A Novel and Green Method for the Synthesis of Highly Substituted Isoquinoline Derivatives in Ionic Liquid

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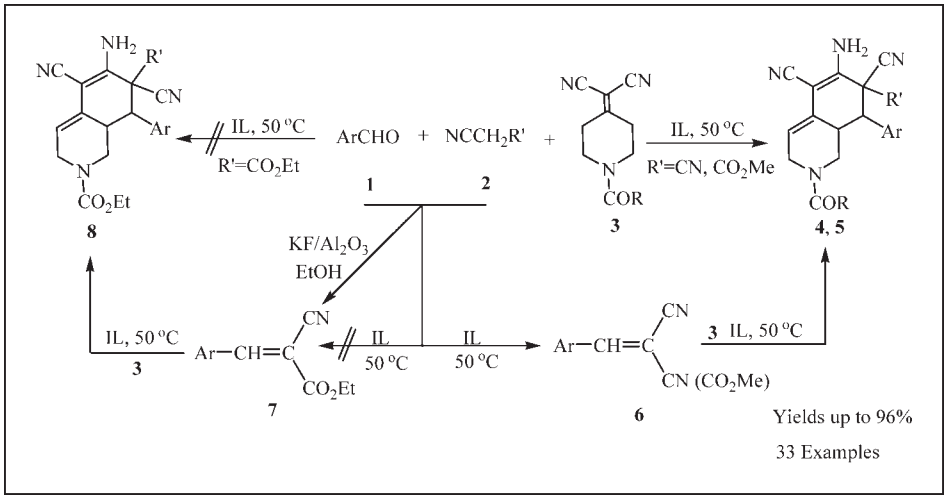

A series of new highly substituted isoquinoline derivatives was obtained from the reaction of 2-(1-substituted piperidin-4-ylidene)malononitrile, benzaldehyde and malononitrile or cyanoacetate in ionic liquid at 50°C. This novel procedure was different from the previous method in the synthesis of isoquinoline using pyridine fragment as reactant to construct benzene ring, and as well as had the advantages of one-pot, mild and environmentally benign. A possible mechanism was proposed based on the further experimental results.

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INTRODUCTION

Multi-component reactions (MCRs) are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step. MCRs are perfectly suited for combinatorial library synthesis, and thus find increasing use in the discovery process for new drugs and agrochemicals [1]. In addition, ionic liquids have attracted increasing interest in the context of green synthesis in recent years. They were initially introduced as alternative green reaction media because of their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility. The possibility of recycling them and the low vapor pressure also ensure their utility in environmentally friendly technologies. They have been used as solvents for a large number of organic transformations [2].

Molecules with heterocyclic substructures are attractive targets for synthesis as they often exhibit diverse and important biological properties, such as isoquinoline derivatives. They have been reported to possess antifungal activity [3], antitumor activity [4], anticoagulant activity [5], anti-inflammatory, and analgesic activity [6]. 3-Cyanoisoquinoline **I** (Fig. 1), was reported as a Kv1.5 antagonist, and evaluated *in vitro* and *in vivo* assays for inhibition of the Kv1.5 potassium channel and its associated cardiac potassium current. Its derivatives afforded with excellent potency, selectivity, and oral bioavailability [7].

Accordingly, novel strategies for the synthesis of isoquinolines continue to receive considerable attention in the field of synthetic organic chemistry [8], except for the known classical isquinoline synthetic methods [9(a)–(f)], *e.g.* Bischler-Napieralski reaction, Pictet-Gams isoquinoline synthesis, Pomeranz-Fritsch reaction, Gabriel-Colman rearrangement, and Pictet-Spengler isoquinoline synthesis. Commonly, amines containing benzene ring

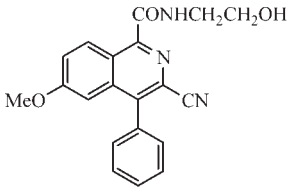


Figure 1. 3-Cyanoisoquinoline.

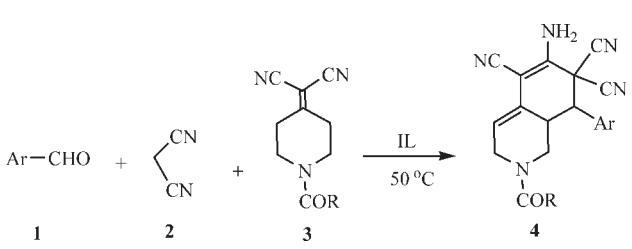
were used as reactants to construct the pyridine nucleus to gain the isoquinolines. On the contrary, our interest was focused on the synthesis of isoquinoline derivatives using a fragment containing pyridine ring as starting material to form benzene moiety. Inspired this novel idea and as part of a continuing effort in our laboratory toward the new methods for the e biologically relevant heterocyclic compounds in ionic liquids [10], herein, we would like to report a novel reaction of 2-(1-substituted-piperidin-4-ylidene)malononitrile, benzaldehyde, and malononitrile or cyanoacetate in the synthesis of highly substituted isoquinoline derivatives.

RESULTS AND DISCUSSION

The three-component reaction of benzaldehyde **1**, malononitrile **2**, and ethyl 4-(dicyanomethylene) piperidine-1-carboxylate **3** (R=OEt) was treated in ionic liquid at 50°C, with ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-arylisoquinoline-2(1*H*)-carboxylate derivatives **4** being obtained in high yields (Scheme 1).

Firstly, optimizations of the reaction conditions, including reaction temperature and solvents, were investigated using 2-chlorobenzaldehyde, malononitrile and ethyl 4-(dicyanomethylene)piperidine-1-carboxylate as model reactants. As summarized in Table 1, the results showed that at room temperature, only trace products were observed by TLC. (Table 1, entry 1). To our delight, the reaction proceeded smoothly in high yield at 50°C, higher temperature 90°C gave a complicated system, only 52% yield of **4a** was isolated by silica gel column chromatography. Moreover, different ionic liquids were further tested as reaction medium and it was observed that [bmim$^+$] [BF$_4^-$] was the best ionic liquid for the reaction (Table 1, entries 4–8). In addition, we also looked into the water and other organic solvent effect at 50°C for this reaction. As showed in Table 1, ionic liquid of [bmim$^+$] [BF$_4^-$] gave the most satisfactory result in comparison with other solvents (Table 1, entries 9–12).

Scheme 1



After the reaction was completed, the reaction mixtures were cooled to room temperature. Water (5 mL) was then added to the mixture and the solid was isolated by filtration. The water in the filtrate was removed by evaporation at reduced pressure, and the ionic liquid in the filtrate could be recycled easily at 80°C *in vacuum* for 4 h. The recovered ionic liquid could be directly used for the same reactions. Alternatively, if the ionic liquid was used for other reactions with different substrates, it was washed with ethyl acetate, followed by evaporation at 80°C *in vacuum* for 3 h. Investigations by using 2-chlorobenzaldehyde, ethyl 4-(dicyanomethylene) piperidine-1-carboxylate, and malononitrile as model substrates proved the successive reuse of ionic liquid. Even in the fourth cycle the yield (87%) of product **4a** is fairly high.

According to the optimized conditions, we next examined the utility of this process (Scheme 1) to synthesize a range of isoquinoline **4**. Various arylaldehydes **1**, bearing either electron-withdrawing groups (such as halide, nitro) or electron-donating groups (such as alkyl group or alkoxyl group), were subjected to react with **3** to give the corresponding isoquinoline derivatives **4** in high yields (Table 2, entries 1–16). Replacing the ethyl 4-(dicyanomethylene)piperidine-1-carboxylate to 2-(1-(3-chlorobenzoyl)piperidin-4-ylidene)malononitrile

Table 1

Synthesis of **4a** at different reaction conditions.[a]

Entry	T/°C	Solvents[b]	Yields[c]/%
1	r.t.	[bmim$^+$][BF$_4^-$]	Trace
2	50	[bmim$^+$][BF$_4^-$]	93
3	90	[bmim$^+$][BF$_4^-$]	52
4	50	[emim$^+$] Br$^-$	82
5	50	[pmim$^+$] Br$^-$	85
6	50	[bmim$^+$]Br$^-$	85
7	50	[emim$^+$][BF$_4^-$]	86
8	50	[pmim$^+$][BF$_4^-$]	84
9	50	H_2O	72
10	50	EtOH	78
11	50	THF	67
12	50	DMF	83

[a] Reaction conditions: ionic liquid (2 mL), 2-chlorobenzaldehyde (0.281 g, 2 mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2 mmol), malononitrile (0.132 g, 2 mmol) and other solvents 10 mL.
[b] bmim = 1-butyl-3-methylimidazolium; emim = 1-ethyl-3-methyli midazolium; pmim=1-methyl-3-propylimidazolium.
[c] Isolated yields.

Table 2

The reactions of 2-(1-substitutedpiperidin-4-ylidene) malononitrile, benzaldehyde, and malononitrile in ionic liquid.[a]

Entry	Ar	R	Products	Time /h	Yields[b]/%
1	2-ClC_6H_4	OEt	**4a**	8	93
2	3,4-$Cl_2C_6H_4$	OEt	**4b**	10	92
3	2,4-$Cl_2C_6H_4$	OEt	**4c**	8	94
4	4-$NO_2C_6H_4$	OEt	**4d**	7	89
5	4-$CH_3C_6H_4$	OEt	**4e**	11	90
6	2-$NO_2C_6H_4$	OEt	**4f**	6	95
7	4-BrC_6H_4	OEt	**4g**	10	90
8	3-ClC_6H_4	OEt	**4h**	9	87
9	3-BrC_6H_4	OEt	**4i**	9	93
10	2-FC_6H_4	OEt	**4j**	7	95
11	2,3-$Cl_2C_6H_4$	OEt	**4k**	8	87
12	2-CNC_6H_4	OEt	**4l**	9	83
13	4-FC_6H_4	OEt	**4m**	8	90
14	2-BrC_6H_4	OEt	**4n**	7	95
15	4-ClC_6H_4	OEt	**4o**	8	93
16	2,3-$OMe_2C_6H_3$	OEt	**4p**	10	87
17	3-ClC_6H_4	3-ClC_6H_4	**4q**	10	84
18	2-FC_6H_4	3-ClC_6H_4	**4r**	9	86
19	2-BrC_6H_4	3-ClC_6H_4	**4s**	9	85
20	2-ClC_6H_4	3-ClC_6H_4	**4t**	9	85

[a] Reaction conditions: ionic liquid (2 mL), benzaldehyde (2 mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2 mmol), malononitrile (0.132 g, 2 mmol).
[b] Isolated yields.

also gave the satisfactory results (Table 2, entries 17–20). As expected, the substrate of malononitrile could be extended to other active methylene compound. Methyl cyanoacetate was also chosen as reactant to treat with benzaldehyde, 4-(dicyanomethylene) piperidine-1-carboxylate (Scheme 2), and was found to generate the corresponding 2-ethyl 7-methyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-arylisoquinoline-2,7(1*H*)-dicarboxylate derivatives (**5a**–**5f**) (Scheme 2) in high yields (Table 3).

However, to our surprise, we failed to get the expected products when ethyl cyanoacetate was used (Scheme 2). This raised an interesting question: why could the methyl cyanoacetate give good results, while ethyl cyanoacetate could not? This also stimulated us to carry out new experiments to find the reason as well as explore the reaction mechanism.

In our continued study, we find the reaction of benzaldehyde and methyl cyanoacetate could be proceeded smoothly to give corresponding methyl 2-cyano-3-(2-chlorophenyl)acrylate **6** in ionic liquid, while other cyanoacetates, such as ethyl or propyl cyanoacetate could not react with benzaldehyde. Perhaps, the reaction activity of ethyl cyanoacetate is less than that of methyl cyanoacetate or malononitrile. The results were agreed to those of the same reactions in water [11] or ethanol [12] without catalyst. Subsequently, we also tested the reaction of **6** and ethyl 4-(dicyanomethylene)piperidine-1-

Scheme 2

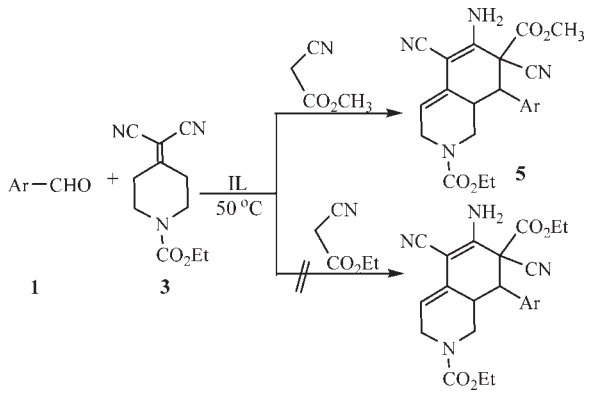


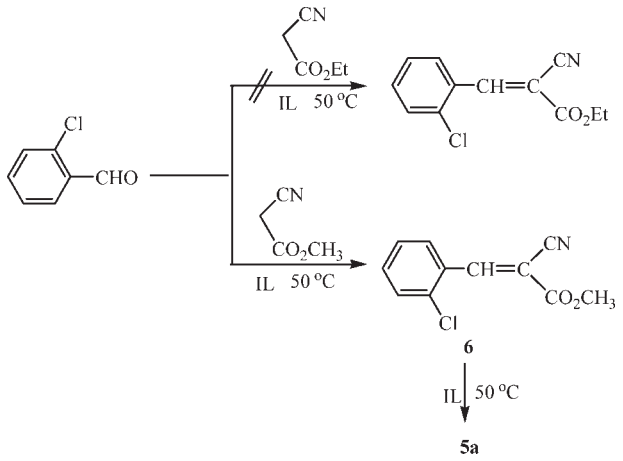
Table 3

The reactions of ethyl 4-(dicyanomethylene)piperidine-1-carboxylate, benzaldehyde, and methyl cyanoacetate in ionic liquid.[a]

Entry	Ar	Products	Time /h	Yields[b] %
1	2-ClC_6H_4	**5a**	12	86
2	2,3-$OMe_2C_6H_3$	**5b**	15	83
3	2,3-$Cl_2C_6H_3$	**5c**	11	87
4	4-BrC_6H_4	**5d**	15	85
5	3,4-$Cl_2C_6H_3$	**5e**	14	87
6	4-ClC_6H_4	**5f**	15	90

[a] Reaction conditions: ionic liquid (2 mL), benzaldehyde (2 mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2 mmol), methyl cyanoacetate (0.198 g, 2 mmol).
[b] Isolated yields.

Scheme 3

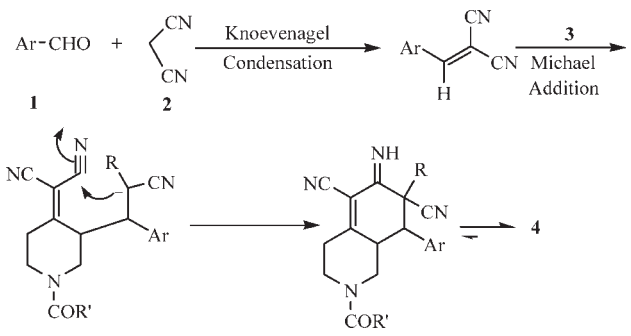


carboxylate **3** in ionic liquid at the same temperature, the desired 2-ethyl 7-methyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-(2-chlorophenyl)isoquinoline-2,7(1*H*)-dicarboxylate **5a** was obtained successfully in high yield of (total yield 78%) (Scheme 3).

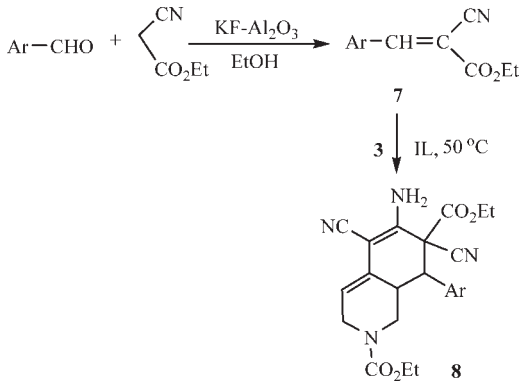
According to the above results, a sequential reaction of the Knoevenagel condensation, Michael addition reaction cyclization and isomerization may take place to give the final products **4**. A tentative mechanism was outlined in Scheme 4.

Encouraged by this result and to obtain the desired diethyl isoquinoline-2,7-dicarboxylate derivatives, a number of ethyl 2-cyano-3-arylacrylate **7** were synthesized by the known Knoevenagel condensation [13] of benzaldehydes and ethyl cyanoacetate in EtOH firstly, and then applied to react with **3** in ionic liquid (Scheme 5). Similarly, **7** smoothly reacted in ionic liquid at 50 °C to give the corresponding diethyl-6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-arylisoquinoline-2,7(1*H*)-dicarboxy late derivatives **8** in high yields (Table 4) as expected. The results were listed in Table 4.

Scheme 4



Scheme 5



CONCLUSION

In conclusion, we have disclosed a green and novel method to synthesize of new highly substituted isoquinoline derivatives was obtained from the reaction of 2-(1-substituted piperidin-4-ylidene)malononitrile, benzaldehyde and malononitrile or cyanoacetate in ionic liquid at 50°C. The note-worthy features of this procedure are different from the previous method in the synthesis of isoquinoline using pyridine fragment as reactant to construct benzene ring, mild reaction conditions, one-pot, high yield, operational simplicity and the environmentally friendly procedure. Meanwhile, [bmim$^+$][BF_4^-] could be reused for several rounds without significant loss of activity.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a TENSOR 27 spectrometer in KBr pellet. ^{1}H NMR spectra were obtained from solution in DMSO-d_6 or $CDCl_3$ with Me_4Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using Bruker-micro TOF-Q-MS analyzer.

Table 4

The reactions of ethyl 2-cyano-3-arylacrylate and ethyl 4-(dicyanomethylene) piperidine-1-carboxylate in ionic liquid.[a]

Entry	Ar	Products	Time /h	Yields[b]%
1	2-$NO_2C_6H_4$	**8a**	6	94
2	4-MeC_6H_4	**8b**	8	96
3	2-ClC_6H_4	**8c**	7	92
4	2,4-$Cl_2C_6H_3$	**8d**	7	94
5	3,4-$Me_2C_6H_3$	**8e**	10	90
6	3-ClC_6H_4	**8f**	9	95
7	4-$OMeC_6H_4$	**8g**	10	92

[a] Reaction conditions: ionic liquid (2 mL), ethyl 2-cyano-3-arylacrylate (2mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2 mmol).
[b] Isolated yields.

General procedure for the syntheses of 6-amino-8-arylisoquinoline derivatives 4. A dry 50 mL flask was charged with arylaldehyde (2.0 mmol), malononitrile (0.132 g, 2.0 mmol), 2-(1-substitutedpiperidin-4-ylidene)malononitrile (2.0 mmol), and ionic liquid of [bmim$^+$][BF_4^-] (2 mL). The reaction mixture was stirred at 50°C for 7–11 h, and then cooled to room temperature. The generated yellow solid was filtered off, and the ionic liquid in filtrate was then recovered for reuse by evaporating at 80°C several h at *vacuum*. The crude yellow products were washed with water and purified by recrystallization from DMF and water, followed by being dried at 50°C several h at *vacuum* to give **4**.

Ethyl 6-amino-8-(2-chlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4a. Mp 230–232°C. IR (KBr)/cm^{-1} 3346, 3207, 3028, 2992, 2937, 2845, 2211, 1655, 1603, 1574, 1486, 1467, 1440, 1396, 1378, 1339, 1299, 1242, 1135, 1028, 1007, 941, 883, 818, 775, 750, 704. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.12–1.15 (m, 3H, CH_3), 2.37–2.40 (m, 1H, CH), 3.04–3.06 (m, 1H, CH), 3.57–3.81 (m, 2H, 2CH) 3.92–4.05 (m, 3H, CH_2O+CH), 4.27–4.37 (m, 1H, CH), 5.72 (s, 1H, CH), 7.55–7.61 (m, 2H, ArH), 7.67–7.69 (m, 3H, ArH+NH_2), 7.81–7.83 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 14.4, 33.8, 40.0, 40.2, 41.2, 43.4, 61.0, 80.1, 111.1, 111.6, 112.7, 115.5, 128.0, 129.99, 130.02, 130.6, 135.1, 136.1, 144.2, 164.1. HRMS-ESI. calcd for $C_{21}H_{18}ClN_5NaO_2$, M + Na^+: 430.1047, found: 430.1018.

Ethyl 6-amino-8-(3,4-dichlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4b. Mp 264–265°C. IR (KBr)/cm^{-1} 3343, 3159, 3063, 2994, 2980, 2209, 1656, 1605, 1488, 1468, 1444, 1396, 1343, 1298, 1248, 1207, 1189, 1136, 1115, 1032, 1007, 896, 814, 981, 761, 728. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15–1.18 (m, 3H, CH_3), 2.35–2.40 (m, 1H, CH), 2.97–3.05 (m, 1H, CH), 3.66–3.78 (m, 2H, 2CH), 3.88–4.03 (m, 3H, CH_2O + CH), 4.28–4.41 (m, 1H, CH), 5.69 (s, 1H, CH), 7.46–7.66 (m, 1H, ArH), 7.67 (s, 2H, NH_2), 7.77–7.92 (m, 2H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 14.4, 32.7, 40.0, 40.2, 42.4, 43.4, 61.0, 80.1, 111.7, 111.8, 112.7, 115.6, 127.3, 131.1, 131.3, 131.4, 132.5, 134.7, 144.1, 167.0. HRMS-ESI. calcd for $C_{21}H_{18}Cl_2N_5O_2$, M + H^+: 442.0838, found: 442.0835.

Ethyl 6-amino-8-(2,4-dichlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4c. Mp 241–243°C. IR (KBr)/cm^{-1} 3340, 3194, 3029, 2984, 2933, 2895, 2847, 2212, 1692, 1653, 1604, 1559, 1478, 1439, 1395, 1341, 1299, 1242, 1110, 1052, 1025, 1005, 884, 864, 821, 783, 771. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.14–1.15 (m, 3H, CH_3), 2.35–2.42 (m, 1H, CH), 3.02–3.08 (m, 1H, CH), 3.52–3.80 (m, 2H, 2CH), 4.02–4.06 (m, 3H, CH_2O + CH), 4.27–4.40 (m, 1H, CH), 5.71 (s, 1H, CH), 7.67 (s, 2H, NH_2), 7.75 (dd, J = 8.4 Hz, 2.0, 1H, ArH), 7.84 (d, J = 8.4 Hz, 1H, ArH), 7.89 (d, J = 2.4 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{21}H_{17}Cl_2N_5NaO_2$, M + Na^+: 464.0657, found: 464.0658.

Ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-(4-nitrophenyl)isoquinoline-2(1H)-carboxylate 4d. Mp 243–244°C. IR (KBr)/cm^{-1} 3430, 3331, 3222, 3079, 2984, 2213, 1679, 1645, 1603, 1526, 1476, 1420, 1386, 1353, 1297, 1277, 1229, 1127, 1111, 1022, 867, 841, 822, 783, 725. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (s, 3H, CH_3), 2.37–2.43 (m, 1H, CH), 3.04–3.10 (m, 1H, CH), 3.66–3.79 (m, 2H, 2CH), 4.01–4.10 (m, 3H, CH_2O + CH), 4.29–4.39 (m, 1H, CH), 5.71 (s, 1H, CH), 7.69 (s, 2H, NH_2), 7.76 (d, J = 8.0 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 8.37–8.49 (m, 2H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}N_6NaO_4$, M + Na^+: 441.1287, found: 441.1272.

Ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-p-tolylisoquinoline-2(1H)-carboxylate 4e. Mp. 244–246°C. IR (KBr)/cm^{-1} 3345, 3164, 3061, 3032, 2982, 2929, 2851, 2211, 1670, 1635, 1517, 1487, 1395, 1344, 1299, 1279, 1190, 1050, 1026, 882, 524, 813, 783, 773, 751. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.14–1.17 (m, 3H, CH_3), 2.36–2.40 (s, 4H, CH_3+CH), 2.94 (b, 1H, CH), 3.68–3.74 (m, 3H, 3CH), 4.00–4.03 (m, 2H, CH_2O), 4.29–4.37 (m, 1H, CH), 5.67 (s, 1H, CH), 7.29–7.38 (m, 3H, ArH), 7.50–7.51 (m, 1H, ArH), 7.61 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{22}H_{21}N_5NaO_2$, M + Na^+: 410.1593, found: 410.1587.

Ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-(2-nitrophenyl)isoquinoline-2(1H)-carboxylate 4f. Mp. 227–228°C. IR (KBr)/cm^{-1} 3345, 3217, 3022, 2989, 2860, 2212, 1675, 1603, 1535, 1485, 1466, 1435, 1399, 1357, 1299, 1236, 1192, 1132, 1026, 941, 883, 862, 820, 763, 731, 696. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.08–1.15 (m, 3H, CH_3), 2.59–2.67 (m, 1H, CH), 3.19–3.22 (m, 1H, CH), 3.68–3.84 (m, 2H, 2CH), 3.94–4.03 (m, 2H, CH_2O), 4.22–4.40 (m, 2H, 2CH), 5.73 (s, 1H, CH), 7.66 (s, 2H, NH_2), 7.80–7.84 (m, 1H, ArH), 7.95–8.02 (m, 1H, ArH), 8.06 (d, J = 7.6 Hz, 1H, ArH), 8.14 (d, J = 8.0 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}N_6NaO_4$, M + Na^+: 441.1287, found: 441.1263.

Ethyl 6-amino-8-(4-bromophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)carboxylate 4g. Mp. 247–248°C. IR (KBr)/cm^{-1} 3344, 3166, 2983, 2210, 1687, 1660, 1605, 1491, 1468, 1443, 1413, 1394, 1342, 1299, 1273, 1246, 1190, 1133, 1077, 1051, 1024, 1012, 883, 833, 814, 778, 767, 754. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (s, 3H, CH_3), 2.34–2.41 (m, 1H, CH), 2.95–2.99 (m, 1H, CH), 3.65–3.85 (m, 3H, 3CH), 3.99–4.05 (m, 2H, CH_2O), 4.28–4.39 (m, 1H, CH), 5.68 (s, 1H, CH), 7.40–7.42 (m, 1H, ArH), 7.59–7.62 (m, 1H, ArH), 7.64 (s, 2H, NH_2), 7.72–7.81 (m, 2H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}BrN_5NaO_2$, M + Na^+: 474.0542, found: 474.0542.

Ethyl 6-amino-8-(3-chlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4h. Mp. 241–243°C. IR (KBr)/cm^{-1} 3342, 3171, 2994, 2849, 2210, 1668, 1602, 1575, 1488, 1469, 1442, 1393, 1377, 1344, 1298, 1247, 1203, 1189, 1132, 1049, 1025, 1008, 888, 814, 798, 781, 750, 711. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 4.15–4.18 (m, 3H, CH_3), 2.34–2.41 (m, 1H, CH), 2.97–3.03 (m, 1H, CH), 3.65–3.78 (m, 2H, 2CH), 3.83–3.89 (m, 1H, CH), 4.02–4.03 (m, 2H, CH_2O), 4.28–4.41 (m, 1H, CH_3), 5.69 (s, 1H, CH), 7.43–7.62 (m, 4H, ArH), 7.66 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{21}H_{18}ClN_5NaO_2$, M + Na^+: 430.1047, found: 430.1046.

Ethyl 6-amino-8-(3-bromophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4i. Mp. 265–267°C. IR (KBr)/ cm^{-1} 3343, 3169, 2995, 2980, 2851, 2208, 1662, 1602, 1571, 1487, 1466, 1441, 1391, 1344, 1297, 1248, 1188, 1122, 1077, 1044, 1024, 1008, 882, 812, 793, 782, 748, 694. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.16–1.17 (m, 3H, CH_3), 2.34–2.41 (m, 1H, CH), 2.96–3.01 (m, 1H, CH), 3.65–3.78 (m, 2H, 2CH), 3.82–3.87 (m, 1H, CH), 3.95–4.03 (m, 2H, CH_2O), 4.29–4.41 (m, 1H, CH), 5.69 (s, 1H, CH), 7.48–7.58 (m, 2H, ArH), 7.66 (s, 2H, NH_2), 7.70–7.79 (m, 2H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}BrN_5NaO_2$, M + Na^+: 474.0542, found: 474.0542.

Ethyl 6-amino-5,7,7-tricyano-8-(2-fluorophenyl)-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4j. Mp. 252–254°C. IR (KBr)/ cm^{-1} 3337, 3182, 3032, 2993, 2937, 2844, 2212, 1650, 1602, 1491, 1444, 1397, 1341, 1299, 1247, 1198, 1181, 1136, 1053, 1028, 1007, 884, 864, 818, 773, 759. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.14–1.15 (m, 3H, CH_3), 2.43–2.46 (m, 1H, CH), 3.03–3.18 (m, 1H, CH), 3.64–3.78 (m, 2H, 2CH), 3.90–4.04 (m, 3H, CH_2O+CH), 4.28–4.39 (m, 1H, CH), 5.70 (s, 1H, CH), 7.33–7.47 (m, 2H, ArH), 7.54–7.64 (m, 3H, ArH+NH_2), 7.72–7.76 (m, 1H, ArH). RMS-ESI. calcd for $C_{21}H_{18}FN_5NaO_2$, M + Na^+: 414.1342, found: 414.1342.

Ethyl 6-amino-8-(2,3-dichlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4k. Mp. 234–235°C. IR (KBr)/ cm^{-1} 3336, 3174, 2993, 2978, 2933, 2844, 2209, 1653, 1487, 1467, 1444, 1391, 1340, 1298, 1274, 1246, 1185, 1164, 1048, 1028, 1008, 889, 817, 800, 780, 757, 741, 697. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.10–1.15 (m, 3H, CH_3), 2.39–2.43 (m, 1H, CH), 3.07 (s, 1H, CH), 3.61–3.80 (m, 2H, 2CH), 3.93–4.02 (m, 2H, CH_2O), 4.16 (d, J = 12.8 Hz, 1H, CH). 4.28–4.38 (m, 1H, CH), 5.72 (s, 1H, CH), 7.64–7.68 (m, 3H, ArH+NH_2), 7.81–7.86 (m, 2H, ArH). HRMS-ESI. calcd for $C_{21}H_{17}Cl_2N_5NaO_2$, M + Na^+: 464.0557, found: 464.0552.

Ethyl 6-amino-5,7,7-tricyano-8-(2-cyanophenyl)-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4l. Mp. 220–222°C. IR (KBr)/ cm^{-1} 3406, 3340, 3222, 3017, 2987, 2225, 2210, 1693, 1634, 1609, 1481, 1435, 1390, 1339, 1301, 1278, 1237, 1130, 1049, 1026, 1007, 888, 822, 776, 759. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.11–1.15 (m, 3H, CH_3), 2.58–2.62 (m, 1H, CH), 3.18 (s, 1H, CH), 3.53–3.77 (m, 3H, 3CH), 3.90–4.02 (m, 2H, CH_2O), 4.29–4.39 (m, 1H, CH), 5.76 (s, 1H, CH), 7.24–7.79 (m, 3H, ArH), 7.99 (s, 2H, NH_2), 8.08 (d, J = 7.6 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{22}H_{18}N_6NaO_2$, M + Na^+: 421.1389, found: 421.1367.

Ethyl 6-amino-5,7,7-tricyano-8-(4-fluorophenyl)-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4m. Mp. 240–242°C. IR (KBr)/ cm^{-1} 3342, 3172, 2984, 2934, 2851, 2211, 1668, 1602, 1515, 1487, 1468, 1443, 1396, 1233, 1299, 1280, 1164, 1134, 1024, 882, 841, 811, 786, 777, 760. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (s, 3H, CH_3), 2.34–2.44 (m, 1H, CH), 2.94–2.98 (m, 1H, CH), 3.65–3.78 (m, 2H, 2CH), 3.83 (d, J = 12.8 Hz, 1H, CH), 3.99–4.02 (m, 2H, CH_2O), 4.29–4.39 (m, 1H, CH), 5.68 (s, 1H, CH), 7.35–7.46 (m, 3H, ArH), 7.51 (s, 2H, NH_2), 7.63–7.68 (m, 1H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}FN_5NaO_2$, M + Na^+: 414.1342, found: 414.1325.

Ethyl 6-amino-8-(2-bromophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4n. Mp. 222–224°C. IR (KBr)/ cm^{-1} 3346, 3202, 2991, 2933, 2861, 2212, 1662, 1648, 1602, 1486, 1473, 1398, 1339, 1298, 1242, 1130, 1050, 1026, 941, 884, 819, 775, 747. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.08–1.15 (m, 3H, CH_3), 2.35–2.41 (m, 1H, CH), 3.07 (s, 1H, CH), 3.54–3.82 (m, 2H, 2CH), 3.90–4.01 (m, 3H, CH_2O+CH), 4.27–4.37 (m, 1H, CH), 5.72 (s, 1H, CH), 7.45–7.49 (m, 1H, ArH), 7.63–7.67 (m, 1H, ArH), 7.70 (s, 2H, NH_2), 7.80–7.86 (m, 2H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}BrN_5NaO_2$, M + Na^+: 474.0542, found: 474.0523.

Ethyl 6-amino-8-(4-chlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4o. Mp. 238–240°C. IR (KBr)/ cm^{-1} 3342, 3169, 2987, 2850, 2211, 1687, 1661′ 1604, 1494, 1442, 1395, 1342, 1299, 1275, 1239, 1132, 1096, 1016, 941, 883, 835, 815, 778, 757. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (s, 3H, CH_3), 2.34–2.44 (m, 1H, CH), 2.98 (s, 1H, CH), 3.65–3.78 (m, 2H, CH_2), 3.85 (d, J = 12.8 Hz, 1H, CH), 3.99–4.05 (m, 2H, CH_2O), 4.26–4.42 (m, 1H, CH), 5.69 (s, 1H, CH), 7.47–7.60 (m, 2H, ArH), 7.64–7.67 (m, 4H, ArH+NH_2). HRMS-ESI. calcd for $C_{21}H_{18}ClN_5NaO_2$, M + Na^+: 430.1047, found: 430.1025.

Ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-(2,3-dimethoxyphenyl)isoquinoline-2(1H)-carboxylate 4p. Mp. 229–231°C. IR (KBr)/ cm^{-1} 3377, 3334, 3191, 2971, 2946, 2837, 2210, 1661, 1605, 1482, 1445, 1393, 1340, 1296, 1271, 1240, 1171, 1137, 1097, 1073, 1044, 1003, 819, 794, 766, 724. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.14 (b, 3H, CH_3), 2.35–2.41 (m, 1H, CH), 2.85–2.88 (m, 1H, CH), 3.59–3.69 (m, 2H, 2CH), 3.78 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 3.91–4.03 (m, 3H, CH_2O + CH), 4.28–4.39 (m, 1H, CH), 5.69 (s, 1H, CH), 7.19–7.20 (m, 2H, ArH), 7.25–7.28 (m, 1H, ArH), 7.60 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{23}H_{24}N_5O_4$, M + H^+: 434.1828, found: 434.1806.

Ethyl 6-amino-2-(3-chlorobenzoyl)-8-(3-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-5,7,7(8H)-tricarbonitrile 4q. Mp. 263–265°C. IR (KBr)/ cm^{-1} 3333, 3192, 2843, 2211, 1642, 1595, 1568, 1481, 1462, 1442, 1397, 1372, 1347, 1300, 1258, 1114, 1085, 1025, 1000, 884, 800, 786, 742, 711, 693. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.67–2.72 (m, 1H, CH), 3.11–3.19 (m, 1H, CH), 3.72–4.18 (m, 3H, 3CH), 4.65–4.70 (m, 1H, CH), 5.78 (s, 1H, CH), 7.30–7.61 (m, 8H, ArH), 7.68 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{25}H_{17}Cl_2N_5NaO$, M + Na^+: 496.0708, found: 496.0708.

Ethyl 6-amino-2-(3-chlorobenzoyl)-8-(2-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-5,7,7(8H)-tricarbonitrile 4r. Mp. 248–250°C. IR (KBr)/ cm^{-1} 3448, 3342, 3191, 2215, 1647, 1602, 1564, 1492, 1451, 396, 1345, 1306, 1285, 1250, 1235, 1127, 1089, 1039, 836, 812, 798, 759, 742, 718, 690. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.76–2.79 (m, 1H, CH), 3.10–3.13 (m, 1H, CH), 3.72–4.20 (m, 3H, 3CH), 4.64–4.69 (m, 1H, CH), 5.78 (s, 1H, CH), 7.21–7.54 (m, 8H, ArH), 7.66 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{25}H_{17}ClFN_5NaO$, M + Na^+: 480.1003, found: 480.1003.

Ethyl 6-amino-2-(3-chlorobenzoyl)-8-(2-bromophenyl)-1,2,3,4-tetrahydroisoquinoline-5,7,7(8H)-tricarbonitrile 4s. Mp. 170–172°C. IR (KBr)/ cm^{-1} 3381, 3168, 2966, 2882, 2213, 1630, 1598, 1440, 1375, 1342, 1281, 1246, 1196, 1160, 1117, 1081, 1049, 1025, 922, 835, 799, 752, 714, 694. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.65–2.71 (m, 1H, CH), 2.99–3.03 (m, 1H, CH), 3.75–4.09 (m, 3H, 3CH), 4.64–4.68 (m, 1H, CH), 5.80 (s, 1H, CH), 7.30–7.50 (m, 6H, ArH), 7.64–7.69 (m, 2H, ArH), 7.71 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{25}H_{17}ClBrN_5NaO$, M + Na^+: 540.0203, found: 540.0215.

Ethyl 6-amino-2-(3-chlorobenzoyl)-8-(2-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-5,7,7(8H)-tricarbonitrile 4t. Mp. 235–237°C. IR (KBr)/ cm^{-1} 3326, 3192, 3069 2941, 2881, 2842, 2212, 1641, 1605, 1568, 1478, 1440, 1398, 1374, 1341, 1301, 1288, 1255, 1120, 1080, 1058, 1039, 813, 799, 774, 748, 707. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.67–2.70 (m, 1H, CH), 3.01–3.16 (m, 1H, CH), 3.77 (d, J = 19.6 Hz, 1H, CH), 3.96–4.14 (m, 2H, 2CH), 4.67 (d, J = 19.6 Hz, 1H, CH), 5.79 (s, 1H, CH), 7.32–7.52 (m, 7H, ArH), 7.65–7.70 (m, 3H, ArH + NH_2). HRMS-ESI. calcd for $C_{25}H_{18}Cl_2N_5O$, M + H^+: 474.0888, found: 474.0881.

General procedure for the syntheses of 2-ethyl 7-methyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-arylisoquinoline-2,7(1*H*)-dicarboxylate derivatives 5. A dry 50 mL flask was charged with arylaldehyde (2.0 mmol), methyl cyanoacetate (0.198 g, 2.0 mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2.0 mmol), and ionic liquid of [bmim$^+$][BF_4^-] (2 mL). The reaction mixture was stirred at 50°C for 11–15 h, and then cooled to room temperature. The generated yellow solid was filtered off, and the ionic liquid in filtrate was then recovered for reuse by evaporating at 80°C several hours at *vacuum*. The crude yellow products were washed with water and purified by recrystallization from DMF and water, followed by being dried at 50°C several hours at *vacuum* to give **5**.

2-Ethyl 7-methyl 6-amino-8-(2-chlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 5a. Mp. 249–251°C. IR (KBr)/ cm^{-1} 3342, 3206, 2986, 2842, 2204, 1758, 1651, 1593, 1483, 1434, 1396, 1328, 1299, 1287, 1248, 1185, 1127, 1018, 926, 881, 816, 781, 749, 705. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.09–1.14 (m, 3H, CH_3), 2.31–2.37 (m, 1H, CH), 2.93–3.07 (m, 1H, CH), 3.61 (s, 3H, CH_3O), 3.73–3.77 (m, 2H, 2CH), 3.91–4.05 (m, 3H, CH_2O+CH), 4.26–4.3 (m, 1H, CH), 5.64 (s, 1H, CH), 7.26 (s, 2H, NH_2), 7.41–7.47 (m, 1H, ArH), 7.54–7.56 (m, 2H, ArH), 7.77–7.79 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 14.3, 33.8, 40.2, 41.4, 43.1, 53.2, 54.2, 60.9, 79.5, 115.4, 116.4, 128.5, 128.9, 129.8, 130.4, 130.8, 131.8, 133.1, 134.1, 148.9, 164.1, 197.2. 1HRMS-ESI. calcd for $C_{27}H_{21}ClN_4NaO_4$, M + Na^+: 463.1149, found: 463.1123.

2-Ethyl 7-methyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-(2,3-dimethoxyphenyl)isoquinoline-2,7(1H)-dicarboxylate 5b. Mp. 260–263°c. IR (KBr)/ cm^{-1} 3347, 3203, 2982, 2957, 2935, 2838, 2204. 1758, 1650, 1595, 1481, 1434, 1397, 1335, 1249, 1189, 1168, 1128, 1096, 1065, 1009, 809, 777, 754. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.14 (b, 3H, CH_3), 2.32–2.42 (m, 1H, CH), 2.77–2.83 (m, 1H, CH), 3.60–3.72 (m, 8H, $2CH_3$+2CH), 3.78–4.02 (m, 6H, CH_3O + $2CH_2O$ + CH), 4.72–4.38 (m, 1H, CH), 5.61 (s, 1H, CH),7.08–7.10 (m, 1H, ArH), 7.15 (s, 2H, NH_2), 7.16–7.20 (m, 2H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 14.4, 33.8, 40.2, 42.1, 43.4, 54.0, 54.1, 55.7, 60.5, 60.9, 79.5, 112.7, 113.0, 115.6, 116.5, 119.0, 124.0, 127.3, 130.7, 147.5, 149.5, 152.2, 164.4, 197.3. HRMS-ESI. calcd for $C_{24}H_{26}N_4NaO_6$, M + Na^+: 489.1750, found: 489.1747.

2-Ethyl 7-methyl 6-amino-8-(2,3-dichlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 5c. Mp. 253–255°C. IR (KBr)/ cm^{-1} 3340, 3286, 3200, 2986, 2958, 2844, 2203, 1758, 1652, 1591, 1483, 1456, 1433, 1397, 1339, 1300, 1250, 1182, 1163, 1128, 1106, 1045, 1015, 887, 814, 785, 750, 722. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.07–1016 (m, 3H, CH_3), 2.34–2.41 (m, 1H, CH), 2.92–2.98 (m, 1H, CH), 3.48–3.75 (m, 5H, CH_3O+2CH), 3.71–4.00 (m, 3H, CH_2O+CH), 4.27–4.34 (m, H, CH_3), 5.65 (s, 1H, CH_3), 7.28 (s, 2H, NH_2),7.57–7.61 (m, 1H, ArH). 7.74–7.79 (m, 2H, ArH). HRMS-ESI. calcd for $C_{22}H_{20}Cl_2N_4NaO_4$, M + Na^+: 497.0759, found: 497.0727.

2-Ethyl 7-methyl 6-amino-8-(4-bromophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 5d. Mp. 257–258°C. IR (KBr)/ cm^{-1} 3194, 2981, 1846, 2207, 1759, 1681, 1595, 1505, 1487, 1455, 1435, 1394, 1337, 1299, 1250, 1189, 1132, 1078, 1012, 889, 840, 771. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (b, 3H, CH_3), 2.40–2.46 (m, 1H, CH), 2.87–2.92 (m, 1H, CH), 3.58 (s, 3H, CH_3O), 3.63–3.75 (m, 3H, 3CH), 4.00–4.05 (m, 2H, CH_2O), 4.29–4.38 (m, 1H, CH), 5.62 (s, 1H, CH), 6.98 (d, J = 8.0 Hz, 1H, ArH), 7.15 (s, 2H, NH_2), 7.53–7.59 (m, 2H, ArH), 7.76 (d, J = 8.0 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{22}H_{21}BrN_4NaO_4$, M + Na^+: 507.0644, found: 507.0643.

2-Ethyl 7-methyl 6-amino-8-(3,4-dichlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 5e. Mp. 270–271°C. IR (KBr)/ cm^{-1} 3350, 3205, 3025, 2994, 2853, 2205, 1759, 1651, 1598, 1487, 1470, 1455, 1435, 1401. 1298, 1250, 1186, 1133, 1033, 1014, 882, 818, 772. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15–1.18 (m, 3H, CH_3), 2.50–2.54 (m, 1H, CH), 2.90–2.96 (m, 1H, CH), 3.44 (d, J = 12.8 Hz, 1H, CH), 3.60 (s, 3H, CH_3O), 3.62–3.78 (m, 1H, CH), 4.01–4.05 (m, 3H, CH_2O + CH), 4.29–4.39 (m, 1H, CH), 5.63 (s, 1H, CH_3), 7.04–7.35 (m, 3H, ArH+NH_2), 7.59–7.68 (m, 1H, ArH), 7.79–7.86 (m, 1H, ArH). HRMS-ESI. calcd for $C_{22}H_{20}Cl_2N_4NaO_4$, M + Na^+: 497.0759, found: 497.0760.

2-Ethyl 7-methyl 6-amino-8-(4-chlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 5f. Mp. 250–252°C. IR (KBr)/ cm^{-1} 3352, 3207, 2980, 2850, 2206, 1759, 1656, 1597, 1489, 1468, 1437, 1397, 1339, 1300, 1249, 1188, 1130, 1096, 1048, 1016, 923, 883, 840, 814, 771, 751, 722. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (b, 3H, CH_3), 2.39–2.47 (m, 1H, CH), 2.86–2.92 (m, 1H, CH), 3.64–3.76 (m, 6H, CH_3O+3CH), 3.99–4.05 (m, 2H, CH_2O), 4.26–4.41 (m, 1H, CH), 5.62 (s, 1H, CH), 7.05 (d, J = 8.0 Hz, 1H, CH), 7.16 (s, 2H, NH_2), 7.45 (d, J = 8.0 Hz, 1H, ArH), 7.62–7.64 (m, 2H, ArH). HRMS-ESI. calcd for $C_{22}H_{21}ClN_4NaO_4$, M + Na^+: 463.1149, found: 463.1129.

General procedure for the syntheses of diethyl-6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-arylisoquinoline-2,7(1*H*)-dicarboxylate derivatives 8. A dry 50 mL flask was charged with ethyl 2-cyano-3-arylacrylate (2.0 mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2.0 mmol), and ionic liquid of [bmim$^+$][BF_4^-] (2 mL). The reaction mixture was stirred at 50°C for 6–10 h, and then cooled to room temperature. The generated yellow solid was filtered off, and the ionic liquid in filtrate was then recovered for reuse by evaporating at 80°C several h at *vacuum*. The crude yellow products were washed with water and purified by recrystallization from DMF and water, followed by being dried at 50°C several h at *vacuum* to give **8**.

Diethyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-(2-nitrophenyl) isoquinoline-2,7(1H)-dicarboxylate 8a. Mp. 235–236°C. IR (KBr)/ cm^{-1} 3404, 3348, 3303, 3237, 2993, 2880, 2844, 2205, 1752, 1662, 1590, 1536, 1479, 1428, 1391, 1352, 1299, 1247, 1194, 1126, 1022, 973, 881, 863, 845, 821, 788, 773, 765, 718. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.14–1.26 (m, 6H, $2CH_3$), 2.75–2.79 (m, 1H, CH), 3.08–3.15 (m, 1H, CH), 3.72–4.06 (m, 7H, $2CH_2O$+3CH), 4.46–4.51 (m, 1H, CH), 4.73 (s, 2H, ArH), 5.92 (s, 1H, CH), 7.54–7.57 (m, 1H, ArH), 7.74–7.81 (m, 2H, ArH), 8.06–8.08 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 12.8, 14.4, 34.3, 40.2, 41.4, 43.4, 54.1, 60.9, 64.0, 79.4, 114.8, 115.2, 116.2, 125.1, 127.4, 128.2, 128.7, 130.4, 133.5, 148.8, 150.8, 163.8, 198.3. HRMS-ESI. calcd for $C_{23}H_{23}N_5NaO_6$, M + Na^+: 488.1546, found: 488.1536.

Diethyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-p-tolylisoquinoline-2,7(1H)-dicarboxylate 8b. Mp. 223–224°C. IR (KBr)/ cm^{-1} 3354, 3214, 3026, 2983, 2931, 2855, 2205, 1754, 1664, 1597, 1518, 1487, 1468, 1441, 1399, 1345, 1298, 1241, 1130, 1020, 885, 857, 817, 771, 748. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 1.14–1.26 (m, 6H, $2CH_3$), 2.35–2.41 (m, 4H, CH_3+CH), 3.04–3.07 (m, 1H, CH), 3.27 (d, J = 12.8 Hz, 1H, CH), 3.71–3.76 (m, 1H, CH), 3.92–4.19 (m, 5H, $2CH_2O$ + CH), 4.43–4.54 (m, 1H, CH), 4.65 (s, 2H, NH_2), 5.87 (s, 1H, CH), 6.89–7.35 (m, 3H, ArH), 7.58–7.63 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 13.3, 14.4, 20.7, 32.8, 40.2, 42.7, 43.4, 54.8, 60.8, 63.3, 79.5, 112.0, 115.6, 116.4, 125.9, 129.0, 129.4, 131.1, 138.1, 149.1, 164.1, 196.7. HRMS-ESI. calcd for $C_{24}H_{26}N_4NaO_4$, M + Na^+: 457.1852, found: 457.1844.

Diethyl 6-amino-8-(2-chlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 8c. Mp. 251–252°C. IR (KBr)/ cm^{-1} 3350, 3222, 3072, 2988, 2940, 2843, 2204, 1751, 1648, 1593, 1487, 1440, 1396, 1340, 1297, 1244, 1201, 1127, 1081, 1023, 883, 855, 816, 773, 751, 704. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 1.06–1.24 (m, 6H, $2CH_3$), 2.43–2.47 (m, 1H, CH), 2.99–3.04 (m, 1H, CH), 3.74–3.86 (m, 2H, 2CH), 4.03–4.22 (m, 5H, $2CH_2O$+1CH), 4.43–4.54 (m, 1H, CH), 4.69 (s, 2H, NH_2), 5.90 (s, 1H, CH), 7.31–7.34 (m, 1H, ArH), 7.41–7.46 (m, 2H, ArH), 7.91 (d, J = 7.6 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{23}H_{23}ClN_4NaO_4$, M + Na^+: 477.1306, found: 477.1288.

Diethyl 6-amino-8-(2,4-dichlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 8d. Mp. 215–216°C. IR (KBr)/ cm^{-1} 3353, 3173, 3033, 2983, 2204, 1758, 1673, 1601,1560, 1482, 1437, 1391, 1338, 1296, 1237, 1112, 1046, 1023, 888, 875, 862, 832, 815, 768. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 1.13–1.26 (m, 6H, $2CH_3$), 2.40–2.45 (m, 1H, CH), 2.96–3.00 (m, 1H, CH), 3.73–3.81 (m, 2H, 2CH), 3.98–4.25 (m, 5H, $2CH_2O$+CH), 4.44–4.56 (m, 1H, CH), 4.79 (s, 2H, NH_2), 5.89 (s, 1H, CH), 7.41–7.44 (m, 2H, ArH), 7.84 (d, J = 8.4 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{23}H_{23}Cl_2N_4O_4$, M + H^+: 489.1096 found: 489.1077.

Diethyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-(3,4-dimethylphenyl)isoquinoline-2,7(1H)-dicarboxylate 8e. Mp. 201–203°C. IR (KBr)/ cm^{-1} 3349, 3210, 2983, 2923, 2209, 1758, 1652, 1593, 1505, 1486, 1467, 1436, 1394, 1375, 1343, 1298, 1244, 1165, 1129, 1105, 1023, 881, 856, 831, 811, 771, 744. ^1H NMR (DMSO-d_6, 400 MHz) δ_H 0.93–0.97 (m, 3H, CH_3), 1.14–1.15 (m, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.34–2.44 (m, 1H, CH), 2.83–2.87 (m, 1H, CH), 3.14–3.20 (m, 1H, CH), 3.62–4.05 (m, 6H, $2CH_2O$+2CH), 4.28–4.40 (m, 1H, CH), 5.60 (s, 1H, CH), 6.72–6.77 (m, 1H, ArH), 7.09 (s, 2H, NH_2), 7.28–7.35 (m, 2H, ArH). HRMS-ESI. calcd for $C_{25}H_{28}N_4NaO_4$, M + Na^+: 471.2008, found: 471.1993.

Diethyl 6-amino-8-(3-chlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 8f. Mp. 235–236°C. IR (KBr)/ cm^{-1} 3351, 3212, 2984, 2933, 2207, 1751, 1659, 1596, 1487, 1439, 1396, 1340, 1297, 1245, 1130, 1020, 890, 856, 809, 770, 710. ^1H NMR (DMSO-d_6, 400 MHz) δ_H 0.94–0.97 (m, 3H, CH_3), 1.15–1.23 (m, 3H, CH_3), 2.43–2.47 (m, 1H, CH), 2.86–2.92 (m, 1H, CH), 3.58–3.75 (m, 2H, 2CH), 3.99–4.09 (m, 5H, $2CH_2O$+CH), 4.28–4.40 (m, 1H, CH), 5.61 (s, 1H, CH), 7.03–7.12 (m, 3H, NH_2+ArH), 7.38–7.61 (m, 3H, ArH). HRMS-ESI. calcd for $C_{23}H_{23}ClN_4NaO_4$, M + Na^+: 477.1306, found: 477.1292.

Diethyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-(4-methoxyphenyl)isoquinoline-2,7(1H)-dicarboxylate 8g. Mp. 185–186°C. IR (KBr)/ cm^{-1} 3354, 3214, 2982, 2934, 2839, 2205, 1752, 1655, 1518, 1487, 1468, 1441, 1398, 1345, 1241, 1183, 1129, 1035, 941, 884, 856, 842, 817, 771. ^1H NMR (DMSO-d_6, 400 MHz) δ_H 0.95–0.99 (m, 3H, CH_3), 1.15 (b, 3H, CH_3), 2.33–2.43 (m, 1H, CH), 2.81–2.92 (m, 1H, CH), 2.23 (d, J = 12.8 Hz, 1H, CH), 3.60–3.82 (m, 5H, CH_3O+2CH), 3.98–4.07 (m, 4H, $2CH_2O$), 4.32–4.38 (m, 1H, CH), 5.60 (m, 1H, CH), 6.88–7.10 (m, 4H, NH_2+ArH), 7.36–7.59 (m, 2H, ArH). HRMS-ESI. calcd for $C_{24}H_{26}N_4NaO_5$, M + Na^+: 473.1801, found: 473.1774.

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