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Environmentally benign one-pot multicomponent synthesis of 1,4-dihydropyridine derivatives applying montmorillonite K10 as reusable catalyst

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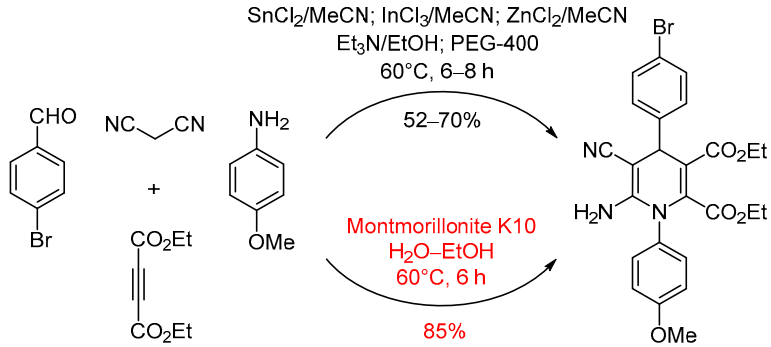


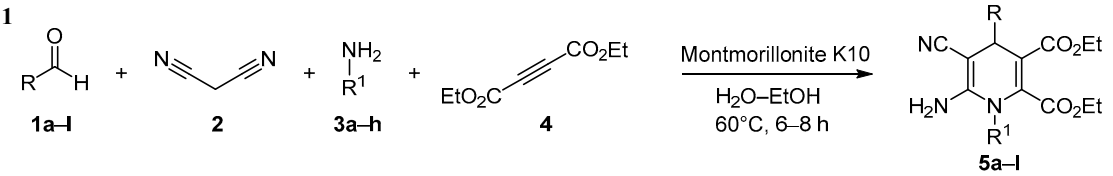
Environmentally benign one-pot multicomponent synthesis of different 1,4-dihydropyridine derivatives using montmorillonite K10 has been achieved. The montmorillonite K10-catalyzed reaction of aromatic aldehyde, malononitrile, substituted aniline, and diethyl acetylenedicarboxylate in H_2O–EtOH allows to obtain structurally diverse 1,4-dihydropyridines in high yields. Possibility to recover and reuse the acidic catalyst in up to five catalytic cycles has been demonstrated. Short reaction times, suppressed formation of side products, inexpensive and nontoxic solvent system, catalyst recovery, and simple workup procedure are the main advantages of the developed synthetic method.

Keywords: 1,4-dihydropyridine, montmorillonite K10, water–ethanol, atom economy, environmentally benign synthesis, one-pot synthesis.

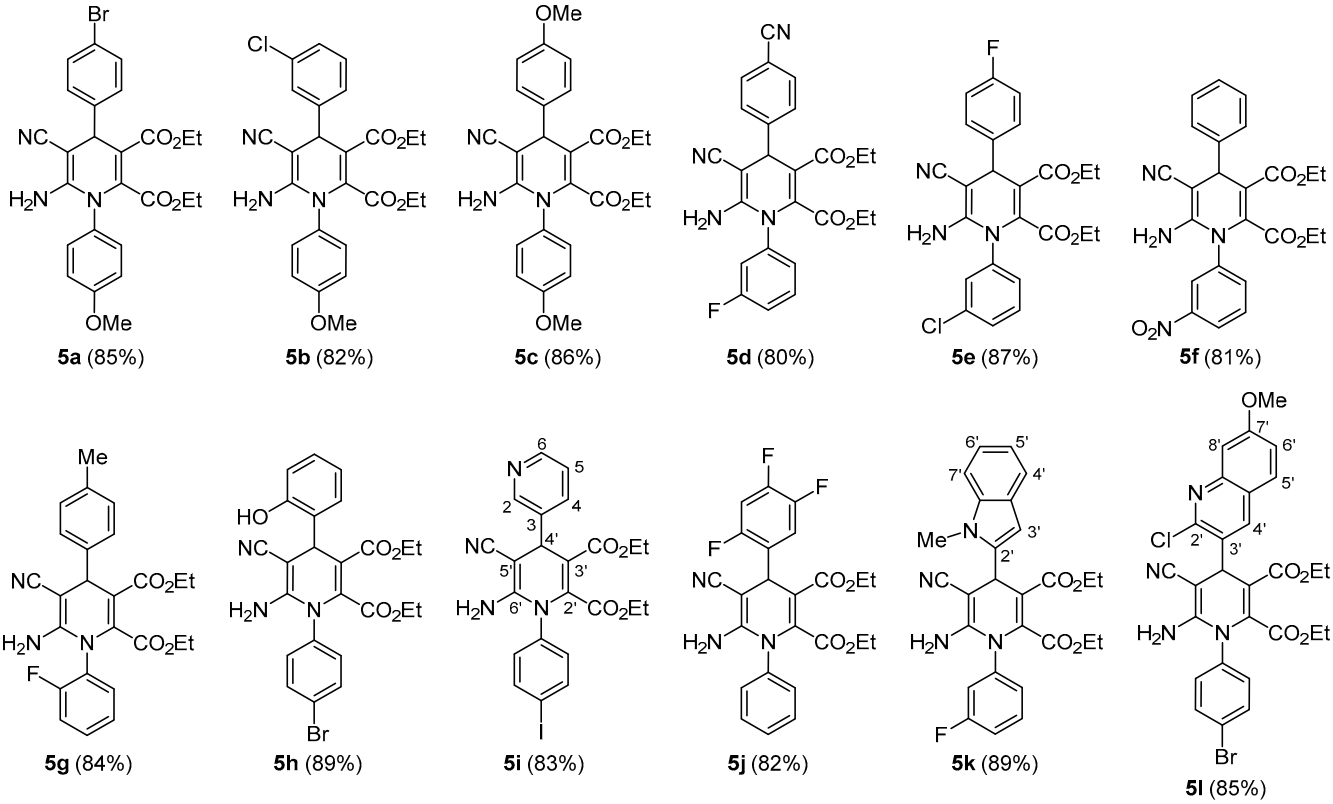
Application of less hazardous reactants, reagents, and solvents, reusable catalysts, and one-pot strategy as well as reduction of reaction time and amounts of side products are the key tools for environmentally benign organic synthesis. Hence, multicomponent reactions (MCRs) and chemical transformations performed in H_2O fit several of these criteria.[1]

Since 1,4-dihydropyridine (1,4-DHP) core is incorporated in many pharmaceuticals, natural biologically active products, and reactants or reagents exploited in organic synthesis, preparation of 1,4-DHP derivatives under environmentally benign conditions is of high importance. Compounds containing this broadly used motif have a wide range of biological activities[2] and have been applied for treatment of hypertension, cardiovascular diseases, Alzheimer's disease, and angina pectoris.[3] Numerous studies regarding drug molecules with 1,4-DHP fragment,

Scheme 1



1a–l **2** **3a–h** **4** **5a–l**



5a (85%) **5b** (82%) **5c** (86%) **5d** (80%) **5e** (87%) **5f** (81%)

5g (84%) **5h** (89%) **5i** (83%) **5j** (82%) **5k** (89%) **5l** (85%)

such as nifedipine, nicardipine, and amlodipine,[4] have been conducted. Many 1,4-DHPs exhibit anti-inflammatory,[2b] antitubercular,[5] and analgesic[6] properties. Moreover, a number of 1,4-DHP derivatives containing ester groups at the C-3 and C-5 atoms of the ring have been used as bronchodilator and antihypertensive agents.[7] Over last two decades, 1,4-DHPs have thereby attracted increased interest and led to challenge of developing new synthetic methods. Since the first studies of 1,4-DHPs performed by Hantzsch,[8] many synthetic paths have been demonstrated to obtain these compounds. For example, Vilsmeier–Haack reaction,[9] chemical transformations using chiral auxiliaries,[10] asymmetric organocatalytic[11] and chemo-enzymatic synthesis,[12] reactions with $(NH_4)_2CO_3$ as source of ammonia,[13] nano-tungsten trioxide-supported sulfonic acid (n-WSA)[14] and sulfated boric acid nanoparticle-catalyzed[15] reactions, and other methods[16] have been successfully applied. However, many of the reported synthetic methods with improved reaction conditions still have several drawbacks, such as exploitation of high temperature, low yields of products, and increased level of chemical waste.

In continuation of our multifaceted research regarding environmentally benign synthesis of novel pyrrole, thiazole, and pyranopyrazole derivatives,[17] herein we present the synthesis of 1,4-DHPs by montmorillonite K10-catalyzed MCR in H_2O–EtOH media. Possibility to recover and reuse montmorillonite K10 up to five catalytic cycles has been demonstrated.

Based on the knowledge in environmentally friendly synthesis and diverse biological activities of 1,4-DHPs, a series of unique and highly promising 1,4-DHPs *via* one-pot MCR in H_2O–EtOH medium were obtained. The reaction of aromatic aldehyde **1a**–**l**, malononitrile (**2**), substituted aniline **3a**–**h**, and diethyl acetylenedicarboxylate (**4**) in the presence of montmorillonite K10 in H_2O–EtOH allowed to obtain compounds **5a**–**l** in high yields (Scheme 1). The structure of compound **5a** as a representative was confirmed by single crystal X-ray crystallographic analysis (Fig. 1).

To evaluate the efficiency of montmorillonite K10 in the investigated reaction, compound **5a** was also synthesized using different catalysts and solvents and yields of product **5a** as well as catalyst reusability were compared (Table 1). When 4-bromobenzaldehyde (**1a**) was treated with malononitrile (**2**), 4-methoxyaniline (**3a**), and diethyl acetylenedicarboxylate (**4**) in the presence of triethylamine in EtOH, 1,4-DHP **5a** was obtained in 70% yield (Table 1, entry 1). Performing $SnCl_2$-catalyzed reaction in MeCN allowed to isolate product **5a** in 56% yield (entry 2). Comparatively low yields of 1,4-DHP **5a** were also obtained when the MCR was conducted in MeCN using $ZnCl_2$ or $InCl_3$ as catalysts (entries 3 and 5). Furthermore, PEG 400-cata-

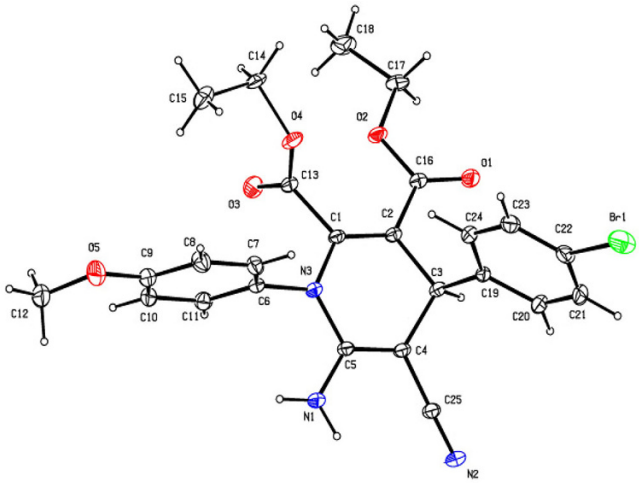


Figure 1. The molecular structure of 1,4-DHP **5a** with atoms represented by thermal vibration ellipsoids of 30% probability.

Table 1. Effects of various catalysts and solvents on the yield of 1,4-DHP **5a***

Entry	Catalyst**	Solvent	Yield, %
1	Et_3N	EtOH	70
2	$SnCl_2·2H_2O$	MeCN	56
3	$ZnCl_2$	MeCN	52
4	PEG 400	–	65
5	$InCl_3$	MeCN	60
6	Montmorillonite K10	H_2O–EtOH	85 (80)***

* Reaction conditions: 4-bromobenzaldehyde (**1a**) (185 mg, 1 mmol), malononitrile (**2**) (66 mg, 1 mmol), 4-methoxyaniline (**3a**) (123 mg, 1 mmol), diethyl acetylenedicarboxylate (**4**) (160 μl, 1 mmol), catalyst, solvent (5 ml), 60°C, 6–8 h.
** Catalyst was used in an amount of 50% by mass relative to 4-bromobenzaldehyde (**1a**).
*** Recovered montmorillonite K10 was used.

lyzed reaction under solvent-free conditions afforded product **5a** in 65% yield (entry 4).

The catalysts tested so far provided low to moderate yield of 1,4-DHP **5a**, and recovery of catalyst could not be achieved. However, montmorillonite K10 in environmentally benign H_2O–EtOH medium was more efficient and allowed to obtain product **5a** in 85% yield (Table 1, entry 6). Furthermore, montmorillonite K10 could be successfully recovered and reused without significant decrease in the yield of compound **5a**. Encouraged by these results, we applied such environmentally friendly reaction conditions for the synthesis of other 1,4-DHPs affording final products **5b**–**l** in 80–89% yield. Moreover, the catalyst could be reused up to five catalytic cycles, as demonstrated for the synthesis of compound **5a** (Fig. 2).

A plausible mechanism of the investigated MCR has been proposed (Scheme 2). The Knoevenagel condensation of aromatic aldehyde and malononitrile (**2**) catalyzed by acidic montmorillonite K10 yields arylidene compound **6**. In addition, arylamine reacts with diethyl acetylenedicarboxylate (**4**) to give 1,3-dipole **7** that may further interact with intermediate **6**. Subsequent cyclization of zwitterion **8** leads to the formation of target 1,4-DHP.

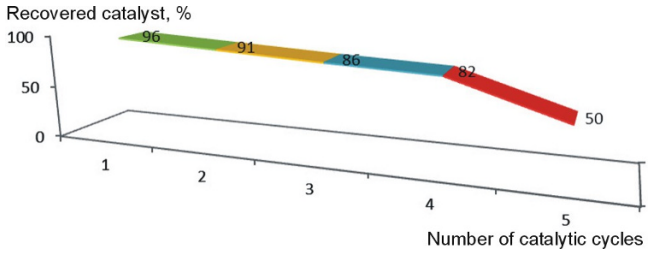
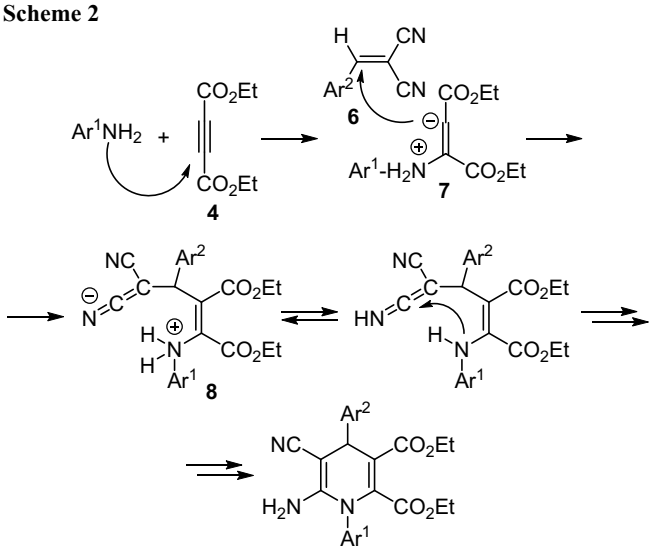


Figure 2. Recovery of montmorillonite K10 in the synthesis of 1,4-DHP **5a**.

Scheme 2



In conclusion, one-pot four-component synthesis of 1,4-DHP derivatives has been accomplished in H_2O–EtOH using montmorillonite K10 as catalyst. The acidic properties of montmorillonite K10 promote the formation of products, and the catalyst may be recovered and reused in up to five catalytic cycles. The developed environmentally benign and cost-effective synthetic approach exhibits several advantages – short reaction times, suppressed formation of side products, inexpensive and nontoxic solvent system, simple workup procedure, and catalyst reusability. Therefore, the presented method may be further exploited to obtain novel 1,4-DHP derivatives with promising biological activities.

Experimental

IR spectra were recorded on a Bruker Alpha FTIR spectrometer in KBr pellets. ^{1}H NMR (500 and 300 MHz for compounds **5a**,**b**,**d**–**l** and **5c**, respectively) and ^{13}C NMR spectra (125 and 75 MHz for compounds **5a**,**b**,**d**–**l** and **5c**, respectively) were acquired on a Bruker Avance 500 spectrometer in $CDCl_3$ solutions. TMS was used as internal standard for ^{1}H NMR spectra, and solvent carbon atom served as internal standard for ^{13}C NMR spectra ($CDCl_3$ 77.27 ppm). Low-resolution mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer (ESI method). HRMS data were obtained using a Thermo Scientific Obitrap mass spectrometer (ESI method). Melting points were measured on a Buchi R-535 micro melting point apparatus. Reaction progress was monitored

by analytical HPLC on a Waters HPLC system equipped with a Waters Atlantis dc18 column (4.6 × 150 mm, 5 μm) and by TLC on pre-coated silica gel GF_{254} plates (visualization by UV light at 254 nm).

Synthesis of 1,4-DHP derivatives 5a–l (General method). Diethyl acetylenedicarboxylate (**4**) (160 μl, 1 mmol) was added to a mixture of aromatic aldehyde **1a**–**l** (1 mmol), aromatic amine **3a**–**h** (1 mmol), malononitrile (**2**) (66 mg, 1 mmol), and montmorillonite K10 (50% by mass relative to aldehyde **1a**–**l**) in H_2O–EtOH, 4:1 (5 ml). The mixture was stirred at 60°C for 6–8 h, and completion of the reaction was confirmed by TLC (eluent hexane–EtOAc, 3:2) and analytical HPLC. EtOAc (6 ml) was then added and the obtained suspension was filtered through a plug of cotton. The filtrate was concentrated under reduced pressure, and crude product was recrystallized from EtOH. The cotton plug containing montmorillonite K10 was soaked in EtOAc (5–7 ml) until the catalyst settled down to the bottom of the beaker. The cotton was removed, EtOAc was decanted, and the obtained powder was dried in oven at 50°C. The recovered montmorillonite K10 could be reused in up to five catalytic cycles.

Diethyl 6-amino-4-(4-bromophenyl)-5-cyano-1-(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5a). Yield 447 mg (85%), yellow solid, mp 150–152°C. IR spectrum, ν, cm^{-1}: 3466 (NH_2), 3341, 3218, 2981, 2183 (C≡N), 1739 (C=O), 1703, 1648, 1570, 1509, 1416, 1369, 1300, 1217, 1107. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.49 (2H, d, *J* = 8.8, H Ar); 7.27–7.24 (4H, m, H Ar); 6.96 (2H, d, *J* = 8.8, H Ar); 4.65 (1H, s, 4-CH); 4.12 (2H, s, NH_2); 4.06–3.87 (4H, m, $2C\underline{H}_2CH_3$); 3.85 (3H, s, OCH_3); 1.10 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 0.99 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 165.0; 163.0; 160.9; 150.3; 144.2; 142.2; 131.8 (2C); 131.7 (2C); 129.0 (2C); 127.1; 120.9; 120.6; 114.9 (2C); 104.6; 62.0; 60.9 (2C); 55.7; 38.3; 13.9; 13.6. Found, *m*/*z*: 526.0946 $[M+H]^+$. $C_{25}H_{25}BrN_3O_5$. Calculated, *m*/*z*: 526.0972.

Diethyl 6-amino-4-(3-chlorophenyl)-5-cyano-1-(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5b). Yield 395 mg (82%), light-brown solid, mp 172–174°C. IR spectrum, ν, cm^{-1}: 3482 (NH_2), 3350, 3278, 3018, 2930, 2184 (C≡N), 1737 (C=O), 1704, 1651, 1571, 1510, 1416, 1370, 1215, 1109, 1031. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.44 (1H, dd, *J* = 7.7, *J* = 1.3, H Ar); 7.37 (1H, d, *J* = 7.9, H Ar); 7.32–7.27 (3H, m, H Ar); 7.19 (1H, t, *J* = 7.8, H Ar); 6.94 (2H, d, *J* = 8.6, H Ar); 5.30 (1H, s, 4-CH); 4.09 (2H, s, NH_2); 3.99–3.89 (4H, m, $2C\underline{H}_2CH_3$); 3.85 (3H, s, OCH_3); 1.06–1.00 (6H, m, $2CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 165.0; 163.1; 160.9; 150.3; 142.9; 142.6; 132.7; 131.8; 130.0; 129.8; 129.0; 128.2; 127.4; 127.2; 120.4; 114.9 (2C); 104.2; 62.0; 61.5; 60.8; 55.7; 35.8; 13.8; 13.6. Found, *m*/*z*: 482.1472 $[M+H]^+$. $C_{25}H_{25}ClN_3O_5$. Calculated, *m*/*z*: 482.1477.

Diethyl 6-amino-5-cyano-1,4-bis(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5c). Yield 411 mg (86%), light-brown solid, mp 156–158°C (mp 168–170°C[18]). IR spectrum, ν, cm^{-1}: 3470 (NH_2), 3348, 3225, 3018, 2978, 2183 (C≡N), 1738 (C=O), 1703, 1650, 1609, 1572, 1414, 1300, 1215, 1176, 1108, 1031. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.30–7.27 (4H, m, H Ar); 6.96 (2H, d, *J* = 8.9, H Ar); 6.90 (2H, d, *J* = 8.7, H Ar); 4.62 (1H, s, 4-CH); 4.06 (2H, s, NH_2); 3.84 (3H, s, OCH_3); 4.03–3.82 (4H, m, $2C\underline{H}_2CH_3$); 3.81 (3H, s, OCH_3); 1.13 (3H, t, *J* = 14.1, $CH_2C\underline{H}_3$); 1.00 (3H, t, *J* = 14.3, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 165.3; 163.2; 160.8; 158.6; 149.9; 141.7; 137.6; 131.7 (2C); 128.3 (2C); 127.4 (2C); 120.8; 114.9; 114.1; 105.4; 62.8; 61.9; 60.8; 55.7; 55.3; 37.9; 14.0; 13.6. Found, *m*/*z*: 478.1977 $[M+H]^+$. $C_{26}H_{28}N_3O_6$. Calculated, *m*/*z*: 478.1972.

Diethyl 6-amino-5-cyano-4-(4-cyanophenyl)-1-(3-fluorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5d). Yield 368 mg (80%), light-brown solid, mp 148–150°C. IR spectrum, ν, cm^{-1}: 3452 (NH_2), 3329, 3019, 2928, 2855, 2230, 2186 (C≡N), 1736 (C=O), 1708, 1653, 1576, 1488, 1417, 1371, 1215, 1108, 1019. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.68 (2H, dd, *J* = 11.3, *J* = 2.6, H Ar); 7.70–7.66 (3H, m, H Ar); 7.53–7.49 (1H, m, H Ar); 7.47 (1H, d, *J* = 8.2, H Ar); 7.18 (1H, d, *J* = 8.2, H Ar); 4.74 (1H, s, 4-CH); 4.29 (2H, s, NH_2); 4.05–3.89 (4H, m, $2C\underline{H}_2CH_3$); 1.07 (3H, t, *J* = 14.3, $CH_2C\underline{H}_3$); 0.99 (3H, t, *J* = 14.3, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 164.4; 163.6; 162.4; 161.6 (d, ^1J = 246); 149.7; 141.8; 136.1 (d, ^3J = 8); 132.7 (2C); 131.2; 127.9 (d, ^4J = 3.0); 126.3 (2C); 119.8; 118.7; 118.2; 118.0 (d, ^2J = 22.0); 110.9; 104.6; 62.3; 61.7; 61.1; 38.9; 13.8; 13.4. Found, *m*/*z*: 461.1627 $[M+H]^+$. $C_{25}H_{22}FN_4O_4$. Calculated, *m*/*z*: 461.1619.

Diethyl 6-amino-1-(3-chlorophenyl)-5-cyano-4-(4-fluorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5e). Yield 409 mg (87%), yellow solid, mp 181–183°C. IR spectrum, ν, cm^{-1}: 3486 (NH_2), 3358, 3017, 2186 (C≡N), 2134, 1736 (C=O), 1705, 1652, 1578, 1507, 1474, 1415, 1370, 1298, 1218, 1157, 1097, 1017. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.52–7.38 (3H, m, H Ar); 7.34–7.23 (3H, m, H Ar); 7.05 (2H, dd, *J* = 14.2, *J* = 2.8, H Ar); 4.66 (1H, s, 4-CH); 4.17 (2H, s, NH_2); 4.06–3.85 (4H, m, $2C\underline{H}_2CH_3$); 1.10 (3H, t, *J* = 14.3, $CH_2C\underline{H}_3$); 1.00 (3H, t, *J* = 14.3, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 164.8; 162.7; 162.6; 160.8 (d, ^1J = 246.0); 149.3; 140.9; 140.5 (d, ^4J = 2.0); 136.1; 135.2; 130.7 (2C); 130.6 (d, ^3J = 5.0); 128.7 (2C); 120.2; 115.5; 115.3 (d, ^2J = 23.0); 105.6; 62.6; 62.0; 60.9; 38.0; 13.7; 13.3. Found, *m*/*z*: 470.1277 $[M+H]^+$. $C_{24}H_{22}ClFN_3O_4$. Calculated, *m*/*z*: 470.1271.

Diethyl 6-amino-5-cyano-1-(3-nitrophenyl)-4-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (5f). Yield 374 mg (81%), yellow solid, mp 175–177°C. IR spectrum, ν, cm^{-1}: 3473 (NH_2), 3384, 3019, 2988, 2179 (C≡N), 1739 (C=O), 1699, 1649, 1577, 1534, 1448, 1415, 1354, 1244, 1216, 1108, 1015. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.37 (1H, d, *J* = 7.7, H Ar); 8.26 (1H, d, *J* = 7.8, H Ar); 7.76–7.69 (2H, m, H Ar); 7.41–7.30 (5H, m, H Ar); 4.70 (1H, s, 4-CH); 4.07 (2H, s, NH_2); 4.02–3.88 (4H, m, $2C\underline{H}_2CH_3$); 1.10 (3H, t, *J* = 14.3, $CH_2C\underline{H}_3$); 1.01 (3H, t, *J* = 14.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 164.9; 162.9; 144.2; 140.6; 136.8; 136.7; 130.9; 130.1; 128.9; 128.5; 127.4; 127.2; 125.6; 125.3; 119.9; 107.0 (2C); 64.9; 62.4; 61.2; 38.7; 13.9; 13.5. Found, *m*/*z*: 463.1610 $[M+H]^+$. $C_{24}H_{23}N_4O_6$. Calculated, *m*/*z*: 463.1612.

Diethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-(*p*-tolyl)-1,4-dihydropyridine-2,3-dicarboxylate (5g). Yield 377 mg (84%), dark-brown solid, mp 168–170°C. IR spectrum, ν, cm^{-1}: 3466 (NH_2), 3376, 3018, 2978, 2186 (C≡N), 1736 (C=O), 1704, 1653, 1579, 1500, 1416, 1370, 1302, 1215, 1107, 1019. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.52–7.50 (1H, m, H Ar); 7.39 (1H, t, *J* = 14.6, H Ar); 7.30–7.24 (4H, m, H Ar); 7.17 (2H, d, *J* = 7.6, H Ar); 4.61 (1H, s, 4-CH); 4.05 (2H, s, NH_2); 4.01–3.83 (4H, m, 2C$\underline{H}_2$CH$_3$); 2.32 (3H, s, CH_3); 1.11 (3H, t, *J* = 14.1, $CH_2C\underline{H}_3$); 0.92 (3H, t, *J* = 14.3, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 164.9; 162.9; 161.0 (d, ^1J = 245.0); 149.1; 141.7; 140.8; 136.6 (d, ^2J = 22.0); 132.7; 132.6; 132.1; 129.2; 127.3; 124.8 (d, ^3J = 7.0); 123.1 (d, ^4J = 3.0); 120.3; 117.1; 117.0; 106.4; 63.6; 61.9; 60.8; 38.4; 21.0; 13.8; 13.3. Found, *m/z*: 450.1799 $[M+H]^+$. $C_{25}H_{25}FN_3O_4$. Calculated, *m/z*: 450.1823.

Diethyl 6-amino-1-(4-bromophenyl)-5-cyano-4-(2-hydroxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5h). Yield 456 mg (89%), light-brown solid, mp 204–206°C. IR spectrum, ν, cm^{-1}: 3469 (NH_2), 3361, 3018, 2984, 2184 (C≡N), 1736 (C=O), 1699, 1650, 1574, 1485, 1455, 1417, 1394, 1371, 1325, 1215, 1109, 1013. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.57 (2H, d, *J* = 8.6, H Ar); 7.25–7.21 (3H, m, H Ar); 7.11 (1H, t, *J* = 14.1, H Ar); 6.92 (1H, t, *J* = 14.1, H Ar); 6.82 (1H, d, *J* = 7.9, H Ar); 4.88 (1H, s, 4-CH); 4.24 (2H, s, NH_2); 4.11–3.80 (4H, m, 2C$\underline{H}_2$CH$_3$); 1.11 (3H, t, *J* = 14.1, $CH_2C\underline{H}_3$); 0.97 (3H, t, *J* = 14.3, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 166.4; 163.0; 153.8; 150.6; 141.6; 134.4; 133.1 (2C); 132.2 (2C); 131.0; 129.2; 128.6; 124.9; 121.0; 120.7; 117.4; 105.1; 62.2; 61.7; 61.6; 33.1; 13.8; 13.4. Found, *m/z*: 512.0815 $[M+H]^+$. $C_{24}H_{23}BrN_3O_5$. Calculated, *m/z*: 512.0833.

Diethyl 6'-amino-5'-cyano-1'-(4-iodophenyl)-1',4'-dihydro-[3,4'-bipyridine]-2',3'-dicarboxylate (5i). Yield 466 mg (83%), pale-yellow solid, mp 191–193°C. IR spectrum, ν, cm^{-1}: 3475 (NH_2), 3368, 3019, 2976, 2150 (C≡N), 1737 (C=O), 1709, 1655, 1577, 1467, 1416, 1371, 1215, 1110, 1023. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.89 (1H, s, H-6); 8.49 (1H, d, *J* = 7.6, H-2); 7.95 (2H, dd, *J* = 7.5, *J* = 1.4, H Ar); 7.54–7.48 (2H, m, H-5, H Ar); 7.30 (1H, d, *J* = 7.4, H Ar); 7.26 (1H, d, *J* = 8.5, H-4); 4.81 (1H, s, 4'-CH); 4.06 (2H, s, NH_2); 4.04–3.83 (4H, m, 2C$\underline{H}_2$CH$_3$); 1.08 (3H, t, *J* = 14.1, $CH_2C\underline{H}_3$); 0.97 (3H, t, *J* = 14.3, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 164.7; 162.3; 149.8; 148.1; 141.2; 140.0; 137.4; 135.9; 135.2; 132.7; 132.0; 129.6; 129.5; 123.6; 123.4; 120.1; 102.5; 62.0; 61.8; 61.0; 37.2; 13.8; 13.4. Found, *m/z*: 545.0678 $[M+H]^+$. $C_{23}H_{22}IN_4O_4$. Calculated, *m/z*: 545.0680.

Diethyl 6-amino-5-cyano-1-phenyl-4-(2,4,5-trifluorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5j). Yield 386 mg (82%), light-brown solid, mp 166–168°C. IR spectrum, ν, cm^{-1}: 3482 (NH_2), 3351, 3018, 2980, 2185 (C≡N), 2170, 1739 (C=O), 1705, 1651, 1573, 1515, 1421, 1371, 1321, 1215, 1146, 1117, 1088, 1018. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.54–7.50 (3H, m, H Ar); 7.37 (2H, dd, *J* = 9.6, *J* = 3.2, H Ar); 7.19–7.14 (1H, m, H Ar); 6.98–6.92 (1H, m, H Ar); 4.87 (1H, s, 4-CH); 4.18 (2H, s, NH_2); 4.09–4.01 (2H, m, C$\underline{H}_2$CH$_3$); 3.96–3.78 (2H, m, C$\underline{H}_2$CH$_3$); 1.14 (3H, t, *J* = 14.3, $CH_2C\underline{H}_3$); 0.93 (3H, t, *J* = 14.3, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 164.7; 162.7; 157.0; 154.9 (dd, ^1J = 247.0, ^3J = 9.0); 150.6 (dd, ^1J = 247.0, ^3J = 9.0); 148.0 (ddd, ^1J = 245.0, ^2J = 13.0, ^4J = 2.0); 145.8; 142.6; 134.9; 130.7 (2C); 129.9 (2C); 128.4; 120.2; 117.5 (dd, ^2J = 19.0, ^3J = 5.0); 105.9; 102.7 (dd, ^2J = 28.0, ^2J = 21.0); 62.1; 61.1; 59.8; 34.0; 13.8; 13.4. Found, *m/z*: 472.1458 $[M+H]^+$. $C_{24}H_{21}F_3N_3O_4$. Calculated, *m/z*: 472.1478.

Diethyl 6-amino-5-cyano-1-(3-fluorophenyl)-4-(1-methyl-1*H*-indol-2-yl)-1,4-dihydropyridine-2,3-dicarboxylate (5k). Yield 451 mg (89%), brown solid, mp 145–147°C. IR spectrum, ν, cm^{-1}: 3478 (NH_2), 3365, 3018, 2928, 2864, 2182 (C≡N), 1736 (C=O), 1707, 1654, 1575, 1467, 1416, 1370, 1317, 1215, 1135, 1104, 1018. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.55 (1H, d, *J* = 7.9, H Ar); 7.47–7.43 (1H, m, H Ar); 7.34 (1H, d, *J* = 7.9, H Ar); 7.24–7.17 (3H, m, H Ar); 7.14–7.07 (2H, m, H Ar); 6.41 (1H, s, H-3'); 4.94 (1H, s, 4-CH); 4.16 (2H, s, NH_2); 4.08–3.94 (4H, m, 2C$\underline{H}_2$CH$_3$); 3.91 (3H, s, NCH_3); 1.07 (3H, t, *J* = 14.1, $CH_2C\underline{H}_3$); 0.99 (3H, t, *J* = 14.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 164.6; 163.6; 162.7; 161.6; 149.9; 143.6; 141.0; 137.7; 136.4; 131.1; 127.6; 126.3; 121.3; 120.3; 119.5; 118.0 (d, *J* = 9.1); 117.8; 109.4; 104.7; 99.9; 62.1; 61.3; 61.1; 30.2; 29.9; 13.8; 13.4. Found, *m/z*: 489.1905 $[M+H]^+$. $C_{27}H_{26}FN_4O_4$. Calculated, *m/z*: 489.1902.

Diethyl 6-amino-1-(4-bromophenyl)-4-(2-chloro-7-methoxyquinolin-3-yl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (5l). Yield 536 mg (85%), brown solid, mp 209–211°C. IR spectrum, ν, cm^{-1}: 3468 (NH_2), 3339, 3018, 2929, 2853, 2184 (C≡N), 1738 (C=O), 1706, 1651, 1622, 1572, 1493, 1418, 1370, 1342, 1216, 1171, 1112, 1036, 1015. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.04 (1H, s, H-4'); 7.91 (1H, d, *J* = 9.1, H-5'); 7.67 (2H, d, *J* = 8.1, H Ar); 7.37 (1H, dd, *J* = 9.2, *J* = 2.7, H-6'); 7.31 (2H, d, *J* = 8.6, H Ar); 7.09 (1H, d, *J* = 2.7, H-8'); 5.34 (1H, s, 4-CH); 4.15 (2H, s, NH_2); 4.01–3.91 (7H, m, 2C$\underline{H}_2$CH$_3$, OCH$_3$); 1.00 (6H, t, *J* = 14.6, 2$CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 164.7; 162.8; 158.2; 150.0; 147.2; 142.8; 142.5; 137.7; 136.4; 133.9 (2C); 133.2 (2C); 132.3; 129.6; 128.7; 125.2; 123.2; 119.9; 105.1; 103.8; 62.4; 61.2; 61.0; 55.7; 36.9; 13.8; 13.5. Found, *m/z*: 611.0694 $[M+H]^+$. $C_{28}H_{25}BrClN_4O_5$. Calculated, *m/z*: 611.0691.

X-ray structural analysis of compound 5a. Crystals were obtained by crystallization from EtOH. Single crystal X-ray crystallographic data were collected at room temperature on a Bruker Smart Apex CCD diffractometer with graphite monochromatic MoKα radiation (λ 0.71073 Å) using ω-scan method.[19] Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Integration and reduction of data were accomplished using SAINT[19] and SMART[20] programs. The structure was solved by direct method, and all non-hydrogen atoms were refined by full-matrix least-squares technique on F^2 using SHELXS97.[21] Anisotropic displacement parameters were included for all non-hydrogen atoms. Atoms C(14) and C(15) were disordered over two sites (C(14)/C(14)' and C(15)/C(15)') and refined with equal site-

occupancy factor of 0.5. DFIX, SIMU, and SADI constraints were applied to the disordered atoms. H atoms were positioned geometrically and treated as riding on their parent C atoms (C–H 0.93–0.97 Å and $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl group H or $1.2U_{eq}(C)$ for other H atoms). The methyl groups were allowed to rotate. Crystal data for compound **5a**: $C_{25}H_{24}BrN_3O_5$, M_r 526.38, triclinic space group $P\bar{1}$; *a* 7.6737(8), *b* 13.4179(13), *c* 13.5891(13) Å; α 112.882(2), β 90.562(2), γ 104.086(2)°; *V* 1241.8(2) Å^3; *T* 294 K; *Z* 2; d_{calc} 1.408 g/cm^3; μ 1.695 mm^{-1}; 11955 reflections measured ($3.42 \leq 2\Theta \leq 50$), 4354 unique ($R_{int}$ 0.0202), which were used in all calculations. The final R_1 was 0.0551 (>2σ(*I*)), and wR_2 was 0.1566 (all data). The complete crystallogrpahic dataset was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1419160).

The Supplementary information file containing ^{1}H and ^{13}C NMR spectral data of compounds **5a**–**l** is available at the journal website at http://link.springer.com/journal/10593.

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