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## MICROWAVE ASSISTED MULTI-COMPONENT SYNTHESIS OF NOVEL BIS(1,4-DIHYDROPYRIDINES) BASED ARENES OR HETEROARENES

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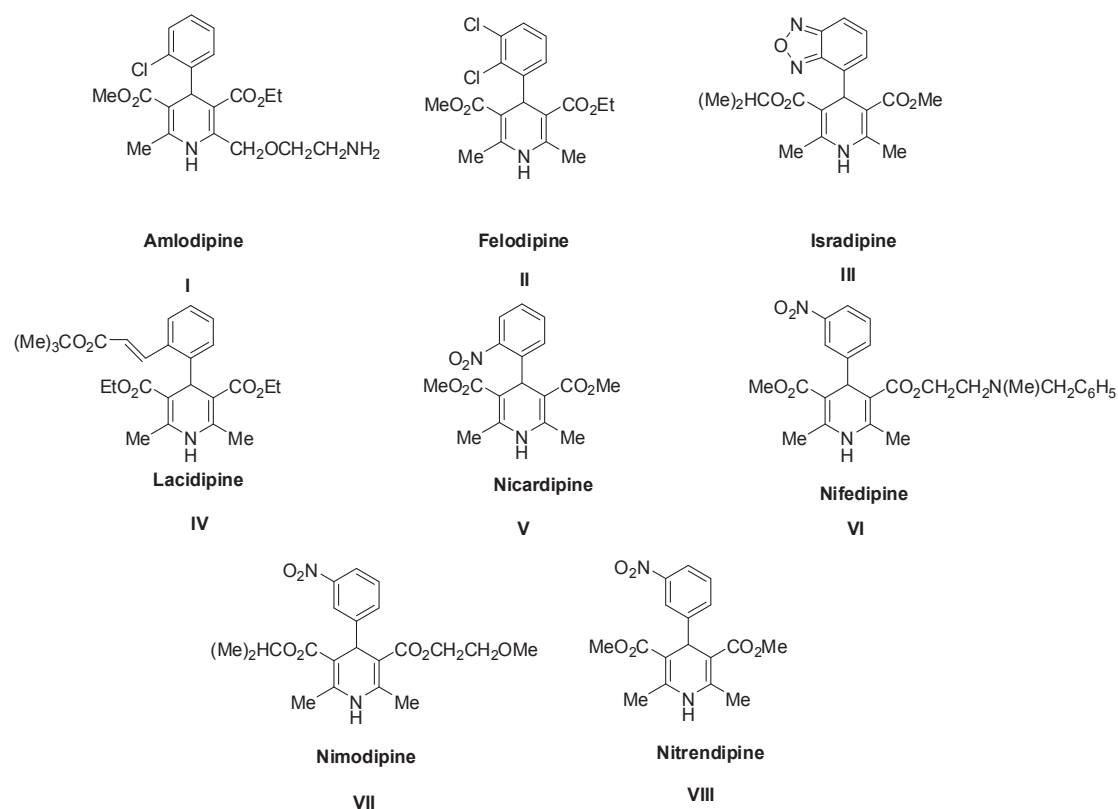
**Abstract** – A synthesis of novel bis-1,4-DHPs was reported. Two possible synthetic approaches for these compounds were investigated. In the first approach the monopodal 1,4-DHPs were used as building blocks for the construction of the target molecules *via* a simple alkylation. In the second strategy the appropriate bis-aldehydes have been synthesized in a first step followed by reaction with four equivalents of 3-aminobut-2-enenitrile using different catalysts under microwave irradiation as well as under conventional heating to give the corresponding bis-1,4-DHPs in good to excellent yield. The oxidative aromatization of some derivatives of the latter compounds into the corresponding bis-2,6-dimethylpyridine-3,5-dicarbonitrile derivatives was achieved using ceric ammonium nitrate (CAN).

### INTRODUCTION

1,4-Dihydropyridines (1,4-DHPs) are a well-known class of biologically active heterocycles. Some of them (Amlodipine I, Felodipine II, Isradipine III, Lacidipine IV, Nicardipine V, Nifedipine VI, Nimodipine VII, Nitrendipine VIII) (Figure 1) have been commercialized and it has been proven that their therapeutic success is related to their efficacy to bind to calcium channels and consequently to decrease the passage of the trans membrane calcium current, associated in smooth muscle with a long lasting relaxation and in cardiac muscle with a reduction of contractility throughout the heart.<sup>1-5</sup> Other studies revealed that 1,4-DHPs exhibit several other medicinal applications, which include neuroprotectant<sup>6</sup> and platelet antiaggregatory activity,<sup>7</sup> in addition to acting as a cerebral anti-ischemic agent in the treatment of Alzheimer's disease<sup>8</sup> and as a chemosensitizer in tumor therapy.<sup>9</sup> They have also been used as antitumor<sup>10</sup> and as drugs in the treatment of a number of other diseases.<sup>7,11,12</sup>

In addition, much attention has been increasingly paid to the synthesis of bis-heterocyclic compounds. Of particular interest would be the bis-heterocycles that encompass heterocyclic rings, which gained importance due to their diverse applications and pharmacological activities.<sup>13,14</sup> Bis-heterocyclic compounds have also numerous applications as electrical materials,<sup>14-16</sup> chelating agents, and metal ligands.<sup>15-21</sup>

Moreover, the application of microwave irradiation as an important green tool to activate and accelerate organic reactions has taken a new dimension and has experienced exponential growth in the last ten years. This technique offers simple, clean, fast, efficient, and economic approach for the synthesis of a large number of organic molecules.<sup>22-29</sup>

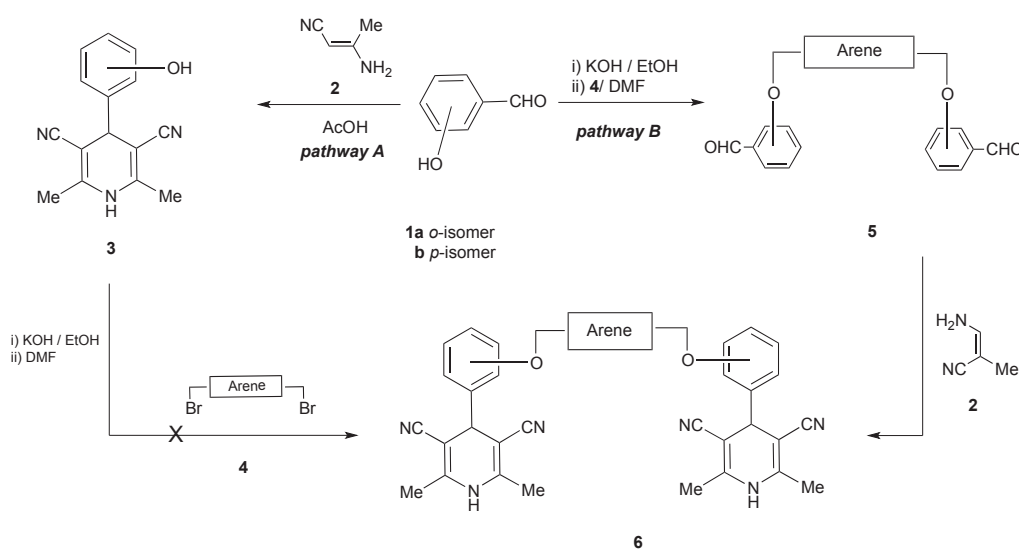


**Figure 1.** Representative examples of important substituted 1,4-dihydropyridines

In connection with these findings and in conjunction to our interest in enamine chemistry<sup>30-39</sup> as well as in the synthesis of bis-heterocycles,<sup>40-51</sup> we report herein on microwave assisted synthesis of a novel series of bis(dihydropyridine-3,5-dicarbonitriles) which are linked to arene or heteroarene cores *via* phoxymethyl spacer. It is expected that the improved synthesis of novel 1,4-DHPs-3,5-dicarbonitrile seems like a reasonable target in medicinal and synthetic organic chemistry.

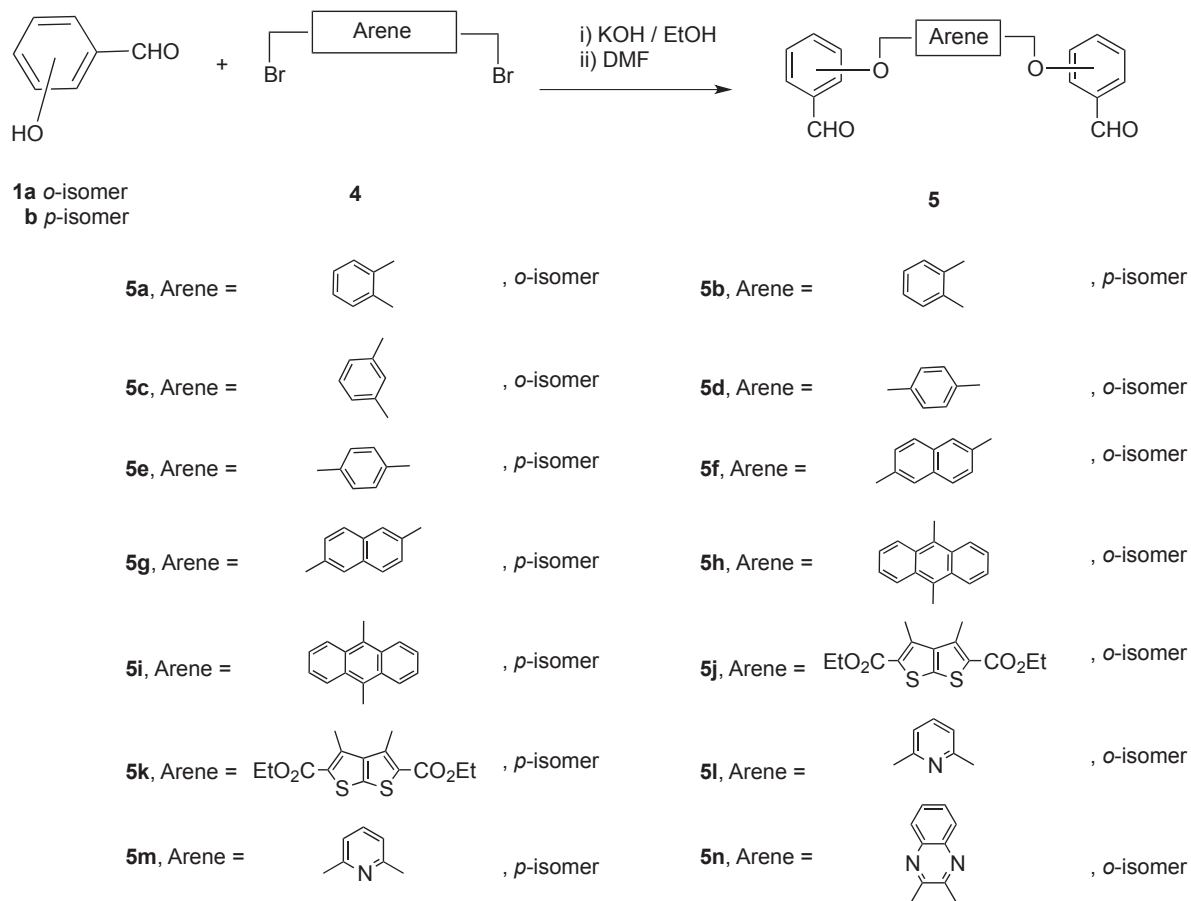
## RESULTS AND DISCUSSION

Two possible synthetic approaches, for the synthesis of the target bipodal 1,4-DHPs **6**, were investigated. In the first approach (Scheme 1, pathway A), the monopodal 1,4-DHPs **3** can serve as building block for the construction of the target molecules *via* a simple alkylation reaction using a mild base. The synthesis of **3** involves one-pot multicomponent coupling reactions (MCRs), of salicylaldehyde **1a** or *p*-hydroxybenzaldehyde **1b** with 3-aminobut-2-enitrile **2** in refluxing acetic acid as described by Kuthan *et al.*<sup>52</sup> Unfortunately, we could not isolate pure samples of the corresponding bis(2,6-dimethyl-4-phenyl-1,4-dihydropyridinyl)benzenes **6** upon treatment of two equivalents of the potassium salt of **3** with the appropriate bis(bromomethyl)arenes **4** in refluxing DMF. The reactions instead gave a mixture of products that were not easily handled and have not been characterized as yet. The first approach, which was ultimately unsuccessful, led us to turn to a new strategy in which the appropriate bis-aldehydes **5** have been synthesized in a first step using the appropriate bis(bromomethyl)arenes **4** and the corresponding hydroxybenzaldehydes **1a,b**. Subsequent reaction of the bis-(aldehydes) **5** with four equivalents of 3-aminobut-2-enitrile **2** should lead to the formation of **6** (Scheme 1, pathway B).



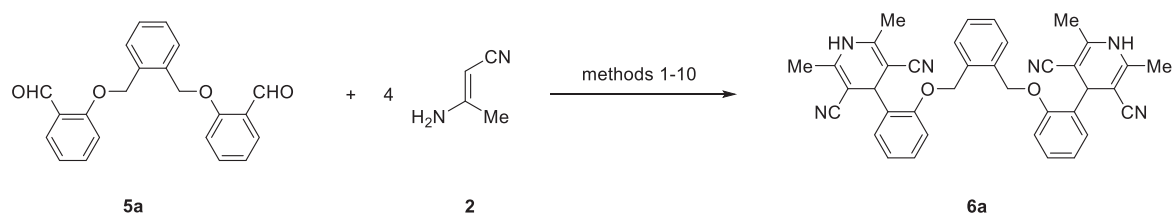
**Scheme 1.** Two possible synthetic approaches for the synthesis of the target bipodal 1,4-DHPs

The required bis-aldehydes **5a-n** were synthesized following reported methods, described by our group or by modification of literature procedure described by other groups.<sup>40,41,47,53–56</sup> Thus, the reaction of the potassium salt of hydroxy aldehydes **1** (obtained upon treatment of 2- and 4-hydroxybenzaldehyde with KOH in EtOH) with the appropriate dibromo compounds **4** in boiling DMF afforded **5** in moderate yields (Scheme 2).<sup>40,41,47,53–56</sup>



**Scheme 2.** Synthesis of the starting bis-aldehydes

We decided to investigate reaction of the bis(aldehydes) **5** with four equivalents of 3-aminobut-2-enenitrile **2** under microwave irradiation as an efficient energetic heating source aiming to maximize reaction conversion and minimize reaction time. Our preliminary investigations were focused on evaluation of different catalysts for the model reaction of 2,2'-(1,2-phenylenebis(methylene))bis(oxy)dibenzaldehyde **5a** with four equivalents of **2** (Scheme 3).



**Scheme 3.** Synthesis of the bis(2,6-dimethyl-4-phenyl-1,4-dihydropyridinyl)benzenes

At first we demonstrated the use of ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate (BMIMBF<sub>4</sub>) as dual solvent-catalyst for the synthesis of **6a** under microwave irradiation. The model reaction was screened under solvent-free conditions as well as in different solvents including water, DMF

and 1,4-dioxane. Unfortunately, in all trials no traces of **6a** were detected (Table 1). We also explored the catalytic activity of *p*-toluenesulfonic acid (*p*-TSA) as low cost, eco-friendly and high reactive catalyst. The reactions were carried out in the presence of polar solvents such as water and DMF or non-polar solvents like toluene and dichloromethane. The reaction has also been carried out under solvent-free conditions. In some trials, especially when the reaction was carried out in polar solvents the <sup>1</sup>H NMR of the reaction products indicated the presence of the target product **6a** in a very few amounts but unfortunately we were not able to isolate it as a pure sample (Table 1). On the other hand, when the reaction was carried out using AcOH, the corresponding bis(1,4-dihydropyridinyl)benzene **6a** can be obtained in 76% yield as a sole reaction product. The best yield was achieved using a catalytic amount of AcOH at 120 °C under microwave irradiation of power 250 W for 10 minutes. Subsequently, with optimal condition in hand, the generality and synthetic scope of this reaction was demonstrated by synthesizing a series of 4,4'-(((phenylenebis(methylene))bis(oxy))bis(phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile) derivatives **6b-e**, in which the 1,4-dihydropyridine-3,5-dicarbonitriles are linked to benzene core *via* phenoxymethyl linkage (Figure 2). For the sake of comparison, the reaction was also carried out under conventional heating in refluxing acetic acid as dual solvent-catalyst for 2 h.

**Table 1.** Optimizing the yield of compound **6a**

Method	Solvent	Catalyst	(% yield) <sup>[a,b]</sup>	
			Thermally	Microwave
1	water	BMIMBF <sub>4</sub>	nil	nil
2	DMF	BMIMBF <sub>4</sub>	nil	nil
3	1,4-dioxane	BMIMBF <sub>4</sub>	nil	nil
4	-	BMIMBF <sub>4</sub>	nil	nil
5	water	<i>p</i> -TSA	trace	trace
6	DMF	<i>p</i> -TSA	trace	trace
7	dichloromethane	<i>p</i> -TSA	nil	nil
8	toluene	<i>p</i> -TSA	nil	nil
9	-	<i>p</i> -TSA	nil	nil
10 <sup>[c]</sup>	AcOH	AcOH	54%	76%

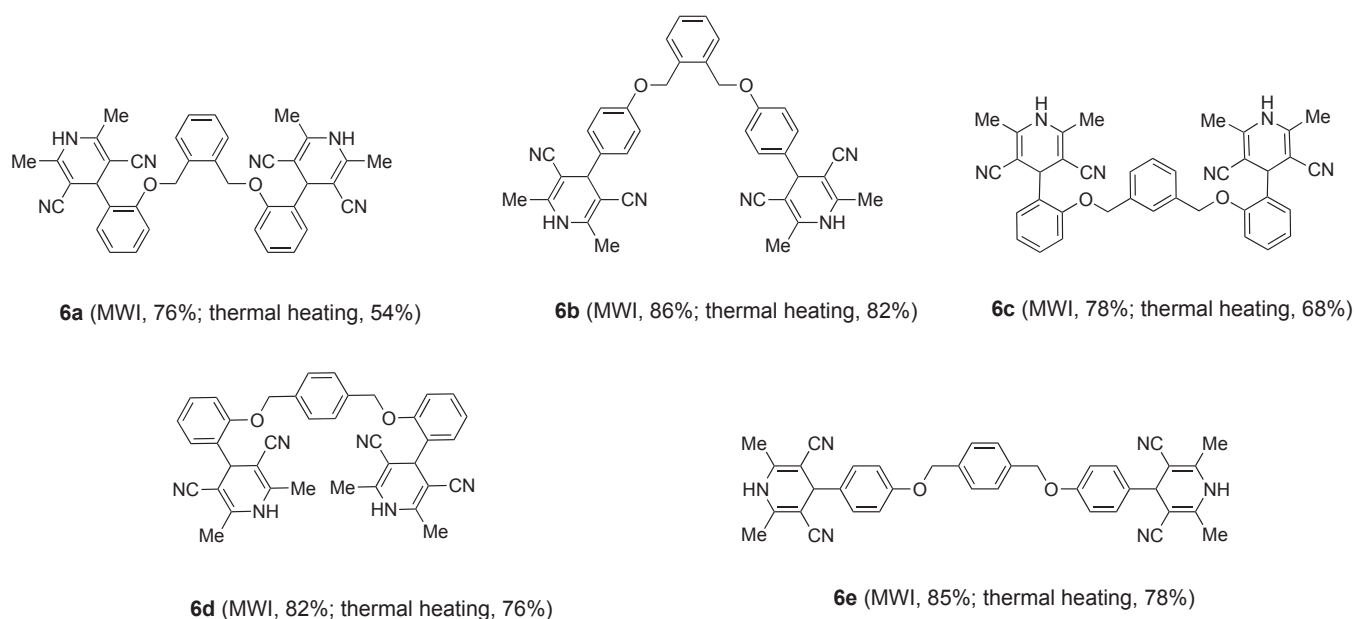
[a] The reaction time is 2 h for thermal heating and 10 min for MW (monitored by TLC).

[b] The reaction was performed under reflux condition at 120 °C or under MW (120 °C, 250 W).

[c] Acetic acid was used as a catalyst and solvent.

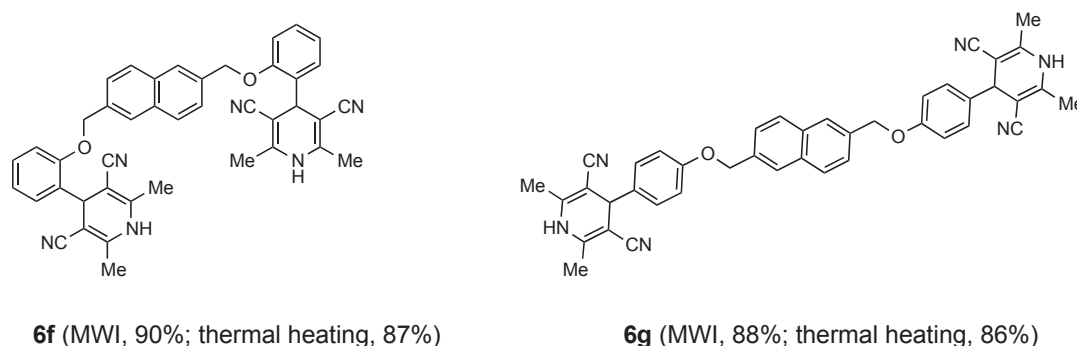
The constitution of the bis-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile derivatives **6a-e** was supported by IR, NMR and MS studies. Thus, the <sup>1</sup>H NMR spectrum of **6e** revealed a characteristic singlet integrated by 12H at 2.03 ppm for the four methyl groups. It also showed a singlet signal at 4.33

ppm for the pyridine-H(4). In addition, it exhibited two singlet signals characteristic for the two  $-OCH_2$  and NH groups at 5.12 and 9.45 ppm, respectively. It also featured aromatic protons at 7.18–7.49 ppm. Furthermore, the  $^{13}C$  NMR spectrum of **6e** was found to be in agreement with the proposed structure, it showed the methyl signal at 17.7 ppm and the pyridine-C(4) at 56 ppm. It also featured a CN signal at 115 ppm. All other carbon signals appeared at their expected positions.



**Figure 2.** Multicomponent synthesis of 1,4-dihydropyridine-3,5-dicarbonitrile **6a-e**

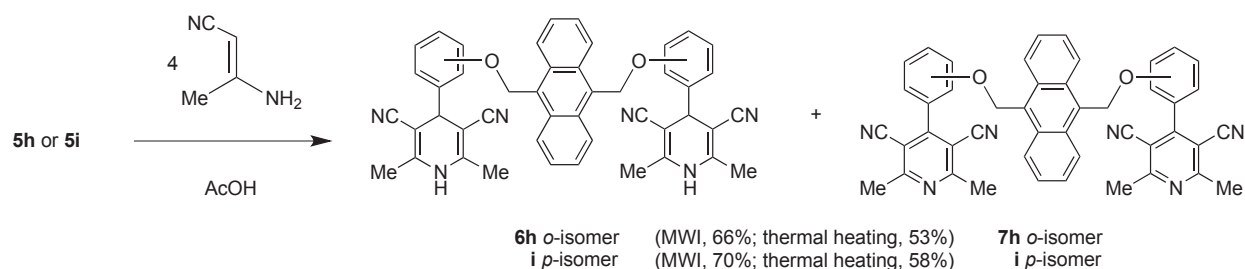
Interestingly, the bis-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile derivatives which are linked to naphthalene core *via* phenoxy-methyl linkage **6f,g** can also be prepared *via* the direct reaction of one mole of the bis-aldehydes **5f,g**, respectively, with four moles of **2** (Figure 3).



**Figure 3.** Bis-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile derivatives linked to naphthalene core

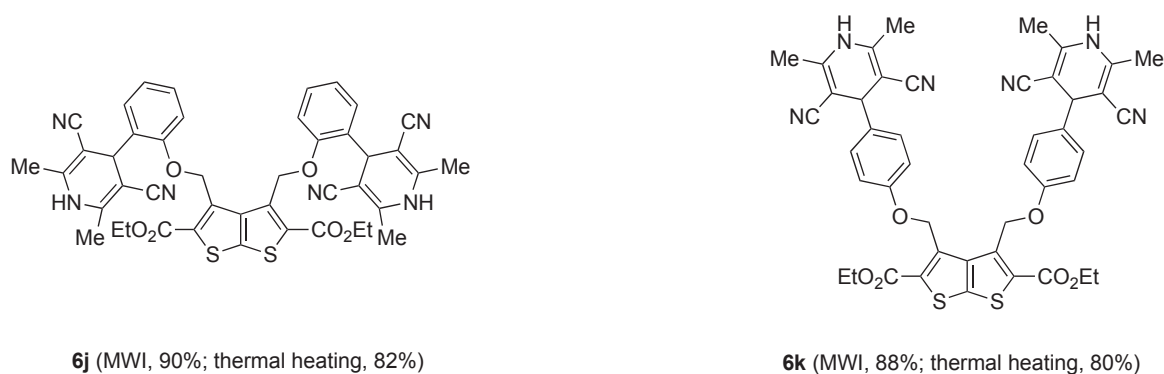
On the other hand, the reaction of the bis-aldehydes **5h,i** linked to the anthracene core *via* phenoxy-methyl linkage with four moles of **2** gives mixtures of the bis-dihydropyridines **6h,i**, and the aromatized products

**7h,i.** Trials to separate these mixtures were unsuccessful (Scheme 4). The spectroscopic characterization of the unseparated mixture **6i** and **7i** exhibited two singlet signals at 4.39 and at 9.47 ppm assigned to the pyridine H(4) and the pyridine-NH, respectively. It also featured two singlet signals at 6.1 and 6.2 ppm assigned to OCH<sub>2</sub> of compounds **6i** and **7i**, respectively. The ratio of **6i** / **7i**, as deduced from the integration of the OCH<sub>2</sub> proton signals is approximately 1: 2 in both compounds, respectively. This indicated that the aromatized pyridines represent the major component of the mixture. Similar results were obtained under conventional heating methods.



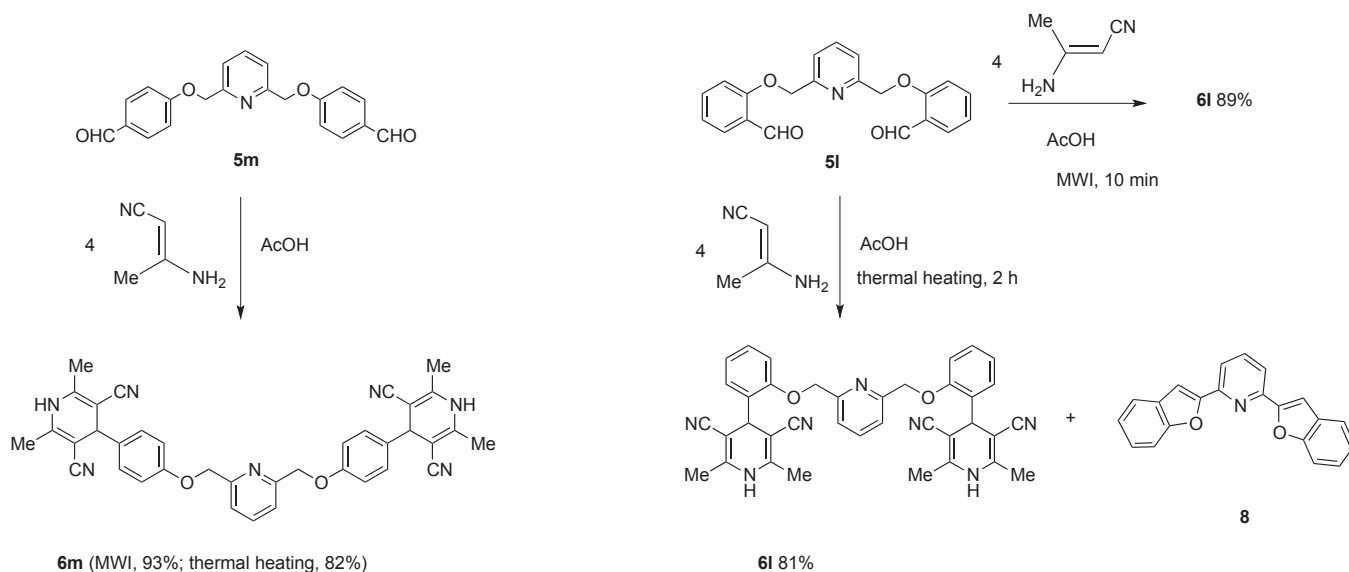
**Scheme 4.** Bis-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile derivatives linked to anthracene core and their aromatized derivatives

Encouraged by the above results, our study was extended to expand the scope of this reaction to prepare some bis-1,4-DHPs **6j** and **6k** linked to thienothiophene core in good yields by the direct reaction of the appropriate bis(aldehydes) **5j** and **5k** with four equivalents of **2** (Figure 4).



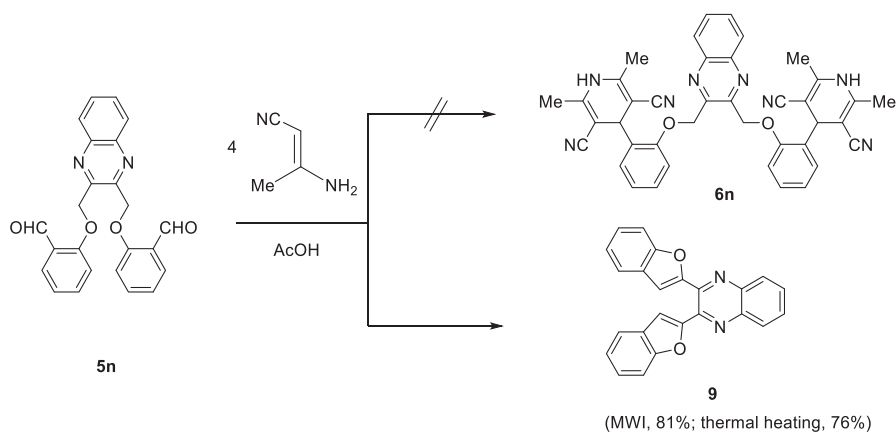
**Figure 4.** Bis-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitriles linked to the thienothiophene core

The same methodology can also be applied for the synthesis of the corresponding bis(dihydropyridines) **6l** and **6m** linked to the pyridine core in good yields upon treatment of the corresponding bis(aldehydes) **5l** and **5m** with four equivalents of **2** (Scheme 5, Table 1). It is noteworthy to mention that carrying out the reaction of **5l** with **2** under conventional heating in refluxing AcOH led to the formation of 2,6-bis[benzo(*b*)furan-2-yl]pyridine **8** as an additional product together with the target **6l**.



**Scheme 5.** Synthesis of bis(dihydropyridines) linked to pyridine core

Motivated by these results, we studied the synthesis of bis(dihydropyridine) **6n** by the reaction of the corresponding bis(2-formylphenoxy)methyl)quinoxaline **5n** with **2** under similar conditions. Unfortunately, the reactions did not lead to the formation of **6n**. Instead, 2,3-bis[benzo[*b*]furan-2-yl]quinoxaline **9** was formed as a sole product. Similar results were obtained under conventional heating in refluxing AcOH (Scheme 6).

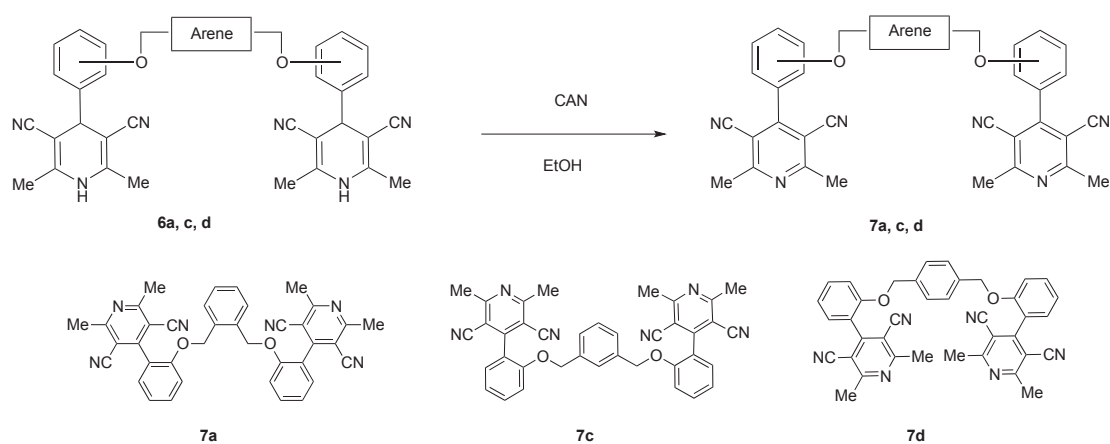


**Scheme 6.** Attempted synthesis of bis(dihydropyridines) linked to quinoxaline core

It is noteworthy to mention that compounds **8** and **9** could be obtained by heating a solution of **5l** or **5n** in refluxing acetic acid in the absence of 3-aminobut-2-enitrile **2**. The formation of **8** and **9** proceeds *via* intramolecular cyclocondensation of the active methylene with the aldehyde group of compound **5**. The enhanced electrophilicity of C-2 and C-6 in the pyridine ring as well as that of C(2) and C(3) in the quinoxaline ring caused by protonation of the nitrogen atoms under the acidic condition activate the



methylene group towards the condensation reaction. It is important to mention that the bis(aldehydes) **5l** and **5n** showed similar behavior when their reactivity towards some bis(aminotriazoles) in refluxing AcOH was investigated.<sup>40,53</sup> These reactions did not lead to the formation of the corresponding macrocyclic Schiff bases and gave instead 2,6-bis[benzo[*b*]furan-2-yl]pyridine and 2,3-bis[benzo[*b*]furan-2-yl]quinoxaline, respectively, as sole products. The bis-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile derivatives **6a**, **6c** and **6d** are easily dehydrogenated into the corresponding pyridines **7a**, **7c** and **7d**, respectively, using catalytic amounts of ceric ammonium nitrate (CAN) (Scheme 7). The structures of compounds **7** were confirmed based on <sup>1</sup>H NMR data that indicated the absence of the signals related to pyridine-H(4) and NH.



**Scheme 7.** Aromatization of some selected bis-1,4-dihydropyridines using CAN

## CONCLUSIONS

We developed an efficient microwave assisted synthesis of previously unreported bis(1,4-dihydropyridine-3,5-dicarbonitriles) which are linked to arene or heteroarene *via* phenoxy methyl groups. Full characterization of these compounds is reported. The newly synthesized compounds are interesting both in their own right as unusual molecules and for their promising pharmacological and biological activities. Due to the mild reaction conditions, good yields, easily accessible starting materials and straightforward product isolation, we think that the new synthetic approach discussed here should provide access for novel new bis(functionalized)heterocycles.

## EXPERIMENTAL

**General:** Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300

NMR spectrometer at 300 MHz ( $^1\text{H}$  NMR) and at 75 MHz ( $^{13}\text{C}$  NMR). Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMQP 1000 EX spectrometer. Analytical thin-layer chromatography was performed using pre-coated silica gel 60778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Microwave experiments were carried out using a CEM Discover Labmate<sup>TM</sup> microwave apparatus (300 W with ChemDriver<sup>TM</sup> Software). All solvents and chemicals were obtained commercially and were used as received.

### **Synthesis of compounds 6a-m: General Procedure**

**Method A:** A mixture of the appropriate bisaldehyde **5** (1 mmol), 3-aminobut-2-enenitrile **2** (4 mmol) and AcOH (1 mL) were mixed in a closed vessel and was irradiated in a focused microwave reactor for 10 min at 120 °C (250 W). The crude solid was isolated and recrystallization from AcOH to afford off-white to pale yellow crystals.

**Method B:** To a solution of the appropriate bisaldehyde **5** (1 mmol) in glacial AcOH (10 mL) 3-aminobut-2-enenitrile **2** (4 mmol) was added. The resulting yellowish solution was heated under reflux for 2 h and then was allowed to cool to rt. Thereupon it was poured over crushed ice and the formed precipitate was filtered off, dried, and purified by recrystallization from AcOH to afford off-white to pale yellow crystals.

*4,4'-(((1,2-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile)* (**6a**): Pale yellow solid, mp 280–282 °C; IR( $\nu$   $\text{cm}^{-1}$ ): 3252 (NH), 2199 (CN);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.94 (s, 12H, 4 CH<sub>3</sub>), 4.80 (s, 2H, 2 pyridine H-4), 5.23 (s, 4H, 2 OCH<sub>2</sub>), 6.99–7.60 (m, 12H, Ar-H), 9.26 (s, 2H, 2 NH). MS (EI, 70 eV):  $m/z$  = 604 [ $\text{M}^+$ ], Anal. Calcd for C<sub>38</sub>H<sub>32</sub>N<sub>6</sub>O<sub>2</sub> (604.70): C, 75.48; H, 5.33; N, 13.90. Found: C, 75.61; H, 5.47; N, 13.97%.

*4,4'-(((1,2-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile)* (**6b**): Yellow solid, mp 302–304 °C; IR( $\nu$   $\text{cm}^{-1}$ ): 3289 (NH), 2200 (CN);  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.03 (s, 12H, 4 CH<sub>3</sub>), 4.32 (s, 2H, pyridine H-4), 5.25 (s, 4H, 2 OCH<sub>2</sub>), 7.04 (d,  $J$  = 8.4 Hz, 4H, ArH's), 7.19 (d,  $J$  = 8.4 Hz, 4H, ArH's), 7.38 (m, 2H, Ar-H), 7.55 (m, 2H, Ar-H) and 9.45 (s, 2H, 2 NH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  17.6, 40.3, 67.1, 82.9, 115.0, 119.2, 128.0, 128.4, 128.7, 135.1, 136.6, 146.3, 157.7. MS (EI, 70 eV):  $m/z$  = 604 [ $\text{M}^+$ ]; Anal. Calcd for C<sub>38</sub>H<sub>32</sub>N<sub>6</sub>O<sub>2</sub> (604.70): C, 75.48; H, 5.33; N, 13.90. Found: C, 75.32; H, 5.40; N, 13.78%.

*4,4'-(((1,3-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile)* (**6c**): Pale yellow solid, mp 286–288 °C; IR( $\nu$   $\text{cm}^{-1}$ ): 3298 (NH), 2199 (CN);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.92 (s, 12H, 4 CH<sub>3</sub>), 4.87 (s, 2H, pyridine H-4), 5.16 (s, 4H, 2 OCH<sub>2</sub>), 6.99–7.65 (m, 12H, Ar-H), 9.30 (s, 2H, 2 NH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  17.6, 34.5, 69.6, 82.1, 112.5,

119.3, 121.2, 126.4, 126.8, 128.4, 128.9, 129.8, 132.0, 137.2, 146.8, 155.2. MS (EI, 70 eV):  $m/z = 604$  [ $M^+$ ], Anal. Calcd for  $C_{38}H_{32}N_6O_2$  (604.70): C, 75.48; H, 5.33; N, 13.90. Found: C, 75.57; H, 5.21; N, 13.79%.

*4,4'-(((1,4-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile) (6d)*: Pale yellow solid, mp 290–292 °C; IR( $\nu$   $cm^{-1}$ ): 3414 (NH), 2199 (CN);  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.98 (s, 12H, 4 CH<sub>3</sub>), 4.83 (s, 2H, 2 pyridine H-4), 5.14 (s, 4H, 2 OCH<sub>2</sub>), 6.99–7.30 (m, 12H, Ar-H), 9.30 (s, 2H, 2 NH).  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  17.6, 34.6, 69.5, 82.0, 112.5, 119.3, 121.2, 127.5, 128.9, 129.8, 131.9, 136.5, 146.9, 155.3. MS (EI, 70 eV):  $m/z = 604$  [ $M^+$ ], Anal. Calcd for  $C_{38}H_{32}N_6O_2$  (604.70): C, 75.48; H, 5.33; N, 13.90. Found: C, 75.39; H, 5.51; N, 13.99%.

*4,4'-(((1,4-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile) (6e)*: Yellow solid, mp 286–288 °C; IR( $\nu$   $cm^{-1}$ ): 3297 (NH), 2201 (CN);  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  2.03 (s, 12H, 4 CH<sub>3</sub>), 4.33 (s, 2H, 2 pyridine H-4), 5.12 (s, 4H, 2 OCH<sub>2</sub>), 7.03 (d,  $J = 8.4$  Hz, 4H, Ar-H), 7.18 (d,  $J = 8.4$  Hz, 4H, Ar-H), 7.49 (s, 4H, Ar-H), and 9.45 (s, 2H, 2 NH);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  17.69 (CH<sub>3</sub>), 55.98 (pyridine-CH-4), 69.02 (OCH<sub>2</sub>), 82.93 (pyridine-C-3), 114.92, 119.26, 127.76, 128.74, 136.53, 136.69 (Ar-C), 146.29 (CN), 157.80 (pyridine-C-2). MS (EI, 70 eV):  $m/z = 604$  [ $M^+$ ]; Anal. Calcd for  $C_{38}H_{32}N_6O_2$  (604.70): C, 75.48; H, 5.33; N, 13.90. Found: C, 75.61; H, 5.28; N, 13.74%.

*4,4'-(((Naphthalene-2,6-diylbis(methylene))bis(oxy))bis(2,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile) (6f)*: Yellow solid, mp 302–304 °C; IR( $\nu$   $cm^{-1}$ ): 3293 (NH), 2202 (CN);  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  1.98 (s, 12H, 4 CH<sub>3</sub>), 4.86 (s, 2H, 2 pyridine H-4), 5.32 (s, 4H, 2 OCH<sub>2</sub>), 6.99–7.27 (m, 8H, Ar-H), 7.63 (d,  $J = 8.4$  Hz, 2H, Ar-H), 7.93 (d,  $J = 8.4$  Hz, 2H, Ar-H), 8.01 (s, 2H, Ar-H) and 9.32 (s, 2H, 2 NH). MS (EI, 70 eV):  $m/z = 654$  [ $M^+$ ]; Anal. Calcd for  $C_{42}H_{34}N_6O_2$  (654.76): C, 77.04; H, 5.23; N, 12.84. Found: C, 77.20; H, 5.40; N, 12.70%.

*4,4'-(((Naphthalene-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile) (6g)*: Yellow solid, mp 164–166 °C; IR( $\nu$   $cm^{-1}$ ): 3305 (NH), 2200 (CN);  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  2.03 (s, 12H, 4 CH<sub>3</sub>), 4.33 (s, 2H, 2 pyridine H-4), 5.28 (s, 4H, 2 OCH<sub>2</sub>), 7.09 (d,  $J = 8.4$  Hz, 4H, Ar-H), 7.21 (d,  $J = 8.4$  Hz, 4H, Ar-H), 7.60 (d,  $J = 8.4$  Hz, 2H, Ar-H), 7.90 (d,  $J = 8.4$  Hz, 2H, Ar-H), 8.01 (s, 2H, Ar-H) and 9.48 (s, 2H, 2 NH).  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  17.9, 40.4, 69.9, 82.4, 115.0, 119.2, 125.4, 126.4, 128.0, 128.8, 131.7, 132.3, 134.3, 136.6, 146.2, 157.8. MS (EI, 70 eV):  $m/z = 654$  [ $M^+$ ]; Anal. Calcd for  $C_{42}H_{34}N_6O_2$  (654.76): C, 77.04; H, 5.23; N, 12.84. Found: C, 76.90; H, 5.05; N, 12.99%.

*Diethyl 3,4-bis((2-(3,5-dicyano-2,6-dimethyl-1,4-dihydropyridin-4-yl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (6j)*: Off-white solid, mp 296–298 °C; IR( $\nu$   $cm^{-1}$ ): 3237 (NH), 2199 (CN), 1713 (CO);  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  1.19 (t,  $J = 7.2$  Hz, 6H, 2  $\underline{CH_3}CH_2O$ ), 1.57 (s, 12H, 4 CH<sub>3</sub>), 4.24 (q,  $J$

= 7.2 Hz, 4H, 2 CH<sub>3</sub>CH<sub>2</sub>O), 4.48 (s, 2H, 2 pyridine H-4), 5.36 (s, 4H, 2 OCH<sub>2</sub>), 6.61–7.16 (m, 8H, Ar-H) and 8.79 (s, 2H, 2 NH). MS (EI, 70 eV): *m/z* = 810 [M<sup>+</sup>]; Anal. Calcd for C<sub>44</sub>H<sub>38</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub> (810.94): C, 65.17; H, 4.72; N, 10.36; S, 7.91. Found: C, 65.02; H, 4.60; N, 10.50; S, 7.99%.

*Diethyl 3,4-bis((4-(3,5-dicyano-2,6-dimethyl-1,4-dihydropyridin-4-yl)phenoxy)methyl)thieno[2,3-*b*]-thiophene-2,5-dicarboxylate (6k)*: Off-white solid, mp 246–248 °C; IR( $\nu$  cm<sup>-1</sup>): 3298 (NH), 2198 (CN); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.27 (t, *J* = 7.2 Hz, 6H, 2 CH<sub>3</sub>CH<sub>2</sub>O), 2.03 (s, 12H, 4 CH<sub>3</sub>), 4.32 (m, 6H, 2 CH<sub>3</sub>CH<sub>2</sub>O and 2 pyridine H-4), 5.60 (s, 4H, 2 OCH<sub>2</sub>), 6.83 (d, *J* = 8.4 Hz, 4H, Ar-H), 7.12 (d, *J* = 8.4 Hz, 4H, Ar-H) and 9.45 (s, 2H, 2 NH). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta$  13.9, 17.7, 40.1, 60.5, 61.9, 82.8, 114.6, 120.5, 134.5, 136.2, 136.4, 136.7, 145.0, 145.8, 146.3, 157.1, 161.2. MS (EI, 70 eV): *m/z* = 810 [M<sup>+</sup>]; Anal. Calcd for C<sub>44</sub>H<sub>38</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub> (810.94): C, 65.17; H, 4.72; N, 10.36; S, 7.91. Found: C, 65.31; H, 4.80; N, 10.22; S, 7.80%.

*4,4'-(((Pyridine-2,6-diylbis(methylene))bis(oxy))bis(2,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile) (6l)*: Off-white solid, mp 294–296 °C; IR( $\nu$  cm<sup>-1</sup>): 3311 (NH), 2196 (CN); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.99 (s, 12H, 4 CH<sub>3</sub>), 4.90 (s, 2H, 2 pyridine H-4), 5.24 (s, 4H, 2 OCH<sub>2</sub>), 7.01–7.27 (m, 8H, Ar-H), 7.52 (d, *J* = 7.5 Hz, 2H, pyridine-CH-3,5), 7.86 (t, *J* = 7.5 Hz, 1H, pyridine-CH-4) and 9.35 (s, 2H, 2 NH). MS (EI, 70 eV): *m/z* = 605 [M<sup>+</sup>]; Anal. Calcd for C<sub>37</sub>H<sub>31</sub>N<sub>7</sub>O<sub>2</sub> (605.69): C, 73.37; H, 5.16; N, 16.19. Found: C, 73.25; H, 5.06; N, 16.32%.

*4,4'-(((Pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile) (6m)*: Off-white solid, mp 235–237 °C; IR( $\nu$  cm<sup>-1</sup>): 3301 (NH), 2199 (CN); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.03 (s, 12H, 4 CH<sub>3</sub>), 4.34 (s, 2H, 2 pyridine H-4), 5.21 (s, 4H, 2 OCH<sub>2</sub>), 7.07 (d, *J* = 8.7 Hz, 4H, Ar-H), 7.21 (d, *J* = 8.7 Hz, 4H, Ar-H), 7.50 (d, *J* = 7.5 Hz, 2H, pyridine-CH-3,5), 7.89 (t, *J* = 7.5 Hz, 1H, pyridine-CH-4) and 9.46 (s, 2H, 2 NH). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta$  17.7, 40.2, 70.2, 82.9, 114.9, 119.3, 120.6, 128.8, 136.8, 137.9, 146.3, 156.4, 157.6. MS (EI, 70 eV): *m/z* = 605 [M<sup>+</sup>]; Anal. Calcd for C<sub>37</sub>H<sub>31</sub>N<sub>7</sub>O<sub>2</sub> (605.69): C, 73.37; H, 5.16; N, 16.19. Found: C, 73.41; H, 5.11; N, 16.09%.

*Synthesis of compounds 7: General Procedure.* To a solution of the appropriate bis-dihydropyridine derivative **6** (1 mmol) in EtOH (10 mL), CAN (5 mmol) was added portion wise over 5 min. The mixture was then refluxed for 2 h. The solution was concentrated to ca 5 mL and poured over crushed ice and the formed precipitate was filtered off, dried, and purified by recrystallization from AcOH to afford pale yellow crystals of compound **7**.

*4,4'-(((1,2-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(2,6-dimethylpyridine-3,5-dicarbonitrile) (7a)*: White solid (52%), mp 264–266 °C; IR( $\nu$  cm<sup>-1</sup>): 2230 (CN); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 2.70 (12H, s, 4 CH<sub>3</sub>), 5.19 (4H, s, 2 OCH<sub>2</sub>), 7.18–7.59 (12H, m, Ar-H). MS (EI, 70 eV): *m/z* (%) = 600 [M<sup>+</sup>]; Anal. Calcd for C<sub>38</sub>H<sub>28</sub>N<sub>6</sub>O<sub>2</sub> (600.67): C, 75.98; H, 4.70; N, 13.99. Found: C, 75.87; H, 4.611;

N, 14.13%.

4-(2-((3-((2-(3,5-Dicyano-2-methylpyridin-4-yl)phenoxy)methyl)benzyl)oxy)phenyl)-2,6-dimethylpyridine-3,5-dicarbonitrile (**7c**): Pale yellow solid (52%), mp 264–266 °C; IR( $\nu$   $\text{cm}^{-1}$ ): 3421 (NH), 2230 (CN);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  2.72 (12H, s, 4 CH<sub>3</sub>), 5.13 (4H, s, 2 OCH<sub>2</sub>), 7.61–7.17 (12H, m, Ar-H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  24.0, 70.0, 107.9, 113.6, 115.3, 121.3, 122.5, 126.3, 126.9, 128.6, 130.1, 132.5, 136.6, 153.8, 154.8, 164.1. MS (EI, 70 eV):  $m/z$  = 600 [ $\text{M}^+$ ], Anal. Calcd for C<sub>38</sub>H<sub>28</sub>N<sub>6</sub>O<sub>2</sub> (600.67): C, 75.98; H, 4.70; N, 13.99. Found: C, 75.82; H, 4.56; N, 14.08%.

4-(2-((4-((2-(3,5-Dicyano-2-methylpyridin-4-yl)phenoxy)methyl)benzyl)oxy)phenyl)-2,6-dimethylpyridine-3,5-dicarbonitrile (**7d**): Pale yellow solid (55%), mp >300 °C; IR( $\nu$   $\text{cm}^{-1}$ ): 3421 (NH), 2230 (CN);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  2.74 (12H, s, 4 CH<sub>3</sub>), 5.15 (4H, s, 2 OCH<sub>2</sub>), 7.61–7.17 (12H, m, Ar-H). MS (EI, 70 eV):  $m/z$  = 600 [ $\text{M}^+$ ], Anal. Calcd for C<sub>38</sub>H<sub>28</sub>N<sub>6</sub>O<sub>2</sub> (600.67): C, 75.98; H, 4.70; N, 13.99. Found: C, 76.08; H, 4.82; N, 13.82%.

2,6-Bis[benzo(*b*)furan-2-yl]pyridine (**8**). A solution of **5l** (10 mmol) in acetic acid (20 ml) was heated under reflux for 1 h. The solid obtained upon cooling was collected and crystallized from AcOH as colorless crystals (MWI, 67%; thermal heating, 50%), mp 233–235 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.31–8.15 (m, 13H, ArHs pyridin Hs, furan Hs). MS (EI, 70 eV):  $m/z$  = 311 [ $\text{M}^+$ ]; Anal. Calcd for C<sub>21</sub>H<sub>13</sub>NO<sub>2</sub> (311.34): C, 81.01; H, 4.21; N, 4.50. Found: C, 81.10; H, 4.40; N, 4.20.

2,3-Bis[benzo(*b*)furan-2-yl]quinoxaline (**9**). With the use of the general procedure, compound **5n** gave crude **9**, which crystallized from EtOH as pale yellow crystals (MWI, 81%; thermal heating, 76%), mp 114–1168 °C;  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  7.20–8.27 (m, ArHs, furan Hs) ppm. MS (EI, 70 eV):  $m/z$  = 362 [ $\text{M}^+$ ]; Anal. Calcd For C<sub>24</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> (362.386) Calcd: C, 79.55; H, 3.89; N, 7.73. Found: C, 79.50; H, 3.60; N, 7.80.

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