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Synthesis of fully-substituted pyridines and dihydropyridines in a highly chemoselective manner utilizing a multicomponent reaction (MCR) strategy†

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An efficient protocol has been developed for the synthesis of pyridines and 1,4-dihydropyridines based on chemoselective multicomponent reactions. Using readily available aldehydes, malononitrile and primary aliphatic amines, this procedure provides a divergent but straightforward access to a wide range of fully substituted pyridines and dihydropyridines *via* a primary amine based chemoselective strategy. Simple reaction procedure, good yields, mild reaction conditions, applicabilility to a wide range of substrates with the aid of chemoselectivity make this present protocol more innovative than existing ones.

Introduction

Multicomponent reactions (MCRs) have attracted much attention recently due to their wide applicability in combinatorial, medicinal and heterocyclic chemistry. Formations of complex molecular architectures with multiple bond-making and/or bond-breaking in a single step along with high atom economy are the key features of MCRs. Chemoselectivity in such reactions is of obvious importance to devise strategies for different target molecules with suitable chemical modifications. In the past decades, many investigators have reported the chemoselectively controlled MCRs with various metal catalysts,[1a–d] solvents[1e–g] and substrate patterns.[1h] In a true sense such chemoselective MCRs represent a unique processes by combining several readily available starting materials to construct different molecular frameworks *via* fine tuning of the reaction conditions.

Construction of functionalized N-heterocycles utilizing MCR strategy has evolved as a new synthetic tool. Nitrogen containing heterocycles show a vast abundance in numerous natural products and several biologically active pharmaceuticals. Among the all heteroaromatic compounds, highly substituted pyridines are unrivaled and also considered as "privileged medicinal scaffolds" because they are partial structures of many natural products, pharmaceuticals, and synthetic organic moieties.[2,3] These pyridine skeletons are the most predominant due to their broad spectrum of potential biological activities as antimitotic agents,[4a] anti-inflammatory agents[4b,c] and anticonvulsants.[5]

They display significant pharmacological properties for regulation of arterial pressure[6] and cholesterol levels in blood.[7] Some polysubstituted pyridines are used as non-linear optical materials,[8] electrical materials,[9] chelating agents in metal ligand chemistry[10] and as fluorescent liquid crystals.[11] Moreover, 2-amino-3-cyanopyridine derivatives have raised significant response as potent inhibitors of HIV-1.[12] Dihydropyridines and their derivatives are key intermediates for the synthesis of several biological active compounds as those for the treatment of cardiovascular disease and hypertension,[13] potent calcium channel antagonist, and agonist.[14] They also have prospective application in other pharmacological activities.[15] Some of these biologically active scaffolds are shown in Fig. 1.

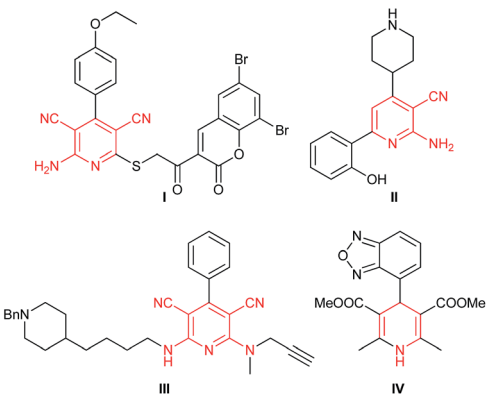

Fig. 1 Some biologically active pyridine and dihydropyridine moieties.

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra and HRMS spectra, X-ray crystallographic data (CIF files) of **4a** and **6d**, spectral data of all compounds and copies of ^{1}H and ^{13}C NMR spectra of products. CCDC 1006358 and 913525. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra08237k

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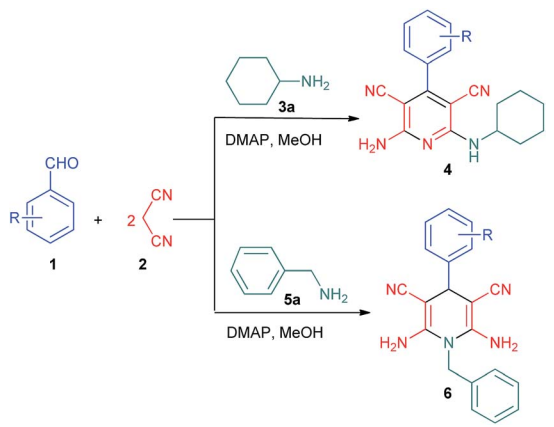
The classical recipes for the construction of pyridine derivatives such as the Hantzsch,[16] Knoevenagel[17] and Chichibabin[18] reactions generally involve condensation of amines and carbonyl compounds. From the 19th century several efficient synthetic procedures have been developed for the synthesis of pyridine derivatives, mostly based on cycloaddition reactions, or cross-coupling chemistry, which initiates the search for new approaches that offer concise and regiospecific strategies, making it topic of considerable interest.[19] Recently several scientists have used the MCR strategy to synthesize highly dense 6-thio-pyridine skeletons from aldehydes, malononitrile and aromatic thiols under basic environments[20] or in presence of ionic liquids.[21] Now-a-days Lewis acid catalysts are also used to produce aryl thiol substituted pyridine moieties.[22] We found during literature survey that the 2-amino-6-alkylamino-3,5-dicyano pyridine derivatives can be synthesized directly from 2-chloro-pyridine moieties[23] or from thio-pyran derivatives.[24] Ramakrishnan *et al.* synthesized[25a] these pyridine skeletons utilizing pyrrolidine from chalcones as well as aromatic aldehydes under reflux conditions for several hours. Use of such secondary amines was also mentioned by Choudhury *et al.* during their synthesis and photo-physical studies of 6-thio-pyridine derivatives.[25b] The fully substituted pyridine skeletons can also be synthesized using aqueous solution of methyl amine or dimethyl amine in excess amounts.[25c] The use of amino triazole compounds with malononitrile and carbonyl groups for the synthesis of 1,2,4-triazolo[4,3-*a*]pyrimidines have also been observed earlier.[25d] The demerits of the above mentioned procedures are longer reaction time, reflux conditions and/or use of excess reagents.[23–25] Over the past several years, various nucleophiles mainly the thiophenols have been used in these reactions.[20–22] However, the use of aliphatic amines as nucleophiles in these reactions were rarely explored. In this paper, we report a novel one-pot primary aliphatic amine based multicomponent domino reaction for the synthesis of polysubstituted pyridine and dihydropyridine derivatives in a highly chemoselective manner from simple and readily available aliphatic amines, aromatic aldehydes and malononitrile with good yields under mild reaction conditions (Scheme 1).



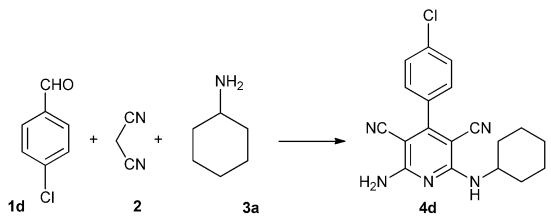
Scheme 1 Differential selectivity during synthesis of fully substituted pyridines and dihydropyridines.

Results and discussion

As initial endeavor, a trial reaction was performed with 1 mmol of 4-chlorobenzaldehyde (**1d**), 2 mmol of malononitrile (**2**) and 1 mmol of cyclohexylamine (**3a**) in methanol as solvent in the presence of 15 mol% 4-dimethylaminopyridine (DMAP) as the catalyst. After 5 h, a solid precipitate (**4d**) was separated out which was characterized from spectroscopic techniques and was found to be the desired fully substituted pyridine derivative (Table 1, entry 1). It was observed that the yield increased upto 81% in presence of 20 mol% of DMAP. However, increasing the amount of catalyst up to 30 mol% did not affect the reaction any longer (Table 1, entries 2 & 3). To verify the effect of solvents the similar reaction was executed with different solvents such as EtOH, CH_3CN, CH_2Cl_2 and H_2O (Table 1, entries 4 to 7). Catalysts with basic nature such as DBU, Et_3N, PPh_3, *N*,*N*-dimethyl aniline (DMA) provided either lower yields or required longer reaction time (Table 1, entries 8 to 11). The reaction prolonged with very poor yield in absence of the catalyst (Table 1, entry 12). It has been observed the 20 mol% DMAP in presence of MeOH is the best reaction conditions for this particular reaction.

With the condition optimized, we next wanted to verify the scope and generality of this reaction with various aromatic aldehydes using malononitrile and cyclohexylamine to generate our desired pyridine moiety (Table 2). Aromatic aldehydes with electron donating functionalities as –Me, –OMe (**4b** & **4c**) procured better yields as compared to electron withdrawing groups as –Cl, –Br (**4d** & **4e**). Unfortunately, no desired product

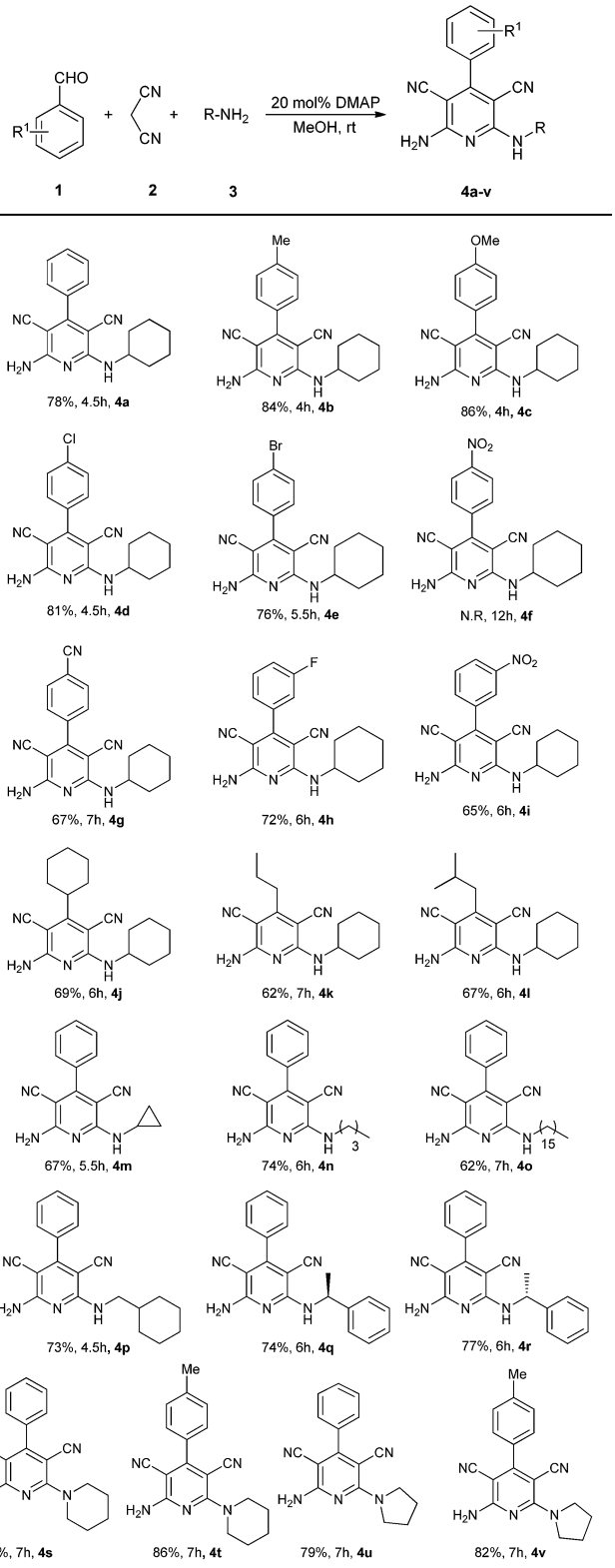
Table 1 Optimization of reaction conditions for the synthesis of functionalized pyridine (**4d**)[a]



Sl. no.	Catalyst (mol%)	Solvent	Time (h)	Yield[b] (%)
1	DMAP (15)	MeOH	5	74
2	DMAP (20)	MeOH	4.5	81
3	DMAP (30)	MeOH	4.5	82
4	DMAP (20)	EtOH	9	35
5	DMAP (20)	CH_3CN	10	26
6	DMAP (20)	CH_2Cl_2	8	57
7	DMAP (20)	H_2O	12	<10
8	DBU (20)	MeOH	7	65
9	Et_3N (20)	MeOH	6	68
10	PPh_3 (20)	MeOH	6.5	62
11	DMA (20)	MeOH	8	57
12	—	MeOH	17	14

[a] All the reactions were performed with 4-chlorobenzaldehyde (1.0 mmol), malononitrile (2.0 mmol) and cyclohexylamine (1.0 mmol) at rt. [b] Isolated yields.

Table 2 Scope of various substituted pyridine derivatives[a]



[a] Isolated yields.

(**4f**) was obtained when the similar reaction was performed with highly electron deficient 4-nitrobenzaldehyde. Still satisfactory results were gained for 4-formylbenzonitrile, 3-fluorobenzaldehyde and 3-nitrobenzaldehyde (**4g** to **4i**) under identical reaction conditions. Even cyclohexane-carboxaldehyde gave the desired pyridine moiety (**4j**). Apart from cyclohexanecarboxaldehyde, other aliphatic aldehydes such as long chain butyraldehyde or 3-methylbutyraldehyde produced the expected pyridine skeletons (**4k** & **4l**) in moderate yields.

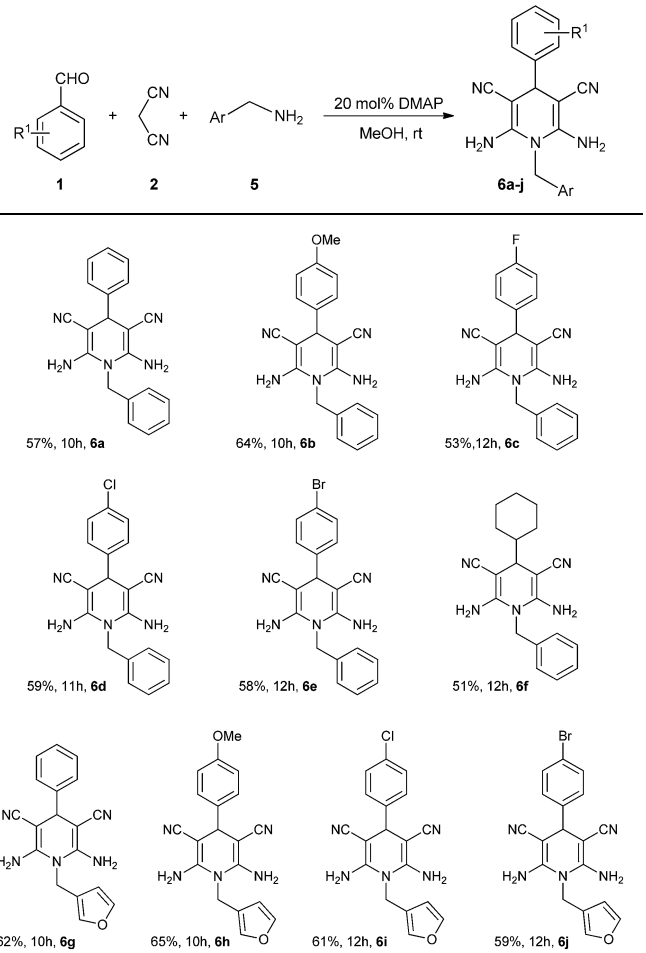
We further extended the scope of the reaction with a series of different primary aliphatic amines utilizing benzaldehyde and malononitrile under similar reaction conditions. From strained cyclopropylamine to acyclic butyl-1-amine upto long chain hexadecan-1-amine led to our desired 6-alkyl amino pyridine derivatives (**4m** to **4o**) in good to moderate yields. Even cyclohexylmethanamine gave corresponding pyridine derivative **4p** in good yields. With chiral primary amines such as (*R*/*S*)-1-phenylethanamine we observed the corresponding pyridine moieties (**4q** & **4r**) bearing chiral centre in the product. Next, we carried out the reactions of malononitrile and benzaldehyde or 4-methylbenzaldehyde with secondary amines such as piperidine or pyrrolidine under similar reaction conditions to generate the anticipated pyridine moieties (**4s** to **4v**) in good to moderate yields.

Encouraged by the above results, we extended the substrate variety utilizing benzylamine with benzaldehyde and malononitrile under similar reaction conditions. After the usual spectroscopic analysis, it was found that the product was 2,6-diamino-1-benzyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbonitrile instead of our expected substituted pyridine derivatives *i.e.* 2-amino-6-(benzylamino)-4-phenylpyridine-3,5-dicarbonitrile. The ^{1}H NMR spectrum of **6a** showed one broad singlet at $\delta = 6.26$ due to the four NH_2 protons, a singlet at $\delta = 3.96$ ppm due to the –CH proton of the dihydropyridine ring and in ^{13}C NMR two peaks at the region of $\delta = 75$–80 ppm, for the carbon atoms attached with the –CN groups in the pyridine rings, were found to be missing. From these observations, it was quite obvious that instead of fully substituted pyridine ring totally substituted dihydropyridine skeleton was formed (Table 3).

To examine the generality of this protocol, we performed the reactions of malononitrile and benzyl amine with different aromatic aldehydes under the optimised condition. The aromatic aldehydes with electron donating substituents as –OMe (**6b**) provided better yield than the electron deficient substituents as –F, –Cl, –Br (**6c** to **6e**). When the reaction was extended for aliphatic aldehydes, the desired dihydropyridine moiety (**6f**) was obtained as product. Replacing the aromatic moiety of the benzyl amine skeleton with heteroaromatic one such as furan-3-ylmethanamine gave the expected highly substituted dihydropyridine ring. These reactions were also repeated successfully even with aromatic aldehydes having different substituents such as –OMe, –Cl, –Br (**6h** to **6j**) in the ring.

However, the reaction did not proceed in presence of aromatic amines. When the reaction was carried with 4-chlorobenzaldehyde, malononitrile and aniline under similar reaction conditions, we isolated only the Knoevenagel product may

Table 3 Scope of various substituted 1,4-dihydropyridine derivatives[a]



[a] Isolated yields.

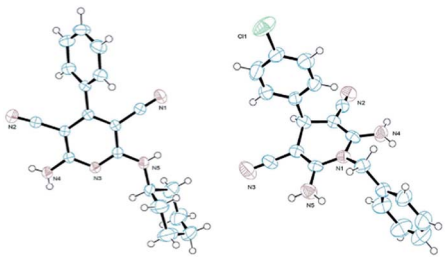


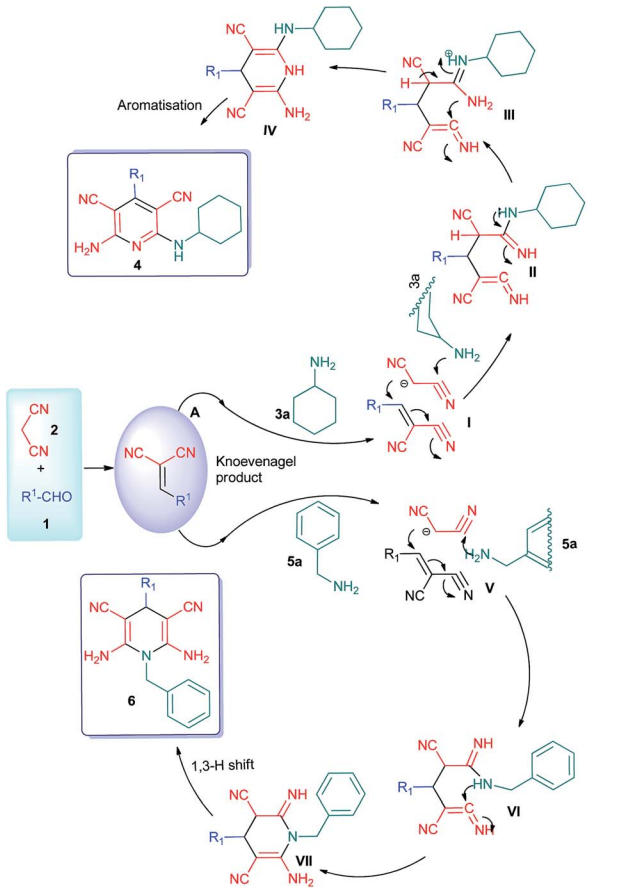
Fig. 2 X-ray crystal structure of **4a** (CCDC 1006358) and **6d** (CCDC 913525).

be due to lower basicity of the aromatic amines. As these pyridine scaffolds are utilized in several step reactions or in natural product synthesis, we wanted to examine its efficiency in large scale. During the synthesis of **4d** in multigram quantities we carried out the reaction with 4-chlorobenzaldehyde, malononitrile and cyclohexylamine under identical reaction condition in 10 mmol scale which afforded the desired product in 2.25 g with a yield of 64%.

The formation of these fully substituted pyridines and dihydropridines were further established by X-ray crystallographic structure analysis of the compound **4a** and **6d** Fig. 2.

Based on literature reports,[20,25] a plausible mechanism for the formation of these fully substituted pyridine **4** and dihydropyridine **6** rings is shown in Scheme 2. The mechanistic approach involves the Knoevenagel condensation of aromatic aldehyde and malonitrile forming adduct **A** in the first step, followed by Michael addition with malononitrile to form a tetracyano intermediate **II** & **VI** by amine. In the next step, the intermediates **III** & **VI** forms dihydropyridine moieties through cyclization as shown in intermediates **IV** & **VII** which is further followed by aromatization for cyclohexylamines and 1,3 H shift for benzyl amines and to form 2-amino-6-alkylamino-3,5-dicyanopyridines **4** and 2,6-diamino-3,5-dicyano dihydropyridines **6**, respectively.

The synthesis of pyridine and dihydropyridine moiety depends mainly on two major characters of the amine groups, the strength of the amine and its steric effect. In a polar protic solvent like MeOH, nucleophilicity as well as basicity of amines together regulate the chemoselectivity issue. According to the literature survey[26] benzylamine is less basic (having lower pK_a values < 10) compared to other amines *viz.* cyclohexylamine, cyclohexylmethylamine, heptylamine, piperidine, pyrrolidine,



Scheme 2 Plausible mechanism for the formation of pyridine and dihydropyridine.

etc. (pK_a values > 10). On the other hand for the amines the effect of delocalization (free bases and its conjugate acids) increases with increasing the basic strength. Thus delocalization is preferred for amines having higher pK_a values (>10) *i.e.* having higher basicity which is followed by further attack of other $-NH_2$ functionality of the amidine group to generate cyclic intermediate **IV** from **III**. However amines containing lower pK_a values (<10) *viz.* benzylamine and furfurylamine, both prefer to behave as nucleophile rather than base. Thus for both these two amines the nitrogen atom directly attacks to form the cyclized moiety **VII** from **VI**. The other regulating factor could be attributed to the steric effect caused by the cyclic ring present next to the amine group, forcing the amine to take the 6th position in the ring instead of initiating the amine group to involve in the ring formation directly. As for the benzylic amines, the carbon atom adjacent to the amine group is substituted by planar aromatic ring, whereas in case of C-methyl-substituent in benzylamines the presence of both methyl and phenyl group in carbon atom adjacent to the amine creates strong steric hindrance to form pyridine ring and not the dihydropyridine moiety.

Conclusions

In summary, we have disclosed a convenient one-pot synthesis of multisubstituted pyridine and dihydropyridine molecule of potent synthetic and pharmacological importance *via* base catalyzed multicomponent reaction utilizing readily available primary aliphatic amines in a highly chemoselective manner.

In case of pyridine rings, the nitrogen atom from the malononitrile is solely responsible for forming the ring where as in dihydropyridines the nitrogen atom of the ring comes from benzyl amines or methyl-furfural amines. Besides simple and mild reaction conditions, chemoselective switch in reaction procedure are the remarkable features of this present protocol. It should be noted that the richness of the functionality in the fully substituted pyridine and dihydropyridine moieties, for example amino and cyano groups, may render these compounds as useful synthons for further synthetic organic transformations.

Experimental section

General procedure

In a dried 25 mL round-bottomed flask was taken a mixture of aldehyde (1.0 mmol), malononitrile (2.0 mmol) and 20 mol% 4-dimethylaminopyridine (DMAP). It was kept for stirring for 1 h at room temperature. After adding the requisite amine (1.0 mmol) into it, the reaction mixture was left for stirring. A thick precipitate separated out after some time, which was then filtered off through a Büchner funnel and the precipitate was washed with 30 mL of hexane–ethyl acetate (7 : 3) to remove unreacted starting material, if any. In case of aliphatic aldehydes, after completion of the reaction the solvent was removed in rotary evaporator. It was extracted with dichloromethane (2 × 10 mL), washed with water and dried over anhydrous Na_2SO_4. It was concentrated *in vacuo* and purified through column chromatography.

2-Amino-6-(cyclohexylamino)-4-phenylpyridine-3,5-dicarbonitrile. White solid (0.247 g, 78%); Mp 250–254 °C;^{1}H NMR (DMSO-D_6, 400 MHz): δ 1.08–1.15 (m, 1H), 1.22–1.31 (m, 2H), 1.38–1.46 (m, 2H), 1.58–1.61 (m, 1H), 1.71–1.80 (m, 4H), 3.96–4.18 (m, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.95 (bs, 2H), 7.4–7.51 (m, 5H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 25.10, 25.14, 31.79, 49.50, 78.97, 80.43, 116.43, 116.57, 128.26, 128.59, 129.85, 135.22, 158.14, 159.72, 161.00; IR (KBr, cm^{-1}): 1559, 1630, 2205, 2925, 3333, 3363, 3484; Anal. calcd for $C_{19}H_{19}N_5$: C, 71.90; H, 6.03; N, 22.07; found: C, 71.98; H, 6.12; N, 21.96. HRMS (ESI) calcd for $C_{19}H_{19}N_5$ (M + H$^+$) 318.1719, found 318.1725.

2-Amino-6-(cyclohexylamino)-4-(*p*-tolyl)pyridine-3,5-dicarbonitrile. White solid (0.278 g, 84%); Mp 213–216 °C;^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15–1.31 (m, 3H), 1.32–1.48 (m, 2H), 1.59–1.7 (m, 1H), 1.71–1.88 (m, 2H), 1.95–2.09 (m, 2H), 2.40 (s, 3H), 3.95–4.05 (m, 1H), 5.44 (s, 1H), 5.47 (s, 2H), 7.3 (d, J = 7.6 Hz, 2H), 7.4 (d, J = 8 Hz, 2H)^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.58, 24.99, 25.57, 32.92, 50.21, 80.04, 82.53, 116.91, 117.07, 128.33, 129.21, 129.53, 129.63, 131.59, 140.85, 158.86, 159.47, 161.22; IR (KBr, cm^{-1}): 1508, 1567, 1596, 2209, 2935, 3311, 3383, 3502.; Anal. calcd for $C_{20}H_{21}N_5$: C, 72.48; H, 6.39; N, 21.13; found: C, 72.57; H, 6.46; N, 21.04. HRMS (ESI) calcd for $C_{20}H_{21}N_5$ (M + H$^+$) 332.1875, found 332.1867.

2-Amino-6-(cyclohexylamino)-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile. White solid (0.297 g, 86%); Mp 208–211 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 1.05–1.19 (m, 1H), 1.2–1.34 (m, 2H), 1.35–1.5 (m, 2H), 1.55–1.65 (m, 1H), 1.67–1.85 (m, 4H), 3.83 (s, 3H), 3.95–4.19 (m, 1H), 6.87 (d, J = 8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 7.28 (bs, 2H), 7.41 (d, J = 8.8 Hz, 2H);^{13}C NMR (DMSO-D_6, 150 MHz): δ 25.40, 25.46, 32.14, 49.78, 55.63, 79.28, 80.72, 114.27, 117.00, 117.12, 127.50, 130.28, 158.60, 159.68, 160.77, 161.43; IR (KBr, cm^{-1}):1482, 1559, 1626, 2208, 2927, 3307, 3341, 3447; Anal. calcd for $C_{20}H_{21}N_5O$: C, 69.14; H, 6.09; N, 20.16; found: C, 69.26; H, 6.18; N, 20.03. HRMS (ESI) calcd for $C_{20}H_{21}N_5O$ (M + H$^+$) 348.1824, found 348.1826.

2-Amino-4-(4-chlorophenyl)-6-(cyclohexylamino)pyridine-3,5-dicarbonitrile. White solid (0.285 g, 81%); Mp 227–230 °C;^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.02–1.2 (m, 1H), 1.21–1.32 (m, 2H), 1.38–1.49 (m, 2H), 1.56–1.65 (m, 1H), 1.68–1.72 (m, 4H), 4.0–4.09 (m, 1H), 6.99 (d, J = 7.8 Hz, 1H), 7.36 (bs, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), ^{13}C NMR ($CDCl_3$, 150 MHz): δ 25.06, 25.09, 31.73, 49.47, 78.87, 80.33, 116.24, 116.37, 128.69, 128.82, 130.24, 130.34, 134.04, 134.70, 158.00, 158.52, 160.86; IR (KBr, cm^{-1}): 1480, 1539, 1629, 2208, 2936, 3311, 3328, 3471; Anal. calcd for $C_{19}H_{18}ClN_5$: C, 64.86; H, 5.16; N, 19.91; found: C, 64.97; H, 5.27; N, 19.78. HRMS (ESI) calcd for $C_{19}H_{18}ClN_5$ (M + H$^+$) 352.1329, found 352.1336.

2-Amino-4-(4-bromophenyl)-6-(cyclohexylamino)pyridine-3,5-dicarbonitrile. White solid (0.301 g, 76%); Mp 239–242 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.06–1.15 (m, 1H), 1.21–1.31 (m, 2H), 1.38–1.47 (m, 2H), 1.57–1.63 (m, 1H), 1.69–1.82 (m, 4H), 3.85–4.10 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 7.36(bs, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), ^{13}C NMR (DMSO-D_6, 150 MHz): δ 25.08, 25.11, 31.75, 49.51, 78.80, 80.28, 116.27, 116.40, 123.46, 130.47, 130.55, 131.66, 131.79, 134.44, 158.01, 158.60,

160.88; IR (KBr, cm^{-1}):1479, 1551, 1628, 2208, 2937, 3225, 3309, 3472; Anal. calcd for $C_{19}H_{18}BrN_5$: C, 57.59; H, 4.58; N, 17.67; found: C, 57.68; H, 4.67; N, 17.56. HRMS (ESI) calcd for $C_{19}H_{18}BrN_5$ (M + H^+) 396.0824, found 396.0828.

2-Amino-4-(4-cyanophenyl)-6-(cyclohexylamino)pyridine-3,5-dicarbonitrile. Yellow solid (0.229 g, 67%); Mp 221–223 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.79–0.91 (m, 2H), 1.35–1.46 (m, 2H), 1.58–1.61 (m, 2H), 1.77–1.82 (m, 2H), 1.96–2.08 (m, 2H), 3.85–4.10 (m, 1H), 5.48 (d, J = 7.8 Hz, 1H), 5.53 (s, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 25.01, 25.61, 32.95, 50.52, 79.85, 80.53, 114.62, 116.05, 116.24, 118.12, 129.43, 132.90, 138.92, 157.20, 158.70, 161.08; IR (KBr, cm^{-1}): 1498, 1577, 1625, 2208, 2932, 3222, 3327; Anal. calcd for $C_{20}H_{18}N_6$: C, 70.16; H, 5.30; N, 24.54; found: C, 70.24; H, 3.43; N, 24.41. MS (ESI) calcd for $C_{20}H_{18}N_6$ (M + H^+) 343.1671, found 343.2391.

2-Amino-6-(cyclohexylamino)-4-(3-fluorophenyl)pyridine-3,5-dicarbonitrile. White solid (0.241 g, 72%); Mp 264–268 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.06–1.15 (m, 1H), 1.20–1.31 (m, 2H), 1.38–1.49 (m, 2H), 1.57–1.62 (m, 1H), 1.69–1.85 (m, 4H), 3.98–4.09 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.34–7.40 (m, 2H), 7.55–7.61 (m, 1H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 25.06, 25.09, 31.71, 49.47, 78.89, 80.36, 115.35, 115.51, 116.14, 116.28, 116.59, 116.72, 124.56, 130.80, 130.86, 137.31, 137.37, 157.96, 158.28, 160.83, 160.89, 165.52; IR (KBr, cm^{-1}):1479, 1559, 1630, 2203, 2926, 3375, 3416, 3490; Anal. calcd for $C_{19}H_{18}FN_5$: C, 68.04; H, 5.41; N, 20.88; found: C, 68.13; H, 5.48; N, 20.79. HRMS (ESI) calcd for $C_{19}H_{18}FN_5$ (M + H^+) 336.1624, found 336.1631.

2-Amino-6-(cyclohexylamino)-4-(3-nitrophenyl)pyridine-3,5-dicarbonitrile. White solid (0.235 g, 65%); Mp 210–213 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 1.04–1.18 (m, 1H), 1.19–1.36 (m, 2H), 1.38–1.5 (m, 2H), 1.55–1.68 (m, 1H), 1.69–1.84 (m, 4H), 3.98–4.11 (m, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.43 (s, 2H), 7.85 (t, J = 7.8 Hz, 1H), 7.97 (d, J = 8 Hz, 1H), 7.34–7.42 (m, 1H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 25.09, 31.75, 49.59, 78.97, 80.48, 116.16, 116.28, 123.37, 124.70, 130.56, 135.18, 136.72, 147.67, 157.42, 157.97, 160.85; IR (KBr, cm^{-1}):1347, 1559, 1653, 2207, 2925, 3331, 3465, 3496; Anal. calcd for $C_{19}H_{18}N_6O_2$: C, 62.97; H, 5.01; N, 23.19; found: C, 63.11; H, 5.18; N, 23.28. HRMS (ESI) calcd for $C_{19}H_{18}N_6O_2$ (M + H^+) 363.1569, found 363.8621.

2-Amino-4-cyclohexyl-6-(cyclohexylamino)pyridine-3,5-dicarbonitrile. Semi solid (0.223 g, 69%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.07–1.24 (m, 3H), 1.25–1.42 (m, 4H), 1.59–1.64 (m, 2H), 1.65–1.80 (m, 5H), 1.82–1.86 (m, 2H), 1.87–2.1 (m, 4H), 2.83–2.96 (m, 1H), 3.85–3.98 (m, 1H), 5.29 (s, 1H), 5.35 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.98, 25.43, 25.63, 26.52, 30.09, 32.97, 44.94, 50.11, 79.08, 81.64, 116.96, 117.27, 159.27, 161.68, 165.45; IR (KBr, cm^{-1}): 1483, 1572, 1631, 2215, 2199, 2926, 3218, 3317, 3403; Anal. calcd for $C_{19}H_{25}N_5$: C, 70.56; H, 7.79; N, 21.65; found: C, 70.65; H, 7.86; N, 21.52. HRMS (ESI) calcd for $C_{19}H_{25}N_5$ (M + H^+) 324.2188, found 324.2194.

2-Amino-6-(cyclohexylamino)-4-propylpyridine-3,5-dicarbonitrile. Solid (0.175 g, 62%); Mp 180–183 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.89–0.97 (m, 1H), 1.02 (t, J = 7.8 Hz, 3H), 1.06–1.25 (m, 3H), 1.32–1.42 (m, 2H), 1.61–1.67 (m, 1H), 1.68–1.79 (m, 3H), 1.93–2.0 (m, 2H), 2.72 (t, J = 7.2 Hz, 2H), 3.88–3.98 (m, 1H), 5.28 (d, J = 7.8 Hz, 1H), 5.34 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.04, 23.28, 25.03, 25.66, 33.06, 36.01, 50.18, 80.41, 82.87, 116.37, 116.55, 158.84, 161.07, 162.05; IR (KBr, cm^{-1}): 1465, 1582, 1628, 2206, 2220, 2854, 3307, 3353, 3495; Anal. calcd for $C_{16}H_{21}N_5$: C, 67.82; H, 7.47; N, 24.71; found: C, 67.94; H, 7.61; N, 24.58. MS (ESI) calcd for $C_{16}H_{21}N_5$ (M + H^+) 284.1875, found 284.2983.

2-Amino-6-(cyclohexylamino)-4-isobutylpyridine-3,5-dicarbonitrile. Solid (0.198 g, 67%); Mp 174–177 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.01 (d, J = 6.6 Hz, 6H), 1.16–1.27 (m, 2H), 1.32–1.41 (m, 2H), 1.61–1.69 (m, 2H), 1.78–1.80 (m, 2H), 1.94–2.0 (m, 2H), 2.08–2.16 (m, 1H), 2.63 (d, J = 7.8 Hz, 2H), 3.89–3.98 (m, 1H), 5.28 (d, J = 7.8 Hz, 1H) 5.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 22.56, 25.04, 25.67, 29.88, 33.07, 42.83, 50.20, 80.93, 83.43, 116.57, 116.76, 158.81, 161.02, 161.17; IR (KBr, cm^{-1}): 1484, 1581, 1629, 2202, 2218, 2927, 3216, 3372, 3499; Anal. calcd for $C_{17}H_{23}N_5$: C, 68.66; H, 7.80; N, 23.55; found: C, 68.78; H, 7.92; N, 23.67.

2-Amino-6-(cyclopropylamino)-4-phenylpyridine-3,5-dicarbonitrile. White solid (0.185 g, 67%); Mp 245–248 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 0.64–0.79 (m, 4H), 2.88–3.00 (m, 1H), 7.3–7.46 (m, 2H), 7.46–7.5 (m, 1H), 7.51–7.6 (m, 3H); ^{13}C NMR (DMSO-D_6, 100 MHz): δ 6.41, 24.67, 79.50, 80.53, 116.22, 116.47, 128.27, 128.53, 129.79, 135.12, 159.55, 160.22, 160.87; IR (KBr, cm^{-1}): 1481, 1510, 1628, 2203, 3327, 3371, 3488; Anal. calcd for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.44; found: C, 69.91; H, 4.83. N, 25.36 HRMS (ESI) calcd for $C_{16}H_{13}N_5$ (M + H^+) 276.1249, found 276.1247.

2-Amino-6-(butylamino)-4-phenylpyridine-3,5-dicarbonitrile. White solid (0.217 g, 74%); Mp 175–177 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 0.81–0.95 (m, 3H), 1.25–1.41 (m, 2H), 1.45–1.62 (m, 2H), 3.38–3.45 (m, 2H), 5.40 (s, 2H), 5.53 (s, 1H), 7.4–7.52 (m, 5H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 13.93, 20.18, 31.09, 41.43, 80.26, 82.69, 116.72, 116.88, 128.46, 129.00, 130.20, 130.65, 134.52, 159.35, 159.77, 161.24; IR (KBr, cm^{-1}):1484, 1559, 1653, 2202, 2925, 3337, 3350, 3460; Anal. calcd for $C_{17}H_{17}N_5$: C, C, 70.08; H, 5.88; N, 24.04; found: C, 70.17; H, 5.97; N, 24.16.

2-Amino-6-(hexadecylamino)-4-phenylpyridine-3,5-dicarbonitrile. White solid (0.285 g, 62%); Mp 90–94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.75–0.88 (m, 3H), 1.09–1.38 (m, 26H), 1.42–1.59 (m, 2H), 3.3–3.42 (m, 2H), 5.46 (s, 2H), 5.62 (s, 1H), 7.38–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.25, 22.81, 25.10, 27.00, 29.37, 29.44, 29.49, 29.67, 29.74, 29.82, 32.05, 36.74, 41.71, 80.19, 82.62, 116.68, 116.84, 128.43, 128.84, 128.94, 129.28, 129.34, 134.52, 159.29, 159.72, 161.22; IR (KBr, cm^{-1}): 1485, 1558, 1628, 2208, 2918, 3228, 3332, 3500; Anal. calcd for $C_{29}H_{41}N_5$: C, 75.77; H, 8.99; N, 15.24; found: C, 75.86; H, 9.12; N, 15.15. HRMS (ESI) calcd for $C_{29}H_{41}N_5$ (M + H^+) 460.3440, found 460.3442.

2-Amino-6-((cyclohexylmethyl)amino)-4-phenylpyridine-3,5-dicarbonitrile. Yellow solid (0.242 g, 73%); Mp 187–191 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.94–1.03 (m, 2H), 1.12–1.31 (m, 2H), 1.55–1.66 (m, 2H), 1.66–1.72 (m, 1H), 1.72–1.84 (m, 4H), 3.33 (t, J = 6.6 Hz, 2H), 5.47 (s, 1H), 5.68 (s, 2H), 7.48–7.57 (m, 5H) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.92, 26.50, 31.00, 37.79, 47.80, 80.27, 82.70, 116.71, 116.86, 128.44, 128.99, 130.64, 134.51, 159.32, 159.91, 161.17; IR (KBr, cm^{-1}): 1482, 1558, 1627, 2203,

2925, 3353, 3369, 3488; Anal. calcd for $C_{20}H_{21}N_5$: C, 72.48; H, 6.39; N, 21.13; found: C, 72.53; H, 6.48; N, 21.27. HRMS (ESI) calcd for $C_{20}H_{21}N_5$ (M + H^+) 332.1875, found 332.1871.

(*S*)-2-Amino-4-phenyl-6-((1-phenylethyl)amino)pyridine-3,5-dicarbonitrile. Yellow solid (0.251 g, 74%); Mp 220–223 °C;^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.53 (d, J = 6.6 Hz, 3H), 5.39–5.45 (m, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.8 Hz, 2H), 7.42–7.47 (m, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.5–7.54 (m, 3H), 7.66 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-D_6, 100 MHz): δ 21.29, 49.45, 79.32, 80.40, 116.32, 116.48, 126.75, 126.78, 128.18, 128.19, 128.28, 128.59, 129.87, 135.16, 144.20, 158.07, 159.92, 160.76; IR (KBr, cm^{-1}): 1553, 1622, 2209, 3217, 3339, 3475; Anal. calcd for $C_{21}H_{17}N_5$: C, 74.32; H, 5.05; N, 20.63; found: C, 74.44; H, 5.12; N, 20.57. HRMS (ESI) calcd for $C_{21}H_{17}N_5$ (M + H^+) 340.1562, found 340.1573.

(*R*)-2-Amino-4-phenyl-6-((1-phenylethyl)amino)pyridine-3,5-dicarbonitrile. Yellow solid (0.262 g, 77%); Mp 217–219 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 1.53 (d, J = 6.8 Hz, 3H), 5.37–5.5 (m, 1H), 7.2–7.26 (m, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.42–7.48 (m, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.5–7.63 (m, 3H), 7.72 (d, J = 8 Hz, 1H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 21.22, 49.41, 79.31, 80.40, 116.24, 116.39, 126.69, 128.12, 128.22, 128.51, 129.78, 135.13, 144.13, 158.03, 159.83, 160.71; IR (KBr, cm^{-1}): 1487, 1553, 1622, 2209, 3217, 3339, 3475; Anal. calcd for $C_{21}H_{17}N_5$: C, 74.32; H, 5.05; N, 20.63; found: C, 74.41; H, 5.15; N, 20.51. HRMS (ESI) calcd for $C_{26}H_{26}N_4O_3$ (M + H^+) 340.1562, found 340.1565.

2-Amino-4-phenyl-6-(piperidin-1-yl)pyridine-3,5-dicarbonitrile. Yellow solid (0.252 g, 83%); Mp 199–203 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 1.45–1.76 (m, 6H), 3.61–3.78 (m, 4H), 7.36–7.6 (m, 5H), ^{13}C NMR (DMSO-D_6, 100 MHz): δ 23.87, 25.54, 48.41, 80.85, 81.50, 116.16, 117.72, 128.50, 128.61, 129.91, 135.35, 159.70, 160.66, 161.76; IR (KBr, cm^{-1}): 1025, 1489, 1568, 1625, 2202, 3414; Anal. calcd for $C_{18}H_{17}N_5$: C, 71.27; H, 5.65; N, 23.09; found: C, 71.34; H, 5.57; N, 23.16. HRMS (ESI) calcd for $C_{18}H_{17}N_5$ (M + H^+) 304.1562, found 304.1571.

2-Amino-6-(piperidin-1-yl)-4-(*p*-tolyl)pyridine-3,5-dicarbonitrile. White solid (0.273 g, 86%); Mp 208–210 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.67–1.78 (m, 6H), 2.49 (s, 3H), 3.78–3.83 (m, 4H), 7.44 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 7.8 Hz, 2H), ^{13}C NMR (DMSO-D_6, 150 MHz): δ 20.95, 23.93, 25.60, 48.49, 80.80, 81.52, 116.36, 117.90, 128.68, 129.12, 132.44, 139.76, 159.83, 160.85, 161.78; IR (KBr, cm^{-1}): 1497, 1579, 1623, 2201, 2936, 3221, 3327, 3478; Anal. calcd for $C_{19}H_{19}N_5$: C, 71.90; H, 6.03; N, 22.07; found: C, 72.04; H, 6.14; N, 22.21. HRMS (ESI) calcd for $C_{19}H_{19}N_5$ (M + H^+) 318.1719, found 318.1718.

2-Amino-4-phenyl-6-(pyrrolidin-1-yl)pyridine-3,5-dicarbonitrile. White solid (0.228 g, 79%); Mp 213–215 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.85–1.94 (m, 4H), 3.65–3.76 (m, 4H), 7.26 (bs, 2H), 7.42–7.47 (m, 2H), 7.5–7.56 (m, 3H), ^{13}C NMR (DMSO-D_6, 150 MHz): δ 24.92, 49.15, 80.01, 80.17, 116.47, 118.18, 128.45, 128.50, 129.74, 135.57, 157.19, 159.59, 161.59; IR (KBr, cm^{-1}):1487, 1531, 1624, 2209, 3217, 3319, 3475; Anal. calcd for $C_{17}H_{15}N_5$: C, 70.57; H, 5.23; N, 24.21; found: C, 70.68; H, 5.31; N, 24.13. HRMS (ESI) calcd for $C_{17}H_{15}N_5$ (M + H^+) 290.1406, found 290.1414.

2-Amino-6-(pyrrolidin-1-yl)-4-(*p*-tolyl)pyridine-3,5-dicarbonitrile. White solid (0.248 g, 82%); Mp 280–283 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.85–1.93 (m, 4H), 2.38 (s, 3H), 3.65–3.72 (m, 4H), 7.24 (bs, 2H), 7.3–7.36 (m, 4H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 20.92, 24.89, 49.12, 79.16, 80.13, 116.54, 118.23, 128.41, 129.02, 132.62, 139.41, 157.27, 159.62, 161.56; IR (KBr, cm^{-1}): 1487, 1565, 1624, 2195, 2209, 3217, 3319, 3475; Anal. calcd for $C_{18}H_{17}N_5$: C, 71.27; H, 5.65; N, 23.09; found: C, 71.36; H, 5.79; N, 22.94. HRMS (ESI) calcd for $C_{18}H_{17}N_5$ (M + H^+) 304.1562, found 304.1565.

2,6-Diamino-1-benzyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbonitrile. White solid (0.310 g, 57%); Mp 221–223 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 3.96 (s, 1H), 4.94 (s, 2H), 6.26 (s, 4H), 6.82–6.88 (m, 2H), 7.11–7.16 (m, 3H), 7.17–7.22 (m, 2H), 7.27–7.33 (m, 3H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 46.75, 61.30, 121.44, 126.50, 126.63, 127.63, 127.70, 128.16, 128.40, 136.61, 145.17, 152.36; IR (KBr, cm^{-1}): 1435, 1651, 2170, 3358, 3379, 3450; Anal. calcd for $C_{20}H_{17}N_5$: C, 73.37; H, 5.23; N, 21.39; found: C, 73.42; H, 5.31; N, 21.27. HRMS (ESI) calcd for $C_{20}H_{17}N_5$ (M + H^+) 328.1562, found 328.1573.

2,6-Diamino-1-benzyl-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarbonitrile. White solid (0.310 g, 64%); Mp 204–206 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 3.70 (s, 3H), 3.93 (s, 1H), 4.95 (s, 2H), 6.24 (s, 4H), 6.71 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 7.17–7.22 (m, 2H), 7.30–7.38 (m, 3H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 46.80, 55.06, 61.78, 113.58, 113.92, 121.53, 126.30, 127.67, 127.75, 128.42, 128.47, 129.80, 136.69, 137.35, 152.22, 158.00; IR (KBr, cm^{-1}): 1430, 1667, 2186, 3214, 3311, 3430; Anal. calcd for $C_{21}H_{19}N_5O$: C, 70.57; H, 5.36; N, 19.59; found: C, 70.64; H, 5.45; N, 19.68. HRMS (ESI) calcd for $C_{21}H_{19}N_5O$ (M + H^+) 358.1668, found 358.1659.

2,6-Diamino-1-benzyl-4-(4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarbonitrile. White solid (0.310 g, 53%); Mp 198–201 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 4.01 (s, 1H), 4.95 (s, 2H), 6.29 (s, 4H), 6.84–6.91 (m, 2H), 6.97 (t, J = 8.4 Hz, 2H), 7.16–7.24 (m, 2H), 7.3–7.38 (m, 3H); ^{13}C NMR (DMSO-D_6, 100 MHz): δ 47.07, 61.47, 114.88, 115.10, 121.48, 127.82, 127.91, 128.63, 136.63, 141.50, 152.57; IR (KBr, cm^{-1}): 1429, 1568, 1656, 2161, 2192, 3236, 3340, 3420; Anal. calcd for $C_{20}H_{16}FN_5$: C, 69.55; H, 4.67; N, 20.28; found: C, 69.67; H, 4.76; N, 20.16. HRMS (ESI) calcd for $C_{20}H_{16}FN_5$ (M + H^+) 346.1468, found 346.1470.

2,6-Diamino-1-benzyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarbonitrile. White solid (0.310 g, 59%); Mp 254–256 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 4.03 (s, 1H), 4.97 (s, 2H), 6.31 (s, 4H), 6.88 (d, J = 8.4 Hz, 2H), 7.15–7.26 (m, 4H), 7.29–7.38 (m, 3H); ^{13}C NMR (DMSO-D_6, 100 MHz): δ 47.05, 61.09, 121.38, 127.82, 127.88, 128.24, 128.60, 131.23, 136.61, 144.28, 152.63; IR (KBr, cm^{-1}): 1431, 1560, 1665, 2188, 3224, 3270, 3324, 3440; Anal. calcd for $C_{20}H_{16}ClN_5$: C, 66.39; H, 4.46; N, 19.36; found: C, 66.47; H, 4.55; N, 19.21. HRMS (ESI) calcd for $C_{20}H_{16}ClN_5$ (M + H^+) 362.1172, found 362.1175.

2,6-Diamino-1-benzyl-4-(4-bromophenyl)-1,4-dihydropyridine-3,5-dicarbonitrile. White solid (0.310 g, 59%); Mp 254–256 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 4.00 (s, 1H), 4.95 (s, 2H), 6.33 (s, 4H), 6.80 (d, J = 8.4 Hz, 2H), 7.15–7.22 (m, 2H), 7.23–7.27 (m, 2H), 7.3–7.38 (m, 5H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 46.99, 60.95, 119.68, 121.36, 127.79, 127.86, 128.59, 128.97, 131.13, 136.58, 144.70, 152.61; IR (KBr, cm^{-1}): 1435, 1575, 1652, 2178, 3213, 3257, 3322, 3449; Anal. calcd for $C_{20}H_{16}BrN_5$: C, 59.13; H, 3.97; N,

17.24; found: C, 59.21; H, 4.08; N, 17.11. HRMS (ESI) calcd for $C_{20}H_{16}BrN_5$ (M + H^+) 406.0667, found 406.0672.

2,6-Diamino-1-benzyl-4-cyclohexyl-1,4-dihydropyridine-3,5-dicarbonitrile. Pale yellow solid (0.170 g, 51%); Mp 213–215 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 0.51–0.6 (m, 1H), 0.62–0.73 (m, 2H), 0.7–0.99 (m, 2H), 1.39–1.44 (m, 2H), 1.45–1.57 (m, 3H), 2.29 (d, J = 6.6 Hz, 1H), 4.86 (s, 2H), 6.12 (s, 4H), 7.21–7.24 (m, 2H), 7.25–7.34 (m, 3H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 25.73, 26.11, 29.27, 46.55, 47.47, 60.04, 122.55, 127.84, 128.38, 128.40, 136.71, 153.14; IR (KBr, cm^{-1}): 1437, 1568, 1654, 2186, 2930, 3329, 3434, 3463; Anal. calcd for $C_{20}H_{23}N_5$: C, 72.04; H, 6.95; N, 21.00; found: C, 72.17; H, 7.08; N, 21.11.

2,6-Diamino-1-(furan-3-ylmethyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarbonitrile. White solid (0.310 g, 62%); Mp 207–210 °C;^{1}H NMR (DMSO-D_6, 400 MHz): δ 3.87 (s, 1H), 4.98 (s, 2H), 6.29 (s, 4H), 6.25–6.27 (m, 1H), 6.42–6.47 (m, 1H), 7.46–7.6 (m, 5H), 7.64 (s, 1H); ^{13}C NMR (DMSO-D_6, 100 MHz): δ 40.83, 62.02, 109.33, 110.45, 121.26, 126.44, 128.25, 142.88, 145.20, 149.61, 152.37; IR (KBr, cm^{-1}): 1433, 1649, 2178, 3216, 3322, 3449; Anal. calcd for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07; found: C, 68.26; H, 4.84; N, 22.16. HRMS (ESI) calcd for $C_{18}H_{15}N_5O$ (M + H^+) 318.1355, found 318.1358.

2,6-Diamino-1-(furan-3-ylmethyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarbonitrile. White solid (0.310 g, 65%); Mp 209–214 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 3.70 (s, 3H), 3.82 (s, 1H), 4.97 (s, 2H), 6.22 (s, 4H), 6.29–6.35 (m, 1H), 6.41–6.49 (m, 1H), 6.67–6.81 (m, 4H), 7.67 (s, 1H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 40.87, 55.03, 62.45, 109.31, 110.50, 113.66, 121.35, 127.52, 137.43, 149.33, 152.20, 157.93; IR (KBr, cm^{-1}): 1435, 1508, 1649, 2170, 2187, 3219, 3321, 3448; Anal. calcd for $C_{19}H_{17}N_5O_2$: C, 65.69; H, 4.93; N, 20.16; found: C, 65.77; H, 5.14; N, 20.02. HRMS (ESI) calcd for $C_{19}H_{17}N_5O_2$ (M + H^+) 348.1460, found 348.1470.

2,6-Diamino-4-(4-chlorophenyl)-1-(furan-3-ylmethyl)-1,4-dihydropyridine-3,5-dicarbonitrile. White solid (0.310 g, 61%); Mp > 300 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 3.86 (s, 1H), 4.98 (s, 2H), 6.23–6.26 (m, 1H), 6.35 (s, 4H), 6.41–6.45 (m, 1H), 6.81 (d, J = 7.6 Hz, 2H), 7.25 (d, J = 7.6 Hz, 2H), 7.70 (s, 1H);^{13}C NMR (DMSO-D_6, 100 MHz): δ 40.98, 61.65, 109.43, 110.57, 121.08, 128.26, 131.05, 143.03, 144.25, 149.54, 152.54; IR (KBr, cm^{-1}): 1432, 1562, 1663, 2187, 3225, 3272, 3324, 3445; Anal. calcd for $C_{18}H_{14}ClN_5O$: C, 61.46; H, 4.01; N, 19.91; found: C, 61.54; H, 4.12; N, 20.02. HRMS (ESI) calcd for $C_{18}H_{14}ClN_5O$ (M + H^+) 352.0965, found 352.0973.

2,6-Diamino-4-(4-bromophenyl)-1-(furan-3-ylmethyl)-1,4-dihydropyridine-3,5-dicarbonitrile. White solid (0.310 g, 59%); Mp > 300 °C;^{1}H NMR (DMSO-D_6, 600 MHz): δ 3.90 (s, 1H), 4.97 (s, 2H), 6.28–6.32 (m, 1H), 6.33 (s, 4H), 6.43–6.49 (m, 1H), 6.76 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.69 (s, 1H); ^{13}C NMR (DMSO-D_6, 150 MHz): δ 40.96, 61.54, 109.45, 110.59, 119.55, 121.09, 128.68, 131.16, 143.07, 144.69, 149.53, 152.55; IR (KBr, cm^{-1}): 1431, 1559, 1665, 2186, 3224, 3271, 3324, 3440; Anal. calcd for $C_{18}H_{14}BrN_5O$: C, 54.56; H, 3.56; N, 17.67; found: C, 54.64; H, 3.67; N, 17.55; HRMS (ESI) calcd for $C_{18}H_{14}BrN_5O$ (M + H^+) 396.0460 found 396.0469.

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