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ORIGINAL ARTICLE

Utility of *N*-aryl 2-aroylhydrazono-propanehydrazonoyl chlorides as precursors for synthesis of new functionalized 1,3,4-thiadiazoles with potential antimicrobial activity

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ABSTRACT

Starting from *N*-aryl 2-aroylhydrazono-propanehydrazonoyl chlorides, a series of new functionalized 1,3,4-thiadiazoles were prepared. The structures of the compounds prepared were confirmed by both elemental and spectral analyses as well as by alternate synthesis. The mechanisms of the studied reactions are outlined. The antimicrobial activities of the compounds prepared were screened and the results showed that most of such compounds exhibit considerable activities.

Introduction

The chemistry of hydrazonoyl halides of the general formula, R—C(X)═NNHR', **1**, has attracted the interest of many research groups since their discovery in 1882 [1]. Their reactions with various reagents and their applications in synthesis of various heterocyclic compounds have been extensively reviewed by Shawali and/or his colleagues [2–14] and others [15,16]. A survey of literature reveals the presence of two contradicting reports [17–19]. In one report [17], it was indicated that reaction of *N*-aryl 2-oxopropane-hydra-zonoyl bromide **2a** with acylhydrazines **3** yielded the corresponding substitution products **4** which upon oxidation afforded the corresponding formazan derivatives **5** (Scheme 1). In contrast, it was recently reported that reaction of *N*-aryl 2-oxopropanehydrazonoyl chlorides **2b** with acylhydrazines **3** yielded the condensation products **6** [18,19] (Scheme 1). In an attempt to provide further evidence for the actual pathway for the reaction of **2b** with acid

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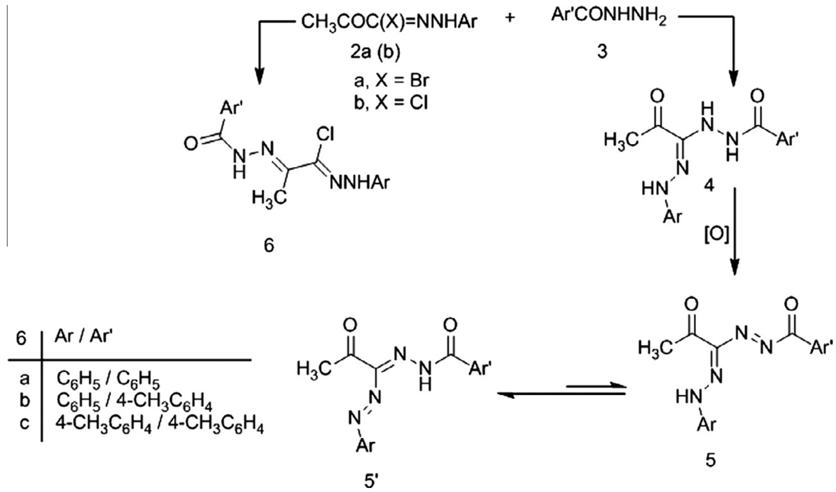


Scheme 1

hydrazides, it was thought interesting to study the reaction of the products **6** with some sulfur dipolarophiles. This is because products of type **6** still have the hydrazonoyl chloride moiety. Our objective after such a study was to explore the utility of compounds of type **6** as precursors in syntheses of new thiadiazoline derivatives of expected biological activities. This is because many 1,3,4-thiadiazoles have been reported to possess several biological activities such as anticancer, antihistaminic and hypoglycemic activities [20–22].

Experimental

All melting points were measured on Electrothermal IA 9000 series digital melting point apparatus. The IR spectra were recorded in potassium bromide disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometer. ^{1}H NMR (300 MHz) was run in deuterated dimethyl sulfoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass Spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. All reactions were followed by TLC (Silica gel, Aluminum Sheets 60 F254, Merck). 2-(2-benzoylhydrazono)-*N′*-phenylpropanehydrazonoyl chloride **6a**, 2-(2-benzoylhydrazono)-N′-p-tolylpropanehydrazonoyl chloride **6b**, 2-(2-(4-methylbenzoyl)hydrazono)-*N′*-(p-tolyl)propanehydrazonoyl chloride **6c,** *methyl N-phenyldithiocarbamate*, methyl benzylidenedithiocarbazate, methyl dithiocarbazate, methyl benzoylcarbodithioate, and 5-phenyl-1,3,4-oxadiazole-2-thiol were prepared as reported in the literature [18,19,23,24].

Synthesis of phenyl 2-(2-benzoylhydrazono)-N′-phenylpropanehydrazonothioate (7)

Method A

A mixture of **6** (0.31 g, 1 mmol) and sodium thiophenolate (0.13 g, 1 mmol) in ethanol (20 mL) was stirred at rt for 2 h, and the solid formed was filtered off, washed with ethanol, dried and recrystallized from ethanol to give **7** as yellow crystals (94%); m.p. 180–182 °C (EtOH); IR: *v* 1591 (C=N), 1653 (C=O), 3193, 3443 (2NH) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 2.19 (s, 3H, CH_3), 6.90–7.89 (m, 15H, ArH's), 9.81 (s, br, 1H, NH), 12.58 (s, br, 1H, NH); Anal. Calcd for $C_{22}H_{20}N_4O_S$ (388.49): C, 68.02; H, 5.19; N, 14.42; S, 8.25 Found C, 68.14; H, 5.21; N, 14.23; S, 8.34%.

Method B

A mixture of **8** (0.27 g, 1 mmol) and benzoylhydrazide (0.13 g, 1 mmol) in ethanol (20 mL) was heated under reflux for 2 h, allowed to cool and the solid formed was filtered off, washed with ethanol, dried and recrystallized from ethanol to give product in 78% yield identical in all aspects (mp., mixed mp. and spectra data) with **7** obtained by method A.

Synthesis of phenyl 2-oxo-N′-phenylpropanehydrazonothioate (8)

A mixture of **2b** (0.19 g, 1 mmol) and sodium thiophenolate (0.13 g, 1 mmol) in ethanol (30 mL) was stirred at rt for 1 h, and then it was left overnight. The solid precipitate formed was filtered off, dried and crystallized from ethanol to give the corresponding product **8** as yellow crystals (83%); m.p. 118 °C (AcOH). IR: *v* 3264 (NH), 1659 (CO), 1600 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d6): δ 2.33 (s, 3H, CH_3), 6.90–7.41 (m, 10H, ArH's), 9.87 (s, br., 1H, NH). Anal. Calcd for $C_{15}H_{14}N_2OS$ (270.35): C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found C, 66.59; H, 5.10; N, 10.28; S, 11.68%.

*Synthesis of iminothiadiazolines **9a,b***

Method A

A mixture of the appropriate **6** (5 mmol) and potassium thiocyanate (0.6 g, 6 mmol) in ethanol (25 mL) was stirred at rt for 24 h. The resulting solid was collected, washed with water, and crystallized from ethanol to give the corresponding product **9**.

Method B

A mixture of the appropriate **6** (0.005 mol) and thiourea (0.38 g, 5 mmol) in ethanol (25 mL) was refluxed for 3 h. The solid product that formed after cooling was collected and crystallized from ethanol to give the corresponding product **9** in 75% yield which proved identical in all aspects with that obtained by method A.

*N′-(1-(5-Imino-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethylidene)-benzo-hydrazide (**9a**)*

Yellow solid (78%); m.p. 210–2 °C (EtOH); IR: ν 1600 (C═N), 1658 (C═O), 3308, 3184 (2NH) cm^{-1}; ^1H NMR (DMSO-d6): δ 2.32 (3H, s, CH_3), 6.90–7.90 (10H, m, ArH's), 10.13 (1H, s, NH), 10.83 (1H, s, NH); ^{13}C NMR: δ 13.4 (CH_3), 126.2, 128.1, 128.9, 130.2, 130.8, 134.5, 140.1, 148.4, 155.3, 161.5, 165.2; MS *m*/*z* (%): 338 ($M^+ + 1$, 5), 337 (M^+, 32), 278 (33), 161 (19), 105 (100), 77 (100). Anal. Calcd for $C_{17}H_{15}N_5OS$ (337.40): C, 60.52; H, 4.48; N, 20.76. Found C, 60.58; H, 4.40; N, 20.56%.

*N′-(1-(5-Imino-4-(p-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethylidene)-benzo-hydrazide (**9b**)*

Yellow solid (72%); m.p. 210 °C (EtOH); IR: ν 1610 (C═N), 1674 (C═O), 3169, 3310 (2NH) cm^{-1}; ^1H NMR (DMSO-d6): δ 2.31 (3H, s, CH_3), 2.50 (3H, s, CH_3), 6.63–8.19 (10H, m, ArH's), 10.63 (1H, s, NH), 11.37 (1H, s, NH); ^{13}C NMR: δ 13.4, 21.1, 121.1, 128.6, 129.9, 131.5, 134.6, 140.4, 148.4, 155.4, 161.4, 164.8; MS *m*/*z* (%): 352 ($M^+ + 1$, 4), 351 (M^+, 14), 161 (12), 105 (100), 77 (54). Anal. Calcd for $C_{18}H_{17}N_5OS$ (351.43): C, 61.52; H, 4.88; N, 19.93. Found C, 61.46; H, 4.92; N, 19.69%.

*Preparation of the N-nitroso derivatives **10a,b***

A cold saturated solution of sodium nitrite (10 mL) was added dropwise to a solution of the appropriate **9** (1 g) in acetic acid (20 mL) in an ice bath while stirring. The reaction mixture was stirred for 30 min. The resulting solid was collected, washed with water, and crystallized from acetone to give the corresponding **10a** and **10b**, respectively.

*N′-(1-[5-(nitrosoimino)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl]ethylidene)benzohydrazide (**10a**)*

Orange solid (69%); m.p. 187–9 °C; IR: ν 1581 (N═O), 1640 (C═N), 1681 (C═O), 3442 (NH) cm^{-1}; ^1H NMR (DMSO-d6): δ 2.29 (3H, s, CH_3), 6.63–8.18 (10H, m, ArH's), 10.63 (1H, s, NH); ^{13}C NMR (DMSO-d6): δ 1.3.4, 126.5, 127.4, 128.9, 130.2, 123.8, 134.7, 139.8, 155.7, 160.9, 161.8, 165.1; MS *m*/*z* (%): 367 ($M^+ + 1$, 4), 367 (M^+, 16), 314 (8), 278 (32), 161 (15), 105 (100), 77 (73). Anal. Calcd for $C_{17}H_{14}N_6O_2S$ (366.40): C, 55.73; H, 3.85; N, 22.94. Found C, 55.89; H, 3.96; N, 22.74%.

*N′-(1-[4-(4-methylphenyl)-5-(nitrosoimino)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-ethylidene)benzohydrazide (**10b**)*

Orange solid (72%); m.p. 182–4 °C; IR: ν 1581 (N═O), 1643 (C═N), 1686 (C═O), 3448 (NH) cm^{-1}; ^1H NMR (DMSO-d6): δ 2.29 (3H, s, CH_3), 2.42 (3H, s, CH_3), 6.62–8.08 (9H, m, ArH's), 10.69 (1H, s, NH); ^{13}C NMR (DMSO-d6): δ 13.4, 20.9, 121.5, 128.9, 130.1, 134.8, 140.8, 156.1, 161.4, 161.7, 164.9; MS *m*/*z* (%): 380 (M^+, 65), 237 (42), 193(43), 151(26), 77(100). Anal. Calcd for $C_{18}H_{16}N_6O_2S$ (380.42): C, 56.83; H, 4.24; N, 22.09. Found C, 56.76; H, 4.35; N, 22.01%.

*N′-(1-(5-oxo-4-(p-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethylidene)benzo-hydrazide (**11b**)*

A solution of compound **10b** (0.5 g) in xylene (20 mL) was refluxed for 15 min and the solvent was evaporated under reduced pressure. The oil residue was triturated with petroleum ether (40–60 °C), and the solid formed was collected and crystallized from ethanol to give **11b** as yellow solid (78%); m.p. 232–4 °C; IR: ν 1666, 1708 (2C═O), 3448(NH) cm^{-1}; ^1H NMR (DMSO-d6): δ 2.26 (3H, s, CH_3), 2.39 (3H, s, CH_3), 7.32–7.79 (9H, m, ArH's), 11.17 (1H, s, NH); ^{13}C NMR (DMSO-d6): δ 13.4, 21.3, 120.3, 130.1, 130.9, 131.4, 123.5, 134.3, 134.6, 139.7, 149.2, 156.5, 160.2, 163.1; MS *m*/*z* (%): 353($M^+ + 1$, 18), 352(M^+, 43), 239(23), 119(100), 84(65). Anal. Calcd for $C_{18}H_{16}N_4O_2S$ (352.41): C, 61.35; H, 4.58; N, 15.90. Found C, 61.33; H, 4.51; N, 15.76%.

*Synthesis of N-((E)-5-((Z)-1-(2-benzoylhydrazono)ethyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)acetamide (**12a**)*

A mixture of **9a** (1 g) in acetic acid (10 mL) and acetic anhydride (5 mL) was heated for 5 min at 70 °C. The reaction mixture was poured onto ice water (40 mL). The solid precipitate was collected and crystallized to give **12a** as yellow solid (71%); m.p. 198 °C (EtOH); IR: ν 1632, 1651, 1709 (3C═O), 3234 (NH) cm^{-1}; ^1H NMR (DMSO-d6): δ 2.17 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.39 (3H, s, CH_3), 7.31–7.83 (9H, m, ArH's), 11.17 (1H, s, NH); ^{13}C NMR (DMSO-d6): δ 13.3, 25.1, 125.6, 127.8, 128.9, 129.7, 130.6, 134.5, 140.2, 146.5, 155.1, 161.2, 164.8, 174.6; MS *m*/*z* (%): 380 ($M^+ + 1$, 2), 379 (M^+, 8), 314 (32), 278 (31), 161 (17), 105 (100), 77(75). Anal. Calcd for $C_{19}H_{17}N_5O_2S$ (379.11): C, 60.14; H, 4.52; N, 18.46. Found C, 60.28; H, 4.64; N, 18.67%.

*Synthesis of 1,3,4-thiadiazoline derivatives **13a–c***

Method A

Triethylamine (0.75 mL, 5 mmol) was added dropwise with stirring to a mixture of methyl *N*-phenyldithiocarbamate (5 mmol) and the appropriate **6a–c** (5 mmol) in ethanol (20 mL) for 30 min. The resulting solid was collected and recrystallized from ethanol to give the corresponding **13**.

Method B

A mixture of the appropriate **6a–c** (5 mmol) and phenylthiourea (0.38 g, 5 mmol) in ethanol (25 mL) was refluxed for 3 h. The solid product that formed after cooling was collected and crystallized from ethanol to give the product **13** which proved identical in all aspects (mp, mixed mp, and spectra) with **13** which obtained by method A.

The products **13a–c** prepared together with their physical constants are given below.

*N′-(1-(4-phenyl-5-(phenylimino)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-ethylidene)-benzohydrazide (**13a**)*

Yellow solid (73%); m.p. 194–6 °C (EtOH); IR: ν 1610 (C═N), 1661 (C═O), 3336 (NH) cm^{-1}; ^1H NMR (DMSO-d6): δ 2.33 (s, 3H, CH_3), 6.91–7.98 (m, 15H, ArH's), 10.73

(s, 1H, NH); ^{13}C NMR (DMSO-d6): δ 13.5, 124.3, 126.4, 127.9, 129.1, 129.7, 129.9, 130.2, 134.4, 140.1, 147.6, 155.7, 161.3, 164.8; MS *m/z* (%): 414 ($M^+ + 1$, 3), 413 (M^+, 8), 374(5), 338 (19), 306 (56), 278 (13), 161 (56), 105 (100), 77 (96), 51 (46). Anal. Calcd for $C_{23}H_{19}N_5OS$ (413.49): C, 66.81; H, 4.63; N, 16.94. Found C, 66.65; H, 4.54; N, 16.76%.

*4-Methyl-N′-(1-(4-phenyl-5-(phenylimino)-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethyl-idene)benzohydrazide (**13b**)*

Yellow solid (78%); m.p. 213–5 °C (EtOH); IR: *ν* 1619 (C=N), 1670(C=O), 3324 (NH) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 2.32 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.03–7.89 (m, 14H, ArH's), 10.79 (s, 1H, NH); MS *m/z* (%): 428 ($M^+ + 1$, 2), 427 (M^+, 5), 333 (32), 261 (5), 243 (4), 209 (17), 105 (100), 77 (70). Anal. Calcd for $C_{24}H_{21}N_5OS$ (427.52): C, 67.43; H, 4.95; N, 16.38. Found C, 67.33; H, 4.78; N, 16.30%.

*4-Methyl-N′-(1-((Z)-5-(phenylimino)-4-(p-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethylidene)benzohydrazide (**13c**)*

Yellow solid (73%); m.p. 196–8 °C (EtOH); IR: *ν* 1614 (C=N), 1674 (C=O), 3313 (NH) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 2.15 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.50 (s,3H, CH_3), 6.94–7.82 (m, 13H, ArH's), 10.71 (s, 1H, NH); ^{13}C NMR (DMSO-d6): δ 13.4, 20.8, 21.5, 121.2, 124.2, 127.8, 129.8, 131.2, 131.3, 134.2, 135.4, 145.1, 147.5, 147.8, 156.1, 161.2, 164.8; MS *m/z* (%): 442($M^+ + 1$, 5), 441(M^+, 3), 306 (9), 225 (8), 175 (15), 119 (100), 105 (27), 77 (24). Anal. Calcd for $C_{25}H_{23}N_5OS$ (441.55): C, 68.00; H, 5.25; N, 15.86. Found C, 67.70; H, 5.29; N, 15.57%.

*Synthesis of 1,3,4-thiadiazoline derivatives **14a–g***

Method A

Triethylamine (0.75 mL, 5 mmol) was added dropwise with stirring to a mixture of methyl arylidenedithiocarbazate (5 mmol) and the appropriate **6a–c** (0.005 mol) in ethanol (20 mL) for 30 min. The resulting solid was collected and crystallized from DMF to give the corresponding product **14a–g**.

*N′-(1-(5-(benzylidenehydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)-ethylidene)benzohydrazide (**14a**)*

Orange solid (86%); m.p. 268 °C (DMF); IR: *ν* 1604 (C=N), 1663 (C=O), 3184 (NH) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 2.43 (3H, s, CH_3), 7.29–8.05 (15H, m, ArH's), 8.47 (1H, s, CH=N), 11.25 (1H, s, NH); MS *m/z* (%): 442 ($M^+ + 2$, 4), 441 ($M^+ + 1$, 15), 440 (M^+, 52), 323 (12), 161 (45), 105 (56), 77 (98). Anal. Calcd for $C_{24}H_{20}N_6OS$ (440.52): C, 65.44; H, 4.58; N, 19.08. Found C, 65.36; H, 4.34; N, 19.02%.

*N′-(1-(5-(benzylidenehydrazono)-4-(p-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-ethylidene)benzo-hydrazide (**14b**)*

Orange solid (80%); m.p. 240–2 °C (DMF); IR: *ν* 1604 (C=N), 1666 (C=O), 3176 (NH) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 2.19 (3H, s, CH_3), 2.44 (3H, s, CH_3), 6.94–7.82 (14H, m, ArH's), 8.45 (1H, s, CH=N), 11.23 (1H, s, NH); MS *m/z* (%): 455 ($M^+ + 1$, 14), 454 (M^+, 39), 337 (12), 161 (34), 105 (100), 77 (79). Anal. Calcd for $C_{25}H_{22}N_6OS$ (454.55): C, 66.06; H, 4.88; N, 18.49. Found C, 66.12; H, 4.67; N, 18.39%.

*N′-(1-(5-(benzylidenehydrazono)-4-(p-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-ethylidene)-4-methylbenzohydrazide (**14c**)*

Orange solid (83%); m.p. 278 °C (DMF); IR: *ν* 1610 (C=N), 1659 (C=O), 3172 (NH) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 2.51 (3H, s, CH_3), 3.30 (3H, s, CH_3), 7.17–7.89 (13H, m, ArH's), 8.34 (1H, s, CH=N), 11.15 (1H, s, NH); MS *m/z* (%): 455 ($M^+ + 1$, 14), 454 (M^+, 39), 337 (12), 161 (34), 105 (100), 77 (79). Anal. Calcd for $C_{26}H_{24}N_6OS$ (468.57): C, 66.64; H, 5.16; N, 17.94. Found C, 66.69; H, 5.12; N, 17.72%.

*N′-(1-(5-((4-chlorobenzylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethylidene)benzohydrazide (**14d**)*

Yellow solid (84%); m.p. 274–6 °C (DMF); IR: *ν* 1610 (C=N), 1663 (C=O), 3177 (NH) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 2.49 (3H, s, CH_3), 7.34–8.04 (14H, m, ArH's), 8.47 (1H, s, CH=N), 11.25 (1H, s, NH); MS *m/z* (%): 477 ($M^+ + 2$, 3), 475 ($M^+ + 1$, 10), 474 (M^+, 10), 161 (30), 105 (100), 77 (68). Anal. Calcd for $C_{24}H_{19}ClN_6OS$ (474.97): C, 60.69; H, 4.03; 7.46; N, 17.69. Found C, 60.47; H, 4.01; N, 17.53%.

*N′-(1-(5-((4-nitrobenzylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethylidene) benzohydrazide (**14e**)*

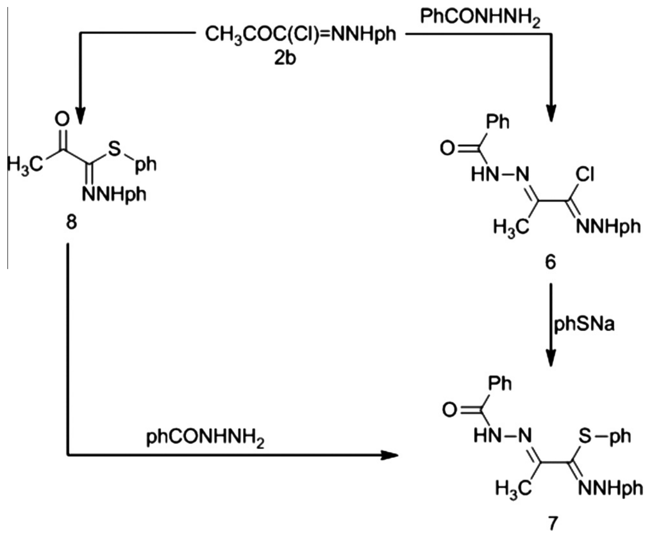
Orange solid (83%); m.p. 260 °C (DMF); IR: *ν* 1604 (C=N), 1663 (C=O), 3187 (NH) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 2.31 (3H, s, CH_3), 7.22–7.90 (14H, m, ArH's), 8.44 (1H, s, CH=N), 11.27 (1H, s, NH); ^{13}C NMR (DMSO-d6): δ 13.4, 20.9, 21.6, 119.4, 124.7, 127.9, 129.8, 131.2, 132.4, 133.4, 134.9, 138.1, 144.3, 145.1, 154.9, 158.8, 160.4, 161.3, 164.8; MS *m/z* (%): 486 ($M^+ + 1$, 8), 485 (M^+, 25), 290 (31), 262 (11), 105 (100), 77 (66). Anal. Calcd for $C_{24}H_{19}N_7O_3S$ (485.52): C, 59.37; H, 3.94; N, 20.19. Found C, 59.30; H, 3.87; N, 20.03%.

*N′-(1-(5-((4-chlorobenzylidene)hydrazono)-4-(p-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethylidene)-4-methylbenzohydrazide (**14f**)*

Orange solid (80%); m.p. 318 °C (DMF); IR: *ν* 1608 (C=N), 1660 (C=O), 3172 (NH) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 2.33 (3H, s, CH_3), 2.43 (3H, s, CH_3), 3.34 (3H, s, CH_3), 7.27–7.90 (12H, m, ArH's), 8.45 (1H, s, CH=N), 11.26 (1H, s, NH); MS *m/z* (%): 504 ($M^+ + 1$, 19), 503 (M^+, 29), 297 (39), 262 (19), 119 (100), 105 (75), 77 (41). Anal. Calcd for $C_{26}H_{23}ClN_6OS$ (503.02): C, 62.08; H, 4.61; N, 16.71. Found C, 62.01; H, 4.54; N, 16.24%.

*4-Methyl-N′-(1-(5-((4-nitrobenzylidene)hydrazono)-4-(p-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethylidene)benzohydrazide (**14g**)*

Orange solid (84%); m.p. 292 °C (DMF); IR: *ν* 1591 (C=N), 1661 (C=O), 3171 (NH) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 2.37 (3H, s, CH_3), 2.49 (3H, s, CH_3), 3.32 (3H, s, CH_3), 7.32–7.89 (12H, m, ArH's), 8.44 (1H, s, CH=N), 11.14 (1H, s, NH); MS *m/z* (%): 514 ($M^+ + 1$, 5), 513 (M^+, 14), 119 (100), 105



Scheme 2

(6), 77 (5). Anal. Calcd for $C_{26}H_{23}N_7O_3S$ (513.57): C, 60.81; H, 4.51; N, 19.09. Found C, 60.67; H, 4.59; N, 19.01%.

Method B

A mixture of **15a** (0.35 g, 1 mmol) and benzaldehyde (0.106 g, 1 mmol) in isopropyl alcohol (15 mL) was refluxed for 30 min. The solid product that formed after cooling was collected and crystallized from acetic acid to give a product proved identical in all aspects (mp, mixed mp, and spectra) with **14a** which was obtained by method A.

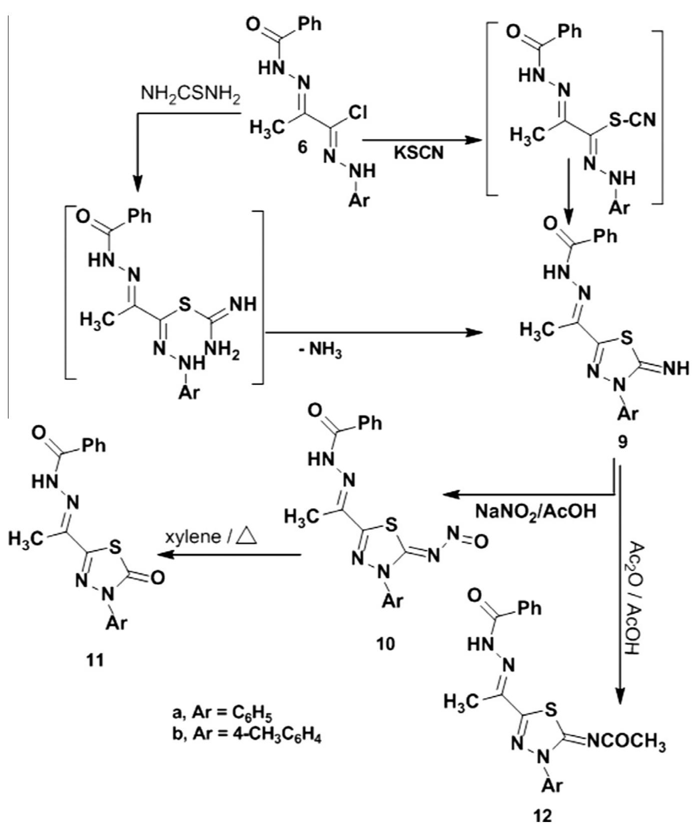
*Synthesis of N′-(1-(5-hydrazono-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)-ethylidene)benzohydrazide **15a***

Triethylamine (0.75 mL, 5 mmol) was added dropwise with stirring to a mixture of methyl dithiocarbazate (0.61 g, 5 mmol) and **6a** (0.98 g, 5 mmol) in ethanol (20 mL) for 30 min. The resulting solid was collected and recrystallized from ethanol to give **15a** as a yellow solid (79%); m.p. 242–4 °C; IR: ν 1600(C=N), 1647 (C=O), 3184, 3435 (NH_2, NH) cm^{-1}; ^1H NMR (DMSO-d6): δ 2.18 (3H, s, CH_3), 6.90–7.90 (12H, m, ArH's, NH_2), 10.25 (1H, s, NH); MS *m/z* (%): 353($M^+ + 1$, 2), 352 (M^+, 12), 284 (13), 174 (14), 105 (51), 55 (100). Anal. Calcd for $C_{17}H_{16}N_6OS$ (352.41): C, 57.94; H, 4.58; N, 23.85. Found C, 57.78; H, 4.45; N, 23.78%.

*Synthesis of N′-(1-(5-(2-benzoylhydrazono)-4-aryl-4,5-dihydro-1,3,4-thiadiazol-2-yl)-ethylidene)-benzohydrazides **16a,b***

Method A

Triethylamine (0.75 mL, 5 mmol) was added dropwise with stirring to a mixture of methyl 2-benzoylhydrazinecarbodithioate (1.13 g, 5 mmol) and the equimolar amount of **6a,b** (5 mmol) in ethanol (20 mL). The resulting solid, which formed after 30 min, was collected and crystallized from DMF to give the corresponding product **16**.



Scheme 3

Method B

Triethylamine (0.75 mL, 5 mmol) was added dropwise with stirring to a mixture of 5-phenyl-1,3,4-oxadiazole-2-thiol (0.89 g, 5 mmol) and the equimolar amount of **6a,b** (5 mmol) in ethanol (20 mL). The resulting solid, which formed after 6 h, was collected and recrystallized from DMF to give the corresponding product **16** in 82% yield as in method A.

*N′-(1-(5-(2-benzoylhydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)-ethylidene)-benzohydrazide (**16a**)*

Orange solid (82%); m.p. 284–6 °C (DMF); IR: *v* 1647 (C=O), 3175, 3448 (2NH) cm^{-1}; ^1H NMR (DMSO-d6): δ 2.34 (s, 3H, CH_3), 7.11–7.80 (m, 15H, ArH's), 8.98 (s, 1H, br, NH), 11.10 (1H, s, br, NH); MS *m/z* (%): 457 ($M^+ + 1$, 76), 456 (M^+, 57), 290 (97), 225 (100), 192 (95), 116 (93), 53 (55). Anal. Calcd for $C_{24}H_{20}N_6O_2S$ (456.52): C, 63.14; H, 4.42; N, 18.41. Found C, 63.11; H, 4.35; N, 18.32%.

*N′-(1-(5-(2-benzoylhydrazono)-4-(p-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-ethylidene)-benzohydrazide (**16b**)*

Orange solid (85%); m.p. 216–8 °C (DMF); IR: *v* 1655 (C=O), 3187, 3441 (2NH) cm^{-1}; ^1H NMR (DMSO-d6): δ 2.21 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.19–7.96 (m, 14H, ArH's), 9.08 (s, br, 1H, NH), 11.17 (s, br, 1H, NH); ^{13}C NMR (DMSO-d6): δ 11.4, 20.8, 119.3, 126.4, 127.8, 128.7, 129.3, 132.6, 133.4, 134.4, 140.1, 153.2, 158.5, 162.4, 164.4, 165.7; MS *m/z* (%): 471 ($M^+ + 1$, 38), 470 (M^+, 28), 403 (39), 286 (43), 206 (39), 137 (54), 105 (72), 77 (100). Anal. Calcd for $C_{25}H_{22}N_6O_2S$ (470.55): C, 63.81; H, 4.71; N, 17.86. Found C, 63.68; H, 4.67; N, 17.67%.

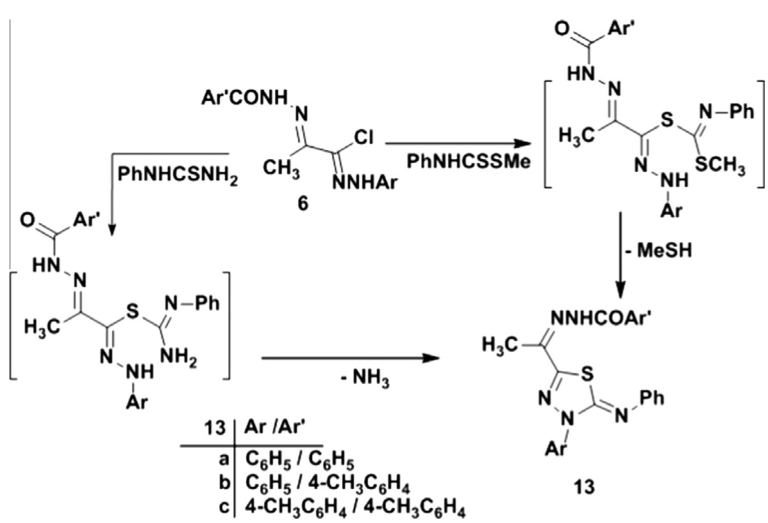
Antimicrobial assay

The biological evaluation was carried out in the Medical Mycology Laboratory of the Regional Center for Mycology and Biotechnology of Al-Azhar University, Cairo, Egypt. The method adopted for such tests is the Agar diffusion method. The microorganism inoculums were uniformly spread using sterile cotton swab on a sterile Petri dish Malt extract agar (for fungi) and nutrient agar (for bacteria). One hundred μL of each sample was added to each well (10 mm diameter holes cut in the agar gel, 20 mm apart from one another). The systems were incubated for 24–48 h at 37 °C (for bacteria) and at 28 °C (for fungi). After incubation, the microorganism's growth was observed. Inhibition of the bacterial and fungal growth was measured as IZD in mm. Tests were performed in triplicate [25].

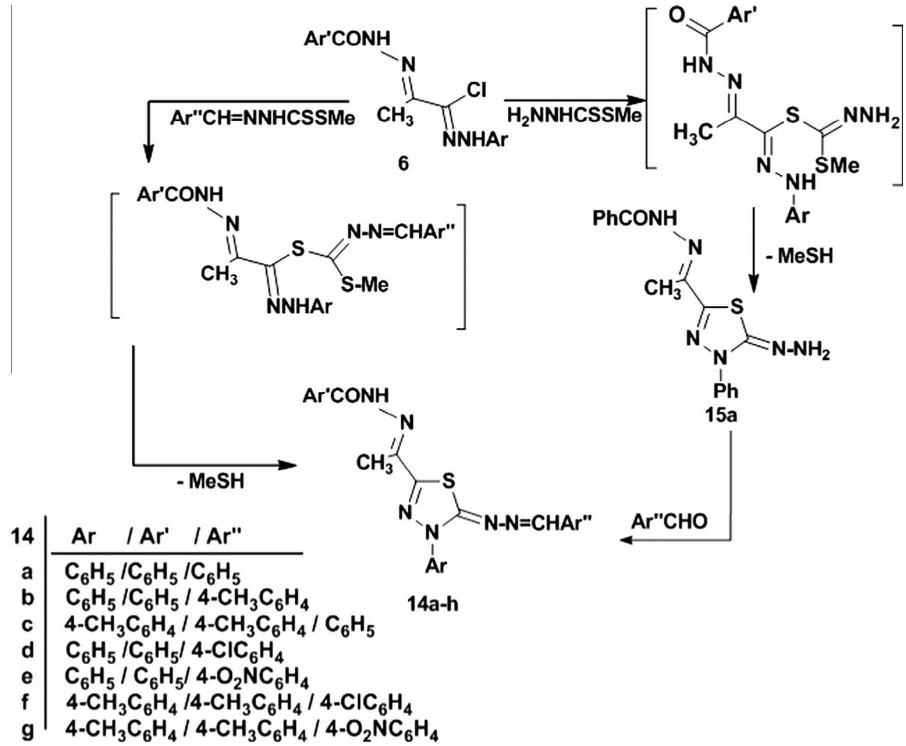
Results and discussion

In our hands, reaction of benzoylhydrazine with each of the hydrazonoyl chlorides **2b** in refluxing ethanol yielded, in each case, the corresponding condensation product **6** as previously reported [18]. The structures of the latter products were confirmed by their chemical reaction as outlined below. Treatment of **6** each with sodium thiophenolate afforded phenyl 2-(2-benzoylhydrazono)-*N′*-phenylpropanehydrazonothioate **7** (Scheme 2). The latter product **7** was alternatively prepared by reacting the hydrazonoyl chloride **2b** with sodium thiophenolate to give phenyl 2-oxo-*N′*-phenylpropanehydrazonothioate **8** and treatment of the latter with benzoylhydrazine (Scheme 2).

Next, reactions of **6** with various sulfur reagents were examined. Thus, treatment of each of compounds **6a, b** with potassium thiocyanate in ethanol gave the corresponding 1,3,4-thiadiazoline derivatives **9a,b,** respectively. The structures of the latter products **9a, b** were elucidated based on their elemental and spectral analyses (IR, MS and ^1H NMR) (see Experimental). In addition, structure **9** was confirmed by alternate synthesis. Thus, treatment of **6** with thiourea in ethanol afforded products identical in all respects with the product obtained by reaction of **6** with potassium thiocyanate (Scheme 3). Furthermore, the assigned structure **9** was confirmed by its chemical reactions. For example, treatment of **9a,b** each with sodium nitrite in acetic acid yielded the corresponding *N*-nitroso derivatives **10a,b,** respectively. Heating of **10b** in xylene gave the thiadiazolone derivative **11b**. In addition, treatment of **9a** with acetyl chloride yielded the corresponding *N*-acetyl derivative **12a** (Scheme 3).



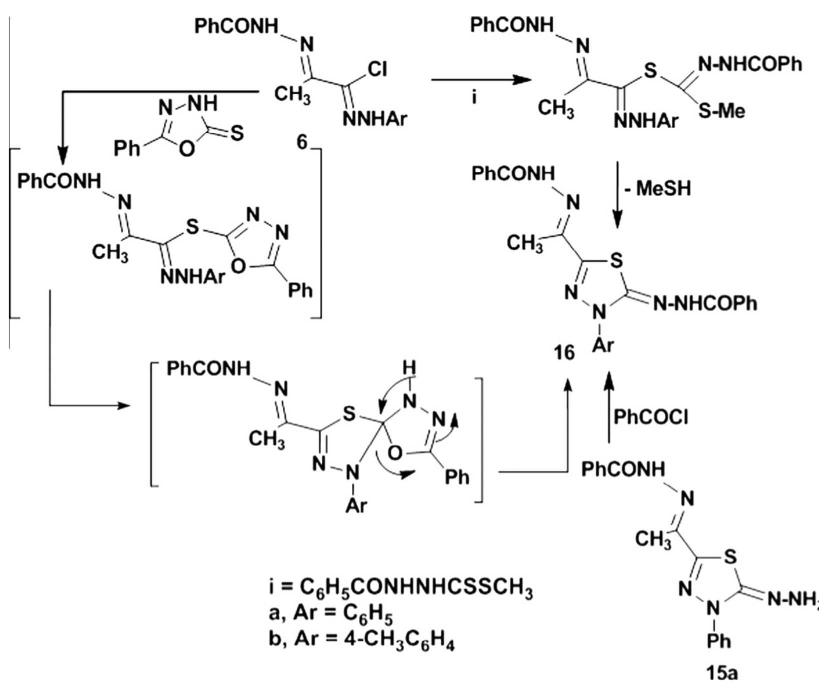
Scheme 4



Scheme 5

Reaction of **6a–c** each with either methyl *N*-phenyldithiocarbamate or phenylthiourea in ethanol yielded in both cases one and same product that proved to be the corresponding 2-phenyliminothiadizoline derivative **13** (Scheme 4). The structures of the isolated products **13a–c** were elucidated based on their elemental and spectral analyses (see Experimental). For example, the infrared spectrum of **13a** showed bands at *ν* 3336 (NH), 1661 (C=O), 1610 (C=N) cm^{-1} and their ^{1}H NMR, in addition to the aromatic proton signals, revealed characteristic signals at δ 2.33 (CH_3) and 10.73 (NH).

Reaction of **6** with methyl 2-(4-substituted benzylidene)hydrazinecarbodithioate in ethanol in the presence of triethylamine afforded, in each case, one isolable product that was identified based upon its spectral (IR, MS and ^{1}H NMR) and elemental analyses as the corresponding thiadiazoline derivative **14** (Scheme 5) (see Experimental). Structure **14**



Scheme 6

Table 1 Antibacterial activity of the synthesized compounds (**9–16**).*

Compounds	Minimal inhibitory concentration in μg/mL (zone of inhibition in mm)			
	Gram-positive bacteria		Gram-negative bacteria	
	Staphylococcus pneumoniae	*Bacillis subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*
9a	16.8 ± 0.37	15.9 ± 0.44	NA	12.6 ± 0.25
10a	15.8 ± 0.44	14.2 ± 0.37	NA	12.0 ± 0.58
11a	18.2 ± 0.44	20.2 ± 0.58	NA	18.0 ± 0.25
12a	19.2 ± 0.17	20.8 ± 0.29	NA	19.5 ± 0.42
13a	16.2 ± 0.44	15.3 ± 0.44	NA	12.8 ± 0.25
13b	16.3 ± 0.44	21.0 ± 0.37	NA	18.0 ± 0.44
14a	13.7 ± 0.44	15.0 ± 0.37	NA	10.0 ± 0.44
14b	9.4 ± 0.37	12.1 ± 0.19	NA	8.3 ± 037
16a	13.8 ± 0.44	17.2 ± 0.25	NA	10.7 ± 0.25
16b	16.5 ± 0.44	21.4 ± 0.37	NA	19.7 ± 0.44
Ampicillin	23.8 ± 0.2	32.4 ± 0.3	–	–
Gentamicin	–	–	17.3 ± 0.1	19.9 ± 0.3

* NA: No activity, data are expressed in the form of mean ± SD.

was confirmed by alternate synthesis. Thus, reaction of **6a** with methyl dithiocarbazate in ethanol in the presence of triethylamine yielded the thiadiazoline derivative **15a**. Treatment of the latter with benzaldehyde in ethanol afforded product that proved identical in all respects (mp., mixed mp., IR, ^{1}H NMR) with **14a** obtained above (Scheme 5).

Similar reaction of **6a,b** each with methyl 2-benzoylhydrazinecarbodithioate yielded the thiadiazoline derivatives **16a,b,** respectively (Scheme 6). The structures of the latter were elucidated based on by elemental and spectral analyses and also by alternate syntheses (see Experimental). Thus, treatment of **6a,b** each with 5-phenyl-1,3,4-oxadiazole-2-thione in refluxing ethanol in the presence of triethylamine afforded products that proved identical in all aspects (mp., mixed mp., and spectra) with those **16a,b** obtained from the foregoing reaction of **6a,b** with methyl 2-benzoylhydrazinecarbodithioate (Scheme 6).

Antimicrobial activity

The newly synthesized compounds **9a, 10a, 11a, 12a, 13a,b, 14a,b,** and **16a,b** were tested for their *in vitro* antibacterial activity against two Gram-positive bacteria namely *Staphylococcus pneumoniae* (SP) and *Bacillis subtilis* (BS) and two Gram-negative bacteria namely *Pseudomonas aeruginosa* (PA) and *Escherichia coli* (EC). They were also tested for their *in vitro* antifungal activity against three fungi species namely *Aspergillus fumigatus* (AF), *Geotrichum candidum* (GC), *Candida albicans* (CA) and *Syncephalastrum racemosum* (SR). The organisms were tested against the activity of solutions of concentration (5 μg/mL) of each compound and using inhibition zone diameter (IZD) in mm as criterion for the antimicrobial activity (agar diffusion well method). The fungicides *Amphotericin B* and the bactericides *Ampicillin, Gentamicin* were used as references to evaluate the potency of the tested compounds under the same conditions. The results are summarized in Tables 1 and 2. Such results indicate the following: (1) Compounds **9a**, **10a**, **11a**, **12a**, **13a**, **13b**, **14a** and **16b** exhibit high inhibitory effects against of *S. pneumoni,* (2) Compounds **9a**, **10a**, **11a**, **12a**, **13a**, **13b**, **14a**, **14b**, **16a** and **16b** exhibit high inhibitory effects against of *B. subtilis* while have no inhibitory effect toward *P. aeruginosa*, (3) Compounds **11a**, **12a**, **13b** and **16b** exhibit high inhibitory effects against *E. coli*, (4) Compound **14b** has moderate inhibitory effect against *S. pneumoniae*. On the other hand, compounds **9a, 10a, 13a, 14a, 14b, and 16a** have moderate inhibitory effect toward *E. coli* and (5) Compounds **9a**, **10a**, **11a**, **12a**, **13a**, **13b**, **14a**, **14b**, **16a** and **16b** exhibit high inhibitory activities against each of *A. fumigatus, S. racemosum and G. candidum*, while compound **14b** has moderate inhibitory activity and all compounds have no activity against *C. albicans*.

Table 2 Antifungal activity of the synthesized compounds (**9–16**).*

Compounds	Minimal inhibitory concentration in μg/Ml (zone of inhibition in mm)			
	Aspergillus fumigatus	*Syncephalastrum racemosum*	*Geotrichum candidum*	*Candida albicans*
9a	15.7 ± 0.44	17.4 ± 0.25	13.9 ± 0.32	NA
10a	14.2 ± 0.44	15.8 ± 0.58	12.4 ± 0.4	NA
11a	17.9 ± 0.22	19.9 ± 0.44	16.8 ± 0.44	NA
12a	18.9 ± 0.22	20.2 ± 0.25	16.8 ± 0.44	NA
13a	14.9 ± 0.58	16.4 ± 0.19	14.7 ± 0.25	NA
13b	18.3 ± 0.44	19.9 ± 0.58	18.0 ± 0.19	NA
14a	13.3 ± 0.25	12.4 ± 0.44	13.6 ± 0.44	NA
14b	9.3 ± 0.15	8.3 ± 0.19	13.3 ± 0.38	NA
16a	13.4 ± 0.58	12.7 ± 0.37	14.3 ± 0.58	NA
16b	19.3 ± 0.44	20.0 ± 0.58	18.2 ± 0.19	NA
Amphotericin B	23.7 ± 0.1	19.7 ± 0.2	28.7 ± 0.2	25.4 ± 0.1

* NA: No activity, data are expressed in the form of mean ± SD.

Conclusion

In conclusion, reaction of acylhydrazines with α-ketohydrazonoyl chlorides yielded the condensation products **6**. The latter products **6** proved to be useful precursors for synthesis of various functionalized 1,3,4-thiadiazole derivatives. The structures of the newly synthesized compounds were confirmed by spectral data, elemental analyses and alternate syntheses. Most of the compounds prepared exhibit considerable antimicrobial activities.

Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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