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A regioselective and convenient one-pot multicomponent synthesis of polyfunctionalized 4-aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidines

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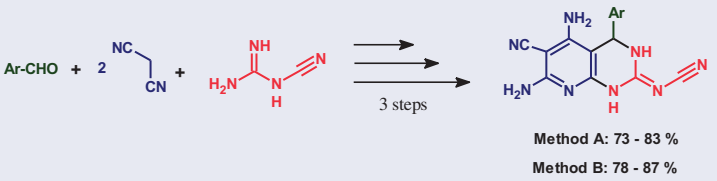
ABSTRACT

A novel series of 5,7-diamino-4-aryl-6-cyano-2-cyanoimino-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidines (aryl-CIDHPPMs) **3a–i** was prepared *via* the one-pot four-component reaction of cyanoguanidine with aromatic aldehydes and malononitrile with molar ratio (1:1:2) using sodium methoxide as catalyst. These new polyfunctionlized aryl-CIDHPPMs were also synthesized by a classical route *via* reaction of cyanoguanidine with the respective arylidenes of malononitrile dimer under the same condition. In the same manner, the reaction of cyanoguanidine with isatinylidene of malononitrile dimer afforded the new *spiro*-pyrido[2,3-*d*]pyrimidines **7**. While using aromatic aldehydes having electron donating groups (hydroxyl or dimethylamino groups) gave 4-Amino-2-aryl-6-methoxypyridine-3,5-dicarbonitrile **5a,b**.

GRAPHICAL ABSTRACT



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Cyanoguanidine; cyanoiminopyrimidine; stereoselective; pyrido[2,3-d]pyrimidine; spiro pyrimidine; multicomponent reactions; MCRs

Introduction

In recent and upcoming years, pyrimidines syntheses *via* multicomponent reactions (MCRs) technique have been achieving immensely important results in the field of medicinal and synthetic organic compounds.[1] Their importance was shown to include the syntheses of poly-functionalized azaheterocyclic compounds *via* one-pot procedures from available simple starting materials.[2] On the other hand, pyrido[2,3-*d*]pyrimidines have received a significant interest in recent years due to their wide range of biological activities.[3] They are used as promising drugs for treatment against inflammatory,[4] bacterial,[5] fungal,[6] hypertensive,[7] leishmania,[8] diarrhea,[9] malaria,[10] viral,[11] and cancer diseases.[12] Also, they act as antihistaminic,[13] antidiuretic,[14] and antitumor agents.[15]

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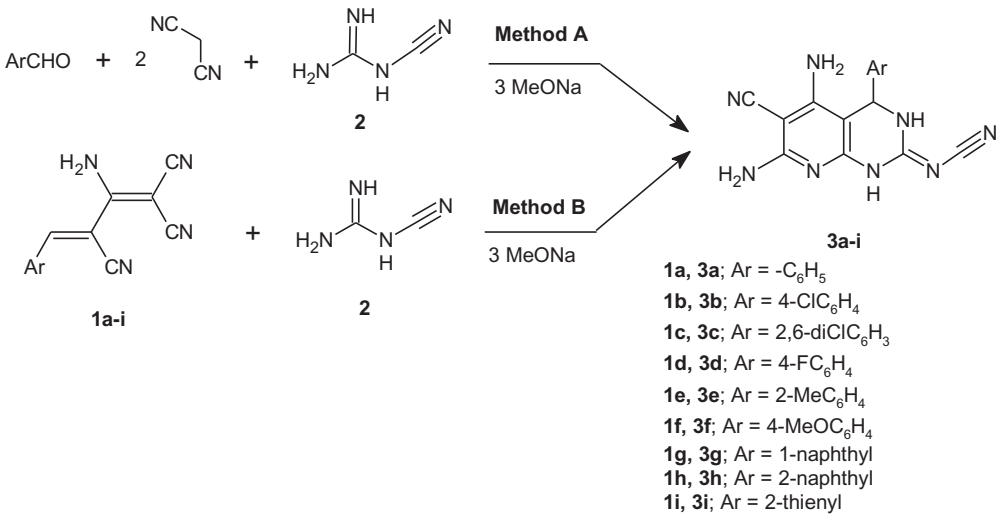


Scheme 1. Synthesis of 4-aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidines (aryl-CIDHPPMs) **3a–i**.

As a result of the above, great efforts have been directed to synthesis of annulated pyrido[2,3-*d*]pyrimidine derivatives. For this purpose, diverse synthetic strategies have been reported for the synthesis of pyrido[2,3-*d*]pyrimidines such as (i) the reaction of 6-aminouracil with different reagents: benzylidenes;[16] enamines;[17] DMAD;[18] or *α,β*-unsaturated carbonyl compounds;[19] (ii) one-pot cyclocondensation of unsaturated esters and malononitrile/ethyl cyanoacetate with amidine derivatives;[20] (iii) the three-component reaction of aromatic aldehyde and 2,6-diaminopyrimidine with Meldrum's acid;[21] and others.[3,22]

Arylmethylidene derivatives of malononitrile dimer **1**, containing the conjugated multiple bonds system, amino and cyano groups in their structures are suitable for the synthesis of diverse heterocyclic compounds through sequence reaction mechanisms and giving possibilities for involving them into intramolecular heterocyclization.[23] As well their reaction with cyanoguanidine is not mentioned in literature earlier.

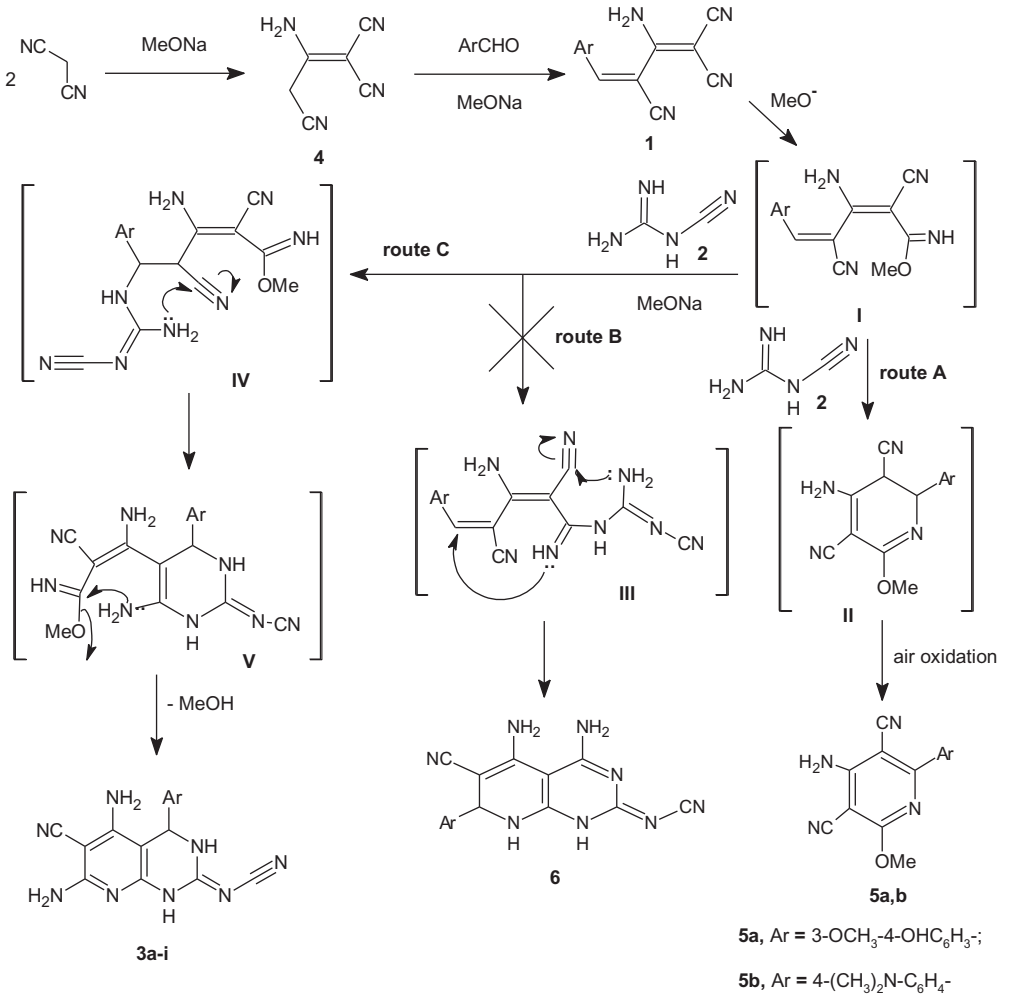
Therefore, in the present work, we design to study the reaction of tricarbonitrile **1** with commercially available 1,3-dinucleophile of cyanoguanidine **2**. The reaction is aimed to prepare the new of 4-aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidine derivatives (aryl-CIDHPPMs) **3a–i** and *spiro*-pyrido[2,3-*d*]pyrimidines **7** *via* an efficient one-pot multicomponent reaction of malononitrile, aromatic aldehydes/isatin, and cyanoguanidine as 2:1:1 molar ratio, respectively. All the reactions were achieved in the presence of sodium methoxide as strong basic catalyst (Schemes 1 and 3).

Results and discussion

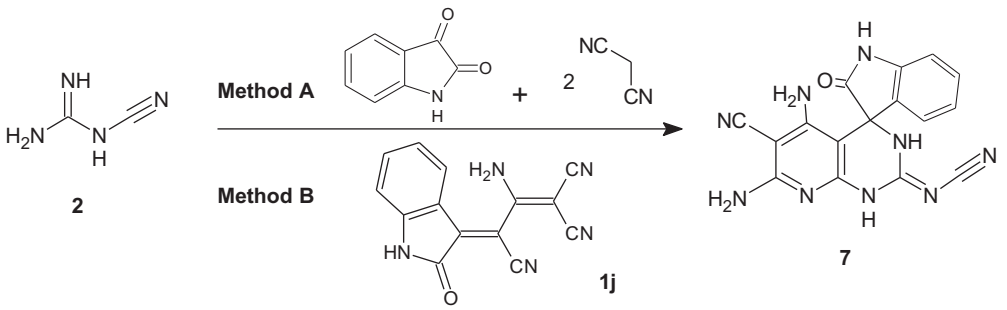
Herein, a new series of 5,7-diamino-4-aryl-6-cyano-2-cyanoimino-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidines (aryl-CIDHPPMs) **3a–i** as a novel class of fused biginelli analogs of 4-aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidines (aryl-CIDHPMs)[2a,24] was synthesized by an efficient one-pot four-component reaction of aromatic aldehydes, two

equivalent amounts of malononitrile and cyanoguanidine **2**, using sodium methoxide as basic catalyst (Method A, Scheme 1). In this method, the formation of the products **3** was achieved in one-pot through three steps: (i) at first, malononitrile was stirred at room temperature in 3 M sodium methoxide for 30 min, (ii) aromatic aldehyde was added to the reaction mixture and further stirred at room temperature for 30 min in 0.5 M sodium methoxide, (iii) finally, the reaction was refluxed for 10 h after addition of cyanoguanidine **2**. The same pyrido[2,3-*d*]pyrimidines **3a–i** was also prepared by the alternative classical route *via* two-component reaction of 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile **1a–i** with cyanoguanidine **2** in the presence of 0.5 M sodium methoxide (Method B, Scheme 1).

The plausible mechanism for the formation of **3** was assumed to proceed *via* the production of un/isolated 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile **1** through two-step sequence reactions (Scheme 2). The arylmethylidene derivatives **1** have a conjugated system,



Scheme 2. Reaction mechanism and stereoselective synthesis of aryl-ClDHPPMs **3a–i** and pyridine-3,5-dicarbonitriles **5a,b**.



Scheme 3 Synthesis of *spiro*-CIDHPPM **7**.

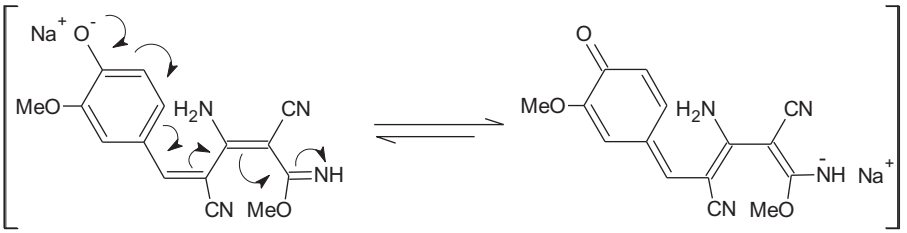


Figure 1. The resonating structure (keto-enol form) of intermediate **I** in basic medium.

in which the partially positive charge appears on numerous positions, therefore its reaction with some nucleophiles is regioselective. In contrast, the nitrile group in cyanoguanidine reduces the nucleophilicity of guanidine fragment, and its reaction with tricarbonitrile **1** can proceed only in the presence of strong nucleophile ethoxide or methoxide anions.[25] While the effect of these anions extends to addition on tricarbonitrile **1** *via* nucleophilic addition of alkoxide anion on cyano group to form the intermediate **I**.[26,27] The intermediate **I** undergoes three possible ways, as shown in Scheme 2. In route **A,** the imino group in intermediate **I** undergoes the intramolecular nucleophilic addition to the olefinic double bond *via* a Michael addition reaction to give intermediate **II**, which is easily aromatized through the deprotonation to afford pyridine-3,5-dicarbonitriles **5a,b** (**5a**: Ar = 3-OCH_3-4-OHC_6H_3-;[26] **5b**: Ar = 4-$(CH_3)_2N$-C_6H_4-[26,27]). This result is agreed with the reported intramolecular cyclization reaction in sodium alkoxide of arylidene dimer of malononitrile **1** having electron donating groups (hydroxyl or dimethylamino groups).[26] In this case, the nucleophilicity of imino group in intermediate **I** is greater than nucleophilicity of guanidine fragment of cyanoguanidine and this may be attributed to the resonance of the conjugated system of butadiene in basic medium with substituted donating groups (hydroxyl or dimethylamino groups) at phenyl group (Figure 1).

In route **B**, the methoxy group in intermediate **I** undergoes nucleophilic substitution by amino cyanoguanidine to form intermediate **III**, which is suitable to cyclize *via* two intramolecular cyclization through addition of respective imino and amino groups on olefin and cyano groups to give pyrido[2,3-*d*]pyrimidines **6**. While in route **C**, the nucleophilic NH_2 group of cyanoguanidine attacks the olefinic double bond *via* a Michael addition reaction to give intermediate **IV**, which undergoes intramolecular cyclization *via* nucleophilic addition of amino group on cyano group giving the intermediate **V**. The formed amino group of intermediate **V** is consequently added to the carbon

imino group, followed by elimination of methanol to afford product **3**. The formation of product **3** instead of its regioselectivity **6** has been unambiguously confirmed through the ^{1}H NMR, ^{13}C NMR, and *NOESY* spectral data.

The chemical structures of the new aryl-CIDHPPMs **3a–i** were confirmed based on their spectral (IR, ^{1}H, ^{13}C NMR, *NOE*) and elemental analysis data. The IR spectra of aryl-CIDHPPMs **3a–i** showed the distinctive absorption band at 2168–2192 cm^{-1}, which is given for cyano cyanoimino group.[2a,24,28] For example, the IR spectrum of **3b** showed characteristic absorption band at 1613 cm^{-1} for C = N, 2172, 2198 cm^{-1} for two C≡N groups, 2945 cm^{-1} for the aliphatic C–H, 3023 cm^{-1} for the aromatic C–H and 3190, 3342, 3417 cm^{-1} for NH_2 and NH groups. Its ^{1}H NMR spectrum showed the presence of three singlet signals at δ 6.33, 6.43 and 10.26 ppm characteristic of two NH_2 and NH-1 groups, respectively; also it exhibited two doublet signals at δ 5.66, 5.67 and 9.12, 9.13 ppm with coupling constant $J = 4.0$ and 3.2 Hz due to CH-4 and NH-3 groups, respectively; and two doublet signals at δ 7.29, 7.31 and 7.41, 7.43 ppm for aromatic *p*-phenylene protons with coupling constant $J = 8.4$ Hz. The ^{13}C NMR spectrum of **3b** showed eight signals at δ 128.9, 129.0, 133.0, 141.6, 150.0, 154.3, 156.5, 161.0 ppm, which are assigned to aromatic and olefinic carbons; one signal at δ 116.9 ppm due to two nitrile groups; while C-4, C-2, and C-6 are characterized by signals at δ 50.4, 70.6 and 88.5 ppm, respectively. The *NOESY* spectrum of compound **3b** (see Supporting Information) showed the correlation signals between the proton at N-3 (δ 9.12, 9.13 ppm) with the corresponding proton at C-4 (δ 5.66, 5.67 ppm) and aromatic protons at δ 7.29, 7.31 ppm; the correlation signals between the two protons of NH_2 at position 5 (δ 6.43 ppm) with the aromatic protons at δ 7.29, 7.31 ppm and proton at C-4 (δ 5.66, 5.67 ppm); also there is a correlation signal between the proton at N-1 (δ 10.26 ppm) and two protons of NH_2 group at position 7 (δ 6.33 ppm), and this supports the presence of amino-imine tautomerization structure.[29]

In light of the foregoing arguments, the possibility of using this novel design to synthesize the new *spiro*-CIDHPPM compounds can be achieved. Thus {5,7-diamino-6-cyano-2′-oxo-1′,2′-dihydro-1*H*-*spiro*[pyrido[2,3-*d*]pyrimidine-4,3′indole]-2(3*H*)-ylidene}cyanamide (**7**) was produced *via* one-pot multicomponent reactions of cyanoguanidine **2**, isatin and malononitrile (Scheme 3, Method A) or *via* classical method through two component reaction of cyanoguanidine **2** with isatinylidene of malononitrile dimer **1j** (Scheme 3, Method B). The analytical data support the structure **7**.

Conclusion

Concisely, we have successfully synthesized a novel series of polyfunctionalized 4-aryl/spiro-2-cyanoimino-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidines (aryl/spiro-CIDHPPMs) by the one-pot four-component reaction, using available starting materials; cyanoguanidine, aromatic aldehydes, and malononitrile as 1:1:2 molar ratio in the presence of sodium methoxide as catalyst. In the same condition of the reaction, using aromatic aldehyde with hydroxyl or dimethylamino substituents gave pyridine-3,5-dicarbonitrile derivatives. Reactions of cyanoguanidine with some reagents are still an interesting and it will achieve good results in the future.

Experimental

All commercially available reagents were purchased from Aldrich, Merck, and Fluka and were used without further purification. All reactions were monitored by thin layer chromatography (TLC) using precoated plates of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F254) using UV light (254 nm/365 nm) for visualization. Melting points were detected with a Kofler melting points apparatus and uncorrected. Infrared spectra were recorded with an FT-IR-ALPHBROKER-Platinum-ATR spectrometer and are given as cm^{-1} using the attenuated total reflection (ATR) method. ^1H NMR and ^{13}C NMR spectra for all compounds were recorded in DMSO-d_6 on a Bruker Bio Spin AG spectrometer at 400 MHz and 100 MHz, respectively. For ^1H NMR, chemical shifts (δ) were given in parts per million (ppm) with reference to tetramethylsilane (TMS) as an internal standard ($\delta = 0$); coupling constants (J) were given in hertz (Hz) and data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets). For ^{13}C NMR, TMS ($\delta = 0$) or DMSO ($\delta = 39.51$) was used as internal standard and spectra were obtained with complete proton decoupling. Elemental analyses were obtained on a Perkin–Elmer CHN-analyzer model.

General procedures for the synthesis of compounds 3a–i, and 7

Method A: general procedure (one-pot four-component reaction)

Malononitrile (0.02 mol, 1.32 g) was stirred at room temperature for 30 min in 10 mL sodium methoxide 3 M (0.69 g sodium metal in 10 mL methanol). Onto the mixture, an aromatic aldehyde, thiophene-2-aldehyde and/or isatin (0.01 mol) in 50 mL methanol was added and stirred for 30 min, then cyanoguanidine **2** (0.01 mol, 0.84 g) was added to the reaction mixture. The resulting mixture was refluxed for about 10 h. After completion of the reaction (monitored using TLC), the reaction mixture was cooled to room temperature, poured into ice-cold distilled water and neutralized to pH ~ 6.5 with dilute hydrochloric acid. The formed precipitate was collected, filtered, washed several times with distilled water, dried, and recrystallized from ethanol.

Method B: general procedure (two-component reaction)

An equimolar mixture of cyanoguanidine **2** (0.01 mol, 0.84 g) and 2-amino-4-(aryl/2-thienyl)-buta-1,3-diene-1,1,3-tricarbonitrile **1a–i** and/or 2-amino-3-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)prop-1-ene-1,1,3-tricarbonitrile **1j** (0.01 mol) was refluxed in 60 mL sodium methoxide 0.5 M (0.69 g sodium metal in 60 mL methanol) for about 10 h. After completion of the reaction (monitored using TLC), the reaction mixture was cooled to room temperature, poured into ice-cold distilled water and neutralized to pH ~ 6.5 with dilute hydrochloric acid. The formed precipitate was collected, filtered, washed several times with distilled water, dried, and recrystallized from ethanol.

*5,7-Diamino-4-(4-chlorophenyl)-6-cyano-2-cyanoimino-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidine (3b).* Yield (Method A 81%, Method B 85%); yellow solid; *m.p.* > 310 °C. IR

(ATR) ν_{max} 3417, 3342, 3190, 3023, 2945, 2198, 2172, 1613 cm^{-1}. ^1H NMR δ 10.26 (s, 1H, NH^1), 9.13, 9.12 (d, $J = 3.2$ Hz, 1H, NH^3), 7.43, 7.41 (d, $J = 8.4$ Hz, 2H, $CH_{arom.}$), 7.31, 7.29 (d, $J = 8.4$ Hz, 2H, $CH_{arom.}$), 6.43 (s, 2H, NH_2), 6.33 (s, 2H, NH_2), 5.67, 5.66 (d, $J = 4.0$ Hz, 1H, CH^4). ^{13}C NMR δ 161.0, 156.5, 154.3, 150.0, 141.6, 133.0, 129.0, 128.9, 116.9 (2CN), 88.5, 70.6, 50.4. Anal. Calcd. for $C_{15}H_{11}ClN_8$ (338.75): C, 53.18; H, 3.27; N, 33.08. Found: C, 52.91; H, 3.22; N, 33.16.

*5,7-Diamino-6-cyano-2-cyanoimino-4-(2-thienyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidine (3i).* Yield (Method A 83%, Method B 87%); brown solid; *m.p.*: 300-302 °C. IR (ATR) ν_{max} 3448, 3322, 3157, 3113, 3023, 2916, 2196, 2179, 1635 cm^{-1}. ^1H NMR δ 10.32 (s, 1H, NH^1), 9.24, 9.23 (d, $J = 3.2$ Hz, 1H, NH^3), 7.40, 7.39 (d, $J = 4.8$ Hz, 1H, $CH_{arom.}$), 7.06, 7.06 (d, $J = 2.7$ Hz, 1H, $CH_{arom.}$), 6.97–6.95 (t, $J = 4.1$ Hz, 1H, $CH_{arom.}$), 6.54 (s, 2H, NH_2), 6.35 (br. s., 2H, NH_2), 5.97, 5.96 (d, $J = 3.7$ Hz, 1H, CH^4). ^{13}C NMR δ 161.0, 156.6, 154.2, 149.7, 147.0, 127.1, 125.9, 125.7, 116.8 (2CN), 89.8, 70.7, 47.1. Anal. Calcd. for $C_{13}H_{10}N_8S$ (310.33): C, 50.31; H, 3.25; N, 36.11. Found: C, 50.23; H, 3.10; N, 36.05.

*{5,7-Diamino-6-cyano-2′-oxo-1′,2′-dihydro-1*H*-spiro[pyrido[2,3-*d*]pyrimidine-4,3′indole]-2(3*H*)-ylidene}cyanamide (7).* Yield (Method A 72%, Method B 77%); brown solid; *m.p.*: > 310 °C. IR (ATR) ν_{max} 3440, 3368, 3334, 3291, 3220, 3062, 2191 (br.), 1748, 1639 cm^{-1}. ^1H NMR δ 12.38 (br. s, 1H, $NH^{1\prime}$), 10.53 (s, 1H, NH^1), 9.88 (s, 1H, NH^3), 7.31–7.26 (m, 1H, $CH_{arom.}$), 7.11, 7.09 (d, $J = 8.0$ Hz, 1H, $CH_{arom.}$), 7.02–6.97 (m, 2H, $CH_{arom.}$), 6.37 (s, 2H, NH_2), 5.33 (s, 2H, NH_2). ^{13}C NMR δ 176.1, 160.6, 156.9, 152.3, 137.2, 130.3, 125.8, 125.2, 122.2, 117.9, 117.1, 116.1, 115.3, 83.7, 70.0, 66.1. Anal. Calcd. for $C_{16}H_{11}N_9O$ (345.31): C, 55.65; H, 3.21; N, 36.51. Found: C, 55.55; H, 3.12; N, 36.47.

General procedures for synthesis of compounds 5a,b

A solution of 2-amino-4-aryl-buta-1,3-diene-1,1,3-tricarbonitrile (**1**, Ar = 3-OCH_3-4-OHC_6H_3-; 4-$(CH_3)_2N$-C_6H_4-) (0.01 mol) with/without cyanoguanidine **2** (0.01 mol, 0.84 g) was refluxed in 60 mL sodium methoxide 0.5 M (0.69 g sodium metal in 60 mL methanol) for about 10 h. After completion of the reaction (monitored using TLC), the reaction mixture was cooled to room temperature, poured into ice-cold distilled water and neutralized to pH ~ 6.5 with dilute hydrochloric acid. The formed precipitate was collected, filtered, washed several times with distilled water, dried, and recrystallized from ethanol.

4-Amino-2-(4-hydroxy-3-methoxyphenyl)-6-methoxypyridine-3,5-dicarbonitrile (5a)

Yield 82%; gray solid; *m.p.*: 264–265 °C (reported *m.p.* 266-267 °C).[26] IR (ATR) ν_{max} 3420, 3364, 3238, 3006, 2956, 2212, 1639 cm^{-1}. ^1H NMR δ 9.70 (br. s, 1H, OH), 7.52–7.51 (m, 3H, NH_2, 1 $CH_{arom.}$), 7.46–7.43 (dd, $J = 1.7$, 8.3 Hz, 1H, $CH_{arom.}$), 6.94, 6.92 (d, $J = 8.3$ Hz, 1H, $CH_{arom.}$), 4.03 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3). Anal. Calcd. for $C_{15}H_{12}N_4O_3$ (296.28): C, 60.81; H, 4.08; N, 18.91. Found: C, 60.75; H, 4.01; N, 18.83.

Full experimental detail, ^{1}H, ^{13}C NMR, and *NOESY* spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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