Enaminones in Heterocyclic Syntheses: Part 4. A New One-Step Synthetic Route to Pyrrolo[3,4-*b*]pyridine and Convenient Syntheses of 1,4-Dihydropyridines and 1,1′-(1,4-Phenylene)bis(1,4-dihydropyridine)

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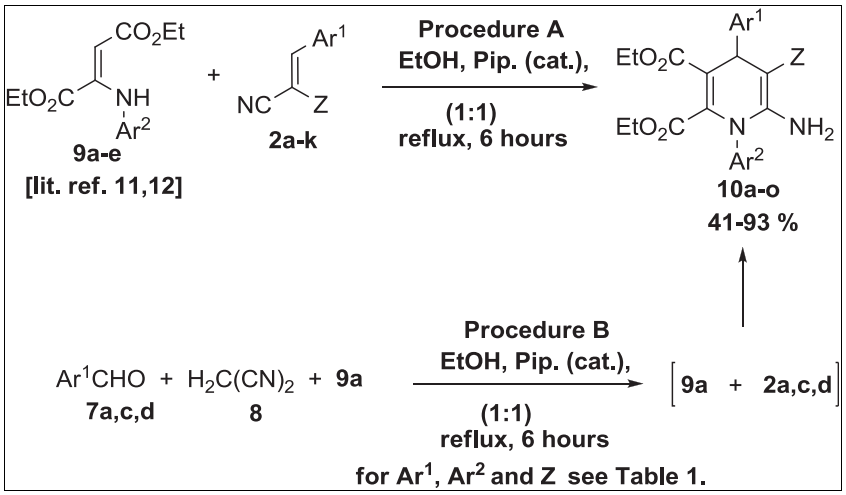

Reactions of cyano olefins with (i) enamino imides afforded novel pyrrolo[3,4-*b*]pyridines; (ii) enamino esters afforded new 1,4-dihydropyridines; and (iii) bisenamino ester afforded new 1,1′-(1,4-phenylene)bis (1,4-dihydropyridine). The new derivatives are planned as suggested drug candidates.

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INTRODUCTION

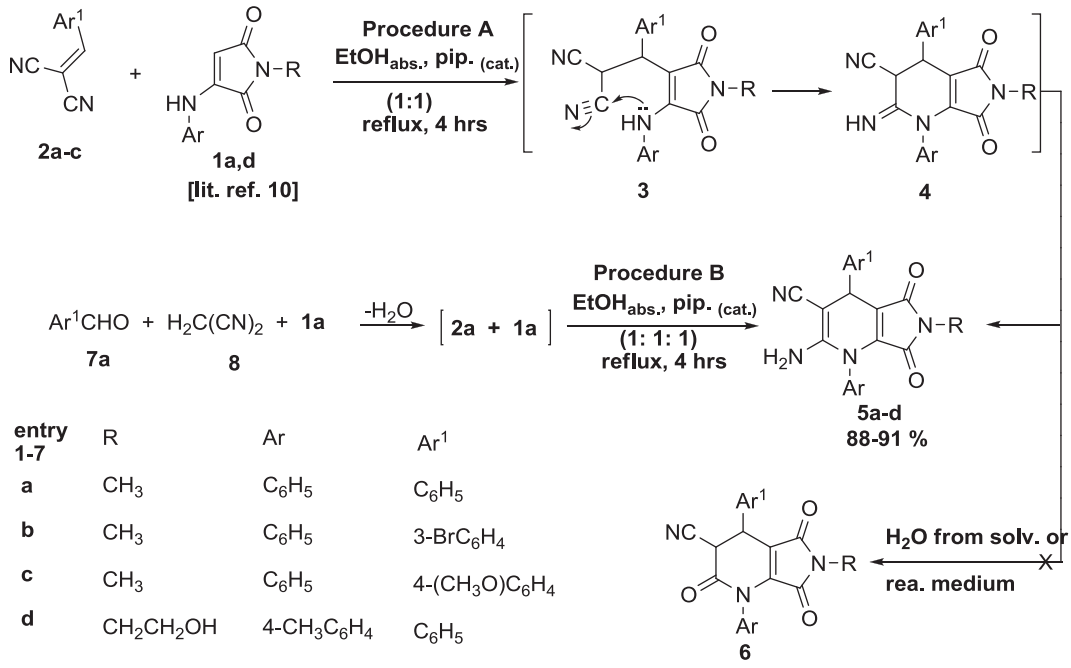
There are few recent reports [1–4] on the synthesis and biological activity of some pyrrolopyridines, and none of them included the use of enamino imides in the synthesis of pyrrolo[3,4-*b*]pyridine. Also, 1,4-dihydropyridine (1,4-DHP) derivatives receive growing interest because of the variety of the high biological activities of some of them, especially their medicinal applications [5,6]. It has been reported [7] that nifedipine [dimethyl 1,2,6-trimethyl-4-(3-methyl-2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate], the first member of the calcium channel blocking medicinal agents, was discovered in 1967 [8] and was launched into the market in 1975 by Bayer [9]. Many structural analogs to nifedipine with better pharmacokinetic profile were developed and used for the treatment of mild and moderate hypertension [7].

In continuation of our work involving enaminones [10,11] and enaminone-related compounds [12] in reactions with activated cyano olefins aiming at the syntheses of polyfunctionally substituted nitrogen heterocycles of potential biological activity, we, herein, report on the first use of the enamino imides 3-arlyamino-1-substituted-pyrrole-2,5-dions **1a**, **d** [13] in reactions with activated cyano olefins **2a–c** as a new, one-step synthetic route to polyfunctionally substituted pyrrolo [3,4-*b*]pyridines **5a–d** (Scheme 1). We also present the first reaction of the enamino esters (anilinofumarates) **9a–e** [14,15] with cyano olefins **2a–k** to synthesize some new 1,4-dihydropyridines **10a–o** (Scheme 2). Our interest is extended to synthesize the new bis(enamino ester) **14** and to involve it in a reaction with the cyano olefins **2a**, **g**, **l** to afford the novel bis(1,4-dihydropyridine) **15a–c** (Scheme 3). In the light of the aforementioned introduction [1–6], the new derivatives **5a–d**, **10a–o**, and **15a–c** are planned as a source of valuable drug candidates.

RESULTS AND DISCUSSION

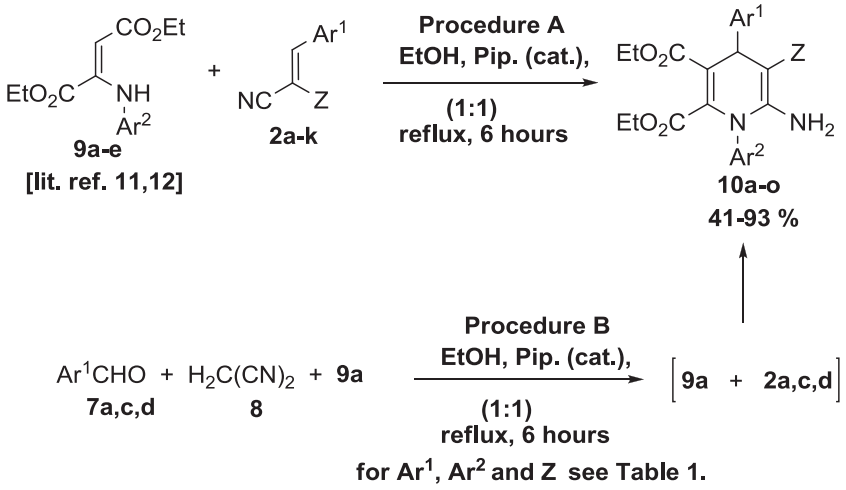
Although the literature is rich with reactions of activated cyano olefins, searching the available literature revealed that the enamino imides **1a**, **d** [13] were not reported before to be involved in a Michael cycloaddition reaction with activated cyano olefins. Thus, **1a** was allowed to react with **2a–c** and **1d** with **2a**, in a molar ratio of 1:1, refluxed

Scheme 1



entry 1-7	R	Ar	Ar^1
a	CH_3	C_6H_5	C_6H_5
b	CH_3	C_6H_5	$3\text{-}BrC_6H_4$
c	CH_3	C_6H_5	$4\text{-}(CH_3O)C_6H_4$
d	CH_2CH_2OH	$4\text{-}CH_3C_6H_4$	C_6H_5

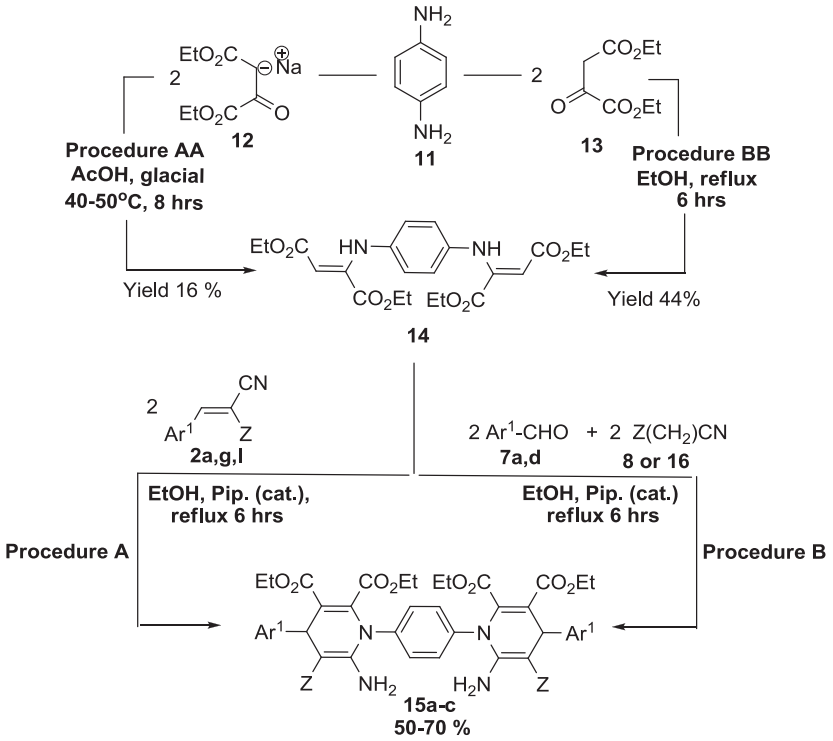
Scheme 2



in absolute ethanol, in the presence of a catalytic amount of piperidine for 4 h (Scheme 1). The reaction product that was deposited on cooling to room temperature was separated off by filtration and was recrystallized from 95% ethanol/water (2:1) mixture or from 95% ethanol to afford **5a–c** and **5d**, respectively. Satisfactory elemental and spectral (IR, ^{1}H NMR, ^{13}C NMR, and MS) analyses (cf. Experimental) have proved these products to be 2-amino-3-cyano-1,4-diaryl-5,7-dioxo-6-substituted-4,5,6,7-tetrahydro-pyrrolo[3,4-*b*]pyridine derivatives **5a–c** and **5d**, respectively (Scheme 1).

The characteristic functional groups of **5a–c** and **5d** showed IR stretching vibration bands in the following regions: (~3471 to ~3448) and (~3367 to ~3309) cm^{-1} (2 bands, NH_2), 2187–2175 cm^{-1} (CN band) and (~ 1770 and ~1708) cm^{-1} (two bands, C═O of cyclic five-membered ring imide with unsaturation, i.e., the pyrrole-2,5-dions moiety). The alcoholic hydroxyl group of **5d** showed a stretching band at 3621 cm^{-1}. The ^{1}H NMR spectrum of, for example, **5a** showed a singlet signal for the protons of each of the N-CH_3, CH-4, and NH_2 groups at δ values of 2.66, 4.61, and 5.65 ppm, respectively. Its ^{13}C NMR spectrum showed

Scheme 3



15a: Z = CN, $Ar^1 = C_6H_5$; **15b**: Z = CN, Ar^1 = 2-BrC_6H_4; **15c**: Z = CO_2Et; $Ar^1 = C_6H_5$

signals at δ 163.30 and 168.35 for two imidic-C, 120.9 ppm for cyano-C, and 60.4 ppm for CH-4. The ^{1}H NMR spectrum of **5d** showed each of the hydroxyl and (two) methylene, moieties of the ethanolamine residue having the same *J* coupling (6 Hz). Each of them showed a triplet signal. These signals were at δ 4.71 and (3.31 and 3.25) ppm, respectively. A mass spectrum of **5d** (mol. wt: 400.43) showed the molecular ion (M^+) as *m*/*z* (400, 10.4%).

Formation of **5** (Scheme 1) can be explained via initial Michael addition of C-4 of **1** to the β-C of the cyano olefin **2** (procedure A), leading to the formation of an acyclic intermediate **3**, which cyclized into the cyclic intermediate **4** via a nucleophilic attack of the amino nitrogen on a cyano carbon. The cyclic intermediate **4** underwent tautomerization into the final product **5a–d** 2-amino-3-cyano-1,4-diaryl-5,7-dioxo-6-substituted-4,5,6,7-tetrahydro-pyrrolo [3,4-*b*]pyridine. Further confirmation of structure **5** was obtained, unambiguously, via a one-pot (1:1:1) reaction of the aldehyde **7a**, malononitrile **8**, and **1a** under the same reaction conditions (procedure B). In this case, **7a** condenses with **8** with the elimination of a water molecule to afford **2a**, which then reacts with **1a** as suggested earlier to produce **5a** whose structure (procedures A and B) was confirmed through melting points, mixture melting points, TLC, and IR analysis.

On the other hand, the possibility of forming the 2-oxo derivative **6** (Scheme 1) was ruled out—as the reaction product—on the same basis of approving **5**.

The present new enamino imide-cyano olefin synthetic route offers the advantage of obtaining the final pyrrolo [3,4-*b*]pyridine product in as simple as the convenient one-step Michael cycloaddition reaction.

In parallel to what is presented for **5a–d**, the reaction of the enamino ester **9a–e** [14,15] with the cyano olefins **2a–k** had afforded the new 6-amino-1,4-diaryl-5-substituted-2,3-diethoxycarbonyl-1,4-dihydropyridine derivatives **10a–o**, which were characterized through elemental and spectral analyses (cf. Scheme 2, Table 1 and Experimental).

Formation of compounds **10a–o** can be explained on the same basis with what was suggested earlier for **5a–d**.

To synthesize the bis(1,4-DHP) **15a–c** (cf. Scheme 3 and Experimental), we have started with the synthesis of the new bis(enamino ester) [tetraethyl 2,2′-(1,4-phenylene) bis(azanediyl) difumarate] **14**. Compound **14** was next allowed to react with either the cyano olefins **2a**, **g**, **l** (procedure A) or with the suitable aldehyde **7a**, **d** and activated cyanomethylene reagent **8**, **16** (procedure B) to afford the novel 1, 1′-(1,4-phenylene)bis(1,4-dihydropyridine) derivatives **15a–c** in 50–70% yield. Compounds **14** and **15a–c** were characterized through elemental and spectral analyses.

Table 1

Compounds **2**, **9**, and **10**.

Procedure No.	Product **10** with Ar^1, Ar^2, and Z No.	Reactant: cyano olefin **2**			Reactant: enamino esters **9**	
		Z	Ar^1	No.	Ar^2	No.
A and B	**10a**	CN	C_6H_5	**2a**	C_6H_5	**9a**
A and B	**10b**	CN	4-$H_3COC_6H_4$	**2c**	C_6H_5	**9a**
A and B	**10c**	CN	4-ClC_6H_4	**2d**	C_6H_5	**9a**
A	**10d**	CN	2-ClC_6H_4	**2e**	C_6H_5	**9a**
A	**10e**	CN	3-$NO_2C_6H_4$	**2f**	C_6H_5	**9a**
A	**10f**	CN	4-$H_3COC_6H_4$	**2c**	4-$H_3COC_6H_4$	**9b**
A	**10g**	CN	C_6H_5	**2a**	4-$H_3CC_6H_4$	**9c**
A	**10h**	CN	C_6H_5	**2a**	4-BrC_6H_4	**9d**
A	**10i**	CN	3-BrC_6H_4	**2b**	4-BrC_6H_4	**9d**
A	**10j**	CN	C_6H_5	**2a**	4-ClC_6H_4	**9e**
A	**10k**	CO_2Et	C_6H_5	**2 g**	C_6H_5	**9a**
A	**10l**	CO_2Et	3-$NO_2C_6H_4$	**2 h**	C_6H_5	**9a**
A	**10m**	CO_2Et	4-$H_3CCONHC_6H_4$	**2i**	4-BrC_6H_4	**9d**
A	**10n**	CO_2Et	2-BrC_6H_4	**2j**	4-BrC_6H_4	**9d**
A	**10o**	$CONH_2$	C_6H_5	**2 k**	C_6H_5	**9a**

Formation of compounds **15a–c** can be explained on the same basis with what was suggested earlier for **5a–d**.

The structural symmetry of **14** and **15a–c** was consistent in their respective spectra (cf. Scheme 3 and Experimental). For example, derivative **15a** showed IR stretching bands in the regions of 3468 and 3318 cm^{-1} for two identical (NH_2) groups, 2189 cm^{-1} for two identical (CN) groups, and (1739) and (1700) cm^{-1} for (C═O) moieties of identical (two) and (two) of its four ethyl ester groups. The ^1H NMR spectrum of **15a** showed each identical pair of ethyl ester groups in the form of a triplet signal and a quartet signal representing the identical pairs of methyl and methylene moieties, respectively. The same trend was continued for the other functional groups and through its ^{13}C NMR spectrum. Although the molecular ion peak could not be detected in the MS spectrum of **15a**, a suggested fragmentation pattern assumes the formation of ions of $H_2NC{\equiv}CCN$ (*m/z* 66, 100%) and C_6H_5 (*m/z* 77, 63.9%).

The technique followed up throughout this work has the advantages of (i) easy construction of the type and position of the desired functional group through starting with readily available and inexpensive raw materials and (ii) application of a time-saving routine work that can be easily handled by a beginner chemist.

EXPERIMENTAL

The purchased diethyl oxalacetate sodium salt [Fluka, assay ≥95.0% (CH), may contain 1% NaOH]. Melting points were obtained on a Gallenkamp melting point apparatus (open capillary tubes) and were uncorrected. ^1H NMR spectra were performed on a Varian Mercury-VX-300 (300 MHz) at the Micro analytical Unit, Cairo University, Giza, Egypt and a Bruker ultra shield Avance III spectrometer (400 and 600 MHz for ^1H NMR and 100 and 150 MHz for ^{13}C NMR) at the Faculty of Science, King Abd-Elaziz University, Jeddah, KSA, with the use of tetramethylsilane as an internal standard and DMSO or $CDCl_3$ as solvents. Chemical shifts were expressed as δ ppm. The IR spectra were performed on a Jasco 4100 FTIR spectrophotometer (KBr pellet) at the Department of Chemistry, Faculty of Science at (New) Damietta, Mansoura University, Damietta branch, Egypt. The electron impact (EI) mass spectra were performed on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV, and the elemental analyses were performed on a Perkin-Elmer 2400 C, H, N elemental analyzer at the Micro Analytical Unit, Cairo University.

Reported procedures were followed for the preparation of 3-arlyamino-2,5-dioxo-1-substituted-3-pyrroline **1a**, **b** [13] and anilinofumarates **9a–e** [14,15].

Synthesis of 2-amino-3-cyano-1,4-diaryl-5,7-dioxo-6-substituted-4,5,6,7-tetrahydro-pyrrolo[3,4-*b*]pyridine derivatives (5a–d).

General procedure A. A mixture of enamino imide (**1a** or **1d**) (0.001 mol), arylidenemalononitrile derivatives **2a–c** (0.001 mol), and two drops of piperidine in 10 mL of absolute ethanol was refluxed on a boiling water bath for 4 h and then allowed to cool to room temperature. The solid product, so deposited, was collected by filtration, washed with drops of cold 95% ethanol, and recrystallized from the appropriate solvent.

General procedure B. The procedure for a mixture of enamino imide (**1a**) (0.001 mol), benzaldehyde **7a** (0.001 mol), malononitrile **8** (0.001 mol), and two drops of piperidine in 10 mL of absolute ethanol was the same as in procedure A.

***2-Amino-3-cyano-5,7-dioxo-1,4-diphenyl-6-methyl-(3-pyrrolino)[3,4-b]*(1,4-dihydro pyridine) (5a).** mp 225–226 °C (95% ethanol), yield 88%, orange fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3463, 3309 (NH_2), 2186 (CN), 1772, 1712 (two C═O), 1677 (C═C), 740, 694 (mono substituted benzene ring); ^1H NMR (600 MHz, DMSO), δ, ppm = 7.53–7.27 (10H, m, aromatic), 5.65 (2H, s, NH_2), 4.61 (1H, s, CH-4), 2.66 (3H, s, CH_3); ^{13}C NMR (150 MHz, DMSO), δ, ppm = 23.05 (CH_3), 60.4 (CH-4), 120.9 (CN), (110.6, 127.05, 127.61, 128.50, 129.42, 134.85, 137.60, 143.99, 151.52), 163.30 (C═O), 168.35 (C═O). *Anal*. Calcd for $C_{21}1H_6N_4O_2$ (mol. wt: 356.38): C, 70.77; H, 4.53; N, 15.72. Found: C, 70.36; H, 4.92; N, 15.63.

***2-Amino-4-(3-bromophenyl)-3-cyano-5,7-dioxo-6-methyl-1-phenyl-(3-pyrrolino)[3,4-b]*(1,4-dihydropyridine) (5b)**. mp 220–222 °C (95% ethanol), yield 91%, orange fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3471, 3367 (NH_2), 2175 (CN), 1770, 1708 (two C=O), 1670 (C=C), 744, 698 (mono substituted benzene ring), 867, 798 (meta disubstituted benzene ring); ^1H NMR (300 MHz, $CDCl_3$), δ, ppm = 7.60–7.27 (9H, m, aromatic), 4.76 (1H, s, CH-4), 4.41 (2H, s, NH_2), 2.83 (3H, s, CH_3).

***2-Amino-3-cyano-5,7-dioxo-4-(4-methoxyphenyl)-6-methyl-1-phenyl-(3-pyrrolino)[3,4-b]*(1,4-dihydropyridine) (5c)**. mp 202–204 °C (95% ethanol), yield 89%, orange fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3451, 3332 (NH_2), 2175 (CN), 1770, 1716 (two C=O), 1677 (C=C), 1249, 1029 (OCH_3), 836 (para disubstituted benzene ring), 744, 690 (mono substituted benzene ring); ^1H NMR (300 MHz, $CDCl_3$), δ, ppm = 7.58–7.56 (2H, m, aromatic), 7.37–7.27 (5H, m, aromatic), 6.95–6.92 (2H, m, aromatic), 4.73 (1H, s, CH-4), 4.36 (2H, s, NH_2), 3.81 (3H, s, OCH_3), 2.81 (3H, s, CH_3).

***2-Amino-3-cyano-5,7-dioxo-6-(2-hydroxyethyl)-4-phenyl-1-(4-tolyl)-(3-pyrrolino)[3,4-b]*(1,4-dihydropyridine) (5d)**. mp 190–192 °C (95% ethanol/water, 2: 1), yield 70%, orange fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3621 (OH), 3448, 3320 (NH_2), 2183 (CN), 1765, 1712 (two C=O), 1678 (C=C), 824 (para disubstituted benzene ring), 744, 705 (mono substituted benzene ring); ^1H NMR (600 MHz, DMSO), δ, ppm = 7.39–7.27 (9H, m, aromatic), 5.62 (2H, s, NH_2), 4.71 (1H, t, J = 6, OH), 4.60 (1H, s, CH-4), 3.31 (2H, t, J = 6, CH_2–N–), 3.25 (2H, t, J = 6, CH_2–O), 2.39 (3H, s, CH_3); ^{13}C NMR (150 MHz, DMSO), δ, ppm = 20.73 (CH_3), 57.62 (CH_2), 57.74 (CH_2), 60.22 (CH-4), 120 (CN), (110.4, 127.04, 128.5, 129.0, 129.96, 132.15, 137.41, 138.99, 144.03, 151.70), 163.21 (C=O), 168.28 (C=O); MS (EI): *m/z* (ion, %): 400 (M^+, 10.4), 91 ($[C_7H_7]^+$, 100); 77 ($[C_6H_5]^+$, 45). *Anal*. Calcd for $C_{23}H_{20}N_4O_3$ (mol. wt: 400.43): C, 68.99; H, 5.03; N, 13.99. Found: C, 68.75; H, 4.83; N, 13.86.

Synthesis of 1,4-dihydropyridine derivatives (10a–o).

General procedure A. A mixture of the appropriate anilinofumarate **9a–e** (0.01 mol), cinnamonitriles **2a–k** (0.01 mol), and two drops of piperidine in 10 mL of absolute ethanol was refluxed on a boiling water bath for 6 h. The reaction mixture was allowed to cool to the room temperature in air. The solid product, so deposited, was collected by filtration and recrystallized from the appropriate solvent. In the case of derivatives **10 k**, **l**, **o** and after cooling to room temperature, we then stirred the reaction mixture for 30 min with 10 mL of 30% ammonium hydroxide solution. The deposited product was filtered off, washed with cold water, and dried in air before crystallization.

General procedure B. The procedure for a mixture of the anilinofumarate **9a** (0.01 mol), appropriate aldehyde **7a**, **c**, **d** (0.01 mol), malononitrile **8** (0.01 mol), and two drops of piperidine in 10 mL of absolute ethanol was the same as in procedure A.

Diethyl 6-amino-5-cyano-1,4-diphenyl-1,4-dihydropyridine-2,3-dicarboxylate (10a). mp 174–175 °C (95% ethanol), yield 80%, yellow fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3471, 3324 (NH_2), 2180 (CN), 1738, 1712 (two C=O), 760, 694 (mono substituted benzene ring); ^1H NMR (400 MHz, DMSO), δ, ppm = 7.52–7.28 (10H, m, aromatic), 5.64 (2H, s, NH_2), 4.51 (1H, s, CH-4), 3.97 (2H, q, OCH_2CH_3), 3.80 (2H, m, OCH_2CH_3), 1.05 (3H, t, OCH_2CH_3), 0.83 (3H, t, OCH_2CH_3); MS (EI): *m/z* (ion, %): 417 (M^+, 4.6), 77 ($[C_6H_5]^+$, 100). *Anal*. Calcd for $C_{24}H_{23}N_3O_4$ (mol. wt: 417.46): C, 69.05; H, 5.55; N, 10.07. Found: C, 68.96; H, 5.20; N, 9.74.

Diethyl 6-amino-5-cyano-4-(4-methoxyphenyl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (10b). mp 144–146 °C (95% ethanol), yield 78%, yellow fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3459, 3324 (NH_2), 2183 (CN), 1742, 1691 (two C=O), 1244, 1032 (OCH_3), 831 (para disubstituted benzene ring), 748, 702 (mono substituted benzene ring); ^1H NMR (400 MHz, DMSO), δ, ppm = 7.50 (3H, m, aromatic), 7.30 (2H, m, aromatic), 7.24 (2H, d, J = 8.36, aromatic), 6.96 (2H, d, J = 8.36, aromatic), 5.58 (2H, s, NH_2), 4.43 (1H, s, CH-4), 3.96 (2H, q, OCH_2CH_3), 3.76 (2H, m, OCH_2CH_3), 3.77 (3H, s, OCH_3), 1.06 (3H, t, OCH_2CH_3), 0.814 (3H, t, OCH_2CH_3). *Anal*. Calcd for $C_{25}H_{25}N_3O_5$ (mol. wt: 447.48): C, 67.10; H, 5.63; N, 9.39. Found: C, 66.80; H, 5.20; N, 9.17.

Diethyl 6-amino-4-(4-chlorophenyl)-5-cyano-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (10c). mp 188–189 °C (95% ethanol), yield 78%, pale yellow fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3447, 3361 (NH_2), 2186 (CN), 1722, 1704 (two C=O), 1103 (C_6H_4Cl), 835 (para disubstituted benzene ring), 739, 698 (mono substituted benzene ring); ^1H NMR (400 MHz, DMSO), δ, ppm = 7.46–7.52 (5H, m, aromatic), 7.33 (4H, d, aromatic), 5.68 (2H, s, NH_2), 4.51 (1H, s, CH-4), 3.96 (2H, q, OCH_2CH_3), 3.76 (2H, m, OCH_2CH_3), 1.04 (3H, t, OCH_2CH_3), 0.815 (3H, t, OCH_2CH_3). *Anal*. Calcd for $C_{24}H_{22}ClN_3O_4$ (Cl = 35.45, mol. wt: 451.90): C, 63.79; H, 4.91; N, 9.30. Found: C, 63.52; H, 4.52; N, 9.02.

Diethyl 6-amino-4-(2-chlorophenyl)-5-cyano-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (10d). mp 141–143 °C (95% ethanol), yield 41%, pale yellow fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3465, 3333 (NH_2), 2176 (CN), 1736, 1709 (two C=O), 1111 (C_6H_4Cl), 760 (ortho disubstituted benzene ring); ^1H NMR (400 MHz, DMSO), δ, ppm = 7.52 (3H, m, aromatic), 7.45 (3H, m, aromatic), 7.37 (2H, m, aromatic), 7.26 (1H, m, aromatic), 5.58 (2H, s, NH_2), 5.11 (1H, s, CH-4), 3.90 (2H, q, OCH_2CH_3), 3.79 (2H, m, OCH_2CH_3), 0.97 (3H, t, OCH_2CH_3), 0.833 (3H, t, OCH_2CH_3). *Anal*. Calcd for $C_{24}H_{22}ClN_3O_4$ (Cl = 35.45, mol. wt: 451.90): C, 63.79; H, 4.91; N, 9.30. Found: C, 63.41; H, 4.23; N, 8.92.

Diethyl 6-amino-5-cyano-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (10e). mp 187–188 °C (95% ethanol), yield 74%, yellow fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3438, 3334 (NH_2), 2183 (CN), 1741, 1687 (two C=O), 1527, 1347 (NO_2), 888, 771, 700 (meta disubstituted benzene ring); ^1H NMR (400 MHz, DMSO), δ, ppm = 8.16 (2H, m, aromatic), 7.81–7.79 (2H, m, aromatic), 7.53 (3H, m, aromatic), 7.36 (2H, m, aromatic), 5.83 (2H, s, NH_2), 4.72 (1H, s, CH-4), 3.97 (2H, q, OCH_2CH_3), 3.78 (2H, m, OCH_2CH_3), 1.05 (3H, t, OCH_2CH_3), 0.80 (3H, t, OCH_2CH_3). *Anal*. Calcd for $C_{24}H_{22}N_4O_6$ (mol. wt: 462.45): C, 62.33; H, 4.79; N, 12.12. Found: C, 61.91; H, 4.90; N, 12.10.

Diethyl 6-amino-5-cyano-1,4-bis(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (10f). mp 178–179 °C (95% ethanol), yield 77%, yellow fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3450, 3315 (NH_2), 2181 (CN), 1743, 1692 (two C=O), 1238, 1020 (OCH_3), 825 (para disubstituted benzene ring); ^1H NMR (400 MHz, DMSO), δ, ppm = 7.22 [4H, dd, J = (8.48, 2), aromatic], 7.03 (2H, d, J = 8.48, aromatic), 6.95 (2H, d, J = 8.48, aromatic), 5.50 (2H, s, NH_2), 4.40 (1H, s, CH-4), 3.97 (2H, q, OCH_2CH_3), 3.77 (2H, m, OCH_2CH_3), 3.80 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 1.06 (3H, t, OCH_2CH_3), 0.87 (3H, t, OCH_2CH_3). *Anal*. Calcd for $C_{26}H_{27}N_3O_6$ (mol. wt: 477.51): C, 65.40; H, 5.70; N, 8.80. Found: C, 65.39; H, 5.35; N, 8.57.

Diethyl 6-amino-5-cyano-4-phenyl-1-p-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (10g). mp 188–190 °C (95% ethanol/water, 3:1), yield 67%, pale yellow fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3472, 3313 (NH_2), 2188 (CN), 1746, 1706 (two C=O), 827 (para disubstituted benzene ring), 696, 749 (mono substituted benzene ring); ^{1}H NMR (400 MHz, DMSO), δ, ppm = 7.40–7.20 (9H, m, aromatic), 5.59 (2H, s, NH_2), 4.49 (1H, s, CH-4), 3.96 (2H, q, O$CH_2$$CH_3$), 3.79 (2H, m, O$CH_2$$CH_3$), 2.35 (3H, s, CH_3), 1.04 (3H, t, OCH_2CH_3), 0.86 (3H, t, OCH_2CH_3). *Anal*. Calcd for $C_{25}H_{25}N_3O_4$ (mol. wt: 431.48): C, 69.59; H, 5.84; N, 9.74. Found: C, 69.46; H, 5.66; N, 9.40.

Diethyl 6-amino-1-(4-bromophenyl)-5-cyano-4-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (10h). mp 187–188 °C (95% ethanol), yield 93%, white fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3456, 3323 (NH_2), 2182 (CN), 1743, 1698 (two C=O), 831 (para disubstituted benzene ring); ^{1}H NMR (600 MHz, DMSO), δ, ppm = 7.71 (2H, d, aromatic), 7.39 (2H, t, aromatic), 7.26 (5H, m, aromatic), 5.78 (2H, s, NH_2), 4.48 (1H, s, CH-4), 3.96 (2H, q, O$CH_2$$CH_3$), 3.86 (2H, m, O$CH_2$$CH_3$), 1.03 (3H, t, OCH_2CH_3), 0.88 (3H, t, OCH_2CH_3); ^{13}C NMR (150 MHz, DMSO), δ, ppm = 13.01 (CH_3), 13.59 (CH_3), 59.43 (OCH_2), 60.38 (OCH_2), 61.45 (CH-4), 120.86 (CN), (104.58, 123.27, 126.78, 126.86, 128.61, 132.50, 132.54, 134.59, 141.20, 145.39, 150.55), 162.27 (C=O), 164.35 (C=O). *Anal*. Calcd for $C_{24}H_{22}BrN_3O_4$ (Br = 79.9, mol. wt: 496.35): C, 58.07; H, 4.47; N, 8.47. Found: C, 57.80; H, 4.87; N, 8.21.

Diethyl 6-amino-4-(3-bromophenyl)-1-(4-bromophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (10i). mp 183–185 °C (95% ethanol), yield 75%, white fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3389, 3325 (NH_2), 2188 (CN), 1742, 1703 (two C=O), 828 (para disubstituted benzene ring), 862, 772, 690 (meta disubstituted benzene ring); MS (EI): *m/z* (ion, %): 575 ($[M+2]^+$, ^{79}Br and ^{81}Br, 12.1), 157 ($[C_6H_4^{81}Br]^+$, 44.7), 155 ($[C_6H_4^{79}Br]^+$, 40.7), 81 ($^{81}Br^+$, 14.1), 79 ($^{79}Br^+$, 13.6), 76 ($[C_6H_4]^+$, 100). *Anal*. Calcd for $C_{24}H_{21}Br_2N_3O_4$ (Br = 79.9, mol. wt: 575.25): C, 50.11; H, 3.68; N, 7.30. Found: C, 49.88; H, 3.77; N, 7.12.

Diethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (10j). mp 178–179 °C (95% ethanol), yield 80%, pale yellow fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3457, 3325 (NH_2), 2182 (CN), 1742, 1701 (two C=O), 1090 (C_6H_4Cl), 833 (para disubstituted benzene ring); ^{1}H NMR (400 MHz, DMSO), δ, ppm = 7.57 (2H, d, aromatic), 7.41–7.27 (7H, m, aromatic), 5.78 (2H, s, NH_2), 4.48 (1H, s, CH-4), 3.95 (2H, q, O$CH_2$$CH_3$), 3.80 (2H, m, O$CH_2$$CH_3$), 1.03 (3H, t, OCH_2CH_3), 0.88 (3H, t, OCH_2CH_3); ^{13}C NMR (100 MHz, DMSO), δ, ppm = 13.6 (CH_3), 14.17 (CH_3), 60.03 (OCH_2), 60.95 (OCH_2), 62.02 (CH-4), 121.43 (CN), (105.17, 127.37, 127.44, 129.19, 130.12, 132.86, 134.72, 135.17, 141.83, 145.98, 151.18), 162.85 (C=O), 164.94 (C=O). *Anal*. Calcd for $C_{24}H_{22}ClN_3O_4$ (Cl = 35.45, mol. wt: 451.90): C, 63.79; H, 4.91; N, 9.30. Found: C, 63.78; H, 4.48; N, 9.10.

Triethyl 6-amino-1,4-diphenyl-1,4-dihydropyridine-2,3,5-tricarboxylate (10k). mp 129–130 °C (95% ethanol/water, 1:1), yield 50%, white needles; ir (KBr), υ_{max}, cm^{-1} = 3390, 3276 (NH_2), 1736, 1709, 1700 (three C=O), 751, 696 (mono substituted benzene ring); ^{1}H NMR (600 MHz, DMSO), δ, ppm = 7.55–7.18 (10H, m, aromatic), 6.81 (2H, s, br, NH_2), 4.89 (1H, s, CH-4), 4.01–3.98 (4H, m, 2O$CH_2$$CH_3$), 3.75 (2H, m, O$CH_2$$CH_3$), 1.10 (3H, t, OCH_2CH_3), 1.07 (3H, t, OCH_2CH_3), 0.821 (3H, t, OCH_2CH_3); ^{13}C NMR (150 MHz, DMSO), δ, ppm = 13.04 (CH_3), 13.70 (CH_3), 14.23 (CH_3), 58.52 (OCH_2), 60.23 (OCH_2), 61.16 (OCH_2), 77.99 (CH-4), (106.49, 126.12, 127.28, 128.04, 129.62, 129.95, 130.41, 135.08, 141.16, 147.02, 151.95), 162.50 (C=O), 164.70 (C=O), 168.37 (C=O). *Anal*. Calcd for $C_{26}H_{28}N_2O_6$ (mol. wt: 464.51): C, 67.23; H, 6.08; N, 6.03. Found: C, 67.02; H, 5.88; N, 5.98.

Triethyl 6-amino-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyridine-2,3,5-tricarboxylate (10l). mp 139–140 °C (95% ethanol), yield 75%, yellow fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3465, 3272 (NH_2), 1740, 1707, 1671 (three C=O), 1522, 1344 (NO_2), 855, 785, 702 (meta disubstituted benzene ring); ^{1}H NMR (600 MHz, DMSO), δ, ppm = 8.17 (1H, m, aromatic), 8.16 (1H, m, aromatic), 7.80 (1H, m, aromatic), 7.686 (1H, t, *J* = 7.8, aromatic), 7.591–7.419 (5H, m, aromatic), 7.00 (2H, s, br, NH_2), 5.0 (1H, s, CH-4), 4.01–3.96 (4H, m, 2O$CH_2$$CH_3$), 3.80 (2H, m, O$CH_2$$CH_3$), 1.10 (3H, t, OCH_2CH_3), 1.06 (3H, t, OCH_2CH_3), 0.834 (3H, t, OCH_2CH_3); ^{13}C NMR (150 MHz, DMSO), δ, ppm = 13.03 (CH_3), 13.63 (CH_3), 14.13 (CH_3), 58.72 (OCH_2), 60.47 (OCH_2), 61.35 (OCH_2), 77.23 (CH-4), (105.36, 121.32, 121.92, 129.71, 129.92, 130.18, 130.44, 134.02, 134.73, 141.96, 147.35, 149.25, 152.05), 162.17 (C=O), 164.33 (C=O), 167.99 (C=O). *Anal*. Calcd for $C_{26}H_{27}N_3O_8$ (mol. wt: 509.51): C, 61.29; H, 5.34; N, 8.25. Found: C, 61.09; H, 5.64; N, 8.27.

Triethyl 4-(4-acetamidophenyl)-6-amino-1-(4-bromophenyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (10m). mp 195–196 °C (95% ethanol), yield 66%; yellow crystals; ir (KBr), υ_{max}, cm^{-1} = 3410, 3400, 3367, 3293 (NH_2, NH), 1739, 1677, 1669 (three ester C=O and acetamido C=O), 825 (para disubstituted benzene ring); ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm = 8.78 (1H, s, br, NH), 7.62–7.27 (8H, m, aromatic), 6.14 (2H, s, br, NH_2), 4.98 (1H, s, CH-4), 4.11–3.95 (4H, m, 2O$CH_2$$CH_3$), 3.90 (2H, m, O$CH_2$$CH_3$), 2.14 (3H, s, $COCH_3$), 1.20 (3H, t, OCH_2CH_3), 1.179 (3H, t, OCH_2CH_3), 0.99 (3H, t, OCH_2CH_3). *Anal*. Calcd for $C_{28}H_{30}BrN_3O_7$ (Br = 79.9, mol. wt: 600.46): C, 56.01; H, 5.04; N, 7.00. Found: C, 55.86; H, 5.01; N, 6.85.

Triethyl 6-amino-4-(2-bromophenyl)-1-(4-bromophenyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (10n). mp 128–130 °C (95% ethanol), yield 70%; yellow crystals; ir (KBr), υ_{max}, cm^{-1} = 3451, 3251 (NH_2), 1735, 1702, 1667 (three C=O), 829 (para disubstituted benzene ring), 755 (ortho disubstituted benzene ring); MS (EI): *m/z* (ion, %): 622 ($[M+2]^+$, ^{79}Br and ^{81}Br, 9.7), 620 (M^+, ^{79}Br and ^{79}Br, 6.9), 157 ($[C_6H_4^{81}Br]^+$, 25.5), 155 ($[C_6H_4^{79}Br]^+$, 22.1), 81 ($^{81}Br^+$, 8.3), 79 ($^{79}Br^+$, 8.3), 76 ($[C_6H_4]^+$, 46.2). *Anal*. Calcd for $C_{26}H_{26}Br_2N_2O_6$ (Br = 79.9, mol. wt: 622.30): C, 50.18; H, 4.21; N, 4.50. Found: C, 50.27; H, 4.02; N, 4.63.

Diethyl 6-amino-5-carbamoyl-1,4-diphenyl-1,4-dihydropyridine-2,3-dicarboxylate (10o). mp 202–203 °C (95% ethanol), yield 79%, yellow fine crystals; ir (KBr), υ_{max}, cm^{-1} = 3444, 3369, 3142 (NH_2), 1728, 1700 (two C=O, ester), 1661 (C=O, amide), 757, 694 (mono substituted benzene ring); ^{1}H NMR (600 MHz, DMSO), δ, ppm = 7.50–7.20 (10H, m, aromatic), 7.08 (2H, s, br, $CONH_2$), 6.48 (2H, s, NH_2), 4.81 (1H, s, CH-4), 4.01 (2H, m, O$CH_2$$CH_3$), 3.75 (2H, m, O$CH_2$$CH_3$), 1.13 (3H, t, OCH_2CH_3), 0.80 (3H, t, OCH_2CH_3); ^{13}C NMR (150 MHz, DMSO), δ, ppm = 13.03 (CH_3), 13.73 (CH_3), 60.08 (OCH_2), 60.99 (OCH_2), 79.94 (CH-4), (105.7, 126.18, 127.42, 128.02, 129.37, 129.6, 130.43, 135.58, 141.1, 146.67, 150.09), 162.69 (C=O), 164.89 (C=O), 171.23 ($CONH_2$). *Anal*. Calcd for $C_{24}H_{25}N_3O_5$ (mol. wt: 435.47): C, 66.19; H, 5.79; N, 9.65. Found: C, 65.90; H, 5.52; N, 9.54.

Synthesis of [tetraethyl 2,2′-(1,4-phenylene)bis(azanediyl)] difumarate (bis enamino ester) (14).

General procedure AA. A mixture of diethyl oxalacetate sodium salt **12** (0.02 mol), *p*-phenylenediamine **11** (0.01 mol), and 10 mL of glacial acetic acid was heated over a water bath at 40–50 °C for 8 h, allowed to cool to room temperature, and then poured into ice water, and the solution was adjusted to pH = 8 with 35% sodium hydroxide solution. The resulting mixture was extracted with methylene chloride (3 × 20 mL). The combined methylene chloride extracts were washed sequentially with 0.5 N HCl (4 × 20 mL) and 0.5 N NaOH (4 × 20 mL). The separated organic phase was washed with water and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give an oily product, which was solidified after trituration with petroleum ether (40–60 °C). Yield: 16%; orange powder, mp 73–75 °C (petroleum ether 40–60 °C: diethyl ether, 3: 1); ir (KBr), υ_{max}, cm^{-1} = 3278 (two NH), 1736, 1672 (four C═O), 813 (para disubstituted benzene ring); ^{1}H NMR (300 MHz, DMSO), δ, ppm = 9.59 (2H, s, 2NH), 6.90 (4H, s, aromatic), 5.21 (2H, s, 2CH, olefinic), 4.15–4.08 (8H, m, 4O*CH*$_2$CH$_3$), 1.21 (6H, t, 2OCH$_2$*CH*$_3$), 1.072 (6H, t, 2OCH$_2$*CH*$_3$). *Anal*. Calcd for $C_{22}H_{28}N_2O_8$ (mol. wt: 448.47): C, 58.92; H, 6.29; N, 6.25. Found: C, 58.51; H, 5.88; N, 5.98.

General procedure BB. A mixture of diethyl oxalacetate **13** (0.02 mol) and *p*-phenylenediamine **11** (0.01 mol) in 20 mL of absolute ethanol was refluxed over a boiling water bath for 6 h, allowed to cool to room temperature, and then poured into ice water. The resulting mixture was extracted with methylene chloride (3 × 20 mL). The combined methylene chloride extracts were washed with water (3 × 30 mL). The separated organic phase was dried with anhydrous Na_2SO_4, and then the procedure was the same as in procedure AA to give **14** (mp, mixture mp, TLC, and IR), yield 44%.

Synthesis of 1,1′-(1,4-phenylene)bis(1,4-dihydropyridine) derivatives (15a–c).

General procedure A. A mixture of the bis enamino ester **14** (0.001 mol), the appropriate cinnamonitrile **2a**, **g**, **l** (0.002 mol), and two drops of piperidine in 10 mL of absolute ethanol was heated under reflux on a boiling water bath for 6 h. The reaction mixture was allowed to cool overnight in the freezer. The solid product, so deposited, was collected by filtration and recrystallized from the appropriate solvent.

General procedure B. The procedure for a mixture of the bis enamino ester **14** (0.001 mol), the appropriate aldehyde **7a**, **d** (0.002 mol), malononitrile **8** (or ethyl cyanoacetate **16**) (0.002 mol), and two drops of piperidine in 10 mL of absolute ethanol was the same as in procedure A.

Tetraethyl 1,1′-(1,4-phenylene)bis(6-amino-5-cyano-4-phenyl-1,4-dihydropyridine-2,3-dicarboxylate) (15a). mp 239–240 °C (95% ethanol/water, 2: 1), yield 70%, pale yellow crystals; ir (KBr), υ_{max}, cm^{-1} = 3468, 3318 (two NH_2), 2189 (two CN), 1738, 1700 (four C═O), 823 (para disubstituted benzene ring), 760, 697 (mono substituted benzene ring); ^{1}H NMR (600 MHz, DMSO), δ, ppm = 7.50 (4H, m, aromatic), 7.39 (4H, m, aromatic), 7.31 (4H, m, aromatic), 7.27 (2H, m, aromatic), 6.0 (4H, s, 2NH_2), 4.51 (2H, s, 2CH-4), 3.96 (4H, q, 2O*CH*$_2$CH$_3$), 3.84 (4H, q, 2O*CH*$_2$CH$_3$), 1.145 (6H, t, 2OCH$_2$*CH*$_3$), 1.027 (6H, t, 2OCH$_2$*CH*$_3$); ^{13}C NMR (150 MHz, DMSO), δ, ppm = 13.28 (2CH_3), 13.63 (2CH_3), 58.09 (2OCH_2), 60.35 (2OCH_2), 61.53 (2CH-4), 121.11 (2CN), (104.1, 126.85, 126.92, 127.0, 128.58, 131.97, 136.29, 136.33, 140.97, 145.69, 145.75, 150.49, 150.72), 162.18 (2C═O), 164.46 (2C═O); MS (EI): *m*/*z* (ion, %): 77 ($C_6H_5^+$, 63.9), 66 ([$H_2NC{\equiv}CCN$]$^+$, 100), 65 ([$HNC{\equiv}CCN$]$^+$, 44.4). *Anal*. Calcd for $C_{42}H_{40}N_6O_8$ (mol. wt: 756.80): C, 66.66; H, 5.33; N, 11.10; Found: C, 66.37; H, 4.99; N, 10.95.

Tetraethyl 1,1′-(1,4-phenylene)bis(6-amino-4-(2-bromophenyl)-5-cyano-1,4-dihydro-pyridine-2,3-dicarboxylate) (15b). mp 245–246 °C (95% ethanol), yield 55%, pale yellow crystals; ir (KBr), υ_{max}, cm^{-1} = 3432, 3333 (two NH_2), 2173 (two CN), 1743, 1709 (four C═O), 818 (para disubstituted benzene ring), 739 (ortho disubstituted benzene ring); ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm = 7.60–7.13 (12H, m, aromatic), 5.32 (2H, s, 2CH-4), 4.15 (4H, s, 2NH_2), 4.03–3.96 (8H, q, 4O*CH*$_2$CH$_3$), 1.18 (6H, t, 2OCH$_2$*CH*$_3$), 1.07 (6H, t, 2OCH$_2$*CH*$_3$). *Anal*. Calcd for $C_{42}H_{38}Br_2N_6O_8$ (Br = 79.9, mol. wt: 914.59): C, 55.16; H, 4.19; N, 9.19. Found: C, 54.88; H, 4.23; N, 9.24.

Hexaethyl 1,1′-(1,4-phenylene)bis(6-amino-4-phenyl-1,4-dihydropyridine-2,3,5-tricarboxylate) (15c). mp 128–129 °C (95% ethanol/water 2:1), yield 60%, pale yellow crystals; ir (KBr), υ_{max}, cm^{-1} = 3535, 3344 (two NH_2); 1735, 1729, 1708 (six C═O), 858 (para disubstituted benzene ring), 759, 697 (mono substituted benzene ring); ^{1}H NMR (600 MHz, DMSO), δ, ppm = 7.65 (2H, m, aromatic), 7.56 (4H, m, aromatic), 7.43 (2H, m, aromatic), 7.34 (4H, m, aromatic), 7.20 (2H, m, aromatic), 6.78 (4H, s, 2NH_2), 4.90 (2H, s, 2CH-4), 4.0 (8H, m, 4O*CH*$_2$CH$_3$), 3.84 (4H, m, 2O*CH*$_2$CH$_3$), 1.12 (6H, t, 2OCH$_2$*CH*$_3$), 1.04 (6H, t, 2OCH$_2$*CH*$_3$), 0.77 (6H, t, 2OCH$_2$*CH*$_3$); ^{13}C NMR (150 MHz, DMSO), δ, ppm = 13.27 (2CH_3), 13.72 (2CH_3), 14.31 (2CH_3), 60.37 (2OCH_2), 61.63 (2OCH_2), 63.14 (2OCH_2), 79.26 (2CH-4), (106.03, 107.32, 110.87, 127.14, 127.30, 128.13, 128.52, 129.81, 131.29, 134.96, 136.72, 137.11, 140.77, 146.62, 151.72, 157.98, 159.03, 159.82), 162.43 (2C═O), 163.17 (2C═O), 164.62 (2C═O). *Anal*. Calcd for $C_{46}H_{50}N_4O_{12}$ (mol. wt: 850.91): C, 64.93; H, 5.92; N, 6.58. Found: C, 64.82; H, 5.77; N, 6.68.

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