KF/Al_2O_3 Mediated Multicomponent Reactions for the Efficient Synthesis of Highly Substituted Dihydropyridines

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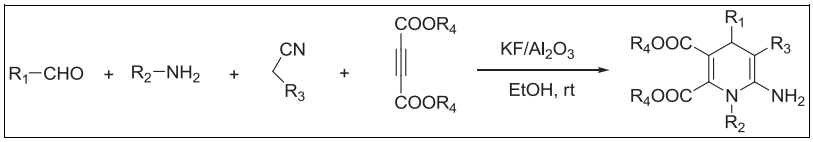

KF/Al_2O_3 was found to be an efficient solid supported catalyst for the facile access of highly substituted dihydropyridine derivatives from the multicomponent reaction of aromatic aldehydes, amines, malononitrile, and alkylacetylenedicarboxylates. The notable advantages of this protocol are reusable catalyst, good yields, applicable to a wide range of substrates for the synthesis of pharmacologically interesting dihydropyridine derivatives.

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INTRODUCTION

Multicomponent reactions (MCRs) are considered as a powerful tool for generating molecular diversity needed for the preparation of bioactive compounds [1,2]. MCRs have some advantages over conventional linear syntheses, including lower costs, shorter reaction times, high degrees of atom economy, structural variations, and environmental friendliness. Considering these, multicomponent reactions have gained substantial interest to both synthetic and medicinal chemists in recent times [3]. The synthesis of N-heterocycles is an important area of research because of their popularity in the synthesis of natural products and drugs [4]. The Hantzsch reaction discovered in 1881 is one of the most useful multicomponent reaction for the synthesis of wide range of bioactive 1,4-dihydropyridines [5].

Substituted 1,4-dihydropyridines are considered as 'privileged scaffold' due to its various pharmaceutical activities [6], for example, Clevidipine [7], Nicardipine [8], Manidipine [9], and others are well-known in pharmacology as calcium channel blockers and used as cardiovascular agents for the treatment of hypertension (Fig. 1). Similarly, substituted dihydropyridines are also found useful for other biological activities such as antioxidant [10,11], antiviral [12], anticancer [13], and anti-tumor activity [14].

From the recent literature, it is evident that the development of new methodology for the efficient synthesis of substituted dihydropyridines has gained notable attention [15,16]. Recently, Ohmura et al. have reported a palladium catalyzed synthesis of silylated dihydropyridines from regioselective silaboration of pyridines [17]. Kirsch et al. have developed a one-pot synthesis of 1,2-dihydropyridines by expanding the diverse reactivity of propargyl vinyl ethers [18]. Similarly, Rodriguez and his co workers have explored the synthesis of 2,5-dihydropyridine derivatives by gold-catalyzed reactions of β-ketoesters and propargylamines [19]. Yan et al. have demonstrated a four-component reaction in presence of equivalent amount of Et_3N as base for the synthesis of poly substituted dihydropyridine derivatives [20].

As a part of our ongoing research in the field of multicomponent reactions [21–23], we were interested to develop a new methodology for the synthesis of highly functionalised 1,4-dihydropyridines employing a re-usable solid supported catalyst. The use of solid-supported catalysts has gained popularity in synthetic community because of their enhanced reactivity as well as selectivity, easy workup procedure, recyclability of the catalyst, and ecofriendly reaction conditions. Among all other solid supported catalysts, alumina supported potassium fluoride (KF) is one of the widely used green catalyst [24]. KF/Al_2O_3 is an inexpensive, reusable, and environmentally benign catalyst, which demonstrate interesting catalytic behavior due to its unique surface properties in various two and multicomponent reactions. In recent years, KF/Al_2O_3 has been proved to be a very useful solid supported basic catalyst in carrying out various organic reactions that include synthesis of fused pyrimidine [25], synthesis of highly substituted pyrrolidines [26], Hydrothiolation of butadiynes [27], acetylation of amines, alcohols, and phenols [28], conversion of aldehydes to nitriles [29], synthesis of carboacyclic nucleosides [30] and synthesis of oxazolidinones [31]. Due to its strongly basic nature it replaces organic bases in a number of reactions such as Sonogashira couplings [32], Suzuki couplings [33], Knoevenagel reactions [34] etc.

RESULTS AND DISCUSSION

Considering the merits of KF/Al_2O_3 and taking cue from the work of Yan et al. [20], we were interested to explore this cheap, readily available, and reusable heterogeneous catalyst for the synthesis of highly substituted 1,4-DHPs.

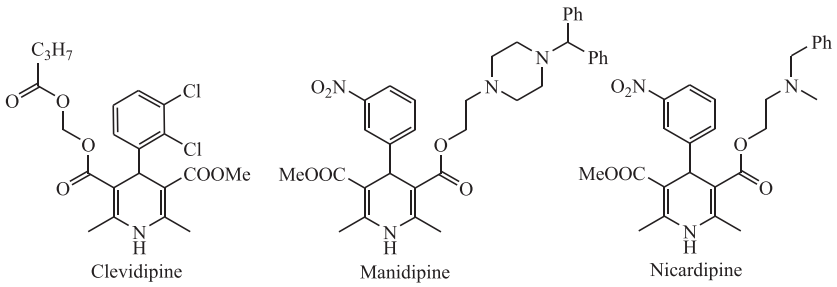


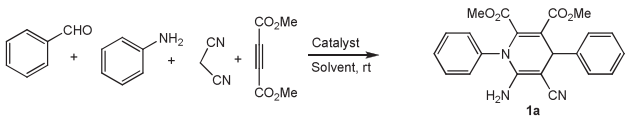
Figure 1. Some pharmacologically important dihydropyridines.

In the preliminary stage of investigation, we focused on systematic evaluation of different solid catalysts for the model reaction of benzaldehyde (1.0 equiv.), aniline (1.0 equiv.) malononitrile (1.0 equiv.), and dimethylacetylene dicarboxylate (1.0 equiv.) at room temperature in ethanol. The reaction was unsuccessful in the absence of any catalyst even after 24 h stirring. Moderate yields of **1a** were found in case of only KF or basic alumina alone. Interestingly, the same reaction provided 80% yield in the presence of KF/Al_2O_3. The exact explanation for the better efficacy of KF/Al_2O_3 in base catalyzed reactions is still a subject of debate in the literature [35]. As per Ando et al., the better catalytic activity of KF/Al_2O_3 may be due to the presence of three basic species (i) co-ordinately unsaturated active fluoride; (ii) the presence of [Al–O$^-$] ion which generates OH^- when water is added; and (iii) the cooperation of F^- and [Al–OH] [36] . A survey of solvents revealed ethanol to be the best choice. Moderate yields were obtained when acetonitrile, DMF and THF was employed as the solvent (Table 1, entries 7, 8 and 10) whereas in water **1a** was formed in poor yield (Table 1, entry 11). When the reaction was performed in dichloromethane only a trace amount product was formed (Table 1, entry 9). Some dependence was also observed on the amount of KF/Al_2O_3 used. The optimum result was obtained in the presence of 20 mol% KF/Al_2O_3 with no significant improvement upon increasing the catalyst loading (Table 1, entry 5).

The scope and limitations of this four-component reaction under optimized reaction conditions were explored using a variety of aldehydes, amines, malononitrile derivatives, and alkylacetylene dicarboxylate, as summarized in Table 2. The reaction proceeded smoothly with benzaldehyde and substituted benzaldehydes tethered with both electron-withdrawing and electron-releasing groups to generate the corresponding products in good yields. In contrast, aliphatic aldehydes such as heptaldehyde and cyclohexane carboxaldehyde are not suitable for this methodology due to the

Table 1

Optimization of reaction conditions.

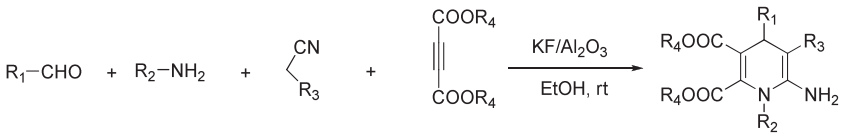


Entry	Catalyst (mol%)	Solvent	Time (h)	Yield[a] (%)
1	none	EtOH	24	0
2	KF (20)	EtOH	10	40
3	Basic Al_2O_3(20)	EtOH	10	55
4	**KF/Al_2O_3(20)**	**EtOH**	**10**	**80**
5	KF/Al_2O_3 (30)	EtOH	10	81
6	KF/Al_2O_3 (10)	EtOH	10	71
7	KF/Al_2O_3 (20)	CH_3CN	10	68
8	KF/Al_2O_3 (20)	DMF	10	64
9	KF/Al_2O_3 (20)	CH_2Cl_2	10	Trace
10	KF/Al_2O_3(20)	THF	10	63
11	KF/Al_2O_3 (20)	H_2O	10	20

Bold indicates the best optimized reaction condition.
[a]Isolated Yield

Table 2

KF/Al_2O_3 mediated four component reactions for the synthesis of functionalized dihydropyridines (**1a–1u**).



Entry	R_1	R_2	R_3	R_4	Product	Reaction time/h	Yield[a] (%)
1	C_6H_5	C_6H_5	CN	Me	**1a**	10	80
2	4-Br-C_6H_4	4-Me-C_6H_4	CN	Me	**1b**	10	82
3	4-Cl-C_6H_4	4-Me-C_6H_4	CN	Me	**1c**	10	83
4	4-OMe-C_6H_4	4-OMe-C_6H_4	CN	Me	**1d**	10	78
5	3-NO_2-C_6H_4	4-OMe-C_6H_4	CN	Me	**1e**	8	84
6	3-NO_2-C_6H_4	4-Cl-C_6H_4	CN	Me	**1f**	8	86
7	4-Br-C_6H_4	4-Cl-C_6H_4	CN	Me	**1g**	10	81
8	4-Br-C_6H_4	4-OMe-C_6H_4	CN	Me	**1h**	10	83
9	3-NO_2-C_6H_4	C_6H_5	CN	Me	**1i**	8	87
10	4-OMe-C_6H_4	4-CN-C_6H_4	CN	Et	**1j**	10	81
11	4-Cl-C_6H_4	C_6H_5-CH_2	CN	Me	**1k**	16	62
12	4-Cl-C_6H_4	2-naph	CN	Me	**1l**	8	79
13	3-NO_2-C_6H_4	4-Me-C_6H_4	COOEt	Et	**1m**	8	83
14	3-NO_2-C_6H_4	C_6H_5	COOEt	Me	**1n**	8	81
15	3-NO_2-C_6H_4	4-Cl-C_6H_4	COOEt	Me	**1o**	8	84
16	4-Cl-C_6H_4	4-OMe-C_6H_4	$CONH_2$	Me	**1p**	24	56
17	4-Cl-C_6H_4	4-Me-C_6H_4	$CONH_2$	Et	**1q**	24	51
18	3-NO_2 C_6H_4	4-Cl-C_6H_4	$CONH_2$	Et	**1r**	24	52
19	4-Cl-C_6H_4	4-Me-C_6H_4	COPh	Me	**1s**	12	65
20	3-NO_2-C_6H_4	C_6H_5	COPh	Me	**1t**	12	63
21	3-NO_2-C_6H_4	4-Cl-C_6H_4	COPh	Et	**1u**	12	64

[a]Isolated yield.

formation of mixture of inseparable compounds. This protocol was proved to be suitable both for aromatic amines bearing electron-donating and withdrawing groups. Bulky amine such as 2-napthyl amine reacted efficiently giving good yield (Table 2, entry 12). Aliphatic amine such as benzylamine gave the desired product with moderate yield (Table 2, entry 11).To expand the scope of malononitrile derivatives, ethyl cyanoacetate, cyanoacetamide, and benzoyl acetonitrile were applied to this methodology. In all these cases, the desired reactions underwent successfully to afford the corresponding dihydropyridines in moderate to good yields. Lastly, the variability of alkylacetylene dicarboxylate was also tested. Similar to dimethylacetylenedicarboxylate, diethylacetylene dicarboxylate also underwent this reaction smoothly to afford the desired products (Table 2, entries 10, 13, 17, 18 and 21). The products were fully characterized by IR, ^1H NMR, ^{13}C NMR spectra and by elemental analysis.

A proposed reaction mechanism for this four-component reaction is outlined in Scheme 1. The active species generated from KF/Al_2O_3 act as basic catalyst for the Knoevenagel condensation of aldehyde and malononitrile or its derivatives to afford electron deficient alkene **A**. Next, aza-Michael addition between arylamine and alkylacetylenedicarboxylate take place to produce intermediate **B**. Subsequently, the reaction of intermediate **A** with intermediate **B** proceeds via Michael type addition mediated by the basic species generated in situ from the KF/Al_2O_3 to provide intermediate **C**. Then, intramolecular addition of the NH group to the C–N triple bond gives the cyclic intermediate **D** that finally transforms to the expected dihydropyridine tautomer **E**.

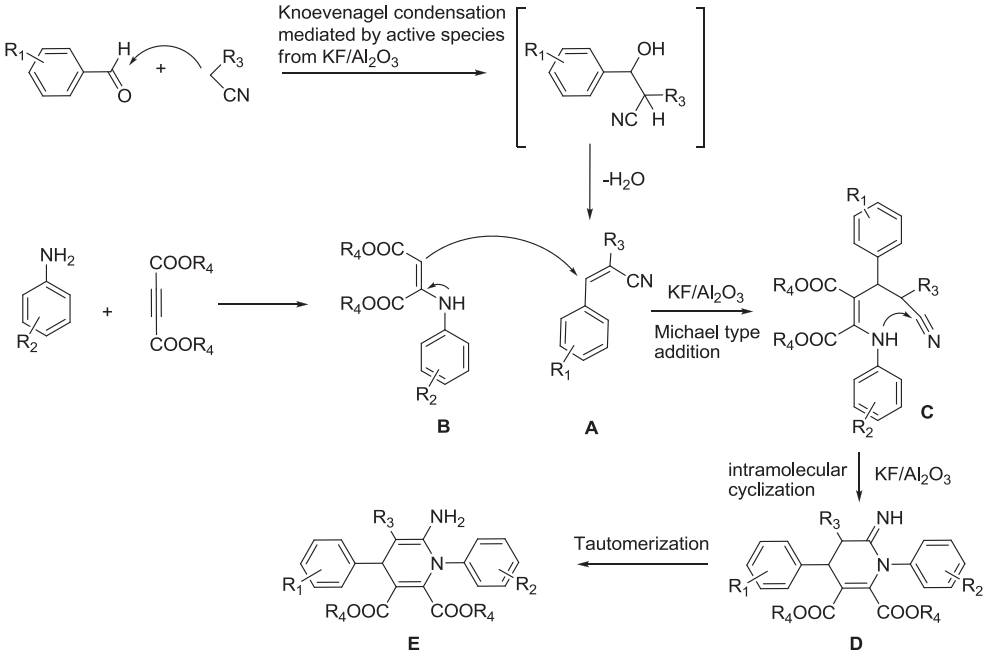
CONCLUSIONS

We have developed a facile and efficient four-component reaction of aldehydes, malononitrile derivatives, amines, and activated alkynes using a solid supported catalyst. A highly substituted ring system containing dihydropyridine core with -NH_2 and -CN functional group can be generated from simple and readily accessible starting materials via this methodology. We believe that because of the presence of various functional groups on these molecules, it might get importance to the synthetic as well as medicinal chemists.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without further purification. IR spectra were recorded in Shimadzu

Scheme 1. Proposed mechanism for the KF/Al_2O_3 mediated synthesis of functionalized dihydropyridines.



FTIR spectrophotometer (Shimadzu Corporation, Japan). ^{1}HNMR spectra and ^{13}C NMR spectra were recorded on Jeol 500 (Jeol Ltd., Japan), Bruker 500 or 400 MHz spectrometer (Bruker BioSpin AG, Switzerland) in $CDCl_3$ using TMS as internal reference. Elemental analyses were carried out in a Perkin Elmer 2400 automatic carbon, hydrogen, nitrogen analyzer (Perkin Elmer, USA) or Elementar Vario EL III (Elementar, Germany). All compounds were characterized by recording melting point, IR, ^{1}H, and ^{13}C NMR and elemental analysis.

Preparation of KF/Al_2O_3. The KF/Al_2O_3 was prepared by dissolving 4 g of KF in 20 mL of water and 6 g of neutral Al_2O_3. The mixture was stirred at 60 °C for 1 h. The water was removed under reduced pressure. The resulting free flowing powder was dried at 120 °C for 5 h to obtain KF/Al_2O_3 [37].

General procedure for the preparation of highly functionalized dihydropyridines (1a). A solution of Benzaldehyde (1.0 mmol), malononitrile (1.0 mmol) and KF/Al_2O_3 (0.2 mmol, 32 mg) were stirred in 3 mL of distilled ethanol at room temperature. Then, a solution of aniline (1.0 mmol) and dimethyl acetylenedicarboxylate (1.0 mmol) in 2 mL ethanol was added to it. The resulting mixture was stirred until the reaction was completed as indicated by TLC (ethyl acetate/hexane, 3:7). The resulting precipitates were collected by filtration and dissolved in ethyl acetate. The catalyst was recovered through filtration and the filtrate was evaporated under reduced pressure to obtain crude product. The crude product was purified by recrystalization method from hot ethanol/acetonitrile to give pure products. After isolation of the product, the remaining KF/Al_2O_3 was dried and reused for two times. The reaction proceeded cleanly with consistent results, although yield was somewhat lesser in the second and third recycles (73 and 68%, respectively).

Dimethyl 6-amino-5-cyano-1,4-diphenyl-1,4-dihydro pyridine-2,3-dicarboxylate (1a). Light yellowish solid; 80%; mp:161–163 °C; IR (KBr): 3465, 3376, 3336, 2950, 2175, 1746, 1707, 1650, 1568, 1492, 1413, 1353, 1247, 1212, 1109, 1076 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.48–7.49 (m, 3H), 7.34–7.38 (m, 6H), 7.25–7.27 (m, 1H), 4.65 (s, 1H), 4.11 (s, 2H), 3.58 (s, 3H), 3.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.9, 163.6, 149.7, 144.8, 141.9, 135.2, 130.6, 130.3, 130.0, 128.9, 127.3, 127.1, 120.6, 105.3, 62.9, 52.7, 52.1, 38.5; Anal. Calcd. for $C_{22}H_{19}N_3O_4$ (389.40): C, 67.86; H, 4.92; N, 10.79. Found: C, 67.94; H, 4.97; N, 10.89.

Dimethyl 6-amino-4-(4-bromophenyl)-5-cyano-1-p-tolyl-1, 4-dihydropyridine-2,3-dicarboxylate (1b). Light yellowish solid; 82%; mp: 185–187 °C; IR (KBr): 3475, 3364, 3033, 2952, 2174, 1741, 1701, 1646, 1575, 1509, 1414, 1356, 1326, 1250, 1113, 1071 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : δ = 7.48 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.62 (s, 1H), 4.12 (s, 2H), 3.58 (s, 3H), 3.45 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 165.6, 163.4, 149.9, 143.9, 142.2, 141.1, 133.1, 132.2, 132.0, 131.8, 129.9, 129.6, 121.1, 120.4, 104.5, 62.1, 52.6, 52.1, 38.1, 21.3; *Anal*. Calcd. for $C_{23}H_{20}BrN_3O_4$ (482.33): C, 57.27; H, 4.18; N, 8.71. Found: C, 57.37; H, 4.24; N, 8.83.

Dimethyl6-amino-4-(4-chlorophenyl)-5-cyano-1-p-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (1c). Light yellowish solid; 83%; mp: 186–188 °C; IR (KBr): 3472, 3360, 3221, 2950, 2175, 1742, 1699, 1646, 1574, 1508, 1413, 1355, 1301, 1248, 1216, 1176, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : δ = 7.33 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 4.65 (s, 1H), 4.09 (s, 2H), 3.58 (s, 3H), 3.46 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 165.6, 163.4, 149.9, 143.5, 142.2, 141.1, 132.9, 132.2, 130.6, 129.9, 128.8, 128.5, 120.4, 104.6, 62.1, 52.6, 52.1, 38.1, 21.3; *Anal*. Calcd. for $C_{23}H_{20}ClN_3O_4$ (437.87): C, 63.09; H, 4.60; N, 9.60. Found: C, 63.18; H, 4.67; N, 9.72.

Dimethyl 6-amino-5-cyano-1,4-bis(4-methoxy phenyl)-1,4-dihydropyridine-2,3-dicarboxylate (1d). Yellow solid; 78%; mp: 159–161 °C; IR (KBr): 3449, 3315, 3215, 2179, 1745, 1709, 1647, 1568, 1510, 1416, 1318, 1256, 1221, 1119, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) : δ = 7.29 (d, *J* = 6.8 Hz, 2H), 7.26 (d, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.4 Hz,

2H), 4.61 (s, 1H), 4.05 (s, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.59 (s, 3H), 3.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.0, 163.8, 149.8, 142.0, 137.5, 137.4, 131.7, 131.5, 128.2, 127.4, 127.3, 120.8, 115.0, 105.3, 62.0, 55.4, 52.7, 52.1, 52.0, 37.7; *Anal*. Calcd. for $C_{24}H_{23}N_3O_6$ (449.45): C, 64.13; H, 5.16; N, 9.35. Found: C, 64.23; H, 5.22; N, 9.48.

Dimethyl 6-amino-5-cyano-1-(4-methoxyphenyl)-4-(3-nitrophenyl)-1,4-dihydro pyridine-2,3-dicarboxylate (1e). Yellow solid; 84%; mp: 184–186 °C; IR (KBr): 3415, 3326, 3231, 3081, 2179, 1747, 1708, 1651, 1568, 1532, 1356, 1250, 1117, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : δ = 8.25 (s, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.77 (s, 1H), 4.23 (s, 2H), 3.85 (s, 3H), 3.60 (s, 3H), 3.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.3, 163.3, 161.0, 150.6, 148.9, 147.2, 142.8, 133.5, 131.5, 129.8, 126.7, 122.5, 122.3, 120.1, 115.3, 104.4, 61.5, 55.7, 52.9, 52.3, 38.7; *Anal*. Calcd. for $C_{23}H_{20}N_4O_7$ (464.43): C, 59.48; H, 4.34; N, 12.06. Found: C, 59.35; H, 4.39; N, 12.17.

Dimethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-(3-nitrophenyl)-1,4-dihydro pyridine-2,3-dicarboxylate (1f). Yellow solid; 86%; mp :195–197 °C; IR (KBr): 3415, 3326, 3230, 3081, 2179, 1747, 1706, 1651, 1570, 1532, 1427, 1356, 1250, 1117, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : δ = 8.23 (s, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 4.77 (s, 1H), 4.20 (s, 2H), 3.61 (s, 3H), 3.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.1, 163.1, 149.9, 148.9, 146.8, 142.0, 137.3, 133.5, 133.2, 131.6, 130.6, 129.9, 122.6, 122.2, 119.7, 105.1, 62.4, 53.0, 52.4, 38.6; *Anal*. Calcd. for $C_{22}H_{17}ClN_4O_6$ (468.85): C, 56.36; H, 3.65; N, 11.95. Found: C, 56.28; H, 3.60; N, 12.06.

Dimethyl 6-amino-4-(4-bromophenyl)-1-(4-chloro phenyl)-5-cyano-1,4-dihydro pyridine-2,3-dicar boxylate (1g). Yellow solid; 81%; mp: 163–165 °C; IR (KBr): 3462, 3317, 3220, 2950, 2190, 1743, 1710, 1651, 1581, 1490, 1417, 1356, 1229, 1118, 1008 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.48 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 4.61 (s, 1H), 4.10 (s, 2H), 3.58 (s, 3H), 3.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) : δ = 165.5, 163.4, 149.5, 143.7, 141.7, 137.0, 133.5, 132.1, 131.7, 130.4, 128.8, 121.3, 120.1, 105.2, 62.9, 52.9, 52.3, 38.2; *Anal*. Calcd. for $C_{22}H_{17}BrClN_3O_4$ (502.74): C, 52.56; H, 3.41; N, 8.36. Found: C, 52.64; H, 3.47; N, 8.49.

Dimethyl 6-amino-4-(4-bromophenyl)-5-cyano-1-(4-methoxyphenyl)-1,4dihydro pyridine-2,3-dicarboxylate (1h). Yellow solid; 83%; mp: 165–167 °C; IR (KBr): 3470, 3336, 3219, 2175, 1745, 1703, 1651, 1577, 1510, 1417, 1356, 1249, 1109, 1009 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : δ = 7.48 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 4.62 (s, 1H), 4.11 (s, 2H), 3.84 (s, 3H), 3.58 (s, 3H), 3.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.7, 163.5, 160.9, 150.1, 144.0, 142.5, 132.0, 131.5, 128.8, 127.0, 121.2, 120.4, 115.1, 104.5, 62.1, 55.7, 52.8, 52.2, 38.2; *Anal*. Calcd. for $C_{23}H_{20}BrN_3O_5$ (498.33): C, 55.43; H, 4.05; N, 8.43. Found: C, 55.35; H, 4.11; N, 8.54.

Dimethyl 6-amino-5-cyano-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (1i). Yellow solid; 87%; mp: 217–219 °C; IR (KBr): 3446, 3336, 3229, 2951, 2178, 1755, 1704, 1651, 1577, 1521, 1421, 1349, 1250, 1213, 1112, 926 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : δ = 7.84 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.12–7.14 (m, 3H), 6.96–6.98 (m, 2H), 4.75 (s, 2H), 4.36 (s, 1H), 3.20 (s, 3H), 3.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.0, 162.9, 150.6, 148.3, 147.3, 142.4, 134.7, 133.2, 130.4, 130.1, 129.7, 129.7, 121.9, 121.7, 120.4, 103.8, 59.7, 52.4, 51.9, 38.6; *Anal*. Calcd. for $C_{22}H_{18}N_4O_6$ (434.40): C, 60.83; H, 4.18; N, 12.90. Found: C, 60.90; H, 4.24; N, 13.03.

Diethyl 6-amino-5-cyano-1-(4-cyanophenyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicar boxylate (1j). Yellow solid; 81%; mp: 140–142 °C; IR (KBr): 3460, 3369, 2983, 2234, 2192, 1726, 1706, 1655, 1589, 1515, 1412, 1373, 1306, 1228, 1178, 1107, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : δ = 7.79 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 7.7 Hz, 2H), 6.90 (d, *J* = 7.4Hz, 2H), 4.63 (s, 1H), 4.02–4.06 (m, 1H), 3.95 (s, 2H), 3.89–3.93 (m, 3H), 3.80 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H);^{13}C NMR ($CDCl_3$, 125 MHz):δ = 165.0, 163.0, 158.9, 148.5, 140.2, 139.8, 136.7, 133.7, 131.6, 128.3, 119.9, 117.2, 114.7, 114.3, 107.2, 62.4, 61.2, 55.4, 37.9, 13.9, 13.5; *Anal*. Calcd. for $C_{26}H_{24}N_4O_5$ (472.49): C, 66.09; H, 5.12; N, 11.86. Found: C, 66.20; H, 5.18; N, 11.99.

Dimethyl 6-amino-1-benzyl-4-(4-chlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (1k). Yellow solid; 62%; mp: 146–148 °C; IR (KBr): 3466, 3346, 3038, 2955, 2188, 1743, 1705, 1645, 1569, 1493, 1434, 1343, 1290, 1215, 1116, 1018 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) : δ = 7.34–7.41 (m, 3H), 7.22–7.29 (m, 4H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.78 (d, *J* = 17.2 Hz, 1H), 4.66 (d, *J* = 17.2 Hz, 1H), 4.57 (s, 1H), 4.15 (s, 2H), 3.77 (s, 3H), 3.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.6, 164.6, 151.3, 142.6, 142.2, 135.0, 132.9, 131.9, 130.1, 129.3, 128.8, 128.4, 126.7, 120.3, 106.9, 65.9, 53.3, 52.2, 50.8, 37.9; *Anal*. Calcd. for $C_{23}H_{20}ClN_3O_4$ (437.87): C, 63.09; H, 4.60; N, 9.60. Found: C, 63.01; H, 4.67; N, 9.72.

Dimethyl 6-amino-4-(4-chlorophenyl)-5-cyano-1-(naphthalen-2-yl)-1,4-dihydro pyridine-2,3-dicarboxylate (1l). Light yellowish solid; 79%; mp: 171–173 °C; IR (KBr): 3455, 3327, 3220, 2945, 2178, 1753, 1712, 1651, 1571, 1422, 1351, 1223, 1120, 1009 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.95 (d, *J* = 8.4 Hz, 2H), 7.89 (t, *J* = 6.8 Hz, 2H), 7.83 (s, 1H), 7.58–7.64 (m, 2H), 7.31–7.36 (m, 4H), 4.68 (s, 1H), 4.12 (s, 2H), 3.58 (s, 3H), 3.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.7, 163.5, 149.9, 143.4, 142.2, 133.5, 133.0, 132.3, 130.3, 129.8, 129.1, 128.5, 128.4, 128.0, 127.7, 126.5, 120.4, 104.9, 62.6, 52.8, 52.2, 38.2; *Anal*. Calcd. for $C_{26}H_{20}ClN_3O_4$ (473.90): C, 65.89; H, 4.25; N, 8.87; Found: C, 65.96; H, 4.30; N, 8.96.

Triethyl 6-amino-4-(3-nitrophenyl)-1-p-tolyl-1,4-dihydropyridine-2,3,5-tricarboxylate (1m). Yellow solid; 83%; mp: 122–124 °C; IR (KBr): 3448, 3264, 3010, 2983, 1737, 1694, 1671, 1643, 1604, 1530, 1373, 1350, 1264, 1197, 1115, 1095, 1009 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : δ = 8.32 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.7Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.29–7.33 (m, 4H), 6.30 (s, 2H), 5.09 (s, 1H), 4.02–4.10 (m, 4H), 3.90–3.96 (m, 1H), 3.79–3.86 (m, 1H), 2.40 (s, 3H), 1.14–1.20 (m, 6H), 0.93–0.96 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) : δ = 169.2, 165.3, 163.3, 151.7, 149.6, 148.3, 142.2, 140.9, 134.3, 132.3, 130.6, 130.5, 128.8, 123.3, 121.4, 106.5, 79.3, 61.9, 60.9, 59.6, 37.5, 21.4, 14.5, 14.1, 13.5; *Anal*. Calcd. for $C_{27}H_{29}N_3O_8$ (523.53): C, 61.94; H, 5.58; N, 8.03. Found: C, 61.85; H, 5.52; N, 8.15.

5-Ethyl 2,3-dimethyl 6-amino-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyridine-2,3,5-tricarboxylate (1n). Yellow solid; 81%; mp: 172–173 °C; IR (KBr): 3472, 3264, 2979, 2951, 1749, 1709, 1667, 1639, 1600, 1530, 1506, 1436, 1354, 1213, 1123, 1095, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : δ = 8.54

(s, 1H), 8.25 (d, $J = 8.0$ Hz, 1H), 7.94 (d, $J = 7.5$ Hz, 1H), 7.70–7.73 (m, 3H), 7.64–7.67 (m, 3H), 6.50 (s, 2H), 5.31 (s, 1H), 4.24–4.30 (m, 2H), 3.61 (s, 3H), 3.82 (s, 3H), 1.41–1.44 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) : 169.1, 165.7, 163.6, 151.4, 149.3, 148.3, 142.2, 134.9, 134.0, 130.7, 130.5, 130.0, 128.8, 123.0, 121.5, 106.6, 79.4, 61.9, 59.6, 52.5, 52.0, 51.9, 37.3, 14.4, 13.5; Anal. Calcd. for $C_{24}H_{23}N_3O_8$ (481.45): C, 59.87; H, 4.82; N, 8.73. Found: C, 59.96; H, 4.90; N, 8.84.

5-Ethyl 2,3-dimethyl 6-amino-1-(4-chloro phenyl)-4-(3-nitrophenyl)-1,4 dihydropyridine-2,3,5-tricarboxylate (1o). Yellow solid; 84%; mp:186–188 °C; IR (KBr): 3442, 3221, 3107, 2985, 2954, 1751, 1710, 1663, 1602, 1523, 1440, 1401, 1345, 1236, 1095, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) : $\delta = 8.31$ (s, 1H), 8.06 (d, $J = 7.6$ Hz, 1H), 7.71 (d, $J = 7.6$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.45 (t, $J = 7.6$ Hz, 1H), 7.39 (d, $J = 8.4$ Hz, 2H), 6.25 (s, 2H), 5.10 (s, 1H), 4.05–4.13 (m, 2H), 3.67 (s, 3H), 3.49 (s, 3H), 1.23 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 169.0, 165.6, 163.6, 151.1, 149.0, 148.4, 141.8, 136.9, 133.9, 133.4, 132.1, 130.3, 128.9, 122.9, 121.5, 107.1, 79.8, 62.2, 59.7, 52.7, 52.1, 37.2, 14.4; *Anal.* Calcd. for $C_{24}H_{22}ClN_3O_8$ (515.90): C, 55.87; H, 4.30; N, 8.15. Found: C, 55.94; H, 4.35; N, 8.29.

Dimethyl 6-amino-5-carbamoyl-4-(4-chloro phenyl)-1-(4-methoxyphenyl)-1,4-dihydro pyridine-2,3-dicarboxylate (1p). Light yellowish solid; 56%; mp: 221–223 °C; IR (KBr): 3451, 3327, 3182, 2950, 2843, 1748, 1685, 1656, 1571, 1480, 1436, 1404, 1335, 1298, 1255, 1218, 1185, 1109, 1062 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.38$ (d, $J = 8.4$ Hz, 2H), 7.26–7.32 (m, 4H), 6.97 (d, $J = 8.8$ Hz, 2H), 6.74 (s, 2H), 4.95 (s, 2H), 4.74 (s, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 171.9, 165.9, 163.7, 160.6, 151.4, 144.2, 141.5, 132.8, 131.7, 129.1, 128.6, 127.2, 114.9, 105.9, 79.2, 55.6, 52.4, 51.9, 38.1; *Anal.* Calcd. for $C_{23}H_{22}ClN_3O_6$ (471.89): C, 58.54; H, 4.70; N, 8.90. Found: C, 58.43; H, 4.76; N, 8.78.

Diethyl 6-amino-5-carbamoyl-4-(4-chloro phenyl)-1-p-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (1q). Light yellowish solid; 51%; mp: 147–149 °C; IR (KBr): 3460, 3327, 3201, 2983, 1757, 1682, 1655, 1573, 1479, 1373, 1256, 1205, 1107, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : $\delta = 7.39$ (d, $J = 8.3$ Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.27 (d, $J = 8.3$ Hz, 2H), 7.23 (d, $J = 8.3$ Hz, 2H), 6.72 (s, 2H), 4.95 (s, 2H), 4.74 (s, 1H), 4.06–4.17 (m, 2H), 3.84–3.90 (m, 1H), 3.75–3.81 (m, 1H), 2.39 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H), 0.92 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 172.0$, 165.5, 163.3, 151.4, 144.3, 141.2, 140.7, 132.9, 132.5, 130.5, 130.4, 129.2, 128.9, 106.0, 79.2, 61.8, 60.9, 38.2, 21.4, 14.2, 13.5; *Anal.* Calcd. for $C_{25}H_{26}ClN_3O_5$ (483.94): C, 62.05; H, 5.42; N, 8.68. Found: C, 62.15; H, 5.48; N, 8.80.

Diethyl 6-amino-5-carbamoyl-1-(4-chlorophenyl)-4-(3-nitrophenyl)-1, 4-dihydropyridine-2,3 di- carboxylate (1r). Light yellowish solid; 52%; mp: 171–173 °C; IR (KBr): 3452, 3335, 3186, 2983, 1745, 1686, 1663, 1530, 1491, 1378, 1350, 1260, 1209, 1099, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : $\delta = 8.34$ (s,1H), 8.10–8.12 (m, 1H), 7.77 (d, $J = 7.7$Hz, 1H), 7.51–7.52 (m, 1H), 7.49 (d, $J = 7.8$ Hz, 2H), 7.37 (d, $J = 8.6$ Hz, 2H) 6.75 (s, 2H), 5.05 (s, 2H), 4.86 (s, 1H), 4.10–4.20 (m, 2H), 3.90–3.96 (m, 1H), 3.80–3.86 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H), 0.96 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 171.5$, 165.0, 162.9, 151.2, 148.8, 147.6, 141.4, 136.9, 133.7, 133.5, 132.2, 130.4, 129.7, 122.8, 122.4, 106.1, 79.2, 62.2, 61.4, 38.6, 14.1, 13.5; *Anal.* Calcd. for $C_{24}H_{23}ClN_4O_7$ (514.91): C, 55.98; H, 4.50; N, 10.88. Found: C, 55.88; H, 4.57; N, 10.99.

Dimethyl 6-amino-5-benzoyl-4-(4-chlorophenyl)-1-p-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (1s). Yellow solid; 65%; mp: 184–186 °C; IR (KBr): 3420, 3049, 2951, 1736, 1703, 1639, 1596, 1450, 1355, 1224, 1111, 1048 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : $\delta = 7.35$–7.39 (m, 3H), 7.32 (d, $J = 8.3$ Hz, 2H),7.22–7.25 (m, 4H), 7.14 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 4.99 (s, 1H), 3.62 (s, 3H), 3.45 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 194.5$, 165.7, 163.7, 154.4, 144.7, 141.5, 141.2, 132.2, 131.8, 131.0, 130.2, 129.9, 129.5, 129.2, 128.6, 128.0, 126.8, 108.7, 89.5, 52.7, 52.2, 38.0, 21.4; *Anal.* Calcd. for $C_{29}H_{25}ClN_2O_5$ (516.97): C, 67.38; H, 4.87; N, 5.42. Found: C, 67.46; H, 4.82; N, 5.53.

Dimethyl 6-amino-5-benzoyl-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (1t). Yellow solid; 63%; mp: 156–157 °C; IR (KBr): 3424, 3068, 2951, 2928, 2853, 1745, 1706, 1643, 1608, 1530, 1452, 1354, 1220, 1123, 1076, 1053, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : $\delta = 7.90$–7.91 (m, 1H), 7.80–7.81 (m, 1H), 7.46–7.51 (m, 3H), 7.36–7.39 (m, 2H), 7.33–7.35 (m, 1H), 7.28–7.31 (m, 2H), 7.22 (t, $J = 8.0$ Hz, 1H), 7.13 (d, $J = 8.5$ Hz, 2H), 7.00 (d, $J = 7.5$ Hz, 1H), 5.02 (s, 1H), 3.40 (s, 3H), 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) : $\delta = 194.2$, 165.3, 163.4, 154.2, 148.4, 148.3, 141.4, 141.2, 134.3, 133.3, 130.9, 130.4, 130.3, 129.4, 129.1, 128.5, 128.4, 126.5, 122.3, 121.7, 108.2, 89.2, 52.7, 52.2, 38.6; *Anal.* Calcd. for $C_{28}H_{23}N_3O_7$ (513.50): C, 65.49; H, 4.51; N, 8.18. Found: C, 65.57; H, 4.57; N, 8.30.

Diethyl 6-amino-5-benzoyl-1-(4-chlorophenyl)-4-(3-nitrophenyl)-1, 4-dihydropyridine-2,3-dicarbo -xylate (1u). 64%; mp: 132–134 °C; IR (KBr): 3428, 3182, 3068, 2983, 1734, 1706, 1659, 1608, 1534, 1443, 1346, 1240, 1213, 1112, 1013 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) : $\delta = 7.98$–8.00 (d, $J = 8.3$ Hz, 1H), 7.86 (s, 1H), 7.54 (d, $J = 8.6$ Hz, 2H), 7.35–7.43 (m, 5H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.21 (d, $J = 8.3$ Hz, 2H), 7.05 (d, $J = 7.4$ Hz, 1H), 5.14 (s, 1H), 4.01–4.10 (m, 2H), 3.95–4.00 (m, 1H), 3.85–3.91 (m, 1H), 1.13 (t, $J = 7.1$ Hz, 3H), 0.99 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) : $\delta = 194.7$, 164.7, 162.9, 154.0, 148.4, 148.2, 141.1, 141.0, 137.3, 133.5, 132.9, 132.0, 130.7, 129.5, 129.1, 128.5, 126.6, 122.4, 121.7, 108.7, 89.4, 62.4, 61.3, 38.6, 14.0, 13.6; *Anal.* Calcd. for $C_{30}H_{26}ClN_3O_7$ (575.99): C, 62.56; H, 4.55; N, 7.30. Found: C, 62.64; H, 4.62; N, 7.34.

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