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Facile synthesis and characterization of novel bis(2-*S*-alkylpyridines) and bis(3-aminothieno[2,3-*b*]pyridines) incorporating 1,3-diarylpyrazole moiety

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ABSTRACT

3-(4-Hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**) is condensed with acetophenone to afford the corresponding unsaturated carbonyl compound **4** whose potassium salt is reacted with 1,4-dibromobutane to afford the bis-unsaturated carbonyl compound **3**. Both carbonyl compounds **3** and **4** are reacted with 2-cyanoethanethioamide, through Michael addition reaction followed by cyclocondensation, to prepare the starting materials bis(pyridine-2(1*H*)-thione) derivative **5** and pyridine-2(1*H*)-thione derivative **8**. Two synthetic routes to synthesize the target materials **7** and **14** are described to get the most efficient method for preparation and maximum yield%. The first route came from the direct alkylation of the bis(pyridine-2(1*H*)-thione) derivative **5** using iodomethane (**6a**) and benzyl chloride (**6b**) to afford the corresponding bis(2-*S*-alkylpyridine) derivatives **7a,b**. The reaction of **5** with halo-containing compounds **10a–d** to synthesize the target materials bis(3-aminothieno[2,3-*b*]pyridine) derivatives **14a–d** failed under various reaction conditions. The second route involves the reaction of pyridine-2(1*H*)-thione derivative **8** with **6a,b** and **10a–d** to afford the corresponding 2-*S*-alkylpyridine derivatives **9a,b** and 3-aminothieno[2,3-*b*]pyridine derivatives **13a–d**, through the formation of 2-*S*-alkylpyridine derivatives **12a–d** followed by a Thrope-Ziegler reaction, whose potassium salts reacted with 1,4-dibromobutane to afford the corresponding target materials **7a,b**

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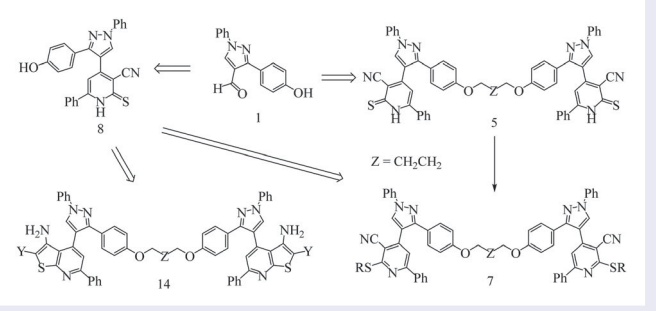
and **14a–d,** respectively. The structures of target molecules were elucidated using elemental analyses and spectral data.



1. Introduction

It had been found that pyrazole derivatives possess significant biological activities, which have stimulated several research studies in both medicinal chemistry or chemical biology [1–4]. Several pyrazoles are well documented to have a wide range of anticancer [5–10], and anti-proliferative [11] activities. Also, pyrazoles exhibited other important antidepressant [12], anticonvulsant [13], and antipyretic [14] bioactivities.

On the other hand, pyridine derivatives with cyano and alkylsulfanyl substituents show significant cardiovascular [15,16], hepatoprotective [17], antioxidant [18], and antiradical [19] bioactivities. Also, the thieno[2,3-*b*]pyridine derivatives show broad pharmacological anticancer [20–23], antiviral [24], anti-inflammatory [25], and antidiabetic [26,27] activities.

The goal of this work was to design and carry out versatile methods for the synthesis of both bis(2-*S*-alkylpyridines) **7** and bis(3-aminothieno[2,3-*b*]pyridines) **14** that incorporate the 1,3-diarylpyrazole moiety with potent biological activity using the bis(pyridine-2(1*H*)-thione) derivative **5** and pyridine-2(1*H*)-thione derivative **8** as starting materials (Figure 1).

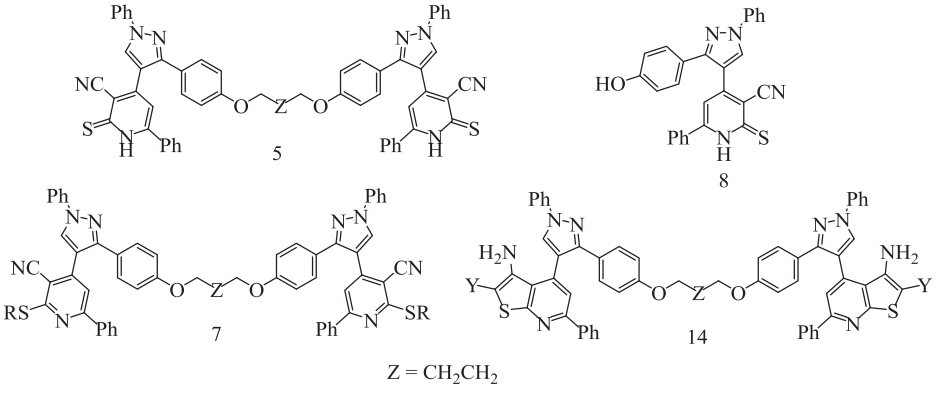


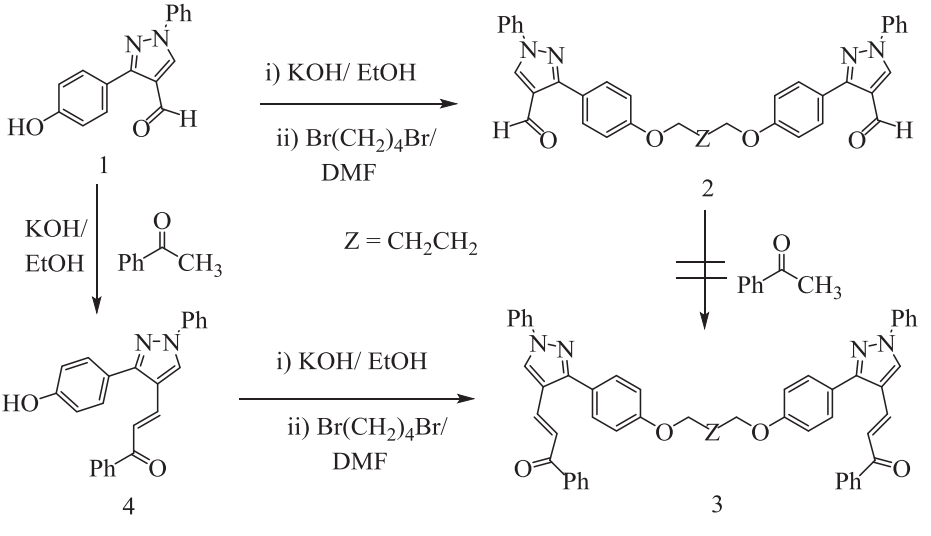
Figure 1. Structure of the starting materials bis(pyridine-2(1*H*)-thione) derivative **5** and pyridine-2(1*H*)-thione derivative **8** and the target molecules bis(2-*S*-alkylpyridines) **7** and bis(3-aminothieno[2,3-*b*]pyridines) **14**.

2. Results and discussion

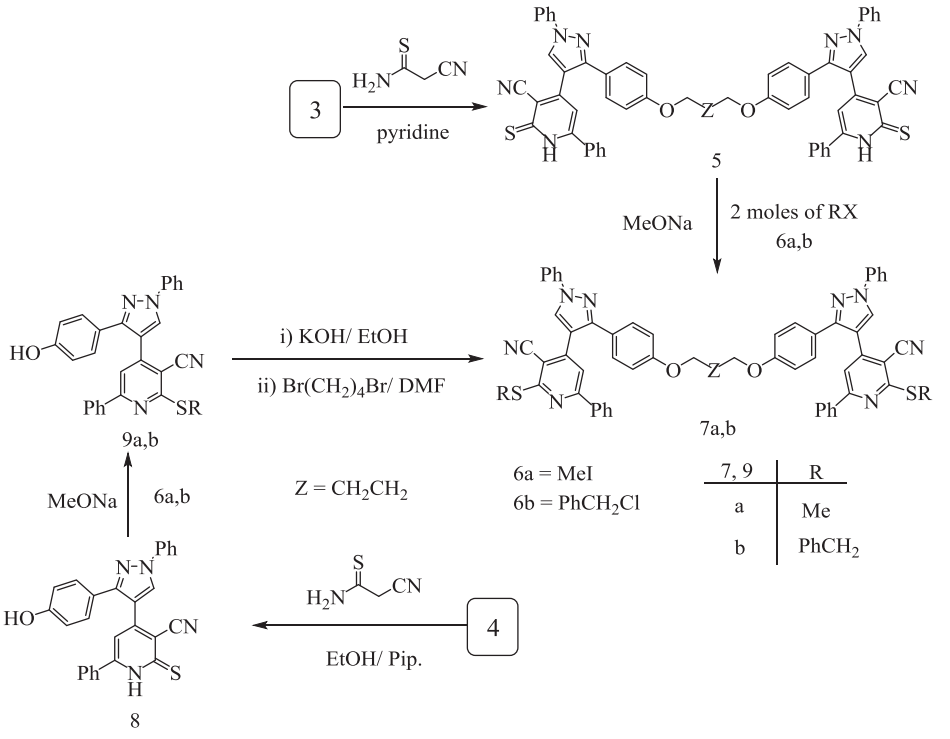
The reaction of the potassium salt of 3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**) [28] with 1,4-dibromobutane in DMF under reflux afforded the corresponding bis(1-phenyl-1*H*-pyrazole-4-carbaldehyde) derivative **2** whose ^{1}H-NMR spectrum revealed the signals for $OCH_2\underline{CH_2}$ (m, 4H, 2.01 δ ppm), $O\underline{CH_2}CH_2$ (t, 4H, 4.21 δ ppm) and CHO (s, 2H, 10.04 δ ppm) (Scheme 1 and Experimental Part). Unexpectedly, the bis-α,β-unsaturated carbonyl derivative **3** could not be isolated from the direct reaction of bis-aldehyde **2** with acetophenone under various reaction conditions (Scheme 1). Another synthetic route was designed to prepare **3**. Thus, it has been found that the potassium salt of 1-phenylprop-2-en-1-one derivative **4** [29] reacted with 1,4-dibromobutane in refluxing DMF to give the corresponding bis(1-phenylprop-2-en-1-one) derivative **3**. The ^{1}H-NMR spectrum of **3** didn't reveal the signal corresponding to OH group and revealed signals of $OCH_2\underline{CH_2}$ (m, 4H, 1.96 δ ppm) and $O\underline{CH_2}CH_2$ (t, 4H, 4.16 δ ppm) (Scheme 1 and Experimental Part).

The synthetic precursor bis(pyridine-2(1*H*)-thione) derivative **5** was prepared *via* the reaction of bis(α,β-unsaturated carbonyl) derivative **3** with 2-cyanoethanethioamide in ratio 1:2 in pyridine under reflux to afford such reaction product whose IR (cm^{-1}) spectrum showed the absorption bands of each of NH group at 3319, CN group at 2213 and CS group at 1559. Its ^{1}H-NMR spectrum revealed the signals of $OCH_2\underline{CH_2}$ (m, 4H, 1.88 δ ppm), $O\underline{CH_2}CH_2$ (t, 4H, 4.05 δ ppm) and two NH protons in addition to 30 aromatic protons (m, 32H, 6.95–8.09 δ ppm) (Scheme 2 and Experimental Part).

The target molecules bis(2-*S*-alkylpyridine) derivatives **7a**,**b** were synthesized in moderate yields by reacting bis(pyridine-2(1*H*)-thione) derivative **5** with haloalkanes **6a**,**b** in boiling methanolic sodium methoxide solution under reflux. Thus, compound **5** reacted with iodomethane (**6a**) to give the corresponding bis-2-methylsulfanylpyridine derivative **7a**, in 42% yield, whose IR spectrum showed the absence of the absorption bands of both CS and NH groups and its ^{1}H-NMR spectrum revealed the absence of the NH signal and



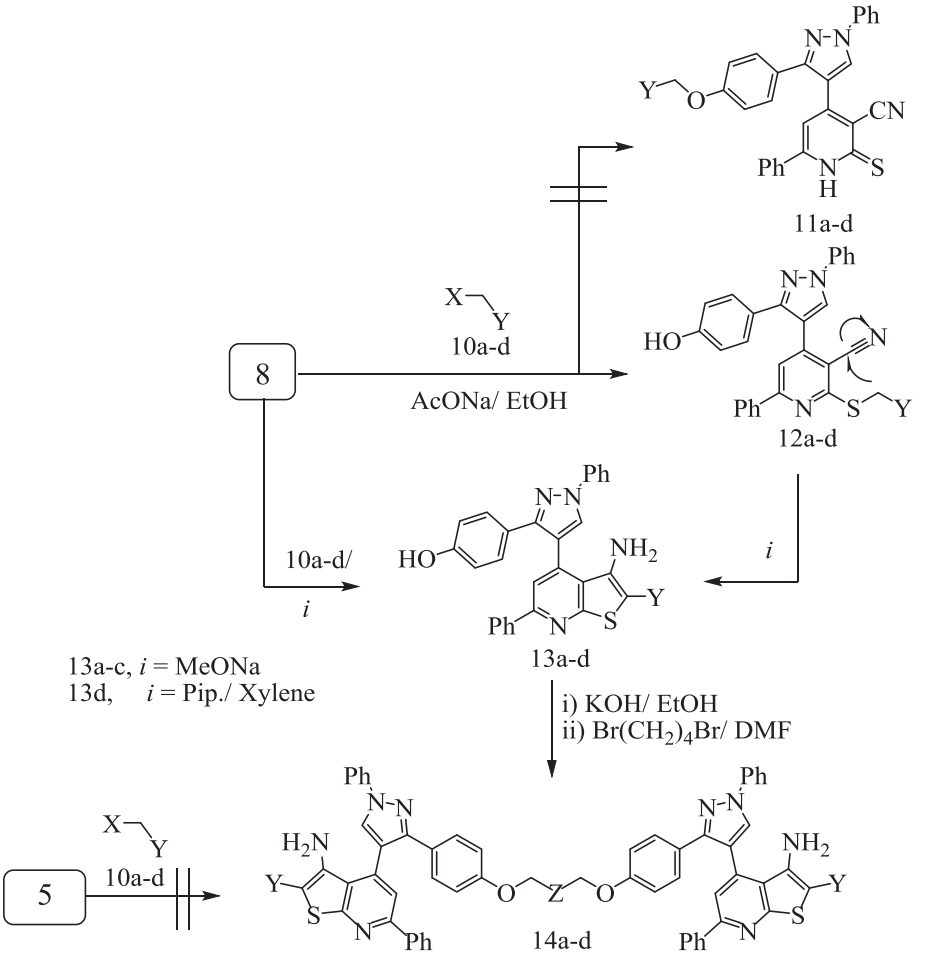
Scheme 1. Synthesis of bis(1-phenylprop-2-en-1-one) derivative **3**.



Scheme 2. Synthesis of bis(2-*S*-alkylpyridine) derivatives **7**.

the presence of S$\underline{CH_3}$ (s, 6H, 2.77 δ ppm). In a similar manner, compound **5** reacted with benzyl chloride (**6b**) to give the corresponding bis-2-benzylsulfanylpyridine derivative **7b**, in 46% yield, whose ^{1}H-NMR spectrum revealed the signal of S$\underline{CH_2}$ (s, 4H, 4.61 δ ppm) (Scheme 2 and Experimental Part).

The structures of **7a,b** were confirmed by its independent synthesis *via* another route in excellent yields. Therefore, 4-(3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**8**) was prepared according to the *literature* procedure [30,31] by reacting α,β-unsaturated carbonyl derivative **4** with 2-cyanoethanethioamide in refluxing ethanol containing few drops of piperidine as a catalyst instead to triethylamine (Scheme 2). The IR (cm^{-1}) spectrum of **8** showed the absorption bands of each of OH group at 3413, NH group at 3315, CN group at 2222 and CS group at 1530. Its ^{1}H-NMR spectrum revealed the signals for NH (s, br, 1H, 14.14 δ ppm) (Experimental Part). Pyridine-2(1*H*)-thione derivative **8** reacted with iodomethane (**6a**) in boiling methanolic sodium methoxide solution under reflux to give the corresponding 2-methylsulfanylpyridine derivative **9a** whose IR spectrum showed the absence of the absorption bands of both CS and NH groups and its ^{1}H-NMR spectrum didn't reveal the signal of NH and revealed the presence of S$\underline{CH_3}$ (s, 3H, 2.76 δ ppm). The potassium salt of **9a** reacted with 1,4-dibromobutane in refluxing DMF to afford **7a**, in 80% yield. In a similar manner, compound **8** reacted with benzyl chloride (**6b**) to give the corresponding 2-benzylsulfanylpyridine derivative **9b** whose potassium salt reacted with 1,4-dibromobutane in DMF to afford **7b**, in 84% yield (Scheme 2 and Experimental Part).



11-14	Y
a	$COCH_3$
b	COC_6H_5
c	COC_6H_4-Cl-4
d	CN

Z = CH_2CH_2

10	X	Y
a	Cl	$COCH_3$
b	Br	COC_6H_5
c	Br	COC_6H_4-Cl-4
d	Cl	CN

Scheme 3. Synthesis of bis(3-aminothieno[2,3-*b*]pyridine) derivatives **14**.

The effort was continued to study the action of halo-containing compounds **10a–d** to synthesize the target materials bis(3-aminothieno[2,3-*b*]pyridine) derivatives **14a–d**. Unfortunately, all trials to direct synthesis of **14a–d** *via* reacting bis-pyridine-2(1*H*)-thione derivative **5** with **10a–d** under various reaction conditions failed (Scheme 3). Therefore, another synthetic route was designed, by reacting pyridine-2(1*H*)-thione derivative **8** with chloroacetone (**10a**) in ethanol containing a catalytic amount of anhydrous sodium acetate to give a reaction product whose IR spectrum (cm^{-1}) showed the absence of absorption

bands of both CS and NH groups and revealed the absorption bands corresponding to OH group at 3393, CN group at 2211 and CO group at 1720 and its ^{1}H-NMR spectrum revealed the absence of an NH signal and the presence of signals corresponding to CO$\underline{CH_3}$ (s, 3H, 2.31 δ ppm), S$\underline{CH_2}$ (s, 2H, 4.37 δ ppm) and OH (s, 1H, 9.66 δ ppm). From the above results, the formation of *O*-alkyl derivative **11a** was excluded and the corresponding 2-*S*-alkylpyridine derivative **12a** was assigned to the reaction product (Scheme 3 and Experimental Part).

Compound **12a** underwent intramolecular cyclization (Thrope-Ziegler reaction) in refluxing methanolic sodium methoxide solution to give the corresponding 3-aminothieno[2,3-*b*]pyridine derivative **13a** whose IR spectrum (cm^{-1}) showed the absence of the absorption band of the CN group and instead a newly born absorption band corresponding to the NH_2 group at 3471 and 3381 and its ^{1}H-NMR spectrum didn't reveal the signal for S$\underline{CH_2}$ but revealed the signal of NH_2 in addition to 15 aromatic protons (m, 17H, 6.67–8.17 δ ppm). The structure of **13a** was confirmed by its independent synthesis by the direct reaction of **8** with **10a** in refluxing methanolic sodium methoxide solution. The potassium salt of **13a** reacted with 1,4-dibromobutane in refluxing DMF to afford **14a** whose IR spectrum showed the absence of the OH group absorption band and its ^{1}H-NMR spectrum revealed the O$CH_2\underline{CH_2}$ (m, 4H, 1.72 δ ppm) and O$\underline{CH_2}CH_2$ (m, 4H, 3.93 δ ppm) signals in addition to the absence of an OH signal (Scheme 3 and Experimental part).

Similarly, compound **8** reacted with 2-bromo-1-phenylethanone (**10b**), 2-bromo-1-(4-chlorophenyl)ethanone (**10c**) and chloroacetonitrile (**10d**) in ethanolic sodium acetate solution under reflux to afford the corresponding 2-*S*-alkylpyridine derivatives **12b–d** respectively. 3-Aminothieno[2,3-*b*]pyridine derivatives **13b–d** could be synthesized either by intramolecular cyclization of compounds **12b–d** or the direct reaction of **8** with **10b–d** in refluxing methanolic sodium methoxide solution, for synthesis of **13b**,**c**, or refluxing xylene containing a catalytic amount of piperidine, for synthesis of **13d**. The potassium salts of **13b–d** reacted with 1,4-dibromobutane in DMF to afford bis(3-aminothieno[2,3-*b*]pyridine) derivatives **14b–d** signal (Scheme 3 and Experimental part).

3. Conclusion

The goal of this study was to describe two efficient procedures for the synthesis of previously unreported bis(2-*S*-alkylpyridines) **7** and bis(3-aminothieno[2,3-*b*]pyridines) **14** with anticipated biological activity *via* the reaction of readily accessible starting compounds, bis(pyridine-2(1*H*)-thione) derivative **5** and pyridine-2(1*H*)-thione derivative **8**.

4. Experimental

4.1. Materials

All organic solvents were acquired from commercial sources and used as received unless otherwise stated. All other chemicals were acquired from Merck, Aldrich or Acros and used without further purification. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile Attenuated Total Reflectance (ATR) sampling accessory on the Nicolet iS10 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on Varian Mercury at

300 MHz spectrophotometer using TMS as an internal standard and DMSO-d_6 as solvent and chemical shifts were expressed as δ ppm units. Elemental analyses were carried out on a EuroVector instrument C, H, N, S analyzer EA3000 Series. Compounds **1** [28], **4** [29] and **8** [30] are prepared according to the *literature* procedures.

4.2. General procedure for synthesis of potassium salts of 1, 4, 9a,b and 13a–d

A solution of KOH (5 mmol/ 3 mL water) was added to the appropriate aromatic hydroxy compounds **1, 4, 9a,b** and **13a–d** (5 mmol) in 20 mL methanol and the mixture was stirred at room temperature for 10 min. The solvent was then removed in *vacuo* and the solid was triturated with dry ether, collected by filtration, dried and used in the next reaction without further purification.

4.3. General procedure for compounds 2, 3, 7a,b and 14a–d

A mixture of 1,4-dibromobutane (5 mmol) and each of the appropriate potassium salt of **1, 4, 9a,b** and **13a–d** (10 mmol) in DMF (25 mL) was heated under reflux for 15 min. The reaction mixture was cooled to room temperature and poured onto ice-cold water. The products were collected by filtration, washed with cold ethanol, dried and recrystallized from the proper solvent to yield **2, 3, 7a,b** and **14a–d**, respectively.

4.3.1. 1,4-Bis(4-(4-formyl-1-phenyl-1H-pyrazol-3-yl)phenoxy)butane (2)

Colorless crystals recrystallized from dioxane (89%); m.p. 190–192°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.01 (m, 4H), 4.21 (t, 4H), 7.14–8.06 (m, 18H), 9.36 (s, 2H), 10.04 (s, 2H); IR (KBr) υ: 2848, 2750, 1689 cm^{-1}; Anal. for $C_{36}H_{30}N_4O_4$ (582.23): C 74.21, H 5.19, N 9.62; found C 74.58, H 5.00, N 9.99.

4.3.2. 1,4-Bis(4-[4-(3-oxo-3-phenylpropenyl)-1-phenyl-1H-pyrazol-3-yl]phenoxy) butane (3)

Yellow crystals recrystallized from dioxane (85%); m.p. 192–194°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.96 (m, 4H), 4.16 (t, 4H), 7.13–8.09 (m, 32H), 9.4 (s, 2H); IR (KBr) υ: 1674 cm^{-1}; Anal. for $C_{52}H_{42}N_4O_4$ (786.32): C 79.37, H 5.38, N 7.12; found C,79.01, H 5.66, N 7.33.

4.3.3. 1,4-Bis(4-[4-(3-cyano-2-methylsulfanyl-6-phenylpyridin-4-yl)-1-phenyl-1H-pyrazol-3-yl]phenoxy)butane (7a)

Colorless crystals recrystallized from dioxane (42% from methylation of **5** or 80% from reaction of **9a** with 1,4-dibromobutane); m.p. 210–212°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.88 (m, 4H), 2.77 (s, 6H), 4.03 (t, 4H), 6.80–8.13 (m, 30H) and 9.00 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 13.48, 26.08, 67.61, 104.48, 115.15, 115.81, 116.67, 117.14, 119.13, 123.13, 124.71, 127.76, 129.44, 130.23, 131.30, 137.16, 139.49, 147.17, 150.63, 151.01, 158.15, 163.55; IR (KBr) υ: 2241 cm^{-1}; Anal. for $C_{60}H_{46}N_8O_2S_2$ (974.32): C 73.90, H 4.75, N 11.49, S 6.58; found C 73.65, H 4.99, N 11.77, S 6.21.

4.3.4. 1,4-Bis(4-[4-(2-benzylsulfanyl-3-cyano-6-phenyl-pyridin-4-yl)-1-phenyl-1H-pyrazol-3-yl]phenoxy)butane (7b)

Colorless crystals recrystallized from ethanol (46% from benzylation of **5** or 84% from reaction of **9b** with 1,4-dibromobutane); m.p. 158–160°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.73 (m, 4H), 3.91 (t, 4H), 4.61 (s, 4H), 6.83–8.16 (m, 40H), 8.91 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 25.65, 66.81, 67.44, 111.79, 115.01, 116.98, 118.71, 119.94, 124.92, 125.15, 127.17, 127.30, 128.10, 128.80, 129.35, 129.63, 129.87, 130.16, 134.15, 134.78, 137.67, 138.02, 139.68, 149.80, 153.12, 159.86; IR (KBr) υ: 2240 cm^{-1}; Anal. for $C_{72}H_{54}N_8O_2S_2$ (1126.38): C 76.71, H 4.83, N 9.94, S 5.69; found C 76.98, H 5.05, N 9.64, S 5.33.

4.3.5. 1,4-Bis(4-[4-(2-acetyl-3-amino-6-phenylthieno[2,3-b]pyridin-4-yl)-1-phenyl-1H-pyrazol-3-yl]phenoxy)butane (14a)

Yellow crystals recrystallized from dioxane (84%); m.p. 244–246°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.72 (m, 4H), 2.10 (s, 6H), 3.93 (t, 4H), 6.84–8.20 (m, 34H), 8.93 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 25.59, 29.59, 67.38, 105.27, 115.03, 116.02, 118.90, 120.25, 122.11, 124.76, 127.16, 128.82, 129.47, 130.07, 137.48, 141.16, 148.39, 149.53, 157.62, 161.47, 162.59, 192.14; IR (KBr) υ: 3470, 3361 cm^{-1}; Anal. for $C_{64}H_{50}N_8O_4S_2$ (1058.34): C 72.57, H 4.76, N 10.58, S 6.05; found C 72.98, H 4.39, N 10.90, S 5.81.

4.3.6. 1,4-Bis(4-[4-(3-amino-2-benzoyl-6-phenylthieno[2,3-b]pyridin-4-yl)-1-phenyl-1H-pyrazol-3-yl]phenoxy)butane (14b)

Yellow crystals recrystallized from dioxane (84%); m.p. 170–172°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.89 (m, 4H), 4.01 (t, 4H), 6.78–8.15 (m, 44H), 8.99 (s, 2H); IR (KBr) υ: 3466, 3361 cm^{-1}; Anal. for $C_{74}H_{54}N_8O_4S_2$ (1182.37): C 75.11, H 4.60, N 9.47, S 5.42; found C 75.44, H 4.99, N 9.05, S 5.08.

4.3.7. 1,4-Bis(4-[4-(3-amino-2-(4-chlorobenzoyl)-6-phenylthieno[2,3-b]pyridin-4-yl)-1-phenyl-1H-pyrazol-3-yl]phenoxy)butane (14c)

Yellow crystals recrystallized from dioxane (87%); m.p. 174–176°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.82 (m, 4H), 3.94 (t, 4H), 6.87–8.14 (m, 42H), 8.93 (s, 2H); IR (KBr) υ: 3457, 3349 cm^{-1}; Anal. for $C_{74}H_{52}Cl_2N_8O_4S_2$ (1250.29): C 70.97, H 4.19, N 8.95, S 5.12; found C 70.54, H 4.01, N 8.77, S 5.36.

4.3.8. 1,4-Bis(4-[4-(3-amino-2-cyano-6-phenylthieno[2,3-b]pyridin-4-yl)-1-phenyl-1H-pyrazol-3-yl]phenoxy)butane (14d)

Yellow crystals recrystallized from dioxane (81%); m.p. 228–230°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.67 (m, 4H), 3.95 (t, 4H), 6.22 (s, 4H), 6.85–8.16 (m, 30H), 8.89 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 25.72, 67.47, 98.72, 114.99, 116.46, 118.85, 119.93, 123.06, 124.89, 127.07, 127.42, 128.81, 129.39, 130.06, 130.32, 137.75, 139.75, 146.37, 149.62, 156.00, 159.05, 160.28, 167.31; IR (KBr) υ: 3469, 3337, 2212 cm^{-1}; Anal. for $C_{62}H_{44}N_{10}O_2S_2$ (1024.31): C 72.64, H 4.33, N 13.66, S 6.25; found C 72.30, H 4.69, N 13.98, S 6.50.

4.4. Procedure for 3-[3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-1-phenylprop-2-en-1-one (4)

A solution of potassium hydroxide (10 mmol) in 2 mL of water was added to a solution of acetophenone (5 mmol) in 10 mL of ethanol. To the above mixture, a solution of 3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**) (5 mmol in 20 mL of ethanol) was added while the reaction mixture was stirred at room temperature. After complete addition, the stirring was continued for 2 h. Then the reaction mixture was poured onto ice-cold water and then neutralized (pH = 7) with diluted HCl. The product so formed was collected by filtration, washed with cold ethanol, dried and then recrystallized from ethanol to yield **4** as yellow crystals (92%); m.p. 214–216°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.93–8.09 (m, 16H), 9.37 (s, 1H), 9.76 (s, 1H); IR (KBr) υ: 3340, 1674 cm^{-1}; Anal. for $C_{24}H_{18}N_2O_2$ (366.14): C 78.67, H 4.95, N 7.65; found C 78.89, H 5.22, N 7.30.

4.5. Procedure for 1,4-bis(4-[4-(3-cyano-6-phenyl-2-thioxo-1,2-dihydropyridin-4-yl)-1-phenyl-1H-pyrazol-3-yl]phenoxy)butane (5)

A mixture of **3** (5 mmol) and 2-cyanoethanethioamide (10 mmol) in 30 mL pyridine was heated under reflux for 5 h. The reaction mixture was cooled, poured onto ice-cold water and the product so formed was collected by filtration, washed with cold ethanol, dried, and recrystallized from ethanol/ dioxane mixture to yield **5** as yellow crystals (63%); m.p. 150–152°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.88 (m, 4H), 4.05 (t, 4H), 6.95–8.09 (m, 32H), 9.01 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 25.85, 67.62, 93.20, 112.27, 115.10, 117.89, 118.18, 124.65, 127.24, 128.42, 128.72, 129.18, 129.95, 130.15, 130.79, 137.03, 138.18, 139.47, 149.05, 150.66, 157.54, 159.18; IR (KBr) υ: 3319, 2213, 1559 cm^{-1}; Anal. for $C_{58}H_{42}N_8O_2S_2$ (946.29): C 73.55, H 4.47, N 11.83, S 6.77; found C 73.18, H 4.23, N 11.99, S 6.95.

4.6. Procedure for 4-(3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (8)

A mixture of each of **4** (5 mmol) and 2-cyanoethanethioamide (5 mmol) in absolute ethanol (30 ml) containing 5 drops of piperidine was heated under reflux for 4 h. The product was collected by filtration, washed with cold ethanol, dried and recrystallized from ethanol/ dioxane mixture to yield **8** as yellow crystals (65%); m.p. 300–302°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.81–8.02 (m, 15H), 9.05 (s, 1H), 9.70 (s, 1H, D_2O-exchangeable), 14.14 (s, br, 1H, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 113.91, 115.86, 117.23, 119.09, 120.32, 123.02, 127.52, 128.42, 128.70, 129.06, 129.91, 130.22, 131.89, 137.06, 139.39, 149.31, 152.27, 157.65, 158.37, 179.95; IR (KBr) υ: 3413, 3315, 2222, 1530 cm^{-1}; Anal. for $C_{27}H_{18}N_4OS$ (446.12): C 72.63, H 4.06, N 12.55, S 7.18; found C 72.21, H 4.38, N 12.17, S 7.00.

4.7. General procedure for compounds 7a,b and 9a,b

A mixture of each of **5** and **8** (5 mmol) and each of haloalkanes **6a,b** (10 mmol for **5** or 5 mmol for **8**) in methanolic sodium methoxide solution (prepared from 10 mmol of

sodium metal in 20 mL of methanol) was heated under reflux for 2 h. The products so formed (after cooling only for **7a,b** or cooling then the reaction mixture was poured onto ice-cold water and neutralized (pH = 7) with diluted HCl for **9a,b**) were collected by filtration, washed with cold ethanol, dried and then recrystallized from the proper solvent to yield **7a,b** and **9a,b** respectively.

4.7.1. 4-[3-(4-Hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-2-(methylsulfanyl)-6-phenyl-nicotinonitrile (9a)

Colorless crystals recrystallized from dioxane (87%); m.p. 262–264°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.76 (s, 3H), 6.76–8.15 (m, 15H), 9.01 (s, 1H), 9.63 (s, 1H, D_2O-exchangeable); IR (KBr) υ: 3340, 2215 cm^{-1}; Anal. for $C_{28}H_{20}N_4OS$ (460.14): C 73.02, H 4.38, N 12.17, S 6.96; found C 73.40, H 4.63, N 11.92, S 6.60.

4.7.2. 2-(Benzylsulfanyl)-4-[3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-6-phenyl-nicotinonitrile (9b)

Colorless crystals recrystallized from dioxane (90%); m.p. 244–246°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.71 (s, 2H), 6.77–8.12 (m, 20H), 9.00 (s, 1H), 9.68 (s, 1H); IR (KBr) υ: 3409, 2233 cm^{-1}; Anal. for $C_{34}H_{24}N_4OS$ (536.17): C 73.10, H 4.51, N 10.44, S 5.97; found C 73.35, H 4.69, N 10.08, S 5.56.

4.8. General procedure for compounds 12a–d

A mixture of **8** (5 mmol) and each of **10a–d** (5 mmol) in ethanol (20 mL) containing anhydrous sodium acetate (5 mmol) was heated under reflux for 1 h. The products so formed were collected by filtration, washed with cold ethanol, dried, and then recrystallized from the proper solvent to give the final products **12a–d** respectively.

4.8.1. 4-[3-(4-Hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-2-(2-oxo-propylsulfanyl)-6-phenylnicotinonitrile (12a)

Yellow crystals recrystallized from ethanol (67%); m.p. 192–194°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.31 (s, 3H), 4.37 (s, 2H), 6.78–8.03 (m, 15H), 9.02 (s, 1H), 9.66 (s, 1H); IR (KBr) υ: 3393, 2211, 1720 cm^{-1}; Anal for $C_{30}H_{22}N_4O_2S$ (502.15): C 71.69, H 4.41, N 11.15, S 6.38; found C 72.00, H 4.28, N 10.88, S 6.72.

4.8.2. 4-[3-(4-Hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-2-(2-oxo-2-phenylethylsulfanyl)-6-phenylnicotinonitrile (12b)

Colorless crystals recrystallized from ethanol (75%); mp. 186–188°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.05 (s, 2H), 6.69–8.16 (m, 20H), 8.92 (s, 1H), 9.67 (s, 1H); IR (KBr) υ: 3378, 2227, 1695 cm^{-1}; Anal. for $C_{35}H_{24}N_4O_2S$ (564.16): C 74.45, H 4.28, N 9.92, S 5.68; found C 74.02, H 4.56, N 10.12, S 5.33.

4.8.3. 2-[2-(4-Chlorophenyl)-2-oxo-ethylsulfanyl]-4-[3-(4-hydroxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-6-phenylnicotinonitrile (12c)

Colorless crystals recrystallized from ethanol (71%); mp. 250–252°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.04 (s, 2H,), 6.71–8.17 (m, 19H), 9.09 (s, 1H), 9.68 (s, 1H); IR (KBr) υ:

3387,2222, 1697 cm^{-1}; Anal. for $C_{35}H_{23}ClN_4O_2S$ (598.12): C 70.17, H 3.87, N 9.35 S 5.35; found C 70.39, H 4.11, N 9.01, S 5.06.

4.8.4. 2-Cyanomethylsulfanyl-4-[3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-6-phenyl-nicotinonitrile (12d)

Colorless crystals recrystallized from ethanol (78%); m.p. 204–206°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.52 (s, 2H), 6.79–8.19 (m, 15H), 9.05 (s, 1H), 9.69 (s, 1H); IR (KBr) υ: 3387, 2215 cm^{-1}; Anal. for $C_{29}H_{19}N_5OS$ (485.13): C 71.73, H 3.94, N 14.42, S 6.60; found C 71.52, H 4.11, N 14.78, S 6.82.

4.9. General procedure 'A' for compounds 13a–c

A mixture of each of **12a–c** (5 mmol) in methanolic sodium methoxide solution (prepared from 10 mmol of sodium metal in 20 mL of methanol) was heated under reflux for 2 h. The reaction mixture was cooled, poured onto ice-cold water and neutralized (pH = 7) with diluted HCl. The products that formed were collected by filtration, washed with cold ethanol, dried and then recrystallized from the proper solvent to give the **13a–c** respectively.

4.10. General procedure 'B' for compounds 13a–c

A mixture of **8** (5 mmol) and each of **10a–c** (5 mmol) in methanolic sodium methoxide solution (prepared from 15 mmol of sodium metal in 20 mL of methanol) was heated under reflux for 4 h. The reaction mixture was cooled, poured onto ice-cold water and neutralized (pH = 7) with diluted HCl. The products that formed were collected by filtration, washed with cold ethanol, dried and then recrystallized from the proper solvent to give the **13a–c** respectively.

4.10.1. 2-Acetyl-3-amino-4-[(3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-6-phenyl-thieno[2,3-b]pyridine (13a)

Pale yellow crystals recrystallized from acetic acid (80% from procedure 'A' or 61% from procedure 'B'); m.p. 180–182°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.37 (s, 3H), 6.67–8.17 (m, 17H), 8.87 (s, 1H), 9.60 (s, 1H); IR (KBr) υ: 3471, 3381 cm^{-1}; Anal for $C_{30}H_{22}N_4O_2S$ (502.15): C 71.69, H 4.41, N 11.15, S 6.38; found C 72.02, H 4.72, N 10.84, S 5.98.

4.10.2. 3-Amino-2-benzoyl-4-[3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-6-phenyl-thieno[2,3-b]pyridine (13b)

Yellow crystals recrystallized from dioxane (85% from procedure 'A' or 62% from procedure 'B'); m.p. 264−268°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.69–8.01 (m, 22H), 9.09 (s, 1H), 9.66 (s, br, 1H); IR (KBr) υ: 3478, 3323 cm^{-1}; Anal. for $C_{35}H_{24}N_4O_2S$ (564.16): C 74.45, H 4.28, N 9.92, S 5.68; found C 74.06, H 4.02, N 10.20, S 5.99.

4.10.3. 3-Amino-2-(4-chlorobenzoyl)-4-[3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-6-phenylthieno[2,3-b]pyridine (13c)

Yellow crystals recrystallized from dioxane (83% from procedure 'A' or 65% from procedure 'B'); m.p. 288–290°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.69–8.18 (m, 21H), 8.95 (s,

1H), 9.62 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 66.81, 103.37, 115.80, 115.95, 118.87, 120.36, 121.54, 123.21, 127.66, 129.04, 129.49, 129.80, 130.08, 130.84, 136.44, 137.40, 139.82, 141.60, 149.94, 151.39, 158.10, 162.87, 187.93; IR (KBr) υ: 3465, 3335 cm^{-1}; Anal. for $C_{35}H_{23}ClN_4O_2S$ (598.12): C 70.17, H 3.87, N 9.35, S 5.35; found C 69.88, H 4.10, N 9.77, S 5.66.

4.11. Procedure 'A' for compound 13d

A mixture of **12d** (5 mmol) and piperidine (5 mL) in dry xylene (20 mL) was heated under reflux for 4 h. After cooling, the reaction mixture was poured onto ice-cold water and neutralized (pH = 7) with diluted HCl. The product that formed was collected by filtration, washed with cold ethanol, dried and then recrystallized from ethanol/dioxane mixture to give **13d**.

4.12. Procedure 'B' for compound 13d

A mixture of **8** (5 mmol), **10d** (5 mmol) and piperidine (5 mL) in dry xylene (20 mL) was heated under reflux for 6 h. After cooling, the reaction mixture was poured onto ice-cold water and neutralized (pH = 7) with diluted HCl. The product that formed was collected by filtration, washed with cold ethanol, dried and then recrystallized from ethanol/ dioxane mixture to give **13d**.

4.12.1. 3-Amino-4-[3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-6-phenylthieno [2,3-b]-pyridine-2-carbonitrile (13d)

Yellow crystals recrystallized from ethanol/dioxane mixture (81% from procedure 'A' or 69% from procedure 'B'); m.p. 292–294°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.02 (s, 2H), 6.69–8.19 (m, 15H), 8.91 (s, 1H), 9.63 (s, br, 1H, D_2O-exchangable); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 73.92, 113.37, 115.57, 118.79, 120.80, 123.10, 127.64, 128.89, 129.49, 130.14, 130.77, 137.26, 139.64, 140.30, 143.37, 150.00, 150.71, 157.21, 158.14, 161.56; IR (KBr) υ: 3465, 3335, 2192 cm^{-1}; Anal. for $C_{29}H_{19}N_5OS$ (485.13): C 71.73, H 3.94, N 14.42, S 6.60; found C 72.05, H 4.25, N 14.06, S 6.13.

Disclosure statement

No potential conflict of interest was reported by the authors.

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