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Convenient synthesis and characterization of new 1,3,4-thiadiazoles and thiazoles incorporating thiophene moiety

Mirna T. Helmy, Monica G. Kamel, Madonna S. Mikhail, Fatma M. Saleh, Hamdi M. Hassaneen*, Ayman W. Erian*, and Mohamed A. Mohamed Teleb

Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt
Email: hamdi_251@yahoo.com, hhassaneen@sci.cu.edu.eg, erian11@hotmail.com

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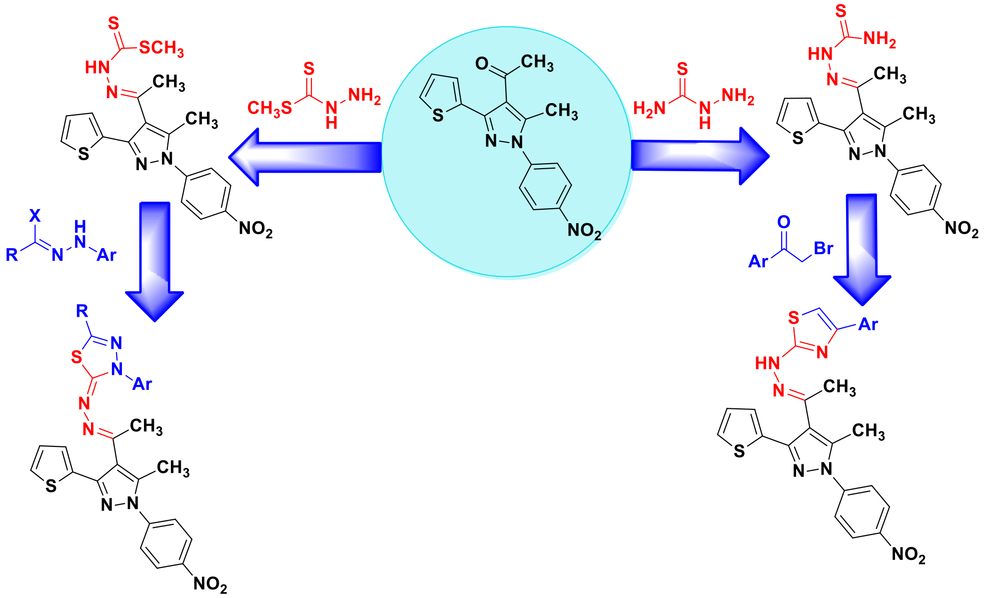
Abstract

Reaction of substituted acetylpyrazole with methyl hydrazinecarbodithioate using hydrochloric acid as a catalyst in absolute ethanol afforded methyl 2-(1-(1*H*-pyrazol-4-yl)ethylidene)hydrazinecarbodithioate derivative. Refluxing of the latter product with hydrazonoyl halides in absolute ethanol in the presence of triethylamine afforded the corresponding 1,3,4-thiadiazoles. Heating the same acetylpyrazole with hydrazinecarbothioamide in refluxing ethanol using hydrochloric acid as a catalyst afforded 2-(1-(1*H*-pyrazol-4-yl)ethylidene)hydrazinecarbothioamide derivative. The reaction of the latter compound with ω-bromoacetophenone derivatives in absolute ethanol at reflux afforded the corresponding thiazole derivatives.



Keywords: 1,3,4-Thiadiazoles, pyrazole, methyl hydrazinecarbodithioate, thiazoles, cycloaddition reaction

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Introduction

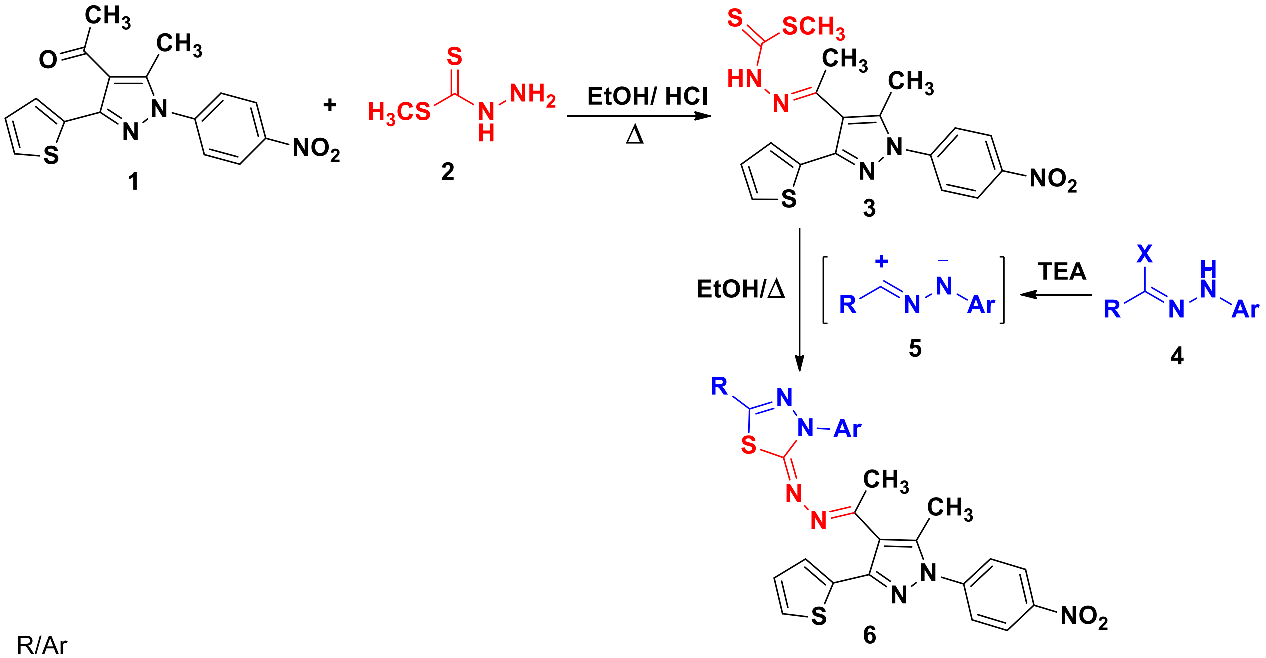
1,3-Dipolar cycloadditions are one of the most effective methods for creating five-membered heterocycles from the reaction between 1,3-dipole, which has 4π electrons, and dipolarophile, which has 2π electrons.[1-5] Reactions of 1,3-dipole as nitrilimines produced from hydrazonoyl halides *via* triethylamine-catalyzed dehydrohalogenation, with dipolarophile as C=S, C=N or C=O containing compound to give five-membered heterocyclic compounds as thiadiazole, triazole or oxazole, respectively. Compounds containing sulfur, and/or nitrogen showed various applications in both medical chemistry and organic synthesis due to their potent and varied biological effects.[6-10] 1,3,4-Thiadiazoles and thiazoles have special interest in medicinal chemistry due to their wide range of biological importance as HIV-protease inhibitory drugs,[11] cytotoxic and antitumor agents,[12-16] antibacterial,[17-19] antiviral agents,[20,21] anti-inflammatory,[22] insecticidal,[23,24] anti-depressant,[25] herbicidal,[26,27] COX-2 inhibitors,[26] antifungal,[28-30] antiparasitic,[31] and antiproliferative.[32,33] It was reported that thiadiazole derivatives were prepared *via* the treatment of hydrazonoyl halides with thiosemicarbazide and their aryl derivatives,[34] potassium thiocyanate[35-39] and carbon disulfide.[40] Moreover, reaction of potassium ethyl xanthate with 1,4-dichloro-1,4-diphenyl-2,3-diazabutadiene,[41] phenylisothiocyanate with *N*-phenylbenzohydrazonoyl chloride[42] and coupling of *N*-nitroso-*N*-arylacetamide with aroyldimethylsulfonium bromides.[43,44] In agreement with our previous research on the use of hydrazonoyl halides to create different nitrogen and sulfur-containing heterocycles,[45–49] we would like to report herein, an efficient method for synthesizing various functionalized derivatives of 1,3,4-thiadiazoles and thiazoles bearing thiophene moiety.

Results and Discussion

Methyl 2-(1-(1*H*-pyrazol-4-yl)ethylidene)hydrazinecarbodithioate derivative **3** was prepared *via* refluxing of acetylpyrazole **1**[50] with methyl hydrazinecarbodithioate **2**[51] using hydrochloric acid as a catalyst in absolute ethanol. Heating of product **3** with hydrazonoyl halides **4**[43,52-59] in refluxing ethanol using triethylamine as a catalyst produced the corresponding 1,3,4-thiadiazole derivatives **6a-i** as shown in Scheme 1. Constitutions of products **6a-i** were identified by their elemental analyses and spectral data (^{1}H NMR, ^{13}C NMR, IR and MS). "The ^{1}H NMR spectrum of compound **6g**, as example, revealed two singlets at δ 2.30 and 2.64 for two CH_3 groups and two multiplet signals at δ 7.08-7.11 and 7.27-7.70 assigned to one thienyl proton and eight aromatic protons. It also featured four doublets at 7.82, 8.14, 8.35 and 8.42 assigned to four aromatic protons and four protons of 4-$NO_2C_6H_4$ group. In addition, 25 signals appeared in its ^{13}C NMR spectrum."

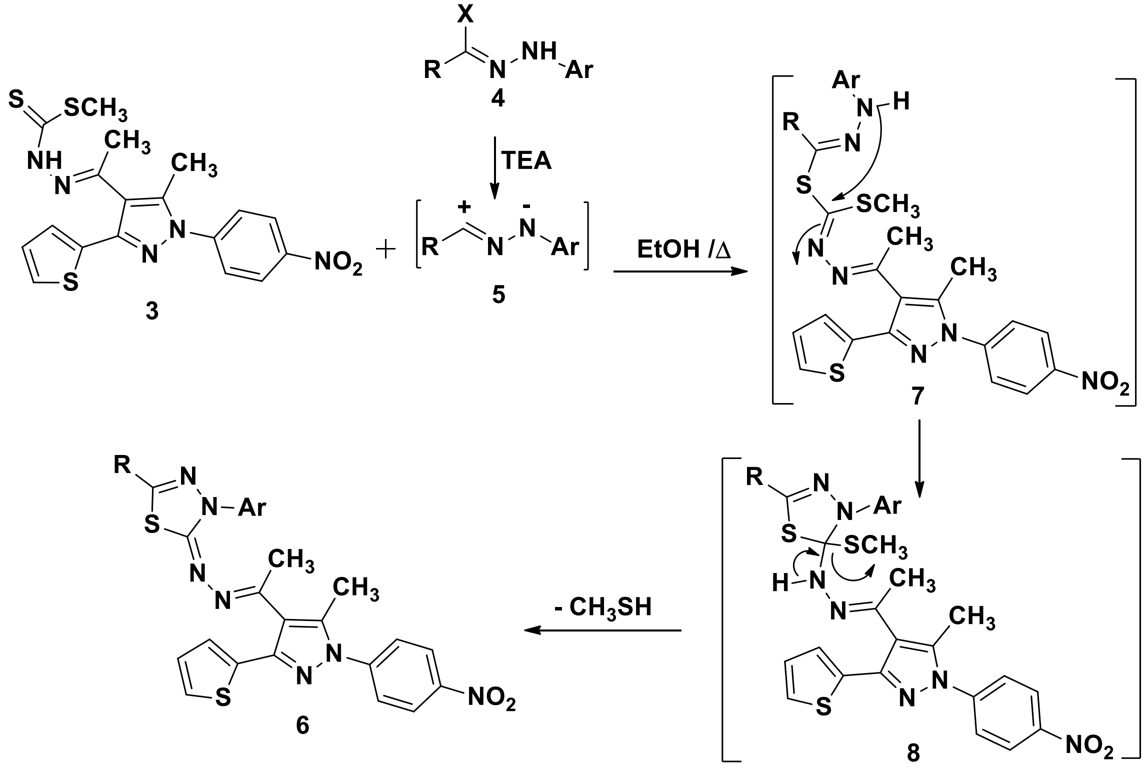
According to the reported mechanism, the reaction started by 1,3-dipolar cycloaddition of nitrilimine **5** to carbon-sulfur double bond of compound **3** to produce thiohydrazonate **7** which underwent intramolecular cyclization to give intermediate **8** which afforded finally compounds **6a-i** by loss of methanethiol (Scheme 2).[7,51,60,61]

Heating of compound **1**[50] with hydrazinecarbothioamide **9** in boiling ethanol using hydrochloric acid as a catalyst gave 2-(1-(1*H*-pyrazol-4-yl)ethylidene)hydrazinecarbothioamide derivative **10** (Scheme 3).[62] Reaction of compound **10** with *ω*-bromoacetophenone derivatives **11a-g** at reflux in absolute ethanol afforded the corresponding thiazole derivatives **12a-g** (Scheme 3). The structures of the isolated products **12a-g** were established by their spectral data and elemental analyses (see Experimental). The ^{1}H NMR spectra of the isolated products **12a-g** showed the presence of exchangeable singlet signal in region δ 10.99-11.46 corresponding to NH proton. The other signals appeared in their expected positions. In addition, IR spectra showed an absorption band in region ν 3447-3449 cm^{-1} corresponding to NH group that confirmed the presence of hydrazo form **12a-g**.

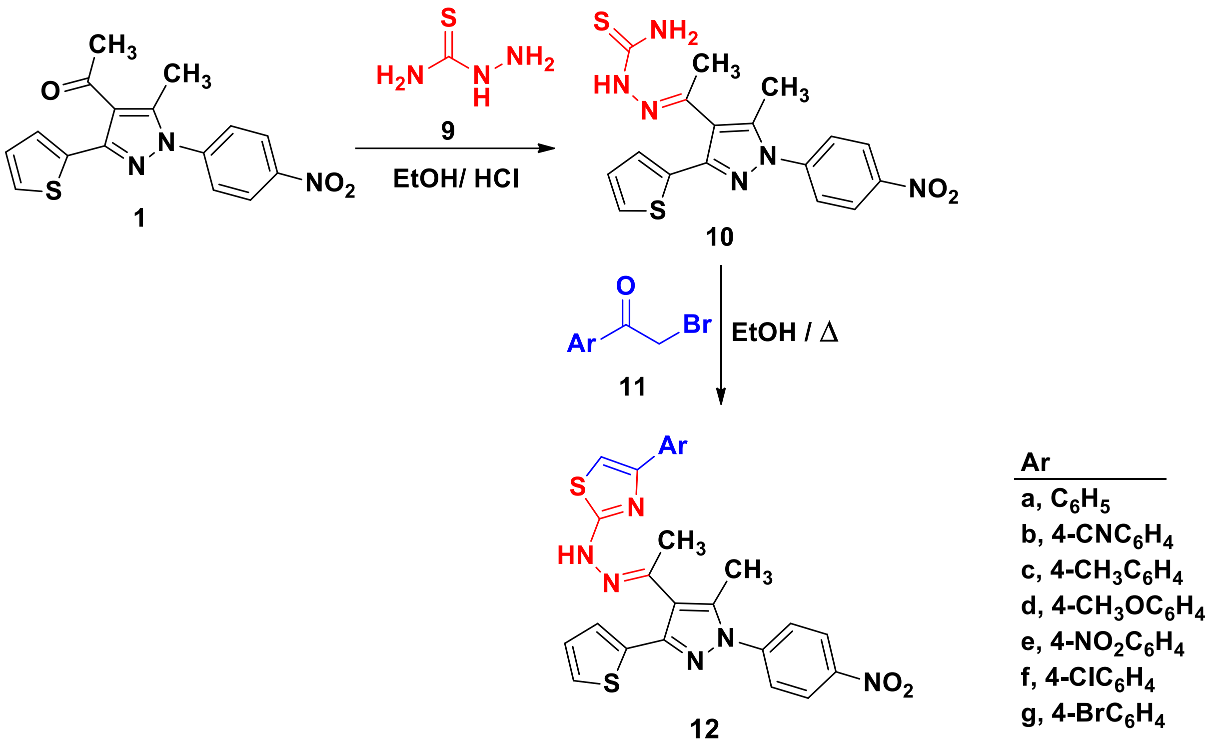


R/Ar
a, C_6H_5/C_6H_5; b, CH_3CO/C_6H_5; c, C_2H_5OCO/C_6H_5; d, $C_6H_5CH{=}CH/C_6H_5$; e, 2-Thienyl/4-$NO_2C_6H_4$;
f, 2-Furyl/4-$NO_2C_6H_4$; g, C_6H_5CO/C_6H_5; h, 2-Thenoyl/C_6H_5; i, 2-Furoyl/C_6H_5.

Scheme 1. Synthesis of 1,3,4-thiadiazole derivatives **6a-i**.



Scheme 2. Proposed mechanism of synthesis 1,3,4-thiadiazole derivatives **6**.

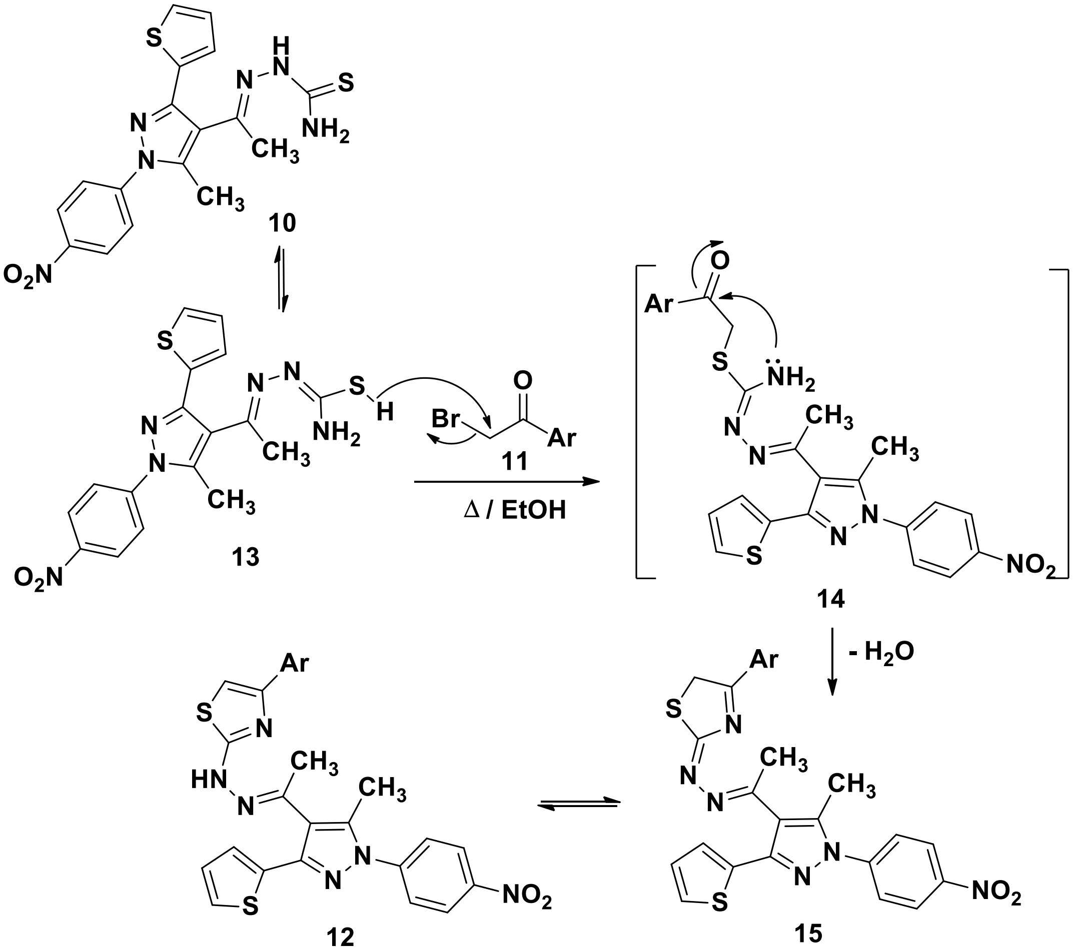


Scheme 3. Synthesis of thiazole derivatives **12**.

The reaction first gave the thiol form **13** *via* tautomerization of the thione form **10** that underwent dehydrobromination by reaction with *ω*-bromoacetophenones **11** to give intermediate **14**. The latter intermediate **14** underwent intramolecular cyclization by dehydration to afford cyclic azo form **15** that tautomerized to cyclic hydrazo form **12** (Scheme 4).

Conclusions

In a simple and fast approach, we prepared new series of 1,3,4-thiadiazoles and thiazoles incorporating thiophene moiety with expected biological activities through 1,3-dipolar cycloaddition reactions. We also confirmed the constitution of the new compounds using the elemental analyses and spectral data (^{1}H NMR, ^{13}C NMR, IR and MS).



Scheme 4. Proposed mechanism of synthesis of thiazole derivatives **12**.

Experimental Section

General. Melting points were determined with Electrothermal 9100 apparatus and are uncorrected. The IR spectra were recorded using a FTIR Bruker–vector 22 spectrophotometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or 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 δ 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". Acetylpyrazole **1**[50], methyl hydrazinecarbodithioate **2**[51] and hydrazonoyl halides **4a-i**[43,52-59] were synthesized by the reported procedures.

Synthesis of methyl 2-(1-(1*H*-pyrazol-4-yl)ethylidene)hydrazinecarbodithioate derivative (3) and 2-(1-(1*H*-pyrazol-4-yl)ethylidene)hydrazinecarbothioamide derivative (10). A mixture of methyl hydrazinecarbodithioate **2** (0.25 g, 2 mmol) or hydrazinecarbothioamide **9** (0.18 g, 2 mmol) and acetylpyrazole **1** (0.65 g, 2 mmol) was dissolved in absolute ethanol (20 mL). To the resulting solution, few drops of conc. hydrochloric acid was added and reaction mixture was refluxed for 3 hr. The resulting solution was cooled, the precipitate that separated was collected and crystallized from a suitable solvent.

Methyl 2-(1-(1*H*-pyrazol-4-yl)ethylidene)hydrazinecarbodithioate derivative (3). Yield (80%); yellow crystals (CH_3CN), mp 172-174°C, IR (ν_{max}, cm^{-1}) ν 3449 (NH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 7.06-7.41 (m, 3H, Thienyl-H), 7.81 (d, 2H, 4-$NO_2C_6H_4$, *J* 8.7 Hz), 8.42 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz) and 9.89 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 17.2, 19.0 (3CH_3), 109.5, 111.8, 113.7, 119.1, 124.8, 124.9, 139.9, 141.1, 143.8, 146.2, 146.4, 148.5 (12C, Ar-C), 199.9 (C=S); MS (EI, 70 eV) *m/z* (%): 431 (M^+, 0.68), 383 (21.64), 325 (54.53), 279 (30.69), 117 (25.93), 90 (23.81), 76 (100.00), 63 (24.58); Anal. Calcd. for $C_{18}H_{17}N_5O_2S_3$ (431.5): C, 50.10; H, 3.97; N, 16.23; S, 22.29. Found: C, 50.18; H, 3.89; N, 16.30; S, 22.21.

2-(1-(1*H*-Pyrazol-4-yl)ethylidene)hydrazinecarbothioamide derivative (10).[62] Yield (81%); yellow crystals (DMF+Ethanol), mp 226-228 °C, IR (ν_{max}, cm^{-1}) ν 3372 (NH), 3240, 3163 (NH_2); ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 6.29 (s, 1H, NH), 7.06-7.40 (m, 3H, Ar-H), 7.81 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz), 8.43 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz) and 8.67 (s, 1H, NH_2), 8.73 (s, 1H, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 18.5 (2CH_3), 109.1, 111.9, 113.2, 119.8, 124.8, 124.9, 141.0, 142.7, 143.6, 144.0, 145.9, 146.6 (13C, Ar-C), 179.2 (C=S) ; MS (EI, 70 eV) *m/z* (%): 400 (M^+, 39.02), 385 (39.08), 325 (37.40), 308 (23.11), 117 (34.64), 90 (37.31), 76 (92.82), 75 (48.50), 60 (100.00); Anal. Calcd. for $C_{17}H_{16}N_6O_2S_2$ (400.48): C, 50.99; H, 4.03; N, 20.99; S, 16.01. Found: C, 50.91; H, 4.11; N, 20.92; S, 16.09.

Synthesis of 1-(5-methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1*H*-pyrazol-4-yl)ethylidene)hydrazono-1,3,4-thiadiazole derivatives (6a-i). To a mixture of methyl 2-(1-(1*H*-pyrazol-4-yl)ethylidene)hydrazinecarbodithioate derivative **3** (0.86 g, 2 mmol) and the appropriate hydrazonoyl halides **4a-i** (2 mmol) dissolved in absolute ethanol (20 mL), triethylamine (2 mL) was added. The reaction mixture was then heated at reflux for 4 h. The precipitated solid was collected and washed with ethanol. The crude product was also crystallized from a suitable solvent to produce the newly synthesized 1,3,4-thiadiazole derivatives **6a-i**.

2-((1-(5-Methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1*H*-pyrazol-4-yl)ethylidene)hydrazono)-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole (6a). Yield (81%); white crystals (CH_3CN), mp 210-212 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 6.60-6.62 (m, 1H, Thienyl-H), 6.87 (d, 1H, Thienyl-H, *J* 3.3 Hz), 7.27-7.94 (m, 11H, Ar-H), 8.38 (d, 2H, Ar-H, *J* 7.8 Hz) and 8.51 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 19.8 (2CH_3), 108.6, 109.5, 111.4, 120.3, 120.8, 121.2, 124.4, 124.9, 125.3, 126.2, 128.4, 128.9, 130.4, 130.6, 140.1, 142.9, 143.7, 144.4, 147.0, 150.4, 155.7, 164.5 (21C, Ar-C); MS (EI, 70 eV) *m/z* (%): 577 (M^+, 25.57), 339 (9.90), 324 (8.27), 135 (13.63), 117 (9.22), 91 (100.00), 77 (48.16), 64 (22.29); Anal. Calcd. for $C_{30}H_{23}N_7O_2S_2$ (577.7): C, 62.38; H, 4.01; N, 16.97; S, 11.10. Found: C, 62.31; H, 4.09; N, 16.90; S, 11.17.

1-(5-((1-(5-Methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1H-pyrazol-4-yl)ethylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethan-1-one (6b): Yield (83%); yellow crystals (CH_3CN), mp 188-190 °C, IR (ν_{max}, cm^{-1}) ν 1690 (CO); ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 7.03-7.54 (m, 6H, Ar-H), 7.70 (d, 1H, Ar-H, *J* = 8.7 Hz), 7.81 (d, 2H, 4-$NO_2C_6H_4$, *J* = 9 Hz), 8.14 (d, 1H, Ar-H, *J* = 8.1 Hz), 8.41 (d, 2H, 4-$NO_2C_6H_4$, *J* = 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 20.0, 25.9 (3CH_3), 108.4, 109.4, 111.5, 120.0, 121.8, 124.7, 126.9, 128.5, 137.8, 139.4, 142.3, 143.0, 143.6, 144.3, 146.7, 156.3, 157.5, 158.7 (18C, Ar-C), 193.0 (C=O); MS (EI, 70 eV) *m/z* (%): 543 (M^+, 82.12), 339 (44.37), 296 (22.72), 117 (38.31), 91 (83.11), 77 (100.00); Anal. Calcd. for $C_{26}H_{21}N_7O_3S_2$ (543.6): C, 57.45; H, 3.89; N, 18.04; S, 11.80. Found: C, 57.53; H, 3.81; N, 18.11; S, 11.87.

Ethyl-5-((1-(5-methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1H-pyrazol-4-yl)ethylidene) hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (6c): Yield (79%); yellow crystals (CH_3CN), mp 166-168 °C, IR (ν_{max}, cm^{-1}) ν 1713 (CO); ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (t, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.58 (q, 2H, CH_2, *J* = 6.9 Hz), 6.57-6.61 (m, 1H, Thienyl-H), 6.78 (d, 1H, Thienyl-H, *J* = 3 Hz), 6.84-7.78 (m, 5H, Ar-H), 7.90 (d, 2H, 4-$NO_2C_6H_4$, *J* = 9 Hz), 8.20 (d, 1H, Ar-H, *J* = 7.8 Hz) and 8.50 (d, 2H, 4-$NO_2C_6H_4$, *J* = 9 Hz); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 13.0, 14.2, 19.7 ($3CH_3$), 63.0 (CH_2O), 108.5, 109.5, 111.5, 119.9, 121.7, 124.7, 126.9, 128.5, 137.9, 139.4, 142.3, 142.9, 143.8, 144.3, 146.8, 156.3, 157.4, 158.7 (17C, Ar-C), 164.7 (C=O); Anal. Calcd. for $C_{27}H_{23}N_7O_4S_2$ (573.6): C, 56.53; H, 4.04; N, 17.09; S, 11.18. Found: C, 56.61; H, 4.12; N, 17.01; S, 11.11.

2-((1-(5-Methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1H-pyrazol-4-yl)ethylidene)hydrazono)-3-phenyl-5-(styryl)-2,3-dihydro-1,3,4-thiadiazole (6d): Yield (77%); yellow crystals (CH_3CN), mp188-190 °C, ^1H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 6.61-6.88 (m, 2H, Thienyl-H), 7.08 (d, 1H, Vinyl-H, *J* = 8.4 Hz), 7.25-7.64 (m, 10H, Ar-H), 7.92 (d, 2H, 4-$NO_2C_6H_4$, *J* = 9 Hz), 8.30 (d, 2H, Ar-H, *J* = 8.4 Hz) and 8.51 (d, 2H, 4-$NO_2C_6H_4$, *J* = 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0, 19.9 ($2CH_3$), 109.2, 114.4, 114.5, 120.0, 122.0, 124.3, 124.5, 125.0, 126.6, 126.8, 128.4, 129.0, 134.4, 138.5, 138.9, 139.7, 141.4, 143.5, 144.2, 146.8, 155.4, 156.2, 157.5, 158.7 (24 C, Ar-C); Anal. Calcd. for $C_{32}H_{25}N_7O_2S_2$ (603.7): C, 63.66; H, 4.17; N, 16.24; S, 10.62. Found: C, 63.59; H, 4.24; N, 16.13; S, 10.70.

2-((1-(5-Methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1H-pyrazol-4-yl)ethylidene)hydrazono)-3-(4-nitrophenyl)-5-(2-thienyl)-2,3-dihydro-1,3,4-thiadiazole (6e): Yield (75%); orange crystals (DMF), mp 220-222 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 7.01-7.04 (m, 1H, Thienyl-H) and 7.09-8.54 (m, 13H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 19.9, 108.5 ($2CH_3$), 109.5, 111.5, 119.9, 121.8, 124.3, 125.0, 126.8, 128.5, 130.7, 134.4, 137.3, 137.9, 139.4, 142.3, 143.0, 143.7, 144.3, 146.9, 156.4, 157.5, 158.7 (22C, Ar-C); MS (EI, 70 eV) *m/z* (%): 628 (M^+, 100.00), 339 (32.75), 296 (12.69), 127 (10.84), 90 (40.82), 76 (27.40), 63 (20.54); Anal. Calcd. for $C_{28}H_{20}N_8O_4S_3$ (628.7): C, 53.49; H, 3.21; N, 17.82; S, 15.30. Found: C, 53.41; H, 3.14; N, 17.91; S, 15.38.

5-(Furan-2-yl)-2-((1-(5-methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1H-pyrazol-4-yl)ethylide-ne)hydrazono)-3-(4-nitrophenyl)-2,3-dihydro-1,3,4-thiadiazole (6f): Yield (76%); yellow crystals (DMF), mp 198-200 °C; ^1H NMR (300 MHz, DMSO–d_6) δ 2.42 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 6.74 (m, 1H, Furyl-H), 6.92 (d, 1H, Furyl-H, *J* = 3 Hz), 7.33-7.36 (m, 1H, Thienyl-H), 7.78 (d, 1H, Ar-H, *J* = 3 Hz) and 7.93-8.59 (m, 10H, Ar-H); ^{13}C NMR (75 MHz, DMSO–d_6) δ 12.8, 19.9 ($2CH_3$), 108.5, 109.5, 111.5, 119.9, 121.8, 124.3, 125.0, 126.8, 128.6, 130.7, 134.4, 137.3, 137.9, 139.4, 142.3, 143.0, 143.7, 144.3, 146.9, 156.4, 157.5, 158.7 (22C, Ar-C); Anal. Calcd. for $C_{28}H_{20}N_8O_5S_2$ (612.6): C, 54.89; H, 3.29; N, 18.29; S, 10.47. Found: C, 54.97; H, 3.22; N, 18.21; S, 10.55.

(5-((1-(5-Methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1H-pyrazol-4-yl)ethylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)(phenyl)methanone (6g): Yield (78%); orange crystals (CH_3CN), mp 152-154 °C, IR (ν_{max}, cm^{-1}) ν 1597 (CO); ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3), 2.64 (s, 3H, CH_3) and 7.08-7.11 (m, 1H, Thienyl-H), 7.27-7.70 (m, 8H, Ar-H), 7.82 (d, 2H, 4-$NO_2C_6H_4$, *J* = 9 Hz), 8.14 (d, 2H, Ar-H, *J* = 8.4 Hz), 8.35 (d, 2H, Ar-H, *J* = 8.7 Hz) and 8.42 (d, 2H, 4-$NO_2C_6H_4$, *J* = 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 19.9 ($2CH_3$), 114.4, 122.0, 124.8, 124.9, 125.7, 126.4, 127.0, 127.4, 127.5, 128.6, 129.0, 130.5, 133.9, 134.6, 138.8, 139.4, 143.8, 144.3, 144.7, 146.5, 157.7, 160.4 (22C, Ar-C), 188.9 (C=O); MS (EI, 70 eV) *m/z* (%): 605 (M^+, 19.28), 339 (10.00), 296 (5.26), 117 (7.29), 105 (100.00), 77 (94.34), 63 (30.51); Anal. Calcd. for $C_{31}H_{23}N_7O_3S_2$ (605.7): C, 61.47; H, 3.83; N, 16.19; S, 10.59. Found: C, 61.54; H, 3.91; N, 16.11; S, 10.51.

(5-((1-(5-Methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1H-pyrazol-4-yl)ethylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)(2-thienyl)methanone (6h): Yield (81%); orange crystals (DMF), mp 192-194 °C, IR (ν_{max}, cm^{-1}) ν 1605 (CO); ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.04-7.98 (m, 11H, Ar-H), 8.21 (d, 2H, Ar-H, *J* = 7.8 Hz) and 8.41 (d, 2H, 4-$NO_2C_6H_4$, *J* = 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 20.0 ($2CH_3$), 108.6, 109.4, 111.6, 120.0, 121.9, 124.4, 125.1, 126.7, 128.6, 130.8, 134.5, 137.4, 138.0, 139.5, 142.4, 143.1, 143.8, 144.4, 147.0, 156.5, 157.6, 158.8 (22C, Ar-C), 185.4 (C=O); Anal. Calcd. for $C_{29}H_{21}N_7O_3S_3$ (611.7): C, 56.94; H, 3.46; N, 16.03; S, 15.72. Found: C, 56.86; H, 3.55; N, 16.11; S, 15.80.

Furan-2-yl(5-((1-(5-methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1H-pyrazol-4-yl)ethylidene)-hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)methanone (6i): Yield (80%); orange crystals (CH_3CN), mp 208-210 °C, IR

(ν_{max}, cm^{-1}) ν 1605 (CO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 6.60-6.62 (m, 1H, Furyl-H), 6.78 (d, 1H, Furyl-H, *J* = 7.5 Hz), 6.86 (d, 1H, Furyl-H, *J* = 3 Hz), 7.48-8.13 (m, 8H, Ar-H), 8.26 (d, 2H, Ar-H, *J* = 8.1 Hz) and 8.52 (d, 2H, 4-$NO_2C_6H_4$ *J* = 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 20.1 (2CH_3), 108.7, 109.7, 111.7, 120.1, 122.0, 124.5, 125.2, 127.0, 128.7, 130.9, 134.6, 137.4, 138.1, 139.6, 142.5, 143.2, 143.8, 144.5, 147.1, 156.6, 157.7, 158.9 (22C, Ar-C), 185.5 (C=O); MS (EI, 70 eV) *m/z* (%): 595 (M$^+$, 20.39), 339 (8.45), 117 (6.63), 95 (100.00), 77 (23.97), 65 (6.18); Anal. Calcd. for $C_{29}H_{21}N_7O_4S_2$ (595.65): C, 58.48; H, 3.55; N, 16.46; S, 10.76. Found: C, 58.40; H, 3.62; N, 16.53; S, 10.83.

Synthesis of 2-(2-(1-(5-methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1*H*-pyrazol-4-yl)ethylidene)hydrazinyl)-thiazoles (12a-g). A mixture of 2-(1-(1H-pyrazol-4-yl)ethylidene)hydrazinecarbothioamide derivative **10** (0.80 g, 2 mmol) and 2-bromo-1-arylethan-1-ones **11a-g** (2 mmol) was dissolved in absolute ethanol (20 mL). The resulting solution was refluxed for 4hr and the resulting solid product that precipitated was collected, washed with ethanol and crystallized from suitable solvent to give the corresponding thiazole derivatives **12a-g**.

2-(2-(1-(5-Methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1*H*-pyrazol-4-yl)ethylidene)hydrazinyl)-4-phenylthiazole (12a). Yield (84%); yellow crystals (CH_3CN), mp 218-220 °C, IR (ν_{max}, cm^{-1}) ν 3449 (NH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 6.77-7.54 (m, 9H, Ar-H), 7.78 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz), 8.43 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz) and 11.19 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 18.6 (2CH_3), 102.4, 112.5, 124.8, 125.5, 126.3, 127.3, 127.7, 128.8, 129.0, 131.4, 133.6, 138.8, 139.4, 143.8, 144.7, 146.3, 146.8, 168.5, 169.4 (19C, Ar-C); MS (EI, 70 eV) *m/z* (%): 500 (M$^+$, 5.74), 467 (21.34), 325 (40.63), 279 (46.52), 134 (100.00), 89 (36.88), 76 (86.85); Anal. Calcd. for $C_{25}H_{20}N_6O_2S_2$ (500.6): C, 59.98; H, 4.03; N, 16.79; S, 12.81. Found: C, 59.90; H, 4.11; N, 16.72; S, 12.89.

4-(2-(2-(1-(5-Methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1*H*-pyrazol-4-yl)ethylidene)hydra-zinyl)thiazol-4-yl)benzonitrile (12b). Yield (81%); yellow crystals (CH_3CN), mp 224-226 °C, IR (ν_{max}, cm^{-1}) ν 3449 (NH), 2222 (CN) ; ^{1}H NMR (300 MHz, DMSO–*d*$_6$) δ 2.45 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.71-6.73 (m, 1H, Thienyl-H), 6.89 (d, 1H, Thienyl-H, *J* 3 Hz), 7.70-8.06 (m, 6H, Ar-H), 8.16 (d, 2H, Ar-H, *J* 8.7 Hz), 8.52 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz) and 11.35 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO–*d*$_6$) δ 12.4, 18.8 (2CH_3), 104.9 (CN), 109.4, 112.0, 118.6, 119.9, 125.1, 125.4, 127.5, 128.9, 132.2, 134.0, 139.6, 142.7, 143.5, 143.9, 144.2, 146.3, 146.9, 150.4, 170.1 (19C, Ar-C); MS (EI, 70 eV) *m/z* (%): 525 (M$^+$, 30.31), 325 (46.44), 279 (54.72), 159 (46.96), 90 (30.88), 76 (100.00); Anal. Calcd. for $C_{26}H_{19}N_7O_2S_2$ (525.6): C, 59.41; H, 3.64; N, 18.65; S, 12.20. Found: C, 59.49; H, 3.56; N, 18.58; S, 12.28.

2-(2-(1-(5-Methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1*H*-pyrazol-4-yl)ethylidene)hydrazinyl)-4-(*p*-tolyl)thiazole (12c). Yield (83%); yellow crystals (CH_3CN), mp 252-254 °C, IR (ν_{max}, cm^{-1}) ν 3448 (NH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 6.56-6.58 (m, 1H, Thienyl-H), 6.82 (d, 1H, Thienyl-H, *J* 3 Hz), 6.91-7.85 (m, 6H, Ar-H), 7.91 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz), 8.52 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz) and 11.30 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 21.1, 24.0 (3CH_3), 108.6, 109.3, 112.8, 119.6, 124.4, 124.9, 129.2, 131.9, 137.5, 139.0, 142.0, 142.9, 143.7, 144.1, 146.4, 151.1, 151.2, 168.2, 169.7 (19C, Ar-C); MS (EI, 70 eV) *m/z* (%): 514 (M$^+$, 38.25), 325 (65.81), 279 (95.31), 148 (87.58), 117 (50.82), 91 (61.37), 76 (100.00); Anal. Calcd. for $C_{26}H_{22}N_6O_2S_2$ (514.6): C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.60; H, 4.38; N, 16.41; S, 12.54.

4-(4-Methoxyphenyl)-2-(2-(1-(5-methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1*H*-pyrazol-4-yl)ethylidene)hydrazinyl)thiazole (12d). Yield (80%); orange crystals (CH_3CN), mp 208-210 °C, IR (ν_{max}, cm^{-1}) ν 3447 (NH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.71-7.65 (m, 8H, Ar-H), 7.86 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz), 8.43 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz) and 10.99 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 23.9 (2CH_3), 55.2 (OCH_3), 112.8, 114.0, 124.7, 124.8, 125.5, 126.3, 126.5, 127.2, 127.8, 133.4, 133.6, 138.5, 143.8, 144.9, 146.5, 147.9, 149.7, 159.5, 168.0 (19C, Ar-C); MS (EI, 70 eV) *m/z* (%): 530 (M$^+$, 73.02), 325 (55.13), 279 (64.19), 164 (71.96), 149 (66.98), 121 (45.49), 76 (100.00); Anal. Calcd. for $C_{26}H_{22}N_6O_3S_2$ (530.6): C, 58.85; H, 4.18; N, 15.84; S, 12.08. Found: C, 58.92; H, 4.10; N, 15.91; S, 12.17.

2-(2-(1-(5-Methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1*H*-pyrazol-4-yl)ethylidene)hydrazinyl)-4-(4-nitrophenyl)thiazole (12e). Yield (85%); orange crystals (DMF+EtOH), mp 260-262 °C, IR (ν_{max}, cm^{-1}) ν 3449 (NH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 6.99-7.02 (m, 1H, Thienyl-H), 7.12-7.72 (m, 9H, Ar-H), 8.32 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz) and 11.20 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 18.5 ($2CH_3$), 102.3, 112.4, 124.7, 125.4, 126.2, 127.2, 127.6, 128.7, 128.9, 131.3, 133.5, 138.7, 139.3, 143.7, 144.6, 146.2, 146.7, 168.4, 169.3 (19C, Ar-C); Anal. Calcd. for $C_{25}H_{19}N_7O_4S_2$ (545.59): C, 55.04; H, 3.51; N, 17.97; S, 11.75. Found: C, 55.11; H, 3.59; N, 17.90; S, 11.83.

4-(4-Chlorophenyl)-2-(2-(1-(5-methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1*H*-pyrazol-4-yl)ethylidene)hydrazinyl)thiazole (12f). Yield (82%); yellow crystals (CH_3CN), mp 214-216 °C, IR (ν_{max}, cm^{-1}) ν 3448 (NH); ^{1}H NMR (300 MHz, DMSO–d_6) δ 2.45 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 6.71-6.73 (m, 1H, Thienyl-H), 6.89 (d, 1H, Thienyl-H, *J* 3 Hz), 7.45-8.07 (m, 8H, Ar-H), 8.52 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz) and 11.30 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO–d_6) δ 12.3, 18.7 ($2CH_3$), 104.9, 109.3, 111.9, 119.8, 125.0, 125.3, 127.4, 128.8, 132.1, 133.9, 139.5, 142.6, 143.4, 143.8, 144.1, 146.2, 146.8, 150.3, 170.0 (19C, Ar-C); Anal. Calcd. for $C_{25}H_{19}ClN_6O_2S_2$ (535.0): C, 56.12; H, 3.58; Cl, 6.63; N, 15.71; S, 11.98. Found: C, 56.20; H, 3.51; Cl, 6.56; N, 15.79; S, 11.90.

4-(4-Bromophenyl)-2-(2-(1-(5-methyl-1-(4-nitrophenyl)-3-(2-thienyl)-1*H*-pyrazol-4-yl)ethylidene)hydrazinyl)thiazole (12g). Yield (86%); yellow crystals (DMF+EtOH), mp 236-238 °C, IR (ν_{max}, cm^{-1}) ν 3448 (NH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 6.63-6.64 (m, 1H, Thienyl-H), 6.69-7.87 (m, 9H, Ar-H), 8.51 (d, 2H, 4-$NO_2C_6H_4$, *J* 9 Hz) and 11.46 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 20.2 ($2CH_3$), 98.9, 109.6, 111.7, 113.1, 115.0, 117.4, 118.1, 119.9, 124.9, 125.3, 127.2, 139.5, 140.9, 143.7, 146.3, 146.8, 152.9, 161.3, 169.7 (19C, Ar-C); Anal. Calcd. for $C_{25}H_{19}BrN_6O_2S_2$ (579.49): C, 51.82; H, 3.30; Br, 13.79; N, 14.50; S, 11.06. Found: C, 51.75; H, 3.38; Br, 13.71; N, 14.57; S, 11.14.

Supplementary Material

Copies of the ^{1}H and ^{13}C NMR spectra of compounds **3, 6a-i, 10, 12a-g** and of the IR and GCMS spectra of **3, 6b, 10, 12b** are given in the supplementary material file associated with this manuscript.

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