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Synthesis of novel bis(dihydropyridine) and terpyridine derivatives

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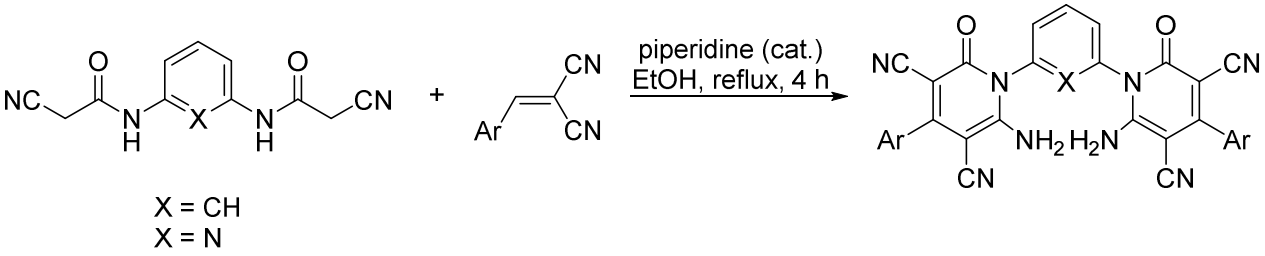
Abstract

A synthesis of novel bis(cyanopyridones) by the reaction of the appropriate bis(cyanoacetamide) with the corresponding arylidenmalononitrile in the presence of basic catalysts was reported. In some cases, the corresponding bis(2-cyano-3-arylacrylamide) derivatives were isolated from these reactions as single products. The multicomponent strategy for the synthesis of the target compounds was also investigated. The utility of bis(cyanoacetamides) as building blocks for novel bisquinolinones was also studied.



Keywords: Cyanoacetylation, biscyanopyridones, terpyridines, biscyanoacetamides, Michael addition

Introduction

Pyridine derivatives are currently an important group of organic compounds that have therapeutic and pharmacological properties.[1] They are used as antibacterial,[2,3] antimicrobial,[4,5] antifungal,[6] cardiotonic,[7] analgesic,[8] antiinflammatory[9] and anti-lung cancer[10] agents. The pyridine moiety is found in structurally simple drugs like isoniazid **I**,[11] ethionamide **II**,[12] amrinone **III**,[13] bupicomide **IV**,[14] pinacidil **V**,[15] torasemide **VI** and omeprazole **VII**[16] (Figure 1).

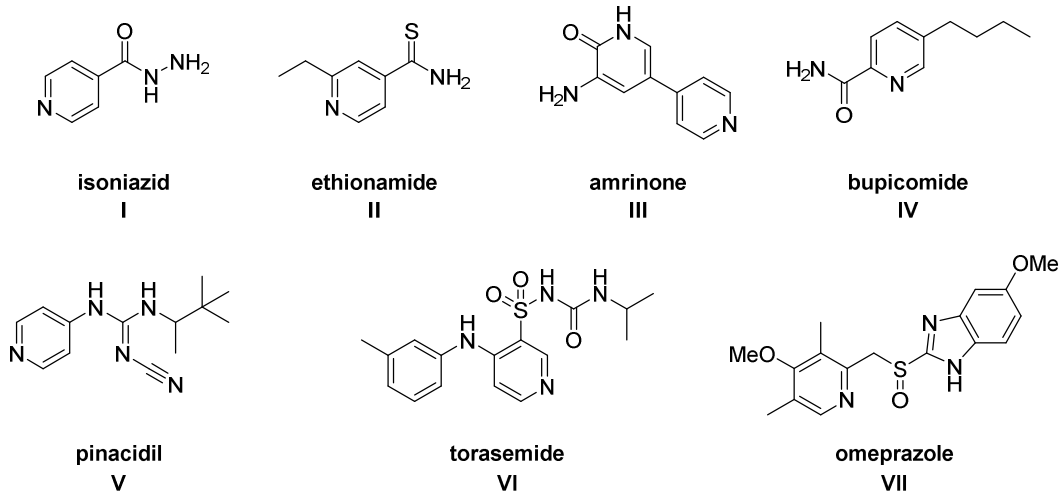
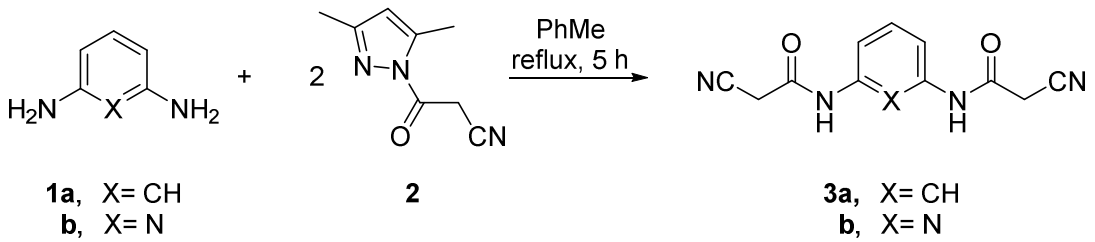


Figure 1. Representative examples of some drugs incorporated pyridine moiety.

In addition, heterocyclic ligands containing nitrogen atoms have drawn a great deal of attention in coordination chemistry and homogeneous catalysis.[17–19] Moreover, 2-cyanoacetamide derivatives attracted attention in the last decades for being useful reagents for the synthesis of a variety of heterocyclic compounds.[20,21] Furthermore, multicomponent reactions (MCRs) constitute an especially attractive synthetic strategy since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. MCRs offer the advantage of simplicity, selectivity, atom-economy and synthetic efficiency over conventional chemical reactions.[22–26] Although the synthesis of biologically interesting 1,2-dihydropyridine-3,5-dicarbonitrile derivatives has been investigated in the past,[27–31] there is still demand for more concise and efficient elucidation of molecular structure. In connection with this finding and in continuation to our work on Michael addition,[32–38] multicomponent reactions,[35–37,39–45] as well as on the synthesis of bis-heterocycles,[41,45–54] we report herein on the synthesis of novel bis(1,2-dihydropyridine-3,5-dicarbonitriles) and terpyridines utilizing 2-cyanoacetamide derivatives as intermediates.

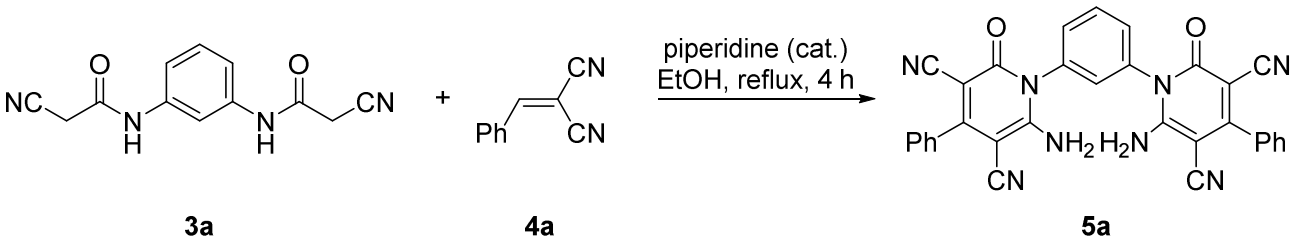
Results and Discussion

Bis(cyanoacetamides) *N,N*'-(1,3-phenylene)bis(2-cyanoacetamide) **3a** and *N,N*'-(pyridine-2,6-diyl)bis(2-cyano-acetamide) **3b** were chosen as key intermediates to a variety of novel biscyanopyridone and terpyridine derivatives. They were prepared in good yields by cyanoacetylation of one equivalent of bisamines **1** with two equivalents of 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile **2** (Scheme 1).



Scheme 1. Synthesis of bis-cyanoacetamides **3a,b.**

The reaction of biscyanoacetamide **3a** with benzylidenemalononitrile derivative **4a** was investigated as a simple model system to find the optimal reaction conditions for the synthesis of the corresponding novel 1,1'-(1,3-phenylene)bis(6-amino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile) derivatives **5a**. The reaction was performed in ethanol or dioxane in the presence of different bases including trimethylamine, piperidine, chitosan, DABCO and DBU (Scheme 2). Although the reaction worked well in refluxing ethanol or dioxane in most catalysts, the best results were achieved using piperidine in ethanol at reflux (Method A). The percentage yields in all cases are cited in Table 1.

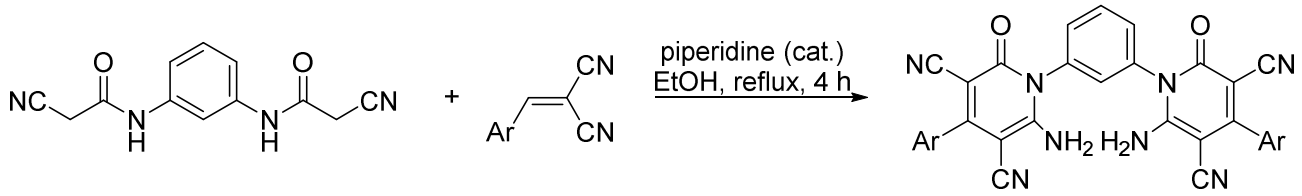


Scheme 2. Reaction of bis(cyanoacetamide) **3a** with benzylidenemalononitrile **4a**.

Table 1. Optimizing the yield of compound **5a**

Entry	Time (h)	Catalyst	Solvent	Yield (%)
1	3	Piperidine	EtOH	88
			Dioxane	80
2	3	DABCO	EtOH	80
			Dioxane	77
3	3	TEA	EtOH	80
			Dioxane	76
4	3	DBU	EtOH	85
			Dioxane	81
5	3	Chitosan	EtOH	69
			Dioxane	71

The successful synthesis of **5a** encouraged us to develop the scope of this reaction. Thus, bis(cyanoacetamide) **3a** was allowed to react with a variety of arylidenemalononitriles **4b-f** under the optimized conditions (Method A). The results showed that all reactions afforded the desired products **5b-f** with good yields (Scheme 3).



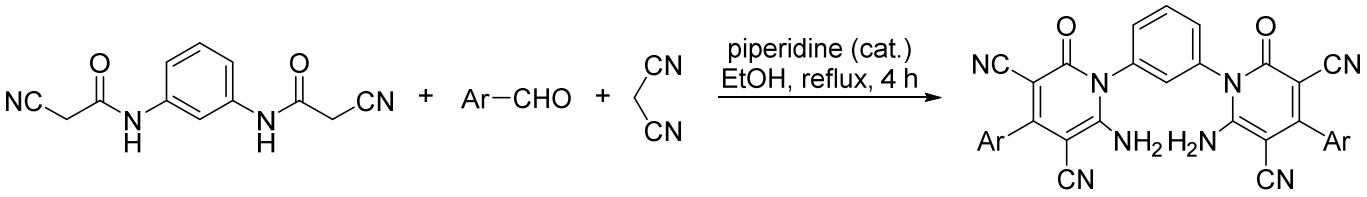
3a

4b, Ar = 4-ClC_6H_4
4c, Ar = 2-$MeOC_6H_4$
4d, Ar = 4-$MeOC_6H_4$
4e, Ar = 4-Tol
4f, Ar = 4-$O_2NC_6H_4$

5b, 81%
5c, 75%
5d, 75%
5e, 83%
5f, 68%

Scheme 3. Reaction of bis(cyanoacetamide) **3a** with a variety of arylidenemalononitriles **4b-f**.

Compounds **5** were also obtained in good to excellent yields *via* a three-component reaction of two equivalents of both arylaldehyde **6** and malononitrile **7** with one equivalent of biscyanoacetamides **3a** in refluxing ethanol in the presence of piperidine as a catalyst (Method B) (Scheme 4).

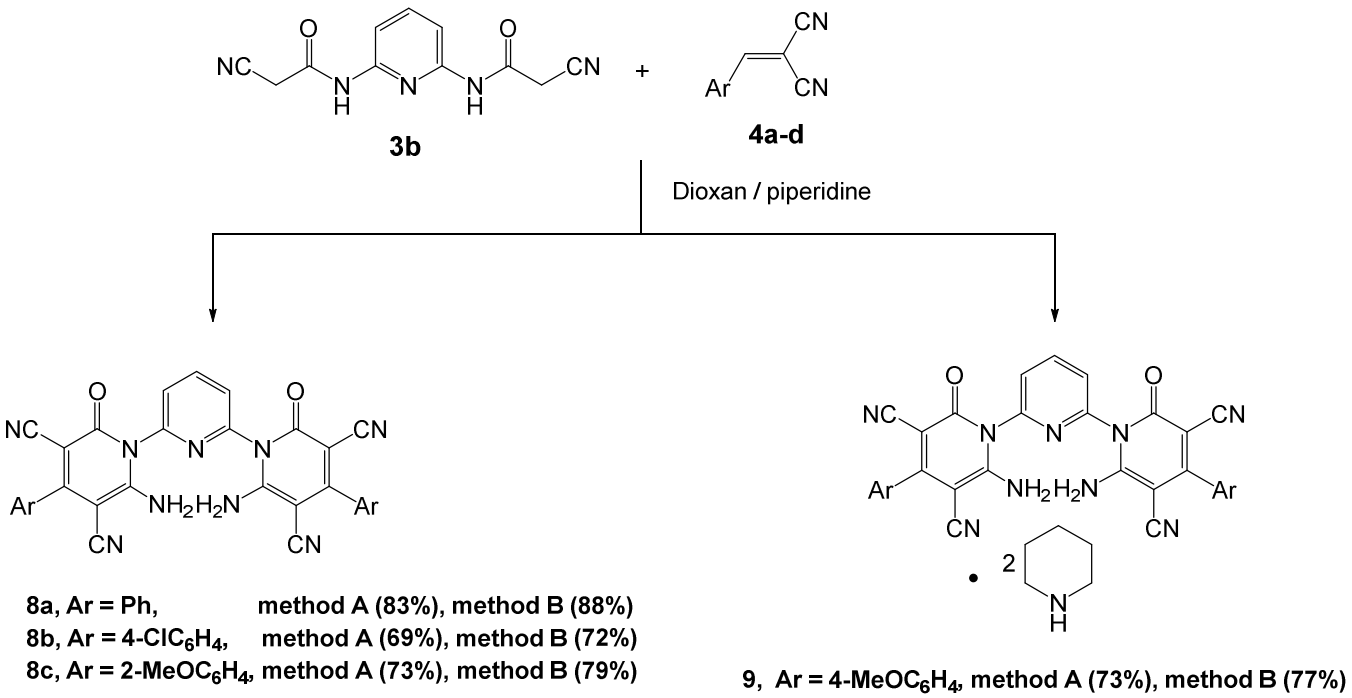


3a **6** **7**

5a, Ar = Ph, 72%
5b, Ar = 4-ClC_6H_4, 84%
5c, Ar = 2-$MeOC_6H_4$, 79%
5d, Ar = 4-$MeOC_6H_4$, 81%
5e, Ar = 4-Tol, 87%
5f, Ar = 4-$O_2NC_6H_4$, 74%

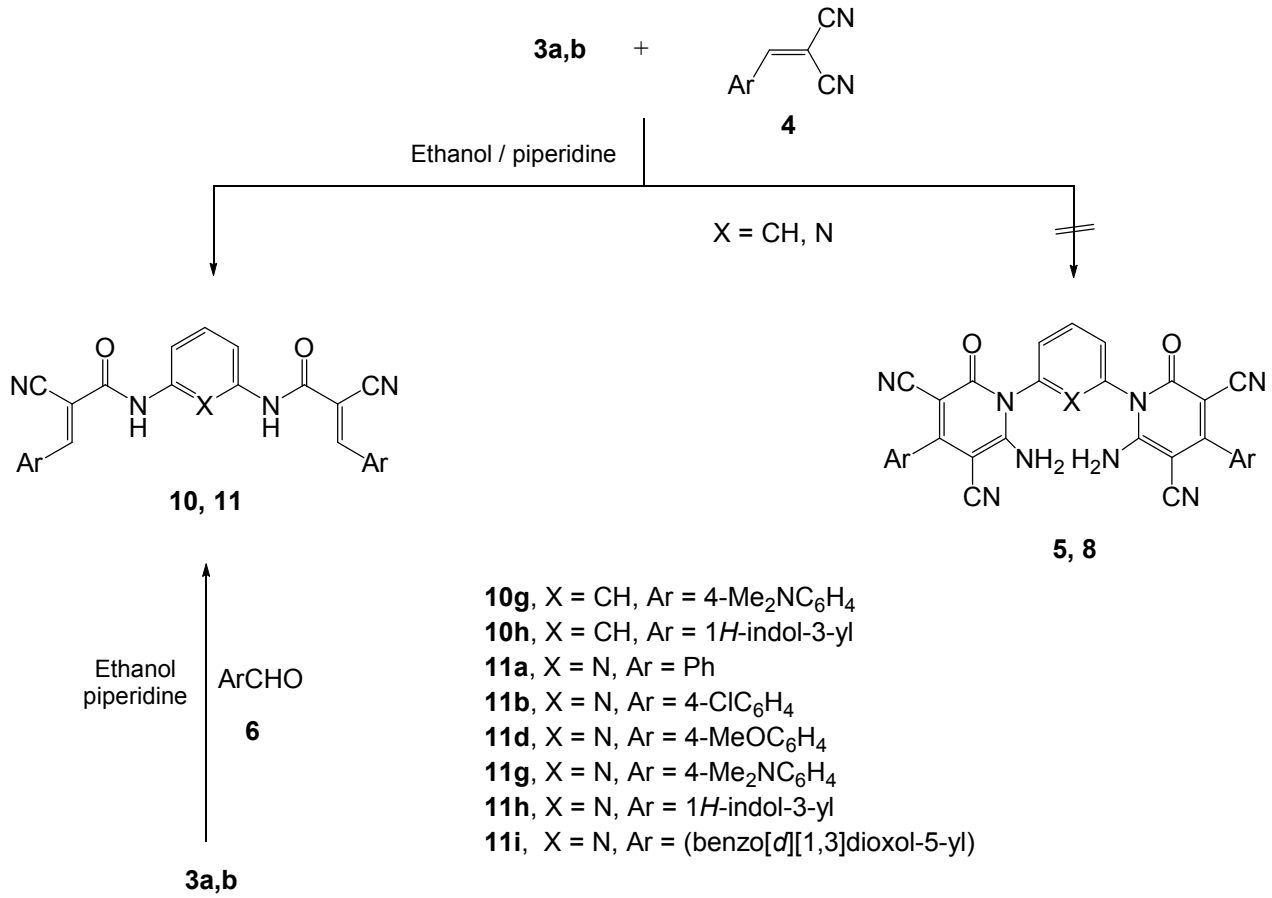
Scheme 4. Three-component reaction of bis(cyanoacetamides) **3** with two equivalents of both arylaldehyde **6** and malononitrile **7**.

On the other hand, the reaction of biscyanoacetamide **3b** with a variety of arylidenemalononitriles proceeded smoothly in refluxing dioxane in the presence of piperidine as a catalyst to give the desired 6,6''-diamino-2,2''-dioxo-4,4''-diaryl-2*H*,2''*H*-[1,2':6',1''-terpyridine]-3,3'',5,5''-tetracarbonitriles **8a-c** in good yields. Compound **9** (Ar = 4-$MeOC_6H_4$), was unexpectedly isolated as piperidinium salt from the reaction of bis-cyanoacetamide **3b** with the corresponding arylidenemalononitrile **4d** (Scheme 5). In this respect, recently the formation of solid state adduct of bis(2*H*-chromen-2-one) with morpholine has been confirmed by single-crystal X-ray diffraction.[48]



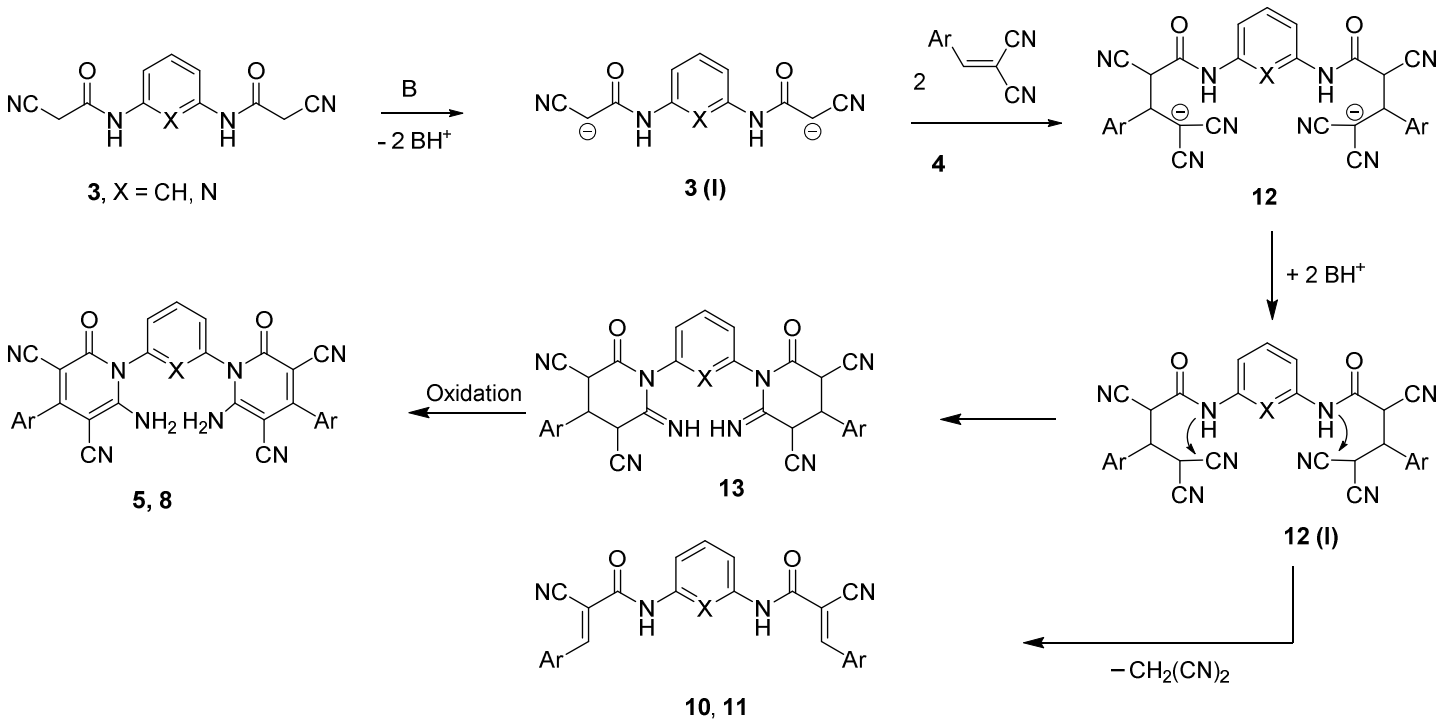
Scheme 5. Reaction of bis-cyanoacetamide **3b** with a variety of arylidenemalononitriles **4a-d**.

Repeated attempts to prepare bisdihydropyridines **5g, 5h,** and terpyridines **8g,** and **8h**, by the reaction of **3a** and **3b,** respectively, with two moles of the appropriate arylidenemalononitriles **4g** and **4h** under similar reaction conditions, were unsuccessful. Instead, the reaction afforded the corresponding *N,N'*-(1,3-phenylene)bis(2-cyano-3-arylacrylamide) derivatives **10g** and **10h** and *N,N'*-(pyridine-2,6-diyl)bis(2-cyano-3-arylacrylamide) **11g** and **11h** as single products in good yield (Scheme 6). The structures of compounds **10g, 10h, 11g** and **11h** were confirmed by comparison with their physical data with authentic samples synthesized from condensation of one mole of each of **3a** and **3b,** respectively, with two moles of the appropriate aldehyde **6** in refluxing ethanol in the presence of piperidine as a basic catalyst (Method C). Similarly, *N,N'*-(pyridine-2,6-diyl)bis(2-cyano-3-arylacrylamide) **11a, 11b, 11d** and **11i** were prepared by condensation of one mole of each of **3b** with two moles of the appropriate aldehyde **6** in refluxing ethanol in the presence of piperidine as a basic catalyst.



Scheme 6. Unexpected formation of bis(2-cyano-3-arylacrylamide) derivatives.

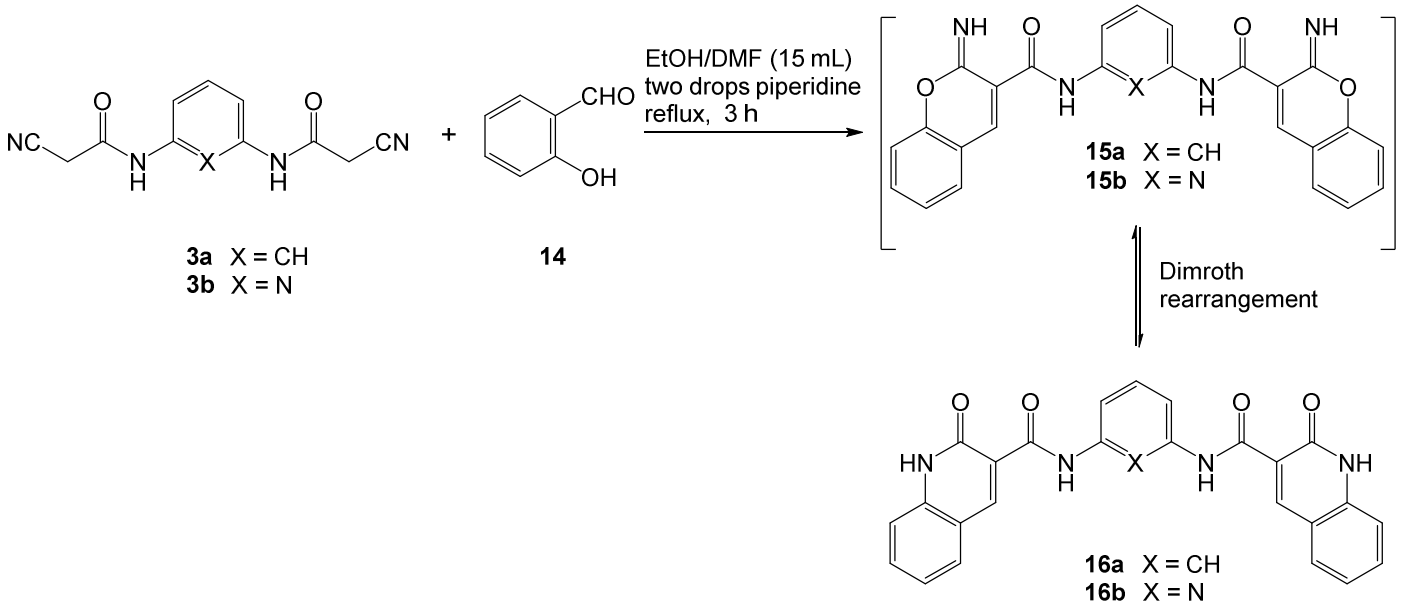
Depending on the above results, one can propose the following mechanism for the formation of compounds **5** and **8** (Scheme 7). Thus, the pyridines **5** and **8** are formed through the initial addition of the active methylene in the cyanoacetamides **3** to the double bond of cinnamonitriles **4** to give the adduct **12** followed by cyclization involving NH of the amide to afford **13**. Subsequent air oxidation of **13** led to the formation of the target compounds **5** and **8**. It is noteworthy to mention that piperidine acts as basic catalyst which generates the carbanionic species **3 (I)**, through carrying the labile protons. The formation of **10** and **11** is assumed to proceed *via* initial formation of the adduct **12**, which then decompose to give **10** and **11**, respectively, *via* elimination of two molecules of malononitrile.



Scheme 7. Proposed mechanistic pathway for the formation of compounds **5**, **8**, **10** and **11**.

The spectroscopic data and elemental analyses of the obtained products **5** and **8** supported the assigned structures. The IR spectrum of **5d** as a representative example exhibits strong stretching frequencies in the region of 3580 and 3476 cm^{-1}, attributable to the amino group, in addition to the presence of a strong absorption band at 2222 cm^{-1} due to a C≡N group. Its ^{1}H NMR spectrum displayed a singlet signal at δ_H 3.86 assigned to the methoxy protons in addition to the presence of a singlet signal at δ_H 8.60 exchangeable with D_2O assignable to the NH_2 protons. Additional evidence supporting this structure was obtained by mass spectrum, which gave a molecular ion at *m*/*z* 606 $[M]^+$. The structures of compounds **10** and **11** were assigned based on their elemental analyses and spectral data. For example, ^{1}H NMR spectrum of **10g** revealed a singlet signal at δ_H 3.08 assignable to the four methyl protons, besides the aromatic and NH protons.

The utility of cyanoacetamides **3** as building blocks for novel bis(quinolinones) was also investigated. Thus, cyclocondensation of **3** with salicylaldehyde **14** in dioxane in the presence of a catalytic amount of piperidine afforded *N,N*′-(1,3-phenylene)bis(2-oxo-1,2-dihydroquinoline-3-carboxamide) **16a** and *N,N*′-(pyridine-2,6-diyl)-bis(2-oxo-1,2-dihydroquinoline-3-carboxamide) **16b**, respectively, in good yields, whereas, the initially formed bis(2-imino-2*H*-chromene-3-carboxamides) **15a** and **15b** undergo Dimroth type rearrangement to give **16a** and **16b**. Similar behavior has been reported by us, whereas the pyridazino[3,4-*d*][1,3]oxazin-5-imine underwent Dimroth type rearrangement into pyrimido[4,5-*c*]pyridazine derivatives.[32]



Scheme 8. Synthesis of bis(2-oxo-1,2-dihydroquinoline-3-carboxamide) **16a** and **16b**.

The IR spectrum of compound **16a** showed absorption bands at 3254 and 1680 cm^{-1} corresponding to NH and carbonyl functions, respectively. Its ^1H NMR spectrum showed two D_2O-exchangeable signals at δ_H 9.27 and 12.88 due to NH protons, in addition to an aromatic multiplet in the region δ_H 7.26-8.05. Its mass spectrum showed a molecular ion peak at *m/z* 450.

Conclusions

We developed an efficient synthesis of bis(cyanoacetamides) and investigated their utility as building blocks for regioselective synthesis of novel biscyanopyridones *via* facile Michael addition reactions with various arylidenemalononitriles. The structures of the new compounds were supported by elemental analyses as well as spectral data. The mechanism proposed for their formation was also discussed. The straightforward synthesis of these compounds from readily available starting material should open a new access for novel bis functionalized heterocycles with potentially interesting biological and pharmaceutical activities.

Experimental Section

General. Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded using an FTIR Bruker– vector 22 spectrophotometer as KBr pellets. The ^1H NMR spectra were recorded in DMSO–d_6 as solvent on Varian Gemini NMR spectrometer at 400 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 or on an AccuTOF-T100LP (JEOL) mass spectrometer in ESI. The elemental analyses were performed at the Micro analytical center, Cairo University. Analytical thin layer chromatography was performed using pre-coated silica gel 60.778 plates (Fluka), and the spots were visualized with UV light at 254 nm.

Synthesis of *N,N'*-(1,3-arylene)bis(2-cyanoacetamide) (3a,b)

General procedure. To a solution of benzene-1,3-diamine (**1a**) (1 mmol) or pyridine-2,6-diamine (**1b**) (1 mmol) in toluene (10 mL), 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (**2**) (2 mmol) was added. The reaction mixture was heated at reflux with stirring for 5 h. The solid product formed was collected and recrystallized from the proper solvent to afford **3a** and **3b**, respectively.

***N,N'*-(1,3-Phenylene)bis(2-cyanoacetamide) (3a).** Colorless powder, (213 mg, 88%) mp 235 ^{o}C (EtOH) and;^{1}H NMR (300 MHz, DMSO): δ 3.877 (s, 4H, 2CH_2), 7.281 (m, 3H, Ar-H), 7.874 (s, 1H, Ar-H) 10.306 (s, 2H, 2NH); Anal. Calcd for $C_{12}H_{10}N_4O_2$ (242.08): C, 59.50; H, 4.16; N, 23.13. Found: C, 59.33; H, 4.01; N, 22.96%.

***N,N'*-(Pyridine-2,6-diyl)bis(2-cyanoacetamide) (3b).** Brown powder, (191 mg, 79%) mp 245 ^{o}C (AcOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.02 (s, 4H, 2 CH_2), 7.72-7.84 (m, 3H, pyridine-H), 10.50 (s, 2H, 2 NH); Anal. Calcd for $C_{11}H_9N_5O_2$ (243.08): C, 54.32; H, 3.73; N, 28.79. Found: C, 53.95; H, 3.36; N, 28.55%.

Synthesis of 1,1'-(1,3-phenylene)bis(6-amino-2-oxo-4-aryl-1,2 dihydropyridine-3,5-dicarbonitrile) 5a-f and *N,N'*-(1,3-phenylene)bis(2-cyano-3-(aryl)acrylamide) 10g,h

Method A. A mixture of *N,N'*-(1,3-phenylene)bis(2-cyanoacetamide) (**3a**) (1 mmol) and 2-arylidene-malononitrile (2 mmol) (**4a-f**) in absolute ethanol (20 mL) was heated at reflux for 4 h in the presence of piperidine as a catalyst. The formed solid product was filtered off and recrystallized from DMF/EtOH to afford **5a-f** or **10g,h**.

Method B. A mixture of *N,N'*-(1,3-phenylene)bis(2-cyanoacetamide) (**3a**) (1 mmol), the appropriate aromatic aldehyde **6** and malononitrile (2 mmol) (**7**) in absolute ethanol (20 mL) was heated at reflux for 4 h in the presence of piperidine as a catalyst. The formed solid product was filtered off and recrystallized from DMF/EtOH to afford **5a-f** or **10g,h,** respectively.

Method C. A mixture of *N,N'*-(1,3-phenylene)bis(2-cyanoacetamide) (**3a**) (1 mmol), the appropriate aromatic aldehyde **6** (2 mmol) in absolute ethanol (20 mL) was heated at reflux for 4 h in the presence of piperidine as a catalyst. The formed solid product was filtered off and recrystallized to afford **10g** and **10h**, respectively.

1,1'-(1,3-Phenylene)bis(6-amino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile) (5a). Yellow powder (376 mg, 69% Method A; 393 mg, 72% Method B), mp > 300 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3411 and 3352 (NH_2), 2225 (CN), 1685 (C=O); ESI-MS: *m/z* 1115 $[2M+Na]^+$ and 569 $[M+ Na]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.55-7.95 (m, 14H, Ar-H), 8.45 (s, 4H, 2 NH_2); ^{13}C NMR: δ 75.7, 88.4, 116.3, 116.8, 128.4, 129.2, 129.7, 130.8, 131.4, 132.9, 135.1, 136.5, 157.9, 159.8, 161.9. Anal. Calcd for $C_{32}H_{18}N_8O_2$ (546.54): C, 70.32; H, 3.32; N, 20.50. Found: C, 70.05; H, 3.54; N, 20.22%.

1,1'-(1,3-Phenylene)bis(6-amino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile) (5b). Yellow powder (498 mg, 81% Method A; 516 mg, 84% Method B), mp > 300 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3447 and 3320 (NH_2), 2214 (CN), 1651 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56-7.86 (m, 12H, Ar-H), 8.70 (s, 4H, 2 NH_2); Anal. Calcd for $C_{32}H_{16}Cl_2N_8O_2$ (615.43): C, 62.45; H, 2.62; N, 18.21. Found: C, 62.21; H, 2.33; N, 17.96%.

1,1'-(1,3-Phenylene)bis(6-amino-4-(2-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile) (5c). Orange powder (454 mg, 75% Method A; 478 mg, 79% Method B), mp > 300 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3566, 3481 (NH_2), 2223 (CN), 1660 (C=O); ESI-MS: *m/z* 629 $[M+ Na]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 7.13-7.92 (m, 12H, Ar-H), 8.42 (s, 4H, 2 NH_2); ^{13}C NMR: δ 56.2, 56.3, 76.5, 89.5, 112.6, 116.1, 116.6, 121.1, 123.9, 129.6, 131.3, 131.5, 132.3, 132.9, 136.5, 156.1, 157.6, 159.7, 160.1. Anal. Calcd for $C_{34}H_{22}N_8O_4$ (606.59): C, 67.32; H, 3.66; N, 18.47. Found: C, 66.98; H, 3.42; N, 18.71%.

1,1'-(1,3-Phenylene)bis(6-amino-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile) (5d). Orange powder (454 mg, 75% Method A; 490 mg, 81% Method B), mp > 300 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3580 and 3476 (NH_2), 2222 (CN), 1660 (C=O); ESI-MS: *m/z* 629 $[M+Na]^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.86 (s, 6H,

2OCH_3), 7.12 (d, 4H, Ar-H), 7.50 (d, 4H, Ar-H), 7.54 -8.86 (m, 4H, Ar-H), 8.60 (s, 4H, 2 NH_2); ^{13}C NMR: δ 55.8, 75.7, 88.0, 114.5, 116.6, 117.1, 126.9, 129.8, 130.3, 131.4, 132.7, 136.6, 157.9, 159.9, 161.3, 161.6. Anal. Calcd for $C_{34}H_{22}N_8O_4$ (606.59): C, 67.32; H, 3.66; N, 18.47. Found: C, 67.58; H, 3.39; N, 18.62%.

1,1'-(1,3-Phenylene)bis(6-amino-2-oxo-4-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarbonitrile) (5e). Yellow powder (476 mg, 83% Method A; 499 mg, 87% Method B), mp > 300 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3532 and 3492 (NH_2), 2226 (CN), 1663 (C=O); ESI-MS: *m/z* 597 [M+ Na]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 6H, 2 CH_3), 7.39-7.95 (m, 12H, Ar-H), 8.46 (s, 4H, 2 NH_2); ^{13}C NMR: δ 21.4, 75.6, 88.3, 116.4, 116.9, 128.4, 129.7, 131.4, 132.2, 132.9, 136.5, 140.7, 157.9, 159.9, 161.9, 162.8. Anal. Calcd for $C_{34}H_{22}N_8O_2$ (574.59): C, 71.07; H, 3.86; N, 19.50. Found: C, 70.89; H, 3.62; N, 19.76%.

1,1'-(1,3-Phenylene)bis(6-amino-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile) (5f). Reddish brown powder (432 mg, 68% Method A; 470 mg, 74% Method B), mp > 300 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3486, 3438 (NH_2), 2221 (CN), 1662 (C=O); ESI-MS: *m/z* 659 [M+ Na]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.57-8.47 (m, 12H, Ar-H), 8.66 (s, 4H, 2 NH_2); ^{13}C NMR: δ 75.6, 88.4, 115.9, 116.4, 124.5, 129.6, 130.2, 131.4, 133.1, 136.4, 141.3, 149.0, 157.9, 159.6, 159.9. Anal. Calcd for $C_{32}H_{16}N_{10}O_6$ (636.53): C, 60.38; H, 2.53; N, 22.00. Found: C, 60.09; H, 2.36; N, 22.35%.

***N,N'*-(1,3-Phenylene)bis(2-cyano-3-(4-(dimethylamino)phenyl)acrylamide) (10g).** Brown powder (378 mg, 75% Method A; 398 mg, 79% Method B; 408 mg, 81% Method C), mp > 300 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3415 (NH), 2218 (CN), 1672 (C=O); ESI-MS: *m/z* 527 [M+ Na]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.08 (s, 12H, 4 CH_3), 6.85-7.94 (m, 12H, Ar-H), 8.07 (s, 2H, 2 CH), 10.10 (s, 2H, 2 NH). Anal. Calcd for $C_{30}H_{28}N_6O_2$ (504.58): C, 71.41; H, 5.59; N, 16.66. Found: C, 71.72; H, 5.81; N, 16.43%.

***N,N'*-(1,3-Phenylene)bis(2-cyano-3-(1*H*-indol-3-yl)acrylamide) (10h).** Reddish brown powder (376 mg, 76% Method A; 401 mg, 81% Method B; 412 mg, 83% Method C), mp > 300 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3735,3304 (NH amid, NH indol), 2213 (CN), 1651 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.26-8.03 (m, 12H, aromatic), 8.16 (s, 2H, 2 CH), 8.55 (s, 2H, indol-H), 8.63 (s, 2H, indol-NH), 10.25 (s, 2H, 2NH); ^{13}C NMR: δ 98.6, 110.1, 113.3, 113.6, 116.8, 119.1, 119.1, 122.1, 123.8, 127.7, 129.2, 131.1, 136.5, 139.4, 143.2, 162.1. Anal. Calcd for $C_{30}H_{20}N_6O_2$ (496.52): C, 72.57; H, 4.06; N, 16.93. Found: C, 72.31; H, 4.25; N, 17.21%.

Synthesis of 6,6''-diamino-4,4''-bisaryl)-2,2''-dioxo-2H,2''*H*-[1,2':6',1''-terpyridine]-3,3'',5,5''-tetracarbonitrile 8a-c, *N,N'*-(pyridine-2,6-diyl)bis(3aryl)-2-cyanoacrylamide) (piperidinium salt) 9 and *N,N'*-(pyridine-2,6-diyl)bis(2-cyano-3-arylacrylamide) 11a,b,d,g-i

Method A. A mixture of *N*,*N*'-(pyridine-2,6-diyl)bis(2-cyanoacetamide) (**3b**) (1 mmol) and 2-arylidene-malononitrile (2 mmol) (**4a-d, 4g** and **4h**) in dioxane (20 mL) was heated at reflux for 4 h in the presence of piperidine as a catalyst. The excess solvent was evaporated in *vacuo*. The crude product was then filtered off and recrystallized from DMF/EtOH to give **8a-c**, **9**, **11a,b,d,g-i**.

Method B. A mixture of *N*,*N*'-(pyridine-2,6-diyl)bis(2-cyanoacetamide) (**3b**) (1 mmol), the appropriate aromatic aldehyde **6** and malononitrile (2 mmol) (**7**) in dioxane (20 mL) was heated at reflux for 4 h in the presence of piperidine as a catalyst. The excess solvent was evaporated in *vacuo*. The crude product was then filtered off and recrystallized from DMF/EtOH to give **8a-c**, **9**, **11a,b,d,g-i**.

Method C. A mixture of *N*,*N*'-(pyridine-2,6-diyl)bis(2-cyanoacetamide) (**3b**) (1 mmol), the appropriate aromatic aldehyde **6** (2 mmol) in absolute ethanol (20 mL) was heated at reflux for 4 h in the presence of piperidine as a catalyst. The formed solid product was filtered off and recrystallized to afford **11a,b,d,g-i**.

6,6''-Diamino-2,2''-dioxo-4,4''-diphenyl-2*H*,2''*H*-[1,2':6',1''-terpyridine]-3,3'',5,5''-tetracarbonitrile (8a). Red powder (454 mg, 83% Method A; 481 mg, 88% Method B), mp > 247 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3488,3367

(NH_2), 2216 (CN), 1663 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.28-8.51 (m, 13H, Ar-H); Anal. Calcd for $C_{31}H_{17}N_9O_2$ (547.53): C, 68.00; H, 3.13; N, 23.02. Found: C, 68.21; H, 3.25; N, 22.89%.

6,6''-Diamino-4,4''-bis(4-chlorophenyl)-2,2''-dioxo-2*H*,2''*H*-[1,2':6',1''-terpyridine]-3,3'',5,5''-tetracarbonitrile (8b). Yellow powder (425 mg, 69%, Method A; 443 mg, 72% Method B), mp > 233 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3412,3305 (NH_2), 2224 (CN), 1655 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.57-7.52 (m, 11H, Ar-H); ^{13}C NMR: δ 75.6, 115.4, 115.8, 127.1, 128.9, 129.9, 133.4, 135.3, 144.2, 146.1, 156.6, 159.1, 160.8. Anal. Calcd for $C_{31}H_{15}Cl_2N_9O_2$ (616.42): C, 60.40; H, 2.45; N, 20.45. Found: C, 60.11; H, 2.72; N, 20.17%.

6,6''-Diamino-4,4''-bis(2-methoxyphenyl)-2,2''-dioxo-2*H*,2''*H*-[1,2':6',1''-terpyridine]-3,3'',5,5''-tetracarbonitrile (8c). Brown powder (455 mg, 75% Method A; 473 mg, 79% Method B), mp > 300 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3457,3328 (NH_2), 2220 (CN), 1678 (C=O); ESI-MS: *m/z* 630 [M+ Na]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 6H, 2 OCH_3) 7.10-7.57, 8.47-8.52 (m, 11H, Ar-H), 7.99 (s, 4H, 2 NH_2). Anal. Calcd for $C_{33}H_{21}N_9O_4$ (607.58): C, 65.23; H, 3.48; N, 20.75. Found: C, 66.98; H, 3.32; N, 20.53%.

6,6''-Diamino-3,3''-bis(imino(piperidin-1-yl)methyl)-4,4''-bis(4-methoxyphenyl)-2,2''-dioxo-2*H*,2''*H*-[1,2':6',1''-terpyridine]-5,5''-dicarbonitrile (9). Pale yellow powder (567 mg, 73% Method A; 598 mg, 77% Method B) ; mp > 240 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3725 (NH) 3542,3436 (NH_2), 2221 (CN), 1667 (C=O); EI-MS: *m/z*: 777.86 (M$^+$, 4.62%), 762.87 (6.12%), 323.25 (46.02%), 312.23 (34.07%), 55 (56.52%) 43.13 (100%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.51 (m, 12H, piperidine-H), 2.82 (t, 8H, piperidine-H), 3.84 (s, 6H, 2 OCH_3), 5.72 (s, 6H, 2 NH & 2 NH_2), 7.07 (d, 4H, Ar-H), 7.45 (d, 4H, Ar-H), 7.60 (d, 2H, pyridine H3 and H5) 8.26 (t, 1H, pyridine H4). Anal. Calcd for $C_{43}H_{43}N_{11}O_4$ (777.87): C, 66.39; H, 5.57; N, 19.81. Found: C, 66.15; H, 5.72; N, 19.55%.

***N,N'*-(Pyridine-2,6-diyl)bis(2-cyano-3-phenylacrylamide) (11a).** Orange powder (343 mg, 82% Method A; 347 mg, 83% Method B; 364 mg, 87% Method C), mp > 300 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3391 (NH), 2207 (CN), 1693 (C=O); ESI-MS: *m/z* 861 [2M+ Na]$^+$, 442 [M+ Na]$^+$, 420 [M+H]$^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.57-8.02 (m, 13H, aromatic), 8.38 (s, 2H, 2 CH), 10.42(s, 2H, 2 NH); ^{13}C NMR: δ 107.2, 111.4, 116.7, 129.7, 131, 132.4, 133.5, 141.2, 150.0, 152.4, 161.2. Anal. Calcd for $C_{25}H_{17}N_5O_2$ (419.43): C, 71.59; H, 4.09; N, 16.70. Found: C, 71.78; H, 4.28; N, 16.44%.

***N,N'*-(Pyridine-2,6-diyl)bis(3-(4-chlorophenyl)-2-cyanoacrylamide) (11b).** Yellow powder (410 mg, 84% Method A; 424 mg, 87% Method B; 429 mg, 88% Method C), mp 282 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3374 (NH), 2212 (CN), 1704 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.68-8.02 (m, 11H, Ar-H), 8.36 (s, 2H, 2 CH), 10.46(s, 2H, 2 NH). Anal. Calcd for $C_{25}H_{15}Cl_2N_5O_2$ (488.32): C, 61.49; H, 3.10; N, 14.34. Found: C, 61.21; H, 3.28; N, 14.62%.

***N,N'*-(Pyridine-2,6-diyl)bis(2-cyano-3-(4-methoxyphenyl) acrylamide) (11d).** Yellow powder (392 mg, 82% Method A; 397 mg, 83% Method B; 411 mg, 86% Method C), mp 290 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3398 (NH), 2202 (CN), 1695 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.87 (s, 6H, 2 OCH_3), 7.15-8.05 (m, 11H, Ar-H), 8.32 (s, 2H, 2 CH), 10.25(s, 2H, 2 NH). Anal. Calcd for $C_{27}H_{21}N_5O_4$ (479.49): C, 67.63; H, 4.41; N, 14.61. Found: C, 67.46; H, 4.62; N, 14.33%.

***N,N'*-(Pyridine-2,6-diyl)bis(2-cyano-3-(4-(dimethylamino) phenyl)acrylamide) (11g).** Yellow powder (389 mg, 77% Method A; 419 mg, 83% Method B; 424 mg, 84% Method C), mp > 300 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3399 (NH), 2197 (CN), 1682 (C=O); Anal. Calcd for $C_{29}H_{27}N_7O_2$ (505.57): C, 68.89; H, 5.38; N, 19.39. Found: C, 69.12; H, 5.55; N, 19.02%.

***N,N'*-(Pyridine-2,6-diyl)bis(2-cyano-3-(1*H*-indol-3-yl)acrylamide) (11h).** Red powder (368 mg, 74% Method A; 397 mg, 80% Method B; 412 mg, 83% Method C), mp 288 ^{o}C (DMF/EtOH); IR (cm^{-1}): 3391, 3283 (NH amid, NH indol), 2203 (CN), 1665 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.26-8.09 (m, 11H, Ar-H), 8.54-8.56 (d, 2H,

indole-H, *J* = 3.9 Hz), 8.76 (s, 2H, 2 CH), 10.16 (s, 2H, 2 NH), 12.47 (s, 2H, indole-H). Anal. Calcd for $C_{29}H_{19}N_7O_2$ (497.51): C, 70.01; H, 3.85; N, 19.71. Found: C, 70.32; H, 4.05; N, 19.42%.

N,N'*-(Pyridine-2,6-diyl)bis(3-(benzo[d][1,3]dioxol-5-yl)-2-cyanoacrylamide) (11i*). Brown powder (350 mg, 69% Method A; 370 mg, 73% Method B; 390 mg, 77% Method C), mp > 300 °C (DMF/EtOH); IR (cm^{-1}): 3328 (NH), 2213 (CN), 1649 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.20 (s, 4H, $2CH_2$), 7.15-7.90 (m, 9H, Ar-H), 8.28 (s, 2H, 2 CH), 10.27 (s, 2H, 2 NH). Anal. Calcd for $C_{27}H_{17}N_5O_6$ (507.45): C, 63.91; H, 3.38; N, 13.80. Found: C, 64.22; H, 3.12; N, 13.54%.

Synthesis of bis(2-oxo-1,2-dihydroquinoline-3-carboxamide) 16a and **16b**

A mixture of the appropriate bis(2-cyanoacetamide) **3a** and **3b** (1 mmol) and 2-hydroxybenzaldehyde (2 mmol) **13** in EtOH/DMF (10 mL) (50:50) in the presence of piperidine as a catalyst was heated at reflux for 4 h. The solid products were then filtered off and recrystallized to give **16a** and **16b**, respectively.

***N,N'*-(1,3-Phenylene)bis(2-oxo-1,2-dihydroquinoline-3-carboxamide) (16a).** Orange powder (364 mg, 81%), mp > 250 °C (DMF); IR (cm^{-1}): 3320 (NH), 3254 (NH), 1680 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.26-8.05 (m,12H, Ar-H), 8.57(s, 2H, Ar-H), 9.27 (s, 2H, 2 NH), 12.88 (s, 2H, 2 NH); ^{13}C NMR: δ 110.9, 115.5, 117.5, 118.8, 120.5, 124.7, 130.6, 133.6, 139.2, 142.2, 150.4, 154.3, 155.9, 160.3. Anal. Calcd for $C_{26}H_{18}N_4O_4$ (450.45): C, 69.33; H, 4.03; N, 12.44. Found: C, 69.15; H, 3.89; N, 12.69%.

***N,N'*-(Pyridine-2,6-diyl)bis(2-oxo-1,2-dihydroquinoline-3-carboxamide) (16b).** Yellow powder (383 mg, 85%), mp > 250 °C (DMF); IR (cm^{-1}): 3372(NH), 3231 (NH), 1672 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29-8.06 (m, 11H, Ar-H), 8.63 (s, 2H, Ar-H), 9.31 (s, 2H, 2 NH), 13.04 (s, 2H, 2 NH). Anal. Calcd for $C_{25}H_{17}N_5O_4$ (451.43): C, 66.51; H, 3.80; N, 15.51. Found: C, 66.83; H, 3.61; N, 15.13%.

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