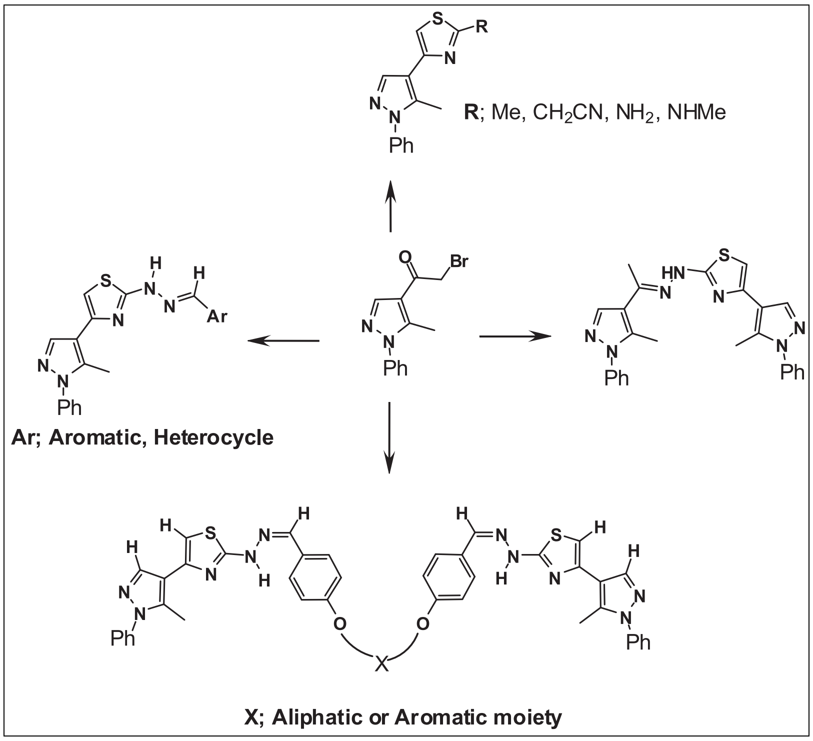
2-Bromo-1-(1*H*-pyrazol-4-yl)ethanone: Versatile Precursor for Novel Mono- and Bis[pyrazolylthiazoles]

Mostafa E. Salem,[a] Ahmed F. Darweesh,[a] Ahmed E. M. Mekky,[a,b] Ahmad M. Farag,[a] and Ahmed H. M. Elwahy[a*]

[a]Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt
[b]On leave to Chemistry Department, Faculty of Science, King Abdulaziz University, North Jeddah, P.O. Box 80203, Jeddah 21589, Saudi Arabia
*E-mail: aelwahy@hotmail.com

Additional Supporting Information may be found in the online version of this article.
Received July 28, 2015
DOI 10.1002/jhet.2571
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).



The synthesis of novel bis(thiazoles) **20a–c** and **23a–c** is reported. Thus, reaction of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**6**) with the corresponding thioamide derivatives **7a,b**, in refluxing EtOH in the presence of triethylamine, afforded 4-pyrazolylthiazoles **8a,b** in good yields. On the other hand, the novel bis(thiazoles) **20a–c** and **23a–c** were obtained from the reaction of **6** with the corresponding benzaldehyde thiosemicarbazones **19a–c**, **22a–c** in refluxing EtOH. Compounds **19a–c** and **22a–c** were obtained by condensation of the corresponding bis(aldehydes) **18a–c** and **21a–c** with thiosemicarbazide.

J. Heterocyclic Chem., **00,** 00 (2016).

INTRODUCTION

Compounds bearing pyrazole nucleus are well known to exhibit a versatile range of biological activities such as antimicrobial [1–4], anti-inflammatory [5–7], antidepressant [8], antiviral [9], and antitumor activities [10]. Among these, 4-functionalized pyrazoles occupy a unique position in medicinal chemistry because of their association with antimicrobial [11], anti-inflammatory [12], antiparasitic [13], and antitumor activities [14].

Moreover, thiazole derivatives have attracted increasing attention because of their numerous pharmacological applications and biological activities, such as anti-inflammatory, analgesic, antimicrobial, anti-HIV, antihypertensive, and herbicidal activity [15–21].

Furthermore, attention has been increasingly paid to the synthesis of bis-heterocyclic compounds in recent years, because of their diverse activities, especially, as antitumor and as antimicrobial [22–40].

Motivated by these findings, we report herein the synthesis of some novel mono- and bis-heterocyclic compounds incorporating a combination of pyrazole and thiazole pharmacophores. The combination of two pharmacophores into a single molecular skeleton is a well-established approach for designing more potent drugs with significant increase in activity.

RESULTS AND DISCUSSION

The desired starting building block; 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**6**) was obtained by a series of reactions as outlined in Scheme 1. Thus, reaction of phenylhydrazine **4** with 3-((dimethylamino) methylene)pentane-2,4-dione (**3**), obtained upon treatment of acetylacetone with dimethylformamide dimethylacetal (DMFDMA), afforded l-aryl-5-methyl-4-acetypyrazole **5** in good yield. Subsequent bromination of **5** with Br_2 in AcOH gave **6** in good yield [41–44] (Scheme 1).

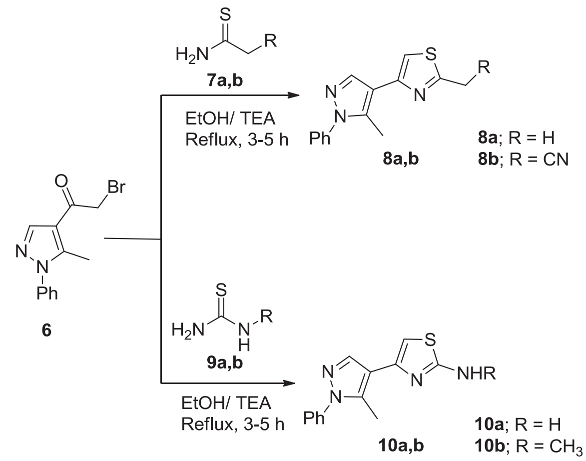
Reaction of compound **6** with the appropriate thioamide derivatives **7a,b**, in refluxing EtOH/TEA, afforded the corresponding 4-pyrazolylthiazoles **8a,b**. Similarly, 2-amino-4-pyrazolylthiazoles **10a,b** were obtained by the reaction of **6** with thiourea derivatives **9a,b** (Scheme 2**)**. The reaction was completed within 3–5 h and the products were obtained in good yields.

Our study was extended to include the synthesis of the new arylidenehydrazinyl-(1*H*-pyrazol-4-yl)thiazol derivatives **12a–i** as outlined in Scheme 3. Thus, reaction of the 4-bromoacetylpyrazole **6** with the corresponding thiosemicarbazone derivatives **11a–i** [45,46], in refluxing EtOH in the presence of few drops of TEA, afforded **12a–i** in 75–85% yields.

The new pyrazol-4-yl)ethylidene)hydrazinyl) arylthiazoles **16a–c** in which ethylidenehydrazinyl is located between the pyrazole and the thiazole ring were also synthesized as outlined in Scheme 4. Thus, reaction of the 2-(1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethylidene)hydrazinecarbothioamide (**14**) with the appropriate 2-bromo-1-arylethanone **15a–c** [45,46] in refluxing EtOH in the presence of few drops of TEA afforded (pyrazol-4-yl)ethylidene)hydrazinyl) arylthiazoles **16a–c** in 60–65% yields. Similarly, 4-(1*H*-pyrazol-4-yl)-2-(2-1*H*-pyrazol-4-yl)ethylidene)hydrazinyl)-thiazole (**17**) in which ethylidene)hydrazinyl)thiazole is located between two pyrazole rings was obtained in 73% yield by the reaction of compound **6** with **14**. Compound **14** was obtained in 73% yield upon treatment of **5** with thiosemicarabazide (**13**) in refluxing ethanol containing few drops of acetic acid (Scheme 4).

The utilization of the bis aldehydes **18a–e** as intermediates in the synthesis of novel bis(5-1*H*-pyrazol-4-yl)thiazol-2-yl) hydrazono)methyl)phenoxy)alkane **20a–e**, in which the pyrazolylthiazolyl hydrazone is linked to alkyl spacer *via* phenoxy group, was also investigated. Thus, reaction of the appropriate bis(aldehydes) **18a–e** with thiosemicarbazide (**13**) in refluxing EtOH containing few drops of AcOH, afforded the corresponding alkylenebis(oxy)bis(2,1-phenylene)bis (methan-1-yl-1-ylidene))bis (hydrazinecarbothioamide) **19a–e**. Subsequent reaction of the latter products with **6** in refluxing ethanol in the presence of few drops of TEA, afforded **20a–e** in 68–77% yields, respectively (Scheme 5).

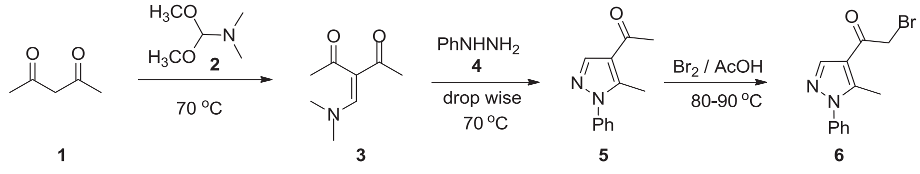
Scheme 2



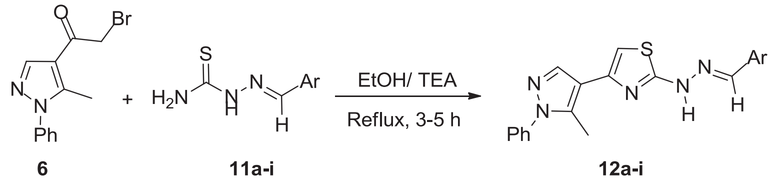
The same methodology was extended to the preparation of bis(1*H*-pyrazol-4-yl)thiazol-2-yl)hydrazono)methyl)phenoxy) arene **23a–c**, in which the pyrazolylthiazolylhydrazones is linked to benzene core *via* phenoxy group as depicted in Scheme 6. Thus, reaction of the appropriate bis(aldehydes) **21a–c** with thiosemicarbazide (**13**) in refluxing EtOH containing few drops of AcOH, gave the corresponding alkylenebis(oxy)bis(2,1-phenylene)bis(methan-1-yl-1-ylidene)) bis (hydrazinecarbothioamide) **22a–c** which upon reaction with **6** in refluxing ethanol in the presence of few drops of TEA, gave **23a–c** in 65–70% yields (Scheme 6).

All of the isolated compounds were characterized by elemental analyses, as well as their spectral data which agree with the proposed structures. The structure of aminothiazoles **10a**,**b** was confirmed by IR, ^{1}H-NMR and mass spectra. Thus, the IR spectrum of **10a**, as a representative example, showed absorption bands at 3349 and 3295 cm^{-1} because of NH_2. Moreover, the absence of the absorption band corresponding to carbonyl stretching frequency of the parent acyl bromide clearly confirmed the formation of **10a.** The ^{1}H NMR spectra of compound **10a** showed a D_2O-exchangeable

Scheme 1

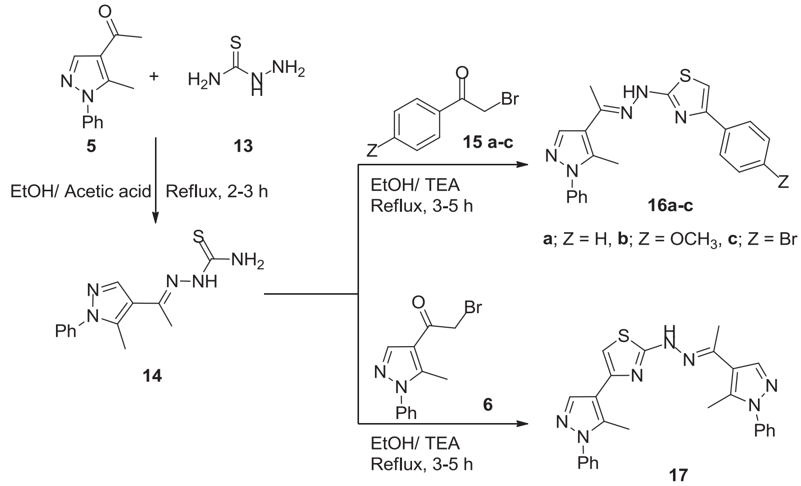


Scheme 3

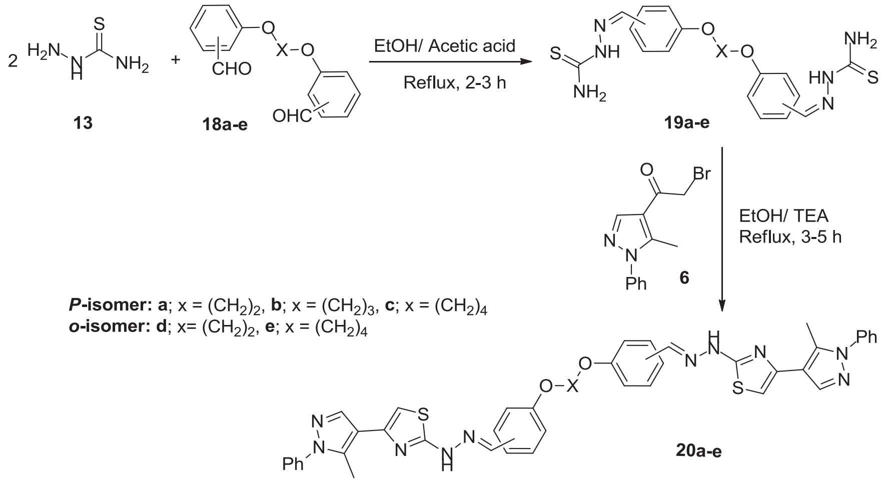


Ar; **a** = C_6H_5, **b** = 4-ClC_6H_4, **c** = 4-$O_2NC_6H_4$, **d** = 4-$Me_2NC_6H_4$, **e** = 4-MeC_6H_4
f = 4-$MeOC_6H_4$, **g** = 4-pyridyl, **h** = 3-pyridyl, **i** = 2-thiophene

Scheme 4



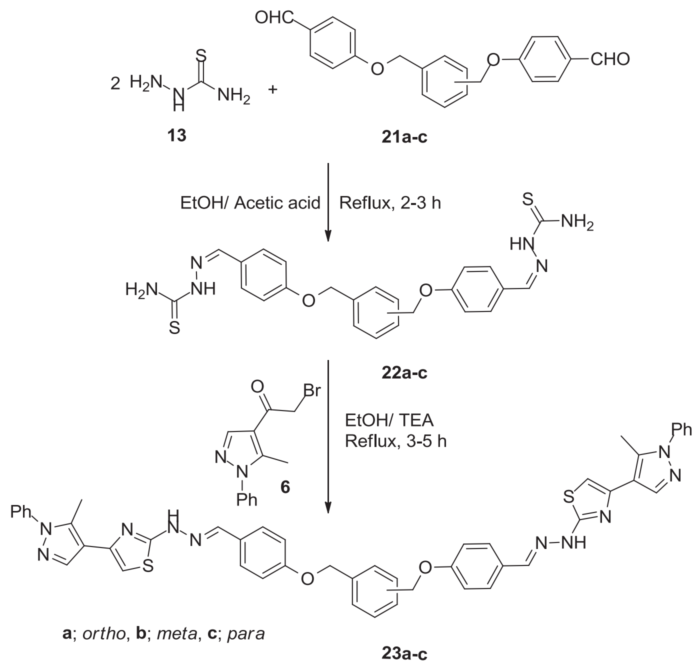
Scheme 5



signal at δ 5.17 because of NH_2 protons and a sharp singlet at δ 6.42 attributed to C-5 proton of the thiazole ring and at δ 7.90 attributed to the C-3 proton of the pyrazole ring. All other protons were seen at the expected chemical shifts and integral values. Mass spectrum of compound **10a** showed an intense molecular ion peak at *m/z* 256, in agreement with its respective molecular formula.

On the other hand, the IR spectrum of bis (thiazolylhydrazone) **20e** as a representative example of these class of compounds revealed an absorption band at

Scheme 6



3427 cm^{-1} because of (NH). Its ^{1}H NMR spectrum showed the presence of a characteristic singlet signal at δ 7.91 because of one methine proton (—N=CH—). Mass spectra of compound **20e** showed a molecular ion peaks at *m/z* 804 (M^+, 0.34%) which is in agreement with its respective molecular formula. The spectra of other bis(thiazoles) **23a–c** showed similar spectral data which are listed in the experimental part.

CONCLUSIONS

We have developed an efficient synthesis of hitherto unreported pyrazolylthiazoles as well as bis(pyrazolylthiazoles) which are linked to alkane or arene core *via* phenoxymethyl group. Full characterization of these compounds is reported. The new synthesized compounds are interesting both in their own right as unusual molecules and for their promising pharmacological and biological activities. Because of the mild reaction condition, good yields, and selectivity, easily accessible starting material and straightforward product isolation, we think that the new synthetic approach discussed here may offer effective new techniques for novel bis (functionalized) heterocycles of expected biological and pharmaceutical activities.

EXPERIMENTAL

General. Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer at 300 MHz (^{1}H NMR) and at 75 MHz (^{13}C NMR. Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMQP 1000 EX spectrometer. Analytical thin-layer chromatography was performed using precoated silica gel 60778 plates (Fluka), and the spots were visualized with UV light at 254 nm. The required bis-aldehydes **18a–e** and **21a–c** were synthesized following reported methods [47].

Synthesis of 4-pyrazolylthiazoles 8a,b. ***General procedure.*** To a mixture of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone (**6**) (2 mmol) and the appropriate thioamide derivatives **7** (2 mmol) in ethanol (20 mL), few drops of TEA were added. The reaction mixture was heated under reflux for 3–5 h, then allowed to cool. The solvent was evaporated in *vacuo*, and the solid residue was collected and recrystallized from ethanol to give the corresponding 4-pyrazolylthiazoles **8a**,**b**.

2-Methyl-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazole 8a. Yellow crystals, (70% yield), mp. 100–102°C; IR: (potassium bromide) 1589 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.55 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 7.03 (s, 1H, thiazole-5-H), 7.47–7.49 (m, 5H, ArH), 7.96 (s, 1H, pyrazole-3-H); ^{13}C-NMR: δ 11.89, 18.78, 111.8, 116.2, 124.8, 127.7, 129.1, 135.7, 138.9, 139.2, 147.7, 164.8; ms: *m/z* (%) 255 (100, M^+). *Anal.* Calcd. for $C_{14}H_{13}N_3S$: C, 65.85; H, 5.13; N, 16.46; S, 12.56. Found: C, 65.52; H, 5.05; N, 16.27; S, 12.33.

2-(4-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)acetonitrile 8b. Deep brown crystals, (65% yield), mp. 122–125°C; IR: (potassium bromide) 2251 (CN), 1589 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.57 (s, 3H, CH_3), 4.17 (s, 2H, CH_2CN), 7.22 (s, 1H, thiazole-5-H), 7.42–7.53 (m, 5H, ArH), 7.96 (s, 1H, pyrazole-3-H); ms: *m/z* (%) 280 (100, M^+). *Anal.* Calcd. for $C_{15}H_{12}N_4S$: C, 64.26; H, 4.31; N, 19.98; S, 11.44. Found: C, 64.12; H, 4.24; N, 19.76; S, 11.25.

Synthesis of 2-amino-4-pyrazolylthiazoles 10a,b. ***General procedure.*** To a mixture of **6** (2 mmol) and the appropriate thiourea derivatives **9** (2 mmol), in ethanol (20 mL), few drops of TEA were added and the reaction mixture was heated under reflux for 3–5 h, then allowed to cool. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from benzene-petroleum ether for **10a** and ethanol for **10b** to give the corresponding 2-amino-4-pyrazolylthiazoles **10a,b**.

4-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-amine 10a. Pale yellow powder, (70% yield), mp. 260–262°C; IR: (potassium bromide) 3349, 3295 (NH_2), 1594 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.52 (s, 3H, CH_3), 5.17 (s, 2H, NH_2), 6.42 (s, 1H, thiazole-5-H), 7.38–7.52 (m, 5H, ArH), 7.90 (s, 1H, pyrazole-3-H); ms: *m/z* (%) 256 (2.53, M^+). *Anal.* Calcd. for $C_{13}H_{12}N_4S$: C, 60.91; H, 4.72; N, 21.86; S, 12.51. Found: C, 60.75; H, 4.56; N, 21.54; S, 12.45.

N-methyl-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-amine 10b. Off-white powder, (65% yield), mp. 160–162°C; IR: (potassium bromide) 3428 (NH), 1562 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.53 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 6.64 (s, 1H, thiazole-5-H), 7.53–7.55 (m, 6H, ArH and NH), 7.88 (s, 1H, pyrazole-3-H); ms: *m/z* (%) 270 (100, M^+). *Anal.* Calcd. for $C_{14}H_{14}N_4S$: C, 62.20; H, 5.22; N, 20.72; S, 11.86. Found: C, 62.09; H, 5.14; N, 20.59; S, 11.64.

Synthesis of arylidenehydrazinyl-(1*H*-pyrazol-4-yl)thiazol 12a–i. ***General procedure.*** To a mixture of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**6**) (1 mmol) and the appropriate thiosemicarbazone **11** (1 mmol) in ethanol (20 mL), few drops of TEA were added, and the mixture was heated under reflux for 3–5 h. The reaction mixture was allowed to cool, and the solvent was evaporated in *vacuo*. The solid residue was collected by filtration and recrystallized from ethanol except for **12c** which was recrystallized from ethanol/DMF to give the corresponding arylidenehydrazinyl-(1*H*-pyrazol-4-yl) thiazoles **12a–i**.

2-(2-Benzylidenehydrazinyl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazole 12a. Yellow crystals, (75% yield), mp. 222–225°C; IR: (potassium bromide) 3426 (NH), 1567 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.49 (s, 3H, CH_3), 6.88 (s, 1H, thiazole-5-H), 7.35–7.94 (m, 10H, ArH), 8.03 (s, 1H, CH=N), 8.04 (s, 1H, pyrazole-3-H), 12.11 (s, 1H, NH); ms: *m/z* (%) 359 (63.07, M^+). *Anal.* Calcd. for $C_{20}H_{17}N_5S$: C, 66.83; H, 4.77; N, 19.48; S, 8.92. Found: C, 66.73; H, 4.56; N, 19.32; S, 8.82.

2-(2-(4-Chlorobenzylidene)hydrazinyl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-thiazole 12b. Yellow crystals, (82% yield), mp. 270–272°C; IR: (potassium bromide) 3352 (NH), 1594 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.54 (s, 3H, CH_3), 6.90 (s, 1H, thiazole-5-H), 7.45–7.68 (m, 9H, ArH), 7.93 (s, 1H, CH=N), 8.02 (s, 1H, pyrazole-3-H), 12.19 (s, 1H, NH); ms: *m/z* (%) 393 (10.90, M^+). *Anal.* Calcd. for $C_{20}H_{16}ClN_5S$: C, 60.98; H, 4.09; N, 17.78; S, 8.14. Found: C, 60.84; H, 4.15; N, 17.65; S, 8.19.

4-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-2-(2-(4-nitrobenzylidene)hydrazinyl)-thiazole 12c. Red crystals, (85% yield), mp. 278–280°C; IR: (potassium bromide) 3430 (NH), 1563 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.54 (s, 3H, CH_3), 6.97 (s, 1H, thiazole-5-H), 7.54–8.12 (m, 9H, ArH), 8.25 (s, 1H, CH=N), 8.27 (s, 1H, pyrazole-3-H), 12.49 (s, 1H, NH); ms: *m/z* (%) 404 (44.92, M^+). *Anal.* Calcd. for $C_{20}H_{16}N_6O_2S$: C, 59.39; H, 3.99; N, 20.78; S, 7.93. Found: C, 59.22; H, 3.68; N, 20.56; S, 7.81.

N,N-dimethyl-4-((2-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)-hydrazono)methyl)aniline 12d. Yellow crystals, (80% yield), mp. 248–250°C; IR: (potassium bromide) 3435 (NH), 1564 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.54 (s, 3H, CH_3), 2.95 (s, 6H, $N(CH_3)_2$), 6.82 (s, 1H, thiazole-5-H), 6.73–7.54 (m, 9H, ArH), 7.56 (s, 1H, CH=N), 7.91 (s, 1H, pyrazole-3-H), 11.75 (s, 1H, NH); ^{13}C-NMR: δ 11.99, 39.72, 101.01, 111.88, 116.91, 122.00, 124.85, 127.48, 127.63, 129.09, 135.36, 138.80, 139.32, 142.18, 144.31, 150.93, 168.30; ms: *m/z* (%) 402 (17.27, M^+). *Anal.* Calcd. for $C_{22}H_{22}N_6S$: C, 65.65; H, 5.51; N, 20.88; S, 7.97. Found: C, 65.84; H, 5.38; N, 20.79; S, 7.73.

4-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-2-(2-(4-methylbenzylidene)hydrazinyl)-thiazole 12e. Yellow crystals, (77% yield), mp. 257–260°C; IR: (potassium bromide) 3424 (NH), 1559 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.32 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.87 (s, 1H, thiazole-5-H), 7.22–7.55 (m, 9H, ArH), 7.92 (s, 1H, CH=N), 8.00 (s, 1H, pyrazole-3-H), 12.02 (s, 1H, NH); ms: *m/z* (%) 373 (29.60, M^+). *Anal.* Calcd. for $C_{21}H_{19}N_5S$: C, 67.53; H, 5.13; N, 18.75; S, 8.59. Found: C, 67.48; H, 5.04; N, 18.66; S, 8.44.

2-(2-(4-Methoxybenzylidene)hydrazinyl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazole 12f. Colorless crystals, (83% yield), mp. 249–250°C; IR: (potassium bromide) 3426 (NH), 1566 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.50 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.85 (s, 1H, thiazole-5-H), 6.86–7.60 (m, 9H, ArH), 7.93 (s, 1H, CH=N), 7.98 (s, 1H, pyrazole-3-H), 11.94 (s, 1H, NH); ms: *m/z* (%) 389 (93.01, M^+). *Anal.* Calcd. for $C_{21}H_{19}N_5OS$: C, 64.76; H, 4.92; N, 17.98; S, 8.23. Found: C, 64.62; H, 4.88; N, 17.85; S, 8.13.

4-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-2-(2-(pyridin-4-ylmethylene)hydrazinyl)-thiazole 12g. Brick red crystals, (80% yield), mp. 280–282°C; IR: (potassium bromide) 3432 (NH), 1567 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.54 (s, 3H, CH_3), 6.97

(s, 1H, thiazole-5-H), 7.44–8.00 (m, 9H, ArH), 8.59 (s, 1H, CH=N), 8.61 (s, 1H, pyrazole-3-H), 12.47 (s, 1H, NH); ^{13}C-NMR: δ 11.95, 102.48, 116.53, 120.08, 124.88, 127.70, 129.11, 135.53, 138.21, 138.77, 139.25, 141.53, 150.10, 167.60; ms: *m/z* (%) 360 (41.78, M$^+$). *Anal.* Calcd. for $C_{19}H_{16}N_6S$: C, 63.31; H, 4.47; N, 23.32; S, 8.90. Found: C, 63.22; H, 4.35; N, 23.39; S, 8.82.

4-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-2-(2-(pyridin-3-ylmethylene) hydrazinyl)-thiazole 12h. Yellow crystals, (78% yield), mp. 242–244°C; IR: (potassium bromide) 3425 (NH), 1568 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.54 (s, 3H, CH_3), 6.93 (s, 1H, thiazole-5-H), 7.43–8.06 (m, 9H, ArH), 8.56 (s, 1H, CH=N), 8.81 (s, 1H, pyrazole-3-H), 12.30 (s, 1H, NH); ms: *m/z* (%) 360 (100, M$^+$). *Anal.* Calcd. for $C_{19}H_{16}N_6S$: C, 63.31; H, 4.47; N, 23.32; S, 8.90. Found: C, 63.22; H, 4.65; N, 23.19; S, 8.82.

4-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-2-(2-(thiophen-2-ylmethylene)-hydrazinyl)thiazole 12i. Yellow crystals, (75% yield), mp. 228–230°C; IR: (potassium bromide) 3435 (NH), 1571 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.53 (s, 3H, CH_3), 6.87 (s, 1H, thiazole-5-H), 7.08–7.57 (m, 8H, ArH), 7.92 (s, 1H, CH=N), 8.21 (s, 1H, pyrazole-3-H), 12.05 (s, 1H, NH); ms: *m/z* (%) 365 (100, M$^+$). *Anal.* Calcd. for $C_{18}H_{15}N_5S_2$: C, 59.15; H, 4.14; N, 19.16; S, 17.55. Found: C, 59.24; H, 4.19; N, 19.02; S, 17.38.

Synthesis of 2-(1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)ethylidene) hydrazine-carbothioamide (14). ***General procedure.*** To a solution of 1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**5**) (10 mmol) in absolute ethanol (25 mL) containing few drops of acetic acid, thiosemicarbazide (**13**) (10 mmol) was added. The reaction mixture was heated under reflux for 3 h then left to cool. The solid formed was collected by filtration and recrystallized from ethanol to give **14**; Colourless crystal, (73% yield), mp. 220–222°C; IR: (potassium bromide) 3388, 3235 (NH_2), 1557 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.29 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.33–8.19 (m, 8H, ArH, pyrazole-3-H, NH_2), 10.13 (s, 1H, NH); *Anal.* Calcd. For $C_{13}H_{15}N_5S$: C, 57.12; H, 5.53; N, 25.62; S, 11.73. Found: C, 57.05; H, 5.45; N, 25.48; S, 11.61.

Synthesis of (pyrazol-4-yl)ethylidene)hydrazinyl) arylthiazoles 16a–c. ***General procedure.*** To a mixture of 2-(1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethylidene)hydrazine-carbothioamide (**14**) (1 mmol) and the corresponding 2-bromo-1-arylethanone **15a–c** (1 mmol) in ethanol (10 mL), few drops of TEA were added. The reaction mixture was heated under reflux for 3–5 h then left to cool. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from ethanol to give the corresponding pyrazol-4-yl)ethylidene) hydrazinyl) arylthiazoles **16a–c**.

2-(2-(1-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)ethylidene)hydrazinyl)-4-phenyl-thiazole 16a. Orange crystals, (64% yield), mp. 154–156°C; IR: (potassium bromide) 3402 (NH), 1568 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.32 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 7.26–7.95 (m, 12H, ArH, thiazole-5-H, pyrazole-3-H), 11.02 (s, 1H, NH); ms: *m/z* (%) 373 (100, M$^+$). *Anal.* Calcd. for $C_{21}H_{19}N_5S$: C, 67.53; H, 5.13; N, 18.75; S, 8.59. Found: C, 67.39; H, 5.04; N, 18.67; S, 8.42.

4-(4-Methoxyphenyl)-2-(2-(1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)ethylidene)-hydrazinyl)thiazole 16b. Orang crystals, (65% yield), mp. 194–196°C; IR: (potassium bromide) 3427 (NH), 1554 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.31 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.94–7.95 (m, 11H, ArH, thiazole-5-H, pyrazole-3-H), 11.02 (s, 1H, NH); ^{13}C-NMR: δ 13.10, 15.80, 55.04, 101.19, 113.88, 119.19, 125.21, 126.78, 127.69, 128.02, 129.12, 136.68, 139.02, 139.46, 143.67, 158.68, 169.79; ms: *m/z* (%) 403 (100, M$^+$). *Anal.* Calcd. for $C_{22}H_{21}N_5OS$: C, 65.49; H, 5.25; N, 17.36; S, 7.95. Found: C, 65.32; H, 5.13; N, 17.29; S, 7.88.

4-(4-Bromophenyl)-2-(2-(1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)ethylidene)-hydrazinyl)thiazole 16c. Brown solid, (60% yield), mp. 190–192°C; IR: (potassium bromide) 3431 (NH), 1568 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.31 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 7.34–7.95 (m, 11H, ArH, thiazole-5-H, pyrazole-3-H), 11.05 (s, 1H, NH); ms: *m/z* (%) 452 (20.41, M$^+$). *Anal.* Calcd. for $C_{21}H_{18}BrN_5S$: C, 55.76; H, 4.01; N, 15.48; S, 7.09. Found: C, 55.93; H, 3.88; N, 15.35; S, 7.16.

Synthesis of 4-(1*H*-pyrazol-4-yl)-2-(2-1*H*-pyrazol-4-yl) ethylidene)hydrazinyl)-thiazole (17). ***General procedure.*** To a mixture of 2-(1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethylidene)hydrazine-carbothioamide (**14**) (1 mmol) and 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**6**) (1 mmol) in ethanol (10 mL), few drops of TEA were added. The reaction mixture was heated under reflux for 3–5 h then left to cool. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from ethanol to give **17** as orange crystals, (73% yield), mp. 230°C; IR: (potassium bromide) 3428 (NH), 1568 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.32 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 6.84 (s, 1H, thiazole-5-H), 7.45–7.59 (m, 11H, ArH), 7.95 (s, 1H, pyrazole-3-H), 10.94 (s, 1H, NH); ^{13}C-NMR: δ 11.98, 13.11, 15.85, 94.23, 101.56, 116.89, 119.22, 124.85, 125.21, 127.65, 128.02, 129.11, 135.41, 136.68, 138.77, 139.02, 139.31 139.47, 143.74, 169.70; ms: *m/z* (%) 453 (36.46, M$^+$). *Anal.* Calcd. for $C_{25}H_{23}N_7S$: C, 66.20; H, 5.11; N, 21.62; S, 7.07. Found: C, 66.10; H, 5.27; N, 21.98; S, 7.17.

Synthesis of alkylenebis(oxy)bis(2,1-phenylene)bis(methan-1-yl-1-ylidene))bis (hydrazinecarbothioamide) 19a–e. ***General procedure.*** To a solution of the appropriate bis (aldehyde) compounds **18a–e** (10 mmol) in absolute ethanol (25 mL) containing few drops of acetic acid, thiosemicarbazide (**13**) (20 mmol) was added. The reaction mixture was heated under reflux for 3 h then allowed to cool. The solid formed was collected by filtration and recrystallized from ethanol/DMF to give **19a–e**.

2,2′-(4,4′-(Ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(methan-1-yl-1-ylidene)-bis(hydrazinecarbothioamide) 19a. Yellow crystals, (72% yield), mp. >300°C; IR: (potassium bromide) 3475, 3411 (NH_2), 3360 (NH), 1597 (C=N) cm^{-1}; ^{1}H-NMR: δ 4.36 (s, 4H, CH_2O), 6.99–8.00 (m, 12H, ArH, NH_2), 8.08 (s, 2H, CH=N), 11.29 (s, 2H, NH); *Anal.* Calcd. For $C_{18}H_{20}N_6\ O_2S_2$: C, 51.90; H, 4.84; N, 20.18; S, 15.40. Found: C, 51.73; H, 4.67; N, 20.10; S, 15.29.

2,2′-(4,4′-(Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) 19b. Yellow crystals, (74% yield), mp. 222–224°C; IR: (potassium bromide) 3420, 3254 (NH_2), 3151 (NH), 1536 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.17 (m, 2H, CH_2), 4.16 (m, 4H, CH_2O), 6.96–7.99 (m, 12H, ArH, NH_2), 8.07 (s, 2H, CH=N), 11.28 (s, 2H, NH); *Anal.* Calcd. For $C_{19}H_{22}N_6O_2S_2$: C, 53.00; H, 5.15; N, 19.52; S, 14.90. Found: C, 52.87; H, 5.01; N, 19.40; S, 14.71.

2,2′-(4,4′-(Butane-1,4-diylbis(oxy))bis(4,1-phenylene))bis(methan-1-yl-1-ylidene)-bis(hydrazinecarbothioamide) 19c. Yellow crystals, (76% yield), mp. >300°C; IR: (potassium bromide) 3338, 3268 (NH_2), 3158 (NH), 1531 (C=N) cm^{-1}; ^{1}H-NMR: δ 1.87 (s, 4H, CH_2), 4.16 (s, 4H, CH_2O), 6.94–7.99 (m, 12H, ArH, NH_2), 8.07 (s, 2H, CH=N), 11.28 (s, 2H, NH); *Anal.* Calcd. For $C_{20}H_{24}N_6O_2S_2$: C, 54.03; H, 5.44; N, 18.90; S, 14.43. Found: C, 53.88; H, 5.31; N, 18.74; S, 14.22.

2,2′-(2,2′-(Ethane-1,2-diylbis(oxy))bis(2,1-phenylene))bis(methan-1-yl-1-ylidene)-bis(hydrazinecarbothioamide) 19d. Yellow crystals, (72% yield), mp. 238–240°C, (Lit. [48]; 245–247°C).

2,2′-(2,2′-(Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(methan-1-yl-1-ylidene)-bis(hydrazinecarbothioamide) 19e. Yellow crystals, (75% yield), mp. 228–230°C; IR: (potassium bromide) 3430, 3358 (NH_2), 3314 (NH), 1531 (C=N) cm^{-1}; ^{1}H-NMR: δ 1.99 (s, 4H, CH_2), 4.12 (s, 4H, CH_2O), 6.92–8.10 (m, 12H, ArH, NH_2), 8.51 (s, 2H, CH=N), 11.45 (s, 2H, NH); *Anal.* Calcd. For $C_{20}H_{24}N_6O_2S_2$: C, 54.03; H, 5.44; N, 18.90; S, 14.43. Found: C, 53.90; H, 5.37; N, 18.79; S, 14.31.

Synthesis of bis(5-1*H*-pyrazol-4-yl)thiazol-2-yl)hydrazono) methyl)phenoxy)-alkane 20a–e. ***General procedure.*** To a mixture of alkylenebis(oxy)bis(2,1-phenylene)bis (methan-1-yl-1-ylidene))bis (hydrazine-carbothioamide) **19a–e** (1 mmol) and 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**6**) (2 mmol) in ethanol (25 mL), few drops of TEA were added. The reaction mixture was heated under reflux for 3–5 h then allowed to cool. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from ethanol/DMF to give **20a–e**.

1,2-Bis(4-((2-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)hydrazono)-methyl)phenoxy)ethane 20a. Orange crystals, (70% yield), mp. 265–267°C; IR: (potassium bromide) 3426 (NH), 1566 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.54 (s, 6H, CH_3), 4.38 (s, 4H, CH_2O), 6.86 (s, 2H, thiazole-5-H), 7.05–7.62 (m, 18H, ArH), 7.92 (s, 2H, CH=N), 7.99 (s, 2H, pyrazole-3-H) 11.96 (s, 2H, NH); ms: *m/z* (%) 776 (0.11, M^+). *Anal.* Calcd. For $C_{42}H_{36}N_{10}\ O_2S_2$: C, 64.93; H, 4.67; N, 18.03; S, 8.25. Found: C, 64.67; H, 4.59; N, 18.31; S, 8.03.

1,3-Bis(4-((2-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)hydrazono)-methyl)phenoxy)propane 20b. Orange crystals, (75% yield), mp. 262–264°C; IR: (potassium bromide) 3432 (NH), 1567 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.21 (m, 2H, CH_2), 2.54 (s, 6H, CH_3), 4.21 (m, 4H, CH_2O), 6.85 (s, 2H, thiazole-5-H), 7.01–7.60 (m, 18H, ArH), 7.92 (s, 2H, CH=N), 7.98 (s, 2H, pyrazole-3-H), 11.94 (s, 2H, NH); ^{13}C-NMR: δ 11.97, 28.53, 64.31, 101.40, 114.80, 116.80, 124.85, 127.16, 127.72, 129.09, 135.40, 138.79, 139.29, 141.07, 159.37, 168.18; ms: *m/z* (%) 790 (0.09, M^+). *Anal.* Calcd. for $C_{43}H_{38}N_{10}\ O_2S_2$: C, 65.30; H, 4.84; N, 17.71; S, 8.11. Found: C, 65.06; H, 4.69; N, 17.46; S, 8.23

1,4-Bis(4-((2-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)hydrazono)-methyl)phenoxy)butane 20c. Orange crystals, (77% yield), mp. 270–272°C; IR: (potassium bromide) 3427 (NH), 1566 (C=N) cm^{-1}; ^{1}H-NMR: δ 1.90 (s, 4H, CH_2), 2.54 (s, 6H, CH_3), 4.09 (s, 4H, CH_2O), 6.85 (s, 2H, thiazole-5-H), 6.99–7.98 (m, 22H, ArH, CH=N, pyrazole-3-H), 11.93 (s, 2H, NH); ms: *m/z* (%) 804 (0.86, M^+). *Anal.* Calcd. for $C_{44}H_{40}N_{10}\ O_2S_2$: C, 65.65; H, 5.01; N, 17.40; S, 7.97. Found: C, 65.89; H, 4.83; N, 17.14; S, 7.76.

1,2-Bis(2-((2-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)hydrazono)-methyl)phenoxy)ethane 20d. Yellow crystals, (68% yield), mp. 215–218°C; IR: (potassium bromide) 3424 (NH), 1565 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.54 (s, 6H, CH_3), 4.45 (s, 4H, CH_2O), 6.84 (s, 2H, thiazole-5-H), 7.05–7.83 (m, 18H, ArH), 7.89 (s, 2H, CH=N), 8.41 (s, 2H, pyrazole-3-H), 12.03 (s, 2H, NH); ms: *m/z* (%) 776 (1.05, M^+). *Anal.* Calcd. For $C_{42}H_{36}N_{10}\ O_2S_2$: C, 64.93; H, 4.67; N, 18.03; S, 8.25. Found: C, 64.77; H, 4.99; N, 18.21; S, 8.13.

1,4-Bis(2-((2-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)hydrazono)-methyl)phenoxy)butane 20e. Yellow crystals, (76% yield), mp. 230–232°C; IR: (potassium bromide) 3427 (NH), 1562 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.01 (br, 4H, CH_2), 2.52 (s, 6H, CH_3), 4.15 (br, 4H, CH_2O), 6.86 (s, 2H, thiazole-5-H), 7.00–7.54 (m, 18H, ArH,), 7.91 (s, 2H, CH=N), 8.45 (s, 2H, pyrazole-3-H), 12.08 (s, 2H, NH); ^{13}C-NMR: δ 11.95, 25.55, 67.74, 101.52, 112.61, 116.77, 120.69, 122.72, 124.84, 127.62, 129.07, 130.46, 135.42, 136.99, 138.79, 139.29, 144.43, 156.42, 168.05; ms: *m/z* (%) 804 (0.34, M^+). *Anal.* Calcd. for $C_{44}H_{40}N_{10}\ O_2S_2$: C, 65.65; H, 5.01; N, 17.40; S, 7.97. Found: C, 65.49; H, 4.79; N, 17.29; S, 7.85.

Synthesis of alkylenebis(oxy)bis(2,1-phenylene)bis(methan-1-yl-1-ylidene))bis (hydrazinecarbothioamide) 22a–c. ***General procedure.*** To a mixture of the appropriate bis(aldehyde) compounds **21a–c** (10 mmol) and thiosemicarbazide (**13**) (20 mmol) in absolute ethanol (25 mL), few drops of acetic acid were added. The reaction mixture was heated under reflux for 3 h then left to cool. The solid formed was collected by filtration and recrystallized from ethanol/DMF to give **22a–c**.

2,2′-(4,4′-(1,2-Phenylenebis(methylene))bis(oxy)bis(4,1-phenylene)) bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) 22a. Yellow crystals, (61% yield), mp. 228–230°C, (Lit. [48]; 220–221°C).

2,2′-(4,4′-(1,3-Phenylenebis(methylene))bis(oxy)bis(4,1-phenylene)) bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) 22b. Yellow crystals, (64% yield), mp. 222–224°C; IR: (potassium bromide) 3495, 3434 (NH_2), 3379 (NH), 1595 (C=N) cm^{-1}; ^{1}H-NMR: δ 5.17 (s, 4H, CH_2O), 7.03–7.99 (m, 16H, ArH, NH_2), 8.07 (s, 2H, CH=N), 11.29 (s, 2H, NH); ms: *m/z* (%) 492 (0.10, M^+). *Anal*. Calcd. For $C_{24}H_{24}N_6O_2S_2$: C, 58.52; H, 4.91; N, 17.06; S, 13.02. Found: C, 58.44; H, 4.83; N, 17.02; S, 12.92.

2,2′-(4,4′-(1,4-Phenylenebis(methylene))bis(oxy)bis(4,1-phenylene)) bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) 22c. Yellow solid, (66% yield), mp. 260–262°C, (Lit. [49]; 250–252°C).

Synthesis of bis(1*H*-pyrazol-4-yl)thiazol-2-yl)hydrazono) methyl)phenoxy)-arene 23a–c. ***General procedure.*** To a mixture of alkylenebis(oxy)bis(2,1-phenylene)bis(methan-1-yl-1-ylidene))bis (hydrazine-carbothioamide) **22a–c** (1 mmol) and 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**6**) (2 mmol) in ethanol/DMF [1:1] (25 mL), few drops of TEA were added. The reaction mixture was heated under reflux for 3–5 h then left to cool. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from ethanol/DMF to give **23a–c**.

1,2-Bis((4-((2-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)hydrazono)-methyl)phenoxy)methyl)benzene 23a. Yellow crystals, (65% yield), mp. 250–252°C; IR: (potassium bromide) 3433 (NH), 1568 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.52 (s, 6H, CH_3), 5.29 (s, 4H, CH_2O), 6.84 (s, 2H, thiazole-5-H), 7.07–7.98 (m, 22H, ArH), 7.91 (s, 2H, CH=N), 7.98 (s, 2H, pyrazole-3-H), 11.95 (s, 2H, NH); ms: *m/z* (%) 853 (21.03, M^+). *Anal*. Calcd. For $C_{48}H_{40}N_{10}O_2S_2$: C, 67.58; H, 4.73; N, 16.42; S, 7.52. Found: C, 67.44; H, 4.68; N, 16.33; S, 7.46.

1,3-Bis((4-((2-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)hydrazono)-methyl)phenoxy)methyl)benzene 23b. Yellow crystals, (65% yield), mp. 268–270°C; IR: (potassium bromide) 3425 (NH), 1565 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.53 (s, 6H, CH_3), 5.18 (s, 4H, CH_2O), 6.85 (s, 2H, thiazole-5-H), 7.07–7.61 (m, 22H, ArH), 7.92 (s, 2H, CH=N), 7.98 (s, 2H, pyrazole-3-H), 11.95 (s, 2H, NH); ms: *m/z* (%) 853 (16.56, M^+). *Anal*. Calcd. For $C_{48}H_{40}N_{10}O_2S_2$: C, 67.58; H, 4.73; N, 16.42; S, 7.52. Found: C, 67.35; H, 4.58; N, 16.30; S, 7.18.

1,4-Bis((4-((2-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)hydrazono)-methyl)phenoxy)methyl)benzene 23c. Orange crystals, (70% yield), mp. 270–274°C; IR: (potassium bromide) 3431 (NH), 1566 (C=N) cm^{-1}; ^{1}H-NMR: δ 2.53 (s, 6H, CH_3), 5.16 (s, 4H, CH_2O), 6.85 (s, 2H, thiazole-5-H), 7.06–7.60 (m, 22H, ArH), 7.92 (s, 2H, CH=N), 7.97 (s, 2H, pyrazole-3-H), 11.95 (s, 2H, NH); ^{13}C-NMR: δ 11.97, 69.05, 101.43, 115.17, 117.09, 124.87, 127.32, 127.69, 127.79, 129.11, 129.33, 135.42, 136.47, 138.78, 139.29, 141.01, 144.27, 159.20, 168.14; ms: *m/z* (%) 853 (33.74, M^+). *Anal*. Calcd. For $C_{48}H_{40}N_{10}O_2S_2$: C, 67.58; H, 4.73; N, 16.42; S, 7.52. Found: C, 67.74; H, 4.55; N, 16.70; S, 7.41.

REFERENCES AND NOTES

[1] Bondock, S.; Fadaly, W.; Metwally, M. A. Eur J Med Chem 2010, 45, 3692.

[2] Prakash, O.; Hussain, K.; Kumar, R.; Wadhwa, D.; Sharma, C.; Aneja, K. R. Org Med Chem Lett 2011, 1, 1.

[3] Lee, K. Y.; Kim, J. M.; Kim, J. N. Tetrahedron Lett 2003, 44, 6737.

[4] Lv, P.-C.; Li, H.-Q.; Sun, J.; Zhou, Y.; Zhu, H.-L. Bioorg Med Chem 2010, 18, 4606.

[5] Sharma, P. K.; Kumar, S.; Kumar, P.; Kaushik, P.; Kaushik, D.; Dhingra, Y.; Aneja, K. R. Eur J Med Chem 2010, 45, 2650.

[6] Li, X.; Liu, J.-L.; Yang, X.-H.; Lu, X.; Zhao, T.-T.; Gong, H.-B.; Zhu, H.-L. Bioorg Med Chem 2012, 20, 4430.

[7] Li, M.; Zhao, B. X. Eur J Med Chem 2014, 85, 311.

[8] Pinna, G.; Loriga, G.; Lazzari, P.; Ruiu, S.; Falzoi, M.; Frau, S.; Pau, A.; Murineddu, G.; Asproni, B.; Pinna, G. A. Eur J Med Chem 2014, 82, 281.

[9] Mert, S.; Kasimogullari, R.; Ica, T.; Colak, F.; Altun, A.; Ok, S. Eur J Med Chem 2014, 78, 86.

[10] Ningaiah, S.; Bhadraiah, U. K.; Doddaramappa, S. D.; Keshavamurthy, S.; Javarasetty, C. Bioorg Med Chem Lett 2014, 24, 245.

[11] Wang, S. F.; Zhu, Y. L.; Zhu, P. T.; Makawana, J. A.; Zhang, Y. L.; Zhao, M. Y.; Lv, P. C.; Zhu, H. L. Bioorg Med Chem 2014, 22, 6201.

[12] Sharma, P. K.; Chandak, N.; Kumar, P.; Sharma, C.; Aneja, K. R. Eur J Med Chem 2011, 46, 241.

[13] Khloya, P.; Kumar, P.; Mittal, A.; Aggarwal, N. K.; Sharma, P. K. Org Med Chem Lett 2013, 3, 1.

[14] Khloya, P.; Celik, G.; Ram, S.; Vullo, V.; Supuran, C. T.; Sharma, P. K. Eur J Med Chem 2014, 76, 284.

[15] Mahler, G.; Serra, G.; Dematteis, S.; Saldana, J.; Domínguez, L.; Manta, E. Bioorg Med Chem Lett 2006, 16, 1309.

[16] Bonde, C. G.; Gaikwad, N. J. Bioorg Med Chem 2004, 12, 2151.

[17] Pontillo, J.; Chen, C. Bioorg Med Chem Lett 2005, 15, 1407.

[18] Pontiki, E.; Hadjipavlou, L. D.; Chaviara, A. T.; Bolos, C. A. Bioorg Med Chem Lett 2006, 16, 2234.

[19] Küçükgüzel, G.; Kocatepe, A.; Clercq, E. D.; Şahin, F.; Güllüce, M. Eur J Med Chem 2006, 41, 353.

[20] Verma, A.; Saraf, S. K. Eur J Med Chem 2008, 43, 897.

[21] Abdel-Wahab, B. F.; Mohamed, S. F.; Amr, A. E.-G. E.; Abdalla, M. M. Monatsh Chem 2008, 139, 1083.

[22] Thurston, D. E.; Bose, D. S.; Thompson, A. S.; Howard, P. W.; Leoni, A.; Croker, S. J.; Jenkins, T. C.; Neidle, S.; Hartley, J. A.; Hurley, L. H. J Org Chem 1996, 61, 8141.

[23] Shaker, R. M. Phosphorus, Sulfur Silicon Relat Elem 1999, 149, 7.

[24] Kamal, A.; Laxman, N.; Ramesh, G.; Neelima, K.; Anand, K. K. Chem Commun 2001 437.
[25] Raasch, A.; Scharfenstein, O.; Trankle, C.; Holzgrabe, U.; Mohr, K. J Med Chem 2002, 45, 3809.
[26] Jain, M.; Khanna, P.; Saxena, A.; Bhagat, S.; Olsen, C. E.; Jain, S. C. Synth Commun 2006, 36, 1863.
[27] Jain, M.; Sakhuja, R.; Khanna, P.; Bhagat, S.; Jain, S. C. Arkivoc 2008, xv, 54.
[28] Yang, G. Y.; Oh, K.-A.; Park, N.-J.; Jung, Y.-S. Bioorg Med Chem 2007, 15, 7704.
[29] Giacomo, B. D.; Bedini, A.; Spadoni, G.; Tarzia, G.; Fraschini, F.; Pannaccib, M.; Lucinib, V. Bioorg Med Chem 2007, 15, 4643.
[30] Holla, B. S.; Gonsalves, R.; Shenoy, S. Eur J Med Chem 2000, 35, 267.
[31] Holla, B. S.; Gonsalves, R.; Rao, B. S.; Shenoy, S.; Gopalakrishna, H. N. Il Farmaco 2001, 56, 899.
[32] Holla, B. S.; Poojary, K. N.; Rao, B. S.; Shivananda, M. K. Eur J Med Chem 2002, 37, 511.
[33] Li, J. T.; Sun, M. X.; He, G. Y.; Xu, X. Y. Ultrason Sonochem 2011, 18, 412.
[34] Wang, Z.; Zhao, C.; Zhao, D.; Li, C.; Ahang, J.; Wang, H. Tetrahedron 2010, 66, 2168.
[35] Diana, P.; Carbone, A.; Barraja, P.; Kelter, G.; Fiebig, H.; Cirrincione, G. Bioorg Med Chem 2010, 18, 4524.
[36] Toyota, K.; Okada, K.; Katsuta, H.; Morita, N. Tetrahedron 2009, 65, 145.
[37] Todd, E. M.; Zimmerman, S. C. Tetrahedron 2008, 64, 8558.
[38] Diana, P.; Carbone, A.; Barraja, P.; Montalbano, A.; Martorana, A.; Dattolo, G.; Gia, O.; Dalla Via, L.; Cirrincione, G. Bioorg Med Chem Lett 2007, 17, 2342.
[39] Blanco, G.; Quintela, J. M.; Peinador, C. Tetrahedron 2007, 63, 2034.
[40] Promarak, V.; Punkvuang, A.; Jungsuttiwong, S.; Saengsuwan, S.; Sudyoadsuk, T.; Keawin, T. Tetrahedron Lett 2007, 48, 3661.
[41] Nagarajan, K.; Arya, V. P.; Shenoy, S. J. J Chem Research (M) 1986 1401.
[42] Shaaban, M. R.; Eldebss, T. M. A.; Darweesh, A. F.; Farag, A. M. J Heterocycl Chem 2008, 45, 1739.
[43] Shaaban, M. R.; Eldebss, T. M. A.; Darweesh, A. F.; Farag, A. M. J Chem Res 2010 8.
[44] Goddard, C. J. J heterocycl Chem 1991, 28, 1607.
[45] Sah, P. P. T.; Daniels, T. C. Recl Trav Chim Pays-Bas 1950, 69, 1545.
[46] Shih, M.-H.; Su, Y.-S.; WU, C.-L. Chem Pharm Bull 2007, 55, 1126.
[47] (a) Ibrahim, Y. A.; Elwahy, A. H. M.; Elkareish, G. M. M. J Chem Res 1994, (S) 414, (M) 2321; (b) Elwahy, A. H. M.; Abbas, A. A.; Ibrahim, Y. A. J Chem Res 1998, (S) 184, (M) 901; (c) Elwahy, A. H. M. J Chem Res 1999, (S) 602, (M) 2582.
[48] Fedorova, O. V.; Mordovskoi, G. G.; Rusinov, G. L.; Ovchinnikova, I. G.; Zueva, M. N.; Kravchenko, M. A.; Chupakhin, O. N. Pharmaceut Chem J 1998, 32, 11.
[49] Yusuf, M.; Solanki, I.; Jain, P. J Chem Sci 2012, 124, 703.