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PAPER

Ultrasound mediated, green innovation for the synthesis of polysubstituted 1,4-dihydropyridines

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An elegant, atom efficient protocol for the synthesis of a series of novel pharmacologically interesting polysubstituted 1,4-dihydropyridines has been developed *via* a one-pot four-component cyclocondensation reaction of aromatic aldehydes, malononitrile, acetylenedicarboxylates and arylamines catalyzed by copper (I) iodide in aqueous medium under ultrasound irradiation. In comparison with the reported methods, our approach is expedient and offers several advantages such as: shorter reaction time, excellent yields, milder conditions, convenient and is environmentally benign. We have herein successfully demonstrated the utility of sonication in a multicomponent reaction (MCR), which exhibits a better functional group tolerance, straightforward product isolation and the purification is by precipitation

Introduction

In the last two decades, enormous thrust and exploration towards inculcating the green chemistry practices have been taking place steadily. Multi-component reactions (MCRs) are one of the major contributions to the field of green chemistry, which have time and again served as the best tools to gain an access into biologically active heterocyclic molecules of interesting properties [1] by a one-pot, single-step process. This approach offers several potential advantages over conventional synthesis. Assembling of N-heterocycles via multi-component strategy is one of the vital areas in synthetic organic chemistry.

These heterocycles are a remarkable scaffold of prime importance to mankind. These heterocyclic skeletons are often an enticing framework for synthetic organic chemists, pharmaceutical and agricultural industries to design compounds of immense chemical and biological interest [2]. Accordingly, molecules containing 1,4-dihydropyridine scaffold are an important class of privileged heterocycles that have been enjoying a relative renaissance of interest owing to the abundance of these components in various natural products, new materials and pharmaceuticals. These ubiquitous motifs are endowed with a wide range of biological applications [3]. They are often used in the treatment of cardiovascular diseases, angina pectoris, Alzheimer's disease and hypertension [4]. Their presence in prominent commercially available drug molecules such as felodipine, amlodipine, nifedipine and nicardipine is well known (**Figure 1**) [5]. The classical methods for the synthesis of 1,4-dihydropyridines usually involve Hantzsch reaction [6], cycloaddition reactions [7], Michael condensation [8], Huisgen dipolar additions [9] and others [10].

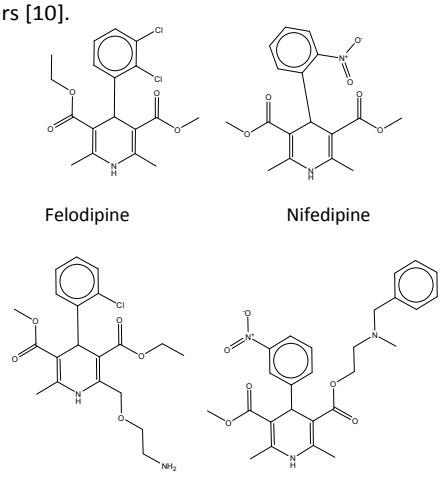

Figure 1. Some biologically potent 1,4 DHPs

A rigorous literature survey reveals that, a few synthetic methodologies have been reported recently which employ varied catalysts and solvents such as: nano particles [11], meglumine [12], KF/Al_2O_3 [13], triethylamine [14], NaOH [15], polyethylene glycol (PEG), ethanol [16], grinding condition [17], trifluoroacetic acid [18], $(NH_4)_2HPO_4$ [19], $Cu(OTf)_2$ [20] and $Sc(OTf)_3$ [21]. Although a variety of approaches have been documented and are found to have their unique advantages, they suffer from one or the other drawbacks such as preparation of the catalyst, use of expensive catalysts, organic bases and organic solvents, prolonged reaction times, exposure to chemicals leading to environmental concerns

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during grinding in grindstone method, require expensive starting materials, unsatisfactory yields and lack of generality.

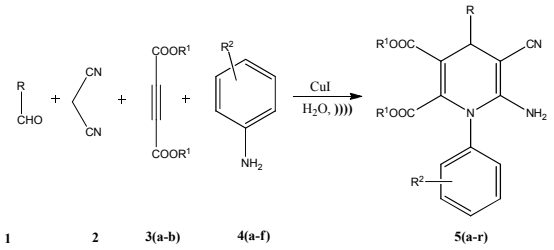
Owing to the prominent aforementioned medicinal profile of 1,4-dihydropyridines, search for the development of better eco sustainable, economical and energy efficient methods remain a challenging task and therefore has attracted keen attention of synthetic and medicinal chemists in designing them.

Another noteworthy recent finding includes the identification of benzofuran and Huisgen's dipole chemistry because of their relevance as building blocks in drug design. Benzofuran is a very prevalent basic core unit of pharmaceutical interest which is found in many natural products (such as moracin, egonol and homoegonol), bioactive molecules and other compounds [22]. Due to their profound chemotherapeutic and physiological properties [23], this scaffold constitutes an integral part of chemical, medicinal and life sciences that has led to a considerable amount of modern research being pursued in many parts of the world. This heterocycle can also serve as versatile biodynamic motif that can be used to construct novel active therapeutic agents [24]. The increasing enthusiasm into this nucleus is due to their ability to display an array of valuable pharmacological activities such as immunomodulatory, anticancer, antihyperglycemic, antiparasitic, kinase inhibitor activities and with applications such as brightening agents, fluorescent sensors, drugs, antioxidants and oxidants [25]. They are regarded as potential medicinal leads in developing therapeutic agents.

Furthermore, the highly active nature of the Huisgen's dipoles play a crucial role in organic synthesis as they are very receptive to participate as key substrates in many kinds of multi-component reactions and have lead to a library of structurally diverse heterocyclic and carbocyclic molecules [26]. They can be conveniently generated by the addition of amines to electron-deficient alkynes which upon further treatment with various electrophiles and other reagents would furnish a number of C-C and C-N bond formation reactions [27].

As part of green chemistry concept, catalysis in aqueous system under sonochemical condition has become an irresistible method after more than two decades of extensive studies in this domain [28]. This approach has proven to be fast, efficient, clean and reliable in chemical laboratories when compared to the traditional methods. Sonochemistry, a frontier area in chemical research has been used increasingly in organic synthesis as it facilitates unusual mechanism for generating high-energy chemistry. The phenomenon of acoustic cavitation, indeed, the backbone of sonochemistry offers immense potentiality in the intensification of reaction rates that can be attributed to the mechanical effects of sound waves (heterogeneous processes) and chemical induction (homogeneous processes) in an energy-efficient manner. It is during the cavitation bubble collapse that immense pressures, temperatures and the extraordinary heating and cooling rates sets in to drive the reactions towards completion in very short times [29]. Rapid reaction rate, simplicity, controllable reaction conditions, high purity of the product, enhance catalyst efficiency and safety of the technique are the essence of sonochemical reactions. These characteristics place sonochemistry amongst the elite of green chemical methods [30]. Since water is non-toxic, abundant natural resource, inexpensive, non-flammable, eco-compatible and is known to facilitate excellent cavitation up to 50–60 °C, it is emerging as the solvent of choice in sonochemistry [31]. As a result of inter and intra molecular non covalent interactions, it causes special effects in reactions leading to assembly processes. Copper (I) iodide, a versatile Lewis acid catalyst has found applications in numerous organic transformations [32]. It holds a great promise for future research as it offers beneficial advantages such as remarkable catalytic activity, operational simplicity, commercial availability, inexpensive, non-corrosive and less toxic nature.

To the best of our knowledge, there are no reports in the literature on the use of copper iodide in water under sonic condition for the synthesis of these nitrogen heterocycles. Encouraged by all these findings, substantial efforts have been made by us to meticulously design a library of diversified potent 1,4-dihydropyridines *via* a one-pot four-component cyclocondensation reaction of aromatic aldehydes, malononitrile, acetylenedicarboxylates and arylamines catalyzed by copper (I) iodide in aqueous medium under ultrasound irradiation as shown in the **Scheme 1**.



Scheme 1: Preparation of polysubstituted 1,4-dihydropyridines **5(a-r)**

Results and discussion

To explore the feasibility and generality of copper (I) iodide catalyzed sonicated domino MCR, the reaction variables including catalyst, reaction solvent, feed ratio of catalyst and energy efficiency were optimized to observe their roles in enhancing the rates and yield of the products. Benzofuran-2-carboxaldehyde, malononitrile, aniline and DMAD were chosen as model substrates.

A variety of catalysts were explored under different reaction conditions (room temperature, reflux temperature of the solvent, microwave and ultrasonic irradiation) and the results are presented in **Table 1**. To rationalize the influence of the catalyst, the four component reaction was first carried out in the absence of catalyst wherein a maximum yield of only 40% could be recorded and most of the starting materials were recovered (**Table 1**, Entry 1). It was further observed that the yield of the reaction hardly improved in the presence of other catalysts which included amino acid (L-Proline), organic nitrogen bases (DBU, piperidine, Et_3N), Lewis acids ($InCl_3$, $Cu(OTf)_2$, CuO, $CuSO_4{\cdot}5H_2O$, CuCN, CuCl, CuBr, $CuNO_3$), amino

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sugar (Meglumine) and inorganic bases (K_2CO_3, NaOH) (**Table 1**, Entries 2–12, 14–17) whereas the use of CuI proved to be superior, as it gave the best yield of **5a** in 30 min (**Table 1**, Entry 13). Hence, CuI under ultrasonic irradiation was preferred for our further studies.

Table 1: Optimization of catalyst for the synthesis of 5a [a]

Entry	Catalyst	Reaction Condition							
		RT (25 °C)		Reflux (80 °C)		MW		US	
		Time (min)	Yield (%) [b]	Time (min)	Yield (%) [b]	Time (min)	Yield (%) [b]	Time (min)	Yield (%) [b]
1	No Catalyst	600	10	600	15	30	40	30	40
2	L-Proline	600	10	600	35	30	50	30	50
3	DBU	600	10	600	25	30	50	30	55
4	Piperidine	600	10	600	30	30	50	30	60
5	Et_3N	600	15	600	30	30	50	30	60
6	$InCl_3$	600	25	600	35	30	50	30	65
7	K_2CO_3	600	60	600	62	30	65	30	67
8	Meglumine	600	85	600	80	30	75	30	60
9	NaOH	600	85	600	86	30	80	30	78
10	$Cu(OTf)_2$	600	70	600	75	30	70	30	78
11	CuO	600	75	600	80	30	70	30	70
12	$CuSO_4{\cdot}5H_2O$	600	65	600	70	30	50	30	55
13	CuI	600	60	600	67	30	84	30	96
14	CuCN	600	40	600	40	30	45	30	47
15	CuCl	600	45	600	50	30	53	30	55
16	CuBr	600	50	600	60	30	63	30	67
17	$CuNO_3$	600	62	600	65	30	68	30	72

[a] *Reaction conditions*: benzofuran-2-carboxaldehyde (1 mmol), malononitrile (1 mmol), aniline (1 mmol), DMAD (1 mmol), catalyst (0.20 mmol) and H_2O (3 mL).
[b] Isolated yields.

Varied solvents (nonpolar, polar aprotic and polar protic solvents) were assessed in order to substantiate the best choice and the results of the findings are tabulated in **Table 2**. We, initially probed this experiment under solvent-free condition and observed that, sonication gave the maximum yield (45%) of **5a** whereas unsatisfactory yields were obtained under other conditions even after prolonged time (**Table 2**, Entry 1).

Furthermore, the studies revealed that, the use of nonpolar solvents made the reactions very lethargic and low yields were isolated (**Table 2**, Entries 2–3), whereas in the case of polar aprotic solvents, moderate yields were obtained (**Table 2**, Entries 4–8) and to our delight, polar protic solvents gave very high yields (**Table 2**, Entries 9–10).

Table 2: Optimization of solvent for the synthesis of 5a [a]

Entry	Solvent	Reaction Condition							
		RT (25 °C)		Reflux		MW		US	
		Time (min)	Yield (%) [b]	Time(min)	Yield (%) [b]	Time (min)	Yield (%) [b]	Time (min)	Yield (%) [b]
1	No Solvent	600	15	600	20	30	25	30	45
2	Toluene	600	16	600	25	30	35	30	45
3	n-Hexane	600	15	600	25	30	40	30	50
4	DCM	600	18	600	30	30	45	30	55
5	THF	600	12	600	35	30	40	30	50
6	DMSO	600	12	600	25	30	30	30	58
7	CH_3CN	600	10	600	20	30	35	30	60
8	DMF	600	05	600	15	30	30	30	55
9	Ethanol	600	10	600	20	30	80	30	87
10	H_2O	600	25	600	50	30	82	30	96

[a] *Reaction conditions*: benzofuran-2-carboxaldehyde (1 mmol), malononitrile (1 mmol), aniline (1 mmol), DMAD (1 mmol), CuI (0.20 mmol) and solvent (3 mL).
[b] Isolated yields.

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Table 3: Optimization of the amount of CuI for the synthesis of 5a [a]

Entry	Amount of CuI (mmol)	Time (min)	Yield [b] (%)
1	0.05	30	50
2	0.10	30	70
3	0.15	30	82
4	0.20	30	96

[a] *Reaction conditions*: benzofuran-2-carboxaldehyde (1 mmol), malononitrile (1 mmol), aniline (1 mmol), DMAD (1 mmol), catalyst and H_2O (3 mL).
[b] Isolated yields.

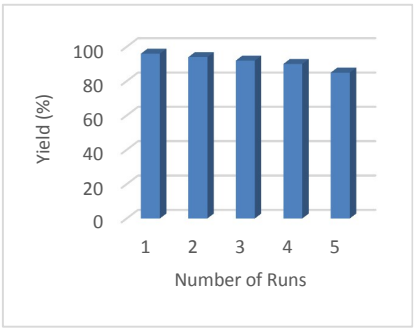

Figure 2. Reusability of CuI for the synthesis of **5(a–r)**

With the expectation to maximize the product yield in short reaction time, the amount of catalyst required to promote this successful transformation was ascertained and the results are summarized in **Table 3**. When the reaction was carried out using 0.05 mmol, 0.10 mmol, 0.15 mmol and 0.20 mmol of the catalyst, the rate of the reaction progressed steadily with lower to good yields. To our pleasure, an excellent chemical yield of 96% was obtained when 0.20 mmol of the catalyst was employed (**Table 3**, Entry 4). Further addition of the catalyst did not show any significant enhancement in the yield of the desired product. Consequently, the best results were achieved by using 0.20 mmol of CuI as catalyst, water as green solvent in the presence of ultrasonic waves for the synthesis of **5a**.

The possibility of recycling the catalyst was then examined. After completion of the reaction (30 min), the reaction mixture was treated with EtOAc (5 mL) to dissolve the product formed, and filtered through a pre-weighed sintered glass crucible. The solid (CuI) present in the sintered glass crucible was repeatedly washed with water and dried in a hot air oven, the crucible was weighed, and the solid (19 mg) was collected and kept aside for reuse. In the present reaction, it was found that 20 mol% of CuI was reusable without appreciable loss of activity for four runs. From the **Figure 2**, it can be seen that, in the first four runs the activity was more or less maintained but after the fourth run the yields were low, which may be due to loss of the catalyst during recovery.

To broaden the scope of the designed protocol, we subjected benzofuran-2-carboxaldehyde and other aromatic aldehydes, malononitrile, diverse substituted aromatic amines (bearing electron donating, electron withdrawing groups), and non-aromatic amines, dialkyl acetylenedicarboxylate (DMAD, DEAD) and CuI as catalyst in water for the tandem one-pot multi-component synthesis of fifteen novel polysubstituted 1,4-dihydropyridines assisted by ultrasound. Gratifyingly, in all the cases these four components congregated successfully into the corresponding 5-cyano-1,4-dihydropyridine-2,3-dicarboxylate analogs in good to excellent yields (**Table 4**, Entries 1–14). Furthermore, the protocol was successfully extended to a series of substituted aromatic aldehydes and excellent yields were obtained (Table 4, Entries 15–19). To our disappointment, complex mixtures of products were observed when non-aromatic amines such as *n*-hexylamine, cyclohexyl amine, ethyl amine and *iso*-propyl amine were used (**Table 4**, Entries 19–22). It was also noted that, the electronic effects of the substituents tethered on the aromatic ring showed marginal effect on the reactivity and did not have much impact on the product yields.

All the products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, ESI-MS and by elemental analysis. In the IR spectrum of compound **5a**, a stretching band at 2187 cm^{-1} appeared which confirms the presence of nitrile group in the product. In the ^{1}H NMR spectrum, three singlets appeared at 3.45, 3.69 and 4.23 ppm indicating the presence of $–CH_3$ protons of the two –COOMe groups and the $–NH_2$ protons of the amino group at C-2 carbon respectively. The proton at the fourth position of the dihydropyridine appeared as a singlet at 4.92 ppm confirming the fusion of malanonitrile and DMAD. The ^{13}C NMR spectrum further confirmed the formation of dihydropyridine by exhibiting a signal at 165.3 ppm for the C-2 carbon of **5a**. The mass spectrometry data showed a peak at m/z 430.1 $[M+H]^+$ which corresponds to the expected formula of the isolated 1,4-dihydropyridine. All these evidences are in the favour of structure **5a**.

Further, the chemical structure of the representative compounds **5b** and **5f** were unequivocally confirmed by single-crystal X-ray diffraction studies as shown in **Figures 3** and **4**. The compounds **5b** and **5f** were recrystallized in ethanol.

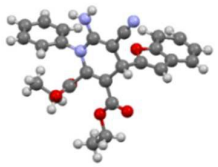

Figure 3. ORTEP plot of compound **5b**

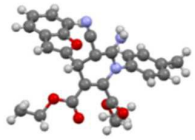

Figure 4. ORTEP plot of compound **5f**

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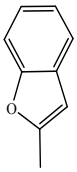
Table 4: Synthesis of 5(a–r) using ultrasound[a]

Entry	Aldehyde R	R^1	R^2	Product	Time (min)	Yield [b] (%)	Melting Point (°C)
1		CH_3	H	**5a**	30	96	193–194
2		C_2H_5	H	**5b**	30	93	182–183
3		CH_3	4-Cl	**5c**	30	91	163–164
4		C_2H_5	4-Cl	**5d**	30	92	151–152
5		CH_3	4-CH_3	**5e**	30	93	133–134
6		C_2H_5	4-CH_3	**5f**	30	93	218–219
7		CH_3	4-NO_2	**5g**	30	89	159–160
8		C_2H_5	4-NO_2	**5h**	30	90	148–149
9		CH_3	2-Cl	**5i**	30	90	203–204
10		C_2H_5	2-Cl	**5j**	30	94	172– 173
11		CH_3	4-OCH_3	**5k**	30	92	160–161
12		C_2H_5	4-OCH_3	**5l**	30	87	144–145
13		CH_3	3-Cl	**5m**	30	90	177–178
14		C_2H_5	3-Cl	**5n**	30	85	161–162
15	3,4,5 $(OCH_3)_3C_6H_2$	CH_3	4-Cl	**5o**	30	90	217–218
16	4-ClC_6H_4	CH_3	4-CH_3	**5p**	30	87	187–188 [16a]
17	4-ClC_6H_4	CH_3	4-Cl	**5q**	30	87	128–129 [14b]
18	3-$NO_2C_6H_4$	CH_3	4-CH_3	**5r**	30	96	213–214 [14b]
19	4-ClC_6H_4	CH_3	*n*-hexylamine	**Intractable mixture**	30	–	–
20	3-$NO_2C_6H_4$	CH_3	cyclohexylamine	**Intractable mixture**	30	–	–
21	3,4,5 $(OCH_3)_3C_6H_2$	CH_3	ethylamine	**Intractable mixture**	30	–	–
22	3,4,5 $(OCH_3)_3C_6H_2$	CH_3	*Iso*-propylamine	**Intractable mixture**	30	–	–

[a] Reaction conditions: aromatic aldehyde (1 mmol), malononitrile (1 mmol), aniline/amine (1 mmol), DMAD/DEAD (1 mmol), CuI (0.20 mmol), H_2O (3 mL) and temp 25 °C (35 kHz constant frequency, 80W).
[b] Isolated yields.

Generally, when ultrasound is passed through a liquid–solid system, bubble cavitation ascends due to variation in bulk pressure and causes a series of unique physical phenomena that can affect the solid. Asymmetric bubble collapse occurs at the interface generating high-pressure/high-velocity microjets and high energetic shockwaves leading to intermolecular reactions in short times. These jets trigger the solid catalyst, causes disruption of the interfacial boundary, intensifies the contact through efficient mixing. As a result localized erosion, particle fragmentation by overall particle size reduction, disengagement of heterogeneous reactants, intermediates, product take place enhancing the overall heat and mass transfer [28b, 33]. Also, the implosive bubble collapse induces extremely high temperatures (as much as 4700 °C) and pressures (10 Pa) in a microscopic region of the sonicated liquid [28c]. As a result the rate of the chemical reaction increases by many folds, which is termed "false sonochemistry" Therefore, it is feasible to assume that these effects are responsible for the chemical enhancement of reactions.

In conclusion, the present study deals with the development of an efficient synthetic strategy to construct complex 1,4-dihydropyridines that could further streamline their syntheses with the aid of greener and harmless sound energy technique.

The attractive features of this procedure are the use of inexpensive starting materials, high atom efficiency, clean reaction profiles, use of ecofriendly solvent, mild reaction conditions, it is general and very high yields are obtained, involes use of an energy efficient techinque which meets the essential precepts of a green chemical approaches. These pharmacophoric frameworks may hopefully provide insights for medicinal chemists to explore their virtue in developing novel pharmaceutical agents to tackle the varied pathological aspects and modify the disease processes. These analogs are of particular interest, as they contain reactive handles and as such could be used as a foundation for the synthesis of more-complex biologically important molecules.

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Experimental section

Material and methods

Reagents and solvents were purchased from Sigma Aldrich. All materials were of commercial reagent grade. Melting points were determined using Thiele's apparatus (con. H_2SO_4) with a calibrated thermometer. The progress of the reaction and the purity of the compounds were monitored by TLC [analytical silica gel plates (Merck60 F_{254})]. Infrared (IR) spectra were recorded using an Agilent Cary 630 FT-IR Spectrophotometer. ^{1}H NMR spectra were recorded on an Advance Bruker instrument operating at 400, 500 MHz and ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$. Chemical shifts were reported in ppm. ESI-MS analysis was carried out using ESI-Q TOF instrument. CHN analysis was performed using Elementar vario MICRO cube analyzer. Sonication was performed using SIDILU Indian make sonic bath operating at 35 kHz (constant frequency, 80W) maintained at 25 °C by circulating water.

General procedure for the synthesis of polysubstituted 1,4-dihydropyridines 5(a-r)

A 50mL flask was charged with benzofuran-2-carboxaldehyde/aromatic aldehyde (1 mmol), malononitrile (1 mmol), copper iodide (0.20 mmol) in water (3 mL) and sonicated (35 kHz) at 25 °C for 10 min. Then a solution of acetylenedicarboxylate/s (1 mmol) and aniline or non-aromatic amine (1 mmol) in water (3 mL) was added to the above flask and the resulting mixture was further sonicated (35 kHz) at 25 °C for an additional 20 min. After completion of the reaction [monitored by TLC, using hexane:ethyl acetate (9:1) as eluent], the reaction mixture was treated with EtOAc (5 mL) to dissolve the product formed, and filtered through a pre-weighed sintered glass crucible. The solid (CuI) present in the sintered glass crucible was repeatedly washed with water and dried in a hot air oven, the crucible was weighed, the solid (19 mg) was collected and kept aside for reuse. The filtrate was then taken into a separating funnel, the organic layer was separated, and dried over anhydrous Na_2SO_4 to get the crude compound which was then recrystallized from ethanol to get the pure product. The structures of all the products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, ESI-MS and CHN analyses.

Spectral data

Dimethyl-6-amino-4-(benzofuran-2-yl)-5-cyano-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (5a):

Yellow crystal; m.p 193–194 °C; IR (ν cm^{-1}): 3336, 2975, 2187, 1740, 1653, 1217; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.45 (s, 3H, -CH_3), 3.69 (s, 3H, -CH_3), 4.23 (s, 2H, -NH_2), 4.92 (s, 1H, -CH), 6.57 (s, 1H, Ar-H), 7.19–7.55 (m, 9H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.4, 51.5, 52.1, 59.9, 103.6, 112.6, 118.9, 120.5, 122.5, 125.0, 127.7, 129.7, 131.2, 132.2, 135.1, 137.1, 141.3, 150.1, 154.3, 157.5, 163.0, 165.3 ppm; ESI-MS, *m/z*: 430.1 $[M+H]^+$; Anal. Calc. for $C_{24}H_{19}N_3O_5$ (%): C, 67.13, H, 4.46, N, 9.79; found: C, 67.18, H, 4.41, N, 9.74.

Diethyl-6-amino-4-(benzofuran-2-yl)-5-cyano-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (5b):

Yellow crystal; m.p 182–183 °C; IR (ν cm^{-1}): 3325, 2952, 2190, 1752, 1651, 1221; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19–1.22 (t, *J* = 7.0 Hz, 3H, -CH_3), 1.39–1.42 (t, *J* = 7.0 Hz, 3H, -CH_3), 4.20–4.25 (q, *J* = 7.0 Hz, 4H, -CH_2), 4.85 (s, 2H, -NH_2), 5.19 (s, 1H, -CH), 6.56 (s, 1H, Ar-H), 7.13–7.55 (m, 9H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 15.3, 30.7, 56.9, 60.3, 61.7, 99.4, 107.0, 110.6, 113.5, 114.1, 118.5, 121.0, 123.2, 126.0, 127.6, 129.6, 131.2, 142.9, 149.8, 156.1, 163.6, 166.9, 169.2 ppm; ESI-MS, *m/z*: 458.1 $[M+H]^+$; Anal. Calc. for $C_{26}H_{23}N_3O_5$ (%): C, 68.26, H, 5.07, N, 9.19; found: C, 68.34, H, 5.02, N, 9.11.

Dimethyl-6-amino-4-(benzofuran-2-yl)-1-(4′-chlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (5c):

Brown powder; m.p 118–119 °C; IR (ν cm^{-1}): 3380, 2945, 2181, 1743, 1621, 1205; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (s, 3H, -CH_3), 3.69 (s, 3H, -CH_3), 4.46 (s, 2H, -NH_2), 5.29 (s, 1H, -CH), 6.57 (s, 1H, Ar-H), 7.19–7.54 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.9, 52.4, 52.9, 59.9, 102.4, 111.3, 119.8, 121.1, 122.8, 124.0, 128.5, 130.4, 131.5, 133.1, 133.8, 137.0, 142.4, 151.0, 155.2, 158.2, 163.2, 165.2 ppm; ESI-MS, *m/z*: 464.0 $[M+H]^+$; Anal. Calc. for $C_{24}H_{18}ClN_3O_5$ (%): C, 62.14, H, 3.91, N, 9.06; found: C, 62.19, H, 3.98, N, 9.03.

Diethyl-6-amino-4-(benzofuran-2-yl)-1-(4′-chlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (5d):

Yellow crystal; m.p 151–152 °C;IR (ν cm^{-1}): 3390, 2983, 2105, 1745, 1668, 1217;^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21–1.25 (t, *J* = 6.8 Hz, 3H, -CH_3), 1.37–1.40 (t, *J* = 6.8 Hz, 3H, -CH_3), 4.07–4.12 (q, *J* = 6.8 Hz, 4H, -CH_2), 4.85 (s, 2H, -NH_2), 5.19 (s, 1H, -CH), 7.25–7.65 (m, 9H, Ar-H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 14.3, 29.0, 57.1, 60.1, 62.2, 94.9, 106.3, 112.4, 112.5, 113.7, 119.4, 122.3, 123.3, 124.8, 127.3, 129.1, 130.2, 143.7, 148.6, 156.9, 163.3, 167.0, 168.5 ppm; ESI-MS, *m/z*: 492.1 $[M+H]^+$; Anal. Calc. for $C_{26}H_{22}ClN_3O_5$ (%): C, 63.48, H, 4.51, N, 8.54; found: C, 63.55, H, 4.59, N, 8.59.

Dimethyl-6-amino-4-(benzofuran-2-yl)-5-cyano-1-*p*-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (5e):

Yellow powder; m.p 133–134 °C; IR (ν cm^{-1}): 3325, 2978, 2105, 1755, 1632, 1219; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H, -CH_3), 3.10 (s, 3H, -CH_3), 3.47 (s, 3H, -CH_3), 4.54 (s, 2H, -NH_2), 4.80 (s, 1H, -CH), 6.82 (s, 1H, Ar-H), 7.20–7.62 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 31.1, 51.5, 52.1, 58.8, 103.1, 112.4, 120.0, 122.8, 124.2, 126.4, 128.7, 130.6, 131.4, 132.6, 133.7, 137.3, 143.6, 149.5, 153.7, 156.9, 161.8, 163.9 ppm; ESI-MS, *m/z*: 444.1 $[M+H]^+$; Anal. Calc. for $C_{25}H_{21}N_3O_5$ (%): C, 67.71, H, 4.77, N, 9.48; found: C, 67.79, H, 4.85, N, 9.42.

Diethyl-6-amino-4-(benzofuran-2-yl)-5-cyano-1-*p*-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (5f):

Yellow crystal; m.p 218–219 °C;IR (ν cm^{-1}): 3397, 2938, 2143, 1751, 1653, 1981; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92–0.95 (t, *J* = 6.8 Hz, 3H, -CH_3), 1.26–1.29 (t, *J* = 6.8 Hz, 3H, -CH_3), 2.39 (s, 3H, -CH_3), 4.19–4.24 (q, *J* = 6.8 Hz, 4H, -CH_2), 4.59 (s, 2H, -NH_2), 4.79 (s, 1H, -CH), 6.84 (s, 1H, Ar-H), 7.21–7.59 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.9, 15.6, 30.5, 55.5, 61.3, 62.5, 101.7, 108.0, 110.7, 113.7, 115.5, 118.0, 120.6, 123.2, 125.0, 128.6, 131.8, 135.1, 142.9, 150.5, 155.5, 162.7, 166.7, 169.2 ppm; ESI-MS, *m/z*: 472.1 $[M+H]^+$;

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Anal. Calc. for $C_{27}H_{25}N_3O_5$ (%): C,68.78, H, 5.34, N, 8.91; found: C, 68.69, H, 5.38, N, 8.98.

Dimethyl 6-amino-4-(benzofuran-2-yl)-5-cyano-1-(4´-nitrophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5g):

Yellow powder; m.p 159–160 °C; IR (ν cm^{-1}): 3341, 2930, 2176, 1752, 1634, 1203; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.45 (s, 3H, -CH_3), 3.70 (s, 3H, -CH_3), 4.37 (s, 2H, -NH_2), 5.29 (s, 1H, -CH), 6.62 (s, 1H, Ar-H), 7.24–7.72 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.9, 52.3, 52.8, 58.5, 104.1, 112.4, 121.4, 122.7, 123.8, 124.6, 125.5, 127.1, 128.2, 130.1, 131.9, 137.1, 143.6, 151.0, 155.0, 158.7, 162.2, 164.2 ppm; ESI-MS, *m/z*: 475.1 $[M+H]^+$; Anal. Calc. for $C_{24}H_{18}N_4O_7$ (%): C, 60.76, H, 3.82, N, 11.81; found: C, 60.84, H, 3.89, N, 11.88.

Diethyl-6-amino-4-(benzofuran-2-yl)-5-cyano-1-(4´-nitrophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5h):

Yellow powder; m.p 148–149 °C; IR (ν cm^{-1}): 3322, 2943, 2195, 1748, 1670, 1233; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12–1.15 (t, *J* = 6.8 Hz, 3H, -CH_3), 1.28–1.31 (t, *J* = 6.8 Hz, 3H, -CH_3), 4.16–4.21 (q, *J* = 6.8 Hz, 4H, -CH_2), 5.43 (s, 1H, -CH), 6.85 (s, 2H, -NH_2), 7.22–7.72 (m, 9H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0, 15.1, 29.4, 57.4, 60.3, 61.5, 101.0, 106.5, 112.0, 112.6, 116.1, 119.6, 123.5, 125.1, 126.9, 129.1, 130.2, 135.4, 144.0, 148.3, 156.6, 163.8, 166.6, 167.5 ppm; ESI-MS, *m/z*: 503.1 $[M+H]^+$; Anal. Calc. for $C_{26}H_{22}N_4O_7$ (%): C, 62.15, H, 4.41, N, 11.15; found: C, 62.21, H, 4.47, N, 11.17.

Dimethyl-6-amino-4-(benzofuran-2-yl)-1-(2´-chlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (5i):

Golden yellow powder; m.p 203–204 °C; IR (ν cm^{-1}): 3327, 2938, 2185, 1747, 1631, 1246; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.47 (s, 3H, -CH_3), 3.68 (s, 3H, -CH_3), 4.19 (s, 2H, -NH_2), 4.88 (s, 1H, -CH), 6.61 (s, 1H, Ar-H), 7.19–7.62 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.5, 52.6, 53.2, 60.1, 103.6, 110.5, 118.7, 120.8, 122.5, 124.7, 128.5, 130.0, 132.6, 135.5, 137.1, 142.3, 146.9, 150.6, 155.5, 157.5, 162.5, 165.4 ppm; ESI-MS, *m/z*: 464.0 $[M+H]^+$; Anal. Calc. for $C_{24}H_{18}ClN_3O_5$ (%): C, 62.14, H, 3.91, N, 9.06; found: C, 62.19, H, 3.98, N, 9.02.

Diethyl-6-amino-4-(benzofuran-2-yl)-1-(2´-chlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (5j):

Golden yellow powder; m.p 172–173 °C; IR (ν cm^{-1}): 3321, 2943, 2156, 1739, 1669, 1287; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18–1.21 (t, *J* = 7.0 Hz, 3H, -CH_3), 1.36–1.39 (t, *J* = 7.0 Hz, 3H, -CH_3), 4.07–4.12 (q, *J* = 7.0 Hz, 4H, -CH_2), 4.42 (s, 2H, -NH_2), 4.78 (s, 1H, -CH), 6.46 (s, 1H, Ar-H), 7.09–7.73 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 14.5, 30.0, 56.8, 60.2, 61.4, 99.5, 107.3, 111.6, 112.5, 115.0, 119.7, 121.3, 123.0, 119.7, 121.3, 123.0, 125.1, 125.7, 129.6, 131.6, 143.0, 148.6, 157.1, 163.7, 166.6, 168.4 ppm; ESI-MS, *m/z*: 492.1 $[M+H]^+$; Anal. Calc. for $C_{26}H_{22}ClN_3O_5$ (%): C, 63.48, H, 4.51, N, 8.54; found: C, 63.42, H, 4.50, N, 8.59.

Dimethyl-6-amino-4-(benzofuran-2-yl)-5-cyano-1-(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5k):

Yellow powder; m.p 160–161 °C; IR (ν cm^{-1}): 3314, 2955, 2163, 1745, 1638, 1209; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50 (s, 3H, -OCH_3), 3.68 (s, 3H, -CH_3), 3.85 (s, 3H, -CH_3), 4.20 (s, 2H, -NH_2), 4.91 (s, 1H, -CH), 6.56 (s, 1H, Ar-H), 7.18–7.54 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.4, 51.6, 52.3, 56.3, 60.0, 103.9, 112.0, 120.6, 121.8, 123.0, 124.5, 128.7, 130.9, 131.6, 133.2, 134.0, 138.0, 140.9, 149.9, 156.4, 159.5, 162.2, 164.6 ppm; ESI-MS, *m/z*: 460.1 $[M+H]^+$; Anal. Calc. for $C_{25}H_{21}N_3O_6$ (%): C, 65.35, H, 4.61, N, 9.15; found: C, 65.21, H, 4.66, N, 9.17.

Diethyl-6-amino-4-(benzofuran-2-yl)-5-cyano-1-(4´-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5l):

Yellow powder; m.p 144–145 °C; IR (ν cm^{-1}): 3357, 2917, 2182, 1746, 1616, 1211; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90–0.94 (t, *J* = 6.8 Hz, 3H, -CH_3), 1.26–1.29 (t, *J* = 6.8 Hz, 3H, -CH_3), 2.29 (s, 3H, -OCH_3), 4.12–4.16 (q, *J* = 6.8 Hz, 4H, -CH_2), 4.53 (s, 2H, -NH_2), 4.82 (s, 1H, -CH), 6.84 (s, 1H, Ar-H), 7.21–7.59 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0, 13.7, 28.4, 52.7, 55.5, 61.6, 62.5, 99.2, 106.6, 112.5, 114.0, 115.1, 118.4, 121.5, 123.4, 125.0, 128.0, 130.4, 134.2, 143.6, 151.7, 157.1, 163.8, 166.1, 167.8 ppm; ESI-MS, *m/z*: 488.1 $[M+H]^+$;

Anal. Calc. for $C_{27}H_{25}N_3O_6$(%): C, C, 66.52, H, 5.17, N, 8.62; found: C, 66.59, H, 5.12, N, 8.60.

Dimethyl-6-amino-4-(benzofuran-2-yl)-1-(3´-chlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (5m):

Yellow powder; m.p 177–178 °C; IR (ν cm^{-1}): 3356, 2957, 2128, 1751, 1676, 1219; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (s, 3H, -CH_3), 3.68 (s, 3H, -CH_3), 4.96 (s, 2H, -NH_2), 5.29 (s, 1H, -CH), 6.73 (s, 1H, Ar-H), 7.20–7.49 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.8, 53.4, 54.1, 62.3, 103.6, 112.5, 119.4, 121.1, 124.2, 125.8, 128.5, 130.1, 132.0, 133.1, 134.5, 137.00, 141.5, 151.5, 154.7, 159.3, 162.1, 166.5 ppm; ESI-MS, *m/z*: 464.0 $[M+H]^+$; Anal. Calc. for $C_{24}H_{18}ClN_3O_5$ (%): C, 2.14, H, 3.91, N, 9.06; found: C, 62.11, H, 3.97, N, 9.01.

Diethyl-6-amino-4-(benzofuran-2-yl)-1-(3´-chlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (5n):

Yellow powder; m.p 161–162 °C; IR (ν cm^{-1}): 3319, 2979, 2167, 1742, 1636, 1269; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17–1.21 (t, *J* = 6.8 Hz, 3H, -CH_3), 1.33–1.36 (t, *J* = 6.8 Hz, 3H, -CH_3), 4.10–4.15 (q, *J* = 6.8 Hz, 4H, -CH_2), 4.79 (s, 2H, -NH_2), 5.05 (s, 1H, -CH), 6.62 (s, 1H, Ar-H), 7.20–7.45 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 16.1, 30.6, 56.4, 60.3, 61.5, 99.7, 107.9, 111.5, 113.8, 115.6, 119.5, 120.7, 123.6, 127.6, 131.7, 133.4, 136.4, 142.7, 148.9, 157.3, 163.8, 165.6, 170.2 ppm; ESI-MS, *m/z*: 492.1 $[M+H]^+$; Anal. Calc. for $C_{26}H_{22}ClN_3O_5$ (%): C, 63.48, H, 4.51, N, 8.54; found: C, 63.43, H, 4.48, N, 8.59.

Dimethyl-6-amino-1-(4´-chlorophenyl)-5-cyano-4-(3´´,4´´,5´´-trimethoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5o):

Yellow powder; m.p 217–218 °C; IR (ν cm^{-1}): 3319, 2979, 2167, 1742, 1636, 1269; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.53 (s, 3H, -CH_3), 3.65 (s, 3H, -CH_3), 3.86 (s, 3H, -OCH_3), 3.90 (s, 6H, -OCH_3), 4.63 (s, 2H, -NH_2), 5.31 (s, 1H, -CH), 6.59 (s, 2H, Ar-H), 7.25–7.49 (m, 4H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.0, 55.1, 55.2, 62.0, 62.6, 63.0, 103.4, 105.3, 115.1, 120.1, 127.7, 130.9, 138.0, 140.6, 141.9, 150.1, 153.0, 160.9, 163.8, 165.5 ppm; ESI-MS, *m/z*: 514.1 $[M+H]^+$; Anal. Calc. for $C_{25}H_{24}ClN_3O_7$ (%): C, 58.43, H, 4.71, N, 8.18; found: C, 58.31, H, 4.80, N, 8.29.

Dimethyl-6-amino-4-(4´-chlorophenyl)-5-cyano-1-*p*-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (5p):

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Yellow powder; m.p 187–188 °C; IR (ν cm^{-1}): 3363, 2921, 2110, 1735, 1659, 1227; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.4 (s, 3H, -CH_3), 3.45 (s, 3H, -OCH_3), 3.59 (s, 3H, -OCH_3), 4.11 (s, 2H, -NH_2), 4.68 (s, 1H, -CH), 7.18–7.29 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 38.5, 52.6, 62.6, 105.6, 112.6, 121.1, 128.5, 129.3, 130.3, 131.1, 132.5, 133.1, 141.0, 142.0, 142.8, 149.1, 162.1, 165.6 ppm; ESI-MS, *m/z*: 438.1 $[M+H]^+$; Anal. Calc. for $C_{23}H_{20}ClN_3O_4$ (%): C, 63.09, H, 4.60, N, 9.60; found: C, 63.18, H, 4.67, N, 9.72.

Dimethyl-6-amino-1,4-*bis*(4´-chlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (5q):

Yellow powder; m.p 128–129 °C; IR (ν cm^{-1}): 3360, 2989, 2119, 1746, 1643, 1210; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41 (s, 3H, -CH_3), 3.69 (s, 3H, -CH_3), 4.13 (s, 2H, -NH_2), 4.63 (s, 1H, -CH), 7.22–7.47 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 36.7, 50.5, 51.1, 56.4, 61.8, 104.6, 120.5, 127.7, 128.4, 129.9, 130.0, 130.7, 131.4, 132.1, 132.6, 134.0, 135.8, 140.8, 141.2, 143.5, 149.7, 157.2, 159.2, 163.9, 164.7 ppm; ESI-MS, *m/z*: 458.1 $[M+H]^+$; Anal. Calc. for $C_{22}H_{17}Cl_2N_3O_4$ (%): C, 57.66, H, 3.74, N, 9.17; found: C, 57.50, H, 4.03, N, 8.95.

Dimethyl-6-amino-5-cyano-4-(3´-nitrophenyl)-1-*p*-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (5r):

Yellow powder; m.p 213–214 °C; IR (ν cm^{-1}): 3382, 2942, 2120, 1749, 1610, 1237; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H, -CH_3), 3.46 (s, 3H, -OCH_3), 3.59 (s, 3H, -OCH_3), 4.18 (s, 2H, -NH_2), 4.82 (s, 1H, -CH), 7.26–8.28 (m, 8H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 20.2, 37.3, 50.8, 51.3, 58.2, 60.3, 103.9, 120.5, 121.6, 122.5, 129.3, 130.1, 130.7, 131.5, 132.6, 134.1, 141.1, 142.5, 146.7, 148.1, 151.9, 162.4 163.9 ppm; ESI-MS, *m/z*: 449.1 $[M+H]^+$; Anal. Calc. for $C_{23}H_{20}N_4O_6$ (%): C, 61.60, H, 4.50, N, 12.49; found: C, 61.49, H, 4.85, N, 12.11.

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Appendix A. Supporting Information

The detailed spectroscopic data of all the new compounds are available free of charge via the Internet. Single crystal data for compounds **5b** (CCDC 1423053) and **5f** (CCDC 1423055) have been deposited in the Cambridge Crystallographic Data Center.

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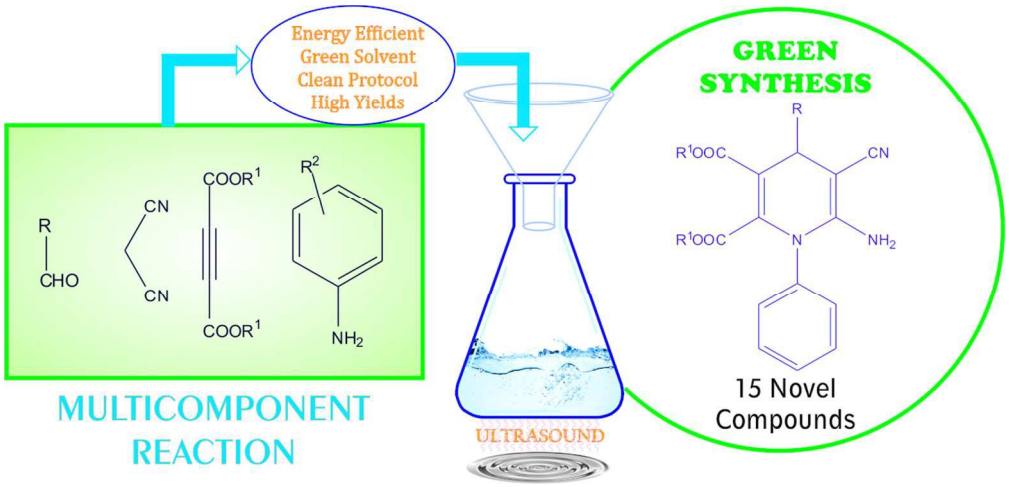

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