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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME BIS(THIOXOPYRIDINE), BIS(PYRAZOLO[3,4-*b*]PYRIDINE), BIS(THIENO[2,3-*b*]PYRIDINE), BIS(1,3,4-THIADIAZOLE) AND BIS-THIOPHENE DERIVATIVES

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Abstract – Condensation of the *N,N′*-(ethane-1,2-diyl)bis(cyanoacetamide) (**1**) with aromatic aldehydes gave the corresponding *N,N*'-(ethane-1,2-diyl)-bis(2-cyano-3-phenylacrylamide) derivatives **2a-c**. The latter products react with 2-cyanothioacetamide to afford 1,2-bis(4-aryl-3,5-dicyano-6-mercapto-2-oxo-1,2-dihydropyridin-1-yl)ethane derivatives **5a-c**. Treatment of 1,2-bis(3,5-dicyano-6-mercapto-2-oxo-4-phenyl-1,2-dihydropyridin-1-yl)ethane (**5a**) or its *S*-methyl derivative **6** with hydrazine hydrate afforded 1,2-bis(3-amino-5-cyano-6,7-dihydro-7-methyl-6-oxo-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)ethane (**7**). Reaction of bis(6-mercaptopyridine) **5b** with chloroacetone gave the 1,2-bis[2-acetyl-3-amino-6,7-dihydro-5-cyano-4-(4-methoxyphenyl)-6-oxothieno[2,3-*b*]pyridine-7-yl]ethane (**9**). Treatment of the bis(cyanoacetamide) **1** with phenyl isothiocyanate afforded *N,N′*-(ethane-1,2-diyl)bis[2-cyano-3-mercapto-3-(phenyl amino)acrylamide] (**11**) which reacts with hydrazonoyl halides **12a,b** or haloketones **15a-c** to give the corresponding *N,N′*-(ethane-1,2-diyl)bis[2-cyano-2-(3,5-disubstituted-2(3*H*)–1,3,4-thiadiazolylidene)acetamides] **14a,b** or *N,N′*- (ethane-1,2-diyl)bis[4-amino-5-substituted-2-(phenylamino)thiophene-3-car boxamide] **16a-c** derivatives, respectively. Antimicrobial evaluation of selected example of the newly synthesized compounds was carried out.

INTRODUCTION

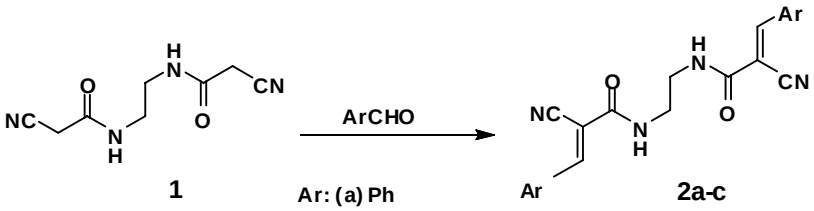
Several substituted pyridine-2-thiones have been found to be useful as antibiotic,[1,2] antiarteriosclerotic,[3] antibacterial,[4] antihyperglycemic[5] and antifungal[6] agents and as inhibitors of the blood coagulation

factor.[7] Also, some thieno[2,3-*b*]pyridine derivatives are known to posses antiviral,[8] antihypertensive[9] and immunostimulating[10] activities. They are also used as gonadtropin-releasing hormone antagonists[11-16] and as lipoxygenases inhibitors.[17] Recently, bis(heterocycles) have received grate deal of attention, not only for being model compounds for main chain polymers,[18-23] but also because many biologically active natural and synthetic products have molecular symmetry.[24]

Encouraged by these findings and in continuation of our previous work aimed at the synthesis of a variety of heterocyclic systems for biological and pharmacological evaluation,[25-33] we have found that *N,N′*-(ethane-1,2-diyl)bis(cyanoacetamide) (**1**), is a versatile, readily accessible building block for the synthesis of several new bisheterocyclic compounds of biological potency.

RESULTS AND DISCUSSION

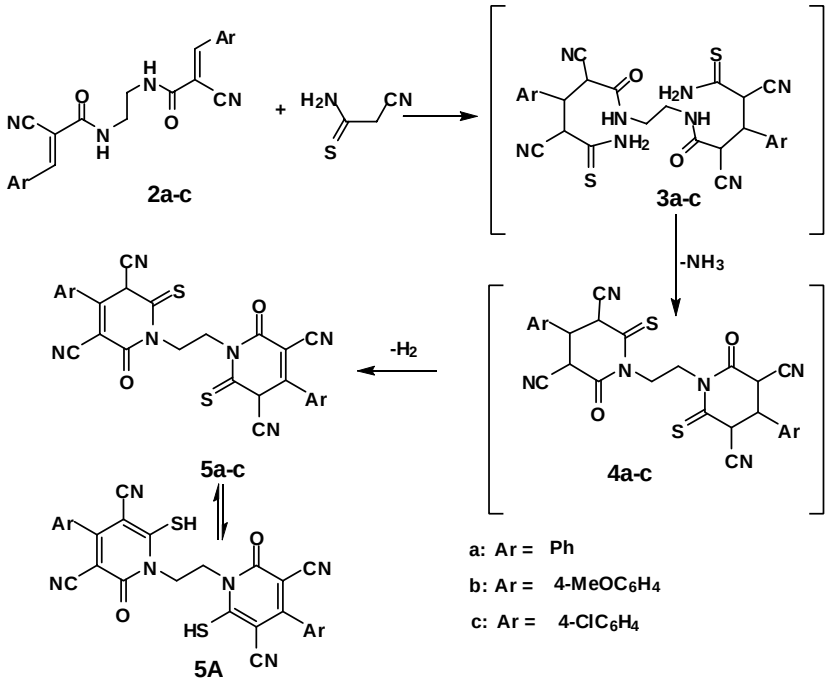
N,N′-(Ethane-1,2-diyl)bis(cyanoacetamide) (**1**)[34] reacts with aromatic aldehydes to afford the corresponding *N,N*'-(ethane-1,2-diyl)bis(2-cyano-3-phenylacrylamide) derivatives **2a-c**[35,36] (Scheme 1). The IR spectrum of compound **2c**, taken as a typical example of the series prepared, revealed absorption bands at 1674, 2214 and 3371 cm^{-1} corresponding to carbonyl, nitrile and NH functions, respectively. Its ^1H NMR spectrum showed signals at δ 3.39, 8.18 and 8.60 D_2O-exchangeable due to CH_2, CH and NH protons in addition to two aromatic protons at δ 7.65 and 7.97.



Scheme 1

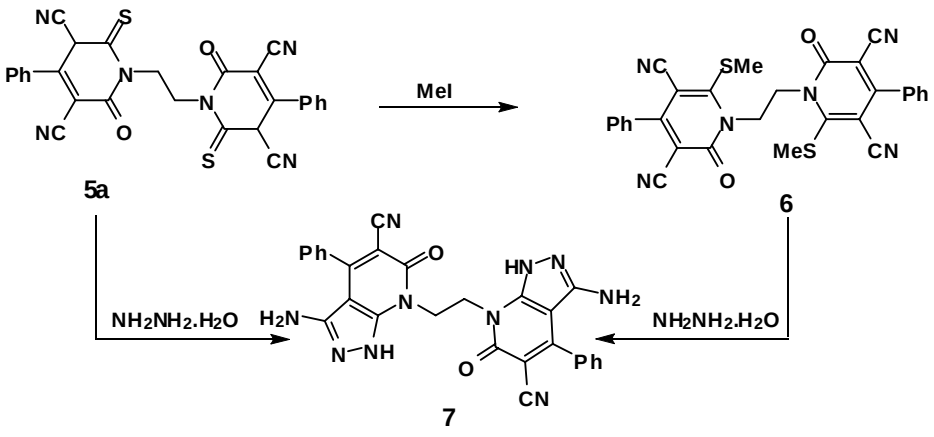
Treatment of the products **2a-c** with 2-cyanothioacetmide[37] furnished 1,2-bis(4-aryl-3,5-dicyano-6-mercapto-2-oxo-1,2-dihydropyridin-1-yl)ethane derivatives **5a-c** (Scheme 2). The IR spectrum of compound **5a**, taken as a typical example of the prepared series, revealed absorption bands at 1543, 1643, and 2217 cm^{-1} corresponding to thiocarbonyl, carbonyl and nitrile functions, respectively. Its ^1H NMR spectrum showed signals at δ 3.4 and 13.1 D_2O-exchangeable due to CH_2 and SH protons in addition to an aromatic multiplet in the region δ 7.49-7.60. Compounds **5a-c** are assumed to be formed *via* an initial *Michael type* adducts **4** followed by an intramolecular cyclization[38] and dehydrogenation to the final products **5a-c** (Scheme 2). Alkylation of compound **5a** with methyl iodide afforded the *S*-alkyl derivative **6** (Scheme 3). The IR spectrum of **6** revealed absorption bands at 1620 and 2214 cm^{-1} corresponding to

carbonyl and two nitrile groups, respectively. Its ^{1}H NMR spectrum revealed signal at δ 2.6 due to SCH_3, signal at δ 3.4 due to CH_2 protons and an aromatic multiplet in the region 7.57-8.02.



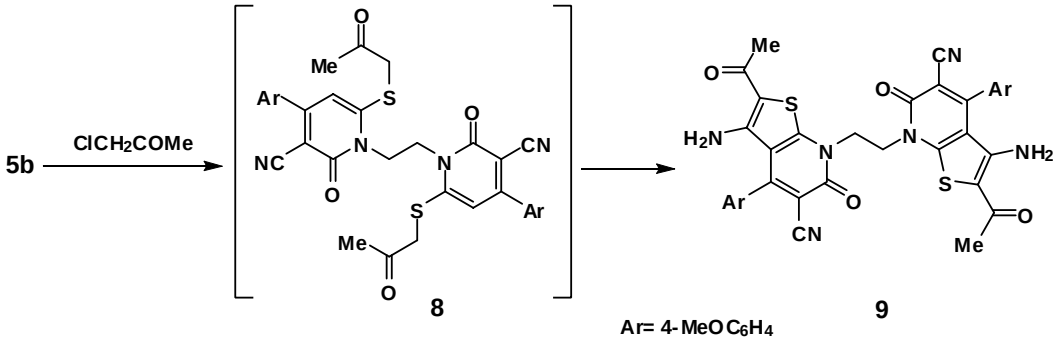
Scheme 2

Reaction of the latter product with hydrazine hydrate gave 7,7'-(ethane-1,2-diyl)bis(3-amino-6,7-dihydro-6-oxo-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile) (**7**) (Scheme 3). The latter product was alternatively prepared from the reaction of the bispyridinethione derivative **5a** also with hydrazine hydrate to give **7** (Scheme 3). The ^{1}H NMR spectrum of compound **7** revealed signal at δ 4.3 due to CH_2, in addition to two D_2O-exchangeable signals at δ 6.83 and 11.94 due to NH_2 and NH protons, respectively in addition to an aromatic multiplet in the region 7.51-7.62.



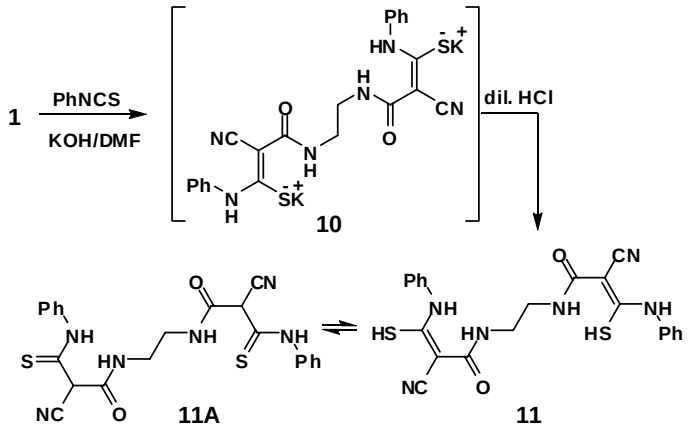
Scheme 3

Compound **5b** reacts with chloroacetone to give bis(thienopyridine) derivative **9** (Scheme 4). The IR spectrum of compound **8** revealed absorption bands at 1636, 1728, 2206, 3333 and 3425 cm^{-1} corresponding to two carbonyl, nitrile and amino functions, respectively. It's ^1H NMR spectrum showed signals at δ 2.35, 3.86, 4.22 and 7.95 D_2O-exchangeable due to CH_3CO, CH_3O, CH_2 and NH_2 protons in addition to an aromatic multiplet in the region δ 7.50-7.54.



Scheme 4

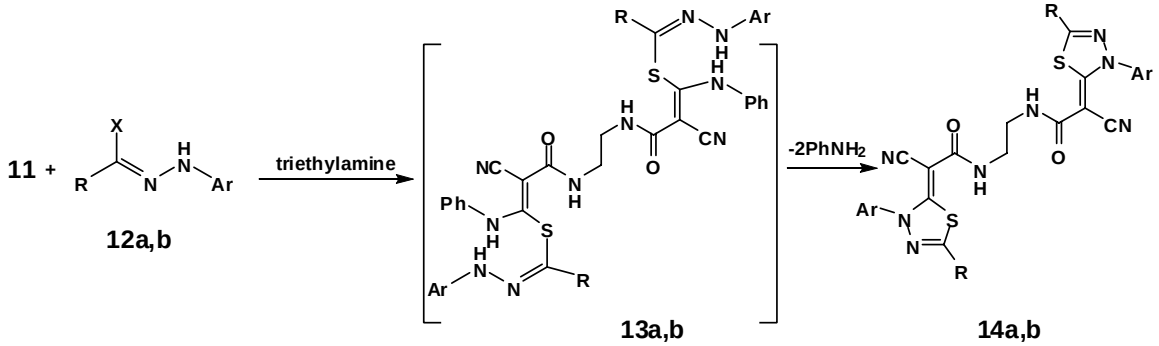
Treatment of the *N,N′*-(ethane-1,2-diyl)bis(cyanoacetamide) (**1**) with phenyl isothiocyanate, in dimethyl-formamide, and in the presence of potassium hydroxide, at rt, followed by treatment with dilute hydrochloric acid, afforded a yellow-colored product identified as *N,N′*-(ethane-1,2-diyl)bis[2-cyano-3-mercapto-3-(phenylamino)acrylamide] (**11**) (Scheme 5). The IR spectrum of the latter product showed absorption bands at 3375, 3286 and 2185 cm^{-1} due to two NH groups and a nitrile functions, respectively. Its ^1H NMR spectrum showed signals at δ 3.32 and three D_2O-exchangeable signals at δ 10.81, 10.97 and 11.94 due to CH_2, 2 NH and SH protons, respectively, in addition to an aromatic multiplet in the region δ 7.08-7.79.



Scheme 5

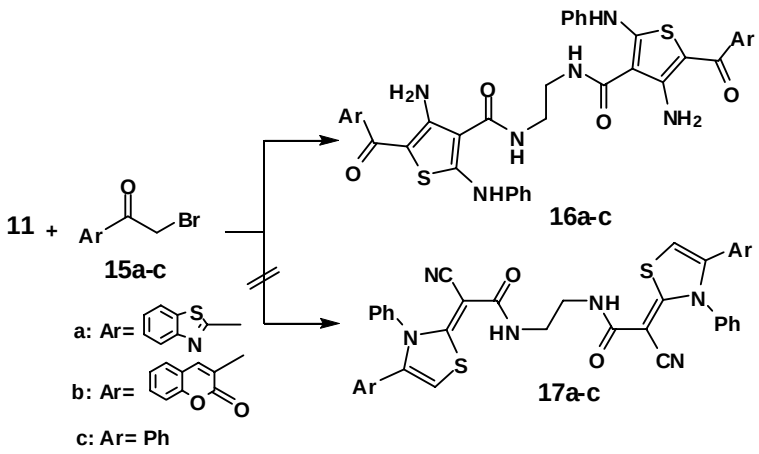
Compound **11** reacts with the hydrazonoyl halide **12a,b**[39,40] to afford the thiadiazole derivatives **14a,b** (Scheme 6). The IR spectrum of compound **14a**, taken as a typical example revealed absorption bands at

1666, 1713, 2218 and 3240 cm^{-1} corresponding to two carbonyls, nitrile and NH functions, respectively. Its ^1H NMR spectrum showed a triplet signal at δ 1.17 (J = 7.2 Hz) due to CH_3 and a quartet signal at δ 4.19 (J = 7.2 Hz) due to CH_2 of ethoxy protons, at δ 3.31 due to CH_2 and at δ 11.79 D_2O-exchangeable corresponding to NH in addition to aromatic protons in the region δ 7.22-7.84. The latter compounds were assumed to be formed *via* elimination of aniline molecule from the none-isolable intermediate to the final products **14a,b** (Scheme 6).



Scheme 6

Compound **11** reacts with 2-(bromoacetyl)benzothiazole (**15a**)[41] to afford the corresponding thiophene derivative **16a** (Scheme 7). The IR spectrum of the isolated product showed absorption bands at 3400, 3352 and 1656 cm^{-1} characteristic for NH_2 and carbonyl groups, respectively. Its ^1H NMR spectrum showed signals at δ 3.47, 8.37 and 10.06 corresponding to CH_2 and two D_2O-exchangeable signals corresponding to two NH protons, in addition to an aromatic multiplet and NH_2 protons in the region δ 7.20-8.2. The foregoing spectral data supported the proposed structure **16a** and ruled out the other possible thiazole structure **17** (Scheme 6). Similarly, compound **11** reacted with 3-(bromoacetyl)benzo[*b*]pyran (**15b**)[42,43] and 1-phenyl-2-bromoethanone (**15c**)[44] under similar reaction conditions and afforded the thiophene derivatives **16b,c**, respectively as shown in Scheme 7.



Scheme 7

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in dimethylsulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The biological evaluation of the products **5b**, **5c**, **14b** and **16b** were carried out in the Medical Mycology Laboratory of the Regional Center for Mycology and Biotechnology of Al-Azhar University, Cairo, Egypt.

N,N'-(Ethane-1,2-diyl)bis(cyanoacetamide) (**1**),[34] 2-cyanothioacetamide,[37] hydrazonoyl halides **11a**,[39] **11b**,[40] 1-(benzothiazol-2-yl)-2-bromoethanone (**15a**),[41] 3-(2-bromoacetyl)-2*H*-chromen-2-one (**15b**),[42,43] 2-bromo-1-phenylethanone (**15c**)[44] were prepared following the literature procedure.

N,N'-(Ethane-1,2-diyl)bis(2-cyano-3-arylacrylamide) derivatives 2a-c.

General procedure:

To an ethanolic solution of the bis(cyanoacetamide) **1** (0.194 g, 1 mmol) and the appropriate aromatic aldehyde (2 mmol), was added few drops of piperdine and the reaction mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure and the residue was triturated with EtOH, filtered off, washed with EtOH and finally purified by recrystallization from DMF/EtOH to afford *N*,*N'*-(ethane-1,2-diyl)bis(2-cyano-3-arylacrylamide) derivatives **2a-c.**

N,N'-(Ethane-1,2-diyl)bis(2-cyano-3-phenylacrylamide) (2a).

Pale yellow crystals, yield: 0.22 g (60%), mp 210-211 ºC; IR (KBr): 3310 (NH), 2208 (C≡N), 1668 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.40 (s, 4H, 2NCH$_2$), 7.56-7.99 (m, 10H, ArH's), 8.20 (s, 2H, 2CH), 8.64 (s, 2H, D$_2$O-exchangeable 2NH). Anal. Calcd for $C_{22}H_{18}O_2N_4$ (370.14): C, 71.34; H, 4.90; N, 15.13. Found: C, 71.36; H, 4.94; N, 15.10%.

N,N'-(Ethane-1,2-diyl)bis[2-cyano-3-(4-methoxyphenyl)acrylamide] (2b).

Pale yellow crystals, yield: 0.29 g (68%), mp 245-246 ºC; IR (KBr): 3356 (NH), 2206 (C≡N), 1666 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.39 (s, 4H, 2NCH$_2$), 3.86 (s, 6H, OCH$_3$), 7.10 (d, 4H, ArH's, J = 8.7 Hz), 7.95-8.0 (d, 4H, ArH's, J = 8.7 Hz), 8.12 (s, 2H, 2CH), 8.47 (s, 2H, D$_2$O-exchangeable 2NH); ^{13}C NMR [DMSO-d_6] δ 38.75, 55.56, 102.76, 114.78, 116.86, 124.41, 132.34, 149.98, 161.65, 162.54. Anal. Calcd for $C_{24}H_{22}O_4N_4$ (430.16): C, 66.97; H, 5.15; N, 13.02. Found: C, 66.94; H, 5.17; N, 13.05%.

N,N'-(Ethane-1,2-diyl)bis[2-cyano-3-(4-chlorophenyl)acrylamide] (2c).

Pale yellow crystals, yield: 0.33 g (77%), mp 274-275 ºC; IR (KBr): 3371 (NH), 2214 (C≡N), 1674 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.39 (s, 4H, 2NCH$_2$), 7.66 (d, 4H, ArH's, J = 8.4 Hz), 7.96 (d, 4H,

ArH's, *J* = 8.4 Hz), 8.18 (s, 2H, 2CH), 8.60 (s, 2H, D_2O-exchangeable 2NH). Anal.Calcd for $C_{22}H_{16}O_2N_4Cl_2$ (438.07): C, 60.15; H, 3.67; N, 12.75; Cl, 16.14. Found: C, 60.17; H, 3.69; N, 12.78; Cl, 16.12%.

1,2-Bis(4-aryl-3,5-dicyano-6-mercapto-2-oxo-1,2-dihydropyridin-1-yl)ethane derivatives 5a-c.

General procedure:

To a solution of the appropriate *N*,*N*'-(ethane-1,2-diyl)bis(2-cyano-3-arylacrylamide) derivatives **2a-c** (1 mmol) in EtOH (20 mL) was added 2-cyanothioacetamide (0.2 g, 2 mmol) and few drops of piperdine then the reaction mixture was heated under reflux for 2 h. The solid product was collected by filtration, washed with EtOH and then recrystallized from DMF/EtOH to give **5a-c**.

1,2-Bis(3,5-dicyano-6-mercapto-2-oxo-4-phenyl-1,2-dihydropyridin-1-yl)ethane (5a).

Yellow crystals, yield: 0.32 g (60%), mp 250-251 ºC; IR (KBr): 1543 (C=S), 1643 (C=O), 2214 (C≡N), 2217 (C≡N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.40 (s, 4H, $2NCH_2$), 7.49-7.60 (m, 10H, ArH's), 13.10 (s, 2H, D_2O-exchangeable 2SH). Anal. Calcd for $C_{28}H_{16}O_2N_6S_2$ (532.08): C, 63.14; H, 3.03; N, 15.78; S, 12.04. Found: C, 63.12; H, 3.07; N, 15.80; S, 12.03%.

1,2-Bis[3,5-dicyano-4-(4-methoxyphenyl)-6-mercapto-2-oxo-1,2-dihydropyridin-1-yl]ethane (5b).

Yellow crystals, yield: 0.41 g (69%), mp 264-265 ºC; IR (KBr): 1546 (C=S), 1638 (C=O), 2214 (C≡N) cm^{-1}. Anal. Calcd for $C_{30}H_{20}O_4N_6S_2$ (592.65): C, 60.80; H, 3.40; N, 14.18; S, 10.82. Found: C, 60.78; H, 3.45; N, 14.15; S, 10.87%.

1,2-Bis[4-(4-chlorophenyl)-3,5-dicyano-6-mercapto-2-oxo-1,2-dihydropyridin-1-yl]ethane (5c).

Yellow crystals, yield: 0.48 g (80%); mp > 300 ºC; IR (KBr): 1547 (C=S), 1643 (C=O), 2217 (C≡N) cm^{-1}; ^1H- NMR (DMSO-d_6): δ 3.40 (s, 4H, $2NCH_2$), 7.57-7.67 (m, 8H, ArH's), 13.05 (s, 2H, D_2O-exchangeable, 2SH). Anal. Calcd for $C_{28}H_{14}O_2N_6S_2Cl_2$ (601.49): C, 55.91; H, 2.35; N, 13.90; S, 10.66; Cl, 11.79. Found: C, 55.93; H, 2.33; N, 13.88; S, 10.68; Cl, 11.75%.

1,2-Bis(3,5-dicyano-6-methylthio-2-oxo-4-phenyl-1,2-dihydropyridin-1-yl)ethane (6).

The bis[6-mercapto-1,2-dihydropyridine] **5a** (0.53 g, 1 mmol) was dissolved in an ethanolic solution of sodium ethoxide [prepared from sodium metal (0.046 g, 2 mg atom) in EtOH (30 mL)], then methyl iodide (0.6 g, 4 mmol) was added gradually to the resulting solution. The reaction mixture was heated under reflux for 2 h, concentrated, allowed to cool, diluted with water. The precipitate that obtained was filtered off, washed with water and recrystallized from EtOH/DMF to produce **6** in 65% yield; mp 268-269 ºC; IR (KBr): 1620 (C=O), 2214 (C≡N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.60 (s, 6H, $2SCH_3$), 3.40 (s, 4H, $2NCH_2$), 7.54-8.02 (m, 10H, ArH's). Anal. Calcd for $C_{30}H_{20}O_2N_6S_2$ (560.65): C, 64.27; H, 3.60; N, 14.99; S, 11.44, found: C, 64.30; H, 3.62; N, 15.00; S, 11.47%.

7,7'-(Ethane-1,2-diyl)bis(3-amino-6,7-dihydro-6-oxo-4-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile) (7)

General procedure:

To a solution of bis(6-mercaptopyridine) **5a** (0.53 g, 1 mmol) or bis(6-methythiopyridine) **6** (0.56 g, 1 mmol) in EtOH (20 mL), hydrazine hydrate (80%, 0.2 ml, 2 mmol) was added and the reaction mixture was refluxed for 4 h, and then left to cool. The solid product so formed was filtered off, washed with EtOH and dried. Recrystallization from EtOH/DMF afforded **7** in 55% and 48% yields from **5a** and **6**, respectively, mp 300-302 ºC; IR (KBr): 3412, 3235, 3105 (NH, NH_2), 1666 (C=O), 2214 (C≡N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.30 (s, 4H, $2NCH_2$), 6.83 (s, 4H, D_2O-exchangeable, $2NH_2$), 7.51-7.62 (m, 10H, ArH's), 11.94 (s, 2H, D_2O-exchangeable, 2NH). Anal. Calcd for $C_{28}H_{20}O_2N_{10}$ (528.18): C, 63.63; H, 3.81; N, 26.50. Found: C, 63.61; H, 3.85; N, 26.47%.

1,2-Bis[2-acetyl-3-amino-5-cyano-6,7-dihydro-4-(4-methoxyphenyl)-6-oxothieno[2,3-b]pyridin-7-yl]ethane (9).

The bis(6-mercaptopyridine) **5b** (0.59 g, 1 mmol) was dissolved in an ethanolic solution of sodium ethoxide [prepared from sodium metal (0.046 g, 2 mg atom) in EtOH (30 mL)], then chloroacetone (4 mmol) was added gradually to the resulting solution. The reaction mixture was heated under reflux for 2 h, concentrated, allowed to cool, diluted with water and left overnight. The precipitate that obtained was filtered off, washed with water and recrystallized from EtOH/DMF to produce pale yellow crystals.

Yield**:** 0.42 g (60%); mp 226-227 ºC ; IR (KBr): 3425 and 3333 (NH_2), 2206 (C≡N). 1728 (C=O), 1636 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.35 (s, 6H, $2CH_3$), 3.86 (s, 6H, $2CH_3$), 4.22 (s, 4H, $2NCH_2$), 7.14-7.52 (m, 8H, ArH's), 7.95 (s, 4H, D_2O-exchangeable $2NH_2$). MS *m/z* (%) 704 (M^+, 91.67). Anal. Calcd for $C_{36}H_{28}O_6N_6S_2$ (704.77): C, 61.35; H, 4.00; N, 11.92; S, 9.10. Found: C, 61.30; H, 4.03; N, 11.90; S, 9.08%.

N,N'-(Ethane-1,2-diyl)bis[2-cyano-3-mercapto-3-(phenylamino)acrylamide] (11).

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in DMF (20 mL) was added the bis(cyanoacetamide) **1** (0.194 g, 1 mmol). After stirring for 30 min, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h, and then the reaction mixture was poured over a cold solution of 0.5 N hydrochloric acid. The solid product that formed was filtered off, washed with water, dried, and finally recrystallized f rom EtOH /DMF mixture to afford yellow crystals of **11** in 60% yield, mp 224-225 ºC; IR (KBr): 3375 (NH), 3286 (NH), 2185(C≡N), 1616 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.32 (s, 4H, $2NCH_2$), 7.08-7.79 (m, 10H, ArH's), 10.81(s, 2H, D_2O-exchangeable, 2NH), 10.97 (s, 2H, D_2O-exchangeable, 2NH), 11.94 (s, 2H, D_2O-exchangeable, 2SH); MS *m/z* (%): 465 (M^++1, 93), 232 (M^+/2, 89). Anal. Calcd for $C_{22}H_{20}N_6O_2S_2$ (464.56): C, 56.88; H, 4.34; N, 18.09; S, 13.80%. Found: C, 56.85; H, 4.30; N, 18.10; S, 13.82%.

Reaction of compound 11 with hydrazonoyl halides 12a,b or haloketones 15a-c

General Procedure*.*

To a solution of the compound **11** (0.464 g, 1 mmol) in EtOH (20 mL), the appropriate hydrazonoyl halides **12a,b** or haloketones **15a-*c*** (2 mmol) were added. Triethylamine (0.2 mmol) was added dropwise and the reaction mixture was refluxed for 1 h then allowed to cool. The formed solid was filtered off, washed with EtOH, and recrystallized from DMF/EtOH to afford the corresponding bis-thiadiazoles **14a,b** or bis-thiophene derivatives **16a-c.**

N,N'-(Ethane-1,2-diyl)bis[2-cyano-2-[5-ethoxycarbonyl-3-(4-nitrophenyl)-2(3H)-1,3,4-thiadiazolylidene)acetamide] (14a).

Green crystals, yield: 0.54 g (72%); mp 158-159 ºC; IR (KBr): 3240 (NH), 2218 (C≡N), 1713 (C=O), 1666 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.17 (t, 6H, $2CH_3$, J = 7.2 Hz), 3.31 (s, 4H, $2NCH_2$), 4.19 (q, 4H, $2CH_2$, J =7.2 Hz), 7.22-7.84 (m, 8H, ArH's), 11.79 (s, 2H, D_2O-exchangeable 2NH). Anal. Calcd for $C_{30}H_{24}O_{10}N_{10}S_2$ (748.70): C, 48.13; H, 3.23; N, 18.71; S, 8.57. Found: C, 48.10; H, 3.22; N, 18.74; S, 8.55%.

N,N'-(Ethane-1,2-diyl)bis[2-cyano-2-[3-(4-nitrophenyl)-5-(thien-2yl-carbonyl)-2(3H)-1,3,4-thiadiazolylidene)acetamide] (14b).

Green crystals, yield: 0.64 g (77%), mp 240-241 ºC; IR (KBr): 3109 (NH), 2195 (C≡N), 1668 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.32 (s, 4H, $2NCH_2$), δ 7.23-8.28 (m, 14H, ArH's), 11.56 (s, 2H, D_2O-exchangeable 2NH). Anal. Calcd for $C_{34}H_{20}O_8N_{10}S_4$ (824.84): C, 49.51; H, 2.44; N, 16.98; S, 15.55. Found: C, 49.53; H, 2.42; N, 16.95; S, 15.57%.

N,N'-(Ethane-1,2-diyl)bis[4-amino-5-(benzothiazol-2-carbonyl)-2-(phenylamino)]thiophene-3-carboxamide (16a).

Yellow crystals, yield: 0.53 g (65%); mp > 300 ºC; IR (KBr): 3420-3333(NH_2+2NH), 1656 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.47 (s, 4H, $2NCH_2$), 7.20-8.20 (m, 22H, ArH's+$2NH_2$), 8.37 (s, 2H, D_2O-exchangeable 2NH), 10.06 (s, 2H, D_2O-exchangeable 2NH); ^{13}C NMR [DMSO-d_6] δ 38.69, 93.57, 121.03, 121.22, 122.74, 124.10, 124.76, 126.64, 126.80, 129.46, 135.52, 152.87, 160.05, 163.95, 164.39. Anal. Calcd for $C_{40}H_{30}O_4N_8S_4$ (814.98): C, 58.95; H, 3.71; N, 13.75; S, 15.74. Found: C, 58.97; H, 3.73; N, 13.72; S, 15.71%.

N,N'-(Ethane-1,2-diyl)bis[4-amino-5-(benzopyran-3-carbonyl)-2-(phenylamino)]thiophene-3-carboxamide (16b).

Green crystals, yield: 0.50 g (60%); mp >300 ºC; IR (KBr): 3420-3333 (NH_2+2NH), 1646 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.37 (s, 4H, $2NCH_2$), 6.75-7.49 (m, 24H, ArH's + 2 NH_2), 10.32 (s, 2H, D_2O-exchangeable 2NH), 11.97 (s, 2H, D_2O-exchangeable 2NH). Anal. Calcd for $C_{44}H_{32}O_8N_6S_2$ (836.89): C, 63.15; H, 3.85; N, 10.04; S, 7.66. Found: C, 63.17; H, 3.87; N, 10.06; S, 7.64%.

N,N'-(Ethane-1,2-diyl)bis[4-amino-5-(benzoyl)-2-(phenylamino)]thiophene-3-carboxamide (16c).

Yellow crystals, yield: 0.48 g (68%); mp 292-293 ºC; IR (KBr): 3317-3395(NH_2 + 2NH), 1638 (C=O)

cm^{-1}; insoluble in common NMR solvents; Anal. Calcd for $C_{38}H_{32}O_4N_6S_2$ (700.83): C, 65.12; H, 4.60; N, 11.99; S, 9.15. Found: 65.15; H, 4.62; N, 11.96; S, 9.16%.

ANTIMICROBIAL ACTIVITY

Compounds **5b**, **5c**, **14b** and **16b** were tested for their antimicrobial activities using four fungal species, namely *Aspergillus fumigatus **AF***, *Penicillium italicum **PI***, *Syncephalastrum racemosum **SR*** and *Candida albicans **CA***. Also, four bacteria species namely, *Staphylcoccus aureus **SA***, *Psedomo naaeruginosa **PA***, *Bacillusubtilis **BS*** and *Escherichia coli **EC*** were tested. The organisms were tested against the activity of solutions of concentration of 1 mg/mL, 2.5 mg/mL and 5 mg/mL of each compound and using an inhibition zone diameter in cm (IZD) as criterion for the antimicrobial activity. The fungicide Terbinafin and the bactericide Chloramphenicol were used as references to evaluate the potency of the tested compounds under the same conditions. The results are summarized in Table 1.

Table 1. Antimicrobial activity of compounds **5b**, **5c**, **14b** and **16b**

Micro-organism/IZD (cm)*

Sample	**5b mg/ml**			**5c mg/ml**			**14b mg/ml**			**16b mg/ml**			**Standard mg/ml**		
mg/ml	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1
(AF)	++	++	+	0	0	0	0	0	0	0	0	0	+++	+++	++
(PI)	++	++	0	0	0	0	0	0	0	0	0	0	+++	+++	++
(SR)	0	0	0	0	0	0	+	+	+	0	0	0	+++	+++	+++
(CA)	++	++	+	0	0	0	0	0	0	0	0	0	++	++	++
(SA)	0	0	0	+	0	0	+	+	+	0	0	0	++	++	++
(PA)	0	0	0	+	0	0	0	0	0	+	+	+	+++	+++	++
(BS)	++	++	+	0	0	0	++	++	+	0	0	0	+++	+++	++
(EC)	0	0	0	0	0	0	0	0	0	0	0	0	++	++	++

***** IZD beyond control/ (sign): 1.1-1.5 cm/ (+++); 0.6-1.0 cm/ (++); 0.1-0.5 cm/ (+); 0 cm (0).

CONCLUSION

In this report, a facile rout for the synthesis of bis(6-mercaptopyridine), bis(pyrazolo[3,4-*b*]pyridine), bis(thienopyridine), bis(1,3,4-thiadiazole) and bis-thiophene derivatives starting from the readily accessible *N,N′*-(ethane-1,2-diyl)bis(cyanoacetamide) is described. The title compounds were synthesized as new products of biological interest and their structures were successfully established by elemental and spectral analyses.

REFERENCES

1. K. Hirai, Y. Iwano, T. Nishi, A.Yoshida, K. Oda, and H. Koyama, US Pat. 5,541,317 [*Chem. Abstr.,* 1996**, 125**, 167690m].
2. Y. Momose and H. Odaka, PCT Int. Appl.WO 97 36,882 [*Chem. Abstr*., 1997**, 117**, 331478n].
3. A.Yoshida, H. Kogen, I. Hayakawa, K. Oda, T. Kasai, K. Shimada, Y. Yoshida, S. Ishihara, F. Saito, Y. Ohata, T. Koga, E. Kitazawa, and T. Tokui, JP 09,202,775 [*Chem. Abstr*., 1997, **127**, 234181c] .
4. J. D. Hinks, A. K. Takel, and E. Hunt, Int. Appl.WO 97 25,309 [*Chem. Abstr*., 1997, **127**, 161997m].
5. J. Wrobel, Z. Li, A. Dietrich, M. McCaleb, B. Mihan, J. Sredy, and D. Sullivan, *J. Med. Chem*., 1998, **41**, 1084.
6. L. Muthusubramanian, R. B. Mitra, S. Rajkumar, and V. S. Rao, *J. Chem. Technol. Biotecnol.*, 1998, **72**, 164.
7. S. I. Klein, M. Czekaj, C. J. Gardner, K. R. Guertin, D. L. Cheney, A. P. Spada, A. S. Bolton, K. Brown, D. Colussi, C. L. Heran, S. R. Morgan, R. J. Leadley, T. C. Dunwiddie, M. H. Perrone, and V. Chu, *J. Med. Chem*., 1998, **41**, 437.
8. Z. Shraideh and A. K. Sallal, *Biomed. Lett.,* 1997, **54**, 233.
9. J. Bompart, L. Giral, G. Malicome, and M. Puygrenier, *Eur. J. Med. Chem*., 1987, **22**, 139.
10. M. E. Schnute, M. M. Cudahy, and A. Scott; PCT Int. Appl. WO, 00 53, 610 [*Chem. Abstr*., 2000, **133**, 222607g].
11. I. Adachi and Y. Hiramatsu, JP Pat., 03, 52, 890 [*Chem. Abstr*., 1991, **115**, 71573t].
12. T. Ooe, M. Sano, H. Kobayashi, and M. Kudome, JP Pat., 07 53, 562 [*Chem. Abstr*., 1995, **123**, 256681k].
13. S. Furuya, N. Choh, K. Kato, and S. Hinuma, PCT Int. Appl. WO 95 28, 405 [*Chem. Abstr*., 1996, **124**, 202226t].
14. N. Cho, M. Harada, T. Imaeda, H. Matsumoto, Y. Hayase, S. Sasaki, S. Furuya, N. Suzuki, S. Okubo, K. Ogi, S. Endo, H. Ondo, and M. Fujino, *J. Med. Chem*., 1998, **41**, 4190.
15. S. Miki, K. Fukuoka, M. Akita, J. Kawakami, S. Furuya, and Y. Ishimaru, PCT Int. Appl. WO 9909, 033 [*Chem. Abstr*., 1999, **130**, 196644h].
16. N. Suzuki, H. Matsumoto, and S. Furuya, Eur. Pat. App. EP 781, 774 [*Chem. Abstr*., 1997, **127**, 135807e].
17. S. Furuya, N. Choh, N. Suzuki, and T. Imada, PCT Int. Appl WO 000,00,493 [*Chem. Abstr*., 2000, **132**, 64179s].
18. S. Furuya, H. Matsumoto, Y. Hayase, N. Suzuki, and T. Imada; PCT Int Appl. WO 97 41, 126

[*Chem. Abstr*., 1998**, 128**, 13211f].

19. H. Vieweg, S. Leistner, J. Prantz, N. Bohm, and G. Wagner*, Pharmazie*, 1992, **47**, 841.
20. A. G. Griffin and T. R. Britt, *J. Am. Chem. Soc*., 1981, **103**, 4957.
21. G. Galli, M. Laus, and A. S. Angeloni, *Makromol. Chem*., 1986, **187**, 289.
22. H. Ringsdorf, B. Schlarh, and J. Venzmer, *Angew. Chem., Int. Ed. Engl.,* 1988, **27**, 115.
23. H. Finkelman, *Angew. Chem., Int. Ed.*, 1987, **26**, 816.
24. C. Aguilera, M. Parra, and G. Fuentes, *Z. Naturforsch*, 1998, **53B**, 367.
25. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *Heterocycles*, 2008, **75**, 887.
26. A. M. Farag, A. S. Mayhoub, S. E. Barakat, and A. H. Bayomi, *Bioorg. Med. Chem.,* 2008, **16**, 881.
27. A. M. Farag, A. S. Mayhoub, S. E. Barakat, and A. H. Bayomi, *Bioorg. Med. Chem.,* 2008, **16**, 4569.
28. A. M. Farag, Y. M. Elkholy, and K. A. Ali, *J. Heterocycl. Chem*., 2008, **45**, 279.
29. M. R. Shaaban, T. S. Saleh, and A. M. Farag, *Heterocycles,* 2007, **71**, 1765.
30. M. R. Shaaban, T. S. Saleh, F. H. Osman, and A. M. Farag, *J. Heterocycl. Chem*., 2007, **44**, 177.
31. A. M. Farag, K. M. Dawood, and N. A. Khedr, *J. Chem. Res.*, 2007, 472.
32. K. M. Dawood, A. M. Farag, and H. A. Abdelaziz, *Heteroatom Chem.,* 2007, **18**, 294.
33. N. A. Hamdy, H. A. Abdel-Aziz, A. M. Farag, and I. M. I. Fakhr, *Monatsh. Chem*., 2007, **138**, 1001.
34. J. Guareschi, *Chem. Ber*., 1892, **25**, 326.
35. Z. Qian, H. Su, and C. T. Mathew, US Pat. 5,654,465*,*1997 [*Chem. Abstr*., 1997, **127**, 205355g].
36. T. A. Hill, J. A. Sakoff, P. J. Robinson, and A. McCluskey, *Austr. J. Chem*., 2005, **58**, 94.
37. U. Schmidt and H. Kubitzek, *Chem. Ber*., 1960, **93**, 1559.
38. G. E. H. Elgemeie, M. M. M. Sallam, S. M. Sherif, and M. H. Elnagdi, *Heterocycles*, 1985, **23**, 3107.
39. A. F. Hegarty, M. P. Cashman, and F. L. Scott, *Chem. Commun.,* 1971, **13**, 884.
40. A. M. Farag and M. S. Algharib, *Org. Prep. Proced. Int*., 1988, **20**, 521.
41. S. N. Sawhney and J. Sing, *Indian J. Chem*., 1970, **8**, 882.
42. N. A. Ismail, *Egypt. J. Pharm. Sci*., 1991, **30**, 685.
43. P. Czerney and H. Hartmann, *J. Prakt. Chem*., 1983, **325**, 551.
44. R. M. Cowper and L. H. Davidson, *Org. Synth. Coll*., 1943, **2**, 480.