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Bis(2-cyanoacetamides): versatile precursors for bis(dihydropyridine-3,5-dicarbonitriles)

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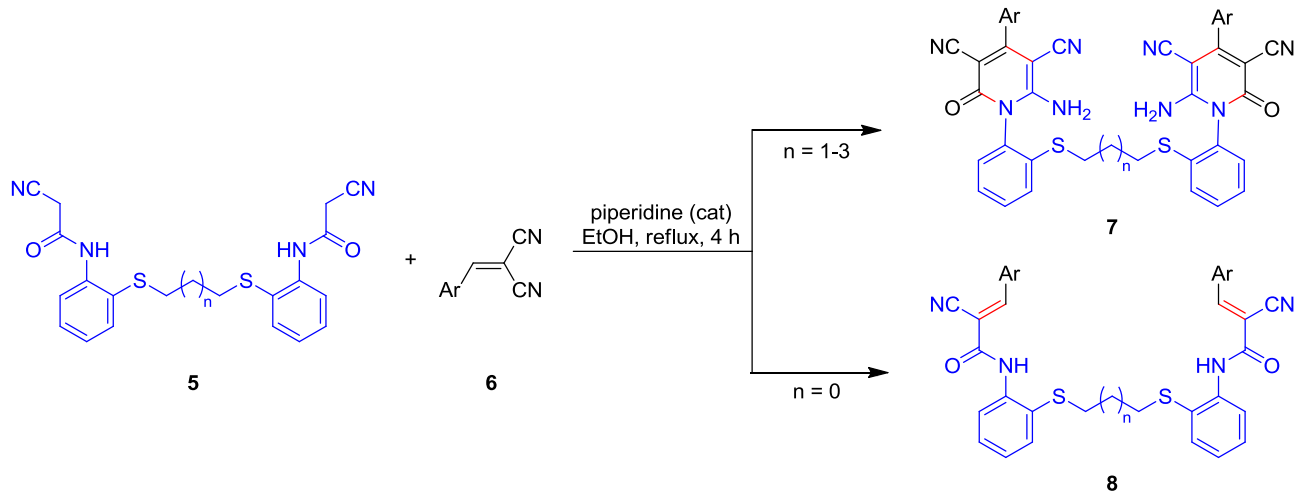
Abstract

Bis(6-amino-1,2-dihydropyridine-3,5-dicarbonitriles) containing thioether linkages are prepared *via* the condensation of bis(cyanoacetamides) with *α*-substituted cinnamonitriles in the presence of piperidine. The target compounds can also be obtained *via* a three-component reaction of bis(cyanoacetamides) with two equivalents of both aldehydes and malononitrile in ethanol containing piperidine as a base.



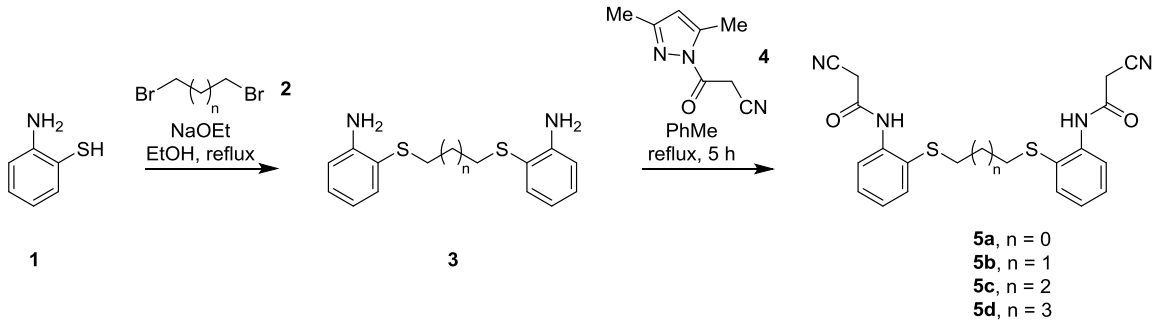
Keywords: Bis(cyanoacetamides), Michael addition, bis(dihydropyridine-3,5-dicarbonitrile), thioether linkage

Introduction

Substituted cyanoacetamides and acrylamides are versatile precursors for the synthesis of a wide variety of nitrogen-containing heterocycles.[1–8] In addition, substituted acrylamides are important intermediates in the synthesis of various dyes, agrochemicals, and pharmacologically active compounds.[9] Pharmaceutical activities include anticancer,[10] antimicrobial,[11–13] and anti-inflammatory.[14] Moreover, pyridine derivatives have received considerable attention as they exhibit a wide range of important biological activities including antiviral,[15,16] antibacterial,[17] antitumor,[18,19] and anti-inflammatory[20] activities. Furthermore, bis-heterocycles have interesting biological properties[21–23] including antitumor activities,[24,25] antihypertensive,[24,26] and antiallergenic.[27] As a part of an ongoing research program on Michael addition reactions,[28–35] bis(heterocycles)[36–46] we report herein, the results of our investigations concerning the different reactivity patterns of bis(cyanoacetamides) containing thioether linkage towards cinnamonitrile derivatives.

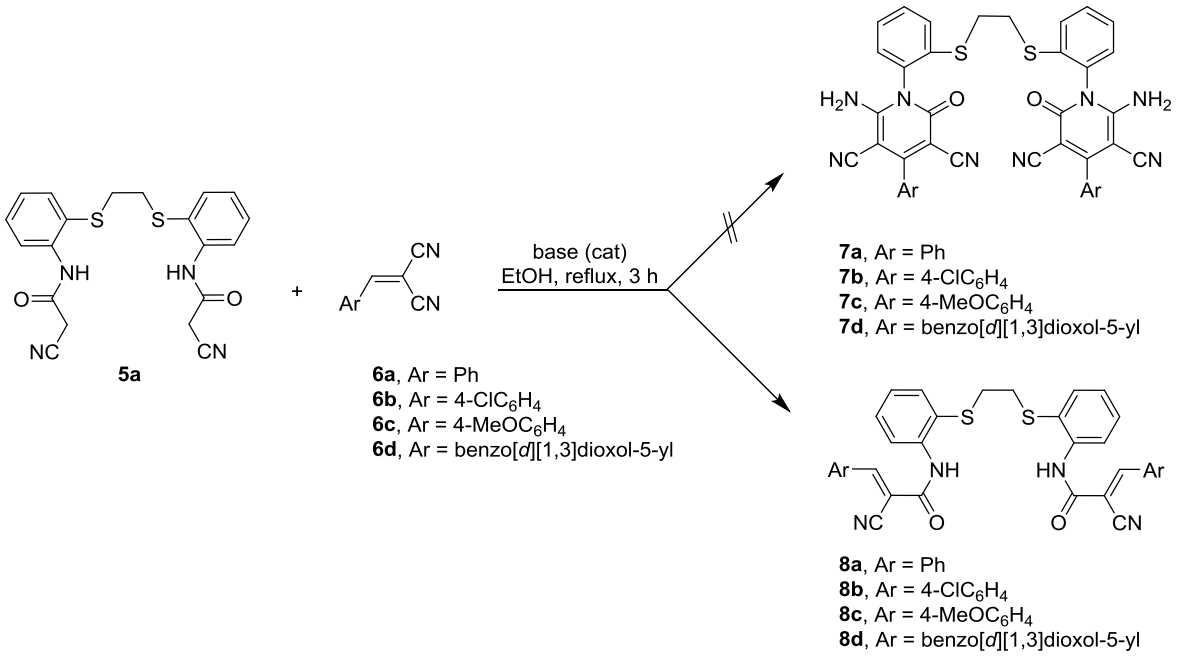
Results and Discussion

The bis(cyanoacetamides) containing thioether linkage **5** were used as key intermediates to a variety of new bis(dihydropyridine-3,5-dicarbonitriles) linked to aliphatic cores *via* thioethers. The bis(2-aminophenyl-thio)alkanes **3** were prepared following the literature procedure[47] *via* the reaction of 2-aminothiophenol **1** with the respective dibromoalkane **2** in refluxing ethanol containing sodium ethoxide. Cyanoacylation of the bis(amines) **3** with 3-(3,5-dimethylpyrazol-1-yl)-3-oxopropanenitrile **4** in toluene at reflux led to the formation of bis(cyanoacetamides) **5** (Scheme 1).



Scheme 1. Synthesis of bis(2-cyanoacetamides) **5a-d**.

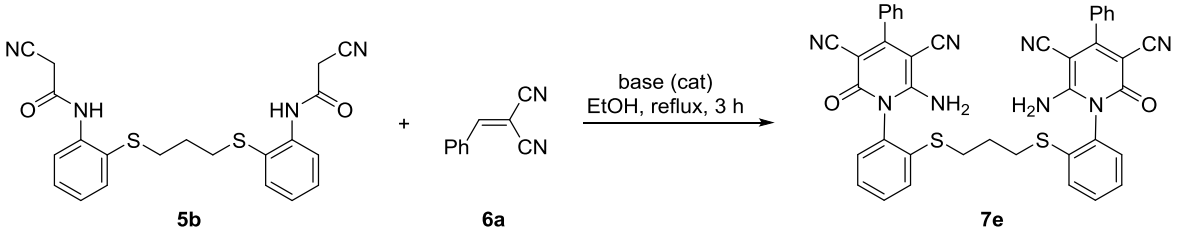
Initial efforts to synthesize bis(6-amino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitriles) **7a-d** *via* the reaction of bis(2-cyanoacetamide) **5a**, with arylidenemalononitriles **6a-d** in refluxing ethanol, failed. Under these conditions the reactions gave instead the corresponding bis(2-cyano-3-phenylacrylamides) **8a-d**.



Scheme 2. Unexpected formation of bis(2-cyano-3-phenylacrylamides) **8a-d**.

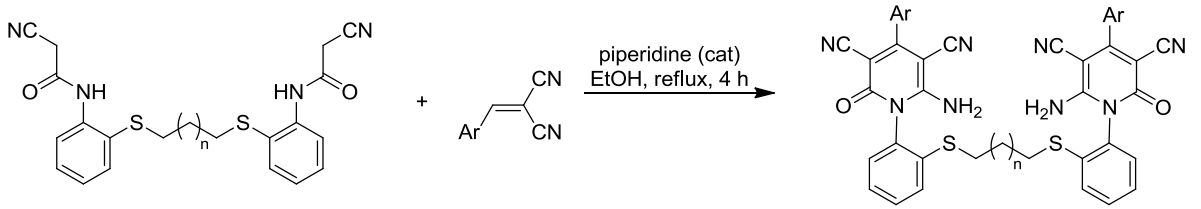
Fortunately, by increasing the number of methylene units between the two cyanoacetamide moieties, the desired products **7** could be obtained. Thus the reaction of bis(2-cyanoacetamide) **5b**, containing propyl linkage with benzylidenemalononitrile **6a** in refluxing ethanol in the presence of a variety of base catalysts including DBU, piperidine, DABCO, and triethylamine afforded the corresponding bis(6-amino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile) **7e** in good yield (Table 1).

Table 1. Optimizing the yield of bis(6-amino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile) **7e**



Entry	Base	Yield 7e (%)
1	DBU	79
2	Piperidine	85
3	DABCO	82
4	Et_3N	78

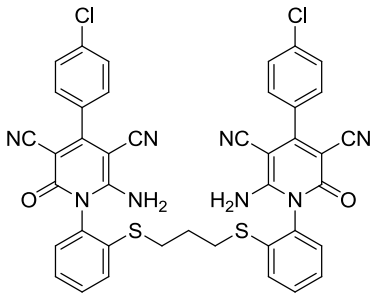
The use of piperidine in ethanol gave marginally better yields. With these conditions in hands, the scope of this reaction was investigated. A variety of bis(cyanoacetamides) containing thioether linkages **5b-d** underwent Michael-type addition reaction to the double bond of arylidenmalononitriles **6a-d** in ethanol at reflux in the presence of piperidine leading to the formation of bis(pyridines) linked *via* thioethers **7** (Scheme 4).



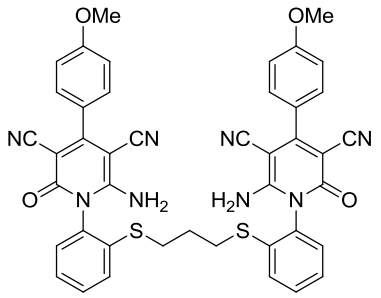
5b-d

6a, Ar = Ph
6b, Ar = 4-ClC_6H_4
6c, Ar = 4-$MeOC_6H_4$
6d, Ar = benzo[*d*][1,3]dioxol-5-yl

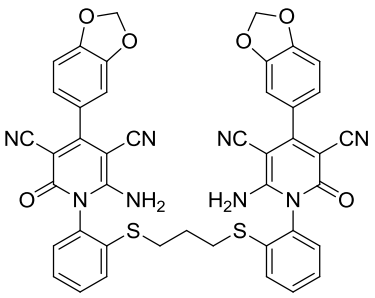
7e-n



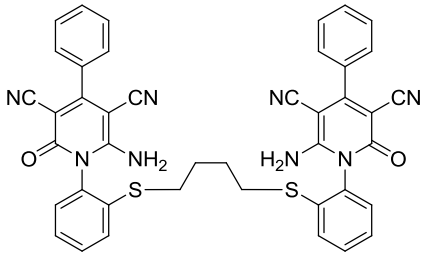
7f



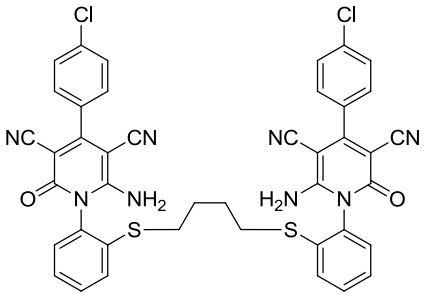
7g



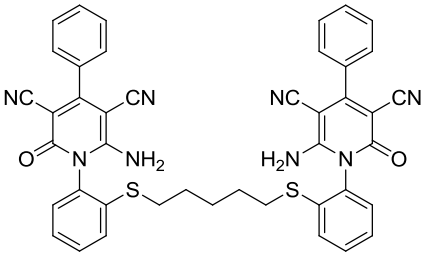
7h



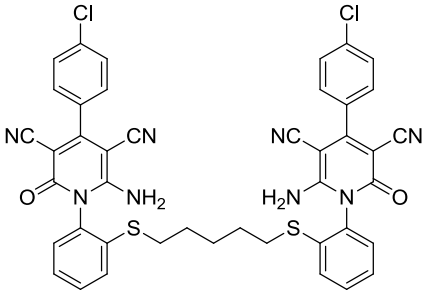
7i



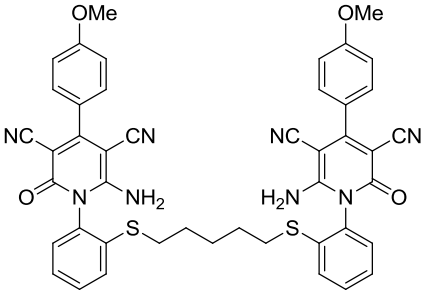
7j



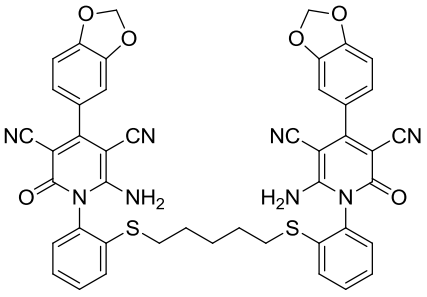
7k



7l



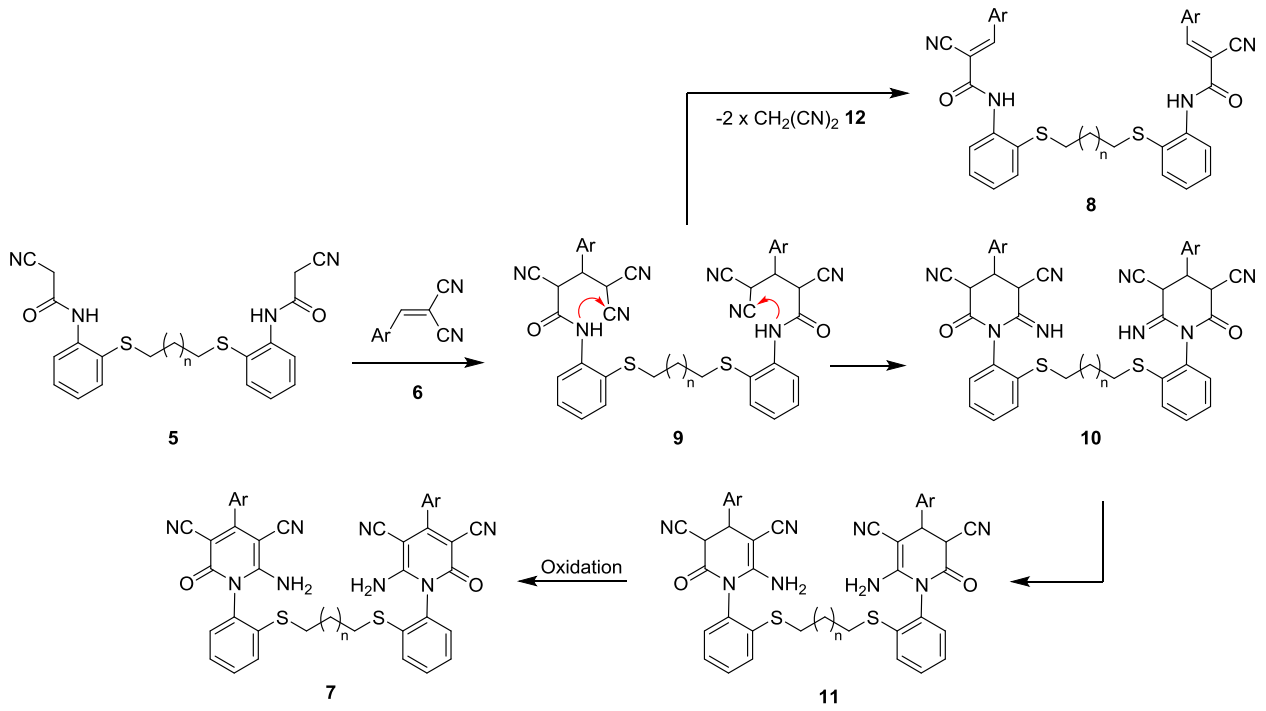
7m



7n

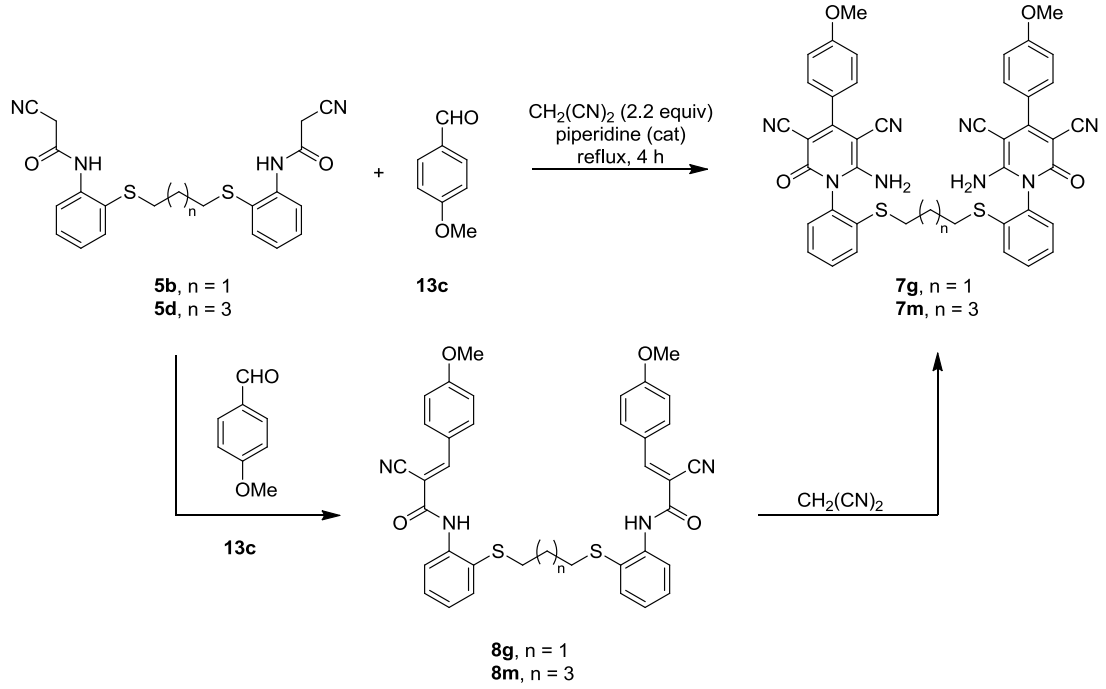
Scheme 4. Synthesis of bis(pyridine) derivatives **7f-n**.

The reaction proceeds most likely *via* initial Michael addition of the bis(cynomethylamide) **5** to the active C=C bond in arylidenemalononitrile **6**, leading to the formation of adduct **9**. The cyclization involving NH and cyano group of the amide **9** leads to the formation of **10**. Isomerization of **10** to **11** and subsequent oxidation leads to the formation of the final isolable products **7** (Scheme 5). In few examples, especially those containing short thioether linkage, the adducts **9**, presumably for steric reasons, did not cyclize to give **7** but gave the bis(2-cyanoacrylamides) **8** *via* the loss of two molecules of malononitrile **12**.



Scheme 5. Proposed mechanism.

This pathway was confirmed by successful isolation of the bis(2-cyanoacrylamides) **8g** and **8m** through the direct reaction of bis(cynoacetamides) **5b** and **5d** with 4-methoxybenzaldehyde **13c**. Subsequent reactions of **8g** and **8m** with malononitrile **12** gave compounds **7g** and **7m**, respectively. Moreover, the three-component reaction of 4-methoxybenzaldehyde **13c**, malononitrile **12** and bis(cynoacetamides) **5b** and **5d** afforded the same products **7g** and **7m**, respectively, in good yield (Scheme 6).



Scheme 6. Synthesis of bis(pyridines) **7** through one pot three component reaction.

Elemental analyses as well as the spectroscopic data of the obtained products **7** support the proposed structures. The IR spectrum of **7f**, as a representative example, indicated the presence of the amino group at $\bar{\upsilon}$ 3437 and 3310 cm^{-1}, C≡N group at $\bar{\upsilon}$ 2216 cm^{-1} and a characteristic band at $\bar{\upsilon}$ 1678 cm^{-1}, which refers to the C=O group. ^{1}H NMR spectrum displayed two broad singlets at δ_H 1.88 and 3.07 assigned to the propane linkage. In addition, it showed a broad singlet signal at δ_H 8.04 exchangeable with D_2O assignable to the NH_2 protons. The aromatic protons appear at their expected positions in the region 7.40-7.68 ppm.

Conclusions

An efficient synthesis of thioether-linked bis(cyanoacetamides) was developed. The compounds were investigated as building blocks for new bis(6-amino-1,2-dihydropyridine-3,5-dicarbonitriles) *via* Michael addition reactions with arylidenemalononitrile derivatives. The structural assignments of the new compounds were supported by spectroscopic data and elemental analyses. A rational mechanistic pathway for the formation of the products was proposed.

Experimental Section

General. Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded using a FTIR Bruker–vector 22 spectrophotometer as KBr pellets. The ^{1}H NMR spectra were recorded in DMSO–d_6 as solvent on Varian Gemini NMR spectrometer at 300 MHz using TMS as internal standard. Chemical shifts are reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS–QP–1000 EX mass spectrometer in EI (70 eV) model. The elemental analyses were performed at the Micro analytical center, Cairo University.

Synthesis of *N,N'*-{[alkane-1,*ω*-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis(2-cyanoacetamide) (5a-d). A solution of 1-cyanoacetyl-3,5-dimethylpyrazole **4** (0.2 mol) was added to a solution of bis(amines) **3a-d** (0.1 mol) in toluene (100 mL) and the mixture was refluxed for 5 h. After cooling, the deposited solid was collected and recrystallized from toluene, yielding **5a-d**, respectively.

***N,N'*-{[Ethane-1,2-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis(2-cyanoacetamide) (5a).** Colorless crystals (390 mg, 95%), mp192-194 ^{o}C (EtOH); IR ($\bar{\upsilon}$ cm^{-1}): 3294 (NH), 2205 (CN), 1682 (CO); ^{1}H NMR (DMSO-d_6): δ_H 3.01 (s, 4H, SCH_2), 3.94 (s, 4H, CH_2CN), 7.16-7.55 (m, 8H, ArH's), 9.73 (s, 2H, 2 NH); Anal. For $C_{20}H_{18}N_4O_2S_2$ (410.51) Calcd: C, 58.52; H, 4.42; N, 13.65. Found: C, 58.31; H, 4.63; N, 13.78%.

***N,N'*-{[Pentane-1,5-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis(2-cyanoacetamide) (5d).** Colorless crystals (384 mg, 85%), mp154-156 ^{o}C (EtOH); IR ($\bar{\upsilon}$ cm^{-1}): 3447, 3306 (NH_2), 2214 (CN), 1670 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.50-1.52 (m, 6H, $SCH_2\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_2S$), 2.85 (t, 4H, $S\underline{CH_2}CH_2CH_2CH_2\underline{CH_2}S$), 3.94 (s, 4H, CH_2-CN), 7.18-7.50 (m, 8H, ArH's), 9.69 (br. s, 2H, 2 NH); Anal. for $C_{23}H_{24}N_4O_2S_2$ (452.59) Calcd: C, 61.04; H, 5.35; N, 12.38. Found: C, 61.23; H, 5.47; N, 12.51%.

General procedure for synthesis of compound 7e-n

Method A. A mixture of bis(2-cyanoacetamides) **5a-d** (1 mmol) and activated cinnamonitriles **6a-d** (2.2 mmol) in absolute ethanol (15 mL) was heated at reflux in the presence of piperidine (0.2 mL) for 3 h. The crude solids were isolated and recrystallized from the proper solvent.

Method B. To a mixture of bis(2-cyanoacetamides) **5a-d**, aromatic aldehydes **13a-d** (2.2 mmol) and malononitrile **11** (2.2 mmol) in absolute ethanol (15 mL) piperidine (0.2 mL) was added. The mixture was heated at reflux for 3 h. The crude solids were isolated and recrystallized from the proper solvent.

1,1'-{[Propane-1,3-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis(6-amino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile) (7e). Brown crystals (Method A. 618 mg, 85%), mp208-210 ^{o}C (Dioxane/EtOH, 25:75) IR ($\bar{\upsilon}$ cm^{-1}): 3441, 3311 (NH_2), 2214 (CN), 1679 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.86-1.90 (m, 2H, $SCH_2\underline{CH_2}CH_2S$), 3.07 (t, 4H, $S\underline{CH_2}CH_2\underline{CH_2}S$), 7.25-7.64 (m, 18H, ArH's), 8.00 (s, br, 4H, 2 NH_2); ^{13}C NMR (DMSO-d_6): δ_C 27.5, 29.7, 74.8, 115.4, 116.1, 127.4, 127.8, 128.6, 129.5, 130.3, 130.7, 132.0, 132.5, 134.4, 156.5, 158.7, 161.5; Anal. for $C_{41}H_{28}N_8O_2S_2$ (728.85) Calcd: C, 67.57; H, 3.87; N, 15.37. Found: C, 67.88; H, 4.12; N, 15.02%.

1,1'-{[Propane-1,3-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[6-amino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile] (7f). Brown crystals (Method A: 438 mg, 55%), mp200-202 ^{o}C (Dioxane/EtOH, 25:75); IR ($\bar{\upsilon}$ cm^{-1}): 3437, 3310 (NH_2), 2216 (CN), 1678 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.85-1.92 (m, 2H, $SCH_2\underline{CH_2}CH_2S$), 3.07 (t, 4H, $S\underline{CH_2}CH_2\underline{CH_2}S$), 7.40-7.68 (m, 16H, ArH's), 8.04 (s, br, 4H, 2 NH_2); Anal. for $C_{41}H_{26}Cl_2N_8O_2S_2$ (797.73) Calcd: C, 61.73; H, 3.29; N, 14.05. Found: C, 61.99; H, 3.50; N, 14.20%.

1,1'-{[Propane-1,3-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[6-amino-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile] (7g). Pale yellow crystals (Method A, 551 mg, 70%; Method B, 592 mg, 75%), mp164-166 ^{o}C (EtOH); IR ($\bar{\upsilon}$ cm^{-1}): 3448, 3304 (NH_2), 2215 (CN), 1669 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.84-1.88 (m, 2H, $SCH_2\underline{CH_2}CH_2S$), 3.07 (t, 4H, $S\underline{CH_2}CH_2\underline{CH_2}S$), 3.86 (s, 6H, 2 $O\underline{CH_3}$), 6.92-7.60 (m, 16H, ArH's), 8.03 (s, br, 4H, 2 NH_2); ^{13}C NMR (DMSO-d_6): δ_C 27.8, 31.7, 55.2, 74.9, 113.9, 115.8, 116.4, 120.7, 126.4, 127.4, 129.5, 129.7, 130.5, 132.5, 135.7, 156.6, 158.9, 160.7, 161.0; Anal. for $C_{43}H_{32}N_8O_4S_2$ (788.90) Calcd: C, 65.47; H, 4.09; N, 14.20. Found: C, 65.19; H, 4.31; N, 14.32%.

1,1'-{[Propane-1,3-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile] (7h). Pale yellow crystals (Method A, 587 mg, 72%), mp208-210 ^{o}C (Dioxane/EtOH, 25:75); IR ($\bar{\upsilon}$ cm^{-1}): 3442, 3326 (NH_2), 2216 (CN), 1675 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.84.1.88 (m, 2H, $SCH_2\underline{CH_2}CH_2S$), 3.09 (t, 4H, $S\underline{CH_2}CH_2\underline{CH_2}S$), 6.16 (s, 4H, 2 $O\underline{CH_2}O$), 6.86-7.62 (m, 14H, ArH's), 7.95 (s, br, 4H, 2 NH_2); Anal. for $C_{43}H_{28}N_8O_6S_2$ (816.87) Calcd: C, 63.23; H, 3.46; N, 13.72. Found: C, 63.00; H, 3.70; N, 13.99%.

1,1'-{[Butane-1,4-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis(6-amino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile) (7i). Pale yellow crystals (Method A 504 mg, 68%), mp> 300 ^{o}C (Dioxane/EtOH, 25:75); IR ($\bar{\upsilon}$ cm^{-1}): 3443, 3315 (NH_2), 2214 (CN), 1677 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.69 (t, 4H, $SCH_2\underline{CH_2}\underline{CH_2}CH_2S$), 2.98 (t, 4H, $S\underline{CH_2}CH_2CH_2\underline{CH_2}S$), 7.40-7.57 (m, 18H, ArH's), 7.96 (s, br, 4H, 2 NH_2); ^{13}C NMR (DMSO-d_6): δ_C 27.5, 31.2, 74.9, 115.5, 116.2, 120.7, 124.9, 127.5, 127.9, 128.6, 129.7, 130.3, 130.7, 132.3, 134.5, 135.6, 156.6, 158.8, 161.6; Anal. for $C_{42}H_{30}N_8O_2S_2$ (742.88) Calcd: C, 67.91; H, 4.07; N, 15.08. Found: C, 67.78; H, 4.24; N, 15.33%.

1,1'-{[Butane-1,4-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[6-amino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile] (7j). Brown crystals (Method A: 405 mg, 50%), mp180-182 ^{o}C (Dioxane/EtOH, 25:75); IR ($\bar{\upsilon}$ cm^{-1}): 3439, 3308 (NH_2), 2213 (CN), 1676 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.68 (t, 4H, $SCH_2\underline{CH_2}\underline{CH_2}CH_2S$), 2.97 (t, 4H, $S\underline{CH_2}CH_2CH_2\underline{CH_2}S$), 7.22-7.67 (m, 16H, ArH's), 8.03 (s, br, 4H, 2 NH_2); Anal. for $C_{42}H_{28}Cl_2N_8O_2S_2$ (811.76) Calcd: C, 62.14; H, 3.48; N, 13.80. Found: C, 62.48; H, 3.66; N, 13.58%.

1,1'-{[Pentane-1,5-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis(6-amino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile) (7k). Pale orange crystals (Method A: 522 mg, 69%), mp192-194 ^{o}C (Dioxane/EtOH, 25:75); IR ($\bar{\upsilon}$ cm^{-1}): 3440, 3314 (NH_2), 2216 (CN), 1680 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.55.1.58 (m, 6H, $SCH_2\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_2S$), 2.95 (t, 4H, $S\underline{CH_2}CH_2CH_2CH_2\underline{CH_2}S$), 7.23-7.57 (m, 18H, ArH's), 7.96 (s, br, 4H, 2 NH_2); ^{13}C NMR (DMSO-d_6): δ_C 27.2, 27.9, 31.7, 74.8, 115.4, 115.9, 120.2, 126.3, 127.4, 127.8, 129.8, 130.2, 130.6, 132.3,

134.4, 135.6, 156.6, 158.7, and 161.5; Anal. for $C_{43}H_{32}N_8O_2S_2$ (756.90) Calcd: C, 68.24; H, 4.26; N, 14.80. Found: C, 68.01; H, 4.10; N, 15.03%.

1,1'-{[Pentane-1,5-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[6-amino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile] (7l). Pale yellow crystals (Method A. 487 mg, 59%), mp156-158 °C (EtOH); IR ($\bar{\upsilon}$ cm^{-1}): 3440, 3316 (NH_2), 2218 (CN), 1681 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.55-1.57 (m, 6H, $SCH_2\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_2S$), 2.91 (t, 4H, $S\underline{CH_2}CH_2CH_2CH_2\underline{CH_2}S$), 7.23-7.68 (m, 16H, ArH's), 8.01 (s, br, 4H, 2 NH_2); Anal. for $C_{43}H_{30}Cl_2N_8O_2S_2$ (825.79) Calcd: C, 62.54; H, 3.66; N, 13.57. Found: C, 62.39; H, 3.28; N, 13.74%.

1,1'-{[Pentane-1,5-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[6-amino-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile] (7m). Pale yellow crystals (Method A. 693 mg, 85%; Method B, 662 mg, 81%)), mp314-316 °C (Dioxane); IR ($\bar{\upsilon}$ cm^{-1}): 3447, 3306 (NH_2), 2214 (CN), 1670 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.55-1.58 (m, 6H, $SCH_2\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_2S$), 2.94 (t, 4H, $S\underline{CH_2}CH_2CH_2CH_2\underline{CH_2}S$), 3.85 (s, 6H, 2 $O\underline{CH_3}$), 7.10-7.61 (m, 16H, ArH's), 7.88 (s, br, 4H, 2 NH_2); Anal. for $C_{45}H_{36}N_8O_4S_2$ (816.96) Calcd: C, 66.16; H, 4.44; N, 13.72. Found: C, 66.35; H, 4.15; N, 13.98%.

1,1'-{[Pentane-1,5-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile] (7n). Pale yellow crystals (Method A. 659 mg, 78%), mp186-188 °C (Dioxane/EtOH, 25:75); IR ($\bar{\upsilon}$ cm^{-1}): 3444, 3327 (NH_2), 2217 (CN), 1676 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.54-1.56 (m, 6H, $SCH_2\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_2S$), 2.94 (t, 4H, $S\underline{CH_2}CH_2CH_2CH_2\underline{CH_2}S$), 6.16 (s, 4H, 2 $O\underline{CH_2}O$), 6.86-7.63 (m, 14H, ArH's), 7.91 (s, br, 4H, 2 NH_2); Anal. for $C_{45}H_{32}N_8O_6S_2$ (844.92) Calcd: C, 63.97; H, 3.82; N, 13.26. Found: C, 63.74; H, 3.99; N, 13.02%.

General procedure for the preparation of compounds (8). A mixture of substituted aldehydes **13** (2 mmol) and bis(2-cyanoacetamide) **5** (1 mmol) was refluxed in ethanol (20 mL) in the presence of piperidine (0.2 mL) for 3 h. The solid products so formed were recrystallized from dioxane or dioxane/EtOH (25:75).

***N,N'*-{[Ethane-1,2-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[2-cyano-3-phenylacrylamide] (8a).** Colorless crystals (558 mg, 95%), mp220-222 °C (Dioxane/EtOH, 25:75); IR ($\bar{\upsilon}$ cm^{-1}): 3294 (NH), 2205 (CN), 1682 (CO); ^{1}H NMR (DMSO-d_6): δ_H 3.05 (s, 4H, SCH_2), 7.22-8.00 (m, 18H, ArH's), 8.36 (s, 2H, 2 $\underline{CH}$=C(CN)), and 9.93 (s, 2H, 2 NH); Anal. For $C_{34}H_{26}N_4O_2S_2$ (586.73) Calcd: C, 69.60; H, 4.47; N, 9.55. Found: C, 69.25; H, 4.69; N, 9.77%.

***N,N'*-{[Ethane-1,2-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[3-(4-chlorophenyl)-2-cyanoacrylamide] (8b).** Colorless crystals (590 mg, 90%), mp246-248 °C (Dioxane); IR ($\bar{\upsilon}$ cm^{-1}): 3290 (NH), 2200 (CN), 1677 (CO); ^{1}H NMR (DMSO-d_6): δ_H 3.02 (s, 4H, SCH_2), 7.19-8.04 (m, 16H, ArH's), 8.33 (s, 2H, 2 $\underline{CH}$=C(CN)), and 9.74 (s, 2H, 2 NH); Anal. for $C_{34}H_{24}Cl_2N_4O_2S_2$ (655.61) Calcd: C, 62.29; H, 3.69; N, 8.55. Found: C, 62.02; H, 3.45; N, 8.78%.

***N,N'*-{[Ethane-1,2-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[2-cyano-3-(4-methoxyphenyl)acrylamide] (8c).** Colorless crystals (563 mg, 87%), mp208-210 °C (Dioxane/EtOH, 25:75); IR ($\bar{\upsilon}$ cm^{-1}): 3290 (NH), 2200 (CN), 1672 (CO); ^{1}H NMR (DMSO-d_6): δ_H 3.28 (s, 4H, SCH_2), 3.93 (s, 6H, OCH_3) 7.10-8.28 (m, 18H, ArH's and $\underline{CH}$=C(CN)), 9.72 (br. s, 2H, 2 NH); Anal. for $C_{36}H_{30}N_4O_4S_2$ (646.78) Calcd: C, 66.85; H, 4.68; N, 8.66. Found: C, 66.72; H, 4.46; N, 8.87%.

***N,N'*-{[Ethane-1,2-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[3-(benzo[*d*][1,3]dioxol-5-yl)-2-cyano-acrylamide] (8d).** Colorless crystals (560 mg, 83%), mp274-276 °C (Dioxane/EtOH, 25:75); IR ($\bar{\upsilon}$ cm^{-1}): 3290 (NH), 2200 (CN), 1672 (CO); ^{1}H NMR (DMSO-d_6): δ_H 3.02 (s, 4H, SCH_2), 6.17 (s, 4H, 2 $O\underline{CH_2}O$), 7.09-7.86 (m, 14H, ArH's), 8.21 (s, 2H, $\underline{CH}$=C(CN)), 9.72 (br. s, 2H, 2 NH); Anal. for $C_{36}H_{26}N_4O_6S_2$ (674.75) Calcd: C, 64.08; H, 3.88; N, 8.30. Found: C, 64.19; H, 3.62; N, 8.45%.

***N,N'*-{[Propane-1,3-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[2-cyano-3-(4-methoxyphenyl)acrylamide] (8g).** Pale yellow crystals (522 mg, 79%), mp202-204 °C (Dioxane/EtOH, 25:75); IR ($\bar{\upsilon}$ cm^{-1}): 3448, 3304 (NH_2), 2215 (CN), 1669 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.741.77 (m, 2H, $SCH_2\underline{CH_2}CH_2S$), 2.97 (t, 4H, $S\underline{CH_2}CH_2\underline{CH_2}S$), 3.87

(s, 6H, 2 O$\underline{CH_3}$), 7.12-7.99 (m, 16H, ArH's), 8.25 (s, 2H, $\underline{CH}$=C(CN)), 9.66 (br. s, 2H, 2 NH); Anal. for $C_{37}H_{32}N_4O_4S_2$ (660.81) Calcd: C, 67.25; H, 4.88; N, 8.48. Found: C, 67.49; H, 4.99; N, 8.55%.

***N,N'*-{[Pentane-1,5-diylbis(sulfanediyl)]bis(2,1-phenylene)}bis[2-cyano-3-(4-methoxyphenyl)acrylamide] (8m).** Pale yellow crystals (585 mg, 85%), mp134-136 ^{o}C (EtOH); IR ($\bar{\upsilon}$ cm^{-1}): 3447, 3306 (NH_2), 2214 (CN), 1670 (CO); ^{1}H NMR (DMSO-d_6): δ_H 1.49-1.50 (m, 6H, $SCH_2\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_2S$), 2.85 (t, 4H, $S\underline{CH_2}CH_2CH_2CH_2\underline{CH_2}S$), 3.87 (s, 6H, 2 O$\underline{CH_3}$), 7.13-8.04 (m, 16H, ArH's), 8.28 (s, 2H, $\underline{CH}$=C(CN)), 9.70 (br. s, 2H, 2 NH); Anal. for $C_{39}H_{36}N_4O_4S_2$ (688.86) Calcd: C, 68.00; H, 5.27; N, 8.13. Found: C, 68.31; H, 5.41; N, 8.03%.

Supplementary Material

Supplementary material for this article is available; copies of ^{1}H NMR spectra of compounds **5a**, **d; 7f**-**i;** and 7**k**-**n** and ^{13}C NMR spectra of compounds **7g**, **i**; **8a**- **d**; and **8g**, **m.** This material can be found *via* the "Supplementary Content" section of this article's webpage.

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