



# Synthesis and biological evaluation of new 1,3,4-thiadiazole derivatives as potent antimicrobial agents

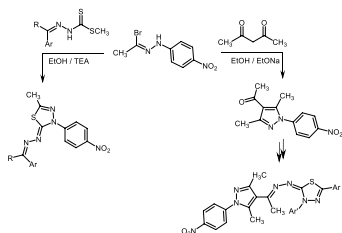
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## Abstract

A series of 1,3,4-thiadiazole derivatives were designed and synthesized using *N*-(4-nitrophenyl)acetohydrazonoyl bromide and 1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethan-1-one as starting materials. The treatment of 1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethan-1-one with methyl hydrazinecarbodithioate or hydrazinecarbothioamide afforded 2-[1-[5-methyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethylidene]hydrazine derivatives. The targeted 1,3,4-thiadiazolyl derivatives were prepared by the reaction of 2-[1-[5-methyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethylidene]hydrazine derivatives with hydrazonoyl chloride derivatives. The reaction of *N*-(4-nitrophenyl)acetohydrazonoyl bromide with 2-[(methylthio)carbonthioyl]hydrazones in absolute ethanol in the presence of triethylamine afforded the corresponding 1,3,4-thiadiazole derivatives. The newly synthesized compounds were fully characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, MS, and elemental analysis. Moreover, the antimicrobial activity of the synthesized 1,3,4-thiadiazole derivatives were tested against *E. coli*, *B. mycooides*, and *C. albicans*. Four compounds outperformed the other produced compounds in terms of antimicrobial activity.

## Graphical abstract



**Keywords** 1,3,4-Thiadiazoles · Alkyl hydrazonoyl bromide · Cycloadditions · IR spectroscopy · Mass spectroscopy · Antimicrobial activity

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## Introduction

Hydrazonoyl halides are a large group of compounds that have the characteristic functional group  $-C(X):NNH-$ . These compounds have gained attention due to their wide biological properties such as anthelmintic, antiarthropodal, antimicrobial, fungicidal, antiscarptic activities, pharmaceutical and industrial applications that make these chemicals an interesting group in medicinal chemistry [1, 2] in addition to their chemical reactivities in the synthesis of various nitrogen, oxygen, sulfur, and selenium containing compounds [3–25]. We are interested in 1,3,4-thiadiazoles

which were formed via reactions of hydrazonoyl halides with potassium thiocyanate [26–30], thiosemicarbazide and its aryl derivatives [31], or carbon disulfide [32], in addition to reactions of *N*-benzylidenebenzo-hydrazonoyl chloride with potassium ethyl xanthate [33], *N*-phenylbenzohydrazonoyl chloride with phenylisothiocyanate [34–36], or coupling of aroyldimethylsulfonium bromides with *N*-nitroso-*N*-arylacetamide [37, 38]. Many substituted 1,3,4-thiadiazole derivatives exhibit wide range of biological activities such as antimicrobial, antituberculosis, antiviral, carbonic anhydrase inhibitor, antitrypanosomal agent, and anticonvulsant activities (Fig. 1) [39–42]. However, little attention has been given towards alkyl hydrazonoyl halides [43, 44] probably due to difficulties in their preparation and storage. The five-membered aromatic heterocyclic ring of pyrazole and its substituted derivatives are significant biological compounds and a series of research studies have been directed towards these type of derivatives. The presence of the pyrazole moiety in pharmacological agents of various drugs shows a broad spectrum of biological activities and pharmaceuticals such as betazole (H2 receptor agonist), rimonabant (anti-obesity), celecoxib (anti-inflammatory), fezolamide (antidepressant), CDPPB (antipsychotic), difenamizole (analgesic) [45–52].

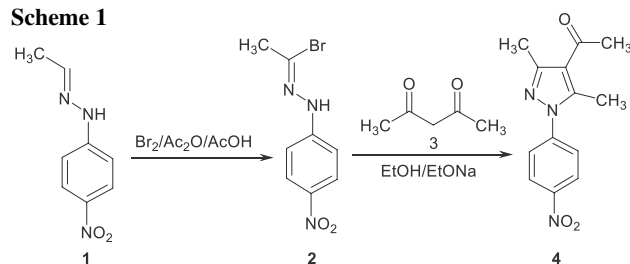
Herein, we reported the potentiality of *N*-(4-nitrophenyl)aceto-hydrazonoyl bromide (2) and 1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethan-1-one (4) in the synthesis of 1,3,4-thiadiazole derivatives. The antimicrobial activity of the newly synthesized 1,3,4-thiadiazole compounds was tested.

## Results and discussion

The starting materials *N*-(4-nitrophenyl)aceto-hydrazonoyl bromide (2) and 1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethan-1-one (4) were prepared in a straightforward manner as reported in the literatures. The bromination of 1-ethylidene-2-(4-nitrophenyl)hydrazine (1) afforded 2 which was treated with acetylacetone (3) in the presence of sodium ethoxide to give compound 4 as shown in Scheme 1 [43, 44, 53].

The treatment of 4 with methyl hydrazinecarbodithioate (5) [54, 55] or hydrazinecarbthioamide (6) in ethanol and in the presence of hydrochloric acid as a catalyst afforded methyl 2-[1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-

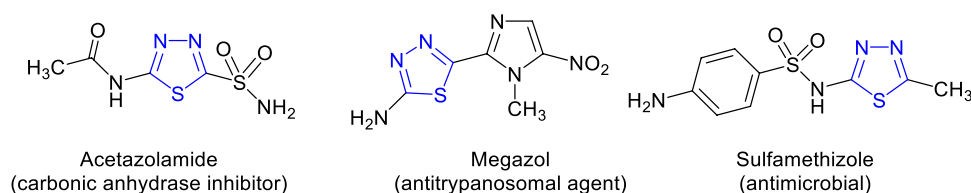
**Scheme 1**



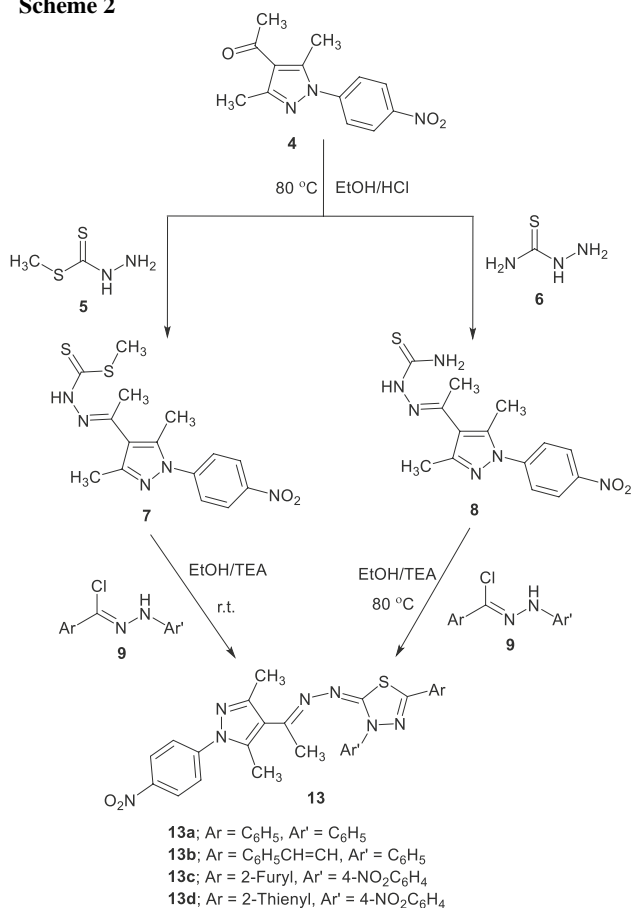
ethylidene]hydrazine-1-carbodithioate (7) or 2-[1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethylidene]hydrazine-1-carbothioamide (8), respectively, as depicted in Scheme 2. The chemical structures of 7 and 8 were elucidated from spectral data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, MS) and elemental analysis. As representative example, the <sup>1</sup>H NMR spectrum of compound 7 showed the following signals: four singlets at  $\delta = 2.37, 2.39, 2.50,$  and  $2.52$  ppm corresponding to four CH<sub>3</sub> groups, pair of doublets at 7.84 ppm and 8.39 ppm corresponding to protons of 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> and singlet signal at 12.27 ppm corresponding to proton of NH group. The <sup>13</sup>C NMR spectrum showed 13 signals corresponding to asymmetric carbon atoms. Also, the mass spectrum of 7 showed a molecular ion peak at  $m/z = 363$ . In addition, the IR spectrum showed band at  $3180\text{ cm}^{-1}$  could be attributed to NH group.

On the other hand, the reaction of compounds 7 and 8 with hydrazonoyl chlorides 9a–9d in the presence of triethylamine at room temperature (in case of 7) or by refluxing (in case of 8) afforded the corresponding pyrazolythiadiazole derivatives 13a–13d as depicted in Scheme 2. As illustrated in Scheme 3, the proposed mechanism for the formation of 13a–13d involved 1,3-addition of nitrilimines 10, which generated in situ by base-catalyzed dehydrochlorination of hydrazonoyl chlorides 9 using triethylamine, to C=S group of methyl 2-[1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethylidene]hydrazine-1-carbodithioate (7) or 2-[1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethylidene]hydrazine-1-carbothioamide (8) led to the initial formation of thiohydrazonate 11 followed by intramolecular cyclization to give cycloadduct 12. The final products 13a–13d formed by the elimination of methyl mercaptan (in case of 7) or ammonia (in case of 8) of the intermediate 12 as shown in Scheme 3. The structures of compounds 13a–13d were elucidated from their spectral data (<sup>1</sup>H NMR, <sup>13</sup>C

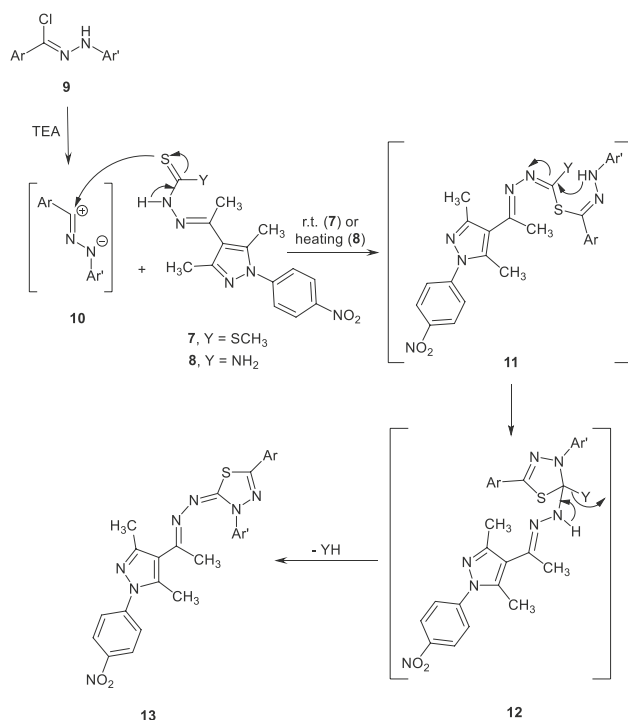
**Fig. 1** Biologically active drugs containing 1,3,4-thiadiazole moiety



## Scheme 2



## Scheme 3

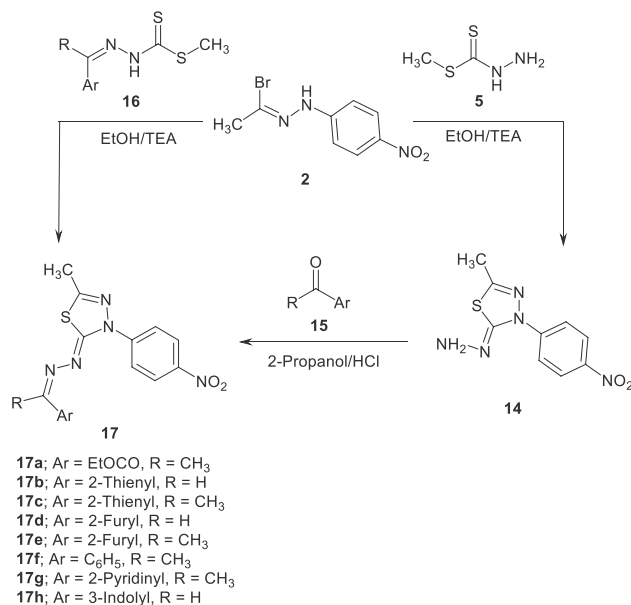


NMR, IR, MS) and elemental analysis. For example, the <sup>1</sup>H NMR spectrum of **13a** showed two singlets at  $\delta = 2.52$  and 2.63 ppm of three CH<sub>3</sub> groups, multiplet at 7.27–7.84 ppm (10H, aromatic protons) and pair of doublets at 8.25 and 8.38 ppm corresponding to the protons of 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>. Its <sup>13</sup>C NMR spectrum showed 21 signals of asymmetric carbon atoms. The mass spectrum showed a molecular ion peak at  $m/z = 509$ . In addition, its IR spectrum revealed the absence of NH and NH<sub>2</sub> bands.

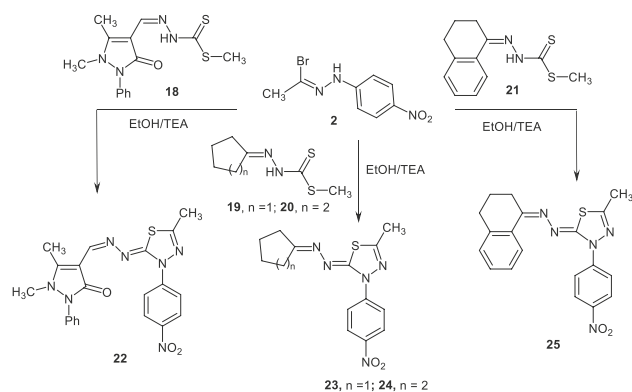
The targeted 1,3,4-thiadiazole derivatives **17a–17h** were synthesized in two different methods. The first pathway, the thiadiazole derivatives **17a–17h** were synthesized in one step by the treatment of **2** with 2-[(methylthio)carbonyl]hydrazones **16a–16h** [52–54] in the presence of triethylamine at room temperature as illustrated in Scheme 4. In the second pathway, by the treatment of *N*-(4-nitrophenyl)-acetohydrazonoyl bromide (**2**) with methyl hydrazinecarbodi-thioate (**5**) to give 2-hydrazono-5-methyl-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole (**14**). Compound **14** was separated and reacted with the appropriate aldehydes or ketones **15** using 2-propanol as a solvent in the presence of hydrochloric acid to afford the corresponding 1,3,4-thiadiazole derivatives **17** (Scheme 4).

The chemical structures of the 1,3,4-thiadiazole compounds **17a–17h** were established by their spectral data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, MS) and elemental analysis. For example, the IR spectrum of **17a** showed characteristic band at 1713 cm<sup>-1</sup> could be attributed to C=O stretching frequency. Its <sup>1</sup>H NMR spectrum showed triplet signal at  $\delta = 1.39$  ppm corresponding to methyl group of OCH<sub>2</sub>CH<sub>3</sub>, two singlet signals at 2.31 and 2.52 ppm corresponding to the CH<sub>3</sub> groups, quartet signal at 4.33 ppm corresponding

## Scheme 4



Scheme 5



to methylene group of  $\text{OCH}_2\text{CH}_3$  and two doublet signals at 8.33 and 8.42 ppm of the protons of  $4\text{-NO}_2\text{C}_6\text{H}_4$ . Its  $^{13}\text{C}$  NMR spectrum showed 12 signals for asymmetric carbon atoms. Its mass spectrum showed the molecular ion peak at  $m/z = 349$ .

Likewise, the treatment of the starting material **2** with methyl carbodithioate derivatives **18–21** under the same conditions afforded the corresponding 1,3,4-thiadiazole derivatives **22–25**, respectively (Scheme 5). The chemical structures of **22–25** were confirmed by the spectral data ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR, MS) and elemental analysis. For example, the  $^1\text{H}$  NMR spectrum of **25** showed multiplet at  $\delta = 1.97\text{--}2.01$  ppm corresponding to  $\text{CH}_2$  group, singlet at 2.50 ppm refer to the  $\text{CH}_3$  group, two triplets at 2.86 and 3.01 ppm corresponding to two  $\text{CH}_2$  groups, multiplet at 7.17–7.32 ppm due to three aromatic protons, doublet at 8.26 ppm due to one aromatic proton and pair of doublets at 8.34 and 8.47 ppm corresponding to protons of  $4\text{-NO}_2\text{C}_6\text{H}_4$ . The  $^{13}\text{C}$  NMR spectrum showed 17 signals for asymmetric carbon atoms. Its mass spectrum showed the molecular ion peak at  $m/z = 379$ .

## Antimicrobial activity

Table 1 and Fig. 2 illustrate the inhibition zones induced by the tested synthesized 1,3,4-thiadiazole derivatives against the tested micro-organisms. All compounds were shown to be capable of reducing the growth of the tested microbial strains.

Antimicrobial susceptibility studies demonstrated that compound **14** outperformed the other produced compounds in terms of antimicrobial activity, with inhibition zones of 21 mm against *E. coli*, 23 mm against *B. mycooides*, and 22 mm against *C. albicans* (Table 1 and Fig. 2). Furthermore, compounds **13a**, **17c**, and **17h** have inhibition zone diameters of 17–18 mm against *E. coli* and *B. mycooides*, respectively, whereas compounds **13a**, **13c**, and **17g** have an inhibition zone diameter of 17 mm against *C. albicans*.

**Table 1** Antimicrobial activity assessment of the new synthesized compounds using agar diffusion method

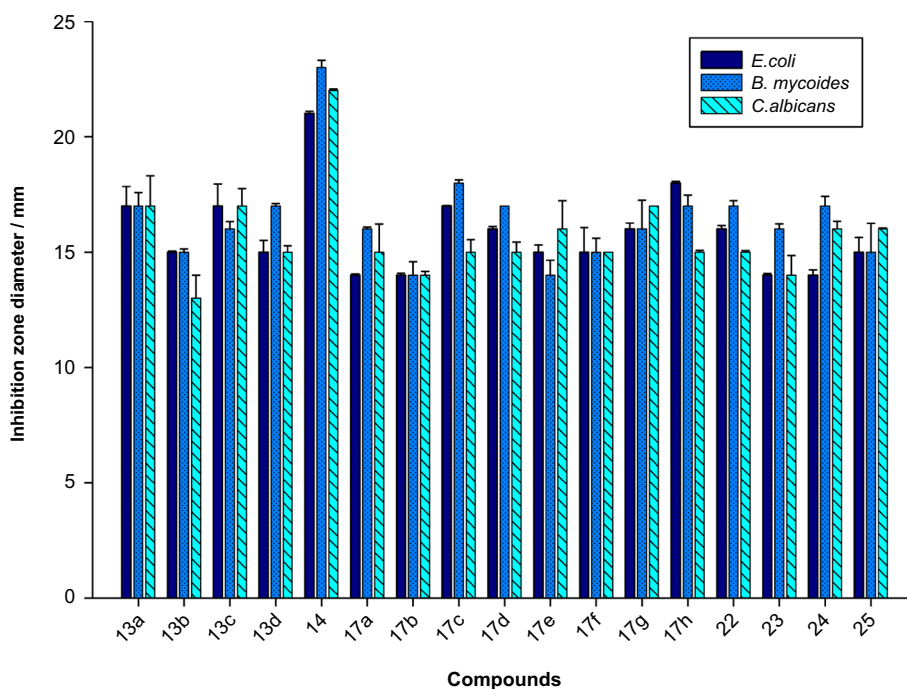
Compound	Inhibition zone diameter/mm		
	<i>E. coli</i>	<i>B. mycooides</i>	<i>C. albicans</i>
<b>13a</b>	17 ± 0.85	17 ± 0.58	17 ± 1.32
<b>13b</b>	15 ± 0.05	15 ± 0.14	13 ± 1.00
<b>13c</b>	17 ± 0.96	16 ± 0.33	17 ± 0.75
<b>13d</b>	15 ± 0.51	17 ± 0.11	15 ± 0.28
<b>14</b>	21 ± 0.10	23 ± 0.31	22 ± 0.06
<b>17a</b>	14 ± 0.05	16 ± 0.08	15 ± 1.21
<b>17b</b>	14 ± 0.08	14 ± 0.58	14 ± 0.16
<b>17c</b>	17 ± 0.02	18 ± 0.14	15 ± 0.54
<b>17d</b>	16 ± 0.11	17 ± 0.00	15 ± 0.44
<b>17e</b>	15 ± 0.31	14 ± 0.65	16 ± 1.23
<b>17f</b>	15 ± 1.06	15 ± 0.60	15 ± 0.00
<b>17g</b>	16 ± 0.26	16 ± 1.25	17 ± 0.00
<b>17h</b>	18 ± 0.08	17 ± 0.47	15 ± 0.08
<b>22</b>	16 ± 0.15	17 ± 0.23	15 ± 0.07
<b>23</b>	14 ± 0.07	16 ± 0.22	14 ± 0.86
<b>24</b>	14 ± 0.23	17 ± 0.42	16 ± 0.34
<b>25</b>	15 ± 0.64	15 ± 1.25	16 ± 0.04
Streptomycin	17 ± 0.75	15 ± 0.00	17 ± 0.1

Compound **17b**, on the other hand, displayed the least antimicrobial activity (inhibition zone of 14 mm) against all tested microbes (Table 1 & Fig. 2). Furthermore, the results showed that the Gram-positive bacterium example (*B. mycooides*) was more vulnerable to the majority of the examined produced chemicals than Gram-negative bacteria (*E. coli*). Streptomycin (10 mcg) as a positive control had lesser antimicrobial efficacy than compound **14**, but findings are comparable to other synthetic compounds evaluated (Table 1).

## Conclusion

*N*-(4-Nitrophenyl)acetohydrazonoyl bromide (**2**) and 1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethan-1-one (**4**) used as a useful precursor in synthesis of new series of 1,3,4-thiadiazole derivatives **13a–13d**, **17a–17h**, and **22–25**. The newly synthesized compounds were evaluated as antimicrobial agents. The maximum antimicrobial activity was reported against gram-positive bacteria (*B. mycooides*), whereas yeast (*C. albicans*) and gram-negative bacteria (*E. coli*) were the least sensitive groups to the chemical compounds. The antibacterial activity of compound **14** was greater than that of the positive control, indicating that this chemical might be used in the future to prevent microbial transmission.

**Fig. 2** Antimicrobial activity assessment of the new synthesized compounds using agar diffusion method



## Experimental

Melting points were measured with Electrothermal 9100 apparatus. The IR spectra were recorded using a FTIR Bruker–vector 22 spectrophotometer as KBr pellets. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  or  $\text{DMSO-}d_6$  as a solvent on Varian Gemini NMR spectrometer at 300 MHz and 75 MHz, respectively, using TMS as internal standard. Chemical shifts were reported as  $\delta$  values in ppm. Mass spectra were recorded with a Shimadzu GCMS–QP–1000 EX mass spectrometer in EI (70 eV) model. The elemental analyses were performed at Microanalytical Center, Cairo University. 1-Ethylidene-2-(4-nitrophenyl)hydrazine (**1**) [43], *N*-(4-nitrophenyl)acetohydrazonoyl bromide (**2**) [44], 1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethan-1-one (**4**) [53], methyl hydrazinecarbodithioate (**5**) [54, 55], *N*-aryl-*C*-substituted methanohydrazonoyl chlorides **9** [56–62], and 2-[(methylthio)carbonyl]hydrazones **16** and **18–21** [63–67] were prepared using the reported procedures.

**Synthesis of 2-[1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethylidene]hydrazine derivatives **7** and **8**** 1-[3,5-Dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethan-1-one (**4**, 1.4 g, 5 mmol) was refluxed with 0.6 g methyl hydrazinecarbodithioate (**5**, 5 mmol) or 0.5 g hydrazinecarbothioamide (**6**, 5 mmol) in 50  $\text{cm}^3$  absolute ethanol for 2 h in the presence of few drops of hydrochloric acid. The resulting solid product that precipitated was collected,

washed with ethanol and crystallized from acetonitrile to give **7** or **8**, respectively.

**Methyl 2-[1-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethylidene]hydrazine-1-carbodithioate (**7**,  $\text{C}_{15}\text{H}_{17}\text{N}_5\text{O}_2\text{S}_2$ )** Yellow crystals; m.p.: 180–182 °C; yield 74%; IR:  $\bar{\nu}=3180$  (NH)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta=2.37$  (s, 3H,  $\text{CH}_3$ ), 2.39 (s, 3H,  $\text{CH}_3$ ), 2.50 (s, 3H,  $\text{CH}_3$ ), 2.52 (s, 3H,  $\text{CH}_3$ ), 7.84 (d, 2H, Ar–H,  $J=8.7$  Hz), 8.39 (d, 2H, Ar–H,  $J=9$  Hz), 12.27 (s, 1H, NH) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ ):  $\delta=13.2$ , 14.4, 17.2, 18.3, 119.7, 124.7, 124.9, 139.6, 143.8, 145.8, 149.0, 149.3, 199.2 ppm; MS (EI, 70 eV):  $m/z$  (%) = 363 ( $\text{M}^+$ , 7.40), 315 (65.07), 257 (26.69), 211 (22.49), 117 (37.22), 91 (36.54), 76 (100), 65 (30.83).

**2-[1-[3,5-Dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]ethylidene]hydrazine-1-carbothioamide (**8**,  $\text{C}_{14}\text{H}_{16}\text{N}_6\text{O}_2\text{S}$ )** Yellow crystals; m.p.: 206–208 °C; yield 71%; IR:  $\bar{\nu}=3222$  and 3293 ( $\text{NH}_2$ ), 3460 (NH)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta=2.29$  (s, 3H,  $\text{CH}_3$ ), 2.31 (s, 3H,  $\text{CH}_3$ ), 2.45 (s, 3H,  $\text{CH}_3$ ), 7.48 (s, 1H,  $\text{NH}_2$ ), 7.84 (d, 2H, Ar–H,  $J=8.7$  Hz), 8.22 (s, 1H,  $\text{NH}_2$ ), 8.38 (d, 2H, Ar–H,  $J=9$  Hz), 10.16 (s, 1H, NH) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ ):  $\delta=12.7$ , 13.7, 17.8, 120.7, 124.5, 124.8, 138.9, 144.0, 144.6, 145.6, 148.7, 178.7 ppm; MS (EI, 70 eV):  $m/z$  (%) = 332 ( $\text{M}^+$ , 30.19), 298 (33.37), 257 (45.23), 211 (51.69), 117 (48.41), 76 (100), 60 (60.49).

**Synthesis of 2-[[1-[5-methyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl]ethylidene]hydrazono]-2,3-dihydro-1,3,4-thiadiazole derivatives 13a–13d** *Method A* A mixture of 0.4 g methyl 2-[1-[3,5-dimethyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl]ethylidene]hydrazine-1-carbodithioate (**7**, 1 mmol) and the appropriate hydrazonoyl chlorides **9a–9d** (1 mmol) was dissolved in 30 cm<sup>3</sup> absolute ethanol. To the resulting solution, triethylamine was added and reaction mixture was stirred for 6 h at room temperature. The resulting solid product that precipitated was collected, washed with ethanol, and crystallized from dimethylformamide to give the corresponding thiadiazole derivatives **13a–13d**.

*Method B* Refluxing of 0.3 g 2-[1-[3,5-dimethyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl]ethylidene]hydrazine-1-carbodithioamide (**8**, 1 mmol) with the appropriate hydrazonoyl chlorides **9a–9d** (1 mmol) in 30 cm<sup>3</sup> absolute ethanol in the presence of triethylamine for 4 h. The resulting solid product that precipitated was collected, washed with ethanol, and crystallized from dimethylformamide to afford the same products **13a–13d**.

**2-[[1-[3,5-Dimethyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl]ethylidene]hydrazono]-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole (13a, C<sub>27</sub>H<sub>23</sub>N<sub>7</sub>O<sub>5</sub>S)** Yellow crystals; m.p.: 218–220 °C; yield 61%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.52 (s, 6H, 2CH<sub>3</sub>), 2.63 (s, 3H, CH<sub>3</sub>), 7.27–7.84 (m, 10H, Ar–H), 8.25 (d, 2H, Ar–H, *J* = 8.4 Hz), 8.38 (d, 2H, Ar–H, *J* = 8.7 Hz) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 13.7, 14.5, 19.1, 120.9, 121.2, 124.6, 124.7, 125.6, 126.2, 128.7, 128.9, 130.4, 130.6, 138.7, 140.1, 144.5, 146.1, 149.8, 150.3, 155.7, 164.0 ppm; MS (EI, 70 eV): *m/z* (%) = 509 (M<sup>+</sup>, 24.33), 243 (16.19), 135 (16.98), 91 (100), 77 (37.27).

**2-[[1-[3,5-Dimethyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl]ethylidene]hydrazono]-3-phenyl-5-styryl-2,3-dihydro-1,3,4-thiadiazole (13b, C<sub>29</sub>H<sub>25</sub>N<sub>7</sub>O<sub>5</sub>S)** Yellow crystals; m.p.: 226–228 °C; yield 63%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.51 (s, 3H, CH<sub>3</sub>), 2.52 (s, 3H, CH<sub>3</sub>), 2.63 (s, 3H, CH<sub>3</sub>), 7.00–7.54 (m, 10H, Ar–H), 7.73 (d, 2H, Ar–H, *J* = 9.3 Hz), 8.18 (d, 2H, Ar–H, *J* = 7.8 Hz), 8.39 (d, 2H, Ar–H, *J* = 9 Hz) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 13.7, 14.5, 19.1, 118.9, 120.9, 121.2, 124.6, 124.6, 125.6, 127.0, 128.7, 128.9, 129.2, 135.1, 136.6, 138.6, 139.8, 144.4, 146.0, 149.8, 150.3, 156.0, 163.0 ppm; MS (EI, 70 eV): *m/z* (%) = 535 (M<sup>+</sup>, 100), 243 (27.54), 219 (15.67), 91 (79.67), 77 (37.95), 64 (16.38).

**2-[[1-[3,5-Dimethyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl]ethylidene]hydrazono]-5-(furan-2-yl)-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole (13c, C<sub>25</sub>H<sub>20</sub>N<sub>8</sub>O<sub>5</sub>S)** Yellow crystals; m.p.: 230–232 °C; yield 61%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.49 (s, 3H, CH<sub>3</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 2.60 (s, 3H, CH<sub>3</sub>), 6.61–6.62 (m, 1H, furyl-H), 7.02 (d, 1H, furyl-H, *J* = 3.6 Hz), 7.62 (d, 1H, furyl-H, *J* = 3.3 Hz), 7.74 (d,

2H, Ar–H, *J* = 9 Hz), 8.35–8.39 (m, 4H, Ar–H), 8.54 (d, 2H, Ar–H, *J* = 9.3 Hz) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 13.5, 14.5, 19.0, 109.4, 110.2, 113.0, 115.6, 124.5, 124.6, 125.5, 138.4, 140.0, 141.8, 143.8, 144.5, 145.9, 146.2, 151.3, 155.0, 158.7, 160.9 ppm; MS (EI, 70 eV): *m/z* (%) = 544 (M<sup>+</sup>, 42.87), 243 (27.55), 122 (39.61), 90 (100), 76 (77.08), 63 (65.39).

**2-[[1-[3,5-Dimethyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl]ethylidene]hydrazono]-3-(4-nitrophenyl)-5-(thiophen-2-yl)-2,3-dihydro-1,3,4-thiadiazole (13d, C<sub>25</sub>H<sub>20</sub>N<sub>8</sub>O<sub>4</sub>S<sub>2</sub>)** Yellow crystals; m.p.: 268–270 °C; yield 60%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.53 (s, 3H, CH<sub>3</sub>), 2.56 (s, 3H, CH<sub>3</sub>), 2.62 (s, 3H, CH<sub>3</sub>), 7.14–7.15 (m, 1H, thienyl-H), 7.44 (d, 1H, thienyl-H, *J* = 3 Hz), 7.54 (d, 1H, thienyl-H, *J* = 3.3 Hz), 7.72 (d, 2H, Ar–H, *J* = 8.7 Hz), 8.02–8.39 (m, 4H, Ar–H), 8.53 (d, 2H, Ar–H, *J* = 9 Hz) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 13.5, 14.5, 19.0, 113.2, 115.2, 124.5, 124.7, 124.7, 127.2, 127.4, 129.6, 134.7, 137.9, 138.5, 142.8, 145.0, 145.40, 145.8, 151.7, 158.3, 159.3 ppm.

**Synthesis of 5-methyl-2-arylidenehydrazono-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole derivatives 17 and 22–25** *Method A* A mixture of 1.3 g *N*-(4-nitrophenyl)acetohydrazonoyl bromide (**2**, 5 mmol) and the appropriate 2-((methylthio)carbonthioyl)hydrazones **16** and **18–21** (5 mmol) was dissolved in 50 cm<sup>3</sup> absolute ethanol. To the resulting solution, 2 cm<sup>3</sup> triethylamine was added and reaction mixture was stirred for 6 h at room temperature. The resulting solid product that precipitated was collected, washed with ethanol, and crystallized from a suitable solvent to give the corresponding 1,3,4-thiadiazole derivatives **17** and **22–25**.

*Method B* Stirring of 0.6 g methyl hydrazinecarbodi-thioate (**5**, 5 mmol) with 1.3 g *N*-(4-nitrophenyl)acetohydrazonoyl bromide (**2**, 5 mmol) in 50 cm<sup>3</sup> absolute ethanol in the presence of 2 cm<sup>3</sup> triethylamine for 6 h at room temperature. The resulting solid product that precipitated was collected and crystallized from dimethylformamide to afford 2-hydrazono-5-methyl-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole **14**. Refluxing of the appropriate aldehydes or ketones **15** with the resulted compound **14** (1.3 g, 5 mmol) in 2-propanol for 2 h in the presence of few drops of hydrochloric acid. The resulting solid product that precipitated was collected, washed with ethanol, and crystallized from a suitable solvent to give the corresponding 1,3,4-thiadiazole derivatives **17** and **22–25**.

**2-Hydrazono-5-methyl-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole (14, C<sub>9</sub>H<sub>9</sub>N<sub>5</sub>O<sub>2</sub>S)** Brown crystals (DMF); m.p.: 196–198 °C; yield 60%; IR:  $\bar{\nu}$  = 3379 and 3325 (NH<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.48 (s, 3H, CH<sub>3</sub>), 6.27 (s, 2H, NH<sub>2</sub>), 8.09 (d, 2H, Ar–H, *J* = 9 Hz), 8.45

(d, 2H, Ar-H,  $J=9.3$  Hz) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta=16.9, 112.9, 124.4, 137.7, 144.2, 149.0, 154.5$  ppm; MS (EI, 70 eV):  $m/z$  (%) = 251 ( $\text{M}^+$ , 10.99), 189 (28.16), 122 (35.44), 90 (100), 76 (58.90), 63 (92.84).

**Ethyl 2-[[5-methyl-3-(4-nitrophenyl)-1,3,4-thiadiazol-2(3H)-ylidene]hydrazono]propanoate (17a,  $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O}_4\text{S}$ )** Yellow crystals ( $\text{CH}_3\text{CN}$ ); m.p.: 168–170 °C; yield 62%; IR:  $\bar{\nu}=1713$  (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta=1.39$  (t, 3H,  $\text{OCH}_2\text{CH}_3$ ,  $J=6.9$  Hz), 2.31 (s, 3H,  $\text{CH}_3$ ), 2.52 (s, 3H,  $\text{CH}_3$ ), 4.33 (q, 2H,  $\text{OCH}_2\text{CH}_3$ ,  $J=6.9$  Hz), 8.33 (d, 2H, Ar-H,  $J=9.3$  Hz), 8.42 (d, 2H, Ar-H,  $J=9.6$  Hz) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta=14.5, 15.3, 17.1, 61.5, 121.5, 125.3, 144.4, 144.4, 153.1, 153.8, 164.7, 169.3$  ppm; MS (EI, 70 eV):  $m/z$  (%) = 349 ( $\text{M}^+$ , 75.53), 276 (77.52), 189 (73.93), 136 (40.05), 90 (100), 63 (64.46).

**5-Methyl-3-(4-nitrophenyl)-2-[(thiophen-2-ylmethylene)hydrazono]-2,3-dihydro-1,3,4-thiadiazole (17b,  $\text{C}_{14}\text{H}_{11}\text{N}_5\text{O}_2\text{S}_2$ )** Yellow crystals (DMF); m.p.: 202–204 °C; yield 63%;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta=2.49$  (s, 3H,  $\text{CH}_3$ ), 7.08–8.59 (m, 8H, Ar-H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta=16.8, 113.9, 124.5, 126.2, 127.2, 128.5, 138.0, 138.4, 142.2, 144.3, 154.9, 160.0$  ppm.

**5-Methyl-3-(4-nitrophenyl)-2-[[1-(thiophen-2-yl)ethylidene]hydrazono]-2,3-dihydro-1,3,4-thiadiazole (17c,  $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}_2\text{S}_2$ )** Yellow crystals ( $\text{CH}_3\text{CN}$ ); m.p.: 208–210 °C; yield 63%;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta=2.49$  (s, 3H,  $\text{CH}_3$ ), 2.50 (s, 3H,  $\text{CH}_3$ ), 7.05–7.37 (m, 3H, thiophenyl-H), 8.32 (d, 2H, Ar-H,  $J=9.3$  Hz), 8.44 (d, 2H, Ar-H,  $J=9.3$  Hz) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta=14.9, 16.0, 113.2, 124.2, 125.0, 127.2, 127.3, 128.4, 138.1, 145.6, 155.8, 158.2, 163.3$  ppm.

**2-[(Furan-2-ylmethylene)hydrazono]-5-methyl-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole (17d,  $\text{C}_{14}\text{H}_{11}\text{N}_5\text{O}_3\text{S}$ )** Brown crystals ( $\text{CH}_3\text{CN}$ ); m.p.: 184–186 °C; yield 61%;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta=2.49$  (s, 3H,  $\text{CH}_3$ ), 6.52–6.53 (m, 1H, furyl-H), 6.81 (d, 1H, furyl-H,  $J=3.3$  Hz), 7.57 (d, 1H, furyl-H,  $J=3.3$  Hz), 8.27–8.42 (m, 5H, Ar-H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta=17.0, 112.0, 114.3, 120.2, 124.5, 140.1, 143.8, 144.8, 145.0, 149.8, 151.1, 165.2$  ppm.

**2-[[1-(Furan-2-yl)ethylidene]hydrazono]-5-methyl-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole (17e,  $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}_3\text{S}$ )** Orange crystals ( $\text{CH}_3\text{CN}$ ); m.p.: 190–192 °C; yield 62%;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta=2.44$  (s, 3H,  $\text{CH}_3$ ), 2.49 (s, 3H,  $\text{CH}_3$ ), 6.50–6.51 (m, 1H, furyl-H), 6.87 (d, 1H, furyl-H,  $J=3.6$  Hz), 7.55 (d, 1H, furyl-H,  $J=3.3$  Hz), 8.33 (d, 2H, Ar-H,  $J=9.6$  Hz), 8.45 (d,

2H, Ar-H,  $J=9.6$  Hz) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta=15.1, 17.0, 111.2, 111.7, 112.1, 124.5, 143.0, 143.5, 144.1, 144.9, 151.2, 152.1, 164.0$  ppm; MS (EI, 70 eV):  $m/z$  (%) = 343 ( $\text{M}^+$ , 22.94), 122 (8.42), 94 (85.98), 66 (100), 63 (13.54).

**5-Methyl-3-(4-nitrophenyl)-2-[(1-phenylethylidene)hydrazono]-2,3-dihydro-1,3,4-thiadiazole (17f,  $\text{C}_{17}\text{H}_{15}\text{N}_5\text{O}_2\text{S}$ )** Yellow crystals (DMF); m.p.: 208–210 °C; yield 60%;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta=2.50$  (s, 3H,  $\text{CH}_3$ ), 2.54 (s, 3H,  $\text{CH}_3$ ), 7.41–7.91 (m, 5H, Ar-H), 8.34 (d, 2H, Ar-H,  $J=9.3$  Hz), 8.47 (d, 2H, Ar-H,  $J=9.3$  Hz) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta=14.9, 16.3, 114.8, 124.6, 126.6, 128.3, 131.1, 138.2, 138.9, 145.4, 156.2, 159.7, 162.4$  ppm.

**5-Methyl-3-(4-nitrophenyl)-2-[[1-(pyridin-2-yl)ethylidene]hydrazono]-2,3-dihydro-1,3,4-thiadiazole (17g,  $\text{C}_{16}\text{H}_{14}\text{N}_6\text{O}_2\text{S}$ )** Yellow crystals ( $\text{CH}_3\text{CN}$ ); m.p.: 210–212 °C; yield 60%;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta=2.51$  (s, 3H,  $\text{CH}_3$ ), 2.63 (s, 3H,  $\text{CH}_3$ ), 7.29–7.33 (m, 1H, pyridinyl-H), 7.71–7.77 (m, 1H, pyridinyl-H), 8.20 (d, 1H, pyridinyl-H,  $J=8.1$  Hz), 8.35 (d, 2H, Ar-H,  $J=9.3$  Hz), 8.48 (d, 2H, Ar-H,  $J=9.3$  Hz), 8.67 (d, 1H, pyridinyl-H,  $J=4.8$  Hz) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta=14.9, 16.2, 112.9, 122.0, 124.7, 126.4, 136.3, 137.6, 144.2, 149.5, 154.5, 155.1, 159.0, 163.2$  ppm; MS (EI, 70 eV):  $m/z$  (%) = 354 ( $\text{M}^+$ , 28.80), 104 (95.27), 90 (30.62), 79 (100), 63 (21.76), 51 (26.10).

**2-[[1(1H-Indol-3-yl)methylene]hydrazono]-5-methyl-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole (17h,  $\text{C}_{18}\text{H}_{14}\text{N}_6\text{O}_2\text{S}$ )** Yellow crystals (DMF +  $\text{H}_2\text{O}$ ); m.p.: 274–276 °C; yield 61%; IR:  $\bar{\nu}=3402$  (NH)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta=2.52$  (s, 3H,  $\text{CH}_3$ ), 7.19–7.27 (m, 2H, indolyl-H), 7.50 (d, 1H, indolyl-H,  $J=9$  Hz), 7.90 (s, 1H, indolyl-H), 8.22 (d, 1H, indolyl-H,  $J=8.7$  Hz), 8.35 (d, 2H, Ar-H,  $J=9.3$  Hz), 8.45 (d, 2H, Ar-H,  $J=9$  Hz), 8.72 (s, 1H, N=CH), 11.71 (s, 1H, NH) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta=16.8, 111.7, 112.1, 119.3, 120.9, 121.9, 122.8, 124.3, 124.8, 132.2, 137.2, 142.8, 144.7, 151.7, 152.6, 161.5$  ppm; MS (EI, 70 eV):  $m/z$  (%) = 378 ( $\text{M}^+$ , 17.56), 222 (10.57), 129 (100), 102 (20.04), 63 (11.10).

**1,5-Dimethyl-4-[[[5-methyl-3-(4-nitrophenyl)-1,3,4-thiadiazol-2(3H)-ylidene]hydrazono]methyl]-2-phenyl-1,2-dihydro-3H-pyrrol-3-one (22,  $\text{C}_{21}\text{H}_{19}\text{N}_7\text{O}_3\text{S}$ )** Yellow crystals (DMF); m.p.: 214–216 °C; yield 63%; IR:  $\bar{\nu}=1620$  (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta=2.49$  (s, 3H,  $\text{CH}_3$ ), 2.64 (s, 3H,  $\text{CH}_3$ ), 3.30 (s, 3H,  $\text{CH}_3$ ), 7.34–7.61 (m, 9H, Ar-H), 8.09 (s, 1H, N=CH) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta=12.8, 17.0, 34.4, 99.6, 126.4, 128.3, 128.3,$

129.7, 129.9, 130.1, 133.0, 134.5, 135.5, 141.3, 152.4, 161.6, 164.1 ppm.

**2-(Cyclopentylidenehydrazono)-5-methyl-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole (23, C<sub>14</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub>S)** Yellow crystals (CH<sub>3</sub>CN); m.p.: 188–190 °C; yield 62%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.81–1.88 (m, 4H, 2CH<sub>2</sub>), 2.46 (s, 3H, CH<sub>3</sub>), 2.53 (t, 2H, CH<sub>2</sub>, *J* = 6.3 Hz), 2.61 (t, 2H, CH<sub>2</sub>, *J* = 6.3 Hz), 8.29 (d, 2H, Ar–H, *J* = 9.6 Hz), 8.41 (d, 2H, Ar–H, *J* = 9.3 Hz) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 16.2, 23.1, 26.2, 32.1, 38.5, 112.5, 124.2, 136.3, 146.4, 154.0, 158.3, 163.4 ppm.

**2-(Cyclohexylidenehydrazono)-5-methyl-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole (24, C<sub>15</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S)** Yellow crystals (CH<sub>3</sub>CN); m.p.: 166–168 °C; yield 60%; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 1.63–1.67 (m, 6H, 3CH<sub>2</sub>), 2.33 (t, 2H, CH<sub>2</sub>, *J* = 6.8 Hz), 2.47 (s, 3H, CH<sub>3</sub>), 2.67 (t, 2H, CH<sub>2</sub>, *J* = 6.9 Hz), 8.32–8.37 (m, 4H, Ar–H) ppm; <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 17.3, 25.8, 26.6, 27.5, 29.6, 35.2, 119.9, 125.4, 143.4, 145.1, 152.2, 163.1, 169.3 ppm.

**2-[(3,4-Dihydronaphthalen-1(2H)-ylidene)hydrazono]-5-methyl-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole (25, C<sub>19</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S)** Orange crystals (CH<sub>3</sub>CN); m.p.: 204–206 °C; yield 61%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.97–2.01 (m, 2H, CH<sub>2</sub>), 2.50 (s, 3H, CH<sub>3</sub>), 2.86 (t, 2H, CH<sub>2</sub>, *J* = 6.3 Hz), 3.01 (t, 2H, CH<sub>2</sub>, *J* = 6.3 Hz), 7.17–7.32 (m, 3H, Ar–H), 8.26 (d, 1H, Ar–H, *J* = 7.5 Hz), 8.34 (d, 2H, Ar–H, *J* = 9.6 Hz), 8.47 (d, 2H, Ar–H, *J* = 9.3 Hz) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 16.80, 21.0, 23.4, 29.3, 113.4, 124.2, 125.2, 126.3, 128.2, 129.2, 131.9, 137.9, 138.8, 144.5, 154.9, 156.2, 163.7 ppm; MS (EI, 70 eV): *m/z* (%) = 379 (M<sup>+</sup>, 29.13), 129 (100), 115 (66.85), 90 (32.83), 63 (20.20).

### Antimicrobial assay

Using the agar well diffusion method, the antimicrobial properties of the produced compounds were tested against Gram-negative bacteria *Escherichia coli*, Gram-positive bacteria *Bacillus mycoides*, and yeast *Candida albicans*. In this procedure, the samples were placed on Petri dishes infected with the specified model microbe (i.e. *E. coli*, *B. mycoides*, and *C. albicans*) in a nutrient agar medium (70,148 Nutrient agar, Fluka) at pH 7.0. Before forming the wells (12 mm in diameter) within the solidified nutritional agar, the microorganisms were dispersed uniformly on the surface of the plates with a sterile glass rod. Each well received 100 mm<sup>3</sup> of each antiseptic solution studied (10 mg/cm<sup>3</sup>). Streptomycin at a concentration of 10 mcg was used as a positive control. The culture plates were cultured at 37 °C for 18 h

before measuring the width of inhibitory zones generated by the various synthesized compounds [48, 68, 69].

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