# Highly efficient four-component synthesis of 2-amino-3-cyanopyridines using doped nano-sized copper(I) oxide ($Cu_2O$) on melamine–formaldehyde resin

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A convenient and facile four-component synthesis is described of 2-amino-3-cyanopyridine derivatives from readily available starting materials catalysed by doped nano-sized $Cu_2O$ on melamine–formaldehyde resin (nano-$Cu_2O$–MFR). In this method, treatment of different aldehydes, ketones, malononitrile, and ammonium acetate in refluxing $H_2O$/EtOH (1:1) in the presence of doped nano-$Cu_2O$–MFR as a highly efficient heterogeneous catalyst affords the corresponding 2-amino-3-cyanopyridines in good to excellent yields. The nano-$Cu_2O$–MFR is a cheap and stable nano-catalyst that could be easily recovered and reused for many consecutive reaction runs without considerable decrease in its activity.

**Keywords:** 2-amino-3-cyanopyridine, heterogeneous nano-catalyst, multi-component reaction, nano-$Cu_2O$–MFR, one-pot synthesis, pyridine derivatives

Due to numerous applications of heterocyclic compounds especially *N*-heterocyclic derivatives in different area of sciences, a great deal of research effort has been focused on developing simple and efficient synthetic procedures for their construction. Among heterocyclic compounds, the pyridine substructure is well known as an important sub-structure found in a variety of natural and synthetic products exhibiting a wide range of biological and pharmacological properties.[1] The naturally occurring compounds like vitamins $B_3$ and $B_6$, nicotine, and nicotinamide adenine dinucleotide phosphate (NADP) contain a pyridine moiety in their structures. In addition, the pyridine ring is a key structural motif present in plenty of drugs having a broad range of biological and pharmacological properties. Moreover, some pyridine derivatives are also involved in coordination chemistry, organocatalysis, supramolecular structures, polymers, non-linear optical materials, electrical materials and agrochemicals.[1] Among pyridine derivatives, 2-amino-3-cyanopyridines have attracted considerable attention due to their remarkable biological properties. 2-Amino-3-cyanopyridine derivatives display abundant biological activities such as anticancer, anti-inflammatory, antiviral, antimicrobial, antihypertensive, antitubercular and antioxidant properties. They have also proved to be potent inhibitors of HIV-1 itegrase and IKK-β as well as $A_{2A}$ adenosine receptor antagonists. Moreover, they have been frequently used as valuable intermediates for the construction of a variety of heterocyclic derivatives.[1]

Due to the remarkable biological properties associated with 2-amino-3-cyanopyridines, many synthetic approaches have been developed to access structurally diverse 2-amino-3-cyanopyridine derivatives.[2] Although most of these procedures are useful and efficient, they are accompanied by one or more drawbacks such as the use of toxic solvents, utilising expensive metal catalysts, long reaction times, complicated reaction procedures, harsh reaction conditions, tedious work-ups, multi-step syntheses, and unsatisfactory yield of the desired products.

Multi-component reactions (MCRs) have emerged as powerful and attractive strategies in medicinal, combinatorial, and organic chemistry.[3] These reactions provide straightforward and rapid access to complex molecules from simple, available precursors in a single step without the isolation of intermediates. Therefore, MCRs are associated with many advantages like atom economy, minimisation of chemical waste and thus lower environmental costs, quantitative yields, and simple experimental procedures. Particularly, MCRs have been widely applied for the construction of structurally diverse heterocyclic compounds.[3] In this regard, the most extensively used strategy for synthesis of 2-amino-3-cyanopyridine derivatives involves the four-component reaction (4CR) of diverse aldehydes, ketones, malononitrile, and ammonium acetate in different conditions.[2] However, the applicability of these methods were restricted by one or more drawbacks like the use of expensive and nonreusable catalysts, unsatisfactory yields, long reaction times, limited scope of substrates, and the use of microwave or ultrasound irradiations. Hence, the development of efficient and applicable methods with suitable generality for synthesis of 2-amino-3-cyanopyridines still remains of great importance.

In recent years, the use of heterogeneous catalysts has attracted much more attention from both environmental and economic concerns. The use of heterogeneous catalysts in organic synthesis offers attractive advantages like thermal stability of the catalyst, minimisation of the chemical wastes, ease of operation, mild reaction conditions, recyclability and reusability of the catalyst. Heterogeneous catalysts have been efficiently employed in various multi-component reactions.[4] It was recently reported that the application of copper nanoparticles on a charcoal catalyst (Cu/C) for the 4CR of aldehyde, ketone, malononitrile, and ammonium acetate in refluxing MeCN afforded the corresponding 2-amino-3-cyanopyridines.[5]

Melamine–formaldehyde resin (MFR) has a unique chemical structure which makes it a suitable and useful solid support for absorbing different metal salts to afford valuable heterogeneous catalysts. The schematic view for the potential hosting of cation and anion by MFR is shown in Fig. 1.[6] Previously, we reported the synthesis and application of doped nano-sized $Cu_2O$ on melamine–formaldehyde resin (nano-$Cu_2O$–MFR) as a novel and highly efficient heterogeneous catalyst in click syntheses of 1,4-disubstituted-1*H*-1,2,3-triazoles having antibacterial activity.[6]

Inspired by the remarkable biological activities of 2-amino-3-cyanopyridines and in continuation of our effort to discover the new applications for nano-$Cu_2O$–MFR in organic synthesis, hereby, we would like report a facile and straightforward synthesis of structurally diverse 2-amino-3-cyanopyridine derivatives *via* the four-component reaction of different aldehydes, ketones, malononitrile, and ammonium acetate in refluxing $H_2O$/EtOH (1:1) in the presence of doped nano-$Cu_2O$–MFR (Scheme 1).

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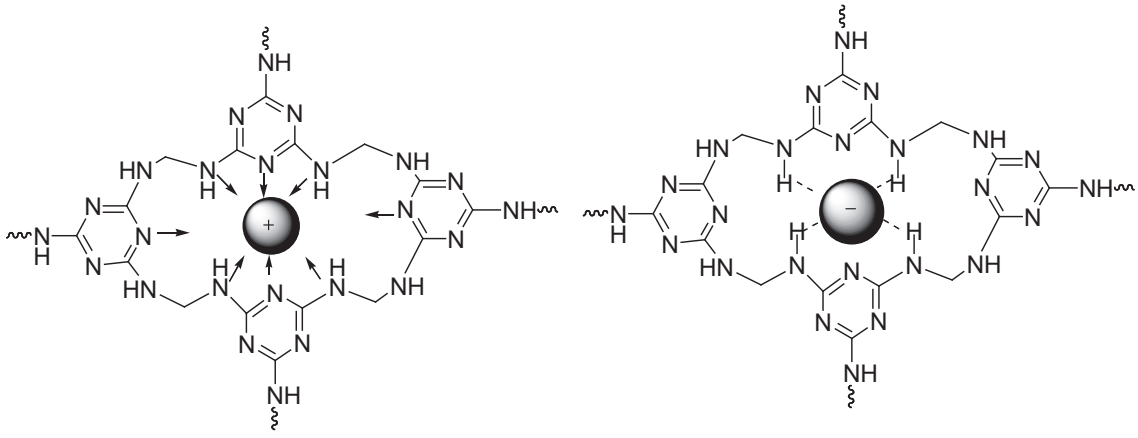
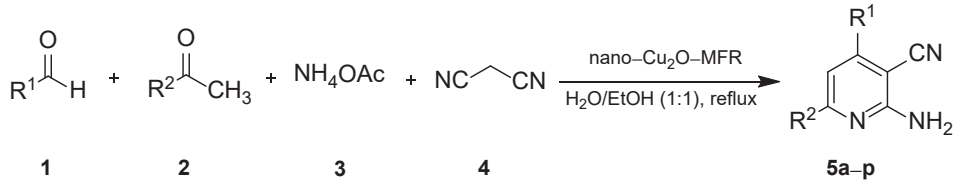


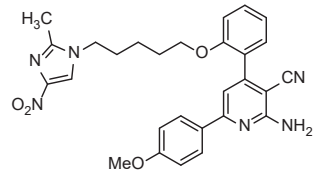
**Fig. 1** The schematic view for the potential hosting of cation (left) and anion (right) by MFR.



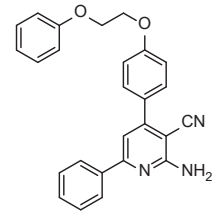

**1** **2** **3** **4** **5a–p**

**5a**: $R^1$= $C_6H_5$; $R^2$= $C_6H_5$
**5b**: $R^1$= 4-Cl–$C_6H_4$; $R^2$= $C_6H_5$
**5c**: $R^1$= pyridin-4-yl; $R^2$= $C_6H_5$
**5d**: $R^1$= thiophen-3-yl; $R^2$= $C_6H_5$
**5e**: $R^1$= Me; $R^2$= $C_6H_5$
**5f**: $R^1$= $C_6H_5$; $R^2$= naphthalen-2-yl
**5g**: $R^1$= $C_6H_5$; $R^2$= Me
**5h**: $R^1$= $C_6H_5$; $R^2$= $(Me)_3C$
**5i**: $R^1$= 2-Cl–$C_6H_4$; $R^2$= 4-OH–$C_6H_4$
**5j**: $R^1$= 3-Br–$C_6H_4$; $R^2$= 4-OH–$C_6H_4$
**5k**: $R^1$= 4-Me–$C_6H_4$; $R^2$= 4-Br–$C_6H_4$
**5l**: $R^1$= 4-OMe–$C_6H_4$; $R^2$= 4-Cl–$C_6H_4$
**5m:** $R^1$= 4-Cl–$C_6H_4$; $R^2$= 4-Cl–$C_6H_4$
**5n:** $R^1$= furan-2-yl; $R^2$= 4-Me–$C_6H_4$

**5o:**



**5p:**



**Scheme 1** Four-component synthesis of 2-amino-3-cyanopyridines **5** using nano-$Cu_2O$–MFR and reactants **1–4**.

## Results and discussion

The first step of this synthetic approach was begun with the optimisation of the reaction conditions. To identify the optimised reaction conditions, 4CR of benzaldehyde, acetophenone, malononitrile, and ammonium acetate in the presence of doped nano-$Cu_2O$–MFR was investigated as a sample reaction. Therefore, the influence of several effective reaction parameters on the progress of the reaction including solvent type, temperature, and catalyst loading were studied in sample reactions to afford 2-amino-4,6-diphenylnicotinonitrile (**5a**). The results obtained are shown in Table 1.

The choice of a suitable solvent is important for the satisfactory conduct of the reaction. In recent years, the use of water as a solvent in reactions has attracted increasingly significant interest mainly from the viewpoints of green chemistry and economic factors. Thus, our initial attempt was to carry out the model reaction in pure water as the green solvent. Thus the model reaction was carried out in refluxing water which affords 81% of 2-amino-4,6-diphenylnicotinonitrile after 2.5 h (Table 1, entry 1). To improve the yield, the effect of water with several polar and nonpolar solvents in 1:1 ratio was screened (Table 1, entries 2–7). As the results in Table 1 indicate, the use of water in combination with the examined solvents afforded low to moderate yields of the desired product **5a** (entries 2 and 4–7). The best result was obtained when a solution of $H_2O$/EtOH (1:1) was employed as the solvent (Table 1, entry 3). Consequently, it was the solvent of choice for achieving all subsequent reactions. In the same circumstances, the use of pure EtOH under reflux conditions did not affect the reaction efficiency (Table 1, entry 8).

We further studied the effect of different temperatures on the progress of the model reaction (Table 1, entries 3 and 9–11). As the data in Table 1 demonstrates, increasing the reaction temperature up to reflux conditions dramatically improved the reaction efficiency (entries 3, 9, and 10). However, a further raise of the reaction temperature led to no distinguishable effect on the progress of the reaction (Table 1, entry 11).

In another complementary experiment, the effect of different amounts of nano-$Cu_2O$–MFR was examined in the current protocol (Table 1, entries 3, 12, and 13). As it is clear from Table 1, when the catalyst loading was increased up to 0.072 mol%, higher yields of product in shorter reaction times were attained (entries 3 and 12). Increasing the catalyst

**Table 1** Effect of various reaction parameters on the model reaction

| Entry | Solvent | Catalyst/mol% | Temperature/°C | Time/h | Yield[c]/% |
|---|---|---|---|---|---|
| 1 | $H_2O$ | nano-$Cu_2O$–MFR (0.072) | reflux | 2.5 | 81 |
| 2 | $H_2O$/toluene[a] | nano-$Cu_2O$–MFR (0.072) | reflux | 3 | 67 |
| 3 | $H_2O$/EtOH[a] | nano-$Cu_2O$–MFR (0.072) | reflux | 1 | 92 |
| 4 | $H_2O$/EtOAc[a] | nano-$Cu_2O$–MFR (0.072) | reflux | 2 | 70 |
| 5 | $H_2O$/DMF[a] | nano-$Cu_2O$–MFR (0.072) | 100 | 4 | 65 |
| 6 | $H_2O$/THF[a] | nano-$Cu_2O$–MFR (0.072) | reflux | 5 | 46 |
| 7 | $H_2O$/MeCN[a] | nano-$Cu_2O$–MFR (0.072) | reflux | 4 | 79 |
| 8 | EtOH | nano-$Cu_2O$–MFR (0.072) | reflux | 3 | 83 |
| 9 | $H_2O$/EtOH[a] | nano-$Cu_2O$–MFR (0.072) | r.t. | 5 | 69 |
| 10 | $H_2O$/EtOH[a] | nano-$Cu_2O$–MFR (0.072) | 70 | 2 | 85 |
| 11 | $H_2O$/EtOH[a] | nano-$Cu_2O$–MFR (0.072) | 110[b] | 1 | 92 |
| 12 | $H_2O$/EtOH[a] | nano-$Cu_2O$–MFR (0.048) | reflux | 1.8 | 89 |
| 13 | $H_2O$/EtOH[a] | nano-$Cu_2O$–MFR (0.096) | reflux | 1 | 92 |
| 14 | $H_2O$/EtOH[a] | CuI | reflux | 3 | 75 |
| 15 | $H_2O$/EtOH[a] | $Cu(OAc)_2$ | reflux | 3 | 71 |
| 16 | $H_2O$/EtOH[a] | CuO | reflux | 3 | 70 |

[a]A mixture of 1:1 solvents were used.
[b]Sealed tube was used.
[c]Isolated yield.

resulted in no improvement in the yield of **5** (Table 1, entry 13). Consequently, 0.072 mol% of nano-$Cu_2O$–MFR was employed for efficient performance of all reactions.

To evaluate the catalytic potency of nano-$Cu_2O$–MFR, 4CR of model substrates was investigated using several copper catalysts under the optimised conditions (Table 1, entries 3 and 14–16). As shown in Table 1, the model reaction was efficiently achieved using nano-$Cu_2O$–MFR to afford 92% of the desired product **5a** (entry 3). The use of other catalysts, such as CuI, $Cu(OAc)_2$ and CuO, provided moderate yields of **5a** (entries 14–16). The satisfactory outcome attained by nano-$Cu_2O$–MFR can be attributed to the presence of a large surface area and the chemical and thermal stability of nano-$Cu_2O$–MFR under the optimised reaction conditions.

An appropriate stoichiometric ratio for aldehyde **1**, ketone **2**, malononitrile **3**, and ammonium acetate **4** to afford 2-amino-4,6-diphenylnicotinonitrile **5** in excellent yield under the optimised conditions was found to be 1:1:1.3:1.5 respectively.

With optimised reaction conditions in hand, we then screened the scope, versatility and general applicability of the present protocol in 4CR of structurally diverse aldehydes, ketones, malononitrile, and ammonium acetate in the presence of doped nano-$Cu_2O$–MFR (Table 2). As is clear from Table 2, doped nano-$Cu_2O$–MFR was shown to be a suitable nano-catalyst that effectively catalyses the present four-component synthesis of 2-amino-3-cyanopyridines.

As shown in Table 2, all reactions proceeded smoothly to afford the desired 2-amino-3-cyanopyridine derivatives in good to excellent yields. Aliphatic, heteroaromatic, and aromatic aldehydes bearing electron rich or electron deficient substituents were used and led to the desired products in good to excellent yields. The application to sterically hindered *ortho*-substituted benzaldehydes provides the desired products **5i** and **5o** in reasonable yields (Table 2, entries 9 and 15). In a further exploration of the reaction scope, the optimised reaction conditions were exploited for different aliphatic and aromatic ketones. It was found that structurally diverse ketones successfully underwent this transformation resulting in good to excellent yields of the desired products in short reaction times.

The applicability of the present protocol on a large scale was investigated by its application for the model reaction under the optimised reaction conditions on a 50 mmol scale which led to the formation of **5a** in 90% yield.

**Table 2** Doped nano-$Cu_2O$–MFR-catalysed synthesis of 2-amino-3-cyanopyridines

| Entry[ref.] | Product[a] | Time/h | Yield[b]/% |
|---|---|---|---|
| 1[7] | **5a** | 1 | 92 |
| 2[7] | **5b** | 1 | 94 |
| 3[8] | **5c** | 1 | 93 |
| 4[5] | **5d** | 1.4 | 89 |
| 5[5] | **5e** | 1.6 | 80 |
| 6[5] | **5f** | 1.6 | 87 |
| 7[5] | **5g** | 1.7 | 85 |
| 8[5] | **5h** | 2 | 82 |
| 9[8] | **5i** | 2 | 77 |
| 10[8] | **5j** | 1.3 | 91 |
| 11[9] | **5k** | 1.3 | 87 |
| 12[7] | **5l** | 1.2 | 88 |
| 13[9] | **5m** | 1 | 93 |
| 14[9] | **5n** | 1.5 | 75 |
| 15 | **5o** | 2 | 74 |
| 16 | **5p** | 1.3 | 90 |

[a]All products were characterised by $^1H$ and $^{13}C$ NMR, IR, CHN, and MS analysis.
[b]Isolated yield.

We also studied the reusability of doped nano-$Cu_2O$–MFR under the optimised reaction conditions (Table 3). The ease of recovery, chemical and thermal stability of nano-$Cu_2O$–MFR allows it to be a recyclable and reusable catalyst which can be efficiently applied for at least 7 reaction runs (Table 3). According to the ICP analysis, the amount of leached copper from nano-$Cu_2O$–MFR is 0.0016% after seven consecutive runs which is essentially negligible.

It is well-established that 1,4-dihydropyridines (1,4-DHPs) are obtained as the main intermediates in the 4CR of aldehydes, ketones, malononitrile, and ammonium acetate and then their subsequent oxidation leads to the formation of the corresponding pyridine derivatives.[1] In the present protocol, the reaction was performed in an open flask under an air atmosphere. Thus, oxidative aromatisation of the 1,4-DHPs efficiently affords the desired pyridine derivatives.

**Table 3** The reusability of nano-$Cu_2O$–MFR

| Run[a] | Time/h | Yield[b]/% |
|---|---|---|
| 1 | 1 | 92 |
| 2 | 1 | 92 |
| 3 | 1 | 91 |
| 4 | 1.1 | 91 |
| 5 | 1.1 | 90 |
| 6 | 1.3 | 89 |
| 7 | 1.3 | 89 |

[a]The entry number corresponds to the trial number.

[b]Isolated yield.

In conclusion, we have described a direct and simple one-pot procedure for synthesis of 2-amino-3-cyanopyridins *via* four-component reaction of aldehydes, ketones, malononitrile, and ammonium acetate in refluxing $H_2O$/EtOH (1:1) in the presence of doped nano-$Cu_2O$–MFR as a highly efficient heterogeneous catalyst. In this protocol, structurally diverse aldehydes and ketones were used successfully to afford the desired pyridine derivatives in good to excellent yields. The nano-$Cu_2O$–MFR is a cheap and stable heterogeneous nano-catalyst that could be simply prepared, recovered, and reused for many reaction runs without considerable reduction in activity.

## Experimental

All chemical reagents were purchased from either Fluka or Merck. Nano-$Cu_2O$–MFR was prepared due to the established procedure.[6] Solvents were purified by standard procedures, and stored over 3Å molecular sieves. Reactions were followed by TLC using SILG/UV 254 silica gel plates. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, 70-230 mesh; ASTM). Melting points were measured using Electrothermal IA 9000 melting point apparatus in open capillary tubes and are uncorrected. IR spectra were obtained using a Shimadzu FTIR-8300 spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded on Brüker Avance-DPX-250/400 spectrometer operating at 250/62.5 MHz, respectively. Chemical shifts are given in δ relative to tetramethylsilane (TMS) as an internal standard, coupling constants *J* are given in Hz. GC/MS was performed on a Shimadzu GC/MS-QP 1000-EX apparatus (m/z; rel.%). Elemental analyses were performed on a Perkin–Elmer 240-B micro-analyser.

*Synthesis of 2-amino-3-cyanopyridines using nano-$Cu_2O$–MFR; general procedure*

In a two-neck round-bottom flask (50 mL) equipped with a condenser was added a mixture of aldehyde (10 mmol), ketone (10 mmol), malononitrile (13 mmol), ammonium acetate (15 mmol), and nano-$Cu_2O$–MFR (0.3 g, 0.072 mol%) in refluxing $H_2O$/EtOH (1:1). After completion of the reaction as indicated by TLC monitoring (Table 2), the reaction mixture was vacuum-filtered using a sintered-glass funnel and the residue was washed with hot EtOH (2 × 10 mL). The filtrate was then evaporated under vacuum to remove the solvent. The remaining foam was dissolved in $CHCl_3$ (100 mL) and subsequently washed with water (2 × 100 mL). Afterward, the organic layer was dried over anhydrous sodium sulfate and evaporated. The crude product was purified by short column chromatography on silica gel eluting with *n*-hexane:EtOAc.

*Recycling the catalyst*

After completion of the reaction, the catalyst was vacuum-filtered from the reaction mixture using a sintered glass funnel followed by successive washing with hot EtOH (2 × 10 mL). The catalyst was then kept in a vacuum oven at 100 °C for 30 minutes and stored in a sealed vessel in a refrigerator.

*2-Amino-4,6-diphenylnicotinonitrile* (**5a**): Pale yellow solid; yield 92%; m.p. 186–187 °C (lit.[7] 186 °C); IR ($\nu_{max}$/cm$^{-1}$): 3427, 3304, 3037, 2204, 1621, 1566, 1454; $^1$H NMR ($CDCl_3$, 250 MHz) δ 5.68 (s, 2H, $NH_2$), 7.21 (s, 1H, pyridine–H5), 7.45–7.61 (m, 8H, ArH), 7.73 (d, *J* = 8.1 Hz, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 92.4, 109.8, 115.0, 115.9, 126.7, 127.3, 128.1, 128.7, 129.5, 130.4, 135.1, 154.9, 157.8, 160.4; MS (EI) *m/z* (%): 271 (11.5) [M]$^+$; Anal. calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49; found: C, 79.76; H, 4.95; N, 15.57%.

*2-Amino-4-(4-chlorophenyl)-6-phenylnicotinonitrile* (**5b**): Pale yellow solid; yield 94%; m.p. 192–193 °C (lit.[7] 190 °C); IR ($\nu_{max}$/cm$^{-1}$): 3400, 3267, 3050, 2201, 1624, 1576, 1470, 1078; $^1$H NMR ($CDCl_3$, 250 MHz) δ 5.71 (s, 2H, $NH_2$), 7.18 (s, 1H, pyridine–H5), 7.27–7.36 (m, 7H, ArH), 7.51 (d, *J* = 8.3 Hz, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 91.8, 109.1, 114.8, 115.6, 127.3, 128.0, 128.7, 130.6, 134.0, 135.2, 136.1, 153.9, 157.8, 160.7; MS (EI) *m/z* (%): 271 (14.8) [M]$^+$; Anal. calcd for $C_{18}H_{12}ClN_3$: C, 70.71; H, 3.96; N, 13.74; found: C, 70.85; H, 4.07; N, 13.82%.

*2-Amino-6-phenyl-4,4'-bipyridine-3-carbonitrile* (**5c**): White solid; yield 93%; m.p. 217–218 °C (lit.[8] 215–218 °C); IR ($\nu_{max}$/cm$^{-1}$): 3360, 3280, 3037, 2214, 1629, 1571, 1456; $^1$H NMR (DMSO-$d_6$, 250 MHz) δ 5.93 (s, 2H, $NH_2$), 7.24–7.50 (m, 6H, ArH), 7.69–7.74 (m, 4H, ArH); $^{13}$C NMR (DMSO-$d_6$, 62.5 MHz) δ 95.2, 110.9, 113.8, 123.8, 126.0, 127.1, 130.5, 138.7, 145.0, 149.6, 152.1, 156.7, 163.4; MS (EI) *m/z* (%): 272 (17.5) [M]$^+$; Anal. calcd for $C_{17}H_{12}N_4$: C, 74.98; H, 4.44; N, 20.58; found: C, 75.04; H, 4.51; N, 20.67%.

*2-Amino-6-phenyl-4-(thiophen-3-yl)nicotinonitrile* (**5d**): White solid; yield 89%; m.p. 212–213 °C (lit.[5] 213–214 °C); IR ($\nu_{max}$/cm$^{-1}$): 3400, 3304, 3025, 2213, 1643, 1575, 1450; $^1$H NMR ($CDCl_3$, 250 MHz) δ 5.48 (s, 2H, $NH_2$), 7.12 (s, 1H, pyridine-H5), 7.31–7.38 (m, 6H, ArH), 7.54 (d, *J* = 8.0 Hz, 1H, thiophene-H5), 7.85 (s, 1H, thiophene-H2); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 94.0, 111.6, 119.8, 121.5, 126.8, 127.9, 128.7, 129.2, 131.1, 132.9, 138.3, 152.6, 157.2, 162.0; MS (EI) *m/z* (%): 277 (21.6) (M$^+$); Anal. calcd for $C_{16}H_{11}N_3S$: C, 69.29; H, 4.00; N, 15.15; Found: C, 69.38; H, 4.13; N, 15.26%.

*2-Amino-4-methyl-6-phenylnicotinonitrile* (**5e**): White solid; yield 80%; m.p. 121–122 °C (lit.[5] 121–122 °C); IR ($\nu_{max}$/cm$^{-1}$): 3455, 3349, 3060, 2985, 2213, 1635, 1558, 1461; $^1$H NMR ($CDCl_3$, 250 MHz) δ 2.29 (s, 3H, $CH_3$), 5.37 (s, 2H, $NH_2$), 7.15 (s, 1H, pyridine-H5), 7.24–7.31 (m, 3H, ArH), 7.72–7.78 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 22.0, 93.7, 114.6, 117.8, 127.0, 128.2, 129.7, 136.4, 152.9, 157.0, 161.8; MS (EI) *m/z* (%): 209 (18.7) [M]$^+$; Anal. calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08; found: C, 74.53; H, 5.36; N, 20.17%.

*2-Amino-6-(naphthalen-2-yl)-4-phenylnicotinonitrile* (**5f**): White solid; yield 87%; m.p. 169–170 °C (lit.[5] 171–172 °C); IR ($\nu_{max}$/cm$^{-1}$): 3460, 3353, 3081, 2210, 1658, 1546, 1459; $^1$H NMR ($CDCl_3$, 250 MHz) δ 5.26 (s, 2H, $NH_2$), 7.11 (s, 1H, pyridine-H5), 7.29–7.37 (m, 4H, ArH), 7.57–7.65 (m, 4H, ArH), 7.80–7.86 (m, 3H, ArH), 8.23 (s, 1H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 95.4, 112.0, 118.1, 124.6, 126.1, 127.0, 127.6, 128.0, 128.5, 128.8, 129.2, 129.7, 130.2, 130.8, 133.8, 134.5, 136.3, 154.7, 158.0, 162.7; MS (EI) *m/z* (%): 321 (25.8) [M]$^+$; Anal. calcd for $C_{22}H_{15}N_3$: C, 82.22; H, 4.70; N, 13.08; found: C, 82.35; H, 4.79; N, 12.98%.

*2-Amino-6-methyl-4-phenylnicotinonitrile* (**5g**): White solid; yield 85%; m.p. 189–190 °C (lit.[5] 188–189 °C); IR ($\nu_{max}$/cm$^{-1}$): 3465, 3340, 3036, 2955, 2214, 1652, 1552, 1475; $^1$H NMR ($CDCl_3$, 250 MHz) δ 2.32 (s, 3H, $CH_3$), 5.65 (s, 2H, $NH_2$), 7.21-7.26 (m, 4H, ArH), 7.53–7.60 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 24.9, 92.8, 109.1, 115.6, 127.7, 128.3, 129.7, 136.8, 152.9, 158.5, 161.3; MS (EI) *m/z* (%): 209 (13.7) [M]$^+$; Anal. calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08; found: C, 74.76; H, 5.38; N, 20.19%.

*2-Amino-6-tert-butyl-4-phenylnicotinonitrile* (**5h**): White solid; yield 82%; m.p. 168–169 °C (lit.[5] 169–170 °C); IR ($\nu_{max}$/cm$^{-1}$): 3427, 3361, 3050, 2949, 2211, 1658, 1541, 1443; $^1$H NMR ($CDCl_3$, 250 MHz) δ 1.34 (s, 9H, 3 × $CH_3$), 5.21 (s, 2H, $NH_2$), 7.05 (s, 1H, pyridine-H5), 7.48–7.56 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 30.73, 35.29, 92.6, 108.5, 115.7, 127.4, 128.1, 129.0, 136.8, 153.6, 159.1, 160.7; MS (EI) *m/z* (%): 251 (18.3) [M]$^+$; Anal. calcd for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72; found: C, 76.58; H, 6.90; N, 16.81%.

*2-Amino-4-(2-chlorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile* (**5i**): White solid; yield 77%; m.p. 193–194 °C (lit.[8] 194–196 °C); IR

($\nu_{max}$/cm$^{-1}$): 3450, 3370, 3218, 3049, 2219, 1652, 1564, 1471, 1082; $^1$H NMR (DMSO-$d_6$, 250 MHz) δ 6.21 (s, 2H, $NH_2$), 7.10 (s, 1H, pyridine-H5), 7.36–7.41 (m, 4H, ArH), 7.57–7.62 (m, 2H, ArH), 7.82 (d, *J* = 8.4 Hz, 2H, ArH), 9.98 (s, 1H, OH); $^{13}$C NMR (DMSO-$d_6$, 62.5 MHz) δ 94.0, 109.7, 116.1, 117.8, 124.9, 127.2, 128.0, 128.5, 129.3, 130.7, 132.3, 136.6, 154.4, 158.9, 160.8, 162.5; MS (EI) *m/z* (%): 321 (25.1) [M]$^+$; Anal. calcd for $C_{18}H_{12}ClN_3O$: C, 67.19; H, 3.76; N, 13.06; found: C, 67.08; H, 3.85; N, 13.14%.

*2-Amino-4-(3-bromophenyl)-6-(4-hydroxyphenyl)nicotinonitrile* (**5j**): White solid; yield 91%; m.p. 227–228 °C (lit.[8] 226–229 °C); IR ($\nu_{max}$/cm$^{-1}$): 3410, 3385, 3348, 3050, 2223, 1659, 1546, 1464, 1070; $^1$H NMR (DMSO-$d_6$, 250 MHz) δ 6.29 (s, 2H, $NH_2$), 7.21 (s, 1H, pyridine-H5), 7.35–7.42 (m, 3H, ArH), 7.60 (d, *J* = 8.2 Hz, 2H, ArH), 7.81 (s, 1H, ArH), 7.98 (d, *J* = 8.2 Hz, 2H, ArH), 10.02 (s, 1H, OH); $^{13}$C NMR (DMSO-$d_6$, 62.5 MHz) δ 91.8, 108.9, 115.7, 116.5, 123.0, 126.1, 127.2, 128.0, 129.1, 129.7, 130.4, 137.5, 156.2, 159.6, 161.3, 163.0; MS (EI) *m/z* (%): 366 (29.4) [M]$^+$; Anal. calcd for $C_{18}H_{12}BrN_3O$: C, 59.03; H, 3.30; N, 11.47; found: C, 59.15; H, 3.38; N, 11.60%.

*2-Amino-6-(4-bromophenyl)-4-*p*-tolylnicotinonitrile* (**5k**): Yellow solid; yield 87%; m.p. 236–237 °C (lit.[9] 235–237 °C); IR ($\nu_{max}$/cm$^{-1}$): 3435, 3371, 3085, 2948, 2210, 1634, 1570, 1439, 1061; $^1$H NMR ($CDCl_3$, 250 MHz) δ 2.28 (s, 3H, $CH_3$), 6.05 (s, 2H, $NH_2$), 7.15 (s, 1H, pyridine-H5), 7.37 (d, *J* = 8.1 Hz, 2H, ArH), 7.50 (d, *J* = 8.3 Hz, 2H, ArH), 7.74 (d, *J* = 8.1 Hz, 2H, a ArH), 7.81–7.85 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 23.5, 91.3, 108.4, 117.6, 123.9, 127.8, 128.3, 129.0, 132.1, 134.0, 136.8, 138.1, 154.9, 158.0, 162.1; MS (EI) *m/z* (%): 364 (23.3) [M]$^+$; Anal. calcd for $C_{19}H_{14}BrN_3$: C, 62.65; H, 3.87; N, 11.54; found: C, 62.54; H, 3.76; N, 11.60%.

*2-Amino-6-(4-chlorophenyl)-4-(4-methoxyphenyl)nicotinonitrile* (**5l**): Yellow solid; yield 88%; m.p. 175–176 °C (lit.[7] 177 °C); IR ($\nu_{max}$/cm$^{-1}$): 3410, 3365, 3100, 2941, 2215, 1653, 1568, 1457, 1126, 1080; $^1$H NMR ($CDCl_3$, 250 MHz) δ 3.47 (s, 3H, $CH_3$), 5.72 (s, 2H, $NH_2$), 7.24 (s, 1H, pyridine-H5), 7.47–7.56 (m, 4H, ArH), 7.70 (d, *J* = 8.0 Hz, 2H, ArH), 7.83 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 58.2, 94.0, 108.9, 114.3, 115.6, 127.2, 127.9, 128.4, 129.0, 129.7, 130.8, 134.7, 153.9, 158.0, 162.6; MS (EI) *m/z* (%): 335 (27.1) [M]$^+$; Anal. calcd for $C_{19}H_{14}ClN_3O$: C, 67.96; H, 4.20; N, 12.51; found: C, 67.82; H, 4.27; N, 12.64%.

*2-Amino-4,6-bis(4-chlorophenyl)nicotinonitrile* (**5m**): Yellow solid; yield 93%; m.p. 248–249 °C (lit.[9] 248–250 °C); IR ($\nu_{max}$/cm$^{-1}$): 3400, 3352, 3064, 2207, 1657, 1535, 1426, 1088; $^1$H NMR ($CDCl_3$, 250 MHz) δ 5.78 (s, 2H, $NH_2$), 7.19 (s, 1H, pyridine-H5), 7.25–7.33 (m, 4H, ArH), 7.69–7.76 (m, 4H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 95.7, 110.5, 116.9, 126.3, 127.7, 128.0, 128.8, 129.4, 130.0, 132.1, 136.6, 154.1, 158.8, 162.9; MS (EI) *m/z* (%): 340 (31.4) [M]$^+$; Anal. calcd for $C_{18}H_{11}Cl_2N_3$: C, 63.55; H, 3.26; N, 12.35; found: C, 63.64; H, 3.37; N, 12.41%.

*2-Amino-4-(furan-2-yl)-6-*p*-tolylnicotinonitrile* (**5n**): Pale yellow solid; yield 75%; m.p. 147–148 °C (lit.[9] 149–151 °C); IR ($\nu_{max}$/cm$^{-1}$): 3407, 3359, 3050, 2947, 2205, 1651, 1545, 1463 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 250 MHz) δ 2.41 (s, 3H, $CH_3$), 5.93 (s, 2H, $NH_2$), 7.18–7.26 (m, 3H, ArH), 7.40–7.46 (m, 2H, ArH), 7.79–7.85 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 21.7, 97.1, 112.8, 113.5, 117.9, 127.4, 129.0, 135.0, 139.2, 141.8, 145.4, 146.1, 148.2, 158.9, 162.7; MS (EI) *m/z* (%): 275 (16.8) [M]$^+$; Anal. calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26; found: C, 74.26; H, 4.87; N, 15.17%.

*2-Amino-6-(4-methoxyphenyl)-4-{2-[5-(2-methyl-4-nitro-1*H*-imidazol-1-yl)pentyloxy] phenyl} nicotinonitrile* (**5o**): Yellow foam; yield 74%; IR ($\nu_{max}$/cm$^{-1}$): 3400, 3376, 3100, 2969, 2218, 1664, 1552, 1539, 1470, 1348, 1124; $^1$H NMR ($CDCl_3$, 250 MHz) δ 1.21–1.27 (m, 2H, $CH_2$), 1.86–1.93 (m, 4H, 2 × $CH_2$), 2.45 (s, 3H, $CH_3$), 3.47 (t, *J* = 7.5 Hz, 2H, $NCH_2$), 3.65 (s, 3H, $OCH_3$), 3.82 (t, *J* = 7.5 Hz, 2H, $OCH_2$), 6.08 (s, 2H, $NH_2$), 7.14 (s, 1H, pyridine-H5), 7.29–7.53 (m, 6H, ArH), 7.85 (s, 1H, imidazole-H5), 7.97 (d, *J* = 8.1 Hz, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 15.8, 24.1, 29.7, 32.0, 48.1, 54.5, 67.0, 96.1, 112.0, 115.2, 116.8, 120.1, 120.8, 127.4, 128.1, 128.9, 129.2, 129.6, 136.8, 146.3, 150.9, 153.6, 156.7, 158.6, 160.2, 163.4; MS (EI) *m/z* (%): 512 (27.4) [M]$^+$; Anal. calcd for $C_{28}H_{28}N_6O_4$: C, 65.61; H, 5.51; N, 16.40; found: C, 65.70; H, 5.43; N, 16.52%.

*2-Amino-4-[4-(2-phenoxyethoxy)phenyl]-6-phenylnicotinonitrile* (**5p**): Pale yellow oil; yield 90%; IR ($\nu_{max}$/cm$^{-1}$): 3415, 3370, 3056, 2972, 2210, 1659, 1540, 1461, 1128; $^1$H NMR ($CDCl_3$, 250 MHz) δ 3.97 (t, *J* = 7.3 Hz, 2H, $OCH_2$), 4.12 (t, *J* = 7.3 Hz, 2H, $OCH_2$), 5.91 (s, 2H, $NH_2$), 7.17–7.41 (m, 4H, ArH), 7.50–7.56 (m, 3H, ArH), 7.80–7.87 (m, 4H, ArH), 7.91 (d, *J* = 8.1 Hz, 2H, ArH), 8.04 (d, *J* = 8.1 Hz, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ 59.8, 60.1, 97.0, 110.3, 114.8, 115.3, 116.9, 120.1, 124.7, 126.9, 127.2, 128.0, 128.6, 129.9, 130.1, 138.1, 154.0, 156.6, 158.0, 162.5; MS (EI) *m/z* (%): 407 (23.6) [M]$^+$; Anal. calcd for $C_{26}H_{21}N_3O_2$: C, 76.64; H, 5.19; N, 10.31; found: C, 76.78; H, 5.27; N, 10.40%.

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