# Silica Sulfuric Acid-Catalyzed Five-component Efficient Synthesis of Five-Substituted Tetrahydropyridines

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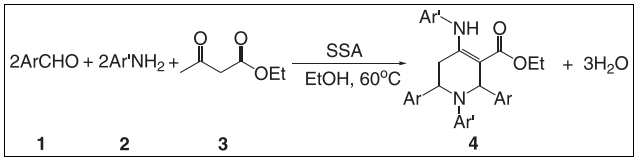


A highly atom-economic one-pot synthesis of five-substituted tetrahydropyridines via a five-component condensation of two equivalents of aromatic aldehyde, two equivalents of aromatic aniline, and one equivalent of β-keto ester catalyzed by silica sulfuric acid is reported. In this reaction, up to five new bonds and one new ring were formed in one pot with water as the only one by-product.

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## INTRODUCTION

Diversity-oriented synthesis is a useful tool at the interface of the fields of organic synthesis and chemical biology [1]. At the heart of diversity-oriented synthesis are the synthetic means needed for the generation of collections of functionally and regiochemically diverse small molecules, particularly those possessing skeletons resembling those naturally found products or drug-like molecules [2].

An efficient method for generating these collections of molecules is multicomponent reactions (MCRs) with subsequent transformations that further increase molecular complexity and diversity, requiring a minimum of time, labor, cost, and waste production [3]. Therefore, the design of novel MCRs for the synthesis of diverse groups of compounds, especially the ones that are biologically active, has commanded great attention [4].

Recently, the researches on MCRs in which more than four components were used have already become a trend. Bonfield *et al*. reported a six-compound to prepare isoindoline via tandem double A3-coupling and [2 + 2 + 2]-cyclo-addition reaction [5]. Brauch *et al*. have extended MCRs to seven components by taking advantage of the different chemoselectivities of the Ugi-Mumm and the Ugi-Smiles reaction [6]. The Orru group developed a one-pot reaction of up to eight components that involves nine new bond formations and 11 points of diversity [7].

The framework of five-substituted tetrahydropyridines is widely found in biologically active natural products and pharmaceuticals [8]. They are also an important class of heterocyclic compounds, and structural units have many functions such as antibacterial [9], anti-inflammation [10], antineoplastic [11,12], and they are used to treat the mental disorders [13]. Some methods for the syntheses of tetrahydropyridines include aza Diels–Alder reaction [14], intramolecular Michael addition [15], Dieckmann condensation [16], photochemical reaction [17], ring-closing metathesis[18], and ene reaction [19]. However, most methods have their limitations such as complex material (Brassard's diene) [20], low yields, expensive catalyst ($InCl_3$, L-proline/TFA, $ZrOCl_2{\cdot}8H_2O$) [21], long reaction time (50 h) [22], and requirement of toxic solvents (such as MeCN) [23].

Silica sulfuric acid (SSA) has been proven as a very useful reagent in organic synthesis [24–26]. To investigate its new application, herein, we report an interesting five-component efficient synthesis of five-substituted tetrahydropyridines via the reaction of aromatic aldehyde (**1**), aromatic aniline (**2**), and β-keto ester (**3**) catalyzed by SSA (Scheme 1).

## RESULTS AND DISCUSSION

Using the conversion of benzaldehyde (**1d**, 2.0 mmol), paraiodoaniline (**2d**, 2.0 mmol), and ethyl acetoacetate (**3**, 1 mmol) as a model reaction, we tested different reaction conditions to optimize the conditions at first. A summary of the optimization experiment is provided in Table 1. It was found that this transformation could not run smoothly except in the presence of SSA (Table 1, entries 1–6). Other acids such as L-proline, camphorsulfonic acid, and TsOH could not be employed as promoters in this reaction. The important role of SSA in this interesting reaction may be attributed to its suitable acidity and supporting function. The combination between SSA and reactants made it act as phase transfer catalysis and enhanced the solubility of reactant in solvent. SSA could be easy separated and recycled five times without significant

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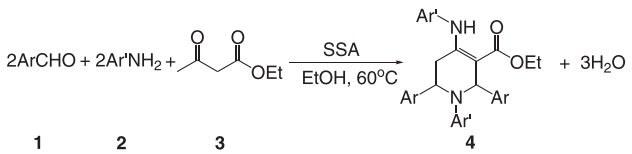
deactivation. Ethanol is superior to [BmIm][$BF_4$] as the solvent (Table 1, entries 4 and 6). It maybe because the basicity of [BmIm][$BF_4$] (pKa $_{[BF4]}$ = 0.5) is too strong to meet this reaction. When 0.1 g of SSA was used, the reaction proceeded in good yield (Table 1, entries 6–8). Finally, when the temperature was increased to 60°C with EtOH as the solvent, the reaction proceeded smoothly (Table 1, entries 7 and 9–11).

To explore the application of this method, the scope of the substrates was evaluated with a variety of aromatic aldehydes and aromatic anilines (Table 2). It appeared that the electronic nature of the substituted groups in the aromatic ring had slightly influence on the yield. It is noteworthy that no remarkable steric hindrance on the reaction was observed, for example, the desired products were obtained in moderate to good yields when the *ortho* substituent on the benzaldehyde were used (Table 2, Entries 7–11).

The possible reaction mechanism was proposed in Scheme 2. SSA can serve as an acidic catalyst for this reaction. We presume that the reaction proceeds via initial formation of **5** through condensation of aryl aldehyde **1** and aromatic aniline **2**. Meanwhile, β-keto ester **3** condensed with another aromatic aniline **2** to give enamine **6**. Subsequently, the enamine **6** reacted with another aromatic aldehyde **1** to give intermediate **7** by the Knoevenagel reaction. Intermediate **7** turned to provide **8** via tautomerization, and then **8** cyclized with **5** to give the expected tetrahydropyridines **4** by an [4 + 2]-aza Diels–Alder reaction. We supposed that the important role of SSA in this reaction is attributed to its apropos acidity and supporting function.

**Scheme 1**




In summary, we have developed a novel and simple SSA-catalyzed five-component condensation for the construction of five-substituted tetrahydropyridines from commercially available starting materials. SSA showed its important role in this interesting reaction. Six bonds were cleaved, and five new bonds (two C-N single bonds, one C=N double bond, one C=C double bond, one C-C single bond) were constructed in the formation of **4**, whereas only three $H_2O$ molecules were removed. One ring of the fused-ring framework was constructed in one pot. This method offers several advantages including inexpensive starting materials, low catalyst loading, and no formation of by-products such as aldol or deamination products. In addition, there are several modifiable and coordinate sites in this one new interesting type of framework, so the subsequent step of the combinatorial development process, namely, structural optimization, should be possible. Future efforts to explore the coordination effect of products and the synthetic utility of the reaction are underway.

## EXPERIMENTAL

General information. IR spectra were recorded with a Varian FTIR-Tensor-27 spectrophotometer (Bruker Daltonic Inc., USA) using KBr optics. $^1$H NMR spectra were recorded at 400 MHz on a Bruker DPX 400 spectrometer (Hitachi, Japan) using TMS as an internal standard and DMSO-$d_6$ as solvent. Mass was determined by using a Bruker TOF-MS high resolution mass spectrometer (USA). All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. SSA was prepared in our lab. Organic solvents were dried and distilled prior to use.

The synthesis of SSA was followed according to the method described in the literature [27].

**Table 1**

Optimization of reaction conditions[a].

| Entry | Catalyst | Amount (g) | Solvent | T(°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| **1** | L-proline | 0.2 | EtOH | 60 | 15 | Nr[c] |
| **2** | Camphorsulfonic acid | 0.2 | EtOH | 60 | 15 | Nr[c] |
| **3** | — | — | [Bmim][$BF_4$] | 60 | 15 | Nr[c] |
| **4** | SSA | 0.2 | [Bmim][$BF_4$] | 60 | 15 | Nr[c] |
| **5** | TsOH | 0.2 | EtOH | 60 | 14 | <5 |
| **6** | SSA | 0.2 | EtOH | 60 | 7 | 80 |
| **7** | SSA | 0.1 | EtOH | 60 | 7 | 86 |
| **8** | SSA | 0.05 | EtOH | 60 | 7 | 78 |
| **9** | SSA | 0.1 | EtOH | 50 | 7 | 70 |
| **10** | SSA | 0.1 | EtOH | 55 | 7 | 78 |
| **11** | SSA | 0.1 | EtOH | 65 | 7 | 85 |

[a]Reactions were performed in 2:2:1 (benzaldehyde: paraiodoaniline: ethyl acetoacetate) in different conditions.
[b]Yield of pure product after crystallization.
[c]No reaction.

**Table 2**

Synthesis of **4** under optimum condition[a].

| Entry | Product | Ar | Ar′ | Time (h) | Yields (%)[b] | Mp (°C) Found | Mp (°C) Reported |
|---|---|---|---|---|---|---|---|
| 1 | 4a | $C_6H_5$ | 4-$FC_6H_4$ | 9 | 74 | 181.2–182.3 | |
| 2 | 4b | $C_6H_5$ | 4-$ClC_6H_4$ | 9 | 78 | 222.0–222.9 | 220.0–221.5 [22] |
| 3 | 4c | $C_6H_5$ | 4-$BrC_6H_4$ | 8 | 80 | 226.9–228.5 | |
| 4 | 4d | $C_6H_5$ | 4-$IC_6H_4$ | 7 | 86 | 243.4–244.9 | |
| 5 | 4e | $C_6H_5$ | 4-$CH_3C_6H_4$ | 8 | 82 | 195.2–196.7 | |
| 6 | 4f | $C_6H_5$ | 4-$OCH_3C_6H_4$ | 9 | 77 | 190.9–192.1 | 172.4–173.9 [22] |
| 7 | 4g | 2-$OCH_3C_6H_4$ | 4-$CH_3C_6H_4$ | 14 | 55 | 166.3–167.2 | |
| 8 | 4h | 2-$OCH_3C_6H_4$ | 4-$FC_6H_4$ | 12 | 68 | 178.2–179.2 | |
| 9 | 4i | 2-$OCH_3C_6H_4$ | 4-$ClC_6H_4$ | 10 | 75 | 197.2–198.6 | |
| 10 | 4j | 2-$OCH_3C_6H_4$ | 4-$BrC_6H_4$ | 9 | 76 | 168.4–169.8 | |
| 11 | 4k | 2-$OCH_3C_6H_4$ | 4-$IC_6H_4$ | 8 | 78 | 227.1–228.0 | |
| 12 | 4l | 4-$FC_6H_4$ | 4-$CH_3C_6H_4$ | 12 | 64 | 196.7–198.9 | |
| 13 | 4m | 4-$FC_6H_4$ | 4-$FC_6H_4$ | 11 | 70 | 205.9–206.6 | |
| 14 | 4n | 4-$FC_6H_4$ | 4-$ClC_6H_4$ | 9 | 74 | 167.4–169.1 | |
| 15 | 4o | 4-$FC_6H_4$ | 4-$BrC_6H_4$ | 10 | 74 | 195.3–197.8 | |
| 16 | 4p | 4-$FC_6H_4$ | 4-$IC_6H_4$ | 10 | 72 | 196.9–198.1 | |
| 17 | 4q | 4-$FC_6H_4$ | 3-Cl-4-$FC_6H_3$ | 13 | 67 | 140.0–141.4 | |
| 18 | 4r | 4-$ClC_6H_4$ | 4-$FC_6H_4$ | 9 | 72 | 236.9–238.4 | |
| 19 | 4s | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | 12 | 68 | 216.2–218.6 | |
| 20 | 4t | 4-$ClC_6H_4$ | 4-$BrC_6H_4$ | 13 | 66 | 199.9–202.1 | |
| 21 | 4u | 4-$ClC_6H_4$ | 4-$IC_6H_4$ | 10 | 72 | 160.0–162.3 | |
| 22 | 4v | 4-$ClC_6H_4$ | 3-Cl-4-$FC_6H_3$ | 14 | 70 | 180.4–181.5 | |
| 23 | 4w | 4-$ClC_6H_4$ | 4-$CH_3C_6H_4$ | 11 | 64 | 188.2–189.1 | |
| 24 | 4x | 4-$ClC_6H_4$ | 4-$OCH_3C_6H_4$ | 10 | 66 | 185.0–186.5 | |
| 25 | 4y | 4-$BrC_6H_4$ | 4-$FC_6H_4$ | 12 | 71 | 208.7–210.2 | |
| 26 | 4z | 4-$IC_6H_4$ | 3-Cl-4-$FC_6H_3$ | 10 | 73 | 206.7–207.8 | |
| 27 | 4aa | 4-$IC_6H_4$ | 4-$OCH_3C_6H_4$ | 8 | 80 | 246.5–247.4 | |
| 28 | 4ab | 4-$IC_6H_4$ | 4-$FC_6H_4$ | 10 | 72 | 221.3–222.6 | |
| 29 | 4ac | 4-$IC_6H_4$ | 4-$ClC_6H_4$ | 9 | 70 | 254.7–255.2 | |
| 30 | 4ad | 4-$IC_6H_4$ | 4- $BrC_6H_4$ | 9 | 74 | 239.0–240.1 | |
| 31 | 4ae | 4-$IC_6H_4$ | 4-$IC_6H_4$ | 12 | 58 | 237.6–238.3 | |
| 32 | 4af | 4-$CNC_6H_4$ | 4-$CH_3C_6H_4$ | 13 | 67 | 178.3–180.5 | |
| 33 | 4ag | 3-$FC_6H_4$ | 4-$OCH_3C_6H_4$ | 12 | 70 | 178.4–179.8 | |
| 34 | 4ah | 3-$FC_6H_4$ | 4-$CH_3C_6H_4$ | 12 | 68 | 148.8–149.3 | |
| 35 | 4ai | 3-$FC_6H_4$ | 4-$ClC_6H_4$ | 10 | 76 | 186.4–186.9 | |
| 36 | 4aj | 3-$FC_6H_4$ | 4-$BrC_6H_4$ | 10 | 73 | 192.2–193.4 | |
| 37 | 4ak | 3-$FC_6H_4$ | 4-$IC_6H_4$ | 9 | 77 | 179.8–180.4 | |
| 38 | 4al | 3-$BrC_6H_4$ | 4-$FC_6H_4$ | 10 | 75 | 181.5–182.5 | |
| 39 | 4am | 4-$OCH_3C_6H_4$ | 4-$BrC_6H_4$ | 10 | 78 | 177.2–179.3 | |
| 40 | 4an | 4-$OCH_3C_6H_4$ | 4-$OCH_3C_6H_4$ | 8 | 74 | 158.5–160.1 | |
| 41 | 4ao | 3,4,5-$(OCH_3)_3C_6H_2$ | 4-$ClC_6H_4$ | 7 | 80 | 165.7–166.2 | |

[a]All reactions were carried out in the scale of aromatic aldehyde (2.0 mmol), aromatic aniline (2.0 mmol), ethyl acetoacetate (1 mmol), and SSA (0.1 g).
[b]Isolated yields.

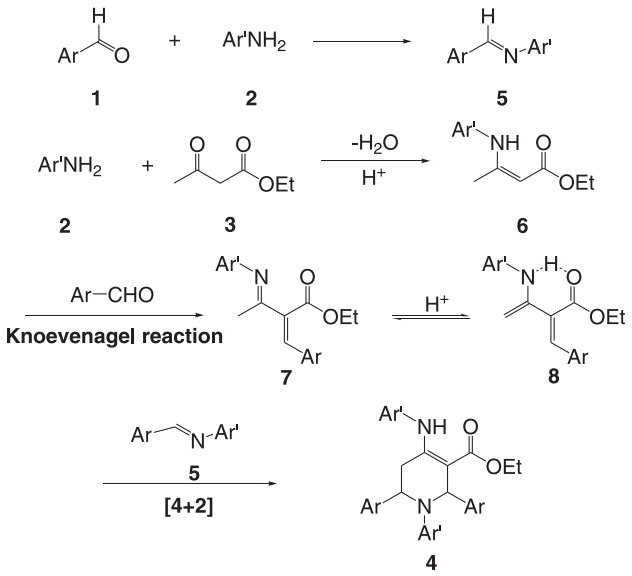
**The procedure for the synthesis of five-substituted tetrahydropyridines derivatives 4**. A mixture of aldehyde (2.0 mmol), aniline (2.0 mmol), β-keto ester (1.0 mmol), SSA (0.1 g), and EtOH (2.0 mL) was stirred at 60°C for 7 to 14 h until complete consumption of the starting material as monitored by TLC. After completion of the reaction, the mixture was diluted with water; the crude solid was filtered and washed with 95% EtOH. The solid residue was then recrystallized (95% EtOH/DMF, 1:4) to provide the pure product **4**.

The spectral data of new products are given next.

**Ethyl 4-(4-fluorophenylamino)-1-(4-fluorophenyl)-1,2,5,6-tetrahydro-2,6-diphenylpyridine-3-carboxylate (4a)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3247, 3012, 2983, 1650, 1605, 1508; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.67 (dd, $J$ = 14.0 and 1.2 Hz, 1H, $H_{5a}$), 2.91 (dd, $J$ = 15.6 and 5.6 Hz, 1H, $H_{5b}$), 4.24–4.44 (m, 2H, $OCH_2$), 5.34 (br s, 1H, $H_6$), 6.27 (s, 1H, $H_2$), 6.36–6.41 (m, 4H, ArH), 6.87 (t, $J$ = 8.8 Hz, 2H, ArH), 6.99 (t, $J$ = 8.8 Hz, 2H, ArH), 7.14–7.34 (m, 10H, ArH), 10.13 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 511.2160 (511.2197).

**Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-1,2,5,6-tetrahydro-2,6-diphenylpyridine-3-carboxylate (4c)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3242, 3060, 2973, 1645, 1602, 1580; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.75 (dd, $J$ = 15.6 and 2.4 Hz, 1H, $H_{5a}$), 2.97 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5b}$), 4.24–4.43 (m, 2H, $OCH_2$), 5.40 (br s, 1H, $H_6$), 6.23 (s, 1H, $H_2$), 6.38 (d, $J$ = 8.8 Hz, 2H, ArH), 6.55 (d, $J$ = 8.8 Hz, 2H, ArH), 7.07–7.18 (m, 10H, ArH), 7.25 (d,

**Scheme 2**




$J$ = 8.8 Hz, 2H, ArH), 7.33–7.37 (m, 2H, ArH), 10.20 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 631.0546 (631.0596).

**Ethyl 4-(4-iodophenylamino)-1,2,5,6-tetrahydro-1-(4-iodophenyl)-2,6-diphenylpyridine-3-carboxylate (4d)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3243, 2981, 1647, 1600, 1578; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 1.38 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.77 (dd, $J$ = 15.6 and 0.8 Hz, 1H, $H_{5a}$), 2.96 (dd, $J$ = 16.0 and 6.0 Hz, 1H, $H_{5b}$), 4.25–4.44 (m, 2H, $OCH_2$), 5.38 (br s, 1H, $H_6$), 6.21–6.27 (m, 5H, ArH and $H_2$), 7.12 (d, $J$ = 7.2 Hz, 2H, ArH), 7.23–7.33 (m, 10H, ArH), 7.47 (d, $J$ = 8.4 Hz, 2H, ArH), 10.15 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 727.0284 (727.0318).

**Ethyl 4-(4-tolylamino)-1,2,5,6-tetrahydro-2,6-diphenyl-1-(4-tolylpyridine)-3-carboxylate (4e)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3245, 3024, 2984, 1649, 1593; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 1.39 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.07 (s, 3H, $ArCH_3$), 2.22 (s, 3H, $ArCH_3$), 2.75 (dd, $J$ = 12.8 and 0.8 Hz, 1H, $H_{5a}$), 2.88 (dd, $J$ = 12.8 and 5.6 Hz, 1H, $H_{5b}$), 4.24–4.44 (m, 2H, $OCH_2$), 5.33 (br s, 1H, $H_6$), 6.24–6.33 (m, 5H, ArH and $H_2$), 6.81 (d, $J$ = 8.8 Hz, 2H, ArH), 6.95 (d, $J$ = 8.0 Hz, 2H, ArH), 7.14–7.32 (m, 10H, ArH), 10.18 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 503.2663 (503.2699).

**Ethyl 4-(4-tolylamino)-1,2,5,6-tetrahydro-2,6-bis(2-methoxyphenyl)-1-(4-tolylpyridine)-3-carboxylate (4g)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3253, 2920, 2834, 1655, 1517; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 1.41 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.14 (s, 3H, $ArCH_3$), 2.25 (s, 3H, $ArCH_3$), 2.79 (dd, $J$ = 15.6 and 5.6 Hz, 1H, $H_{5a}$), 2.95 (dd, $J$ = 15.6 and 2.0 Hz, 1H, $H_{5b}$), 3.61 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 4.22–4.43 (m, 2H, $OCH_2$), 5.39 (br s, 1H, $H_6$), 6.14–6.16 (m, 2H, ArH and $H_2$), 6.32 (d, $J$ = 8.4 Hz, 2H, ArH), 6.42 (s, 1H, ArH), 6.77–6.92 (m, 8H, ArH), 7.02 (d, $J$ = 6.8 Hz, 1H, ArH), 7.13–7.24 (m, 3H, ArH), 9.68 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 563.2931 (563.2910).

**Ethyl 4-(4-fluorophenylamino)-1-(4-fluorophenyl)-1,2,5,6-tetrahydro-2,6-bis(2-methoxyphenyl)pyridine-3-carboxylate (4h)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3240, 3020, 2978, 1654, 1613, 1485; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 1.42 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.08 (d, $J$ = 4.0 Hz, 2H, $CH_2$), 3.66 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 4.25–4.43 (m, 2H, $OCH_2$), 5.36 (br s, 1H, $H_6$), 6.19–6.22 (m, 2H, ArH and $H_2$), 6.29–6.33 (m, 2H, ArH), 6.37 (s, 1H, ArH), 6.72–6.85 (m, 7H, ArH), 6.91 (d, $J$ = 8.4 Hz, 1H, ArH), 6.98 (d, $J$ = 7.6 Hz, 1H, ArH), 7.12 (dd, $J$ = 8.0 and 1.6 Hz, 1H, ArH), 7.19–7.25 (m, 2H, ArH), 9.66 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 571.2414 (571.2408).

**Ethyl 4-(4-chlorophenylamino)-1-(4-chlorophenyl)-1,2,5,6-tetrahydro-2,6-bis(2-methoxyphenyl)pyridine-3-carboxylate (4i)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3247, 2979, 2898, 1656, 1612, 1504; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 1.43 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.81 (dd, $J$ = 15.6 and 5.6 Hz, 1H, $H_{5a}$), 2.91 (dd, $J$ = 15.6 and 2.4 Hz, 1H, $H_{5b}$), 3.67 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 4.24–4.44 (m, 2H, $OCH_2$), 5.38 (br s, 1H, $H_6$), 6.16 (d, $J$ = 8.8 Hz, 2H, ArH and $H_2$), 6.32 (d, $J$ = 9.2 Hz, 2H, ArH), 6.39 (s, 1H, ArH), 6.79–6.85 (m, 3H, ArH), 6.91–7.09 (m, 7H, ArH), 7.19–7.25 (m, 2H, ArH), 9.66 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 603.1861 (603.1817).

**Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-1,2,5,6-tetrahydro-2,6-bis(2-methoxyphenyl)pyridine-3-carboxylate (4j)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3250, 2978, 2876, 1656, 1611, 1585; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 1.34 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.80 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5a}$), 2.90 (dd, $J$ = 16.0 and 1.6 Hz, 1H, $H_{5b}$), 3.69 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 4.19–4.39 (m, 2H, $OCH_2$), 5.42 (br s, 1H, $H_6$), 6.17–6.22 (m, 4H, ArH and $H_2$), 6.29 (s, 1H, ArH), 6.80–6.88 (m, 3H, ArH), 6.97–7.07 (m, 3H, ArH), 7.16–7.32 (m, 6H, ArH), 9.54 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 691.0876 (691.0807).

**Ethyl 4-(4-iodophenylamino)-1,2,5,6-tetrahydro-1-(4-iodophenyl)-2,6-bis(2-methoxyphenyl)pyridine-3-carboxylate (4k)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3246, 3030, 2976, 1654, 1606, 1581; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 1.33 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.79 (dd, $J$ = 12.0 and 5.6 Hz, 1H, $H_{5a}$), 2.92 (dd, $J$ = 14.8 and 1.6 Hz, 1H, $H_{5b}$), 3.68 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 4.19–4.39 (m, 2H, $OCH_2$), 5.40 (br s, 1H, $H_6$), 6.07 (d, $J$ = 8.4 Hz, 4H, ArH and $H_2$), 6.28 (s, 1H, ArH), 6.79–6.87 (m, 3H, ArH), 6.96–7.06 (m, 3H, ArH), 7.20–7.31 (m, 4H, ArH), 7.45 (d, $J$ = 8.4 Hz, 2H, ArH), 9.53 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 787.0514 (787.0530).

**Ethyl 4-(4-tolylamino)-2,6-bis(4-fluorophenyl)-1,2,5,6-tetrahydro-1-(4-tolylpyridine)-3-carboxylate 4l**:. White solid. IR (KBr, ν, $cm^{-1}$): 3236, 2998, 2869, 1650, 1596, 1516; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.07 (s, 3H, $ArCH_3$), 2.23 (s, 3H, $ArCH_3$), 2.73 (dd, $J$ = 14.4 and 2.0 Hz, 1H, $H_{5a}$), 2.88 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5b}$), 4.22–4.42 (m, 2H, $OCH_2$), 5.33 (br s, 1H, $H_6$), 6.22 (s, 1H, $H_2$), 6.30 (d, $J$ = 8.8 Hz, 2H, ArH), 6.37 (d, $J$ = 8.4 Hz, 2H, ArH), 6.83 (d, $J$ = 8.4 Hz, 2H, ArH), 7.00 (d, $J$ = 8.0 Hz, 2H, ArH), 7.11–7.15 (m, 6H, ArH), 7.30–7.34 (m, 2H, ArH), 10.20 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 539.2563 (539.2510).

**Ethyl 4-(4-fluorophenylamino)-1,2,6-tris(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4m)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3243, 2986, 2889, 1649, 1605, 1507; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.67 (dd, $J$ = 15.6 and 2.0 Hz, 1H, $H_{5a}$), 2.90 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5b}$), 4.22–4.42 (m, 2H, $OCH_2$), 5.34 (br s, 1H, $H_6$),

6.20 (s, 1H, $H_2$), 6.33–6.37 (m, 2H, ArH), 6.53–6.56 (m, 2H, ArH), 6.89 (t, $J$ = 8.8 Hz, 2H, ArH), 7.05 (t, $J$ = 8.8 Hz, 2H, ArH), 7.12–7.17 (m, 6H, ArH), 7.32–7.35 (m, 2H, ArH), 10.16 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 547.2017 (547.2009).

**Ethyl 4-(4-chlorophenylamino)-1-(4-chlorophenyl)-2,6-bis(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4n)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3237, 3068, 2978, 1649, 1495; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.38 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.75 (dd, $J$ = 15.6 and 2.4 Hz, 1H, $H_{5a}$), 2.97 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5b}$), 4.24–4.43 (m, 2H, $OCH_2$), 5.40 (br s, 1H, $H_6$), 6.23 (s, 1H, $H_2$), 6.38 (d, $J$ = 8.8 Hz, 2H, ArH), 6.55 (d, $J$ = 8.8 Hz, 2H, ArH), 7.07–7.18 (m, 8H, ArH), 7.25 (d, $J$ = 8.8 Hz, 2H, ArH), 7.33–7.37 (m, 2H, ArH), 10.20 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 579.1483 (579.1418).

**Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-2,6-bis(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4o)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3240, 3032, 2978, 1649, 1592, 1492; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.76 (dd, $J$ = 14.4 and 1.2 Hz, 1H, $H_{5a}$), 2.97 (dd, $J$ = 15.6 and 5.6 Hz, 1H, $H_{5b}$), 4.23–4.43 (m, 2H, $OCH_2$), 5.39 (br s, 1H, $H_6$), 6.22 (s, 1H, $H_2$), 6.34 (d, $J$ = 9.2 Hz, 2H, ArH), 6.50 (d, $J$ = 8.8 Hz, 2H, ArH), 7.12–7.21(m, 8H, ArH), 7.32–7.39 (m, 4H, ArH), 10.18 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 667.0434 (667.0407).

**Ethyl 4-(4-iodophenylamino)-2,6-bis(4-fluorophenyl)-1,2,5,6-tetrahydro-1-(4-iodophenyl)pyridine-3-carboxylate (4p)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3246, 3021, 2963, 1654, 1604, 1578; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.77 (dd, $J$ = 15.6 and 2.0 Hz, 1H, $H_{5a}$), 2.96 (dd, $J$ = 15.6 and 5.2 Hz, 1H, $H_{5b}$), 4.23–4.42 (m, 2H, $OCH_2$), 5.38 (br s, 1H, $H_6$), 6.22 (t, $J$ = 8.2 Hz, 3H, ArH and $H_2$), 6.35 (d, $J$ = 8.2 Hz, 2H, ArH), 7.11–7.17 (m, 6H, ArH), 7.31–7.35 (m, 4H, ArH), 7.52 (d, $J$ = 8.2 Hz, 2H, ArH), 10.17 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 763.0107 (763.0130).

**Ethyl 4-(3-chloro-4-fluorophenylamino)-1-(3-chloro-4-fluorophenyl)-2,6-bis(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4q)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3243, 2998, 2876, 1649, 1581; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.47 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.60 (dd, $J$ = 15.2 and 1.2 Hz, 1H, $H_{5a}$), 2.78 (dd, $J$ = 15.2 and 5.6 Hz, 1H, $H_{5b}$), 4.30–4.52 (m, 2H, $OCH_2$), 5.03 (br s, 1H, $H_6$), 6.24 (s, 1H, $H_2$), 6.26–6.34 (m, 3H, ArH), 6.43–6.45 (m, 1H, ArH), 6.84 (t, $J$ = 9.0 Hz, 1H, ArH), 6.91–7.05 (m, 5H, ArH), 7.08–7.12 (m, 2H, ArH), 7.19–7.22 (m, 2H, ArH), 10.21 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 615.1237 (615.1229).

**Ethyl 4-(4-fluorophenylamino)-2,6-bis(4-chlorophenyl)-1-(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4r)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3247, 3012, 2871, 1651, 1612, 1505; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.44 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.61 (dd, $J$ = 15.6 and 2.8 Hz, 1H, $H_{5a}$), 2.77 (dd, $J$ = 15.2 and 5.6 Hz, 1H, $H_{5b}$), 4.27–4.48 (m, 2H, $OCH_2$), 5.01 (br s, 1H, $H_6$), 6.25 (s, 1H, $H_2$), 6.34–6.38 (m, 4H, ArH), 6.78 (t, $J$ = 8.8 Hz, 2H, ArH), 6.85 (t, $J$ = 8.4 Hz, 2H, ArH), 7.05 (d, $J$ = 8.4 Hz, 2H, ArH), 7.19–7.25 (m, 6H, ArH), 10.19 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 579.1494 (579.1418).

**Ethyl 4-(4-chlorophenylamino)-1,2,6-tris(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4s)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3246, 2996, 2867, 1652, 1600, 1493; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.44 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.68 (dd, $J$ = 15.2 and 2.4 Hz, 1H, $H_{5a}$), 2.81 (dd, $J$ = 15.2 and 6.0 Hz, 1H, $H_{5b}$), 4.29–4.49 (m, 2H, $OCH_2$), 5.05 (br s, 1H, $H_6$), 6.28–6.37 (m, 5H, ArH and $H_2$), 7.02 (t, $J$ = 8.6 Hz, 4H, ArH), 7.12 (d, $J$ = 8.4 Hz, 2H, ArH), 7.19–7.25 (m, 6H, ArH), 10.25 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 611.0846 (611.0827).

**Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4t)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3241, 3063, 2981, 1650, 1609, 1513; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.77 (dd, $J$ = 14.4 and 1.2 Hz, 1H, $H_{5a}$), 2.91 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5b}$), 4.23–4.42 (m, 2H, $OCH_2$), 5.39 (br s, 1H, $H_6$), 6.20 (s, 1H, $H_2$), 6.32 (d, $J$ = 8.8 Hz, 2H, ArH), 6.34 (d, $J$ = 8.8 Hz, 2H, ArH), 7.10 (d, $J$ = 8.4 Hz, 2H, ArH), 7.20 (d, $J$ = 8.8 Hz, 2H, ArH), 7.33–7.41 (m, 8H, ArH), 10.19 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 698.9826 (698.9816).

**Ethyl 4-(4-iodophenylamino)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydro-1-(4-iodophenyl)pyridine-3-carboxylate (4u)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3243, 2982, 1652, 1612, 1503; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.45 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.71 (dd, $J$ = 15.2 and 2.4 Hz, 1H, $H_{5a}$), 2.81 (dd, $J$ = 15.2 and 5.6 Hz, 1H, $H_{5b}$), 4.29–4.49 (m, 2H, $OCH_2$), 5.04 (br s, 1H, $H_6$), 6.14 (d, $J$ = 8.4 Hz, 2H, ArH and $H_2$), 6.24 (t, $J$ = 11.0 Hz, 3H, ArH), 7.02 (d, $J$ = 8.4 Hz, 2H, ArH), 7.19–7.25 (m, 6H, ArH), 7.31 (d, $J$ = 9.2 Hz, 2H, ArH), 7.46 (d, $J$ = 8.8 Hz, 2H, ArH), 10.25 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 794.9508 (794.9539).

**Ethyl 4-(3-chloro-4-fluorophenylamino)-1-(3-chloro-4-fluorophenyl)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4v)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3240, 3030, 2978, 1654, 1618, 1517; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.65 (dd, $J$ = 14.4 and 1.2 Hz, 1H, $H_{5a}$), 2.96 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5b}$), 4.23–4.43 (m, 2H, $OCH_2$), 5.40 (br s, 1H, $H_6$), 6.18 (s, 1H, $H_2$), 6.32–6.36 (m, 1H, ArH), 6.38–6.40 (m, 1H, ArH), 6.57 (dd, $J$ = 8.4 and 2.4 Hz, 1H, ArH), 6.66–6.70 (m, 1H, ArH), 7.11–7.15 (m, 3H, ArH), 7.28 (t, $J$ = 9.2 Hz, 1H, ArH), 7.33–7.42 (m, 6H, ArH), 10.09 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 647.0621 (647.0638).

**Ethyl 4-(4-tolylamino)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydro-1-(4-tolylpyridine)-3-carboxylate (4w)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3243, 3047, 2988, 1659, 1610, 1504; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.36 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.06 (s, 3H, $ArCH_3$), 2.23 (s, 3H, $ArCH_3$), 2.74 (dd, $J$ = 14.0 and 1.6 Hz, 1H, $H_{5a}$), 2.91 (dd, $J$ = 15.6 and 5.6 Hz, 1H, $H_{5b}$), 4.21–4.40 (m, 2H, $OCH_2$), 5.33 (br s, 1H, $H_6$), 6.20 (s, 1H, $H_2$), 6.28 (d, $J$ = 8.8 Hz, 2H, ArH), 6.39 (d, $J$ = 8.0 Hz, 2H, ArH), 6.82 (d, $J$ = 8.4 Hz, 2H, ArH), 7.00 (d, $J$ = 8.4 Hz, 2H, ArH), 7.11 (d, $J$ = 8.4 Hz, 2H, ArH), 7.32–7.37 (m, 6H, ArH), 10.20 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 571.1984 (571.1919).

**Ethyl 4-(4-methoxyphenylamino)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydro-1-(4-methoxyphenyl)pyridine-3-carboxylate (4x)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3244, 3047, 2978, 1654, 1618, 1517; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.34 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.66 (dd, $J$ = 15.6 and 2.0 Hz, 1H, $H_{5a}$), 2.86 (dd, $J$ = 16.0 and 5.2 Hz, 1H, $H_{5b}$), 3.56 (s, 3H, $OCH_3$), 3.72 (s, 3H, $OCH_3$), 4.19–4.38 (m, 2H, $OCH_2$), 5.26 (br s, 1H, $H_6$), 6.12 (s, 1H, $H_2$), 6.31 (d, $J$ = 9.2 Hz, 2H, ArH), 6.47 (d, $J$ = 8.8 Hz, 2H, ArH), 6.66 (d, $J$ = 9.2 Hz, 2H, ArH), 6.76 (d,

$J$ = 8.8 Hz, 2H, ArH), 7.11 (d, $J$ = 8.4 Hz, 2H, ArH), 7.30–7.37 (m, 6H, ArH), 10.13 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 603.1848 (603.1817).

**Ethyl 4-(4-fluorophenylamino)-2,6-bis(4-bromophenyl)-1-(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4y)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3248, 3020, 1652, 1614, 1497; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.36 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.68 (dd, $J$ = 16.0 and 1.2 Hz, 1H, $H_{5a}$), 2.89 (dd, $J$ = 15.2 and 5.6 Hz, 1H, $H_{5b}$), 4.21–4.41 (m, 2H, $OCH_2$), 5.32 (br s, 1H, $H_6$), 6.15 (s, 1H, $H_2$), 6.32–6.35 (m, 2H, ArH), 6.73–6.76 (m, 2H, ArH), 7.03–7.07 (m, 4H, ArH), 7.22–7.29 (m, 6H, ArH), 7.39 (d, $J$ = 8.4 Hz, 2H, ArH), 10.14 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 667.0389 (667.0407).

**Ethyl 4-(3-chloro-4-fluorophenylamino)-1-(3-chloro-4-fluorophenyl)-1,2,5,6-tetrahydro-2,6-bis(4-iodophenyl)pyridine-3-carboxylate (4z)**:. Yellow solid. IR (KBr, ν, $cm^{-1}$): 3236, 2968, 2855, 1653, 1501; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.62 (dd, $J$ = 14.4 and 0.8 Hz, 1H, $H_{5a}$), 2.93 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5b}$), 4.22–4.42 (m, 2H, $OCH_2$), 5.35 (br s, 1H, $H_6$), 6.14 (s, 1H, $H_2$), 6.32–6.35 (m, 1H, ArH), 6.38–6.40 (m, 1H, ArH), 6.47 (dd, $J$ = 6.4 and 1.6 Hz, 1H, Ar), 6.66–6.70 (m, 1H, ArH), 6.93 (d, $J$ = 8.0 Hz, 2H, ArH), 7.10–7.15 (m, 3H, ArH), 7.28 (t, $J$ = 9.2 Hz, 1H, ArH), 7.67–7.71 (m, 4H, ArH), 10.07 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 830.9391 (830.9351).

**Ethyl 4-(4-methoxyphenylamino)-1,2,5,6-tetrahydro-2,6-bis(4-iodophenyl)-1-(4-methoxyphenyl)pyridine-3-carboxylate (4aa)**:. Yellow solid. IR (KBr, ν, $cm^{-1}$): 3244, 2996, 2857, 1659, 1617, 1586; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.34 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.80 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5a}$), 2.91 (dd, $J$ = 16.0 and 1.6 Hz, 1H, $H_{5b}$), 3.69 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 4.19–4.39 (m, 2H, $OCH_2$), 5.42 (br s, 1H, $H_6$), 6.17–6.22 (m, 4H, ArH and $H_2$), 6.29 (s, 1H, ArH), 6.80–6.88 (m, 3H, ArH), 6.97–7.07 (m, 3H, ArH), 7.16–7.32 (m, 6H, ArH), 9.54 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 755.0616 (755.0631).

**Ethyl 4-(4-fluorophenylamino)-1-(4-fluorophenyl)-1,2,5,6-tetrahydro-2,6-bis(4-iodophenyl)pyridine-3-carboxylate (4ab)**:. Yellow solid. IR (KBr, ν, $cm^{-1}$): 3241, 3050, 2954, 1650, 1590, 1513; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.36 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.66 (dd, $J$ = 15.6 and 1.6 Hz, 1H, $H_{5a}$), 2.93 (dd, $J$ = 15.6 and 5.6 Hz, 1H, $H_{5b}$), 4.20–4.40 (m, 2H, $OCH_2$), 5.29 (br s, 1H, $H_6$), 6.13 (s, 1H, $H_2$), 6.31–6.35 (m, 2H, ArH), 6.55–6.58 (m, 2H, ArH), 6.87–6.91 (m, 4H, ArH), 7.04 (t, $J$ = 8.6 Hz, 2H, ArH), 7.13 (d, $J$ = 8.4 Hz, 2H, ArH), 7.64–7.68 (m, 4H, ArH), 10.14 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 763.0190 (763.0130).

**Ethyl 4-(4-chlorophenylamino)-1-(4-chlorophenyl)-1,2,5,6-tetrahydro-2,6-bis(4-iodophenyl)pyridine-3-carboxylate (4ac)**:. Yellow solid. IR (KBr, ν, $cm^{-1}$): 3243, 2975, 2894, 1649, 1602, 1590, 1492; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.75 (dd, $J$ = 12.0 and 1.6 Hz, 1H, $H_{5a}$), 3.00 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5b}$), 4.22–4.42 (m, 2H, $OCH_2$), 5.35 (br s, 1H, $H_6$), 6.16 (s, 1H, $H_2$), 6.36 (d, $J$ = 9.2 Hz, 2H, ArH), 6.58 (d, $J$ = 8.8 Hz, 2H, ArH), 6.90 (d, $J$ = 8.4 Hz, 2H, ArH), 7.08 (d, $J$ = 8.8 Hz, 2H, ArH), 7.14 (d, $J$ = 8.4 Hz, 2H, ArH), 7.25 (d, $J$ = 8.8 Hz, 2H, ArH), 7.63–7.70 (m, 4H, ArH), 10.19 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 794.9599 (794.9539).

**Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-1,2,5,6-tetrahydro-2,6-bis(4-iodophenyl)pyridine-3-carboxylate (4ad)**:. Yellow solid. IR (KBr, ν, $cm^{-1}$): 3246, 3027, 2988, 1647, 1602, 1486; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.36 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.75 (dd, $J$ = 16.0 and 1.2 Hz, 1H, $H_{5a}$), 2.99 (dd, $J$ = 15.8 and 5.6 Hz, 1H, $H_{5b}$), 4.22–4.41 (m, 2H, $OCH_2$), 5.33 (br s, 1H, $H_6$), 6.15 (s, 1H, $H_2$), 6.31 (d, $J$ = 8.8 Hz, 2H, ArH), 6.52 (d, $J$ = 8.8 Hz, 2H, ArH), 6.89 (d, $J$ = 8.4 Hz, 2H, ArH), 7.13 (d, $J$ = 8.0 Hz, 2H, ArH), 7.19 (d, $J$ = 9.2 Hz, 2H, ArH), 7.37 (d, $J$ = 8.8 Hz, 2H, ArH), 7.63–7.69 (m, 4H, ArH), 10.16 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 882.8526 (882.8529).

**Ethyl 4-(4-iodophenylamino)-1,2,5,6-tetrahydro-1,2,6-tris(4-iodophenyl) pyridine-3-carboxylate (4ae)**:. Yellow solid. IR (KBr, ν, $cm^{-1}$): 3245, 2987, 2871, 1650, 1609, 1515; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.36 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.76 (dd, $J$ = 16.0 and 2.4 Hz, 1H, $H_{5a}$), 2.98 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5b}$), 4.22–4.41 (m, 2H, $OCH_2$), 5.33 (br s, 1H, $H_6$), 6.14 (s, 1H, $H_2$), 6.21 (d, $J$ = 9.2 Hz, 2H, ArH), 6.38 (d, $J$ = 8.4 Hz, 2H, ArH), 6.68 (d, $J$ = 8.4 Hz, 2H, ArH), 7.12 (d, $J$ = 8.4 Hz, 2H, ArH), 7.32 (d, $J$ = 8.8 Hz, 2H, ArH), 7.52 (d, $J$ = 8.4 Hz, 2H, ArH), 7.62–7.69 (m, 4H, ArH), 10.16 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 978.8213 (978.8180).

**Ethyl 4-(4-tolylamino)-2,6-bis(4-cyanophenyl)-1,2,5,6-tetrahydro-1-(4-tolyl pyridine)-3-carboxylate (4af)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3246, 3010, 2976, 2230, 1653, 1573; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.38 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.07 (s, 3H, $ArCH_3$), 2.24 (s, 3H, $ArCH_3$), 2.78 (dd, $J$ = 16.0 and 2.4 Hz, 1H, $H_{5a}$), 2.95 (dd, $J$ = 15.6 and 5.6 Hz, 1H, $H_{5b}$), 4.24–4.44 (m, 2H, $OCH_2$), 5.47 (br s, 1H, $H_6$), 6.27 (t, $J$ = 7.6 Hz, 2H, ArH and $H_2$), 6.41 (d, $J$ = 8.0 Hz, 2H, ArH), 6.84 (d, $J$ = 8.4 Hz, 3H, ArH), 7.02 (d, $J$ = 8.0 Hz, 2H, ArH), 7.28 (d, $J$ = 8.4 Hz, 2H, ArH), 7.51 (d, $J$ = 8.4 Hz, 2H, ArH), 7.75–7.81 (m, 4H, ArH), 10.18 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 553.2632 (553.2604).

**Ethyl 4-(4-methoxyphenylamino)-2,6-bis(3-fluorophenyl)-1,2,5,6-tetrahydro-1-(4-methoxyphenyl)pyridine-3-carboxylate (4ag)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3247, 2987, 2836, 1646; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.35 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.67 (dd, $J$ = 15.2 and 2.0 Hz, 1H, $H_{5a}$), 2.89 (dd, $J$ = 16.0 and 6.0 Hz, 1H, $H_{5b}$), 3.59 (s, 3H, $OCH_3$), 3.71 (s, 3H, $OCH_3$), 4.22–4.41 (m, 2H, $OCH_2$), 5.33 (br s, 1H, $H_6$), 6.18 (s, 1H, $H_2$), 6.35 (d, $J$ = 8.8 Hz, 2H, ArH), 6.43 (d, $J$ = 8.8 Hz, 2H, ArH), 6.63–6.71 (m, 2H, ArH), 6.75 (d, $J$ = 8.8 Hz, 2H, ArH), 6.89 (t, $J$ = 8.0 Hz, 1H, ArH), 6.96 (d, $J$ = 7.6 Hz, 1H, ArH), 7.02–7.09 (m, 3H, ArH), 7.14–7.18 (m, 1H, ArH), 7.31–7.39 (m, 2H, ArH), 10.13 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 571.2455 (571.2408).

**Ethyl 4-(4-tolylamino)-2,6-bis(3-fluorophenyl)-1,2,5,6-tetrahydro-1-(4-tolylpyridine)-3-carboxylate (4ah)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3243, 2976, 2834, 1659, 1607, 1572; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.38 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.08 (s, 3H, $ArCH_3$), 2.24 (s, 3H, $ArCH_3$), 2.76 (dd, $J$ = 15.6 and 1.2 Hz, 1H, $H_{5a}$), 2.93 (dd, $J$ = 15.6 and 6.8 Hz, 1H, $H_{5b}$), 4.24–4.44 (m, 2H, $OCH_2$), 5.39 (br s, 1H, $H_6$), 6.25 (s, 1H, $H_2$), 6.32 (d, $J$ = 8.4 Hz, 2H, ArH), 6.38 (d, $J$ = 8.0 Hz, 2H, ArH), 8.85–8.89 (m, 3H, ArH), 6.95–7.07 (m, 6H, ArH), 7.18 (d, $J$ = 8.0 Hz, 1H, ArH), 7.31–7.40 (m, 2H, ArH), 10.21 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M+H]^+$ found (expected): 539.2551 (539.2510).

**Ethyl 4-(4-chlorophenylamino)-1-(4-chlorophenyl)-2,6-bis(3-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4ai)**:. Yellow solid. IR (KBr, ν, $cm^{-1}$): 3244, 3019, 2926, 1651; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.38 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.78 (dd, $J$ = 16.4 and 1.6 Hz, 1H, $H_{5a}$), 3.03 (dd,

$J$ = 16.0 and 2.0 Hz, 1H, $H_{5b}$), 4.25–4.45 (m, 2H, $OCH_2$), 5.45 (br s, 1H, $H_6$), 6.25 (s, 1H, $H_2$), 6.40 (d, $J$ = 8.8 Hz, 2H, ArH), 6.57 (d, $J$ = 8.8 Hz, 2H, ArH), 6.86 (d, $J$ = 10.0 Hz, 1H, ArH), 6.94 (d, $J$ = 8.0 Hz, 1H, ArH), 7.06–7.11 (m, 5H, ArH), 7.19 (d, $J$ = 7.6 Hz, 1H, ArH), 7.25 (d, $J$ = 8.4 Hz, 2H, ArH), 7.32–7.42 (m, 2H, ArH), 10.20 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M + H]^+$ found (expected): 579.1478 (579.1418).

**Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-2,6-bis (3-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4aj)**:. Yellow solid. IR (KBr, ν, $cm^{-1}$): 3243, 2978, 2886, 1649, 1589; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.78 (dd, $J$ = 16.4 and 2.0 Hz, 1H, $H_{5a}$), 3.03 (dd, $J$ = 16.0 and 5.2 Hz, 1H, $H_{5b}$), 4.25–4.45 (m, 2H, $OCH_2$), 5.44 (br s, 1H, $H_6$), 6.24 (s, 1H, $H_2$), 6.36 (d, $J$ = 9.2 Hz, 2H, ArH), 6.51 (d, $J$ = 8.4 Hz, 2H, ArH), 6.87 (d, $J$ = 10.0 Hz, 1H, ArH), 6.94 (d, $J$ = 7.6 Hz, 1H, ArH), 7.06–7.10 (m, 3H, ArH), 7.20 (t, $J$ = 8.8 Hz, 3H, ArH), 7.31–7.42 (m, 4H, ArH), 10.19 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M + H]^+$ found (expected): 667.0472 (667.0407).

**Ethyl 4-(4-iodophenylamino)-2,6-bis(3-fluorophenyl)-1,2,5,6-tetrahydro-1-(4-iodophenyl)pyridine-3-carboxylate (4ak)**:. Yellow solid. IR (KBr, ν, $cm^{-1}$): 3246, 3012, 2986, 1649, 1606, 1573; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.37 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.79 (dd, $J$ = 16.0 and 1.6 Hz, 1H, $H_{5a}$), 3.02 (dd, $J$ = 15.6 and 6.0 Hz, 1H, $H_{5b}$), 4.25–4.45 (m, 2H, $OCH_2$), 5.43 (br s, 1H, $H_6$), 6.23–6.27 (m, 3H, ArH and $H_2$), 6.37 (d, $J$ = 8.8 Hz, 2H, ArH), 6.85–6.88 (m, 1H, ArH), 6.93 (d, $J$ = 8.0 Hz, 1H, ArH), 7.05–7.10 (m, 3H, ArH), 7.18 (d, $J$ = 7.6 Hz, 1H, ArH), 7.31–7.40 (m, 4H, ArH), 7.53 (d, $J$ = 8.4 Hz, 2H, ArH), 10.18 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M + H]^+$ found (expected): 763.0142 (763.0130).

**Ethyl 4-(4-fluorophenylamino)-2,6-bis(3-bromophenyl)-1-(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4al)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3245, 3020, 2986, 1659; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.38 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.67 (dd, $J$ = 16.0 and 2.0 Hz, 1H, $H_{5a}$), 2.89 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5b}$), 4.23–4.46 (m, 2H, $OCH_2$), 5.38 (br s, 1H, $H_6$), 6.20 (s, 1H, $H_2$), 6.35–6.38 (m, 2H, ArH), 6.50–6.54 (m, 2H, ArH), 6.93 (t, $J$ = 8.8 Hz, 2H, ArH), 7.04 (t, $J$ = 8.8 Hz, 3H, ArH), 7.24–7.32 (m, 4H, ArH), 7.42–7.46 (m, 2H, ArH), 7.51(s, 1H, ArH), 10.11 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M + H]^+$ found (expected): 667.0358 (667.0401).

**Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-1,2,5,6-tetrahydro-2,6-bis(4-methoxyphenyl)pyridine-3-carboxylate (4am)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3244, 2986, 2834, 1646, 1606, 1573; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.35 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.67 (dd, $J$ = 15.2 and 2.0 Hz, 1H, $H_{5a}$), 2.89 (dd, $J$ = 16.0 and 6.0 Hz, 1H, $H_{5b}$), 3.60 (s, 3H, $OCH_3$), 3.71 (s, 3H, $OCH_3$), 4.23–4.43 (m, 2H, $OCH_2$), 5.33 (br s, 1H, $H_6$), 6.18 (s, 1H, $H_2$), 6.35 (d, $J$ = 8.8 Hz, 2H, ArH), 6.43 (d, $J$ = 8.8 Hz, 2H, ArH), 6.63–6.71 (m, 2H, ArH), 6.75 (d, $J$ = 8.8 Hz, 2H, ArH), 6.89 (t, $J$ = 8.0 Hz, 1H, ArH), 6.96 (d, $J$ = 7.6 Hz, 1H, ArH), 7.02–7.09 (m, 3H, ArH), 7.14–7.18 (m, 1H, ArH), 7.31–7.39 (m, 2H, ArH), 10.13 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M + H]^+$ found (expected): 690.0678 (690.0729).

**Ethyl 4-(4-methoxyphenylamino)-1,2,5,6-tetrahydro-1,2,6-tris(4-methoxy phenyl) pyridine-3-carboxylate (4an)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3246, 2920, 2834, 1655, 1517; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.40 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.79 (dd, $J$ = 15.6 and 5.6 Hz, 1H, $H_{5a}$), 2.95 (dd, $J$ = 15.6 and 2.0 Hz, 1H, $H_{5b}$), 3.68 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 4.22–4.43(m, 2H, $OCH_2$), 5.39 (br s, 1H, $H_6$), 6.14–6.16 (m, 2H, ArH and $H_2$), 6.32 (d, $J$ = 8.4 Hz, 2H, ArH), 6.42 (s, 1H, ArH), 6.77–6.92 (m, 8H, ArH), 7.02 (d, $J$ = 6.8 Hz, 1H, ArH), 7.13–7.24 (m, 3H, ArH), 9.68 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M + H]^+$ found (expected): 594.2781 (594.2730).

**Ethyl 4-(4-chlorophenylamino)-1-(4-chlorophenyl)-1,2,5,6-tetrahydro-2,6-bis(3,4,5-trimethoxyphenyl)pyridine-3-carboxylate (4ao)**:. White solid. IR (KBr, ν, $cm^{-1}$): 3248, 2998, 2876, 1651, 1606, 1589; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.36 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.74 (dd, $J$ = 13.6 and 1.2 Hz, 1H, $H_{5a}$), 3.04 (dd, $J$ = 16.0 and 5.6 Hz, 1H, $H_{5b}$), 3.59 (s, 6H, $OCH_3$), 3.64 (s, 6H, $OCH_3$), 3.69 (s, 6H, $OCH_3$), 4.23–4.46 (m, 2H, $OCH_2$), 5.33 (br s, 1H, $H_6$), 6.19 (s, 1H, $H_2$), 6.41 (s, 2H, ArH), 6.45–6.51 (m, 4H, ArH), 6.56 (s, 2H, ArH), 7.12 (d, $J$ = 9.2 Hz, 2H, ArH), 7.22 (d, $J$ = 8.8 Hz, 2H, ArH), 10.20 (s, 1H, NH); HRMS (ESI) *m/z*: Calcd for $[M + H]^+$ found (expected): 723.2267 (723.2240).

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