Macedonian Journal of Chemistry and Chemical Engineering, Vol. **33**, No. 2, pp. 189–198 (2014)

MJCCA9 – 647
Received: April 11, 2014
Accepted: September 30, 2014

ISSN 1857-5552, e-ISSN 1857-5625
UDC: 547.789
Original scientific paper

SYNTHESIS AND CHARACTERIZATION OF NOVEL 1,3-THIAZOLE AND 2-AMINO-1,3,4-THIADIAZOLE DERIVATIVES

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Thiosemicarbazone derivatives **3a–e** were synthesized by the reaction of various aldehydes **1a–e** with 4-methyl thiosemicarbazide **2** in 78% to 90% yield. Then, the thiazole moieties of the target materials **5a–e** were obtained in high yields (71–93%) using the Hantzsch reaction utilizing thiosemicarbazone derivatives **3a–e** with ethyl-2-chloroacetoacetic ester. The substituted nitrile derivatives **7a–e** were obtained in moderate to high yield (58–84%) from the reaction of compounds **5a–e** with chloroacetonitrile by the nucleophilic aliphatic substitution reaction in the presence of anhydrous potassium carbonate. Finally, substituted 2-amino-1,3,4-thiadiazole compounds **9a–e** were obtained in moderate to good yields (51–62%) from the reaction of thiosemicarbazide with substituted nitrile derivatives **7a–e**. As a result, compounds that all share a high disposition for biological activities were obtained. The structures of the newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis, and mass spectrometric techniques.

Keywords: thiosemicarbazone; 1,3-thiazole; 2-amino-1,3,4-thiadiazole; Hantzsch reaction

СИНТЕЗА И КАРАКТЕРИЗАЦИЈА НА НОВИ ДЕРИВАТИ НА 1,3-ТИАЗОЛ И 2-АМИНО-1,3,4-ТИАДИАЗОЛ

Тиосемикарбазонските деривати **3a–e** беа синтетизирани при реакција на разни алдехиди **1a–e** со 4-метилтиосемикарбазид **2** со принос од 78 до 90%. Тиазолските прстени на целните соединенија **5a–e** беа добиени со висок принос од 71–93% со реакцијата на Hantzsch со примена на тиосемикарбазонските деривати **3a–e** и етил-2-хлороацетооцетен естер. Супституираните нитрилни деривати **7a–e** беа добиени со умерен до висок принос при реакција на соединенијата **5a–e** со хлороацетонитрил при нуклеофилна алифатична супституција во присуство на безводен калиумкарбонат. Конечно, супституираните 2-амино-1,3,4-тиодиазолните соединенија **9a–e** беа добиени со умерен до добар принос (51–62%) при реакција на тиосемикарбазид со супституирани нитрилни деривати **7a–e**. Сите овие добиени соединенија покажуваат висока биолошка активност. Структурите на новосинтетизираните соединенија беа потврдени по пат на IR, ^{1}H NMR, ^{13}C NMR, елементарна анализа и масеноспектрометриски техники.

Клучни зборови: тиосемикарбазон; 1,3-тиазол; 2-амино-1,3,4-тиадиазол; реакција на Hantzsch

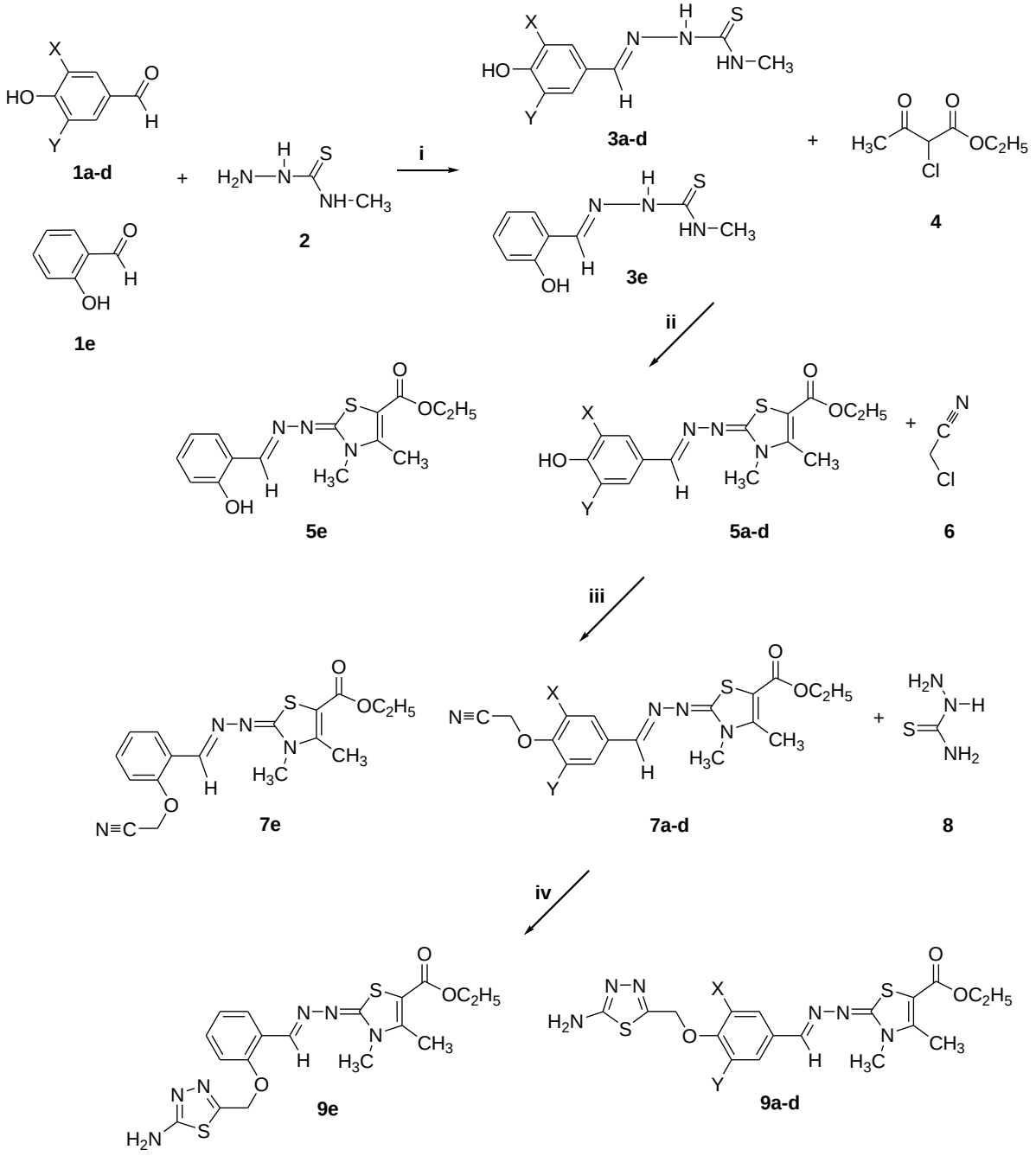
1. INTRODUCTION

In recent years, despite the discovery and analysis of an increasing number of compounds exhibiting biological properties, their usage has been limited due to application difficulties, the emergence of drug resistance, unwanted side effects, and pharmacokinetic deficiencies. Thus, great efforts have been made by chemists to analyze and synthesize compounds exhibiting biological activities that have the potential to be used in medicinal chemistry. Thiazoles, thiadiazoles, and their heterocyclic derivatives have attracted continuing interest over the years because of their varied biological properties [1–3].

Thiazole and thiadiazole derivatives are known to exhibit various biological activities, such as anti-allergy [4], antihypertensive [5], anti-in-

flammatory [6–7], anti-schizophrenia [8], antifungal [9], antibacterial [10], antimicrobial [11–13], analgesic [14], anti-HIV [15], anticonvulsant [16], antidepressant [17], and anti-cancer [18–21] properties. Other uses of heterocyclic compounds containing nitrogen and sulfur include manufacturing biocides, dyes [22–24], and plant-growth regulators [25]. Thus, the synthesis of thiazole and thiadiazole derivatives is currently of great importance to the scientific community.

The purpose of the present study was to obtain and characterize novel thiosemicarbazone, 1,3-thiazole, nitrile, and 2-amino-1,3,4-thiadiazole derivatives (Scheme 1).



Scheme 1. Synthetic pathway for the preparation of target compounds **(3, 5, 7, 9 a–e).**

2. EXPERIMENTAL

Materials and methods

Melting points were recorded on a Gallenkamp melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-Mercury 200 MHz spectrometer. The IR spectra were measured in potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrometer. The mass spectra were measured with a Micromass Quattro LC/ULTIMA LC-MS/MS spectrometer in the positive ion mode using pyridine-methanol as a solvent. Elemental analysis was performed on a Hewlett-Packard 185 CHN analyzer. Elemental values of the synthesized compounds agreed with the calculated ones. All of the chemicals were obtained from Fluka Chemie AG Buchs (Switzerland). Compounds **3d** [26], **3e** [27], **5d** [26], and **5e [**27] have been published.

General method for the synthesis of thiosemicarbazone derivatives (3a–c)

In a round-bottomed flask, compounds **1a–c** (0.0125 mol) and 4-methyl thiosemicarbazide **2** (0.0125 mol) were heated to 160°C without solvent in an oil bath and stirred for 4 h. Dimethylformamide (DMF) was added to the reaction and dissolved. Water was then added to the solution and a solid precipitated. The solution was filtered, and the solid was washed with ethanol. The precipitated solid was recrystallized from an appropriate solvent to afford the desired compound.

1-(4-Hydroxybenzylidene)-4-methylthiosemicarbazide (3a). The solid obtained was washed with H_2O and recrystallized (yield: 2.04 g, 78%); white solid, mp 224–225°C (from EtOH-water, 1:1) IR (KBr) (ν_{max}, cm^{-1}), 3342 (OH), 3178 (NH), 3009 (Ar-CH), 2936 (Aliph. CH), 1599 (C=N), 1562 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 2.98–3.00 (d, 3H, N-CH_3), Ar-H [6.76–6.80 (d, 2H), 7.59–7.63 (d, 2H)], 7.94 (s, 1H, CH=N), 8.36, (s, 1H, NH-CH_3), 9.88, (s, 1H, OH), 11.26, (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 30.66, 115.44, 125.15, 128.86, 159.06, 142.04, 177.22. MS(ESI-*m/z*): $(M+1)^+$: 210.39. Anal. for $C_9H_{11}N_3OS$ (Mw 209.27). Found % C 51.68; H 5.24; N 20.14. Calculated % C 51.65; H 5.30; N 20.08.

1-(4-Hydroxy-3-methoxybenzylidene)-4-methylthiosemicarbazide (3b). The solid obtained was washed with H_2O, alcohol and recrystallized (yield: 2.48 g, 83%); yellow solid, mp 195–196°C (from DMF-EtOH, 1:1) IR (KBr) (ν_{max}, cm^{-1}), 3358 (OH), 3147 (NH), 2999 (Ar-CH), 2954 (Aliph. CH), 1599 (C=N), 1553 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 3.01–3.03 (d, 3H, N-CH_3), 3.83 (s, 3H, (OCH_3)), Ar-H [6.77–6.80 (d, 1H), 7.07–7.12 (d, 1H), 7.40 (s, 1H)], 7.93, (s, 1H, CH=N), 8.35–8.37, (d, 1H, NH-CH_3), 9.47, (s, 1H, OH), 11.30, (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 30.70, 55.70, 109.66, 115.24, 121.87, 127.54, 142.37, 147.90, 148.63, 177.22. MS(ESI-*m/z*): $(M+1)^+$: 240.14. Anal. for $C_{10}H_{13}N_3O_2S$ (Mw 239.29). Found % C 50.27; H 5.34; N 17.49. Calculated % C 50.19; H 5.48; N 17.56.

1-(4-Hydroxy-3,5-dimethylbenzylidene)-4-methylthiosemicarbazide (3c). The solid obtained was washed with H_2O and recrystallized (yield: 2.70 g, 90%); white solid, mp 214–215°C (from EtOH) IR (KBr) (ν_{max}, cm^{-1}), 3100–3450 (OH), 3165 (NH), 3001 (Ar-CH), 2971 (Aliph. CH), 1591 (C=N), 1483 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 2.17 (s, 6H, CH_3), 2.99 (s, 3H, N-CH_3), Ar-H [7.34 (s, 2H)], 7.88 (s, 1H, CH=N), 8.74 (bs, 1H, NH-CH_3), 8.79 (s, 1H, OH), 11.32 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 17.25, 31.45, 125.10, 125.73, 128.25, 143.20, 155.87, 177.84. MS(ESI-*m/z*): $(M+1)^+$: 238.02; Anal. for $C_{11}H_{15}N_3OS$ (Mw 237.32). Found % C 55.55; H 6.41; N 17.75. Calculated % C 55.67; H 6.37; N 17.71.

General method for the synthesis of 1,3-thiazole derivatives (5a–c)

In a two-necked flask, compounds **3a–c** (0.009 mol) were suspended in absolute ethanol. The solution of compound **4** (0.009 mol) in absolute ethanol was then dropped into the suspension for 30 min. The reaction mixture was refluxed for 3 days and the clear color of the mixture turned to yellow. The crude product was filtrated and washed with water. The precipitated solid was recrystallized from an appropriate solvent to afford the desired compound.

(*E*)-Ethyl 2-(2-(4-hydroxybenzylidene)hydrazono)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate (5a). The solid was recrystallized (yield: 2.67 g, 93%); white crystals, mp 289–290°C (from DMF-EtOH-H_2O, 1:4:1) IR (KBr) (ν_{max}, cm^{-1}), 3150–3450 (OH), 3026 (Ar-CH), 2980 (Aliph. CH), 1700 (C=O), 1603 (C=N), 1278, 1262, 1234 (C-O-C), 1084 (OCH_2-CH_3). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.20–1.28 (t, 3H, Ester-CH_3), 2.52 (s, 3H, Thiazole-CH_3), 3.38 (s, 3H, N-CH_3), 4.14–4.21 (q, 2H, Ester-OCH_2), Ar-H [6.79–6.84 (d, 2H), 7.54–7.59 (s, 2H)], 8.22 (s, 1H, CH=N),

9.90 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 12.45, 14.12, 31.28, 60.22, 100.87, 115.51, 125.81, 128.82, 148.25, 152.67, 159.17, 161.34, 165.27. MS(ESI-*m/z*): $(M+1)^+$: 320.02; Anal. for $C_{15}H_{17}N_3O_3S$ (Mw 319.38). Found % C 56.48; H 5.31; N 13.25. Calculated % C 56.41; H 5.37; N 13.16.

(*E*)-Ethyl 2-(2-(4-hydroxy-3-methoxybenzylidene)hydrazono)-3,4-dimethyl-2,3-dihydro-thiazole-5-carboxylate (5b). The solid obtained was washed with H_2O and recrystallized (yield: 2.86 g, 91%); yellow solid, mp 169–170°C (from DMF-EtOH-water, 1:4:1) IR (KBr) (ν_{max}, cm^{-1}), 3100–3470 (OH), 3053 (Ar-CH), 2934 (Aliph. CH), 1655 (C=O), 1579 (C=N), 1266–1196 (C-O-C), 1087 (OCH_2-CH_3). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.21–1.27 (t, 3H, Ester-CH_3), 2.51 (s, 3H, Thiazole-CH_3), 3.39 (s, 3H, N-CH_3), 3.81 (s, 3H, OCH_3), 4.15-4.21 (q, 2H, Ester-OCH_2), Ar-H [6.80–6.84 (d, 1H)], 7.14–7.18 (d, 1H), 7.29 (s, 1H)], 8.21 (s, 1H, CH=N), 9.49 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 12.48, 14.20, 31.35, 55.42, 60.27, 100.48, 109.93, 115.48, 121.44, 126.23, 147.70, 148.27, 148.68, 152.99, 161.37, 165.13. MS(ESI-*m/z*): $(M+1)^+$: 350.05. Anal. for $C_{16}H_{19}N_3O_4S$ (Mw 349.40). Found % C 55.02; H 5.51; N 12.06. Calculated % C 55.00; H 5.48; N 12.03.

(*E*)-Ethyl 2-(2-(4-hydroxy-3,5-dimethylbenzylidene)hydrazono)-3,4-dimethyl-2,3-dihydro-thiazole-5-carboxylate (5c). The solid obtained was washed with EtOH then diethyl ether, and was recrystallized (yield: 2.22 g, 71%); light-yellow solid, mp 203–204°C (from DMF-EtOH, 1:5) IR (KBr) (ν_{max}, cm^{-1}), 3437 (OH), 3120 (Ar-CH), 2976 (Aliph. CH), 1672 (C=O), 1585 (C=N), 1293–1189 (C-O-C), 1093 (OCH_2-CH_3). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.26 (s, 3H, Ester-CH_3), 2.21 (s, 6H, CH_3), 2.53 (s, 3H, Thiazole-CH_3), 3.38 (s, 3H, N-CH_3), 4.20 (s, 2H, Ester-OCH_2), Ar-H [7.31 (s, 2H)], 8.17 (s, 1H, CH=N), 8.71 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 12.41, 14.10, 16.31, 31.25, 60.17, 100.70, 124.27, 125.67, 127.41, 148.21, 153.18, 155.14, 161.31, 164.88. MS(ESI-*m/z*): $(M+1)^+$: 348.12. Anal. for $C_{17}H_{21}N_3O_3S$ (Mw 347.43). Found % C 58.69; H 6.18; N 12.12. Calculated % C 58.77; H 6.09; N 12.09.

General method for the synthesis of nitrile derivatives (7a–e)

In a two-necked flask, compounds **5a–e** (0.01 mol) and K_2CO_3 (0.015 mol) were dissolved in dry acetone, and the solution was stirred for 1 hour at room temperature. Compound **6** was then dropped into this solution. The reaction mixture was refluxed for 2 days. The solution was filtrated and the solid was obtained. The precipitated solid was recrystallized from an appropriate solvent to afford the desired compound.

(*E*)-Ethyl 2-(2-(4-(cyanomethoxy)benzylidene) hydrazono)-3,4-dimethyl-2,3-dihydro-thiazole-5-carboxylate (7a). The solid obtained was washed with acetone and recrystallized (yield: 3.01 g, 84%); yellow crystals, mp 194–195°C (from DMF-acetone, 1:3) IR (KBr) (ν_{max}, cm^{-1}), 3051 (Ar-CH), 2972 (Aliph. CH), 2255 (C≡N), 1673 (C=O), 1597 (C=N), 1289–1231 (C-O-C), 1089 (OCH_2-CH_3). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.19–1.26 (t, 3H, Ester-CH_3), 2.53 (s, 3H, Thiazole-CH_3), 3.37 (s, 3H, N-CH_3), 4.12–4.21 (q, 2H, Ester-OCH_2), 5.21(s, 2H, Ar-OCH_2), Ar-H [7.09–7.14 (d, 2H), 7.70–7.75, d, 2H)], 8.51 (s, 1H, CH=N). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 13.26, 14.90, 32.16, 54.19, 61.12, 101.94, 115.77, 117.19, 129.49, 130.01, 149.06, 152.56, 158.19, 162.08, 167.06. MS(ESI-*m/z*): $(M+1)^+$: 359.02. Anal. for $C_{17}H_{18}N_4O_3S$ (Mw 358.41). Found % C 56.92; H 5.03; N 15.68. Calculated % C 56.97; H 5.06; N 15.63.

(*E*)-Ethyl 2-(2-(4-(cyanomethoxy)-3-methoxybenzylidene)hydrazono)-3,4-dimethyl-2,3-dihydro-thiazole-5-carboxylate (7b). The solid obtained was washed with acetone and recrystallized (yield: 2.45 g, 63%); white solid, mp 184–185°C (from acetone-chloroform, 3:1) IR (KBr) (ν_{max}, cm^{-1}), 3073 (Ar-CH), 2972 (Aliph. CH), 2245 (C≡N), 1689 (C=O), 1582 (C=N), 1268–1146 (C-O-C), 1085 (OCH_2-CH_3). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.21–1.27 (t, 3H, Ester-CH_3), 2.52 (s, 3H, Thiazole-CH_3), 3.36 (s, 3H, N-CH_3), 3.84 (s, 3H, OCH_3), 4.13–4.23 (q, 2H, Ester-OCH_2), 5.17 (s, 2H, Ar-OCH_2), Ar-H [7.13–7.17 (d, 1H), 7.28–7.33, d, 1H), 7.40, s, 1H)], 8.28 (s, 1H, CH=N). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 13.31, 14.93, 32.18, 55.09, 56.26, 61.12, 102.04, 110.68, 115.52, 116.71, 121.31, 130.90, 147.73, 148.99, 150.21, 152.91, 162.11, 166.94. MS(ESI-*m/z*): $(M+1)^+$: 389.10. Anal. for $C_{18}H_{20}N_4O_4S$ (Mw 388.44). Found % C 55.52; H 5.12; N 14.40. Calculated % C 55.66; H 5.19; N 14.42.

(*E*)-Ethyl 2-(2-(4-(cyanomethoxy)-3,5-dimethylbenzylidene)hydrazono)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate (7c). The solid obtained was recrystallized (yield: 3.17 g, 82%); yellow crystals, mp 174–175°C (from petroleum ether-chloroform, 1:1) IR (KBr) (ν_{max}, cm^{-1}), 3046 (Ar-CH), 2979 (Aliph. CH), 2269 (C≡N), 1691 (C=O), 1588 (C=N), 1262–1159 (C-O-C), 1081

(OCH_2-CH_3). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.20–1.27 (t, 3H, Ester-CH_3), 2.28 (s, 3H, CH_3), 2.52 (s, 3H, Thiazole-CH_3), 3.39 (s, 3H, N-CH_3), 4.14–4.22 (q, 2H, Ester-OCH_2), 4.94 (s, 2H, Ar-OCH_2), Ar-H [7.42 (s, 2H)], 8.22 (s, 1H, CH=N). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 13.29, 14.96, 16.82, 32.22, 58.03, 61.16, 101.98, 117.81, 124.27, 128.47, 131.74, 149.13, 152.72, 156.22, 162.09, 167.18. MS(ESI-*m/z*): $(M+1)^+$: 387.04. Anal. for $C_{19}H_{22}N_4O_3S$ (Mw 386.47). Found % C 59.17; H 5.82; N 14.49. Calculated % C 59.05; H 5.74; N 14.50.

(*E*)-Ethyl 2-(2-(4-(cyanomethoxy)-3,5-dimethoxybenzylidene)hydrazono)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate (7d). The solid obtained was recrystallized (yield: 3.01 g, 72%); white solid, mp 220–221°C (from acetone) IR (KBr) (ν, cm^{-1}), 3068 (Ar-CH), 2972 (Aliph. CH), 2243 (C≡N), 1665 (C=O), 1579 (C=N), 1302–1240 (C-O-C), 1091 (OCH_2-CH_3); ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.25 (s, 3H, Ester-CH_3), 2.49 (s, 3H, Thiazole-CH_3), 3.41 (s, 3H, N-CH_3) (3.84 (s, 6H, OCH_3), 4.17–4.24 (s, 2H, Ester-OCH_2), 4.92 (s, 2H, Ar-OCH_2), Ar-H [7.10 (s, 2H)], 8.28 (s, 1H, CH=N); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 13.31, 14.91, 32.81, 55.29, 56.54, 61.32, 102.28, 110.84, 115.32, 116.91, 117.75, 121.51, 130.55, 146.54, 147.95, 150.35, 152.19, 162.25, 167.25. MS(ESI-*m/z*): $(M+1)^+$: 419.29. Anal. for $C_{19}H_{22}N_4O_5S$ (Mw 418.47). Found % C 54.50; H 5.35; N 13.44. Calculated % C 54.53; H 5.30; N 13.39.

(2*Z*,2*E*)-Ethyl 2-(2-(2-(cyanomethoxy)benzylidene)hydrazono)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate (7e). The solid obtained was recrystallized, (yield: 2.08 g, 58%); brownish solid, mp 195–196°C (from petroleum ether-chloroform-acetone, 1:1:1) IR (KBr) (ν_{max}, cm^{-1}), 3073 (Ar-CH), 2978 (Aliph. CH), 2248 (C≡N), 1676 (C=O), 1597 (C=N), 1265–1169 (C-O-C), 1088 (OCH_2-CH_3). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.19–1.27 (t, 3H, Ester-CH_3), 2.53 (s, 3H, Thiazole-CH_3), 3.41 (s, 3H, N-CH_3), 4.13–4.22 (q, 2H, Ester-OCH_2), 5.23 (s, 2H, Ar-OCH_2), Ar-H [6.90-6.94 (dd, 1H), 7.13–7.22 (dd, 1H), 7.43–7.47 (d, 1H), 7.84–7.93 (m, 1H)], 8.28 (s, 1H, CH=N). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 13.29, 14.90, 32.28, 54.83, 61.21, 102.13, 117.21, 114.09, 122.67, 126.95, 131.65, 147.53, 149.23, 155.28, 156.54, 162.19, 167.54. MS(ESI-*m/z*): $(M+1)^+$: 359.09. Anal. for $C_{17}H_{18}N_4O_3S$ (Mw 358.41). Found % C 56.91; H 5.09; N 15.70. Calculated % C 56.97; H 5.06; N 15.63.

General method for the synthesis of 2-amino-1,3,4-thiadiazole derivatives (9a–e)

In a round-bottomed flask, a mixture of compounds **7a–e** (0.00553 mol) and compound **8** (0.00829 mol) in trifluoroacetic acid (5 ml) at 60–70°C was stirred for 5 h. The reaction mixture was poured into 200 ml of ice-cold water and neutralized with ammonia. The solid obtained was washed with H_2O and crystallized from an appropriate solvent to afford the desired compound.

(*E*)-Ethyl 2-(2-(4-((2-amino-1,3,4-thiadiazol-5-yl)methoxy)benzylidene)hydrazono)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate (9a). The solid obtained was recrystallized (yield: 1.36 g, 57%); yellow solid, mp 256–257°C (from DMF-EtOH, 1:2) IR (KBr) (ν_{max}, cm^{-1}), 3313–3095 (NH_2), 3030 (Ar-CH), 2982 (Aliph. CH), 1698 (C=O), 1601 (C=C), 1577 (N-C-S), 1540 (C=N), 1088 (OCH_2-CH_3), 1260–1170 (C-O-C). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.24 (s, 3H, Ester-CH_3), 2.52 (s, 3H, Thiazole-CH_3), 3.36 (s, 3H, N-CH_3), 4.80 (s, 2H, Ester-OCH_2), 5.32 (s, 2H, Ar-OCH_2), Ar-H [7.10 (s, 2H), 7.69 (s, 2H)], 7.34 (s, 2H, NH_2), 8.27 (s, 1H, CH=N). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 13.30, 14.86, 31.22, 55.25, 60.16, 64.98, 100.65, 109.41, 112.55, 120.65, 129.42, 146.75, 151.24, 152.86, 153.92, 163.76, 167.25, 170.55. MS(ESI-*m/z*): $(M+1)^+$: 433.24. Anal. for $C_{18}H_{20}N_6O_3S_2$ (Mw 432.52). Found % C 49.84; H 4.58; N 19.38. Calculated % C 49.91; H 4.66; N 19.43.

(*E*)-Ethyl 2-(2-(4-((2-amino-1,3,4-thiadiazol-5-yl)methoxy)-3,5-dimethoxy)benzylidene)hydrazono)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate (9b). The solid obtained was recrystallized (yield: 1.48 g, 58%); yellow solid, mp 224–225°C (from DMF-EtOH, 1:1) IR (KBr) (ν_{max}, cm^{-1}), 3307–3121 (NH_2), 3034 (Ar-CH), 2986 (Aliph. CH), 1676 (C=O), 1577 (C=C), 1546 (N-C-S), 1500 (C=N), 1085–1132 (OCH_2-CH_3), 1276–1227 (C-O-C). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.23 (s, 3H, Ester-CH_3), 2.52 (s, 3H, Thiazole-CH_3), 3.38 (s, 3H, N-CH_3), 3.80 (s, 3H), 4.19 (s, 2H, Ester-OCH_2), 5.30 (s, 2H, Ar-OCH_2), Ar-H [7.18 (s, 1H), 7.26 (s, 1H), 7.53 (s, 1H)], 7.34 (s, 2H, NH_2), 8.26 (s, 1H, CH=N). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 13.32, 14.96, 32.21, 56.25, 61.16, 65.58, 101.85, 110.41, 114.85, 121.66, 129.52, 148.95, 149.16, 150.04, 153.26, 154.52, 162.16, 166.64, 170.67. MS(ESI-*m/z*): $(M+1)^+$: 463.08. Anal. for $C_{19}H_{22}N_6O_4S_2$ (Mw 462.55). Found % C 49.27; H 4.86; N 18.28. Calculated % C 49.34; H 4.79; N 18.17.

(*E*)-Ethyl 2-(2-(4-((2-amino-1,3,4-thiadiazol-5-yl)methoxy)-3,5-dimethyl-benzylidene)hydrazono)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate (9c). The solid obtained was recrystallized (yield: 1.29 g, 51%); light-yellow solid, mp 227–228°C (from DMF-EtOH, 1:8) IR (KBr) (ν_{max}, cm^{-1}), 3281–3131 (NH_2), 3043 (Ar-CH), 2963 (Aliph. CH), 1688 (C=O), 1583 (C=C), 1536 (N-C-S), 1504 (C=N), 1086 (OCH_2-CH_3), 1266-1147 (C-O-C). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.20–1.26 (t, 3H, Ester-CH_3), 2.23 (s, 6H, CH_3), 2.50 (s, 3H, Thiazole-CH_3), 3.37 (s, 3H, N-CH_3), 4.14–4.19 (q, 2H, Ester-OCH_2), 4.97 (s, 2H, Ar-OCH_2), Ar-H [7.34 (s, 2H)], 7.36 (s, 2H, NH_2), 8.19 (s, 1H, CH=N). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 13.26, 14.93, 16.91, 32.40, 61.13, 68.54, 101.95, 128.35, 131.05, 131.75, 149.04, 152.94, 154.61, 156.89, 162.10, 166.96, 170.68. MS(ESI-*m/z*): $(M+1)^+$: 461.28. Anal. for $C_{20}H_{24}N_6O_3S_2$ (Mw 460.57). Found % C 52.28; H 5.19; N 18.30. Calculated % C 52.16; H 5.25; N 18.25.

(*E*)-Ethyl 2-(2-(4-((2-amino-1,3,4-thiadiazol-5-yl)methoxy)-3,5-dimethoxy-benzylidine)hydrazono)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate (9d). The solid obtained was washed with H_2O and recrystallized (yield: 1.55 g, 57%); yellow solid, mp 211–212°C (from DMF-EtOH, 1:4) IR (KBr) (ν_{max}, cm^{-1}), 3297–3109 (NH_2), 3053 (Ar-CH), 2966 (Aliph. CH), 1694 (C=O), 1611 (C=C), 1581 (N-C-S), 1540 (C=N), 1085–1121 (OCH_2-CH_3), 1264–1160 (C-O-C). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.23 (s, 3H, Ester-CH_3), 2.51 (s, 3H, Thiazole-CH_3), 3.39 (s, 3H, N-CH_3), 3.81 (s, 6H, N-CH_3), 4.17–4.19 (s, 2H, Ester-OCH_2), 5.05 (s, 2H, Ar-OCH_2), Ar-H [7.04 (s, 2H)], 7.34 (s, 2H, NH_2), 8.25 (s, 1H, CH=N). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 13.35, 14.94, 30.87, 56.60, 61.21, 69.12, 102.08, 104.85, 131.70, 137.55, 149.10, 153.28, 153.74, 155.28, 162.13, 167.08, 170.87 MS(ESI-*m/z*): $(M+1)^+$: 493.08. Anal. for $C_{20}H_{24}N_6O_5S_2$ (Mw 492.57). Found % C 48.89; H 4.99; N 17.13. Calculated % C 48.77; H 4.91; N 17.06.

(2*Z*,2*E*)-Ethyl 2-(2-(2-((2-amino-1,3,4-thiadiazol-5-yl)methoxy)-benzylidene)hydrazono)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate (9e). The solid obtained was recrystallized (yield: 1.48 g, 62%); yellow solid, mp 247–248°C (from DMF-EtOH, 1:8) IR (KBr) (ν_{max}, cm^{-1}), 3285–3169 (NH_2), 3064 (Ar-CH), 2977 (Aliph. CH), 1672 (C=O), 1597 (C=C), 1537 (N-C-S), 1522 (C=N), 1081 (OCH_2-CH_3), 1267–1228 (C-O-C). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm), 1.19–1.26 (t, 3H, Ester-CH_3), 2.51 (s, 3H, Thiazole-CH_3), 3.39 (s, 3H, N-CH_3), 4.13–4.20 (q, 2H, Ester-OCH_2), 5.35 (s, 2H, Ar-OCH_2), Ar-H [7.01–7.05 (m, 1H), 7.19–7.23, d, 1H), 7.35 (s, 1H), 7.85–7.92 (s, 1H)], 7.34 (s, 2H, NH_2), 8.50 (s, 1H, CH=N). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm), 13.26, 14.90, 32.26, 61.17, 65.45, 102.11, 114.16, 122.40, 126.13, 131.94, 147.90, 149.13, 154.37, 154.53, 156.44, 162.08, 167.61, 170.57. MS(ESI-*m/z*): $(M+1)^+$: 433.24. Anal. for $C_{18}H_{20}N_6O_3S_2$ (Mw 432.52). Found % C 50.08; H 4.71; N 19.47. Calculated % C 49.98; H 4.66; N 19.43.

3. RESULTS AND DISCUSSION

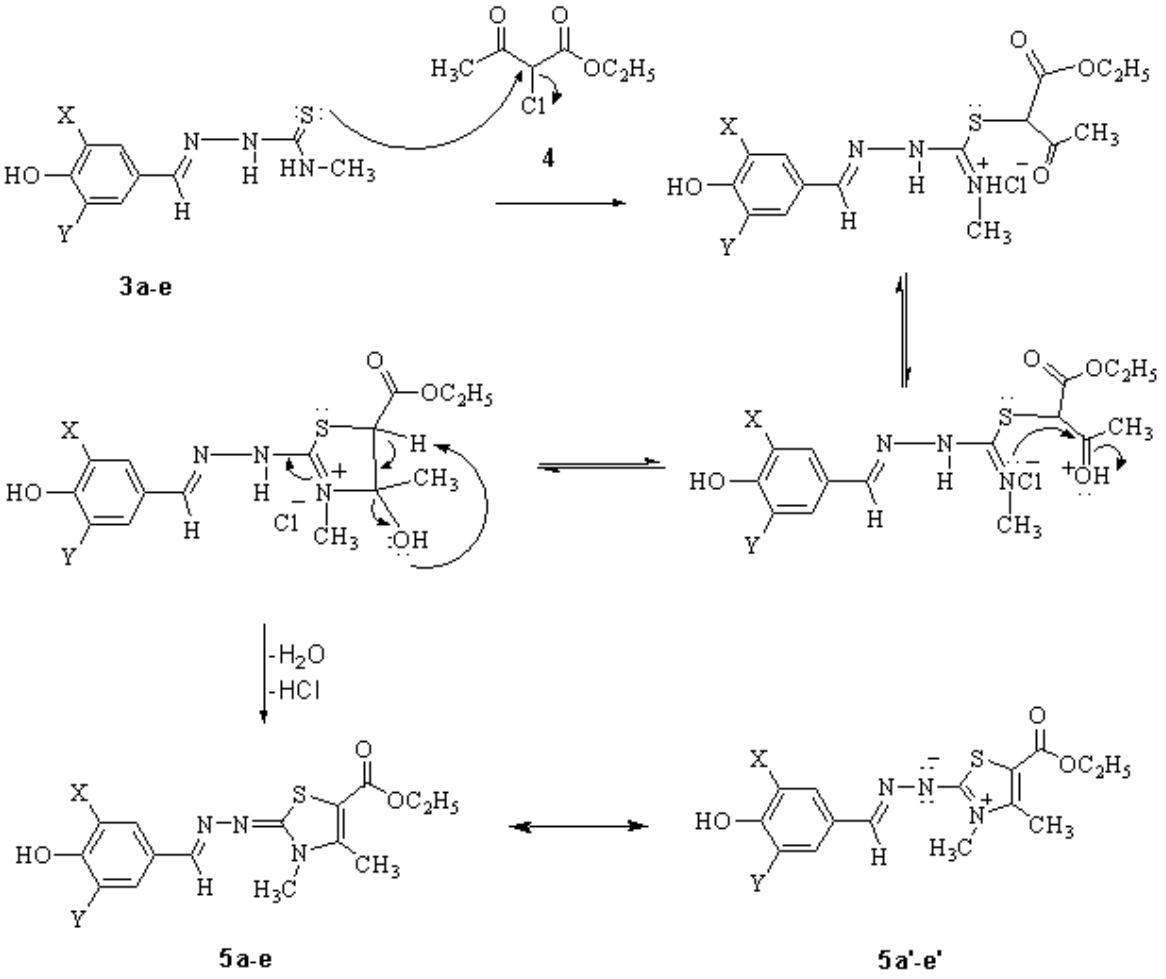
In the first part of the study, thiosemicarbazone derivatives **3a–e** were synthesized via the reaction of various aldehyde derivatives **1a–e** with 4-methyl-thiosemicarbazide. In the IR spectral data of compounds **3a–e**, signals belonging to the aldehyde carbonyl group that appeared at 1650–1730 cm^{-1} disappeared, and υ(NH) and υ(CH=N) stretching frequencies were observed at 3147–3178 cm^{-1} and 1583–1599 cm^{-1}, respectively. The presence of new absorption at 1583–1599 cm^{-1} belonging to (CH=N) supported the data indicating that the thiosemicarbazones derivatives **3a–e** were successfully prepared. Also, structures of the thiosemicarbazone derivatives **3a–e** were identified with the assistance of NMR spectroscopy.

In the ^{1}H NMR spectra of compounds **3a–e**, the proton signals were recorded at 8.34–8.37 ppm (NH-CH_3) integrating for one proton (controlled by exchanging with D_2O). N(2)H protons were observed between 11.26 and 11.32 ppm integrating for one proton (exchangeable with D_2O). In the ^{1}H NMR spectra of compounds **3a–e**, another characteristic proton signal belonging to CH=N was observed at 7.88–7.94 ppm integrating for one proton. In the ^{1}H NMR data of compounds **3a–e**, the signals of the aldehyde protons and the -NH_2 protons of 4-methyl-3-thiosemicarbazide disappeared and a new signal belonging to the protons of the CH=N group was observed at 7.88–7.94 ppm. Furthermore, in the ^{13}C NMR data, the signal of carbon from the carbonyl group of aldehyde derivatives disappeared, and a new signal appeared at 142.04–143.20 ppm belonging to the iminic carbon.

In the ^{13}C NMR spectral data of compounds **3a–e**, while C=O belonging to the ^{13}C NMR signal of compounds **1a–e** that appeared at 185–195 ppm disappeared, the ^{13}C NMR signals belonging to the C=S group of compounds **3a–e** were observed at 177.22–177.84 ppm. It has been reported that the peak of the spectral data is quite specific [28]. On

the other hand, the mass spectra of compounds **3a–e** confirmed the structure of **3a–e** by molecular ion peaks.

In the second part of the study, the thiazole moieties of the target materials were obtained using the Hantzsch reaction from the reaction thiosemicarbazone derivatives **3a–e** with ethyl-2-chloroacetoacetic ester at a 1:1 ratio in absolute ethanol in high yields (Scheme 1). According to this reaction mechanism, the compounds of **5a–e** could be resonance forms. However, the spectral data and physical parameters showed that the compounds of **5a–e** have the exo-imine form in the 2-position of the thiazole group. The reaction mechanism is shown in Scheme 2.



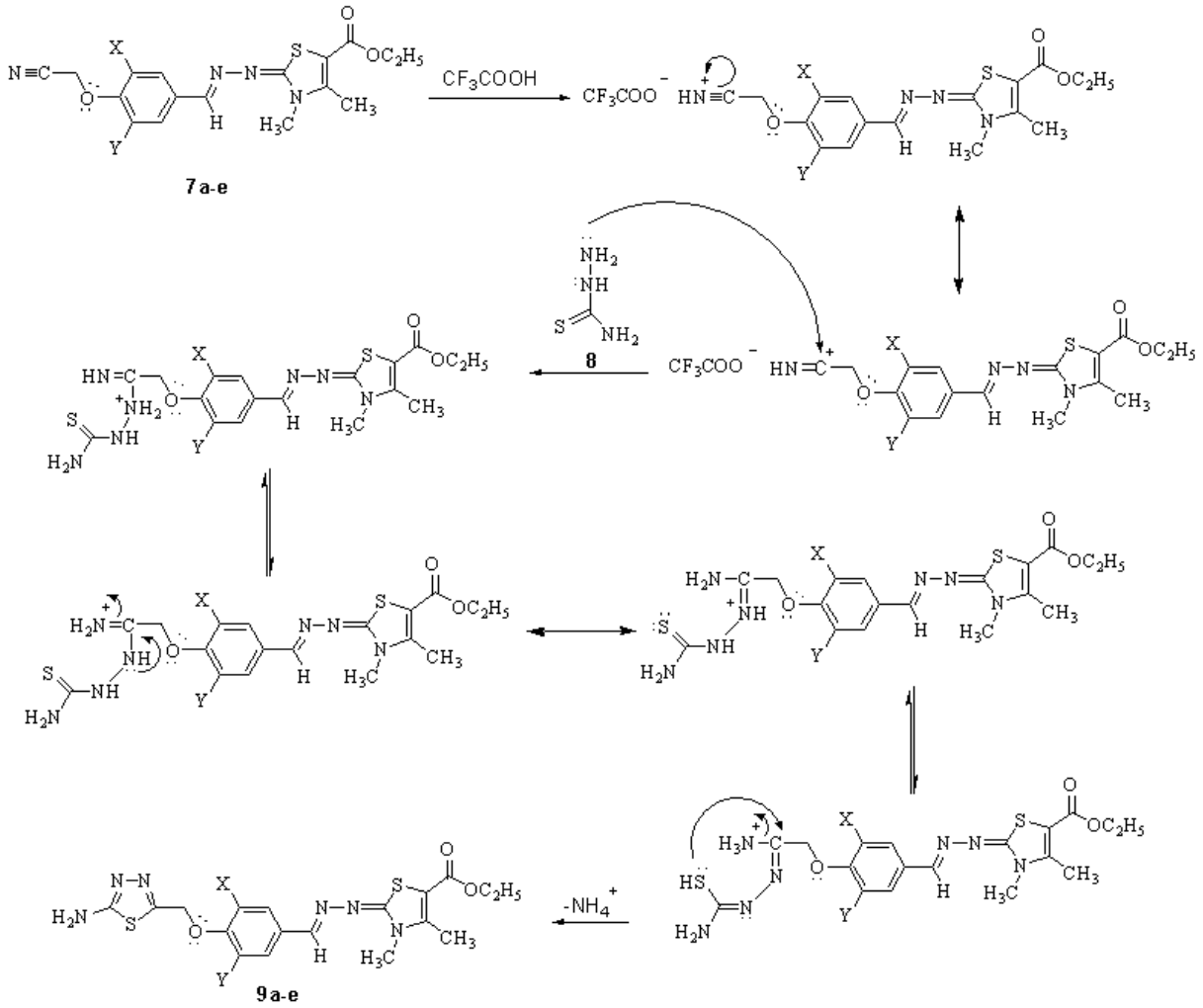
Scheme 2. The mechanism of the Hantzsch thiazole synthesis

The most characteristic IR data for the synthesized compounds **5a–e** appeared at 1655–1700 cm^{-1} (C=O stretching), 1579–1603 cm^{-1} (CH=N stretching), and 1189–1293 cm^{-1} (C-O-C stretching). The absence of absorption of the -NH groups of compounds **3a–e** in the IR spectra of compounds **5a–e** confirmed the realization of the reaction. Furthermore, the ^{1}H NMR spectra showed the absence of the -N(2)H signals of the compounds **3a–e** and the presence of the new methyl and ethoxy group signals at 3.37–3.39, 4.14–4.23 (for OCH_2) and 1.20–1.28 ppm (for CH_3 of ethoxy group), respectively. The ^{1}H NMR spectra of compounds **5a–e** also supported the proposed structure. The ^{13}C NMR spectra of **5a–e** provided satisfactory data for their characterization. The ^{13}C NMR signals of the compounds **5a–e** of the -CH_3 and -OCH_2 ester group and the carbons of the thiazole ring -CH_3 and -OCH_2 were observed at 12.41–60.27 ppm. This spectral data provides the strongest evidence for sp^3-hybridized carbons. In addition, C(5) and C(4) of the thiazole ring were observed at 100.48–100.87 and 148.21–148.28 ppm, respectively. The exo N(2')=C(2) carbon data of the

thiazole ring appeared at 161.31–161.37 ppm in the ^{13}C NMR spectra [29]. The signals of the thione group (C=S) from the compounds **3a–e** disappeared, and new signals were observed at 60.17–60.27 ppm (-OCH_2), 14.10–14.20 ppm (-CH_3), 12.41–12.54 ppm (-OCH_2CH_3). On the other hand, the mass spectra of compounds **5a–e** supported the structure of **5a–e** by molecular ion peaks.

In the third part of the study, substituted nitrile derivatives **7a–e** were obtained from the reaction of compounds **5a–e** with chloroacetonitrile (Scheme 1). The preparations of the substituted nitrile derivatives **7a–e** were achieved by the nucleophilic aliphatic substitution reaction of chloroacetonitrile with compounds **5a–e** [30]. The structures of compounds were confirmed by spectral investigation. In the IR spectra, the formations of compounds **7a–e** were clearly defined by the disappearance of -OH absorption of compounds **5a–e**, and the appearance of a -C≡N absorption band between 2243 and 2269 cm^{-1}. The ^{1}H NMR spectra of compounds **7a–e** were also in good agreement with the structures of the synthesized compounds **7a–e**. The phenolic -OH signal of compounds **5a–e** disappeared after the nucleophilic aliphatic substitution reaction. The integral ratios of the aliphatic (-CH_2) proton signals were obtained as expected. The -CH_2 protons of compounds **7a–e** were observed at 4.12–4.24 ppm integrating for two protons (exchangeable with D_2O). In the ^{13}C NMR spectra, the signals seen at 116.71–117.81 ppm indicated the presence of nitrile carbon for compounds **7a–e**. Additionally, the mass spectra of compounds **7a–e** validated the structure of **7a–e** by molecular ion peaks.

In the last part of the study, substituted 2-amino-1,3,4-thiadiazole compounds **9a–e** were obtained from the reaction of thiosemicarbazide with substituted nitrile derivatives **7a–e** in the presence of trifluoroacetic acid (TFA) (Scheme 1). The reaction mechanism is shown in Scheme 3.



Scheme 3. The mechanism of the substituted 2-amino-1,3,4-thiadiazole synthesis.

In the IR spectra of compounds **9a–e**, -NH_2 was observed at 3131–3313 cm^{-1}, and the C-O-C stretching frequency was observed at 1020–1132 cm^{-1}. In the ^{1}H NMR spectra of compounds **9a–e**, the proton signals from the methylene group (-CH_2) were recorded at 4.97–5.35 ppm integrating for two protons. -NH_2 was observed at 7.27–7.36 ppm integrating for two protons (exchangeable with D_2O). In the ^{13}C NMR spectra of compounds **9a–e**, the signals belonging to the thiadiazole ring (C-2 and C-5) were observed in the aromatic region while the signal belonging to the -C≡N group disappeared. The thiadiazole rings of compounds **9a–e** were observed at 153.74–154.61 ppm for C-2 and 170.57–170.87 for C-5. The ^{13}C NMR signals of the methylene group were observed between 65.45 and 69.12 ppm. On the other hand, the mass spectra of compounds **9a–e** confirmed the structure of compounds **9a–e** by molecular ion peaks.

Generally, the presence of electron-donor groups led to increased product yields. However, in the presence of 2,6-disubstituted electron-donor groups, either low yields were obtained or the target compounds could not be obtained because of steric effects. Thus, in this study, 3,5-disubstituted electron-donor groups were used, and the obtained reaction yields were presented in experimental section.

In this study, novel thiosemicarbazone, 1,3-thiazole, nitrile and 2-amino-1,3,4-thiadiazole derivatives were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis, and mass spectral analysis techniques. The methods used in this study are applicable for obtaining compounds with a strong potential for biological activity.

Acknowledgments. We thank Professor İ. Değirmencioğlu and Professor K. Serbest for their valuable contributions.

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