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Synthesis of novel bis(nicotinecarbonitrile) derivatives

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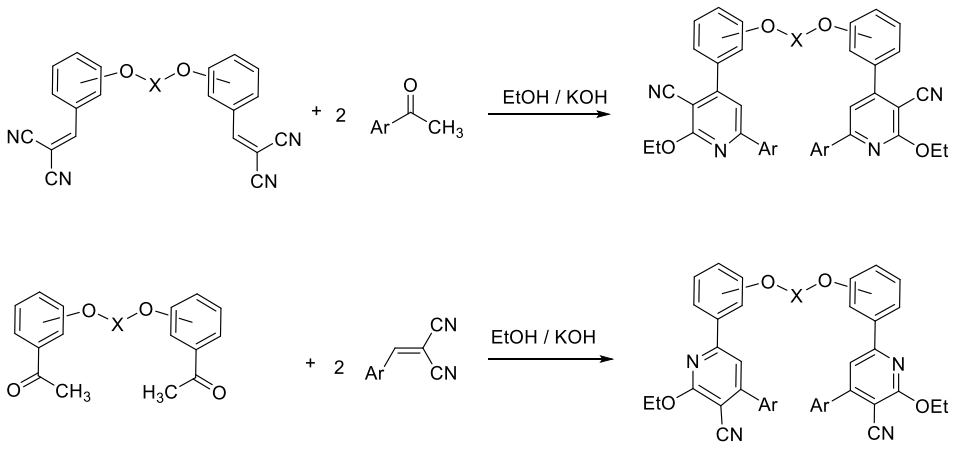
Abstract

A series of bis(nicotinecarbonitriles) were prepared *via* the reaction of bis arylidenemalononitriles with acetophenone in ethanolic potassium hydroxide solution. The isomeric bis(nicotinecarbonitriles) could also be obtained by the reaction of arylidenemalononitriles with bis acetophenone under similar conditions.The reaction was assumed to take place *via* Michael addition followed by cyclization due to the alkoxide nucleophilic attack at one of the nitrile groups. Alternative syntheses of both isomeric derivatives were also reported.

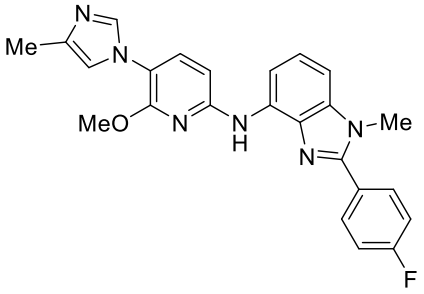


Keywords: Bis(nicotinecarbonitriles), bis(arylidenemalononitriles), bis(chalcones), Michael addition, cyclization

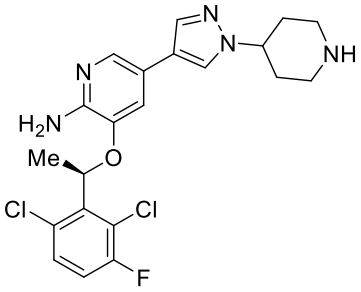
Introduction

Pyridine derivatives are an important class of azaheterocycle found in many natural products. They have occupied a unique position in the field of medicinal chemistry (cf. Figure 1)[1] due to their wide range of biological and pharmacological activities[2–9]. In this respect, some pyridine derivatives have been reported to exhibit antibacterial[10], antimicrobial[11,12] , antifungal[13], cardiotonic[14], analgesic[15], antiinflammatory[16] and anti-lung cancer[17] activities. Alternatively, some pyridine derivatives also represent the most interesting heterocyclic units in some agrochemical targets (cf. Figure 2)[18–20].

Due to the continued importance of the pyridine core in both biological and chemical fields, different methodologies for pyridine synthesis have been developed[21–24]. Among them, one-pot multicomponent reactions, remain the most interesting one in the synthesis of pyridine as well as different heterocycles and natural products[25–29]. Modification of such strategies continues to be an interesting theme in literature. As a consequence of this interest and in continuation of our work on Michael addition[30–37], multicomponent reactions[33–36,38–44] as well as on the synthesis of bis-heterocyclic with a suitable spacer[40,44–54], we report herein the results of our investigations concerning the synthesis of novel bis(nicotinecarbonitrile) derivatives.

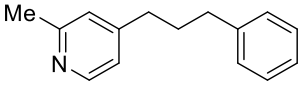


γ-Secretase modulator
Treatment of Alzheimer's disease

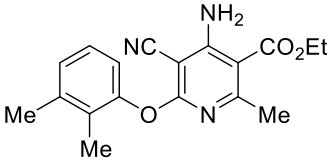


Crizotinib (Xalkori, pfizer)
Treatment of lung cancer

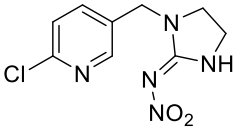
Figure 1



Antifungul



Herbicide

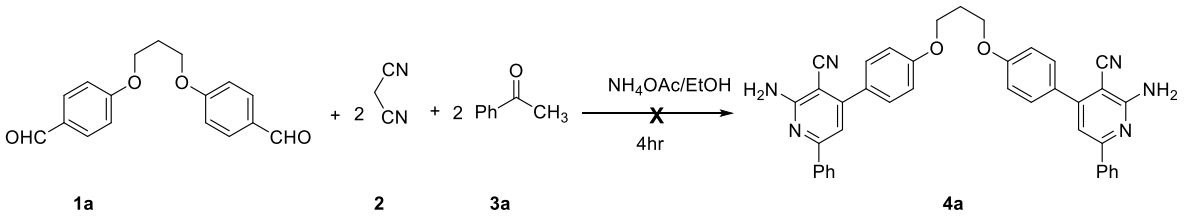


Insecticide

Figure 2

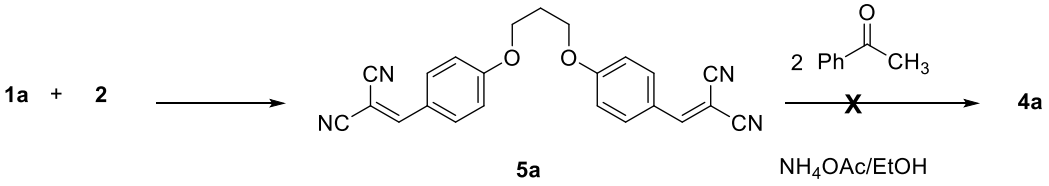
Results and Discussion

Firstly, we studied the attempted synthesis of bis pyridines **4** *via* a four-component reaction of bis aldehydes **1**[33,39], malononitrile **2**, acetopheone derivatives **3a-c** and NH_4OAc in refluxing ethanol (Scheme 1).



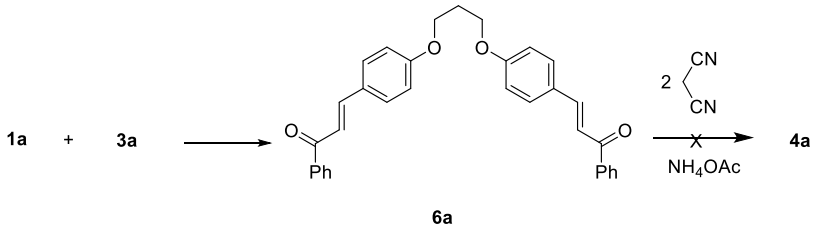
Scheme 1

Unfortunately, under these conditions we could not isolate a pure sample of the corresponding bis pyridine **4**. The reaction instead gave a product that was not easily handled and has not been characterized as yet. The reaction is assumed to proceed firstly *via* two-component reaction between the bis aldehyde **1** and malononitrile **2** to give a desired intermediate bis-arylidene-malononitrile **5**[33,39] which then subsequently reacts with acetophenone **3a** in the presence of ammonium acetate to give **4** (Scheme 2).



Scheme 2

The reaction may also proceed *via* firstly formation of chalcone **6**[55] by condensing **1** with acetophenone **3**. The pyridine was assumed to be formed by the reacting of **6** with malononitrile in the presence of ammonium acetate (Scheme 3).



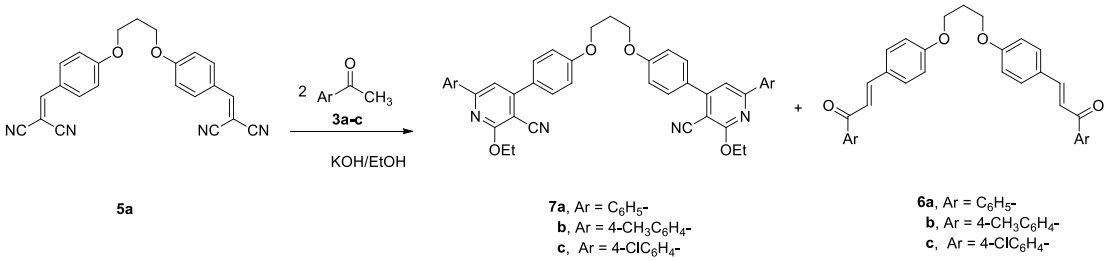
Scheme 3

It is noteworthy to mention that attempts to carry out a stepwise reaction through the isolation of the bis-arylidenemalononitrile derivative **5a** followed by reaction with acetophenone **3a** in the presence of ammonium acetate were also unsuccessful. Compound **5a** was obtained by Knoevenagel condensation of one mole of bis-aldehyde **1a** with two moles of malononitrile **2** in ethanol in the presence of piperidine as a basic catalyst. The melting point as well as the ^{1}H NMR spectral data of compound **5a** were in agreement to the reported values[33,39]. The ^{1}H NMR spectrum of compound **5a** indicated the presence of singlet signal integrated by two protons at δ 8.37 ppm assigned to vinyl hydrogenes. In additions, it indicated quintet signal at δ 2.25 ppm and triplet signal at 4.29 ppm for methylene protons. The aromatic protons appeared as two doublet at δ 7.20 and 7.96 ppm with the same coupling constant (J = 9 Hz).

Moreover, the bis-chalcone **6a** was also prepared as previously reported[55], by the reaction of bis-aldehyde **1a** with two moles of acetophenone **3a** in 4% ethanolic potassium hydroxide solution. Attempts to obtain the bis-pyridine **4a** by the reaction of **6a** with malononitrile **2** in the presence of ammonium acetate were also unsuccessful.

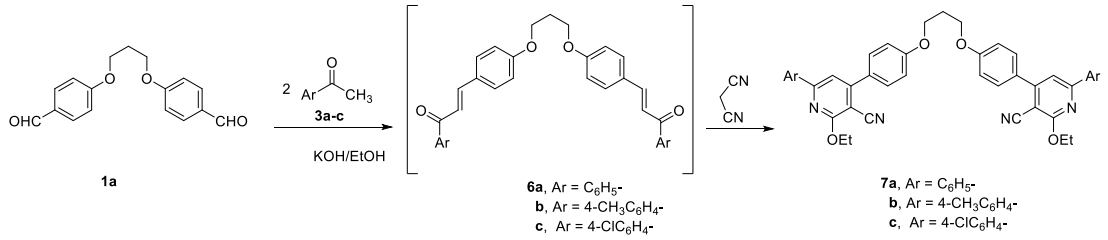
In search for an alternative pathway to prepare the target bis-pyridines, our attention turned to utilize KOH in ethanol as a basic catalyst instead of ammonium acetate. Thus, we studied the reaction of bis-arylidenemalononitrile **5a** with acetophenone **3a** in ethanolic potassium hydroxide solution at room temperature. The progress of the reaction was monitored on TLC. The reaction successfully afforded the corresponding bis-pyridine **7a** in a 63% yield. The bis-chalcone **6a** was also isolated from the reaction mixture as a minor product (Scheme 4).

Similarly, the bis pyridines **7b,c** were obtained by reaction of **5a** with the corresponding ketone **3b** and **3c**. Although the ^{1}H NMR of the reaction mixtures indicate the presence of few amount of the corresponding chalcones **6b** and **6c**, we were not able to isolate pure sample of these compounds (Scheme 4).



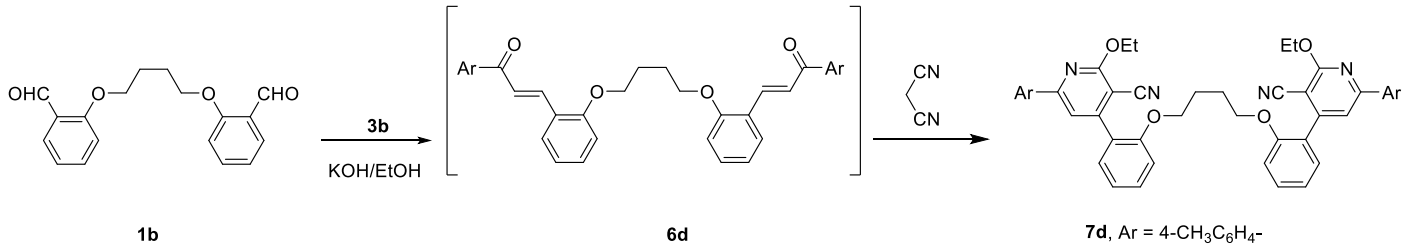
Scheme 4

The structure of **7a-c** was confirmed by alternative synthesis *via* stirring a mixture of bis-aldehyde **1a** and acetophenone derivatives **3a-c** in ethanol-KOH mixture to give the corresponding bis-chalcones **6** in 65-80% yields. Subsequent reaction of **6** with malononitrile in ethanol at reflux leads to the formation of compounds **7** as sole products (Scheme 5).



Scheme 5

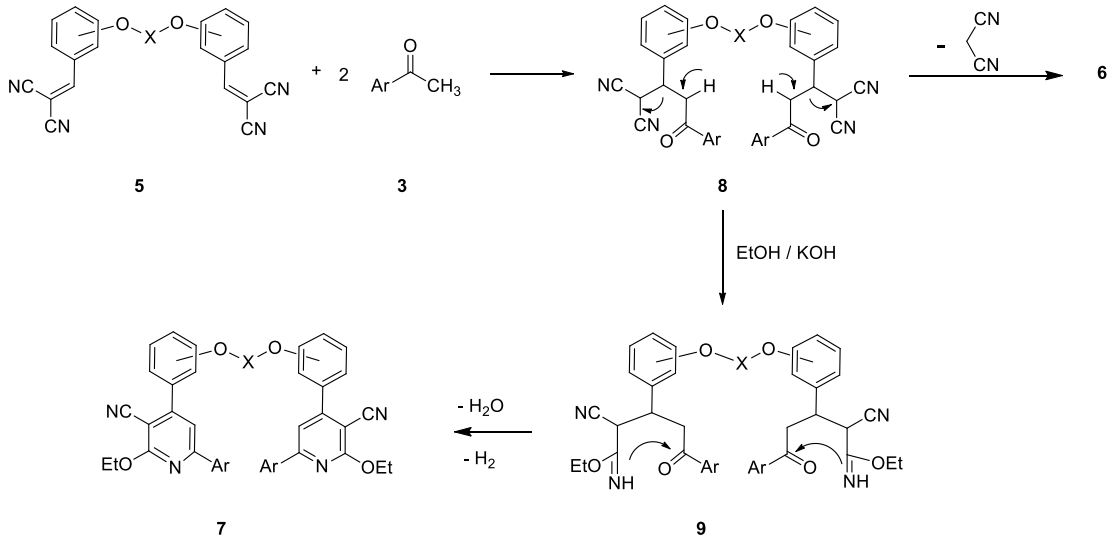
Similarly, the bis-pyridine **7d** was obtained in 61% yield by the reaction of the appropriate bis aldehyde **1b** with 4-methylacetophenone **3b** and malononitrile in ethanolic potassium hydroxide solution (Scheme 6).



Scheme 6

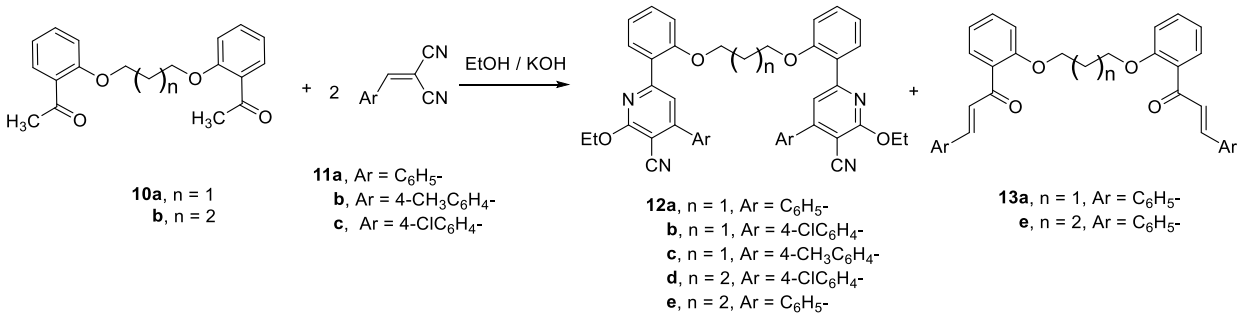
Moreover, the structure of **7** was confirmed by spectroscopic tools as well as elemental analyses data. The IR spectra of **7** reveal the presence of a nitrile stretching vibration band at 2213–2223 cm^{-1} region and lack any band assignable for a carbonyl function. The ^{1}H-NMR spectra of **7** exhibit the presence of the ethoxide moiety (δ =1.46–1.54 ''triplet of CH_3'', δ =4.55– 4.66 ''quartet for OCH_2'') as well as the pyridine H-5 at δ =7.27–7.40 confirming the cyclized form structure.

The reaction was assumed to take place through addition of **3** to the β-carbon of ylidene **5** affording the Michael adduct intermediate **8**. The latter due to attack of the ethoxide anion at one of the nitrile groups gives intermediate **9** which underwent cyclization followed by dehydration and subsequent dehydrogenation giving finally the isolable product **7** (Scheme 7). The bis-chalcone **6** may be formed *via* decomposition of **8** through elimination of malononitrile.



Scheme 7

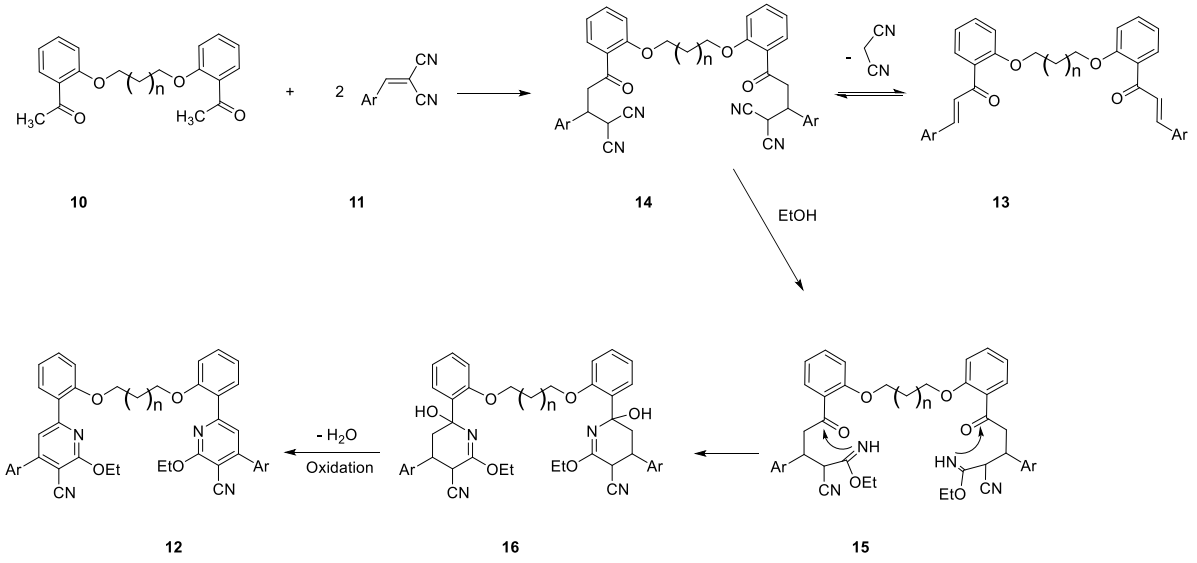
Our study was extended to include the synthesis of novel isomeric bis- pyridines **12** by the reaction of bis acetophenone **10** with arylidenemalononitriles **11** in ethanolic potassium hydroxide solution at room temperature. In some cases the bis-chalcones **13**[55] were successfully isolated from the reaction mixture as a minor product (Scheme 8).



Scheme 8

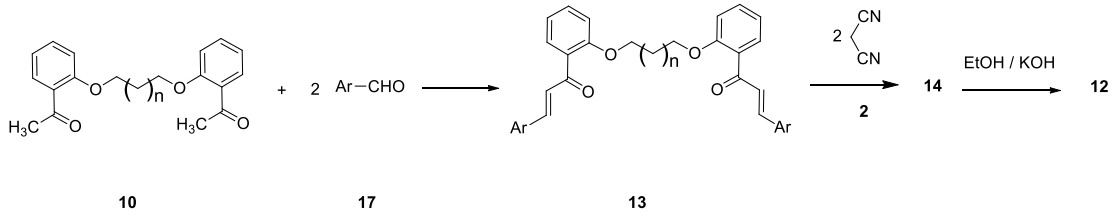
The reaction was assumed to take place through addition of **10** to the β-carbon of ylidene **11** affording the Michael adduct intermediate **14**. The latter due to attack of the ethoxide anion at one of the nitrile groups gives **15** which underwent cyclization followed by dehydration and subsequent dehydrogenation gives finally the isolable product **12** (Scheme 9).

The bis-chalcone **13** may be formed *via* decomposition of **14** through elimination of malononitrile.



Scheme 9

The structure of **17** was confirmed by authentication with samples prepared from bis-chalcones **13**, obtained in *situ* from the reaction of bis-acetophenones **10** with the appropriate aldehydes **17**, upon treatment with malononitrile in ethanolic solution containing KOH (Scheme 10).



Scheme 10

Furthermore, the structure of **12** was established by spectroscopic and elemental analyses data. The IR spectra reveal a band attributed to the nitrile group at 2213–2223 cm^{-1} and the absence of a band assignable for the carbonyl group confirming the cyclized form structure. In addition, ^{1}H NMR spectra display the ethoxide protons at δ 1.46–1.54 ''triplet of CH_3''and at δ 4.55– 4.66 ''quartet for OCH_2'') confirming the involvement of ethoxide function.

Conclusions

We have developed an efficient synthesis of novel bis(nicotines) which are linked to ether linkage *via* phenyl groups. Full characterization of these compounds is reported. The newly synthesized compounds were easily prepared in good yields under mild reaction conditions from readily available starting materials. The synthetic strategies used in this work should provide access for novel new bis(functionalized) heterocycles with promising pharmacological and biological activities.

Experimental Section

General. Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded using an FTIR Bruker– vector 22 spectrophotometer as KBr pellets. The ^{1}H NMR spectra were recorded in DMSO–d6 as solvent on Varian Gemini NMR spectrometer at 400 MHz 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 or on an AccuTOF-T100LP (JEOL) mass spectrometer in ESI. The elemental analyses were performed at the Micro analytical center, Cairo University. Analytical thin layer chromatography was performed using pre-coated silica gel 60.778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Compounds **5**[33,39] and **6**[55] have been synthesized as previously reported.

General procedure for 4,4'-((Alkane-1,n-diylbis(oxy))bis(phenylene))bis(2-ethoxy-6-arylnicotinonitriles) (7a-d). Method A. A mixture of bisaldehyde derivative **(1)** (1 mmol) and malononitrile (2 mmol) in absolute ethanol (20 ml) was heated at reflux for 30 min. in the presence of piperidine as a catalyst. The obtained solid was filtered, washed with ethanol and added to a solution of the appropriate acetophenone derivative **(3a-c)** (2 mmol) in ethanolic KOH (20 ml, 4%). The reaction mixture was stirred overnight at room temperature. The resulting solid was collected by filteration, and was separated from traces of compounds **6** by preparative thin-layer chromatography using DCM as an eluent where compounds **7a-d** showed a value of R.F. equals to 0.92-0.98. Compounds **7a-d** were further purified by recrystallization from DMF/EtOH.

Method B. The appropriate acetophenone derivative **(3a-c)** (2 mmol) was dissolved in ethanolic KOH solution (20 ml, 4%) and added to a solution of the corresponding bisaldehyde **(1)** (1 mmol) in ethanol (10 ml). The reaction mixture was then stirred overnight to afford compounds **6a-d** which were filtered off and washed with ethanol. The solid product was added to malononitrile (2 mmol) in ethanolic KOH solution (20 ml, 4%). The reaction mixture was then heated at reflux for 2hr. The solid products obtained upon cooling were purified as described in method A to give compounds **7**.

4,4'-((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(2-ethoxy-6-phenylnicotinonitrile) (7a). (69% yield) as colorless crystals, mp 220^{o}C; IR (cm^{-1}): 2214 (CN), 1587 (C=N), 1244 (C-O-C); ESI-MS: *m/z* 695[M+Na^+] and 673 [M+H^+]; ^{1}H-NMR (300 MHz, DMSO): δ 141-1.46 (t, 6H, $2CH_3$, *J* 6.9 Hz), 2.25-2.29 (m, 2H, CH_2, *J* 6 Hz), 4.26-4.30

(t, 4H, $2CH_2$, *J* 6 Hz), 4.59-4.66 (q, 4H, $2CH_2$, *J* = 6.9 Hz), 7.16-8.24 (m, 18H, aromatic), 7.75 (s, 2H, H-5 pyridine); ^{13}C-NMR: δ 14.32, 62.97, 94.23, 113.28, 114.80, 115.58, 121.45, 127.34, 128.83, 130.21, 160.02. Anal. Calcd for $C_{43}H_{36}N_4O_4$ (672.79): C, 76.77; H, 5.39; N, 8.33. Found: C, 77.05; H, 5.22; N, 8.45.

4,4'-((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(2-ethoxy-6-(*p*-tolyl)nicotinonitrile) (7b).(66% yield) as colorless crystals, mp 235°C; IR (cm^{-1}): 2210 (CN), 1589 (C=N), 1238 (C-O-C); EI-MS: *m/z* 702 (M^++2, 4.37%), 700 (M^+, 19.25%), 386 (18.07%), 369 (27.81%), 267 (32.14%), 239 (63.03%)%), 105 (100.00%); ^{1}H-NMR (300 MHz, DMSO):δ 140-1.44 (t, 6H, $2CH_3$, *J* 7.2 Hz), 2.24-2.28(m, 2H, CH_2, *J* 6 Hz), 2.36 (s, 6H, $2CH_3$), 4.25-4.29 (t, 4H, $2CH_2$, *J* 6 Hz), 4.56-4.63 (q, 4H, $2CH_2$, *J* 7.2 Hz), 7.14-8.12 (m, 16H, aromatic), 7.67 (s, 2H, H-5 pyridine); ^{13}C-NMR: δ 14.29, 20.88, 62.86, 64.45, 78.05, 112.80, 114.75, 120.44, 120.46, 127.24, 128.05, 129.41, 130.14, 140.44, 159.96. Anal. Calcd for $C_{45}H_{40}N_4O_4$ (700.82): C, 77.12; H, 5.75; N, 7.99. Found: C, 77.37; H, 5.95; N, 8.32.

4,4'-((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(6-(4-chlorophenyl)-2-ethoxynicotinonitrile) (7c). (63% yield) as colorless crystals, mp 214°C; IR (cm^{-1}): 2215 (CN), 1587 (C=N), 1242 (C-O-C); ESI-MS: *m/z* 741[M+H^+]; ^{1}H-NMR (300 MHz, DMSO): δ 140-1.45 (t, 6H, $2CH_3$, *J* 6.9Hz), 2.24 (m, 2H, CH_2), 4.25-4.29 (t, 4H, $2CH_2$, *J* 5.7Hz), 4.55-4.61 (q, 4H, $2CH_2$, *J* 6.9Hz), 7.15-8.28 (m, 16H, aromatic), 7.78 (s, 2H, H-5 pyridine). Anal. Calcd for $C_{43}H_{34}Cl_2N_4O_4$ (741.66): C, 69.64; H, 4.62; Cl, 9.56; N, 7.55. Found: C, 69.77; H, 4.83; Cl, 9.32; N, 7.32.

4,4'-((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(2-ethoxy-6-(*p*-tolyl)nicotinonitrile) (7d) (61% yield) as a colorless crystals, mp 198°C; IR (cm^{-1}): 2221 (CN), 1590.02 (C=N), 1250 (C-O-C); ^{1}H-NMR (300 MHz, DMSO): δ 135-1.40 (t, 6H, $2CH_3$, *J* 6.9 Hz), 1.69 (t, 4H, $2CH_2$), 2.34(s, 6H, $2CH_3$), 3.96 (t, 4H, $2CH_2$), 4.51-4.58 (q, 4H, $2CH_2$, *J* 6.9 Hz), 7.02-8.04 (m, 16H, aromatic), 7.60 (s, 2H, H-5 pyridine). Anal. Calcd for $C_{46}H_{42}N_4O_4$ (686.80): C, 77.29; H, 5.92; N, 7.84. Found: C, 77.48; H, 5.65; N, 7.53.

General procedure for 6,6'-((alkane-1,n-diylbis(oxy))bis(2,1-phenylene))bis(2-ethoxy-4-Arylnicotinonitriles) (12a-e). Method A. Bis acetophenone derivative **(10)** (1 mmol) was dissolved in ethanolic KOH solution (20 ml, 4%) and added to a solution of the appropriate arylidenemalononitrile derivative **(11a-c)** (2 mmol). The reaction mixture was stirred overnight at room temperature. The solid products were collected by filteration, washed by water then by ethanol. The solid product were then separated from traces of compouds **13** by thin layer chromatography using DCM as an eluent where compounds **12a-e** showed a value of R.F. equals to 0.92-0.98. Compounds **12a-e** were further purified by recrystallization from ethanol.

Method B. The appropriate bis acetophenone derivative **(10)** (1 mmol) was dissolved in ethanolic KOH solution (20 ml, 4%) and added to a solution of the corresponding aromatic aldehyde **(17a-c)** (2 mmol) in ethanol (10 ml). The reaction mixture was then stirred overnight to afford **13a-e**. The solid product formed was collected by filteration, and added to malononitrile (2 mmol) in ethanolic KOH solution (20 ml, 4%). The reaction mixture was then heated at reflux with stirring for 2hr. The resulting solid products upon cooling were purified as described in method A to give compounds **12a-e**.

6,6'-((Propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(2-ethoxy-4-phenylnicotinonitrile) (12a). (71% yield) as colorless crystals, mp 157°C; IR (cm^{-1}): 2222 (CN), 1586 (C=N), 1234 (C-O-C); ESI-MS: *m/z* 1367 [2M+Na]$^+$ and 673 [M+H]$^+$; ^{1}H-NMR (300 MHz, DMSO): δ 1.22-1.43 (t, 6H, $2CH_3$, *J* 7.2 Hz), 2.16-2.19 (m, 2H, CH_2, *J* 5.4 Hz), 4.14-4.18 (t, 4H, $2CH_2$, *J* 5.4 Hz), 4.52-4.59 (q, 4H, $2CH_2$, *J* 7.2 Hz), 6.95-7.52 (m, 16H, aromatic), 7.68 (s, 2H, H-5 pyridine), 7.93-7.96 (dd, 2H, H-3 phenylene); ^{13}C-NMR: δ 14.29, 32.57, 62.96, 65.07, 91.57, 112.85, 115.22, 118.11, 120.87, 126.04, 128.12, 128.74, 129.79, 130.77, 130.87, 131.65, 135.93, 155.08, 155.97, 156.48, 163.54. Anal. Calcd for $C_{43}H_{36}N_4O_4$ (672.77): C, 76.77; H, 5.39; N, 8.33. Found: C, 76.35; H, 4.97; N, 8.05.

6,6'-((Propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(4-(4-chlorophenyl)-2-ethoxynicotinonitrile) (12b). (62% yield) as colorless crystals, mp 185°C; IR (cm^{-1}): 2218 (CN), 1589 (C=N), 1238 (C-O-C); ^{1}H-NMR (300 MHz, DMSO): δ 1.38-1.43 (t, 6H, $2CH_3$, *J* 6 Hz), 2.19 (m, 2H, CH_2), 4.15-4.15 (t, 4H, $2CH_2$), 4.52-4.59 (q, 4H, $2CH_2$, *J* 6

Hz), 6.98-7.52 (m, 14H, aromatic), 7.67 (s, 2H, H-5 pyridine), 7.95-7.98 (dd, 2H, H-3 phenylene). Anal. Calcd for $C_{43}H_{34}Cl_2N_4O_4$ (741.66): C, 69.64; H, 4.62; Cl, 9.56; N, 7.55. Found: C, 69.41; H, 4.46; Cl, 9.78; N, 7.81.

6,6'-((Propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(2-ethoxy-4-(*p*-tolyl)nicotinonitrile) (12c). (78% yield) as colorless crystals, mp 170°C; IR (cm^{-1}): 2222 (CN), 1587 (C=N), 1235 (C-O-C); ^{1}H-NMR (300 MHz, DMSO): δ 138-1.42 (t, 6H, $2CH_3$, *J* 6.9 Hz), 2.20 (m, 2H, CH_2), 2.26 (s, 6H, $2CH_3$), 4.17-4.21 (t, 4H, $2CH_2$, *J* 6 Hz), 4.52-4.56 (q, 4H, $2CH_2$, *J* 6.9 Hz), 7.00-7.40 (m, 14H, aromatic), 7.67 (s, 2H, H-5 pyridine), 7.96-7.98 (d, 2H, H-3 phenylene); ^{13}C-NMR: δ 14.32, 20.74, 63.12, 65.11, 91.33, 112.80, 115.33, 117.89, 120.51, 120.58, 120.86, 125.96, 127.90, 129.28, 130.80, 131.57, 133.03, 133.11, 139.60, 155.02, 155.80, 156.51, 163.60. Anal. Calcd for $C_{45}H_{40}N_4O_4$ (700.82): C, 77.12; H, 5.75; N, 7.99. Found: C, 77.48; H, 5.68; N, 8.19.

6,6'-((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(4-(4-chlorophenyl)-2-ethoxynicotinonitrile) (12d). (59% yield) as colorless crystals, mp 141°C; IR (cm^{-1}): 2223 (CN), 1587 (C=N), 1236 (C-O-C); ^{1}H-NMR (300 MHz, DMSO): δ 141-1.46 (t, 6H, $2CH_3$, *J* 6.9 Hz), 1.81 (t, 4H, $2CH_2$), 3.94 (t, 4H, $2CH_2$), 4.57-4.64 (q, 4H, $2CH_2$, *J* 6.9 Hz), 7.04-7.51 (m, 14H, aromatic), 7.63 (s, 2H, H-5 pyridine), 8.07-8.10 (dd, 2H, H-3 phenylene); ^{13}C-NMR: δ 14.27, 26.55, 63.02, 67.68, 91.10, 112.50, 114.97, 117.89, 120.43, 120.70, 125.31, 128.39, 129.69, 130.80, 131.83, 134.41, 134.65, 153.57, 155.70, 156.97, 164.24. Anal. Calcd for $C_{44}H_{36}Cl_2N_4O_4$ (755.69): C, 69.93; H, 4.80; Cl, 9.38; N, 7.41. Found: C, 69.71; H, 4.68; Cl, 9.02; N, 7.76.

6,6'-((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(2-ethoxy-4-phenylnicotinonitrile) (12e) (69% yield) as colorless crystals, mp 152°C; IR (cm^{-1}): 2221 (CN), 1583 (C=N), 1232 (C-O-C); EI-MS: *m/z* 686 (M^+, 3.62%), 643 (11.27%), 316 (66.51%), 301 (57.07%), 55 (100%); ^{1}H-NMR (300 MHz, DMSO): δ 140-1.45 (t, 6H, $2CH_3$, *J* 7.2 Hz), 1.81(t, 4H, $2CH_2$), 3.95 (t, 4H, $2CH_2$), 4.55-4.62 (q, 4H, $2CH_2$, J 7.2 Hz), 7.04-7.50 (m, 14H, aromatic), 7.69 (s, 2H, H-5 pyridine), 8.04-8.07 (dd, 2H, H-3 phenylene). Anal. Calcd for $C_{44}H_{38}N_4O_4$ (686.80): C, 76.95; H, 5.58; N, 8.16. Found: C, 76.72; H, 5.35; N, 8.44.

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