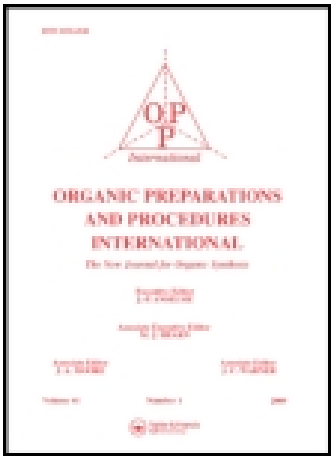

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Rapid and Efficient Synthesis of 1,4-Dihydropyridines using a Sulfonic Acid-functionalized Ionic Liquid

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4-Aryl-l,4-dihydropyridines (1,4-DHPs) constitute a major class of drugs used in the management of cardiovascular diseases.[1,2] They are analogues of NADH co-enzymes and an important class of drugs.[3] Current literature reveals that they possess a variety of biological activities such as anti-cancer,[4] broncho-dilating,[5] anti-diabetic,[6] neurotropic[7] anti-anginal[8] and other pharmacological properties.[9] In particular, indenopyridines initially developed as anti-histamines,[10] are one of the most important privileged medicinal scaffolds. They exhibit fungicidal, cytotoxic, phosphodiesterase inhibitory, coronary dilating and calcium modulating activities, and are useful inhibitors of spermatogenesis in animals.[11,12] The preparation of 1,4-dihydropyridines by the classical Hantzsch synthesis, involve a three-component condensation of an aldehyde with ethyl acetoacetate, and ammonia in acetic acid or in refluxing ethanol.[13–18]

These methods suffer from drawbacks such as long reaction times, lower yields, use of large volumes of organic solvents and harsh refluxing conditions. Several more efficient methods have recently been developed for the synthesis of fused derivatives of dihydropyridines, and include the use of microwaves,[19,20] ionic liquids,[21–23] metal triflates,[24,25] iodine,[26] L-proline,[27] ceric ammonium nitrate (CAN),[28] BINOL-phosphoric acid derivatives,[29] iron (III) trifluoroacetate,[30] $K_7[PW_{11}CoO_{40}]$,[31] also grinding/solvent-free conditions.[32] Although most of these processes offer distinct advantages, but some of them still have their own limitations in terms of yields, longer reaction times, difficult work-up. In some cases, the catalysts used are harmful to environment and cannot be reused. Therefore, an efficient method for the preparation of 1,4-DHP derivatives is still desirable. Ionic liquids have attracted extensive interest as excellent alternatives to organic solvents, due to their favorable properties. They have been found to be the solvents of choice for a large array of organic reactions and as catalyst at the same time.[33–38] Many of these ionic

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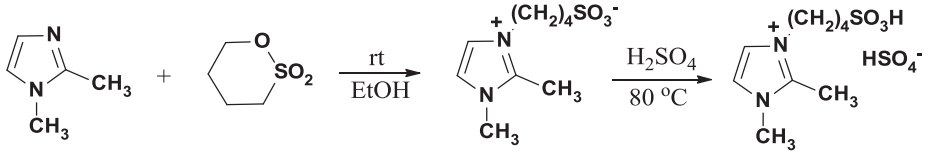
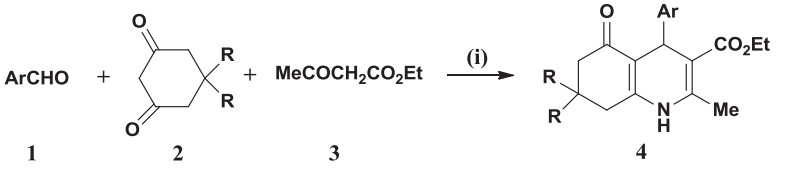
liquids, unlike many conventional solvents, are non-flammable and exert no detectable vapor pressure. The use of ionic liquids as reaction media may offer a convenient solution to both the solvent emission and catalytic recycling problems.

These observations led us to attempt the synthesis of some 1,4-DHPs scaffolds in the presence of SO_3H-functional Brønsted-acidic halogen-free ionic liquid [DMBSI]HSO_4 which bears a butanesulfonic acid group in 1,2-dimethylimidazolium cation as catalyst (*Scheme 1*).



Scheme 1

In continuation of our recent interest in the development of efficient and environmentally friendly procedures for the synthesis of biologically important heterocycles,[39–42] it was thought worthwhile to devise an efficient and eco-friendly method for the synthesis of 4-aryl-l,4-dihydropyridine derivatives to provide privileged scaffolds for the generation of target compounds for drug discovery. In this protocol 4-aryl-l,4-dihydropyridines were synthesized by a rapid and efficient one-pot four-component approach, using 1,2-dimethyl-3-butanesulfonyl imidazolium bisulfate (**[DMBSI]HSO_4**) ionic liquid under solvent-free conditions in high to excellent yields (*Scheme 2*).



(i) NH_4OAc, [DMBSI]HSO_4, 60 °C

a) Ar = C_6H_5, R = Me; b) Ar = 4-FC_6H_4, R = Me; c) Ar = 4-ClC_6H_4, R = Me; d) Ar = 4-MeC_6H_4, R = Me; e) Ar = 4-HOC_6H_4, R = Me; f) Ar = 4-$CF_3C_6H_4$, R = Me; g) Ar = 4-MeOC_6H_4, R = Me; h) Ar = 3-HOC_6H_4, R = Me; i) Ar = 3-MeOC_6H_4, R = Me; j) Ar = pyridyl, R = Me; k) Ar = 2,4-$Cl_2C_6H_4$, R = Me; l) Ar = 2-Thienyl, R = Me; m) Ar = naphthalen-1-yl, R = Me; n) Ar = C_6H_5, R = H; o) Ar = 4-ClC_6H_4, R = H; p) Ar = 4-MeC_6H_4, R = H; q) Ar = 4-FC_6H_4, R = H; r) Ar = 4-MeOC_6H_4, R = H; s) Ar = 4-HOC_6H_4, R = H; t) Ar = 3-HOC_6H_4, R = H; u) Ar = 4-CHOC_6H_4, R = H

Scheme 2

In the initial experiments, different solvents and temperatures in the presence of ionic liquid **[DMBSI]HSO_4** were screened for the synthesis of 4-aryl-l,4-dihydropyridines **4c**. As a model experiment to determine the ideal conditions, equimolar amounts of 4-chlorobenzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate were condensed

in the presence of **[DMBSI]HSO_4** in various solvents. The results showed that the use of **[DMBSI]HSO_4** under solvent-free conditions at 60°C for 3 min is the most efficient condition. To optimize the reaction conditions, we also verified the amount of catalyst needed for the preparation of **4c**, and the best result was obtained using 0.06 g (0.18 mmol) [DMBSI]HSO_4/1 mmol substrate.

The ionic liquid is easily separated from the reaction medium by washing with water. To demonstrate its reusability the washed ionic liquid is distilled under vacuum for reuse in subsequent reactions. After four successive runs, catalytic activity of the catalyst was retained without significant loss of activities. The advantages of present method in comparisons with other reported methods for the synthesis of the 4-aryl-l,4-dihydropyridines, are summarized in *Table 1*.

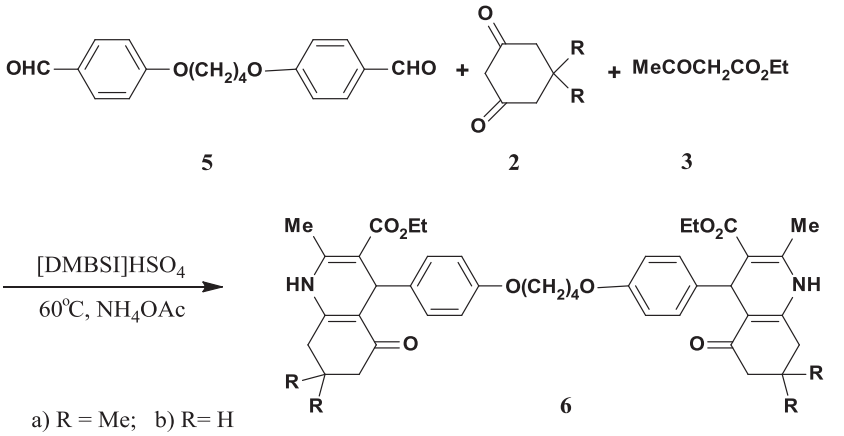
Table 1
Comparison of Synthesis of **4a** in the Presence of Different Catalysts[a]

Entry	Catalyst	Condition	Time	Yield (%)[lit.]
1	$HClO_4$-SiO_2	Solvent-free/90°C	8 min	95[43]
2	$K_7[PW_{12}CoO_{40}]$	CH_3CN/reflux	35 min	80[44]
3	L-proline	C_2H_5OH/Reflux	6 h	92[45]
4	$Yb(OTf)_3$	C_2H_5OH/rt	5 h	90[46]
5	Nanocrystalline TiO_2	Solvent-free/70°C	35 min	90[47]
6	Ni^0-nanoparticle	Solvent-free/rt	15 min	95[48]
7	$[HMIM]BF_4$	Solvent-free/90°C	10 min	95[49]
8	[MBSI]HSO_4[b]	Solvent-free/80°C	10 min	75
9	[DMBSI]HSO_4	Solvent-free/60°C	3 min	94[c]

(a) Reaction conditions: benzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate. (b) 1-Methyl-3-butanesulfonylimidazolium bisulfate. (c) The present work.

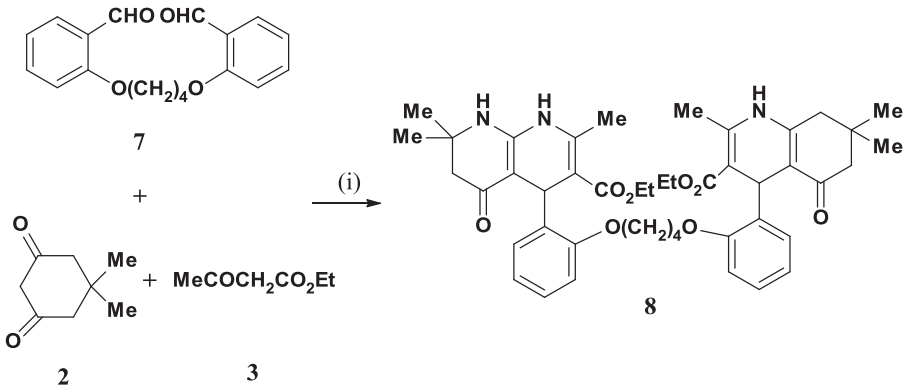
To demonstrate the efficiency and applicability of the present method, various arylaldehydes were used for the synthesis of a variety of 4-aryl-l,4-dihydropyridine derivatives. As shown in *Table 2*, aryl aldehydes (**1**) bearing either electron-withdrawing or electron-donating groups, reacted well to give the corresponding products **4** in high yields (80–95%). Interestingly, this one-pot multi-component approach also afforded an efficient protocol for the synthesis of *bis*-4-aryl-l,4-dihydropyridines (**6, 8**, *Table 2, Schemes 3 and 4*) in excellent yields (85–92%).

Encouraged by these results, we extended the scope of this protocol to the synthesis of fused tricyclic 4-aryl-l,4-dihydropyridines by the reaction of equimolar amounts of arylaldehyde (**1**), 1,3-indanedione (**9**), ethyl acetoacetate (**3**) and NH_4OAc in the presence of [DMBSI]HSO_4 under the aforementioned optimized solvent-free conditions and obtained indenopyridines (*Scheme 5*) in excellent yields (88–95%) and short reaction times (2–5 min) (*Table 2*).



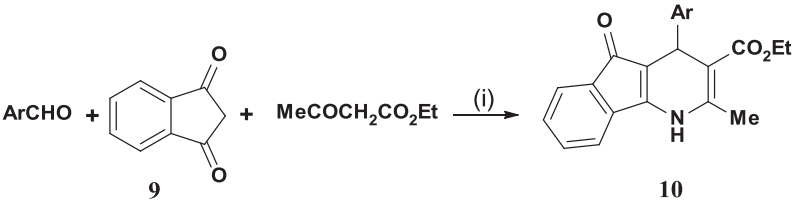
a) R = Me; b) R= H

Scheme 3



(i) NH_4OAc, $[DMBSI]HSO_4$, 60 °C

Scheme 4



(i) NH_4OAc, $[DMBSI]HSO_4$, 60 °C

a) 4-MeC_6H_4; b) 4-ClC_6H_4; c) 4-FC_6H_4; d) 3-ClC_6H_4; e) 2,4-$Cl_2C_6H_3$; f) 4-$(CH_3)_2CHC_6H_4$

Scheme 5

Table 2
Synthesis of 4-Aryl-l,4-dihydropyridine **4a–4u, 6a, 6b, 8, 10a–10f**

Compound	Yield[a] (%)	Time (min.)	mp. (°C)	Lit. mp.[lit.] (°C)
4a	94	3	206–208	202–204[46]
4b	95	3	188–191	184–186[46]
4c	94	3	240–242	245–246[50]
4d	90	5	258–259	260–261[46]
4e	90	6	233–235	232–234[46]
4f	95	2	193–194	188–190[51]
4g	80	12	247–249	245–247[52]
4h	90	5	220–222	220–222[53]
4i	87	6	202–204	202–204[52]
4j	85	3	70–73	66–67[46]
4k	95	3	241–243	241–244[46]
4l	94	6	227–230	223–225[52]
4m	80	6	203–205	198–200[54]
4n	80	7	243–244	240–241[55]
4o	85	3	236–238	234–235[54]
4p	80	12	238–240	241–242[54]
4q	85	2	244–246	243–244[54]
4r	78	10	200–203	193–195[40]
4s	80	6	225–227	220–222[40]
4t	95	3	270–271	—
4u	80	6	>300	—
6a	90	5	257–258	—
6b	92	5	143–145	—
8	85	6	138–140	—
10a	90	3	249–251	—
10b	92	2	216–218	—
10c	95	2	224–226	—
10d	93	3	200–203	—
10e	95	2	208–210	—
10f	88	4	259–260	—

The reaction profile of the present protocol is very clean and no side-products are formed. The structures of all the newly synthesized products were confirmed by spectroscopic (IR, ^{1}H-NMR, ^{13}C-NMR) and elemental analyses and for the known derivatives, by comparison of their spectroscopic data and melting points with those of literature reports. Attempts to extend these conditions to aliphatic aldehydes such as propionaldehyde or butyraldehyde with dimedone, ethyl acetoacetate and ammonium acetate, gave a complex mixture due to aldol condensations.

In summary, we have successfully demonstrated remarkable catalytic activity of $[DMBSI]HSO_4$ as an emerging green catalyst and developed a reliable, clean and eco-friendly, benign protocol for the synthesis of versatile 1,4-dihydropyridine derivatives. The operational simplicity, easy work-up of the products, use of $[DMBSI]HSO_4$ as a green catalyst, mild reaction conditions, short reaction times, high to excellent yields, solvent-free conditions and reusability of the catalyst, are the advantages of this protocol. The method is amenable for the iterative generation of combinatorial libraries.

Experimental Section

Mps were recorded on a Büchi B-545 apparatus in open capillary tubes. IR spectra (KBr) were determined on a Shimadzu IR-470 spectrometer. NMR spectra were recorded on a Bruker DRX (500 and 400 MHz) (^{1}H) and Bruker DRX (125 and 100 MHz) (^{13}C) in DMSO-d_6 and $CDCl_3$ as solvent with TMS as an internal standard; δ was quoted in ppm and J in Hz. Elemental analyses were performed on a Carlo-Erba EA1110CNNO-S analyzer and agreed (within 0.30) with the calculated values. Chemicals were purchased from Merck and Fluka. All solvents used were dried and distilled according to standard procedures. The SO_3H-functionalized ionic liquid $[DMBSI]HSO_4$ was synthesized according to the literature.[56,57]

Synthesis of 1,2-Dimethylimidazolium-3-butanesulfonate (DMIBS)

To a solution of 1,2-dimethylimidazole (9.61 g, 0.10 mol) in ethanol (25 ml) 1,4-butanesultone (13.60 g, 0.10 mol) was added in portions over 30 min, and the mixture was then stirred for 48 h at room temperature. The white precipitate thus formed was collected and washed with petroleum ether (2 × 10 ml). The product was recrystallized from EtOH, to give DMIBS as white solid, mp. 268–270°C, in 95% yield.

Synthesis of 1,2-Dimethyl-3-butanesulfonylimidazolium Bisulfate

Equimolar amounts of 1,2-dimethylimidazoliumbutanesulfonate (DMIBS) and sulfuric acid solutions (96%) were mixed and stirred for 6 h at 80°C. The reaction mixture was subjected to drying under vacuum (10 mm Hg) at 70° for 2 h to remove any volatile. The residue was washed by stirring with ether (2 × 10 ml) to remove unreached material and dried under vacuum again (10 mm Hg) for 30 min. The IL was obtained quantitatively in high purity as a colorless viscous oil.[57]

^{1}H-NMR (400 MHz, D_2O): δ 1.45 (m, 2H, –CH_2–), 1.68 (m, 2H, –CH_2–), 2.32 (s, 3H, CH_3), 2.66 (t, J = 7.6, -CH_2-S), 3.49 (s, 3H, CH_3), 3.88 (t, J = 7.2, 2H, -CH_2-N), 7.05 (d, J = 2.0, 1H, CH =), 7.10 (d, J = 2.0, 1H, =CH); ^{13}C-NMR (100 MHz, D_2O): δ 8.6, 20.9, 27.6, 34.4, 47.3, 50.0, 120.7, 122.0, 144.1.

Anal. Cald. for $C_9H_{18}N_2O_7S_2$ (330.38): C, 32.72; H, 5.49; N, 8.48. Found: C, 32.56; H, 5.41; N, 8.35.

General Procedure for the Preparation of 4a–4u, 6a, 6b, 8, 10a–10f

A mixture of 1 mmol each of ethyl acetoacetate, NH_4OAc, 1,3-diketone and aldehyde in a flask containing a magnetic stirring bar and $[DMBSI]HSO_4$ (0.18 mmol, 0.06 g)

was heated at 60°C in an oil bath. Stirring at 60°C was continued until disappearance of the starting materials (monitored by TLC, SiO_2, ethyl acetate/petroleum ether: 1/3). The reaction mixture was cooled to RT and stirred with water. The resultant solid product was collected and the aqueous filtrate containing the ionic liquid was saved for recycling (see below). The solid obtained was stirred with ethyl acetate and collected again to furnish the desired pure product (when 1,3-indandione was used as the 1,3-diketone, the product was washed with petroleum ether).

The aqueous filtrate was evaporated to recover the ionic liquid. The crude recovered liquid was washed with diethyl ether (2 × 5 ml) and dried under vacuum to be reused in subsequent reactions.

Spectroscopic data for selected products:

Ethyl 1,4,5,6,7,8-Hexahydro-4-(p-anisyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (4g)

White powder, IR (KBr. cm^{-1}): 3290, 3070, 2950, 1688, 1600; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 3H, CH_3), 1.08 (s, 3H), 1.23 (t, $J = 7.2$, 3H, CH_3), 2.17, 2.25 (d, $J = 16.0$, diastereotopic $\underline{CH_2}$-CNH), 2.21, 2.32 (d, $J = 16.8$, diastereotopic $\underline{CH_2}$-CO), 2.38 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.10 (q, $J = 7.2$, 2H, O$\underline{CH_2}$-CH_3), 5.02 (s, 1H, CH), 6.35 (br s, 1H, NH), 6.76 (d, $J = 8.8$, 2H, Ar-H), 7.24 (d, $J = 8.8$, 2H, Ar-H).

Ethyl 1,4,5,6,7,8-Hexahydro-4-(3-hydroxyphenyl)-2-methyl-5-oxoquinoline-3-carboxylate (4t)

White powder, IR (KBr. cm^{-1}): 3400, 3290, 1670, 1605; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.14 (t, $J = 7.1$, 3H, OCH_2-$\underline{CH_3}$), 1.89 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 2.32 (s, 3H, CH_3), 2.29–2.52 (m, 4H, $\underline{CH_2}$-CH_2-$\underline{CH_2}$), 4.00 (q, $J = 7.1$, 2H, O$\underline{CH_2}$-CH_3), 4.95 (s, 1H, CH), 5.1 (br s, 1H, NH), 6.54 (d, $J = 8.3$, 1H, Ar-H), 6.70 (m, 2H, Ar-H), 6.94 (t, $J = 8.0$, 1H, Ar-H), 8.58 (br s, 1H, OH).

Anal. Cald. for $C_{19}H_{21}NO_4$ (327.37): C, 69.71; H, 6.47; N, 4.28. Found: C, 69.92; H, 6.40; N, 4.21.

Ethyl 4-(4-Formylphenyl)-1,4,5,6,7,8-hexahydro-2-methyl-5-oxoquinoline-3-carboxylate (4u)

White powder, IR (KBr. cm^{-1}): 3280, 3200, 2904, 3080, 2840, 2750, 1690, 1600; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.13 (t, $J = 7.0$, 3H, OCH_2-$\underline{CH_3}$), 1.88–2.14 (m, 6H, CH_2), 2.20 (s, 3H, CH_3), 4.00 (q, $J = 7.0$, 2H, O$\underline{CH_2}$-CH_3), 4.84 (s, 1H, CH), 6.82 (br s, 1H, NH), 6.95–7.01 (m, 4H, Ar-H), 6.70–6.72 (m, 2H, Ar-H), 9.10 (s, 1H, CHO); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 14.6, 18.8, 21.2, 26.6, 35.2, 37.2, 59.5, 104.2, 111.3, 127.2, 127.3, 127.4, 145.2, 145.4, 152.1, 167.5, 195.2, 205.5.

Anal. Cald. for $C_{20}H_{21}NO_4$ (339.39): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.61; H, 6.08; N, 4.26.

***bis*-Ethyl 4,5,6,7,8-Hexahydro-4-(4-ethoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (6a)**

White powder, IR (KBr. cm^{-1}): 3300, 3200, 3080, 2950, 1700, 1600; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.08 (s, 6H, CH_3), 1.23 (t, $J = 7.0$, 6H, CH_2-$\underline{CH_3}$), 1.90 (br s, 4H), 2.14–2.32 (m, 8H, CH_2), 2.39 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.95 (br s, 4H, O$\underline{CH_2}$-CH_2), 4.09 (q, $J = 7.0$, 4H, O$\underline{CH_2}CH_3$), 5.01 (s, 2H, CH), 6.45 (br s, 2H, NH), 6.74 (d, $J = 8.6$, 4H, Ar-H), 7.21 (d, $J = 8.6$, 4H, Ar-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.8, 14.3, 19.4, 19.5, 26.0, 26.1, 27.2, 28.2, 29.5, 32.6, 32.7, 35.6, 35.7, 41.1, 41.2, 48.3, 50.7, 53.7, 59.8, 61.9, 67.3, 67.5, 106.4, 112.4, 112.5, 113.8, 113.9, 114.0, 128.9, 129.0, 139.5, 143.1, 143.2, 143.3, 147.8, 148.1, 157.2, 167.6, 195.5, 195.6.

Anal. Cald. for $C_{46}H_{56}N_2O_8$ (764.95): C, 72.23; H, 7.38; N, 3.66. Found: C, 72.10; H, 7.21; N, 3.52.

***bis*-Ethyl 4-(4-Ethoxyphenyl)-1,4,5,6,7,8-hexahydro-2-methyl-5-oxoquinoline-3-carboxylate (6b)**

White powder, IR (KBr. cm^{-1}): 3300, 3200, 3080, 2940, 1695, 1600; ^{1}H-NMR (400 MHz, DMSO): δ 1.14 (t, $J = 7.0$, 6H, $OCH_2\underline{CH_3}$), 1.80–2.30 (m, 16H, CH_2, OCH_2-$\underline{CH_2}$), 2.28 (s, 6H, CH_3), 3.93 (br s, 4H, O$\underline{CH_2}$-CH_2), 3.98 (q, $J = 7.0$, O$\underline{CH_2}$-CH_3), 4.83 (s, 2H, CH), 6.74 (d, $J = 8.6$, 4H, Ar-H), 7.03 (d, $J = 8.6$, 4H, Ar-H), 9.08 (br s, 2H, N-H); ^{13}C-NMR (100 MHz, $CDCl_3$-d_6): δ 14.7, 18.7, 21.3, 26.0, 26.6, 35.1, 37.2, 59.5, 67.4, 104.3, 111.8, 114.2, 128.8, 140.5, 1450, 151.6, 157.2, 167.4, 195.2.

Anal. Cald. for $C_{42}H_{48}N_2O_8$ (708.84): C, 71.17; H, 6.82; N, 3.95. Found: C, 71.05; H, 6.64; N, 3.86.

***bis*-Ethyl 1,4,5,6,7,8-Hexahydro-4-(2-ethoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (8)**

White powder, IR (KBr. cm^{-1}): 3300, 3085, 2950, 1700, 1680, 1646, 1600; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.19 (t, $J = 7.0$, 3H, OCH_2-$\underline{CH_3}$), 1.20 (t, $J = 7.2$, 3H, OCH_2-$\underline{CH_3}$), 2.01–2.20 (m, 8H, CH_2), 2.22–2.27 (m, 4H, OCH_2-$\underline{CH_2}$), 2.29 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.00–4.09 (m, 8H, O$\underline{CH_2}$-CH_2, O$\underline{CH_2}$-CH_3), 5.37 (s, 2H, CH), 6.83 (d, $J = 7.6$, 2H, Ar-H), 6.84 (t, $J = 7.2$, 2H, Ar-H), 7.10 (td, $J = 7.8$, 1.5, 2H, Ar-H), 7.35 (d, $J = 7.2$, 2H, Ar-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.3, 19.0, 20.4, 26.8, 27.2, 29.6, 32.5, 40.8, 50.9, 59.6, 68.3, 105.3, 111.5, 120.0, 127.3, 128.8, 131.5, 135.0, 143.7, 149.9, 156.8, 168.0, 196.1.

Anal. Cald. for $C_{46}H_{56}N_2O_8$ (764.95): C, 72.23; H, 7.38; N, 3.66. Found: C, 72.16; H, 7.23; N, 3.71.

***Ethyl* 4,5-Dihydro-2-methyl-5-oxo-4-*p*-tolyl-1*H*-indeno[1,2-*b*]pyridine-3-carboxylate (10a)**

Red powder, IR (KBr. cm^{-1}): 3250, 3080, 1700, 1630, 1580; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.17 (t, $J = 7.0$, 3H, OCH_2-$\underline{CH_3}$), 2.28 (s, 3H, CH_3), 2.51 (s, 3H, Ar-CH_3), 4.07 (q, 2H, $J = 7.0$, O$\underline{CH_2}$-CH_3), 5.00 (s, 1H, CH), 6.75 (br s, 1H, NH), 7.06 (d, $J = 7.6$, 2H, Ar-H), 7.24 (d, $J = 7.6$, 2H, Ar-H), 7.29–7.39 (m, 4H, Ar-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ

14.1, 19.9, 21.1, 36.8, 60.0, 108.3, 111.0, 116.8, 121.4, 127.8, 130.0, 131.2, 134.0, 135.9, 136.2, 142.9, 143.1, 152.6, 167.4, 192.0.

Anal. Cald. for $C_{23}H_{21}NO_3$ (359.15): C, 76.86; H, 5.89; N, 3.90. Found: C, 76.82; H, 5.75; N, 3.81.

Ethyl 4-(4-Chlorophenyl)-4,5-dihydro-2-methyl-5-oxo-1H-indeno[1,2-b]pyridine-3-carboxylate (10b)

Red powder, IR (KBr. cm^{-1}): 3274, 1701, 1639, 1506; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.16 (t, $J = 7.1$, 3H, OCH_2-$\underline{CH_3}$), 2.51 (s, 3H, CH_3), 4.07 (q, $J = 7.1$, 2H, O$\underline{CH_2}$-CH_3), 5.02 (s, 1H, CH), 7.02 (br s, 1H, NH), 7.12 (m, 1H, Ar-H), 7.22 (d, $J = 8.4$, 2H, Ar-H), 7.29–7.32 (m, 4H, Ar-H), 7.38 (m, 1H, Ar-H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.4, 19.4, 37.2, 60.1, 107.0, 109.7, 119.1, 121.1, 128.1, 128.4, 129.7, 129.8, 130.1, 131.5, 131.9, 134.4, 136.9, 145.5, 145.8, 154.3, 167.7, 192.4.

Anal. Calcd. for $C_{22}H_{18}ClNO_3$ (379.84): C, 69.57; H, 4.78; N, 3.69. Found: C, 69.50; H, 4.85; N, 3.73.

Ethyl 4-(4-Fluorophenyl)-4,5-dihydro-2-methyl-5-oxo-1H-indeno[1,2-b]pyridine-3-carboxylate (10c)

Red powder, IR (KBr. cm^{-1}): 3350, 3095, 1690, 1650, 1620; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.16 (t, $J = 7.1$, 3H, OCH_2-$\underline{CH_3}$), 2.48 (s, 3H, CH_3), 4.08 (m, 2H, O$\underline{CH_2}$-CH_3), 5.03 (s, 1H, CH), 6.96 (t, $J = 8.6$, 2H, Ar-H), 7.13 (m, 1H, Ar-H, Ar-H), 7.29–7.34 (m, 5H, Ar-H), 7.38 (m, 1H, Ar-H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.5, 20.1, 37.2, 60.5, 108.4, 110.8, 115.3 (d, $^2J_{C\text{-}F} = 21.24$), 117.7, 121.8, 129.8 (d, $^3J_{C\text{-}F} = 8.04$), 130.6, 131.8, 134.3, 136.4, 142.1, 144.0, 153.5, 161.6 (d, $^1J_{C\text{-}F} = 246.10$), 167.7, 192.7.

Anal. Calcd. for $C_{22}H_{18}FNO_3$ (363.38): C, 72.72; H, 4.99; N, 3.85. Found: C, 72.65; H, 5.13; N, 3.76.

Ethyl 4-(3-Chlorophenyl)-4,5-dihydro-2-methyl-5-oxo-1H-indeno[1,2-b]pyridine-3-carboxylate (10d)

Red powder, IR (KBr. cm^{-1}): 3260, 1700, 1635, 1580; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.17 (t, $J = 7.2$, 3H, OCH_2-$\underline{CH_3}$), 2.55 (s, 3H, CH_3), 4.09 (m, 2H, O$\underline{CH_2}$-CH_3), 5.02 (s, 1H, CH), 6.66 (br s, 1H, NH), 7.09–7.13 (m, 2H, Ar-H), 7.14 (t, $J = 1.6$, 1H, Ar-H), 7.20 (t, $J = 7.8$, 1H, Ar-H), 7.27–7.43 (m, 4H, Ar-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0, 20.1, 37.2, 60.2, 107.5, 110.3, 116.7, 121.7, 126.4, 126.6, 128.0, 129.4, 130.3, 131.3, 133.7, 134.1, 135.9, 143.7, 147.8, 152.5, 167.0, 191.8.

Anal. Cald. for $C_{22}H_{18}ClNO_3$ (379.84): C, 69.57; H, 4.78; N, 3.69. Found: C, 69.51; H, 4.61; N, 3.85.

Ethyl 4-(2,4-Dichlorophenyl)-4,5-dihydro-2-methyl-5-oxo-1H-indeno[1,2-b]pyridine-3-carboxylate (10e)

Red powder, IR (KBr. cm^{-1}): 3269, 1699, 1637; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.17 (t, $J = 7.1$, 3H, $OCH_2\underline{CH_3}$), 2.48 (s, 3H, CH_3), 4.06–4.09 (m, 2H, O$\underline{CH_2}$-CH_3), 5.40 (s, 1H,

CH), 7.12 (m, 1H, Ar-H), 7.16 (dd, $J = 8.7, 2.0$, 1H, Ar-H), 7.29–7.32 (m, 5H, Ar-H), 7.37 (m, 1H, Ar-H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.4, 20.2, 35.4, 60.6, 107.6, 109.8, 117.8, 121.8, 127.6, 129.6, 130.8, 131.8, 132.2, 133.0, 134.3, 134.3, 136.2, 142.3, 144.9, 153.7, 167.4, 192.2.

Anal. Calcd. for $C_{22}H_{17}Cl_2NO_3$ (414.28): C, 63.78; H, 4.14; N, 3.38. Found: C, 63.71; H, 4.07; N, 3.30.

Ethyl 4,5-Dihydro-4-(4-isopropylphenyl)-2-methyl-5-oxo-1H-indeno[1,2-b]pyridine-3-carboxylate (10f)

Red powder, IR (KBr. cm^{-1}): 3280, 3090, 2950, 1700, 1638, 1600; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.17 (t, $J = 7.1$, 3H, OCH_2-$\underline{CH_3}$), 1.22 (d, $J = 6.90$, 6H, CH-($\underline{CH_3}$)$_2$), 2.55 (s, 3H, CH_3), 2.84 (sept., $J = 6.9$, 1H, $\underline{CH}$-(CH_3), 4.07–4.12 (m, 2H, $O\underline{CH_2}$-CH_3), 5.02 (s, 1H, CH), 6.50 (br s, 1H, NH), 7.07 (d, $J = 6.6$, 1H, Ar-H), 7.12 (d, $J = 8.1$, 2H, Ar-H), 7.27 (d, $J = 8.1$, 2H, Ar-H), 7.34–7.39 (m, 2H, Ar-H), 7.40 (d, $J = 7.1$, 1H, Ar-H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.4, 19.6, 24.4, 34.0, 37.2, 60.2, 108.0, 110.7, 118.5, 121.3, 126.5, 128.1, 130.0, 131.4, 134.7, 144.1, 144.1, 146.8, 154.1, 168.1, 192.7.

Anal. Calcd. for $C_{25}H_{25}NO_3$ (387.47): C,77.49; H, 6.50; N, 3.61. Found: C, 77.42; H, 6.41; N, 3.69.

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