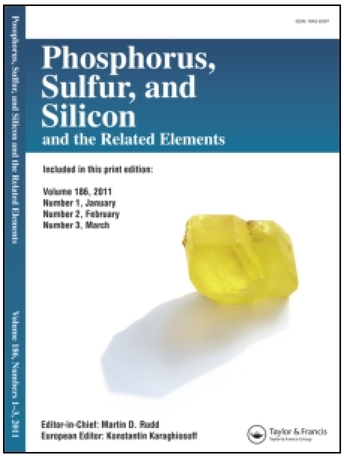

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SYNTHESIS AND CHARACTERIZATION OF SOME NEW HETEROCYCLES INCORPORATING THE 1-PHENYL-5-(2-THIENYL)PYRAZOLE MOIETY

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1-Phenyl-3-(2-thienyl)-1H-pyrazole-5-carbohydrazide 4 was prepared from 2-acetylthiophene by reaction with diethyl oxalate and phenylhydrazine followed by hydrazine hydrate. The reaction of the hydrazide 4 with phthalic anhydride, aromatic aldehydes, and alkene derivatives gave imide 5, hydrazones 6a–d, and bis-pyrazoles 7 and 8, respectively, while its reaction with phenyl isothiocyanate led to thiosemicarbazide 9. The reaction of the latter with ethyl bromoacetate and phenacylbromide afforded 4-thiazolidinone 10 and 1,3-thiazole 11 derivatives, respectively. Reaction of 4 with carbon disulfide in the presence of potassium hydroxide gave potassium hydrazinecarbodithioate derivative 12, which was used as a starting material in the preparation of 2-thioxothiazol-3(2H)-yl)-5-(2-thienyl)-1H-pyrazole-3-carboxamide 14; 1,3,4-thiadiazol-2(3H)-ylidene)-1-phenyl-5-(2-thienyl)-1H-pyrazole-3-carbohydrazides 16a–c; 4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)pyrazole derivative 13; Schiff bases 17a,b; and 1,2,4-triazolo[3,4-b][1,3,4]thiadiazine derivatives 18 and 19a–e.

Keywords 2-Acetylthiophene; acid hydrazides; bis-pyrazoles; 3-(2-thienyl)-1H-pyrazoles; 1,2,4-triazolo[3,4-b][1,3,4]thiadiazines

INTRODUCTION

A literature survey revealed that several nitrogen-, oxygen-, and sulfur-containing heterocyclic compounds incorporating thiophene residues have been found to possess interesting biological properties.[1–5] Hydrazides and their functional derivatives have been used to prepare a series of antitubercular and antibacterial preparations.[6,7] Many heterocyclic compounds directly prepared from hydrazides possess valuable biological and physicochemical properties.[8] In the same sense, compounds including a pyrazole nucleus are known to possess analgesic, anti-inflammatory, antipyretic, antiarrhythmic, tranquilizing, muscle relaxant, psychoanaleptic, anticonvulsant, hypotensive, monoamine oxidase inhibitor, antidiabetic, and antibacterial activities.[9–16] Also, some thiazole derivatives have been reported to possess tuberculostatic, antibacterial, and antifungal activities.[17–21]

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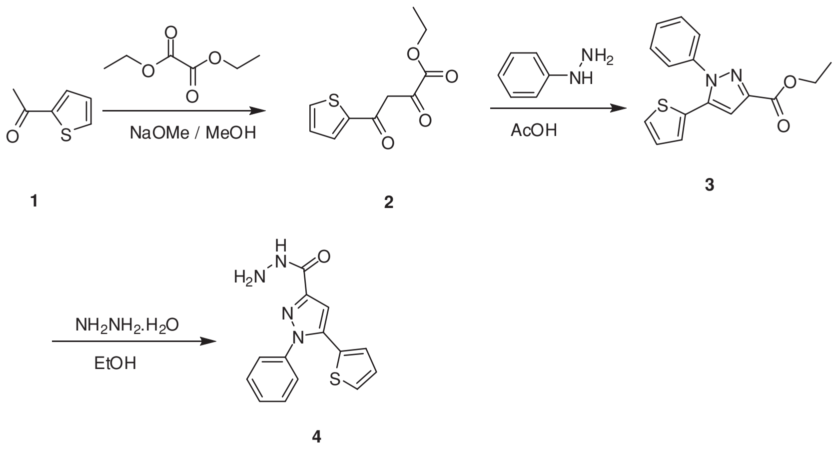
Moreover various sulfur compounds have been found to have other biological properties.[22–25] In view of these reports and in continuation with our previous work in the synthesis of biologically active heterocycles,[26–30] in this article we detail our synthesis of some new heterocycles with 1-phenyl-5-(thiophen-2-yl)-pyrazole moiety.

RESULTS AND DISCUSSION

Ethyl 2-thienoylpyruvate **2** was prepared by the reaction of 2-acetylthiophene with diethyl oxalate in sodium methoxide.[31] The reaction of **2** with phenylhydrazine in boiling acetic acid led to ethyl pyrazole-3-carboxylate derivative **3**, and the action of hydrazine hydrate on the ester **3** gave the target hydrazide **4** (Scheme 1).

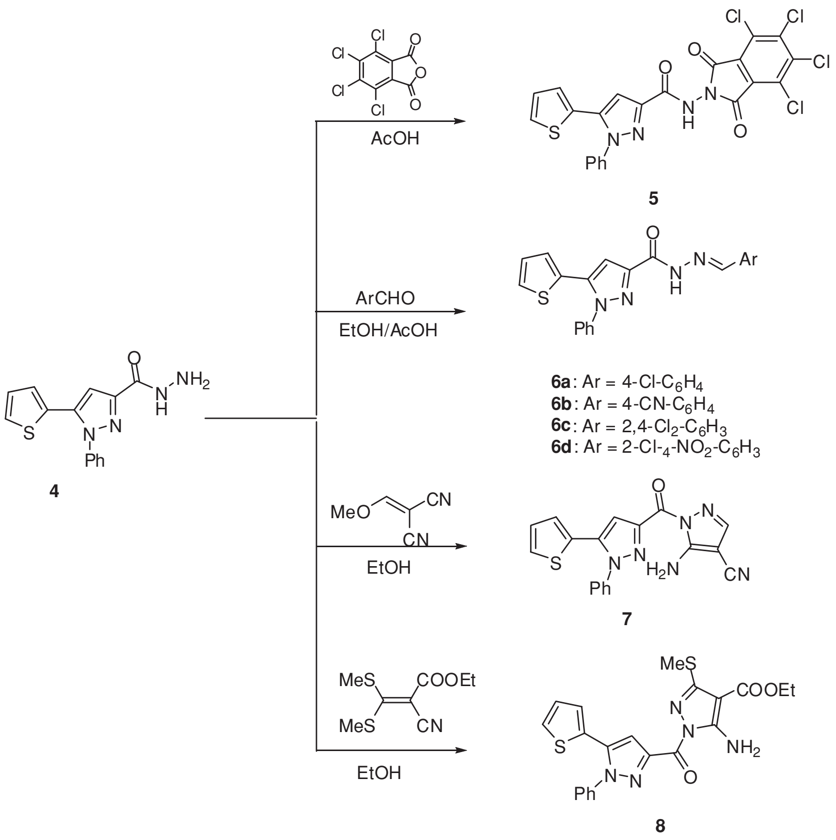


Scheme 1

The structure of compounds **3** and **4** was confirmed by their spectral data. For example, the IR spectrum of ester **3** showed a characteristic absorption band at 1727 cm^{-1} due to the presence of the ester-carbonyl group, while the IR spectrum of the hydrazide **4** showed sharp absorption bands at 3311, 3253 and 3215 cm^{-1} attributed to the NH_2 and NH groups.

Treatment of the acid hydrazide **4** with tetrachlorophthalic anhydride in refluxing glacial acetic acid afforded the imide **5**. The IR spectrum of compound **5** showed three absorption bands in the region 1685–1778 cm^{-1} characteristic for three carbonyl groups. Also its mass spectrum displayed a molecular ion peak at *m/z* 414, which was in agreement with the calculated mass and molecular formula. The reaction of **4** with different aromatic aldehydes, namely, 4-chlorobenzaldehyde, 4-cyanobenzaldehyde, 2,4-dichlorobenzaldehyde, and 2-chloro-4-nitrobenzaldehyde, afforded the corresponding hydrazones **6a–d**. The ^1H NMR spectrum of **6d** showed a singlet proton at δ 9.84 ppm attributed to $-C\underline{H}=N-$ (Scheme 2).

In the same sense, the reaction of hydrazide **4** with alkenes derivatives, namely 2-(methoxymethylene)malononitrile or ethyl 2-cyano-3,3-bis(methylthio)acrylate, in refluxing ethanol afforded the bi-pyrazole derivatives **7** and **8**, respectively. The IR spectrum of compound **7** showed characteristic absorption band at 2222 cm^{-1} due to the presence



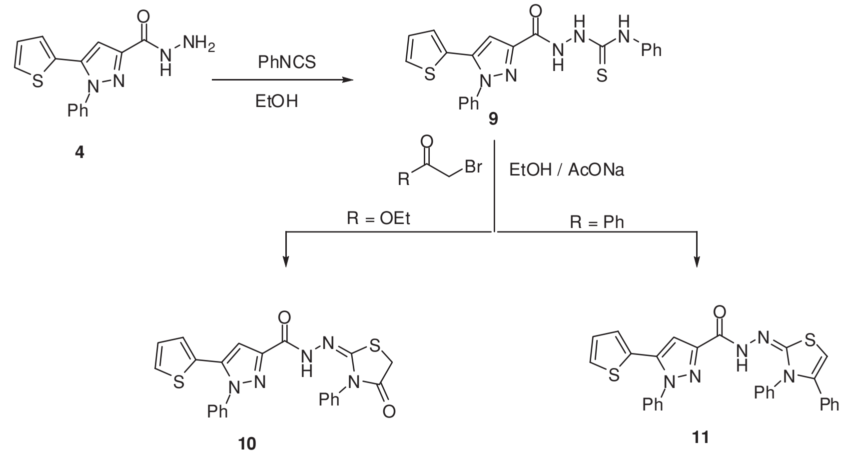
Scheme 2

of carbonitrile group, while the IR spectrum of compound **8** revealed absorption bands at 3317 and 3361 cm^{-1} indicating the presence of an amino group (Scheme 2).

On the other hand, acid hydrazides have long been known to react with isothiocyanates and α-haloketones to afford a variety of heterocyclic derivatives.[32–37] Thus, thiosemicarbazide **9** was achieved by the reaction of hydrazide **4** with phenylisothiocyanate, which upon treatment with ethyl bromoacetate or phenacyl bromide in boiling ethanol containing anhydrous sodium acetate, afforded 4-thiazolidinone **10** and 1,3-thiazole **11**, respectively (Scheme 3).

The IR spectrum of **10** revealed an absorption band at 1645 and 1680 cm^{-1} due to the two carbonyl groups, while its ^{1}H NMR showed a singlet signal at δ 4.12 ppm corresponding to the methylene protons of the thiazolidene ring. ^{1}H NMR of compound **11** displayed one singlet at δ 5.45 ppm corresponding to the thiazole ring proton.

Acid hydrazides can be considered as useful intermediates leading to the formation of several heterocycles such as 1,2,4-triazoles and 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines.[38,39] Treatment of **4** with carbon disulfide in ethanol, in the presence of potassium hydroxide, resulted in the formation of potassium salt of hydrazinecarbodithioate **12**. Treatment of the salt **12** with hydrazine hydrate in aqueous ethanol afforded the corresponding 4-amino-1,2,4-triazole-5-thione **13**. Reaction of **12** with phenacyl bromide in refluxing ethanol



Scheme 3

afforded thiazolidene derivative **14**, while its reaction with some hydrazonoyl chlorides **15a–c** in refluxing ethanol gave **16a–c** (Scheme 4).

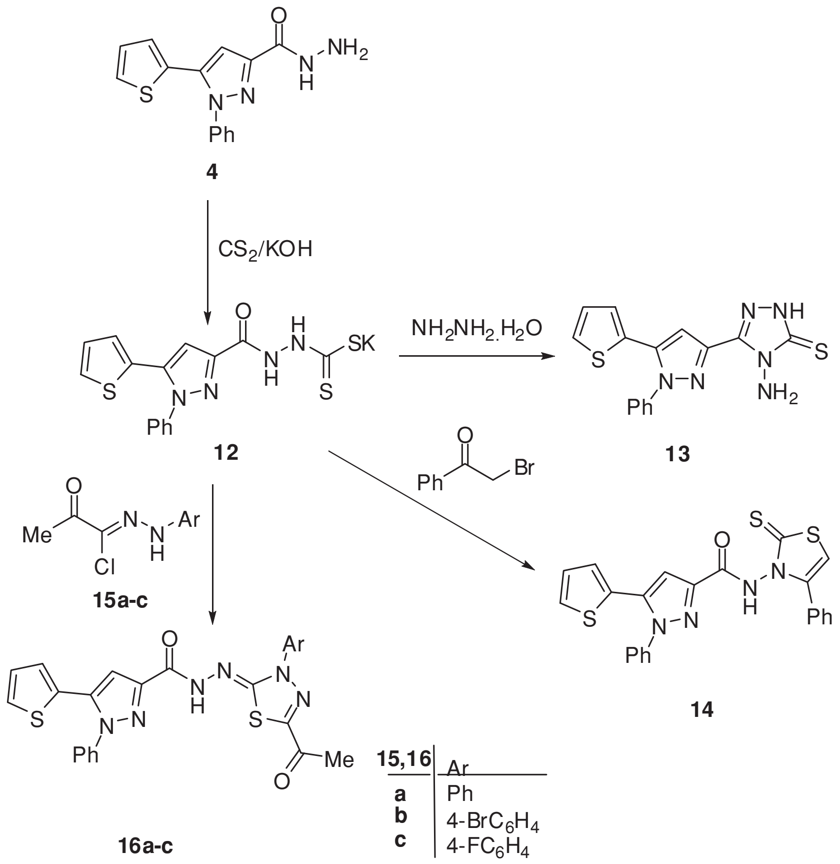
The structures of compounds **13**, **14**, and **16a–c** were in agreement with spectral and analytical data. For example, the IR spectrum of compound **13** revealed absorption bands at 3315, 3108, 3094 cm^{-1} corresponding to NH and NH_2 groups, while the ^{1}H NMR of compound **14** displayed a singlet at 8.09 ppm attributed to C$\underline{H}$ of 2-thioxothiazole ring, and the mass spectra of **13**, **14**, and **16a** displayed molecular ion peaks at *m/z* 340, 460, and 486, respectively, which was in agreement with their calculated masses.

It worth mentioning that the Schiff bases **17a**,**b** were produced by the reaction of 4-amino-1,2,4-triazole-5-thione derivative **13** with substituted benzaldehydes in refluxing ethanol containing a few drops of glacial acetic acid as a catalyst. The reaction of **13** with phenacyl bromide or hydrazonoyl chlorides **15a–e** in ethanol containing a catalytic amount of triethylamine furnished [1,2,4]triazolo[3,4-b][1,3,4]thiadiazine derivatives **18** and **19a–e**, respectively (Scheme 5).

The structures of compounds **17a**,**b**, **18**, and **19a–e** were established based on both microanalytical and spectral data. For example, the ^{1}H NMR spectrum of compound **17b** showed one singlet signal at δ 9.03 ppm attributed to $-N{=}C\underline{H}-$, while ^{1}H NMR of compound **18** showed a singlet signal at δ 5.21 ppm corresponding to the two protons of $-S-CH_2$ in thiadiazine ring. The mass spectrum of compound **19a** showed the molecular ion peak at m/z 561; this fitted exactly with the calculated mass.

EXPERIMENTAL

All melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data were obtained from the Microanalytical Unit, Cairo University, Giza, Egypt. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The ^{1}H NMR spectra were recorded at 270 MHz on a Varian EM-360 spectrometer using TMS as an internal standard. The mass spectra were performed using a Varian MAT CH-5 spectrometer (70 eV). All reactions were monitored by TLC (0.25 mm



15,16	Ar
a	Ph
b	4-BrC$_6$H$_4$
c	4-FC$_6$H$_4$

Scheme 4

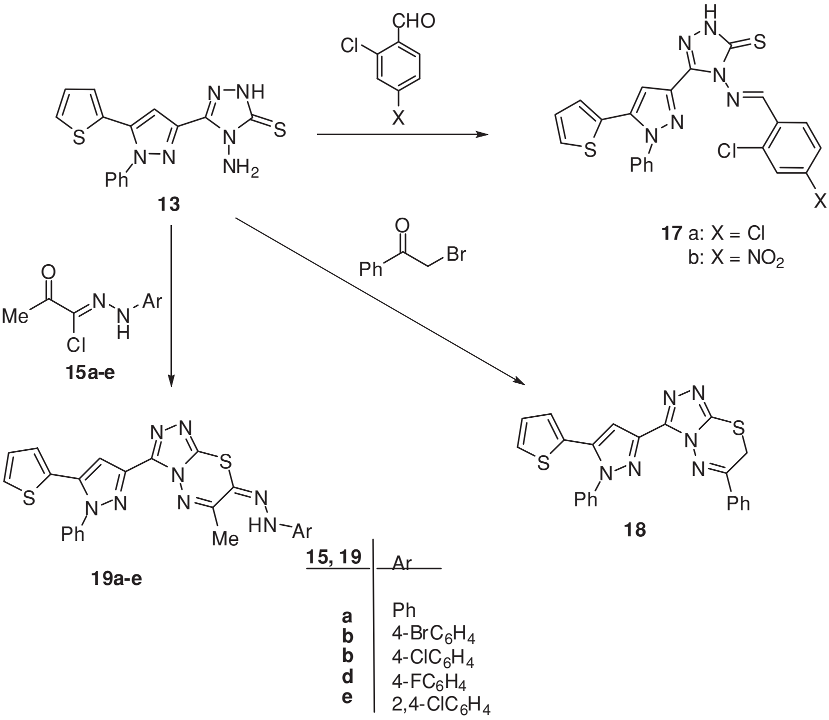
silica gel, aluminum sheets 60 F$_{254}$, Merck). Ethyl 2,4-dioxo-4-(thiophen-2-yl)butanoate was prepared according to the procedure in the literature.[31]

Ethyl 1-Phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carboxylate (3)

A mixture of ethyl 2,4-dioxo-4-(thiophen-2-yl)butanoate **2** (2.26 g, 10 mmol) of glacial acetic acid (30 mL) and phenylhydrazine (1.08 g, 10 mmol) was refluxed for 30 min, and then cooled and poured into water (200 mL). The precipitate was filtered off and recrystallized from dilute ethanol, giving 86% of **3** with mp 109–110°C (colorless). IR (KBr) ν_{max}/cm^{-1} 1631 (C=N); 1727 (C=O); ^{1}H NMR (DMSO-d$_6$): δ1.51 (t, 3H, CH$_3$), 4.22 (q, 2H, CH$_2$), 7.07 (s, 1H, pyrazole-H); 7.15–7.62 (m, 8H, Ar—H); Ms *m/z* (%): 298 (M$^+$, 100). Anal. Calcd. for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.53; H, 4.90; N, 9.51; S, 10.87.

1-Phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carbohydrazide (4)

To a solution of **3** (1.49 g, 5 mmol) in absolute ethanol (25 mL), hydrazine hydrate (1.2 mL, 15 mmol) was added, and the mixture was boiled until a chromatographic check showed



15, 19	Ar
a	Ph
b	4-BrC$_6$H$_4$
b	4-ClC$_6$H$_4$
d	4-FC$_6$H$_4$
e	2,4-ClC$_6$H$_4$

Scheme 5

the absence of **3** from the reaction mixture. The ethanol was distilled off, and the residue was poured into ice water (200 mL). The precipitate was filtered off and recrystallized from dilute ethanol, giving 82% of **4** with mp 158–159°C (colorless). IR(KBr) ν_{max}/cm^{-1} 1594 (C=N); 1661 (C=O); ^{1}H NMR (DMSO-d$_6$): δ 4.48 (s, 2H, NH$_2$, D$_2$O exchangeable), 7.07 (s, 1H, pyrazole-H); 7.10–7.59 (m, 8H, Ar—H), 9.61 (s, 1H, NH, D$_2$O exchangeable); Ms *m/z* (%): 284 (M$^+$, 100). Anal. Calcd. for $C_{14}H_{12}N_4OS$: C, 59.14; H, 4.25; N, 19.70; S, 11.28. Found: C, 59.31; H, 4.41; N, 19.79; S, 11.53.

N-(4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl)-1-phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carboxamide (5)

A mixture of **4** (0.28 g, 1 mmol) and tetrachlorophthalic anhydride (0.29 g, 1 mmol) in glacial acetic acid (25 mL) was refluxed for 5 h. The reaction mixture was evaporated under reduced pressure. The obtained residue was solidified with ether, filtered off, and crystallized from AcOH-H$_2$O to give 86% of **5** with mp 256–257°C (colorless). IR(KBr) ν_{max}/cm^{-1} 1595 (C=N); 1685, 1741, 1778 (3C=O); ^{1}H NMR (DMSO-d$_6$): δ 7.03 (s, 1H, pyrazole-H); 7.17–7.62 (m, 8H, Ar—H), 9.62 (s, 1H, NH, D$_2$O exchangeable); Ms *m/z* (%):552 (M$^+$, 43), 284 (100). Anal. Calcd. for $C_{22}H_{10}C_{14}N_4O_3S$: C, 47.85; H, 1.83; N, 10.15; S, 5.81. Found: C, 48.02; H, 1.91; N, 10.32; S, 5.94.

Synthesis of Hydrazones 6a–d

A mixture of **4** (0.28 g, 1 mmol) and the appropriate aromatic aldehydes, namely 4-chlorobenzaldehyde, 4-cyanobenzaldehyde, 2,4-dichlorobenzaldehyde, or 2-chloro-4-nitrobenzaldehyde (1 mmol), in absolute ethanol (30 mL) in the presence of few drops of glacial acetic acid was refluxed for 2 h. The formed solid was filtered off, dried, and crystallized from EtOH/DMF (3:1) to give **6a–d**.

N′-(4-Chlorobenzylidene)-1-phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carbo hydrazide (6a). Yield (83%, colorless); mp 218–220°C; IR(KBr) ν_{max}/cm^{-1} 1608 (C=N); 1662 (C=O); ^1H NMR (DMSO-d_6): δ 7.06 (s, 1H, pyrazole-H); 7.14–7.63 (m, 12H, Ar—H), 9.87 (s, 1H, CH); 12.3 (s, 1H, NH, D_2O exchangeable); Ms *m/z* (%): 406 (M^+, 100). Anal. Calcd. for $C_{21}H_{15}ClN_4OS$: C, 61.99; H, 3.72; N, 13.77; S, 7.88. Found: C, 62.31; H, 3.86; N, 13.84; S, 8.12.

N′-(4-Cyanobenzylidene)-1-phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carbo hydrazide (6b). Yield (68%, colorless); mp 200–201°C; IR(KBr) ν_{max}/cm^{-1} 1612 (C=N), 1699 (C=O), 2222 (CN); ^1H NMR (DMSO-d_6): δ 7.03 (s, 1H, pyrazole-H); 7.12–7.66 (m, 12H, Ar—H), 9.89 (s, 1H, CH); 12.34 (s, 1H, NH, D_2O exchangeable); Ms *m/z* (%): 397 (M^+, 100). Anal. Calcd. for $C_{22}H_{15}N_5OS$: C, 66.48; H, 3.80; N, 17.62; S, 8.07. Found: C, 66.58; H, 3.94; N, 17.78; S, 8.22.

N′-(2,4-Dichlorobenzylidene)-1-phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carbohydrazide (6c). Yield (76%, colorless); mp 236–237°C; IR(KBr) ν_{max}/cm^{-1} 1609 (C=N), 1691 (C=O); ^1H NMR (DMSO-d_6): δ 7.03 (s, 1H, pyrazole-H); 7.10–7.63 (m, 11H, Ar—H), 9.88 (s, 1H, CH); 12.43 (s, 1H, NH, D_2O exchangeable); Ms *m/z* (%): 441(M^+, 100). Anal. Calcd. for $C_{21}H_{14}Cl_2N_4OS$: C, 57.15; H, 3.20; N, 12.69; S, 7.27. Found: C, 57.31; H, 3.54; N, 12.78; S, 7.46.

N′-(2-Chloro-4-nitrobenzylidene)-1-phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carbohydrazide (6d). Yield (88%, colorless); mp 241–243°C; IR(KBr) ν_{max}/cm^{-1} 1621 (C=N), 1685 (C=O); ^1H NMR (DMSO-d_6): δ 7.06 (s, 1H, pyrazole-H); 7.12–7.65 (m, 11H, Ar—H), 9.84 (s, 1H, CH); 12.51 (s, 1H, NH, D_2O exchangeable); Ms *m/z* (%): 451(M^+, 100). Anal. Calcd. for $C_{21}H_{14}ClN_5O_3S$: C, 55.82; H, 3.12; N, 15.50; S, 7.10. Found: C, 55.91; H, 3.34; N, 15.79; S, 7.26.

Synthesis of Bis-pyrazoles 7 and 8

To a solution of **4** (0.28 g, 1 mmol) in anhydrous ethanol (20 mL), 2-(methoxy methylene)malononitrile (in the case of **7**) or ethyl 2-cyano-3,3-bis(methylthio)acrylate (in the case of **8**) (1 mmol) was added, and the reaction mixtures were refluxed for 4–6 h. The products, which separated upon cooling, were collected by filtration and recrystallized from ethanol to give compounds **7** and **8**, respectively.

5-Amino-1-(5-(thiophene-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-1H-pyra zole-4-carbonitrile (7). Yield (72%, colorless); mp >300°C; IR(KBr) ν_{max}/cm^{-1} 1635 (C=N); 1689 (C=O), 2222 (CN), 3287, 3223 (NH_2); ^1H NMR (DMSO-d_6): δ 7.07 (s, 1H, pyrazole-H); 7.14–7.57 (m, 8H, Ar—H), 7.91 (s, 1H, CH), 10.32 (s, 2H, NH_2, D_2O exchangeable); Ms *m/z* (%): 360 (M^+, 36), 284 (100). Anal. Calcd. for $C_{18}H_{12}N_6OS$: C, 59.99; H, 3.36; N, 23.32; S, 8.90. Found: C, 60.21; H, 3.52; N, 23.49; S, 9.07.

Ethyl 5-Amino-1-(5-(thiophen-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-3-(methylthio)-1H-pyrazole-4-carboxylate (8). Yield (62%, gray); mp 194–195°C; IR(KBr) ν_{max}/cm^{-1} 1626 (C=N); 1674 (C=O), 1697 (C=O, ester), 3361, 3317 (NH_2);

^{1}H NMR (DMSO-d$_6$): 1.33(t, 3H, CH$_3$), 2.49 (s, 3H, SCH$_3$), 4.36 (q, 2H, CH$_2$), δ 7.06 (s, 1H, pyrazole-H); 7.15–7.62 (m, 8H, Ar—H), 9.96 (s, 2H, NH$_2$, D$_2$O exchangeable); Ms *m/z* (%): 453 (M$^+$, 31), 284 (100). Anal. Calcd. for $C_{21}H_{19}N_5O_3S_2$: C, 55.61; H, 4.22; N, 15.44; S, 14.14. Found: C, 55.72; H, 4.51; N, 15.68; S, 14.31.

2-(5-(Thiophen-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-N-phenylhydrazinecarbothioamide (9)

A mixture of **4** (1.42 g, 5 mmol) and phenylisothiocyante (0.67 g, 5 mmol) in absolute ethanol (30 mL) was heated under reflux for 3 h. The formed solid was filtered off and recrystallized from ethanol-dimethyl formamide, giving 78% of **9** with mp 208–210°C (colorless). ν_{max}/cm^{-1} 1269 (C=S), 1601 (C=N); 1649 (C=O), 3303–3148 (NH); ^{1}H NMR (DMSO-d$_6$): δ 7.07 (s, 1H, pyrazole-H); 7.10–7.62 (m, 13H, Ar—H), 975, 10.42 (2s, 3H, 3NH, D$_2$O exchangeable); Ms *m/z* (%): 419 (M$^+$, 12), 284 (100). Anal. Calcd. for $C_{21}H_{17}N_5OS_2$: C, 60.12; H, 4.08; N, 16.69; S, 15.29. Found: C, 60.32; H, 4.21; N, 16.77; S, 15.41.

5-(Thiophen-2-yl)-N′-(4-oxo-3-phenylthiazolidin-2-ylidene)-1-phenyl-1H-pyrazole-3-carbohydrazide (10)

A mixture of **9** (0.42 g, 1 mmol) and ethyl bromoacetate (0.17 g, 1 mmol) in absolute ethanol (30 mL) containing anhydrous sodium acetate (0.33 g, 4 mmol) was heated under reflux for 6 h. The reaction mixture was cooled, diluted with water, and allowed to stand overnight. The precipitated solid was filtered off and recrystallized from ethanol to give **10** in 58% with mp 159–160°C (colorless). IR(KBr) ν_{max}/cm^{-1} 1612 (C=N); 1645 (C=O), 1739 (C=O), 3423 (NH); ^{1}H NMR (DMSO-d$_6$): δ 4.12 (s, 2H, CH$_2$), 4.17 (s, 1H, NH, D$_2$O exchangeable), 7.06 (s, 1H, pyrazole-H), 7.12–7.66 (m, 13H, Ar—H); Ms *m/z* (%): 459 (M$^+$, 16), 77 (100). Anal. Calcd. for $C_{23}H_{17}N_5O_2S_2$: C, 60.11; H, 3.73; N, 15.24; S,13.96. Found: C, 60.32; H, 3.96; N, 15.42; S, 14.08.

5-(Thiophen-2-yl)-N′-(3,4-diphenylthiazol-2-(3H)-ylidene)-1-phenyl-1H-pyrazole-3-carbohydrazide (11)

A mixture of **9** (0.42 g, 1 mmol) and phenacylbromide (0.2 g, 1 mmol) in absolute ethanol (30 mL) containing anhydrous sodium acetate (0.33 g, 4 mmol) was heated under reflux for 6 h. The reaction mixture was cooled, and the formed solid was filtered off and recrystallized from ethanol-DMF to give **11** (58%) with mp 197–198°C (colorless). IR(KBr) ν_{max}/cm^{-1} 1608(C=N); 1641 (C=O), 3402 (NH); ^{1}H NMR (DMSO-d$_6$): δ 5.45 (s, 1H, thiazole-H), 7.03 (s, 1H, pyrazole-H), 7.10–7.64 (m, 18H, Ar—H); 10.78 (s, 1H, NH, D$_2$O exchangeable); Ms *m/z* (%): 519 (M$^+$, 22), 77 (100). Anal. Calcd. for $C_{29}H_{21}N_5OS_2$: C, 67.03; H, 4.07; N, 13.48; S, 12.34. Found: C, 67.31; H, 4.24; N, 13.71; S, 12.53.

Potassium 2-(1-Phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carbonyl) hydrazinecarbodithioate (12)

To a solution of hydrazide **4** (2.84 g, 10 mmol) in ethanol (100 mL), a solution of potassium hydroxide (0.84 g, 15 mmol) in water (10 mL) and carbon disulfide (5 mL) was added. The reaction mixture was heated under reflux for 3 h. The solvent was evaporated under reduced pressure until dryness, then the residue was treated with dry benzene (30 mL). The formed precipitate was collected by filtration, washed with ether, and dried to afford the potassium salt **12** (80% yield, colorless). IR (KBr) ν_{max}/cm^{-1} 3370, 3130 (2NH), 1650 (C=O) cm^{-1}.

4-Amino-3-(1-phenyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-1H-1,2,4-triazole-5(4H)-thione (13)

To a solution of potassium salt **12** (3.97 g, 10 mmol) in ethanol (20 mL) and water (20 mL), hydrazine hydrate (1 mL) was added. The reaction mixture was heated under reflux for 3 h, left to cool, and then poured in crushed ice. The resulted solution was acidified with dilute hydrochloric acid to pH 7. The resulting solid was collected by filtration, washed with water, and crystallized from ethanol to give 1,2,4-triazole-5-thione derivative **13** in 73% yield with mp 219–220°C (pale yellow). IR (KBr) ν_{max}/cm^{-1} 1296 (C=S), 1625 (C=N); 3315, 3108, 3094 (NH_2 and NH); ^{1}H NMR (DMSO-d$_6$): δ 7.06 (s, 1H, pyrazole-H); 7.15–7.63 (m, 8H, Ar—H), 10.02 (s, 2H, NH_2, D_2O exchangeable), 12.99 (s, 1H, NH, D_2O exchangeable); MS *m/z* (%): 340 (M$^+$, 25.78), 326 (100). Anal. Calcd. for $C_{15}H_{12}N_6S_2$: C, 52.92; H, 3.55; N, 24.69; S, 18.84. Found: C, 52.97; H, 3.93; N, 25.01; S, 19.10.

1-Phenyl-N-(4-phenyl-2-thioxothiazol-3(2H)-yl)-5-(thiophen-2-yl)-1H-pyrazole-3-carboxamide (14)

A mixture of potassium salt **12** (0.79 g, 2 mmol) and phenacyl bromide (0.4 g, 2 mmol) in ethanol (20 mL) was heated under reflux for 3 h. The formed solid was collected by filtration, washed with ethanol, dried, and recrystallized from ethanol/DMF to afford thiazole derivative **14** in 58% yield with mp 213–215°C (colorless); IR (KBr) ν_{max}/cm^{-1} 1592 (C=N), 1676 (C=O), 3116 (NH); ^{1}H NMR (DMSO-d$_6$): δ 7.08 (s, 1H, pyrazole-H), 7.21–8.02 (m, 13H, Ar—H), 8.09 (s, 1H, CH), 9.31 (s, 1H, NH, D_2O exchangeable); MS *m/z* (%): 460 (M$^+$, 0.11), 105 (100). Anal. Calcd. for $C_{23}H_{16}N_4OS_3$: C, 59.98; H, 3.50; N, 12.16; S, 20.88. Found: C, 60.21; H, 3.93; N, 12.32; S, 21.09.

N′-(5-Acetyl-3-aryl1,3,4-thiadiazol-2(3H)-ylidene)-1-phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carbohydrazides (16a–c)

To a solution of potassium salt **12** (0.79 g, 2 mmol) in ethanol (20 mL), the appropriate hydrazonoyl chloride **15a–c** (2 mmol) was added. The reaction mixture was heated under reflux for 3 h. The formed solid was collected by filtration, washed with ethanol, dried, and recrystallized from ethanol/DMF to afford **16a–c**.

N′-(5-Acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-1-phenyl-5-(thio phen-2-yl)-1H-pyrazole-3-carbohydrazide (16a). Yield (84%, dark yellow), mp 280–82°C; IR (KBr) ν_{max}/cm^{-1} 1614 (C=N); 1673 (C=O), 3110 (NH); ^{1}H NMR (DMSO-d$_6$): δ 2.57 (s, 3H, CH_3), 7.05 (s, 1H, pyrazole-H); 7.13–8.02 (m, 13H, Ar—H), 11.28 (s, 1H, NH, D_2O exchangeable); MS *m/z* (%): 486 (M$^+$, 67.89), 253 (100). Anal. Calcd. for $C_{24}H_{18}N_6O_2S_2$: C, 59.24; H, 3.73; N, 17.27; S, 13.18. Found: C, 59.51; H, 3.97; N, 17.42; S, 13.39.

N′-(5-Acetyl-3-(4-bromophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-1-phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carbohydrazide (16b). Yield (86%, orange) mp 217–218°C; IR (KBr) ν_{max}/cm^{-1} 1608 (C=N); 1680 (C=O), 3182 (NH); ^{1}H NMR (DMSO-d$_6$): δ 2.54 (s, 3H, CH_3), 7.03 (s, 1H, pyrazole-H); 7.17–8.02 (m, 12H, Ar—H), 11.15 (s, 1H, NH, D_2O exchangeable); MS *m/z* (%): 565 (M$^+$, 67.20), 253 (100). Anal.

Calcd. for $C_{24}H_{17}BrN_6O_2S_2$: C, 50.98; H, 3.03; N, 14.86; S, 11.34. Found: C, 51.23; H, 3.98; N, 15.02; S, 11.63.

N′-(5-Acetyl-3-(4-fluorophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-1-phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carbohydrazide (16c). Yield (79%, orange), mp 193–195°C; IR (KBr) ν_{max}/cm^{-1} 1613 (C=N); 1681 (C=O), 3188 (NH); ^1H NMR (DMSO-d_6): δ 2.52 (s, 3H, CH_3), 7.04 (s, 1H, pyrazole-H); 7.15–7.98 (m, 12H, Ar—H), 11.22 (s, 1H, NH, D_2O exchangeable); MS *m/z* (%): 504 (M^+, 55.02), 253 (100). Anal. Calcd. for $C_{24}H_{17}FN_6O_2S_2$: C, 57.13; H, 3.40; N, 16.66; S, 12.71. Found: C, 57.43; H, 3.67; N, 16.93; S, 12.91.

4-(Arylideneamino)-3-(1-phenyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-1H-1,2,4-triazole-5(4H)-thione (17a,b)

A mixture of appropriate aromatic aldehyde (2 mmol) and 4-amino-1,2,4-triazole-5(4H)-thione derivative **13** (0.68 g, 2 mmol) in ethanol (20 mL) in the presence of glacial acetic acid (0.2 mL) was refluxed for 4 h. The solid product was collected by filtration, washed with ethanol, and crystallized from EtOH/DMF to afford **17a**,**b**.

4-(2,4-Dichlorobenzylideneamino)-3-(1-phenyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-1H-1,2,4-triazole-5(4H)-thione (17a). Yield (87%, yellow), mp 203–205°C; IR (KBr) ν_{max}/cm^{-1} 1621 (C=N); 3100 (NH); ^1H NMR (DMSO-d_6): δ 7.08 (s, 1H, pyrazole-H); 7.22–7.86 (m, 11H, Ar—H), 9.01 (s, 1H, CH), 12.41 (s, H, NH, D_2O exchangeable); MS *m/z* (%): 497 (M^+, 58.02), 89(100). Anal. Calcd. for $C_{22}H_{14}Cl_2N_6S_2$: C, 53.12; H, 2.84; N, 16.90; S, 12.89. Found: C, 53.42; H, 3.11; N, 17.09; S, 13.12.

4-(2-Chloro-4-nitrobenzylideneamino)-3-(1-phenyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-1H-1,2,4-triazole-5(4H)-thione (17b). Yield (83%, yellow), mp 224–225°C; IR (KBr) ν_{max}/cm^{-1} 1618 (C=N); 3187 (NH); ^1H NMR (DMSO-d_6): δ 7.07 (s, 1H, pyrazole-H); 7.20–7.89 (m, 11H, Ar—H), 9.03 (s, 1H, CH), 12.38 (s, H, NH, D_2O exchangeable); MS *m/z* (%): 507 (M^+, 58.02), 89(100). Anal. Calcd. for $C_{22}H_{14}ClN_7O_2S_2$: C, 52.02; H, 2.78; N, 19.30; S, 12.62. Found: C, 52.31; H, 3.04; N, 19.54; S, 12.91.

6-Phenyl-3-(1-phenyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (18)

A mixture of **13** (0.68 g, 2 mmol) and phenacyl bromide (0.4 g, 2 mmol) in absolute ethanol (30 mL) containing a catalytic amount of triethyl amine was heated under reflux for 3 h. The formed precipitate was filtered off, washed with ethanol, dried, and recrystallized from EtOH/DMF to give 75% of **18** with mp 210–212°C (colorless). IR (KBr) ν_{max}/cm^{-1} 1602(C=N); ^1H NMR (DMSO-d_6): δ 5.21 (s, 2H, CH_2), 7.08 (s, 1H, pyrazole-H); 7.21–8.09 (m, 13H, Ar—H); MS *m/z* (%): 440 (M^+, 3.99), 105 (100). Anal. Calcd. for $C_{23}H_{16}N_6S_2$: C, 62.71; H, 3.66; N, 19.08; S, 14.56. Found: C, 62.97; H, 3.89; N, 19.43; S, 14.76.

6-Methyl-3-(1-phenyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-7-(2-arylhydrazono)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (19a–e)

A mixture of 1,2,4-triazole-5-thione **13** (0.68 g, 2 mmol) and the appropriate hydrazonyl chloride (2 mmol) in absolute ethanol (30 mL) containing 2 mmol of triethyl amine was heated under reflux for 3 h. The precipitated solid was collected by filtration, washed with ethanol, dried, and then crystallized from EtOH/DMF to afford **19a–e**.

6-Methyl-3-(1-phenyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-7-(2-phenylhydrazono)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (19a). Yield (68%, orange), mp 280–281°C; IR (KBr) ν_{max}/cm^{-1} 1612 (C=N); ^1H NMR (DMSO-d_6): δ 2.61 (s, 3H, CH_3), 7.03 (s, 1H, pyrazole-H); 7.10–7.64 (m, 13H, Ar—H), 10.31 (s, 1H, NH, D_2O exchangeable); MS *m/z* (%): 482 (M^+, 6.03), 105 (100). Anal. Calcd. for $C_{24}H_{18}N_8S_2$: C, 59.73; H, 3.76; N, 23.22; S, 13.29. Found: C, 59.97; H, 3.81; N, 23.52; S, 13.73.

7-(2-(4-Bromophenyl)hydrazono)-6-methyl-3-(1-phenyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (19b). Yield (71%, red), mp 225–226°C; IR (KBr) ν_{max}/cm^{-1} 1610 (C=N); ^1H NMR (DMSO-d_6): δ 2.56 (s, 3H, CH_3), 7.01 (s, 1H, pyrazole-H); 7.16–8.01 (m, 12H, Ar—H), 10.33 (s, 1H, NH, D_2O exchangeable); MS *m/z* (%): 561(M^+, 10.01), 105(100). Anal. Calcd. for $C_{24}H_{17}BrN_8S_2$: C, 51.34; H, 3.05; N, 19.96; S, 11.42. Found: C, 51.63; H, 3.32; N, 20.27; S, 11.62.

7-(2-(4-Chlorophenyl)hydrazono)-6-methyl-3-(1-phenyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (19c). Yield (71%, yellow), mp 216–218°C; IR (KBr) ν_{max}/cm^{-1} 1608 (C=N); ^1H NMR (DMSO-d_6): δ 2.53 (s, 3H, CH_3), 7.00 (s, 1H, pyrazole-H); 7.12–8.00 (m, 12H, Ar—H), 10.28 (s, 1H, NH, D_2O exchangeable); MS *m/z* (%): 517(M^+, 6.31), 105(100). Anal. Calcd. for $C_{24}H_{17}ClN_8S_2$: C, 55.75; H, 3.31; N, 21.67; S, 12.40. Found: C, 55.89; H, 3.78; N, 21.97; S, 12.84.

7-(2-(4-Flurophenyl)hydrazono)-6-methyl-3-(1-phenyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (19d). Yield (76%, red) mp 208–210°C; IR (KBr) ν_{max}/cm^{-1} 1611 (C=N); ^1H NMR (DMSO-d_6): δ 2.55 (s, 3H, CH_3), 7.01 (s, 1H, pyrazole-H); 7.14–8.06 (m, 12H, Ar—H), 10.23 (s, 1H, NH, D_2O exchangeable); MS *m/z* (%): 500(M^+, 11.36), 105(100). Anal. Calcd. for $C_{24}H_{17}FN_8S_2$: C, 57.59; H, 3.42; N, 22.39; S, 12.81. Found: C, 57.73; H, 3.81; N, 22.63; S, 12.96.

7-(2-(2,4-Dichlorophenyl)hydrazono)-6-methyl-3-(1-phenyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (19e). Yield (70%, dark yellow) mp 170–172°C; IR (KBr) ν_{max}/cm^{-1} 1618 (C=N); ^1H NMR (DMSO-d_6): δ 2.58 (s, 3H, CH_3), 7.01 (s, 1H, pyrazole-H); 7.10–7.94 (m, 11H, Ar—H), 10.49 (s, 1H, NH, D_2O exchangeable); MS *m/z* (%): 551(M^+, 15.36), 105(100). Anal. Calcd. for $C_{24}H_{16}Cl_2N_8S_2$: C, 52.27; H, 2.92; N, 20.32; S, 11.63. Found: C, 52.56; H, 2.30; N, 20.64; S, 11.94.

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