 72.68; H, 9.91; N, 5.30. Found C, 72.61; H, 9.88; N, 5.00.

4-(α-tocopheryl) methyl)-1,2,3-selenadiazole (5).

Semicarbazone 3 (5.44 g, 0.01mol) was dissolved in glacial acetic acid with vigorous stirring and gentle heating to 70ºC. The solution was treated with selenium dioxide powder (1.66 g, 0.015 mmol, and the mixture was kept under vigorous stirring. After ca. 2 min the color of the mixture becomes red. The reaction was complete in 24 hrs. The mixture was filtered to remove unreacted selenium and the filtrates poured into ice water and extracted with Chloroform (3 × 50 mL). The combined organic layers were washed with

saturated sodium hydrogen carbonate solution. dried over magnesium sulphate and the solvent was removed under vacuum to afford the crude compound 5, which was further purified by column chromatography (hexane/ ethylacetate V/V 10:1) to give pale yellow oil compound 5, 2.87 g, yield 50%. IR (KBr) ν_{max} 3073, 2920, 2850, 1463 cm^{-1}. ^{1}H NMR (Chloroform) δ, ppm: 8.50 (1H, s, CH-Selenadiazole), 4.25 (2H, s, OCH_2), 2.10 (3H, s, CH_3), 1.95 (3H, s, CH_3), 1.92 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.96 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.9, 12.6, 15.7, 19.5, 20.5, 21.3, 22.8, 22.9, 23.7, 24.5, 24.8, 24.9, 25.9, 27.9 , 31.3, 31.5, 32.2, 36.3, 37.3, 38.5, 39.1, 40.3, 70.2 , 74.7, 117.5, 123.2, 125.5, 128.1, 132.1, 147.6, 148.1, 155.3. MS m/z (%): 602 [$M^+ + Na^+$, isotope Se-patern,10], Anal. Calcd. for $C_{32}H_{52}N_2O_2Se$: C, 66.76; H, 9.10; N,4.87. Found C, 66.61; H, 9.88; N, 4.67.

4-(α-tocopheryl) methyl)-1,2,3-telluradiazole (6).

Similarly, TeO_2 was used in the prior technique to synthesis 1,2,3-selenadiazole, but the end product was not obtained 6.

Synthesis of 1-(4-substitutedphenyl)-2-(α-tocopheryl) ethanone (7a-d).

General Procedure

In dimethylformamide (20 mL), 4-substituted phenacy bromide (4-methoxy;4-nitro-4-fluoro and 4-cyano) (0.005 mol) and NaOH (0.20 g, 0.005 mol) were added to the derivative 1 (2.15 g, 0.005 mol). Mixed compounds were stirred for 24 hrs, at room temperature, then added ethylacetate (30 mL) and brine (20 mL). The aqueous was extracted with ethylacetate (15 mL × 2), the combined ethylacetate was washed with brine (15 mL × 2), water (15 mL × 1), and dried over $MgSO_4$. After that, the solvent was removed and the products obtained without purification as pale yellow oil compounds 7a-d;

7a; 1.73 g, yield, 60 %. IR (KBr) ν_{max} 1685 (C=O) cm^{-1}. ^{1}H NMR (Chloroform) δ, ppm: 7.50, 8.00 (4H, m, Ph-ring) , 4.92 (2H, s, OCH_2), 3.95 (3H, s, Ph-OCH_3), 2.20 (3H, s, CH_3), 2.20 (3H, s, CH_3), 1.90 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.97 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.8, 12.8, 15.9, 19.7, 20.5, 21.3, 22.6, 22.7, 23.7, 24.5, 24.8, 24.9, 25.9, 27.9, 31.3, 31.5, 32.2, 36.5, 37.5, 38.3, 39.2, 40.2, 55.3, 70.1, 74.9, 113.6, 114.4, 117.7, 123.1, 124.8, 126.4, 128.3, 129.1, 130.6, 147.8, 148.2, 163.9, 193.0 (C, CO). MS m/z (%): 579 [M^+, 30], Anal. Calcd. for $C_{38}H_{58}O_4$: C, 78.85; H, 10.10. Found C, 78.80; H, 10.00.

7b; 4.16 g, yield, 70 %. IR (KBr) ν_{max} 1695 (C=O) cm^{-1}. ^{1}H NMR (Chloroform) δ, ppm: 7.25, 8.50 (4H, m, Ph-ring) , 4.95 (2H, s, OCH_2), 2.22 (3H, s, CH_3), 2.20 (3H, s, CH_3), 1.92 (3H, m, 3CH), 1.66 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.96 (12H, m, $4CH_3$).^{13}CNMR δ, ppm: 11.9, 12.8, 15.9, 19.5, 20.4, 21.3, 22.7, 22.8, 23.7, 24.2, 24.3, 24.7, 25.9, 27.9, 31.3, 31.5, 32.4, 36.6, 37.5, 38.3, 39.2, 40.1, 70.2, 74.9, 113.6, 114.3, 117.6, 123.0, 124.7, 126.3, 128.2, 129.0, 130.7, 147.8, 148.3, 162.4, 171.0 (C, CO).

MS m/z (%): 593 [M^+, 20], Anal. Calcd. for $C_{37}H_{55}NO_5$: C, 74.83; H, 9.34; N, 2.36. Found C, 74.82; H, 9.30; N, 2.11.

7c; 3.68 g, yield, 65 %. IR (KBr) ν_{max} 1690 (C=O) cm^{-1}. ^{1}H NMR (Chloroform) δ, ppm: 7.15, 8.20 (4H, m, Ph-ring), 4.75 (2H, s, OCH_2), 2.20 (3H, s, CH_3), 2.19 (3H, s, CH_3), 1.86 (3H, m, 3CH), 1.68 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.95 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.8, 12.8, 15.9, 19.5, 20.4, 21.3, 22.7, 22.8, 23.7, 24.2, 24.3, 24.7, 25.9, 27.9, 31.3, 31.5, 32.4, 36.6, 37.5, 38.3, 39.2, 40.1, 70.2, 74.9, 113.6, 114.3, 117.6, 123.0, 124.7, 126.3, 128.2, 129.0, 130.7, 147.8, 148.3, 162.4, 170.0 (C, CO).

MS m/z (%): 567 [M^+, 25], Anal. Calcd. for $C_{37}H_{55}FO_3$: C, 78.40; H, 9.78. Found C, 78.22; H, 9.55.

7d; 3.44 g, yield, 60 %. IR (KBr) ν_{max} 2217 (CN); 1690 (C=O) cm^{-1}. ^{1}H NMR (Chloroform) δ, ppm: 7.12, 8.50 (4H, m, Ph-ring), 4.55 (2H, s, OCH_2), 2.15 (3H, s, CH_3), 2.19 (3H, s, CH_3), 1.82 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.99 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.9, 12.8, 15.9, 19.5, 20.4, 21.3, 22.7, 22.8, 23.7, 24.2, 24.3, 24.7, 25.9, 27.9, 31.3, 31.5, 32.4, 36.6, 37.5, 38.3, 39.2, 40.1, 70.2, 74.9, 113.5, 114.3, 116.8, 118.3, 123.0, 124.7, 126.3, 128.2, 129.0, 130.7, 147.8, 148.2, 162.8, 174.0 (C, CO).

MS m/z (%): 573 [M^+-1, 30], Anal. Calcd. for $C_{38}H_{55}NO_3$: C, 79.53; H, 9.66; N, 2.44. Found C, 79.52; H, 9.45; N, 2.33.

2-(1-(4-substitutedphenyl)-2-(α-tocopheryl) ethylidene)hydrazinecarboxamide (8a-d)

In ethanol (50 mL) semicarbazide hydrochloride (0.01 mmol), mixed with sodium acetate (0.015 mol) was heated under reflux for 30 min. The precipitated sodium chloride was filtered from the hot solution and derivatives (7a-d) (0.01 mol) were added to the hot solution. The reaction mixture was heated for a further 2hrs., then diluted with ethylacetate (50 mL) and brine (30 mL), the aqueous was extracted with ethyl acetate (15 mL × 2), the combined ethylacetate was washed with brine (20 mL × 2), water (20 mL x 1), dried over $MgSO_4$. After removal of the solvent, the residue was purified by Colum chromatography (hexane/ethylacetate V/V 10:1) to give pale yellow oil compounds (8a-d),

8a; 3.50 g, yield 55 %. IR (KBr) ν_{max} 3400,3350,3149 (NH, NH_2); 1665 (C=O-amide) cm^{-1}. ^{1}H NMR (Chloroform) δ, ppm: 9.59 (1H, s, NH); 7.50, 8.00 (4H, m, Phenyl-ring); 6.95 (2H, s, NH_2); 3.98 (3H, s, OCH_3); 4.20 (2H, s, OCH_2), 2.15 (3H, s, CH_3), 2.19 (3H, s, CH_3), 1.86 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.97 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.9, 12.8, 15.9, 19.5, 20.8, 21.5, 22.7, 22.8, 23.8, 24.4, 24.7, 24.9, 25.9, 27.9, 31.3, 31.5, 32.3, 36.5, 37.6, 38.7, 39.8, 40.2, 55.8, 74.8, 114.5, 114.8, 115.2, 116.3, 117.6, 123.1, 125.8, 128.4, 128.8, 129.0, 147.5, 148.4, 162.5, 155.5, 157.0 (C, CO). MS m/z (%): 635 [M^+-1, 40]. Anal. Calcd. for $C_{39}H_{61}N_3O_4$: C, 73.66; H, 9.67.

8b; 3.90 g, yield 60 %. IR (KBr) ν_{max} 3420,3350,3149 (NH, NH_2); 1665 (C=O-amide) cm^{-1}. ^1H NMR (Chloroform) δ, ppm: 9.59 (1H, s, NH); 7.20, 8.50 (4H, m, Phenyl-ring); 6.95 (2H, s, NH_2); 4.50 (2H, s, OCH_2), 2.20 (3H, s, CH_3), 2.19 (3H, s, CH_3), 1.85 (3H, m, 3CH), 1.68 (6H, m, $2CH_3$), 1.46 (22H, m, $11CH_2$), 0.97 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.8, 12.8, 15.9, 19.4, 20.7, 21.5, 22.6, 22.8, 23.6, 24.4, 24.7, 24.9, 25.9, 27.9, 31.4, 31.5, 32.2, 36.5, 37.5, 38.7, 39.7, 40.1, 74.8, 114.5, 114.8, 115.2, 116.3, 117.6, 123.1, 125.7, 128.5, 128.8, 129.0, 147.5, 148.4, 162.5, 155.5, 158.0 (C, CO). MS m/z (%): 650 [M^+ -1, 50], Anal. Calcd. for $C_{38}H_{58}N_4O_5$: C, 70.12; H, 8.98; N, 8.61. Found C, 70.00; H, 8.75; N, 8.35.

8c; 3.90 g, yield 60 %. IR (KBr) ν_{max} 3400, 3350, 3149 (NH, NH_2); 1655 (C=O-amide) cm^{-1}. ^1H NMR (Chloroform) δ, ppm: 9.50 (1H, s, NH); 7.25, 8.00 (4H, m, Phenyl-ring); 6.90 (2H, s, NH_2); 4.50 (2H, s, OCH_2), 2.19 (3H, s, CH_3), 2.07 (3H, s, CH_3), 1.86 (3H, m, 3CH), 1.67 (6H, m, $2CH_3$), 1.46 (22H, m, $11CH_2$), 0.95 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.9 12.8, 15.9, 19.4, 20.7, 21.5, 22.6, 22.8, 23.6, 24.4, 24.7, 24.8, 25.9, 27.9, 31.4, 31.5, 32.2, 36.5, 37.5, 38.7, 39.7, 40.1, 74.8, 114.5, 114.8, 115.2, 116.3, 117.6, 123.1, 125.7, 128.5, 128.8, 129.0, 147.5, 148.4, 162.5, 155.5, 159.0 (C, CO). MS m/z (%): 623 [M^+ -1, 10], Anal. Calcd. for $C_{38}H_{58}FN_3O_3$: C, 73.16; H, 9.37; N, 6.74. Found C, 73.10; H, 9.15; N, 6.55.

8d; 3.79 g, yield 60%. IR (KBr) ν_{max} 3400, 3350, 3149 (NH, NH_2); 1655 (C=O-amide); 2217 (CN) cm^{-1}. ^1H NMR (Chloroform) δ, ppm: 9.59 (1H, s, NH); 7.25, 8.00 (4H, m, Phenyl-ring); 6.95 (2H, s, NH_2); 4.50 (2H, s, OCH_2), 2.18 (3H, s, CH_3), 2.19 (3H, s, CH_3), 1.87 (3H, m, 3CH), 1.67 (6H, m, $2CH_3$), 1.46 (22H, m, $11CH_2$), 0.95 (12H, m, $4CH_3$).^{13}CNMR δ, ppm: 11.8, 12.8, 15.9, 19.4, 20.7, 21.5, 22.6, 22.8, 23.7, 24.4, 24.7, 24.8, 25.9, 27.9, 31.4, 31.5, 32.2, 36.5, 37.5, 38.7, 39.7, 40.1, 74.8, 114.5, 114.8, 115.2, 116.3, 117.6, 118.5, 123.1, 125.7, 128.5, 128.8, 129.0, 147.5, 148.4, 162.5, 155.5, 157.8 (C, CO). MS m/z (%): 630 [M^+ +1, 20], Anal. Calcd. for $C_{39}H_{58}N_4O_3$: C, 74.25; H, 9.27; N, 8.88. Found C, 74.15; H, 9.10; N, 8.65.

5-(4-substitutedphenyl)-4-(α-tocopheryl) methyl)-1,2,3-thiadiazole (9a-c).

Thionyl chloride (5 mL) was stirred at 0ºC and the semicarbazone derivatives 8a-d (0.01 mol) was added in small portion. After that the mixture was stirred at room temperature overnight until no more HCl gas was produced. The remaining thionyl chloride was evaporated under vacuum. CH_2Cl_2 (15 mL) was added and the resulting mixture was decomposed with saturated sodium carbonate. The organic layer was washed with water and dried on anhydrous sodium sulfate. The products 9a-d were purified by column chromatography (hexane/ ethylacetate V/V 10:1) to give pale yellow oil compounds 9a-d;

9a; 2.54 g, yield 40%. IR (KBr) ν_{max} 3073, 2920, 2850, 1463 cm^{-1}. ^1H NMR (Chloroform) δ, ppm: 7.00-8.20 (4H, m, Ph-ring), 4.20 (2H, s, OCH_2), 3.95 (3H, s, OCH_3), 2.19 (3H, s, CH_3), 2.19 (3H, s, CH_3), 1.85 (3H, m, 3CH), 1.69 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.90 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.9, 12.5, 15.6, 19.5, 20.5, 21.6, 22.7, 22.8, 23.5, 24.5, 24.6, 24.8, 25.9, 27.9, 31.4, 31.6, 32.4, 36.6, 37.7, 38.3, 39.5, 40.1, 55.6, 70.1, 74.3, 114.5, 115.7, 117.6, 123.2, 125.3, 128.4, 128.5, 129.4, 130.8, 132.3, 132.0, 147.5, 148.4, 155.5. MS m/z (%): 634 [M^+-1, 25], Anal. Calcd. for $C_{39}H_{58}N_2O_3S$: C, 73.77; H, 9.21; N, 4.41. Found C, 73.65; H, 9.00; N, 4.20.

9b; 2.93 g, yield 45 %. IR (KBr) ν_{max} 3073, 2920, 2850, 1463 cm^{-1}. ^1H NMR (Chloroform) δ, ppm: 7.00-8.30 (4H, m, Ph-ring), 4.20 (2H, s, OCH_2), 2.20 (3H, s, CH_3), 2.16 (3H, s, CH_3), 1.85 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.46 (22H, m, $11CH_2$), 0.95 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.9, 12.5, 15.9, 19.5, 20.5, 21.5, 22.8, 22.9, 23.5, 24.3, 24.6, 24.8, 25.9, 27.9, 31.4, 31.5, 32.2, 36.6, 37.6, 38.3, 39.5, 40.2, 70.1, 74.2, 114.5, 115.7, 117.6, 123.2, 125.5, 128.4, 128.5, 129.4, 130.8, 132.3, 132.0, 147.8, 148.2, 156.5. MS m/z (%): 649 [M^+-1, 15], Anal. Calcd. for $C_{38}H_{55}N_3O_4S$: C, 70.22; H, 8.53; N, 6.47. Found C, 70.15; H, 8.40; N, 6.27.

9c; 2.49 g, yield 40 %. IR (KBr) ν_{max} 3073, 2920, 2850, 1463 cm^{-1}. ^1H NMR (Chloroform) δ, ppm: 7.00-8.50 (4H, m, Ph-ring), 4.50 (2H, s, OCH_2), 2.20 (3H, s, CH_3), 2.15 (3H, s, CH_3), 1.85 (3H, m, 3CH), 1.65(6H, m, $2CH_3$), 1.44 (22H, m, $11CH_2$), 0.95 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.6, 12.5, 15.9, 19.5, 20.5, 21.5, 22.8, 22.9, 23.5, 24.3, 24.6, 24.8, 25.9, 27.9, 31.4, 31.5, 32.2, 36.6, 37.6, 38.3, 39.5, 40.2, 70.1, 74.2, 114.5, 115.7, 117.6, 123.2, 125.5, 128.4, 128.5, 129.4, 130.8, 132.3, 132.0, 147.8, 148.2, 154.5. MS m/z (%): 622 [M^+-1, 10], Anal. Calcd. for $C_{38}H_{55}FN_2O_2S$: C, 73.27; H, 8.90; N, 4.50 Found C, 73.05; H, 8.70; N, 4.35.

9d; 2.52 g, yield 40 %. IR (KBr) ν_{max} 3073, 2920, 2850, 1463; 2217 (CN) cm^{-1}. ^1H NMR (Chloroform) δ, ppm: 7.00-8.30 (4H, m, Ph-ring), 4.20 (2H, s, OCH_2), 2.21 (3H, s, CH_3), 2.19 (3H, s, CH_3), 1.85 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.46 (22H, m, $11CH_2$), 0.95 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.8, 12.5, 15.9, 19.5, 20.5, 21.5, 22.8, 22.9, 23.5, 24.3, 24.6, 24.8, 25.9, 27.9, 31.4, 31.5, 32.2, 36.6, 37.6, 38.3, 39.5, 40.2, 70.1, 74.2, 114.5, 115.7, 117.6, 118,3, 123.2, 125.5, 128.4, 128.5, 129.4, 130.8, 132.3, 132.0, 147.8, 148.2, 155.5. MS m/z (%): 629 [M^+-1, 20], Anal. Calcd. for $C_{39}H_{55}N_3O_2S$: C, 74.36; H, 8.80; N, 6.67. Found C, 74.15; H, 8.60; N, 6.45.

5-(4-substitutedphenyl)-4-(α-tocopheryl) methyl)-1,2,3-selenadiazole (10a-c).

Semicarbazone 8a-d (0.01 mol) was dissolved in gl. CH_3COOH and gentle heating to 70ºC. Selenium dioxide powder (0.015 mmol) was added and the mixture was kept under vigorous stirring. After 2 min. the color of the mixture becomes red. The reaction was complete in 24 hrs., unreacted selenium was removed and the filtrates poured into ice water and extracted with Chloroform (3×50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution. dried over magnesium sulphate and the solvent was removed under vacuum to afford the crude compound 5, which was further purified by column chromatography

(hexane/ethylacetate V/V 10:1) to give pale yellow oil compounds 10a-d.

10a; 2.38 g, yield 35 %. IR (KBr) ν_{max} 3073, 2920, 2850, 1463 cm^{-1}. ^{1}H NMR (Chloroform) δ, ppm: 7.00-7.99 (4H, m, Ph-ring), 4.95 (2H, s, OCH_2), 3.95 (3H, s, OCH_3), 2.21 (3H, s, CH_3), 2.19 (3H, s, CH_3), 1.85 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.95 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.9, 12.5, 15.6, 19.5, 20.5, 21.6, 22.7, 22.8, 23.5, 24.5, 24.6, 24.8, 25.9, 27.9, 31.4, 31.6, 32.4, 36.6, 37.7, 38.3, 39.5, 40.1, 55.6, 70.1, 74.3, 114.5, 115.7, 117.6, 123.2, 125.3, 128.4, 128.5, 129.4, 130.8, 132.3, 132.0, 147.5, 148.4, 152.5. MS m/z (%): 682 [M^+, 40], Anal. Calcd. for $C_{39}H_{58}N_2O_3Se$: C, 68.70; H, 8.57; N, 4.11. Found C, 68.55; H, 8.51; N, 4.10.

10b; 2.79 g, yield 40 %. IR (KBr) ν_{max} 3073, 2920, 2850, 1463 cm^{-1}. ^{1}H NMR (Chloroform) δ, ppm: 7.15-8.50 (4H, m, Ph-ring), 4.99 (2H, s, OCH_2), 2.20 (3H, s, CH_3), 2.18 (3H, s, CH_3), 1.86 (3H, m, 3CH), 1.64 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.96 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.9, 12.5, 15.9, 19.5, 20.5, 21.5, 22.8, 22.9, 23.5, 24.3, 24.6, 24.8, 25.9, 27.9, 31.4, 31.5, 32.2, 36.6, 37.6, 38.3, 39.5, 40.2, 70.1, 74.2, 114.5, 115.7, 117.6, 123.2, 125.5, 128.4, 128.5, 129.4, 130.8, 132.3, 132.0, 147.8, 148.2, 156.5. MS m/z (%): 697 [M^+, 25], Anal. Calcd. for $C_{38}H_{55}N_3O_4Se$: C, 65.50; H, 7.96; N, 6.03. Found C, 65.35; H, 7.90; N, 6.00.

10c; 2.01 g, yield 30 %. IR (KBr) ν_{max} 3073, 2920, 2850, 1463 cm^{-1}. ^{1}H NMR (Chloroform) δ, ppm: 7.10-8.20 (4H, m, Ph-ring), 4.90 (2H, s, OCH_2), 2.20 (3H, s, CH_3), 2.07 (3H, s, CH_3), 1.86 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.45 (22H, m, $11CH_2$), 0.95 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.6, 12.5, 15.9, 19.5, 20.5, 21.5, 22.8, 22.9, 23.5, 24.3, 24.6, 24.8, 25.9, 27.9, 31.4, 31.5, 32.2, 36.6, 37.6, 38.3, 39.5, 40.2, 70.1, 74.2, 114.5, 115.7, 117.6, 123.2, 125.5, 128.4, 128.5, 129.4, 130.8, 132.3, 132.0, 147.8, 148.2, 152.5. MS m/z (%): 670 [M^+, 10], Anal. Calcd. for $C_{38}H_{55}FN_2O_2Se$: C, 68.14; H, 8.28; N, 4.18 Found C, 68.00; H, 8.15; N, 4.15.

10d; 2.37 g, yield 35 %. IR (KBr) ν_{max} 3073, 2920, 2850, 1463; 2221 (CN) cm^{-1}. ^{1}H NMR (Chloroform) δ, ppm: 7.00-8.00 (4H, m, Ph-ring), 4.20 (2H, s, OCH_2), 2.21 (3H, s, CH_3), 2.19 (3H, s, CH_3), 1.85 (3H, m, 3CH), 1.65 (6H, m, $2CH_3$), 1.46 (22H, m, $11CH_2$), 0.96 (12H, m, $4CH_3$). ^{13}CNMR δ, ppm: 11.8, 12.5, 15.9, 19.5, 20.5, 21.5, 22.8, 22.9, 23.5, 24.3, 24.6, 24.8, 25.9, 27.9, 31.4, 31.5, 32.2, 36.6, 37.6, 38.3, 39.5, 40.2, 70.1, 74.2, 114.5, 115.7, 117.6, 118,3, 123.2, 125.5, 128.4, 128.5, 129.4, 130.8, 132.3, 132.0, 147.8, 148.2, 154.5. MS m/z (%): 676 [M^+-1, 10], Anal. Calcd. for $C_{39}H_{55}N_3O_2Se$: C, 69.21; H, 8.19; N, 6.21. Found C, 69.15; H, 8.12; N, 6.15.

Assay for Biological Activity

Culture of Microorganisms

The biological screening was carried out at the Department of Biochemistry Faculty of Agriculture Cairo University, Giza, Egypt. For the inoculum of bacterial, nutrient broth was applied as the growth medium. The culture was maintained at 4ºC on nutrient agar plates/slants and at 70ºC as 40% glycerol stocks.

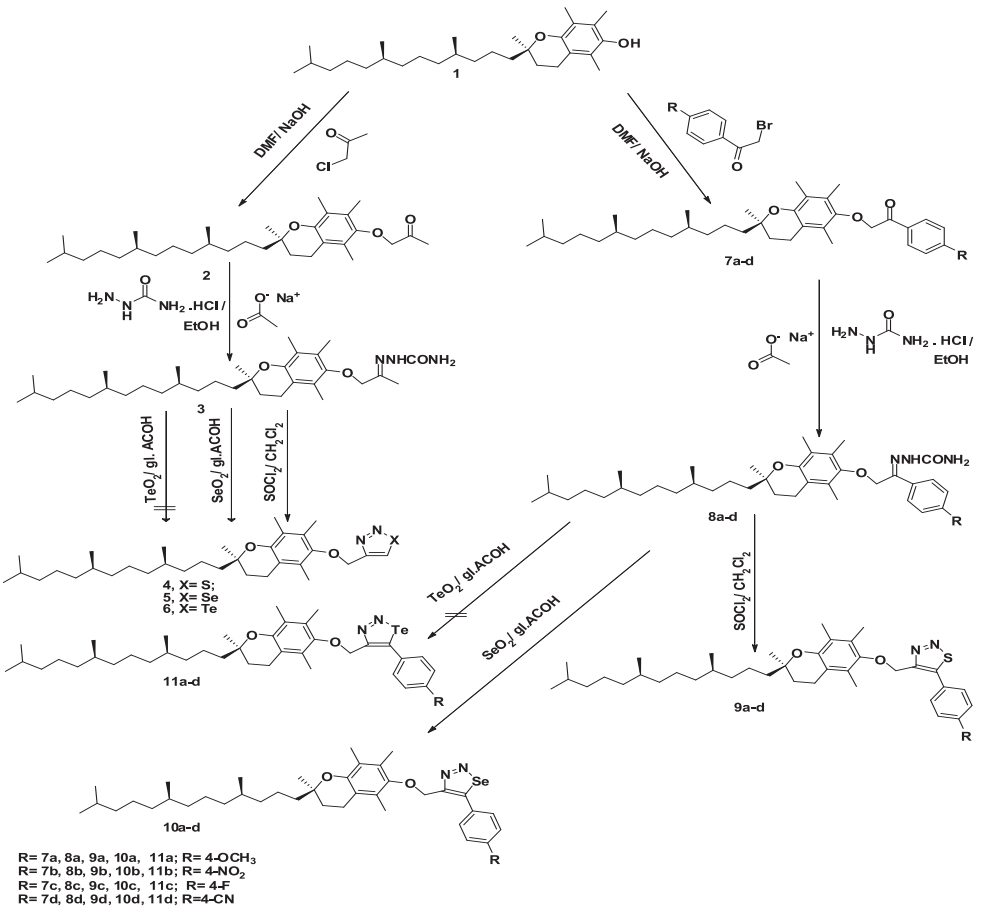
Determination of Antibacterial Activity

A novel synthesized compounds "4, 5, 9a-d and 10a-d" (100 µg/mL in dimethyl sulfoxide) was determined in vitro against a variety of pathogenic microorganisms, such as Gram-positive bacteria *(*i.e., *Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative bacteria *(*i.e., *Pseudomonas aeruginosa* and *Salmonella typhimurium*), in nutrient agar media by measuring the zone of inhibition in mm using the disc diffusion method [10]. In addition, both *Tetracycline* was used as standard antibacterial agent and served as positive control for antimicrobial activity. As a negative control, all test microorganisms were treated to (dimethyl sulfoxide).

Results and Discussion

Chemistry

Our target compounds (4, 9a-d) and (5, 10a-d) respectively, two pathways were followed; The first way, started from α-Tocopherol with chloroacetone in the presence of dimethylformamide/NaOH to give derivative (2) followed by the reaction with semicarbazide hydrochloride forming derivative (3) namely, vitamin e/ hydrazine- carboxamide. IR spectroscopy analysis of compounds (3) appeared characteristic bands for semicarbazone derivative at 3400, 3350, 3149 (NH, NH_2); 1655 (ketone-amide) cm^{-1}. Also, ^{1}H and ^{13}C NMR spectroscopy supported the synthesized novel compound 3. ^{1}H-NMR (Chloroform) δ = 8.95 (1H, s, NH); 6.00 (2H, s, NH_2); 4.20 (2H, s, OCH_2), 1.91 (3H, s, CH_3) 2.17 (3H, s, CH_3, 2-CH_3), 2.09 (3H, s, CH_3, 5-CH_3) in addition data confirmed the peaks for the number of hydrogen in vitamin e. For ^{13}C-NMR data agreement with the number of carbon atoms. Reactions of compound 3 with thionyl chloride and selenium dioxide with ring closure gave our targeted compounds 4 and 5 respectively. While reaction of 3 with tellurium oxide in acetic acid as a solvent to give 1,2,3-telluradiazole derivative (6) was failed (Scheme 1). All spectroscopic data with agreement with our targeted compounds 4 and 5. For example, IR data showed disappearance of (NH, NH_2) and (C=O) groups as a results of ring closure for both two products 4 and 5. The second way, started from α-Tocopherol with 4-substituted phenacybromide (4-methoxy;4-nitro-4-fluoro and 4-cyano) in the presence of dimethylformamide/NaOH to form derivatives (7a-d) followed by the reaction with $NH_2CONHNH_2.HCl$ in the presence of sodium acetate forming derivatives (8a-d). Reaction of derivatives 8a-d with thionyl chloride and selenium dioxide yielding new products (9a-d) and (10a-d) respectively. The results of the spectroscopic examination agreed with the newly synthesized compounds 9a-d and 10a-d. The end product (11a-d)



Scheme 1: Synthesis of vitamin e containing thiadiazole and selenadiazole derivatives by the reaction of Vitamin E with chloro acetone and/ or acetophenone derivatives

(Scheme 1) was not produced using the same method to synthesize 1,2,3-thia/selenadiazole derivatives. TeO_2 was used in replacement of $SOCl_2$/ SeO_2. Whereas a similar reaction with tellurium dioxide was not successful in the formation of 1,2,3-telluradiazole, the reaction may pass through polymeric or telluroxodiazole intermediates, causing tellurium loss and formation of an active free radical.

Antimicrobial Activity

Compounds (4, 5, 9a-d, and 10a-d) were studied and tested for antibacterial activity against Gram-positive (*Bacillus cereus* (*B. cereus*) and Gram-negative (*Pseudomonas aeruginosa* (*P. aeruginosa*) and *Salmonella typhimurium* (*S. typhimurium*) bacteria. The data in the findings are displayed (see Table 1). Data showed that α-tocopherol as a parent compound has no antibacterial activity against the tested organisms. Both *Gram-positive* and *Gram-negative* bacteria were inhibited by the activated synthesized compounds 4 and 9a-d. Compound 4 exhibited inhibition zones at (14) and (13) mm against Gram-negative bacteria (*P. aeruginosa*) and (*S. typhimurium*), respectively, while 9d (4-CN-substituted/1,2,3-thiadiazole/-tocopherol) showed excellent activity against Gram-positive bacteria *S. aureus* (19 mm) and *P. Subtilis* (18 mm). Furthermore, compound 9d inhibited Gram-negative bacteria (*P. aeruginosa*) and (*S. typhimurium*) in zones 15 and 16 mm. This indicates that the newly activated compound 9d, in addition to compounds 4, 9a, 9b, and 9c, have antibacterial activity and broad spectrum for both Gram (negative and positive) bacteria. From the data listed in (Table 1) the order of reactivity against bacteria as follows: 9d>9a>9c>9b>4. However, derivatives (1,2,3-selenadiazole/ α-tocopherol) (5 and 10a-d) exhibit moderate antibacterial effect against only Gram-positive bacteria, *Bacillus cereus* (*B. cereus*) & *Staphylococus aureus* (*S. aureus*). On the other hand, Gram-negative bacteria, demonstrated resistance to all compounds (5 and 10a-d). As a result, connecting vitamin e to the 1,2,3-thiadiazole ring activated the parent molecule (1) vitamin e (α-tocopherol), yielding a novel biological class of compounds 9d, 9a, 9c, and 9b in addition compound 4.

Conclusions

Thiadiazole and selenadiazole compounds were used to create a new class of Vitamin e. Vitamin e containing thiadiazoles (9a-d) shown excellent antibacterial activity

Table 1. Diameter of inhibition zone (mm) by synthesized compounds (4, 5, 9a-d and 10a-d) against pathogenic bacteria.

Strain	Inhibition zone (mm)			
Compounds No.	*B. subtilis*	*S. aureus*	*P. aeruginosa*	*S. typhimurium*
	Bacteria (G^+)		Bacteria (G^-)	
[a] Tetracycline	22	24	20	19
1 (α-tocopherol)	-ve	-ve	-ve	-ve
4	10	12	13	14
5	11	12	-ve	-ve
9a	17	16	14	16
9b	14	17	15	13
9c	16	18	16	15
9d	18	19	15	16
10a	15	11	-ve	-ve
10b	11	12	-ve	-ve
10c	12	14	-ve	-ve
10d	14	11	-ve	-ve

[a] reference bacteria; Bs: *Bacillus subtilis*; Sa: *Staphylococcus aureus*; St: S*almonella typhimurium*; G+: Gram-positive bacteria; G-: Gram-negative bacteria. As negative control dimethylsulfoxid was used for all test microorganisms.

and a broad spectrum against *Gram-negative* and Gram-positive bacteria. The antibacterial activity of derivative (9d), which contains the (-CN) group, is significantly influenced, followed by the methoxy group (-OCH_3) in compound (9a), and finally the (-F) group in compound (9c). Only Gram-positive bacteria are resistant to vitamin e that contains Selenadiazoles (10a-c). Compounds (4) with vitamin e - bearing parent thiadiazoles (without any derivatives) have moderate effectiveness against *Gram-positive* and *Gram-negative* bacteria. Furthermore, Vitamin e with parent selenadiazoles (without any derivatives) has only limited action against Gram-positive bacteria. That means thiadiazole derivatives (-CN, -OCH_3, F, and NO_2) contribute to antibacterial action in this class of compounds.

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Conflict of Interest

The authors declare no conflict of interest.

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