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Catalyst-free one-pot synthesis and antioxidant evaluation of highly functionalized novel 1,4-dihydropyridine derivatives

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Abstract A catalyst-free greener protocol for the most effective one-pot synthesis of 2,6-diamino-4-aryl-1-propyl/cyclohexyl-1,4-dihydropyridine-3,5-dicarbonitrile derivatives has been developed using a simple three-component reaction of structurally diverse aldehydes, malononitrile and *n*-propylamine/cyclohexylamine at an ambient temperature. The formation of 1,4-dihydropyridines could be achieved in aqueous methanol in a single synthetic process involving no chromatography. The newly synthesized highly functionalized 1,4-DHPs have been screened for their in vitro antioxidant activity using the DPPH radical scavenging technique and the results were good in comparison with a standard drug.

Keywords 1,4-Dihyropyridine · *n*-Propylamine · Cyclohexylamine · DPPH radical scavenging · Antioxidant activity

Introduction

The development of greener methodologies to facilitate the construction of biologically diverse heterocyclic scaffolds based on privileged structures is an intense materialization of organic synthesis [1]. In the past decade, functionalization of C–H bond has been one of the most attractive and existing approaches in which environmentally benign processes to build newer chemical bonds have attracted the most attention. Multicomponent reactions (MCRs) have been considered as important tools in combinatorial chemistry due to their ability to synthesize novel 'drug-like' small molecules with superior applications [2–4]. In recent years, pollution-free chemical processes using metal-free catalysts have become highly

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desirable and some equivalent metal-free bases are easily available making the reaction costs lower.

Synthesis of pyridine-based heterocyclic compounds has predominant importance from the viewpoint of the discovery of novel drug molecules for the treatment of cancer, asthma, hypoxia, kidney disease, epilepsy, Parkinson's diseases [5] and Prion-induced fatal neurodegenerative diseases, such as Creutzteldt-Jacob disease in humans, bovine spongiform encephalopathy and scrapie in sheep [6]. 2-Amino-3-cyanopyridine scaffolds have diverse applications, such as anti-tumor [7], cardiotonic [8], and anti-inflammatory, and as novel IKK-β inhibitors [9], A_{2A} adenosine receptor antagonists [10] and potent inhibitors of HIV-1 integrase [11]. The synthesized pyridine derivatives bearing nitrile functionality are used as valuable intermediates for the synthesis of various N-heterocycles [12, 13]. In terms of the synthetic community, the high reactivity connected with 1,4-DHPs possesses vital applications in modern drug discovery. Generally, 1,4-dihydropyridines have been synthesized by the Hantzsch method, which involves the cyclocondensation of β-ketoester, aldehyde and ammonia in refluxing alcohol for long reaction times leading to only moderate yields [14–16]. Although a number of synthetic methods have been reported for 2-amino-3-cyanopyridines, with catalysts like nano ZnO [17], Et_3N [18, 19], piperidine [20], KOH [21], cellulose-SO_3H [22], SiO_2-sulfonic acid [23], etc., many of them suffer from any one of demerits such as prolonged reaction time, unsatisfactory yield, high temperature and harsh reaction conditions.

During the metabolic reactions, a variety of free radicals are generated and quenched by an efficient antioxidant network in the body. When the production of these species crosses their antioxidant mechanism, it leads to oxidative damage of tissues leading to diseases, especially degenerative diseases [24]. In this paper, we are reporting a greener protocol for the synthesis of highly functionalized 1,4-dihydropyridine derivatives and their antioxidant properties, evaluated using the DPPH (2,2´-diphenyl-1-picrylhydrazyl) method. The DPPH radical scavenging evaluation is a standard and rapid technique for the potent antioxidant studies of the synthesized compounds by a photometric method [25].

Experimental

Reagents and equipments

All the reagents and solvents were purchased from commercial sources and were freshly used after being purified by standard techniques. Reactions were monitored by TLC using silica gel-coated plates with ethyl acetate/hexanes as the mobile phase. Melting points were measured with an electrothermal apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a BRUKER DRX-400 spectrometer in $CDCl_3$ and chemical shifts are expressed in δ units using TMS as an internal standard. IR spectra were recorded on a Bruker FT-IR27 spectrophotometer using KBr optics. Mass spectrum was recorded on GCMS-Q-TOF spectrometer.

Typical procedure for the synthesis of 2,6-diamino-1,4-dihydropyridine-3,5-dicarbonitrile derivatives

To a stirred mixture of aromatic aldehyde (3.0 mmol) and malononitrile (6.0 mol) in aqueous methanol (60 %, 20 ml), *n*-propylamine/cyclohexylamine (3.5 mmol) was added at room temperature and, from the resulting solution, the products were precipitated within the time mentioned in Tables 1 and 2. After this (monitored by TLC using ethyl acetate: hexanes 1:2), the desired products were filtered, air-dried and recrystallized from methanol.

Table 1 Synthesis of 2,6-diamino-4-(aryl)-1-propyl-1,4-dihydropyridine-3,5-dicarbonitriles

Entry	R	Product[a]	Time (h)	Yield (%)[b]	M.pt (°C)
1	H	**4a**	3.0	84	182–184
2	4-Cl	**4b**	2.5	88	220–222
3	4-OMe	**4c**	3.0	83	218–220
4	4-F	**4d**	2.5	86	172–174
5	4-Br	**4e**	2.5	87	230–232
6	4-CH_3	**4f**	3.0	82	226–228
7	4-OH	**4g**	3.0	80	240–242
8	3-NO_2	**4h**	2.5	86	244–246
9	2-Cl	**4i**	3.0	84	250–252

[a] Reaction of aromatic aldehyde (3 mmol), malononitrile (3 mmol) and *n*-propylamine (3.5 mmol) in aqueous methanol (60 %, 20 ml) at room temperature

[b] Isolated yield

Table 2 Synthesis of 2,6-diamino-4-(aryl)-1-cyclohexyl-1,4-dihydropyridine-3,5-dicarbonitriles

Entry	R	Product[a]	Time (h)	Yield (%)[b]	M.pt (°C)
1	H	**6a**	3.0	82	224–226
2	4-Cl	**6b**	2.5	85	228–230
3	4-OMe	**6c**	3.0	81	220–222
4	4-F	**6d**	2.5	84	262–264
5	4-Br	**6e**	2.5	82	242–244
6	4-CH_3	**6f**	3.0	81	238–240
7	4-OH	**6g**	3.0	79	248–250
8	3-NO_2	**6h**	2.5	84	266–268
9	2-Cl	**6i**	3.0	83	262–264

[a] Reaction of aromatic aldehyde (3 mmol), malononitrile (3 mmol) and cyclohexylamine (3.5 mmol) in aqueous methanol (60 %, 20 ml) at room temperature

[b] Isolated yield

DPPH assay

The evaluation of antioxidant activity of the synthesized 1,4-DHPs has been performed by stable DPPH-free radicals, according to a modified procedure from that reported by Keshwal et al. [26] using DPPH (0.59 mg/250 ml) in methanol. Based on this, 0.1 ml of the test compound (in five different concentrations), 1.5 ml of methanol and 0.5 ml of DPPH solution were added and mixed thoroughly. The mixture was incubated at 25 °C for 60 min in the dark and the absorbance of reaction liquid was measured at 517 nm.

The percentage of scavenging activity of the tested compounds was calculated by using the formula.

$$\text{Scavenging effect } (\%) = (A_0 - A_1)/A_0 \times 100$$

where A_0 is the absorbance of the control (water instead of sample) and A_1 is the absorbance of the sample.

Characterization data

2,6-Diamino-4-phenyl-1-propyl-1,4-dihydropyridine-3,5-dicarbonitrile (**4a**): Yellow crystals; mp 182–184 °C; IR (KBr) (υ_{max}, cm^{-1}): 3,344, 3,312 (NH_2), 2,170 (CN), 1,063 (C–N); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.98 (t, 3H, CH_3, J = 7.4 Hz) 1.52 (h, 2H, CH_2, J = 7.2 Hz) 3.46 (t, 2H, CH_2 J = 6.0 Hz), 4.08 (s, 1H, CH), 5.72 (s, 2H, NH_2), 7.28 (d, 2H, ArH, J = 8.0 Hz), 7.32 (t, 1H, ArH, J = 7.6 Hz), 7.37 (t, 2H, ArH J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 12.10, 21.52, 36.14, 45.62, 56.41, 116.21, 125.80, 127.72, 130.10, 148.47, 162.58; MS(ESI) *m/z* 280 $(M + H)^+$; Anal. Calcd for $C_{16}H_{17}N_5$: C, 68.79; H, 6.13; N, 25.07 %. Found: C, 68.72; H, 6.07; N, 25.01 %.

2,6-Diamino-4-(4-bromophenyl)-1-propyl-1,4-dihydropyridine-3,5-dicarbonitrile (**4e**): Yellow crystals; mp 230–232 °C; IR (KBr) (υ_{max}, cm^{-1}): 3,357, 3,329 (NH_2), 2,203 (CN), 1,024 (C–N); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 0.99 (t, 3H, CH_3, J = 7.6 Hz), 1.59 (h, 2H, CH_2, J = 7.2 Hz) 3.46 (t, 2H, CH_2, J = 6.0 Hz) 3.97 (s, 1H, CH), 5.41 (s, 2H, NH_2), 7.42 (d, 2H, ArH, J = 8.8 Hz), 7.69 (d, 2H, ArH, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 10.32, 21.50, 42.31, 79.03, 115.42, 128.72, 131.63, 135.83, 156.86, 158.57, 159.96; MS(ESI) m/z 359 $(M + H)^+$; Anal. Calcd for $C_{16}H_{16}BrN_5$: C, 53.64; H, 4.50; N, 19.55 %. Found: C, 53.60; H, 4.42; N, 19.52 %.

2,6-Diamino-1-propyl-4-(*p*-tolyl)-1,4-dihydropyridine-3,5-dicarbonitrile (**4f**): Yellow crystals; mp 226–228 °C; IR (KBr) (υ_{max}, cm^{-1}): 3,352, 3,306 (NH_2), 2,207 (CN), 1,027 (C–N); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.92 (t, 3H, CH_3, J = 7.6 Hz) 1.56 (h, 2H, CH_2, J = 7.2 Hz) 2.34 (s, 3H, CH_3), 3.38 (t, 2H, CH_2, J = 6.8 Hz) 3.92 (s, 1H, CH), 5.37 (s, 2H, NH_2), 7.25 (d, 2H, ArH, J = 8.0 Hz), 7.35 (d, 2H, ArH, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 11.36, 21.47, 22.58, 43.30, 116.71, 116.85, 128.23, 129.57, 131.40, 140.84, 159.29, 161.05; MS (ESI) *m/z* 294 $(M + H)^+$; Anal. Calcd for $C_{17}H_{19}N_5$: C, 69.60; H, 6.53; N, 23.87 %. Found: C, 69.50; H, 6.47; N, 23.83 %.

2,6-Diamino-1-cyclohexyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbonitrile (**6a**): Dark Yellow crystals; mp 224–226 °C; IR (KBr) (υ_{max}, cm^{-1}): 3,352, 3,317 (NH_2), 2,203 (CN), 1,096 (C–N); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.22 (m, 4H, CH_2), 1.50 (m, 2H, CH_2), 1.72 (m, 4H, CH_2), 2.48 (p, 1H, CH), 4.14 (s, 1H, CH), 5.92 (s, 2H, NH_2), 7.25 (d, 2H, ArH, J = 7.8 Hz), 7.36 (t, 2H, ArH, J = 7.2 Hz), 7.37 (t, 1H, ArH, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.53, 27.21, 32.04, 36.15, 57.01, 116.27, 125.42, 127.92, 130.21, 146.71, MS(ESI) *m/z* 320 $(M + H)^+$; Anal. Calcd for $C_{19}H_{21}N_5$: C, 71.45; H, 6.63; N, 21.93 %. Found: C, 71.40; H, 6.58; N, 21.90 %.

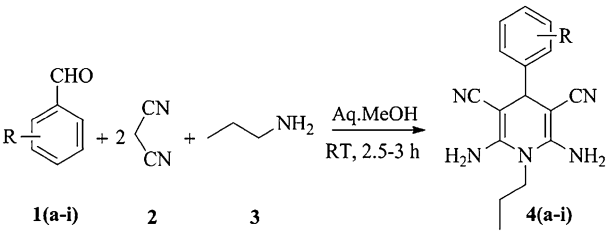
2,6-Diamino-4-(4-bromophenyl)-1-cyclohexyl-1,4-dihydropyridine-3,5-dicarbonitrile (**6e**): Yellowish white crystals; mp 242–244 °C; IR (KBr) (υ_{max}, cm^{-1}): 3,396, 3,338 (NH_2), 2,220 (CN), 1,016 (C–N); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.98 (m, 4H, CH_2), 1.52 (m, 4H, CH_2), 1.68 (m, 4H, CH_2), 3.38 (m, 1H, CH), 4.12 (s, 1H, CH), 5.58 (s, 2H, NH_2), 7.12 (d, 2H, ArH, J = 8.4 Hz), 7.58 (d, 2H, ArH, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.72, 31.64, 36.37, 50.77, 55.30, 83.83, 115.34, 125.59, 130.04, 132.32, 159.54, 166.70; MS(ESI) *m/z* 399 $(M + H)^+$; Anal. Calcd for $C_{19}H_{20}BrN_5$: C, 57.29; H, 5.06; N, 17.58 %. Found: C, 57.22; H, 5.01; N, 17.55 %.

2,6-Diamino-1-cyclohexyl-4-(*p*-tolyl)-1,4-dihydropyridine-3,5-dicarbonitrile (**6f**): Dark Yellow crystals; mp 238–240 °C; IR (KBr) (υ_{max}, cm^{-1}): 3,343, 3,312 (NH_2), 2,210 (CN), 1,019 (C–N); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.24 (m, 4H, CH_2), 1.53 (m, 2H, CH_2), 1.68 (m, 4H, CH_2), 2.56 (p, 1H, CH), 3.83 (s, 1H, OCH_3), 4.46 (s, 1H, CH), 5.73 (s, 2H, NH_2), 6.89 (d, 2H, ArH, J = 8.0 Hz), 7.14 (d, 2H, ArH, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.32, 27.10, 32.41, 36.30, 55.54, 57.62, 114.24, 116.05, 130.23, 134.63, 156.76, 161.36; MS(ESI) *m/z* 334 $(M + H)^+$; Anal. Calcd for $C_{20}H_{23}N_5$: C, 72.04; H, 6.95; N, 21.00 %. Found: C, 71.95; H, 6.90; N, 20.89 %.

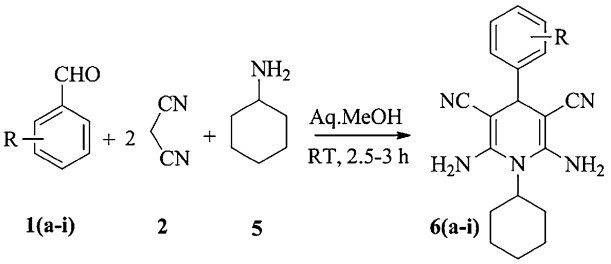
Results and discussion

To optimize the reaction conditions, initially we have tried the reaction of 4-chlorobenzaldehyde (**1b**) with two equivalents of malononitrile (**2**) and *n*-propylamine (**3**) in ethanol as a model reaction without any added catalysts. The reaction proceeded smoothly even at room temperature resulting in the formation of the target molecule (**4b**) with 58 % of yield in more than 5 h of reaction time. Then, we tried the same reaction with various solvents and the best results were obtained while using 60 % aqueous methanol as the solvent with a slight excess of amine.

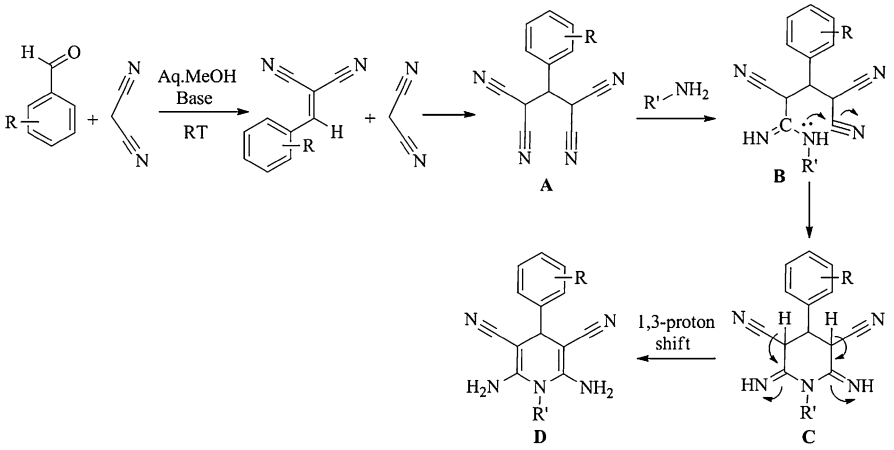
In this reaction, the initial Knoevenagel condensation step might be promoted by one of the excess reagents, namely, the *n*-propylamine (**3**) instead of using any other external base as a catalyst. With these optimized reaction conditions, a variety of substituted aromatic aldehydes (**1a—i**) have been utilized for the synthesis of a series of 2,6-diamino-1-propyl-3,5-dicyano-1,4-dihydropyridine derivatives (Scheme 1). The reactions of different aldehydes possessing either electron-withdrawing or electron-donating substituents produced heterocyclic compounds with good yields,



Scheme 1 Synthesis of 2,6-diamino-3,5-dicyano-1,4-dihydropyridine derivatives



Scheme 2 Synthesis of 2,6-diamino-3,5-dicyano-1,4-dihydropyridine derivatives



Scheme 3 The suggested mechanism for the one-pot synthesis of highly functionalized 1,4-dihydropyridines

ranging from 80 to 88 %. The unsubstituted benzaldehyde provided the corresponding 1,4-DHP of about 84 % yield (Table 1, Entry 1).

The formation of cyclized 1,4-DHP molecule was confirmed by the ^{1}H NMR spectrum, in which the two singlets appeared at δ 3.92 and 5.37 ppm, corresponding

to the methine proton (–CH–) and the free amine proton ($–NH_2$). IR shows a peak at 2,207 cm^{-1} that specifies the presence of nitrile moiety and peaks at 3,352 and 3,306 cm^{-1} representing the presence of $–NH_2$ group. Impressed by the results obtained in the above case, we extended the utility of this MCR with cyclohexylamine (**5**) in the place of *n*-propylamine (**3**) (Scheme 2). Under the above optimized reaction conditions, the three-component reaction of aromatic aldehydes, malononitrile and cyclohexylamine gave the corresponding 2,6-diamino-1-cyclohexyl-1,4-dihydropyridine-3,5-dicarbonitriles in 79–85 % (Table 2).

Table 3 Free radical scavenging activity of the synthesized 1,4-DHPs (**4a—i**) using DPPH assay

Entry	Compound	DPPH RSA[a] (2 mg/ml)	
		(%)	IC_{50} value (mg)
1	**4a**	73.59 ± 0.87	0.887
2	**4b**	90.44 ± 1.28	0.196
3	**4c**	51.25 ± 1.12	1.953
4	**4d**	74.38 ± 1.02	0.422
5	**4e**	76.25 ± 1.04	0.248
6	**4f**	57.67 ± 1.24	1.260
7	**4g**	50.31 ± 0.93	1.988
8	**4h**	68.11 ± 1.15	0.993
9	**4i**	86.43 ± 1.11	0.210
10	Ascorbic acid	92.22 ± 1.13	0.143

[a] Antioxidant activities were expressed in percentage compared with ascorbic acid. The data represent mean value (SEM) of three duplicates

Table 4 Free radical scavenging activity of the synthesized 1,4-DHPs (**6a—i**) using DPPH assay

Entry	Compound	DPPH RSA[a] (2 mg/ml)	
		(%)	IC_{50} value (mg)
1	**6a**	62.14 ± 1.39	0.922
2	**6b**	81.71 ± 1.23	0.231
3	**6c**	56.34 ± 1.09	1.139
4	**6d**	70.94 ± 0.59	0.646
5	**6e**	73.45 ± 1.32	0.238
6	**6f**	55.60 ± 1.19	1.387
7	**6g**	57.08 ± 1.32	1.086
8	**6h**	62.38 ± 1.45	1.388
9	**6i**	76.70 ± 1.28	0.280
10	Ascorbic acid	92.22 ± 1.37	0.143

[a] Antioxidant activities were expressed in percentage compared with standard ascorbic acid. The data represent mean value (SEM) of three duplicates

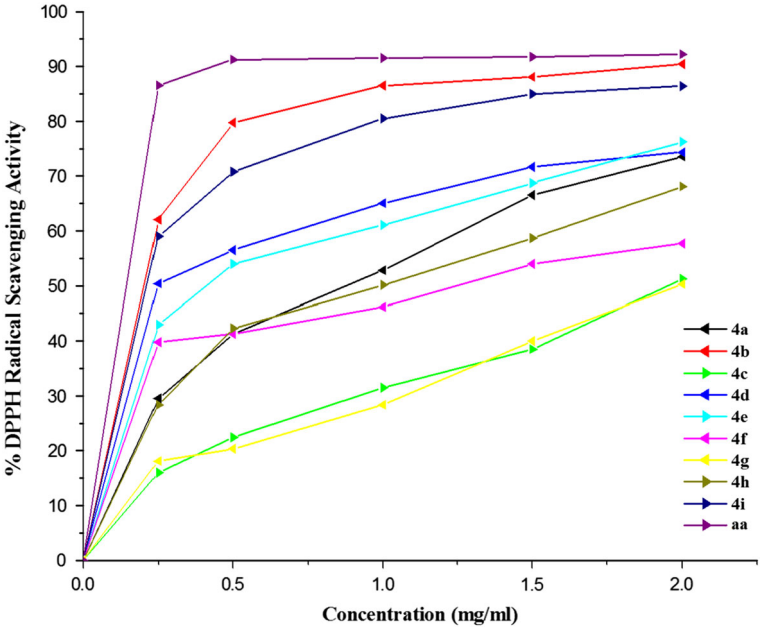


Fig. 1 Free radical scavenging activity of 2,6-diamino-4-aryl-1-propyl-1,4-dihydropyridine-3,5-dicarbonitriles

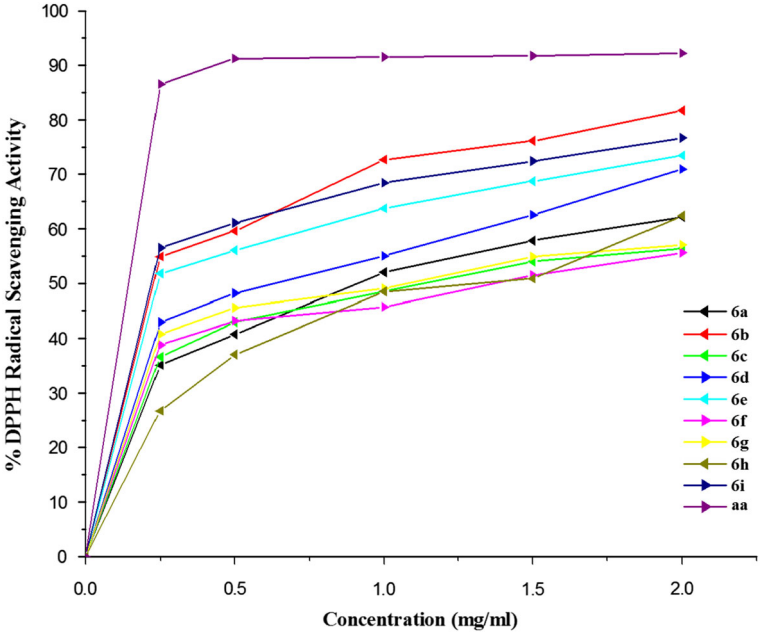
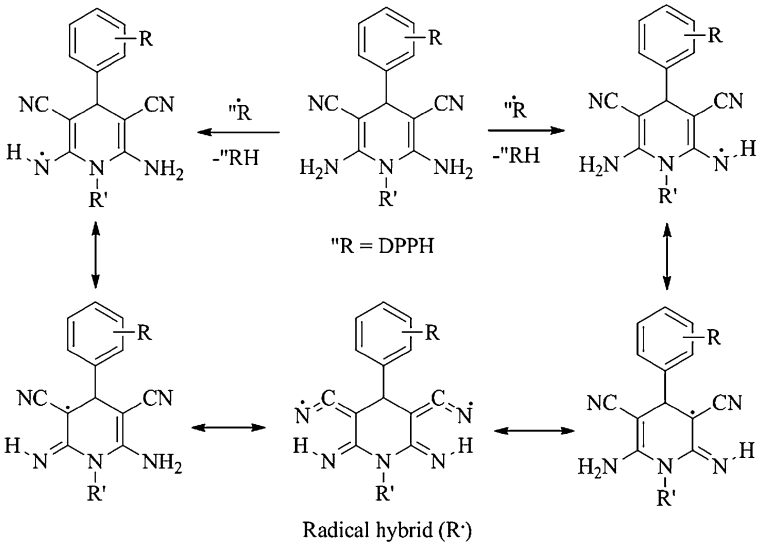


Fig. 2 Free radical scavenging activity of 2,6-diamino-4-aryl-1-cyclohexyl-1,4-dihydropyridine-3,5-dicarbonitriles



Scheme 4 Plausible steps for all synthesized 1,4-DHP's interacting with DPPH radical

A plausible mechanism for the three-component synthesis of diamino-1,4-dihydropyridine-dicarbonitrile derivatives at ambient temperature is presented in Scheme 3. Initially, the amine promotes the Knoevenagel condensation between aromatic aldehyde and malononitrile producing an arylidenemalononitrile which undergoes Michael addition with another mole of malononitrile, resulting in the formation of tetracyano intermediate **A**. In the second step, amine acting as a stronger nucleophile attacks the cyano group of intermediate **A** to give **B**. The third step involves the intra-molecular nucleophilic addition of the imino group to one of the cyano groups through a 1,3-proton shift to give nitrogen containing intermediate **C**. Finally, **C** undergoes tautomerization (i.e., imino to enamino) resulting in the formation of highly functionalized 1,4-dihydropyridine (**D**).

Radical scavenging activities of the synthesized compounds were screened by following the interacting ability of DHP derivatives with DPPH as the stable free radical. Decreased absorbance of the synthesized compounds with different concentrations indicated that the compounds possess significant radical scavenging abilities. The results obtained for the synthesized 1,4-DHPs are depicted in Tables 3 and 4 and graphically represented in Figs. 1 and 2. The values are expressed in percentage of inhibition and 50 % inhibitory concentration (the concentration of the test sample required the scavenging of 50 % free radicals) and compared with the ascorbic acid as standard. Initially, compound **4b** was selected as a model compound for evaluating its DPPH radical scavenging activity in five different concentrations, i.e. 2, 4, 6, 8, 10 mg/ml, and better activity was observed with 2 mg/ml. All the other compounds were screened for their antioxidant activity using 2 mg/ml concentrations.

The antioxidant activity of compounds in the series **4a—i** and **6a—i** is perhaps due to the presence of an N–H group, which can donate a hydrogen atom to the DPPH radical. After donating a hydrogen atom, compounds **4a—i** and **6a—i** exist in a radical form that is stabilized by resonance as shown in Scheme 4. Due to the greater electronegativity, the antioxidant properties of compounds with halogens are high.

The results indicated that some of the tested compounds are noteworthy for their antioxidant properties. Particularly, halogen-containing compounds **4b**, **6b**, **4d, 6d, 4e**, **6e**, **4i** and **6i** were most efficient with enhanced activity, whereas the insertion of the electron-donating OMe, CH_3 and OH groups, in **4c**, **4f** and **4 g**, respectively, decreased their radical scavenging ability. Among the compounds tested, **4b** and **6b** exhibited good antioxidant activities closer to the standard drug which may be attributed to the presence of a chlorine moiety on the aryl ring.

Conclusion

In summary, we have developed a greener and effective protocol leading to selective and high yielding novel 2,6-diamino-4-aryl-1-propyl/cyclohexyl-1,4-dihydropyridine-3,5-dicarbonitrile derivatives using a one-pot three-component reaction of aromatic aldehydes, malononitrile and *n*-propyl/cyclohexylamines without using any external catalysts at ambient temperature. This method provided several notable advantages such as operational simplicity, milder conditions and good yields. Antioxidant activities of all the synthesized compounds were measured using DPPH radical technique in which chlorine containing 1,4-DHPs showed maximum radical scavenging activity.

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