Synthesis of novel bis(dihydropyridine) and terpyridine derivatives

Ali M. S. Hebishy, a Ismail A. Abdelhamidb* and Ahmed H. M. Elwahyb*

a Chemistry Department, Faculty of Science, Helwan University, Cairo-Egypt
b Chemistry Department, Faculty of Science, Cairo University, Giza-Egypt
E-mail: ismail_shafy@yahoo.com, aelwahy@hotmail.com

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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

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Introduction

Pyridine derivatives are currently an important group of organic compounds that have therapeutic and pharmacological properties. They are used as antibacterial, antimicrobial, antifungal, cardiotonic, analgesic, antiinflammatory, and anti-lung cancer agents. The pyridine moiety is found in structurally simple drugs like isoniazid I, ethionamide II, amrinone III, bupicomide IV, pinacidil V, torasemide VI and omeprazole VII (Figure 1).

![Figure 1. Representative examples of some drugs incorporated pyridine moiety.](image)

In addition, heterocyclic ligands containing nitrogen atoms have drawn a great deal of attention in coordination chemistry and homogeneous catalysis. Moreover, 2-cyanoacetamide derivatives attracted attention in the last decades for being useful reagents for the synthesis of a variety of heterocyclic compounds. 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. Although the synthesis of biologically interesting 1,2-dihydropyridine-3,5-dicarbonitrile derivatives has been investigated in the past, 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, multicomponent reactions as well as on the synthesis of bis-heterocycles, 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-cyanoacetamide) 3b were chosen as key intermediates to a variety of novel bscyanopyridone 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-1H-pyrazol-1-yl)-3-oxopropanenitrile 2 (Scheme 1).
Scheme 1. Synthesis of bis-cyanoacetamides 3a,b.

The reaction of bis-cyanoacetamide 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

<table>
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<th>Entry</th>
<th>Time (h)</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
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<td>3</td>
<td>Piperidine</td>
<td>EtOH</td>
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<td></td>
<td>Dioxane</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>DABCO</td>
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<td></td>
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<td>4</td>
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<td></td>
<td></td>
<td>Dioxane</td>
<td>71</td>
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</tbody>
</table>

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).
Scheme 3. Reaction of bis(cyanoacetamide) 3a with a variety of aryldenemalononitriles 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 bis(cyanoacetamides) 3a in refluxing ethanol in the presence of piperidine as a catalyst (Method B) (Scheme 4).

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 bis(cyanoacetamide) 3b with a variety of aryldenemalononitriles proceeded smoothly in refluxing dioxane in the presence of piperidine as a catalyst to give the desired 6,6''-diamino-2,2''-dioxy-4,4''-diaryl-2H,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 aryldenemalononitrile 4d (Scheme 5). In this respect, recently the formation of solid state adduct of bis(2H-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 \(N,N'-(1,3\text{-phenylene})\text{bis}(2\text{-cyano-3-arylacrylamide})\) derivatives 10g and 10h and \(N,N'-(\text{pyridine-2,6-diyl})\text{bis}(2\text{-cyano-3-arylacrylamide})\) 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, \(N,N'-(\text{pyridine-2,6-diyl})\text{bis}(2\text{-cyano-3-arylacrylamide})\) 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 cinnaminitriles 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 \(\delta_\text{H} 3.86\) assigned to the methoxy protons in addition to the presence of a singlet signal at \(\delta_\text{H} 8.60\) exchangeable with D\(_2\)O assignable to the NH 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 \(\delta_\text{H} 3.08\) 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 \(N,N'-(1,3\text{-phenylene})\text{bis}(2\text{-oxo-1,2-dihydroquinoline-3-carboxamide})\) 16a and \(N,N'-(\text{pyridine-2,6-diyl})\text{bis}(2\text{-oxo-1,2-dihydroquinoline-3-carboxamide})\) 16b, respectively, in good yields, whereas, the initially formed bis(2-imino-2H-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.\(^3\)
Scheme 8. Synthesis of bis(2-oxo-1,2-dihydroquinolone-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 \(^1\)H NMR spectrum showed two D\(_2\)O-exchangeable signals at \(\delta_H\) 9.27 and 12.88 due to NH protons, in addition to an aromatic multiplet in the region \(\delta_H\) 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 bicyanopyridones \textit{via} facile Michael addition reactions with various aryldienemalononitriles. 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 \(^1\)H 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 \(\delta\) 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 \( N,N^-'(1,3\text{-arylene})\text{bis}(2\text{-cyanoacetamide}) \) (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-1H-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.

\( N,N^-'(1,3\text{-Phenylene})\text{bis}(2\text{-cyanoacetamide}) \) (3a). Colorless powder, (213 mg, 88%) mp 235 °C (EtOH) and; \(^1\)H NMR (300 MHz, DMSO-\( d_6 \)): \( \delta \) 3.877 (s, 4H, 2CH2), 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\(_4\)O\(_2\) (242.08): C, 59.50; H, 4.16; N, 23.13. Found: C, 59.33; H, 4.01; N, 22.96%.

\( N,N^-'(\text{Pyridine}-2,6\text{-diyl})\text{bis}(2\text{-cyanoacetamide}) \) (3b). Brown powder, (191 mg, 79%) mp 245 °C (AcOH); \(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) 4.02 (s, 4H, 2 CH2), 7.72-7.84 (m, 3H, pyridine-H), 10.50 (s, 2H, 2 NH); Anal. Calcd for C\(_{11}\)H\(_9\)N\(_3\)O\(_2\) (243.08): C, 54.32; H, 3.73; N, 28.79. Found: C, 53.95; H, 3.36; N, 28.55%.

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

**Method A.** A mixture of \( N,N^-'(1,3\text{-phenylene})\text{bis}(2\text{-cyanoacetamide}) \) (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 \( N,N^-'(1,3\text{-phenylene})\text{bis}(2\text{-cyanoacetamide}) \) (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 \( N,N^-'(1,3\text{-phenylene})\text{bis}(2\text{-cyanoacetamide}) \) (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.

\( 1,1^-'(1,3\text{-Phenylene})\text{bis}(6\text{-amino-2-oxo-4-aryl-1,2 dihydropyridine-3,5-dicarbonitrile}) \) (5a). Yellow powder (376 mg, 69% Method A; 393 mg, 72% Method B), mp > 300 °C (DMF/EtOH); IR (cm\(^{-1}\))): 3447 and 3320 (NH\(_2\)), 2214 (CN), 1651 (C=O); ESI-MS: m/z 1115 [2M+Na]\(^+\) and 569 [M+ Na]\(^+\); \(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) 7.55-7.95 (m, 14H, Ar-H), 8.45 (s, 4H, 2 NH\(_2\)); \(^1^3\)C NMR: \( \delta \) 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\(_8\)O\(_2\) (546.54): C, 70.32; H, 3.32; N, 20.50. Found: C, 70.05; H, 3.54; N, 20.22%.

\( 1,1^-'(1,3\text{-Phenylene})\text{bis}(6\text{-amino-4-(4-chlorophenyl)-2-oxo-1,2 dihydropyridine-3,5-dicarbonitrile}) \) (5b). Yellow powder (498 mg, 81% Method A; 516 mg, 84% Method B), mp > 300 °C (DMF/EtOH); IR (cm\(^{-1}\))): 3447 and 3320 (NH\(_2\)), 2214 (CN), 1651 (C=O); \(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) 7.56-7.86 (m, 12H, Ar-H), 8.70 (s, 4H, 2 NH\(_2\)); Anal. Calcd for C\(_{32}\)H\(_{16}\)Cl\(_2\)N\(_8\)O\(_2\) (615.43): C, 62.45; H, 2.62; N, 18.21. Found: C, 62.21; H, 2.33; N, 17.96%.

\( 1,1^-'(1,3\text{-Phenylene})\text{bis}(6\text{-amino-4-(2-methoxyphenyl)-2-oxo-1,2 dihydropyridine-3,5-dicarbonitrile}) \) (5c). Orange powder (454 mg, 75% Method A; 478 mg, 79% Method B), mp > 300 °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-\( d_6 \)): \( \delta \) 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\(_2\)); \(^1^3\)C NMR: \( \delta \) 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\(_{22}\)O\(_4\) (606.59): C, 67.32; H, 3.66; N, 18.47. Found: C, 66.98; H, 3.42; N, 18.71%.

\( 1,1^-'(1,3\text{-Phenylene})\text{bis}(6\text{-amino-4-(4-methoxyphenyl)-2-oxo-1,2 dihydropyridine-3,5-dicarbonitrile}) \) (5d). Orange powder (454 mg, 75% Method A; 490 mg, 81% Method B), mp > 300 °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-\( d_6 \)): \( \delta \) 3.86 (s, 6H,
20CH$_3$), 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$_8$O$_4$ (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 °C (DMF/EtOH); IR (cm$^{-1}$): 3486, 3438 (NH$_2$), 2221 (CN), 1662 (C=O); ESI-MS: m/z 579 [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, 16.43%. Found: C, 60.09; H, 2.36; N, 16.43%.

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 °C (DMF/EtOH); IR (cm$^{-1}$): 3735, 3304; $^1$H NMR (400 MHz, DMSO-d$_6$): δ 7.57-8.03 (m, 12H, aromatic), 8.07 (s, 2H, 2 CH), 10.10 (s, 2H, 2 NH). Anal. Calcd for C$_{30}$H$_{28}$N$_6$O$_2$ (504.58): C, 71.41; H, 5.59; N, 16.67. Found: C, 71.72; H, 5.81; N, 16.43%.

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

**Method A.** A mixture of N,N’-(pyridine-2,6-diyil)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-diyil)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-diyil)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.
(NH₂)), 2216 (CN), 1663 (C=O); ¹H NMR (300 MHz, DMSO-d₆): δ 7.28-8.51 (m, 13H, Ar-H); Anal. Calcd for C₃₁H₁₇N₉O₂ (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-2H,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 °C (DMF/EtOH); IR (cm⁻¹): 3412,3305 (NH₂), 2224 (CN), 1665 (C=O); ¹H NMR (300 MHz, DMSO-d₆): δ 7.57-7.52 (m, 11H, Ar-H); ¹³C NMR: δ 75.6, 115.4, 115.8, 127.1, 128.9, 133.4, 135.3, 144.2, 146.1, 156.8. Anal. Calcd for C₄₃H₃₁Cl₂N₂O₂ (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-2H,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 > 233 °C (DMF/EtOH); IR (cm⁻¹): 3457,3328 (NH), 2216 (CN), 1663 (C=O); Anal. Calcd for C₃₃H₂₁N₉O₄ (547.53): 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-phenylacrylamide) (11a). Orange powder (343 mg, 82% Method A; 347 mg, 83% Method B; 364 mg, 87% Method C), mp > 300 °C (DMF/EtOH); IR (cm⁻¹): 3391 (NH), 2207 (CN), 1693 (C=O); ESI-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%); ¹H NMR (300 MHz, DMSO-d₆): δ 1.51 (m, 12H, piperidine-H), 2.82 (t, 8H, piperidine-H), 3.84 (s, 6H, 2 OCH₃) 7.10-7.57, 8.47-8.52 (m, 11H, Ar-H), 7.99 (s, 4H, 2 NH₂). Anal. Calcd for C₃₄H₃₄N₁₀O₄ (505.57): 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 °C (DMF/EtOH); IR (cm⁻¹): 3374 (NH), 2212 (CN), 1704 (C=O); ¹H NMR (300 MHz, DMSO-d₆): δ 7.68-8.02 (m, 13H, aromatic), 8.38 (s, 2H, 2 CH), 10.42 (s, 2H, 2 NH₂); ¹³C 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 C₂₅H₁₇N₃O₂ (449.43): 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(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 °C (DMF/EtOH); IR (cm⁻¹): 3399 (NH), 2202 (CN), 1695 (C=O); ¹H NMR (300 MHz, DMSO-d₆): δ 3.87 (s, 6H, 2 OCH₃) 7.15-8.05 (m, 11H, Ar-H), 8.32 (s, 2H, 2 CH), 10.25 (s, 2H, 2 NH₂). Anal. Calcd for C₂₅H₁₇Cl₂N₃O₂ (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-dimethylamino) phenyl)acrylamide) (11g). Yellow powder (389 mg, 77% Method A; 419 mg, 83% Method B; 424 mg, 84% Method C), mp > 300 °C (DMF/EtOH); IR (cm⁻¹): 3399 (NH), 2197 (CN), 1682 (C=O); Anal. Calcd for C₂₉H₂₉N₃O₂ (505.57): C, 68.89; H, 5.57; N, 19.34. Found: C, 69.12; H, 5.55; N, 19.02%.

N,N'-(Pyridine-2,6-diyl)bis(2-cyano-3-(1H-indol-3-yl)acrylamide) (11h). Red powder (368 mg, 74% Method A; 397 mg, 80% Method B; 412 mg, 83% Method C), mp 288 °C (DMF/EtOH); IR (cm⁻¹): 3391, 3283 (NH amid, NH indol), 2203 (CN), 1665 (C=O); ¹H NMR (300 MHz, DMSO-d₆): 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_{7}O_{2} (497.51): C, 70.01; H, 3.85; 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; 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), 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_{5}O_{6} (507.45): C, 63.91; H, 3.38; N, 13.80. Found: C, 64.22; H, 3.12; N, 13.54%.

_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 7.26-8.06 (m,12H, 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_{5}O_{4} (451.43): C, 66.51; H, 3.80; N, 15.13%.

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References

   https://doi.org/10.11648/j.jddmc.20150101.11
   https://doi.org/10.1021/jm980274l
   https://doi.org/10.2298/JSC091127003K
   https://doi.org/10.3998/ark.5550190.0010.e06
   https://doi.org/10.1016/j.ejmech.2005.06.005

   https://doi.org/10.1016/S0960-894X(02)01046-6


    http://dx.doi.org/10.3998/ark.5550190.0006.114


    https://doi.org/10.1074/jbc.M110751200

    https://doi.org/10.1253/jcj.63.605

    https://doi.org/10.1002/cpt1975182145


    https://doi.org/10.2165/00003495-199549010-00009

    https://doi.org/10.1039/C3NJ01209C

    https://doi.org/10.3390/90600440

    https://doi.org/10.3906/kim-1512-44

    https://doi.org/10.1070/RC1999v068n09ABEH000533


    https://doi.org/10.1021/cr100108k

    https://doi.org/10.1039/C0CS00013B

    https://doi.org/10.1021/cr2003954

    https://doi.org/10.1021/cr100233r


https://doi.org/10.1080/00397910008087441


https://doi.org/10.3998/ark.5550190.0017.324

https://doi.org/10.1002/jhet.2373

https://doi.org/10.1016/j.tet.2015.12.024

https://doi.org/10.1080/17415993.2014.975131

https://doi.org/10.2174/157017941106141023114039

https://doi.org/10.1002/jhet.5570440636