# Synthesis of Novel Bis(pyrido[2,1-*a*]isoquinolines) Linked to Aliphatic or Aromatic Core *via* Ether Linkage

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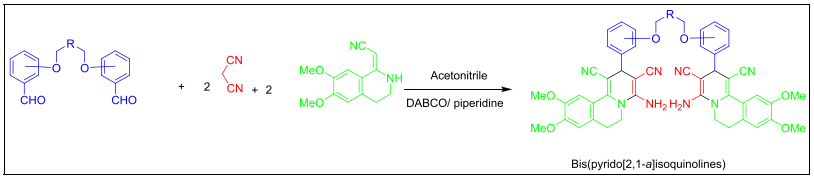
Received November 10, 2018
DOI 10.1002/jhet.3565
Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com).




A synthesis of novel bis(pyrido[2,1-*a*]isoquinoline-1,3-dicarbonitriles) by the multicomponent reaction of 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)acetonitrile with the corresponding bis(aldehydes) and malononitrile in the presence of basic catalysts was reported.

*J. Heterocyclic Chem.*, **00,** 00 (2019).

## INTRODUCTION

Isoquinolines are of considerable interest as they constitute the core structural element of many alkaloids such as columbamine **I** [1], palmatinem **II** [1], papaverine **III** [2], and berberine **IV** [3]. They have a wide range of bioactivities including anti-inflammatory [4–6], cardiovascular [5], anticancer [7–9], antidepressant [5,10], antimalarial [11], and anti-HIV [12]. In addition, several patents indicated that azaphenanthrene of types **V** and **VI** (Fig. 1) are useful for the treatment and/or prophylaxis of diabetes or non-insulin-dependent diabetes [13–15]. Moreover, the growing interest in the chemistry of bis(heterocycles) has recently been recognized, many of which show beneficial bioactivities [16–23] and find use as pharmaceutical agents [16–19] or organic materials [24,25]. Moreover, multicomponent reactions (MCRs) provide rapid and easy access to plenty of heterocycles [23,26–30]. MCRs have several advantages such as short reaction times, selectivity, minimal manipulation, and high atom economy [31–42]. Due to their efficiency and simplicity, MCRs have been used in drug design [43,44]. Recently, there has been an increased interest in the utility of Michael addition reaction in *C*—*C* bond formation reactions [45–49]. In continuation to our efforts to simplify the synthesis of significant biologically active compounds [8,20,21,26,50–56], we report herein the syntheses of novel bis(azaphenanthrene) analogues *via* one-pot three-component reaction of bis(aldehydes) and malononitrile with 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)acetonitrile.

## RESULTS AND DISCUSSION

In the first step, the bis(aldehydes) **1** were prepared following the literature procedure *via* the reaction of the appropriate hydroxyaldehydes with the respective dibromoalkane in refluxing ethanol containing sodium ethoxide [23,28,49,57]. The reaction of bis(aldehydes) with malononitrile **2** and 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)acetonitrile **3** [58] in the presence of a basic catalyst to give **4** was then studied. Our preliminary study was focused on evaluation of different solvents and catalysts for the reaction of 4,4′-(ethane-1,2-diylbis(oxy))dibenzaldehyde **1a** or 2,2′-(propane-1,3-diylbis(oxy))dibenzaldehyde **1b** with two equivalents of both **2** and **3** (Scheme 1). The reactions were performed in different solvents (water, ethanol, acetonitrile, and dioxane) (Table 1). To find the best reaction conditions, the reactions were also carried out in the presence of various catalysts including triethylamine, piperidine, DABCO, as well as piperidine/DABCO mixture under conventional heating. The best yields were obtained when the reactions were carried out in acetonitrile as a solvent using piperidine/DABCO mixture as a catalyst (Table 1, entry 4).

The structures of the bis(pyrido[2,1-*a*]isoquinoline-1,3-dicarbonitriles) **4** were confirmed based on IR, MS, and NMR spectra. Thus, the $^1$H NMR spectrum of **4b** revealed a characteristic singlet at 4.73 ppm for the pyridine-H2. It also indicated a singlet signal at 6.13 ppm for the amino group. All other signals appeared at their expected positions.

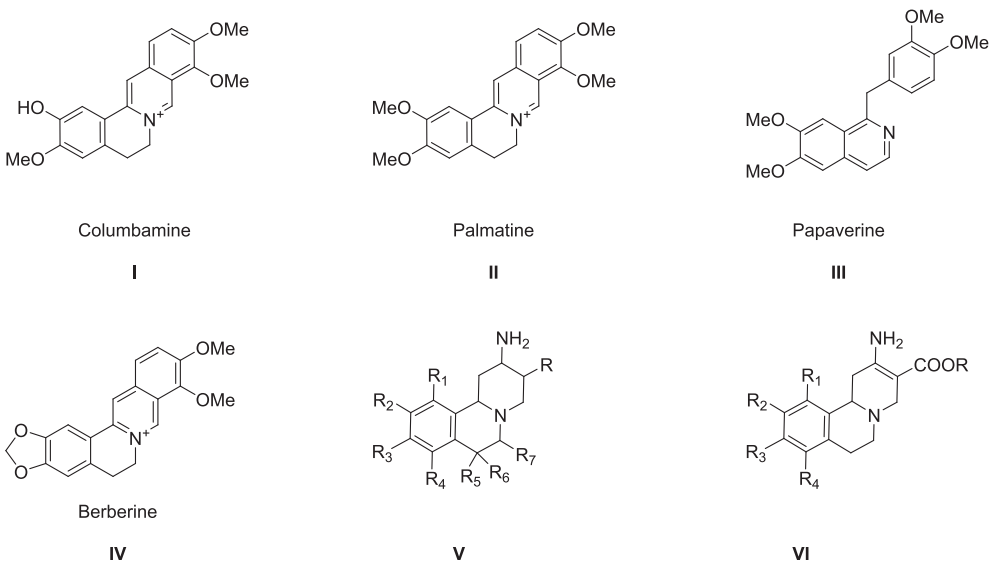



**Figure 1.** Examples of bioactive alkaloids incorporating isoquinoline moiety.

**Scheme 1.** Synthesis of bis(pyrido[2,1-*a*]isoquinoline-1,3-dicarbonitriles) linked to aliphatic core *via* ether linkage **4a**,**b**.

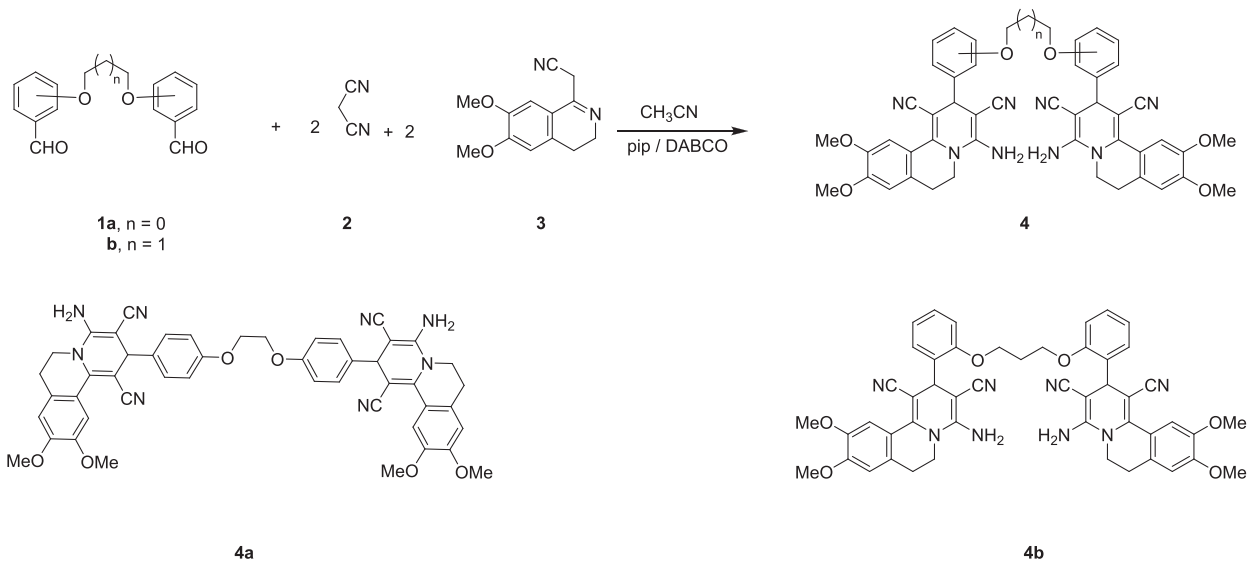
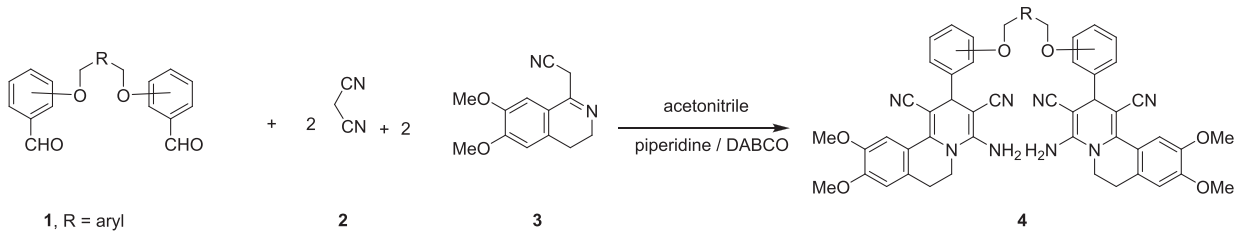



**Table 1**

Optimizing the reaction conditions for the synthesis of bis(pyrido[2,1-*a*]isoquinoline-1,3-dicarbonitriles) **4**.

| | | (% Yield) | | | |
|---|---|---|---|---|---|
| | | $Et_3N$ | Piperidine | DABCO | Piperidine–DABCO |
| Entry | Solvent | **4a/4b** | **4a/4b** | **4a/4b** | **4a/4b** |
| 1 | Water | Nil | Nil | Nil | Nil |
| 2 | Ethanol | Trace | Trace | 25/22 | 32/30 |
| 3 | 1,4-Dioxane | 33/31 | 40/35 | 38/33 | 45/42 |
| 4 | Acetonitrile | 50/43 | 65/58 | 67/60 | 72/68 |

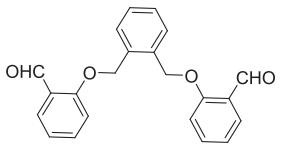
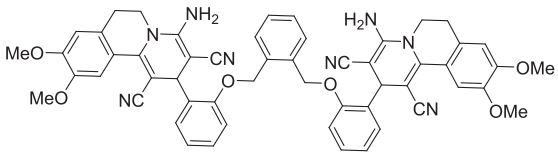
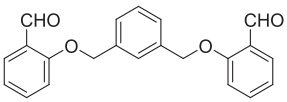
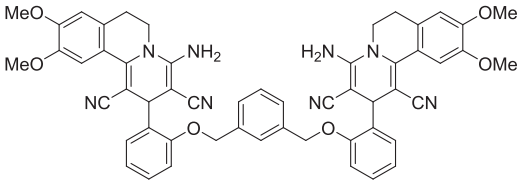
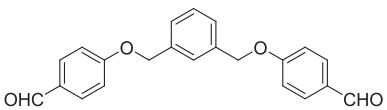
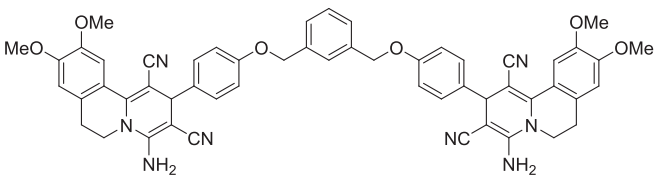
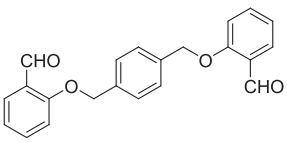
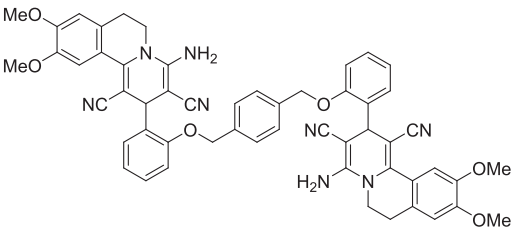
**Scheme 2.** Synthesis of bis(pyrido[2,1-*a*]isoquinoline-1,3-dicarbonitriles) linked to aromatic core *via* ether linkage **4c–g**.




**1**, R = aryl **2** **3** **4**

**Table 2**

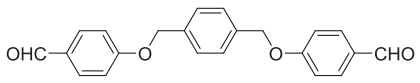
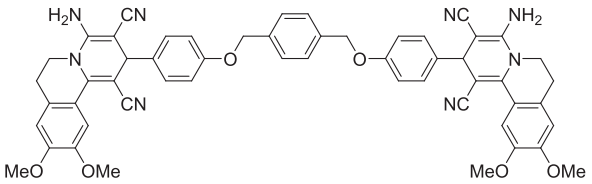
Bis(pyrido[2,1-*a*]isoquinoline-1,3-dicarbonitriles) **4c–g**.

| Aldehydes **1** | Products **4** |
|---|---|
|  **1c** |  **4c** |
|  **1d** |  **4d** |
|  **1e** |  **4e** |
|  **1f** |  **4f** |

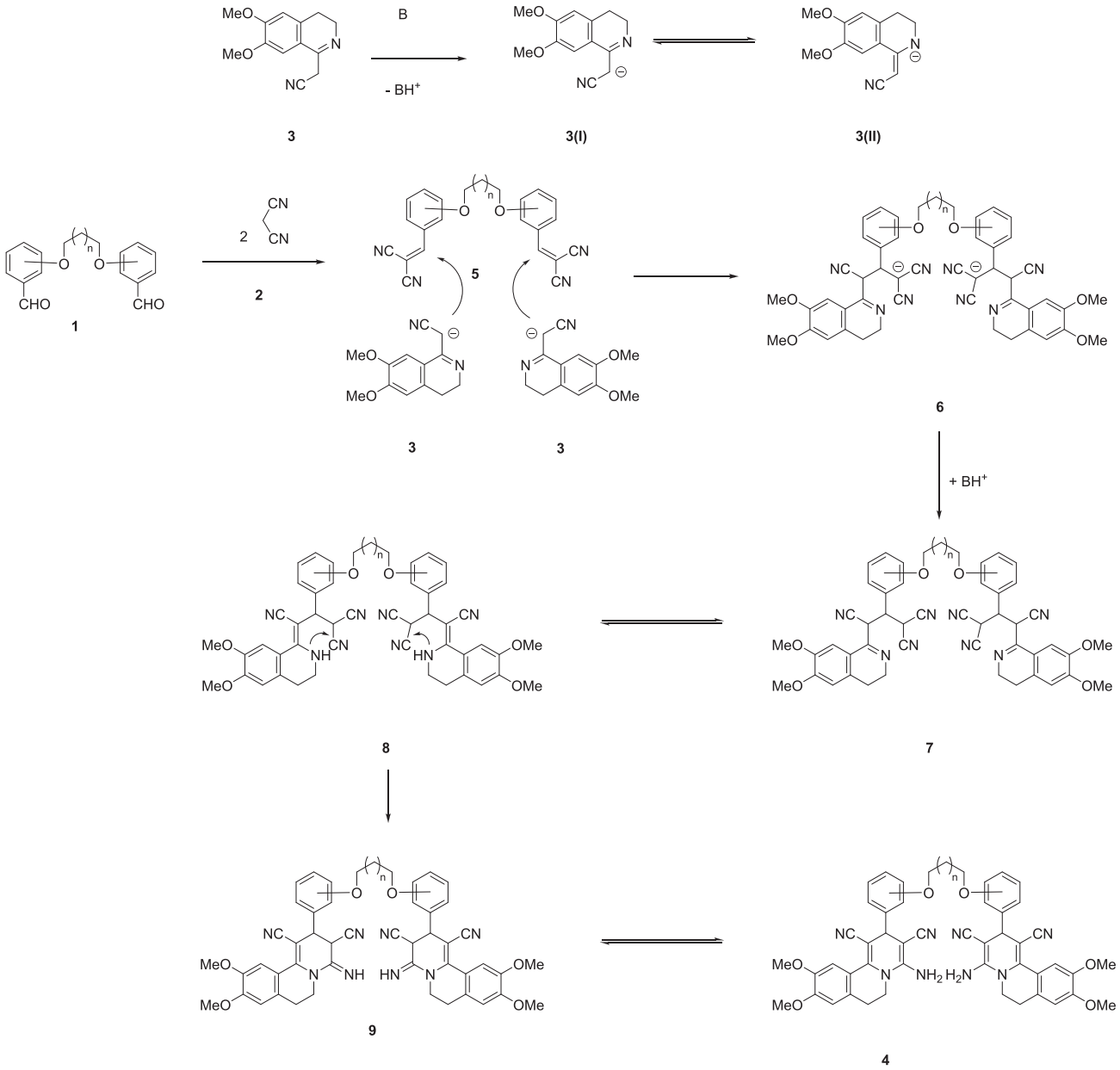
(*Continues*)

**Table 2**

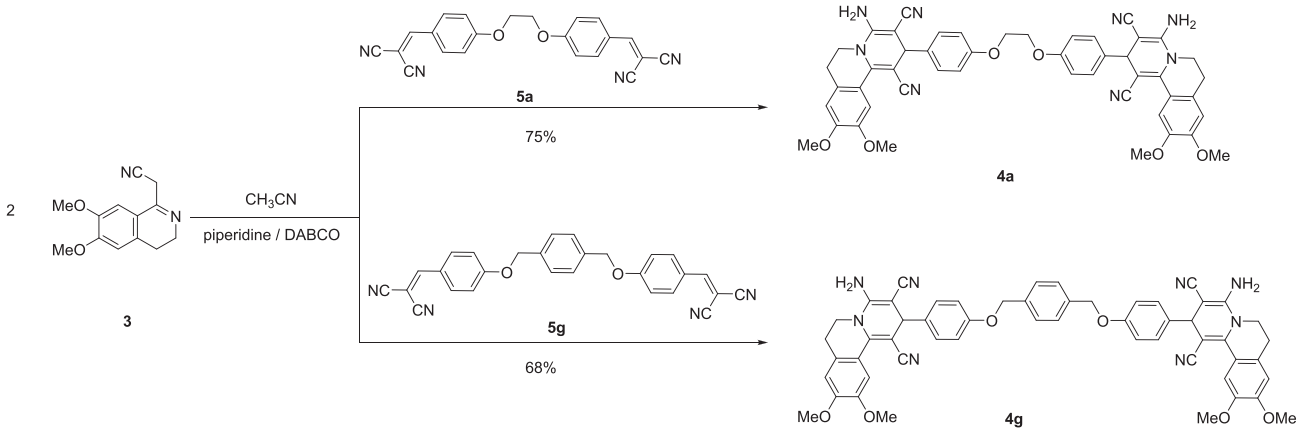
(*Continued*)

| Aldehydes **1** | Products **4** |
|---|---|
|  **1g** |  **4g** |

**Scheme 3.** Proposed pathway for the synthesis of the bis(pyrido[2,1-*a*]isoquinoline-1,3-dicarbonitriles) **4**.



**Scheme 4.** Stepwise synthesis of compounds **4a** and **4g**.




Encouraged by the earlier results, the bis(pyrido[2,1-*a*] isoquinoline-1,3-dicarbonitriles) that are linked to benzene core *via* phenoxymethyl linkage **4c**–**4g** were also prepared *via* the direct reaction of one mole of the appropriate bis(aldehydes) **1c**–**1g**, respectively, with two moles of both **2** and **3** (Scheme 2 and Table 2).

The reaction involves the initial formation of bis(arylidenemalononitriles) **5** *via* Knoevenagel condensation of one equivalent of bis(aldehyde) derivatives **1** with two equivalents of malononitrile **2**. Compound **5** can be considered as a Michael acceptor, while 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl) acetonitrile **3** can be envisioned as the Michael donor. The basic catalyst abstract hydrogen from compound **3** giving **3(I)**. Then, one mole of compound **5** was reacted with two moles of **3(I)** to yield the Michael adduct **6**. The intermediate **6** abstracts the proton again from the conjugate acid ($BH^+$) to afford **7**. Intermediate **7** tautomerizes into **8** that undergoes intramolecular cyclization that involves both amino and cyano groups leading to the formation of **9**. Isomerization of compound **9** gave the final isolable products **4** (Scheme 3).

This pathway was confirmed by successful isolation of the bis(arylidenemalononitriles) **5a** [49] and **5g** [28,49] through the direct reaction of bis(aldehydes) **1a** and **1g** with malononitrile **2**. Subsequent reactions of **5a** or **5g** with 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl) acetonitrile **3** affords the respective compounds **4a** and **4g** in 75% and 68% (Scheme 4).

## CONCLUSION

We have developed an efficient synthesis of novel bis(azaphenanthrene-dicarbonitriles) that are linked to aliphatic or aromatic spacer *via* phenoxymethyl groups. Full characterization of these compounds is reported. We assume that the new synthetic methodology discussed here should provide facile access for novel bis(functionalized)heterocycles.

## EXPERIMENTAL

"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 and $^{13}$C NMR spectra were recorded in DMSO–$d_6$ as solvent on Varian Gemini NMR spectrometer at 300 MHz and 75 MHz, respectively, 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" [59].

**General procedure for synthesis of compounds 4a–g.** ***Method A.*** A mixture of bis(aldehydes) **1a–g** (1 mmol), malononitrile **2** (132 mg, 2 mmol), and 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)acetonitrile **3** (460 mg, 2 mmol) was heated at reflux in dry acetonitrile (10 mL) in the presence of piperidine/DABCO (0.1 mL/0.05 g) for 5 h. The excess solvent was evaporated at reduced pressure. The crude product was crystallized from EtOH/dioxane (10 mL, 1:1, v/v).

***Method B (for 4a and 4g).*** A mixture of bis(alrylidenemalononitriles) **5a** or **5g** (1 mmol) and 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)acetonitrile **3** (460 mg, 2 mmol) was heated at reflux in dry acetonitrile (10 mL) in the presence of piperidine/DABCO (0.1 mL/ 0.05 g) for 5 h. The excess solvent was evaporated at reduced pressure. The crude product was crystallized from EtOH/dioxane (10 mL, 1:1, v/v).

***2,2′-((Ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(4-amino-9,10-dimethoxy-6,7-dihydro-2H-pyrido[2,1-a] isoquinoline-1,3-dicarbonitrile) (4a).*** Yellowish green crystals (method A, 594 mg, 72%; method B, 619 mg,

75%), mp 306–308°C, IR (KBr): *v* 3433, 3335 ($2NH_2$), 2286, 2190 (2CN) $cm^{-1}$, $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.85 (m, 4H, $2NCH_2CH_2$), 3.57 (m, 4H, $2NCH_2CH_2$), 3.75 (s, 6H, $2CH_3O$-9), 3.82 (s, 6H, $2CH_3O$-10), 4.22 (s, 2H, 2C*H*), 4.29 (s, 4H, $2OCH_2$), 6.22 (br s, 4H, $2NH_2$), 6.95–7.59 (m, 12H, Ar*H*) ppm, $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ 28.0 ($NCH_2CH_2$), 41.5 (*C*H), 43.7 ($NCH_2CH_2$), 55.6 ($OCH_3$), 55.7 ($OCH_3$), 58.1 (*C*3), 66.3 ($OCH_2$), 84.3 (*C*1), 110.7 (Ar—*C*H), 112.5 (Ar—*C*H), 114.5 (Ar—*C*H), 117.8 (*C*N), 119.9 (*C*N), 121.0, 121.4 (Ar—C), 127.9 (Ar—*C*H), 133.9, 145.3, 146.6, 150.5, 152.6 (Ar—C), 157.6 (*C*—$NH_2$) ppm, MS (EI, 70 eV): *m/z* 826 $[M]^+$, *Anal*. Calcd for $C_{48}H_{42}N_8O_6$: C, 69.72; H, 5.12; N, 13.55. Found: C, 69.38; H, 5.54; N, 13.18.

***2,2′-((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(4-amino-9,10-dimethoxy-6,7-dihydro-2H-pyrido[2,1-a] isoquinoline-1,3-dicarbonitrile) (4b).*** Yellow crystals (571 mg, 68%), mp 248–250°C, IR (KBr): *v* 3434, 3339 ($2NH_2$), 2287, 2217 (2CN) $cm^{-1}$, $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.35 (m, 2H, $OCH_2CH_2$), 2.91 (m, 4H, $2NCH_2CH_2$), 3.53 (m, 4H, $2NCH_2CH_2$), 3.75 (s, 6H, $2CH_3O$-9), 3.82 (s, 6H, $2CH_3O$-10), 4.25 (m, 4H, $2OCH_2$), 4.73 (s, 2H, 2C*H*), 6.13 (br s, 4H, $2NH_2$), 6.90–7.65 (m, 12H, Ar*H*) ppm, $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ 28.0 ($NCH_2CH_2$), 28.6 ($OCH_2CH_2$), 34.6 (*C*H), 42.2 ($NCH_2CH_2$), 55.5 ($OCH_3$), 55.6 ($OCH_3$), 57.6 (*C*3), 65.2 ($OCH_2$), 83.2 (*C*1), 110.7 (Ar—*C*H), 111.9 (Ar—*C*H), 119.9 (Ar—*C*H), 120.9 (*C*N), 121.4 (*C*N), 127.9, 128.3 (Ar—C), 130.4 (Ar—*C*H), 131.6, 146.1, 146.6, 150.5, 153.2 (Ar—C), 155.3 (*C*—$NH_2$) ppm, MS (EI, 70 eV): *m/z* 840 $[M]^+$, *Anal*. Calcd for $C_{49}H_{44}N_8O_6$: C, 69.99; H, 5.27; N, 13.33. Found: C, 69.73; H, 5.10; N, 13.48.

***2,2′-(((1,2-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(4-amino-9,10-dimethoxy-6,7-dihydro-2H-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile) (4c).*** Yellowish orange crystals (659 mg, 73%), mp 308–310°C, IR (KBr): *v* 3437, 3341 ($2NH_2$), 2289, 2219 (2CN) $cm^{-1}$, $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.87 (m, 4H, $2NCH_2CH_2$), 3.60 (m, 4H, $2NCH_2CH_2$), 3.73 (s, 6H, $2CH_3O$-9), 3.81 (s, 6H, $2CH_3O$-10), 4.75 (s, 2H, 2C*H*), 5.22 (m, 4H, $2OCH_2$), 6.17 (br s, 4H, $2NH_2$), 6.94–7.62 (m, 16H, Ar*H*) ppm, MS (EI, 70 eV): *m/z* 902 $[M]^+$, *Anal*. Calcd for $C_{54}H_{46}N_8O_6$: C, 71.83; H, 5.13; N, 12.41. Found: C, 71.59; H, 4.89; N, 12.18.

***2,2′-(((1,3-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(4-amino-9,10-dimethoxy-6,7-dihydro-2H-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile) (4d).*** Yellowish green crystals (623 mg, 69%), mp 182–184°C, IR (KBr): *v* 3434, 3339 ($2NH_2$), 2287, 2217 (2CN) $cm^{-1}$, $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.84 (m, 4H, $2NCH_2CH_2$), 3.44 (m, 4H, $2NCH_2CH_2$), 3.74 (s, 6H, $2CH_3O$-9), 3.80 (s, 6H, $2CH_3O$-10), 4.76 (s, 2H, 2C*H*), 5.10 (m, 4H, $2OCH_2$), 6.17 (br s, 4H, $2NH_2$), 6.91–7.60 (m, 16H, Ar*H*) ppm, $^{13}C$ NMR (75 MHz, DMSO-d6): δ 28.2 (NCH2CH2), 42.3 (CH), 44.3 (NCH2CH2), 55.6 (OCH3), 55.7 (OCH3), 57.8 (C3), 69.5 (OCH2), 83.6 (C1), 110.8 (Ar—CH), 111.3 (Ar—CH), 112.6 (Ar—CH), 120.1 (CN), 121.1 (CN), 121.6 (Ar—C), 126.7 (Ar—CH), 128.5 (Ar—CH), 128.6 (Ar—CH), 128.7 (Ar—CH), 129.7 (Ar—C), 130.5 (Ar—CH), 132.1 (Ar—CH), 137.5, 146.0, 146.7, 150.6, 153.2 (Ar—C), 155.3 (C—NH2) ppm, MS (EI, 70 eV): *m/z* 902 $[M]^+$, *Anal*. Calcd for $C_{54}H_{46}N_8O_6$: C, 71.83; H, 5.13; N, 12.41. Found: C, 71.48; H, 5.45; N, 12.09.

***2,2′-(((1,3-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(4-amino-9,10-dimethoxy-6,7-dihydro-2H-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile) (4e).*** Yellowish green crystals (686 mg, 76%), mp 180–182°C, IR (KBr): *v* 3433, 3339 ($2NH_2$), 2285, 2216 (2CN) $cm^{-1}$, $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.86 (m, 4H, $2NCH_2CH_2$), 3.46 (m, 4H, $2NCH_2CH_2$), 3.75 (s, 6H, $2CH_3O$-9), 3.82 (s, 6H, $2CH_3O$-10), 4.21 (s, 2H, 2C*H*), 5.12 (m, 4H, $2OCH_2$), 6.22 (br s, 4H, $2NH_2$), 6.98–7.89 (m, 16H, Ar*H*) ppm, $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ 28.0 ($NCH_2CH_2$), 40.6 (*C*H), 42.3 ($NCH_2CH_2$), 55.8 ($OCH_3$), 56.1 ($OCH_3$), 58.4 (*C*3), 69.3 ($OCH_2$), 84.3 (*C*1), 110.8 (Ar—*C*H), 112.7 (Ar—*C*H), 114.8 (Ar—*C*H), 117.8, 120.0 (*C*N), 121.4 (*C*N), 127.1 (Ar—*C*), 127.9 (Ar—*C*H), 128.6 (Ar—*C*), 130.1 (Ar—*C*H), 130.3 (Ar—*C*H), 130.6 (Ar—*C*H), 134.0, 137.4, 145.4, 146.8, 150.7, 152.7 (Ar—*C*), 157.7 (*C*—$NH_2$) ppm, MS (EI, 70 eV): *m/z* 902 $[M]^+$, *Anal*. Calcd for $C_{54}H_{46}N_8O_6$: C, 71.83; H, 5.13; N, 12.41. Found: C, 71.57; H, 5.02; N, 12.67.

***2,2′-(((1,4-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(4-amino-9,10-dimethoxy-6,7-dihydro-2H-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile) (4f).*** Yellow crystals (650 mg, 72%), mp 192–194°C, IR (KBr): *v* 3434, 3336 ($2NH_2$), 2285, 2219 (2CN) $cm^{-1}$, $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.84 (m, 4H, $2NCH_2CH_2$), 3.45 (m, 4H, $2NCH_2CH_2$), 3.74 (s, 6H, $2CH_3O$-9), 3.81 (s, 6H, $2CH_3O$-10), 4.76 (s, 2H, 2C*H*), 5.17 (m, 4H, $2OCH_2$), 6.18 (br s, 4H, $2NH_2$), 6.95–7.60 (m, 16H, Ar*H*) ppm, $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ 28.1 ($NCH_2CH_2$), 41.6 (*C*H), 42.3 ($NCH_2CH_2$), 55.7 ($OCH_3$), 55.9 ($OCH_3$), 57.7 (*C*3), 69.6 ($OCH_2$), 83.6 (*C*1), 110.9 (Ar—*C*H), 111.3 (Ar—*C*H), 112.7 (Ar—*C*H), 120.0 (*C*N), 120.5 (*C*N), 121.2 (Ar—*C*H), 121.5 (Ar—*C*), 127.1 (Ar—*C*), 127.5 (Ar—*C*H), 128.5, 130.5 (Ar—*C*), 132.2 (Ar—*C*H), 136.7, 146.0, 146.7, 150.6, 153.2 (Ar—*C*), 155.4 (*C*—$NH_2$) ppm, MS (EI, 70 eV): *m/z* 902 $[M]^+$, *Anal*. Calcd for $C_{54}H_{46}N_8O_6$: C, 71.83; H, 5.13; N, 12.41. Found: C, 71.62; H, 4.96; N, 12.05.

***2,2′-(((1,4-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(4-amino-9,10-dimethoxy-6,7-dihydro-2H-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile) (4g).*** Yellow crystals (Method A, 596 mg, 66%; Method B, 613 mg, 68%), mp 208–210°C, IR (KBr): *v* 3432, 3340 ($2NH_2$),

2288, 2214 (2CN) $cm^{-1}$, $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.99 (m, 4H, $2NCH_2CH_2$), 3.43 (m, 4H, $2NCH_2CH_2$), 3.76 (s, 6H, $2CH_3O$-9), 3.82 (s, 6H, $2CH_3O$-10), 4.21 (s, 2H, 2C*H*), 5.01 (m, 4H, $2OCH_2$), 6.22 (br s, 4H, $2NH_2$), 6.97–7.89 (m, 16H, Ar*H*) ppm, $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ 28.1 ($NCH_2CH_2$), 42.3 (*C*H), 44.2 ($NCH_2CH_2$), 55.7 ($OCH_3$), 55.9 ($OCH_3$), 58.4 (*C*3), 69.1 ($OCH_2$), 84.2 (*C*1), 110.8 (Ar—*C*H), 114.8 (Ar—*C*H), 115.1 (Ar—*C*H), 120.0 (*C*N), 120.5 (*C*N), 127.9 (Ar—*C*H), 128.5, 130.2 (Ar—*C*), 130.5 (Ar—*C*H), 134.0 (Ar—*C*), 136.7, 145.4, 146.8, 150.7, 152.7 (Ar—*C*), 157.7 (*C*—$NH_2$) ppm, MS (EI, 70 eV): *m/z* 902 $[M]^+$, *Anal*. Calcd for $C_{54}H_{46}N_8O_6$: C, 71.83; H, 5.13; N, 12.41. Found: C, 71.59; H, 4.85; N, 12.67.

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